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DEPARTAMENTO DE QUÍMICA ORGÁNICA II

Michael Initiated Organocatalytic Cascade Reactions

MEMORIA PRESENTADA POR

Iker Riaño Castela

PARA OPTAR AL GRADO DE DOCTOR

CON MENCIÓN "DOCTOR INTERNACIONAL"

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Universidad del País Vasco Euskal Herriko Unibertsitatea

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El Tribunal designado por la Comisión de Postgrado de la UPV/EHU para calificar la Tesis Doctoral arriba indicada y reunido en el día de la fecha, una vez efectuada la defensa por el/la doctorando/a y contestadas las objeciones y/o sugerencias que se le han formulado, ha otorgado por_____la calificación de:

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A Uxue

A mi familia

A mis amigos y amigas

Quiero expresar mi agradecimiento a los Profesores Dra. Marisa Carrillo y Dr. Jose L. Vicario por la dirección y supervisión de este trabajo así como por la ayuda y confianza depositadas en mí. Igualmente agradezco a los Profesores Dr. Efraím Reyes y Dra. Uxue Uria y al resto del grupo de investigación por su continuo apoyo durante este periodo. También me gustaría agradecer a las personas que de una forma u otra han contribuido a la realización de este trabajo.

I must also mention Professor Christmann. I would like to thank him for the opportunity he gave me to work in his lab, as well as for all the time he dedicated to me during my stay there; always trying to make it the most enriching experience possible.

Agradezco a la UPV/EHU por la concesión de una "beca para formación y perfeccionamiento de personal investigador" y por la subvención general a grupos de investigación EHUA 12/09 y UFI QOSYC 11/22. De la misma manera, agradezco al Gobierno Vasco por la subvención a grupos IT328-10 y al MICINN (Proyecto CTQ2011-22790) por la financiación otorgada, así como a Petronor S.A. por su generosa donación de hexano.

Abstract

In the work compiled in this thesis, different methodologies have been developed based on Michael initiated cascade reactions in order to obtain enantioenriched interesting products, employing chiral amines as stereoinductors elements, under iminium ion activation.

In this sense, firstly we studied the versatility of 4-alkenyl-5*H*-1,2,3-oxathiazol-2,2-dioxides as multifunctional reagents in cascade processes. On the one hand, it has been demonstrated their ability as Michael donor/acceptor in Michael/Michael cascade reactions, using enals as initial acceptors, under iminium/enamine manifold. In addition, by transforming the obtained cycloadducts it has been possible to achieve the 1,2-aminoalcohol moiety, as well as to synthesize bicycle[3.1.0]hexanes, due to the ability of the sulfonate as leaving group. On the other hand, 4-alkenyl-5*H*-1,2,3-oxathiazol-2,2-dioxides have been used in the formation of this type of complex bicyclic structures through Michael/Michael/transannular nucleophilic substitution/imine hydrolysis cascade sequence.

Secondly, several pyrrolidine derivatives have been synthesized in a stereocontrol way through one-pot Michael/intramolecular condensation/reduction sequence between aminomalonates and α,β-unsaturated ketones, employing chiral primary amines as catalysts. Moreover, they have been satisfactorily transformed into the corresponding proline derivatives, by the base-promoted intramolecular C→N acyl transfer reaction, followed by deprotection of the resulting carbamate.

Finally, as part of a short stay in the Prof. M. Christmann group at Free University of Berlin, I could take part in a project related to the synthesis of (+)-

Greek tobacco lactone, completing the synthesis in 7 steps and with an overall yield of 7%.

Resumen

En el presente trabajo de investigación se han desarrollado diversas metodologías basadas en reacciones en cascada iniciadas por adiciones de Michael, con el fin de obtener productos enantioenriquecidos de interés, empleando aminas quirales como elementos estereoinductores de la reacción, bajo activación *via* ion iminio.

En este sentido, en primer lugar se ha estudiado la versatilidad sintética de los 2,2-dióxidos de 4-alquenil-5*H*-1,2,3-oxatiazol como reactivos multifuncionales en procesos en cascada. Por un lado, se ha demostrado su capacidad como dadores/aceptores de Michael en reacciones en cascada Michael/Michael, empleando enales como aceptores iniciales combinando los modos de activación iminio y enamina. Adicionalmente, mediante la transformación de los cicloaductos obtenidos ha sido posible la obtención de la agrupación 1,2-amino alcohol, así como la síntesis de compuestos bicíclicos complejos, haciendo uso de la habilidad de la unidad sulfonato como grupo saliente. Por otro lado, los 2,2-dióxidos de 4-alquenil-5*H*-1,2,3-oxatiazol se han empleado en la formación de dichas estructuras bicíclicas mediante un proceso en cascada Michael/Michael/sustitución nucleófila transanular/hidrólisis de imina.

En segundo lugar, se han sintetizado derivados de pirrolidina de manera esterecontrolada mediante un proceso one-pot Michael/condensación intramolecular/reducción entre aminomalonatos y cetonas α,β-insaturadas, empleando aminas primarias como catalizadores. Además, han sido eficazmente transformados en los correspondientes derivados de prolina, mediante transposición intramolecular C→N de acilo seguido de desprotección del carbamato resultante.

Finalmente, y como parte de una estancia corta llevada a cabo en el grupo del Prof. M. Christmann en la Universidad Libre de Berlín, pude tomar parte en el proyecto dirigido a la síntesis del producto natural *(+)-Greek tobacco lactone*, pudiéndose completar su síntesis en un total de 7 pasos con un rendimiento global del 7%.

Laburpena

Doktorego tesi honetan, kaskada erreakzioetan oinarritutako metodologia desberdinak aztertu dira, kaskadaren hasarazle gisa Michael adizio bidezko erreakzioa oinarritzat hartuz. Erreakzioaren elementu estereoinduzitzaile bezala amina kiralak erabili dira eta iminio bidezko aktibazioaren bitartez, interesdun produktu enantioaberastuak prestatu dira.

Lehenik eta behin, kaskada prozesuetarako erreaktibo multifuntzional gisa, 4-alkenil-5*H*-1,2,3-oxatiazol-2,2-dioxidoak erabili dira beraien aldakortasun sintetikoa ikasteko helburuarekin. Alde batetik, beraien Michael emaile/hartzaile gaitasuna frogatu da Michael/Michael bidezko kaskada erreakzioetan, hasierako hartzaile bezala enalak erabiliz eta iminio eta enamina bidezko aktibazioak konbinatuz. Gainera, lortutako produktuen transformazioen bidez, 1,2-aminoalkohol taldea lortzea posible izan da, baita konposatu bizikliko konplexuak ere, sulfonatoaren talde ateragarri izaerari esker. Bestalde, 4-alkenil-5*H*-1,2,3-oxatiazol-2,2-dioxidoak, egitura bizikliko hauen eraketan erabili dira Michael/Michael/ordezkapen nukleozale transanular/imina hidrolisi kaskada prozesu-sekuentziaren bitartez.

Bestalde, pirrolidina eratorri sintetikoak modu estereokontrolatuan prestatu dira, *one-pot* bidezko Michael/kondentsazio intramolekular/erredukzio prosezuaren bitartez, aminomalonatoak eta zetona α,β-asegabetuak erabiliz, eta amina primariodun katalizatzaileez baliatuz. Gainera, hauek modu eraginkor batean transformatu dira prolina deribatuetan, azilo taldearen C→N transposizio intramolekular eta ondorengo karbamatoaren desbabespenari esker.

Azkenik, Berlineko Freie Unibertsitateko Prof. M. Christmann-en taldean buruturiko egonaldi laburrean, *(+)-Greek tobacco lactone* produktu naturalaren sintesian parte hartzeko aukera izanda, sintesi totala %7ko etekin globalarekin eta 7 pausutan osatzea posible izan zen.

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1

Introduction

1. ORGANOCATALYSIS

Asymmetric organocatalysis is a synthetic methodology complementary to metal catalysis[1] and enzymatic transformations[2] that in the last years has been widely studied in the field of asymmetric synthesis. This method consists on the increase of the rate of several chemical reactions influenced by substoichiometric amounts of a small chiral organic compound, which does not contain a metal atom in its structure.[3]

The advent of organocatalysis at the end of 1990's brought the perspective of an additional mode of catalysis with notable advantages. Usually the reactions can be performed under aerobic conditions with wet solvents, due to the stability of the intermediates participating in the catalytic cycle towards these conditions. Moreover, organocatalysts are, in general, commercially available, environmentally friendly and cheaper than most of the metal-based catalysts. Therefore, it is possible to save cost, time and energy, simplifying the experimental procedure and reducing chemical waste. For these reasons, organocatalysis is considered a highly powerful tool for the synthesis of enantioenriched compounds, having increased notably the number of publications

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[1] Metal catalysis: a) *Transition Metals for Organic* Synthesis, 2nd ed. (Eds.: Beller, M.; Bolm, C.), Wiley-VCH, Weinheim, **2004**; b) *Transition Metal Reagents and Catalysts* (Ed.: Tsuji, J.), John Wiley and Sons, Chichester, **2000**; c) *Application of Transition Metal Catalysts in Organic Synthesis* (Eds.: Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D.), Springer, Heidelberg, **1999**.

[2] Enzyme catalysis: a) *Enzyme Catalysis in Organic Chemistry*, 3rd ed. (Eds.: Drauz, K.; Gröger, H.; May, O.), Wiley-VCH, Weinheim, **2012**; b) Tao, J.; Zhao, L.; Ran, N. *Org. Process Res. Dev.* **2007**, *11*, 259; c) Benkovic, S. J.; Hammes-Schiffer, S. *Science* **2003**, *301*, 1196; d) Bruice, T. C. *Acc. Chem. Res.* **2002**, *35*, 139; e) *Enzymes in Synthetic Organic Chemistry*, 1st ed. (Eds.: Wong, C. H.; Whitesides, G. M.), Tetrahedron Organic Chemistry Series, Vol. 12, Oxford, **1994**.

[3] a) MacMillan, D. W. C. *Nature* **2008**, *455*, 304; b) List, B.; Yang, J. W. *Science* **2006**, *313*, 1584; c) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; d) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726.

in the past decade.[4] In spite of these advantages, this field still presents several limitations. On the one hand, the typical organocatalytic reactions require for long reaction times and high catalyst loadings, presenting low turnover numbers. On the other hand, these factors might limit the potential uses of organocatalysis for industrial applications. However organocatalysts can be used in larger quantities than metal-based ones for the same price, avoiding the presence of metal traces, which is a crucial aspect to consider with respect to applications in medicinal chemistry,[5] in order to prepare compounds for *in vitro* bioassays. In addition, the application of organocatalysis in the total synthesis of target molecules has increased significantly in recent years.[6] Despite all these advances there are still synthetic problems that can only be dealt with the use of metal and/or enzymatic catalysts, being the development of new asymmetric organocatalytic methodologies still a necessity nowadays.

Although the development of organocatalysis is recent, the first well established enantioselective reaction on a prochiral substrate in the absence of an enzyme, and using a chiral organic compound as a stereoinductor in a substoichiometric amount, can be attributed to Bredig and Fiske in 1913. They reported the synthesis of mandelonitrile from the addition of HCN to

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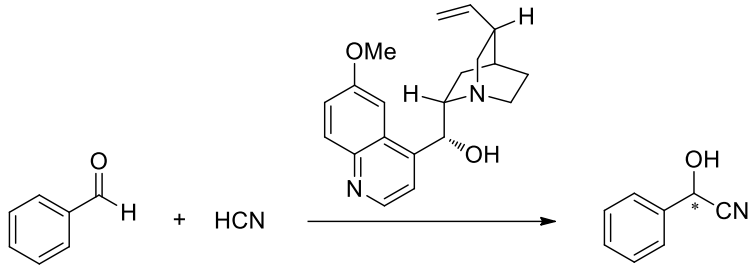
[4] For selected reviews on organocatalysis, see: a) Jacobsen, E. N.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20618; b) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178; c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; d) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; e) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267; f) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo N. T. *Drug Discovery Today* **2006**, *12*, 8.

[5] For selected reviews on organocatalysis applied to medicinal chemistry, see: a) Alemán, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774; b) Jaroch, S.; Weinmann, H.; Zeitler, K. *ChemMedChem* **2007**, *2*, 1261.

[6] Organocatalysis in total synthesis: a) Sun, B.-F. *Tetrahedron Lett.* **2015**, *56*, 2133; b) Abbasov, M. E.; Romo, D. *Nat. Prod. Rep.* **2014**, *31*, 1318; c) *Organocatalysis in Total Synthesis* (Ed.: Dalko, P. I.), Wiley-VCH, Weinheim, **2013**; d) *Asymmetric Organocatalysis in Natural Product Synthesis* (Ed.: Waser, M.), Springer, Wien, **2012**; e) Marqués-López, E.; Herrera, R. P.; Christmann, M. *Nat.Prod. Rep.* **2010**, *27*, 1138.

benzaldehyde, using quinine or quinidine as chiral catalyst (Scheme 1.1).[7] The resulting enantiomeric excess of the obtained cyanohydrins was very poor, (around 8% ee). However this work is considered the basis of future investigations in the field.



Scheme 1.1

In 1928, Wolfgang Langebeck reported that low molecular weight organic molecules, such as simple amino acids, can be used to explain and mimic the catalytic activity and selectivity of enzymes. Subsequently, he introduced for the first time the term "organic catalysis" to define the reactions promoted by organic molecules.[8] In 1949, he also published a book entitled "Organic Catalysts and Their Relations with Enzymes",[9] considered as the first one in the field of organocatalysis.

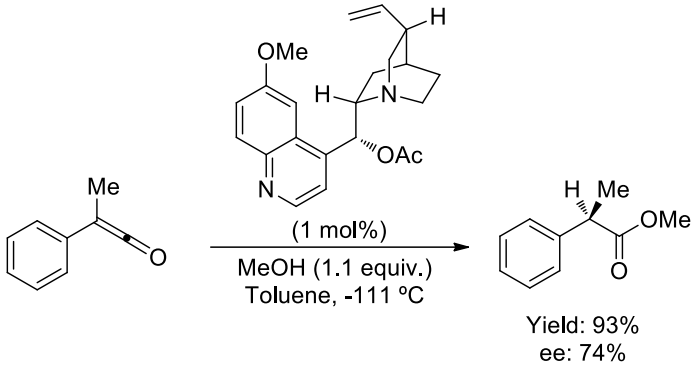
Pracejus and co-workers, in 1960, published probably the first organocatalytic reaction with a significant level of enantioselectivity, consisting on the addition of methanol to methylphenylketene, and employing *O*-

[7] Bredig, G.; Fiske, P. S. *Biochem. Z.* **1913**, *46*, 7.

[8] a) Langebeck, W. *Angew. Chem.* **1928**, *41*, 740; b) Langebeck, W. *Angew. Chem.* **1932**, *45*, 97.

[9] Langebeck, W. *Die Organiche Katalysatoren und ihre Beziehungen zu den Fermenten*, Springer-Verlag, Berlin, **1949**.

acetylquinine as catalyst. They obtained 74% ee in the final product, which was determined through polarimetry (Scheme 1.2).[10]



Scheme 1.2

An important progress regarding the enantioselectivity of these reactions took place in 1971, independently by two industry research groups at Hoffmann-La Roche[11] and Schering-Plough.[12] The reaction, currently known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction, consisted on the use of the natural amino acid L-proline as catalyst in an intramolecular aldol reaction, providing enantioenriched synthetic useful intermediates for the preparation of several bioactive products, such as steroids and terpenes (Scheme 1.3).

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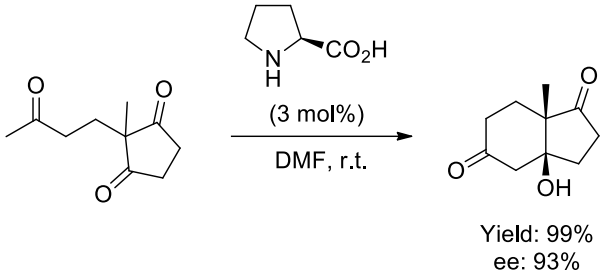
10 Pracejus, H. *Justus Liebig Ann. Chem.* **1960**, *634*, 9.

11 a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615; b) Hajos, Z. G.; Parrish, D. R. *Asymmetric Synthesis of Optically Active Polycyclic Organic Compounds*. German Patent DE 2102623, **1971**.

12 a) Eder, U.; Sauer, G.; Wiechert, R. *Optically Active 1,5-Indanone and 1,6-Naphthalenedione*. German Patent DE 2014757, **1971**; b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496.



Scheme 1.3

Other significant landmarks in the development of asymmetric organocatalysis appeared from 1980 to the late 90's such as, for example, the enantioselective alkylation of enolates employing quaternary ammonium salts derivated from cinchona alkaloids as catalysts, based on the concept of phase-transfer catalysis.[13] Another relevant milestone is the use of chiral Brønsted acids (cyclic dipeptides or thioureas) by Inoue[14] or Jacobsen[15] for the asymmetric hydrocyanation of aldehydes and imines respectively.

Surprisingly, in spite of the synthetic interest of this methodology, the field of organocatalysis as we know it nowadays was not well recognized by scientists until the 21st century, when two papers about the potential activity of aminocatalysis were reported in 2000. On the one hand, Barbas III and List published their well-known enantioselective intermolecular aldol reaction

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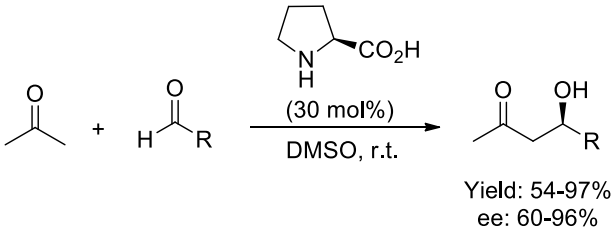
[13] a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414; b) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353; c) Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710; d) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.

[14] Oku, J.; Inoue, S. *J. Chem. Soc. Chem. Commun.* **1981**, 229.

[15] a) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012; b) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

catalized by L-proline (Scheme 1.4),[16] as the culmination of an intensive research that started with the use of aldolase antibodies as catalysts for the aldol reaction.[17] With the evidence of enamine intermediate formation in the enzymatic reaction of class I aldolases, they tried to explain the mechanism, developing the intermolecular aldol reaction, using the simple aminoacid L-proline in order to mimic the behaviour of the active site of the enzyme. They demonstrated that this aminoacid was able to catalyze the synthesis of aldols, in high yields and enantioselectivities, through the reaction between acetone and different aldehydes *via* enamine intermediates formed by condensation of the secondary amine with the ketone, this species acting as a nucleophile.



Scheme 1.4

The results obtained by Barbas III and List opened the opportunity to apply this mechanistic manifold to the synthesis of α-functionalized ketones and aldehydes, where the enamine intermediate reacts as a potential nucleophile with a variety of electrophiles.[18]

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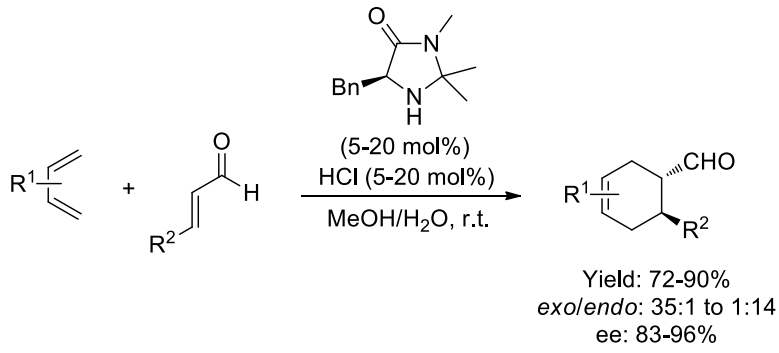
[16] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

[17] For a full account, see: Barbas III, C. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 42.

[18] For some general reviews on enamine catalysis, see: a) Desmarchelier, A.; Coeffard, V.; Moreau, X.; Greck, C. *Tetrahedron* **2014**, *70*, 2491; b) Kano, T.; Maruoka, K. *Chem. Sci.* **2013**, *4*, 907; c) Rios, R.; Moyano, A. *Catalytic Asymmetric Conjugate Reactions* (Ed.: Córdova, A.), Wiley-VCH, Weinheim, **2010**, d) Kano, T.; Maruoka, K. *Chem. Commun.* **2008**, 5465; e) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123; f) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

On the other hand, in the same year, MacMillan developed the first highly enantioselective organocatalytic Diels-Alder reaction catalyzed by a chiral imidazolidinone-based salt, introducing iminium activation as a new concept (Scheme 1.5).[19] After the formation of the iminium salt intermediate through condensation between the secondary amine and the α,β-unsaturated carbonyl compound, the LUMO energy of the dienophile decreases, favouring the orbital overlap in the Diels-Alder reaction. After this work, this type of catalysts and other secondary amines have demonstrated to be a powerful tool in asymmetric synthesis under this activation manifold.[20]



Scheme 1.5

After these initial steps, the field has experienced an impressive development with the appearance of new organocatalytic activation mechanisms and their application in multiple organic reactions of special relevance in synthesis. In this sense, a positive aspect that is very often highlighted with respect to the usefulness of organocatalytic methodologies is associated to the metal-free

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[19] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

[20] For some general reviews on iminium activation, see: a) Bartoli, G.; Melchiorre, P. *Synlett* **2008**, 1759; b) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416; c) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79.

approach that these procedures imply. Moreover, several experimental protocols have been implemented in the last years in order to make organocatalysis a more sustainable alternative[21] like, for example, through the use of friendlier reaction conditions, such as water[22] or ionic liquids[23] as solvents. Other alternatives rely on the design of more selective and recoverable catalysts, like supported catalysts in continuous-flow processes,[24] the reduction of catalyst loadings (up to less than 5-10 mol%),[25] the development of cascade and/or multicomponent reactions[26] or by means of the application of more energy-efficient activation techniques like microwave, ultrasound and ball milling, thus reducing the reaction time by increasing reactivity.[27] For all of these reasons, organocatalysis is nowadays a field of recognized interest, being still necessary to continue with the search of new and more efficient catalysts and their application in methodologies directed towards the preparation of enantioenriched compounds.

Without doubt, the most important point for the success of this methodology was the identification of the different generic activation modes, asymmetric induction and reactivity behind the participation of each organocatalysts across the

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21 For general review, see: Hernández, J. G.; Juaristi, E. *Chem. Commun.* **2012**, *48*, 5396.

22 a) Giacalone, F.; Gruttadauria, M. *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications* (Ed.: Dalko, P. I.), Wiley-VCH, Weinheim, **2013**; b) Mase, N.; Barbas III, C. F. *Org. Biomol. Chem.* **2010**, *8*, 4043; c) Raj, M.; Singh, V. K. *Chem. Commun.* **2009**, 6687; d) Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33.

23 a) Luo, S.; Zhang, L.; Cheng, J.-P. *Chem. Asian J.* **2009**, *4*, 1184; b) Domínguez de María, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 6960.

24 a) Atodiresei, I.; Vila, C.; Rueping, M. *ACS Catal.* **2015**, *5*, 1972; b) Rodríguez-Escrich, C.; Pericàs, M. A. *Eur. J. Org. Chem.* **2015**, 1173; c) Finelli, F. G.; Miranda, L. S. M.; de Souza, R. O. M. A. *Chem. Commun.* **2015**, *51*, 3708.

25 For a selected review, see: Giacalone, F.; Gruttadauria, M.; Agrigento, P; Noto, R. *Chem. Soc. Rev.* **2012**, *41*, 2406.

26 a) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969; b) Guillena, G.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693.

27 a) Kranjc, K.; Kočevar, M. *Curr. Org. Chem.* **2013**, *17*, 457; b) Bruckmann, A.; Krebs, A.; Bolm, C. *Green Chem.* **2008**, *10*, 1131.

corresponding catalytic cycle. The main utility of these models relies on the fact that they are easy to apply as a template in new transformations. A general way to classify organocatalytic activation manifolds is related to the type of interaction between the catalyst and the substrate during the reaction. In this sense, there are two possibilities: a) processes including the formation of covalent adducts (covalent catalysis), and b) those based on non-covalent interactions, such as ion pairs or hydrogen bonds (non-covalent catalysis). Figure 1.1 shows the different activation modes and some representative examples of organic catalysts employed in each one.

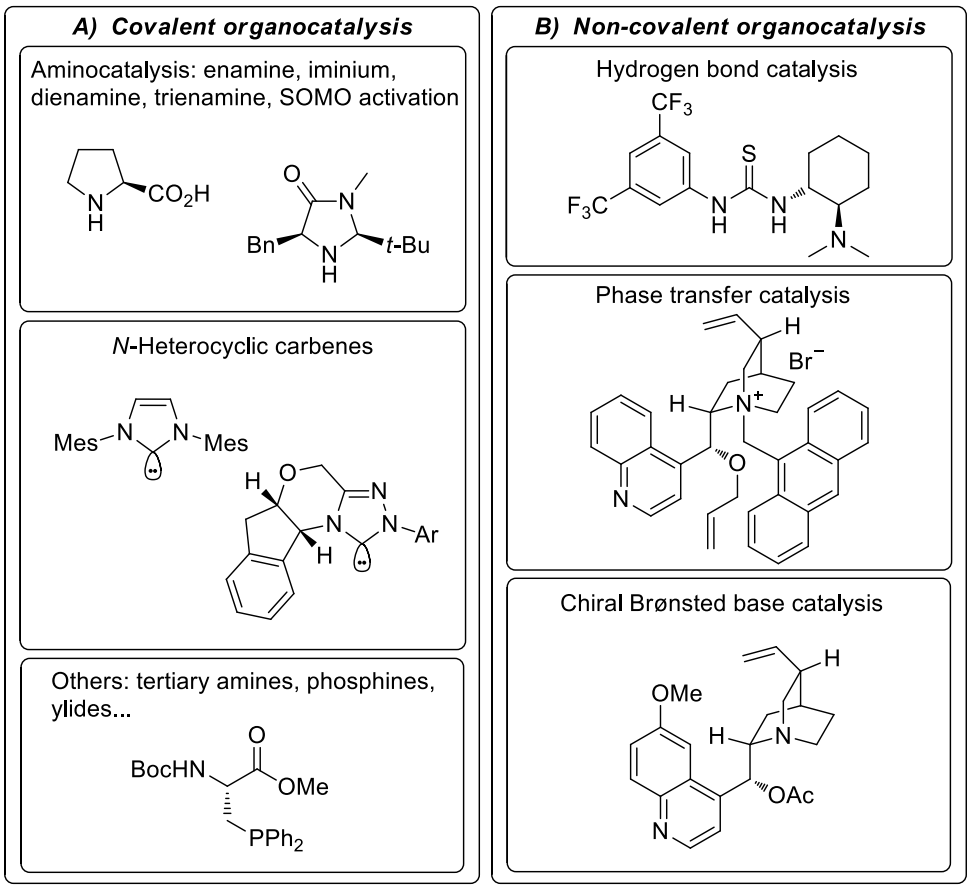

Figure 1.1

Covalent organocatalysis consists on the formation of a covalently bonded intermediate between the catalyst and the substrate through a reversible reaction, followed by the desired formation of new bond(s), to finish with the cleavage of the covalently bonded catalyst-product intermediate, in order to obtain the product and recover the catalyst ready to participate in another catalytic cycle. This activation is among the most widely used and thoroughly studied type of organocatalysis to date. As an advantage, the chiral inductor provides, in general,

a good stereocontrol, due to the strong nature of the catalyst-substrate interaction. On the other hand, for the same reason the turnover number might be negatively affect, being necessary higher catalyst loadings and also longer reaction times to achieve good conversion. In covalent catalysis, the most studied activation is aminocatalysis, which consists on the use of primary or secondary amines as catalysts that are able to activate carbonyl compounds through the formation of reactive azomethine species by condensation. In this context, the most commonly used are enamine[18] and iminium ion[20] methodologies, although there are other variants, such as dienamine,[28] trienamine,[29] tetraenamine[30] and vinilogous iminium,[31] and the radical iminium ion, known as SOMO catalysis.[32] *N*-heterocyclic carbenes are other important class of covalent catalysis, which activate the carbonyl substrate by the formation of a nucleophilic intermediate, known as Breslow intermediate, which is able to react with an electrophilic species. The most interesting and important property of these last catalysts is their

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[28] For a review in dienamine catalysis, see: a) Fraile, A.; Alemán, J. *Synlett* **2015**, *26*, 1940; b) Christmann, M. *Asymmetric Synthesis II: More Methods and Applications* (Eds.: Christmann, M.; Bräse, S.), Wiley-VCH, Weinheim, **2012**; c) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865; for pioneering work, see d) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973.

[29] For a review in trienamine catalysis, see: a) Reboredo, S.; Parra, A.; Alemán, J. *Asym. Catal.* **2013**, *1*, 24; b) Kumar, I.; Ramaraju, P.; Mir, N. A. *Org. Biomol. Chem.* **2013**, *11*, 709; c) Arceo, E.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 5290; for pioneering work, see: d) Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053.

[30] For examples on tetraenamine catalysis, see: a) Zhou, Q.-Q.; Xiao, Y.-C.; Yuan, X.; Chen, Y.-C. *Asian J. Org. Chem.* **2014**, *3*, 545; b) Stiller, J.; Poulsen, P. H.; Cruz, D. C.; Dourado, J.; Davis, R. L.; Jørgensen, K. A. *Chem. Sci*. **2014**, *5*, 2052.

[31] For a selected review, see: Lear, M. J.; Hayashi, Y. *ChemCatChem* **2013**, *5*, 3499.

[32] For selected examples on SOMO catalysis, see: a) Jui, N. T.; Garber, J. A. O.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 11400; b) Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027; c) Graham, T. H.; Jones, C. M.; Jui, N. T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 16494; d) Jang, H.-Y.; Hong, J.-B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004; e) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582; f) Bertelsen. S.; Nielsen, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 7356.

capacity to invert the reactivity of aldehydes, from being typically electrophilic to act as nucleophiles, through an umpolung process.[33]

On the other hand, the non-covalent organocatalysis is based on weaker interactions between the catalyst and the substrate, being this property an advantage, comparing to covalent catalysis, due to the lower requirement of catalyst loading and reaction times. However, this can lead to a poorer control of the stereoselectivity of the reaction, owing to the higher degree of conformational freedom. In this category, the most studied approach is the one in which the catalyst activates the substrate by the formation of multiple hydrogen bonds.[34] This kind of catalysts presents different functional groups in their structure that contain acidic protons that are able to activate the substrate by coordination with heteroatoms present in the molecule, decreasing the electron density at that point and, as a consequence, improving the reactivity. Moreover, the spatial arrangement around the reaction site can be tuned, in order to control the stereochemical outcome. Within this group, chiral phosphoric or sulfonic acids,[35]

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[33] For selected reviews about the *N*-heterocyclic carbenes, see: a) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307; b) Dwivedi, S.; Gupta, S.; Das, S. *Curr. Organocatal.* **2014**, *1*, 13; c) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511; d) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606; d) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988; e) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534.

[34] For some general reviews on catalysis by hydrogen bonds formation, see: a) *Hydrogen Bonding in Organic Synthesis* (Ed.: Pihko, P. M.), Wiley-VCH, Weinheim, **2009**; b) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516; c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713; d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; e) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289.

[35] For recent reviews on phosphoric or sulfonic acids as donors, see: a) Akiyama, T.; Mori, K. *Chem. Rev.* **2015**, *115*, 9277; b) Mori, K.; Takahiko, A. *Comprehensive Enantioselective Organocatalysis* (Ed.: Dalko, P. I.), Wiley-VCH, Weinheim, **2013**; c) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539; d) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156; e) Terada, M. *Synthesis* **2010**, *12*, 1929.

(thio)ureas,[36] guanidines,[37] squaramides,[38] etc. can be found. Another type of non-covalent catalysis is the ion-pairing catalysis[39] that consists on the interation between the substrate and the catalyst by the formation of chiral ion pairs. Phase-transfer catalysis (PTC)[40] is one of the most studied cases, in which typically chiral cation-directed catalysts, such as quaternary ammonium or phosphonium salts, have been used in reactions between two substances located in different immiscible phases. The general advantages of this method are its simple experimental procedure, mild reaction conditions and the non-toxicity of reagents. Finally, chiral Brønsted base catalysis[41] is also based on electrostatic interactions, activating pro-nucleophiles by deprotonation.

Finally, it is also important to mention that, within these different activation methodologies, the mechanism of the reaction and the subsequent catalytic intermediates have to be clearly identified in order to gain further insights that can assist the development process of a given organocatalytic reaction, with the purpose of clarifying anomalous outcomes and/or identifying novel reactivity patterns.[42]

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[36] For a selected reviews on (thio)ureas as catalysts, see: a) Held, F. E.; Tsogoeva, S. B. *Catal. Sci. Technol.* **2016**, *6*, 645; b) Fang, X.; Wang, C.-J. *Chem. Commun.* **2015**, *51*, 1185; c) Takemoto, Y. *Chem. Pharm. Bull.* **2010**, *58*, 593; d) Connon, S. *Synlett* **2009**, 354; e) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187.

[37] For a recent review on guanidines as catalysts, see: Selig, P. *Synthesis* **2013**, *45*, 703.

[38] For specific reviews on squaramides as catalysts, see: a) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253; b) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 6890.

[39] For a general review, see: Brak, K.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2013**, *52*, 534.

[40] For recent reviews on chiral phase-transfer catalysis, see: a) Kaneko, S.; Kumatabara, Y.; Shirakawa, S. *Org. Biomol. Chem.* **2016**, accepted; b) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312; c) Jew, S.; Park, H. *Chem. Commun.* **2009**, 7090; d) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222.

[41] For a selected review on chiral Brønsted base catalysis, see: Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632

[42] For a selected review, see: Holland, M. C.; Gilmour, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 3862.

2. PRECEDENTS OF THE GROUP

Historically, our research group has been very active in the development of new methodologies in the field of asymmetric synthesis and their application to the synthesis of target molecules, such as chiral building blocks, drugs and natural products. Initially, the methodological tool to achieve the required stereocontrol was the chiral auxiliary strategy, using satisfactorily the β-aminoalcohol (*S*,*S*)-(+)-pseudoephedrine in conventional enolate chemistry[43] and diverse conjugate addition reactions.[44]

In the last years, the group moved its interest to organocatalysis, being especially active in using aminocatalysis. The first work reported by the group was based on the enamine activation, and consisted in a Michael reaction between aldehydes and β-nitroacrolein dimethyl acetal,[45] using prolinol derivatives as catalysts and obtaining very promising results. This investigation was completed with the transformation of obtained Michael adducts through a simple and effective protocol for the synthesis of highly functionalized enantioenriched pyrrolidines (Scheme 1.6).[46]

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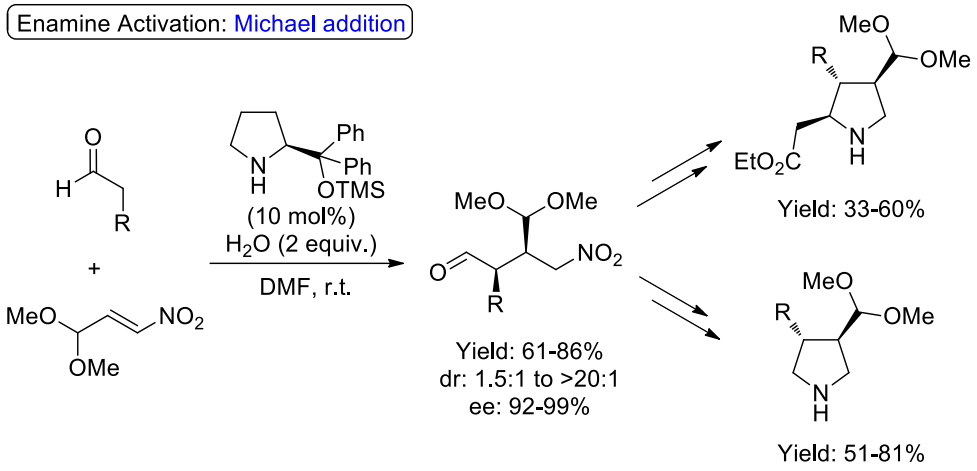
[43] Latest aldol reaction: a) Ocejo, M.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *J. Org. Chem.* **2011**, *76*, 460; latest Mannich reaction: b) Iza, A.; Vicario, J. L.; Carrillo, L.; Badía, D. *Synthesis* **2006**, 4065; latest electrophilic amination reaction: c) Vicario, J. L.; Badía, D.; Carrillo, L.; Anakabe, E. *Tetrahedron: Asymmetry* **2002**, *13*, 745; azidirine ring opening reaction: d) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 5801.

[44] Conjugated additions: a) Ocejo, M.; Carrillo, L.; Badía, D.; Vicario, J. L.; Fernández, N.; Reyes, E. *J. Org. Chem.* **2009**, *74*, 4404; b) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Uria, U.; Iza, A. *J. Org. Chem.* **2006**, *71*, 7763; aza-Michael reactions: c) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L.; Ruiz, N. *J. Org. Chem.* **2005**, *70*, 8790; d) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2004**, *69*, 2588; 1,4-addition/α-alkylation tandem reaction: e) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Iza, A.; Uria, U. *Org. Lett.* **2006**, *8*, 2535.

[45] Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2006**, *8*, 6135.

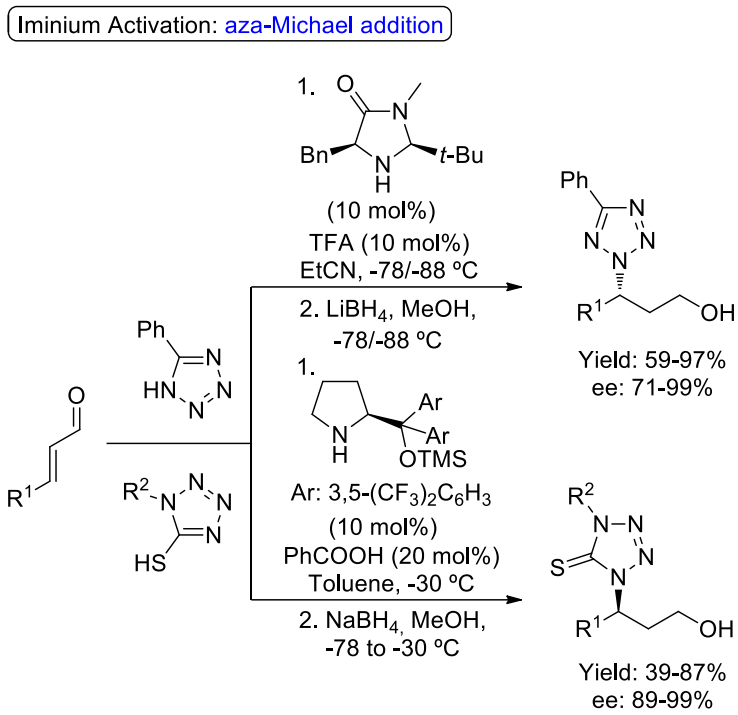
[46] Ruiz, N.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Uria, U. *Chem. Eur. J.* **2008**, *14*, 9357.



Scheme 1.6

Simultaneously, the iminium ion catalysis has also been widely studied and successfully employed in the group. Initially, the aza-Michael reaction was performed using α,β-unsaturated aldehydes as Michael acceptors and several nitrogen heterocycles as pro-nucleophiles, obtaining the best results employing the MacMillan's catalyst[47] or *O*-trimethylsilyl diarylprolinol[48] according to the different substitution patterns of heterocycle (Scheme 1.7). Due to the ability of tetrazol moiety to undergo chemical transformations, several high interest compounds were prepared, like chiral ureas and formamidines.

[47] Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L. *Chem. Commun.* **2007**, 2509.
[48] Uria, U.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2011**, *13*, 336.

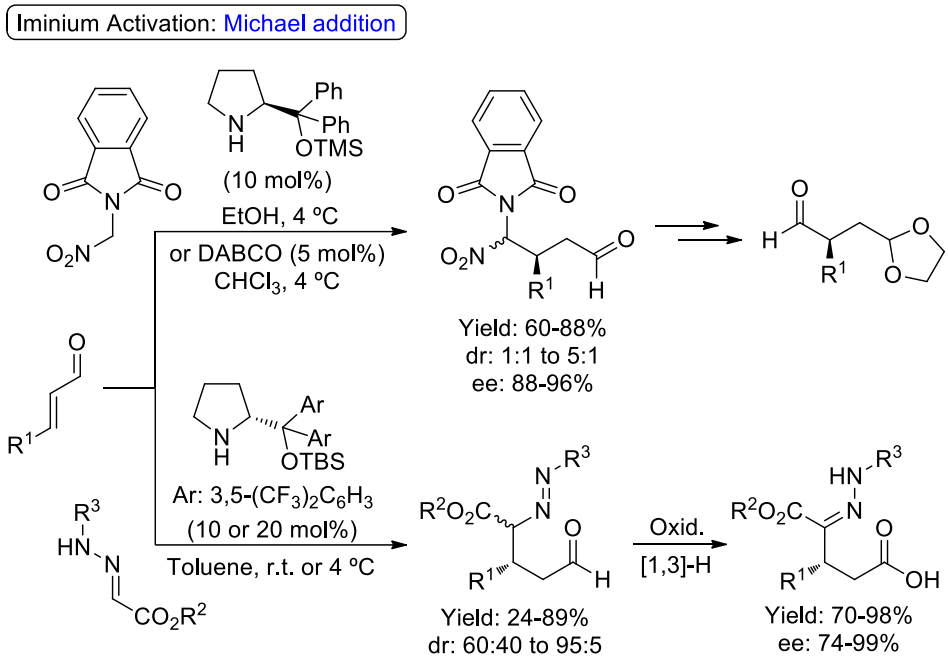


Scheme 1.7

Continuing with Michael-type reactions with α,β-unsaturated aldehydes under iminium activation, the group has developed two different protocols employing acyl anion equivalents in umpolung transformations. In the first example *N*-nitromethylphthalimide was used as hydroxymoyl anion equivalent obtaining very good results. The obtained products can be easily transformed to the corresponding chiral oximes that could be subsequently derived to aldehydes through a simple process, without racemization.[49] Additionally, in another example, hydrazones have been employed as masked glyoxyl anion equivalents in the enantioselective conjugate addition to α,β-unsaturated aldehydes. After

[49] Alonso, B.; Reyes, E.; Carrillo, L.; Vicario, J. L.; Badía, D. *Chem. Eur. J.* **2011**, *17*, 6048.

oxidation/[1,3]-H shift procedure the subsequent γ-hydrazono carboxylic acids could be obtained (Scheme 1.8).[50]



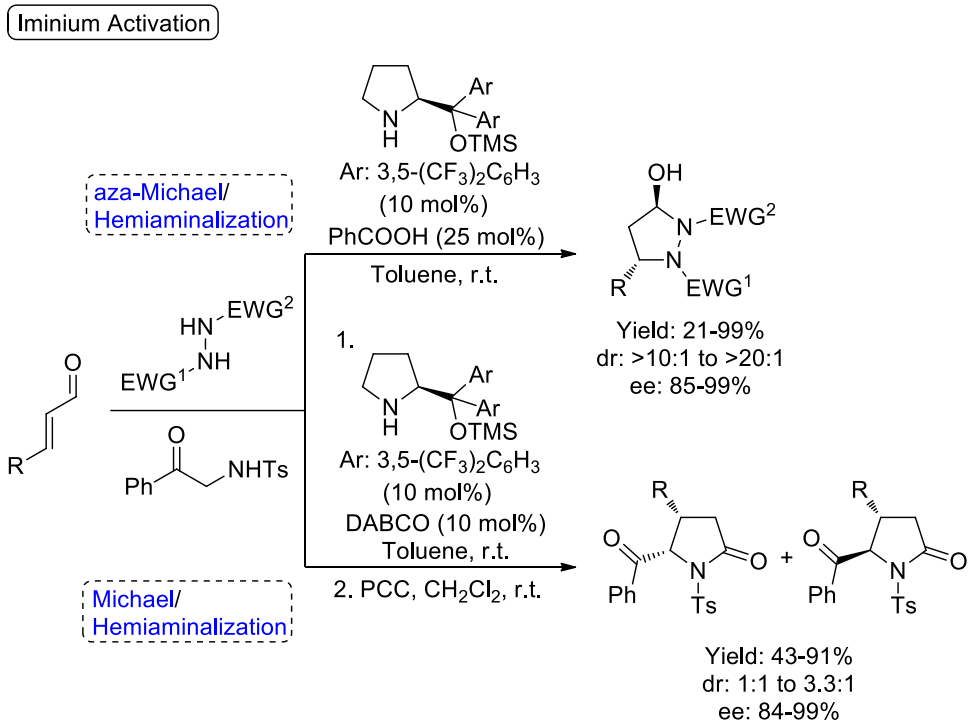
Scheme 1.8

The iminium activation concept has also been efficiently used in cascade reactions initiated by conjugated addition that are subsequently followed by hemiaminalization (shown on Scheme 1.9). On the one hand, aza-Michael/hemiaminal formation process between enals and *N*,*N'*-disubstituted hydrazides was developed to achieve polysubstituted enantioenriched pirazolidine type heterocycles.[51] On the other hand, Michael/hemiaminal formation cascade

[50] Fernández, M.; Uria, U.; Vicario, J. L.; Reyes, E.; Carrillo, L. *J. Am. Chem. Soc.* **2012**, *134*, 11872.

[51] Fernández, M.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Adv. Synth. Catal.* **2012**, *354*, 371.

reaction between α,β-unsaturated aldehydes and aminoacetophenone was developed, in which the obtained adducts were converted into γ-lactams in good yields after oxidation.[52]



Scheme 1.9

This type of activation was also used in the development of the first example of a formal (3+2) cycloaddition reaction between α,β-unsaturated aldehydes and azomethine ylides, the latest being generated *in situ* from aminomalonate imines. This reaction provided access to densely functionalized

[52] Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Adv. Synth. Catal.* **2013**, *355*, 653.

pyrrolidines in good yields and excellent stereocontrol (see Scheme 1.10).[53] It should be pointed out that computational calculations were also performed in order to get some insight on the mechanism of the reaction. DFT calculations revealed that the reaction consisted on a Michael/Mannich cascade reaction and not on a concerted [3+2] cycloaddition, therefore combining iminium and enamine activation in a typical Michael initiated cascade reaction.[54] This revealed us the ability of cascade reactions to the preparation of complex molecules, by combination of different activation modes of the aminocatalysis. Moreover, a multicomponent procedure was developed for this reaction, starting directly from diethyl aminomalonate and aromatic aldehydes, instead of preformed imine, and using also α,β-unsaturated aldehydes as Michael acceptors.[55] Alternatively, isoquinolinium and phthalizinium methylides have also been employed, as stable azomethine ylides, in the same type of reaction, using MacMillan-type catalyst (Scheme 1.10).[56]

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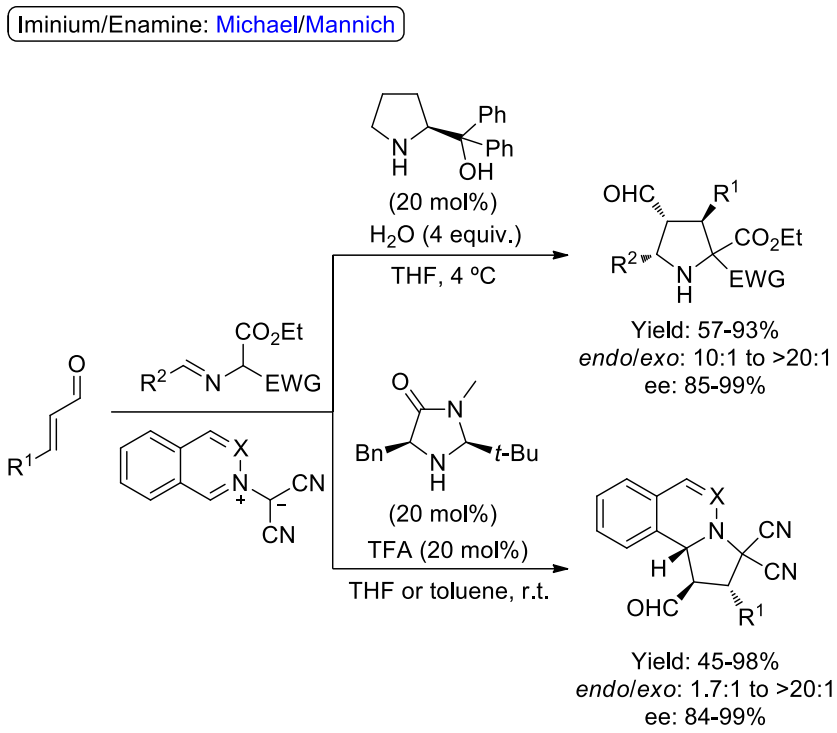
53 a) Ugarriza, I.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Asymmetric Catal.* **2015**, *2*, 26; b) Reboredo, S.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Adv. Synth. Catal.* **2011**, *353*, 3307; c) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5168.

54 Reboredo, S.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; de Cózar, A.; Cossío, F. P. *Chem. Eur. J.* **2012**, *18*, 7179.

55 Reboredo, S.; Vicario, J. L.; Carrillo, L.; Reyes, E.; Uria, U. *Synthesis* **2013**, *45*, 2669.

56 Fernández, N.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *Chem. Commun.* **2011**, *47*, 12313.



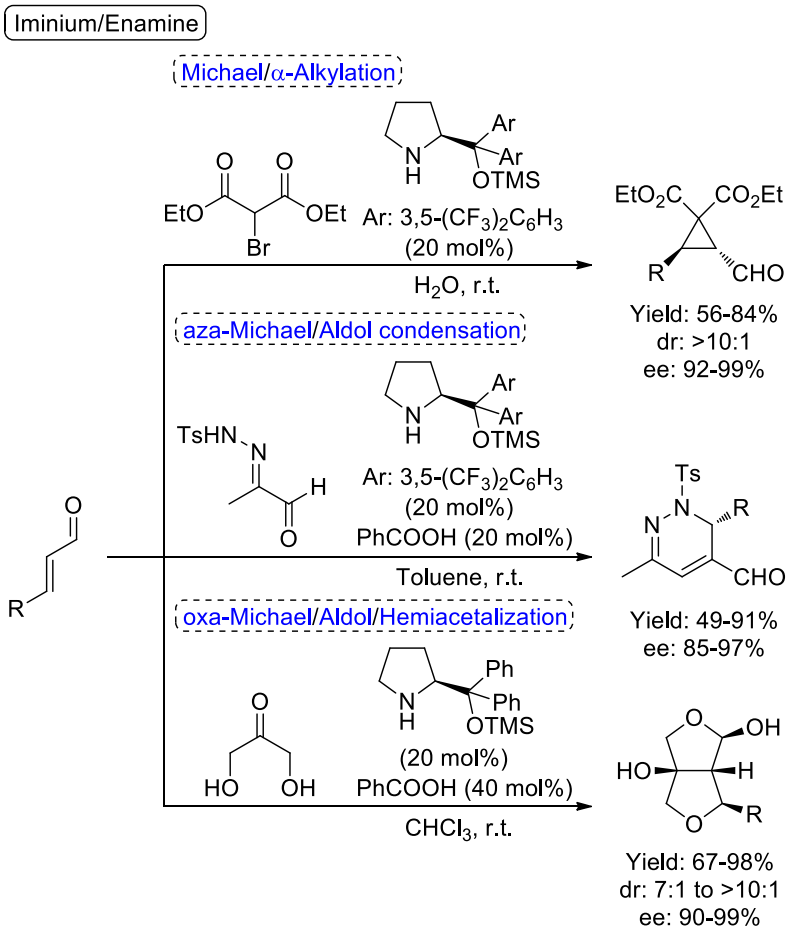
Scheme 1.10

In connection with this topic, our group has developed several cascade processes applying the iminium/enamine manifold, in a satisfactory way (see Scheme 1.11). One example is the ciclopropanation of enals through iminium ion-assisted Michael addition of bromomalonates to enals, followed by intramolecular α-alkylation of the resulting enamine intermediate, using water as solvent.[57] The same activation strategy was applied in the synthesis of dihydropyridazines through an aza-Michael/aldol condensation domino reaction.[58] Finally, the

[57] a) Martínez, J. I.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *ChemCatChem* **2013**, *5*, 2240; b) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; Pesquera, A. *Synthesis* **2010**, 701.

[58] Fernández, M.; Vicario, J. L.; Reyes, E.; Carrillo, L.; Badía, D. *Chem. Commun.* **2012**, *48*, 2092.

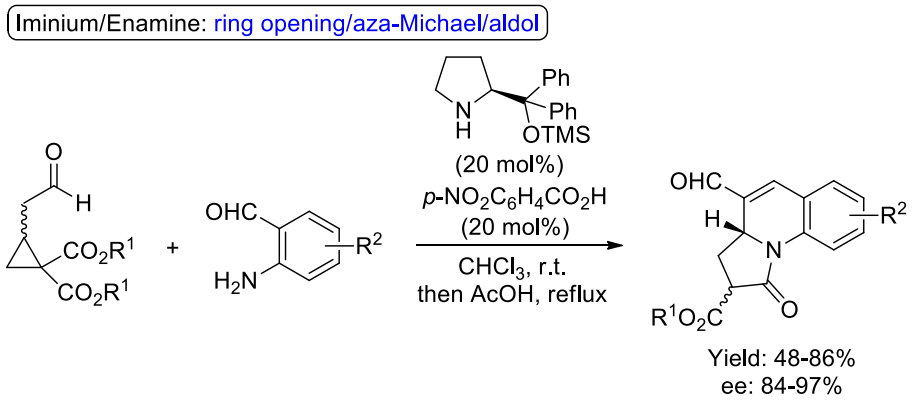
enantioselective synthesis of polysubstituted furofuranes was described as a result of a complex oxa-Michael/aldol/hemiacetalization cascade process by reaction of dihydroxyacetone with different enals. In this reaction two new C-O bonds and a C-C bond were formed, with the generation of four stereogenic centers.[59]



Scheme 1.11

[59] Reyes, E.; Talavera, G.; Vicario, J. L.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 5701.

Recently, our group has developed a straightforward access to enantioenriched pyrroloquinoline derivatives through a one-pot process consisting of cyclopropane ring opening/aza-Michael/aldol condensation cascade reaction followed by a one-pot acid-promoted lactamization. In this reaction, different aminobenzaldehydes reacted with conveniently functionalized cyclopropaneacetaldehydes (Scheme 1.12),[60] being the latter activated by a chiral secondary amine that generates a donor-acceptor cyclopropane, which has the potential to undergo a ring opening process, leading to the formation of an electrophilic α,β-unsaturated iminium ion that is able to participate in the iminium/enamine cascade sequence.



Scheme 1.12

On the other hand, the group has also satisfactorily surveyed the possibility of combining enamine catalysis with the principle of vinylogy, making use of the formation of intermediates like dienamines and trienamines in cycloaddition chemistry. In this sense, dienamine catalysis has been used in a formal [2+2] cycloaddition between α-hydroxymethylnitrostyrene and enolizable α,β-

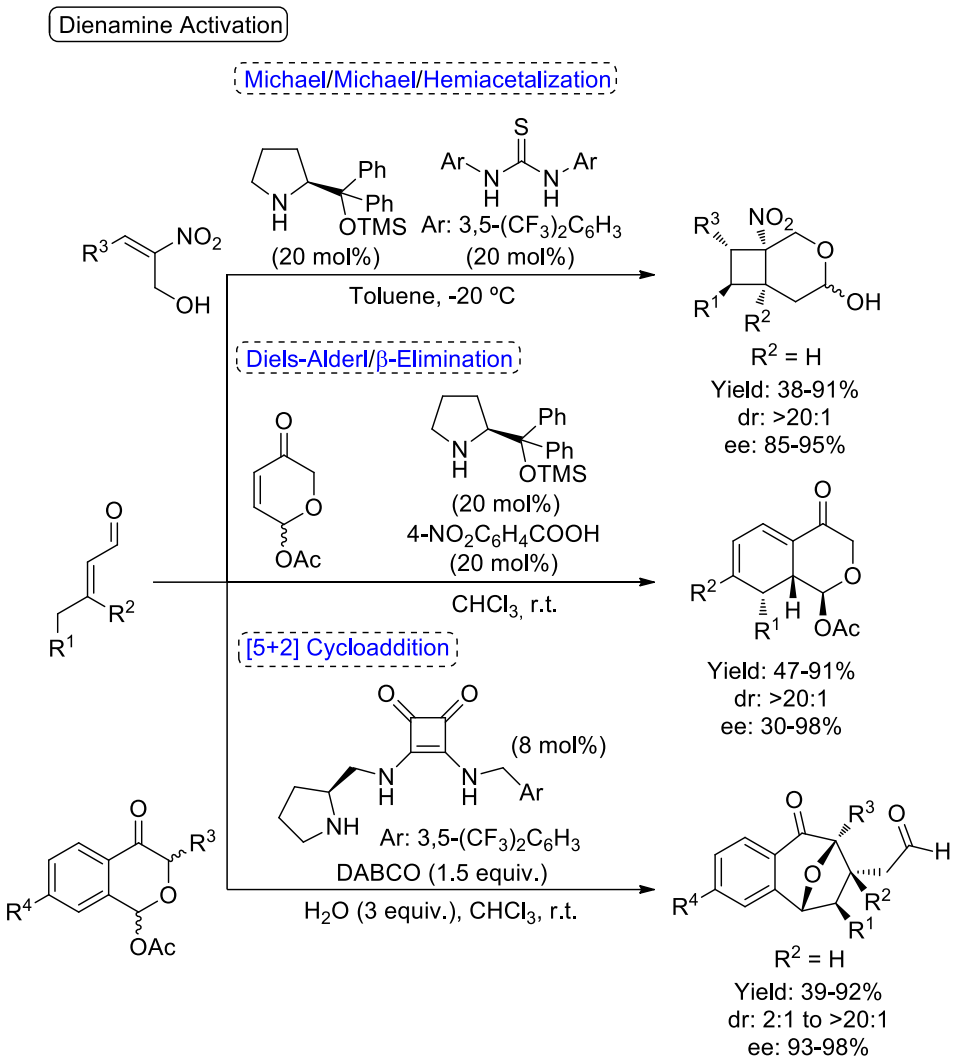
[60] Sánchez-Díez, E.; Vesga, D. L.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Org. Lett.* **2016**, *18*, 1270.

unsaturated aldehydes, followed by an intramolecular hemiacetalization process to afford polysubstituted cyclobutanes in good yields and excellent stereocontrol (shown on Scheme 1.13).[61] In a different approach dienamine catalysis has been used in the formation of enantioenriched tetrahydro-1*H*-isochromanes through a Diels-Alder/β-elimination process, starting from the same type of aldehydes and using racemic 5-acyloxydihydropyranones as dienophiles.[62] To finish with this type of catalysis, recently the group has developed an enantioselective [5+2] cycloaddition reaction with oxidopyrylium ylides generated *in situ* from substituted acetoxypyranones in the presence of a Brønsted base, to obtain 8-oxabicyclo[3.2.1]octane derivatives in very good yields and excellent enantioselectivities (Scheme 1.13).[63]

[61] Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 4104.

[62] Orue, A.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Org. Lett.* **2012**, *14*, 3740.

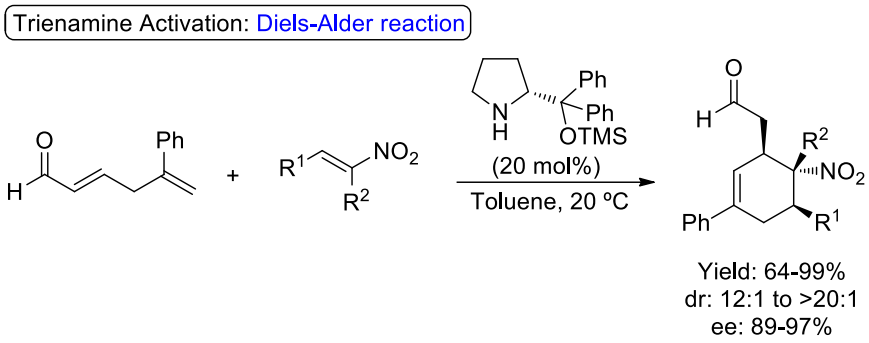
[63] a) Roca-López, D.; Uria, U.; Reyes, E.; Carrillo, L.; Jørgensen, K. A.; Vicario, J. L.; Merino, P. *Chem. Eur. J.* **2016**, *22*, 884; b) Orue, A.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 1.



Scheme 1.13

The trienamine activation manifold has been successfully applied in the Diels-Alder reaction between unconjugated 2,5-dienals and nitrostyrenes to obtain densely functionalized cyclohexenes in excellent yields and stereoselectivities.

The related fully conjugated α,β,γ,δ-unsaturated aldehydes failed as diene precursors in the same reaction, translating into a better ability of the unconjugated enals to condense with the amine catalyst, leading to the same vinylogous trienamine intermediate (Scheme 1.14).[64]



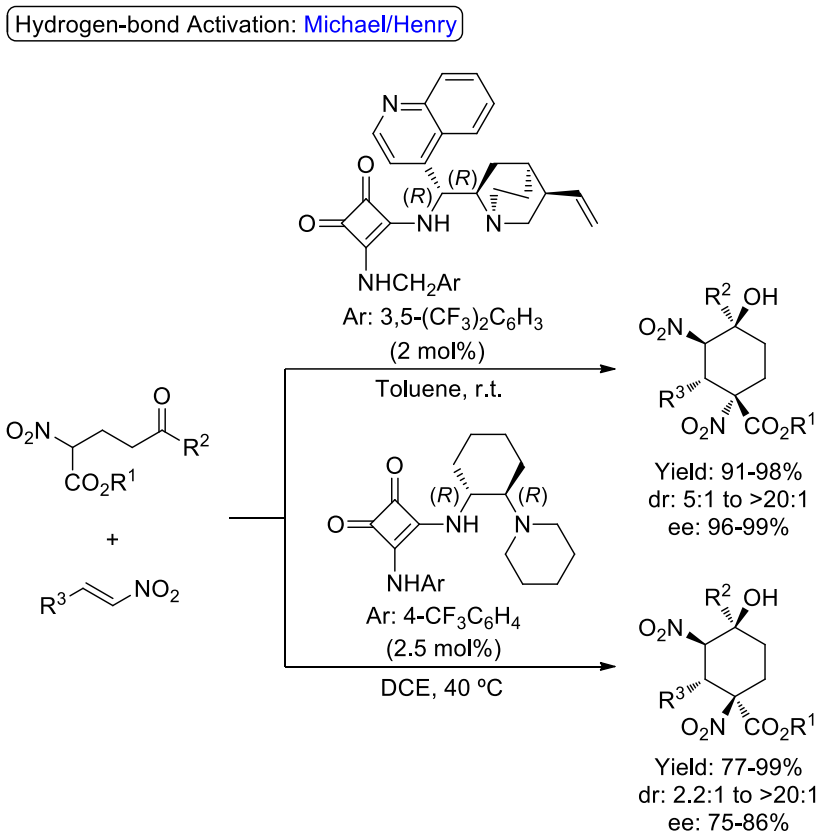
Scheme 1.14

Apart from aminocatalysis, the group has explored other organocatalytic activation methodologies, such as hydrogen-bonding catalysis and more recently *N*-heterocyclic carbene catalysis. Thus, the group has developed an enantioselective and diastereodivergent procedure to the synthesis of polysubstituted cyclohexanes through Michael/Henry cascade reaction employing hydrogen-bond activation, by reaction between nitroalkenes and α-nitro-δ-oxo esters. It has been demonstrated that two similar bifunctional squaramides containing a chiral 1,2-diamine backbone with the same absolute configuration lead to the diastereodivergent formation of the corresponding products (see Scheme 1.15).[65] Moreover, this procedure has been satisfactorily extended to a diastereodivergent intermolecular Michael reaction of nitroalkenes as Michael

[64] Prieto, L.; Talavera, G.; Uria, U.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Chem. Eur. J.* **2014**, *20*, 2145.

[65] Martínez, J. I.; Villar, L.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Adv. Synth. Catal.* **2014**, *356*, 3627.

acceptors and nitroacetates as donors towards the obtention of enantioenriched 2,4-dinitro esters.[66]

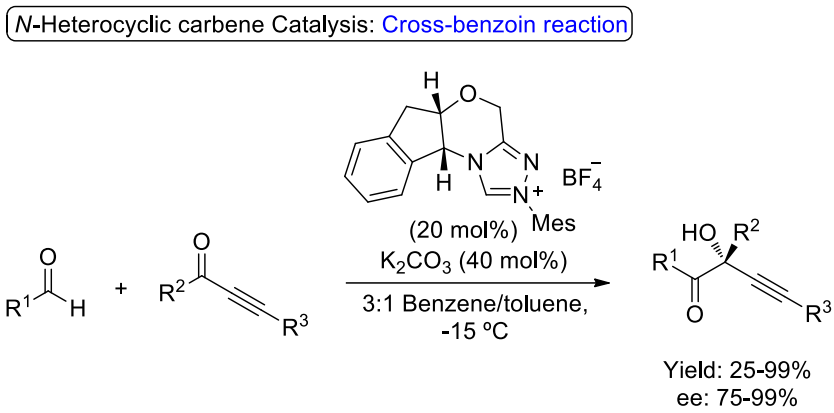


Scheme 1.15

Finally, the group has applied the *N*-heterocyclic carbene catalysis to the enantioselective synthesis of tertiary propargylic alcohols through cross-benzoin

[66] Martínez, J. I.; Uria, U.; Muñiz, M.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Beilstein J. Org. Chem.* **2015**, *11*, 2577.

reaction between aldehydes and ynones, obtaining good yields and enantioselectivities (Scheme 1.16).[67]



Scheme 1.16

[67] Sánchez-Díez, E.; Fernández, M.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Chem. Eur. J.* **2015**, *21*, 8384.

3. GENERAL OBJETIVES

The present work has been carried out in line with the research field of the group. Accordingly, it is focused on the development of new asymmetric methodologies, employing the organocatalysis as a main tool, specifically, the aminocatalysis applied to the search of new cascade reactions to the obtention of high functionalized carbo- and heterocycles, initiated by conjugated addition. In this sense, this research work will be divided into two different parts, including a chapter detailing the work performed in the context of a short stay in Free University of Berlin under the supervision of Prof. M. Christmann.

The first general objective will be developed the potential activity of 4-alkenyl-5*H*-1,2,3-oxathiazole 2,2-dioxides as a Michael donor/acceptors in aminocatalytic cascade reactions with enals, using the iminium/enamine manifold. As it is shown in Figure 1.2, this type of substrates presents a pronucleophilic carbon at the 5-position that can participate as Michael donor in conjugate additions, moreover, it can act as electrophile due to the high ability of sulfonate as leaving group. Additionally, this class of α,β-unsaturated cyclic sulfamidate imines have the potential to participate as Michael acceptor, being this class of substrate excellent precursors for cascade reactions.

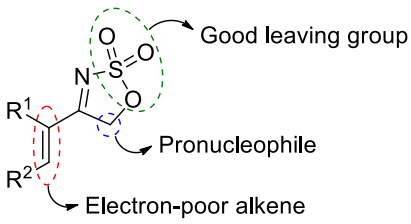
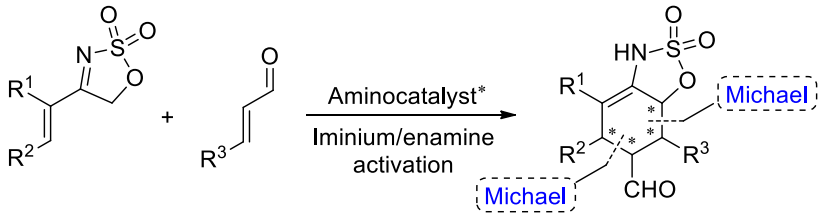


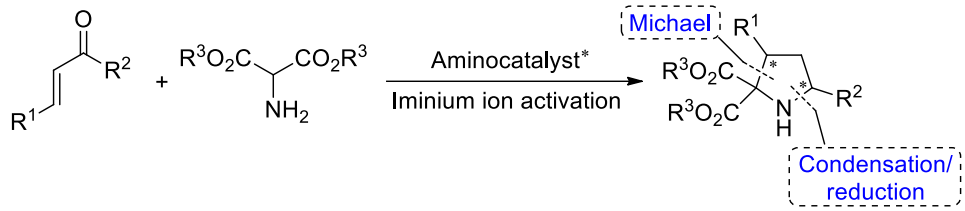
Figure 1.2

With this in mind, we will first develop the aminocatalyzed Michael/Michael cascade reaction employing α,β-unsaturated aldehydes as the initial Michael acceptors, *via* iminium activation, using as nucleophile this type of cyclic sulfamidate imines, followed by a second Michael addition of the subsequent enamine to the α,β-unsaturated sulfamidate imine, to the obtention of chiral polycyclic structures (Scheme 1.17). Moreover, due to the presence of several functionalities, such as the sulfonate group, we envisioned many possibilities for performing different chemical manipulations on the structure.



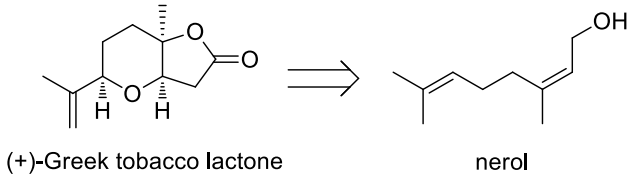
Scheme 1.17

The second general objective will be design a new methodology for the organocatalytic synthesis of proline derivatives. In this sense, we will first develop a Michael-initiated cascade reaction between aminomalonates as donors, and enones as acceptors, under the iminium ion activation, followed by intramolecular condensation of the primary amine with the ketone. The reduction of the resulting imine would provide the corresponding chiral pyrrolidines (Scheme 1.18). If the reaction proceeds in a satisfactory way, the obtained pyrrolidines can be transformed into the corresponding *N*-protected prolines through a known intramolecular C→N acyl rearrangement.



Scheme 1.18

Finally, a short chapter about the work carried out in the group of Prof. M. Christmann in Free University of Berlin during my stay there. This proyect consisted on the total synthesis of the natural product (+)-Greek tobacco lactone, starting from the commercially available nerol (Scheme 1.19).



Scheme 1.19

2

2

4-Alkenyl-5*H*-1,2,3-oxathiazole 2,2-dioxides in Michael/Michael cascade reactions

1. INTRODUCTION: ORGANOCATALYTIC CASCADE REACTIONS INITIATED BY CONJUGATE ADDITION

Before starting to describe the different aspects related to cascade reactions, it is important to define several general concepts about this area. Sequential transformations or one-pot processes involve multiple transformations followed by a single workup step. In 1993, Tietze divided the one-pot reactions into two groups, domino and consecutive reactions. He defined a domino, cascade or tandem process as involving "*two or more consecutive reactions in which subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step*", which take place under the same reaction conditions, without adding additional reagents and/or catalysts; and a consecutive reaction, being the only different with the cascade reactions that the addition of one or more catalysts or reagents is required after the first transformation, without purifications, to obtain the final product.[1] In 2001, Faber added, referring to cascade and domino processes, that "*both individual reactions belong tightly together and are rather difficult to perform in a stepwise or independent fashion. As a consequence, the intermediate between both steps is likely to be unstable and often eludes isolation and characterization*". In contrast, he defined tandem processes as two-step reactions that can be carried out separately, in a consecutive fashion.[2] Few years later, others classified cascade or domino reactions with strict conditions.[3] Fogg and dos Santos added to the definition of domino (cascade) reaction that multiple transformations, which

[1] a) Tietze, L. F. *Chem Rev.* **1996**, *96*, 115; b) Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed.* **1993**, *32*, 131.

[2] Mayer, S. F.; Kroutil, W.; Faber, K. *Chem. Soc. Rev.* **2001**, *30*, 332.

[3] a) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1; b) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365.

involve this kind of reactions, should take place through a single catalytic mechanism. On the other hand, they described the tandem process as a sequential transformation, but in this case, *via* two or more mechanistically distinct catalytic processes. More recently, Jørgensen and co-workers have developed a classification and nomenclatural method that is able to describe asymmetric catalytic one-pot reactions, based on the relative position of the enantiodifferentiating step, the total number of manual operations and the number of all bonds formed.[4] In spite of this, and as Nicolau has pointed out,[5] there are several authors that often used indifferently the terms domino, cascade and tandem. For this reason, the several organocatalytic cascade processes described in the literature will be covered in the following lines without distinction between these descriptors.

Cascade reactions constitute a powerful tool in synthetic chemistry due to their ability to achieve the formation of complex molecules in a single step. These transformations present several positive features, such as atom economy and less operational time, avoiding protection/deprotection steps and the isolation of intermediates, and therefore reducing the generation of waste. Specifically, as it has been mentioned in the previous chapter, organocatalytic cascade reactions are aligned with several of the principles of green chemistry. This type of reactions, with the suitable catalyst, can be highly regio- and stereoselective, with the consequent obtention of enantioenriched compounds. Taking this into account, the different activation manifolds of organocatalysis can be combined, this serving as an excellent platform to develop new cascade routes to the synthesis of chiral compounds, as it can be seen by the large number of publications.[6]

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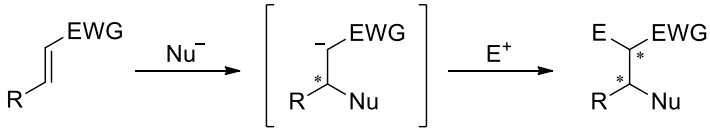
[4] Albrecht, Ł.; Jiang, H.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 8492.

[5] Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134.

[6] For some reviews on organocatalytic cascade reactions, see: a) Vetica, F.; de Figueiredo, R. M.; Orsini, M.; Tofani, D.; Gasperi, T. *Synthesis* **2015**, *47*, 2139; b) Volla, C. M. R.; Atodiresei, I.;

Among the several possibilities, the conjugate addition reaction is one of the most powerful tools to promote cascade processes due to the formation of a nucleophilic intermediate, after the initial nucleophilic attack to an electron deficient olefin, such as unsaturated carbonyl compounds, which can react with an electrophile both intramolecularly and intermolecularly (Scheme 2.1).

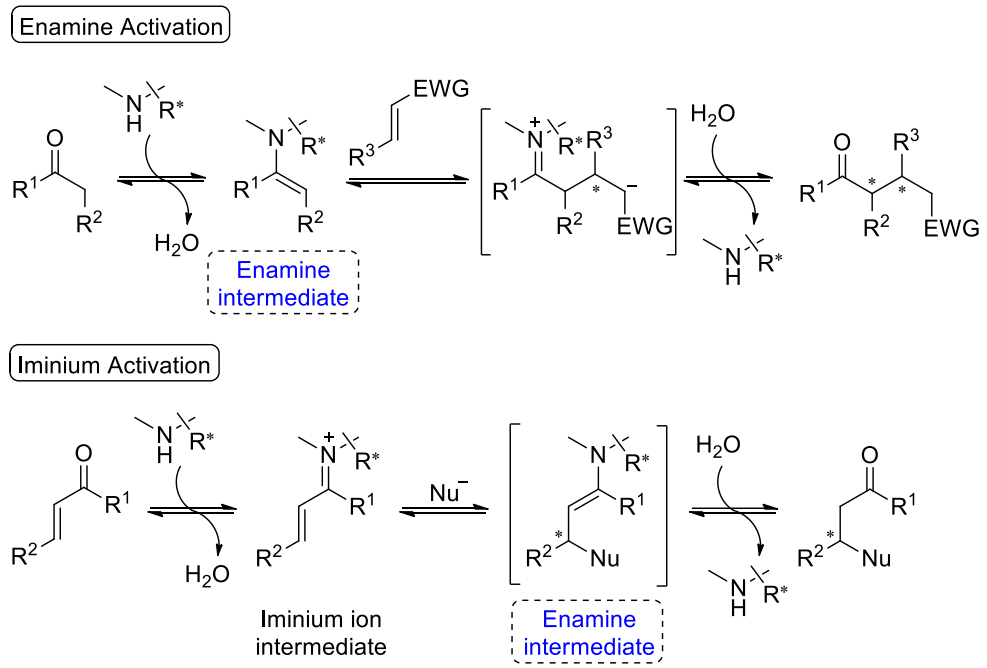


EWG: -CHO, -COR, -CO_2R, -$CONR_2$, -CN, -SO_2R, -NO_2, ...

Scheme 2.1

Within the field of organocatalysis, the use of chiral amines as catalysts (aminocatalysis) for asymmetric cascade reactions, particularly when they are initiated by a conjugate addition, has been one of the most studied activation manifolds in this particular context. The ability of this kind of catalysts to activate carbonyl compounds and to provide high stereoselectivity to the process, especially through the combination of enamine and iminium ion activation (see Scheme 2.2), is probably the reason for the wide use of this methodology in cascade reactions.

Rueping, M. *Chem. Rev.* **2014**, *114*, 2390; c) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442; d) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237; e) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; for specific reviews on aminocatalytic cascade reaction, see: f) Song, A.; Wang, W. *Catalytic Cascade Reactions* (Eds.: Xu, P.-F.; Wang, W.), John Wiley & Sons, p. 1-52, New Jersey, **2014**; g) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037.



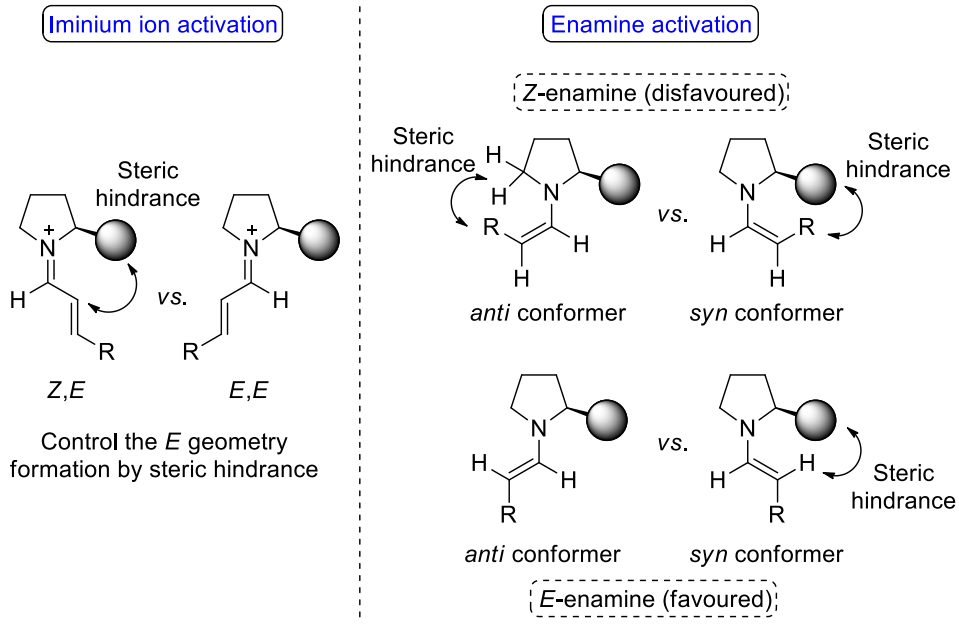
Scheme 2.2

As it can be observed in the previous scheme, the enamine activation consists on the formation of an enamine intermediate, through the initial condensation of a primary or secondary amine with the corresponding enolizable aldehyde or ketone. After condensation a chiral iminium salt is formed, increasing the acidity of the proton in α-position. This results in the formation of an enamine, being the latter a more active nucleophile than the starting aldehyde or ketone, and that therefore can react with an electrophile, such as a Michael acceptor. Finally, the adduct presents an iminium ion moiety that needs to be hydrolyzed, in order to recover the catalyst and to obtain the product. On the other hand, iminium catalysis consists on the formation of an iminium ion, through the condensation of the amine catalyst and an α,β-unsaturated aldehyde or ketone, which leads to a decrease in the energy of the LUMO with respect to the starting substrate. Thus,

this species has an enhanced electrophilicity and can be attacked by different nucleophiles through conjugate addition. After the nucleophilic attack, an enamine intermediate is formed, which has the potential to react with an electrophile in an intra- or intermolecular fashion, depending on the functionality of the substrate or on the addition of an external electrophile. Consequently, the iminium salt is formed, obtaining the product after the corresponding release of the catalyst, through a hydrolysis process. In summary, the combination of both activation methods allows the development of cascade processes under the iminium/enamine manifold. It should be pointed out that in some cases, the catalyst is hydrolyzed before a second or another step in cascade process, resulting in a reaction of the Michael adduct that depends on its functionalities to react intramolecularly or with external reactive, controlling the stereochemical outcome by the substrate chirality.

It is important to mention that the catalysts, in addition to participate by promoting the reaction through the activation of the substrates, they also incorporate a chiral element within their structure that is able to differentiate both diastereotopic faces of the activated intermediate. In this sense, there are two ways for exerting this stereodiscrimination; by steric control or by introducing a stereodirecting element. Typically, the catalyst presents a bulky group that blocks one of the stereotopic faces of the intermediate. The second possibility consists on the introduction of a convenient substituent, such as a hydrogen bond donor, able to direct the nucleophilic attack through its face, *via* secondary interactions. Another aspect to be considered is that the catalyst has to exert an efficient control regarding the geometry of the catalytically generated azomethine intermediate (iminium ion or enamine), because the presence of mixtures of *Z*/*E* isomers on the iminium ion or of *syn*/*anti* conformers on the enamine intermediate, combined with an efficient stereochemical bias of their respective prostereogenic faces still

will lead to the formation of mixture of enantiomers. In general, when catalysts with stereodirecting elements are used, this is not a problem, because this type of substituents determines the configuration of the reactive intermediate. However, in the case of catalysts that exert their stereochemical influence through steric bias, need to be large enough both to exert good π-facial discrimination and also to determine the geometry of the intermediate (see Scheme 2.3). In the case of cascade processes initiated by conjugate addition *via* enamine activation, in general, after the 1,4-addition of the enamine to a Michael acceptor, the formed iminium ion is hydrolyzed and the acyclic intermediate subsequently reacts without the participation of amine catalyst and under substrate control. The case of iminium ion activation is completely different because after the conjugate addition to the activated Michael acceptor, the catalyst remains bounded with the generated enamine, being able to carry out the following step under its control.



Scheme 2.3

It should be pointed out that, both chiral primary and secondary amines can be used as catalysts when applying these two activation manifolds and this depends on the type of substrate. In general, aldehydes condense fast with secondary amines, which means that chiral pyrrolidines, derived from commercial enantiopure proline are typically used as catalysts. However, secondary amines condense very slowly with ketones due to the lower electrophility of the carbonyl group and the higher steric crowding of the generated intermediate compared with the corresponding aldehydes. Moreover, the control of the geometry is more difficult in case of ketones due to the fact that the generated iminium ion has substituents with similar size attached to the azomethine carbon that can lead to a mixture of stereoisomers. For these reasons, it has been demonstrated that chiral primary amines have the ability to activate ketones efficiently,[7] being the condensation between both reagents more favoured in terms of reactivity and sterical requirements. Moreover, this would also permit a more effective geometry control on the *Z*/*E* stereochemistry of the double bond (Figure 2.1).

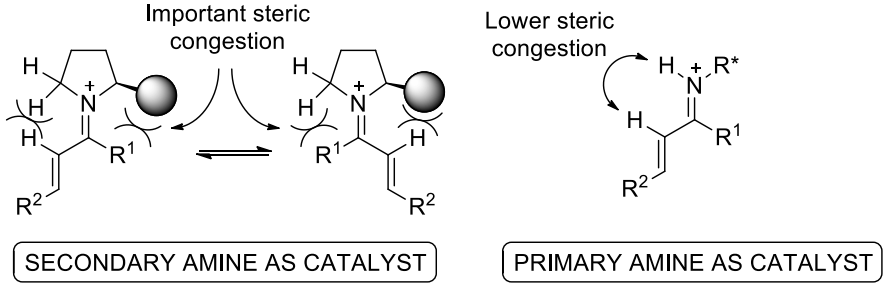


Figure 2.1

[7] For some reviews on the use of primary amines as catalysts, see: a) Duan, J.; Li, P. *Catal. Sci. Technol.* **2014**, *4*, 311; b) Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 9748; c) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807; d) Chen, Y.-C. *Synlett* **2008**, 1919; e) Bartoli, G.; Melchiorre, P. *Synlett* **2008**, 1759.

Apart from the use of aminocatalysis in cascade reactions initiated by conjugate addition, there are other ways to activate the Michael acceptors and/or donors. One of these methodologies is the use of the hydrogen bond catalysis,[8] which consist on the activation of the substrate by the formation of a network of hydrogen bonds that increment the reactivity of the Michael acceptor, modulating the chiral space in the Michael addition. Due to the weak interactions between the substrate and catalyst, after the conjugate addition step, sometimes the subsequent step is controlled by the substrate. Finally, other activation manifolds, such as *N*-heterocyclic carbenes and phase-transfer catalysts, have been less studied in this field.

In conclusion, the capacity of the different activation methods of organocatalysis to developed cascade reactions, specifically initiated by conjugate addition, has been demonstrated in the last years. According to the objectives of this thesis, we will present in the following sections some selected examples illustrating different cascade reactions initiated by Michael-type reactions focused on Michael/Michael cascade reactions for the construction of complex carbocyclic scaffolds.

1.1. Michael/Michael cascade reactions

Organocatalytic Michael/Michael cascade methodology has been successfully used for the straightforward access to enantioenriched polysubstituted (poly)cyclic compounds. Taking into account the different organocatalytic activation modes shown previously, and the ability to combine most of them, the

[8] For specific reviews on hydrogen-bond mediated cascade reactions, see: a) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253; b) Jiang, J.; Gong, L.-Z. *Catalytic Cascade Reactions* (Eds.: Xu, P.-F.; Wang, W.), John Wiley & Sons, p. 53-122, New Jersey, **2014**; c) Lv, F.; Liu, S.; Hu, W. *Asian J. Org. Chem.* **2013**, *2*, 824.

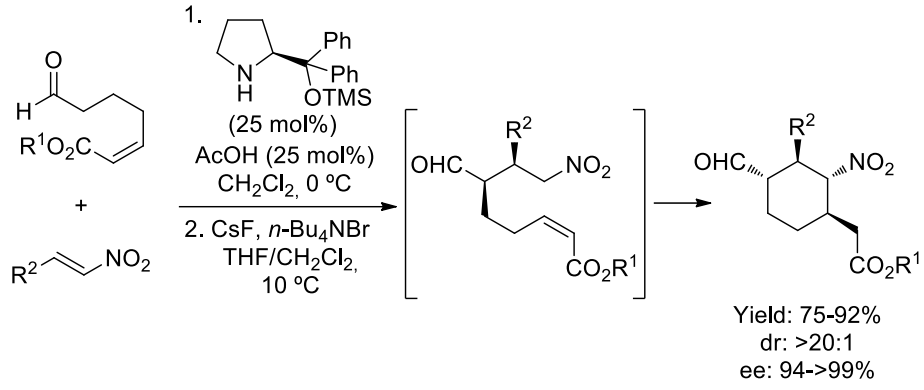
Michael/Michael cascade reactions will be classified depending on the mechanistic manifold operating in the process. For this type of methodology, the presence of two unsaturated systems with different reactivities is generally necessary. These engage in a cascade reaction started by the initial conjugate addition to one of the Michael acceptors followed by an intramolecular reaction between the nucleophilic intermediate generated in this initial step and the second Michael acceptor. For obvious reasons, it should be noted that these two Michael acceptor systems do not have to interfere with each other, and therefore one system has to be more reactive than the other in the first conjugate addition and the second should be reactive enough to undergo the second Michael reaction.

1.1.1. Michael/Michael cascade processes initiated by conjugate addition under enamine activation

In general, for an intramolecular double Michael cascade reaction initiated by conjugate addition under enamine activation, a conveniently functionalized substrate is required that incorporates an enolizable aldehyde or ketone together with the Michael acceptor. This general approach is followed by Hong an co-workers that used as a Michael donor/acceptor 7-oxohep-2-enoates and diverse nitroalkenes as Michael acceptors, employing diphenylprolinol derivative as catalyst and obtaining tetrasubstituted cyclohexanes with excellent estereocontrol (Scheme 2.4).[9] The reaction consists on enamine formation between the aldehyde and the catalyst, followed by Michael addition to the nitroalkene. It should be noted that this is not a real cascade reaction, because the first Michael adduct needs the addition of an external base to promote the second 1,4-addition, not participating the catalyst in this step. Moreover, when the (*E*)-7-oxohep-2-enoate

[9] Hong, B.-C.; Nimje, R. Y.; Wu, M.-F.; Sadani, A. A. *Eur. J. Org. Chem.* **2008**, 1449.

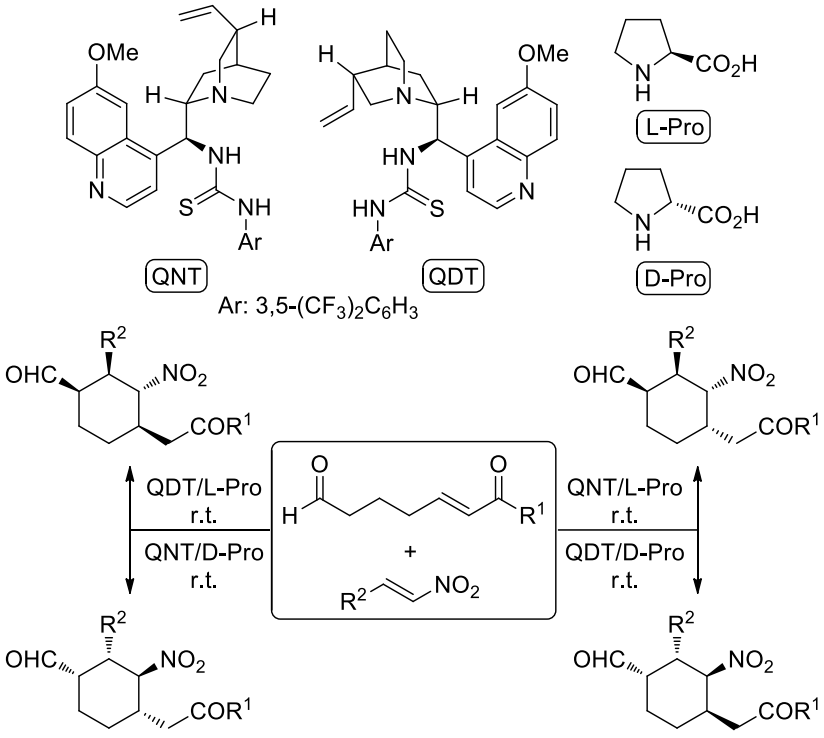
was used, a mixture of diastereoisomers was observed. Nevertheless, with the *Z*-diastereoisomer the product was obtained as a single diastereoisomer.



Scheme 2.4

Recently, Zhao and co-workers have developed a highly diastereodivergent synthesis of tetrasubstituted six member rings, employing the same type of substrates that in the previous case.[10] The control of the diastereoselectivity was achieved through controlling the stereochemistry of each single step of the cascade reaction using pseudodiastereoisomeric modularly designed organocatalysts self-assembled between proline and thioureas, the latter derived from cinchona alkaloids. By the combination of both enantiomers of proline and the pseudoenantiomers of cinchona derived thioureas, pseudodiastereoisomeric catalysts were formed, achieving the desired diastereodivergence (Scheme 2.5).

[10] Rana, N. K.; Huang, H.; Zhao, C.-G. *Angew. Chem. Int. Ed.* **2014**, *53*, 7619.



Scheme 2.5

In this sense, it was possible to obtain selectively four possible 1,2-*syn* stereoisomers, by combining appropriately the catalysts, being the first step controlled through enamine catalysis and the second step through non-covalent interactions exerted by the bifunctional tertiary amine/thiourea. After the formation of 1,2-*syn* stereoisomers, the corresponding 1,2-*anti* stereoisomers could be prepared heating the reaction, thus allowing the selective synthesis of eight possible stereoisomers of these tetrasubstituted enantioenriched cyclohexane derivatives. This type of reaction has also been extended to 6-oxohex-2-enoates, to the obtention of the corresponding five member rings in a Michael/Michael

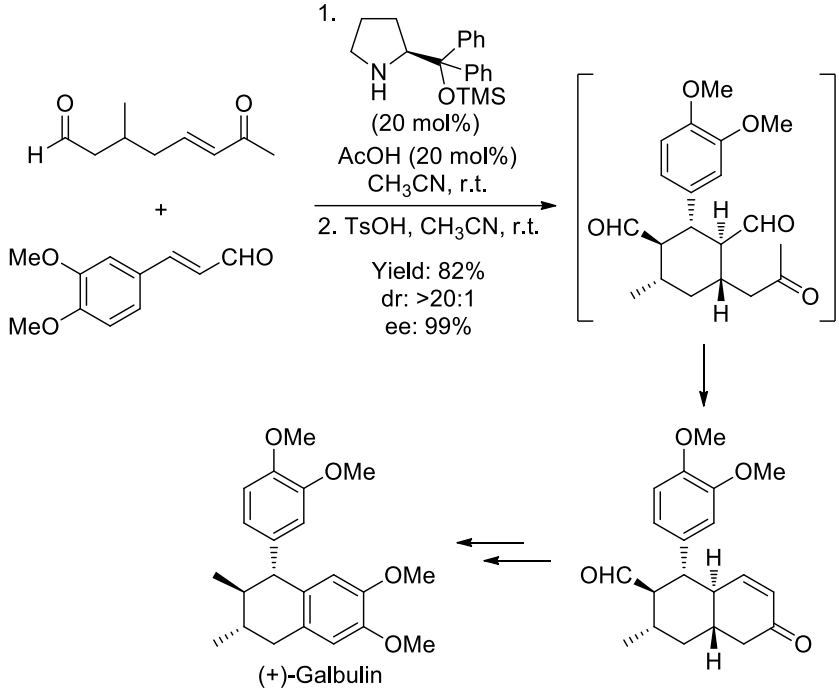
cascade process, using in this case *trans*-perhydroindolic acid as efficient catalyst.[11]

Other approaches to Michael/Michael cascade reactions have been developed using α,β-unsaturated aldehydes as the first Michael acceptor and 7-oxooct-5-enals[12] as the Michael donor/acceptor, employing *O*-TMS diphenylprolinol as catalyst. In this case, firstly an intermolecular Michael addition takes place between both activated 7-oxooct-5-enal and α,β-unsaturated aldehyde, followed by an intramolecular Michael addition of the generated enamine to the α,β-unsaturated ketone. After the double Michael cascade reaction, by the addition of TsOH, aldol condensation occurs in one-pot fashion. This transformation was successfully applied towards the synthesis of (+)-galbulin, employing racemic (*E*)-3-methyl-7-oxooct-5-enal as the first Michael donor, yielding the key intermediate with total diastereocontrol (Scheme 2.6).[13] A kinetic resolution of the racemic compound was observed because one of both enantiomers was not able to react due to steric reasons.

11 An, Q.; Shen, J.; Butt, N.; Liu, D.; Liu, Y.; Zhang, W. *Synthesis* **2013**, *45*, 1612.

12 a) Hong, B.-C.; Nimje, R. Y.; Liao, J.-H. *Org. Biomol. Chem.* **2009**, *7*, 3095; for a related example, see: b) Hong, B.-C.; Sadani, A. A.; Nimje, R. Y.; Dange, N. S.; Lee, G.-H. *Synthesis* **2011**, 1887.

13 Hong, B.-C.; Hsu, C.-S.; Lee, G.-H. *Chem. Commun.* **2012**, *48*, 2385.

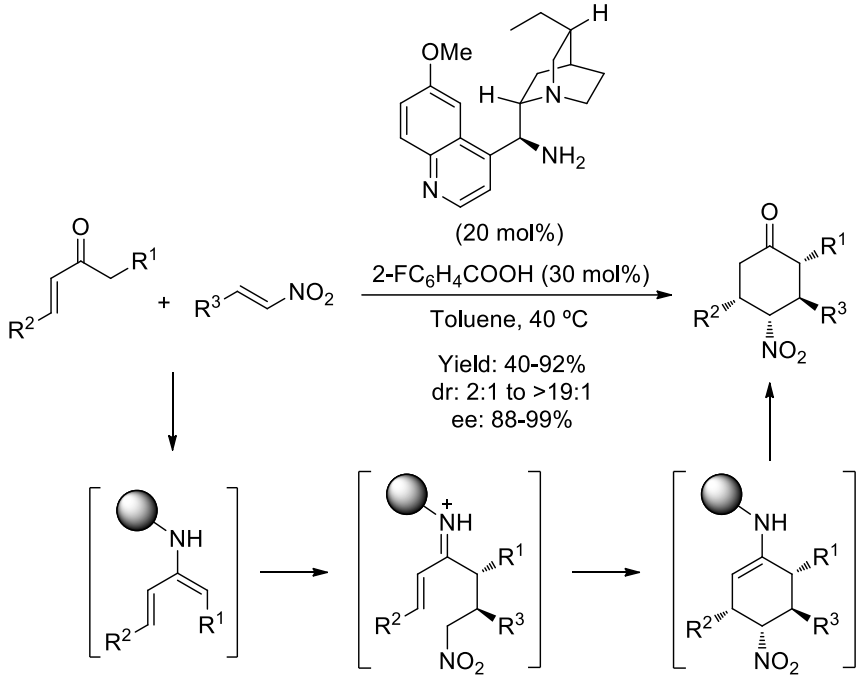


Scheme 2.6

In 2009, Melchiorre and co-workers studied the possibility of using ketones as Michael donors in Michael/Michael cascade reactions using chiral primary amine catalysis. As it has already been mentioned before, primary amines activate ketones more effectively than the respective secondary amines owing to the formation of a less sterically crowded enamine and with a more efficient control of its geometry. In this sense, simple chiral primary amines derived from natural cinchona alkaloids were evaluated as catalysts in the reaction of acyclic enones with different Michael acceptors, such as nitrostyrenes (Scheme 2.7).[14] Cyclohexanones were obtained with up to four stereocenters, in high yields and

[14] Wu, L.-Y.; Bencivenni, G.; Mancinelli, M.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 7196.

excellent stereocontrol, using 9-*epi*-9-amino-9-deoxyhydroquinine and 2-fluorobenzoic acid as the catalytic system.

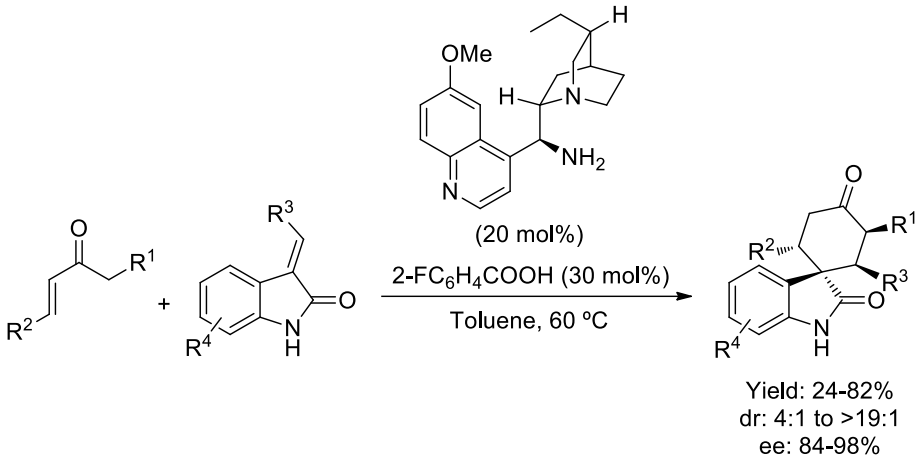


Scheme 2.7

The mechanism of this reaction consists on the activation of the α,β-unsaturated ketone, generating an enamine that undergoes Michael addition with the electron-poor alkene. The iminium ion formed can react intramolecularly through a second Michael addition to obtain the corresponding cycloadducts in a formal [4+2] cycloaddition. The reaction was extended to other Michael acceptors, such as α-cyanocinnamates or *N*-protected maleimides.

Melchiorre and co-workers also applied this general reaction scheme to synthesize spirocyclic oxindoles in very good yields and enantioselectivities (see

Scheme 2.8).[15] Unprotected oxindole derivatives were employed as the initial Michael acceptors and several α,β-unsaturated ketones as the precursors of catalytically generated nucleophilic dienamine intermediates formed after condensation with the catalyst. Later on, the same group also applied this approach towards the efficient obtention of spirocyclic benzofuranone cyclohexanones starting from benzofuranone derivatives and different enones, using the same catalytic system.[16] Recently, Wang *et al.* have developed an efficient synthesis of spiropyrazolone derivatives by reaction between unsaturated ketones and unsaturated pyrazolones, applying analogous approach with a quinine-based catalyst and using benzoic acid as cocatalyst.[17]



Scheme 2.8

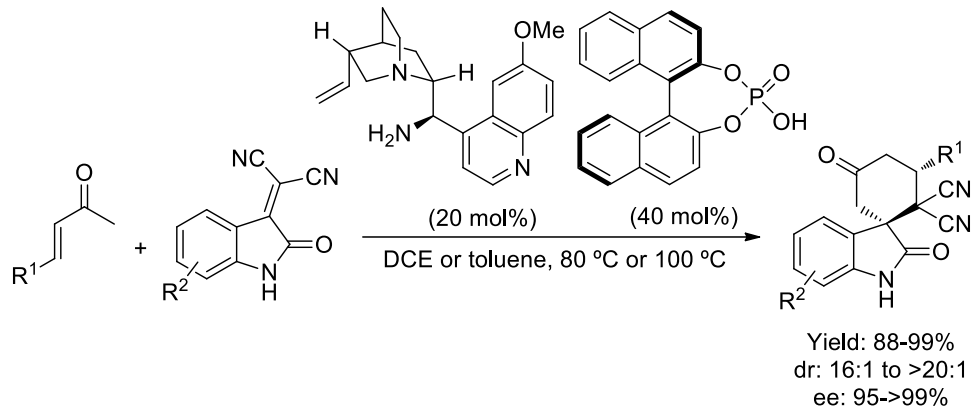
A similar approach for the preparation of spirooxindole derivatives was developed by Wang and co-workers, through the reaction between several α,β-

[15] Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.-P.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 7200.

[16] Cassani, C.; Tian, X.; Escudero-Adán, E. C.; Melchiorre, P. *Chem. Commun.* **2011**, *47*, 233.

[17] Liang, J.; Chen, Q.; Liu, L.; Jiang, X.; Wang, R. *Org. Biomol. Chem.* **2013**, *11*, 1441.

unsaturated ketones and isatylidene malononitrile derivatives *via* double Michael cascade reaction (see Scheme 2.9),[18] observing a difference in regioselectivity in the formation of spiro[cyclohexane-1,3'-indoline]-2',3-dione, compared with the system used by Melchiorre, due to stronger electron-withdrawing character of the two cyano groups. Excellent results were obtained regarding the yield and the stereocontrol of the reaction, requiring the matched combination of a cinchona-based chiral primary amine and a (*R*)-BINOL-based phosphoric acid as chiral counteranion.



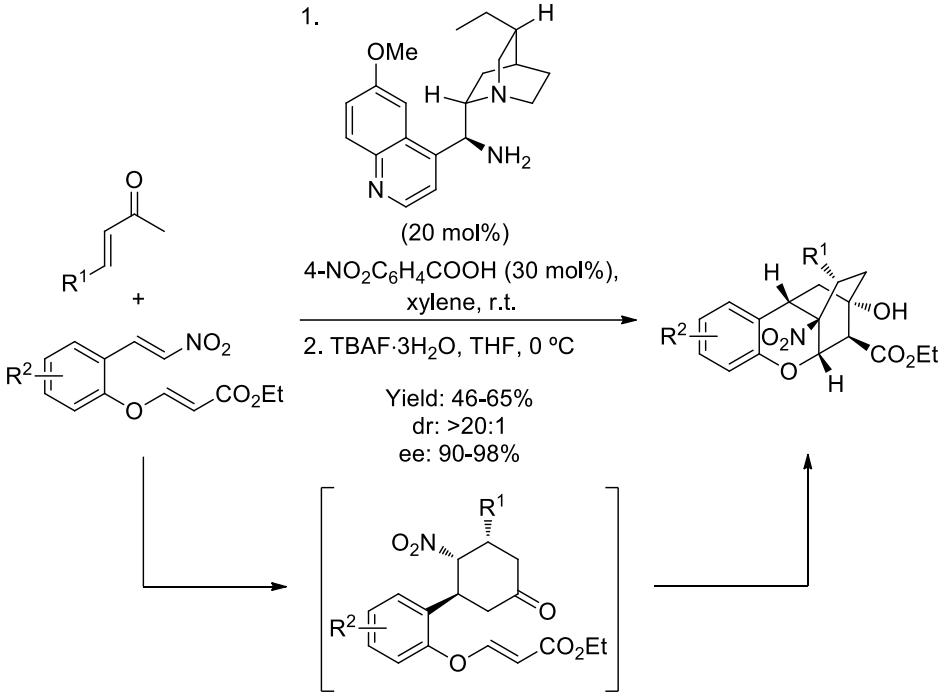
Scheme 2.9

In related work, Xu and co-workers employed enones and different types of nitrostyrenes, having an enoate in the *ortho* position, in a Michael/Michael cascade reaction catalyzed by primary amines.[19] After the double Michael reaction, a base was added to the reaction vessel in order to generate a nucleophilic nitronate and this initiated an intramolecular Michael/aldol cascade

[18] a) Lan, Y.-B.; Zhao, H.; Liu, Z.-M.; Liu, G.-G.; Tao, J.-C.; Wang, X.-W. *Org. Lett.* **2011**, *13*, 4866; for another example using *N*-protected isatylidene malononitrile, see: b) Huang, H.; Bihani, M.; Zhao, J. C.-G. *Org. Biomol. Chem.* **2016**, *14*, 1755.

[19] Yu, D.-F.; Wang, Y.; Xu, P.-F. *Adv. Synth. Catal.* **2011**, *353*, 2960.

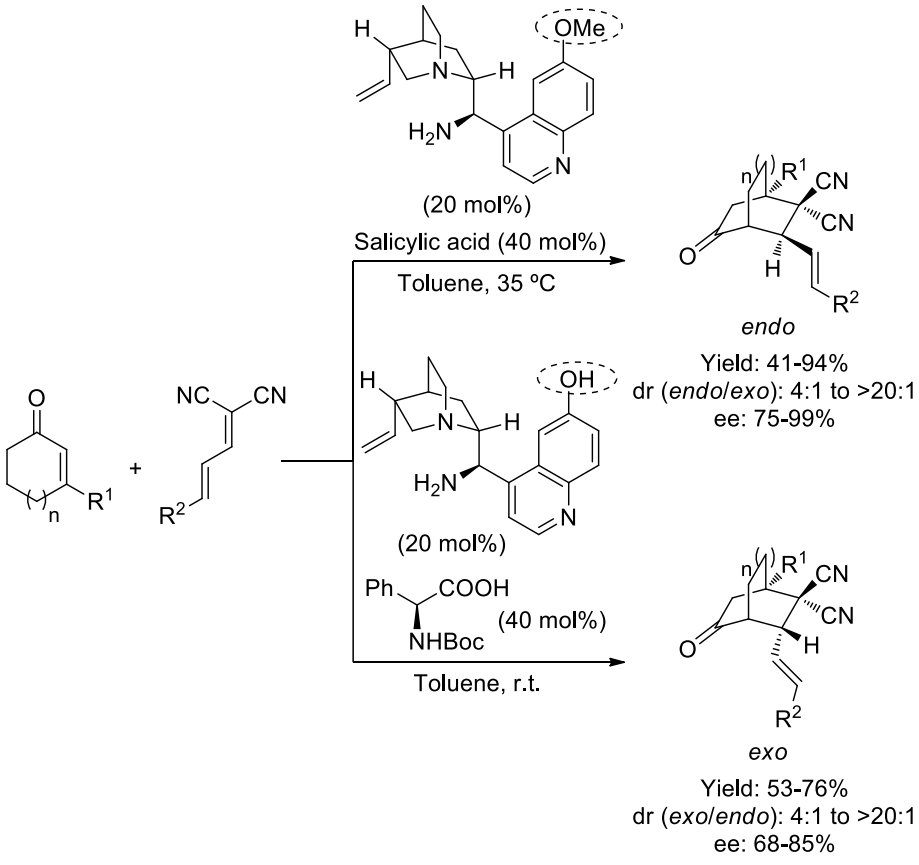
reaction resulting in the formation of tetracyclic ring system incorporating both a chroman and bicycle[2.2.2]octane structural moieties (Scheme 2.10).



Scheme 2.10

In 2012, Chen and co-workers developed a stereodivergent formal [4+2] cycloaddition using in this case cyclic β-susbstituted enones and polyconjugated malononitriles as the initial Michael acceptors. A concerted cycloaddition pathway was initially proposed but, after isolation of several Michael adducts that were identified as intermediates of the reaction, a double Michael cascade reaction was proposed as a more realistic pathway. The *endo* and *exo* diastereoisomers could be selectively prepared by varying the nature of primary amine catalyst and the cocatalyst. In particular, the presence of a hydroxyl group in the quinoline moiety

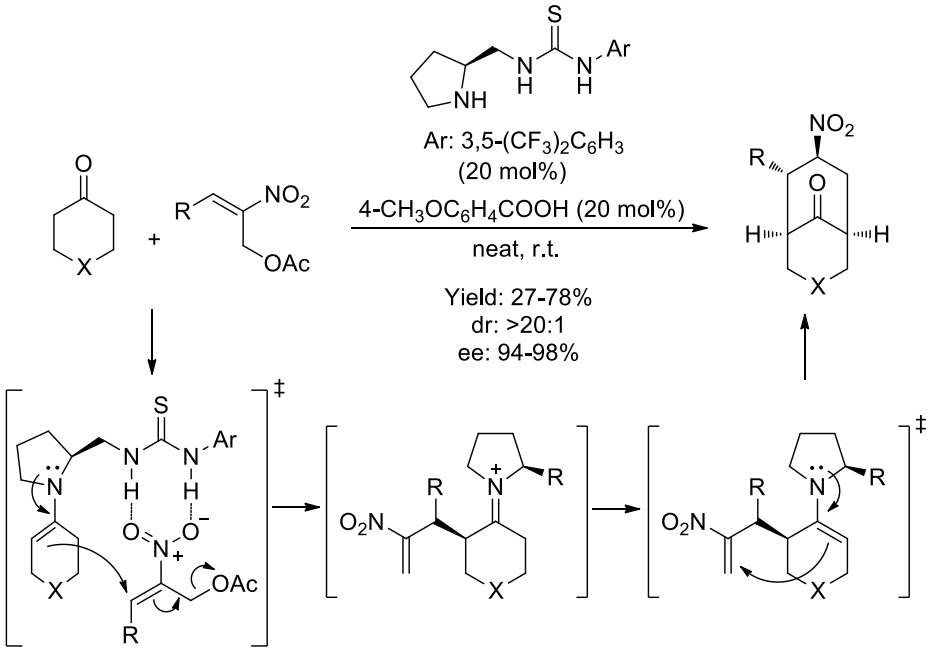
of the quinine-based catalyst favours the formation of the *exo* diastereisomer through hydrogen bond interactions. On the other hand, avoiding the presence of non-covalent interactions the *endo* diastereoisomer is mainly formed (Scheme 2.11).[20]



Scheme 2.11

[20] Feng, X.; Zhou, Z.; Zhou, R.; Zhou, Q.-Q.; Dong, L.; Chen, Y.-C. *J. Am. Chem. Soc.* **2012**, *134*, 19942.

An interesting work in this field was reported by Li and co-workers,[21] in which the possibility of using cyclic ketones as double Michael donors and 2-nitroallyl acetates as double Michael acceptors in a Michael/elimination/Michael cascade reaction was surveyed. In this case, a bifunctional pyrrolidine/thiourea catalyst was used as the initial activating agent of the pronucleophile (Scheme 2.12).



Scheme 2.12

It is noteworthy that the additional hydrogen bond donor functionality of the catalyst was found to be crucial in the reaction outcome, presumably being this

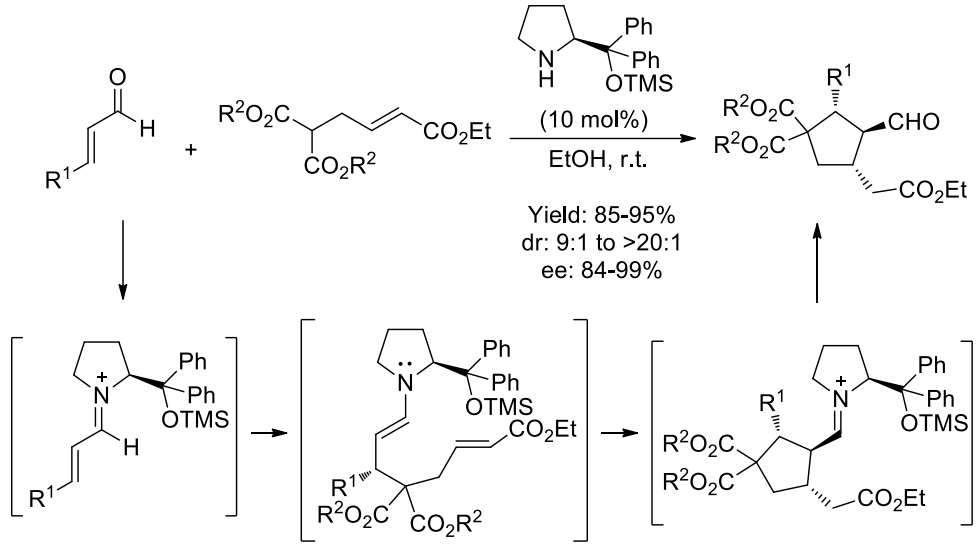
[21] Cao, C.-L.; Zhou, Y.-Y.; Zhou, J.; Sun, X.-L.; Tang, Y.; Li, Y.-X.; Li, G.-Y.; Sun, J. *Chem. Eur. J.* **2009**, *15*, 11384.

involved in the activation of the nitroolefin through the two Michael-type reaction steps.

1.1.2. Michael/Michael cascade processes initiated by conjugate addition under iminium ion activation

There are several examples in which the initial activation consists on the formation of an iminium ion starting from an unsaturated aldehyde or ketone that plays as the Michael acceptor in the first conjugate addition step and subsequently as the Michael donor, *via* enamine formation, in the second conjugate addition. This involves the use of a functionalized substrate containing C-H acidic moiety able to play the role of Michael donor as the starting nucleophilic reagent that initiates the cascade reaction, together with an activated double bond with the ability to react intramolecularly with the enamine generated after the first conjugate addition. In this sense, the first aminocatalytic asymmetric double Michael cascade reaction initiated by iminium ion formation and following the iminium/enamine manifold, was developed by Wang and co-workers for the synthesis of highly functionalized cyclopentanes (see Scheme 2.13).[22] Different α,β-unsaturated aldehydes were used as the initial Michael acceptors and malonic ester reagents containing an α,β-unsaturated ester moiety as bifunctional compounds. Under the optimal conditions, several enantioenriched cyclopentanes were prepared, using diphenylprolinol trimethylsilyl ether as the best catalyst.

[22] Zu, L.; Li, H.; Xie, H.; Wang, J.; Jiang, W.; Tang, Y.; Wang, W. *Angew. Chem. Int. Ed.* **2007**, *46*, 3732.



Scheme 2.13

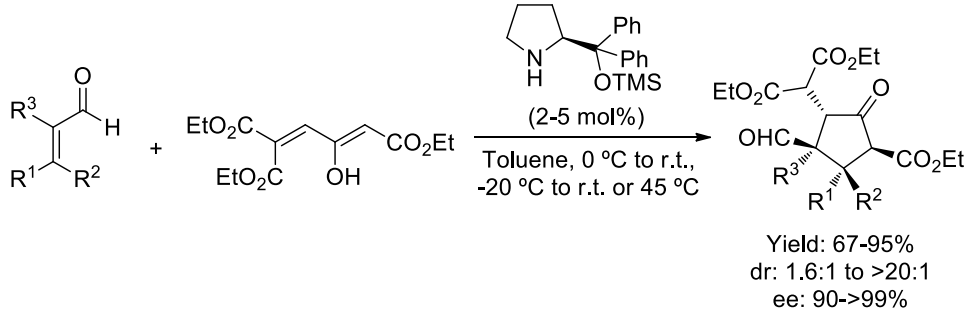
Córdova and co-workers, developed a nitro-Michael/Michael cascade reaction following a similar approach, but employing δ-nitro-α,β-unsaturated esters as bifunctional reagents, leading to cyclopentanes with four contiguous stereogenic centers in excellent yields and enantioselectivities.[23] In this case, a basic additive was necessary to increment the yield and selectivity, being DABCO the best one. By contrast, acid additives reduced the stereocontrol of the reaction.

Few years later, Ma *et al.*,[24] reported the enantioselective synthesis of cyclopentanones through double Michael addition, using β-keto esters bearing a highly electron-deficient olefin as bifunctional compounds (Scheme 2.14). A rather low catalyst loading (2-5 mol%) was enough for the completion of the

[23] Zhao, G.-L.; Ibrahem, I.; Dziedzic, P.; Sun, J.; Bonneau, C.; Córdova, A. *Chem. Eur. J.* **2008**, *14*, 10007.

[24] Ma, A.; Ma, D. *Org. Lett.* **2010**, *12*, 3634.

reaction, obtaining very good results with a wide range of substituted α,β-unsaturated aldehydes, including α,β- and β,β-disubstituted enals, therefore increasing the interest of the methodology.

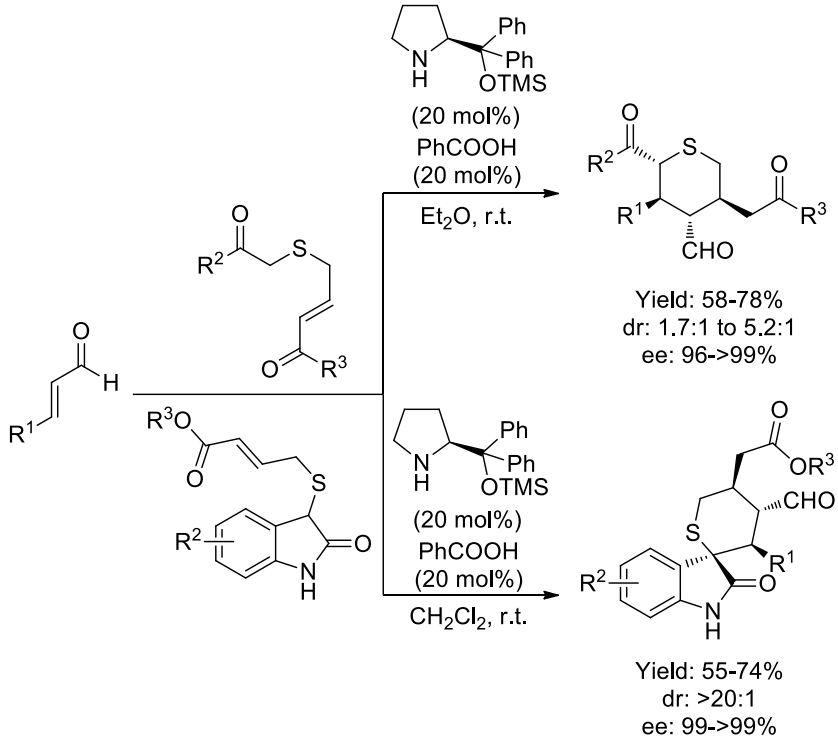


Scheme 2.14

Recently, Sheng and co-workers have applied this methodology to the efficient obtention of tetrahydrothiopyrans[25] and spirotetrahydrothiopyrans[26] employing ketothioeter enones as new bifunctional substrates, and enals as activated Michael acceptors (Scheme 2.15). It is an alternative methodology to the formation of sulfur-containing cyclic compounds. It should be noted that one of the spirooxindole derivatives (R^1 = 4-BrC_6H_4; R^2 = 2-Br; R^3 = Me) was a potent inhibitor of p53-MDM2 protein-protein interaction, showing also good antitumor activity, which reinforces the importance of the methodology.

[25] Wang, S.; Zhang, Y.; Dong, G.; Wu, S.; Fang, K.; Li, Z.; Miao, Z.; Yao, J.; Li, H.; Li, J.; Zhang, W.; Wang, W.; Sheng, C. *Org. Lett.* **2014**, *16*, 692.

[26] Wang, S.; Jiang, Y.; Wu, S.; Dong, G.; Miao, Z.; Zhang, W.; Sheng, C. *Org. Lett.* **2016**, *18*, 1028.

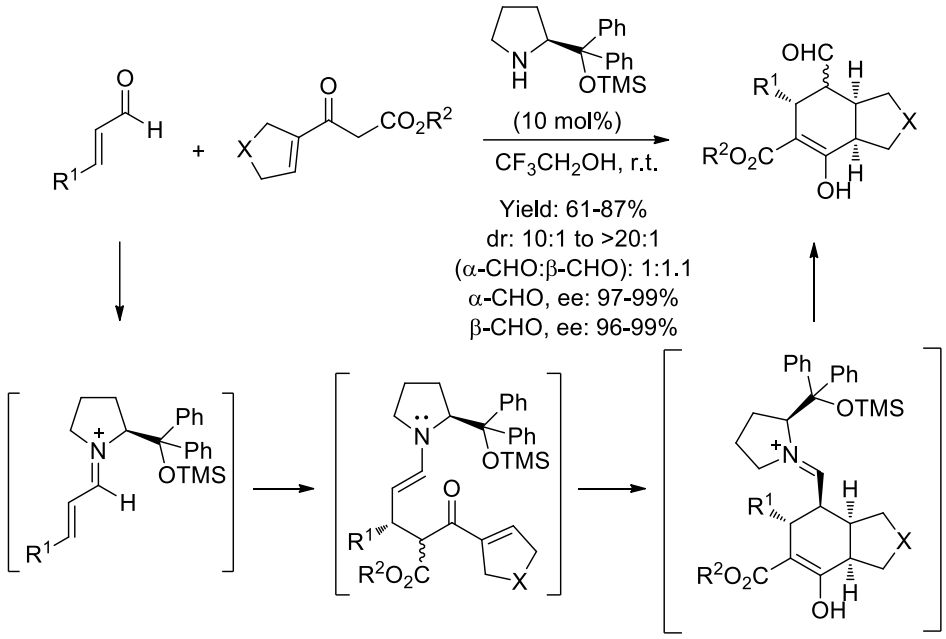


Scheme 2.15

In a different context, there are several reports, in which γ,δ-unsaturated β-ketoesters (Nazarov reagents) have been surveyed as bifunctional compounds in combination with α,β-unsaturated aldehydes, in Michael/Michael cascade reactions, using secondary amines as catalysts. In 2008, Jørgensen and co-workers employed unsubstituted Nazarov reagents in the double Michael addition but, surprisingly, an unexpected Michael/Morita-Baylis-Hillman cascade reaction was observed.[27] However, in an independent work, Gong *et al.* had already developed a novel organocatalytic formal [3+3] cycloaddition reaction using β-aryl

[27] Cabrera, S.; Alemán, J.; Bolze, P.; Bertelsen, S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 121.

substituted Nazarov reagents that involved an initial Michael reaction under iminium catalysis.[28] With this in mind, Brenner and co-workers successfully developed a Michael/Michael cascade reaction, employing Nazarov reagents, in which the olefin was incorporated into a carbocycle.[29] Under the optimal conditions, with *O*-TMS diphenylprolinol as catalyst and trifluoroethanol as solvent, several α,β-unsaturated aldehydes were reacted, leading to the corresponding fused bicycles in excellent enantioselectivities (Scheme 2.16).



Scheme 2.16

The proposed mechanism involves the initial activation of the enal by condensation with the secondary amine, forming the iminium ion intermediate

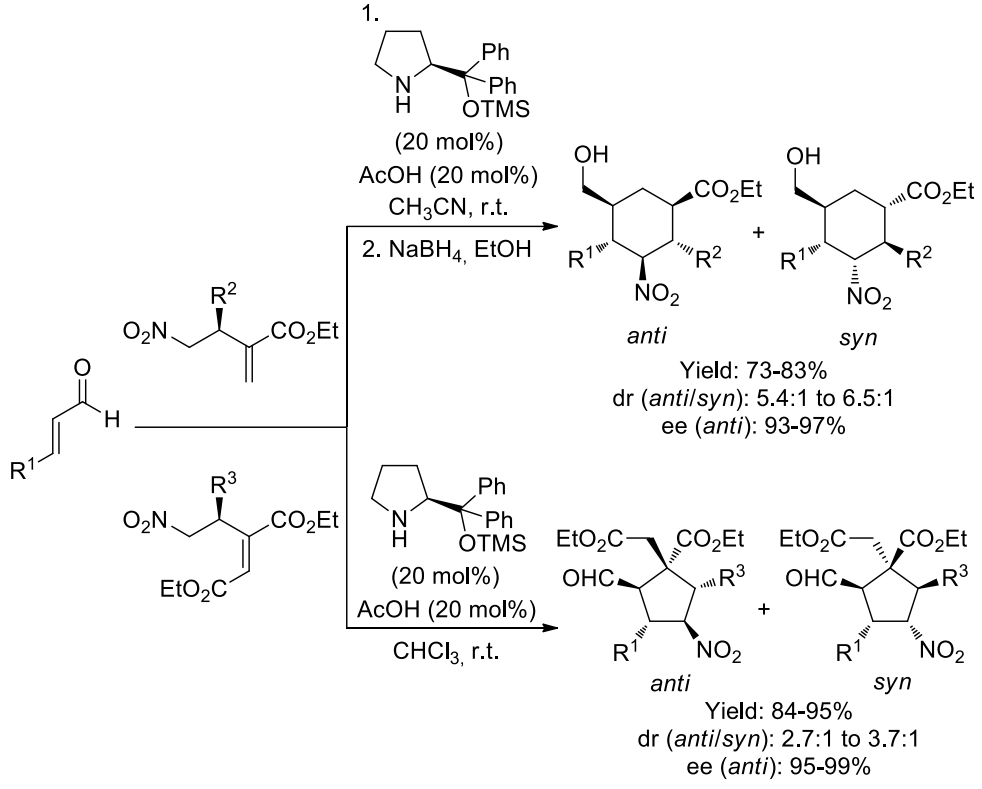
[28] Zhu, M.-K.; Wei, Q.; Gong, L.-Z. *Adv. Synth. Catal.* **2008**, *350*, 1281.
[29] McGarraugh, P. G.; Brenner, S. E. *Org. Lett.* **2009**, *11*, 5654.

with enhanced electrophilicity that undergoes the first Michael addition through nucleophilic attack of the activated methylene group of the Nazarov reagent. The generated enamine intermediate subsequently reacts through a second 1,4-addition to the C-C double bond of the Nazarov reagent and finally, the catalyst is released and the product is obtained. The formation of three diastereoisomers was observed, one as a minor byproduct, and the others as a result of the epimerization of the α-position of the aldehyde. Few years later, the same group extended the optimized conditions to both alkyl- and aryl-substituted unsaturated β-ketoesters, obtaining the corresponding cyclohexenes in good yields and excellent enantioselectivities.[30] Surprinsingly, in contrast to the work of Gong and co-workers,[28] the double Michael addition proceeded well with β-aryl substituted Nazarov reagents, most likely due to the effect of the solvent assuming that with protic solvents employed by Brenner, the second Michael acceptor was activated by hydrogen bonding.

In 2011, Hong and co-workers developed a nitro-Michael/Michael cascade reaction between several α,β-unsaturated aldehydes and different bifunctional reagents (shown on Scheme 2.17).[31] These last were prepared in around 60% ee first by Michael addition of carbethoxymethylenetriphenylphosphorane to nitroalkenes using a chiral thiourea as catalyst and next Wittig reaction with ethyl glyoxylate or formaldehyde. These products were subjected to Michael/Michael cascade reaction with enals towards the synthesis of enantioenriched pentasubstituted cyclopentane and cyclohexanecarbaldehydes. With the racemic mixture of the bifunctional reagent very low diastereomeric ratios were observed, being the diastereoselectivity controlled by the substrate.

---

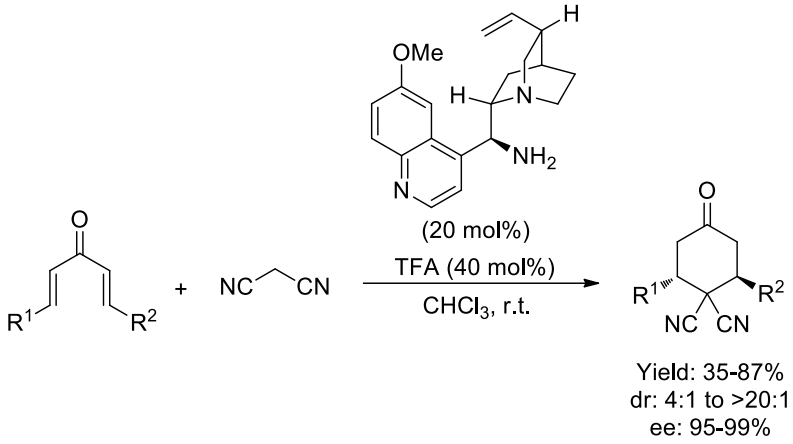
[30] McGarraugh, P. G.; Jones, J. H.; Brenner-Moyer, S. E. *J. Org. Chem.* **2011**, *76*, 6309.
[31] Hong, B.-C.; Nimje, R. Y.; Lin, C.-W.; Liao, J.-H. *Org. Lett.* **2011**, *13*, 1278.



Scheme 2.17

As it has been mentioned before, in general the Michael/Michael cascade reactions with enals activated through the iminium/enamine manifold typically involve substrates having both a pro-nucleophile and a Michael acceptor. Nevertheless, there are several examples, in which dienones that presents two Michael acceptors on the same molecule, are activated by iminium ion formation, using chiral primary amines as efficient catalysts. Relatedly, Yan and co-workers developed the synthesis of cyclohexanone derivatives in good yields and stereoselectivities, by double conjugate addition of malononitrile, to dienones, using 9-*epi*-9-amino-9-deoxyquinine as catalyst and trifluoroacetic acid (TFA) as

cocatalyst (Scheme 2.18).[32] The reaction worked well with aryl substituents in β-position of the dienone, but failed with β-alkyl substituents.



Scheme 2.18

This type of dienones was also used in double Michael cascade reaction with *N*-protected 3-unsubstituted oxindoles. Under the optimal conditions, using 9-*epi*-9-amino-9-deoxycinchonine as catalyst and (*S*)-BINOL-phosphoric acid as cocatalyst, several spirocyclic oxindoles were prepared in very good yields and excellent stereocontrol.[33] The protecting group on the nitrogen of oxindole was found to be necessary for the success of the reaction (see Scheme 2.19). Wang and co-workers were able to develop the same type of reaction using commercially available *N*-unprotected 3-unsubstituted oxindole and derivatives with the employment of cinchona-based primary amine and chiral amino acid derivative as

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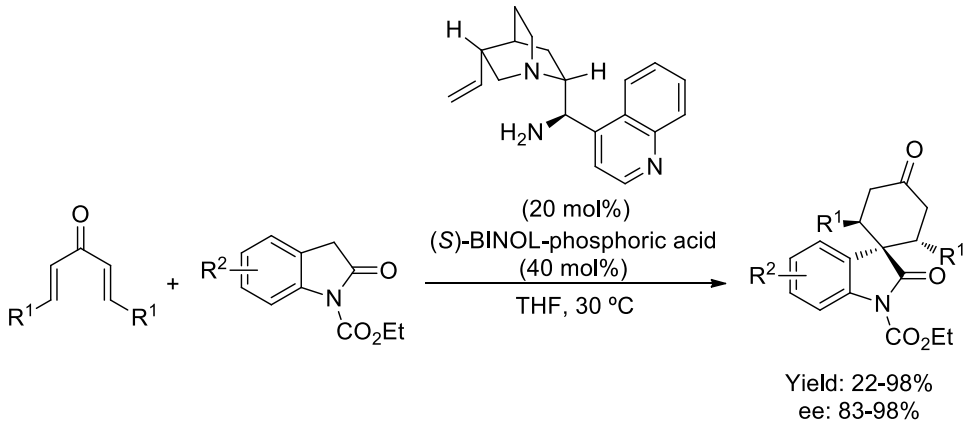
[32] a) Li, X.-M.; Wang, B.; Zhang, J.-M.; Yan, M. *Org. Lett.* **2011**, *13*, 374; for a similar example using non-covalent bonded catalysis, see: b) de Fusco, C.; Lattanzi, A. *Eur. J. Org. Chem.* **2011**, 3728.

[33] Wang, L.-L.; Peng, L.; Bai, J.-F.; Jia, L.-N.; Luo, X.-Y.; Huang, Q.-C.; Xu, X.-Y.; Wang, L.-X. *Chem. Commun.* **2011**, *47*, 5593.

catalytic system.[34] They also developed satisfactorily this [5+1] Michael/Michael cascade reaction with *N*-phenyl protected pyrazolones as dinucleophiles. More recently, Veselý and co-workers have extended the methodology towards the obtention of sulfur-containing spirocyclic scaffolds, starting from the dione system and different sulfur-containing dinucleophiles, such as benzothiophenone and *N*-phenylrhodanine, obtaining moderate to good yields and stereoselectivities.[35]



Scheme 2.19

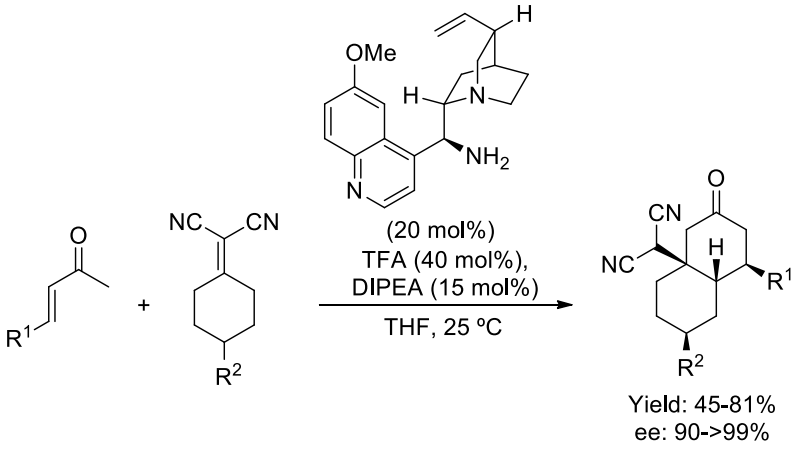
From a different point of view, there are also several examples regarding vinylogous versions of the Michael/Michael cascade sequence based on iminium ion catalysis. One example is the one developed by Chen *et al.*,[36] who used substituted alkylidenemalononitriles as vinylogous pronucleophiles in the double Michael cascade reaction (see Scheme 2.20). A plausible mechanism of the

[34] Wu, B.; Chen, J.; Li, M.-Q.; Zhang, J.-X.; Xu, X.-P.; Ji, S.-J.; Wang, X.-W. *Eur. J. Org. Chem.* **2012**, 1318.

[35] Géant, P.-Y.; Urban, M.; Remeš, M.; Císařová, I.; Veselý, J. *Eur. J. Org. Chem.* **2013**, 7979.

[36] a) Kang, T.-R.; Xie, J.-W.; Du, W.; Feng, X.; Chen, Y.-C. *Org. Biomol. Chem.* **2008**, *6*, 2673; for a pioneering work on asymmetric vinylogous Michael addition, see: b) Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem. Int. Ed.* **2007**, *46*, 389.

reaction consists on the 1,4-addition of the deprotonated γ-position of the alkylidenemalononitrile to the iminium ion derived from the enone by condensation with 9-*epi*-9-amino-9-deoxyquinine. Then, the second Michael addition occurs through the reaction between the nucleophilic enamine, generated after the first Michael addition, and the α,α-dicyanoalkene. It is also possible that this last Michael reaction could proceed without catalyst activation, only with the assistance of an external base. In addition, a desymmetrization process occurred, when 4-substituted cyclohexylidenemalononitriles were employed. Under the optimal conditions, a variety of bicyclic compounds were prepared in very good yields and stereoselectivities, as single diastereoisomers.

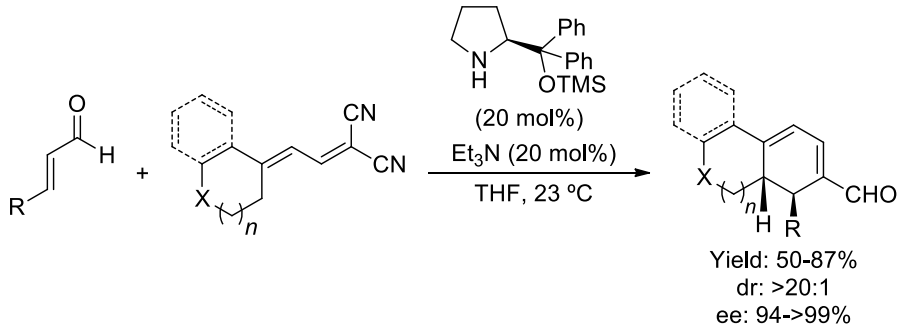


Scheme 2.20

Recently, Zanardi and co-workers have developed a similar reaction but employing enals instead of enones, and allylidene malononitriles as remotely enolizable nucleophiles.[37] The reaction proceeded in a similar way compared to

[37] Brindani, N.; Rassu, G.; Dell'amico, L.; Zambrano, V.; Pinna, L.; Curti, C.; Sartori, A.; Battistini, L.; Casiraghi, G.; Pelosi, G.; Greco, D.; Zanardi, F. *Angew. Chem. Int. Ed.* **2015**, *54*, 7386.

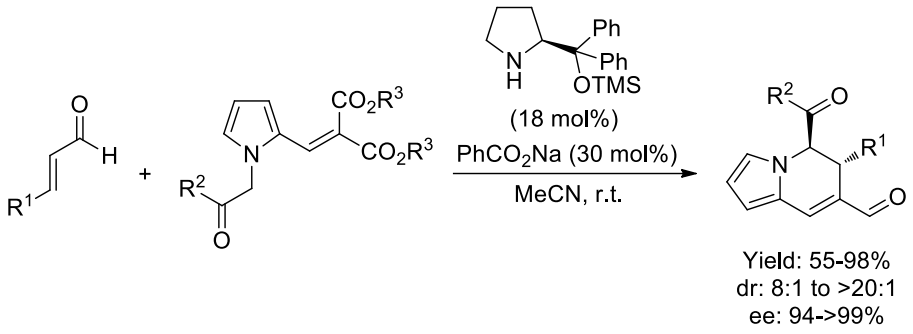
the previous example, but after the vinylogous double Michael addition, a retro-Michael reaction occurs, releasing the malononitrile unit. In this case, L-prolinol TMS-ether and triethylamine were used as the catalytic system, affording polycyclic carbaldehydes in good yields and excellent diastereo- and enantioselectivities (Scheme 2.21).



Scheme 2.21

Finally, a pioneering example of a Michael/Michael/retro-Michael cascade reaction proceeding through initial iminium ion formation, reported by Barbas III and co-workers should also be presented,[38] which consists on the enantioselective synthesis of 5,6-dihydroindolizines, by the reaction between α,β-unsaturated aldehydes, as acceptor/donor substrates, and *N*-protected dialkyl 2-((1*H*-pyrrol-2-yl)methylene) malonates as donor/acceptor compounds, in which the α-position of a pyrrole enolate would act as an electron-donor intermediate. Excellent results were obtained related to the yield and the stereocontrol (Scheme 2.22).

[38] Jiang, X.; Tan, B.; Barbas III, C. F. *Angew. Chem. Int. Ed.* **2013**, *52*, 9261.



Scheme 2.22

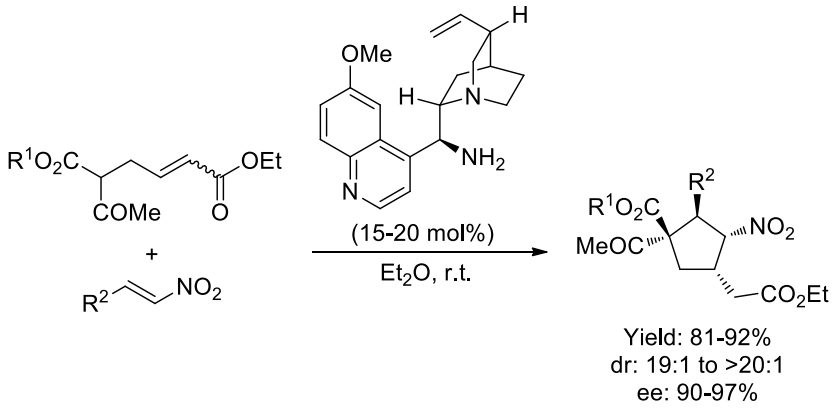
1.1.3. Michael/Michael cascade processes activated by H-bond catalysis

Hydrogen bond catalysis has been satisfactorily applied to the development of asymmetric double Michael cascade reactions, activating the substrates by the formation of networks of hydrogen bonds between catalyst and substrates, and being able to modulate the chiral space around the reaction point. The fact that catalyst-substrate interactions are weak in nature entails the possibility that, once the initial conjugate addition step that initiates the cascade process has taken place, the catalyst might not be involved in the second step, this one proceeding exclusively through substrate control. In some other examples, this is not the case and the catalyst remains bonded to all the reaction intermediates that participate in the cascade reaction therefore exerting its stereochemical influence across the whole process.

One illustrative example of Michael/Michael cascade reactions under this type of activation manifold is the reported by Zhong and co-workers showing the synthesis of enantioenriched polysubstituted cyclopentanes.[39] Several nitroalkenes were employed as the initial Michael acceptors and 5-acetylhex-2-enedioate

[39] Tan, B.; Shi, Z.; Chua, P. J.; Zhong, G. *Org. Lett.* **2008**, *10*, 3425.

derivatives as the functionalized donor, using a cinchona-based primary amine as hydrogen bonding catalyst (shown on Scheme 2.23). Later, a similar unsaturated ester with an enolizable malonate was employed together with a selected nitroolefin in the construction of the tetracyclic core of lycorine-type alkaloids.[40]



Scheme 2.23

In 2012, Cobb and co-workers reported the application of bifunctional thiourea derivatives to the enantioselective Michael/Michael cascade reaction of several nitroalkenes to 6-nitrohex-2-enoates, towards the synthesis of tetrasubstituted cyclohexanes in good yields and excellent stereocontrol (Scheme 2.24).[41]

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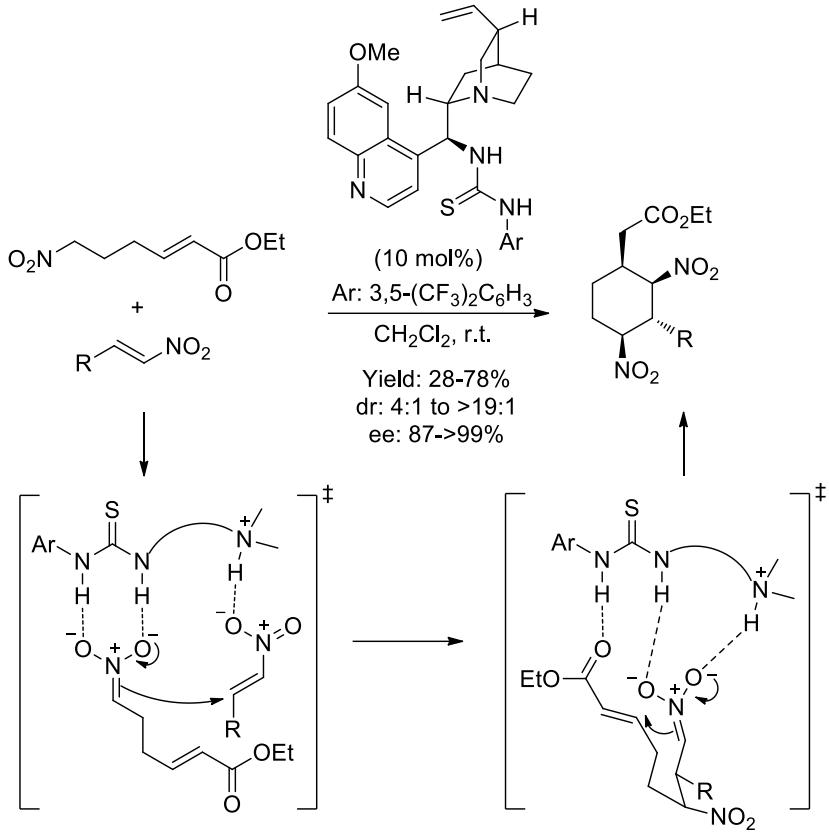
[40] Wang, Y.; Luo, Y.-C.; Zhang, H.-B.; Xu, P.-F. *Org. Biomol. Chem.* **2012**, *10*, 8211.

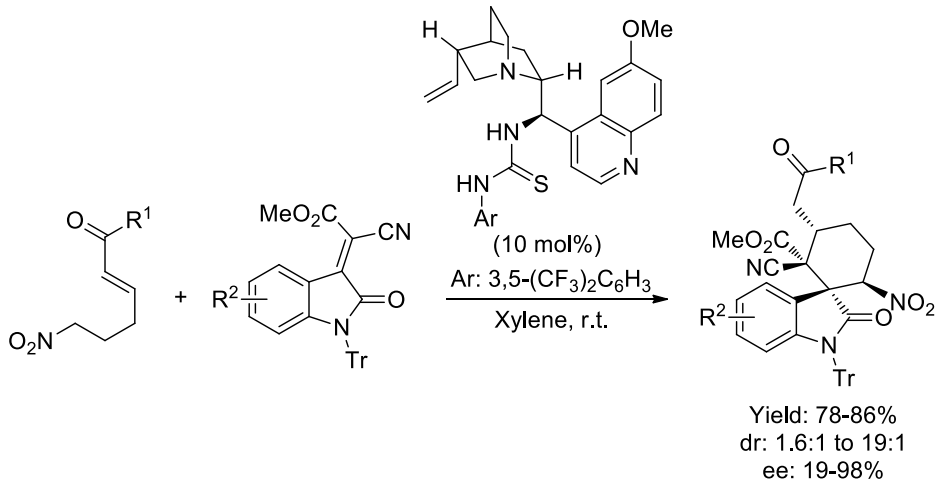
[41] a) Rajkumar, S.; Shankland, K.; Brown, G. D.; Cobb, A. J. A. *Chem. Sci.* **2012**, *3*, 584; for a pioneering work, see: b) Nodes, W. J.; Nutt, D. R.; Chippindale, A. M.; Cobb, A. J. A. *J. Am. Chem. Soc.* **2009**, *131*, 16016.



Scheme 2.24

This methodology has also been applied to the preparation of spirocyclic compounds, as shown across a large number of publications. In general, all these approaches make use of methyleneindolinones or related compounds as the initial Michael acceptors, in combination with a suitable functionalized pronucleophile incorporating the second Michael acceptor moiety. As representative example, Scheme 2.25 shows the synthesis of spirooxindole derivatives with four adjacent stereocenters including two contiguous quaternary stereogenic centers, in high

yields and moderate to excellent stereoselectivities, employing 6-nitrohex-2-en-1-ones as the initial donor and quinidine-derived thiourea as catalyst.[42]



Scheme 2.25

On the other hand, there is another example, in which oxindoles, incorporating a substituent that contained an activated double bond in 3-position, were used as the initial Michael donors, and in this case making use of the higher reactivity of nitroolefins as the initial acceptors. Spirocyclopentaneoxindoles were obtained in excellent yields, diastereo- and enantioselectivities, under the optimal conditions, employing a bifunctional thiourea catalyst bearing central and axial chiral elements, developed by the same group (Scheme 2.26).[43]

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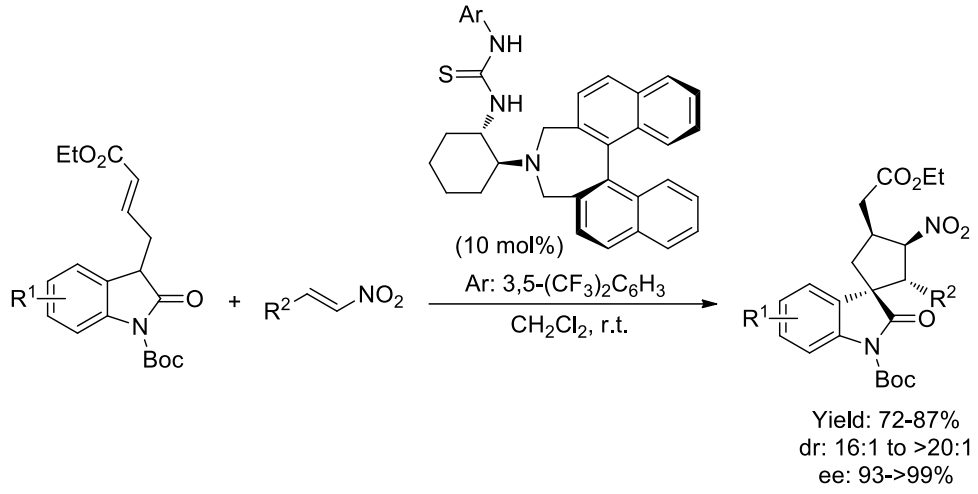
[42] a) Abbaraju, S.; Ramireddy, N.; Rana, N. K.; Arman, H.; Zhao, J. C.-G. *Adv. Synth. Catal.* **2015**, *357*, 2633; for related examples, see: b) Zhou, M.-Q.; Zuo, J.; Cui, B.-D.; Zhao, J.-Q.; You, Y.; Bai, M.; Chen, Y.-Z.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2014**, *70*, 5787; c) Wei, Q.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 1008.

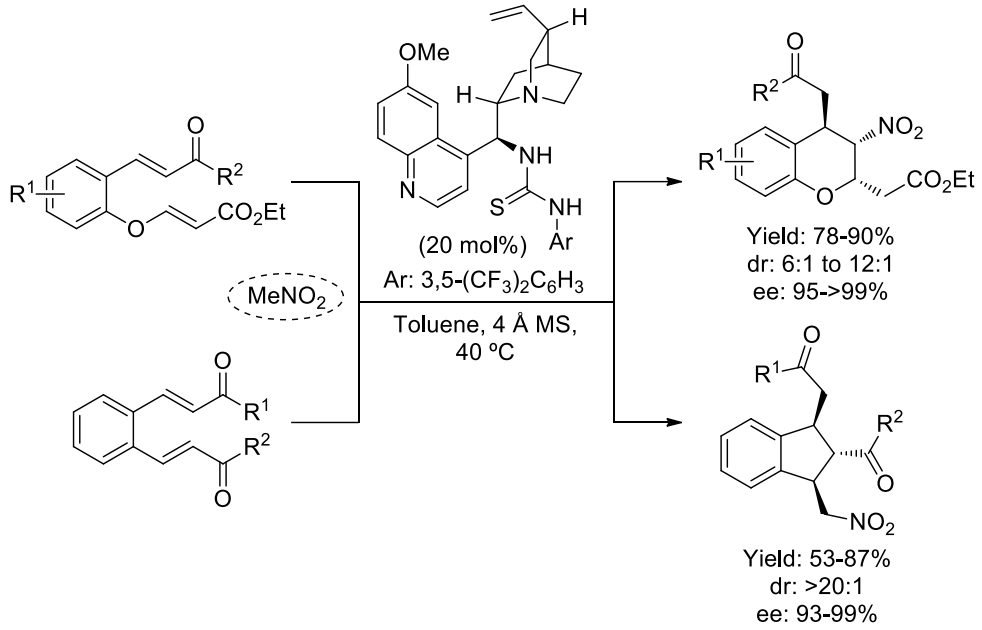
[43] a) Li, Y.-M.; Li, X.; Peng, F.-Z.; Li, Z.-Q.; Wu, S.-T.; Sun, Z.-W.; Zhang, H.-B.; Shao, Z.-H. *Org. Lett.* **2011**, *13*, 6200; for a related example, see: b) Sun, W.; Hong, L.; Zhu, G.; Wang, Z.; Wei, X.; Ni, J.; Wang, R. *Org. Lett.* **2014**, *16*, 544.



Scheme 2.26

In a different point of view, Gu and co-workers employed nitromethane as double nucleophile and chalcone derivatives as double Michael acceptors, with the obtention of polysubstituted chromans in high yields and enantioselectivities, using the hydroquinine-based thiourea as catalyst (see Scheme 2.27).[44] In contrast, by the use of *o*-divinylbenzenes, as double Michael acceptors, instead of previous chalcones, Wang *et al.* have been able to control the regioselectivity after the first Michael addition of nitromethane, towards the product obtained by the nucleophilic attack of the resulting enolate. Under the optimal conditions, aryl substituents were well tolerated, obtaining enantioenriched trisubstituted indanes as single diastereoisomers (see Scheme 2.27).[45]

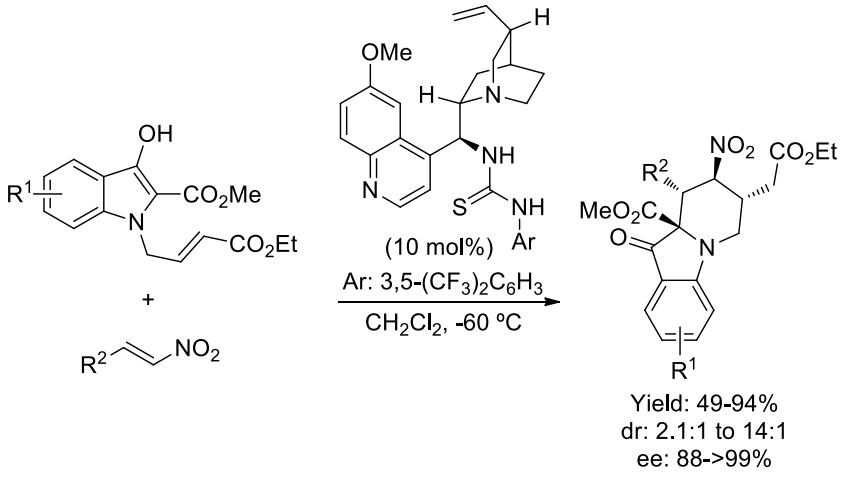
[44] Jia, Z.-X.; Luo, Y.-C.; Cheng, X.-N.; Xu, P.-F.; Gu, Y.-C. *J. Org. Chem.* **2013**, *78*, 6488.
[45] Li, N.; Liu, G.-G.; Chen, J.; Pan, F.-F.; Wu, B.; Wang, X.-W. *Eur. J. Org. Chem.* **2014**, 2677.



Scheme 2.27

Finally, the use of indolin-3-one derivatives in Michael/Michael cascade reactions catalyzed by cinchona-based bifunctional thiourea has been recently reported. This reaction involves the initial Michael reaction of the starting material through the C-2 carbon of the indole moiety with nitroalkenes under catalyst activation, which is followed by the intramolecular Michael reaction. This methodology shows up as an excellent approach to enantioenriched *N*-fused piperidinoindolines furnishing good yields, moderate diastereoselectivities and excellent enantioselectivities (Scheme 2.28).[46]

[46] Zhao, Y.-L.; Wang, Y.; Cao, J.; Liang, Y.-M.; Xu, P.-F. *Org. Lett.* **2014**, *16*, 2438.



Scheme 2.28

In summary, across these introductory pages it has been clearly stablished the important progress made in the development of catalytic enantioselective Michael/Michael cascade reactions through the application of different organocatalytic activation manifolds. Moreover, the usefulness of this type of reactions has been fully demonstrated through the synthesis of substituted cyclic compounds with different degrees of complexity. However, and in spite of all the publications in this field, the development of new asymmetric double Michael cascade reactions towards the novel synthesis of enantioenriched carbo- and heterocyclic rings with different functionalities still remains necessary, due to the importance of this type of molecules as building blocks towards the preparation of interesting target compounds.

2. SPECIFIC OBJECTIVES AND WORK PLAN

Taking into account the revised literature, and despite the large number of examples reported that involve organocatalytic enantioselective Michael/Michael cascade reactions, we considered that the development of new polyfunctional reagents that can participate as Michael donor-acceptor compounds able to react intermolecularly with a second Michael acceptor under organocatalytic conditions is still a field of great interest. In particular, with a focus on the development of new reagents that incorporate additional reactive motifs that could be used as the starting point for the synthesis of more complex molecules.

In this sense, we have focused our attention in alkenyl sulfamidate imines such as the general structure depicted in Figure 2.2, as suitable polyfunctional reagents to develop a Michael/Michael cascade process. During the last decade, cyclic sulfamidate imines, in particular, five-membered ring heterocycles, such as 5*H*-1,2,3-oxathiazole 2,2-dioxides, have received much attention due to their versatility as reagents in organic synthesis.

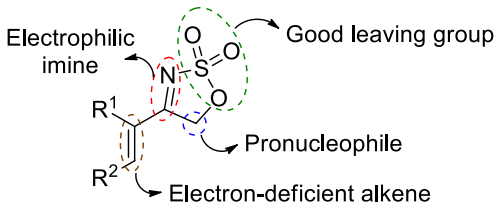


Figure 2.2

A remarkable feature of this particular type of reagents is the presence of an imine moiety activated by the electron-withdrawing sulfonyl group, whose

reactivity has been widely studied in 1,2-additions[47] and hydrogenations.[48] Moreover, in most of these works the obtained cyclic sulfamidates have been used as building blocks towards the synthesis of a wide variety of compounds, taking advantage of the presence of the sulfonate as good leaving group. In particular, and related to the use of this type of compounds in the field of organocatalysis, there is one example, in which the imine acts as a heterodienophile in an enantioselective [4+2] cycloaddition.[49] In this work, He and co-workers employed six-membered cyclic sulfamidate imines as heterodienophiles and *in situ* generated dienes *via* enamine activation of enones, therefore using a chiral primary amine as catalyst (Scheme 2.29). Several disubstituted piperidin-4-ones were obtained in good yields with high stereocontrol.

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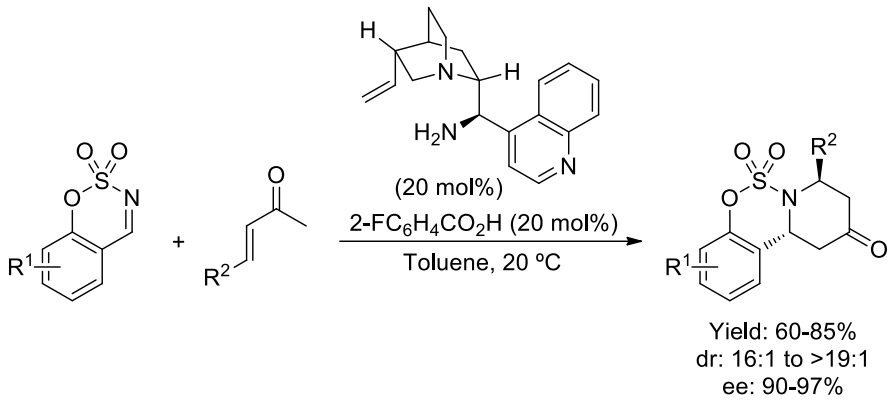
47 a) Kong, J.; McLaughlin, M.; Belyk, K.; Mondschein, R. *Org. Lett.* **2015**, *17*, 5520; b) Chen, Y.-J.; Chen, Y.-H.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.* **2014**, *16*, 3400; c) Nishimura, T.; Ebe, Y.; Fujimoto, H.; Hayashi, T. *Chem. Commun.* **2013**, *49*, 5504; d) Luo, Y.; Hepburn, H. B.; Chotsaeng, N.; Lam, H. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 8309; e) Chang, S.; Lee, E. E. *Synthesis* **2010**, 2361; f) Zhu, B.-H.; Zheng, J.-C.; Yu, C.-B.; Sun, X.-L.; Zhou, Y.-G.; Shen, Q.; Tang, Y. *Org. Lett.* **2010**, *12*, 504.

48 a) Seo, Y. J.; Kim, J.; Lee, H.-K. *J. Org. Chem.* **2015**, *80*, 8887; b) Kim, J.; Seo, Y. J.; Kang, S.; Han, J.; Lee, H.-K. *Chem. Commun.* **2014**, *50*, 13706; c) Lee, H.-K.; Kang, S.; Choi, E. B. *J. Org. Chem.* **2012**, *77*, 5454; d) Han, J.; Kang, S.; Lee, H.-K. *Chem. Commun.* **2011**, *47*, 4004; e) Lee, S. A.; Kwak, S. H.; Lee, K.-I. *Chem. Commun.* **2011**, *47*, 2372; f) Kang, S.; Han, J.; Lee, E. S.; Choi, E. B.; Lee, H.-K. *Org. Lett.* **2010**, *12*, 4184; g) Wang, Y.-Q.; Yu, C.-B.; Wang, D.-W.; Wang, X.-B.; Zhou, Y.-G. *Org. Lett.* **2008**, *10*, 2071.

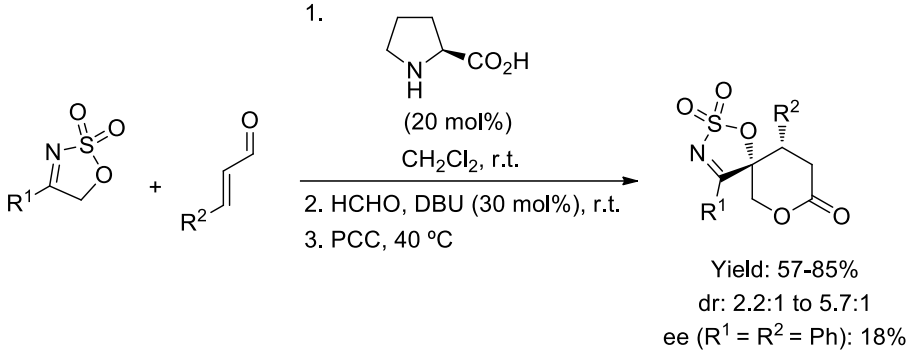
49 Liu, Y.; Kang, T.-R.; Liu, Q.-Z.; Chen, L.-M.; Wang, Y.-C.; Liu, J.; Xie, Y.-M.; Yang, J.-L.; He, L. *Org. Lett.* **2013**, *15*, 6090.



Scheme 2.29

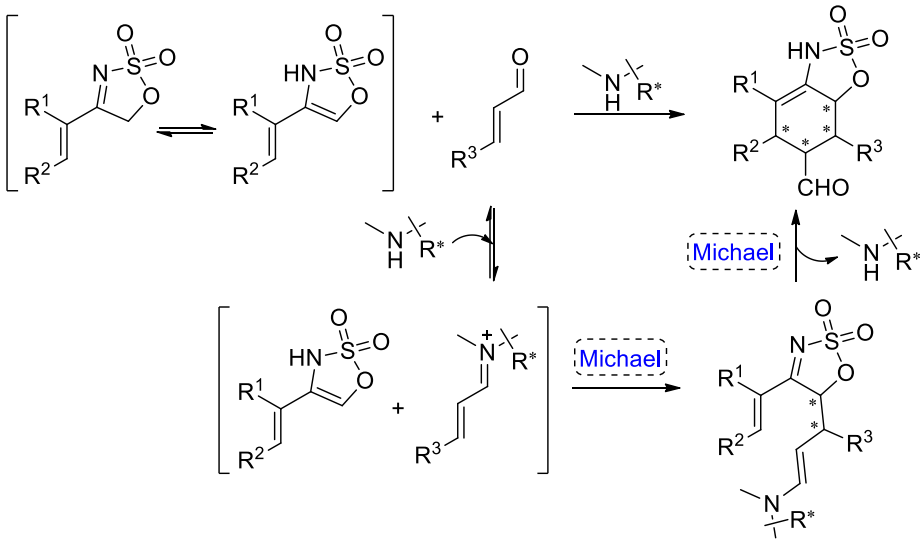
In contrast, there are few examples in the literature describing the potential reactivity of the pronucleophilic point located at the 5-position of this type of sulfamidate imines (see Figure 2.2). In one recent example, Samanta and co-workers have developed a Michael/aldol/hemiacetalization sequence carried out in a one-pot manner, in which the use of 4-aryl-5*H*-1,2,3-oxathiazole 2,2-dioxides as double nucleophiles is described, employing α,β-unsaturated aldehydes and formaldehyde as electrophiles. Several spiro-sulfamidate imine fused δ-lactone derivatives were obtained, after *in situ* oxidation of the corresponding lactols, in good yields, with moderate to good diastereoselectivities but with poor enantiocontrol in general (Scheme 2.30),[50] although it should be noted that in one single case an excellent enantioselectivity with moderate diastereoselectivity was achieved, using *O*-TMS diphenyl prolinol as catalyst at 4 ºC.

[50] a) Majee, D.; Biswas, S.; Mobin, S. M.; Samanta, S. *Tetrahedron Lett.* **2014**, *55*, 4553; for a related example, see: b) Majee, D.; Srivastava, A.; Mobin, S. M.; Samanta, S. *RSC Advances* **2013**, *3*, 11502.



Scheme 2.30

Taking into account that this type of five-membered cyclic sulfamidate imines are relatively unexplored in the chemical literature related to their use as reagents under organocatalytic conditions and knowing the potential activity of this moiety, we initially proposed the use of 4-alkenyl-5*H*-1,2,3-oxathiazole 2,2-dioxides as suitable reagents in organocatalytic Michael/Michael cascade reactions with enals under iminium activation of the latter. Particularly, the presence of acidic protons at the 5-position together with the α,β-unsaturation of the sulfamidate imine would favour the formation of an enamine tautomer that can be consider as a potential nucleophile in an initial intermolecular Michael reaction with an activated α,β-unsaturated aldehyde *via* iminium ion formation with a chiral secondary amine as catalyst, followed by a second 1,4-addition of the generated enamine to the alkenyl sulfamidate imine, resulting in the formation of a polysubstituted cyclohexene after the release of the catalyst through a hydrolysis process (Scheme 2.31).



Scheme 2.31

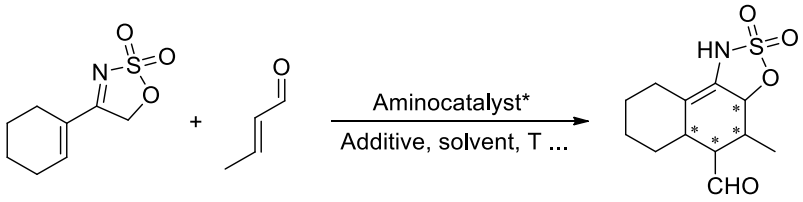
On the other hand, as shown in the Figure 2.2, the presence of a reactive azomethine functionality and a sulfonate group anticipates many different possibilities for carrying out further chemical manipulations on the structure of the enantioenriched adducts obtained initially. For this reason, we established as the second objective of the present work, the study of the synthetic versatility of the oxathiazole 2,2-dioxide moiety, in order to obtain molecules of higher complexity.

With the objectives in mind, the following work plan was proposed:

1. Synthesis of the starting materials. Initially, the corresponding 4-alkenyl-5*H*-1,2,3-oxathiazole 2,2-dioxides with different type of substituents in both α- and β-position of the alkene have to be prepared using simple and straightforward methodologies.

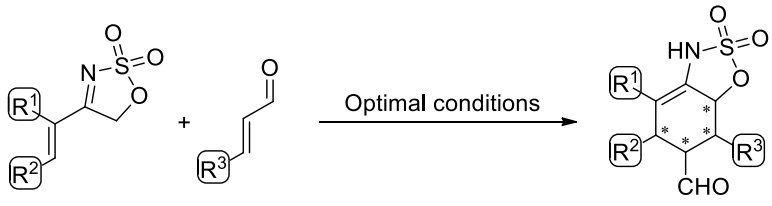
2. Viability of the Michael/Michael cascade reaction. Having prepared the desired α,β-unsaturated cyclic sulfamidate imines, the viability of the Michael/Michael cascade reaction will be surveyed using 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide and (*E*)-crotonaldehyde as model substrates, and a variety of chiral secondary amines as catalysts.

3. Optimization of the reaction conditions. Once the feasibility of the process is demonstrated, different reaction parameters, such as catalyst, additive, solvent and temperature will be optimized, in order to obtain the corresponding decaline derivative in high yield and stereocontrol (Scheme 2.32).



Scheme 2.32

4. Scope of the reaction. Having stablished the best reaction conditions, several cyclic alkenyl sulfamidate imines and different substituted enals will be tested, in order to obtain a series of chiral cyclohexenes and decaline derivatives (Scheme 2.33). Through these experiments, the scope and limitations of the methodology will be stablished.



Scheme 2.33

5. *Transformation of the cycloadducts.* Several transformations will be explored in order to check the potential applications of the prepared compounds containing the sulfamidate moiety as chiral building blocks.

3. RESULTS AND DISCUSSION

Considering all the examples found in the literature about the organocatalytic Michael/Michael cascade reactions, and having proposed the different objectives and work plan, we will present and discuss the results achieved on this part of the research work.

3.1. Organocatalytic Michael/Michael cascade reaction

3.1.1. Synthesis of the starting materials

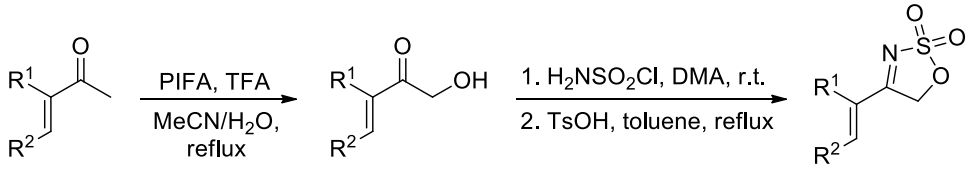
A stated previously, we started with the synthesis of non commercially available 4-alkenyl-5*H*-1,2,3-oxathiazole 2,2-dioxides. In this sense, the desired five-membered cyclic sulfamidate imines were prepared through a two step route, starting from the corresponding alkenyl methyl ketones **1**. These are commercially available or can be easily prepared through literature procedures.[51] The synthesis started with the α-hydroxylation of these starting ketones **1** under acidic conditions using [bis(trifluoroacetoxy)iodo]benzene (PIFA) as the stoichiometric oxidant, following a known procedure.[52] With α-hydroxy ketones **2** in hands, the synthesis continued with the formation of the cyclic sulfamidate imines **3** through sulfonylation of the primary alcohol with sulfamoyl chloride in DMA as solvent, followed by acid-catalyzed intramolecular condensation.[48c] Sulfamoyl chloride has to be prepared from commercially available chlorosulfonyl isocyanate by reaction with formic acid. Thus, a series of α,β-unsaturated sulfamidate imines were prepared in moderate overall yields, including several examples that

[51] a) de Paula, B. R. S.; Zampieri, D. S.; Rodrigues, J. A. R.; Moran, P. J. S. *Tetrahedron: Asymmetry* **2013**, *24*, 973; b) Austin, W. F.; Zhang, Y.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3905.

[52] Moriarty, R. M.; Berglund, B. A.; Penmasta, R. *Tetrahedron Lett.* **1992**, *33*, 6065.

incorporated both aliphatic and aromatic substituents at the terminal carbon atom of the alkenyl substituent (Table 2.1).

Table 2.1: Synthesis of 4-alkenyl-5*H*-1,2,3-oxathiazole 2,2-dioxides **3**.



1 **2** **3**

Entry	R^1	R^2	3	Yield 2 (%)	Yield 3 (%)
1	$-(CH_2)_4-$		**3a**	46	77
2	$-(CH_2)_3-$		**3b**	-	7[a]
3	Me	Me	**3c**	28	56
4	Me	Et	**3d**	24	69
5	Me	Ph	**3e**	40	66

[a] The yield of product **3b** was calculated over the two reactions, without isolating the corresponding α-hydroxy ketone.

It should be pointed out that after selective n.O.e. NMR experiments conducted on cyclic sulfamidate imines **3c** and **3e**, we concluded that the acyclic alkenes presented *E*-configuration, as confirmed by the existence of a strong n.O.e. between H^1 and the protons of the CH_2, and no n.O.e. between the protons of the CH_2 and the protons of the methyl group (Figure 2.3).

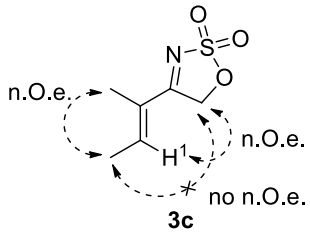


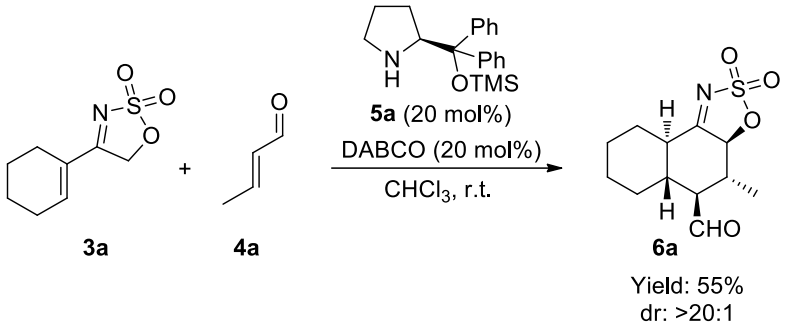
Figure 2.3

3.1.2. Viability of the Michael/Michael cascade reaction

Once the desired α,β-unsaturated cyclic sulfamidate imines **3** have been synthesized, we started the study of the proyected organocatalytic Michael/Michael cascade process, evaluating the viability of the reaction. In this sense, the reaction between 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3a** and (*E*)-crotonaldehyde **4a** was used as a representative model system at room temperature, in the presence of chiral secondary amine **5a** as catalyst using $CHCl_3$ as solvent. Amine **5a** has been recognized as a privileged chiral organocatalyst to activate enals under iminium/enamine manifold in cascade processes.[53] The reaction did not lead to any product when it was carried out under these conditions and similarly, no product formation was observed when benzoic acid was incorporated as cocatalyst which is known to favour the formation of iminium ions. Satisfactorily, when a Brønsted base such as DABCO (20 mol%) was used as cocatalyst, the decaline derivative **6a** was isolated, as a result of a final enamine/imine tautomerization step, in 55% yield and as a single diastereoisomer, as determined by ^{1}H-NMR analysis of the non-purified reaction

[53] a) Meninno, S.; Lattanzi, A. *Chem. Commun.* **2013**, *49*, 3821; b) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248; c) Xu, L.-W.; Li, L.; Shi, Z.-H. *Adv. Synth. Catal.* **2010**, *352*, 243; d) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922; e) Palomo, C.; Mielgo, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 7876.

mixture, and obtaining full conversion of the cyclic sulfamidate imine **3a** after 24 hours at room temperature (Scheme 2.34). It should be pointed out that the reaction did not take place without the presence of the catalyst **5a**, when DABCO was used as the only catalytic system.



Scheme 2.34

The incorporation of a Brønsted base as additive was found to be completely necessary for the success of the reaction, presumably because it contributes to the formation of a nucleophilic species through deprotonation of substrate **3a** that next undergoes the Michael/Michael cascade reaction. At this point, and with the objective to determine the enantiomeric excess of **6a**, a racemic standard was required, which was easily prepared by carrying out the reaction in the presence of an equimolar mixture of the (*R*) and (*S*) enantiomers of the catalyst **5a**, under the reaction conditions shown on Scheme 2.34. The obtained racemic cycloadduct **(±)-6a** was subjected to HPLC analysis on a chiral stationary phase, achieving the separation of the enantiomers with a Chiralpak IA chiral column and a mixture of 90:10 *n*-hexane/*i*-PrOH as eluent, in a 1.0 mL/min flow. When the chiral cycloadduct **6a**, obtained through the (*S*)-**5a** catalyzed reaction, was subjected to HPLC analysis using these conditions, an excellent 92% ee was observed. The obtained chromatograms are depicted in Figure 2.4.

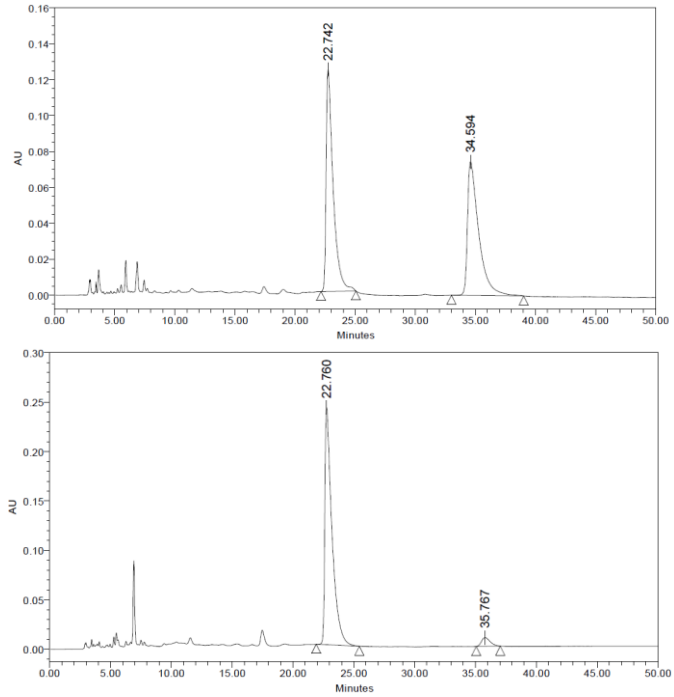


Figure 2.4

Moreover, cycloadduct **6a** was isolated as a yellow solid that could be recrystallized, obtaining suitable crystals for performing X-ray analysis and therefore being able to determine at this point the absolute stereostructure of the adduct obtained in the Michael/Michael cascade process. The structure of **6a**, depicted in Figure 2.5, showed a 3a*S*,4*R*,5*S*,5a*R*,9a*R* configuration, which also entails the preferential formation of the decaline framework in a *trans* configuration.

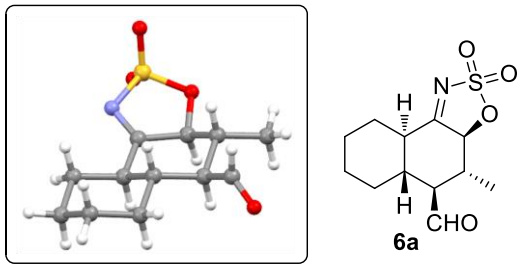
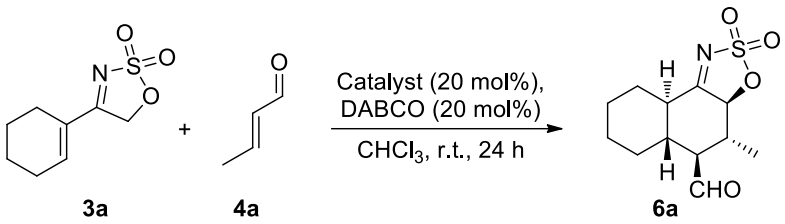


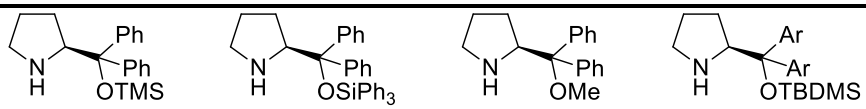
Figure 2.5

3.1.3. Optimization of the reaction conditions

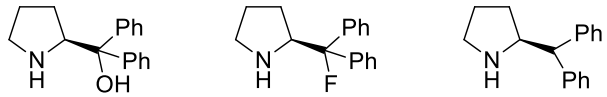
Having demonstrated the ability of the prepared sulfamidate imine **3a** to act as Michael donor-acceptor in the projected double Michael cascade reaction with enals under iminium activation and after the excellent result obtained in the experiment shown on Scheme 2.34 regarding the stereoselectivity, we proceeded to study the reaction conditions, in order to specifically improve the yield of the reaction without affecting the stereocontrol. Initially, we surveyed a series of secondary amine catalysts (20 mol%), using DABCO (20 mol%) as cocatalyst in $CHCl_3$ at room temperature (Table 2.2).

Table 2.2: Screening of reaction conditions: Secondary amine catalyst.[a]





5a	**5b**[e]	**5c**	**5d**[e]
Yield: 55%[b]	Yield: 47%	Yield: 50%	Yield: n.r.[f]
dr: >20:1[c]	dr: >20:1	dr: >20:1	dr: n.d.[g]
ee: 92%[d]	ee: 95%	ee: 93%	ee: n.d.[g]



5e	**5f**	**5g**
Yield: n.r.[f]	Yield: <5%	Yield: 51%
dr: n.d.[g]	dr: n.d.[g]	dr: >20:1
ee: n.d.[g]	ee: n.d.[g]	ee: 66%

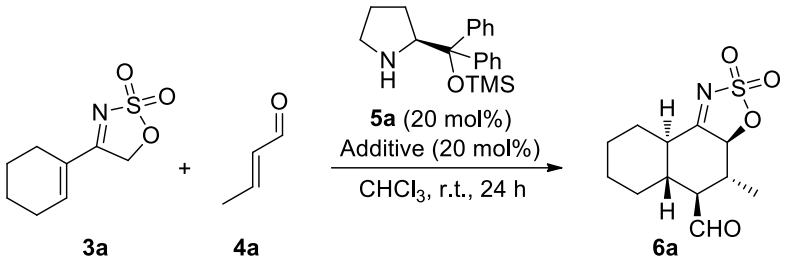
[a] The reaction was performed in 0.15 mL of $CHCl_3$ and 0.15 mmol scale of **3a**, using 1.5 equiv. of **4a**. [b] Isolated product yield after flash column chromatography. [c] Diastereomeric ratios determined by ^{1}H-NMR analysis of non purified reaction mixtures. [d] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **6a**. [e] The reaction was carried out for 48 hours. [f] No reaction. [g] Not determined.

After analyzing these results, it can be observed that changing the nature of the *O*-substituent of the diphenyl prolinol archetypical catalyst to the bulkier triphenylsilyl group or the smaller methyl group (catalysts **5b** and **5c**) led to similar results compared with the initial catalyst **5a**, observing a slower reaction in the case of catalyst **5b**. On the other hand, when a catalyst with higher steric

hindrance (catalyst **5d**) was employed, the formation of the product was not observed, and the same happened when catalysts with stereo-directing groups were used, such as the simple diphenylprolinol **5e**. The use of its derivative **5f** resulted in a very low conversion. Finally, catalyst **5g** maintained the activity but the stereochemical control was significantly poorer, concluding that the secondary amine **5a** initially used in our first experiment was the best catalyst for the reaction. It should be noted that in all cases only one diastereoisomer was observed.

Because of the relevance of the Brønsted base in the reaction, we continued with the screening of other possible bases as cocatalysts, trying both with organic and inorganic Brønsted bases. As it can be observed in Table 2.3, the use of other organic bases (entries 2-5) did not improve the result obtained with DABCO (entry 1). On the other hand, no product was detected when an inorganic base such as Na_2CO_3 (entry 6) was used.

Table 2.3: Screening of reaction conditions: Brønsted base additive.[a]

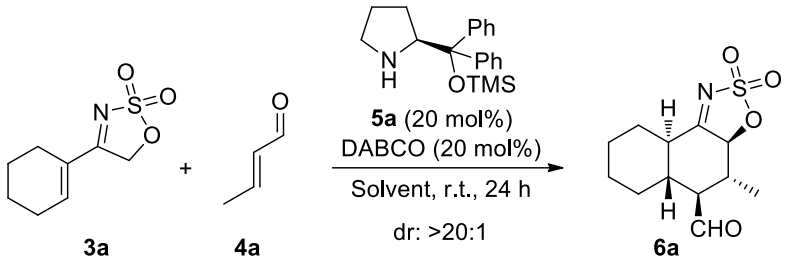


Entry	Additive	Yield (%)[b]	dr[c]	ee (%)[d]
1	DABCO	55	>20:1	92
2	DBU	24	>20:1	90
3	Et_3N	34	>20:1	91
4	DMAP	45	>20:1	91
5	Pyridine	n.d.[e]	n.d.[e]	n.d.[e]
6	Na_2CO_3	n.r.[f]	n.d.[e]	n.d.[e]

[a] The reaction was performed in 0.15 mL of $CHCl_3$ and 0.15 mmol scale of **3a**, using 1.5 equiv. of **4a**. [b] Isolated product yield after flash column chromatography. [c] Diastereomeric ratios determined by ^{1}H-NMR analysis of non purified reaction mixtures. [d] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **6a**. [e] Not determined. [f] No reaction.

Having demonstrated that DABCO was the best additive for the reaction, we proceeded to carry out the cascade process using different solvents in order to study the influence of this parameter in the reaction (Table 2.4). The use of other halogenated solvents, such as CH_2Cl_2 and 1,2-dichloroethane, did not provide better results than the obtained with $CHCl_3$ (entries 2-3 *vs*. entry 1). When other solvents with different polarities and properties were used (entries 4-7), the yield of the reaction was adversely affected, even though the stereoselectivity was not harmed.

Table 2.4: Screening of reaction conditions: Solvent.[a]



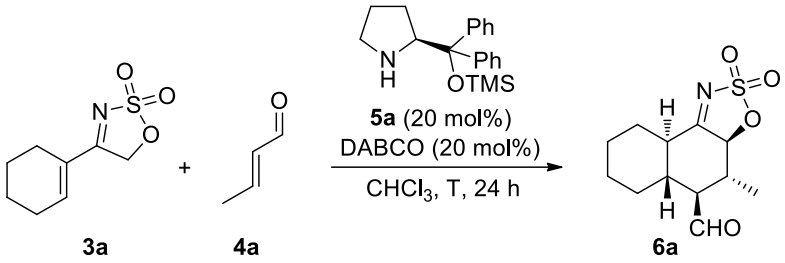
Entry	Solvent	Yield (%)[b]	ee (%)[c]
1	$CHCl_3$	55	92
2	CH_2Cl_2	49	94
3	DCE	51	92
4	THF	33	93
5	Et_2O	20	93
6	*i*-PrOH	16	96
7	Toluene	30	92

[a] The reaction was performed in 0.15 mL of solvent and 0.15 mmol scale of **3a**, using 1.5 equiv. of **4a**. [b] Isolated product yield after flash column chromatography. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **6a**.

With the previous results in hands, we next considered to evaluate the effect of the temperature (Table 2.5). In this sense, we initially tried with a higher temperature, observing that the reaction performed poorly, isolating cycloadduct **6a** in a lower yield (entry 2). On the other hand, at lower temperatures the reaction was found to be cleaner, obtaining a 60% yield and 96% ee at -30 ºC, although requiring for a longer reaction time (entry 4). When the reaction was carried out at an even lower temperature (-50 ºC), only trace amounts of product **6a** were detected by ^{1}H-NMR analysis of the crude reaction mixture after 48 hours (entry 5). Taking -30 ºC as the best temperature, we next decided to change the dilution of the reaction. From these experiments, we concluded that reducing the

concentration to the half, the yield was slightly increased (entry 6). Moreover, when the reaction was carried out under an inert atmosphere and using dry $CHCl_3$ as solvent, we were able to isolate the decaline derivative **6a** in 66% yield (entry 7).

Table 2.5: Screening of reaction conditions: Temperature.[a]



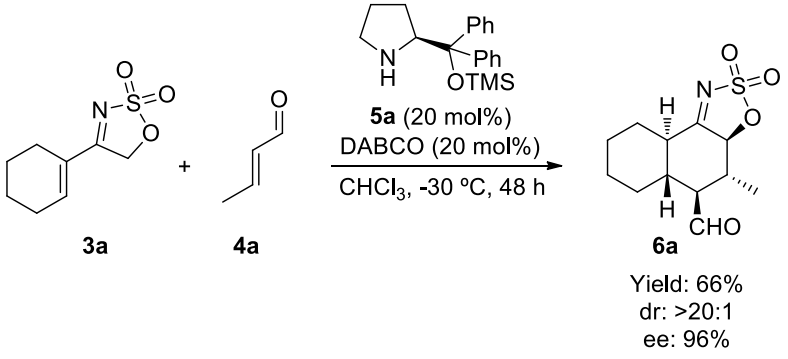
3a **4a** **6a**

Entry	T (ºC)	Yield (%)[b]	dr[c]	ee (%)[d]
1	r.t.	55	>20:1	92
2	50	45	>20:1	90
3	4	56	>20:1	92
4[e]	-30	60	>20:1	96
5[e]	-50	<5	n.d.[f]	n.d.[f]
6[e,g]	-30	62	>20:1	95
7[e,g,h]	-30	66	>20:1	96

[a] The reaction was performed in 0.15 mL of $CHCl_3$ and 0.15 mmol scale of **3a**, using 1.5 equiv. of **4a**. [b] Isolated product yield after flash column chromatography. [c] Diastereomeric ratios determined by ^{1}H-NMR analysis of non purified reaction mixtures. [d] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **6a**. [e] The reaction was carried out for 48 hours. [f] Not determined. [g] The reaction was performed in 0.30 mL of $CHCl_3$ and 0.15 mmol scale of **3a**. [h] Dry $CHCl_3$ was used under inert atmosphere.

Taking into account all the results obtained after the evaluation of the different reaction parameters, we concluded that the best conditions for the Michael/Michael cascade reaction between 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-

oxathiazole 2,2-dioxide **3a** and (*E*)-crotonaldehyde **4a** were those shown in the entry 7 of the Table 2.5, that involved a 20 mol% of **5a** as catalyst with 20 mol% of DABCO as cocatalyst in dry $CHCl_3$ under inert atmosphere at -30 ºC for 48 hours (Scheme 2.35).

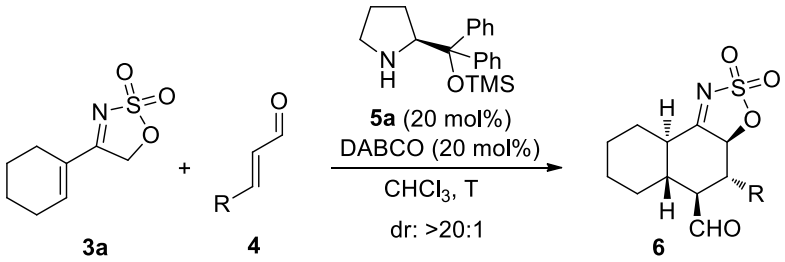


Scheme 2.35

3.1.4 Scope of the reaction

Having established the optimal reaction conditions, we proceeded to investigate the performance of other α,β-unsaturated aldehydes and cyclic sulfamidate imines containing different substitution patterns, in order to study the scope and limitations of the reaction. Continuing with the previously used imine **3a**, the reaction was tested using enals with different β-alkyl substituents. As it can be appreciated in the Table 2.6, using the (*E*)-hex-2-enal **4c** under the optimized conditions, good results were obtained but requiring long reaction times, comparing with the result achieved with the less bulkier (*E*)-crotonaldehyde **4a** (entry 2 *vs*. entry 1). In order to improve the reaction rate, the reaction was carried out increasing the amount of aldehyde **4c**, without obtaining any improvement (entry 3). At this point, we decided to carry out the reaction at room temperature, observing very good results regarding the rate, the yield and the stereoselectivity of the process using 2 equiv. of the corresponding aldehyde (entry 5).

Table 2.6: Evaluation of the bulkier (*E*)-hex-2-enal **4c** in the reaction with the imine **3a**.[a]

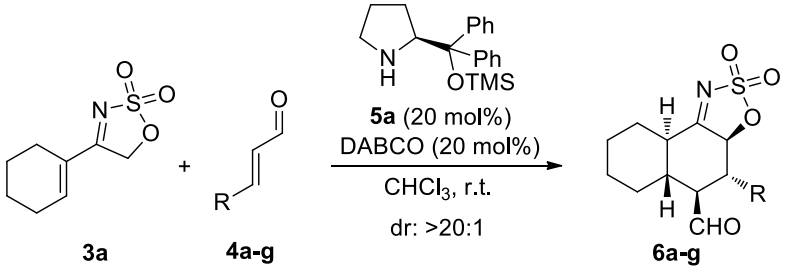


Entry	R (4)	3a:4 (equiv.)	T (ºC)	Time (h)	Yield (%)[b]	ee (%)[c]
1	Me (**4a**)	1:1.5	-30	48	66	96
2	*n*-Pr (**4c**)	1:1.5	-30	192	67	97
3	*n*-Pr (**4c**)	1:2	-30	192	73	97
4	*n*-Pr (**4c**)	1:1.5	r.t.	72	67	94
5	*n*-Pr (**4c**)	1:2	r.t.	60	71	96

[a] The reaction was performed in 0.30 mL of dry $CHCl_3$ and 0.15 mmol scale of **3a**. [b] Isolated product yield after flash column chromatography. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **6**.

With the conditions shown in the entry 5 of the Table 2.6, other β-alkyl substituted enals **4** were tested, using the sulfamidate imine **3a**. As it can be seen in Table 2.7, the reaction proceeded in a satisfactory way in all of the cases, obtaining a series of decaline derivatives **6a-g** with five contiguous stereocenters, in good yields, excellent enantioselectivities and as single diastereoisomers. It should be pointed out that the size of the β-alkyl chain did not considerably affect the yield nor the stereoselectivity of the reaction, and the inclusion of β-ramified alkyl chains was also well tolerated (entries 2-7). Finally, we studied the possibility to carry out the reaction on larger scale, observing similar yield and enantioselectivity when 0.5 g of **3a** was used in the reaction with enal **4c** as a model substrate (entry 3 *vs*. entry 8).

Table 2.7: Scope of the reaction using sulfamidate imine **3a** and β-alkyl substituted enals.[a]



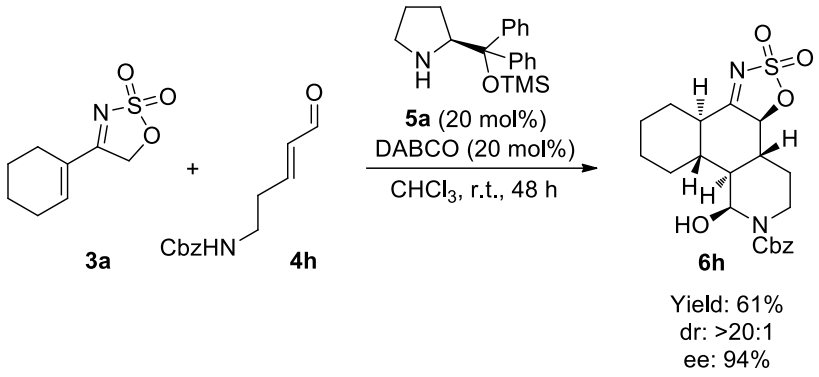
3a **4a-g** **6a-g**

Entry	R (4)	6	Time (h)	Yield (%)[b]	ee (%)[c]
1[d]	Me (**4a**)	**6a**	48	66	96
2	Et (**4b**)	**6b**	60	66	95
3	*n*-Pr (**4c**)	**6c**	60	71	96
4	*n*-Bu (**4d**)	**6d**	72	67	95
5	*i*-Bu (**4e**)	**6e**	60	65	97
6	*n*-C_5H_{11} (**4f**)	**6f**	72	61	95
7	*n*-C_6H_{13} (**4g**)	**6g**	72	57	95
8[e]	*n*-Pr (**4c**)	**6c**	60	67	95

[a] The reaction was performed in 0.30 mL of dry $CHCl_3$ and 0.15 mmol scale of **3a**, using 2 equiv. of **4**. [b] Isolated product yield after flash column chromatography. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **6**. [d] The reaction was carried out at -30 ºC using 1.5 equiv. of **4a**. [e] Reaction performed on a 0.5 g scale of **3a**.

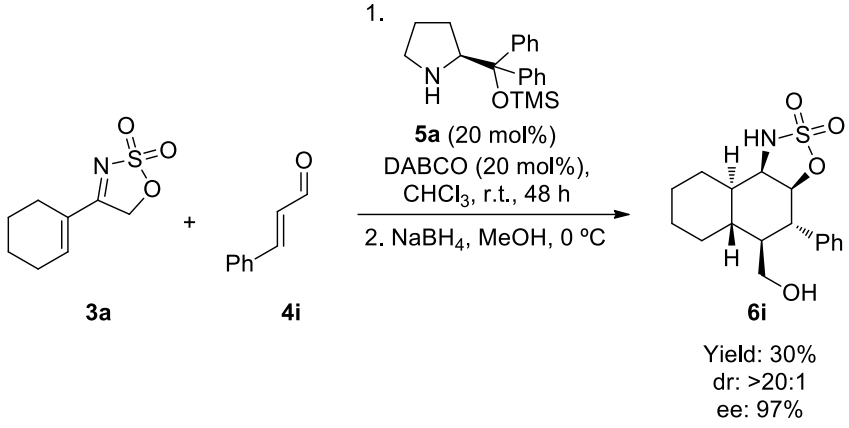
On the other hand, we also evaluated the use of functionalized α,β-unsaturated δ-aminoaldehyde **4h** as the initial Michael acceptor, to demonstrate the functional group compatibility of the developed methodology. Under the optimal conditions shown in the entry 5 of the Table 2.6, the Michael/Michael cascade reaction was followed by the intramolecular attack of the protected amine to the formyl group, affording the corresponding hemiaminal **6h** in good yield and excellent enantioselectivity (Scheme 2.36). Moreover, after the formation of six stereogenic centers, only one diastereoisomer was detected by ^{1}H-NMR analysis,

forming only the anomer, with a large preference for the axial orientation, confirmed by n.O.e. experiments.



Scheme 2.36

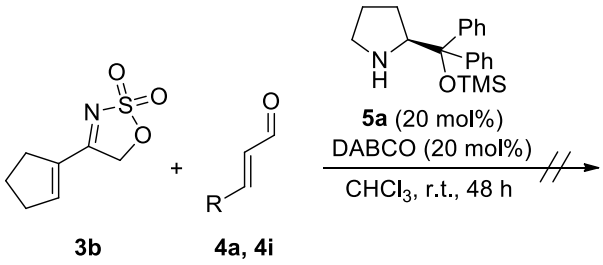
At this point, and continuing with the use of the cyclic sulfamidate imine **3a**, we decided to extend the reaction to different β-aryl substituted α,β-unsaturated aldehydes, observing the formation of considerable secondary products, that disfavoured the obtention of the desired product, which we were unable to purify. For this reason, we decided to reduce *in situ* both the formyl and the azomethine moieties after the Michael/Michael cascade operation, in order to be capable of purifying the corresponding decaline. In this sense, using (*E*)-cinnamaldehyde **4i** as a representative enal, we isolated the cyclic sulfamidate **6i**, after extensive reduction with $NaBH_4$ in MeOH at 0 ºC, in high enantioselectivity and as a single diastereoisomer, but in poor yield (Scheme 2.37).



Scheme 2.37

In order to improve these results, we tested the reaction at lower temperature with the aim of minimizing the formation of byproducts, only observing poorer yield.

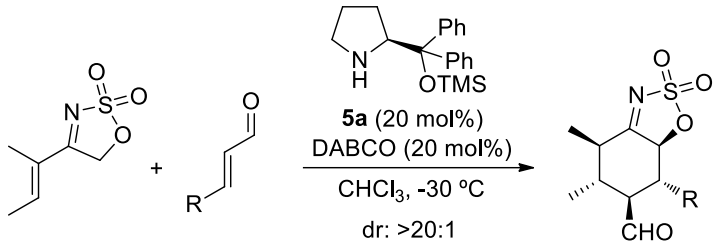
We next surveyed the performance of the sulfamidate imine **3b**, with the purpose of obtaining octahydro-1*H*-indene derivatives. After several experiments, both with β-alkyl and β-aryl substituted enals, only a complex mixture of compounds was observed, not detecting any characteristic signal of a possible cyclization product by ^{1}H-NMR analysis (Scheme 2.38).



Scheme 2.38

On the other hand, we continued with the scope of the reaction using the more conformationally flexible sulfamidate imine **3c**. Interestingly, in this case the reaction took place satisfactorily with a variety of β-aryl substituted α,β-unsaturated aldehydes under the optimized conditions shown in the entry 7 of the Table 2.5, carrying out the reaction at low temperature. As shown in Table 2.8, the resulting polysubstituted cyclohexanes **7a-k** were obtained in very good yields and excellent enantioselectivities using (*E*)-cinnamaldehyde **4i** (entry 1) and other β-aryl substituted enals, both with electron-donating (entry 2 and entries 4-6) and electron-withdrawing (entries 7-8 and 10-12) substituents at the aryl ring. In contrast, no reaction was detected with enals incorporating *ortho*-substituted aryl substituents (entries 3 and 9), observing only a complex mixture of products. Unfortunately, the same reaction with (*E*)-crotonaldehyde **4a** yielded the cyclohexane **7k** in poor yield, albeit with excellent stereocontrol (entry 13). With β-alkyl substituted enals containing longer alkyl chains, very low conversions were observed, not being able to improve these results using higher temperatures. In all cases only one diastereoisomer was detected, but it should be noted that in some of these cases (entries 2 and 10) it was necessary to leave the reaction at room temperature during four hours after full conversion, to achieve total diastereocontrol towards the formation of thermodynamically more stable product.

Table 2.8: Scope of the reaction using sulfamidate imine **3c** and different enals.[a]



3c **4** **7a-k**

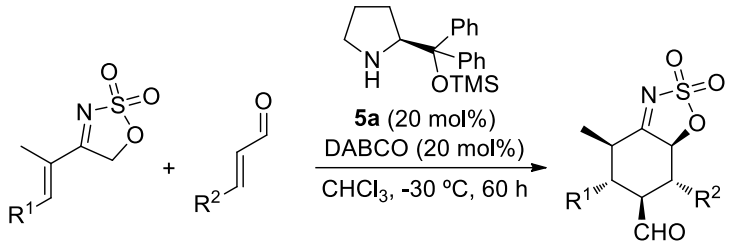
Entry	R (4)	7	Time (h)	Yield (%)[b]	ee (%)[c]
1	Ph (**4i**)	**7a**	60	66	98
2[d]	4-MeC_6H_4 (**4j**)	**7b**	60	59	>99
3	2-$MeOC_6H_4$ (**4k**)	-	48	n.r.[e]	n.d.[f]
4	4-$MeOC_6H_4$ (**4l**)	**7c**	48	65	>99
5	4-AcO-3-$MeOC_6H_3$ (**4m**)	**7d**	48	72	>99
6	3,5-$(MeO)_2C_6H_3$ (**4n**)	**7e**	60	71	99
7	4-ClC_6H_4 (**4o**)	**7f**	60	65	98
8	4-BrC_6H_4 (**4p**)	**7g**	60	67	96
9	2-$NO_2C_6H_4$ (**4q**)	-	48	n.r.[e]	n.d.[f]
10[d]	4-$NO_2C_6H_4$ (**4r**)	**7h**	60	73	96
11	4-CNC_6H_4 (**4s**)	**7i**	48	73	98
12	4-$CF_3C_6H_4$ (**4t**)	**7j**	60	67	98
13	Me (**4a**)	**7k**	48	36	91

[a] The reaction was performed in 0.30 mL of dry $CHCl_3$ and 0.15 mmol scale of **3c**, using 1.5 equiv. of **4**. [b] Isolated product yield after flash column chromatography. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **7**. [d] Full diastereocontrol was achieved leaving stirring the reaction during four hours at room temperature after full conversion. [e] No reaction. [f] Not determined.

With these results in hand, we next decided to extend the reaction to other related α,β-unsaturated sulfamidate imines, such as **3d** incorporating longer alkyl

chains at the β-position, and also surveyed the possibility to use substrate **3e** that incorporates a phenyl group at this position (Table 2.9). With sulfamidate imine **3d** similar results of those obtained before with sulfamidate imine **3c** were observed, achieving good yields and excellent stereoselectivities (entries 1-5). It should be highlighted that in some of these cases the presence of a minor diastereisomer was detected by ^{1}H-NMR analysis, even after stirring the reaction at room temperature after full conversion in order to facilitate the interconversion of minor diastereoisomer into the thermodynamically favoured one. We were unable to isolate this minor one but it is likely to be the diastereoisomer with the substituents derived from the alkenyl moiety of the starting sulfamidate imine in *cis* position, due to the equilibrium existing between the last formed enamine and the finally obtained imine in the course of the reaction. In the case of sulfamidate imine **3e**, the reactions took place with poorer yields, but excellent results were obtained concerning the stereoselectivity (entries 6, 8 and 9). The observed low yields can be attributed to the lower electrophilicity of the α,β-unsaturated sulfamidate imine **3e**, due to the extended conjugation of the unsaturated system with the aromatic ring. In fact, when enals incorporating electron-rich β-aryl substituents were tested, we did not observe the formation of the corresponding products (entry 7).

Table 2.9: Scope of the reaction using sulfamidate imines **3d** and **3e**, and different enals.[a]



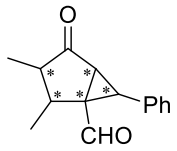
3d-e **4** **7l-s**

Entry	R^1 (3)	R^2 (4)	7	Yield (%)[b]	dr[c]	ee (%)[d]
1	Et (**3d**)	Ph (**4i**)	**7l**	57	>20:1	96
2	Et (**3d**)	4-$MeOC_6H_4$ (**4l**)	**7m**	66	10:1	99
3	Et (**3d**)	3,5-$(MeO)_2C_6H_3$ (**4n**)	**7n**	61	8:1	99
4	Et (**3d**)	4-BrC_6H_4 (**4p**)	**7o**	62	8:1	97
5	Et (**3d**)	4-$NO_2C_6H_4$ (**4r**)	**7p**	50	13:1	94
6[e,f]	Ph (**3e**)	Ph (**4i**)	**7q**	30	>20:1	99
7[f]	Ph (**3e**)	4-$MeOC_6H_4$ (**4l**)	**-**	n.r.[g]	n.d.[h]	n.d.[h]
8[f]	Ph (**3e**)	4-BrC_6H_4 (**4p**)	**7r**	26	>20:1	>99
9[f]	Ph (**3e**)	4-$NO_2C_6H_4$ (**4r**)	**7s**	35	>20:1	98

[a] The reaction was performed in 0.30 mL of dry $CHCl_3$ and 0.15 mmol scale of **3d**, using 1.5 equiv. of **4**. [b] Isolated product yield after flash column chromatography. [c] Diastereomeric ratios determined by ^{1}H-NMR analysis of non purified reaction mixtures. [d] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **7**. [e] The reaction carried out for 84 hours. [f] The reaction was performed in 0.40 mL of dry $CHCl_3$ and 0.20 mmol scale of **3e**, using 2 equiv. of **4**. [g] No reaction. [h] Not determined.

It is noteworthy that during all these experiments, and in particular when sulfamidate imines incorporating an acyclic alkene **3c-e** in combination with β-aryl substituted enals were used, the formation of an additional byproduct in small amounts was observed. In the reaction between sulfamidate imine **3c** and (*E*)-cinnamaldehyde **4i**, we were able to isolate and characterize this product (**8a**) in

<10% yield, corresponding to a possible Michael/Michael cascade reaction, followed by a transannular nucleophilic substitution/imine hydrolysis sequence (Figure 2.6). This compound was isolated as a single diastereoisomer. This interesting finding prompted us to study in detail this new reactivity that constitute an efficient approach to the synthesis of bicycle[3.1.0]hexane scaffolds. This chemistry will be described later on within this chapter.



8a

Figure 2.6

Continuing with the cycloaddition reaction, we had previously confirmed the absolute configuration of the decaline derivative **6a** by X-ray analysis, also demonstrating the formation of the *trans*-decaline framework, which is more stable than the corresponding *cis* stereoisomer. The fact that a possible equilibration between *cis*/*trans* isomers could take place in some cases did not allow to extend this configuration to the cyclohexanes **7** based on mechanistic analogy. However, we were able to confirm that the cyclohexane **7a** had all the substituents in the same orientation than the decaline derivative **6a**, through single crystal X-ray analysis (see Figure 2.7), showing a 4*R*,5*R*,6*S*,7*S*,7a*S* absolute configuration, which could be extended to the cycloadducts **6** and **7** by analogy with full reliability.

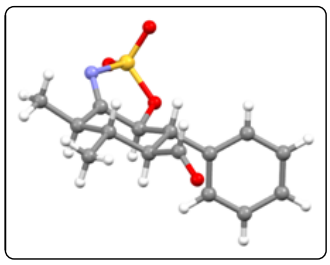
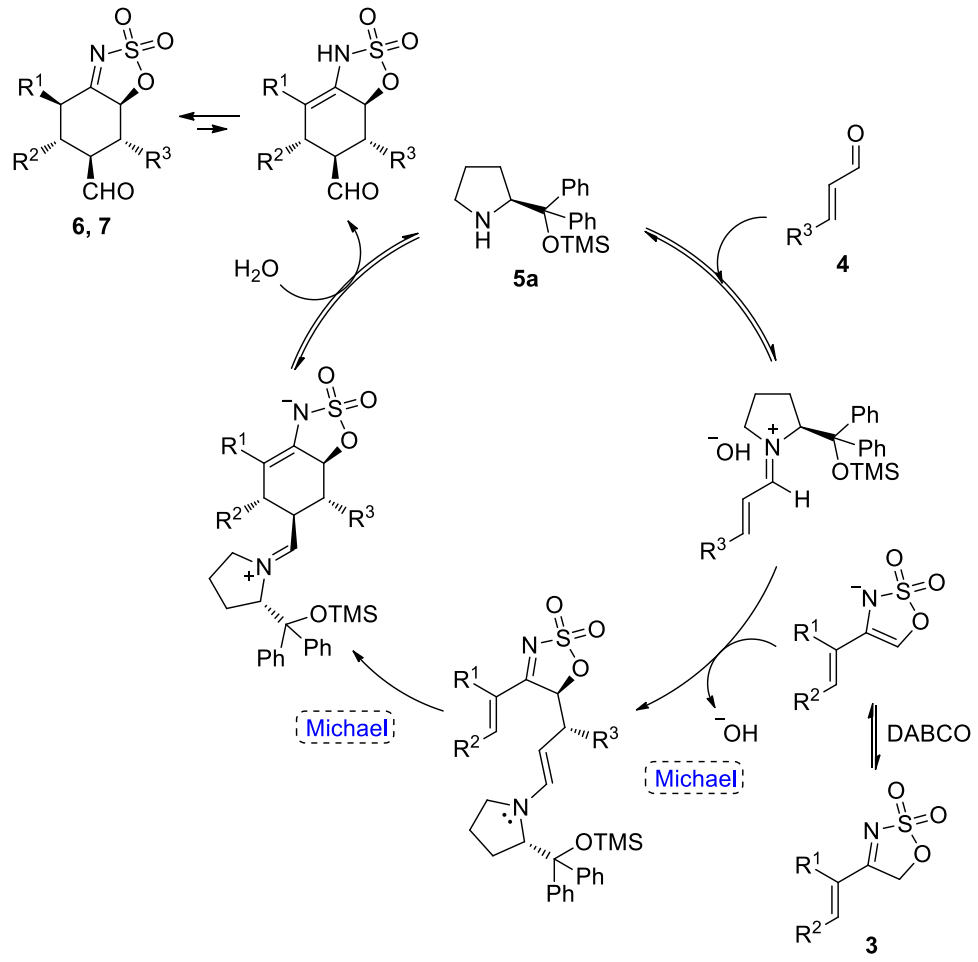


Figure 2.7

A plausible mechanism for this transformation is proposed in Scheme 2.39. Taking into account the absolute configuration of the obtained cycloadducts, we propose a stepwise mechanism that consists on an aminocatalytic Michael/Michael cascade reaction under iminium/enamine manifold. Initially, the iminium ion is formed by condensation between the aldehyde and the aminocatalyst, decreasing the energy of its LUMO, which is followed by the Michael addition of the active nucleophile, generated from the activation of the sulfamidate imine by DABCO, to the iminium ion through its less hindered *Re* face. After the first Michael reaction, in which the first two stereogenic centers are generated, the (*E*)-enamine intermediate is formed, which is able to undergo a second Michael addition to the α,β-unsaturated sulfamidate imine through its less hindered face, forming two new stereocenters in *anti*-relative arrangement. Finally, the catalyst is released by hydrolysis, followed by imine/enamine tautomerization towards the obtention of the final adduct **6** and **7**. It should be noted that in this equilibrium a new stereogenic center is generated, being presumably controlled by thermodynamic issues, leading to the most stable diastereoisomer with all substituents in equatorial positions.



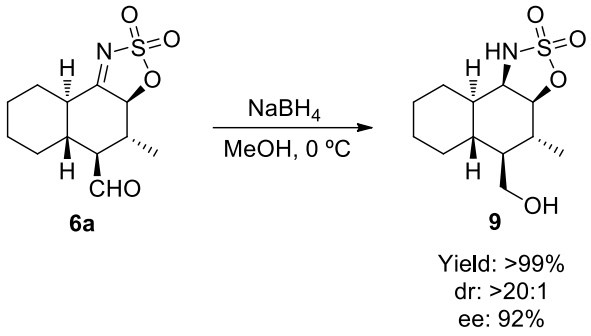
Scheme 2.39

3.1.5 Transformation of the cycloadducts

Having stablished a good protocol for the Michael/Michael cascade reaction, which allows the synthesis of a wide variety of enantioenriched

polysubstituted cyclohexanes and decaline derivatives, we proceeded to exploit the reactivity of the sulfamidate imine scaffold.

Initially, using the cycloadduct **6a** as a model substrate, we decided to obtain the corresponding sulfamidate by the reduction of the imine group. The treatment with the conditions previously used in the Scheme 2.37, *i.e.* $NaBH_4$ in MeOH at 0 ºC, afforded the corresponding sulfamidate **9** and also reducing the formyl group, in excellent yield, as a single diastereoisomer and keeping the enantiopurity of the starting material (Scheme 2.40).

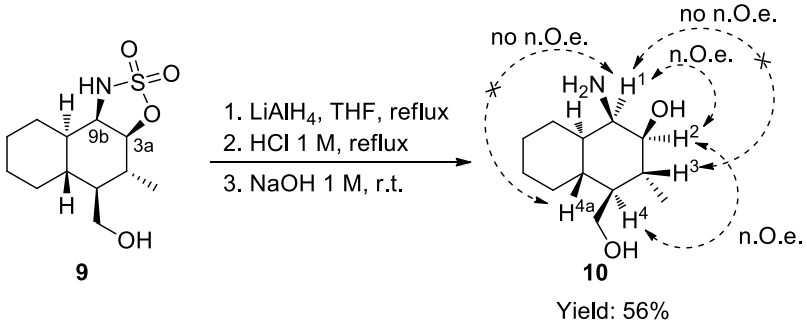


Scheme 2.40

The cyclic sulfamidates are synthetically interesting compounds due to their applicability to the preparation of different products with heteroatomic functional groups, through regiospecific ring-opening reactions with several nucleophiles.[54] One of the most useful transformations is the synthesis of β-amino alcohols, which are a common moiety found in natural and synthetic products. Chiral 1,2-amino alcohols can be used as building blocks for the preparation of a wide range of

[54] For some reviews on the reactivity of cyclic sulfamidates, see: a) Megía-Fernández, A.; Morales-Sanfrutos, J.; Hernández-Mateo, F.; Santoyo-González, F. *Curr. Org. Chem.* **2011**, *15*, 401; b) Bower, J. F.; Rujirawanich, J.; Gallagher, T. *Org. Biomol. Chem.* **2010**, *8*, 1505; c) Meléndez, R. E.; Lubell, W. D. *Tetrahedron* **2003**, *59*, 2581.

biologically active natural and unnatural compounds or as chiral auxiliaries, catalyst or ligands.[55] For this reason, we decided to prepare the vicinal amino alcohol from the corresponding cyclic sulfamidate, following a well-known procedure.[48c] Thus, the reduction of the sulfamidate **9** with $LiAlH_4$, followed by hydrolytic treatment, afforded the β-amino alcohol **10** with retention of stereochemistry at C-3a and C-9b in good yield and without any epimerization of the stereocenters initially generated during the cascade process (Scheme 2.41). The *cis*-relation between the amino and hydroxy group was confirmed by NMR experiments, due to the presence of n.O.e. between H^1 and H^2, and the absence of n.O.e. between H^1 and H^3, and between H^1 and H^{4a}.



Scheme 2.41

[55] For some reviews, see: a) Weng, C.; Zhang, H.; Xiong, X.; Lu, X.; Zhou, Y. *Asian J. Chem.* **2014**, *26*, 3761; b) Karjalainen, O. K.; Koskinen, A. M. P. *Org. Biomol. Chem.* **2012**, *10*, 4311; c) Della Sala, G.; Russo, A.; Lattanzi, A. *Curr. Org. Chem.* **2011**, *15*, 2147; d) de Parrodi, C. A.; Juaristi, E. *Synlett* **2006**, 2699; e) Lee, H.-S.; Kang, S. H. *Synlett*, **2004**, 1673; f) Bergmeier, S. C. *Tetrahedron*, **2000**, *56*, 2561; g) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

3.2. Transannular S_N2 reaction: Synthesis of bicycle[3.1.0]hexanes

After finishing with the previous Michael/Michael cascade reaction we decided to go back to the minor side product **8a** obtained in the reaction between the sulfamidate imine **3c** and (*E*)-cinnamaldehyde **4i** under the conditions shown in the entry 1 of the Table 2.8. This type of polycyclic structures containing a fused cyclopropane moiety is widespreadly found in many natural products.[56] Furthermore, these congested molecules are useful synthetic intermediates in the synthesis of complex compounds[57] due to their rigid structure and high π character. Moreover, the formation of this product would demonstrate the applicability of the studied sulfamidate imines **3**. In view of the potential interest of this reaction we decided to survey the possibility of carrying out a one-pot or cascade sequence involving the initial double Michael cascade reaction followed by a transannular S_N2-type reaction that closes the bicyclic system. In this sense, we initially tried to carry out the transannular nucleophilic substitution/imine hydrolysis sequence using the Michael/Michael cycloadduct **7a** and different bases, such as DABCO, at different temperatures. In all cases the reaction did not take place, observing the decomposition of the substrate under the hardest conditions. At this point, we decided to use an achiral primary amine, such as benzhydrylamine, in order to favour the imine formation by condensation with the hindered aldehyde. The reaction failed, when catalytic amount (20 mol%) of benzhydrylamine was used, observing the formation of the corresponding imine when equimolecular amount of the primary amine was employed at room temperature. After trying at different temperatures, we found that using the

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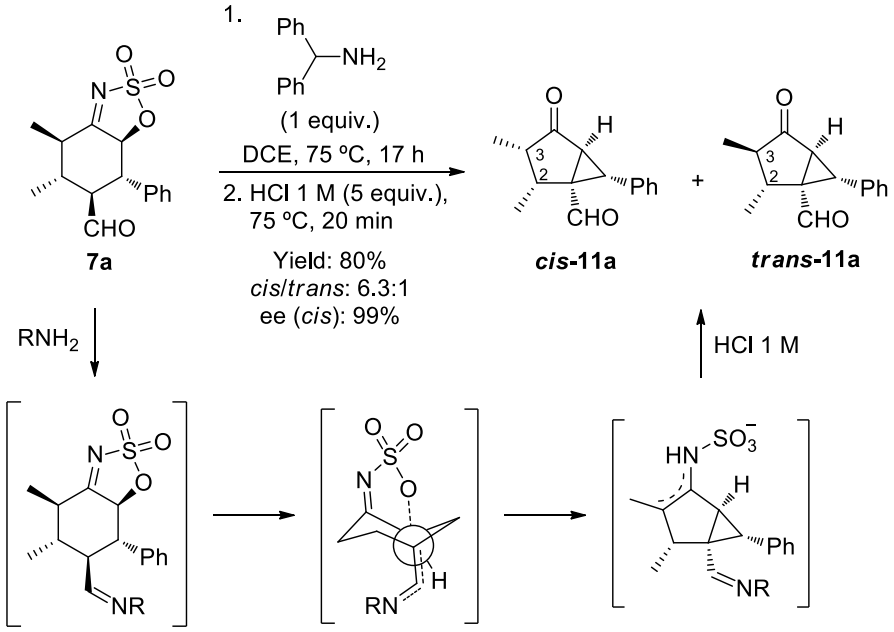
[56] For a selected review, see: Chen, D. Y.-K.; Pouwer, R. H.; Richard, J.-A. *Chem. Soc. Rev.* **2012**, *41*, 4631.

[57] For some reviews, see: a) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804; b) Tang, P.; Qin, Y. *Synthesis*, **2012**, *44*, 2969.

enantioenriched Michael/Michael adduct **7a** with 1 equiv. of benzhydrylamine in DCE at 75 ºC after 17 hours, bicyclic compound **11a** was isolated in 80% yield as a mixture of two diastereoisomers in a 6.3:1 ratio, after hydrolysis of the resulting imines with HCl 1 M at 75 ºC (Scheme 2.42). Interestingly, none of the isolated diastereoisomers of **11a** were the previously found diastereoisomer **8a**.



Scheme 2.42

After n.O.e. experiments performed on both diastereisomers of **11a**, we concluded that the major product was the 2,3-*cis* diastereoisomer and the minor was the 2,3-*trans* one (Figure 2.8). In both diastereoisomers, the presence of n.O.e. was observed between the proton of the aldehyde and the protons of the aromatic ring, and no n.O.e. between the proton of the aldehyde and H^6, showing that the aldehyde, the phenyl group and H^5 were in the same side. In the case of the major diastereoisomer, significant n.O.e. was appreciated between H^6 and H^3, and

between H^6 and H^2, indicating a *cis* configuration of the substituents at C-2 and C-3 (***cis*-11a**). In the minor diastereoisomer, the presence of n.O.e. was observed between H^6 and the protons of the methyl group at C-3, and between H^6 and H^2, indicating a *trans* configuration of the substituents at C-2 and C-3 (***trans*-11a**).

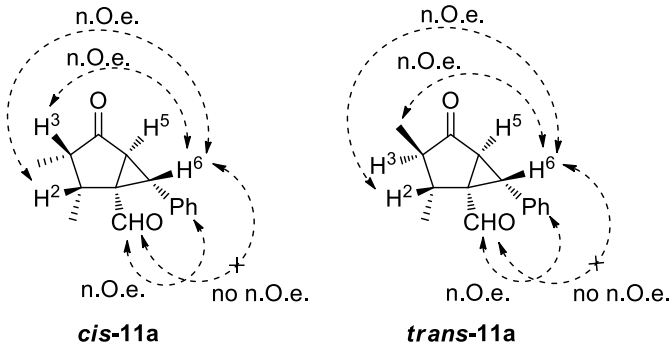


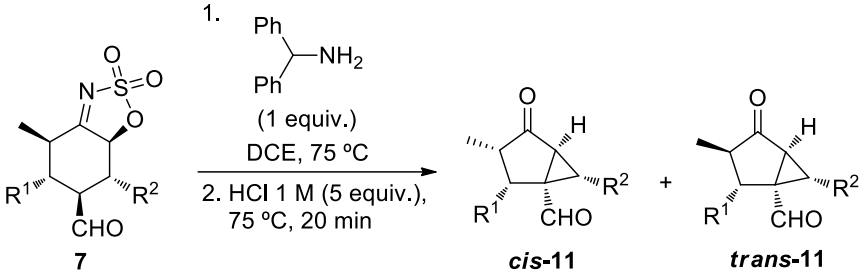
Figure 2.8

It should be noted that the enantiopurity of the major diastereoisomer ***cis*-11a** was verified by HPLC analysis, obtaining 99% ee. The separation conditions were achieved using a racemic standard, prepared from racemic **7a**, consisting on the use of the Chiralpak AS-H chiral column and a mixture of 90:10 *n*-hexane/*i*-PrOH as eluent, in a 1.0 mL/min flow.

Regarding the mechanism for this reaction a plausible proposal is shown on the Scheme 2.42, in which first an imine is proposed to be formed by condensation between the primary amine and the aldehyde, followed by the consequent enamine formation, which would be able to attack intramolecularly to the sulfonate group through an *anti* nucleophilic substitution, forming the bicycle[3.1.0]hexane scaffold, after hydrolysis of the corresponding imines. Due to the presence of an acidic proton at C-3 position, this stereocenter can epimerize to form the most stable diastereoisomer isolated in our case.

With the best conditions in our hands (shown in Scheme 2.42), we proceeded to extend the reaction to other Michael/Michael cycloadducts **7**. As shown in the Table 2.10, when double Michael products with methyl group at R^1 and different substituents in the aromatic ring at R^2 (entries 1-10) were tested, good results were obtained regarding the yield and diastereoselectivity, in most cases, observing the decomposition of the starting material only for compounds **7c** and **7e** (entries 3 and 5). On the other hand, when cycloadducts incorporated bulky groups at R^1, such as ethyl or phenyl group, the reaction performed poorly, observing a complex mixture of products (entries 11-12), only being able to purify the bicyclic compound **11i** in moderate yield and diastereocontrol (entry 13). In general, when cycloadducts with strong electron-withdrawing groups in the aromatic ring at R^2 were used, slower reactions were observed and consequently the products were isolated in moderated yield, due to the decomposition of the starting material (entries 8, 9 and 13). Finally, we tried to carry out the reaction with alkyl substitutents at R^2 of the cycloadduct, such as **6a** and **7k**, only observing the condensation product with the primary amine.

Table 2.10: Transannular nucleophilic substitution/imine hydrolysis sequence of various Michael/Michael cycloadducts **7**.



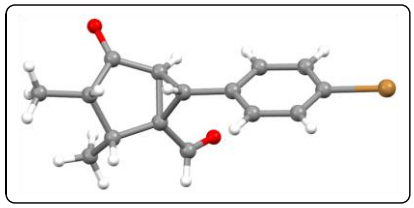
7 ***cis*-11** ***trans*-11**

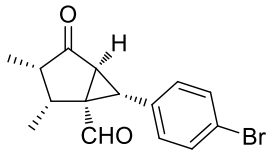
Entry	R^1, R^2 (7)	11	Time (h)	Yield (%)[a]	*cis*:*trans*[b]
1	Me, Ph (**7a**)	**11a**	17	80	6.3:1
2	Me, 4-MeC_6H_4 (**7b**)	**11b**	17	77	6.7:1
3	Me, 4-$MeOC_6H_4$ (**7c**)	-	17	n.d.[c]	n.d.[c]
4	Me, 4-AcO-3-$MeOC_6H_3$ (**7d**)	**11c**	17	71	6.7:1
5	Me, 3,5-$(MeO)_2C_6H_3$ (**7e**)	-	17	n.d.[c]	n.d.[c]
6	Me, 4-ClC_6H_4 (**7f**)	**11d**	17	71	6.1:1
7	Me, 4-BrC_6H_4 (**7g**)	**11e**	17	72	5.9:1
8	Me, 4-$NO_2C_6H_4$ (**7h**)	**11f**	36	51	6.3:1
9	Me, 4-CNC_6H_4 (**7i**)	**11g**	36	58	6.3:1
10	Me, 4-$CF_3C_6H_4$ (**7j**)	**11h**	17	75	6.3:1
11	Et, Ph (**7l**)	-	17	n.d.[c]	n.d.[c]
12	Ph, Ph (**7q**)	-	17	n.d.[c]	n.d.[c]
13	Ph, 4-$NO_2C_6H_4$ (**7s**)	**11i**	36	57	3:1

[a] Combined yield of both diastereoisomers after flash column chromatography. [b] Diastereomeric ratios determined by ^{1}H-NMR analysis of non purified reaction mixtures. [c] Not determined.

Luckily, the compound **11e** was isolated as a yellow solid that could be recrystallized, determining the absolute configuration by single crystal X-ray

analysis, and confirming the configuration previously proposed based on NMR experiments (shown in Figure 2.8). The crystal structure of **11e** is depicted in Figure 2.9 showing an 1*S*,2*R*,3*S*,5*S*,6*R* absolute configuration. The remaining compounds **11** were assigned by mechanistic analogy.



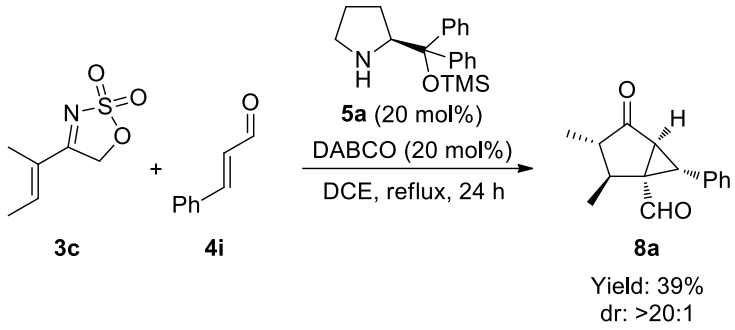


11e

Figure 2.9

Having demonstrated the ability of the Michael/Michael cascade products to undergo the transannular nucleophilic substitution/imine hydrolysis sequence, and knowing that after the double Michael cascade reaction the resulting iminium ion intermediate can tautomerize to form the corresponding enamine, we next decided to try the Michael/Michael/transannular S_N2/imine hydrolysis cascade sequence. In this sense, and based on the previously formation of the bicyclic compound **8a**, we started the study of this reaction using sulfamidate imine **3c** and (*E*)-cinnamaldehyde **4i** as a model substrates, testing first the reaction at different temperatures in the presence of 20 mol% of (*S*)-α,α-diphenylprolinol trimethylsilyl ether **5a** and 20 mol% of DABCO as cocatalyst in 1,2-dichloroethane (DCE) instead of $CHCl_3$, due to its higher boiling point. We observed that at higher temperatures the formation of the bicycle[3.1.0]hexane derivative **8a** was favoured, disfavouring the formation of the Michael/Michael product **7a**. After several experiments, we found that at reflux of DCE, the cycloadduct **7a** was not formed, isolating the bicyclic compound **8a** in 39% yield and as a single

diastereoisomer, as determined by ^{1}H-NMR analysis of the non-purified reaction mixture, obtaining full conversion after 24 hours (Scheme 2.43).



Scheme 2.43

At this stage, we decided to determine the enantiomeric excess of the obtained compound **8a**, in order to evaluate the success of the reaction regarding the stereoselectivity. For this reason, we first proceeded to prepare a racemic standard carrying out the reaction in the presence of an equimolecular mixture of (*R*) and (*S*) enantiomers of the catalyst **5a**. Both enantiomers of **(±)-8a** were separated by HPLC using a Chiralpak AS-H chiral column and a mixture of 90:10 *n*-hexane/*i*-PrOH as eluent, in a 1.0 mL/min flow. Under these conditions, the chiral cycloadduct **8a** was subjected to HPLC analysis, observing an excellent enantiomeric excess of 95% (Figure 2.10).

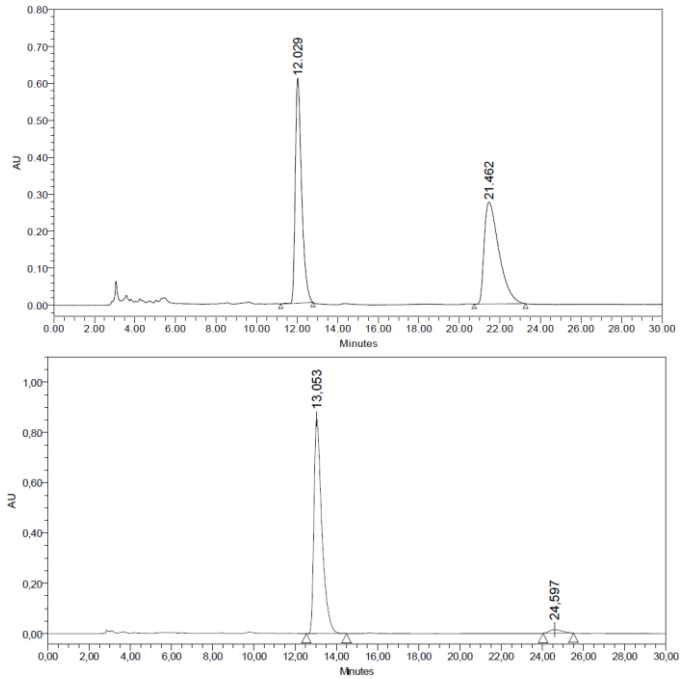
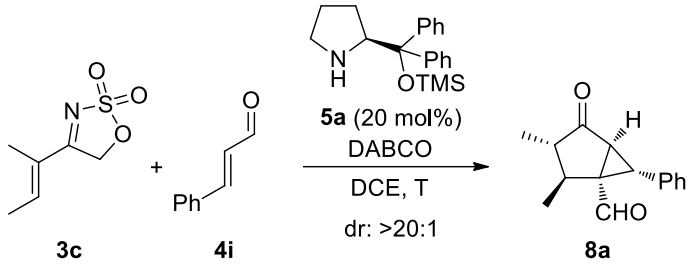


Figure 2.10

We next proceeded to optimize the reaction in order to improve the low yield previously obtained. In this sense, we initially tested the influence of the temperature, the amount of the Brønsted base additive and the ratio between the reagents, using the previous model system, in order to find better reaction conditions for the preparation of the bicyclic compound **8a** (Table 2.11). When the amount of DABCO was increased, reflux conditions were not neccesary to obtain compound **8a** without the formation of **7a**, being able to carry out the reaction at 75 ºC. As it can be observed in entry 3, using 3 equiv. of DABCO led to cycloadduct **8a** in higher yield (53%) after 12 hours, keeping excellent stereoselectivity. These results were not improved using more excess of enal (entry 5). Next, we decided to reduce the temperature maintaining the amount of

additive (entries 6-7), observing lower yields due to the competitive formation of cycloadduct **7a**. Following the reaction by ^{1}H-NMR, using the conditions shown in the entry 3, we could observe that the starting material **3c** was consumed very fast, forming a complex mixture of products, with several signals in the typical range of aldehydes. Stirring the reaction for 12 hours, all the signal evolved to single one showing that a mixture of stereoisomeric intermediates was formed that slowly converted into one single product that after purification showed to be **8a**. The same reaction without aldehyde **4i** resulted in a fast decomposition of the sulfamidate imine **3c**. From these experiments we can conclude that the moderate yield observed initially could be due to the instability of the imine **3c** or of the intermediates formed during the reaction. For this reason, in order to increase the yield, we performed the reaction in two different ways: (1) By adding the substrate **3c** portionwise during 1 hour (entry 8) and (2) with excess of the cyclic sulfamidate imine **3c** (entry 9), not observing better results regarding the yield of the reaction in any of the cases.

Table 2.11: Screening of reaction conditions: Temperature and proportion of additive and reagents.[a]



3c **4i** **8a**

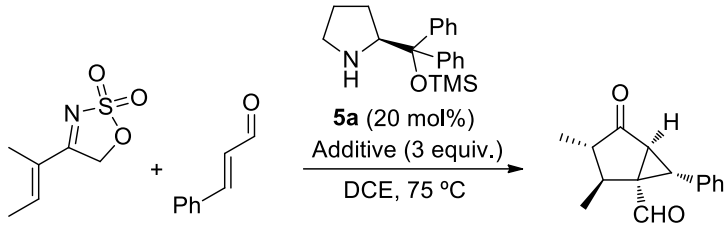
Entry	3c:4i (equiv.)	DABCO (equiv.)	T (ºC)	Yield (%)[b]	ee (%)[c]
1	1:1.5	0.2	reflux	39	95
2	1:1.5	1	75	40	95
3	1:1.5	3	75	53	94
4	1:1.5	5	75	51	94
5	1:3	3	75	53	93
6	1:1.5	3	50	43	95
7	1:1.5	3	r.t.	30	96
8[d]	1:1.5	3	75	43	95
9[e]	1.5:1	3	75	34	n.d.[f]

[a] The reaction was performed in 0.30 mL of DCE and 0.15 mmol scale of **3c**. [b] Isolated product yield after flash column chromatography. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **8a**. [d] Portionwise addition of **3c** during one hour. [e] The reaction was performed in 0.15 mmol scale of **4i**. [f] Not determined.

From these experiments, we concluded that carrying out the reaction at 75 ºC, and using a large amount of the Brønsted base (3 equiv.) were the best conditions to promote the reaction. At this point, we also decided to evaluate the effect of other Brønsted bases in the reaction, in order to favour the formation of the bicyclic compound **8a** (Table 2.12). In all cases poorer results were observed regarding the yield comparing with the obtained with DABCO (entries 2-6 *vs*.

entry 1), not observing any reactivity with DBU and TMP, as hindered bases (entries 2 and 6).

Table 2.12: Screening of reaction conditions: Additive.[a]



3c **4i** **8a**

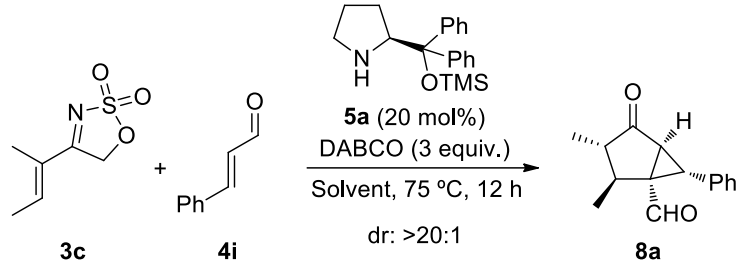
Entry	Additive	Time (h)	Yield (%)[b]	dr[c]	ee (%)[d]
1	DABCO	12	53	>20:1	94
2	DBU	12	n.r.[e]	n.d.[f]	n.d.[f]
3	Et_3N	36	29	>20:1	94
4	DIPEA	36	23	>20:1	96
5	DMAP	36	23	>20:1	94
6	TMP	12	n.r.[e]	n.d.[f]	n.d.[f]

[a] The reaction was performed in 0.30 mL of DCE and 0.15 mmol scale of **3c**, using 1.5 equiv. of **4i**. [b] Isolated product yield after flash column chromatography. [c] Diastereomeric ratios determined by ^{1}H-NMR analysis of non purified reaction mixtures. [d] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **8a**. [e] No reaction. [f] Not determined.

We next evaluated the influence of the solvent in the reaction (Table 2.13). Different polar aprotic solvents were tested, observing that 1,4-dioxane performed in similar terms as DCE (entry 2 *vs*. entry 1), while the use of more polar ones, such as MeCN and DMF (entries 3 and 4), affected negatively the yield of the reaction. We also tried with a polar protic solvent like *i*-PrOH (entry 5), in order to verify if its ability as hydrogen donor was beneficial for the reaction, not observing any improvement. Finally, the use of a less polar solvent, like toluene

(entry 6), did not translate into a better yield. We could also observe that in all solvents tested excellent stereocontrol was observed, obtaining the higher yield with DCE.

Table 2.13: Screening of reaction conditions: Solvent.[a]

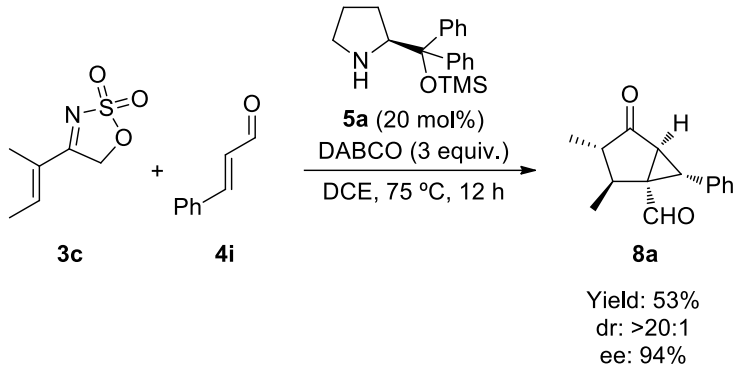


3c **4i** **8a**

Entry	Solvent	Yield (%)[b]	ee (%)[c]
1	DCE	53	94
2	1,4-dioxane	48	92
3	MeCN	35	94
4	DMF	19	92
5	*i*-PrOH	35	93
6	Toluene	42	90

[a] The reaction was performed in 0.30 mL of solvent and 0.15 mmol scale of **3c**, using 1.5 equiv. of **4i**. [b] Isolated product yield after flash column chromatography. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **8a**.

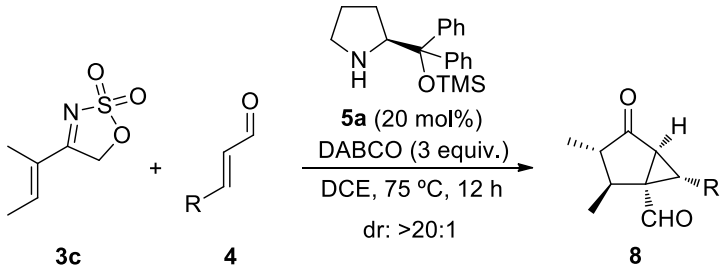
Having studied the different variables of the reaction, we concluded that the optimal conditions for the synthesis of bicycle[3.1.0]hexane derivative **8a** by one-pot reaction of the cyclic sulfamidate **3c** and (*E*)-cinnamaldehyde **4i** are the use of 20 mol% of catalyst **5a** and 3 equiv. of DABCO as additive in DCE at 75 ºC (Scheme 2.44).



Scheme 2.44

With the best conditions in hands, we continued with the study of the scope of the reaction, trying first with different β-aryl substituted enals, using cyclic sulfamidate imine **3c** as starting material (Table 2.14).

Table 2.14: Scope of the reaction using sulfamidate imine **3c** and β-aryl substituted enals.[a]



3c **4** **8**

Entry	R (4)	8	Yield (%)[b]	ee (%)[c]
1	Ph (**4i**)	**8a**	53	94
2	4-MeC_6H_4 (**4j**)	**8b**	55	93
3	2-$MeOC_6H_4$ (**4k**)	**8c**	39	90
4	4-$MeOC_6H_4$ (**4l**)	**8d**	43	94
5	4-AcO-3-$MeOC_6H_3$ (**4m**)	**8e**	51	94
6	3,5-$(MeO)_2C_6H_3$ (**4n**)	**8f**	42	92
7	4-ClC_6H_4 (**4o**)	**8g**	52	92
8	4-BrC_6H_4 (**4p**)	**8h**	46	90
9	2-$NO_2C_6H_4$ (**4q**)	**8i**	47	92
10	4-$NO_2C_6H_4$ (**4r**)	**8j**	32	86
11	4-CNC_6H_4 (**4s**)	**8k**	41	89
12	4-$CF_3C_6H_4$ (**4t**)	**8l**	54	90

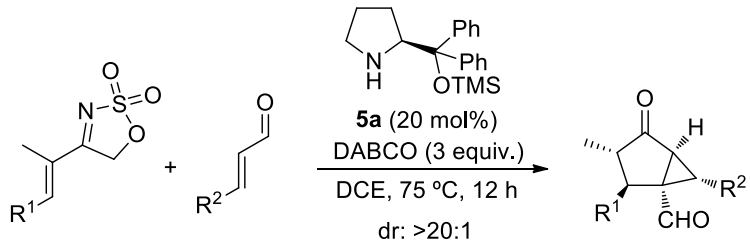
[a] The reaction was performed in 0.30 mL of DCE and 0.15 mmol scale of **3c**, using 1.5 equiv. of **4**. [b] Isolated product yield after flash column chromatography. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **8**.

As it can be observed in the Table 2.14, the reaction proceeded in moderate yields and very good to excellent enantioselectivities in all cases, both with electron-donor (entries 2-6) and electron-withdrawing substituents (entries 7-12) in the aromatic ring of a variety of β-aryl substituted enals, providing the

corresponding bicyclic compounds **8** as single diastereoisomers. In contrast to the Michael/Michael reaction, in this case the reaction took place with *ortho*-substituted aromatic enals in modest yields (entries 3 and 9). Unfortunately, when (*E*)-crotonaldehyde or another β-alkyl substituted enal were examined, the decomposition of the starting reagents were observed.

On the other hand, we extended the reaction to β-ethyl and β-phenyl substituted sulfamidate imines **3d** and **3e**, using aromatic enals with different substituents (Table 2.15). With imine **3d** low to moderate yields were achieved, isolating the corresponding products in high enantiopurity and as a single diastereoisomers (entries 1-3). When substrate **3e** was used, moderate yields were obtained (entries 4-7), observing a significant drop in the enantioselectivity when enals with electron-poor substituents on the aromatic ring at β-position were employed (entries 6-7).

Table 2.15: Scope of the reaction using sulfamidate imines **3d** and **3e**, and β-aryl substituted enals.[a]



3d-e **4** **8**

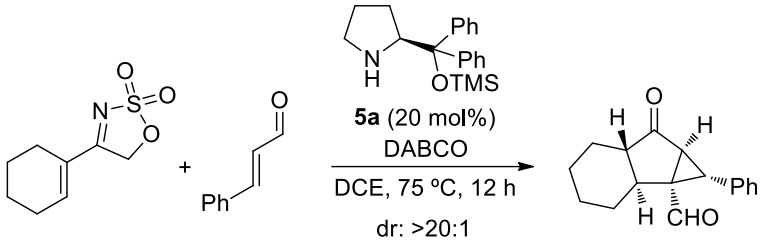
Entry	R^1 (3)	R^2 (4)	8	Yield (%)[b]	ee (%)[c]
1	Et (**3d**)	Ph (**4i**)	**8m**	43	91
2	Et (**3d**)	4-$MeOC_6H_4$ (**4l**)	**8n**	41	90
3	Et (**3d**)	4-BrC_6H_4 (**4p**)	**8o**	30	86
4	Ph (**3e**)	Ph (**4i**)	**8p**	49	93
5	Ph (**3e**)	4-AcO-3-$MeOC_6H_3$ (**4m**)	**8q**	51	90
6	Ph (**3e**)	4-BrC_6H_4 (**4p**)	**8r**	42	75
7	Ph (**3e**)	4-$NO_2C_6H_4$ (**4r**)	**8s**	46	76

[a] The reaction was performed in 0.30 mL of DCE and 0.15 mmol scale of **3**, using 1.5 equiv. of **4**. [b] Isolated product yield after flash column chromatography. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **8**.

At this stage, with the purpose of obtaining the tricycle compound derived from the sulfamidate imine **3a**, we tried to carry out the reaction under the previous optimal conditions by reacting the imine **3a** and (*E*)-cinnamaldehyde **4i** (see entry 1, Table 2.16), observing the formation of the desired product **12a**, together with the Michael/Michael product. We also observed by NMR the formation of an unknown product that could not be isolated. In order to avoid the formation of secondary products, we increased the amount of DABCO to 5 equiv., not detecting the formation of these byproducts, and isolating the corresponding tricycle **12a** in low yield, but in excellent enantiopurity and as a single

diastereoisomer (entry 2). We also tried with excess of the sulfamidate imine **3a**, keeping the high stereocontrol and increasing the yield with 1.5 equiv. of **3a** (entry 3).

Table 2.16: Screening for the best reaction conditions using the sulfamidate imine **3a**.[a]



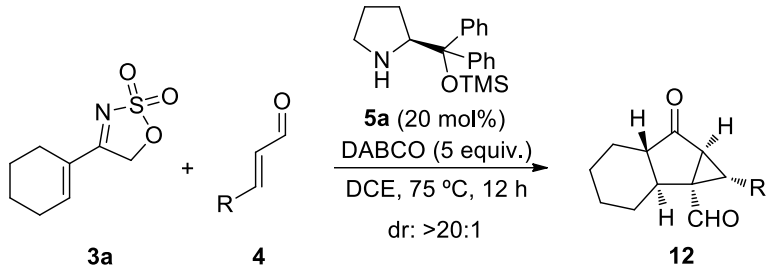
3a **4i** **12a**

Entry	3a:4i (equiv.)	DABCO (equiv.)	Yield (%)[b]	ee (%)[c]
1	1:1.5	3	n.d.[d]	n.d.[d]
2	1:1.5	5	38	98
3[e]	1.5:1	5	46	98
4[e]	2:1	5	44	98

[a] The reaction was performed in 0.30 mL of DCE and 0.15 mmol scale of **3a**. [b] Isolated product yield after flash column chromatography. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **12a**. [d] Not determined. [e] The reaction was performed in 0.15 mmol scale of **4i**.

With the conditions shown in the entry 3 of the Table 2.16, we surveyed different β-aryl substituted enals using the substrate **3a** (Table 2.17). The reaction proceeded in low to moderate yields and excellent stereocontrol regardless of the electronic nature of the aromatic ring (entries 2-3). In contrast, the reaction failed when β-alkyl substituted enals, such as (*E*)-crotonaldehyde or (*E*)-hex-2-enal, were used.

Table 2.17: Scope of the reaction using sulfamidate imine **3a** and β-aryl substituted enals.[a]

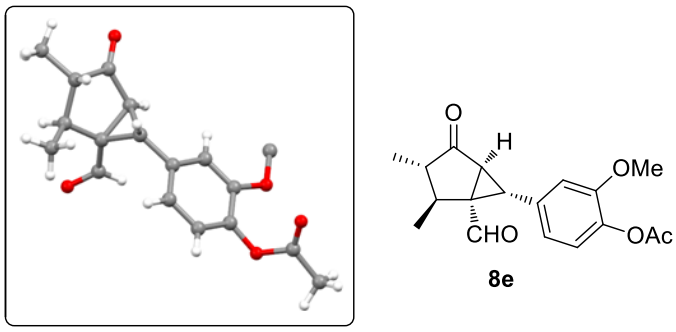


3a **4** **12**

Entry	R (4)	12	Yield (%)[b]	ee (%)[c]
1	Ph (**4i**)	**12a**	46	98
2	4-MeOC$_6$H$_4$ (**4l**)	**12b**	34	96
3	4-BrC$_6$H$_4$ (**4p**)	**12c**	38	96

[a] The reaction was performed in 0.30 mL of DCE and 0.15 mmol scale of **4**, using 1.5 equiv. of **3a**. [b] Isolated product yield after flash column chromatography. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **12**.

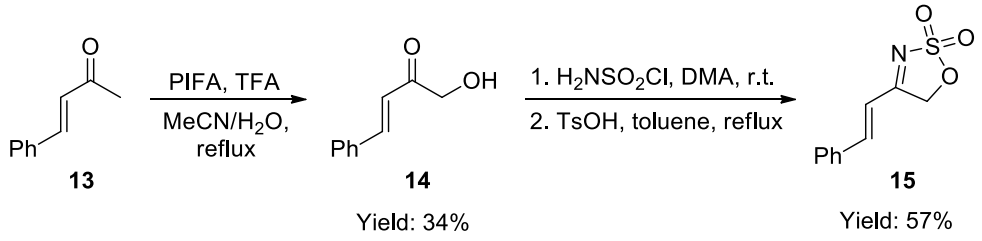
Finally, we were also able to determine the absolute configuration of the product **8e** by single crystal X-ray analysis (Figure 2.11), showing a 1*S*,2*S*,3*S*,5*S*,6*R* configuration at the five formed stereocenters. The stereostructure of all other compounds **8** and **12** was stablished based on mechanistic analogy.



8e

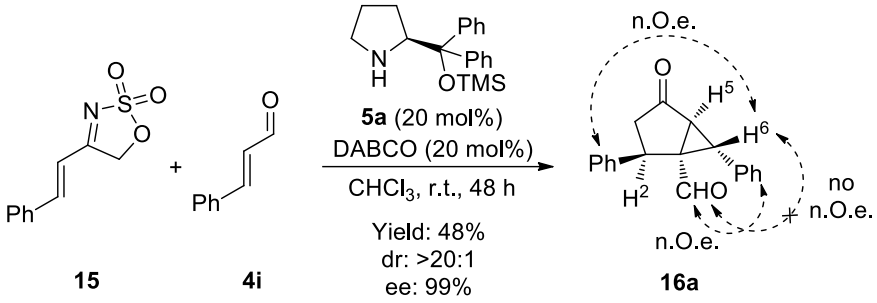
Figure 2.11

At this stage, we decided to prepare a new α,β-unsaturated sulfamidate imine without any substituent in α-position of the alkenyl moiety (Scheme 2.45). In this sense, α-hydroxy ketone **14** was firstly synthetized, in 34% yield, starting from commercially available (*E*)-4-phenylbut-3-en-2-one **13** following the previously used procedure.[52] Finally, the desired sulfamidate imine **15** was prepared in 57% yield from the corresponding compound **14**, through the previously employed methodology.[48c]



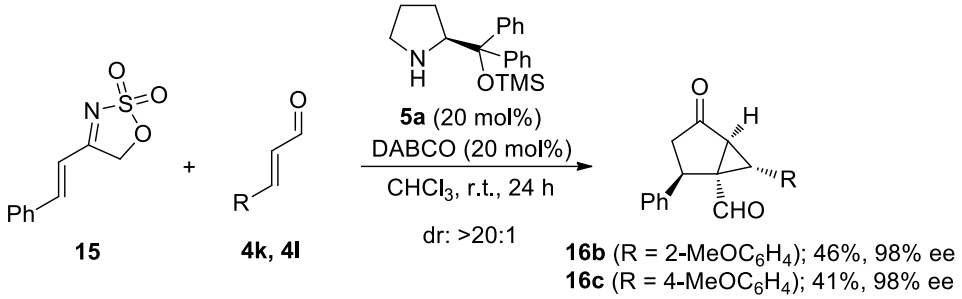
Scheme 2.45

Having prepared the compound **15**, we initially tried to form the Michael/Michael cascade product, using the reaction conditions shown in the entry 1 of the Table 2.8, with (*E*)-cynnamaldehyde **4i**, 20 mol% of catalyst **5a** and DABCO, in dry $CHCl_3$ at -30 ºC. After 2 days, low conversion was observed, but surprisingly, the bicyclic compound was found to be the major product, observing also the formation of the Michael/Michael cascade product. At room temperature, full conversion was achieved, isolating the bicycle **16a** in 48% yield and as a single diastereoisomer in 99% ee (Scheme 2.46). The configuration of the stereocenters were confirmed by NMR experiments, matching with the configuration of bicycles **8** and tricycles **12**, due to the presence of n.O.e. between H^6 and the protons of the aromatic ring at C-2, and between the proton of the aldehyde and the protons of the phenyl group at C-6.



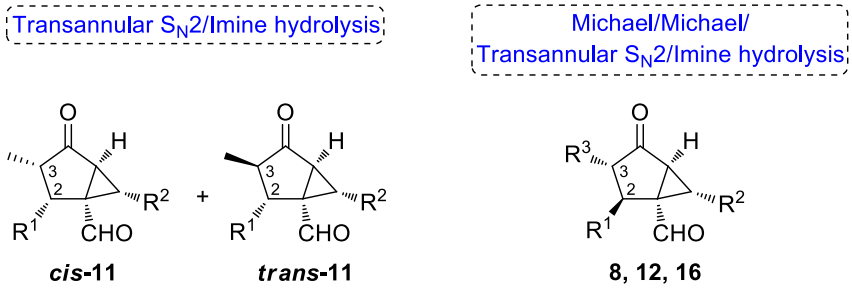
Scheme 2.46

It should be pointed out that the double Michael product was only observed as minor product. Trying higher temperatures, better results were not achieved. We could satisfactorily extend the reaction to other enals with electron-donating groups in the aromatic ring (Scheme 2.47).



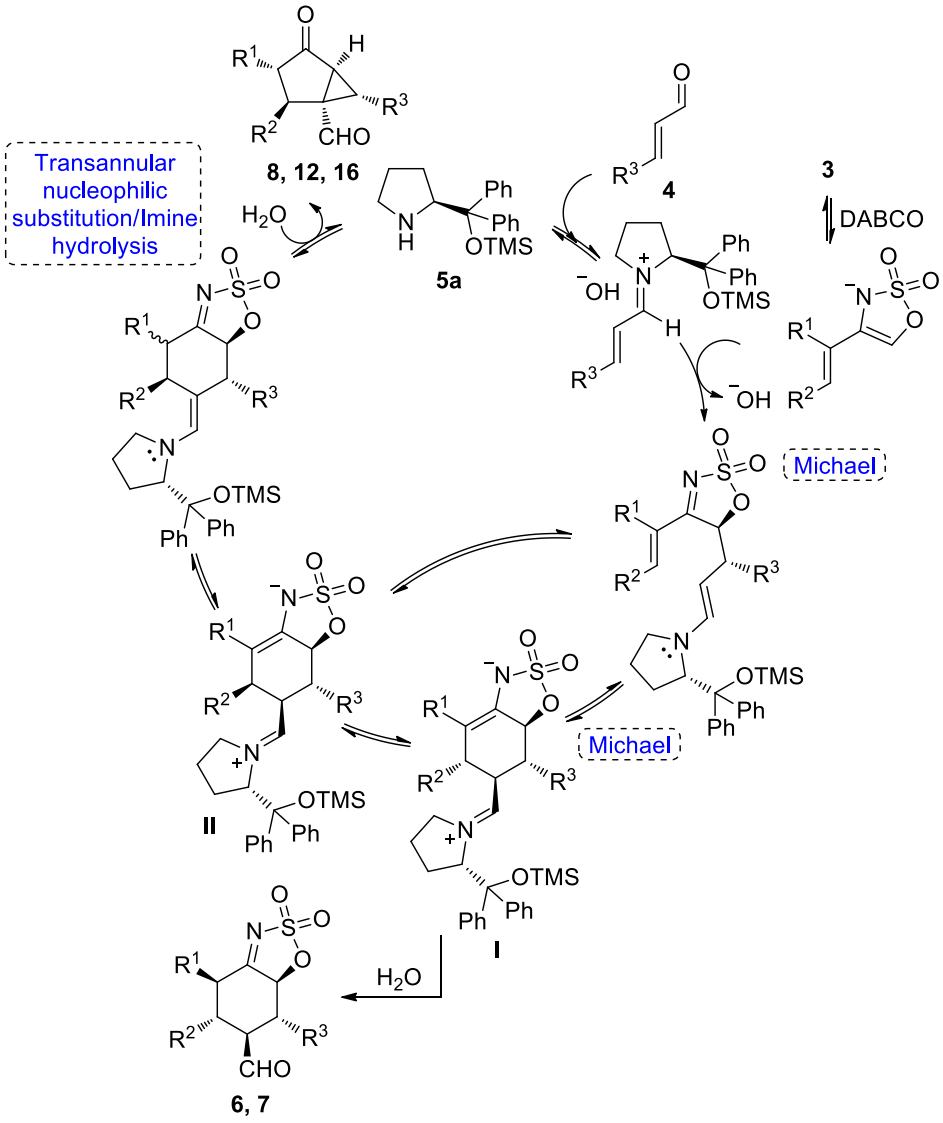
Scheme 2.47

In summary, different diastereoisomers of the bicycle[3.1.0]hexane derivative can be prepared through two different approaches, as it can be observed in Scheme 2.48.



Scheme 2.48

In the transannular nucleophilic substitution/imine hydrolysis cascade reaction of double Michael cycloadducts **7**, the configuration of obtained bicyclic compounds **11** match with the configuration of the starting reagent, only observing the epimerization of the stereocenter at the C-3 carbon, due to the presence of an acidic proton. However, in the Michael/Michael/transannular nucleophilic substitution/imine hydrolysis cascade sequence, the configuration of the stereocenter at the C-2 carbon is the opposite compared with the double Michael product **7**. In this case, this position does not present an acidic proton, so the reaction has to take place through another mechanistic pathway compared with the previously developed Michael/Michael cascade reaction. In this sense, we propose the mechanism shown in Scheme 2.49 as the most plausible one.

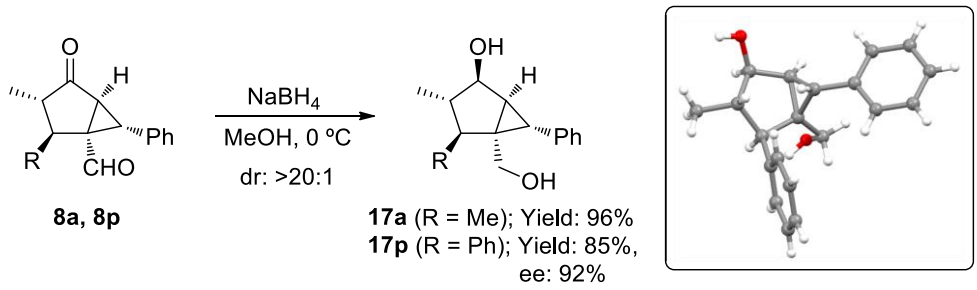


Scheme 2.49

Initially, after the iminium ion formation by condensation between the enal and the catalyst, the first Michael addition takes place between the activated

nucleophile and the iminium ion through its less hindered face, generating the corresponding enamine. Then, an intramolecular Michael addition takes place, towards the formation of the most stable intermediate **I**, which can evolve to the double Michael cycloadduct **7** after the hydrolysis of the catalyst. This intermediate is in equilibrium with the intermediate **II**, through a retro-Michael reaction. Depending on the reaction conditions and on the substituents of the sulfamidate imine **3**, the formation of the intermediate **II** is favoured. This last one is able to evolve to the corresponding enamine, which can attack intramolecularly to the sulfonate group position through a transannular S_N2-type reaction that after the hydrolysis of both imines, the catalyst is recovered and the desired cyclopropane is obtained. At this point, it should be highlighted that further experiments and computacional studies are needed, in order to confirm our mechanistic proposal.

Having shown the usefulness of this methodology in the preparation of a set of interesting bicyclic and tricyclic compounds containing a fused cyclopropane moiety, we proceeded to evaluate the synthetic possibilities of these cycloadducts. In this way, we initially tried the selective reduction of the formyl group of compound **8a**, using a mild reducing agent, such as sodium triacetoxyborohydride, observing low conversion and a mixture of mono- and direduced compounds. For this reason, we decided to reduce both carbonyl groups of compounds **8a** and **8p** as selected examples, employing sodium borohydride as a reducing agent, in MeOH at 0 ºC, isolating diols **17a** and **17p** in excellent yields and as single diastereoisomers, as checked by ^{1}H-NMR analysis. It should be highlighted that the product **17p** was recrystallized, determining the configuration of the generated new stereocenter by single crystal X-ray analysis (Scheme 2.50).

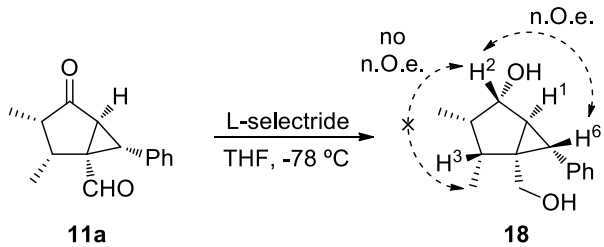


8a, 8p

17a (R = Me); Yield: 96%
17p (R = Ph); Yield: 85%, ee: 92%

Scheme 2.50

Next, we tried to carry out the reduction of the diastereoisomer **11a** obtained by cyclization of adduct **7a**, and using the same conditions than in the previous case, obtaining a 1:1 mixture of the two possible diastereoisomers. Fortunately, when L-selectride was used as a more sterically hindered reductant at low temperature, only one diastereoisomer was obtained (Scheme 2.51). The configuration of the generated stereocenter in the diol **18** was determined by NOESY experiments, observing n.O.e. between H^2 and H^6 and no n.O.e. between H^2 and the protons of the methyl group, indicating that the hydroxy group was on the opposite site, comparing with the diol obtained from the other diastereoisomer **8a**.



11a **18**

Yield: 93%
dr: >20:1

Scheme 2.51

4. CONCLUSIONS

Considering all the results presented in this chapter, some conclusions are drawn:

1. A novel aminocatalytic enantioselective Michael/Michael cascade reaction, promoted by DABCO and (*S*)-diphenylprolinol trimethylsilyl ether, has been developed using several 4-alkenyl-5*H*-1,2,3-oxathiazole 2,2-dioxides and enals following the iminium/enamine manifold, being able to prepare a series of chiral *trans*-decalines derivatives and polysubstituted cyclohexanes in good yields and excellent stereoselectivities. Furthermore, this reaction allows the use of enals and sulfamidate imines with both aliphatic and aromatic substituents in different positions.

2. The 5*H*-1,2,3-oxathiazole 2,2-dioxide moiety could be employed as a masked β-amino alcohol, which can be prepared from the obtained double Michael products through a simple diastereoselective reduction/hydrolysis sequence.

3. It can be accessed to bicycle[3.1.0]hexane scaffolds in very good yields and diastereoselectivities from the corresponding Michael/Michael cycloadducts through a transannular nucleophilic substitution/imine hydrolysis sequence, demonstrating the usefulness of the cyclic sulfamidate imine moiety

4. Finally, the synthetic ability of the α,β-unsaturated cyclic sulfamidate imines have been demonstrated through an organocatalytic multiple cascade reaction, consisting on a Michael/Michael/transannular nucleophilic substitution/imine hydrolysis sequence, towards the synthesis of enantioenriched bicyclic and tricyclic compounds in moderate yields and obtaining a different

diastereoisomer that in the previous case. It should be noted that different substitution patterns are admitted, with the limitation of β-alkyl substituted enals, with which no reaction was observed.

3

3

Organocatalytic approach to chiral proline derivatives

1. INTRODUCTION: ORGANOCATALYTIC ASYMMETRIC SYNTHESIS OF PYRROLIDINE DERIVATIVES

Nitrogen-containing structural moieties are widely present in nature including, among others, chiral five-membered heterocycles. Specifically, the pyrrolidine framework and derivatives, like for example prolines, are part of many natural and synthetic compounds with interesting biological and pharmaceutical activities.[1] Moreover, they can be employed as building blocks, ligands or organocatalysts.[2] For these reasons, during the last decade, many strategies have been reported towards the asymmetric synthesis of stereodefined pyrrolidine derivatives. Among the various synthetic approaches, organocatalysis has been postulated as a powerful tool in this field during the last years.[3] In this sense, within the different organocatalytic methodologies for the synthesis of chiral pyrrolidine derivatives, we will focus on three main strategies based on the type of disconnection, relying on the construction of the heterocyclic architecture through a ring closure process (Figure 3.1).

---

[1] For selected reviews, see: a) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247; b) Hanessian, S. *ChemMedChem* **2006**, *1*, 1300; c) Pyne, S. G.; Tang, M.-Y. *Curr. Org. Chem.* **2005**, *9*, 1393; d) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773; e) Pearson, W. H. *Studies in Natural Product Chemistry* (Ed.: Atta-ur-Rahman), Elsevier, Vol. 1, p. 323, New York, **1998**; f) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825.

[2] For selected reviews, see: a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471; b) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416; c) *Asymmetric Organocatalysis* (Eds.: Berkessel, A.; Gröger, H.), Wiley-VCH, Weinheim, **2005**; d) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719; e) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; f) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; g) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159.

[3] For recent reviews, see: a) Randjelovic, J.; Simic, M.; Tasic, G.; Husinec, S.; Savic, V. *Curr. Org. Chem.* **2014**, *18*, 1073; b) Kumar, I. *RSC Adv.* **2014**, *4*, 16397; c) Han, M.-Y.; Jia, J.-Y.; Wang, W. *Tetrahedron Lett.* **2014**, *55*, 784; d) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156.

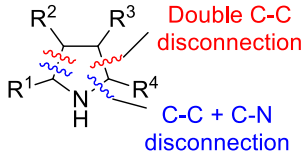


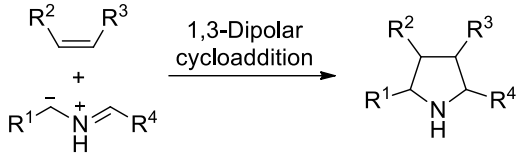
Figure 3.1

In this context, the most studied are those involving a double C-C bond disconnection, through a typical 1,3-dipolar cycloaddition, and a consecutive C-C and C-N bond disconnection or vice versa, in one-pot fashion.

1.1. Double C-C bond disconnection strategy

The construction of the pyrrolidine scaffold, following a double C-C bond disconnection strategy, has been widely investigated through the [3+2] cycloaddition with azomethine ylides as 1,3-dipoles (Scheme 3.1), as it can be appreciated in the large number of publications.[4] Within the different activation modes of the organocatalysis, the 1,3-dipolar cycloadditions will be classified in two main groups, the aminocatalytic reactions and hydrogen bonding activated reactions.

[4] For some reviews, see: a) Narayan, R.; Potowsky, M.; Jia, Z.-J.; Antonchick A. P.; Waldmann, H. *Acc. Chem. Res.* **2014**, *47*, 1296; b) Nájera, C.; Sansano, J. M. *J. Organomet. Chem.* **2014**, *771*, 78; c) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6784; d) Garner, P.; Kaniskan, H. U. *Curr. Org. Synth.* **2010**, *7*, 348; e) Nájera, C.; Sansano, J. M.; Yus, M. *J. Braz. Chem. Soc.* **2010**, *21*, 377; f) Nájera, C.; Sansano, J. M. *Top. Heterocycl. Chem.* **2008**, *12*, 117; g) Nájera, C.; Sansano, J. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6272.

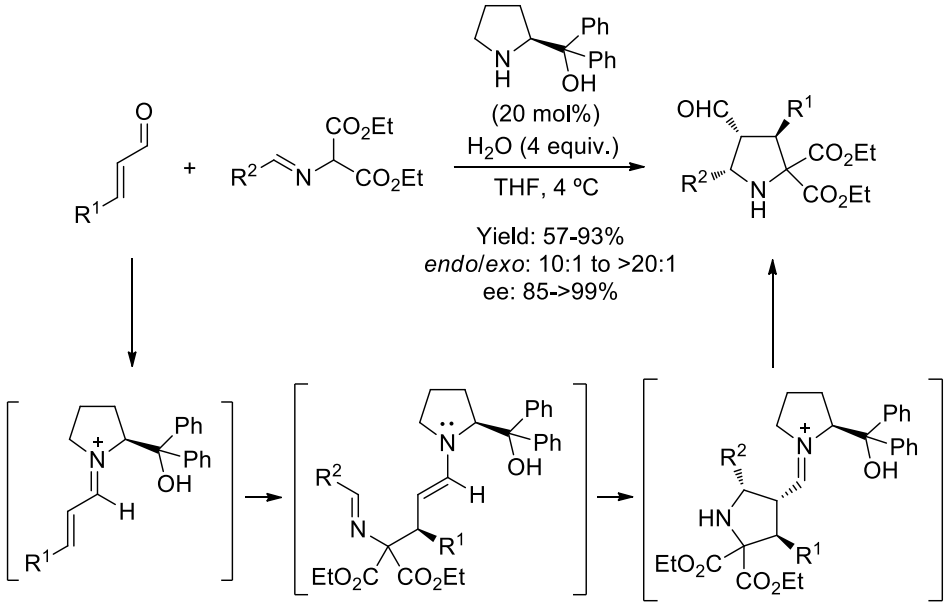


Scheme 3.1

Within the aminocatalytic 1,3-dipolar cycloadditions, the first example was reported in 2007, by our group,[5] employing diphenylprolinol as the optimal catalyst. Several chiral pyrrolidines were obtained in high yields and excellent stereocontrol, by reaction between *in situ* generated azomethine ylides, through a 1,2-prototropy process of imines derived from aminomalonates, and α,β-unsaturated aldehydes activated by iminium ion formation (see Scheme 3.2). After DFT calculations it was concluded that the reaction consisted on an initial Michael addition of the dipole to the preactivated enal, as the rate determining step, followed by intramolecular Mannich reaction of the subsequent enamine, thus discarding the concerted pathway.[6]

[5] Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5168.

[6] Reboredo, S.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; de Cózar, A.; Cossío, F. P. *Chem. Eur. J.* **2012**, *18*, 7179.



Scheme 3.2

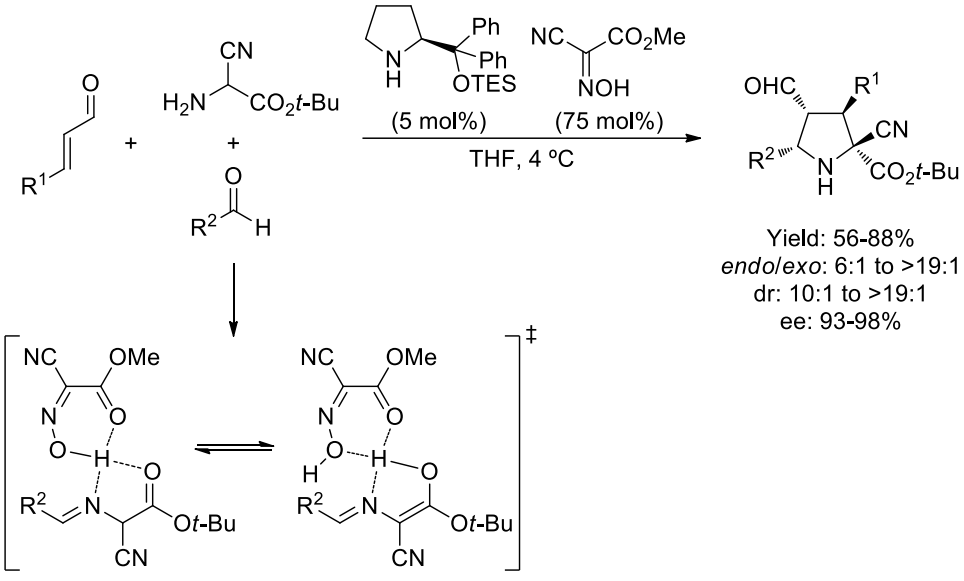
The obtained adducts were satisfactorily transformed into *N*-containing bicyclic and tricyclic compounds,[7] and the reaction was carried out in a multicomponent version, without the preformation of the imine.[8] Additionally, the reaction was extended to the use of azomethine ylides with two different electron-withdrawing groups, imino cyanoacetates, controlling the 2,5-diastereoselectivity through the formation of an intramolecular hydrogen bond between the protonated imine and the ethoxycarbonyl group. As a result, pyrrolidine derivatives were obtained with up to four stereogenic centers, including a quaternary one, in good yields and excellent stereoselectivities.[9] Related with this topic, in the same year,

[7] a) Iza, A.; Ugarriza, I.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Tetrahedron* **2013**, *69*, 8878; b) Iza, A.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E.; Martínez, J. I. *Org. Biomol. Chem.* **2010**, *8*, 2238.

[8] Reboredo, S.; Vicario, J. L.; Carrillo, L.; Reyes, E.; Uria, U. *Synthesis* **2013**, *45*, 2669.

[9] Reboredo, S.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Adv. Synth. Catal.* **2011**, *353*, 3307.

Córdova and co-workers developed a diastereo- and enantioselective dynamic multicomponent transformation between enals, aldehydes and protected α-cyanoglycine esters. The stereochemical outcome was successfully controlled by the cooperative combination of hydrogen bonds and iminium activation, using *O*-protected diphenyl prolinol as catalyst and methyl oximinocyanoacetate as a hydrogen-bond-donating cocatalyst (Scheme 3.3).[10]

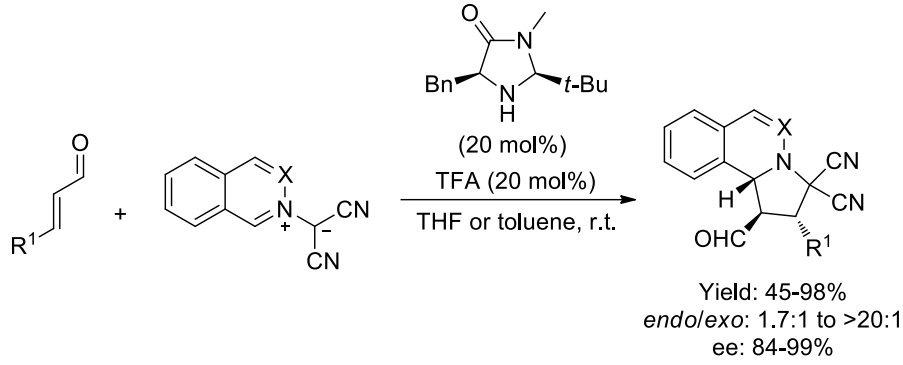


Scheme 3.3

It should be noted that our group also developed this reaction with acrolein as substrate providing C-3 unsubstituted pyrrolidines as single diastereoisomers, with good enantioselection, employing in this case L-proline as catalyst.[11] Moreover, 1,3-dipolar cycloaddition using stable azomethine ylides, such as isoquinolinium and phthalizinium methylides, was also studied obtaining

[10] Lin, S.; Deiana, L.; Zhao, G.-L.; Sun, J.; Córdova, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 7624.
[11] Ugarriza, I.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Asymm. Catal.* **2015**, *2*, 26.

polysubstituted chiral pyrroloisoquinolines and pyrrolophthalazines in high yields and good enantiocontrol (Scheme 3.4).[12]

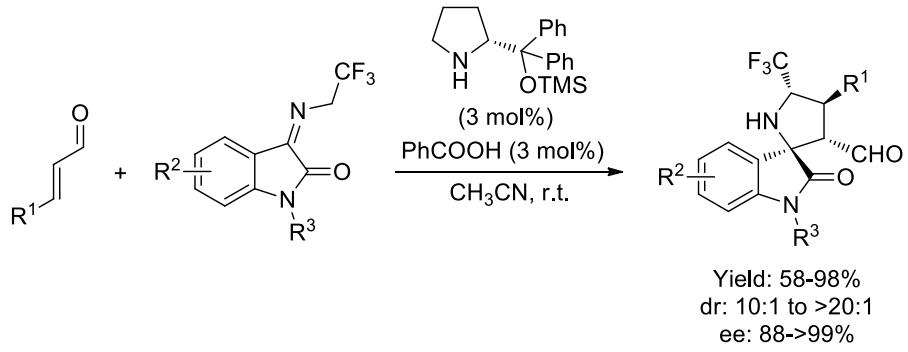


Scheme 3.4

Recently, aminocatalysis has been applied in the asymmetric synthesis of CF_3-containing spiro[pyrrolidin-3,2'-oxindoles], employing enals and unprecedented 1,3-dipoles, which were obtained by the condensation of trifluoroethylamine and isatins.[13] Under the optimal conditions, with low catalyst loading, a serie of spirooxindoles, including unprotected spirooxindoles, were prepared in excellent yields, diastereo- and enantioselectivities (Scheme 3.5).

[12] Fernández, N.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *Chem. Commun.* **2011**, *47*, 12313.

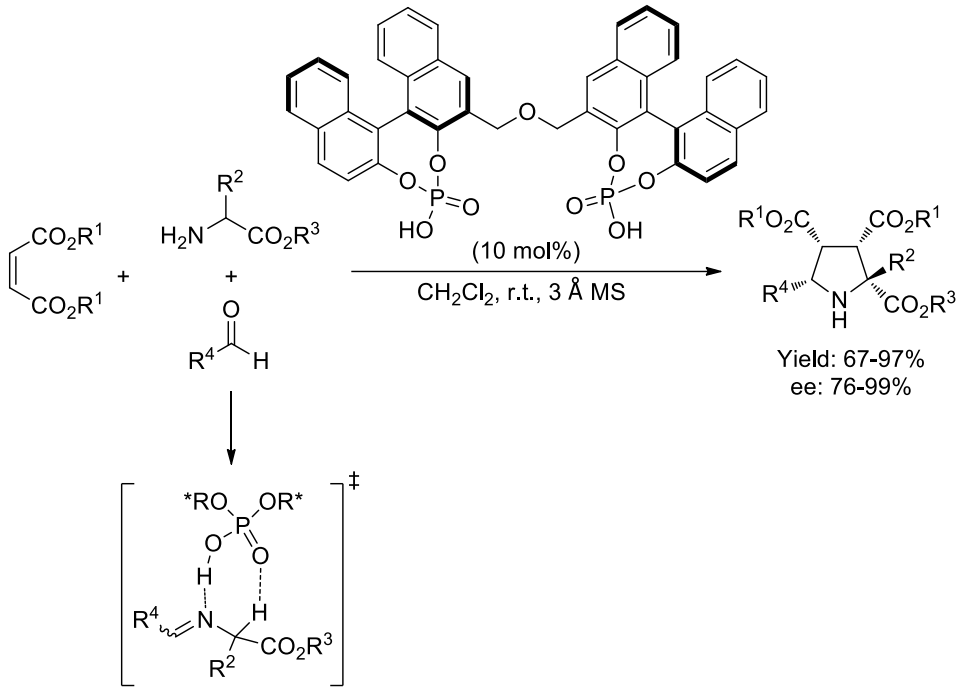
[13] Ma, M.; Zhu, Y.; Sun, Q.; Li, X.; Su, J.; Zhao, L.; Zhao, Y.; Qiu, S.; Yan, W.; Wang, K.; Wang, R. *Chem. Commun.* **2015**, *51*, 8789.



Scheme 3.5

In spite of the progress of aminocatalytic formal 1,3-dipolar cycloaddition, dipolarophiles are limited to enals. For this reason, a significant advance has been observed during the last years regarding the development of hydrogen bond catalysis in this reaction. In 2008, Gong and co-workers developed a Brønsted acid catalyzed, three-component, asymmetric 1,3-dipolar cycloaddition, by reaction between aldehydes, aminomalonates and several maleates as dipolarophiles, affording the corresponding pyrrolidines in high yields and excellent enantioselectivities (Scheme 3.6).[14] With this work, the concept of the formation of chiral Brønsted acid bonded dipole able to participate in new asymmetric 1,3-dipolar cycloaddition was established.

[14] Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 5652.



Scheme 3.6

One year later, Gong *et al.* extended successfully the three-component 1,3-dipolar cycloaddition to methyleneindolinones as dipolarophiles, using the same type of dipoles and a phosphoric acid as catalyst, towards the synthesis of spiro[pyrrolidin-3,3'-oxindole] derivatives with an unusual regioselectivity and excellent stereoselectivities.[15] Moreover, this type of architecture is presented in many biologically relevant molecules, increasing the interest of the proyect. In this case, relying on theoretical calculations, it can be concluded that both the methyleneindolinone and the azomethine ylide are hydrogen bonded with the chiral acid, providing the excellent stereocontrol and regioselectivity. The unusual

[15] Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819.

observed regioselectivity is not directed by electronic effect but it is presumably controlled by the stabilization stemming from the favourable π-π stacking interaction between the conjugate esters and the oxindole ring. With these precedents, the [3+2] cycloaddition was satisfactorily extended by the same group employing the same type of azomethine ylides and changing the nature of dipolarophile, trying with quinone derivatives,[16] methyl 2-(2-nitrophenyl)acrylates,[17] fumarates and vinyl ketones and esters.[18]

In 2010, the first asymmetric intramolecular 1,3-dipolar cycloaddition was developed catalyzed by BINOL-derived phosphoric acid, by reaction between aldehydes that incorporated dipolarophile functionalities, and α-aryl amino esters. After the formation of the imine and the subsequent dipole, the intramolecular cycloaddition is occurred, obtaining the corresponding chromeno[4,3-*b*]pyrrolidine derivatives with very good results (Scheme 3.7).[19]

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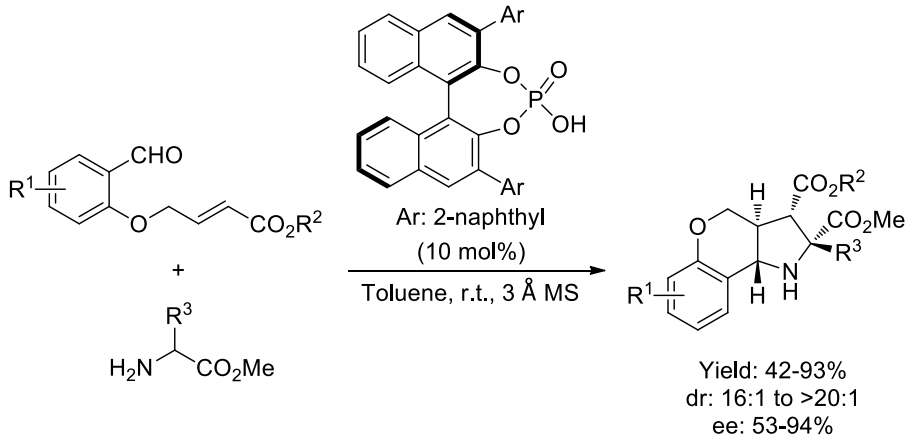
16 Wang, C.; Chen, X.-H.; Zhou, S.-M.; Gong, L.-Z. *Chem. Commun.* **2010**, *46*, 1275.

17 Cheng, M.-N.; Wang, H.; Gong, L.-Z. *Org. Lett.* **2011**, *13*, 2418.

18 He, L.; Chen, X.-H.; Wang, D.-N.; Luo, S.-W.; Zhang, W.-Q.; Yu, J.; Ren, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2011**, *133*, 13504.

19 a) Li, N.; Song, J.; Tu, X.-F.; Liu, B.; Chen, X.-H.; Gong, L.-Z. *Org. Biomol. Chem.* **2010**, *8*, 2016; for a recent example of the synthesis of chromeno[4,3-*b*]pyrrolidine derivatives through a [3+2] cycloaddition/intramolecular transesterification sequence, see: b) Tian, L.; Xu, G.-Q.; Li, Y.-H.; Liang, Y.-M.; Xu, P.-F. *Chem. Commun.* **2014**, *50*, 2428.



Scheme 3.7

Azomethine ylides are usually generated from the corresponding aldehydes, and rarely ketones have been used as the precursors of this type of 1,3-dipoles. In this sense, the same group employed for the first time azomethine ylides derived from the condensation between unsymmetrical cyclic ketones, such as isatin derivatives, with aminomalonates towards the obtention of spiro[pyrrolidin-3,2'-oxindoles], using maleates as dipolarophiles under chiral phosphoric acid catalysis (shown on Scheme 3.8).[20] More recently, different azomethine ylides derived from isatin derivatives have also been successfully used with other dipolarophiles, such as nitroalkenes,[21] maleimides[22] and methyleneindolinones.[23] With the last one, 3,3'-pyrrolidinyldispirooxindoles containing two contiguous quaternary stereogenic centers were obtained in high yields and stereoselectivities.

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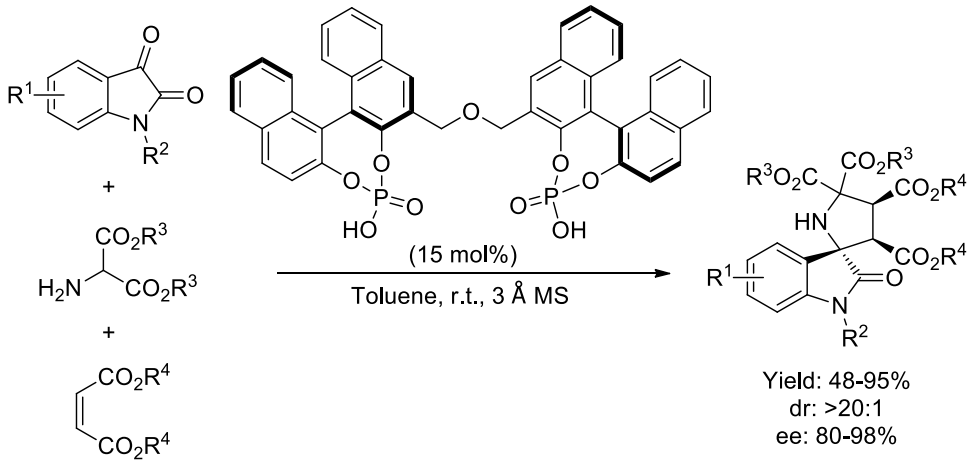
[20] Shi, F.; Tao, Z.-L.; Luo, S.-W.; Tu, S.-J.; Gong, L.-Z. *Chem. Eur. J.* **2012**, *18*, 6885.

[21] a) Sun, Q.; Li, X.; Su, J.; Zhao, L.; Ma, M.; Zhu, Y.; Zhao, Y.; Zhu, R.; Yan, W.; Wang, K.; Wang, R. *Adv. Synth. Catal.* **2015**, *357*, 3187; b) Tian, L.; Hu, X.-Q.; Li, Y.-H.; Xu, P.-F. *Chem. Commun.* **2013**, *49*, 7213.

[22] Zhao, H.-W.; Yang, Z.; Meng, W.; Tian, T.; Li, B.; Song, X.-Q.; Chen, X.-Q.; Pang, H.-L. *Adv. Synth. Catal.* **2015**, *357*, 2492.

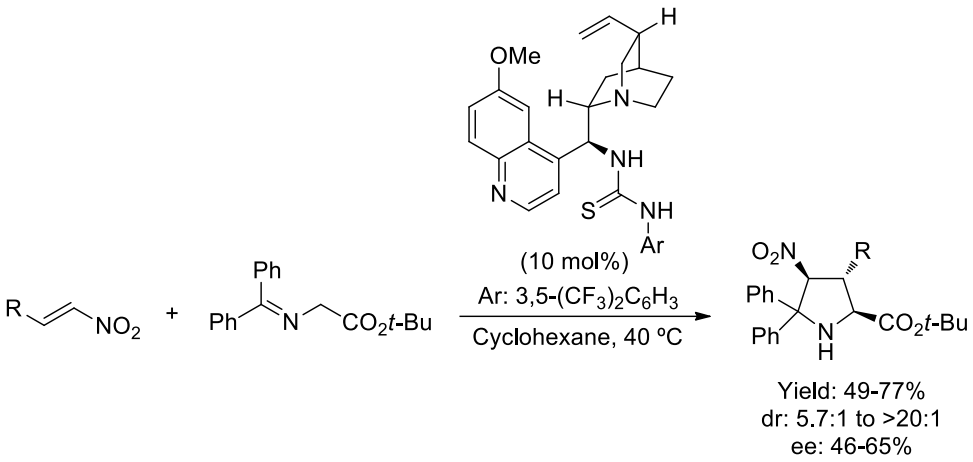
[23] Dai, W.; Jiang, X.-L.; Wu, Q.; Shi, F.; Tu, S.-J. *J. Org. Chem.* **2015**, *80*, 5737.



Scheme 3.8

On the other hand, Zhang and co-workers described the first asymmetric [3+2] cycloaddition of azomethine ylides with nitroalkenes, employing in this case a bifunctional thiourea as hydrogen-bonding catalyst. Under the optimal conditions, pyrrolidines were obtained with high diastereoselectivities but with low to moderate enantiocontrol (Scheme 3.9).[24]

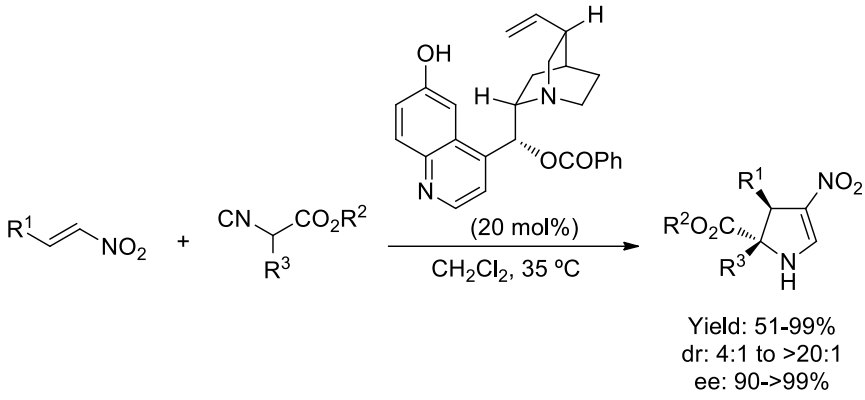
[24] Xue, M.-X.; Zhang, X.-M.; Gong, L.-Z. *Synlett* **2008**, 691.



Scheme 3.9

Isocyanoesters can also be used as 1,3-dipoles in the organocatalyzed [3+2] cycloaddition reactions conducing to pyrrolines as initially developed by Gong *et al.* using cinchona alkaloid-derived chiral base as catalyst to form 2,3-dihydropyrroles with excellent results (Scheme 3.10).[25] It should be noted that the hydroxy group present in the quinoline moiety of the catalyst acts as hydrogen-bond donor increasing the stereoselectivity of the process.

[25] Guo, C.; Xue, M.-X.; Zhu, M.-K.; Gong, L.-Z. *Angew. Chem. Int. Ed.* **2008**, *47*, 3414.



Scheme 3.10

Latter, Wang and co-workers described the use of isocyanoesters with methyleneindolinones in a quinine-based bifunctional thiourea catalyzed [3+2] reaction, towards the obtention of 3,3'-pyrrolidinyl spirooxindoles in high enantiocontrol, after the corresponding reduction of the resulting imine (Scheme 3.11).[26] The diastereoselectivity could be controlled by simply changing the *N*-protecting group. With a stereodirecting group at this position, the *anti* diastereoisomer was obtained as the mayor product, while the *syn* diastereiosomer appeared as the predominant product when a group without any directing element was used. A similar approach was developed by Yan and co-workers, employing the same type of isocyanoacetates, but in this case, isatylidene malononitrile derivatives were used as dipolarophiles, observing different regioselectivity than in the previous case, due to the high electron-attractor character of nitriles.[27]

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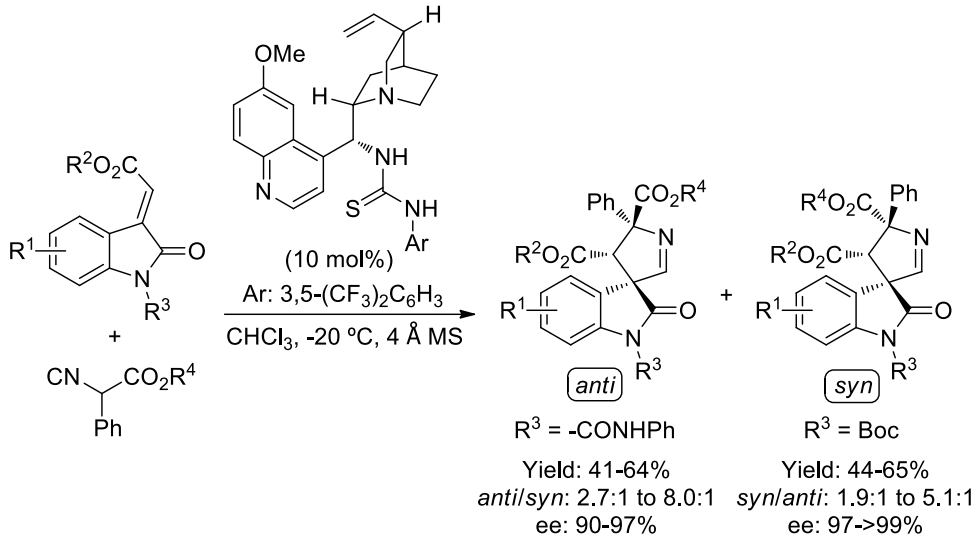
[26] Wang, L.-L.; Bai, J.-F.; Peng, L.; Qi, L.-W.; Jia, L.-N.; Guo, Y.-L.; Luo, X.-Y.; Xu, X.-Y.; Wang, L.-X. *Chem. Commun.* **2012**, *48*, 5175.

[27] Wei, W.-T.; Chen, C.-X.; Lu, R.-J.; Wang, J.-J.; Zhang, X.-J.; Yan, M. *Org. Biomol. Chem.* **2012**, *10*, 5245.

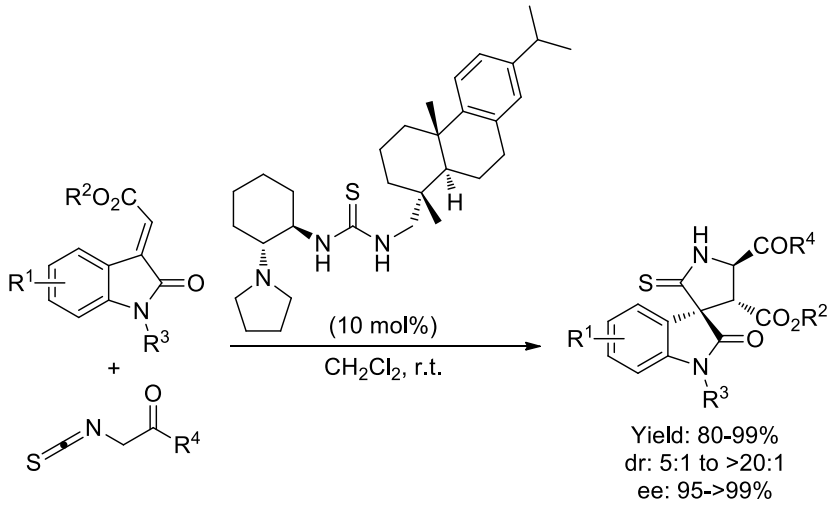


Scheme 3.11

Finally, there are also several examples, in which α-isothiocyanato imides are used as 1,3-dipoles in organocatalytic [3+2] cycloaddition. The groups of Wang and Barbas III, respectively, reported the asymmetric [3+2] reaction between this type of imides and methyleneindolinones, employing in both cases bifunctional organocatalysts.[28] The work of Wang *et al.* is shown on Scheme 3.12, in which a series of 3,3'-thiopyrrolidonyl spirooxindoles were obtained in excellent yields, diastereo- and enantioselectivities. Moreover, these compounds were easily transformable into the corresponding 3,3'-pyrrolidinyl spirooxindoles, without any loss of stereoselectivity. Recently, similar reports have been published

[28] a) Tan, B.; Zeng, X.; Leong, W. W. Y.; Shi, Z.; Barbas III, C. F.; Zhong, G. *Chem. Eur. J.* **2012**, *18*, 63; b) Cao, Y.; Jiang, X.; Liu, L.; Shen, F.; Zhang, F.; Wang, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 9124.

employing 3-isothiocyanato oxindoles as dienophiles and different electron-poor olefins as dipolarophiles.[29]



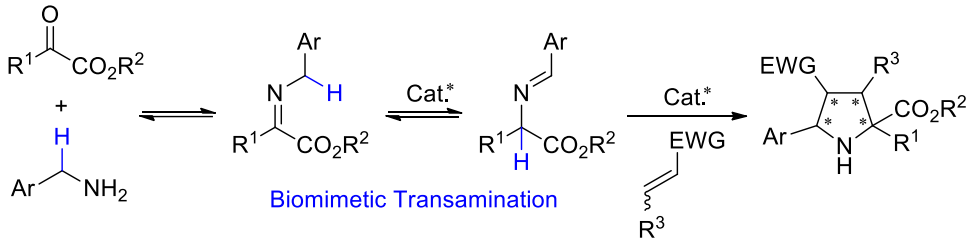
Scheme 3.12

In 2013, Gong and co-workers, based on the enzyme-catalyzed transamination reactions occurring in nature, developed the first asymmetric biomimetic multi-component 1,3-dipolar cycloaddition of benzylamine derivatives and α-keto esters with several electron-deficient olefins (Scheme 3.13).[30] The azomethine ylide was generated *in situ*, under phosphoric acid activation, from a 1,3-proton shift reaction of the ketimine formed from the corresponding α-keto ester and amine. Under the optimal conditions, with bisphosphoric acid as catalyst, diverse polysubstituted pyrrolidines were obtained in high yields and stereoselectivities.

---

[29] a) Kayal, S.; Mukherjee, S. *Eur. J. Org. Chem.* **2014**, 6696; b) Wu, H.; Zhang, L.-L.; Tian, Z.-Q.; Huang, Y.-D.; Wang, Y.-M. *Chem. Eur. J.* **2013**, *19*, 1747; c) Liu, X.-L.; Han, W.-Y.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2013**, *15*, 1246.

[30] Guo, C.; Song, J.; Gong, L.-Z. *Org. Lett.* **2013**, *15*, 2676.



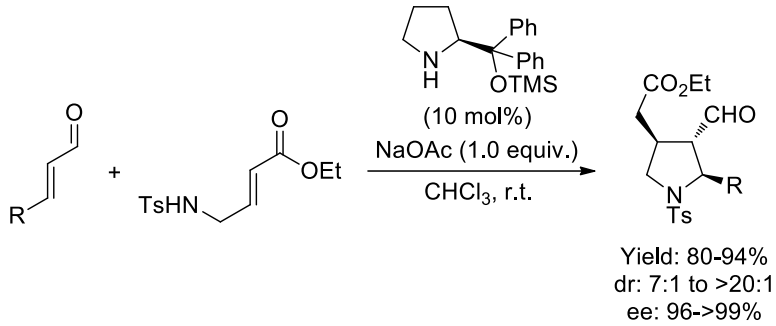
Scheme 3.13

1.2. Consecutive C-N and C-C bond disconnection strategy

Within the double disconnection strategies to achieve the pyrrolidine moiety, there are several organocatalytic examples based on the simultaneous C-N and C-C bond disconnection pathway. In general, this strategy involves an initial aza-Michael reaction with activated alkenes followed by the C-C bond formation through a ring closure process. In this sense, the first organocatalytic aza-Michael/Michael cascade reaction towards the synthesis of chiral pyrrolidines was accomplished by Wang and co-workers,[31] in the reaction between α,β-unsaturated aldehydes and *N*-protected 4-amino-2-butenoates. Aminocatalysis was used to activate the enal through the iminium/enamine manifold. In this case, the possibility of an undesired intramolecular lactamization was prevented with the *trans* geometry of the *N*-protected ethyl 4-amino-2-butenoate. As a result, several enantioenriched pyrrolidines were prepared in excellent yields using (*S*)-α,α-diphenylprolinol trimethylsilyl ether as catalyst, and in the presence of stoichiometric amounts of sodium acetate as Brønsted base (Scheme 3.14). In

[31] Li, H.; Zu, L.; Xie, H.; Wang, J.; Wang, W. *Chem. Commun.* **2008**, 5636.

related reports, nitroalkenes activated by hydrogen bond catalysis have been used.[32]

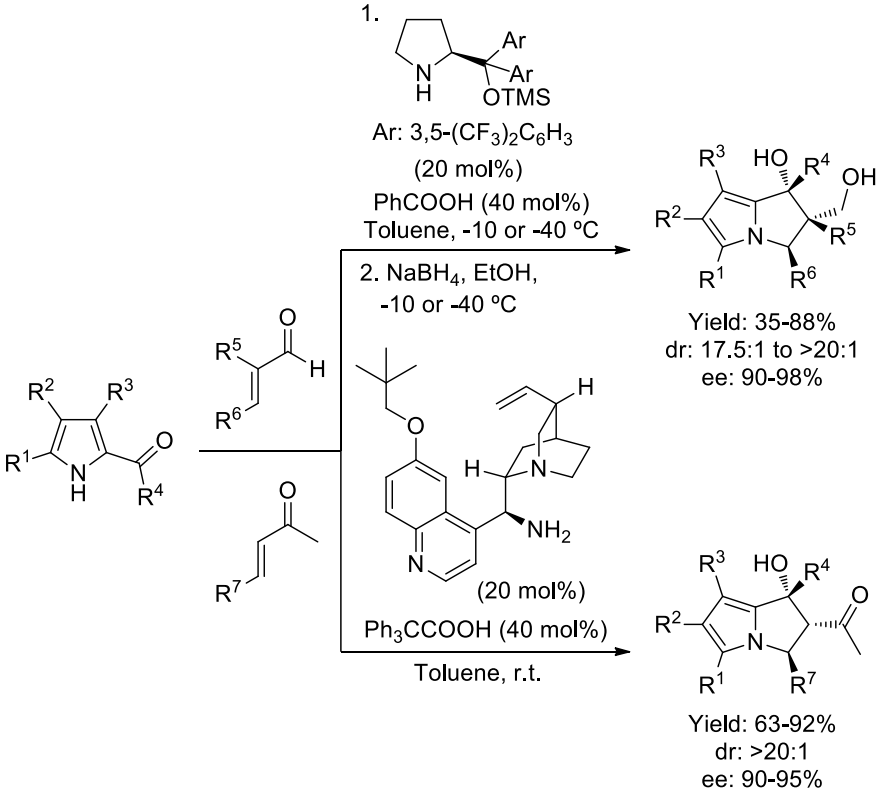


Scheme 3.14

Following a different strategy, Cho and co-workers have developed an aminocatalytic aza-Michael/aldol cascade reaction towards the obtention of chiral polysubstituted pyrrolizines in good yields and excellent stereoselectivities. This approach involved the use of 2-acylpyrroles as pronucleophiles and enals or enones as Michael acceptors, reacting through the iminium/enamine manifold (Scheme 3.15).[33]

[32] a) Zhao, B.-L.; Lin, Y.; Yan, H.-H.; Du, D.-M. *Org. Biomol. Chem.* **2015**, *13*, 11351; b) Noole, A.; Pehk, T.; Järving, I.; Lopp, M.; Kanger, T. *Tetrahedron: Asymmetry* **2012**, *23*, 188.

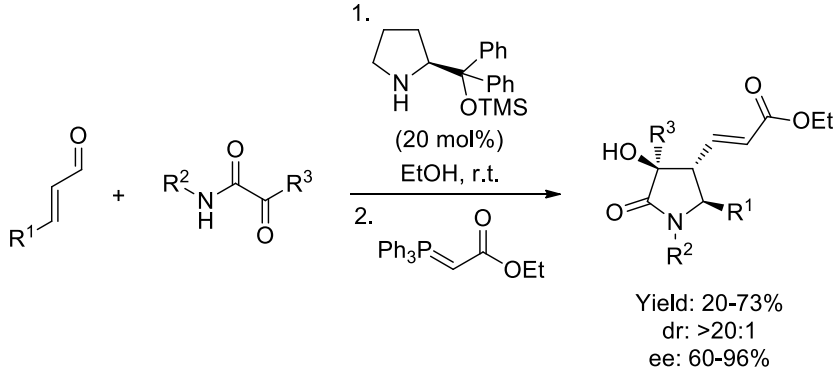
[33] a) Lee, H.-J.; Cho, C.-W. *Eur. J. Org. Chem.* **2014**, 387; b) Lee, H.-J.; Cho, C.-W. *J. Org. Chem.* **2013**, *78*, 3306; c) Bae, J.-Y.; Lee, H.-J.; Youn, S.-H.; Kwon, S.-H.; Cho, C.-W. *Org. Lett.* **2010**, *12*, 4352.



Scheme 3.15

Recently, using the same methodology, Enders and co-workers have developed an *O*-TMS diphenylprolinol catalyzed aza-Michael/aldol cascade reaction between α-ketoamides and enals, followed by Wittig reaction in a one-pot fashion. Based on the iminium/enamine sequence, a variety of substituted pyrrolidin-2-ones were prepared in good to excellent enantioselectivities and as single diastereoisomers (Scheme 3.16).[34]

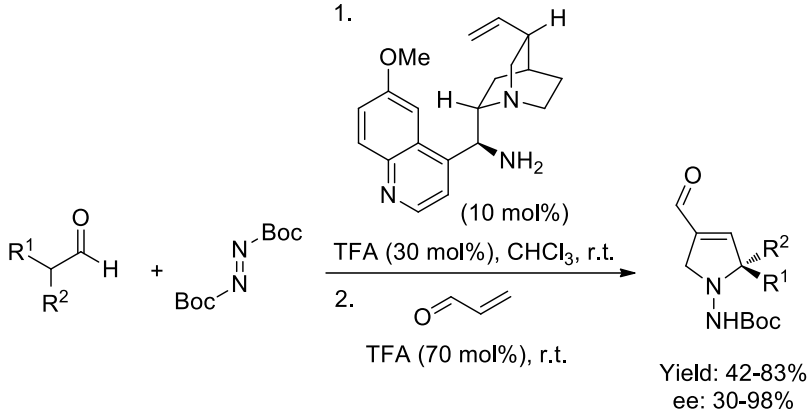
[34] Joie, C.; Deckers, K.; Enders, D. *Synthesis* **2014**, *46*, 799.



Scheme 3.16

To finish with the approaches involving the consecutive C-N and C-C bond formation strategy, there is another interesting example, in which Moreau *et al.* were able to convert α,α-disubstituted aldehydes into 2,2-disubstituted-3-pyrrolines through a primary amine-catalyzed α-amination/aza-Michael/aldol condensation proceeding in a one-pot sequence (see Scheme 3.17).[35] In this process, the aldehyde underwent an initial α-amination with di-*tert*-butylazodicarboxylate catalyzed by a primary amine and TFA as cocatalyst. Under these acidic conditions, the selective *N*-Boc cleavage occurred, followed by organocatalyzed aza-Michael/aldol condensation sequence with an acroleine that was added afterwards to the reaction mixture.

[35] Desmarchelier, A.; Coeffard, V.; Moreau, X.; Greck, C. *Chem. Eur. J.* **2012**, *18*, 13222.

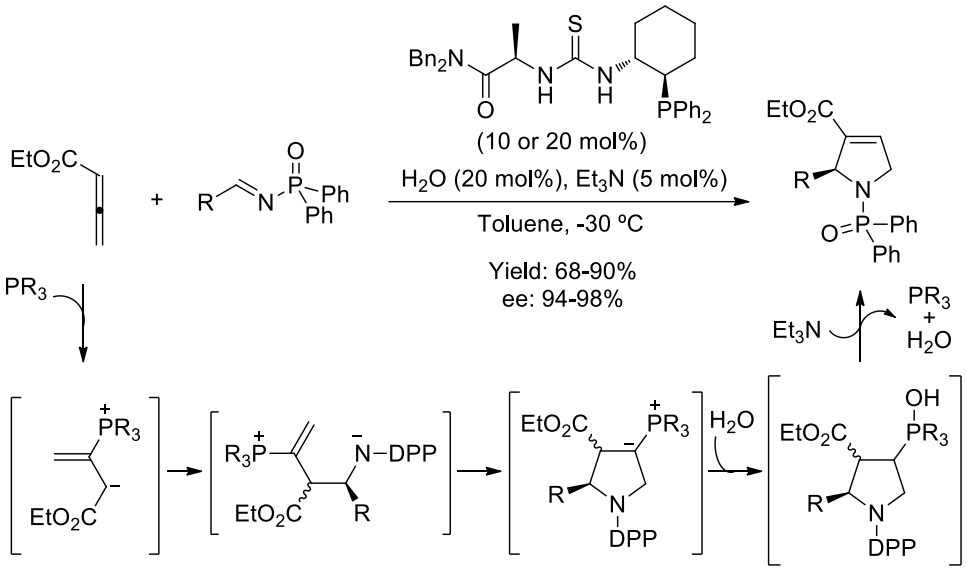


Scheme 3.17

1.3. Consecutive C-C and C-N bond disconnection strategy

The formation of pyrrolidine derivatives through the initial formation of a C-C bond followed by C-N bond formation has been less explored.[3b] In the last years, several organocatalytic examples have been reported, which can be classified as cascade processes initiated by Mannich-type reaction. Most of these cases are based on a formal [3+2] cycloaddition between 1,3-carbon dipole precursors with imines as dipolarophiles. In general, this approach has been less considered due to the difficulty to find a suitable way for the *in situ* generation of a suitable carbon-based 1,3-donor-acceptor system and the low reactivity of imines in nucleophilic additions, being necessary its activation, for example, by introducing a strong electron-withdrawing group on the nitrogen atom, in order to increase its electrophilicity. Apart from this, there are more organocatalytic examples within this disconnection strategy that consist on the use of double donor and double acceptor compounds towards the obtention of the pyrrolidine framework.

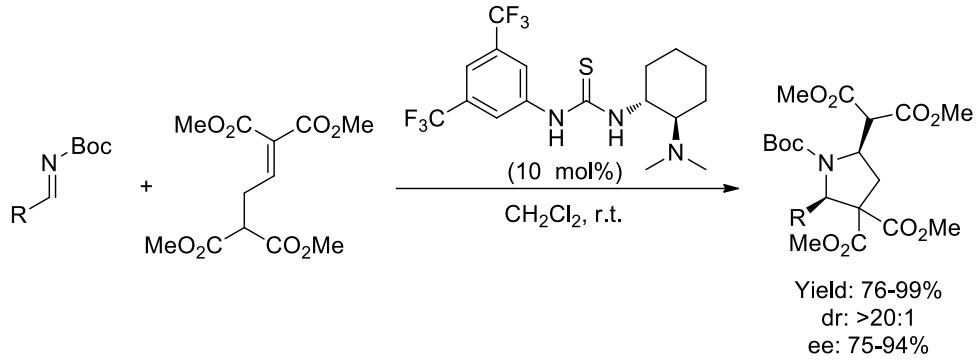
Scheme 3.18 shows the example of Jacobsen and co-workers, who developed the synthesis of chiral substituted 2-aryl-2,5-dihydropyrroles *via* phosphinothiourea catalyzed [3+2] cycloaddition between electron-poor allenes and *N*-diphenylphosphinoyl (DPP) imine. Under the optimal conditions, excellent enantioselectivities were obtained for a variety of (hetero)aryl imines.[36] The reaction consisted on the initial attack of the phosphine catalyst to the allene, forming a stable carbanion that underwent addition to the imine. In this step the thiourea was proposed to remind bounded to the imine by coordination with the carbonyl group of the phosphinoyl moiety, thus controlling the stereoselectivity. Then, the amide moiety was proposed to react intramolecularly to the remaining vinylphosphonium salt that, after protonation and formation of hydroxyphosphorane followed by base-promoted elimination, delivered the corresponding 2,5-dihydropyrroles.



Scheme 3.18

[36] Fang, Y.-Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660.

Based on hydrogen bond catalysis, Enders and co-workers described in 2010 the first Mannich/aza-Michael cascade reaction employing a chiral bifunctional thiourea as catalyst.[37] The reaction between *N*-Boc-protected aryl aldimines and γ-malonate-substituted α,β-unsaturated esters afforded the desired trisubstituted pyrrolidines in good to excellent yields and enantioselectivities (see Scheme 3.19). Recently, the same group applied a similar methodology, consisting on a Mannich/*N*-deprotection/aza-Michael sequence, towards the synthesis of 3,3'-pyrrolidinyl-dispirooxindoles, with two vicinal spiro-stereocenters, in good yields and excellent stereoselectivities by reacting *N*-Boc-protected isatin-derived ketimines and 3-substituted oxindole containing an α,β-unsaturated ester moiety, as donor-Michael acceptor.[38]

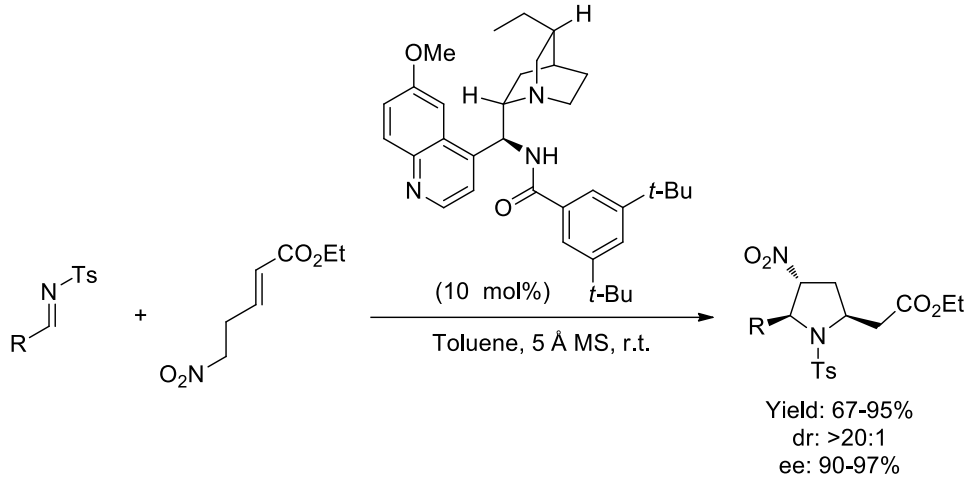


Scheme 3.19

Similarly, Huang and co-workers developed an aza-Henry/aza-Michael cascade reaction, employing *N*-tosyl-protected aldimines and 5-nitropent-2-enoates as donor-acceptor system, under bifunctional catalysis using a Cinchona alkaloid-

[37] Enders, D.; Göddertz, D. P.; Beceño, C.; Raabe, G. *Adv. Synth. Catal.* **2010**, *352*, 2863.
[38] Zhao, K.; Zhi, Y.; Puttreddy, R.; Rissanen, K.; Enders, D. *Chem. Commun.* **2016**, *52*, 2249.

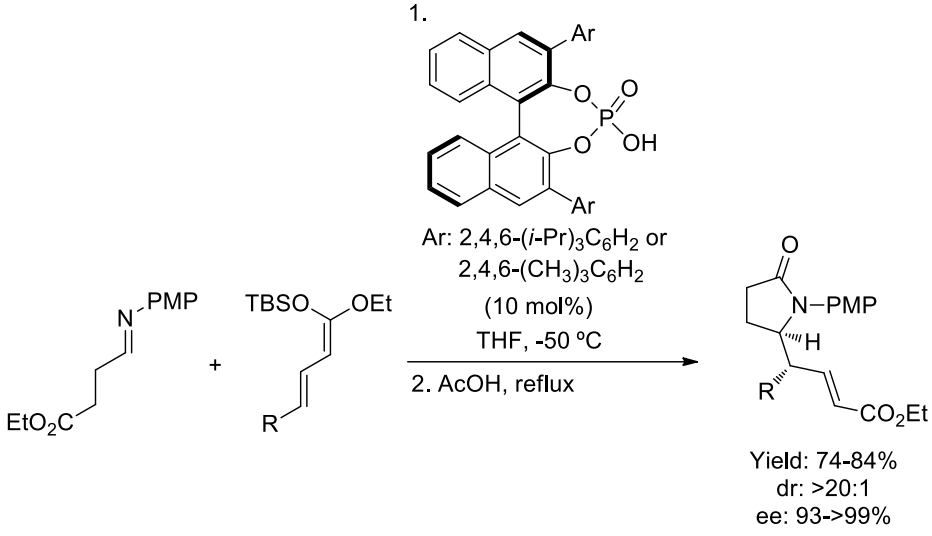
derived carbamate organocatalyst.[39] The reaction began with an organocatalytic reversible aza-Henry reaction, followed by dynamic kinetic resolution (DKR)-driven aza-Michael cyclization, affording 2,3,5-trisubstituted pyrrolidines in good yields and high enantio- and diastereoselectivities (Scheme 3.20).



Scheme 3.20

There is another interesting example that also uses a hydrogen bonding catalyst, in which Schneider *et al.* developed a highly enantioselective vinylogous Mukaiyama-Mannich reaction followed by lactamization to the formation of γ-lactams in one-pot fashion. Moreover, they transformed the obtained lactams into the corresponding pyrrolidines in very good yields (Scheme 3.21).[40]

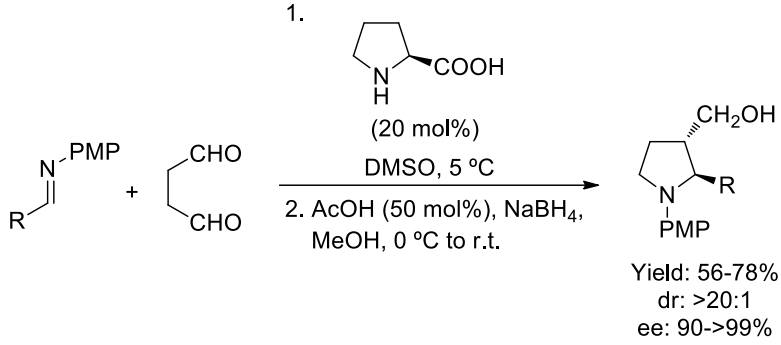
[39] Cheng, T.; Meng, S.; Huang, Y. *Org. Lett.* **2013**, *15*, 1958.
[40] Abels, F.; Lindemann, C.; Schneider, C. *Chem. Eur. J.* **2014**, *20*, 1964.



Scheme 3.21

Based on aminocatalysis, Kumar and co-workers developed an asymmetric Mannich/cyclization cascade reaction catalized by L-proline for the obtention of 2,3-disubstituted pyrrolidines in good yields and excellent stereoselectivities. The reaction consisted on the initial enamine activation of succinaldehyde, followed by Mannich reaction with *N*-PMP protected aldimines and hemiaminalization. This cascade process was followed by reductive amination and simultaneous aldehyde reduction, resulting in the formal [3+2] cycloaddition in a one-pot sequence (Scheme 3.22).[41]

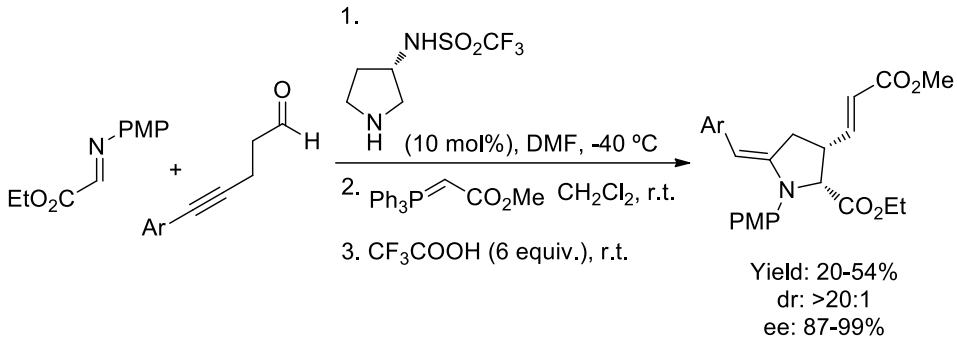
[41] Kumar, I.; Mir, N. A.; Gupta, V. K.; Rajnikant *Chem. Commun.* **2012**, *48*, 6975.



Scheme 3.22

In 2013, De Paolis *et al.* reported another example based on enamine activation, consisting on a one-pot Mannich/Wittig olefination/hydroamination sequence for the synthesis of polysubstituted pyrrolidines with excellent results regarding the stereoselectivity.[42] The reaction started with the Mannich reaction between *N*-heteroarylalkyne aldehyde and *N*-protected aldimine catalyzed by a chiral secondary amine, followed by the Wittig olefination of the aldehyde adduct, to finish with the 5-*exo-dig* hydroamination of the alkyne, promoted by Brønsted acid (Scheme 3.23).

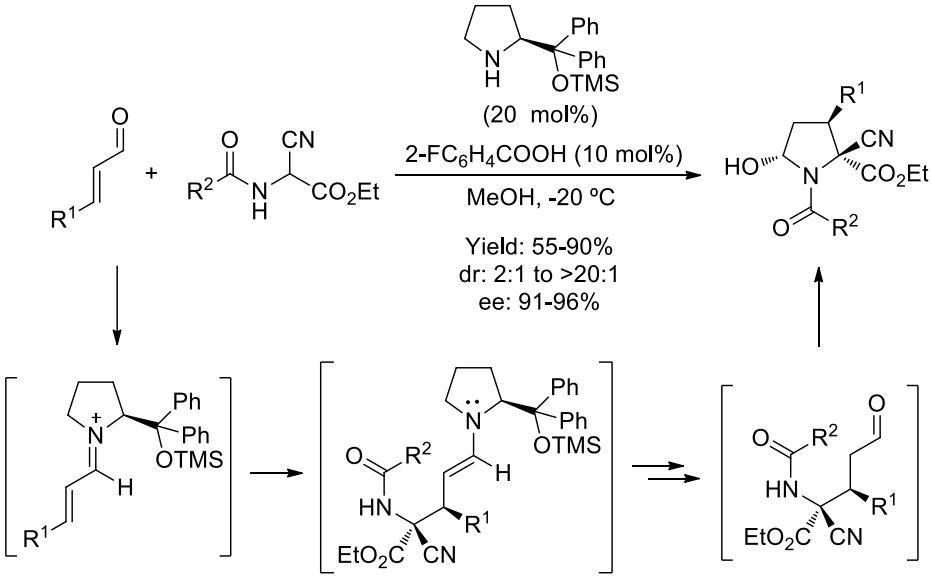
[42] Jean, A.; Blanchet, J.; Rouden, J.; Maddaluno, J.; De Paolis, M. *Chem. Commun.* **2013**, *49*, 1651.



Scheme 3.23

On the other hand, there are several works related to the synthesis of pyrrolidine derivatives through different approaches that those cascades initiated by Mannich reactions. For example, in 2012, Córdova and co-workers developed the use of α-cyanoglycine esters in asymmetric Michael/hemiaminal cascade reaction towards the synthesis of 5-hydroxyproline derivatives.[43] The reaction consists on an initial Michael addition to an enal catalyzed by *O*-TMS diphenylprolinol *via* iminium ion activation, followed by the releasing of the catalyst and intramolecular hemiaminal formation to afford the desired pyrrolidine derivatives in good yields and stereoselectivities (Scheme 3.24).

[43] Breistein, P.; Johansson, J.; Ibrahem, I.; Lin, S.; Deiana, L.; Sun, J.; Córdova, A. *Adv. Synth. Catal.* **2012**, *354*, 1156.



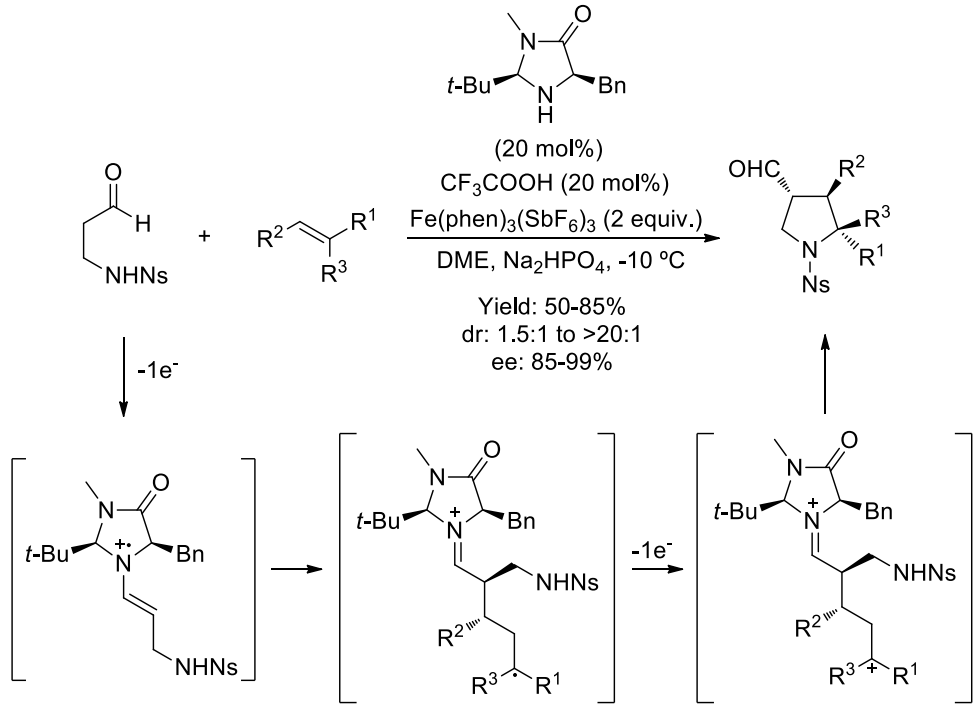
Scheme 3.24

There are other related aminocatalytic examples, in which Michael/hemiaminal cascade methodology is also efficiently used towards the obtention of the pyrrolidine moiety.[44] For example, MacMillan and co-workers developed the enantioselective (3+2) cycloaddition between β-amino aldehydes and several olefins towards the synthesis of stereochemically complex *N*-protected pyrrolidines under SOMO-activation (see Scheme 3.25).[45] Under the optimal conditions, using imidazolidinone catalyst and iron(III)trisphenanthroline as oxidant, high yields and good to excellent stereoselectivities were obtained. Regarding the mechanism, firstly the catalyst condenses with the β-amino aldehyde, forming the corresponding radical enamine, due to the presence of an

[44] a) Scorzelli, F.; Di Mola, A.; Croce, G.; Palombi, L.; Massa, A. *Tetrahedron Lett.* **2015**, *56*, 2787; b) Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Adv. Synth. Catal.* **2013**, *355*, 653.

[45] Jui, N. T.; Garber, J. A. O.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 11400.

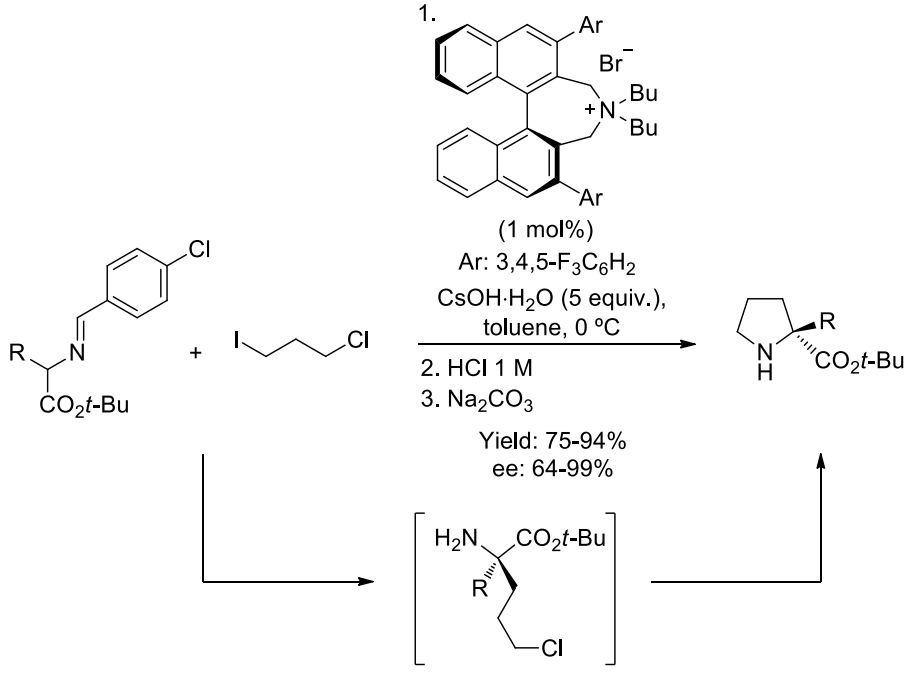
oxidant. Then, the generated three-π-electron radical cation attacks to the alkene furnishing a radical species that after oxidation a cationic intermediate is formed, which is vulnerable to the intramolecular nucleophilic addition of the amine.



Scheme 3.25

Maruoka *et al.* reported an example of this type of disconnection using the phase-transfer catalysis as a stereoinducting methodology.[46] The asymmetric synthesis of α-substituted proline derivatives through a double alkylation process between α-substituted-α-amino acid derivatives and dihaloalkanes employing a chiral quaternary ammonium salt as catalyst was explored affording the final adducts with very good results (Scheme 3.26).

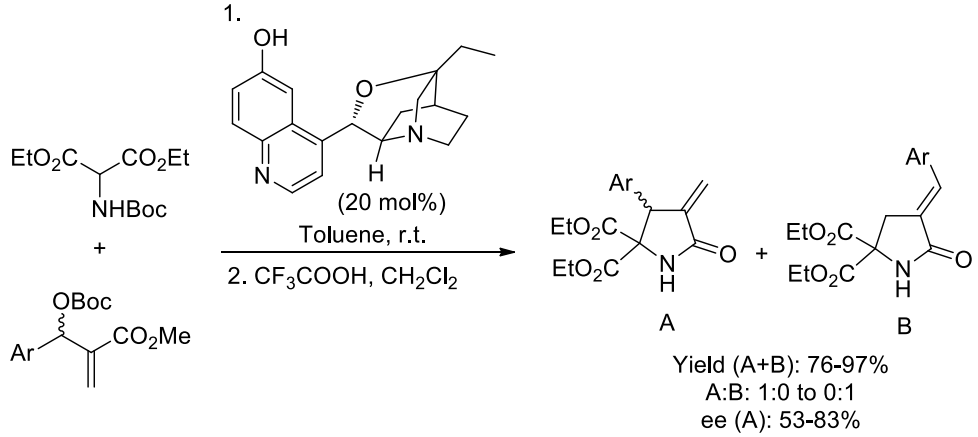
[46] Kano, T.; Sakamoto, R.; Mii, H.; Wang, Y.-G.; Maruoka, K. *Tetrahedron* **2010**, *66*, 4900.



Scheme 3.26

Recently, Rios and co-workers developed the asymmetric synthesis of α-methylene-γ-lactams, employing a chiral Lewis base as a stereoinducting tool. The reaction between protected 2-aminomalonates and Morita-Baylis-Hillman carbonates afforded the corresponding lactams in good yields and moderate enantioselectivities, through the nucleophilic substitution of MBH carbonates by aminomalonate, followed by a favoured 5-*exo*-*trig* cyclization (Scheme 3.27).[47]

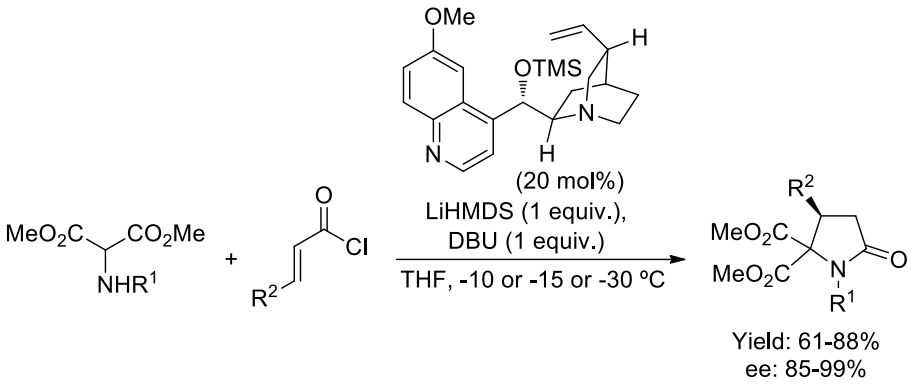
[47] Companyó, X.; Geant, P.-Y.; Mazzanti, A.; Moyano, A.; Rios, R. *Tetrahedron*, **2014**, *70*, 75.



Scheme 3.27

Based on the use of *N*-protected 2-aminomalonates as double donors, Romo *et al.* developed the synthesis of pyrrolidinones through chiral tertiary amine catalyzed Michael/proton transfer/lactamization cascade reaction employing α,β-unsaturated acyl chlorides as substrates (Scheme 3.28). Furthermore, they satisfactorily transformed one of these lactams (R^1 = H; R^2 = 4-ClC_6H_4) into the corresponding pyrrolidine, which is a precursor for the melanocortin-4 receptor agonist.[48] First, an activated α,β-unsaturated acylammonium species is formed, by reaction of the tertiary amine catalyst with the acyl chloride, followed by the Michael reaction of the aminomalonate. After the proton transfer, an intramolecular lactamization is occurred releasing the tertiary amine catalyst, and affording the corresponding lactams in good yields and excellent enantioselectivities.

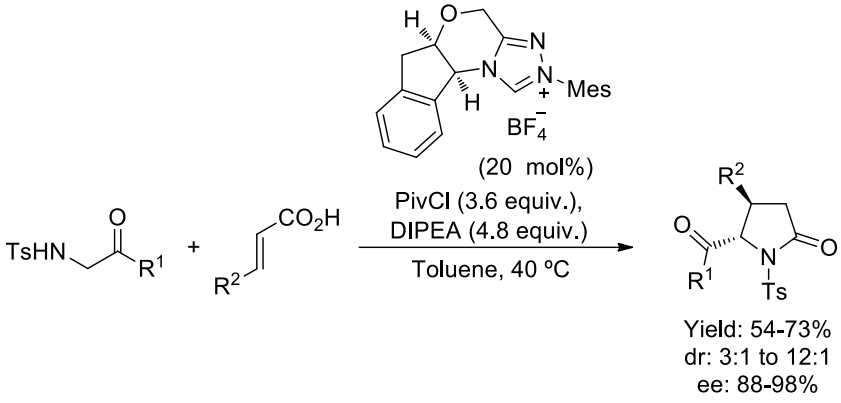
[48] Vellalath, S.; Van, K. N.; Romo, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 13688.



Scheme 3.28

It should be pointed out that concerning this pyrrolidine synthesis strategy, there are more examples using different organocatalytic activations, such as *N*-heterocyclic carbene catalysis.[49] In the latest example, Wang and co-workers, described the enantioselective synthesis of pyrrolidinone derivatives by reacting α-amino ketones and α,β-unsaturated carboxylic acids. These last ones, after *in situ* formation of the corresponding anhydrides, can be activated by *N*-heterocyclic carbenes through the generation of α,β-unsaturated acyl azolium intermediates. The α-amino ketone is able to attack through Michael addition to the previously formed intermediate that after proton transfer, the nucleophilic amine is able to attack intramolecularly through a lactamization process, regenerating the catalyst and affording the final pyrrolidinones in good yields, moderate to good diastereoselectivities and excellent enantiocontrol (Scheme 3.29).

[49] a) Chen, X.-Y.; Gao, Z.-H.; Song, C.-Y.; Zhang, C.-L.; Wang, Z.-X.; Ye, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 11611; b) Zhang, B.; Feng, P.; Sun, L.-H.; Cui, Y.; Ye, S.; Jiao, N. *Chem. Eur. J.* **2012**, *18*, 9198.



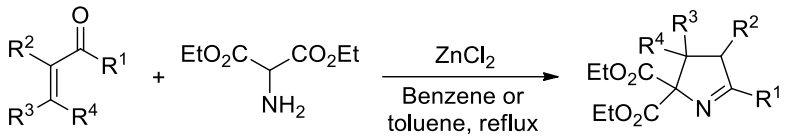
Scheme 3.29

In summary, it could be highlighted the ability of the organocatalysis applied to the asymmetric synthesis of pyrrolidine derivatives, as it can be observed in the large number of presented publications, through the mentioned strategies.

2. SPECIFIC OBJECTIVES AND WORK PLAN

From the presented literature review in the introduction of this chapter, we can conclude that there are plenty of organocatalytic examples regarding the synthesis of chiral pyrrolidine derivatives, owing to the great interest of the compounds containing the pyrrolidine framework. In spite of this, and as it has been observed, within the different disconnection pathways, the simultaneous C-C and C-N bond formation strategy, specifically employing double donor and double acceptor substrates, are less explored.

Inspired by the work of Laronze and co-workers,[50] in which the cyclocondensation reaction of conjugated ketones with diethyl aminomalonate in benzene or toluene under reflux was described, using stoichiometric amount of anhydrous zinc chloride as Lewis acid, yielding the 3,4-dihydro-2*H*-pyrroles as a racemic mixture (see Scheme 3.30), we envisioned that this reaction can be carried out applying the organocatalysis in order to obtain the products in a stereoselective manner.

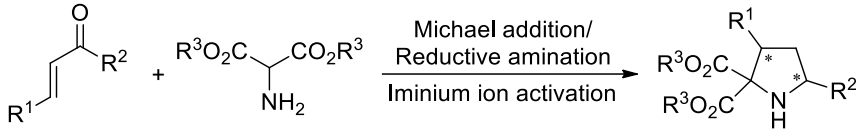


Scheme 3.30

With this work in mind and taking into account the reviewed literature, we planned as a general objective the preparation of chiral polysubstituted proline derivatives. For this purpose, we initially proposed that an α,β-unsaturated ketone

[50] Itoua, G. B.; Laronze, J.-Y. *Synthesis* **1987**, 353.

could be activated *via* iminium ion formation being able to act as Michael acceptor with enhanced electrophilicity, able to react with a dialkyl aminomalonate undergoing a Michael addition product that after hydrolysis of the catalyst, the primary amine derived from the aminomalonate can condense intramolecularly with the resulting ketone, affording the corresponding 1-pyrroline. The reduction of the imine moiety would lead to the formation of the target pyrrolidines (see Scheme 3.31). Due to the use of an enone as Michael acceptor, we considered the employment of a chiral primary amine as catalyst, owing to its known ability to activate ketones,[51] to render the initial conjugate addition enantioselective.



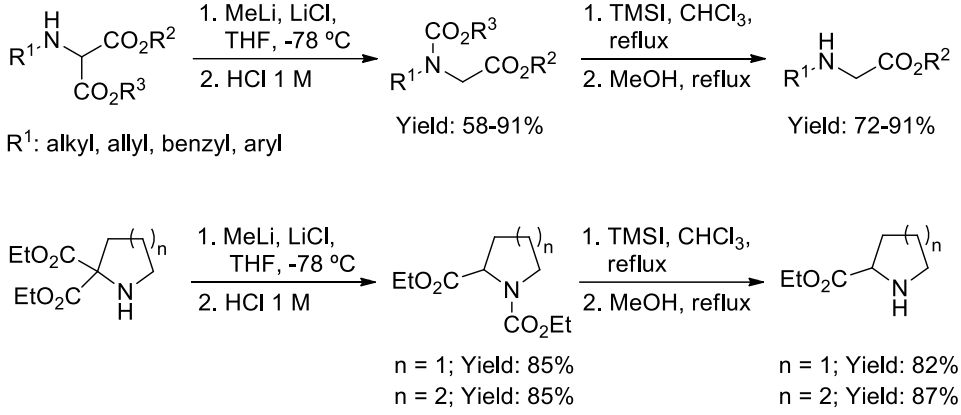
Scheme 3.31

Then, the obtained pyrrolidine 2,2-dicarboxylates should be transformed into the desired proline derivatives, in order to illustrate their potential applications as chiral building blocks, through the recently developed intramolecular base-promoted C→N acyl transfer reaction.[52] This methodology has been satisfactorily employed in our group towards the obtention of *N*-protected α-amino acids from *N*-substituted α-aminomalonates, obtaining very good yields in most of the cases (Scheme 3.32). Finally, the *N*-deprotection of the carbamate should allow us to obtain a variety of α-amino acids derivatives.

---

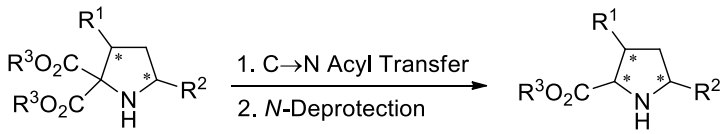
[51] For selected reviews on the use of primary amines as catalysts, see: a) Duan, J.; Li, P. *Catal. Sci. Technol.* **2014**, *4*, 311; b) Melchiorre, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 9748; c) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807; d) Chen, Y.-C. *Synlett* **2008**, 1919; e) Bartoli, G.; Melchiorre, P. *Synlett* **2008**, 1759.

[52] Ugarriza, I.; Uria, U.; Carrillo, L.; Vicario, J. L.; Reyes, E. *Chem. Eur. J.* **2014**, *20*, 11650.



Scheme 3.32

It should be noted that after the corresponding C→N acyl rearrangement a new stereogenic center would be formed, which needs to be controlled by the stereoinduction exerted by the substrate (Scheme 3.33).



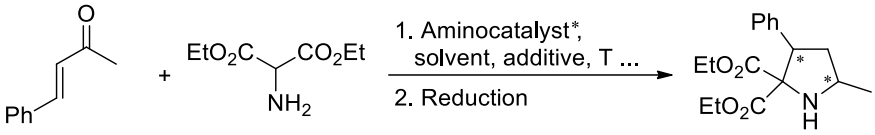
Scheme 3.33

Based on the presented objectives, we proposed the following work plan:

1. Study of the Michael/condensation/reduction process. Initially, we will study the possibility of the synthesis of pyrrolidine derivatives using the reaction between (*E*)-4-phenylbut-3-en-2-one and diethyl aminomalonate as model system, and in the presence of a chiral primary amine as catalyst. The obtained pyrroline will be reduced using standard conditions to afford the desired pyrrolidines. The

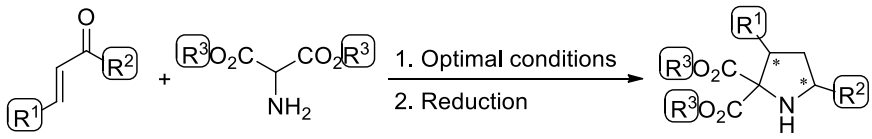
regioselectivity of the initial Michael reaction should be suitably controlled due to the ambident nature of the aminomalonate nucleophile.

2. Optimization of the reaction conditions. Having demonstrated the success of the reaction, we will proceed to survey different experimental variables, such as solvent, additive, catalyst and temperature, using the same reaction model, in order to carry out the reaction with the optimal yield and stereocontrol (Scheme 3.34).



Scheme 3.34

3. Scope of the reaction. With the best conditions in hands, we will evaluate various Michael acceptors, studying the effect of different substitution patterns on the reactivity and enantioselectivity of the reaction. Furthermore, different dialkyl aminomalonates will be tested (Scheme 3.35).



Scheme 3.35

4. Transformation of the adducts: Synthesis of proline derivatives. Finally, we will focus on the application of the intramolecular base-promoted C→N acyl transfer reaction into these pyrrolidine 2,2-dicarboxylates, with the purpose of obtaining *N*-protected proline ester derivatives. If the reaction takes

place efficiently, the corresponding carbamates will subsequently be deprotected in order to achieve the desired unprotected proline esters.

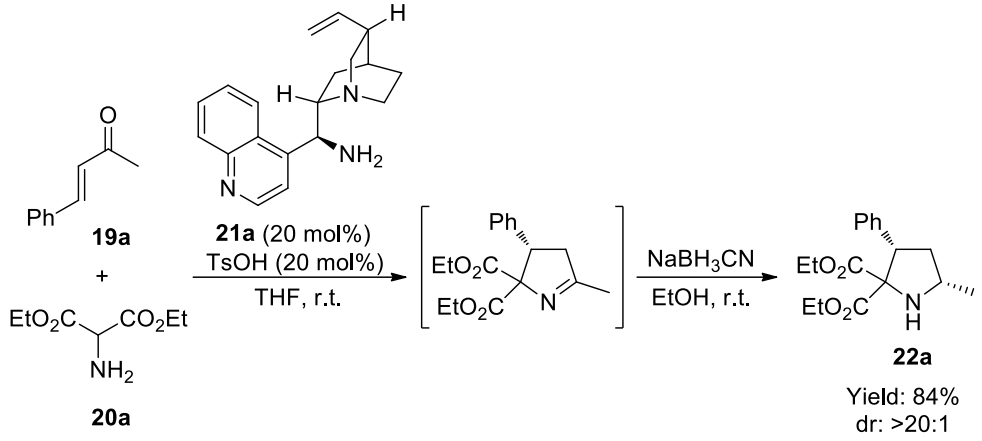
3. RESULTS AND DISCUSSION

Once the different examples found in the literature about the topic have been reviewed and commented, and the specific objectives and work plan have been established, we will proceed with the presentation and the corresponding discussion of the most relevant results obtained on this part of our research.

3.1. Study of the Michael/condensation/reduction process

We started our study by evaluating the viability of the reaction. In this sense, the reaction between (*E*)-4-phenylbut-3-en-2-one **19a** and diethyl aminomalonate **20a**, was used as a representative model system in the presence of 9-*epi*-9-amino-9-deoxycinchonidine **21a** as primary amine catalyst derived from Cinchona alkaloids, in THF as solvent and at room temperature. In order to favour the formation of the iminium ion, *p*-toluenesulfonic acid was also added as a Brønsted acid cocatalyst in the same ratio than the catalyst. The reaction was followed by ^{1}H-NMR, through the observation of several characteristic signals related to the formation of the expected cyclic imine, such as the singlet signal corresponding to the methyl group of the pyrroline at 2.24 ppm, and obtaining full chemical conversion after 180 hours. However, when we tried to purify the product by flash column chromatography, only decomposition was observed, due to the instability of the imine. For this reason, we proceeded to the reduction of the resulting pyrroline in a one-pot fashion, employing $NaBH_3CN$ in EtOH as solvent. Pyrrolidine **22a** was obtained as a single diastereoisomer in excellent yield after purification by flash column chromatography (Scheme 3.36). The latter finding indicated that the stereogenic center generated after the initial Michael addition

step was able to exert an effective asymmetric induction on the reduction of the imine group.



Scheme 3.36

At this point, the relative configuration of the stereogenic centers formed in the one-pot process was determined through NOESY experiment. The presence of significant n.O.e. was observed between the protons of the aromatic ring and one of the two diastereotopic protons at C-4, exclusively, H^{4a}, and between the protons of the methyl group and H^{4a}. No n.O.e. was appreciated between H^{4b} and the aromatic protons, and between H^{4b} and the methyl protons. This indicated a *cis* relative configuration of substituents at C-3 and C-5 (Figure 3.2).

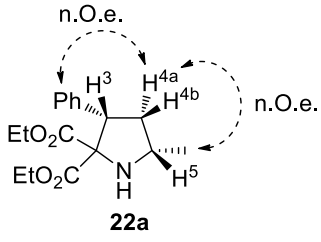


Figure 3.2

For the determination of the enantiomeric excess of the cycloadduct **22a**, the preparation of a racemic compound was necessary. Thus, the same reaction was performed in the presence of benzhydrylamine as non-chiral primary amine catalyst, obtaining, after reduction of the corresponding 3,4-dihydropyrrole, the racemic pyrrolidine **(±)-22a**, which was subjected to HPLC analysis on chiral stationary phase. The separation of both enantiomers was achieved employing a Chiralpak IA chiral column with a mixture of 98:2 *n*-hexane/*i*-PrOH as eluent, in a 1.0 mL/min flow. With these conditions, we measured the enantiomeric excess of the adduct **22a** obtained using catalyst **21a**, observing that a 78% ee has been achieved. Both chromatograms are shown on Figure 3.3. With this result, we decided to check the enantiocontrol exerted by its quasienantiomer, 9-*epi*-9-amino-9-deoxycinchonine, with which the opposite enantiomer was obtained in a 68% ee, lower than in the previous case.

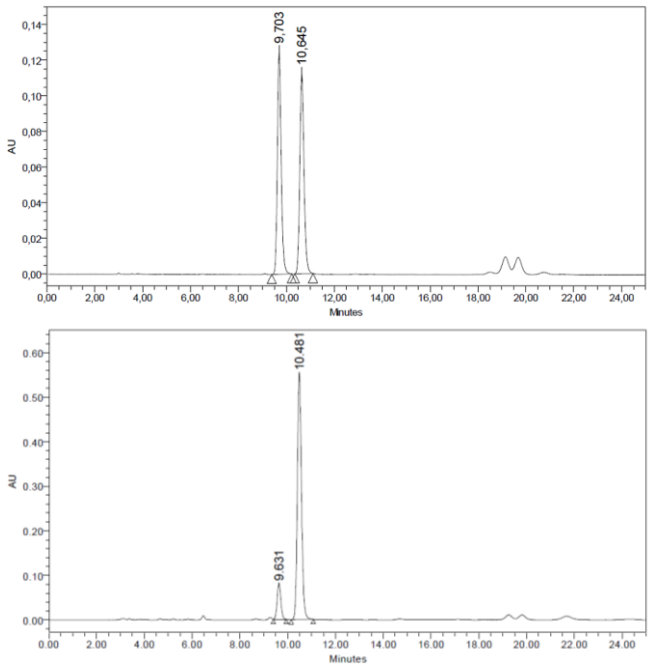
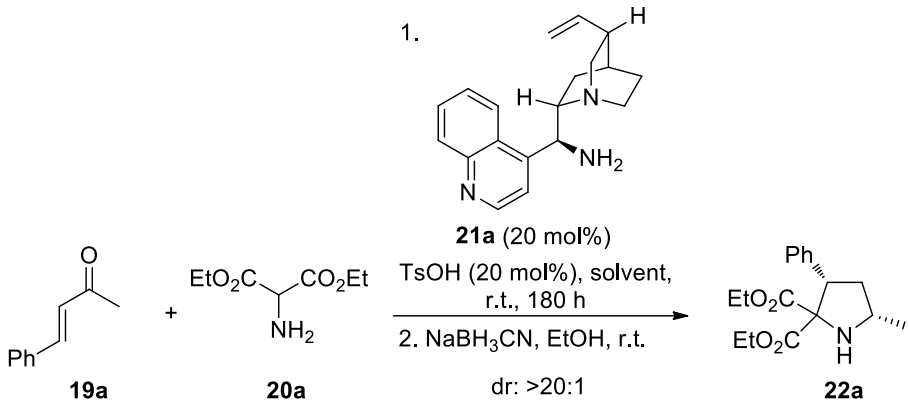


Figure 3.3

3.2. Optimization of the reaction conditions

After the initial result obtained in the experiment shown on Scheme 3.36, we proceeded to evaluate different reaction conditions, in order to improve the outcome of the reaction. First, we evaluated the influence of solvents with different properties. The results are summarized in the Table 3.1.

Table 3.1: Screening of reaction conditions: Solvent.[a]



19a **20a** **22a**

Entry	Solvent	Yield (%)[b]	ee (%)[c]
1	THF	84	78
2	Et_2O	61	62
3	$CHCl_3$	78	76
4	CH_2Cl_2	63	68
5	EtOAc	80	78
6	CH_3CN	59	51
7	DMF	63	8
8	EtOH	88	20
9	Toluene	67	65

[a] The reaction was performed in 2 mL of solvent and 0.4 mmol scale of **19a**, using 1.4 equiv. of **20a**. [b] Isolated product yield in two-step reaction after flash column chromatography. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **22a**.

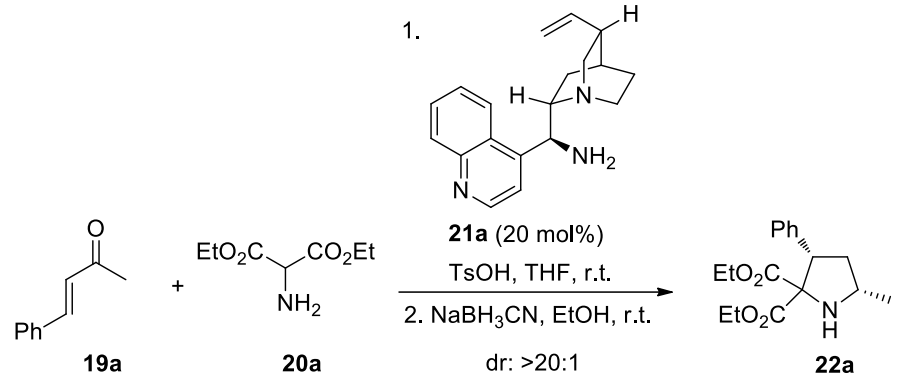
As shown in Table 3.1, the best results were obtained with THF, $CHCl_3$ and EtOAc as solvents (entries 1, 3 and 5). The use of more polar solvents, such as CH_3CN and DMF, resulted in a reduction of the enantiomeric excess (entries 6 and 7), observing also low stereocontrol when a polar protic solvent was employed

(entry 8). In the presence of a non polar solvent the stereochemical outcome was not improved (entry 9).

In order to increase the enantioselectivity of the reaction, we decided to study the effect of the ratio between the amount of catalyst and the acidic additive (see Table 3.2), taking into account previous works of Melchiorre and co-workers,[53] in which the ability of the acid cocatalyst to modify the three-dimensional structure of the catalyst, has been described. In particular, these reports indicate that the anion of the acidic additive assembles to both the iminium ion and the protonated tertiary amine of the activated intermediate, making it more rigid and therefore leading to a better stereocontrol in the reaction. The presence of multiple basic points at the structure of the catalyst also implies that the acid cocatalyst might be needed in excess with respect to the amount of cinchona alkaloid-based catalyst.

[53] a) Moran, A.; Hamilton, A.; Bo, C.; Melchiorre, P. *J. Am. Chem. Soc.* **2013**, *135*, 9091; b) Tian, X.; Cassani, C.; Liu, Y.; Moran, A.; Urakawa, A.; Galzerano, P.; Arceo, E.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 17934.

Table 3.2: Screening of reaction conditions: Amount of additive.[a]



19a **20a** **22a**

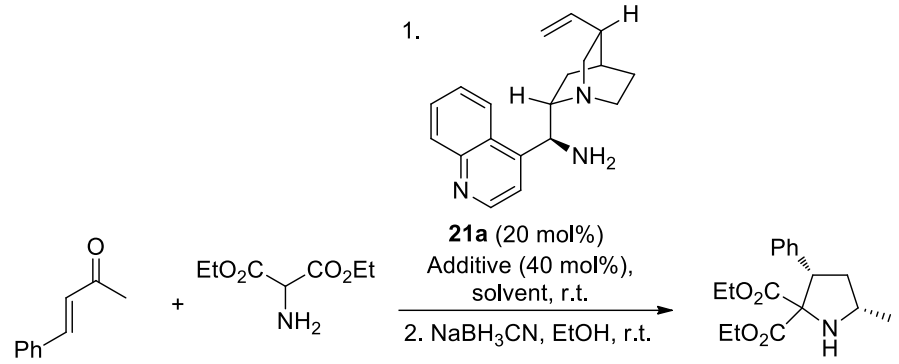
Entry	TsOH (mol%)	Time (h)	Yield (%)[b]	ee (%)[c]
1	20	180	84	78
2	30	72	82	81
3	40	60	86	83
4	60	48	84	83
5[d]	40	48	85	80

[a] The reaction was performed in 2 mL of THF and 0.4 mmol scale of **19a**, using 1.4 equiv. of **20a**. [b] Isolated product yield in two-step reaction after flash column chromatography. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **22a**. [d] The reaction was carried out using 2.0 equiv. of **20a**.

From the experiments shown in the Table 3.2, it was concluded that increasing the amount of additive, the enantioselectivity and the rate of the reaction were improved, keeping an excellent yield (entries 1-4). It was found that the best result was obtained using double amount of acid than catalyst (entry 3), not observing any improvement in the reaction outcome with more amount of cocatalyst (entry 4). We also tried the reaction using double amount of aminomalonate **20a** than enone **19a**, not achieving better results (entry 5).

We next decided to evaluate different acidic additives, keeping the double amount of additive than catalyst, and carrying out the reaction in THF, $CHCl_3$ and EtOAc, which were the solvents that performed better in the reaction (entries 1, 3 and 5 in Table 3.1). From the results shown in Table 3.3, in the case of use THF as solvent (entries 1-6), it can be observed that employing CH_3SO_3H with similar pK_a compared to TsOH, better results were observed regarding the rate and the enantioselectivity of the process (entry 2 *vs*. entry 1). However, reducing the acidity of the additive, the reaction outcome was proportionally getting worse (entries 3-6). The additives that showed better results, were also tested in $CHCl_3$ (entries 7-9), observing in this case the opposite reaction performance regarding the acidity, finding better results with TFA as additive, but requiring long reaction time (entry 9). Finally, EtOAc was tested as solvent (entries 10-12) using the same three additives, observing in this case worse yields while decreasing the acidity, obtaining the best results when TsOH was used (entry 10). Taking into account all the results, we concluded that the optimal conditions were the use of THF as solvent and CH_3SO_3H as cocatalyst (entry 2).

Table 3.3: Screening of reaction conditions: Brønsted acid additive.[a]

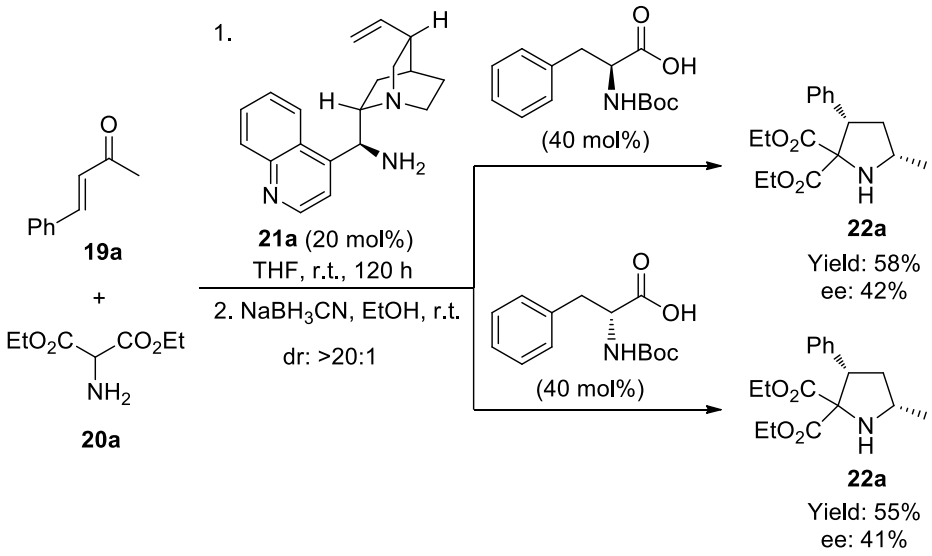


19a **20a** dr: >20:1 **22a**

Entry	Solvent	Additive	pK_a[b]	Time (h)	Yield (%)[c]	ee (%)[d]
1	THF	TsOH	-2.8	60	86	83
2	THF	CH_3SO_3H	-2.6	42	89	89
3	THF	TFA	-0.2	72	92	82
4	THF	DPP	1.9	60	85	75
5[e]	THF	4-$NO_2C_6H_4CO_2H$	3.4	132	58	54
6[f]	THF	$PhCO_2H$	4.2	168	50	20
7	$CHCl_3$	TsOH	-2.8	84	84	78
8	$CHCl_3$	CH_3SO_3H	-2.6	156	80	83
9	$CHCl_3$	TFA	-0.2	120	87	87
10	EtOAc	TsOH	-2.8	84	90	85
11	EtOAc	CH_3SO_3H	-2.6	204	81	80
12	EtOAc	TFA	-0.2	84	72	85

[a] The reaction was performed in 2 mL of solvent and 0.4 mmol scale of **19a**, using 1.4 equiv. of **20a**. [b] pK_a values measured in H_2O. Perrin, D. D.; Serjeant, E. P.; Dempsey, B. *pK_a Predictions for Organic Acids and Bases*, Chapman and Hall, London, **1981**. [c] Isolated product yield in two-step reaction after flash column chromatography. [d] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **22a**. [e] Conversion of 84% (calculated by ^{1}H-NMR analysis of the non purified reaction mixture). [f] Conversion of 73% (calculated by ^{1}H-NMR analysis of the non purified reaction mixture).

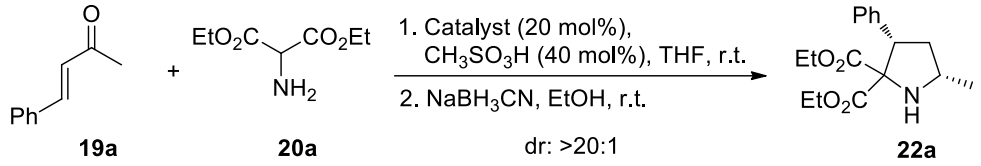
Additionally, we tried to improve the enantioselectivity using chiral Brønsted acid, in order to find the matching combination. When chiral aminoacids were employed, such as *N*-Boc-L-phenylalanine and its enantiomer, worse results were obtained regarding the yield and enantioselectivity (Scheme 3.37), while with higher acidity additives, like chiral phosphoric acids, low conversion or no reaction was observed.



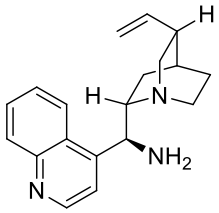
Scheme 3.37

Concurrently, we studied a selection of some other primary amine catalysts, like several cinchona alkaloid-base derivatives (catalysts **21b-d** in Table 3.4) and thiourea derivatives (catalysts **21e** and **21f** in Table 3.4), with the purpose of improving the enantiocontrol.

Table 3.4: Screening of reaction conditions: Primary amine catalyst.[a]

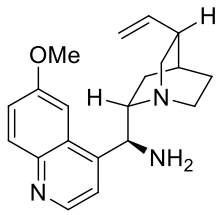


19a **20a** **22a**



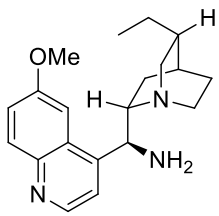
21a

Yield: 89%[b]
ee: 89%[c]



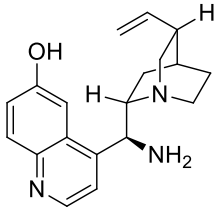
21b

Yield: 93%
ee: 83%



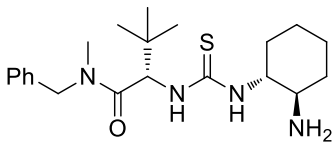
21c

Yield: 79%
ee: 73%



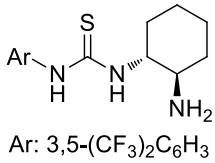
21d

Yield: 74%
ee: 90%



21e[d]

Yield: 62%
ee: -36%



Ar: 3,5-$(CF_3)_2C_6H_3$

21f[d]

Yield: 54%
ee: -81%

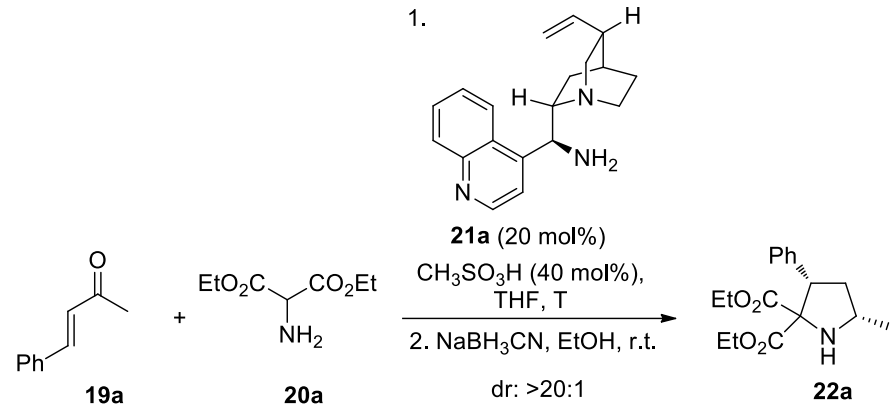
[a] The reaction was performed in 2 mL of THF and 0.4 mmol scale of **19a**, using 1.4 equiv. of **20a**. [b] Isolated product yield in two-step reaction after flash column chromatography. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **22a**. [d] The reaction was carried out without the presence of acid cocatalyst, obtaining 76% of conversion (calculated by ^{1}H-NMR analysis of the non purified reaction mixture).

The use of the primary amines derived from quinine and hydroxyquinine (**21b** and **21c**) did not improve the previous results obtained by the catalyst derived from cinchonidine **21a**. When 9-*epi*-9-amino-9-deoxy-6-hydroxycinchonidine **21d** was used as catalyst, the enantioselectivity remained

unchanged but the yield was slightly decreased. We also carried out the reaction with bifunctional primary amine/thiourea catalysts such as the Jacobsen thiourea derivative **21e** and the Takemoto thiourea derivative **21f** in absence of the acid cocatalyst, owing to the acidic nature of the thiourea moiety. In both cases, full conversion was not achieved and the opposite enantiomer was obtained as a major product, without any improvement in the enantioselectivity. To conclude, 9-*epi*-9-amino-9-deoxycinchonidine was chosen as the best catalyst for the stereochemical outcome.

Finally, we also proceeded to carry out the reaction at different temperatures, with the aim of observing the effect on the enantiocontrol (Table 3.5). At higher temperature, the enantioselectivity was significantly decreased (entry 2), while at lower temperatures the rate of the reaction decreased, not achieving full conversion at -30 ºC after long reaction time (entries 3-4). In conclusion, performing the reaction at room temperature was the best option regarding the rate, the yield and the enantiopurity.

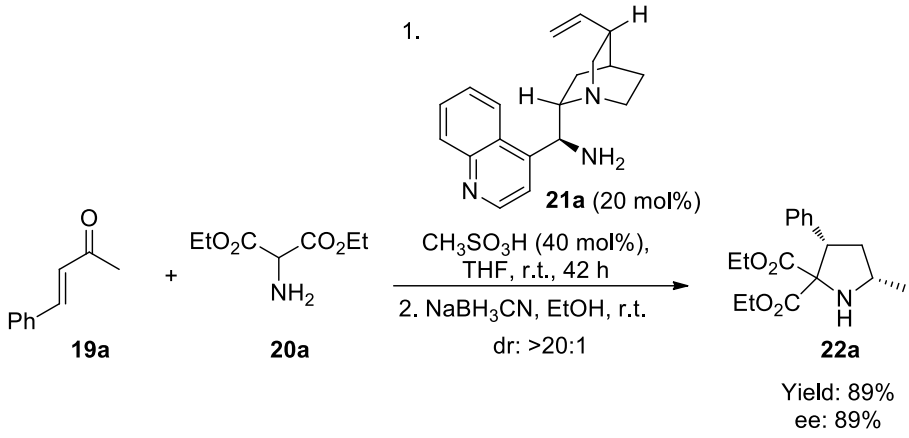
Table 3.5: Screening of reaction conditions: Temperature.[a]



Entry	T (ºC)	Time (h)	Yield (%)[b]	ee (%)[c]
1	r.t.	42	89	89
2	50	24	83	76
3	4	84	83	90
4[d]	-30	240	53	86

[a] The reaction was performed in 2 mL of THF and 0.4 mmol scale of **19a**, using 1.4 equiv. of **20a**. [b] Isolated product yield in two-step reaction after flash column chromatography. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **22a**. [d] Conversion of 76% (calculated by ^{1}H-NMR analysis of the non purified reaction mixture).

At this point, after taking into account a wide variety of optimization experiments, we established that the best conditions for the Michael/condensation cascade reaction between (*E*)-4-phenylbut-3-en-2-one **19a** and diethyl aminomalonate **20a** were the use of 20 mol% of 9-*epi*-9-amino-9-deoxycinchonidine **21a** as catalyst with 40 mol% of methanesulfonic acid as cocatalyst in THF at room temperature, followed by the diastereoselective reduction of the generated imine in one-pot fashion, employing $NaBH_3CN$ in EtOH at room temperature (Scheme 3.38).

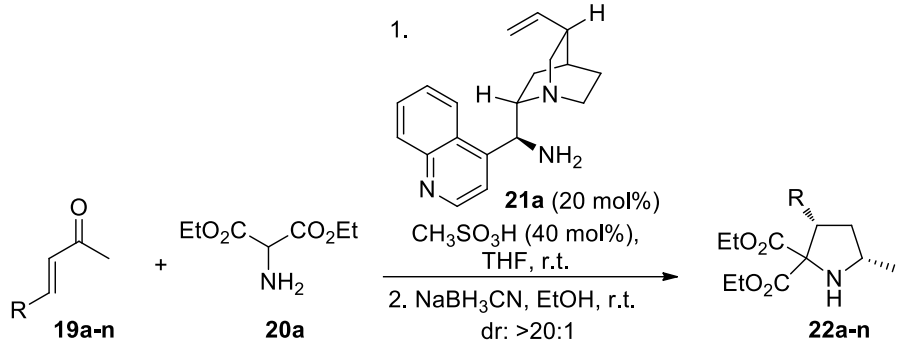


Scheme 3.38

3.3. Scope of the reaction

After studying the reaction conditions and decided the optimal protocol, we proceeded to extend the methodology to the use of other α,β-unsaturated ketones containing different substitution patterns, in order to determine the scope and limitations of the cascade reaction. First, we studied the addition of diethyl aminomalonate **20a** to different β-(hetero)aryl substituted enones **19a-n** under the optimized conditions (Table 3.6). Excellent results were obtained both with β-aryl and heteroaryl-substituted α,β-unsaturated ketones, regardless of the electronic nature of the aryl substituent, leading to the desired pyrrolidines in high yields and enantioselectivities, and as single diastereoisomers after the reduction step. It can be observed that enones incorporating electron-donating groups at the aryl substituent required longer reaction times than enones with electron-withdrawing groups (entries 5, 9 and 12). The position of the substituent at the aryl group also had a reasonable influence on the reaction rate (entries 3-9). In the case of use heteroaryl substituted enones, higher yields and enantioselectivities were observed performing the reaction with TFA as cocatalyst in $CHCl_3$ (entries 13-14 *vs*. 15-16).

Table 3.6: Scope of the reaction using a series of β-substituted enones.[a]

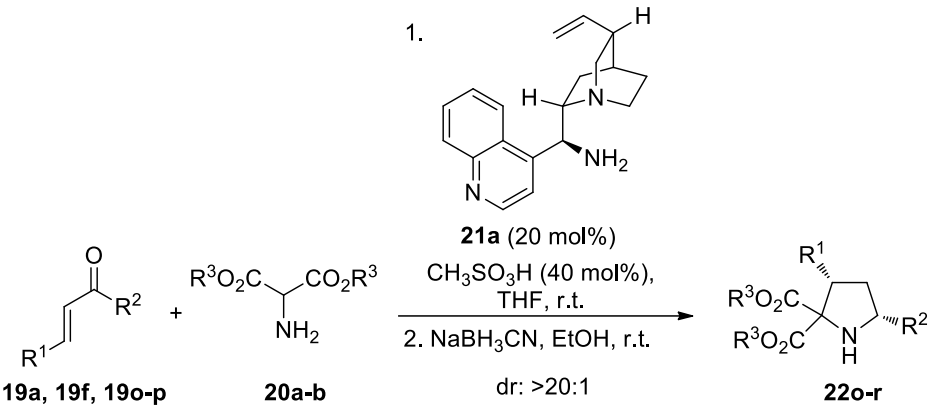


Entry	R (19)	22	Time (h)	Yield (%)[b]	ee (%)[c]
1	Ph (**19a**)	**22a**	42	89	89
2	4-MeC_6H_4 (**19b**)	**22b**	41	70	90
3	2-MeOC_6H_4 (**19c**)	**22c**	119	67	89
4	3-MeOC_6H_4 (**19d**)	**22d**	68	77	89
5	4-MeOC_6H_4 (**19e**)	**22e**	41	79	89
6	2,6-$(MeO)_2C_6H_4$ (**19f**)	**22f**	97	63	77
7	3,5-$(MeO)_2C_6H_4$ (**19g**)	**22g**	29	67	87
8	2-FC_6H_4 (**19h**)	**22h**	42	78	89
9	4-FC_6H_4 (**19i**)	**22i**	26	74	89
10	4-ClC_6H_4 (**19j**)	**22j**	27	78	89
11	4-$CF_3C_6H_4$ (**19k**)	**22k**	23	53	87
12	4-$NO_2C_6H_4$ (**19l**)	**22l**	20	70	86
13	2-Furyl (**19m**)	**22m**	72	73	76
14	2-Thienyl (**19n**)	**22n**	96	72	78
15[d]	2-Furyl (**19m**)	**22m**	120	80	86
16[d]	2-Thienyl (**19n**)	**22n**	120	81	87

[a] The reaction was performed in 2 mL of solvent and 0.4 mmol scale of **19**, using 1.4 equiv. of **20a**. [b] Isolated product yield in two-step reaction after flash column chromatography. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **22**. [d] Reaction carried out using TFA as an additive and $CHCl_3$ as a solvent.

Once it was analyzed the effect of different aryl and heteroaryl substituents at β-position of the Michael acceptor, we decided to employ several aminomalonates and enones with different substituents at β and α'-position (Table 3.7). A more sterically demanding ethyl group at the α'-position of the unsaturated ketone was also well tolerated (entry 1), decreasing the yield and the reaction rate, comparing with the less congested compound, however with α'-aryl-substituted enones, a class of substrates that are not generally suitable for iminium ion activation, the reaction did not work efficiently. For instance, with (*E*)-1-phenylbut-2-en-1-one as Michael acceptor the reaction did not progress, observing a complex mixture of products, while the reaction with (*E*)-chalcone **19p** furnished the intermediate pyrroline after the cascade reaction in low yield and moderate enantiocontrol (entry 2). This intermediate proved to be unreactive towards reduction under our optimal conditions, probably due to the conjugated character of the azomethine moiety, but fortunately, in this case we were able to isolate the pyrroline by flash column chromatography. It should be noted that, the reaction with alkyl substituents in α' and β-position of the enone, such as (*E*)-pent-3-en-2-one, resulted in a dirty reaction, not observing the desired 1-pyrroline. We also surveyed the (*E*)-3-methyl-4-phenylbut-3-en-2-one, with methyl group in α-position, only recovering starting material, presumably because of the more overcrowded system. On the other hand, the reaction was carried out satisfactorily when dimethyl aminomalonate **20b** was used (entries 3 and 4), obtaining the corresponding pyrrolidines in very good yields and enantioselectivities.

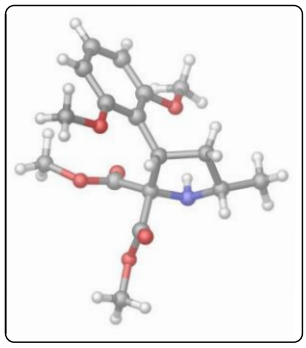
Table 3.7: Scope of the reaction using different aminomalonates and enones.[a]

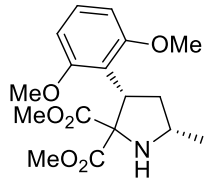


Entry	R^1, R^2 (19)	R^3 (20)	22	Time (h)	Yield (%)[b]	ee (%)[c]
1	4-$MeOC_6H_4$, Et (**19o**)	Et (**20a**)	**22o**	168	65	89
2[d]	Ph, Ph (**19p**)	Et (**20a**)	**22p**	192	31	58
3	Ph, Me (**19a**)	Me (**20b**)	**22q**	41	91	90
4	2,6-$(MeO)_2C_6H_4$, Me (**19f**)	Me (**20b**)	**22r**	72	67	80

[a] The reaction was performed in 2 mL of solvent and 0.4 mmol scale of **19**, using 1.4 equiv. of **20**. [b] Isolated product yield in two-step reaction after flash column chromatography. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phase of the compound **22**. [d] The intermediate pyrroline was isolated.

Fortunately, pyrrolidine **22r** was isolated as a white solid that could be recrystallized, determining the absolute configuration by single crystal X-ray analysis, and confirming the *cis* configuration of substituents at C-3 and C-5. The crystal structure of **22r** is depicted in Figure 3.4 showing a 3*S*,5*S* configuration at the two stereogenic centers generated during the one-pot process. This can be extended by mechanistic analogy to the other prepared pyrrolidines **22a-r**.



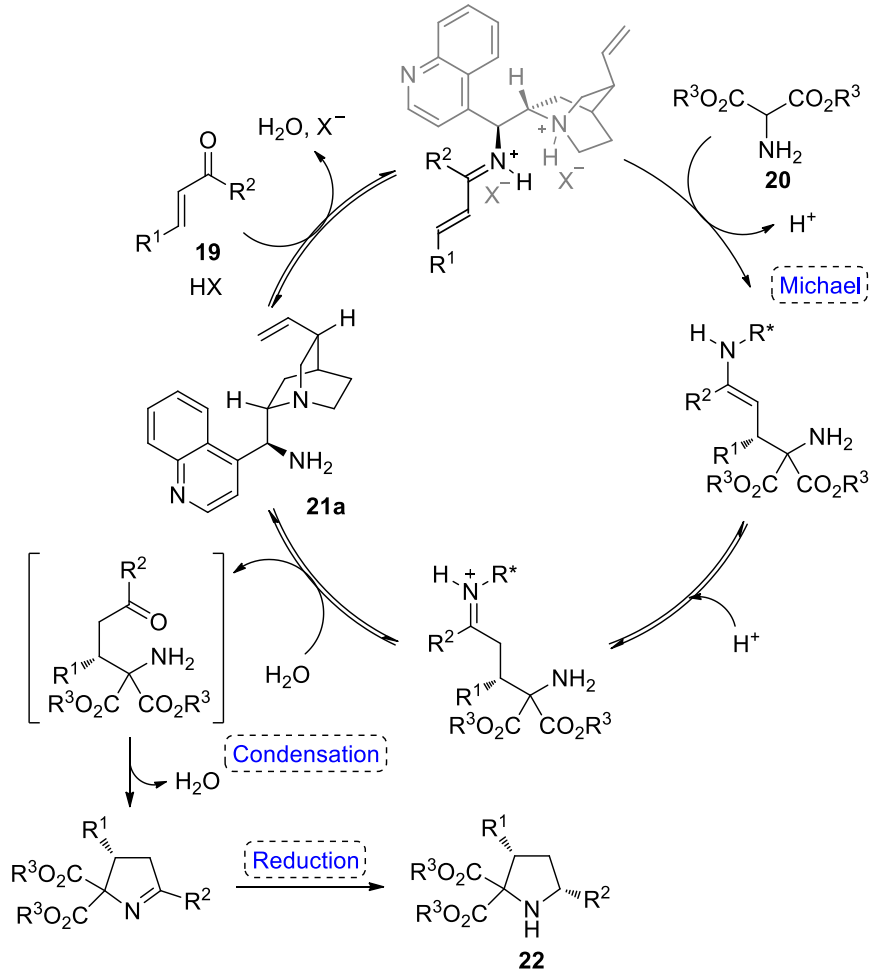


22r

Figure 3.4

Regarding the mechanism of the reaction (see Scheme 3.39), we proposed, after all experimental studies, that the reaction consisted on a Michael/condensation cascade reaction by reacting enones and dialkyl aminomalonates using a primary amine as catalyst. First, the iminium ion intermediate is formed, with the *E* configuration, by condensation of the enone with the aminocatalyst, followed by the Michael addition of the aminomalonate to the less hindered *Re* face of the activated species. Owing to the relevance of the acidic additive on the stereochemical outcome, improving the enantioselectivity with double amount of acid than catalyst, we proposed, based on the results by Melchiorre and co-workers,[53] that the anions of the acid cocatalyst are assembled to the activated intermediate, by formation of ion-pairs both with the iminium ion and the protonated tertiary amine, thus modulating the chiral space, and blocking in this case the *Si* stereotopic face. After the Michael addition, an enamine intermediate is formed, followed by the subsequent protonation towards the generation of the iminium ion. The hydrolysis of this intermediate regenerates the catalyst and provides the Michael adduct that is able to cyclize *via* intramolecular condensation of the primary amine with the resulting carbonyl group, obtaining the corresponding chiral pyrrolines. Finally, *cis*-3,5-disubstituted pyrrolidines are

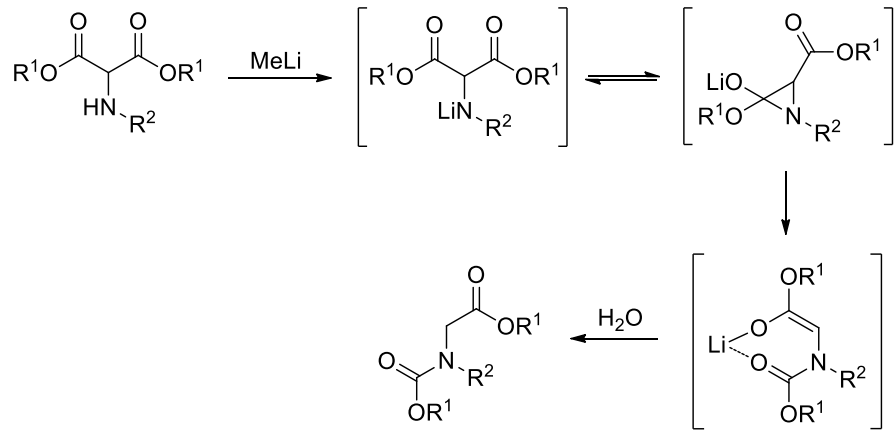
obtained after the diastereoselective reduction of pyrrolines, under substrate control with the hydride reagent approaching from the less hindered face.



Scheme 3.39

3.4. Transformation of the adducts: Synthesis of proline derivatives

At this point, with the objective of synthesizing the corresponding chiral prolines from the already prepared enantioenriched pyrrolidine 2,2-dicarboxylates, we proceeded to apply the base-promoted intramolecular C→N acyl transfer reaction, previously developed in our group.[52] The reaction consists on the initial deprotonation of the secondary amine through the use of an organolithium base, such as MeLi, followed by the nucleophilic attack of the subsequent anion to one of the two carboxylate groups, forming an azidirine-type compound that was previously confirmed in our group.[52] The highly strained azidirine can evolve to the corresponding enolate through an irreversible ring-opening process, followed by protonation by the addition of water, forming the consequent carbamate (Scheme 3.40).

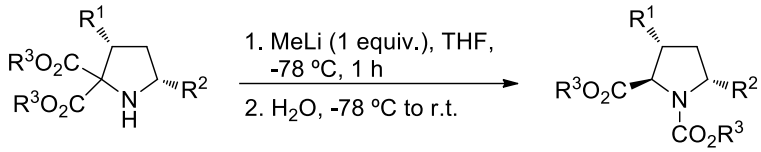


Scheme 3.40

In this sense, when compounds **22a-o** and **22q-r** were treated with one equivalent of methyllithium in dry THF at -78 ºC during 1 hour, the expected *N*-protected proline ester derivatives were obtained after quenching the reaction

through dropwise addition of water at -78 ºC (Table 3.8). The rearrangement took place with high yields in all of the cases, with the exception of proline **23l**, which was isolated with poor conversion (entry 12). Moreover, all proline ester derivatives were obtained with moderate to excellent diastereoselectivities with respect to the generation of a new stereogenic center at C-2. As it can be observed, with more congested compounds, such as pyrrolidines with *ortho* and *meta* substituents in the aromatic ring at C-3 (entries 3, 4 and 8), the diastereoselectivities were significantly better. It should be noted that when the rearrangement took place from 5-ethyl-substituted pyrrolidine **22o** (entry 15), the diastereomeric ratio was improved (dr: 3:1 to dr: 6:1) when the reaction was quenched through dropwise addition of *t*-BuOH in dry THF at -78 ºC. Unfortunately, this procedure could not be extended to the other pyrrolidines.

Table 3.8: Synthesis of *N*-protected proline derivatives.



22a-o, 22q-r **23a-o, 23q-r**

Entry	R^1	R^2	R^3	23	Yield (%)[a]	dr[b]
1	Ph	Me	Et	**23a**	84	7:1
2	4-MeC_6H_4	Me	Et	**23b**	80	10:1
3	2-$MeOC_6H_4$	Me	Et	**23c**	78	>20:1
4	3-$MeOC_6H_4$	Me	Et	**23d**	77	>20:1
5	4-$MeOC_6H_4$	Me	Et	**23e**	73	6:1
6	2,6-$(MeO)_2C_6H_4$	Me	Et	**23f**	73	3:1
7	3,5-$(MeO)_2C_6H_4$	Me	Et	**23g**	84	10:1
8	2-FC_6H_4	Me	Et	**23h**	85	17:1
9	4-FC_6H_4	Me	Et	**23i**	71	6:1
10	4-ClC_6H_4	Me	Et	**23j**	86	7:1
11	4-$CF_3C_6H_4$	Me	Et	**23k**	80	5:1
12[c]	4-$NO_2C_6H_4$	Me	Et	**23l**	60	7:1
13	2-Furyl	Me	Et	**23m**	78	9:1
14	2-Thienyl	Me	Et	**23n**	84	13:1
15[d]	4-$MeOC_6H_4$	Et	Et	**23o**	89	6:1
16	Ph	Me	Me	**23q**	80	10:1
17	2,6-$(MeO)_2C_6H_4$	Me	Me	**23r**	75	3:1

[a] Isolated product yield of the mixture of diastereoisomers after flash column chromatography. [b] Diastereomeric ratios determined by ^{1}H-NMR analysis of non purified reaction mixtures. [c] Calculated yield over a conversion of 40% (calculated by ^{1}H-NMR analysis of the non purified reaction mixture). [d] Reaction quenched through dropwise addition of *t*-BuOH in dry THF at -78 ºC.

In order to confirm the configuration of the new stereogenic center formed at C-2, a NOESY experiment was performed on *N*-protected proline ester **23a** (see Figure 3.5). The presence of significant n.O.e. was observed between H^2 and the protons of the aromatic ring and the absence of n.O.e.was appreciated between H^2 and H^3, indicating a 2,3-*trans* configuration of the major diastereoisomer.

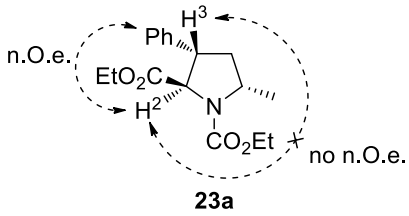
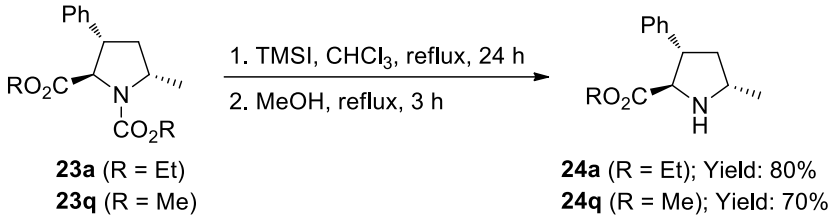


Figure 3.5

Finally, we proceeded to perform the *N*-deprotection of some representative compounds in order to demonstrate the synthetic potential of this methodology to access to polysubstituted chiral proline ester derivatives. The deprotection could be carried out using TMSI in chloroform under reflux, followed by the addition of methanol to decompose the previously formed silyl carbamate.[54] Under these conditions, the deprotection of ethyl and methyl carbamates **23a** and **23q** took place in high yields without epimerization of any of the stereogenic centers present in the molecule (Scheme 3.41).

[54] Cheng, J.; Xu, L.; Stevens, E. D.; Trudell, M. L. *J. Heterocyclic Chem.* **2004**, *41*, 569.



23a (R = Et)
23q (R = Me)

24a (R = Et); Yield: 80%
24q (R = Me); Yield: 70%

Scheme 3.41

Moreover, the spectroscopic data of the compound **24a** matched to the reported same product,[55] confirming the absolute stereochemistry proposed for all proline ester derivatives.

[55] Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331.

4. CONCLUSIONS

Taking into account the results obtained in this chapter, several conclusions can be presented:

1. An aminocatalytic one-pot Michael addition/intramolecular condensation/diastereoselective reduction sequence is presented as a novel methodology for the regioselective synthesis of polysubstituted chiral pyrrolidines in high yields and enantioselectivities, allowing the use of a wide variety of enones as Michael acceptors.

2. The possibility of carrying out the reaction in a one-pot fashion, without the purification of the pyrroline intermediate, and the use of very simple and cheap starting materials, allows the preparation of the target molecules following a straightforward procedure.

3. The resulting pyrrolidines can be transformed into the corresponding *N*-protected proline esters in very good yields and diastereoselectivities, through a base-promoted intramolecular C→N acyl transfer reaction. In addition, the deprotection can be successfully performed following a well-known and easy procedure, affording the desired enantioenriched unprotected proline ester derivatives, demonstrating the usefulness of this methodology.

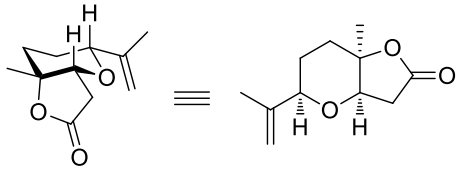
4

4

Total synthesis of (+)-Greek tobacco lactone

1. INTRODUCTION

In 1993, Wahlberg *et al.* isolated thirteen lactones from an extract of sun-cured leaves of Greek tobacco.[1] Some of them were new natural products, including the (3a*R*, 5*R*, 7a*R*)-7a-methyl-5-(prop-1-en-2-yl)hexahydro-2*H*-furo[3,2-*b*]pyran-2-one, known as (+)-Greek tobacco lactone (Figure 4.1).



(+)-Greek tobacco lactone

Figure 4.1

During the last years, this natural product has attracted considerable attention due to its simple but interesting structure, being composed by a unique *cis*-fused tetrahydropyran-butyrolactone core. Although nowadays the biological activity is unknown, it should be pointed out that the *cis*-fused tetrahydropyran moiety is commonly found in many natural products.[2] Since 2007, three total synthesis of (+)-Greek tobacco lactone have been reported, following different strategies, which will be summarized in the following lines.

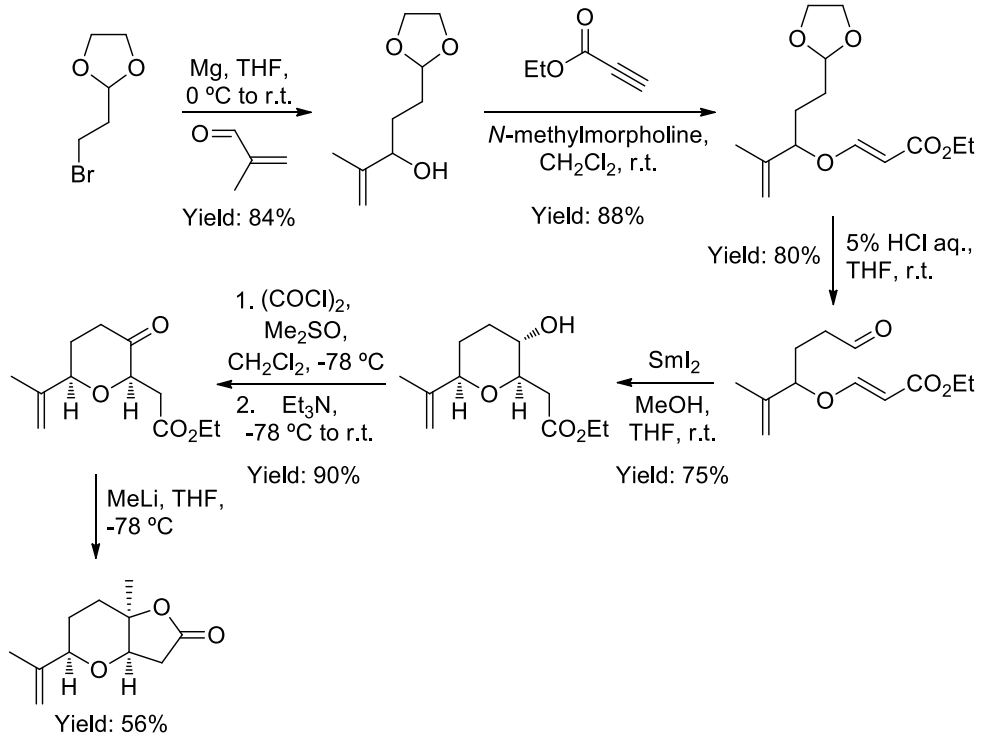
---

[1] Pettersson, T.; Eklund, A.-M.; Wahlberg, I. *J. Agric. Food Chem.* **1993**, *41*, 2097.

[2] For some examples, see: a) Suchaichit, N.; Kanokmedhakul, K.; Panthama, N.; Poopasit, K.; Moosophon, P.; Kanokmedhakul, S. *Fitoterapia* **2015**, *103*, 206; b) Lin, Y.-S.; Lin, J.-H.; Chang, C.-C.; Lee, S.-S. *J. Nat. Prod.* **2015**, *78*, 181; c) Hwang, B. S.; Yoon, E. Y.; Kim, H. S.; Yih, W.; Park, J. Y.; Jeong, H. J.; Rho, J.-R. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3023; d) Ono, M.; Takaki, Y.; Takatsuji, M.; Akiyama, K.; Okawa, M.; Kinjo, J.; Miyashita, H.; Yoshimitsu, H.; Nohara, T. *Chem. Pharm. Bull.* **2012**, *60*, 1083; e) Kito, K.; Ookura, R.; Yoshida, S.; Namikoshi, M.; Ooi, T.; Kusumi, T. *Org. Lett.* **2008**, *10*, 225; f) Wright, A. E.; Botelho, J. C.; Guzmán, E.; Harmody, D.; Linley, P.; McCarthy, P. J.; Pitts, T. P.; Pomponi, S. A.; Reed, J. K. *J. Nat. Prod.* **2007**, *70*, 412.

The first total synthesis was reported by Clark and co-workers in six steps with an overall yield of 22% of a racemic mixture (see Scheme 4.1).[3] The synthesis started with the reaction of methacrolein with the Grignard reagent prepared *in situ* from the commercially available alkyl bromide, obtaining the allylic alcohol in excellent yield. The alkylation of the hydroxyl group with ethyl propiolate, followed by the acetal deprotection afforded the corresponding aldehyde. As key step, the aldehyde was treated with samarium(II) iodide in the presence of methanol to afford the tetrahydropyran core through an intramolecular reductive cyclization in good yield. Swern oxidation of the resulting alcohol furnished the corresponding ketone, which after 1,2-addition of methyllithium, followed by an intramolecular lactonization in one-pot fashion, afforded the natural product in a diastereoselective way, completing the six steps of the total synthesis. Through this synthesis the characterization of the (+)-Greek tobacco lactone was completed, allowing the correction of a misassigned carbonyl group in the original ^{13}C-NMR spectrum reported by Wahlberg *et al.* Moreover, with this work the relative stereochemistry was confirmed by NMR spectroscopy.

[3] Clark, J. S.; Hayes, S. T.; Blake, A. J.; Gobbi, L. *Tetrahedron Lett.* **2007**, *48*, 2501.

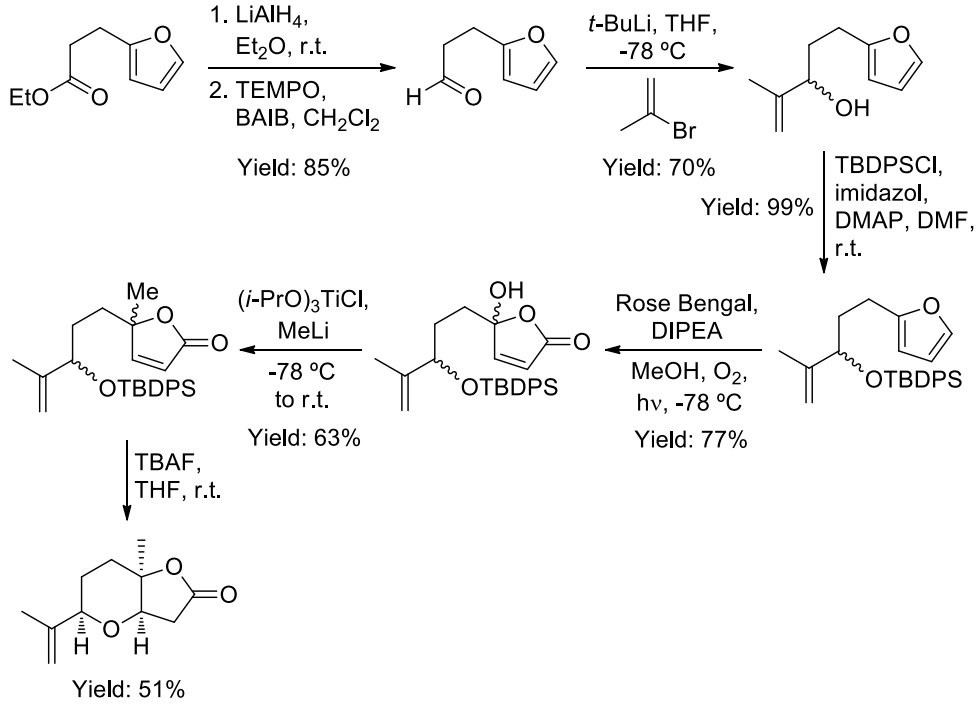


Scheme 4.1

In 2012, Fall and co-workers developed another total synthesis of the natural product, requiring seven steps with an overall yield of 15%.[4] As it is shown on Scheme 4.2, the commercially available ester can be transformed into the corresponding aldehyde in two steps. The addition of the *in situ* metalated vinyl bromide furnished an alcohol that was protected as *t*-butyldiphenylsilylether. The furan moiety was oxidized employing a singlet oxygen conditions previously employed by the same group, with the use of Rose bengal dye as photosensitizers,[5] obtaining a tertiary alcohol. Then, the angular methyl group was formed by the

[4] Zuñiga, A.; Pazos, G.; Besada, P.; Fall, Y. *Tetrahedron Lett.* **2012**, *53*, 4293.
[5] Teijeira, M.; Suárez, P. L.; Gómez, G.; Terán, C.; Fall, Y. *Tetrahedron Lett.* **2005**, *46*, 5889.

addition of $(i\text{-PrO})_3TiCH_3$ to the previously generated alcohol, and finally, the desired product was obtained by the intramolecular nucleophilic attack of the secondary alcohol to the unsaturated lactone, after deprotection of the hydroxyl group in one-pot fashion.



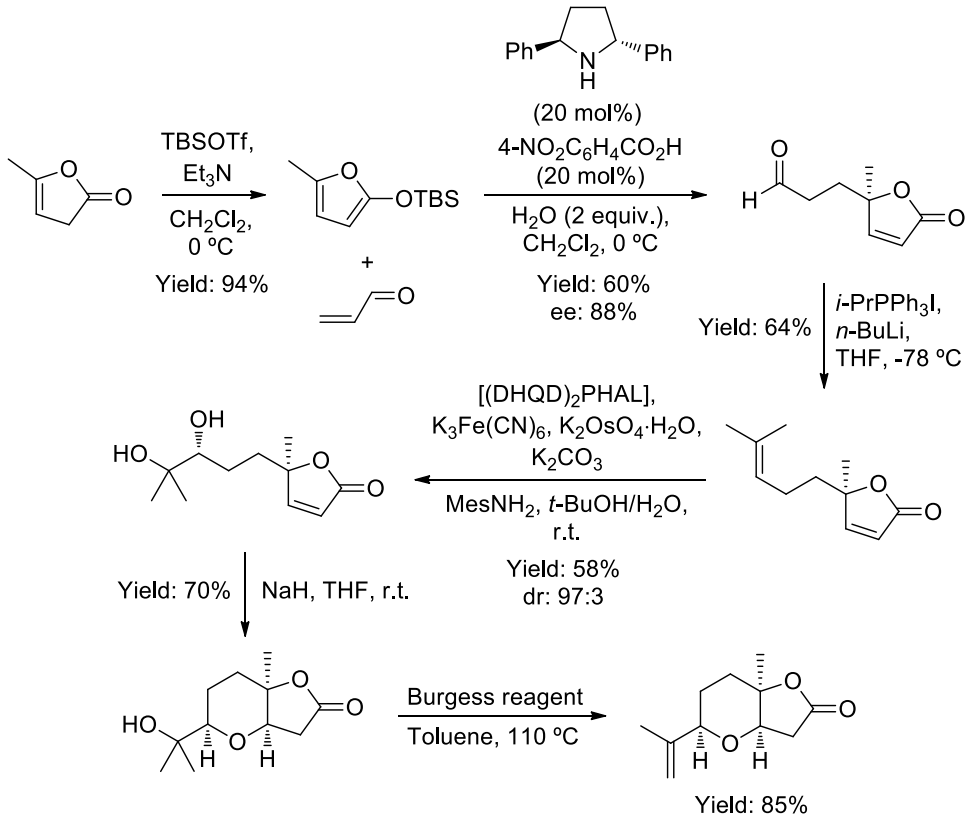
Scheme 4.2

It should be noted that until the last step, non-optically pure compounds were used for the different reactions, observing in the final cylization step the presence of only two diastereoisomers, but in very low diastereomeric ratio (dr: 1.7:1), being the mayor product the Greek tobacco lactone as a racemic mixture.

Because of lack of stereocontrol, recently, Pihko and co-workers have developed a protecting-group-free enantioselective route to (+)-Greek tobacco lactone in six steps and an overall yield of 12% (see Scheme 4.3).[6] Firstly, the silyloxyfuran derivative was easily prepared from the commercially available 5-methylfuran-2(3*H*)-one. The formed product was used in an aminocatalytic Mukaiyama-Michael reaction, previously described by the same group,[7] with acrolein, under the iminium ion activation, obtaining the corresponding aldehyde in an enantioenriched way (88% ee). Then, the last one was subjected to Wittig olefination conditions, affording an alkene, which after asymmetric Sharpless dihydroxylation was converted into the corresponding diol in excellent diastereoselectivity after recrystallization. An oxa-Michael reaction of the secondary alcohol to the α,β-unsaturated lactone using basic conditions was carried out in order to give the 6-*exo*-*trig* cyclization product. Finally, the synthesis was completed after the elimination of the tertiary alcohol towards the construction of the isopropenyl side chain.

6 Siitonen, J. H.; Pihko, P. M. *Synlett* **2014**, *25*, 1888.

7 Kemppainen, E. K.; Sahoo, G.; Piisola, A.; Hamza, A.; Kótai, B.; Pápai, I.; Pihko, P. M. *Chem. Eur. J.* **2014**, *20*, 5983.


Ph
N
H
Ph
(20 mol%)
TBSOTf,
Et3N
CH2Cl2,
0 ºC
Yield: 94%
OTBS
+
O
4-NO2C6H4CO2H
(20 mol%)
H2O (2 equiv.),
CH2Cl2, 0 ºC
Yield: 60%
ee: 88%
Yield: 64%
i-PrPPh3I,
n-BuLi,
THF, -78 ºC
[(DHQD)2PHAL],
K3Fe(CN)6, K2OsO4·H2O,
K2CO3
MesNH2, t-BuOH/H2O,
r.t.
Yield: 58%
dr: 97:3
Yield: 70%
NaH, THF, r.t.
Burgess reagent
Toluene, 110 ºC
Yield: 85%

Scheme 4.3

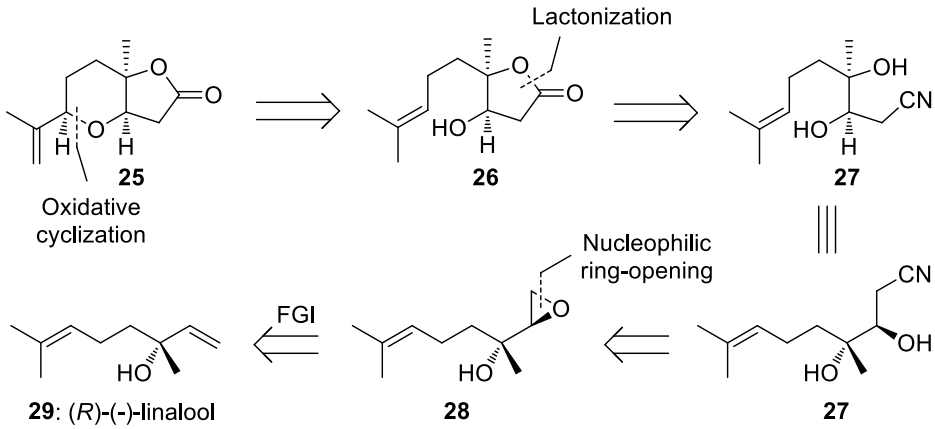
2. OBJECTIVES AND PREVIOUS APPROACHES IN THE GROUP

The total synthesis of terpenoids and terpene-like structures is considered a great challenge for the synthetic chemists. This type of compounds usually presents one oxidized carbon atoms that may favour the design of a retrosynthetic pathway, but, in general, the use of protecting groups and several changes in the oxidation state of multiple atoms are required. In this sense, with the purpose of minimizing the number of steps for a given target molecule, an alternative is proposed, consisting on the identification of terpene substructures in a compound of interest, in order to reduce the number of carbon-carbon bond formation in the synthetic route. The use of this strategy in total synthesis is one of the subjects of the M. Christmann research group at the Institute for Chemistry and Biochemistry – Organic Chemistry at the Free University of Berlin, where I incorporated in the context of a short stay, from January to April of 2015. Using this methodology, they have completed the first total synthesis of *englerin A* and derivatives starting from the commercially available nepetalactone, a bicyclic monoterpenoid.[8]

Taking into account the different routes developed towards the synthesis of (+)-Greek tobacco lactone **25**, and based on the previously mentioned approach, they initially proposed as objective the synthesis of this molecule in less steps, with only one carbon-carbon bond formation, two oxidations strategies and a functional group transformation. The initial retrosynthetic analysis, shown on Scheme 4.4, consisted on a disconnection of the tetrahydropyran moiety of the natural product and displacement of the double bond leading to the lactone **26**

[8] a) Radtke, L.; Willot, M.; Sun, H.; Ziegler, S.; Sauerland, S.; Strohmann, C.; Fröhlich, R.; Habenberger, P.; Waldmann, H.; Christmann, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 3998; b) Willot, M.; Radtke, L.; Könning, D.; Fröhlich, R.; Gessner, V. H.; Strohmann, C.; Christmann, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 9105.

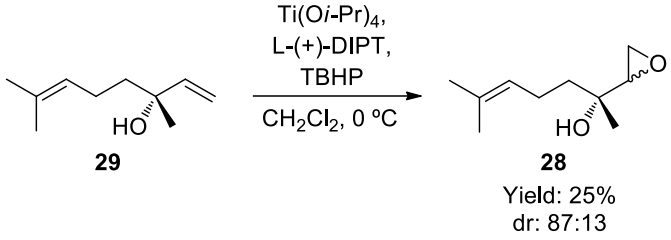
bearing a hydroxyl group and a trisubstituted alkene, which are suitable functionalities for an oxidative cyclization catalyzed by palladium(II). The lactone can be obtained through a lactonization process from the corresponding alcohol and carboxylic acid, which can be prepared by hydrolyzing the corresponding nitrile **27**. This one can be synthetized by nucleophilic ring-opening of the terminal epoxide **28**, prepared through a diastereoselective epoxidation of the monosubstituted double bond of the commercially available (*R*)-(-)-linalool **29**, naturally occurring terpene alcohol.



Scheme 4.4

First, the diastereoselective epoxidation of the terminal alkene of **29** using several strategies was surveyed in the group. In this case, it was not easy to predict the stereochemical outcome of the product, due to the stereocenter present on the substrate. For this reason, the reaction was initially performed under asymmetric Sharpless epoxidation conditions, using both enantiomers of the chiral ligand, and obtaining low yields and moderate to good diastereoselectivities. In order to improve the reaction outcome, vanadium catalyzed epoxidation conditions were used, observing poorer results regarding the diastereoselectivity. In summary, the

best results were achieved under Sharpless epoxidation conditions, obtaining the product in low yield and as inseparable mixture of diastereoisomers (Scheme 4.5).

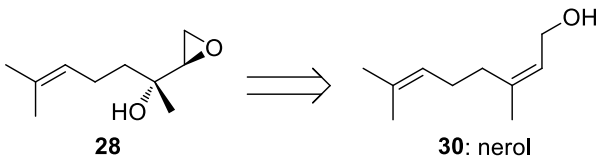


29 **28**

Yield: 25%
dr: 87:13

Scheme 4.5

At this point, and with the purpose of obtaining the desired epoxide **28** as a single diastereoisomer, an alternative was suggested, consisting on four synthetic steps starting from the commercially available nerol **30**, a structural isomer of linalool (Scheme 4.6), based on a previous work.[9]



28 **30**: nerol

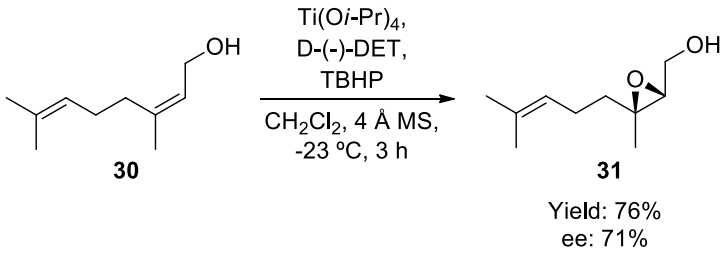
Scheme 4.6

Taking into account the proposed alternative, the general objective of the present research work consisted on the total synthesis of the (+)-Greek tobacco lactone starting from nerol.

[9] Hashimoto, M.; Yanagiya, M.; Shirahama, H. *Chem. Lett.* **1988**, 645.

3. RESULTS AND DISCUSSION

As it mentioned above, the stereoselective synthesis of the epoxide **28**, can be carried out in four steps starting from the readily available nerol. The first step consisted on an enantioselective epoxidation of the allylic alcohol **30**. For this purpose, we chose the procedure described by Sharpless,[10] due to the expected regioselectivity, the availability of the reagents and high enantiomeric excesses observed in similar reactions. In this case, in order to achieve the correct enantiomer (2*R*,3*S*)-**31**, D-(-)-diethyl tartrate was used as chiral ligand, under conditions previously employed by the group in a satisfactory way, obtaining the desired epoxide **31** in very good yield and with moderate enantiocontrol (Scheme 4.7).

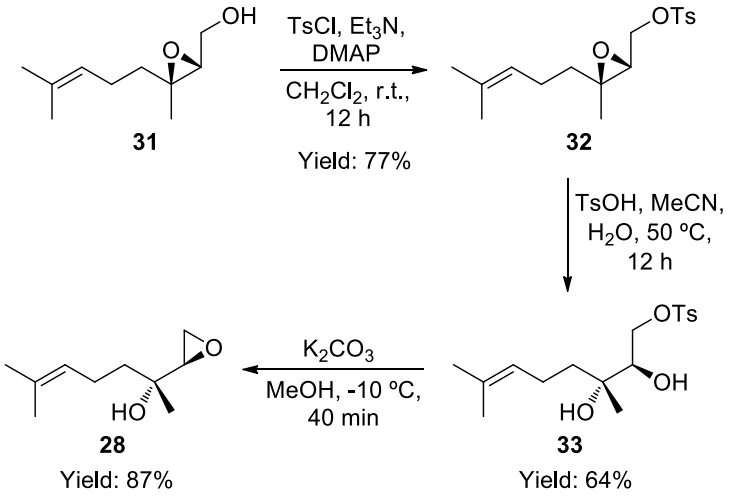


Scheme 4.7

The obtained epoxide **31** is a constitutional isomer of the epoxide **28**, having the opposite configuration at C-3 with respect to the required on the natural product. In order to achieve the desired epoxide, first the alcohol was protected as the sulfonate **32**, thus becoming a good leaving group. In this sense, applying known conditions,[11] the sulfonate ester **32** was isolated in 77% yield (see Scheme

[10] Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
[11] Riou, M.; Barriault, L. *J. Org. Chem.* **2008**, *73*, 7436.

4.8). Then, we proceeded to the epoxide opening under acidic conditions in S_N1 like fashion, by attacking of water as a weak nucleophile, in order to obtain the diol compound **33**, with inversion of configuration at C-3. The reaction was carried out using TsOH in MeCN and water, obtaining the diol **33** in good yield (shown on Scheme 4.8). At this point, we proceeded to the formation of the terminal epoxide using basic conditions, through an intramolecular nucleophilic substitution of the secondary hydroxyl group to the electrophilic carbon, displacing the tosylate unit. The reaction was performed using K_2CO_3 as a base in MeOH, at low temperature, in order to avoid the base-catalyzed Payne rearrangement,[12] towards the obtention of the more substituted epoxide. In the conditions shown on Scheme 4.8, the desired epoxide **28** was obtained in very good yield, as a unique structural isomer.



Scheme 4.8

[12] Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

Then, with the aim of obtain the nitrile compound **27** through a regioselective ring opening, different cyanide sources were tested. The use of KCN as the nucleophilic agent, employing different metal salts, such as $LiClO_4$, has been previously reported in the synthesis of 1,2-hydroxy nitriles from oxiranes in high yields.[13] In our case, no reaction was observed, detecting a complex mixture of products when only KCN was used. Diethyl aluminium cyanide (Nagata's reagent), also has been used in epoxide opening reactions, as a cyanide donor and a Lewis acid.[14] When Et_2AlCN 1 M was used in toluene at r.t., the reaction performed excellently, observing that the nucleophilic attack occurred on the less substituted carbon of the oxirane ring, obtaining the expected nitrile **27** in good yield (Scheme 4.9).

Scheme 4.9

We next proceeded to carry out the hydrolysis of the nitrile. Based on the work of Benedetti and co-workers,[14b] an aqueous solution of NaOH was used, in order to hydrolyze the nitrile group towards the formation of the corresponding carboxylate. Then, the solution was carefully acidified until reaching pH = 2, forming the desired (4*R*,5*R*)-lactone **26** in very good yield after 17 hours at room temperature (Scheme 4.10). In spite of working in mild acidic conditions,

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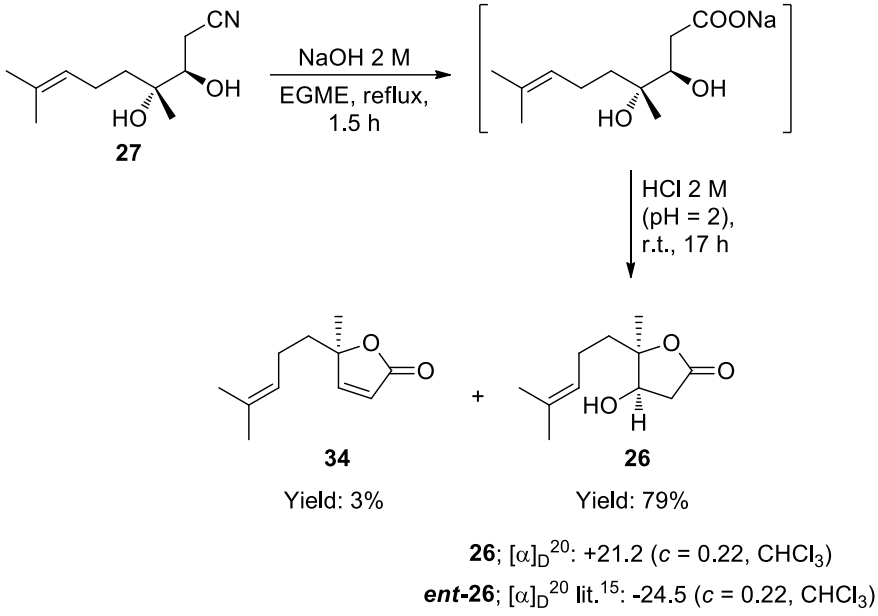
[13] Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.* **1991**, *32*, 4775.

[14] a) García Ruano, J. L.; Fernández-Ibáñez, M. A.; Martín Castro, A. M.; Rodríguez Ramos, J. H.; Rubio Flamarique, A. C. *Tetrahedron: Asymmetry* **2002**, *13*, 1321; b) Benedetti, F.; Berti, F.; Norbedo, S. *Tetrahedron Lett.* **1999**, *40*, 1041.

undesired elimination product **34** was observed, but in a very low yield. At this point, we were able to compare the obtained specific rotation value of the compound **26** with the reported data of the opposite enantiomer,[15] concluding that we were preparing the correct diastereoisomer in an enantioenriched way.



Scheme 4.10

At this stage, we proceeded to continue with the study of the final step of the total synthesis of the Greek tobacco lactone, consisting on a palladium(II) catalyzed Wacker-type oxidative cyclization. It should be highlighted that the following experiments were performed using the lactone ***ent*-26** prepared by the group, which has the opposite configuration compared with the natural product,

[15] Viturro, C. I.; Maier, M. S.; Stortz, C. A.; de la Fuente, J. R. *Tetrahedron: Asymmetry* **2001**, *12*, 991.

because the L-(+)-DET chiral ligand employed in the first step is more cost efficient than its enantiomer.

We initially tested the reaction under the conditions developed by Stoltz and co-workers using catalytic amounts of $Pd(OCOCF_3)_2$, pyridine as ligand, Na_2CO_3 as base and 3 Å molecular sieves in toluene under oxygen atmosphere,[16] but no product formation was observed even at elevated temperature and after long reaction time (entry 1 of Table 4.1). When a stronger base, such as *t*-BuOK, was used, only the elimination product ***ent*-34** was observed (entry 2). As an alternative, the conditions used by Zhang *et al.* for the synthesis of chiral chroman derivatives were also tested. These involved the use of catalytic amounts of $Pd(OCOCF_3)_2$, a chiral ligand and *p*-benzoquinone as oxidizing agent in MeOH at 60 ºC.[17] In our case, pyridine was used as ligand, not detecting the formation of the desired product (entry 3). The same negative result was observed by applying the conditions reported by Hosokawa and co-workers,[18] which employed catalytic amounts of $Pd(OAc)_2$ and $Cu(OAc)_2$, this last one being required to reoxidize Pd(0), and O_2 as stoichiometric oxidizing agent for copper (entry 4). At this point, typical Wacker oxidation conditions were also tested, detecting the consumption of the starting material, but observing the formation of product **35**, as elucidated by NMR experiments, in 28% yield (entry 5). The structure of oxepane derivative **35** was further confirmed by single crystal X-ray analysis (Figure 4.2), also allowing to establish the (4*S*,5*S*) configuration of the lactone ***ent*-26**.

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16 Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778.
17 Liu, Q.; Wen, K.; Zhang, Z.; Wu, Z.; Zhang, Y. J.; Zhang, W. *Tetrahedron* **2012**, *68*, 5209.
18 Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318.

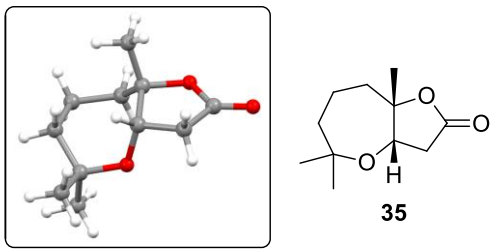
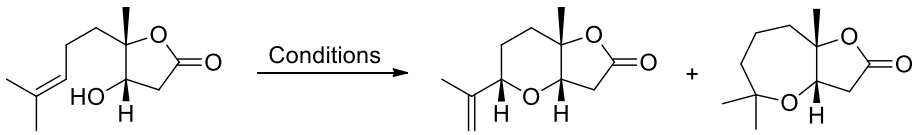


Figure 4.2

The formation of this compound was explained through a Lewis acid catalyzed nucleophilic addition of the hydroxyl group to the most substituted carbon of the double bond, followed by protonation to afford the oxepane derivative **35**.

Table 4.1: Palladium(II) catalyzed oxycyclization.



***ent*-26** ***ent*-25** **35**

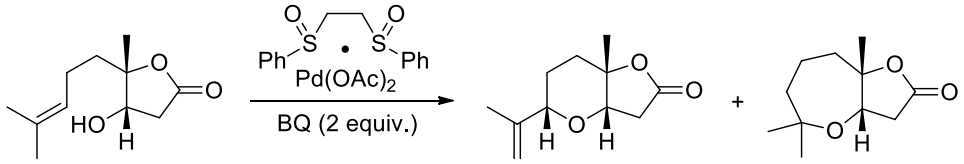
Entry	Pd(II) (equiv.)	Ligand (equiv.)	Additive (equiv.)	Solvent	T (ºC)	Yield (%)[a]
1	$Pd(OCOCF_3)_2$ (0.05)	Py (0.2)	Na_2CO_3 (2), O_2	Toluene	80	n.r.[b]
2[c]	$Pd(OCOCF_3)_2$ (0.05)	Py (0.2)	*t*-BuOK (2), O_2	Toluene	80	n.d.[d]
3	$Pd(OCOCF_3)_2$ (0.2)	Py (0.2)	BQ (4)	MeOH	60	n.r.[b]
4	$Pd(OAc)_2$ (0.1)	-	$Cu(OAc)_2$ (0.1), O_2	MeOH	35	n.r.[b]
5	$PdCl_2$ (0.2)	-	$CuCl_2$ (3)	MeOH	r.t.	28[e]

[a] Isolated product yield after flash column chromatography. [b] No reaction. [c] The elimination product ***ent*-34** was observed. [d] Not determined. [e] Isolated yield of the compound **35**.

As an alternative, we focused on carrying out this transformation through oxidative cyclizations by allylic C-H activation using the White catalyst as a palladium source. Based on the work of Belani and co-workers,[19] we tested the oxidative cyclization using the White catalyst under different conditions, employing in all cases *p*-benzoquinone as oxidizing agent (Table 4.2). Initially, 10 mol% of catalyst was used in the presence of a slight excess of acetic acid, in CH_2Cl_2 at 40 ºC, observing very low conversion towards the compound ***ent*-25** and in moderate diastereoselectivity (entry 1). In order to improve the conversion, we increased the catalyst loading and changed the solvent to 1,4-dioxane, heating the mixture at 80 ºC, observing a slight increase in the conversion (entry 2). In both cases, the product ***ent*-25** could not be properly purified. Additionally, we tested the reaction with a stoichiometric amount of the White catalyst, obtaining a complex mixture of products (entry 3). Taking into account previous reports,[20] we decided to use a Lewis acid as cocatalyst, such as AgOTf, observing full conversion of the starting material towards the formation of the oxepane derivative **35** in 61% yield (entry 4).

[19] Ayyagari, N.; Belani, J. D. *Synlett* **2014**, *25*, 2350.
[20] Ammann, S. E.; Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2014**, *136*, 10834.

Table 4.2: Evaluation of the White catalyst in the reaction.



***ent*-26** ***ent*-25** **35**

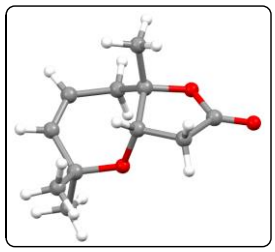
Entry	Cat. (equiv.)	Additive (equiv.)	Solvent	T (ºC)	Conv. (%)[a]	Yield (%)[b]	dr[c]
1	0.1	AcOH (1.1)	CH_2Cl_2	40	13	n.d.[d]	85:15
2	0.2	AcOH (1.1)	1,4-Dioxane	80	28	n.d.[d]	84:16
3	1	AcOH (1.1)	1,4-Dioxane	80	n.d.[d]	n.d.[d]	n.d.[d]
4	0.1	AgOTf (0.1)	1,4-Dioxane	80	>95	61[e]	-

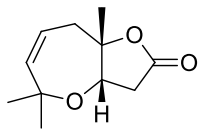
[a] Conversions determined by ^{1}H-NMR analysis of non purified reaction mixtures. [b] Isolated product yield after flash column chromatography. [c] Diastereomeric ratios determined by ^{1}H-NMR analysis of non purified reaction mixtures. [d] Not determined. [e] Isolated yield of the compound **35**.

In similar studies, Semmelhack and co-workers had previously used stoichiometric amounts of $Pd(OAc)_2$ in several solvents, of which DMSO showed highest conversion rates.[21] The experiments carried out following this type of procedure are shown in the Table 4.3. First, we tested the reaction using stoichiometric amounts of $Pd(OAc)_2$ in DMSO at r.t., but only recovering the starting material (entry 1). Raising the temperature of the reaction to 80 ºC and after 24 hours, low conversion was observed towards the formation of the product ***ent*-25** and with poor diastereoselectivity. In this case, we could isolate the target compound in 19% yield (entry 2). It should be highlighted that in longer reaction times the conversion was not increased. With the purpose of improving the reaction outcome, we decided to use an inorganic base to favour the deprotonation

[21] Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.* **1989**, *30*, 4925.

process, observing only traces of the product (entry 3). At this point, we proposed to change the palladium source in order to promote the product formation, performing the reaction in DMSO at 80 ºC (entries 4-6). With $PdCl_2$ and Na_2PdCl_4, very low conversion was observed, in contrast, with a Pd(II) species containing more electron-withdrawing groups, such as $Pd(OCOCF_3)_2$, moderate conversion was observed, isolating the compound ***ent*-25** in 30% yield as a mixture of diastereoisomers (dr: 81:19), and byproduct **36** in 21% yield (entry 6), as a result of the oxidative cyclization on the more substituted carbon of the double bond. The identity of this compound was unambiguously established by X-ray analysis (Figure 4.3).

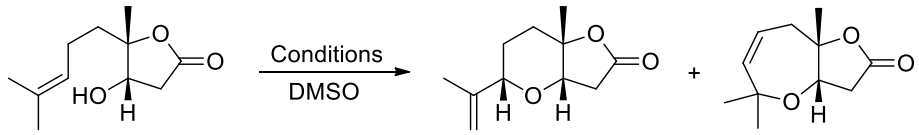




36

Figure 4.3

Table 4.3: Study of several reaction conditions using stoichiometric amounts of Pd source.



***ent*-26** ***ent*-25** **36**

Entry	Pd(II) source	Additive (equiv.)	T (ºC)	Conv. (%)[a]	(*ent*-25:36) Yield (%)[b]	dr[c]
1	$Pd(OAc)_2$	-	r.t.	n.r.[d]	-	-
2	$Pd(OAc)_2$	-	80	32	19:-	63:37
3	$Pd(OAc)_2$	Na_2CO_3 (2)	80	<5	n.d.[e]	n.d.[e]
4	$PdCl_2$	-	80	<5	n.d.[e]	n.d.[e]
5	Na_2PdCl_4	-	80	<5	n.d.[e]	n.d.[e]
6	$Pd(OCOCF_3)_2$	-	80	54	30:21	81:19
7[f]	$Pd(OCOCF_3)_2$	-	80	>95	n.d.[e]	83:17
8	$Pd(OCOCF_3)_2$	-	80 (MW)	59	40:14	85:15
9	$Pd(OCOCF_3)_2$	-	100 (MW)	62	n.d.[e]	71:29

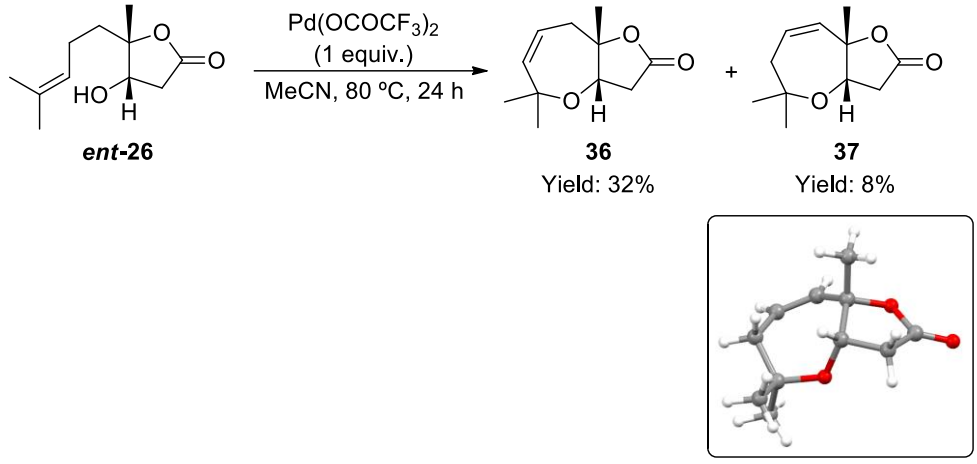
[a] Conversions determined by ^{1}H-NMR analysis of non purified reaction mixtures. [b] Isolated product yield of each compound after flash column chromatography. [c] Diastereomeric ratios determined by ^{1}H-NMR analysis of non purified reaction mixtures. [d] No reaction. [e] Not determined. [f] Portionwise addition of the Pd source during 7.5 hours.

It should be noted that in the previous cases no full conversion was achieved, even with stoichiometric amounts of palladium(II) species. For this reason, first we decided to add the palladium source portionwise, in order to achieve full conversion. After the portionwise addition during 7.5 hours the comsuption of the starting material was observed but a complex mixture of products were detected, including the desired product ***ent*-25** (entry 7). Next, we proposed to try the microwave-assisted reaction, due to its known ability to

increase the rate and the yield of the reaction.[22] In this sense, when we carried out the reaction at 80 ºC assisted by microwave irradiation during 8 hours, using stoichiometric amounts of $Pd(OCOCF_3)_2$, similar conversion was achieved but compound ***ent*-25** was isolated in better yield (40%) albeit as a mixture of diastereoisomers (dr: 85:15), identifying again the formation of the tetrahydrooxepine derivative **36**, which was isolated in 14% yield (entry 8). Finally, we tested the reaction at a higher temperature (entry 9), observing a sluggish reaction, being unable to isolate properly the target compound.

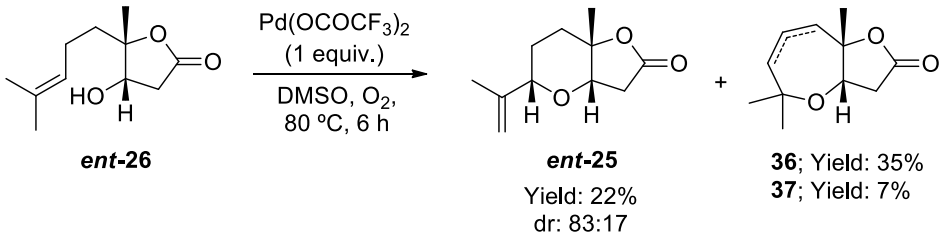
At this stage, we decided to study the effect of the solvent in the reaction, using stoichiometric amounts of $Pd(OCOCF_3)_2$ and heating at 80 ºC, without the use of the microwave oven. When aprotic polar solvents were tested such as dioxane, DMF and DMPU, a complex mixture of products were obtained, detecting very low formation of the desired product. The same problem was observed with halogenated solvents, such as DCE, trifluorotoluene and chlorobenzene; with a protic one, like *i*-PrOH and with a less polar one, such as toluene. Surprisingly, in the case of use MeCN as solvent, full conversion was achieved, but isolating compound **36** as the major product, together with an isomer, as a result of the reinsertion of the palladium species followed by the corresponding β-hydrogen elimination, with an overall 40% yield (Scheme 4.11). As it can be observed, the structure of the new formed product **37** was also confirmed by X-ray analysis.

[22] For a selected review, see: Kranjc, K.; Kočevar, M. *Curr. Org. Chem.* **2013**, *17*, 457.



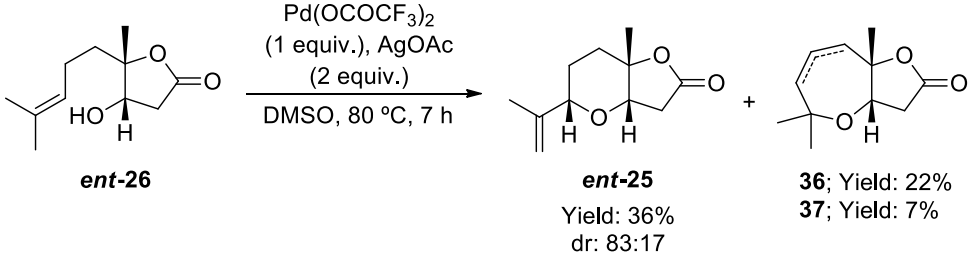
Scheme 4.11

Continuing with the objective of the natural product synthesis, we proposed to use an oxidizing agent in this reaction, keeping the use of stoichiometric amounts of the catalyst, in order to improve the conversion of the reaction. The conditions shown in the entry 6 of the Table 4.3 were selected to carry out the following experiments. When molecular oxygen was used as an oxidizing agent, full conversion was achieved after 6 hours, observing a mixture of three products, ***ent*-25**, **36** and **37**, in a good overall yield, but isolating the enantiomer of the natural product **25** in poor yield (Scheme 4.12).



Scheme 4.12

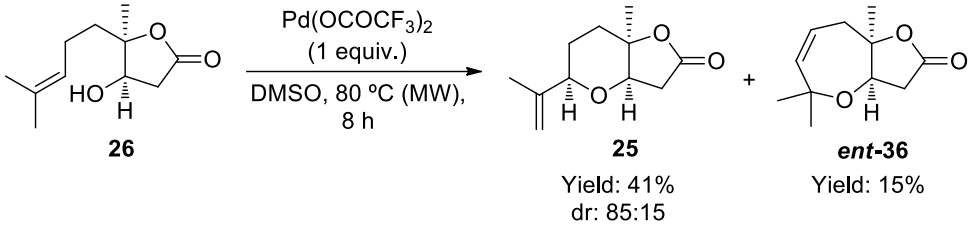
Having obtained full conversion, we reduced the amount of the catalyst to the half, observing full conversion after 24 hours, but not improving the formation of the compound ***ent*-25**. We also tried to perform the reaction at 50 ºC, observing again a similar ratio between the previous formed three products. Changing the oxidant to *p*-benzoquinone or $Cu(OAc)_2$, only low conversions were reached. On the other hand, when AgOAc was used as an oxidant, full conversion was achieved after 7 hours, observing again a mixture of the previously obtained three products, but in this case the ***ent*-25** was isolated as the major product in 36% yield and with moderate diastereoselectivity (Scheme 4.13), not improving the result obtained in the case of use the conditions shown in the entry 8 of the Table 4.3. With these last conditions, we tested the reaction under microwave irradiation, observing very low conversion of the product ***ent*-25**. Additionally, different silver salts were tested, not improving the result obtained with the AgOAc.



Scheme 4.13

In summary, the use of molecular oxygen or silver salts as oxidizing agents, increased the reaction rate, but a mixture of tetrahydropyran and tetrahydrooxepine derivatives were observed, isolating the target compound ***ent*-25** in low yield. With the conditions shown in the entry 8 of the Table 4.3, we decided to carry out the reaction using the lactone **26**, in order to prepare the (+)-

Greek tobacco lactone **25**, which was isolated in 41% yield with moderate diastereoselectivity, and also observing the formation of the product ***ent*-36** in 15% yield (Scheme 4.14). It should be pointed out that the mesured specific rotation value matched with the one reported in the literature.[6]



25; $[\alpha]_D^{20}$: +33.0 (*c* = 0.1, CH_2Cl_2)

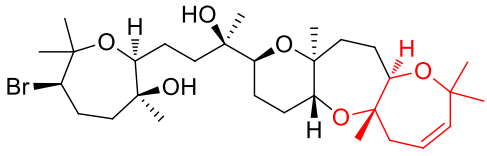
25; $[\alpha]_D^{20}$ lit.: +36.0 (*c* = 0.1, CH_2Cl_2)

Scheme 4.14

On the other hand, it should be highlighted that the formation of unsaturated seven-membered rings through an oxidative cyclization is a less explored field.[23] Moreover, our formed tetrahydrooxepine derivative **36** can be regarded as a structural part of the natural product *armatol A* (Figure 4.4). The total synthesis of this natural product was described by Jamison and co-workers,[24] constructing the terminal tetrahydrooxepine ring system from the corresponding hydrazone, through the Shapiro reaction, in only 6% yield. It should be noted that in our case we could be able to prepare this diastereoisomer through the methodology developed up to this moment, starting the synthesis from geraniol.

[23] Wu, L.; Qiu, S.; Liu, G. *Org. Lett.* **2009**, *11*, 2707.

[24] Underwood, B. S.; Tanuwidjaja, J.; Ng, S.-S.; Jamison, T. F. *Tetrahedron* **2013**, *69*, 5205.

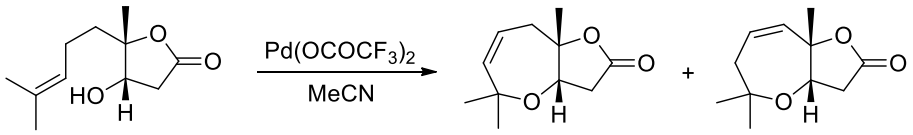


armatol A

Figure 4.4

For these reasons, we decided to carry out a parallel study directed to improve the reaction outcome towards the formation of unsaturated seven-membered oxepane rings. As it can be appreciated in the Scheme 4.11, the reaction in MeCN only afforded the both isomers of the tetrahydrooxepine derivatives. With this in mind, we initially tested the reaction of ***ent*-26** using molecular oxygen as oxidant, observing full conversion after 1.5 hours, and isolating the compound **36** in 52% yield and its isomer **37** in 18% yield, improving the previous obtained result (entry 2 *vs*. entry 1 of the Table 4.4). With this promising result, we decided to decrease the amount of the palladium species, in order to carry out the reaction in catalytic conditions. With 0.5 equiv. of $Pd(OCOCF_3)_2$ similar results were obtained regarding the yield and the reaction rate (entry 3), but with 0.2 equiv. very low conversion was detected (entry 4). Using 0.5 equiv. of the Pd source as optimal amount, we tried to reduce the temperature, not observing full conversion after 24 hours (entry 5). With the purpose of promoting the reaction we used pyridine as ligand, not observing the formation of the product (entry 6).

Table 4.4: Evaluation of the 7-*endo-trig* cyclization.



***ent*-26** **36** **37**

Entry	$Pd(OCOCF_3)_2$ (equiv.)	Oxidant	T (ºC)	Conv. (%)[a]	(36:37) Yield (%)[b]	(36:37)[c]
1	1	-	80	>95	32:8	3.8:1
2	1	O_2	80	>95	52:18	3.6:1
3	0.5	O_2	80	>95	49:15	3.8:1
4	0.2	O_2	80	n.d.[d]	n.d.[d]	2.8:1
5	0.5	O_2	50	60	n.d.[d]	3.8:1
6[e]	0.5	O_2	80	n.r.[f]	-	-

[a] Conversions determined by ^{1}H-NMR analysis of non purified reaction mixtures. [b] Isolated product yield of each compound after flash column chromatography. [c] Ratios determined by ^{1}H-NMR analysis of non purified reaction mixtures. [d] Not determined. [e] Pyridine (1 equiv.) was used as ligand. [f] No reaction.

In summary, with 0.5 equiv. of $Pd(OCOCF_3)_2$ in MeCN at 80 ºC, we were able to prepare the tetrahydrooxepine derivatives in a good overall yield. However, the 7-*endo-trig* cyclization has to be more investigated, with the aim of obtaining the tetrahydrooxepine derivative in catalytic and totally regioselective way, being able to extend this methodology to other substrates.

4. CONCLUSIONS

Taking into account the results presented throughout this chapter, some conclusions can be outlined:

1. The total synthesis of the (+)-Greek tobacco lactone was completed, starting from nerol, in seven steps and with an overall yield of 7%. It should be noted that it is possible to prepare both enantiomers of the natural product and possibly, different diastereoisomers starting the total synthesis from geraniol with the *E*-configuration in the alkene. In the final step, the oxidative cyclization, stoichiometric amounts of palladium source were needed, obtaining a moderate yield and diastereoselectivity of the natural product. For this reason, further studies are necessary in order to increase the overall yield of the process.

2. Additionally, changing the reaction conditions, we selectivily prepared 7-*endo-trig* cyclization adducts in good yield although as mixture of C=C bond regioisomers, using substoichiometric amounts of Pd species. Furthermore, the approach developed here can be applicable to the construction of tetrahydrooxepine moiety of more complex natural products, such as *armatol A*, which require further investigations.

5

5

Final conclusions

1. CONCLUSIONS

Throughout the present work it has been demonstrated that the cascade processes initiated by conjugate additions, under iminium ion activation, represent a powerful tool for the enantioselective synthesis of polysubstituted compounds with a high level of complexity, in a simple way. From all the obtained results, we could conclude the following:

a) 4-Alkenyl-5*H*-1,2,3-oxathiazole 2,2-dioxides in Michael/Michael cascade reactions: It has been demonstrated that this type of compounds are able to participate in different cascade reactions due to their functionality. Initially, a novel aminocatalytic Michael/Michael cascade reaction has been developed, employing these compounds with enals, under iminium/enamine manifold, using a chiral secondary amine as catalyst, towards the formation of cyclohexanes and decaline derivatives in good yields and excellent stereocontrol. The 5*H*-1,2,3-oxathiazole 2,2-dioxide scaffold could be employed as a masked 1,2-amino alcohol that can be prepared from the previously obtained cycloadducts, which can also be transformed into the corresponding bicycle[3.1.0]hexane derivatives in very good yields, through a transannular S_N2 reaction/imine hydrolysis sequence, demonstrating the versatility of the sulfamidate imine moiety. Moreover, it is possible to prepare a different diastereoisomer of the bicycle[3.1.0]hexanes in moderate yields and excellent stereoselectivities through an organocatalytic multiple cascade reaction, consisting on a Michael/Michael/transannular nucleophilic substitution/imine hydrolysis sequence between 4-alkenyl-5*H*-1,2,3-oxathiazole 2,2-dioxides and enals.

b) Organocatalytic approach to chiral proline derivatives: An aminocatalytic one-pot Michael/intramolecular condensation/diastereoselective reduction sequence, between aminomalonates and enones, has been developed as a novel methodology towards the synthesis of enantioenriched polysubstituted pyrrolidines in high yields, under iminium ion activation. The obtained pyrrolidine 2,2-dicarboxylates can be transformed into the corresponding *N*-protected proline derivatives in very good yields and diastereoselectivities, through a base-promoted intramolecular C→N acyl rearrangement, that after deprotection of the resulting carbamates, the desired unprotected proline esters are obtained in good yields, demonstrating the utility of this methodology.

c) Total synthesis of (+)-Greek tobacco lactone: The total synthesis of this natural product has been completed in seven steps and with an overall yield of 7%, starting from the commercially available nerol. Moreover, changing the reaction conditions of the last step, the oxidative cyclization, it was possible to obtain the 7-*endo*-*trig* cyclization product in good yield, but as a mixture of isomers, using substoichiometric amounts of Pd species.

6

6

Experimental

3.2. Synthesis of prolines **23a-o** and **23q-r**

3.3. Synthesis of prolines **24a** and **24q**

4. Total synthesis of (+)-Greek tobacco lactone

4.1. Synthesis of adduct **31**

4.2. Synthesis of adduct **32**

4.3. Synthesis of adduct **33**

4.4. Synthesis of adduct **28**

4.5. Synthesis of adduct **27**

4.6. Synthesis of β-hydroxylactone **26**

4.7. Synthesis of (+)-Greek tobacco lactone **25**

4.8. Synthesis of cycloadduct **35**

4.9. Synthesis of cycloadducts **36** and **37**

1. GENERAL METHODS AND MATERIALS

NMR: Monodimensional and/or bidimensional nuclear magnetic resonance proton and carbon spectra (^{1}H-NMR and ^{13}C-NMR) were acquired at 25 ºC on a Bruker AC-300 spectrometer (300 MHz for ^{1}H and 75.5 MHz for ^{13}C), Jeol ECX 400 spectrometer (400 MHz for ^{1}H and 100.7 MHz for ^{13}C), Bruker AC-500 spectrometer (500 MHz for ^{1}H and 125.7 MHz for ^{13}C) and a Bruker AVANCE III 700 spectrometer (700 MHz for ^{1}H and 176.2 MHz for ^{13}C). Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H-NMR, $CDCl_3$, 77.0 ppm for ^{13}C-NMR. MeOH, 4.87 ppm and 3.31 ppm for ^{1}H-NMR, CD_3OD, 49.1 ppm for ^{13}C-NMR. CH_3COCH_3, 2.05 ppm for ^{1}H-NMR, CD_3COCD_3, 206.7 ppm and 29.9 ppm for ^{13}C-NMR) and coupling constants (*J*) in hertz (Hz). The following abbreviations are used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; app d, apparent doublet; app t, apparent triplet; dd, doublet of doublets; ddd, doublet of doublets of doublets; dq, doublet of quartets; m, multiplet; bs, broad signal. ^{13}C-NMR spectra were acquired on a broad band decoupled mode using DEPT experiments (Distortionless Enhancement by Polarization Transfer) for assigning different types of carbon environment. Selective n.O.e., NOESY, COSY, HSQC and HMBC experiments were acquired to confirm precise molecular conformation and to assist in deconvoluting complex multiplet signals.[1]

IR: Infrared spectra (IR) were measured in a Jasco FT/IR 4100 in the interval between 4000 and 400 cm^{-1} with a 4 cm^{-1} resolution. Only characteristic bands are given in each case.

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[1] Kinss, M.; Sanders, J. K. M. *J. Mag. Res.* **1984**, *56*, 518.

MS: Mass spectra (MS) were recorded on an Agilent 7890A gas chromatograph coupled to an Agilent 5975C quadropole mass spectrometer under electronic impact ionization (EI) 70 eV. The obtained data is presented in mass units (m/z) and the values found in brackets belong to the relative intensities comparing to the base peak (100%).

M.p.: Melting points were measured in a Stuart SMP30 apparatus in open capilliary tubes and are uncorrected.

Polarimetry: Optical rotations were measured at 20 ºC on a Jasco P-2000 polarimeter with a sodium lamp at 589 nm and a path length of 1 dm. Solvent and concentration (g/dL) are specified in each case.

HRMS: High resolution mass spectrometry experiments were performed in an Acquity GC coupled to a TOF mass spectrometer (GCT Micromass) using chemical ionization (CI) or on an Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using electrospray ionization (ESI) at the SGIker Unit of the University of the Basque Country (UPV/EHU).

HPLC: High performance liquid chromatography on a chiral stationary phase experiments were performed in a Waters 2695 chromatograph coupled to a Waters 2998 photodiode array detector. Daicel Chiralpak AD-H, AS-H and IA, and Chiralcel OZ-3 columns (0.46 cm x 25 cm) were used; specific conditions are indicated for each case.

X-Ray: X-ray data collections were performed in an *Agilent Supernova* diffractometer equipped with an *Atlas* CCD area detector, and a CuKα micro-focus source with multilayer optics (λ = 1.54184 Å, 250 μm FWHM beam size) at the SGIker Unit of the University of the Basque Country (UPV/EHU). The quality

of the crystals was checked under a polarizing microscope, and a suitable crystal or fragment was mounted on a Mitegen Micromount™ using Paratone-N inert oil and transferred to the diffractometer. Alternatively, an *Oxford Diffraction Xcalibur 2* diffractometer equipped with a *Sapphire 2* CCD area detector, and a MoKα sealed-tube source with graphite monochromator (λ = 0.71073 Å, 0.5 mm collimator) was used. The samples were kept at 100(1) K with a *Oxford Cryosystems Cryostream 700* cooler.

Miscellaneous: Reactions were monitored using analytical thin layer chromatography (TLC), in pre-coated aluminium-backed plates (Merck Kieselgel 60 F254). These were visualized by ultraviolet irradiation or by immersion in phosphomolybdic acid or $KMnO_4$-H_2SO_4 ethanolic solutions.[2] For flash chromatography Merck 60, 230-400 mesh silica gel was used.[3]

Anhydrous solvents were purified and dried with activated molecular sieves prior to use.[4] For the removal of solvents under reduced pressure Büchi R-210 rotary evaporators were used.

For reactions carried out under inert conditions, the argon was previously dried through a column of P_2O_5 and a column of KOH and $CaCl_2$. All the glassware was dried for 12 hours prior to utilizing in an oven at 140 ºC and allowed to cool under a dehumidified atmosphere.[5]

Reactions at reduced temperatures were carried out using a Termo Haake EK90 refrigerator.

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[2] Stahl, E. *Thin Layer Chromatography*, Springer-Verlag, Berlin, **1969**.

[3] Still, W. C.; Kann, H.; Mitra, A. J. *J. Org. Chem*. **1978**, *43*, 2923.

[4] Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, Elsevier, Oxford, **2003**.

[5] Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Boranes*, John Wiley & Sons, New York, **1975**.

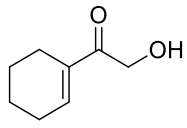
2. 4-ALKENYL-5*H*-1,2,3-OXATHIAZOLE 2,2-DIOXIDES IN MICHAEL/MICHAEL CASCADE REACTIONS

2.1. Synthesis of α-hydroxy ketones 2a and 2c-e.

General procedure:

To a mixture of CH_3CN/H_2O (5:1 mL), trifluoroacetic acid (2.00 mmol) and the corresponding alkenyl methyl ketone **1** (1.00 mmol) were added. Then [bis(trifluoroacetoxy)iodo]benzene (2.00 mmol) was added and the reaction was stirred under reflux during the time specified in each case and then allowed to reach room temperature. The solvent was removed under vacuum and H_2O (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with a solution of saturated aqueous $NaHCO_3$ (3 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography (FC) with the indicated eluent to obtain the corresponding α-hydroxy ketone **2**.

1-(Cyclohex-1-en-1-yl)-2-hydroxyethanone (2a)



Following the general procedure, **2a** (256 mg, 1.83 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a yellow oil after 5 hours, starting from 1-(cyclohex-1-en-1-yl)ethanone **1a** (0.51 mL, 4.00 mmol), trifluoroacetic acid (0.61 mL, 8.00 mmol) and [bis(trifluoroacetoxy)iodo]benzene (3.44 g, 8.00 mmol) in a mixture of CH_3CN/H_2O (20:4 mL) as solvent.

Yield: 46%.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 6.81-6.71 (m, 1H, $CH_2C\mathbf{H}$), 4.42 (s, 2H, $C\mathbf{H}_2OH$), 3.42 (s, 1H, O**H**), 2.23-2.08 (m, 4H, $C\mathbf{H}_2CH$+$C\mathbf{H}_2CCH$), 1.63-1.44 (m, 4H, $CH_2C\mathbf{H}_2C\mathbf{H}_2CH_2$).

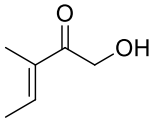
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 198.7 (**C**O), 141.2 ($CH_2\mathbf{C}H$), 136.2 ($CH_2\mathbf{C}CH$), 64.1 ($\mathbf{C}H_2OH$), 25.9 ($\mathbf{C}H_2CH$), 22.7 ($\mathbf{C}H_2CCH$), 21.5, 21.4 ($CH_2\mathbf{C}H_2\mathbf{C}H_2CH_2$).

IR (ATR) cm^{-1}: 3458 (O-H st), 1664 (C=O st).

MS (EI) m/z (relative abundance): 140 (2), 124 (1), 109 (100), 81 (63), 65 (6), 53 (26).

HRMS: Calculated for $[C_8H_{13}O_2]^+$: 141.0916 $[M+H]^+$; found: 141.0918.

(*E*)-1-Hydroxy-3-methylpent-3-en-2-one (2c)



Following the general procedure, **2c** (634 mg, 5.56 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 6:4) as a yellow oil after 4 hours, starting from 3-methylpent-3-en-2-one **1c** (2.34 mL, 20.00 mmol), trifluoroacetic acid (3.06 mL, 40.00 mmol) and [bis(trifluoroacetoxy)iodo]benzene (17.73 g, 40.00 mmol) in a mixture of CH_3CN/H_2O (100:20 mL) as solvent.

Yield: 28%.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 6.71-6.61 (m, 1H, $CH_3C\mathbf{H}$), 4.51 (s, 2H, $C\mathbf{H}_2OH$), 3.42 (s, 1H, O**H**), 1.90-1.84 (m, 3H, $C\mathbf{H}_3CH$), 1.84-1.80 (m, 3H, $C\mathbf{H}_3C$).

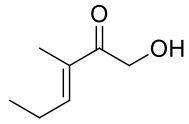
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 199.2 (**C**O), 138.8 (CH_3**C**H), 135.2 (CH_3**C**), 64.2 (**C**H_2OH), 14.6 (**C**H_3CH), 10.8 (**C**H_3C).

IR (ATR) cm^{-1}: 3440 (O-H st), 1674 (C=O st).

MS (EI) m/z (relative abundance): 114 (7), 97 (11), 83 (66), 69 (18), 59 (34), 55 (100).

HRMS: Calculated for $[C_6H_{11}O_2]^+$: 115.0759 $[M+H]^+$; found: 115.0764.

(*E*)-1-Hydroxy-3-methylhex-3-en-2-one (2d)



Following the general procedure, **2d** (311 mg, 2.42 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a yellow oil after 2 hours, starting from (*E*)-3-methylhex-3-en-2-one[6] **1d** (1.14 g, 10.17 mmol), trifluoroacetic acid (1.56 mL, 20.34 mmol) and [bis(trifluoroacetoxy)iodo]benzene (9.02 g, 20.34 mmol) in a mixture of CH_3CN/H_2O (50:10 mL) as solvent.

Yield: 24%.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 6.59-6.51 (m, 1H, CH_2C**H**), 4.54 (s, 2H, C**H**$_2$OH), 3.44 (s, 1H, O**H**), 2.35-2.22 (m, 2H, C**H**$_2$CH), 1.86-1.82 (m, 3H, C**H**$_3$C), 1.09 (t, J = 7.6 Hz, 3H, C**H**$_3$$CH_2$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 199.5 (**C**O), 145.5 (CH_2**C**H), 133.6 (CH_3**C**), 64.2 (**C**H_2OH), 22.2 (**C**H_2CH), 12.8 (**C**H_3CH_2), 11.0 (**C**H_3C).

IR (ATR) cm^{-1}: 3462 (O-H st), 1667 (C=O st).

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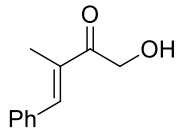
6 Austin, W. F.; Zhang, Y.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3905.

MS (EI) m/z (relative abundance): 128 (2), 111 (2), 97 (100), 79 (2), 69 (62), 53 (13).

HRMS: Calculated for $[C_7H_{13}O_2]^+$: 129.0916 $[M+H]^+$; found: 129.0911.

(*E*)-1-Hydroxy-3-methyl-4-phenylbut-3-en-2-one (2e)



Following the general procedure, **2e** (1.36 g, 7.70 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) as a yellow oil after 2 hours, starting from 3-methyl-4-phenylbut-3-en-2-one[7] **1e** (3.07 g, 19.17 mmol), trifluoroacetic acid (2.94 mL, 38.33 mmol) and [bis(trifluoroacetoxy)iodo]benzene (17.00 g, 38.33 mmol) in a mixture of CH_3CN/H_2O (95:19 mL) as solvent.

Yield: 40%.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.49-7.36 (m, 6H, C_{arom}-**H**+C_{arom}-C**H**), 4.71 (s, 2H, C**H**$_2$OH), 3.49 (s, 1H, O**H**), 2.19-2.13 (m, 3H, C**H**$_3$C).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 200.0 (**C**O), 139.8 (C_{arom}-**C**H), 135.0 (**C**$_{arom}$-C), 133.8 (CH$_3$**C**), 129.9, 129.2, 128.6 (**C**$_{arom}$-H), 64.7 (**C**H$_2$OH), 13.0 (**C**H$_3$C).

IR (ATR) cm^{-1}: 3457 (O-H st), 1665 (C=O st).

MS (EI) m/z (relative abundance): 176 (1), 145 (81), 117 (58), 115 (100), 91 (37), 77 (11), 51 (13).

HRMS: Calculated for $[C_{11}H_{12}O_2Na]^+$: 199.0735 $[M+Na]^+$; found: 199.0740.

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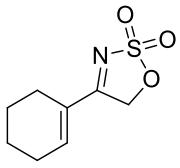
[7] de Paula, B. R. S.; Zampieri, D. S.; Rodrigues, J. A. R.; Moran, P. J. S. *Tetrahedron: Asymmetry* **2013**, *24*, 973.

2.2. Synthesis of 4-alkenyl-5*H*-1,2,3-oxathiazole 2,2-dioxides 3a-e.

General procedure:

To a solution of the corresponding α-hydroxy ketone **2** (1.00 mmol) in dry DMA (2.5 mL) under inert atmosphere, sulfamoyl chloride (2.00 mmol), previously released from chlorosulfonyl isocyanate with formic acid following representative procedure,[8] was added portionwise. After stirring at room temperature for 2 hours, the reaction mixture was diluted with EtOAc (10 mL) and washed with brine (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. Then *p*-toluenesulfonic acid (0.10 mmol) and toluene (2.5 mL) were added, and the reaction was stirred under reflux for 1 hour with a Dean-Stark receiver. The mixture was diluted with EtOAc (10 mL) and washed with a solution of saturated aqueous $NaHCO_3$ (3 × 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by flash column chromatography (FC) with the indicated eluent to give the corresponding cyclic sulfamidate imine **3**.

4-(Cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide (3a)



Following the general procedure, **3a** (283 mg, 1.41 mmol) was isolated by FC (hexanes/EtOAc gradient from 6:4 to 1:1) as a yellow solid, starting from α-hydroxy ketone **2a** (256 mg, 1.83 mmol) and sulfamoyl chloride (423 mg, 3.66 mmol) in dry DMA (5 mL), and then *p*-toluenesulfonic acid (35 mg, 0.18 mmol) using toluene (5 mL) as solvent.

Yield: 77%.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 6.80-6.77 (m, 1H, CH_2CH), 5.31 (s, 2H, OCH_2), 2.40-2.35 (m, 4H, CH_2CH+CH_2CCH), 1.81-1.61 (m, 4H, $CH_2CH_2CH_2CH_2$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 175.7 (CN), 146.8 (CH_2CH), 131.3 (CH_2CCH), 74.0 (OCH_2), 26.9 (CH_2CH), 24.2 (CH_2CCH), 21.3, 21.1 ($CH_2CH_2CH_2CH_2$).

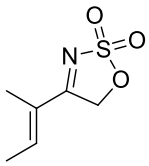
IR (ATR) cm^{-1}: 1632 (C=C st), 1570 (C=N st), 1354 (SO_2 st as), 1186 (SO_2 st sym).

M.p. (hexanes/EtOAc) (ºC): 151-153.

MS (EI) m/z (relative abundance): 201 (87), 186 (13), 172 (5), 160 (1), 144 (2), 136 (5), 120 (33), 106 (100), 92 (56), 79 (88), 66 (26), 52 (33).

HRMS: Calculated for $[C_8H_{12}NO_3S]^+$: 202.0538 $[M+H]^+$; found: 202.0525.

(*E*)-4-(1-Methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide (3c)



Following the general procedure, **3c** (544 mg, 3.10 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 6:4) as a yellow solid, starting from α-hydroxy ketone **2c** (634 mg, 5.56 mmol) and sulfamoyl chloride (1.28 g, 11.12 mmol) in dry DMA (14 mL), and then *p*-toluenesulfonic acid (106 mg, 0.56 mmol) using toluene (14 mL) as solvent.

Yield: 56%.

8 Lee, H.-K.; Kang, S.; Choi, E. B. *J. Org. Chem.* **2012**, *77*, 5454.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 6.59-6.52 (m, 1H, $CH_3C\mathbf{H}$), 5.32 (s, 2H, $OC\mathbf{H}_2$), 2.01-1.99 (m, 6H, $C\mathbf{H}_3CH+C\mathbf{H}_3C$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 176.6 (**C**N), 144.2 ($CH_3\mathbf{C}H$), 130.2 ($CH_3\mathbf{C}$), 74.1 ($O\mathbf{C}H_2$), 15.6 ($\mathbf{C}H_3CH$), 12.5 ($\mathbf{C}H_3C$).

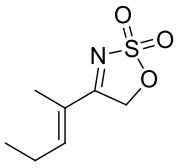
IR (ATR) cm^{-1}: 1638 (C=C st), 1561 (C=N st), 1351 (SO_2 st as), 1181 (SO_2 st sym).

M.p. (hexanes/EtOAc) (ºC): 122-124.

MS (EI) m/z (relative abundance): 175 (39), 160 (1), 135 (1), 110 (4), 94 (14), 81 (100), 75 (1), 66 (21), 54 (46).

HRMS: Calculated for $[C_6H_{10}NO_3S]^+$: 176.0381 $[M+H]^+$; found: 176.0376.

(*E*)-4-(1-Methylbut-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide (3d)



Following the general procedure, **3d** (305 mg, 1.61 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 6:4) as an orange solid, starting from α-hydroxy ketone **2d** (300 mg, 2.34 mmol) and sulfamoyl chloride (541 mg, 4.68 mmol) in dry DMA (6 mL), and then *p*-toluenesulfonic acid (44 mg, 0.23 mmol) using toluene (6 mL) as solvent.

Yield: 69%.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 6.46-6.40 (m, 1H, $CH_2C\mathbf{H}$), 5.33 (s, 2H, $OC\mathbf{H}_2$), 2.42-2.32 (m, 2H, $C\mathbf{H}_2CH$), 2.00 (s, 3H, $C\mathbf{H}_3C$), 1.10 (t, J = 7.6 Hz, 3H, $C\mathbf{H}_3CH_2$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 176.9 (**C**N), 150.8 ($CH_2\mathbf{C}H$), 128.7 ($CH_3\mathbf{C}$), 74.2 ($O\mathbf{C}H_2$), 23.0 ($\mathbf{C}H_2CH$), 12.6, 12.6 ($\mathbf{C}H_3C+\mathbf{C}H_3CH_2$).

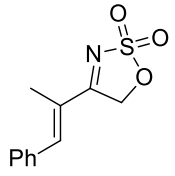
IR (ATR) cm^{-1}: 1631 (C=C st), 1563 (C=N st), 1346 (SO_2 st as), 1190 (SO_2 st sym).

M.p. (hexanes/EtOAc) (ºC): 56-58.

MS (EI) m/z (relative abundance): 189 (15), 174 (16), 162 (1), 149 (3), 135 (1), 124 (7), 110 (33), 94 (100), 80 (29), 68 (48), 53 (39).

HRMS: Calculated for $[C_7H_{12}NO_3S]^+$: 190.0538 $[M+H]^+$; found: 190.0523.

(*E*)-4-(1-Phenylprop-1-en-2-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide (3e)



Following the general procedure, **3e** (1.05 g, 4.41 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) as a white solid, starting from α-hydroxy ketone **2e** (1.18 g, 6.69 mmol) and sulfamoyl chloride (1.55 g, 13.39 mmol) in dry DMA (17 mL), and then *p*-toluenesulfonic acid (127 mg, 0.67 mmol) using toluene (17 mL) as solvent.

Yield: 66%.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.52-7.41 (m, 5H, C_{arom}-**H**), 7.20 (app d, *J* = 1.2 Hz, 1H, C_{arom}-C**H**), 5.48 (s, 2H, OC**H**$_2$), 2.34 (d, *J* = 1.2 Hz, 3H, C**H**$_3$C).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 177.2 (**C**N), 143.6 (C_{arom}-**C**H), 134.1 (**C**$_{arom}$-C), 130.3, 130.3 (**C**$_{arom}$-H), 129.0 (CH_3**C**), 128.9 (**C**$_{arom}$-H), 74.1 (O**C**H_2), 14.8 (**C**H_3C).

IR (ATR) cm^{-1}: 1618 (C=C st), 1563 (C=N st), 1359 (SO_2 st as), 1196 (SO_2 st sym).

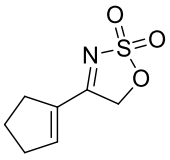
M.p. (hexanes/EtOAc) (ºC): 142-144.

MS (EI) m/z (relative abundance): 237 (4), 207 (1), 172 (4), 157 (100), 143 (33), 130 (11), 115 (76), 102 (4), 91 (20), 77 (10), 63 (9), 51 (10).

HRMS: Calculated for $[C_{11}H_{12}NO_3S]^+$: 238.0538 $[M+H]^+$; found: 238.0542.

Procedure for the synthesis of 4-alkenyl-5H-1,2,3-oxathiazole 2,2-dioxide ***3b****.*

4-(Cyclopent-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide (3b)



To a mixture of CH_3CN/H_2O (100:20 mL), trifluoroacetic acid (3.06 mL, 40.00 mmol) and 1-(cyclopent-1-en-1-yl)ethanone **1b** (2.38 mL, 20.00 mmol) were added. Then [bis(trifluoroacetoxy)iodo]benzene (17.73 g, 40.00 mmol) was added and the reaction was stirred under reflux during 5 hours and then allowed to reach room temperature. The solvent was removed under vacuum and H_2O (100 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 200 mL) and the combined organic layers were washed with a solution of saturated aqueous $NaHCO_3$ (3 × 200 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure obtaining the corresponding α-hydroxy ketone **2b**, which was employed in the following step without further purification. To a solution of α-hydroxy ketone **2b** in dry DMA (50 mL) under inert atmosphere, sulfamoyl chloride (4.62 g, 40.00 mmol) was added portionwise. After stirring at room temperature for 2 hours, the reaction mixture was diluted with EtOAc (200 mL) and washed with brine (3 × 200 mL). The resulting organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. Then *p*-toluenesulfonic acid (380 mg, 2.00 mmol) and toluene (50 mL) were added, and the reaction was stirred under reflux for 1 hour

with a Dean-Stark receiver. The mixture was diluted with EtOAc (200 mL) and washed with a solution of saturated aqueous $NaHCO_3$ (3 × 200 mL). The resulting organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. After purification by flash column chromatography (FC) (hexanes/EtOAc gradient from 6:4 to 1:1) the cyclic sulfamidate imine **3b** (258 mg, 1.38 mmol) was isolated as a brown solid.

Yield: 7%.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 6.94-6.86 (m, 1H, $CH_2C\mathbf{H}$), 5.30 (s, 2H, $OC\mathbf{H}_2$), 2.81-2.65 (m, 4H, $C\mathbf{H}_2CH$+$C\mathbf{H}_2CCH$), 2.12-2.00 (m, 2H, $CH_2C\mathbf{H}_2CH_2$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 171.9 (**C**N), 150.8 ($CH_2\mathbf{C}H$), 135.9 ($CH_2\mathbf{C}CH$), 74.3 ($O\mathbf{C}H_2$), 35.0 ($\mathbf{C}H_2CCH$), 31.4 ($\mathbf{C}H_2CH$), 22.4 ($CH_2\mathbf{C}H_2CH_2$).

IR (ATR) cm^{-1}: 1612 (C=C st), 1565 (C=N st), 1347 (SO_2 st as), 1178 (SO_2 st sym).

M.p. (hexanes/EtOAc) (ºC): 134-136.

MS (EI) m/z (relative abundance): 187 (33), 159 (1), 122 (2), 106 (13), 93 (79), 80 (12), 66 (100), 53 (7).

HRMS: Calculated for $[C_7H_{10}NO_3S]^+$: 188.0381 $[M+H]^+$; found: 188.0383.

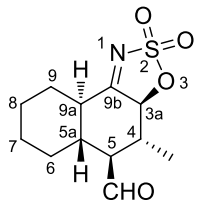
2.3. Synthesis of decalines 6a-i.

General procedure:

The α,β-unsaturated aldehyde **4** (1.50 or 2.00 mmol) was added to a solution of (*S*)-diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (0.20 mmol, 20

mol%), DABCO (0.20 mmol, 20 mol%) and the 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3a** (1.00 mmol) in dry $CHCl_3$ (2 mL) under inert atmosphere. The reaction mixture was stirred at the indicated temperature in each case, following its evolution by ^{1}H-NMR. After consumption of the starting material, the product was isolated directly by flash column chromatography (FC) with the indicated eluent, obtaining the decalines **6a-i**. The racemic standards for HPLC separation conditions were prepared under the same reaction conditions, using in these cases a 1:1 ratio of (*R*)- and (*S*)-diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether (0.20 mmol, 20 mol%) as catalyst at room temperature.

(3a*S*,4*R*,5*S*,5a*R*,9a*R*)-4-Methyl-4,5,5a,6,7,8,9,9a-octahydro-3a*H*-naphtho[1,2-*d*][1,2,3]oxathiazole-5-carbaldehyde 2,2-dioxide (6a)



Following the general procedure, **6a** (27 mg, 0.099 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a yellow solid after 48 hours at -30 ºC, starting from 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3a** (30 mg, 0.150 mmol) and (*E*)-crotonaldehyde **4a** (19 μL, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 66%.

dr: >20:1.

ee: 96%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 22.19 min, τ_{minor} = 35.53 min.

$[\alpha]_D^{20}$: +1.2 (*c* = 0.69, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.49 (d, *J* = 4.2 Hz, 1H, C-5C**H**O), 4.81 (d, *J* = 10.6 Hz, 1H, **H**-3a), 2.39-2.28 (m, 1H, **H**-9a), 2.25-2.17 (m, 3H, **H**-4+**H**-5+**H**-9_a), 1.97-1.87 (m, 1H, **H**-8_a), 1.86-1.76 (m, 3H, **H**-5a+**H**-6_a+**H**-7_a), 1.68-1.54 (m, 1H, **H**-9_b), 1.36-1.22 (m, 3H, **H**-6_b+**H**-7_b+**H**-8_b), 1.19 (d, *J* = 6.0 Hz, 3H, C-4C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 200.4 (C-5**C**HO), 185.5 (**C**-9b), 89.9 (**C**-3a), 58.5 (**C**-5), 44.5 (**C**-9a), 43.6 (**C**-5a), 40.7 (**C**-4), 31.3 (**C**-6), 26.2 (**C**-9), 25.0 (**C**-7), 24.4 (**C**-8), 17.0 (C-4**C**H_3).

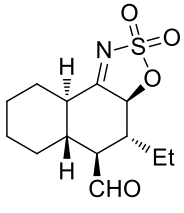
IR (ATR) cm^{-1}: 1725 (C=O st), 1630 (C=N st), 1368 (SO_2 st as), 1194 (SO_2 st sym).

M.p. (*n*-hexane/*i*-PrOH) (ºC): 137-139.

MS (EI) m/z (relative abundance): 271 (5), 243 (12), 227 (46), 214 (3), 201 (25), 192 (15), 178 (58), 162 (31), 150 (29), 134 (9), 122 (16), 108 (36), 91 (19), 81 (49), 71 (100), 55 (37).

HRMS: Calculated for $[C_{12}H_{18}NO_4S]^+$: 272.0957 $[M+H]^+$; found: 272.0946.

(3a*S*,4*R*,5*S*,5a*R*,9a*R*)-4-Ethyl-4,5,5a,6,7,8,9,9a-octahydro-3a*H*-naphtho[1,2-*d*][1,2,3]oxathiazole-5-carbaldehyde 2,2-dioxide (6b)



Following the general procedure, **6b** (28 mg, 0.099 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a yellow oil after 60 hours at room temperature, starting from 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3a** (30 mg, 0.150 mmol) and (*E*)-pent-2-enal **4b** (29 μL, 0.300 mmol) in

the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 66%.

dr: >20:1.

ee: 95%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 17.93 min, τ_{minor} = 25.57 min.

$[\alpha]_D^{20}$: +1.9 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.47 (d, *J* = 4.5 Hz, 1H, C-5C**H**O), 5.01 (d, *J* = 10.7 Hz, 1H, **H**-3a), 2.40-2.16 (m, 4H, **H**-9a+**H**-4+**H**-5+**H**-9_a), 1.96-1.87 (m, 1H, **H**-8_a), 1.83-1.76 (m, 3H, **H**-5a+**H**-6_a+**H**-7_a), 1.74-1.66 (m, 1H, **H**-9_b), 1.62-1.49 (m, 2H, C-4C**H**$_2$), 1.35-1.21 (m, 3H, **H**-6_b+**H**-7_b+**H**-8_b), 0.97 (t, *J* = 7.5 Hz, 3H, C-4CH_2C**H**$_3$).

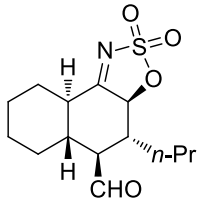
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 200.4 (C-5**C**HO), 186.2 (**C**-9b), 87.2 (**C**-3a), 55.6 (**C**-5), 45.6 (**C**-9a), 44.4 (**C**-5a), 43.4 (**C**-4), 31.4 (**C**-6), 26.3 (**C**-9), 25.0 (**C**-7), 24.4 (**C**-8), 23.1 (C-4**C**H_2), 8.7 (C-4CH_2**C**H_3).

IR (ATR) cm^{-1}: 1725 (C=O st), 1631 (C=N st), 1369 (SO_2 st as), 1194 (SO_2 st sym).

MS (EI) m/z (relative abundance): 285 (6), 256 (11), 241 (24), 228 (16), 216 (5), 205 (78), 192 (93), 176 (100), 164 (36), 148 (27), 136 (35), 125 (34), 108 (55), 95 (40), 81 (97), 67 (69), 55 (63).

HRMS: Calculated for $[C_{13}H_{20}NO_4S]^+$: 286.1113 $[M+H]^+$; found: 286.1116.

(3a*S*,4*R*,5*S*,5a*R*,9a*R*)-4-Propyl-4,5,5a,6,7,8,9,9a-octahydro-3a*H*-naphtho[1,2-*d*][1,2,3]oxathiazole-5-carbaldehyde 2,2-dioxide (6c)



Following the general procedure, **6c** (32 mg, 0.107 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a yellow oil after 60 hours at room temperature, starting from 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3a** (30 mg, 0.150 mmol) and (*E*)-hex-2-enal **4c** (35 μL, 0.300 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 71%.

dr: >20:1.

ee: 96%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 30.01 min, τ_{minor} = 42.72 min.

$[\alpha]_D^{20}$: +2.8 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.47 (d, *J* = 4.4 Hz, 1H, C-5C**H**O), 4.97 (d, *J* = 10.4 Hz, 1H, **H**-3a), 2.37-2.24 (m, 3H, **H**-9a+**H**-4+**H**-5), 2.22-2.15 (m, 1H, **H**-9_a), 1.96-1.88 (m, 1H, **H**-8_a), 1.86-1.75 (m, 3H, **H**-5a+**H**-6_a+**H**-7_a), 1.61-1.22 (m, 8H, **H**-9_b+**H**-6_b+**H**-7_b+**H**-8_b+C-4(C**H**$_2$)$_2$), 0.91 (t, *J* = 7.0 Hz, 3H, C-4$(CH_2)_2$C**H**$_3$).

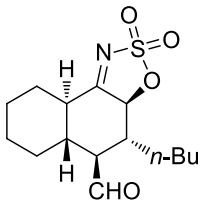
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 200.4 (C-5**C**HO), 185.9 (**C**-9b), 88.1 (**C**-3a), 56.6 (**C**-5), 44.8 (**C**-9a), 44.4 (**C**-5a), 43.5 (**C**-4), 33.3 (C-4(**C**H$_2$)$_2$), 31.4 (**C**-6), 26.3 (**C**-9), 25.0 (**C**-7), 24.4 (**C**-8), 18.3 (C-4(**C**H$_2$)$_2$), 14.1 (C-4$(CH_2)_2$**C**H$_3$).

IR (ATR) cm^{-1}: 1725 (C=O st), 1631 (C=N st), 1369 (SO_2 st as), 1194 (SO_2 st sym).

MS (EI) m/z (relative abundance): 299 (5), 270 (11), 255 (16), 235 (13), 219 (76), 206 (45), 190 (100), 176 (24), 164 (37), 150 (30), 136 (25), 125 (32), 108 (45), 95 (47), 81 (67), 67 (58), 55 (64).

HRMS: Calculated for $[C_{14}H_{22}NO_4S]^+$: 300.1270 $[M+H]^+$; found: 300.1258.

(3a*S*,4*R*,5*S*,5a*R*,9a*R*)-4-Butyl-4,5,5a,6,7,8,9,9a-octahydro-3a*H*-naphtho[1,2-*d*][1,2,3]oxathiazole-5-carbaldehyde 2,2-dioxide (6d)



Following the general procedure, **6d** (32 mg, 0.101 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a yellow oil after 72 hours at room temperature, starting from 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3a** (30 mg, 0.150 mmol) and (*E*)-hept-2-enal **4d** (39 μL, 0.300 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 67%.

dr: >20:1.

ee: 95%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 27.02 min, τ_{minor} = 36.08 min.

$[\alpha]_D^{20}$: +2.3 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.47 (d, *J* = 4.4 Hz, 1H, C-5C**H**O), 4.99 (d, *J* = 10.5 Hz, 1H, **H**-3a), 2.38-2.24 (m, 3H, **H**-9a+**H**-4+**H**-5), 2.21-2.16 (m,

1H, **H**-9_a), 1.91-1.88 (m, 1H, **H**-8_a), 1.85-1.76 (m, 3H, **H**-5a+**H**-6_a+**H**-7_a), 1.65-1.24 (m, 10H, **H**-9_b+**H**-6_b+**H**-7_b+**H**-8_b+C-4(C**H**$_2$)$_3$), 0.88 (t, J = 7.0 Hz, 3H, C-4(CH$_2$)$_3$C**H**$_3$).

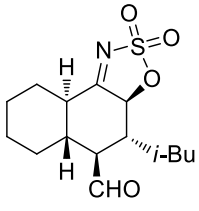
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 200.5 (C-5**C**HO), 186.1 (**C**-9b), 88.0 (**C**-3a), 56.4 (**C**-5), 44.8 (**C**-9a), 44.4 (**C**-5a), 43.5 (**C**-4), 31.4 (**C**-6), 30.6 (C-4(**C**H$_2$)$_3$), 26.8 (C-4(**C**H$_2$)$_3$), 26.3 (**C**-9), 25.0 (**C**-7), 24.4 (**C**-8), 22.7 (C-4(**C**H$_2$)$_3$), 13.8 (C-4(CH$_2$)$_3$**C**H$_3$).

IR (ATR) cm^{-1}: 1724 (C=O st), 1632 (C=N st), 1371 (SO_2 st as), 1195 (SO_2 st sym).

MS (EI) m/z (relative abundance): 313 (3), 233 (45), 220 (28), 204 (100), 190 (16), 176 (15), 164 (25), 148 (17), 125 (23), 109 (22), 95 (29), 81 (43), 67 (39), 55 (45).

HRMS: Calculated for $[C_{15}H_{24}NO_4S]^+$: 314.1426 $[M+H]^+$; found: 314.1420.

(3a*S*,4*R*,5*S*,5a*R*,9a*R*)-4-Isobutyl-4,5,5a,6,7,8,9,9a-octahydro-3a*H*-naphtho[1,2-*d*][1,2,3]oxathiazole-5-carbaldehyde 2,2-dioxide (6e)



Following the general procedure, **6e** (30 mg, 0.097 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a yellow oil after 60 hours at room temperature, starting from 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3a** (30 mg, 0.150 mmol) and (*E*)-5-methylhex-2-enal **4e** (34 mg, 0.300 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 65%.

dr: >20:1.

ee: 97%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 26.32 min, τ_{minor} = 32.17 min.

$[\alpha]_D^{20}$: +5.3 (*c* = 0.69, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.46 (d, *J* = 4.4 Hz, 1H, C-5C**H**O), 4.89 (d, *J* = 10.1 Hz, 1H, **H**-3a), 2.35-2.16 (m, 4H, **H**-9a+**H**-4+**H**-5+**H**-9_a), 1.94-1.89 (m, 1H, **H**-8_a), 1.84-1.75 (m, 3H, **H**-5a+**H**-6_a+**H**-7_a), 1.63-1.22 (m, 7H, **H**-9_b+**H**-6_b+**H**-7_b+**H**-8_b+C-4C**H**$_2$+C**H**$(CH_3)_2$), 0.91-0.87 (m, 6H, CH(C**H**$_3)_2$).

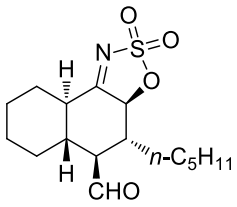
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 200.4 (C-5**C**HO), 185.4 (**C**-9b), 90.0 (**C**-3a), 58.4 (**C**-5), 44.4 (**C**-9a), 43.3 (**C**-5a), 43.0 (**C**-4), 42.9 (C-4**C**H_2), 31.4 (**C**-6), 26.3 (**C**-9), 25.6 (**C**H$(CH_3)_2$), 25.0 (**C**-7), 24.4 (**C**-8), 23.3, 21.9 (CH(**C**$H_3)_2$).

IR (ATR) cm^{-1}: 1725 (C=O st), 1632 (C=N st), 1368 (SO_2 st as), 1194 (SO_2 st sym).

MS (EI) m/z (relative abundance): 233 (82), 204 (46), 176 (61), 162 (11), 146 (95), 120 (100), 106 (40), 91 (32), 77 (30), 64 (19).

HRMS: Calculated for $[C_{15}H_{24}NO_4S]^+$: 314.1426 $[M+H]^+$; found: 314.1421.

(3a*S*,4*R*,5*S*,5a*R*,9a*R*)-4-Pentyl-4,5,5a,6,7,8,9,9a-octahydro-3a*H*-naphtho[1,2-*d*][1,2,3]oxathiazole-5-carbaldehyde 2,2-dioxide (6f)



Following the general procedure, **6f** (30 mg, 0.092 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 8:2) as a yellow oil after 72 hours at room temperature, starting from 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3a** (30 mg, 0.150 mmol) and (*E*)-oct-2-enal **4f** (45 μL, 0.300 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 61%.

dr: >20:1.

ee: 95%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 25.69 min, τ_{minor} = 34.01 min.

$[\alpha]_D^{20}$: +3.4 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.47 (d, *J* = 4.4 Hz, 1H, C-5C**H**O), 4.99 (d, *J* = 10.4 Hz, 1H, **H**-3a), 2.38-2.24 (m, 3H, **H**-9a+**H**-4+**H**-5), 2.22-2.16 (m, 1H, **H**-9_a), 1.93-1.88 (m, 1H, **H**-8_a), 1.85-1.74 (m, 3H, **H**-5a+**H**-6_a+**H**-7_a), 1.66-1.22 (m, 12H, **H**-9_b+**H**-6_b+**H**-7_b+**H**-8_b+C-4(C**H**$_2$)$_4$), 0.87 (t, *J* = 6.9 Hz, 3H, C-4$(CH_2)_4$C**H**$_3$).

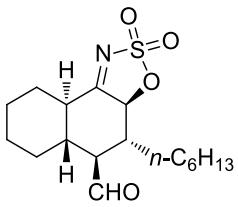
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 200.4 (C-5**C**HO), 186.0 (**C**-9b), 88.0 (**C**-3a), 56.4 (**C**-5), 44.9 (**C**-9a), 44.4 (**C**-5a), 43.5 (**C**-4), 31.7 (C-4(**C**H_2)$_4$), 31.4 (**C**-6), 30.8 (C-4(**C**H_2)$_4$), 26.3 (**C**-9), 25.0 (**C**-7), 24.4 (**C**-8), 24.3, 22.3 (C-4(**C**H_2)$_4$), 13.9 (C-4$(CH_2)_4$**C**H_3).

IR (ATR) cm^{-1}: 1724 (C=O st), 1632 (C=N st), 1372 (SO_2 st as), 1195 (SO_2 st sym).

MS (EI) m/z (relative abundance): 327 (6), 281 (38), 234 (89), 207 (100), 164 (33), 136 (49), 108 (34), 81 (68), 55 (90).

HRMS: Calculated for $[C_{16}H_{26}NO_4S]^+$: 328.1583 $[M+H]^+$; found: 328.1585.

(3a*S*,4*R*,5*S*,5a*R*,9a*R*)-4-Hexyl-4,5,5a,6,7,8,9,9a-octahydro-3a*H*-naphtho[1,2-*d*][1,2,3]oxathiazole-5-carbaldehyde 2,2-dioxide (6g)



Following the general procedure, **6g** (29 mg, 0.085 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 8:2) as a yellow oil after 72 hours at room temperature, starting from 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3a** (30 mg, 0.150 mmol) and (*E*)-non-2-enal **4g** (50 μL, 0.300 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 57%.

dr: >20:1.

ee: 95%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 26.36 min, τ_{minor} = 34.75 min.

$[\alpha]_D^{20}$: +2.3 (*c* = 1.01, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.47 (d, *J* = 4.3 Hz, 1H, C-5C**H**O), 4.99 (d, *J* = 10.4 Hz, 1H, **H**-3a), 2.39-2.23 (m, 3H, **H**-9a+**H**-4+**H**-5), 2.21-2.14 (m, 1H, **H**-9_a), 1.95-1.87 (m, 1H, **H**-8_a), 1.84-1.75 (m, 3H, **H**-5a+**H**-6_a+**H**-7_a), 1.66-

1.20 (m, 14H, **H**-9$_b$+**H**-6$_b$+**H**-7$_b$+**H**-8$_b$+C-4(C**H**$_2$)$_5$), 0.87 (t, *J* = 6.4 Hz, 3H, C-4(CH$_2$)$_5$C**H**$_3$).

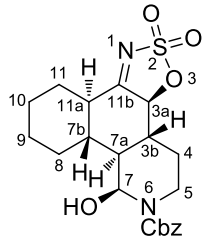
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 200.4 (C-5**C**HO), 186.0 (**C**-9b), 88.0 (**C**-3a), 56.4 (**C**-5), 44.9 (**C**-9a), 44.4 (**C**-5a), 43.5 (**C**-4), 31.5 (C-4(**C**H$_2$)$_5$), 31.4 (**C**-6), 30.9, 29.2 (C-4(**C**H$_2$)$_5$), 26.3 (**C**-9), 25.0 (**C**-7), 24.7 (C-4(**C**H$_2$)$_5$), 24.4 (**C**-8), 22.5 (C-4(**C**H$_2$)$_5$), 14.0 (C-4(CH$_2$)$_5$**C**H$_3$).

IR (ATR) cm^{-1}: 1725 (C=O st), 1632 (C=N st), 1371 (SO_2 st as), 1197 (SO_2 st sym).

MS (EI) m/z (relative abundance): 341 (2), 281 (12), 261 (54), 232 (5), 207 (28), 146 (13), 96 (20), 79 (18), 55 (24).

HRMS: Calculated for $[C_{17}H_{28}NO_4S]^+$: 342.1739 $[M+H]^+$; found: 342.1725.

(3a*S*,3b*R*,7*S*,7a*S*,7b*R*,11a*R*)-Benzyl 7-hydroxy-4,5,7,7a,7b,8,9,10,11,11a-decahydro-3a*H*-benzo[*h*][1,2,3]oxathiazolo[5,4-*f*]isoquinoline-6(3b*H*)-carboxylate 2,2-dioxide (6h)



Following the general procedure, **6h** (38 mg, 0.092 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 6:4) as a yellow oil after 48 hours at room temperature, starting from 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3a** (30 mg, 0.150 mmol) and (*E*)-benzyl (5-oxopent-3-en-1-yl)carbamate **4h** (70 μL, 0.300 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 61%.

dr: >20:1.

ee: 94%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 33.52 min, τ_{minor} = 63.03 min.

$[\alpha]_D^{20}$: +7.1 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.40-7.32 (m, 5H, C_{arom}-**H**), 5.98-5.92 (m, 1H, **H**-7), 5.15 (s, 2H, OC**H**$_2$), 4.73 (d, *J* = 10.8 Hz, 1H, **H**-3a), 4.05-3.97 (m, 1H, **H**-5$_a$), 3.23-3.17 (m, 1H, **H**-5$_b$), 2.46 (bs, 1H, O**H**), 2.26-2.11 (m, 5H, **H**-3b+**H**-11a+**H**-11$_a$+**H**-8$_a$+**H**-4$_a$), 1.92-1.83 (m, 2H, **H**-9$_a$+**H**-10$_a$), 1.72-1.59 (m, 2H, **H**-7b+**H**-11$_b$), 1.48-1.40 (m, 2H, **H**-7a, **H**-4$_b$), 1.32-1.24 (m, 2H, **H**-9$_b$+**H**-10$_b$), 1.18-1.10 (m, 1H, **H**-8$_b$).

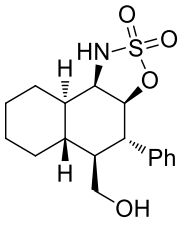
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 186.1 (**C**-11b), 156.1 (N**C**O), 136.0 (**C**$_{arom}$-C), 128.7, 128.4, 128.0 (**C**$_{arom}$-H), 89.9 (**C**-3a), 73.6 (**C**-7), 67.7 (O**C**H$_2$), 45.2 (**C**-7a), 45.1 (**C**-11a), 44.3 (**C**-7b), 41.7 (**C**-3b), 37.5 (**C**-5), 29.8 (**C**-4), 29.4 (**C**-8), 26.2 (**C**-11), 25.1, 24.7 (**C**-9+**C**-10).

IR (ATR) cm^{-1}: 3408 (O-H st), 1682 (C=O st), 1629 (C=N st), 1369 (SO_2 st as), 1197 (SO_2 st sym).

MS (EI) m/z (relative abundance): 207 (13), 218 (4), 147 (18), 129 (100), 112 (24), 83 (17), 70 (31), 57 (38).

HRMS: Calculated for $[C_{21}H_{26}N_2O_6SNa]^+$: 457.1409 $[M+Na]^+$; found: 457.1410.

(3a*S*,4*S*,5*S*,5a*R*,9a*R*,9b*R*)-5-(Hydroxymethyl)-4-phenyldecahydro-1*H*-naphtho[1,2-*d*][1,2,3]oxathiazole 2,2-dioxide (6i)



Following the general procedure, **6i** (15 mg, 0.045 mmol) was isolated by FC (hexanes/EtOAc gradient from 6:4 to 1:1) as a white solid after 48 hours at room temperature, starting from 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3a** (30 mg, 0.150 mmol) and (*E*)-cinnamaldehyde **4i** (28 μL, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent, followed by reduction with $NaBH_4$ (7 mg, 0.180 mmol) in MeOH (2 mL) at 0 ºC during 15 minutes and quenched with a solution of saturated aqueous NH_4Cl (1.5 mL). The mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure.

Yield: 30%.

dr: >20:1.

ee: 97%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 26.01 min, τ_{minor} = 17.56 min.

$[\alpha]_D^{20}$: -92.5 (*c* = 0.44, MeOH).

^{1}H-NMR (δ, ppm) (MeOD, 300 MHz): 7.35-7.23 (m, 5H, C_{arom}-**H**), 4.92-4.88 (m, 1H, **H**-3a), 4.10-4.04 (m, 1H, **H**-9b), 3.62 (dd, *J* = 11.2, 2.3 Hz, 1H, C**H**$_a$H$_b$OH), 3.40-3.29 (m, 1H, **H**-4), 3.05 (dd, *J* = 11.2, 2.0 Hz, 1H, CH$_a$**H**$_b$OH), 2.19-2.10 (m, 1H, **H**-6$_a$), 1.87-1.66 (m, 5H, **H**-7$_a$+**H**-8$_a$+**H**-9$_a$+**H**-5a+**H**-9a), 1.44-1.29 (m, 4H, **H**-5+**H**-9$_b$+**H**-7$_b$+**H**-8$_b$), 1.00-0.86 (m, 1H, **H**-6$_b$).

^{13}C-NMR (δ, ppm) (MeOD, 125.7 MHz): 142.0 (**C**$_{arom}$-C), 130.2, 129.7, 128.1 (**C**$_{arom}$-H), 92.0 (**C**-3a), 61.9 (**C**-9b), 58.7 (**C**H$_2$OH), 47.9 (**C**-5), 47.2 (**C**-4), 43.2 (**C**-9a), 35.8 (**C**-5a), 31.8 (**C**-9), 31.1 (**C**-6), 27.6, 27.3 (**C**-7+**C**-8).

IR (ATR) cm^{-1}: 3551 (O-H st), 1339 (SO_2 st as), 1185 (SO_2 st sym).

M.p. (hexanes/EtOAc) (ºC): 177-179.

MS (EI) m/z (relative abundance): 281 (38), 239 (13), 207 (100), 179 (13), 148 (60), 117 (24), 91 (44), 64 (26).

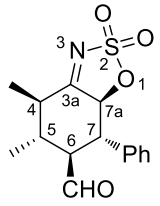
HRMS: Calculated for $[C_{17}H_{24}NO_4S]^+$: 338.1426 $[M+H]^+$; found: 338.1431.

2.4. Synthesis of cyclohexanes 7a-s.

General procedure:

The α,β-unsaturated aldehyde **4** (1.50 or 2.00 mmol) was added to a solution of (*S*)-diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (0.20 mmol, 20 mol%), DABCO (0.20 mmol, 20 mol%) and the corresponding 4-alkenyl-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c-e** (1.00 mmol) in dry $CHCl_3$ (2 mL) under inert atmosphere. The reaction mixture was stirred at -30 ºC, following its evolution by ^{1}H-NMR. After consumption of the starting material, in the indicated cases, it was necessary to leave the reaction at room temperature during four hours in order to improve the diastereoselectivity of the process. Finally, the product was isolated directly by flash column chromatography (FC) with the indicated eluent, obtaining the cycloadducts **7a-s**. The racemic standards for HPLC separation conditions were prepared under the same reaction conditions, using in these cases a 1:1 ratio of (*R*)- and (*S*)-diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether (0.20 mmol, 20 mol%) as catalyst at room temperature.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-4,5-Dimethyl-7-phenyl-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7a)



Following the general procedure, **7a** (30 mg, 0.099 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a yellow solid after 60 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-cinnamaldehyde **4i** (28 μL, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 66%.

dr: >20:1.

ee: 98%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 50.49 min, τ_{minor} = 39.03 min.

$[\alpha]_D^{20}$: -50.3 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.34 (d, *J* = 3.8 Hz, 1H, C-6C**H**O), 7.40-7.20 (m, 5H, C_{arom}-**H**), 5.28 (d, *J* = 11.5 Hz, 1H, **H**-7a), 3.23 (app t, *J* = 11.7 Hz, 1H, **H**-7), 2.95-2.82 (m, 1H, **H**-6), 2.60 (dq, *J* = 12.6, 6.3 Hz, 1H, **H**-4), 2.08-1.93 (m, 1H, **H**-5), 1.43 (d, *J* = 6.3 Hz, 3H, C-4C**H**$_3$), 1.18 (d, *J* = 6.5 Hz, 3H, C-5C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 199.7 (C-6**C**HO), 186.2 (**C**-3a), 135.0 (**C**$_{arom}$-C), 129.5, 128.8, 127.8 (**C**$_{arom}$-H), 89.1 (**C**-7a), 57.9 (**C**-6), 51.5 (**C**-7), 41.7 (**C**-4), 40.2 (**C**-5), 17.6 (C-5**C**H_3), 13.0 (C-4**C**H_3).

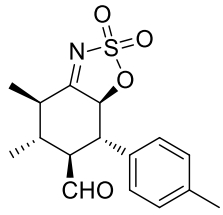
IR (ATR) cm^{-1}: 1727 (C=O st), 1631 (C=N st), 1369 (SO_2 st as), 1198 (SO_2 st sym).

M.p. (hexanes/EtOAc) (ºC): 142-144 (Decomposed).

MS (EI) m/z (relative abundance): 307 (7), 278 (21), 198 (100), 182 (31), 145 (13), 131 (64), 117 (15), 104 (31), 91 (58), 77 (32), 64 (11), 51 (12).

HRMS: Calculated for $[C_{15}H_{18}NO_4S]^+$: 308.0957 $[M+H]^+$; found: 308.0954.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-4,5-Dimethyl-7-(*p*-tolyl)-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7b)



Following the general procedure, **7b** (28 mg, 0.088 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 6:4) as a yellow oil after 60 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-4-methylcinnamaldehyde **4j** (33 mg, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent. After full conversion, the reaction was stirred at room temperature during four hours to achieve only one diastereoisomer.

Yield: 59%.

dr: >20:1.

ee: >99%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 20.88 min, τ_{minor} = -.

$[\alpha]_D^{20}$: -71.8 (*c* = 1.03, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.34 (d, *J* = 3.9 Hz, 1H, C-6C**H**O), 7.17 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 7.11 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 5.25 (d, *J* = 11.3 Hz, 1H, **H**-7a), 3.20 (app t, *J* = 11.7 Hz, 1H, **H**-7), 2.91-2.79 (m, 1H, **H**-6), 2.59 (dq, *J* = 12.6, 6.3 Hz, 1H, **H**-4), 2.33 (s, 3H, C_{arom}-C**H**$_3$), 2.06-1.92 (m, 1H, **H**-5), 1.43 (d, *J* = 6.3 Hz, 3H, C-4C**H**$_3$), 1.18 (d, *J* = 6.5 Hz, 3H, C-5C**H**$_3$).

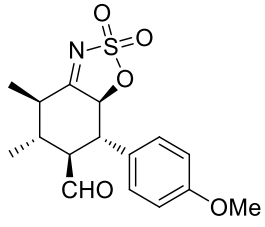
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 199.7 (C-6**C**HO), 186.1 (**C**-3a), 138.8, 132.0 ($\mathbf{C}_{arom}$-C), 130.2, 127.6 ($\mathbf{C}_{arom}$-H), 89.2 (**C**-7a), 58.0 (**C**-6), 51.2 (**C**-7), 41.7 (**C**-4), 40.1 (**C**-5), 21.1 (C_{arom}-**C**H$_3$), 17.7 (C-5**C**H$_3$), 13.0 (C-4**C**H$_3$).

IR (ATR) cm^{-1}: 1727 (C=O st), 1626 (C=N st), 1368 (SO_2 st as), 1198 (SO_2 st sym).

MS (EI) m/z (relative abundance): 321 (12), 292 (16), 212 (100), 196 (33), 145 (39), 128 (17), 115 (30), 91 (27), 77 (11).

HRMS: Calculated for $[C_{16}H_{20}NO_4S]^+$: 322.1113 $[M+H]^+$; found: 322.1115.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-7-(4-Methoxyphenyl)-4,5-dimethyl-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7c)



Following the general procedure, **7c** (33 mg, 0.098 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 6:4) as a yellow oil after 48 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-4-methoxycinnamaldehyde **4l** (37 mg, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 65%.

dr: >20:1.

ee: >99%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 21.73 min, τ_{minor} = -.

$[\alpha]_D^{20}$: -60.5 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.33 (d, *J* = 3.9 Hz, 1H, C-6C**H**O), 7.14 (d, *J* = 8.6 Hz, 2H, C_{arom}-**H**), 6.88 (d, *J* = 8.6 Hz, 2H, C_{arom}-**H**), 5.22 (d, *J* = 11.3 Hz, 1H, **H**-7a), 3.78 (s, 3H, OC**H**$_3$), 3.19 (app t, *J* = 11.7 Hz, 1H, **H**-7), 2.90-2.78 (m, 1H, **H**-6), 2.58 (dq, *J* = 12.6, 6.3 Hz, 1H, **H**-4), 2.07-1.89 (m, 1H, **H**-5), 1.42 (d, *J* = 6.3 Hz, 3H, C-4C**H**$_3$), 1.17 (d, *J* = 6.4 Hz, 3H, C-5C**H**$_3$).

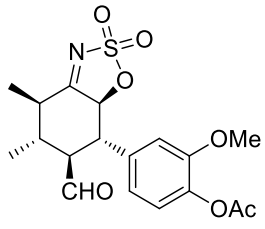
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 199.8 (C-6**C**HO), 186.2 (**C**-3a), 159.8 (**C**$_{arom}$-C), 128.9 (**C**$_{arom}$-H), 126.9 (**C**$_{arom}$-C), 114.8 (**C**$_{arom}$-H), 89.3 (**C**-7a), 58.1 (**C**-6), 55.3 (O**C**H$_3$), 50.8 (**C**-7), 41.7 (**C**-4), 40.1 (**C**-5), 17.6 (C-5**C**H$_3$), 13.0 (C-4**C**H$_3$).

IR (ATR) cm^{-1}: 1726 (C=O st), 1625 (C=N st), 1368 (SO_2 st as), 1197 (SO_2 st sym).

MS (EI) m/z (relative abundance): 337 (32), 281 (15), 256 (17), 228 (93), 207 (40), 160 (56), 134 (100), 108 (57), 91 (28), 64 (28).

HRMS: Calculated for $[C_{16}H_{20}NO_5S]^+$: 338.1062 $[M+H]^+$; found: 338.1053.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-7-(4-Acetoxy-3-methoxyphenyl)-4,5-dimethyl-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7d)



Following the general procedure, **7d** (43 mg, 0.108 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 6:4) as a yellow oil after 48 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-4-acetoxy-3-methoxycinnamaldehyde **4m** (52 mg, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 72%.

dr: >20:1.

ee: >99%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 85.52 min, τ_{minor} = -.

$[\alpha]_D^{20}$: -46.1 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.36 (d, *J* = 3.7 Hz, 1H, C-6C**H**O), 7.02 (d, *J* = 8.1 Hz, 1H, C_{arom}-**H**), 6.85-6.76 (m, 2H, C_{arom}-**H**), 5.23 (d, *J* = 11.2 Hz, 1H, **H**-7a), 3.81 (s, 3H, OC**H**$_3$), 3.20 (app t, *J* = 11.7 Hz, 1H, **H**-7), 2.95-2.86 (m, 1H, **H**-6), 2.59 (dq, *J* = 12.6, 6.4 Hz, 1H, **H**-4), 2.30 (s, 3H, OCOC**H**$_3$), 2.04-1.89 (m, 1H, **H**-5), 1.41 (d, *J* = 6.4 Hz, 3H, C-4C**H**$_3$), 1.17 (d, *J* = 6.5 Hz, 3H, C-5C**H**$_3$).

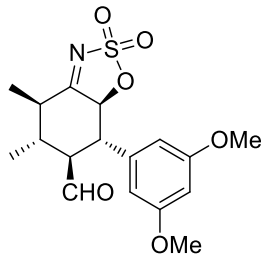
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 199.6 (C-6**C**HO), 185.9 (**C**-3a), 168.7 (O**C**OCH$_3$), 151.7, 140.0, 133.8 (**C**$_{arom}$-C), 123.7, 119.4, 112.3 (**C**$_{arom}$-H), 88.9 (**C**-7a), 57.6 (**C**-6), 56.1 (O**C**H$_3$), 51.3 (**C**-7), 41.7 (**C**-4), 40.3 (**C**-5), 20.7 (OCO**C**H$_3$), 17.6 (C-5**C**H$_3$), 13.0 (C-4**C**H$_3$).

IR (ATR) cm^{-1}: 1762 (OC=O st), 1727 (C=O st), 1629 (C=N st), 1367 (SO_2 st as), 1196 (SO_2 st sym).

MS (EI) m/z (relative abundance): 281 (46), 253 (10), 207 (100), 177 (12), 129 (59), 96 (17), 64 (33).

HRMS: Calculated for $[C_{18}H_{22}NO_7S]^+$: 396.1117 $[M+H]^+$; found: 396.1126.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-7-(3,5-Dimethoxyphenyl)-4,5-dimethyl-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7e)



Following the general procedure, **7e** (39 mg, 0.106 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 6:4) as a yellow oil after 60 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-3,5-dimethoxycinnamaldehyde[9] **4n** (43 mg, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 71%.

dr: >20:1.

ee: 99%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 56.28 min, τ_{minor} = 42.95 min.

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[9] Barcelos, R. C.; Pastre, J. C.; Caixeta, V.; Vendramini-Costa, D. B.; de Carvalho, J. E.; Pilli, R. A. *Bioorg. Med. Chem.* **2012**, *20*, 3635.

$[\alpha]_D^{20}$: -38.8 (*c* = 0.90, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.38 (d, *J* = 3.6 Hz, 1H, C-6C**H**O), 6.39 (t, *J* = 2.2 Hz, 1H, C_{arom}-**H**), 6.35 (d, *J* = 2.2 Hz, 2H, C_{arom}-**H**), 5.27 (d, *J* = 11.3 Hz, 1H, **H**-7a), 3.77 (s, 6H, 2 × OC**H**$_3$), 3.13 (app t, *J* = 11.7 Hz, 1H, **H**-7), 2.90-2.77 (m, 1H, **H**-6), 2.57 (dq, *J* = 12.6, 6.4 Hz, 1H, **H**-4), 2.03-1.91 (m, 1H, **H**-5), 1.42 (d, *J* = 6.4 Hz, 3H, C-4C**H**$_3$), 1.18 (d, *J* = 6.5 Hz, 3H, C-5C**H**$_3$).

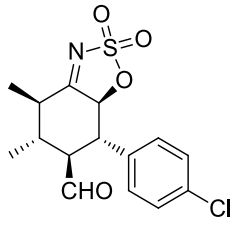
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 199.5 (C-6**C**HO), 186.0 (**C**-3a), 161.5, 137.3 (**C**$_{arom}$-C), 105.9, 100.1 (**C**$_{arom}$-H), 88.8 (**C**-7a), 57.8 (**C**-6), 55.4 (O**C**H_3), 51.8 (**C**-7), 41.7 (**C**-4), 40.2 (**C**-5), 17.6 (C-5**C**H_3), 13.0 (C-4**C**H_3).

IR (ATR) cm^{-1}: 1726 (C=O st), 1629 (C=N st), 1367 (SO_2 st as), 1197 (SO_2 st sym).

MS (EI) m/z (relative abundance): 348 (5), 277 (23), 217 (13), 191 (15), 164 (100), 113 (21), 71 (33).

HRMS: Calculated for $[C_{17}H_{22}NO_6S]^+$: 368.1168 $[M+H]^+$; found: 368.1167.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-7-(4-Chlorophenyl)-4,5-dimethyl-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7f)



Following the general procedure, **7f** (44 mg, 0.130 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 6:4) as a yellow solid after 60 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (35 mg, 0.200 mmol) and (*E*)-4-chlorocinnamaldehyde **4o** (52 mg, 0.300 mmol) in the presence of DABCO (4 mg, 0.040 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (14 mg, 0.040 mmol) and using dry $CHCl_3$ (0.4 mL) as solvent.

Yield: 65%.

dr: >20:1.

ee: 98%. Determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 16.28 min, τ_{minor} = 18.19 min.

$[\alpha]_D^{20}$: -55.9 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.36 (d, *J* = 3.9 Hz, 1H, C-6C**H**O), 7.38-7.31 (m, 2H, C_{arom}-**H**), 7.20-7.14 (m, 2H, C_{arom}-**H**), 5.22 (d, *J* = 11.3 Hz, 1H, **H**-7a), 3.23 (app t, *J* = 11.7 Hz, 1H, **H**-7), 2.94-2.79 (m, 1H, **H**-6), 2.60 (dq, *J* = 12.7, 6.4 Hz, 1H, **H**-4), 2.07-1.91 (m, 1H, **H**-5), 1.42 (d, *J* = 6.4 Hz, 3H, C-4C**H**$_3$), 1.19 (d, *J* = 6.5 Hz, 3H, C-5C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 199.4 (C-6**C**HO), 185.9 (**C**-3a), 134.8, 133.6 (**C**$_{arom}$-C), 129.7, 129.1 (**C**$_{arom}$-H), 88.8 (**C**-7a), 57.8 (**C**-6), 50.8 (**C**-7), 41.7 (**C**-4), 40.3 (**C**-5), 17.6 (C-5**C**H_3), 12.9 (C-4**C**H_3).

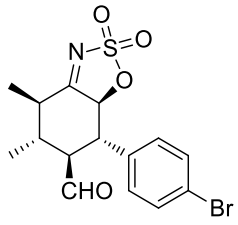
IR (ATR) cm^{-1}**:** 1728 (C=O st), 1626 (C=N st), 1360 (SO_2 st as), 1202 (SO_2 st sym).

M.p. (hexanes/EtOAc) (ºC): 188-190 (Decomposed).

MS (EI) m/z (relative abundance): 258 (53), 207 (100), 180 (16), 147 (31), 119 (17), 79 (19), 50 (31).

HRMS: Calculated for $[C_{15}H_{17}NO_4SCl]^+$: 342.0567 $[M+H]^+$; found: 342.0553.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-7-(4-Bromophenyl)-4,5-dimethyl-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7g)



Following the general procedure, **7g** (39 mg, 0.100 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 6:4) as an orange solid after 60 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-4-bromocinnamaldehyde **4p** (49 mg, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 67%.

dr: >20:1.

ee: 96%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 29.41 min, τ_{minor} = 22.99 min.

$[\alpha]_D^{20}$: -62.3 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.35 (d, *J* = 3.8 Hz, 1H, C-6C**H**O), 7.50 (d, *J* = 8.5 Hz, 2H, C_{arom}-**H**), 7.11 (d, *J* = 8.5 Hz, 2H, C_{arom}-**H**), 5.23 (d, *J* = 11.3 Hz, 1H, **H**-7a), 3.21 (app t, *J* = 11.7 Hz, 1H, **H**-7), 2.93-2.81 (m, 1H, **H**-6), 2.60 (dq, *J* = 12.6, 6.4 Hz, 1H, **H**-4), 2.06-1.92 (m, 1H, **H**-5), 1.42 (d, *J* = 6.4 Hz, 3H, C-4C**H**$_3$), 1.19 (d, *J* = 6.5 Hz, 3H, C-5C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 199.4 (C-6**C**HO), 185.9 (**C**-3a), 134.1 (**C**$_{arom}$-C), 132.6, 129.5 (**C**$_{arom}$-H), 122.9 (**C**$_{arom}$-C), 88.7 (**C**-7a), 57.7 (**C**-6), 50.8 (**C**-7), 41.7 (**C**-4), 40.3 (**C**-5), 17.6 (C-5**C**H$_3$), 13.0 (C-4**C**H$_3$).

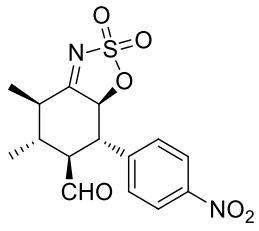
IR (ATR) cm^{-1}: 1726 (C=O st), 1630 (C=N st), 1369 (SO_2 st as), 1198 (SO_2 st sym).

M.p. (hexanes/EtOAc) (ºC): 110-112.

MS (EI) m/z (relative abundance): 305 (53), 281 (36), 207 (89), 180 (29), 147 (59), 119 (3), 84 (100), 51 (41).

HRMS: Calculated for $[C_{15}H_{17}NO_4SBr]^+$: 386.0062 $[M+H]^+$; found: 386.0072.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-4,5-Dimethyl-7-(4-nitrophenyl)-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7h)



Following the general procedure, **7h** (39 mg, 0.110 mmol) was isolated by FC (hexanes/EtOAc gradient from 6:4 to 1:1) as a yellow oil after 60 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-4-nitrocinnamaldehyde **4r** (41 mg, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent. After full conversion, the reaction was stirred at room temperature during four hours to achieve only one diastereoisomer.

Yield: 73%.

dr: >20:1.

ee: 96%. Determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 41.51 min, τ_{minor} = 49.45 min.

$[\alpha]_D^{20}$: -54.8 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.42 (d, *J* = 3.7 Hz, 1H, C-6C**H**O), 8.22 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 7.44 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 5.28 (d, *J* = 11.3 Hz, 1H, **H**-7a), 3.40 (app t, *J* = 11.7 Hz, 1H, **H**-7), 3.02-2.93 (m, 1H, **H**-6), 2.67 (dq, *J* = 12.7, 6.4 Hz, 1H, **H**-4), 2.10-1.97 (m, 1H, **H**-5), 1.45 (d, *J* = 6.4 Hz, 3H, C-4C**H**$_3$), 1.24 (d, *J* = 6.5 Hz, 3H, C-5C**H**$_3$).

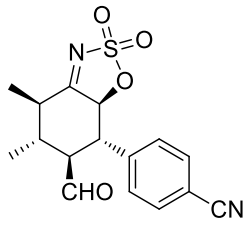
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 198.9 (C-6**C**HO), 185.5 (**C**-3a), 148.0, 142.4 (**C**$_{arom}$-C), 129.0, 124.6 (**C**$_{arom}$-H), 88.1 (**C**-7a), 57.5 (**C**-6), 50.8 (**C**-7), 41.8 (**C**-4), 40.6 (**C**-5), 17.6 (C-5**C**H_3), 12.9 (C-4**C**H_3).

IR (ATR) cm^{-1}: 1726 (C=O st), 1629 (C=N st), 1521 (NO_2 st as), 1372 (SO_2 st as), 1347 (NO_2 st sym), 1199 (SO_2 st sym).

MS (EI) m/z (relative abundance): 281 (34), 245 (40), 207 (100), 170 (41), 142 (69), 115 (57), 91 (25), 64 (33).

HRMS: Calculated for $[C_{15}H_{17}N_2O_6S]^+$: 353.0807 $[M+H]^+$; found: 353.0815.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-7-(4-Cyanophenyl)-4,5-dimethyl-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7i)



Following the general procedure, **7i** (37 mg, 0.110 mmol) was isolated by FC (hexanes/EtOAc gradient from 6:4 to 1:1) as a yellow oil after 48 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-4-cyanocinnamaldehyde[10] **4s**

[10] Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2003**, *5*, 777.

(35 mg, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 73%.

dr: >20:1.

ee: 98%. Determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 35.29 min, τ_{minor} = 44.40 min.

$[\alpha]_D^{20}$: -59.9 (*c* = 0.83, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.39 (d, *J* = 3.7 Hz, 1H, C-6C**H**O), 7.67 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 7.37 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 5.24 (d, *J* = 11.3 Hz, 1H, **H**-7a), 3.32 (app t, *J* = 11.7 Hz, 1H, **H**-7), 2.98-2.86 (m, 1H, **H**-6), 2.64 (dq, *J* = 12.6, 6.4 Hz, 1H, **H**-4), 2.08-1.95 (m, 1H, **H**-5), 1.44 (d, *J* = 6.4 Hz, 3H, C-4C**H**$_3$), 1.23 (d, *J* = 6.5 Hz, 3H, C-5C**H**$_3$).

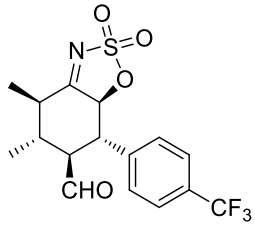
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 198.9 (C-6**C**HO), 185.5 (**C**-3a), 140.5 (**C**$_{arom}$-C), 133.1, 128.8 (**C**$_{arom}$-H), 118.0 (C_{arom}-**C**N), 112.9 (**C**$_{arom}$-C), 88.2 (**C**-7a), 57.4 (**C**-6), 51.1 (**C**-7), 41.7 (**C**-4), 40.5 (**C**-5), 17.6 (C-5**C**H$_3$), 12.9 (C-4**C**H$_3$).

IR (ATR) cm^{-1}: 2229 (C≡N st), 1725 (C=O st), 1627 (C=N st), 1372 (SO_2 st as), 1198 (SO_2 st sym).

MS (EI) m/z (relative abundance): 281 (10), 253 (31), 225 (32), 197 (62), 180 (14), 154 (100), 116 (31), 77 (19), 51 (15).

HRMS: Calculated for $[C_{16}H_{17}N_2O_4S]^+$: 333.0909 $[M+H]^+$; found: 333.0917.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-4,5-Dimethyl-7-(4-(trifluoromethyl)phenyl)-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7j)



Following the general procedure, **7j** (38 mg, 0.101 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 6:4) as a yellow oil after 60 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-4-(trifluoromethyl)cinnamaldehyde[9] **4t** (45 mg, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 67%.

dr: >20:1.

ee: 98%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 27.65 min, τ_{minor} = 22.09 min.

$[\alpha]_D^{20}$: -33.4 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.39 (d, *J* = 3.7 Hz, 1H, C-6C**H**O), 7.64 (d, *J* = 8.0 Hz, 2H, C_{arom}-**H**), 7.38 (d, *J* = 8.0 Hz, 2H, C_{arom}-**H**), 5.26 (d, *J* = 11.3 Hz, 1H, **H**-7a), 3.33 (app t, *J* = 11.7 Hz, 1H, **H**-7), 3.01-2.87 (m, 1H, **H**-6), 2.70-2.56 (m, 1H, **H**-4), 2.09-1.95 (m, 1H, **H**-5), 1.44 (d, *J* = 6.3 Hz, 3H, C-4C**H**$_3$), 1.22 (d, *J* = 6.4 Hz, 3H, C-5C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 199.1 (C-6**C**HO), 185.6 (**C**-3a), 139.2 (**C**$_{arom}$-C), 131.1 (q, $^2J_{CF}$ = 32.9 Hz, **C**$_{arom}$-CF_3), 128.4 (**C**$_{arom}$-H), 126.4 (q,

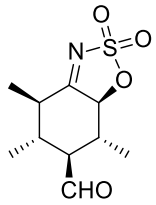
$^3J_{CF}$ = 3.5 Hz, **C**$_{arom}$-H), 123.7 (q, $^1J_{CF}$ = 272.1 Hz, **C**F_3), 88.5 (**C**-7a), 57.6 (**C**-6), 51.0 (**C**-7), 41.8 (**C**-4), 40.5 (**C**-5), 17.6 (C-5**C**H_3), 12.9 (C-4**C**H_3).

IR (ATR) cm^{-1}: 1727 (C=O st), 1622 (C=N st), 1369 (SO_2 st as), 1199 (SO_2 st sym).

MS (EI) m/z (relative abundance): 266 (14), 239 (11), 215 (36), 199 (38), 172 (18), 155 (32), 127 (10), 113 (52), 100 (50), 85 (14), 71 (100), 58 (23).

HRMS: Calculated for $[C_{16}H_{17}NO_4SF_3]^+$: 376.0830 $[M+H]^+$; found: 376.0829.

(4*R*,5*R*,6*S*,7*R*,7a*S*)-4,5,7-Trimethyl-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7k)



Following the general procedure, **7k** (13 mg, 0.054 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a yellow oil after 48 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-crotonaldehyde **4a** (19 μL, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 36%.

dr: >20:1.

ee: 91%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 18.02 min, τ_{minor} = 20.46 min.

$[\alpha]_D^{20}$: -19.5 (*c* = 0.67, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.48 (d, *J* = 4.1 Hz, 1H, C-6C**H**O), 4.82 (d, *J* = 10.8 Hz, 1H, **H**-7a), 2.45 (dq, *J* = 12.7, 6.4 Hz, 1H, **H**-4), 2.23-2.13 (m, 2H, **H**-6+**H**-7), 1.94-1.85 (m, 1H, **H**-5), 1.40 (d, *J* = 6.4 Hz, 3H, C-4C**H**$_3$), 1.19 (d, *J* = 6.0 Hz, 3H, C-7C**H**$_3$), 1.14 (d, *J* = 6.5 Hz, 3H, C-5C**H**$_3$).

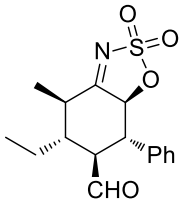
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 200.2 (C-6**C**HO), 186.4 (**C**-3a), 89.8 (**C**-7a), 59.3 (**C**-6), 41.5 (**C**-4), 40.1 (**C**-5), 39.7 (**C**-7), 17.7 (C-5**C**H_3), 16.9 (C-7**C**H_3), 13.0 (C-4**C**H_3).

IR (ATR) cm^{-1}: 1725 (C=O st), 1629 (C=N st), 1367 (SO_2 st as), 1196 (SO_2 st sym).

MS (EI) m/z (relative abundance): 217 (22), 202 (32), 188 (13), 175 (16), 152 (86), 136 (51), 124 (28), 110 (25), 96 (23), 69 (100), 55 (68).

HRMS: Calculated for $[C_{10}H_{16}NO_4S]^+$: 246.0800 $[M+H]^+$; found: 246.0789.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-5-Ethyl-4-methyl-7-phenyl-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7l)



Following the general procedure, **7l** (28 mg, 0.086 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a yellow solid after 60 hours, starting from (*E*)-4-(1-methylbut-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3d** (28 mg, 0.150 mmol) and (*E*)-cinnamaldehyde **4i** (28 μL, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 57%.

dr: >20:1.

ee: 96%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 51.80 min, τ_{minor} = 60.44 min.

$[\alpha]_D^{20}$: -64.1 (*c* = 0.44, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.34 (d, *J* = 4.1 Hz, 1H, C-6C**H**O), 7.40-7.21 (m, 5H, C_{arom}-**H**), 5.23 (d, *J* = 11.1 Hz, 1H, **H**-7a), 3.25 (app t, *J* = 11.5 Hz, 1H, **H**-7), 3.12-3.03 (m, 1H, **H**-6), 2.81 (dq, *J* = 12.5, 6.4 Hz, 1H, **H**-4), 2.14-2.05 (m, 1H, **H**-5), 1.82-1.71 (m, 1H, C-5C**H**$_a$H$_b$), 1.61-1.51 (m, 1H, C-5CH$_a$**H**$_b$), 1.40 (d, *J* = 6.4 Hz, 3H, C-4C**H**$_3$), 0.97 (t, *J* = 7.5 Hz, 3H, C-5CH$_2$C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 199.3 (C-6**C**HO), 186.8 (**C**-3a), 135.1 (**C**$_{arom}$-C), 129.5, 128.9, 127.8 (**C**$_{arom}$-H), 88.9 (**C**-7a), 53.9 (**C**-6), 51.7 (**C**-7), 44.9 (**C**-5), 37.8 (**C**-4), 21.4 (C-5**C**H$_2$), 12.6 (C-4**C**H$_3$), 7.2 (C-5CH$_2$**C**H$_3$).

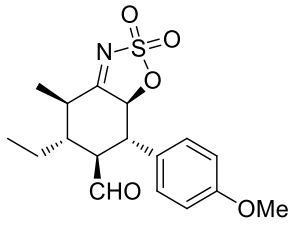
IR (ATR) cm^{-1}: 1726 (C=O st), 1626 (C=N st), 1368 (SO_2 st as), 1196 (SO_2 st sym).

M.p. (hexanes/EtOAc) (ºC): 167-169.

MS (EI) m/z (relative abundance): 238 (24), 207 (28), 147 (19), 129 (10), 112 (23), 83 (20), 57 (38).

HRMS: Calculated for $[C_{16}H_{20}NO_4S]^+$: 322.1113 $[M+H]^+$; found: 322.1123.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-5-Ethyl-7-(4-methoxyphenyl)-4-methyl-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7m)



Following the general procedure, **7m** (35 mg, 0.099 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 6:4) as a yellow solid after 60 hours, starting from (*E*)-4-(1-methylbut-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3d** (28 mg, 0.150 mmol) and (*E*)-4-methoxycinnamaldehyde **4l** (37 mg, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 66%.

dr: 10:1.

ee: 99%. Determined by HPLC using a Chiralcel OZ-3 column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 30.50 min, τ_{minor} = 23.85 min.

$[\alpha]_D^{20}$: -68.6 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.32 (d, *J* = 4.1 Hz, 1H, C-6C**H**O), 7.14 (d, *J* = 8.6 Hz, 2H, C_{arom}-**H**), 6.88 (d, *J* = 8.6 Hz, 2H, C_{arom}-**H**), 5.19 (d, *J* = 11.1 Hz, 1H, **H**-7a), 3.78 (s, 3H, OC**H**$_3$), 3.20 (app t, *J* = 11.5 Hz, 1H, **H**-7), 3.08-2.99 (m, 1H, **H**-6), 2.84-2.74 (m, 1H, **H**-4), 2.10-2.00 (m, 1H, **H**-5), 1.80-1.70 (m, 1H, C-5C**H**$_a$H$_b$), 1.58-1.48 (m, 1H, C-5CH$_a$**H**$_b$), 1.38 (d, *J* = 6.3 Hz, 3H, C-4C**H**$_3$), 0.95 (t, *J* = 7.5 Hz, 3H, C-5CH$_2$C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 199.6 (C-6**C**HO), 187.0 (**C**-3a), 159.8 (**C**$_{arom}$-C), 128.9 (**C**$_{arom}$-H), 127.0 (**C**$_{arom}$-C), 114.8 (**C**$_{arom}$-H), 89.2 (**C**-7a),

55.3 (O**C**H_3), 54.1 (**C**-6), 51.0 (**C**-7), 44.7 (**C**-5), 37.8 (**C**-4), 21.4 (C-5**C**H_2), 12.6 (C-4**C**H_3), 7.2 (C-5CH_2**C**H_3).

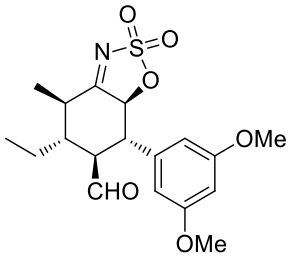
IR (ATR) cm^{-1}: 1726 (C=O st), 1626 (C=N st), 1370 (SO_2 st as), 1197 (SO_2 st sym).

M.p. (hexanes/EtOAc) (ºC): 68-70.

MS (EI) m/z (relative abundance): 244 (12), 215 (100), 187 (12), 175 (26), 134 (28), 121 (25), 91 (13), 77 (8).

HRMS: Calculated for $[C_{17}H_{22}NO_5S]^+$: 352.1219 $[M+H]^+$; found: 352.1236.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-7-(3,5-Dimethoxyphenyl)-5-ethyl-4-methyl-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7n)



Following the general procedure, **7n** (35 mg, 0.092 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 6:4) as a yellow oil after 60 hours, starting from (*E*)-4-(1-methylbut-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3d** (28 mg, 0.150 mmol) and (*E*)-3,5-dimethoxycinnamaldehyde **4n** (43 mg, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 61%.

dr: 8:1.

ee: 99%. Determined by HPLC using a Chiralcel OZ-3 column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 17.84 min, τ_{minor} = 32.09 min.

$[\alpha]_D^{20}$: -34.4 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.37 (d, *J* = 3.8 Hz, 1H, C-6C**H**O), 6.40-6.34 (m, 3H, C_{arom}-**H**), 5.26 (d, *J* = 11.0 Hz, 1H, **H**-7a), 3.77 (s, 6H, 2 × OC**H**$_3$), 3.20-3.07 (m, 1H, **H**-7), 3.07-2.97 (m, 1H, **H**-6), 2.85-2.75 (m, 1H, **H**-4), 2.08-1.99 (m, 1H, **H**-5), 1.76-1.68 (m, 1H, C-5C**H**$_a$H$_b$), 1.59-1.49 (m, 1H, C-5CH$_a$**H**$_b$), 1.38 (d, *J* = 6.3 Hz, 3H, C-4C**H**$_3$), 0.95 (t, *J* = 7.5 Hz, 3H, C-5CH$_2$C**H**$_3$).

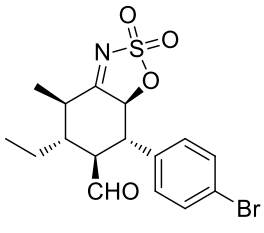
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 199.4 (C-6**C**HO), 187.0 (**C**-3a), 161.5, 137.5 (**C**$_{arom}$-C), 106.0, 100.0 (**C**$_{arom}$-H), 88.8 (**C**-7a), 55.4 (O**C**H$_3$), 53.8 (**C**-6), 51.9 (**C**-7), 44.9 (**C**-5), 37.8 (**C**-4), 21.3 (C-5**C**H$_2$), 12.6 (C-4**C**H$_3$), 7.2 (C-5CH$_2$**C**H$_3$).

IR (ATR) cm^{-1}**:** 1725 (C=O st), 1627 (C=N st), 1368 (SO_2 st as), 1196 (SO_2 st sym).

MS (EI) m/z (relative abundance): 348 (8), 263 (29), 231 (12), 189 (27), 164 (100), 113 (33), 91 (9), 77 (6).

HRMS: Calculated for $[C_{18}H_{24}NO_6S]^+$: 382.1324 $[M+H]^+$; found: 382.1323.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-7-(4-Bromophenyl)-5-ethyl-4-methyl-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7o)



Following the general procedure, **7o** (37 mg, 0.093 mmol) was isolated as a mixture of diastereoisomers by FC (hexanes/EtOAc gradient from 7:3 to 6:4) as a yellow oil after 60 hours, starting from (*E*)-4-(1-methylbut-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3d** (28 mg, 0.150

mmol) and (*E*)-4-bromocinnamaldehyde **4p** (49 mg, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 62%.

dr: 8:1.

ee: 97%. Determined by HPLC using a Chiralcel OZ-3 column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 21.40 min, τ_{minor} = 14.66 min.

$[\alpha]_D^{20}$: -53.5 (*c* = 1.07, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (*denotes minor diastereoisomer signals): 9.34 (d, *J* = 4.1 Hz, 1H, C-6C**H**O), 7.49 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 7.11 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 5.37* (d, *J* = 11.1 Hz, 1H, **H**-7a), 5.18 (d, *J* = 11.2 Hz, 1H, **H**-7a), 3.49-3.36* (m, 1H, **H**-7), 3.23 (app t, *J* = 11.5 Hz, 1H, **H**-7), 3.10-2.98 (m, 1H, **H**-6), 2.81 (dq, *J* = 12.5, 6.3 Hz, 1H, **H**-4), 2.26-2.16* (m, 1H, **H**-5), 2.13-2.01 (m, 1H, **H**-5), 1.84-1.70 (m, 1H, C-5C**H**$_a$H$_b$), 1.58-1.48 (m, 1H, C-5CH$_a$**H**$_b$), 1.38 (d, *J* = 6.3 Hz, 3H, C-4C**H**$_3$), 1.31* (d, *J* = 7.3 Hz, 3H, C-4C**H**$_3$), 1.12* (t, *J* = 7.4 Hz, 3H, C-5CH$_2$C**H**$_3$), 0.96 (t, *J* = 7.5 Hz, 3H, C-5CH$_2$C**H**$_3$).

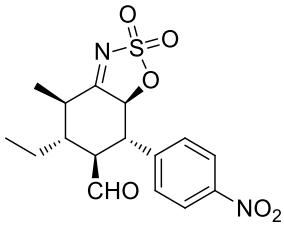
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor diastereoisomer signals): 199.6*, 199.1 (C-6**C**HO), 195.6*, 186.8 (**C**-3a), 134.3*, 134.2 (**C**$_{arom}$-C), 132.6, 132.3*, 130.5*, 129.5 (**C**$_{arom}$-H), 122.9, 122.3* (**C**$_{arom}$-C), 88.7, 86.6* (**C**-7a), 53.7, 52.8* (**C**-6), 51.0, 48.4* (**C**-7), 45.3*, 44.9 (**C**-5), 37.8, 35.4* (**C**-4), 23.1*, 21.4 (C-5**C**H$_2$), 12.6, 11.2* (C-4**C**H$_3$), 10.9*, 7.2 (C-5CH$_2$**C**H$_3$).

IR (ATR) cm^{-1}: 1724 (C=O st), 1626 (C=N st), 1371 (SO_2 st as), 1198 (SO_2 st sym).

MS (EI) m/z (relative abundance): 293 (57), 265 (54), 251 (14), 186 (29), 171 (56), 157 (100), 143 (32), 129 (71), 115 (57), 102 (31), 77 (22), 63 (16).

HRMS: Calculated for $[C_{16}H_{19}NO_4SBr]^+$: 400.0218 $[M+H]^+$; found: 400.0234.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-5-Ethyl-4-methyl-7-(4-nitrophenyl)-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7p)



Following the general procedure, **7p** (27 mg, 0.075 mmol) was isolated as a mixture of diastereoisomers by FC (hexanes/EtOAc gradient from 6:4 to 1:1) as a yellow solid after 60 hours, starting from (*E*)-4-(1-methylbut-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3d** (28 mg, 0.150 mmol) and (*E*)-4-nitrocinnamaldehyde **4r** (41 mg, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 50%.

dr: 13:1.

ee: 94%. Determined by HPLC using a Chiralpak OZ-3 column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 61.50 min, τ_{minor} = 41.73 min.

$[\alpha]_D^{20}$: -59.4 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (*denotes minor diastereoisomer signals): 9.43* (d, *J* = 3.8 Hz, 1H, C-6C**H**O), 9.40 (d, *J* = 3.9 Hz, 1H, C-6C**H**O), 8.22 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 7.44 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 5.43* (d, *J* =

11.2 Hz, 1H, **H**-7a), 5.25 (d, *J* = 11.2 Hz, 1H, **H**-7a), 3.41 (app t, *J* = 11.5 Hz, 1H, **H**-7), 3.20-3.11 (m, 1H, **H**-6), 2.87 (dq, *J* = 12.5, 6.3 Hz, 1H, **H**-4), 2.16-2.06 (m, 1H, **H**-5), 1.86-1.75 (m, 1H, C-5C**H**$_a$H$_b$), 1.63-1.51 (m, 1H, C-5CH$_a$**H**$_b$), 1.40 (d, *J* = 6.3 Hz, 3H, C-4C**H**$_3$), 1.00 (t, *J* = 7.5 Hz, 3H, C-5CH$_2$C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 198.7 (C-6**C**HO), 186.3 (**C**-3a), 148.0, 142.5 (**C**$_{arom}$-C), 129.1, 124.5 (**C**$_{arom}$-H), 88.1 (**C**-7a), 53.6 (**C**-6), 51.0 (**C**-7), 45.3 (**C**-5), 37.9 (**C**-4), 21.4 (C-5**C**H$_2$), 12.5 (C-4**C**H$_3$), 7.2 (C-5CH$_2$**C**H$_3$).

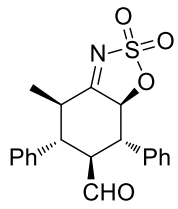
IR (ATR) cm^{-1}: 1725 (C=O st), 1627 (C=N st), 1520 (NO_2 st as), 1373 (SO_2 st as), 1348 (NO_2 st sym), 1199 (SO_2 st sym).

M.p. (hexanes/EtOAc) (ºC): 91-93.

MS (EI) m/z (relative abundance): 281 (9), 207 (29), 147 (21), 129 (100), 112 (25), 71 (24), 57 (42).

HRMS: Calculated for $[C_{16}H_{18}N_2O_6SNa]^+$: 389.0783 $[M+Na]^+$; found: 389.0787.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-4-Methyl-5,7-diphenyl-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7q)



Following the general procedure, **7q** (22 mg, 0.060 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) as a yellow solid after 84 hours, starting from (*E*)-4-(1-phenylprop-1-en-2-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3e** (48 mg, 0.200 mmol) and (*E*)-cinnamaldehyde **4i** (50 μL, 0.400 mmol) in the presence of DABCO (4 mg, 0.040 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (14 mg, 0.040 mmol) and using dry $CHCl_3$ (0.4 mL) as solvent.

Yield: 30%.

dr: >20:1.

ee: 99%. Determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 18.20 min, τ_{minor} = 21.02 min.

$[\alpha]_D^{20}$: -3.3 (*c* = 1.00, acetone).

^{1}H-NMR (δ, ppm) (CD_3COCD_3, 300 MHz): 9.25 (d, *J* = 3.9 Hz, 1H, C-6C**H**O), 7.49-7.29 (m, 10H, C_{arom}-**H**), 6.04 (d, *J* = 11.3 Hz, 1H, **H**-7a), 4.00-3.87 (m, 1H, **H**-6), 3.72-3.49 (m, 2H, **H**-4+**H**-7), 3.35 (app t, *J* = 11.5 Hz, 1H, **H**-5), 1.10 (d, *J* = 6.4 Hz, 3H, C-4C**H**$_3$).

^{13}C-NMR (δ, ppm) (CD_3COCD_3, 75.5 MHz): 200.5 (C-6**C**HO), 188.6 (**C**-3a), 139.8, 137.8 (**C**$_{arom}$-C), 130.0, 129.9, 129.2, 129.2, 129.1, 128.8 (**C**$_{arom}$-H), 90.7 (**C**-7a), 58.1 (**C**-6), 53.0 (**C**-5), 52.5 (**C**-7), 41.9 (**C**-4), 13.5 (C-4**C**H$_3$).

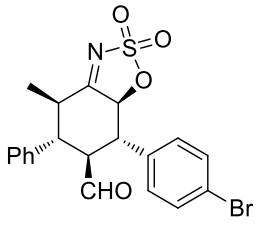
IR (ATR) cm^{-1}: 1713 (C=O st), 1626 (C=N st), 1370 (SO_2 st as), 1200 (SO_2 st sym).

M.p. (hexanes/EtOAc) (ºC): 189-191 (Decomposed).

MS (EI) m/z (relative abundance): 286 (100), 243 (22), 207 (82), 180 (31), 127 (11), 103 (5), 78 (14), 50 (36).

HRMS: Calculated for $[C_{20}H_{20}NO_4S]^+$: 370.1113 $[M+H]^+$; found: 370.1110.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-7-(4-Bromophenyl)-4-methyl-5-phenyl-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7r)



Following the general procedure, **7r** (23 mg, 0.052 mmol) was isolated by FC (hexanes/EtOAc gradient from 6:4 to 1:1) as a yellow solid after 60 hours, starting from (*E*)-4-(1-phenylprop-1-en-2-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3e** (48 mg, 0.200 mmol) and (*E*)-4-bromocinnamaldehyde **4p** (87 mg, 0.400 mmol) in the presence of DABCO (4 mg, 0.040 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (14 mg, 0.040 mmol) and using dry $CHCl_3$ (0.4 mL) as solvent.

Yield: 26%.

dr: >20:1.

ee: >99%. Determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 17.72 min, τ_{minor} = -.

$[\alpha]_D^{20}$: -13.4 (*c* = 1.00, acetone).

^{1}H-NMR (δ, ppm) (CD_3COCD_3, 300 MHz): 9.24 (d, *J* = 3.8 Hz, 1H, C-6C**H**O), 7.60-7.30 (m, 9H, C_{arom}-**H**), 6.02 (d, *J* = 11.2 Hz, 1H, **H**-7a), 4.02-3.91 (m, 1H, **H**-6), 3.70-3.53 (m, 2H, **H**-4+**H**-7), 3.33 (app t, *J* = 11.5 Hz, 1H, **H**-5), 1.09 (d, *J* = 6.4 Hz, 3H, C-4C**H**$_3$).

^{13}C-NMR (δ, ppm) (CD_3COCD_3, 75.5 MHz): 200.5 (C-6**C**HO), 188.3 (**C**-3a), 139.7, 137.4 (**C**$_{arom}$-C), 132.9, 131.3, 130.1, 130.1, 128.9 (**C**$_{arom}$-H), 122.6 (**C**$_{arom}$-C), 90.4 (**C**-7a), 57.8 (**C**-6), 53.0 (**C**-5), 51.8 (**C**-7), 41.9 (**C**-4), 13.4 (C-4**C**H_3).

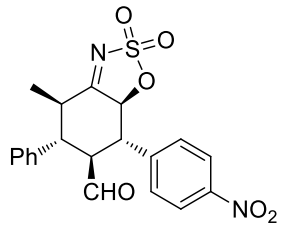
IR (ATR) cm^{-1}: 1710 (C=O st), 1626 (C=N st), 1367 (SO_2 st as), 1198 (SO_2 st sym).

M.p. (hexanes/EtOAc) (ºC): 184-186 (Decomposed).

MS (EI) m/z (relative abundance): 281 (37), 236 (5), 207 (100), 157 (39), 115 (42), 77 (24), 58 (37).

HRMS: Calculated for $[C_{20}H_{17}NO_4SBr]^-$: 446.0062 $[M-H]^-$; found: 446.0090.

(4*R*,5*R*,6*S*,7*S*,7a*S*)-4-Methyl-7-(4-nitrophenyl)-5-phenyl-5,6,7,7a-tetrahydro-4*H*-benzo[*d*][1,2,3]oxathiazole-6-carbaldehyde 2,2-dioxide (7s)



Following the general procedure, **7s** (29 mg, 0.070 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) as a yellow solid after 60 hours, starting from (*E*)-4-(1-phenylprop-1-en-2-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3e** (48 mg, 0.200 mmol) and (*E*)-4-nitrocinnamaldehyde **4r** (72 mg, 0.400 mmol) in the presence of DABCO (4 mg, 0.040 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (14 mg, 0.040 mmol) and using dry $CHCl_3$ (0.4 mL) as solvent.

Yield: 35%.

dr: >20:1.

ee: 98%. Determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 26.61 min, τ_{minor} = 62.43 min.

$[\alpha]_D^{20}$: -30.8 (*c* = 1.00, acetone).

^{1}H-NMR (δ, ppm) (CD_3COCD_3, 300 MHz): 9.26 (d, *J* = 3.5 Hz, 1H, C-6C**H**O), 8.26 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 7.80 (d, *J* = 8.8 Hz, 2H, C_{arom}-**H**), 7.55-7.32 (m, 5H, C_{arom}-**H**), 6.12 (d, *J* = 11.2 Hz, 1H, **H**-7a), 4.19-4.07 (m, 1H, **H**-6), 3.80 (app t, *J* = 11.5 Hz 1H, **H**-7), 3.75-3.63 (m, 1H, **H**-4), 3.38 (app t, *J* = 11.6 Hz, 1H, **H**-5), 1.12 (d, *J* = 6.4 Hz, 3H, C-4C**H**$_3$).

^{13}C-NMR (δ, ppm) (CD_3COCD_3, 75.5 MHz): 200.4 (C-6**C**HO), 188.1 (**C**-3a), 148.7, 145.4, 139.5 (**C**$_{arom}$-C), 130.6, 130.1, 129.1, 129.0, 124.8 (**C**$_{arom}$-H), 90.0 (**C**-7a), 57.5 (**C**-6), 53.0 (**C**-5), 51.8 (**C**-7), 42.0 (**C**-4), 13.3 (C-4**C**H$_3$).

IR (ATR) cm^{-1}: 1710 (C=O st), 1627 (C=N st), 1519 (NO_2 st as), 1370 (SO_2 st as), 1349 (NO_2 st sym), 1200 (SO_2 st sym).

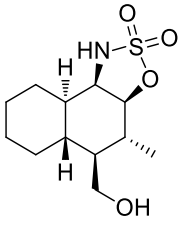
M.p. (hexanes/EtOAc) (ºC): 229-231 (Decomposed).

MS (EI) m/z (relative abundance): 281 (18), 207 (54), 154 (51), 115 (9), 77 (100), 50 (34).

HRMS: Calculated for $[C_{20}H_{17}N_2O_6S]^-$: 413.0807 $[M-H]^-$; found: 413.0835.

2.5. Synthesis of cyclic sulfamidate 9.

(3a*S*,4*R*,5*S*,5a*R*,9a*R*,9b*R*)-5-(Hydroxymethyl)-4-methyldecahydro-1*H*-naphtho[1,2-*d*][1,2,3]oxathiazole 2,2-dioxide (9)



$NaBH_4$ (5 mg, 0.119 mmol) was added to a solution of the cycloadduct **6a** (27 mg, 0.099 mmol) in MeOH (1 mL) at 0 ºC. The mixture was stirred at 0 ºC for 10 minutes, then a solution of saturated aqueous NH_4Cl (1 mL) was added to quench the reaction and it was stirred for another 5 minutes. The mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried

with anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. After purification by flash column chromatography (FC) (hexanes/EtOAc gradient from 6:4 to 1:1) the cyclic sulfamidate **9** (27 mg, 0.099 mmol) was isolated as a white solid.

Yield: >99%.

dr: >20:1.

ee: 92%. Determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 20.14 min, τ_{minor} = 22.86 min.

$[\alpha]_D^{20}$: -66.8 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 5.27 (d, *J* = 9.0 Hz, 1H, N**H**), 4.35 (dd, *J* = 10.4, 5.0 Hz, 1H, **H**-3a), 4.06-4.00 (m, 1H, **H**-9b), 3.88-3.72 (m, 2H, C**H**$_2$OH), 2.28-2.07 (m, 3H, O**H**+**H**-4+**H**-6$_a$), 1.83-1.72 (m, 3H, **H**-7$_a$+**H**-8$_a$+**H**-9$_a$), 1.59-1.41 (m, 2H, **H**-9a+**H**-5a), 1.32-1.20 (m, 3H, **H**-7$_b$+**H**-8$_b$+**H**-9$_b$), 1.12 (d, *J* = 6.4 Hz, 3H, C-4C**H**$_3$), 0.87-0.73 (m, 2H, **H**-5+**H**-6$_b$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 91.8 (**C**-3a), 60.2 (**C**-9b), 57.7 (**C**H$_2$OH), 47.1 (**C**-5), 41.9 (**C**-9a), 34.0 (**C**-5a), 32.9 (**C**-4), 30.4 (**C**-9), 29.8 (**C**-6), 26.1, 25.8 (**C**-7+**C**-8), 15.2 (C-4**C**H$_3$).

IR (ATR) cm^{-1}: 3547 (O-H st), 3261 (N-H st), 1342 (SO_2 st as), 1184 (SO_2 st sym).

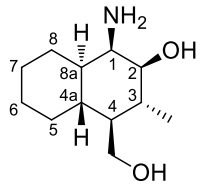
M.p. (hexanes/EtOAc) (ºC): 155-157.

MS (EI) m/z (relative abundance): 245 (24), 190 (14), 163 (20), 148 (100), 133 (14), 119 (19), 105 (40), 91 (27), 70 (36), 55 (22).

HRMS: Calculated for $[C_{12}H_{22}NO_4S]^+$: 276.1270 $[M+H]^+$; found: 276.1272.

2.6. Synthesis of β-amino alcohol 10.

(1*R*,2*S*,3*R*,4*S*,4a*R*,8a*R*)-1-Amino-4-(hydroxymethyl)-3-methyldecahydronaphthalen-2-ol (10)



To a suspension of $LiAlH_4$ (52 mg, 1.380 mmol) in dry THF (5 mL) a solution of the sulfamidate **9** (127 mg, 0.460 mmol) in dry THF (10 mL) was added dropwise at 0 ºC under inert atmosphere. The reaction mixture was stirred under reflux for 1 hour, and HCl 1 M (1 mL) was added at room temperature. Then, the reaction was stirred under reflux for 1 hour more and cooled down to room temperature. The mixture was washed with CH_2Cl_2 (3 × 10 mL). The aqueous layer was basified with NaOH 1 M and then was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure, obtaining the β-amino alcohol **10** (55 mg, 0.258 mmol) as a white solid, without further purification.

Yield: 56%.

$[\alpha]_D^{20}$: -37.1 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 3.83-3.71 (m, 2H, C**H**$_2$OH), 3.12 (dd, *J* = 10.6, 4.1 Hz, 1H, **H**-2), 2.86-2.80 (m, 1H, **H**-1), 2.36 (bs, 3H, N**H**$_2$+O**H**), 2.12-1.99 (m, 1H, **H**-5$_a$), 1.83-1.68 (m, 2H, **H**-6$_a$+**H**-7$_a$), 1.66-1.46 (m, 2H, **H**-3+**H**-8$_a$), 1.40-1.14 (m, 6H, **H**-4a+**H**-8a+**H**-8$_b$+**H**-6$_b$+**H**-7$_b$+O**H**), 1.07 (d, *J* = 6.3 Hz, 3H, C-3C**H**$_3$), 0.86-0.66 (m, 2H, **H**-5$_b$+**H**-4).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 76.1 (**C**-2), 58.6 (**C**H$_2$OH), 56.0 (**C**-1), 49.4 (**C**-4), 44.8 (**C**-8a), 33.3 (**C**-4a), 33.3 (**C**-3), 30.6 (**C**-5), 30.3 (**C**-8), 26.3, 26.2 (**C**-6+**C**-7), 15.5 (C-3**C**H$_3$).

IR (ATR) cm^{-1}: 3356 (O-H st).

M.p. (CH_2Cl_2) (ºC): 102-104.

MS (EI) m/z (relative abundance): 207 (94), 129 (100), 84 (23), 57 (52).

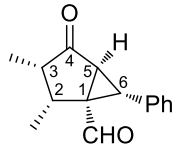
HRMS: Calculated for $[C_{12}H_{24}NO_2]^+$: 214.1807 $[M+H]^+$; found: 214.1810.

2.7. Synthesis of bicyclic compounds 11a-i.

General procedure:

To a solution of the corresponding Michael/Michael cycloadduct **7** (1.00 mmol) in DCE (2 mL), benzhydrylamine was added (1.00 mmol). The reaction was stirred at 75 ºC until it was completed. A solution of HCl 1 M (5.00 mmol) was added at 75 ºC, and the reaction was stirred during 20 minutes. Then, the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude product was charged onto silica gel and subjected to flash chromatography (FC) with the indicated eluent, obtaining the desired bicycles **11a-i**. The racemic compounds for HPLC separation conditions were prepared under the same reaction conditions, using in these cases the racemic Michael/Michael cycloadduct **(±)-7**.

(1*S*,2*R*,3*S*,5*S*,6*R*)-2,3-Dimethyl-4-oxo-6-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (*cis*-11a)



Following the general procedure, ***cis*-11a** (24 mg, 0.105 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 17 hours, starting from cycloadduct **7a** (46 mg,

0.150 mmol) and benzhydrylamine (28 mg, 0.150 mmol) using DCE (0.3 mL) as solvent.

Yield: 70%.

dr: 6.3:1.

ee: 99%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 14.73 min, τ_{minor} = 21.14 min.

$[\alpha]_D^{20}$: +76.7 (*c* = 0.56, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.04 (s, 1H, C**H**O), 7.35-7.23 (m, 5H, C_{arom}-**H**), 3.38 (d, *J* = 4.2 Hz, 1H, **H**-6), 3.13 (d, *J* = 4.2 Hz, 1H, **H**-5), 3.10-2.97 (m, 1H, **H**-2), 2.74-2.60 (m, 1H, **H**-3), 1.09 (d, *J* = 7.0 Hz, 3H, C-2C**H**$_3$), 1.01 (d, *J* = 7.0 Hz, 3H, C-3C**H**$_3$).

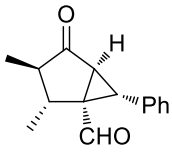
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 210.3 (**C**-4), 197.9 (**C**HO), 132.6 (**C**$_{arom}$-C), 128.8, 128.8, 127.8 (**C**$_{arom}$-H), 49.3 (**C**-1), 41.1 (**C**-3), 37.8 (**C**-6), 36.5 (**C**-5), 34.6 (**C**-2), 13.2 (C-2**C**H_3), 8.5 (C-3**C**H_3).

IR (ATR) cm^{-1}: 1731 (C=O st), 1703 (C=O st).

MS (EI) m/z (relative abundance): 228 (16), 213 (1), 200 (11), 185 (16), 171 (31), 157 (27), 143 (100), 129 (94), 115 (56), 103 (9), 91 (33), 77 (24), 65 (12), 51 (12).

HRMS: Calculated for $[C_{15}H_{17}O_2]^+$: 229.1229 $[M+H]^+$; found: 229.1231.

(1*S*,2*R*,3*R*,5*S*,6*R*)-2,3-Dimethyl-4-oxo-6-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (*trans*-11a)



Following the general procedure, ***trans*-11a** (3 mg, 0.015 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 17 hours, starting from cycloadduct **7a** (46 mg, 0.150 mmol) and benzhydrylamine (28 mg, 0.150 mmol) using DCE (0.3 mL) as solvent.

Yield: 10%.

dr: 1:6.3.

$[\alpha]_D^{20}$: +113.9 (*c* = 0.27, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.23 (s, 1H, C**H**O), 7.35-7.20 (m, 5H, C_{arom}-**H**), 3.24 (d, *J* = 4.9 Hz, 1H, **H**-5), 2.92 (d, *J* = 4.9 Hz, 1H, **H**-6), 2.58-2.46 (m, 1H, **H**-2), 2.15-2.02 (m, 1H, **H**-3), 1.46 (d, *J* = 7.0 Hz, 3H, C-2C**H**$_3$), 1.26 (d, *J* = 7.7 Hz, 3H, C-3C**H**$_3$).

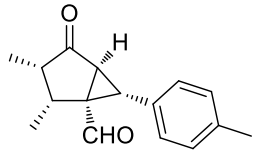
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 211.7 (**C**-4), 197.0 (**C**HO), 132.1 (**C**$_{arom}$-C), 128.8, 128.7, 127.8 (**C**$_{arom}$-H), 53.6 (**C**-3), 49.0 (**C**-1), 41.2 (**C**-2), 40.2 (**C**-5), 39.2 (**C**-6), 19.7 (C-2**C**H_3), 17.5 (C-3**C**H_3).

IR (ATR) cm^{-1}: 1730 (C=O st), 1705 (C=O st).

MS (EI) m/z (relative abundance): 228 (20), 213 (2), 200 (12), 185 (18), 171 (34), 157 (27), 143 (100), 129 (97), 115 (64), 103 (10), 91 (41), 77 (28), 65 (15), 51 (15).

HRMS: Calculated for $[C_{15}H_{17}O_2]^+$: 229.1229 $[M+H]^+$; found: 229.1230.

(1*S*,2*R*,3*S*,5*S*,6*R*)-2,3-Dimethyl-4-oxo-6-(*p*-tolyl)bicyclo[3.1.0]hexane-1-carbaldehyde (11b)



Following the general procedure, **11b** (15 mg, 0.064 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 17 hours, starting from cycloadduct **7b** (27 mg, 0.083 mmol) and benzhydrylamine (16 mg, 0.083 mmol) using DCE (0.16 mL) as solvent.

Yield: 77%.

dr: 6.7:1.

$[\alpha]_D^{20}$: +76.7 (*c* = 0.44, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.03 (s, 1H, C**H**O), 7.15-7.08 (m, 4H, C_{arom}-**H**), 3.34 (d, *J* = 4.2 Hz, 1H, **H**-6), 3.10 (d, *J* = 4.2 Hz, 1H, **H**-5), 3.08-2.96 (m, 1H, **H**-2), 2.71-2.59 (m, 1H, **H**-3), 2.31 (s, 3H, C_{arom}-C**H**$_3$), 1.08 (d, *J* = 7.0 Hz, 3H, C-2C**H**$_3$), 1.00 (d, *J* = 7.0 Hz, 3H, C-3C**H**$_3$).

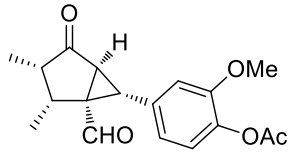
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 210.4 (**C**-4), 198.1 (**C**HO), 137.6 (**C**$_{arom}$-C), 129.5 (**C**$_{arom}$-H), 129.4 (**C**$_{arom}$-C), 128.7 (**C**$_{arom}$-H), 49.3 (**C**-1), 41.1 (**C**-3), 37.6 (**C**-6), 36.7 (**C**-5), 34.6 (**C**-2), 21.0 (C_{arom}-**C**H$_3$), 13.2 (C-2**C**H$_3$), 8.5 (C-3**C**H$_3$).

IR (ATR) cm^{-1}**:** 1731 (C=O st), 1703 (C=O st).

MS (EI) m/z (relative abundance): 242 (23), 227 (4), 213 (9), 199 (14), 186 (25), 171 (51), 157 (100), 143 (78), 128 (49), 115 (41), 105 (31), 91 (22), 77 (23), 65 (13), 51 (10).

HRMS: Calculated for $[C_{16}H_{19}O_2]^+$: 243.1385 $[M+H]^+$; found: 243.1381.

(1*S*,2*R*,3*S*,5*S*,6*R*)-6-(4-Acetoxy-3-methoxyphenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (11c)



Following the general procedure, **11c** (10 mg, 0.033 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 6:4) as a yellow oil after 17 hours, starting from cycloadduct **7d** (18 mg, 0.047 mmol) and benzhydrylamine (9 mg, 0.047 mmol) using DCE (0.1 mL) as solvent.

Yield: 71%.

dr: 6.7:1.

$[\alpha]_D^{20}$: +48.1 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.05 (s, 1H, C**H**O), 6.99-6.94 (m, 1H, C_{arom}-**H**), 6.85-6.80 (m, 2H, C_{arom}-**H**), 3.81 (s, 3H, OC**H**$_3$), 3.35 (d, *J* = 4.1 Hz, 1H, **H**-6), 3.10-2.97 (m, 2H, **H**-5+**H**-2), 2.71-2.56 (m, 1H, **H**-3), 2.29 (s, 3H, OCOC**H**$_3$), 1.09 (d, *J* = 7.0 Hz, 3H, C-2C**H**$_3$), 1.00 (d, *J* = 7.0 Hz, 3H, C-3C**H**$_3$).

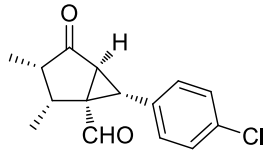
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 210.1 (**C**-4), 197.7 (**C**HO), 168.8 (O**C**OCH$_3$), 151.3, 139.3, 131.4 ($\mathbf{C}_{arom}$-C), 123.1, 121.0, 113.0 ($\mathbf{C}_{arom}$-H), 56.0 (O**C**H$_3$), 49.2 (**C**-1), 41.1 (**C**-3), 37.4 (**C**-6), 36.8 (**C**-5), 34.5 (**C**-2), 20.6 (OCO**C**H$_3$), 13.2 (C-2**C**H$_3$), 8.5 (C-3**C**H$_3$).

IR (ATR) cm^{-1}**:** 1764 (OC=O st), 1731 (C=O st), 1703 (C=O st).

MS (EI) m/z (relative abundance): 316 (5), 274 (100), 257 (4), 245 (18), 231 (9), 218 (40), 203 (40), 189 (57), 175 (41), 157 (22), 137 (29), 115 (27), 103 (9), 91 (19), 77 (23), 55 (14).

HRMS: Calculated for $[C_{18}H_{21}O_5]^+$: 317.1389 $[M+H]^+$; found: 317.1397.

(1*S*,2*R*,3*S*,5*S*,6*R*)-6-(4-Chlorophenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (11d)



Following the general procedure, **11d** (20 mg, 0.077 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 17 hours, starting from cycloadduct **7f** (36 mg, 0.108 mmol) and benzhydrylamine (20 mg, 0.108 mmol) using DCE (0.22 mL) as solvent.

Yield: 71%.

dr: 6.1:1.

$[\alpha]_D^{20}$: +75.4 (*c* = 0.66, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.12 (s, 1H, C**H**O), 7.29 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 7.17 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 3.31 (d, *J* = 4.2 Hz, 1H, **H**-6), 3.12-2.99 (m, 2H, **H**-5+**H**-2), 2.71-2.59 (m, 1H, **H**-3), 1.09 (d, *J* = 7.0 Hz, 3H, C-2C**H**$_3$), 1.01 (d, *J* = 7.0 Hz, 3H, C-3C**H**$_3$).

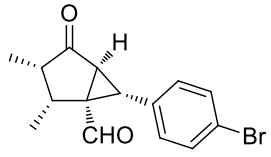
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 210.0 (**C**-4), 197.3 (**C**HO), 133.8, 131.1 ($\mathbf{C}_{arom}$-C), 130.2, 129.0 ($\mathbf{C}_{arom}$-H), 49.4 (**C**-1), 41.1 (**C**-3), 37.2 (**C**-6), 36.5 (**C**-5), 34.6 (**C**-2), 13.4 (C-2**C**H_3), 8.5 (C-3**C**H_3).

IR (ATR) cm^{-1}: 1731 (C=O st), 1700 (C=O st).

MS (EI) m/z (relative abundance): 262 (29), 245 (1), 234 (11), 219 (19), 206 (51), 191 (21), 177 (65), 163 (22), 153 (21), 143 (100), 128 (61), 115 (59), 101 (20), 89 (23), 77 (20), 63 (20), 51 (16).

HRMS: Calculated for $[C_{15}H_{14}O_2Cl]^-$: 261.0682 $[M-H]^-$; found: 261.0679.

(1*S*,2*R*,3*S*,5*S*,6*R*)-6-(4-Bromophenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (11e)



Following the general procedure, **11e** (17 mg, 0.055 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a yellow solid after 17 hours, starting from cycloadduct **7g** (29 mg, 0.076 mmol) and benzhydrylamine (14 mg, 0.076 mmol) using DCE (0.16 mL) as solvent.

Yield: 72%.

dr: 5.9:1.

$[\alpha]_D^{20}$: +68.0 (*c* = 0.49, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.13 (s, 1H, C**H**O), 7.44 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 7.11 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 3.28 (d, *J* = 4.1 Hz, 1H, **H**-6), 3.13-2.99 (m, 2H, **H**-5+**H**-2), 2.73-2.59 (m, 1H, **H**-3), 1.09 (d, *J* = 7.0 Hz, 3H, C-2C**H**$_3$), 1.01 (d, *J* = 7.0 Hz, 3H, C-3C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 209.9 (**C**-4), 197.2 (**C**HO), 131.9 (**C**$_{arom}$-H), 131.6 (**C**$_{arom}$-C), 130.5 (**C**$_{arom}$-H), 121.8 (**C**$_{arom}$-C), 49.4 (**C**-1), 41.1 (**C**-3), 37.2 (**C**-6), 36.4 (**C**-5), 34.6 (**C**-2), 13.4 (C-2**C**H$_3$), 8.5 (C-3**C**H$_3$).

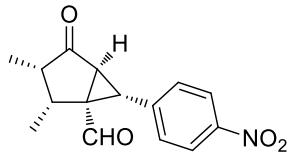
IR (ATR) cm^{-1}: 1732 (C=O st), 1704 (C=O st).

M.p. (hexanes/EtOAc) (ºC): 102-104.

MS (EI) m/z (relative abundance): 306 (14), 280 (5), 263 (8), 250 (27), 235 (8), 223 (8), 209 (3), 195 (8), 183 (6), 171 (47), 155 (20), 142 (100), 128 (69), 115 (51), 102 (21), 81 (19), 63 (17), 51 (13).

HRMS: Calculated for $[C_{15}H_{14}O_2Br]^-$: 305.0177 $[M-H]^-$; found: 305.0171.

(1*S*,2*R*,3*S*,5*S*,6*R*)-2,3-Dimethyl-6-(4-nitrophenyl)-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (11f)



Following the general procedure, **11f** (14 mg, 0.051 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 6:4) as a yellow oil after 36 hours, starting from cycloadduct **7h** (35 mg, 0.100 mmol) and benzhydrylamine (19 mg, 0.100 mmol) using DCE (0.2 mL) as solvent.

Yield: 51%.

dr: 6.3:1.

$[\alpha]_D^{20}$: +55.4 (*c* = 0.40, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.30 (s, 1H, C**H**O), 8.18 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 7.40 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 3.36 (d, *J* = 4.4 Hz, 1H, **H**-6), 3.20-3.07 (m, 2H, **H**-5+**H**-2), 2.76-2.64 (m, 1H, **H**-3), 1.12 (d, *J* = 7.0 Hz, 3H, C-2C**H**$_3$), 1.04 (d, *J* = 7.0 Hz, 3H, C-3C**H**$_3$).

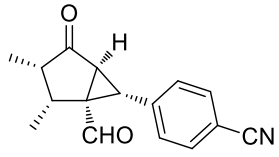
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 209.3 (**C**-4), 196.2 (**C**HO), 147.3, 140.2 ($\mathbf{C}_{arom}$-C), 129.8, 123.9 ($\mathbf{C}_{arom}$-H), 50.1 (**C**-1), 41.1 (**C**-3), 37.3 (**C**-6), 36.5 (**C**-5), 34.6 (**C**-2), 13.6 (C-2**C**H_3), 8.5 (C-3**C**H_3).

IR (ATR) cm^{-1}**:** 1733 (C=O st), 1703 (C=O st), 1519 (NO_2 st as), 1345 (NO_2 st sym).

MS (EI) m/z (relative abundance): 273 (16), 257 (2), 245 (30), 230 (27), 217 (42), 200 (52), 188 (13), 170 (37), 155 (23), 142 (100), 128 (77), 115 (77), 102 (25), 89 (23), 77 (26), 63 (24), 51 (16).

HRMS: Calculated for $[C_{15}H_{14}NO_4]^-$: 272.0923 $[M-H]^-$; found: 272.0923.

(1*S*,2*R*,3*S*,5*S*,6*R*)-6-(4-Cyanophenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (11g)



Following the general procedure, **11g** (15 mg, 0.058 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 36 hours, starting from cycloadduct **7i** (33 mg, 0.100 mmol) and benzhydrylamine (19 mg, 0.100 mmol) using DCE (0.2 mL) as solvent.

Yield: 58%.

dr: 6.3:1.

$[\alpha]_D^{20}$: +92.8 (*c* = 0.64, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.25 (s, 1H, C**H**O), 7.61 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 7.34 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 3.33 (d, *J* = 4.4 Hz, 1H, **H**-6), 3.17-3.04 (m, 2H, **H**-5+**H**-2), 2.75-2.61 (m, 1H, **H**-3), 1.10 (d, *J* = 7.0 Hz, 3H, C-2C**H**$_3$), 1.02 (d, *J* = 7.0 Hz, 3H, C-3C**H**$_3$).

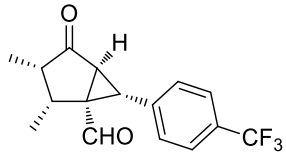
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 209.4 (**C**-4), 196.4 (**C**HO), 138.2 ($\mathbf{C}_{arom}$-C), 132.4, 129.6 ($\mathbf{C}_{arom}$-H), 118.2 (C_{arom}-**C**N), 111.7 ($\mathbf{C}_{arom}$-C), 50.0 (**C**-1), 41.1 (**C**-3), 37.5 (**C**-6), 36.3 (**C**-5), 34.6 (**C**-2), 13.5 (C-2**C**H$_3$), 8.5 (C-3**C**H$_3$).

IR (ATR) cm^{-1}: 2227 (C≡N st), 1732 (C=O st), 1704 (C=O st).

MS (EI) m/z (relative abundance): 253 (17), 234 (1), 225 (22), 210 (29), 197 (51), 182 (27), 168 (84), 154 (100), 140 (54), 127 (23), 116 (35), 101 (12), 89 (14), 77 (18), 63 (13), 53 (14).

HRMS: Calculated for $[C_{16}H_{16}NO_2]^+$: 254.1181 $[M+H]^+$; found: 254.1197.

(1*S*,2*R*,3*S*,5*S*,6*R*)-2,3-Dimethyl-4-oxo-6-(4-(trifluoromethyl)phenyl)bicyclo[3.1.0]hexane-1-carbaldehyde (11h)



Following the general procedure, **11h** (22 mg, 0.075 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 17 hours, starting from cycloadduct **7j** (38 mg, 0.100 mmol) and benzhydrylamine (19 mg, 0.100 mmol) using DCE (0.2 mL) as solvent.

Yield: 75%.

dr: 6.3:1.

$[\alpha]_D^{20}$: +54.1 (*c* = 0.58, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.17 (s, 1H, C**H**O), 7.58 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 7.36 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 3.36 (d, *J* = 4.2 Hz, 1H, **H**-6), 3.16-3.04 (m, 2H, **H**-5+**H**-2), 2.75-2.61 (m, 1H, **H**-3), 1.10 (d, *J* = 7.0 Hz, 3H, C-2C**H**$_3$), 1.02 (d, *J* = 7.0 Hz, 3H, C-3C**H**$_3$).

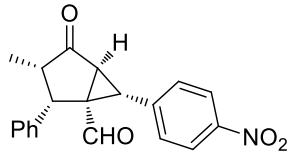
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 209.7 (**C**-4), 196.8 (**C**HO), 136.8 (**C**$_{arom}$-C), 130.0 (q, $^2J_{CF}$ = 32.8 Hz, **C**$_{arom}$-CF_3), 129.3 (**C**$_{arom}$-H), 125.7 (q, $^3J_{CF}$ = 3.7 Hz, **C**$_{arom}$-H), 123.8 (q, $^1J_{CF}$ = 272.3 Hz, **C**F_3), 49.6 (**C**-1), 41.1 (**C**-3), 37.3 (**C**-6), 36.4 (**C**-5), 34.6 (**C**-2), 13.4 (C-2**C**H_3), 8.5 (C-3**C**H_3).

IR (ATR) cm^{-1}**:** 1733 (C=O st), 1705 (C=O st).

MS (EI) m/z (relative abundance): 296 (22), 277 (9), 268 (34), 253 (40), 240 (54), 225 (33), 211 (83), 191 (72), 177 (56), 159 (48), 143 (100), 128 (48), 115 (50), 95 (19), 81 (35), 69 (14), 55 (28).

HRMS: Calculated for $[C_{16}H_{14}O_2F_3]^-$: 295.0946 $[M-H]^-$; found: 295.0935.

(1*R*,2*S*,3*S*,5*S*,6*R*)-3-Methyl-6-(4-nitrophenyl)-4-oxo-2-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (11i)



Following the general procedure, **11i** (25 mg, 0.076 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 6:4) as a yellow oil after 36 hours, starting from cycloadduct **7s** (55 mg, 0.133 mmol) and benzhydrylamine (25 mg, 0.133 mmol) using DCE (0.26 mL) as solvent.

Yield: 57%.

dr: 3:1.

$[\alpha]_D^{20}$: +121.5 (*c* = 0.82, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.23 (s, 1H, C**H**O), 8.18 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 7.43 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 7.36-7.25 (m, 3H, C_{arom}-**H**), 7.18-6.90 (m, 2H, C_{arom}-**H**), 4.22 (d, *J* = 8.4 Hz, 1H, **H**-2), 3.44 (d, *J* = 4.7 Hz, 1H, **H**-6), 3.37 (d, *J* = 4.7 Hz, 1H, **H**-5), 3.04-2.91 (m, 1H, **H**-3), 0.69 (d, *J* = 7.0 Hz, 3H, C-3C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 209.8 (**C**-4), 195.6 (**C**HO), 147.3, 140.0, 137.9 ($\mathbf{C}_{arom}$-C), 130.0, 130.0, 129.3, 127.9, 123.7 ($\mathbf{C}_{arom}$-H), 49.8 (**C**-1), 46.9 (**C**-2), 42.3 (**C**-3), 38.4 (**C**-5), 37.8 (**C**-6), 9.8 (C-3**C**H_3).

IR (ATR) cm^{-1}**:** 1733 (C=O st), 1708 (C=O st), 1519 (NO_2 st as), 1345 (NO_2 st sym).

MS (EI) m/z (relative abundance): 335 (16), 307 (7), 279 (34), 250 (37), 204 (100), 141 (21), 115 (99), 91 (65), 51 (22).

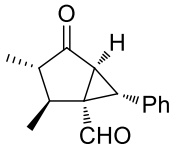
HRMS: Calculated for $[C_{20}H_{16}NO_4]^-$: 334.1079 $[M-H]^-$; found: 334.1077.

2.8. Synthesis of bicyclic compounds 8a-s.

General procedure:

The α,β-unsaturated aldehyde **4** (1.50 mmol) was added to a solution of diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (0.20 mmol, 20 mol%), DABCO (3.00 mmol) and the corresponding 4-alkenyl-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c-e** (1.00 mmol) in DCE (2 mL). The reaction was stirred at 75 ºC until it was completed. A saturated solution of NH_4Cl (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude product was charged onto silica gel and subjected to flash chromatography (FC) with the indicated eluent, obtaining the desired bicycles **8a-s**. The racemic compounds for HPLC separation conditions were prepared under the same reaction conditions, using in these cases a 1:1 ratio of (*R*)- and (*S*)-diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether (0.20 mmol, 20 mol%) as catalyst.

(1*S*,2*S*,3*S*,5*S*,6*R*)-2,3-Dimethyl-4-oxo-6-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (8a)



Following the general procedure, **8a** (18 mg, 0.079 mmol) was isolated by FC (hexanes/EtOAc gradient 9:1 to 8:2) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-cinnamaldehyde **4i** (28 μL, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 53%.

dr: >20:1.

ee: 94%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 13.43 min, τ_{minor} = 25.74 min.

$[\alpha]_D^{20}$: +34.4 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.85 (s, 1H, C**H**O), 7.40-7.27 (m, 5H, C_{arom}-**H**), 3.29 (d, *J* = 4.4 Hz, 1H, **H**-6), 3.11 (d, *J* = 4.4 Hz, 1H, **H**-5), 2.59 (dq, *J* = 9.7, 6.5 Hz, 1H, **H**-2), 1.89 (dq, *J* = 9.7, 6.9 Hz, 1H, **H**-3), 1.33 (d, *J* = 6.5 Hz, 3H, C-2C**H**$_3$), 1.10 (d, *J* = 6.9 Hz, 3H, C-3C**H**$_3$).

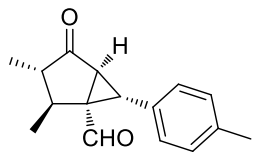
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 209.7 (**C**-4), 197.4 (**C**HO), 132.2 (**C**$_{arom}$-C), 129.0, 128.9, 128.0 (**C**$_{arom}$-H), 49.1 (**C**-1), 45.1 (**C**-3), 39.6 (**C**-5), 36.5 (**C**-2), 35.2 (**C**-6), 16.2 (C-2**C**H_3), 12.2 (C-3**C**H_3).

IR (ATR) cm^{-1}: 1731 (C=O st), 1697 (C=O st).

MS (EI) m/z (relative abundance): 228 (18), 207 (67), 171 (35), 143 (82), 129 (100), 115 (56), 91 (48), 77 (40), 51 (15).

HRMS: Calculated for $[C_{15}H_{15}O_2]^-$: 227.1072 $[M-H]^-$; found: 227.1080.

(1*S*,2*S*,3*S*,5*S*,6*R*)-2,3-Dimethyl-4-oxo-6-(*p*-tolyl)bicyclo[3.1.0]hexane-1-carbaldehyde (8b)



Following the general procedure, **8b** (20 mg, 0.082 mmol) was isolated by FC (hexanes/EtOAc gradient 9:1 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c**

(26 mg, 0.150 mmol) and (*E*)-4-methylcinnamaldehyde **4j** (33 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 55%.

dr: >20:1.

ee: 93%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 12.13 min, τ_{minor} = 20.12 min.

$[\alpha]_D^{20}$: +27.7 (*c* = 0.50, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.85 (s, 1H, C**H**O), 7.24-7.13 (m, 4H, C_{arom}-**H**), 3.25 (d, *J* = 4.3 Hz, 1H, **H**-6), 3.08 (d, *J* = 4.3 Hz, 1H, **H**-5), 2.57 (dq, *J* = 9.7, 6.5 Hz, 1H, **H**-2), 2.34 (s, 3H, C_{arom}-C**H**$_3$), 1.87 (dq, *J* = 9.7, 6.9 Hz, 1H, **H**-3), 1.31 (d, *J* = 6.5 Hz, 3H, C-2C**H**$_3$), 1.09 (d, *J* = 6.9 Hz, 3H, C-3C**H**$_3$).

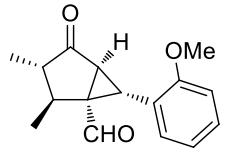
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 209.9 (**C**-4), 197.7 (**C**HO), 137.8 (**C**$_{arom}$-C), 129.7 (**C**$_{arom}$-H), 129.1 (**C**$_{arom}$-C), 128.8 (**C**$_{arom}$-H), 49.1 (**C**-1), 45.1 (**C**-3), 39.7 (**C**-5), 36.5 (**C**-2), 35.0 (**C**-6), 21.1 (C_{arom}-**C**H$_3$), 16.2 (C-2**C**H$_3$), 12.2 (C-3**C**H$_3$).

IR (ATR) cm^{-1}: 1732 (C=O st), 1698 (C=O st).

MS (EI) m/z (relative abundance): 242 (26), 207 (19), 186 (26), 171 (50), 157 (100), 143 (78), 128 (48), 115 (35), 105 (28), 91 (24), 77 (21), 51 (8).

HRMS: Calculated for $[C_{16}H_{17}O_2]^-$: 241.1229 $[M-H]^-$; found: 241.1226.

(1*S*,2*S*,3*S*,5*S*,6*R*)-6-(2-Methoxyphenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (8c)



Following the general procedure, **8c** (15 mg, 0.058 mmol) was isolated by FC (hexanes/EtOAc gradient 8:2 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-2-methoxycinnamaldehyde **4k** (37 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 39%.

dr: >20:1.

ee: 90%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 18.10 min, τ_{minor} = 40.71 min.

$[\alpha]_D^{20}$: -24.7 (*c* = 0.49, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.64 (s, 1H, C**H**O), 7.34-7.27 (m, 2H, C_{arom}-**H**), 6.99-6.91 (m, 1H, C_{arom}-**H**), 6.88-6.83 (m, 1H, C_{arom}-**H**), 3.82 (s, 3H, OC**H**$_3$), 3.13 (d, *J* = 4.5 Hz, 1H, **H**-6), 2.99 (d, *J* = 4.5 Hz, 1H, **H**-5), 2.60 (dq, *J* = 9.7, 6.5 Hz, 1H, **H**-2), 1.91 (dq, *J* = 9.7, 6.9 Hz, 1H, **H**-3), 1.33 (d, *J* = 6.5 Hz, 3H, C-2C**H**$_3$), 1.10 (d, *J* = 6.9 Hz, 3H, C-3C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 210.4 (**C**-4), 197.7 (**C**HO), 158.2 (**C**$_{arom}$-C), 129.5, 129.4 (**C**$_{arom}$-H), 121.1 (**C**$_{arom}$-C), 120.7, 110.2 (**C**$_{arom}$-H), 55.3

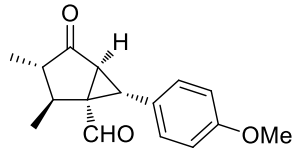
(O**C**H_3), 48.1 (**C**-1), 45.1 (**C**-3), 39.7 (**C**-5), 36.6 (**C**-2), 31.2 (**C**-6), 15.5 (C-2**C**H_3), 12.2 (C-3**C**H_3).

IR (ATR) cm^{-1}: 1719 (C=O st), 1694 (C=O st).

MS (EI) m/z (relative abundance): 258 (89), 241 (7), 230 (10), 215 (19), 202 (92), 185 (100), 173 (60), 159 (75), 144 (35), 128 (47), 115 (76), 102 (17), 91 (74), 77 (41), 65 (18), 51 (16).

HRMS: Calculated for $[C_{16}H_{17}O_3]^-$: 257.1178 $[M-H]^-$; found: 257.1190.

(1*S*,2*S*,3*S*,5*S*,6*R*)-6-(4-Methoxyphenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (8d)



Following the general procedure, **8d** (17 mg, 0.065 mmol) was isolated by FC (hexanes/EtOAc gradient 8:2 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-4-methoxycinnamaldehyde **4l** (37 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 43%.

dr: >20:1.

ee: 94%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 22.05 min, τ_{minor} = 37.60 min.

$[\alpha]_D^{20}$: +30.8 (*c* = 0.50, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.86 (s, 1H, C**H**O), 7.21 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 6.88 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 3.80 (s, 3H, OC**H**$_3$), 3.23 (d, *J* = 4.4 Hz, 1H, **H**-6), 3.05 (d, *J* = 4.4 Hz, 1H, **H**-5), 2.56 (dq, *J* = 9.7, 6.5 Hz, 1H, **H**-2), 1.86 (dq, *J* = 9.7, 6.9 Hz, 1H, **H**-3), 1.31 (d, *J* = 6.5 Hz, 3H, C-2C**H**$_3$), 1.09 (d, *J* = 6.9 Hz, 3H, C-3C**H**$_3$).

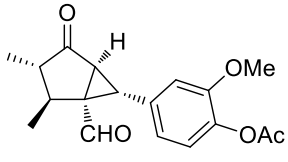
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 209.9 (**C**-4), 197.8 (**C**HO), 159.2 ($\mathbf{C}_{arom}$-C), 130.0 ($\mathbf{C}_{arom}$-H), 124.0 ($\mathbf{C}_{arom}$-C), 114.4 ($\mathbf{C}_{arom}$-H), 55.3 (O**C**H$_3$), 49.2 (**C**-1), 45.2 (**C**-3), 40.0 (**C**-5), 36.5 (**C**-2), 34.7 (**C**-6), 16.2 (C-2**C**H$_3$), 12.2 (C-3**C**H$_3$).

IR (ATR) cm^{-1}: 1732 (C=O st), 1698 (C=O st).

MS (EI) m/z (relative abundance): 258 (82), 241 (3), 229 (17), 215 (14), 202 (96), 187 (55), 173 (84), 159 (59), 145 (34), 135 (22), 121 (100), 102 (24), 91 (26), 77 (37), 65 (14), 51 (14).

HRMS: Calculated for $[C_{16}H_{17}O_3]^-$: 257.1178 $[M-H]^-$; found: 257.1188.

(1*S*,2*S*,3*S*,5*S*,6*R*)-6-(4-Acetoxy-3-methoxyphenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (8e)



Following the general procedure, **8e** (24 mg, 0.076 mmol) was isolated by FC (hexanes/EtOAc gradient 8:2 to 6:4) as a yellow solid after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-4-acetoxy-3-methoxycinnamaldehyde **4m** (52 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 51%.

dr: >20:1.

ee: 94%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 27.99 min, τ_{minor} = 47.73 min.

$[\alpha]_D^{20}$: +18.3 (*c* = 0.89, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.90 (s, 1H, C**H**O), 7.03-6.98 (m, 1H, C_{arom}-**H**), 6.90-6.83 (m, 2H, C_{arom}-**H**), 3.83 (s, 3H, OC**H**$_3$), 3.25 (d, *J* = 4.4 Hz, 1H, **H**-6), 3.05 (d, *J* = 4.4 Hz, 1H, **H**-5), 2.58 (dq, *J* = 9.7, 6.5 Hz, 1H, **H**-2), 2.30 (s, 3H, OCOC**H**$_3$), 1.87 (dq, *J* = 9.7, 6.9 Hz, 1H, **H**-3), 1.32 (d, *J* = 6.5 Hz, 3H, C-2C**H**$_3$), 1.09 (d, *J* = 6.9 Hz, 3H, C-3C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 209.6 (**C**-4), 197.2 (**C**HO), 168.8 (O**C**OCH$_3$), 151.5, 139.5, 131.1 (**C**$_{arom}$-C), 123.3, 121.2, 113.0 (**C**$_{arom}$-H), 56.0 (O**C**H$_3$), 49.1 (**C**-1), 45.1 (**C**-3), 39.8 (**C**-5), 36.5 (**C**-2), 35.0 (**C**-6), 20.6 (OCO**C**H$_3$), 16.2 (C-2**C**H$_3$), 12.2 (C-3**C**H$_3$).

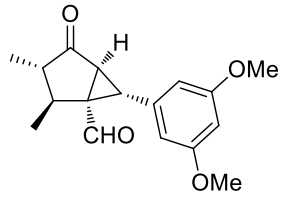
IR (ATR) cm^{-1}: 1763 (OC=O st), 1731 (C=O st), 1697 (C=O st).

M.p. (hexanes/EtOAc) (ºC): 99-101.

MS (EI) m/z (relative abundance): 288 (29), 274 (3), 256 (100), 241 (66), 227 (6), 213 (11), 201 (33), 185 (5), 169 (9), 152 (21), 139 (7), 115 (16), 102 (4), 89 (3), 77 (6), 55 (4).

HRMS: Calculated for $[C_{18}H_{19}O_5]^-$: 315.1233 $[M-H]^-$; found: 315.1259.

(1*S*,2*S*,3*S*,5*S*,6*R*)-6-(3,5-Dimethoxyphenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (8f)



Following the general procedure, **8f** (18 mg, 0.063 mmol) was isolated by FC (hexanes/EtOAc gradient 8:2 to 6:4) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-3,5-dimethoxycinnamaldehyde **4n** (43 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 42%.

dr: >20:1.

ee: 92%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 25.08 min, τ_{minor} = 30.14 min.

$[\alpha]_D^{20}$: +6.7 (*c* = 0.74, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.86 (s, 1H, C**H**O), 6.43 (d, *J* = 2.1 Hz, 2H, C_{arom}-**H**), 6.38 (t, *J* = 2.1 Hz, 1H, C_{arom}-**H**), 3.78 (s, 6H, 2 × OC**H**$_3$), 3.22 (d, *J* = 4.4 Hz, 1H, **H**-6), 3.06 (d, *J* = 4.4 Hz, 1H, **H**-5), 2.57 (dq, *J* = 9.6, 6.5 Hz, 1H, **H**-2), 1.85 (dq, *J* = 9.6, 6.9 Hz, 1H, **H**-3), 1.31 (d, *J* = 6.5 Hz, 3H, C-2C**H**$_3$), 1.09 (d, *J* = 6.9 Hz, 3H, C-3C**H**$_3$).

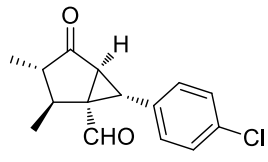
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 209.7 (**C**-4), 197.4 (**C**HO), 161.3, 134.4 ($\mathbf{C}_{arom}$-C), 107.1, 99.6 ($\mathbf{C}_{arom}$-H), 55.4 (O**C**H$_3$), 49.0 (**C**-1), 45.1 (**C**-3), 39.6 (**C**-5), 36.4 (**C**-2), 35.2 (**C**-6), 16.2 (C-2**C**H$_3$), 12.2 (C-3**C**H$_3$).

IR (ATR) cm^{-1}: 1731 (C=O st), 1697 (C=O st).

MS (EI) m/z (relative abundance): 288 (24), 271 (20), 260 (5), 245 (8), 231 (14), 215 (61), 203 (37), 189 (100), 174 (18), 158 (15), 145 (11), 128 (17), 115 (23), 102 (8), 91 (15), 77 (15), 63 (7), 51 (6).

HRMS: Calculated for $[C_{17}H_{19}O_4]^-$: 287.1283 $[M-H]^-$; found: 287.1275.

(1*S*,2*S*,3*S*,5*S*,6*R*)-6-(4-Chlorophenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (8g)



Following the general procedure, **8g** (21 mg, 0.078 mmol) was isolated by FC (hexanes/EtOAc gradient 9:1 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-4-chlorocinnamaldehyde **4o** (39 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 52%.

dr: >20:1.

ee: 92%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 15.47 min, τ_{minor} = 25.23 min.

$[\alpha]_D^{20}$: +29.7 (*c* = 0.85, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.85 (s, 1H, C**H**O), 7.37-7.30 (m, 2H, C_{arom}-**H**), 7.27-7.21 (m, 2H, C_{arom}-**H**), 3.22 (d, *J* = 4.4 Hz, 1H, **H**-6), 3.06 (d, *J*

= 4.4 Hz, 1H, **H**-5), 2.58 (dq, *J* = 9.6, 6.5 Hz, 1H, **H**-2), 1.87 (dq, *J* = 9.6, 6.9 Hz, 1H, **H**-3), 1.32 (d, *J* = 6.5 Hz, 3H, C-2C**H**$_3$), 1.09 (d, *J* = 6.9 Hz, 3H, C-3C**H**$_3$).

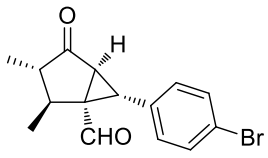
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 209.4 (**C**-4), 196.9 (**C**HO), 134.0, 130.8 (**C**$_{arom}$-C), 130.3, 129.3 (**C**$_{arom}$-H), 49.1 (**C**-1), 45.1 (**C**-3), 39.6 (**C**-5), 36.5 (**C**-2), 34.4 (**C**-6), 16.3 (C-2**C**H_3), 12.2 (C-3**C**H_3).

IR (ATR) cm^{-1}: 1732 (C=O st), 1698 (C=O st).

MS (EI) m/z (relative abundance): 262 (41), 234 (11), 207 (71), 177 (80), 143 (100), 115 (57), 81 (40), 77 (28), 53 (18).

HRMS: Calculated for $[C_{15}H_{14}O_2Cl]^-$: 261.0682 $[M-H]^-$; found: 261.0686.

(1*S*,2*S*,3*S*,5*S*,6*R*)-6-(4-Bromophenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (8h)



Following the general procedure, **8h** (21 mg, 0.069 mmol) was isolated by FC (hexanes/EtOAc gradient 9:1 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-4-bromocinnamaldehyde **4p** (49 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 46%.

dr: >20:1.

ee: 90%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 17.41 min, τ_{minor} = 26.38 min.

$[\alpha]_D^{20}$: +28.3 (*c* = 0.65, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.86 (s, 1H, C**H**O), 7.50 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 7.18 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 3.20 (d, *J* = 4.5 Hz, 1H, **H**-6), 3.06 (d, *J* = 4.5 Hz, 1H, **H**-5), 2.58 (dq, *J* = 9.6, 6.5 Hz, 1H, **H**-2), 1.87 (dq, *J* = 9.6, 6.9 Hz, 1H, **H**-3), 1.32 (d, *J* = 6.5 Hz, 3H, C-2C**H**$_3$), 1.10 (d, *J* = 6.9 Hz, 3H, C-3C**H**$_3$).

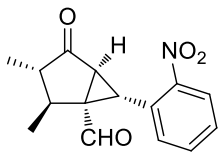
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 209.3 (**C**-4), 196.8 (**C**HO), 132.2 ($\mathbf{C}_{arom}$-H), 131.4 ($\mathbf{C}_{arom}$-C), 130.6 ($\mathbf{C}_{arom}$-H), 122.0 ($\mathbf{C}_{arom}$-C), 49.0 (**C**-1), 45.1 (**C**-3), 39.5 (**C**-5), 36.5 (**C**-2), 34.5 (**C**-6), 16.2 (C-2**C**H_3), 12.2 (C-3**C**H_3).

IR (ATR) cm^{-1}: 1732 (C=O st), 1698 (C=O st).

MS (EI) m/z (relative abundance): 306 (16), 278 (5), 265 (9), 250 (32), 235 (10), 221 (9), 209 (4), 193 (8), 171 (50), 155 (21), 142 (100), 128 (70), 115 (50), 102 (21), 77 (16), 63 (15), 51 (11).

HRMS: Calculated for $[C_{15}H_{14}O_2Br]^-$: 305.0177 $[M-H]^-$; found: 305.0172.

(1*S*,2*S*,3*S*,5*S*,6*R*)-2,3-Dimethyl-6-(2-nitrophenyl)-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (8i)



Following the general procedure, **8i** (19 mg, 0.070 mmol) was isolated by FC (hexanes/EtOAc gradient 8:2 to 6:4) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-2-nitrocinnamaldehyde **4q** (41 mg, 0.225 mmol) in the presence of

DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 47%.

dr: >20:1.

ee: 92%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 25.73 min, τ_{minor} = 68.40 min.

$[\alpha]_D^{20}$: -66.8 (*c* = 0.54, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.91 (s, 1H, C**H**O), 8.00 (dd, *J* = 8.0, 1.0 Hz, 1H, C_{arom}-**H**), 7.70-7.61 (m, 1H, C_{arom}-**H**), 7.60-7.48 (m, 2H, C_{arom}-**H**), 3.57 (d, *J* = 4.6 Hz, 1H, **H**-6), 3.04 (d, *J* = 4.6 Hz, 1H, **H**-5), 2.61 (dq, *J* = 9.9, 6.6 Hz, 1H, **H**-2), 1.97 (dq, *J* = 9.9, 6.9 Hz, 1H, **H**-3), 1.39 (d, *J* = 6.6 Hz, 3H, C-2C**H**$_3$), 1.12 (d, *J* = 6.9 Hz, 3H, C-3C**H**$_3$).

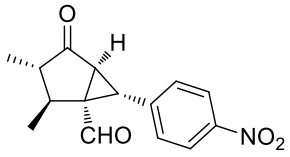
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 209.2 (**C**-4), 195.6 (**C**HO), 150.1 (**C**$_{arom}$-C), 133.5, 131.5, 129.3 (**C**$_{arom}$-H), 127.8 (**C**$_{arom}$-C), 125.1 (**C**$_{arom}$-H), 48.9 (**C**-1), 45.2 (**C**-3), 39.7 (**C**-5), 37.4 (**C**-2), 32.8 (**C**-6), 15.7 (C-2**C**H_3), 12.1 (C-3**C**H_3).

IR (ATR) cm^{-1}: 1733 (C=O st), 1703 (C=O st), 1525 (NO_2 st as), 1348 (NO_2 st sym).

MS (EI) m/z (relative abundance): 244 (10), 228 (10), 210 (12), 200 (19), 182 (29), 169 (46), 156 (23), 144 (25), 135 (100), 115 (60), 102 (25), 91 (70), 79 (57), 63 (26), 51 (27).

HRMS: Calculated for $[C_{15}H_{16}NO_4]^+$: 274.1079 $[M+H]^+$; found: 274.1077.

(1*S*,2*S*,3*S*,5*S*,6*R*)-2,3-Dimethyl-6-(4-nitrophenyl)-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (8j)



Following the general procedure, **8j** (13 mg, 0.048 mmol) was isolated by FC (hexanes/EtOAc gradient 8:2 to 6:4) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-4-nitrocinnamaldehyde **4r** (41 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 32%.

dr: >20:1.

ee: 86%. Determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 24.55 min, τ_{minor} = 28.64 min.

$[\alpha]_D^{20}$: +32.9 (*c* = 0.57, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.90 (s, 1H, C**H**O), 8.24 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 7.49 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 3.28 (d, *J* = 4.6 Hz, 1H, **H**-6), 3.15 (d, *J* = 4.6 Hz, 1H, **H**-5), 2.62 (dq, *J* = 9.6, 6.5 Hz, 1H, **H**-2), 1.91 (dq, *J* = 9.6, 6.9 Hz, 1H, **H**-3), 1.36 (d, *J* = 6.5 Hz, 3H, C-2C**H**$_3$), 1.12 (d, *J* = 6.9 Hz, 3H, C-3C**H**$_3$).

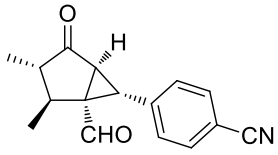
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 208.6 (**C**-4), 195.8 (**C**HO), 147.6, 139.9 ($\mathbf{C}_{arom}$-C), 129.9, 124.2 ($\mathbf{C}_{arom}$-H), 49.4 (**C**-1), 45.1 (**C**-3), 39.5 (**C**-5), 36.7 (**C**-2), 34.4 (**C**-6), 16.3 (C-2**C**H$_3$), 12.2 (C-3**C**H$_3$).

IR (ATR) cm^{-1}: 1733 (C=O st), 1699 (C=O st), 1519 (NO_2 st as), 1344 (NO_2 st sym).

MS (EI) m/z (relative abundance): 273 (25), 257 (2), 245 (33), 230 (30), 217 (45), 200 (55), 188 (14), 170 (36), 155 (21), 142 (100), 128 (73), 115 (68), 102 (24), 89 (20), 77 (23), 63 (19), 51 (15).

HRMS: Calculated for $[C_{15}H_{14}NO_4]^-$: 272.0923 $[M-H]^-$; found: 272.0927.

(1*S*,2*S*,3*S*,5*S*,6*R*)-6-(4-Cyanophenyl)-2,3-dimethyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (8k)



Following the general procedure, **8k** (16 mg, 0.062 mmol) was isolated by FC (hexanes/EtOAc gradient 8:2 to 6:4) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-4-cyanocinnamaldehyde **4s** (35 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 41%.

dr: >20:1.

ee: 89%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 28.72 min, τ_{minor} = 64.64 min.

$[\alpha]_D^{20}$: +43.0 (*c* = 0.53, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.87 (s, 1H, C**H**O), 7.67 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 7.43 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 3.25 (d, *J* = 4.5 Hz, 1H, **H**-6), 3.11 (d, *J* = 4.5 Hz, 1H, **H**-5), 2.61 (dq, *J* = 9.5, 6.5 Hz, 1H, **H**-2), 1.89 (dq, *J* = 9.5, 6.9 Hz, 1H, **H**-3), 1.34 (d, *J* = 6.5 Hz, 3H, C-2C**H**$_3$), 1.11 (d, *J* = 6.9 Hz, 3H, C-3C**H**$_3$).

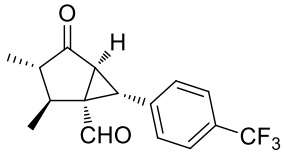
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 208.8 (**C**-4), 196.0 (**C**HO), 137.9 ($\mathbf{C}_{arom}$-C), 132.8, 129.7 ($\mathbf{C}_{arom}$-H), 118.1 (C_{arom}-**C**N), 112.1 ($\mathbf{C}_{arom}$-C), 49.3 (**C**-1), 45.1 (**C**-3), 39.3 (**C**-5), 36.7 (**C**-2), 34.6 (**C**-6), 16.3 (C-2**C**H$_3$), 12.2 (C-3**C**H$_3$).

IR (ATR) cm^{-1}: 2228 (C≡N st), 1732 (C=O st), 1701 (C=O st).

MS (EI) m/z (relative abundance): 253 (25), 238 (8), 225 (26), 210 (32), 197 (59), 182 (29), 168 (89), 154 (100), 140 (52), 127 (23), 116 (32), 101 (11), 91 (4), 81 (15), 63 (11), 53 (11).

HRMS: Calculated for $[C_{16}H_{14}NO_2]^-$: 252.1025 $[M-H]^-$; found: 252.1030.

(1*S*,2*S*,3*S*,5*S*,6*R*)-2,3-Dimethyl-4-oxo-6-(4-(trifluoromethyl)phenyl)bicyclo[3.1.0]hexane-1-carbaldehyde (8l)



Following the general procedure, **8l** (24 mg, 0.081 mmol) was isolated by FC (hexanes/EtOAc gradient 9:1 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylprop-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3c** (26 mg, 0.150 mmol) and (*E*)-4-(trifluoromethyl)cinnamaldehyde **4t** (45 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 54%.

dr: >20:1.

ee: 90%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 10.32 min, τ_{minor} = 17.87 min.

$[\alpha]_D^{20}$: +16.2 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.85 (s, 1H, C**H**O), 7.63 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 7.44 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 3.28 (d, *J* = 4.5 Hz, 1H, **H**-6), 3.13 (d, *J* = 4.5 Hz, 1H, **H**-5), 2.61 (dq, *J* = 9.5, 6.5 Hz, 1H, **H**-2), 1.90 (dq, *J* = 9.5, 6.9 Hz, 1H, **H**-3), 1.34 (d, *J* = 6.5 Hz, 3H, C-2C**H**$_3$), 1.11 (d, *J* = 6.9 Hz, 3H, C-3C**H**$_3$).

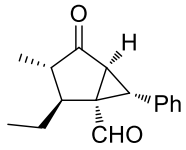
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 209.1 (**C**-4), 196.4 (**C**HO), 136.5 ($\mathbf{C}_{arom}$-C), 130.4 (q, $^2J_{CF}$ = 32.8 Hz, $\mathbf{C}_{arom}$-CF_3), 129.4 ($\mathbf{C}_{arom}$-H), 126.0 (q, $^3J_{CF}$ = 3.7 Hz, $\mathbf{C}_{arom}$-H), 123.8 (q, $^1J_{CF}$ = 272.3 Hz, **C**F_3), 49.1 (**C**-1), 45.1 (**C**-3), 39.3 (**C**-5), 36.6 (**C**-2), 34.5 (**C**-6), 16.3 (C-2**C**H_3), 12.2 (C-3**C**H_3).

IR (ATR) cm^{-1}: 1734 (C=O st), 1699 (C=O st).

MS (EI) m/z (relative abundance): 296 (38), 268 (43), 240 (65), 211 (97), 171 (54), 143 (100), 115 (49), 81 (34), 53 (22).

HRMS: Calculated for $[C_{16}H_{14}O_2F_3]^-$: 295.0946 $[M-H]^-$; found: 295.0942.

(1*S*,2*S*,3*S*,5*S*,6*R*)-2-Ethyl-3-methyl-4-oxo-6-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (8m)



Following the general procedure, **8m** (16 mg, 0.065 mmol) was isolated by FC (hexanes/EtOAc gradient 9:1 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylbut-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3d** (28 mg, 0.150 mmol) and (*E*)-cinnamaldehyde **4i** (28 μL, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 43%.

dr: >20:1.

ee: 91%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 13.74 min, τ_{minor} = 27.37 min.

$[\alpha]_D^{20}$: -10.0 (*c* = 0.92, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.85 (s, 1H, C**H**O), 7.40-7.28 (m, 5H, C_{arom}-**H**), 3.30 (d, *J* = 4.5 Hz, 1H, **H**-6), 3.06 (d, *J* = 4.5 Hz, 1H, **H**-5), 2.65-2.53 (m, 1H, **H**-2), 2.04-1.90 (m, 1H, **H**-3), 1.81-1.69 (m, 2H, C**H**$_2$CH$_3$), 1.19-1.08 (m, 6H, C-3C**H**$_3$+CH$_2$C**H**$_3$).

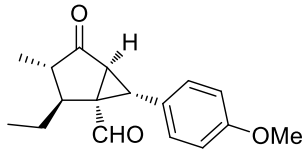
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 210.0 (**C**-4), 197.0 (**C**HO), 132.3 (**C**$_{arom}$-C), 129.0, 128.9, 128.0 (**C**$_{arom}$-H), 48.5 (**C**-1), 44.6 (**C**-3), 42.4 (**C**-2), 39.7 (**C**-5), 35.1 (**C**-6), 26.0 (**C**H$_2$CH$_3$), 14.1 (C-3**C**H$_3$), 12.5 (CH$_2$**C**H$_3$).

IR (ATR) cm^{-1}: 1732 (C=O st), 1698 (C=O st).

MS (EI) m/z (relative abundance): 242 (25), 213 (14), 199 (7), 185 (67), 171 (47), 157 (44), 141 (30), 129 (100), 105 (13), 91 (50), 77 (28), 67 (12), 51 (11).

HRMS: Calculated for $[C_{16}H_{17}O_2]^-$: 241.1229 $[M-H]^-$; found: 241.1225.

(1*S*,2*S*,3*S*,5*S*,6*R*)-2-Ethyl-6-(4-methoxyphenyl)-3-methyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (8n)



Following the general procedure, **8n** (17 mg, 0.062 mmol) was isolated by FC (hexanes/EtOAc gradient 8:2 to 6:4) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylbut-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3d** (28 mg, 0.150 mmol) and (*E*)-4-methoxycinnamaldehyde **4l** (37 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 41%.

dr: >20:1.

ee: 90%. Determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (97:3)]; flow rate 1.0 mL/min; τ_{major} = 23.13 min, τ_{minor} = 21.83 min.

$[\alpha]_D^{20}$: +10.7 (*c* = 0.96, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.87 (s, 1H, C**H**O), 7.21 (d, *J* = 8.6 Hz, 2H, C_{arom}-**H**), 6.88 (d, *J* = 8.6 Hz, 2H, C_{arom}-**H**), 3.80 (s, 3H, OC**H**$_3$), 3.24 (d, *J* = 4.5 Hz, 1H, **H**-6), 3.00 (d, *J* = 4.5 Hz, 1H, **H**-5), 2.62-2.50 (m, 1H, **H**-2), 2.01-

1.88 (m, 1H, **H**-3), 1.80-1.67 (m, 2H, C**H**$_2$CH$_3$), 1.16-1.06 (m, 6H, C-3C**H**$_3$+CH$_2$C**H**$_3$).

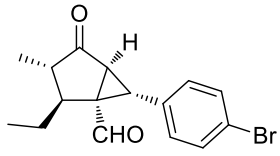
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 210.2 (**C**-4), 197.3 (**C**HO), 159.2 (**C**$_{arom}$-C), 130.0 (**C**$_{arom}$-H), 124.0 (**C**$_{arom}$-C), 114.4 (**C**$_{arom}$-H), 55.3 (O**C**H$_3$), 48.6 (**C**-1), 44.6 (**C**-3), 42.4 (**C**-2), 40.0 (**C**-5), 34.6 (**C**-6), 26.0 (**C**H$_2$CH$_3$), 14.2 (C-3**C**H$_3$), 12.5 (CH$_2$**C**H$_3$).

IR (ATR) cm^{-1}: 1731 (C=O st), 1699 (C=O st).

MS (EI) m/z (relative abundance): 272 (50), 255 (4), 243 (19), 229 (3), 216 (42), 199 (46), 187 (36), 174 (16), 159 (27), 145 (24), 135 (18), 121 (100), 108 (17), 91 (19), 77 (28), 65 (9), 55 (10).

HRMS: Calculated for $[C_{17}H_{19}O_3]^-$: 271.1334 $[M-H]^-$; found: 271.1328.

(1*S*,2*S*,3*S*,5*S*,6*R*)-6-(4-Bromophenyl)-2-ethyl-3-methyl-4-oxobicyclo[3.1.0]hexane-1-carbaldehyde (8o)



Following the general procedure, **8o** (14 mg, 0.045 mmol) was isolated by FC (hexanes/EtOAc gradient 9:1 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-methylbut-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3d** (28 mg, 0.150 mmol) and (*E*)-4-bromocinnamaldehyde **4p** (49 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 30%.

dr: >20:1.

ee: 86%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 18.25 min, τ_{minor} = 26.86 min.

$[\alpha]_D^{20}$: +15.8 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.87 (s, 1H, C**H**O), 7.50 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 7.18 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 3.20 (d, *J* = 4.6 Hz, 1H, **H**-6), 3.01 (d, *J* = 4.6 Hz, 1H, **H**-5), 2.63-2.41 (m, 1H, **H**-2), 2.02-1.89 (m, 1H, **H**-3), 1.80-1.67 (m, 2H, C**H**$_2$CH$_3$), 1.17-1.07 (m, 6H, C-3C**H**$_3$+CH$_2$C**H**$_3$).

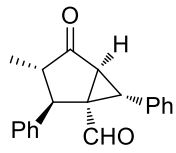
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 209.6 (**C**-4), 196.5 (**C**HO), 132.2 ($\mathbf{C}_{arom}$-H), 131.4 ($\mathbf{C}_{arom}$-C), 130.5 ($\mathbf{C}_{arom}$-H), 122.0 ($\mathbf{C}_{arom}$-C), 48.4 (**C**-1), 44.6 (**C**-3), 42.5 (**C**-2), 39.6 (**C**-5), 34.4 (**C**-6), 26.0 (**C**H$_2$CH$_3$), 14.2 (C-3**C**H$_3$), 12.5 (CH$_2$**C**H$_3$).

IR (ATR) cm^{-1}: 1731 (C=O st), 1701 (C=O st).

MS (EI) m/z (relative abundance): 320 (30), 292 (8), 277 (5), 264 (55), 249 (25), 235 (21), 222 (8), 209 (7), 185 (58), 169 (51), 156 (74), 141 (100), 128 (100), 115 (90), 95 (50), 77 (33), 67 (36), 55 (20).

HRMS: Calculated for $[C_{16}H_{16}O_2Br]^-$: 319.0334 $[M-H]^-$; found: 319.0335.

(1*R*,2*R*,3*S*,5*S*,6*R*)-3-methyl-4-oxo-2,6-diphenylbicyclo[3.1.0]hexane-1-carbaldehyde (8p)



Following the general procedure, **8p** (21 mg, 0.073 mmol) was isolated by FC (hexanes/EtOAc gradient 9:1 to 8:2) as a yellow oil after 12 hours, starting from (*E*)-4-(1-phenylprop-1-en-2-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3e** (36 mg, 0.150 mmol) and (*E*)-cinnamaldehyde **4i** (28 μL, 0.225 mmol) in the presence of DABCO (50 mg,

0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 49%.

dr: >20:1.

ee: 93%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 14.61 min, τ_{minor} = 29.31 min.

$[\alpha]_D^{20}$: +25.7 (*c* = 0.83, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.89 (s, 1H, C**H**O), 7.55-7.50 (m, 2H, C_{arom}-**H**), 7.46-7.39 (m, 2H, C_{arom}-**H**), 7.37-7.23 (m, 6H, C_{arom}-**H**), 3.81 (d, *J* = 10.1 Hz, 1H, **H**-2), 3.68 (d, *J* = 4.5 Hz, 1H, **H**-6), 3.16 (d, *J* = 4.5 Hz, 1H, **H**-5), 2.58 (dq, *J* = 10.1, 6.9 Hz, 1H, **H**-3), 1.20 (d, *J* = 6.9 Hz, 3H, C-3C**H**$_3$).

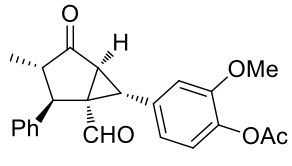
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 208.4 (**C**-4), 196.4 (**C**HO), 139.7, 131.9 (**C**$_{arom}$-C), 129.0, 128.9, 128.8, 128.1, 127.5, 127.5 (**C**$_{arom}$-H), 48.7 (**C**-1), 46.4 (**C**-2), 44.2 (**C**-3), 38.7 (**C**-5), 36.0 (**C**-6), 13.0 (C-3**C**H_3).

IR (ATR) cm^{-1}: 1732 (C=O st), 1699 (C=O st).

MS (EI) m/z (relative abundance): 290 (17), 273 (1), 262 (4), 247 (4), 234 (14), 215 (9), 205 (100), 191 (10), 171 (14), 156 (6), 144 (11), 128 (25), 115 (40), 103 (8), 91 (40), 77 (15), 65 (6), 51 (6).

HRMS: Calculated for $[C_{20}H_{17}O_2]^-$: 289.1229 $[M-H]^-$; found: 289.1236.

(1*R*,2*R*,3*S*,5*S*,6*R*)-6-(4-Acetoxy-3-methoxyphenyl)-3-methyl-4-oxo-2-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (8q)



Following the general procedure, **8q** (29 mg, 0.077 mmol) was isolated by FC (hexanes/EtOAc gradient 7:3 to 1:1) as a yellow oil after 12 hours, starting from (*E*)-4-(1-phenylprop-1-en-2-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3e** (36 mg, 0.150 mmol) and (*E*)-4-acetoxy-3-methoxycinnamaldehyde **4m** (52 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 51%.

dr: >20:1.

ee: 90%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 26.85 min, τ_{minor} = 38.87 min.

$[\alpha]_D^{20}$: +19.1 (*c* = 0.81, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.95 (s, 1H, C**H**O), 7.53-7.46 (m, 2H, C_{arom}-**H**), 7.45-7.29 (m, 3H, C_{arom}-**H**), 7.01-6.95 (m, 1H, C_{arom}-**H**), 6.84-6.78 (m, 2H, C_{arom}-**H**), 3.86-3.76 (m, 4H, **H**-2+OC**H**$_3$), 3.63 (d, *J* = 4.5 Hz, 1H, **H**-6), 3.10 (d, *J* = 4.5 Hz, 1H, **H**-5), 2.57 (dq, *J* = 10.0, 6.9 Hz, 1H, **H**-3), 2.30 (s, 3H, OCOC**H**$_3$), 1.20 (d, *J* = 6.9 Hz, 3H, C-3C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 208.3 (**C**-4), 196.2 (**C**HO), 168.8 (O**C**OCH$_3$), 151.5, 139.6, 139.6, 130.7 (**C**$_{arom}$-C), 128.9, 127.5, 127.5, 123.3,

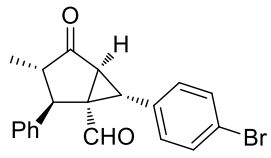
121.0, 112.8 (**C**$_{arom}$-H), 55.9 (O**C**H$_3$), 48.8 (**C**-1), 46.3 (**C**-2), 44.2 (**C**-3), 38.9 (**C**-5), 35.8 (**C**-6), 20.6 (OCO**C**H$_3$), 13.0 (C-3**C**H$_3$).

IR (ATR) cm^{-1}: 1764 (OC=O st), 1732 (C=O st), 1699 (C=O st).

MS (EI) m/z (relative abundance): 378 (5), 336 (100), 308 (4), 280 (33), 251 (53), 235 (5), 218 (54), 190 (41), 165 (15), 137 (32), 115 (32), 91 (31), 77 (18), 51 (7).

HRMS: Calculated for $[C_{23}H_{21}O_5]^-$: 377.1389 $[M-H]^-$; found: 377.1392.

(1*R*,2*R*,3*S*,5*S*,6*R*)-6-(4-Bromophenyl)-3-methyl-4-oxo-2-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (8r)



Following the general procedure, **8r** (23 mg, 0.063 mmol) was isolated by FC (hexanes/EtOAc gradient 9:1 to 7:3) as a yellow oil after 12 hours, starting from (*E*)-4-(1-phenylprop-1-en-2-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3e** (36 mg, 0.150 mmol) and (*E*)-4-bromocinnamaldehyde **4p** (49 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 42%.

dr: >20:1.

ee: 75%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 21.69 min, τ_{minor} = 47.16 min.

$[\alpha]_D^{20}$: +34.2 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.89 (s, 1H, C**H**O), 7.52-7.37 (m, 7H, C_{arom}-**H**), 7.11 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 3.80 (d, *J* = 10.2 Hz, 1H, **H**-2), 3.58 (d, *J* = 4.5 Hz, 1H, **H**-6), 3.10 (d, *J* = 4.5 Hz, 1H, **H**-5), 2.57 (dq, *J* = 10.2, 6.9 Hz, 1H, **H**-3), 1.20 (d, *J* = 6.9 Hz, 3H, C-3C**H**$_3$).

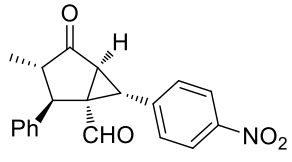
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 208.0 (**C**-4), 195.8 (**C**HO), 139.5 ($\mathbf{C}_{arom}$-C), 132.2 ($\mathbf{C}_{arom}$-H), 131.0 ($\mathbf{C}_{arom}$-C), 130.4, 128.9, 127.6, 127.4 ($\mathbf{C}_{arom}$-H), 122.2 ($\mathbf{C}_{arom}$-C), 48.7 (**C**-1), 46.4 (**C**-2), 44.1 (**C**-3), 38.6 (**C**-5), 35.3 (**C**-6), 13.0 (C-3**C**H_3).

IR (ATR) cm^{-1}: 1732 (C=O st), 1700 (C=O st).

MS (EI) m/z (relative abundance): 368 (14), 342 (3), 327 (2), 312 (13), 285 (8), 271 (2), 250 (4), 231 (5), 215 (18), 204 (100), 189 (8), 171 (29), 143 (10), 128 (28), 115 (47), 102 (20), 91 (30), 77 (19), 63 (10), 51 (9).

HRMS: Calculated for $[C_{20}H_{16}O_2Br]^-$: 367.0334 $[M-H]^-$; found: 367.0340.

(1*R*,2*R*,3*S*,5*S*,6*R*)-3-Methyl-6-(4-nitrophenyl)-4-oxo-2-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (8s)



Following the general procedure, **8s** (23 mg, 0.069 mmol) was isolated by FC (hexanes/EtOAc gradient 8:2 to 6:4) as a yellow oil after 12 hours, starting from (*E*)-4-(1-phenylprop-1-en-2-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3e** (36 mg, 0.150 mmol) and (*E*)-4-nitrocinnamaldehyde **4r** (41 mg, 0.225 mmol) in the presence of DABCO (50 mg, 0.450 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 46%.

dr: >20:1.

ee: 76%. Determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.8 mL/min; τ_{major} = 40.91 min, τ_{minor} = 37.61 min.

$[\alpha]_D^{20}$: +47.7 (*c* = 0.81, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.94 (s, 1H, C**H**O), 8.20 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 7.53-7.36 (m, 7H, C_{arom}-**H**), 3.84 (d, *J* = 10.1 Hz, 1H, **H**-2), 3.65 (d, *J* = 4.7 Hz, 1H, **H**-6), 3.20 (d, *J* = 4.7 Hz, 1H, **H**-5), 2.63 (dq, *J* = 10.1, 6.9 Hz, 1H, **H**-3), 1.22 (d, *J* = 6.9 Hz, 3H, C-3C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 207.4 (**C**-4), 195.0 (**C**HO), 147.6, 139.5, 139.1 (**C**$_{arom}$-C), 129.7, 129.1, 127.8, 127.4, 124.2 (**C**$_{arom}$-H), 49.0 (**C**-1), 46.7 (**C**-2), 44.0 (**C**-3), 38.6 (**C**-5), 35.2 (**C**-6), 13.0 (C-3**C**H_3).

IR (ATR) cm^{-1}: 1734 (C=O st), 1700 (C=O st), 1519 (NO_2 st as), 1345 (NO_2 st sym).

MS (EI) m/z (relative abundance): 335 (16), 318 (15), 292 (9), 279 (34), 262 (6), 250 (41), 234 (13), 215 (25), 204 (100), 189 (29), 171 (15), 142 (15), 128 (42), 115 (99), 102 (28), 91 (57), 77 (31), 63 (16), 51 (18).

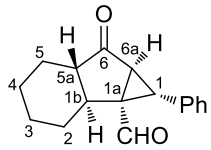
HRMS: Calculated for $[C_{20}H_{16}NO_4]^-$: 334.1079 $[M-H]^-$; found: 334.1079.

2.9. Synthesis of tricyclic compounds 12a-c.

General procedure:

The α,β-unsaturated aldehyde **4** (1.00 mmol) was added to a solution of diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (0.20 mmol, 20 mol%), DABCO (5.00 mmol) and 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3a** (1.50 mmol) in DCE (2 mL). The reaction was stirred at 75 ºC until it was completed. A saturated solution of NH_4Cl (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude product was charged onto silica gel and subjected to flash chromatography (FC) with the indicated eluent, obtaining the desired tricycles **12a-c**. The racemic compounds for HPLC separation conditions were prepared under the same reaction conditions, using in these cases a 1:1 ratio of (*R*)- and (*S*)-diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether (0.20 mmol, 20 mol%) as catalyst.

(1*R*,1a*S*,1b*S*,5a*S*,6a*S*)-6-oxo-1-phenyldecahydrocyclopropa[*a*]indene-1a-carbaldehyde (12a)



Following the general procedure, **12a** (18 mg, 0.069 mmol) was isolated by FC (hexanes/EtOAc gradient 9:1 to 7:3) as a yellow oil after 12 hours, starting from 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3a** (45 mg, 0.225 mmol) and (*E*)-cinnamaldehyde **4i** (19 μL, 0.150 mmol) in the presence of DABCO (84 mg, 0.750 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 46%.

dr: >20:1.

ee: 98%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 19.87 min, τ_{minor} = 41.63 min.

$[\alpha]_D^{20}$: +49.7 (*c* = 0.69, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.87 (s, 1H, C**H**O), 7.42-7.23 (m, 5H, C_{arom}-**H**), 3.60 (d, *J* = 4.3 Hz, 1H, **H**-1), 2.91 (d, *J* = 4.3 Hz, 1H, **H**-6a), 2.43-2.30 (m, 1H, **H**-1b), 2.29-2.21 (m, 1H, **H**-2_a), 2.09-2.01 (m, 1H, **H**-5_a), 1.93-1.80 (m, 3H, **H**-5a+**H**-3_a+**H**-4_a), 1.45-1.33 (m, 2H, **H**-2_b+**H**-3_b), 1.27-1.18 (m, 2H, **H**-5_b+**H**-4_b).

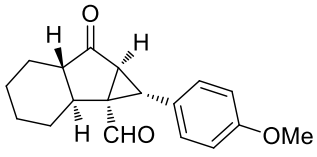
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 207.5 (**C**-6), 197.8 (**C**HO), 132.5 ($\mathbf{C}_{arom}$-C), 129.0, 128.9, 128.0 ($\mathbf{C}_{arom}$-H), 47.5 (**C**-5a), 47.0 (**C**-1a), 41.5 (**C**-1b), 37.6 (**C**-6a), 36.8 (**C**-1), 29.2 (**C**-2), 25.9, 25.8 (**C**-3+**C**-4), 24.7 (**C**-5).

IR (ATR) cm^{-1}: 1731 (C=O st), 1698 (C=O st).

MS (EI) m/z (relative abundance): 254 (39), 237 (3), 226 (19), 207 (10), 197 (23), 183 (27), 165 (23), 155 (35), 141 (51), 129 (85), 115 (95), 103 (21), 91 (100), 77 (48), 65 (21), 55 (21).

HRMS: Calculated for $[C_{17}H_{19}O_2]^+$: 255.1385 $[M+H]^+$; found: 255.1387.

(1*R*,1a*S*,1b*S*,5a*S*,6a*S*)-1-(4-Methoxyphenyl)-6-oxodecahydrocyclopropa[*a*]indene-1a-carbaldehyde (12b)



Following the general procedure, **12b** (14 mg, 0.051 mmol) was isolated by FC (hexanes/EtOAc gradient 9:1 to 7:3) as a yellow oil after 12 hours, starting from 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3a** (45 mg, 0.225 mmol) and (*E*)-4-methoxycinnamaldehyde **4l** (25 mg, 0.150 mmol) in the presence of DABCO (84 mg, 0.750 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 34%.

dr: >20:1.

ee: 96%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 18.36 min, τ_{minor} = 42.20 min.

$[\alpha]_D^{20}$: +74.0 (*c* = 0.75, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.88 (s, 1H, C**H**O), 7.20 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 6.88 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 3.80 (s, 3H, OC**H**$_3$), 3.55 (d, *J* = 4.2 Hz, 1H, **H**-1), 2.85 (d, *J* = 4.2 Hz, 1H, **H**-6a), 2.41-2.29 (m, 1H, **H**-1b), 2.29-2.19 (m, 1H, **H**-2$_a$), 2.08-2.00 (m, 1H, **H**-5$_a$), 1.93-1.77 (m, 3H, **H**-5a+**H**-3$_a$+**H**-4$_a$), 1.45-1.32 (m, 2H, **H**-2$_b$+**H**-3$_b$), 1.27-1.17 (m, 2H, **H**-5$_b$+**H**-4$_b$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 207.7 (**C**-6), 198.1 (**C**HO), 159.2 (**C**$_{arom}$-C), 130.0 (**C**$_{arom}$-H), 124.4 (**C**$_{arom}$-C), 114.4 (**C**$_{arom}$-H), 55.3 (O**C**H$_3$), 47.6 (**C**-

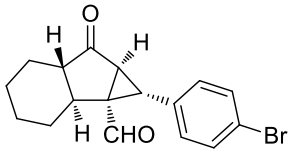
5a), 47.1 (**C**-1a), 41.5 (**C**-1b), 38.0 (**C**-6a), 36.4 (**C**-1), 29.2 (**C**-2), 25.9, 25.8 (**C**-3+**C**-4), 24.8 (**C**-5).

IR (ATR) cm^{-1}: 1728 (C=O st), 1695 (C=O st).

MS (EI) m/z (relative abundance): 284 (40), 267 (4), 255 (35), 239 (5), 227 (10), 213 (8), 199 (6), 187 (12), 171 (21), 159 (22), 145 (22), 135 (14), 121 (100), 107 (15), 91 (25), 77 (23), 55 (11).

HRMS: Calculated for $[C_{18}H_{21}O_3]^+$: 285.1491 $[M+H]^+$; found: 285.1494.

(1*R*,1a*S*,1b*S*,5a*S*,6a*S*)-1-(4-Bromophenyl)-6-oxodecahydrocyclopropa[*a*]indene-1a-carbaldehyde (12c)



Following the general procedure, **12c** (19 mg, 0.057 mmol) was isolated by FC (hexanes/EtOAc gradient 9:1 to 7:3) as a yellow oil after 12 hours, starting from 4-(cyclohex-1-en-1-yl)-5*H*-1,2,3-oxathiazole 2,2-dioxide **3a** (45 mg, 0.225 mmol) and (*E*)-4-bromocinnamaldehyde **4p** (32 mg, 0.150 mmol) in the presence of DABCO (84 mg, 0.750 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using DCE (0.3 mL) as solvent.

Yield: 38%.

dr: >20:1.

ee: 96%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 17.70 min, τ_{minor} = 47.53 min.

$[\alpha]_D^{20}$: +54.8 (*c* = 0.66, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.87 (s, 1H, C**H**O), 7.49 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 7.17 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 3.52 (d, *J* = 4.3 Hz, 1H, **H**-1), 2.85 (d, *J* = 4.3 Hz, 1H, **H**-6a), 2.42-2.29 (m, 1H, **H**-1b), 2.29-2.21 (m, 1H, **H**-2_a), 2.11-2.01 (m, 1H, **H**-5_a), 1.95-1.79 (m, 3H, **H**-5a+**H**-3_a+**H**-4_a), 1.44-1.31 (m, 2H, **H**-2_b+**H**-3_b), 1.27-1.17 (m, 2H, **H**-5_b+**H**-4_b).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 207.0 (**C**-6), 197.2 (**C**HO), 132.2 ($\mathbf{C}_{arom}$-H), 131.7 ($\mathbf{C}_{arom}$-C), 130.6 ($\mathbf{C}_{arom}$-H), 122.0 ($\mathbf{C}_{arom}$-C), 47.5 (**C**-5a), 46.9 (**C**-1a), 41.5 (**C**-1b), 37.4 (**C**-6a), 36.0 (**C**-1), 29.2 (**C**-2), 25.8, 25.8 (**C**-3+**C**-4), 24.7 (**C**-5).

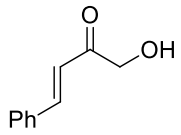
IR (ATR) cm^{-1}: 1732 (C=O st), 1697 (C=O st).

MS (EI) m/z (relative abundance): 332 (48), 315 (5), 303 (17), 289 (7), 275 (22), 263 (13), 249 (12), 235 (18), 222 (30), 207 (25), 195 (27), 182 (27), 169 (63), 153 (60), 141 (73), 128 (97), 115 (100), 102 (44), 77 (50), 55 (39).

HRMS: Calculated for $[C_{17}H_{16}O_2Br]^-$: 331.0334 $[M-H]^-$; found: 331.0321.

2.10. Synthesis of α-hydroxy ketone 14.

(*E*)-1-Hydroxy-4-phenylbut-3-en-2-one (14)



To a mixture of CH_3CN/H_2O (75:15 mL), trifluoroacetic acid (2.30 mL, 30.00 mmol) and (*E*)-4-phenylbut-3-en-2-one **13** (2.19 g, 15.00 mmol) were added. Then [bis(trifluoroacetoxy)iodo]benzene (13.30 g, 30.00 mmol) was added and the reaction was stirred under reflux during 4 hours and then allowed to reach room temperature. The solvent was removed under vacuum and H_2O (75 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 150 mL) and the combined

organic layers were washed with a solution of saturated aqueous $NaHCO_3$ (3 × 150 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. After purification by flash column chromatography (FC) (hexanes/EtOAc gradient from 7:3 to 1:1) the α-hydroxy ketone **14** (825 mg, 5.09 mmol) was isolated as a yellow oil.

Yield: 34%.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.66 (d, *J* = 16.3 Hz, 1H, C_{arom}-C**H**), 7.58-7.53 (m, 2H, C_{arom}-**H**), 7.43-7.37 (m, 3H, C_{arom}-**H**), 6.75 (d, *J* = 16.3 Hz, 1H, C**H**CO), 4.53 (d, *J* = 3.3 Hz, 2H, C**H**$_2$OH), 3.43 (s, 1H, O**H**).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 198.1 (**C**O), 144.1 (C_{arom}-**C**H), 133.9 (**C**$_{arom}$-C), 131.1, 129.1, 128.5 (**C**$_{arom}$-H), 121.4 (**C**HCO), 67.1 (**C**H$_2$OH).

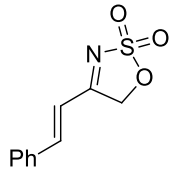
IR (ATR) cm^{-1}: 3447 (O-H st), 1668 (C=O st).

MS (EI) m/z (relative abundance): 162 (1), 131 (100), 103 (65), 77 (42), 51 (21).

HRMS: Calculated for $[C_{10}H_{11}O_2]^+$: 163.0759 $[M+H]^+$; found: 163.0760.

2.11. Synthesis of 4-alkenyl-5*H*-1,2,3-oxathiazole 2,2-dioxide 15.

(*E*)-4-Styryl-5*H*-1,2,3-oxathiazole 2,2-dioxide (15)



To a solution of α-hydroxy ketone **14** (751 mg, 4.63 mmol) in dry DMA (12 mL) under inert atmosphere, sulfamoyl chloride (1.07 g, 9.26 mmol) was added portionwise. After stirring at room temperature for 2 hours, the reaction mixture was diluted with EtOAc (45 mL) and washed with brine (3 × 45 mL). The resulting organic layer

was dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. Then *p*-toluenesulfonic acid (88 mg, 0.46 mmol) and toluene (12 mL) were added, and the reaction was stirred under reflux for 1 hour with a Dean-Stark receiver. The mixture was diluted with EtOAc (45 mL) and washed with a solution of saturated aqueous $NaHCO_3$ (3 × 45 mL). The resulting organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. After purification by flash column chromatography (FC) (hexanes/EtOAc gradient from 7:3 to 4:6) the sulfamidate imine **15** (586 mg, 2.62 mmol) was isolated as a brown solid.

Yield: 57%.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.62-7.44 (m, 6H, C_{arom}-**H**+C_{arom}-C**H**), 7.02 (d, *J* = 16.6 Hz, 1H, C**H**CN), 5.39 (s, 2H, OC**H**$_2$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 174.2 (**C**N), 148.2 (C_{arom}-**C**H), 133.1 (**C**$_{arom}$-C), 132.4, 129.4, 128.8 (**C**$_{arom}$-H), 116.6 (**C**HCN), 74.1 (O**C**H$_2$).

IR (ATR) cm^{-1}**:** 1625 (C=C st), 1557 (C=N st), 1358 (SO_2 st as), 1187 (SO_2 st sym).

M.p. (hexanes/EtOAc) (ºC): 172-174.

MS (EI) m/z (relative abundance): 207 (30), 158 (13), 130 (76), 102 (37), 77 (38), 64 (100), 51 (26).

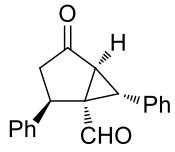
HRMS: Calculated for $[C_{10}H_{10}NO_3S]^+$: 224.0381 $[M+H]^+$; found: 224.0386.

2.12. Synthesis of bicyclic compounds 16a-c.

General procedure:

The α,β-unsaturated aldehyde **4** (1.50 mmol) was added to a solution of diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (0.20 mmol, 20 mol%), DABCO (0.20 mmol, 20 mol%) and (*E*)-4-styryl-5*H*-1,2,3-oxathiazole 2,2-dioxide **15** (1.00 mmol) in dry $CHCl_3$ (2 mL) under inert atmosphere. The reaction was stirred at room temperature until it was completed. The obtained crude product was charged onto silica gel and subjected to flash chromatography (FC) with the indicated eluent, obtaining the desired bicycles **16a-c**. The racemic compounds for HPLC separation conditions were prepared under the same reaction conditions, using in these cases a 1:1 ratio of (*R*)- and (*S*)-diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether (0.20 mmol, 20 mol%) as catalyst.

(1*S*,2*R*,5*S*,6*R*)-4-oxo-2,6-diphenylbicyclo[3.1.0]hexane-1-carbaldehyde (16a)



Following the general procedure, **16a** (20 mg, 0.072 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 7:3) as a yellow oil after 48 hours, starting from (*E*)-4-styryl-5*H*-1,2,3-oxathiazole 2,2-dioxide **15** (33 mg, 0.150 mmol) and (*E*)-cinnamaldehyde **4i** (28 μL, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 48%.

dr: >20:1.

ee: 99%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 35.97 min, τ_{minor} = 47.30 min.

$[\alpha]_D^{20}$: +113.3 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.99 (s, 1H, C**H**O), 7.45-7.24 (m, 10H, C_{arom}-**H**), 4.44 (app t, *J* = 10.0 Hz, 1H, **H**-2), 3.44 (d, *J* = 4.7 Hz, 1H, **H**-6), 3.21 (d, *J* = 4.7 Hz, 1H, **H**-5), 2.87 (dd, *J* = 18.6, 9.9 Hz, 1H, **H**-3_a), 2.58 (dd, *J* = 18.6, 10.0 Hz, 1H, **H**-3_b).

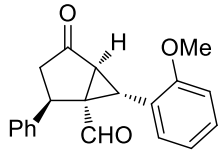
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 206.8 (**C**-4), 196.5 (**C**HO), 140.1, 131.6 (**C**$_{arom}$-C), 129.1, 128.8, 128.6, 128.1, 127.3, 127.2 (**C**$_{arom}$-H), 50.1 (**C**-1), 40.4 (**C**-3), 40.1 (**C**-5), 37.4 (**C**-2), 35.1 (**C**-6).

IR (ATR) cm^{-1}: 1734 (C=O st), 1698 (C=O st).

MS (EI) m/z (relative abundance): 276 (11), 258 (2), 247 (3), 234 (12), 215 (10), 205 (100), 191 (12), 178 (9), 157 (15), 144 (23), 128 (29), 115 (51), 103 (13), 91 (47), 77 (23), 65 (9), 51 (11).

HRMS: Calculated for $[C_{19}H_{15}O_2]^-$: 275.1072 $[M-H]^-$; found: 275.1071.

(1*S*,2*R*,5*S*,6*R*)-6-(2-methoxyphenyl)-4-oxo-2-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (16b)



Following the general procedure, **16b** (21 mg, 0.069 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 6:4) as a yellow oil after 24 hours, starting from (*E*)-4-styryl-5*H*-1,2,3-oxathiazole 2,2-dioxide **15** (33 mg, 0.150 mmol) and

(*E*)-2-methoxycinnamaldehyde **4k** (37 mg, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 46%.

dr: >20:1.

ee: 98%. Determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 10.73 min, τ_{minor} = 12.04 min.

$[\alpha]_D^{20}$: +40.7 (*c* = 0.66, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.74 (s, 1H, C**H**O), 7.59-7.48 (m, 2H, C_{arom}-**H**), 7.42-7.33 (m, 2H, C_{arom}-**H**), 7.32-7.26 (m, 3H, C_{arom}-**H**), 7.01-6.90 (m, 1H, C_{arom}-**H**), 6.83-6.74 (m, 1H, C_{arom}-**H**), 4.44 (app t, *J* = 10.0 Hz, 1H, **H**-2), 3.52 (s, 3H, OC**H**$_3$), 3.43 (d, *J* = 4.6 Hz, 1H, **H**-6), 3.04 (d, *J* = 4.6 Hz, 1H, **H**-5), 2.78 (dd, *J* = 18.5, 9.8 Hz, 1H, **H**-3$_a$), 2.65 (dd, *J* = 18.5, 10.3 Hz, 1H, **H**-3$_b$).

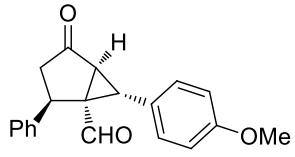
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 207.3 (**C**-4), 196.7 (**C**HO), 158.2, 139.6 ($\mathbf{C}_{arom}$-C), 129.7, 129.5, 128.2, 128.0, 127.0, 120.6 ($\mathbf{C}_{arom}$-H), 120.4 ($\mathbf{C}_{arom}$-C), 110.3 ($\mathbf{C}_{arom}$-H), 54.7 (O**C**H$_3$), 49.2 (**C**-1), 40.2 (**C**-3), 40.1 (**C**-5), 37.9 (**C**-2), 31.0 (**C**-6).

IR (ATR) cm^{-1}: 1732 (C=O st), 1702 (C=O st).

MS (EI) m/z (relative abundance): 306 (83), 289 (8), 277 (6), 264 (20), 247 (8), 235 (100), 220 (37), 202 (61), 187 (31), 174 (33), 159 (24), 145 (20), 128 (38), 115 (82), 103 (28), 91 (96), 77 (52), 65 (20), 51 (25).

HRMS: Calculated for $[C_{20}H_{17}O_3]^-$: 305.1178 $[M\text{-}H]^-$; found: 305.1175.

(1*S*,2*R*,5*S*,6*R*)-6-(4-methoxyphenyl)-4-oxo-2-phenylbicyclo[3.1.0]hexane-1-carbaldehyde (16c)



Following the general procedure, **16c** (19 mg, 0.062 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 6:4) as a yellow oil after 24 hours, starting from (*E*)-4-styryl-5*H*-1,2,3-oxathiazole 2,2-dioxide **15** (33 mg, 0.150 mmol) and (*E*)-4-methoxycinnamaldehyde **4l** (37 mg, 0.225 mmol) in the presence of DABCO (3 mg, 0.030 mmol), diphenyl-2-pyrrolidinemethanoltrimethylsilyl ether **5a** (10 mg, 0.030 mmol) and using dry $CHCl_3$ (0.3 mL) as solvent.

Yield: 41%.

dr: >20:1.

ee: 98%. Determined by HPLC using a Chiralpak AD-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 13.40 min, τ_{minor} = 11.95 min.

$[\alpha]_D^{20}$: +45.5 (*c* = 0.27, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 9.00 (s, 1H, C**H**O), 7.41-7.28 (m, 5H, C_{arom}-**H**), 7.18 (d, *J* = 8.6 Hz, 2H, C_{arom}-**H**), 6.87 (d, *J* = 8.6 Hz, 2H, C_{arom}-**H**), 4.42 (app t, *J* = 10.0 Hz, 1H, **H**-2), 3.80 (s, 3H, OC**H**$_3$), 3.39 (d, *J* = 4.6 Hz, 1H, **H**-6), 3.15 (d, *J* = 4.6 Hz, 1H, **H**-5), 2.86 (dd, *J* = 18.6, 9.9 Hz, 1H, **H**-3$_a$), 2.56 (dd, *J* = 18.6, 10.1 Hz, 1H, **H**-3$_b$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 206.9 (**C**-4), 196.8 (**C**HO), 159.3, 140.2 (**C**$_{arom}$-C), 129.7, 128.8, 127.3, 127.1 (**C**$_{arom}$-H), 123.4 (**C**$_{arom}$-C), 114.5 (**C**$_{arom}$-H), 55.3 (O**C**H_3), 50.2 (**C**-1), 40.5 (**C**-3), 40.5 (**C**-5), 37.3 (**C**-2), 34.7 (**C**-6).

IR (ATR) cm^{-1}: 1737 (C=O st), 1699 (C=O st).

MS (EI) m/z (relative abundance): 306 (75), 289 (6), 277 (25), 264 (21), 247 (10), 235 (100), 220 (31), 202 (62), 189 (23), 174 (46), 159 (22), 145 (55), 135 (13), 121 (94), 102 (30), 91 (44), 77 (48), 63 (16), 51 (20).

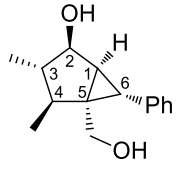
HRMS: Calculated for $[C_{20}H_{17}O_3]^-$: 305.1178 $[M-H]^-$; found: 305.1176.

2.13. Synthesis of diols 17a and 17p.

General procedure:

$NaBH_4$ (2.00 mmol) was added to a solution of the cyclopropane **8** (1.00 mmol) in MeOH (10 mL) at 0 ºC. The mixture was stirred at 0 ºC for 30 minutes, then a solution of saturated aqueous NH_4Cl (1 mL) was added to quench the reaction and it was stirred for another 5 minutes. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The obtained crude product was charged onto silica gel and subjected to flash chromatography (FC) with the indicated eluent, obtaining the desired diols **17a** and **17p**.

(1*S*,2*R*,3*S*,4*S*,5*S*,6*R*)-5-(Hydroxymethyl)-3,4-dimethyl-6-phenylbicyclo[3.1.0]hexan-2-ol (17a)



Following the general procedure, **17a** (17 mg, 0.072 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 1:1 to 3:7) as a yellow oil, starting from cyclopropane **8a** (17 mg, 0.075 mmol) and $NaBH_4$ (6 mg, 0.150 mmol) in MeOH (700 μL) at 0 ºC.

Yield: 96%.

dr: >20:1.

$[\alpha]_D^{20}$: -52.3 (*c* = 0.69, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.32-7.14 (m, 5H, C_{arom}-**H**), 4.05 (dd, *J* = 7.2, 4.9 Hz, 1H, **H**-2), 3.60 (d, *J* = 12.1 Hz, 1H, C**H**$_a$H$_b$OH), 3.27 (d, *J* = 12.1 Hz, 1H, CH$_a$**H**$_b$OH), 2.46 (d, *J* = 4.0 Hz, 1H, **H**-6), 2.11 (app t, *J* = 4.4 Hz, 1H, **H**-1), 2.01-1.86 (m, 1H, **H**-4), 1.45 (s, 2H, 2 × OH), 1.13 (d, *J* = 6.5 Hz, 3H, C-4C**H**$_3$), 1.11-1.02 (m, 4H, **H**-3+C-3C**H**$_3$).

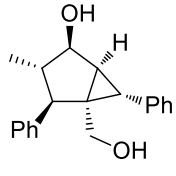
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 137.6 (**C**$_{arom}$-C), 128.6, 128.3, 126.2 (**C**$_{arom}$-H), 80.0 (**C**-2), 62.6 (**C**H$_2$OH), 45.2 (**C**-3), 42.1 (**C**-4), 40.4 (**C**-5), 31.8 (**C**-1), 24.7 (**C**-6), 16.0 (C-3**C**H$_3$), 15.0 (C-4**C**H$_3$).

IR (ATR) cm^{-1}: 3328 (O-H st).

MS (EI) m/z (relative abundance): 232 (1), 214 (14), 196 (32), 181 (46), 169 (49), 158 (35), 143 (56), 129 (73), 115 (58), 105 (24), 91 (100), 77 (41), 65 (17), 51 (19).

HRMS: Calculated for $[C_{15}H_{20}O_2Na]^+$: 255.1361 $[M+Na]^+$; found: 255.1362.

(1*S*,2*R*,3*S*,4*R*,5*R*,6*R*)-5-(Hydroxymethyl)-3-methyl-4,6-diphenylbicyclo[3.1.0]hexan-2-ol (17p)



Following the general procedure, **17p** (12 mg, 0.041 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 1:1 to 3:7) as a yellow solid, starting from cyclopropane **8p** (14 mg, 0.048 mmol) and $NaBH_4$ (4 mg, 0.095 mmol) in MeOH (500 μL) at 0 ºC.

Yield: 85%.

dr: >20:1.

ee: 92%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; τ_{major} = 23.27 min, τ_{minor} = 11.71 min.

$[\alpha]_D^{20}$: +4.8 (*c* = 0.68, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.47-7.16 (m, 10H, C_{arom}-**H**), 4.20 (dd, *J* = 8.1, 4.8 Hz, 1H, **H**-2), 3.51 (d, *J* = 12.0 Hz, 1H, C**H**$_a$H$_b$OH), 3.18 (d, *J* = 12.0 Hz, 1H, CH$_a$**H**$_b$OH), 3.10 (d, *J* = 10.8 Hz, 1H, **H**-4), 3.05 (d, *J* = 3.7 Hz, 1H, **H**-6), 2.19 (app t, *J* = 4.4 Hz, 1H, **H**-1), 1.89-1.52 (m, 3H, **H**-3+2 × O**H**), 1.06 (d, *J* = 6.5 Hz, 3H, C-3C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 141.0, 137.1 (**C**$_{arom}$-C), 128.8, 128.7, 128.3, 127.9, 127.0, 126.4 (**C**$_{arom}$-H), 79.6 (**C**-2), 61.9 (**C**H$_2$OH), 52.4 (**C**-4), 44.1 (**C**-3), 39.9 (**C**-5), 30.0 (**C**-1), 25.5 (**C**-6), 15.8 (C-3**C**H$_3$).

IR (ATR) cm^{-1}**:** 3304 (O-H st).

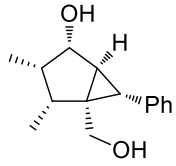
M.p. (hexanes/EtOAc) (ºC): 148-150.

MS (EI) m/z (relative abundance): 276 (8), 258 (35), 246 (39), 228 (19), 215 (29), 205 (21), 191 (14), 178 (17), 165 (50), 155 (33), 144 (32), 129 (83), 115 (72), 105 (23), 91 (100), 77 (37), 65 (14), 51 (19).

HRMS: Calculated for $[C_{20}H_{22}O_2Na]^+$: 317.1518 $[M+Na]^+$; found: 317.1512.

2.14. Synthesis of diol 18.

(1*S*,2*S*,3*S*,4*R*,5*S*,6*R*)-5-(Hydroxymethyl)-3,4-dimethyl-6-phenylbicyclo[3.1.0]hexan-2-ol (18)



L-Selectride 1 M in THF (122 μL, 0.122 mmol) was added to a solution of the cyclopropane **11a** (11 mg, 0.049 mmol) in dry THF (0.5 mL) at -78 ºC under inert atmosphere. The mixture was stirred at -78 ºC for 2.5 hours, then a solution of saturated aqueous NH_4Cl (1 mL) was added at -78 ºC to quench the reaction and it was stirred for another 5 minutes at room temperature. The mixture was extracted with AcOEt (3 × 5 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. After purification by flash column chromatography (FC) (hexanes/EtOAc gradient from 6:4 to 1:1) the diol **18** (11 mg, 0.046 mmol) was isolated as a yellow oil.

Yield: 93%.

dr: >20:1.

$[\alpha]_D^{20}$: -20.3 (*c* = 0.62, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.33-7.18 (m, 5H, C_{arom}-**H**), 4.14 (app d, *J* = 4.6 Hz, 1H, **H**-2), 3.91 (d, *J* = 12.1 Hz, 1H, C**H**$_a$H$_b$OH), 3.30 (d, *J* = 12.1 Hz, 1H, CH$_a$**H**$_b$OH), 2.42-2.28 (m, 1H, **H**-4), 2.21 (d, *J* = 3.9 Hz, 1H, **H**-6), 2.10-1.96 (m, 2H, **H**-1+**H**-3), 1.56 (s, 2H, 2 × OH), 1.13 (d, *J* = 7.4 Hz, 3H, C-4C**H**$_3$), 1.03 (d, *J* = 7.2 Hz, 3H, C-3C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 137.8 (**C**$_{arom}$-C), 128.5, 128.4, 126.2 (**C**$_{arom}$-H), 76.7 (**C**-2), 60.4 (**C**H_2OH), 43.0 (**C**-5), 38.6, 38.4 (**C**-3+**C**-4), 33.6 (**C**-1), 29.5 (**C**-6), 14.4 (C-4**C**H_3), 9.6 (C-3**C**H_3).

IR (ATR) cm^{-1}: 3368 (O-H st).

MS (EI) m/z (relative abundance): 214 (12), 196 (28), 181 (38), 169 (26), 158 (49), 143 (99), 129 (81), 115 (61), 105 (25), 91 (100), 77 (45), 65 (17), 51 (21).

HRMS: Calculated for $[C_{15}H_{20}O_2Na]^+$: 255.1361 $[M+Na]^+$; found: 255.1369.

3. ORGANOCATALYTIC APPROACH TO CHIRAL PROLINE DERIVATIVES

3.1. Synthesis of pyrrolidines 22a-r.

General procedure for the Michael addition/imine formation step:

The aminomalonate[11] **20** (0.56 mmol) was added to a solution of 9-*epi*-9-amino-9-deoxycinchonidine[12] **21a** (0.08 mmol, 20 mol%), the corresponding acid (0.16 mmol, 40 mol%), and α,β-unsaturated ketone **19** (0.40 mmol) in the indicated solvent (2 mL). The reaction was stirred at room temperature, following its evolution by ^{1}H-NMR. After consumption of the starting material, the solvent was removed obtaining the corresponding cyclic imine, which was reduced without further purification as follows. The racemic compounds for HPLC separation conditions were prepared under the same conditions, using in these cases benzhydrylamine (0.08 mmol, 20 mol%) instead of catalyst **21a**, followed by the reduction of the resulting imine.

General procedure for the reduction step:

$NaBH_3CN$ (0.80 mmol) was added to a solution of the crude cyclic imine in dry EtOH (15 mL) under inert atmosphere. The mixture was stirred at room temperature for 2 hours, HCl (1 M) was added till reaching an acidic pH and it was stirred for another 10 minutes. The solvent was removed under reduced

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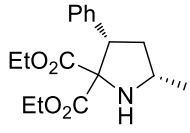
[11] The aminomalonate **20** was obtained from the commercially available ammonium salt (1.00 mmol) after dissolving in a solution of $NaHCO_3$ (1.00 mmol) in water (1 mL) and extracting with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were dried over $NaSO_4$, filtered and concentrated under vacuum, obtaining the corresponding amine.

[12] Oliva, C. G.; Silva, A. M. S.; Resende, D. I. S. P.; Paz, F. A. A.; Cavaleiro, J. A. S. *Eur. J. Org. Chem.* **2010**, 3449.

pressure and a saturated solution of NaCl (10 mL) was added, followed by the addition of NaOH (4 M) till a basic pH was observed, and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The pyrrolidines **22a-r** were obtained following this procedure, and purified by flash column chromatography (FC) with the indicated eluent.

(3*S*,5*S*)-Diethyl 5-methyl-3-phenylpyrrolidine-2,2-dicarboxylate (22a)



Following the general procedure, **22a** (110 mg, 0.36 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a colourless oil after 42 hours, starting from diethyl 2-aminomalonate **20a** (98 mg, 0.56 mmol) and (*E*)-4-phenylbut-3-en-2-one **19a** (59 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 89%.

dr: >20:1.

ee: 89%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 10.28 min, τ_{minor} = 9.42 min.

$[\alpha]_D^{20}$: -20.8 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.46-7.03 (m, 5H, C_{arom}-**H**), 4.41-4.25 (m, 2H, **H**-3+$CH_3C\mathbf{H}_aH_b$), 4.14 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_a\mathbf{H}_b$), 3.78 (dq, *J* = 10.6, 7.1 Hz, 1H, $CH_3C\mathbf{H}_cH_d$), 3.42 (dq, *J* = 10.6, 7.1 Hz, 1H, $CH_3CH_c\mathbf{H}_d$), 3.32-3.17 (m, 1H, **H**-5), 2.79 (bs, 1H, N**H**), 2.29 (ddd, *J* = 12.3, 7.0,

5.4 Hz, 1H, **H**-4$_a$), 1.82-1.67 (m, 1H, **H**-4$_b$), 1.35 (d, *J* = 6.1 Hz, 3H, C-5C**H**$_3$), 1.24 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 0.72 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$).

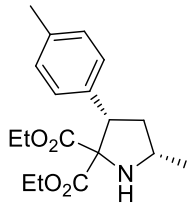
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 171.3, 170.3 (**C**O$_2$Et), 140.1 (**C**$_{arom}$-C), 128.6, 128.0, 126.9 (**C**$_{arom}$-H), 77.9 (**C**-2), 61.8, 61.5 (CH$_3$**C**H$_2$), 53.6 (**C**-5), 50.9 (**C**-3), 41.6 (**C**-4), 19.9 (C-5**C**H$_3$), 14.0, 13.3 (**C**H$_3$CH$_2$).

IR (ATR) cm^{-1}: 1723 (C=O st).

MS (EI) m/z (relative abundance): 232 (M^+ - CO_2Et, 100), 204 (8), 186 (2), 170 (1), 159 (11), 144 (9), 127 (11), 116 (43), 103 (3), 91 (8), 77 (3), 65 (1), 55 (4), 44 (1), 29 (6).

HRMS: Calculated for $[C_{17}H_{24}NO_4]^+$: 306.1705 $[M+H]^+$; found: 306.1706.

(3*S*,5*S*)-Diethyl 5-methyl-3-(*p*-tolyl)pyrrolidine-2,2-dicarboxylate (22b)



Following the general procedure, **22b** (89 mg, 0.28 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a colourless oil after 41 hours, starting from diethyl 2-aminomalonate **20a** (98 mg, 0.56 mmol) and (*E*)-4-(*p*-tolyl)but-3-en-2-one **19b** (64 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 70%.

dr: >20:1.

ee: 90%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 14.02 min, τ_{minor} = 12.50 min.

$[\alpha]_D^{20}$: -26.8 (*c* = 1.03, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.15 (d, *J* = 8.1 Hz, 2H, C_{arom}-**H**), 7.00 (d, *J* = 8.1 Hz, 2H, C_{arom}-**H**), 4.35-4.17 (m, 2H, **H**-3+$CH_3C\mathbf{H}_aH_b$), 4.09 (dq, *J* = 10.8, 7.1 Hz, 1H, $CH_3CH_a\mathbf{H}_b$), 3.74 (dq, *J* = 10.6, 7.1 Hz, 1H, $CH_3C\mathbf{H}_cH_d$), 3.41 (dq, *J* = 10.6, 7.1 Hz, 1H, $CH_3CH_c\mathbf{H}_d$), 3.27-3.11 (m, 1H, **H**-5), 2.74 (bs, 1H, N**H**), 2.29-2.14 (m, 4H, **H**-4_a+C_{arom}-C**H**$_3$), 1.75-1.60 (m, 1H, **H**-4_b), 1.29 (d, *J* = 6.1 Hz, 3H, C-5C**H**$_3$), 1.19 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 0.70 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$).

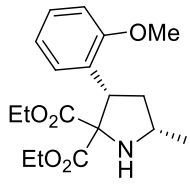
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 171.2, 170.4 (**C**O_2Et), 136.8, 136.3 (**C**$_{arom}$-C), 128.6, 128.4 (**C**$_{arom}$-H), 77.8 (**C**-2), 61.6, 61.3 (CH_3**C**H_2), 53.5 (**C**-5), 50.5 (**C**-3), 41.6 (**C**-4), 20.9 (C_{arom}-**C**H_3), 19.9 (C-5**C**H_3), 13.9, 13.2 (**C**H_3CH_2).

IR (ATR) cm^{-1}: 1724 (C=O st).

MS (EI) m/z (relative abundance): 246 (M^+ - CO_2Et, 100), 218 (4), 201 (6), 184 (1), 173 (13), 155 (13), 145 (5), 130 (38), 115 (55), 103 (4), 91 (5), 77 (3), 65 (1), 55 (4), 45 (1), 29 (5).

HRMS: Calculated for $[C_{18}H_{26}NO_4]^+$: 320.1862 $[M+H]^+$; found: 320.1862.

(3*S*,5*S*)-Diethyl 3-(2-methoxyphenyl)-5-methylpyrrolidine-2,2-dicarboxylate (22c)



Following the general procedure, **22c** (90 mg, 0.27 mmol) was isolated by FC (hexanes/EtOAc 8:2) as a colourless oil after 119 hours, starting from diethyl 2-aminomalonate **20a** (98 mg, 0.56

mmol) and (*E*)-4-(2-methoxyphenyl)but-3-en-2-one[13] **19c** (71 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 67%.

dr: >20:1.

ee: 89%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 4.90 min, τ_{minor} = 7.39 min.

$[\alpha]_D^{20}$: +1.0 (*c* = 1.03, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.24 (dd, *J* = 7.6, 1.7 Hz, 1H, C_{arom}-**H**), 7.14 (ddd, *J* = 8.2, 7.6, 1.7 Hz, 1H, C_{arom}-**H**), 6.87-6.81 (m, 1H, C_{arom}-**H**), 6.78 (dd, *J* = 8.2, 1.1 Hz, 1H, C_{arom}-**H**), 4.72 (dd, *J* = 9.8, 8.0 Hz, 1H, **H**-3), 4.30 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_aH_b$), 4.14 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_aH_b$), 3.86-3.71 (m, 4H, OCH_3+$CH_3CH_cH_d$), 3.48 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_cH_d$), 3.30-3.13 (m, 1H, **H**-5), 2.86 (bs, 1H, N**H**), 2.29 (ddd, *J* = 12.3, 8.0, 5.9 Hz, 1H, **H**-4_a), 1.76-1.62 (m, 1H, **H**-4_b), 1.31 (d, *J* = 6.2 Hz, 3H, C-5C**H**$_3$), 1.23 (t, *J* = 7.1 Hz, 3H, C**H**$_3$$CH_2$), 0.75 (t, *J* = 7.1 Hz, 3H, C**H**$_3$$CH_2$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 171.1, 169.8 (**C**O_2Et), 157.7, 129.8 (**C**$_{arom}$-C), 129.1, 127.8, 120.4, 110.3 (**C**$_{arom}$-H), 77.6 (**C**-2), 61.7, 61.1 (CH_3**C**H_2), 55.3 (O**C**H_3), 53.5 (**C**-5), 44.4 (**C**-3), 41.3 (**C**-4), 19.9 (C-5**C**H_3), 14.0, 13.4 (**C**H_3CH_2).

IR (ATR) cm^{-1}: 1731 (C=O st).

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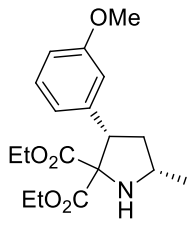
[13] McConville, M.; Saidi, O.; Blacker, J.; Xiao, J. *J. Org. Chem.* **2009**, *74*, 2692.

MS (EI) m/z (relative abundance): 262 (M^+ - CO_2Et, 100), 234 (1), 216 (32), 201 (30), 186 (5), 174 (5), 155 (11), 146 (13), 127 (14), 117 (5), 107 (3), 91 (9), 77 (4), 65 (1), 55 (4), 44 (1), 29 (4).

HRMS: Calculated for $[C_{18}H_{26}NO_5]^+$: 336.1811 $[M+H]^+$; found: 336.1800.

(3*S*,5*S*)-Diethyl 3-(3-methoxyphenyl)-5-methylpyrrolidine-2,2-dicarboxylate (22d)



Following the general procedure, **22d** (104 mg, 0.31 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a colourless oil after 68 hours, starting from diethyl 2-aminomalonate **20a** (98 mg, 0.56 mmol) and (*E*)-4-(3-methoxyphenyl)but-3-en-2-one[14] **19d** (71 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 77%.

dr: >20:1.

ee: 89%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 4.96 min, τ_{minor} = 6.91 min.

$[\alpha]_D^{20}$: -26.8 (*c* = 0.98, CH_2Cl_2).

[14] Feng, X.-W.; Li, C.; Wang, N.; Li, K.; Zhang, W.-W.; Wang, Z.; Yu, X.-Q. *Green Chem.* **2009**, *11*, 1933.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.30-7.21 (m, 1H, C_{arom}-**H**), 7.15 (ddd, *J* = 8.1, 7.5, 1.7 Hz, 1H, C_{arom}-**H**), 6.90-6.75 (m, 2H, C_{arom}-**H**), 4.73 (dd, *J* = 9.8, 8.0 Hz, 1H, **H**-3), 4.31 (dq, *J* = 10.8, 7.1 Hz, 1H, $CH_3C\mathbf{H}_aH_b$), 4.15 (dq, *J* = 10.8, 7.1 Hz, 1H, $CH_3CH_a\mathbf{H}_b$), 3.86-3.72 (m, 4H, $OC\mathbf{H}_3$+$CH_3C\mathbf{H}_cH_d$), 3.49 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_c\mathbf{H}_d$), 3.31-3.14 (m, 1H, **H**-5), 2.87 (bs, 1H, N**H**), 2.30 (ddd, *J* = 12.3, 8.0, 5.9 Hz, 1H, **H**-4_a), 1.78-1.62 (m, 1H, **H**-4_b), 1.32 (d, *J* = 6.2 Hz, 3H, C-5C$\mathbf{H}_3$), 1.24 (t, *J* = 7.1 Hz, 3H, $C\mathbf{H}_3CH_2$), 0.76 (t, *J* = 7.1 Hz, 3H, $C\mathbf{H}_3CH_2$).

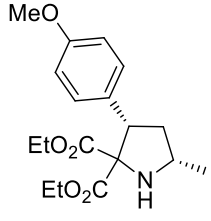
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 169.6, 168.7 (**C**O_2Et), 157.7, 140.1 (**C**$_{arom}$-C), 127.3, 119.2, 112.6, 111.0 (**C**$_{arom}$-H), 76.2 (**C**-2), 60.2, 59.9 ($CH_3\mathbf{C}H_2$), 53.5 ($O\mathbf{C}H_3$), 51.9 (**C**-5), 49.3 (**C**-3), 40.1 (**C**-4), 18.3 (C-5**C**H_3), 12.4, 11.7 (**C**H_3CH_2).

IR (ATR) cm^{-1}: 1724 (C=O st).

MS (EI) m/z (relative abundance): 262 (M^+ - CO_2Et, 100), 234 (4), 216 (2), 201 (3), 188 (8), 174 (6), 161 (5), 146 (30), 127 (9), 117 (6), 103 (2), 91 (5), 77 (3), 65 (1), 55 (3), 41 (1), 29 (4).

HRMS: Calculated for $[C_{18}H_{26}NO_5]^+$: 336.1811 $[M+H]^+$; found: 336.1794.

(3*S*,5*S*)-Diethyl 3-(4-methoxyphenyl)-5-methylpyrrolidine-2,2-dicarboxylate (22e)



Following the general procedure, **22e** (106 mg, 0.32 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a colourless oil after 41 hours, starting from diethyl 2-aminomalonate **20a** (98 mg, 0.56 mmol) and (*E*)-4-(4-methoxyphenyl)but-3-en-2-one **19e** (71 mg, 0.40 mmol) in the

presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 79%.

dr: >20:1.

ee: 89%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 5.14 min, τ_{minor} = 7.47 min.

$[\alpha]_D^{20}$: -28.6 (*c* = 0.99, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.19 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 6.74 (d, *J* = 8.7 Hz, 2H, C_{arom}-**H**), 4.36-4.16 (m, 2H, **H**-3+$CH_3C\mathbf{H}_aH_b$), 4.09 (dq, *J* = 10.8, 7.1 Hz, 1H, $CH_3CH_a\mathbf{H}_b$), 3.83-3.68 (m, 4H, $OC\mathbf{H}_3$+$CH_3C\mathbf{H}_cH_d$), 3.43 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_c\mathbf{H}_d$), 3.25-3.11 (m, 1H, **H**-5), 2.67 (bs, 1H, N**H**), 2.21 (ddd, *J* = 12.3, 7.0, 5.4 Hz, 1H, **H**-4_a), 1.74-1.59 (m, 1H, **H**-4_b), 1.29 (d, *J* = 6.1 Hz, 3H, C-5C$\mathbf{H}_3$), 1.19 (t, *J* = 7.1 Hz, 3H, $C\mathbf{H}_3CH_2$), 0.74 (t, *J* = 7.1 Hz, 3H, $C\mathbf{H}_3CH_2$).

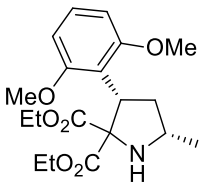
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 171.3, 170.4 ($\mathbf{C}O_2Et$), 158.6, 131.9 ($\mathbf{C}_{arom}$-C), 129.5, 113.3 ($\mathbf{C}_{arom}$-H), 77.7 (**C**-2), 61.7, 61.4 ($CH_3\mathbf{C}H_2$), 55.2 ($O\mathbf{C}H_3$), 53.4 (**C**-5), 50.1 (**C**-3), 41.6 (**C**-4), 19.9 (C-5$\mathbf{C}H_3$), 13.9, 13.4 ($\mathbf{C}H_3CH_2$).

IR (ATR) cm^{-1}: 1722 (C=O st).

MS (EI) m/z (relative abundance): 262 (M^+ - CO_2Et, 100), 234 (1), 216 (1), 201 (10), 189 (15), 174 (9), 155 (17), 146 (23), 127 (19), 115 (3), 103 (2), 91 (5), 77 (3), 65 (1), 55 (5), 42 (1), 19 (4).

HRMS: Calculated for $[C_{18}H_{26}NO_5]^+$: 336.1811 $[M+H]^+$; found: 336.1797.

(3*S*,5*S*)-Diethyl 3-(2,6-dimethoxyphenyl)-5-methylpyrrolidine-2,2-dicarboxylate (22f)



Following the general procedure, **22f** (92 mg, 0.25 mmol) was isolated by FC (hexanes/EtOAc 1:1) as a colourless oil after 97 hours, starting from diethyl 2-aminomalonate **20a** (98 mg, 0.56 mmol) and (*E*)-4-(2,6-dimethoxyphenyl)but-3-en-2-one[15] **19f** (82 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 63%.

dr: >20:1.

ee: 77%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 6.36 min, τ_{minor} = 5.27 min.

$[\alpha]_D^{20}$: -20.8 (*c* = 0.99, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.07 (t, *J* = 8.3 Hz, 1H, C_{arom}-**H**), 6.46 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 5.12 (app t, *J* = 9.0 Hz, 1H, **H**-3), 4.29 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3C\mathbf{H}_aH_b$), 4.11 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_a\mathbf{H}_b$), 3.83-3.70 (m, 7H, 2 × $OC\mathbf{H}_3$+$CH_3C\mathbf{H}_cH_d$), 3.59 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_c\mathbf{H}_d$), 3.24-3.07 (m, 1H, **H**-5), 2.93 (bs, 1H, N**H**), 2.17 (ddd, *J* = 12.0, 9.0, 6.7 Hz, 1H, **H**-4_a), 1.94-1.80 (m, 1H, **H**-4_b), 1.30 (d, *J* = 6.2 Hz, 3H, C-5C$\mathbf{H}_3$), 1.21 (t, *J* = 7.1 Hz, 3H, $C\mathbf{H}_3CH_2$), 0.74 (t, *J* = 7.1 Hz, 3H, $C\mathbf{H}_3CH_2$).

[15] Ballerini, E.; Minuti, L.; Piermatti, O. *J. Org. Chem.* **2010**, *75*, 4251.

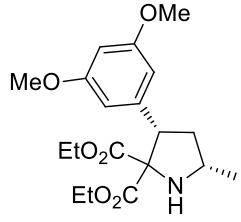
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 171.1, 169.1 (**C**O_2Et), 158.6 ($\mathbf{C}_{arom}$-C), 127.6 ($\mathbf{C}_{arom}$-H), 118.7 ($\mathbf{C}_{arom}$-C), 104.1 ($\mathbf{C}_{arom}$-H), 78.7 (**C**-2), 61.8, 60.8 ($CH_3\mathbf{C}H_2$), 56.0 ($O\mathbf{C}H_3$), 54.7 (**C**-5), 40.5 (**C**-3), 40.3 (**C**-4), 19.5 (C-5$\mathbf{C}H_3$), 14.0, 13.4 ($\mathbf{C}H_3CH_2$).

IR (ATR) cm^{-1}: 1731 (C=O st).

MS (EI) m/z (relative abundance): 292 (M^+ - CO_2Et, 100), 264 (11), 246 (13), 231 (23), 215 (7), 201 (5), 191 (3), 176 (10), 155 (10), 146 (4), 127 (11), 102 (2), 91 (4), 77 (2), 55 (3), 41 (1), 29 (3).

HRMS: Calculated for $[C_{19}H_{28}NO_6]^+$: 366.1917 $[M+H]^+$; found: 366.1901.

(3*S*,5*S*)-Diethyl 3-(3,5-dimethoxyphenyl)-5-methylpyrrolidine-2,2-dicarboxylate (22g)



Following the general procedure, **22g** (98 mg, 0.27 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a colourless oil after 29 hours, starting from diethyl 2-aminomalonate **20a** (98 mg, 0.56 mmol) and (*E*)-4-(3,5-dimethoxyphenyl)but-3-en-2-one[16] **19g** (82 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 67%.

dr: >20:1.

[16] Zumbansen, K.; Döhring, A.; List, B. *Adv. Synth. Catal.* **2010**, *352*, 1135.

ee: 87%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 5.91 min, τ_{minor} = 8.39 min.

$[\alpha]_D^{20}$: -27.4 (*c* = 1.01, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 6.47 (d, *J* = 2.3 Hz, 2H, C_{arom}-**H**), 6.29 (t, *J* = 2.3 Hz, 1H, C_{arom}-**H**), 4.32 (dq, *J* = 10.8, 7.1 Hz, 1H, $CH_3C\mathbf{H}_aH_b$), 4.22 (dd, *J* = 11.2, 7.0 Hz, 1H, **H**-3), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H, $CH_3CH_a\mathbf{H}_b$), 3.88-3.72 (m, 7H, 2 × $OC\mathbf{H}_3$+$CH_3C\mathbf{H}_cH_d$), 3.54 (dq, *J* = 10.6, 7.1 Hz, 1H, $CH_3CH_c\mathbf{H}_d$), 3.29-3.13 (m, 1H, **H**-5), 2.68 (bs, 1H, N**H**), 2.25 (ddd, *J* = 12.3, 7.0, 5.3 Hz, 1H, **H**-4_a), 1.76-1.59 (m, 1H, **H**-4_b), 1.32 (d, *J* = 6.1 Hz, 3H, C-5C$\mathbf{H}_3$), 1.23 (t, *J* = 7.1 Hz, 3H, $C\mathbf{H}_3CH_2$), 0.79 (t, *J* = 7.1 Hz, 3H, $C\mathbf{H}_3CH_2$).

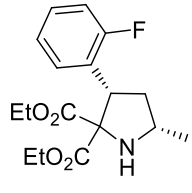
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 171.2, 170.4 ($\mathbf{C}O_2Et$), 160.4, 142.5 ($\mathbf{C}_{arom}$-C), 106.6, 99.2 ($\mathbf{C}_{arom}$-H), 77.7 (**C**-2), 61.8, 61.5 ($CH_3\mathbf{C}H_2$), 55.3 ($O\mathbf{C}H_3$), 53.6 (**C**-5), 51.1 (**C**-3), 41.7 (**C**-4), 19.9 (C-5$\mathbf{C}H_3$), 14.0, 13.4 ($\mathbf{C}H_3CH_2$).

IR (ATR) cm^{-1}: 1724 (C=O st).

MS (EI) m/z (relative abundance): 292 (M^+ - CO_2Et, 100), 246 (2), 218 (6), 204 (3), 191 (4), 176 (17), 155 (5), 127 (5), 109 (2), 91 (2), 77 (1), 55 (2), 41 (1), 29 (3).

HRMS: Calculated for $[C_{19}H_{28}NO_6]^+$: 366.1917 $[M+H]^+$; found: 366.1903.

(3*S*,5*S*)-Diethyl 3-(2-fluorophenyl)-5-methylpyrrolidine-2,2-dicarboxylate (22h)



Following the general procedure, **22h** (100 mg, 0.31 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a colourless oil after 42 hours, starting from diethyl 2-

aminomalonate **20a** (98 mg, 0.56 mmol) and (*E*)-4-(2-fluorophenyl)but-3-en-2-one[17] **19h** (66 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 78%.

dr: >20:1.

ee: 89%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 15.79 min, τ_{minor} = 13.19 min.

$[\alpha]_D^{20}$: -31.6 (*c* = 1.03, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.32 (dt, *J* = 7.6, 1.6 Hz, 1H, C_{arom}-**H**), 7.22-7.09 (m, 1H, C_{arom}-**H**), 7.09-6.89 (m, 2H, C_{arom}-**H**), 4.62 (dd, *J* = 9.6, 7.9 Hz, 1H, **H**-3), 4.30 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3C\mathbf{H}_aH_b$), 4.14 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_a\mathbf{H}_b$), 3.82 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3C\mathbf{H}_cH_d$), 3.54 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_c\mathbf{H}_d$), 3.32-3.15 (m, 1H, **H**-5), 2.84 (bs, 1H, N**H**), 2.35 (ddd, *J* = 12.8, 7.9, 6.0 Hz, 1H, **H**-4_a), 1.76-1.54 (m, 1H, **H**-4_b), 1.33 (d, *J* = 6.1 Hz, 3H, C-5C$\mathbf{H}_3$), 1.23 (t, *J* = 7.1 Hz, 3H, C$\mathbf{H}_3CH_2$), 0.80 (t, *J* = 7.1 Hz, 3H, C$\mathbf{H}_3CH_2$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 170.7, 169.6 (**C**O_2Et), 161.1 (d, $^1J_{CF}$ = 247.1 Hz, $\mathbf{C}_{arom}$-F), 129.8 (d, $^3J_{CF}$ = 4.1 Hz, $\mathbf{C}_{arom}$-H), 128.3 (d, $^3J_{CF}$ = 8.4 Hz, $\mathbf{C}_{arom}$-H), 128.1 (d, $^2J_{CF}$ = 13.9 Hz, $\mathbf{C}_{arom}$-C), 123.8 (d, $^4J_{CF}$ = 3.5 Hz, $\mathbf{C}_{arom}$-H), 115.0 (d, $^2J_{CF}$ = 23.1 Hz, $\mathbf{C}_{arom}$-H), 77.6 (**C**-2), 61.9, 61.4 ($CH_3\mathbf{C}H_2$), 53.3 (**C**-5), 43.0 (**C**-3), 41.7 (**C**-4), 19.9 (C-5**C**H_3), 14.0, 13.3 (**C**H_3CH_2).

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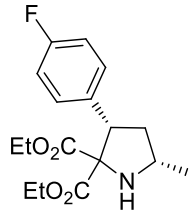
[17] Lin, Y.-M.; Li, Z.; Casarotto, V.; Ehrmantraut, J.; Nguyen, A. N. *Tetrahedron Lett.* **2007**, *48*, 5531.

IR (ATR) cm^{-1}: 1724 (C=O st).

MS (EI) m/z (relative abundance): 250 (M^+ - CO_2Et, 100), 222 (11), 201 (2), 190 (1), 176 (15), 162 (6), 149 (11), 134 (43), 109 (8), 96 (1), 81 (1), 68 (1), 55 (3), 29 (5).

HRMS: Calculated for $[C_{17}H_{23}NO_4F]^+$: 324.1611 $[M+H]^+$; found: 324.1601.

(3*S*,5*S*)-Diethyl 3-(4-fluorophenyl)-5-methylpyrrolidine-2,2-dicarboxylate (22i)



Following the general procedure, **22i** (95 mg, 0.29 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a colourless oil after 26 hours, starting from diethyl 2-aminomalonate **20a** (98 mg, 0.56 mmol) and (*E*)-4-(4-fluorophenyl)but-3-en-2-one[13] **19i** (66 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 74%.

dr: >20:1.

ee: 89%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (99:1)]; flow rate 1.0 mL/min; τ_{major} = 14.52 min, τ_{minor} = 13.65 min.

$[\alpha]_D^{20}$: -26.7 (*c* = 0.99, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.35-7.23 (m, 2H, C_{arom}-**H**), 7.00-6.86 (m, 2H, C_{arom}-**H**), 4.41-4.21 (m, 2H, **H**-3+$CH_3C\mathbf{H}_aH_b$), 4.14 (dq, *J* = 10.7, 7.1

Hz, 1H, $CH_3CH_a\mathbf{H}_b$), 3.81 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3C\mathbf{H}_cH_d$), 3.48 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_c\mathbf{H}_d$), 3.31-3.15 (m, 1H, **H**-5), 2.76 (bs, 1H, N**H**), 2.27 (ddd, *J* = 12.3, 7.0, 5.4 Hz, 1H, **H**-4_a), 1.77-1.54 (m, 1H, **H**-4_b), 1.33 (d, *J* = 6.1 Hz, 3H, C-5C$\mathbf{H}_3$), 1.23 (t, *J* = 7.1 Hz, 3H, C$\mathbf{H}_3CH_2$), 0.78 (t, *J* = 7.1 Hz, 3H, C$\mathbf{H}_3CH_2$).

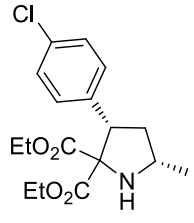
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 171.1, 170.2 (**C**O_2Et), 161.9 (d, $^1J_{CF}$ = 245.4 Hz, $\mathbf{C}_{arom}$-F), 135.8 (d, $^4J_{CF}$ = 3.2 Hz, $\mathbf{C}_{arom}$-C), 130.1 (d, $^3J_{CF}$ = 7.9 Hz, $\mathbf{C}_{arom}$-H), 114.7 (d, $^2J_{CF}$ = 21.1 Hz, $\mathbf{C}_{arom}$-H), 77.7 (**C**-2), 61.8, 61.5 ($CH_3\mathbf{C}H_2$), 53.4 (**C**-5), 50.0 (**C**-3), 41.7 (**C**-4), 19.9 (C-5**C**H_3), 13.9, 13.4 (**C**H_3CH_2).

IR (ATR) cm^{-1}: 1724 (C=O st).

MS (EI) m/z (relative abundance): 250 (M^+ - CO_2Et, 100), 222 (7), 201 (3), 188 (1), 177 (12), 155 (8), 134 (21), 127 (11), 109 (9), 88 (1), 55 (5), 44 (1), 29 (5).

HRMS: Calculated for $[C_{17}H_{23}NO_4F]^+$: 324.1611 $[M+H]^+$; found: 324.1599.

(3*S*,5*S*)-Diethyl 3-(4-chlorophenyl)-5-methylpyrrolidine-2,2-dicarboxylate (22j)



Following the general procedure, **22j** (104 mg, 0.31 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a colourless oil after 27 hours, starting from diethyl 2-aminomalonate **20a** (98 mg, 0.56 mmol) and (*E*)-4-(4-chlorophenyl)but-3-en-2-one **19j** (72 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent,

followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 78%.

dr: >20:1.

ee: 89%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 13.42 min, τ_{minor} = 12.14 min.

$[\alpha]_D^{20}$: -34.0 (*c* = 0.99, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.27-7.10 (m, 4H, C_{arom}-**H**), 4.35-4.16 (m, 2H, **H**-3+$CH_3C\mathbf{H}_aH_b$), 4.09 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_a\mathbf{H}_b$), 3.77 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3C\mathbf{H}_cH_d$), 3.46 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_c\mathbf{H}_d$), 3.27-3.12 (m, 1H, **H**-5), 2.73 (bs, 1H, N**H**), 2.23 (ddd, *J* = 12.3, 7.0, 5.4 Hz, 1H, **H**-4_a), 1.72-1.55 (m, 1H, **H**-4_b), 1.29 (d, *J* = 6.1 Hz, 3H, C-5C$\mathbf{H}_3$), 1.19 (t, *J* = 7.1 Hz, 3H, C$\mathbf{H}_3CH_2$), 0.74 (t, *J* = 7.1 Hz, 3H, C$\mathbf{H}_3CH_2$).

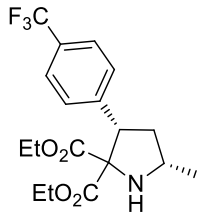
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 171.0, 170.1 (**C**O_2Et), 138.6, 132.6 (**C**$_{arom}$-C), 129.9, 128.0 (**C**$_{arom}$-H), 77.6 (**C**-2), 61.8, 61.5 ($CH_3\mathbf{C}H_2$), 53.4 (**C**-5), 50.1 (**C**-3), 41.4 (**C**-4), 19.9 (C-5**C**H_3), 14.0, 13.3 (**C**H_3CH_2).

IR (ATR) cm^{-1}: 1724 (C=O st).

MS (EI) m/z (relative abundance): 266 (M^+ - CO_2Et, 100), 238 (5), 220 (1), 193 (8), 178 (5), 165 (3), 150 (27), 138 (1), 127 (11), 115 (6), 103 (2), 89 (4), 78 (1), 55 (4), 29 (5).

HRMS: Calculated for $[C_{17}H_{23}NO_4Cl]^+$: 340.1316 $[M+H]^+$; found: 340.1313.

(3*S*,5*S*)-Diethyl 5-methyl-3-(4-(trifluoromethyl)phenyl)pyrrolidine-2,2-dicarboxylate (22k)



Following the general procedure, **22k** (79 mg, 0.21 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a colourless oil after 23 hours, starting from diethyl 2-aminomalonate **20a** (98 mg, 0.56 mmol) and (*E*)-4-(4-(trifluoromethyl)phenyl)but-3-en-2-one[16] **19k** (86 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 53%.

dr: >20:1.

ee: 87%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 5.58 min, τ_{minor} = 6.97 min.

$[\alpha]_D^{20}$: -23.4 (*c* = 1.03, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.64-7.36 (m, 4H, C_{arom}-**H**), 4.40-4.26 (m, 2H, **H**-3+$CH_3C\mathbf{H}_aH_b$), 4.14 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_a\mathbf{H}_b$), 3.77 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3C\mathbf{H}_cH_d$), 3.45 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_c\mathbf{H}_d$), 3.34-3.19 (m, 1H, **H**-5), 2.82 (bs, 1H, N**H**), 2.30 (ddd, *J* = 12.4, 7.1, 5.4 Hz, 1H, **H**-4_a), 1.79-1.65 (m, 1H, **H**-4_b), 1.34 (d, *J* = 6.1 Hz, 3H, C-5C$\mathbf{H}_3$), 1.23 (t, *J* = 7.1 Hz, 3H, C$\mathbf{H}_3CH_2$), 0.70 (t, *J* = 7.1 Hz, 3H, C$\mathbf{H}_3CH_2$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 171.0, 170.0 (**C**O_2Et), 144.4 ($\mathbf{C}_{arom}$-C), 129.3 (q, $^2J_{CF}$ = 32.5 Hz, $\mathbf{C}_{arom}$-CF_3), 129.0 ($\mathbf{C}_{arom}$-H), 124.8 (q, $^3J_{CF}$ = 3.7 Hz,

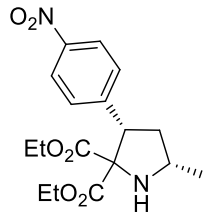
C$_{arom}$-H), 124.2 (q, $^{1}J_{CF}$ = 271.8 Hz, **C**F$_3$), 77.7 (**C**-2), 62.0, 61.6 (CH$_3$**C**H$_2$), 53.5 (**C**-5), 50.4 (**C**-3), 41.3 (**C**-4), 19.9 (C-5**C**H$_3$), 13.9, 13.2 (**C**H$_3$CH$_2$).

IR (ATR) cm^{-1}: 1727 (C=O st).

MS (EI) m/z (relative abundance): 300 (M$^+$ - CO$_2$Et, 100), 272 (13), 254 (1), 240 (1), 226 (14), 199 (15), 184 (35), 159 (5), 127 (6), 103 (1), 89 (1), 55 (4), 29 (5).

HRMS: Calculated for [C$_{18}$H$_{23}$NO$_4$F$_3$]$^+$: 374.1579 [M+H]$^+$; found: 374.1569.

(3*S*,5*S*)-Diethyl 5-methyl-3-(4-nitrophenyl)pyrrolidine-2,2-dicarboxylate (22l)



Following the general procedure, **22l** (98 mg, 0.28 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a colourless oil after 20 hours, starting from diethyl 2-aminomalonate **20a** (98 mg, 0.56 mmol) and (*E*)-4-(4-nitrophenyl)but-3-en-2-one[16] **19l** (77 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 70%.

dr: >20:1.

ee: 86%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 15.16 min, τ_{minor} = 19.05 min.

$[\alpha]_D^{20}$: -29.5 (*c* = 0.98, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.14-8.07 (m, 2H, C_{arom}-**H**), 7.54-7.48 (m, 2H, C_{arom}-**H**), 4.39-4.26 (m, 2H, **H**-3+$CH_3C\mathbf{H}_aH_b$), 4.16 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_a\mathbf{H}_b$), 3.82 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3C\mathbf{H}_cH_d$), 3.49 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_c\mathbf{H}_d$), 3.35-3.21 (m, 1H, **H**-5), 2.81 (bs, 1H, N**H**), 2.35 (ddd, *J* = 12.6, 7.2, 5.5 Hz, 1H, **H**-4_a), 1.77-1.63 (m, 1H, **H**-4_b), 1.34 (d, *J* = 6.1 Hz, 3H, C-5C$\mathbf{H}_3$), 1.24 (t, *J* = 7.1 Hz, 3H, C$\mathbf{H}_3CH_2$), 0.76 (t, *J* = 7.1 Hz, 3H, C$\mathbf{H}_3CH_2$).

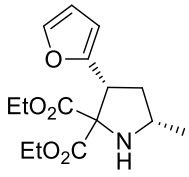
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 170.8, 169.6 (**C**O_2Et), 148.3, 146.9 (**C**$_{arom}$-C), 129.5, 128.1 (**C**$_{arom}$-H), 77.7 (**C**-2), 62.1, 61.7 ($CH_3\mathbf{C}H_2$), 53.4 (**C**-5), 50.2 (**C**-3), 41.4 (**C**-4), 20.0 (C-5**C**H_3), 14.0, 13.5 (**C**H_3CH_2).

IR (ATR) cm^{-1}**:** 1724 (C=O st), 1522 (NO_2 st as), 1343 (NO_2 st sym).

MS (EI) m/z (relative abundance): 277 (M^+ - CO_2Et, 100), 261 (1), 249 (8), 231 (3), 203 (6), 189 (2), 172 (1), 157 (11), 142 (5), 130 (5), 115 (8), 103 (2), 89 (3), 77 (2), 55 (2), 41 (1), 29 (4).

HRMS: Calculated for $[C_{17}H_{23}N_2O_6]^+$: 351.1556 $[M+H]^+$; found: 351.1542.

(3*R*,5*S*)-Diethyl 3-(furan-2-yl)-5-methylpyrrolidine-2,2-dicarboxylate (22m)



Following the general procedure, **22m** (94 mg, 0.32 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a colourless oil after 120 hours, starting from diethyl 2-aminomalonate **20a** (98 mg, 0.56 mmol) and (*E*)-4-(furan-2-yl)but-3-en-2-one **19m** (54 mg, 0.40 mmol) in the presence of trifluoroacetic acid (18 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol)

and using $CHCl_3$ (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 80%.

dr: >20:1.

ee: 86%. Determined by HPLC using a Chiralcel OZ-3 column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 8.99 min, τ_{minor} = 11.09 min.

$[\alpha]_D^{20}$: -26.4 (*c* = 1.01, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.29 (dd, *J* = 1.9, 0.7 Hz, 1H, C_{arom}-**H**), 6.25 (dd, *J* = 3.2, 1.9 Hz, 1H, C_{arom}-**H**), 6.14 (d, *J* = 3.2 Hz, 1H, C_{arom}-**H**), 4.41-4.28 (m, 2H, **H**-3+$CH_3C\mathbf{H}_aH_b$), 4.13 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_a\mathbf{H}_b$), 3.99 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3C\mathbf{H}_cH_d$), 3.71 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_c\mathbf{H}_d$), 3.29-3.16 (m, 1H, **H**-5), 2.80 (bs, 1H, N**H**), 2.24 (ddd, *J* = 12.3, 7.0, 5.4 Hz, 1H, **H**-4_a), 1.78-1.69 (m, 1H, **H**-4_b), 1.32 (d, *J* = 6.2 Hz, 3H, C-5C**H**$_3$), 1.24 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$), 0.99 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$).

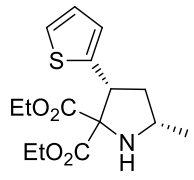
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 170.7, 170.3 (**C**O_2Et), 153.2 (**C**$_{arom}$-C), 141.5, 110.2, 107.1 (**C**$_{arom}$-H), 76.6 (**C**-2), 62.0, 61.9 ($CH_3\mathbf{C}H_2$), 53.8 (**C**-5), 45.1 (**C**-3), 39.8 (**C**-4), 19.9 (C-5**C**H_3), 13.9, 13.6 (**C**H_3CH_2).

IR (ATR) cm^{-1}: 1727 (C=O st).

MS (EI) m/z (relative abundance): 222 (M^+ - CO_2Et, 100), 201 (7), 176 (3), 149 (20), 127 (24), 106 (25), 91 (3), 79 (6), 67 (1), 55 (8), 41 (1), 29 (6).

HRMS: Calculated for $[C_{15}H_{22}NO_5]^+$: 296.1498 $[M+H]^+$; found: 296.1498.

(3*R*,5*S*)-Diethyl 5-methyl-3-(thiophen-2-yl)pyrrolidine-2,2-dicarboxylate (22n)



Following the general procedure, **22n** (101 mg, 0.32 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a yellow oil after 120 hours, starting from diethyl 2-aminomalonate **20a** (98 mg, 0.56 mmol) and (*E*)-4-(thiophen-2-yl)but-3-en-2-one **19n** (62 mg, 0.40 mmol) in the presence of trifluoroacetic acid (18 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol) and using $CHCl_3$ (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 81%.

dr: >20:1.

ee: 87%. Determined by HPLC using a Chiralcel OZ-3 column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 8.11 min, τ_{minor} = 10.00 min.

$[\alpha]_D^{20}$: -22.4 (*c* = 0.97, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.13 (dd, *J* = 5.0, 1.2 Hz, 1H, C_{arom}-**H**), 6.97-6.88 (m, 2H, C_{arom}-**H**), 4.51 (dd, *J* = 11.4, 6.7 Hz, 1H, **H**-3), 4.35 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3C\mathbf{H}_aH_b$), 4.17 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_a\mathbf{H}_b$), 3.89 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3C\mathbf{H}_cH_d$), 3.62 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_c\mathbf{H}_d$), 3.36-3.18 (m, 1H, **H**-5), 2.56 (bs, 1H, N**H**), 2.38 (ddd, *J* = 12.1, 6.7, 5.4 Hz, 1H, **H**-4_a), 1.84-1.71 (m, 1H, **H**-4_b), 1.34 (d, *J* = 6.2 Hz, 3H, C-5C$\mathbf{H}_3$), 1.26 (t, *J* = 7.1 Hz, 3H, C$\mathbf{H}_3CH_2$), 0.88 (t, *J* = 7.1 Hz, 3H, C$\mathbf{H}_3CH_2$).

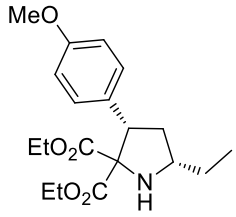
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 168.9, 168.2 (**C**O_2Et), 140.5 (**C**$_{arom}$-C), 124.3, 123.5, 121.9 (**C**$_{arom}$-H), 75.4 (**C**-2), 59.8, 59.7 (CH_3**C**H_2), 51.4 (**C**-5), 44.3 (**C**-3), 40.3 (**C**-4), 17.9 (C-5**C**H_3), 11.9, 11.4 (**C**H_3CH_2).

IR (ATR) cm^{-1}: 1724 (C=O st).

MS (EI) m/z (relative abundance): 238 (M^+ - CO_2Et, 100), 201 (8), 190 (1), 176 (1), 165 (18), 155 (20), 137 (4), 127 (24), 110 (4), 97 (7), 82 (3), 68 (2), 55 (8), 45 (4), 29 (6).

HRMS: Calculated for $[C_{15}H_{22}NO_4S]^+$: 312.1270 $[M+H]^+$; found: 312.1269.

(3*S*,5*S*)-Diethyl 5-ethyl-3-(4-methoxyphenyl)pyrrolidine-2,2-dicarboxylate (22o)



Following the general procedure, **22o** (92 mg, 0.26 mmol) was isolated by FC (hexanes/EtOAc 8:2) as a colourless oil after 168 hours, starting from diethyl 2-aminomalonate **20a** (98 mg, 0.56 mmol) and (*E*)-1-(4-methoxyphenyl)pent-1-en-3-one **19o** (76 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 65%.

dr: >20:1.

ee: 89%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 4.66 min, τ_{minor} = 6.86 min.

$[\alpha]_D^{20}$: -24.1 (*c* = 1.02, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.28-7.20 (m, 2H, C_{arom}-**H**), 6.81-6.74 (m, 2H, C_{arom}-**H**), 4.31 (dq, *J* = 10.8, 7.1 Hz, 1H, $CH_3C\mathbf{H}_aH_bO$), 4.23-4.08 (m, 2H, **H**-3+$CH_3CH_aH_bO$), 3.86-3.73 (m, 4H, $O\mathbf{CH}_3$+$CH_3C\mathbf{H}_cH_dO$), 3.50 (dq, *J* = 10.7, 7.2 Hz, 1H, $CH_3CH_c\mathbf{H}_dO$), 3.08-2.98 (m, 1H, **H**-5), 2.75 (bs, 1H, N**H**), 2.28 (ddd, *J* = 12.6, 7.3, 5.6 Hz, 1H, **H**-4_a), 1.87-1.72 (m, 1H, C-5$C\mathbf{H}_aH_b$), 1.70-1.66 (m, 1H, **H**-4_b), 1.64-1.48 (m, 1H, C-5$CH_a\mathbf{H}_b$), 1.23 (t, *J* = 7.1 Hz, 3H, $C\mathbf{H}_3CH_2O$), 0.97 (t, *J* = 7.5 Hz, 3H, C-5$CH_2C\mathbf{H}_3$), 0.78 (t, *J* = 7.1 Hz, 3H, $C\mathbf{H}_3CH_2O$).

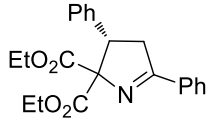
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 171.4, 170.4 ($\mathbf{C}O_2Et$), 158.6, 132.3 ($\mathbf{C}_{arom}$-C), 129.6, 113.3 ($\mathbf{C}_{arom}$-H), 77.4 (**C**-2), 61.7, 61.4 ($CH_3\mathbf{C}H_2O$), 59.5 ($O\mathbf{C}H_3$), 55.3 (**C**-5), 49.4 (**C**-3), 39.3 (**C**-4), 28.2 (C-5$\mathbf{C}H_2$), 14.0, 13.4 ($\mathbf{C}H_3CH_2O$), 11.4 (C-5$CH_2\mathbf{C}H_3$).

IR (ATR) cm^{-1}: 1722 (C=O st).

MS (EI) m/z (relative abundance): 276 (M^+ - CO_2Et, 100), 246 (1), 230 (1), 216 (1), 203 (7), 186 (2), 169 (16), 141 (13), 121 (3), 104 (1), 91 (3), 69 (3), 54 (1), 29 (4).

HRMS: Calculated for $[C_{19}H_{28}NO_5]^+$: 350.1967 $[M+H]^+$; found: 350.1948.

(3*S*)-Diethyl 3,5-diphenyl-3,4-dihydro-2*H*-pyrrole-2,2-dicarboxylate (22p)



Following the general procedure, **22p** (34 mg, 0.09 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) as a yellow oil after 192 hours, starting from diethyl 2-aminomalonate **20a** (74 mg, 0.42 mmol) and (*E*)-1,3-diphenylprop-2-en-1-one **19p** (62 mg, 0.30 mmol) in the presence of methanesulfonic acid (12 mg, 0.12 mmol),

9-*epi*-9-amino-9-deoxycinchonidine **21a** (18 mg, 0.06 mmol) and using THF (1.5 mL) as solvent.

Yield: 31%.

ee: 58%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (97:3)]; flow rate 1.0 mL/min; τ_{major} = 33.56 min, τ_{minor} = 24.49 min.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 8.02-7.96 (m, 2H, C_{arom}-**H**), 7.52-7.40 (m, 3H, C_{arom}-**H**), 7.27-7.17 (m, 5H, C_{arom}-**H**), 4.54 (dd, *J* = 9.0, 5.6 Hz, 1H, **H**-3), 4.40 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3C\mathbf{H}_aH_b$), 4.21 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3CH_a\mathbf{H}_b$), 3.81 (dq, *J* = 10.7, 7.1 Hz, 1H, $CH_3C\mathbf{H}_cH_d$), 3.71-3.54 (m, 2H, $CH_3CH_c\mathbf{H}_d$+**H**-4_a), 3.40 (dd, *J* = 17.4, 5.6 Hz, 1H, **H**-4_b), 1.30 (t, *J* = 7.1 Hz, 3H, $C\mathbf{H}_3CH_2$), 0.84 (t, *J* = 7.1 Hz, 3H, $C\mathbf{H}_3CH_2$).

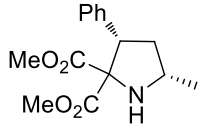
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 177.6 (**C**-5), 168.9, 167.5 (**C**O_2Et), 139.5, 133.1 (**C**$_{arom}$-C), 131.5, 128.4, 128.3, 128.2, 128.1, 127.2 (**C**$_{arom}$-H), 91.5 (**C**-2), 62.1, 61.1 ($CH_3\mathbf{C}H_2$), 48.3 (**C**-3), 43.6 (**C**-4), 13.9, 13.4 (**C**H_3CH_2).

IR (ATR) cm^{-1}: 1729 (C=O st).

MS (EI) m/z (relative abundance): 365 (1), 292 (M^+ - CO_2Et, 100), 246 (12), 233 (15), 219 (37), 191 (11), 187 (90), 165 (4), 140 (4), 115 (24), 105 (62), 91 (7), 77 (17), 65 (2).

HRMS: Calculated for $[C_{22}H_{24}NO_4]^+$: 366.1705 $[M+H]^+$; found: 306.1701.

(3*S*,5*S*)-Dimethyl 5-methyl-3-phenylpyrrolidine-2,2-dicarboxylate (22q)



Following the general procedure, **22q** (101 mg, 0.37 mmol) was isolated by FC (hexanes/EtOAc 8:2) as a colourless oil after 41 hours, starting from dimethyl 2-aminomalonate **20b**

(82 mg, 0.56 mmol) and (*E*)-4-phenylbut-3-en-2-one **19a** (59 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 91%.

dr: >20:1.

ee: 90%. Determined by HPLC using a Chiralpak IA column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 11.86 min, τ_{minor} = 10.17 min.

$[\alpha]_D^{20}$: -28.0 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.33-7.07 (m, 5H, C_{arom}-**H**), 4.30 (dd, *J* = 11.3, 7.1 Hz, 1H, **H**-3), 3.75 (s, 3H, C**H**$_3$O), 3.30-3.17 (m, 1H, **H**-5), 3.12 (s, 3H, C**H**$_3$O), 2.80 (bs, 1H, N**H**), 2.35-2.21 (m, 1H, **H**-4_a), 1.80-1.69 (m, 1H, **H**-4_b), 1.34 (d, *J* = 6.1 Hz, 3H, C-5C**H**$_3$).

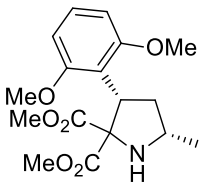
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 171.8, 170.7 (**C**O_2Me), 139.7 (**C**$_{arom}$-C), 128.4, 128.1, 127.0 (**C**$_{arom}$-H), 78.1 (**C**-2), 53.9 (**C**-5), 53.1, 52.3 (**C**H_3O), 51.3 (**C**-3), 41.5 (**C**-4), 19.8 (C-5**C**H_3).

IR (ATR) cm^{-1}: 1727 (C=O st).

MS (EI) m/z (relative abundance): 218 (M^+ - CO_2Me, 100), 184 (2), 173 (6), 158 (11), 141 (18), 131 (9), 116 (47), 103 (3), 91 (8), 77 (4), 68 (3), 59 (4), 42 (3), 28 (2).

HRMS: Calculated for $[C_{15}H_{20}NO_4]^+$: 278.1392 $[M+H]^+$; found: 278.1380.

(3*S*,5*S*)-Dimethyl 3-(2,6-dimethoxyphenyl)-5-methylpyrrolidine-2,2-dicarboxylate (22r)



Following the general procedure, **22r** (91 mg, 0.27 mmol) was isolated by FC (hexanes/EtOAc gradient from 6:4 to 4:6) as a white solid after 72 hours, starting from dimethyl 2-aminomalonate **20b** (98 mg, 0.56 mmol) and (*E*)-4-(2,6-dimethoxyphenyl)but-3-en-2-one **19f** (82 mg, 0.40 mmol) in the presence of methanesulfonic acid (15 mg, 0.16 mmol), 9-*epi*-9-amino-9-deoxycinchonidine **21a** (23 mg, 0.08 mmol) and using THF (2 mL) as solvent, followed by the reduction using sodium cyanoborohydride (50 mg, 0.80 mmol) and EtOH as solvent (15 mL).

Yield: 67%.

dr: >20:1.

ee: 80%. Determined by HPLC using a Chiralpak AS-H column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 7.71 min, τ_{minor} = 6.47 min.

$[\alpha]_D^{20}$: -17.5 (*c* = 0.66, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.11 (t, *J* = 8.3 Hz, 1H, C_{arom}-**H**), 6.50 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 5.18-5.12 (m, 1H, **H**-3), 3.78 (s, 6H, 2 × C_{arom}-O**C**$\mathbf{H}_3$), 3.76 (s, 3H, CO_2**C**$\mathbf{H}_3$), 3.25-3.14 (m, 4H, CO_2**C**$\mathbf{H}_3$+**H**-5), 2.18 (ddd, *J* = 12.0, 9.1, 6.6 Hz, 1H, **H**-4_a), 1.93 (ddd, *J* = 12.0, 10.4, 9.1 Hz, 1H, **H**-4_b), 1.33 (d, *J* = 6.2 Hz, 3H, C-5**C**$\mathbf{H}_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 171.6, 169.7 (**C**O_2Me), 158.5 (**C**$_{arom}$-C), 127.7 (**C**$_{arom}$-H), 118.2 (**C**$_{arom}$-C), 104.1 (**C**$_{arom}$-H), 78.7 (**C**-2), 55.6

(C_{arom}-O**C**H_3), 54.8 (**C**-5), 53.2, 51.8 (CO_2**C**H_3), 40.9 (**C**-3), 40.0 (**C**-4), 19.5 (C-5**C**H_3).

IR (ATR) cm^{-1}: 1727 (C=O st).

M.p. (hexanes/EtOAc) (ºC): 118-120.

MS (EI) m/z (relative abundance): 278 (M^+ - CO_2Me, 100), 246 (11), 231 (22), 216 (8), 204 (3), 191 (4), 176 (11), 161 (3), 141 (25), 113 (20), 91 (16), 77 (3), 59 (3), 42 (2), 28 (1).

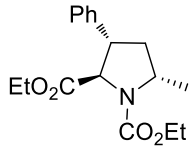
HRMS: Calculated for $[C_{17}H_{24}NO_6]^+$: 338.1604 $[M+H]^+$; found: 338.1595.

3.2. Synthesis of prolines 23a-o and 23q-r.

General procedure:

MeLi (1.00 mmol) was added dropwise to a solution of the corresponding pyrrolidine **22** (1.00 mmol) in dry THF (10 mL) at -78 ºC under inert atmosphere. The reaction was stirred during 1 hour at -78 ºC and then the reaction was quenched with the dropwise addition of water (1 mL) at -78 ºC. The reaction mixture was warmed to room temperature, subsequently brine (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The obtained crude product was charged onto silica gel and subjected to flash column chromatography (FC) yielding the desired product **23**.

(2*R*,3*S*,5*S*)-Diethyl 5-methyl-3-phenylpyrrolidine-1,2-dicarboxylate (23a)



Following the general procedure, **23a** (44 mg, 0.14 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22a** (52 mg, 0.17 mmol) and methyllithium (0.12 mL of a 1.46 M solution in diethyl ether, 0.17 mmol), using dry THF (1.7 mL) as solvent.

Yield: 84%.

dr: 7:1.

$[\alpha]_D^{20}$: -51.2 (*c* = 0.44, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.4:1, *denotes minor rotamer signals): 7.36-7.23 (m, 5H, C_{arom}-**H**), 4.51* (d, *J* = 6.2 Hz, 1H, **H**-2), 4.43 (d, *J* = 6.6 Hz, 1H, **H**-2), 4.25-4.03 (m, 5H, C-2$CO_2C\mathbf{H}_2CH_3$+$NCO_2C\mathbf{H}_2CH_3$+**H**-5), 3.48-3.31 (m, 1H, **H**-3), 2.66-2.43 (m, 1H, **H**-4_a), 1.90-1.74 (m, 1H, **H**-4_b), 1.40-1.14 (m, 9H, C-2$CO_2CH_2C\mathbf{H}_3$+$NCO_2CH_2C\mathbf{H}_3$+C-5C$\mathbf{H}_3$).

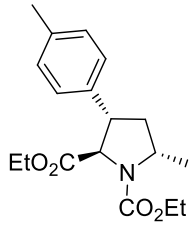
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 172.6, 172.2* (C-2**C**O_2Et), 155.4*, 154.5 (N**C**O_2Et), 140.7, 140.6* (**C**$_{arom}$-C), 128.7, 127.1, 127.1 (**C**$_{arom}$-H), 66.7, 66.4* (**C**-2), 61.4*, 61.0, 60.9 (C-2$CO_2\mathbf{C}H_2CH_3$+$NCO_2\mathbf{C}H_2CH_3$), 55.1, 54.2* (**C**-5), 47.9, 47.1* (**C**-3), 41.7*, 41.4 (**C**-4), 21.5*, 20.3 (C-5**C**H_3), 14.6*, 14.5, 14.2, 14.1* (C-2$CO_2CH_2\mathbf{C}H_3$+$NCO_2CH_2\mathbf{C}H_3$).

IR (ATR) cm^{-1}: 1742 (C=O st), 1708 (NC=O st).

MS (EI) m/z (relative abundance): 305 (1), 260 (1), 232 (M^+ - CO_2Et, 100), 216 (2), 204 (10), 188 (12), 172 (1), 160 (29), 144 (4), 129 (7), 117 (16), 104 (3), 91 (9), 77 (2), 55 (2).

HRMS: Calculated for $[C_{17}H_{24}NO_4]^+$: 306.1705 $[M+H]^+$; found: 306.1699.

(2*R*,3*S*,5*S*)-Diethyl 5-methyl-3-(*p*-tolyl)pyrrolidine-1,2-dicarboxylate (23b)



Following the general procedure, **23b** (26 mg, 0.08 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22b** (32 mg, 0.10 mmol) and methyllithium (0.07 mL of a 1.48 M solution in diethyl ether, 0.10 mmol), using dry THF (1.0 mL) as solvent.

Yield: 80%.

dr: 10:1.

$[\alpha]_D^{20}$: -63.2 (*c* = 0.61, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.4:1, *denotes minor rotamer signals): 7.19-7.09 (m, 4H, C_{arom}-**H**), 4.47* (d, *J* = 6.7 Hz, 1H, **H**-2), 4.40 (d, *J* = 6.9 Hz, 1H, **H**-2), 4.26-4.00 (m, 5H, C-2$CO_2C\mathbf{H}_2CH_3$+$NCO_2C\mathbf{H}_2CH_3$+**H**-5), 3.41-3.30 (m, 1H, **H**-3), 2.63-2.42 (m, 1H, **H**-4_a), 2.33 (s, 3H, C_{arom}-$C\mathbf{H}_3$), 1.90-1.69 (m, 1H, **H**-4_b), 1.42-1.13 (m, 9H, C-2$CO_2CH_2C\mathbf{H}_3$+$NCO_2CH_2C\mathbf{H}_3$+C-5$C\mathbf{H}_3$).

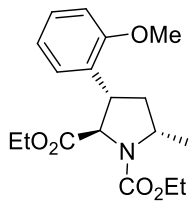
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 172.6, 172.3* (C-2$\mathbf{C}O_2$Et), 155.4*, 154.5 (N$\mathbf{C}O_2$Et), 137.6, 137.5*, 136.8, 136.7* ($\mathbf{C}_{arom}$-C), 129.3, 127.0 ($\mathbf{C}_{arom}$-H), 66.8, 66.5* (**C**-2), 61.3*, 61.0, 60.9 (C-2$CO_2\mathbf{C}H_2CH_3$+$NCO_2\mathbf{C}H_2CH_3$), 55.1, 54.2* (**C**-5), 47.6, 46.7* (**C**-3), 41.8*, 41.5 (**C**-4), 21.5* (C-5$\mathbf{C}H_3$), 21.0 (C_{arom}-$\mathbf{C}H_3$), 20.3 (C-5$\mathbf{C}H_3$), 14.6*, 14.5, 14.2, 14.1* (C-2$CO_2CH_2\mathbf{C}H_3$+$NCO_2CH_2\mathbf{C}H_3$).

IR (ATR) cm^{-1}: 1743 (C=O st), 1710 (NC=O st).

MS (EI) m/z (relative abundance): 319 (2), 246 (M^+ - CO_2Et, 100), 230 (4), 218 (11), 202 (12), 186 (1), 174 (29), 158 (5), 145 (5), 131 (20), 117 (7), 105 (6), 91 (7), 77 (2), 55 (2).

HRMS: Calculated for $[C_{18}H_{26}NO_4]^+$: 320.1862 $[M+H]^+$; found: 320.1852.

(2*R*,3*S*,5*S*)-Diethyl 3-(2-methoxyphenyl)-5-methylpyrrolidine-1,2-dicarboxylate (23c)



Following the general procedure, **23c** (30 mg, 0.09 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22c** (38 mg, 0.12 mmol) and methyllithium (0.08 mL of a 1.40 M solution in diethyl ether, 0.12 mmol), using dry THF (1.2 mL) as solvent.

Yield: 78%.

dr: >20:1.

$[\alpha]_D^{20}$: -54.0 (*c* = 1.20, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.4:1, *denotes minor rotamer signals): 7.29-7.19 (m, 2H, C_{arom}-**H**), 6.95-6.90 (m, 1H, C_{arom}-**H**), 6.86 (d, *J* = 8.1 Hz, 1H, C_{arom}-**H**), 4.63* (d, *J* = 5.4 Hz, 1H, **H**-2), 4.51 (d, *J* = 5.9 Hz, 1H, **H**-2), 4.27-4.01 (m, 5H, C-2$CO_2C\mathbf{H}_2CH_3$+$NCO_2C\mathbf{H}_2CH_3$+**H**-5), 3.82 (s, 3H, $OC\mathbf{H}_3$), 3.77-3.65 (m, 1H, **H**-3), 2.62-2.41 (m, 1H, **H**-4_a), 1.86-1.72 (m, 1H, **H**-4_b), 1.35-1.14 (m, 9H, C-2$CO_2CH_2C\mathbf{H}_3$+$NCO_2CH_2C\mathbf{H}_3$+C-5$C\mathbf{H}_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 172.8, 172.5* (C-2$\mathbf{C}O_2$Et), 157.0 ($\mathbf{C}_{arom}$-C), 155.6*, 154.7 ($N\mathbf{C}O_2$Et), 129.3*, 129.1 ($\mathbf{C}_{arom}$-C), 128.1, 128.0*, 127.1, 120.5, 120.4*, 110.5, 110.4* ($\mathbf{C}_{arom}$-H),

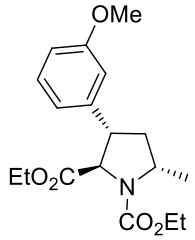
65.2, 65.0* (**C**-2), 61.3*, 60.9, 60.8 (C-2CO_2**C**H_2CH_3+NCO_2**C**H_2CH_3), 55.2 (O**C**H_3), 55.0, 54.1* (**C**-5), 41.8, 41.1* (**C**-3), 39.7*, 39.3 (**C**-4), 21.7*, 20.6 (C-5**C**H_3), 14.6*, 14.5, 14.2, 14.1* (C-2CO_2CH_2**C**H_3+NCO_2CH_2**C**H_3).

IR (ATR) cm^{-1}: 1743 (C=O st), 1705 (NC=O st).

MS (EI) m/z (relative abundance): 335 (7), 289 (4), 262 (M^+ - CO_2Et, 100), 246 (3), 233 (5), 218 (8), 203 (1), 190 (34), 174 (5), 161 (5), 147 (11), 131 (8), 115 (5), 91 (14), 77 (3), 55 (2).

HRMS: Calculated for $[C_{18}H_{26}NO_5]^+$: 336.1811 $[M+H]^+$; found: 336.1808.

(2*R*,3*S*,5*S*)-Diethyl 3-(3-methoxyphenyl)-5-methylpyrrolidine-1,2-dicarboxylate (23d)



Following the general procedure, **23d** (14 mg, 0.04 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22d** (18 mg, 0.05 mmol) and methyllithium (0.04 mL of a 1.53 M solution in diethyl ether, 0.05 mmol), using dry THF (0.5 mL) as solvent.

Yield: 77%.

dr: >20:1.

$[\alpha]_D^{20}$: -47.5 (*c* = 0.99, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.4:1, *denotes minor rotamer signals): 7.28-7.20 (m, 1H, C_{arom}-**H**), 6.85 (d, *J* = 7.7 Hz, 1H, C_{arom}-**H**), 6.82-6.75 (m, 2H, C_{arom}-**H**), 4.49* (d, *J* = 6.6 Hz, 1H, **H**-2), 4.43 (d, *J* = 6.8 Hz, 1H, **H**-2), 4.26-4.01 (m, 5H, C-2CO_2C**H**$_2CH_3$+NCO_2C**H**$_2CH_3$+**H**-5), 3.80 (s, 3H,

OC**H**$_3$), 3.41-3.32 (m, 1H, **H**-3), 2.62-2.47 (m, 1H, **H**-4$_a$), 1.90-1.71 (m, 1H, **H**-4$_b$), 1.45-1.11 (m, 9H, C-2$CO_2CH_2CH_3$+$NCO_2CH_2CH_3$+C-5C**H**$_3$).

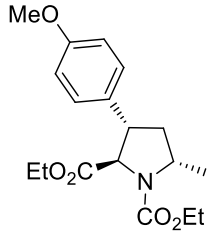
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 172.6, 172.2* (C-2**C**O_2Et), 159.8 (**C**$_{arom}$-C), 155.4*, 154.5 (N**C**O_2Et), 142.4, 142.3* (**C**$_{arom}$-C), 129.6, 119.4, 113.3, 113.2*, 112.1 (**C**$_{arom}$-H), 66.6, 66.4* (**C**-2), 61.4*, 61.1, 61.0, 60.9* (C-2CO_2**C**H_2CH_3+NCO_2**C**H_2CH_3), 55.2 (O**C**H_3), 55.0, 54.2* (**C**-5), 47.8, 47.0* (**C**-3), 41.7*, 41.3 (**C**-4), 21.5*, 20.4 (C-5**C**H_3), 14.6*, 14.5, 14.2, 14.1* (C-2CO_2CH_2**C**H_3+NCO_2CH_2**C**H_3).

IR (ATR) cm^{-1}: 1742 (C=O st), 1705 (NC=O st).

MS (EI) m/z (relative abundance): 335 (1), 262 (M^+ - CO_2Et, 100), 246 (4), 234 (5), 218 (7), 206 (2), 190 (18), 174 (2), 162 (3), 147 (6), 134 (3), 121 (3), 103 (1), 91 (4), 78 (1), 65 (1).

HRMS: Calculated for $[C_{18}H_{26}NO_5]^+$: 336.1811 $[M+H]^+$; found: 336.1798.

(2*R*,3*S*,5*S*)-Diethyl 3-(4-methoxyphenyl)-5-methylpyrrolidine-1,2-dicarboxylate (23e)



Following the general procedure, **23e** (52 mg, 0.16 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22e** (71 mg, 0.21 mmol) and methyllithium (0.16 mL of a 1.35 M solution in diethyl ether, 0.21 mmol), using dry THF (2.1 mL) as solvent.

Yield: 73%.

dr: 6:1.

$[\alpha]_D^{20}$: -57.4 (*c* = 1.04, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.4:1, *denotes minor rotamer signals): 7.17 (d, *J* = 8.6 Hz, 2H, C_{arom}-**H**), 6.86 (d, *J* = 8.6 Hz, 2H, C_{arom}-**H**), 4.43* (d, *J* = 6.8 Hz, 1H, **H**-2), 4.35 (d, *J* = 6.9 Hz, 1H, **H**-2), 4.26-4.01 (m, 5H, C-2$CO_2C\mathbf{H}_2CH_3$+$NCO_2C\mathbf{H}_2CH_3$+**H**-5), 3.79 (s, 3H, $OC\mathbf{H}_3$), 3.39-3.29 (m, 1H, **H**-3), 2.60-2.41 (m, 1H, **H**-4_a), 1.87-1.69 (m, 1H, **H**-4_b), 1.43-1.13 (m, 9H, C-2$CO_2CH_2C\mathbf{H}_3$+$NCO_2CH_2C\mathbf{H}_3$+C-5$C\mathbf{H}_3$).

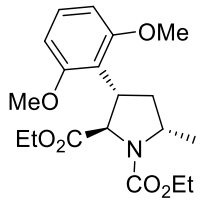
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 172.6, 172.2* (C-2$\mathbf{C}O_2$Et), 158.7 ($\mathbf{C}_{arom}$-C), 155.4*, 154.4 ($N\mathbf{C}O_2$Et), 132.5, 132.4* ($\mathbf{C}_{arom}$-C), 128.1, 114.0 ($\mathbf{C}_{arom}$-H), 67.0, 66.7* (**C**-2), 61.3*, 61.0, 60.9 (C-2$CO_2\mathbf{C}H_2CH_3$+$NCO_2\mathbf{C}H_2CH_3$), 55.3 ($O\mathbf{C}H_3$), 55.0, 54.1* (**C**-5), 47.2, 46.4* (**C**-3), 41.9*, 41.6 (**C**-4), 21.5*, 20.3 (C-5$\mathbf{C}H_3$), 14.6*, 14.5, 14.2, 14.1* (C-2$CO_2CH_2\mathbf{C}H_3$+$NCO_2CH_2\mathbf{C}H_3$).

IR (ATR) cm^{-1}: 1742 (C=O st), 1705 (NC=O st).

MS (EI) m/z (relative abundance): 335 (5), 262 (M^+ - CO_2Et, 100), 246 (2), 233 (9), 218 (6), 206 (5), 190 (17), 174 (3), 161 (5), 147 (15), 134 (5), 116 (9), 103 (2), 91 (7), 77 (2), 55 (2).

HRMS: Calculated for $[C_{18}H_{26}NO_5]^+$: 336.1811 $[M+H]^+$; found: 336.1795.

(2*R*,3*S*,5*S*)-Diethyl 3-(2,6-dimethoxyphenyl)-5-methylpyrrolidine-1,2-dicarboxylate (23f)



Following the general procedure, **23f** (32 mg, 0.09 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22f** (44 mg, 0.12 mmol) and methyllithium (0.09 mL of a 1.31 M solution in diethyl ether, 0.12 mmol), using dry THF (1.2 mL) as solvent.

Yield: 73%.

dr: 3:1.

$[\alpha]_D^{20}$: +54.6 (*c* = 1.01, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.3:1, *denotes minor rotamer signals): 7.16 (t, *J* = 8.3 Hz, 1H, C_{arom}-**H**), 6.50 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 4.62* (d, *J* = 8.5 Hz, 1H, **H**-2), 4.48 (d, *J* = 8.6 Hz, 1H, **H**-2), 4.29-3.78 (m, 6H, C-2$CO_2C\mathbf{H}_2CH_3$+$NCO_2C\mathbf{H}_2CH_3$+**H**-5+**H**-3), 3.75 (s, 6H, 2 × O**CH**$_3$), 2.96-2.72 (m, 1H, **H**-4_a), 2.21-1.96 (m, 1H, **H**-4_b), 1.55-1.50 (m, 3H, C-5**CH**$_3$), 1.29* (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$), 1.19 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$), 0.98 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$), 0.91* (t, *J* = 7.1 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$).

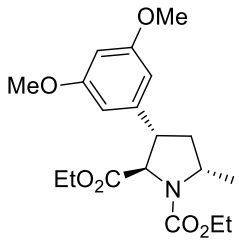
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 171.4*, 171.3 (C-2**C**O_2Et), 159.6 (**C**$_{arom}$-C), 155.6*, 154.7 (N**C**O_2Et), 128.3, 128.2* (**C**$_{arom}$-H), 112.7*, 112.6 (**C**$_{arom}$-C), 103.8 (**C**$_{arom}$-H), 62.8*, 62.5 (**C**-2), 61.0*, 60.8, 60.2 (C-2$CO_2\mathbf{C}H_2CH_3$+$NCO_2\mathbf{C}H_2CH_3$), 55.4 (O**C**H_3), 54.5, 54.0* (**C**-5), 38.0, 37.8* (**C**-3), 35.8*, 35.1 (**C**-4), 21.2*, 20.1 (C-5**C**H_3), 14.6, 13.8, 13.7* (C-2$CO_2CH_2\mathbf{C}H_3$+$NCO_2CH_2\mathbf{C}H_3$).

IR (ATR) cm^{-1}: 1744 (C=O st), 1698 (NC=O st).

MS (EI) m/z (relative abundance): 292 (M^+ - CO_2Et, 100), 263 (1), 246 (1), 220 (11), 204 (2), 191 (2), 177 (3), 161 (4), 147 (3), 132 (1), 121 (3), 103 (1), 91 (5), 79 (1), 68 (1), 56 (1).

HRMS: Calculated for $[C_{19}H_{28}NO_6]^+$: 366.1917 $[M+H]^+$; found: 366.1907.

(2*R*,3*S*,5*S*)-Diethyl 3-(3,5-dimethoxyphenyl)-5-methylpyrrolidine-1,2-dicarboxylate (23g)



Following the general procedure, **23g** (52 mg, 0.14 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22g** (61 mg, 0.17 mmol) and methyllithium (0.11 mL of a 1.48 M solution in diethyl ether, 0.17 mmol), using dry THF (1.7 mL) as solvent.

Yield: 84%.

dr: 10:1.

$[\alpha]_D^{20}$: -47.7 (*c* = 0.65, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.5:1, *denotes minor rotamer signals): 6.42 (d, *J* = 2.0 Hz, 2H, C_{arom}-**H**), 6.35 (t, *J* = 2.0 Hz, 1H, C_{arom}-**H**), 4.47* (d, *J* = 6.7 Hz, 1H, **H**-2), 4.41 (d, *J* = 6.6 Hz, 1H, **H**-2), 4.27-3.99 (m, 5H, C-2$CO_2C\mathbf{H}_2CH_3$+N$CO_2C\mathbf{H}_2CH_3$+**H**-5), 3.78 (s, 6H, 2 × O$C\mathbf{H}_3$), 3.40-3.25 (m, 1H, **H**-3), 2.63-2.42 (m, 1H, **H**-4_a), 1.89-1.69 (m, 1H, **H**-4_b), 1.46-1.12 (m, 9H, C-2$CO_2CH_2C\mathbf{H}_3$+N$CO_2CH_2C\mathbf{H}_3$+C-5$C\mathbf{H}_3$).

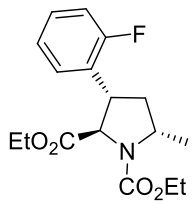
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 172.6, 172.2* (C-2$\mathbf{C}O_2$Et), 161.0 ($\mathbf{C}_{arom}$-C), 155.4*, 154.5 (N$\mathbf{C}O_2$Et), 143.2, 143.0* ($\mathbf{C}_{arom}$-C), 105.4, 98.8*, 98.7 ($\mathbf{C}_{arom}$-H), 66.5, 66.4* (**C**-2), 61.4*, 61.1, 61.0, 60.9* (C-2$CO_2\mathbf{C}H_2CH_3$+N$CO_2\mathbf{C}H_2CH_3$), 55.3 (O$\mathbf{C}H_3$), 55.0, 54.1* (**C**-5), 48.0, 47.2* (**C**-3), 41.6*, 41.2 (**C**-4), 21.5*, 20.4 (C-5$\mathbf{C}H_3$), 14.6*, 14.4, 14.2, 14.1* (C-2$CO_2CH_2\mathbf{C}H_3$+N$CO_2CH_2\mathbf{C}H_3$).

IR (ATR) cm^{-1}: 1742 (C=O st), 1703 (NC=O st).

MS (EI) m/z (relative abundance): 365 (8), 319 (2), 292 (M^+ - CO_2Et, 100), 264 (2), 248 (5), 220 (11), 203 (2), 177 (4), 161 (2), 145 (1), 119 (1), 91 (1), 77 (1), 55 (1).

HRMS: Calculated for $[C_{19}H_{28}NO_6]^+$: 366.1917 $[M+H]^+$; found: 366.1934.

(2*R*,3*S*,5*S*)-Diethyl 3-(2-fluorophenyl)-5-methylpyrrolidine-1,2-dicarboxylate (23h)



Following the general procedure, **23h** (50 mg, 0.15 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22h** (59 mg, 0.18 mmol) and methyllithium (0.13 mL of a 1.40 M solution in diethyl ether, 0.18 mmol), using dry THF (1.8 mL) as solvent.

Yield: 85%.

dr: 17:1.

$[\alpha]_D^{20}$: -46.8 (*c* = 1.36, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.4:1, *denotes minor rotamer signals): 7.34-7.29 (m, 1H, C_{arom}-**H**), 7.26-7.19 (m, 1H, C_{arom}-**H**), 7.14-7.09 (m, 1H, C_{arom}-**H**), 7.07-6.98 (m, 1H, C_{arom}-**H**), 4.59* (d, *J* = 6.0 Hz, 1H, **H**-2), 4.47 (d, *J* = 6.4 Hz, 1H, **H**-2), 4.29-4.01 (m, 5H, C-2$CO_2C\mathbf{H}_2CH_3$+N$CO_2C\mathbf{H}_2CH_3$+**H**-5), 3.68-3.60 (m, 1H, **H**-3), 2.66-2.44 (m, 1H, **H**-4_a), 1.91-1.74 (m, 1H, **H**-4_b), 1.41-1.12 (m, 9H, C-2$CO_2CH_2C\mathbf{H}_3$+N$CO_2CH_2C\mathbf{H}_3$+C-5C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 172.3, 171.9* (C-2**C**O_2Et), 160.8 (d, $^1J_{CF}$ = 246.2 Hz, **C**$_{arom}$-F), 155.5*, 154.5

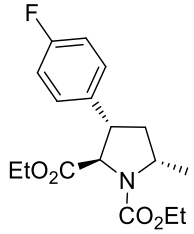
(N**C**O_2Et), 128.8 (d, $^3J_{CF}$ = 8.2 Hz, **C**$_{arom}$-H), 128.7* (d, $^3J_{CF}$ = 8.3 Hz, **C**$_{arom}$-H), 127.9 (d, $^3J_{CF}$ = 3.6 Hz, **C**$_{arom}$-H), 127.8 (d, $^2J_{CF}$ = 26.7 Hz, **C**$_{arom}$-C), 124.3 (d, $^4J_{CF}$ = 3.4 Hz, **C**$_{arom}$-H), 115.6 (d, $^2J_{CF}$ = 22.2 Hz, **C**$_{arom}$-H), 115.5* (d, $^2J_{CF}$ = 22.2 Hz, **C**$_{arom}$-H), 65.4, 65.1* (**C**-2), 61.4*, 61.2, 61.1, 61.0* (C-2CO_2**C**H_2CH_3+NCO_2**C**H_2CH_3), 55.0, 54.0* (**C**-5), 41.2, 40.4* (**C**-3), 40.2*, 39.8 (**C**-4), 21.5*, 20.4 (C-5**C**H_3), 14.6*, 14.5, 14.1, 14.0* (C-2CO_2CH_2**C**H_3+NCO_2CH_2**C**H_3).

IR (ATR) cm^{-1}: 1746 (C=O st), 1709 (NC=O st).

MS (EI) m/z (relative abundance): 323 (4), 250 (M^+ - CO_2Et, 100), 234 (1), 222 (10), 206 (17), 190 (1), 178 (42), 162 (5), 150 (4), 135 (14), 122 (3), 109 (11), 96 (1), 83 (1), 56 (1).

HRMS: Calculated for $[C_{17}H_{23}NO_4F]^+$: 324.1611 $[M+H]^+$; found: 324.1603.

(2*R*,3*S*,5*S*)-Diethyl 3-(4-fluorophenyl)-5-methylpyrrolidine-1,2-dicarboxylate (23i)



Following the general procedure, **23i** (41 mg, 0.13 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22i** (58 mg, 0.18 mmol) and methyllithium (0.13 mL of a 1.35 M solution in diethyl ether, 0.18 mmol), using dry THF (1.8 mL) as solvent.

Yield: 71%.

dr: 6:1.

$[\alpha]_D^{20}$: -47.9 (*c* = 1.01, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.3:1, *denotes minor rotamer signals): 7.25-7.19 (m, 2H, C_{arom}-**H**), 7.07-6.95 (m, 2H, C_{arom}-**H**), 4.43* (d, *J* = 6.7 Hz, 1H, **H**-2), 4.36 (d, *J* = 6.9 Hz, 1H, **H**-2), 4.26-4.02 (m, 5H, C-2$CO_2C\mathbf{H}_2CH_3$+N$CO_2C\mathbf{H}_2CH_3$+**H**-5), 3.41-3.31 (m, 1H, **H**-3), 2.60-2.46 (m, 1H, **H**-4_a), 1.85-1.68 (m, 1H, **H**-4_b), 1.43-1.11 (m, 9H, C-2$CO_2CH_2C\mathbf{H}_3$+N$CO_2CH_2C\mathbf{H}_3$+C-5C$\mathbf{H}_3$).

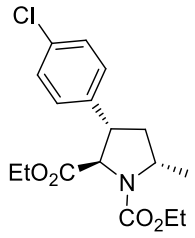
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 172.4, 172.0* (C-2**C**O_2Et), 161.9 (d, $^{1}J_{CF}$ = 245.6 Hz, **C**$_{arom}$-F), 155.3*, 154.4 (N**C**O_2Et), 136.2 (**C**$_{arom}$-C), 128.7 (d, $^{3}J_{CF}$ = 8.0 Hz, **C**$_{arom}$-H), 115.5 (d, $^{2}J_{CF}$ = 21.4 Hz, **C**$_{arom}$-H), 66.9, 66.7* (**C**-2), 61.4*, 61.1, 61.0 (C-2$CO_2\mathbf{C}H_2CH_3$+N$CO_2\mathbf{C}H_2CH_3$), 55.0, 54.1* (**C**-5), 47.2, 46.4* (**C**-3), 41.9*, 41.6 (**C**-4), 21.4*, 20.3 (C-5**C**H_3), 14.6*, 14.4, 14.2, 14.1* (C-2$CO_2CH_2\mathbf{C}H_3$+N$CO_2CH_2\mathbf{C}H_3$).

IR (ATR) cm^{-1}: 1742 (C=O st), 1706 (NC=O st).

MS (EI) m/z (relative abundance): 323 (1), 250 (M^+ - CO_2Et, 100), 234 (1), 222 (6), 206 (9), 178 (29), 162 (4), 150 (4), 135 (19), 122 (3), 109 (12), 95 (1), 82 (2), 68 (1), 55 (2).

HRMS: Calculated for $[C_{17}H_{23}NO_4F]^+$: 324.1611 $[M+H]^+$; found: 324.1593.

(2*R*,3*S*,5*S*)-Diethyl 3-(4-chlorophenyl)-5-methylpyrrolidine-1,2-dicarboxylate (23j)



Following the general procedure, **23j** (73 mg, 0.21 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22j** (85 mg, 0.25 mmol) and methyllithium (0.19 mL of a 1.31 M solution in diethyl ether, 0.25 mmol), using dry THF (2.5 mL) as solvent.

Yield: 86%.

dr: 7:1.

$[\alpha]_D^{20}$: -78.5 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.3:1, *denotes minor rotamer signals): 7.30 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 7.19 (d, *J* = 8.4 Hz, 2H, C_{arom}-**H**), 4.45* (d, *J* = 6.4 Hz, 1H, **H**-2), 4.38 (d, *J* = 6.8 Hz, 1H, **H**-2), 4.27-3.97 (m, 5H, C-2$CO_2C\mathbf{H}_2CH_3$+N$CO_2C\mathbf{H}_2CH_3$+**H**-5), 3.43-3.28 (m, 1H, **H**-3), 2.64-2.44 (m, 1H, **H**-4_a), 1.87-1.66 (m, 1H, **H**-4_b), 1.45-1.11 (m, 9H, C-2$CO_2CH_2C\mathbf{H}_3$+N$CO_2CH_2C\mathbf{H}_3$+C-5$C\mathbf{H}_3$).

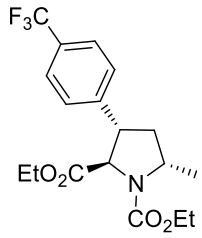
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 172.3, 172.0* (C-2$\mathbf{C}O_2$Et), 155.3*, 154.4 (N$\mathbf{C}O_2$Et), 139.2, 139.1*, 132.9 ($\mathbf{C}_{arom}$-C), 128.8, 128.5 ($\mathbf{C}_{arom}$-H), 66.6, 66.4* (**C**-2), 61.5*, 61.2, 61.1, 61.0* (C-2$CO_2\mathbf{C}H_2CH_3$+N$CO_2\mathbf{C}H_2CH_3$), 55.0, 54.1* (**C**-5), 47.3, 46.4* (**C**-3), 41.7*, 41.4 (**C**-4), 21.5*, 20.3 (C-5$\mathbf{C}H_3$), 14.6*, 14.5, 14.2, 14.1* (C-2$CO_2CH_2\mathbf{C}H_3$+N$CO_2CH_2\mathbf{C}H_3$).

IR (ATR) cm^{-1}: 1742 (C=O st), 1704 (NC=O st).

MS (EI) m/z (relative abundance): 339 (1), 266 (M^+ - CO_2Et, 100), 252 (1), 238 (6), 222 (9), 194 (30), 181 (2), 166 (4), 151 (9), 129 (13), 115 (13), 101 (2), 82 (4), 77 (2), 55 (4).

HRMS: Calculated for $[C_{17}H_{23}NO_4Cl]^+$: 340.1316 $[M+H]^+$; found: 340.1302.

(2*R*,3*S*,5*S*)-Diethyl 5-methyl-3-(4-(trifluoromethyl)phenyl)pyrrolidine-1,2-dicarboxylate (23k)



Following the general procedure, **23k** (39 mg, 0.10 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22k** (49 mg, 0.13 mmol) and methyllithium (0.10 mL of a 1.31 M solution in diethyl ether, 0.13 mmol), using dry THF (1.3 mL) as solvent.

Yield: 80%.

dr: 5:1.

$[\alpha]_D^{20}$: -55.1 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.3:1, *denotes minor rotamer signals): 7.59 (d, *J* = 8.1 Hz, 2H, C_{arom}-**H**), 7.39 (d, *J* = 8.1 Hz, 2H, C_{arom}-**H**), 4.53* (d, *J* = 5.8 Hz, 1H, **H**-2), 4.45 (d, *J* = 6.4 Hz, 1H, **H**-2), 4.28-4.01 (m, 5H, C-2$CO_2C\mathbf{H}_2CH_3$+N$CO_2C\mathbf{H}_2CH_3$+**H**-5), 3.53-3.36 (m, 1H, **H**-3), 2.70-2.48 (m, 1H, **H**-4_a), 1.90-1.71 (m, 1H, **H**-4_b), 1.44-1.13 (m, 9H, C-2$CO_2CH_2C\mathbf{H}_3$+N$CO_2CH_2C\mathbf{H}_3$+C-5C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 172.2, 171.8* (C-2**C**O_2Et), 155.4*, 154.4 (N**C**O_2Et), 144.9 (**C**$_{arom}$-C), 129.5 (q,

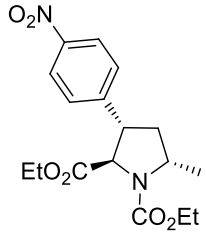
$^{2}J_{CF}$ = 32.7 Hz, **C**$_{arom}$-CF_3), 127.6 (**C**$_{arom}$-H), 125.6 (q, $^{3}J_{CF}$ = 3.6 Hz, **C**$_{arom}$-H), 124.0 (q, $^{1}J_{CF}$ = 272.0 Hz, **C**F_3), 66.5, 66.2* (**C**-2), 61.5*, 61.2, 61.1, 61.0* (C-2CO_2**C**H_2CH_3+NCO_2**C**H_2CH_3), 55.0, 54.1* (**C**-5), 47.5, 46.7* (**C**-3), 41.6*, 41.2 (**C**-4), 21.5*, 20.4 (C-5**C**H_3), 14.6*, 14.4, 14.2, 14.1* (C-2CO_2CH_2**C**H_3+NCO_2CH_2**C**H_3).

IR (ATR) cm^{-1}: 1743 (C=O st), 1706 (NC=O st).

MS (EI) m/z (relative abundance): 373 (1), 300 (M^+ - CO_2Et, 100), 286 (1), 272 (4), 256 (12), 228 (28), 200 (2), 185 (4), 159 (3), 145 (1), 129 (4), 115 (1), 82 (1), 55 (1).

HRMS: Calculated for $[C_{18}H_{23}NO_4F_3]^+$: 374.1579 $[M+H]^+$; found: 374.1565.

(2*R*,3*S*,5*S*)-Diethyl 5-methyl-3-(4-nitrophenyl)pyrrolidine-1,2-dicarboxylate (23l)



Following the general procedure, **23l** (13 mg, 0.04 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22l** (54 mg, 0.15 mmol) and methyllithium (0.10 mL of a 1.53 M solution in diethyl ether, 0.15 mmol), using dry THF (1.5 mL) as solvent.

Yield: 60%.[18]

dr: 7:1.

$[\alpha]_D^{20}$: -72.7 (*c* = 0.61, CH_2Cl_2).

[18] Calculated yield over a conversion of 40%.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.1:1, *denotes minor rotamer signals): 8.20 (d, *J* = 8.6 Hz, 2H, C_{arom}-**H**), 7.45 (d, *J* = 8.6 Hz, 2H, C_{arom}-**H**), 4.55* (d, *J* = 6.5 Hz, 1H, **H**-2), 4.47 (d, *J* = 6.3 Hz, 1H, **H**-2), 4.27-4.08 (m, 5H, C-2$CO_2C\mathbf{H}_2CH_3$+$NCO_2C\mathbf{H}_2CH_3$+**H**-5), 3.58-3.41 (m, 1H, **H**-3), 2.71-2.51 (m, 1H, **H**-4_a), 1.89-1.75 (m, 1H, **H**-4_b), 1.40-1.19 (m, 9H, C-2$CO_2CH_2C\mathbf{H}_3$+$NCO_2CH_2C\mathbf{H}_3$+C-5$C\mathbf{H}_3$).

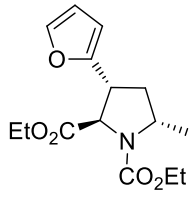
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 171.9, 171.6* (C-2**C**O_2Et), 155.4*, 154.3 (N**C**O_2Et), 148.4, 147.1 (**C**$_{arom}$-C), 128.1, 124.0 (**C**$_{arom}$-H), 66.3, 66.1* (**C**-2), 61.6*, 61.3, 61.3, 61.2* (C-2$CO_2\mathbf{C}H_2CH_3$+$NCO_2\mathbf{C}H_2CH_3$), 55.0, 54.1* (**C**-5), 47.5, 46.6* (**C**-3), 41.6*, 41.2 (**C**-4), 21.5*, 20.4 (C-5**C**H_3), 14.6*, 14.5, 14.2, 14.2* (C-2$CO_2CH_2\mathbf{C}H_3$+$NCO_2CH_2\mathbf{C}H_3$).

IR (ATR) cm^{-1}: 1742 (C=O st), 1705 (NC=O st), 1521 (NO_2 st as), 1346 (NO_2 st sym).

MS (EI) m/z (relative abundance): 277 (M^+ - CO_2Et, 100), 261 (2), 249 (4), 233 (13), 205 (39), 187 (10), 177 (2), 159 (8), 143 (2), 129 (12), 115 (10), 103 (2), 91 (4), 77 (2), 55 (2).

HRMS: Calculated for $[C_{17}H_{23}N_2O_6]^+$: 351.1556 $[M+H]^+$; found: 351.1540.

(2*R*,3*R*,5*S*)-Diethyl 3-(furan-2-yl)-5-methylpyrrolidine-1,2-dicarboxylate (23m)



Following the general procedure, **23m** (29 mg, 0.10 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22m** (37 mg, 0.13 mmol) and methyllithium (0.10 mL of a 1.31 M solution in

diethyl ether, 0.13 mmol), using dry THF (1.3 mL) as solvent.

Yield: 78%.

dr: 9:1.

$[\alpha]_D^{20}$: -47.3 (*c* = 1.01, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.3:1, *denotes minor rotamer signals): 7.36-7.31 (m, 1H, C_{arom}-**H**), 6.36-6.25 (m, 1H, C_{arom}-**H**), 6.20-6.12 (m, 1H, C_{arom}-**H**), 4.60* (d, *J* = 4.4 Hz, 1H, **H**-2), 4.53 (d, *J* = 4.7 Hz, 1H, **H**-2), 4.26-4.00 (m, 5H, C-2$CO_2C\mathbf{H}_2CH_3$+$NCO_2C\mathbf{H}_2CH_3$+**H**-5), 3.53-3.40 (m, 1H, **H**-3), 2.60-2.40 (m, 1H, **H**-4_a), 2.04-1.87 (m, 1H, **H**-4_b), 1.32-1.12 (m, 9H, C-2$CO_2CH_2C\mathbf{H}_3$+$NCO_2CH_2C\mathbf{H}_3$+C-5$C\mathbf{H}_3$).

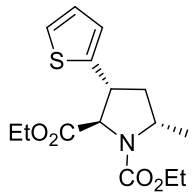
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 172.2, 171.9* (C-2$\mathbf{C}O_2$Et), 155.4*, 154.4 ($N\mathbf{C}O_2$Et), 154.2*, 154.1 ($\mathbf{C}_{arom}$-C), 141.8, 110.3, 105.7, 105.6* ($\mathbf{C}_{arom}$-H), 64.5 (**C**-2), 61.4*, 61.3, 61.2, 61.0* (C-2$CO_2\mathbf{C}H_2CH_3$+$NCO_2\mathbf{C}H_2CH_3$), 54.6, 53.7* (**C**-5), 41.5, 40.6* (**C**-3), 37.3*, 36.9 (**C**-4), 21.4*, 20.4 (C-5$\mathbf{C}H_3$), 14.6*, 14.5, 14.2, 14.1* (C-2$CO_2CH_2\mathbf{C}H_3$+$NCO_2CH_2\mathbf{C}H_3$).

IR (ATR) cm^{-1}**:** 1735 (C=O st), 1703 (NC=O st).

MS (EI) m/z (relative abundance): 295 (16), 250 (1), 222 (M^+ - CO_2Et, 100), 206 (4), 194 (9), 178 (12), 162 (1), 150 (32), 134 (4), 122 (7), 107 (12), 94 (5), 79 (8), 68 (2), 55 (3).

HRMS: Calculated for $[C_{15}H_{22}NO_5]^+$: 296.1498 $[M+H]^+$; found: 296.1489.

(2*R*,3*R*,5*S*)-Diethyl 5-methyl-3-(thiophen-2-yl)pyrrolidine-1,2-dicarboxylate (23n)



Following the general procedure, **23n** (52 mg, 0.17 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22n** (62 mg, 0.20 mmol) and methyllithium (0.14 mL of a 1.48 M solution in diethyl ether, 0.20 mmol), using dry THF (2.0 mL) as solvent.

Yield: 84%.

dr: 13:1.

$[\alpha]_D^{20}$: -51.1 (*c* = 1.01, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.4:1, *denotes minor rotamer signals): 7.22-7.16 (m, 1H, C_{arom}-**H**), 6.96-6.90 (m, 2H, C_{arom}-**H**), 4.50* (d, *J* = 6.1 Hz, 1H, **H**-2), 4.43 (d, *J* = 6.3 Hz, 1H, **H**-2), 4.26-3.99 (m, 5H, C-2$CO_2C\mathbf{H}_2CH_3$+N$CO_2C\mathbf{H}_2CH_3$+**H**-5), 3.69-3.62 (m, 1H, **H**-3), 2.71-2.52 (m, 1H, **H**-4_a), 1.98-1.79 (m, 1H, **H**-4_b), 1.42-1.13 (m, 9H, C-2$CO_2CH_2C\mathbf{H}_3$+N$CO_2CH_2C\mathbf{H}_3$+C-5$C\mathbf{H}_3$).

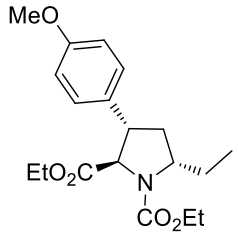
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 172.1, 171.8* (C-2**C**O_2Et), 155.2*, 154.3 (N**C**O_2Et), 144.3 ($\mathbf{C}_{arom}$-C), 126.9, 124.3, 124.2*, 124.0 ($\mathbf{C}_{arom}$-H), 67.3, 67.2* (**C**-2), 61.4*, 61.2, 61.1, 61.0* (C-2$CO_2\mathbf{C}H_2CH_3$+N$CO_2\mathbf{C}H_2CH_3$), 54.9, 54.0* (**C**-5), 43.3, 42.6* (**C**-3), 42.1*, 41.7 (**C**-4), 21.4*, 20.3 (C-5$\mathbf{C}H_3$), 14.6*, 14.5, 14.2, 14.1* (C-2$CO_2CH_2\mathbf{C}H_3$+N$CO_2CH_2\mathbf{C}H_3$).

IR (ATR) cm^{-1}: 1742 (C=O st), 1705 (NC=O st).

MS (EI) m/z (relative abundance): 311 (6), 238 (M^+ - CO_2Et, 100), 222 (4), 210 (5), 194 (5), 182 (1), 166 (15), 150 (3), 137 (3), 123 (12), 110 (3), 97 (7), 79 (2), 65 (1), 53 (1).

HRMS: Calculated for $[C_{15}H_{22}NO_4S]^+$: 312.1270 $[M+H]^+$; found: 312.1255.

(2*R*,3*S*,5*S*)-Diethyl 5-ethyl-3-(4-methoxyphenyl)pyrrolidine-1,2-dicarboxylate (23o)



Following the general procedure, **23o** (49 mg, 0.14 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22o** (55 mg, 0.16 mmol) and methyllithium (0.10 mL of a 1.53 M solution in diethyl ether, 0.16 mmol), using dry THF (1.6 mL) as solvent. The reaction was quenched with the dropwise addition of *t*-BuOH (0.06 mL, 0.63 mmol) in dry THF (1 mL) at -78 ºC.

Yield: 89%.

dr: 6:1.

$[\alpha]_D^{20}$: -52.2 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.3:1, *denotes minor rotamer signals): 7.17 (d, *J* = 8.6 Hz, 2H, C_{arom}-**H**), 6.86 (d, *J* = 8.6 Hz, 2H, C_{arom}-**H**), 4.38* (d, *J* = 7.1 Hz, 1H, **H**-2), 4.33 (d, *J* = 7.1 Hz, 1H, **H**-2), 4.26-4.02 (m, 4H, C-2$CO_2C\mathbf{H}_2CH_3$+N$CO_2C\mathbf{H}_2CH_3$), 4.00-3.87 (m, 1H, **H**-5), 3.80 (s, 3H, O$C\mathbf{H}_3$), 3.42-3.26 (m, 1H, **H**-3), 2.54-2.37 (m, 1H, **H**-4_a), 2.33-2.17 (m, 1H, C-5$C\mathbf{H}_aH_b$), 2.07-1.93* (m, 1H, C-5$C\mathbf{H}_aH_b$), 1.93-1.74 (m, 1H, **H**-4_b), 1.52-1.36 (m, 1H, C-5$CH_a\mathbf{H}_b$), 1.32-1.12 (m, 6H, $CO_2CH_2C\mathbf{H}_3$+C-5$CH_2C\mathbf{H}_3$), 0.90-0.78 (m, 3H, $CO_2CH_2C\mathbf{H}_3$).

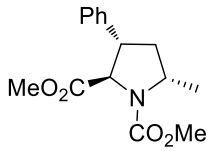
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 172.5, 172.1* (C-2**C**O_2Et), 158.7 (**C**$_{arom}$-C), 155.3*, 154.4 (N**C**O_2Et), 132.5, 132.3* (**C**$_{arom}$-C), 128.1, 114.0 (**C**$_{arom}$-H), 67.1, 66.9* (**C**-2), 61.3*, 61.0, 60.9 (C-2CO_2**C**H_2CH_3+NCO_2**C**H_2CH_3), 60.5, 59.6* (**C**-5), 55.3 (O**C**H_3), 47.3, 46.5* (**C**-3), 38.6*, 38.3 (**C**-4), 27.1*, 26.1 (C-5**C**H_2), 14.6*, 14.4, 14.2, 14.1* (C-2CO_2CH_2**C**H_3+NCO_2CH_2**C**H_3), 9.8, 9.6* (C-5CH_2**C**H_3).

IR (ATR) cm^{-1}: 1742 (C=O st), 1706 (NC=O st).

MS (EI) m/z (relative abundance): 349 (3), 320 (4), 276 (M^+ - CO_2Et, 100), 248 (7), 232 (3), 218 (1), 204 (11), 187 (1), 174 (11), 160 (2), 147 (13), 130 (12), 115 (3), 91 (5), 77 (2), 58 (1).

HRMS: Calculated for $[C_{19}H_{28}NO_5]^+$: 350.1967 $[M+H]^+$; found: 350.1949.

(2*R*,3*S*,5*S*)-Dimethyl 5-methyl-3-phenylpyrrolidine-1,2-dicarboxylate (23q)



Following the general procedure, **23q** (61 mg, 0.22 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22q** (76 mg, 0.27 mmol) and methyllithium (0.19 mL of a 1.48 M solution in diethyl ether, 0.27 mmol), using dry THF (2.7 mL) as solvent.

Yield: 80%.

dr: 10:1.

$[\alpha]_D^{20}$: -58.9 (*c* = 1.19, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.2:1, *denotes minor rotamer signals): 7.37-7.19 (m, 5H, C$_{arom}$-**H**), 4.54* (d, *J* = 6.4 Hz, 1H, **H**-2), 4.47 (d, *J* = 6.4 Hz, 1H, **H**-2), 4.22-4.00 (m, 1H, **H**-5), 3.79-3.60 (m, 6H, C-

2$CO_2C\mathbf{H}_3$+$NCO_2C\mathbf{H}_3$), 3.50-3.33 (m, 1H, **H**-3), 2.66-2.44 (m, 1H, **H**-4_a), 1.93-1.75 (m, 1H, **H**-4_b), 1.37 (d, *J* = 6.0 Hz, 3H, C-5C**H**$_3$), 1.26* (d, *J* = 6.1 Hz, 3H, C-5C**H**$_3$).

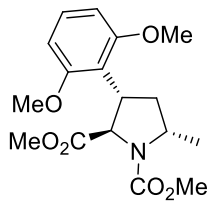
^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 173.0, 172.7* (C-2**C**O_2Me), 155.8*, 154.8 (N**C**O_2Me), 140.6, 140.4* (**C**$_{arom}$-C), 128.7, 127.2, 127.0 (**C**$_{arom}$-H), 66.5, 66.4* (**C**-2), 55.2, 54.2* (**C**-5), 52.6, 52.2 (C-2$CO_2\mathbf{C}H_3$+$NCO_2\mathbf{C}H_3$), 47.8, 47.0* (**C**-3), 41.7*, 41.3 (**C**-4), 21.4*, 20.3 (C-5**C**H_3).

IR (ATR) cm^{-1}: 1747 (C=O st), 1699 (NC=O st).

MS (EI) m/z (relative abundance): 277 (1), 262 (1), 218 (M^+ - CO_2Me, 100), 202 (10), 186 (3), 170 (1), 158 (5), 143 (18), 128 (8), 117 (27), 103 (4), 91 (15), 77 (4), 59 (11).

HRMS: Calculated for $[C_{15}H_{20}NO_4]^+$: 278.1392 $[M+H]^+$; found: 278.1381.

(2*R*,3*S*,5*S*)-Dimethyl 3-(2,6-dimethoxyphenyl)-5-methylpyrrolidine-1,2-dicarboxylate (23r)



Following the general procedure, **23r** (10 mg, 0.03 mmol) was isolated by FC (hexanes/EtOAc gradient from 9.5:0.5 to 7:3) as a colourless oil, starting from pyrrolidine **22r** (14 mg, 0.04 mmol) and methyllithium (0.03 mL of a 1.53 M solution in diethyl ether, 0.04 mmol), using dry THF (0.4 mL) as solvent.

Yield: 75%.

dr: 3:1.

$[\alpha]_D^{20}$: +60.7 (*c* = 0.99, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz) (rotamers ratio 1.4:1, *denotes minor rotamer signals): 7.17 (t, *J* = 8.3 Hz, 1H, C_{arom}-**H**), 6.51 (d, *J* = 8.3 Hz, 2H, C_{arom}-**H**), 4.60* (d, *J* = 8.4 Hz, 1H, **H**-2), 4.48 (d, *J* = 8.5 Hz, 1H, **H**-2), 4.11-4.02 (m, 1H, **H**-5), 4.01-3.84 (m, 1H, **H**-3), 3.80-3.63 (m, 9H, 2 × C_{arom}-OC**H**$_3$+CO_2C**H**$_3$), 3.46 (s, 3H, CO_2C**H**$_3$), 2.92-2.70 (m, 1H, **H**-4$_a$), 2.17-1.98 (m, 1H, **H**-4$_b$), 1.55-1.49 (m, 3H, C-5C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz) (*denotes minor rotamer signals): 171.8 (C-2**C**O_2Me), 159.5 (**C**$_{arom}$-C), 156.0*, 155.1 (N**C**O_2Me), 128.4 (**C**$_{arom}$-H), 112.5*, 112.4 (**C**$_{arom}$-C), 103.8 (**C**$_{arom}$-H), 62.8*, 62.4 (**C**-2), 55.5 (C_{arom}-O**C**H_3), 54.7, 54.0* (**C**-5), 52.3*, 52.2, 51.3 (C-2CO_2**C**H_3+NCO_2**C**H_3), 38.0, 37.5* (**C**-3), 35.7*, 34.9 (**C**-4), 21.2*, 20.1 (C-5**C**H_3).

IR (ATR) cm^{-1}: 1746 (C=O st), 1698 (NC=O st).

MS (EI) m/z (relative abundance): 337 (2), 305 (1), 278 (M^+ - CO_2Me, 100), 262 (1), 246 (2), 219 (1), 204 (2), 188 (4), 175 (1), 161 (6), 147 (3), 134 (1), 121 (4), 105 (1), 91 (6), 77 (2), 59 (6).

HRMS: Calculated for $[C_{17}H_{24}NO_6]^+$: 338.1604 $[M+H]^+$; found: 338.1596.

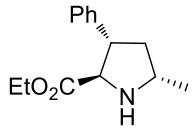
3.3. Synthesis of prolines 24a and 24q.

General procedure:

Trimethylsilyl iodide (10.00 mmol) was added dropwise to a solution of **23** (1.00 mmol) in dry $CHCl_3$ (66.7 mL) under inert atmosphere. The reaction mixture was refluxed during 24 hours, then MeOH (37.3 mL) was added and the mixture was refluxed for 3 hours more. The reaction was allowed to reach room temperature and then the solvent was removed under reduced pressure. Et_2O (5 mL) and few drops of HCl conc. were added and the solution was stirred for 15

minutes at room temperature. The mixture was washed with Et_2O (3 × 20 mL). The liquid phase was basified by the addition of aqueous NH_3, and it was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed *in vacuo*, yielding the desired product **24** without further purification.

(2*R*,3*S*,5*S*)-Ethyl 5-methyl-3-phenylpyrrolidine-2-carboxylate (24a)



Following the general procedure, **24a** (36 mg, 0.15 mmol) was obtained as a colourless oil, starting from proline **23a** (59 mg, 0.19 mmol), trimethylsilyl iodide (0.27 mL, 1.9 mmol) and $CHCl_3$ (10.0 mL), followed by the addition of MeOH (5.6 mL).

Yield: 80%.

$[\alpha]_D^{20}$: -60.5 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.33-7.16 (m, 5H, C_{arom}-**H**), 4.26-4.01 (m, 2H, $CH_3C\mathbf{H}_2$), 3.84 (d, *J* = 7.4 Hz, 1H, **H**-2), 3.58-3.42 (m, 1H, **H**-5), 3.42-3.28 (m, 1H, **H**-3), 2.47-2.25 (m, 2H, **H**-4_a+N**H**), 1.67-1.56 (m, 1H, **H**-4_b), 1.25 (d, *J* = 6.1 Hz, 3H, C-5C**H**$_3$), 1.19 (t, *J* = 7.1 Hz, 3H, C**H**$_3$CH$_2$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 175.2 (**C**O_2Et), 143.0 (**C**$_{arom}$-C), 128.5, 127.4, 126.6 (**C**$_{arom}$-H), 67.2 (**C**-2), 60.9 ($CH_3\mathbf{C}H_2$), 54.6 (**C**-5), 50.8 (**C**-3), 44.0 (**C**-4), 21.2 (C-5**C**H$_3$), 14.2 (**C**H$_3$CH$_2$).

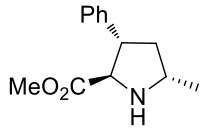
IR (ATR) cm^{-1}: 1730 (C=O st).

MS (EI) m/z (relative abundance): 161 (13), 160 (M^+ - CO_2Et, 100), 144 (4), 129 (4), 117 (10), 100 (2), 91 (9), 83 (4), 73 (3), 63 (1), 55 (4).

HRMS: Calculated for $[C_{14}H_{20}NO_2]^+$: 234.1494 $[M+H]^+$; found: 234.1484.

The spectral data is in agreement with previous report.[19]

(2*R*,3*S*,5*S*)-Methyl 5-methyl-3-phenylpyrrolidine-2-carboxylate (24q)



Following the general procedure, **24q** (33 mg, 0.15 mmol) was obtained as a colourless oil, starting from pyrrolidine **23q** (61 mg, 0.22 mmol), trimethylsilyl iodide (0.30 mL, 2.2 mmol) and $CHCl_3$ (11.0 mL), followed by the addition of MeOH (6.4 mL).

Yield: 70%.

$[\alpha]_D^{20}$: -66.3 (*c* = 1.01, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 300 MHz): 7.38-7.21 (m, 5H, C_{arom}-**H**), 3.88 (d, *J* = 7.3 Hz, 1H, **H**-2), 3.68 (s, 3H, C**H**$_3$O), 3.55-3.44 (m, 1H, **H**-5), 3.43-3.35 (m, 1H, **H**-3), 2.42 (bs, 1H, N**H**), 2.32 (ddd, *J* = 12.4, 7.4, 5.2 Hz, 1H, **H**-4$_a$), 1.66-1.55 (m, 1H, **H**-4$_b$), 1.25 (d, *J* = 6.1 Hz, 3H, C-5C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 75.5 MHz): 175.8 (**C**O_2Me), 143.0 (**C**$_{arom}$-C), 128.6, 127.3, 126.7 (**C**$_{arom}$-H), 67.1 (**C**-2), 54.6 (**C**-5), 52.1 (**C**H_3O), 50.6 (**C**-3), 44.1 (**C**-4), 21.0 (C-5**C**H_3).

IR (ATR) cm^{-1}**:** 1731 (C=O st).

MS (EI) m/z (relative abundance): 204 (1), 183 (1), 160 (M^+ - CO_2Me, 100), 144 (5), 128 (5), 115 (21), 103 (3), 91 (15), 83 (12), 72 (4), 65 (3), 55 (11).

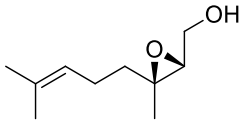
HRMS: Calculated for $[C_{13}H_{18}NO_2]^+$: 220.1338 $[M+H]^+$; found: 220.1323.

[19] Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331.

4. TOTAL SYNTHESIS OF (+)-GREEK TOBACCO LACTONE

4.1. Synthesis of adduct 31.

((2*R*,3*S*)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl)methanol (31)



A mixture of 4 Å molecular sieves (4.5 g) and dry CH_2Cl_2 (250 mL) under inert atmosphere, was cooled to -23 ºC. Then, titanium isopropoxide (9.5 mL, 32.4 mmol) and D-(-)-diethyl tartrate (7.0 mL, 40.9 mmol) were added and stirred for 30 minutes. A solution of *t*-butyl hydrogen peroxide (5.5 M in decanes, 32.0 mL, 176.0 mmol) was added dropwise and stirred for 30 minutes. Nerol (28.5 mL, 162.0 mmol) was added dropwise over 50 minutes, and then stirred at -23 ºC for 3 hours. The reaction was quenched by the addition of H_2O (185 mL) at 0 ºC and stirred for 5 hours. After the addition of aqueous NaOH 7.5 M (37 mL), the solution was saturated with NaCl and filtered through Celite. The filtrate was extracted with CH_2Cl_2 (3 × 200 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. After purification by flash column chromatography (FC) (*n*-hexane/EtOAc gradient from 3:1 to 2:1) the epoxide **31** (20.9 g, 123.0 mmol) was isolated as a yellow oil.

Yield: 76%.

ee: 71%. Determined by chiral GC using a Supelco β-Dex 120 column; oven temp. 140 ºC isocratic; τ_{major} = 10.32 min, τ_{minor} = 9.52 min.

$[\alpha]_D^{20}$: +13.1 (*c* = 1.00, $CHCl_3$).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 500 MHz): 5.10-5.05 (m, 1H, C=C**H**), 3.79 (ddd, *J* = 11.6, 6.9, 4.3 Hz, 1H, C**H**$_a$H$_b$OH), 3.66-3.61 (m, 1H, CH$_a$**H**$_b$OH), 2.95

(dd, *J* = 6.9, 4.3 Hz, 1H, OC**H**), 2.26-2.22 (m, 1H, O**H**), 2.17-2.01 (m, 2H, C=CHC**H**$_2$), 1.69-1.61 (m, 4H, CC**H**$_3$+CC**H**$_a$H$_b$), 1.61-1.58 (m, 3H, CC**H**$_3$), 1.46 (ddd, *J* = 13.8, 9.9, 6.9 Hz, 1H, CCH$_a$**H**$_b$), 1.32 (s, 3H, OCC**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 125.7 MHz): 132.4 (**C**=CH), 123.2 (C=**C**H), 64.3 (O**C**H), 61.5 (O**C**CH$_3$), 61.2 (**C**H$_2$OH), 33.1 (C**C**H$_2$), 25.6 (C**C**H$_3$), 24.1 (C=CH**C**H$_2$), 22.1 (C**C**H$_3$), 17.6 (OC**C**H$_3$).

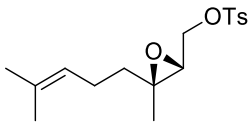
IR (ATR) cm^{-1}**:** 3423 (O-H st).

HRMS: Calculated for $[C_{10}H_{18}O_2Na]^+$: 193.1204 $[M+Na]^+$; found: 193.1218.

The spectral data is in agreement with previous reports.[20]

4.2. Synthesis of adduct 32.

((2*R*,3*S*)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl)methyl 4-methylbenzenesulfonate (32)



To a solution of *p*-toluenesulfonyl chloride (1.22 g, 6.38 mmol) and DMAP (169 mg, 1.38 mmol) in dry CH_2Cl_2 (40 mL) under inert atmosphere, a solution of the epoxide **31** (773 mg, 4.54 mmol) in dry CH_2Cl_2 (8 mL) was added dropwise at room temperature. Then, Et_3N (1.71 mL, 12.26 mmol) was added dropwise and stirred for 12 hours at room temperature. A solution of saturated aqueous NH_4Cl (20 mL) was added and after separation of the layers, the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous

[20] a) Malkov, A. V.; Bourhani, Z.; Kočovský, P. *Org. Biomol. Chem.* **2005**, *3*, 3194; b) Banwell, M. G.; Bui, C. T.; Simpson, G. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 791.

Na_2SO_4, filtered and concentrated under reduced pressure. After purification by flash column chromatography (FC) (*n*-hexane/EtOAc 8:1) the epoxide **32** (1.13 g, 3.50 mmol) was isolated as a yellow oil.

Yield: 77%.

$[\alpha]_D^{20}$: +22.9 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz): 7.79 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 7.34 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 5.06-4.93 (m, 1H, C=C**H**), 4.16 (dd, *J* = 11.1, 5.0 Hz, 1H, C**H**$_a$H$_b$OTs), 4.03 (dd, *J* = 11.1, 6.4 Hz, 1H, CH$_a$**H**$_b$OTs), 2.95 (dd, *J* = 6.3, 5.0 Hz, 1H, OC**H**), 2.44 (s, 3H, C_{arom}-C**H**$_3$), 2.13-1.97 (m, 2H, C=CHC**H**$_2$), 1.66 (s, 3H, CC**H**$_3$), 1.57 (s, 3H, CC**H**$_3$), 1.50 (ddd, *J* = 14.1, 9.5, 5.9 Hz, 1H, CC**H**$_a$H$_b$), 1.40-1.32 (m, 1H, CCH$_a$**H**$_b$), 1.28 (s, 3H, OCC**H**$_3$).

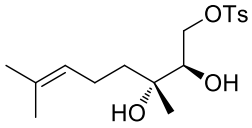
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.7 MHz): 145.0, 132.5 (**C**$_{arom}$-C), 132.4 (**C**=CH), 129.8, 127.8 (**C**$_{arom}$-H), 122.8 (C=**C**H), 68.4 (**C**H$_2$OTs), 60.9 (O**C**CH$_3$), 59.9 (O**C**H), 32.8 (C**C**H$_2$), 25.5 (C**C**H$_3$), 23.8 (C=CH**C**H$_2$), 21.6 (C_{arom}-**C**H$_3$), 21.5 (C**C**H$_3$), 17.4 (OC**C**H$_3$).

IR (ATR) cm^{-1}: 1360 (SO_2 st as), 1175 (SO_2 st sym).

HRMS: Calculated for $[C_{17}H_{24}O_4SNa]^+$: 347.1293 $[M+Na]^+$; found: 347.1308.

4.3. Synthesis of adduct 33.

(2*R*,3*R*)-2,3-Dihydroxy-3,7-dimethyloct-6-en-1-yl 4-methylbenzenesulfonate (33)



A solution of epoxide **32** (1.25 g, 3.86 mmol) in CH_3CN (8.8 mL) and H_2O (6.1 mL) was warmed up to 50 ºC. TsOH (44 mg, 0.23 mmol) was added and the reaction was stirred for 12 hours at 50 ºC. After cooling to room temperature, the mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. After purification by flash column chromatography (FC) (*n*-hexane/EtOAc gradient from 1:1 to 2:3) the diol **33** (845 mg, 2.47 mmol) was isolated as a yellow oil.

Yield: 64%.

$[\alpha]_D^{20}$: +11.3 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 500 MHz): 7.80 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 7.35 (d, *J* = 8.2 Hz, 2H, C_{arom}-**H**), 5.10-5.04 (m, 1H, C=C**H**), 4.22 (dd, *J* = 10.4, 2.7 Hz, 1H, C**H**$_a$H$_b$OTs), 4.03 (dd, *J* = 10.4, 8.2 Hz, 1H, CH$_a$**H**$_b$OTs), 3.74-3.68 (m, 1H, C**H**OH), 2.72 (d, *J* = 4.1 Hz, 1H, O**H**), 2.45 (s, 3H, C_{arom}-C**H**$_3$), 2.05-1.97 (m, 2H, C=CHC**H**$_2$), 1.67 (s, 3H, CC**H**$_3$), 1.60-1.44 (m, 5H, CC**H**$_3$+CC**H**$_2$), 1.11 (s, 3H, HOCC**H**$_3$).

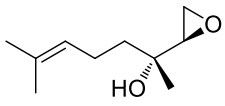
^{13}C-NMR (δ, ppm) ($CDCl_3$, 125.7 MHz): 145.1, 132.6 (**C**$_{arom}$-C), 132.2 (**C**=CH), 130.0, 127.9 (**C**$_{arom}$-H), 123.8 (C=**C**H), 74.1 (**C**HOH), 73.3 (HO**C**CH$_3$), 71.4 (**C**H$_2$OTs), 38.8 (C**C**H$_2$), 25.6 (C**C**H$_3$), 22.1 (C=CH**C**H$_2$), 22.0 (HOC**C**H$_3$), 21.6 (C_{arom}-**C**H$_3$), 17.6 (C**C**H$_3$).

IR (ATR) cm^{-1}: 3512 (O-H st), 1357 (SO_2 st as), 1174 (SO_2 st sym).

HRMS: Calculated for $[C_{17}H_{26}O_5SNa]^+$: 365.1399 $[M+Na]^+$; found: 365.1415.

4.4. Synthesis of adduct 28.

(*R*)-6-Methyl-2-((*R*)-oxiran-2-yl)hept-5-en-2-ol (28)



To a solution of diol **33** (550 mg, 1.61 mmol) in MeOH (6 mL), K_2CO_3 (555 mg, 4.02 mmol) was added at -10 ºC and the reaction was stirred for 40 min at this temperature. After that the mixture was powered into a solution of 10% citric acid (8.5 mL) and extracted with Et_2O (4 × 10 mL). The combined organic phases were washed with brine (30 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. After purification by flash column chromatography (FC) (*n*-hexane/EtOAc gradient from 4:1 to 1:1) the epoxide **28** (238 mg, 1.40 mmol) was isolated as a yellow oil.

Yield: 87%.

$[\alpha]_D^{20}$: -2.6 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.13-5.05 (m, 1H, C=C**H**), 2.94 (dd, *J* = 4.0, 2.9 Hz, 1H, OC**H**), 2.74 (dd, *J* = 5.1, 2.9 Hz, 1H, OC**H**$_a$H$_b$), 2.66 (dd, *J* = 5.1, 4.0 Hz, 1H, OCH$_a$**H**$_b$), 2.14-2.04 (m, 2H, C=CHC**H**$_2$), 1.66 (s, 3H, CC**H**$_3$), 1.63-1.55 (m, 5H, CC**H**$_3$+CC**H**$_2$), 1.16 (s, 3H, HOCC**H**$_3$).

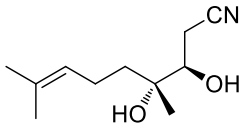
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.7 MHz): 131.8 (**C**=CH), 124.0 (C=**C**H), 69.2 (HO**C**CH$_3$), 57.6 (O**C**H), 43.2 (O**C**H$_2$), 41.1 (C**C**H$_2$), 25.6 (C**C**H$_3$), 22.7 (HOC**C**H$_3$), 22.1 (C=CH**C**H$_2$), 17.6 (C**C**H$_3$).

IR (ATR) cm^{-1}: 3448 (O-H st).

HRMS: Calculated for $[C_{10}H_{18}O_2Na]^+$: 193.1204 $[M+Na]^+$; found: 193.1206.

4.5. Synthesis of adduct 27.

(3*R*,4*R*)-3,4-Dihydroxy-4,8-dimethylnon-7-enenitrile (27)



To a solution of epoxide **28** (210 mg, 1.23 mmol) in dry toluene (10.5 mL) at 0 ºC, Et_2AlCN (1 M in toluene, 1.36 mL, 1.36 mmol) was added dropwise. The reaction was stirred at room temperature for 5 hours.Then, the mixture was diluted with EtOAc (10 mL) and cooled to 0 ºC, followed by the addition of NaF (135 mg, 3.21 mmol) and water (1 mL). The evolving gas is collected into a basic aqueous solution (NaOH 2 M). The resulting mixture was stirred at room temperature for 30 minutes, filtered through a pad of Na_2SO_4 and evaporated to dryness. After purification by flash column chromatography (FC) (*n*-hexane/EtOAc gradient from 2:1 to 1:1) the nitrile **27** (175 mg, 0.89 mmol) was isolated as a yellow solid.

Yield: 72%.

$[\alpha]_D^{20}$: +13.0 (*c* = 1.00, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz): 5.09-5.03 (m, 1H, C=C**H**), 3.79-3.72 (m, 2H, C**H**OH+O**H**), 2.63 (bs, 1H, O**H**), 2.58-2.49 (m, 2H, C**H**$_2$CN), 2.08-1.96 (m, 2H, C=CHC**H**$_2$), 1.65 (s, 3H, CC**H**$_3$), 1.58 (s, 3H, CC**H**$_3$), 1.54-1.46 (m, 2H, CC**H**$_2$), 1.10 (s, 3H, HOCC**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.7 MHz): 132.2 (**C**=CH), 123.7 (C=**C**H), 119.0 (**C**N), 74.0 (HO**C**CH_3), 72.4 (**C**HOH), 38.2 (C**C**H_2), 25.6 (C**C**H_3), 22.1 (C=CH**C**H_2), 21.4 (HOC**C**H_3), 21.0 (**C**H_2CN), 17.6 (C**C**H_3).

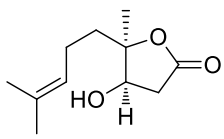
IR (ATR) cm^{-1}: 3441 (O-H st), 2253 (C≡N st).

M.p. (*n*-hexane/AcOEt) (ºC): 55-57.

HRMS: Calculated for $[C_{11}H_{19}NO_2Na]^+$: 220.1313 $[M+Na]^+$; found: 220.1342.

4.6. Synthesis of β-hydroxylactone 26.

(4*R*,5*R*)-4-Hydroxy-5-methyl-5-(4-methylpent-3-en-1-yl)dihydrofuran-2(3*H*)-one (26)



To a solution of nitrile **27** (149 mg, 0.76 mmol) in EGME (750 μL), an aqueous solution of NaOH 2 M (2.0 mL) was added and the mixture was heated under reflux for 1.5 hours. Then, the solution was acidified with HCl 2 M to pH = 2 and stirred for 17 hours at room temperature. After extraction with Et_2O (8 mL), the resulting aqueous phase was saturated with NaCl and further extracted with Et_2O (3 × 8 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (FC) (*n*-hexane/EtOAc gradient from 2:1 to 1:1) afforded the β-hydroxylactone **26** (119 mg, 0.60 mmol) as a colourless oil and the elimination product **34** (4 mg, 0.02 mmol) as a colourless oil.

Yield: 79%.

$[\alpha]_D^{20}$: +21.2 (*c* = 0.22, $CHCl_3$).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 700 MHz): 5.17-5.14 (m, 1H, C=C**H**), 4.19 (dd, *J* = 6.1, 2.1 Hz, 1H, C**H**OH), 2.94 (dd, *J* = 18.0, 6.1 Hz, 1H, $O_2CC\mathbf{H}_aH_b$), 2.51 (dd, *J* = 18.0, 2.1 Hz, 1H, $O_2CCH_a\mathbf{H}_b$), 2.25 (bs, 1H, O**H**), 2.18-2.06 (m, 2H, C=CHC$\mathbf{H}_2$), 1.85 (ddd, *J* = 14.1, 10.2, 5.4 Hz, 1H, $CC\mathbf{H}_aH_b$), 1.79 (ddd, *J* = 14.1, 10.4, 6.5 Hz, 1H, $CCH_a\mathbf{H}_b$), 1.70 (s, 3H, $CC\mathbf{H}_3$), 1.63 (s, 3H, $CC\mathbf{H}_3$), 1.35 (s, 3H, $OCC\mathbf{H}_3$).

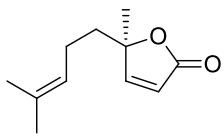
^{13}C-NMR (δ, ppm) ($CDCl_3$, 100.7 MHz): 175.7 (**C**O), 132.6 (**C**=CH), 123.4 (C=**C**H), 90.1 ($O\mathbf{C}CH_3$), 73.2 (**C**HOH), 38.4 ($O_2C\mathbf{C}H_2$), 33.9 ($C\mathbf{C}H_2$), 25.5 ($C\mathbf{C}H_3$), 22.9 ($OC\mathbf{C}H_3$), 22.3 (C=CH$\mathbf{C}H_2$), 17.6 ($C\mathbf{C}H_3$).

IR (ATR) cm^{-1}: 3428 (O-H st), 1749 (C=O st).

HRMS: Calculated for $[C_{11}H_{18}O_3Na]^+$: 221.1154 $[M+Na]^+$; found: 221.1170.

The spectral data is in agreement with previous report.[21]

(*R*)-5-Methyl-5-(4-methylpent-3-en-1-yl)furan-2(5*H*)-one (34)



Yield: 3%.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 700 MHz): 7.34 (d, *J* = 5.6 Hz, 1H, $O_2CC\mathbf{H}$=CH), 6.00 (d, *J* = 5.6 Hz, 1H, O_2CCH=C**H**), 5.04-4.98 (m, 1H, C=C**H**), 2.03-1.96 (m, 1H, C=CHC$\mathbf{H}_aH_b$), 1.94-1.87 (m, 1H, C=CHC$H_a\mathbf{H}_b$), 1.85 (ddd, *J* = 14.0, 10.5, 5.4 Hz, 1H, $CC\mathbf{H}_aH_b$), 1.72 (ddd, *J* = 14.0, 10.7, 5.2 Hz, 1H, $CCH_a\mathbf{H}_b$), 1.66 (s, 3H, $CC\mathbf{H}_3$), 1.56 (s, 3H, $CC\mathbf{H}_3$), 1.46 (s, 3H, $OCC\mathbf{H}_3$).

[21] Viturro, C. I.; Maier, M. S.; Stortz, C. A.; de la Fuente, J. R. *Tetrahedron: Asymmetry* **2001**, *12*, 991.

^{13}C-NMR (δ, ppm) ($CDCl_3$, 176.2 MHz): 172.6 (**C**O), 160.2 (O_2CCH=**C**H), 132.7 (**C**=CH), 122.8 (C=**C**H), 120.4 (O_2C**C**H=CH), 88.9 (O**C**CH_3), 38.2 (C**C**H_2), 25.6 (C**C**H_3), 24.0 (OC**C**H_3), 22.4 (C=CH**C**H_2), 17.7 (C**C**H_3).

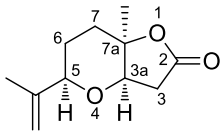
IR (ATR) cm^{-1}: 1752 (C=O st).

HRMS: Calculated for $[C_{11}H_{16}O_2Na]^+$: 203.1048 $[M+Na]^+$; found: 203.0992.

The spectral data is in agreement with previous report.[22]

4.7. Synthesis of (+)-Greek tobacco lactone 25.

(3a*R*,5*R*,7a*R*)-7a-Methyl-5-(prop-1-en-2-yl)hexahydro-2*H*-furo[3,2-*b*]pyran-2-one (25)



A mixture of β-hydroxylactone **26** (35 mg, 0.176 mmol) and palladium(II) trifluoroacetate (60 mg, 0.176 mmol) in dry DMSO (1.8 mL) under inert atmosphere, was stirred at 80 ºC using microwave irradiation during 8 hours. The reaction mixture was allowed to reach room temperature and then filtered over silica gel. The filtrate was concentrated under reduced pressure and purificated by flash column chromatography (FC) (*n*-hexane/EtOAc gradient from 4:1 to 1:1), obtaining the (+)-Greek tobacco lactone **25** (14 mg, 0.072 mmol) as a colourless oil.

Yield: 41%.

dr: 85:15.

$[\alpha]_D^{20}$: +33.0 (*c* = 0.1, CH_2Cl_2).

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[22] Siitonen, J. H.; Pihko, P. M. *Synlett* **2014**, *25*, 1888.

^{1}H-NMR (δ, ppm) ($CDCl_3$, 700 MHz): 4.97-4.95 (m, 1H, CC**H**$_a$H$_b$), 4.86-4.84 (m, 1H, CCH$_a$**H**$_b$), 4.08 (app d, *J* = 4.3 Hz, 1H, **H**-3a), 3.74-3.71 (m, 1H, **H**-5), 2.88 (dd, *J* = 17.5, 4.3 Hz, 1H, **H**-3$_a$), 2.54 (dd, *J* = 17.5, 0.6 Hz, 1H, **H**-3$_b$), 2.32-2.28 (m, 1H, **H**-7$_a$), 1.73-1.67 (m, 5H, CC**H**$_3$+**H**-7$_b$+**H**-6$_a$), 1.60-1.57 (m, 1H, **H**-6$_b$), 1.31 (s, 3H, C-7aC**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 176.2 MHz): 175.7 (**C**-2), 144.8 (C-5**C**), 111.4 (C**C**H$_2$), 81.6 (**C**-7a), 78.6, 77.5 (**C**-3a+**C**-5), 38.2 (**C**-3), 32.3 (**C**-7), 25.2 (C-7a**C**H$_3$), 25.1 (**C**-6), 18.4 (C**C**H$_3$).

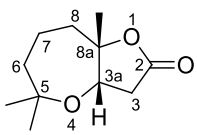
IR (ATR) cm^{-1}**:** 1777 (C=O st).

HRMS: Calculated for $[C_{11}H_{16}O_3Na]^+$: 219.0997 $[M+Na]^+$; found: 219.0997.

The spectral data is in agreement with previous report.[23]

4.8. Synthesis of cycloadduct 35.

(3a*S*,8a*S*)-5,5,8a-Trimethylhexahydrofuro[3,2-*b*]oxepin-2(3*H*)-one (35)



A mixture of β-hydroxylactone **26** (20.4 mg, 0.103 mmol), benzoquinone (22.3 mg, 0.206 mmol), White catalyst (5.2 mg, 0.010 mmol) and silver trifluoromethanesulfonate (2.6 mg, 0.010 mmol) in dry dioxane (0.3 mL) under inert atmosphere, was stirred at 80 ºC during 18 hours. The reaction was allowed to reach room temperature and then brine (5 mL) was added, followed by the extraction with EtOAc (3 × 5 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. After purification by flash column

[23] Clark, J. S.; Hayes, S. T.; Blake, A. J.; Gobbi, L. *Tetrahedron Lett.* **2007**, *48*, 2501.

chromatography (FC) (*n*-hexane/EtOAc gradient from 3:1 to 2:1) the cycloadduct **35** (12.5 mg, 0.063 mmol) was obtained as a white solid.

Yield: 61%.

$[\alpha]_D^{20}$: -26.2 (*c* = 0.50, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 400 MHz): 4.01 (app d, *J* = 7.7 Hz, 1H, **H**-3a), 2.96 (dd, *J* = 18.7, 7.7 Hz, 1H, **H**-3_a), 2.45 (app d, *J* = 18.7 Hz, 1H, **H**-3_b), 2.25-2.14 (m, 1H, **H**-8_a), 1.84-1.74 (m, 2H, **H**-8_b+**H**-7_a), 1.67-1.59 (m, 1H, **H**-6_a), 1.51-1.42 (m, 2H, **H**-7_b+**H**-6_b), 1.33 (d, *J* = 0.8 Hz, 3H, C-8aC**H**$_3$), 1.22 (s, 3H, C-5C**H**$_3$), 1.13 (s, 3H, C-5C**H**$_3$).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 176.2 MHz): 175.0 (**C**-2), 90.7 (**C**-8a), 76.8 (**C**-5), 73.3 (**C**-3a), 37.1 (**C**-3), 36.0 (**C**-6), 32.8 (**C**-8), 27.5 (C-5**C**H$_3$), 26.7 (C-5**C**H$_3$), 23.0 (C-8a**C**H$_3$), 18.4 (**C**-7).

IR (ATR) cm^{-1}: 1766 (C=O st).

M.p. (CH_2Cl_2) (ºC): 79-81.

HRMS: Calculated for $[C_{11}H_{18}O_3Na]^+$: 221.1154 $[M+Na]^+$; found: 221.1166.

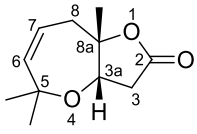
4.9. Synthesis of cycloadducts 36 and 37.

*General procedure for the synthesis of cycloadducts **36** and **37**.*

To a mixture of the β-hydroxylactone **26** (26.6 mg, 0.134 mmol) and palladium trifluoroacetate (23.0 mg, 0.067 mmol), dry acetonitrile (0.5 mL) was added. The flask was evacuated and back-filled with O_2 (3 × balloon), heated to 80 ºC and allowed to stir under O_2 (1 atm) during 90 minutes. The mixture was

allowed to reach room temperature and then filtered over silica gel. The filtrate was concentrated under reduced pressure and purificated by flash column chromatography (FC) (*n*-hexane/EtOAc gradient from 4:1 to 3:1), obtaining the cycloadduct **36** (12.8 mg, 0.065 mmol) and **37** (4.0 mg, 0.020 mmol) as a white solids in a 3.8:1 ratio.

(3a*S*,8a*S*)-5,5,8a-Trimethyl-3,3a,8,8a-tetrahydrofuro[3,2-*b*]oxepin-2(3*H*)-one (36)



Yield: 49%.

$[\alpha]_D^{20}$: -52.2 (*c* = 0.50, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 700 MHz): 5.51 (ddd, *J* = 11.0, 8.8, 5.4 Hz, 1H, **H**-7), 5.39-5.36 (m, 1H, **H**-6), 4.07 (app d, *J* = 7.0 Hz, 1H, **H**-3a), 3.08-3.04 (m, 1H, **H**-8_a), 2.91 (dd, *J* = 18.3, 7.1 Hz, 1H, **H**-3_a), 2.47 (app d, *J* = 18.3 Hz, 1H, **H**-3_b), 2.16 (dd, *J* = 12.8, 8.8 Hz, 1H, **H**-8_b), 1.33 (d, *J* = 1.0 Hz, 3H, C-8aC**H**$_3$), 1.32 (s, 3H, C-5C**H**$_3$), 1.24 (s, 3H, C-5C**H**$_3$).

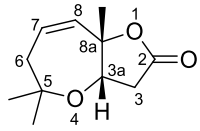
^{13}C-NMR (δ, ppm) ($CDCl_3$, 176.2 MHz): 175.2 (**C**-2), 138.0 (**C**-6), 121.3 (**C**-7), 90.3 (**C**-8a), 79.2 (**C**-5), 73.7 (**C**-3a), 36.8 (**C**-3), 32.8 (**C**-8), 29.2 (C-5**C**H_3), 25.2 (C-5**C**H_3), 23.4 (C-8a**C**H_3).

IR (ATR) cm^{-1}**:** 1773 (C=O st).

M.p. (CH_2Cl_2) (ºC): 87-89.

HRMS: Calculated for $[C_{11}H_{16}O_3Na]^+$: 219.0997 $[M+Na]^+$; found: 219.1014.

(3a*S*,8a*S*)-5,5,8a-Trimethyl-3,3a,5,6-tetrahydrofuro[3,2-*b*]oxepin-2(8a*H*)-one (37)



Yield: 15%.

$[\alpha]_D^{20}$: -28.5 (*c* = 0.20, CH_2Cl_2).

^{1}H-NMR (δ, ppm) ($CDCl_3$, 500 MHz): 5.80-5.76 (m, 1H, **H**-8), 5.68 (ddd, *J* = 10.8, 8.6, 5.8 Hz, 1H, **H**-7), 4.17 (app d, *J* = 6.5 Hz, 1H, **H**-3a), 2.96 (dd, *J* = 18.1, 6.5 Hz, 1H, **H**-3_a), 2.48 (app d, *J* = 18.1 Hz, 1H, **H**-3_b), 2.39-2.33 (m, 1H, **H**-6_a), 1.93 (ddd, *J* = 14.9, 8.6, 1.0 Hz, 1H, **H**-6_b), 1.39 (s, 3H, C-8a**C**H_3), 1.21 (s, 3H, C-5**C**H_3), 1.17 (s, 3H, C-5**C**H_3).

^{13}C-NMR (δ, ppm) ($CDCl_3$, 176.2 MHz): 174.5 (**C**-2), 132.4 (**C**-8), 123.6 (**C**-7), 91.8 (**C**-8a), 76.2 (**C**-5), 72.7 (**C**-3a), 37.3 (**C**-3), 36.5 (**C**-6), 27.6 (C-5**C**H_3), 25.9 (C-5**C**H_3), 24.7 (C-8a**C**H_3).

IR (ATR) cm^{-1}: 1765 (C=O st).

M.p. (CH_2Cl_2) (ºC): 83-85.

HRMS: Calculated for $[C_{11}H_{16}O_3Na]^+$: 219.0997 $[M+Na]^+$; found: 219.1013.

Appendix

Appendix

Abbreviations, acronyms and symbols

Ac	Acetyl
app d	Apparent doublet
app t	Apparent triplet
Ar	Aryl
ATR	Attenuated total reflectance
BAIB	(Diacetoxyiodo)benzene
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BQ	*p*-Benzoquinone
bs	Broad signal
c	Concentration (measured in g/100mL)
$\mathbf{C_{arom}}$	Aromatic carbon
Cat	Catalyst
Cbz	Benzyloxycarbonyl
CI	Chemical ionization
Conv.	Conversion
COSY	Correlation spectroscopy
δ	Chemical shift
d	Doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,5-diazabycyclo[5.4.0]undec-5-ene
DCE	1,2-dichloroethane
dd	Doublet of doublets

ddd	Doublet of doublets of doublets
DEPT	Distortionless Enhancement by Polarization Transfer
DET	Diethyl tartrate
DFT	Density functional theory
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
DIPEA	*N*,*N*-Diisopropylethylamine
DIPT	Diisopropyl tartrate
DKR	Dynamic kinetic resolution
DMA	*N*,*N*-Dimethylacetamide
DMAP	*N*,*N*-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	Dimethylsulfoxide
DPP	Diphenylphosphoric acid
dq	Doublet of quartets
dr	Diastereomeric ratio
E	Electrophile
ee	Enantiomeric excess
EGME	2-Methoxyethanol
EI	Electron ionization
ent	Enantiomer
equiv.	Equivalent
ESI	Electrospray ionization
et al.	*Et alii* (and others)
eV	Electron volt
EWG	Electron-withdrawing group
FC	Flash chromatography
FGI	Functional group interconversion
FT	Fourier transform
GC	Gas chromatography
HMBC	Heteronuclear multiple bond correlation

HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation spectroscopy
i.e.	*Id est* (that is)
IR	Infrared
J	Coupling constant
LiHDMS	Lithium bis(trimethylsilyl)amide
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
M.p.	Melting point
m/z	Mass-to-charge ratio
M^+	Molecular ion
MBH	Morita-Baylis-Hillman
Mes	Mesityl
MS	Mass spectrometry or Molecular sieves
MW	Microwave
n.d.	Not determined
n.O.e.	Nuclear Overhauser effect
n.r.	No reaction
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect correlation spectroscopy
Ns	*p*-Nitrobenzenesulfonyl
Nu	Nucleophile
PCC	Pyridinium chlorochromate
phen	Phenanthroline
PIFA	Bis-trifluoroacetoxy iodobenzene
PMP	*p*-Methoxyphenyl
ppm	Parts per million
Pro	Proline
PTC	Phase Transfer Catalysis
Py	Pyridine

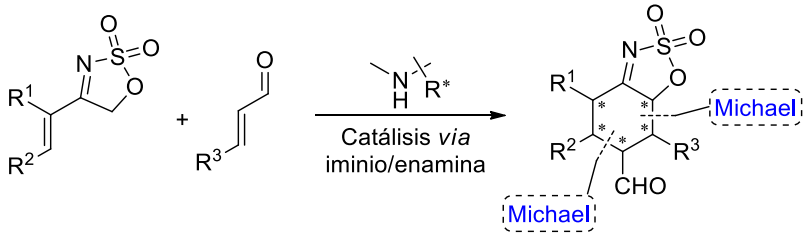
q	Quartet
QDT	Quinidine thiourea
QNT	Quinine thiourea
QTOF	Quadrupole-time of flight
R	Alkyl group or substituent
r.t.	Room temperature
s	Singlet
SOMO	Single Occupied Molecular Orbital
t	Triplet
T	Temperature
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*Tert*-Butyl hydroperoxide
TBS/TBDMS	*tert*-Butyldimethylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethysilyl
τ_{major}	Retention time of the major enantiomer
τ_{minor}	Retention time of the minor enantiomer
Tr	Trityl/triphenylmethyl
Ts	Tosyl
UPLC	Ultra performance liquid chromatography
vs.	Versus
X	Halogen or heteroatom
&	And

Resumen extendido

En el presente trabajo de investigación se han desarrollado diversas metodologías basadas en reacciones en cascada iniciadas por adiciones de Michael, con el fin de obtener productos de interés de manera enantioenriquecida, empleando aminas quirales como elementos estereoinductores de la reacción, bajo activación *via* ion iminio.

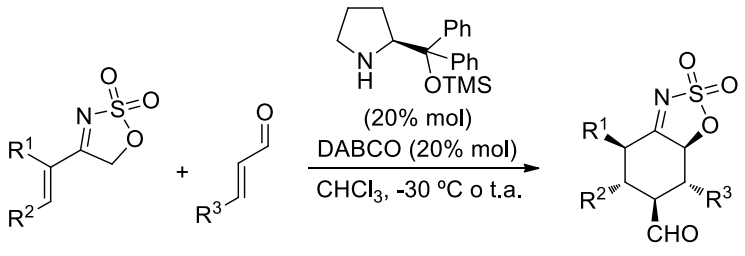
En concreto, las reacciones en cascada Michael/Michael, aplicando la organocatálisis como herramienta estereoinductora, permiten la síntesis de compuestos carbo- y heterocíclicos polisustituidos de manera enantiocontrolada. Esto está basado en el diseño adecuado de nuevos sustratos con diferentes funcionalidades capaces de participar en este tipo de reacciones. En ese sentido, y dada la experiencia de nuestro grupo en el campo de la organocatálisis asimétrica, nos propusimos como primer objetivo del presente trabajo el estudio de la versatilidad sintética de los 2,2-dióxidos de 4-alquenil-5*H*-1,2,3-oxatiazol como reactivos multifuncionales en procesos en cascada.

Así, en primer lugar, se ha demostrado la aplicabilidad de este tipo de sustratos como dadores/aceptores de Michael en reacciones en cascada, junto a aldehídos α,β-insaturados, iniciadas por adición de Michael bajo activación *via* ion iminio, seguida de otra adición conjugada mediante catálisis *via* enamina, empleando una amina secundaria quiral como elemento estereoinductor de la reacción y una base como cocatalizador, obteniéndose compuestos cíclicos polisustituidos (Esquema 1).



Esquema 1

Una vez demostrada la viabilidad de la reacción, y tras un proceso de optimización, se determinaron las mejores condiciones para llevar a cabo la reacción, las cuales dependían del tipo de sustrato inicial. De esta manera, se consiguió extender la metodología de manera eficaz al empleo de enales con diferentes sustituyentes en posición β, así como al empleo de varios 2,2-dióxidos de 4-alquenil-5*H*-1,2,3-oxatiazol, con sustituyentes de diferente naturaleza. Así, se obtuvo una serie de ciclohexanos y derivados de decalina con muy buenos rendimientos y con excelentes estereoselectividades (Esquema 2).

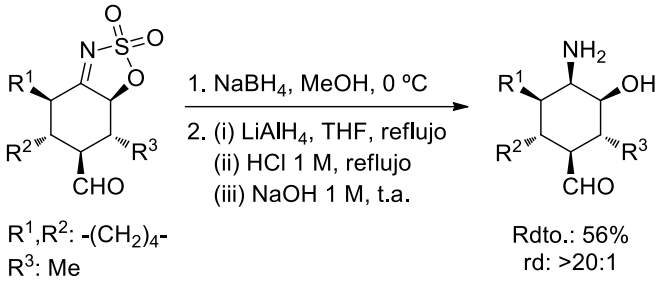


R^1: Me
R^2: Me, Et, Ph
R^1,R^2: -$(CH_2)_4$-
R^3: Sustituyentes alquílicos y aromáticos

Rdto.: 26-73%
rd: 8:1->20:1
ee: 91->99%

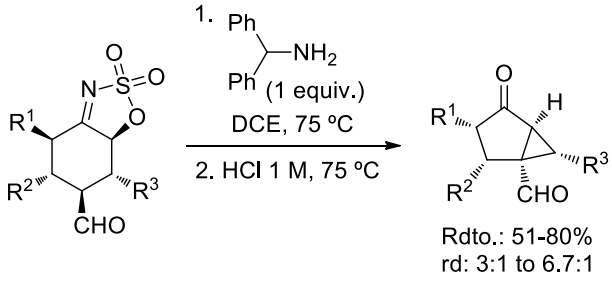
Esquema 2

Además, se estudió la versatilidad de los cicloaductos obtenidos teniendo en cuenta la habilidad del sulfonato como grupo saliente. Por un lado, se demostró la obtención de la agrupación 1,2-amino alcohol, mediante transformación de uno de los cicloaductos como ejemplo representativo (Esquema 3).



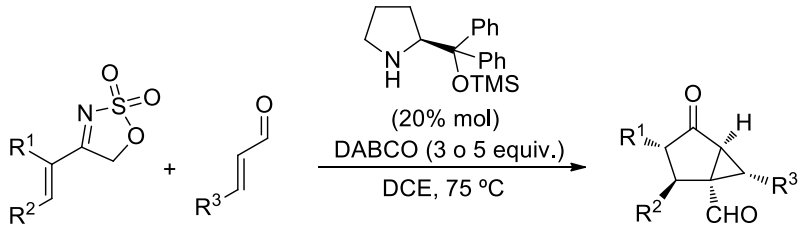
Esquema 3

Por otro lado, se consiguieron preparar compuestos bicíclicos de mayor complejidad, con anillos de tres y cinco miembros fusionados, de manera eficaz mediante un proceso de sustitución nucleófila transanular, seguido de hidrólisis de la imina resultante, empleando una amina primaria aquiral como promotora de la reacción. (Esquema 4).



Esquema 4

Teniendo en cuenta el tipo de reactividad observado, procedimos a llevar a cabo la síntesis de estos compuestos bicíclicos mediante un proceso en cascada Michael/Michael/S_N2 transanular/hidrólisis de la imina, a partir de los 2,2-dióxidos de 4-alquenil-5*H*-1,2,3-oxatiazol y enales. Tras un proceso de optimización se llegó a la conclusión general de que aumentando la temperatura y los equivalentes de base la reacción en cascada se veía favorecida, dándose, inesperadamente, la formación de otro diastereoisómero. De esta manera, se extendió la reacción, obteniéndose una gran variedad de compuestos bicíclicos y tricíclicos con rendimientos moderados y con un excelente estereocontrol (Esquema 5). Además, en varios casos se ha llevado a cabo la síntesis diastereoselectiva de los correspondientes dioles, mediante reducción de los dos grupos carbonilo presentes en el biciclo.



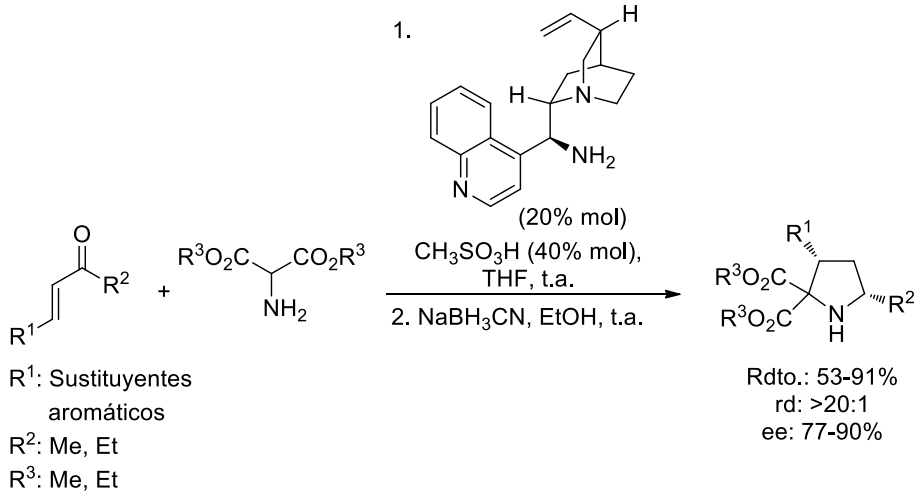
R^1: H, Me
R^2: Me, Et, Ph
R^1,R^2: -$(CH_2)_4$-
R^3: Sustituyentes aromáticos

Rdto.: 30-55%
rd: >20:1
ee: 75-99%

Esquema 5

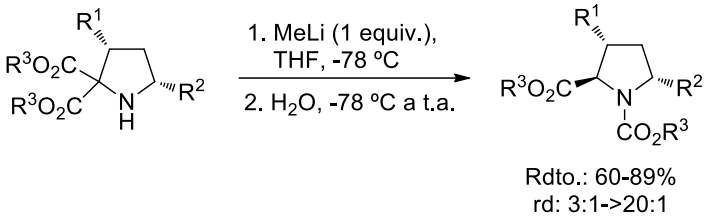
Como segundo objetivo principal de la presente memoria, se ha desarrollado una metodología organocatalítica dirigida a la síntesis de derivados de prolina de manera estereocontrolada. Así, en primera instancia, se comenzó con la preparación de pirrolidinas quirales mediante una reacción en cascada

Michael/condensación intramolecular entre aminomalonatos y cetonas α,β-insaturadas, seguida de la reducción diastereoselectiva de la imina resultante en *one-pot*. Para ello, se empleó una amina primaria quiral derivada de la cinchona como catalizador, y un ácido de Brønsted como cocatalizador, el cual resultó ser clave en el curso estereoquímico de la reacción. En las mejores condiciones, se evaluaron una serie de enonas β-arílicas y varios aminomalonatos, obteniéndose en todos los casos muy buenos resultados (Esquema 6).



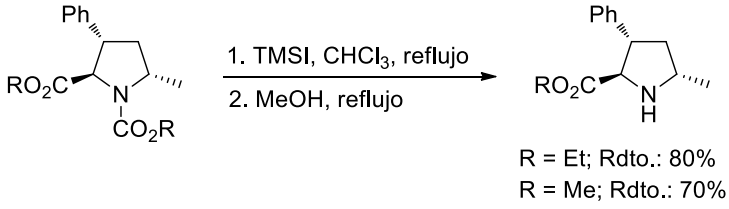
Esquema 6

Con el fin de preparar las prolinas correspondientes, las pirrolidinas obtenidas se sometieron a un proceso de transposición C→N de acilo, promovido por base, obteniéndose los correspondientes carbamatos con muy buenos rendimientos y diastereoselectividades (Esquema 7).



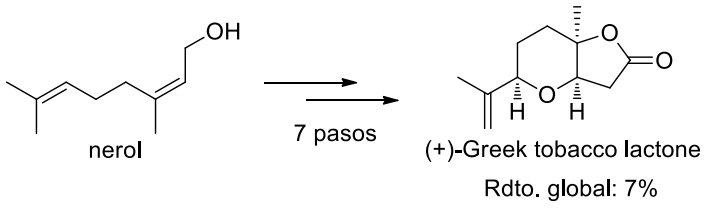
Esquema 7

Por último, tras desprotección mediante un sencillo procedimiento, se obtuvieron los esteres de prolina objetivo con buenos rendimientos (Esquema 8).



Esquema 8

Finalmente, se recoge el trabajo llevado a cabo en una estancia de tres meses realizada en el grupo del profesor M. Christmann en la Universidad libre de Berlín. En dicho periodo, se desarrolló la síntesis total de la *(+)-Greek tobacco lactone*, pudiéndose completar en un total de siete pasos con un rendimiento global del 7%, partiendo del producto natural nerol (Esquema 9).



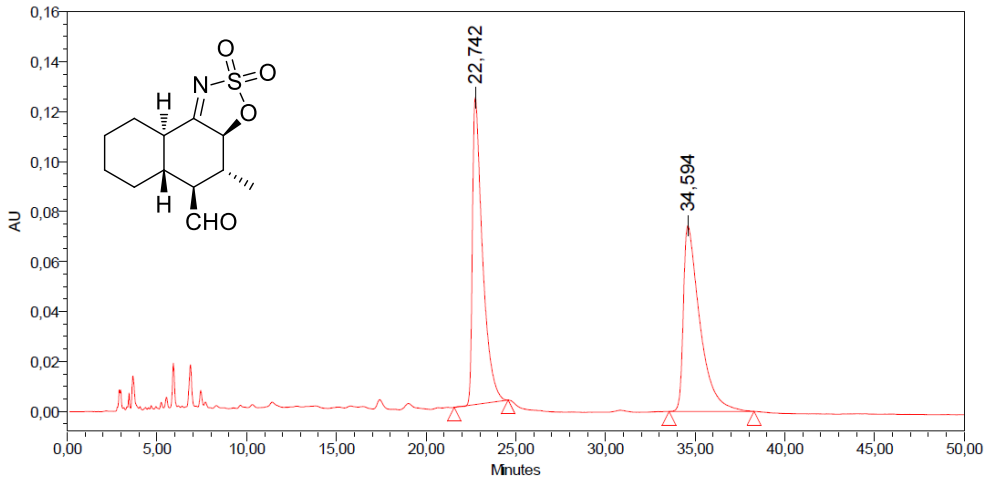
Esquema 9

Parte del trabajo recogido en la presente memoria ha dado lugar a las siguientes publicaciones:

1. "*4-Alkenyl-5H-1,2,3-oxathiazole 2,2-dioxides in Catalytic and Enantioselective [4+2] Cycloaddition through Iminium Activation. Straightforward Access to the trans-Decaline Framework and to Densely Functionalized Cyclohexanes*".
Iker Riaño, Uxue Uria, Luisa Carrillo, Efraim Reyes, Jose L. Vicario.
Org. Chem. Front. **2015**, *2*, 206.

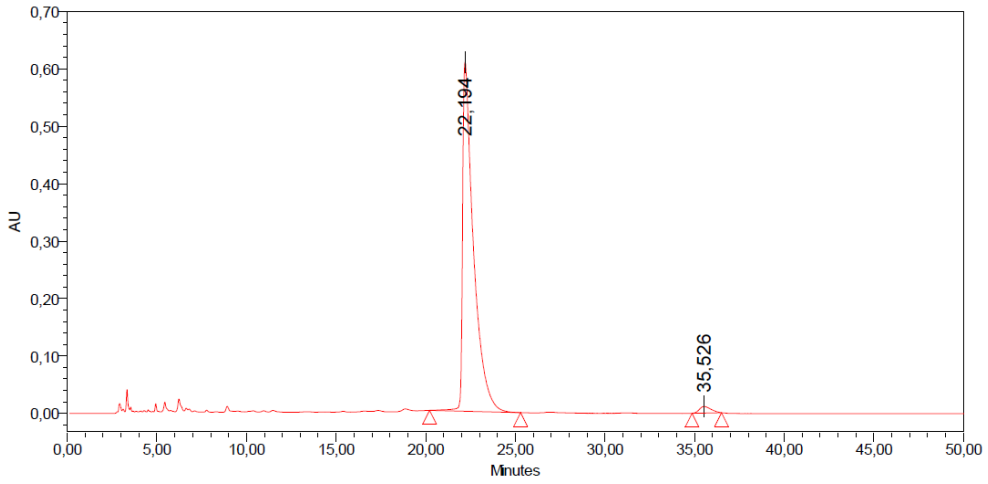
2. *"Organocatalytic Enantio- and Diastereoselective Synthesis of 3,5-Disubstituted Prolines"*.
Iker Riaño, Estibaliz Díaz, Uxue Uria, Efraim Reyes, Luisa Carrillo, Jose L. Vicario.
Chem. Commun. **2016**, *52*, 2330.

HPLC traces



Peak Results

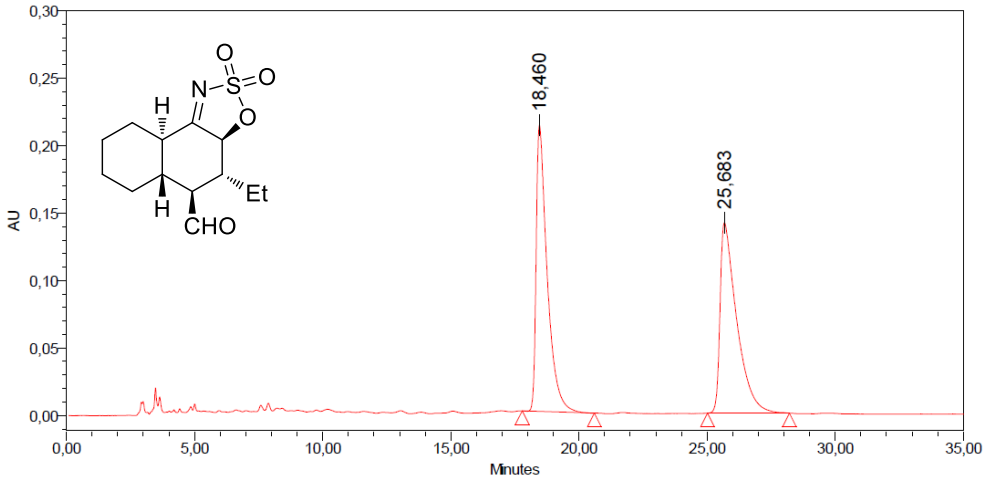
	RT	Area	Height	% Area
1	22,742	4789360	122852	50,24
2	34,594	4743920	74334	49,76



Peak Results

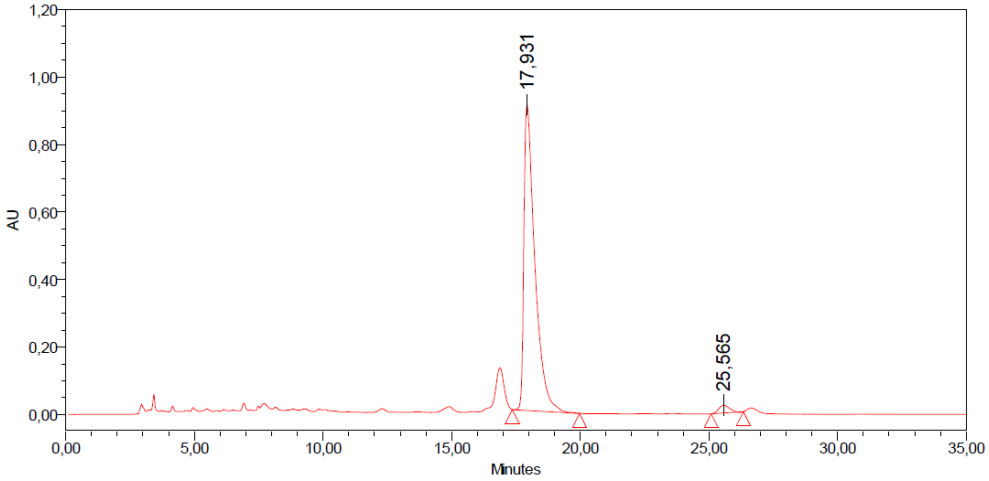
	RT	Area	Height	% Area
1	22,194	25606176	608234	98,04
2	35,526	513050	11405	1,96

HPLC chromatogram of the racemic and chiral compound **6a**.



Peak Results

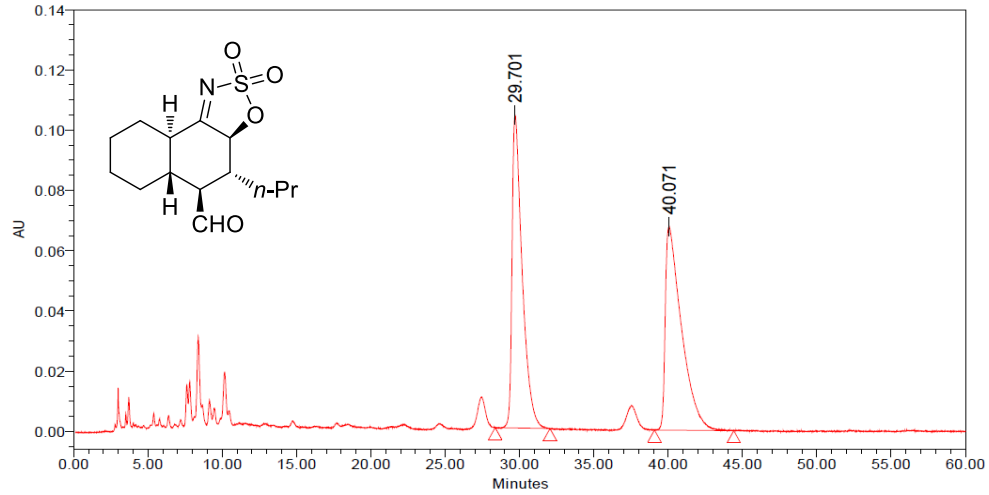
	RT	Area	Height	% Area
1	18,460	6313276	212107	49,84
2	25,683	6352907	141218	50,16



Peak Results

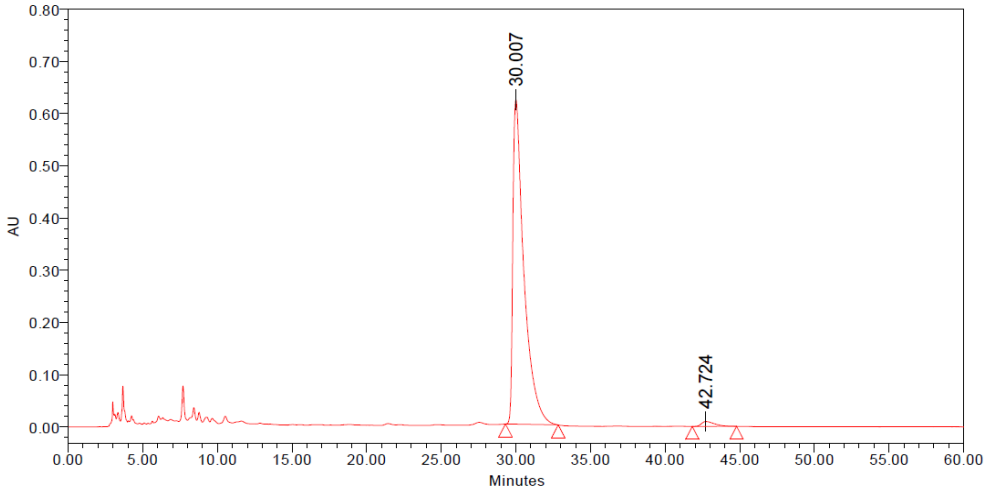
	RT	Area	Height	% Area
1	17,931	26753206	906906	97,53
2	25,565	677631	22795	2,47

HPLC chromatogram of the racemic and chiral compound **6b**.



Peak Results

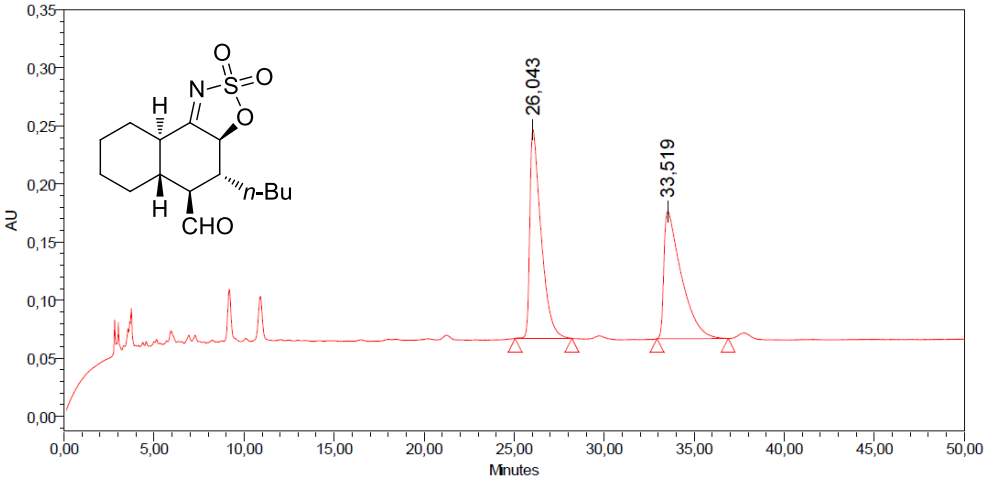
	RT	Area	Height	% Area
1	29.701	4917935	103907	49.05
2	40.071	5108666	67458	50.95



Peak Results

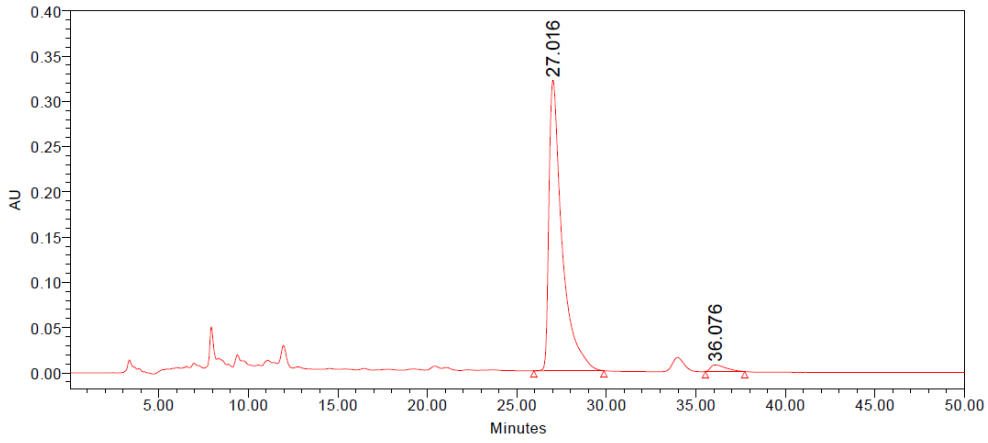
	RT	Area	Height	% Area
1	30.007	32067635	621893	98.23
2	42.724	576270	9511	1.77

HPLC chromatogram of the racemic and chiral compound **6c**.



Peak Results

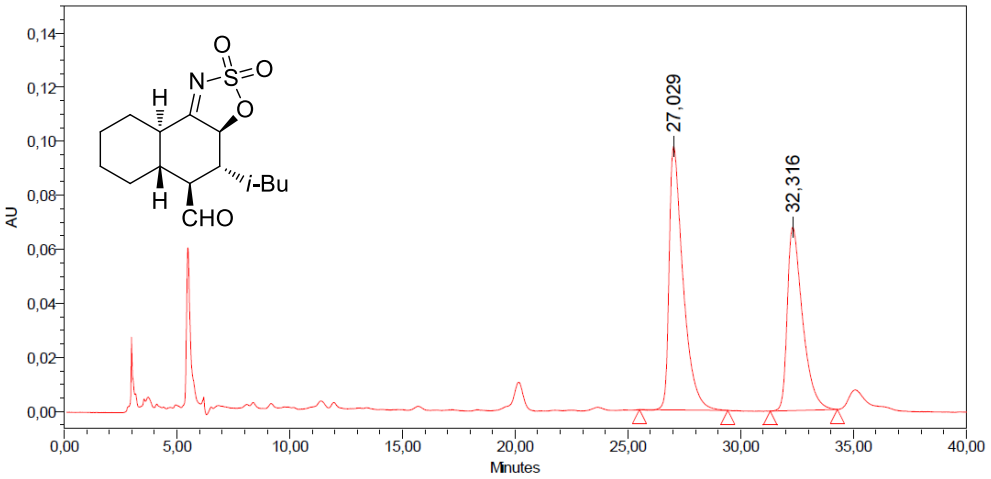
	RT	Area	Height	% Area
1	26,043	7820157	179693	51,53
2	33,519	7355514	109539	48,47



Peak Results

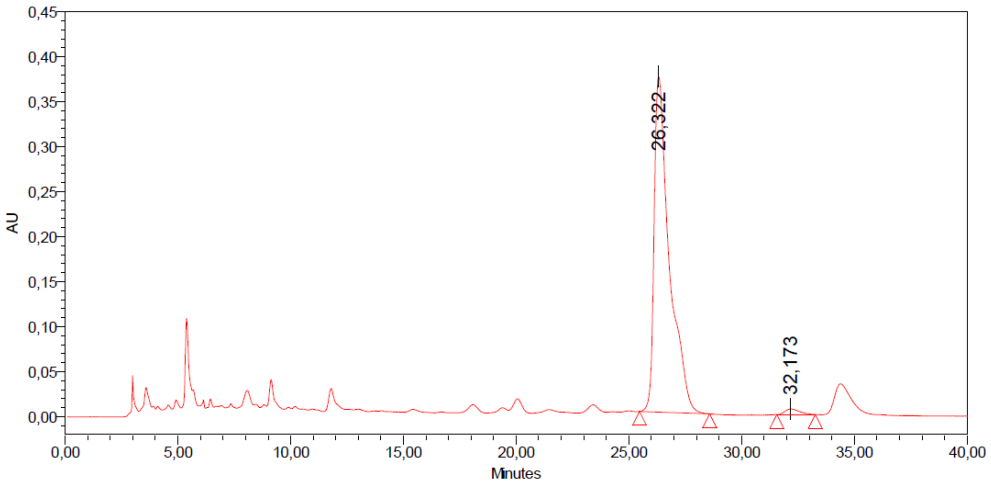
	RT	Area	Height	% Area
1	27.016	16288880	321059	97.38
2	36.076	438468	7407	2.62

HPLC chromatogram of the racemic and chiral compound **6d**.



Peak Results

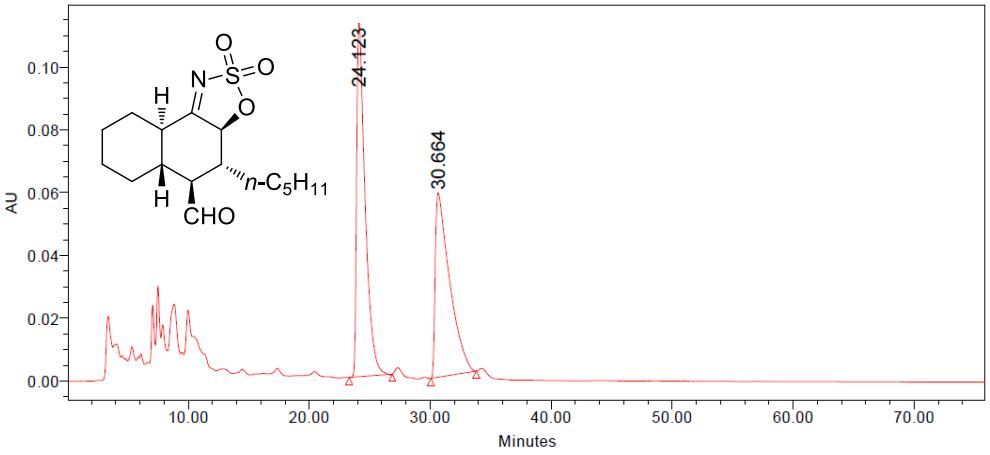
	RT	Area	Height	% Area
1	27,029	4185089	97444	56,67
2	32,316	3199552	67778	43,33



Peak Results

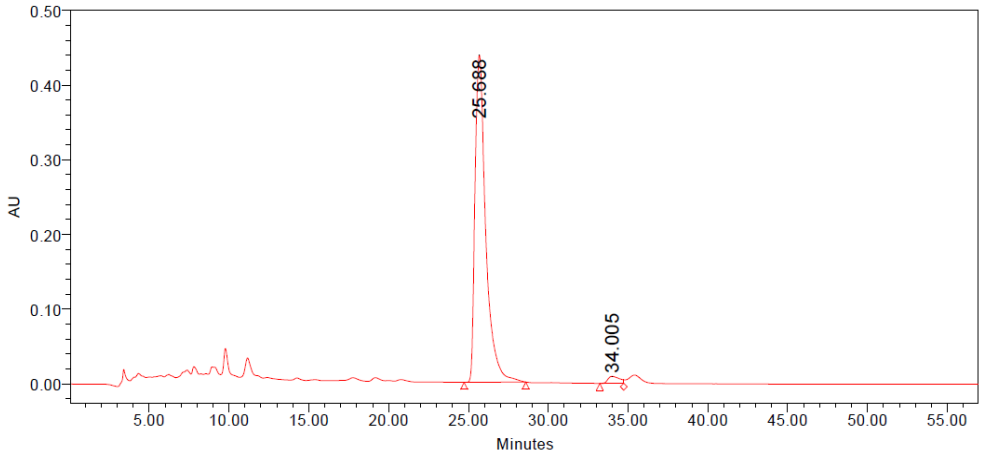
	RT	Area	Height	% Area
1	26,322	17387788	372726	98,47
2	32,173	271011	6245	1,53

HPLC chromatogram of the racemic and chiral compound **6e**.



Peak Results

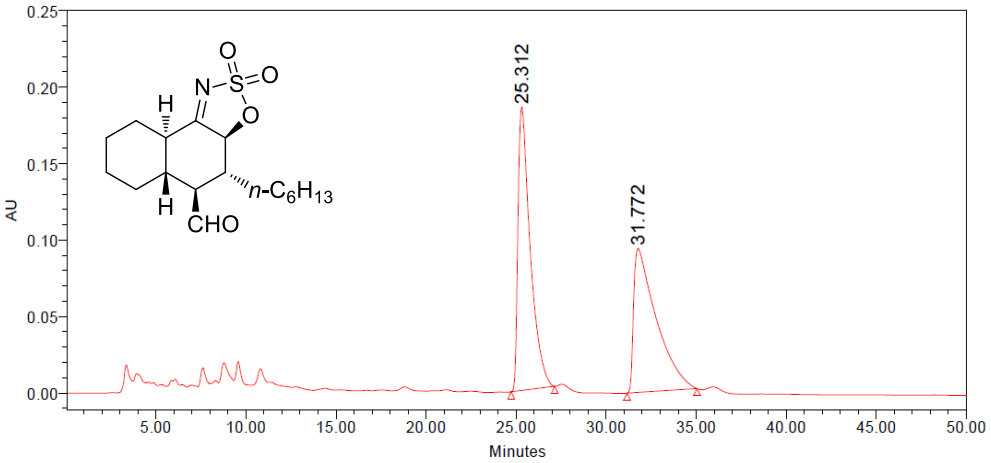
	RT	Area	Height	% Area
1	24.123	5503027	112550	53.11
2	30.664	4857768	58586	46.89



Peak Results

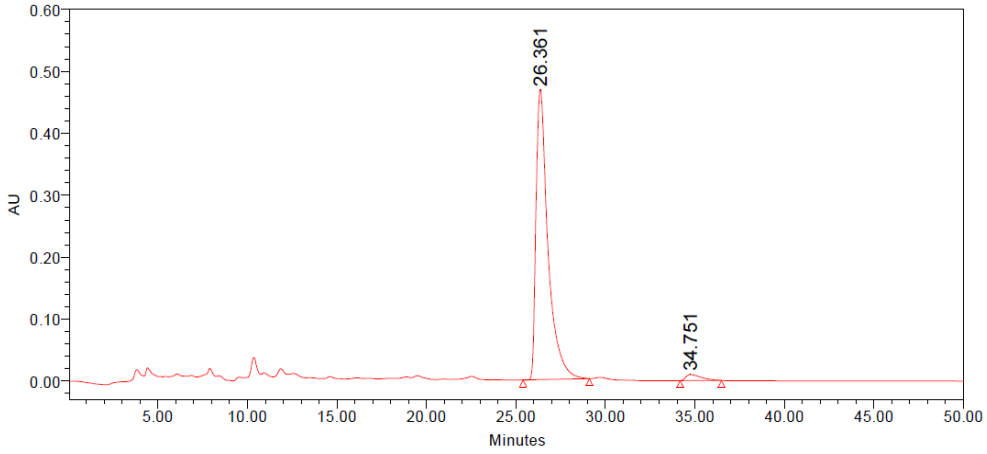
	RT	Area	Height	% Area
1	25.688	20523329	438109	97.78
2	34.005	465631	9289	2.22

HPLC chromatogram of the racemic and chiral compound **6f**.



Peak Results

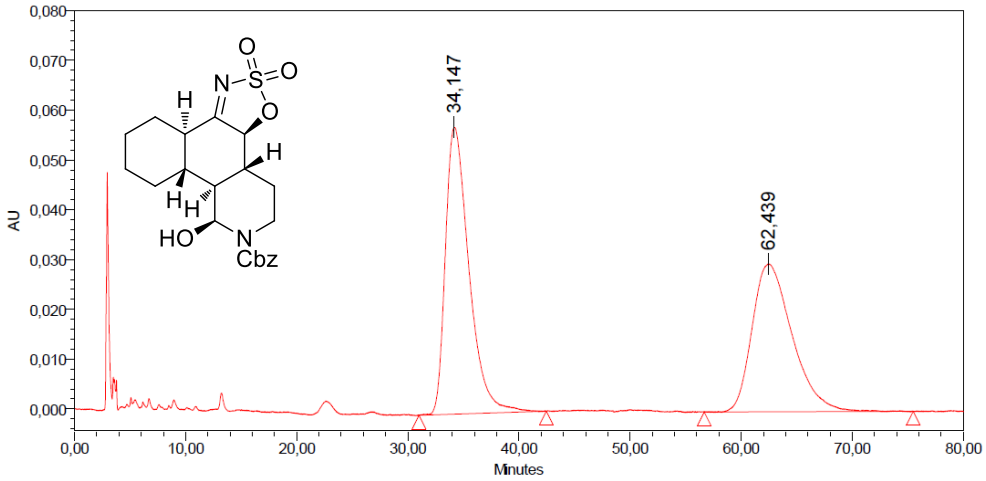
	RT	Area	Height	% Area
1	25.312	8748420	184850	51.55
2	31.772	8223231	94075	48.45



Peak Results

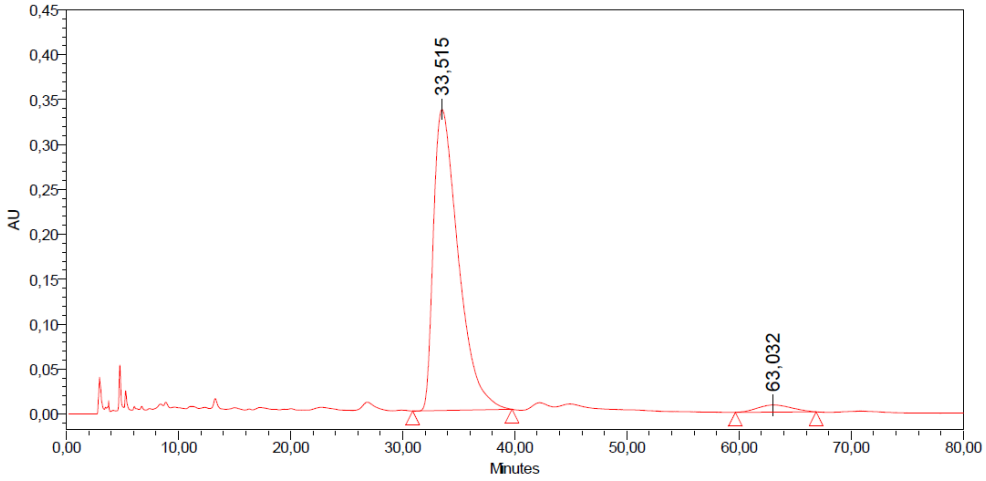
	RT	Area	Height	% Area
1	26.361	21703719	468410	97.42
2	34.751	574235	9722	2.58

HPLC chromatogram of the racemic and chiral compound **6g**.



Peak Results

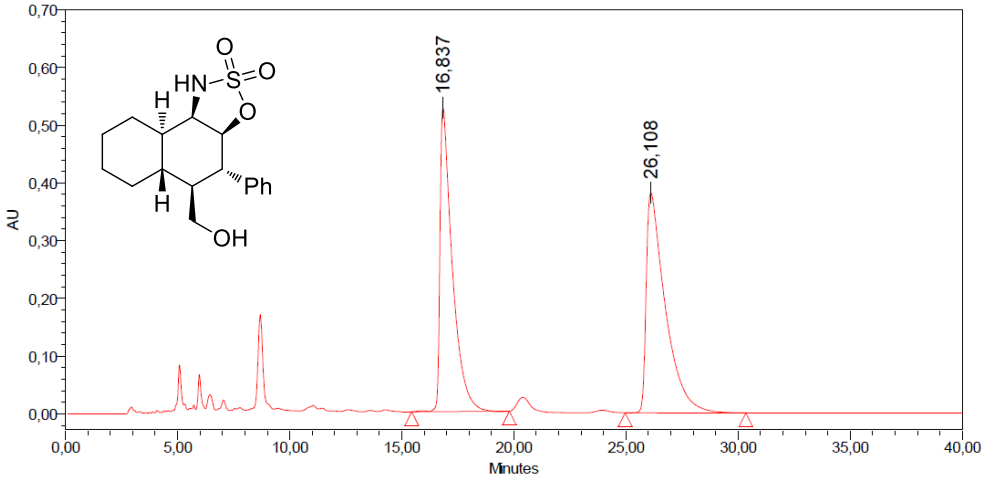
	RT	Area	Height	% Area
1	34,147	8487050	57634	53,28
2	62,439	7442958	29757	46,72



Peak Results

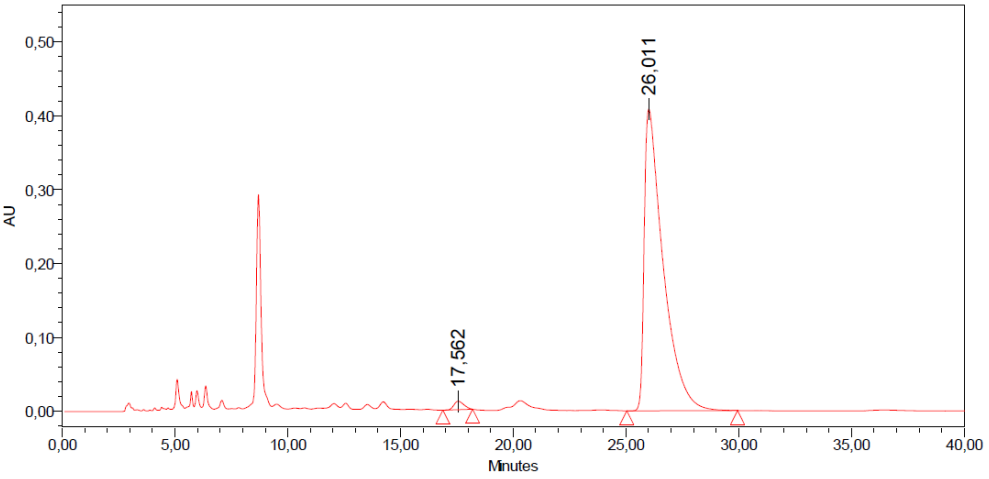
	RT	Area	Height	% Area
1	33,515	51553691	335362	96,83
2	63,032	1688099	8021	3,17

HPLC chromatogram of the racemic and chiral compound **6h**.



Peak Results

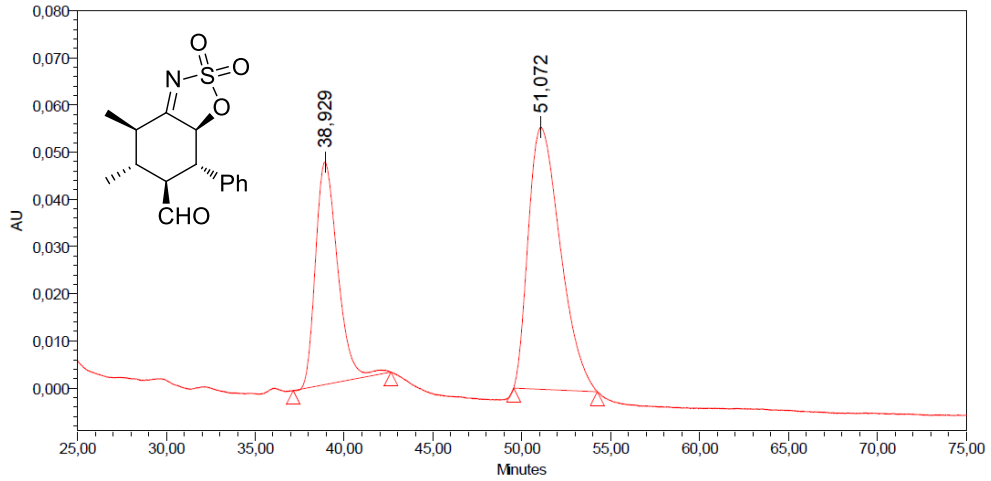
	RT	Area	Height	% Area
1	16,837	20030856	525963	47,14
2	26,108	22463497	381100	52,86



Peak Results

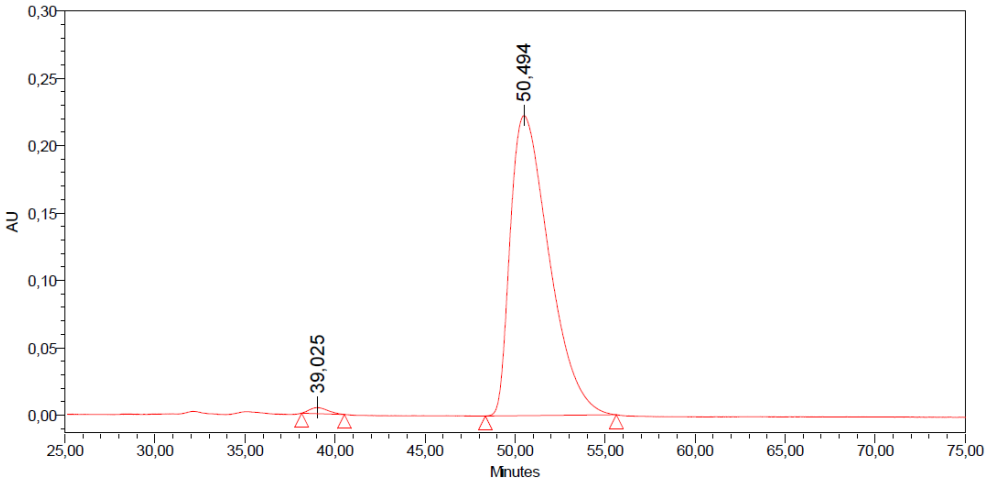
	RT	Area	Height	% Area
1	17,562	350476	11372	1,45
2	26,011	23800853	408669	98,55

HPLC chromatogram of the racemic and chiral compound **6i**.



Peak Results

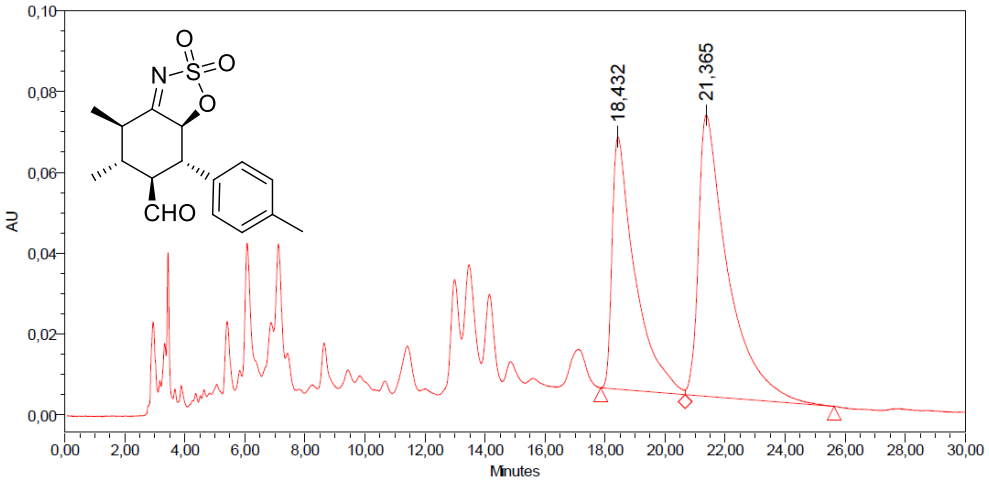
	RT	Area	Height	% Area
1	38,929	4093760	47164	37,04
2	51,072	6959917	55576	62,96



Peak Results

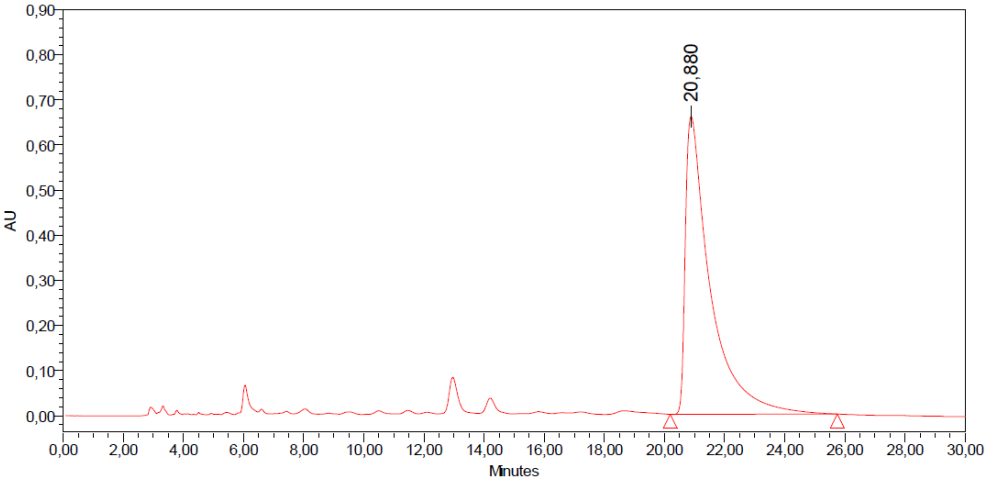
	RT	Area	Height	% Area
1	39,025	321870	4523	0,96
2	50,494	33377481	222605	99,04

HPLC chromatogram of the racemic and chiral compound **7a**.



Peak Results

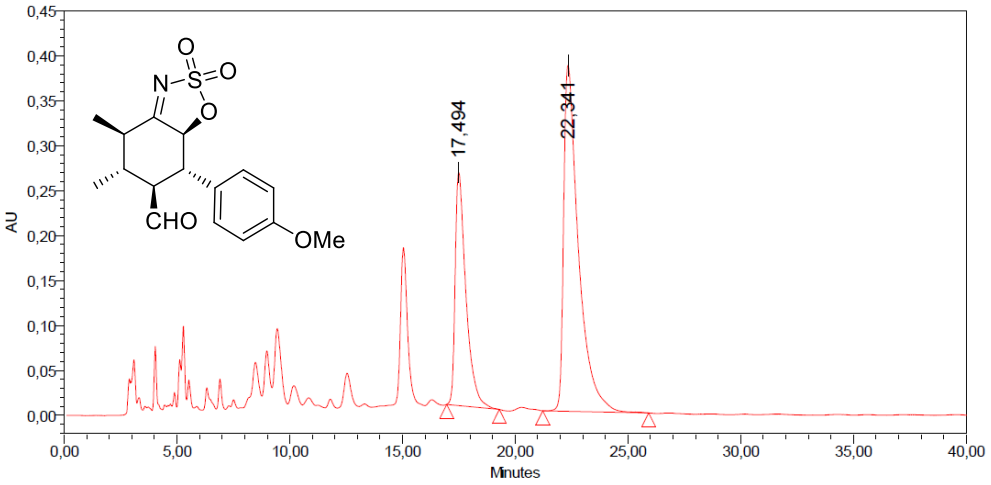
	RT	Area	Height	% Area
1	18,432	3308580	62411	41,13
2	21,365	4734809	69562	58,87



Peak Results

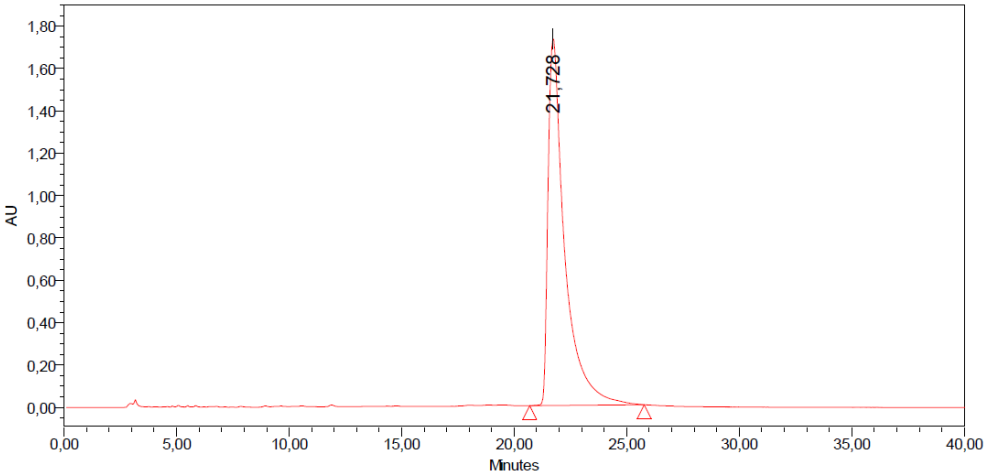
	RT	Area	Height	% Area
1	20,880	38000072	660532	100,00

HPLC chromatogram of the racemic and chiral compound **7b**.



Peak Results

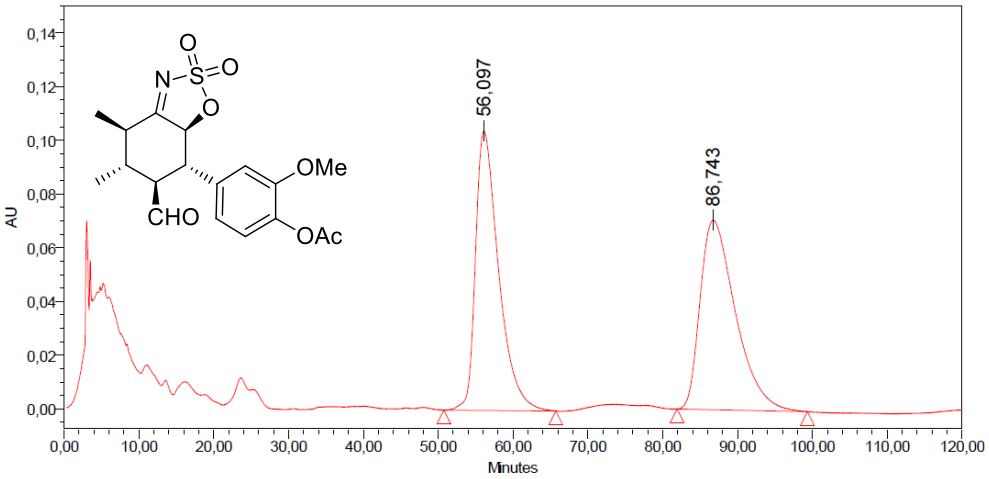
	RT	Area	Height	% Area
1	17,494	8598545	259394	32,82
2	22,341	17597735	385178	67,18



Peak Results

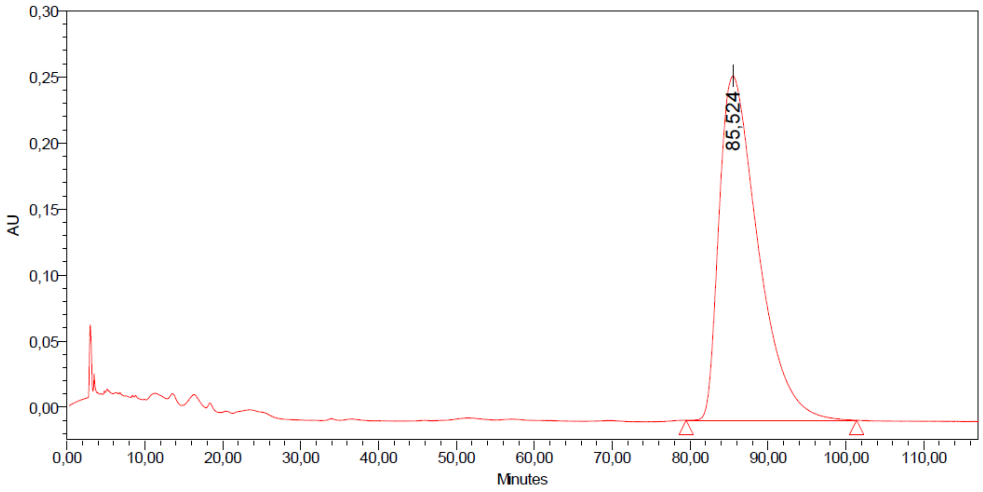
	RT	Area	Height	% Area
1	21,728	88781931	1729262	100,00

HPLC chromatogram of the racemic and chiral compound **7c**.



Peak Results

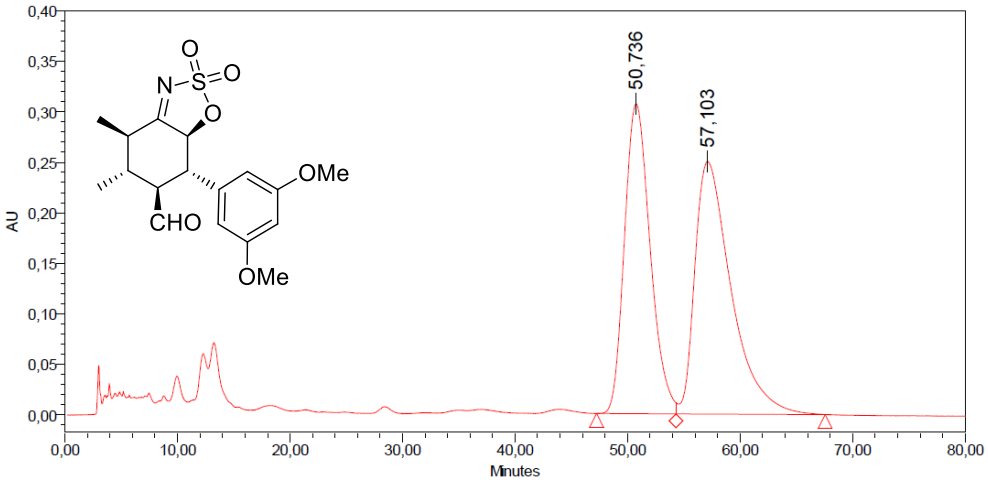
	RT	Area	Height	% Area
1	56,097	22345932	104126	49,05
2	86,743	23214366	70629	50,95



Peak Results

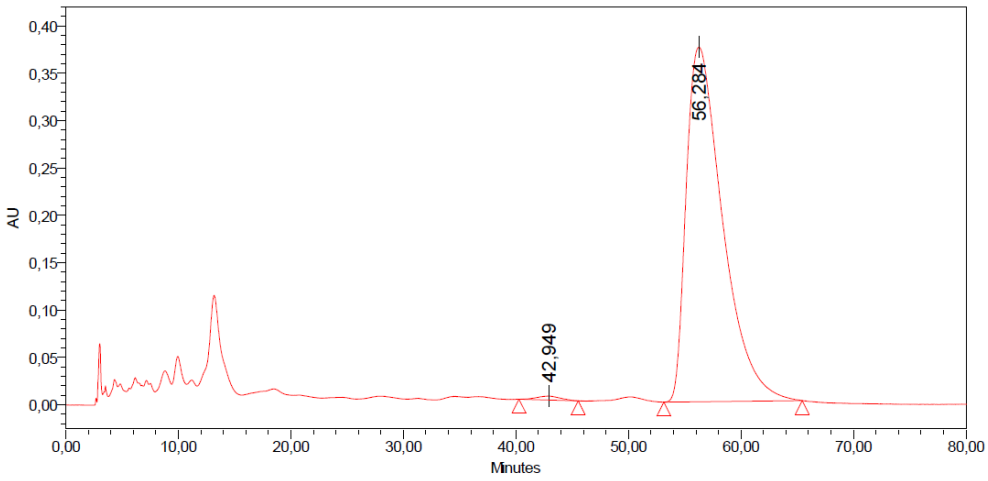
	RT	Area	Height	% Area
1	85,524	90597450	260775	100,00

HPLC chromatogram of the racemic and chiral compound **7d**.



Peak Results

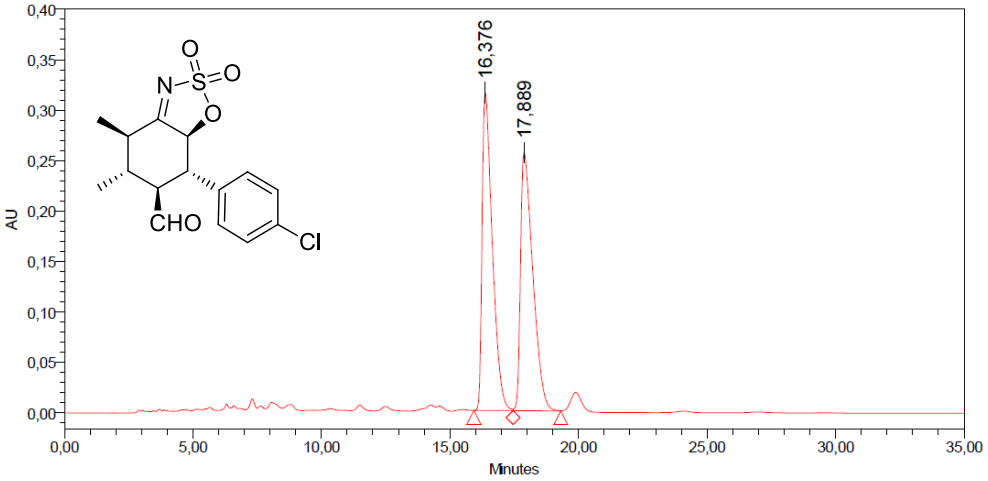
	RT	Area	Height	% Area
1	50,736	48608446	306936	46,49
2	57,103	55952811	250185	53,51



Peak Results

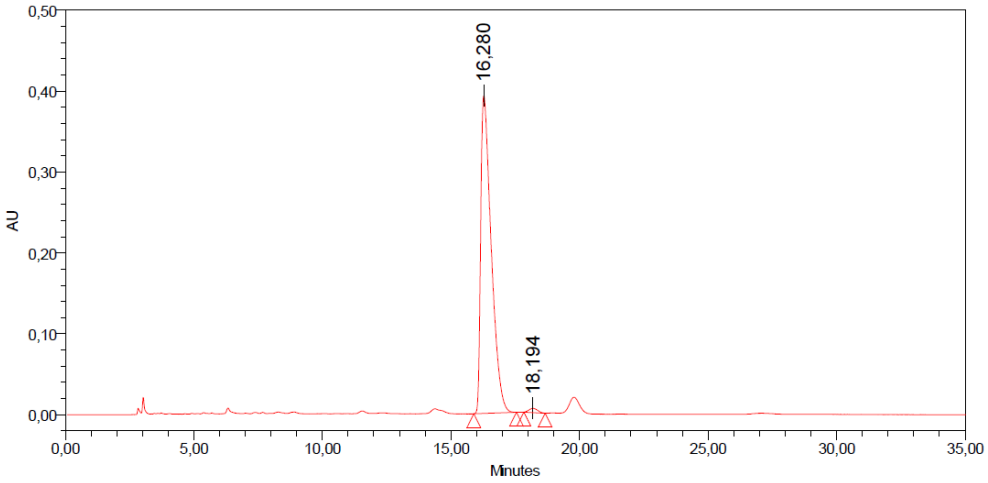
	RT	Area	Height	% Area
1	42,949	625770	4315	0,74
2	56,284	84242777	374307	99,26

HPLC chromatogram of the racemic and chiral compound **7e**.



Peak Results

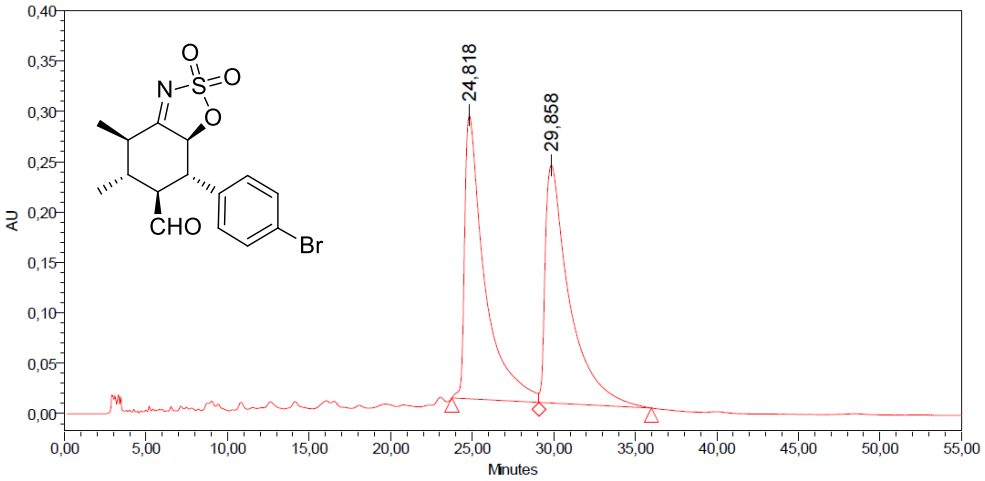
	RT	Area	Height	% Area
1	16,376	8724484	314971	50,65
2	17,889	8501878	255727	49,35



Peak Results

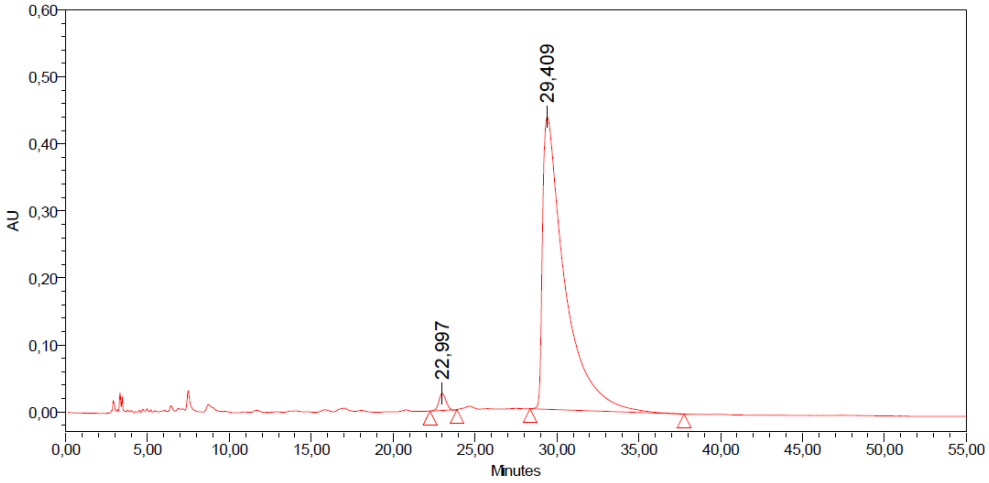
	RT	Area	Height	% Area
1	16,280	11160618	393048	98,92
2	18,194	121854	5273	1,08

HPLC chromatogram of the racemic and chiral compound **7f**.



Peak Results

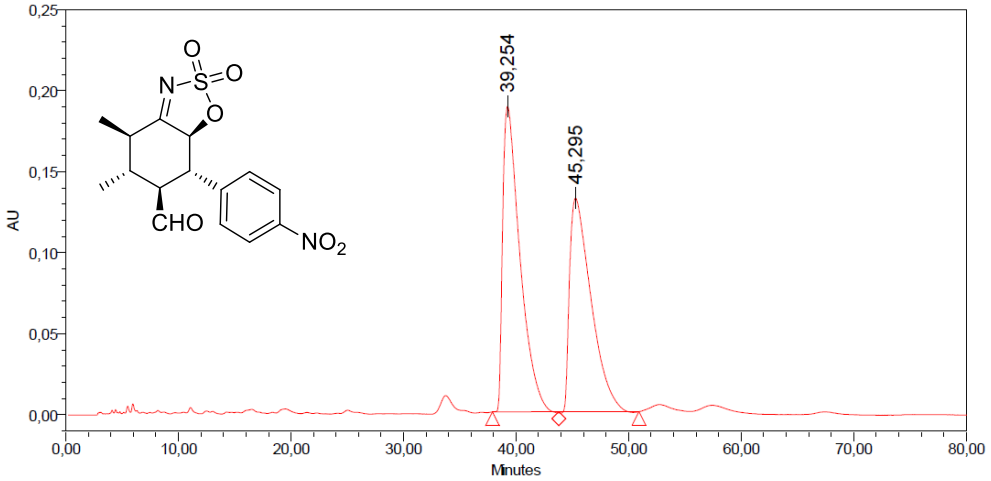
	RT	Area	Height	% Area
1	24,818	23927356	281329	49,62
2	29,858	24298166	236073	50,38



Peak Results

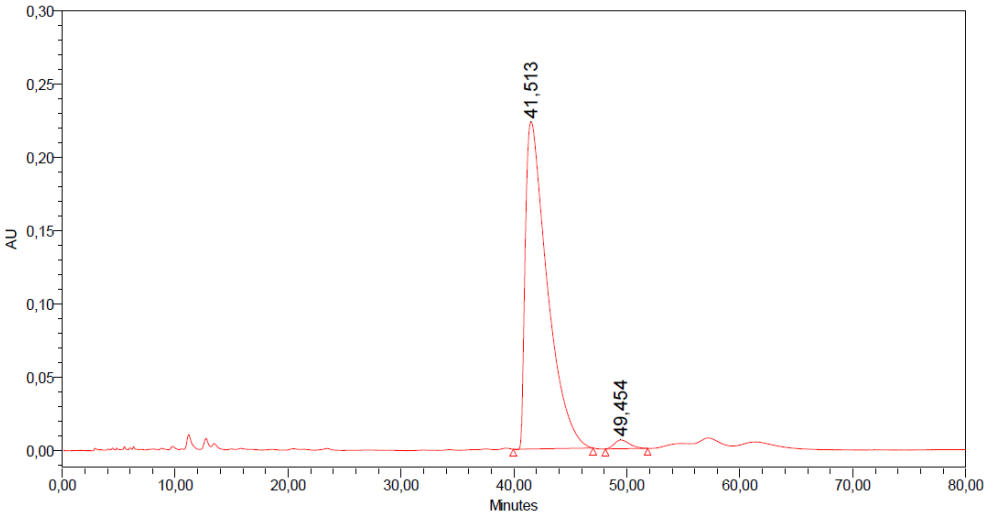
	RT	Area	Height	% Area
1	22,997	774859	25461	1,85
2	29,409	41069774	436562	98,15

HPLC chromatogram of the racemic and chiral compound **7g**.



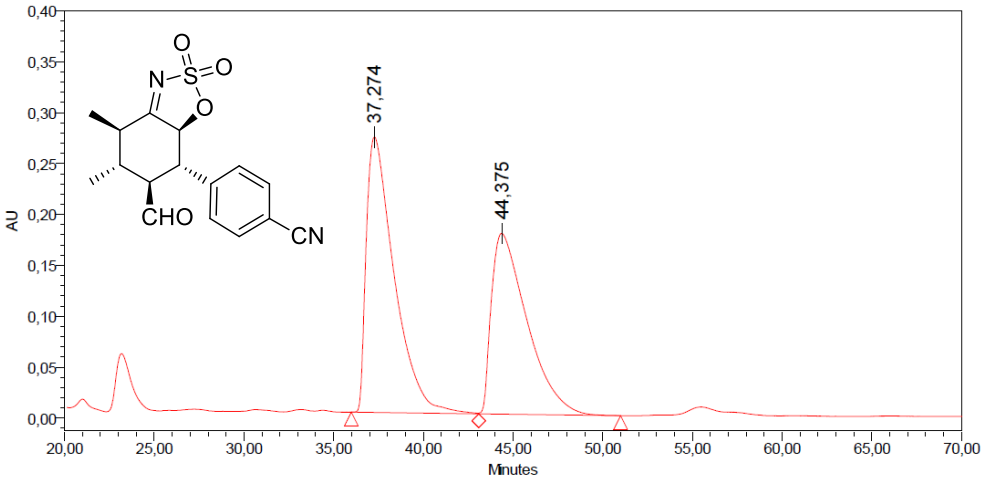
Peak Results

	RT	Area	Height	% Area
1	39,254	20112694	188616	53,45
2	45,295	17516961	131899	46,55



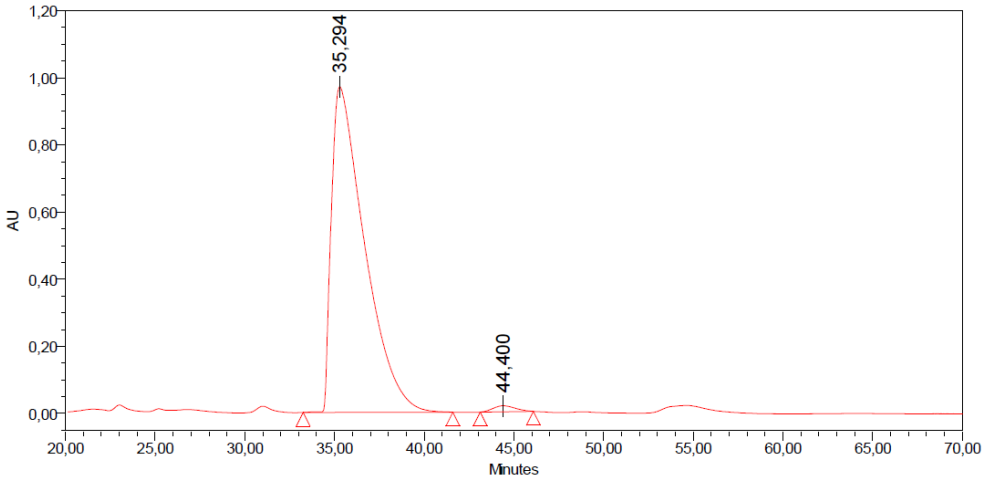
	RT	Area	% Area	Height
1	41,513	30038168	98,17	223403
2	49,454	560510	1,83	5967

HPLC chromatogram of the racemic and chiral compound **7h**.



Peak Results

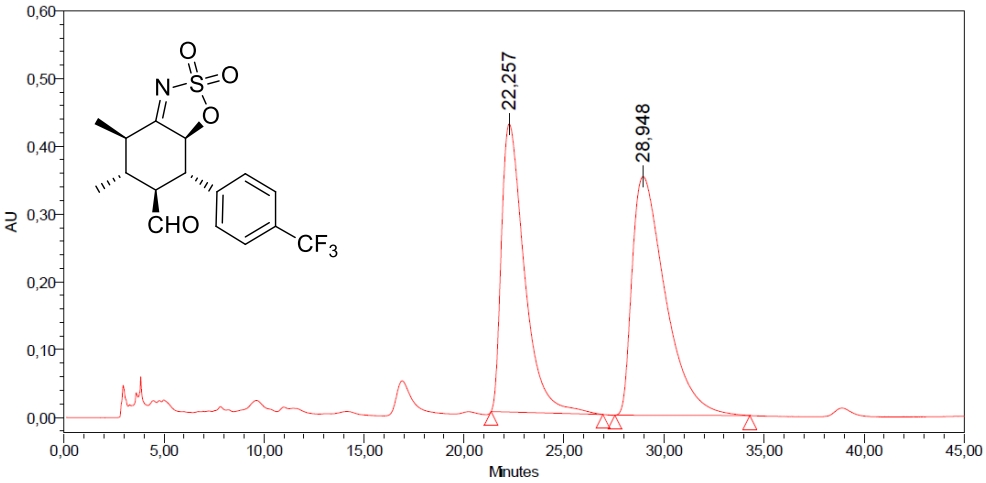
	RT	Area	Height	% Area
1	37,274	29326157	270595	54,50
2	44,375	24485096	177517	45,50



Peak Results

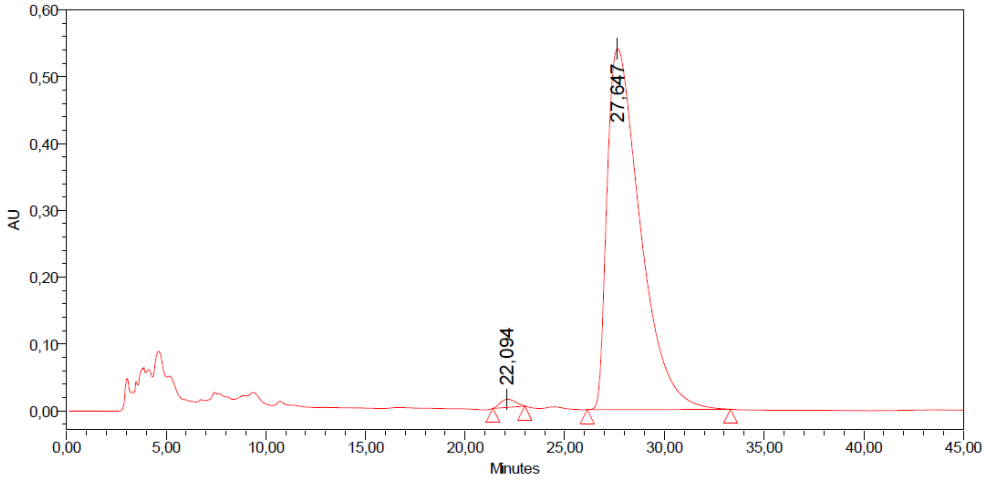
	RT	Area	Height	% Area
1	35,294	124825663	970133	98,79
2	44,400	1532061	17801	1,21

HPLC chromatogram of the racemic and chiral compound **7i**.



Peak Results

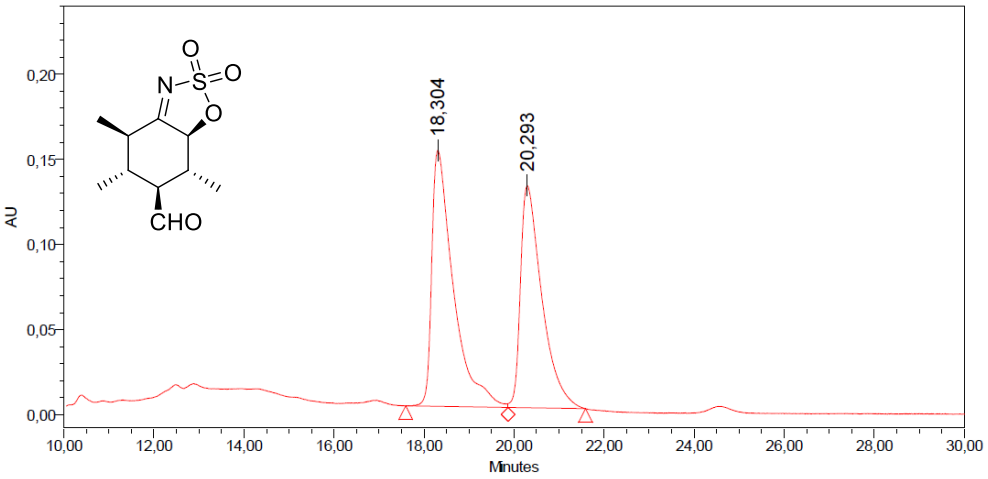
	RT	Area	Height	% Area
1	22,257	34085797	425077	45,56
2	28,948	40733155	352433	54,44



Peak Results

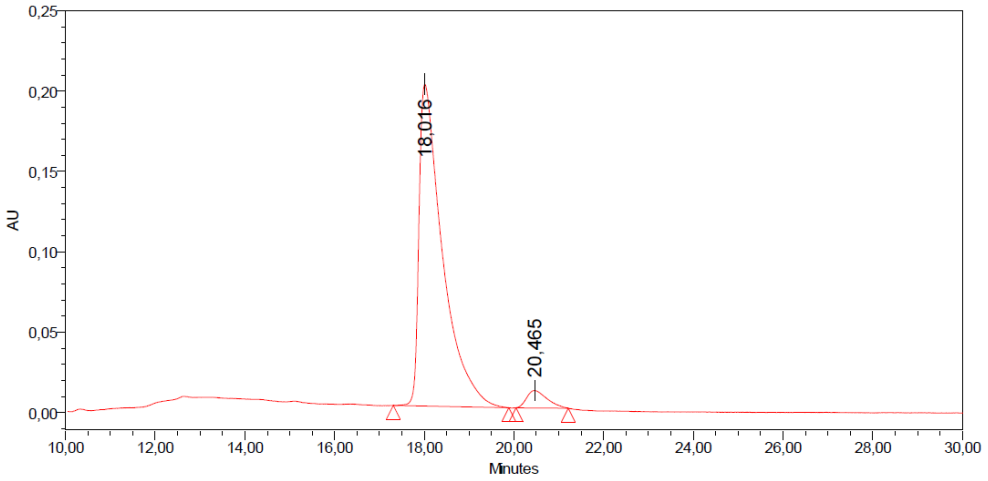
	RT	Area	Height	% Area
1	22,094	634329	12166	1,00
2	27,647	62572502	540136	99,00

HPLC chromatogram of the racemic and chiral compound **7j**.



Peak Results

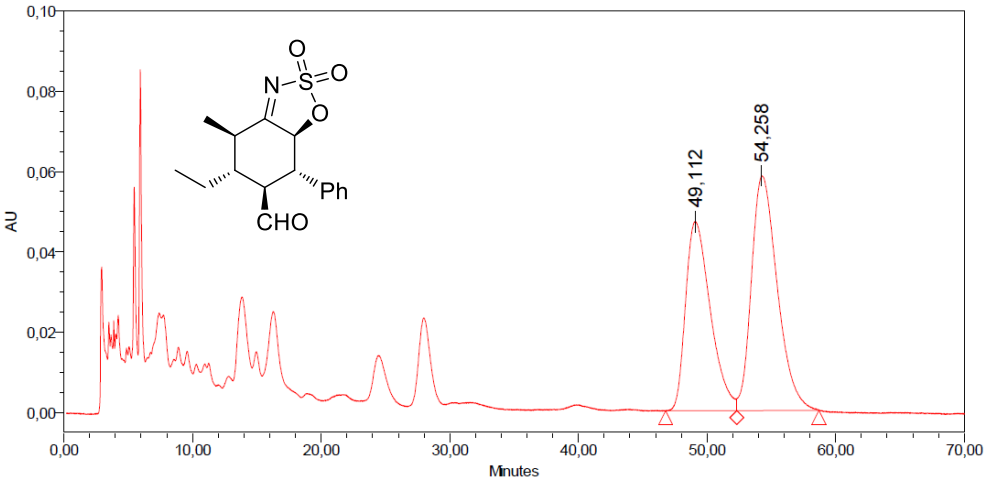
	RT	Area	Height	% Area
1	18,304	5011002	150323	53,74
2	20,293	4312996	130491	46,26



Peak Results

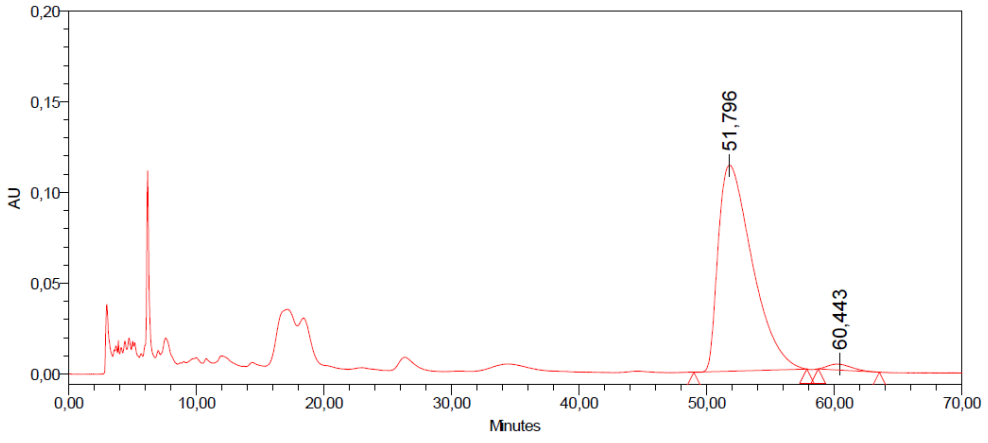
	RT	Area	Height	% Area
1	18,016	7253671	200111	95,49
2	20,465	342876	10880	4,51

HPLC chromatogram of the racemic and chiral compound **7k**.



Peak Results

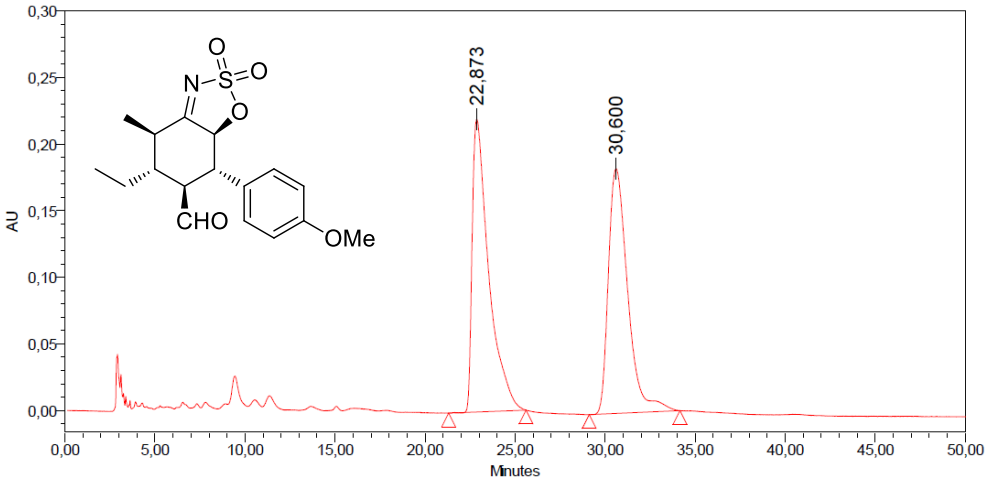
	RT	Area	Height	% Area
1	49,112	6308070	47100	43,54
2	54,258	8180481	58445	56,46



Peak Results

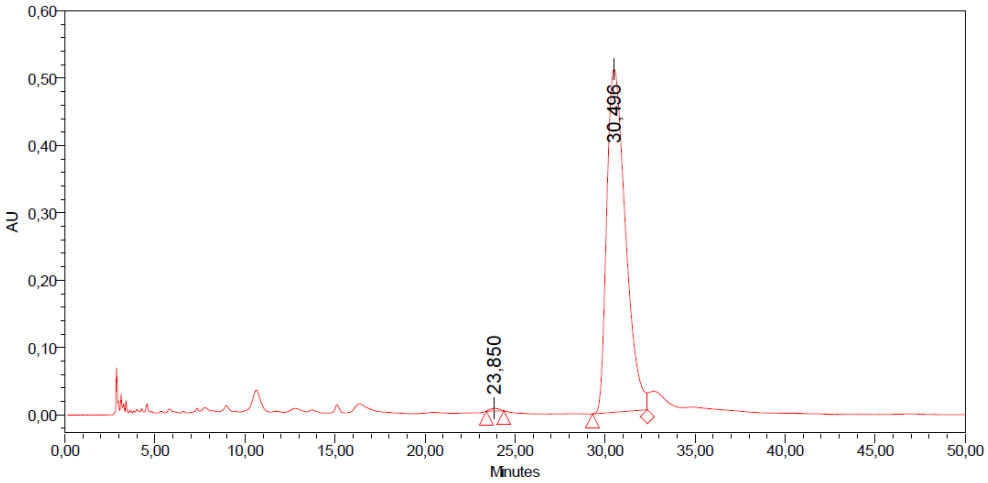
	Name	RT	Area	Height	% Area
1		51,796	21031296	113460	98,05
2		60,443	418660	3261	1,95

HPLC chromatogram of the racemic and chiral compound **7l**.



Peak Results

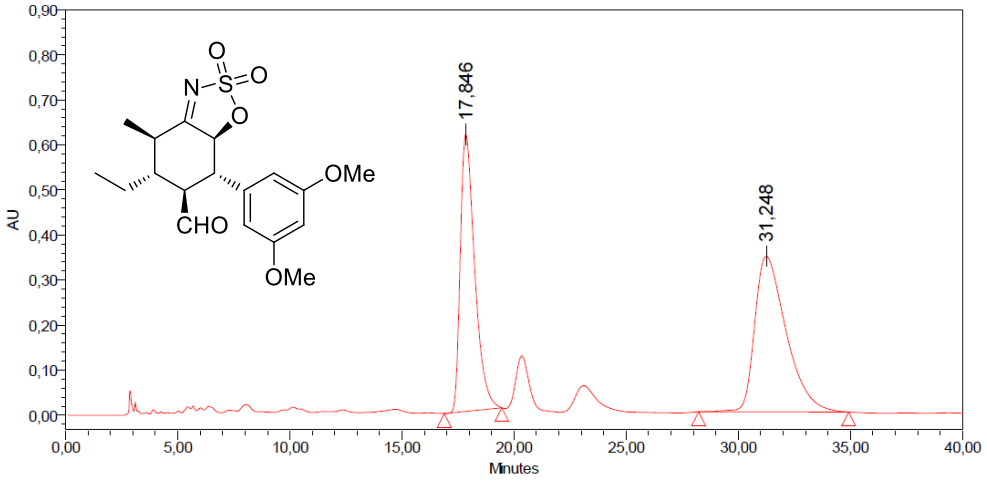
	RT	Area	Height	% Area
1	22,873	14030097	219763	50,61
2	30,600	13693412	183620	49,39



Peak Results

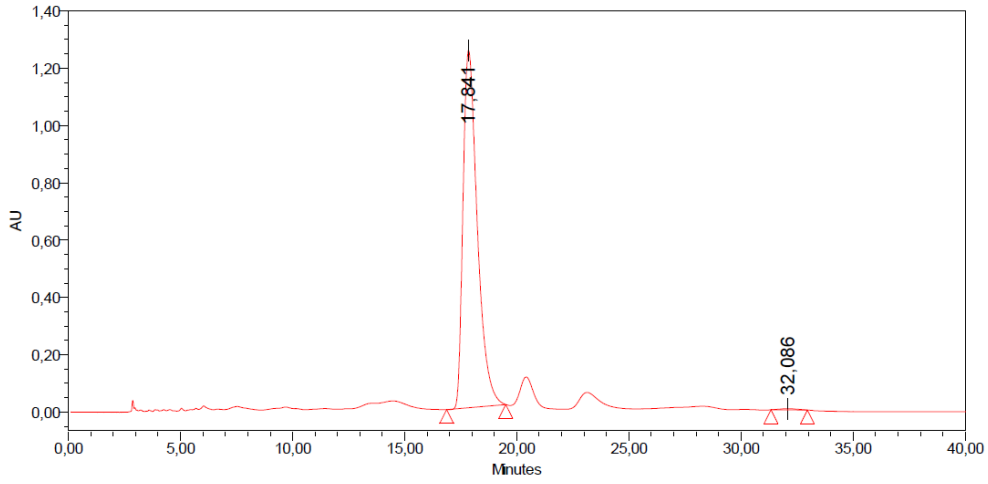
	RT	Area	Height	% Area
1	23,850	138765	4029	0,37
2	30,496	36903502	510027	99,63

HPLC chromatogram of the racemic and chiral compound **7m**.



Peak Results

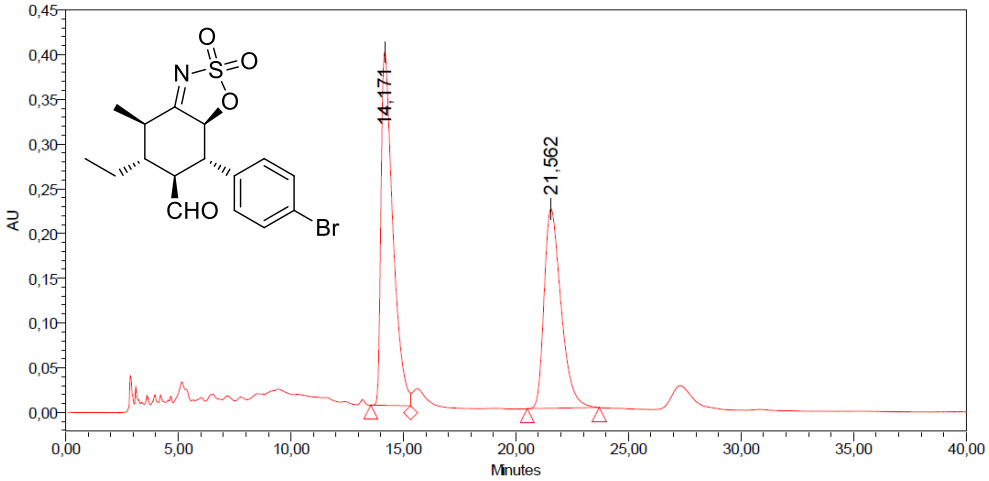
	RT	Area	Height	% Area
1	17,846	27424110	615396	44,83
2	31,248	33746955	345690	55,17



Peak Results

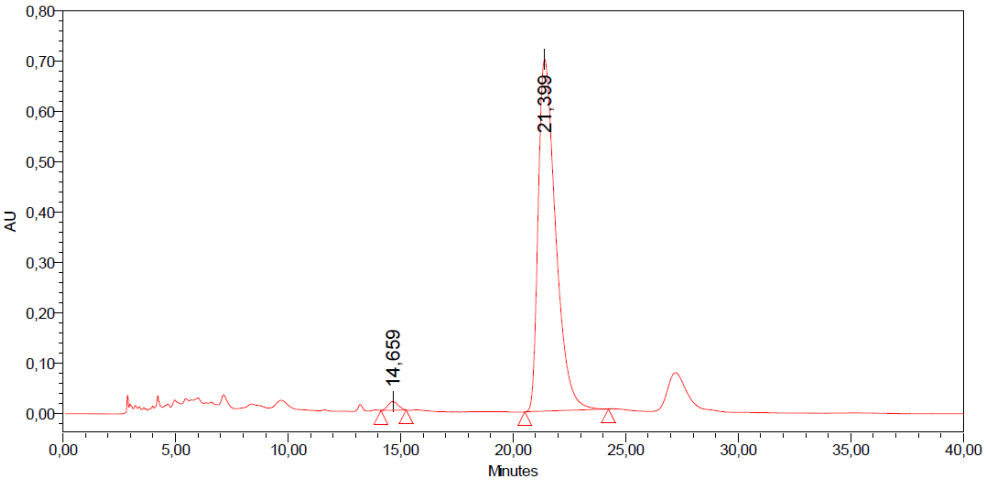
	RT	Area	Height	% Area
1	17,841	55188693	1247033	99,56
2	32,086	244965	4326	0,44

HPLC chromatogram of the racemic and chiral compound **7n**.



Peak Results

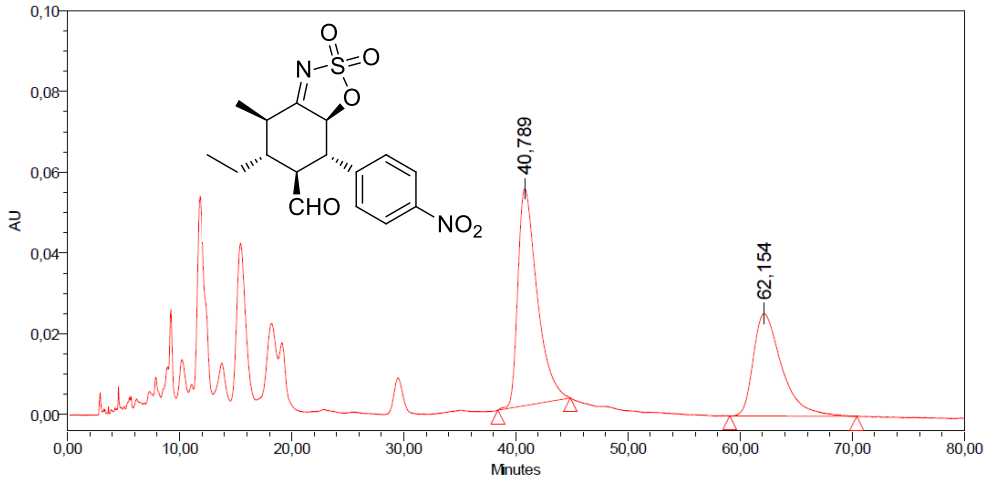
	RT	Area	Height	% Area
1	14,171	14429146	394829	55,31
2	21,562	11660796	223107	44,69



Peak Results

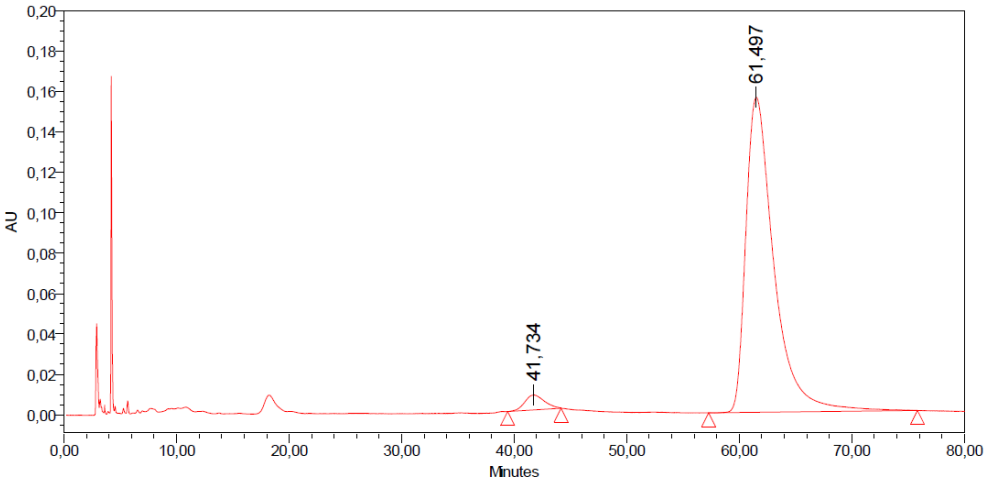
	RT	Area	Height	% Area
1	14,659	533007	17135	1,40
2	21,399	37607284	698724	98,60

HPLC chromatogram of the racemic and chiral compound **7o**.



Peak Results

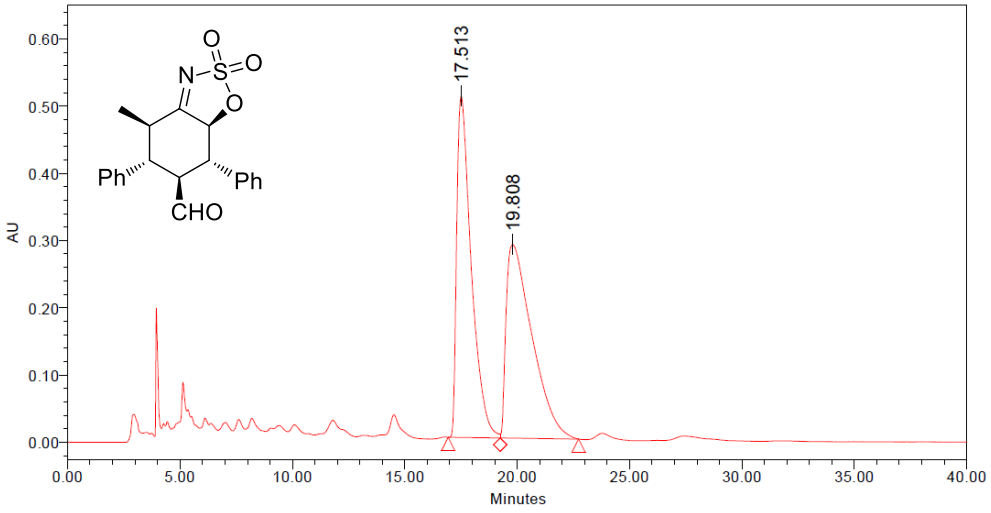
	RT	Area	Height	% Area
1	40,789	6418776	53722	59,01
2	62,154	4458823	25386	40,99



Peak Results

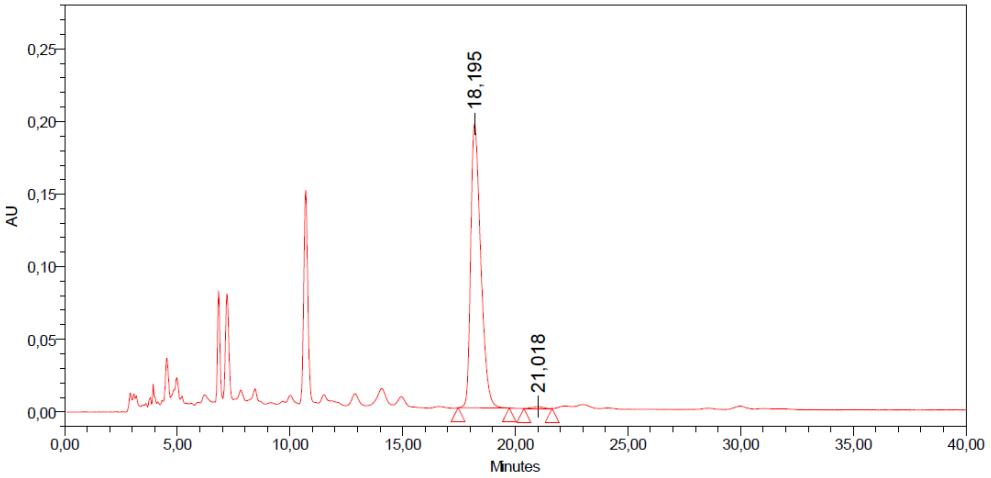
	RT	Area	Height	% Area
1	41,734	890699	7438	3,19
2	61,497	27043713	155971	96,81

HPLC chromatogram of the racemic and chiral compound **7p**.



Peak Results

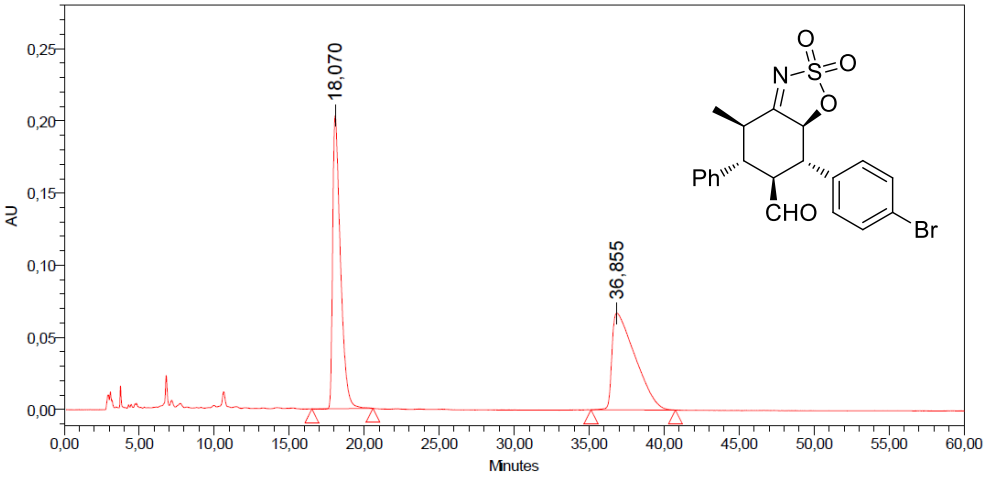
	RT	Area	Height	% Area
1	17.513	22936217	507839	49.83
2	19.808	23089293	288031	50.17



Peak Results

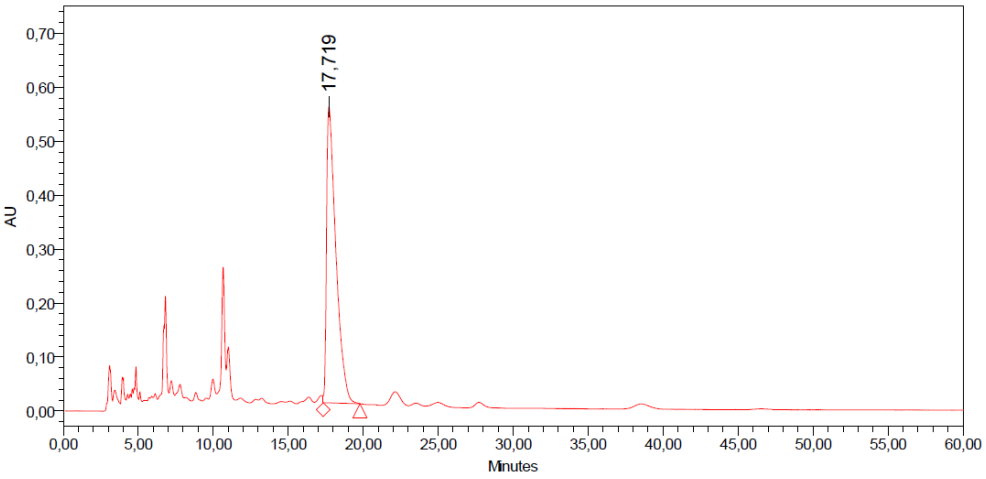
	RT	Area	Height	% Area
1	18,195	6045041	195691	99,32
2	21,018	41170	1252	0,68

HPLC chromatogram of the racemic and chiral compound **7q**.



Peak Results

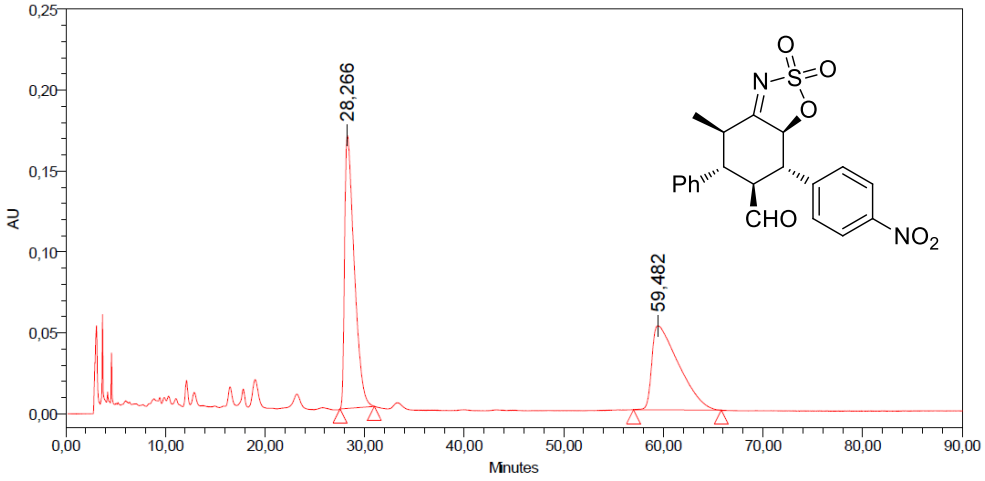
	RT	Area	Height	% Area
1	18,070	7340081	203095	50,61
2	36,855	7163723	67044	49,39



Peak Results

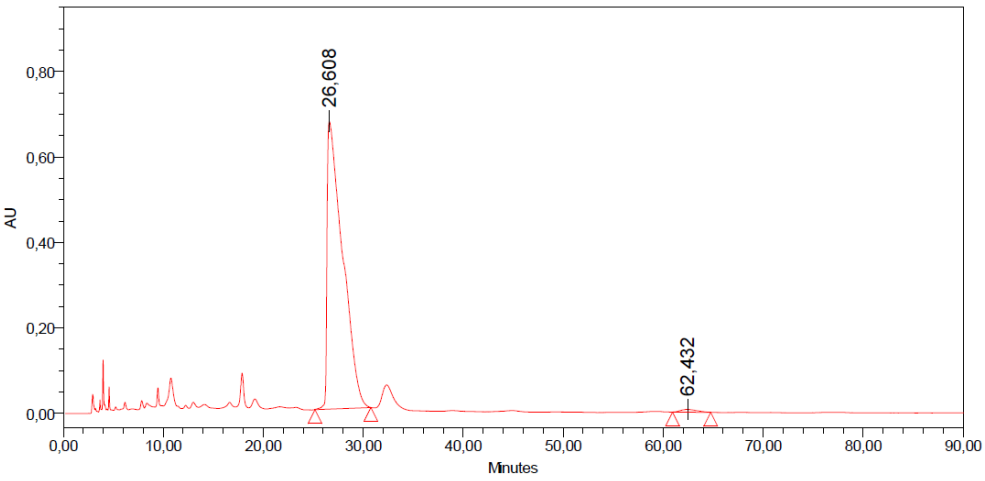
	RT	Area	Height	% Area
1	17,719	23729138	549075	100,00

HPLC chromatogram of the racemic and chiral compound **7r**.



Peak Results

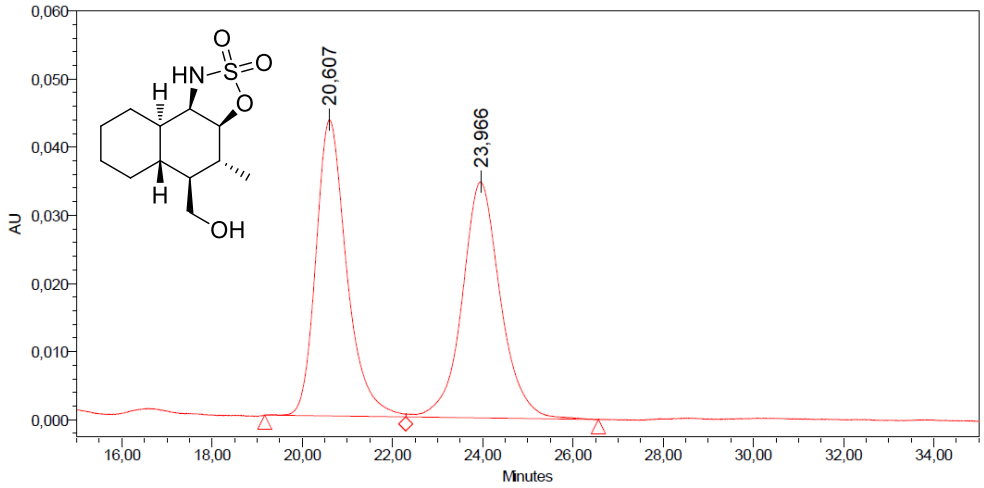
	RT	Area	Height	% Area
1	28,266	11290681	168756	53,78
2	59,482	9701791	52039	46,22



Peak Results

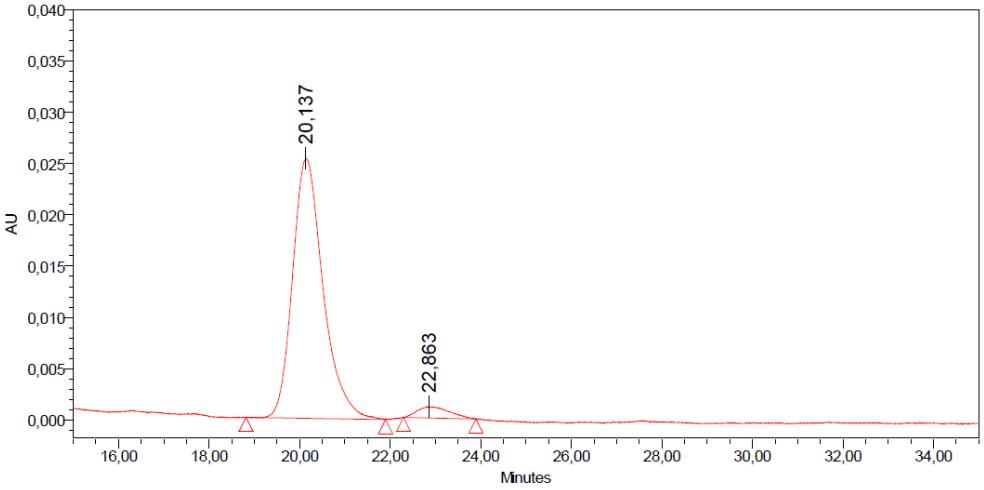
	RT	Area	Height	% Area
1	26,608	72367177	673430	99,00
2	62,432	732302	6466	1,00

HPLC chromatogram of the racemic and chiral compound **7s**.



Peak Results

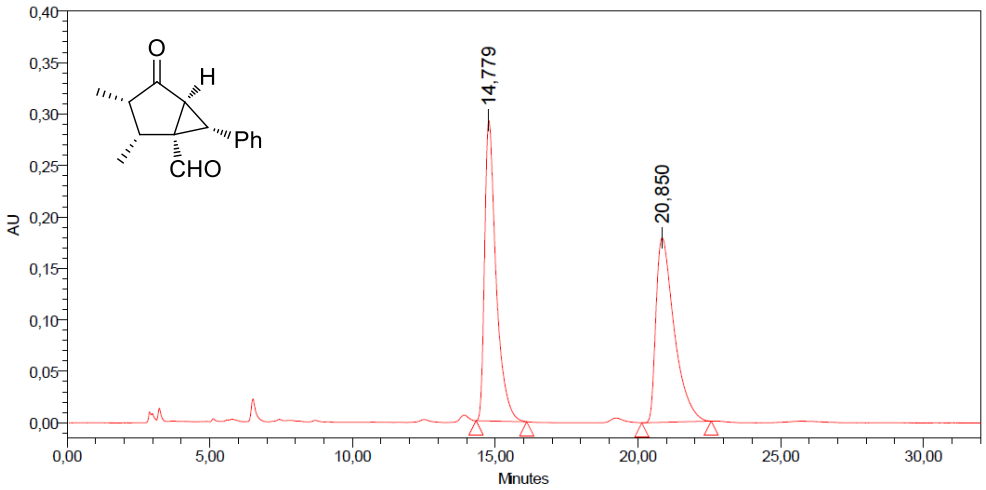
	RT	Area	Height	% Area
1	20,607	2058510	43473	50,18
2	23,966	2043448	34635	49,82



Peak Results

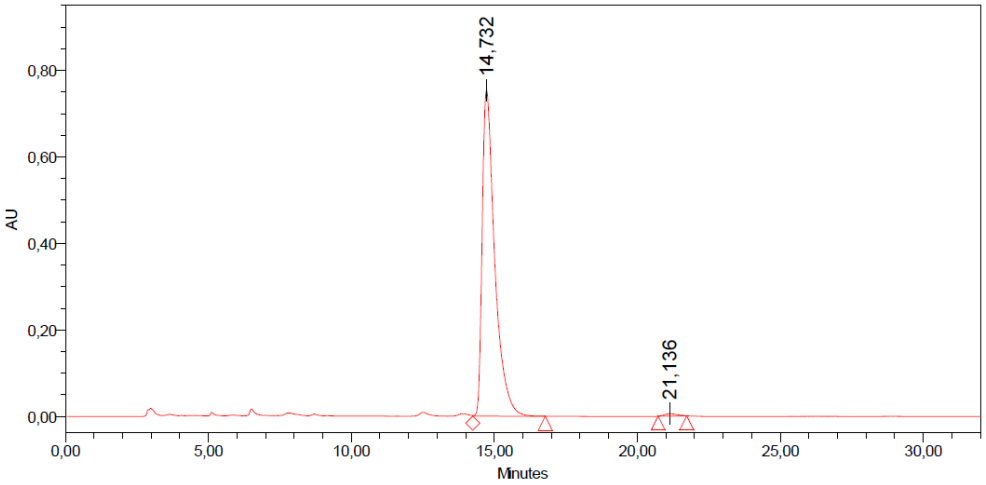
	RT	Area	Height	% Area
1	20,137	1187215	25380	95,55
2	22,863	55304	1137	4,45

HPLC chromatogram of the racemic and chiral compound **9**.



Peak Results

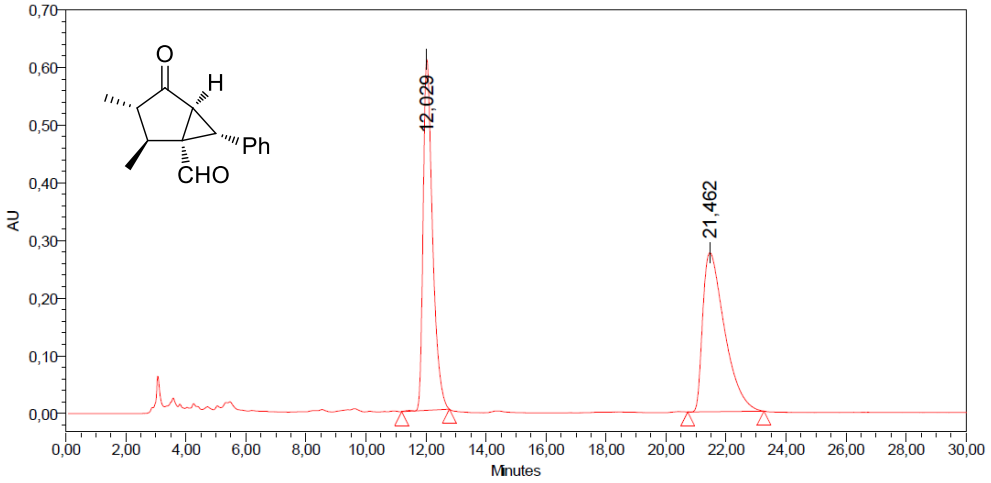
	RT	Area	Height	% Area
1	14,779	8175466	292211	50,67
2	20,850	7960020	179331	49,33



Peak Results

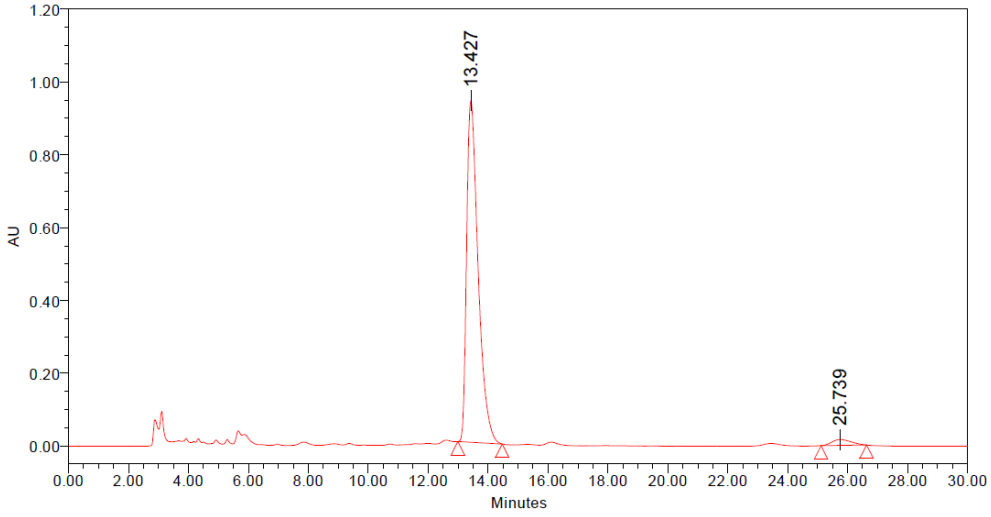
	RT	Area	Height	% Area
1	14,732	22931117	753804	99,28
2	21,136	166509	5424	0,72

HPLC chromatogram of the racemic and chiral compound ***cis*-11a**.



Peak Results

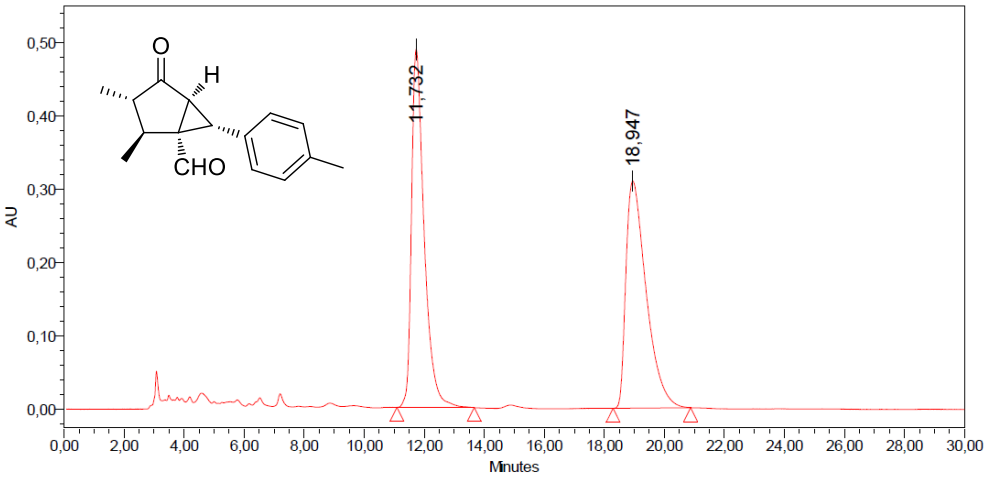
	RT	Area	Height	% Area
1	12,029	13228453	608544	48,73
2	21,462	13919090	275659	51,27



Peak Results

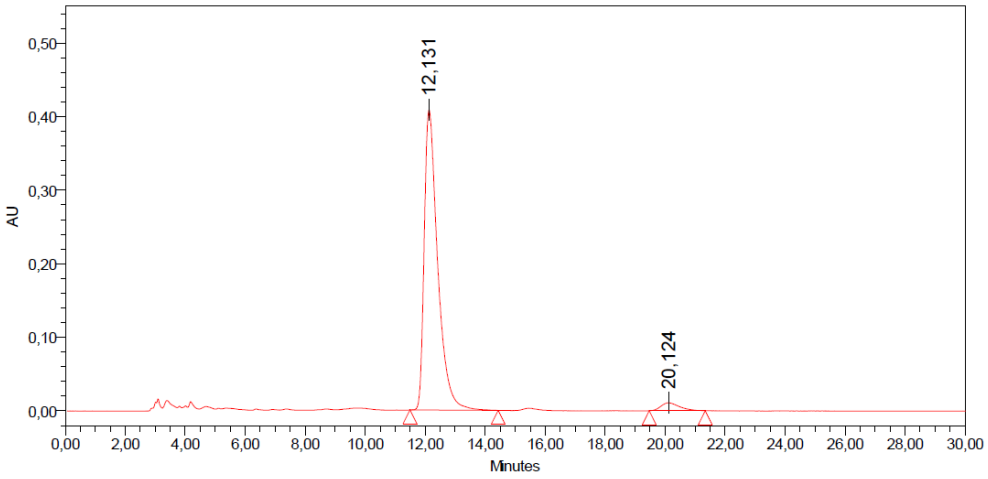
	RT	Area	Height	% Area
1	13.427	24886189	937017	97.19
2	25.739	719754	16164	2.81

HPLC chromatogram of the racemic and chiral compound **8a**.



Peak Results

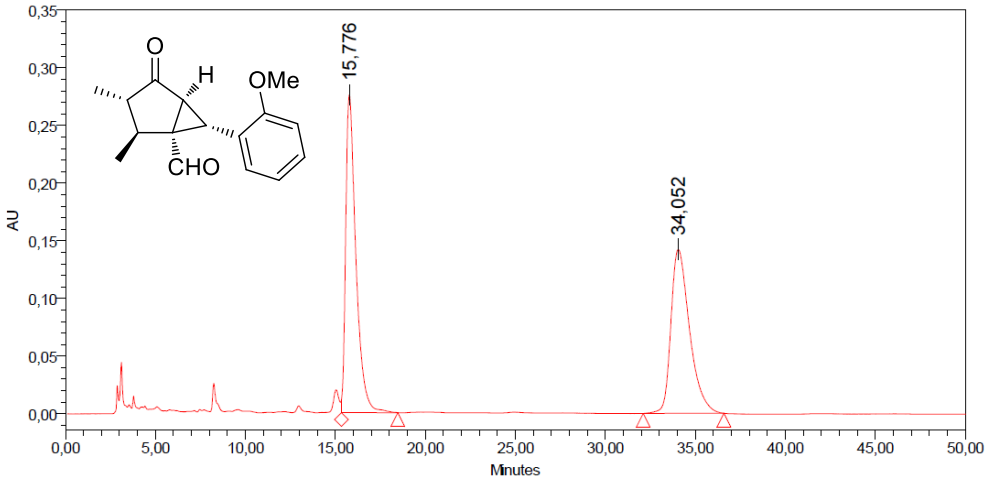
	RT	Area	Height	% Area
1	11,732	14256526	488542	49,54
2	18,947	14520729	309828	50,46



Peak Results

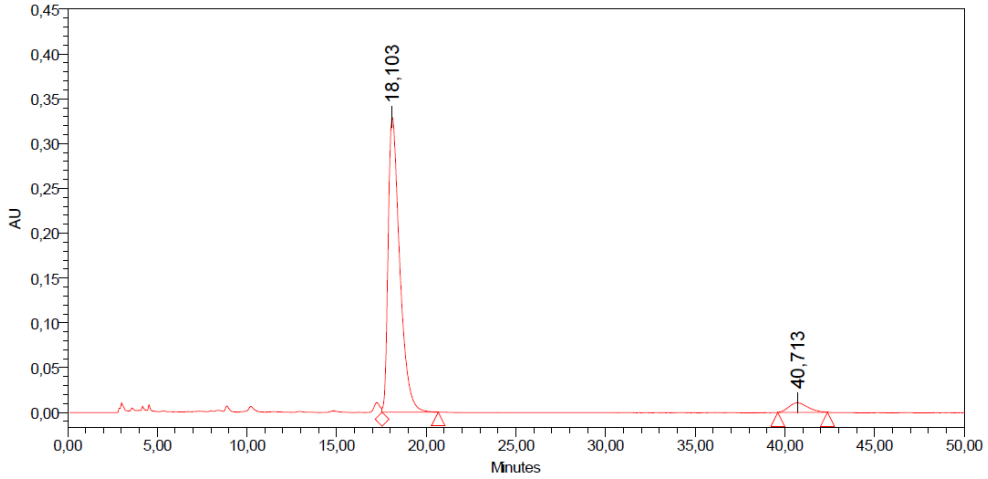
	RT	Area	Height	% Area
1	12,131	12716617	408110	96,44
2	20,124	468943	10835	3,56

HPLC chromatogram of the racemic and chiral compound **8b**.



Peak Results

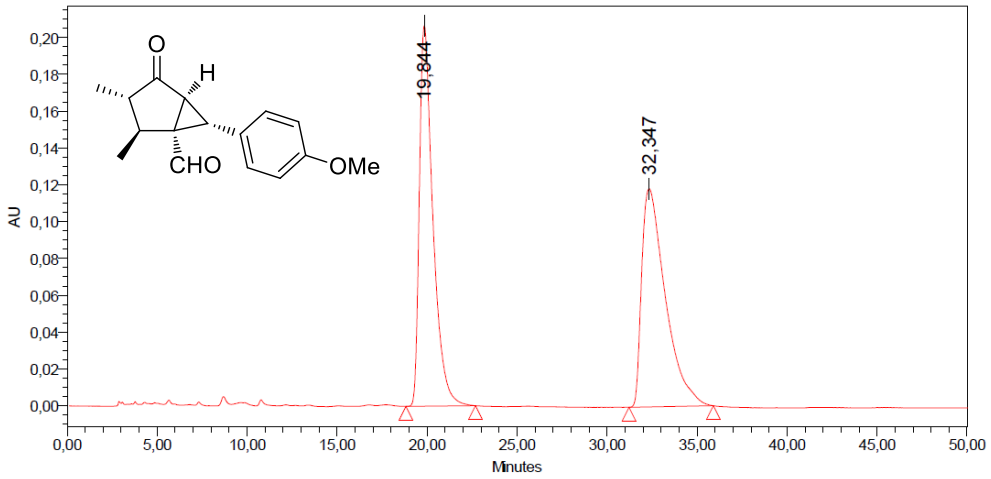
	RT	Area	Height	% Area
1	15,776	10822928	275488	51,40
2	34,052	10231711	142180	48,60



Peak Results

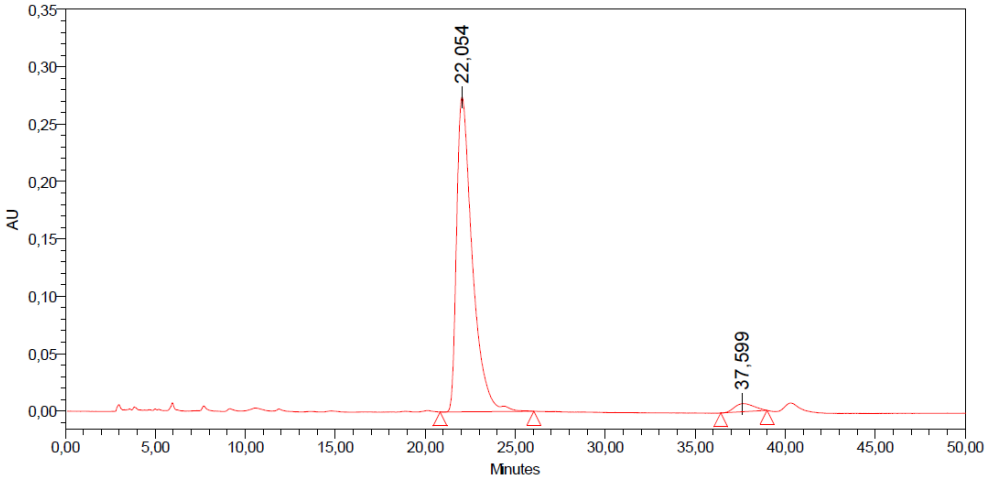
	RT	Area	Height	% Area
1	18,103	14766168	329604	94,99
2	40,713	779170	10630	5,01

HPLC chromatogram of the racemic and chiral compound **8c**.



Peak Results

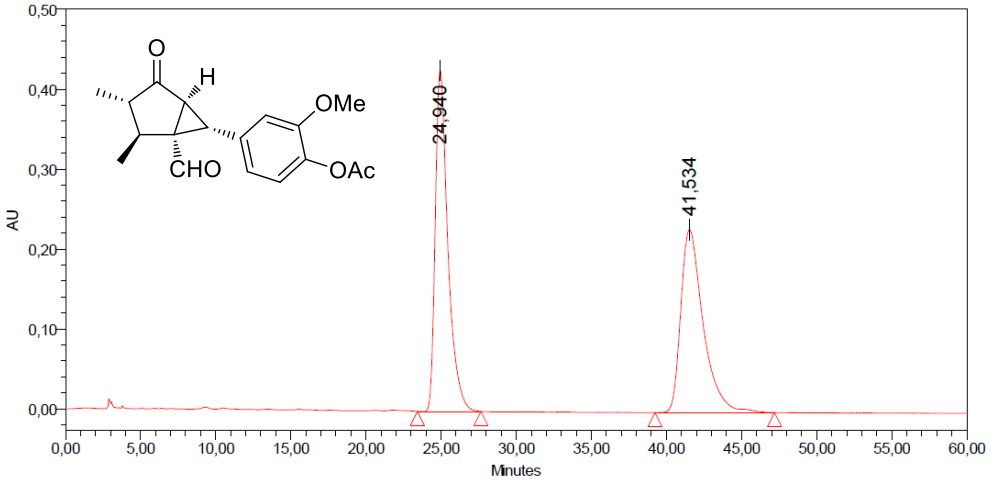
	RT	Area	Height	% Area
1	19,844	10810651	206677	49,96
2	32,347	10828184	118526	50,04



Peak Results

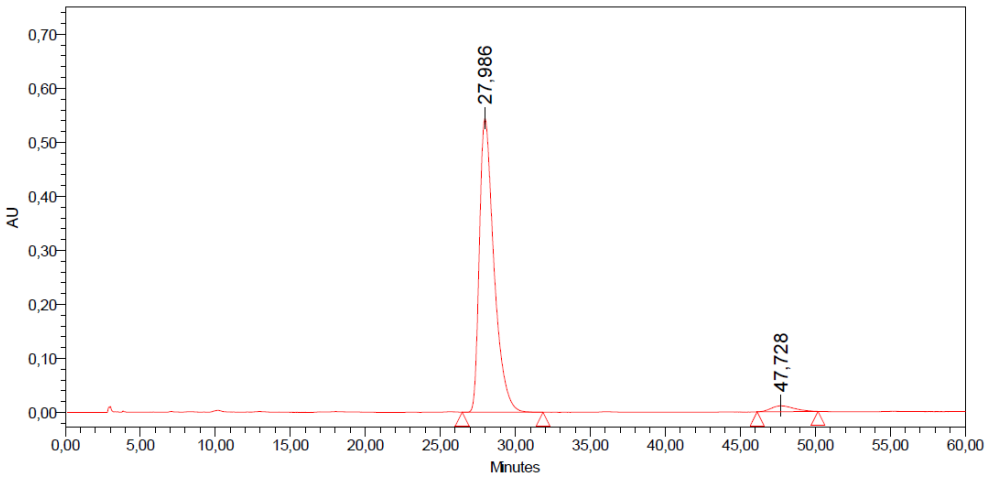
	RT	Area	Height	% Area
1	22,054	16654757	274468	96,92
2	37,599	529196	7143	3,08

HPLC chromatogram of the racemic and chiral compound **8d**.



Peak Results

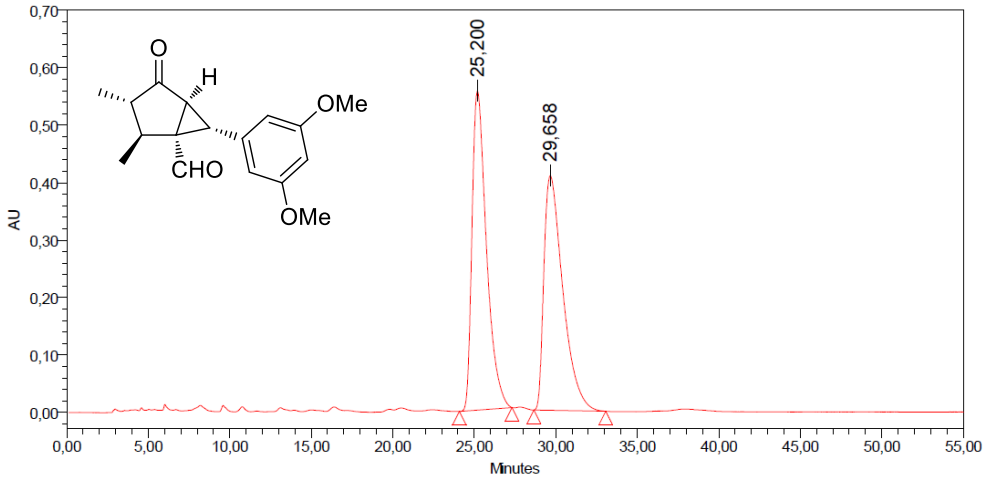
	RT	Area	Height	% Area
1	24,940	24846193	426758	51,20
2	41,534	23683112	228838	48,80



Peak Results

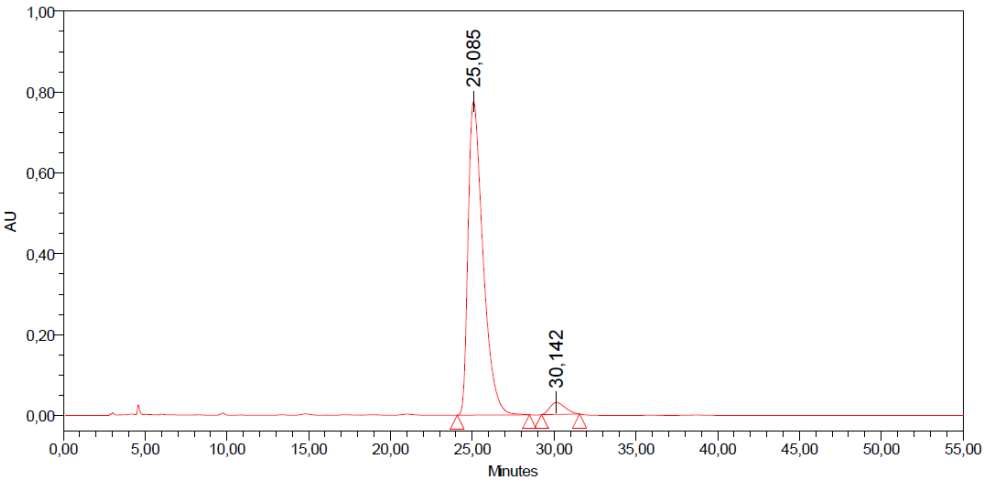
	RT	Area	Height	% Area
1	27,986	36692160	544162	96,92
2	47,728	1165330	10935	3,08

HPLC chromatogram of the racemic and chiral compound **8e**.



Peak Results

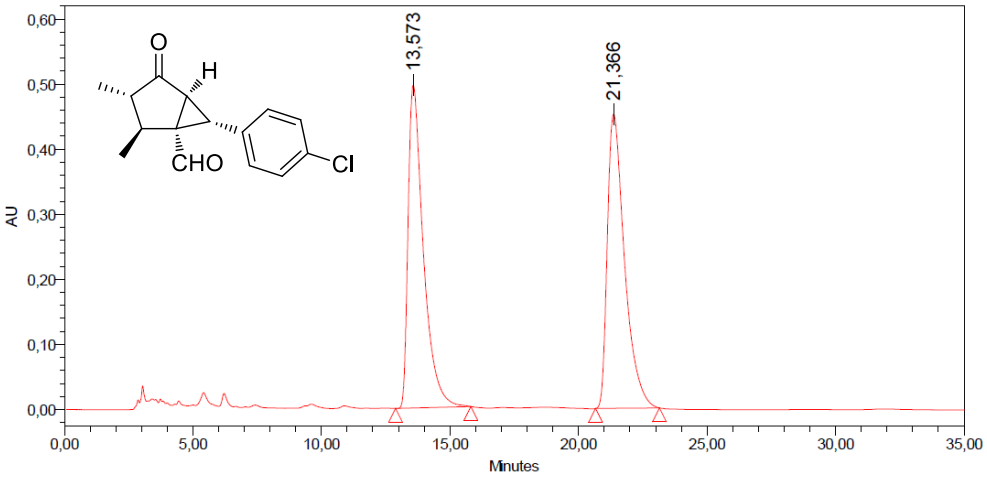
	RT	Area	Height	% Area
1	25,200	34243109	555397	50,95
2	29,658	32970278	408248	49,05



Peak Results

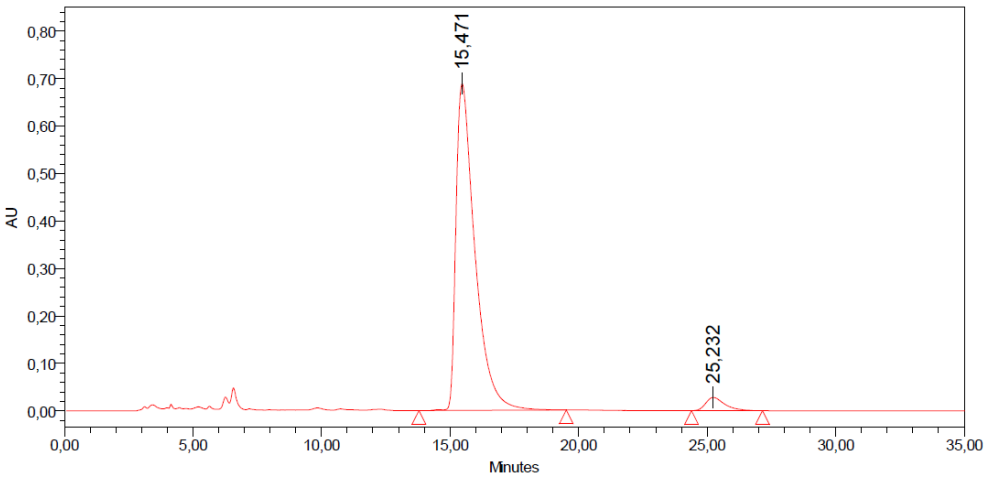
	RT	Area	Height	% Area
1	25,085	49131181	776060	96,19
2	30,142	1946803	29815	3,81

HPLC chromatogram of the racemic and chiral compound **8f**.



Peak Results

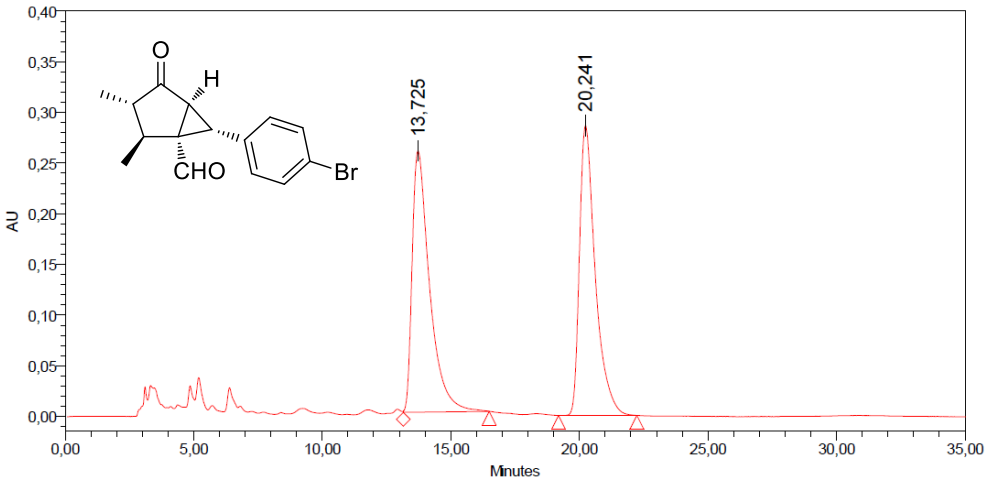
	RT	Area	Height	% Area
1	13,573	20465449	496273	49,32
2	21,366	21033816	452222	50,68



Peak Results

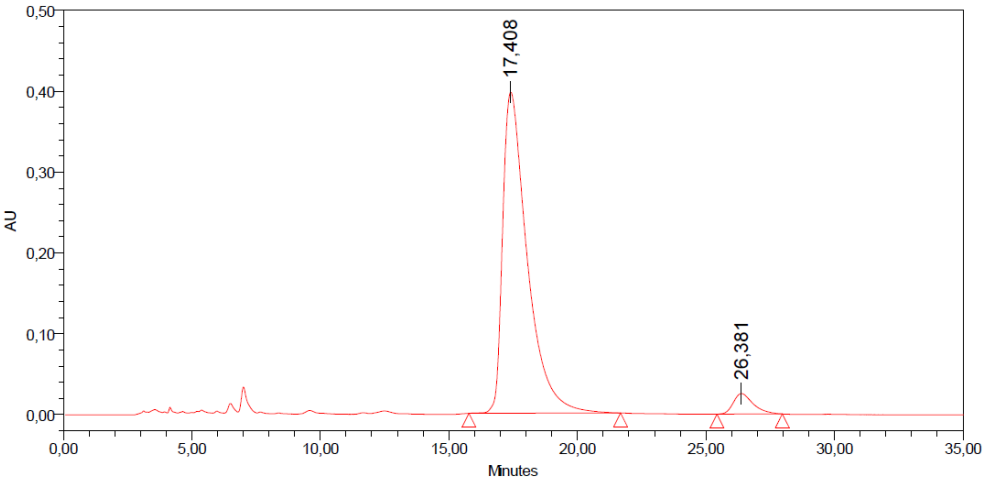
	RT	Area	Height	% Area
1	15,471	35264572	688258	96,12
2	25,232	1424065	27762	3,88

HPLC chromatogram of the racemic and chiral compound **8g**.



Peak Results

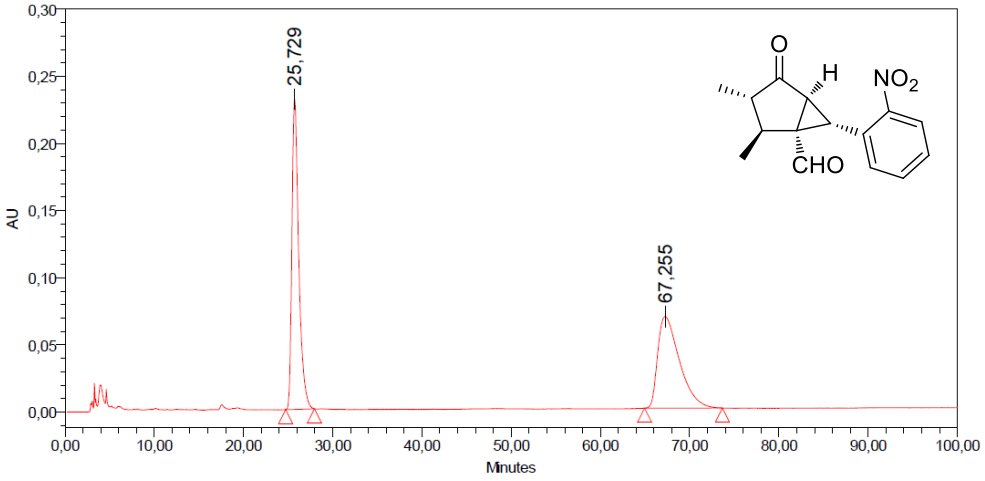
	RT	Area	Height	% Area
1	13,725	12179269	257976	49,87
2	20,241	12242515	285927	50,13



Peak Results

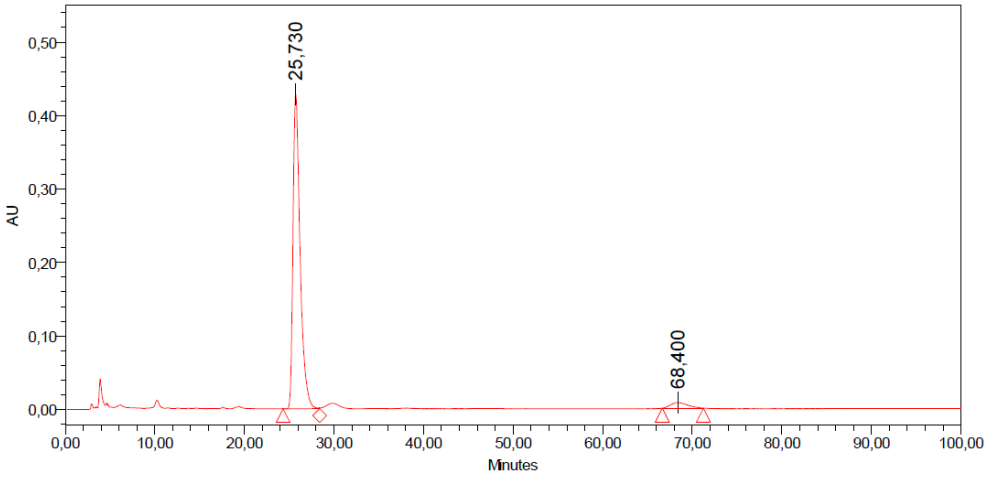
	RT	Area	Height	% Area
1	17,408	26406127	397147	95,12
2	26,381	1355743	25324	4,88

HPLC chromatogram of the racemic and chiral compound **8h**.



Peak Results

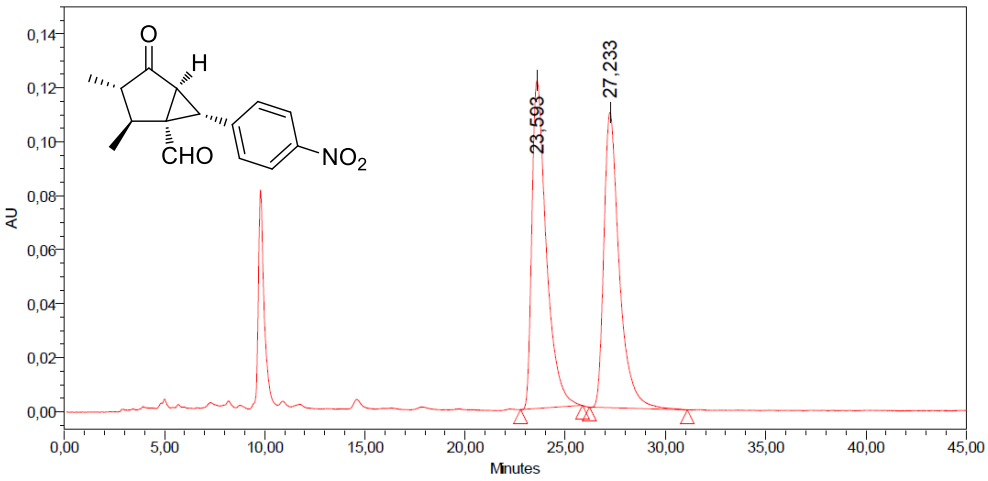
	RT	Area	Height	% Area
1	25,729	12273059	230973	51,57
2	67,255	11525970	68259	48,43



Peak Results

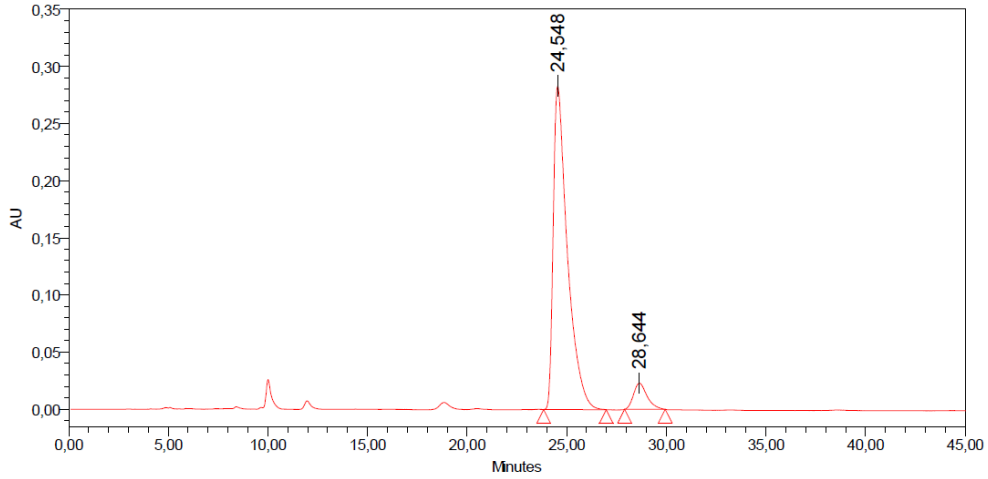
	RT	Area	Height	% Area
1	25,730	23551116	428307	95,94
2	68,400	997221	7603	4,06

HPLC chromatogram of the racemic and chiral compound **8i**.



Peak Results

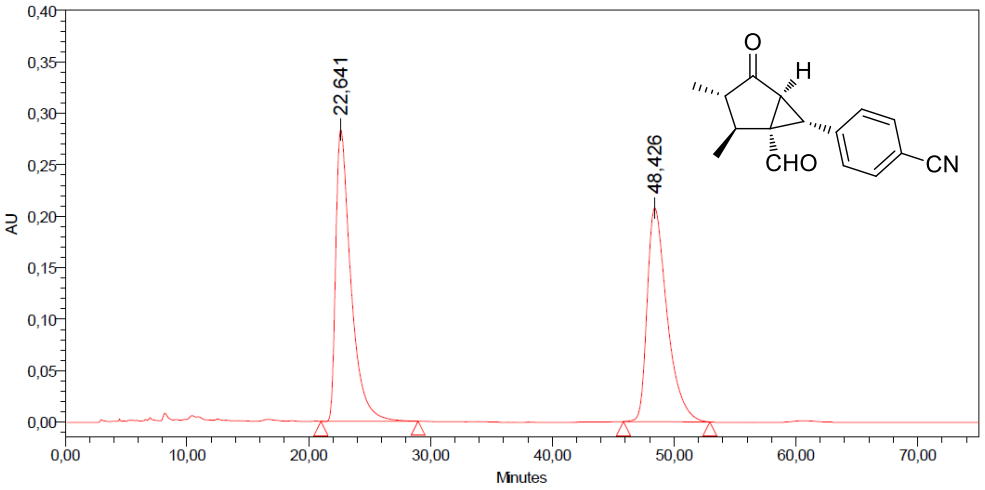
	RT	Area	Height	% Area
1	23,593	6079645	121641	50,96
2	27,233	5851263	109471	49,04



Peak Results

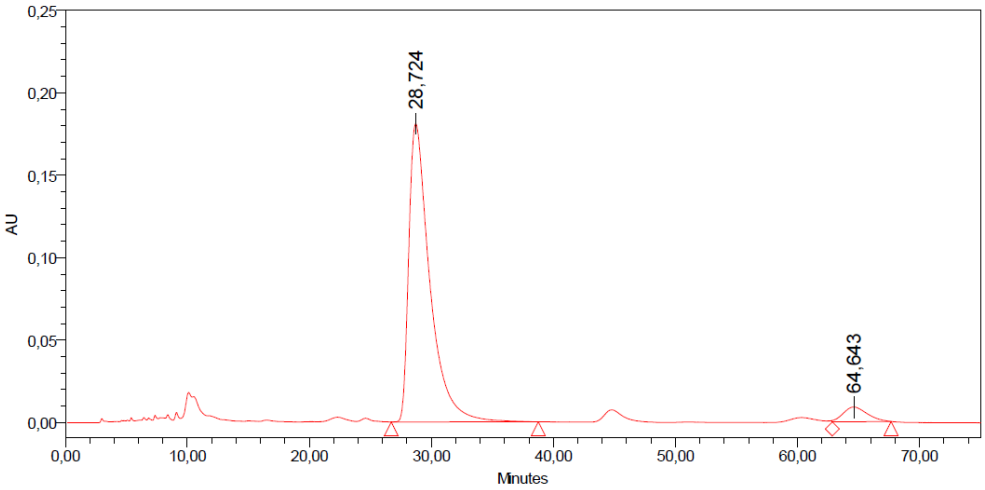
	RT	Area	Height	% Area
1	24,548	13956016	282983	92,80
2	28,644	1082160	22896	7,20

HPLC chromatogram of the racemic and chiral compound **8j**.



Peak Results

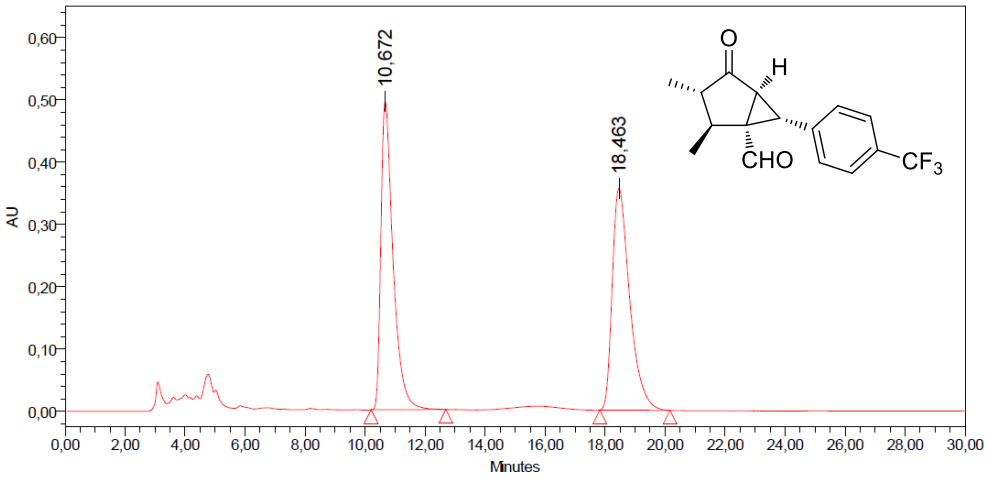
	RT	Area	Height	% Area
1	22,641	24477651	283463	50,82
2	48,426	23687334	207644	49,18



Peak Results

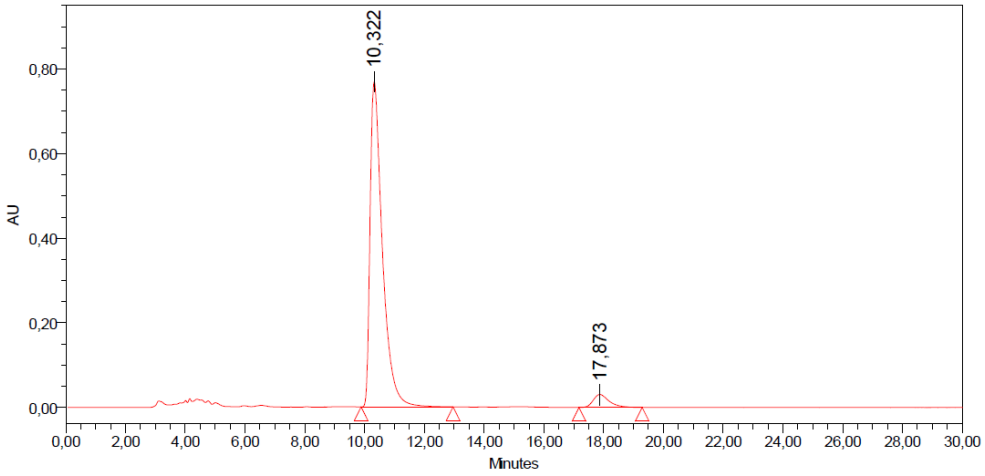
	RT	Area	Height	% Area
1	28,724	21663731	180935	94,66
2	64,643	1221325	8937	5,34

HPLC chromatogram of the racemic and chiral compound **8k**.



Peak Results

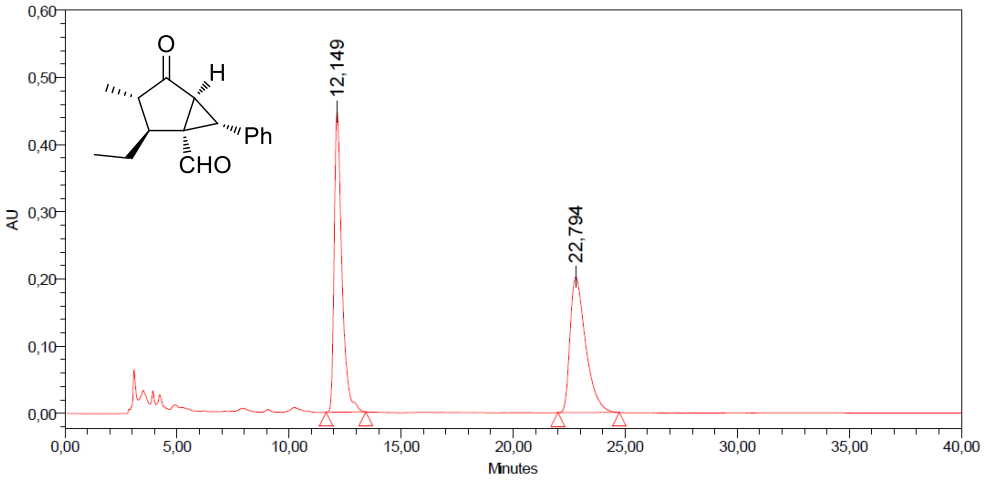
	RT	Area	Height	% Area
1	10,672	13954410	495306	49,27
2	18,463	14368096	356044	50,73



Peak Results

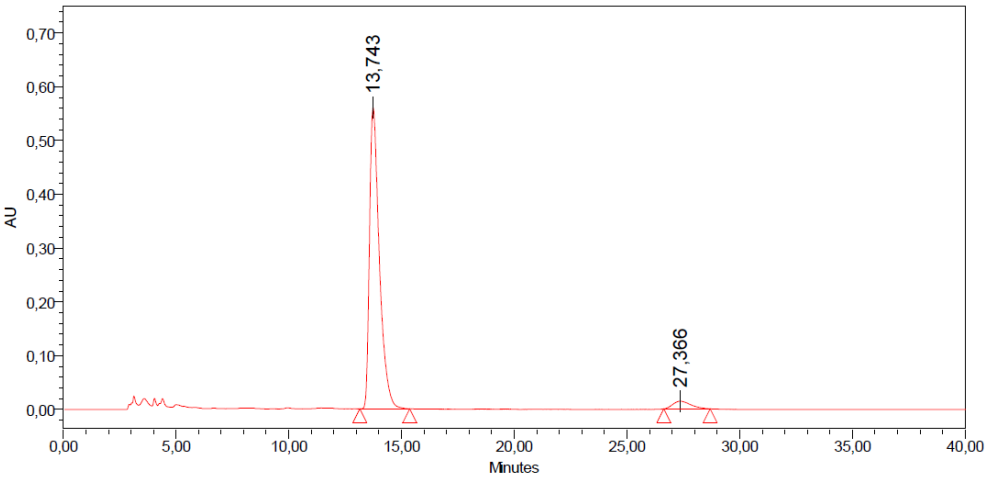
	RT	Area	Height	% Area
1	10,322	22067427	768728	95,11
2	17,873	1133898	30682	4,89

HPLC chromatogram of the racemic and chiral compound **8l**.



Peak Results

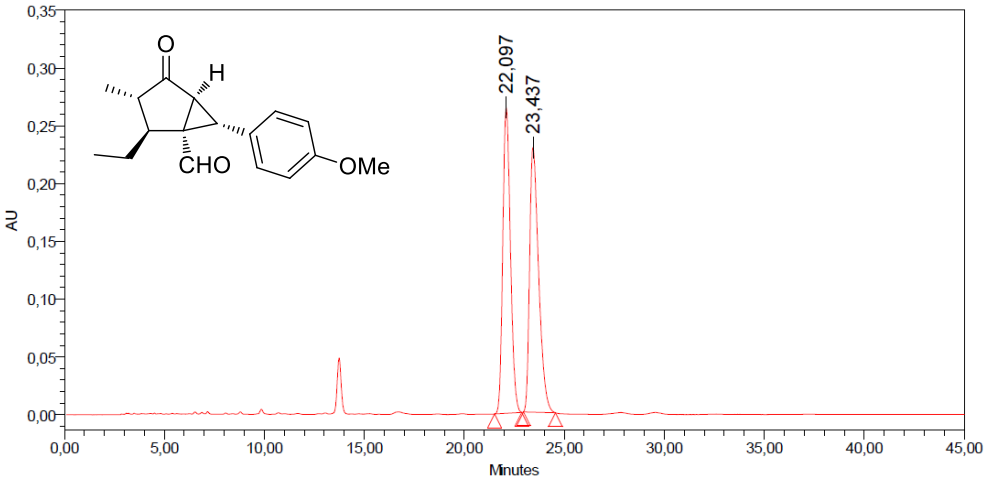
	RT	Area	Height	% Area
1	12,149	10720670	447242	52,26
2	22,794	9792081	201882	47,74



Peak Results

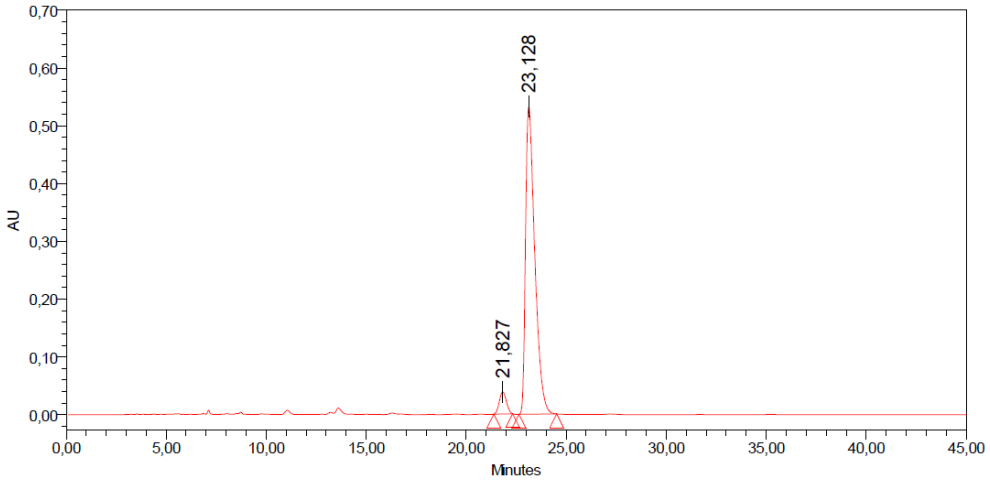
	RT	Area	Height	% Area
1	13,743	17042777	559980	95,64
2	27,366	777855	14141	4,36

HPLC chromatogram of the racemic and chiral compound **8m**.



Peak Results

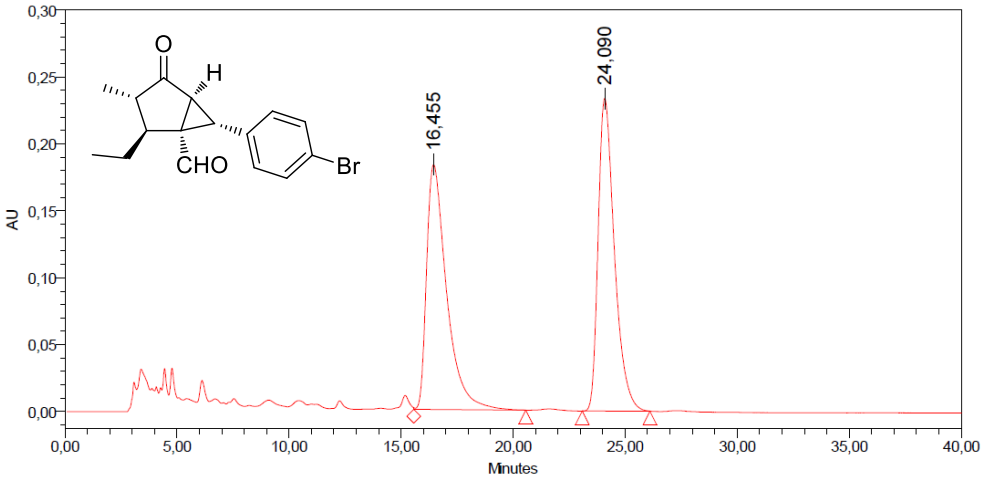
	RT	Area	Height	% Area
1	22,097	7012198	264894	49,33
2	23,437	7202594	229071	50,67



Peak Results

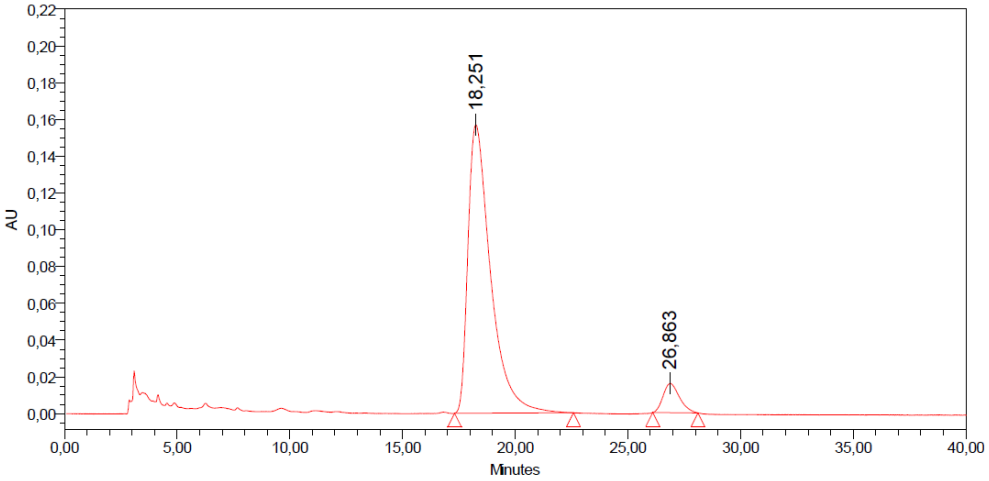
	RT	Area	Height	% Area
1	21,827	939878	38251	5,21
2	23,128	17110924	532087	94,79

HPLC chromatogram of the racemic and chiral compound **8n**.



Peak Results

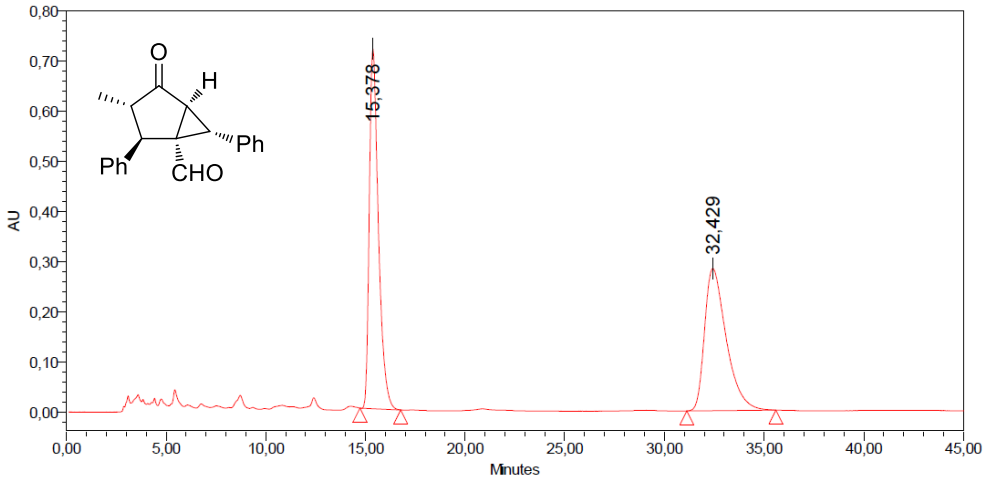
	RT	Area	Height	% Area
1	16,455	11368041	183019	49,09
2	24,090	11791861	233742	50,91



Peak Results

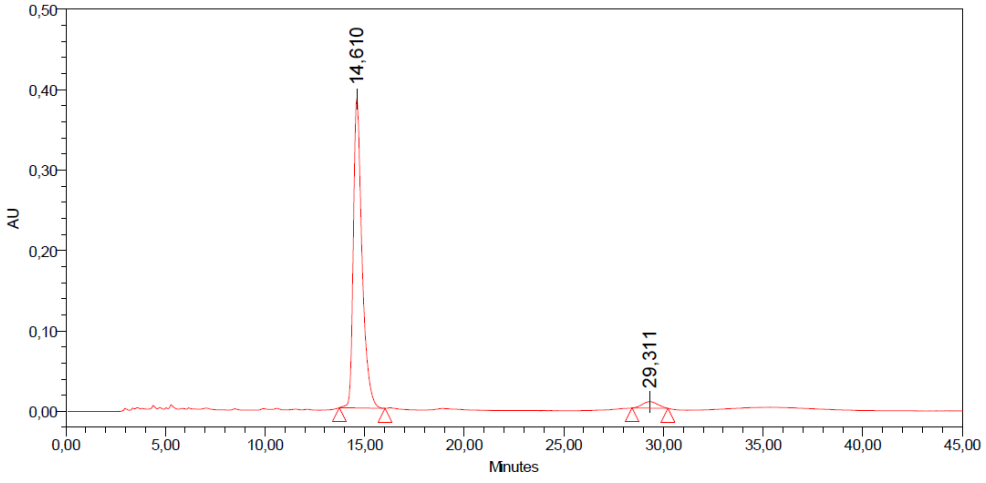
	RT	Area	Height	% Area
1	18,251	10951017	156906	93,20
2	26,863	799389	15929	6,80

HPLC chromatogram of the racemic and chiral compound **8o**.



Peak Results

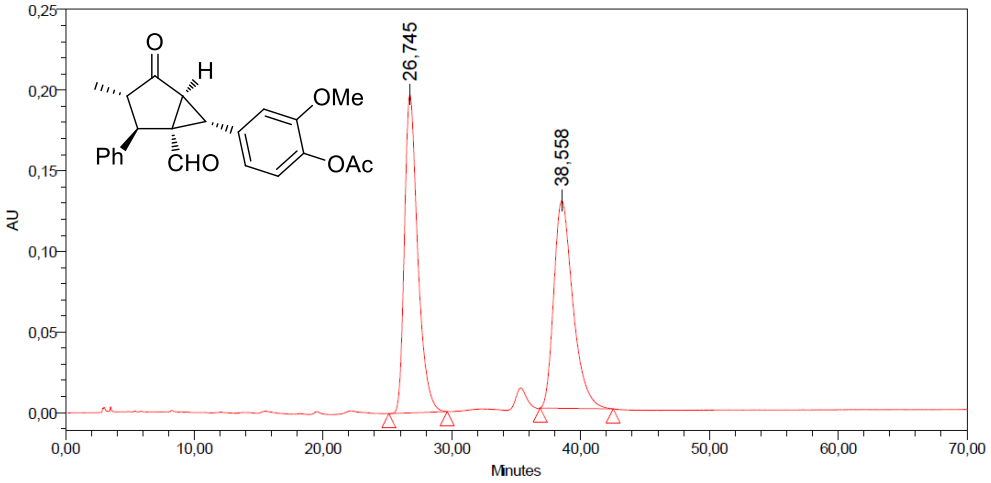
	RT	Area	Height	% Area
1	15,378	22764300	717301	51,56
2	32,429	21386039	283434	48,44



Peak Results

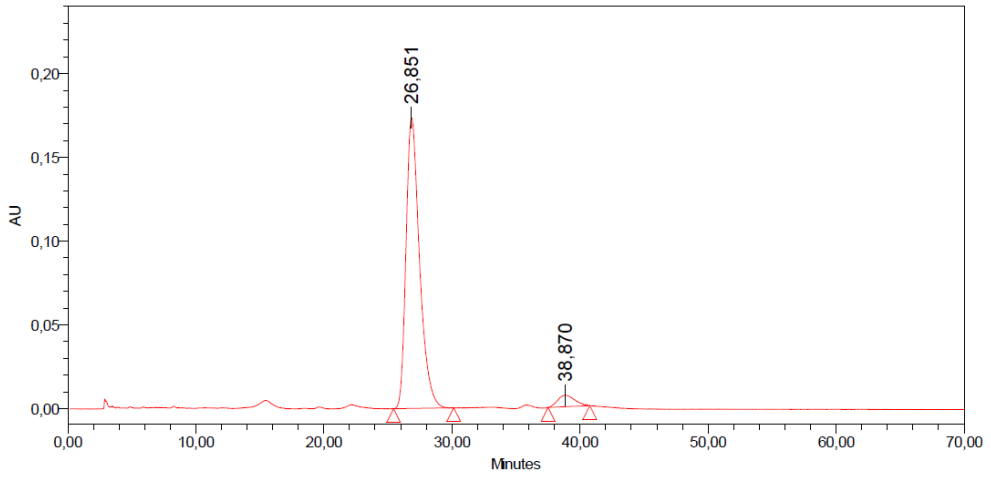
	RT	Area	Height	% Area
1	14,610	11671169	384087	96,40
2	29,311	436169	8156	3,60

HPLC chromatogram of the racemic and chiral compound **8p**.



Peak Results

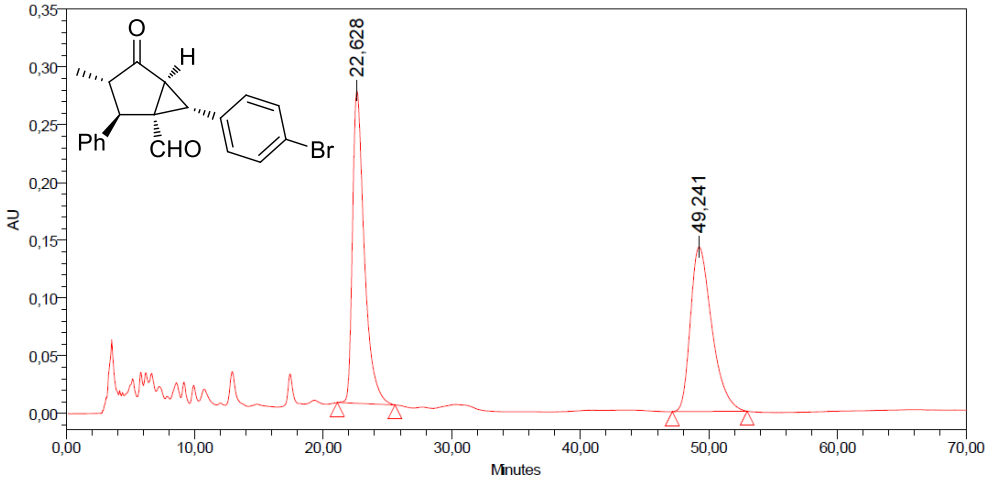
	RT	Area	Height	% Area
1	26,745	14126561	197387	51,55
2	38,558	13279578	128643	48,45



Peak Results

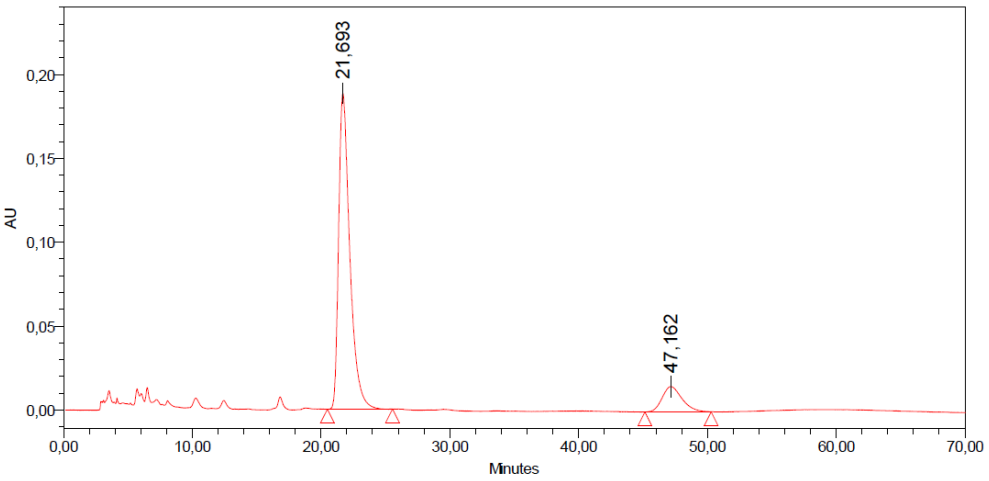
	RT	Area	Height	% Area
1	26,851	12704987	173510	95,22
2	38,870	637668	6907	4,78

HPLC chromatogram of the racemic and chiral compound **8q**.



Peak Results

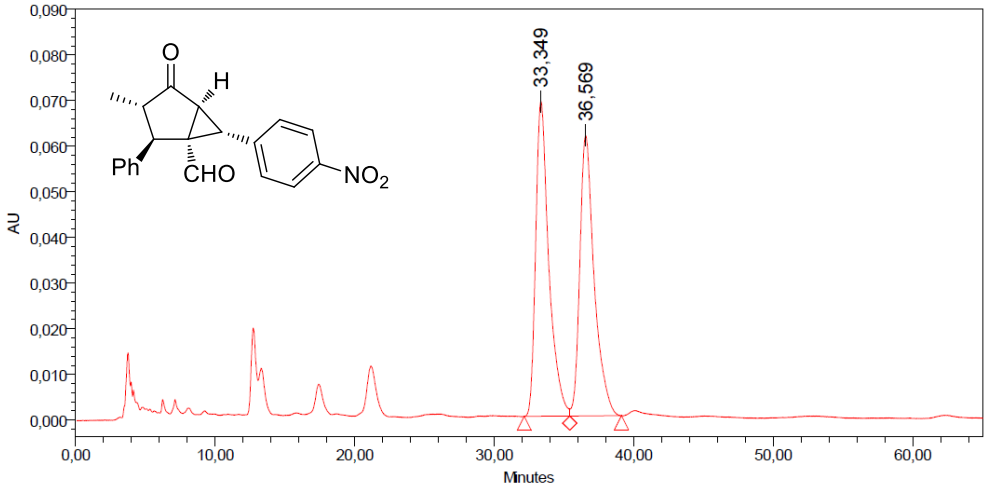
	RT	Area	Height	% Area
1	22,628	17286487	270836	51,21
2	49,241	16472876	142467	48,79



Peak Results

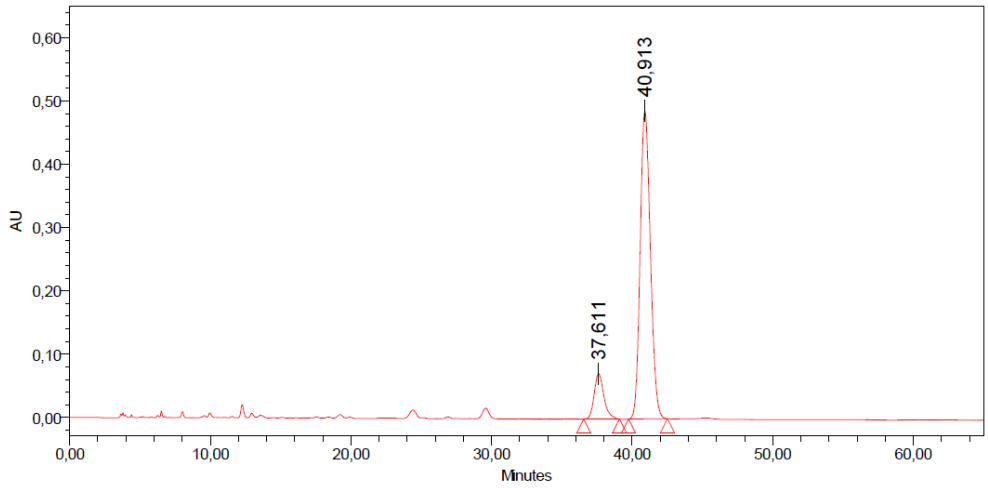
	RT	Area	Height	% Area
1	21,693	11310241	188302	87,49
2	47,162	1616797	15173	12,51

HPLC chromatogram of the racemic and chiral compound **8r**.



Peak Results

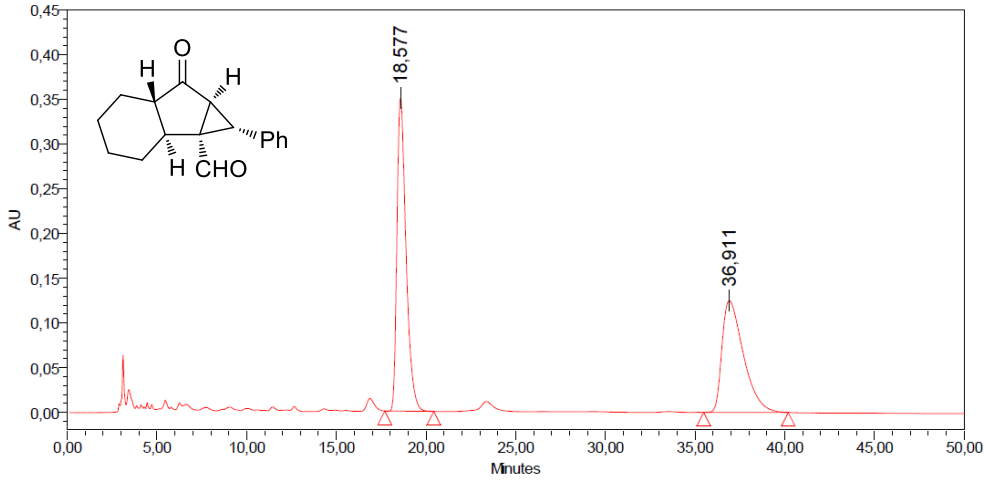
	RT	Area	Height	% Area
1	33,349	4523258	68956	50,68
2	36,569	4402418	61456	49,32



Peak Results

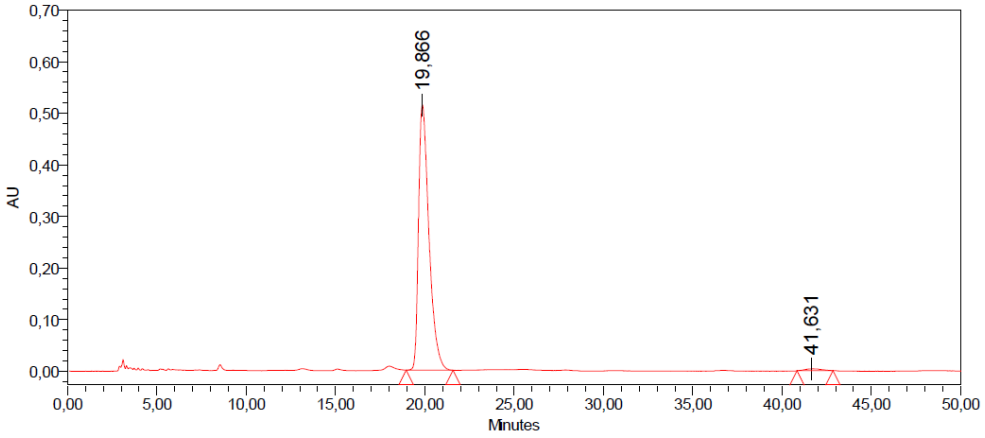
	RT	Area	Height	% Area
1	37,611	3427723	71614	12,23
2	40,913	24610667	486910	87,77

HPLC chromatogram of the racemic and chiral compound **8s**.



Peak Results

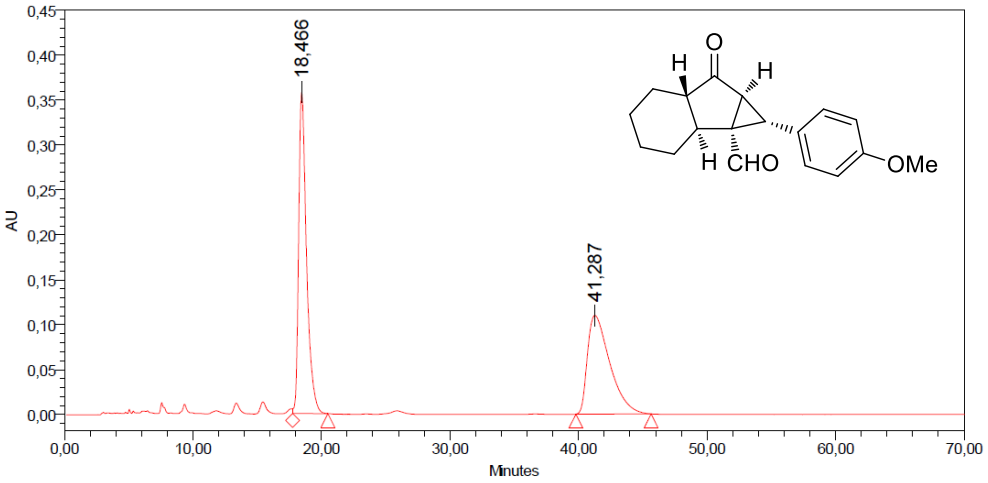
	RT	Area	Height	% Area
1	18,577	12355009	349943	54,39
2	36,911	10359178	124932	45,61



Peak Results

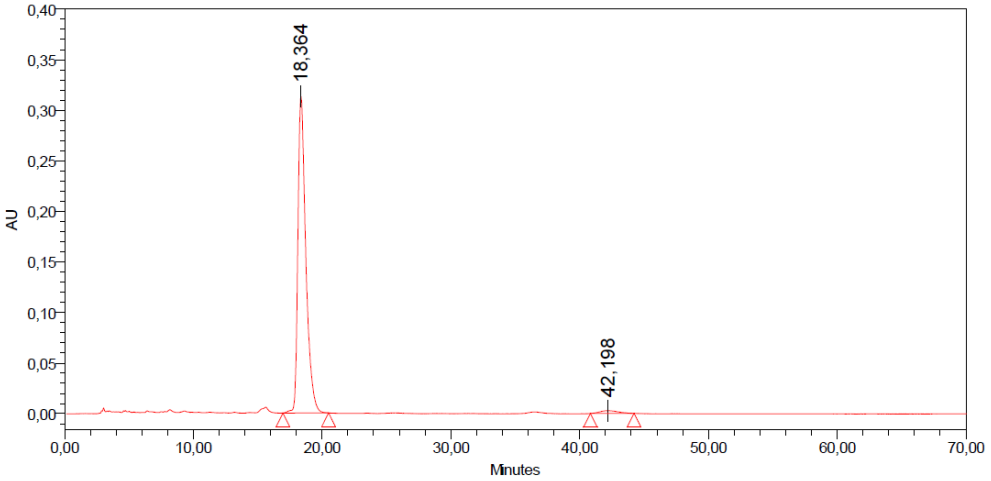
	RT	Area	Height	% Area
1	19,866	20812767	513972	98,87
2	41,631	238086	3748	1,13

HPLC chromatogram of the racemic and chiral compound **12a**.



Peak Results

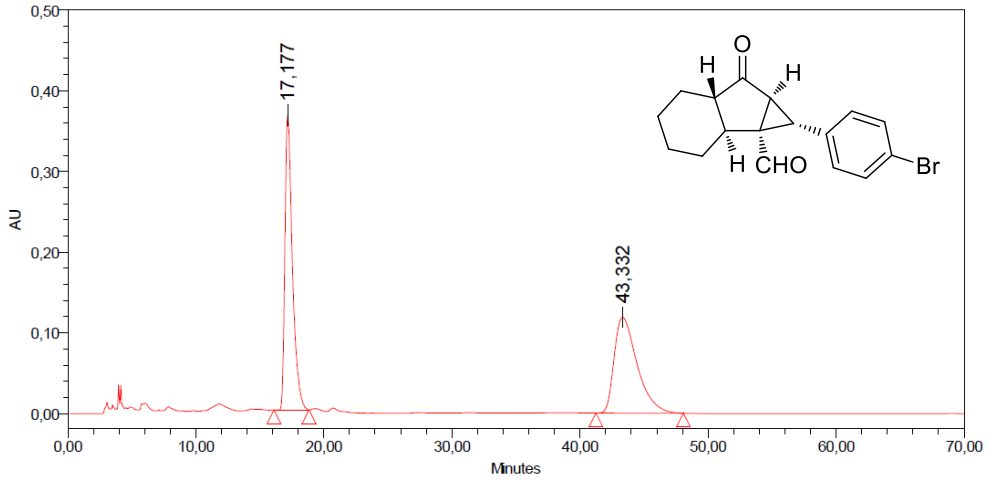
	RT	Area	Height	% Area
1	18,466	15184918	357754	53,38
2	41,287	13262031	109874	46,62



Peak Results

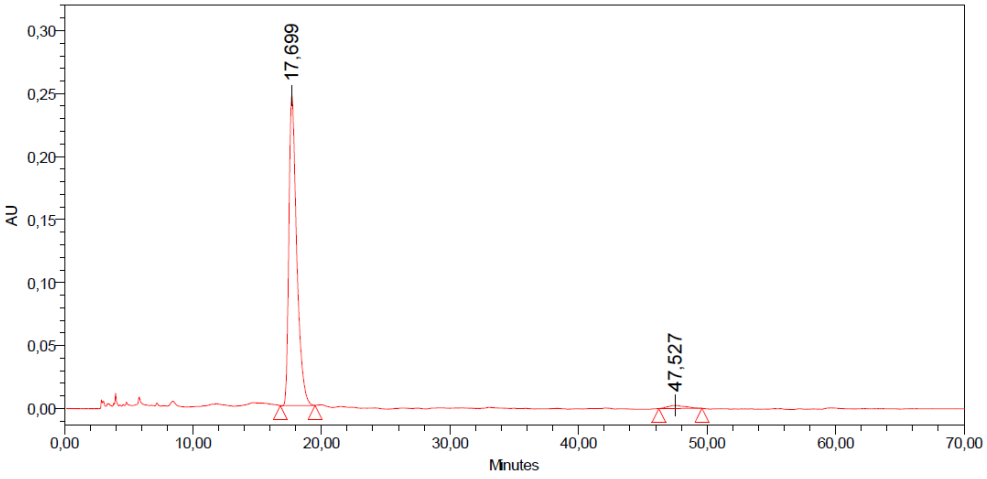
	RT	Area	Height	% Area
1	18,364	13406932	312986	98,00
2	42,198	273471	2859	2,00

HPLC chromatogram of the racemic and chiral compound **12b**.



Peak Results

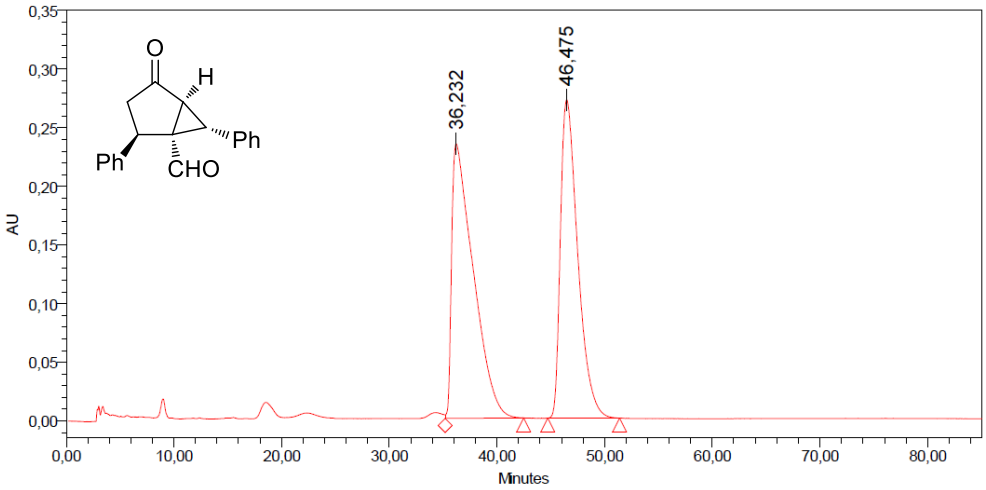
	RT	Area	Height	% Area
1	17,177	14862421	365444	50,14
2	43,332	14778707	118724	49,86



Peak Results

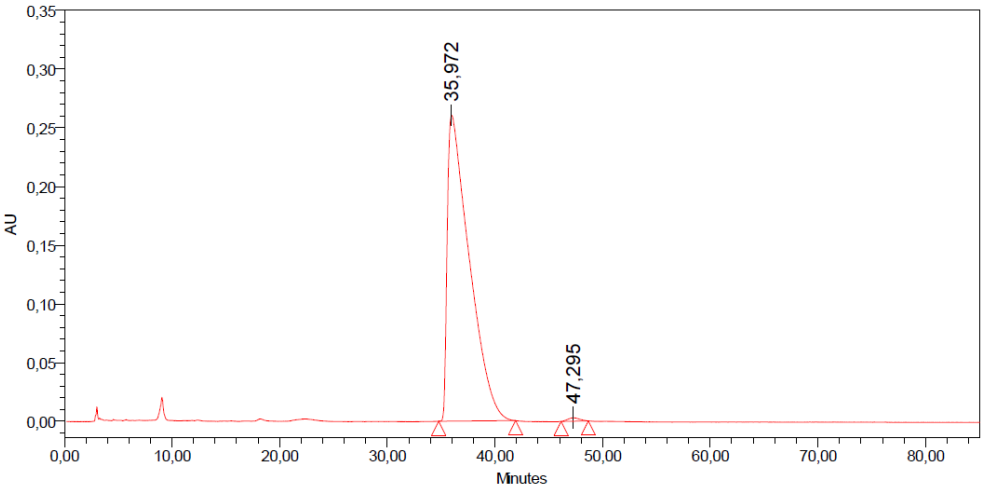
	RT	Area	Height	% Area
1	17,699	10402425	246182	97,78
2	47,527	236443	2448	2,22

HPLC chromatogram of the racemic and chiral compound **12c**.



Peak Results

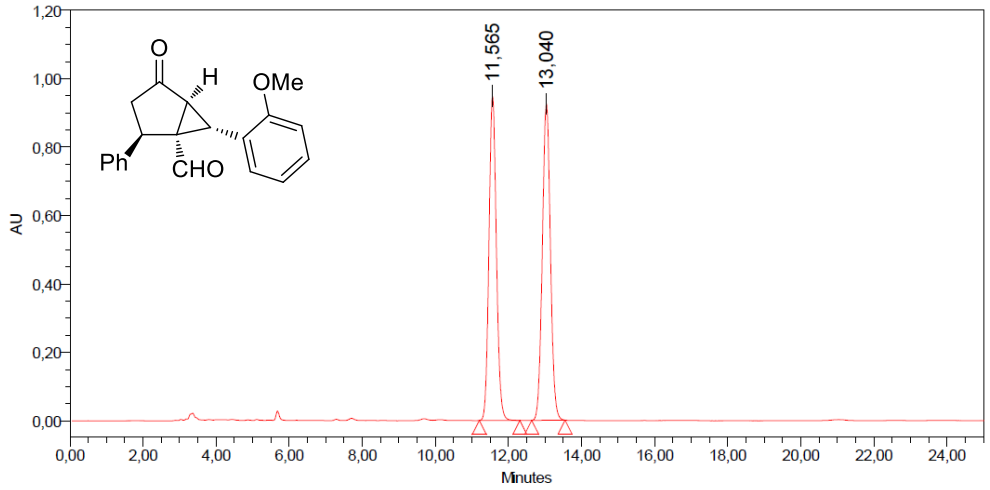
	RT	Area	Height	% Area
1	36,232	32652222	234035	51,85
2	46,475	30316562	271473	48,15



Peak Results

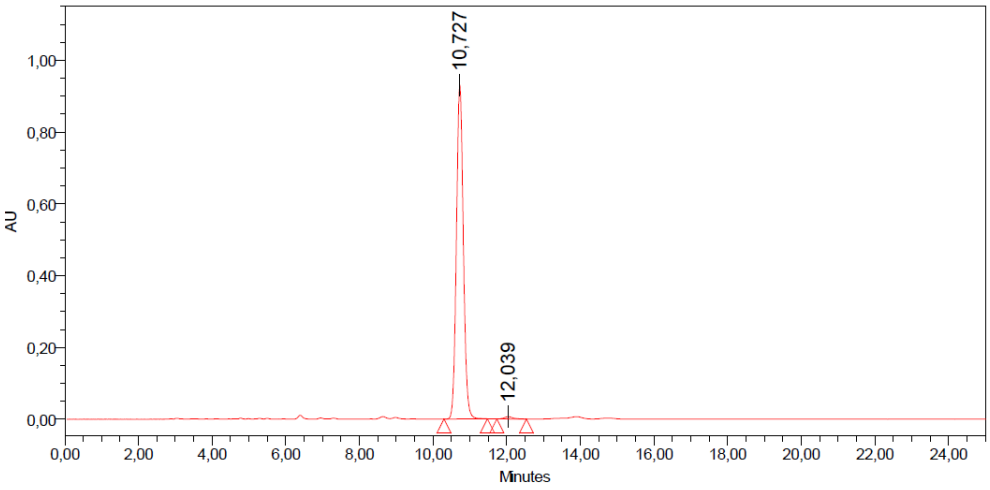
	RT	Area	Height	% Area
1	35,972	37070773	260533	99,41
2	47,295	219071	2907	0,59

HPLC chromatogram of the racemic and chiral compound **16a**.



Peak Results

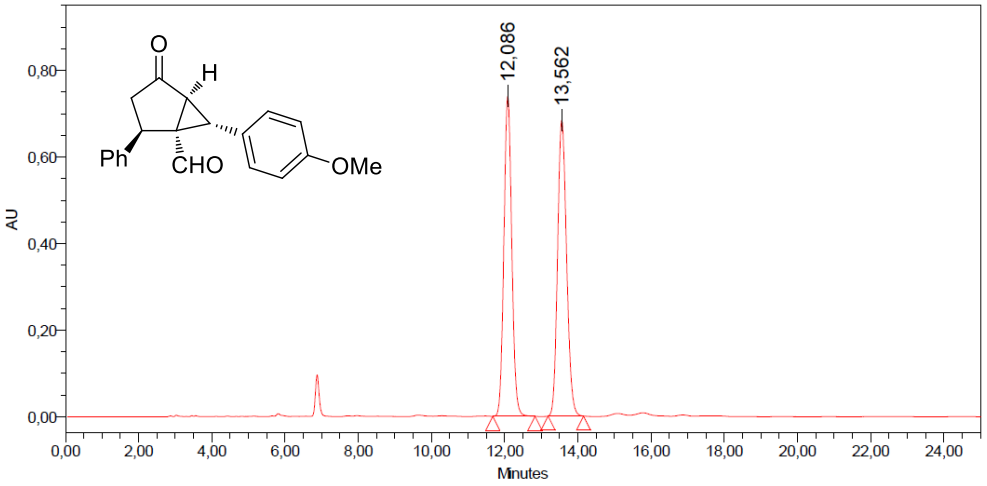
	RT	Area	Height	% Area
1	11,565	13377279	947978	48,32
2	13,040	14305851	925017	51,68



Peak Results

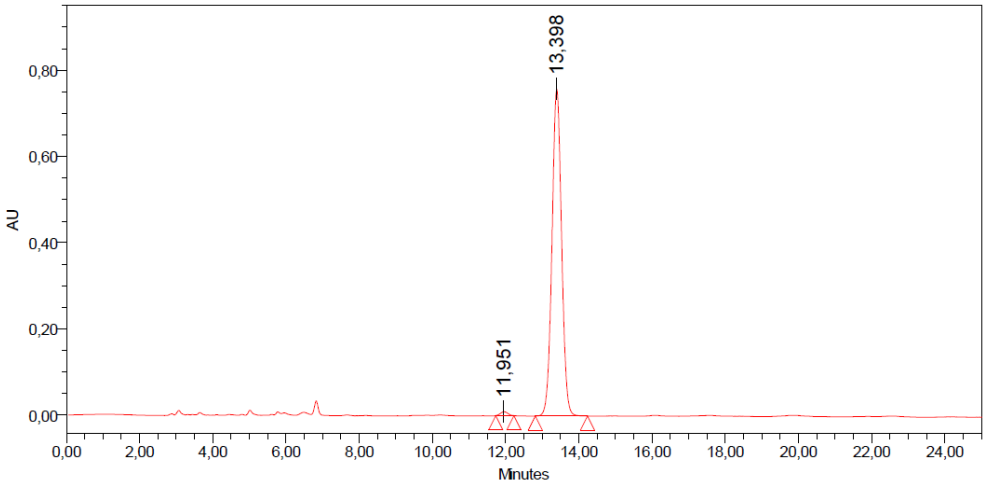
	RT	Area	Height	% Area
1	10,727	12120251	929901	99,18
2	12,039	99913	6177	0,82

HPLC chromatogram of the racemic and chiral compound **16b**.



Peak Results

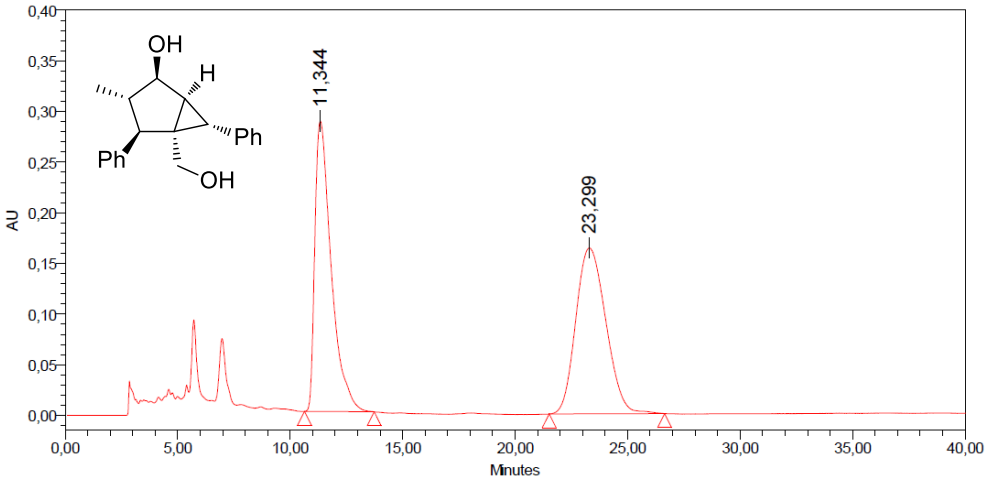
	RT	Area	Height	% Area
1	12,086	11098385	739802	48,82
2	13,562	11634403	683395	51,18



Peak Results

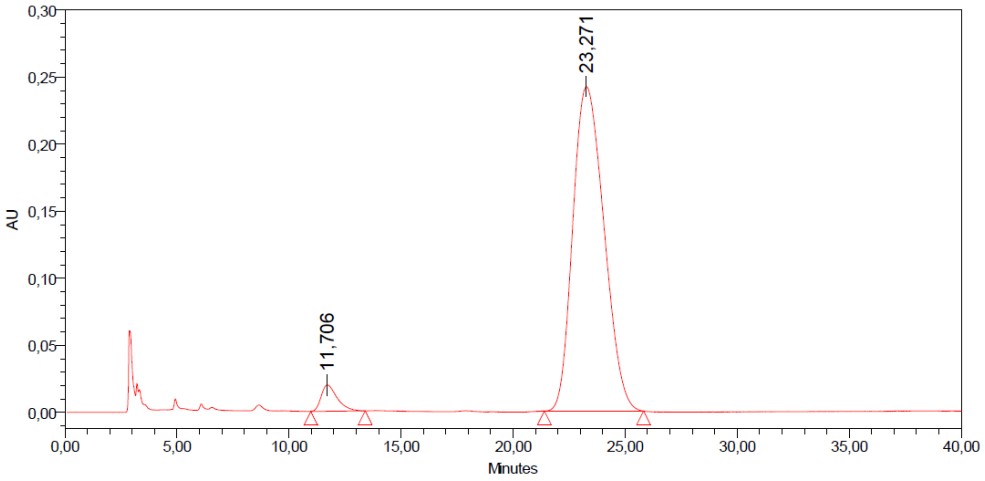
	RT	Area	Height	% Area
1	11,951	125395	8960	0,90
2	13,398	13791870	759242	99,10

HPLC chromatogram of the racemic and chiral compound **16c**.



Peak Results

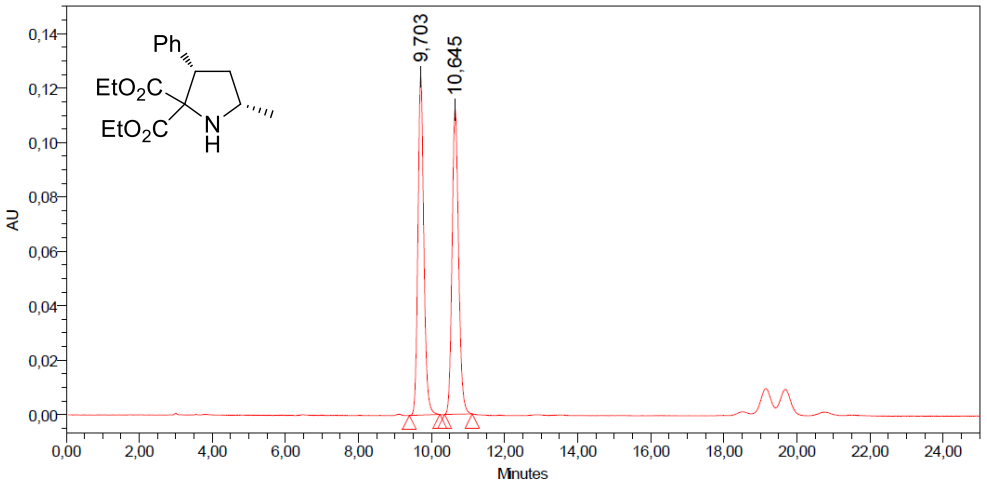
	RT	Area	Height	% Area
1	11,344	14504479	286794	48,76
2	23,299	15244019	163784	51,24



Peak Results

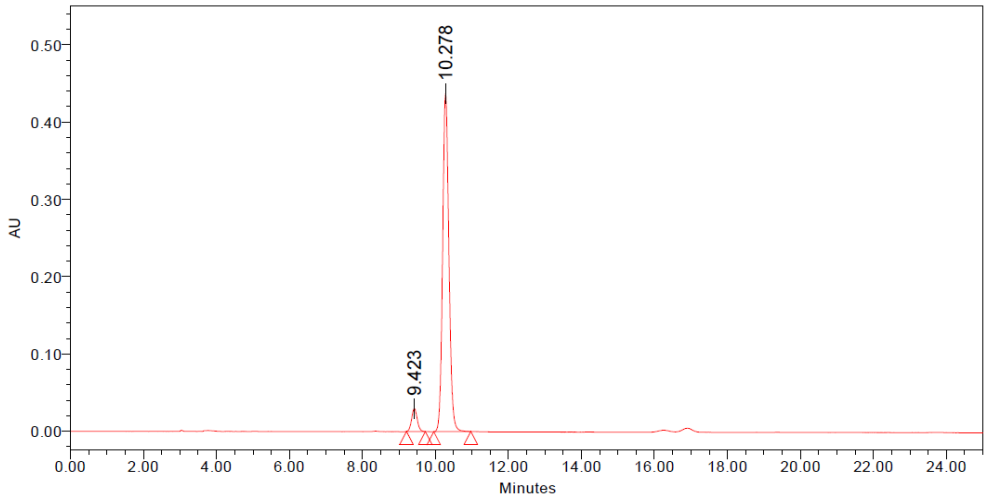
	RT	Area	Height	% Area
1	11,706	969600	19609	3,98
2	23,271	23403521	242000	96,02

HPLC chromatogram of the racemic and chiral compound **17p**.



Peak Results

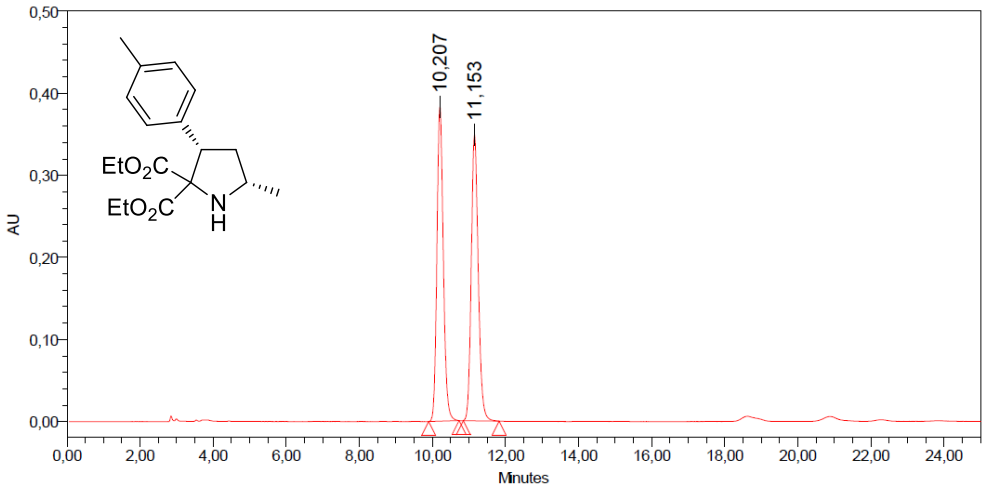
	RT	Area	Height	% Area
1	9,703	1398535	124407	50,20
2	10,645	1387574	111983	49,80



Peak Results

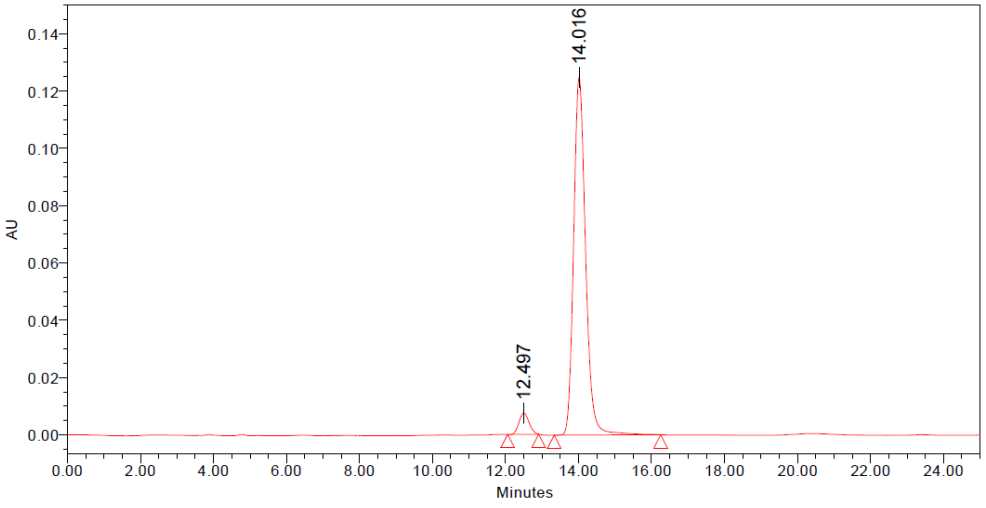
	RT	Area	Height	% Area
1	9.423	315202	29741	5.70
2	10.278	5215836	437512	94.30

HPLC chromatogram of the racemic and chiral compound **22a**.



Peak Results

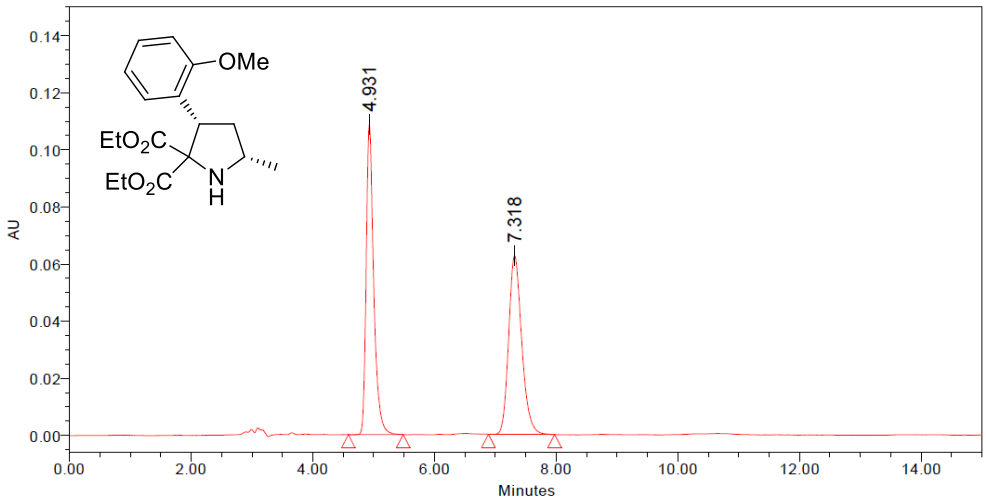
	RT	Area	Height	% Area
1	10,207	4650842	383012	50,02
2	11,153	4646964	348691	49,98



Peak Results

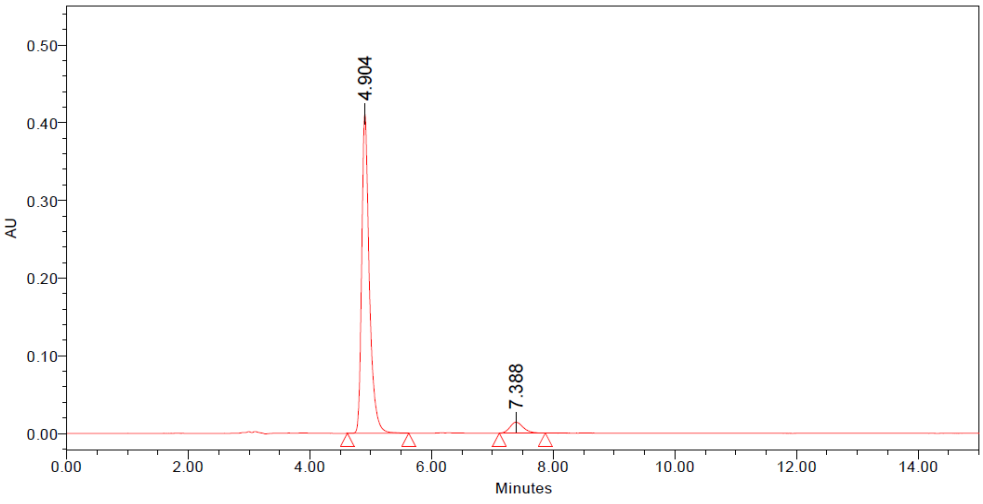
	RT	Area	Height	% Area
1	12.497	142993	7463	4.79
2	14.016	2840602	124899	95.21

HPLC chromatogram of the racemic and chiral compound **22b**.



Peak Results

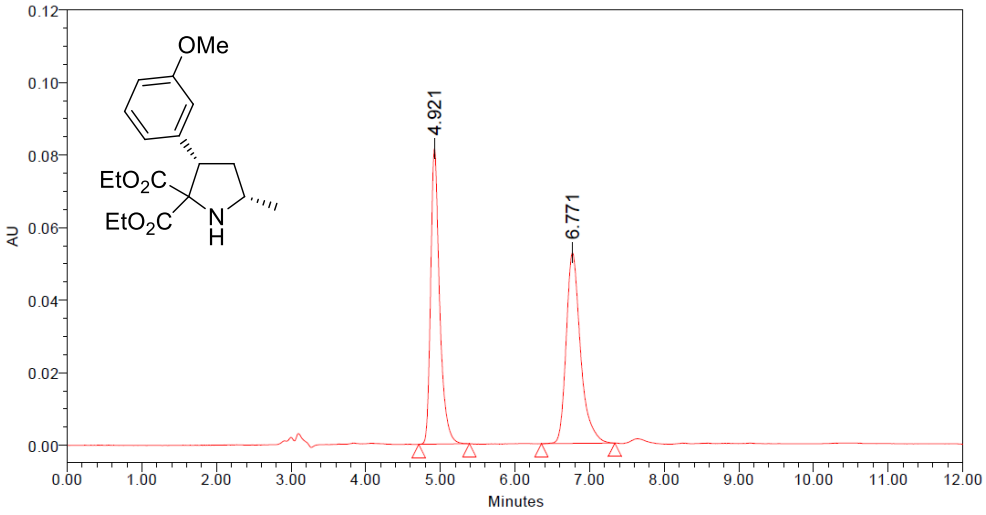
	RT	Area	Height	% Area
1	4.931	934230	108493	50.06
2	7.318	932149	62518	49.94



Peak Results

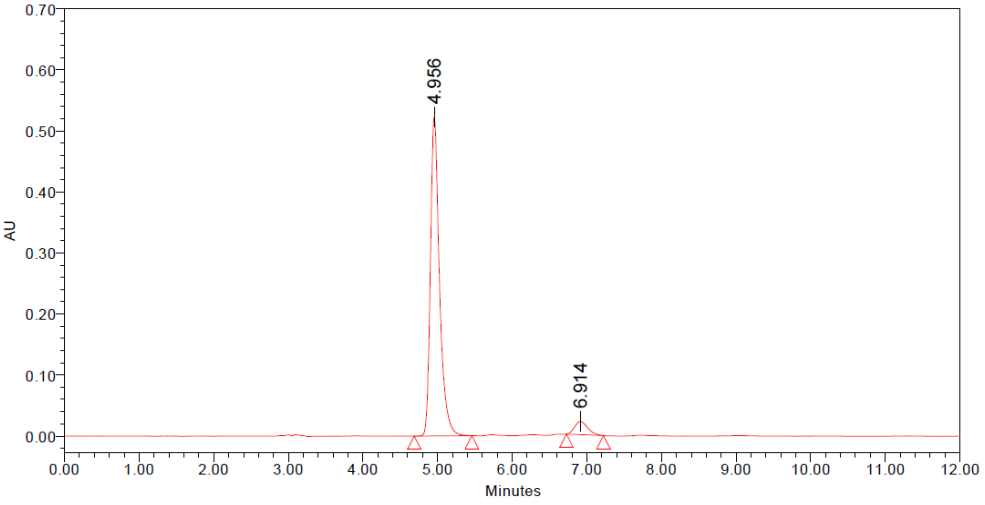
	RT	Area	Height	% Area
1	4.904	3586032	411198	94.40
2	7.388	212681	14047	5.60

HPLC chromatogram of the racemic and chiral compound **22c**.



Peak Results

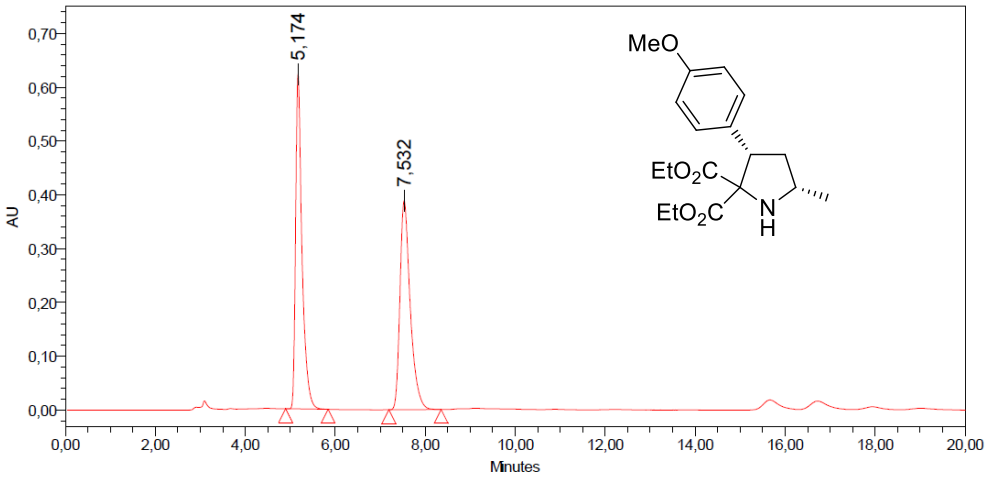
	RT	Area	Height	% Area
1	4.921	679016	81427	49.22
2	6.771	700413	52555	50.78



Peak Results

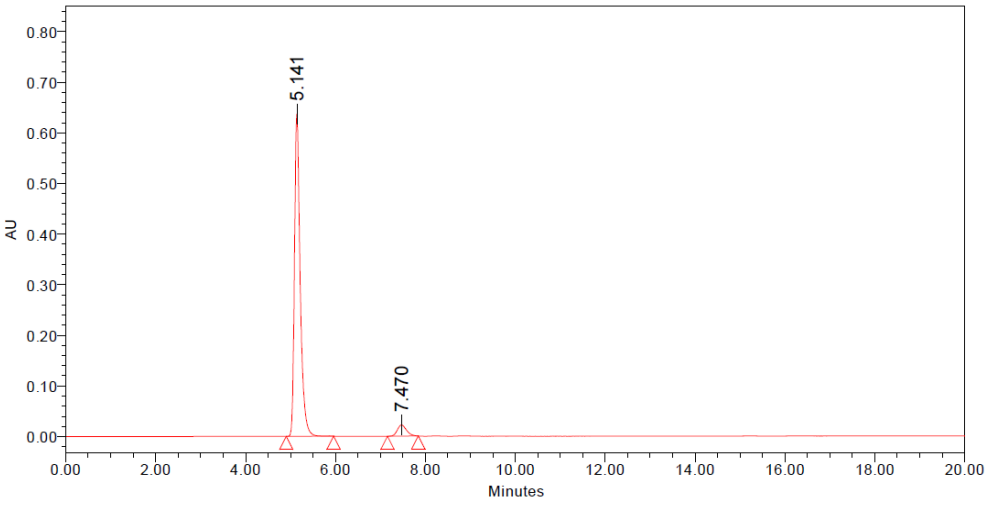
	RT	Area	Height	% Area
1	4.956	4404646	522619	94.39
2	6.914	261759	21592	5.61

HPLC chromatogram of the racemic and chiral compound **22d**.



Peak Results

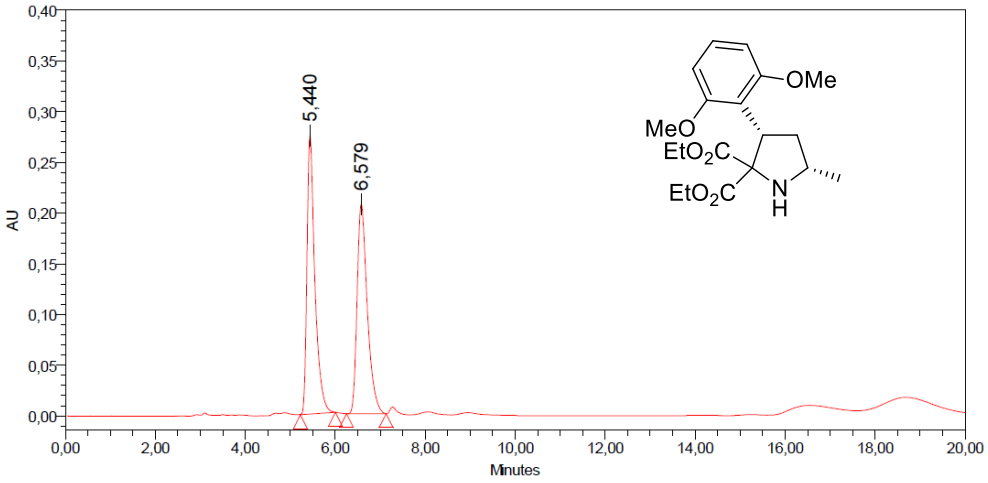
	RT	Area	Height	% Area
1	5,174	6172301	622489	50,04
2	7,532	6161384	388361	49,96



Peak Results

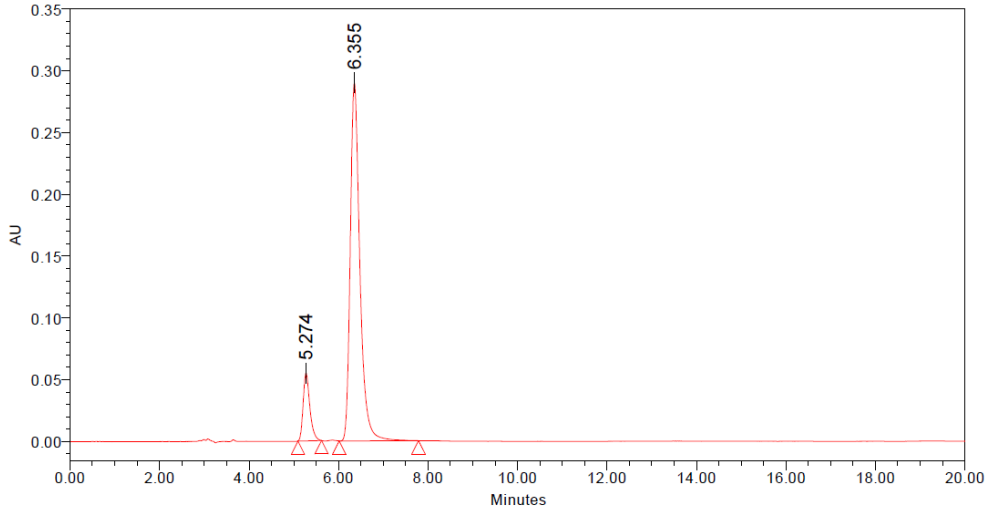
	RT	Area	Height	% Area
1	5.141	5627218	637135	94.74
2	7.470	312626	22108	5.26

HPLC chromatogram of the racemic and chiral compound **22e**.



Peak Results

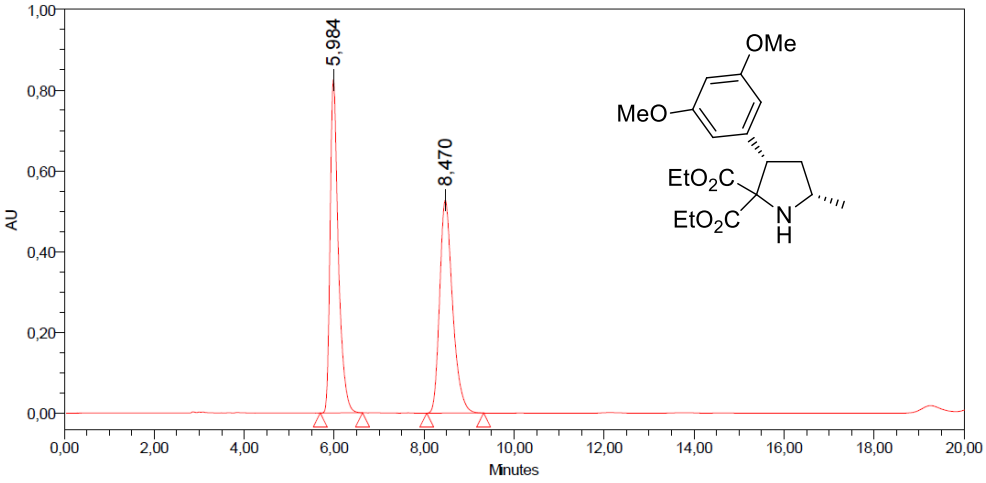
	RT	Area	Height	% Area
1	5,440	3339232	274513	50,61
2	6,579	3258505	206768	49,39



Peak Results

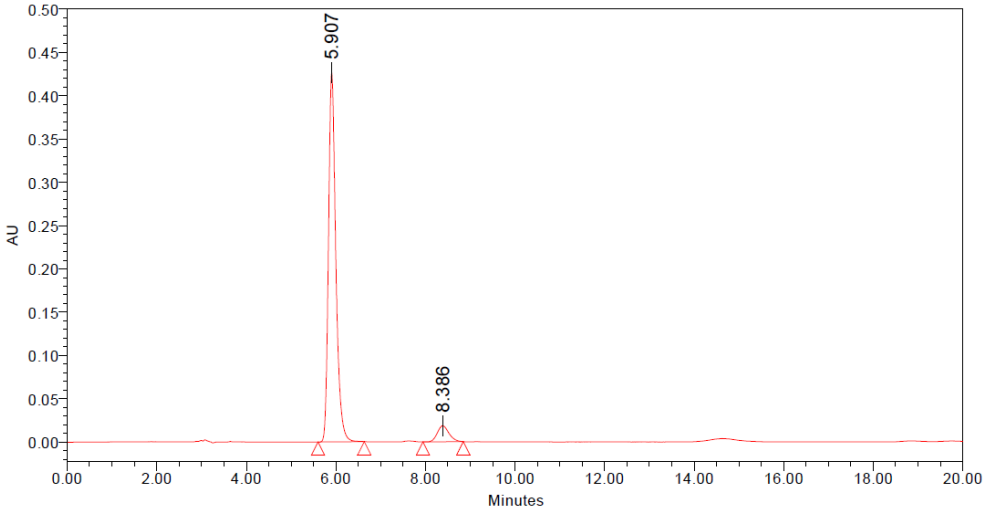
	RT	Area	Height	% Area
1	5.274	570010	54906	11.64
2	6.355	4324913	289569	88.36

HPLC chromatogram of the racemic and chiral compound **22f**.



Peak Results

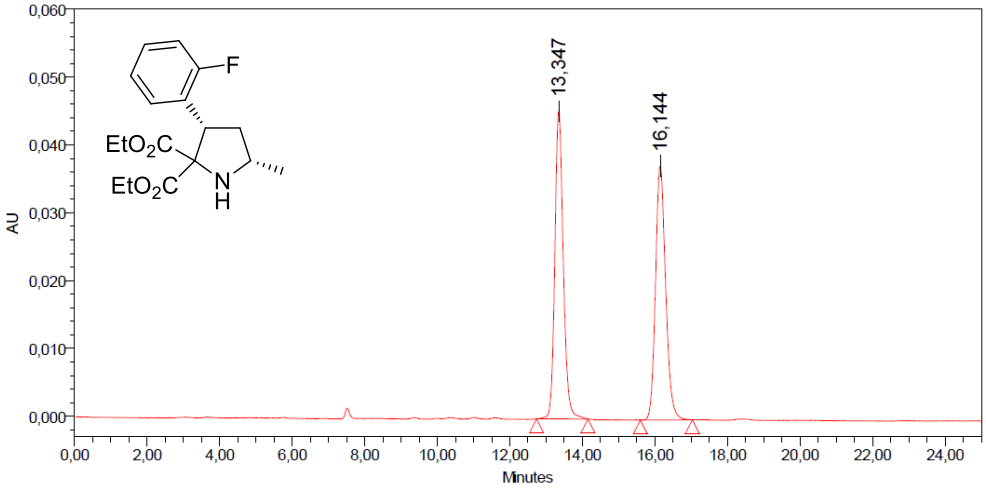
	RT	Area	Height	% Area
1	5,984	10501858	825795	49,90
2	8,470	10542975	527655	50,10



Peak Results

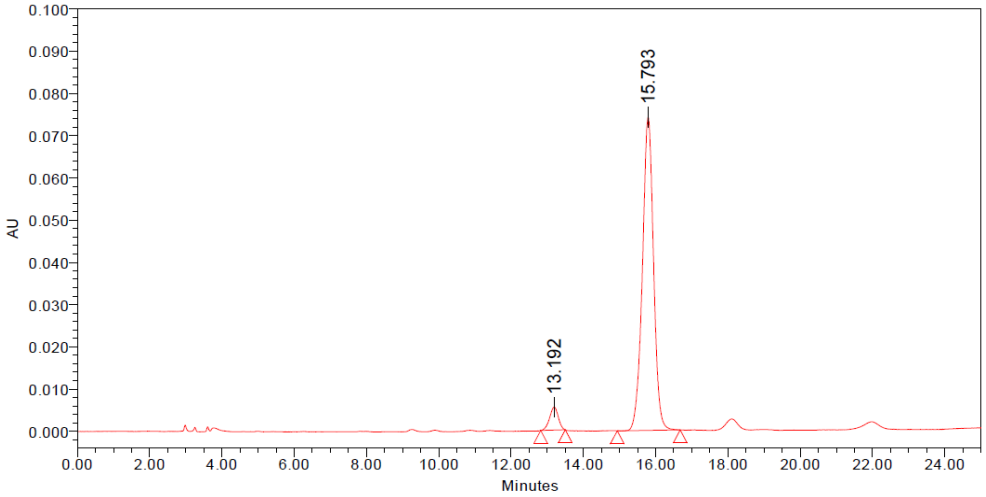
	RT	Area	Height	% Area
1	5.907	4856909	425995	93.58
2	8.386	333097	18454	6.42

HPLC chromatogram of the racemic and chiral compound **22g**.



Peak Results

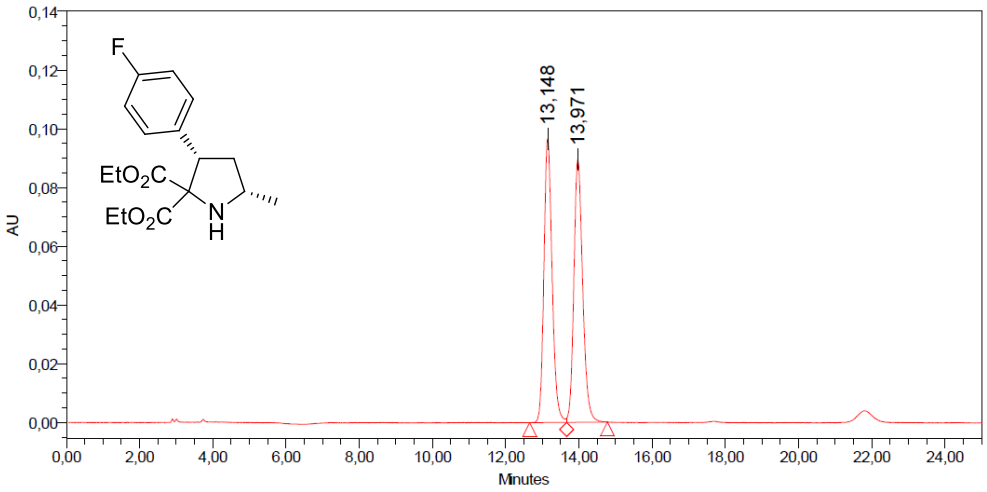
	RT	Area	Height	% Area
1	13,347	733244	45318	50,18
2	16,144	727943	37441	49,82



Peak Results

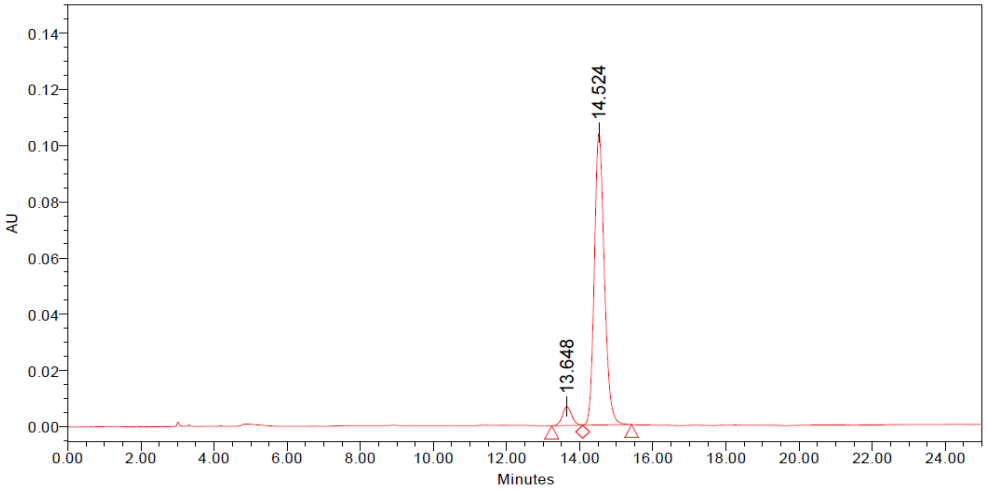
	RT	Area	Height	% Area
1	13.192	90739	5469	5.40
2	15.793	1588615	74150	94.60

HPLC chromatogram of the racemic and chiral compound **22h**.



Peak Results

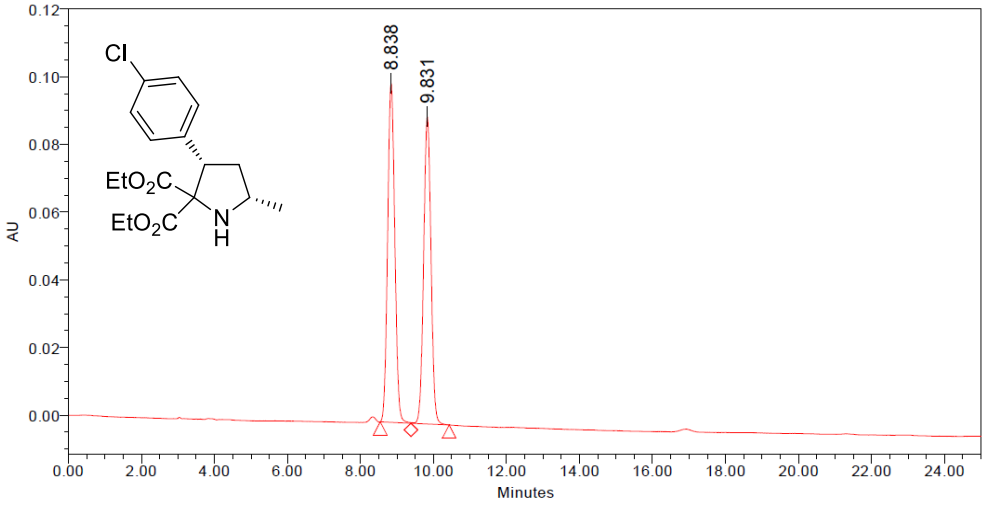
	RT	Area	Height	% Area
1	13,148	1501235	96639	49,95
2	13,971	1503958	89427	50,05



Peak Results

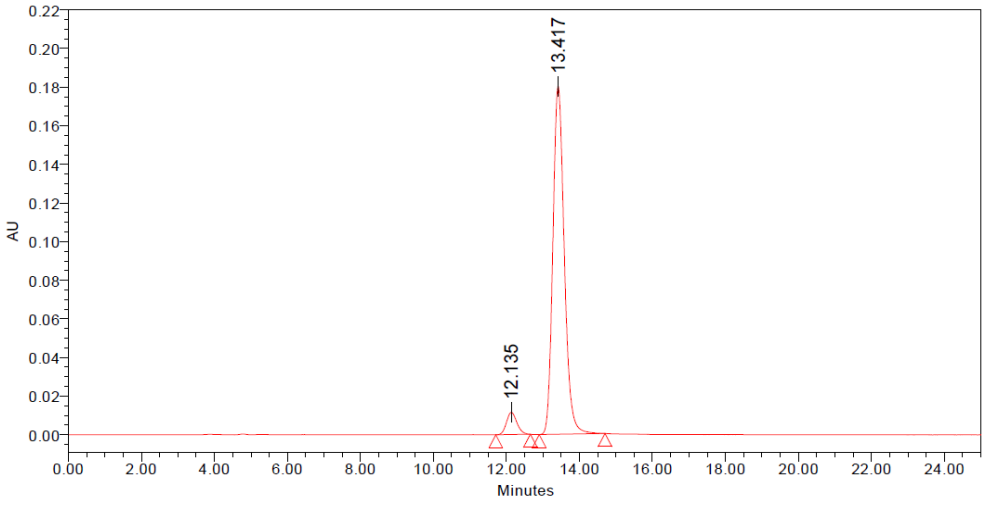
	RT	Area	Height	% Area
1	13.648	119590	6740	5.71
2	14.524	1973697	103916	94.29

HPLC chromatogram of the racemic and chiral compound **22i**.



Peak Results

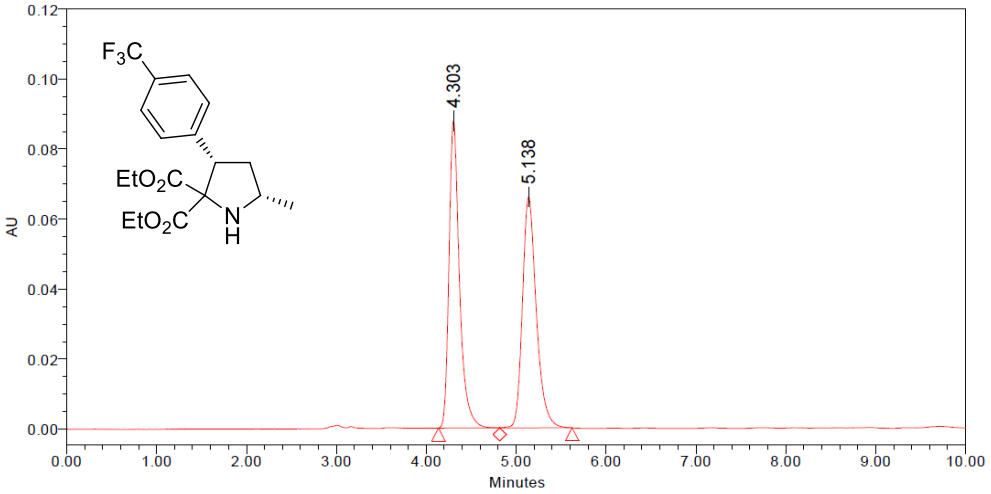
	RT	Area	Height	% Area
1	8.838	1362143	100127	51.86
2	9.831	1264430	90758	48.14



Peak Results

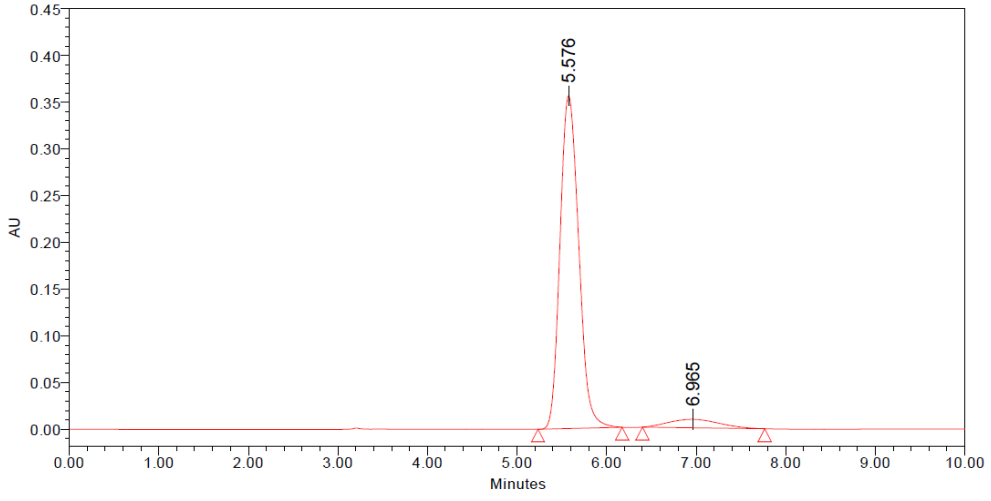
	RT	Area	Height	% Area
1	12.135	226635	11483	5.48
2	13.417	3906595	180220	94.52

HPLC chromatogram of the racemic and chiral compound **22j**.



Peak Results

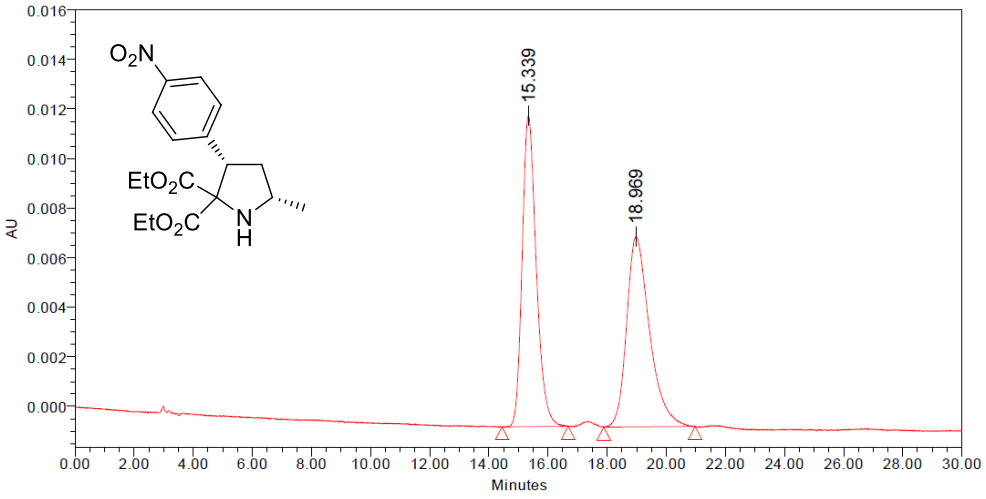
	RT	Area	Height	% Area
1	4.303	709427	87758	50.09
2	5.138	706974	65971	49.91



Peak Results

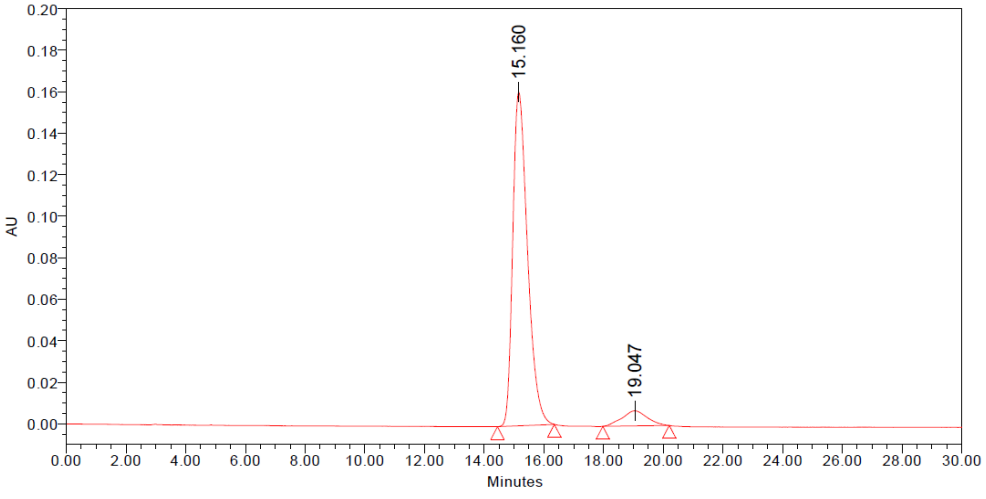
	RT	Area	Height	% Area
1	5.576	5160061	355987	93.61
2	6.965	352222	8969	6.39

HPLC chromatogram of the racemic and chiral compound **22k**.



Peak Results

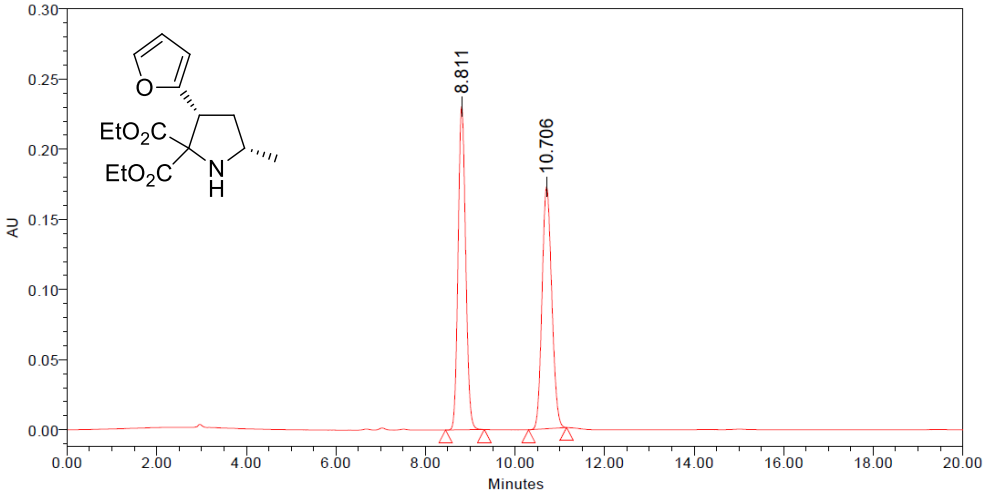
	RT	Area	Height	% Area
1	15.339	415308	12549	50.07
2	18.969	414215	7685	49.93



Peak Results

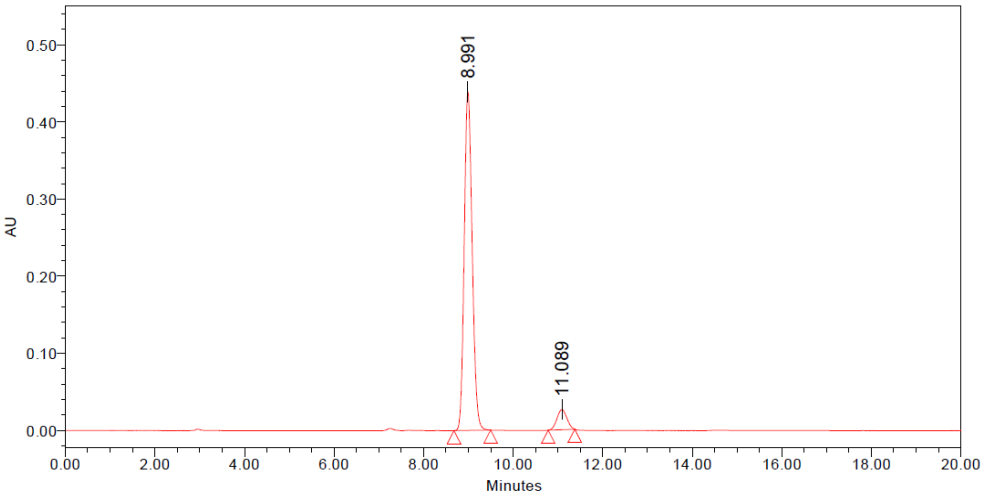
	RT	Area	Height	% Area
1	15.160	5504455	160812	92.78
2	19.047	428300	7281	7.22

HPLC chromatogram of the racemic and chiral compound **22l**.



Peak Results

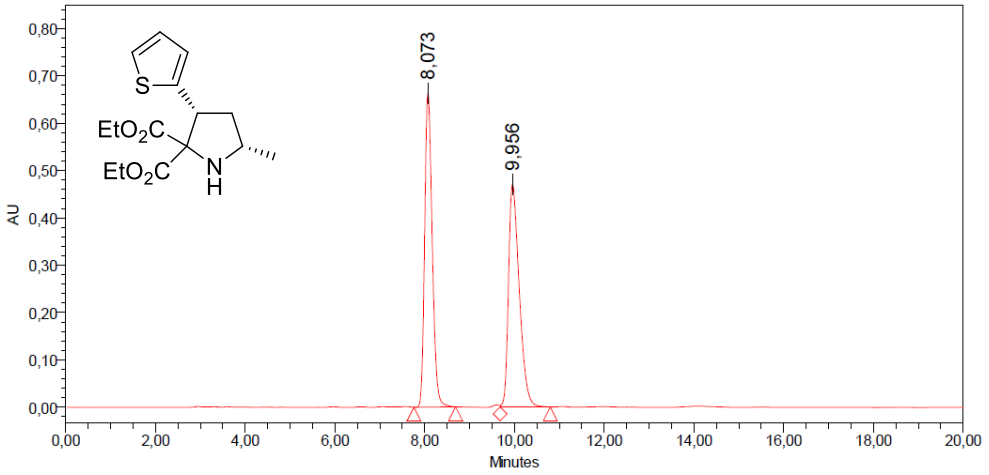
	RT	Area	Height	% Area
1	8.811	2713222	230459	51.05
2	10.706	2601954	172430	48.95



Peak Results

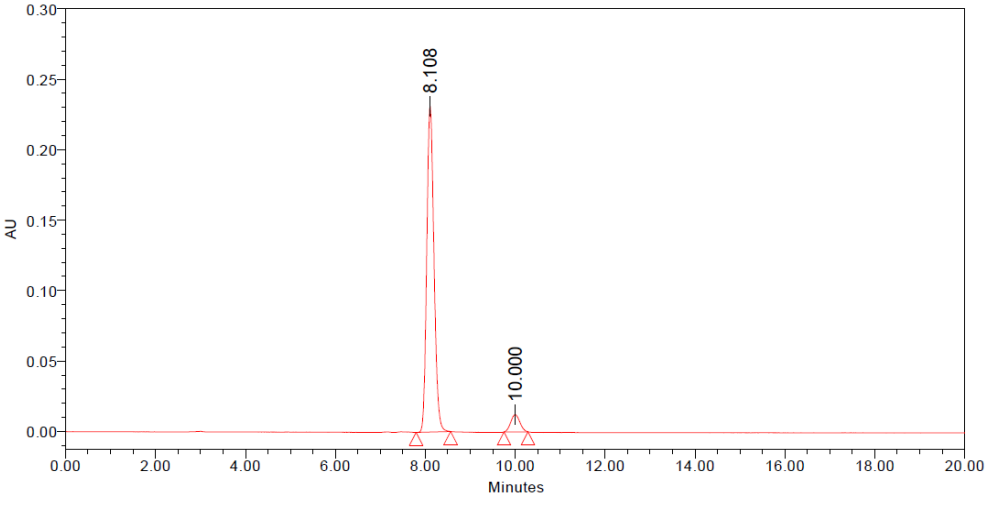
	RT	Area	Height	% Area
1	8.991	5403375	438930	93.04
2	11.089	403916	26237	6.96

HPLC chromatogram of the racemic and chiral compound **22m**.



Peak Results

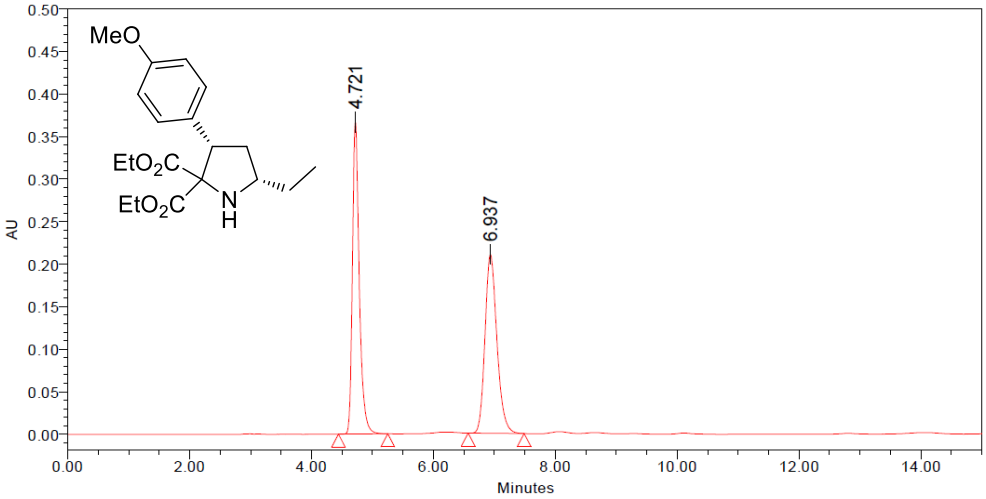
	RT	Area	Height	% Area
1	8,073	7761492	663579	49,83
2	9,956	7814550	470455	50,17



Peak Results

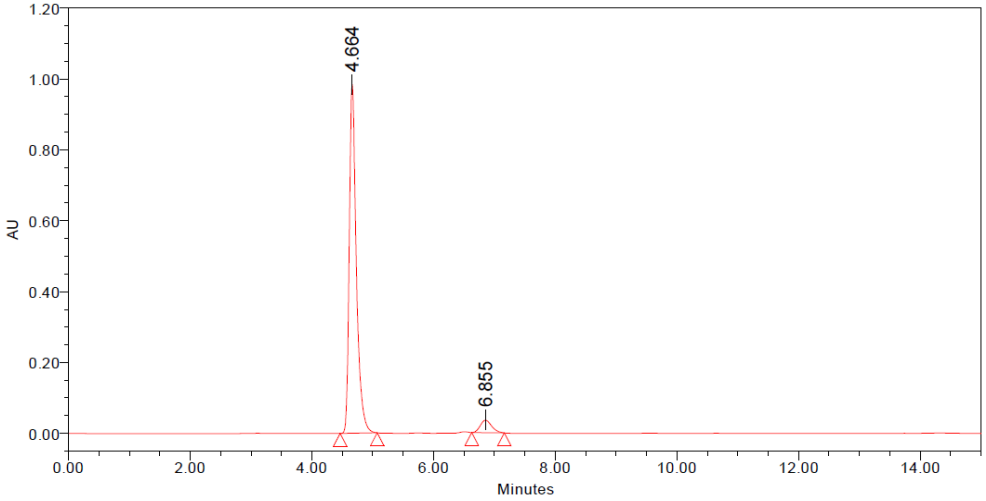
	RT	Area	Height	% Area
1	8.108	2575512	231220	93.72
2	10.000	172515	12280	6.28

HPLC chromatogram of the racemic and chiral compound **22n**.



Peak Results

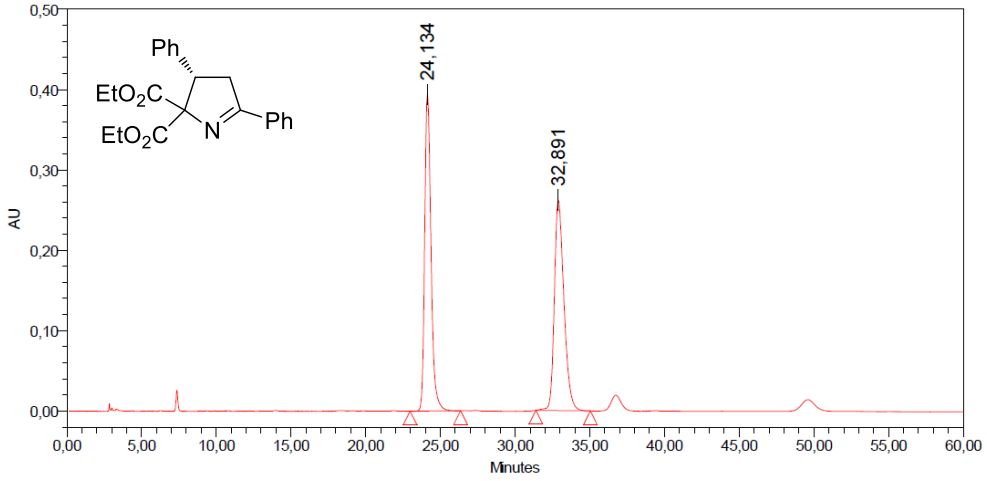
	RT	Area	Height	% Area
1	4.721	2866295	366837	50.03
2	6.937	2863058	210076	49.97



Peak Results

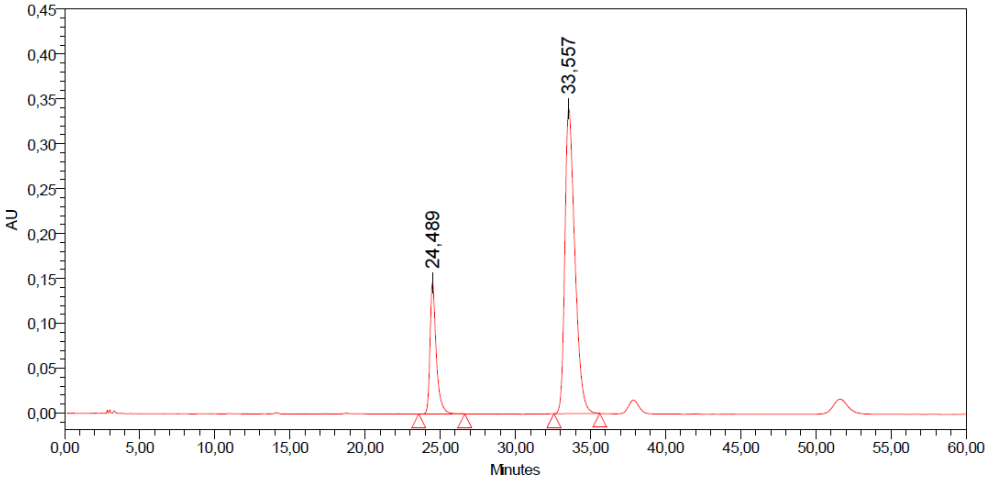
	RT	Area	Height	% Area
1	4.664	7924428	983671	94.56
2	6.855	455638	35157	5.44

HPLC chromatogram of the racemic and chiral compound **22o**.



Peak Results

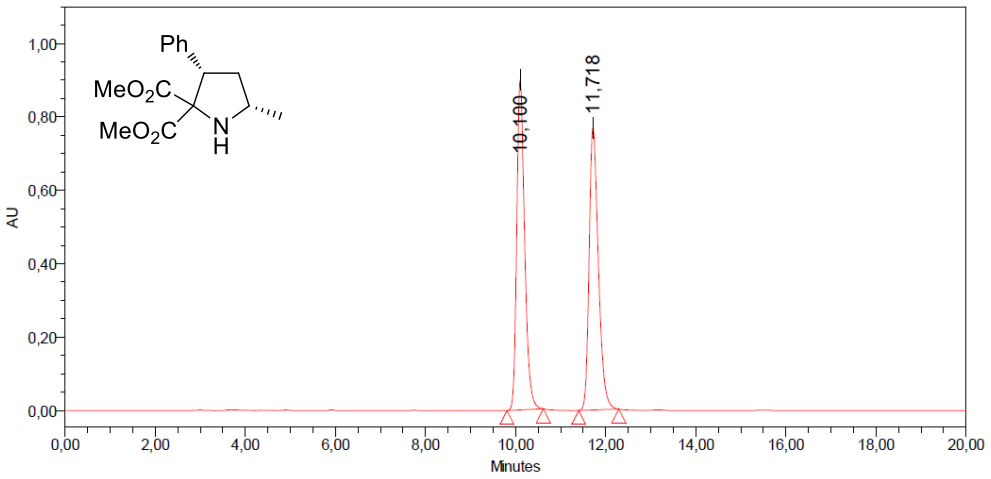
	RT	Area	Height	% Area
1	24,134	11667211	393971	50,01
2	32,891	11663966	261824	49,99



Peak Results

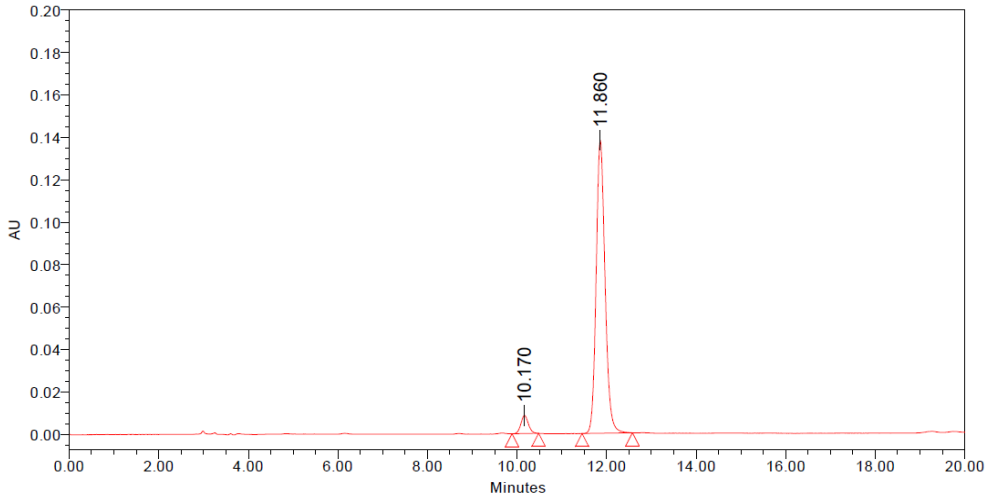
	RT	Area	Height	% Area
1	24,489	4180429	146021	21,00
2	33,557	15721786	339615	79,00

HPLC chromatogram of the racemic and chiral compound **22p.**



Peak Results

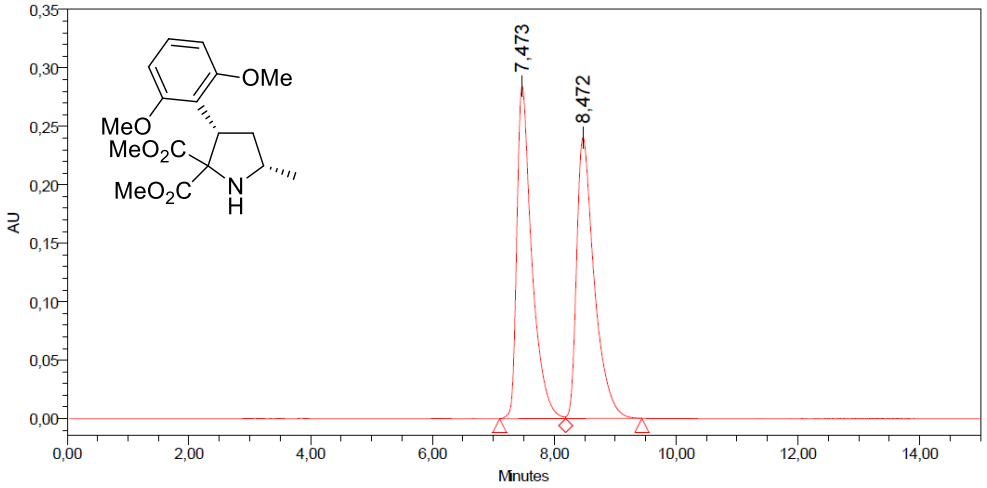
	RT	Area	Height	% Area
1	10,100	10915786	899422	49,94
2	11,718	10939887	769120	50,06



Peak Results

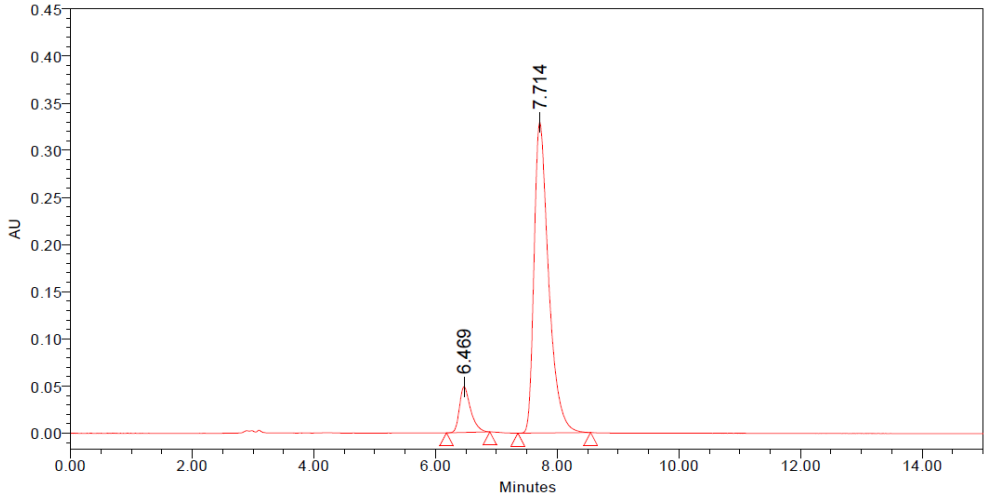
	RT	Area	Height	% Area
1	10.170	99103	8492	4.94
2	11.860	1908312	138016	95.06

HPLC chromatogram of the racemic and chiral compound **22q.**



Peak Results

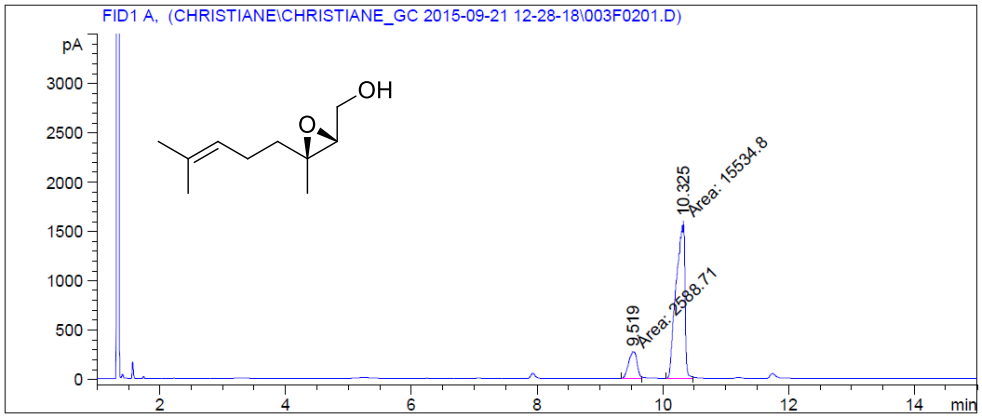
	RT	Area	Height	% Area
1	7,473	4853557	284376	50,15
2	8,472	4824113	240279	49,85



Peak Results

	RT	Area	Height	% Area
1	6.469	615991	48441	10.09
2	7.714	5491317	329327	89.91

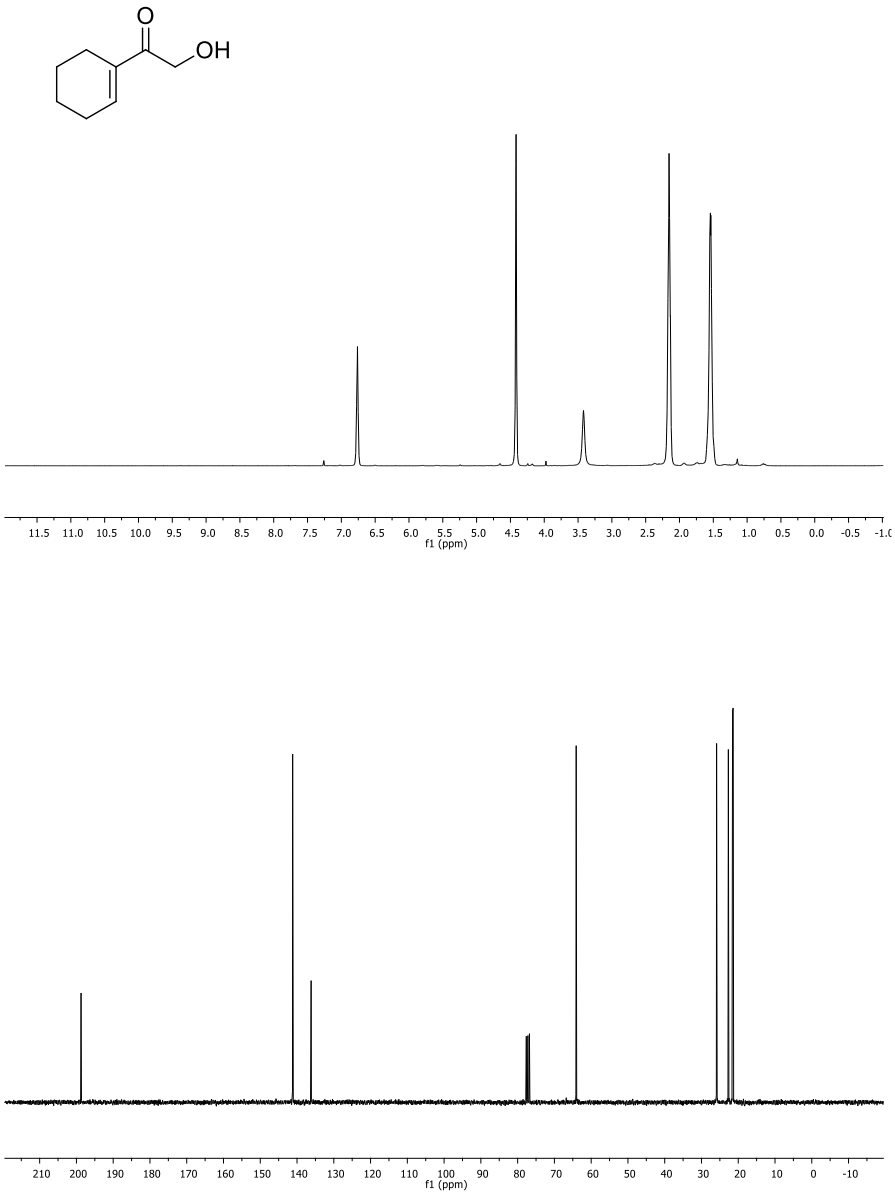
HPLC chromatogram of the racemic and chiral compound **22r.**



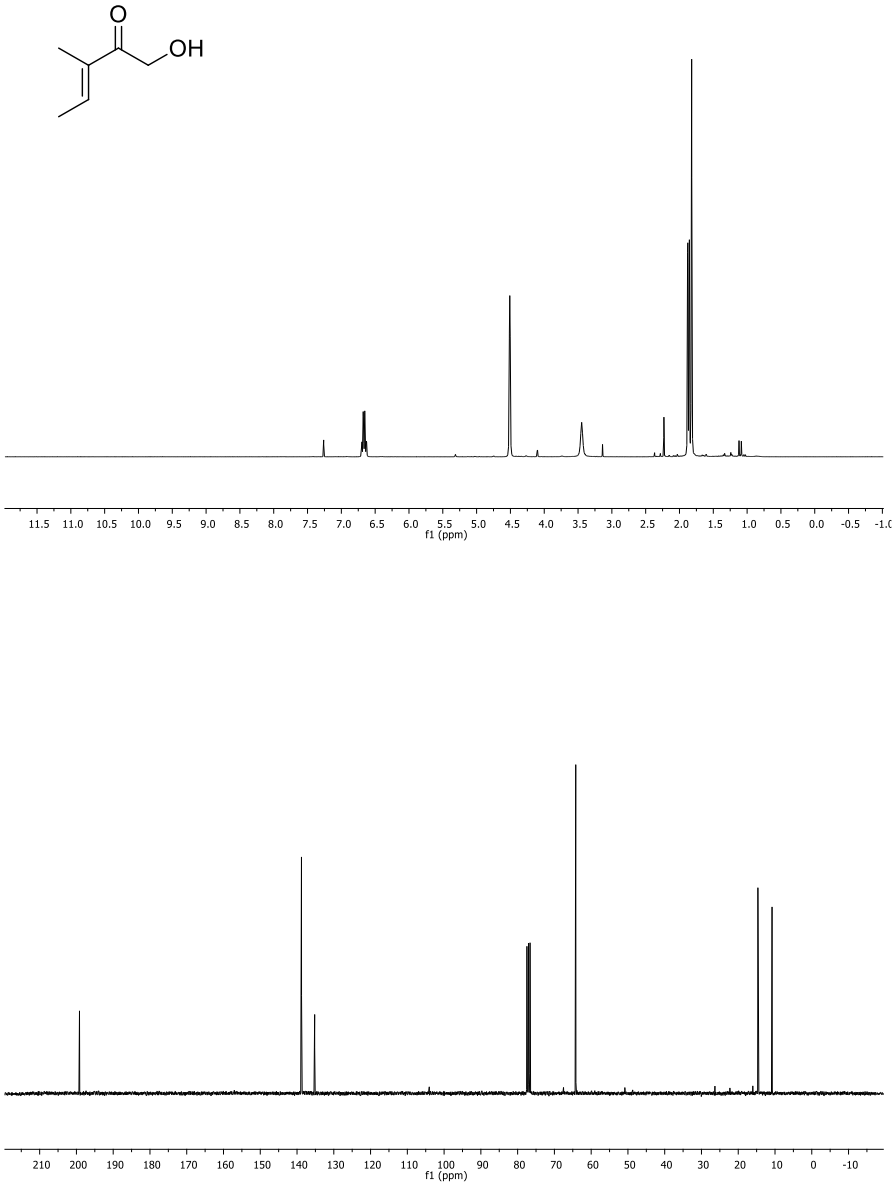
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	9.519	MM T	0.1550	2588.70752	278.34286	14.28368
2	10.325	MM T	0.1618	1.55348e4	1600.50818	85.71632

HPLC chromatogram of the chiral compound **31.**

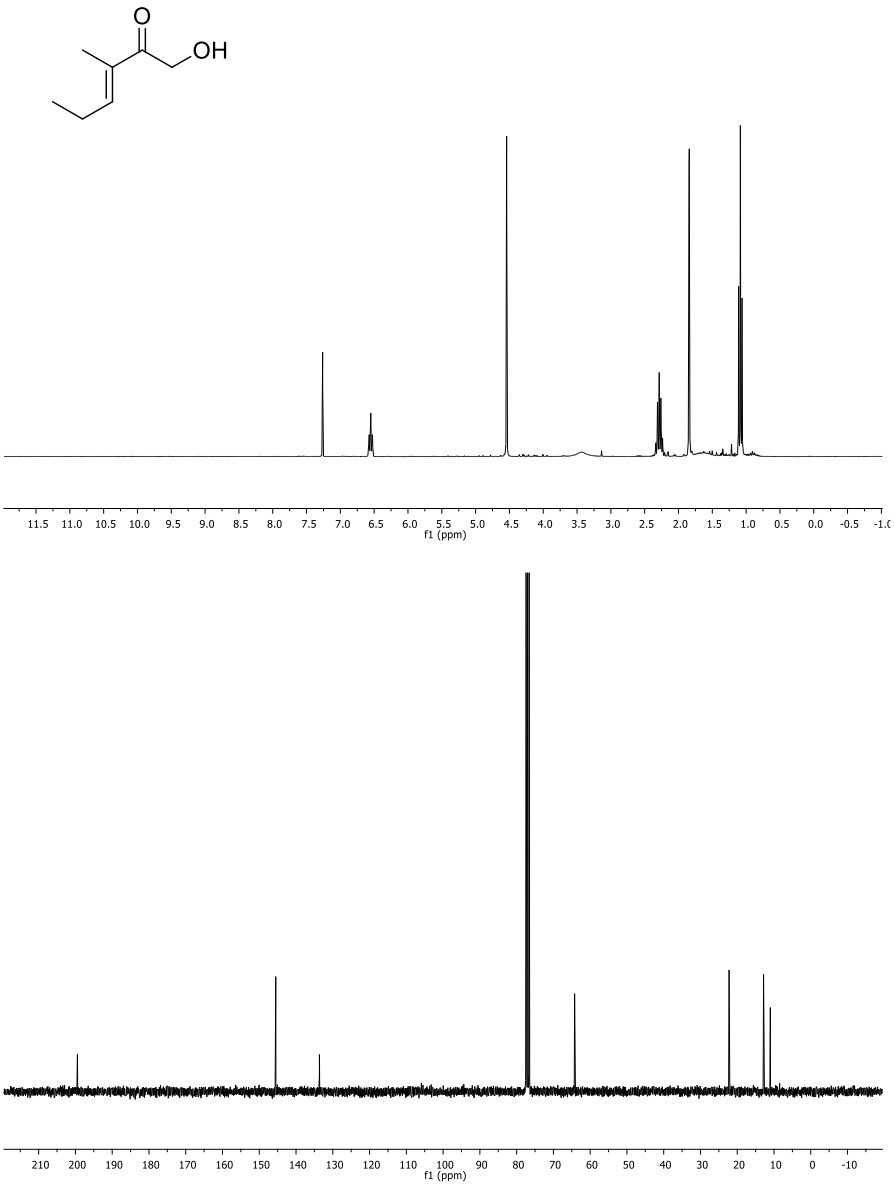
^{1}H- and ^{13}C-NMR spectra



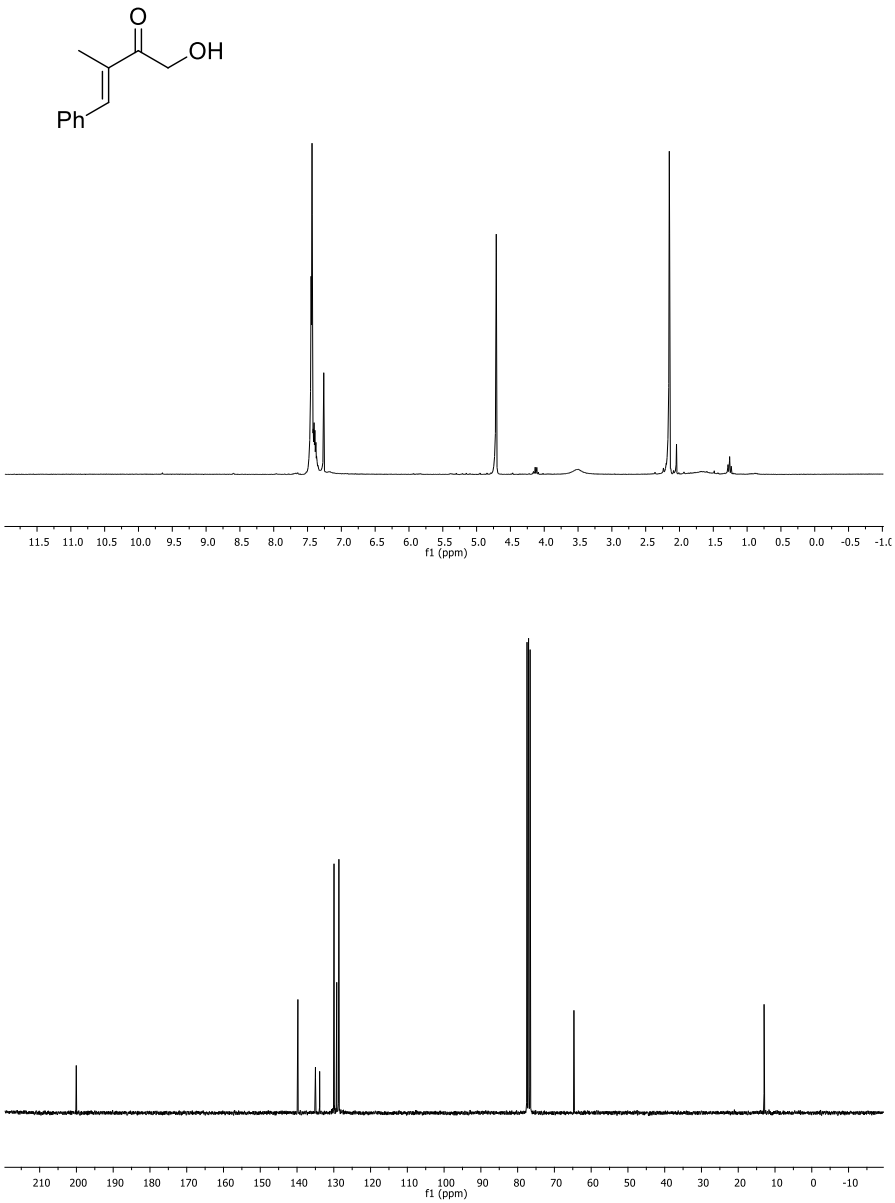
^{1}H-NMR and ^{13}C-NMR spectra of compound **2a**.



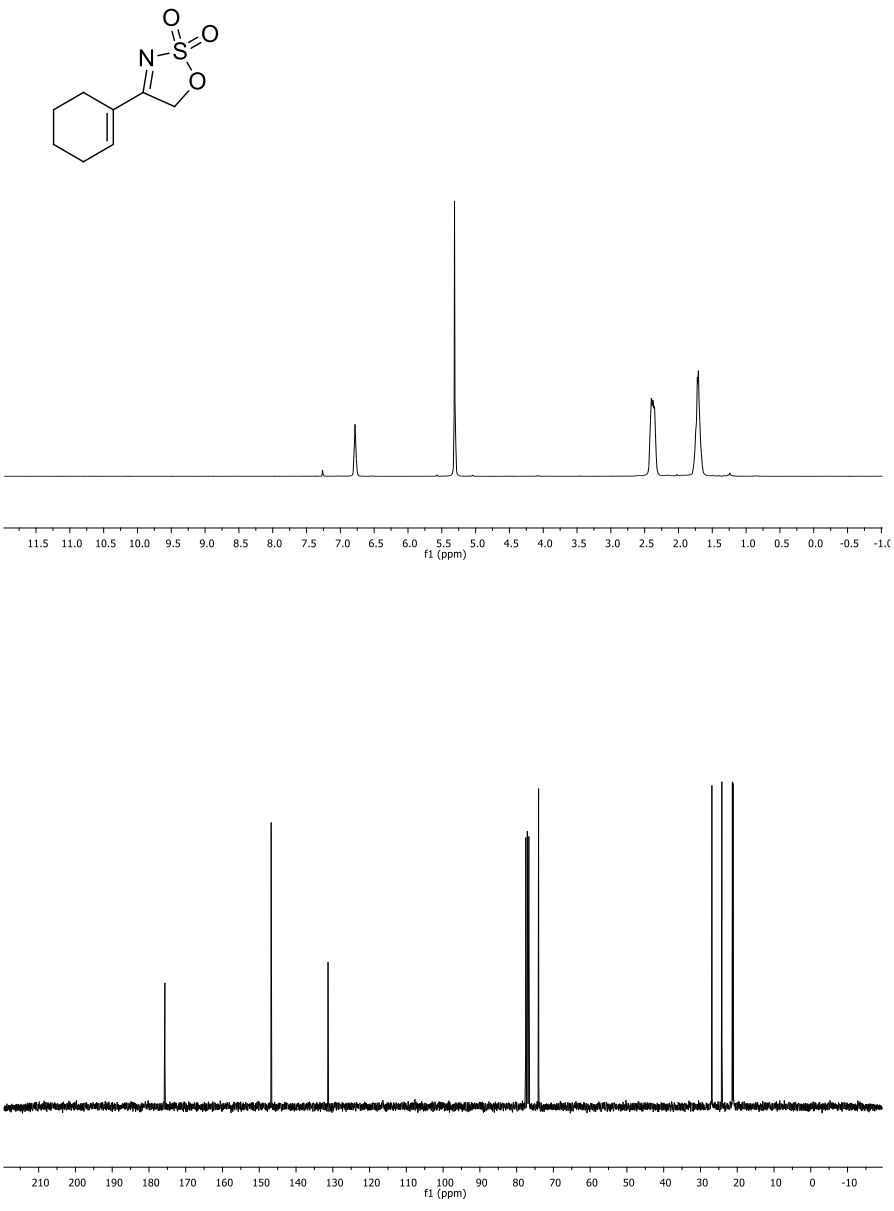
^{1}H-NMR and ^{13}C-NMR spectra of compound **2c**.



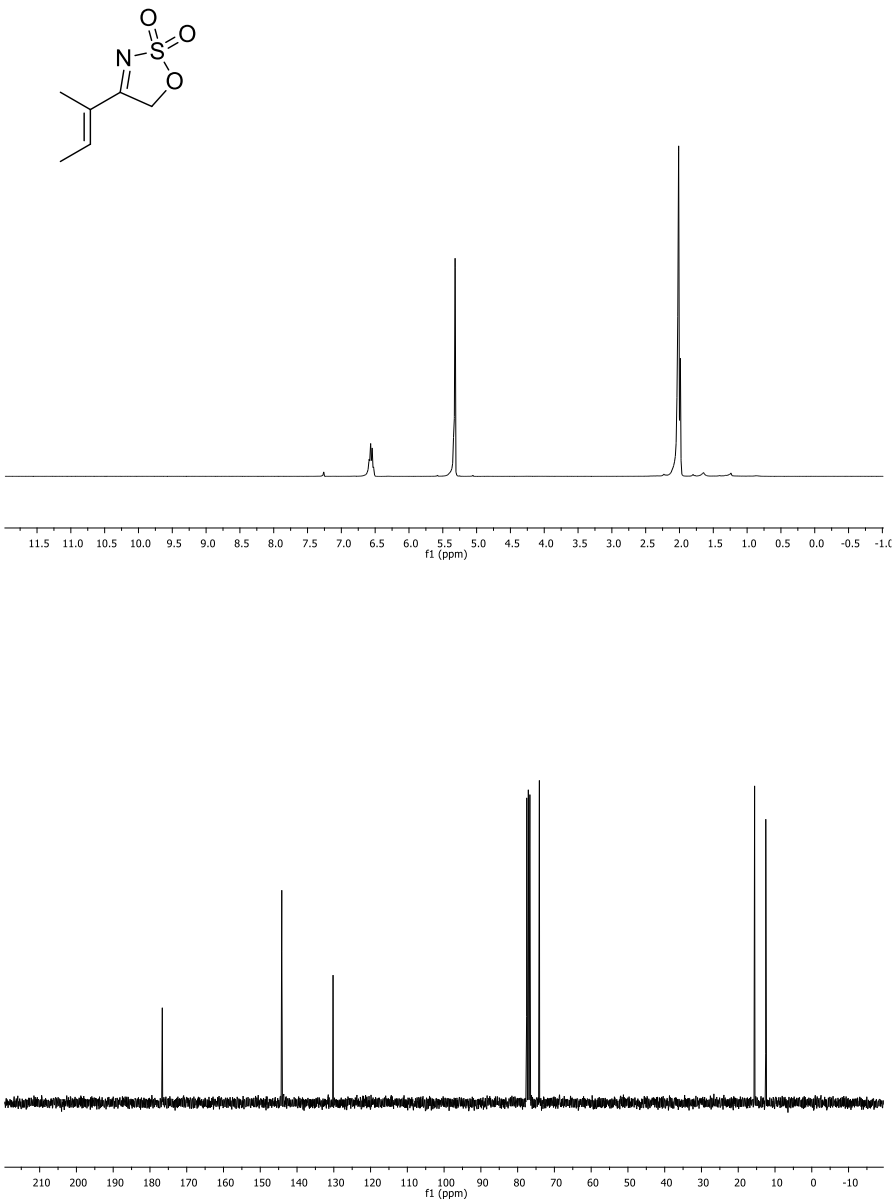
^{1}H-NMR and ^{13}C-NMR spectra of compound **2d**.



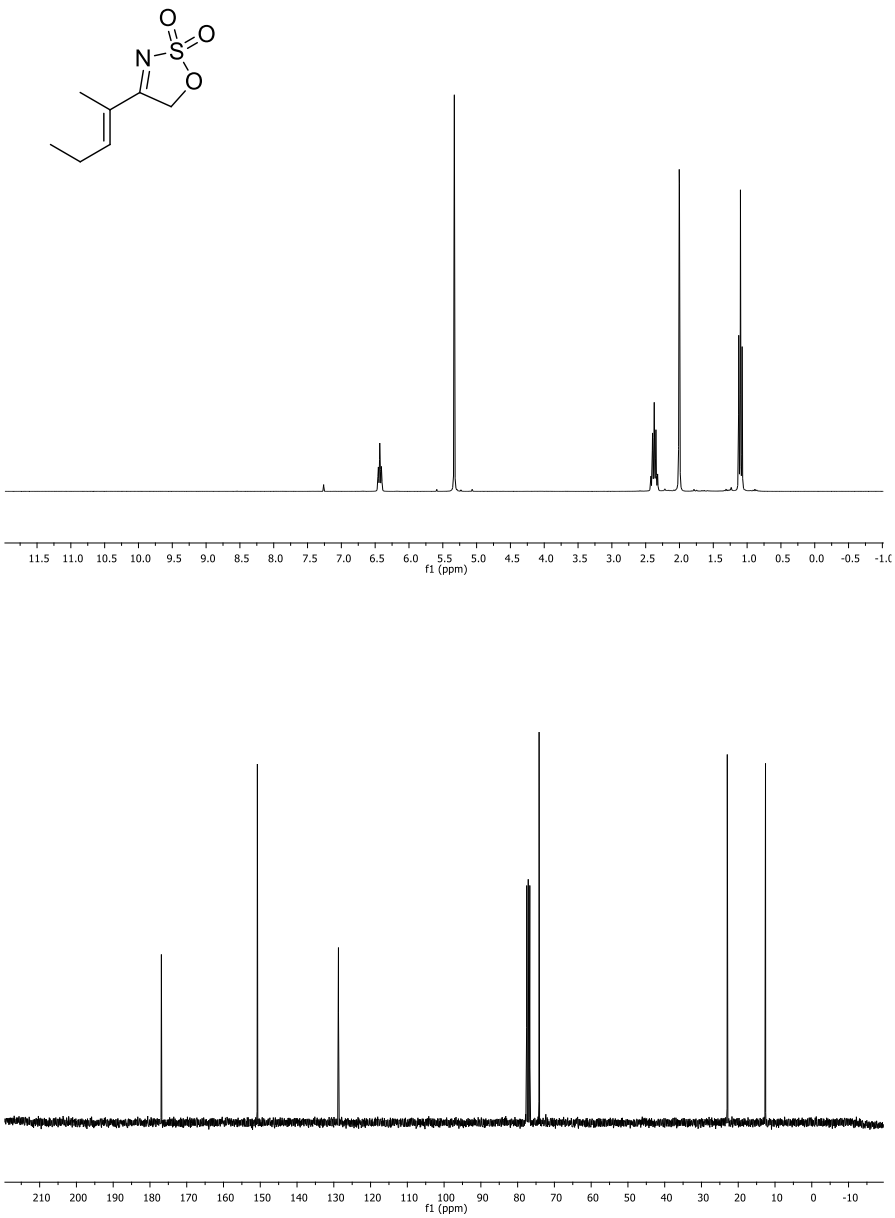
^{1}H-NMR and ^{13}C-NMR spectra of compound **2e**.



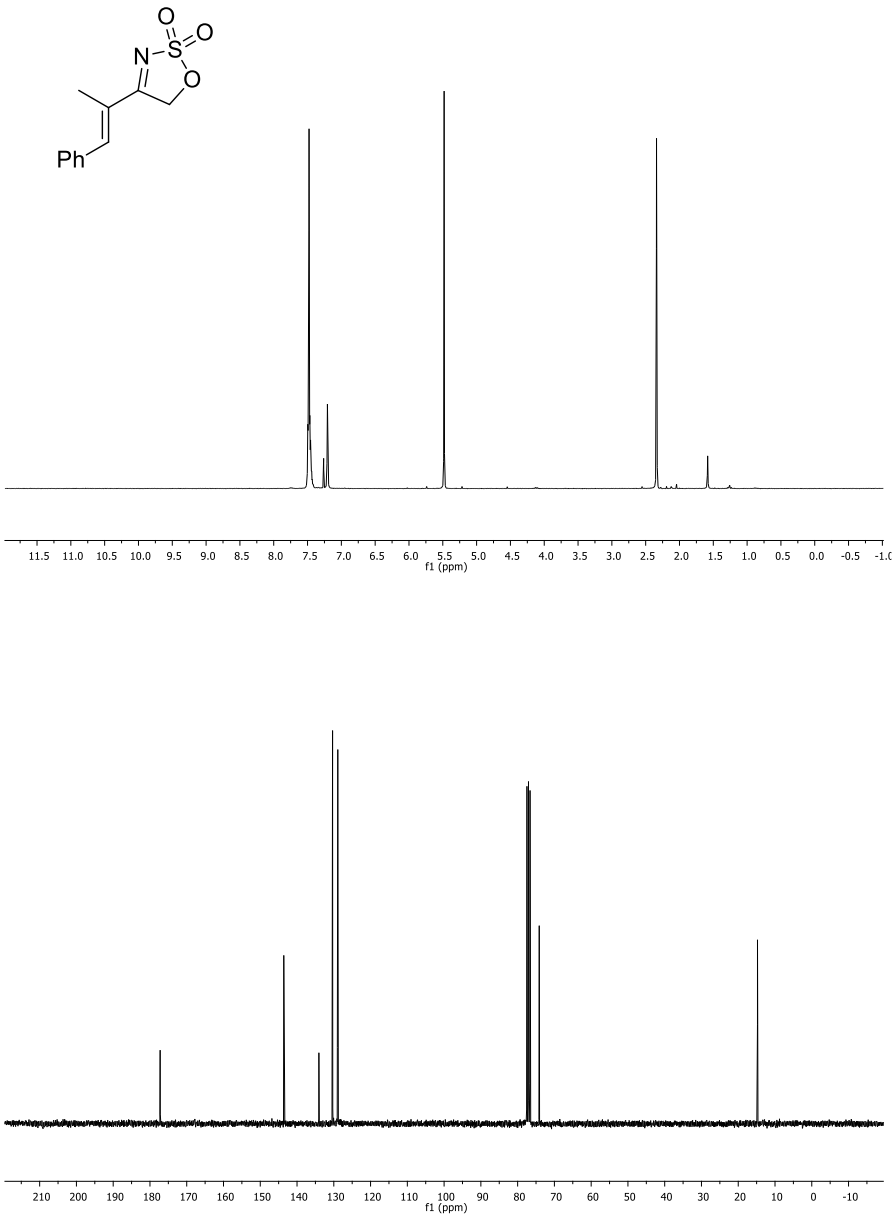
^{1}H-NMR and ^{13}C-NMR spectra of compound **3a**.



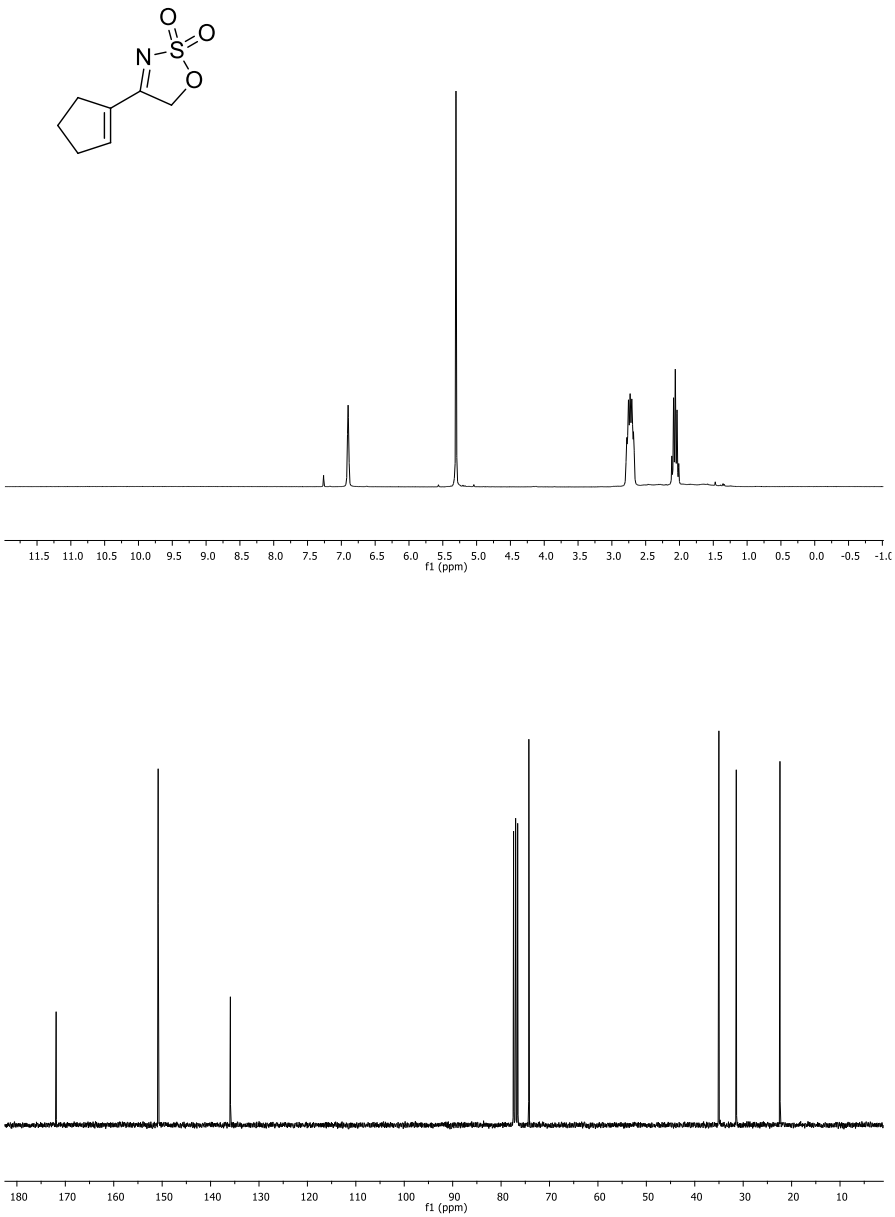
^{1}H-NMR and ^{13}C-NMR spectra of compound **3c**.



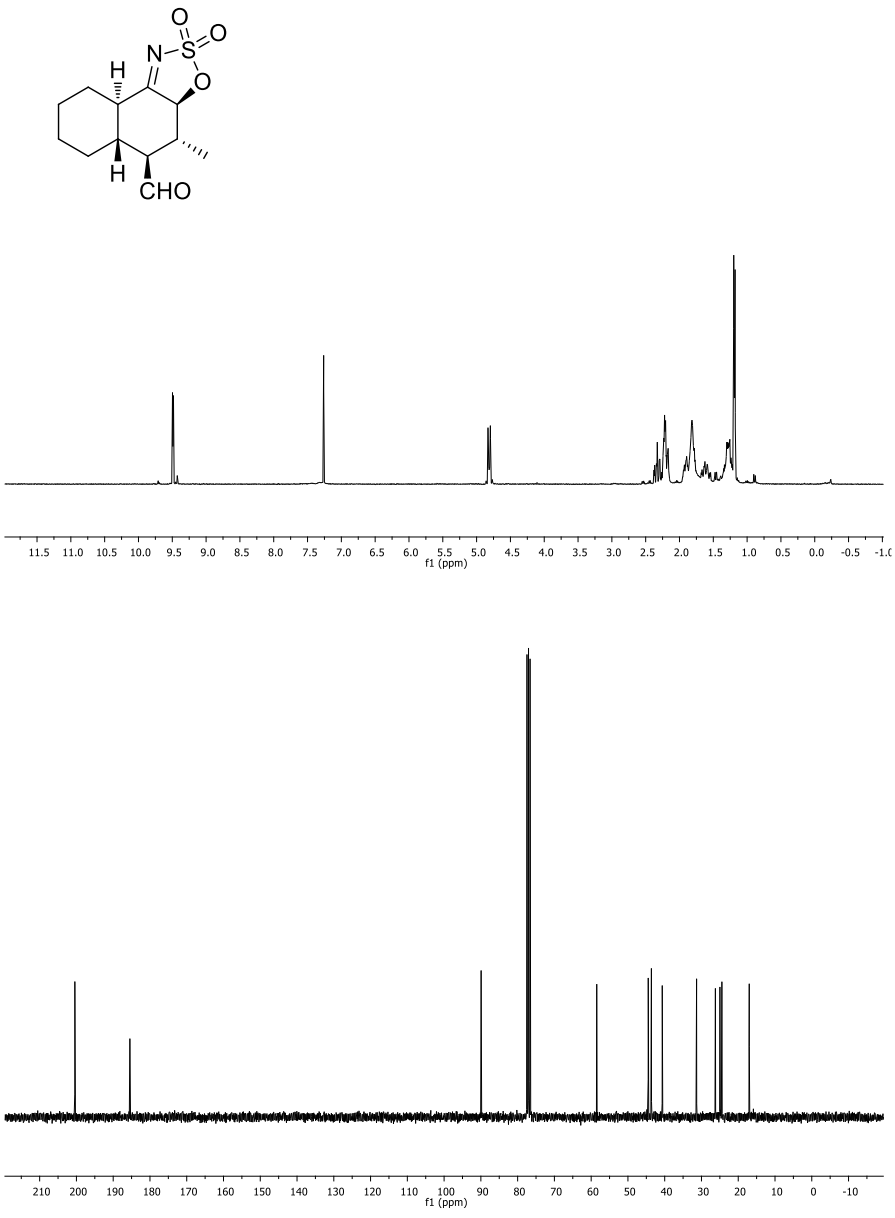
^{1}H-NMR and ^{13}C-NMR spectra of compound **3d**.



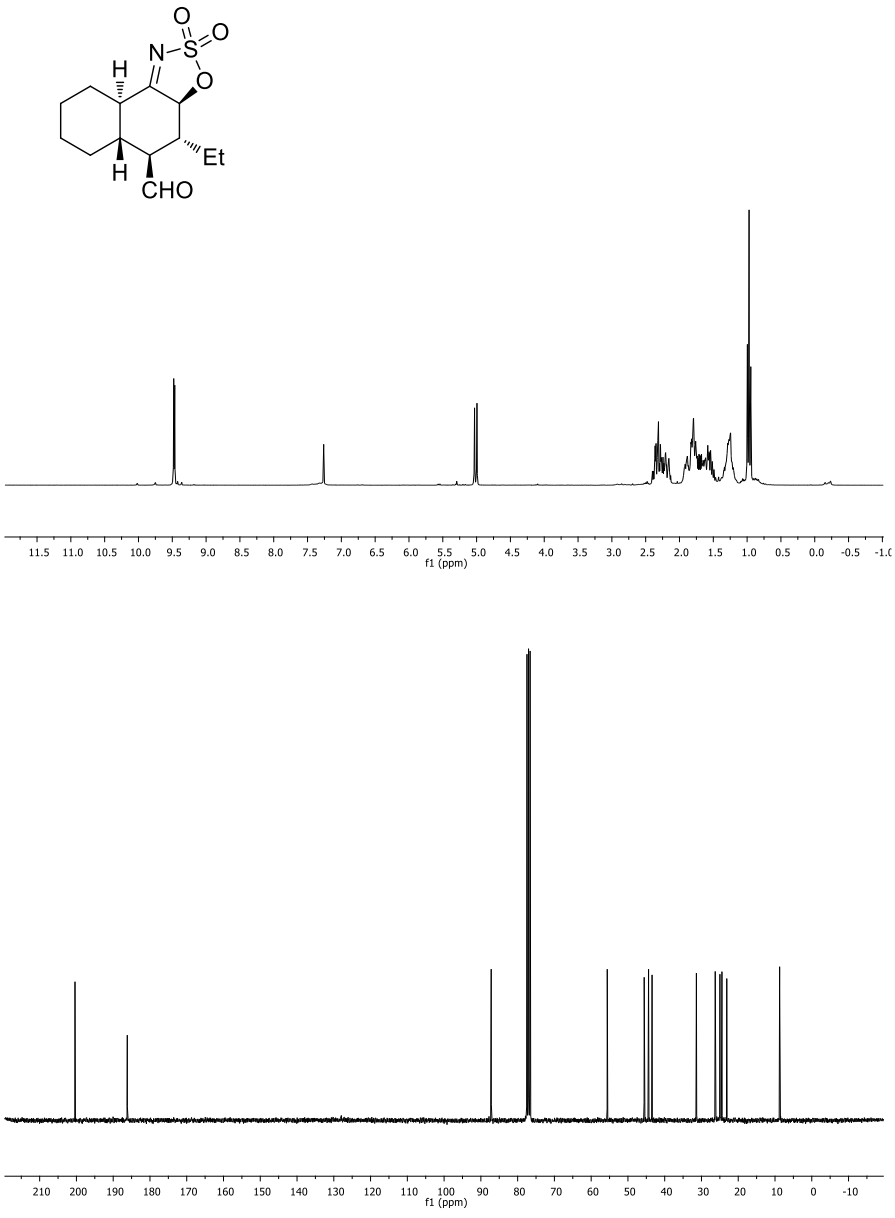
^{1}H-NMR and ^{13}C-NMR spectra of compound **3e**.



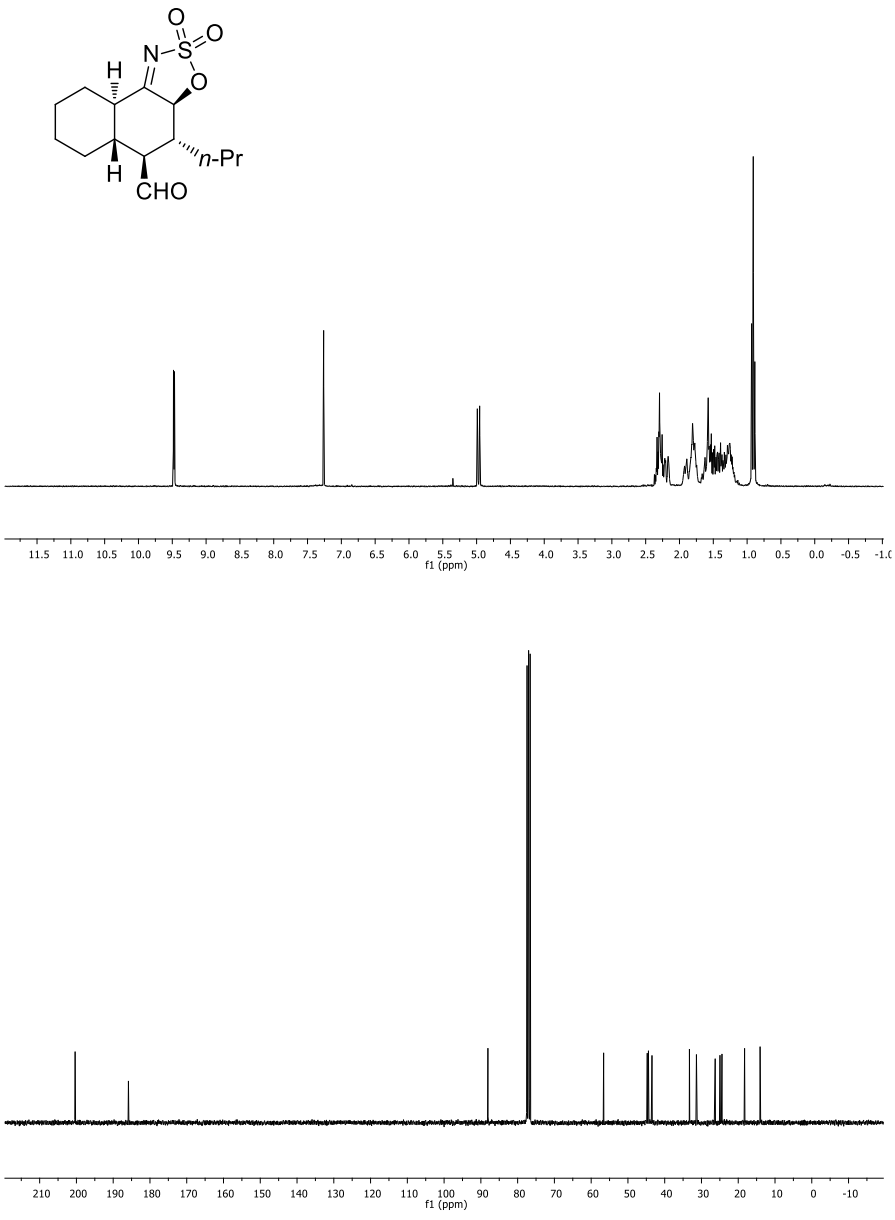
^{1}H-NMR and ^{13}C-NMR spectra of compound **3b**.



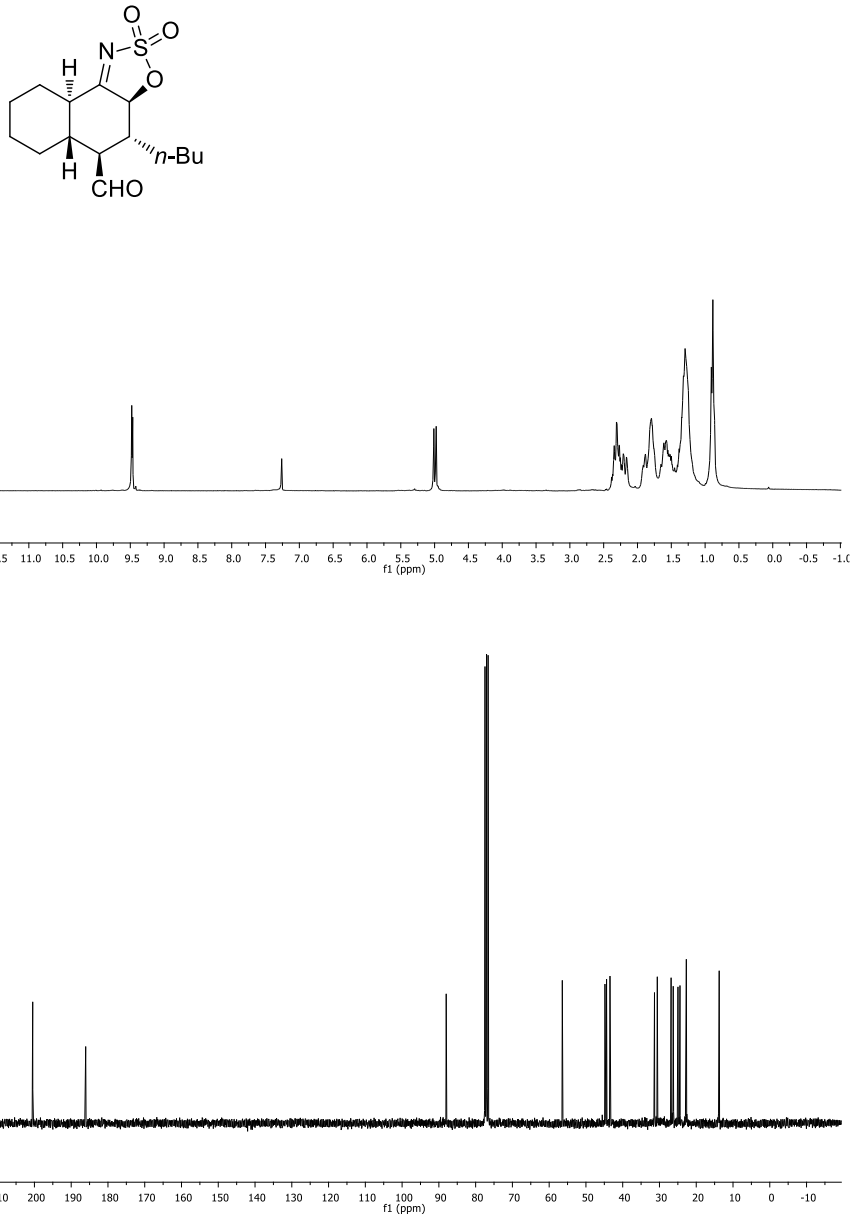
^{1}H-NMR and ^{13}C-NMR spectra of compound **6a**.



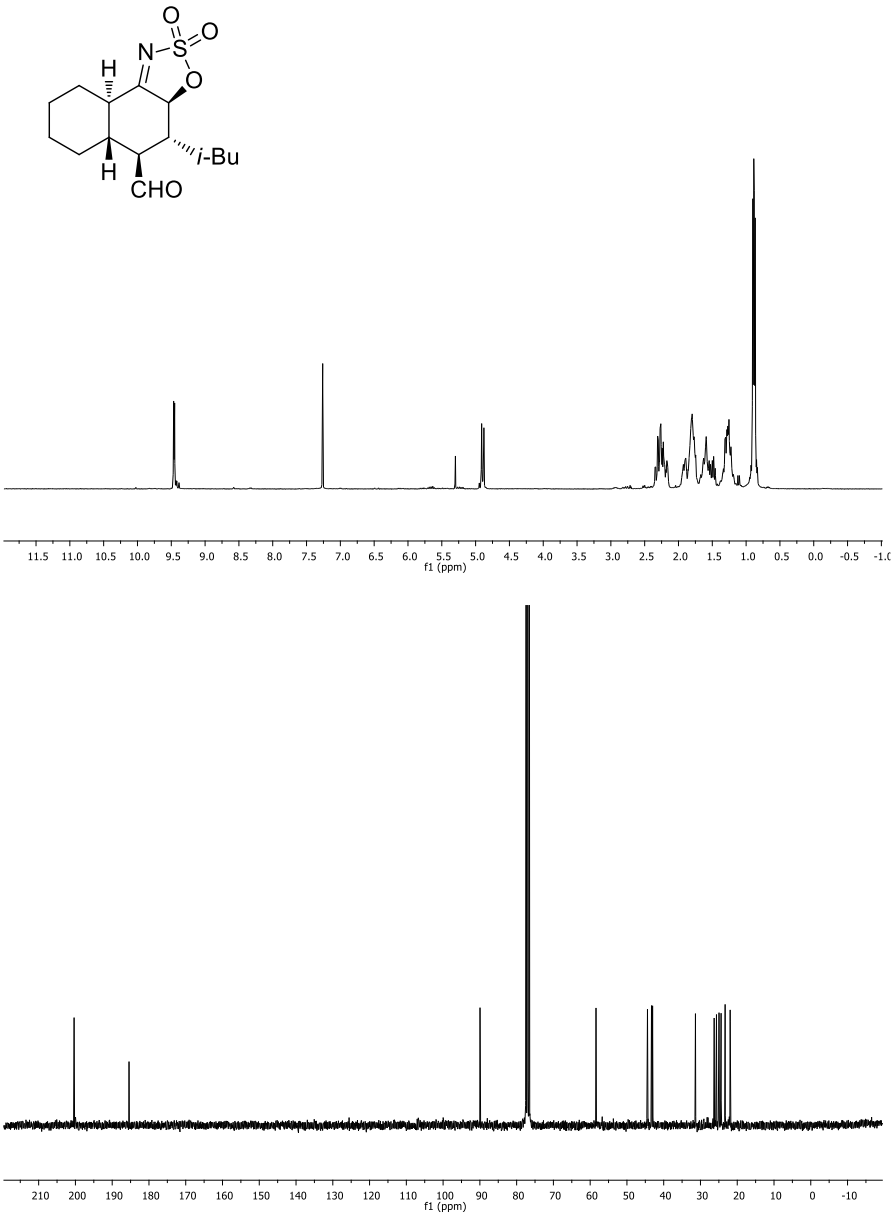
^{1}H-NMR and ^{13}C-NMR spectra of compound **6b**.



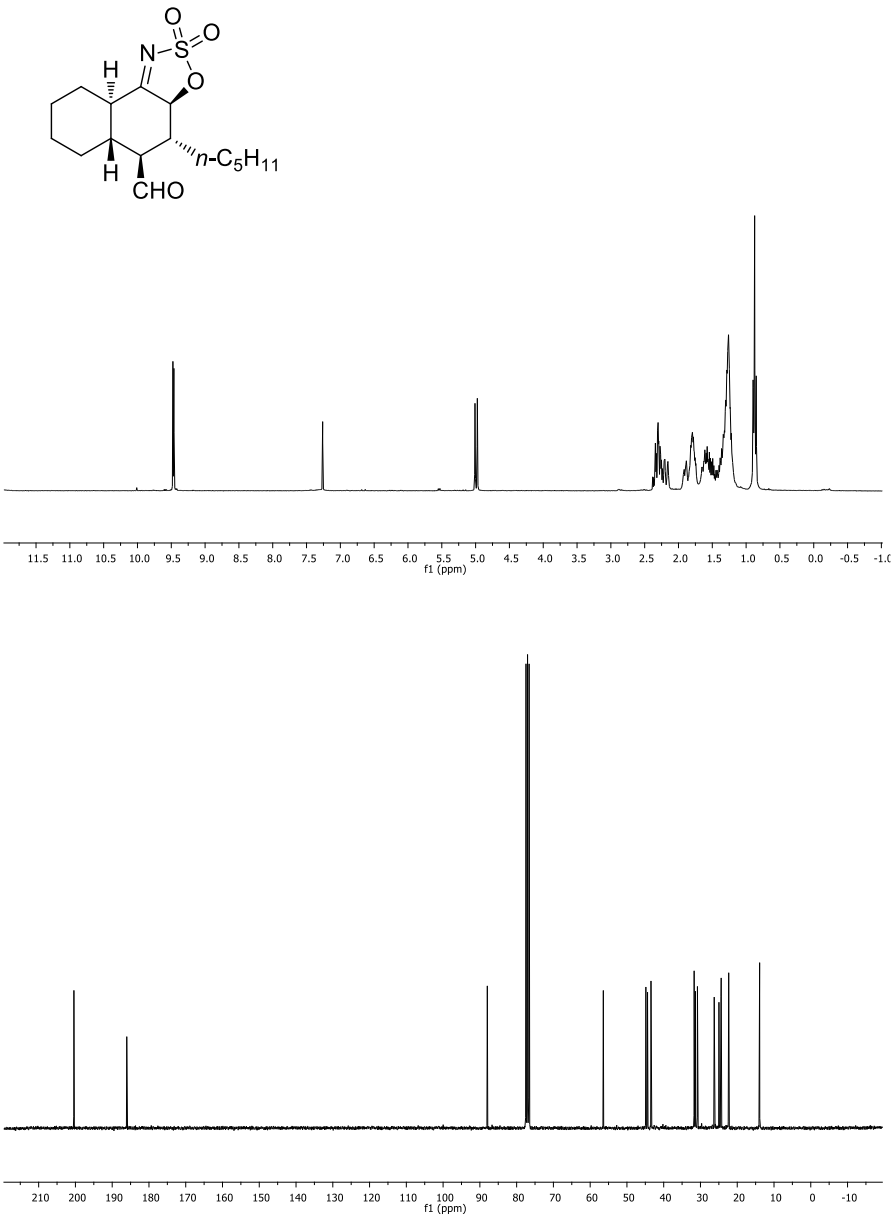
^{1}H-NMR and ^{13}C-NMR spectra of compound **6c**.



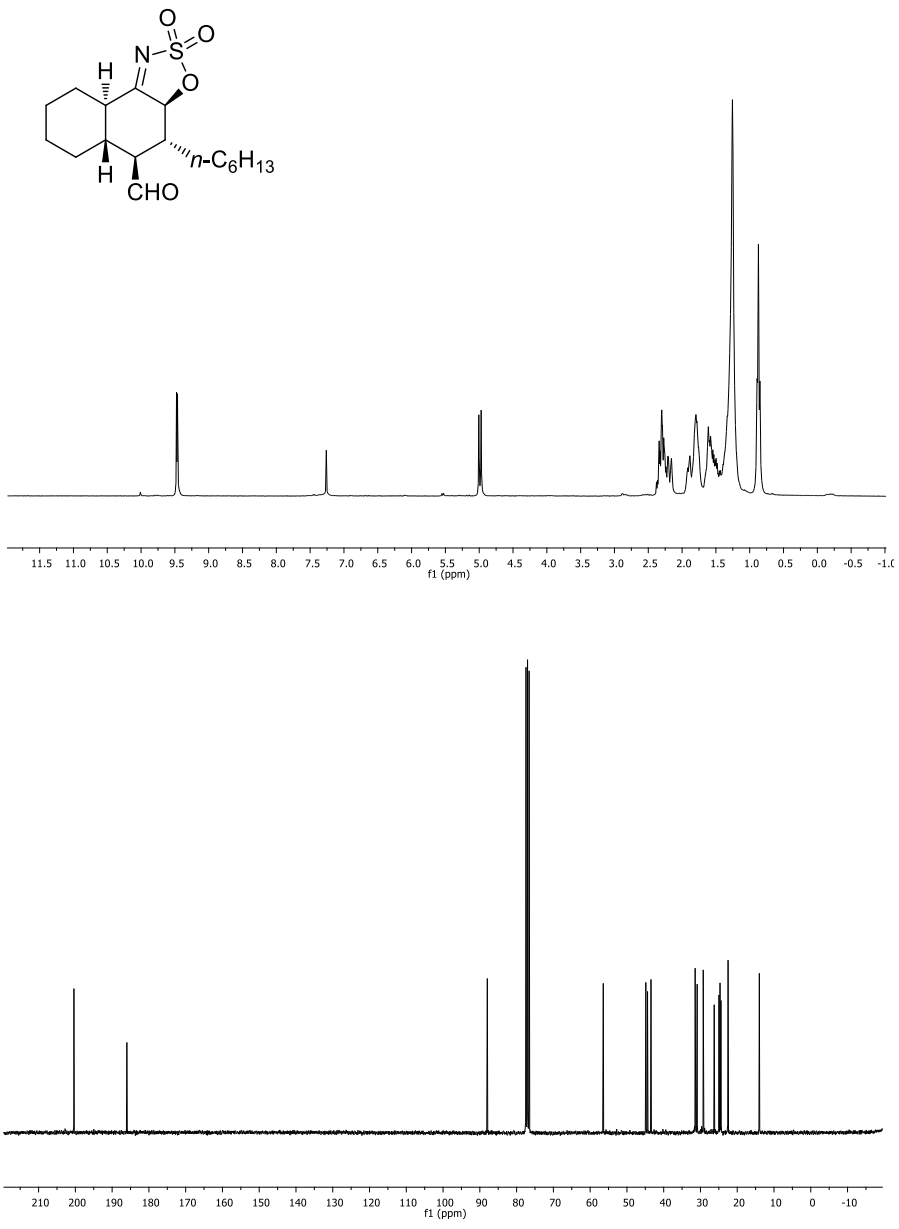
^{1}H-NMR and ^{13}C-NMR spectra of compound **6d**.



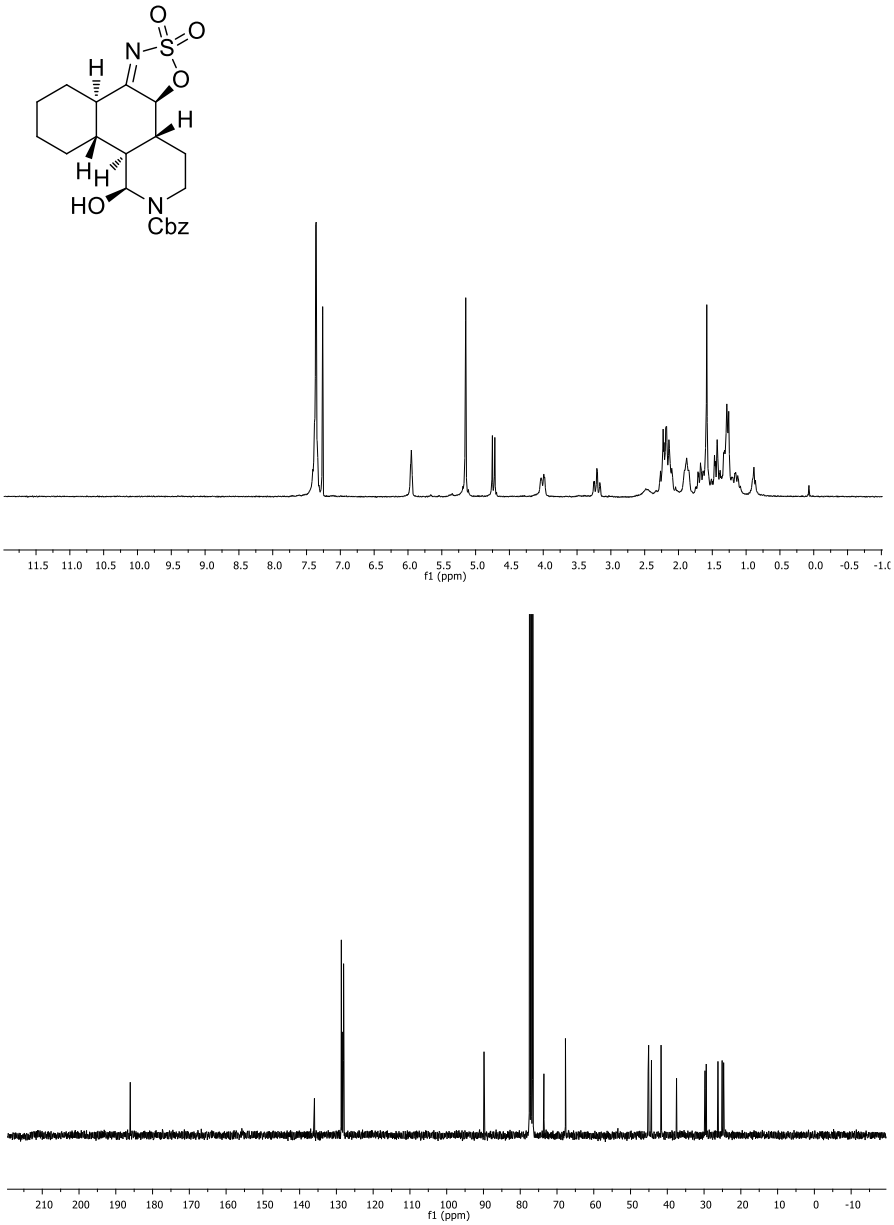
^{1}H-NMR and ^{13}C-NMR spectra of compound **6e**.

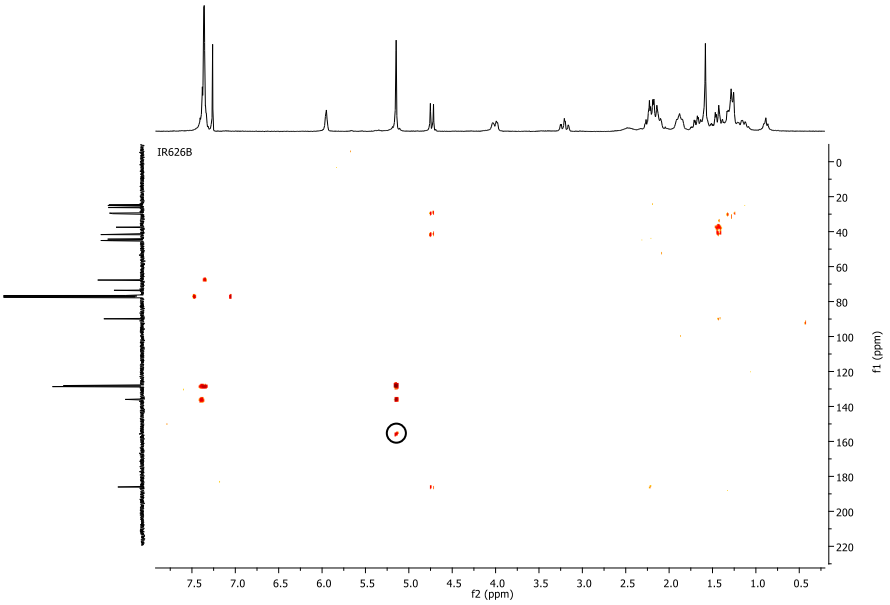


^{1}H-NMR and ^{13}C-NMR spectra of compound **6f**.

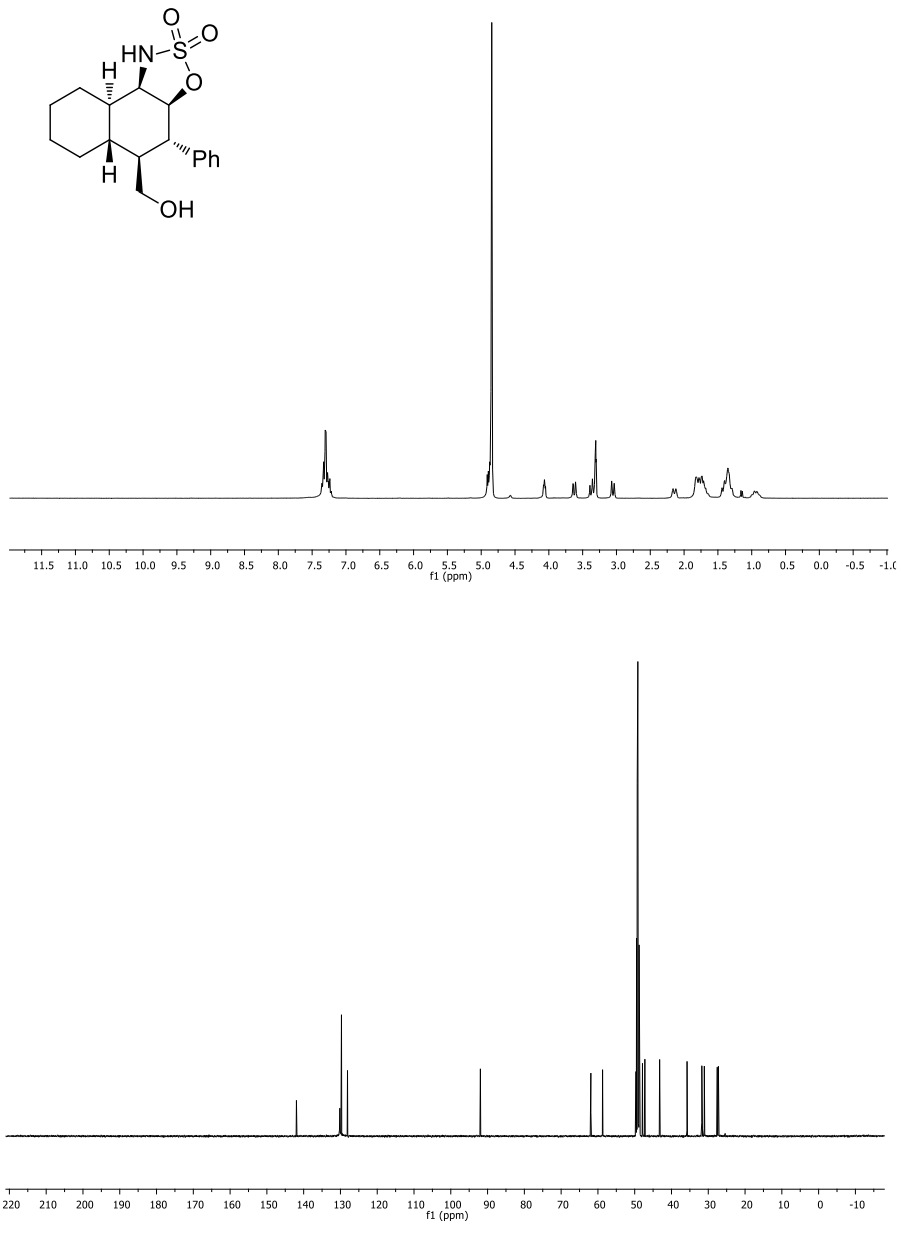


^{1}H-NMR and ^{13}C-NMR spectra of compound **6g**.

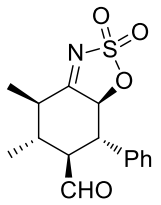

O
N
S
O
O
H
H
H
H
HO
N
Cbz
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

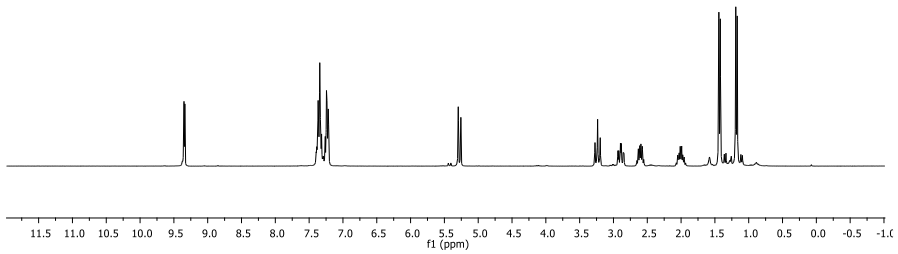


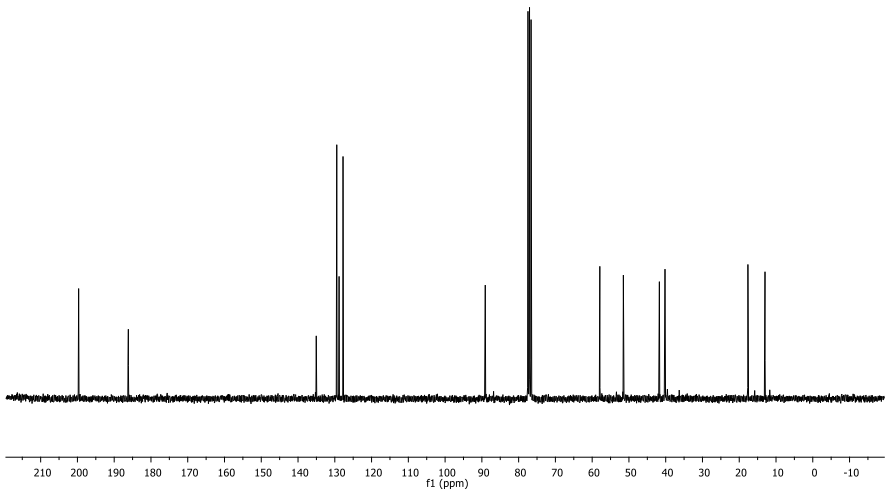
^{1}H-NMR, ^{13}C-NMR and HMBC spectra of compound **6h**.



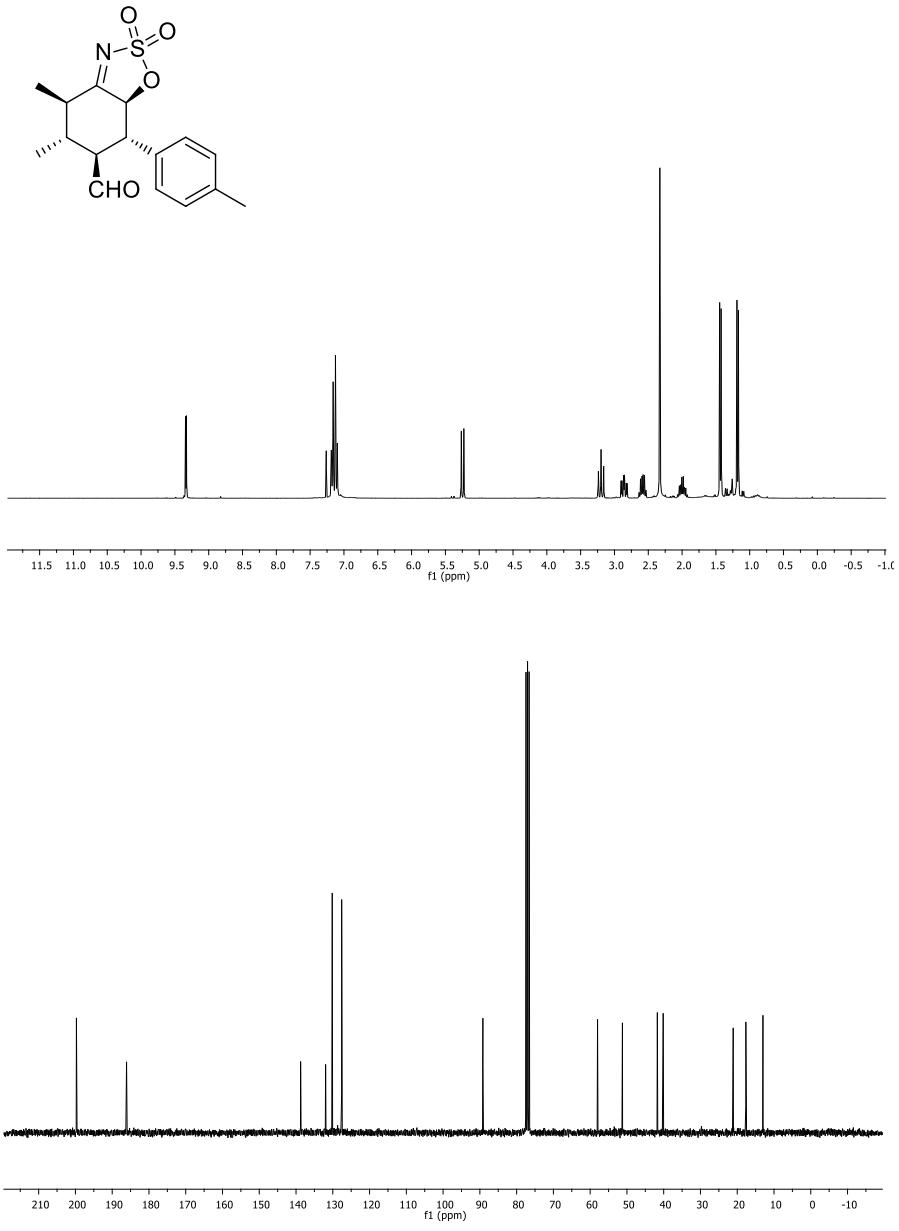
^{1}H-NMR and ^{13}C-NMR spectra of compound **6i**.



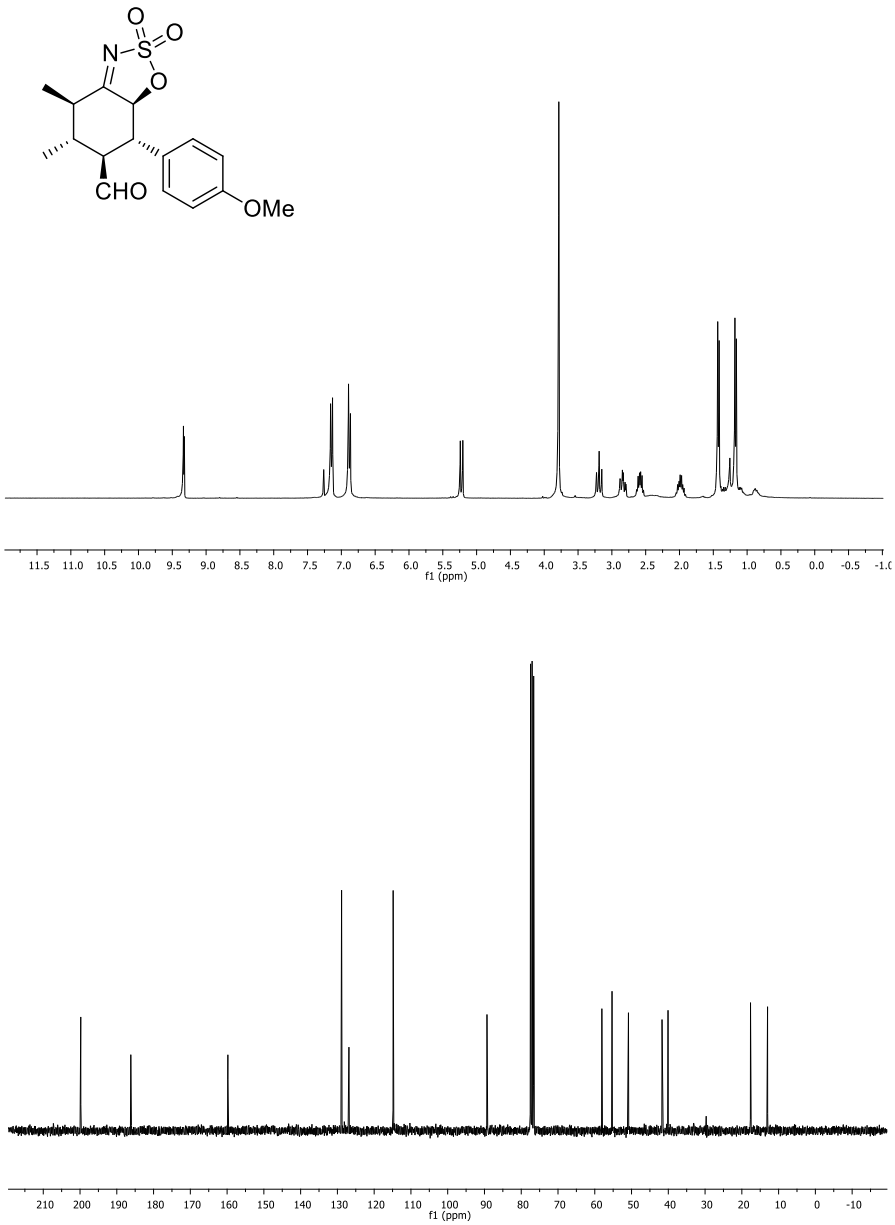




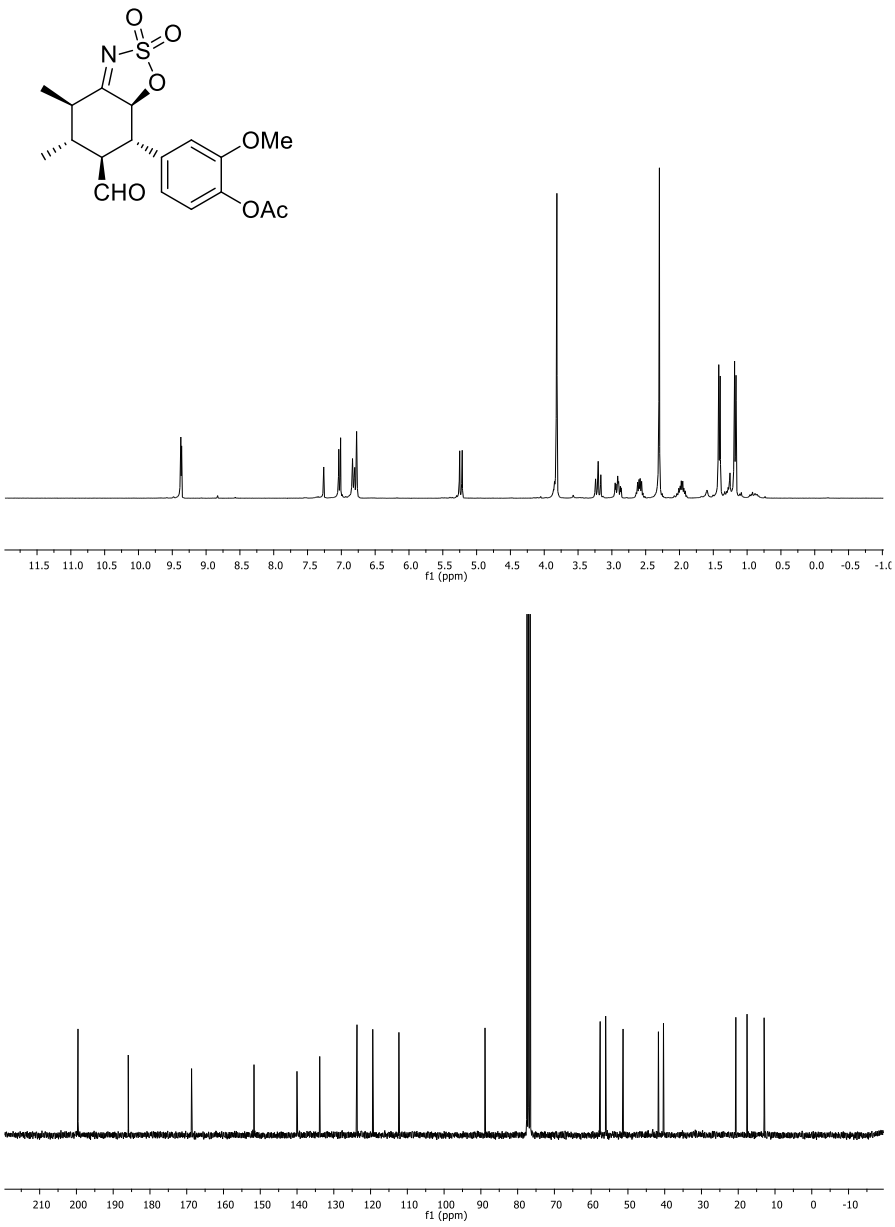
^{1}H-NMR and ^{13}C-NMR spectra of compound **7a**.



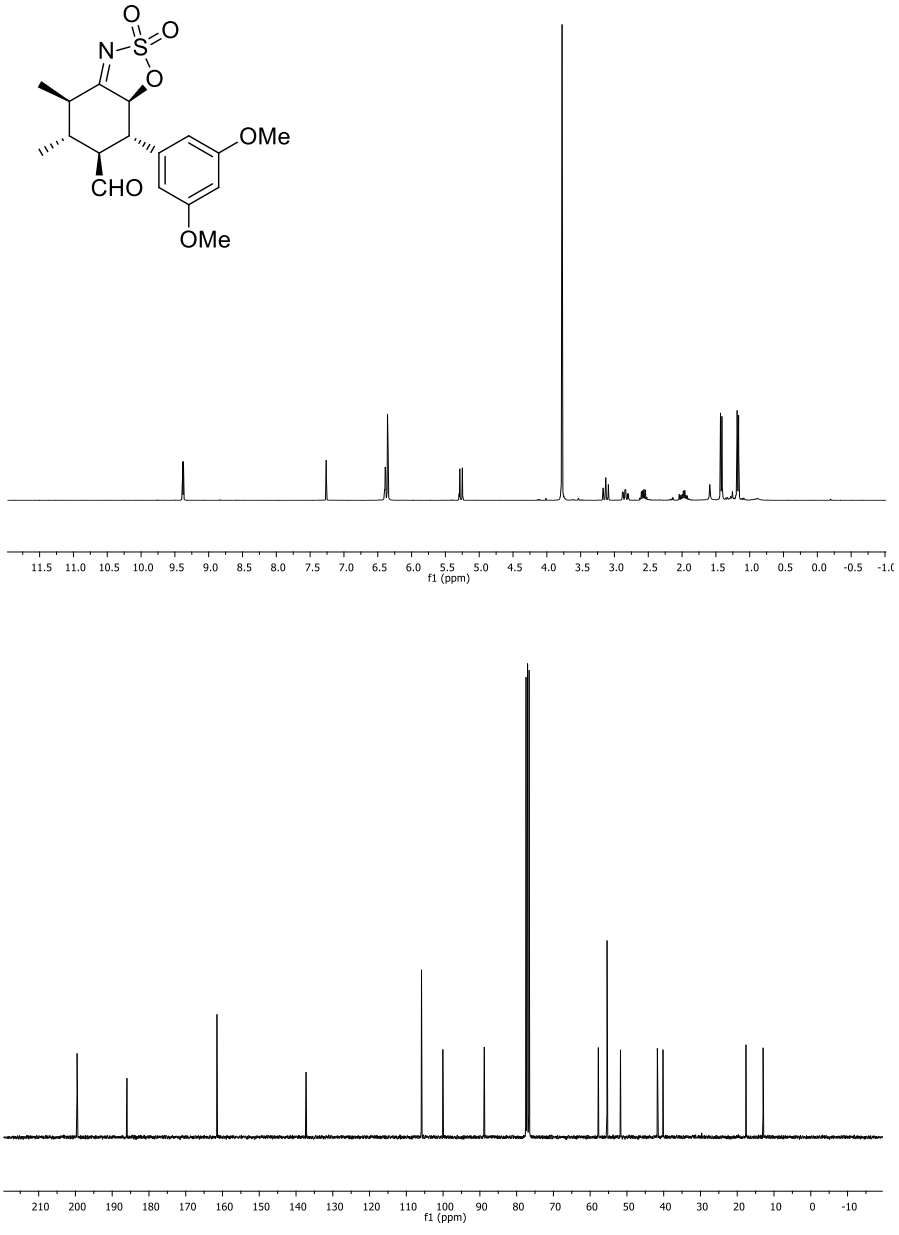
^{1}H-NMR and ^{13}C-NMR spectra of compound **7b**.



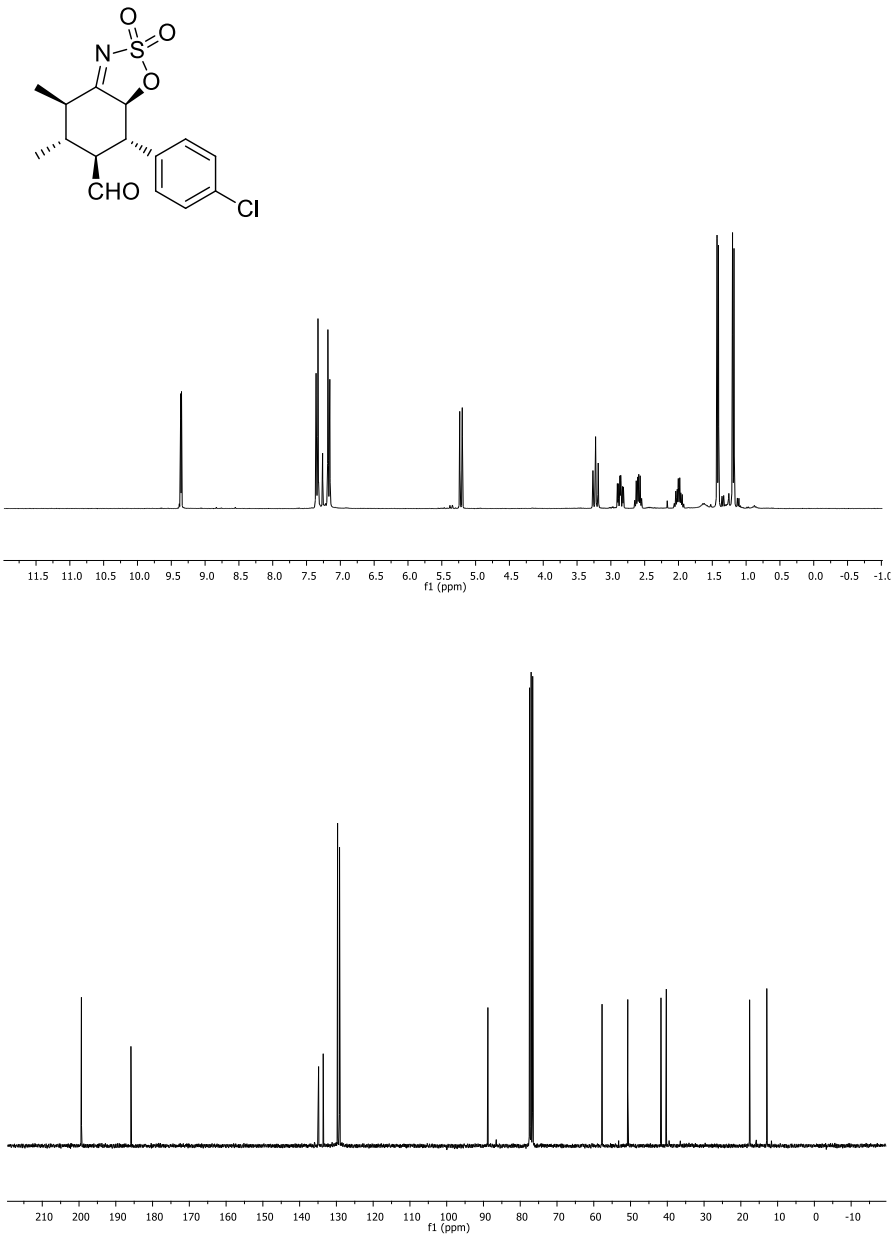
^{1}H-NMR and ^{13}C-NMR spectra of compound **7c**.



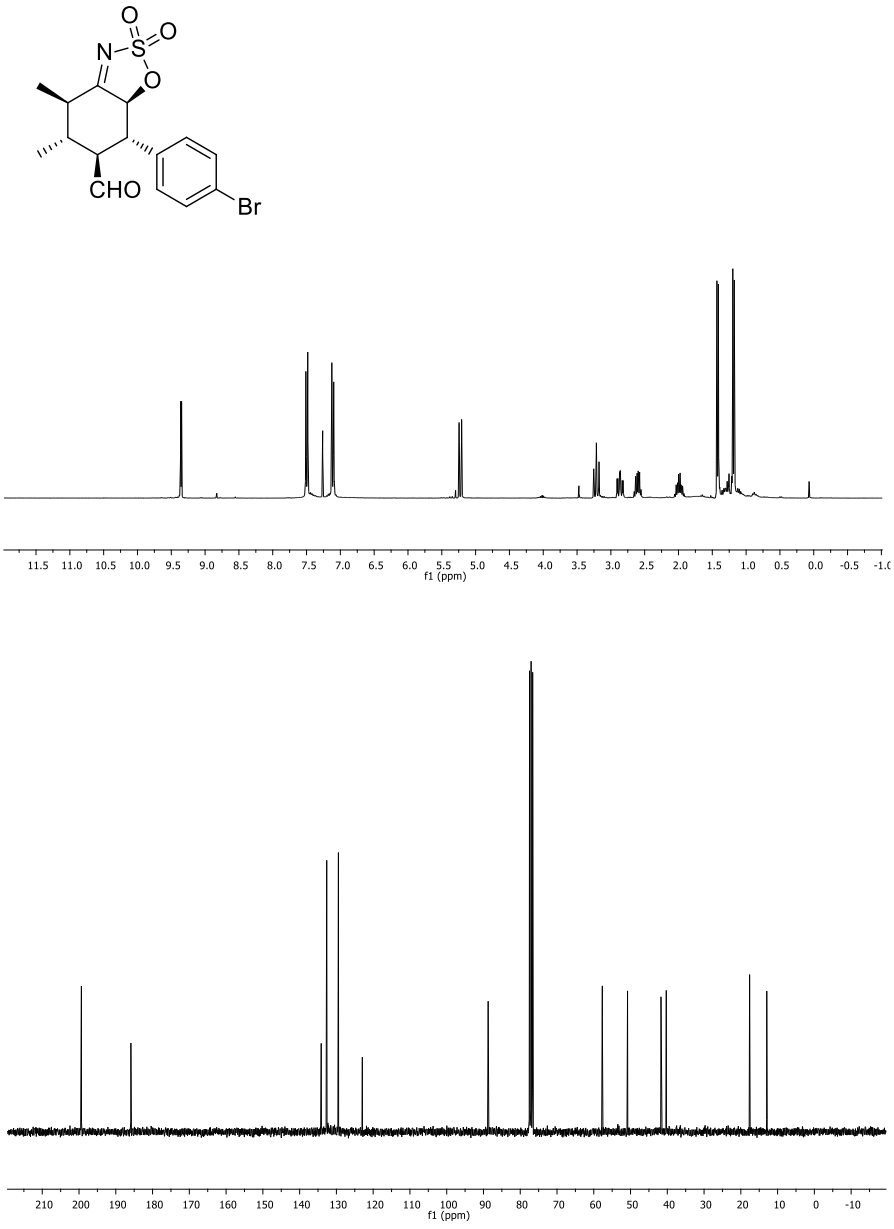
^{1}H-NMR and ^{13}C-NMR spectra of compound **7d**.



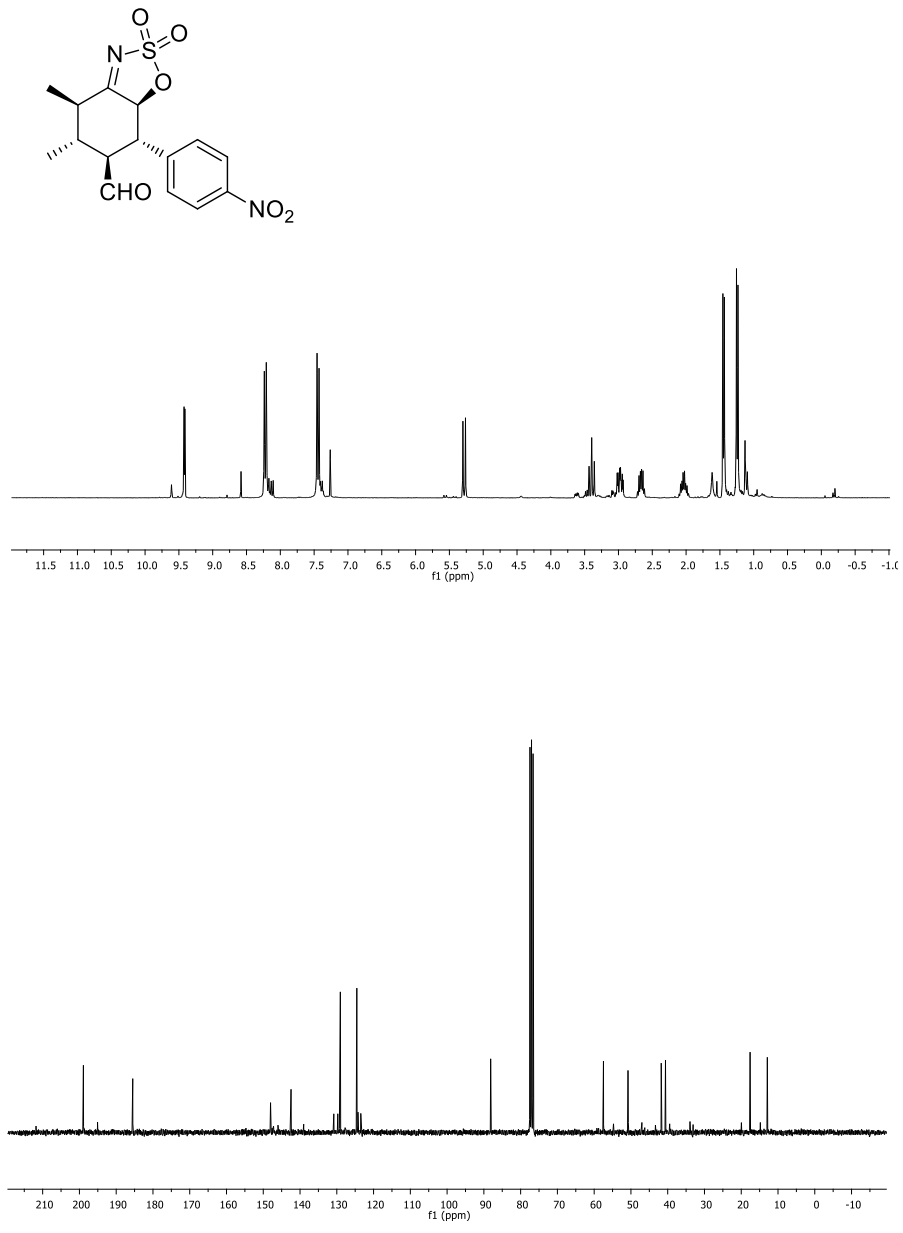
^{1}H-NMR and ^{13}C-NMR spectra of compound **7e**.



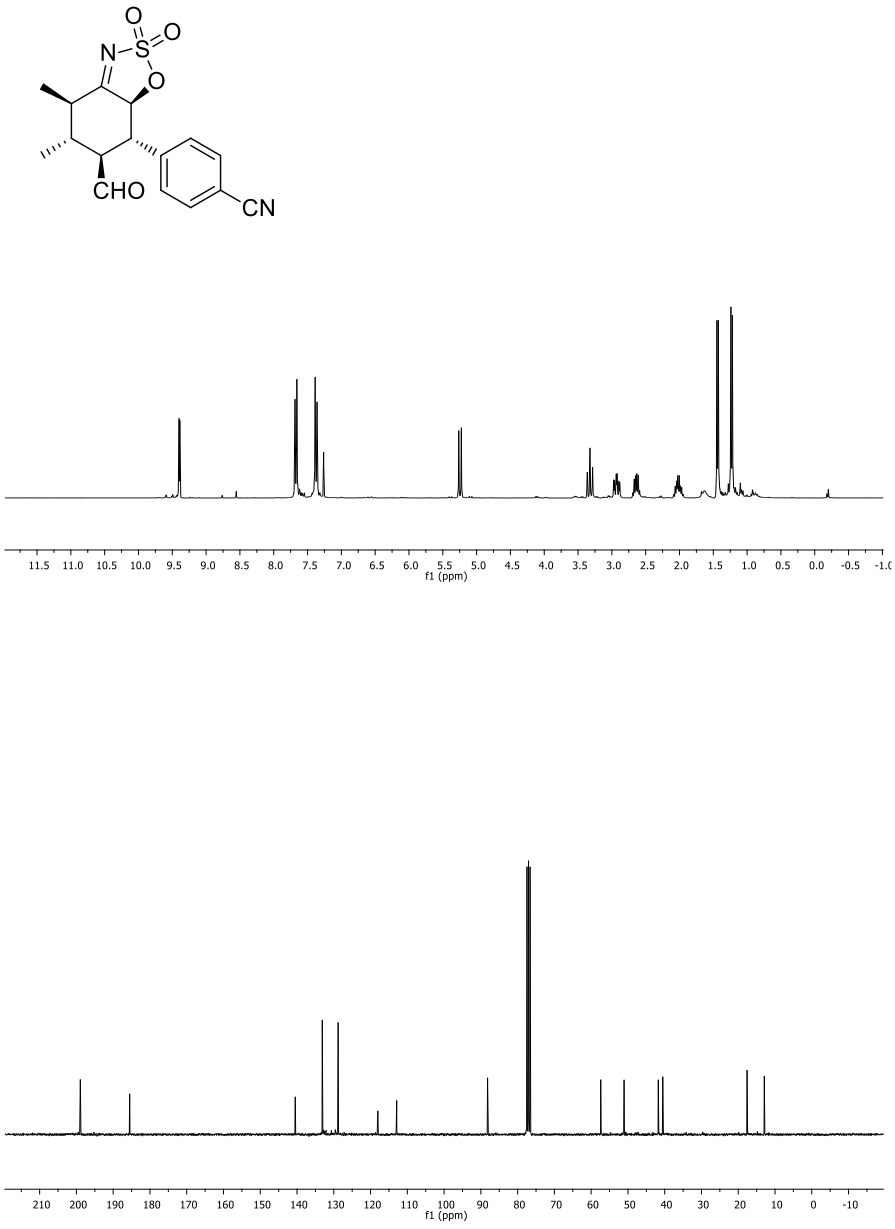
^{1}H-NMR and ^{13}C-NMR spectra of compound **7f**.



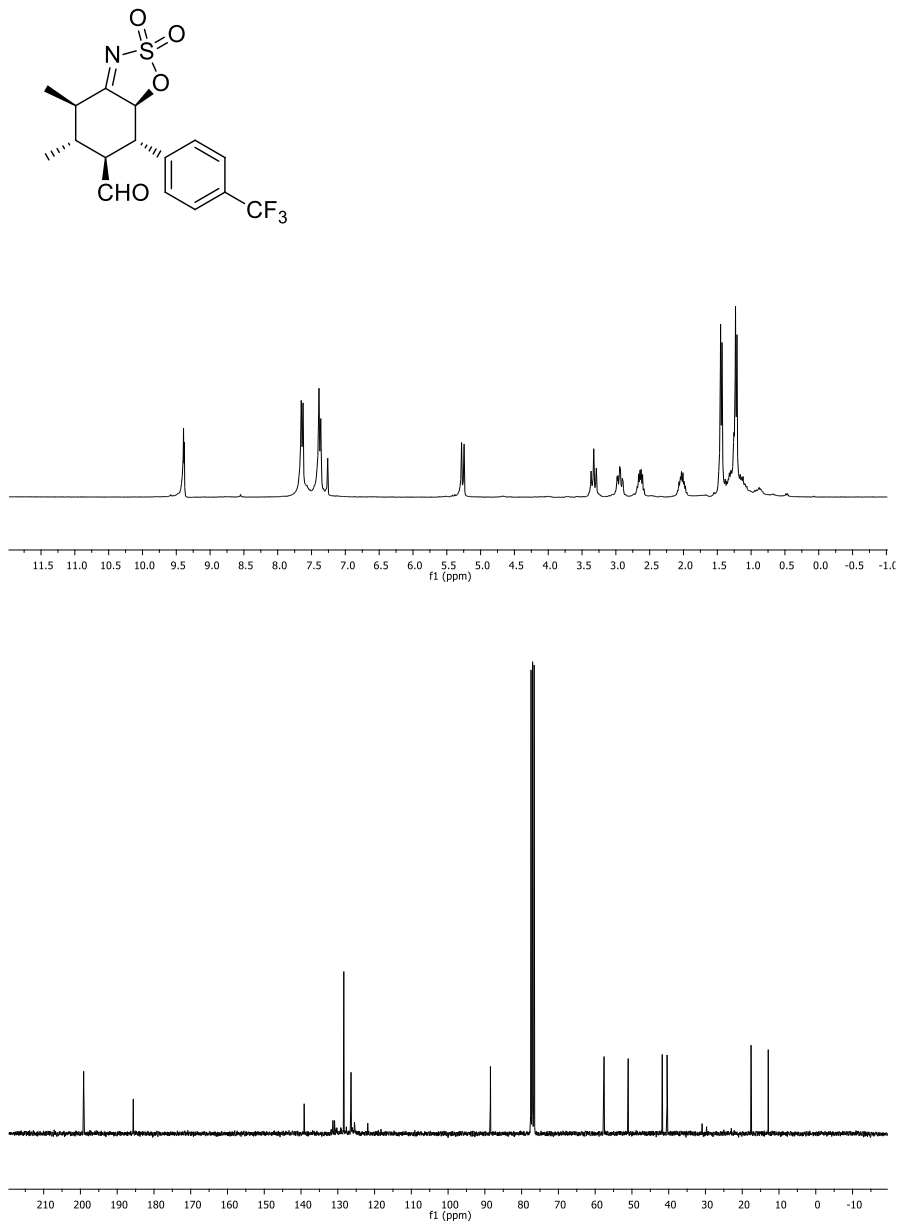
^{1}H-NMR and ^{13}C-NMR spectra of compound **7g**.



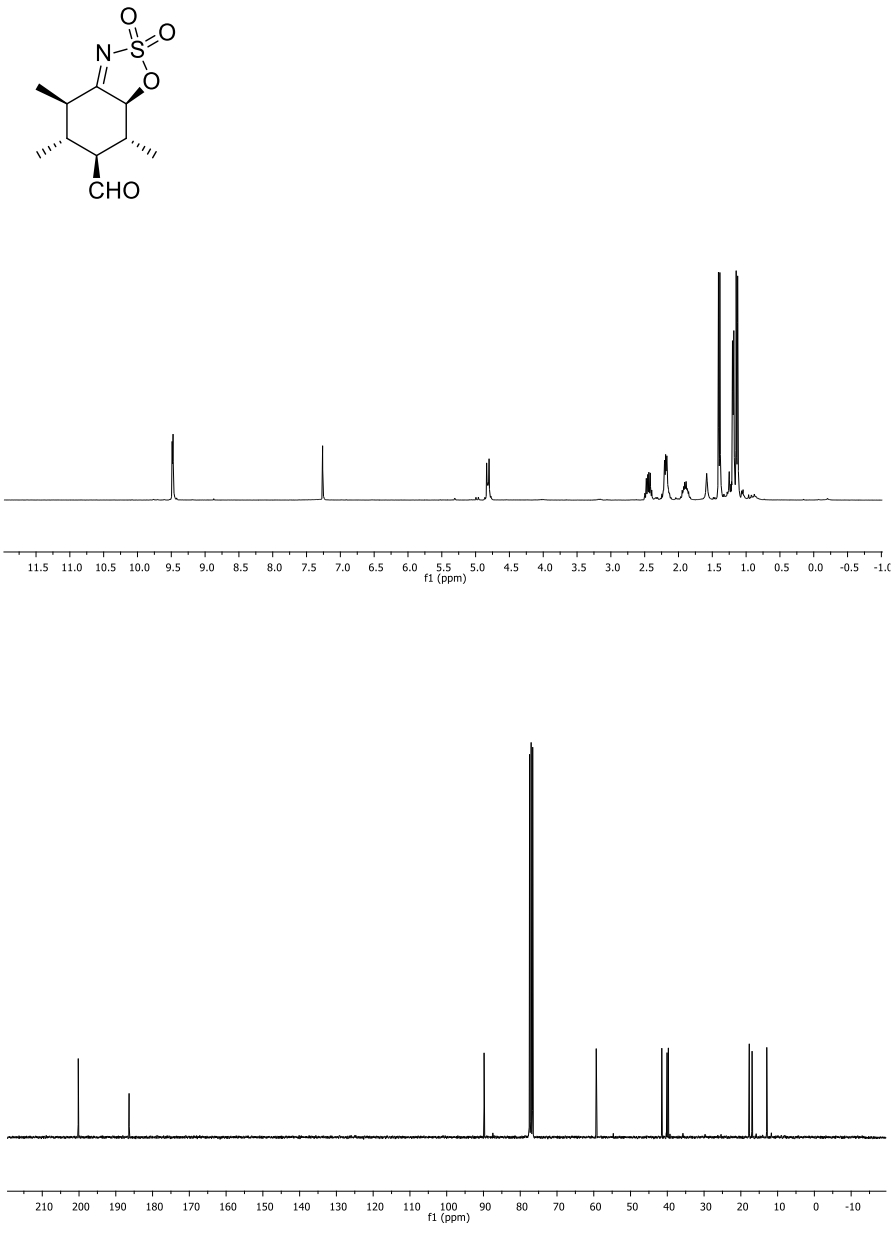
^{1}H-NMR and ^{13}C-NMR spectra of compound **7h**.



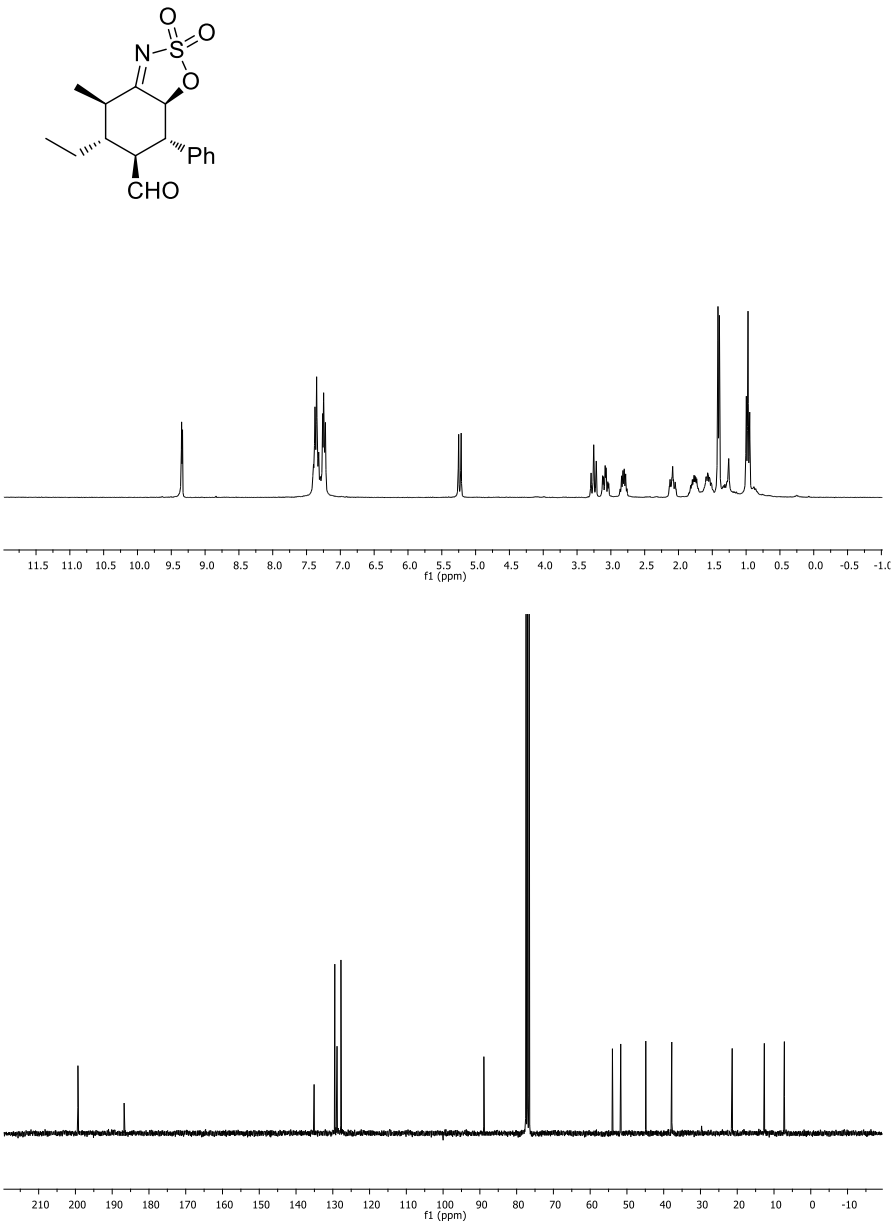
^{1}H-NMR and ^{13}C-NMR spectra of compound **7i**.



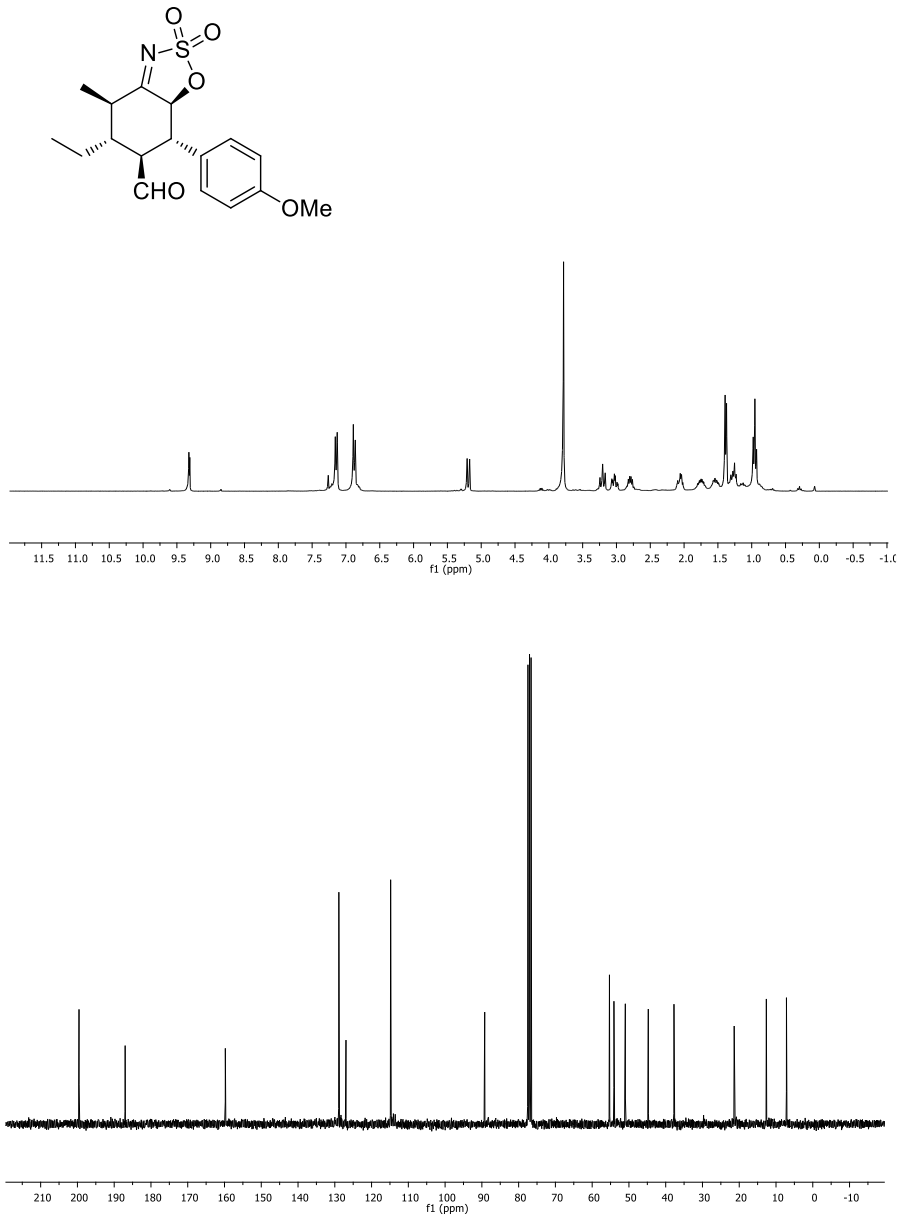
^{1}H-NMR and ^{13}C-NMR spectra of compound **7j**.



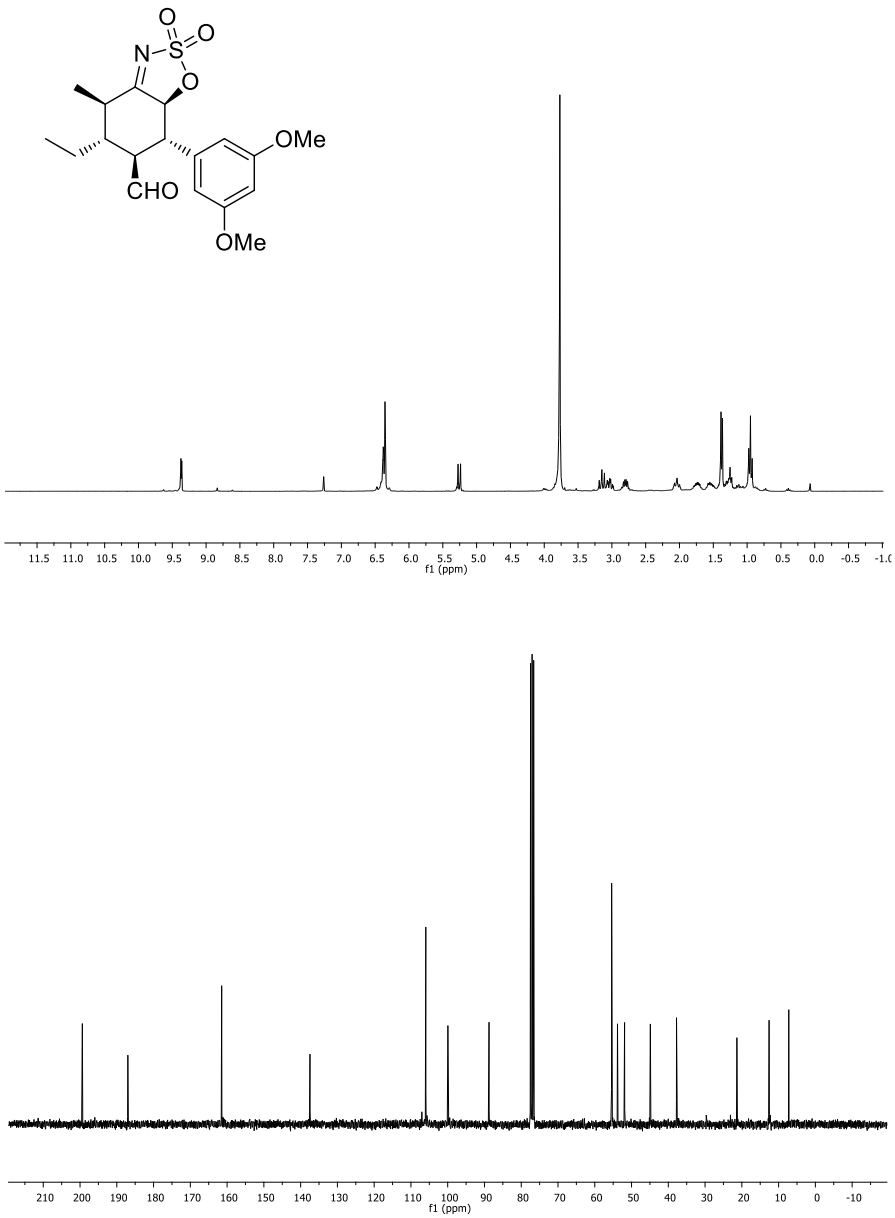
^{1}H-NMR and ^{13}C-NMR spectra of compound **7k**.



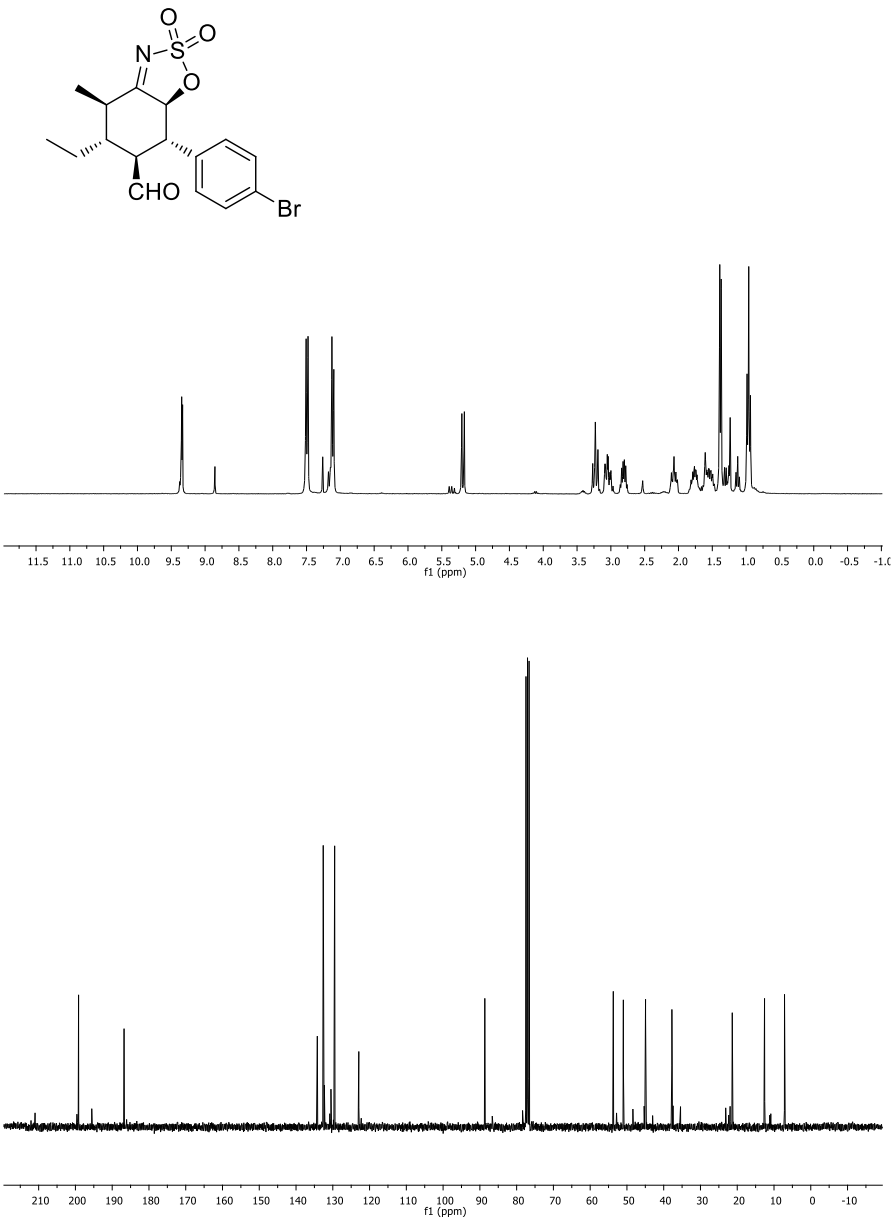
^{1}H-NMR and ^{13}C-NMR spectra of compound **7l**.



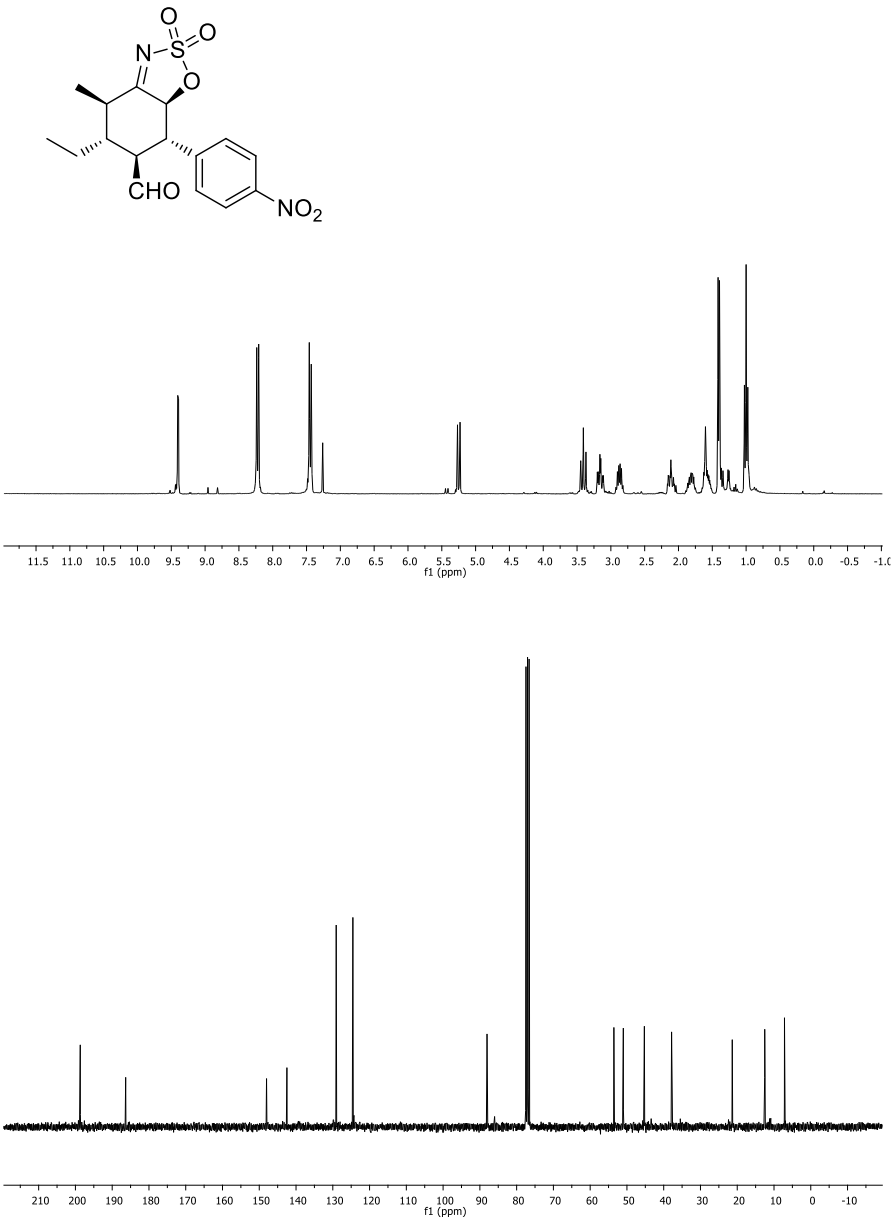
^{1}H-NMR and ^{13}C-NMR spectra of compound **7m**.



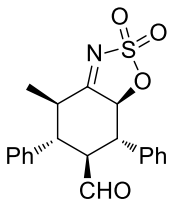
^{1}H-NMR and ^{13}C-NMR spectra of compound **7n**.

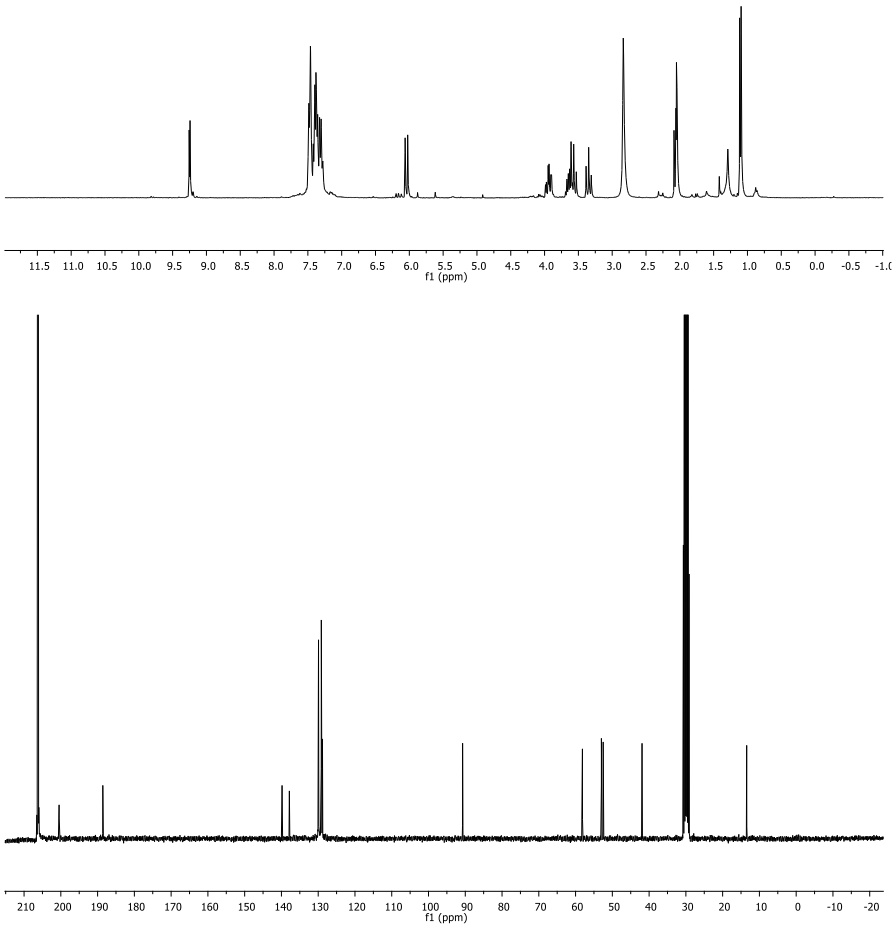


^{1}H-NMR and ^{13}C-NMR spectra of compound **7o**.

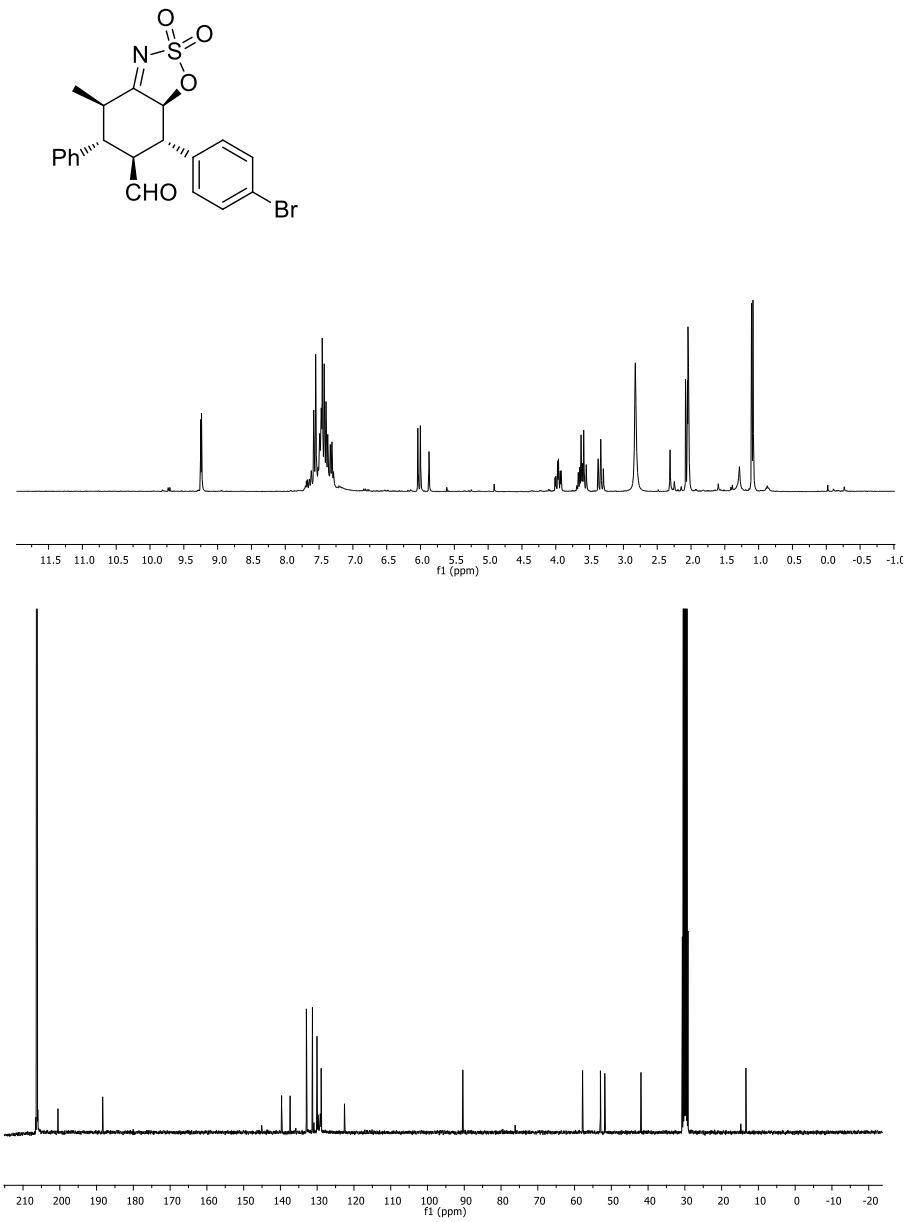


^{1}H-NMR and ^{13}C-NMR spectra of compound **7p**.

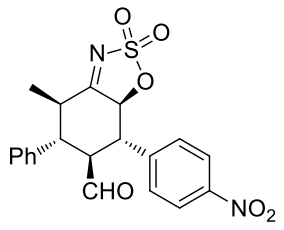


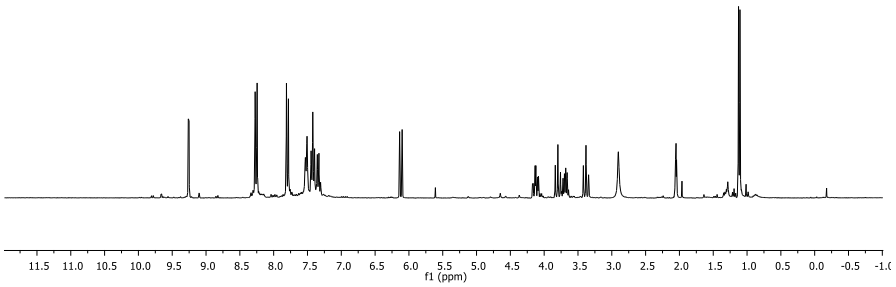


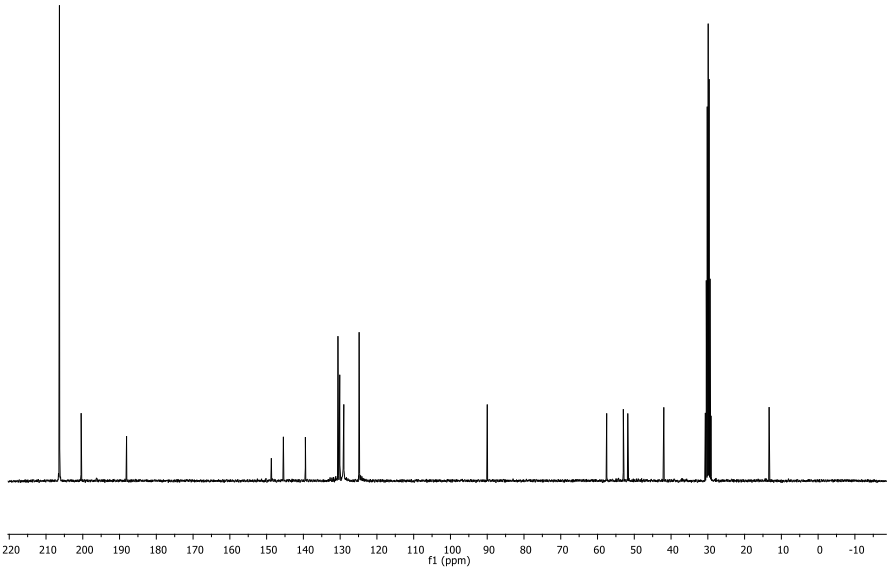
^{1}H-NMR and ^{13}C-NMR spectra of compound **7q**.



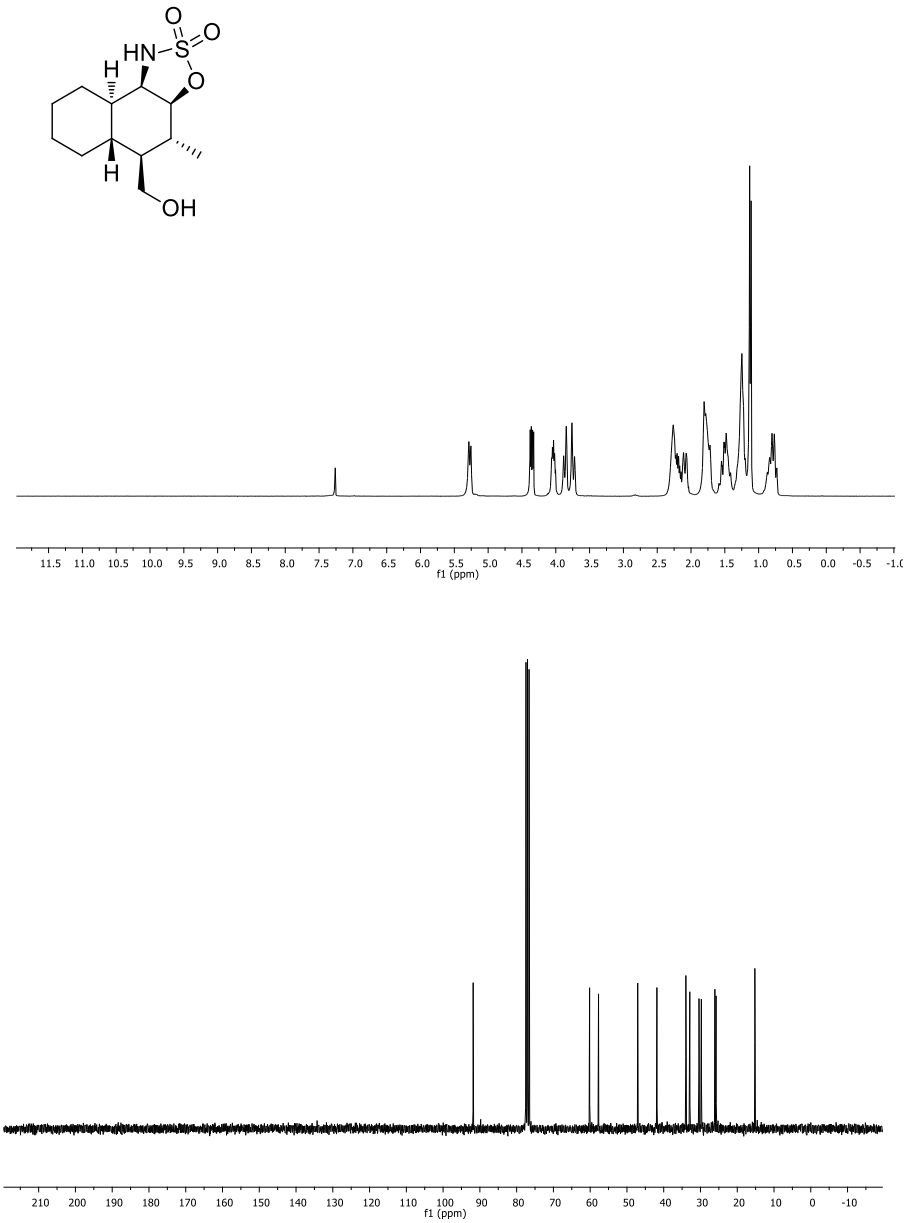
^{1}H-NMR and ^{13}C-NMR spectra of compound **7r**.



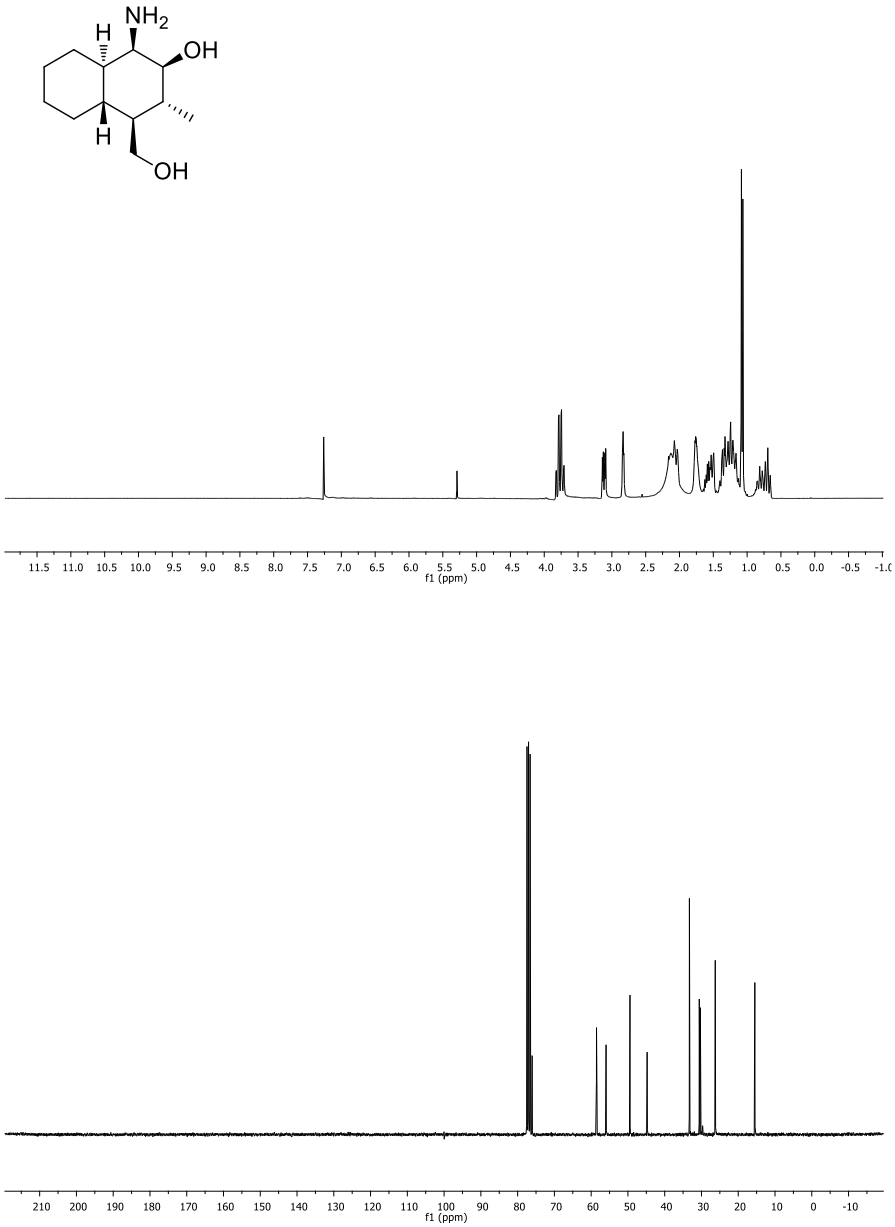




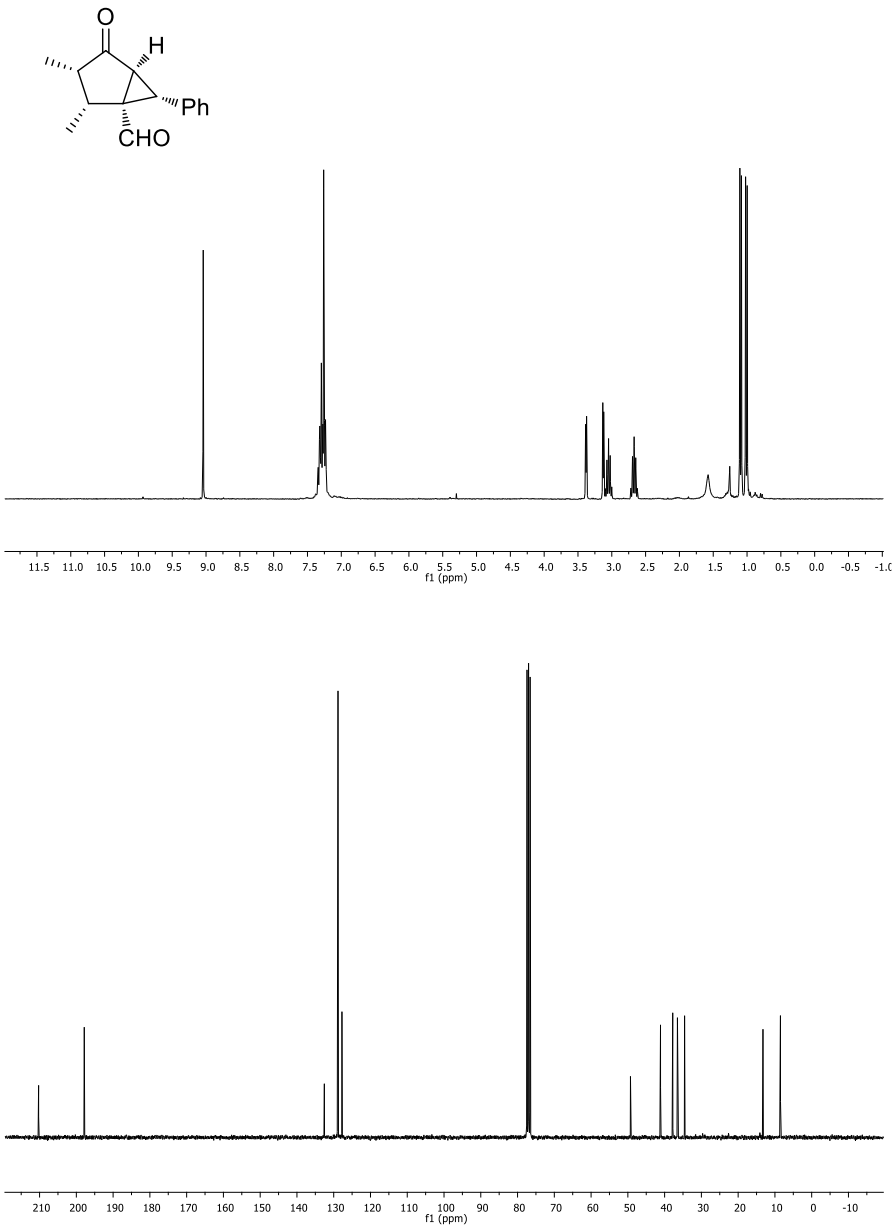
^{1}H-NMR and ^{13}C-NMR spectra of compound **7s**.



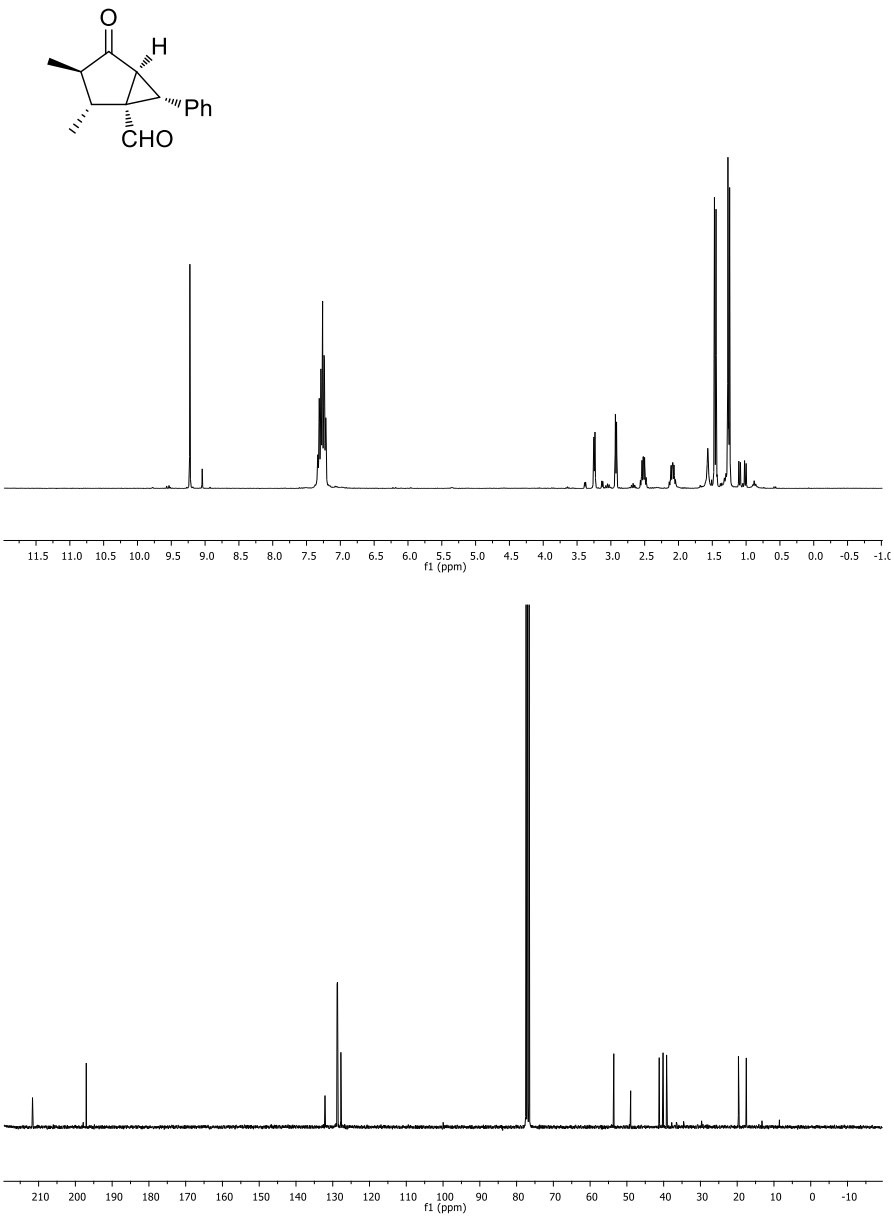
^{1}H-NMR and ^{13}C-NMR spectra of compound **9**.



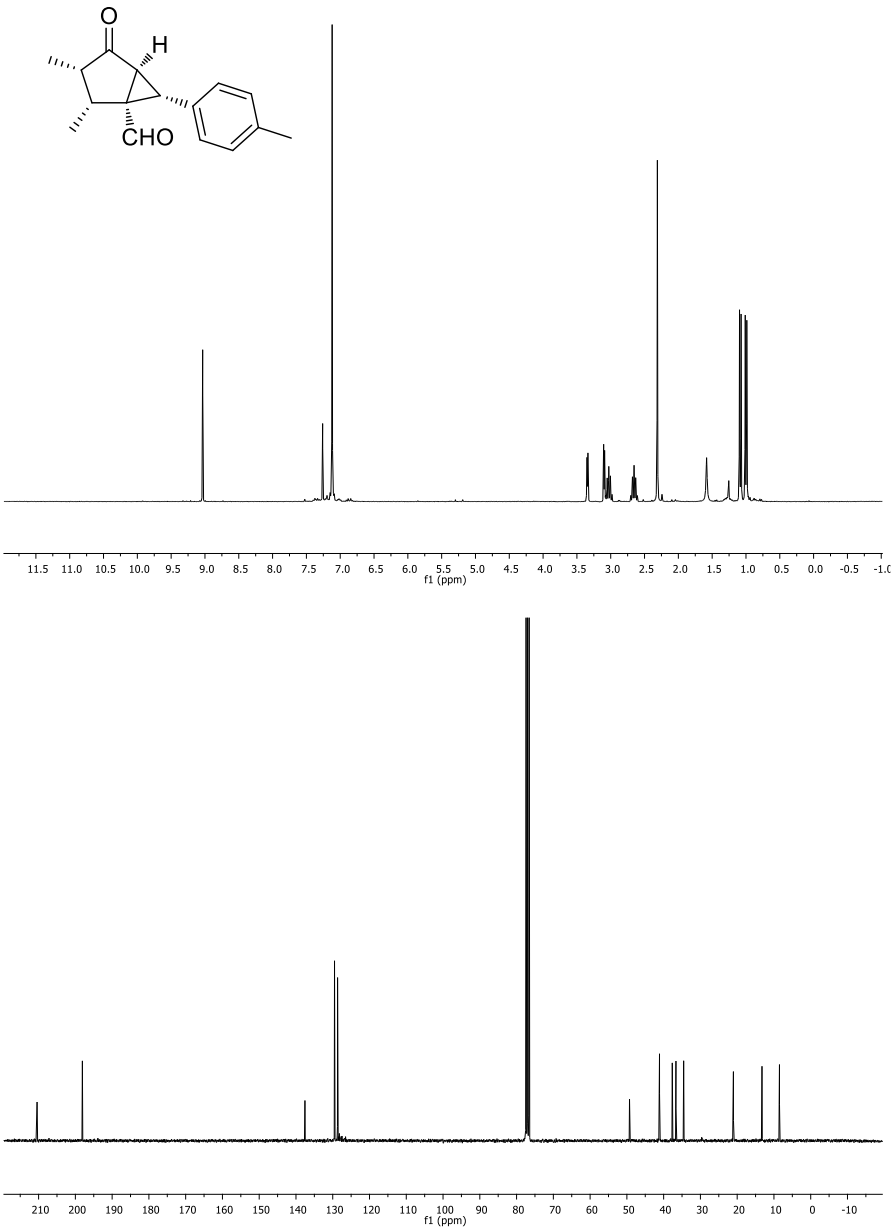
^{1}H-NMR and ^{13}C-NMR spectra of compound **10**.



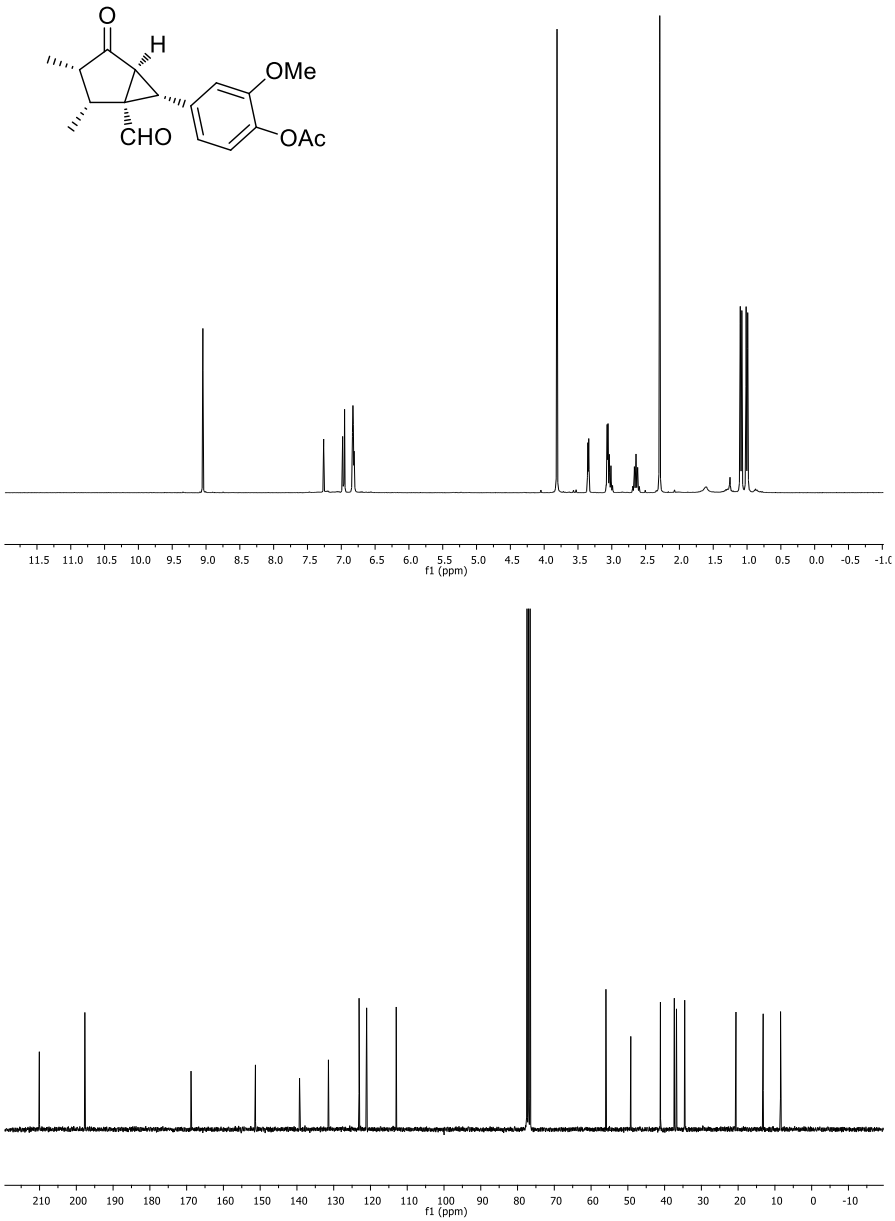
^{1}H-NMR and ^{13}C-NMR spectra of compound ***cis*-11a**.



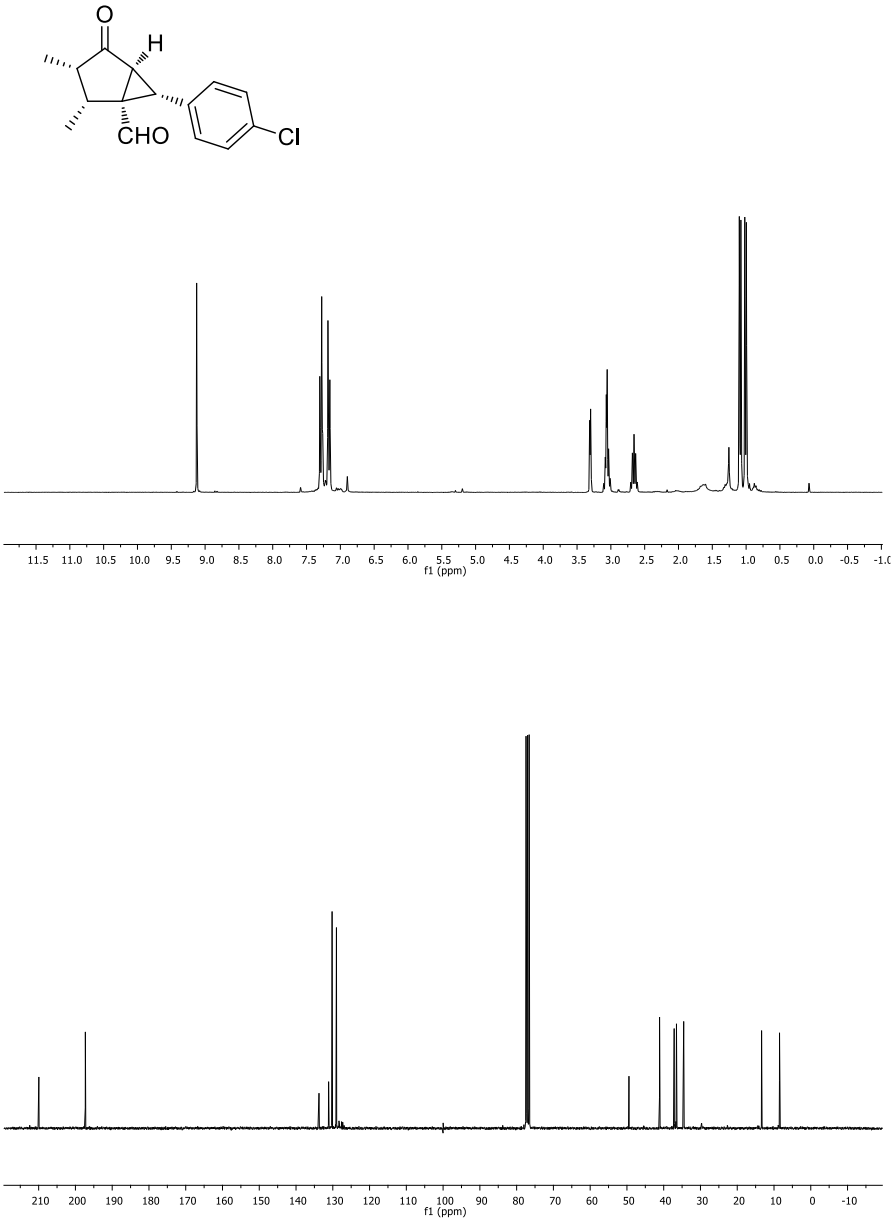
^{1}H-NMR and ^{13}C-NMR spectra of compound ***trans*-11a**.



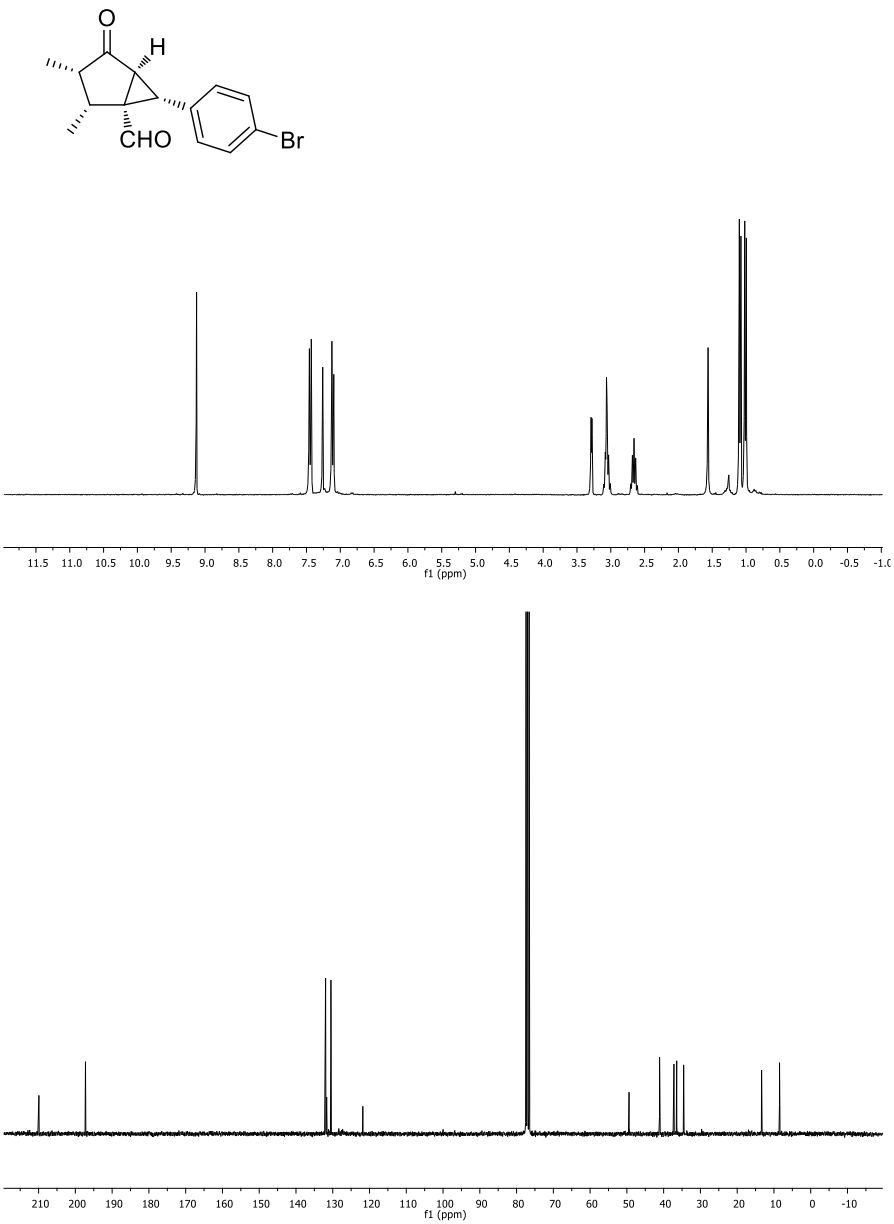
^{1}H-NMR and ^{13}C-NMR spectra of compound **11b**.



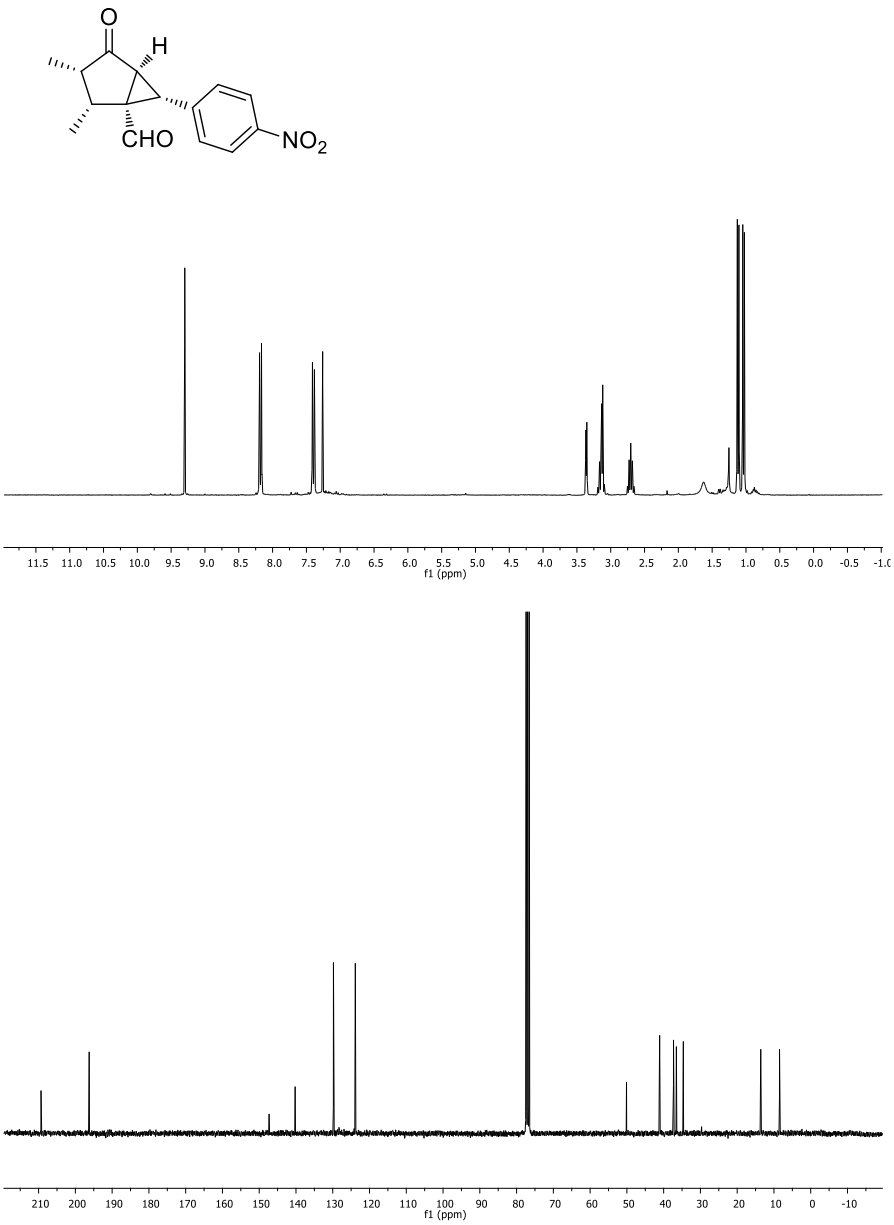
^{1}H-NMR and ^{13}C-NMR spectra of compound **11c**.



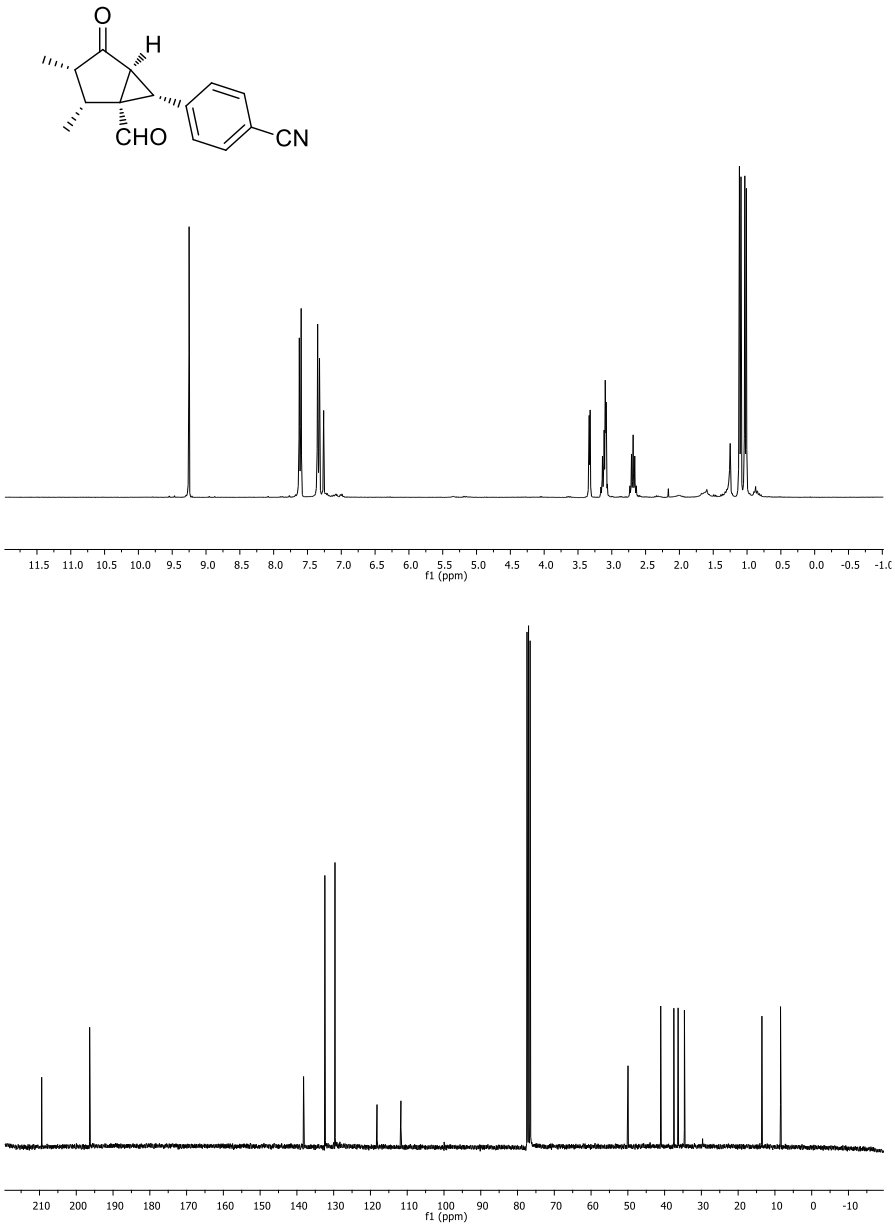
^{1}H-NMR and ^{13}C-NMR spectra of compound **11d**.



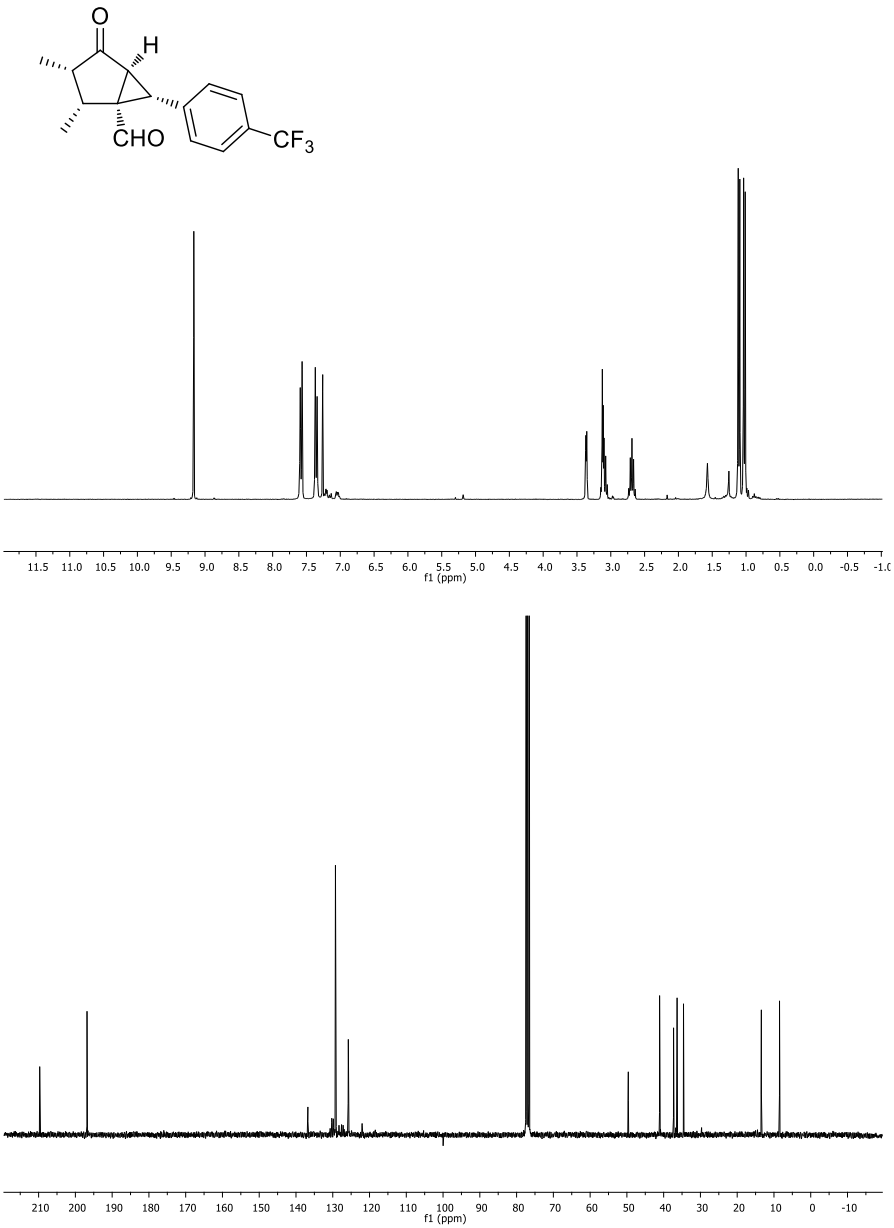
^{1}H-NMR and ^{13}C-NMR spectra of compound **11e**.



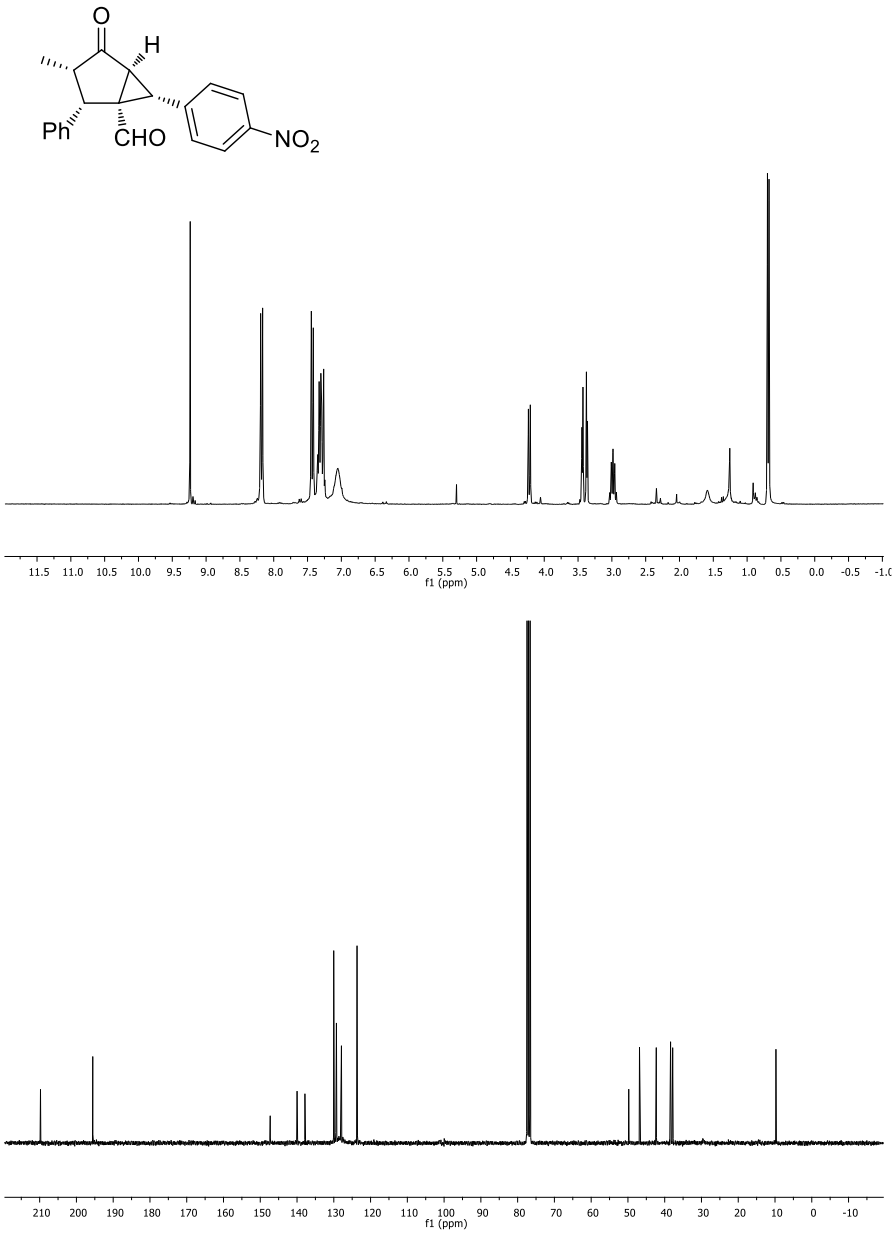
^{1}H-NMR and ^{13}C-NMR spectra of compound **11f**.



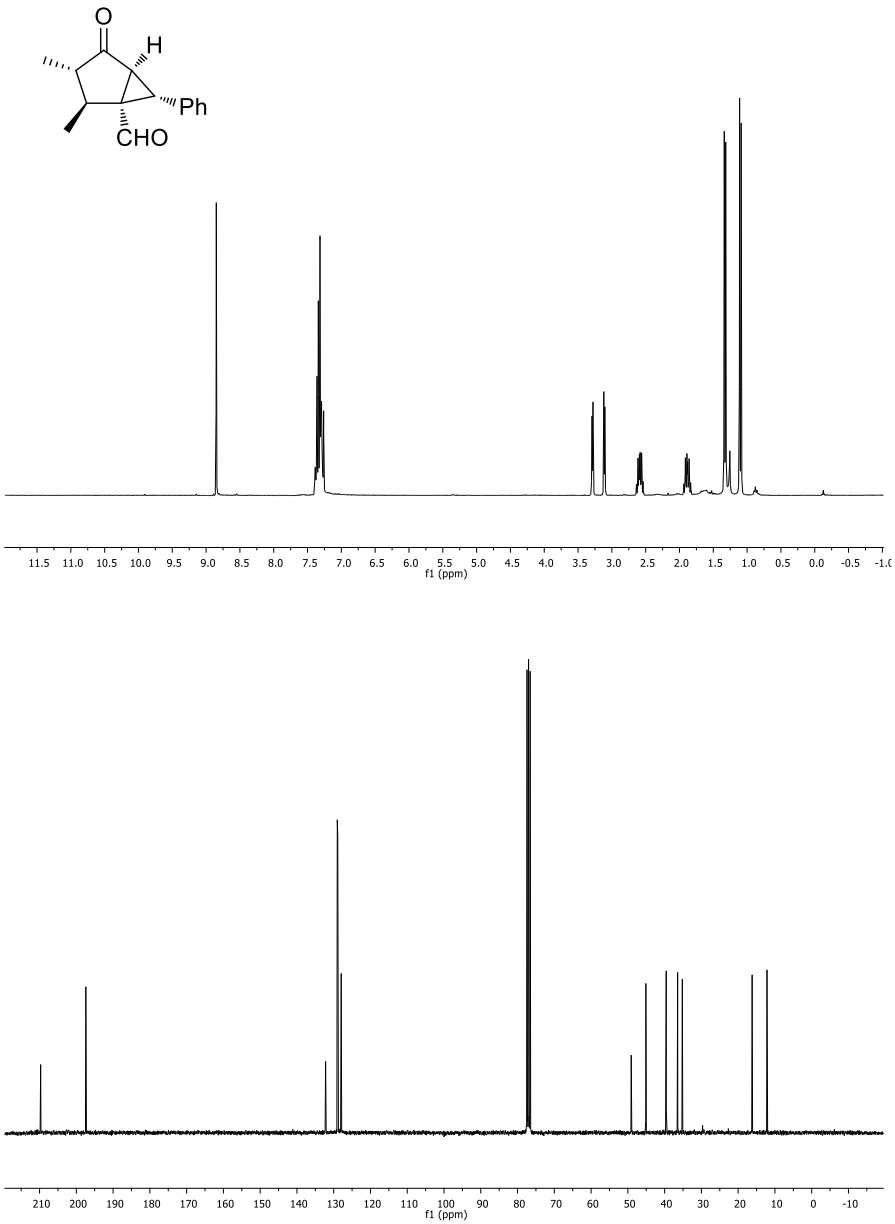
^{1}H-NMR and ^{13}C-NMR spectra of compound **11g**.



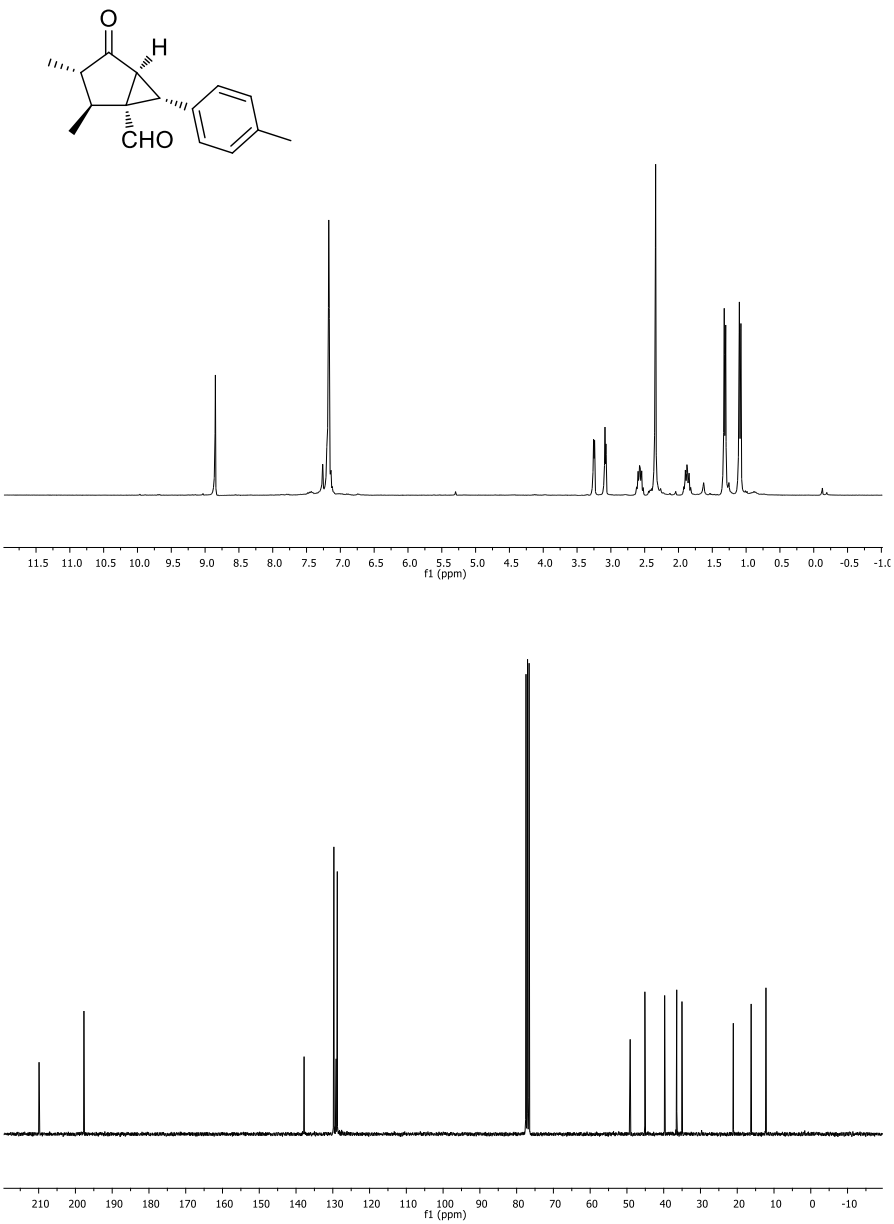
^{1}H-NMR and ^{13}C-NMR spectra of compound **11h**.



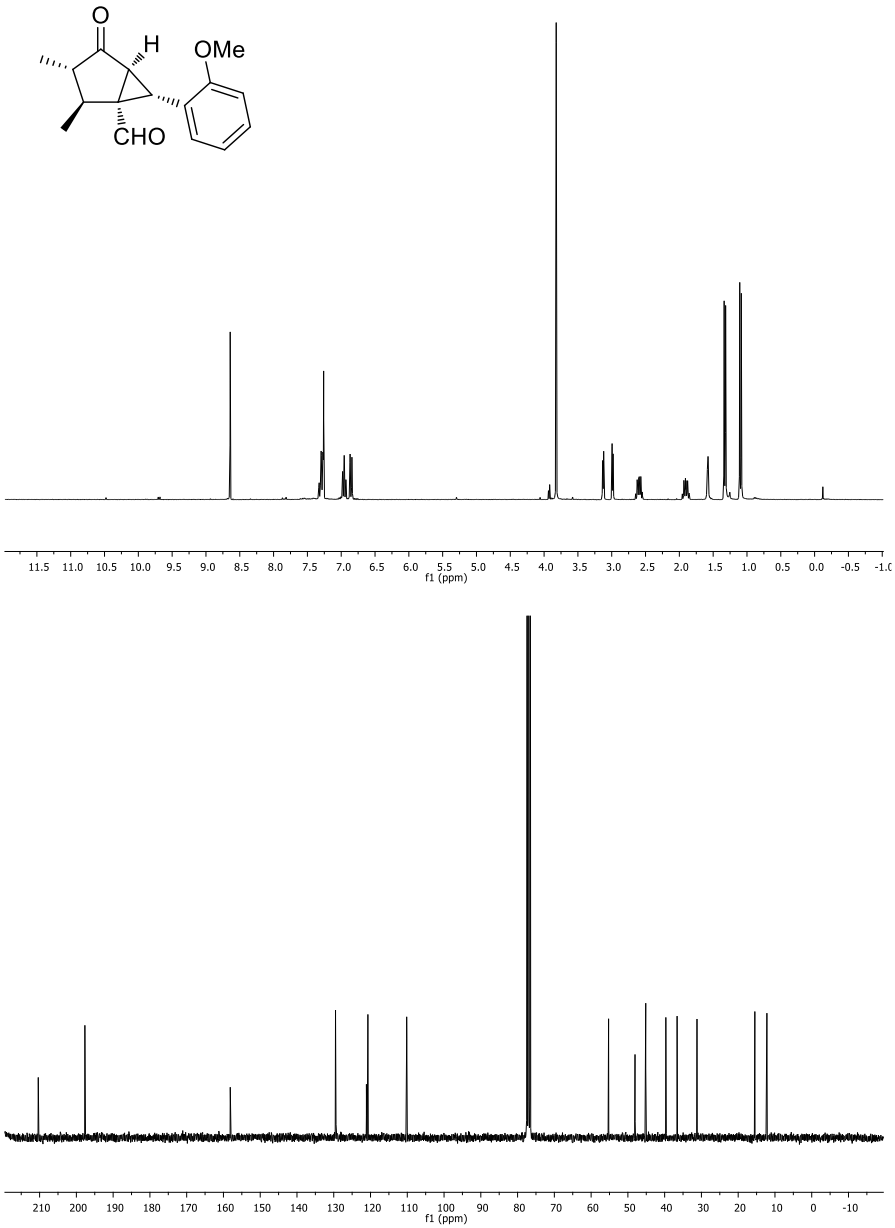
^{1}H-NMR and ^{13}C-NMR spectra of compound **11i**.



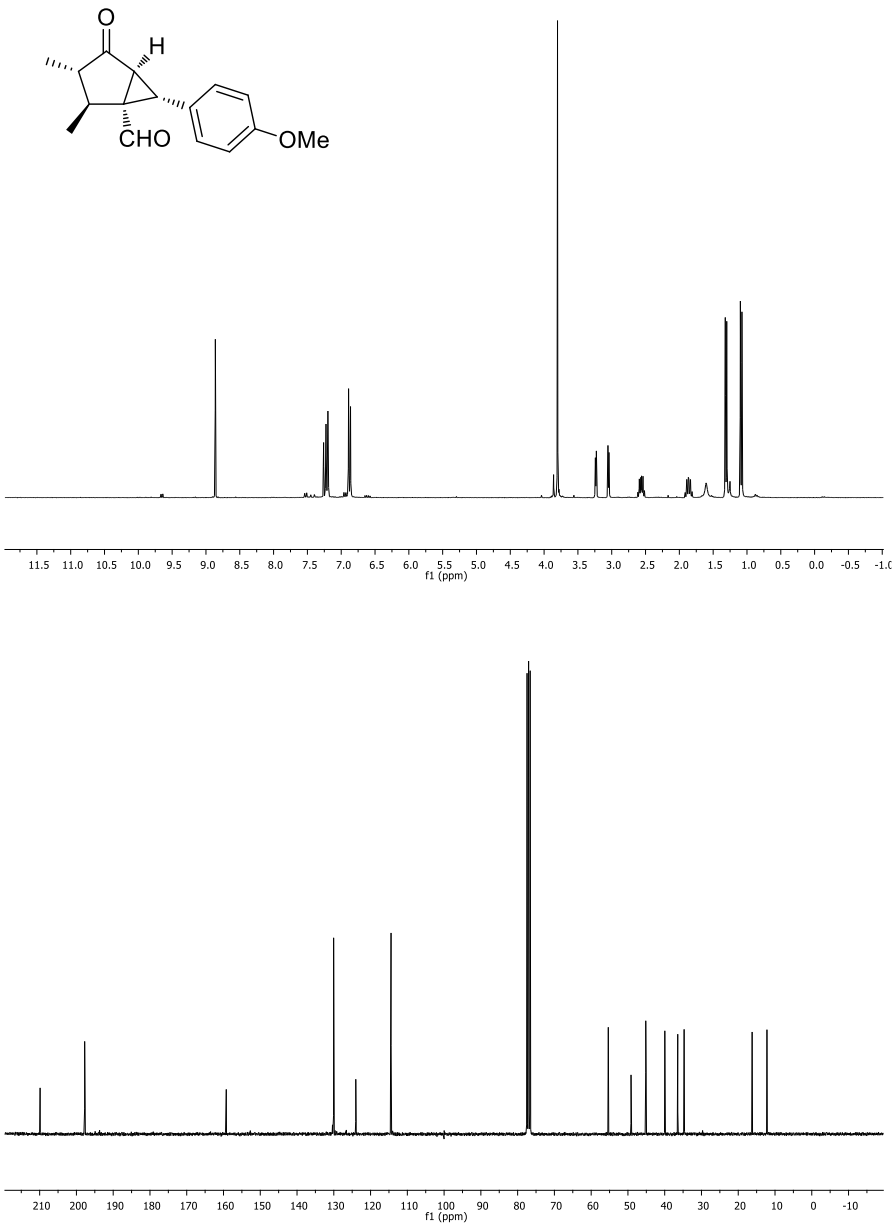
^{1}H-NMR and ^{13}C-NMR spectra of compound **8a**.



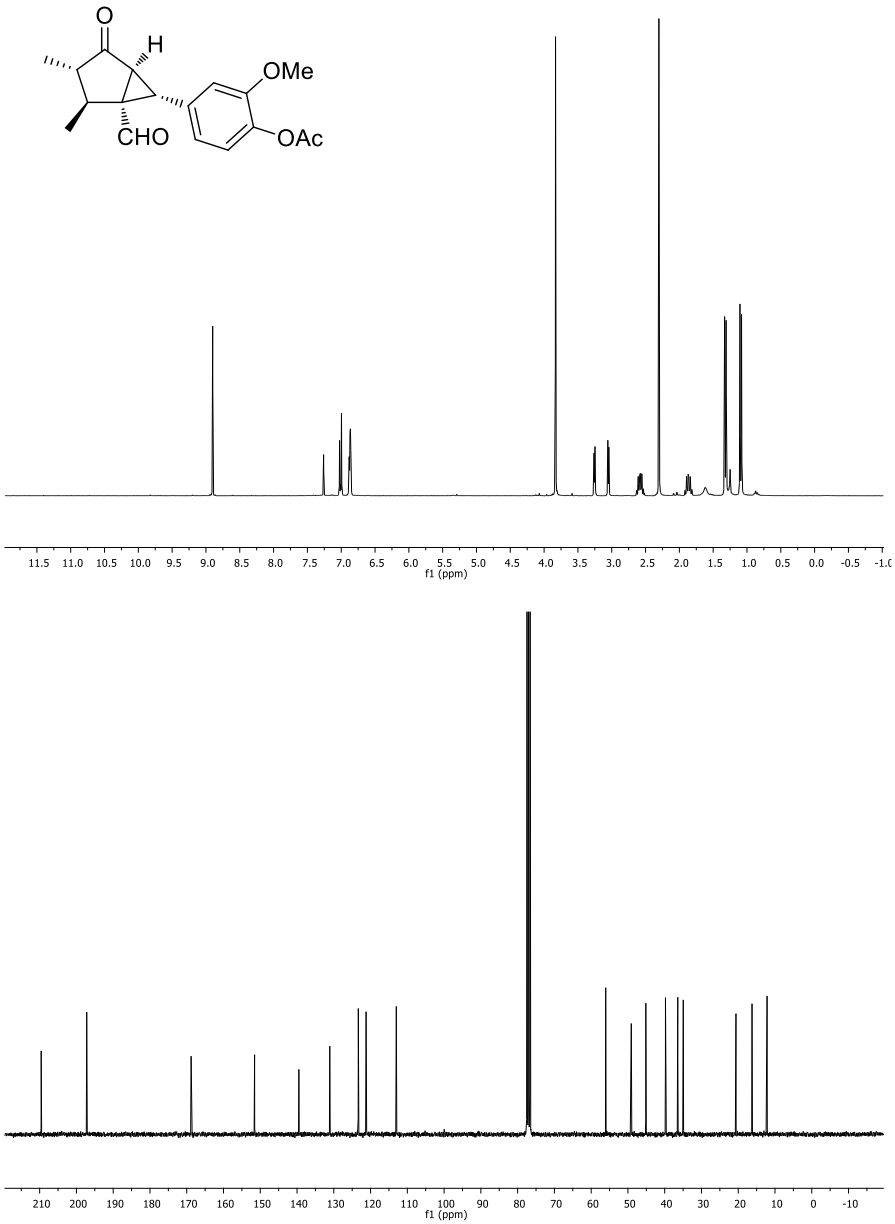
^{1}H-NMR and ^{13}C-NMR spectra of compound **8b**.



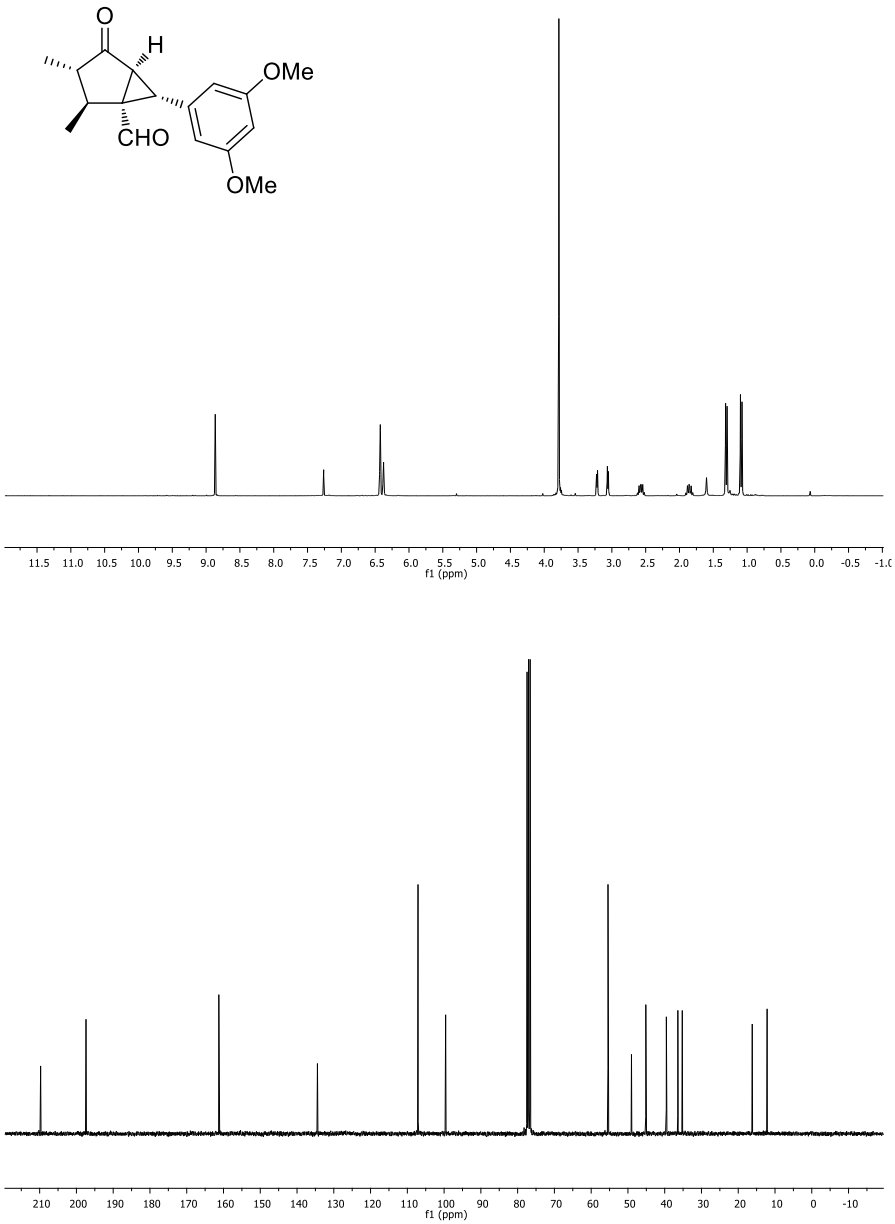
^{1}H-NMR and ^{13}C-NMR spectra of compound **8c**.



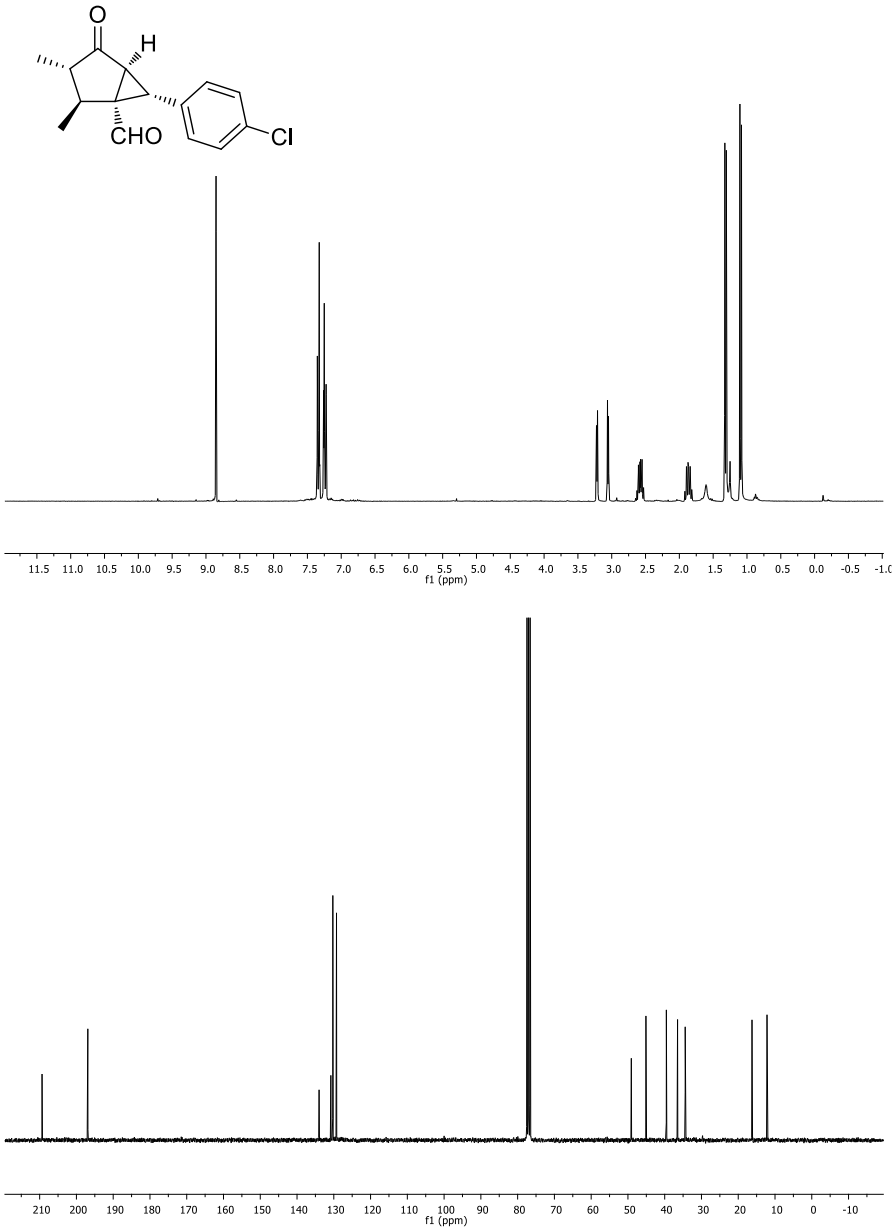
^{1}H-NMR and ^{13}C-NMR spectra of compound **8d**.



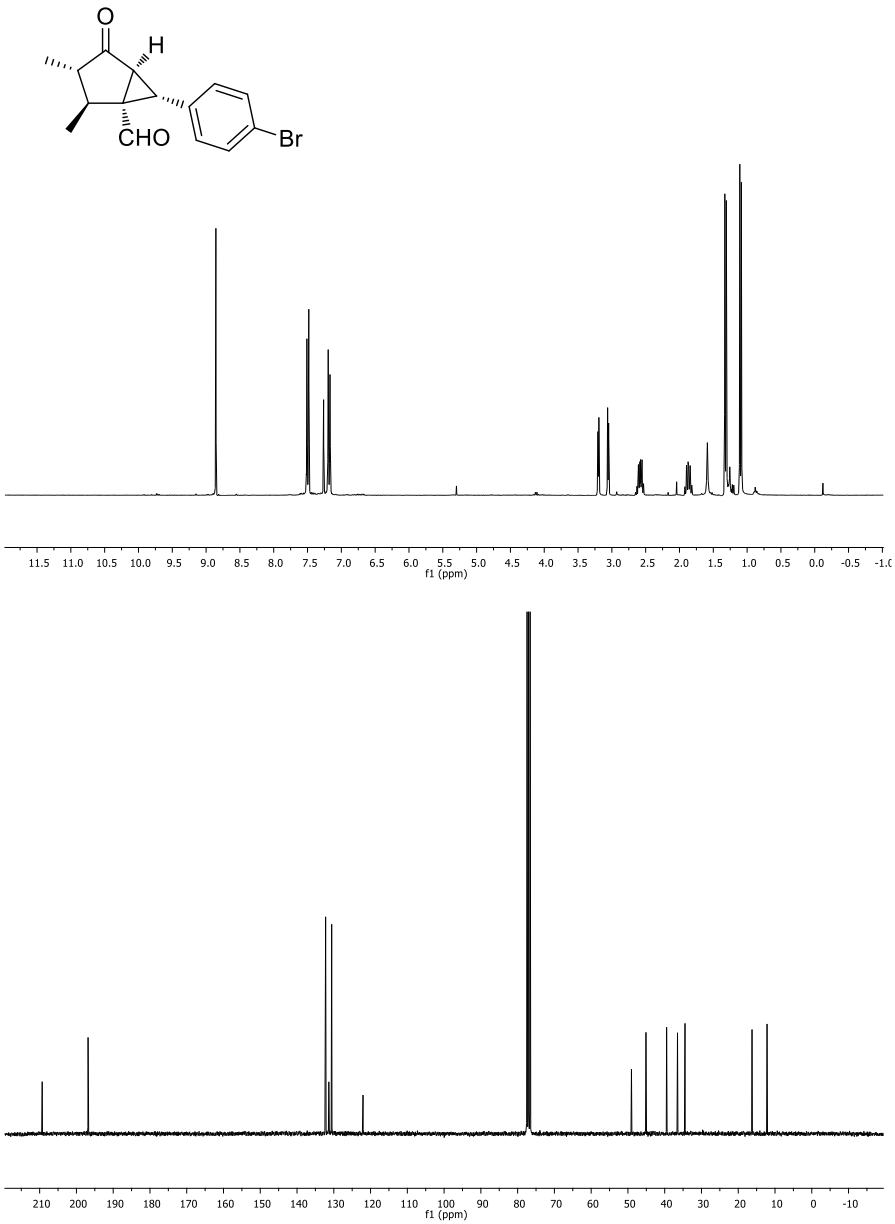
^{1}H-NMR and ^{13}C-NMR spectra of compound **8e**.



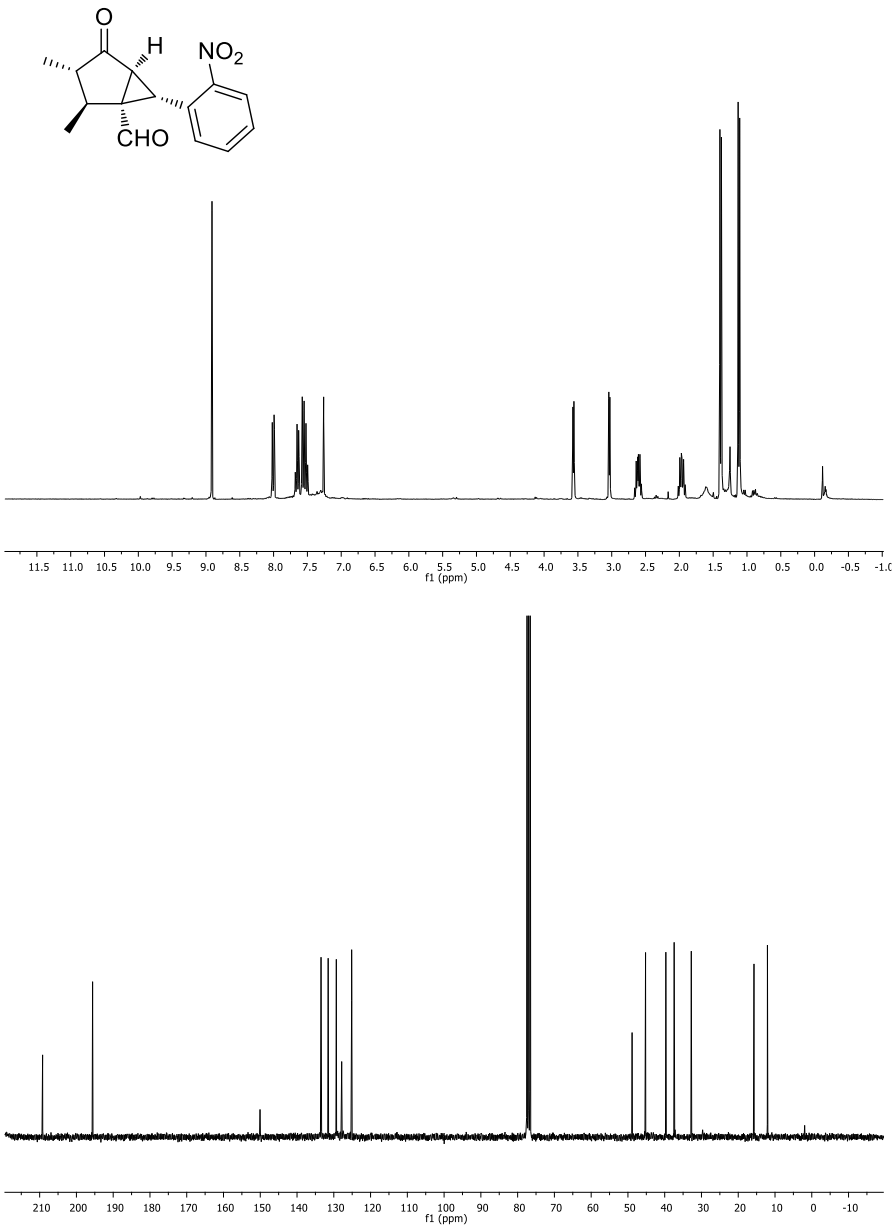
^{1}H-NMR and ^{13}C-NMR spectra of compound **8f**.



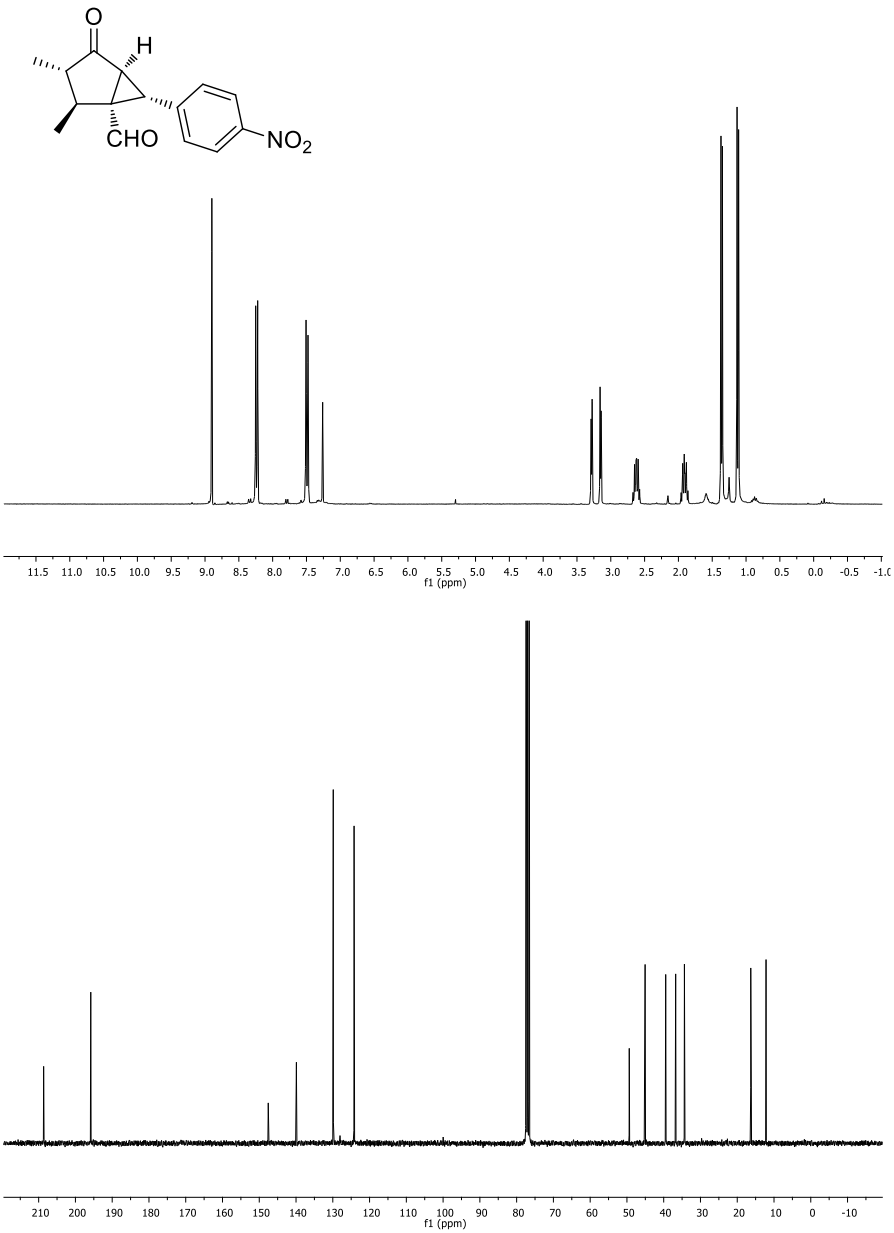
^{1}H-NMR and ^{13}C-NMR spectra of compound **8g**.



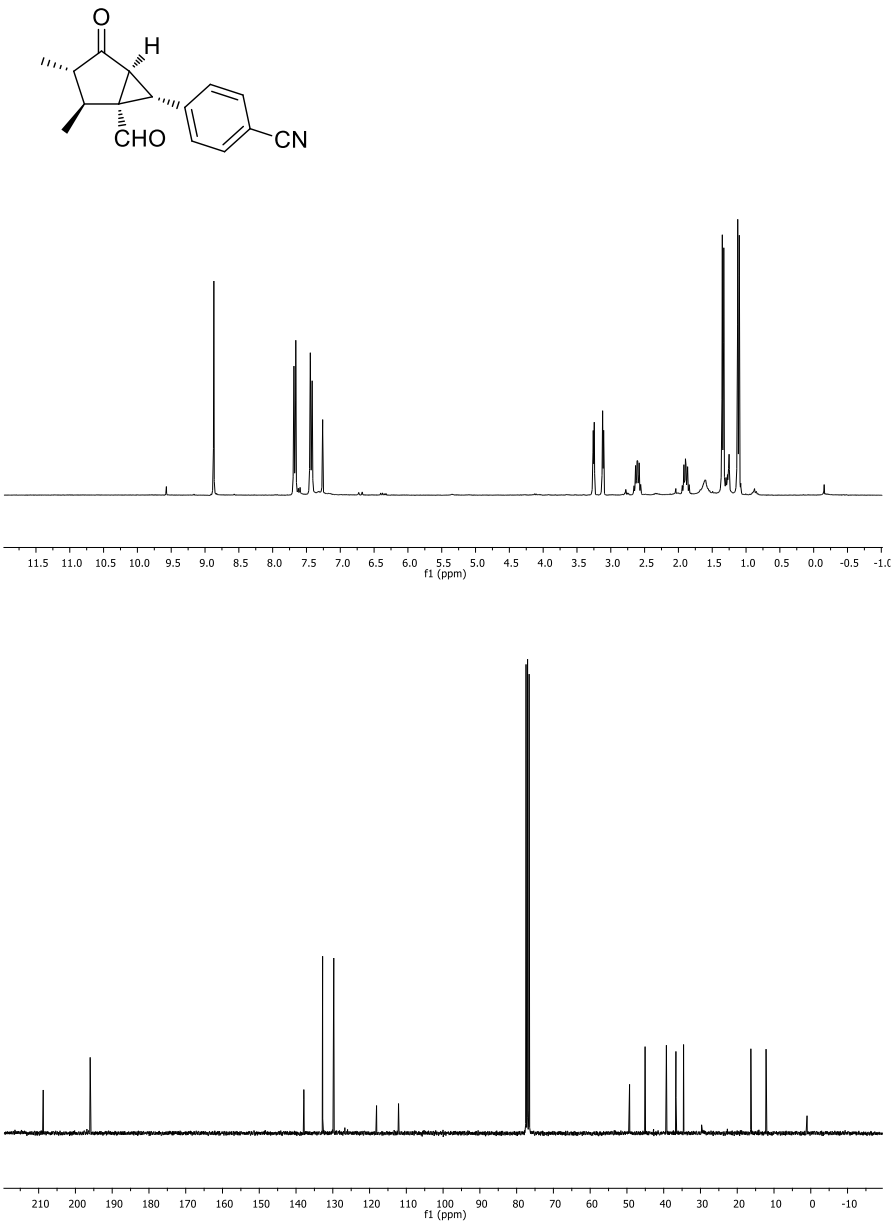
^{1}H-NMR and ^{13}C-NMR spectra of compound **8h**.



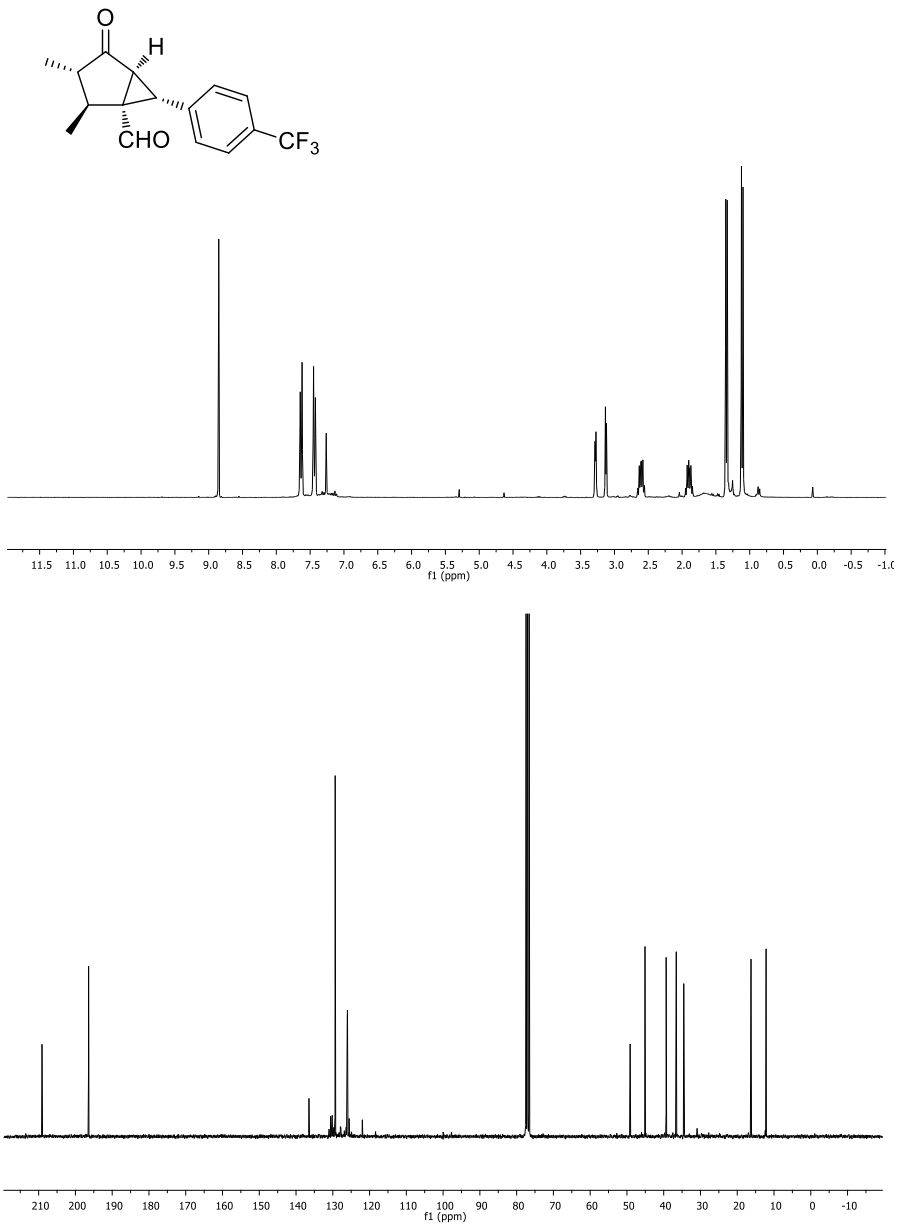
^{1}H-NMR and ^{13}C-NMR spectra of compound **8i**.



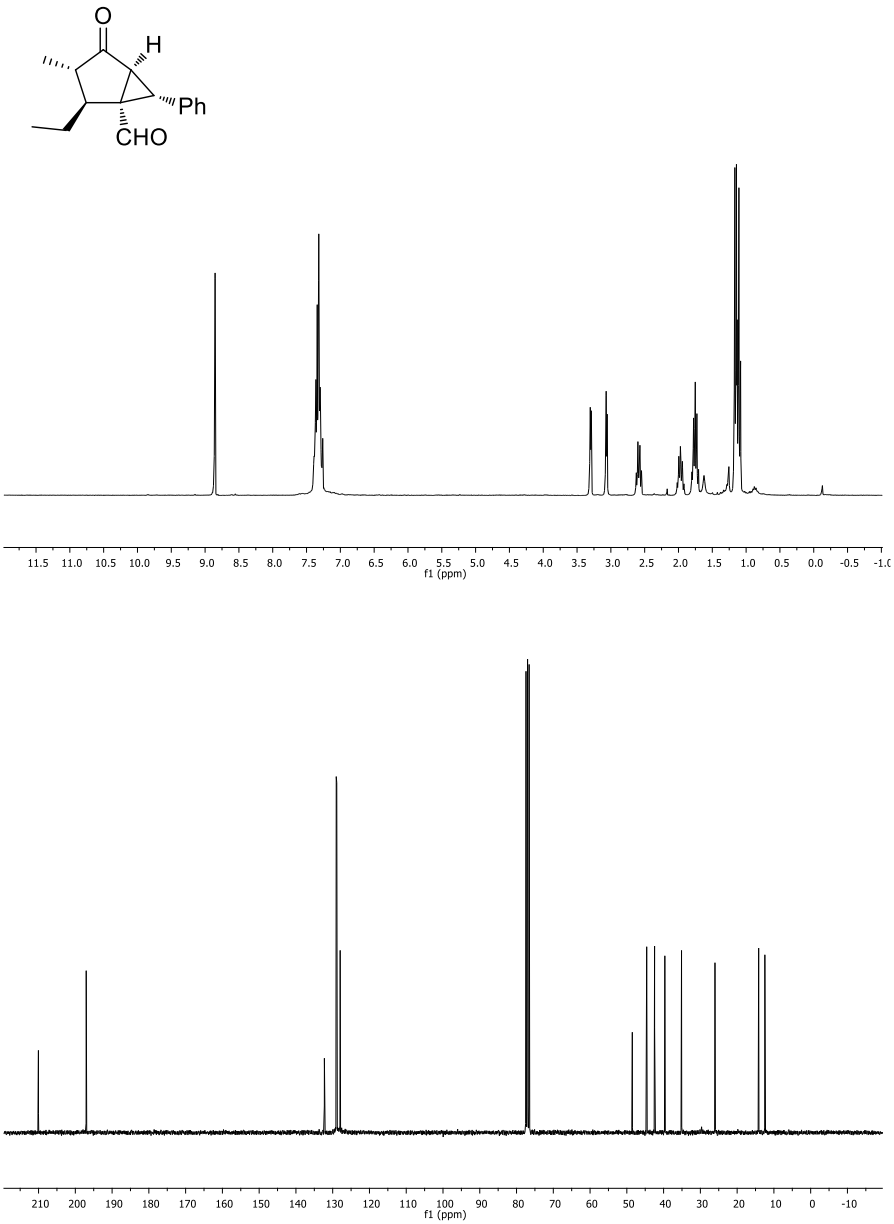
^{1}H-NMR and ^{13}C-NMR spectra of compound **8j**.



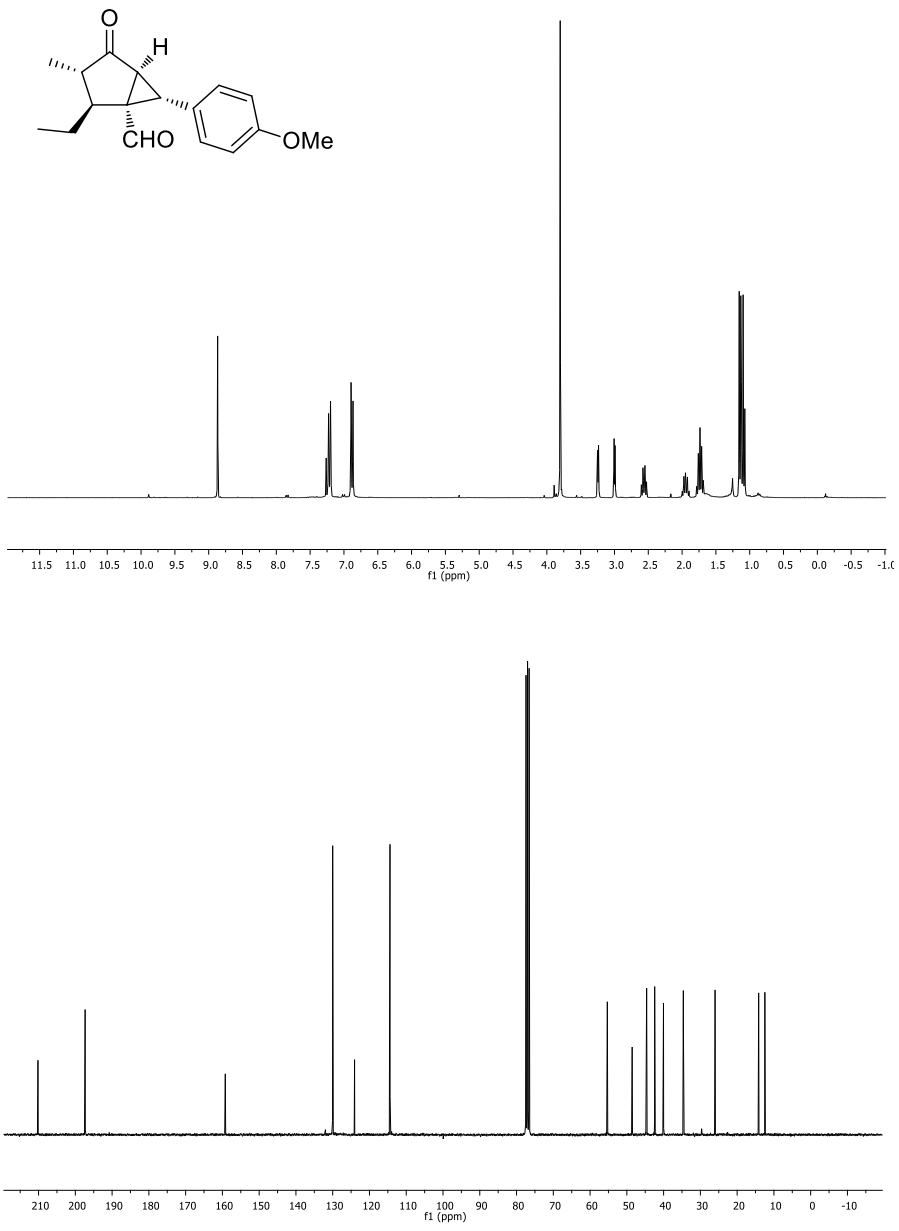
^{1}H-NMR and ^{13}C-NMR spectra of compound **8k**.



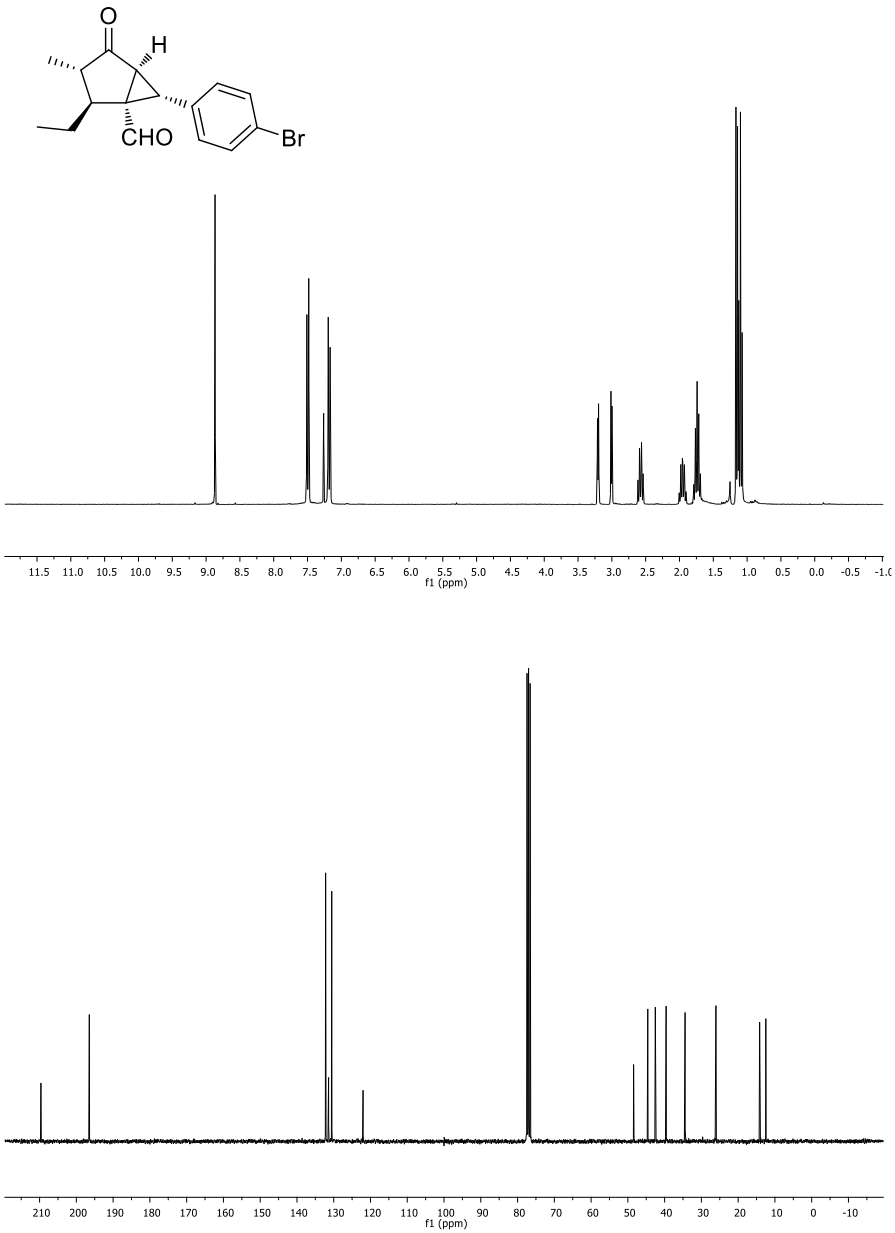
^{1}H-NMR and ^{13}C-NMR spectra of compound **8l**.



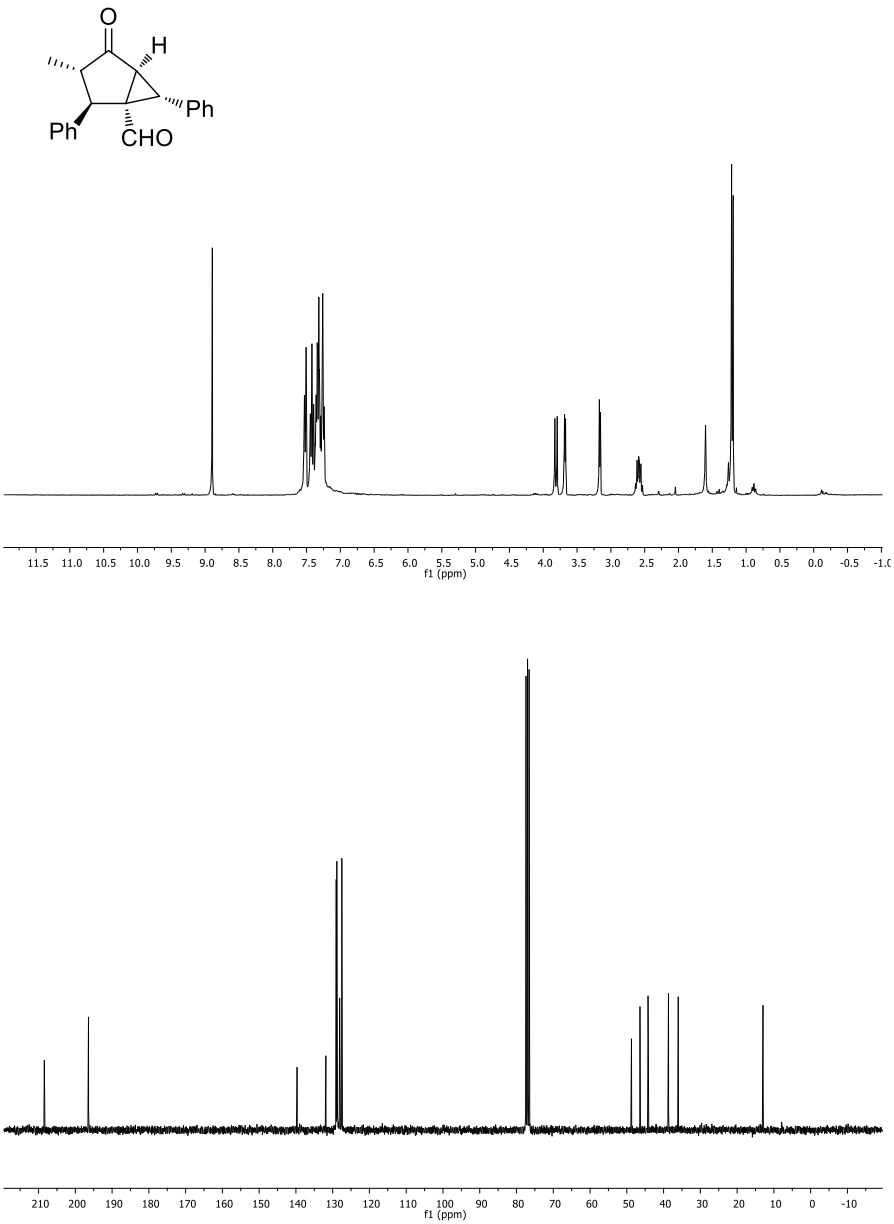
^{1}H-NMR and ^{13}C-NMR spectra of compound **8m**.



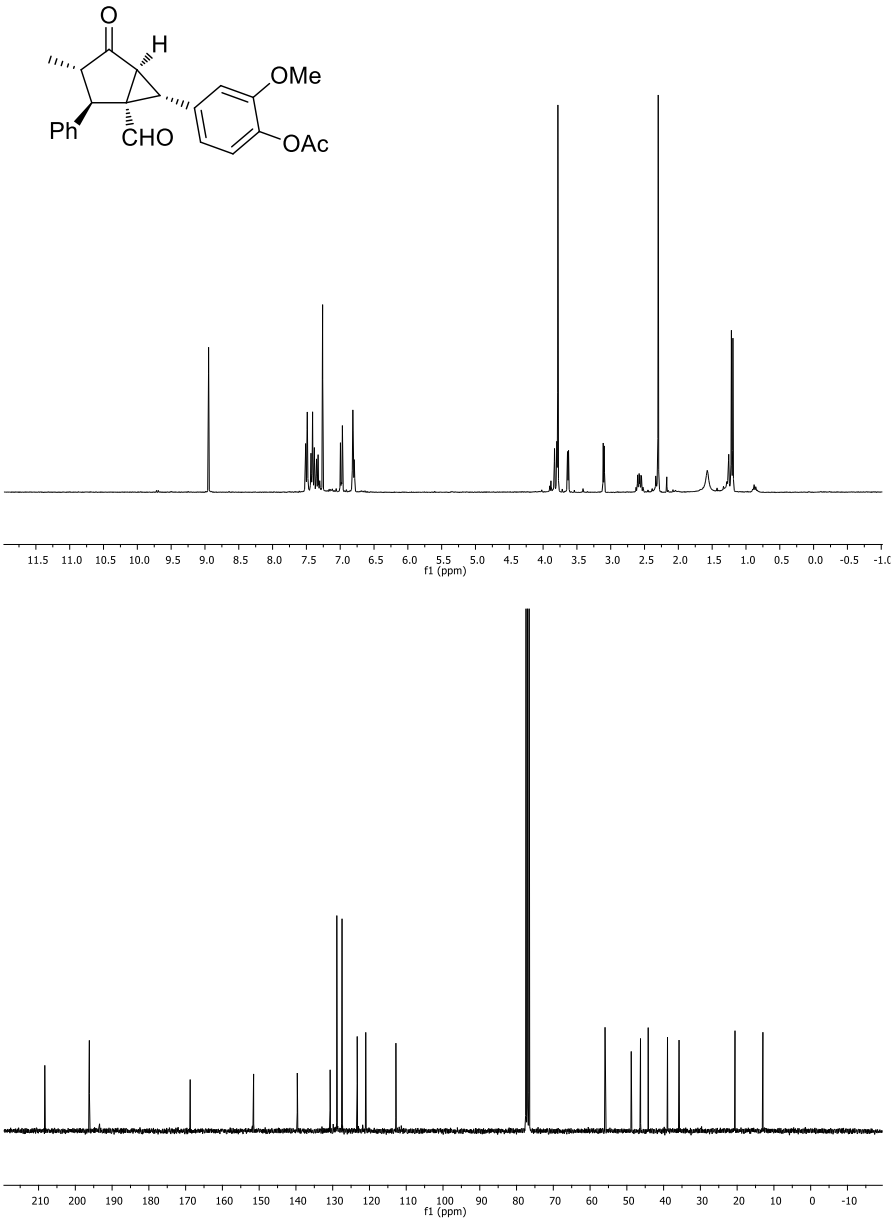
^{1}H-NMR and ^{13}C-NMR spectra of compound **8n**.



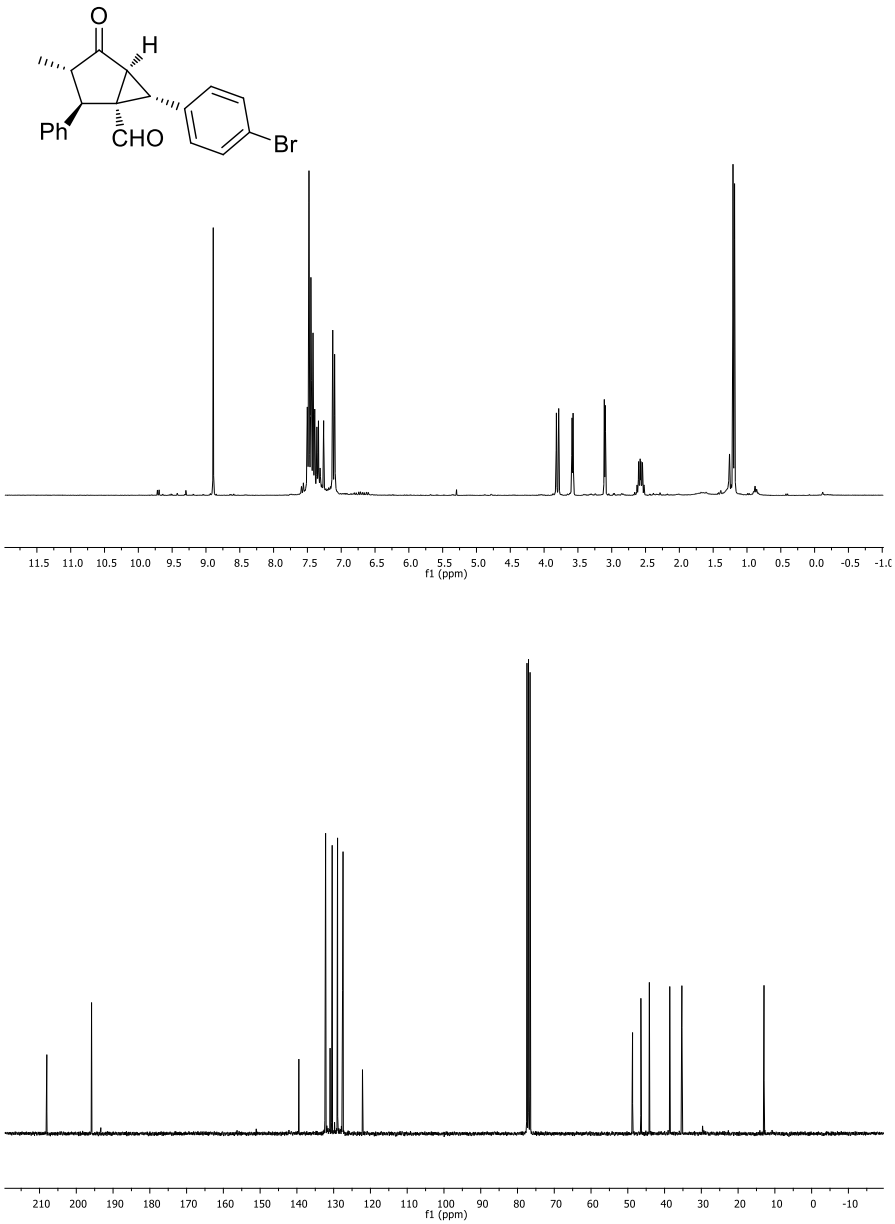
^{1}H-NMR and ^{13}C-NMR spectra of compound **8o**.



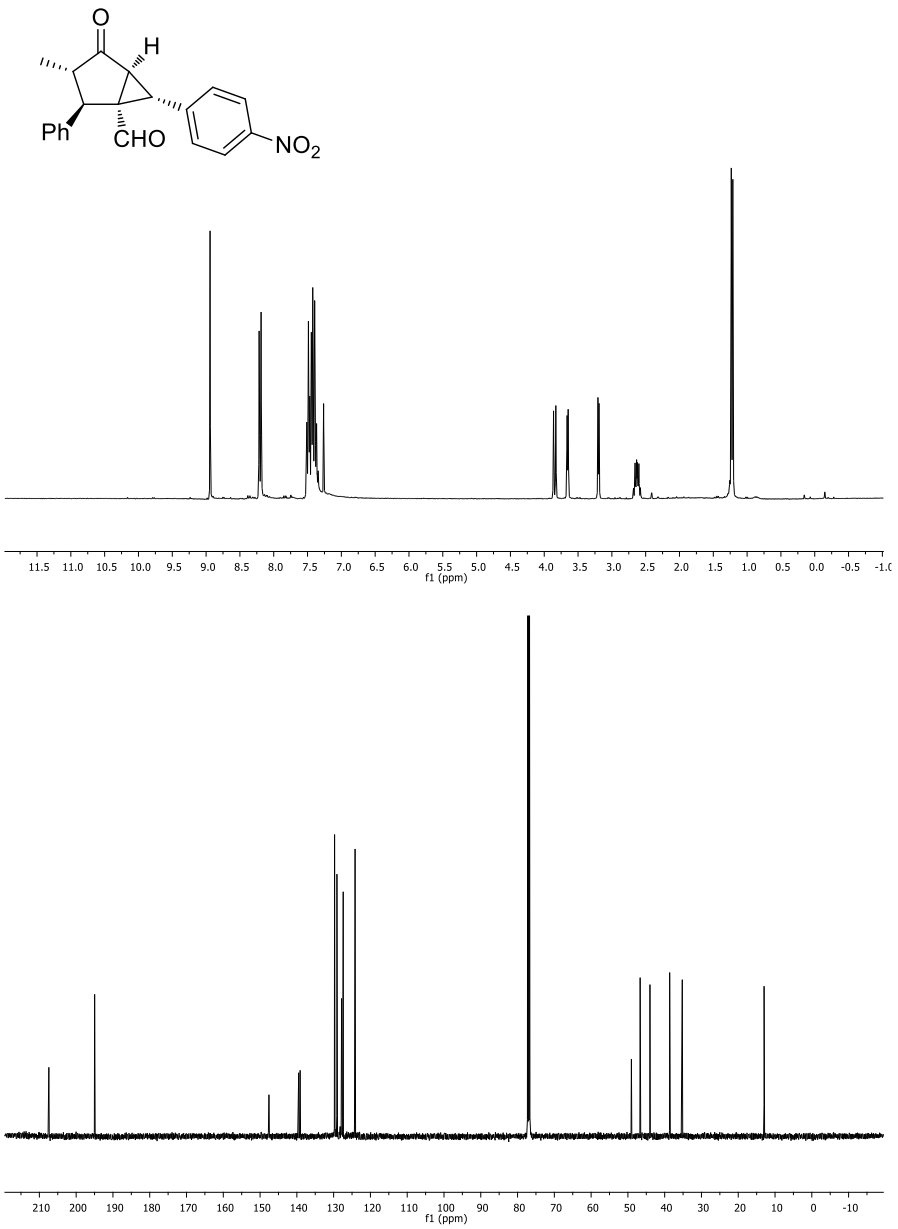
^{1}H-NMR and ^{13}C-NMR spectra of compound **8p**.



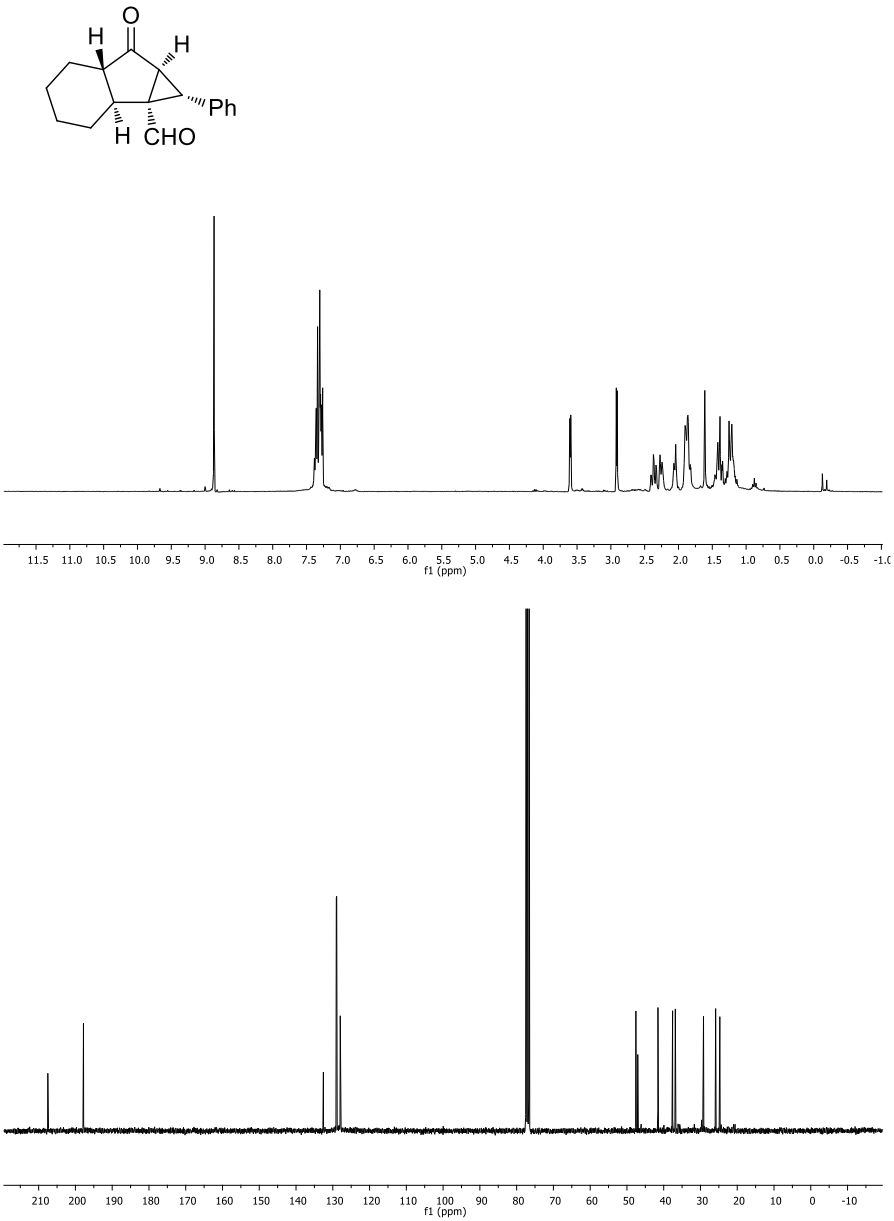
^{1}H-NMR and ^{13}C-NMR spectra of compound **8q**.



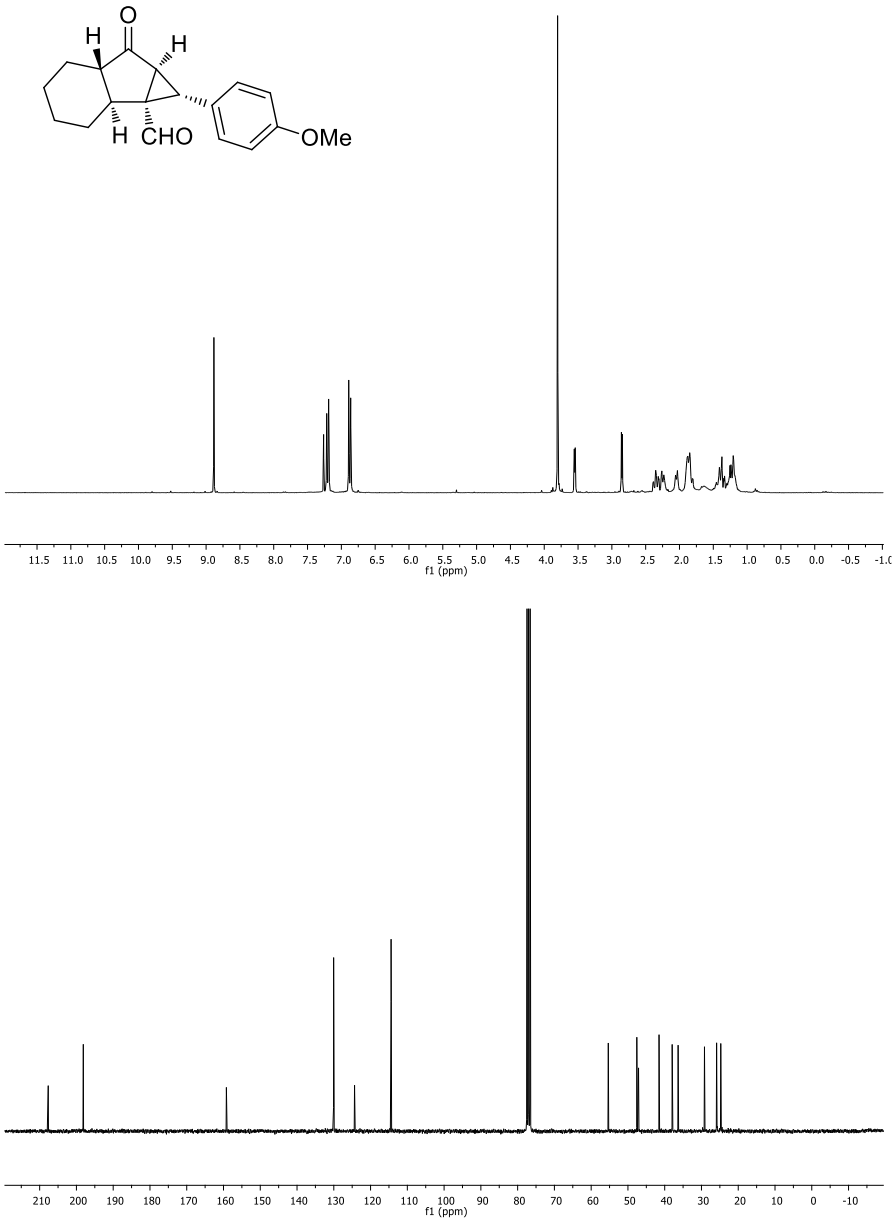
^{1}H-NMR and ^{13}C-NMR spectra of compound **8r**.



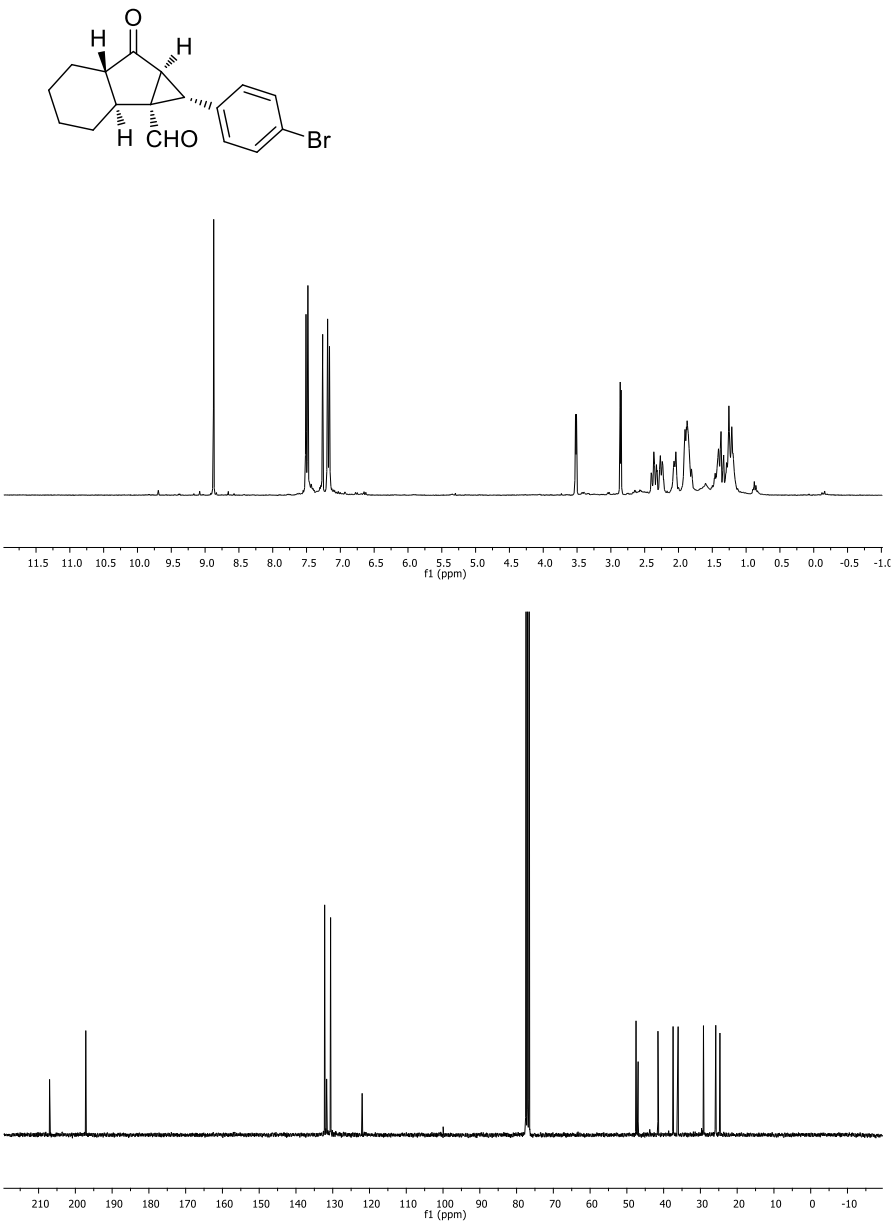
^{1}H-NMR and ^{13}C-NMR spectra of compound **8s**.



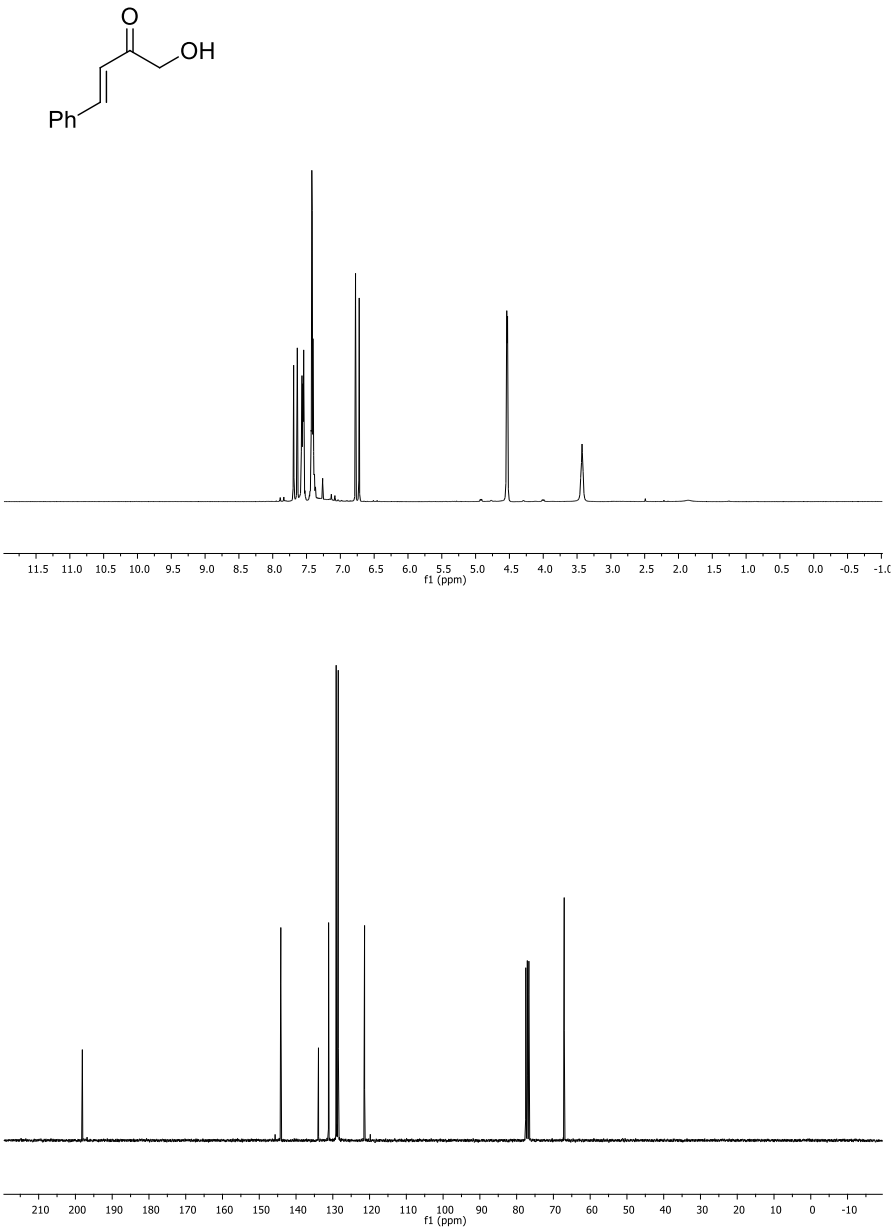
^{1}H-NMR and ^{13}C-NMR spectra of compound **12a**.



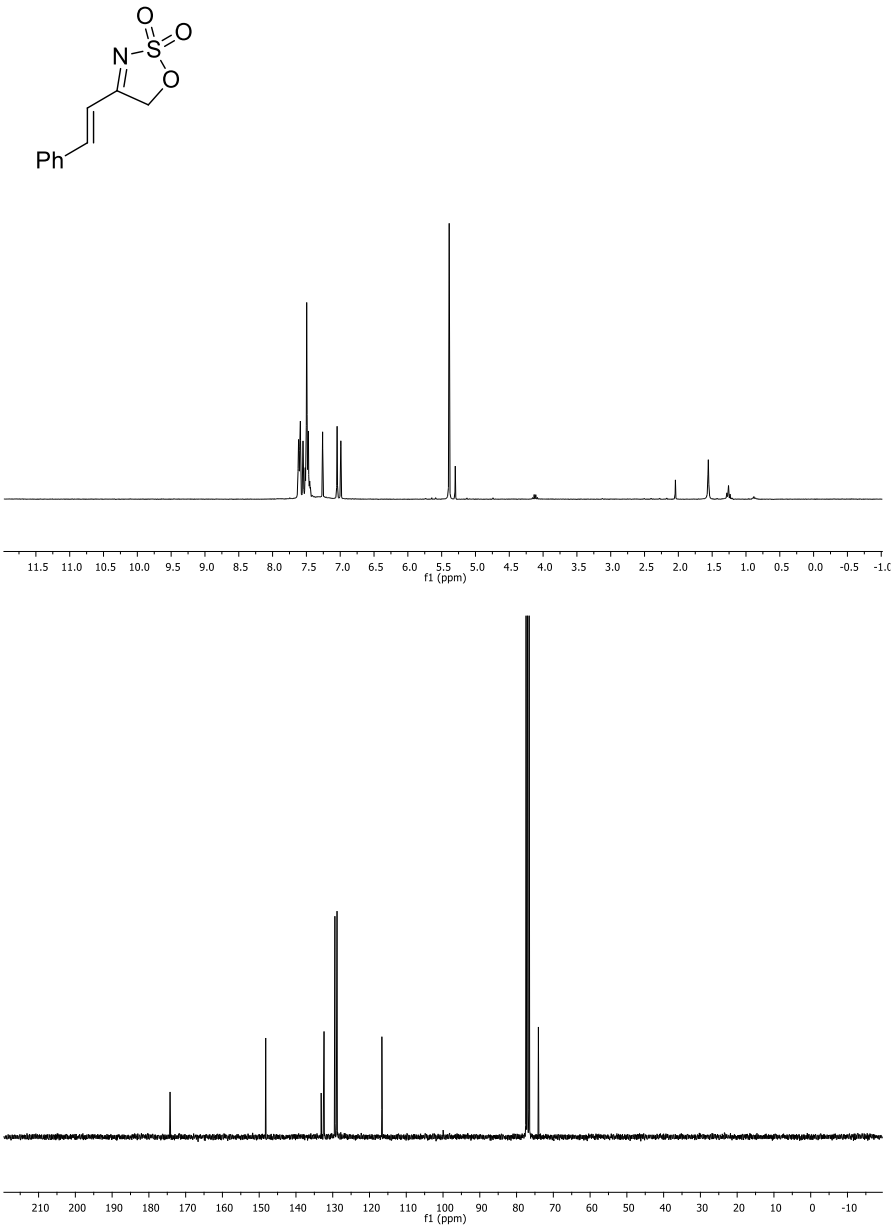
^{1}H-NMR and ^{13}C-NMR spectra of compound **12b**.



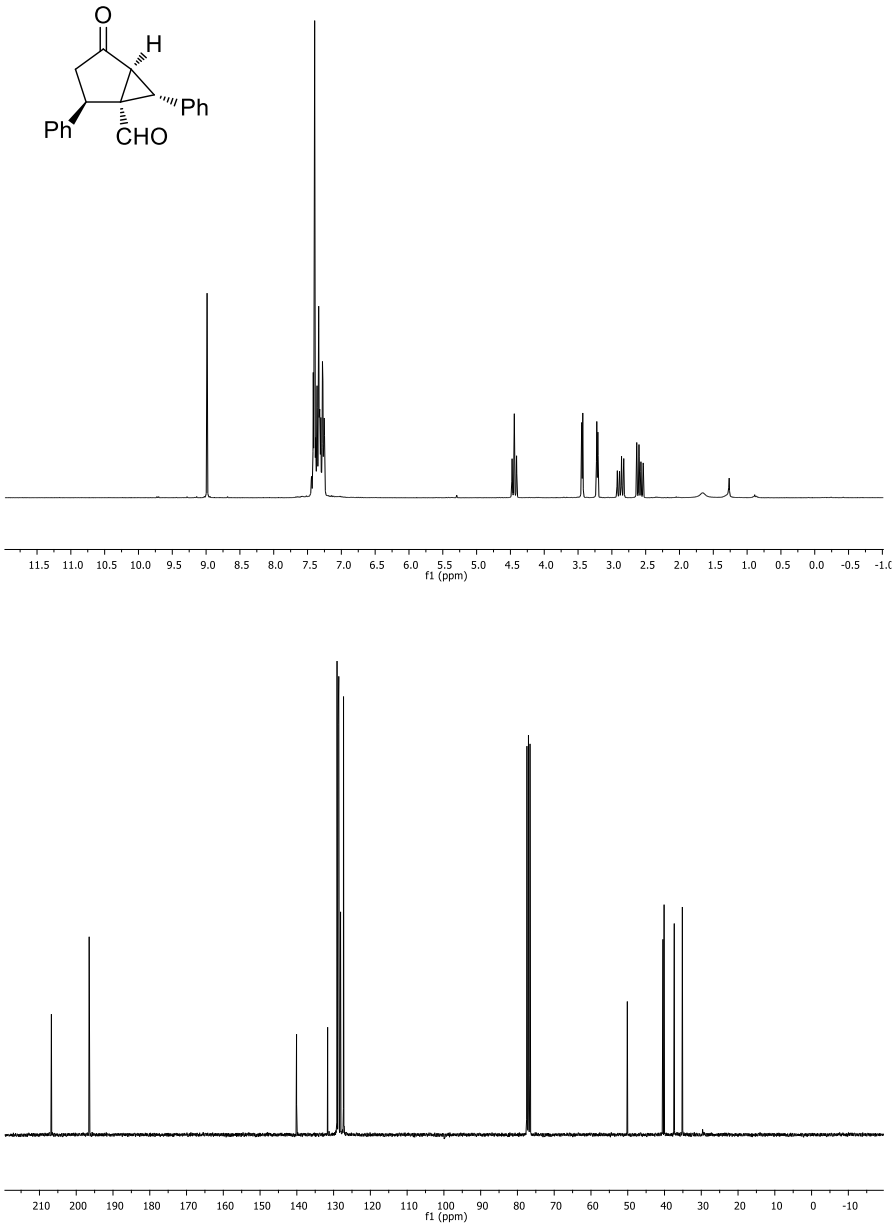
^{1}H-NMR and ^{13}C-NMR spectra of compound **12c**.



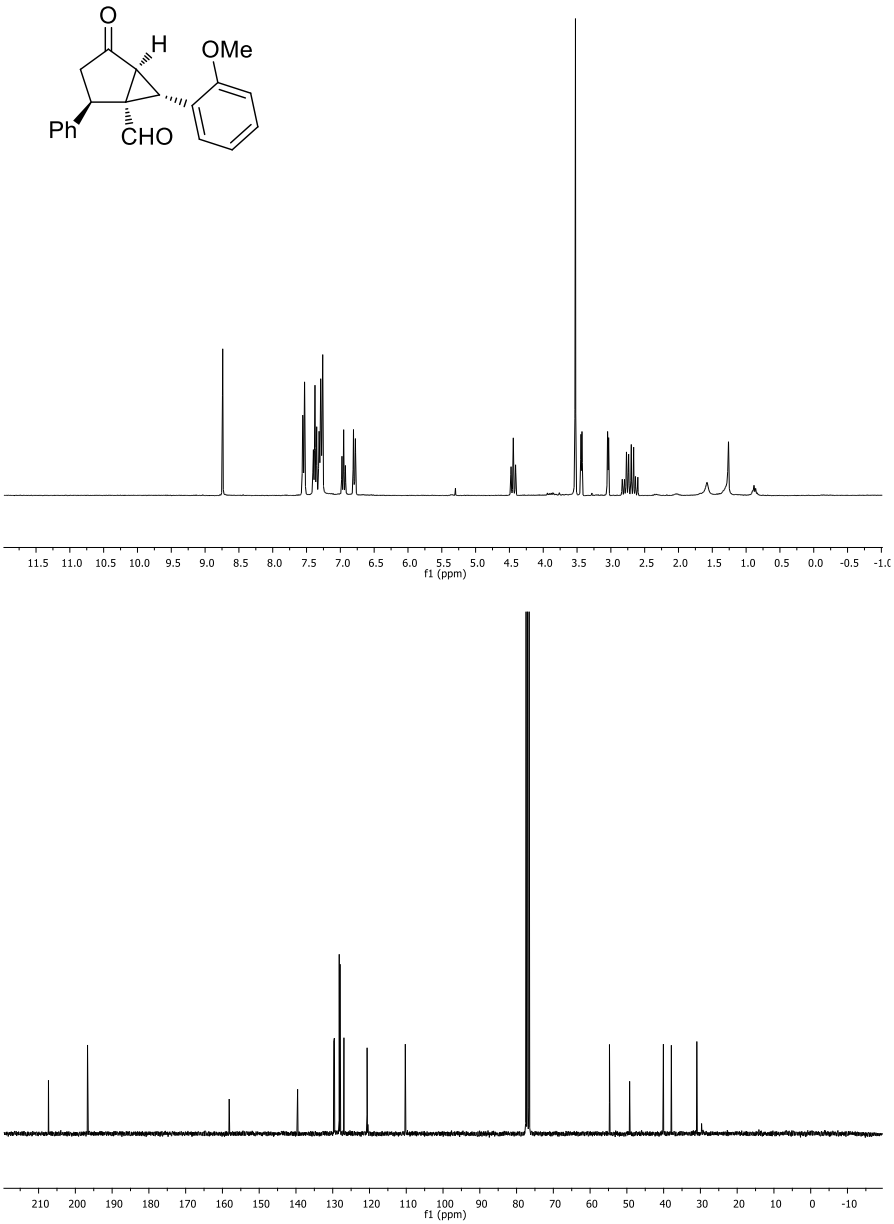
^{1}H-NMR and ^{13}C-NMR spectra of compound **14**.



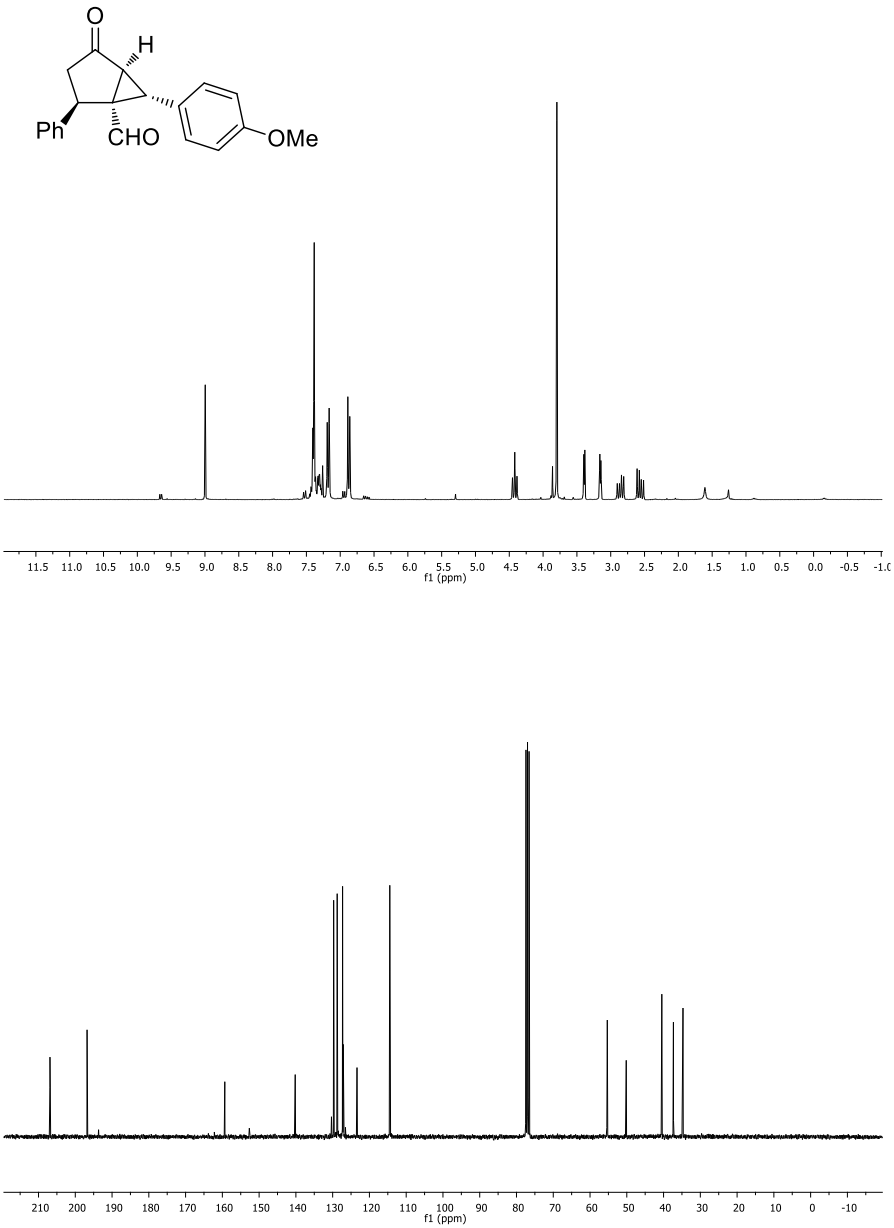
^{1}H-NMR and ^{13}C-NMR spectra of compound **15**.



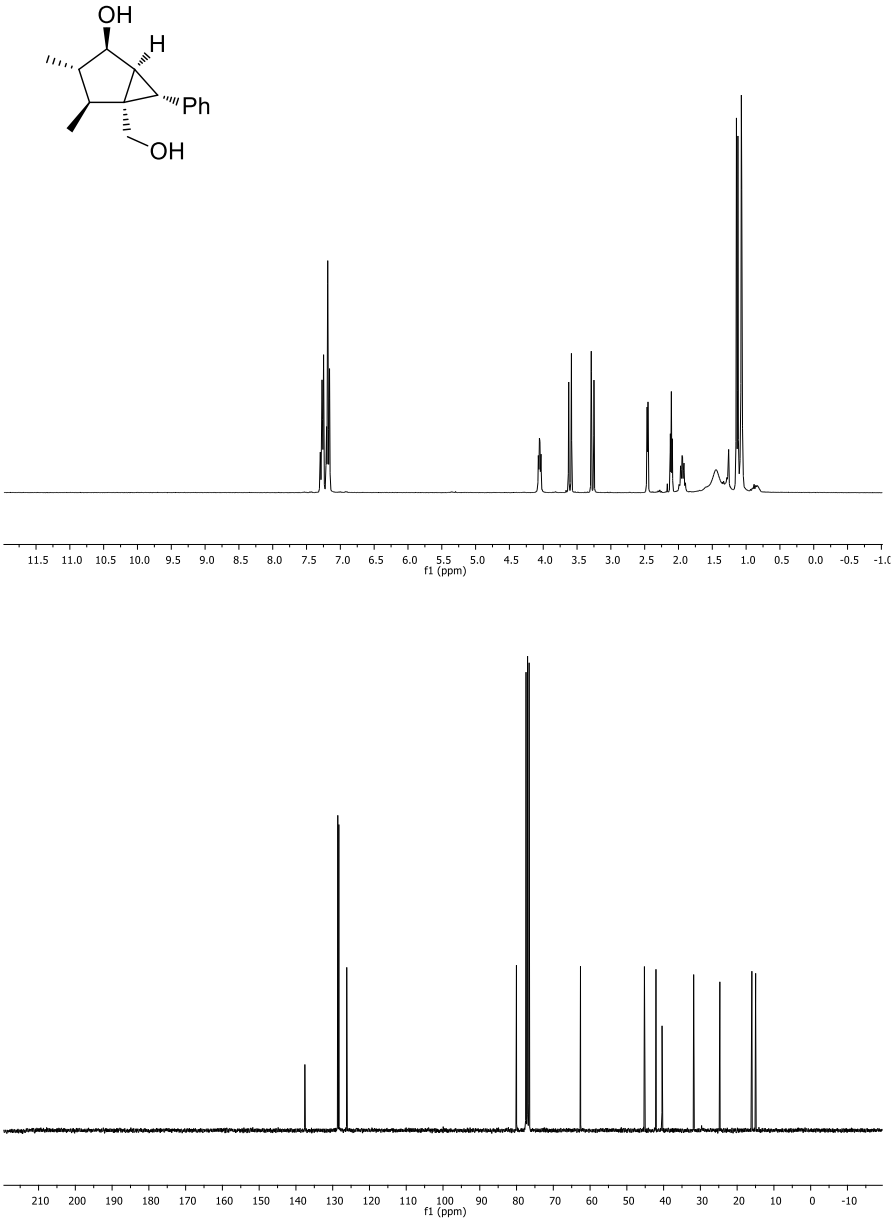
^{1}H-NMR and ^{13}C-NMR spectra of compound **16a**.



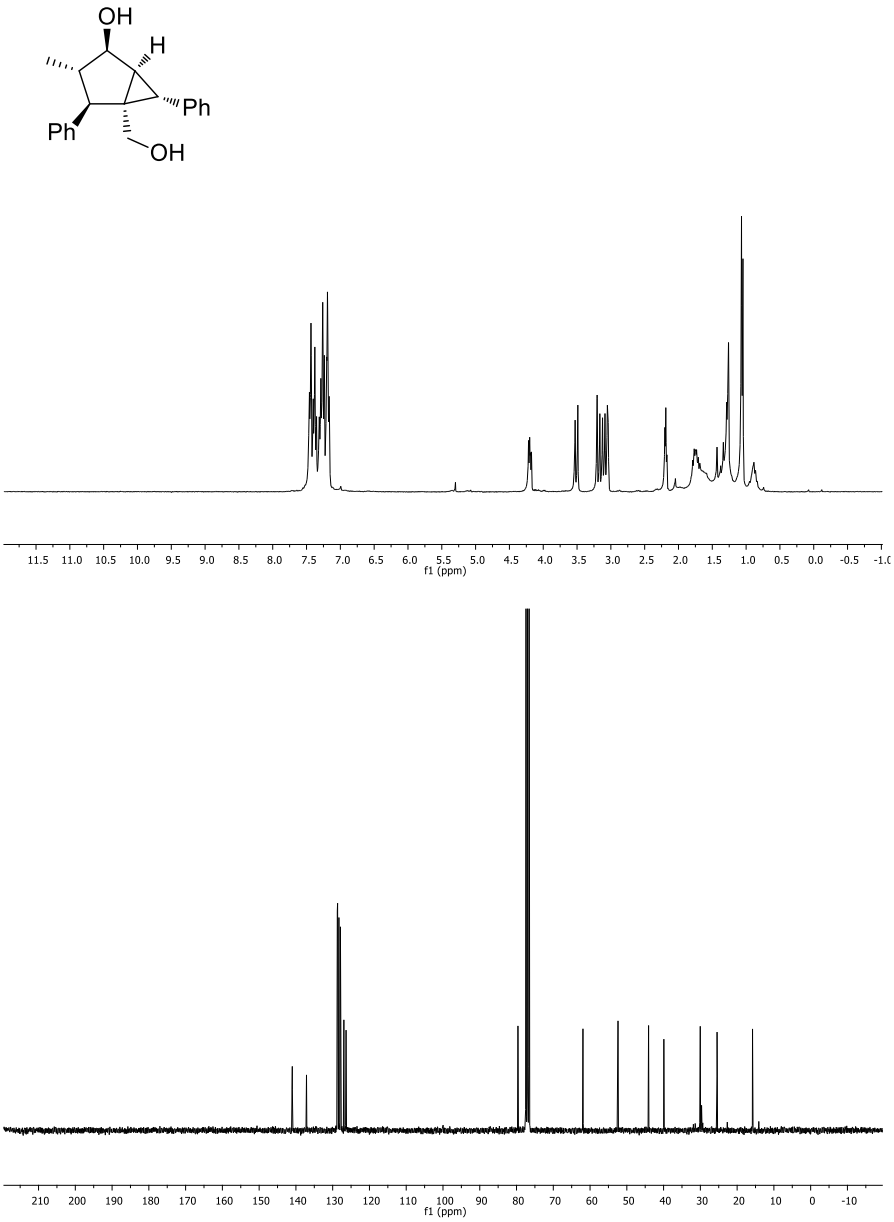
^{1}H-NMR and ^{13}C-NMR spectra of compound **16b**.



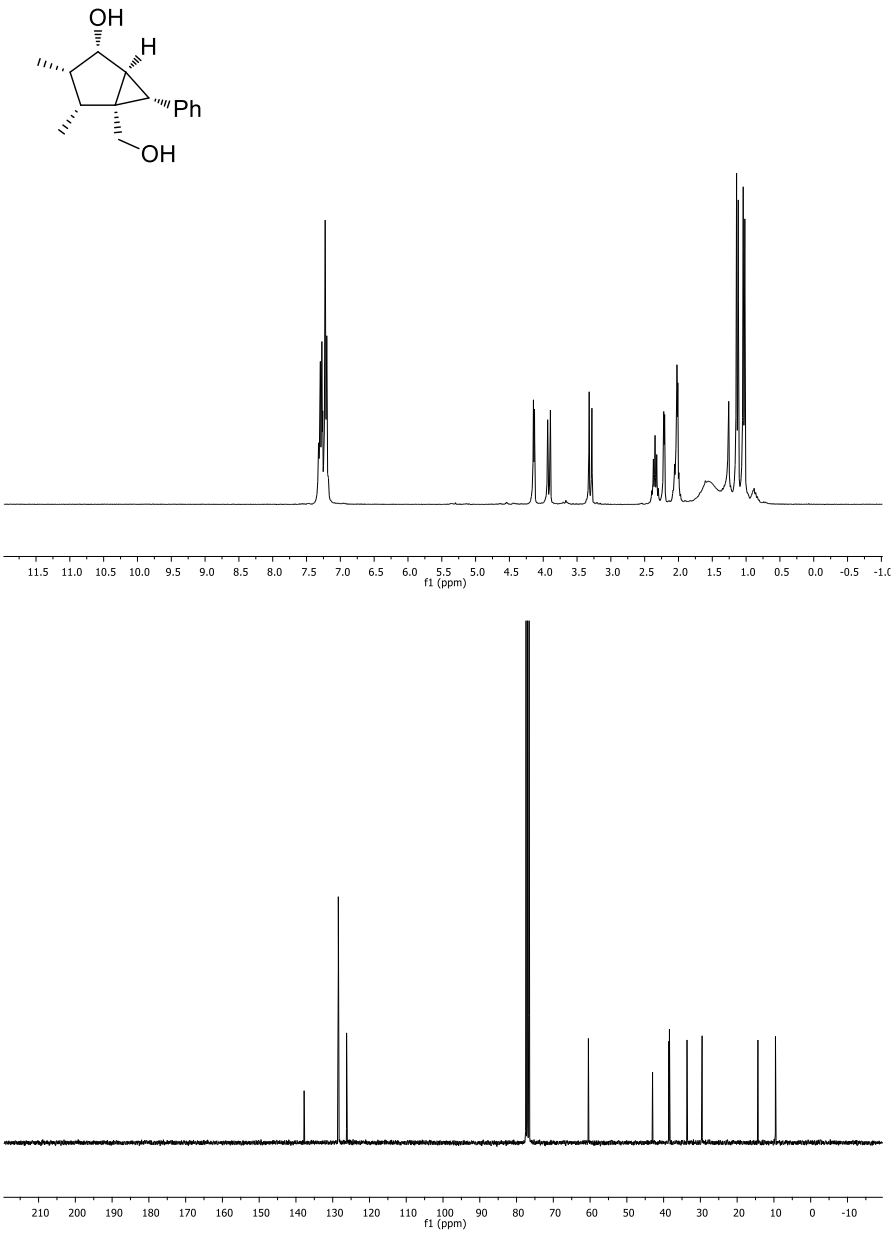
^{1}H-NMR and ^{13}C-NMR spectra of compound **16c**.



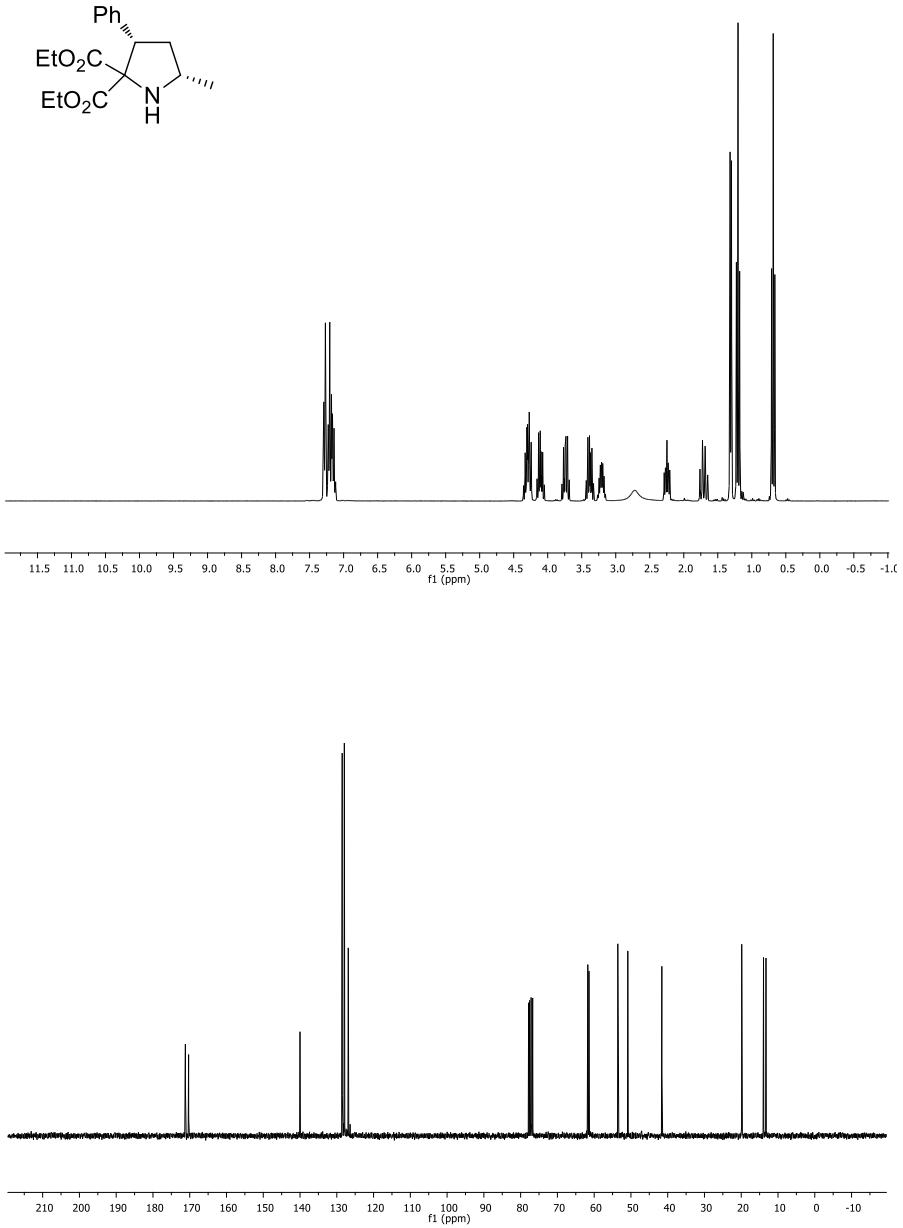
^{1}H-NMR and ^{13}C-NMR spectra of compound **17a**.



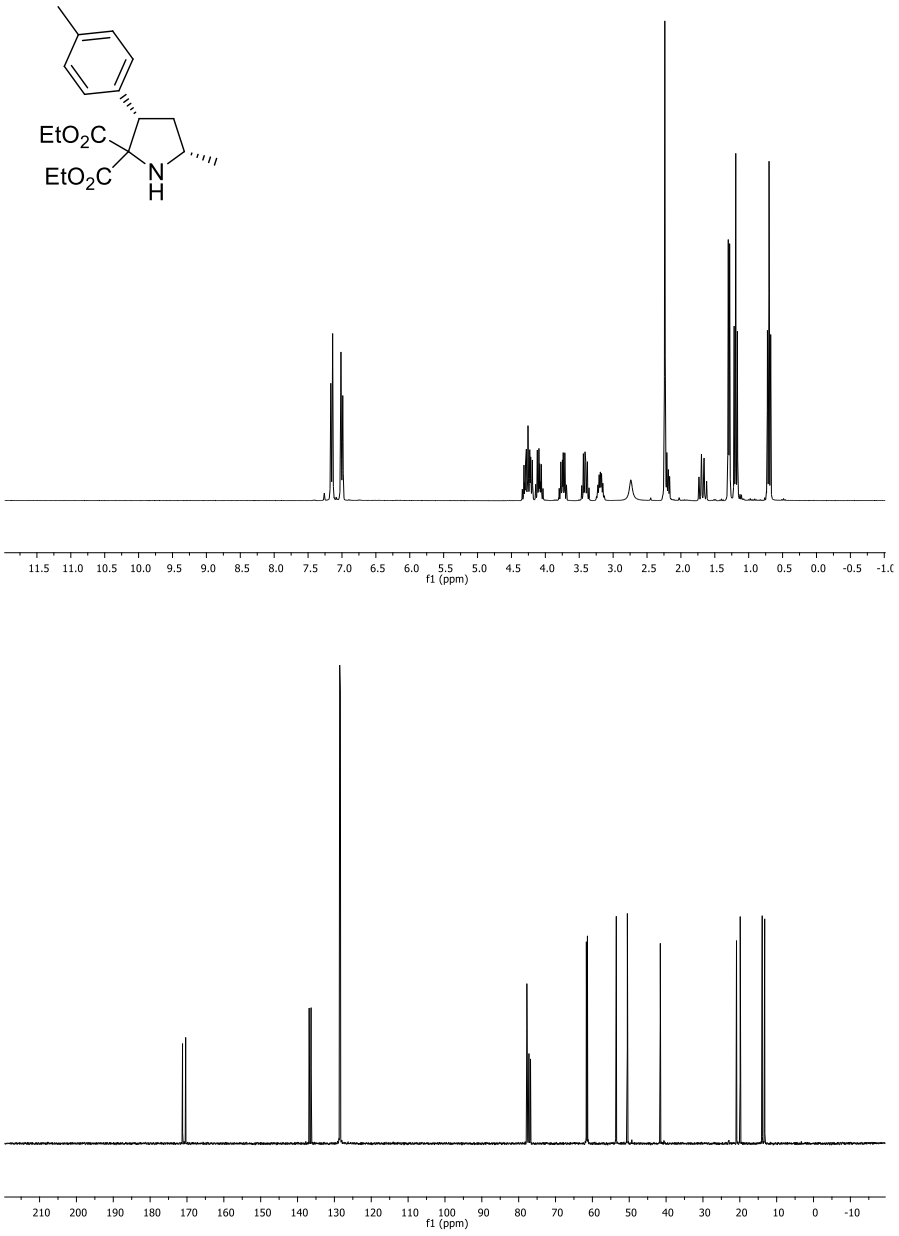
^{1}H-NMR and ^{13}C-NMR spectra of compound **17p**.



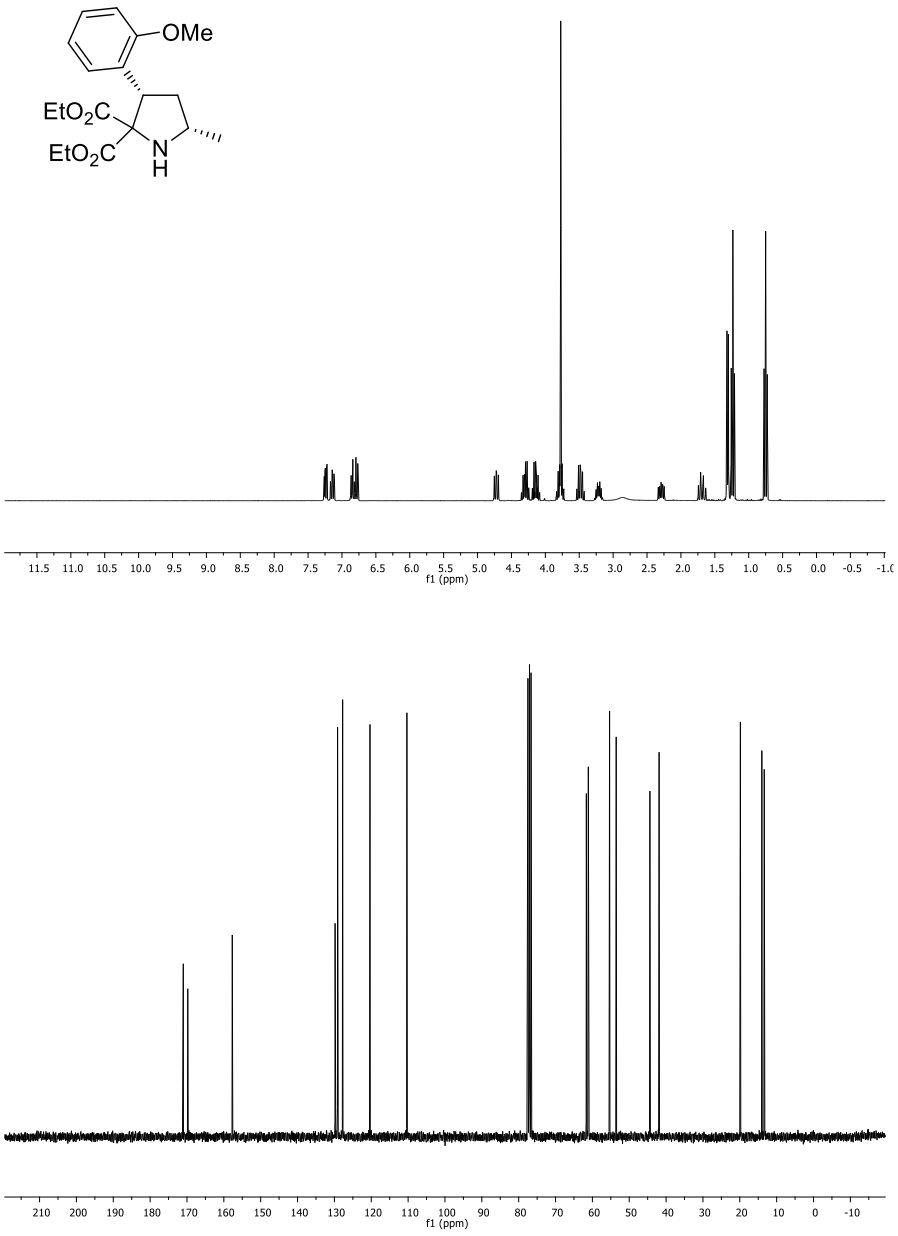
^{1}H-NMR and ^{13}C-NMR spectra of compound **18**.



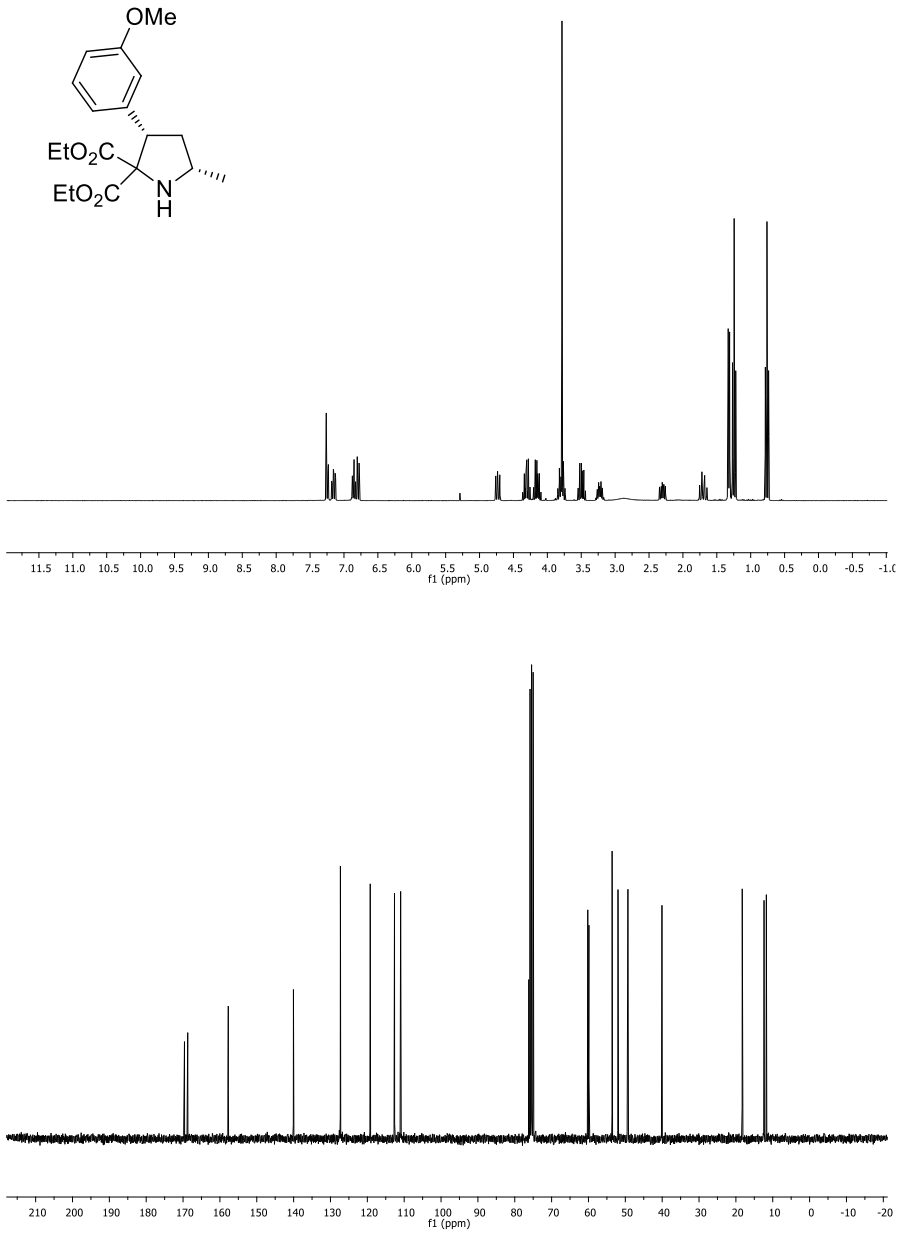
^{1}H-NMR and ^{13}C-NMR spectra of compound **22a**.



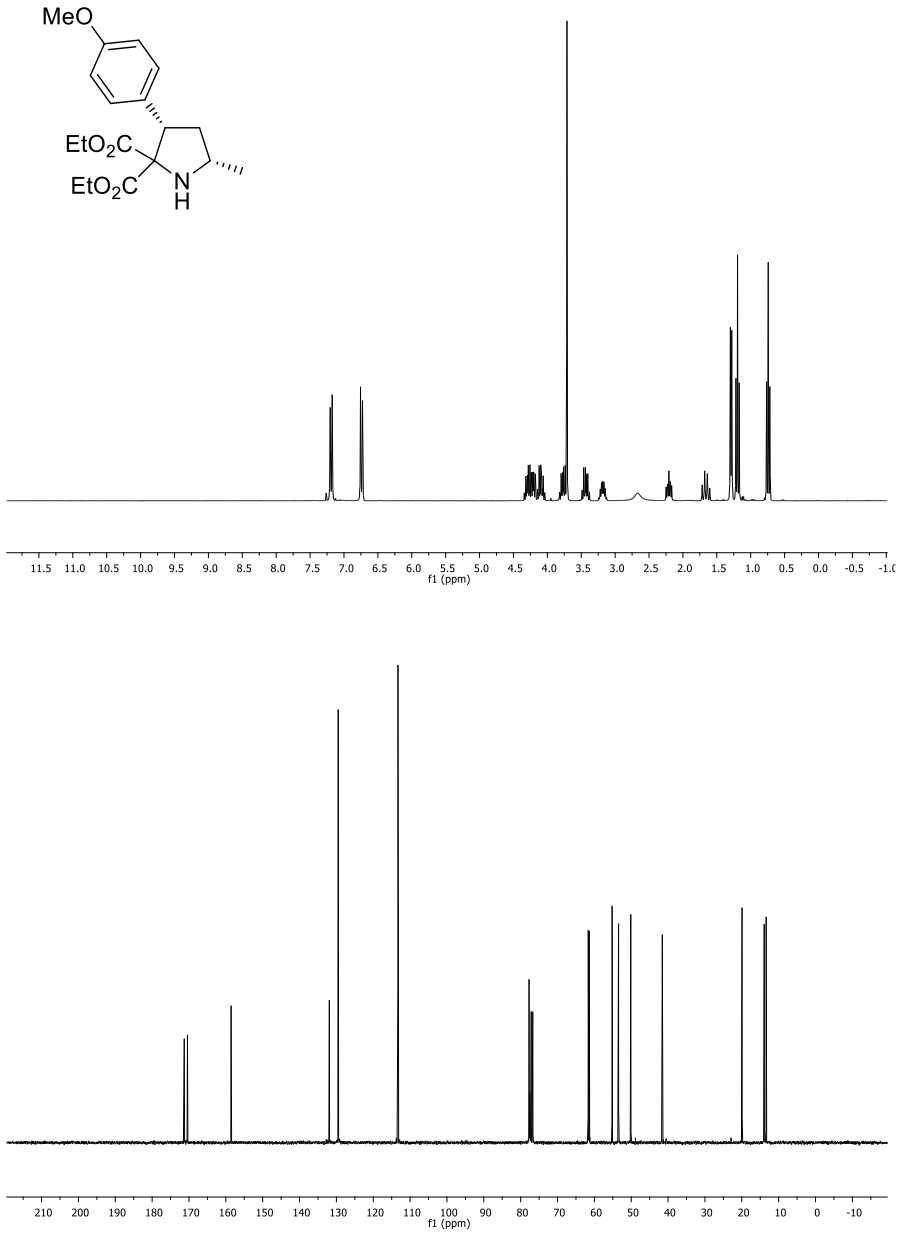
^{1}H-NMR and ^{13}C-NMR spectra of compound **22b**.



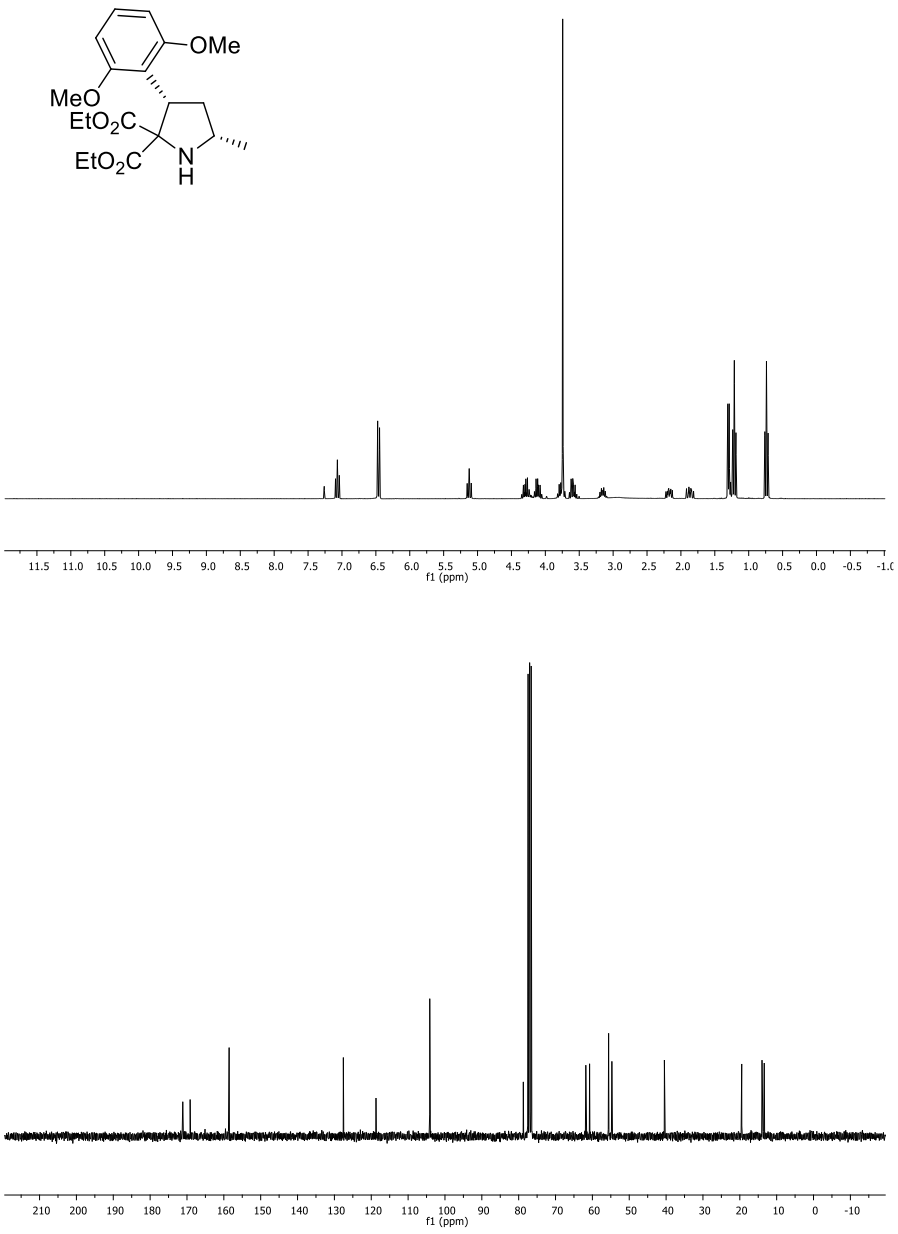
^{1}H-NMR and ^{13}C-NMR spectra of compound **22c**.



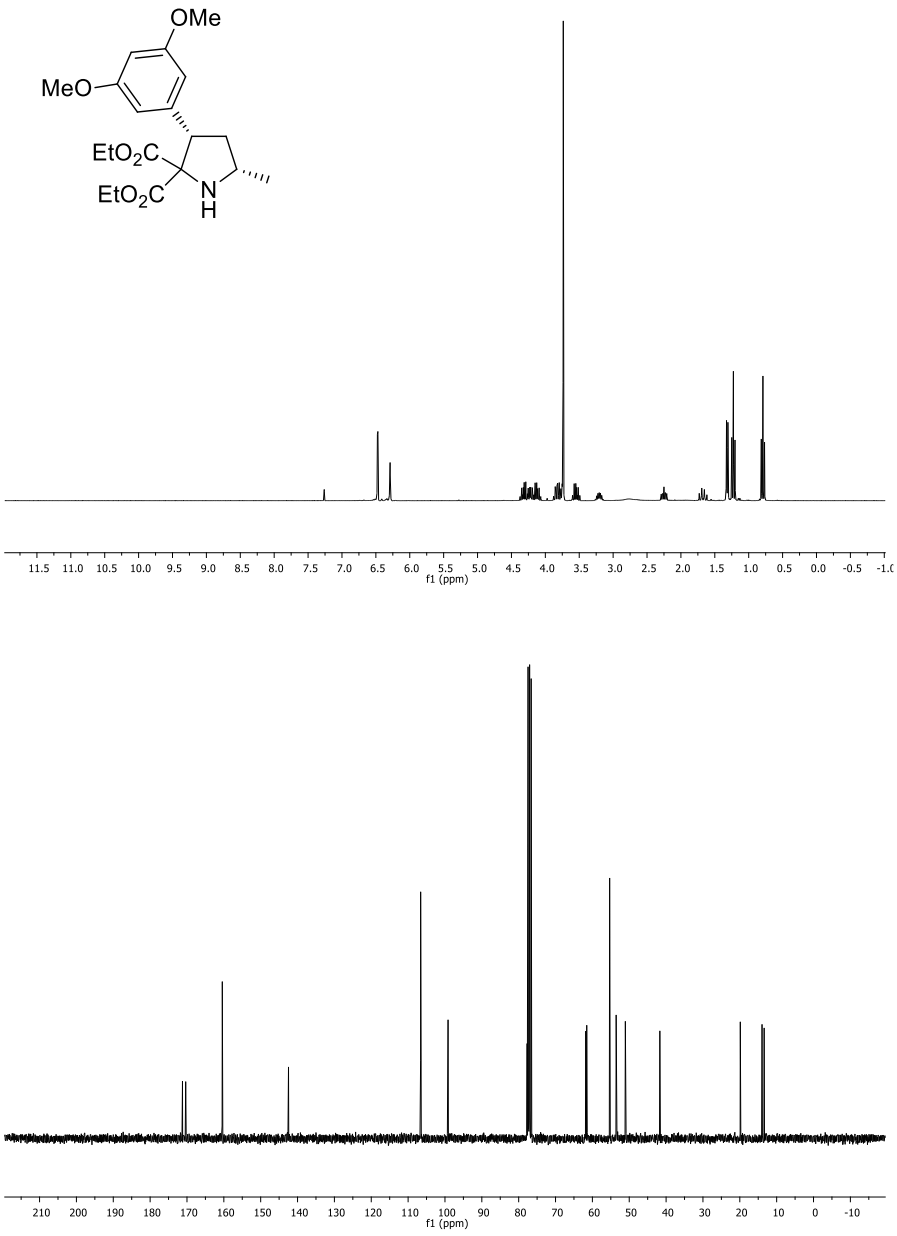
^{1}H-NMR and ^{13}C-NMR spectra of compound **22d**.



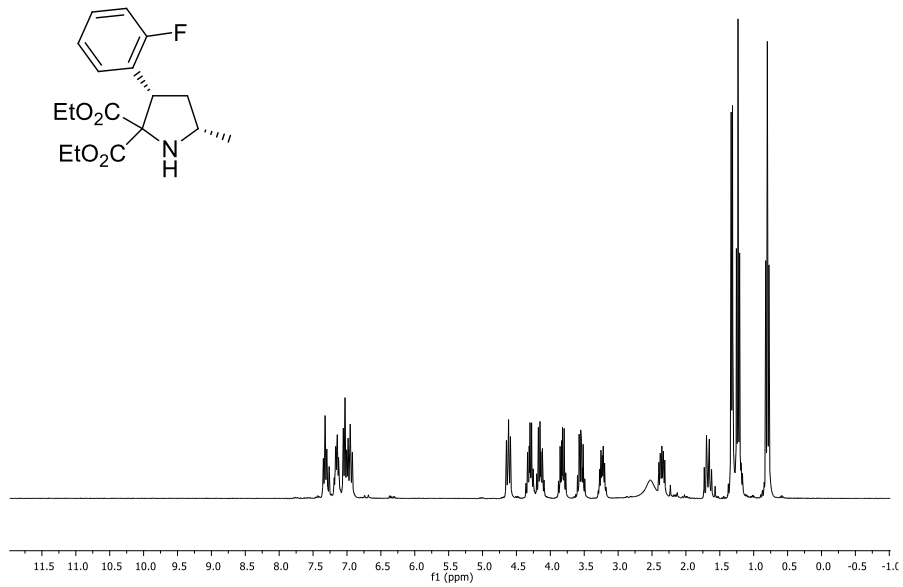
^{1}H-NMR and ^{13}C-NMR spectra of compound **22e**.

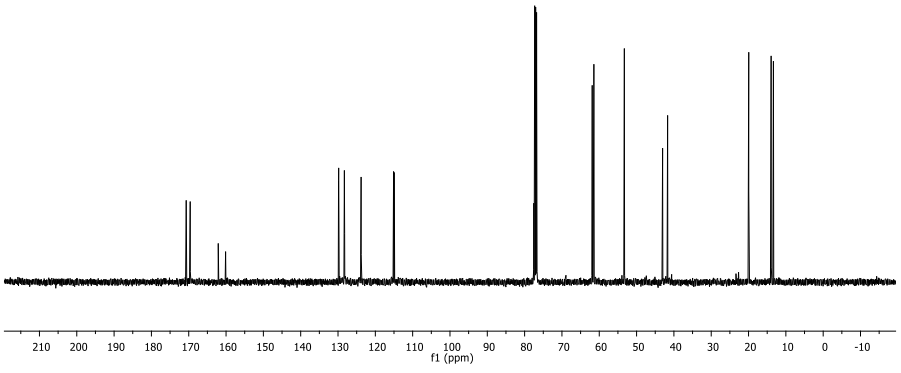


^{1}H-NMR and ^{13}C-NMR spectra of compound **22f**.

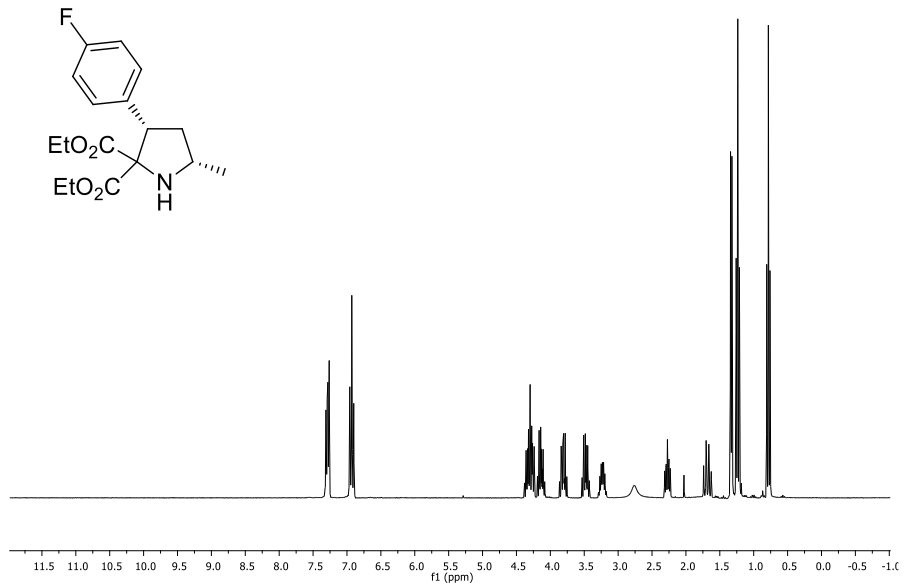


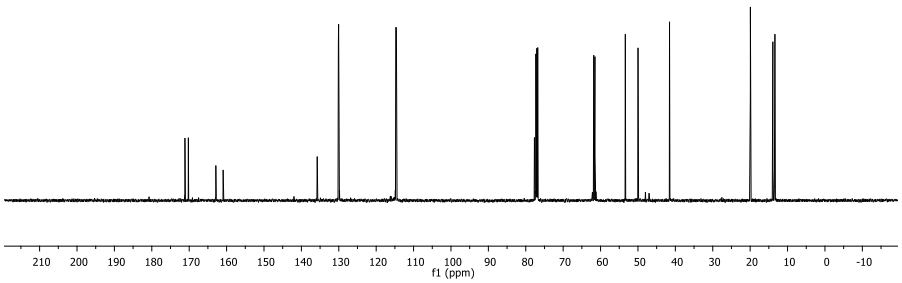
^{1}H-NMR and ^{13}C-NMR spectra of compound **22g**.



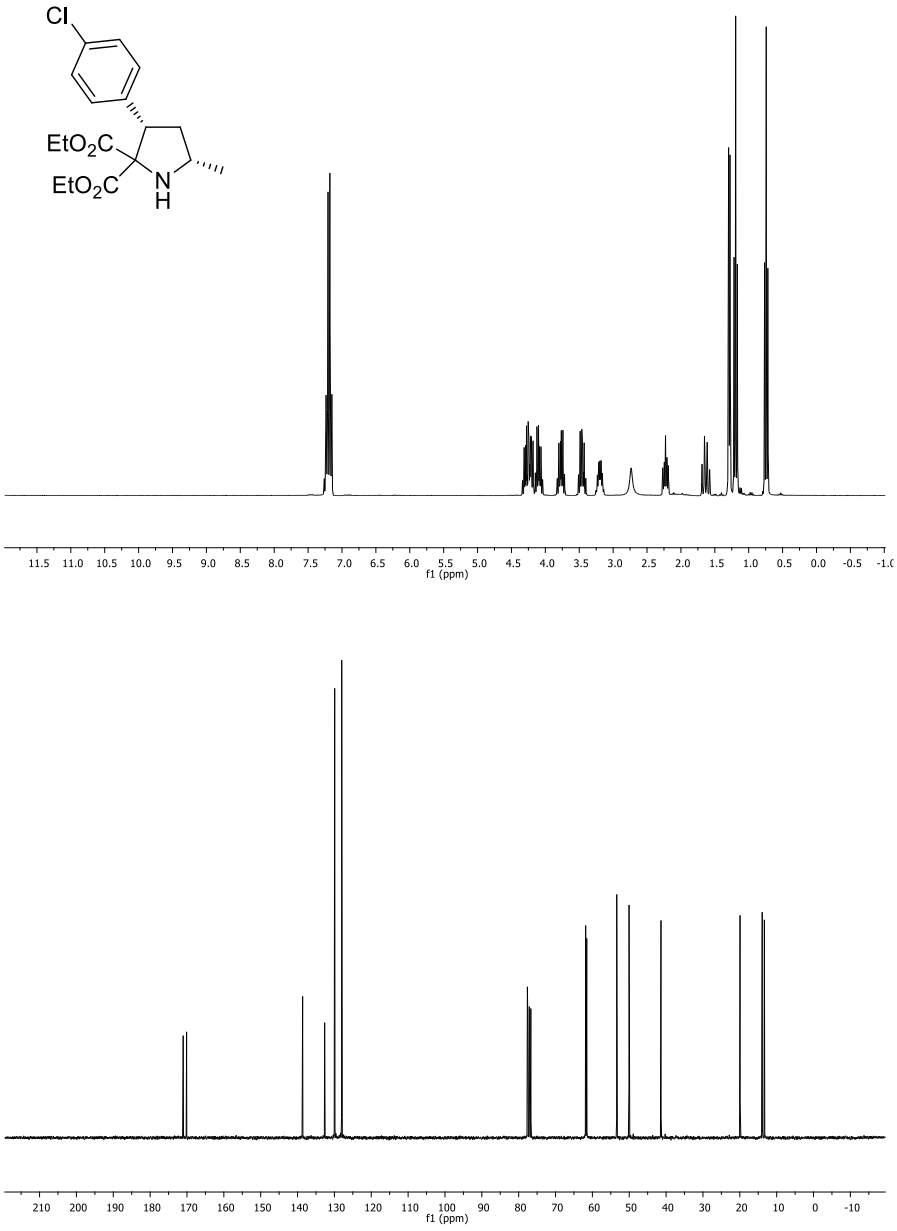


^{1}H-NMR and ^{13}C-NMR spectra of compound **22h**.

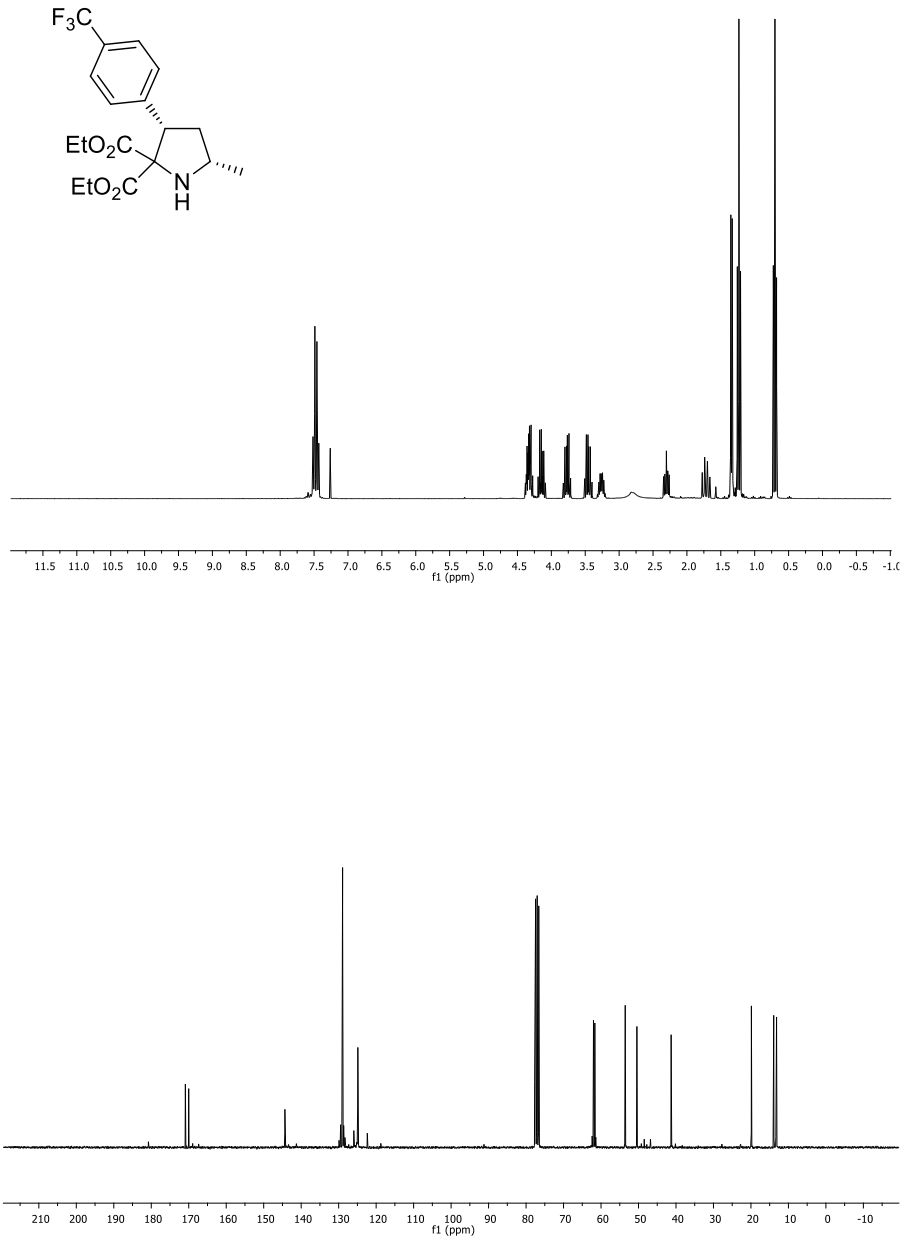




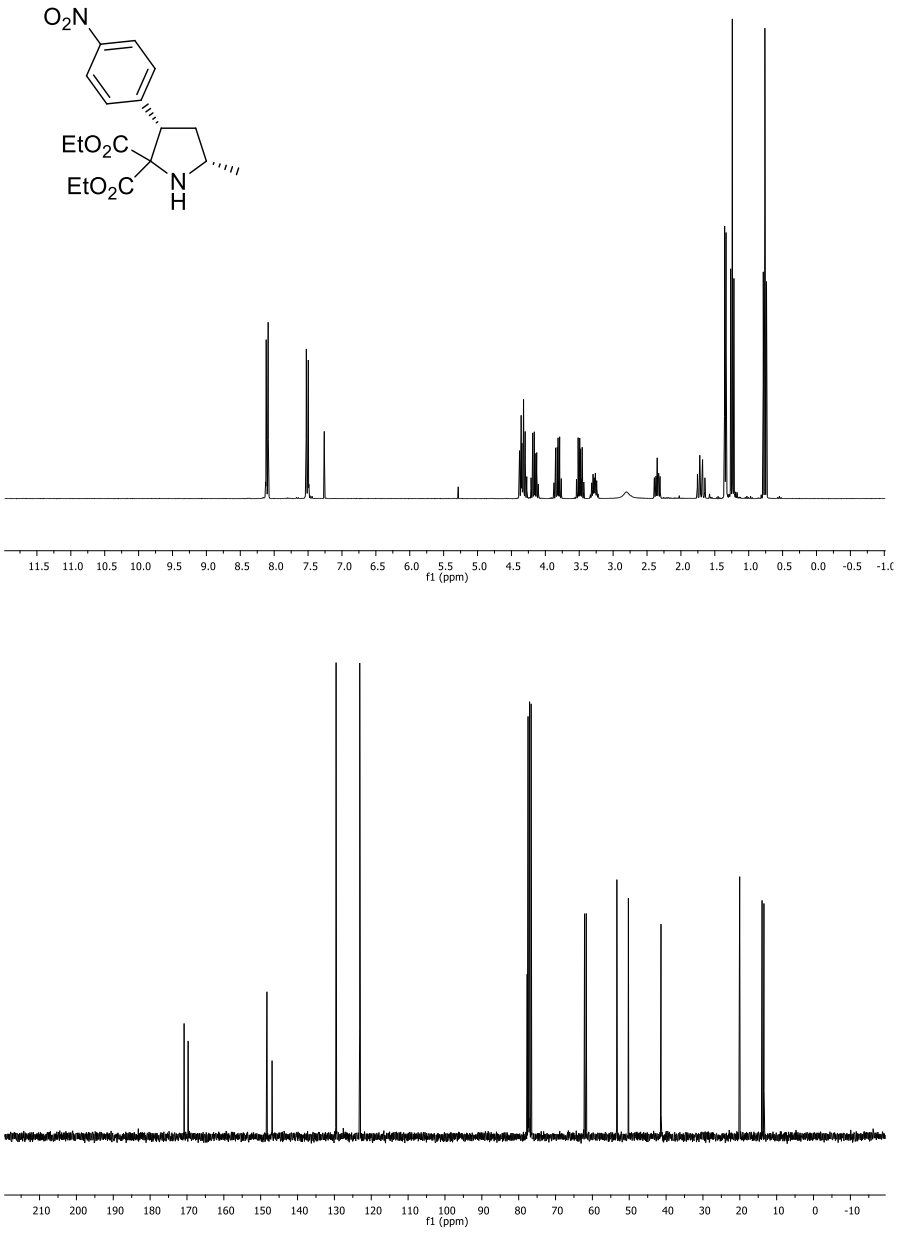
^{1}H-NMR and ^{13}C-NMR spectra of compound **22i**.



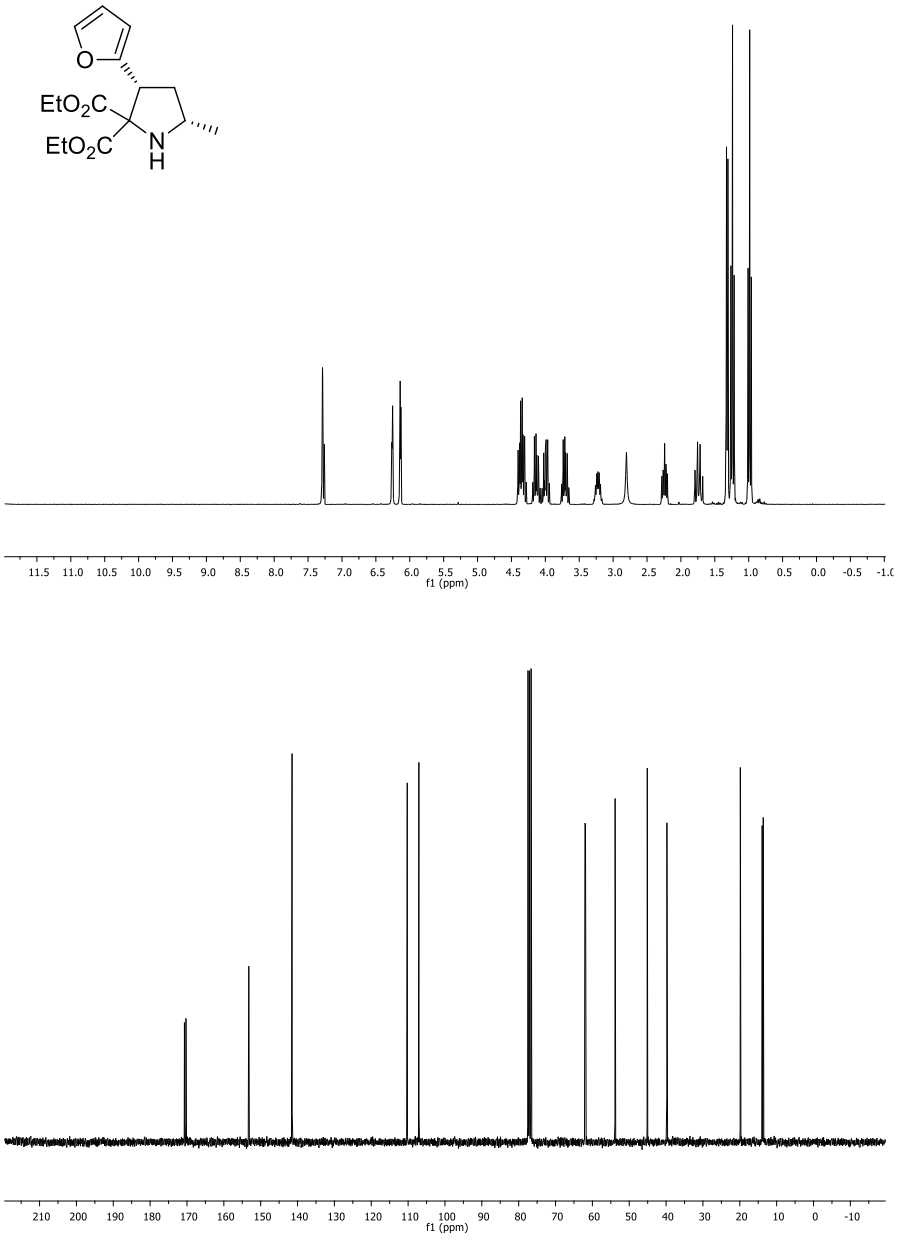
^{1}H-NMR and ^{13}C-NMR spectra of compound **22j**.



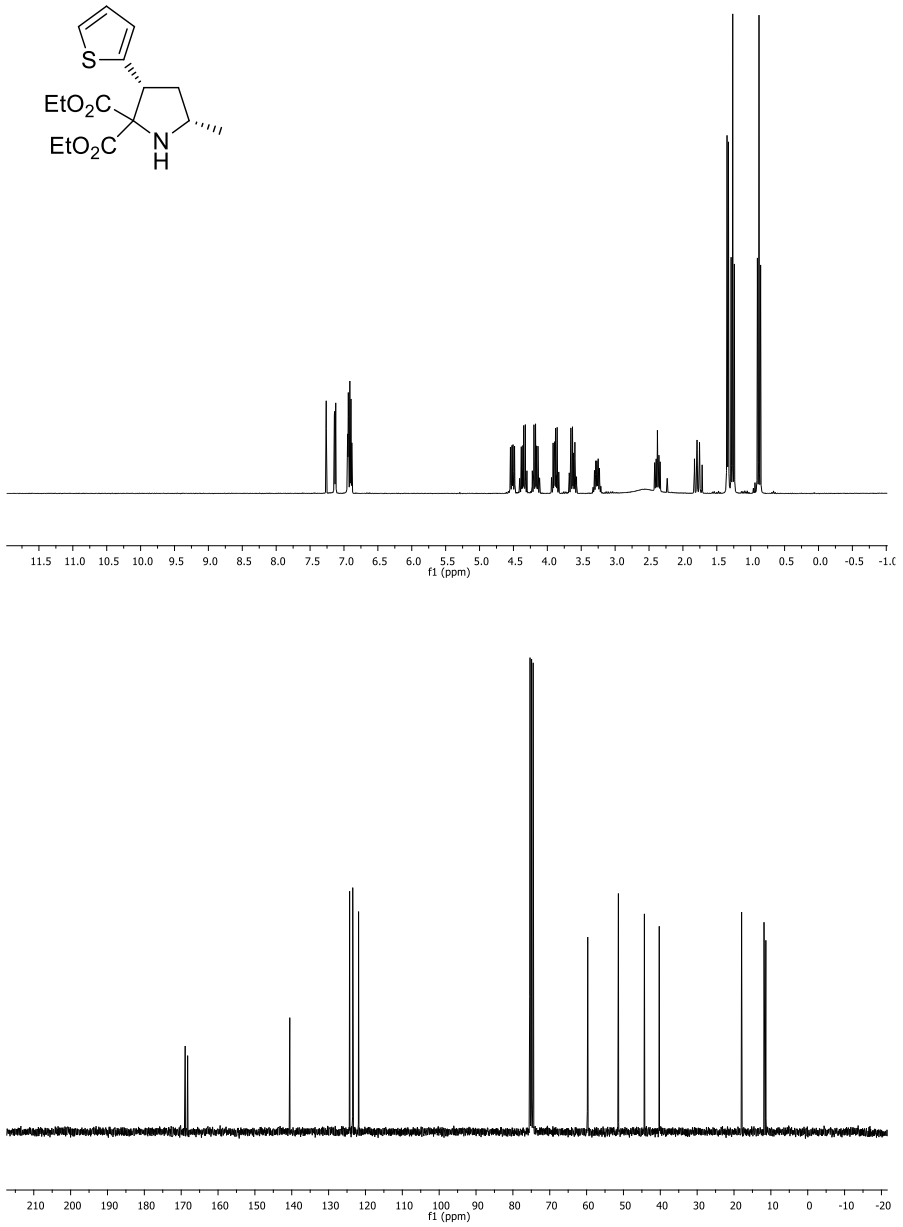
^{1}H-NMR and ^{13}C-NMR spectra of compound **22k**.



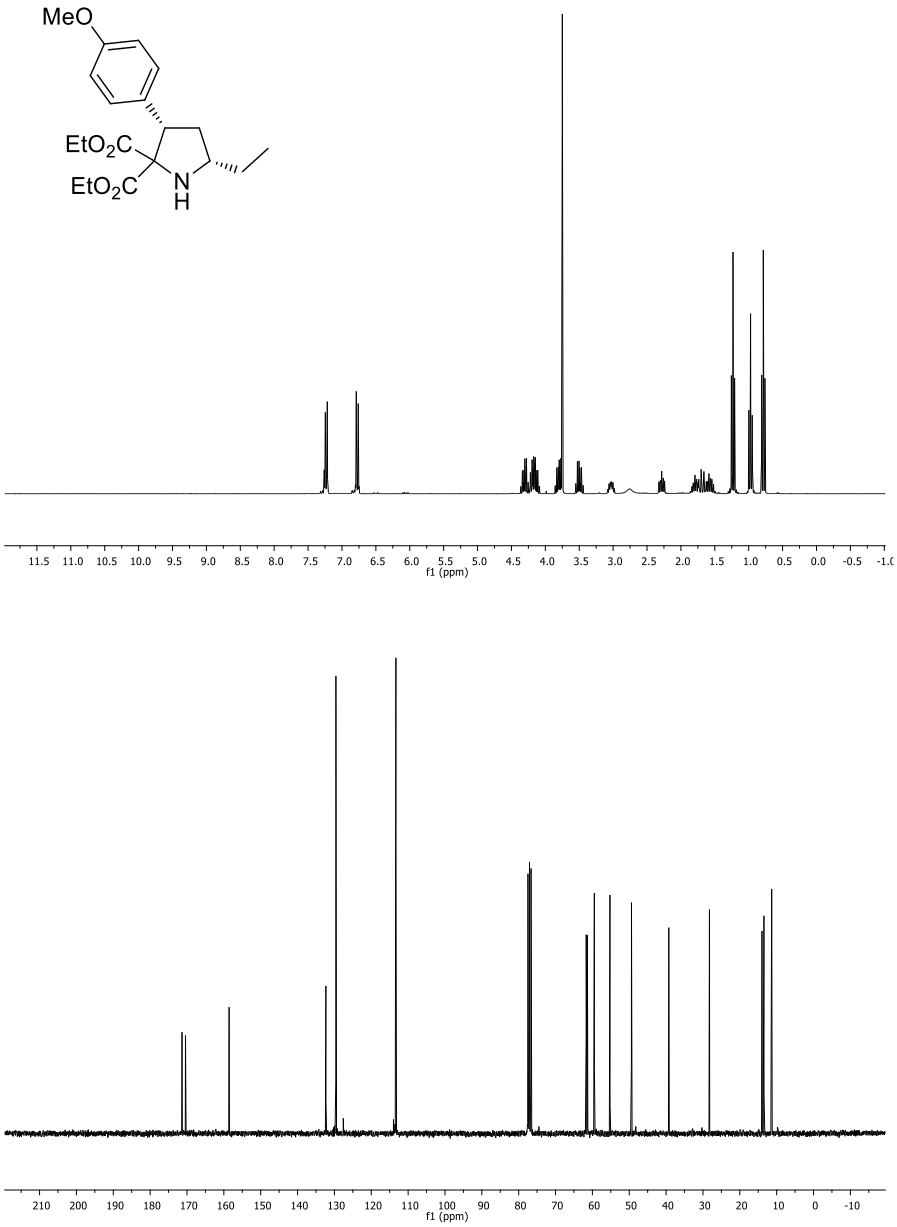
^{1}H-NMR and ^{13}C-NMR spectra of compound **22l**.



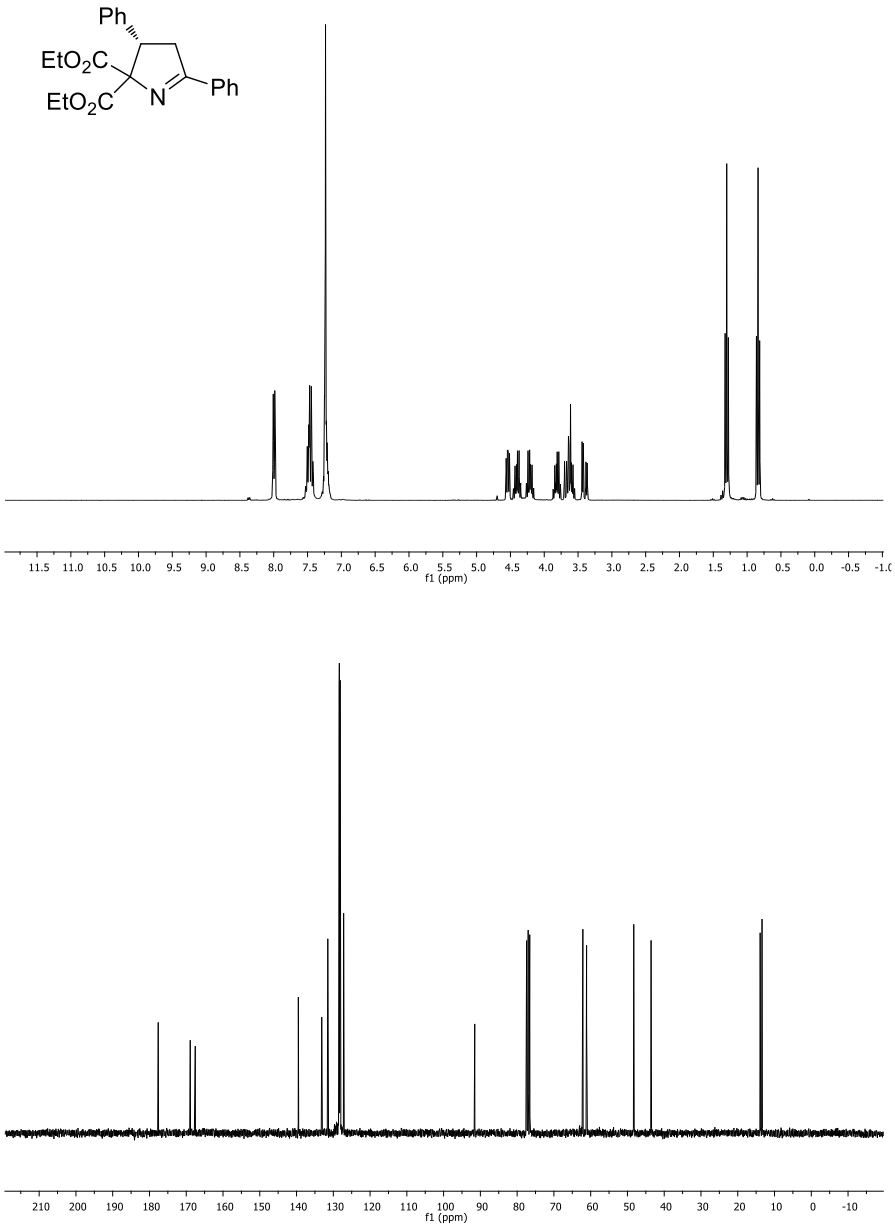
^{1}H-NMR and ^{13}C-NMR spectra of compound **22m**.



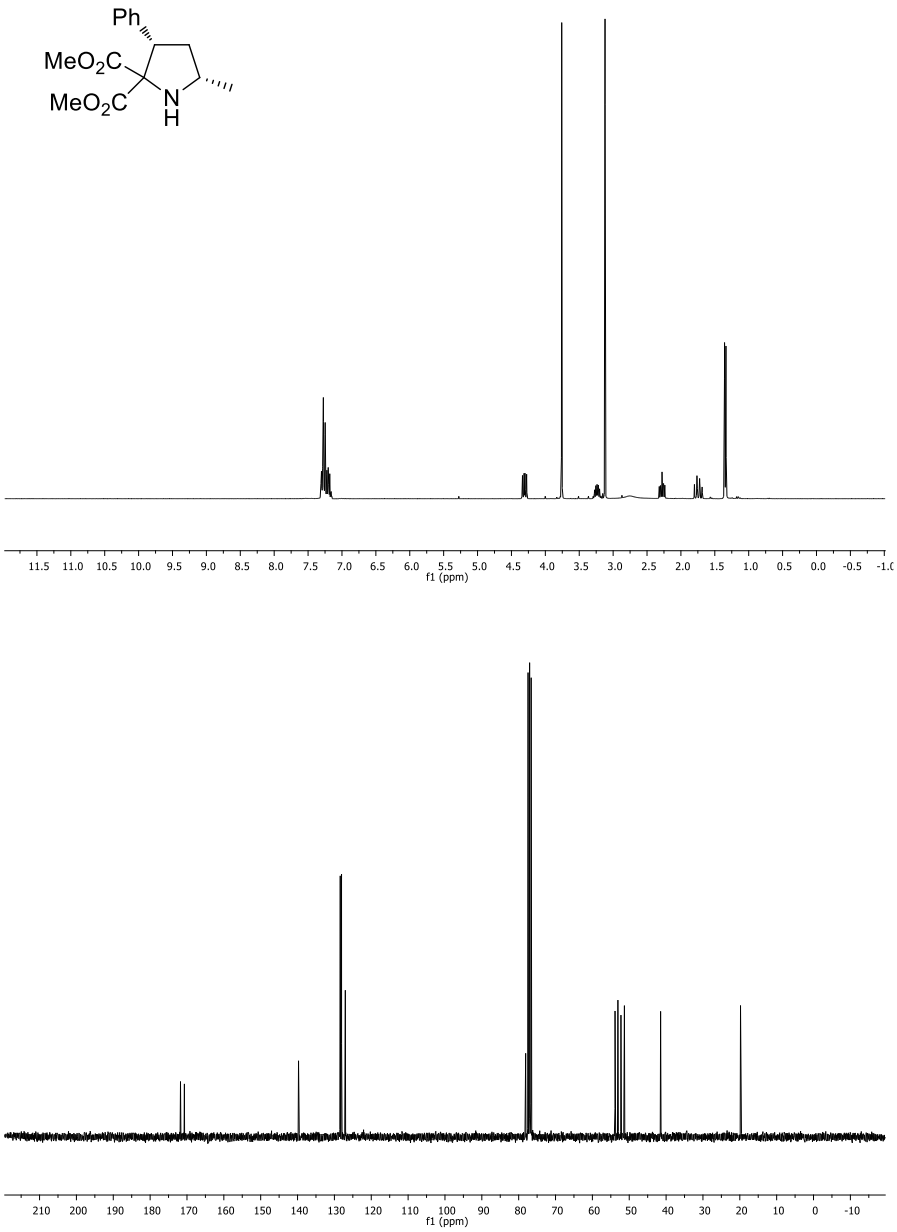
^{1}H-NMR and ^{13}C-NMR spectra of compound **22n**.



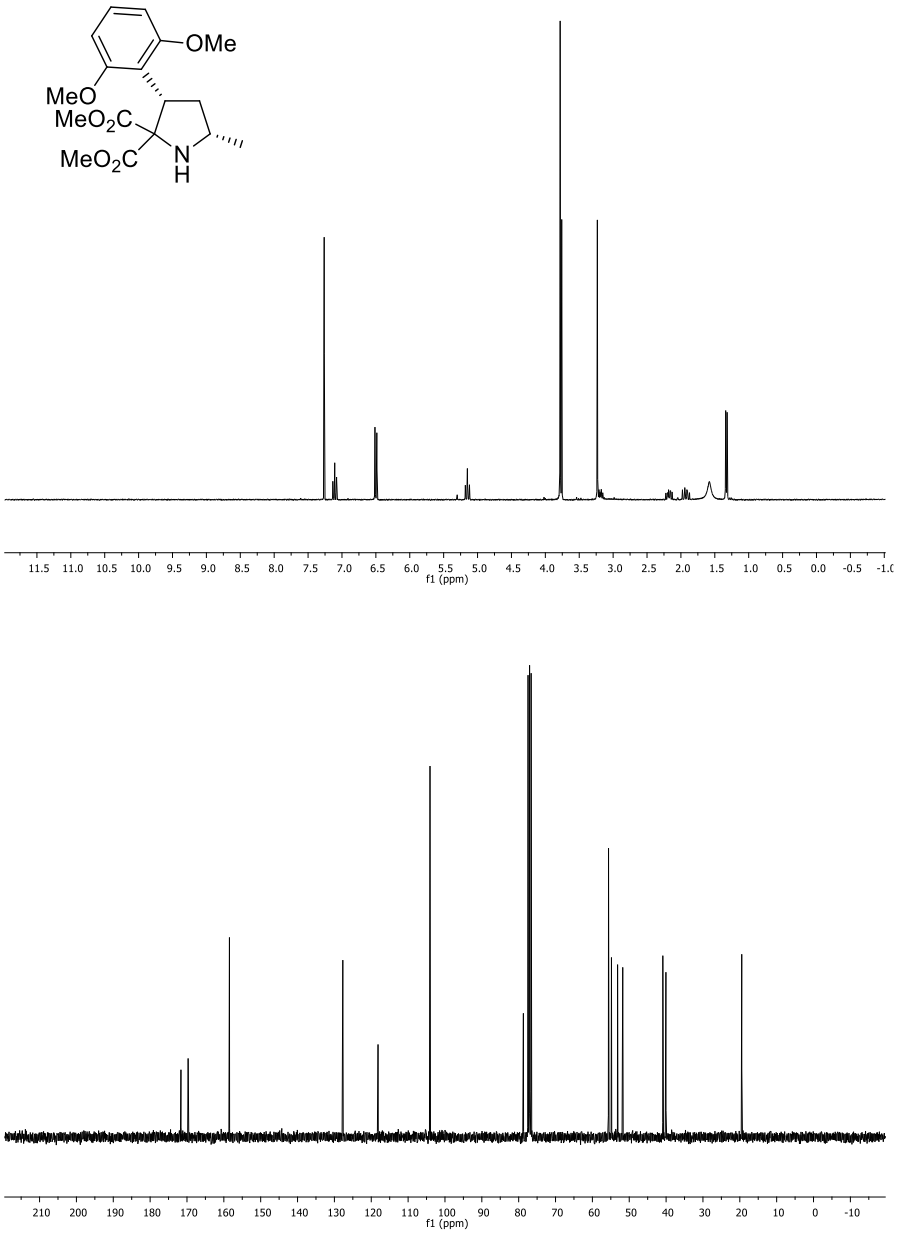
^{1}H-NMR and ^{13}C-NMR spectra of compound **22o**.



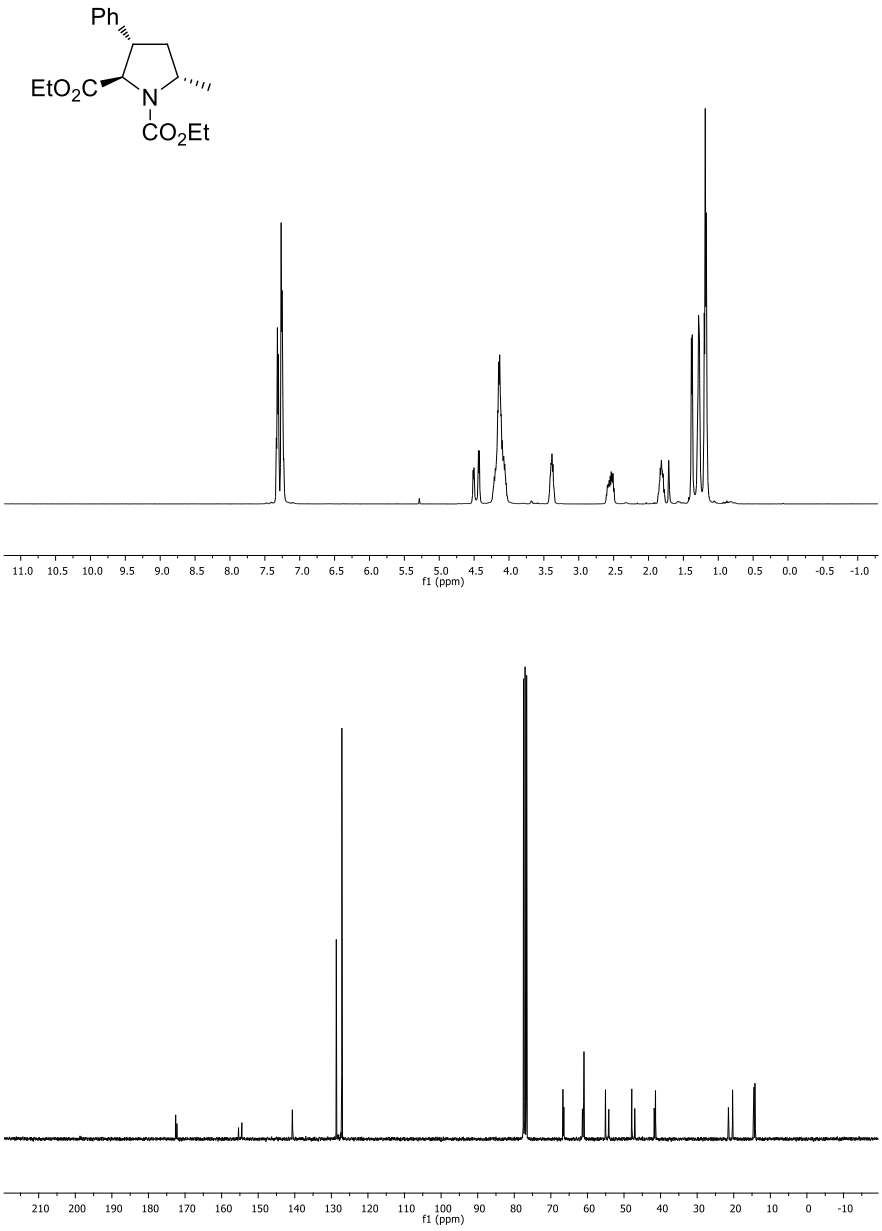
^{1}H-NMR and ^{13}C-NMR spectra of compound **22p**.



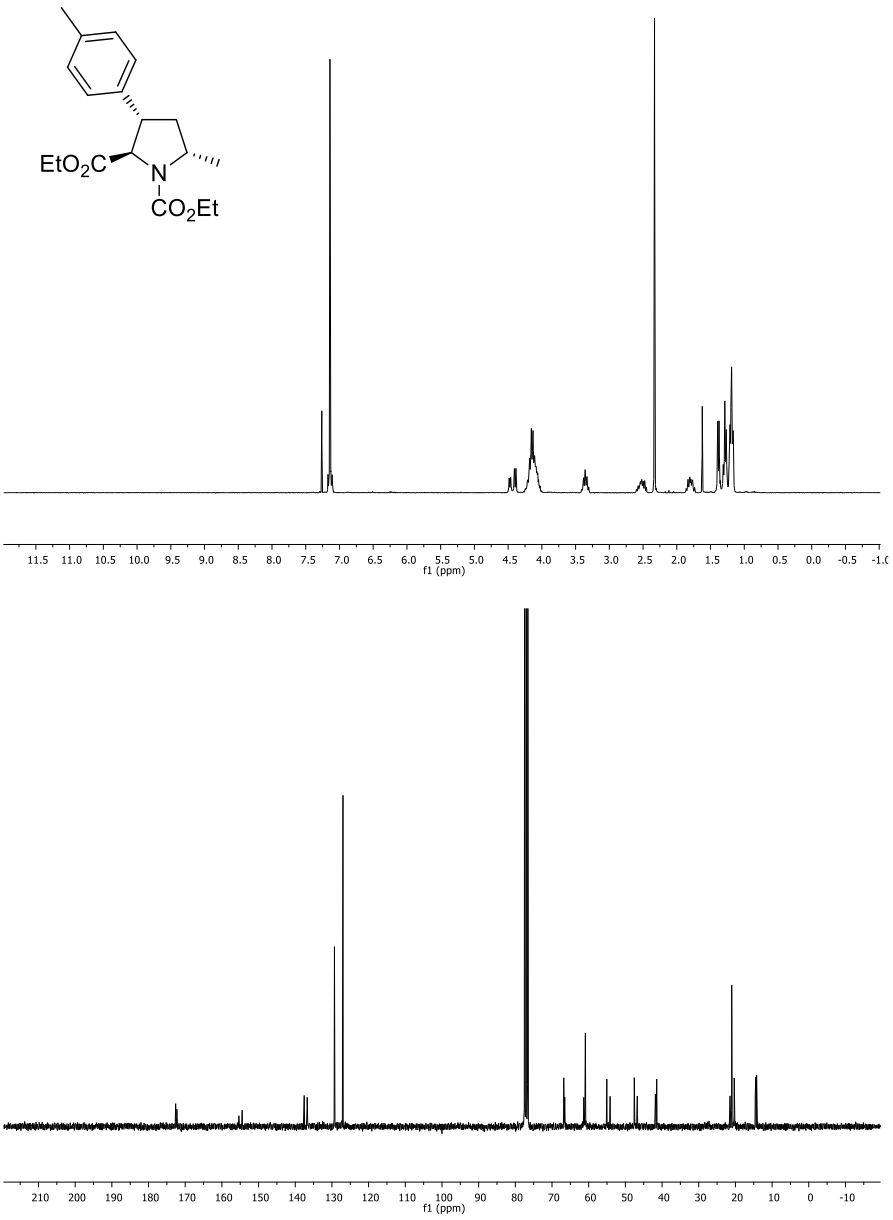
^{1}H-NMR and ^{13}C-NMR spectra of compound **22q**.



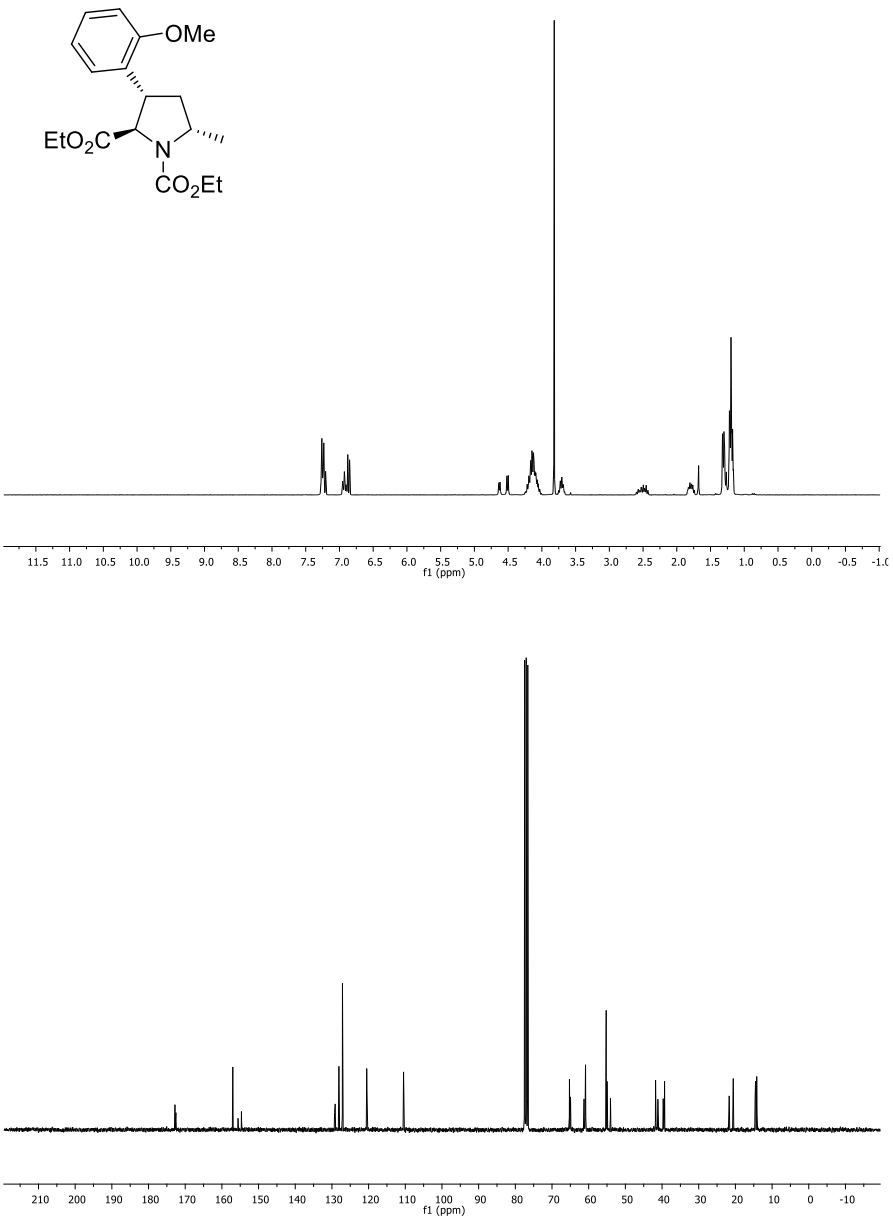
^{1}H-NMR and ^{13}C-NMR spectra of compound **22r**.



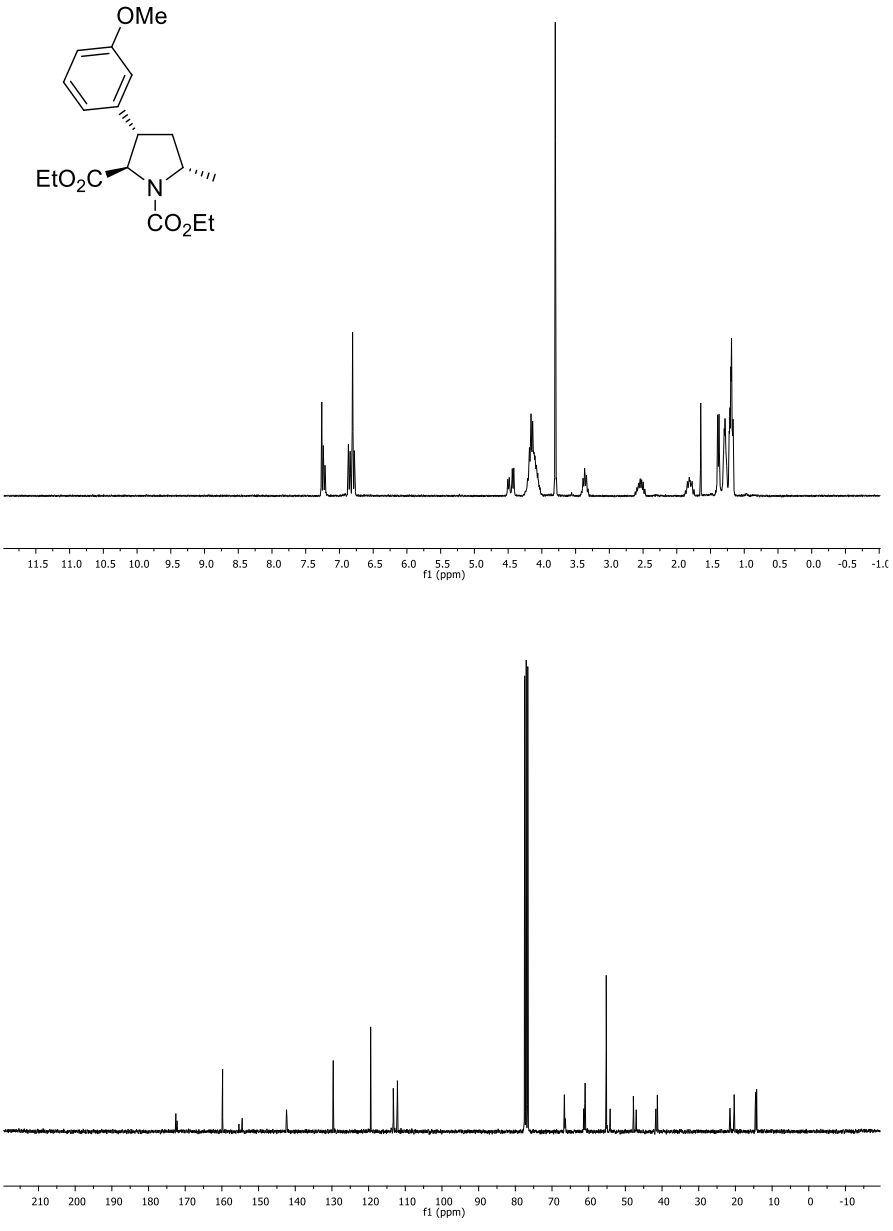
^{1}H-NMR and ^{13}C-NMR spectra of compound **23a**.



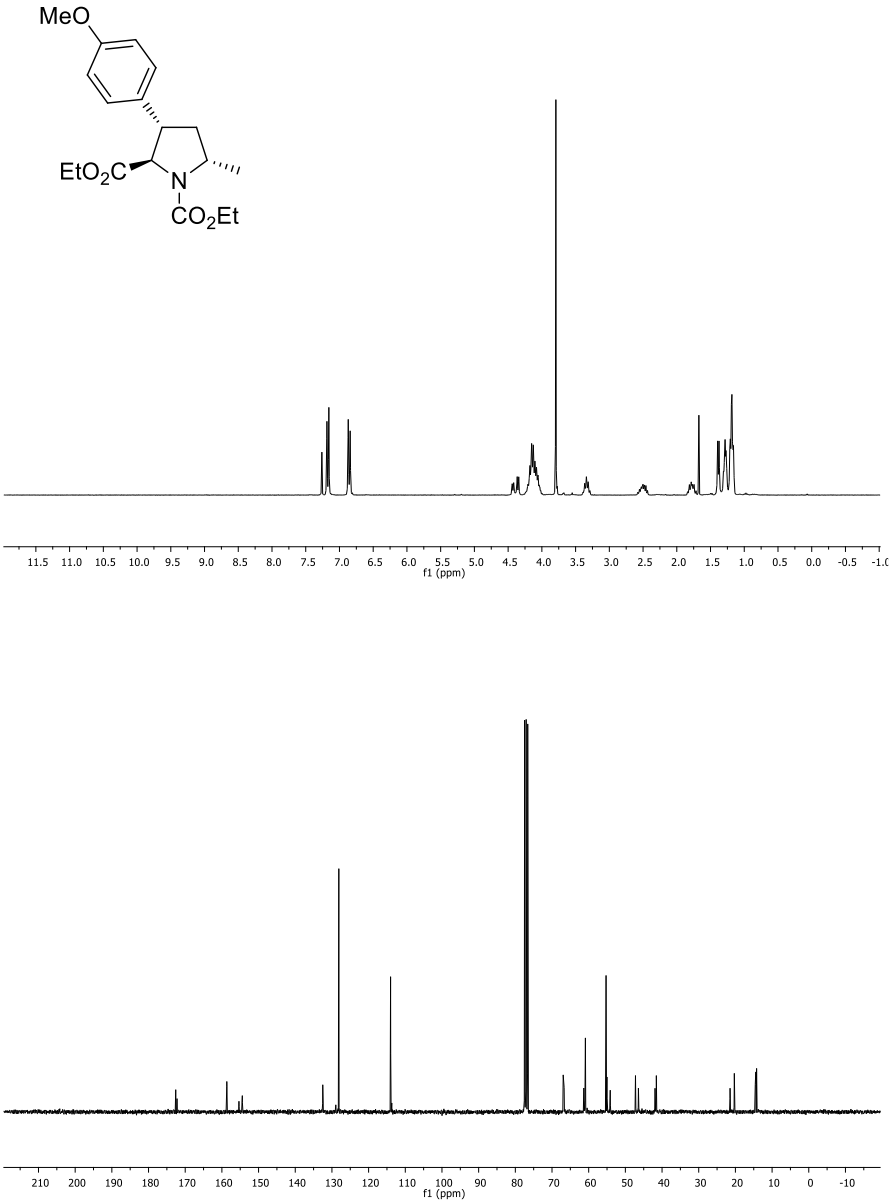
^{1}H-NMR and ^{13}C-NMR spectra of compound **23b**.



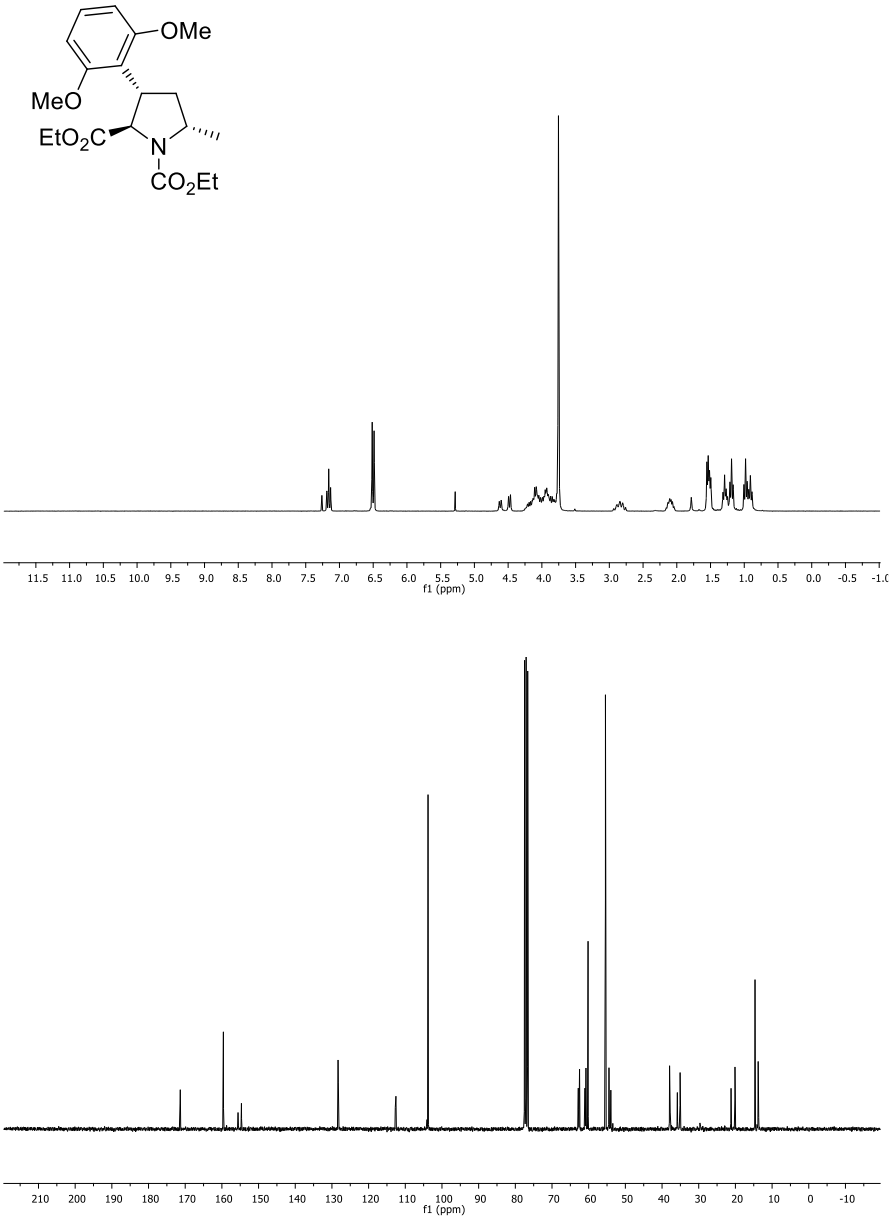
^{1}H-NMR and ^{13}C-NMR spectra of compound **23c**.



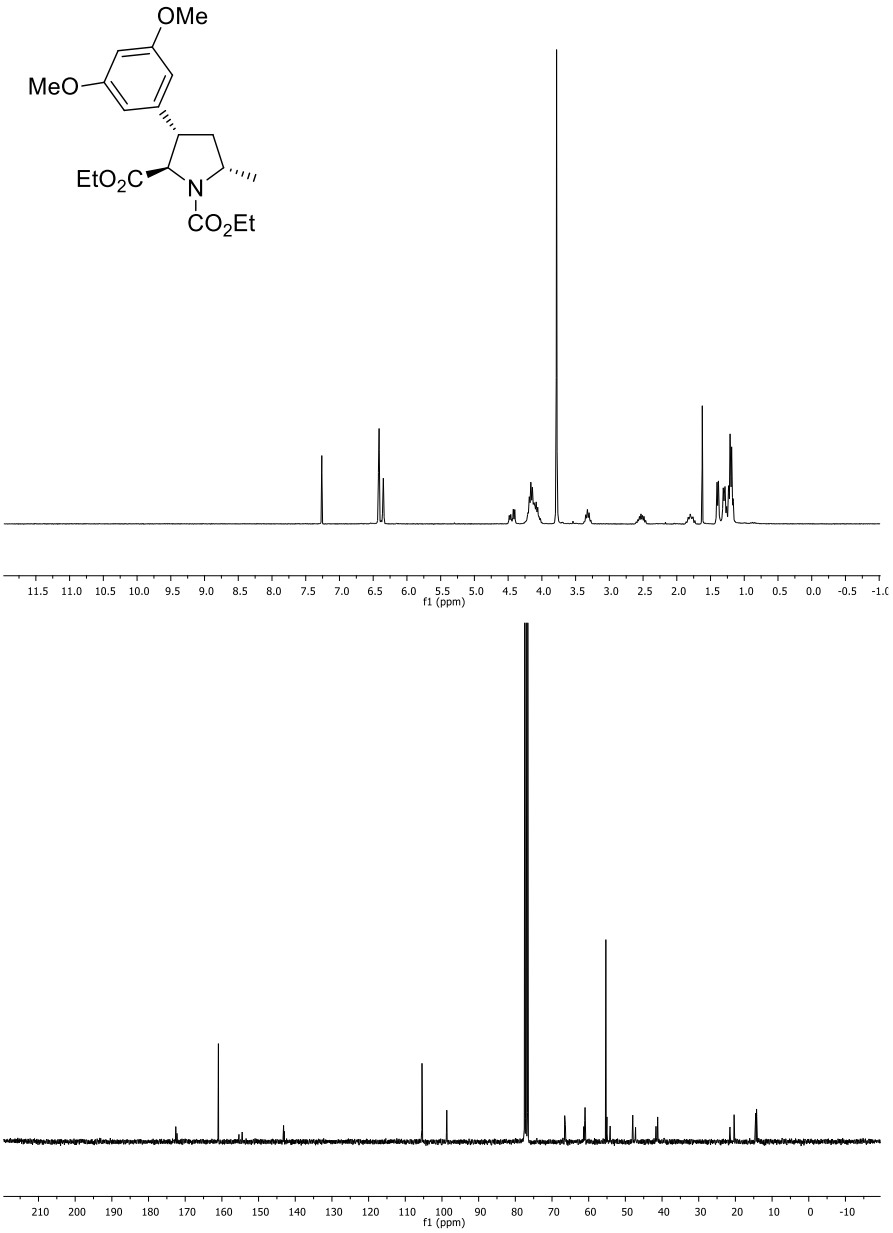
^{1}H-NMR and ^{13}C-NMR spectra of compound **23d**.



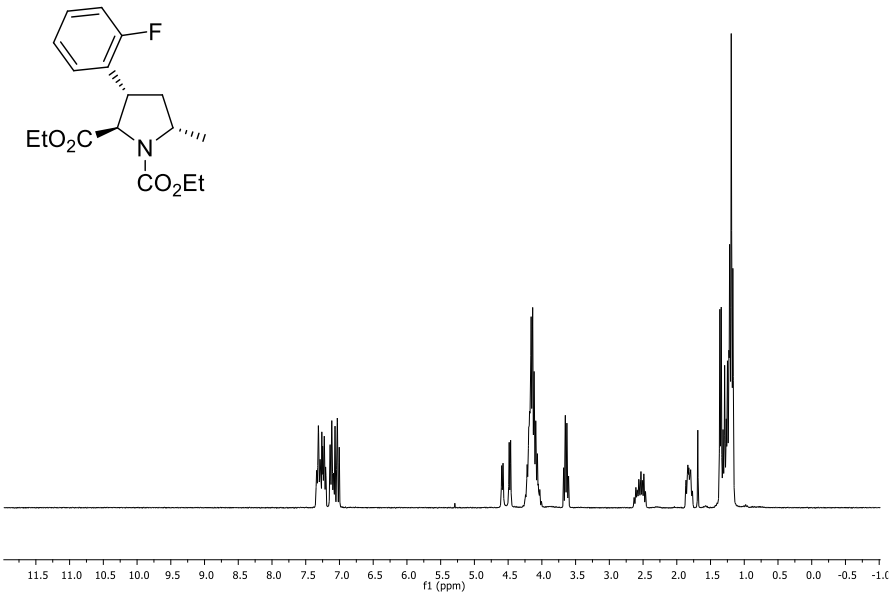
^{1}H-NMR and ^{13}C-NMR spectra of compound **23e**.

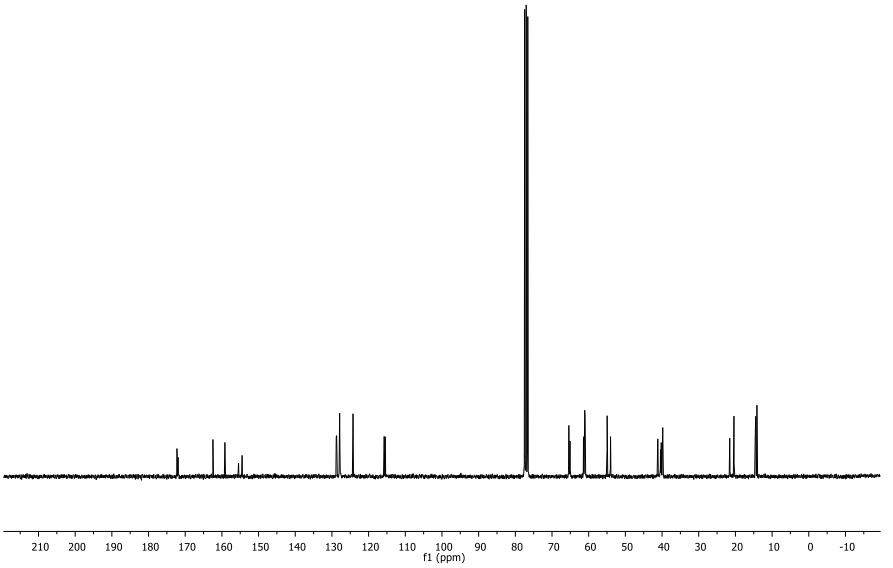


^{1}H-NMR and ^{13}C-NMR spectra of compound **23f.**

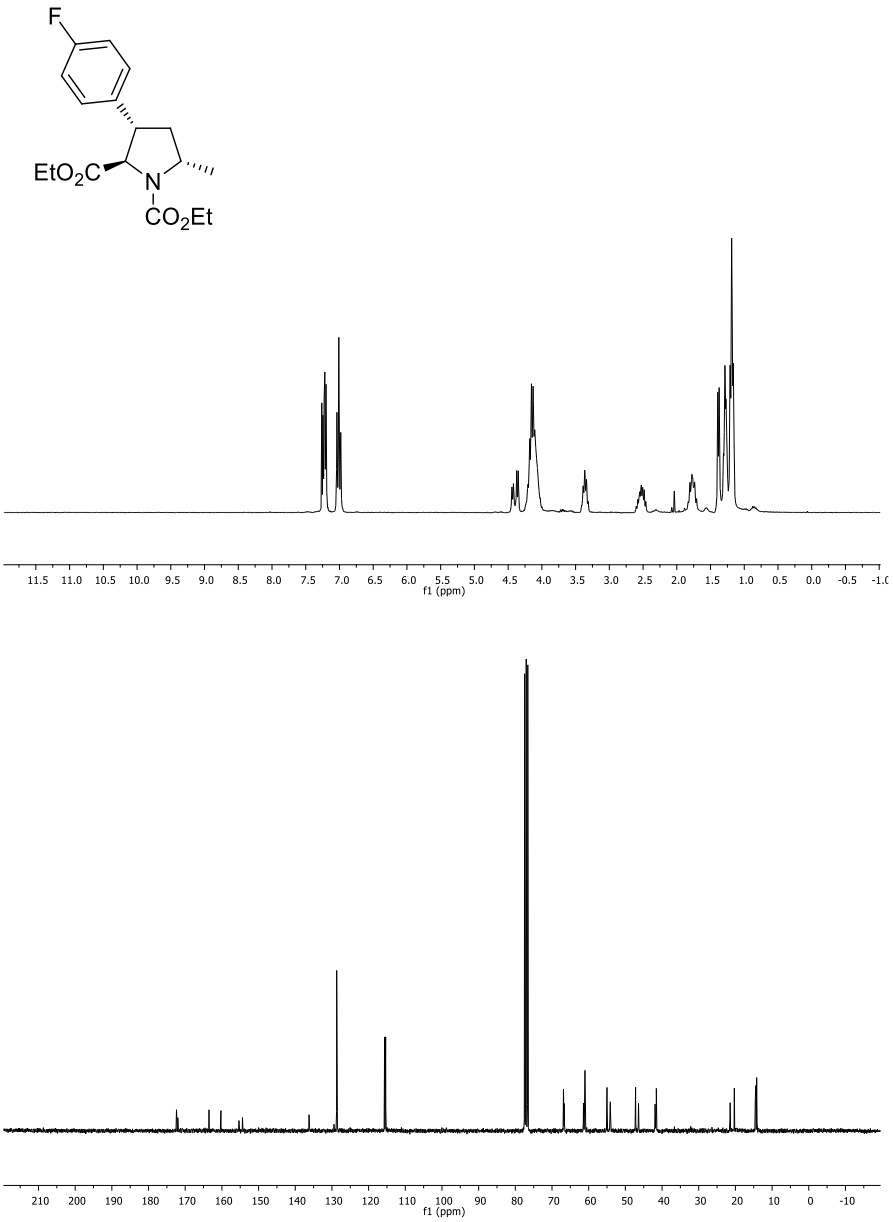


^{1}H-NMR and ^{13}C-NMR spectra of compound **23g.**

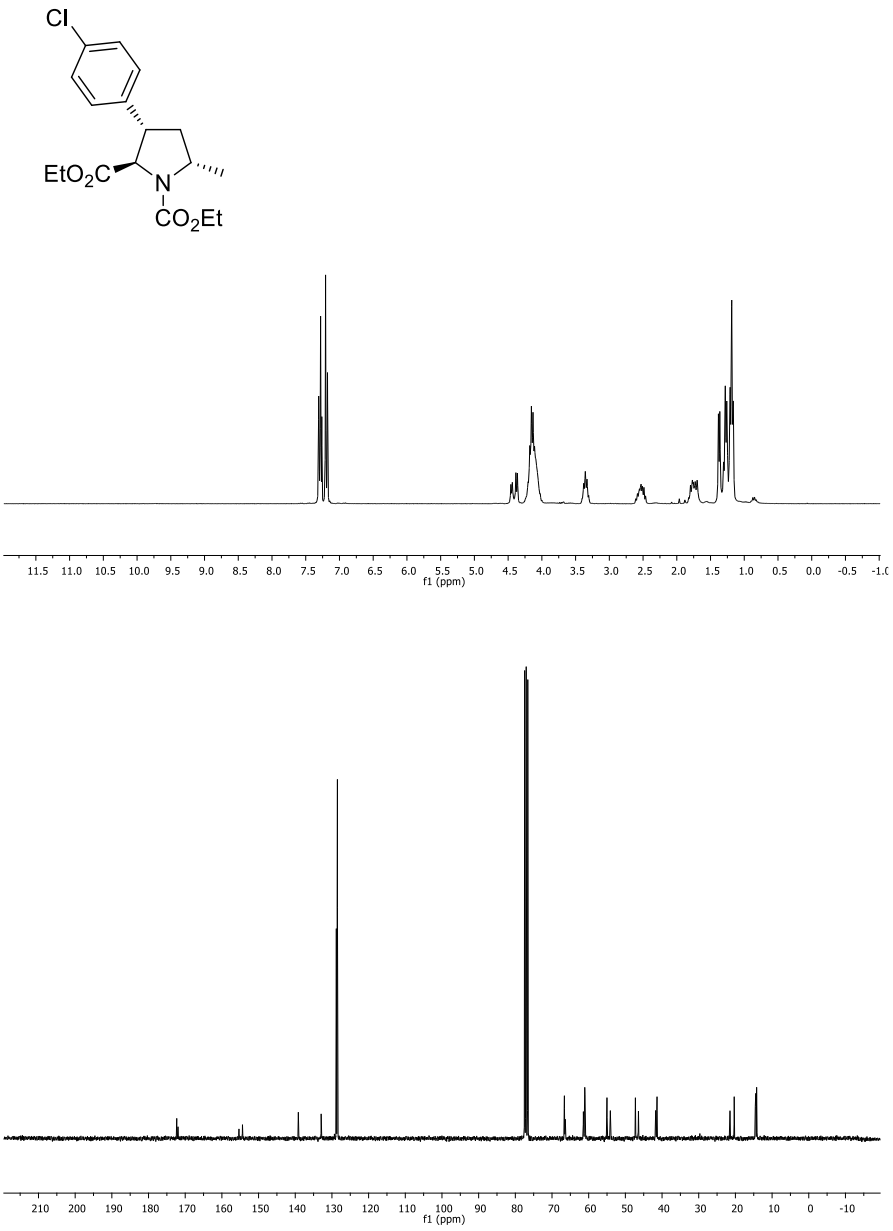




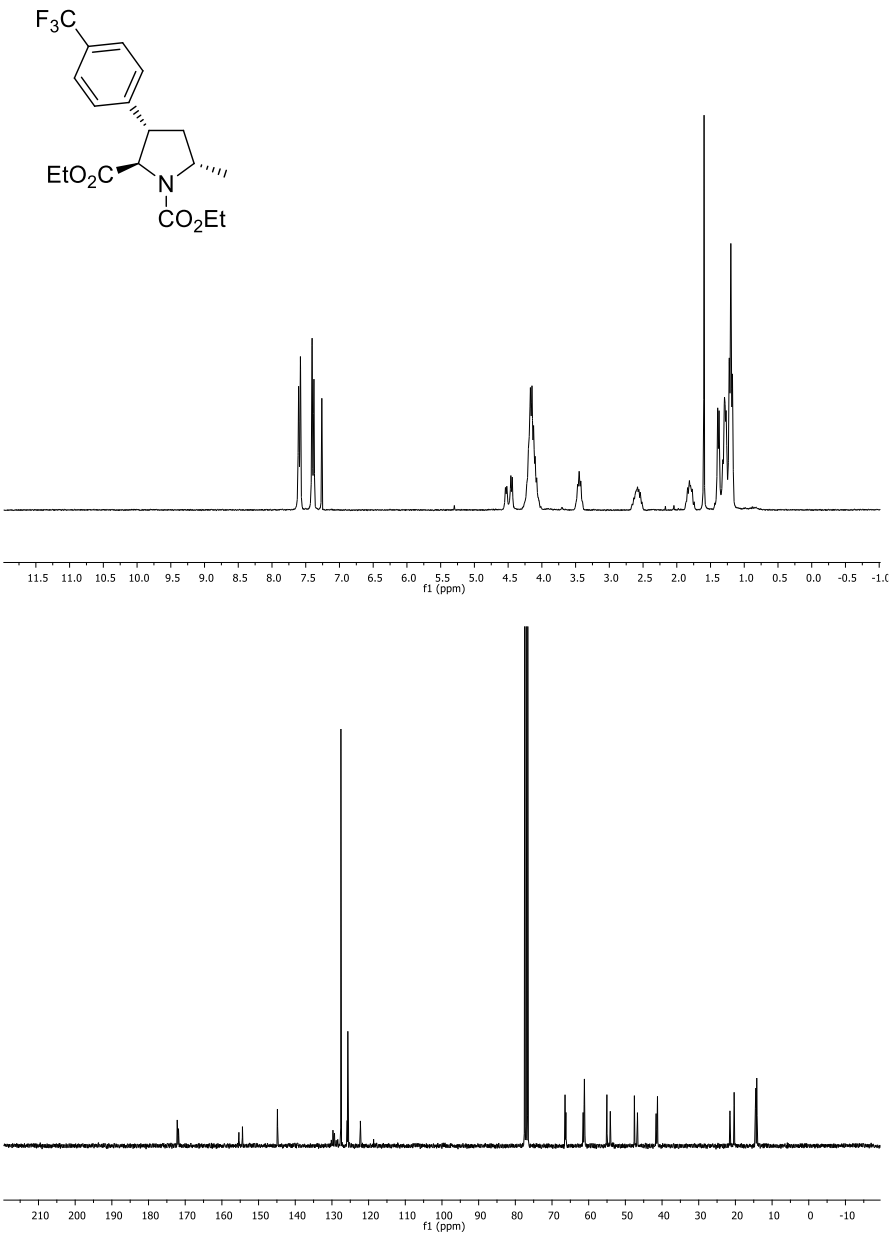
^{1}H-NMR and ^{13}C-NMR spectra of compound **23h.**



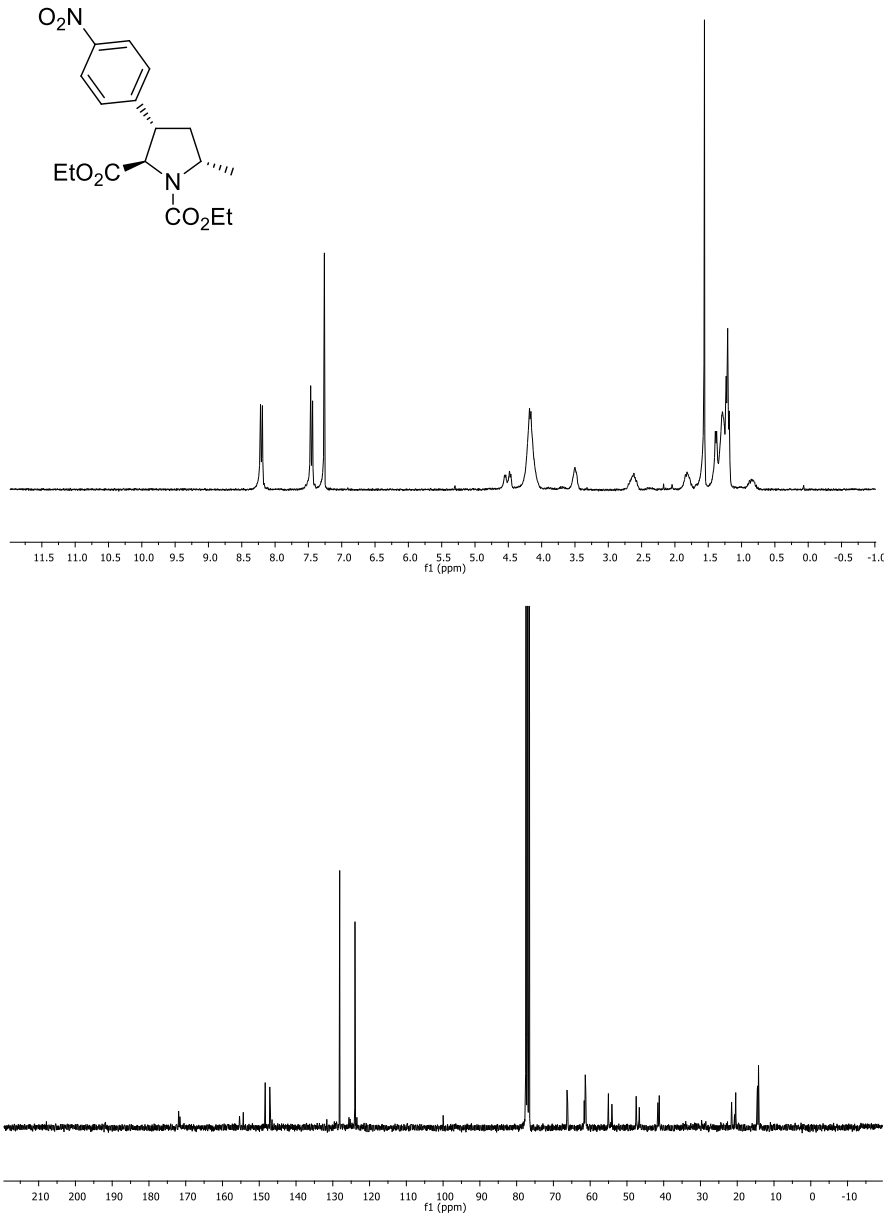
^{1}H-NMR and ^{13}C-NMR spectra of compound **23i.**



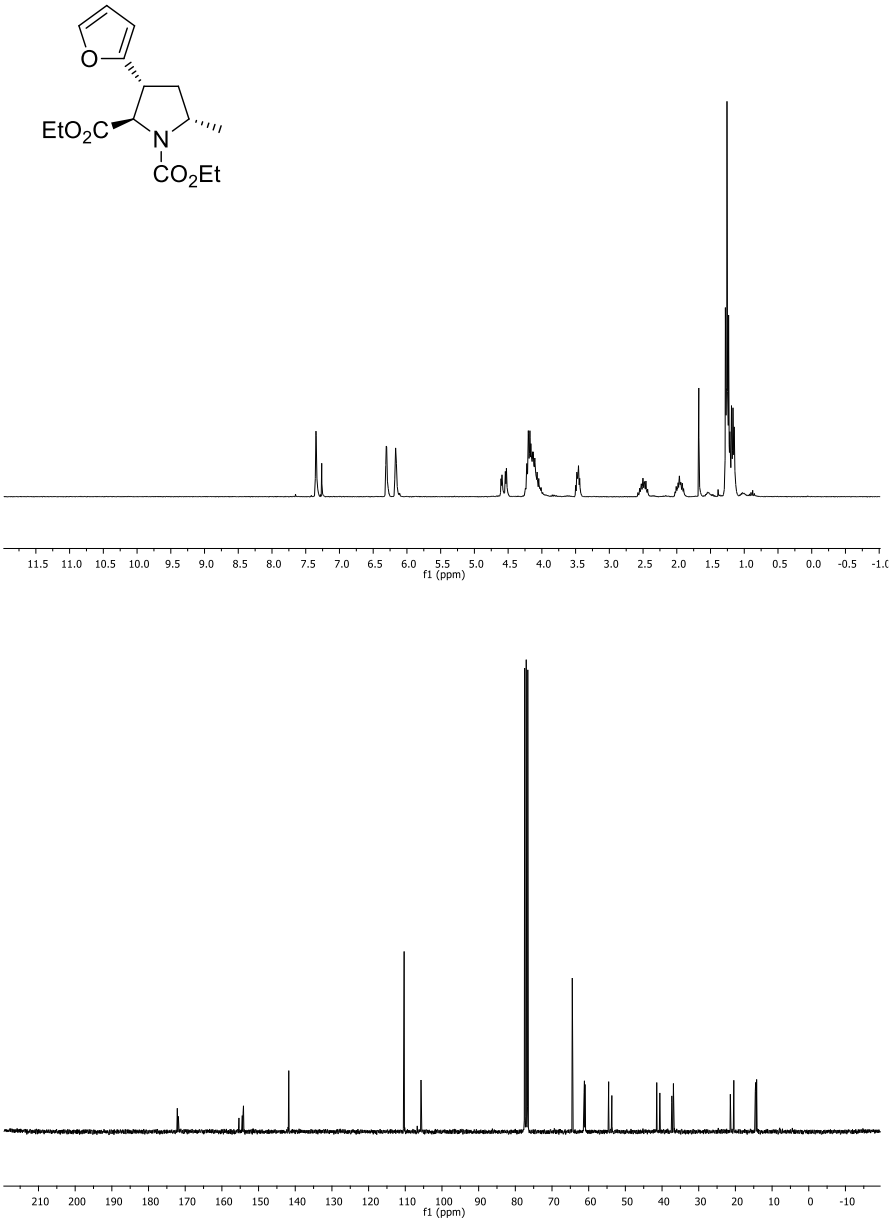
^{1}H-NMR and ^{13}C-NMR spectra of compound **23j**.



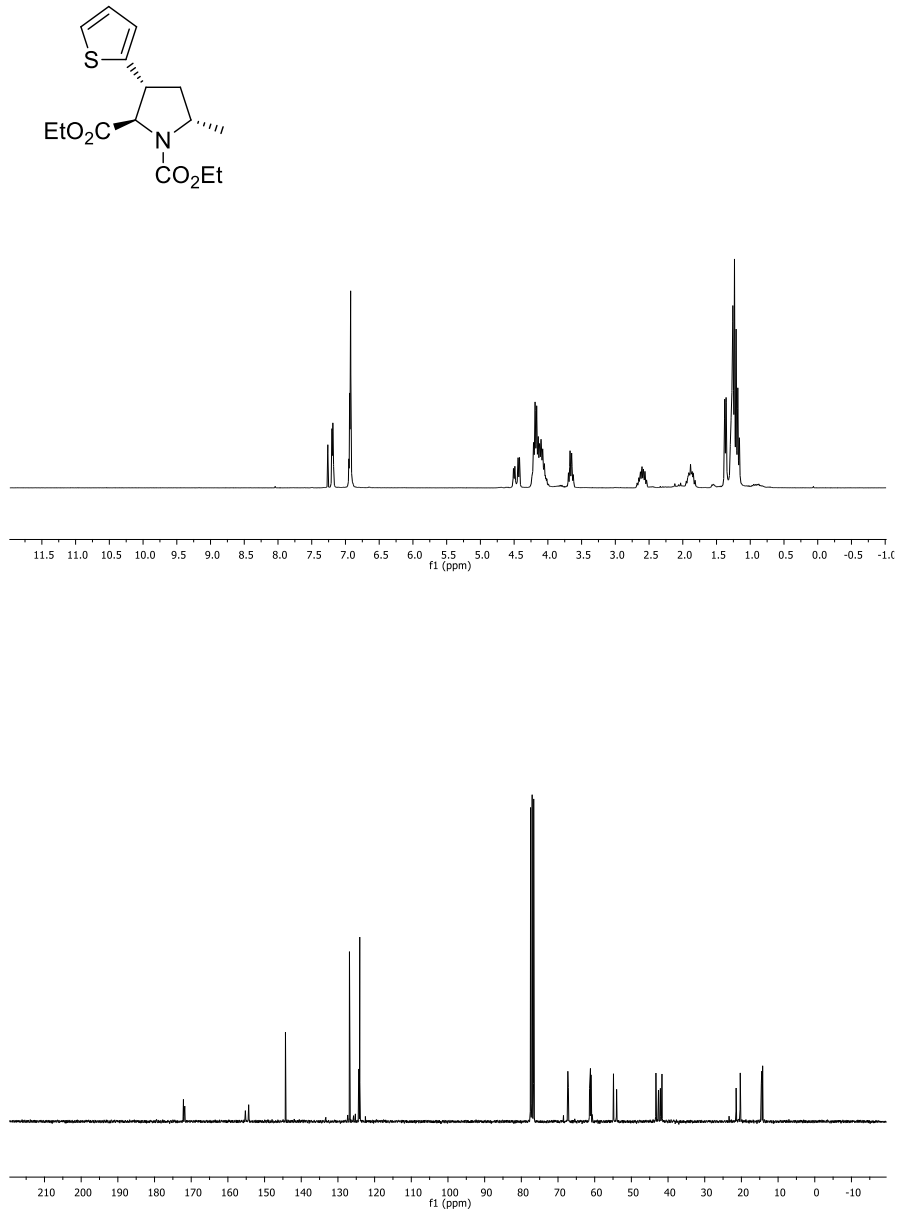
^{1}H-NMR and ^{13}C-NMR spectra of compound **23k**.



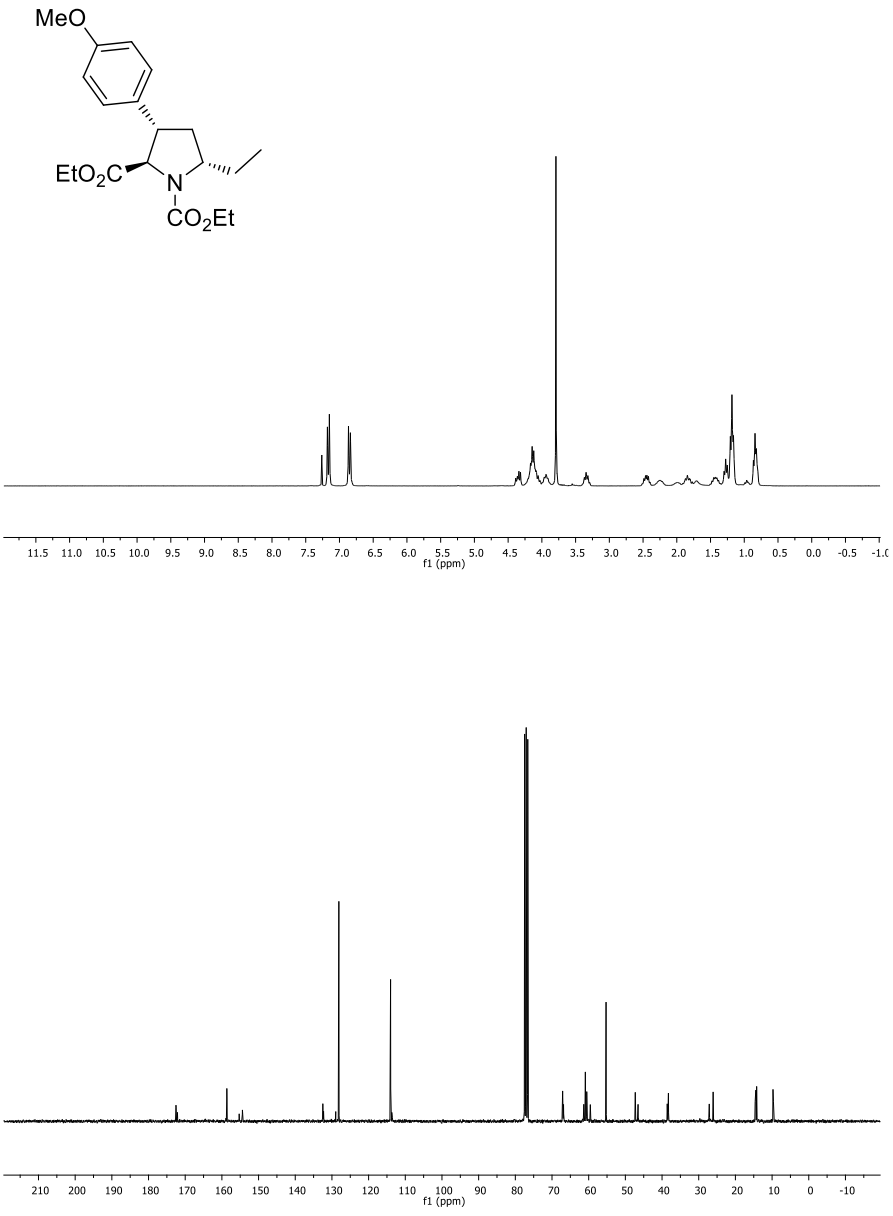
^{1}H-NMR and ^{13}C-NMR spectra of compound **23l**.



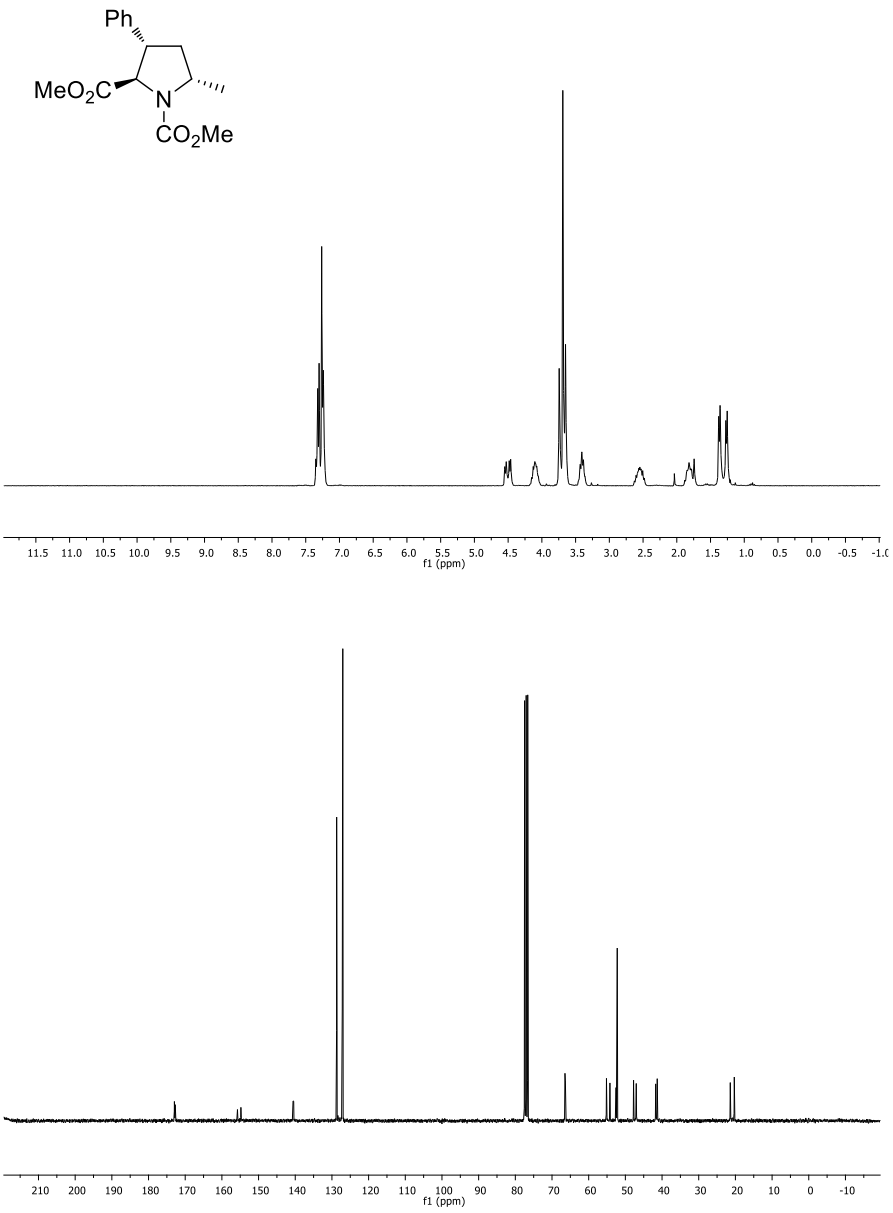
^{1}H-NMR and ^{13}C-NMR spectra of compound **23m**.



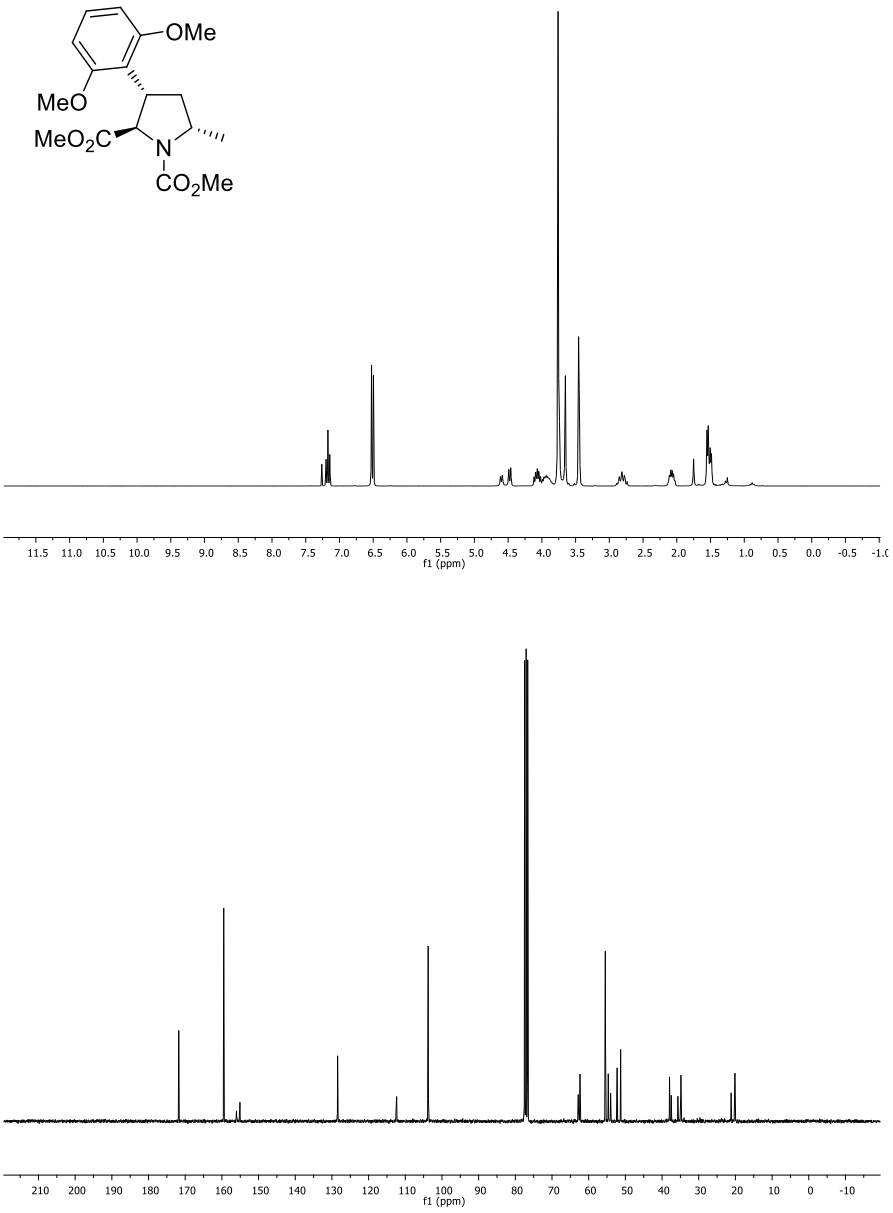
^{1}H-NMR and ^{13}C-NMR spectra of compound **23n**.



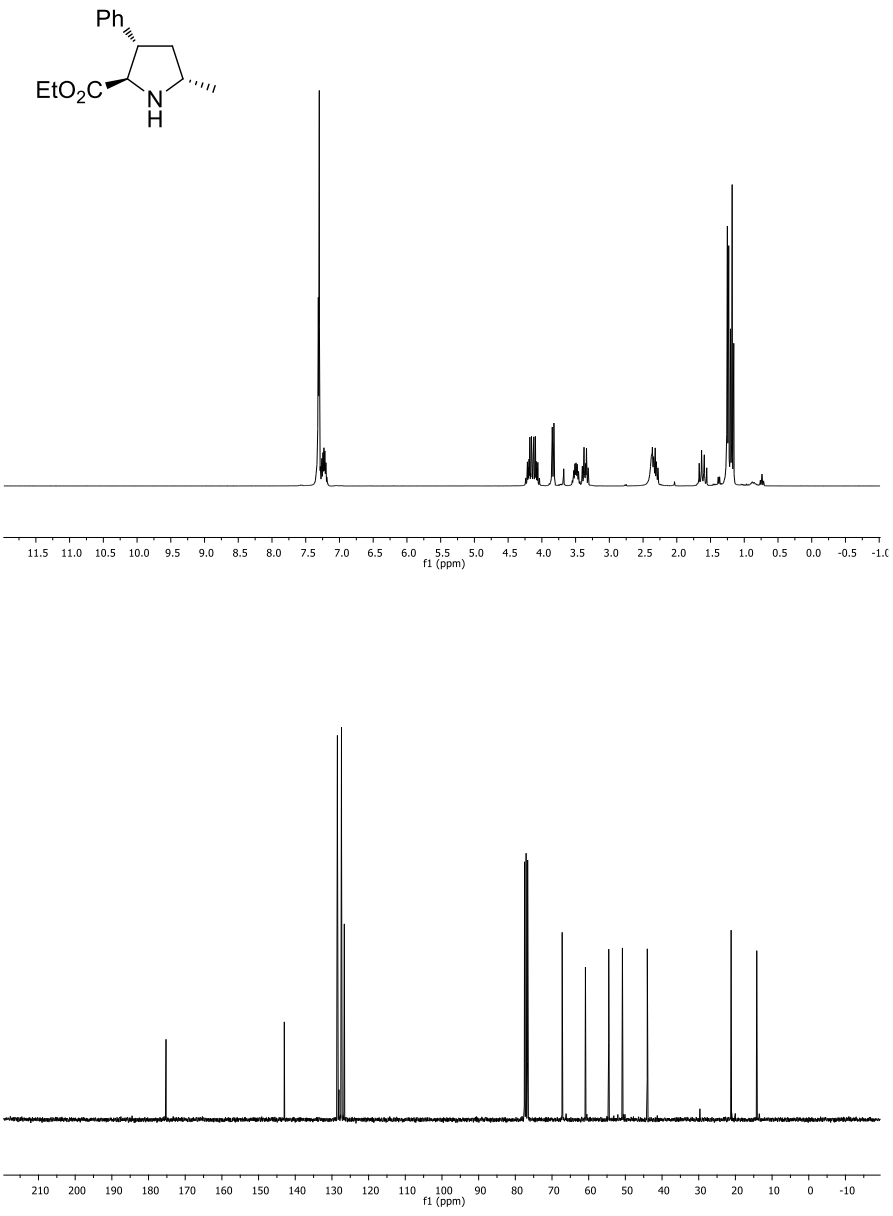
^{1}H-NMR and ^{13}C-NMR spectra of compound **23o**.



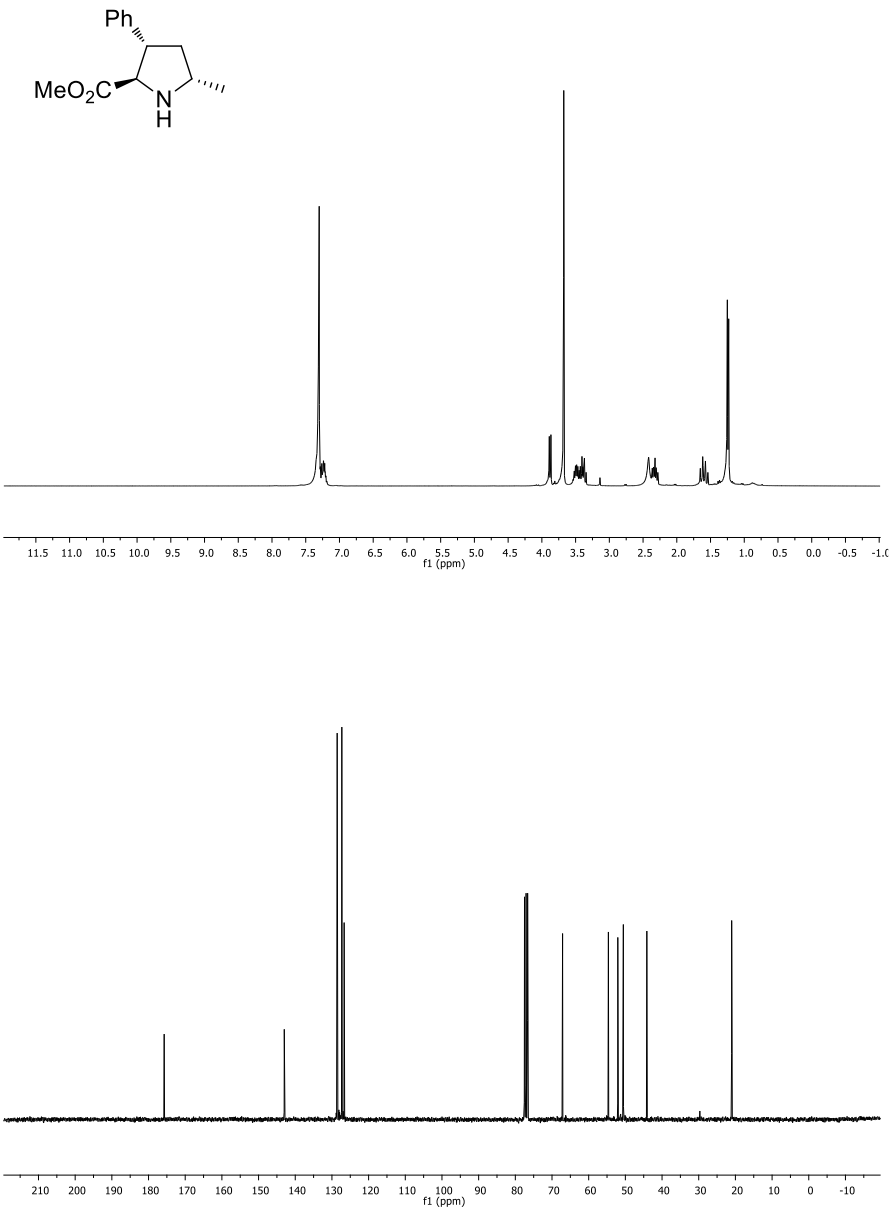
^{1}H-NMR and ^{13}C-NMR spectra of compound **23q**.



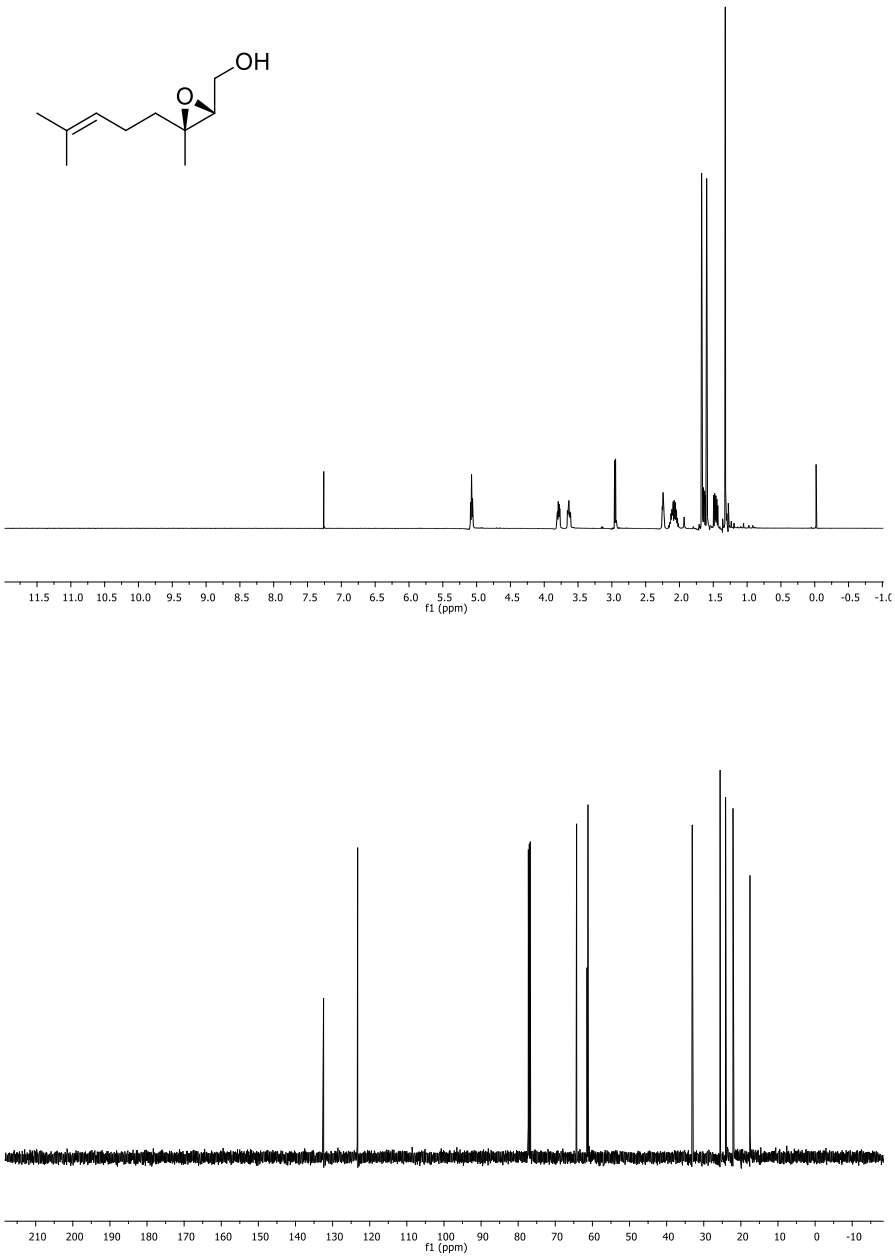
^{1}H-NMR and ^{13}C-NMR spectra of compound **23r**.



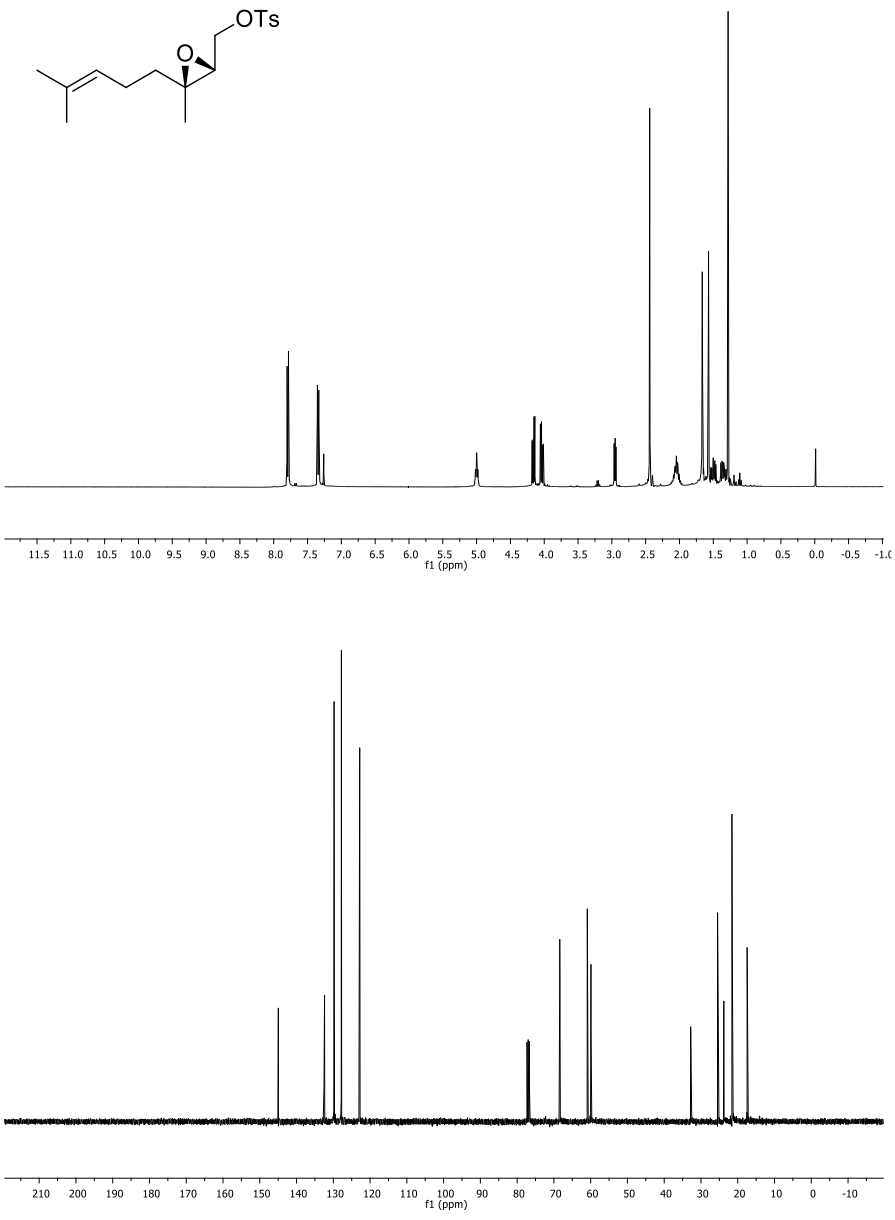
^{1}H-NMR and ^{13}C-NMR spectra of compound **24a**.



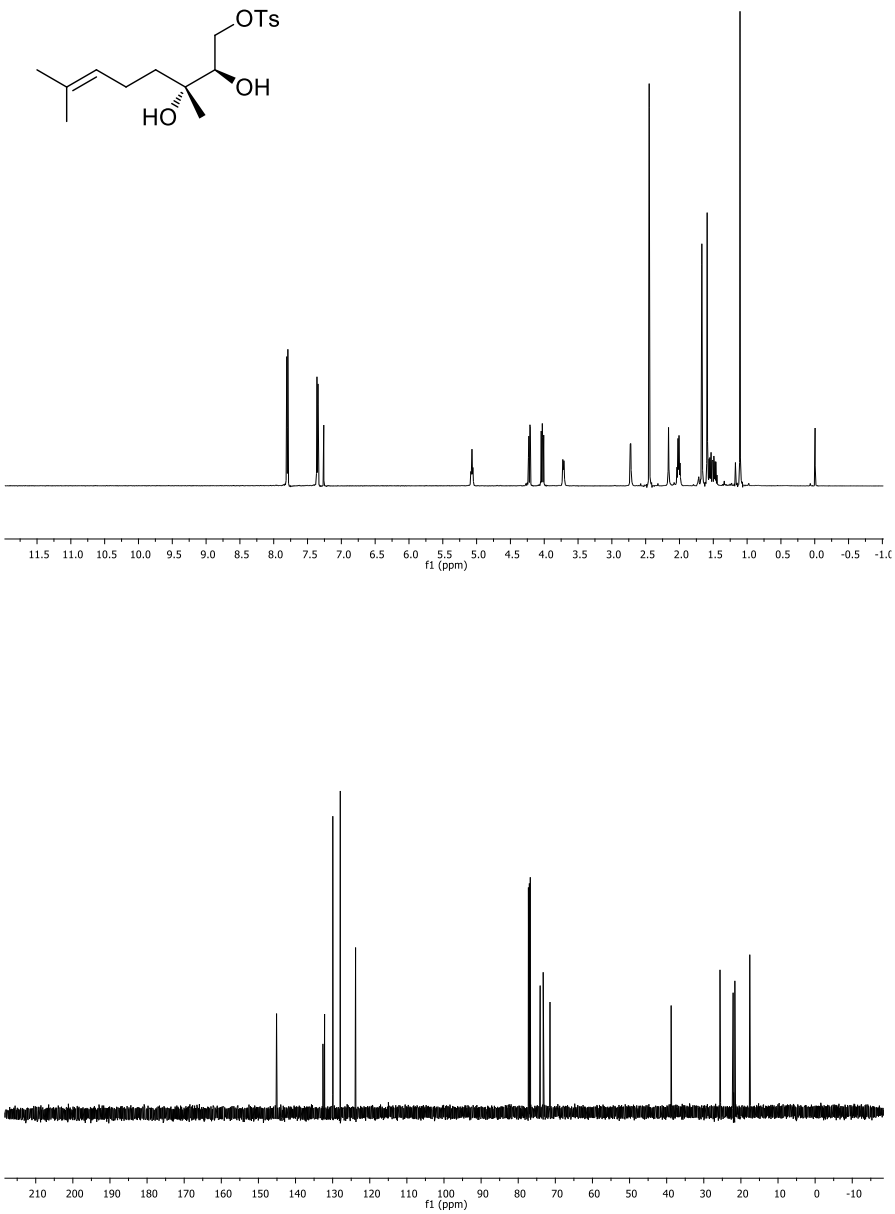
^{1}H-NMR and ^{13}C-NMR spectra of compound **24q**.



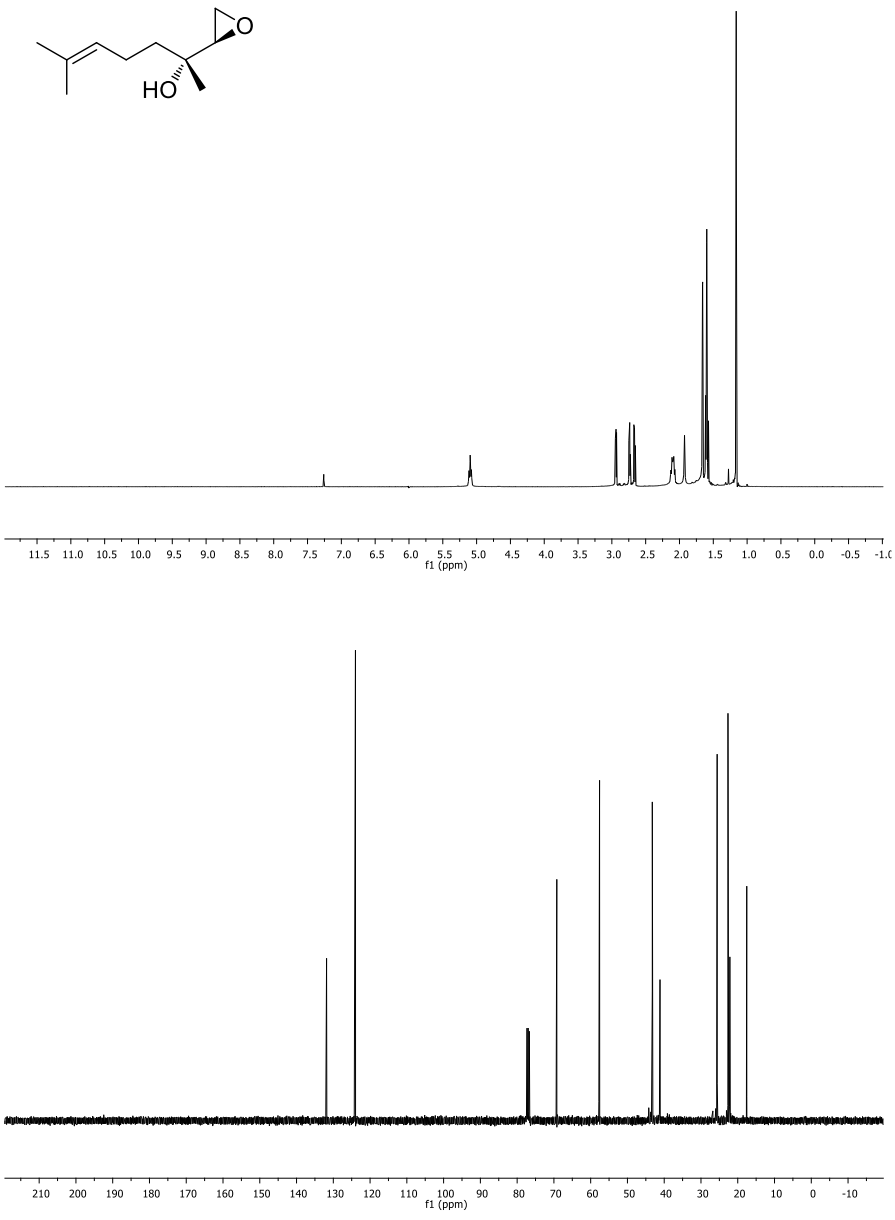
^{1}H-NMR and ^{13}C-NMR spectra of compound **31**.



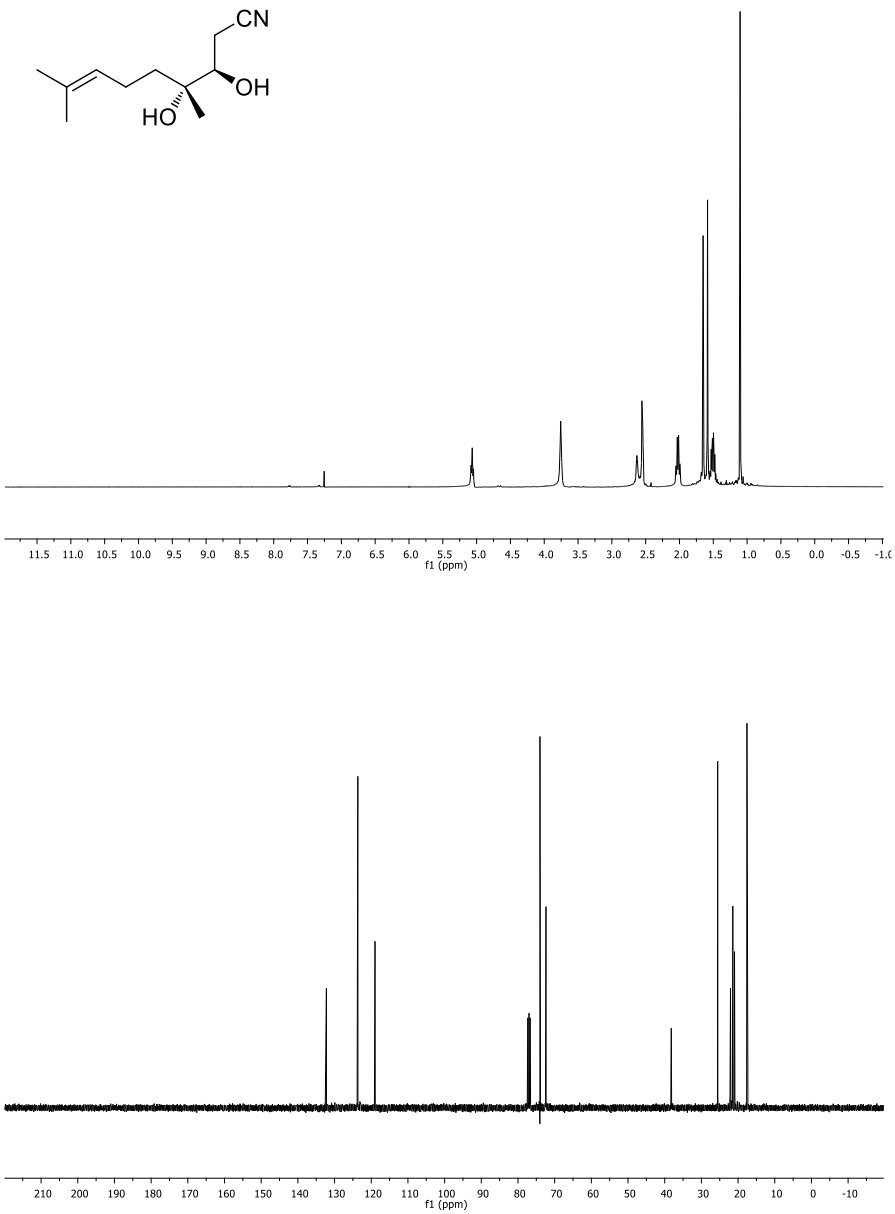
^{1}H-NMR and ^{13}C-NMR spectra of compound **32**.



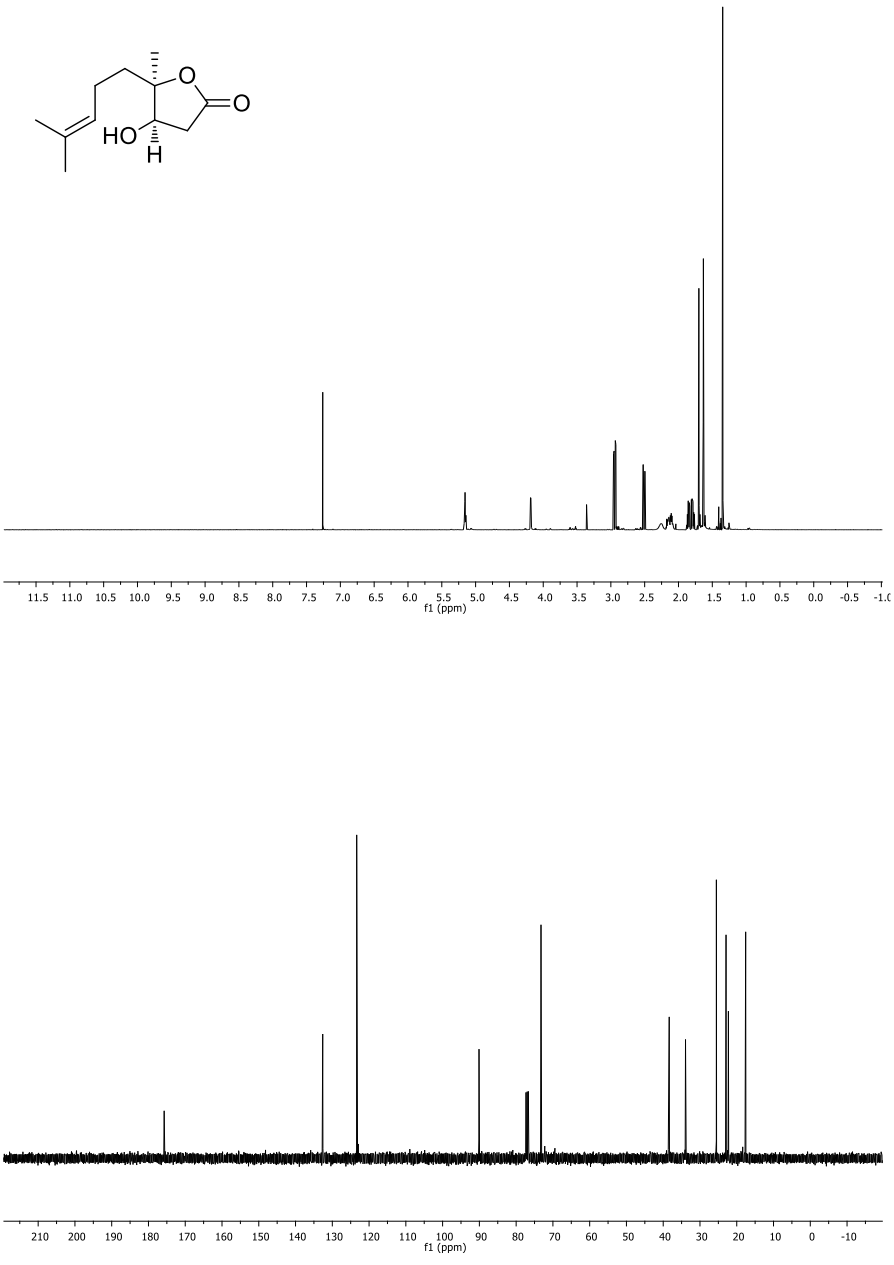
^{1}H-NMR and ^{13}C-NMR spectra of compound **33**.



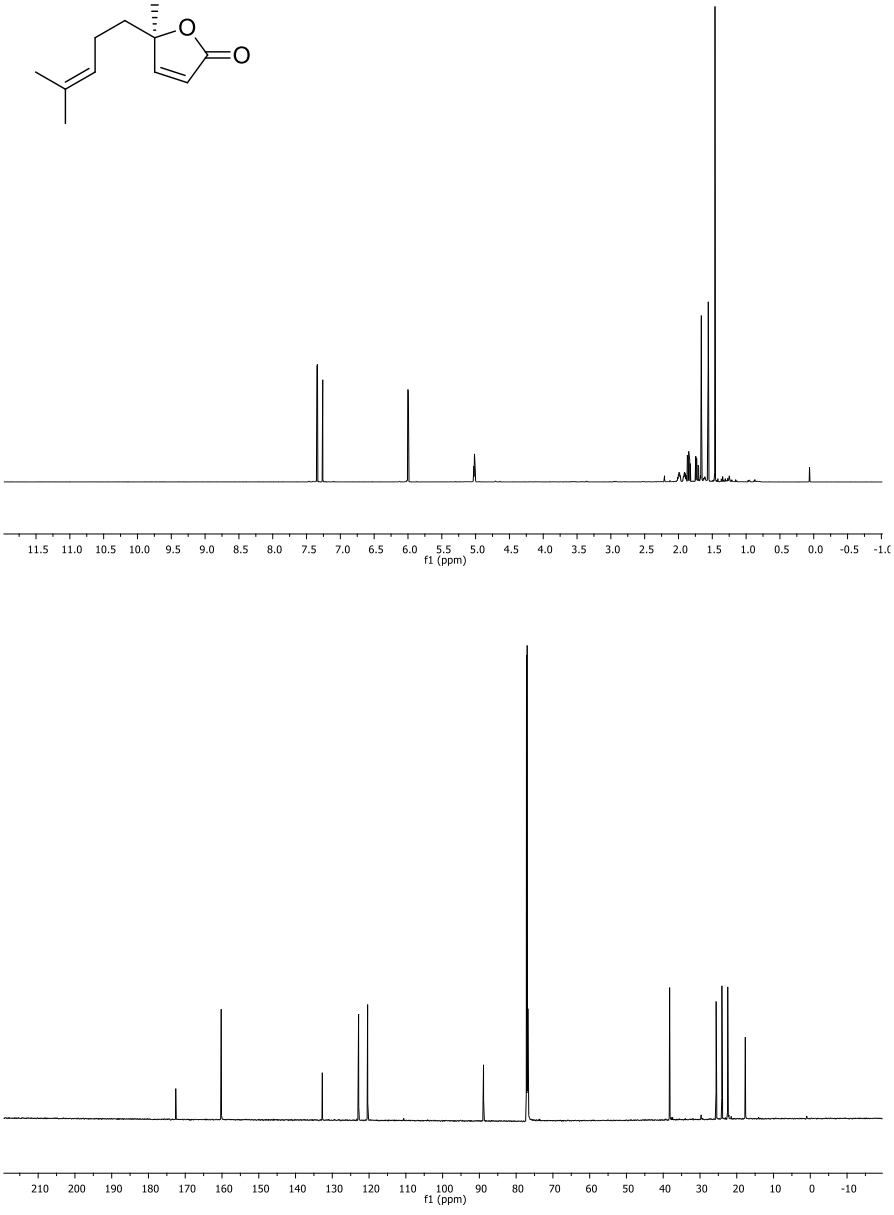
^{1}H-NMR and ^{13}C-NMR spectra of compound **28**.



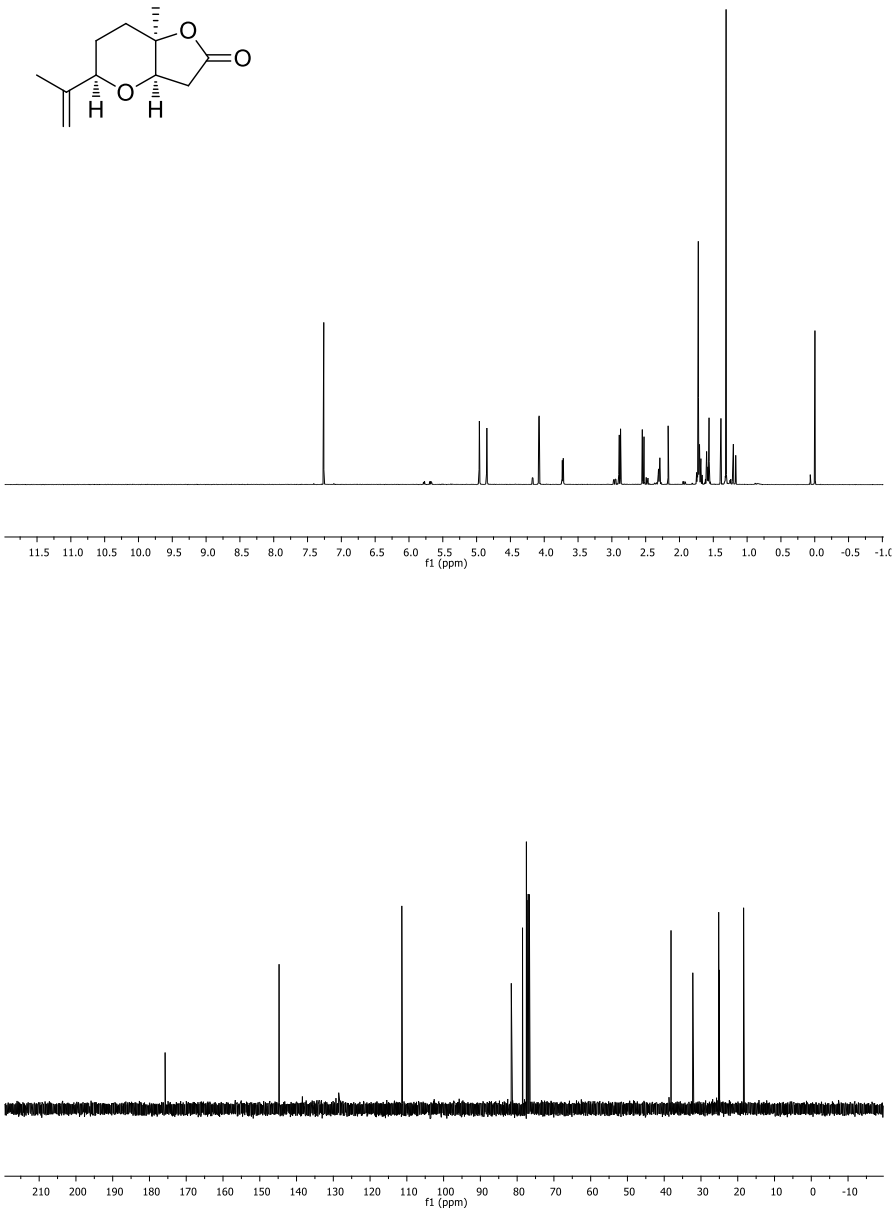
^{1}H-NMR and ^{13}C-NMR spectra of compound **27**.



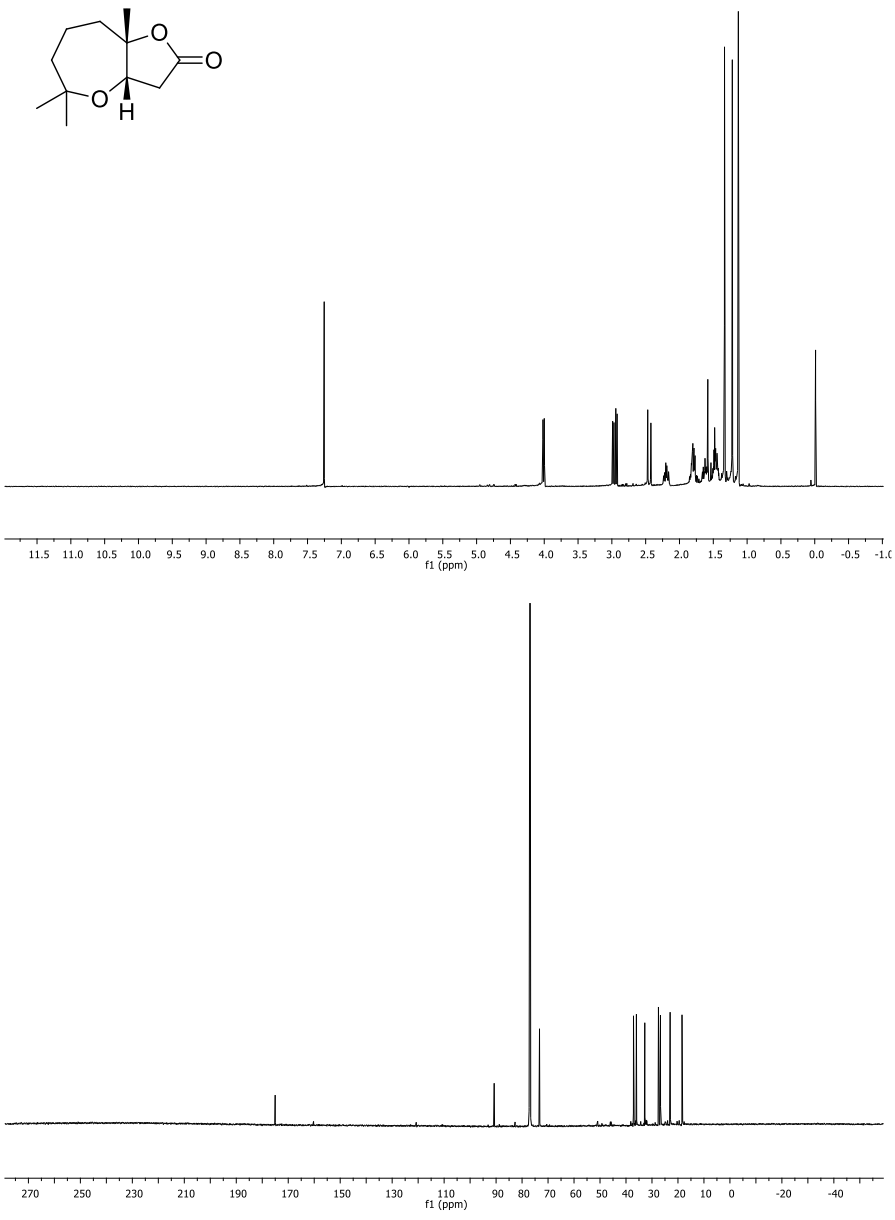
^{1}H-NMR and ^{13}C-NMR spectra of compound **26**.



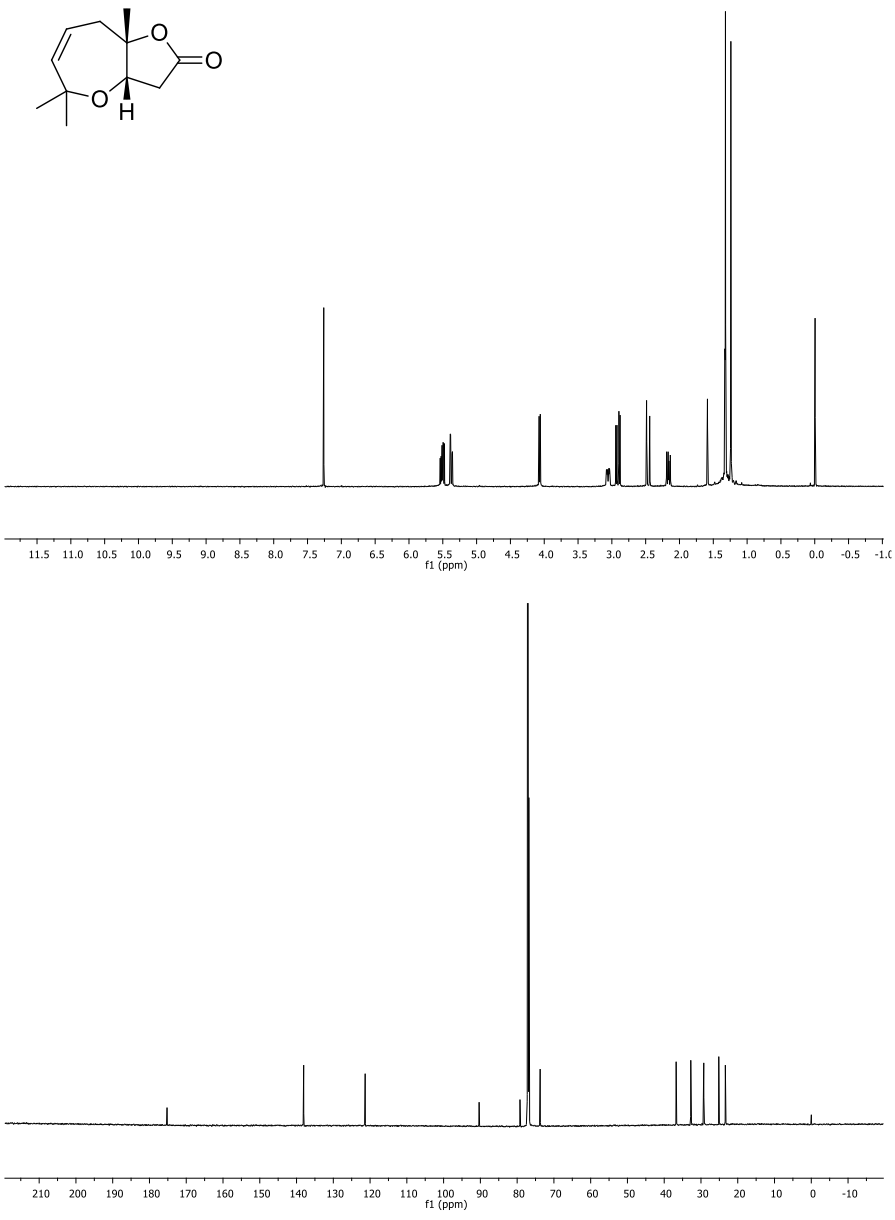
^{1}H-NMR and ^{13}C-NMR spectra of compound **34**.



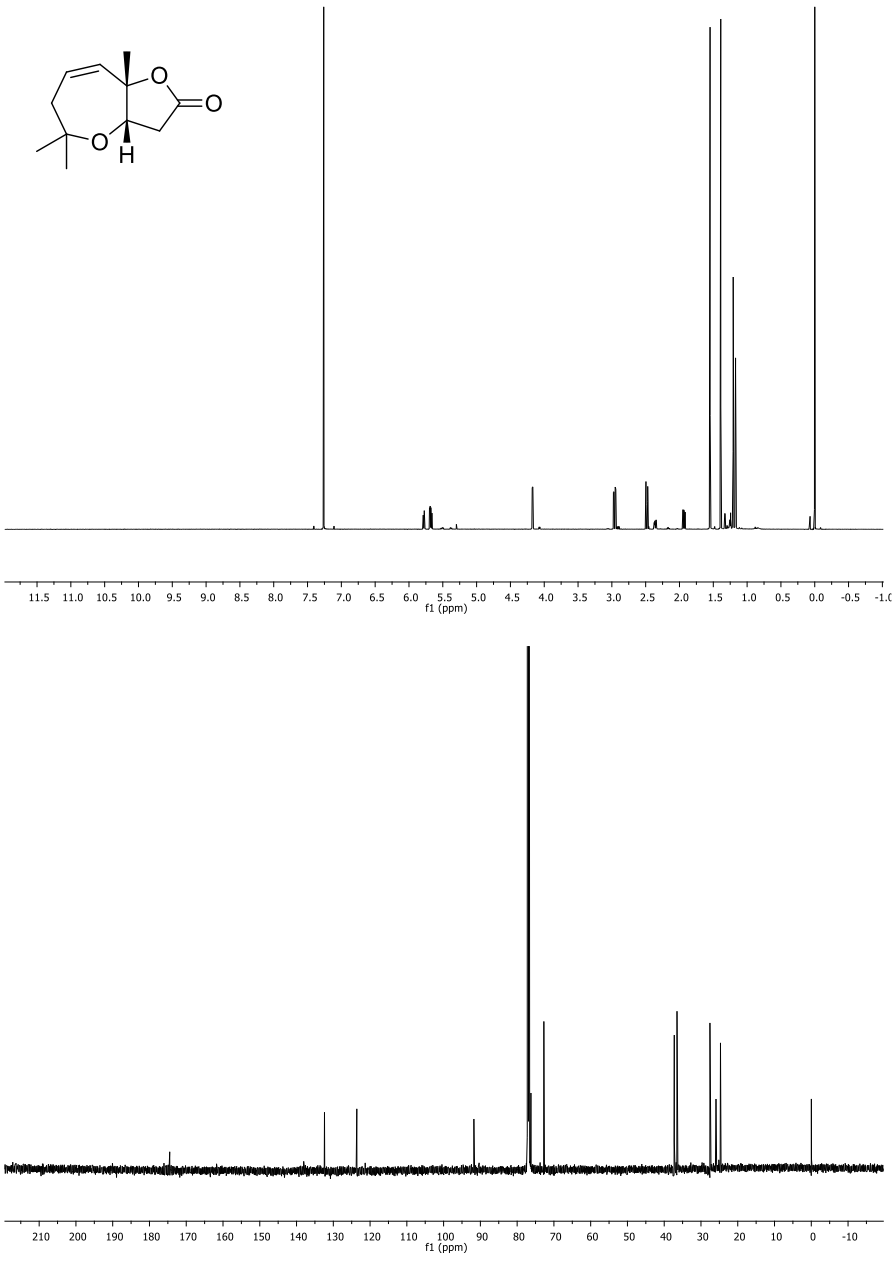
^{1}H-NMR and ^{13}C-NMR spectra of compound **25**.



^{1}H-NMR and ^{13}C-NMR spectra of compound **35**.



^{1}H-NMR and ^{13}C-NMR spectra of compound **36**.



^{1}H-NMR and ^{13}C-NMR spectra of compound **37**.