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Una nueva aproximación a la síntesis de heterociclos pirrolofusionados basada en la reacción de amidación de alquinos asistida por el reactivo de yodo hipervalente PIFA

MEMORIA PRESENTADA POR

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A mi familia y a Unai

A Jokin

Tatsachen gibt es nicht, nur Interpretationen.

No existen hechos, solo interpretaciones.

There is no facts, only interpretations.

Friedrich Nietzsche (1844-1900)

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1. "*A quick synthesis of 1-arylpyrrolopyrazinones from linear alkynylamide derivatives*"
Leticia M. Pardo, Imanol Tellitu, Esther Domínguez
Synthesis **2010**, *6*, 971.

2. "*A versatile PIFA-mediated approach to structurally diverse pyrrolo(benzo)diazepines from linear alkynylamides*"
Leticia M. Pardo, Imanol Tellitu, Esther Domínguez
Tetrahedron **2010**, *66*, 5811.

3. "*Development of a new non-sugar based strategy for the synthesis of the hydroxylated indolizidinone skeleton*"
Leticia M. Pardo, Imanol Tellitu, Esther Domínguez
Synlett, en imprenta.

4. "*Application of the intramolecular PIFA-mediated amidation of alkynes to the synthesis of substituted indolizidinones*"
Leticia M. Pardo, Imanol Tellitu, Esther Domínguez.
Enviado.

Asimismo se han realizado las siguientes comunicaciones a congresos:

1. "*Designing a common route to structurally diverse pyrrolo-fused heterocycles*"
Leticia M. Pardo, Imanol Tellitu, Esther Domínguez
Tenth Tetrahedron Symposium
París (Francia), Junio 2009 (Póster)

2. "*Preparación de pirrolopirazinonas por reacción de amidación intramolecular de alquinos mediada por PIFA"*
Leticia M. Pardo, Imanol Tellitu, Esther Domínguez
XXXII Reunión Bienal de la Real Sociedad Española de Química
Oviedo (España), Septiembre 2009 (Comunicación oral)

3. "*A versatile PIFA-mediated approach to structurally diverse pyrrolo(benzo)diazepines from linear alkynylamides*"
Leticia M. Pardo, Imanol Tellitu, Esther Domínguez
3rd International Conference on Hypervalent Iodine Chemistry
Burdeos (Francia), Julio 2010 (Comunicación oral)

4. *"A diastereodivergent approach to C-8 arylated polyhydroxylated indolizidinones"*

Leticia M. Pardo, Imanol Tellitu, Esther Domínguez

Twelfth Tetrahedron Symposium

Sitges (España), Junio 2011 (Póster)

5. *"A novel diastereoselective synthesis of polyhydroxylated indolizidinones"*

Letícia M. Pardo, Imanol Tellitu, Esther Dominguez

17th European Symposium in Organic Chemistry

Creta (Grecia), Julio 2011 (Póster)

6. *"Synthesis of heteroaromatic iodonium salts under non-basic conditions"*

Marcin Bielawski, Leticia M. Pardo, Ylva Wikmark, Berit Olofsson

17th European Symposium in Organic Chemistry

Creta (Grecia), Julio 2011 (Póster)

Resumen

En la presente memoria se describe el trabajo de investigación llevado a cabo en relación al desarrollo de nuevas aplicaciones sintéticas de la reacción de heterociclación de alquinos funcionalizados mediante el empleo del reactivo de yodo hipervalente [*bis*(trifluoroacetoxi)yodo]benceno (PIFA).

En particular, se ha estudiado y aprovechado la eficacia de la reacción de amidación intramolecular de alquinos mediada por PIFA, previamente puesta a punto en nuestro grupo de investigación, para la síntesis de sistemas pirrolidinónicos como paso clave para el acceso a sistemas pirrolopirazinónicos, pirrolodiazepínicos y pirrolobenzodiazepínicos.

De modo análogo, la aplicación de esta metodología sobre alquinilamidas convenientemente sustituidas ha proporcionado un nuevo acceso a derivados indolizidínicos polihidroxilados a través de una ruta sencilla y estereocontrolada.

Finalmente, se desarrolló un procedimiento one-pot rápido, sencillo y eficiente para la síntesis de sales de diarilyodonio, incluidas aquéllas impedidas estéricamente.

Abstract

In this dissertation, our work on the search for new applications in organic synthesis for the heterocyclization of functionalizated alkynes through the use of hypervalent iodine [*bis*(trifluoroacetoxy)iodo]benzene (PIFA) will be presented.

In particular, we have studied and taken advantage of the efficiency of the PIFA-mediated alkyne amidation reaction, previously optimized in our research group, for the synthesis of the pyrrolidinone skeleton as the key step in the preparation of a number of pyrrolopyrazinone, pyrrolodiazepinone and pyrrolobenzodiazepinone derivatives.

In a similar way, the application of this strategy to properly substituted alkynylamides has allowed the access to a simple and stereocontrolled route to the synthesis of polyhydroxylated indolizidinone scaffolds.

Finally, a fast, efficient and simple one-pot procedure for the synthesis of heteroaryl iodonium salts was developed, allowing the synthesis of diverse compounds, including those with sterically hindered moieties.

Nota:

Las referencias bibliográficas de esta Tesis Doctoral se recogen al pie de cada página y son independientes en cada uno de los Capítulos en que se divide la Memoria, por lo que en los casos en que se ha considerado oportuno han sido repetidas para comodidad del lector.

Acrónimos y abreviaturas

Å	Amstrong
Ac	Acetilo, actínido, acetyl
ADN	Ácido desoxirribonucleico
anh.	Anhydrous
app.	Apparent
aq.	Acuoso, aqueous
Ar	Arilo, aryl
ARN	Ácido ribonucleico
atm	Atmósfera
Bn	Bencilo
^{t}Boc	*terc*-Butoxicarbonilo, *tert*-butoxycarbonyl
br	Broad

$^{(t)}$Bu	(*terc*)-Butilo, (*tert*)-butyl
ºC	Grados centígrados, grade Celsius
Carom	Aromatic carbon
Cat.	Catalizador
Cbz	Benciloxicarbonilo
ccf	Cromatografía en capa fina
CI	Chemical ionization
COSY	Correlation Spectroscopy
Cp	Ciclopentadienilo
m-CPBA	*m*-Chloroperbenzoic acid
Cy	Ciclohexilo
d	Doublet
DCC	N,N'-Diciclohexilcarbodiimida, N,N'-dicyclohexylcarbodiimide
DCM	Dichloromethane
dd	Doublet of doublets
DEPT	Distortionless Enhancement by Polarization Transfer
DHQ	Dihidroquinina
DHQD	Dihidroquinidina
DIBAL	Hidruro de isobutilaluminio
DMAP	4-Dimetilaminopiridina, 4-dimethylaminopyridine

DMF	Dimethylformamide
DMP	Peryodano de Dess-Martin
DMSO	Dimetilsulfóxido, dimethylsulfoxide
Dpp	Difenilfosfinoilo
dr	Proporción diastereomérica, diastereomeric ratio
Dte.	Disolvente
E	Electrófilo
EDC	1-Etil-3-(3-dimetilaminopropil)carbodiimida, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
EI	Electronic impact
equiv.	Equivalente(s), equivalent(s)
ESI	Electrospray ionization
Et	Etilo, ethyl
et al.	and others
EtOAc	Ethylacetate
eV	Electronvolt
g	Gram(s)
GP	Grupo protector
h	Hora(s),

	hour(s)
Harom	Aromatic proton
Hex	Hexanos, hexanes
HOBt	N-Hidroxibenzotriazol, N-hydroxybenzotriazole
HRMS	High Resolution Mass Spectroscopy
HSQC	Heteronuclear Single Quantum Coherence
HTIB	[Hidroxi(tosiloxi)yodo]benceno
IBX	Óxido de 1-hidroxi-1,2-benzoyodoxol-3(1*H*)ona
Ind	Indenilo
IOB	Fenilyodosilo
IR	Infrared
J	Coupling constant
kJ	Kilojulio
L	Ligando, Ligand
LAH	Hidruro de litio y aluminio, lithium aluminium hydride
Ln	Lantánido
M	Molar, metal
m	Multiplet
Me	Metilo, methyl

Mes	Mesitilo, mesityl
MeOH	Methanol
mg	Miligram(s)
MHz	Megahertz
min	Minute(s)
mL	Mililiter(s)
mmol	Milimol(s)
MOM	Metoximetilo
Mp	Melting point
MS	Mass Spectroscopy
NMO	N-Óxido de N-metilmorfolina, N-methylmorpholine-N-oxide
NMP	N-metilftalimida
NMR	Nuclear magnetic resonante
NOE	Efecto nuclear Overhauser
NOESY	Nuclear Overhauser Enhancement Spectroscopy
O	Orto
Ox	Oxidante
P	Para
PBD	Pirrolobenzodiazepina
Ph	Fenilo, phenyl
PHAL	Ftalazina

PIDA	(Diacetoxi)yodobenceno, (diacetoxy)iodobenzene
PIFA	[*Bis*(trifluoroacetoxi)yodo]benceno, [*bis*(trifluoroacetoxy)yodo]benzene
PMB	*p*-Metoxibencilo
PMP	*p*-Metoxifenilo, *p*-methoxyphenyl
^{i}Pr	Isopropyl
Psi	Pound(s) force per square inch
Py	Piridina
q	Quaternary, quartet
RCM	Reacción de metátesis de cierre de anillo, Ring Closing Metathesis
Rdto	Rendimiento
red	Reducción
RMN	Resonancia magnética nuclear
rt, RT	Room temperature
S	Singlet
sat.	Saturado
T	Temperatura
t	Tiempo, triplet, tertiary
t.a.	Temperatura ambiente
TBAF	Fluoruro de tetrabutilamonio

TBS, TBDMS	*terc*-Butildimetilsililo
TEA	Trietilamina
Tf	Trifluorometanosulfonilo, trifluoromethanesulfonyl
TFA	Ácido trifluoroacético, trifluoroacetic acid
TFEA	2,2,2-Trifluoroetanol, 2,2,2-trifluoroethanol
THF	Tetrahidrofurano, tetrahydrofurane
TIPS	Triisopropilsililo
tlc	Thin Layer Chromatography
TMEDA	N,N,N',N'-tetrametiletilendiamina
TMS	Trimetilsililo
Tol.	Tolueno
TPP	Tetrafenilporfirina
TRIP	1,3,5-Triisopropylphenyl
Ts	Tosilo, tosyl
VIH	Virus de la inmunodeficiencia humana
wt	Weight

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Capítulo 3: Conclusiones

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1

Introducción

1. AMINACIÓN DE ENLACES MÚLTIPLES CARBONO-CARBONO

La importancia de las reacciones de formación de enlaces Carbono-Nitrógeno, C-N, en síntesis orgánica reside en que las distintas funcionalidades resultantes que pueden generarse están presentes en gran parte de las moléculas orgánicas, y son especialmente importantes en aquéllas con actividad fisiológica.[1] Los métodos disponibles para la formación de estas uniones implican, generalmente, el desplazamiento de una función oxigenada por un nucleófilo nitrogenado,[2] la transposición de compuestos carbonílicos (Curtius, Beckmann)[3] y la aminación reductora de aldehídos o cetonas.

Al grupo de métodos mencionados, clásicos y bien establecidos todos ellos, se les vienen uniendo más recientemente aquéllos basados en la adición de un fragmento N-H sobre un enlace múltiple C-C. Esta es una reacción ligeramente exotérmica.[4] Sin embargo, a pesar de ser un proceso termodinámicamente favorable, está impedido por la elevada energía de

1. (a) Dewick, P. M. en *"Medicinal Natural Products"*, Wiley: England, 1997. (b) Nicolaou, K. C.; Vourlomis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 44.

2. Mitsunobu, O. en *"Comprehensive Organic Synthesis"*, Trost, B. M.; Fleming, I.; Pergamon: Oxford, 1991, 6, 65.

3. (a) Marouka, K.; Yamamoto, H. en *"Comprehensive Organic Synthesis"*, Trost, B. M.; Fleming, I. Pergamon: Oxford, 1991, 6, 763. (b) Shioiri, T. en *"Comprehensive Organic Synthesis"*, Trost, B. M.; Fleming, I. Pergamon: Oxford, 1991, 6, 795.

4. Estudios computacionales pueden consultarse en: (a) Sitha, S.; Jewell. L. L. *Tetrahedron* **2010**, *66*, 3030. Cita original en: Steinborn, D.; Taube, R. *Z. Chem*. **1986**, *26*, 349. (b) Benson, S. W. en *"Thermodynamicals Kinetics: Methods for the Estimation of the Thermochemical Data and Rate Parameters"*, 2ª Ed., John Wiley & Sons Inc., 1976.

activación necesaria para la aproximación entre la amina y el alqueno o el alquino, especialmente cuando no están desactivados electrónicamente, ya que el par no enlazante del nitrógeno crea una gran repulsión electrostática sobre el enlace múltiple.[4a,5] Por ejemplo, la adición directa de una amina sobre un doble enlace se observa si éste está sustituido por grupos tales como carbonilo o nitrilo, pero no sobre olefinas simples.[6] Por otro lado, la adición [2+2] del enlace N-H sobre el alqueno está prohibida por simetría orbital y además es desfavorable debido a la gran diferencia de energía entre el orbital π (C=C) y el σ (N-H) Por todo esto, es esencial actuar bien sobre el alqueno, alquino o sobre el resto nitrogenado para favorecer la reacción.

Este grupo de métodos, que posibilitan estos procesos tanto de forma intermolecular como intramolecular sobre olefinas o alquinos simples, aparecen resumidos en el *Esquema 1.1*. Así, la reacción de *hidroaminación* consiste en la adición formal de enlaces N-H sobre enlaces múltiples C-C con reducción de dicho enlace. La reacción de *aminación oxidante* es particularmente interesante, ya que el producto final conserva la función insaturada, lo cual permite realizar sobre ella posteriores modificaciones. Por último, la previa activación de los enlaces múltiples C-C *empleando agentes electrófilos*, resulta ser una estrategia interesante que conduce a la obtención de los correspondientes productos funcionalizados.

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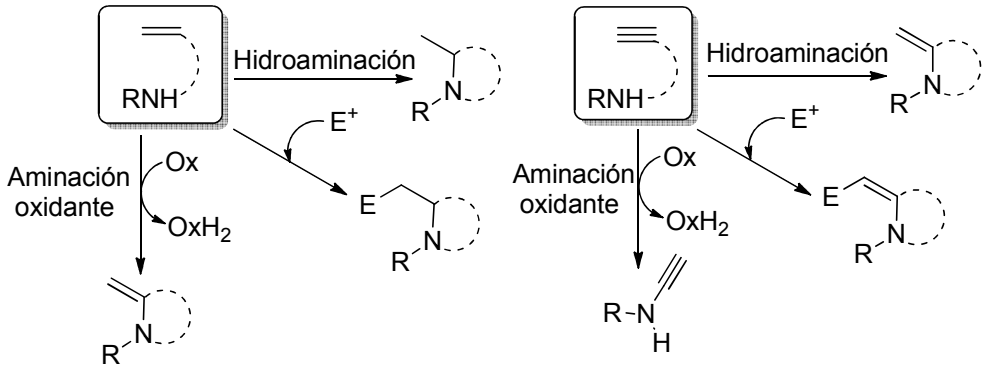
5. Taube, R. en *"Applied Homogeneous Catalysis with Organometallic Compounds"*, VCH, 1996.

6. (a) Simonyan, G. S.; Beileryan, N. M.; Pirumyan E. G.; Roque, J. –P.; Boyer, B. *Catalysis* **2001**, *42*, 474. (b) Suminov, S. I.; Kost, A. N. *Russ. Chem. Rev.* **1969**, *38*, 884. (c) Vercruysse, K.; Dejugnat, C.; Munoz, A.; Etemand-Moghadam, G. *Eur. J. Org. Chem.* **2000**, 281. (d) Burgada, R.; Mohri, A. *Phosphorus Sulfur* **1982**, *13*, 85. (e) Gibson, M. S. en *"The Chemistry of the Amino Group"*, Patai, S., Ed.; Interscience; New York, 1968.



Esquema 1.1. Alternativas para la aminación de enlaces múltiples C-C.

Para ceñirnos a la química que se pretende desarrollar en este trabajo, y para ubicarla en su adecuado contexto, en el siguiente apartado profundizaremos en las propuestas bibliográficas relativas a las reacciones de aminación de alquinos, exclusivamente, de manera tanto intra- como intermolecular.

2. AMINACIÓN DE ALQUINOS

El atractivo sintético del uso de aminas primarias y secundarias en reacciones de adición sobre alquinos reside en que los productos obtenidos, enaminas e iminas, pueden ser empleados en transformaciones posteriores con diferentes usos sintéticos.[7] Ha de destacarse, además, que los alquinos experimentan reacciones de aminación mucho más fácilmente que las olefinas debido tanto a razones estéricas como a la relativa debilidad de los enlaces π presentes en alquinos (aproximadamente 70 kJ/mol más débiles que los enlaces π de olefinas). A continuación, presentaremos algunos de los diferentes métodos que permiten estas reacciones.

2.1. Hidroaminación de alquinos.

Por las razones de tipo energético ya mencionadas, las aminas no reaccionan generalmente de manera espontánea con alquinos, si bien un triple enlace puede experimentar la adición directa de una amina si el sistema es deficiente en electrones, por ejemplo, al estar sustituido por grupos fluorados, alcoxilados o acilados.[8] Como consecuencia, las reacciones de aminación de alquinos simples han de promoverse con el empleo de ciertos catalizadores.

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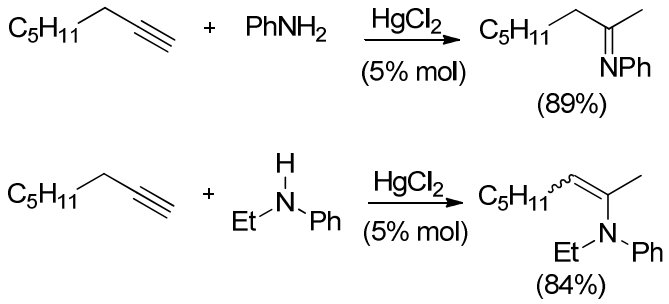
7. Una revisión sobre ciclaciones desencadenadas por hidroaminaciones de alquinos se puede consultar en: Patil, N. T.; Singh, V. *J. Organomet. Chem.* **2011**, *696*, 419.

8. Dahlen, K.; Wallen, E. A. A.; Grotli, M.; Luthman, K. *J. Org. Chem.*, **2006**, *71*, 6863. Originalmente citado en: Chekulaeva, I. A.; Kondrateva, L. V. *Russ. Chem. Rev. (Engl. Transl.)* **1965**, *34*, 669.

Está documentado que diversos catalizadores metálicos promueven la reacción de ***hidroaminación*** de enlaces múltiples, tanto de manera inter- como intramolecular.[9] Llevada a cabo sobre alquinos, dicha reacción conduce a la formación de enaminas, que, generalmente, isomerizan a su tautómero imínico. Hace más de 30 años, Barluenga y colaboradores, consiguieron promover reacciones de aminación de alquinos empleando *sales de mercurio y talio* en proporciones tanto estequiométricas como catalíticas.[10] Sin embargo, debido a su toxicidad, estos catalizadores cayeron en desuso, si bien revelaron su eficacia en la activación del triple enlace frente al ataque nucleofílico de las aminas (*Esquema 1.2*).

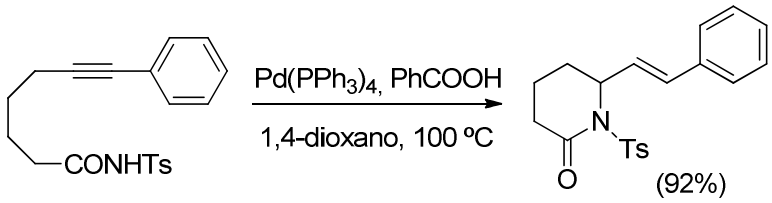


Esquema 1.2. Primeras aminaciones de alquinos.

9. Revisiones sobre el tema se pueden encontrar en: (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Nobis, M.; Drießen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983. (c) Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C. G.; Seayad, J.; Thiel, O. R.; Tillack, A.; Trauthwein, H. *Synlett* **2002**, 1579. (d) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (e) Doye, S. *Synlett* **2004**, 1653. (f) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (g) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407. (h) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubela, F.; Tada, M. *Chem. Rev.* **2008**, 3795.

10. (a) Aznar, F.; Barluenga, J. *Synthesis* **1977**, 195. (b) Rodes, R.; Liz, R.; Aznar, F.; Barluenga, J. *J. Chem. Soc., Perkin Trans I* **1980**, 2732.

Los *catalizadores de paladio* son, sin duda, los más ampliamente usados en las reacciones de hidroaminación catalítica de alquinos.[11] El *Esquema 1.3* muestra, a modo de ejemplo, cómo pueden promover reacciones de lactamización de alquinilamidas con elevados rendimientos.[12]



Esquema 1.3. Reacción de lactamización de alquinilamidas.

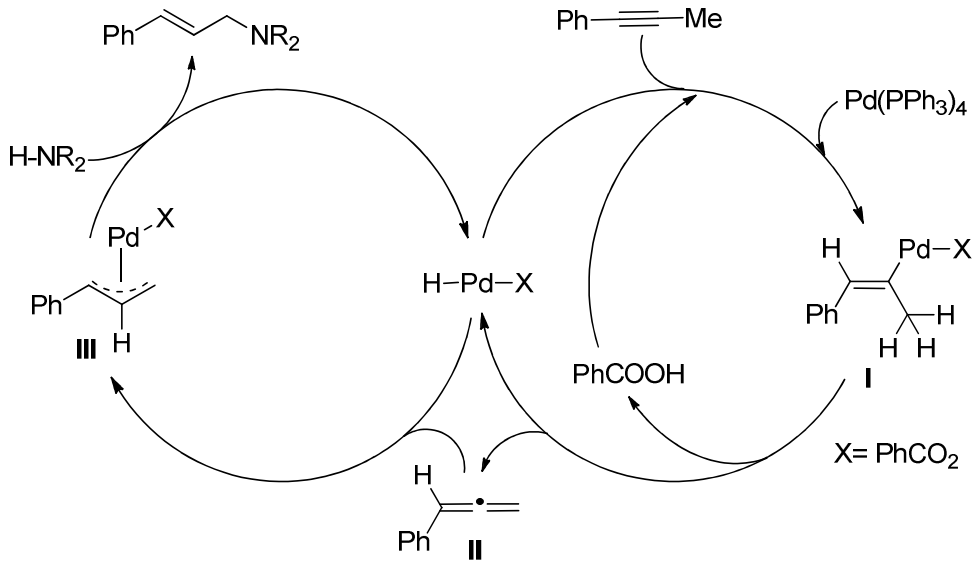
Una descripción más detallada del modo en que transcurre este proceso, aplicado a la aminación de 1-fenilpropino, aparece reflejada en el *Esquema 1.4*.[13] Lo esencial de la presencia del ácido benzoico en el medio de reacción radica en que, junto al $Pd(PPh_3)_4$, genera un alquenilpaladio **I**, especie activa que inicia el primer ciclo catalítico, dando lugar al intermedio **II**. En un segundo ciclo catalítico, la hidropaladación del aleno da lugar a

11. Las primeras referencias del uso de catalizadores de paladio para hidroaminaciones de enlaces múltiples se remontan a más de 30 años atrás, con la publicación de reacciones de aminación oxidante de olefinas. Para una revisión sobre este tema, véase: (a) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285.

12. Patil, N. T.; Huo, Z.; Bajracharya, G. B.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 3612.

13. Si bien el esquema muestra el mecanismo para la hidroaminación intermolecular, también es aplicable a la reacción intramolecular: Kadota, I.; Shibuya, A.; Lutete, M. L.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570.

una especie de π-alilpaladio **III** que reacciona con la amina para conducir al producto deseado y regenerar la especie activa de hidruro de paladio.

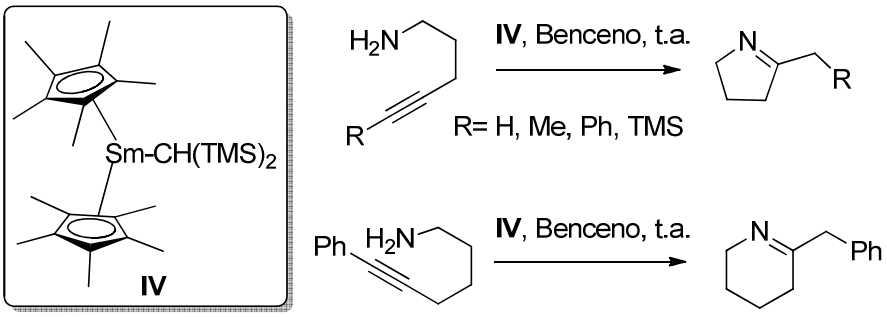


Esquema 1.4. Mecanismo propuesto para la hidroaminación de alquinos catalizada por paladio.

Los *organolantánidos* de tipo $Cp^*_2LnCH(TMS)$ y de tipo $Me_2SiCp^{\#}_2LnCH(TMS)_2$ ($Cp^*=\pi^5$-C_5Me_5, $Cp^{\#}=\pi^5$-C_5Me_4, Ln=Sm, Lu, Nd)[14] constituyen un grupo de catalizadores ampliamente empleados en las reacciones de hidroaminación intermolecular de alquinos. Con ellos también

14. Para una revisión sobre el empleo de organolantánidos en reacciones de hidroaminación de enlaces múltiples, véase: (a) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (b) Hannedouche, J.; Collin, J.; Trifonov, A.; Schulz, E. *J. Organomet. Chem.* **2011**, *696*, 255.

se ha acometido la ciclación intramolecular de aminoalquinos para dar lugar a heterociclos pirrolidínicos y piperidínicos (*Esquema 1.5*).[15]

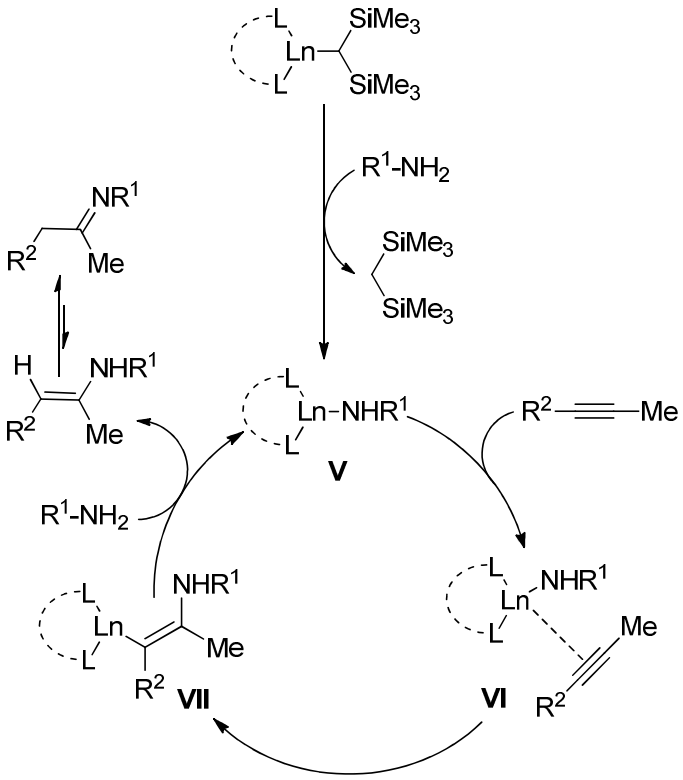


Esquema 1.5. Reacción de aminación intramolecular de alquinos.

Se ha propuesto que la reacción mencionada transcurre a través del mecanismo mostrado en el *Esquema 1.6*. En este caso, la especie catalítica de la reacción (intermedio **V**) es una amida lantánida, generada tras el desplazamiento del grupo *bis*(trimetilsilil)metilo por el grupo nitrogenado, que inserta regioselectivamente el alquino para dar lugar a un complejo alquinil-lantánido (intermedio **VI**). La protonación del enlace Ln-C en **VII** por una nueva molécula de la amina da lugar a la enamina precursora del

15. (a) Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 4108. (b) Gagné, M. R.; Nolan, S. P.; Marks, T. J. *Organometallics* **1990**, *9*, 1716. (c) Giardello, M. A.; Conticello, V. P.; Brard, L.; Sabat, M.; Rheingold, A. L.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10212. (d) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295.

producto final junto con la regeneración de la especie **V**, que inicia un nuevo ciclo catalítico.[16]



Esquema 1.6. Mecanismo propuesto para la reacción de aminación intermolecular de alquinos catalizada por organolantánidos.

16. Estudios cinéticos realizados confirman este mecanismo para las hidroaminaciones catalizadas por organolantánidos tanto inter- como intramoleculares: Ryu, J. -S.; Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584.

Conviene destacar que la alta eficacia que muestran los catalizadores mencionados hasta el momento queda devaluada, por una parte, por su elevada sensibilidad, lo que obliga al empleo de condiciones de reacción muy rigurosas, y, por otra parte, por su elevada oxofilia, lo cual impide que el proceso pueda extenderse a moléculas con funcionalidades coordinantes como éteres y grupos próticos (alcoholes y ácidos carboxílicos).

Entre los numerosos catalizadores empleados para abordar esta problemática han de citarse ciertos *complejos de titanio*, ya que no solo han demostrado su capacidad para catalizar eficientemente la hidroaminación de alquinos sino que, además, transcurren con un gran control regioselectivo. Así, la reacción de arilalquinos terminales asistida por el reactivo comercial Ind_2TiMe_2 (catalizador **VIII**) conduce mayoritariamente al isómero anti-Markovnikov, mientras que la reacción de alquilalquinos terminales con arilaminas muestra la orientación opuesta (*Esquema 1.7, Reacción 1*).[17]

Por otro lado, el uso de catalizadores del tipo **IX** en la hidroaminación de alquinos alifáticos con alquilaminas proporciona mayoritariamente el producto anti-Markovnikov. Estos catalizadores, por el contrario, conducen de manera exclusiva al producto Markovnikov cuando la reacción tiene lugar con aminas aromáticas estéricamente impedidas (*Esquema 1.7, Reacción 2*).[18]

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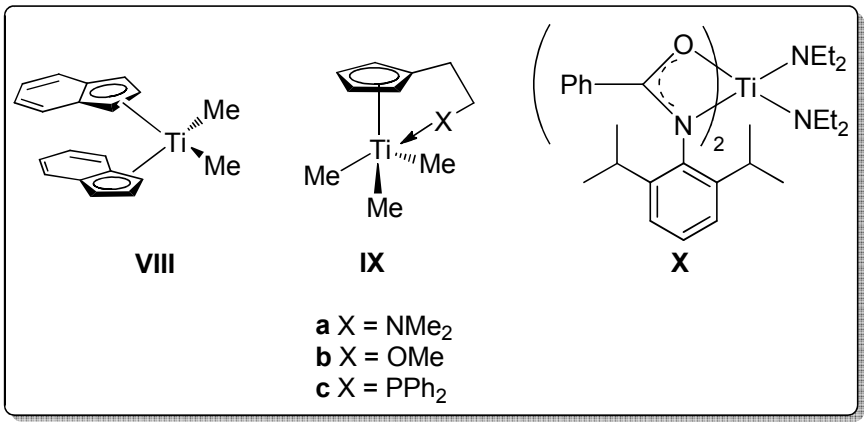
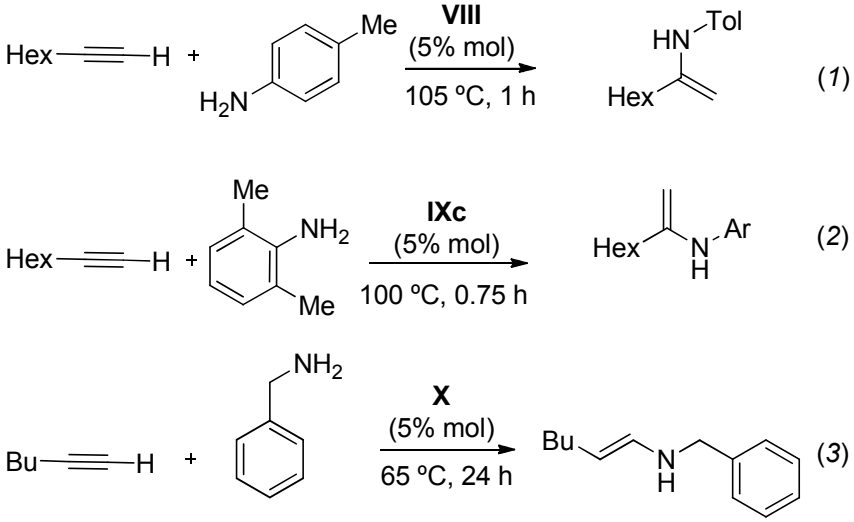
17. Heutling, A.; Pohlki, F.; Doye, S. *Chem. Eur. J.* **2004**, *10*, 3059.

18. (a) Oñate, E.; Esteruelas, A.; Lopez, A. M.; Mateo, A. C. *Organometallics* **2005**, *24*, 5084. (b) Oñate, E.; Esteruelas, A.; Lopez, A. M.; Mateo, A. C. *Organometallics* **2006**, *25*, 1448. (c) Buil, M. L.; Esteruelas, A.; Lopez, A. M.; Mateo, A. C. *Organometallics* **2006**, *25*, 4079.

Un ejemplo interesante de esta regioselectividad se encuentra en el uso del catalizador **X**, el cual facilita que una amina estéricamente menos impedida reaccione con varios alquinos alifáticos para dar lugar al producto anti-Markovnikov casi exclusivamente (*Esquema 1.7, Reacción 3*).[19]

19. Zhang, Z.; Schafer, L. L. *Org. Lett.* **2003**, *5*, 4733.

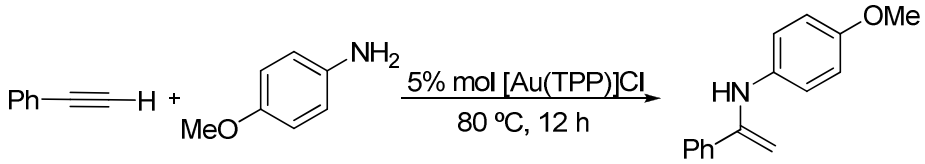




Esquema 1.7. Ejemplos de reacciones de hidroaminación intermolecular de alquinos catalizada por complejos de titanio.

Cuando los ejemplos anteriores se han extendido al uso de *catalizadores actínidos* tipo $Cp^*_2AcMe_2$ (donde Ac=U, Th) se ha verificado que tanto la quimio- como la regioselectividad del proceso dependen fuertemente de la naturaleza del catalizador y del volumen de la amina, y no tanto de la naturaleza del alquino. [20]

Se ha publicado, asimismo, la efectividad de algunos *catalizadores de oro*, como $(Ph_3P)AuCH_3$, para las reacciones de hidroaminación de alquinos.[21] A diferencia de los catalizadores de titanio, el uso de porfirinas de oro (III) en este tipo de procesos conduce a la formación exclusiva del producto Markonikov (*Esquema 1.8*).[22]



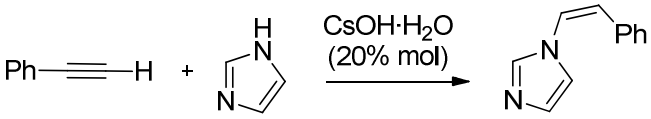
Esquema 1.8. Ejemplo de hidroaminación intermolecular de alquinos catalizada por porfirinas de oro (III).

20. (a) Haskel, A.; Straub, T.; Eisen, M. S. *Organometallics* **1996**, *15*, 3773. (b) Straub, T.; Haskel, A.; Neyroud, T. G.; Kapon, M.; Botoshansky, M.; Eisen, M. S. *Organometallics* **2001**, *20*, 5017. Una revisión sobre el empleo de organoactinidos se encuentra en: Eisen, M. S. *Top. Organomet. Chem.* **2010**, *31*, 157.

21. Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349. Revisiones sobre el empleo de catalizadores de oro en las reacciones de hidroaminación de enlaces múltiples C-C se encuentran en: (a) WidenHoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555. (b) Hashmi, A.; Stephen, K.; Buehrle, M. *Aldrichimica Acta* **2010**, *43*, 27.

22. Zhou, C. -Y.; Chan, P. W. H.; Che, C. -H. *Org. Lett.* **2006**, *8*, 325.

Las hidroaminaciones de alquinos *catalizadas por base* pueden ilustrarse con la adición de heterociclos nitrogenados a fenilacetileno para conducir a heterociclos enamínicos, lo que se muestra en el *Esquema 1.9*. Sin embargo, y a pesar de que con su uso se satisface el problema de la estabilidad de estos catalizadores frente a los enunciados al principio del apartado, su compatibilidad con la presencia de, por ejemplo, grupos hidroxilos en los sustratos queda por resolver ya que, en ocasiones, las fuertes condiciones de reacción requeridas pueden dar lugar a procesos de oligomerización.[23]

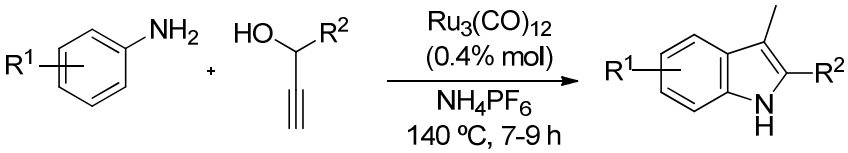


Esquema 1.9. Ejemplo de hidroaminación de alquinos catalizada por CsOH.

Así, debido a su baja afinidad por el oxígeno, los *complejos de rutenio* se han mostrado altamente eficientes para catalizar procesos de adición de aminas a alquinos terminales a partir de una gran variedad de

23. (a) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193. (b) Rodriguez, A.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 2488. (c) Lane, C.; Snieckus, V. *Synlett* **2000**, 1294. Una revisión sobre el empleo de bases para las reacciones de hidroaminación de olefinas y alquinos se encuentra en: Seayad, J.; Hartung, C. G.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795.

sustratos con diferentes grupos funcionales.[24] Tal como se muestra en el *Esquema 1.10*, la aminación intermolecular de alcoholes propargílicos con anilinas puede conseguirse mediante el empleo combinado de $Ru_3(CO)_{12}$ y NH_4PF_6, para preparar indoles 2,3-disustituidos.[25]



R^1 = H, *p*-Me, *o*-Me, *p*-Cl, *p*-MeO
R^2 = Me, Et, *n*-pentilo, Ph

Esquema 1.10. Ejemplo de reacción de aminación de alquino terminal catalizada por un complejo de rutenio.

Como mostraremos en este último bloque, la búsqueda de catalizadores que promueven con efectividad procesos de hidroaminación de alquinos se ha extendido a un amplio abanico de otros elementos metálicos. Por ejemplo, los *catalizadores de platino* son eficaces en las reacciones de adición de aminas a alquinos terminales.[26] Del mismo modo, el uso de

24. (a) Yi, C. S.; Yun, S. Y. *J. Am. Chem. Soc.* **2005**, *127*, 17000. (b) Kondo, T.; Okada, T.; Suzuki, T.; Mitsudo, T. *J. Organomet. Chem.* **2001**, *622*, 149.

25. Tokunaga, M.; Ota, M.; Haga, M. Wakatsuki, Y. *Tetrahedron Lett.* **2001**, *42*, 3865.

26. Brunet, J.-J.; Chu, N. C.; Diallo, O.; Vicendau, S. *J. Mol. Catal. A: Chem*. **2005**, *240*, 245.

complejos de zirconio permite la reacción de hidroaminación intramolecular de una gran variedad de aminas.[27]

Los *catalizadores de plata*[28] *y cobre*[29] también son eficaces en la reacción de aminación de alquinos, si bien merece destacarse el uso de *catalizadores de zinc y cobre inmovilizados*. De esta manera, se han llevado a cabo hidroaminaciones a través de sistemas heterogéneos de distintos tipos. El empleo de un sistema líquido-líquido, usando $Zn(OTf)_2$ como catalizador,[30] tiene la gran ventaja de que, debido a la sencilla recuperación del catalizador tras la reacción, permite su uso en grandes cantidades con escalas de reacción ventajosas. Otro método heterogéneo usado en la hidroaminación intermolecular de alquinos terminales con aminas aromáticas se basa en el uso del intercambio de metales de transición con la montmorillonita K-10,[31] una arcilla ácida formada por dos capas de sílica intercalada con otra octaédrica de alúmina, que puede intercambiar cationes con los metales de transición. Su empleo, en combinación con Cu^{2+}, permite obtener el producto de adición Markovnikov selectivamente (*Esquema 1.11).*

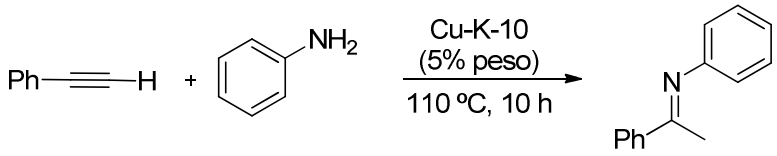
27. (a) Kim, H.; Livinghouse T.; Lee, P. H. *Tetrahedron* **2008**, *64*, 2525. (b) Born, K.; Doye, S. *Eur. J. Org. Chem*. **2012**, 764.

28. (a) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885. (b) van Esseveld, B. C. J.; Vervoor, P. W. H.; van Delft, F. L.; Rutjes, F. P. T. *J. Org. Chem.* **2005**, *70*, 1791. (c) Trost, B. M.; Fandrick, D. R. *Org. Lett.* **2005**, *7*, 823.

29. Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126.

30. Bodis, J.; Müller, T. E.; Lercher, J. A. *Green Chem.* **2003**, *5*, 227.

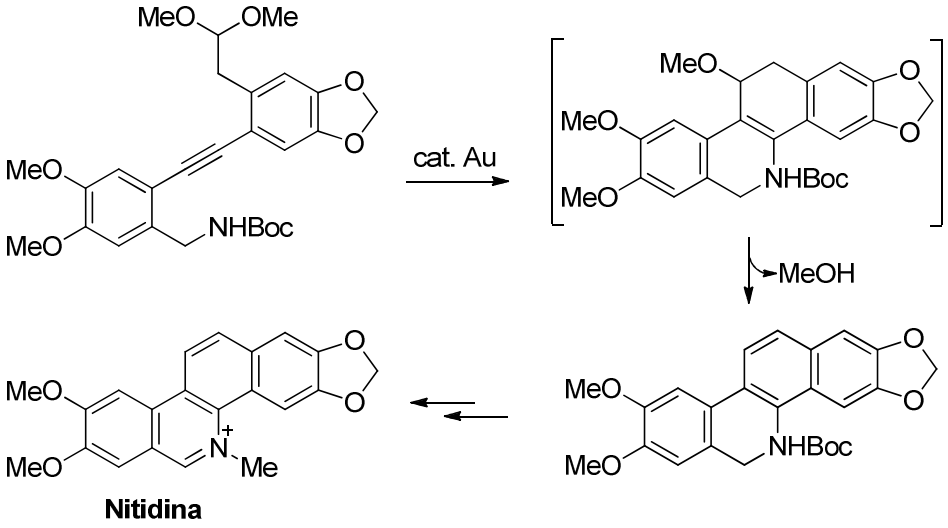
31. Shanbhag, G. V.; Kumbar, S. M.; Joseph, T.; Halligudi, S. B. *Tetrahedron Lett.* **2006**, *47*, 141.



Esquema 1.11. Empleo de catalizadores inmovilizados en la reacción de aminación de alquinos.

En la bibliografía se encuentran numerosos ejemplos sobre la inclusión de la reacción estudiada en rutas sintéticas conducentes a la preparación de productos naturales. Por dar únicamente un ejemplo de ello, se muestra en el *Esquema 1.12* la síntesis del alcaloide nitidina facilitada por un catalizador de oro (AuCl[(*o*-biPh)(^{t}Bu)$_2$P]Cl/AgNTf$_2$).[32]

32. Enomoto, T.; Girard, A. -L.; Yasui, Y.; Takemoto, Y. *J. Org. Chem.* **2009**, *74*, 9158.



Esquema 1.12. Síntesis del producto natural nitidina mediante el empleo de la reacción de hidroamonación de alquinos catalizada por oro.

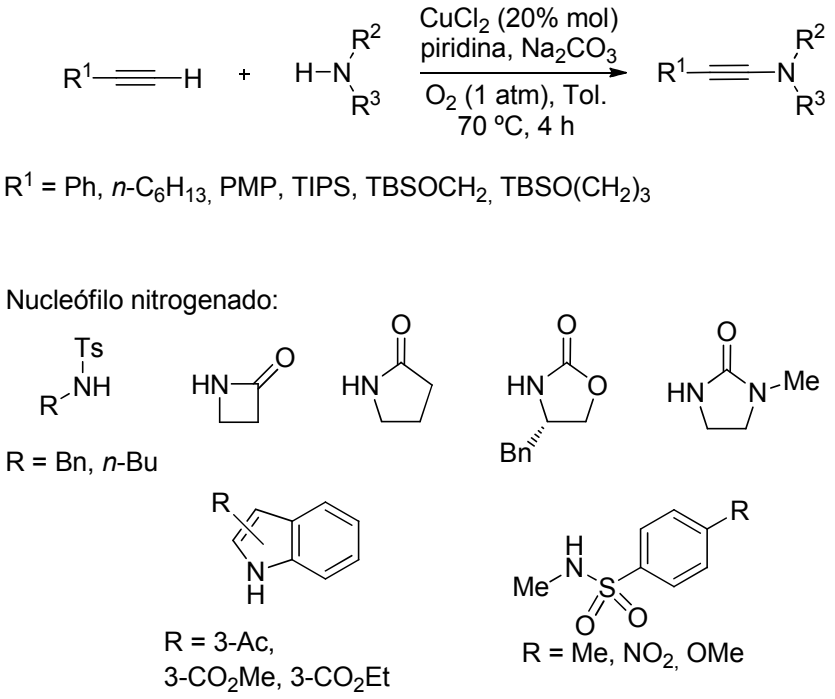
2.2. Aminación oxidante de alquinos.

Ya en la década de los años 80 se publicaron reacciones de aminación oxidante de olefinas[11] con $PdCl_2$ como catalizador y benzoquinona o $CuCl_2$ como agentes oxidantes primarios,[33] que derivaron posteriormente en el desarrollo de numerosos sistemas catalíticos para este tipo de procesos. Por el contrario, las publicaciones sobre reacciones de ***aminación oxidante*** de alquinos son mucho más escasas.

Recientemente, se ha verificado, por primera vez, el éxito de este tipo de reacciones para la preparación directa de inamidas a partir de alquinos y una gran variedad de diferentes compuestos nitrogenados (*Esquema 1.13*).[34]

33. (a) Hegedus, L. S.; Allen, G. F.; Waterman, E. L. *J. Am. Chem. Soc.* **1976**, *98*, 2674. (b) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800. (c) McDonald, R. I.; Liu, G.; Stahl S. S. *Chem. Rev.* **2011**, *111*, 2981.

34. Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833.



Esquema 1.13. Síntesis de inamidas a través de la reacción de aminación oxidante de alquinos.

En general, en esta reacción, los alquinos electrón deficientes son menos efectivos, mientras que los alquinos ricos en electrones presentan elevados rendimientos. De entre la serie de nucleófilos nitrogenados evaluados en su acción frente al fenilacetileno, ha de mencionarse que las pirrolidinonas no son efectivas para este acoplamiento.

2.3. Uso de reactivos electrófilos.

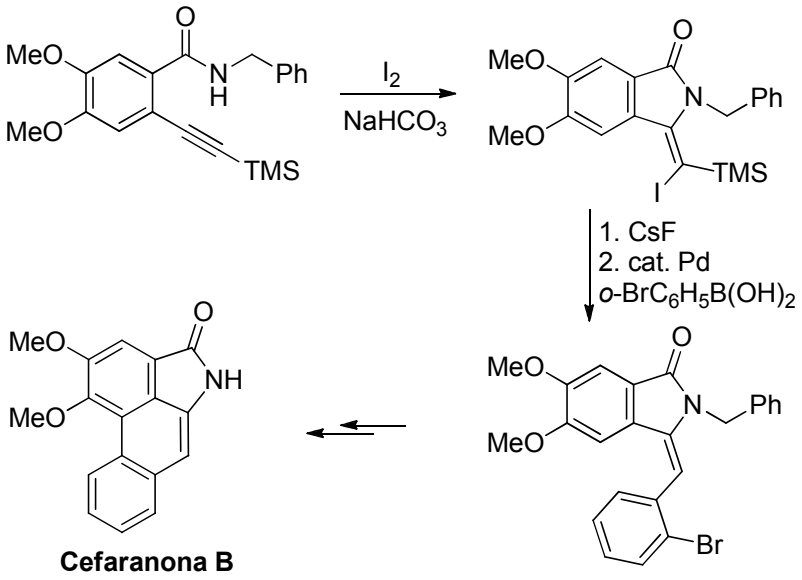
Del mismo modo a como hemos comentado para el uso de catalizadores metálicos, algunos ***reactivos electrófilos*** son capaces de activar enlaces múltiples formando especies intermedias reactivas para que puedan ser atacadas por nucleófilos nitrogenados de un modo más eficaz.[35] Siguiendo esta estrategia, se ha preparado una gran variedad de isoquinolinas,[36] indoles[37] e isoindoles[38] con elevados rendimientos en condiciones de reacción suaves, empleando reactivos de yodo, selenio y azufre como agentes electrófilos. Por ejemplo, tal como se muestra en el *Esquema 1.14*, uno de los pasos claves en la síntesis del alcaloide cefaranona B se caracteriza por el empleo de yodo molecular. En este ejemplo, y en los que siguen, queda expuesto, también, cómo el electrófilo que queda incorporado en el producto se convierte, generalmente, en un punto de diversificación estructural de la molécula, lo que incrementa el atractivo de este método.

35. (a) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321. (b) Castellanos, A.; Fletcher, S. P. *Chem. Eur. J.* **2011**, *17*, 5766.

36. (a) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437. (b) Ding, Q.; Wu, J. *Adv. Synth. Catal.* **2008**, *350*, 1850.

37. (a) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037. (b) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 62.

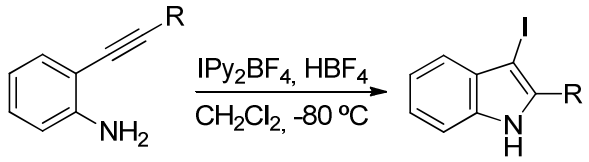
38. (a) Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432. (b) Smith, K.; El-Hiti, G. A.; Hegazy, A. S.; Kanuki, B. *Beilstein J. Org. Chem.* **2011**, *7*, 1219.



Esquema 1.14. Empleo de yodo molecular como reactivo electrófilo en la síntesis del alcaloide cefaranona B.

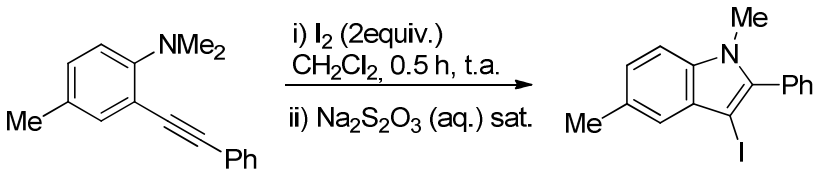
Por otra parte, la síntesis de yodoindoles ha sido descrita con diferentes reactivos electrófilos. Así, como se muestra en el *Esquema 1.15*, el reactivo tetrafluoroborato de yodobis(piridina) promueve la ciclación de diferentes aminas permitiendo incluso la reacción de aminas sin proteger.[39]

39. Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406.



Esquema 1.15. Empleo del reactivo de Barluenga en la preparación de yodoindoles.

Finalmente, cabe mencionar que la reacción de aminación de alquinos promovida por yodo molecular[37b] constituye un método muy eficaz de síntesis de yodoindoles (*Esquema 1.16*).



Esquema 1.16. Reacción de aminación de alquinos promovida por yodo molecular en la síntesis de yodoindoles.

En este ámbito de la aminación de olefinas y alquinos promovida por el empleo de reactivos electrófilos puede encuadrarse el trabajo de investigación que nuestro grupo viene realizando en los últimos años. En particular, nos hemos centrado en la reacción de aminación intramolecular,

tanto de olefinas como de alquinos, promovida por el reactivo de yodo hipervalente [*bis*(trifluoroacetoxi)yodo]benceno (PIFA).

En el siguiente apartado describiremos detalladamente las características de los reactivos de I(III), centrándonos tanto en su carácter electrófilo, capaz de activar triples enlaces, como en su carácter oxidante, lo que posibilita la transformación de un resto nitrogenado en un potente electrófilo.

3. USO DE LOS REACTIVOS DE YODO HIPERVALENTE EN PROCESOS DE AMINACIÓN DE ENLACES MÚLTIPLES CARBONO-CARBONO

3.1. Consideraciones generales.

En las últimas décadas, la química de los reactivos de yodo hipervalente se ha ido desarrollando a pasos agigantados ante la evidencia de que permiten realizar gran variedad de transformaciones orgánicas, siendo de aplicación, por tanto, en multitud de diseños sintéticos.[40]

La reactividad tan variada de estos compuestos se debe, principalmente, a la electrofilia que presenta el átomo de yodo en dichas moléculas, fruto de la debilidad y polaridad del enlace hipervalente, y al carácter de "super grupo saliente" que posee el yodobenceno,[41] principal subproducto de la reacción. Su comportamiento se asemeja, en muchos casos, al de los compuestos de coordinación de metales de transición, ya que

40. (a) Varvoglis, A. en "*Hypervalent Iodine in Organic Synthesis"*; Academic Press: San Diego,1997. (b) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (c) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. (d) Zhdankin. V. V. *Curr. Org. Synth*. **2005**, *2*, 121. (e) Ladziata, U.; Zhdankin. V. V. *ARKIVOC* **2006**, *ix*, 26. (f) Zhdankin. V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (g) Zhdankin. V. V.; Stang, P. J. *Chem. Rev.* **1996**, *96*, 1123. (h) Varvoglis, A. *Tetrahedron* **1997**, *54*, 1179. (i) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (j) Zhdankin, V. V.; Stang, P. J. *Chem. Rev*. **2008**, *108*, 5299. (k) Silva, L. F. Jr.; Olofsson, B. *Natural Product Reports* **2011**, *28*, 1722. (l) Turner, C. D.; Ciufolini, M. A. *Arkivoc* **2011**, *(i)*, 410.

41. La pérdida de yodobenceno a partir de una sal de yodonio es comparable a la pérdida de nitrógeno de una sal de diazonio y ha sido estimada para el caso particular de sales de alquenilyodonio en $8x10^5$ veces superior a la del grupo triflato: Okuyama, T.; Takino, T.; Sueda, T.; Ochiai, M. *J. Am. Chem. Soc*. **1995**, *117*, 3360.

evolucionan a través de mecanismos de reacción formalmente idénticos a los de la química organometálica.[42]

El término hipervalencia[43] es de aplicación cuando elementos de los grupos 15-18 de la Tabla Periódica presentan una valencia mayor que la predicha por la Teoría de Lewis-Langmuir, es decir, cuando su capa de valencia está formada por 10 o 12 electrones. De hecho, en los reactivos más importantes de yodo hipervalente dicho elemento presenta estado de oxidación III (yodanos) o V (peryodanos), y cuenta con 10 o 12 electrones de valencia, respectivamente. Con las excepciones del reactivo de Dess-Martin y su precursor, el ácido *o*-yodosilbenzoico, la mayoría de ellos pertenecen a familias en las que el átomo de yodo posee un número de coordinación 2 o 3.[42a]

Tal como muestra la *Figura 1.1*, en los compuestos tipo **XI**,[44] el grupo menos electronegativo (L_1) está unido al yodo por un enlace covalente normal y se sitúa en la parte ecuatorial de una bipirámide trigonal. Los otros ligandos (L_2 y L_3) se hallan en las posiciones axiales unidos ambos a un orbital 5p del átomo de yodo. De este modo se forma un sistema lineal que contiene 3 centros y 4 electrones (3c-4e). Estos enlaces 3c-4e, comúnmente llamados enlaces hipervalentes, son más largos y más débiles que los enlaces covalentes normales. La mayor densidad electrónica está

42. (a) Martin, J. C. *Science* **1983**, *221*, 509. (b) Akiba, K.; Yamamoto, Y. *Heteroatom Chem.* **2007**, *18*, 161. (c) Akiba, K. *Heteroatom Chem.* **2011**, *22*, 207.

43. Término acuñado en: Musher, J. I. *Angew. Chem., Int. Ed. Eng.* **1969**, *8*, 54.

44. En esta notación se indica, entre paréntesis, el número de electrones de valencia alrededor del átomo de yodo, seguido del número de ligandos unidos a él.

situada en los extremos del eje que une los tres centros y, por ello, los ligandos más electronegativos (L_2 y L_3) estabilizan los yodanos.[40a]

En los compuestos tipo **XII**, se establecen dos enlaces hipervalentes ortogonales (3c-4e) y un enlace covalente normal, adoptando el conjunto geometría pirámide cuadrada, pseudo bipirámide trigonal o pseudo octahédrica en función de los ligandos que porte el yodo.

En compuestos con la estructura tipo **XIII**, por ejemplo, el fenil-yodosilo, los enlaces hipervalentes se crean por la interacción de dos orbitales simplemente ocupados del ligando y un orbital 5p doblemente ocupado del átomo de yodo (2c-4e). Este enlace se encuentra fuertemente polarizado y la molécula se expresa más correctamente con una representación zwitteriónica.

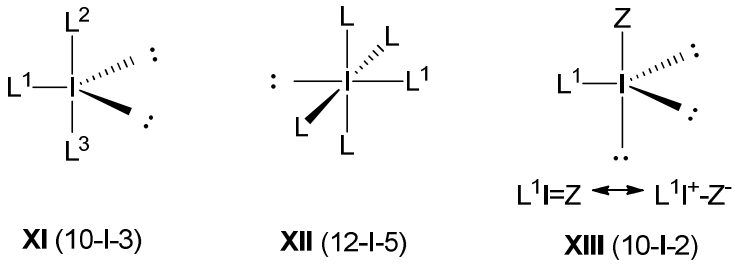
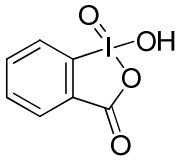
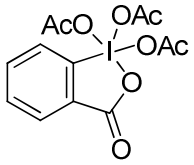


Figura 1.1. Estructura de los compuestos de yodo hipervalente.

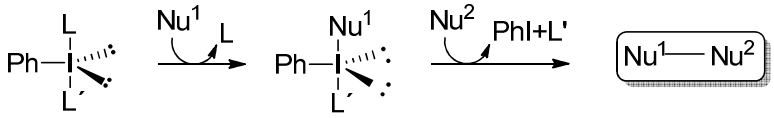
Los reactivos de yodo hipervalente son conocidos desde finales del siglo XIX, cuando se sintetizó por primera vez el dicloroyodobenceno,[45] primer miembro de esta familia de compuestos. Desde entonces, el gran interés en el uso de nuevas metodologías sintéticas que eviten el empleo de sustancias tóxicas, peligrosas o agresivas con el medio, ha impulsado la búsqueda de nuevas aplicaciones de este tipo de compuestos en sustitución de reactivos metálicos, así como la preparación de nuevos compuestos organoyodados polivalentes. En la *Tabla 1.1* se muestran algunos de los reactivos de yodo hipervalente comerciales más empleados así como las referencias donde se describe su preparación.

45. Willgerodt, C. *J. Prakt. Chem.* **1886**, *33*,154.

Tabla 1.1. Reactivos de yodo hipervalente comerciales más comunes.

Reactivo	Nombre/Acrónimo	Tipo	Referencia
$PhI(OAc)_2$	(Diacetoxiyodo)benceno/**PIDA**	I(III)	*Org. Synth.* **1973**, 660
$PhI(OCOCF_3)_2$	[*Bis*(trifluoroacetoxi)yodo]benceno/**PIFA**	I(III)	*Synthesis* **1975**, 445
PhI(OH)OTs	[Hidroxi(tosiloxi)yodo]benceno/**HTIB**	I(III)	*J. Org. Chem.* **1977**, *42*, 1476
PhIO	Fenilyodosilo/**IOB**	I(III)	*Org. Synth.* **1973**, 658
$PhIO_2$	Fenilyodilo	I(V)	*J. Org. Chem.* **1993**, *58*, 1264
	Óxido de 1-hidroxi-1,2-benzyodoxol-3(*1H*)ona/**IBX**	I(V)	*J. Org. Chem.* **1999**, *64*, 4537
	1,1,1-Triacetoxi-1,1-dihidro-1,2-benzyodoxol-3(*1H*)-ona/**DMP**	I(V)	*J. Am. Chem. Soc.* **1991**, *113*, 7277

El *Esquema 1.17* recoge las dos características principales que muestran en su acción este tipo de reactivos, esto es, la posibilidad de intercambio de ligandos en el átomo de yodo, sin cambio en el estado de oxidación, y el intercambio de ligandos con eliminación reductora de yodobenceno.



Esquema 1.17. Reactividad general de los compuestos de yodo hipervalente.

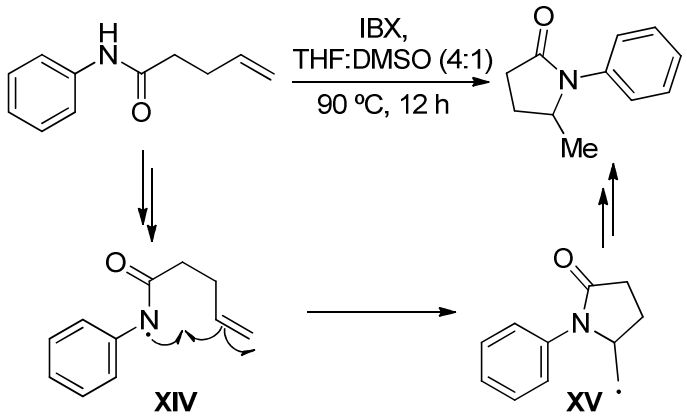
Por todo esto, la mayoría de las reacciones promovidas por reactivos de yodo hipervalente transcurren sobre sustratos oxidables o nucleófilos, y las de oxidación son, precisamente, el tipo de transformación que domina la reactividad de estos compuestos, bien en procesos de oxidación directa,[46] o bien en reacciones de funcionalización, degradación, transposición y ciclación oxidantes, a través de mecanismos tanto iónicos como radicalarios.[47]

Ciñéndonos al objeto de esta introducción, ha de mencionarse que se han descrito métodos de amidación de olefinas mediados por reactivos de yodo pentavalentes, como es el caso del IBX, que han conducido a la formación de diferentes heterociclos nitrogenados como δ-lactamas, carbamatos cíclicos, 1,2-hidroxiaminas y aminoazúcares, a partir de las

46. La oxidación de alcoholes a compuestos carbonílicos empleando reactivos de yodo hipervalente está ampliamente documentada. Una revisión reciente sobre el tema se puede encontrar en: Uyanik, M.; Ishihara, K. *Aldrichimica Acta* **2010**, *43*, 83.

47. (a) Muraki, T.; Togo, H.; Yokoyama, M. *Rev. Het. Chem.* **1997**, *17*, 213. (b) Togo, H.; Katohgi, M. *Synlett* **2001**, 565.

correspondientes N-arilamidas.[48] Para su descripción mecanística se propone la generación de un intermedio radical amidilo de tipo **XIV** que experimenta un proceso de ciclación 5-exo-trig sobre el doble enlace para dar lugar a la especie **XV**, la cual atrapa un átomo de hidrógeno del disolvente (THF) generando, así, el producto deseado (*Esquema 1.18*).



Esquema 1.18. Mecanismo simplificado para la reacción de amidación olefínica mediada por IBX.

En términos generales, los radicales centrados en el nitrógeno reaccionan con funciones orgánicas saturadas e insaturadas para formar enlaces carbono-nitrógeno y producir un nuevo radical centrado en el carbono, el cual puede ser atrapado mediante una reacción de transferencia

48. (a) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 625. (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233.

de grupo a través de un mecanismo en cadena. Así, la secuencia más empleada implica la generación de la especie radicalaria y la posterior ciclación intramolecular con un resto olefínico.[49]

Debido a la capacidad electroatractora del grupo carbonilo, los radicales amidilo presentan carácter electrófilo y una reactividad intermedia entre los radicales amidilo neutros y los cationes radicales (*Figura 1.2*).

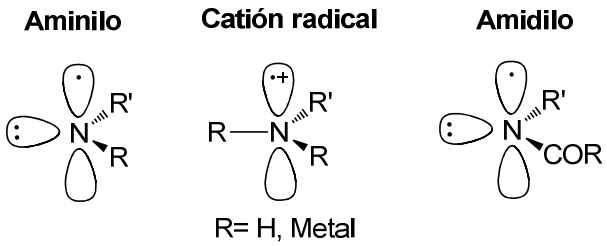
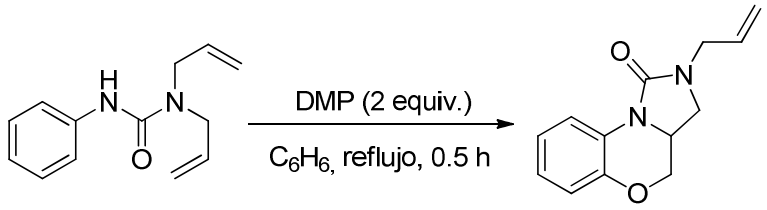


Figura 1.2. Radicales centrados en el nitrógeno.

En el *Esquema 1.19* se muestra otro ejemplo de preparación de heterociclos nitrogenados a través de un proceso de aminación de olefinas promovido por el reactivo de Dess-Martin, uno de los reactivos de yodo hipervalente más popularmente extendido.[50]

49. Seguiremos en este apartado introductorio ilustrando los precedentes de la acción de los reactivos de yodo hipervalente en la reacción de aminación de olefinas únicamente, ya que la de alquinos era inexistente cuando nuestro grupo inició sus investigaciones en este terreno.

50. (a) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 622. (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Sugita, K. *J. Am. Chem. Soc.* **2002**, *124*, 2212.



Esquema 1.19. Ejemplo de aminación de olefinas promovida por DMP.

3.2. Antecedentes en nuestro grupo de investigación.

Dada su acentuada reactividad, nos hemos sentido especialmente atraídos por el comportamiento del reactivo de yodo hipervalente [*bis*(trifluoroacetoxi)yodo]benceno (PIFA), un compuesto comercial de bajo coste que se presenta como un sólido cristalino estable. Este reactivo ha sido empleado en multitud de diferentes transformaciones, tales como oxidación fenólica,[51] sustitución electrófila aromática,[52] acoplamiento biarílico oxidativo,[53] adición oxidativa a olefinas,[54] desprotección de ditioacetales[55] y amidación electrófila aromática,[56] entre otros.

Si bien las primeras investigaciones de nuestro grupo en las que se recurrió a tal reactivo se centraron en su capacidad para la formación de enlaces C-C a través de procesos de acoplamiento biarílico oxidativo,[57]

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51. (a) Tamura, Y.; Yakura T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (b) Venkateswarlu, R.; Kamakshi, C.; Subas, P. V.; Moinuddin, S. G. A.; Reddy, D. R. S.; Ward, R. S.; Welter, A.; Gelbrich, T.; Hursthouse, M. B.; Coles, S. J.; Light, M. E. *Tetrahedron* **2006**, *62*, 4463.

52. (a) Kita,Y.; Tohma, H.; Inagaki, M.; Hatenaka, K.; Yakura, T. *Tetrahedron Lett.* **1991**, *32*, 4321. (b) D'Auria, M.; Mauriello, G. *Tetrahedron Lett.* **1995**, *36*, 4883.

53. (a) Dohi, T.; Morimoto, K.; Maruyama, A.; Kita, Y. *Org. Lett.* **2006**, *8*, 2007. (b) Tang, C.; Li, Z.; Wang, Y.; Xu, J.; Kong, L.; Yao, H.; Wu, X. *Tetrahedron Lett.* **2011**, *52*, 3275. (c) Hackelöer. K.; Schnakenburg, G.; Waldvogel, S. R. *Eur. J. Org. Chem.* **2011**, 6314.

54. Celik, M.; Alp, C.; Coskun, B.; Gültekin, M. S.; Balci, M. *Tetrahedron Lett.* **2006**, *47*, 3659.

55. (a) Store, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287. (b) Fleming, F. F.; Funk, L.; Altundas, R.; Tu, Y. *J. Org. Chem.* **2001**, *66*, 6502.

56. (a) Kikugawa, Y.; Kawase, M. *Chem. Lett.* **1990**, 581. (b) Romero, A. G.; Darlington, W. H.; Jacobsen, E. J.; Mickelson, J. W. *Tetrahedron Lett.* **1996**, *37*, 2361. (c) Romero, A. G.; Darlington, W. H.; McMillan, M. W. *J. Org. Chem.* **1997**, *62*, 6582. (d) Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053. (e) Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 2353. (f) Chang, C.-Y.; Yang, T.-K. *Tetrahedron: Asymmetry* **2003**, *14*, 2081. (g) Wardrop, D. J.; Burge, M. S.; Zhang, W.; Ortiz, J. A. *Tetrahedron Lett.* **2003**, *44*, 2587.

57. Véase, por ejemplo: (a) Olivera, R.; SanMartin, R. Domínguez, E. *J. Org. Chem.* **2000**, *65*, 7010. (b) Moreno, I.; Tellitu, I.; Herrero, M. T.; SanMartin, R.; Domínguez, E. *Curr. Org. Chem.* **2002**, *6*,

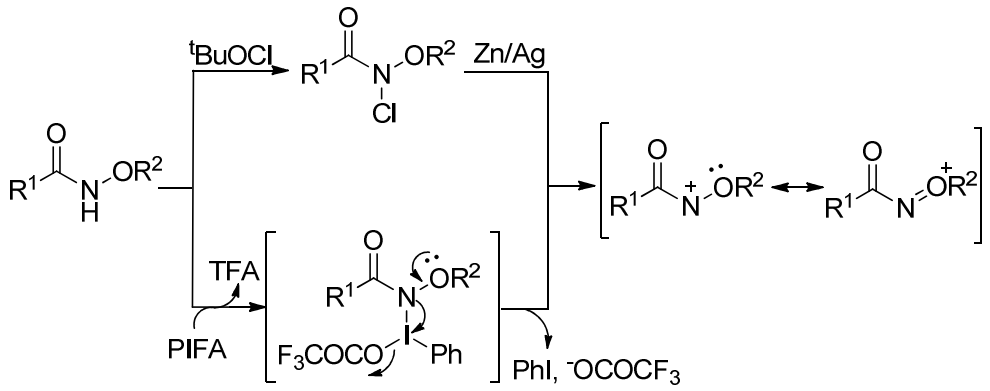
actualmente nuestra investigación cursa sobre su capacidad oxidante, con el propósito de acceder a compuestos N-heterocíclicos mediante la formación de enlaces C-N.

Una de las principales características que ha de destacarse en el reactivo de yodo hipervalente PIFA es su capacidad para generar intermedios N-acilnitrénicos a partir de amidas. La formación de este tipo de intermedios fue descrita por primera durante el estudio de la reacción de oxidación de *N*-cloro-*N*-metoxiamidas con sales de zinc y plata.[58] Algo más tarde se observó que cuando amidas primarias sustituidas por un grupo metoxilo (N-metoxiamidas) son tratadas con PIFA, también conducen a la formación de estos intermedios,[56a] que se habían mostrado muy eficaces como electrófilos en reacciones de sustitución electrófila aromática.[59] Esta metodología, por lo tanto, evita el paso previo de cloración de las alcoxiamidas, inhibe, en su caso, la formación de subproductos de cloración aromática, y evita, finalmente, el empleo de cantidades estequiométricas de sales metálicas, minimizando los problemas de solubilidad, toxicidad y gasto económico (*Esquema 1.20*).

1433. (c) Moreno, I.; Tellitu, I.; SanMartin, R.; Domínguez, E. *Eur. J. Org. Chem.* **2002**, 2126. (d) Churruca, F.; SanMartin, R.; Carril, M.; Urtiaga, K.; Solans, X.; Tellitu, I.; Domínguez, E. *J. Org. Chem.* **2005**, *70*, 3178. (e) Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Eur. J. Org. Chem.* **2005**, 2481.

58. (a) Glover, S. A.; Goosen, A.; McCleland, C. W.; Schoonraad, J. L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2555. (b) Kikugawa, Y.; Kawase, M. *J. Am. Chem. Soc.* **1984**, *106*, 5728.

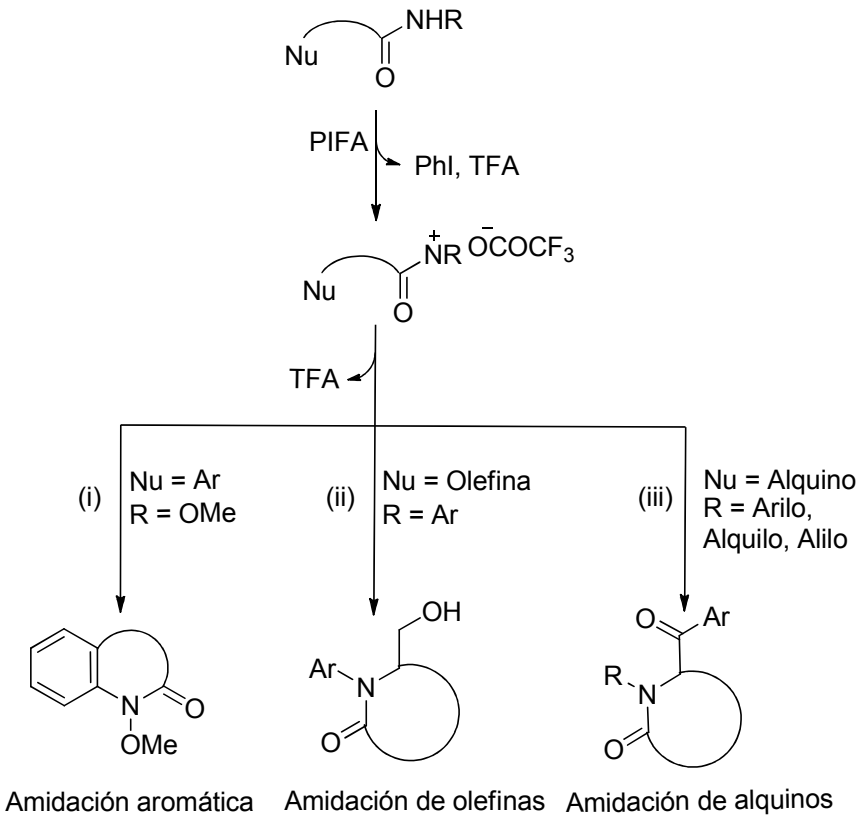
59. (a) Kikugawa, Y.; Shimada, M. *Chem. Lett.* **1987**, 1771. (b) Glover, S. A.; Goosen, A.; McCleland, C.; Schoonraad, J. L. *Tetrahedron* **1987**, *43*, 2577. (c) Kawase, M.; Kitamura, T.; Kikugawa, Y. *J. Org. Chem.* **1989**, *54*, 3394. (d) Glover, S. A.; Scott, A. P. *Tetrahedron* **1989**, *45*, 1763. (e) Kawase, M.; Miyake, Y.; Sakamoto, T.; Shimada, M.; Kikugawa, Y. *Tetrahedron* **1989**, *45*, 1653. (f) Kikugawa, Y.; Shimada, M.; Matsumoto, K. *Heterocycles* **1994**, *37*, 293.



Esquema 1.20. Formación de intermedios N-acilnitrenios a partir de N-metoxiamidas.

En nuestro grupo de investigación hemos venido aplicando esta estrategia sintética a través de tres enfoques diferentes: (i) la *amidación electrófila aromática*, que tiene lugar sobre N-metoxiamidas que porten un resto aromático en la posición requerida; (ii) la *amidación de olefinas*, que, a partir de los sustratos acíclicos adecuados N-arilsustituidos, conduce a la formación de isoquinolinonas, isoindolinonas, pirrolidinas y piperidinas hidroximetil sutituidas; (iii) y, por último, su extensión a la *amidación de alquinos*, lo que permite construir 5-aroil-pirrolidinonas a partir de alquinilamidas lineales N-sustituidas (*Esquema 1.21*).[60]

60. En las páginas siguientes se darán detalles adicionales que ayudarán a comprender mejor lo expuesto, de modo un tanto simplificado, en el *Esquema 1.21*.



Esquema 1.21. Enfoques de nuestra estrategia sintética.

Como hemos comentado anteriormente, la propuesta inicialmente desarrollada por Kikugawa para promover procesos de *amidación electrófila aromática* por acción del reactivo PIFA, se ha aplicado, en nuestro grupo, a

la síntesis de quinolin-2-onas fusionadas a heterociclos,[61] 1,4-diazepin-2-onas[62] y pirrolo[2,1-c]1,4-diazepin-2-onas[63] (*Figura 1.3*).

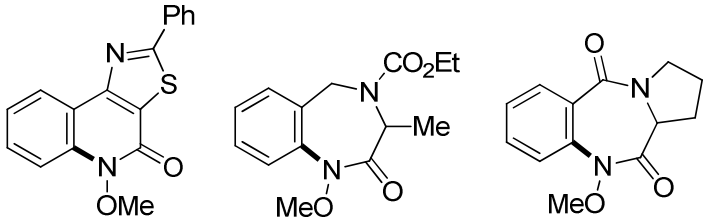


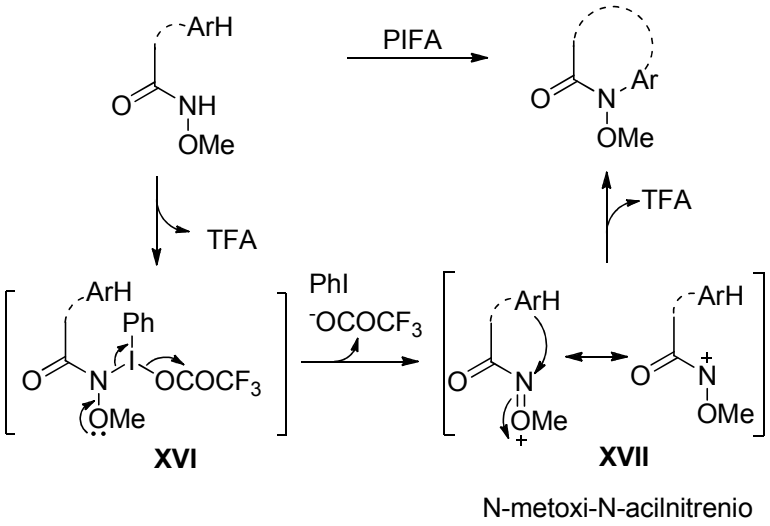
Figura 1.3. Heterociclos sintetizados en nuestro grupo.

Este proceso puede explicarse a través del mecanismo que se recoge en el *Esquema 1.22*. Así, la adición de PIFA sobre una N-metoxiamida da lugar a un proceso de intercambio de ligandos en el átomo de yodo que culmina en la generación de una especie intermedia **XVI.** La fragmentación de este intermedio conduce a la formación de la especie catiónica electrófila **XVII**, estabilizada por el grupo metoxílico adyacente, y susceptible de reaccionar con un nucleófilo aromático.

61. (a) Herrero, M. T.; Tellitu, I.; Hernández, S.; Domínguez, E.; Moreno, I.; SanMartin, R. *ARKIVOC* **2002**, 31. (b) Herrero, M. T.; Tellitu, I.; Hernández, S.; Domínguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron* **2002**, *58*, 8581.

62. (a) Herrero, M. T.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron Lett.* **2002**, *43*, 8273. (b) Correa, A.; Herrero, M. T.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron* **2003**, *59*, 7103.

63. Correa, A.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *J. Org. Chem.* **2005**, *70*, 2256.

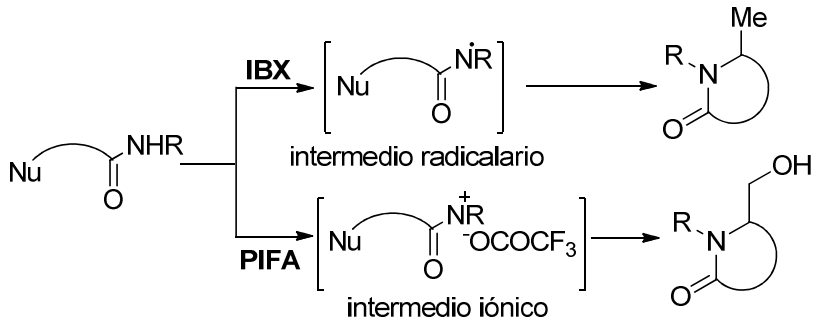


Esquema 1.22. Mecanismo propuesto para la amidación electrófila aromática mediada por PIFA.

Por otro lado, al tiempo que Nicolaou publicaba sus trabajos sobre la ciclación radicalaria de amidas insaturadas mediante el uso del reactivo IBX (*Esquema 1.18*, página 33), nuestro grupo elaboró un novedoso proceso de *amidohidroxilación de olefinas* intramolecular que venía promovido por el reactivo PIFA (*Esquema 1.23*). Este proceso, desarrollado para la preparación de isoquinolinonas e isoindolinonas,[64] fue extendido

64. Serna, S.; Tellitu, I.; Domínguez, E.; Moreno, I; SanMartín, R. *Tetrahedron Lett.* **2003**, *44*, 3483.

posteriormente a la preparación de pirrolidinas y piperidinas hidroximetil sutituidas.[65]

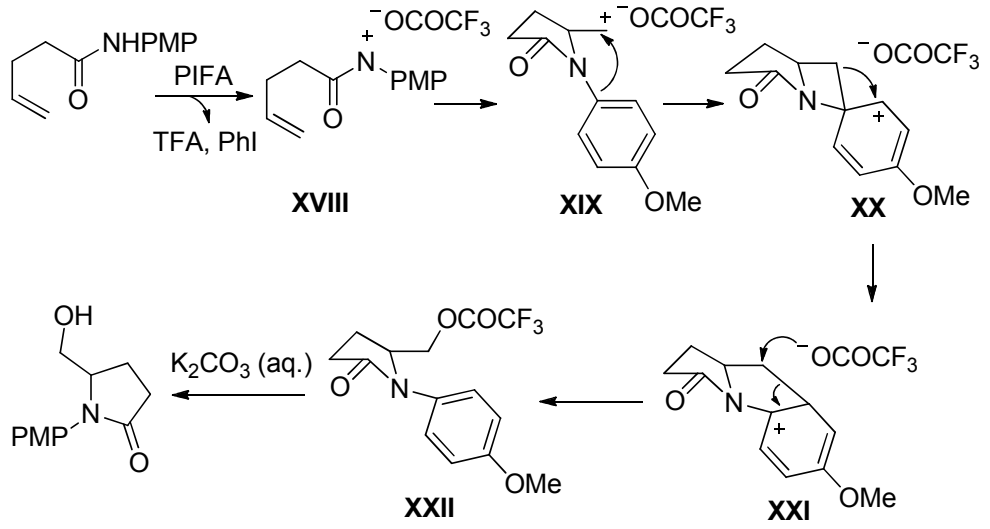


Esquema 1.23. Amidación de olefinas mediada por IBX y PIFA (Nu=olefina).

La observación experimental de que la heterociclación precisaba de sustituyentes arílicos sobre el nitrógeno amídico nos llevó a proponer el mecanismo descrito en el *Esquema 1.24*. Así, el ión acilnitrenio **XVIII**, resultado de la oxidación de la función amídica por el reactivo PIFA, reacciona intramolecularmente en modo exo con el resto olefínico para conducir a un intermedio deficitario **XIX**. Este evoluciona por un ataque ipso del grupo arilo adyacente hacia un carbocatión más estable **XX**, el cual sufre una migración 1,2 proporcionando el intermedio más estable **XXI** que, a su vez, es atacado por el grupo trifluoroacetato generado a partir del

65. (a) Correa, A.; Tellitu, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 8316. (b) Serna, S.; Tellitu, I.; Domínguez, E.; Moreno, I; SanMartín, R. *Org. Lett.* **2005**, *7*, 14, 3073. (c) Tellitu, I.; Urrejola, A.; Serna, S.; Moreno, I; Herrero, M. T.; Domínguez, E.; SanMartín, R.; Correa, A. *Eur. J. Org. Chem.* **2007**, 437.

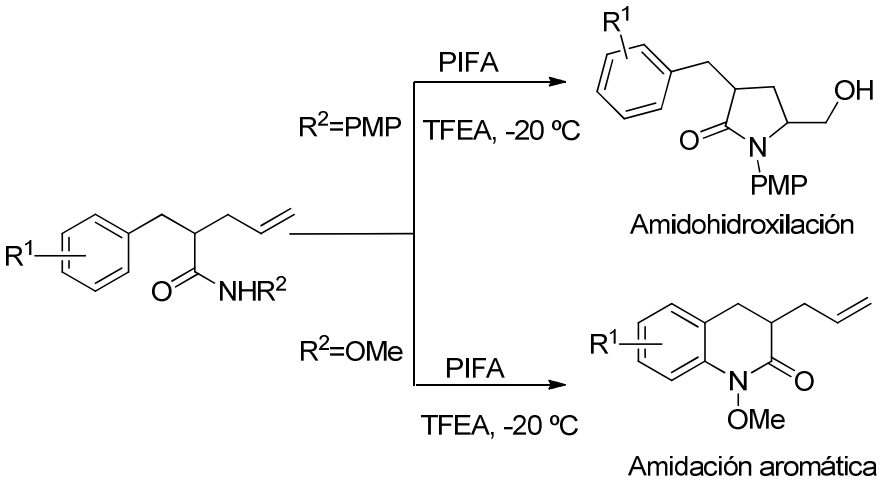
reactivo PIFA dando lugar al trifluoroéster **XXII**. La hidrólisis, durante la elaboración en medio acuoso básico, conduce al producto final de la reacción.



Esquema 1.24. Mecanismo propuesto para la reacción de amidohidroxilación de olefinas mediada por PIFA.

Una clara evidencia de la importancia de la sustitución de la función amida en el curso de la reacción vino de la mano del experimento resumido en el *Esquema 1.25*. En este ensayo se preparó una acetamida doblemente funcionalizada, por un resto bencílico y por otro alílico, y se llevó a reaccionar en presencia del reactivo PIFA. Observamos que la naturaleza del sustituyente amídico gobierna la reacción con completa

quimioselectividad ya que mientras un sustrato N-arilamídico evoluciona a través de un proceso de amidohidroxilación, sustratos N-metoxiamídicos dan lugar a procesos de amidación electrófila aromática.[66]



Esquema 1.25. Amidohidroxilación *versus* amidación electrófila aromática.

La posterior extensión de esta metodología permitió constatar un casi total paralelismo entre el comportamiento de olefinas y alquinos frente al reactivo de yodo hipervalente PIFA. En este segundo caso se consiguió optimizar, empleando condiciones experimentales muy similares, un nuevo proceso de construcción de 5-aroil-pirrolidinonas a partir de alquinilamidas.[65b] Es de destacar que mientras el proceso de

66. Serna, S.; Tellitu, I.; Domínguez, E.; Moreno, I; SanMartín, R. *Tetrahedron* **2004**, *60*, 6533.

amidohidroxilación de olefinas promovida por PIFA ocurre única y exclusivamente con amidas aromáticas bajo las condiciones de reacción empleadas por nuestro grupo,[66] la reacción llevada a cabo con alquinos tiene lugar tanto sobre amidas aromáticas como alquílicas.[67] El *Esquema 1.26* muestra dos mecanismos alternativos que permiten explicar este hecho.

Así, en el caso de amidas N-aril sustituidas, el ión nitrenio **XXIII** se ve estabilizado por el efecto dador de este grupo facilitando, de este modo, su reacción intramolecular con el resto alquínico y conduciendo al intermedio **XXIV**, el cual es atacado por un resto trifluoroacetato. El trifluoroéster resultante **XXV** rinde la pirrolidinona tras la elaboración básica de la reacción.

Por otro lado, proponemos, en el caso de sustratos N-alquilamídicos, que un hipotético intermedio N-acil-N-alquilnitrenio no podría generarse al no estar la carga positiva estabilizada adecuadamente. Así, se postula que, en lugar de oxidar al nitrógeno amídico, el reactivo de yodo hipervalente promueve la activación del triple enlace generando un intermedio electrofílico **XXVI**, que, tras la pérdida de un grupo trifluoroacetato y ciclación intramolecular, resulta en el intermedio **XXVII**. Este intermedio es atacado por un anión trifluoroacetato para dar lugar al producto trifluoroacetoxilado **XXVIII** que, tras una elaboración básica, resulta en la obtención de la N-alquilpirrolidinona final.

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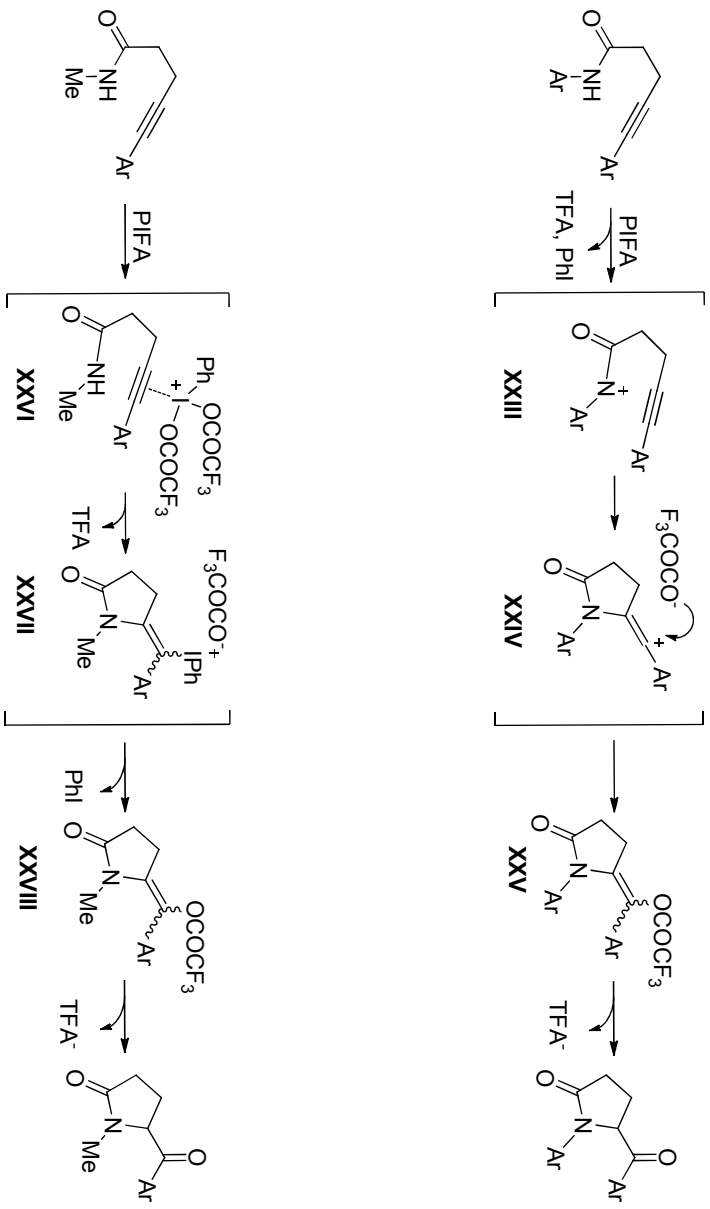
67. Tellitu, I.; Serna, S.; Herrero, M. T.; Moreno, I; Domínguez, E.; SanMartín, R. *J. Org. Chem.* **2007**, *72*, 1526.

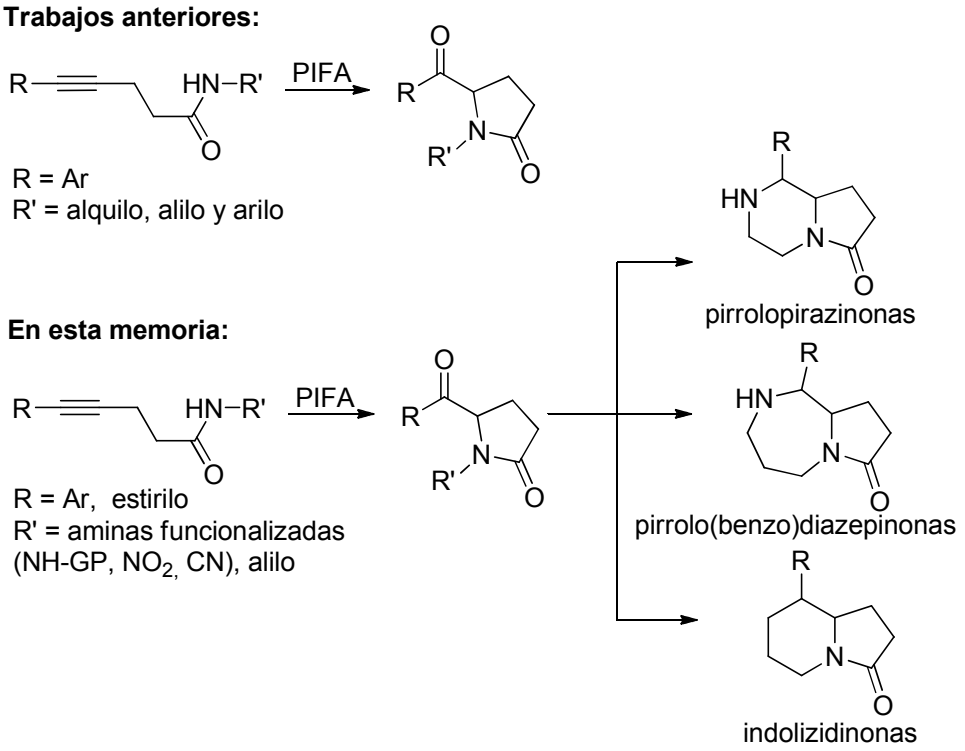


Esquema 1.26. Mecanismos propuestos para la reacción de amidación de alquinos mediada por PIFA.

4. OBJETIVOS Y PLAN DE TRABAJO

Tal y como se ha indicado en la introducción de esta memoria, nuestro grupo de investigación ha venido desarrollando una novedosa metodología de amidación de enlaces múltiples carbono-carbono en la que intermedios acilnitrenios, generados a partir de las correspondientes amidas por acción del reactivo de yodo hipervalente PIFA, reaccionan intramolecularmente con fragmentos alquínicos. La puesta a punto de esta nueva reacción permitió, en su momento, acceder a la obtención de heterociclos 5-aroilpirrolidinónicos a partir de alquinilamidas N-sustituidas lineales.[65b,67]

En el trabajo de investigación que se presenta, se pretende que la introducción de un sustituyente polifuncional sobre el nitrógeno permita, una vez formada la pirrolidinona, aprovechar tanto los grupos funcionales existentes sobre el nitrógeno como los que se generan en la reacción (el grupo carbonilo cetónico) para acometer una segunda ciclación intramolecular. Para ello extenderemos el estudio de la reacción de amidación de alquinos a un número más amplio y diverso de estructuras que puedan ser transformadas en diferentes familias de compuestos bicíclicos de naturaleza pirrolidínica. De este modo, podremos señalar su alcance y limitaciones, y reuniremos evidencias experimentales que nos ayudarán a formular argumentos mecanísticos con los que explicar nuestros logros y dificultades (*Esquema 1.27*).



Esquema 1.27. Plan de trabajo.

Se desarrollará, en suma, una nueva ruta para el acceso a heterociclos policíclicos nitrogenados basados en el sistema pirrolidínico, cuya construcción tendrá al reactivo de yodo hipervalente PIFA como promotor de la etapa clave del proceso. Así, en los capítulos siguientes se mostrará la síntesis de pirrolopirazinonas, pirrolodiazepinonas, pirrolobenzo-diazepinonas e indolizidinonas, todos ellos de enorme interés por sus potenciales aplicaciones farmacológicas.

2

Resultados y discusión

1. Síntesis de pirrolopirazinonas.
2. Síntesis de pirrolodiazepinonas y pirrolobenzodiazepinonas.
3. Síntesis de indolizidinonas.

1. SÍNTESIS DE PIRROLOPIRAZINONAS

Las pirrolopirazinonas son derivados de gran utilidad en el área farmacológica ya que encuentran un gran campo de aplicación como principios activos potenciadores de la memoria. Desde el descubrimiento del piracetam y de su análogo hidroxilado oxipiracetam se han introducido numerosas variaciones estructurales sobre el esqueleto básico para maximizar su actividad biológica así como para elucidar su mecanismo de acción.[68] En la *Figura 2.1* se muestran, junto a los anteriores, ejemplos de estos fármacos, tales como el pramiracetam o el nefiracetam, todos ellos caracterizados estructuralmente por contener un núcleo de 2-pirrolidinona sustituido en la posición 1 por un grupo aminoetilo. En ocasiones, este grupo aminoetilo puede encontrarse integrado dentro de un ciclo fusionado al esqueleto de pirrolidina, como es el caso del unifiram, un principio activo

68. Revisiones sobre las propiedades farmacológicas y usos del piracetam se encuentra en: (a) Winblad, B. *CNS Drug Rev*. **2005**, *11*, 169. (b) Leuner, K.; Kurz, C.; Guidetti, G.; Orgogozo, J. M.; Müller, W. E. *Frontiers in Neuroscience* **2010**, *4*, 44.

que muestra propiedades potenciadoras de la memoria cuatro órdenes de magnitud mayores que las del piracetam,[69] y también el caso del dimiracetam, de diez a cien veces más potente que el piracetam.[70]

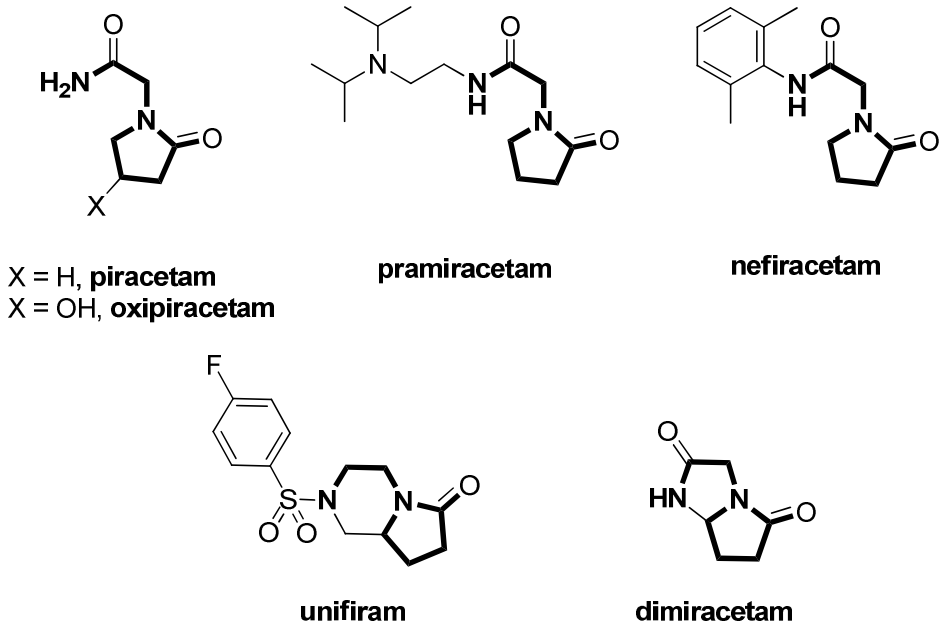
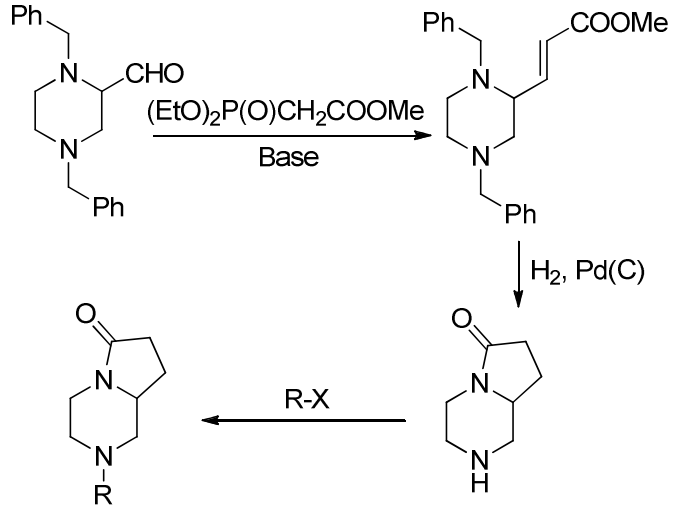


Figura 2.1. Pirrolopirazinonas con propiedades farmacológicas.

69. (a) Manetti, D.; Ghelardini, C.; Bartolini, A.; Bellucci, C.; Dei, S.; Galeotti, N.; Gualtieri, F.; Romanelli, M. N.; Scapecchi, S.; Teodori, E. *J. Med. Chem*. **2000**, *43*, 1969. (b) Martini, E.; Ghelardini, C.; Bertucci, C.; Dei, S.; Gualtieri, F.; Guandalini, L.; Manetti, D.; Scapecchi, S.; Teodori, E.; Romanelli, M. N. *Med. Chem*. **2005**, *1*, 473. (c) Manetti, D.; Ghelardini, C.; Bartolini, A.; Dei, S.; Galeotti, N.; Gualtieri, F.; Romanelli, M. N.; Teodori, E. *J. Med. Chem*. **2000**, *43*, 4499. (d) Martina, E.; Norcini, M.; Ghelardini, C.; Manetti, D.; Dei, S.; Guandalini, L; Melchiorre, M.; Pagella, S.; Scapecchi, S.; Teodori, E.; Romanelli, M. N. *Bioorg. Med. Chem*. **2008**, *16*, 10034.

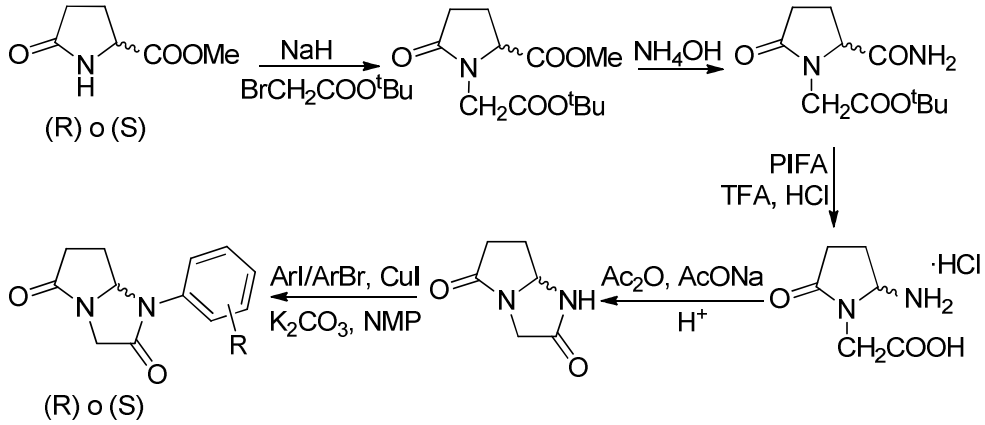
70. (a) Farina, C.; Gagliardi, S.; Ghelardini, C.; Martinelli, M.; Norcini, M.; Parini, C.; Petrillo, P.; Ronzoni, S. *Bioorg. Med. Chem*. **2008**, *16*, 3224. (b) Pinza, M.; Farina, C.; Cerri, A.; Pfeiffer, U.; Riccaboni, M. T.; Banfi, S.; Biagetti, R.; Pozzi, O.; Magnani, M.; Dorigotti, L. *J. Med. Chem*. **1993**, *36*, 4214.

Debido a la importante actividad biológica de este tipo de compuestos, se han publicado muchas y diferentes estrategias para su obtención. Para ilustrar este apartado hemos seleccionado únicamente dos, conceptualmente diferentes entre sí, y diferentes de nuestra propuesta sintética. Así, por ejemplo, numerosos derivados pirrolopirazinónicos se han sintetizado según muestra el *Esquema 2.1*. En este caso, la reacción del 1,4-dibencil-2-piperazincarboxaldehído con el iluro obtenido del [1-(metoxicarbonil)metil]fosfonato de dietilo da lugar al correspondiente aducto que, bajo condiciones de debencilación, cicla espontáneamente. El biciclo pirrolopirazinónico así construido mantiene un átomo de nitrógeno disponible como punto de diversificación estructural por reacción con haluros de acilo, sulfonilo y bencilo.[69a]



Esquema 2.1. Estrategia para la síntesis de pirrolopirazinonas.

Recientemente, se ha publicado una nueva ruta enantioselectiva para la obtención de derivados del dimiracetam a través del uso alternativo de precursores enantiopuros de derivados de prolina, es decir, sustratos con el fragmento pirrolidínico preformado (*Esquema 2.2).*[70a]

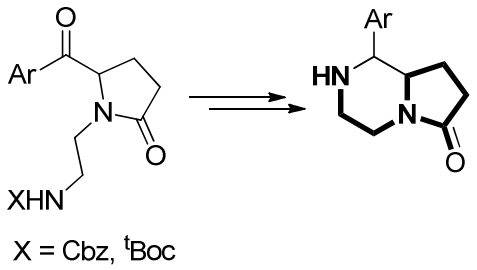


Esquema 2.2. Estrategia para la síntesis de pirrolopirazinonas enantioméricamente puras.

Nosotros planteamos una alternativa a estas estrategias con un diseño sintético que incluye la reacción de amidación de alquinos descrita por nuestro grupo como paso clave en la construcción del sistema pirrolidínico.[71] Así, se evaluará el comportamiento de alquinilamidas que incluyan un grupo amino adicional convenientemente situado, para permitir

71. (a) Serna, S.; Tellitu, I.; Domínguez, E.; Moreno, I; SanMartín, R. *Org. Lett.* **2005**, *7*, 14, 3073. (b) Tellitu, I.; Serna, S.; Herrero, M. T.; Moreno, I; Domínguez, E.; SanMartín, R. *J. Org. Chem.* **2007**, *72*, 1526.

una posterior ciclación intramolecular para obtener las pirrolopirazinonas objetivo (*Esquema 2.3*).

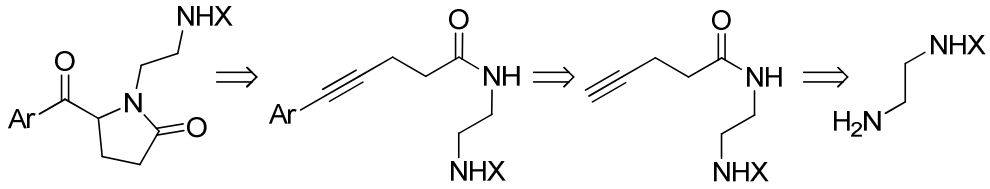


Esquema 2.3. Estrategia a desarrollar en este trabajo.

Para evaluar esta aproximación hay que tener en cuenta distintos aspectos. Por un lado, tanto la naturaleza del grupo protector como la del arilo podría ser determinante en las distintas etapas de la síntesis. Por otro lado, hay que prestar atención al diastereocontrol a través de la secuencia sintética, a fin de lograr un diseño competitivo, sin un aumento significativo en el número de pasos de la síntesis.

1.1. Síntesis de 1-arilpirrolopirazinonas a partir de N-aminoetilpentinimidas.

Una vez fijados los objetivos, el correspondiente análisis retrosintético llevó a seleccionar una serie de amidas convenientemente sustituidas como punto de partida de la síntesis (*Esquema 2.4).*

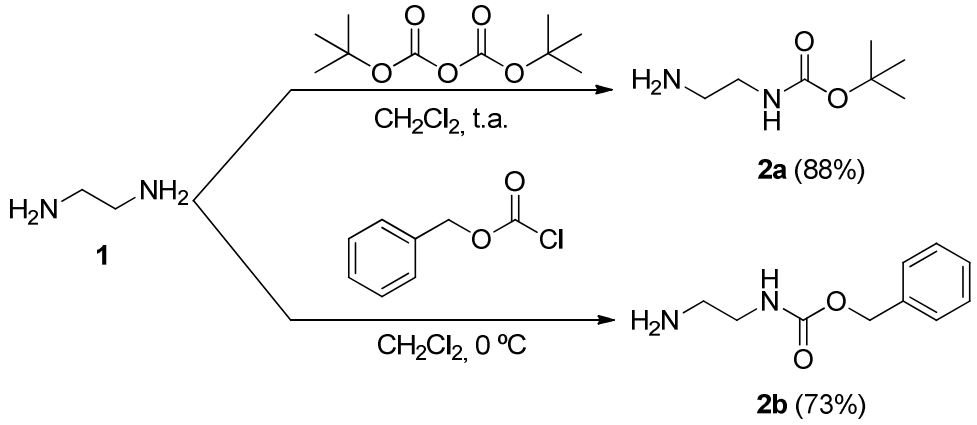


Esquema 2.4. Retrosíntesis para la preparación de las pirrolopirazinonas.

Experiencias previas en nuestro grupo han mostrado que la presencia de restos amino o hidroxilo libres no es compatible con la reacción de heterociclación de amidas insaturadas mediada por el reactivo de yodo hipervalente PIFA, por lo que consideramos necesaria la protección del grupo amino.

Con tal fin, se eligieron como grupos protectores el ^{t}Boc y el Cbz para la reacción de monoprotección de la etilendiamina (**1**) con objeto de evaluar comparativamente su comportamiento en la etapa de ciclación. Así, los productos **2a** y **2b** fueron preparados con buenos rendimientos por reacción con dicarbonato de di-*terc*-butilo y cloroformiato de bencilo,

respectivamente, siguiendo procedimientos bibliográficos (*Esquema 2.5*).[72,73]



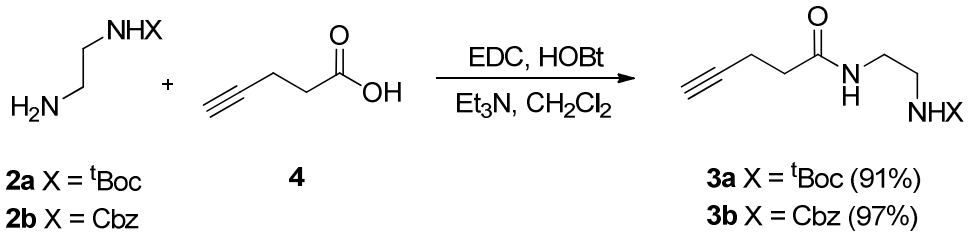
Esquema 2.5. Protección de la amina de partida.

A su vez, las amidas **3a**,**b** (*Esquema 2.6*) se prepararon con excelentes rendimientos por tratamiento del ácido 4-pentinoico (**4**) con las diaminas protegidas previamente preparadas (**2a**,**b**) en presencia de HOBt y EDC·HCl como agentes activantes.[74]

72. Guy, J.; Caron, K; Dufresne, S.; Michnick, S. W.; Skene, W.G.; Keillor, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 11969.

73. Krivickas, S. J.; Tamanini, E.; Todd, M. H.; Watkinson, M. *J. Org. Chem.* **2007**, *72*, 8280.

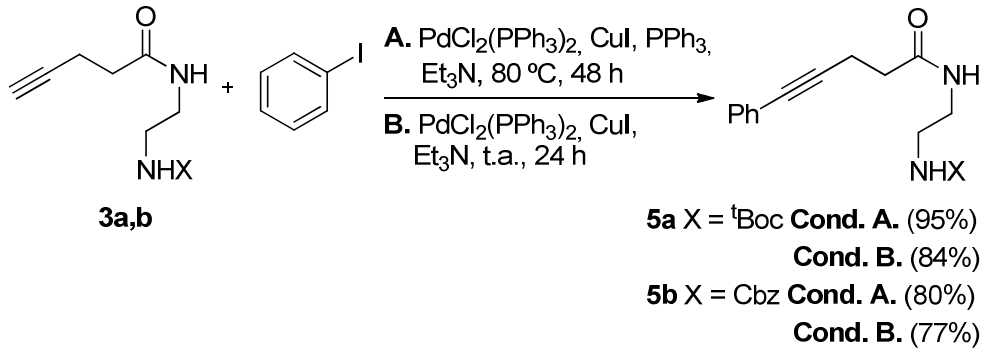
74. (a) Sukekatsu, N. *Chem. Lett.* **1997**, 1. (b) Grayson, I. *Speciality Chemicals* **2000**, 86.



Esquema 2.6. Amidación de las aminas **2a** y **2b**.

Posteriormente, sobre estas amidas se ensayaron diferentes condiciones experimentales con el fin de optimizar la reacción de Sonogashira incorporando así el resto arilo en la posición terminal del triple enlace. Para ello, se evaluaron dos variantes de la reacción y se ensayaron sobre las amidas **3a,b** en combinación con yodobenceno. Tal y como muestra el *Esquema 2.7,* el empleo de condiciones agresivas (condiciones **A**) resultó en un rendimiento ligeramente mayor que la alternativa **B**. Sin embargo, esta última proporcionó resultados más atractivos combinando los parámetros de tiempo de reacción, rendimiento y temperatura.[75]

75. Una revisión reciente sobre la reacción de Sonogashira puede encontrarse en: (a) Heravi, M. M.; Sadjadi, S. *Tetrahedron* **2009**, *65*, 7761. (b) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874. (c) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084. (d) Doucet, H.; Hierso, J. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 834.



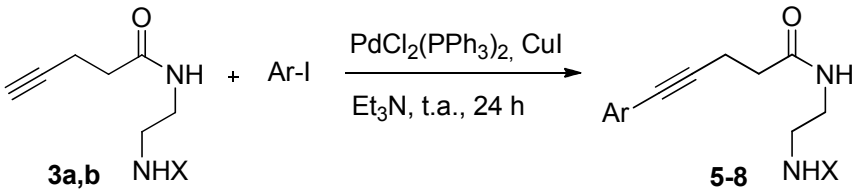
3a,b

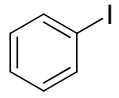
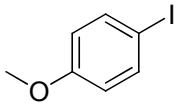
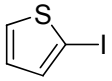
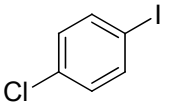
5a X = ^{t}Boc **Cond. A.** (95%)
Cond. B. (84%)
5b X = Cbz **Cond. A.** (80%)
Cond. B. (77%)

Esquema 2.7. Reacción de Sonogashira.

Una vez decidido el procedimiento a seguir, la reacción de los diferentes yoduros de arilo con las amidas **3a** y **3b** permitió preparar una serie de amidas **5-8a,b** con buenos rendimientos. La *Tabla 2.1* muestra cómo, de manera casi general, los mejores rendimientos se consigueron al emplear ^{t}Boc como grupo protector.

Tabla 2.1. Obtención de los compuestos **5-8** a través de una reacción de Sonogashira.



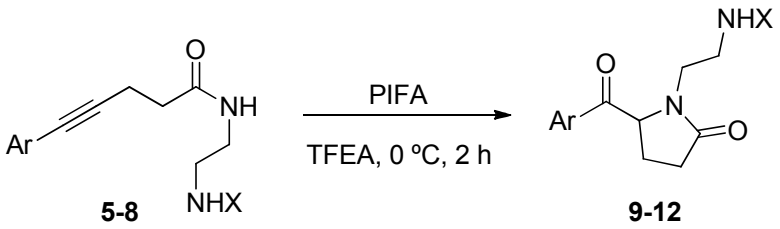
Entrada	Sustrato	X	Ar-I	Producto	Rdto (%)[(a)]
1	**3a**	^{t}Boc		**5a**	84
2	**3b**	Cbz		**5b**	77
3	**3a**	^{t}Boc		**6a**	90
4	**3b**	Cbz		**6b**	75
5	**3a**	^{t}Boc		**7a**	88
6	**3b**	Cbz		**7b**	79
7	**3a**	^{t}Boc		**8a**	80
8	**3b**	Cbz		**8b**	90

[(a)] Rendimiento de producto cromatográficamente puro.

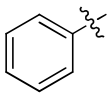
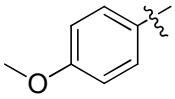
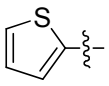
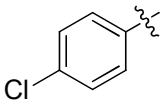
Una vez sintetizadas, las amidas **5-8a,b** fueron tratadas con el reactivo PIFA bajo las condiciones optimizadas por nuestro grupo de investigación,[71] para conducir a las pirrolidin-2-onas deseadas **9-12a,b** (*Tabla 2.2*). Los resultados muestran que ambos grupos protectores son eficientes en esta reacción, si bien, de manera general nuevamente, el ^{t}Boc permite lograr mejores rendimientos (el mecanismo de la reacción de ciclación con PIFA se estudiará en detalle en el apartado *Consideraciones mecanísticas*, página 232).

Por otro lado, la elección de los sustituyentes arilos en el contexto general de la síntesis no fue trivial. Basándonos en nuestros estudios anteriores, en los que observamos que alquinilamidas sustituidas en la posición terminal por anillos aromáticos fuertemente desactivados (nitrofenilo) no permitían acceder al derivado pirrolidínico deseado, limitamos nuestro estudio a sustratos activados (*p*-metoxifenilo, tienilo; *entradas 3-6*), no activados (fenilo; *entradas 1,2*) y moderadamente desactivados (*p*-clorofenilo; *entradas 7,8*).

Tabla 2.2. Ciclación asistida por PIFA para la obtención de los compuestos **9**-**12**.



5-8 **9-12**

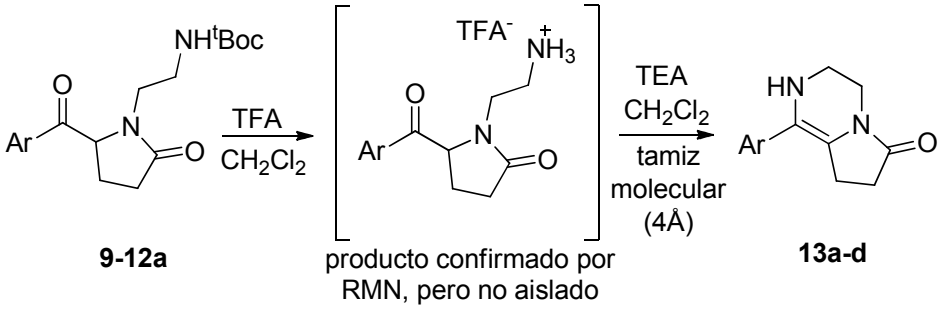
Entrada	Sustrato	X	Ar	Producto	Rdto (%)[(a)]
1	**5a**	^{t}Boc		**9a**	55
2	**5b**	Cbz		**9b**	53
3	**6a**	^{t}Boc		**10a**	74
4	**6b**	Cbz		**10b**	68
5	**7a**	^{t}Boc		**11a**	94
6	**7b**	Cbz		**11b**	81
7	**8a**	^{t}Boc		**12a**	54
8	**8b**	Cbz		**12b**	79

[(a)] Rendimiento de producto cromatográficamente puro.

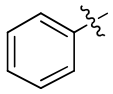
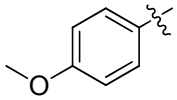
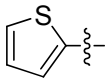
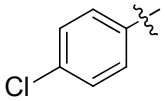
Una vez sintetizadas las pirrolidinonas, nos dispusimos a preparar las pirrolopirazinonas proyectadas. Así, los compuestos **9-12a,b** fueron desprotegidos bajo las condiciones adecuadas para poder acometer posteriores procesos de aminación reductiva intramolecular.

Por una parte, las N-aminoetilpirrolidinonas **9-12a**, protegidas como *terc*-butilcarbamatos, fueron desprotegidas en medio ácido (TFA) para liberar el grupo amino y permitir, sin posterior purificación, un proceso de ciclación bajo condiciones de deshidratación, empleando tamiz molecular (4Å) y medio básico. Así, se obtuvieron, con rendimientos moderados, las pirrolopirazinonas insaturadas objetivo **13a-d** como resultado de un proceso de isomerización posterior a la formación del intermedio bicíclico imínico (*Tabla 2.3*).

Tabla 2.3. Reacciones de ciclación de los compuestos **9-12a**.



9-12a producto confirmado por RMN, pero no aislado **13a-d**

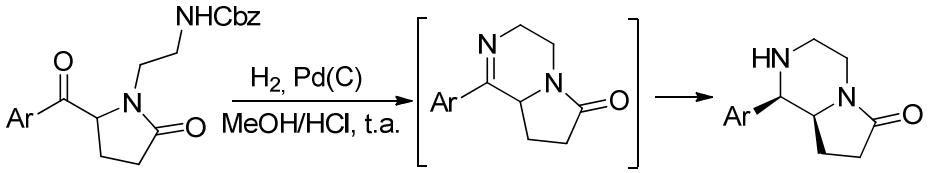
Entrada	Sustrato	Ar	Producto	Rdto (%)[a]
1	**9a**		**13a**	41
2	**10a**		**13b**	33
3	**11a**		**13c**	39
4	**12a**		**13d**	34

[a] Rendimiento de producto cromatográficamente puro.

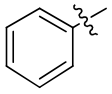
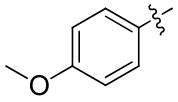
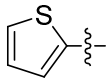
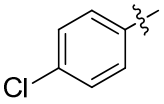
Paralelamente, tal y como muestra la *Tabla 2.4*, procedimos a la hidrogenación catalítica de las N-aminoetilpirrolidinonas **9-12b** protegidas por el grupo Cbz. Transcurridas 12 horas de reacción no se observó ningún cambio (ccf) en el progreso de la reacción. Bajo estas condiciones, la liberación del grupo protector, la ciclación intramolecular, y la hidrogenación del intermedio imínico resultante, tuvo lugar secuencialmente

en la misma etapa de la síntesis. Así, una vez liberada la amina, se evidenció la formación de los derivados bicíclicos **14a,b,d** y, además, si bien con rendimientos moderados, la heterociclación tuvo lugar de forma totalmente diastereocontrolada. Los experimentos de RMN de protón bidimensionales realizados (*Figura 2.2*), muestran la existencia de NOE entre los hidrógenos H-1 y H-8a de la molécula.[76]

Tabla 2.4. Reacciones de heterociclación de los compuestos **9-12b**.



9-12b **14**

Entrada	Sustrato	Ar	Producto	Rdto (%)[(a)]
1	**9b**		**14a**	40
2	**10b**		**14b**	43
3	**11b**		**11b**	----
4	**12b**		**14d**	46

[(a)] Rendimiento de producto cromatográficamente puro.

76. En la Figura 2.2 se muestran los experimentos NOE selectivos, pulsando sobre los protones H-1 y H-8a.

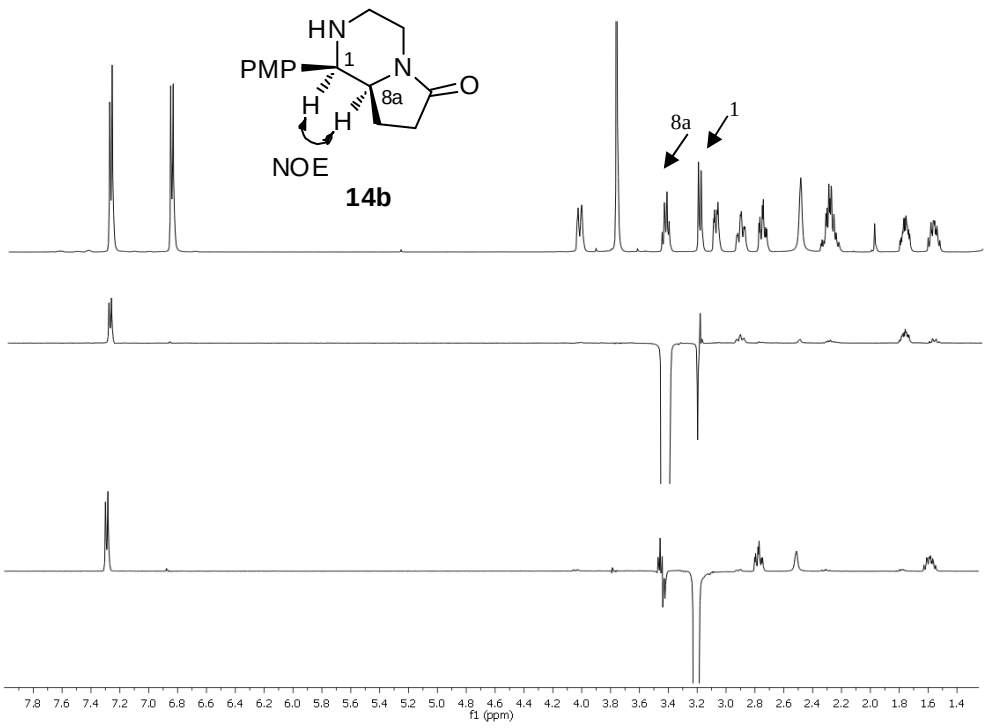
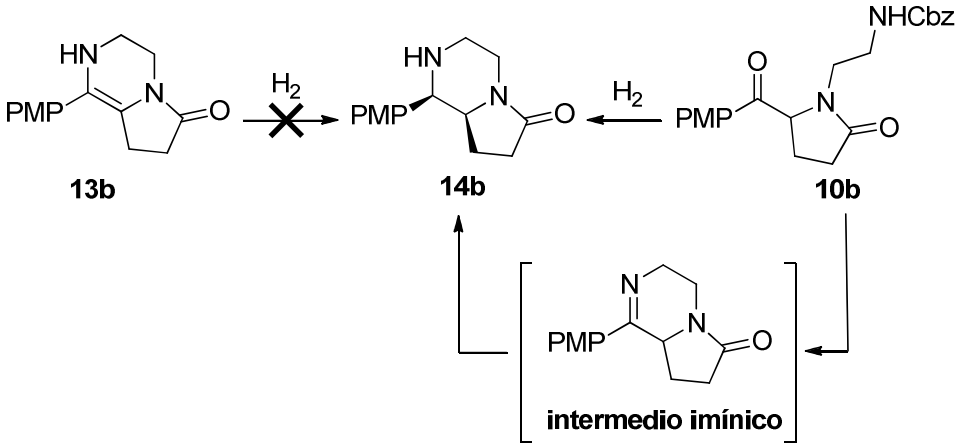


Figura 2.2. Espectro NOE selectivo realizado sobre el compuesto **14b**.

La formación del intermedio de reacción imínico mostrado en la tabla anterior se postuló en base a un experimento adicional realizado. En él se trató de hidrogenar, en las condiciones mostradas, el compuesto enamínico **13b**, con objeto de transformarlo igualmente en el compuesto **14b**. Sin embargo, la recuperación del sustrato inalterado permitió concluir que el proceso de hidrogenación catalítica tiene lugar sobre el enlace imínico y no

sobre el enamínico, aparentemente inerte en las condiciones ensayadas, confirmando así el intermedio de reacción propuesto (*Esquema 2.8*).

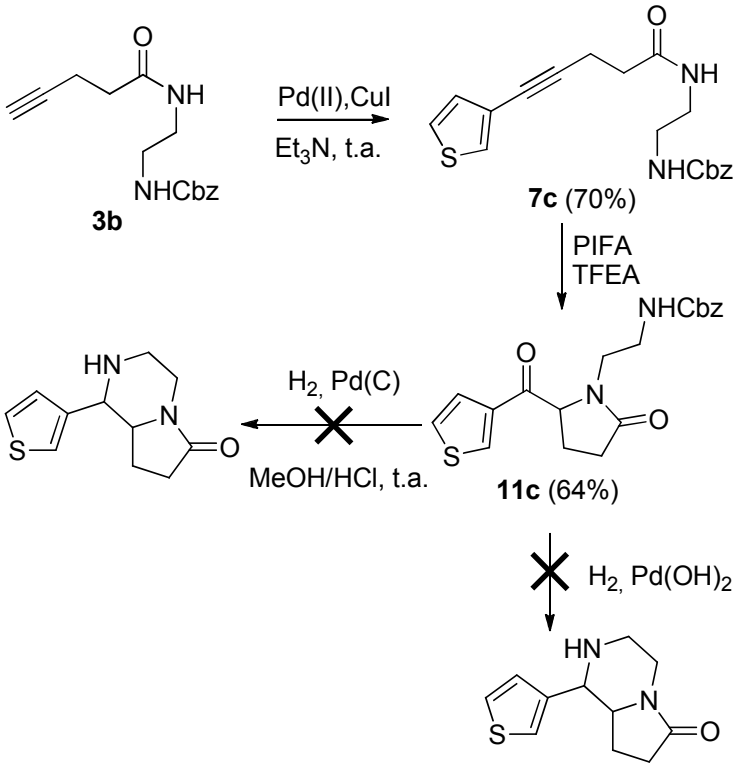


Esquema 2.8. Ensayos para descartar la formación de un intermedio enamínico en la reacción de hidrogenación de **9-12**.

A la vista de los resultados es de destacar el comportamiento diferenciado del compuesto **13c**, que contiene un resto tienilo, ya que se mostró totalmente inerte a la acción del hidrógeno, incluso empleando otros catalizadores de paladio, tales como $Pd(OH)_2$. Es conocido que los compuestos sulfurados son venenos muy efectivos de los catalizadores de paladio, inhibiendo tanto procesos de quimisorción de pequeñas moléculas como procesos de hidrogenación.[77] Para explicar este fenómeno se han propuesto teorías que combinan tanto efectos estéricos como electrónicos.

77. Rodriguez, J. A. *Prog. Surf. Sci.* **2006**, *81*, 141.

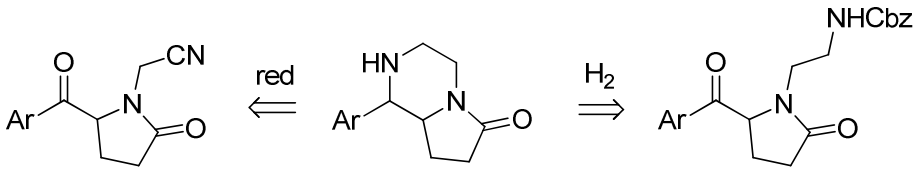
Por ello, en un último intento de obtener pirrolopirazinonas tienil sustituidas, y pensando que el átomo de azufre y el oxígeno carbonílico podrían actuar cooperativamente en el secuestro del catalizador, se sintetizó el regioisómero **11c**, que contiene un resto 3-tiofenilo en su estructura (*Esquema 2.9*). No obstante, si bien los compuestos **7c** y **11c** se obtuvieron, según el procedimiento habitual, la reacción de hidrogenación catalítica fue infructuosa, obteniéndose el producto de partida sin alterar.



Esquema 2.9. Ensayos para la obtención de la pirrolopirazinona 3-tienil sustituida.

1.2. Ensayos hacia una síntesis alternativa de pirrolopirazinonas a partir de α-aminonitrilos.

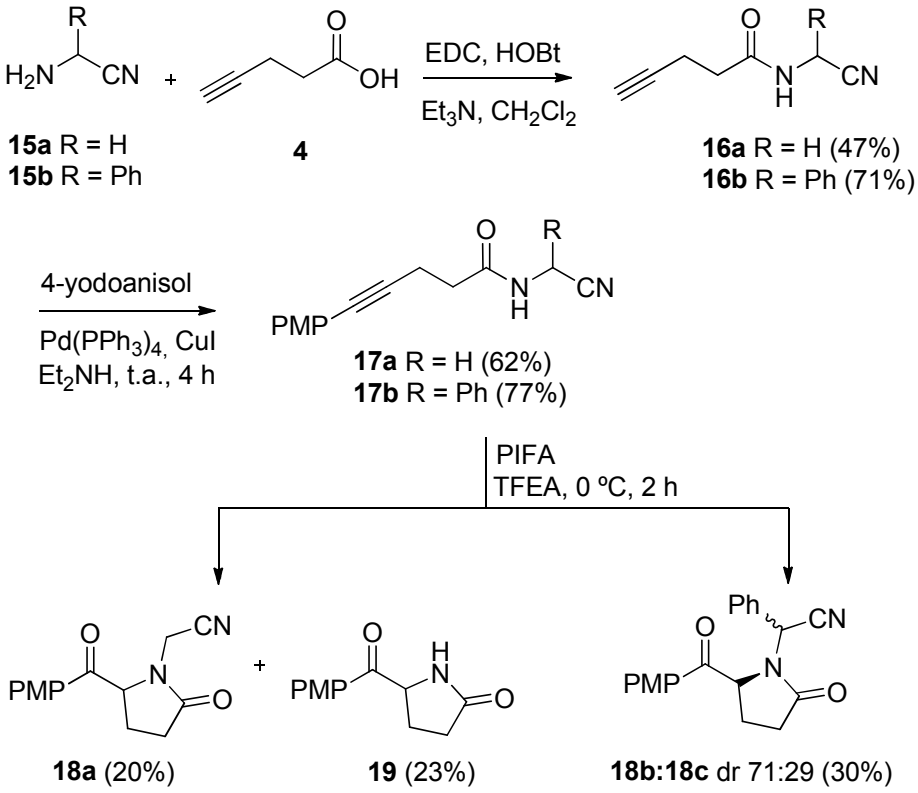
Si bien en el apartado anterior se ha descrito una novedosa metodología para la síntesis de compuestos 1-arilpirrolopirazinónicos, se ha desarrollado paralelamente una alternativa sintética en la que la función nitrogenada proviene de un grupo nitrilo incluido convenientemente en la estructura del sustrato pirrolidinónico (*Esquema 2.10*), lo que evita las etapas de protección y desprotección necesarias en las alternativas anteriores. Al mismo tiempo, el nuevo enfoque permitirá evaluar, por primera vez, el comportamiento del grupo nitrilo frente al reactivo PIFA en el contexto de la reacción de amidación de alquinos. Finalmente, el uso de α-aminonitrilos quirales como productos de partida permitirá obtener eventualmente, mediante inducción asimétrica, compuestos enantioméricamente enriquecidos. A modo de ensayo preliminar se emplearon α-aminonitrilos racémicos y comerciales.



Esquema 2.10. Estrategias planteadas para la preparación de las pirrolopirazinonas.

Para llevar a cabo esta síntesis se procedió de manera análoga a la ya descrita en este capítulo, comenzando por preparar las amidas **16a,b** a partir de los correspondientes α-aminonitrilos comerciales **15a,b**. Debido a su buen comportamiento en la síntesis de las pirrolopirazinonas **13-14b**, se escogió el 4-yodoanisol como único fragmento arílico con el que optimizar el proceso.

A continuación, las amidas **17a,b** se trataron con PIFA bajo las condiciones habituales proporcionando las pirrolidinonas deseadas **18**. Sin embargo, según muestra el *Esquema 2.11*, los rendimientos obtenidos fueron muy bajos para ambos compuestos, probablemente por la desactivación que ejerce el grupo nitrilo sobre el nitrógeno. Esta desactivación también parece responsable del bajo rendimiento obtenido en la formación de la función amida. Además, a partir de la amida **17a** se obtuvo un producto identificado como **19**, en proporción similar a **18a**, procedente de la pérdida del resto nitrilo y que no se detectó al realizar la reacción sobre **17b**.



Esquema 2.11. Preparación de las pirrolidinonas precursoras **18**.

Por otra parte, la inducción prevista para la generación del estereocentro C-5 en **18** no fue pronunciada. Así, a partir de la amida **17b**, se obtuvieron dos pirrolidinonas diastereoméricas **18b** y **18c** en proporción 71:29 que pudieron ser aisladas por cromatografía en columna flash. Debido a las dificultades asociadas a la determinación estereoquímica en moléculas

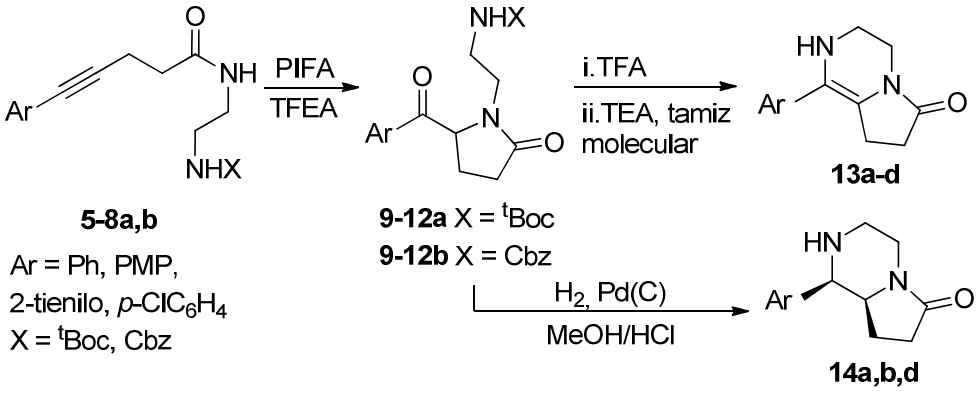
conformacionalmente inestables, y al hecho de que los resultados se hallaban lejos de ser los deseables, no se procedió a la identificación estereoquímica de cada uno de estos dos estereoisómeros.

A pesar del bajo rendimiento obtenido en la reacción de ciclación mediada por PIFA conducente a las N-cianometilpirrolidinonas **18a-c**, se continuó con la síntesis a fin de evaluar la viabilidad de la ruta diseñada. Así, dichos heterociclos se sometieron a las condiciones clásicas de hidrogenación catalítica (PtO_2, MeOH/HCl; Ni-Raney, MeOH) con vistas a promover un proceso de aminación reductiva. Sin embargo, las diferentes condiciones de reacción ensayadas condujeron a mezclas complejas de productos sin determinar entre los que no se pudo aislar ni identificar el producto bicíclico deseado.

1.3. Visión de conjunto.

Se ha descrito un novedoso método de obtención de 1-arilpirrolopirazinonas a través de un proceso secuencial de amidación intramolecular de alquinos por acción del reactivo de yodo hipervalente PIFA, seguido de una reacción de aminación reductiva entre el grupo amino del sustrato original y el grupo cetónico desarrollado en la etapa previa de ciclación.

Así, el empleo del reactivo PIFA en la reacción de heterociclación intramolecular conducente a la obtención de los pirrolidinonas **9-12a,b**, paso clave en la síntesis, dio el resultado esperado. Posteriormente, la liberación del grupo amino, protegido por ^{t}Boc en los compuestos **9-12a** y por Cbz en los compuestos **9-12b**, permitió un proceso de aminación que resultó en las pirrolopirazinonas **13a-d** y **14a,b,d**, respectivamente, con rendimientos globales entre 13-29% para **13** (5 pasos) y 14-32% para **14** (5 pasos).



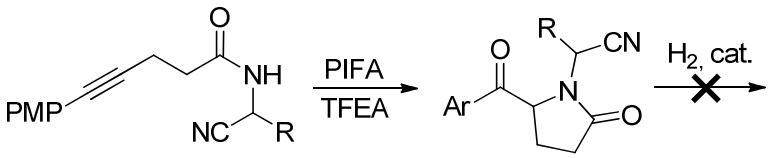
5-8a,b
Ar = Ph, PMP, 2-tienilo, *p*-ClC$_6$H$_4$
X = ^{t}Boc, Cbz

9-12a X = ^{t}Boc
9-12b X = Cbz

13a-d

14a,b,d

En una alternativa sintética, se emplearon alquinilamidas sustituidas por un grupo nitrilo como fuente de la necesaria función nitrogenada. Sin embargo, ni los rendimientos obtenidos en su reacción con el reactivo PIFA fueron los deseables (compuestos **18a-c**), ni la posterior reducción del grupo nitrilo/ciclación intramolecular mediante hidrogenación catalítica resultó en la formación de las pirrolopirazinonas esperadas.



17a R = H
17b R = Ph

18a R = H
18b,c R = Ph

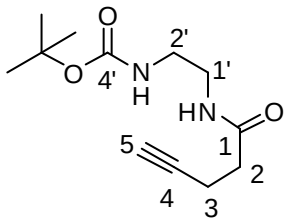
1.4. Experimental procedures.

1.4.1. General methods and materials.

All reagents were purchased and used as received. All solvents used in reactions were dried and purified according to standard procedures. All air- or moisture-sensitive reactions were performed under argon. The glassware was oven dried (140ºC) overnight and purged with argon prior to use. Melting points were measured using open glass capillaries on a Gallenkamp instrument and are uncorrected. Infrared spectra were recorded as thin films on a Perkin-Elmer instrument and peaks are reported in cm^{-1}. Only representative absorptions are given. Flash chromatography was carried out on SiO_2 (silica gel 60, 230–400 mesh ASTM). NMR spectra were recorded on a Bruker AV300 instrument (300 MHz for ^{1}H and 75.4 MHz for ^{13}C) and on a Bruker AV500 instrument (500 MHz for ^{1}H and 125.8 MHz for ^{13}C) at 20-25 ºC unless otherwise stated. Chemical shifts (δ) were measured in ppm relative to chloroform (δ=7.26 for ^{1}H or 77.0 for ^{13}C) as internal standard. Coupling constants, *J*, are reported in hertz. DEPT and several bidimensional NMR experiments (NOESY, COSY, HSQC) were used to assist with the assignation of the signals and structural determinations. Mass spectra were recorded under electron impact (70 eV) or chemical ionization conditions on a Micromass GCT instrument.

1.4.2. Typical procedure for the synthesis of amides 3 and 16.

N-(2-N'-tert-butoxycarbonylaminoethyl)pent-4-ynamide (**3a**).



A solution of 4-pentynoic acid (**4**) (740 mg, 7.2 mmol) in 5 mL of DCM was added to a magnetically stirred solution of EDC·HCl (2.0 g, 10.8 mmol) and HOBt (1.5 g, 10.8 mmol) in 20 mL of the same solvent followed by the addition of the monoprotected diamine **2a**[78] (1.74 g, 10.8 mmol) that was dissolved in 5 mL of DCM. The mixture was cooled to 0 ºC and Et_3N (1.15 g, 10.8 mmol) was added dropwise and was left to react at rt overnight. Then, the reaction was diluted with DCM, water (25 mL) was added, the mixture was decanted and the organic layer was consecutively washed with 20 mL of HCl (aq., 5%), 20 mL of a saturated solution of aqueous $NaHCO_3$, and 20 mL of a saturated solution of NaCl. The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The resultant oil was crystallized from Et_2O to afford amide **3a** as a white solid (91%).

mp 107–108 ºC (Et_2O).

^{1}H NMR ($CDCl_3$) δ 6.24 (br s, 1H, NH), 4.88 (br s, 1H, NH), 3.41-3.27 (m, 4H, H-1', H-2'), 2.53-2.40 (m, 4H, H-2, H-3), 2.00 (t, *J*=2.6, 1H, H-5), 1.44 (s, 9H, ^{t}Bu).

78. For physical and spectroscopic data of compound **2a** see reference 72.

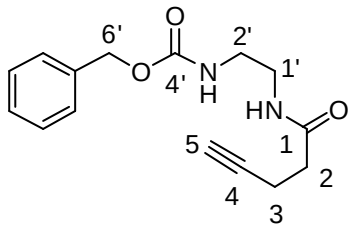
^{13}C NMR ($CDCl_3$) δ 171.7 (C-1), 156.9 (C-4'), 82.9 (C-4), 79.8 (*C*-$(CH_3)_3$), 69.3 (C-5), 40.7, 40.1, 35.3 (C-1', C-2', C-2), 28.3 (C-(*C*$H_3)_3$), 14.9 (C-3).

IR (film) υ 3284, 2978, 1655.

MS (M+1, CI) *m/z* (%) 213 (21), 185 (32), 167 (42), 141 (100), 124 (72), 57 (24).

HRMS calculated for $C_{12}H_{20}N_2O_3 \cdot H^+$ 241.1552, found 241.1877.

N-(2-N'-benzyloxycarbonylaminoethyl)pent-4-ynamide (**3b**).



According to the typical procedure, amide **3b** was obtained from monoprotected amine **2b**[79] in 97% yield as a white solid after purification by crystallization from hexanes.

mp 108–110 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.36-7.31 (m, 5H, Harom), 6.14 (br s, 1H, NH), 5.18 (s, 1H, NH), 5.10 (s, 2H, H-6'), 3.39-3.35 (m, 4H, H-1', H-2'), 2.49-2.33 (m, 4H, H-2, H-3), 1.98 (br s, 1H, H-5).

^{13}C NMR ($CDCl_3$) δ 171.6 (C-1), 157.2 (C-4'), 136.3 (q-Carom), 128.3, 128.2, 128.1 (t-Carom), 83.9 (C-4), 69.3 (C-5), 66.7 (C-6'), 40.8, 40.2 (C-2', C-1'), 35.2 (C-2), 14.9 (C-3).

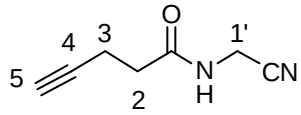
IR (film) υ 3307, 1690, 1643.

79. For physical and spectroscopic data of compound **2b** see reference 73.

MS (M+1, CI) *m/z* (%) 167 (48), 107 (18), 91 (100), 87 (17), 79 (28).

HRMS calculated for $C_{15}H_{18}N_2O_3 \cdot H^+$ 275.1396, found 275.1399.

N-(cyanomethyl)pent-4-ynamide (**16a**).



According to the typical procedure, amide **16a** was obtained from 2-aminoacetonitrile (**15a**) in 47% yield as a colourless oil.

^{1}H NMR ($CDCl_3$) δ 6.92 (br s, 1H, NH), 4.18 (d, *J*=5.7, 2H, H-1'), 2.55-2.45 (m, 4H, H-2, H-3), 2.03 (s, 1H, H-5).

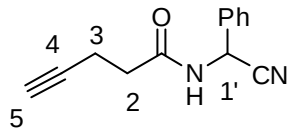
^{13}C NMR ($CDCl_3$) δ 172.3 (CO), 116.6 (CN), 82.6 (C-4), 69.7 (C-5), 34.2, 27.7 (C-1', C-2), 14.4 (C-3).

IR (film) υ 3298, 1685.

MS (M+1, CI) *m/z* (%) 137 (100), 110 (46).

HRMS calculated for $C_7H_8N_2O \cdot H^+$ 137.0715, found 137.0716.

N-(1-phenylcyanomethyl)pent-4-ynamide (**16b**).



According to the typical procedure, amide **16b** was obtained from 2-amino-2-phenylacetonitrile (**15b**) in 71% yield as a yellow solid after purification by crystallization from hexanes.

mp 98–100 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ7.46-7.39 (m, 5H, Harom), 6.84 (d, *J*=8.2, 1H, NH), 6.08 (d, *J*=8.2, 1H, H-1'), 2.55-2.42 (m, 4H, H-2, H-3), 1.99 (s, 1H, H-5).

^{13}C NMR ($CDCl_3$) δ 170.6 (CO), 133.1 (q-Carom), 129.6, 129.3, 127.0 (t-Carom), 117.4 (CN), 82.3 (C-4), 69.9 (C-5), 44.1 (C-1'), 34.7, 14.6 (C-2, C-3).

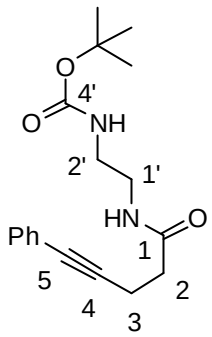
IR (film) υ 3307, 1690.

MS (M+1, CI) *m/z* (%) 213 (47), 186 (100).

HRMS calculated for $C_{13}H_{12}N_2O \cdot H^+$ 213.1028, found 213.1023.

1.4.3. Typical procedure for the Sonogashira coupling reaction. Synthesis of compounds 5-8 and 17.

N-(2-N'-tert-butoxycarbonylaminoethyl)-5-phenylpent-4-ynamide (**5a**).



A solution of iodobenzene (550 mg, 2.7 mmol), $PdCl_2(PPh_3)_2$ (15 mg, 0.02 mmol) and amide **3a** (939 mg, 4.0 mmol) in Et_3N (15 mL) was stirred at rt for 15 min. Then, CuI (8 mg, 0.04 mmol) was added and the mixture was stirred for 24 h. The whole crude was purified by column chromatography (EtOAc) to afford amide **5a** as a white solid that was triturated in hexanes (84%).

mp 118–120 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.39-7.36 (m, 2H, Harom), 7.28-7.25 (m, 3H, Harom), 6.36 (br s, 1H, NH), 4.93 (br s, 1H, NH), 3.41-3.26 (m, 4H, H-2, H-3), 2.74 (t, *J*=7.3, 2H, H-1'/H-2'), 2.46 (t, *J*=7.3, 2H, H-2'/H-1') 1.42 (s, 9H, ^{t}Bu).

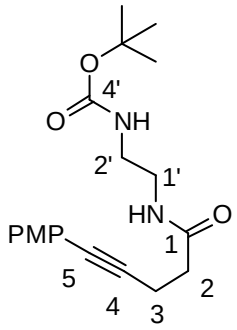
^{13}C NMR ($CDCl_3$) δ 171.8 (C-1), 156.9 (C-4'), 131.6, 127.8 (t-Carom), 123.4 (q-Carom), 88.4, 81.4 (C-4, C-5), 79.7 (*C*-$(CH_3)_3$), 40.8, 40.3 (C-1', C-2'), 35.6 (C-2), 28.3 (C-(*C*$H_3)_3$), 15.9 (C-3).

IR (Film) υ 3284, 2967, 1649, 1549.

MS (M+1, CI) *m/z* (%) 289 (26), 261 (100), 243 (13), 217 (56), 57 (39).

HRMS calculated for $C_{18}H_{24}N_2O_3 \cdot H^+$ 317.1865, found 317.1860.

N-(2-N'-tert-butoxycarbonylaminoethyl)-5-p-methoxyphenylpent-4-ynamide (**6a**).



According to the typical procedure, amide **6a** was obtained from amide **3a** in 90% as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes.

mp 109–111 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.33-7.30 (d, *J*=8.8, 2H, Harom), 6.82-6.79 (d, *J*=8.8, 2H, Harom), 6.28 (br s, 1H, NH), 4.88 (br s, 1H, NH), 3.80 (s, 3H, OCH_3), 3.43-3.23 (m, 4H, H-2, H-3), 2.72 (t, *J*=7.3, 2H, H-1'/H-2'), 2.48 (t, *J*=7.3, 2H, H-2'/H-1'), 1.43 (s, 9H, ^{t}Bu).

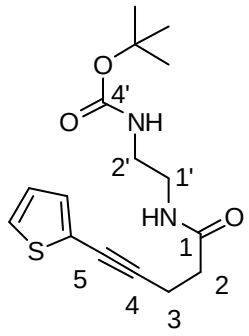
^{13}C NMR ($CDCl_3$) δ 172.0 (C-1), 159.2 (C-4'), 156.9, 132.9 (q-Carom), 115.6, 113.8 (t-Carom), 86.8, 81.5 (C-4, C-5), 79.5 (*C*-$(CH_3)_3$), 56.2 (OCH_3), 40.5, 40.3 (C-1', C-2'), 35.6 (C-2), 26.3 (C-(*C*$H_3)_3$), 15.9 (C-3).

IR (film) υ 3296, 2967, 1689, 1643.

MS (M+1, CI) *m/z* (%) 291 (100), 290 (28), 273 (27), 247 (44), 231 (45), 230 (65).

HRMS calculated for $C_{19}H_{26}N_2O_4 \cdot H^+$ 347.1971, found 347.1972.

N-(2-N'-tert-butoxycarbonylaminoethyl)-5-(2-thienyl)pent-4-ynamide (**7a**).



According to the typical procedure, amide **7a** was obtained from amide **3a** in 88% as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes.

mp 128–130 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.18-7.12 (m, 2H, Harom), 6.99-6.91 (m, 1H, Harom), 6.34 (br s, 1H, NH), 4.93 (br s, 1H, NH), 3.39-3.27 (m, 4H, H-2, H-3), 2.76 (t, *J*=7.3, 2H, H-1'/H-2'), 2.64 (t, *J*=7.3, 2H, H-2'/H-1'), 1.43 (s, 9H, ^{t}Bu).

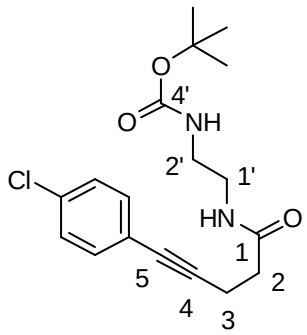
^{13}C NMR ($CDCl_3$) δ 171.7 (C-1), 156.9 (C-4'), 131.3, 126.8, 126.3 (t-Carom), 123.5 (q-Carom), 92.5, 79.6 (C-4, C-5), 74.5 (*C*-$(CH_3)_3$), 40.7, 40.3 (C-1', C-2'), 35.3 (C-2), 28.3 (C-(*C*$H_3)_3$), 16.1 (C-3).

IR (film) υ 3284, 2967, 1690, 1649.

MS (M+1, CI) *m/z* (%) 267 (100), 249 (23), 223 (44), 206 (50), 180 (26).

HRMS calculated for $C_{16}H_{22}N_2O_3{}^{32}S{\cdot}H^+$ 323.1429, found 323.1440.

N-(2-N'-tert-butoxycarbonylaminoethyl)-5-p-chlorophenylpent-4-ynamide (**8a**).



According to the typical procedure, amide **8a** was obtained from amide **3a** in 80% as a pale yellow solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes.

mp 131–132 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.32 (d, *J*=9.2, 2H, Harom), 7.23 (d, *J*=9.2, 2H, Harom), 6.37 (br s, 1H, NH), 4.90 (br s, 1H, NH), 3.39-3.25 (m, 4H, H-2, H-3), 2.73 (t, *J*=7.3, 2H, H-1'/H-2'), 2.46 (t, *J*=7.3, 2H, H-2'/H-1'), 1.43 (s, 9H, ^{t}Bu).

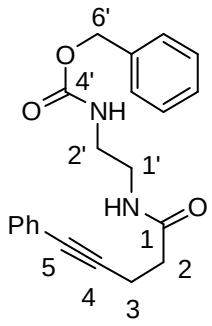
^{13}C NMR ($CDCl_3$) δ 171.7 (C-1), 157.0 (C-4'), 132.8, 128.5 (t-Carom), 133.7, 122.0 (q-Carom), 89.5, 80.3 (C-4, C-5), 79.7 (*C*-$(CH_3)_3$), 40.8, 40.3 (C-1', C-2'), 35.4 (C-2), 28.3 (C-(*C*$H_3)_3$), 15.9 (C-3).

IR (film) υ 3296, 2967, 1684, 1637.

MS (M+1, CI) *m/z* (%) 323 (17), 295 (91), 277 (50), 251 (100), 234 (57), 192 (30).

HRMS calculated for $C_{18}H_{23}{}^{35}ClN_2O_3{\cdot}H^+$ 351.1475, found 351.1465.

N-(2-N'-benzyloxycarbonylaminoethyl)-5-phenylpent-4-ynamide (**5b**).



According to the typical procedure, amide **5b** was obtained from amide **3b** in 77% yield as a white solid after purification by column chromatography followed by crystallization of the resultant oil in hexanes.

mp 151–152 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.39-7.26 (m, 10H, Harom), 6.17 (br s, 1H, NH), 5.17-5.07 (m, 3H, NH, H-16'), 3.38 (m, 4H, H-2, H-3), 2.72 (t, *J*=7.2, 2H, H-1'/H-2'), 2.44 (t, *J*=7.2, 2H, H-2'/H-1').

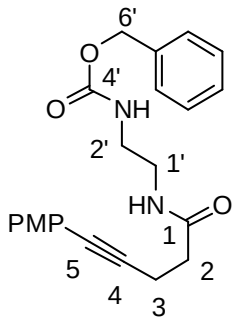
^{13}C NMR ($CDCl_3$) δ 171.9 (C-1), 157.2 (C-4'), 136.3, 131.5 (q-Carom), 128.5, 128.3, 128.1, 127.9, 123.4 (t-Carom), 88.3, 81.5 (C-4, C-5), 66.9 (C-6'), 41.0, 40.9 (C-1', C-2'), 35.6 (C-2), 15.9 (C-3).

IR (film) υ 3296, 3070, 1690, 1637.

MS (M+1, CI) *m/z* (%) 351 (20), 286 (100), 266 (18), 243 (23), 91 (61), 79 (19).

HRMS calculated for $C_{21}H_{22}N_2O_3{\cdot}H^+$ 351.1709, found 351.1708.

N-(2-N'-benzyloxycarbonylaminoethyl)-5-p-methoxyphenylpent-4-ynamide (**6b**).



According to the typical procedure, amide **6b** was obtained from amide **3b** in 75% as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes.

mp 124–125 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.34-7.29 (m, 7H, Harom), 6.80-6.77 (d, *J*=8.8, 2H, Harom), 6.17 (br s, 1H, NH), 5.13-5.07 (m, 3H, NH, H-6'), 3.78 (s, 3H, OCH_3), 3.41-3.34 (m, 4H, H-2, H-3), 2.70 (t, *J*=7.1, 2H, H-1'/H-2'), 2.43 (t, *J*=7.1, 2H, H-2'/H-1').

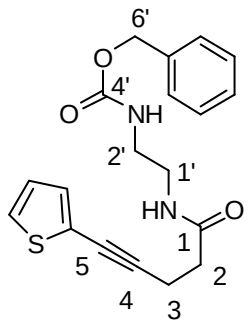
^{13}C NMR ($CDCl_3$) δ 172.0 (C-1), 159.3, 136.4, 115.5 (q-Carom), 157.0 (C-4'), 132.9, 128.5, 128.2, 128.1, 113.9 (t-Carom), 86.7, 81.3 (C-4, C-5), 66.8 (C-6'), 56.2 (OCH_3), 41.0 (C-2'), 40.3, 35.7 (C-1', C-2), 15.9 (C-3).

IR (film) υ 3296, 1684, 1637.

MS (M+1, CI) *m/z* (%) 381 (22), 273 (65), 272 (44), 231 (100), 91 (78), 79 (29).

HRMS calculated for $C_{22}H_{24}N_2O_4 \cdot H^+$ 381.1814, found 381.1818.

N-(2-N'-benzyloxycarbonylaminoethyl)-5-(2-thienyl)pent-4-ynamide (**7b**).



According to the typical procedure, amide **7b** was obtained from amide **3b** in 79% as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes.

mp 127–128 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.36-7.33 (m, 5H, Harom), 7.17-7.11 (m, 2H, Harom), 6.93-6.90 (m, 1H, Harom), 6.17 (br s, 1H, NH), 5.13-5.07 (m, 3H, NH, H-6'), 3.41-3.34 (m, 4H, H-2, H-3), 2.70 (t, *J*=7.1, 2H, H-1'/H-2'), 2.43 (t, *J*=7.1, 2H, H-2'/H-1').

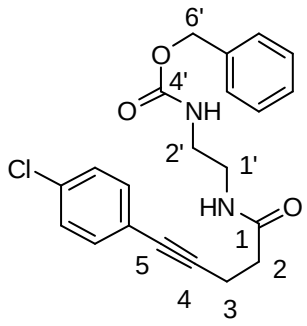
^{13}C NMR ($CDCl_3$) δ 171.8 (C-1), 157.2 (C-4'), 136.3, 123.4 (q-Carom), 131.4, 128.5, 128.2, 128.1, 126.9, 126.3 (t-Carom), 92.4, 74.7 (C-4, C-5), 66.9 (C-6'), 40.9, 40.4 (C-1', C-2'), 35.3 (C-2), 16.1 (C-3).

IR (film) υ 3296, 3070, 1690, 1637.

MS (M+1, CI) *m/z* (%) 296 (11), 249 (39), 248 (30), 208 (14), 207 (100), 164 (16), 108 (22).

HRMS calculated for $C_{19}H_{20}N_2O_3{}^{32}S{\cdot}H^+$ 357.1213, found 357.1289.

N-(2-N'-benzyloxycarbonylaminoethyl)-5-p-chlorophenylpent-4-ynamide (**8b**).



According to the typical procedure, amide **8b** was obtained from amide **3b** in 90% as a pale yellow solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes.

mp 169–170 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.34-7.21 (m, 9H, Harom), 6.22 (br s, 1H, NH), 5.18 (br s, 1H, NH) 5.07 (s, 2H, H-6'), 3.40-3.34 (m, 4H, H-2, H-3), 2.70 (t, *J*=7.2, 2H, H-1'/H-2'), 2.43 (t, *J*=7.2, 2H, H-2'/H-1').

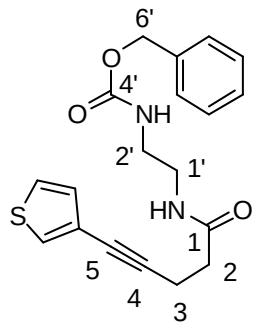
^{13}C NMR ($CDCl_3$) δ 171.7 (C-1), 157.2 (C-4'), 136.3, 133.8, 121.9 (q-Carom), 132.8, 128.5, 128.2, 126.9, 126.3 (t-Carom), 89.4, 80.4 (C-4, C-5), 66.9 (C-6'), 40.9, 40.5 (C-1', C-2'), 35.4 (C-2), 15.9 (C-3).

IR (film) υ 3284, 1684, 1637.

MS (M+1, CI) *m/z* (%) 385 (11), 324 (10), 279 (40), 277 (100), 237 (23), 235 (73), 193 (11).

HRMS calculated for $C_{21}H_{21}{}^{35}ClN_2O_3{\cdot}H^+$ 385.1319, found 385.1315.

N-(2-N'-benzyloxycarbonylaminoethyl)-5-(3-thienyl)pent-4-ynamide (**7c**).



According to the typical procedure, amide **7c** was obtained from amide **3b** in 70% as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes.

mp 150–151 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.37-7.30 (m, 6H, Harom), 7.21-7.19 (m, 1H, Harom), 7.06-7.02 (m, 1H, Harom), 6.34 (br s, 1H, NH), 5.30 (br s, 1H, NH), 5.07 (s, 2H, H-6'), 3.42-3.30 (m, 4H, H-2, H-3), 2.69 (t, *J*=7.2, 2H, H-1'/H-2'), 2.33 (t, *J*=7.2, 2H, H-2'/H-1').

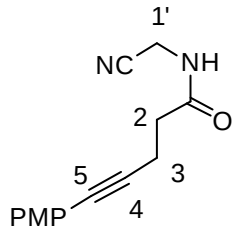
^{13}C NMR ($CDCl_3$) δ 172.0 (C-1), 157.2 (C-4'), 136.4, 123.4 (q-Carom), 129.9, 128.6, 128.1, 125.2, 122.3 (t-Carom), 87.9, 66.9 (C-4, C-5), 40.9, 40.3 (C-1', C-2'), 35.5, 15.9 (C-2, C-3).

IR (film) υ 3300, 3078, 1685, 1641.

MS (M+1, CI) *m/z* (%) 357 (60), 249 (100), 248 (50), 207 (64), 163 (14).

HRMS calculated for $C_{19}H_{20}N_2O_3{}^{32}S{\cdot}H^+$ 357.1273, found 357.1289.

N-(cyanomethyl)-5-(4-methoxyphenyl)pent-4-ynamide (**17a**).



A solution of $Pd(PPh_3)_4$ (335 mg, 0.29 mmol), CuI (110 mg, 0.58 mmol) y 4-iodoanisole (678 mg, 2.9 mmol) in Et_2NH (15 mL) was stirred at rt for 5 min. Then, a solution of the amide **16a** (430 mg, 3.1 mmol) was slowly added in THF (3.0 mL) and the mixture was stirred for 4 h. The crude was diluted with EtOAc, filtered and washed with saturated NH_4Cl. The aqueous phase was extracted with EtOAc (3x20 mL), dried over anh. Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The crude was purified by column chromatography (EtOAc) to afford amide **17a** as a white solid that was triturated in hexanes (62%).

mp 92–93 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.30 (d, *J*=8.8, 2H, Harom), 6.80 (d, *J*=8.8, 2H, Harom), 6.76 (br s, 1H, NH), 4.15 (d, *J*=5.7, 2H, H-1'), 3.77 (s, 3H, OCH_3), 2.75 (t, *J*=7.2, 2H, H-2/H-3), 2.72 (t, *J*=7.2, 2H, H-3/H-2).

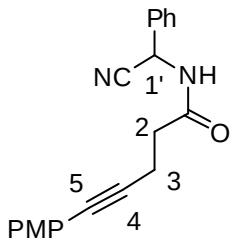
^{13}C NMR ($CDCl_3$) δ 171.9 (C-1), 149.4, 116.2, 115.3 (q-Carom, CN) 133.0, 114.0 (t-Carom), 86.2, 81.7 (C-4, C-5), 55.2 (OCH_3), 36.1, 27.5, 15.6 (C-1', C-2, C-3).

IR (film) υ 3284 , 1669 .

MS (M+1, CI) *m/z* (%) 243 (21), 216 (100), 201 (15).

HRMS calculated for $C_{14}H_{14}N_2O_2 \cdot H^+$ 243.1134, found 243.1128.

5-(4-methoxyphenyl)-N-(1-phenylcyanomethyl)pent-4-ynamide (**17b**).



According to the previous procedure, amide **17b** was obtained from amide **16b** in 77% as a pale yellow solid after purification by column chromatography (DCM) followed by crystallization from hexanes.

mp 83–84 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.45-7.21 (m, 5H, Harom), 7.17 (d, *J*=8.8, 2H, Harom), 6.77 (d, *J*=8.2, 1H, NH), 6.92 (d, *J*=8.8, 2H, Harom), 6.10 (d, *J*=8.2, 1H, H-1'), 3.78 (s, 3H, OCH_3), 2.74-2.70 (m, 2H, H-2/H-3), 2.53-2.50 (m, 2H, H-3/H-2).

^{13}C NMR ($CDCl_3$) δ 170.9 (C-1), 159.4, 127.0, 117.5, 115.1 (q-Carom, CN), 133.1, 133.0, 129.5, 129.3, 113.9 (t-Carom), 86.1, 82.0 (C-4, C-5), 55.3 (OCH_3), 44.1 (C-1'), 35.2, 15.8 (C-2, C-3).

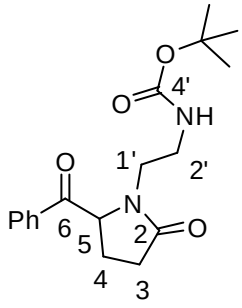
IR (film) υ 3296, 1690.

MS (M+1, CI) *m/z* (%) 319 (50), 293 (100), 204 (23).

HRMS calculated for $C_{20}H_{18}N_2O_2 \cdot H^+$ 319.1447, found 319.1454.

1.4.4. Typical procedure for the PIFA-mediated cyclization reaction. Synthesis of pyrrolidinones 9-12 and 18.

5-benzoyl-*N*-(2-*N*'-tert-butoxycarbonylaminoethyl)pyrrolidin-2-one (**9a**).



A solution of alkynylamide **5a** (250 mg, 0.8 mmol) in TFEA (12 mL) was stirred and cooled to 0 ºC and a solution of PIFA (526.8 mg, 1.2 mmol) in 6 mL of the same solvent was added dropwise. The reaction mixture was stirred at that temperature for 2 h. For the work up, aqueous Na_2CO_3 (10%) was added and the mixture extracted with DCM (3x20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave the desired product **9a** as a chromatographically pure yellowish oil (55%).

^{1}H NMR ($CDCl_3$) δ 7.99 (d, *J*=7.1, 2H, Harom), 7.64-7.63 (m, 1H, Harom), 7.55-7.50 (m, 2H, Harom), 5.39-5.35 (m, 1H, H-5), 4.90 (br s, 1H, NH), 3.80-3.77 (m, 1H, H-1'/H-2'), 3.49-3.40 (m, 1H, H-2'/H-1'), 3.11-3.02 (m, 2H, H-1'/H-2'), 2.44-2.30 (m, 3H, H-3/H-4), 2.11-2.01 (m, 1H, H-4/H-3), 1.41 (s, 9H, ^{t}Bu).

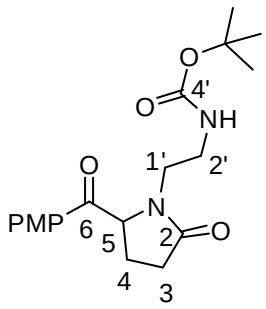
^{13}C NMR ($CDCl_3$) δ 197.1 (C-6), 176.3 (C-2), 156.3 (C-4'), 134.0 (q-Carom), 129.0, 128.6, 128.4 (t-Carom), 79.2 (*C*-$(CH_3)_3$), 61.8 (C-5), 42.2, 33.2 (C-1, C-2), 29.3 (C-4), 28.3 (C-(*C*$H_3)_3$), 23.5 (C-3).

IR (film) υ 3331, 2967, 1690, 1519.

MS (EI) *m/z* (%) 332 (36), 317 (31), 305 (100), 287 (26), 277 (16).

HRMS calculated for $C_{18}H_{24}N_2O_4$ 332.1736, found 332.1731.

N-(2-N'-tert-butoxycarbonylaminoethyl)-5-(p-methoxybenzoyl)pyrrolidin-2-one (**10a**).



According to the typical procedure, pyrrolidinone **9a** was obtained from amide **6a** in 74% as a white solid after purification by column chromatography (EtOAc) followed by crystallization from EtOAc.

mp 111–113 ºC (EtOAc).

^{1}H NMR ($CDCl_3$) δ 7.97 (d, *J*=8.7, 2H, Harom), 6.99 (d, *J*=8.7, 2H, Harom), 5.34-5.30 (m, 1H, H-5), 4.92 (br s, 1H, NH), 3.89 (s, 3H, OCH_3), 3.80-3.76 (m, 1H, H-1'/H-2'), 3.51-3.33 (m, 1H, H-2'/H-1'), 3.11-3.06 (m, 2H, H-1'/H-2'), 2.50-1.97 (m, 4H, H-3, H-4), 1.41 (s, 9H, ^{t}Bu).

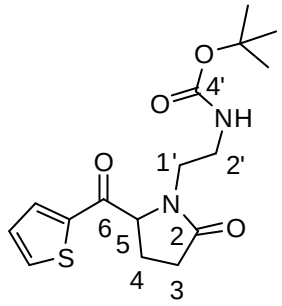
^{13}C NMR ($CDCl_3$) δ 195.7 (C-6), 176.4 (C-2), 156.3 (C-4'), 164.2, 127.1 (q-Carom), 130.8, 114.2 (t-Carom), 79.1 (*C*-$(CH_3)_3$), 61.5 (C-5), 55.5 (OCH_3), 42.2, 38.2 (C-1, C-2), 29.4 (C-3), 28.3 (C-(*C*$H_3)_3$), 23.7 (C-4).

IR (film) υ 3331, 2967, 1684, 1596, 1508.

MS (M+1, CI) *m/z* (%) 246 (15), 245 (83), 244 (100), 215 (5).

HRMS calculated for $C_{19}H_{26}N_2O_5 \cdot H^+$ 363.1875, found 363.1877.

N-(2-N'-tert-butoxycarbonylaminoethyl)-5-(2-thienylcarbonylpyrrolidin)-2-one (**11a**).



According to the typical procedure, pyrrolidinone **11a** was obtained from amide **7a** in 94% as a yellowish oil after purification by column chromatography (EtOAc).

^{1}H NMR ($CDCl_3$) δ 7.79-7.70 (m, 2H, Harom), 7.19-7.14 (m, 1H, Harom), 5.18-5.09 (m, 2H, NH, H-5), 3.75-3.72 (m, 1H, H-1'/H-2'), 3.41-3.37 (m, 1H, H-2'/H-1'), 3.11-2.88 (m, 2H, H-1'/H-2'), 2.44-2.27 (m, 3H, H-3/H-4), 2.12-2.10 (m, 1H, H-4/H-3), 1.35 (s, 9H, ^{t}Bu).

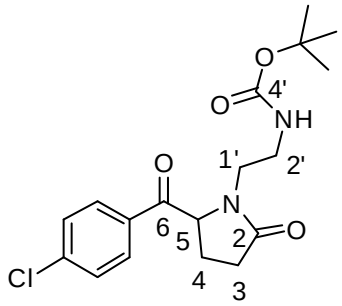
^{13}C NMR ($CDCl_3$) δ 190.8 (C-6), 176.3 (C-2), 156.2 (C-4'), 141.1 (q-Carom), 135.2, 132.9, 128.6 (t-Carom), 79.1 (*C*-$(CH_3)_3$), 62.3 (C-5), 42.2, 38.2 (C-1, C-2), 29.4 (C-3), 28.3 (C-(*C*$H_3)_3$), 24.0 (C-4).

IR (film) υ 3331, 2967, 1684, 1514.

MS (M+1, CI) *m/z* (%) 265 (4), 222 (20), 221 (93), 220 (100), 191 (11).

HRMS calculated for $C_{16}H_{22}N_2O_4{}^{32}S{\cdot}H^+$ 339.1378, found 339.1334.

N-(2-N'-tert-butoxycarbonylaminoethyl)-5-(p-chlorobenzoyl)pyrrolidin-2-one (**12a**).



According to the typical procedure, pyrrolidinone **12a** was obtained from amide **8a** in 54% as a yellowish oil after purification by column chromatography (EtOAc).

^{1}H NMR ($CDCl_3$) δ 7.91 (d, *J*=8.4, 2H, Harom), 7.47 (d, *J*=8.4, 2H, Harom), 5.35-5.28 (m, 1H, H-5), 5.00 (br s, 1H, NH), 3.87-3.75 (m, 1H, H-1'/H-2'), 3.50-3.27 (m, 1H, H-2'/H-1'), 3.12-2.94 (m, 2H, H-1'/H-2'), 2.49-2.32 (m, 3H, H-3/H-4), 2.02-1.86 (m, 1H, H-4/H-3), 1.39 (s, 9H, ^{t}Bu).

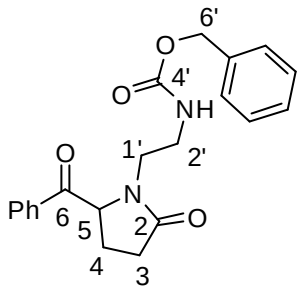
^{13}C NMR ($CDCl_3$) δ 196.0 (C-6), 176.1 (C-2), 156.4 (C-4'), 140.6, 132.4 (q-Carom), 129.9, 129.4 (t-Carom), 79.3 (*C*-$(CH_3)_3$), 61.6 (C-5), 42.1, 30.0 (C-1, C-2), 28.3 (C-3), 28.2 (C-(*C*$H_3)_3$), 23.4 (C-4).

IR (film) υ 3343, 2967, 1690, 1588, 1519.

MS (M+1, CI) *m/z* (%) 294 (20), 280 (15), 267 (21), 266 (91), 238 (100), 194 (17), 180 (19).

HRMS calculated for $C_{18}H_{23}{}^{35}ClN_2O_4{\cdot}H^+$ 367.1424, found 367.1317.

5-benzoyl-N-(2-N'-benzyloxycarbonylaminoethyl)pyrrolidin-2-one (**9b**).



According to the typical procedure, pyrrolidinone **9b** was obtained from amide **5b** in 53% yield as a yellowish oil after purification by column chromatography (EtOAc).

^{1}H NMR ($CDCl_3$) δ 7.92-7.80 (m, 2H, Harom), 7.60-7.55 (m, 1H, Harom), 7.48-7.43 (m, 2H, Harom), 7.26-7.23 (m, 5H, Harom), 5.83-5.76 (m, 1H, NH), 5.35-5.29 (m, 1H, H-5), 5.06 (d, *J*=12.3, 1H, H-6'), 4.94 (d, *J*=12.3, 1H, H-6'), 2.97-2.74 (m, 4H, H-1', H-2'), 2.40-2.19 (m, 3H, H-3/H-4), 1.89-1.83 (m, 1H, H-4/H-3).

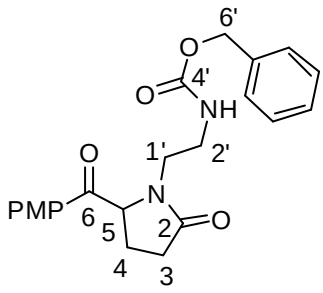
^{13}C NMR ($CDCl_3$) δ 197.2 (C-6), 176.5 (C-2), 156.9 (C-4'), 136.8, 134.1 (q-Carom), 132.1, 129.0, 128.4, 128.0, 127.9 (t-Carom), 66.4 (C-6'), 62.0 (C-5), 42.1, 38.9 (C-1', C-2'), 29.3, 23.5 (C-3, C-4).

IR (film) υ 3331, 2931, 1690, 1525, 1449.

MS (M+1, CI) *m/z* (%) 259 (75), 216 (40), 215 (100), 214 (75), 153 (29), 108 (35).

HRMS calculated for $C_{21}H_{22}N_2O_4 \cdot H^+$ 367.1656, found 367.1653.

N-(2-N'-benzyloxycarbonylaminoethyl)-5-(p-methoxybenzoyl)pyrrolidin-2-one (**10b**).



According to the typical procedure, pyrrolidinone **10b** was obtained from amide **6b** in 68% as a yellowish oil after purification by column chromatography (EtOAc).

^{1}H NMR ($CDCl_3$) δ 7.92 (d, *J*=8.6, 2H, Harom), 7.33-7.30 (m, 5H, Harom), 6.97 (d, *J*=8.6, 2H, Harom), 5.31-5.24 (m, 2H, NH, H-5), 5.10 (d, *J*=12.2, 1H, H-6'), 5.03 (d, *J*=12.2, 1H, H-6'), 3.89 (s, 3H, OCH_3), 3.80-3.75 (m, 1H, H-1'/H-2'), 3.60-3.49 (m, 1H, H-2'/H-1'), 3.24-3.09 (m, 2H, H-1'/H-2'), 2.43-2.25 (m, 3H, H-3/H-4), 1.95-1.74 (m, 1H, H-4/H-3).

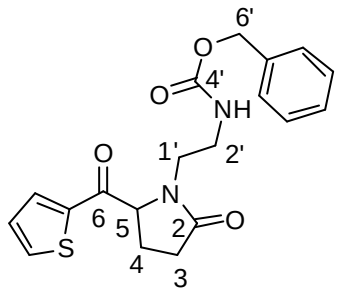
^{13}C NMR ($CDCl_3$) δ 195.6 (C-6), 176.5 (C-2), 156.8 (C-4'), 164.3, 136.7, 114.2 (q-Carom), 128.1, 128.0, 127.9, 127.0 (t-Carom), 66.6 (C-5), 61.7 (C-6'), 56.6 (OCH_3), 42.2, 39.1 (C-1', C-2'), 29.4, 23.9 (C-3, C-4).

IR (film) υ 3331, 2943, 1684, 1596, 1514.

MS (M+1, CI) *m/z* (%) 290 (14), 289 (100), 246 (26), 245 (13), 153 (13).

HRMS calculated for $C_{22}H_{24}N_2O_5 \cdot H^+$ 397.1763, found 397.1767.

N-(2-N'-benzyloxycarbonylaminoethyl)-5-(2-thienylcarbonyl)pyrrolidin-2-one (**11b**).



According to the typical procedure, pyrrolidinone **11b** was obtained from amide **7b** in 81% as a yellowish oil after purification by column chromatography (EtOAc).

^{1}H NMR ($CDCl_3$) δ 7.75-7.67 (m, 2H, Harom), 7.27-7.22 (m, 5H, Harom), 7.14-7.11 (m, 1H, Harom), 5.79-5.73 (m, 1H, NH), 5.13-5.10 (m, 1H, H-5), 5.03 (d, *J*=12.2, 1H, H-6'), 4.96 (d, *J*=12.2, 1H, H-6'), 3.76-3.68 (m, 1H, H-1'/H-2'), 3.49-3.30 (m, 1H, H-2'/H-1'), 3.20-2.96 (m, 2H, H-1'/H-2'), 2.30-2.14 (m, 3H, H-3/H-4), 1.97-1.90 (m, 1H, H-4/H-3).

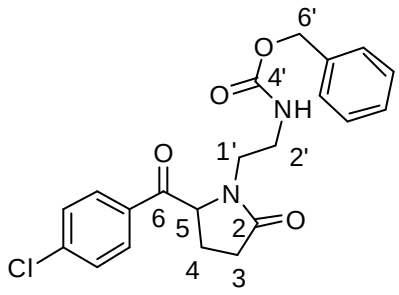
^{13}C NMR ($CDCl_3$) δ 190.8 (C-6), 176.5 (C-2), 156.8 (C-4'), 141.0, 135.3 (q-Carom), 128.7, 128.4, 128.0, 127.9 (t-Carom), 66.4 (C-5), 62.7 (C-6'), 42.0, 38.7 (C-1', C-2'), 29.4, 24.0 (C-3, C-4).

IR (film) υ 3319, 3072, 1678, 1590.

MS (M+1, CI) *m/z* (%) 329 (8), 256 (34), 222 (38), 221 (100), 220 (69), 108 (34).

HRMS calculated for $C_{19}H_{20}N_2O_4{}^{32}S{\cdot}H^+$ 373.1222, found 373.1224.

N-(2-N'-benzyloxycarbonylaminoethyl)-5-(p-chlorobenzoyl)pyrrolidin-2-one (**12b**).



According to the typical procedure, pyrrolidinone **12b** was obtained from amide **8b** in 79% as a yellowish oil after purification by column chromatography (EtOAc).

^{1}H NMR ($CDCl_3$) δ 7.88 (d, *J*=8.4, 2H, Harom), 7.47 (d, *J*=8.4, 2H, Harom), 7.32-7.25 (m, 5H, Harom), 5.42-5.36 (m, 1H, NH), 5.30-5.28 (m, 1H, H-5), 5.09 (d, *J*=12.2, 1H, H-6'), 5.02 (d, *J*=12.2, 1H, H-6'), 3.86-3.77 (m, 1H, H-1'/H-2'), 3.49-3.30 (m, 1H, H-2'/H-1'), 3.20-2.96 (m, 2H, H-1'/H-2'), 2.32-2.20 (m, 2H, H-3/H-4), 1.87-1.80 (m, 1H, H-4/H-3).

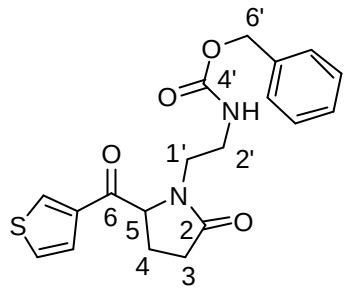
^{13}C NMR ($CDCl_3$) δ 196.0 (C-6), 176.3 (C-2), 156.8 (C-4'), 140.7, 136.6, 132.3 (q-Carom), 129.8, 129.4, 128.5, 128.1, 127.9 (t-Carom), 66.6 (C-5), 61.8 (C-6'), 42.1, 38.7 (C-1', C-2'), 29.2, 23.4 (C-3, C-4).

IR (film) υ 3319, 2943, 1690, 1590, 1525.

MS (M+1, CI) *m/z* (%) 295 (33), 293 (100), 252 (10), 250 (84), 289 (77), 153 (95), 108 (26).

HRMS calculated for $C_{21}H_{21}{}^{35}ClN_2O_4 \cdot H^+$ 401.1268, found 401.1261.

N-(2-N'-benzyloxycarbonylaminoethyl)-5-(3-thienylcarbonyl)pyrrolidin-2-one (**11c**).



According to the typical procedure, pyrrolidinone **11c** was obtained from amide **7c** in 64% as a yellowish solid after purification by column chromatography (EtOAc).

^{1}H NMR ($CDCl_3$) δ 8.14 (s, 1H, Harom), 7.56-7.54 (m, 1H, Harom), 7.39-7.33 (m, 6H, Harom), 5.39 (br s, 1H, NH), 5.12-5.00 (m, 3H, H-5, H-6'), 3.85-3.76 (m, 1H, H-1'/H-2'), 3.52-3.45 (m, 1H, H-2', H-1'), 3.19-3.04 (m, 2H, H-1'/ H-2'), 2.42-2.22 (m, 3H, H-3/H-4), 2.00-1.93 (m, 1H, H-4/H-3).

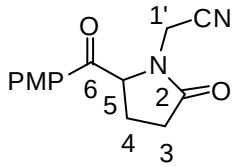
^{13}C NMR ($CDCl_3$) δ 191.8 (C-6), 176.5 (C-2), 156.8 (C-4), 139.1, 136.5 (q-Carom), 133.3, 128.5, 128.1, 128.0, 127.2, 127.0 (t-Carom), 66.6 (C-5), 62.9 (C-6'), 42.0, 38.8 (C-1', C-2'), 29.3, 23.7 (C-3, C-4).

IR (film) υ 3315, 3088, 1685, 1528.

MS (M+1, CI) *m/z* (%) 373 (10), 329 (27), 265 (100), 261 (16), 222 (27), 153 (24).

HRMS calculated for $C_{19}H_{20}N_2O_4{}^{32}S{\cdot}H^+$ 373.1222, found 373.1224.

N-cyanomethyl-5-p-methoxyphenylpyrrolidinone (**18a**).



According to the typical procedure, pyrrolidinone **18a** was obtained from amide **17a** in 20% as a yellowish oil after purification by column chromatography (EtOAc).

^{1}H NMR ($CDCl_3$) δ 7.92 (d, *J*=8.8, 2H, Harom), 6.98 (d, *J*=8.8, 2H, Harom), 5.28-5.24 (m, 1H, H-5), 4.86 (d, *J*=17.7, 1H, H-1'), 3.88 (s, 3H, OCH_3), 3.81 (d, *J*=17.7, 1H, H-1'), 2.55-2.39 (m, 3H, H-3/H-4), 2.10-1.00 (m, 1H, H-4/H-3).

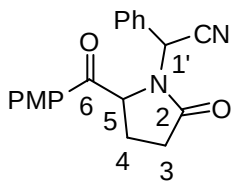
^{13}C NMR ($CDCl_3$) δ 194.1 (C-6), 174.8 (C-2), 164.6, 126.3 (q-Carom), 130.9, 114.9 (t-Carom), 114.4 (CN), 60.9 (C-5), 55.7 (OCH_3), 30.0, 28.6, 23.4 (C-1', C-3, C-4).

IR (film) υ 3331, 1690, 1519.

MS (M+1, CI) *m/z* (%) 259 (100), 232 (45), 204 (36).

HRMS calculated for $C_{14}H_{14}N_2O_3 \cdot H^+$ 259.1083, found 259.1078.

5-p-methoxyphenyl-N-(1-phenylcyanomethyl)pyrrolidin-2-one (**18b, 18c**).



According to the typical procedure, pyrrolidinone **18b** and **18c** were obtained as an inseparable diastereomeric mixture (71:29) from amide **17b** in 30% as a yellowish oil after purification by column chromatography (Et_2O).

^{1}H NMR ($CDCl_3$) δ 7.75/7.60 (d, *J*=8.7/8.9, 2x 2H, Harom), 7.36-7.30 (m, 7H, Harom), 7.19-7.15 (m, 3H, Harom), 6.89/6.86 (d, *J*=8.7/8.9, 2x 2H, Harom), 6.35/6.37 (s, 2x 1H, H-1'), 5.16/4.77 (d, *J*=9.0/9.3, 2x 1H, H-5), 3.85/3.83 (s, 2x 3H, OCH_3), 2.62-2.22 (m, 2x 3H, H-3/H-4), 2.00-1.90 (m, 1x 1H, H-4/H-3).

^{13}C NMR ($CDCl_3$) δ 194.4/194.2 (C-6), 175.3 (C-2), 164.3/164.1, 131.3/130.7, 126.8/126.7 (q-Carom), 130.7/130.3, 129.7/129.5, 129.4/128.8, 128.5/127.6, 114.3/114.0 (t-Carom), 116.3/115.5 (CN), 58.6/58.1, 47.3/46.1 (C-1', C-5), 55.6 (OCH_3), 28.9, 24.5/24.3 (C-3, C-4).

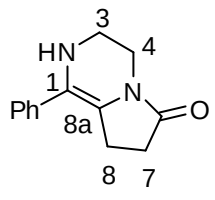
IR (film) υ 3331, 1690, 1525.

MS (M+1, CI) *m/z* (%) 335 (100), 308 (87), 118 (19).

HRMS calculated for $C_{20}H_{18}N_2O_3 \cdot H^+$ 335.1396, found 335.1403.

1.4.5. Typical procedure for the intramolecular amination reaction. Synthesis of pyrazinones 13.

1-phenyl-3,4,7,8-tetrahydropyrrolo[1,2-a]pyrazin-6(2H)-one (**13a**).



A solution of pyrrolidinone **9a** (170 mg, 0.5 mmol) in TFA/DCM 1/1 (20 mL) was stirred for 30 min. An aliquot was taken to confirm (^{1}H NMR) that the protecting group was completely released. Then, solvents were removed under vacuum and the residue was taken in 50 mL of DCM, cooled to 0 ºC and treated with Et_3N (0.7 mL, 5 mmol). After stirring for 20 min,

molecular sieve (4 Å) was added and the stirring continued for 15 additional minutes. The mixture was then filtered through celite, and washed with 20 mL of a saturated aqueous solution of $NaHCO_3$, and finally extracted with EtOAc (3x25 mL). The combined organic extracts were dried and evaporated at reduced pressure, and the resulting residue purified by column chromatography (EtOAc/MeOH, 95/5) to afford pyrazinone **13a** as a yellowish oil that was crystallized from MeOH (41%).

mp 127–128 ºC (MeOH).

^{1}H NMR ($CDCl_3$) δ 7.95 (d, *J*=8.0, 2H, Harom), 7.43-7.36 (m, 3H, Harom) 5.14 (br s, 1H, NH), 4.05-3.95 (m, 2H, H-3, H-4), 3.68-3.57 (m, 1H, H-3), 3.23-3.16 (m, 1H, H-4), 2.71-2.59 (m, 1H, H-8), 2.37-2.25 (m, 2H, H-7, H-8), 2.09-1.96 (m, 1H, H-7).

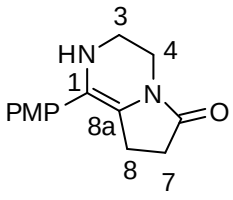
^{13}C NMR ($CDCl_3$) δ 173.1 (CO), 165.2 (C-1), 135.9 (q-Carom), 130.2, 128.3, 128.1 (t-Carom), 83.9 (C-8a), 48.1, 32.6 (C-3, C-4), 32.5, 29.4 (C-7, C-8).

IR (film) υ 3236, 1667.

MS (M+1, CI) *m/z* (%) 215 (72), 214 (100), 213 (14), 185 (10).

HRMS calculated for $C_{13}H_{14}N_2O{\cdot}H^+$ 215.1184, found 215.1191.

1-(4-methoxyphenyl)-3,4,7,8-tetrahydropyrrolo[1,2-a]pyrazin-6(2H)-one (**13b**).



According to the typical procedure, pyrrolidinone **13b** was obtained from amide **10a** in 33% as a yellowish solid by purification by column chromatography (EtOAc/MeOH, 70/30) followed by crystallization from methanol.

mp 131–132 ºC (MeOH).

^{1}H NMR ($CDCl_3$) δ 7.96 (d, *J*=9.0, 2H, Harom), 6.93 (d, *J*=9.0, 2H, Harom) 4.14-4.02 (m, 2H, H-3, H-4), 3.87 (s, 3H, OCH_3), 3.70-3.58 (m, 1H, H-3), 3.22-3.12 (m, 1H, H-4), 2.75-2.66 (m, 1H, H-8), 2.48-2.34 (m, 2H, H-7, H-8), 2.14-2.04 (m, 1H, H-7), 1.64 (br s, 1H, NH).

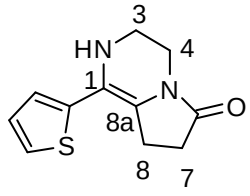
^{13}C NMR ($CDCl_3$) δ 172.8 (CO), 163.9 (C-1), 161.2, 113.6 (q-Carom), 129.7, 128.3 (t-Carom), 84.0 (C-8a), 55.3 (OCH_3), 48.0, 32.8 (C-3, C-4), 32.7, 29.3 (C-7, C-8).

IR (film) υ 3355, 1696.

MS (M+1, CI) *m/z* (%) 245 (71), 244 (100), 243 (53), 242 (42).

HRMS calculated for $C_{14}H_{16}N_2O_2 \cdot H^+$ 245.1290, found 245.1288.

1-(2-thienyl)-3,4,7,8-tetrahydropyrrolo[1,2-a]pyrazin-6(2H)-one (**13c**).



According to the typical procedure, pyrrolidinone **13c** was obtained from amide **11a** in 39% as a yellowish solid by purification by column chromatography (EtOAc/MeOH, 95/5) followed by crystallization from methanol.

mp 131–132 ºC (MeOH).

^{1}H NMR ($CDCl_3$) δ 7.64-7.39 (m, 2H, Harom), 7.08-7.06 (m, 1H, Harom) 4.12-3.93 (m, 2H, H-3, H-4), 3.91-3.79 (m, 1H, H-3), 3.66-3.58 (m, 1H, H-4), 3.18-2.80 (m, 1H, H-8), 2.79-2.56 (m, 2H, H-7, H-8), 2.42-2.22 (m, 1H, H-7), 1.68 (br s, 1H, NH).

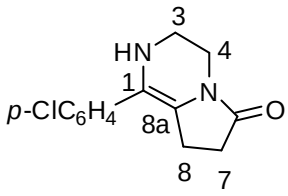
^{13}C NMR ($CDCl_3$) δ 173.0 (CO), 160.3 (C-1), 141.4 (q-Carom), 129.2, 129.1, 127.7 (t-Carom), 83.9 (C-8a), 48.1, 33.6 (C-3, C-4), 32.9, 29.3 (C-7, C-8).

IR (film) υ 3296, 1690.

MS (M+1, CI) *m/z* (%) 221 (67), 220 (100), 153 (13), 127 (14).

HRMS calculated for $C_{11}H_{12}N_2O^{32}S{\cdot}H^+$ 221.0749, found 221.0739.

1-(p-chlorophenyl)-3,4,7,8-tetrahydropyrrolo[1,2-a]pyrazin-6(2H)-one (**13d**).



According to the typical procedure, pyrrolidinone **13d** was obtained from amide **12a** in 34% as a yellowish oil by purification by column chromatography (EtOAc/MeOH, 95/5).

^{1}H NMR ($CDCl_3$) δ 7.92 (d, *J*=8.7, 2H, Harom), 7.37 (d, *J*=8.7, 2H, Harom), 4.10-3.99 (m, 2H, H-3, H-4), 3.70-3.57 (m, 1H, H-3), 3.48 (s, 1H, NH), 3.25-3.14 (m, 1H, H-4), 2.74-2.62 (m, 1H, H-8), 2.38-2.27 (m, 1H, H-7), 2.05-1.98 (m, 2H, H-8, H-7).

^{13}C NMR ($CDCl_3$) δ 173.0 (CO), 163.9 (C-1), 136.4, 134.2 (q-Carom), 129.5, 128.6 (t-Carom), 83.8 (C-8a), 48.2, 32.7 (C-3, C-4), 32.6, 29.3 (C-7, C-8).

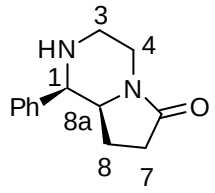
IR (film) υ 3302, 1678.

MS (M+1, CI) *m/z* (%) 249 (58), 248 (100), 213 (11).

HRMS calculated for $C_{13}H_{13}{}^{35}ClN_2O{\cdot}H^+$ 249.0795, found 249.0783.

1.4.6. Typical procedure for the intramolecular reductive amination reaction. Synthesis of pyrazinones 14.

(+/-)-(1R,8aS)-1-phenylhexahydropyrrolo[1,2-a]pyrazin-6-one (**14a**).



A solution of pyrrolidinone **9b** (209.5 mg, 0.6 mmol) dissolved in 6 mL of MeOH and 0.5 mL of HCl (1M) was hydrogenated (70 psi) in the presence of Pd/C overnight. The catalyst was filtered through celite and the solution treated with 15 mL of an aqueous solution of Na_2CO_3 (20%). The mixture was extracted with DCM (3x15 mL), the combined organic extracts were dried with Na_2SO_4, and the solvent evaporated under vacuum. The resulting oil was purified by column chromatography (MeOH) to afford pyrazinone **14a** as a yellowish oil (40%).

^{1}H NMR ($CDCl_3$) δ 7.37-7.26 (m, 5H, Harom), 4.61 (d, *J*=8.0, 1H, H-1), 3.79-3.77 (m, 1H, H-8a), 3.71-3.68 (m, 1H, H-3), 3.47-3.44 (m, 1H, H-3), 3.38-3.36 (m, 1H, H-4), 2.93-2.90 (m, 1H, H-4), 2.45-2,38 (m, 1H, H-7), 2.26-2.19 (m, 1H, H-7), 1.90-1.83 (m, 1H, H-8), 1.72-1.68 (m, 1H, H-8).

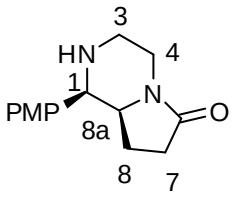
^{13}C NMR ($CDCl_3$) δ 177.5 (CO), 141.4 (q-Carom), 128.5, 127.9, 127.0 (t-Carom), 77.1 (C-1), 66.6 (C-8a), 46.8, 39.2 (C-3, C-4), 30.1, 22.6 (C-7, C-8).

IR (film) υ 3350, 1655.

MS (M+1, CI) *m/z* (%) 217 (39), 215 (100), 214 (76), 153 (29), 108 (35).

HRMS calculated for $C_{13}H_{16}N_2O{\cdot}H^+$ 217.1341, found 217.1348.

(+/-)-(1R,8aS)-1-(p-methoxyphenyl)hexahydropyrrolo[1,2-a]pyrazin-6-one (**14b**).



According to the typical procedure, pyrrolidinone **14b** was obtained from amide **10b** in 43% as a yellowish oil after purification by column chromatography (EtOAc).

^{1}H NMR ($CDCl_3$) δ 7.27 (d, *J*=8.7, 2H, Harom), 6.85 (d. *J*=8.7, 2H, Harom), 4.09-4.04 (m, 1H, H-3), 3.76 (s, 3H, OCH_3), 3.48-3.43 (m, 1H, H-8a), 3.22 (d, *J*=9.3, 1H, H-1), 3.13-3.10 (m, 1H, H-3), 2.97-2.91 (m, 1H, H-4), 2.82-2.76 (m, 1H, H-4), 2.46-2.26 (m, 3H, NH, H-7), 1.84-1.77 (m, 1H, H-8), 1.64-1.56 (m, 1H, H-8).

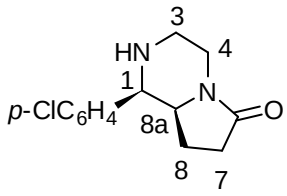
^{13}C NMR ($CDCl_3$) δ 173.7 (CO), 159.5, 131.6 (q-Carom), 128.8, 114.0 (t-Carom), 79.7 (C-1), 61.9 (C-8a), 55.2 (OCH_3), 45.4, 40.2 (C-3, C-4), 30.1, 21.6 (C-7, C-8).

IR (film) υ 3425, 1667.

MS (M+1, CI) *m/z* (%) 247 (100), 246 (66), 230 (28), 161 (13).

HRMS calculated for $C_{14}H_{18}N_2O_2 \cdot H^+$ 247.1447, found 247.1440.

(+/-)-(1R,8aS)-1-(p-chlorophenyl)hexahydropyrrolo[1,2-a]pyrazin-6-one (**14d**).



According to the typical procedure, pyrrolidinone **14d** was obtained from amide **12b** in 46% as a yellowish oil after purification by column chromatography (MeOH).

^{1}H NMR ($CDCl_3$) δ 7.42-7.33 (m, 4H, Harom), 4.12-4.09 (m, 1H, H-3), 3.54-3.49 (m, 1H, H-8a), 3.30 (d, *J*=9.2, 1H, H-1), 3.17-3.14 (m, 1H, H-4), 3.00-2.96 (m, 1H, H-3), 2.86-2.80 (m, 1H, H-4), 2.42-2.29 (m, 2H, H-7), 1.98 (br s, 1H, NH), 1.84-1.80 (m, 1H, H-8), 1.66-1.62 (m, 1H, H-8).

^{13}C NMR ($CDCl_3$) δ 173.7 (CO), 139.6, 128.5 (q-Carom), 128.7, 127.7 (Carom), 68.3 (C-1), 61.9 (C-8a), 45.4, 40.3 (C-3, C-4), 30.1, 21.6 (C-7, C-8).

IR (film) υ 3387, 1667.

MS (M+1, CI) *m/z* (%) 251 (10), 218 (14), 217 (100), 216 (60), 200 (23).

HRMS calculated for $C_{13}H_{15}{}^{35}ClN_2O{\cdot}H^+$ 251.0951, found 251.0953.

2. SÍNTESIS DE PIRROLODIAZEPINONAS Y PIRROLO-BENZODIAZEPINONAS

La actividad biológica de muchos compuestos antitumorales de bajo peso molecular parece estar relacionada con el modo y especificidad con que interactúan con secuencias concretas de ADN. De hecho, en la mayoría de los fármacos contra el cáncer, su efecto antitumoral reside en la capacidad de inhibir los procesos de síntesis de proteínas o de los ácidos nucleicos (ADN o ARN). La preparación de dichos compuestos antitumorales resulta, sin embargo, laboriosa, debido a la compleja naturaleza del ADN.

En este contexto, la síntesis del esqueleto de pirrolo[1,2-*c*][1,4]benzodiazepina, PBD, ha sido objeto de numerosas aproximaciones sintéticas ya que dichos heterociclos conforman el esqueleto básico de los

agentes antitumorales conocidos como antramicinas,[80] productos naturales que tienen la habilidad de reconocer y unirse a secuencias específicas del ADN. En la *Figura 2.3* se muestra la estructura general de las PBDs, así como diversos análogos con reconocida capacidad antibiótica y antitumoral.[81]

80. Aislado y caracterizado por primera vez en : (a) Leimgruber, W.; Stefanovic, V.; Schenker, F.; Karr, A.; Berger, J. *J. Am. Chem. Soc.* **1965**, *87*, 5791. (b) Leimgruber, W.; Batcho, A. D.; Schenker, F. *J. Am. Chem. Soc.* **1965**, *87*, 5793.

81. Sintetizados por primera vez en : *Macetramicina*: Kunimoto, S.; Masuda, T.; Kanbayashi, N.; Hamada, M.; Naganawa, H.; Miyamoto, M.; Takeuchi, T.; Umetawa, H. *J. Antibiotics* **1980**, *33*, 665. *Porotramicina*: Tsunakawa, M.; Kamei, H.; Konishi, M.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiotics* **1988**, *41*, 1366. *Tomamicina:* Arima, K.; Kohsaka, M.; Tamura, G.; Imanaka, H.; Sakai, H. *J. Antibiotics* **1972**, *25*, 437. *Protracarcina:* Shimizu, K.; Kawamoto, I.; Tomita, F.; Morinoto, M.; Fujimoto, K. *J. Antibiotics* **1982**, *35*, 972. *Chicamicina:* Konishi, M.; Ohkura, H.; Naruse, N.; Kawaguchi, H. *J. Antibiotics* **1984**, *37*, 200. *Abeimicina:* Hochlowski, J. E.; Andrés, W. W.; Theriault, R. J.; Jackson, M.; McAlpine, J. B. *J. Antibiotics* **1987**, *40*, 145. *Neotramicina A y B:* Takeuchi, T.; Miyamoto, M.; Ishizuka, M.; Naganawa, H.; Kondo, S.; Hamada, M; Umezawa, H. *J. Antibiotics* **1976**, *29*, 93. *DC-81*: (a) Thurston, D. E.; Thompson, A. S. *Chem. Brit.* **1990**, *26*, 767. (b) Bose, D. S.; Jones, G. B.; Thurston, D. E. *Tetrahedron* **1992**, *48*, 751.

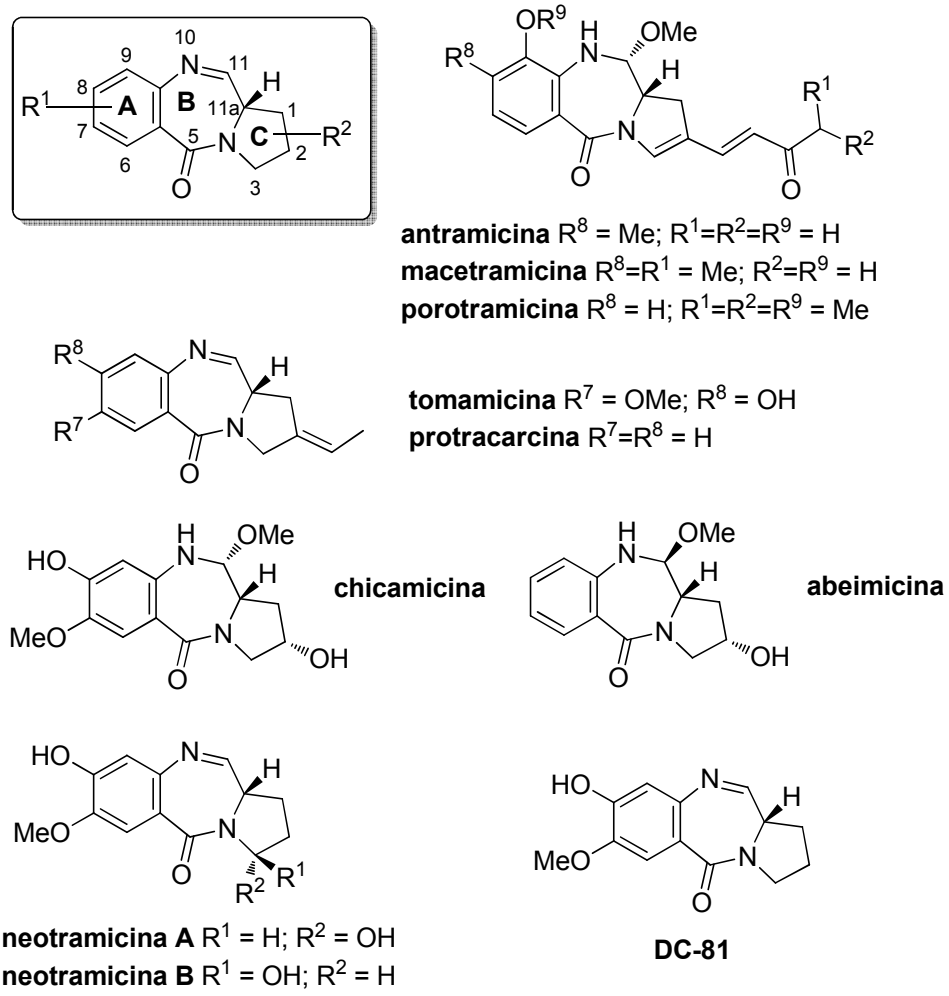
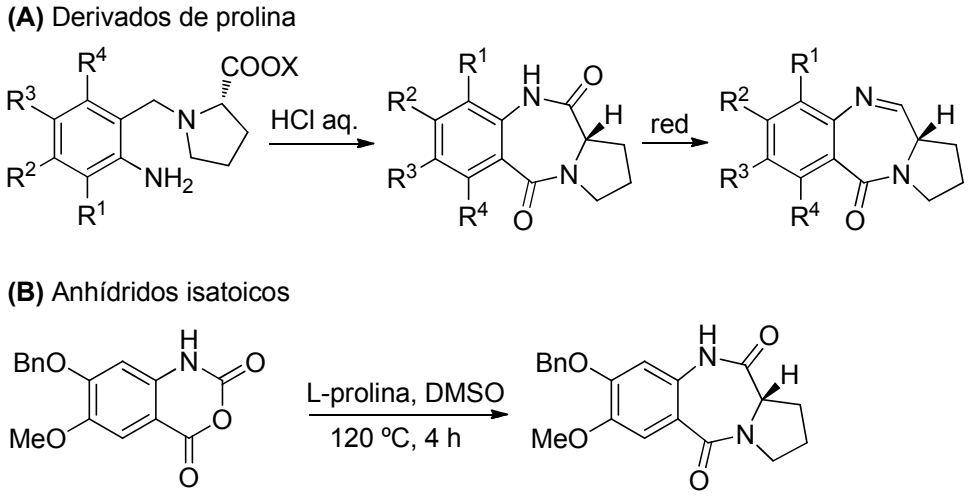


Figura 2.3. Diferentes PBDs con actividad farmacológica.

Desde el descubrimiento de la antramicina, en 1965,[80] se han desarrollado numerosas estrategias sintéticas de PBDs incluida la propia

antramicina. De manera general,[82] las dos aproximaciones más habituales para la síntesis de PBDs se basan en el uso de derivados de N-(2-aminobencil)prolina convenientemente sustituidos[83] y de anhídridos isatoicos[84] (*Esquema 2.12*).



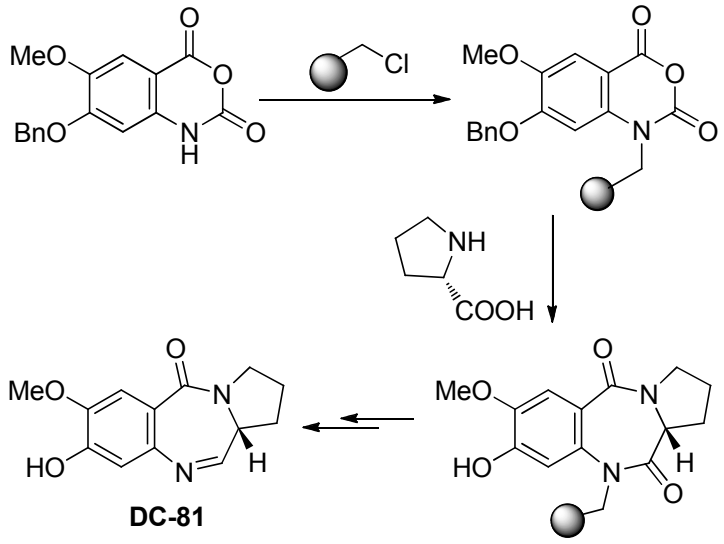
Esquema 2.12. Estrategias habituales para la preparación de PBDs.

82. Para una lectura sobre los diferentes métodos de síntesis de PBDs véase: (a) Antonow, D.; Thurston, D. E.; *Chem. Rev*. **2011**, *111*, 2815. (b) Kamal, A.; Rao, M. V.; Laxman, N.; Ramesh, G.; Reddy, G. S. K. *Curr. Med. Chem. Anti-Cancer Agents* **2002**, *2*, 215. (c) Hu, W. –P.; Wang, J. –J.; Lin, F. –L.; Lin, Y. –C.; Lin, S. –R.; Hsu, M. –H. *J. Org. Chem*. **2001**, *66*, 2881. (d) Thurston, D. E.; Bose, D. S. *Chem. Rev*. **1994**, *94*, 433.

83. (a) O'Neil, I. A.; Thompson, S.; Murray, C. L.; Kalindjian, S. B. *Tetrahedron Lett*. **1998**, *39*, 7787. (b) Molina, P.; Díaz, I.; Tárraga, A. *Tetrahedron* **1995**, *51*, 5617. (c) Eguchi, S.; Yamashita, K.; Matsushita, Y.; Kakehi, A. *J. Org. Chem*. **1995**, *60*, 4006. (d) Kamal, A.; Praveen Reddy, B. S.; Narayan Reddy, B. S. *Tetrahedron Lett*. **1996**, *37*, 2281. (e) Thurston, D. E.; Murty, V. S.; Langley, D. R.; Jones, G. B. *Synthesis* **1990**, 81.

84. Por ejemplo en: (a) Clark, R. L.; Carter, K. C.; Mullen, A. B.; Coxon, G. D.; Owusu-Dapaah, G.; McFarlane, E.; Thi, M. D. D.; Grant, M. H.; Tettey, J. N. A.; Mackay, S. P. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 624. (b) Wang, T.; Lui, A. S.; Cloudsdale, I. S. *Org. Lett*. **1999**, *1*, 1835. (c) Kamal, A.; Reddy, B. S. N.; Reddy, G. S. K. *Synlett* **1999**, 1251. (d) Kamal, A.; Ramulu, P.; Srinivas, O.; Ramesh, G. *Bioorg. Med. Chem.* **2003**, *13*, 3955. (e) Kamal, A.; Ramulu, P.; Srinivas, O.; Ramesh, G. *Bioorg. Med. Chem.* **2003**, *13*, 3577.

También se han aplicado las ventajas de la síntesis en fase sólida a la obtención de PBDs. En el *Esquema 2.13* se muestra el uso de esta aproximación para la síntesis del DC-81.[85]

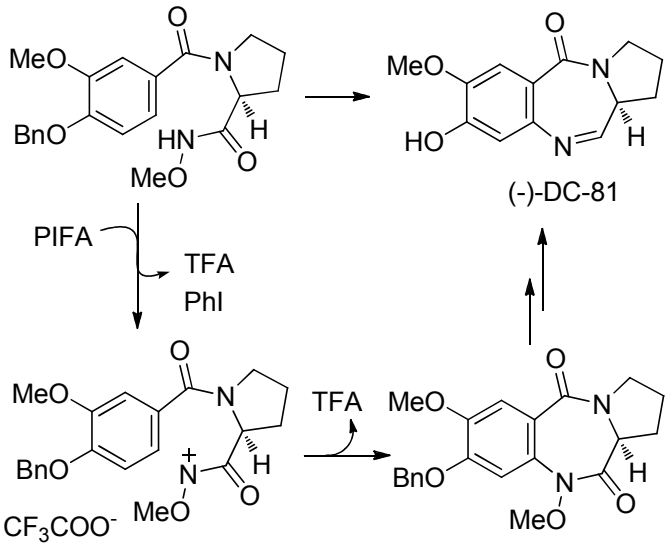


Esquema 2.13. Síntesis en fase sólida del DC-81.

Nuestro grupo de investigación llevó a cabo con notable éxito una novedosa ruta para la obtención enantiocontrolada del antibiótico (-)-DC-81. En este caso, el tratamiento de una amida N-metoxi sustituida, derivada de L-prolina, con el reactivo PIFA facilitó la construcción de su esqueleto base tricíclico por formación de un nuevo enlace C-N a través de un proceso de

85. Kamal, A.; Reddy, K. L.; Devaiah, V.; Shankaraiah, N. *Synlett* **2004**, 1841.

amidación electrófila aromática por formación de un intermedio N-acilnitrénico. Posteriores modificaciones permitieron la obtención del DC-81 y se pudo comprobar que la pureza óptica del derivado de L-prolina de partida se transmitía íntegramente al producto final (*Esquema 2.14*).[86] Esta alternativa sintética presenta la ventaja de constar de sólo 9 pasos, con un rendimiento global del 19%.[87]

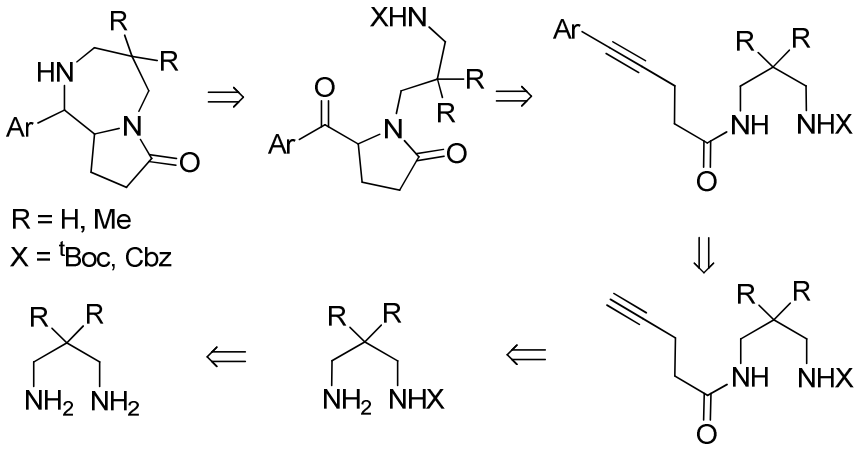


Esquema 2.14. Estrategia sintética para la preparación del DC-81 desarrollada por nuestro grupo.

86. Correa, A.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *J. Org. Chem*. **2005**, *70*, 2256.

87. Algunas de las síntesis publicadas para el DC-81 pueden encontrarse en: (a) Referencia 81. (b) Kamal, A.; Praveen Reddy, B. S.; Narayan Reddy, B. S. *Tetrahedron Lett*. **1996**, *37*, 6803. (c) Prabhu, K. R.; Sivanand, P. S.; Chandrsekaran, S. *Synlett* **1998**, 47. (d) Kamal, A.; Howard, P. H.; Narayan Reddy, B. S.; Praveen Reddy, B. S.; Thurston, D. E. *Tetrahedron* **1997**, *53*, 3223. (e) Referencia 83d. (f) Referencia 85. (g) Kamal, A.; Shankaraiah, N.; Reddy, K. L.; Devaiah, V. *Tetrahedron Lett.* **2006**, *47*, 4253.

Se presenta ahora una extensión de la estrategia expuesta en el apartado anterior a la obtención tanto de pirrolodiazepinas[88] como de pirrolobenzodiazepinas[89] (*Esquema 2.15*). Se valorará el comportamiento de alquinilamidas que porten un fragmento propilendiamínico monoprotegido convenientemente situado con el fin de permitir una posterior ciclación intramolecular a los compuestos deseados.



Esquema 2.15. Retrosíntesis para el acceso a pirrolodiazepinas.

88. Aunque en la bibliografía se encuentran numerosos ejemplos para la síntesis de PBD, el número de referencias para la preparación de pirrolodiazepinas es mucho menor. Algunos ejemplos se encuentran en: (a) Malamidou-Xenikaki, E.; Spyroudis, S.; Tsanakopoulou, M.; Hadjipavlou-Litina, D. *J. Org. Chem*. **2009**, *74*, 7315. (b) Dyker, G.; Thöne, A.; Henkel, G. *Beilstein J. Org. Chem*. **2007**, *3*, 28. (c) Katritzky, A. R.; Jain, R.; Akhmedova, R.; Xu, Y. –J. *ARKIVOC* **2003**, *ix*, 4.

89. Ejemplos para la síntesis de PBD-3-onas se pueden encontrar en: (a) Lee, J. Y.; Im, I.; Webb, T. R.; McGrath, D.; Song, M. -R.; Kim, Y. -C. *Bioorganic Chemistry* **2009**, *37*, 90. (b) Zhao, D. –M.; Ma, C.; Sha, Y.; Liu, J. –H.; Cheng, M. –S. *Acta Cryst. Sect. E* **2008**, *64*, 266. (c) Witt, A.; Gustavsson, A.; Bergman, J. *J. Heterocycl. Chem*. **2003**, *40*, 29.

2.1. Síntesis de pirrolodiazepinonas a partir de N-aminopropilpentinamidas.

Para llevar a cabo la investigación planteada, se comenzó por preparar una serie de amidas lineales polifuncionalizadas. Como ya se ha mencionado en el apartado anterior, la experiencia de nuestro grupo ha puesto de manifiesto que la presencia de grupos aminos o hidroxilos libres no es compatible con la reacción de heterociclación de amidas insaturadas mediada por PIFA, por lo que fue preciso proceder a su protección.

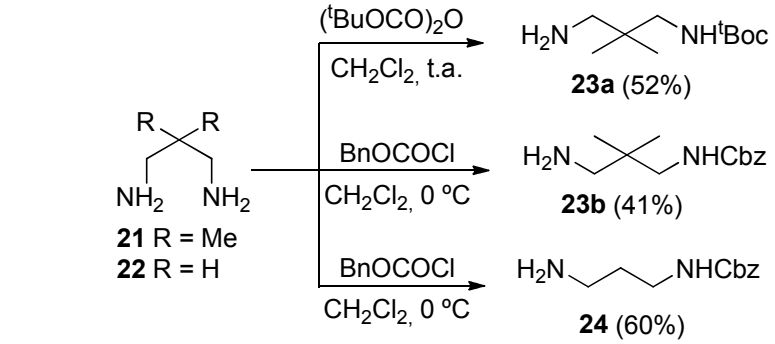
En esta ocasión (*Tabla 2.5*), y de manera análoga a lo expuesto en el apartado anterior, se eligieron dos grupos protectores habituales (^{t}Boc y Cbz) para la reacción de monoprotección de las diaminas de partida **21** y **22**, lo que debería conducir a la obtención de esqueletos pirrolodiazepínicos con diferente grado de instauración, en función del modo en el que ambos grupos protectores son retirados en la etapa previa a la formación del biciclo final. Así, las aminas monoprotegidas (**23a,b** y **24**)[90] fueron preparadas con rendimientos moderados[91] por reacción del 2,2-dimetil-1,3-diaminopropano (compuesto comercial **21**) y del 1,3-diaminopropano (compuesto comercial **22**) con di-*terc*-butildicarbonato y cloroformiato de bencilo. Posteriormente, los carbamatos **23a,b** se transformaron en las amidas **25a,b** con excelentes rendimientos por reacción con el ácido 4-pentinoico (**4**) en presencia de HOBt y EDC·HCl como agente activantes. Paralelamente, se comprobó que

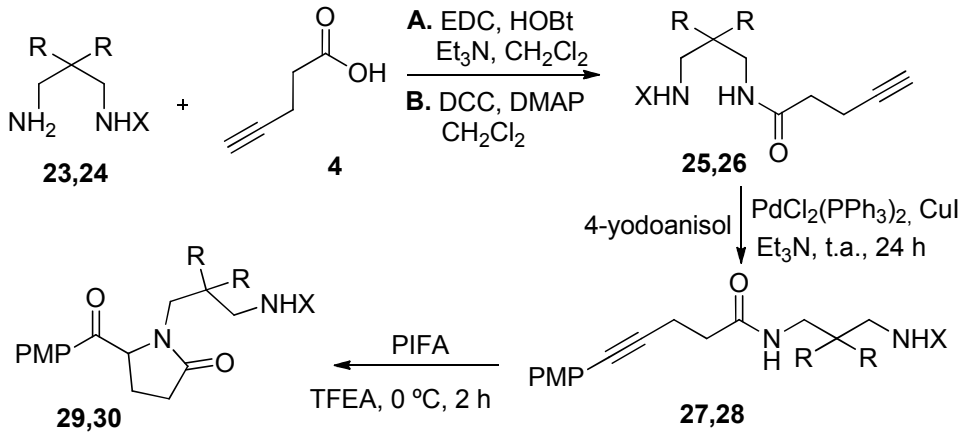
90. Debido a la mayor eficiencia en la síntesis con el grupo protector Cbz, la amina **24** sólo fue protegida con este grupo.
91. Una limitación relacionada con la necesidad de evitar procesos de múltiple protección.

la amida **26** se obtuvo de modo más satisfactorio al ser preparada en presencia de DCC y DMAP como agentes activantes a partir de **24**. Las amidas preparadas se sometieron a las condiciones de Sonogashira que requieren CuI y $PdCl_2(PPh_3)_2$ como catalizadores, para incorporar el resto arilo terminal. En esta ocasión, la reacción se optimizó empleando 4-yodoanisol lo que supuso la entrada del sustituyente arilo que, en la síntesis previa de pirrolopirazinonas, mostró un mejor comportamiento.

Una vez sintetizadas las amidas **27a,b** y **28**, se procedió a su tratamiento con el reactivo PIFA, bajo las condiciones habituales, dando lugar a las pirrolidin-2-onas deseadas **29a,b** y **30** con buenos rendimientos.

Tabla 2.5. Síntesis de precursores.

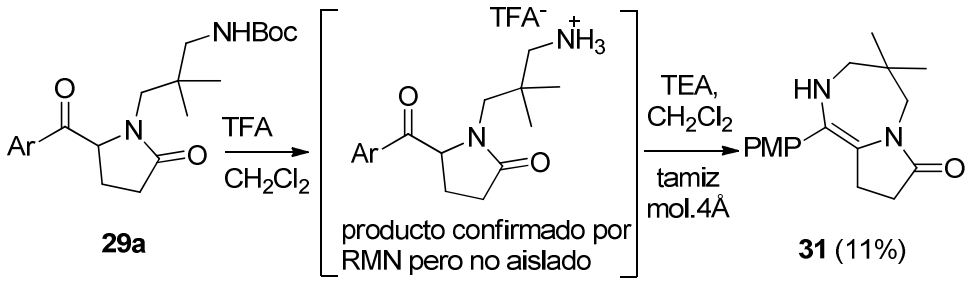




Entrada	Sustrato	R	X	Amidación	Sonogashira[a]	Ciclación[a]
1	**23a**	Me	tBoc	**25a** (97%)[a],[c]	**27a** (43%)	**29a** (83%)
2	**23b**	Me	Cbz	**25b** (87%)[a],[c]	**27b** (66%)	**29b** (89%)
3	**24**	H	Cbz	**26** (93%)[b],[d]	**28** (60%)	**30** (70%)

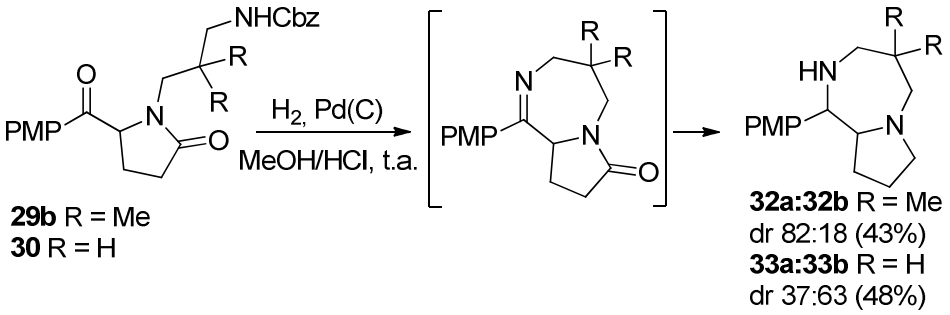
[a] Rendimiento de producto cromatográficamente puro.
[b] Rendimiento de producto puro cristalizado (Et_2O).
[c] Condiciones de amidación **A.**
[d] Condiciones de amidación **B.**

Una vez sintetizadas, las pirrolidinonas **29a,b** y **30** fueron desprotegidas. Así, al igual que en el apartado anterior, la pirrolidinona **29a** se desprotegió bajo condiciones ácidas (TFA). La amina así obtenida se sometió a condiciones de ciclodeshidratación en medio básico con tamiz molecular para dar lugar al biciclo **31** como resultado de un proceso de isomerización de un previo intermedio imínico. En cualquier caso, el rendimiento para esta transformación resultó ser muy pobre (*Esquema 2.16*).



Esquema 2.16. Desprotección/ciclodeshidratación de la pirrolidinona **29a**.

Paralelamente, la hidrogenación catalítica de los compuestos **29b** y **30,** protegidos como O-bencilcarbamatos, condujo con rendimientos moderados, a los biciclos **32a,b** y **33a,b**, respectivamente, como una mezcla de dos diastereoisómeros inseparables. Tal transformación resulta ser una combinación sucesiva de etapas de desprotección, posterior ciclación intramolecular y final reducción de la unión azometínica (*Esquema 2.17*).



Esquema 2.17. Desprotección/ciclodeshidratación de las pirrolidinonas **29b** y **30**.

La caracterización estructural de estas moléculas se realizó mediante diversos experimentos de RMN tanto monodimensionales como bidimensionales. En la *Figura 2.4* se muestra, a modo de ejemplo, parte del espectro de ^{1}H-RMN del compuesto **32**, para el que se destacan las señales selecccionadas que han servido para determinar las proporciones diastereoméricas.

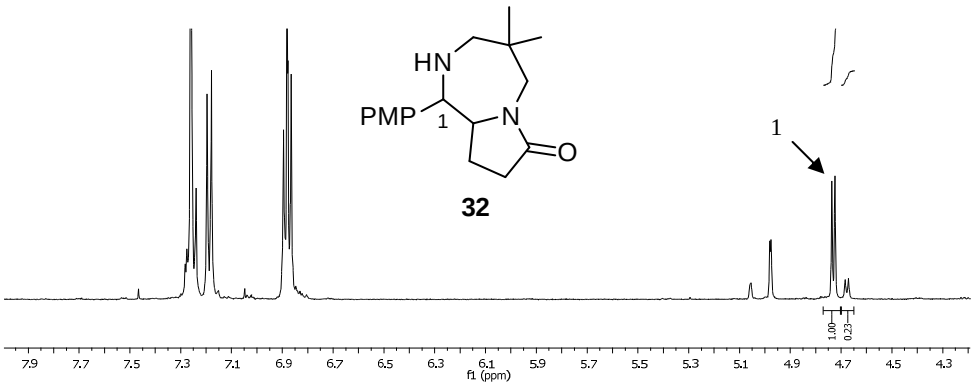
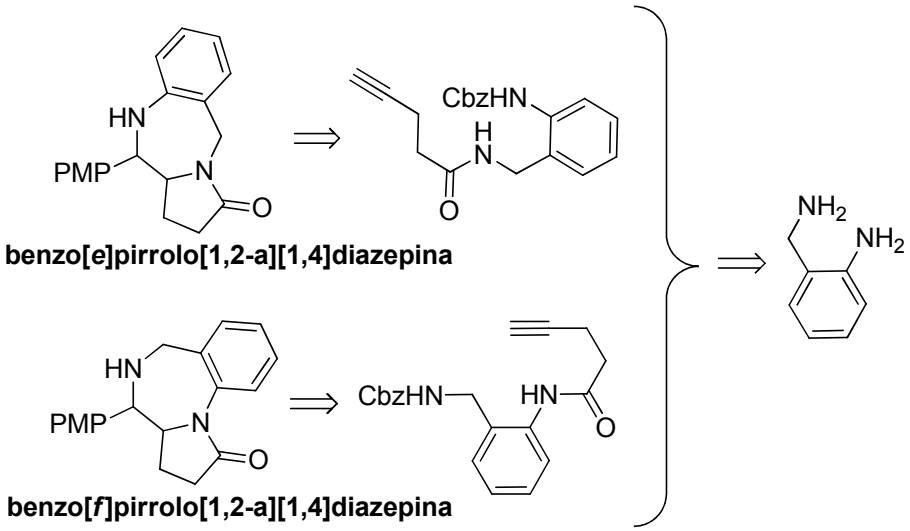


Figura 2.4. Espectro ^{1}H-RMN del compuesto **32**.

2.2. Síntesis de pirrolobenzodiazepinonas a partir de N-aminobencilpentinamidas.

Extendiendo el esquema general mostrado previamente para la síntesis de pirrolodiazepinonas, planteamos la posibilidad de aplicar esta ruta para la obtención pirrolobenzodiazepinonas. Para ello, se requiere una serie de precursores que permitan posteriormente construir la estructura tricíclica deseada (*Esquema 2.18)*. Así, habríamos accedido a una novedosa y sencilla estrategia para la obtención de dos regiosisomeros pirrolobenzodiazepínicos, uno con una fusión más común (benzo[*e*]pirrolo[2,1-*a*][1,4]diazepinona) y el otro con una fusión menos habitual (benzo[*f*]pirrolo[1,2-*a*][1,4]diazepinona), aprovechando la marcada diferencia de nucleofilia entre los grupos amino de la 2-aminobencilamina de partida, tal y como describiremos en los siguientes párrafos.[92]

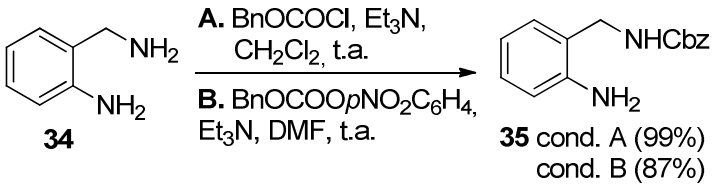
92. La primera publicación para la síntesis de pirrolo[1,2-*a*]benzodiazepinonas se encuentra en: Mucedda, M.; Muroni, D.; Saba, A.; Manassero, C. *Tetrahedron* **2007**, *63*, 12232.



Esquema 2.18. Retrosíntesis para el acceso a las PBDs.

En esta ocasión, y ante los pobres resultados obtenidos anteriormente en la reacción de heterociclación intramolecular de **29a**, se decidió restringir nuestro estudio únicamente a la vía que emplea el grupo Cbz como agente protector del grupo amínico. Así, se valoraron dos condiciones experimentales para la obtención de la amina monoprotegida a partir de **34**. Por un lado, se recurrió al uso de cloroformiato de bencilo en presencia de trietilamina como aditivo, lo que resultó en la obtención del producto deseado **35** con rendimiento cuantitativo. Y, por otro lado, se introdujo el grupo protector Cbz empleando carbonato de *p*-nitrofenilbencilo bajo similares condiciones de reacción empleando DMF como disolvente. En

ambos casos, se consiguió la formación del compuesto deseado **35** con un rendimiento excelente (*Esquema 2.19*).



Esquema 2.19. Protección de la amina de partida.

A continuación se preparó la amida **36** con buen rendimiento por tratamiento con el ácido 4-pentinoico (**4**) en presencia de HOBt y EDC·HCl como activantes.

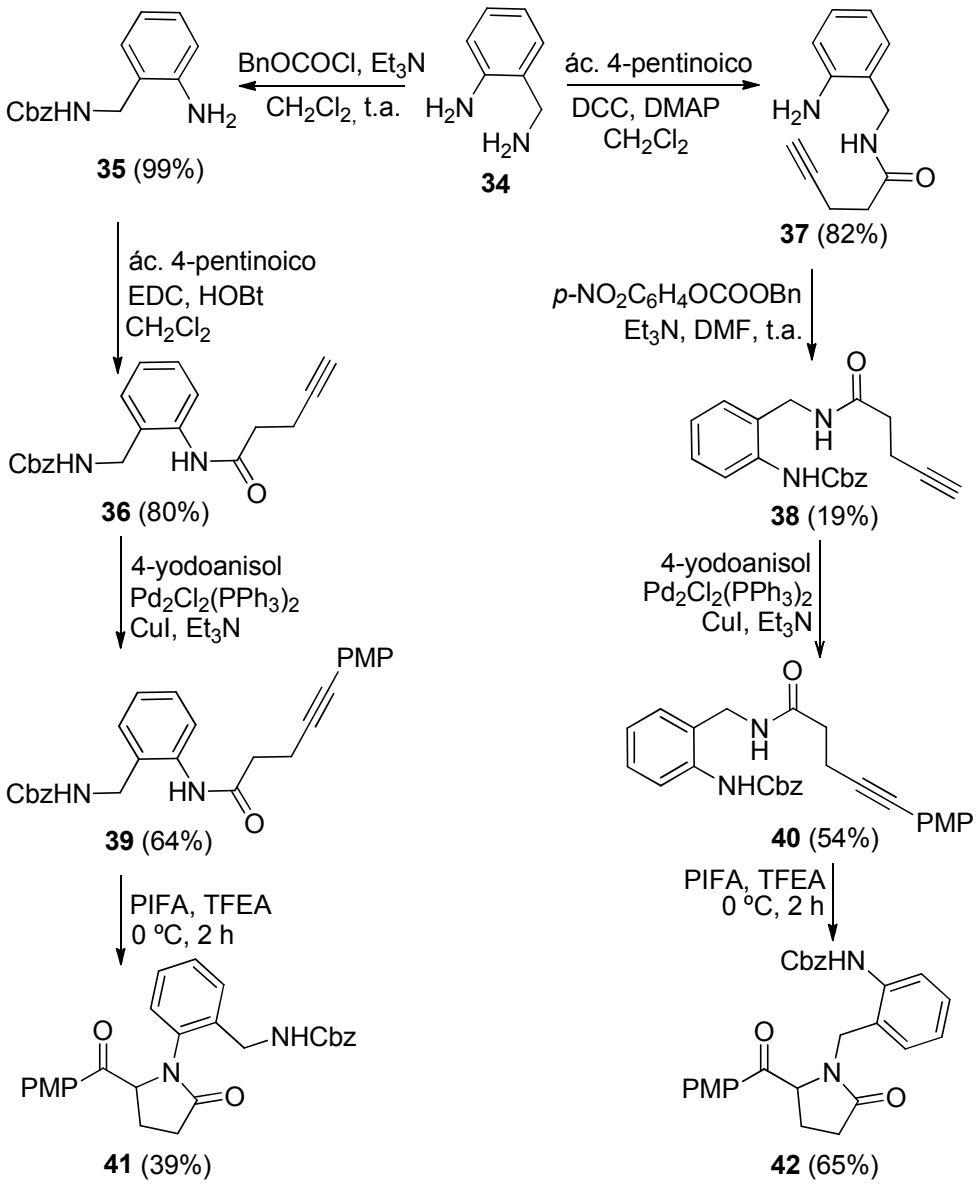
Paralelamente, para preparar la amida **37** a partir de **34** y del ácido 4-pentinoico (*Esquema 2.20*) hubo de recurrirse a la acción de DCC y DMAP como activantes, ya que en presencia de HOBt y EDC la amidación no tuvo lugar. Su protección, para dar el compuesto **38**, se realizó por tratamiento con carbonato de *p*-nitrofenilbencilo para solventar su inercia cuando el ensayo lo realizamos en presencia de cloroformiato de bencilo.[93]

Sobre estas amidas, **36** y **38**, se llevó a cabo la reacción de Sonogashira con 4-yodoanisol, empleando $PdCl_2(PPh_3)_2$ y CuI como

93. Un ejemplo del empleo del *p*-nitrofenilbencilo para la protección del grupo amino se encuentra en: Papot, S.; Bachmann, C.; Combaud, D.; Gesson, J. P. *Tetrahedron* **1999**, *55*, 4699.

catalizadores, obteniéndose los compuestos **39** y **40**, respectivamente, con rendimientos moderados.

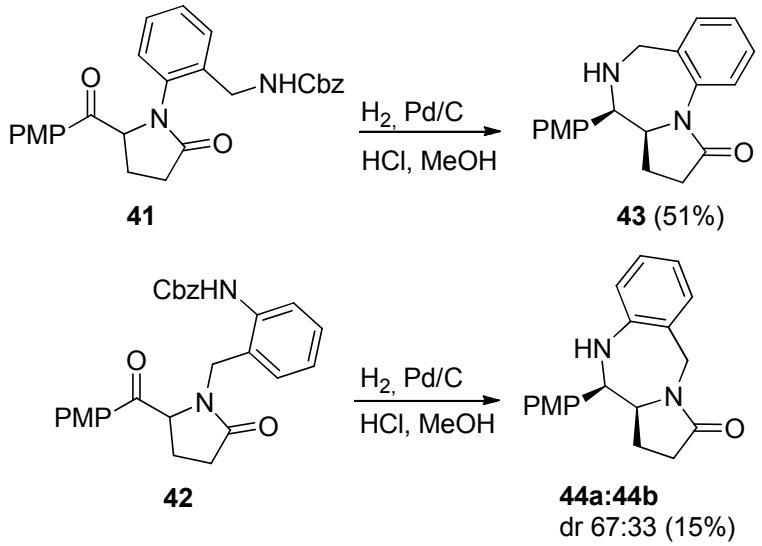
A continuación, se procedió al tratamiento de estas amidas con el reactivo PIFA bajo las condiciones optimizadas, dando lugar a las pirrolidin-2-onas correspondientes **41** y **42** con rendimientos aceptables.



Esquema 2.20. Preparación de las pirrolidinonas precursoras **41** y **42**.

Una vez sintetizadas las pirrolidinonas **41** y **42**, nos dispusimos a preparar las pirrolobenzodiazepinonas objetivo. Así, las pirrolidinonas fueron desprotegidas bajo condiciones estándar para acometer sobre los productos resultantes posteriores procesos de aminación reductiva intramolecular conducentes, en su caso, a los compuestos deseados.

Es de destacar que, bajo las condiciones de hidrogenación catalitica habituales, la pirrolobenzodiazepinona **43** se sintetizó de forma totalmente diastereoselectiva, aunque con rendimiento moderado. Por otro lado, bajo idénticas condiciones, el compuesto **44** no solo se obtuvo como mezcla de diastereoisómeros, sino también con bajo rendimiento (*Esquema 2.21*).

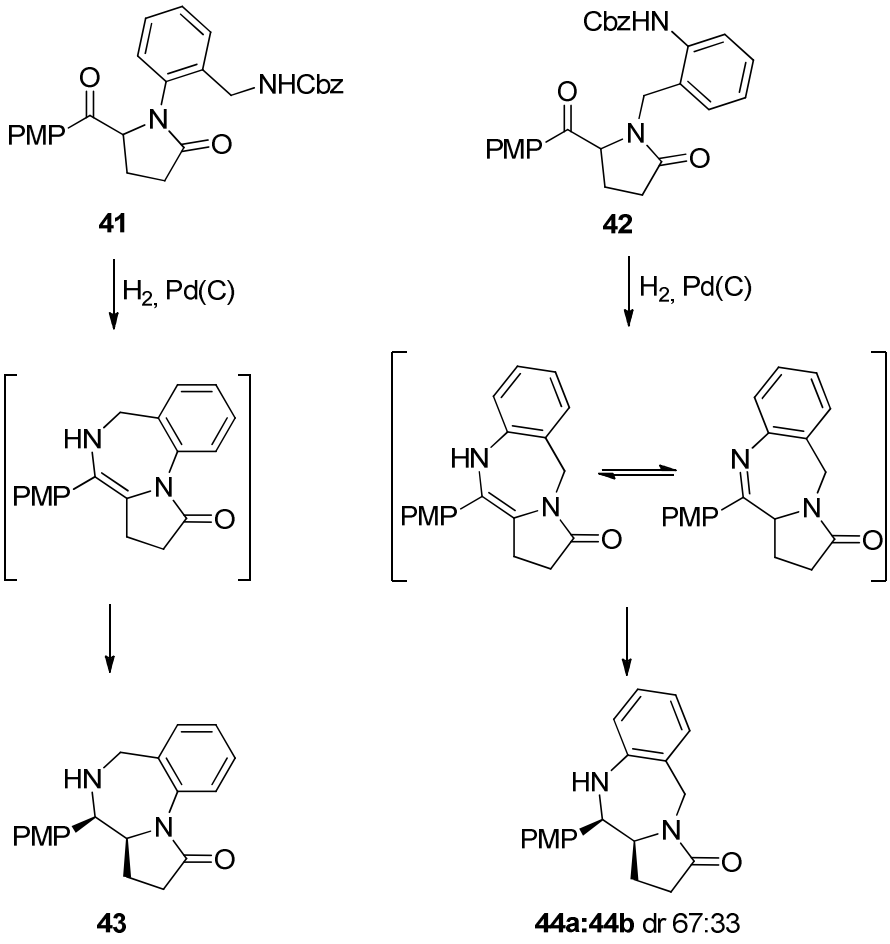


Esquema 2.21. Síntesis de las PBDs **43** y **44**.

En este caso, planteamos que la diferencia en la estereoselectividad de la reacción puede ser tomada como argumento para proponer la identidad

del intermedio que se genera en la etapa de ciclodeshidratación. Así, postulamos que en la reacción del compuesto **41** se formará un intermedio enamínico, estabilizado por conjugación extendida al grupo *p*-metoxifenilo, que resultará en el compuesto **43** de forma totalmente diastereoselectiva como resultado de una adición sin de hidrógeno.

Por otro lado, el intermedio de reacción propuesto para la formación del compuesto **44** se encuentra en un equilibrio enamínico-imínico, ya que este último tautómero está estabilizado por su conjugación con el anillo aromático y con el grupo *p*-metoxifenilo. Dado que las dos caras diastereotópicas alrededor del grupo imínico no están claramente diferenciadas, el diastereocontrol se verá aminorado (*Esquema 2.22*).



Esquema 2.22. Propuesta mecanística para la formación de los compuestos **43** y **44**.

2.3. Síntesis alternativa para la obtención del esqueleto de PBD.

La síntesis de la pirrolobenzodiazepinona **43** resultó especialmente interesante debido al completo control estereoquímico obtenido, así como por su inusual estructura en relación a la fusión de anillos. Sin embargo, en la síntesis diseñada para el compuesto **44** tanto el rendimiento global como el estereocontrol no fueron aceptables. Por ello, nos propusimos desarrollar una nueva alternativa para la obtención de dicho compuesto que evitase los pasos de protección.

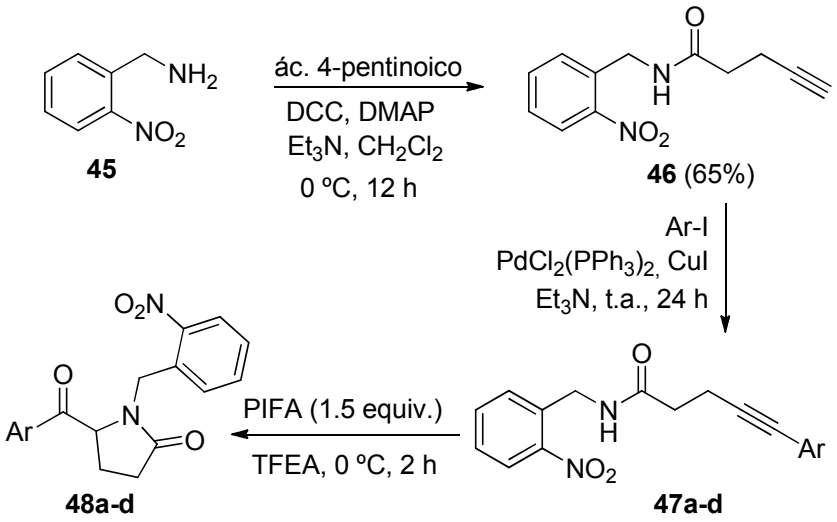
Así, se seleccionó la 2-nitrobencilamina (compuesto comercial, **45**) como sustrato de partida, ya que, una vez preparado el correspondiente sistema 5-aroilpirrolidinónico, la reducción del grupo funcional nitro, bajo condiciones de aminación reductiva intramolecular, debería proporcionar el compuesto deseado.[94]

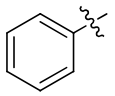
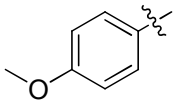
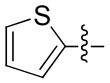
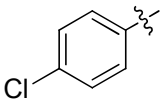
Para llevar a cabo el planteamiento sintético expuesto *(Tabla 2.6)* se transformó la bencilamina **45** en la amida **46**, en un proceso asistido por el uso de DCC y DMAP, y posteriormente se trató con una serie de yoduros de arilo en presencia de CuI y $PdCl_2(PPh_3)_2$ como catalizadores. Ello dio como resultado la formación de una serie de alquinilamidas **47a-d**. A continuación, se trataron con PIFA, bajo las condiciones habituales de reacción, para dar lugar a una serie de pirrolidinonas **48a-d** con un rango de

94. También evaluamos el 2-aminobenzonitrilo como producto de partida con idéntico fin sintético. Sin embargo, la reacción de éste con el ácido 4-pentinoico para dar lugar a la correspondiente amida (tanto con los activantes EDC y HOBt como con DCC y DMAP) no tuvo lugar.

rendimientos aceptable, tras llevarse a cabo diversos ensayos para su optimización.

Tabla 2.6. Síntesis de las pirrolidinonas **48a-d**.



Entrada	Ar	Sonogashira[a]	Ciclación[a]
1		**47a** (52%)	**48a** (81%)
2		**47b** (55%)	**48b** (69%)
3		**47c** (82%)	**48c** (77%)
4		**47d** (80%)	**48d** (57%)

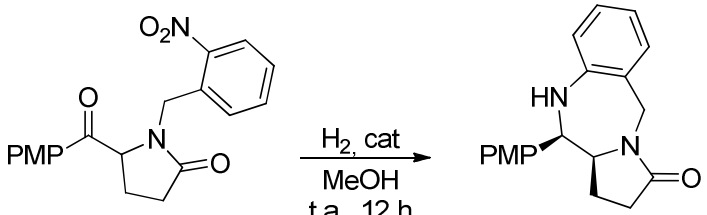
[a] Rendimiento de producto cromatográficamente puro.

Para acometer la última etapa sintética, se procedió a someter el grupo nitro a diferentes condiciones de reducción. En la bibliografía se encuentran fácilmente ejemplos de reducciones de este grupo funcional bajo condiciones de hidrogenación con diversos catalizadores (Pd/C, PtO_2, $Pd(OH)_2$, $PtCl_4$, $PtCl_6$,…),[95] por lo que seleccionamos esta opción, frente al uso de reductores nucleófilos. De hecho, con estos últimos, el proceso combinado de reducción-aminación reductiva en una única etapa no es posible.

La búsqueda de las condiciones óptimas para llevar a cabo esta reacción se realizó preliminarmente con el compuesto **48b**. La *Tabla 2.7* muestra que, de entre los cinco catalizadores empleados, destaca el uso de PtO_2 ya que es el que conduce al esqueleto de PBD esperado con excelente rendimiento y, a la vez, con un control estereoquímico más acusado. (*entrada 5*).

95. Rylander, P. N. *Catalytic Hydrogenation in Organic Syntheses*; Academic Press: New York, 1979, 114.

Tabla 2.7. Reacciones de hidrogenación catalítica.



48b **44**

Entrada	Catalizador	Producto	dr	Rdto (%)[a]
1	**Pd/C**[b]	mezcla sin determinar	----	----
2	**Pd negro**	**49**	----	71
3	**$Pd(OH)_2$**	**44**	53:47	72
4	**Ni/Ra**	**44**	38:62	58
5	**PtO_2**	**44**	84:18	92

[a] Rendimiento de producto cromatográficamente puro.
[b] En presencia de HCl.

Resultados menos atractivos se obtuvieron con el uso de otros catalizadores (*entradas 3* y *4*), y cursando con menor rendimiento y peor diastereoselectividad. Por otro lado, el uso de paladio negro como catalizador no fue útil, ya que se obtuvo únicamente el correspondiente amino derivado **49** (*Figura 2.5*) por reducción del grupo nitro. Finalmente señalaremos que el empleo de Pd/C en las condiciones optimizadas para la

síntesis de pirrolopirazinonas (*Tabla 2.4*, página 65) resultó, en este caso, en una mezcla intratable de productos (*entrada 1*).

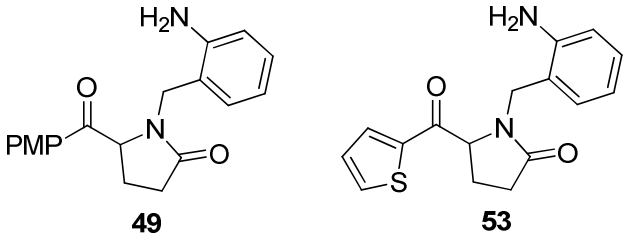
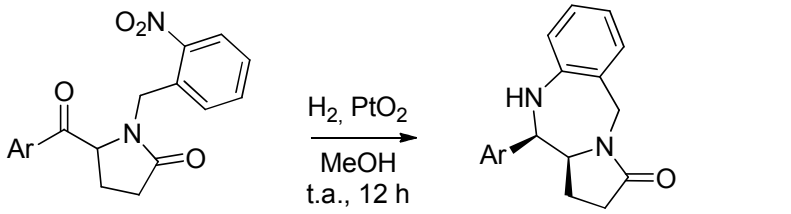


Figura 2.5. Estructura de las pirrolidinonas **49** y **53**.

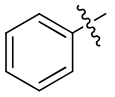
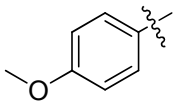
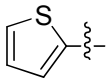
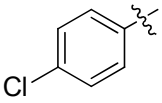
Una vez seleccionadas las condiciones de reacción óptimas, se acometió la reacción de hidrogenación catalítica sobre la serie de pirrolidinonas **48a-d**. Los resultados recogidos en la *Tabla 2.8* muestran resultados muy dispersos. Si bien la síntesis de las pirrolobenzodiazepinonas **44, 50 y 52** se consiguió con buenos rendimientos (*Entradas 1, 2* y *4*) y elevado diastereocontrol, la formación del compuesto **51** resultó infructuosa. En su lugar, y junto a una gran proporción de producto inalterado, se identificó el compuesto **53** (*Figura 2.5*), resultante de la reducción del grupo nitro a amino. Todos los intentos de llevar a cabo la posterior heterociclación resultaron fallidos aunque se exploraron distintas condiciones de reacción.

Tabla 2.8. Formación de las pirrolobenzodiazepinonas.



48a-d

44 Ar = PMP; **51** Ar = 2-tienil
50 Ar = Ph; **52** Ar = *p*-ClC_6H_4

Entrada	Ar	Pirrolidinona	Producto[(a)]	dr
1		**48a**	**50** (95%)	77:23
2		**48b**	**44** (92%)	84:18
3		**48c**	**53** (70%)	-----
4		**48d**	**52** (49%)	71:29

[(a)] Rendimiento de producto cromatográficamente puro.

La caracterización estructural y estereoquímica de estas moléculas se realizó mediante diversos experimentos de RMN monodimensionales y bidimensionales. En la *Figura 2.6*, a modo de ejemplo, se muestran los experimentos NOE selectivos realizados para el compuesto **44**, en los que puede observarse la existencia de un acusado NOE entre los hidrógenos H-1 y H-9a de la molécula, lo que revela su orientación relativa sin.

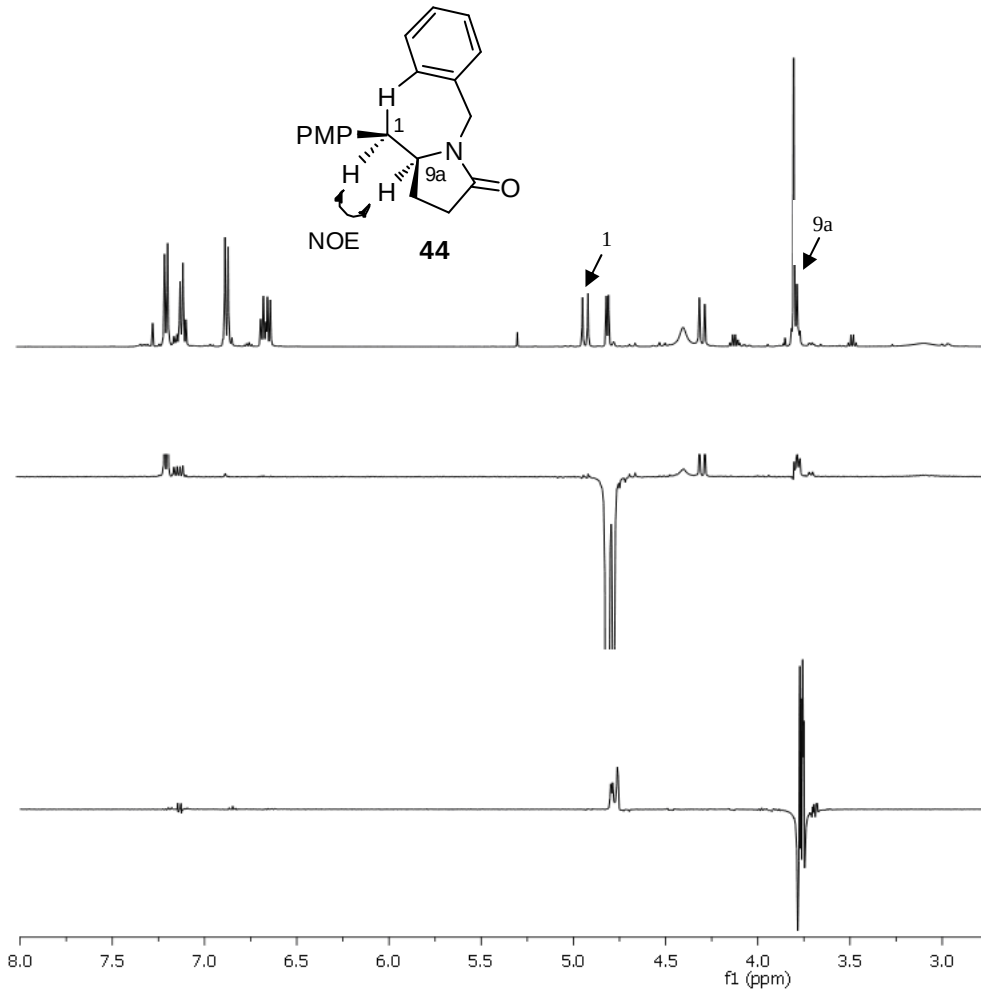
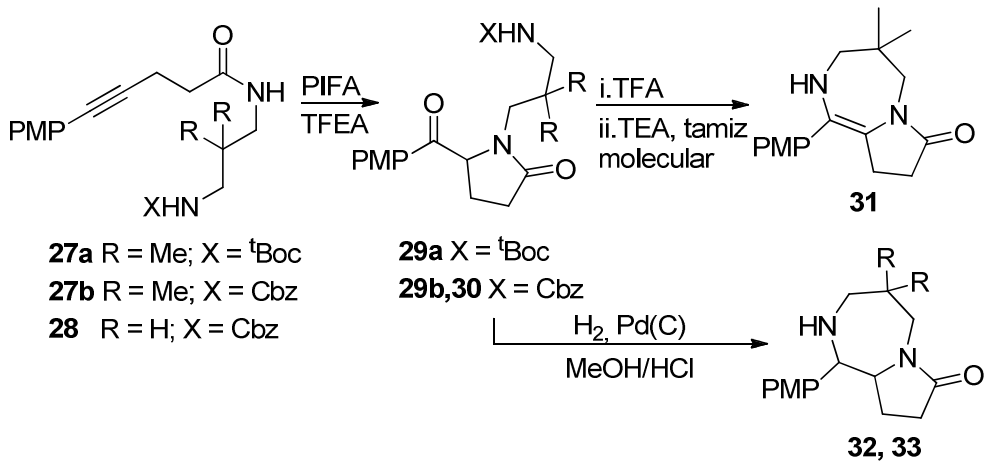


Figura 2.6. Espectro NOE selectivo realizado sobre la PBD **44**.

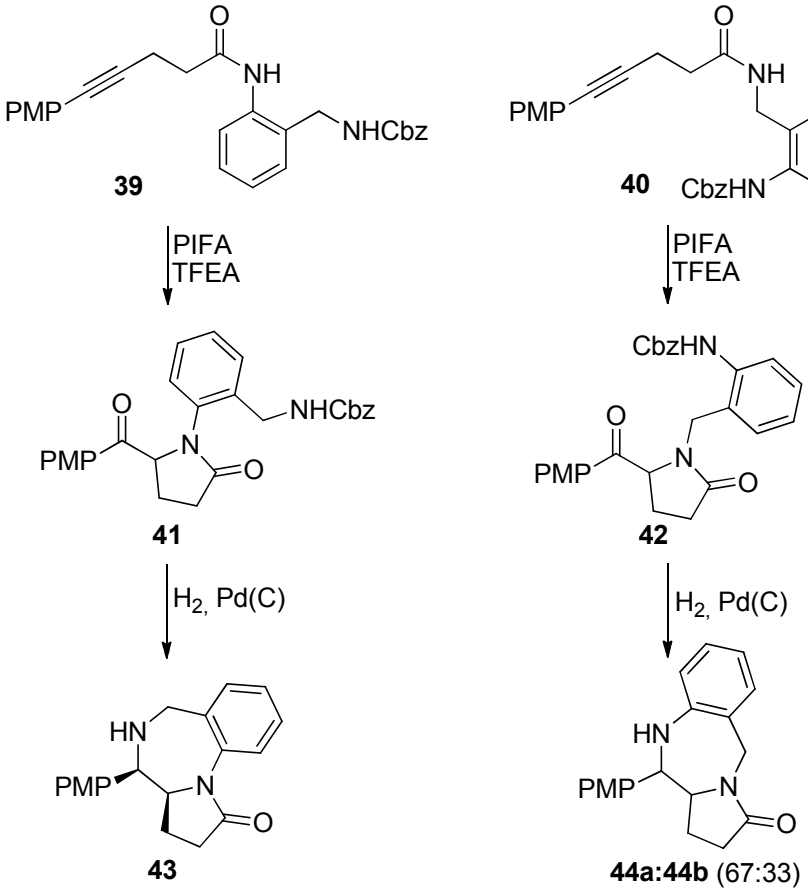
2.4. Visión de conjunto.

En este apartado se ha descrito un nuevo método de obtención de pirrolodiazepinonas y pirrolobenzodiazepinonas a través de un proceso combinado de amidación intramolecular de N-aminopropilalquinilamidas asistido por el reactivo de yodo hipervalente PIFA y posterior ciclodeshidratación.

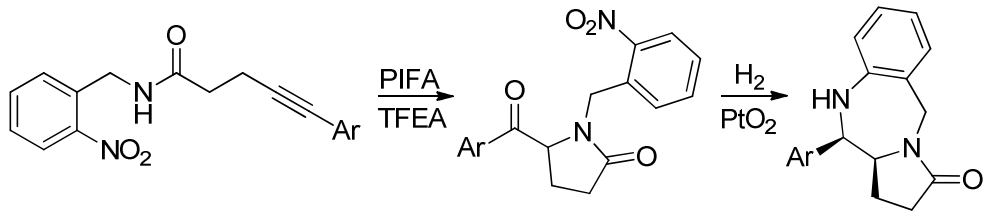
Así, la preparación de las pirrolidinonas **29** y **30,** intermedios clave en la síntesis de las pirrolodiazepinas tuvo lugar satisfactoriamente. La posterior liberación del grupo amino proporcionó las pirrolodiazepinonas **31**, **32** y **33**, a través de un proceso de ciclodeshidratación, con rendimientos globales del 4% para el compuesto **31**, 22% para el compuesto **32** y del 19% para el compuesto **33**.



Del mismo modo, se prepararon las pirrolidinonas **41** y **42** que, tras la liberación del grupo amino/ciclodeshidratación, rindieron las pirrolobenzodiazepinas **43** y **44**, respectivamente, con rendimientos globales del 10% para el compuesto **43** y menor del 1% para el compuesto **44**, si bien esta última se obtuvo como mezcla de isómeros, probablemente debido al diferente resultado estereoquímico en la hidrogenación de la mezcla tautomérica imina-enamina en la que se estabiliza el intermedio de reacción.



Posteriormente, se desarrolló una alternativa para la obtención de pirrolobenzodiazepinas a partir de nitrobencilamidas. La síntesis de las pirrolidinonas **48** bajo la acción del reativo PIFA tuvo lugar con buenos rendimientos, y la sucesiva reducción del grupo nitro en presencia de óxido de platino (IV) como catalizador permitió el proceso de heterociclación para acceder a los compuestos deseados **50**, **44** y **52**, con rendimientos globales del 26% para el compuesto **50**, 23% para el compuesto **44** y del 14% para el compuesto **52**. Esta alternativa sintética llevó a la obtención mayoritaria del estereoisómero sin que pudo ser aislado y caracterizado en cada caso.



48a-d
Ar = Ph, PMP,
2-tienilo, *p*-ClC$_6$H$_4$

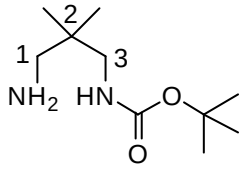
48a-d

44 Ar = PMP
50 Ar = Ph
52 Ar = *p*-ClC$_6$H$_4$

2.5. Experimental procedures.

2.5.1. Procedures for the synthesis of monoprotected diamines 23 and 24.

N-tert-butoxycarbonyl-2,2-dimethylpropane-1,3-diamine (**23a**).



A stirred solution of di-*tert*-butyl dicarbonate (3.26 g, 15 mmol) in DCM (10 mL) was added dropwise to a solution of 2,2-dimethylpropane-1,3-diamine (**21**) (3 mL, 30 mmol) in 30 mL of the same solvent at rt. The mixture was stirred for 20 h min. Then, the solvent was removed under vacuum and the crude was dissolved in EtOAc (30 mL). The solution was washed with saturated Na_2CO_3, decanted and dried over anh. Na_2SO_4. Removal of the solvent under vacuum afforded a residue that was purified by column chromatography (EtOAc) to render carbamate **23a** as a white solid after trituration in hexanes (52%).

mp 56-58 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 5.36 (br s, 1H, NH), 2.84 (d, *J*= 5.9, 2H, H-3), 2.33 (s, 2H, H-1), 1.50 (s, 2H, NH_2), 1.29 (s, 9H, ^{t}Bu), 0.71 (s, 6H, C_2-(C*H*$_3$)$_2$).

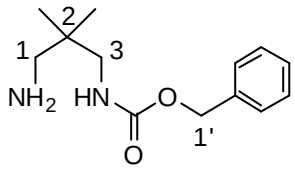
^{13}C NMR ($CDCl_3$) δ 156.4 (CO), 78.7 (*C*-(CH_3)$_3$), 50.4 (C-1), 48.2 (C-3), 35.7 (C-2), 28.3, 23.1 (C_2-(*C*H_3)$_2$).

IR (film) υ 3355, 2944, 1684.

MS (M+1, CI) *m/z* (%) 203 (2), 202 (7), 175 (10), 157 (25), 147 (83), 129 (100), 117 (60), 103 (41).

HRMS calculated for $C_{10}H_{22}N_2O_2 \cdot H^+$ 203.1760, found 203.1768.

N-benzyloxycarbonyl-2,2-dimethyl-1,3-propanediamine (**23b**).



A stirred solution of benzyl chloroformiate (2.9 mL, 21 mmol) in 50 mL of DCM was added dropwise over 85 min to a solution of 2,2-dimethylpropane-1,3-diamine (**21**) (4.3 g, 42 mmol) in 70 mL of the same solvent at 0 ºC. The mixture was stirred for additional 90 min, the temperature was raised to rt and stirring was continued for 24 h. Then, the solid formed was filtered, and the solution was washed with brine (3x40 mL), decanted and dried over anh. Na_2SO_4. Removal of the solvent under vacuum afforded an oil that was purified by column chromatography (EtOAc) to render carbamate **23b** as a colorless oil (41%).

^{1}H NMR ($CDCl_3$) δ 7.37-7.12 (m, 5H, Harom), 6.05 (br s, 1H, NH), 5.02 (s, 2H, H-1'), 2.99 (s, 2H, H-3), 2.42 (s, 2H, H-1), 1.88 (s, 2H, NH_2), 0.79 (s, 6H, C_2-(CH_3)$_2$).

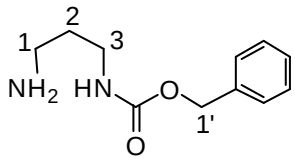
^{13}C NMR ($CDCl_3$) δ 157.1 (CO), 136.8 (q-Carom), 128.4, 128.0 (t-Carom), 66.5 (C-1'), 50.4 (C-1), 49.1 (C-3), 35.6 (C-2), 23.3 (C_2-(CH_3)$_2$).

IR (film) υ 3320, 2944, 1702.

MS (M+1, CI) *m/z* (%) 237 (8), 129 (100), 108 (22), 107 (13).

HRMS calculated for $C_{13}H_{20}N_2O \cdot H^+$ 237.1603, found 237.1611.

N-benzyloxycarbonyl-1,3-propanediamine (**24**).



According to the typical procedure for compound **23b**, carbamate **24** was obtained from diamine **22** in a 60% yield and purified by column chromatography (EtOAc) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ 7.32-7.26 (m, 5H, Harom), 5.55 (br s, 1H, NH), 5.06 (s, 2H, H-1'), 3.26-3.22 (m, 2H, H-3), 2.80-2.67 (m, 2H, H-1), 1.61-1.56 (m, 2H, H-2), 1.46 (br s, 2H, NH_2).

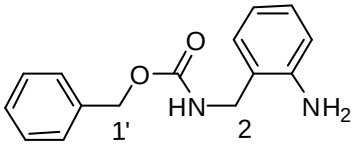
^{13}C NMR ($CDCl_3$) δ 156.6 (CO), 136.7 (q-Carom), 128.5, 128.0 (t-Carom), 66.5 (C-1'), 39.6 (C-3), 39.1 (C-1), 33.0 (C-2).

IR (film) υ 3325, 2931, 1683.

MS (M+1, CI) *m/z* (%) 209 (41), 165 (10), 108 (26), 101 (100).

HRMS calculated for $C_{11}H_{16}N_2O_2 \cdot H^+$ 209.1290, found (M+ethylene) 237.1304.

2-amino-N-(benzyloxycarbonyl)benzylamine (**35**).



A stirred solution of benzyl chloroformiate (0.3 mL, 2.05 mmol) in 50 mL of DCM was added dropwise over 85 min to a solution of benzylamine **34** (0.5 g, 4.1 mmol)[96] and Et_3N (0.3 mL, 6.1 mmol) in 6 mL of the same solvent at 0 ºC. The mixture was stirred for additional 90 min, the temperature was raised to rt and stirring was continued for 24 h. Then, a white precipitate was filtered, and the solution was washed with brine (3x40 mL), decanted and dried over anh. Na_2SO_4. Removal of the solvent under vacuum afforded an oil that was purified by column chromatography (MeOH) to render carbamate **35** as a yellowish solid that was triturated in hexanes (99%).

mp 52-53 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.36-7.34 (m, 5H, Harom), 7.15-7.03 (m, 2H, Harom), 6.74-6.65 (m, 2H, Harom), 5.32 (br s, 1H, NH), 5.12 (s, 2H, H-1'), 4.28 (d, *J*=6.1, 2H, H-2), 4.09 (br s, 2H, NH_2).

^{13}C NMR ($CDCl_3$) δ 157.0 (CO), 145.4, 136.4, 129.2 (q-Carom), 131.6, 128.6, 128.2, 128.1, 122.3, 118.1, 116.0 (t-Carom), 67.0 (C-1'), 42.5 (C-2).

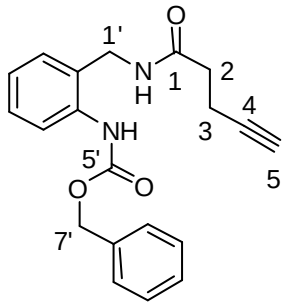
IR (film) υ 3349, 3029, 1692.

MS (M+1, CI) *m/z* (%) 257 (32), 256 (100), 196 (38), 149 (47), 148 (25), 121 (26), 106 (39).

96. An excess of starting material was employed to avoid an undesired *N,N*'-diprotection process.

HRMS calculated for $C_{15}H_{16}N_2O_2 \cdot H^+$ 257.1290, found 257.1293.

N-[(2-benzyloxycarbonylamino)benzyl]-4-pentynamide (**38**).



Benzyl *p*-nitrophenylcarbonate (683 mg, 2.5 mmol) and Et_3N (1.1 mL, 7.5 mmol) were added successively into a solution of amide **37** (1.0 g, 4.9 mmol) in DMF (15 mL). The mixture was magnetically stirred at rt for 12 h under inert atmosphere. Then, solvent was removed under vacuum; the residue was taken in 40 mL of DCM and washed with a saturated solution of Na_2CO_3 (30 mL). The decanted organic phase was dried with anh. Na_2SO_4, the solvent removed under vacuum, and the resulting residue was purified by column chromatography (hexanes/EtOAc, 1/1) to afford **38** as a white solid that was triturated in hexanes (19%).

mp 110-111 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 8.79 (br s, 1H, NH), 7.90 (d, *J*=8.4, 1H, Harom), 7.44-7.04 (m, 8H, Harom), 6.29 (m, 1H, NH), 5.23 (s, 2H, H-7'), 4.37 (d, *J*=6.4, 2H, H-1'), 2.51-2.46 (m, 2H, H-2/H-3), 2.38-2.34 (m, 2H, H-3/H-2), 1.92 (t, *J*=2.6, 1H, H-5).

^{13}C NMR ($CDCl_3$) δ 172.0 (C-1), 154.5 (C-5'), 136.8 (q-Carom), 136.6, 128.5, 128.0, 123.9, 123.8, 122.4 (t-Carom), 82.5 (C-4), 69.6 (C-5), 66.7 (C-7'), 40.6 (C-1'), 35.1 (C-2), 14.8 (C-3).

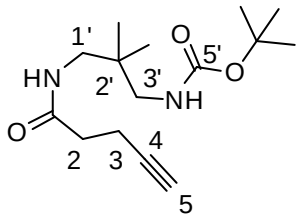
IR (film) υ 3290, 3073, 1650, 1559.

MS (M+1, CI) *m/z* (%) 230 (11, M+1–Cbz), 229 (75), 227 (21), 149 (30), 147 (100), 132 (20).

HRMS calculated for [$C_{20}H_{20}N_2O_3 \cdot H^+$ – Cbz] 230.1055, found 230.1024.

2.5.2. Typical procedure for the acylation of amines. Synthesis of compounds 25 and 36.

N-(3-tert-butoxycarbonyl-2,2-dimethyl-3-propyl)-4-pentynamide (**25a**).



A solution of 4-pentynoic acid (**4**) (640 mg, 6.5 mmol) in 5 mL of DCM was added to a magnetically stirred solution of EDC·HCl (1.9 g, 9.9 mmol) and HOBt (1.35 g, 9.9 mmol) in 20 mL of the same solvent followed by the addition of the monoprotected diamine **23a** (1.9 g, 9.9 mmol) dissolved in 5 mL of DCM. The mixture was cooled to 0 ºC and Et_3N (1.4 mL, 9.9 mmol) was added dropwise and left to react at rt overnight. Then, the reaction was diluted with DCM, water (25 mL) was added, the mixture was decanted, and the organic layer was consecutively washed with 20 mL of HCl (aq., 5%), 20 mL of a saturated solution of aqueous $NaHCO_3$, and 20 mL of a saturated solution of NaCl. The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The resultant chromatographically pure

yellowish oil was identified as amide **25a** (97%) and used without any further purification.

^{1}H NMR ($CDCl_3$) δ 6.79 (br s, 1H, NH), 5.18-5.16 (m, 1H, NH), 3.02 (d, *J*=6.8, 2H, H-1'), 2.87 (d, *J*=6.8, 2H, H-3'), 2.51-2.56 (m, 2H, H-2/H-3), 2.40-2.45 (m, 2H, H-3/H-2), 1.97 (t, *J*=2.5, 1H, H-5), 1.43 (s, 9H, ^{t}Bu), 0.85 (s, 6H, ($C_{2'}$-(CH_3)$_2$).

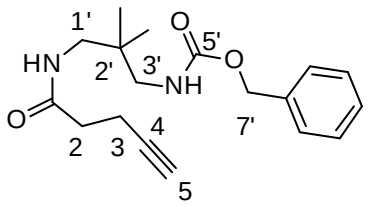
^{13}C NMR ($CDCl_3$) δ (ppm) 171.4 (C-1), 157.1 (C-5'), 83.1 (C-4), 79.5 (*C*-(CH_3)$_3$), 69.2 (C-5), 47.3 (C-3'), 45.4 (C-1'), 36.4 (C-2), 35.7 (C-2'), 28.4 (^{t}Bu), 23.4 ($C_{2'}$-(*C*H_3)$_2$), 15.1 (C-3).

IR (film) υ 3307, 1712, 1654.

MS (M+1, CI) *m/z* (%) 283 (1), 282 (2), 255 (13), 277 (25), 209 (31), 183 (100), 181 (17), 166 (31) 153 (23).

HRMS calculated for $C_{15}H_{26}N_2O_3 \cdot H^+$ 283.2022, found 283.2032.

N-(3-benzyloxycarbonylamino-2,2-dimethylpropyl)-4-pentynamide (**25b**).



According to the typical procedure amide **25b** was prepared from monoprotected amine **23b** as a white solid in 87% yield as a colourless oil.

^{1}H NMR ($CDCl_3$) δ 7.26-7.18 (m, 5H, Harom), 6.23 (br s, 1H, NH), 5.02 (s, 2H, H-7'), 2.94 (d, *J*=6.6, 2H, H-1'), 2.87 (d, *J*=6.6, 2H, H-3'), 2.46-2.40

(m, 2H, H-2/H-3), 2.36-2.32 (m, 2H, H-3/H-2), 1.94 (s, 1H, H-5), 0.78 (s, 6H, $C_{2'}$-(CH_3)$_2$).

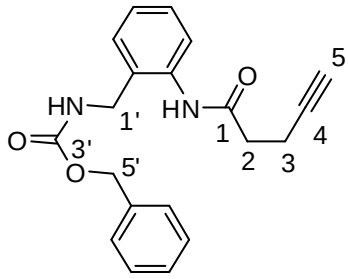
^{13}C NMR ($CDCl_3$) δ 172.0 (C-1), 157.6 (C-5'), 136.7 (q-Carom), 128.4, 128.0, 127.9 (t-Carom), 83.0 (C-4), 69.5 (C-5), 66.5 (C-7'), 47.5 (C-3'), 45.8 (C-1'), 35.4, 36.4 (C-2, C-2'), 23.5 ($C_{2'}$-(CH_3)$_2$), 15.2 (C-3).

IR (film) υ 3296, 1702, 1649.

MS (M+1, CI) *m/z* (%) 317 (12), 273 (37), 209 (100), 153 (17), 129 (27), 110 (17).

HRMS calculated for $C_{18}H_{24}N_2O_3 \cdot H^+$ 317.1865, found: 317.1858.

N-[(2-benzyloxycarbonylaminomethyl)phenyl]-4-pentynamide (**36**).



According to the typical procedure amide **36** was prepared from monoprotected amine **35** as a white solid in 80% yield. It was purified by crystallization from Et_2O.

mp 121-122 ºC (Et_2O).

^{1}H NMR ($CDCl_3$) δ 9.31 (br s, 1H, NH), 8.06-8.04 (m, 1H, Harom), 7.34-7.06 (m, 8H, Harom), 5.54 (br s, 1H, NH), 5.12 (s, 2H, H-5'), 4.30 (d, *J*=6.7, 2H, H-1'), 2.66-2.58 (m, 4H, H-2, H-3), 2.00 (s, 1H. H-5).

^{13}C NMR ($CDCl_3$) δ 170.2 (C-1), 157.8 (C-3'), 136.4, 136.0, 116.1 (q-Carom), 130.4, 129.0, 128.7, 128.6, 128.5, 128.4, 128.1, 124.6, 123.3 (t-

Carom), 83.1 (C-4), 69.1 (C-5), 67.5 (C-5'), 42.0 (C-1'), 35.9 (C-2), 14.8 (C-3).

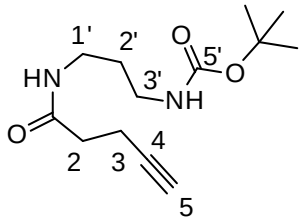
IR (film) υ 3295, 3024, 1686, 1653.

MS (M+1, CI) *m/z* (%) 337 (8), 276 (20), 201 (12), 185 (28), 149 (25), 108 (100), 107 (76).

HRMS calculated for $C_{20}H_{20}N_2O_3 \cdot H^+$: 337.1552, found: 337.1598.

2.5.3. Typical procedure for the acylation of amines. Synthesis of compounds 26, 37 and 46.

N-(3-benzyloxycarbonyl-aminopropyl)-4-pentynamide (**26**).



Amine **24** (1.6 g, 7.7 mmol) was added to a cold (0 ºC) solution of DCC (1.7 g, 8.5 mmol), DMAP (50 mg, 0.4 mmol), and 4-pentynoic acid (**4**) (833 mg, 8.5 mmol) in DCM (80 mL) and the mixture was stirred overnight. Then, a white solid (urea) was filtered and the solvent was evaporated at reduced pressure. The residue was purified by column chromatography (MeOH) to afford **26** as a white solid that was triturated in Et_2O (93%).

mp 60-61 ºC (Et_2O).

^{1}H NMR ($CDCl_3$) δ 7.37-7.26 (m, 5H, Harom), 6.32 (br s, 1H, NH), 5.34 (br s, 1H, NH), 5.09 (s, 2H, H-7'), 3.33-3.20 (m, 4H, H-1', H-3'), 2.54-2.49

(m, 2H, H-2/H-3), 2.41-2.36 (m, 2H, H-3/H-2), 1.99 (s, 1H, H-5), 1.66-1.64 (m, 2H, H-2').

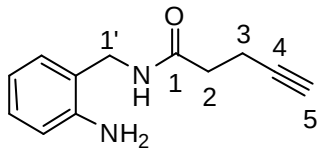
^{13}C NMR ($CDCl_3$) δ 171.6 (C-1), 156.8 (C-5'), 128.5, 128.0 (Carom), 82.9 (C-4), 69.3 (C-5), 66.7 (C-7'), 37.6, 36.0 (C-1', C-3'), 35.4 (C-2), 30.0 (C-2'), 15.0 (C-3).

IR (film) υ 3300, 2926, 1700, 1648.

MS (M+1, CI) *m/z* (%) 289 (55), 245 (46), 197 (20), 181 (100), 153 (16), 136 (18), 111 (20).

HRMS calculated for $C_{16}H_{20}N_2O_3 \cdot H^+$ 289.1552, found 289.1551.

N-(2-aminobenzyl)-4-pentynamide (**37**).



According to the typical procedure amide **37** was prepared from benzylamine **33** and purified as a white solid in 82% yield by column chromatography (hexanes/EtOAc, 1/1) followed by crystallization from Et_2O.

mp 76-77 ºC (Et_2O).

^{1}H NMR ($CDCl_3$) δ 7.10-6.99 (m, 2H, Harom), 6.67-6.60 (m, 2H, Harom), 6.48 (br s, 1H), 4.30 (d, *J*=6.1, 2H, H-1'), 4.11 (br s, 2H, NH_2), 2.48-2.43 (m, 2H, H-2/H-3), 2.36-2.31 (m, 2H, H-3/H-2), 1.97 (s, 1H, H-5).

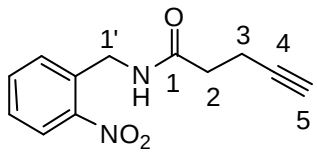
^{13}C NMR ($CDCl_3$) δ 171.6 (C-1), 145.5, 130.6 (q-Carom), 129.2, 121.9, 117.8, 115.8 (t-Carom), 83.0 (C-4), 69.5 (C-5), 40.8 (C-1'), 35.1 (C-2), 14.9 (C-3).

IR (film) υ 3292, 3059, 1643.

MS (M+1, CI) *m/z* (%) 203 (35), 202 (100), 134 (10), 121 (31), 106 (81).

HRMS calculated for $C_{12}H_{14}N_2O_3 \cdot H^+$ 203.1184, found 203.1186.

N-(2-nitromethylphenyl)-4-pentynamide (**46**).



According to the typical procedure amide **46** was prepared from benzylamine **45** as a yellowish solid in a 65% yield. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration of the resultant solid in hexanes.

mp 62-63 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.96 (d, *J*=8.1, 1H, Harom), 7.58-7.50 (m, 2H, Harom), 7.40-7.34 (m, 1H, Harom), 7.01-6.97 (m, 1H, NH), 4.62 (d, *J*=6.3, 2H, H-1'), 2.43-2.36 (m, 4H, H-2, H-3), 1.93 (s, 1H, H-5).

^{13}C NMR ($CDCl_3$) δ 171.6 (C-1), 148.1, 133.7 (q-Carom), 133.9, 131.5, 128.5, 125.0 (t-Carom), 82.7 (C-4), 69.5 (C-5), 41.1 (C-1'), 35.0 (C-2), 14.8 (C-3).

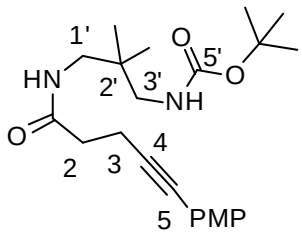
IR (film) υ 3296, 1653.

MS (M+1, CI) *m/z* (%) 233 (100), 225 (16), 186 (30), 153 (26), 136 (43), 135 (12).

HRMS calculated for $C_{12}H_{12}N_2O_3 \cdot H^+$ 233.0926, found 233.0936.

2.5.4. Typical procedure for the Sonogashira coupling reaction. Synthesis of compounds 27, 28, 39 and 47.

N-(3-tert-butoxycarbonyl-2,2-dimethyl-3-propyl)-5-(4-methoxyphenyl)-4-pentynamide (**27a**).



A solution of 4-iodoanisole (1.4 g, 6.0 mmol), $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol), CuI (23 mg, 0.12 mmol) and carbamate **25a** (1.7 g, 6.0 mmol) in Et_3N (15 mL) was stirred at 80 ºC for 24 h. When cooled, water (3 mL) was added, the mixture was extracted with EtOAc (3x25 mL), and the combined organic extracts were dried over anh. Na_2SO_4. Once the solvent was evaporated under vacuum, the whole crude was purified by column chromatography (hexanes/EtOAc, 1/1) to afford amide **27a** as a yellowish oil (43%).

^{1}H NMR ($CDCl_3$) δ 7.28 (d, *J*=8.8, 2H, Harom), 6.86 (br s, 1H, NH), 6.78 (d, *J*=8.8, 2H, Harom), 5.28 (m, 1H, NH), 3.77 (s, 3H, OCH_3), 3.02 (d, *J*=6.8, 2H, H-3'), 2.84 (d, *J*=6.8, 2H, H-1'), 2.73 (t, *J*=7.1, 2H, H-2/H-3), 2.48 (t, *J*=7.1, 2H, H-3/H-2) 1.42 (s, 9H, ^{t}Bu), 0.82 (s, 6H, $C_{2'}$-(CH_3)$_2$).

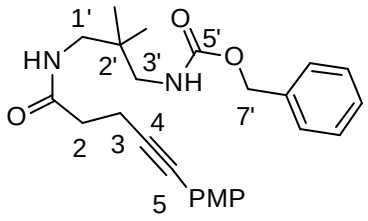
^{13}C NMR ($CDCl_3$) δ 171.8 (C-1), 157.1 (C-5'), 159.2, 132.9 (q-Carom), 133.2, 114.5 (t-Carom), 86.9 (C-4), 81.2 (*C*-$(CH_3)_3$), 79.3 (C-5), 55.2 (OCH_3), 47.1 (C-1'), 45.5 (C-3'), 36.4 (C-2), 36.1 (C-2'), 28.4 (^{t}Bu), 23.4 ($C_{2'}$-(*C*$H_3)_2$), 16.2 (C-3).

IR (film) υ 3325, 2964, 1655, 1607.

MS (M+1, CI) *m/z* (%) 389 (12), 361 (14), 333 (100), 315 (50), 289 (74), 273 (23), 271 (21), 211 (16), 203 (26).

HRMS calculated for $C_{22}H_{32}N_2O_4 \cdot H^+$ 389.2440, found 389.2447.

N-(3-benzyloxycarbonylamino-2,2-dimethylpropyl)-5-(4-methoxyphenyl)-4-pentynamide (**27b**).



According to the typical procedure amide **27b** was prepared from carbamate **25b** in 66% yield as a yellowish oil. It was purified by column chromatography (hexanes/EtOAc, 1/1).

^{1}H NMR ($CDCl_3$) δ 7.46-7.26 (m, 7H, Harom), 6.78 (d, *J*=8.9, 2H, Harom), 6.62-6.60 (m, 1H, NH), 5.64-5.62 (m, 1H, NH), 5.09 (s, 2H, H-7'), 3.78 (s, 3H, OCH_3), 3.05 (d, *J*=6.8, 2H, H-1'), 2.93 (d, *J*=6.8, 2H, H-3'), 2.72 (t, *J*=7.1, 2H, H-2/H-3), 2.48 (t, *J*=7.1, 2H, H-3/H-2), 0.85 (s, 6H, $C_{2'}$-(C*H*$_3)_2$).

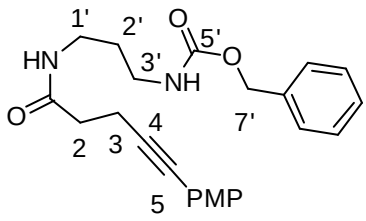
^{13}C NMR ($CDCl_3$) δ 172.0 (C-1), 157.5 (C-5'), 159.2, 132.9 (q-Carom), 128.5, 128.1, 128.0 (t-Carom), 113.8 (C-4), 86.8 (C-5), 66.8 (C-7'), 55.2 (OCH_3), 47.5 (C-3'), 45.7 (C-1'), 36.4 (C-2), 36.1 (C-2'), 23.3 ($C_{2'}$-(CH_3)$_2$), 16.2 (C-3).

IR (film) υ 3323, 2960, 1704, 1657.

MS (M+1, CI) *m/z* (%) 423 (17), 315 (100), 313 (14), 273 (37), 216 (10).

HRMS calculated for $C_{25}H_{30}N_2O_4 \cdot H^+$ 423.2284, found 423.2287.

N-(3-benzyloxycarbonylaminopropyl)-5-(4-methoxyphenyl)-4-pentynamide (**28**).



According to the typical procedure amide 2**8** was prepared from carbamate **26** in 60% yield as a white solid. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration in hexanes.

mp 114-116 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.35-7.29 (m, 7H, Harom), 6.80 (d, *J*=8.8, 2H, Harom), 6.20 (br s, 1H, NH), 5.25 (br s, 1H, NH), 5.09 (s, 2H, H-7'), 3.78 (s, 3H, OCH_3), 3.36-3.30 (m, 2H, H-1'), 3.25-3.20 (m, 2H, H-3'), 2.72 (t, *J*=7.2, 2H, H-2/H-3), 2.46 (t, *J*=7.2, 2H, H-3/H-2), 1.65-1.62 (m, 2H, H-2').

^{13}C NMR ($CDCl_3$) δ 171.8 (C-1), 159.3 (C-5'), 136.0, 115.5 (q-Carom),

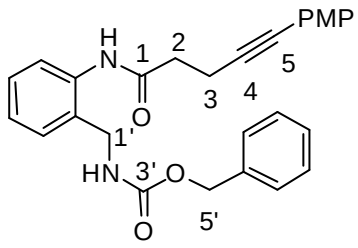
132.9, 128.5, 128.1, 128.0, 113.9 (t-Carom), 86.8 (C-4), 81.3 (C-5), 66.7 (C-7'), 55.2 (OCH_3), 37.5, 36.6 (C-1', C-3'), 35.9 (C-2), 30.1 (C-2'), 16.1 (C-3).

IR (film) υ 3325, 2950, 1678, 1643.

MS (M+1, CI) *m/z* (%) 288 (40), 287 (79), 245 (40), 189 (70), 188 (73), 159 (48), 147 (63), 135 (80), 101 (100).

HRMS calculated for [$C_{23}H_{26}N_2O_4 \cdot H^+$ – Cbz] 288.1474, found 288.1487.

N-[(2-benzyloxycarbonylaminomethyl)phenyl]-5-(4-methoxyphenyl)-4-pentyamide (**39**).



According to the typical procedure amide **39** was prepared from carbamate **36** in 64% yield as a yellowish solid after purification by column chromatography (hexanes/EtOAc, 1/1) followed by trituration of the resultant solid in hexanes.

mp 125-126 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 9.32 (s, 1H, NH), 8.08 (d, *J*=8.1, 1H, Harom), 7.33-7.07 (m, 10H, Harom), 6.79 (d, *J*=8.6, 2H, Harom), 5.44-5.42 (m, 1H, NH), 5.11 (s, 2H, H-5'), 4.28 (d, *J*=6.7, 2H, H-1'), 3.78 (s, 3H, OCH_3), 2.87-2.80 (m, 2H, H-2/H-3), 2.73-2.68 (m, 2H, H-3/H-2).

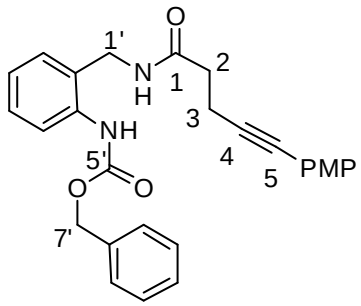
^{13}C NMR ($CDCl_3$) δ 170.5 (C-1), 159.1 (C-3'), 157.7, 136.0, 133.0, 123.4, 115.9 (q-Carom), 133.0, 129.0, 128.6, 128.3, 128.1, 124.6, 123.4, 115.9, 113.8 (t-Carom), 87.1 (C-4), 81.1 (C-5), 67.5 (C-5'), 55.2 (OCH_3), 41.9 (C-1'), 36.5 (C-2), 16.0 (C-3).

IR (film) υ 3295, 3054, 1689.

MS (M+1, CI) *m/z* (%) 443 (19), 335 (49), 293 (40), 187 (61), 149 (100), 147 (50), 135 (14), 108 (41), 107 (25).

HRMS calculated for $C_{27}H_{26}N_2O_4 \cdot H^+$ 443.1971, found 443.1953.

N-[(2-benzyloxycarbonylamino)benzyl]-5-(4-methoxyphenyl)-4-pentyamide (**40**).



According to the typical procedure amide **40** was prepared from carbamate **38** in 54% yield as a white solid. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration in hexanes.

mp 109-110 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 9.03 (br s, 1H, NH), 7.88 (d, *J*=8.0, 1H, Harom), 7.43-7.21 (m, 11H, Harom), 6.75 (d, *J*=8.6, 1H, Harom), 6.64 (br s, 1H), 5.22 (s, 2H, H-7'), 4.34 (d, *J*=6.4, 2H, H-1'), 3.78 (s, 3H, OCH_3), 2.66 (t, *J*=7.1, 2H, H-2/H-3), 2.40 (t, *J*=7.1, 2H, H-3/H-2).

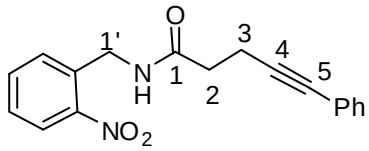
^{13}C NMR ($CDCl_3$) δ 172.4 (C-1), 154.6 (C-5'), 136.8, 136.7, 127.6, 115.3, 86.4 (q-Carom), 132.9, 128.5, 123.8, 123.7, 122.3 (t-Carom), 81.6 (C-4), 72.9 (C-5), 66.6 (C-7'), 55.3 (OCH_3), 40.5 (C-1'), 35.5 (C-2), 15.9 (C-3).

IR (film) υ 3300, 3073, 1727, 1646.

MS (M+1, CI) *m/z* (%) 336 (23, M+1–Cbz), 335 (100), 293 (98), 199 (14), 188 (52), 160 (26), 147 (35).

HRMS calculated for [$C_{27}H_{26}N_2O_4 \cdot H^+$ – Cbz] 336.1474, found 336.1440.

N-(2-nitrobenzyl)-5-phenyl-4-pentynamide (**47a**).



According to the typical procedure amide **47a** was prepared from amide **46** in 52% yield as a yellowish solid. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration in hexanes.

mp 82-83 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.97 (d, *J*=8.0, 1H, Harom), 7.68 (d, *J*=7.6, 1H, Harom), 7.50 (t, *J*=7.5, 1H, Harom), 7.39 (t, *J*=7.7, 1H, Harom), 7.31-7.23 (m, 5H, Harom), 6.58-6.56 (m, 1H, NH), 4.71 (d, *J*=6.4, 2H, H-1'), 2.74 (t, *J*=7.1, 2H, H-2/H-3), 2.50 (t, *J*=7.1, 2H, H-3/H-2).

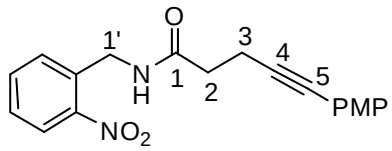
^{13}C NMR ($CDCl_3$) δ 171.3 (CO), 148.3, 133.6, 123.3 (q-Carom), 134.1, 132.4, 131.5, 128.6, 128.2, 127.8, 125.0 (t-Carom), 88.0 (C-4), 81.7 (C-5), 41.2 (C-1'), 35.7 (C-2), 15.9 (C-3).

IR (film) υ 3294, 1653.

MS (M+1, CI) *m/z* (%) 309 (100), 291 (10), 172 (8), 136 (17), 115 (12).

HRMS calculated for $C_{18}H_{16}N_2O_3 \cdot H^+$ 309.1239, found 309.1231.

5-(4-methoxyphenyl)-N-(2-nitrobenzyl)-4-pentynamide (**47b**).



According to the typical procedure amide **47b** was prepared from amide **46** in 55% yield as a white solid. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration in hexanes.

mp 98-99 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.92 (d, *J*=8.1, 1H, Harom), 7.61 (d, *J*=7.6, 1H, Harom), 7.39-7.17 (m, 4H, Harom), 6.91-6.89 (m, 1H, NH), 6.73 (d, *J*=8.7, 2H, Harom), 4.65 (d, *J*=6.3, 2H, H-1'), 3.74 (s, 3H, OCH_3), 2.70-2.65 (m, 2H, H-2/H-3), 2.49-2.44 (m, 2H, H-3/H-2).

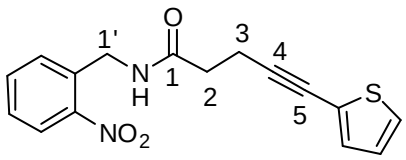
^{13}C NMR ($CDCl_3$) δ 171.7 (CO), 159.2, 148.1, 133.8, 115.4 (q-Carom), 134.0, 132.9, 131.5, 128.4, 124.9, 113.8 (t-Carom), 86.6 (C-4), 81.4 (C-5), 55.2 (OCH_3), 41.1 (C-1'), 35.6 (C-2), 15.9 (C-3).

IR (film) υ 3290, 1653.

MS (M+1, CI) *m/z* (%) 339 (100), 297 (28), 291 (10), 203 (53), 158 (10), 136 (27).

HRMS calculated for $C_{19}H_{18}N_2O_4 \cdot H^+$ 339.1345, found 339.1346.

N-(2-nitrobenzyl)-5-(2-thienyl)-4-pentynamide (**47c**).



According to the typical procedure amide **47c** was prepared from amide **46** in 82% yield as a brown solid. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration in hexanes.

mp 58-60 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.90 (d, *J*=8.0, 1H, Harom), 7.56 (d, *J*=7.5, 1H, Harom), 7.40 (t, *J*=7.2, 1H, Harom), 7.30 (t, *J*=7.6, 1H, Harom), 7.11-6.99 (m, 3H, Harom), 6.85 (m, 1H, NH), 4.63 (d, *J*=6.1, 2H, H-1'), 2.69 (t, *J*=7.0, 2H, H-2/H-3), 2.46 (t, *J*=7.0, 2H, H-3/H-2).

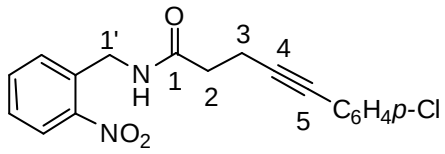
^{13}C NMR ($CDCl_3$) δ (ppm) 171.5 (CO), 148.0, 133.7, 123.4 (q-Carom), 133.9, 131.4, 131.2, 128.4, 126.8, 126.3, 124.9 (t-Carom), 92.4 (C-4), 74.7 (C-5), 41.0 (C-1'), 35.2 (C-2), 16.1 (C-3).

IR (film) υ 3290, 1652.

MS (M+1, CI) *m/z* (%) 315 (100), 297 (14), 273 (55), 267 (14), 203 (29), 178 (46), 136 (83).

HRMS calculated for $C_{16}H_{14}N_2O_3{}^{32}S \cdot H^+$ 315.0803, found 315.0807.

5-(4-chlorophenyl)-N-(2-nitrobenzyl)-4-pentynamide (**47d**).



According to the typical procedure amide **47d** was prepared from amide **46** in 80% yield as a white solid. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration in hexanes.

mp 101-102 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.99 (d, *J*=8.1, 1H, Harom), 7.68 (d, *J*=6.5, 1H, Harom), 7.54 (t, *J*=7.5, 1H, Harom), 7.41 (t, *J*=7.7, 1H, Harom), 7.25-7.18 (m, 4H, Harom), 6.54-6.52 (m, 1H, NH), 4.70 (d, *J*=6.4, 2H, H-1'), 2.73 (t, *J*=7.1, 2H, H-2/H-3), 2.49 (t, *J*=7.1, 2H, H-3/H-2).

^{13}C NMR ($CDCl_3$) δ 171.1 (CO), 148.3, 133.5 (q-Carom), 134.1, 132.8, 132.6, 128.7, 128.5, 125.0 (t-Carom), 89.1 (C-4), 80.6 (C-5), 41.3 (C-1'), 35.5 (C-2), 15.8 (C-3).

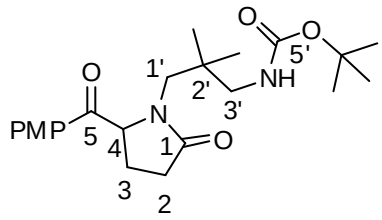
IR (film) υ 3290, 1648.

MS (M+1, CI) *m/z* (%) 343 (100), 325 (11), 301 (11), 295 (22).

HRMS calculated for $C_{18}H_{15}{}^{35}ClN_2O_3 \cdot H^+$ 343.0849, found 343.0851.

2.5.5. Typical procedure for the PIFA-mediated heterocyclization. Synthesis of pyrrolidinones 29, 30, 41, 42 and 48.

N-(3-tert-butoxycarbonylamino-2,2-dimethylpropyl)-5-(4´-methoxybenzoyl)-2-pyrrolidinone (**29a**).



A solution of alkynylamide **27a** (900 mg, 2.3 mmol) in TFEA (12 mL) was stirred at 0 ºC and a solution of PIFA (1.4 g, 3.4 mmol) in 15 mL of the same solvent was added dropwise. The reaction mixture was stirred at that temperature for 2 h. For the work up, aqueous Na_2CO_3 (10%) was added and the mixture extracted with DCM (3x20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave the desired product 2**9a** as a chromatographically pure yellowish oil (83%).

^{1}H NMR ($CDCl_3$) δ 7.92 (d, *J*=8.9, 2H, Harom), 6.99 (d, *J*=8.9, 2H, Harom), 6.07 (m, 1H, NH), 5.26 (d, *J*=8.8, 1H, H-4), 3.89 (s, 3H, OCH_3), 3.77 (d, *J*=14.6, 1H, H-1'/H-3'), 3.24-3.16 (m, 1H, H-3'/H-1'), 2.67-2.60 (m, 1H, H-1'/H-3'), 2.47-2.35 (m, 3H, H-2/H-3), 2.25 (d, *J*=14.6, 1H, H-3/H-1), 2.06-1.99 (m, 1H, H-3/H-2), 1.41 (s, 9H, ^{t}Bu), 0.90 (s, 3H, $C_{2'}$-(CH_3)$_2$), 0.85 (s, 3H, $C_{2'}$-(CH_3)$_2$).

^{13}C NMR ($CDCl_3$) δ 195.2 (C-5), 177.6 (C-1), 156.7 (C-5'), 164.3, 127.1 (q-Carom), 130.7, 114.3 (t-Carom), 78.5 (*C*-(CH_3)$_3$), 64.3 (C-4), 55.6

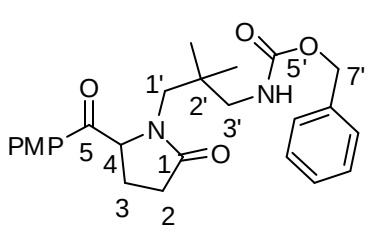
(OCH_3), 50.3 (C-1'), 47.1 (C-3'), 37.2 (C-2'), 28.9 (C-2), 28.4 (^{t}Bu), 24.7 (C-3), 23.7 ($C_{2'}$-(CH_3)$_2$).

IR (film) υ 3328, 2967, 1686, 1601.

MS (M+1, CI) *m/z* (%) 405 (1), 331 (94), 305 (68), 287 (100), 213 (18), 195 (40).

HRMS calculated for $C_{22}H_{32}N_2O_5 \cdot H^+$ 405.2345, found 405.2354.

N-(3-benzyloxycarbonylamino-2,2-dimethylpropyl)-5-(4´-methoxybenzoyl)-2-pyrrolidinone (**29b**).



According to the typical procedure pyrrolidinone **29b** was obtained from **27b** in 89% yield. It was purified by column chromatography (EtOAc) as a yellowish oil.

^{1}H NMR ($CDCl_3$) δ 7.93 (d, *J*=8.8, 2H, Harom), 7.35-7.28 (m, 5H, Harom), 6.99 (d, *J*=8.8, 2H, Harom), 6.49-6.47 (m, 1H, NH), 5.27 (d, *J*=9.1, 1H, H-4), 5.11 (d, *J*=12.3, 1H, H-7'), 5.04 (d, *J*=12.3, 1H, H-7'), 3.89 (s, 3H, OCH_3), 3.76 (d, *J*=14.8, 1H, H-1'/H-3'), 3.26-3.24 (m, 1H, H-3'/H-1'), 2.74-2.70 (m, 1H, H-1'/H-3'), 2.49-2.36 (m, 3H, H-2/H-3), 2.26 (d, *J*=14.8, 1H, H-1'/H-3'), 2.06-1.99 (m, 1H, H-3/H-2), 0.92 (s, 3H, $C_{2'}$-(CH_3)$_2$), 0.86 (s, 3H, $C_{2'}$-(CH_3)$_2$).

^{13}C NMR ($CDCl_3$) δ 195.1 (C-5), 177.7 (C-1), 157.2 (C-5'), 164.3, 137.0, 114.3 (q-Carom), 130.7, 128.4, 127.9, 127.8, 127.0 (t-Carom), 66.3 (C-4),

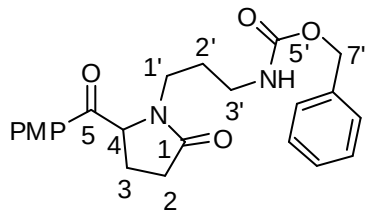
64.3 (C-7'), 55.6 (OCH_3), 50.3 (C-1'), 47.7 (C-3'), 37.2 (C-2'), 28.9 (C-2), 24.7 (C-3), 23.6 ($C_{2'}$-(CH_3)$_2$).

IR (film) υ 3338, 2962, 1682, 1600.

MS (M+1, CI) *m/z* (%) 439 (1), 359 (10), 331 (100), 303 (11), 195 (47).

HRMS calculated for $C_{25}H_{30}N_2O_5 \cdot H^+$ 439.2233, found 439.2249.

N-(3-benzyloxycarbonylaminopropyl)-5-(4´-methoxybenzoyl)-2-pyrrolidinone (**30**).



According to the typical procedure pyrrolidinone **30** was obtained from **28** in 70% yield. It was purified by column chromatography (EtOAc) as a yellowish oil.

^{1}H NMR ($CDCl_3$) δ 7.93 (d, *J*=8.8, 2H, Harom), 7.33-7.26 (m, 5H, Harom), 6.97 (d, *J*=8.8, 2H, Harom), 5.61 (m, 1H, NH), 5.15-5.02 (m, 3H, H-7', H-4), 3.89 (s, 3H, OCH_3), 3.71-3.56 (m, 1H, H-1'/H-3'), 3.41-3.27 (m, 1H, H-3'/H-1'), 3.16-3.02 (m, 2H, H-1'/H-3'), 2.52-2.34 (m, 3H, H-2/H-3), 2.02-1.98 (m, 1H, H-3/H-2), 1.70-1.58 (m, 2H, H-2').

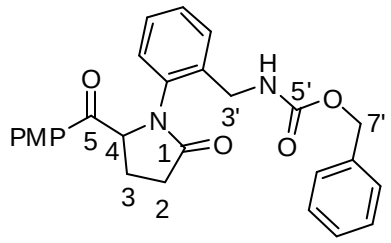
^{13}C NMR ($CDCl_3$) δ 195.4 (C-5), 176.4 (C-1), 164.3 (C-5'), 136.7, 127.1 (q-Carom), 130.7, 128.4, 128.0, 114.3 (t-Carom), 66.4 (C-7'), 61.8 (C-4), 55.6 (OCH_3), 39.3 (C-1'), 37.9 (C-3'), 29.5 (C-2), 27.4 (C-2'), 23.8 (C-3).

IR (film) υ 3332, 2938, 1685, 1599, 1512.

MS (M+1, CI) *m/z* (%) 304 (12, M+1–Cbz), 303 (79), 260 (28), 167 (100), 135 (17).

HRMS calculated for [$C_{23}H_{26}N_2O_5 \cdot H^+$ – Cbz] 304.1423, found 304.1390.

N-[(2-benzyloxycarbonylaminomethyl)phenyl]-5-(4´-methoxybenzoyl)-2-pyrrolidinone (**41**).



According to the typical procedure pyrrolidinone **41** was obtained from **39** in 39% yield. It was purified by column chromatography (hexanes/EtOAc, 1/1) as a pale brown oil.

^{1}H NMR ($CDCl_3$) δ 7.87 (d, *J*=8.6, 2H, Harom), 7.49 (br s, 1H, NH), 7.37-7.22 (m, 8H, Harom), 6.91 (d, *J*=8.8, 2H, Harom), 5.69-5.65 (m, 1H, H-4), 5.13 (s, 2H, H-7'), 4.56-4.54 (m, 2H, H-3'), 3.84 (s, 3H, OCH_3), 2.52-2.23 (m, 3H, H-2/H-3), 2.15-2.07 (m, 1H, H-3/H-2).

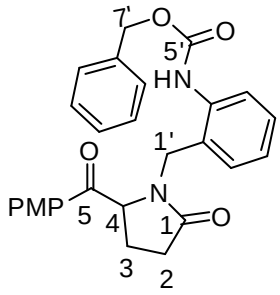
^{13}C NMR ($CDCl_3$) δ 195.1 (C-5), 164.3 (C-1), 156.8 (C-5'), 136.8, 136.1, 127.0 (q-Carom), 130.8, 128.5, 128.3, 128.1, 128.0, 114.2 (t-Carom), 66.6 (C-7'), 64.9 (C-4), 55.6 (OCH_3), 41.4 (C-3'), 30.1 (C-2), 24.5 (C-3).

IR (film) υ 3354, 1693, 1599.

MS (M+1, CI) *m/z* (%) 459 (6), 351 (17), 323 (20), 308 (100), 215 (63), 135 (11).

HRMS calculated for $C_{27}H_{26}N_2O_5 \cdot H^+$ 459.1920, found 459.1900.

N-[(2-benzyloxycarbonylamino)benzyl]-5-(4´-methoxybenzoyl)-2-pyrrolidinone (**42**).



According to the typical procedure pyrrolidinone **42** was obtained from **40** in 65% yield. It was purified by column chromatography (hexanes/EtOAc, 1/1) as a yellowish oil.

^{1}H NMR ($CDCl_3$) δ 8.90 (s, 1H, NH), 8.02 (d, *J*=8.1, 1H, Harom), 7.86 (d, *J*=8.7, 2H, Harom), 7.46-7.26 (m, 6H, Harom), 6.97-6.89 (m, 4H, Harom), 5.22 (s, 2H, H-7'), 5.03-4.98 (m, 3H, H-1',H-4), 3.87 (s, 3H, OCH_3), 2.52-2.28 (m, 3H, H-2/H-3), 2.02-1.88 (m, 1H, H-3/H-2).

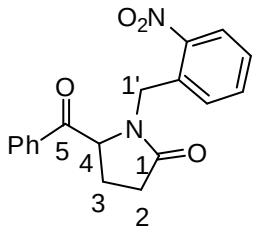
^{13}C NMR ($CDCl_3$) δ 194.8 (C-5), 176.4 (C-1), 164.4 (C-5'), 154.3, 137.4, 136.8, 124.9 (q-Carom), 130.7, 129.3, 128.5, 128.0, 127.9, 123.1, 121.7, 114.3 (t-Carom), 66.5 (C-7'), 60.6 (C-4), 55.6 (OCH_3), 42.8 (C-1'), 29.2 (C-2), 23.5 (C-3).

IR (film) υ 3251, 1732, 1679, 1597.

MS (M+1, CI) *m/z* (%) 352 (22, M+1–Cbz), 351 (100), 215 (84), 132 (33).

HRMS calculated for [$C_{27}H_{26}N_2O_5 \cdot H^+$ – Cbz] 352.1323, found 352.1387.

5-benzoyl-N-(2-nitrobenzyl)-2-pyrrolidinone (**48a**).



According to the typical procedure pyrrolidinone **48a** was obtained from **47a** in 81% yield. It was purified as a yellowish oil by column chromatography (EtOAc).

^{1}H NMR ($CDCl_3$) δ 7.91-7.88 (m, 3H, Harom), 7.66-7.56 (m, 3H, Harom), 7.49-7.40 (m, 3H, Harom), 5.22-5.15 (m, 2H, H-1', H-4), 4.41 (d, *J*=15.8, 1H, H-1'), 2.50-2.43 (m, 3H, H-2/H-3), 2.05-2.02 (m, 1H, H-3/H-2).

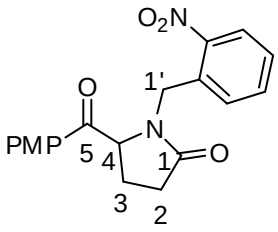
^{13}C NMR ($CDCl_3$) δ 196.5 (C-5), 176.2 (C-1), 148.7, 133.9, 131.8 (q-Carom), 134.0, 133.6, 131.3, 129.0, 128.6, 128.3, 124.7 (Carom), 62.0 (C-4), 42.7 (C-1'), 28.9 (C-2), 23.4 (C-3).

IR (film) υ 1696, 1525.

MS (M+1, CI) *m/z* (%) 325 (100), 219 (86), 136 (18).

HRMS calculated for $C_{18}H_{16}N_2O_4 \cdot H^+$ 325.1188, found 325.1185.

5-(4-methoxybenzoyl)-N-(2-nitrobenzyl)-2-pyrrolidinone (**48b**).



According to the typical procedure pyrrolidinone **48b** was obtained from **47b** in 69% yield. It was purified by column chromatography (hexanes/EtOAc, 1/1) as a yellowish solid that was triturated in hexanes.

mp 55-58 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ 7.88-7.82 (m, 3H, Harom), 7.59-7.57 (m, 2H, Harom), 7.48-7.38 (m, 1H, Harom), 6.92 (d, *J*=8.8, 2H, Harom), 5.19-5.10 (m, 2H, H-1', H-4), 4.30 (d, *J*=16.0, 1H, H-1'), 3.84 (s, 3H, OCH_3), 2.52-2.33 (m, 3H, H-2/H-3), 2.09-1.97 (m, 1H, H-3/H-2).

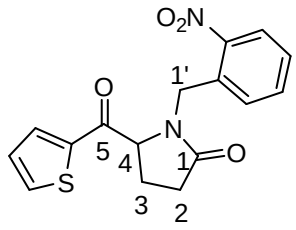
^{13}C NMR ($CDCl_3$) δ 195.0 (C-5), 176.2 (C-1), 164.2, 148.7, 132.0, 126.9 (q-Carom), 133.5, 131.3, 130.7, 128, 124.6, 114.2 (t-Carom), 61.7 (C-4), 55.6 (OCH_3), 42.8 (C-1'), 29.0 (C-2), 23.6 (C-3).

IR (film) υ 1690, 1600.

MS (M+1, CI) *m/z* (%) 355 (100), 219 (62), 135 (13).

HRMS calculated for $C_{19}H_{18}N_2O_5 \cdot H^+$ 355.1294, found 355.1302.

N-(2-nitrobenzyl)-5-(2-thienyl)-2-pyrrolidinone (**48c**).



According to the typical procedure pyrrolidinone **48c** was obtained from **47c** in 77% yield. It was purified as a yellowish oil by column chromatography (EtOAc).

^{1}H NMR ($CDCl_3$) δ 7.88 (d, *J*=8.1, 1H, Harom), 7.70-7.65 (m, 2H, Harom), 7.57 (d, *J*=4.2, 2H, Harom), 7.43-7.37 (m, 1H, Harom), 6.12 (t, *J*=4.2, 1H, Harom), 5.13 (d, *J*=16.0, 1H, H-1'), 4.98 (d, *J*=8.2, 1H, H-4), 4.40 (d, *J*=16.0, 1H, H-1'), 2.53-2.43 (m, 3H, H-2/H-3), 2.17-2.01 (m, 1H, H-3/H-2).

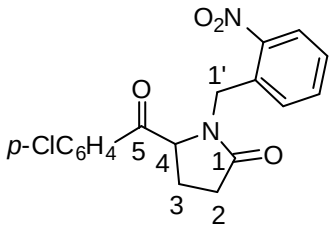
^{13}C NMR ($CDCl_3$) δ 190.0 (C-5), 176.1 (C-1), 148.7, 140.8, 131.8 (q-Carom), 135.0, 133.6, 132.6, 131.4, 128.7, 128.6, 124.7 (t-Carom), 62.9 (C-4), 42.8 (C-1'), 29.0 (C-2), 24.0 (C-3).

IR (film) υ 1695, 1523.

MS (M+1, CI) *m/z* (%) 331 (100), 219 (91), 136 (20).

HRMS calculated for $C_{16}H_{14}N_2O_5{}^{32}S\cdot H^+$ 331.0753, found 331.0760.

5-(4-chlorobenzoyl)-N-(2-nitrobenzyl)-2-pyrrolidinone (**48d**).



According to the typical procedure pyrrolidinone **48d** was obtained from **47d** in 57% yield. It was purified as a colorless oil by column chromatography (EtOAc).

^{1}H NMR ($CDCl_3$) δ 7.88-7.80 (m, 3H, Harom), 7.66-7.56 (m, 2H, Harom), 7.43 (d, *J*=8.6, 3H, Harom), 5.16-5.11 (m, 2H, H-1', H-4), 4.37 (d, *J*=15.6, 1H, H-1'), 2.45-2.41 (m, 3H, H-2/H-3), 2.00-1.98 (m, 1H, H-3/H-2).

^{13}C NMR ($CDCl_3$) δ 195.4 (C-5), 175.9 (C-1), 171.1, 148.8, 132.3, 131.8 (q-Carom), 133.6, 131.9, 129.7, 129.3, 128.7, 124.6 (t-Carom), 61.9 (C-4), 42.5 (C-1'), 28.9 (C-2), 23.3 (C-3).

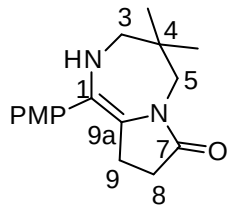
IR (film) υ 1697, 1524.

MS (M+1, CI) *m/z* (%) 361 (23), 360 (14), 359 (70), 219 (100), 136 (22).

HRMS calculated for $C_{18}H_{15}{}^{35}ClN_2O_4 \cdot H^+$ 359.0799, found 359.0798.

2.5.6. Procedure for the intramolecular amination reaction. Synthesis of diazepine 31.

1-(4-methoxyphenyl)-4,5,8,9-tetrahydro-2H-pyrrolo[1,2-a][1,4]diazepin-7(3H)-one (**31**).



A solution of pyrrolidinone 2**9a** (800 mg, 1.9 mmol) in TFA/DCM 1/1 (25 mL) was stirred for 30 min. An aliquot was taken to confirm (^{1}H NMR) that the protecting group was completely released. Then, solvent was removed under vacuum to remove both solvents and the residue was taken in 50 mL of DCM, cooled to 0 ºC and treated with Et_3N (0.7 mL, 5 mmol). After stirring for 20 min, molecular sieve (4 Å) was added and the stirring continued for 15 additional minutes. The mixture was then filtered through celite, washed with 20 mL of a saturated aqueous solution of $NaHCO_3$, and finally extracted with EtOAc (3x25 mL). The combined organic extracts were dried with anh. Na_2SO_4 and solvent evaporated at reduced pressure. The resulting residue purified by column chromatography (EtOAc) to afford pyrazinone **31** as a brown oil (11%).

^{1}H NMR ($CDCl_3$) δ 7.85 (d, *J*=8.9, 2H, Harom), 7.74 (m, 1H, NH), 6.92 (d, *J*=8.9, 2H, Harom), 3.82 (s, 3H, OCH_3), 3.59-3.38 (m, 2H, H-3), 3.09 (d, *J*=6.7, 1H, H-5), 2.71-2.69 (m, 3H, H-8/H-9), 2.70-2.67 (m, 1H, H-5), 2.01 (s, 1H, H-9/H-8), 0.93 (s, 6H, C_4-(CH_3)$_2$).

^{13}C NMR ($CDCl_3$) δ 178.7 (C-7), 178.6 (C-1), 166.8 (C-9a), 162.1, 126.8 (q-Carom), 128.8, 113.7 (t-Carom), 55.4 (OCH_3), 45.8, 45.6 (C-3, C-5), 37.7 (C-4), 28.1(C-8, C-9), 24.1 (C_4-(CH_3)$_2$).

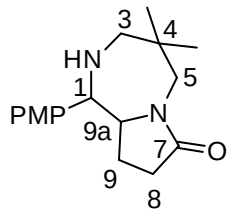
IR (film) υ 3385, 2966, 1698.

MS (M+1, CI) *m/z* (%) 317 (6), 206 (21), 167 (12), 135 (100).

HRMS calculated for $C_{17}H_{22}N_2O_2 \cdot H^+$ 287.1760, found ([M+3] + ethylene) 317.1609.

2.5.7. Typical procedure for the reductive amination. Synthesis of diazepines 32, 33, 43 and 44.

1-(4-methoxyphenyl)-4,4-dimethyl-octahydro-pyrrolo[1,2-a][1,4]diazepin-7-one (**32**).



A solution of pyrrolidinone **29b** (930 mg, 2.1 mmol) in 10 mL of MeOH and 0.5 mL of HCl (1M) was hydrogenated (70 psi) in the presence of Pd/C overnight. The catalyst was filtered through celite and the solution treated with 15 mL of an aqueous solution of Na_2CO_3 (20%). The mixture was extracted with DCM (3x15 mL), the combined organic extracts were dried with Na_2SO_4, and the solvent evaporated under vacuum. The resulting oil was purified by column chromatography (MeOH) to afford diazepinone **32** as a brown oil (43%) as an inseparable mixture of both diastereoisomers (82:18). Reported data is given for the both of them.

^{1}H NMR ($CDCl_3$) δ 7.29/7.25 (d, *J*=8.2, 2H, Harom), 6.86-6.80 (m, 4H, Harom), 5.12 (br s, 1H, NH), 4.80 (d, *J*=5.7, 1H, H-1)/4.03-4.00 (m, 1H, H-1), 3.96-3.91/3.89-3.85 (m, 1H, H-9a), 3.77/3.75 (s, 3H, OCH_3), 3.65-3.62/3.44-3.42 (m, 1H, H-3), 3.25-3.20 (m, 2H, H-3), 3.08-2.79 (m, 4H, H-5), 2.56-2.54/2.15-2.10 (m, 1H, H-9/H-8), 2.05-1.99/1.82-1.72 (m, 3H, H-9/H-8), 1.13/0.98/ 0.96/0.87 (s, 3H, C_4-(CH_3)$_2$).

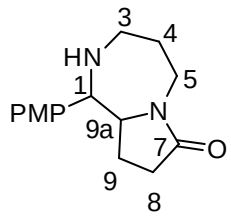
^{13}C NMR ($CDCl_3$) δ 177.4/176.8 (C-1), 159.2, 158.8 (q-Carom), 127.6, 127.1, 113.9, 113.5 (Carom), 74.7/72.9 (C-1), 71.5/69.0 (C-9a), 55.4/55.3 (OCH_3), 52.7/49.5 (C-5), 49.3/47.9 (C-3), 29.6/24.8 (C-4), 24.7/24.3 (C-8), 24.0/23.9 (C_4-(CH_3)$_2$), 20.9/19.1 (C-9).

IR (film) υ 3285, 2955, 1673.

MS (M+1, CI) *m/z* (%) 289 (43), 169 (33).

HRMS calculated for $C_{17}H_{24}N_2O_2 \cdot H^+$: 289.1916, found: 289.1925.

1-(4-methoxyphenyl)-octahydro-pyrrolo[1,2-a][1,4]diazepin-7-one (**33**).



According to the typical procedure diazepinone **33** was obtained from pyrrolidinone **30** in 48% yield. It was purified by column chromatography (MeOH) as a colorless oil as an inseparable mixture of both isomers (37:63). Reported data is given for the both of them.

^{1}H NMR ($CDCl_3$) δ 7.27/7.21 (d, *J*=8.5, 2H, Harom), 6.88-6.82 (m, 4H,

Harom), 5.08 (br s, 1H, NH), 4.60 (d, *J*=6.7, 1H, H-1)/3.84-3.79 (m, 1H, H-1), 3.78/3.77 (s, 3H, OCH_3), 3.73-3.69/3.63-3.56 (m, 1H, H-9a), 3.48-3.35/2.39-2.32 (m, 2H, H-3), 2.93-2.87/2.84-2.79 (m, 1H, H-5)/2.77-2.70 (m, 2H, H-5), 2.18-2.10 (m, 2H, H-9)/2.10-2.00 (m, 1H, H-9), 1.99-1.85 (m, 3H, H-8/H-9), 1.82-1.73/1.71-1.64 (m, 1H, H-4), 1.63-1.55 (m, 2H, H-4).

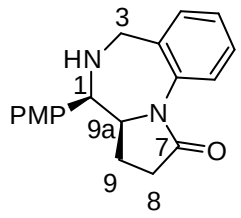
^{13}C NMR ($CDCl_3$) δ 176.6/176.1 (C-7), 158.8, 158.5, 133.1, 133.8 (q-Carom), 127.7, 127.0, 114.0, 113.7 (t-Carom), 75.6/71.2 (C-1), 65.7/63.6 (C-9a), 55.2/40.6 (OCH_3), 39.9/39.2 (C-3/C-5), 38.3/30.5 (C-5/C-3), 30.1/ 29.5 (C-2), 21.0 (C-8), 17.7 (C-9).

IR (film) υ 3349, 1663.

MS (M+1, CI) *m/z* (%) 261 (84), 244 (26), 206 (27), 141 (100).

HRMS calculated for $C_{15}H_{20}N_2O_2 \cdot H^+$ 261.1603, found 261.1615.

(+/-)-(4R,3aR)-(4-methoxyphenyl)-2,3,3a,4,5,6-hexahydro-benzo[f]pyrrolo[1,2-a][1,4]diazepin-1-one (**43**).



According to the typical procedure diazepinone **43** was obtained from pyrrolidinone **41** in 51% yield as a single diastereoisomer. It was purified by column chromatography (MeOH) as a yellowish oil.

^{1}H NMR ($CDCl_3$) δ 7.23-6.76 (m, 8H, Harom), 5.00-

4.98 (m, 1H, H-1), 4.67 (d, *J*=17.0, 1H, H-3), 4.55 (d, *J*=17.0, 1H, H-3), 4.47-4.45 (m, 1H, H-9a), 3.79 (s, 3H, OCH_3), 2.42-2.33 (m, 1H, H-8/H-9), 2.09-1.95 (m, 3H, H-9/H-8).

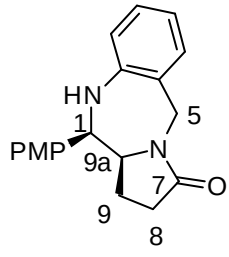
^{13}C NMR ($CDCl_3$) δ 160.6 (C-7), 159.3, 137.5, 132.3, 119.3 (q-Carom), 127.7, 127.4, 126.1, 123.2, 113.6, 111.3 (t-Carom), 72.3 (C-1), 62.7 (C-9a), 55.2 (OCH_3), 48.7 (C-3), 29.1 (C-8), 21.1 (C-9).

IR (film) υ 3310, 1670.

MS (M+1, CI) *m/z* (%) 309 (30), 291 (13), 172 (28), 171 (100).

HRMS calculated for $C_{19}H_{20}N_2O_2 \cdot H^+$ 309.1603, found 309.1615.

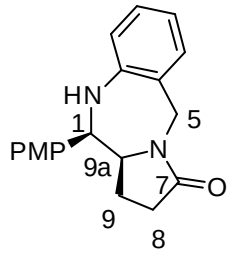
(+/-)-*(11R,11aR)-11-(4-methoxyphenyl)-1,2,5,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-3-one* (**44**).



According to the typical procedure diazepinone **44** was obtained from pyrrolidinone **42** in 15% yield. It was purified as a yellowish oil by column chromatography (MeOH) as an inseparable mixture of isomers (67:33). Both diastereoisomers could be partially purified by column chromatography (Et_2O) followed by trituration in the same solvent (see next section for spectroscopic information).

2.5.8. Typical procedure for the reductive amination. Synthesis of diazepines 44, 50, 52 and 59.

(+/-)-(11R,11aR)-11-(4-methoxyphenyl)-1,2,5,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-3-one (**44**).



A solution of pyrrolidinone **48b** (500 mg, 1.4 mmol) in 10 mL of MeOH was hydrogenated (70 psi) in the presence of PtO_2 (50 mg) overnight. The catalyst was filtered through celite and the solution was evaporated under vacuum. The resulting chromatographically pure white solid was identified as a diastereoisomeric mixture of diazepinone **44** in a combined 92% yield. Both diastereoisomers could be partially purified by column chromatography (Et_2O) followed by trituration in the same solvent. Reported data is given for the isolated major (*syn*) stereoisomer.

mp 68-70 ºC (Et_2O).

^{1}H NMR ($CDCl_3$) δ 7.22-7.08 (m, 4H, Harom), 6.88-6.83 (m, 2H, Harom), 6.67-6.62 (m, 2H, Harom), 4.92 (d, *J*=6.0, 1H, H-5), 4.79 (d, *J*=14.6, 1H, H-1), 4.38-4.27 (m, 2H, NH, H-5), 3.79-3.75 (m, 4H, OCH_3, H-9a), 2.06-1.83 (m, 2H, H-9/H-8), 1.76-1.69 (m, 2H, H-8/H-9).

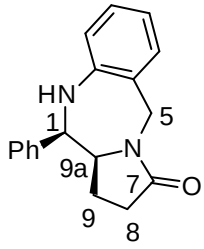
^{13}C NMR ($CDCl_3$) δ 176.5 (C-7), 159.5, 145.9, 132.7, 120.1 (q-Carom), 131.8, 129.2, 127.6, 117.4, 115.6, 113.9 (t-Carom), 75.0 (C-1), 61.7 (C-9a), 55.3 (OCH_3), 43.0 (C-5), 29.7 (C-8), 21.0 (C-9).

IR (film) υ 3358, 2931, 1655.

MS (M+1, CI) *m/z* (%) 309 (24), 204 (11), 190 (64), 189 (27), 106 (100).

HRMS calculated for $C_{19}H_{20}N_2O_2 \cdot H^+$ 309.1603, found 309.1609.

(+/-)-(11R,11aR)-11-phenyl-1,2,5,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-3-one (**50**).



According to the typical procedure diazepinone **50** was obtained from pyrrolidinone **48a** in combined 95% yield as a mixture of diastereoisomers that could be partially purified by column chromatography (Et_2O). Reported data is given for the isolated major (syn) stereoisomer.

mp 131-132 ºC (Et_2O).

^{1}H NMR ($CDCl_3$) δ 7.37-7.28 (m, 5H, Harom), 7.12-7.05 (m, 2H, Harom), 6.68-6.63 (m, 2H, Harom), 4.93 (d, *J*=14.6, 1H, H-5), 4.86 (d, *J*=5.7, 1H, H-1), 4.25 (d, *J*=14.6, 1H, H-5), 3.82-3.80 (m, 1H, H-9a), 2.08-1.75 (m, 4H, H-9, H-8).

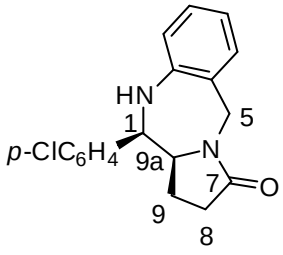
^{13}C NMR ($CDCl_3$) δ 176.5 (C-7), 145.8, 140.7, 120.0 (q-Carom), 131.8, 129.2, 128.6, 128.3, 126.4, 117.4, 115.6 (t-Carom), 75.6 (C-1), 61.7 (C-9a), 43.1 (C-5), 29.7 (C-8), 21.2 (C-9).

IR (film) υ 3357, 1651.

MS (M+1, CI) *m/z* (%) 279 (9), 204 (13), 190 (11), 189 (53), 106 (100).

HRMS calculated for $C_{18}H_{18}N_2O \cdot H^+$ 279.1497, found 279.1511.

(+/-)-(11R,11aR)-11-(4-chlorophenyl)-1,2,5,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-3-one (**52**).



According to the typical procedure diazepinone **52** was obtained from pyrrolidinone **48d** in 49% yield as a 71:29 mixture of syn/anti diastereoisomers that could be partially purified by column chromatography (Et_2O). Reported data is given for the major (syn) stereoisomer.

mp 239-240 ºC (Et_2O).

^{1}H NMR ($CDCl_3$) δ 7.29-7.26 (m, 2H, Harom), 7.22-7.19 (m, 3H, Harom), 7.11-7.06 (m, 1H, Harom), 6.79-6.76 (m, 1H, Harom), 6.55-6.53 (m, 1H, Harom), 4.99 (m, 1H, H-1), 4.67 (d, *J*=17.0, 1H, H-5), 4.55 (d, *J*=17.0, 1H, H-5), 4.47-4.45 (m, 1H, H-9a), 3.79 (br s, 1H, NH), 2.42-1.95 (m, 4H, H-9, H-8).

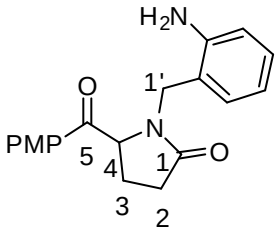
^{13}C NMR ($CDCl_3$) δ 174.5 (C-7), 146.2, 136.4, 134.1, 124.6 (q-Carom), 129.9, 129.0, 128.7, 128.2, 121.1, 119.4 (t-Carom), 63.5, 62.1 (C-1, C-9a), 44.8 (C-5), 30.2 (C-8), 20.2 (C-9).

IR (film) υ 3327, 1678.

MS (M+1, CI) *m/z* (%) 313 (100), 279 (7), 229 (45), 227 (54).

HRMS calculated for $C_{18}H_{17}{}^{35}ClN_2O\cdot H^+$ 313.1108, found 313.1111.

N-(2´-aminobenzyl)-5-(4-methoxybenzoyl)-2-pyrrolidinone (**49**).



A solution of pyrrolidinone **48b** (500 mg, 1.4 mmol) in 10 mL of MeOH was hydrogenated (70 psi) in the presence of Pd black (25 mg) overnight. The catalyst was filtered through celite and the solution was evaporated under vacuum. The resulting chromatographically pure white solid (98% yield) was triturated in MeOH and identified as pyrrolidinone **49**.

mp 136-137 ºC (MeOH).

^{1}H NMR (CD_3COCD_3) δ 7.96 (d, *J*=8.9, 2H, Harom), 7.04 (d, *J*=8.9, 2H, Harom), 6.96 (t, *J*=7.6, 1H, Harom), 6.75 (d, *J*=7.0, 1H, Harom), 6.67 (d, *J*=8.0, 1H, Harom), 6.40 (d, *J*=7.3, 1H, Harom), 5.06-5.03 (m, 1H, H-4), 4.92 (d, *J*=14.7, 1H, H-1'), 4.85-4.83 (m, 2H, NH_2), 3.80 (s, 3H, OCH_3), 3.76 (d, *J*=14.7, 1H, H-1'), 2.52-2.30 (m, 3H, H-2/H-3), 1.93-1.84 (m, 1H, H-3/H-2).

^{13}C NMR (CD_3COCD_3) δ 195.5 (C-5), 175.9 (C-1), 164.2, 145.9, 127.2, 118.8 (q-Carom), 131.3, 130.7, 129.4, 117.3, 115.5, 114.2 (t-Carom), 60.0 (C-4), 55.6 (OCH_3), 42.7 (C-1'), 29.6 (C-2), 23.3 (C-3).

IR (film) υ 3359, 2931, 1679, 1599.

MS (M+1, CI) *m/z* (%) 324 (30), 307 (70), 306 (100), 223 (19), 189 (40), 106 (90).

HRMS calculated for $C_{19}H_{20}N_2O_3 \cdot H^+$ 324.1474, found 324.1481.

3. SÍNTESIS DE INDOLIZIDINONAS

El sistema indolizidínico es parte del esqueleto de gran número de compuestos naturales presentes en plantas, animales, bacterias y hongos, por lo que las indolizidinonas, consideradas "privileged structures", han sido ampliamente estudiadas desde el punto de vista sintético y por su acción biológica.[97] Especial atención requieren las indolizidinas polihidroxiladas,[98] tales como la lentiginosina, castanospermina o swainsonina (*Figura 2.7*), ya

97. (a) Nakanishi, K. en "*Comprehensive Natural Products Chemistry*"; Barton, D. H. B., Ed.; Elsevier Science: Oxford, 1999; Vol. 4, p 25. (b) Dewick, P. M. "*Medicinal Natural Products*"; Wiley: 1998; p. 289. (c) Michael, J. P. *Nat. Prod. Rep*. **2005**, *22*, 603. (d) Michael, J. P. *Nat. Prod. Rep*. **2007**, *24*, 191. (e) Michael, J. P. *Nat. Prod. Rep*. **2008**, *25*, 139. (f) Arnone A.; Broggini G.; Passarella, D.; Terraneo, A.; Zecchi, G. *J. Org. Chem*. **1998**, *63*, 9279.

98. (a) Paolucci, C.; Mattioli, L. *J. Org. Chem*. **2001**, *66*, 4787. (b) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem*. **2002**, *67*, 7774. (c) Carretero, J. C.; Arrayas, R. G. *J. Org. Chem*. **1998**, *63*, 2993. (d) El Nemr, A. E. *Tetrahedron* **2000**, *56*, 8579. (e) Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045. (f) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (g) Torres-Sanchez, M. I.; Borrachero, P.; Cabrera-Escribano, F.; Gomez-Guillen, M.; Angulo-Alvarez, M.; Alvarez, E.; Favre, S.; Vogel, P. *Tetrahedron Asymmmetry* **2007**, *18*, 1809.

que, además de su capacidad inhibidora de las glicosidasas,[99] han sido citados como potenciales agentes terapéuticos contra la diabetes,[100] cáncer[101] y VIH.[102]

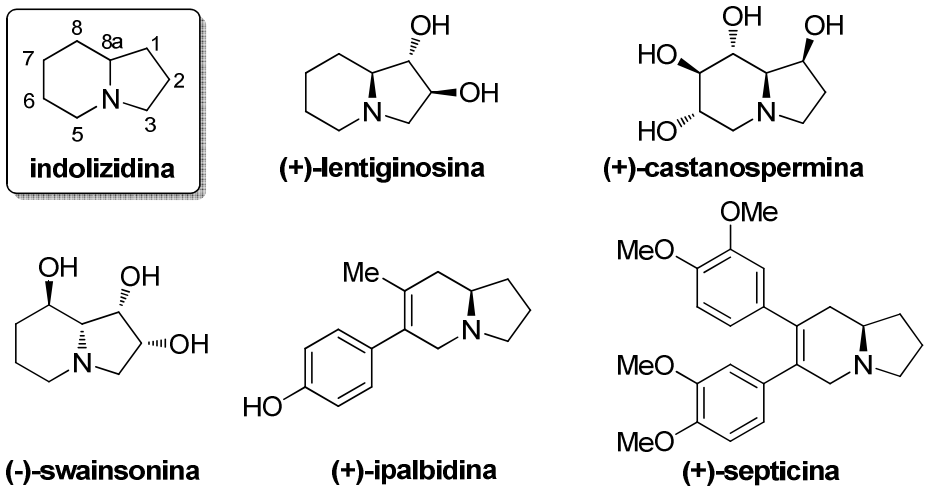


Figura 2.7. Algunos compuestos indolizidínicos de interés sintético.

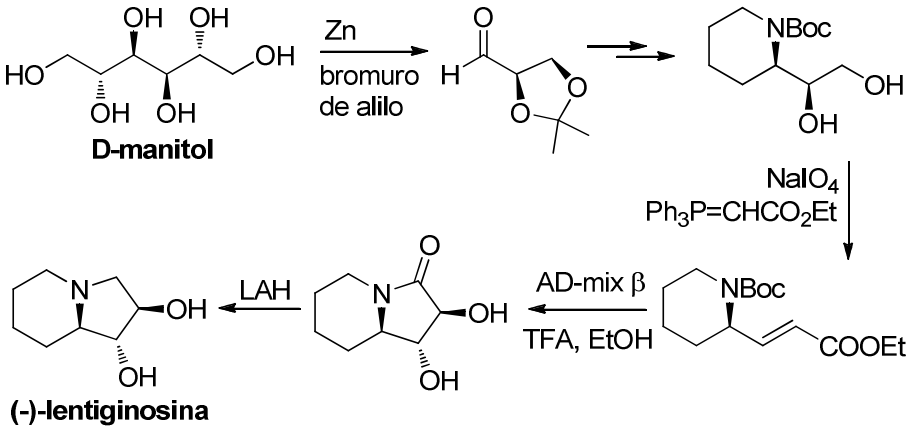
99. (a) Díaz, L.; Bujons, J.; Casas, J.; Llebaria, A.; Delgado, A. *J. Med. Chem.* **2010**, *53*, 5248. (b) Sinnot, M. L *Chem. Rev*. **1990**, *90*, 1171.

100. (a) Platt, F. M.; Neises, G. R.; Reinkensmeier, G.; Townsend, M. J.; Perry, V. H.; Proia, R. L.; Winchester, B.; Dwek, R. A.; Butters, T. D. *Science* **1997**, *276*, 428. (b) Nojima, H.; Kimura, I.; Chen, F. –J.; Sugihara, Y.; Haruno, M.; Kato, A.; Asano, N. *J. Nat. Prod.* **1998**, *61*, 397.

101. (a) Gross, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935. (b) Pili, R.; Chang, J.; Partis, R. A.; Mueller, R. A.; Chrest, F. J.; Passaniti, A. *Cancer Res.* **1995**, *55*, 2920. (c) Zhao, B. X.; Wang, Y.; Zhang, D. M.; Jiang, R. W.; Wang, G. C.; Shi, J. M.; Huang, X. J; Chen, W. M.; Che, C. T.; Ye, W. C. *Org. Lett.* **2011**, *13*, 3888. (d) Oredipe, O. A.; Furbert-Harris, P. M.; Laniyan, I.; Green, W. R.; White, S. L.; Olden, K.; Parish-Gause, D.; Vaughn, T.; Griffin, W. M.; Sridhar, R. *International inmunopharmacology* **2003**, *3*, 445.

102. (a) De Clercq, E. *Med. Res. Rev.* **2000**, *20*, 323. (b) Wikler, D. A.; Holan, G. *J. Med. Chem.* **1989**, *32*, 2084.

En los últimos años hemos sido testigos de un gran desarrollo de diferentes diseños de síntesis para estos heterociclos. Debido a las ventajas que presenta recurrir al empleo de estructuras que contienen una estereoquímica bien definida, las estrategias basadas en el uso de carbohidratos, uno de los representantes más versatiles del "chiral pool", para la preparación de indolizidinas polihidroxiladas han sido ampliamente descritas, especialmente aquellas que parten de D-manitol, D-ribosa, D-glucosa o L-sorbosa, como se muestra, a modo de ejemplo, en el *Esquema 2.23.*[103]



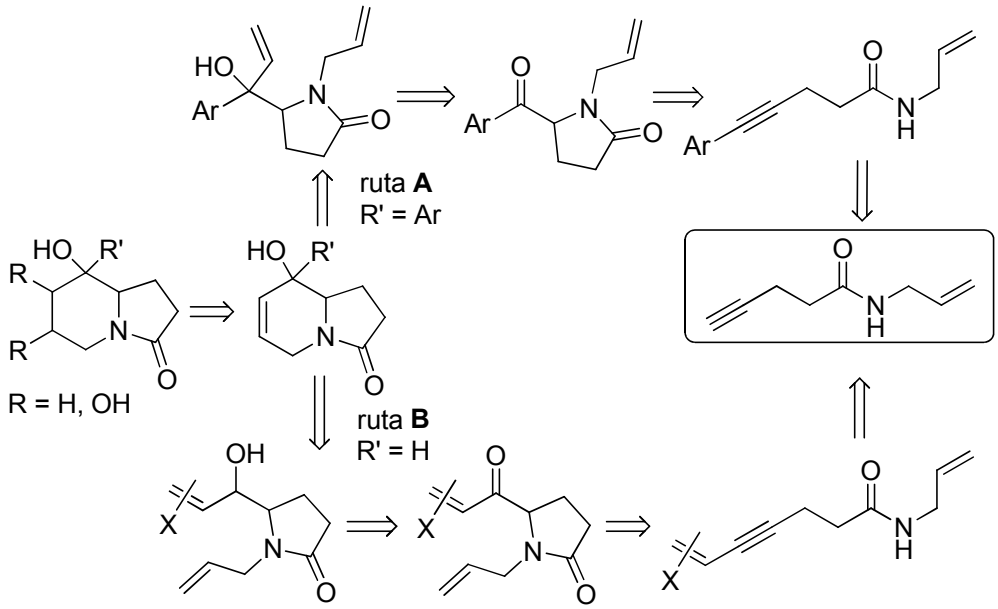
Esquema 2.23. Síntesis de (-)-lentiginosina partiendo de D-manitol.

103. Ejemplos de estas síntesis pueden encontrarse en: (a) Kamal, A.; Vangala, S. R. *Tetrahedron* **2011**, *67*, 1341. (b) Hu, X. –G.; Bartholomew, B.; Nash, R. J.; Wilson, F. X.; Fleet, G. W. J.; Nakagawa, S.; Kato, A.; Jia, Y. –M.; van Well, R.; Yu, C. –Y. *Org. Lett.* **2010**, *12*, 2562. (c) Izquierdo, I.; Tamayo, J. A.; Rodríguez, M.; Franco, F.; Lo Re, D. *Tetrahedron* **2008**, *64*, 7910. (d) Karanjule, N. S.; Markad, S. D.; Shinde, V. S.; Dhavale, D. D. *J. Org. Chem.* **2006**, *71*, 4667.

Sin embargo, estas aproximaciones están limitadas, en ocasiones, por su falta de flexibilidad estructural y estereoquímica, y por el excesivo número de etapas sintéticas requeridas debido, principalmente, a la introducción de pasos de protección y desprotección. En cualquier caso, estas estrategias no están libres de que, ocasionalmente, conduzcan a mezclas diastereoméricas durante la generación de estereocentros adicionales. Por lo tanto, prestar especial atención a su control es siempre un aspecto de gran importancia.

Por otro lado, diferentes estudios sugieren que pequeñas modificaciones estructurales y estereoquímicas pueden provocar cambios considerables en su actividad biológica.[98] Como consecuencia, cualquier esfuerzo por desarrollar nuevas estrategias versátiles no basadas en el empleo de carbohidratos, que permitan introducir variaciones en el esqueleto y en la estereoquímica de indolizidinas polihidroxiladas representaría un avance significativo.

En este trabajo, presentamos una nueva aplicación de la estrategia expuesta anteriormente para acceder a indolizidinonas polihidroxiladas de manera estereocontrolada (*Esquema 2.24*). Para ello, introduciremos restos arilos (ruta **A**) y restos alquenilos (ruta **B**) en el triple enlace de la alquinilamida de partida, que aportarán, así, la primera diversificación estructural perseguida en los derivados finales.



Esquema 2.24. Propuesta retrosintética para la preparación de indolizidinonas.

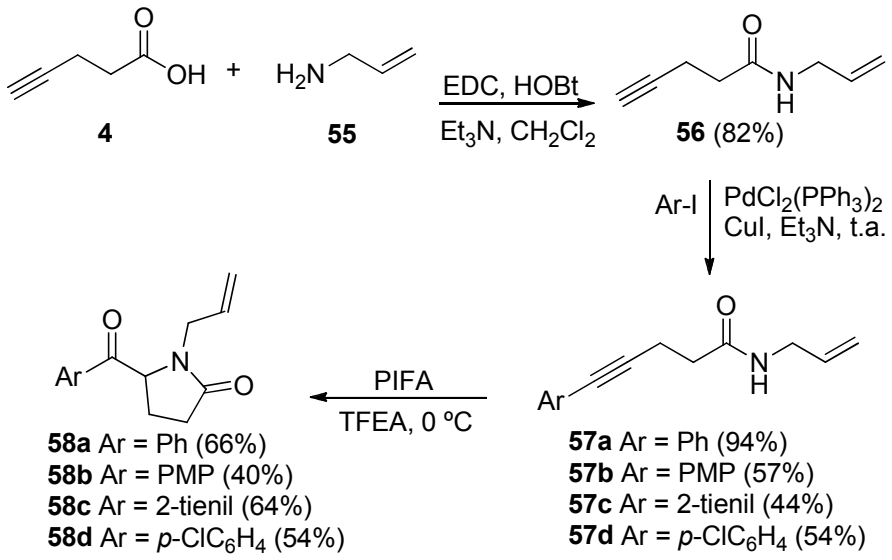
Tras una primera ciclación mediada por PIFA conducente a la construcción del esqueleto pirrolidinónico, desarrollaremos un grupo hidroxilo a partir del grupo cetónico, que finalmente estará presente en la posición C-8 de los futuros sistemas indolizidínicos, bien a través de un proceso de adición nucleófila con un organometálico, o bien por reducción del carbonilo cetónico. Planteamos también una segunda ciclación intramolecular catalizada por rutenio a partir de los dos restos olefínicos que dará lugar al esqueleto indolizidínico, cuyo doble enlace podrá ser

posteriormente modificado para dar lugar a nuevos derivados indolizidínicos.

3.1 Síntesis de 8-aril-8-hidroxiindolizidinonas a partir de 5-aril-4-pentinamidas.

Para poder acometer la síntesis de los compuestos proyectados se comenzó por preparar una serie de amidas lineales polifuncionalizadas. Para ello seleccionamos las pirrolidinonas **60a-d** como intermedios sintéticos clave del proceso. Estos derivados contienen un resto alílico y un resto vinílico que posibilitará la reacción de metátesis intramolecular (*Ring closing metathesis, RCM*).

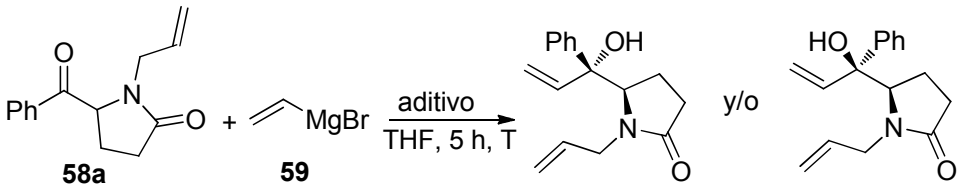
Así, la amida **56** fue preparada con buen rendimiento por reacción del ácido 4-pentinoico (**4**) con alilamina (compuesto comercial **55**) en presencia de HOBt y EDC·HCl como agentes activantes. Esta amida se sometió a la variante habitual de la reacción de Sonogashira, que requiere el empleo de CuI y $PdCl_2(PPh_3)_2$ como catalizadores, para incorporar el resto arilo terminal (compuestos **57a-d**). Una vez sintetizadas estas amidas, se procedió a su tratamiento con el reactivo PIFA, bajo las condiciones habituales, dando lugar a las pirrolidin-2-onas **58a-d** (*Esquema 2.25*).



Esquema 2.25. Preparación de las pirrolidinonas precursoras **58**.

A continuación, se evaluaron diferentes condiciones de reacción para introducir un resto vinílico sobre el carbono cetónico. Tal proceso se optimizó sobre la pirrolidinona **58a** (*Tabla 2.9*) por acción del bromuro de vinilmagnesio (**59**) asistida por distintos aditivos ($ZnCl_2$, $CeCl_3$, $Mg(ClO_4)_2$, CuI y éter 18-corona-6), a diferentes temperaturas en THF como disolvente. El objetivo de este estudio fue no solo verificar la viabilidad de la incorporación del resto vinílico en la posición adecuada, sino que, además, ésta tuviera lugar de modo diastereodivergente.

Tabla 2.9. Optimización de la reacción de adición al grupo cetónico en **58a**.



58a **59** **60a anti** (5R,1'R) **60a sin** (5R,1'S)

Entrada	59 (equiv.)	T (ºC)	Aditivo (equiv.)	60a anti:sin[(a)(b)]
1	1.75	refl.	---	67:33 (86%)
2	4.0	refl.	---	45:55
3	4.0	refl.	18-C-6 (4.0)	29:71
4	4.0	t.a.	---	29:71
5	4.0	t.a.	$ZnCl_2$ (1.1)	9:91
6	4.0	0	---	29:71
7	4.0	-20	---	17:83
8	4.0	-20	$Mg(ClO_4)_2$ (3.0)	---[(c)]
9	4.0	-20	$ZnCl_2$ (1.1)	5:95 (90%)
10	4.0	-20	CuI (4.0)	37:63
11	4.0	-20	18-C-6 (4.0)	37:63
12	1.5	-78	---	---[(c)]
13	2.2	-78	---	33:67
14	4.0	-78	---	23:77
15	4.0	-78	$ZnCl_2$ (1.1)	0:100[(d)]
16	4.0	-78	$CeCl_3$ (4.0)	29:71

[(a)] Nomenclatura sin/anti en relación a las posiciones de los grupos nitrogenado e hidroxilo en el esqueleto indolizidínico.

[(b)] A menos que se indique lo contrario, todos los ensayos concluyeron con la completa transformación del sustrato **58a**.

[(c)] Se recuperó el sustrato de partida inalterado.

[(d)] En los espectros de RMN se observó sustrato **58a**.

Los datos recogidos en la *Tabla 2.10* muestran que temperaturas elevadas favorecen la formación del producto anti, -si bien nunca se consiguió de manera totalmente estereoselectiva (*entrada 1*)-, mientras que a bajas temperaturas la formación del isómero sin fue preferente (*entradas 7, 13* y *14*). La presencia de un pequeño exceso de $ZnCl_2$, usando THF como disolvente y con un exceso del reactivo de Grignard a -20 ºC permitió la síntesis del compuesto **60a sin** de manera casi totalmente estereoselectiva con un rendimiento del 90% (*entrada 9*). No obstante, aunque a -78 ºC esta diastereoselectividad fue prácticamente total (*entrada 15*), la conversión no, obteniéndose una gran cantidad de sustrato de partida sin reaccionar. El empleo de aditivos, tales como éteres corona, organocéricos[104] y organocupratos[105] se ha introducido, como mostraban algunos precedentes, para promover la estereoselectividad de la reacción de adición nucleófila al carbonilo. Sin embargo, en nuestro caso, ninguno de los ensayos realizados en presencia de estos aditivos (*entradas 3,8,10* y *16*) permitió mejorar los resultados obtenidos en las *entradas 1* y *9* para la obtención de los compuestos **60a anti** y **60a sin**, respectivamente.

La diferente diastereoselectividad que muestra esta reacción puede explicarse en base a dos modelos teóricos propuestos para la adición nucleófila a cetonas (*Figura 2.8*). El modelo de Felkin-Ahn, con el que

104. (a) Liu, H.-J.; Shia, K.-S.; Shang, X.; Zhu, B.-Y. *Tetrahedron* **1999**, *55*, 3803. (b) Imamoto, T.; Hatajima, T.; Ogata, K. *Tetrahedron Lett.* **1991**, *32*, 2787.

105. Ejemplos sobre el uso de organocupratos en reacciones de adición: (a) Lopez, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2004**, *126*, 12784. (b) Kiyotsuka, Y.; Katayama, Y.; Acharya, H. P.; Hyodo, T.; Kobayashi, y. *J. Org. Chem.* **2009**, *74*, 1939.

explicamos la obtención preferente del isómero anti, requiere de una ordenación determinada que posibilite el ataque del nucleófilo con la menor oposición posible.[106] Por otro lado, el modelo quelato anula la movilidad conformacional del sustrato maximizando, por tanto, las diferencias en el ambiente estérico alrededor de las dos caras diastereotópicas del grupo carbonilo. En nuestro caso, el empleo de especies quelatantes debería rendir el diasteroisómero sin.[107]

106. Anh, N. T. *Top. Curr. Chem.* **1980**, *80*, 145.
107. Cram, D. J.; Abd-Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.

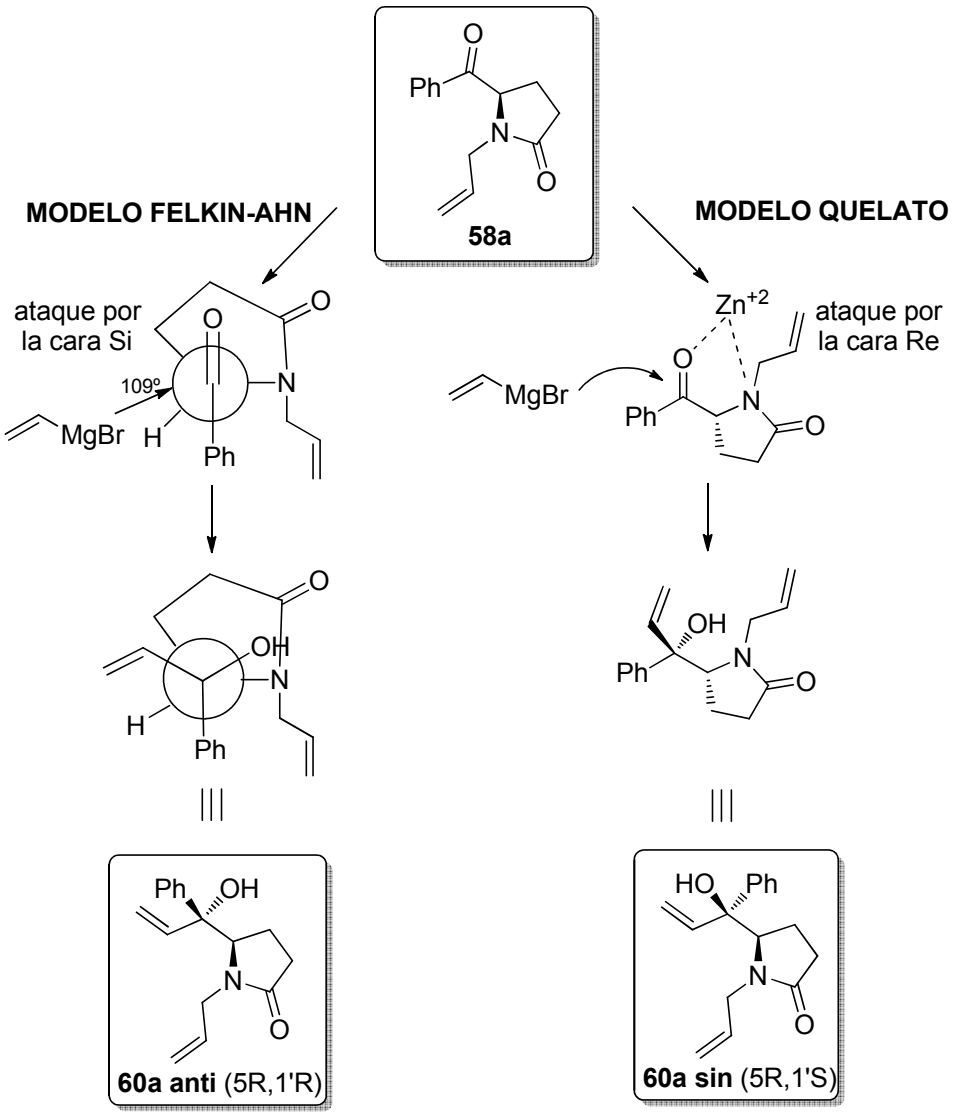
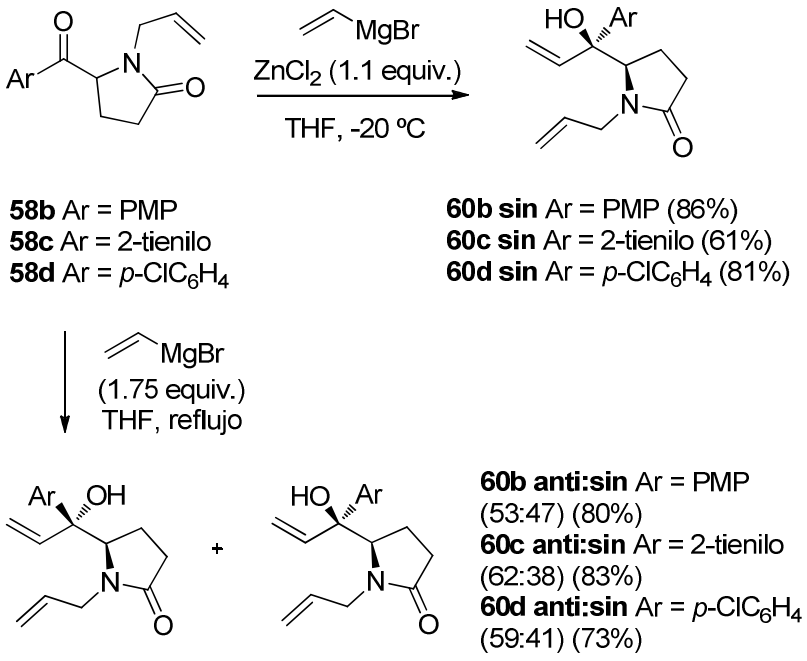


Figura 2.8. Modelos teóricos para la adición nucleófila a cetonas.

Una vez evaluadas las condiciones más eficientes para esta reacción, se procedió a extender el protocolo sintético a una serie de pirrolidinonas **60b-d** en sus dos formas diastereoméricas (*Esquema 2.26*). Especialmente notable es el hecho de que la proporción diastereomérica de los compuestos **60b-c**, resultante de la reacción de adición del vinilmagnesiano a las pirrolidinonas **58b-d**, llegue no solo a modificarse sino incluso a invertirse, lo que da muestras de lo sensible que es esta reacción tanto a factores experimentales como estructurales.



Esquema 2.26. Preparación de las pirrolidinonas **60**.

Cabe mencionar que, si bien la síntesis de los compuestos **60a-d anti** no se consiguió de manera estereoselectiva, las cuatro parejas de diastereoisómeros pudieron ser separadas por cromatografía en columna, y, por lo tanto, identificadas. Sin embargo, ante la imposibilidad de obtener cantidades significativas de este isómero, tanto por técnicas cromatográficas como por cristalización, se optó por continuar nuestros estudios sintéticos a partir de los derivados **60a-d sin**, por una parte, y a partir de mezclas diastereoméricas de los compuestos **60a-d**, enriquecidos en el isómero **anti**, por otra.

A fin de formar el esqueleto indolizidínico, las pirrolidinonas **60a-d** se sometieron a la reacción de metátesis olefínica.[108] La metátesis olefínica de cierre de anillo (*Ring Closing Methatesis, RCM*) permite la formación de alquenos cíclicos de diverso tamaño mediante el uso de catalizadores metálicos. Tal transformación no es sencilla de forma genérica por otros métodos, por lo que ha sido ampliamente empleada sobre todo en la síntesis de productos naturales.[109]

En nuestro caso particular, evaluamos la eficacia de los catalizadores de Grubbs de primera y segunda generación. Ambos catalizadores de rutenio son estables al aire y, si bien el descubrimiento del catalizador de Grubbs I mostró desde un inicio una alta selectividad y capacidad de iniciar

108. Una revisión sobre metátesis, isomerización olefínica y otras reacciones secundarias derivadas del uso de catalizadores de rutenio puede encontrarse en: Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865. Para ilustrar algún ejemplo del uso de la reacción RCM para la síntesis de indolizidinas, véase: Ben-Othman, R.; Othman, M.; Ciamala, K.; Knorr, M.; Strohmann, C.; Decroix, B. *Tetrahedron* **2009**, *65*. 4846.

109. Prunet, J. *Eur. J. Org. Chem.* **2011**, 3634.

el proceso de metátesis en presencia de alcoholes, agua y ácidos carboxílicos, su baja reactividad dio paso a una serie de mejoras que dieron lugar, entre otros, a la preparación del catalizador de Grubbs de segunda generación, Grubbs II, de idéntica aplicación al catalizador de Grubbs I, pero con mayor actividad (*Figura 2.9*). [110]

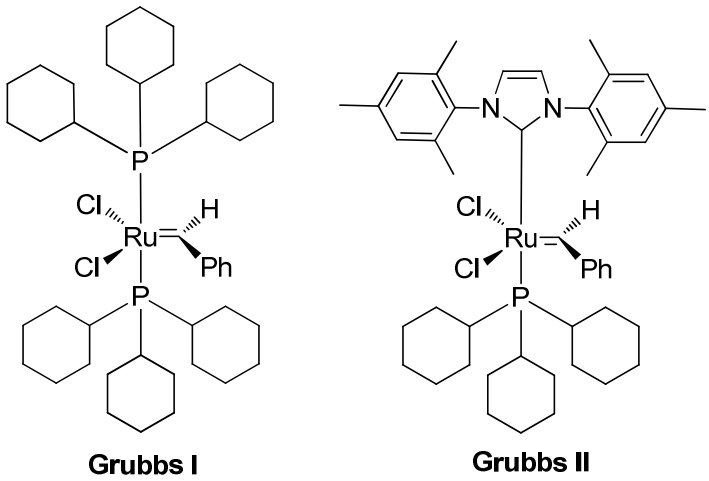


Figura 2.9. Catalizadores de Grubbs de primera y segunda generación.

En diversos ensayos preliminares llevados a cabo sobre la mezcla diastereomérica de la pirrolidinona **60a** se observaron resultados similares independientemente de la naturaleza del catalizador de Grubbs empleado,

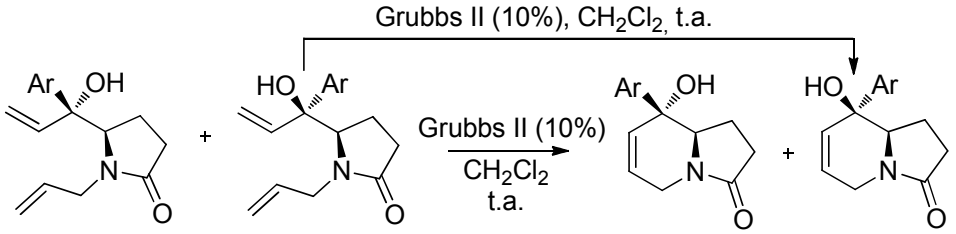
110. Una revisión reciente sobre los catalizadores de Grubbs: Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev*. **2010**, *110*, 1746.

así como en relación a la temperatura de reacción (temperatura ambiente y de reflujo) o en relación al disolvente (tolueno o diclorometano).

En atención a los rendimientos de reacción obtenidos ligeramente superiores y a lo suave de las condiciones empleadas, se optó finalmente por usar el catalizador de Grubbs de segunda generación, a temperatura ambiente y con diclorometano como disolvente. Una vez seleccionadas las condiciones, se aplicaron a la serie **60b-d** lo que condujo a las correspondientes indolizidinonas **61a-d**, tal y como se muestra en la *Tabla 2.10*. Así, cuando se empleó la mezcla de isómeros como sustrato (*entradas 1*, *3*, *5* y *7*), esa misma proporción diastereomérica se mantuvo en los productos, lo que muestra ausencia de epimerización en el transcurso del proceso. Por otro lado, no se observa ningún tipo de tendencia diferenciada en la reacción en función del resto arilo o del diastereoisómero presente en el sustrato de partida.[111]

111. La caracterización estructural de estos compuestos se realizó mediante diversos experimentos de RMN, tanto de protón como de carbono trece, monodimensionales y bidimensionales. Una vez obtenida la estereoquímica de estos compuestos bicíclicos se infirió la de los compuestos acíclicos precursores.

Tabla 2.10. Reacción de metátesis olefínica de los compuestos **60a-d.**



60a-d anti:sin **61a-d anti:sin**

Entrada	Sustrato	60a-d anti:sin	61a-d anti:sin (rdto.)[a]
1	**60a** Ar = Ph	67:33	**61a** 67:33 (66%)
2		0:100	**61a** 0:100 (65%)
3	**60b** Ar = PMP	53:47	**61b** 53:47 (60%)
4		0:100	**61b** 0:100 (65%)
5	**60c** Ar = 2-Tienilo	62:38	**61c** 62:38 (69%)
6		0:100	**61c** 0:100 (60%)
7	**60d** Ar = *p*-ClC_6H_4	59:41	**61d** 59:41 (65%)
8		0:100	**61d** 0:100 (58%)

[a] Rendimiento de producto cromatográficamente puro.

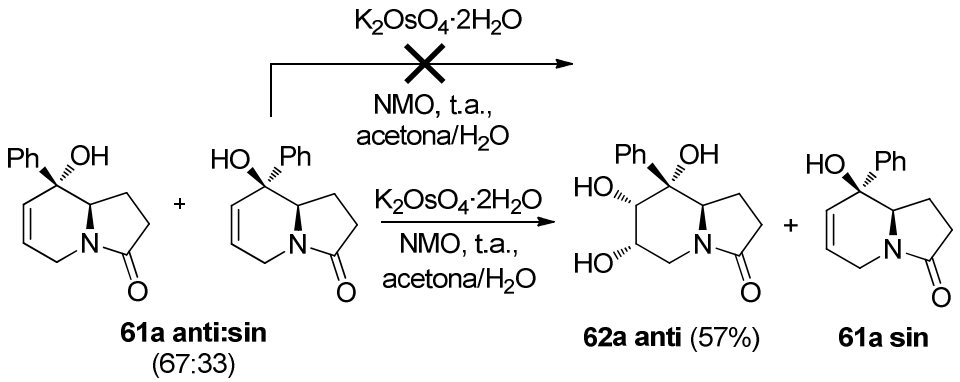
3.1.1. Ensayos de dihidroxilación.

Tal y como hemos comentado anteriormente, una de las características más atractivas que ofrece nuestra estrategia radica en el hecho de que el esqueleto indolizidínico formado presenta un doble enlace en su estructura, lo que constituye un nuevo punto de diversificación funcional. Debido a la actividad biológica y terapeútica que presentan las indolizidinonas polihidroxiladas, descrita en el inicio de este capítulo, decidimos dihidroxilar los compuestos **61a-d**, extendiendo así, nuestra aproximación al acceso a nuevos compuestos indolizidínicos polihidroxilados.

El proceso de conversión de un doble enlace en un diol vecinal con estereoquímica relativa sin ha sido ampliamente estudiado. Entre los procedimientos más comúnmente empleados para este fin se encuentra el método de Upjohn,[112] que requiere el uso de una cantidad catalítica de tetróxido de osmio junto con N-metilmorfolina-N-óxido (NMO) como oxidante primario. En nuestro caso, se evaluó una variante de estas condiciones, inicialmente con el compuesto **61a**, en la que, debido a su alta toxicidad, el tetróxido de osmio se sustituyó por el osmiato de potasio dihidratado ($K_2OsO_4 \cdot 2H_2O$) (*Esquema 2.27*). Cuando la reacción se llevó a cabo con el isómero **61a sin**, el empleo de estas condiciones no resultó en el compuesto deseado, obteniéndose el sustrato inalterado. Sin embargo,

112. (a) VanRheenen, V.; Kelly, C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973. (b) Deubel, D. V.; Frenking, G. *Acc. Chem, Res*. **2003**, *36*, 645.

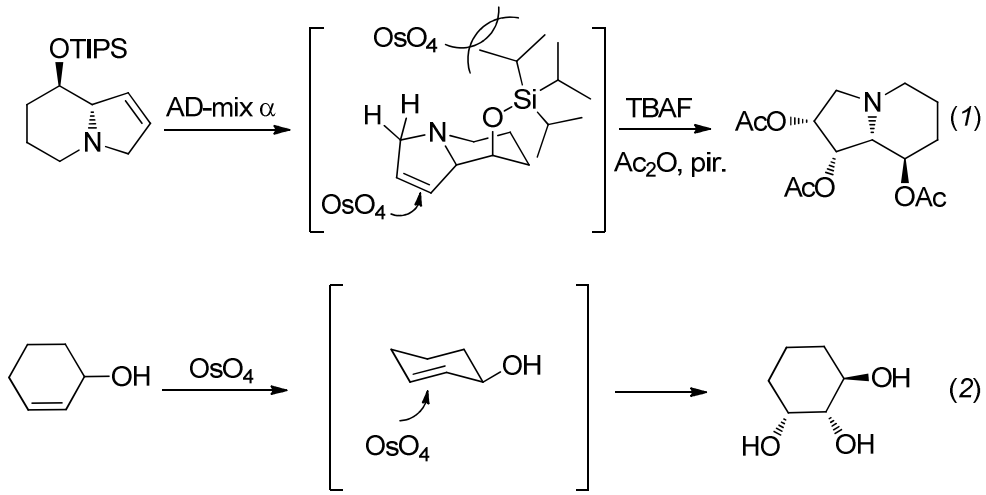
cuando la mezcla diastereomérica **61a anti:sin** (en este caso de proporción 67:33) se trató bajo idénticas condiciones de reacción, únicamente el diastereoisómero anti evolucionó hacia el correspondiente compuesto **62a anti**, con rendimiento moderado, dejando al estereoisómero **61a sin** nuevamente inalterado.



Esquema 2.27. Reacciones de dihidroxilación.

La literatura consultada acumula un buen número de precedentes en los que se señala que la estereoquímica de los produtos de dihidroxilación con catalizadores de osmio puede venir determinada tanto por efectos estéricos como por efectos electrónicos. En el *Esquema 2.28* (*reacción 1*) se describe la dihidroxilación de una indolizidinona C(8)-sililoxilada con un catalizador de osmio (AD-mix α) para la que, con el fin de evitar la interacción no enlazante entre el agente dihidroxilante y los hidrógenos axial

del carbono 8a y alílico y el gran impedimento estérico creado por el gran volumen del grupo protector sililado, el ataque del catalizador tiene lugar por la cara opuesta a éste, formando el compuesto *cis* dihidroxilado como el producto mayoritario.[113] En la reacción siguiente (*reacción 2*) se muestra el primer ejemplo descrito en el que se observa cómo los efectos electrónicos que se generan entre el grupo hidroxilo y el OsO_4 dirigen la reacción de modo que el catalizador se aproxima preferentemente por la cara opuesta a éste. [114]



Esquema 2.28. Ejemplos sobre la influencia de efectos estéricos y electrónicos en la estereoquímica de la reacción de dihidroxilación.

113. Ceccon, J.; Greene, A. E.; Poisson, J. –F. *Org. Lett.* **2006**, *8*, 4739.
114. (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247. (b) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. (c) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947.

Nuestra hipótesis para explicar el hecho de que solo el diastereoisómero **61a anti** reaccione, así como el resultado estereoquímico de su transformación, se basa en la diferente conformación preferente que adoptarían estas moléculas. Según nuestra propuesta, el resultado de la reacción vendrá dado por cuál de los grupos (hidroxilo o fenilo) ocupará las posiciones pseudoaxial y pseudoecuatorial en cada uno de los dos diastereoisómeros. Así, proponemos que, en el caso de la molécula **61a anti**, el grupo fenilo, ubicado en una posición pseudoaxial, bloquea el acercamiento del reactivo de osmio al doble enlace por la cara en donde se encuentra. El grupo hidroxilo estaría en una posición pseudoecuatorial que lo aleja de la nube π del doble enlace, aminorando el efecto repulsivo electrónico que se opondría al acercamiento del reactivo por su misma cara. Sin embargo, en el caso de la molécula **61a sin**, este último efecto estaría más acusado al disponerse el grupo hidroxilo en la posición pseudoaxial. Si a ello añadimos que el grupo fenilo sigue manifestando su control estérico, a pesar de alejarse en una posición pseudoecuatorial, podremos explicar la inercia de este diastereoisómero a la acción del agente de dihidroxilación (*Figura 2.10*).

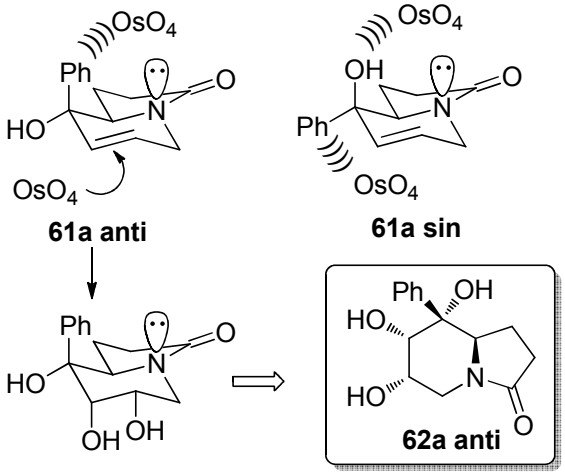


Figura 2.10. Probable explicación de la estereoquímica desarrollada en el triol **62a anti**.

Este razonamiento es coherente con el resultado estereoquímico "todo sin" para referirnos a la disposición relativa de los tres grupos hidroxilos en el producto **62a anti**.

Con objeto de conseguir la dihidroxilación deseada sobre el isómero **61a sin**, se ensayaron otros métodos bien reconocidos que posibilitan esta transformación. Así, el empleo de $KMnO_4$ da lugar a un éster cíclico que resulta hidrolizado en medio acuoso básico (*Esquema 2.29, Reacción 1*).

Otro método de dihidroxilación, empleado principalmente en la preparación enantioselectiva de 1,2-dioles a partir de olefinas proquirales, es

la dihidroxilación de Sharpless.[115] Este procedimiento consiste en el uso de preparados comerciales (AD-mix α y AD-mix β) que contienen un catalizador de osmio, un oxidante y un ligando quiral (generalmente $(DHQD)_2PHAL$, $(DHQ)_2PHAL$ o derivados). El ligando acelera la reacción y transfiere la información quiral. (*Esquema 2.29, Reacción 2*).

Según Donohue y colaboradores,[116] el uso de TMEDA como aditivo en la reacción de dihidroxilación resulta en la formación de un complejo OsO_4/TMEDA que es capaz de realizar las dihidroxilaciones de manera sin selectiva. También se han publicado recientemente progresos en el uso del reactivo de yodo hipervalente PIFA en reacciones de síntesis de 1,2-dioles,[117] previa formación de un producto bis(trifluoroacetoxilado) que posteriormente será hidrolizado bajo condiciones básicas (*Esquema 2.29, Reacción 3*).

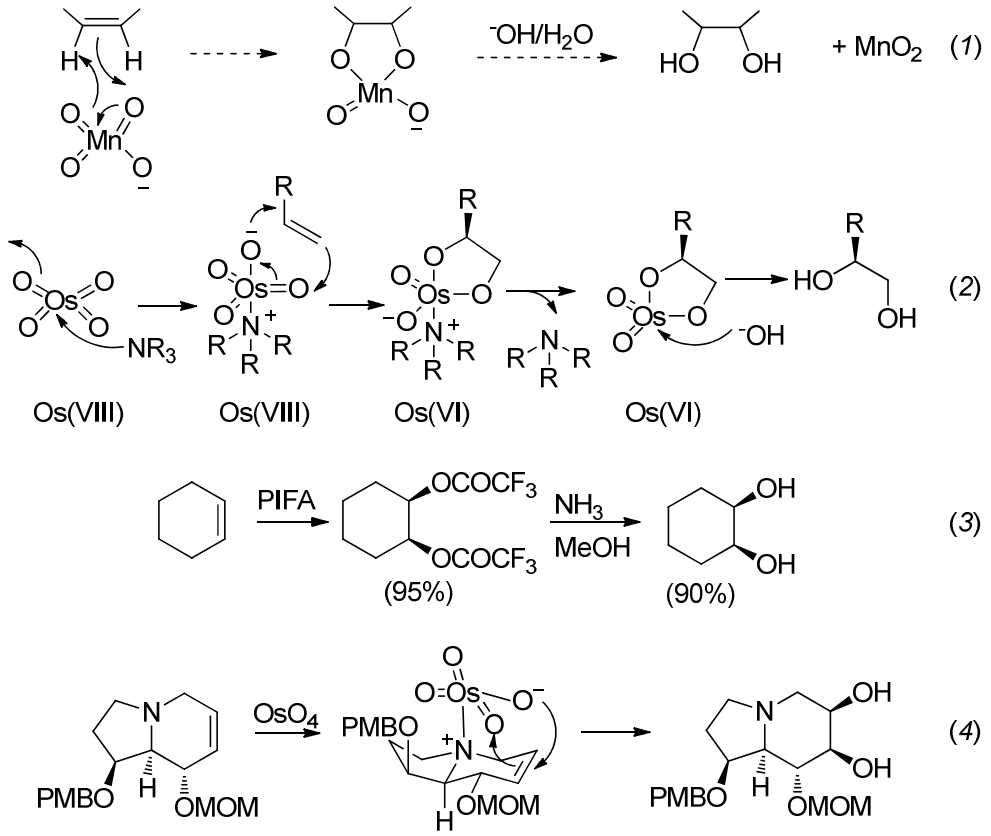
Nuestra propia experiencia indicó, sin embargo, que ninguno de estos procedimientos relatados anteriormente resultó en la obtención de los dihidroxi derivados deseados, recuperándose en todos los casos, tanto para el sustrato **61a anti** como para **61a sin**, el producto de partida inalterado.

---

115. Para una revisión sobre la dihidroxilación catalítica asimétrica, véase: (a) Zaitsev, A. B.; Adolfsson, H. *Synthesis* **2006**, 1725. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

116. Donohue, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946.

117. (a) Çelik, M.; Alp, C.; Coşkun, B.; Gütelkin, M. S.; Balci, M. *Tetrahedron Lett.* **2006**, *47*, 3659. (b) Tellitu, I.; Domínguez, E. *Tetrahedron*, **2008**, *64*, 2465

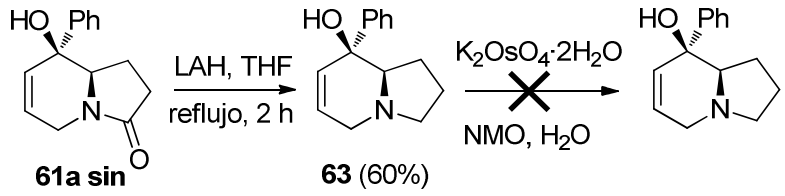


Esquema 2.29. Métodos de dihidroxilación ensayados.

Recientemente se han publicado diversos trabajos en los que la sin diastereoselectividad de la reacción de dihidroxilación con osmio se ha explicado mediante la formación de un intermedio en el que el par de electrones del nitrógeno adopta una configuración trans en la molécula para

formar un complejo con el osmio y dirigir la adición. (*Esquema 2.29, Reacción 4*).[118]

En base a este precedente, y para evitar que la capacidad coordinante del átomo de nitrógeno no se vea aminorada por su carácter amídico, se optó por reducir el grupo carbonilo del compuesto **61a sin**, en este caso con hidruro de litio y aluminio, para dar lugar al compuesto **63** con un rendimiento del 60%. A continuación, el compuesto **63** se sometió a las condiciones Upjohn ya mencionadas pero, desgraciadamente dieron lugar nuevamente al producto de partida sin alterar (*Esquema 2.30*).

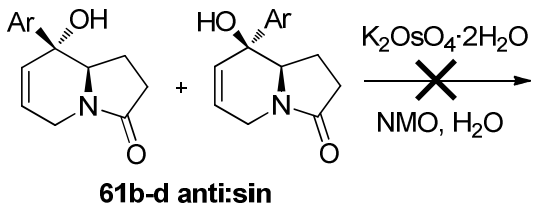


Esquema 2.30. Ensayos para la dihidroxilación del esqueleto indolizidínico.

Lamentablemente y, a pesar del esfuerzo empleado, ninguno de los métodos ensayados dio lugar al compuesto deseado, de tal modo que concluimos que la reacción de dihidroxilación únicamente tiene lugar bajo condiciones Upjohn. Así, aplicamos estas condiciones al resto de la serie de indolizidinonas **61b-d** pero, desgraciadamente y de modo inexplicable para

118. Louvel, J.; Botuha, C.; Chemla, F.; Demont, E.; Ferreira, F.; Pérez-Luna, A. *Eur. J. Org. Chem.* **2010**, 2921.

nosotros, en todos los casos se obtuvo el producto de partida sin reaccionar, siendo **62a anti**, por lo tanto, la única indolizidinona polihidroxilada que pudimos preparar (*Esquema 2.31*).



61b-d anti:sin

Esquema 2.31. Ensayos para la dihidroxilación de los compuestos **61b-d**.

La determinación estructural del compuesto **62a anti** se realizó mediante diversos experimentos de RMN de protón y de carbono trece tanto monodimensionales como bidimensionales. En la *Figura 2.11* se muestra, a modo de ejemplo, los experimentos NOE selectivos realizados sobre los protones H-7 y H-8a del compuesto **62a anti**, donde puede obsevarse la relación entre H-6 y H-7.

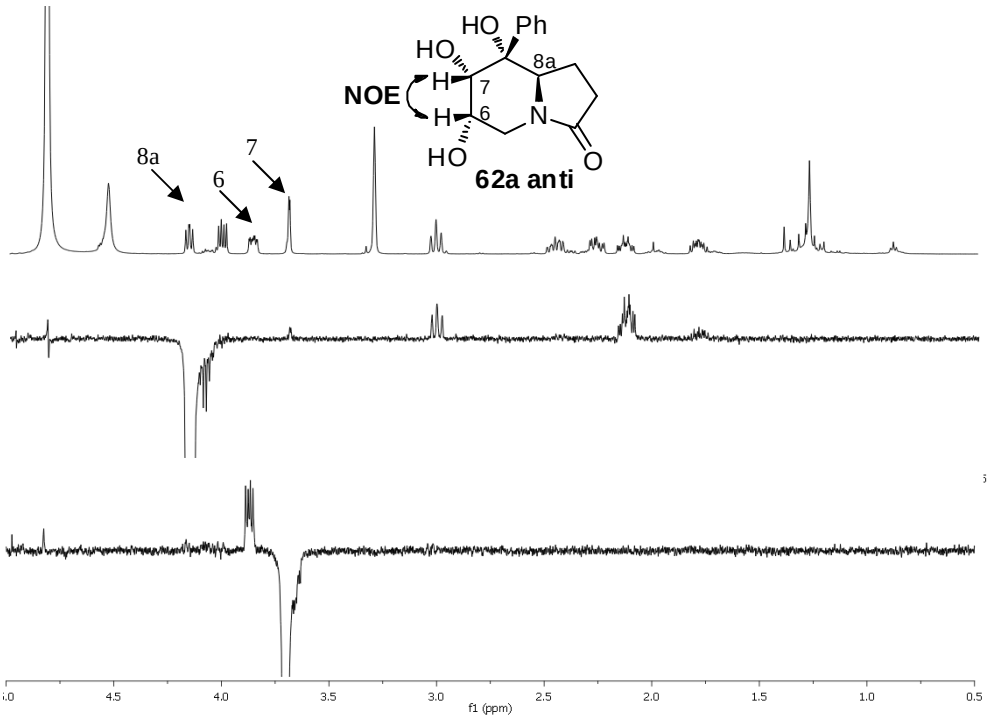


Figura 2.11. Espectro NOE selectivo realizado sobre el compuesto **62a anti**.

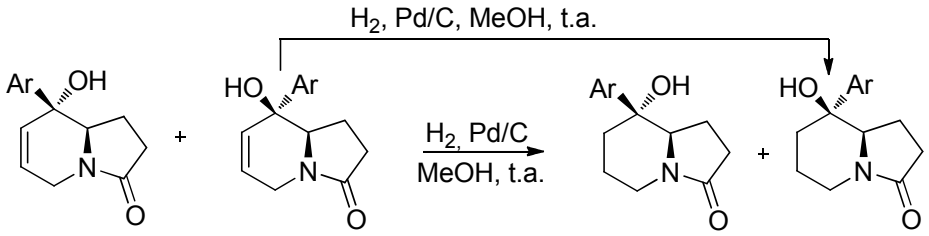
3.1.2. Ensayos de hidrogenación.

Si bien hasta ahora nos habíamos centrado en preparar esqueletos indolizidínicos polihidroxilados, decidimos sintetizar, a partir de las indolizidinas insaturadas **61**, estructuras carentes de funcionalización en las posiciones C-6 y C-7 del anillo. Este tipo de esqueletos también está presente en diferentes productos naturales como, por ejemplo, la lentiginosina y la swainsonina.

Para ello, la mezcla anti:sin de la indolizidinona **61a** se sometió a condiciones de hidrogenación catalítica. En esta ocasión, ambos isómeros reaccionaron, para dar lugar, de este modo, a los compuestos **64a anti** y **64a sin** con rendimientos moderados y sin que la proporción diastereomérica se alterara. A pesar de los esfuerzos realizados, no conseguimos separar los isómeros resultantes mediante técnicas cromatográficas o de cristalización. Un experimento posterior sobre el compuesto **61a sin** permitió la obtención del compuestos **64a sin** de manera aislada, lo cual facilitó la determinación estructural de la mezcla de isómeros **64a sin:anti** anteriormente formada.

La extensión de esta reacción a la serie de indolizidinonas **61b-d** permitió la síntesis de los compuestos **64b-d** con rendimientos moderados, como se muestra en la *Tabla 2.11*.

Tabla 2.11. Reacción de hidrogenación de los compuestos **61b-d**.



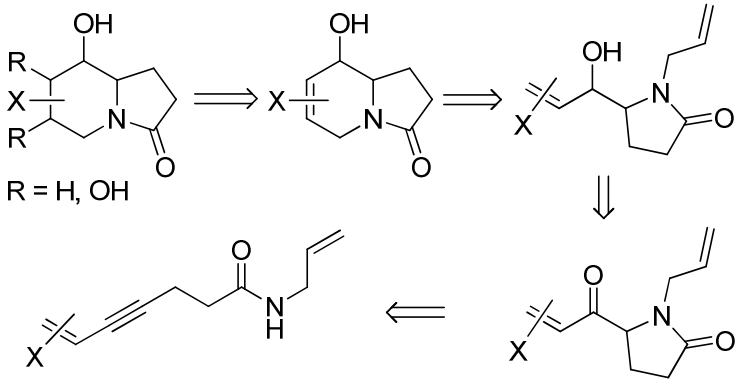
61a-d anti:sin **64a-d anti:sin**

Entrada	Sustrato	61a-d anti:sin	64a-d anti:sin (rdto.)[a]
1	**61a** Ar = Ph	67:33	**64a** 67:33 (69%)
2		0:100	**64a** 0:100 (60%)
3	**61b** Ar = PMP	53:47	**64b** 53:47 (67%)
4		0:100	**64b** 0:100 (63%)
5	**61c** Ar = 2-tienilo	62:38	**64c** 62:38 (68%)
6		0:100	**64c** 0:100 (56%)
7	**61d** Ar = *p*-ClC_6H_4	59:41	**64d** 59:41 (65%)
8		0:100	**64d** 0:100 (53%)

[a] Rendimiento de producto cromatográficamente puro.

3.2 Síntesis de 8-hidroxiindolizidinonas a partir de 5-alquenil-4-pentinamidas.

Una vez evaluada la viabilidad del diseño sintético frente a la obtención de derivados indolizidínicos C(8)-aril sustituidos, se comenzó el estudió de su adecuación a sustratos alquinilamídicos con grupos alquenilos de diferente naturaleza en la posición terminal del triple enlace. Conseguiríamos así una ruta de fácil acceso hacia la síntesis del esqueleto indolizidínico, presente en numerosos productos naturales, y cuya sustitución en las posiciones C(6) y C(7) (X, en el *Esquema 2.32*) vendría dada por la estructura del resto olefínico insertado en el triple enlace.



Esquema 2.32. Retrosíntesis para el acceso a los derivados indolizidínicos.

Aún con la mente puesta en la incorporación en el esqueleto final de otras variables estructurales, y siguiendo la pauta del apartado anterior, se

comenzó por la preparación de la pirrolidinona **68a**, un intermedio sintético clave que contiene un resto alílico y un resto olefínico que posibilitarán, posteriormente, una reacción de ciclación intramolecular para dar lugar a los productos bicíclicos objetivo.

Para la incorporación del resto estirilo terminal sobre la amida **56** se empleó la variante de la reacción de Sonogashira habitual, que requiere CuI y $PdCl_2(PPh_3)_2$ como catalizadores. En esta ocasión, al tratarse de un compuesto no comercial, el (*E*)-β-bromoestireno requerido (compuesto **65**) hubo de ser preparado a través de una reacción de Hunsdiecker a partir del ácido *trans*-cinámico y de la N-bromosuccinimida siguiendo procedimientos bibliográficos.[119] Sin embargo, cuando se enfrentó al alquino **56**, la reacción de Sonogashira no dio lugar al producto de acoplamiento deseado (compuesto **66a**), sino únicamente al compuesto **67**, resultado de un doble acoplamiento tanto sobre la posición deseada como sobre el átomo de nitrógeno amídico.[120] Por ello, decidimos modificar las condiciones de reacción elevando la temperatura y haciendo participar a la trifenilfosfina como cocatalizador. Todo ello resultó en la obtención del compuesto **66a** con un rendimiento moderado, cuyo posterior tratamiento con el reactivo PIFA, bajo las condiciones habituales, dio lugar a la pirrolidin-2-ona **68a** con un rendimiento sintéticamente aceptable (*Esquema 2.33*).

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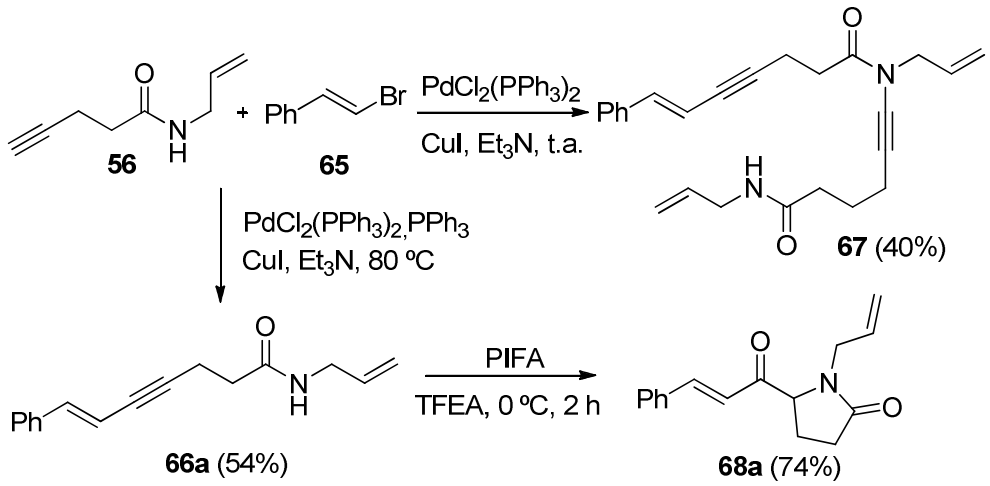
119. Tanto el procedimiento experimental como los datos espectroscópicos del compuesto **65** pueden encontrarse en: Chowdhury, S.; Roy, S. *J. Org. Chem.* **1997**, *62*, 199.

120. Ejemplos de este tipo de acoplamientos N-Csp pueden encontrase en: (a) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011. (b) Villeneuve, K.; Riddell, N.; Tam, W. *Tetrahedron* **2006**, *62*, 3823.

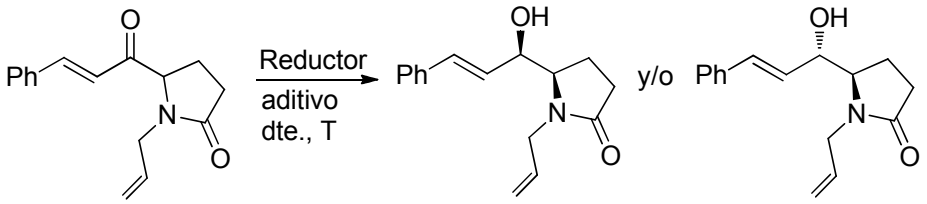


Esquema 2.33. Preparación de la pirrolidinona precursora **66a**.

A continuación, se evaluaron distintas condiciones de reacción para transformar el grupo cetónico de la pirrolidinona **68a** en una función hidroxilo de modo diastereoselectivo.[121] En nuestro caso, realizamos una serie de experimentos (*Tabla 2.12*) que nos permitió valorar el comportamiento de este compuesto frente a varios agentes reductores ($NaBH_4$, L-selectride, DIBAL-H y BH_3·THF), en presencia y ausencia de distintas sales metálicas ($ZnCl_2$, $CeCl_3$, $NiBr_2$ y $TiCl_4$) y en distintos disolventes (MeOH, tolueno, THF y CH_2Cl_2) y temperaturas.

121. (a) Kim, B. C.; Lee, W. K. *Tetrahedron* **1996**, *52*, 12117. (b) Yun, J. M.; Sim, T. B.; Hahm, H. S.; Lee, W. K. *J. Org. Chem.* **2003**, *68*, 7675.

Tabla 2.12. Ensayos encaminados a la optimización de la reacción de reducción de la pirrolidinona **68a.**



68a **69a sin** (5R,1'R) **69a anti** (5R,1'S)

Entrada	Reductor (equiv.)	Aditivo (equiv.)	T (ºC)	t (horas)	Dte.	69a sin:anti[(a)(b)]
1	$NaBH_4$ (2.0)	---	0	0.5	MeOH	70:30
2	$NaBH_4$ (2.0)	$CeCl_3$ (1.5)	0	0.5	MeOH	75:25
3	$NaBH_4$ (2.0)	$NiBr_2$ (1.5)	-78	0.5	MeOH	68:32
4	$NaBH_4$ (2.0)	$ZnCl_2$ (2.0)	-78	2	MeOH	37:63 (46%)
5	$NaBH_4$ (2.0)	$TiCl_4$ (1.5)	-78	0.5	MeOH	---[(c)]
6	L-selectride (2.0)	---	-78	0.5	THF	100:0 (70%)
7	L-selectride (2.0)	$ZnCl_2$ (1.5)	-78	0.5	THF	100:0
8	DIBAL-H (2.0)	---	-78	12	Tolueno	---[(c)]
9	BH_3·THF (5.0)	---	reflujo	0.5	THF	---[(d)]

[(a)] Nomenclatura sin/anti en relación a las posiciones de los grupos nitrogenado e hidroxilo en el futuro esqueleto indolizidínico.
[(b)] A menos que se indique lo contrario, todos los ensayos concluyeron con la completa transformación del sustrato **68a**.
[(c)] Se recuperó el sustrato de partida inalterado.
[(d)] En los espectros de RMN se observaron mezclas de productos sin determinar.

Por su sencillez experimental decidimos comenzar este estudio por valorar el comportamiento de $NaBH_4$ como agente reductor. El resultado de

su acción sobre **68a** condujo a la formación del compuesto **69a sin** con una diastereoselectividad moderada (*entradas 1-3*). Sin embargo, el uso de un reductor más voluminoso, como es el organoborano L-selectride, dio lugar al compuesto **69a sin** como único producto de reacción (*entradas 6* y *7*). El uso de agentes coordinantes como aditivos (*entradas 2-5*) nos permitió variar la proporción diastereomérica de la reacción, excepto con el uso de tetracloruro de titanio (*entrada 5*), ya que inactivó por completo al sustrato. El empleo de otros agentes reductores (DIBAL-H y BH_3·THF) condujo a la obtención tanto del sustrato de partida sin alterar (*entrada 8*), como de mezclas de productos sin identificar (*entrada 9*). Desafortunadamente, la síntesis del compuesto **69a anti** no pudo llevarse a cabo de manera estereoselectiva, si bien los isómeros pudieron separarse mediante cromatografía en columna para su completa caracterización estructural.

La diastereoselectividad que presenta la reacción puede explicarse de modo análogo a como se explicó la transformación de **58a** (*Figura 2.8*, página 190). Así, fijado el confórmero más reactivo que predice el modelo Felkin-Ahn, el ataque del L-selectride provocará su conversión en el estereoisómero **69a sin** de modo exclusivo. En presencia de $ZnCl_2$ (y de modo menos relevante para el resto de aditivos ensayados) por el contrario, el estereocontrol viene fijado por la acusada discriminación de las dos caras diastereotópicas del grupo carbonilo a reducir una vez que el sustrato quelatado es sometido a rigidez conformacional. No obstante, el hecho de que el grado de diasterocontrol conducente al compuesto **69a anti** no sea el óptimo está indicando que la estabilidad de dicho quelato, en relación a su

forma abierta, es limitada, probablemente debido a la menor basicidad del nitrógeno amídico (*Figura 2.12*).

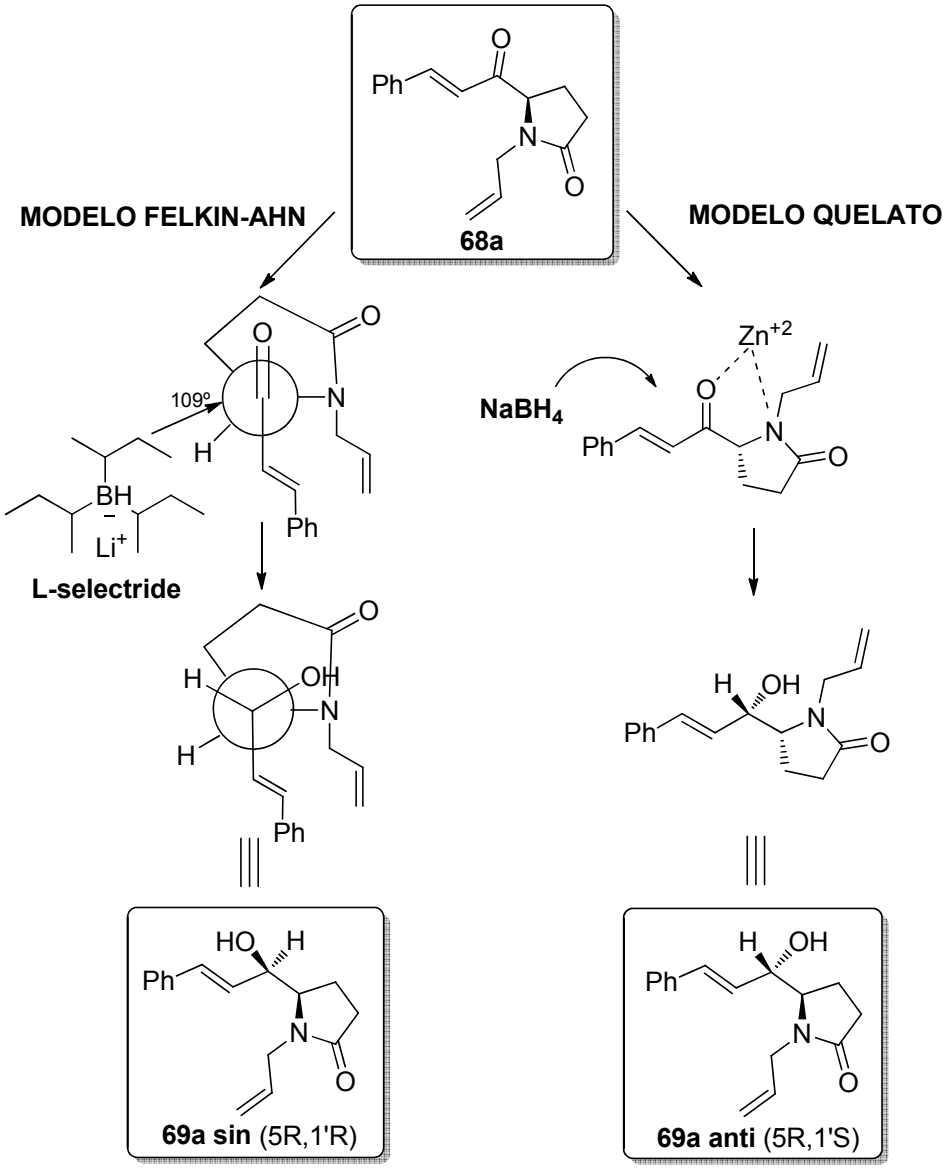
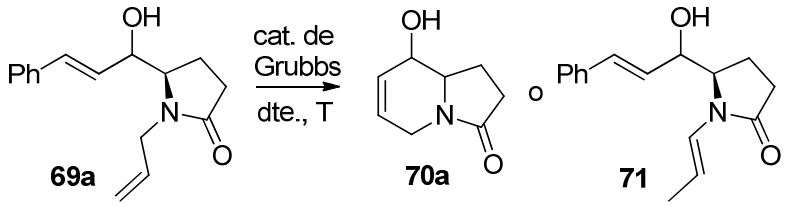


Figura 2.12. Modelos teóricos para la reducción estereocontrolada del grupo cetónico en **68a**.

A continuación, y con objeto de formar el esqueleto indolizidínico proyectado, la mezcla diastereomérica de las pirrolidinonas **69a** se sometió a la reacción de metátesis olefínica. Durante el proceso de optimización de esta etapa, se evaluó el uso de los catalizadores de Grubbs I y II, así como el empleo de distintos disolventes y temperaturas de reacción. Así, según muestra la *Tabla 2.13*, la transformación deseada para obtener el compuesto **70a** solo tuvo lugar en presencia del catalizador de Grubbs II a reflujo de tolueno (*entrada 4*). En el resto de los casos (*entradas 1-3*), se obtuvo el compuesto **71** como resultado de la isomerización del doble enlace alílico.

Teniendo en cuenta los resultados mostrados anteriormente (*Tabla 2.11*, página 207), parece evidente que la necesidad de aumentar la temperatura de reacción para vencer la inercia del sustrato viene motivada por la sustitución de la olefina. De hecho, en los casos anteriores con olefinas terminales (transformación de **60** en **61**), la reacción de ciclación transcurre bajo condiciones suaves asistida por cualquiera de los dos catalizadores de Grubbs I o Grubbs II.

Tabla 2.13. Evaluación de diferentes condiciones de reacción de metátesis olefínica ensayadas sobre **69a**.



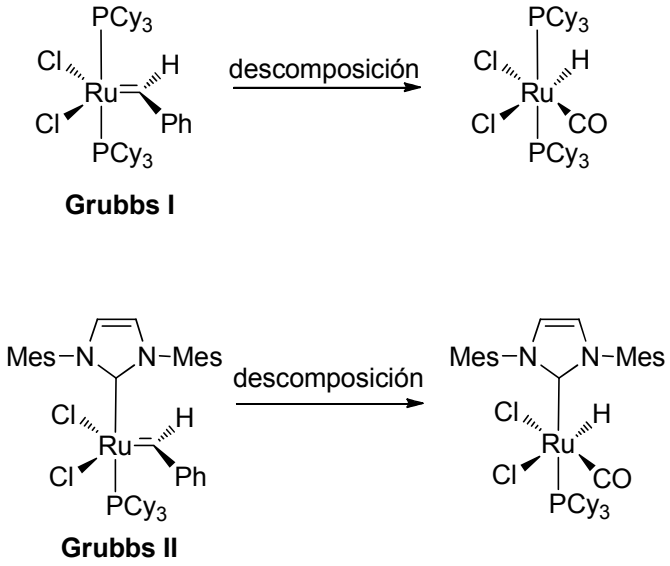
69a **70a** **71**

Entrada	Catalizador	T (ºC)	Disolvente	Producto
1	Grubbs II	t.a.	CH_2Cl_2	**71**
2	Grubbs II	reflujo	CH_2Cl_2	**71**
3	Grubbs I	reflujo	Tolueno	**71**
4	Grubbs II	reflujo	Tolueno	**70a** (80%)[(a)]

[(a)] Rendimiento de producto cromatográficamente puro.

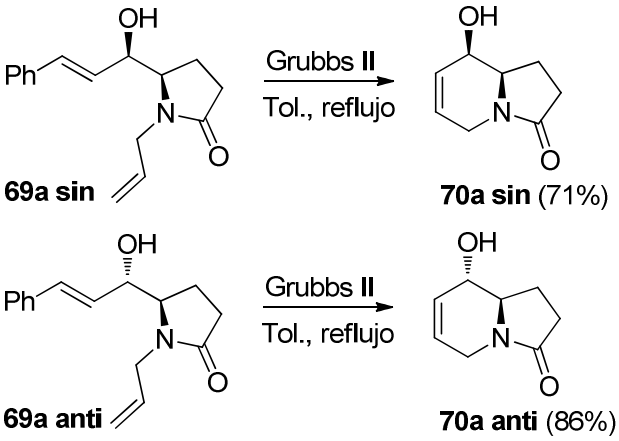
La isomerización de olefinas y la propia reacción de RCM son dos procesos que pueden coexistir bajo unas mismas condiciones de reacción, y si bien el mecanismo para aquélla no es aún completamente conocido, suele responsabilizarse al hidruro de rutenio, especie generada *in situ* a partir de la degradación del catalizador de Grubbs (*Esquema 2.34*).[122]

122. Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414. Con respecto al uso del catalizador de Grubbs II para la reacción de isomerización de olefinas, como ocurre en nuestro caso, puede consultarse: (a) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4732. (b) Kobayashi, T.; Mitsuhiro, A.; Shuto, S. *Org. Biomol. Chem.* **2011**, *9*, 1219. (c) Donohue, T. J.; O'Riordan, T. J. C.; Rosa, C. P. *Angew. Chem. Int. Ed.* **2009**, *48*, 1014.



Esquema 2.34. Hidruros de rutenio generados por la descomposición de los catalizadores de Grubbs I y II.

Una vez seleccionadas las condiciones de reacción más adecuadas, sometimos a las pirrolidinonas **69a sin** y **69a anti**, de modo independiente, a tratamiento con el catalizador GII a reflujo de tolueno. Tal experimento dio como resultado la obtención de los correspondientes productos de ciclación indolizidínicos **70a sin** y **70a anti** con buenos rendimientos y sin aparente epimerización en ninguno de los dos estereocentros del sustrato de partida (*Esquema 2.35*).



Esquema 2.35. Reacción de metátesis olefínica (RCM). Construcción del esqueleto indolizidínico **70**.

La caracterización estructural y estereoquímica de estas moléculas se realizó mediante diversos experimentos de RMN tanto monodimensionales como bidimensionales. En la *Figura 2.13* se muestra, a modo de ejemplo, los espectros NOE selectivos realizados para el compuesto **70a sin**, donde se observa la relación existente entre los protones H-8 y H-8a que confirma su estructura.

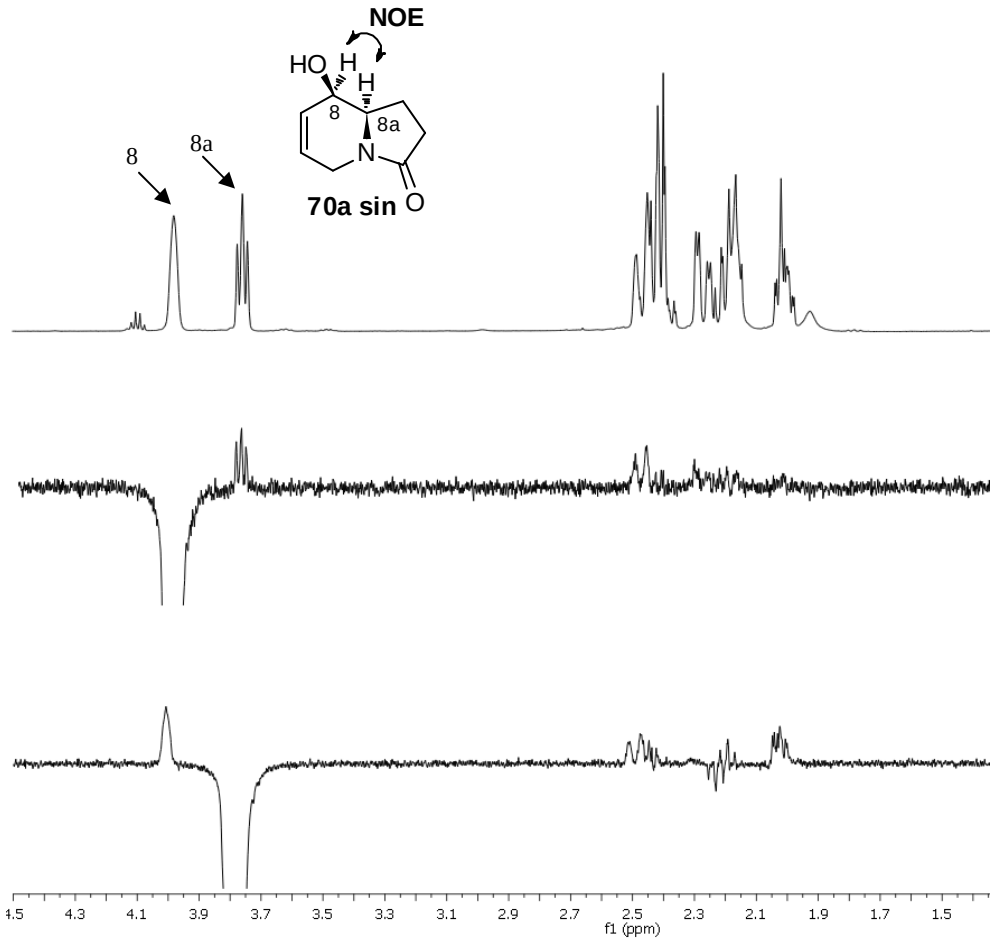
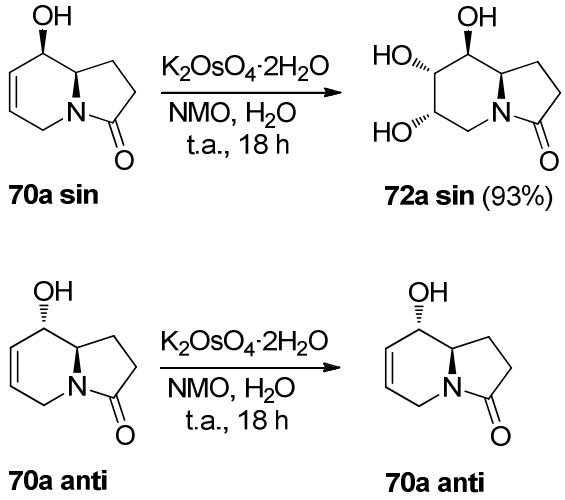


Figura 2.13. Espectro NOE selectivo realizado sobre la indolizidinona **70a sin**.

A continuación y, de modo semejante a lo descrito en el apartado anterior, decidimos extender nuestra aproximación a nuevos compuestos indolizidínicos. Para ello sometimos a los compuestos **70a sin** y **70a anti** a

las condiciones de dihidroxilación e hidrogenación ya optimizadas para los compuestos **61a-d**.

Así, la reacción de dihidroxilación sobre **70a sin** se llevó a cabo empleando la variante de Upjohn habitual ($K_2OsO_4 \cdot H_2O$, NMO, H_2O), lo cual condujo a la formación del compuesto **72a sin** para el que el control estereoelectrónico ejercido por el grupo hidroxílico en el sustrato de partida orienta la entrada del agente oxidante por la cara contraria a donde él se encuentra.. Sin embargo, de manera análoga a lo observado en la reacción de dihidroxilación del compuesto **61a sin**, el compuesto **70a anti** no sufrió modificación alguna durante la reacción y el sustrato de partida se recuperó inalterado. En esta ocasión no encontramos ninguna hipótesis razonable para explicar este hecho (*Esquema 2.36*).



Esquema 2.36. Ensayos de dihidroxilación llevados a cabo sobre las indolizidinonas **70a**.

Los experimentos de RMN de protón, tanto monodimensionales como bidimensionales, realizados sobre el compuesto **72a sin** permitieron determinar su estereoquímica. En particular es de destacar (*Figura 2.14*) la relación entre los protones H-6 y H-7, evidenciada mediante el empleo de un experimento NOE selectivo, que nos permitió proponer su estructura.

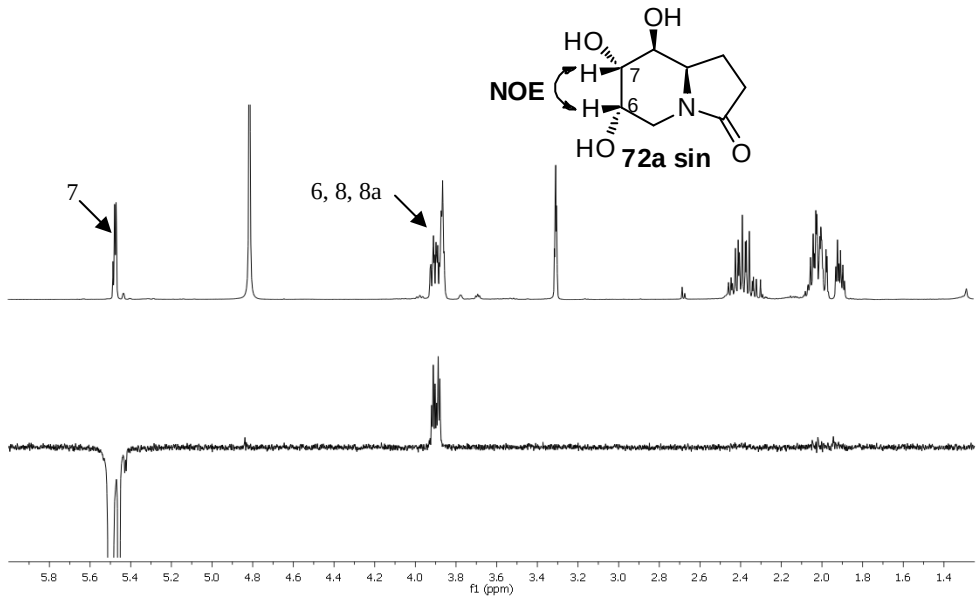
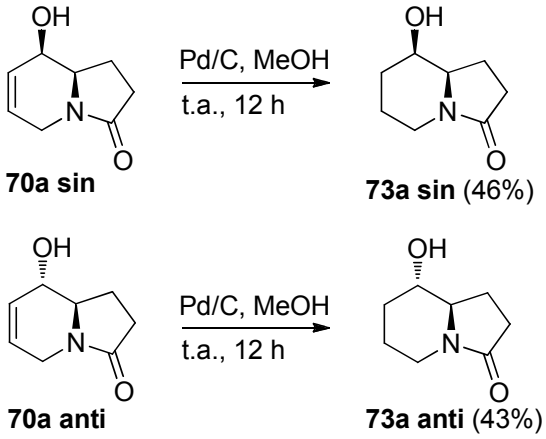


Figura 2.14. Espectro NOE selectivo realizado sobre la indolizidinona **72a sin**.

De modo complementario, realizamos la hidrogenación del doble enlace del compuesto **70a**, en sus dos variantes estereoméricas, mediante el empleo de Pd/C como catalizador. Tal experimento condujo a la formación

de los compuestos **73a sin** y **73a anti** con rendimientos moderados, si bien el compuesto **73a anti** no pudo purificarse apropiadamente (*Esquema 2.37*).

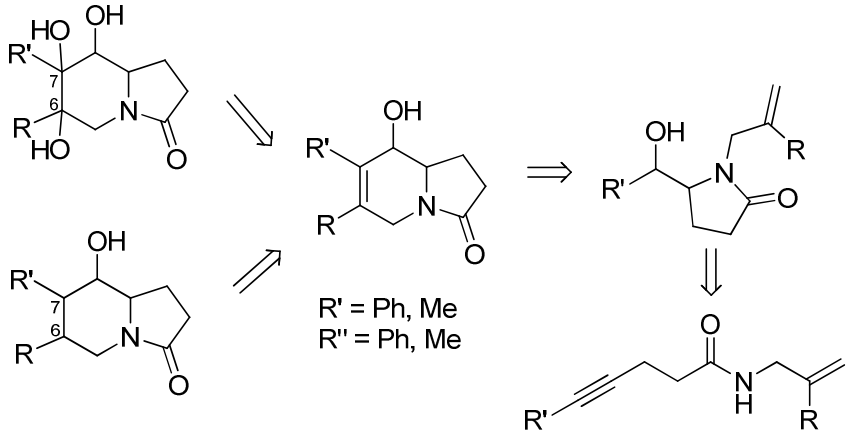


Esquema 2.37. Reacciones de hidrogenación de los compuestos **70a**.

3.2.1. Estudio del alcance de la estrategia sintética.

A fin de estudiar el alcance de la aproximación establecida en el punto anterior, se evaluaron las distintas reacciones que componen esta rutina partiendo de sustratos con diferente sustitución, de tal modo que, si se tuviera éxito, se conseguiría acceder a indolizidinonas sustituidas en posición 6 y 7. De acuerdo con nuestro plan sintético, mostrado en el *Esquema 2.38*, una adecuada selección de la alilamina de partida determinaría la naturaleza del sustituyente a introducir en la posición 6, mientras que el resto olefínico insertado en la pentinamida de partida alojaría, finalmente, un determinado sustituyente sobre el carbono C-7 de la indolizidinona deseada.

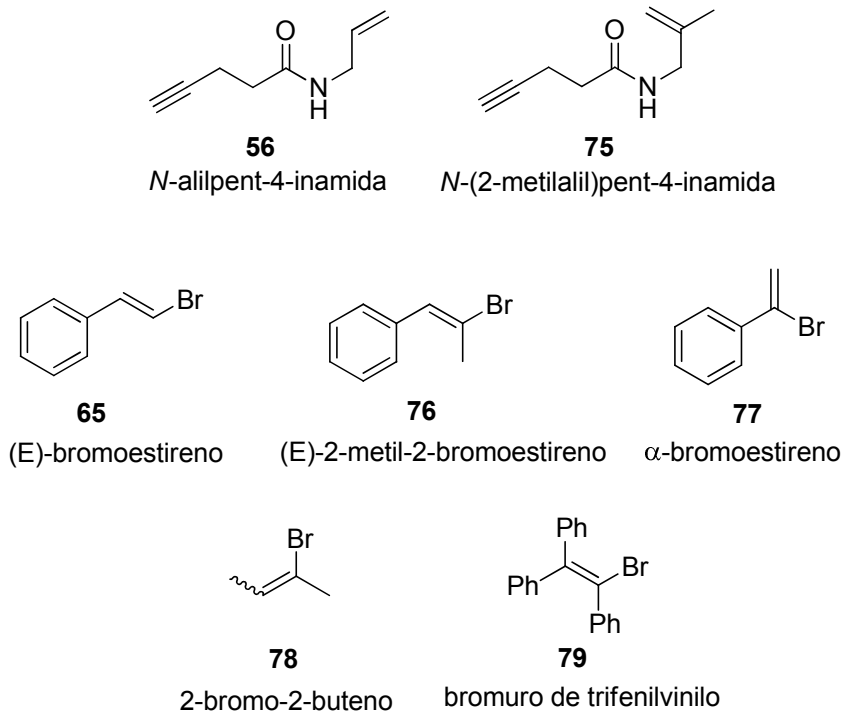
Así, se dispuso la combinación de una serie de alilamidas junto con una serie de bromuros de alquenilo que rendirán un conjunto de derivados amídicos para ser utilizados en nuestro protocolo sintético general.



Esquema 2.38. Retrosíntesis para la preparación de una serie de indolizidinonas.

Así, la amida **75** fue preparada, con un rendimiento del 84%, por reacción del ácido 4-pentinoico (**4**) con la 2-metilalilamina (compuesto comercial **74**) en presencia de HOBt y EDC·HCl como agentes activantes. Asimismo, tuvimos que preparar algunos haluros de alquenilo, no disponibles comercialmente, para su introducción en los sustratos alquínicos a través de la reacción de Sonogashira. En consecuencia, el compuesto **76** fue preparado (70%) a través de una reacción de Hunsdiecker, mientras que el compuesto **77** se sintetizó a partir de fenilacetileno en presencia de DIBAL-H y con Ni(dpp)Cl_2 como catalizador (69%) tal y como reflejaba el procedimiento bibliográfico seguido (*Esquema 2.39*).[123]

123. Tanto los procedimientos experimentales como los datos espectroscópicos de estos compuestos pueden encontrarse en: (para el compuesto **76**) Van Alem, K.; Belder, G.; Lodder, G.; Zuilhof, H.; *J. Org. Chem*. **2005**, *70*, 179. (Para el compuesto **77**) Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961.



56 *N*-alilpent-4-inamida

75 *N*-(2-metilalil)pent-4-inamida

65 (E)-bromoestireno

76 (E)-2-metil-2-bromoestireno

77 α-bromoestireno

78 2-bromo-2-buteno

79 bromuro de trifenilvinilo

Esquema 2.39. Productos de partida empleados.

El empleo de las condiciones de la reacción de Sonogashira habituales (CuI y $PdCl_2(PPh_3)_2$) para la preparación de los compuestos **66b-g** fue infructuoso ya que únicamente detectamos la presencia de sustratos inalterados en el crudo de reacción. Por ello, decidimos emplear una cantidad catalítica de trifenilfosfina como aditivo y elevar la temperatura de

reacción para, obtener los compuestos **66b,f** con rendimientos moderados.[124] Este procedimiento no resultó ser general ya que hubo de recurrirse a una última variante de esta reacción, que emplea $Pd(PPh_3)_4$ y CuI como catalizadores, para posibilitar la síntesis de los compuestos **66c,d,g**,[125] también en este caso con rendimientos moderados. Sin embargo, la preparación de la amida **66e** no fue posible bajo ninguna de las condiciones descritas.

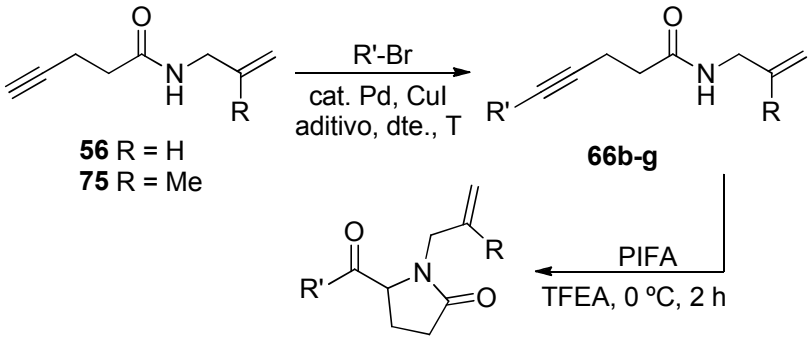
A continuación, las amidas **66b-d,f,g** se trataron con el reactivo PIFA, bajo las condiciones habituales, para dar lugar a las pirrolidin-2-onas deseadas **68b,d,f,g** con rendimientos moderados. El compuesto **68c**, sin embargo, no pudo sintetizarse con éxito debido, probablemente, a que su estructura no facilita la estabilidad del intermedio catiónico por el que transcurre esta reacción (*Tabla 2.14*).[126]

124. Brimble, M. A.; Pavia, G. S.; Stevenson, R. J. *Tetrahedron Lett.* **2002**, *43*, 1735.

125. El compuesto **66d** se preparó por reacción de la amida **56** con el compuesto **78**, disponible comercialmente. Este reactivo se empleó como mezcla de isómeros E/Z por motivos económicos y porque, tras el paso de metátesis olefínica, ambos conducirían al mismo producto.

126. Nuestra hipótesis para el mecanismo de esta reacción se desarrollará en detalle en el apartado siguiente.

Tabla 2.14. Síntesis de las pirrolidin-2-onas **68b-g**.



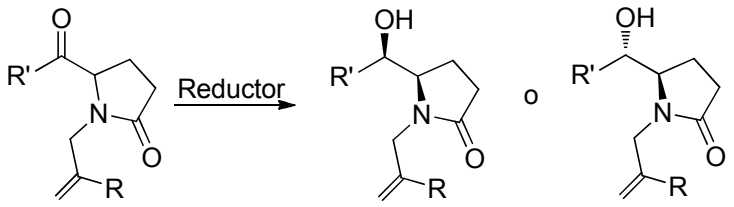
Entrada	Sustrato	R'-Br	Sonogashira[a]	Pirrolidinona[a]
1	**56**	**76**	**66b** (45%)[b]*	**68b** (41%)
2	**56**	**77**	**66c** (40%)[c]*	---
3	**56**	**78**	**66d** (60%)[c]	**68d** (59%)
4	**56**	**79**	---	---
5	**75**	**65**	**66f** (75%)[b]	**68f** (63%)
6	**75**	**76**	**66g** (47%)[c]	**68g** (37%)

[a] Rendimiento de producto cromatográficamente puro.
[b] Condiciones: $PdCl_2(PPh_3)_2$, PPh_3, CuI, Et_3N, 80 ºC.
[c] Condiciones: $Pd(PPh_3)_4$, CuI, Et_2NH, t.a.
* No pudieron conseguirse muestras analíticamente puras de estos compuestos, por lo que se emplearon en el siguiente paso sin una mayor purificación.

Una vez sintetizadas, las pirrolidinonas **68b,d,f** se trataron bajo las condiciones de reacción de reducción del carbonilo cetónico optimizadas anteriormente (*Tabla 2.15*). Sobre el compuesto **68g** no se realizó ningún experimento, puesto que, en base a los pobres resultados obtenidos, se

decidió abandonar la síntesis. Como cabría prever, la obtención diastereocontrolada de las pirrolidinonas **69b,d,f sin** tuvo lugar con éxito empleando L-selectride como reductor (*entradas 1-3*). Sin embargo, el pobre diastereocontrol y rendimiento global obtenidos en la preparación de **69b anti**, nos desanimó a extender la serie de pirrolodinonas **69 anti** más allá de este primer modelo para el que la purificación cromatográfica, al menos, pudo realizarse satisfactoriamente (*entrada 1*).

Tabla 2.15. Síntesis de las pirrolidinonas **69b,d,f**.

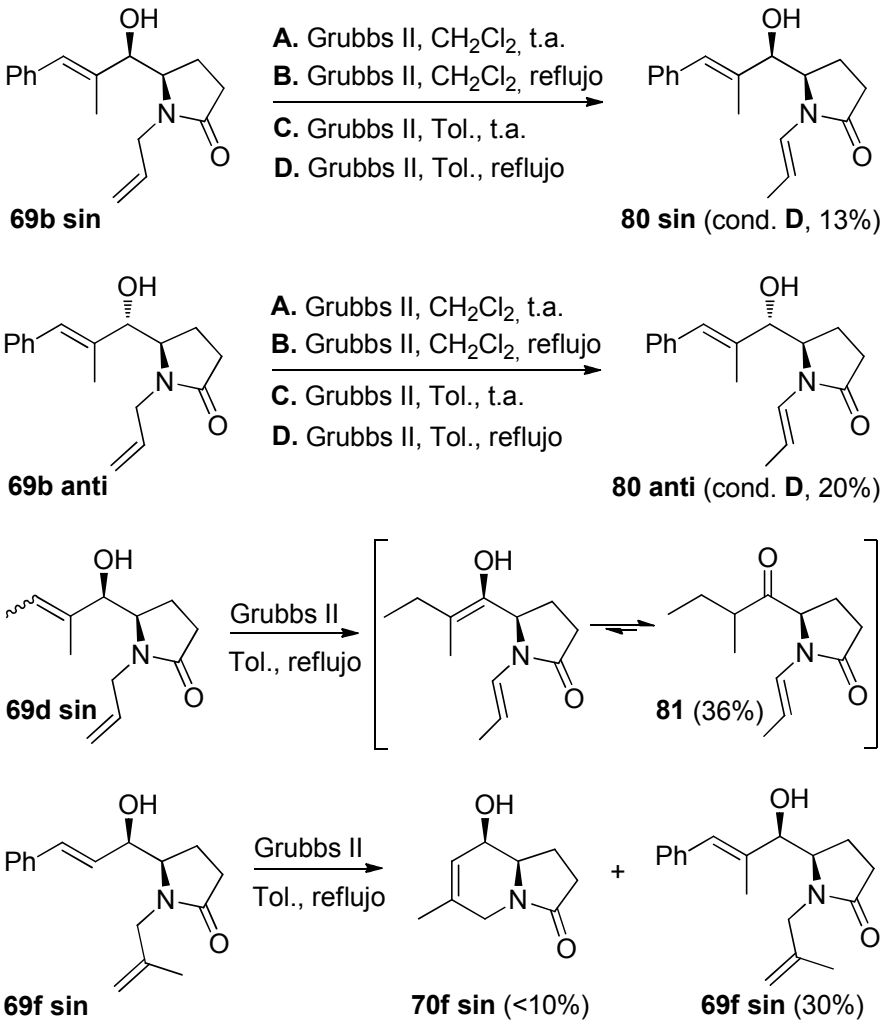


68b,d,f **69b,d,f sin** (5R,1'R) **69b anti** (5R,1'S)

Entrada	Sustrato	Producto[(a)]	
		L-selectride	$NaBH_4/ZnCl_2$
1	**68b** (R = H, R' = 2-metilestirilo)	**69b sin** (61%)	**69b anti** (37%)
2	**68d** (R = H, R' = 2-butenilo)	**69d sin** (75%)	---
3	**68f** (R = Me, R' = estirilo)	**69f sin** (90%)	---

[(a)] Rendimiento de producto cromatográficamente puro.

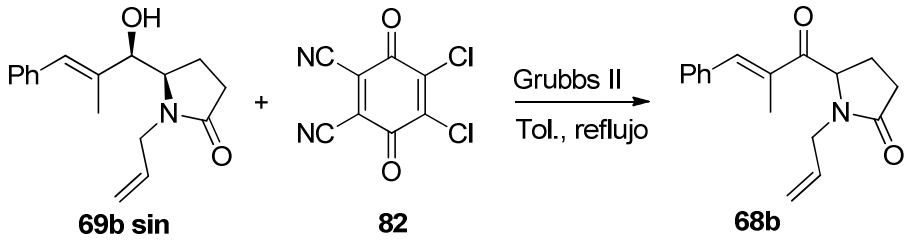
A continuación, se aplicaron las condiciones de reacción de metátesis olefínica optimizadas (catalizador de Grubbs II, tolueno a reflujo) sobre los compuestos **69b,d,f**. Sin embargo, estas condiciones solo tuvieron éxito en la síntesis del compuesto **70f sin** y, además, con un rendimiento extremadamente bajo. Observamos, de forma análoga a ocasiones anteriores, que el empleo de estas condiciones de reacción sobre el resto de compuestos (**69b,d**) dio lugar al producto de isomerización del doble enlace cuando la reacción se llevó a cabo sobre el compuesto **69b** (compuesto **80**), y al producto de una doble isomerización cuando se empleó el compuesto **69d** como sustrato (compuesto **81**). Cualquiera de las modificaciones experimentales valoradas para subsanar esta incidencia no alteraron estos resultados (*Esquema 2.40*).



Esquema 2.40. Ensayos para la obtención del esqueleto indolizidínico.

Paralelamente, se llevó a cabo un único ensayo adicional para posibilitar la transformación del compuesto **69b sin** en la indolizidina

deseada. Para ello, evaluamos su comportamiento bajo las condiciones de reacción habituales en presencia de 2,3-diciano-5,6-dicloro-1,4-benzoquinona (**82**). Se halla descrito en la bibliografía que el uso de benzoquinonas electrón deficientes puede prevenir la isomerización de dobles enlaces en procesos que conllevan el uso de catalizadores de rutenio. Sin embargo, en nuestro caso, tal aditivo únicamente actuó para oxidar el grupo hidroxilo y revertir, por tanto, al compuesto **68b** (*Esquema 2.41*).



Esquema 2.41. Ensayo para evitar la reacción de isomerización olefínica.

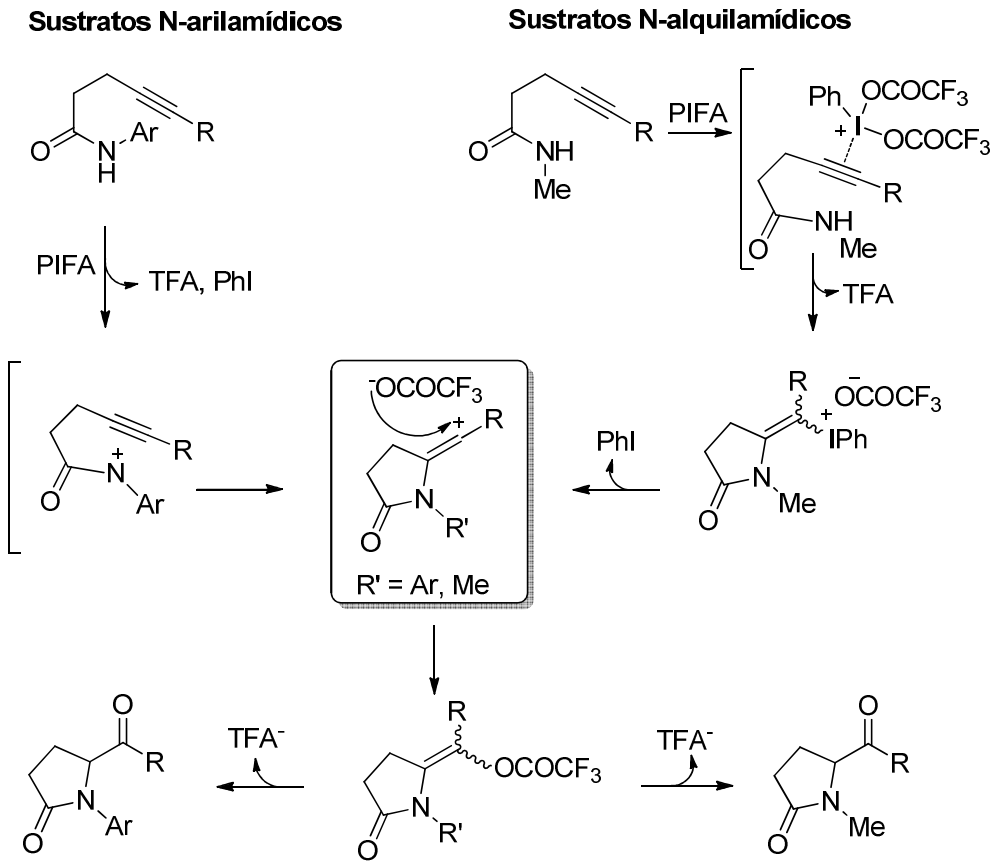
En base a los resultados mostrados en este apartado, se llegó a la conclusión de que no es posible, por el momento, preparar esqueletos indolizidínicos sin restricciones estructurales aplicando nuestro diseño sintético. Para poder explicar la falta de éxito en nuestra estrategia, es necesario conocer y analizar los aspectos mecanísticos de las distintas reacciones que tienen lugar en la secuencia sintética, cuestiones a las que dedicaremos el próximo apartado.

3.3. Consideraciones mecanísticas.

En la introducción de esta memoria se han expuesto nuestras propuestas mecanísticas para el proceso de construcción de 5-aroil-pirrolidinonas a partir de alquinilamidas por acción del reactivo de yodo hipervalente PIFA. Así, se presentan dos mecanismos complementarios, en función de la sustitución que presentan las alquinilamidas en el átomo de nitrógeno. Por un lado, planteamos que, cuando empleamos amidas N-aril sustituidas como sustratos, la reacción transcurre a través de un intermedio N-acil-N-arilnitrenio estabilizado por el grupo arilo, de modo que se facilitaría su ciclación intramolecular con el resto alquínico. Por otro lado, asumiendo que sustituyentes alquílicos no pueden estabilizar intermedios nitrénicos, proponemos que el reactivo de yodo hipervalente actuaría activando el triple enlace para generar un intermedio electrófilo que sufriría una ciclación intramolecular (*Esquema 2.42*).

Ambas propuestas mecanísticas comparten un intermedio común: el catión vinílico destacado en el centro del esquema. Es la naturaleza de esta especie la que determina, en base a su estabilidad, el éxito de la ciclación. Por ello, la discusión anterior respecto a la verdadera función del reactivo de yodo (III) al inicio del proceso pierde relevancia desde el punto de vista práctico.

Revisemos, en base a esta idea, qué ha ocurrido cuando se ha intentado la preparación de las pirrolidinonas recogidas en la Figura 2.16.



Esquema 2.42. Propuestas mecanísticas para la reacción de amidación de alquinos mediada por PIFA.

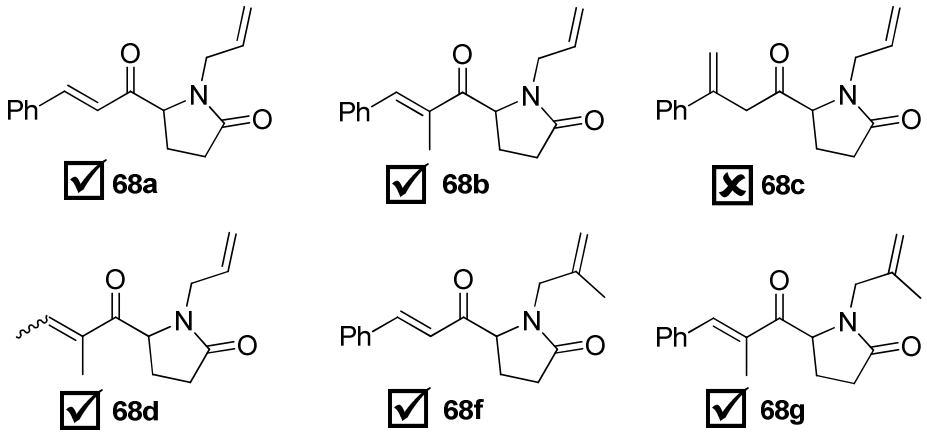
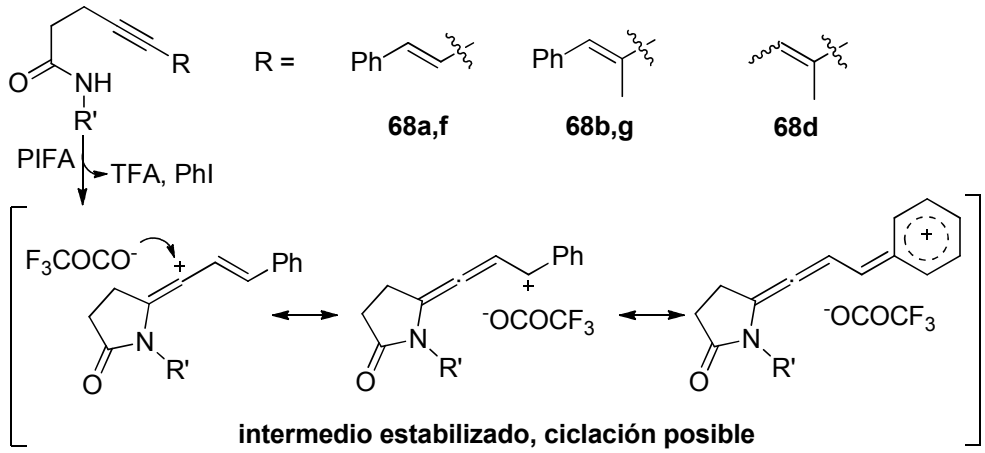


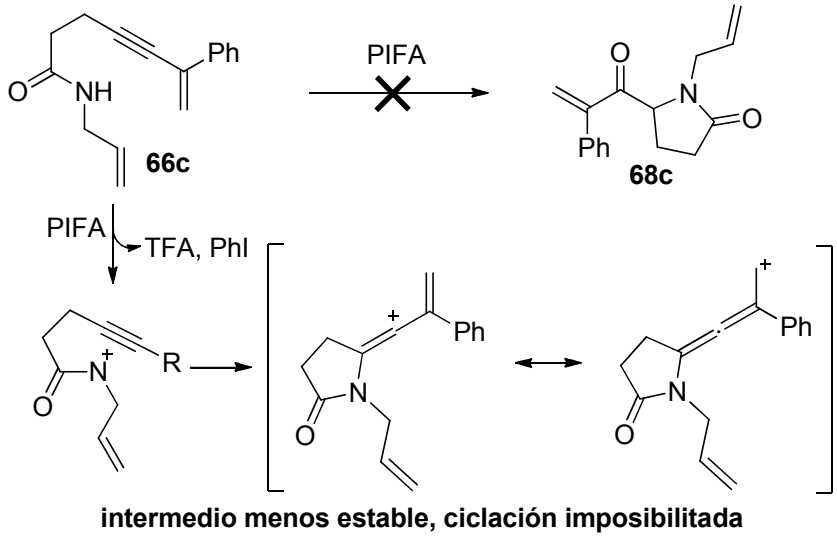
Figura 2.16. Resumen de las pirrolidinonas ensayadas.

Así, en el proceso de formación de las pirrolidinonas **68a,b,f,g**, el carbocatión generado tras el ataque del reactivo PIFA estará estabilizado mediante deslocalización por resonancia por el resto olefínico y, de modo extendido, por el resto fenilo en posición terminal, o por un efecto inductivo adicional aportado por un grupo metilo en el proceso de formación de **68d** (*Esquema 2.43*).



Esquema 2.43. Intermedio propuesto para la formación de pirrolidinonas.

Por el contrario, el carbocatión que se genera a partir de la amida **66c**, no se encuentra especialmente estabilizado, al ser primario en una de sus formas resonantes, por lo que la formación del compuesto **68c** no tiene lugar (*Esquema 2.44*).



Esquema 2.44. Intermedio no estabilizado en la formación de las pirrolidinonas.

En lo que respecta a la segunda reacción de ciclación del diseño sintético general, ya hemos mencionado a lo largo de este capítulo que la isomerización de olefinas mediada por catalizadores de rutenio durante la reacción de metátesis olefínica no es un proceso inusual, y que es relativamente común que acompañe al propio proceso de ciclación.[108] Si bien en ocasiones este proceso secundario puede ser útil, en nuestro caso, se trata de una reacción indeseable que resulta en los compuestos **71, 80 sin, 80 anti y 81** (*Figura 2.17*).[122]

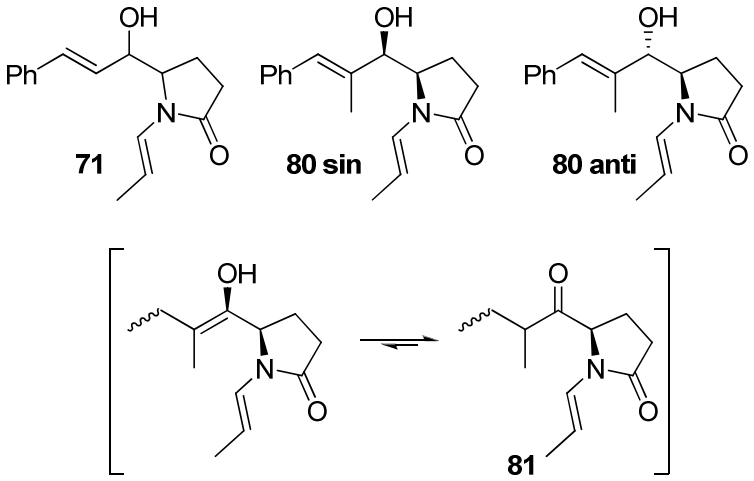


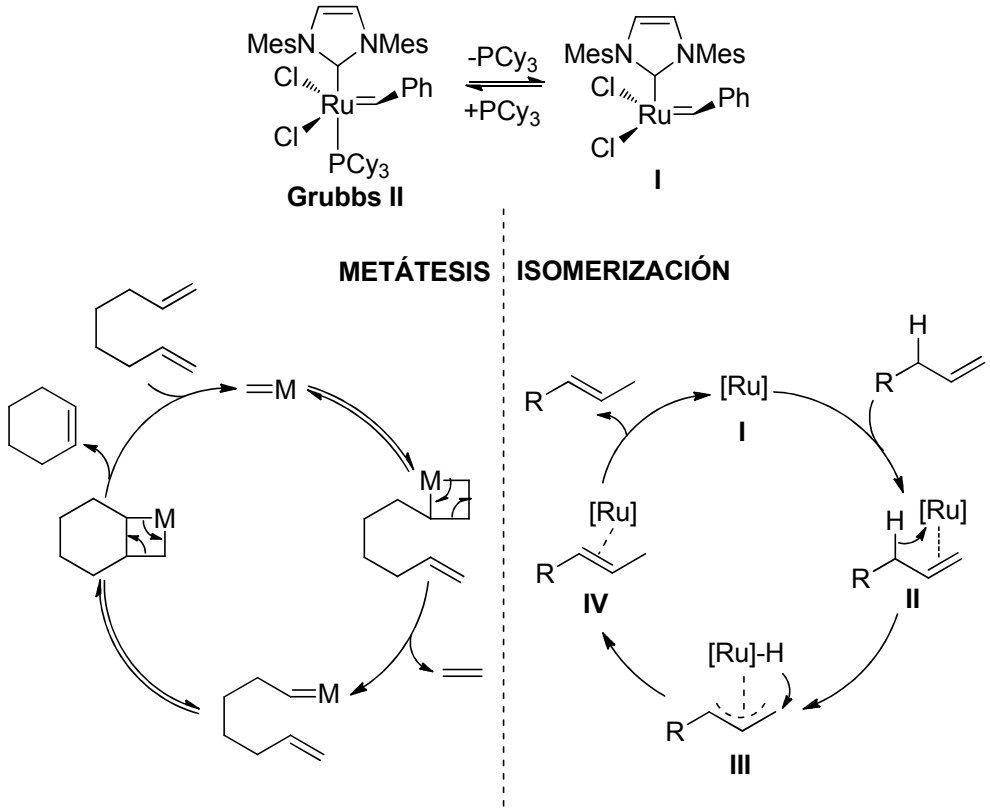
Figura 2.17. Productos de isomerización obtenidos durante la RCM.

La explicación a la formación de estos productos de isomerización ha de buscarse, obviamente, en el mecanismo de la reacción de metátesis olefínica de cierre de anillo. El paso clave de esta reacción es la formación de un ciclometalobutano, que puede revertir en los sustratos o en la formación del producto deseado. Es posible que la dificultad en la formación de este intermedio, que conducirá al producto de partida, sea también la clave para explicar el establecimiento de procesos alternativos que se observan al emplear olefinas con mayor grado de sustitución.

Así, ya hemos mencionado que, a pesar de que el mecanismo de la reacción de isomerización no está completamente establecido, se propone la formación de un hidruro de rutenio derivado de la degradación del

catalizador de Grubbs como responsable del proceso. Una de las hipótesis presentadas para poder explicar este proceso, basado en el mecanismo conocido para los hidruros π-alílicos,[127] consiste en suponer una coordinación de la olefina a un fragmento del catalizador de rutenio (intermedio **I**) para formar un complejo π (intermedio **II**) que posibilita una migración 1,3 de hidruro. Ello conduce a un complejo σ-alquilo/π-alilo (intermedio **III**), que, a través de un proceso de eliminación reductora dará lugar al intermedio **IV**. La disociación de éste resultará en la olefina isomerizada y regenerará la especie catalítica **V** (*Esquema 2.45*).[128]

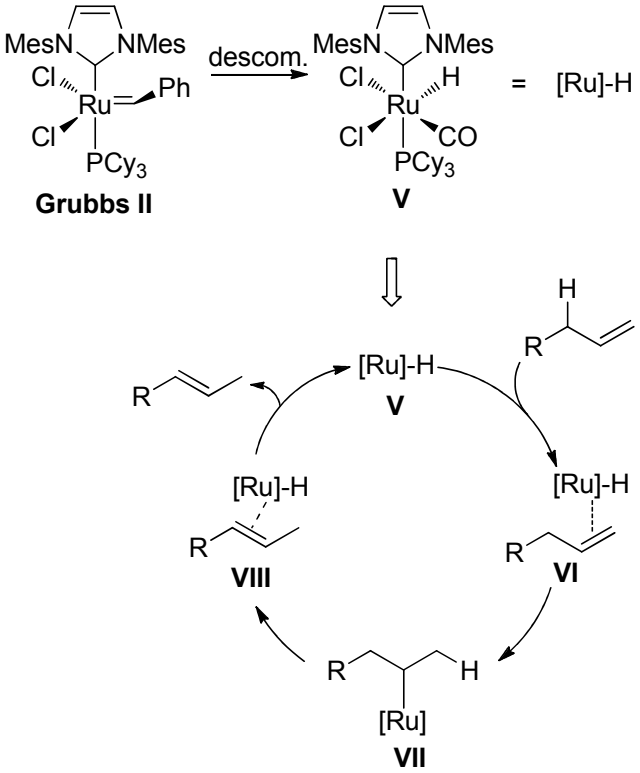
127. McGrath, D. V.; Grubbs, R. H. *Organometallics* **1994**, *12*, 224.
128. Bourgeois, D.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *J. Organomet. Chem.* **2002**, *643-644*, 247.



Esquema 2.45. Mecanismos de metátesis e isomerización olefínica.

En el mecanismo anteriormente descrito se asume que el intermedio **III** se forma como resultado de la migración de un hidruro desde la posición alílica de la olefina al centro metálico del catalizador. Sin embargo, en esta segunda propuesta, que ocurriría a través de una secuencia de

hidrometalación seguida de β-eliminación del hidruro, requiere la coordinación del hidruro de rutenio (intermedio **V**) a la olefina de partida para formar el complejo **VI**. A continuación tendrá lugar la hidrometalación, que resultará en el complejo **VII**, cuya β-eliminación formará el complejo π **VIII** y que, finalmente, se disociará para dar lugar al producto isomerizado junto con la especie catalítica **V** regenerada (*Esquema 2.46*).[108]

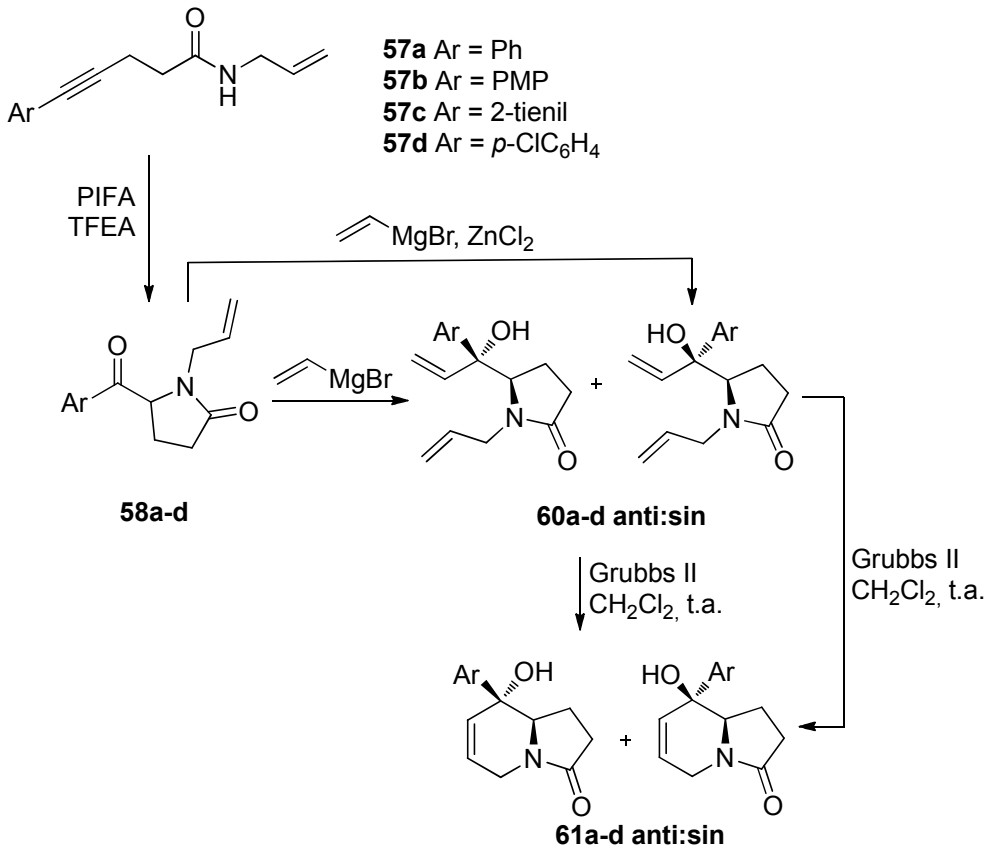


Esquema 2.46. Segundo mecanismo propuesto para la isomerización olefínica.

3.4. Visión de conjunto.

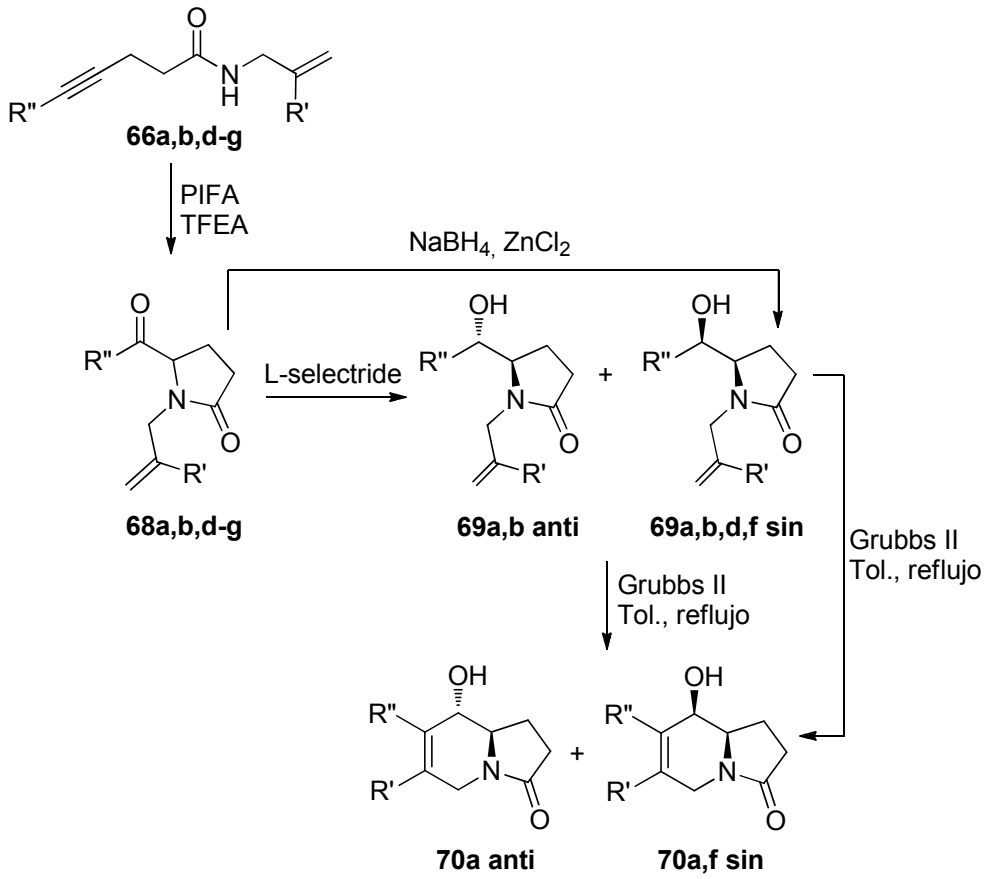
En este tercer apartado de la Memoria se ha procedido a la preparación de derivados indolizidínicos a partir de alquinilamidas funcionalizadas, donde el empleo del reactivo de yodo hipervalente, por una parte, y el empleo de catalizadores de rutenio, por otra, facilitan los pasos clave de ciclación intramolecular conducentes a los sistemas objetivo.

Así, la preparación de las pirrolidinonas **58a-d**, intermedios en la síntesis de las 8-aril-8-hidroxiindolizidinonas fue llevada a cabo con éxito por amidación intramolecular con la participación del reactivo PIFA. La introducción posterior de un resto vinílico de manera (parcialmente) estereoselectiva permitió la síntesis de los compuestos **60a-d**, si bien los isómeros anti no pudieron ser obtenidos de forma aislada. Por último, la reacción de metátesis olefínica bajo la acción del catalizador de Grubbs II rindió los compuestos indolizidínicos **61a-d**.



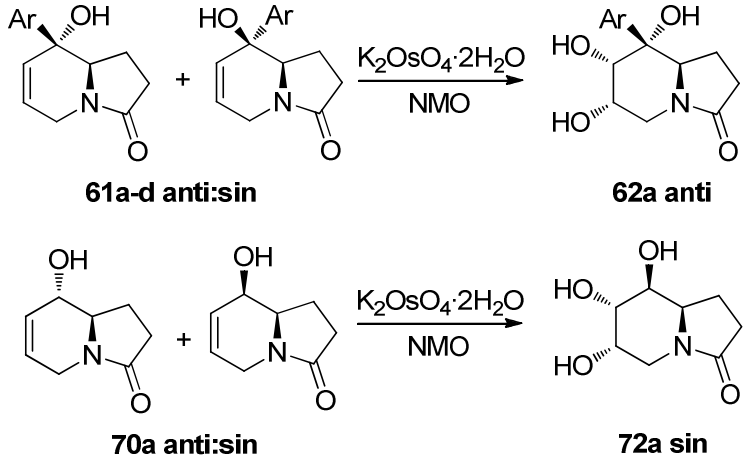
Por otro lado, las pirrolidinonas **68a-g**, intermedios sintéticos de las las 8-hidroxiindolizidinonas objetivo, fueron preparadas con rendimientos aceptables, excepto para el compuesto **68c** debido, probablemente, a la falta de estabilidad del intermedio a través del cual debería formarse. La posterior reducción del carbonilo cetónico para dar lugar al isómero sin de los compuestos **69a,b,d,f** tuvo lugar de manera satisfactoria. Desafortunadamente, la reacción de metátesis olefínica solo tuvo lugar en la

síntesis de los compuestos **70a** y **70f**, si bien en este último caso el rendimiento no fue aceptable. En el resto de los casos se obtuvieron productos de isomerización del doble enlace, resultado, probablemente, de la acción de un proceso de degradación del catalizador de Grubbs II.

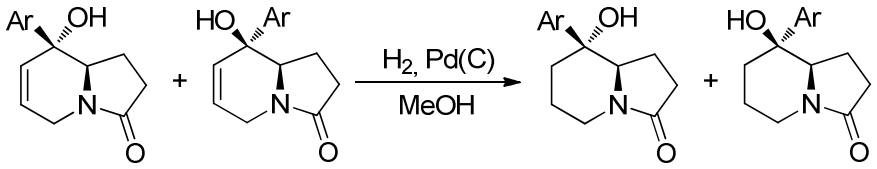


A continuación, los compuestos indolizidínicos sintetizados **61a-d** y **70a** fueron tratados bajo condiciones de dihidroxilación. Sin embargo, solo los compuestos **61a anti** y **70a sin** pudieron ser transformados en las

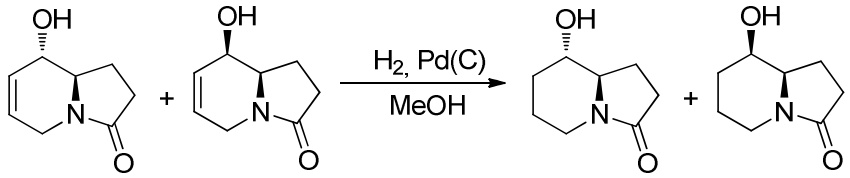
indolizidinonas polihidroxiladas **62a anti** y **72a sin**, con rendimientos globales del 16 y 15%, respectivamente. En el resto de los casos, a pesar de las diferentes condiciones ensayadas (AD-mix α, AD-mix β, OsO_4/TMEDA, PIFA), se obtuvo el producto de partida inalterado.



Paralelamente, los compuestos indolizidínicos **61a-d** y **70a** se hidrogenaron para dar lugar a los compuestos **64a-d** y **73a** con éxito.



61a-d anti:sin **64a-d anti:sin**

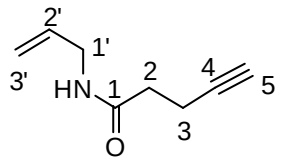


70a anti:sin **73a anti:sin**

3.5. Experimental procedures.

3.5.1. Typical procedure for the synthesis of amides 56 and 75.

N-allyl-4-pentynamide (**56**).



A solution of 4-pentynoic acid (**4**) (640 mg, 6.5 mmol) in 5 mL of DCM was added to a magnetically stirred solution of EDC·HCl (1.9 g, 9.9 mmol) and HOBt (1.35 g, 9.9 mmol) in 30 mL of the same solvent followed by the addition of N-allylamine (**55**) (0.75 mL, 9.9 mmol) dissolved in 10 mL of DCM. The mixture was cooled to 0 ºC and Et_3N (1.4 mL, 9.9 mmol) was added dropwise and was left to react at rt overnight. Then, the reaction was diluted with DCM and water (30 mL), the mixture decanted, and the aqueous phase extracted with DCM (3x15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The resultant chromatographically pure colorless oil was triturated with cold Et_2O to afford amide **56** as a while solid (82%).

mp 46-48 ºC (Et_2O).

^{1}H NMR ($CDCl_3$) δ (ppm) 5.90-5.77 (m, 2H, H-2', NH), 5.23-5.11 (m, 2H, H-3'), 3.91-3.88 (m, 2H, H-1'), 2.57-2.51 (m, 2H, H-2/H-3), 2.44-2.39 (m, 2H, H-3/H-2), 2.00 (t, *J*=2.0, 1H, H-5).

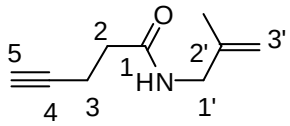
^{13}C NMR ($CDCl_3$) δ (ppm) 170.7 (C-1), 134.0 (C-2'), 116.4 (C-3'), 82.9 (C-4), 69.3 (C-5), 41.9 (C-1'), 35.3 (C-2), 14.9 (C-3).

IR (film) υ 3295, 1648.

MS [M+1, CI] *m/z* (%) 138 (100), 136 (8).

HRMS calculated for $C_8H_{11}NO \cdot H^+$ 138.0919, found 138.0925.

N-(2-methylallyl)pent-4-ynamide (**75**).



According to the typical procedure for compound **56**, amide **75** was obtained from 2-methylallylamine (**74**) in 84% yield as a colorless oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 6.10 (br s, 1H, NH), 4.81 (d, *J*=5.4, 2H, H-3'), 3.78 (d, *J*=5.4, 2H, H-1'), 2.51-2.39 (m, 4H, H-2, H-3), 1.97 (d, *J*=2.4, 1H, H-5), 1.70 (s, 3H, $C_{2'}$-C*H*$_3$).

^{13}C NMR ($CDCl_3$) δ (ppm) 171.0 (C-1), 141.8 (C-2'), 110.9 ($C_{2'}$-*C*H_3), 83.0 (C-5), 69.3 (C-4), 45.1 (C-1'), 35.3 (C-2), 20.3 (C-3'), 14.9 (C-3).

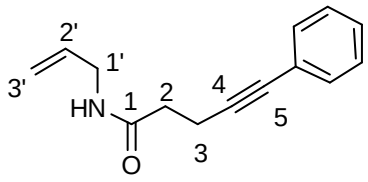
IR (film) υ 3295, 1652.

MS [M, EI] *m/z* (%) 152 (100), 151 (5).

HRMS calculated for $C_9H_{13}NO$ 152.1075, found 152.1077.

3.5.2. Procedures for the Sonogashira coupling reaction. Synthesis of compounds 57, 66 and 67.

N-allyl-5-phenylpent-4-ynamide (**57a**).



A solution of iodobenzene (0.5 mL, 4.05 mmol), $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol) and amide **56** (555 mg, 4.05 mmol) in Et_3N (20 mL) was stirred at rt for 15 min. Then, CuI (8 mg, 0.04 mmol) was added and the mixture was stirred for 24 h. The whole crude was purified by column chromatography (hexanes/EtOAc, 1/1) to afford amide **57a** as a white solid that was triturated in Et_2O (94%).

mp 72–73 ºC (Et_2O).

^{1}H NMR ($CDCl_3$) 7.37-7.32 (m, 2H, Harom), 7.25-7.23 (m, 3H, Harom), 6.30 (br s, 1H, NH), 5.89-5.74 (m, 1H, H-2'), 5.22-5.06 (m, 2H, H-3'), 3.90-3.86 (m, 2H, H-1'), 2.76-2.70 (m, 2H, H-2/H-3), 2.51-2.45 (m, 2H, H-3/H-2).

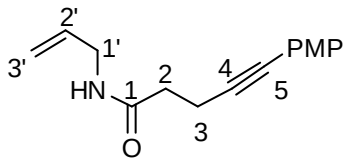
^{13}C NMR ($CDCl_3$) δ (ppm) 171.1 (C-1), 133.9, 131.4, 128.1, 127.7 (t-Carom, C-7), 123.3 (q-Carom), 116.1 (C-3'), 88.4 (C-4), 81.4 (C-5), 41.8, 35.4, 15.8 (C-3, C-2, C-1').

IR (film) υ 3301, 1631.

MS (M, EI) *m/z* (%) 213 (15), 212 (41), 185 (45), 184 (98), 172 (100), 170 (31), 128 (67).

HRMS calculated for $C_{15}H_{14}NO$ 213.1154, found 213.1149.

N-allyl-5-(4-methoxyphenyl)pent-4-ynamide (**57b**).



According to the typical procedure for compound **57a**, amide **57b** was obtained from amide **56** in 57% as a yellowish solid after purification by column chromatography (hexanes/EtOAc, 2/8) followed by crystallization from Et_2O.

mp 82-83 ºC (Et_2O).

^{1}H NMR ($CDCl_3$) δ (ppm) 7.28 (d, *J*=8.7, 2H, Harom), 6.77 (d, *J*=8.7, 2H, Harom), 6.10 (br s, 1H, NH), 5.88-5.75 (m, 1H, H-1'), 5.21-5.07 (m, 2H, H-3'), 3.88 (t, *J*=5.6, 2H, H-1'), 3.76 (s, 3H, OCH_3), 2.71 (t, *J*=7.2, 2H, H-2/H-3), 2.47 (t, *J*=7.2, 2H, H-3/H-2).

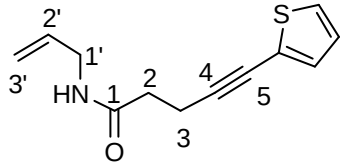
^{13}C NMR ($CDCl_3$) δ (ppm) 171.2 (C-1), 159.3, 115.5 (q-Carom), 134.4, 132.9, 113.8 (t-Carom, C-2') 116.2 (C-3'), 86.8(C-4), 81.4, (C5), 55.2 (OCH_3), 41.9, 35.8, 15.9 (C-2, C-3, C-1').

IR (film) υ 3310, 1633.

MS (M+1, CI) *m/z* (%) 244 (100), 243 (44), 202 (50), 145 (10).

HRMS calculated for $C_{15}H_{17}NO_2{\cdot}H^+$ 244.1337, found 244.1345.

N-allyl-5-(2-thienyl)pent-4-ynamide (**57c**).



According to the typical procedure for compound **57a**, amide **57c** was obtained from amide **56** in 44% as a white solid after purification by column chromatography (hexanes/EtOAc, 2/8) followed by crystallization from Et_2O.

mp 68-69 ºC (Et_2O)

^{1}H NMR ($CDCl_3$) δ (ppm) 7.18-7.10 (m, 2H, Harom), 6.93-6.91 (m, 1H, Harom), 5.97 (br s, 1H, NH), 5.90-5.77 (m, 1H, H-2'), 5.23-5.09 (m, 2H, H-3'), 3.91 (t, *J*=5.5, 2H, H-1'), 2.77 (t, *J*=7.3, 2H, H-2/H-3), 2.48 (t, *J*=7.3, 2H, H-3/H-2).

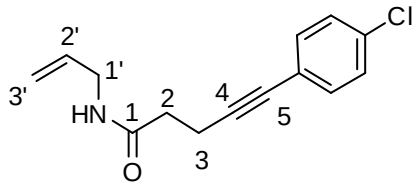
^{13}C NMR ($CDCl_3$) δ (ppm) 170.9 (C-1), 134.0, 131.4, 126.3, (t-Carom, C-2'), 123.5 (q-Carom), 116.4 (C-3'), 92.5 (C-4), 74.8 (C-5), 42.0, 35.4, 16.2 (C-2, C-3, C-1').

IR (film) υ 3305, 1633.

MS (M+1, CI) *m/z* (%) 220 (100), 179 (47), 178 (96), 135 (10).

HRMS calculated for $C_{12}H_{13}{}^{32}SNO{\cdot}H^+$ 220.0796, found 220.0790.

N-allyl-5-(4-chlorophenyl)pent-4-ynamide (**57d**).



According to the typical procedure for compound **57a**, amide **57d** was obtained from amide **56** in 54% as a white solid after purification by column chromatography (hexanes/EtOAc, 2/8) followed by crystallization from Et_2O.

mp 196-197 ºC (Et_2O).

^{1}H NMR ($CDCl_3$) δ (ppm) 7.30-7.22 (m, 4H, Harom), 5.88-5.77 (m, 2H, H-2', NH), 5.23-5.09 (m, 2H, H-3'), 3.91 (t, *J*=5.7, 2H, H-1'), 2.75 (t, *J*=7.2, 2H, H-2/H-3), 2.48 (t, *J*=7.2, 2H, H-3/H-2).

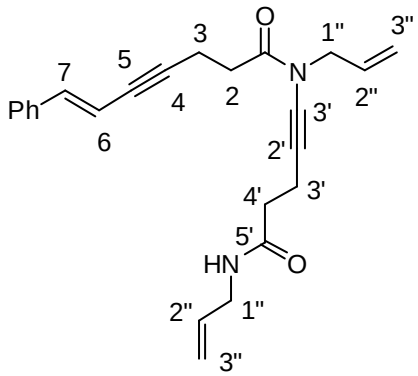
^{13}C NMR ($CDCl_3$) δ (ppm) 170.9 (C-1), 134.1, 132.8, 128.5 (t-Carom, C-2'), 133.8, 121.9 (q-Carom), 116.4 (C-3'), 89.5 (C-4), 80.5, (C-5), 42.0, 35.5, 15.9 (C-2, C-3, C-1').

IR (film) υ 3305, 1631.

MS (M+1, CI) *m/z* (%) 248 (100), 247 (25), 206 (42), 149 (10).

HRMS calculated for $C_{14}H_{14}{}^{35}ClNO{\cdot}H^+$ 248.0842, found 248.0839.

(E)-N-allyl-N-[(5-(allylaminocarbonyl)pent-1-yn-1-yl]-7-phenylhept-6-en-4-ynamide (**67**).

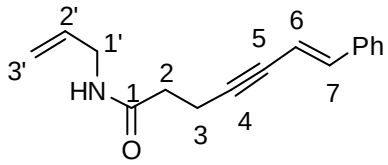


According to the typical procedure for compound **57a**, amide **67** was obtained from amide **56** and *E*-bromostyrene (**65**) in 40% as a yellow solid after purification by column chromatography (hexanes/EtOAc, 1/1) followed by crystallization from Et_2O.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.28-7.20 (m, 5H, Harom), 6.79 (d, *J*=16.4, 1H, H-7), 6.38 (br s, 1H, NH), 6.05 (d, *J*=16.4, 1H, H-6), 5.88-5.69 (m, 2H, H-2”), 5.12 (dd, *J*=5.7, 17.1, 2H, H-3”), 5.05 (d, *J*=10.2, 2H, H-3”), 3.85-3.80 (m, 4H, H-1”), 2.68-2.35 (m, 8H, H-3, H-4, H-3’, H-4’).

^{13}C NMR ($CDCl_3$) δ (ppm) 171.2, 171.1 (C-1’, C-5’), 140.5 (C-7), 136.3 (q-Carom), 134.2 (C-2), 128.6, 128.3, 126.0 (Carom), 116.0 (C-3”), 108.3 (C-6), 90.9, 83.0, 80.5, 69.2 (C-4, C-5, C-1’, C-2’), 60.3, 41.9 (C-1”), 35.5, 35.1, 16.1, 14.1 (C-2, C-3, C-3’, C-4’).

N-Allyl-7-phenyl-4-in-6-heptenamide (**66a**).



A solution of (*E*)-bromostyrene (**65**) (500 mg, 3 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), PPh_3 (23 mg, 0.09 mmol) and amide **56** (615 mg, 4.5 mmol) in Et_3N (15 mL) was stirred at 40 ºC for 15 minutes. Then, CuI (17 mg, 0.09 mmol) was added and the new mixture was stirred at 80 ºC until total consumption of the starting material (tlc, 6 h). Finally, all volatiles were eliminated under vacuum and the residue was purified by column chromatography (EtOAc) to render amide **66a** as a yellowish solid, which was triturated in Et_2O (54%).

mp 68-70 ºC (Et_2O).

^{1}H NMR ($CDCl_3$) δ (ppm) 7.37-7.29 (m, 5H, Harom), 6.87 (d, *J*=16.2, 1H, H-7), 6.11 (d, *J*=16.2, 1H, H-6), 5.91-5.80 (m, 1H, H-2'), 5.74 (br s, 1H, NH), 5.26-5.13 (m, 2H, H-3'), 3.73 (t, *J*=5.7, 2H, H-1'), 2.73 (t, *J*=5.7, 2H, H-2/H-3), 2.46 (t, *J*=7.1, 2H, H-3/H-2).

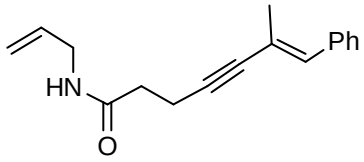
^{13}C NMR ($CDCl_3$) δ (ppm) 170.9 (C-1), 140.8, 134.1 (C-7, C-6), 136.3 (q-Carom), 128.7, 128.5, 126.1 (t-Carom), 116.4 (C-3'), 108.2 (C-2'), 90.8, 80.8 (C-4, C-5), 42.0, 35.7, 16.2 (C-3, C-2, C-1').

IR (film) υ 3295, 1638.

MS (M+1, CI) *m/z* (%) 240 (100), 198 (32), 155 (23), 141 (25).

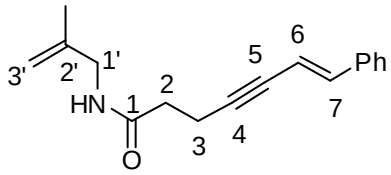
HRMS calculated for $C_{16}H_{17}NO{\cdot}H^+$ 240.1388, found 240.1392.

(E)-N-allyl-6-methyl-7-phenylhept-6-en-4-ynamide (**66b**).



According to the typical procedure for compound **66a**, amide **66b** was obtained from amide **56** and bromide **76** in 45% as a colorless oil after purification by column chromatography (hexanes/EtOAc, 1/1).

(E)-N-(2-methylallyl)-7-phenylhept-6-en-4-ynamide (**66f**).



According to the typical procedure for compound **66a**, amide **66f** was obtained from amide **75** and bromide **65** after purification by column chromatography (EtOAc) as a yellowish solid which was triturated in hexanes (75%).

mp 60-62 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ (ppm) 7.29-7.18 (m, 5H, Harom), 6.94 (br s, 1H, NH), 6.81 (d, *J*=16.2, 1H, H-7), 6.07 (d, *J*=16.2, 1H, H-6), 4.77 (s, 1H, H-3'), 4.85 (s, 1H, H-3'), 3.76 (d, *J*=5.5, 2H, H-1'), 2.68 (t, *J*=6.8, 2H, H-2/H-3), 2.46 (t, *J*=6.8, 2H, H-3/H-2), 1.69 (s, 3H, $C_{2'}$-C*H*$_3$).

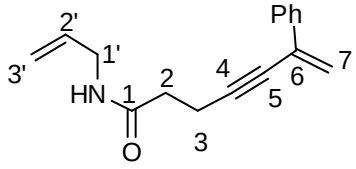
^{13}C NMR ($CDCl_3$) δ (ppm) 171.5 (C-1), 142.0 (C-2'), 140.5 (C-7), 136.3 (q-Carom), 128.7, 128.4, 126.1 (t-Carom), 110.7, 108.5 (C-3', C-6), 91.4 (C-4), 80.6, (C-5), 45.0, 35.4, 20.3, 16.3 (C-2, C-3, C-1', $C_{2'}$-*C*H$_3$).

IR (film) υ 3295, 1638.

MS (M+1, CI) *m/z* (%) 254 (100), 253 (13), 183 (3).

HRMS calculated for $C_{17}H_{19}NO \cdot H^+$ 254.1545, found 254.1551.

N-allyl-6-phenylhept-6-en-4-ynamide (**66c**).



A solution of α-bromostyrene (**77**) (263 mg, 1.1 mmol), $Pd(PPh_3)_4$ (135 mg, 0.11 mmol), and CuI (45 mg, 0.22 mmol) in Et_2NH (13 mL) was stirred for 5 min prior to the dropwise addition of a solution of amide **56** (178 mg, 1.3 mmol) in 3.5 mL of THF. The new mixture was stirred at rt until total consumption of the starting material (tlc, 4 h). Then, the mixture was diluted with EtOAc, filtered and washed with a saturated solution of NH_4Cl (1x30mL). The aqueous phase was extracted with EtOAc (3x20 ml), and the combined organic extracts were dried over Na_2SO_4, filtered, and the volatiles eliminated under vacuum. The residue was purified by column chromatography (hexanes) to render amide **66c** as a yellowish oil (40%).

^{1}H NMR ($CDCl_3$) δ (ppm) 7.61 (d, *J*=6.9, 2H, Harom), 7.32-7.27 (m, 3H, Harom), 6.34 (br s, 1H, NH), 5.83 (s, 1H, H-7), 5.77-5.74 (m, 1H, H-2'), 5.56 (s, 1H, H-7), 5.18-5.09 (m, 2H, H-3'), 3.86 (t, *J*=4.6, 2H, H-1'), 2.74 (t, *J*=7.1, 2H, H-2/H-3), 2.48 (t, *J*=7.1, 2H, H-3/H-2).

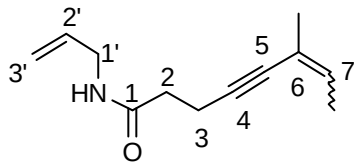
^{13}C NMR ($CDCl_3$) δ (ppm) 171.2 (C-1), 137.4, 130.6 (q-Carom, C-6), 134.1 (C-2'), 128.7, 128.2, 126.0 (t-Carom), 120.0, 116.4 (C-3', C-7), 90.1 (C-4), 80.7 (C-5), 42.0, 35.5, 16.0 (C-2, C-3 C-1').

IR (film) υ 1669.

MS (M+1, CI) *m/z* (%) 240 (100), 198 (12), 157 (10).

HRMS calculated for $C_{16}H_{17}NO \cdot H^+$ 240.1388, found 240.1384.

N-allyl-6-methyl-4-in-6-octenamide (**66d**).



According to the typical procedure for compound **66c**, amide **66d** was obtained from amide **56** and bromide **78** in 60% after purification by column chromatography (hexanes) as a yellowish oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.23 (br s, 1H, NH), 5.69-5.43 (m, 2H, H-2', H-7), 5.00 (d, *J*=16.6, 1H, H-3'), 4.90 (d, *J*=10.2, 1H, H-3'), 3.67 (s, 2H, H-1'), 2.51-2.27 (m, 4H, H-2, H-3), 1.58-1.44 (m, 6H, C_6-C*H*$_3$, C_7-C*H*$_3$).

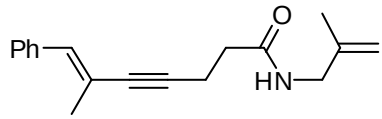
^{13}C NMR ($CDCl_3$) δ (ppm) 171.7/171.6 (C-1), 134.2 (C-7), 130.9 (C-2'), 118.6/118.4 (C-6), 115.6/115.5 (C-3'), 92.1, 84.3, 84.2, 80.3 (C-5, C-4), 41.8/41.7, (C-1'), 35.5/35.4 (C-2), 23.1, 16.8, 15.9, 15.8, 15.7,13.7 (C-3, C_6-*C*H$_3$, C_7-*C*H$_3$).

IR (film) υ 1669.

MS (M+1, CI) *m/z* (%) 192 (100), 191 (13), 150 (7).

HRMS calculated for $C_{12}H_{17}NO \cdot H^+$ 192.1388, found 192.1385.

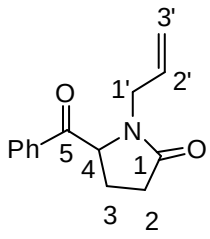
(E)-6-methyl-N-(2-methylallyl)-7-phenylhept-6-en-4-ynamide (**66g**).



According to the typical procedure for compound **66c**, amide **66g** was obtained from amide **75** and bromide **76** in 47% after purification by column chromatography (hexanes/EtOAc, 1/1) as a yellowish oil.

3.5.3. Typical procedure for the PIFA-mediated heterocyclization. Synthesis of pyrrolidinones 58 and 68.

N-allyl-5-benzoylpyrrolidin-2-one (**58a**).



A solution of alkynylamide **57a** (1.8 g, 8.45 mmol) in TFEA (110 mL) was stirred at 0 ºC and a solution of PIFA (5.45 g, 12.67 mmol) in 60 mL of the same solvent was added dropwise. The reaction mixture was stirred at that temperature for 2 h. For the work up, aqueous Na_2CO_3 (10%) was added and the mixture extracted with DCM (3x20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave the desired product **58a** as a chromatographically pure yellowish oil (66%).

^{1}H NMR ($CDCl_3$) δ (ppm) 7.91 (d, *J*=7.1, 2H, Harom), 7.63-7.45 (m, 3H, Harom), 5.78-5.55 (m, 1H, H-2'), 5.15-5.02 (m, 3H, H-1', H-3'), 4.51-4.45 (m, 1H, H-4), 3.39 (dd, *J*=15.0, 7.9, 1H, H-1'), 2.42-2.39 (m, 3H, H-2/H-3), 2.01-1.96 (m, 1H, H-3/H-2).

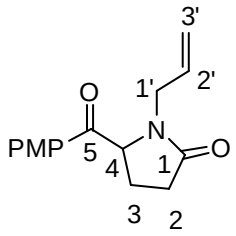
^{13}C NMR ($CDCl_3$) δ (ppm) 196.8 (C-5), 175.0 (C-1), 134.0 (q-Carom), 133.9, 132.3 128.9, 128.2 (t-Carom, C-2'), 118.6 (C-3'), 60.6 (C-4), 44.2 (C-6), 29.4 (C-2), 23.0 (C-3).

IR (film) υ 1690.

MS (M, EI) *m/z* (%) 229 (1), 124 (100), 105 (23).

HRMS calculated for $C_{14}H_{15}NO_2$ 229.1103, found 229.1111.

N-(1-allyl-5-(4-methoxybenzoyl)pyrrolidin-2-one (**58b**).



According to the typical procedure pyrrolidinone **58b** was obtained from **57b** in 40% yield. It was purified by column chromatography (EtOAc) as a yellowish solid.

mp 72-73 ºC (Et_2O).

^{1}H NMR ($CDCl_3$) δ (ppm) 7.86 (d, *J*=8.9, 2H, Harom), 6.91 (d, *J*=8.9, 2H, Harom), 5.72-5.59 (m, 1H, H-2'), 5.10-4.99 (m, 3H, H-1', H-3'), 4.45-4.38 (m, 1H, H-4), 3.82 (s, 3H, OCH_3), 3.37-3.30 (m, 1H, H-1'), 2.44-2.33 (m, 3H, H-2/H-3), 1.96-1.90 (m, 1H, H-3/H-2).

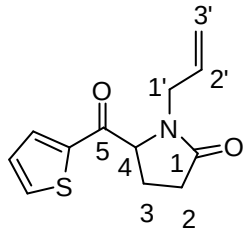
^{13}C NMR ($CDCl_3$) δ (ppm) 195.4 (C-5), 175.2 (C-1), 164.2, 127.1 (q-Carom), 132.5, 130.6 128.9, 114.2 (t-Carom, C-2'), 118.5 (C-3'), 60.4 (C-4), 55.6 (OCH_3), 44.3 (C-1'), 29.6 (C-2), 23.4 (C-3).

IR (film) υ 1690.

MS (M+1, CI) *m/z* (%) 260 (100), 124 (40).

HRMS calculated for $C_{15}H_{17}NO_3 \cdot H^+$ 260.1287, found 260.1277.

N-allyl-5-(2-thiophenecarbonyl)pyrrolidin-2-one (**58c**).



According to the typical procedure pyrrolidinone **58c** was obtained from **57c** in 64% yield. It was purified by column chromatography (EtOAc) as a yellowish oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.71-7.67 (m, 2H, Harom), 7.13-7.10 (m, 1H, Harom), 5.65-5.56 (m, 1H, H-2'), 5.06-4.90 (m, 3H, H-1', H-3'), 4.39-4.32 (m, 1H, H-4), 3.37-3.29 (m, 1H, H-1'), 2.46-2.31 (m, 3H, H-2/H-3), 2.03-1.93 (m, 1H, H-3/H-2).

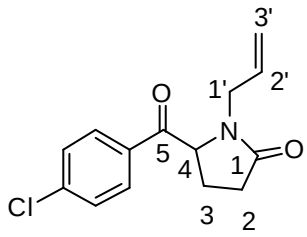
^{13}C NMR ($CDCl_3$) δ (ppm) 190.5 (C-5), 175.1 (C-1), 140.9 (q-Carom), 135.1, 132.6 132.2, 128.6 (t-Carom, C-2'), 118.8 (C-3'), 61.7 (C-4), 44.3 (C-1'), 29.5 (C-2), 23.7 (C-3).

IR (film) υ 1690.

MS (M+1, CI) *m/z* (%) 236 (100), 124 (48).

HRMS calculated for $C_{12}H_{13}{}^{32}SNO_2 \cdot H^+$ 236.0745, found 236.0734.

N-allyl-5-(4-chlorobenzoyl)pyrrolidin-2-one (**58d**).



According to the typical procedure pyrrolidinone **58d** was obtained from **57d** in 54% yield. It was purified by column chromatography (EtOAc) as a yellowish oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.81 (d, *J*=8.6, 2H, Harom), 7.40 (d, *J*=8.6, 2H, Harom), 5.66-5.56 (m, 1H, H-2'), 5.08-4.97 (m, 3H, H-1', H-3'), 4.41-4.35 (m, 1H, H-4), 3.37-3.29 (m, 1H, H-1'), 2.44-2.32 (m, 3H, H-2/H-3), 1.93-1.87 (m, 1H, H-3/H-2).

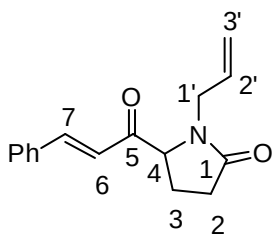
^{13}C NMR ($CDCl_3$) δ (ppm) 195.8 (C-5), 175.0 (C-1), 140.5, 132.5 (q-Carom), 132.4, 129.7 129.3 (t-Carom, C-2'), 118.7 (C-3'), 60.7 (C-4), 44.3 (C-1'), 29.4 (C-2), 23.1 (C-3).

IR (film) υ 1697.

MS (M+1, CI) *m/z* (%) 264 (100), 124 (47).

HRMS calculated for $C_{14}H_{14}{}^{35}ClNO_2 \cdot H^+$ 264.5791, found 264.0785.

N-allyl-5-(3-phenylacryloyl)-pyrrolidin-2-one (**68a**).



According to the typical procedure pyrrolidinone **68a** was obtained from **66a** in 74% yield. It was purified by column chromatography (EtOAc) as a yellowish oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.70 (d, *J*=15.8, 1H, H-7), 7.54-7.39 (m, 5H, Harom), 6.76 (d, *J*=15.8, 1H, H-6), 5.75-5.62 (m, 1H, H-2'), 5.15-5.08 (m, 2H, H-3'), 4.53-4.41 (m, 2H, H-4, H-1'), 3.46-3.38 (m, 1H, H-1'), 2.48-2.33 (m, 3H, H-2, H-3), 2.00-1.93 (m, 1H, H-3).

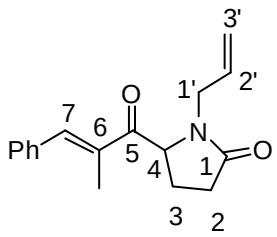
^{13}C NMR ($CDCl_3$) δ (ppm) 197.2 (C-5), 175.2 (C-1), 145.2 (C-7), 133.9 (q-Carom), 132.1, 131.2, 129.1, 128.6, 121.4 (t-Carom, C-2', C-6), 118.8 (C-3'), 63.7 (C-4), 44.5 (C-1'), 29.6 (C-3), 21.4 (C-2).

IR (film) υ 1692, 1609.

MS [M+1] *m/z* (%) 256 (89), 124 (100).

HRMS calculated for $C_{16}H_{17}NO_2 \cdot H^+$ 256.1338, found 256.1335.

(E)-1-allyl-5-(2-methyl-3-phenylacryloyl)pyrrolidin-2-one (**68b**).



According to the typical procedure pyrrolidinone **68b** was obtained from **66b** in 41% yield. It was purified by column chromatography (EtOAc) as a yellowish oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.46-7.36 (m, 5H, Harom), 5.78-5.65 (m, 1H, H-2'), 5.20-5.05 (m, 3H, H-3', H-1'), 4.48-4.42 (m, 1H, H-4), 3.39-3.31 (m, 1H, H-1'), 2.50-2.35 (m, 3H, H-2/H-3), 2.10 (s, 3H, C_6-CH_3), 1.99-1.83 (m, 1H, H-3/H-2).

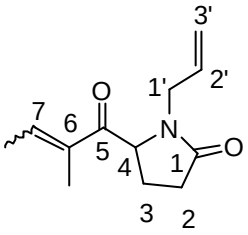
^{13}C NMR ($CDCl_3$) δ (ppm) 199.0 (C-5), 175.3 (C-1), 140.0 (C-7), 135.3, 135.1 (q-Carom, C-6), 132.7, 129.9, 129.2, 128.6 (t-Carom, C-2'), 118.5 (C-3'), 59.9 (C-4), 44.3 (C-1'), 29.5 (C-3), 23.6 (C-2), 13.4 (C_6-*C*H_3).

IR (film) υ 1692, 1609.

MS [M+1] *m/z* (%) 270 (100), 124 (23).

HRMS calculated for $C_{17}H_{19}NO_2 \cdot H^+$ 270.1494, found 270.1501.

N-allyl-5-(2,3-dimetylacryloyl)-pyrrolidin-2-one (**68d**).



According to the typical procedure pyrrolidinone **68b** was obtained from **66b** in 59% yield. It was purified by column chromatography (EtOAc) as a yellowish oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 6.49-6.42 (m, 1H, H-7), 5.35-5.24 (m, 1H, H-2'), 4.76-4.61 (m, 3H, H-3', H-1'), 3.97 (dd, *J*=15.3, 4.8, 1H, H-4), 3.06-2.87 (m, 1H, H-1'), 1.98 (d, *J*=3.2, 3H, C_6-C*H*$_3$), 1.63-1.43 (m, 7H, C_7-C*H*$_3$, H-3, H-2).

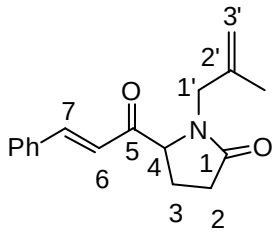
^{13}C NMR ($CDCl_3$) δ (ppm) 197.8 (C-5), 174.9 (C-1), 139.1 (C-7), 136.0 (C-6), 132.4 (C-2'), 117.8 (C-3'), 59.3 (C-4), 43.9 (C-1'), 29.2 (C-2), 23.3 (C-3), 14.7, 10.8 (C_6-*C*H_3, C_7-*C*H_3).

IR (film) υ 1692, 1609.

MS [M+1] *m/z* (%) 208 (100), 180 (2), 124 (4).

HRMS calculated for $C_{12}H_{17}NO_2 \cdot H^+$ 208.1338, found 208.1331.

5-cinnamoyl-1-(2-methylallyl)pyrrolidin-2-one (**68f**).



According to the typical procedure pyrrolidinone **68f** was obtained from **66f** in 63% yield. It was purified by column chromatography (EtOAc) as a yellowish oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.71 (d, *J*=16.0, 1H, H-7), 7.58-7.56 (m, 2H, Harom), 7.43-7.41 (m, 3H, Harom), 6.77 (d, *J*=16.0, 1H, H-6), 4.87 (s, 1H, H-3'), 4.74 (s, 1H, H-3'), 4.47-4.42 (m, 2H, H-4, H-1'), 3.31 (d, *J*=15.2, 1H, H-1'), 2.53-2.35 (m, 3H, H-2/H-3), 2.03-1.99 (m, 1H, H-3/H-2), 1.67 (s, 3H, $C_{2'}$-C*H*$_3$).

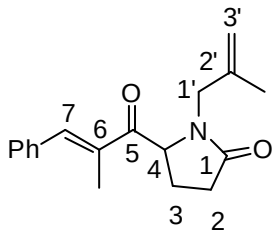
^{13}C NMR ($CDCl_3$) δ (ppm) 197.1 (C-5), 175.4 (C-1), 145.1 (C-7), 139.9 (C-2'), 133.9 (q-Carom), 131.2, 129.1, 128.6 (t-Carom), 121.5 (C-6), 113.8 (C-3'), 63.4 (C-4), 47.7 (C-1'), 29.5 (C-2), 22.4 (C-3), 20.1 (C_7-*C*H$_3$).

IR (film) υ 1690, 1603.

MS [M+1] *m/z* (%) 270 (100), 254 (3), 138 (8).

HRMS calculated for $C_{17}H_{19}NO_2 \cdot H^+$ 270.1494, found 270.1500.

(E)-5-(2-methyl-3-phenylacryloyl)-1-(2-methylallyl)pyrrolidin-2-one (**68g**).



According to the typical procedure pyrrolidinone **68g** was obtained from **66g** in 37% yield. It was purified by column chromatography (EtOAc) as a yellowish oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.47-7.28 (m, 5H, Harom), 5.03-4.99 (m, 1H, H-3'), 4.85 (s, 3H, C_6-C*H*$_3$), 4.75 (s, 1H, H-1'), 4.41 (d, *J*=15.0, 1H, H-4), 3.34-3.21 (m, 2H, H-3', H-1'), 2.52-2.37 (m, 3H, H-2/H-3), 2.08 (s, 3H, $C_{2'}$-C*H*$_3$), 1.99-1.96 (m, 1H, H-3/H-2).

^{13}C NMR ($CDCl_3$) δ (ppm) 199.0 (C-5), 175.5 (C-1), 141.3 (C-7), 139.9 (C-2'), 135.1 (C-6), 132.0 (q-Carom), 129.9, 129.1, 128.6 (t-Carom), 113.5 (C-3'), 59.7 (C-1'), 47.6 (C-4), 29.5 (C-3), 23.6 (C-2), 20.1 (C_6-*C*H$_3$), 13.4 ($C_{2'}$-*C*H$_3$).

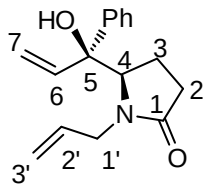
IR (film) υ 1690, 1603.

MS [M+1] *m/z* (%) 284 (100), 270 (3).

HRMS calculated for $C_{18}H_{21}NO_2 \cdot H^+$ 284.1651, found 284.1647.

3.5.4. Typical procedure for the carbonyl addition reaction. Synthesis of pyrrolidinones 60 syn.

(+/-)-(5R,1'S)-1-allyl-5-(1-hydroxy-1-phenylallyl)pyrrolidin-2-one (**60a syn**).



$ZnCl_2$ (30 mg, 0.22 mmol) was added to a solution of pyrrolidinone **58a** (50 mg, 0.2 mmol) in THF (2 mL). After 30 min, mixture was cold to -20 ºC and a vinylmagnesium bromide solution was added (0.8 mL, 1.0M in THF). After 5 h, 4 mL of a saturated solution of NH_4Cl were added. The whole mixture was extracted with DCM (3x10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave pyrrolidinone **60a syn** as a chromatographically pure yellowish oil (90%).

^{1}H NMR ($CDCl_3$) δ (ppm) 7.26-7.13 (m, 5H, Harom), 6.29-6.20 (m, 1H, H-6), 5.57-5.51 (m, 1H, H-2'), 5.45 (d, *J*=17.2, 1H, H-7), 5.27 (d, *J*=10.8, 1H, H-7), 5.08 (d, *J*=10.2, 1H, H-3'), 4.90 (d, *J*=17.1, 1H, H-3'), 4.26-4.19 (m, 1H, H-1'), 4.09-4.05 (m, 1H, H-4), 2.98-3.90 (m, 1H, H-1'), 2.28-1.86 (m, 4H, H-2, H-3).

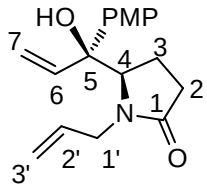
^{13}C NMR ($CDCl_3$) δ (ppm) 176.9 (C-1), 143.4 (q-Carom), 140.0 (C-6), 132.6 (C-2'), 128.5 127.6, 125.7 (t-Carom), 117.5 (C-3'), 115.5 (C-7), 79.3 (C-5), 64.5 (C-4), 44.5 (C-1'), 30.0 (C-2), 21.3 (C-3).

IR (film) υ 3368, 1670.

MS (M+1, CI) *m/z* (%) 258 (100), 240 (23), 124 (54).

HRMS calculated for $C_{16}H_{19}NO_2 \cdot H^+$ 258.1494, found 258.1501.

(+/-)-(5R,1'R)-1-allyl-5-(1-hydroxy-1-[4-methoxyphenyl)allyl]pyrrolidin-2-one (**60b syn**).



According to the typical procedure pyrrolidinone **60b syn** was obtained from **59b** in 86% yield. It was purified by column chromatography (EtOAc) as a yellowish oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.34 (d, *J*=8.8, 2H, Harom), 6.88 (d, *J*=8.8, 2H, Harom), 6.30-6.21 (m, 1H, H-6), 5.67-5.54 (m, 1H, H-2'), 5.45 (d, *J*=17.1, 1H, H-7), 5.31 (d, *J*=10.8, 1H, H-7), 5.12 (d, *J*=10.2, 1H, H-3'), 4.99 (d, *J*=17.1, 1H, H-3'), 4.31-4.27 (m, 1H, H-1'), 4.05-4.02 (m, 1H, H-4), 3.80 (s, 3H, OCH_3), 3.20-3.12 (m, 1H, H-1'), 2.32-1.68 (m, 4H, H-2, H-3).

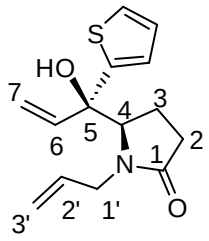
^{13}C NMR ($CDCl_3$) δ (ppm) 176.9 (C-1), 159.1 (q-Carom), 139.3 (C-6), 132.7 (C-2'), 127.0, 117.5 (t-Carom), 115.7 (C-3'), 113.9 (C-7), 79.3 (C-5), 64.7 (C-4), 55.3 (OCH_3), 44.7 (C-1'), 30.1 (C-2), 21.3 (C-3).

IR (film) υ 3394, 1668.

MS (M+1, CI) *m/z* (%) 288 (100), 272 (13), 270 (23), 163 (17).

HRMS calculated for $C_{17}H_{21}NO_3 \cdot H^+$ 288.1599, found 288.1605.

(+/-)-(5R,1'S)-1-allyl-5-[1-hydroxy-1-(2-thienyl)allyl]pyrrolidin-2-one (**60c syn**).



According to the typical procedure pyrrolidinone **60c syn** was obtained from **59c** in 61% yield. It was purified by column chromatography (EtOAc) as a brown oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.28-7.26 (m, 1H, Harom), 6.99-6.95 (m, 2H, Harom), 6.29-6.20 (m, 1H, H-6), 5.76-5.63 (m, 1H, H-2'), 5.54 (d, *J*=17.2, 1H, H-7), 5.37 (d, *J*=10.6, 1H, H-7), 5.16 (d, *J*=10.2, 1H, H-3'), 5.04 (br s, 1H, OH), 4.36 (d, *J*=17.2, 1H, H-3'), 4.04-3.97 (m, 1H, H-1'), 3.53-3.41 (m, 1H, H-4), 2.92 (s, 1H, H-1'), 2.22-1.91 (m, 4H, H-2, H-3).

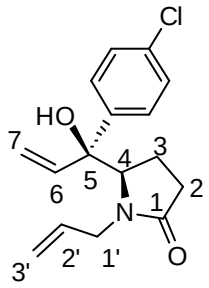
^{13}C NMR ($CDCl_3$) δ (ppm) 176.7 (C-1), 148.0 (q-Carom), 138.6 (C-6), 132.8 (C-2'), 127.1, 125.4, 124.5 (t-Carom), 117.6 (C-3'), 116.8 (C-7), 79.0 (C-5), 65.6 (C-4), 45.0 (C-1'), 29.9 (C-2), 21.4 (C-3).

IR (film) υ 3339, 1670.

MS (M, EI) *m/z* (%) 263 (100), 246 (20), 124 (93).

HRMS calculated for $C_{14}H_{17}{}^{32}SNO_2$ 263.0980, found 263.0957.

(+/-)-(5R,1'S)-1-allyl-5-[1-(4-chlorophenyl)-1-hydroxyallyl]pyrrolidin-2-one (**60d syn**).



According to the typical procedure pyrrolidinone **60d syn** was obtained from **59d** in 81% yield. It was purified by column chromatography (EtOAc) as a yellowish oil.

^{1}H NMR (MeOD) δ (ppm) 7.50 (d, *J*=8.7, 2H, Harom), 7.35 (d, *J*=8.7, 2H, Harom), 6.41-6.31 (m, 1H, H-6), 5.65-5.52 (m, 1H, H-2'), 5.46 (d, *J*=17.2, 1H, H-7), 5.31 (d, *J*=10.5, 1H, H-7), 5.09 (d, *J*=10.5, 1H, H-3'), 4.96 (d, *J*=17.2, 1H, H-3'), 4.21 (br s, 1H, OH), 4.15-4.11 (m, 2H, H-1', H-4), 3.14-3.04 (m, 1H, H-1'), 2.10-1.96 (m, 4H, H-2, H-3).

^{13}C NMR (MeOD) δ (ppm) 179.4 (C-1), 144.2, 134.3 (q-Carom), 141.8 (C-6), 133.4 (C-2'), 129.3, 129.1 (t-Carom), 117.8 (C-3'), 116.0 (C-7), 80.0 (C-5), 66.5 (C-4), 45.8 (C-1'), 30.9 (C-2), 22.3 (C-3).

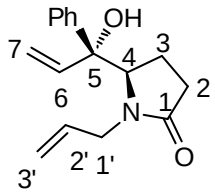
IR (film) υ 3354, 1668.

MS (M+1, CI) *m/z* (%) 292 (100), 276 (15), 234 (10), 167 (12).

HRMS calculated for $C_{16}H_{18}{}^{35}ClNO_2\ H^+$ 292.1104, found 292.1107.

3.5.5. Typical procedure for the nucleophilic addition to the keto-carbonyl group. Synthesis of pyrrolidinones 60 anti.

(+/-)-(5R,1'R)-1-allyl-5-(1-hydroxy-1-phenylallyl)pyrrolidin-2-one (**60a anti**).

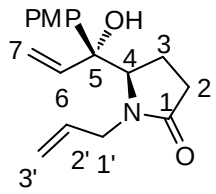


A vinylmagnesium bromide solution (0.35 mL, 1.0M in THF) was added to a solution of pyrrolidinone **58a** (50 mg, 0.2 mmol) in THF (2 mL) and the temperature was raised to 40 ºC. After 5 h, 4 mL of a saturated solution of NH_4Cl were added and the whole mixture was extracted with DCM (3x10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave pyrrolidinone **60a anti** and **60a syn** in 67:33 ratio (86% combined yield). Only the data for **60a anti** isomer is reported.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.46-7.26 (m, 5H, Harom), 6.49-6.40 (m, 1H, H-6), 5.60-5.44 (m, 1H, H-2'), 5.47 (d, *J*=17.2, 1H, H-7), 5.23 (d, *J*=10.8, 1H, H-7), 5.18 (d, *J*=10.2, 1H, H-3'), 5.07 (d, *J*=17.1, 1H, H-3'), 4.50-4.45 (m, 1H, H-1'), 4.12-4.06 (m, 1H, H-4), 3.58-3.50 (m, 1H, H-1'), 2.28-1.80 (m, 4H, H-2, H-3).

^{13}C NMR ($CDCl_3$) δ (ppm) 177.2 (C-1), 143.7 (q-Carom), 141.9 (C-6), 132.8 (C-2'), 128.5, 127.3 125.7 (t-Carom), 117.9 (C-3'), 114.1 (C-7), 78.9 (C-5), 64.4 (C-4), 45.1 (C-1'), 30.0 (C-2), 21.4 (C-3).

(+/-)-(5R,1'R)-1-allyl-5-[1-hydroxy-1-(4-methoxyphenyl)allyl]pyrrolidin-2-one (**60b anti**).

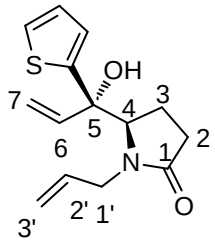


According to the typical procedure pyrrolidinones **60b anti** and **60b syn** were obtained from **59b** in a 53:47 ratio (80% combined yield). It was purified by column chromatography (EtOAc) as a yellowish oil. Only the data for **60b anti** isomer is reported.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.34 (d, *J*=8.8, 2H, Harom), 6.88 (d, *J*=8.8, 2H, Harom), 6.49-6.36 (m, 1H, H-6), 5.94-5.80 (m, 1H, H-2'), 5.45 (d, *J*=17.1, 1H, H-7), 5.31 (d, *J*=10.8, 1H, H-7), 5.19-5-15 (m, 1H, H-3'), 4.99 (d, *J*=17.1, 1H, H-3'), 4.46-4.41 (m, 1H, H-1'), 4.15-4.10 (m, 1H, H-4), 3.79 (s, 3H, OCH_3), 3.56-3.48 (m, 1H, H-1'), 2.32-1.68 (m, 4H, H-2, H-3).

^{13}C NMR ($CDCl_3$) δ (ppm) 177.2 (C-1), 159.1 (q-Carom), 139.9 (C-6), 132.7 (C-1'), 126.8, 117.9 (t-Carom), 115.7 (C-3'), 113.4 (C-7), 78.9 (C-5), 64.6 (C-4), 55.3 (OCH_3), 44.5 (C-1'), 30.1 (C-2), 21.3 (C-3).

(+/-)-(5R,1'R)-1-allyl-5-[1-hydroxy-1-(2-thienyl)allyl]pyrrolidin-2-one (**60c anti**).

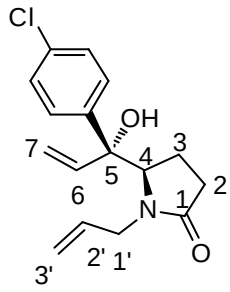


According to the typical procedure pyrrolidinones **60c anti** and **60c syn** were obtained from **59c** in a 62:38 ratio (83% combined yield). It was purified by column chromatography (EtOAc) as a brown oil. Only the data for **60c anti** isomer is reported.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.28-7.26 (m, 1H, Harom), 6.99-6.95 (m, 2H, Harom), 6.44-6.35 (m, 1H, H-6), 5.80-5.62 (m, 1H, H-2'), 5.58 (d, *J*=17.2, 1H, H-7), 5.34 (d, *J*=10.6, 1H, H-7), 5.16 (d, *J*=10.2, 1H, H-3'), 5.04 (br s, 1H, OH), 4.46 (d, *J*=17.2, 1H, H-3'), 4.04-3.97 (m, 1H, H-1'), 3.53-3.41 (m, 1H, H-4), 2.95 (s, 1H, H-1'), 2.22-1.91 (m, 4H, H-2, H-3).

^{13}C NMR ($CDCl_3$) δ (ppm) 176.7 (C-1), 148.0 (q-Carom), 140.0 (C-6), 135.8 (C-2'), 126.9, 125.6, 124.7 (t-Carom), 117.4 (C-3'), 116.9 (C-7), 68.2 (C-5), 65.6 (C-4), 45.2 (C-1'), 29.8 (C-2), 21.4 (C-3).

(+/-)-(5R,1'R)-1-allyl-5-[1-(4-chlorophenyl)-1-hydroxyallyl]pyrrolidin-2-one (**60d anti**).



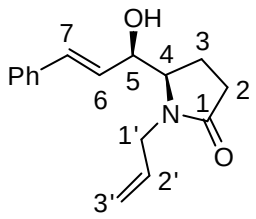
According to the typical procedure pyrrolidinones **60d anti** and **60d syn** were obtained from **59d** in a 59:41 ratio (73% combined yield). It was purified by column chromatography (EtOAc) as a yellowish oil. Only the data for **60d anti** isomer is reported.

^{1}H NMR (MeOD) δ (ppm) 7.51-7.35 (m, 4H, Harom), 6.53-6.45 (m, 1H, H-6), 5.88-5.72 (m, 1H, H-2'), 5.47 (d, *J*=17.2, 1H, H-7), 5.31 (d, *J*=10.5, 1H, H-7), 5.19 (d, *J*=10.5, 1H, H-3'), 4.96 (d, *J*=17.2, 1H, H-3'), 4.21 (br s, 1H, OH), 4.40-4.35 (m, 2H, H-1', H-4), 3.14-3.04 (m, 1H, H-1'), 2.10-1.96 (m, 4H, H-2, H-3).

^{13}C NMR (MeOD) δ (ppm) 179.4 (C-1), 142.6, 134.3 (q-Carom), 142.1 (C-6), 134.0 (C-2'), 129.3, 129.1 (t-Carom), 117.4 (C3'), 116.0 (C-7), 80.0 (C-5), 65.3 (C-4), 45.1 (C-1'), 30.8 (C-2), 23.4 (C-3).

3.5.6. Typical procedure for the reduction of the keto-carbonyl group. Synthesis of pyrrolidinones 69 syn.

(+/-)-(5R,1'R)-N-allyl-5-(1-hydroxy-3-phenylallyl)-pyrrolidin-2-one (**69a syn**).



A solution of L-selectride (1.8 mL, 1.0 M in THF) was added dropwise to a cold (-78 ºC) solution of pyrrolidinone **68a** (230 mg, 0.9 mmol) in 4.5 mL of the same solvent. After 30 min, temperature was raised to rt and 2 mL of an aqueous solution of NaOH (10%) was added. The whole mixture was extracted with DCM (3x10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave pyrrolidinone **69a syn** as a chromatographically pure yellowish oil (70%).

^{1}H NMR ($CDCl_3$) δ (ppm) 7.30-7.17 (m, 5H, Harom), 6.59 (d, *J*=15.9, 1H, H-7), 6.10 (dd, *J*=15.9, 6.00, 1H, H-6), 5.72-5.65 (m, 1H, H-2'), 5.14 (d, *J*=4.5, 1H, H-3'), 5.10 (s, 1H, H-3'), 4.39-4.25 (m, 2H, H-4, H-5), 3.76-3.64 (m, 2H, H-1'), 2.88 (br s, 1H, OH), 2.36-1.98 (m, 4H, H-2, H-3).

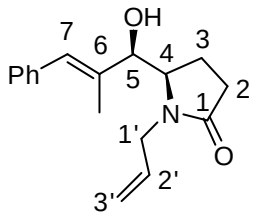
^{13}C NMR ($CDCl_3$) δ (ppm) 175.9 (C-1), 136.2 (q-Carom), 132.8, 132.3, 128.7, 128.0, 127.5, 126.5 (t-Carom, C-2', C-7, C-6), 117.8 (C-3'), 73.4 (C-5), 61.6 (C-4), 44.7 (C-1'), 30.2 (C-3), 20.5 (C-2).

IR (film) υ 3374, 1670.

MS (M+1, CI) *m/z* (%) 258 (100), 240 (30), 239 (11), 124 (42).

HRMS calculated for $C_{16}H_{19}NO_2 \cdot H^+$ 258.1494, found 258.1507.

(+/-)-(4R,1'R,2'E)-1-allyl-5-(1-hydroxy-2-methyl-3-phenylallyl)pyrrolidin-2-one (**69b syn**).



According to the typical procedure pyrrolidinone **69b syn** was obtained from **68b** in a 61% yield. It was purified by column chromatography (EtOAc) as a colourless oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.37-7.24 (m, 5H, Harom), 6.54 (s, 1H, H-7), 5.82-5.75 (m, 1H, H-2'), 5.22-5.16 (m, 2H, H-3'), 4.39 (d, *J*=15.0, 1H, H-1'), 4.19 (d, *J*=6.8, 1H, H-5), 3.97-3.86 (m, 2H, H-1', H-4), 2.55-2.25 (m, 4H, H-2, H-3), 1.89 (s, 3H, C_6-C*H*$_3$).

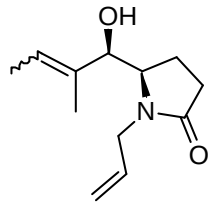
^{13}C NMR ($CDCl_3$) δ (ppm) 175.8 (C-1), 137.6, 136.8 (q-Carom, C-6), 133.4, 128.9, 128.3, 128.2, 126.9 (t-Carom, C-2', C-7), 117.2 (C-3'), 81.3 (C-5), 59.8 (C-4), 45.3 (C-1'), 30.1 (C-3), 22.1 (C-2), 14.0 (C_6-*C*H$_3$).

IR (film) υ 3363, 1668.

MS (M+1, CI) *m/z* (%) 272 (100), 254 (18), 124 (34).

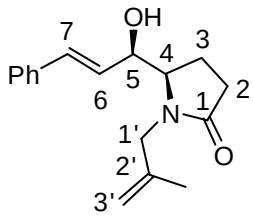
HRMS calculated for $C_{17}H_{21}NO_2 \cdot H^+$ 272.1651, found 272.1662.

(+/-)-(5R,1'R)-1-allyl-5-(1-hydroxy-2-methylbut-2-en-1-yl)pyrrolidin-2-one (**69d syn**).



According to the typical procedure pyrrolidinone **69d syn** was obtained from **68d** in a 75% yield. It was purified by column chromatography (EtOAc) as a colourless oil.

(+/-)-(5R,1'R,2'E)-5-(1-hydroxy-3-phenylallyl)-1-(2-methylallyl)pyrrolidin-2-one (**69f syn**).



According to the typical procedure pyrrolidinone **69f sin** was obtained from **68f** in a 90% yield. It was purified by column chromatography (EtOAc) as a colourless oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.31-7.19 (m, 5H, Harom), 6.62 (d, *J*=16.0, 1H, H-7), 6.11 (dd, *J*=16.0, 5.6, 1H, H-6), 4.86 (s, 1H, H-3'), 4.76 (s, 1H, H-3'), 4.41 (br s, 1H, H-5), 4.30 (d, *J*=15.5, 1H, H-1'), 3.71-3.57 (m, 2H, H-1', H-4), 2.40-2.22 (m, 3H, H-2, H-3), 1.99-1.97 (m, 1H, H-3/H-2), 1.62 (s, 3H, $C_{2'}$-CH_3).

^{13}C NMR ($CDCl_3$) δ (ppm) 176.0 (C-1), 140.2 (C-2'), 136.3 (q-Carom), 132.0, 128.6, 127.9, 127.7, 126.4 (t-Carom, C-6, C-7), 112.7 (C-3'), 73.0 (C-5), 61.3 (C-4), 47.6 (C-1'), 30.2 (C-2), 20.4 ($C_{2'}$-*C*H_3), 20.1 (C-3).

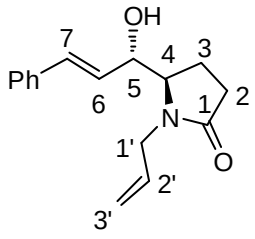
IR (film) υ 3359, 1668.

MS (M+1, CI) *m/z* (%) 272 (100), 254 (18), 124 (34).

HRMS calculated for $C_{17}H_{21}NO_2 \cdot H^+$ 272.1651, found 272.1662.

3.5.7. Typical procedure for the reduction of the keto-carbonyl group. Synthesis of pyrrolidinones 69 anti.

(+/-)-(5R,1'S,2'E)-N-allyl-5-(1-hydroxy-3-phenylallyl)-pyrrolidin-2-one (**69a anti**).



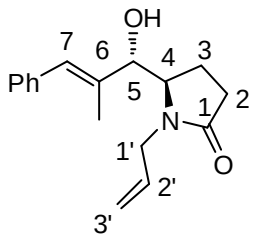
Solid $NaBH_4$ (68 mg, 1.8 mmol) was added in one portion to a cold (-78 ºC) solution of pyrrolidinone **68a** (230 mg, 0.9 mmol) in MeOH (5 mL). After 30 min, H_2O (2 mL) was added and temperature was raised to rt. The whole mixture was extracted with DCM (3x10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (MeCN) rendered, independently, pyrrolidinone **69a anti** and **69a syn** as a chromatographically pure yellowish oils in a 63:37 ratio (46% combined yield). Only the data for **69a anti** isomer is reported.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.40-7.25 (m, 5H, Harom), 6.73 (d, *J*=16.0, 1H, H-7), 6.14 (dd, *J*=16.0, 5.5, 1H, H-6), 5.87-5.74 (m, 1H, H-2'), 5.27 (d, *J*=9.2, 1H, H-3'), 5.23 (s, 1H, H-3'), 4.63 (s, 1H, H-5), 4.36 (dd, *J*=15.5, 4.8, 1H, H-4), 3.72 (dd, *J*=16.2, 6.9, 2H, H-1'), 2.92 (br s, 1H, OH), 2.59-

2.47 (m, 1H, H-2/H-3), 2.32-2.26 (m, 1H, H-3/H-2), 2.14-1.87 (m, 2H, H-2, H-3).

^{13}C NMR ($CDCl_3$) δ (ppm) 176.1 (C-1), 136.4 (q-Carom), 132.8, 132.1, 128.7, 127.3, 126.5 (t-Carom, C-2', C-7, C-6), 118.2 (C-3'), 70.7 (C-5), 61.9 (C-4), 43.6 (C-1'), 30.6 (C-3), 18.2 (C-2).

(+/-)-(5R,1'S,2'E)-1-allyl-5-(1-hydroxy-2-methyl-3-phenylallyl)pyrrolidin-2-one (**69b anti**).



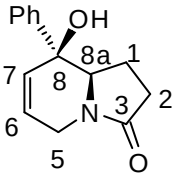
According to the typical procedure pyrrolidinones **69b anti** and **69b syn** were obtained from **68b** (37% combined yield). It was purified by column chromatography (MeCN) as a yellowish oil. Only the data for **69b anti** isomer is reported.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.37-7.21 (m, 5H, Harom), 6.72 (s, 1H, H-7), 5.84-5.80 (m, 1H, H-2'), 5.30-5.23 (m, 2H, H-3'), 4.45-4.38 (m, 2H, H-1'), 3.85-3.83 (m, 1H, H-5), 3.70-3.62 (m, 1H, H-4), 2.60-2.00 (m, 7H, H-2, H-3, C_6-C*H*$_3$).

^{13}C NMR ($CDCl_3$) δ (ppm) 176.1 (C-1), 137.4, 135.9 (q-Carom,C-6), 133.0, 129.0, 128.2, 126.6, 125.9 (t-Carom, C-2', C-7), 118.3 (C-3'), 73.2 (C-5), 59.8 (C-4), 43.4 (C-1'), 30.6 (C-3), 17.5 (C-2), 15.8 (C_6-*C*H$_3$).

3.5.8. Typical procedure for the olefin metathesis reaction. Synthesis of indolizidinones 61 and compound 71.

(+/-)-(8S,8aR)-8-hydroxy-8-phenyl-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**61a syn**).



Grubbs II catalyst (5 mg, 10% wt) was added in one portion onto a solution of pyrrolidinone **60a syn** (50 mg, 0.2 mmol) in DCM (10 mL) at rt. After 12 h, the solvent was eliminated under vacuum and the resulting residue was column chromatographed (EtOAc) to afford indolizidinone **61a syn** as a white solid that was triturated in Et_2O (65%).

mp 162-165 ºC (Et_2O).

^{1}H NMR ($CDCl_3$) δ (ppm) 7.41-7.26 (m, 5H, Harom), 5.97 (d, *J*=10.3, 1H, H-7), 5.82 (d, *J*=10.3, 1H, H-6), 4.48 (d, *J*=18.8, 1H, H-5), 3.79 (d, *J*=7.7, 1H, H-8a), 3.63 (d, *J*=18.8, 1H, H-5), 2.79 (br s, 1H, OH), 2.02-1.75 (m, 3H, H-1, H-2), 1.41-1.27 (m, 1H, H-2/H-1).

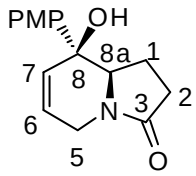
^{13}C NMR ($CDCl_3$) δ (ppm) 174.9 (C-3), 139.0 (q-Carom), 133.5 (C-6), 128.2 127.8, 126.5 (t-Carom), 123.7 (C-7), 73.9 (C-8), 63.0 (C-8a), 40.0 (C-5), 29.2 (C-2), 18.8 (C-1).

IR (film) υ 3359, 1670.

MS (M+1, CI) *m/z* (%) 230 (100), 212 (83), 211 (53), 146 (34).

HRMS calculated for $C_{14}H_{15}NO_2 \cdot H^+$ 230.1181, found 230.1191.

(+/-)-(8S,8aR)-8-hydroxy-8-(4-methoxyphenyl)-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**61b syn**).



According to the typical procedure indolizidinone **61b syn** was obtained from **60b syn** in 65% yield. It was purified by column chromatography (EtOAc) as a brown oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.23 (d, *J*=8.7, 2H, Harom), 6.85 (d, *J*=8.7, 2H, Harom), 5.94 (d, *J*=10.2, 1H, H-7), 5.79 (d, *J*=10.2, 1H, H-6), 4.46 (d, *J*=18.9, 1H, H-5), 3.77 (br s, 4H, H-8a, OCH_3), 3.61 (d, *J*=18.9, 1H, H-5), 2.57 (br s, 1H, OH), 1.97-1.77 (m, 4H, H-1, H-2).

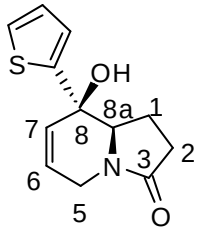
^{13}C NMR ($CDCl_3$) δ (ppm) 174.8 (C-3), 159.3, 131.4 (q-Carom), 133.7 (C-6), 127.7, 123.5 (t-Carom), 133.5 (C-7), 73.6 (C-8), 63.0 (C-8a), 55.2 (OCH_3), 39.9 (C-5), 29.2 (C-2), 18.8 (C-1).

IR (film) υ 3389, 1670.

MS (M+1, CI) *m/z* (%) 260 (100), 242 (99), 241 (77), 240 (41), 223 (11), 176 (53).

HRMS calculated for $C_{15}H_{17}NO_3 \cdot H^+$ 260.1286, found 260.1285.

(+/-)-(8R,8aR)-8-hydroxy-8-(thien-2-yl)-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**61c syn**).



According to the typical procedure indolizidinone **61c syn** was obtained from **60c syn** in 60% yield. It was purified by column chromatography (EtOAc) as a brown oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.31-7.25 (m, 1H, Harom), 7.00-6.93 (m, 1H, Harom), 6.81-6.77 (m, 1H, Harom) 6.04-5.88 (m, 2H, H-6, H-7), 4.45 (d, *J*=19.3, 1H, H-5), 3.87-3.82 (m, 1H, H-8a), 3.61 (d, *J*=19.3, 1H, H-5), 3.12 (br s, 1H, OH), 2.11-2.00 (m, 3H, H-1, H-2), 1.41-1.31 (m, 1H, H-1/H-2).

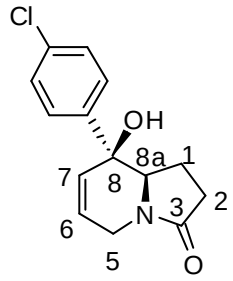
^{13}C NMR ($CDCl_3$) δ (ppm) 175.0 (C-3), 144.8 (q-Carom) 133.7 (C-6), 127.3, 126.2, 125.4 (t-Carom), 123.6 (C-7), 73.3 (C-8), 62.6 (C-8a), 39.9 (C-5), 29.0 (C-2), 19.0 (C-1).

IR (film) υ 3330, 1670.

MS (M+1, CI) *m/z* (%) 236 (100), 218 (89), 217 (64), 152 (60).

HRMS calculated for $C_{12}H_{13}{}^{32}SNO_2 \cdot H^+$ 236.0745, found 236.0741

(+/-)-(8S,8aR)-8-(4-chlorophenyl)-8-hydroxy-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**61d syn**).



According to the typical procedure indolizidinone **61d syn** was obtained from **60d syn** in 58% yield. It was purified by column chromatography (EtOAc) as a brown oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.36-7.27 (m, 4H, Harom), 6.00 (d, *J*=10.6, 1H, H-7), 5.80 (d, *J*=10.6, 1H, H-6), 4.51 (d, *J*=19.2, 1H, H-5), 3.78 (d, *J*=8.3, 1H, H-8a), 3.63 (d, *J*=19.2, 1H, H-5), 2.33 (br s, 1H, OH), 1.98-1.54 (m, 4H, H-1, H-2).

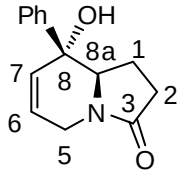
^{13}C NMR ($CDCl_3$) δ (ppm) 174.6 (C-3), 159.3, 131.4 (q-Carom) 133.1 (C-6), 128.3, 128.0 (t-Carom), 133.1 (C-7), 124.3 (C-8), 63.0 (C-8a), 40.0 (C-5), 29.1 (C-2), 18.7 (C-1).

IR (film) υ 3387, 1670.

MS (M+1, CI) *m/z* (%) 264 (100), 248 (36), 246 (40).

HRMS calculated for $C_{14}H_{14}{}^{35}ClNO_2 \cdot H^+$ 264.0791, found 264.0804.

(+/-)-(8R,8aR)-8-hydroxy-8-phenyl-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**61a anti**).

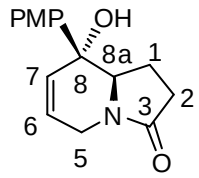


According to the typical procedure indolizidinones **61a anti** and **61a syn** were obtained from **60a** in a 67:33 ratio (66% combined yield). It was purified by column chromatography (EtOAc) as a yellowish oil. Only the data for **61a anti** isomer is reported.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.43-7.30 (m, 5H, Harom), 6.01 (s, 2H, H-7, H-6), 3.79 (d, *J*=7.7, 1H, H-8a), 3.71 (dd, *J*=3.7, 2H, H-5), 3.42 (br s, 1H, OH), 2.58-2.14 (m, 4H, H-1, H-2).

^{13}C NMR ($CDCl_3$) δ (ppm) 175.5 (C-3), 142.8 (q-Carom), 132.6 (C-6), 128.0 127.6, 126.6 (t-Carom), 123.3 (C-7), 71.6 (C-8), 64.0 (C-8a), 40.1 (C-5), 30.3 (C-2), 17.3 (C-1).

(+/-)-(8S,8aR)-8-hydroxy-8-(4-methoxyphenyl)-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**61b anti**).

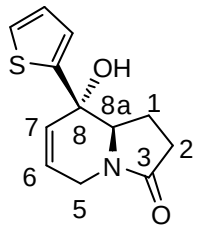


According to the typical procedure indolizidinones **61b anti** and **61b syn** were obtained from **60b** in a 53:47 ratio (60% combined yield). It was purified by column chromatography (EtOAc) as a brown oil. Only the data for **61b anti** isomer is reported.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.23 (d, *J*=8.7, 2H, Harom), 6.85 (d, *J*=8.7, 2H, Harom), 5.98 (s, 2H, H-6, H-7), 4.46 (d, *J*=18.9, 1H, H-5), 3.80 (br s, 4H, H-8a, OCH_3), 3.61 (d, *J*=18.9, 1H, H-5), 2.57 (br s, 1H, OH), 1.97-1.77 (m, 4H, H-1, H-2).

^{13}C NMR ($CDCl_3$) δ (ppm) 175.4 (C-3), 158.8, 132.9 (q-Carom), 133.7 (C-6), 126.8, 126.5 (t-Carom), 134.9 (C-7), 71.5 (C-8), 63.9 (C-8a), 55.3 (OCH_3), 40.0 (C-5), 30.3 (C-2), 17.4 (C-1).

(+/-)-(8S,8aR)-8-hydroxy-8-(thien-2-yl)-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**61c anti**).

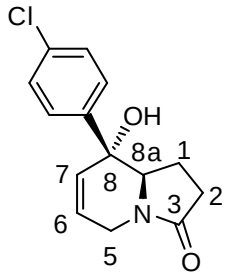


According to the typical procedure indolizidinones **61c anti** and **61c syn** were obtained from **60c** in a 62:38 ratio (69% combined yield). It was purified by column chromatography (EtOAc) as a brown oil. Only the data for **61c anti** isomer is reported.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.31-7.25 (m, 1H, Harom), 7.00-6.93 (m, 1H, Harom), 6.81-6.77 (m, 1H, Harom) 6.92 (s, 2H, H-6, H-7), 4.45 (d, *J*=19.3, 1H, H-5), 3.87-3.82 (m, 1H, H-8a), 3.61 (d, *J*=19.3, 1H, H-5), 3.12 (br s, 1H, OH), 2.11-2.00 (m, 3H, H-1, H-2), 1.41-1.31 (m, 1H, H-1/H-2).

^{13}C NMR ($CDCl_3$) δ (ppm) 175.4 (C-3), 147.4 (q-Carom) 132.71 (C-6), 127.1, 126.8, 125.1 (t-Carom), 123.4 (C-7), 71.3 (C-8), 63.7 (C-8a), 40.0 (C-5), 29.5 (C-2), 18.0 (C-1).

(+/-)-(8R,8aR)-8-(4-chlorophenyl)-8-hydroxy-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**61d anti**).

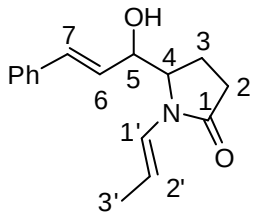


According to the typical procedure indolizidinones **61d anti** and **61d syn** were obtained from **60d** in a 59:41 ratio (65% combined yield). It was purified by column chromatography (EtOAc) as a brown oil. Only the data for **61d anti** isomer is reported.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.36-7.27 (m, 4H, Harom), 6.09 (s, 2H, H-6, H-7), 4.51 (d, *J*=19.2, 1H, H-5), 3.78 (d, *J*=8.3, 1H, H-8a), 3.63 (d, *J*=19.2, 1H, H-5), 2.33 (br s, 1H, OH), 1.98-1.54 (m, 4H, H-1, H-2).

^{13}C NMR ($CDCl_3$) δ (ppm) 175.4 (C-3), 159.6, 132.9 (q-Carom), 133.6 (C-6), 129.1, 128.3 (t-Carom), 134.9 (C-7), 123.2 (C-8), 63.9 (C-8a), 40.0 (C-5), 30.2 (C-2), 18.7 (C-1).

5-(1-hydroxy-3-phenylallyl)-N-(1-propenyl)pyrrolidin-2-one (**71**).



According to the typical procedure pyrrolidinone **71** was obtained from **69a** in a 63:37 ratio (20% combined yield). It was purified by column chromatography (EtOAc) as a brown oil.

^{1}H NMR (syn + anti) ($CDCl_3$) δ (ppm) 7.42-7.25 (m, 10H, Harom), 6.85-6.60 (m, 4H, H-7, H-1'), 6.24-6.07 (m, 2H, H-6), 5.33-5.21/5.15-5.06 (m, 1H, H-2'), 4.90/4.78 (s, 1H, H-5), 4.21-4.16/4.04-4.01

(m, 1H, H-4), 3.76-3.64 (m, 2H, H-1'), 2.78-1.93 (m, 8H, H-2, H-3), 1.79-1.76 (m, 6H, H-3').

^{13}C NMR ($CDCl_3$) δ (ppm) 174.1/173.4 (C-1), 136.3 (q-Carom), 132.5, 131.7, 128.7, 128.0, 127.8, 126.5, 126.2, 123.7, 123.3 (t-Carom, C-1', C-7, C-6), 108.2/107.9 (C-2'), 70.7/69.6 (C-5), 61.0/60.6 (C-4), 31.3/30.8 (C-2), 19.2/18.3 (C-3), 15.6/15.5 (C-3').

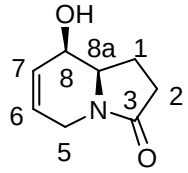
IR (film) υ 3394, 1663.

MS (M+1, CI) *m/z* (%) 258 (49), 240 (54), 200 (100), 124 (57).

HRMS calculated for $C_{16}H_{19}NO_2 \cdot H^+$ 258.1494, found 258.1506.

3.5.9. Typical procedure for the olefin metathesis reaction. Synthesis of indolizidinones 70 and compounds 80 and 81.

(+/-)-(8R,8aR)-8-hydroxy-1,5,8,8a-tetrahydro-2H-indolizidin-3-one **(70a syn).**



Grubbs II catalyst (3 mg, 10% wt) was added in one portion onto a solution of pyrrolidinone **69a syn** (90 mg, 0.35 mmol) in toluene (10 mL) and temperature was raised to reflux. After 4 h, the mixture was cooled to rt and solvent was eliminated under vacuum. The resulting residue was column chromatographed (EtOAc) to afford indolizidinone **70a syn** as a white solid that was triturated in hexanes (71%).

mp 111-113 ºC (hexanes).

^{1}H NMR ($CDCl_3$) δ (ppm) 6.83 (d, *J*=7.0, 1H, H-7), 4.96 (dd, *J*=11.9, 5.9, 1H, H-6), 3.98 (s, 1H, H-8), 3.76 (dd, *J*=16.1, 8.0, 1H, H-8a), 2.51-1.95 (m, 7H, H-1, H-2, H-5, OH).

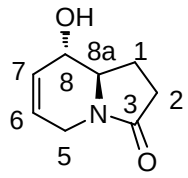
^{13}C NMR ($CDCl_3$) δ (ppm) 172.7 (C-3), 121.8 (C-7), 105.0 (C-6), 63.4 (C-8), 58.9 (C-8a), 31.6 (C-5), 30.7 (C-2), 20.1 (C-1).

IR υ 3359, 1670.

MS [M+1] *m/z* (%) 154 (100), 153 (37), 136 (12).

HRMS calculated for $C_8H_{11}NO_2 \cdot H^+$ 154.0868, found 154.0866.

(+/-)-(8S,8aR)-8-hydroxy-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**70a anti**).

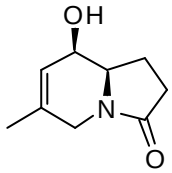


According to the typical procedure inodlizidinone **70a anti** was obtained from **69a anti** in a 86% combined yield. It was purified by column chromatography (EtOAc) as a brown oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 6.72 (d, *J*=7.5, 1H, H-7), 5.05-5.00 (m, 1H, H-6), 3.68-3.60 (m, 1H, H-8), 3.54-3.45 (m, 1H, H-8a), 2.97 (br s, 1H, OH), 2.45-1.39 (m, 4H, H-1/H-2/H-5), 2.20-2.11 (m, 1H, H-1/H-2/H-5), 1.83-1.76 (m, 1H, H-1/H-2/H-5).

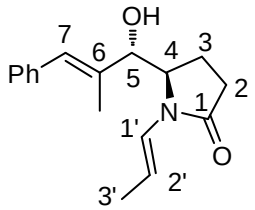
^{13}C NMR ($CDCl_3$) δ (ppm) 171.9 (C-3), 121.2 (C-7), 107.2 (C-6), 70.4 (C-8), 60.4 (C-8a), 32.5 (C-5), 31.1 (C-2), 24.3 (C-1).

(+/-)-(8R,8aR)-8-hydroxy-6-methyl-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**70f syn**).



According to the typical procedure inodlizidinone **70f syn** was obtained from **69f syn** in a <10% combined yield. It was purified by column chromatography (EtOAc) as a colourless oil.

(+/-)-(5R,1'S,2'E)-5-(1-hydroxy-2-methyl-3-phenylallyl)-1-(prop-1-en-1-yl)pyrrolidin-2-one (**80 anti**).



According to the typical procedure pyrrolidinone **80 anti** was obtained from **69b anti** in a 20% yield. It was purified by column chromatography (EtOAc) as a brown oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.38-7.24 (m, 5H, Harom), 6.87-6.77 (m, 2H, H-7, H-1'), 5.18-5.09 (m, 1H, H-2'), 4.72 (s, 1H, H-5), 4.17-4.08 (m, 1H, H-4), 2.75-2.66 (m, 1H, H-2/H-3), 2.34-2.20 (m, 3H, H-3, H-2) 1.92 (s, 3H, C_6-C*H*$_3$), 1.79 (s, 3H, H-3').

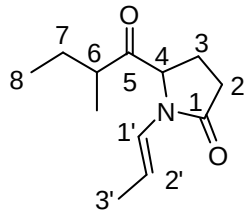
^{13}C NMR ($CDCl_3$) δ (ppm) 174.2 (C-1), 136.0, 129.0 (q-Carom, C-6), 128.3, 128.2, 126.6, 125.9, 123.4 (t-Carom, C-1', C-7), 107.5 (C-2'), 72.6 (C-5), 59.1 (C-4), 31.4 (C-2), 17.7 (C-3), 16.0, 15.6 (C-3', C_6-*C*H$_3$).

IR (film) υ 3374, 1670.

MS [M+1] *m/z* (%) 272 (100), 254 (18), 124 (36).

HRMS calculated for $C_{17}H_{21}NO_2 \cdot H^+$ 272.1651, found 272.1662.

N-(1-propenyl)-5-(2-methylbutanoyl)-pyrrolidin-2-one (**81**).



According to the typical procedure pyrrolidinone **81** was obtained from **69d syn** in a 36% yield. It was purified by column chromatography (EtOAc) as a colourless oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 6.80 (d, *J*=14.5, 2H, H-1'), 4.73-4.63 (m, 2H, H-2'), 4.51 (d, *J*=9.6, 2H, H-5), 2.65-2.23 (m, 6H, H-6, H-4), 1.95-1.68 (m, 8H, H-3, H-7), 1.63 (dd, *J*=6.6, 1.5, 6H, H-3'), 1.13/1.07 (d, *J*=7.0, 3H, C_6-C*H*$_3$), 0.92-0.82 (m, 6H, H-8).

^{13}C NMR ($CDCl_3$) δ (ppm) 211.2/210.5 (C-5), 172.8/172.8 (C-1), 123.9/123.8 (C-1'), 107.4/107.2 (C-2'), 63.6/63.1 (C-4), 44.5/44.0 (C-6), 29.5/29.4 (C-2), 26.3/25.4 (C-7), 21.7/21.4 (C-3), 17.0, 15.6, 15.2, 11.8, 11.4 (C_6-*C*H$_3$, C-3', C-8).

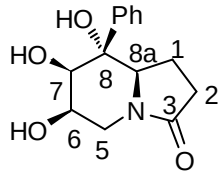
IR (film) υ 1689, 1609.

MS [M+1] *m/z* (%) 210 (100), 208 (4).

HRMS calculated for $C_{12}H_{19}NO_2 \cdot H^+$ 210.1494, found 210.1488

3.5.10. Typical procedure for dihydroxylation reaction. Synthesis of compounds 62a anti and 72a syn.

(+/-)-(6R,7R,8R,8aR)-6,7,8-trihydroxy-8-phenylhexahydroindolizin-3(2H)-one (**62a anti**).



$K_2OsO_4 \cdot 2H_2O$ (4 mg, 0.01 mmol) and N-methylmorpholine-N-oxide (50 mg, 0.42 mmol) were sequentially added to 2 mL of an acetone/water (1/1) solution of indolizidinone **61a anti:syn** in a 67:33 ratio (50 mg, 0.2 mmol). The mixture was stirred at rt for 18 h, and then filtered through celite. The volatiles were eliminated and the residue was column chromatographed (EtOAc) to render trihydroxyindolizidinone **62a anti** as a white solid which was triturated in Et_2O (57%).

mp 183-184 ºC (Et_2O).

^{1}H NMR (MeOD) δ (ppm) 7.50-7.47 (m, 2H, Harom), 7.37-7.27 (m, 3H, Harom), 4.21-4.17 (m, 1H, H-8a), 4.04-3.98 (m, 1H, H-5), 3.89-3.83 (m, 1H, H-6), 3.71 (s, 1H, H-7), 3.06-2.99 (m, 1H, H-5), 2.55-2.09 (m, 3H, H-1, H-2), 1.87-1.75 (m, 1H, H-2/H-1).

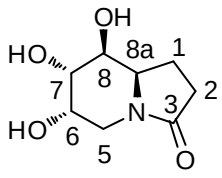
^{13}C NMR (MeOD) δ (ppm) 176.6 (C-3), 142.7 (q-Carom), 129.2, 128.5, 128.3, (t-Carom), 78.0 (C-7), 76.3 (C-8), 65.4 (C-6), 60.8 (C-8a), 40.9 (C-5), 31.7 (C-2), 18.6 (C-1).

IR (film) υ 3408, 1658.

MS (M+1, CI) *m/z* (%) 264 (100), 246 (33), 230 (33), 228 (61), 212 (26), 210 (17), 190 (12), 140 (17), 115 (13), 84 (11).

HRMS calculated for $C_{14}H_{17}NO_4 \cdot H^+$ 264.1236, found 264.1244.

(+/-)-(6S,7S,8S,8aR)-6,7,8-trihydroxy-hexahydro-indolizidin-3-one (**72a syn**).



According to the typical procedure indolizidinone **72a syn** was obtained from **70a syn** in a 93% yield. It was purified by column chromatography (EtOAc) as a colourless oil.

^{1}H NMR (MeOD) δ (ppm) 5.48 (d, *J*=3.7, 1H, H-5), 3.94-3.64 (m, 3H, H-8, H-8a, H-5), 2.49-2.29 (m, 2H, H-7, H-6), 2.11-1.87 (m, 4H, H-1, H-2).

^{13}C NMR (MeOD) δ (ppm) 177.5 (C-3), 74.5 (C-8), 68.2, 65.0, 57.2 (C-8a, C-6, C-7), 35.2 (C-1/C-2), 32.5 (C-5), 19.6 (C-2/C-1).

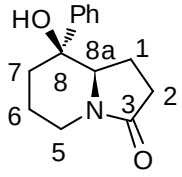
IR (film) υ 3408, 1660.

MS [M+1] *m/z* (%) 188 (10), 171 (10), 170 (100), 152 (63).

HRMS calculated for $C_8H_{13}NO_4 \cdot H^+$ 188.0923, found 188.0845.

3.5.11. Typical procedure for hydrogenation reaction. Synthesis of indolizidinones 64 and 73.

(+/-)-(8S,8aR)-8-hydroxy-8-phenylhexahydroindolizin-3(2H)-one (**64a syn**).



A solution of pyrrolidinone **61a syn** (930 mg, 2.1 mmol) in 10 mL of MeOH was hydrogenated (70 psi) in the presence of Pd/C overnight. The catalyst was filtered through celite and the resulting oil was purified by column chromatography (MeOH) to afford indolizidinone **64a syn** as a white solid oil which was triturated in Et_2O (60%).

mp 144-148 ºC (Et_2O).

^{1}H NMR ($CDCl_3$) δ (ppm) 7.47 (d, *J*=7.4, 2H, Harom), 7.35-7.26 (m, 3H, Harom), 4.22 (d, *J*=13.1, 1H, H-5), 3.71 (t, *J*=8.3, 1H, H-8a), 2.85-2.77, 2.74 (m, H-5, OH), 2.41-2.04 (m, 4H, H-6/H-7/H-1/H-2), 1.92-1.64 (m, 4H, H-6/H-7/H-1/H-2).

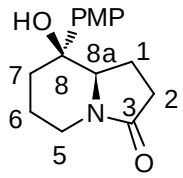
^{13}C NMR (MeOD) δ (ppm) 184.5 (C-3), 143.7 (q-Carom), 128.0, 127.9, 126.7 (t-Carom), 73.6 (C-8), 67.4 (C-8a), 40.8 (C-5), 40.4 (C-7), 31.1 (C-2), 21.4 (C-6), 19.8 (C-1).

IR (film) υ 3379, 1663.

MS (M+1, CI) *m/z* (%) 232 (100), 214 (47), 213 (28).

HRMS calculated for $C_{14}H_{17}NO_2 \cdot H^+$ 232.1337, found 232.1343.

(+/-)-(8S,8aR)-8-hydroxy-8-(4-methoxyphenyl)hexahydroindolizin-3(2H)-one (**64b syn**).



According to the typical procedure indolizidinone **64b syn** was obtained from **61b syn** in 63% yield. It was purified by column chromatography (EtOAc) as a yellowish oil.

^{1}H NMR (MeOD) δ (ppm) 7.37 (d, *J*=8.9, 2H, Harom), 6.88 (d, *J*=8.9, 2H, Harom), 4.10 (d, *J*=13.2, 1H, H-5), 3.77-3.71 (m, 4H, H-8a, OCH_3), 2.91-2.81 (m, 1H, H-5), 2.40-1.69 (m, 8H, H-1, H-2, H-6, H-7).

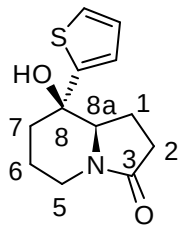
^{13}C NMR (MeOD) δ (ppm) 176.6 (C-3), 160.0, 136.6 (q-Carom), 128.8, 114.4 (t-Carom), 73.7 (C-8), 67.7 (C-8a), 56.7 (OCH_3), 41.0 (C-5), 40.5 (C-7), 31.1 (C-2), 21.6 (C-6), 19.7 (C-1).

IR (film) υ 3379, 1660.

MS (M+1, CI) *m/z* (%) 262 (67), 244 (100), 243 (49).

HRMS calculated for $C_{15}H_{19}NO_3 \cdot H^+$ 262.1443, found 262.1455.

(+/-)-(8R,8aR)-8-hydroxy-8-(thien-2-yl)hexahydroindolizin-3(2H)-one (**64c syn**).



According to the typical procedure indolizidinone **64c syn** was obtained from **61c syn** in 56% yield. It was purified by column chromatography (EtOAc) as a yellowish oil.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.26-7.18 (m, 1H, Harom), 6.95-

6.87 (m, 2H, Harom), 4.17-4.13 (m, 1H, H-8a), 3.61-3.56 (m, 1H, H-5), 3.75-2.67 (m, 1H, H-5), 2.28-1.66 (m, 9H, H-1, H-2, H-6, H-7, OH).

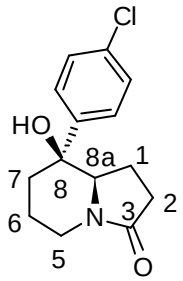
^{13}C NMR ($CDCl_3$) δ (ppm) 174.8 (C-3), 146.3 (q-Carom), 126.8, 124.3, 123.7 (t-Carom), 73.9 (C-8), 66.0 (C-8a), 39.4 (C-5), 39.1 (C-7), 30.1 (C-2), 21.0 (C-6), 18.1 (C-1).

IR (film) υ 3334, 1660.

MS (M+1, CI) *m/z* (%) 238 (100), 222 (14), 220 (48), 219 (23).

HRMS calculated for $C_{12}H_{15}{}^{32}SNO\cdot H^+$ 238.0902, found 238.0913.

(+/-)-(8S,8aR)-8-(4-chlorophenyl)-8-hydroxyhexahydroindolizin-3(2H)-one (**64d syn**).



According to the typical procedure indolizidinone **64d syn** was obtained from **61d syn** in 53% yield. It was purified by column chromatography (EtOAc) as a brown oil.

^{1}H NMR (MeOD) δ (ppm) 7.44 (d, *J*=8.7, 2H, Harom), 7.33 (d, *J*=8.7, 2H, Harom), 4.14-4.10 (m, 1H, H-5), 3.80-3.73 (m, 1H, H-8a), 2.90-2.83 (m, 1H, H-5), 2.39-1.69 (m, 8H, H-1, H-2, H-6, H-7).

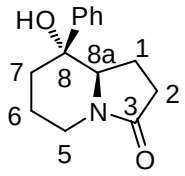
^{13}C NMR (MeOD) δ (ppm) 176.7 (C-3), 144.8, 134.0 (q-Carom), 129.4, 129.1 (t-Carom), 73.6 (C-8), 67.4 (C-8a), 40.8 (C-5), 40.5 (C-7), 31.1 (C-2), 21.4 (C-6), 19.8 (C-1).

IR (film) υ 3379, 1660.

MS (M+1, CI) *m/z* (%) 266 (100), 250 (10), 248 (19).

HRMS calculated for $C_{14}H_{16}{}^{35}ClNO_2 \cdot H^+$ 266.0948, found 266.0948.

(+/-)-(8R,8aR)-8-hydroxy-8-phenylhexahydroindolizin-3(2H)-one (**64a anti**).

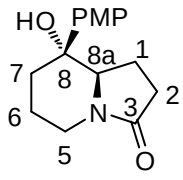


According to the typical procedure pyrrolidinones **64a anti** and **64a syn** were obtained from **61a** in a 67:33 ratio (69% combined yield). It was purified by column chromatography (EtOAc) as a yellowish oil. Only the data for **64a anti** isomer is reported.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.47 (d, *J*=7.4, 2H, Harom), 7.33-7.25 (m, 3H, Harom), 4.21 (d, *J*=13.1, 1H, H-5), 3.70 (t, *J*=8.3, 1H, H-8a), 2.86-2.76, 2.74 (m+s, 2H, H-5, OH), 2.41-2.04 (m, 4H, H-6/H-7/H-1/H-2), 1.90-1.63 (m, 4H, H-6/H-7/H-1/H-2).

^{13}C NMR (MeOD) δ (ppm) 184.4 (C-3), 143.7 (q-Carom), 128.1, 127.9, 126.8 (t-Carom), 73.6 (C-8), 67.5 (C-8a), 40.9 (C-5), 40.3 (C-7), 31.3 (C-2), 21.4 (C-6), 19.8 (C-1).

(+/-)-(8R,8aR)-8-hydroxy-8-(4-methoxyphenyl)hexahydroindolizin-3(2H)-one (**64b anti**).

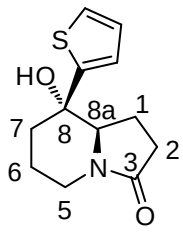


According to the typical procedure pyrrolidinones **64b anti** and **64b syn** were obtained from **61b** in a 53:47 ratio (67% combined yield). It was purified by column chromatography (EtOAc) as a yellowish oil. Only the data for **64b anti** isomer is reported.

^{1}H NMR (MeOD) δ (ppm) 7.36 (d, *J*=8.9, 2H, Harom), 6.89 (d, *J*=8.9, 2H, Harom), 4.11 (d, *J*=13.2, 1H, H-5), 3.75-3.71 (m, 4H, H-8a, OCH_3), 2.91-2.83 (m, 1H, H-5), 2.38-1.65 (m, 8H, H-1, H-2, H-6, H-7).

^{13}C NMR (MeOD) δ (ppm) 176.5 (C-3), 160.0, 135.6 (q-Carom), 128.8, 114.3 (t-Carom), 73.6 (C-8), 67.5 (C-8a), 56.7 (OCH_3), 40.9 (C-5), 40.5 (C-7), 32.1 (C-2), 21.6 (C-6), 19.7 (C-1).

(+/-)-(8S,8aR)-8-hydroxy-8-(thien-2-yl)hexahydroindolizin-3(2H)-one (**64c anti**).

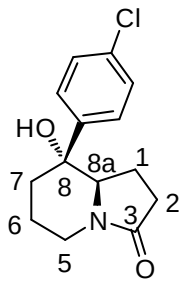


According to the typical procedure indolizidinones **64c anti** and **64c syn** were obtained from **64c** in a 62:38 ratio (68% combined yield). It was purified by column chromatography (EtOAc) as a yellowish oil. Only the data for **64c anti** isomer is reported.

^{1}H NMR ($CDCl_3$) δ (ppm) 7.40-7.37 (m, 1H, Harom), 6.93-6.90 (m, 1H, Harom), 6.87-6.83 (m, 1H, Harom), 3.85-3.80 (m, 1H, H-8a), 3.39-3.23 (m, 2H, H-5), 2.23-1.43 (m, 8H, H-1, H-2, H-6, H-7).

^{13}C NMR ($CDCl_3$) δ (ppm) 174.8 (C-3), 146.2 (q-Carom), 126.6, 124.3, 123.7 (t-Carom), 74.0 (C-8), 66.1 (C-8a), 39.3 (C-5), 39.2 (C-7), 30.1 (C-2), 21.0 (C-6), 18.1 (C-1).

(+/-)-(8R,8aR)-8-(4-chlorophenyl)-8-hydroxyhexahydroindolizin-3(2H)-one (**64d anti**).

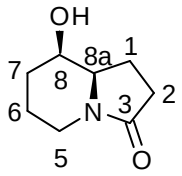


According to the typical procedure indolizidinones **64d anti** and **64d syn** were obtained from **64d** in a 59:41 ratio (65% combined yield). It was purified by column chromatography (EtOAc) as a yellowish oil. Only the data for **64d anti** isomer is reported.

^{1}H NMR (MeOD) δ (ppm) 7.44 (d, *J*=8.7, 2H, Harom), 7.33 (d, *J*=8.7, 2H, Harom), 4.14-4.10 (m, 1H, H-5), 3.80-3.73 (m, 1H, H-8a), 2.90-2.83 (m, 1H, H-5), 2.39-1.69 (m, 8H, H-1, H-2, H-6, H-7).

^{13}C NMR (MeOD) δ (ppm) 176.7 (C-3), 143.7, 134.0 (q-Carom), 129.3, 128.1 (t-Carom), 73.8 (C-8), 67.5 (C-8a), 40.9 (C-5), 40.4 (C-7), 31.1 (C-2), 21.4 (C-6), 19.8 (C-1).

(+/-)-(8R,8aR)-8-hydroxyhexahydroindolizin-3(2H)-one (**73a syn**).



According to the typical procedure indolizidinones **73a syn** was obtained from **70a syn** in a 46% yield. It was purified by column chromatography (EtOAc) as a colourless oil.

^{1}H NMR (MeOD) δ (ppm) 4.13-4.09 (m, 1H, H-8), 3.81 (s, 1H, OH), 3.55-3.51 (m, 1H, H-8a), 2.65-1.24 (m, 10H, H-1, H-2, H-5, H-6, H-7).

^{13}C NMR (MeOD) δ (ppm) 174.7 (C-3), 66.5 (C-8), 60.9 (C-8a), 39.9 (C-5), 30.8 (C-2), 30.4 (C-7), 19.3 (C-6), 17.7 (C-1).

IR (film) υ 3379, 1660.

MS (M+1, CI) *m/z* (%) 156 (100), 155 (17), 138 (13).

HRMS calculated for $C_8H_{13}NO_2 \cdot H^+$ 156.1025, found 156.1024.

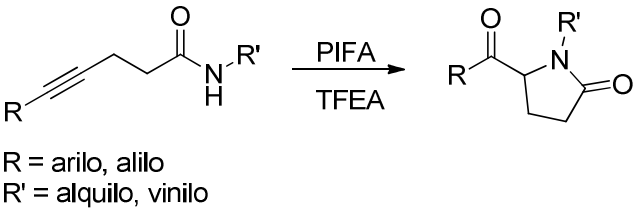
3

Conclusiones

En el presente trabajo de investigación se han mostrado nuevas aplicaciones del reactivo de yodo hipervalente PIFA en la preparación de intermedios clave para la síntesis de diversos heterociclos pirrolidínicos presentes en numerosos productos naturales. Así, el empleo de este reactivo ha permitido la obtención de 5-aroilpirrolidinonas mediante una amidación intramolecular de alquinos. Dichos heterociclos pudieron ser transformados en derivados pirrolopirazinónicos, pirrolodiazepínicos, pirrolobenzo-diazepínicos e indolizidínicos en un número limitado de pasos.

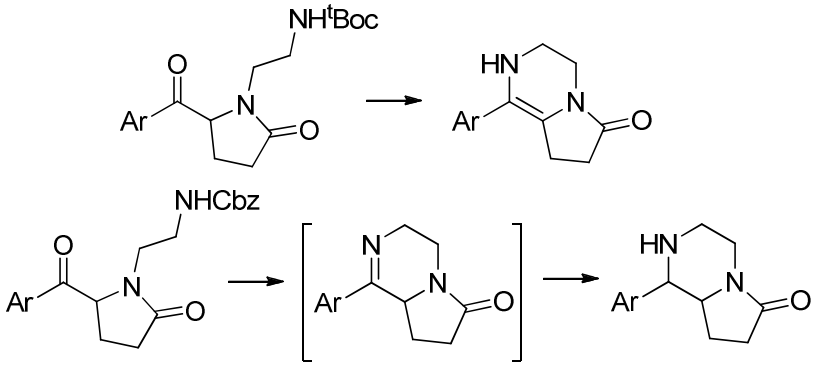
A continuación se presentan las principales conclusiones extraídas de esta investigación:

El reactivo de yodo hipervalente [*bis*(trifluoroacetoxi)yodo]benceno, PIFA, se ha mostrado altamente eficaz en la reacción de amidación intramolecular de alquinos a partir de sustrato sustituidos en la posición terminal del triple enlace tanto por grupos aromáticos como por grupos vinílicos. Del mismo modo, la reacción tiene lugar satisfactoriamente cuando se emplean amidas N-alquil o N-alil sustituidas. A partir de los resultados obtenidos concluimos que, para que la reacción de heterociclación tenga lugar, aparenta ser necesaria la sustitución del triple enlace por un grupo que estabilice el déficit de carga que se genera en tal proceso.



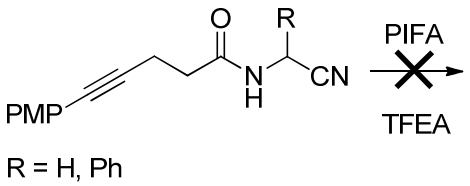
R = arilo, alilo
R' = alquilo, vinilo

El empleo de sustratos que contienen un grupo aminoetilo adicional permitió el acceso al sistema bicíclico pirrolopirazinónico en diferentes grados de oxidación de manera totalmente diastereocontrolada. Ensayos posteriores nos llevaron a postular la formación de un intermedio imínico en la etapa de aminación intramolecular que sucede a la etapa de desprotección.



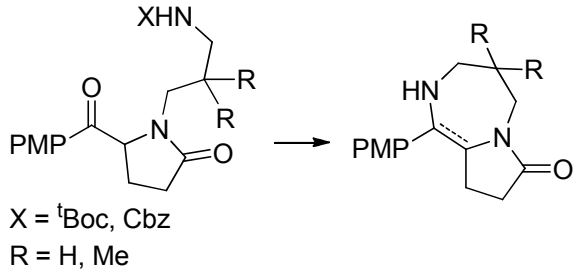
El empleo de sustratos N-cianometil-alquinilamídicos ha resultado ser una alternativa inviable en la formación del esqueleto pirrolidinónico,

probablemente debido a que la fuerte desactivación que provoca el grupo carbonitrilo no permite la reacción de ciclación promovida por PIFA, un proceso basado en la generación de un intermedio deficitario que ha de estabilizarse para que resulte productivo.



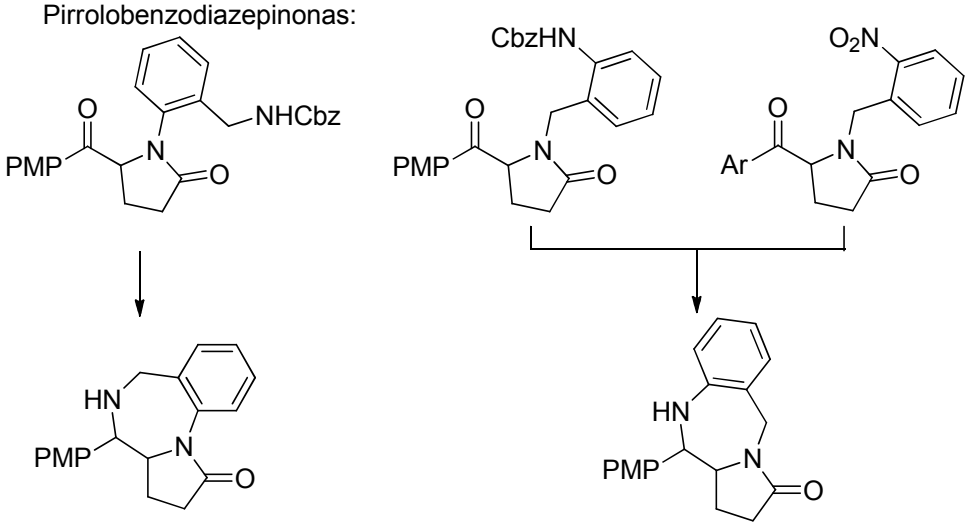
Esta estrategia sintética general encaminada a la preparación de heterociclos pirrolo-fusionados se verificó nuevamente cuando se aplicó a sustratos análogos a los anteriores que contenían fragmentos propilendiamínicos monoprotegidos. Ello ha supuesto, por lo tanto, el diseño y la ejecución de una nueva vía de acceso a compuestos pirrolodiazepínicos. La preparación de sus análogos pirrolobenzodiazepínicos resultó igualmente posible a partir tanto de sustratos N-aminometilfenilamídicos como de sustratos N-nitrobencilamídicos. En este caso, el origen del estereocontrol observado puede explicarse en función de la estabilización de los intermedios imínicos y enamínicos que se someten a la etapa de hidrogenación.

Pirrolodiazepinonas:



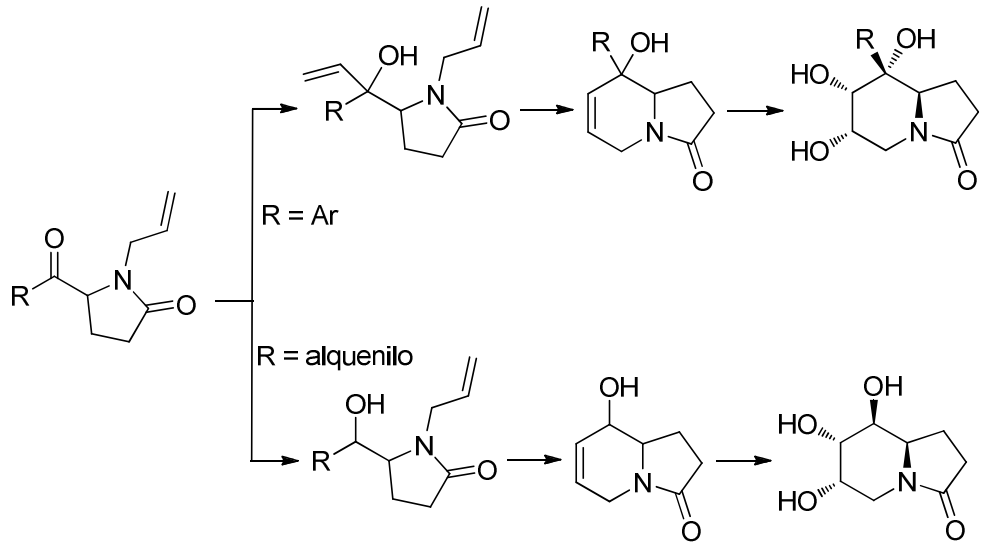
X = ^{t}Boc, Cbz
R = H, Me

Pirrolobenzodiazepinonas:



La síntesis de estructuras indolizidínicas 8-hidroxi-sustituidas se llevó igualmente a cabo a través de nuestro diseño sintético a partir de N-alil-5-estirilpentinamidas, si bien solo uno de los dos posibles diastereoisómeros se consiguió con absoluto estereocontrol. La extensión del proceso a

sustratos que porten diferentes sustituyentes en el nitrógeno amídico y en la posición terminal del triple enlace ha encontrado serias dificultades. En primer lugar, la reacción de metátesis para generar el cierre de anillo ha resultado ser muy dependiente del grado de sustitución de los fragmentos olefínicos. Hemos observado que la mayor sustitución induce procesos indeseados de isomerización, lo que imposibilitó, en muchos casos la obtención del producto deseado.

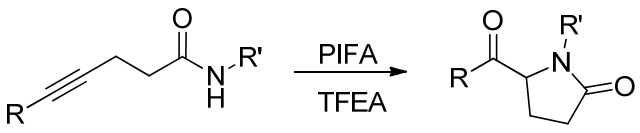


.

In this dissertation, we have shown new applications of the PIFA-assisted intramolecular alkyne amidation reaction towards the preparation of pyrrolidinone derivatives as key intermediate in the synthesis of a number of pirrolo-fused heterocycles. In particular, this strategy has allowed the access to pyrrolopyrazinone, pyrrolodiazepinone, pyrrolobenzodiazepinone and indolizidinone derivatives in few steps.

We present now the conclusions drawn from our research:

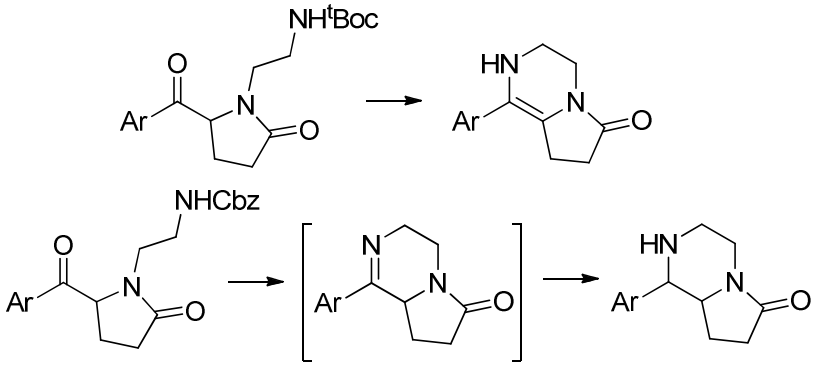
[*Bis*(trifluoroacetoxy)iodo]benzene (PIFA) efficiently assists the intramolecular alkyne amidation reaction when activated aryl and alkenyl groups are located at the terminal position of the starting alkynylamide precursors. The reaction is also efficient when N-alkyl or N-allyl amides are used. Therefore, the efficiency of the reaction relies on the presence of an appropriate group positioned on the triple bond in order to stabilize the charge deficit created during the cyclization process.



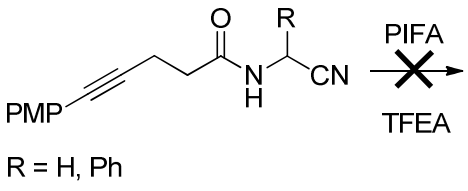
R = aryl, allyl
R' = alkyl, vinyl

N-Aminoethylpentynamides can be considered adequate starting material for the stereocontrolled access to the pyrrolopyrazinone scaffold

according to our synthetic design. Further studies led us to suggest the formation of an imine intermediate, during the intramolecular amination step.

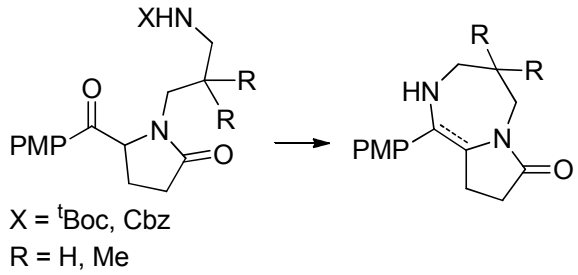


When N-cyanomethylamides were employed, the formation of the corresponding pyrrolidine skeleton resulted to be unfeasible, probably due to the strong deactivation that the CN group exerts. Under these circumstances, the required deficient intermediate cannot be stabilized, making the whole process not productive.



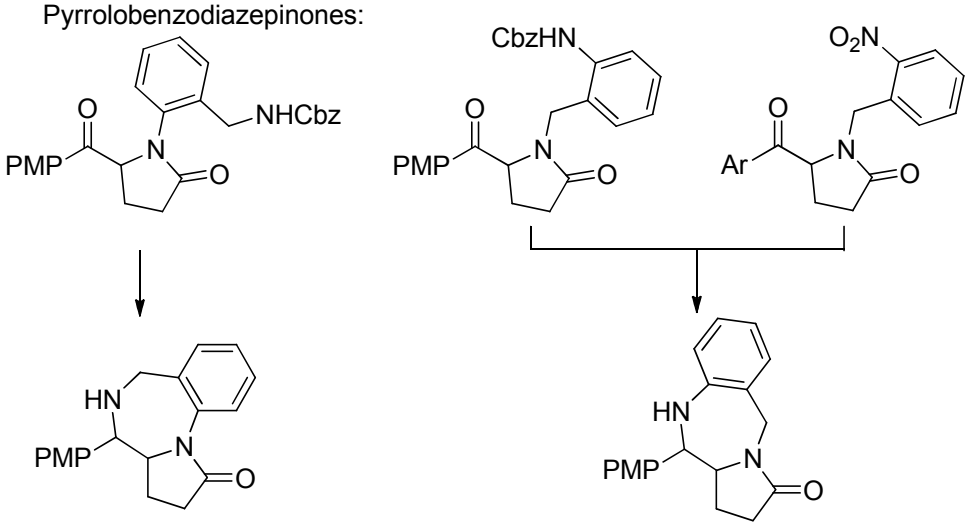
The application of our general synthetic strategy to N-aminopropylpentynamide substrates led to the construction of the pyrrolodiazepinone skeleton. Analogously, the synthesis of pyrrolobenzodiazepinones has been achieved from either N-aminomethylphenylamide or N-nitrobenzylamide substrates. In this case, the stereocontrol of the reaction is based on the variable tautomeric equilibrium between the imine/enamine intermediates that are submitted to the hydrogenation process.

Pyrrolodiazepinones:



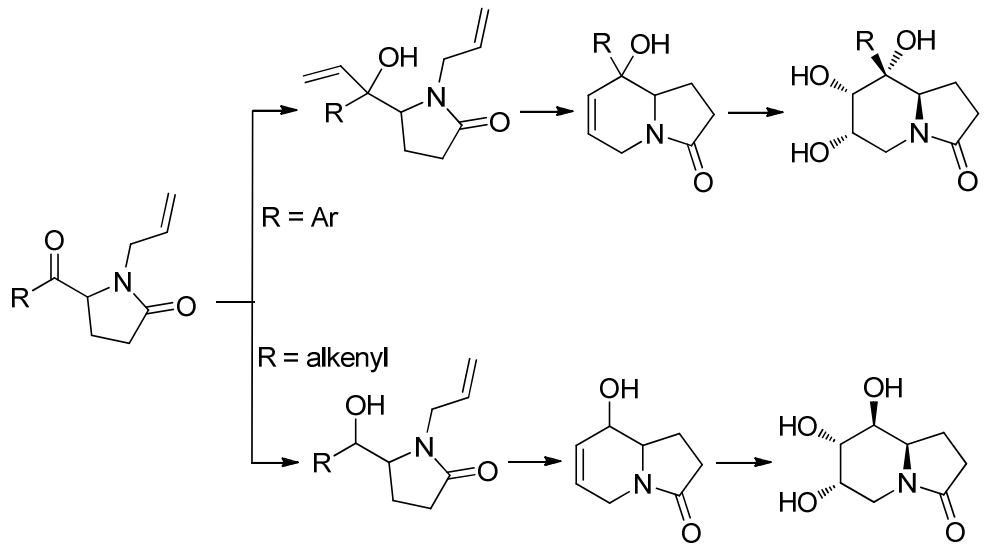
X = ^{t}Boc, Cbz
R = H, Me

Pyrrolobenzodiazepinones:



The synthesis of 8-hydroxy-substituted indolizidine structures could also be carried out through our synthetic design from N-allyl-5-stirylpentynamides, although only one of the two possible diastereomers was obtained with high estereocontrol. The extension of the process to substrates carrying different substituents on the amidic nitrogen and at the

terminal position of the triple bond has found serious difficulties. First, the metathesis reaction employed to generate the ring closure has proved to be highly dependent on the degree of substitution of the olefinic fragments. We have observed that increased substitution induces unwanted isomerization processes, which made impossible, in many cases, the desired result.



4

Heteroaromatic Iodonium Salts

1. INTRODUCTION TO DIARYL IODONIUM SALTS

Diaryliodonium salts were first discovered in 1894.[129] This class of iodine (III) reagents has recently gained considerable attention,[130] as they provide a mild, non-toxic and low cost alternative to the use of metals such as Hg, Pb or Pd in arylation reactions.[131]

Thus, diaryliodonium salts are often applied in metal-catalyzed coupling reactions,[131,132] in α-arylations of carbonyl compounds,[133] as photoinitiators in polymerizations,[134] as benzyne generators[135] and also as precursor to ^{18}F-labelled radio ligands.[136]

1.1. Structure, reactivity and synthesis of diaryliodonium salts

A diaryliodonium salt consists of two aryl moieties bound to a central iodine atom, together with an anion (*Figure 4.1*). The anion not only influences the solubility of the salt, but also the reactivity and stability.

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129. Hartmann, C.; Meyer, V. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 426.

130. For a review on this topic, see: (a) Merritt, E. A.; Olofsson, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 9052. (b) Richardson, R. D.; Wirth, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4402. (c) Richardson, R. D.; Wirth, T. *Angew. Chem. Int. Ed.* **2006**, *118*, 4510. (d) Wirth, T. *Angew. Chem. Int. Ed.* **2006**, 117, 3722. (e) Wirth, T. *Angew. Chem. Int. Ed.* **2006**, *44*, 3656.

131. Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997.

132. Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924.

133. (a) Aggarwal, V. K.; Olofsson, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5516. (b) Ryan, J. H.; Stang, P. J. *Tetrahedron Lett.* **1997**, *38*, 5061. (c) Gao, P.; Portoghese, P. S. *J. Org. Chem.* **1995**, *60*, 2276. (d) Beringer, F. M.; Daniel, W. J.; Galton, S. A.; Rubin, G. *J. Org. Chem.* **1966**, *31*, 4315.

134. (a) Crivello, J. V. J. Polym. Sci. Part A: Polym. Chem. **1999**, 37, 4241. (b) Toba, Y. J. Photopolym. Sci. Technol. **2003**, 16, 115.

135. Kitamura, T.; Yamane, M.; Inoue, K.; Todaka, M.; Fukatsu, N.; Meng, Z.; Fujiwara, Y. *J. Am. Chem. Soc.* **1999**, *121*, 11674.

136. Zhang, M.-R.; Kumata, K.; Suzuki, K. *Tetrahedron Lett.* **2007**, *48*, 8632.

Generally, diaryliodonium salts containing non-nucleophilic anions such as BF_4^- and TfO^- have better solubility and stability, and are thus preferred over halide anions (Cl^-, Br^- and I^-). If the two aryl groups of the salt are identical, the salt is symmetric, whereas if they are not identical the salt is unsymmetric. The use of symmetric salts is often preferred in organic synthesis as this avoids selectivity issues in aryl transfer reactions. However, in cases where starting materials are expensive and selective transfer of one aryl group is possible, unsymmetric salts are desirable.

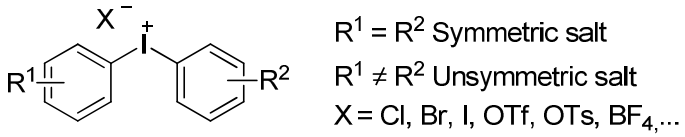


Figure 4.1. General structure of diaryliodonium salts.

X-ray crystallography has been used to show that in the solid state, iodine (III) compounds have a T-shaped structure, in which the iodine and the two apical ligands share a hypervalent bond (*Figure 4.2*). However, the structure of these salts in solution is still debated and is thought to depend on both nature of the anion and the solvent.[137]

137. Ochiai, M. *Top. Curr. Chem.* **2003**, *224*, 5.

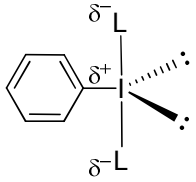
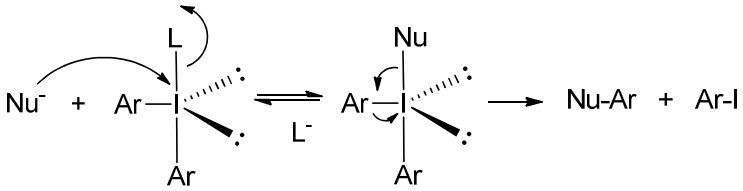


Figure 4.2. Geometry of a λ^3-iodane.

Diaryliodonium salts are electrophilic reagents which react with nucleophiles via nucleophilic attack on the electron-deficient iodine (III) centre. After the initial Nu-I bond formation and release of one of the ligands, the reductive elimination yields the product, releasing Ar-I (*Scheme 4.1*).[138]

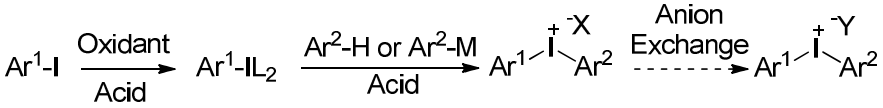


Scheme 4.1. General reactivity of diaryliodonium salts.

The most common method of synthesizing diaryliodonium salts involves the conversion of an aryl iodide into an aryliodine (III) compound

138. (a) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*, VCH, Weinheim, **1992**. (b) Varvoglis, A. *Hypervalent Iodine Chemistry*, Springer, Berlin, **2003**.

by treatment with an inorganic oxidant under acidic conditions.[139] Subsequent ligand exchange with an arene or an organometallic reagent yields the diaryliodonium salt under acidic or neutral conditions. The anion, which usually originates from the acid, is often exchanged to give a more readily isolable salt (*Scheme 4.2*).



Scheme 4.2. Acidic route to diaryliodonium salts.

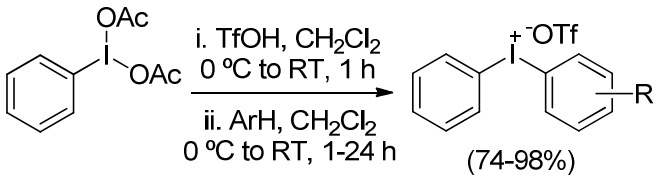
The use of triflic acid in the above reaction affords triflate salts directly with no need for anion exchange. When the iodine (III) reagent PIDA (diacetoxyiodobenzene) is treated with triflic acid, $[PhI(OAc)_2 \cdot 2TfOH]$ is formed. Subsequent addition of an electron-rich arene results in the formation of a diaryliodonium triflate (*Scheme 4.3*).[140] This reactivity has also been observed when reacting silanes, stannanes and boron reagents together with pre-formed iodine (III) reagents.[141]

---

139. A review on this topic can be found in: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *102*, 5299. (c) Reference 130a.

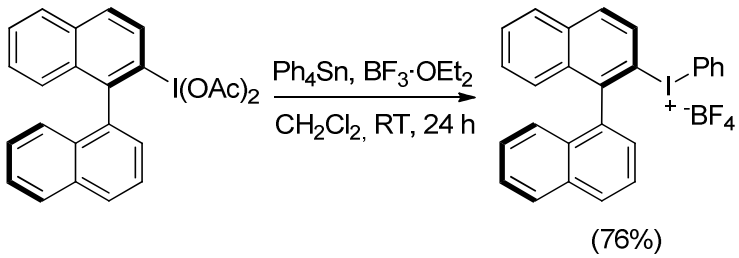
140. (a) Kitamura, T.; Matsuyuki, J.; Taniguchi, H. *Synthesis* **1994**, 147. (b) Kitamura, T.; Furuki, R.; Nagata, K.; Taniguchi, H.; Stang, P. J. *J. Org. Chem.* **1992**, *57*, 6810.

141. When using silanes, see: Koser, G. F.; Wettach, R. H. Smith, C. S. *J. Org. Chem.* **1980**, *45*, 1543. For stannanes, see, for example: Zhdankin, V. V.; Scheuller, M. C.; Stang, P. J. *Tetrahedron Lett.* **1993**, *34*, 6853. For boranes, see an example in: Carroll, M. A.; Pike, V. W.: Widdowson, D. A. *Tetrahedron Lett.* **2000**, *41*, 5393.



Scheme 4.3. Synthesis of diaryliodonium salts from PIDA.

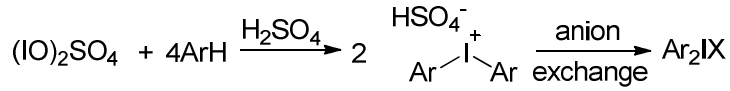
The synthesis of chiral diaryliodonium salts has also been reported. For example, Ochiai *et al.* prepared a chiral tetrafluoroborate salt from 2-(diacetoxyiodo)-1,1'-binaphthyl with tetraphenylstannane in the presence of boron trifluoride etherate (*Scheme 4.4*)[142]



Scheme 4.4. Synthesis of a chiral diaryliodonium salt.

142. Ochiai, M.; Kitagawa, Y.; Takayama, N.; Takaoka, Y.; Shiro, M. *J. Am. Chem. Soc.* **1990**, *112*, 5677.

The use of inorganic hypervalent iodine reagents provides a shorter route to diaryliodonium salts. For example, arenes can be treated with with iodic acid, iodosylsulfate or iodine (III) trifluoroacetate to form diaryliodonium salts which, after an anion exchange, generate the corresponding diaryliodonium halides (*Scheme 4.5*).[143]



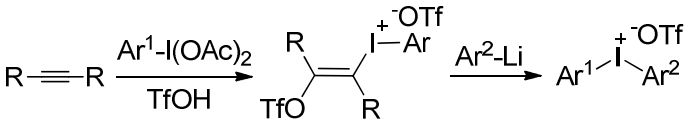
Scheme 4.5. Inorganic hypervalent iodine (III) reagents used in the synthesis of diaryliodonium salts.

All of the reactions described until now are performed under acidic conditions. However, substrates containing acid-sensitive substituents or certain heteroatoms cannot be used under these conditions. A frequently employed method for the preparation of symmetric heteroaryliodonium salts is ligand exchange on β-(dichloroiodo)chloroethylene with a lithiated arene (*vide infra*).[144] When an unsymmetric salt is desired, treatment of pre-formed vinyliodonium salts with aryllithium is a successful strategy. These

143. (a) Beringer, F. M.; Drexler, M.; Gindler, E. M.; Lumpkin, C. C. *J. Am. Chem. Soc.* **1953**, *75*, 2705. (b) Beringer, F. M.; Falk, R. A.; Karniol, M.: Lillien, I.; Masulio, G.; Mausner, M.; Sommer, E. *J. Am. Chem. Soc.* **1959**, *81*, 342.

144. (a) Beringer, F. M.; Nathan, R. A. *J. Org. Chem.* **1969**, *34*, 685. (c) Beringer, F. M.; Nathan, R. A. *J. Org. Chem.* **1970**, *35*, 2095. (c) Stang, P. J.; Olenyuk, B.; Chen, K. *Synthesis* **1995**, 937.

approaches are especially useful in the preparation of nitrogen containing *bis*(heteroaryl)iodonium salts (*Scheme 4.6*).[145]

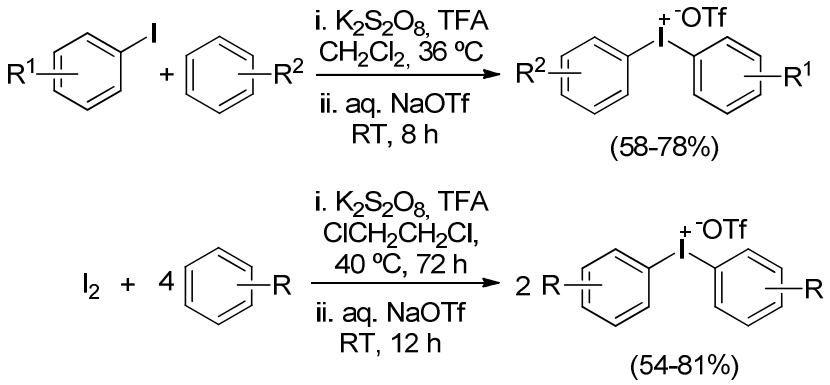


Scheme 4.6. Synthesis of diaryliodonium salts by adding lithiated arenes to vinyl iodonium salts.

The progress in the synthesis of diaryliodonium salts involves a one-pot oxidation and ligand exchange reaction in order to obtain the diaryliodonium salts directly from arenes and either an iodoarene or molecular iodine (*Scheme 4.7).*[146]

145. (a) Kitamura, T.; Furuki, R.; Taniguchi, H.; Stang, P. J. *Tetrahedron Lett.* **1990**, *31*, 703. (b) Kitamura, T.; Furuki, R.; Taniguchi, H.; Stang, P. J. *Tetrahedron* **1992**, *48*, 7149. (c) Kitamura, T.; Kotani, M.; Fujiwara, Y. *Tetrahedron Lett.* **1996**, *33*, 3721. (d) Pirguliyev, N. S.; Brel, V. K.; Akhmedov, N. G.; Zefirov, N. S. *Syntehsis* **2000**, 81.

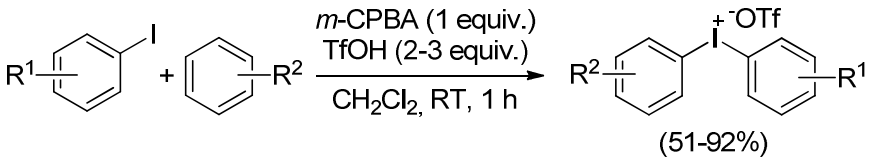
146. (a) Hossain, M. D.; Kitamura, T. *Tetrahedron* **2006**, *62*, 6955. (b) Hossain, M. D.; Kitamura, T. *Tetrahedron Lett.* **2006**, *47*, 7889. (c) Hossain, M. D.; Ikegami, Y.; Kitamura, T. *J. Org. Chem.* **2006**, *71*, 9903.



Scheme 4.7. Examples of Kitamura´s one-pot syntheses of diaryliodonium salts.

An example of this strategy is the one-pot synthesis of a wide range of symmetric and unsymmetric diaryliodonium triflates, including some heteroaryliodonium salts, from aryliodides and arenes. In this case, *m*-CPBA was selected as the oxidant and the triflic acid was employed to both activate the oxidant and deliver the triflate anion to the salt. Using this method, diaryliodonium triflates were obtained in high yields with short reaction times and without need for excess reagents (*Scheme 4.8*).[147]

147. (a) Bielawski, M.; Olofsson, B. *Chem. Comm.* **2007**, 2521. (b) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610.



Scheme 4.8. Example of Olofsson´s one-pot syntheses of diaryliodonium salts.

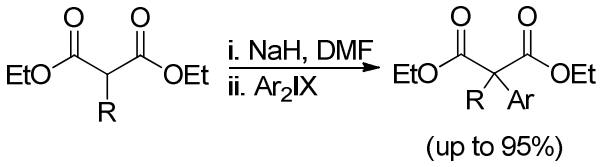
1.2. Applications of diaryliodonium salts in Organic Synthesis.

The range of applications of diaryliodonium salts in organic synthesis has expanded over the last decade, and includes α-arylation of carbonyl compounds, metal-catalyzed cross coupling reactions, arylation of heteroatom nucleophiles, benzyne generation and dearomatization of phenols.

The use of diaryliodonium salts in reactions with nucleophiles leads to transfer of one of the two aryl moieties. As mentioned earlier, although symmetric diaryliodonium salts are generally preferred over unsymmetric salts, in some situations, the use of unsymmetric salts is desirable. In metal mediated reactions with unsymmetric salts, the least sterically hindered arene is selectively transferred; if steric bulk is not a factor, then the most electron-rich arene is preferentially transferred. Conversely, when diaryliodonium salts are employed in non-metal mediated reactions the most electron-deficient arene is normally transferred, although there are reports of

different reactivity when an ortho-substituent is present in one of the arenes.[148]

One of the most well studied reactions of diaryliodoniums salts is α-arylation of carbonyl compounds.[133] For example, a highly efficient arylation of malonates is depicted in *Scheme 4.9*.[148c]

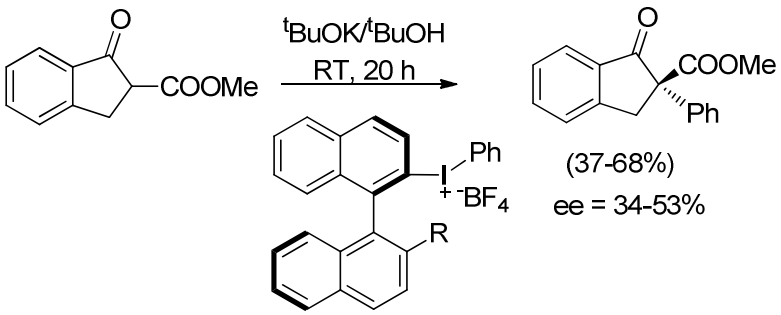


Scheme 4.9. Arylation of malonates.

Although this reaction has been thoroughly investigated, asymmetric variants are less common. In 1999, Ochiai *et al.* reported the use of chiral iodonium salts as a source of asymmetric induction in the arylation of β-ketoesters (*Scheme 4.10*).[149]

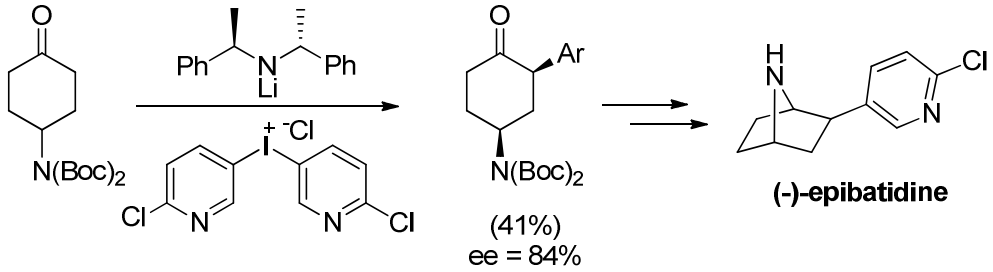
148. (a) Reference 130a. (b) Reference 132. (c) Oh, C. H.; Kim, J. S.; Jung, H. H. *J. Org. Chem.* **1999**, *64*, 1338.

149. Ochiai, M.; Kitagawa, Y.; Takayama, N.; Takaoka, Y.; Shiro, M. *J. Am. Chem. Soc.* **1999**, *121*, 9233.



Scheme 4.10. Asymmetric arylation using chiral iodonium salts.

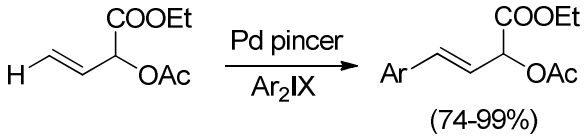
In the example depicted in *Scheme 4.11* a pyridyl salt is used for the arylation of the cyclohexanone after enolization with a chiral base, as a key step in the total synthesis of (-)-epibatidine.[133a]



Scheme 4.11. Asymmetric arylation used for the preparation of (-)-epibatidine.

Considering the excellent leaving group ability of the iodobenzene group, diaryliodonium salts have been widely used in cross-coupling

reactions,[131,132] especially in combinations with a copper or palladium catalyst. This method has been employed for the arylation of alkenes and both aliphatic and aromatic alkynes. The use of a mixture of palladium and copper catalysts along with diphenyliodonium tosylate or triflate allows the phenylation of enynes, propargylic ketones and propargylic esters, functional groups that are normally unreactive in metal-catalyzed couplings with aryl iodides.[150] Regarding alkenes, it has recently been found that palladium pincer complexes can react with diaryliodonium salts in order to arylate allylic acetates and electron-rich alkenes (*Scheme 4.12*).[151]



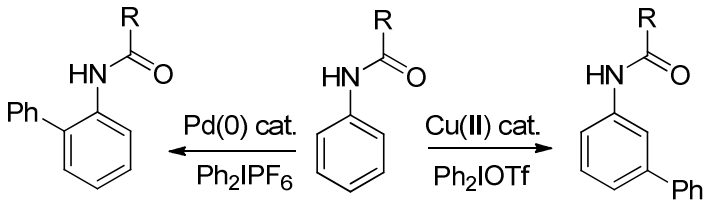
Scheme 4.12. Heck-type coupling with Pd pincer complexes.

Cross-coupling reactions involving C-H activation through the use of diaryliodonium salts have become increasingly widespread over the last decade. A striking example of this is the use of diaryliodonium salts in a *meta*-selective copper-catalyzed C-H bond arylation, reported by Phipps and

150. Radhakrishnan, U.; Stang, P. J. *Org. Lett.* **2001**, *3*, 859.

151. (a) Szabo, J. K. *J. Mol. Cat. A* **2010**, *324*, 56. (b) Aydin, J.; Larsson, J. M.; Selander, N.; Szabó, J. K. *Org. Lett*. **2009**, *11*, 2852.

Gaunt in 2009. Interestingly, when palladium (II) catalysts are used in this reaction, the usual *ortho*-product is obtained. (*Scheme 4.13*).[152]



Scheme 4.13. *meta*-Selective C-H activation/arylation.

Arylation of heteroatom nucleophiles, such as phenols, aliphatic and aromatic amines and sulphur and selenium nucleophiles has also been achieved using diaryliodonium salts, leading to diaryl ethers, *N*-arylated compounds, aryl thioethers and selenoethers, and triarylsulphonium and selenonium salts.[153]

152. (a) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (b) Daugulis, O.; Zaitsev, V. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4046.

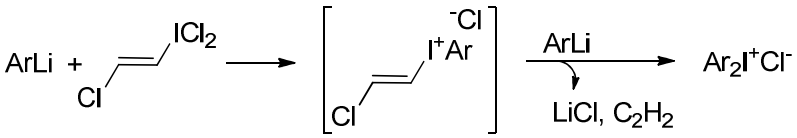
153. (a) Beringer, F. M.; Brierley, A.; Drexler, M.; Gindler, E. M.; Lumpkin, C. C. *J. Am. Chem. Soc.* **1953**, *75*, 2708. (b) Ley, S. V.; Thomas, W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (c) Petersen, T. B.; Khan, R.; Olofsson, B. *Org. Lett.* **2011**, *13*, 3462. (d) Jalalian, N.; Ishikawa, E. E.; Silva, L. F.; Olofsson, B. *Org. Lett.* **2011**, *13*, 1552.

2. Heteroaromatic iodonium salts

Like diaryliodonium salts, heteroaromatic iodonium salts, where at least one of the aryl moieties is a heterocycle, can be used as arylating agents, providing a selective, efficient and non-toxic method for the preparation of heterocyclic molecules.

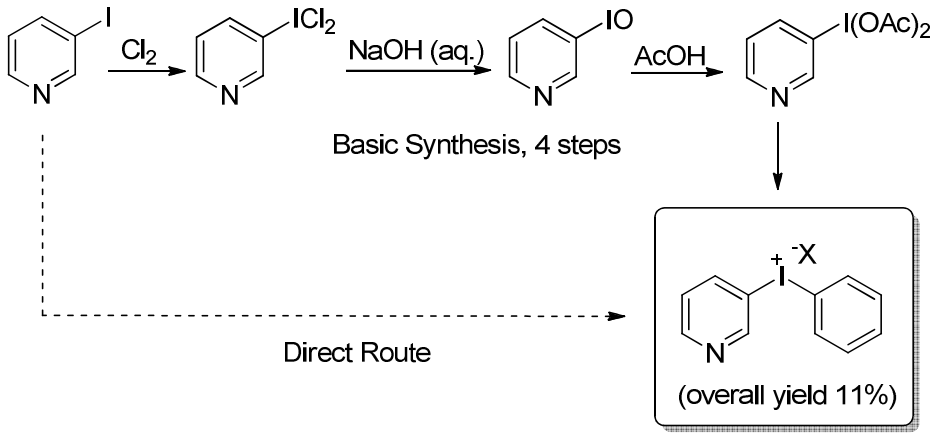
2.1. Synthesis of heteroaromatic iodonium salts

While numerous methods for the preparation of diaryliodonium salts exist, only some of these routes are suitable for the preparation of heteroaromatic iodonium salts. Stang and co-workers reported a route to pyridine- and quinolone-based diaryliodonium chlorides through the reaction of the appropriate aryllithium with β-chlorovinyliodonium chloride (*Scheme 4.14*).[144c]



Scheme 4.14. Synthesis of diaryliodonium salts via β-chlorovinyliodonium chloride.

Recently, a four step route to (phenyl)(3-pyridyl)iodonium salts was reported.[154] In this route, chlorine gas is required to prepare the initial iodine (III) species, as a direct route to the pyridyliodonium salt is not known (*Scheme 4.15*).



Scheme 4.15. Carroll and co-workers approach to (aryl)(3-pyridyl)iodonium salts.

Despite the apparent difficulty of this transformation, Olofsson and co-workers have reported a one-step synthesis of diaryliodonium salts under acidic conditions, which, in some cases, can be used to prepare heteroaromatic salts (*Scheme 4.8*, page 323). During my collaboration with the Olofsson group, my task was to study this reaction in order to devise a one-step method for the synthesis of heteroaromatic iodonium salts, based

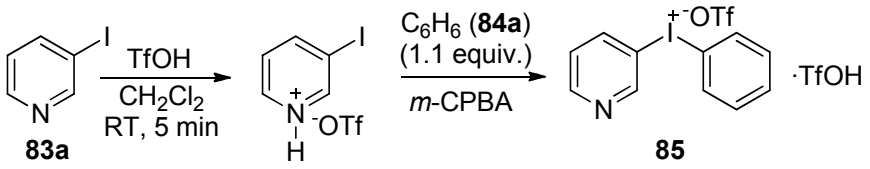
154. Carroll, M. A.; Nairne, J.; Woodcroft, J. L. *J. Label. Comp. Radiopharm.* **2007**, *50*, 452.

on the success of the one-pot synthesis of diaryliodonium salts employing *m*-CPBA.[147,155]

A preliminary study of this reaction had previously been carried out within the group (*Table 4.1*). Thus, it was determined that the use of an excess of the oxidant and 4 equivalents of TfOH (*entries 1-4*) improved the yield. It was found that the reaction proceeds extremely rapidly, with the best yield being obtained when the time was decreased to 30 minutes (*entries 4-6*). Lowering the temperature resulted in a loss of reactivity, but good yields were obtained at 60 ºC. Further studies on this reaction led us to the conclusion that protonation of the nitrogen before the addition of the oxidant resulted in selective oxidation of the iodine, with the proton acting as a protecting group, preventing oxidation of the nitrogen. Thus, a five minute reaction of TfOH with the substrate, followed by the addition of the oxidant would guarantee that only oxidation of the iodine took place when the *m*-CPBA was added.

155. (a) Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, *73*, 4602. (b) Zhu, M.; Jalalian, N.; Olofsson, B. *Synlett* **2008**, 592.

Table 4.1. Optimization studies.



Entry	*m*-CPBA (equiv.)	TfOH (equiv.)	T (ºC)	Time (h)	85 Yield (%)
1	1.1	3.0	80	3	54
2	1.5	3.0	80	3	60
3	2.0	3.0	80	3	52
4	1.5	4.0	80	3	68
5	1.5	4.0	80	10 min	48
6	1.5	4.0	80	0.5	60
7	1.5	4.0	RT	0.5	---[(a)]
8	1.5	4.0	40	0.5	---[(a)]
9	1.5	4.0	60	0.5	69

[(a)] No product could be isolated.

To determine the scope of this reaction, a number of nitrogen-containing iodoarenes **83a-f** were tested under these conditions with sterically hindered arenes **84b-c** (*Figure 4.3*). The sterically hindered arene will act as a dummy ligand and promote a selective transfer of the heteroaryl group in metal mediated reactions.

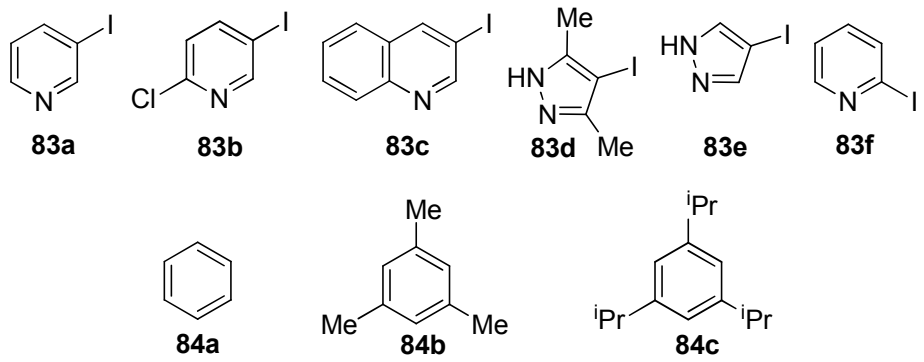
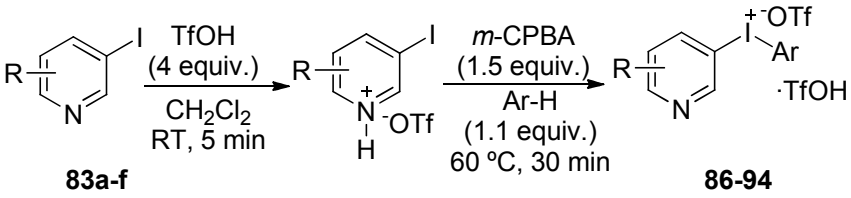


Figure 4.3. Substrates employed in the synthesis of diaryliodonium salts.

The results in *Table 4.2* show that the reaction of 3-iodopyridine (**83a**) was successful with both mesitylene (**84b**) and 1,3,5-triisopropylbenzene (**84c**) (*entries 1* and *2*). The desired products were also obtained when reacting 3-iodoquinoline (**83c**; *entries 4 and 5*) and pyrazoles **83d** and **83e** (*entries 6-9*) with **84b** and **84c** under the optimized conditions. Unfortunately, 2-iodopyridine (**83f**) did not react and protonated starting material was obtained (*entry 10*).

Table 4.2. Synthesis of heteroaryl iodonium salts.



83a-f **86-94**

Entry	Iodoarene	Ar-H	Product	Yield (%)
1	**83a**	**84b**	**86**	70
2	**83a**	**84c**	**87**	59
3	**83b**	**84b**	**88**[(a)]	47
4	**83c**	**84b**	**89**	77
5	**83c**	**84c**	**90**	82
6	**83d**	**84b**	**91**	67
7	**83d**	**84c**	**92**	70
8	**83e**	**84b**	**93**	75
9	**83e**	**84c**	**94**	75
10	**83f**	**84b**	**---**	**---**

[(a)] Isolated as non-protonated salt.

3. CONCLUSIONS

A fast, efficient and simple one-pot synthesis of heteroaryl iodonium salts has been developed. Heteroaryl iodonium salts are obtained in a protonated form directly from iodoarenes, using *m*-CPBA as oxidant and triflic acid. Further studies are being conducted in order to allow the isolation of non-protonated salts.

This reaction allows the synthesis of a large number of compounds, including those with sterically hindered moieties. However, further studies on the effect of substituent type and substitution pattern on different hetero-iodoarenes are necessary in order to fully evaluate the scope of the methodology.

4. EXPERIMENTAL PROCEDURES

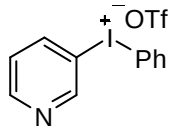
4.1. General methods and materials.

NMR spectra were recorded using MeOD-d_4 as solvent. Chemical shifts are given in ppm relative to the residual peak for MeOD-d_4 (^{1}H-NMR δ 3.31, ^{13}C-NMR 49.0) with multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad, app: apparent), integration and coupling constants (Hz). All reaction were carried out in sealed tubes to allow for reactions above the boiling point of CH_2Cl_2, and run without any precautions to avoid moisture or air, *i.e.* without inert gas or dried solvent. TfOH (≥ 99%) was stored under an argon atmosphere. Newly purchased *m*-CPBA contains a variable quantity of H_2O. Prior to use, *m*-CPBA was dried in batches under vacuum for 1 h and the percentage of active oxidant determined by iodometric titration.[156] The dried, titrated *m*-CPBA was then stored at 4 °C for future use. All other reagents were used as received without further purification (or synthesized and purified according to literature procedures where stated).

156. A. I. Vogel, B. S. Furniss, A. J. Hannaford, V. Rogers, P. W. G. Smith, A. R. Tatchell *Textbook of Practical Organic Chemistry*, Longman, London, New York, **1978**.

4.2. Typical procedure for the synthesis of heteroaryl iodonium salts 85-94.

3-(phenyliodonio)pyridinium triflate (**85**).



3-Iodopyridine (**83a**, 50 mg, 0.24 mmol) was dissolved in CH_2Cl_2 (1 mL) and TfOH (4 equiv.) was added. The mixture was stirred for 5 minutes before the addition of *m*-CPBA (1.5 equiv.), followed by the addition of benzene (**84a**, 1.1 equiv.). The reaction mixture was stirred at 60 °C for 30 minutes before being allowed to cool to room temperature and concentrated. Et_2O was added (1 mL) to the vial and the solution cooled to 0 °C and stirred for 30 minutes to give a precipitate. The precipitate was isolated by filtration and washed with Et_2O (3x1 mL) to give compound **85** as a light grey solid in 69% yield.

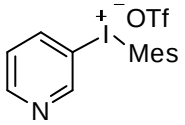
mp: 127-130 °C (Et_2O).

^{1}H-NMR (5.0 mg in 0.5 mL MeOD-d_4, 400 MHz): δ 9.29 (d, *J*=1.6, 1H), 8.86 (dd, *J*=1.2, 4.8, 1H), 8.70 (ddd, *J*=1.2, 2.0, 8.4, 1H), 8.25 (app. d, *J*=8.5, 2H), 7.73 (app. t, *J*=7.6, 1H), 7.65 (ddd, *J*=0.8, 5.2, 8.4, 1H), 7.57 (app. t, *J*=8.0, 2H).

^{13}C-NMR (20.0 mg in 0.5 mL MeOD-d_4, 100 MHz): δ 152.3, 151.1, 147.2, 136.9, 134.2, 133.5, 129.2, 121.8 (q, *J*=316), 116.3, 115.4.

HRMS (ESI): *m/z* calculated for $C_{11}H_9NI$ $[M - OTf^- - TfOH]^+$ 281.9774, found 281.9759.

3-(mesityliodonio)pyridinium triflate (**86**).



According to the typical procedure, compound **86** was obtained from **83a** and **84b** in 70% yield as a beige solid.

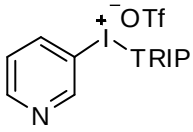
mp: 153-155 °C (Et_2O).

^{1}H-NMR (10.2 mg in 0.5 mL MeOD-d_4, 400 MHz): δ 9.14 (d, *J*=1.9, 1H), 8.90 (dd, *J*=5.0, 1.2, 1H), 8.54 (ddd, *J*=8.4, 2.2, 1.4, 1H), 7.76 (ddd, *J*=8.5, 5.2, 0.7, 1H), 7.30 (s, 2H), 2,71 (s, 6H), 2.40 (s, 3H).

^{13}C-NMR (20.0 mg in 0.5 mL MeOD-d_4, 100 MHz): δ 150.6, 150.0, 147.1, 146.6, 143.8, 131.7, 129.7, 122.4, 121.7 (q, *J*=317), 113.4, 27.1, 21.0.

HRMS (ESI): *m/z* calculated for $C_{14}H_{15}NI$ $[M - OTf^- - TfOH]^+$ 324.0244, found 324.0252.

3-[(2,4,6-triisopropylphenyl)iodonio]pyridinium triflate (**87**).



According to the typical procedure, compound **87** was obtained from **83a** and **84c** in 59% yield as a white solid.

mp: 149-150 °C (Et_2O).

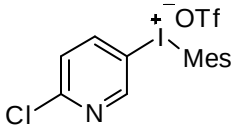
^{1}H-NMR (5.0 mg in 0.5 mL MeOD-d_4, 400 MHz): δ 9.00 (dd, *J*=0.6, 2.3, 1H), 8.82 (dd, *J*=1.3, 4.8, 1H), 8.34 (ddd, *J*=1.3, 2.3, 8.3, 1H), 7.64 (ddd,

J=0.8, 4.8, 8.4, 1H), 7.37 (s, 2H), 3.45-3.40 (m, 2H), 3.06-2.99 (m, 1H), 1.31 (d, *J*=6.8, 12H), 1.27 (d, *J*=7.0, 6H).

^{13}C-NMR (20.0 mg in 0.5 mL MeOD-d_4, 100 MHz): δ 157.6, 153.6, 151.0, 150.6, 145.9, 129.5, 126.8, 123.3, 121.8 (q, *J*=316), 114.1, 40.8, 35.4, 24.5, 24.0.

HRMS (ESI): *m/z* calculated $C_{20}H_{17}NI$ [M - OTf^- - TfOH]$^+$ 408.1183, found 408.1192.

mesityl(6-chloro-3-pyridyl)iodonium triflate (**88**).



According to the typical procedure, compound **88** was obtained from **83b** and **84c** in 47% yield as a brown solid.

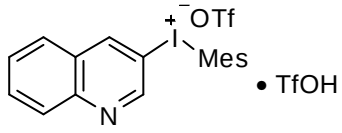
mp: 163-164 °C (Et_2O).

^{1}H-NMR (MeOD-d_4, 400 MHz): δ 8.82 (dd, *J* = 0.7, 2.4, 1H), 8.28 (dd, *J* = 2.4, 8.6, 1H), 7.58 (dd, *J* = 0.5, 8.5, 1H), 7.26 (s, 2H), 2,67 (s, 6H), 2.36 (s, 3H).

^{13}C-NMR (MeOD-d_4, 100 MHz): δ 155.9, 154.3, 146.3, 145.4, 143.5, 131.5, 129.2, 122.4, 121.8 (q, *J* = 314), 111.4, 27.0, 21.0.

HRMS (ESI): *m/z* calculated for $C_{14}H_{14}ClNI$ [M – OTf]$^+$ 357.9854, found 357.9843.

3-(mesityliodonio)quinolinium triflate (**89**).



According to the typical procedure, compound **89** was obtained from **83c** and **84b** in 77% yield as a light brown solid.

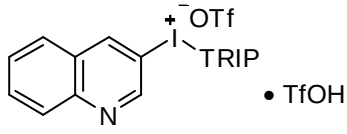
mp: 155-156 °C (Et_2O).

^{1}H-NMR (MeOD-d_4, 400 MHz): δ 9.22 (d, *J*=2.2, 1H), 9.15 (d, *J*=2.0, 1H), 8.15 (d, *J*=8.8, 1H), 8.09 (d, *J*=8.2, 1H), 8.04-7.99 (m, 1H), 7.85-7.79 (m, 1H), 7.27 (s, 2H), 2.74 (s, 6H), 2.36 (s, 3H).

^{13}C-NMR (MeOD-d_4, 100 MHz): δ 150.2, 149.5, 146.5, 144.2, 143.8, 136.7, 131.6, 131.4, 131.2, 130.5, 125.8, 122.7, 121.7 (q, *J*=316), 107.3, 27.2, 21.0.

HRMS (ESI): *m/z* calculated for $C_{18}H_{17}NI$ $[M - OTf^- - TfOH]^+$ 374.0400, found 374.0399.

3-[(2,4,6-triisopropylphenyl)iodonio]quinolinium triflate (**90**).



According to the typical procedure, compound **90** was obtained from **83c** and **84c** in 82% yield as an off-white solid.

mp: 135-138 °C (Et_2O).

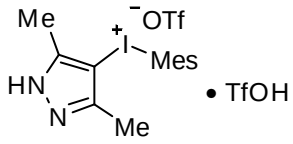
^{1}H NMR (MeOD-d_4, 400 MHz): δ 9.19 (d, *J*=2.2, 1H), 9.16 (d, *J*=1.6, 1H), 8.15 (d, *J*=8.5, 1H), 8.10 (d, *J*=8.3, 1H), 8.06-8.00 (m, 1H), 7.87-7.81 (m,

1H), 7.37 (s, 2H), 3.61-3.51 (m, 2H), 3.07-2.96 (m, 1H), 1.33 (d, *J*=6.6, 12H), 1.26 (d, *J*=6.8, 6H).

^{13}C NMR (MeOD-d_4, 100 MHz): δ 157.6, 153.7, 150.4, 148.1, 145.5, 136.2, 131.3, 131.0, 130.3, 127.1, 126.8, 123.9, 121.9 (q, *J*=316), 108.4, 40.9, 35.5, 24.7, 24.1.

HRMS (ESI): *m/z* calculated for $C_{24}H_{29}NI$ [M - OTf^- - TfOH]$^+$ 458.1339, found 458.1314.

4-(mesityliodonio)-3,5-dimethyl-1H-pyrazol-2-ium triflate (**91**).



According to the typical procedure, compound **91** was obtained from **83d** and **84b** in 67% yield as a pale brown solid.

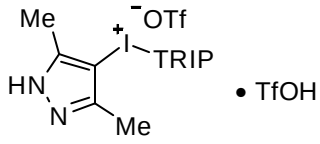
mp: 148-152 °C (Et_2O).

^{1}H-NMR (5.9 mg in 0.5 mL MeOD-d_4, 400 MHz): δ 7.20 (s, 2H), 2.64 (s, 6H), 2.35 (s, 9H).

^{13}C-NMR (MeOD-d_4, 100 MHz): δ 149.8, 145.4, 142.9, 131.4, 121.3, 121.8 (q, *J*=316), 81.0, 26.6, 20.9, 12.3.

HRMS (ESI): *m/z* calculated for $C_{14}H_{18}N_2I$ [M - OTf^- - TfOH]$^+$ 341.0509, found 341.0515.

3,5-Dimethyl-4-[(2,4,6-triisopropylphenyl)iodonio]-1H-pyrazol-2-ium triflate (**92**).



According to the typical procedure, compound **92** was obtained from **83d** and **84c** in 70% yield as an off-white solid.

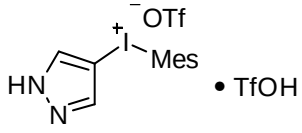
mp: 141-142 °C (Et_2O).

^{1}H-NMR (25. 3 mg in 0.5 mL MeOD-d_4, 400 MHz): δ 7.30 (s, 2H), 3.41-3.34 (m, 2H), 3.03-2.96 (m, 1H), 2.38 (s, 6H), 1.29 (d, *J*=6.8, 12H), 1.25 (d, *J*=6.8, 6H).

^{13}C-NMR (MeOD-d_4, 100 MHz): δ 156.5, 153.0, 149.7, 126.3, 122.9, 121.8 (q, *J*=316), 82.0, 40.5, 35.3, 24.4, 24.0, 12.3.

HRMS (ESI): *m/z* calculated for $C_{20}H_{30}N_2I$ $[M - OTf^- - TfOH]^+$ 425.1448, found 425.1451.

4-(mesityliodonio)-1H-pyrazol-2-ium triflate (**93**).



According to the typical procedure, compound **93** was obtained from **83e** and **84b** in 75% yield as a brown solid.

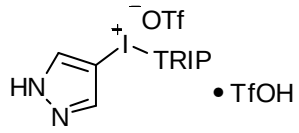
mp: 169-171 °C (Et_2O).

^{1}H-NMR (5.8 mg in 0.5 mL MeOD-d_4, 400 MHz): δ 8.23 (s, 2H), 7.19 (s, 2H), 2.71 (d, 6H), 2.34 (s, 3H).

^{13}C-NMR (5.8 mg in 0.5 mL MeOD-d_4, 100 MHz): δ 145.5, 142.7, 140.3, 131.0, 124.2, 121.8 (q, *J*=316), 79.0, 27.0, 21.0.

HRMS (ESI): *m/z* calculated for $C_{12}H_{14}N_2I$ [M - OTf^- - TfOH]$^+$ 313.0196, found 313.0192.

4-[(2,4,6-triisopropylphenyl)iodonio]-1H-pyrazol-2-ium triflate (**94**).



According to the typical procedure, compound **94** was obtained from **83e** and **84c** in 75% yield as an off-white solid.

mp: 175-179 °C (Et_2O).

^{1}H-NMR (4.7 mg in 0.5 mL MeOD-d_4, 400 MHz): δ 8.16 (s, 2H), 7.28 (s, 2H), 3.57-3.48 (m, 2H), 3.02-2.95 (m, 1H), 1.35 (d, *J*=6.7, 12H), 1.25 (d, *J*=6.8, 6H).

^{13}C-NMR (4.7 mg in 0.5 mL MeOD-d_4, 100 MHz): δ 156.5, 152.5, 140.1, 126.0, 125.6, 121.8 (q, *J*=317), 79.8, 40.4, 35.4, 24.4, 24.0.

HRMS (ESI): *m/z* calculated for $C_{18}H_{26}N_2I$ [M - OTf^- - TfOH]$^+$ 397.1135, found 397.1142.

Anexo I

Papers

A Quick Entrance to the Synthesis of 1-Aryl-pyrrolopyrazinones from Linear Alkynylamide Derivatives

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Abstract: A quick approach to the synthesis of pyrrolopyrazinone derivatives based on a formal double addition across a triple bond of properly substituted substrates is presented. The key cyclization step features the PIFA-mediated formation of a 5-aroylpyrrolidinone nucleus from appropriately functionalized *N*-protected N-aminoethylamides. After removal of the protections, the free amino group is used to accomplish a second heterocyclization process onto the developed carbonyl group. Adequate manipulation of these protecting groups and selection of the reaction conditions gives rise to a series of the target pyrrolopyrazinones in different hydrogenated levels.

Keywords: hypervalent iodine, alkynylamides, PIFA, reductive amination, pyrazinones

The pharmacological and medical literature uses the term nootropic to refer to those drugs that are used as memory enhancers. From the first studies carried out with piracetam (**A**), and its hydroxylated analog oxiracetam (**B**), a number of structural modifications have been introduced in order to maximize the biological activity of this class of therapeutics and also with the aim of clarifying their mechanism of action.[1]

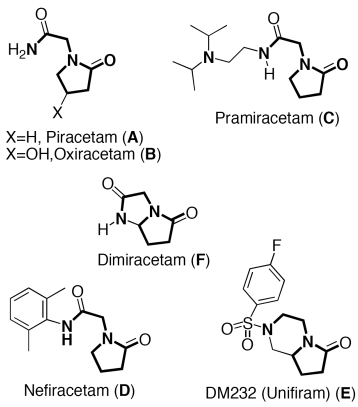


Figure 1 Selected representative and widely used examples of nootropic agents (**A-F**).

Apart of these two, a few of them have been also marked as nootropic drugs –i.e. pramiracetam (**C**),[2] and nefiracetam (**D**)[3] (see Figure 1)–. The vast majority of these derivatives are structurally characterized by a 2-pyrrolidinone nucleus substituted at 1-position by an aminoethyl group and, in few cases, this motif is conformationally constrained in a heterocycle fused to the pyrrolidinone skeleton. This is the case for both DM232 (unifiram) (**E**), which has been reported to show cognition-enhancing properties with a potency four orders of magnitude greater than piracetam,[4] and dimiracetam (**F**), a pyrroloimidazole derivative 10-100 times more potent than piracetam.[5]

Recently our group has discovered a straightforward cyclization of linear *N*-substituted alkynylamides to give 5-aroyl-pyrrolidinones by means of the hypervalent iodine reagent PIFA [(*bis*-trifluoroacetoxy)iodobenzene)] (see Figure 2). The extension of this preliminary study was very limited and only the behavior of substrates carrying simple alkyl, aryl and allyl groups as the amide substituents was tested.[6] According to this, as the next stage of our research we wished to evaluate the actual potential of this methodology by studying the behavior of more complex alkynylamides that include an additional amine group specifically located on the amide fragment of the substrate.

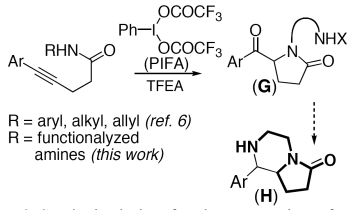
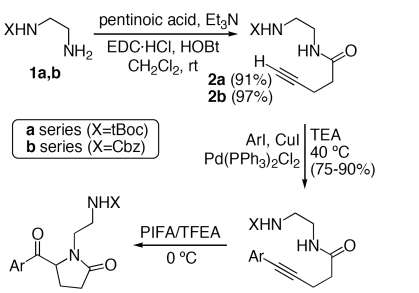


Figure 2 Synthetic design for the preparation of pyrazinones of type **H**.

Therefore, our synthetic design was conceived to allow a second intramolecular cyclization between the residual amine group and the keto-carbonyl group of **G** to afford the pyrrolopyrazinones of type **H**. In other words, in this work we present an original route to prepare a series of derivatives with the pyrrolopyrazinone skeleton as model compounds that eventually could show potential biological activity.[7]

Two usual protecting groups (X=tBoc and X=Cbz) for the terminal amino group were selected to evaluate their behavior under the PIFA-mediated cyclization conditions.[8] Thus, preparation of alkynylamides **3-6** was performed in

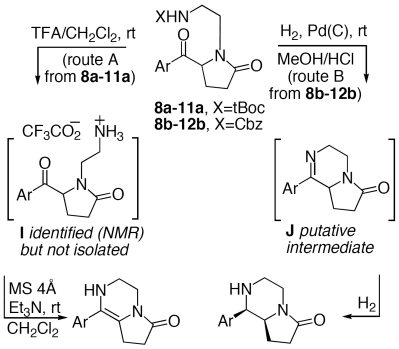
a two-step sequence as follows (see Scheme 1). First, the formation of the amide linkage between the known mono-protected diamines **1a,b** and pentynoic acid was accomplished in almost quantitative yields for both cases with the aid of EDC and HOBt as activating agents.[9] Subsequent insertion of the aryl groups at the terminal position of the triple bond was efficiently performed (75-90%) by a Sonogashira coupling reaction using CuI and Pd(II) as catalysts.[10] The selection of the aryl fragments for this reaction was done on the basis that, in our preliminary study,[6] alkynylamides substituted at the terminal position by deactivated aryl rings could not be transformed into the corresponding pyrrolidinone derivatives. Only activated (PMP, thienyl), non-activated (Ph), and moderately deactivated (ClC_6H_4) aryl substituted substrates (as in **3-6**) were expected to succeed in the desired heterocyclization step.[11,12] Thus, the key cyclization step took place by treatment of amides **3-6** with an slight excess (1.25 eq) of PIFA in trifluoroethanol (TFEA) as solvent at room temperature to afford the desired pyrrolidinone series **8-11** in good to excellent yields (53-94%), a transformation that proceeded to completion in less than two hours with no noticeable difference in the behavior of both protecting groups.



8a/b, Ar=Ph (55/53%) **3a/b**, Ar=Ph (84/77%)
9a/b, Ar=PMP (74/68%) **4a/b**, Ar=PMP (90/75%)
10a/b, Ar=pClC_6H_4 (54/79%) **5a/b**, Ar=pClC_6H_4 (80/90%)
11a/b, Ar=2-Thioph (94/81%) **6a/b**, Ar=2-Thioph (80/79%)
12b, Ar=3-Thioph (64%) **7b**, Ar=3-Thioph (70%)

Scheme 1 Preparation and reactivity of functionalized alkynylamides **3-7**. Synthesis of 5-aroylpyrrolidinones **8-12**.

At this point of the research we embarked in our next endeavor to prepare the bicyclic pyrazinones.[13] At first stage, in both cases (**a** and **b** series), the protecting groups had to be removed. Therefore, pyrrolidinones **8a-11a** were deprotected under acidic (TFA) conditions and, without any further purification, the resulting non-isolated intermediates **I** (release of the ^{t}Bu group was confirmed by ^{1}H NMR) were submitted to a cyclization process under dehydrating conditions (see Scheme 2). Under such circumstances the unsaturated pyrrolopyrazinones **13a-d** were obtained in 33-41% yields, probably as the result of the isomerization of the imine intermediate. On the other hand, pyrrolidinones **8b-10b** were transformed directly into the reduced analogues **14a-c** in similar yields (40-46%) under palladium catalyzed hydrogenation conditions by a one-pot sequential of Cbz-deprotection and intramolecular reductive amination reaction.[14] Extensive NMR studies led us to conclude that the cyclization took place with complete syn diastereoselectivity.[15] As an exception, all attempts to transform the 5-(thienylcarbonyl)-substituted pyrrolidinones **11b** and **12b** into the desired bicyclic derivative **14d,e** resulted in the complete recovery of the starting material unchanged.[16]



13a, Ar=Ph (41%) **14a**, Ar=Ph (40%)
13b, Ar=PMP (33%) **14b**, Ar=PMP (43%)
13c, Ar=pClC_6H_4 (34%) **14c**, Ar=pClC_6H_4 (46%)
13d, Ar=2-Thioph (39%) **14d**, Ar=2-Thioph (see text)
14e, Ar=3-Thioph (see text)

Scheme 2 Synthesis of pyrrolopirazinones **13** and **14**.

In conclusion, the present investigation shows that the intramolecular PIFA–mediated alkyne amidation reaction on relatively complex substrates has proven to be an efficient alternative to prepare highly functionalized pyrrolidinones. As a demonstration of its usefulness, when this transformation is coupled with a second intramolecular amination step, the overall process results in a simple and rapid protocol for the synthesis of a series of pyrrolopyrazinone derivatives of different oxidation states.

All reagents were purchased and used as received. All solvents used in reactions were dried and purified according to standard procedures. All air- or moisture-sensitive reactions were performed under argon. The glassware was oven dried (140 ºC) overnight and purged with argon prior to use. Melting points were measured using open glass capillaries and are uncorrected. Infrared spectra were recorded as thin films and peaks are reported in cm^{-1}. Only representative absorptions are given. Flash chromatography was carried out on SiO_2 (silica gel 60, 230–400 mesh ASTM). NMR spectra were recorded on a 300 instrument (300 MHz for ^{1}H and 75.4 MHz for ^{13}C) at 20-25 ºC unless otherwise stated. Chemical shifts (δ) were measured in ppm relative to chloroform (δ=7.26 for ^{1}H or 77.0 for ^{13}C) as internal standard. Coupling constants, *J*, are reported in hertz. DEPT and several bidimensional NMR experiments (COSY, HSQC) were

used to assist with the assignation of the signals and structural determinations. Mass spectra were recorded under electron impact (70 eV) or chemical ionization conditions.

Typical procedure for the synthesis of amides 2. Synthesis of *N*-(2-*N*'-tert-butoxycarbonylaminoethyl)-pent-4-ynamide (2a).
A solution of 4-pentynoic acid (740 mg, 7.2 mmol) in 5 mL of CH_2Cl_2 was added to a magnetically stirred solution of EDC·HCl (2.0 g, 10.8 mmol) and HOBt (1.5 g, 10.8 mmol) in 20 mL of the same solvent followed by the addition of the monoprotected diamine **1a**[9a] (1.74 g, 10.8 mmol) that was dissolved in 5 mL of CH_2Cl_2. The mixture was cooled to 0 ºC and Et_3N (1.15 g, 10.8 mmol) was added dropwise and was left to react at room temperature overnight. Then, the reaction was diluted with CH_2Cl_2, water (25 mL) was added, the mixture was decanted and the organic layer was consecutively washed with 20 mL of HCl (aq., 5%), 20 mL of a saturated solution of aqueous $NaHCO_3$, and 20 mL of a saturated solution of NaCl. The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The resultant oil was crystallized from Et_2O to afford amide **2a** as a white solid (91%):

Mp 107–108 ºC (Et_2O).

IR (film) υ 3284, 2978, 1655.

^{1}H NMR ($CDCl_3$) δ 6.24 (br s, 1H), 4.88 (br s, 1H), 3.41-3.27 (m, 4H), 2.53-2.40 (m, 4H), 2.00 (t, *J*=2.6, 1H), 1.44 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 171.7, 156.9, 82.9, 79.8, 69.3, 40.7, 40.1, 35.3, 28.3, 14.9.

MS (M+1, CI) *m/z* (%) 213 (21), 185 (32), 167 (42), 141 (100), 124 (72), 57 (24).

HRMS calcd for $C_{12}H_{20}N_2O_3$•H^+ 241.1552, found 241.1877.

***N*-(2-*N*'-benzyloxycarbonylaminoethyl)pent-4-ynamide (2b).** According to the typical procedure, amide **2b** was obtained from monoprotected amine **1b**[9b] in 97% yield as a white solid after purification by crystallization from hexanes:

Mp 108–110 ºC (hexanes).

IR (film) υ 3307, 1690, 1643.

^{1}H NMR ($CDCl_3$) δ 7.36-7.31 (m, 5H), 6.14 (br s, 1H), 5.18 (s, 1H), 5.10 (s, 2H), 3.39-3.35 (m, 4H), 2.33-2.49 (m, 4H), 1.98 (br s, 1H).

^{13}C NMR ($CDCl_3$) δ 171.6, 157.2, 136.3, 128.3, 128.2, 128.1, 83.9, 69.3, 66.7, 40.8, 40.2, 35.2, 14.9.

MS (M+1, CI) *m/z* (%) 167 (48), 107 (18), 91 (100), 87 (17), 79 (28).

HRMS calcd for $C_{15}H_{18}N_2O_3$•H^+ 275.1396, found 275.1399.

Typical procedure for the Sonogashira coupling reaction. Synthesis of *N*-(2-*N*'-tert-butoxycarbonyl-aminoethyl)-5-phenyl-pent-4-ynamide (3a).

A solution of iodobenzene (550 mg, 2.7 mmol), $PdCl_2(PPh_3)_2$ (15 mg, 0.02 mmol), PPh_3 (12 mg, 0.04 mmol), and amide **2a** (939 mg, 4.0 mmol) in Et_3N (15 mL) was stirred at 40 ºC for 15 min. Then, CuI (8 mg, 0.04 mmol) was added and the mixture was heated at 80 ºC for two days. The whole crude was purified by column chromatography (EtOAc) to afford amide **3a** as a white solid that was triturated in hexanes (95%):

Mp 118–120 ºC (hexanes).

IR (film) υ 3284, 2967, 1649, 1549.

^{1}H NMR ($CDCl_3$) δ 7.39-7.36 (m, 2H), 7.28-7.25 (m, 3H), 6.36 (br s, 1H), 4.93 (br s, 1H), 3.41-3.26 (m, 4H), 2.74 (t, *J*=7.3, 2H), 2.46 (t, *J*=7.3, 2H) 1.42 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 171.8, 156.9, 131.6, 127.8, 123.4, 88.4, 81.4, 79.7, 40.8, 40.3, 35.6, 28.3, 15.9.

MS (M+1, CI) *m/z* (%) 289 (26), 261 (100), 243 (13), 217 (56), 57 (39).

HRMS calcd for $C_{18}H_{24}N_2O_3$•H^+ 317.1865, found 317.1860.

***N*-(2-*N*'-tert-butoxycarbonylaminoethyl)-5-p-methoxyphenyl-pent-4-ynamide (4a).** According to the typical procedure, amide **4a** was obtained from amide **2a** in 90% as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes:

Mp 109–111 ºC (hexanes).

IR (film) υ 3296, 2967, 1689, 1643.

^{1}H NMR ($CDCl_3$) δ 7.33-7.30 (d, *J*= 8.8, 2H), 6.82-6.79 (d, *J*= 8.8, 2H), 6.28 (br s, 1H), 4.88 (br s, 1H), 3.80 (s, 3H), 3.43-3.23 (m, 4H), 2.72 (t, *J*= 7.3, 2H), 2.48 (t, *J*= 7.3, 2H), 1.43 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 172.0, 159.2, 156.9, 132.9, 115.6, 113.8, 86.8, 81.5, 79.5, 56.2, 40.5, 40.3, 35.6, 26.3, 15.9.

MS (M+1, CI) *m/z* (%) 291 (100), 290 (28), 273 (27), 247 (44), 231 (45), 230 (65).

HRMS calcd for $C_{19}H_{26}N_2O_4$•H^+ 347.1971, found 347.1972.

***N*-(2-*N*'-tert-butoxycarbonylaminoethyl)-5-p-chlorophenyl-pent-4-ynamide (5a).** According to the typical procedure, amide **5a** was obtained from amide **2a** in 80% as a pale yellow solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes:

Mp 131–132 ºC (hexanes).

IR (film) υ 3296, 2967, 1684, 1637.

^{1}H NMR ($CDCl_3$) δ 7.32 (d, *J*=9.2, 2H), 7.23 (d, *J*=9.2, 2H), 6.37 (br s, 1H), 4.90 (br s, 1H), 3.39-3.25 (m, 4H), 2.73 (t, *J*= 7.3, 2H), 2.46 (t, *J*= 7.3, 2H), 1.43 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 171.7, 157.0, 133.7, 132.8, 128.5, 122.0, 89.5, 80.3, 79.7, 40.8, 40.3, 35.4, 28.3, 15.9.

MS (M+1, CI) *m/z* (%) 323 (17), 295 (91), 277 (50), 251 (100), 234 (57), 192 (30).

HRMS calcd for $C_{18}H_{23}ClN_2O_3$•H^+ 351.1475, found 351.1465.

***N*-(2-*N*'-tert-butoxycarbonylaminoethyl)-5-(2-thienyl)-pent-4-ynamide (6a).** According to the typical procedure, amide **6a** was obtained from amide **2a** in 88% as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes:

Mp 128–130 ºC (hexanes).

IR (film) υ 3284, 2967, 1690, 1649.

^{1}H NMR ($CDCl_3$) δ 7.18-7.12 (m, 2H), 6.99-6.91 (m, 1H), 6.34 (br s, 1H), 4.93 (br s, 1H), 3.39-3.27 (m, 4H), 2.76 (t, *J*=7.3, 2H), 2.64 (t, *J*= 7.3, 2H), 1.43 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 171.7, 156.9, 131.3, 126.8, 126.3, 123.5, 92.5, 79.6, 74.5, 40.7, 40.3, 35.3, 28.3, 16.1.

MS (M+1, CI) *m/z* (%) 267 (100), 249 (23), 223 (44), 206 (50), 180 (26).

HRMS calcd for $C_{16}H_{22}N_2O_3S•H^+$ 323.1429, found 323.1440.

***N*-(2-*N*'-benzyloxycarbonylaminoethyl)-5-phenyl-pent-4-ynamide (3b).** According to the typical procedure, amide **3b** was obtained from amide **2b** in 80% yield as a white solid after purification by column chromatography followed by crystallization of the resultant oil in hexanes:

Mp 151–152 ºC (hexanes).

IR (film) υ 3296, 3070, 1690, 1637.

^{1}H NMR ($CDCl_3$) δ 7.39-7.26 (m, 10H), 6.17 (br s, 1H), 5.17-5.07 (m, 3H), 3.38 (m, 4H), 2.72 (t, *J*= 7.2, 2H), 2.44 (t, *J*=7.2, 2H).

^{13}C NMR ($CDCl_3$) δ 171.9, 157.2, 136.3, 131.5, 128.5, 128.3, 128.1, 127.9, 123.4, 88.3, 81.5, 66.9, 41.0, 40.9, 40.3, 35.6, 15.9.

MS (M+1, CI) *m/z* (%) 351 (20), 286 (100), 266 (18), 243 (23), 91 (61), 79 (19).

HRMS calcd for $C_{21}H_{22}N_2O_3•H^+$ 351.1709, found 351.1708.

***N*-(2-*N*'-benzyloxycarbonylaminoethyl)-5-p-methoxyphenyl-pent-4-ynamide (4b).** According to the typical procedure, amide **4b** was obtained from amide **2b** in 75% as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes:

Mp 124–125 ºC (hexanes).

IR (film) υ 3296, 1684, 1637.

^{1}H NMR ($CDCl_3$) δ 7.34-7.29 (m, 7H), 6.80-6.77 (d, *J*=8.8, 2H), 6.17 (br s, 1H), 5.13-5.07 (m, 3H), 3.78 (s, 3H), 3.41-3.34 (m, 4H), 2.70 (t, *J*=7.1, 2H), 2.43 (t, *J*=7.1, 2H).

^{13}C NMR ($CDCl_3$) δ 172.0, 159.3, 157.0, 136.4, 132.9, 128.5, 128.2, 128.1, 115.5, 113.9, 86.7, 81.3, 66.8, 56.2, 41.0, 40.3, 35.7, 15.9.

MS (M+1, CI) *m/z* (%) 381 (22), 273 (65), 272 (44), 231 (100), 91 (78), 79 (29).

HRMS calcd for $C_{22}H_{24}N_2O_4•H^+$ 381.1814, found 381.1818.

***N*-(2-*N*'-benzyloxycarbonylaminoethyl)-5-p-chlorophenyl-pent-4-ynamide (5b).** According to the typical procedure, amide **5b** was obtained from amide **2b** in 90% as a pale yellow solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes:

Mp 169–170 ºC (hexanes).

IR (film) υ 3284, 1684, 1637.

^{1}H NMR ($CDCl_3$) δ 7.34-7.21 (m, 9H), 6.22 (br s, 1H), 5.18 (br s, 1H) 5.07 (s, 2H), 3.40-3.34 (m, 4H), 2.70 (t, *J*=7.2, 2H), 2.43 (t, *J*=7.2, 2H).

^{13}C NMR ($CDCl_3$) δ 171.7, 157.2, 136.3, 133.8, 132.8, 128.5, 128.2, 126.9, 126.3, 121.9, 89.4, 80.4, 66.9, 40.9, 40.5, 35.4, 15.9.

MS (M+1, CI) *m/z* (%) 385 (11), 324 (10), 279 (40), 277 (100), 237 (23), 235 (73), 193 (11).

HRMS calcd for $C_{21}H_{21}ClN_2O_3•H^+$ 385.1319, found 385.1315.

***N*-(2-*N*'-benzyloxycarbonylaminoethyl)-5-(2-thienyl)-pent-4-ynamide (6b).** According to the typical procedure, amide **6b** was obtained from amide **2b** in 79% as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes.

Mp 127–128 ºC (hexanes).

IR (film) υ 3296, 3070, 1690, 1637.

^{1}H NMR ($CDCl_3$) δ 7.36-7.33 (m, 5H), 7.17-7.11 (m, 2H), 6.93-6.90 (m, 1H), 6.17 (br s, 1H), 5.13-5.07 (m, 3H), 3.41-3.34 (m, 4H), 2.70 (t, *J*=7.1, 2H), 2.43 (t, *J*=7.2, 2H).

^{13}C NMR ($CDCl_3$) δ 171.8, 157.2, 136.3, 131.4, 128.5, 128.2, 128.1, 126.9, 126.3, 123.4, 92.4, 74.7, 66.9, 40.9, 40.4, 35.3, 16.1.

MS (M+1, CI) *m/z* (%) 296 (11), 249 (39), 248 (30), 208 (14), 207 (100), 164 (16), 108 (22).

HRMS calcd for $C_{19}H_{20}N_2O_3S•H^+$ 357.1273, found 357.1289.

***N*-(2-*N*'-benzyloxycarbonylaminoethyl)-5-(3-thienyl)-pent-4-ynamide (7b).** According to the typical procedure, amide **7b** was obtained from amide **2b** in 70% as a white solid after purification by column chromatography (EtOAc) followed by crystallization from hexanes:

Mp 150–151 ºC (hexanes).

IR (film) υ 3300, 3078, 1685, 1641.

^{1}H NMR ($CDCl_3$) δ 7.37-7.30 (m, 6H), 7.21-7.19 (m, 1H), 7.06-7.02 (m, 1H), 6.34 (br s, 1H), 5.30 (br s, 1H), 5.07 (s, 2H), 3.42-3.30 (m, 4H), 2.69 (t, *J*=7.2, 2H), 2.33 (t, *J*=7.2, 2H).

^{13}C NMR ($CDCl_3$) δ 172.0, 157.2, 136.4, 125.2, 129.9, 128.6, 128.1, 123.4, 122.3, 87.9, 66.9, 40.9, 40.3, 35.5, 15.9.

HRMS calcd for $C_{19}H_{20}N_2O_3S•H^+$ 357.1273, found 357.1289.

Typical procedure for the PIFA-mediated cyclization reaction. Synthesis of 5-benzoyl-*N*-(2-*N*'-tert-butoxy-carbonylaminoethyl)pyrrolidin-2-one (8a).

A solution of alkynylamide **3a** (250 mg, 0.8 mmol) in CF_3CH_2OH (12 mL) was stirred and cooled to 0 ºC and a solution of PIFA (526.8 mg, 1.2 mmol) in 6 mL of the same solvent was added dropwise. The reaction mixture was stirred at that temperature for 2 h. For the work up, aqueous Na_2CO_3 (10%) was added and the mixture extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatogra-

phy (EtOAc) gave the desired product **8a** as a chromatographically pure yellowish oil (55%):

IR (film) υ 3331, 2967, 1690, 1519.

^{1}H NMR ($CDCl_3$) δ 7.99 (d, *J*=7.1, 2H), 7.64-7.63 (m, 1H), 7.55-7.50 (m, 2H), 5.39-5,35 (m, 1H), 4.90 (br s, 1H), 3.80-3.77 (m, 1H), 3.49-3.40 (m, 1H), 3.11-3.02 (m, 2H), 2.44-2.30 (m, 3H), 2.11-2.01 (m, 1H), 1.41 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 197.1, 176.3, 156.3, 134.0, 129.0, 128.4, 79.2, 61.8, 42.2, 33.2, 29.3, 28.3, 23.5.

MS (EI) *m/z* (%) 332 (36), 317 (31), 305 (100), 287 (26), 277 (16).

HRMS calcd for $C_{18}H_{24}N_2O_4$ 332.1736, found 332.1731.

***N*-(2-*N*'-tert-butoxycarbonylaminoethyl)-5-(*p*-methoxybenzoyl)-pyrrolidin-2-one (9a).** According to the typical procedure, pyrrolidinone **9a** was obtained from amide **4a** in 74% as a white solid after purification by column chromatography (EtOAc) followed by crystallization from EtOAc:

Mp 111–113 ºC (EtOAc).

IR (film) υ 3331, 2967, 1684, 1596, 1508.

^{1}H NMR ($CDCl_3$) δ 7.97 (d, *J*=8.7, 2H), 6.99 (d, *J*=8.7, 2H), 5.34-5.30 (m, 1H), 4.92 (br s, 1H), 3.89 (s, 3H), 3.80-3.76 (m, 1H), 3.51-3.33 (m, 1H), 3.11-3.06 (m, 2H), 2.50-1.97 (m, 4H), 1.41 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 195.7, 176.4, 164.2, 156.3, 130.8, 127.1, 114.2, 79.1, 61.5, 55.5, 42.2, 38.2, 29.4, 28.3, 23.7.

MS (M+1, CI) *m/z* (%) 246 (15), 245 (83), 244 (100), 215 (5).

HRMS calcd for $C_{19}H_{26}N_2O_5$•H^+ 363.1920, found 363.1877.

***N*-(2-*N*'-tert-butoxycarbonylaminoethyl)-5-(p-chlorobenzoyl)pyrrolidin-2-one (10a).** According to the typical procedure, pyrrolidinone **10a** was obtained from amide **5a** in 54% as a yellowish oil after purification by column chromatography (EtOAc):

IR (film) υ 3343, 2967, 1690, 1588, 1519.

^{1}H NMR ($CDCl_3$) δ 7.91 (d, *J*=8.4, 2H), 7.47 (d, *J*=8.4, 2H), 5.35-5.28 (m, 1H), 5.00 (br s, 1H), 3.87-3.75 (m, 1H), 3.50-3.27 (m, 1H), 3.12-2.94 (m, 2H), 2.49-2.32 (m, 3H), 2.02-1.86 (m, 1H), 1.39 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 196.0, 176.1, 156.4, 140.6, 132.4, 129.9, 129.4, 79.3, 61.6, 42.1, 30.0, 28.3, 28.2, 23.4.

MS (M+1, CI) *m/z* (%) 294 (20), 280 (15), 267 (21), 266 (91), 238 (100), 194 (17), 180 (19).

HRMS calcd for $C_{18}H_{23}ClN_2O_4$•H^+ 367.1425, found 367.1317.

***N*-(2-*N*'-tert-butoxycarbonylaminoethyl)-5-(2-thienylcarbonypyrrolidin)-2-one (11a).** According to the typical procedure, pyrrolidinone **11a** was obtained from amide **6a** in 94% as a yellowish oil after purification by column chromatography (EtOAc):

IR (film) υ 3331, 2967, 1684, 1514.

^{1}H NMR ($CDCl_3$) δ 7.79-7.70 (m, 2H), 7.19-7.14 (m, 1H), 5.18-5.09 (m, 2H), 3.75-3.72 (m, 1H), 3.41-3.37 (m, 1H), 3.11-2.88 (m, 2H), 2.44-2.27 (m, 3H), 2.12-2.10 (m, 1H), 1.35 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 190.8, 176.3, 156.2, 141.1, 135.2, 132.9, 128.6, 79.1, 62.3, 42.2, 38.2, 29.4, 28.3, 24.0.

MS (M+1, CI) *m/z* (%) 265 (4), 222 (20), 221 (93), 220 (100), 191 (11).

HRMS calcd for $C_{16}H_{22}N_2O_4S$•H^+ 339.1379, found 339.1334.

5-Benzoyl-*N*-(2-*N*'-benzyloxycarbonylaminoethyl)-pyrrolidin-2-one (8b). According to the typical procedure, pyrrolidinone **3b** was obtained from amide **3b** in 53% yield as a yellowish oil after purification by column chromatography (EtOAc):

IR (film) υ 3331, 2931, 1690, 1525, 1449.

^{1}H NMR ($CDCl_3$) δ 7.92-7.80 (m, 2H), 7.60-7.55 (m, 1H), 7.48-7.43 (m, 1H), 7.26-7.23 (m, 5H), 5.83-5.76 (m, 1H), 5.35-5.29 (m, 1H), 5.06 (d, *J*=12.3, 1H), 4.94 (d, *J*=12.3, 1H), 2.97-2.74 (m, 4H), 2.40-2.19 (m, 3H), 1.89-1.83 (m, 1H).

^{13}C NMR ($CDCl_3$) δ 197.2, 176.5, 156.9, 136.8, 134.1, 132.1, 129.0, 128.4, 128.0, 127.9, 66.4, 62.0, 42.1, 38.9, 29.3, 23.5..

MS (M+1, CI) *m/z* (%) 259 (75), 216 (40), 215 (100), 214 (75), 153 (29), 108 (35).

HRMS calcd for $C_{21}H_{22}N_2O_4$•H^+ 367.1658, found 367.1653.

***N*-(2-*N*'-benzyloxycarbonylaminoethyl)-5-(*p*-methoxybenzoyl)-pyrrolidin-2-one (9b).** According to the typical procedure, pyrrolidinone **9b** was obtained from amide **4b** in 68% as a yellowish oil after purification by column chromatography (EtOAc):

IR (film) υ 3331, 2943, 1684, 1596, 1514.

^{1}H NMR ($CDCl_3$) δ 7.92 (d, *J*=8.6, 2H), 7.33-7.30 (m, 5H), 6.97 (d, *J*=8.6, 2H), 5.31-5.24 (m, 2H), 5.10 (d, *J*=12.2, 1H), 5.03 (d, *J*=12.2, 1H), 3.89 (s, 3H), 3.80-3.75 (m, 1H), 3.60-3.49 (m, 1H), 3-24-3.09 (m, 2H), 2.43-2.25 (m, 3H), 1.95-1.74 (m, 1H).

^{13}C NMR ($CDCl_3$) δ 195.6, 176.5, 164.3, 156.8, 136.7, 128.1, 128.0, 127.9, 127.0, 114.2, 66.6, 61.7, 56.6, 42.2, 39.1, 29.4, 23.9.

MS (M+1, CI) *m/z* (%) 290 (14), 289 (100), 246 (26), 245 (13), 153 (13).

HRMS calcd for $C_{22}H_{24}N_2O_5$•H^+ 397.1763, found 397.1767.

***N*-(2-*N*'-benzyloxycarbonylaminoethyl)-5-(p-chlorobenzoyl)-pyrrolidin-2-one (10b).** According to the typical procedure, pyrrolidinone **10b** was obtained from amide **5b** in 79% as a yellowish oil after purification by column chromatography (EtOAc):

IR (film) υ 3319, 2943, 1690, 1590, 1525.

^{1}H NMR ($CDCl_3$) δ 7.88 (d, *J*=8.4, 2H), 7.47 (d, *J*=8.4, 2H), 7.32-7.25 (m, 5H), 5.42-5.36 (m, 1H), 5.30-5.28 (m, 1H), 5.09 (d, *J*=12.2, 1H), 5.02 (d, *J*=12.2, 1H), 3.86-3.77 (m, 1H), 3.49-3.30 (m, 1H), 3.20-2.96 (m, 2H), 2.32-2.20 (m, 2H), 1.87-1.80 (m, 1H).

^{13}C NMR ($CDCl_3$) δ 196.0, 176.3, 156.8, 140.7, 136.6, 132.3, 129.8, 129.4, 128.5, 128.1, 127.9, 66.6, 61.8, 42.1, 38.7, 29.2, 23.4.

MS (M+1, CI) *m/z* (%) 295 (33), 293 (100), 252 (10), 250 (84), 289 (77), 153 (95), 108 (26).

HRMS calcd for $C_{21}H_{21}ClN_2O_4•H^+$ 401.1268, found 401.1261.

***N*-(2-*N*'-benzyloxycarbonylaminoethyl)-5-(2-thienylcarbonyl)-pyrrolidin-2-one (11b).** According to the typical procedure, pyrrolidinone **11b** was obtained from amide **6b** in 81% as a yellowish oil after purification by column chromatography (EtOAc):

IR (film) υ 3319, 3072, 1678, 1590.

^{1}H NMR ($CDCl_3$) δ 7.75-7.67 (m, 2H), 7.27-7.22 (m, 5H), 7.14-7.11 (m, 1H), 5.79-5.73 (m, 1H), 5.13-5.10 (m, 1H), 5.03 (d, *J*=12.2, 1H), 4.96 (d, *J*=12.2, 1H), 3.76-3.68 (m, 1H), 3.49-3.30 (m, 1H), 3.20-2.96 (m, 2H), 2.30-2.14 (m, 3H), 1.97-1.90 (m, 1H).

^{13}C NMR ($CDCl_3$) δ 190.8, 176.5, 156.8, 141.0, 135.3, 128.7, 128.4, 128.0, 127.9, 66.4, 62.7, 42.0, 38.7, 29.4, 24.0.

MS (M+1, CI) *m/z* (%) 329 (8), 256 (34), 222 (38), 221 (100), 220 (69), 108 (34).

HRMS calcd for $C_{19}H_{20}N_2O_4S•H^+$ 373.1222, found 373.1224.

***N*-(2-*N*'-benzyloxycarbonylaminoethyl)-5-(3-thienylcarbonyl)-pyrrolidin-2-one (12b).** According to the typical procedure, pyrrolidinone **12b** was obtained from amide **7b** in 64% as a yellowish solid after purification by column chromatography (EtOAc):

IR (film) υ 3315, 3088, 1685, 1528.

^{1}H NMR ($CDCl_3$) δ 8.14 (br s, 1H), 7.56-7.54 (m, 1H), 7.39-7.33 (m, 1H), 5.39 (br s, 1H), 5.12-5-00 (m, 3H), 3.85-3.76 (m, 1H), 3.52-3.45 (m, 1H), 3.19-3.04 (m, 2H), 2.42-2.22 (m, 3H), 2.00-1.93 (m, 1H).

^{13}C NMR ($CDCl_3$) δ 191.8, 176.5, 156.8, 139.1, 136.5, 133.3, 128.5, 128.1, 128.0, 127.2, 127.0, 66.6, 62.9, 42.0, 38.8, 29.3, 23.7.

HRMS calcd for $C_{19}H_{20}N_2O_4S•H^+$ 373.1222, found 373.1224.

Typical procedure for the intramolecular amination reaction. Synthesis of 1-phenyl-3,4,7,8-tetrahydro-pyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (13a).

A solution of pyrrolidinone **8a** (170 mg, 0.5 mmol) in TFA/CH_2Cl_2 1/1 (20 mL) was stirred for 30 min. An aliquot was taken to confirm (^{1}H NMR) that the protecting group was completely released. Then, solvent was removed under vacuum to remove both solvents and the residue was taken in 50 mL of CH_2Cl_2, cooled to 0 ºC and treated with Et_3N (0.7 mL, 5 mmol). After stirring for 20 min, molecular sieve (4 Å) was added and the stirring continued for 15 additional minutes. The mixture was then filtered through celite, washed with 20 mL of a saturated aqueous solution of $NaHCO_3$, and finally extracted with EtOAc (3x25 mL). The combined organic extracts were dried and evaporated at reduced pressure, and the resulting residue purified by column chromatography (EtOAc/MeOH, 95/05) to afford pyrazinone **13a** as a yellowish oil that was finally crystallized from methanol (41%):

Mp 127–128 ºC (MeOH).

IR (film) υ 3236, 1667.

^{1}H NMR ($CDCl_3$) δ 7.95 (d, *J*=8.0, 2H), 7.43-7.36 (m, 3H) 5.14 (br s, 1H), 4.05-3.95 (m, 2H), 3.68-3.57 (m, 1H), 3.23-3.16 (m, 1H), 2.71-2.59 (m, 1H), 2.37-2.25 (m, 2H), 2.09-1.96 (m, 1H).

^{13}C NMR ($CDCl_3$) δ 173.1, 165.2, 135.9, 130.2, 128.3, 128.1, 83.9, 48.1, 32.6, 32.5, 29.4.

MS (M+1, CI) *m/z* (%) 231 (12), 215 (72), 214 (100), 213 (14), 185 (10).

HRMS calcd for $C_{13}H_{14}N_2O•H^+$ 215.1184, found 215.1191.

1-(*p*-Methoxyphenyl)-3,4,7,8-tetrahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (13b). According to the typical procedure, pyrrolidinone **13b** was obtained from amide **9a** in 33% as a yellowish solid by purification by column chromatography (EtOAc/MeOH, 70/30) followed by crystallization from methanol:

Mp 131–132 ºC (MeOH).

IR (film) υ 3355, 1696.

^{1}H NMR ($CDCl_3$) δ 7.96 (d, *J*=9.0, 2H), 6.93 (d, *J*=9.0, 2H) 4.14-4.02 (m, 2H), 3.87 (s, 3H), 3.70-3.58 (m, 1H), 3.22-3.12 (m, 1H), 2.75-2.66 (m, 1H), 2.48-2.34 (m, 2H), 2.14-2.04 (m, 1H), 1.64 (br s, 1H).

^{13}C NMR ($CDCl_3$) δ 172.8, 163.9, 161.2, 129.7, 128.3, 113.6, 84.0, 55.3, 48.0, 32.8, 32.7, 29.3.

MS (M+1, CI) *m/z* (%) 261 (43), 245 (71), 244 (100), 243 (53), 242 (42).

HRMS calcd for $C_{14}H_{16}N_2O_2•H^+$ 245.1290, found 245.1288.

1-(*p*-Chlorophenyl)-3,4,7,8-tetrahydropyrrolo[1,2-*a*]pyrazin-6(2*H*)-one (13c). According to the typical procedure, pyrrolidinone **13c** was obtained from amide **10a** in 34% as a yellowish oil by purification by column chromatography (EtOAc/MeOH, 95/5):

IR (film) υ 3302, 1678.

^{1}H NMR ($CDCl_3$) δ 7.92 (d, *J*=8.7, 2H), 7.37 (d, *J*=8.7, 2H), 4.10-3.99 (m, 2H), 3.70-3.57 (m, 1H), 3.48 (s, 1H), 3.25-3.14 (m, 1H), 2.74-2.62 (m, 1H), 2.38-2.27 (m, 2H), 2.05-1.98 (m, 1H).

^{13}C NMR ($CDCl_3$) δ 173.0, 163.9, 136.4, 134.2, 129.5, 128.6, 83.8, 48.2, 32.7, 32.6, 29.3.

MS (M+1, CI) *m/z* (%) 265 (16), 250 (36), 249 (58), 248 (100), 213 (11).

HRMS calcd for $C_{13}H_{13}{}^{35}ClN_2O•H^+$ 249.0795, found 249.0783.

1-(2-Thienyl)-3,4,7,8-tetrahydropyrrolo[1,2-*a*]-pyrazin-6(2*H*)-one (13d). According to the typical procedure, pyrrolidinone **13d** was obtained from amide **11a** in 39% as a yellowish solid by purification by column chromatography (EtOAc/MeOH, 95/5) followed by crystallization from methanol:

Mp 131–132 ºC (MeOH).

IR (film) υ 3296, 1690.

^{1}H NMR ($CDCl_3$) δ 7.64-7.39 (m, 2H), 7.08-7.06 (m, 1H) 4.12-3.93 (m, 2H), 3.91-3.79 (m, 1H), 3.66-3.58 (m, 1H), 3.18-2.80 (m, 1H), 2.79-2.56 (m, 2H), 2.42-2.22 (m, 1H), 1.68 (br s, 1H).

^{13}C NMR ($CDCl_3$) δ 173.0, 160.3, 141.4, 129.2, 129.1, 127.7, 83.9, 48.1, 33.6, 32.9, 29.3.

MS (M+1, CI) *m/z* (%) 237 (99), 221 (67), 220 (100), 153 (13), 127 (14).

HRMS calcd for $C_{11}H_{12}N_2OS•H^+$ 221.0749, found 221.0739.

Typical procedure for the intramolecular reductive amination reaction. Synthesis of (1*R*,8a*S*)-1-phenylhexahydropyrrolo[1,2-*a*]pyrazin-6(7*H*)-one (14a).

A solution of pyrrolidinone **8b** (209.5 mg, 0.6 mmol) in 6 mL of MeOH and 0.5 mL of HCl (1M) was hydrogenated (70 psi) in the presence of Pd/C overnight. The catalyst was filtered through celite and the solution treated with 15 mL of an aqueous solution of Na_2CO_3 (20%). The mixture was extracted with CH_2Cl_2 (3x15 mL), the combined organic extracts were dried with Na_2SO_4, and the solvent evaporated under vacuum. The resulting oil was purified by column chromatography (MeOH) to afford pyrazine **14a** as a yellowish oil (40%):

IR (film) υ 3350, 1655.

^{1}H NMR ($CDCl_3$) δ 7.37-7.26 (m, 5H), 4.61 (d, *J*=8.0, 1H), 3.79-3.77 (m, 1H), 3.71-3.68 (m, 1H), 3.47-3.44 (m, 1H), 3.38-3.36 (m, 1H), 2.93-2.90 (m, 1H), 2.45-2,38 (m, 1H), 2.26-2.19 (m, 1H), 1.90-1.83 (m, 1H), 1.72-1.68 (m, 1H).

^{13}C NMR ($CDCl_3$) δ 177.5, 141.4, 128.5, 127.9, 127.0, 77.1, 66.6, 46.8, 39.2, 30.1, 22.6.

MS (M+1, CI) *m/z* (%) 259 (74), 216 (39), 215 (100), 214 (76), 153 (29), 108 (35).

HRMS calcd for $C_{13}H_{16}N_2O•H^+$ 217.1341, found 217.1348.

(1*R*,8a*S*)-1-(*p*-Methoxyphenyl)hexahydropyrrolo[1,2-*a*]pyrazin-6(7*H*)-one (14b). According to the typical procedure, pyrrolidinone **14b** was obtained from amide **9b** in 43% as a yellowish oil after purification by column chromatography (EtOAc):

IR (film) υ 3425, 1667.

^{1}H NMR ($CDCl_3$) δ 7.27 (d, *J*=8.7, 2H), 6.85 (d. *J*=8.7, 2H), 4.09-4.04 (m, 1H), 3.76 (s, 3H), 3.48-3.43 (m, 1H), 3.22 (d, *J*=9.3, 1H), 3.13-3.10 (m, 1H), 2.97-2.91 (m, 1H), 2.82-2.76 (m, 1H), 2.46-2.26 (m, 3H), 1.84-1.77 (m, 1H), 1.64-1.56 (m, 1H).

^{13}C NMR ($CDCl_3$) δ 173.7, 159.5, 131.6, 128.8, 114.0, 79.7, 61.9, 55.2, 45.4, 40.2, 30.1, 21.6.

MS (M+1, CI) *m/z* (%) 275 (15), 258 (15), 247 (100), 246 (66), 230 (28), 161 (13).

HRMS calcd for $C_{14}H_{18}N_2O_2•H^+$ 247.1447, found 247.1440.

(1*R*,8a*S*)-1-(*p*-Chlorophenyl)hexahydropyrrolo[1,2-*a*] -pyrazin-6(7*H*)-one (14c). According to the typical procedure, pyrrolidinone **14c** was obtained from amide **10b** in 46% as a yellowish oil after purification by column chromatography (MeOH):

^{1}H NMR ($CDCl_3$) δ 7.42-7.33 (m, 4H), 4.12-4.09 (m, 1H), 3.54-3.49 (m, 1H), 3.30 (d, *J*= 9.2, 1H), 3.17-3.14 (m, 1H), 3.00-2.96 (m, 1H), 2.86-2.80 (m, 1H), 2.42-2.29 (m, 2H), 1.98 (br s, 1H), 1.84-1.80 (m, 1H), 1.66-1.62 (m, 1H).

^{13}C NMR ($CDCl_3$) δ 173.7, 139.6, 128.7, 128.5, 127.7, 68.3, 61.9, 45.4, 40.3, 30.1, 21.6.

IR (film) υ 3387, 1667.

MS (M+1, CI) *m/z* (%) 245 (10), 218 (14), 217 (100), 216 (60), 200 (23).

HRMS calcd for $C_{13}H_{15}ClN_2O•H^+$ 251.0951, found 251.0953.

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(11) These results led us to propose a mechanism in which the activated triple bond easily coordinates with the I(III) reagent and, hence, assisting the nucleophilic attack of the amidic nitrogen. In addition, alkyl-substituted alkynes also failed in the PIFA-mediated cyclization step.

(12) For recent books or reviews concerning the chemistry of the hypervalent iodine reagents, see: (a) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH: New York, 1992. (b) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: London, 1997. (c) Wirth, T., Ed. *Hypervalent Iodine Chemistry*; Springer-Verlag: Berlin, 2003. (d) Togo, H.; Katoghi, M. *Synlett* **2001**, 566. (e) Togo, H.; Sakurani, M. *Synlett* **2002**, 1966. (f) Zhdankin, V. V.; Stang, P. J. *Chem. Rev*. **2002**, *102*, 2523. (g) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 11. (h) Stang, P. J. *J. Org. Chem*. **2003**, *68*, 2997 (i) Wirth, T. *Angew. Chem., Int. Ed*. **2005**, *44*, 3656. (j) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed*. **2006**, *45*, 4402. (k) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, 3759. (l) Quideau, S.; Pouységu, L.; Deffiieux, D. *Synlett* **2008**, 467. (m) Zhdankin, V. V.; Stang, P. J. *Chem. Rev*. **2008**, *108*, 5299. (n) Zhdankin, V. V. *ARKIVOC* **2009**, i, 1.

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(14) Additional attempts to hydrogenate unsaturated pyrrolopirazinone **13a** to afford **14a** resulted in the recovery of the starting material unchanged. Apparently, hydrogenation of the imine intermediate **J** seems to be a much quicker process compared to the isomerization process that would lead to its enamine tautomer.

(15) Diastereoisomers **14** showed a significant NOE between the H-1 and H-8a protons indicating that they are located on the same face of the heterocyclic ring.

(16) It is known that, in some cases, thiophene-containing olefins can be unreactive under Pd catalyzed hydrogenation conditions.

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A versatile PIFA-mediated approach to structurally diverse pyrrolo(benzo)diazepines from linear alkynylamides

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Dedicated to the memory of our colleague and friend José Manuel Concellón

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ABSTRACT

The addition of the hypervalent iodine reagent PIFA [phenyliodine(III) bis(trifluoroacetate)] to a series of properly substituted *N*-(3-aminopropyl)alkynylamides results in the efficient formation of a functionalized 5-aroyl-2-pyrrolidinone skeleton. By proper manipulations of the N(1)-substituents, through consecutive deprotection and/or reductive amination steps, a second cyclization process occurs yielding the target heterocycles. As it will be disclosed, the overall process is open to structural modifications that gives rise to a series of pyrrolo(benzo)diazepine derivatives.

1. Introduction

The performance of synthetic studies on a particular structural motif with well-recognized biological or pharmacological actions has been a recurrent approach for the development of new methodologies in organic synthesis. Not surprisingly, the pyrrolo[1,2-*c*][1,4]benzodiazepine skeleton (PBD), as being part of the naturally-occurring DNA-interactive antitumor antibiotics known as the 'anthramycines',[1] has been the target for a number of different approaches. In general terms,[2] the use of adequately substituted *N*-(2-aminobenzoyl)proline derivatives[3] and isatoic anhydrides[4] are still the two main entrances to the synthesis of PBD derivatives. Such little options for the preparation of a type of heterocycle that requires as much structural diversity as possible for biological studies were recently enlarged by our group in a novel design for the enantiocontrolled synthesis of the antibiotic (−)-DC-81 that featured the intramolecular PIFA-assisted cyclization[5] of *N*-methoxyamides of type **1**, derived from L-proline, to render optically pure **2** (see Fig. 1).[6] From a mechanistic point of view, it is accepted that in this transformation the deficient *N*-acylnitrenium intermediate **I**, generated by the action of the I(III) reagent,[7] is intramolecularly captured by the arene system to perform the ring closure process.[8]

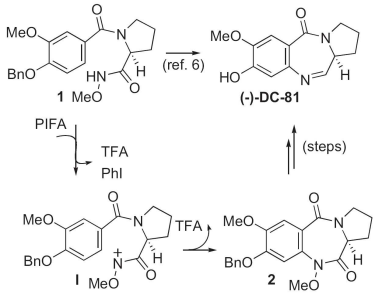

Figure 1. First approach to a PIFA-mediated synthesis of a pyrrolo(benzo)diazepine skeleton designed in our group.

Convinced of the need for developing novel and more versatile approaches to the preparation of PBD derivatives, we wish to report here a new routine to prepare such type of heterocycles based on the intramolecular formal double addition of a diamino fragment across both positions of a triple bond (from **3** to **4** in Fig. 2) assisted,

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once again, by the hypervalent iodine reagent PIFA. This proposal, adapted from our previous communications,[9] is based on the alternative activation of the electronically enriched triple bond by PIFA (instead of nitrogen oxidation) to give an electrophilic intermediate **II** that reacts intramolecularly with the nucleophilic amide to give **III**. Reaction of **III** with a free trifluoroacetate ligand delivered by PIFA results in the formation of a nonisolable ester **IV**, which after basic hydrolysis during the work up affords the substituted pyrrolidinone skeleton **V**. Finally, subtle selection of fragment ∑ will eventually lead to the final heterocycle **4** through application of reductive amination conditions.

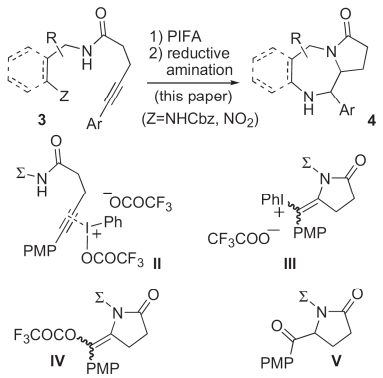
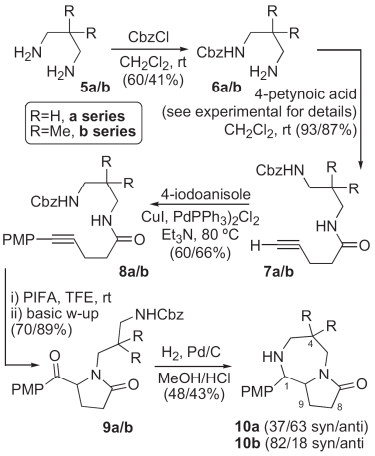


Figure 2. Second approach to a PIFA-mediated synthesis of a pyrrolo(benzo)diazepine skeleton designed in our group.

The fact that the present approach allows the preparation of both pyrrolodiazepine and pyrrolobenzodiazepine derivatives[10] by a common route and, additionally, with a less common oxygenated function at the C-3 position of the PBD skeleton, reinforces the interest for its development.[11]

2. Results and discussion

According to our synthetic plan, the preparation of the target molecules required bringing a number of different components together in a linear multifunctional molecule using 1,3-diaminopropane (**5a**) and 1,3-diamino-2,2-dimethylpropane (**5b**) as starting materials (see Scheme 1). Therefore, these compounds were first protected[12] as carbamates **6a**,**b** and then transformed into amides **7a**,**b** using pentynoic acid under standard conditions in very high yields. To accomplish the first part of the synthesis, a Sonogashira coupling reaction[13] was envisaged to include an activated *para*-methoxyphenyl group (PMP) at the terminal position of the triple bond. When all parts of substrates **8a**,**b** were assembled, they were submitted to the PIFA-mediated cyclization conditions. Thus, treatment of amides **8a**,**b** with a slight excess (1.5 equiv) of the hypervalent iodine reagent in trifluoroethanol (TFE) as solvent at room temperature, followed by a basic aqueous work up, rendered the 5-aroyl-2-pyrrolidinones **9a**,**b** in which the protected 3-aminopropyl appendage remained unaltered and ready to be used in the second cyclization step. Accordingly, treatment of derivatives **9a**,**b** under an atmosphere of H_2 (70 psi) using Pd(C) as catalyst in acidic methanol rendered pyrrolodiazepines **10a**,**b** in 48 and 43% yields, respectively, through a combination of three consecutive single processes (deprotection, intramolecular addition to the carbonyl group, and reduction of the resultant imine). It must be mentioned that an intensive spectroscopic study led to the conclusion that both substrates **10a**,**b** were formed as inseparable mixtures of *syn*/*anti* diastereoisomers in different proportions and with opposed preferences for the relative configuration of the new stereogenic center generated at C-1.

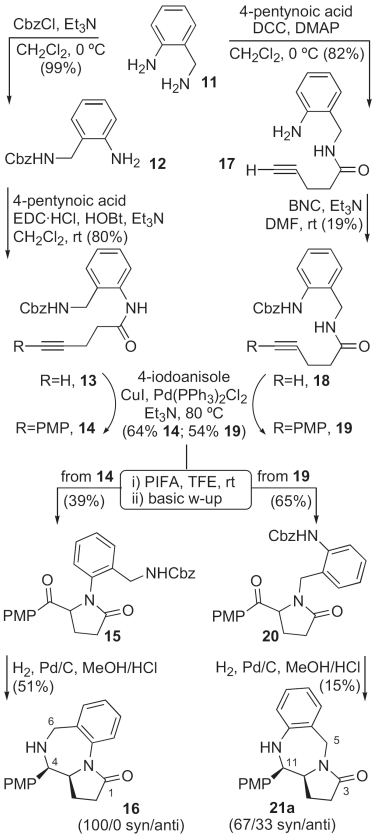


Scheme 1. Preparation of pyrrolodiazepinones **10a**,**b**.

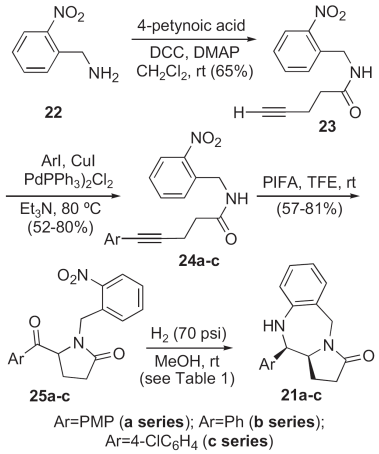
To the view of these results we planned to extend this synthetic strategy to the preparation of the PBD skeleton and, coherently, we selected 2-aminobenzylamine (**11**) as the starting material. As opposed to the previous design that started from symmetric diamines **5a**,**b**, the alteration in the order of protection/amidation events when applied to diamine **11** will eventually lead to two different regioisomers. Therefore, in order to demonstrate the versatility of this approach, we embarked in the preparation of both tricyclic derivatives following the route depicted in Scheme 2.

Taking advantage of the markedly different nucleophilicity of both amino groups in **11**, regioisomers **13** and **18** could be independently prepared by altering the sequence of amidation and protection steps. Successive Sonogashira coupling reaction under standard conditions, and PIFA-mediated cyclization rendered, respectively, pyrrolidinones **15** and **20** that were finally submitted to hydrogenation conditions. We were happy to find that, as anticipated, both regioisomeric pyrrolo-benzo[*f*]-1,4-diazepin-1-one **16** and pyrrolo-benzo[*e*]-1,4-diazepin-3-one **21a** were obtained, although with different results. In fact, while PBD **16**, which features a less common fusion of the three rings, was obtained from **15** in a reasonable yield (51%) and with complete *syn* diastereoselectivity, the efficiency of the synthesis of PBD **21a**, on the contrary, was not satisfactory at all (extremely low overall yield and poor diastereoselectivity in the final step), especially due to the difficulties associated to the protection step (from **17** to **18**)[14] and in the final cyclization (from **20** to **21a**).

As a consequence, we decided to explore a new protection-free synthetic alternative, outlined in Scheme 3, which starts now from 2-nitrobenzylamine (**22**) following a similar routine as before. Thus, after successive steps of amidation, Sonogashira coupling, and PIFA-mediated intramolecular cyclization, pyrrolidinone **25a** was prepared and submitted to the final reductive cyclization step. This part of the synthesis was optimized with respect to the use of



Scheme 2. Preparation of PBDs **16** and **21a**.



Scheme 3. Synthetic alternative for the preparation of PBDs **21a**–**c**.

different catalysts able to accomplish the reduction of the nitro group and the in situ heterocyclization under hydrogenation conditions. The results, summarized in Table 1, show that the best conditions to transform **25a** into PBD **21a** required the use of PtO_2 as catalyst (entry 1) working under a H_2 atmosphere (70 psi) at room temperature.[15] Some other attempts that include the use of other catalysts (entries 2 and 3) resulted in a less efficient transformation. It must be also mentioned that while the same conditions employed to transform **9** into **10**, and **15** into **16**, happened to be unproductive for **25a** (entry 4), the use of Pd black resulted exclusively in the reduction of the nitro group as the final stage of the reaction (entry 5). The addition of an extra amount of catalysts did not result in a further progress. In addition, the diastereoselectivity of the process was clearly favored with the use of PtO_2.

To the view of these results we decided to extend the synthetic strategy depicted in Scheme 3 to the preparation of a small series of derivatives **21a**–**c**, in which the aryl fragment located at C-11 is modified. Under such circumstances, 11-phenylPBD **21b** and 11-(4-chlorophenyl)PBD **21c** were obtained in reasonable good yields with good diastereoselectivities (entries 6–7 in Table 1).

Table 1
Optimization of the reductive cyclization of **25a**–**c** into **21a**–**c**

Entry	25	21	Conditions[a]	Yield (%)	(*syn*/*anti*)[b]
1	**a**	**a**	PtO_2/MeOH	92	(84/16)
2	**a**	**a**	Ra-Ni/MeOH[c]	58	(38/62)
3	**a**	**a**	$Pd(OH)_2$, MeOH	72	(53/47)
4	**a**	**a**	Pd(C)/MeOH-HCl	0[d]	—
5	**a**	**a**	Pd black/MeOH	71[e]	—
6	**b**	**b**	PtO_2/MeOH	95	(77/23)
7	**c**	**c**	PtO_2/MeOH	49	(71/29)

[a] A 10 wt% quantity of catalyst was employed.
[b] Determined from the crude ^1H NMR.
[c] The reduction of the NO_2 group to render *N*-(2′-aminobenzyl)-5-(4-methoxybenzoyl)-2-pyrrolidinone (**26a**) (98% yield) was the only process that could be detected when a limited amount (5 wt%) of catalyst was employed. The reaction progressed to the final compound in 58% yield with an additional amount of catalyst.
[d] A complex mixture of products was obtained.
[e] Isolated yield for pyrrolidinone **26a**.

3. Conclusions

In conclusion, we have shown that the intramolecular PIFA-mediated alkyne amidation reaction on *N*-(3-aminopropyl), *N*-(2-aminomethylphenyl), *N*-(2-aminobenzyl), and *N*-(2-nitrobenzyl) substituted substrates has proven to be an efficient alternative to prepare highly functionalized pyrrolidinones. As a demonstration of its usefulness, when this transformation is coupled with a second intramolecular amination step, the overall process results in a simple and rapid protocol for the synthesis of a series of pyrrolodiazepinone and pyrrolobenzodiazepinone derivatives.

4. Experimental section

4.1. General procedures

All reagents were purchased and used as received. All solvents used in reactions were dried and purified according to standard procedures. All air- or moisture-sensitive reactions were performed under argon. The glassware was oven dried (140 °C) overnight and purged with argon prior to use. Melting points were measured

using open glass capillaries and are uncorrected. Infrared spectra were recorded as thin films and peaks are reported in cm^{-1}. Only representative absorptions are given. Flash chromatography was carried out on SiO_2 (silica gel 60, 230–400 mesh ASTM). NMR spectra were recorded on a 300 instrument (300 MHz for ^1H and 75.4 MHz for ^{13}C) at 20–25 °C unless otherwise stated. Chemical shifts (δ) were measured in parts per million relative to chloroform (δ=7.26 for ^1H or 77.0 for ^{13}C) as internal standard. Coupling constants, *J*, are reported in hertz. DEPT and several bidimensional NMR experiments (COSY, HSQC, NOESY) were used to assist with the assignation of the signals and structural and stereochemical determinations. Mass spectra were recorded under electron impact (70 eV) or chemical ionization conditions.

4.2. Typical procedure for the benzyloxycarbonylation of diamines 5

*4.2.1. Synthesis of N-benzyloxycarbonyl-1,3-propanediamine (**6a**).* A stirred solution of benzyl chloroformiate (2.9 mL, 21 mmol) in 50 mL of CH_2Cl_2 was added dropwise over 85 min to a solution of 1,3-propanediamine **5a** (3.11 g, 42 mmol) in 70 mL of the same solvent at 0 °C. The mixture was stirred for additional 90 min, the temperature was raised to rt, and stirring was continued for 24 h. Then, the solid that was formed (the HCl salt of the excess of starting material) was filtered, and the solution was washed with brine (3×40 mL), decanted and dried over Na_2SO_4 (anhyd). Removal of the solvent under vacuum afforded an oil that was purified by column chromatography (EtOAc) to render carbamate **6a** as a colorless oil (60%): ^1H NMR ($CDCl_3$) δ (ppm) 7.32–7.26 (m, 5H), 5.55 (br s, 1H), 5.06 (s, 2H), 3.26–3.22 (m, 2H), 2.80–2.67 (m, 2H), 1.61–1.56 (m, 2H), 1.46 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 156.6, 136.7, 128.5, 128.0, 66.5, 39.6, 39.1, 33.0; IR ν (cm^{-1}) 3325, 2931, 1683; MS [M+1] *m/z*: 209 (41), 165 (10), 108 (26), 101 (100).

*4.2.2. N-Benzyloxycarbonyl-2,2-dimethyl-1,3-propanediamine (**6b**).* According to the typical procedure, carbamate **6b** was obtained from diamine **5b** in a 41% yield and purified by column chromatography (EtOAc) as a colorless oil: ^1H NMR ($CDCl_3$) δ (ppm) 7.37–7.12 (m, 5H), 6.05 (br s, 1H), 5.02 (s, 2H), 2.99 (s, 2H), 2.42 (s, 2H), 1.88 (s, 2H), 0.79 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm) 157.1, 136.8, 128.4, 128.0, 66.5, 50.4, 49.1, 35.6, 23.3; IR ν (cm^{-1}) 3320, 2944, 1702: MS [M+1] *m/z*: 237 (8). 129 (100). 108 (22). 107 (13): HRMS calcd for $C_{13}H_{20}N_2O{\cdot}H^+$: 237.1603, found: 237.1611.

*4.2.3. Synthesis of 2-amino-N-(benzyloxycarbonyl)benzylamine (**12**).* A stirred solution of benzyl chloroformiate (0.3 mL, 2.05 mmol) in 50 mL of CH_2Cl_2 was added dropwise over 85 min to a solution of benzylamine **11** (0.5 g, 4.1 mmol)[16] and Et_3N (0.3 mL, 6.1 mmol) in 6 mL of the same solvent at 0 °C. The mixture was stirred for additional 90 min, the temperature was raised to rt, and stirring was continued for 24 h. Then, a white precipitate was filtered, and the solution was washed with brine (3×40 mL), decanted and dried over Na_2SO_4 (anhyd). Removal of the solvent under vacuum afforded an oil that was purified by column chromatography (MeOH) to render carbamate **12** as a yellowish solid that was triturated in hexanes (99%): mp 52–53 °C (hexanes); ^1H NMR ($CDCl_3$) δ (ppm) 7.36 (s, 5H), 7.15–7.03 (m, 2H), 6.74–6.65 (m, 2H), 5.32 (br s, 1H), 5.12 (s, 2H), 4.28 (d, *J*=6.1, 2H), 4.09 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 157.0, 145.4, 136.4, 129.2, 128.6, 128.2, 128.1, 122.3, 118.1, 116.0, 67.0, 42.5; IR ν (cm^{-1}) 3349, 3029, 1692; MS [M+1] *m/z*: 257 (32), 256 (100), 196 (38), 149 (47), 148 (25), 121 (26), 106 (39); HRMS calcd for $C_{15}H_{16}N_2O_2{\cdot}H^+$: 257.1290, found: 257.1293.

*4.2.4. Synthesis of N-[(2-N′-benzyloxycarbonylamino)benzyl]-4-pentyamide (**18**).* Benzyl *para*-nitrophenyl carbonate (683 mg, 2.5 mmol) and Et_3N (1.1 mL, 7.5 mmol) were added, successively, into a solution of amide **17** (1.0 g, 4.9 mmol) in DMF (15 mL). The mixture was magnetically stirred at rt for 12 h under inert atmosphere. Then, solvent was removed under vacuum; the residue was taken in 40 mL of CH_2Cl_2 and washed with a saturated solution of Na_2CO_3 (30 mL). The decanted organic phase was dried with Na_2SO_4 (anhyd), the solvent removed under vacuum, and the resulting residue was purified by column chromatography (hexanes/EtOAc, 1/1) to afford **18** as a white solid that was triturated in hexanes (19%): mp 110–111 °C (hexanes); ^1H NMR ($CDCl_3$) δ (ppm) 8.79 (br s, 1H), 7.90 (d, *J*=8.4, 1H), 7.44–7.04 (m, 8H), 6.29 (m, 1H), 5.23 (s, 2H), 4.37 (d, *J*=6.4, 2H), 2.51–2.46 (m, 2H), 2.38–2.34 (m, 2H), 1.92 (t, *J*=2.6, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.0, 154.5, 136.8, 136.6, 128.5, 128.0, 123.9, 123.8, 122.4, 82.5, 69.6, 66.7, 40.6, 35.1, 14.8; IR ν (cm^{-1}) 3290, 3073, 1650, 1559; MS [M+1] *m/z*: 230 (11, M+1−Cbz), 229 (75), 227 (21), 149 (30), 147 (100), 132 (20); HRMS calcd for [$C_{20}H_{20}N_2O_3{\cdot}H^+$−Cbz] 230.1055, found: 230.1024.

4.3. Typical procedure for the acylation of amines. Method 1

*4.3.1. Synthesis of N-(3-N′-benzyloxycarbonyl-aminopropyl)-4-pentynamide (**7a**).* Amine **6a** (1.6 g, 7.7 mmol) was added to a cold (0 °C) solution of DCC (1.7 g, 8.5 mmol), DMAP (50 mg, 0.4 mmol), and 4-pentynoic acid (833 mg, 8.5 mmol) in CH_2Cl_2 (80 mL) and the mixture was stirred overnight. Then, a white solid (urea) was filtered and the solvent was evaporated at reduced pressure. The residue was purified by column chromatography (MeOH) to afford **7a** as a white solid that was triturated in cold ether (93%): mp 60–61 °C (Et_2O); ^1H NMR ($CDCl_3$) δ (ppm) 7.37–7.26 (m, 5H), 6.32 (br s, 1H), 5.34 (br s, 1H), 5.09 (s, 2H), 3.33–3.20 (m, 4H), 2.54–2.49 (m, 2H), 2.41–2.36 (m, 2H), 1.99 (s, 1H), 1.66–1.64 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.6, 128.5, 128.0, 82.9, 69.3, 37.6, 36.0, 35.4, 30.0, 15.0; IR ν (cm^{-1}) 3300, 2926, 1700, 1648; MS [M+1] *m/z*: 289 (55), 245 (46), 197 (20), 181 (100), 153 (16), 136 (18), 111 (20); HRMS calcd for $C_{16}H_{20}N_2O_3{\cdot}H^+$: 289.1552, found: 289.1551.

*4.3.2. Synthesis of N-(2-aminobenzyl)-4-pentynamide (**17**).* According to the typical procedure amide **17** was prepared from amine **11** and purified as a white solid in 82% yield by column chromatography (hexanes/EtOAc, 1/1) followed by crystallization from Et_2O: mp 76–77 °C (Et_2O); ^1H NMR ($CDCl_3$) δ (ppm) 7.10–6.99 (m. 2H). 6.67–6.60 (m. 2H). 6.48 (br s. 1H). 4.30 (d. *J*=6.1. 2H). 4.11 (br s, 2H), 2.48–2.43 (m, 2H), 2.36–2.31 (m, 2H), 1.947(s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.6, 145.5, 130.6, 129.2, 121.9, 117.8, 115.8, 83.0, 69.5, 40.8, 35.1, 14.9; IR ν (cm^{-1}) 3292, 3059, 1643; MS [M+1] *m/z*: 203 (35), 202 (100), 134 (10), 121 (31), 106 (81); HRMS calcd for $C_{12}H_{14}N_2O_3{\cdot}H^+$: 203.1184, found: 203.1186.

*4.3.3. N-(2-Nitromethylphenyl)-4-pentynamide (**23**).* According to the typical procedure amide **23** was prepared from benzylamine **22** as a yellowish solid in a 65% yield. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration of the resultant solid in hexanes: mp 62–63 °C (hexanes); ^1H NMR ($CDCl_3$) δ (ppm) 7.96 (d, *J*=8.1, 1H), 7.58–7.50 (m, 2H), 7.40–7.34 (m, 1H), 7-01–6.97 (m, 1H), 4.62 (d, *J*=6.3, 2H), 2.43–2.36 (m, 4H), 1.93 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.6, 148.1, 133.7, 133.9, 131.5, 128.5, 125.0, 82.7, 69.5, 41.1, 35.0, 14.8; IR ν (cm^{-1}) 3296, 1653, 1524; MS [M+1] *m/z*: 233 (100), 225 (16), 186 (30), 153 (26), 136 (43), 135 (12); HRMS calcd for $C_{12}H_{12}N_2O_3{\cdot}H^+$: 233.0926, found: 233.0936.

4.4. Typical procedure for the acylation of amines. Method 2

*4.4.1. Synthesis of N-(3-N′-benzyloxycarbonylamino-2,2-dimethyl-propyl)-4-pentynamide (**7b**).* A solution of 4-pentynoic acid (640 mg, 6.5 mmol) in 5 mL of CH_2Cl_2 was added to a magnetically stirred solution of EDC·HCl (1.9 g, 9.9 mmol) and HOBt (1.35 g,

9.9 mmol) in 20 mL of the same solvent followed by the addition of the monoprotected diamine **6b** (2.35 g, 9.9 mmol) dissolved in 5 mL of CH_2Cl_2. The mixture was cooled to 0 °C and Et_3N (1.4 mL, 9.9 mmol) was added dropwise, and was left to react at room temperature overnight. Then, the reaction was diluted with CH_2Cl_2, water (25 mL) was added, the mixture was decanted, and the organic layer was consecutively washed with 20 mL of HCl (5% aq), 20 mL of a saturated solution of aqueous $NaHCO_3$, and 20 mL of a saturated solution of NaCl. The organic layer was dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The resultant chromatographically pure colorless oil was identified as amide **7b** (87%) and used without any further purification: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.26–7.18 (m, 5H), 6.23 (br s, 1H), 5.02 (s, 2H), 2.94 (d, J=6.6, 2H), 2.87 (d, J=6.6, 2H), 2.46–2.40 (m, 2H), 2.36–2.32 (m, 2H), 1.94 (s, 1H), 0.78 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.0, 157.6, 136.7, 128.4, 128.0, 127.9, 83.0, 69.5, 66.5, 47.5, 45.8, 36.4, 23.5, 15.2; IR ν (cm^{-1}) 3296, 1702, 1649; MS [M+1] m/z: 317 (12), 273 (37), 209 (100), 153 (17), 129 (27), 110 (17); HRMS calcd for $C_{18}H_{24}N_2O_3\cdot H^+$ 317.1865, found: 317.1858.

*4.4.2. N-[(2-N′-Benzyloxycarbonylaminomethyl)phenyl]-4-pentyamide (**13**).* According to the typical procedure amide **13** was prepared from monoprotected amine **12** as a white solid in 80% yield. It was purified by crystallization from Et_2O: mp 121–122 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ (ppm) 9.31 (br s, 1H), 8.06–8.04 (m, 1H), 7.34–7.06 (m, 8H), 5.54 (br s, 1H), 5.12 (s, 2H), 4.30 (d, J=6.7, 2H), 2.66–2.58 (m, 4H), 2.00 (s, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.2, 157.8, 136.4, 136.0, 116.1, 130.4, 129.0, 128.7, 128.6, 128.5, 128.4, 128.1, 124.6, 123.3, 83.1, 69.1, 67.5, 42.0, 35.9, 14.8; IR ν (cm^{-1}) 3295, 3024, 1686, 1653; MS [M+1] m/z: 337 (8), 276 (20), 201 (12), 185 (28), 149 (25), 108 (100), 107 (76); HRMS calcd for $C_{20}H_{20}N_2O_3\cdot H^+$: 337.1552, found: 337.1598.

4.5. Typical procedure for the Sonogashira coupling reaction

*4.5.1. Synthesis of N-(3-N′-benzyloxycarbonylaminopropyl)-5-(4-methoxyphenyl)-4-pentynamide (**8a**).* A solution of *para*-iodoanisole (1.4 g, 6.0 mmol), $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol), and carbamate **7a** (2.35 g, 6.0 mmol) in Et_3N (15 mL) was stirred at 80 °C for 24 h. When cooled, water (3 mL) was added, the mixture was extracted with EtOAc (3×25 mL), and the combined organic extracts were dried over Na_2SO_4 (anhyd). Once the solvent was evaporated under vacuum, the whole crude was purified by column chromatography (hexanes/EtOAc, 1/1) to afford amide **8a** as a white solid that was triturated in hexanes (60%): mp 114–116 °C (hexanes): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.35–7.29 (m, 7H). 6.80 (d, J=8.8. 2H), 6.20 (br s, 1H), 5.25 (br s, 1H), 5.09 (s, 2H), 3.78 (s, 3H), 3.36–3.30 (m, 2H), 3.25–3.20 (m, 2H), 2.72 (t, J=7.2, 2H), 2.46 (t, J=7.2, 2H), 1.65–1.62 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.8, 159.3, 136.0, 115.5, 132.9, 128.5, 128.1, 128.0, 113.9, 86.8, 81.3, 66.7, 55.2, 37.5, 36.6, 35.9, 30.1, 16.1; IR ν (cm^{-1}) 3325, 2950, 1678, 1643; MS [M+1] m/z: 288 (M+1–Cbz), 287 (79), 245 (40), 189 (70), 188 (73), 159 (48), 147 (63), 135 (80), 101 (100); HRMS calcd for [$C_{23}H_{26}N_2O_4\cdot H^+$–Cbz] 288.1474, found: 288.1487.

*4.5.2. N-(3-N′-Benzyloxycarbonylamino-2,2-dimethylpropyl)-5-(4-methoxyphenyl)-4-pentynamide (**8b**).* According to the typical procedure amide **8b** was prepared from carbamate **7b** in 66% yield as a yellowish oil. It was purified by column chromatography (hexanes/EtOAc, 1/1): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.46–7.26 (m, 7H), 6.78 (d, J=8.9, 2H), 6.62–6.60 (m, 1H), 5.64–5.62 (m, 1H), 5.09 (s, 2H), 3.78 (s, 3H), 3.05 (d, J=6.8, 2H), 2.93 (d, J=6.8, 2H), 2.72 (t, J=7.1, 2H), 2.48 (t, J=7.1, 2H), 0.85 (s, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.0, 157.5, 159.2, 132.9, 128.5, 128.1, 128.0, 113.8, 86.8, 66.8, 55.2, 47.5, 45.7, 36.4, 36.1, 23.3, 16.2; IR ν (cm^{-1}) 3323, 2960, 1704, 1657; MS [M+1] m/z: 423 (17), 315 (100), 313 (14), 273 (37), 216 (10); HRMS calcd for $C_{25}H_{30}N_2O_4\cdot H^+$: 423.2284, found: 423.2287.

*4.5.3. N-[(2-N′-Benzyloxycarbonylaminomethyl)phenyl]-5-(4-methoxyphenyl)-4-pentyamide (**14**).* According to the typical procedure amide **14** was prepared from carbamate **13** in 64% yield as a yellowish solid after purification by column chromatography (hexanes/EtOAc, 1/1) followed by trituration of the resultant solid in hexanes: mp 125–126 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ (ppm) 9.32 (s, 1H), 8.08 (d, J=8.1, 1H), 7.33–7.07 (m, 10H), 6.79 (d, J=8.6, 2H), 5.44–5.42 (m, 1H), 5.11 (s, 2H), 4.28 (d, J=6.7, 2H), 3.78 (s, 3H), 2.87–2.80 (m, 2H), 2.73–2.68 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.5, 159.1, 157.7, 136.0, 133.0, 129.0, 128.6, 128.3, 128.1, 124.6, 123.4, 115.9, 113.8, 87.1, 81.1, 67.5, 55.2, 41.9, 36.5, 16.0; IR ν (cm^{-1}) 3295, 3054, 1689; MS [M+1] m/z: 443 (19), 335 (49), 293 (40), 187 (61), 149 (100), 147 (50), 135 (14), 108 (41), 107 (25); HRMS calcd for $C_{27}H_{26}N_2O_4\cdot H^+$: 443.1971, found: 443.1953.

*4.5.4. N-[(2-N-Benzyloxycarbonylamino)benzyl]-5-(4-methoxyphenyl)-4-pentyamide (**19**).* According to the typical procedure amide **19** was prepared from carbamate **18** in 54% yield as a white solid. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration in hexanes: mp 109–110 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ (ppm) 9.03 (s, 1H), 7.88 (d, J=8.0, 1H), 7.43–7.21 (m, 11H), 6.75 (d, J=8.6, 1H), 6.64 (br s, 1H), 5.22 (s, 2H), 4.34 (d, J=6.4, 2H), 3.78 (s, 3H), 2.66 (t, J=7.1, 2H), 2.40 (t, J=7.1, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.4, 154.6, 136.8, 136.7, 132.9, 128.5, 127.6, 123.8, 123.7, 122.3, 115.3, 86.4, 81.6, 72.9, 66.6, 55.3, 40.5, 35.5, 15.9; IR ν (cm^{-1}) 3300, 3073, 1727, 1646; MS [M+1] m/z: 336 (23, M+1–Cbz), 335 (100), 293 (98), 199 (14), 188 (52), 160 (26), 147 (35); HRMS calcd for [$C_{27}H_{26}N_2O_4\cdot H^+$–Cbz] 336.1474, found: 336.1440.

*4.5.5. 5-(4-Methoxyphenyl)-N-(2-nitrobenzyl)-4-pentynamide (**24a**).* According to the typical procedure amide **24a** was prepared from amide **23** in 62% yield as a white solid. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration in hexanes: mp 98–99 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.92 (d, J=8.1, 1H), 7.61 (d, J=7.6, 1H), 7.39–7.17 (m, 4H), 6.91–6.89 (m, 1H), 6.73 (d, J=8.7, 2H), 4.65 (d, J=6.3, 2H), 3.74 (s, 3H), 2.70–2.65 (m, 2H), 2.49–2.44 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.7, 159.2, 148.1, 133.8, 115.4, 134.0, 132.9, 131.5, 128.4, 124.9, 113.8, 86.6, 81.4, 55.2, 41.1, 35.6, 15.9; IR ν (cm^{-1}) 3290, 1653, 1509; MS [M+1] m/z: 339 (100), 297 (28), 291 (10), 203 (53), 158 (10), 136 (27); HRMS calcd for $C_{19}H_{18}N_2O_4\cdot H^+$: 339.1345, found: 339.1346.

*4.5.6. N-(2-Nitrobenzyl)-5-phenyl-4-pentynamide (**24b**).* According to the typical procedure amide **24b** was prepared from amide **23b** in 52% yield as a yellowish solid. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration in hexanes: mp 82–83 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.97 (d, J=8.0, 1H), 7.68 (d, J=7.6, 1H), 7.50 (t, J=7.5, 1H), 7.39 (t, J=7.7, 1H), 7.31–7.23 (m, 5H), 6.58–6.56 (m, 1H), 4.71 (d, J=6.4, 2H), 2.74 (t, J=7.1, 2H), 2.50 (t, J=7.2, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.3, 148.3, 134.1, 133.6, 132.4, 131.5, 128.6, 128.2, 127.8, 125.0, 123.3, 88.0, 81.7, 41.2, 35.7, 15.9; IR ν (cm^{-1}) 3294, 1653, 1523; MS [M+1] m/z: 309 (100), 291 (10), 172 (8), 136 (17), 115 (12); HRMS calcd for $C_{18}H_{16}N_2O_3\cdot H^+$: 309.1239, found: 309.1231.

*4.5.7. 5-(4-Chlorophenyl)-N-(2-nitrobenzyl)-4-pentynamide (**24c**).* According to the typical procedure amide **24c** was prepared from amide **23c** in 80% yield as a white solid. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by trituration in hexanes: mp 101–102 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.99 (d, J=8.1, 1H), 7.68 (d, J=6.5, 1H), 7.54 (t, J=7.5, 1H), 7.41 (t, J=7.7, 1H),

7.25–7.18 (m, 4H), 6.54–6.52 (m, 1H), 4.70 (d, J=6.4, 2H), 2.73 (t, J=7.1, 2H), 2.49 (t, J=7.0, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.1, 148.3, 134.1, 133.5, 132.8, 132.6, 128.7, 128.5, 125.0, 89.1, 80.6, 41.3, 35.5, 15.8; IR ν (cm^{-1}) 3290, 1648, 1523; MS [M+1] m/z: 345 (34), 343 (100), 325 (11), 301 (11), 295 (22); HRMS calcd for $C_{18}H_{15}{}^{35}ClN_2O_3\cdot H^+$: 343.0849, found: 343.0851.

4.6. Typical procedure for the PIFA-mediated heterocyclization

*4.6.1. N-(3-N′-Benzyloxycarbonylaminopropyl)-5-(4′-methoxybenzoyl)-2-pyrrolidinone (**9a**).* A solution of alkynylamide **8a** (315 mg, 0.8 mmol) in CF_3CH_2OH (12 mL) was stirred at 0 °C and a solution of PIFA (526.8 mg, 1.2 mmol) in 6 mL of the same solvent was added dropwise. The reaction mixture was stirred at that temperature for 2 h. For the work up, aqueous Na_2CO_3 (10%) was added and the mixture extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave the desired product **9a** as a chromatographically pure yellowish oil (70%): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.93 (d, J=8.8, 2H), 7.33–7.26 (m, 5H), 6.97 (d, J=8.8, 2H), 5.61 (m, 1H), 5.15–5.02 (m, 3H), 3.89 (s, 3H), 3.71–3.56 (m, 1H), 3.41–3.27 (m, 1H), 3.16–3.02 (m, 2H), 2.52–2.34 (m, 3H), 2.02–1.98 (m, 1H), 1.70–1.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 195.4, 176.4, 164.3, 136.7, 130.7, 128.4, 128.0, 127.81, 114.3, 66.4, 61.8, 55.6, 39.3, 37.9, 29.5, 27.4, 23.8; IR ν (cm^{-1}) 3332, 2938, 1685, 1599, 1512; MS [M+1] m/z: 304 (12, M+1−Cbz), 303 (79), 260 (28), 167 (100), 135 (17); HRMS calcd for [$C_{23}H_{26}N_2O_5\cdot H^+$−Cbz] 304.1423, found: 304.1390.

*4.6.2. N-(3-N′-Benzyloxycarbonylamino-2,2-dimethylpropyl)-5-(4′-methoxybenzoyl)-2-pyrrolidi-none (**9b**).* According to the typical procedure pyrrolidinone **9b** was obtained from **8b** in 89% yield. It was purified by column chromatography (EtOAc) as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.93 (d, J=8.8, 2H), 7.35–7.28 (m, 5H), 6.99 (d, J=8.8, 2H), 6.49–6.47 (m, 1H), 5.27 (d, J=9.1, 1H), 5.11 (d, J=12.3, 1H), 5.04 (d, J=12.3, 1H), 3.89 (s, 3H), 3.76 (d, J=14.8, 1H), 3.26–3.24 (m, 1H), 2.74–2.70 (m, 1H), 2.49–2.36 (m, 3H), 2.26 (d, J=14.8, 1H), 2.06–1.99 (m, 1H), 0.92 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm) 195.1, 177.7, 164.3, 157.2, 137.0, 130.7, 128.4, 127.9, 127.8, 127.0, 114.3, 66.3, 64.3, 55.6, 50.3, 47.7, 37.2, 28.9, 24.7, 23.6; IR ν (cm^{-1}) 3338, 2962, 1682, 1600; MS [M+1] m/z: 439 (1), 359 (10), 331 (100), 303 (11), 195 (47); HRMS calcd for $C_{25}H_{30}N_2O_5\cdot H^+$: 439.2233, found: 439.2249.

*4.6.3. N-[(2-N′-Benzyloxycarbonylaminomethyl)phenyl]-5-(4′-methoxybenzoyl)-2-pyrrolidinone (**15**).* According to the typical procedure pyrrolidinone **15** was obtained from **14** in 39% yield. It was purified by column chromatography (hexanes/EtOAc, 1/1) as a pale brown oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.87 (d, J=8.6, 2H), 7.49 (br s, 1H), 7.37–7.22 (m, 8H), 6.91 (d, J=8.8, 2H), 5.69–5.65 (m, 1H), 5.13 (s, 2H), 4.56–4.54 (m, 2H), 3.84 (s, 3H), 2.52–2.23 (m, 3H), 2.15–2.07 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 195.1, 164.3, 156.8, 136.8, 136.1, 127.0, 130.8, 128.5, 128.3, 128.1, 128.0, 114.2, 66.6, 64.9, 55.6, 41.4, 30.1, 24.5; IR ν (cm^{-1}) 3354, 1693, 1599; MS [M+1] m/z: 459 (6), 351 (17), 323 (20), 308 (100), 215 (63), 135 (11); HRMS calcd for $C_{27}H_{26}N_2O_5\cdot H^+$: 459.1920, found: 459.1900.

*4.6.4. N-[(2-N′-Benzyloxycarbonylamino)benzyl]-5-(4′-methoxybenzoyl)-2-pyrrolidinone (**20**).* According to the typical procedure pyrrolidinone **20** was obtained from **19** in 65% yield. It was purified by column chromatography (hexanes/EtOAc, 1/1) as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 8.90 (s, 1H), 8.02 (d, J=8.1, 1H), 7.86 (d, J=8.7, 2H), 7.46–7.26 (m, 6H), 6.97–6.89 (m, 4H), 5.22 (s, 2H), 5.03–4.98 (m, 3H), 3.87 (s, 3H), 2.52–2.28 (m, 3H), 2.02–1.88 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 194.8, 176.4, 164.4, 154.3, 137.4, 136.8, 124.9, 130.7, 129.3, 128.5, 128.0, 127.9, 123.1, 121.7, 114.3, 66.5, 60.6, 55.6, 42.8, 29.2, 23.5; IR ν (cm^{-1}) 3251, 1732, 1679, 1597; MS [M+1] m/z: 352 (22, M+1−Cbz), 351 (100), 215 (84), 132 (33); HRMS calcd for [$C_{27}H_{26}N_2O_5\cdot H^+$−Cbz] 352.1323, found: 352.1387.

*4.6.5. 5-(4-Methoxybenzoyl)-N-(2-nitrobenzyl)-2-pyrrolidinone (**25a**).* According to the typical procedure pyrrolidinone **25a** was obtained from **24a** in 69% yield. It was purified by column chromatography (hexanes/EtOAc, 1/1) as a yellowish solid that was triturated in hexanes: mp 55–58 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.88–7.82 (m, 3H), 7.59–7.57 (m, 2H), 7.48–7.38 (m, 1H), 6.92 (d, J=8.8, 2H), 5.19–5.10 (m, 2H), 4.30 (d, J=16.0, 1H), 3.84 (s, 3H), 2.52–2.33 (m, 3H), 2.09–1.97 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 195.0, 176.2, 164.2, 148.7, 133.5, 132.0, 131.3, 130.7, 128.6, 126.9, 124.6, 114.2, 61.7, 55.6, 42.8, 29.0, 23.6; IR ν (cm^{-1}) 1690, 1600, 1524; MS [M+1] m/z: 355 (100), 219 (62), 135 (13); HRMS calcd for $C_{19}H_{18}N_2O_5\cdot H^+$: 355.1294, found: 355.1302.

*4.6.6. 5-Benzoyl-N-(2-nitrobenzyl)-2-pyrrolidinone (**25b**).* According to the typical procedure pyrrolidinone **25b** was obtained from **24b** in 81% yield. It was purified as a yellowish oil by column chromatography (EtOAc): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.91–7.88 (m, 3H), 7.66–7.56 (m, 3H), 7.49–7.40 (m, 3H), 5.22–5.15 (m, 2H), 4.41 (d, J=15.8, 1H), 2.50–2.43 (m, 3H), 2.05–2.02 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 196.5, 176.2, 148.7, 133.9, 131.8, 134.0, 133.6, 131.3, 129.0, 128.6, 128.3, 124.7, 62.0, 42.7, 28.9, 23.4; IR ν (cm^{-1}) 1696, 1525; MS [M+1] m/z: 326 (20), 325 (100), 219 (86), 136 (18); HRMS calcd for $C_{18}H_{16}N_2O_4\cdot H^+$: 325.1188, found: 325.1185.

*4.6.7. 5-(4-Chlorobenzoyl)-N-(2-nitrobenzyl)-2-pyrrolidinone (**25c**).* According to the typical procedure pyrrolidinone **25a** was obtained from **24a** in 57% yield. It was purified as a colorless oil by column chromatography (EtOAc): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.88–7.80 (m, 3H), 7.66–7.56 (m, 2H), 7.43 (d, J=8.6, 3H), 5.16–5.11 (m, 2H), 4.37 (d, J=15.6, 1H), 2.45–2.41 (m, 3H), 2.00–1.98 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 195.4, 175.9, 171.1, 148.8, 132.3, 131.8, 133.6, 131.9, 129.7, 129.3, 128.7, 124.6, 61.9, 42.5, 28.9, 23.3; IR ν (cm^{-1}) 1697, 1524; MS [M+1] m/z: 361 (23), 360 (14), 359 (70), 219 (100), 136 (22); HRMS calcd for $C_{18}H_{15}{}^{35}ClN_2O_4\cdot H^+$: 359.0799, found: 359.0798.

4.7. Typical procedure for the reductive amination (method 1)

*4.7.1. Synthesis of 1-(4-methoxyphenyl)-octahydro-pyrrolo[1,2-a][1,4]diazepin-7-one (**10a**).* A solution of pyrrolidinone **9a** (246 mg, 0.6 mmol) in 6 mL of MeOH and 0.5 mL of HCl (1 M) was hydrogenated (70 psi) in the presence of Pd/C overnight. The catalyst was filtered through Celite and the solution treated with 15 mL of an aqueous solution of Na_2CO_3 (20%). The mixture was extracted with CH_2Cl_2 (3×15 mL), the combined organic extracts were dried with Na_2SO_4, and the solvent evaporated under vacuum. The resulting oil was purified by column chromatography (MeOH) to afford diazepinone **10a** as a colorless oil (48%) as an inseparable mixture of both diastereoisomers. Reported data is given for the both of them: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.27 (d, J=8.8, 2H), 7.21 (d, J=8.5, 2H), 6.88–6.82 (m, 4H), 5.08 (br s, 1H), 4.60 (d, J=6.7, 1H), 3.84–3.79 (m, 1H), 3.82–3.79 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.73–3.69 (m, 1H), 3.63–3,56 (m, 1H), 3.48–3.35 (m, 2H), 2.93–2.87 (m, 1H), 2.84–2.79 (m, 1H), 2.77–2.70 (m, 2H), 2.39–2.32 (m, 2H), 2.18–2.10 (m, 2H), 2.10–2.00 (m, 1H), 1.99–1.85 (m, 3H), 1.82–1.73 (m, 1H), 1.71–1.64 (m, 1H), 1.63–1.55 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.6, 176.1, 158.8, 158.5, 133.1, 133.8, 127.7, 127.0, 114.0, 113.7, 75.6, 71.2, 65.7, 63.6, 55.2, 40.6, 39.9, 39.2, 38.3, 30.5, 30.1, 29.5, 21.0, 17.7;

IR ν (cm^{-1}) 3349, 1663; HRMS calcd for $C_{15}H_{20}N_2O_2 \cdot H^+$: 261.1603, found: 261.1615.

*4.7.2. 4,4-Dimethyl-1-(4-methoxyphenyl)-octahydro-pyrrolo[1,2-a][1,4]diazepin-7-one (**10b**).* According to the typical procedure diazepinone **10b** was obtained from pyrrolidinone **9b** in 43% yield. It was purified by column chromatography (MeOH) as a pale brown oil as an inseparable mixture of both isomers. Reported data is given for the both of them: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.29 (d, J=8.4, 2H), 7.25 (d, J=8.0, 2H), 6.86–6.80 (m, 4H), 5.12 (br s, 1H), 4.80 (d, J=5.7, 1H), 4.03–4.00 (m, 1H), 3.96–3.91 (m, 1H), 3.89–3.85 (m, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.65–3.62 (m, 1H), 3.44–3.42 (m, 1H), 3.25–3.20 (m, 1H), 3.08–2.79 (m, 4H), 2.56–2.54 (m, 1H), 2.15–2.10 (m, 1H), 2.05–1.99 (m, 3H), 1.82–1.72 (m, 3H), 1.13 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm) 177.4, 176.8, 127.6, 159.2, 158.8, 127.1, 113.9, 113.5, 74.7, 72.9, 71.5, 69.0, 55.4, 55.3, 52.7, 49.5, 49.3, 47.9, 29.6, 24.8, 24.7, 24.3, 24.0, 23.9, 20.9, 19.1; IR ν (cm^{-1}) 3285, 2955, 1673; HRMS calcd for $C_{17}H_{24}N_2O_2 \cdot H^+$: 289.1916, found: 289.1925.

*4.7.3. 4-(4-Methoxyphenyl)-2,3,3a,4,5,6-hexahydro-benzo[f]pyrrolo[1,2-a][1.4]diazepin-1-one (**16**).* According to the typical procedure diazepinone **16** was obtained from pyrrolidinone **15** in 51% yield. It was purified by column chromatography (MeOH) as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.23–6.76 (m, 8H), 5.00–4.98 (m, 1H), 4.67 (d, J=17.0, 1H), 4.55 (d, J=17.0, 1H), 4.47–4.45 (m, 1H), 3.79 (s, 3H), 2.42–2.33 (m, 1H), 2.09–1.95 (m, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm) 160.6, 159.3, 137.5, 132.3, 119.3, 127.7, 127.4, 126.1, 123.2, 113.6, 111.3, 72.3, 62.7, 55.2, 48.7, 29.1, 21.1; IR ν (cm^{-1}) 3310, 1670; MS [M+1] m/z: 309 (30), 291 (13), 172 (28), 171 (100); HRMS calcd for $C_{19}H_{20}N_2O_2 \cdot H^+$: 309.1603, found: 309.1615.

*4.7.4. 11-(4-Methoxyphenyl)-1,2,5,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-3-one (**21a**).* According to the typical procedure diazepinone **21a** was obtained from pyrrolidinone **20** in 15% yield. It was purified as a yellowish oil by column chromatography (MeOH) as an inseparable mixture of both isomers.

4.8. Typical procedure for the reductive amination (method 2)

*4.8.1. Synthesis of 11-(4-methoxyphenyl)-1,2,5,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-3-one (**21a**).* A solution of pyrrolidinone **25a** (500 mg, 1.4 mmol) in 10 mL of MeOH was hydrogenated (70 psi) in the presence of PtO_2 (50 mg) overnight. The catalyst was filtered through Celite and the solution was evaporated under vacuum. The resulting chromatographically pure white solid was identified as a diastereoisomeric mixture of diazepinone **21a** in a combined 92% yield. Both diastereoisomers could be partially purified by column chromatography (Et_2O) followed by triturating in the same solvent. Reported data is given for the isolated major (*syn*) stereoisomer: mp (Et_2O) 68–70 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 7.22–7.08 (m, 4H), 6.88–6.83 (m, 2H), 6.67–6.62 (m, 2H), 4.92 (d, J=6.0, 1H), 4.79 (d, J=14.6, 1H), 4.38–4.27 (m, 2H), 3.79–3.75 (m, 4H), 2.06–2.00 (m, 1H), 1.90–1.83 (m, 1H), 1.76–1.69 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.5, 159.5, 145.9, 132.7, 120.1, 131.8, 129.2, 127.6, 117.4, 115.6, 113.9, 75.0, 61.7, 55.3, 43.0, 29.7, 21.0; IR ν (cm^{-1}) 3358, 2931, 1655; MS [M+1] m/z: 309 (24), 204 (11), 190 (64), 189 (27), 106 (100); HRMS calcd for $C_{19}H_{20}N_2O_2 \cdot H^+$: 309.1603, found: 309.1609.

*4.8.2. 11-Phenyl-1,2,5,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-3-one (**21b**).* According to the typical procedure diazepinone **21b** was obtained from pyrrolidinone **25b** in combined 95% yield as a mixture of diastereoisomers that could be partially purified by column chromatography (Et_2O). Reported data is given for the isolated major (*syn*) stereoisomer: mp (Et_2O) 131–132 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 7.37–7.28 (m, 5H), 7.12–7.05 (m, 2H), 6.68–6.63 (m, 2H), 4.93 (d, J=14.6, 1H), 4.86 (d, J=5.7, 1H), 4.25 (d, J=14.6, 1H), 3.82–3.80 (m, 1H), 2.08–2.02 (m, 1H), 1.99–1.75 (m, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.5, 145.8, 140.7, 120.0, 131.8, 129.2, 128.6, 128.3, 126.4, 117.4, 115.6, 75.6, 61.7, 43.1, 29.7, 21.2; IR ν (cm^{-1}) 3357, 1651; MS [M+1] m/z: 279 (9), 204 (13), 190 (11), 189 (53), 106 (100); HRMS calcd for $C_{18}H_{18}N_2O \cdot H^+$: 279.1497, found: 279.1511.

*4.8.3. 11-(4-Chlorophenyl)-1,2,5,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-3-one (**21c**).* According to the typical procedure diazepinone **21c** was obtained from pyrrolidinone **25c** in 49% yield as a 71/29 mixture of *syn*/*anti* diastereoisomers that could be partially purified by column chromatography (Et_2O). Reported data is given for the major (*syn*) stereoisomer: mp (Et_2O) 239–240 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 7.29–7.26 (m, 2H), 7.22–7.19 (m, 3H), 7.11–7.06 (m, 1H), 6.79–6.76 (m, 1H), 6.55–6.53 (m, 1H), 4.99 (m, 1H), 4.67 (d, J=17.0, 1H), 4.55 (d, J=17.0, 1H), 4.47–4.45 (m, 1H), 3.79 (br s, 1H), 2.42–2.33 (m, 1H), 2.09–1.95 (m, 3H); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.5, 146.2, 136.4, 134.1, 124.6, 129.9, 129.0, 128.7, 128.2, 121.1, 119.4, 63.5, 62.1, 44.8, 30.2, 20.2; IR ν (cm^{-1}) 3327, 1678; MS [M+1] m/z: 315 (33), 313 (100), 279 (7), 229 (45), 227 (54); HRMS calcd for $C_{18}H_{17}{}^{35}ClN_2O \cdot H^+$: 313.1108, found: 313.1111.

*4.8.4. Synthesis of N-(2′-aminobenzyl)-5-(4-methoxybenzoyl)-2-pyrrolidinone (**26a**).* A solution of pyrrolidinone **25a** (500 mg, 1.4 mmol) in 10 mL of MeOH was hydrogenated (70 psi) in the presence of PtO_2 (25 mg) overnight. The catalyst was filtered through Celite and the solution was evaporated under vacuum. The resulting chromatographically pure white solid (98% yield) was triturated in MeOH and identified as pyrrolidinone **26a**: mp 136–137 °C (MeOH); ^{1}H NMR (CD_3COCD_3) δ (ppm) 7.96 (d, J=8.9, 2H), 7.04 (d, J=8.9, 2H), 6.96 (t, J=7.6, 1H), 6.75 (d, J=7.0, 1H), 6.67 (d, J=8.0, 1H), 6.40 (d, J=7.3, 1H), 5.06–5.03 (m, 1H), 4.92 (d, J=14.7, 1H), 4.85–4.83 (m, 2H), 3.80 (s, 3H), 3.76 (d, J=14.7, 1H), 2.52–2.30 (m, 3H), 1.93–1.84 (m, 1H); ^{13}C NMR (CD_3COCD_3) δ (ppm) 195.5, 175.9, 164.2, 145.9, 131.3, 130.7, 129.4, 127.2, 118.8, 117.3, 115.5, 114.2, 60.0, 55.6, 42.7, 29.6, 23.3; IR ν (cm^{-1}) 3359, 2931, 1679, 1599; MS [M+1] m/z: 325 (16), 324 (30), 307 (70), 306 (100), 223 (19), 189 (40), 106 (90); HRMS calcd for $C_{19}H_{20}N_2O_3 \cdot H^+$: 324.1474, found: 324.1481.

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Supplementary data

Supplementary data for this article can be found in the online version, at doi:10.1016/j.tet.2010.05.080. These data include MOL files and InChIKeys of the most important compounds described in this article.

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16. An excess of starting material was employed to avoid an undesired *N,N′*-diprotection process.

Development of a New Non-sugar Based Strategy for the Synthesis of the Hydroxylated Indolizidinone Skeleton.

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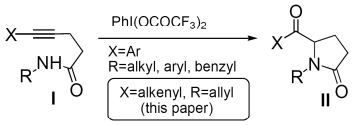
A few years ago, our group discovered that properly substituted alkynylamides of type **I** could be easily transformed into 5-aroylpyrrolidinones **II** by the aid of the hypervalent iodine reagent PIFA [phenyliodine(III)-*bis*-trifluoroacetate]. We suggested that the I(III) reagent can either activate the triple bond by transferring its electrophilicity to it, which in the presence of an internal nucleophile (i. e. the amide functional group) gives rise to a new C–N connection, or, alternatively, it can oxidize the amide group to generate an N-acylnitrenium intermediate that can capture the alkyne functionality with the same synthetic destiny.[1] As opposed to the related PIFA-mediated olefin amidohydroxylation reaction,[2] which demands more strict structural requirements, such transformation can be achieved on a variable branch of substrates including N-alkyl, N-aryl, and N-benzyl substituted amides as shown in Scheme 1.

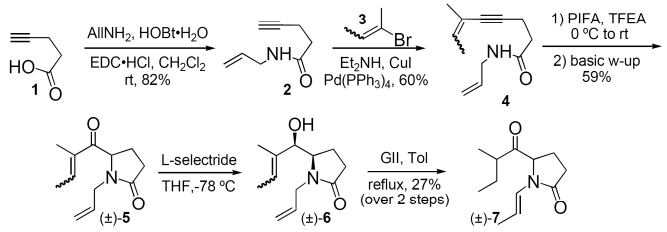


Scheme 1 PIFA-mediated construction of the pyrrolidinone nucleus.

As highly functionalized materials, derivatives of type **II** can be also considered as starting points for new transformations and, in fact, we have recently demonstrated the value of this approach in the preparation of pyrrolodiazepinone and pyrrolobenzodiazepinone derivatives from N-(3-aminopropyl), N-(2-aminomethylphenyl), and N-(2-nitrobenzyl) substituted pyrrolidinones,[3] and also in the synthesis of pyrrolopyrazinones from N-aminoethylpyrrolidinones[4] by the inclusion, in both cases, of an additional reductive amination step. Having established the potential of the present strategy as a general route to the synthesis of pyrrolidine-containing heterocycles, we recently focused on its application to the synthesis of polyhydroxylated indolizidinones, a more challenging objective.

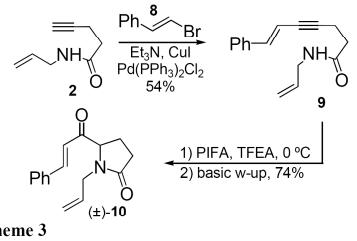
Castanospermine and swainsonine are probably the most well known examples of the polyhydroxyindolizidine alkaloids family. Apart from their strong glycosidase inhibitory activity,[5] some other potential uses as chemotherapeutic agents against diabetes,[6] cancer,[7] and HIV[8] have been reported for them or their analogues.[9] As a result, the design of efficient syntheses of these heterocycles has been a long-lasting issue for the organic chemists. Because of the benefits of using privileged structures with well-defined stereochemistry from the chiral pool, the carbohydrate-based synthetic strategies for the preparation of polyhydroxylated indolizidines has a widespread presence in the specialized literature, mainly for those strategies that start from D-mannitol, D-ribose, D-glucose or L-sorbose, among others.[10] But these approaches are occasionally limited by their lack of stereochemical flexibility and, in some cases, are usually longer than desired mainly because of the introduction of unavoidable protection and deprotection steps. On the other hand, different studies have suggested that subtle structural and stereochemical modifications of the target molecules may cause considerable changes in their biological activity.[11] Consequently, any effort to develop flexible non-sugar based strategies for the construction of the skeleton of polyhydroxylated indolizidines would be of great significance.[12] In summary, here we will show a new, short and diastereoselective preparation of racemic 6,7,8-trihydroxyindolizindin-3-one and some ancillary studies related to it.

Thus, according to our previously reported experiences, the synthetic design (Scheme 2) dictated the judicious construction of an alkynylamide of type **4** as the key synthetic intermediate. In addition, and as a deliberated requisite, the synthesis was initially designed according to the commercial availability of all the components of our target skeleton. Consequently, N-allylamide **2**, easily prepared from pentynoic acid (**1**), was connected to (E/Z)-2-bromobutene (**3**)[13] by a Sonogashira coupling reaction[14] resulting in the formation of **4**, which was treated with a slight excess (1.5 equivalents) of the hypervalent iodine reagent in trifluoroethanol (TFEA) as solvent, followed by a basic aqueous work up. This protocol rendered the 5-alkenoyl-2-pyrrolidinone (±)-**5** in a good overall yield. Then, application of L-selectride reduction conditions, which had been claimed to afford high levels of diastereocontrol in the reduction of structurally similar systems, resulted in the chemoselective transformation of the keto carbonyl group to afford pyrrolidinone (±)-**6** as a single syn stereoisomer.[15] Regrettably, all attempts to perform the projected Ru-mediated cyclization step on it ended up in the isomerization of both olefinic fragments to afford a diastereoisomeric mixture (syn/anti) of (±)-**7**. Those attempts included the use of Grubbs I and Grubbs II catalysts, and the use of different solvents (CH_2Cl_2 and toluene) and temperatures (rt and solvent reflux).[16]



Scheme 2

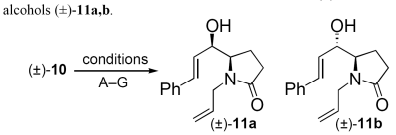
To the view of these results, we envisaged that such olefin isomerization could be prevented if a conjugated system, structurally related to (±)-**6**, were constructed at the terminal position of the double bond. For that purpose, a phenyl group was selected and, therefore, we embarked on the preparation of alkynylamide **9** following the same strategy as before (see Scheme 3). Consequently, amide **2** was coupled with β-bromostyrene (**8**), a reactant that was prepared as a single E-isomer from cinnamic acid by a modified catalytic Hunsdiecker reaction.[17] When all parts of substrate **9** were assembled, it was submitted to the above mentioned cyclization conditions employing the hypervalent iodine reagent PIFA. This protocol rendered the desired 5-alkenoyl-2-pyrrolidinone (±)-**10** in 33% overall yield (three steps from **1**).



Scheme 3

In the process to transform the keto group into the hydroxy functionality, we considered of interest to have both diastereoisomers (syn-**11a** and anti-**11b**) at our disposal and, towards this end, the application of a number of reductive protocols on (±)-**10** in the absence and in the presence of chelating agents was evaluated. This survey is summarized in Table 1, which results from the combination of three reductive agents ($NaBH_4$, L-selectride and DIBAL-H), a number of metal sources ($ZnCl_2$, $CeCl_3$, $NiBr_2$, and $TiCl_4$), and different solvents (MeOH, toluene and THF). For the sake of simplicity, $NaBH_4$ was employed in the first place leading to alcohol syn-**11a** with a modest diastereoselctivity. Fortunately, when the use of a more sterically demanding reducing agent such as L-selectride was tested, we were rewarded with a completely diastereoselective transformation (conditions B) leading to syn-**11a**, a result that can be explained by considering a Felkin-Ahn model for the nucleophilic addition to the carbonyl group. In contrast, we met only limited success in the preparation of anti-**11b** when the reaction was attempted in the presence of a number of coordinating agents with different Lewis acidity. In fact, under the best circumstances (conditions C), the use of $NaBH_4$ in combination with $ZnCl_2$ produced a chromatographically separable mixture (dr 63/37) of both diastereoisomers. Apparently, the adoption of a chelated arrangement in (±)-**10** in the presence of a coordinating metal seems to be poorly favored probably due to the low basic nature of the amidic nitrogen. Finally, it was observed that substrate (±)-**10** resulted to be completely inert in the presence of DIBAL-H and in the presence of $TiCl_4$.

Table 1 Selected conditions for the reduction of (±)-**10** to afford alcohols (±)-**11a,b**.

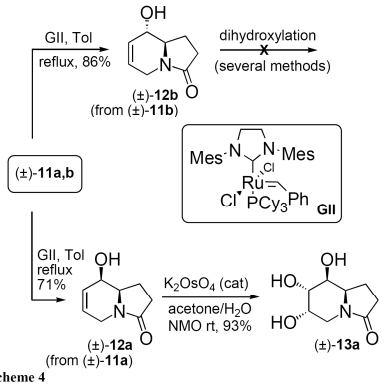


Conditions	dr **11a/11b** [a]
(A) $NaBH_4$, MeOH, 0 ºC	70/30 [b]
(B) L-selectride, THF, -78 ºC	100/0
(C) $NaBH_4$, $ZnCl_2$, MeOH, -78 ºC	63/37 [c]
(D) $NaBH_4$, $CeCl_3$, MeOH, 0 ºC	75/25
(E) $NaBH_4$, $TiCl_4$, MeOH, -78 ºC	--- [d]
(F) $NaBH_4$, $NiBr_2$, MeOH, -78 ºC	68/32
(G) DIBAL-H, Tol, -78 ºC	--- [d]

[a] Determined by ^{1}HNMR from the crude reaction. [b] In 70% combined yield. [c] In 46% combined yield. [d] Substrate (±)-**10** was recovered completely unchanged.

Considering that substrate (±)-**6** behaved more reactive in the presence of Grubbs II catalyst in refluxing toluene, over other tested alternatives, we applied those conditions to the 1,5-diallyl-pyrrolidinones (±)-**11a,b** (see Scheme 4). Satisfactorily, both stereoisomers rendered the corresponding indolizidinones (±)-**12a,b** in good yields (71 and 86%, respectively) with no need of previous OH protection.[18] To complete the synthesis, 8-hydroxy-indolizidinone (±)-**12a** was submitted to the action of an array of standard dihydroxylation agents ($KMnO_4$, OsO_4 and K_2OsO_4)[19] resulting in an almost quantitative formation of the 6,7,8-trihydroxyindolizidinone (±)-**13a** when, in particular, Upjohn reaction conditions were applied. In depth

[1]HNMR studies carried out on (±)-**13a**, the only diastereoisomer which was formed, revealed the relative configuration of all its stereocenters (rac-6S,7S,8S,9R).[20] Consequently, the configuration at the new C-6,7 stereogenic centers in the indolizidine system may be rationalized on the basis of a stereoelectronic control that the existing C(8)–OH group exerts leading to a preferential anti attack of the oxidative reagent. Interestingly, and with no apparent explanation, when submitted to a number of dihydroxylation conditions, indolizidinone (±)-**12b** resulted to be inert under all circumstances.



Scheme 4

In conclusion, the design of a new, short, and efficient strategy for the preparation of a trihydroxyindolizidinone skeleton has been achieved in racemic fashion from highly and properly functionalized linear alkynylamides.[21] The introduction of two key cyclization steps (PIFA mediated alkyne amidation and a RCM step) established the construction of the required unsaturated bicyclic skeleton on which the final dihydroxylation process is performed. It must be highlighted that all four continuous sterogenic centers are produced in a complete diastereoselective fashion and with no need of undesirable protection steps in any of the stages of the synthesis.

Acknowledgements

Financial support from the University of the Basque Country and Basque Government (GIU 06/87) and the Spanish Ministry of Education and Science (CTQ2007-64501/BQU and CTQ2010-20703) is gratefully acknowledged. L. M. P. thanks the University of the Basque Country for a predoctoral scholarship.

Supporting Information for this article is avalilable online at http:// www.thieme-connect.com/ejournals/toc/synlett.

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(21) *Representative procedure for the PIFA-mediated heterocyclization. Synthesis of (rac)-N-allyl-5-(3-phenylacryloyl)-pyrrolidin-2-one (±)-**10.*** A solution of alkynylamide **9** (885 mg, 3.7 mmol) in CF_3CH_2OH (30 mL) was stirred at 0 ºC and a solution of PIFA (2.3 g, 5.5 mmol) in 25 mL of the same solvent was added dropwise. The reaction mixture was stirred at that temperature for 2 hours. For the work up, aqueous Na_2CO_3 (20%, 30 mL) was added and the mixture extracted with CH_2Cl_2 (2x40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave pyrrolidinone as a chromatographically pure yellowish oil (74%). Following the representative procedure, pyrrolidinone (±)-**10** was obtained from **9** (74%) and purified by flash chromatography (EtOAc) as a yellowish oil. ^{1}H NMR ($CDCl_3$) δ (ppm) 7.70 (d, *J*=15.8, 1H), 7.54-7.39 (m, 5H), 6.76 (d, *J*=15.8, 1H), 5.75-5.62 (m, 1H), 5.15-5.08 (m, 2H), 4.53-4.41 (m, 2H), 3.46-3.38 (m, 1H), 2.48-2.33 (m, 3H), 2.00-1.93 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 197.2, 175.2, 145.2, 133.9, 132.1, 131.2, 129.1, 128.6, 121.4, 118.8, 63.7, 44.5, 29.6, 21.4; IR υ (cm^{-1}) 1692, 1609 (CO); HRMS calculated for $C_{16}H_{17}NO_2{\cdot}H^+$: 256.1338, found: 256.1335.

*Representative procedure for the L-selectride reductive step. Synthesis of rac-(5R,1'R)-N-allyl-5-(1-hydroxy-3-phenylallyl)-pyrrolidin-2-one (±)-**11a**.* A solution of L-Selectride® (1.8 mL, 1.0 M in THF) was added dropwise to a cold (-78 ºC) solution of pyrrolidinone (±)-**10** (230 mg, 0.9 mmol) in 4.5 mL of the same solvent. After 30 min, temperature was raised to room temperature and 2 mL of an aqueous solution of NaOH (10%) was added. The whole mixture was extracted with CH_2Cl_2 (3x10 mL), the combined organic layers were dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave pyrrolidinone (±)-**11a** as a chromatographically pure yellowish oil (70%). ^{1}H NMR ($CDCl_3$) δ (ppm) 7.30-7.17 (m, 5H), 6.59 (d, *J*=15.9, 1H), 6.10 (dd, *J*= 15.9, 6.00, 1H), 5.72-5.65 (m, 1H), 5.14 (d, *J*=4.5, 1H), 5.10 (s, 1H), 4.39-4.25 (m, 2H), 3.76-3.64 (m, 2H), 2.88 (brs, 1H), 2.36-1.98 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 175.9, 136.2, 132.8, 132.3, 128.7, 128.0, 127.5, 126.5, 117.8, 73.4, 61.6, 44.7, 30.2, 20.5; IR υ (cm^{-1}) 3374, 1670; HRMS calculated for $C_{16}H_{19}NO_2{\cdot}H^+$: 258.1494, found: 258.1507.

*Representative procedure for the dihydroxylation step: Synthesis of rac-(6S,7S,8S,9R)-6,7,8-trihydroxy-hexahydroindolizidin-3-one (±)-**13a**.* $K_2OsO_4{\cdot}2H_2O$ (7 mg, 0.015 mmol) and N-methylmorpholine-N-oxide (70 mg, 0.6 mmol) were sequentially added to 2 mL of an acetone/water (1/1) solution of indolizidinone (±)-**12a** (50 mg, 0.3 mmol). The mixture was stirred at room temperature for 18 hours, and then filtered through celite. The volatiles were eliminated and the residue was column chromatographed (EtOAc) to render trihydroxyindolizidinone (±)-**13a** as a colorless oil (93%). ^{1}H NMR (MeOD) δ (ppm) 5.48 (d, *J*=3.7, 1H), 3.94-3.64 (m, 3H), 2.49-2.29 (m, 2H), 2.11-1.87 (m, 4H); ^{13}C NMR (MeOD) δ (ppm) 177.5, 74.5, 68.2, 65.0, 57.2, 35.2, 32.5, 19.6; IR υ (cm^{-1}) 3408, 1660; HRMS calculated for $C_8H_{13}NO_4{\cdot}H^+$: 188.0923, found: 188.0915.

Application of the intramolecular PIFA-mediated amidation of alkynes to the synthesis of substituted indolizidinones.

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Abstract.
The construction of the title compounds has been achieved from properly substituted linear alkynylamides through the suitable combination of two key cyclization steps. First, an intramolecular PIFA-mediated alkyne amidation protocol leads to the creation of the pyrrolidinone nucleus, which under proper manipulation of the generated keto-carbonyl group permits the assembling of the indolizidinone skeleton by the introduction of a subsequent ring-closing olefin metathesis step. Finally, its transformation into a series of substituted mono- and trihydroxylated indolizidinone derivatives is achieved by manipulation of the remaining unsaturated fragment under hydrogenation and dihydroxylation conditions.

Keywords: hypervalent iodine; alkynylamides; PIFA; olefin metathesis; indolizidinones

1. Introduction.

Some years ago, our group demonstrated that the intramolecular amidation of properly substituted alkynes (**I**) can be performed in the presence of the hypervalent iodine reagent PIFA [bis(trifluoroacetoxy)phenyliodane] to render a series of 5-aroyl- and 5-alkenoyl-2-pyrrolidinones of type **II** (see Figure 1).[1] As a constituent of the framework of a number of important heterocycles, we considered the construction of highly functionalized pyrrolidinone skeletons as a main object of our research. In this context, the subtle selection of different groups (X and R in **II**) would represent a new starting point for the synthesis of a number of nitrogen containing heterocycles and, in fact, we have recently confirmed the value of this approach in the preparation of pyrrolodiazepinone and pyrrolobenzodiazepinone derivatives from N-(3-aminopropyl)-, N-(2-aminomethylphenyl)-, and N-(2'-nitrobenzyl)-substituted pyrrolidinones,[2] and also in the synthesis of pyrrolo-pyrazinones from N-(2'-aminoethyl)pyrrolidinones[3] by the inclusion, in both cases, of an additional reductive amination step.

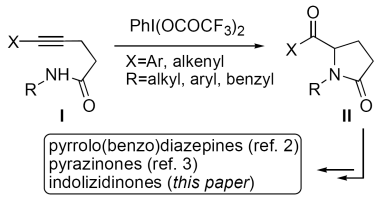


Figure 1. PIFA-mediated construction of substituted pyrrolidinones.

With the aim of expanding the applicability of the proposed synthetic strategy, we show in this paper our efforts to prepare differently substituted indolizidinones of type **III** starting from 5-aryl- and 5-alkenyl-N-allylpentynamides **V**.[4] According to the retrosynthetic analysis shown Figure 2, the success of our plan will rely on two key cyclization steps: (i) the PIFA mediated alkyne amidation to render **IV**, in which the presence of the hydroxy group will be developed by the insertion of an additional reductive step or, alternatively, with the addition of an organometallic vinylic reagent to the previously generated keto-carbonyl group, and (ii) a ring closing metathesis step performed on the N-allyl group and the remaining olefin fragment. Manipulation of the resultant unsaturation –across C(6) and C(7) positions– under reductive and oxidative conditions will be also attempted as a source for higher structural diversity in the final mono- and trihydroxylated indolizidinones that will be eventually prepared, our final challenge.

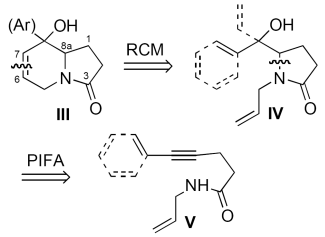


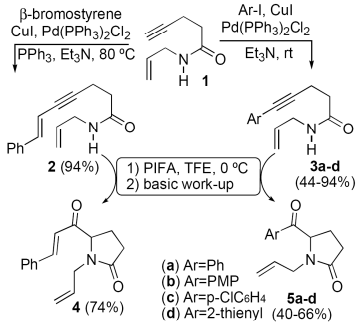
Figure 2. Key retrosynthetic disconnections for the construction of the indolizidinone skeleton.

Polyhydroxylated indolizidines have been the target of a myriad of well-established and novel synthetic approaches as a result of the relevant biological activity that these naturally occurring –or synthetically derived– heterocycles display.[5] For this purpose, the selection of a number of carbohydrates, mainly D-mannitol, D-ribose, D-glucose or L-sorbose, among others, from the chiral pool has been a recurrent option to create the indolizidine skeleton.[6] These strategies benefit from the well defined stereochemistry that will be induced in the final compounds but, contrarily, they are occasionally limited by their lack of stereochemical flexibility and, in some cases, are usually longer than desired mainly because of the introduction of unavoidable protection and deprotection steps. Therefore, we show in this paper our efforts to design a new protecting-free non-sugar based route to the synthesis of racemic 8-hydroxy-indolizidinones.[7]

2. Results and discussion.

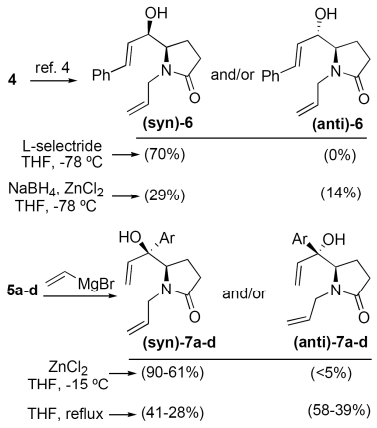
Looking for a high structural diversity in the final compounds, our synthetic design was conceived to incorporate a number of aryl and alkenyl groups at the terminal position of the starting N-allyl-5-pentynamide (**1**) in the first stage of the synthesis, as shown in Scheme 1. For that purpose, the required Sonogashira coupling process had to be optimized with respect to the nature of the halide component of the reaction.[8] Thus, the experimental conditions employed to obtain amides **3a-d**, which required a series of aryl iodides and the catalytic use of CuI and $Pd(PPh_3)_2Cl_2$ in triethylamine as solvent at room temperature, had to be modified with the additional participation of PPh_3 and working at solvent reflux temperature to prepare amide **2** from **1** and (*E*)-β-bromostyrene.[9] When all parts of substrates **2** and **3a-d** were assembled, they were submitted to the PIFA-mediated cyclization conditions. Thus, treatment of these alkynylamides **2** and **3** with a slight excess (1.5 equivalents) of the hypervalent iodine reagent in trifluoroethanol (TFE) as solvent at room temperature, followed by a basic aqueous work up (aq. K_2CO_3), rendered the corresponding 5-styryl- and 5-aroyl-2-pyrrolidinones **4** and **5a-d** in acceptable yields.

Prior to the planned ring closing metathesis step, we found that both types of pyrrolidinones **4** and **5** had to be manipulated. Considering that, in the case of pyrrolidinone **4**, all attempts to perform the projected cyclization didn't afford the expected results under a number of Ru-catalyzed conditions, a reductive step to generate the corresponding hydroxy group was introduced. Complementary, and with the same purpose, 5-aroylpyrrolidinones **5a-d** were submitted to the action of vinylmagnesium bromide in order to fix the olefin fragment and, at the same time, to develop the hydroxy group that eventually will be located at the C(8) position of the indolizidinone skeleton. In any case, both processes, the reduction of the keto group and the addition of the Grignard reagent, were studied with the aim to obtain pure samples of both possible syn/anti diastereoisomers, as it will be now disclosed.[10]



Scheme 1. Preparation of pyrrolidinones **4** and **5a-d**.

The survey to perform the diastereoselective reduction of **4** was carried out by combining a number of different reducing agents, solvents, and coordinating metal sources (see Scheme 2). In particular, when a sterically demanding reducing agent such as L-selectride was tested in THF at -78 ºC, we were rewarded with a completely diastereoselective transformation leading to **(syn)-6**.[11] In contrast, we met only limited success in the preparation of **(anti)-6**. In fact, under the best circumstances, the use of $NaBH_4$ in combination with $ZnCl_2$ –which was introduced with the aim to induce a chelated-controlled addition– produced a chromatographically separable mixture of both diastereoisomers. On the other hand, the selection of the adequate conditions to conduct the diastereodivergent addition of vinylmagnesium bromide to pyrrolidinones **5a-d** was also examined (see Scheme 2). Thus, it was found that when the reaction was performed under chelate-controlled conditions, a series of pyrrolidinones (**syn**)-**7a-d** was obtained with complete diastereocontrol in good to excellent yields. Particularly, the behavior of $ZnCl_2$ resulted to be superior over other additives that were also studied, such as $Mg(ClO_4)_2$, 18-crown-6, $CeCl_3$, or CuI.[12] Contrarily, none of the experimental conditions that were tested with the aim to prepare pyrrolidinones (**anti**)-**7a-d** led to good levels of diastereocontrol (up to 66/34 for **7a**).[13]

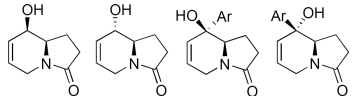


Scheme 2. Preparation of hydroxylated pyrrolidinones **6** and **7a**.

With these materials in hand, we moved to our next synthetic step. In order to overcome a number of difficulties associated to the lack of reactivity and partial olefin isomerization[14] that were detected in our preliminary assays, a combination of several experimental parameters –the use of Grubbs I or Grubbs II catalysts (see Figure 3), the use of different solvents (CH_2Cl_2 and toluene), and different temperatures (rt and solvent reflux)– had to be optimized to perform the ring closing metathesis reaction on derivatives **6** and **7**.[15]

Figure 3. First (**GI**) and second (**GII**) generation Grubbs' catalysts.

Such optimization process led to the conclusion (see Table 1) that whereas the transformation of either (**syn**)-**6** or (**anti**)-**6** into the corresponding indolizidinones **8** had to be performed under the assistance of **GII** catalyst in refluxing toluene (71 and 86% yield, respectively), the preparation of indolizidinones **9a-d** required the use of CH_2Cl_2 as solvent at room temperature with the aid of Grubbs' **GII** catalyst as well (58-66 yield).[16] The ^{1}H NMR-based stereochemical analysis of the crude samples revealed that the projected cyclization resulted to be successful in the absence of OH protection and with no detectable epimerization in none of the cases under study.[17]



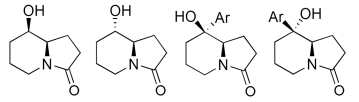
(syn)-8 **(anti)-8** **(syn)-9a-d** **(anti)-9a-d**

Table 1. Preparation of a series of indolizidinones **8** and **9**.[a), b)]

entry	Ar	substrate (*syn*/*anti*)	product (*syn*/*anti*)	yield (%)
1	---	**6** (100/0)	**8** (100/0)	71
2	---	**6** (0/100)	**8** (0/100)	86
3	Ph	**7a** (33/67)	**9a** (33/67)	66
4	Ph	**7a** (100/0)	**9a** (100/0)	65
5	PMP	**7b** (53/47)	**9b** (53/47)	60
6	PMP	**7b** (100/0)	**9b** (100/0)	65
7	p-ClC_6H_4	**7c** (41/59)	**9c** (41/59)	65
8	p-ClC_6H_4	**7c** (100/0)	**9c** (100/0)	58
9	2-thienyl	**7d** (38/62)	**9d** (38/62)	65
10	2-thienyl	**7d** (100/0)	**9d** (100/0)	58

[a)] **GII** catalyst was employed in refluxing toluene for the transformation of compound **6**, and in CH_2Cl_2 at room temperature for the transformation of compounds **7a-d**. [b)] The diastereomeric composition was determined from the crude ^{1}H NMR.

To conclude our projected research, the resultant unsaturation generated on indolizidinones **8** and **9** was submitted to new manipulations, both under reductive and oxidative conditions, in order to extend the structural diversity of the series of indolizidinone derivatives that can be prepared. Firstly, (see Table 2) it was found that treatment of separated samples of both diastereoisomers **8** under an atmosphere of H_2 (70 psi) using Pd(C) as catalyst in MeOH rendered indolizidinones (**syn**)-**10** and (**anti**)-**10** in a moderate 46 and 43% yields, respectively. Similarly, when indolizidines **9** were submitted to the same reaction conditions, a series of indolizidinones **11a-d** was prepared in moderate to good yields.



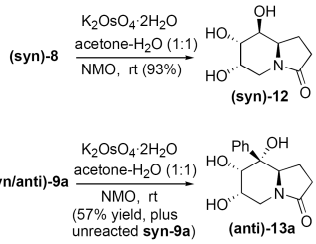
(syn)-10 **(anti)-10** **(syn)-11a-d** **(anti)-11a-d**

Table 2. Preparation of a series of indolizidinones **10** and **11**.[a), b)]

entry	Ar	substrate (*syn*/*anti*)	product (*syn*/*anti*)	yield (%)
1	---	**8** (100/0)	**10** (100/0)	46
2	---	**8** (0/100)	**10** (0/100)	43
3	Ph	**9a** (33/67)	**11a** (33/67)	69
4	Ph	**9a** (100/0)	**11a** (100/0)	60
5	PMP	**9b** (53/47)	**12b** (53/47)	67
6	PMP	**9b** (100/0)	**12b** (100/0)	63
7	p-ClC_6H_4	**9c** (41/59)	**13c** (41/59)	65
8	p-ClC_6H_4	**9c** (100/0)	**13c** (100/0)	53
9	2-thyenyl	**9d** (38/62)	**14d** (38/62)	68
10	2-thyenyl	**9d** (100/0)	**14d** (100/0)	56

[a)] All reactions were performed in MeOH as solvent at room temperature, and in the presence of 10% Pd(C). [b)] The diastereomeric composition was determined from the crude ^{1}H NMR.

Finally, we found that the projected dihydroxylation step, that would render the desired trihydroxylated indolizidinone skeleton, resulted to be much more problematic.[18] In fact, although indolizidinone (**syn**)-**8** behaved as expected to render the 6,7,8-trihydroxyindolizidinone (**syn**)-**12** in an excellent 93% yield under modified Upjohn conditions,[19] for which the stereochemical outcome is the result of a stereoelectronic repulsion with the existing C(8)-hydroxy group,[20] indolizidinone (**anti**)-**8** resulted to be inexplicably unreactive under all different conditions that were tested. Similarly, none of all syn or anti indolizidinones **9** produced the desired trihydroxylated derivatives when submitted to an array of different dihydroxylation conditions, except for (**anti**)-**9a**. Thus, when a syn/anti mixture of (**syn**/**anti**)-**9a** was treated with $K_2OsO_4{\cdot}2H_2O$ under Upjohn conditions, pure (**anti**)-**13a** was obtained in 57% yield (86% based on consumed starting material) together with unreacted (**syn**)-**9a**.



Scheme 3. Preparation of hydroxylated pyrrolidinones (**syn**)-**12** and (**anti**)-**13a**.

Although the explanation for the dramatic difference in the observed reactivity with respect to the nature of the aryl ring in the series of indolizidinones **9a-d** is out of our knowledge, –in fact, only **9a** appears to be reactive enough–, we can suggest (see Figure 4) a possible explanation for the higher reactivity of (**anti**)-**9a** over its diastereoisomer (**syn**)-**9a**. If we assume that substrate **9a** is stabilized in a half-chair conformation, the allylic substituents at C(8) will occupy pseudo-axial and pseudo-equatorial positions. Now, in the case of the syn-stereoisomer, the oxidative reagent will find opposition for its approach to both faces of the double bond, due to electronic repulsion with the hydroxy group located in the pseudoaxial position –in combination with the nitrogen lone pair–, in one case, and to the steric hindrance that the bulky phenyl group exerts in the opposite face. But, although the latter repulsion also exists for the phenyl group in the anti-stereoisomer, the electronic repulsion that the hydroxy group induces is diminished since it lies far from the double bond because of its pseudoequatorial location. Consequently, this situation is also in agreement with the all-syn relationships that the three hydroxy groups display in indolizidinone (**anti**)-**13a**.

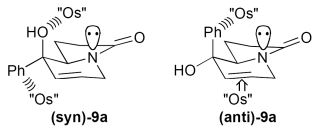


Figure 4. Possible explanation for the different reactivity of (**syn**)- and (**anti**)-**9** towards the dihydroxylation reagent.

3. Conclusions

In summary, the design of a new, short, and efficient strategy for the preparation of a series of unsaturated, saturated, and substituted indolizidinones has been achieved –in racemic fashion– from highly and properly functionalized linear alkynylamides. The combination of two key cyclization steps (PIFA mediated alkyne amidation and a RCM step) allowed the creation of the required unsaturated bicyclic skeletons on which the final hydrogenation and dihydroxylation processes were performed. It must be highlighted that all four continuous stereogenic centers in the final compounds are produced in a complete diastereoselective fashion and with no need of undesirable protection steps in any of the stages of the synthesis.

4. Experimental Section.

4.1. General procedures. All reagents were purchased and used as received. All solvents used in reactions were dried and purified according to standard procedures. All air- or moisture-sensitive reactions were performed under argon. The glassware was oven dried (140 ºC) overnight and purged with argon prior to use. Melting points were measured using open glass capillaries and are uncorrected. Infrared spectra were recorded as thin films and peaks are reported in cm^{-1}. Only representative absorptions are given. Flash chromatography was carried out on SiO_2 (silica gel 60, 230–400 mesh ASTM). NMR spectra were recorded on a 300 instrument (300 MHz for ^1H and 75.4 MHz for ^{13}C) at 20-25 ºC unless otherwise stated. Chemical shifts (δ) were measured in ppm relative to chloroform (δ=7.26 for ^1H or 77.0 for ^{13}C) as internal standard. Coupling constants, *J*, are reported in hertz. DEPT and several bidimensional NMR experiments (COSY, HSQC, NOESY) were used to assist with the assignation of the signals and structural and stereochemical determinations. Mass spectra were recorded under electron impact (EI, 70 eV) or chemical ionization conditions (CI).

4.2. Synthesis of N-allyl-4-pentynamide (1). A solution of 4-pentynoic acid (640 mg, 6.5 mmol) in 5 mL of DCM was added to a magnetically stirred solution of EDC·HCl (1.9 g, 9.9 mmol) and HOBt (1.35 g, 9.9 mmol) in 30 mL of the same solvent followed by the addition of allylamine (0.75 mL, 9.9 mmol) dissolved in 10 mL of DCM. The mixture was cooled to 0 ºC and Et_3N (1.4 mL, 9.9 mmol) was added dropwise and was left to react at rt overnight. Then, the reaction was diluted with DCM and water (30 mL), the mixture decanted, and the aqueous phase extracted with DCM (3x 15 mL). The combined organic

layers were dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The resultant chromatographically pure colorless oil was triturated with cold Et_2O to afford amide **1** as a while solid (82%): mp 46-48 ºC (Et_2O); ^{1}H NMR ($CDCl_3$) δ (ppm) 5.90-5.77 (m, 2H), 5.23-5.11 (m, 2H), 3.91-3.88 (m, 2H), 2.57-2.51 (m, 2H), 2.44-2.39 (m, 2H), 2.00 (t, *J*=2.0, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.7, 134.0, 116.4, 82.9, 69.3, 41.9, 35.3, 14.9; IR υ (cm^{-1}) 3295, 1648; MS [CI] *m/z*: 138 (100), 136 (8); HRMS calcd for $C_8H_{11}NO{\cdot}H^+$ 138.0919, found 138.0925.

4.3. Synthesis of (*E*)-N-allyl-5-(β-styryl)-4-pentynamide (2). A solution of (*E*)-β-bromostyrene (500 mg, 3 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), PPh_3 (23 mg, 0.09 mmol), and amide **1** (615 mg, 4.5 mmol) in Et_3N (20 mL) was stirred at 40 ºC for 15 min. Then, CuI (17 mg, 0.09 mmol) was added and the stirring was continued at 80 ºC until total consumption of the starting material (tlc, 6 h). Then, after cooling, the solvent was evaporated under vacuum and the residue purified by column chromatography (EtOAc) to afford amide **2** as a yellowish solid that was crystallized from Et_2O (54%): mp 68-70 ºC (Et_2O); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.37-7.29 (m, 5H), 6.87 (d, *J*=16.2, 1H), 6.11 (d, *J*=16.2, 1H), 5.91-5.80 (m, 1H), 5.74 (br s, 1H), 5.26-5.13 (m, 2H), 3.73 (t, *J*=5.6, 11.2, 2H), 2.73 (t, *J*=5.8, 12.7, 2H), 2.46 (t, *J*=7.1, 14.3, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.9, 140.8, 134.1, 128.7, 128.5, 126.1, 116.4, 108.2, 90.8, 80.8, 42.0, 35.7, 16.2; IR υ (cm^{-1}) 3295, 1638; MS [CI] *m/z*: 240 (100), 198 (32), 155 (23), 141 (25); HRMS calcd for $C_{16}H_{17}NO{\cdot}H^+$ 240.1388, found 240.1392.

4.4. Typical procedure for the Sonogashira coupling reaction.

4.4.1. Synthesis of N-allyl-5-phenyl-4-pentynamide (3a). A solution of iodobenzene (0.5 mL, 4.05 mmol), $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol), CuI (15 mg, 0.08 mmol), and amide **1** (555 mg, 4.05 mmol) in Et_3N (20 mL) was stirred at room temperature until total consumption of the starting material (tlc, 72 h). Then, water (30 mL) was added, the mixture was extracted with EtOAc (3x25 mL), and the combined organic extracts were dried over Na_2SO_4 (anh). Once the solvent was evaporated under vacuum, the whole crude was purified by column chromatography (hexanes/EtOAc, 1/1) to afford amide **3a** as a white solid that was crystallized from Et_2O (94%): mp 72-73 ºC (Et_2O); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.37-7.32 (m, 2H), 7.25-7.23 (m, 3H), 6.30 (br s, 1H), 5.89-5.74 (m, 1H), 5.22-5.06 (m, 2H), 3.90-3.86 (m, 2H), 2.76-2.70 (m, 2H), 2.51-2.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.1, 133.9, 131.4, 128.1, 127.7, 123.3, 116.1, 88.4, 81.4, 41.8, 35.4, 15.8; IR υ (cm^{-1}) 3301, 1631; MS [EI] *m/z*: 213 (15), 212 (41), 185 (45), 184 (98), 172 (100), 170 (31), 128 (67); HRMS calcd for $C_{14}H_{15}NO$ 213.1154, found 213.1149.

4.4.2. N-allyl-5-(4-methoxyphenyl)-4-pentynamide (3b). According to the typical procedure, amide **3b** was prepared from amide **1** and 4-iodoanisole in 57% yield as a yellowish solid. It was purified by column chromatography (hexanes/EtOAc, 2/8) followed by crystallization from Et_2O: mp 82-83 ºC (Et_2O); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.28 (d, *J*=8.7, 2H), 6.77 (d, *J*=8.7, 2H), 6.10 (br s, 1H), 5.88-5.75 (m, 1H), 5.21-5.07 (m, 2H), 3.88 (t, *J*=5.6, 2H), 3.76 (s, 3H), 2.71 (t, *J*=7.2, 2H), 2.47 (t, *J*=7.2, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.2, 159.3, 134.4, 132.9, 115.5, 113.8, 116.2, 86.8, 81.4, 55.2, 41.9, 35.8, 15.9; IR υ (cm^{-1}) 3310, 1633; MS [CI] *m/z:* 244 (100), 243 (44), 202 (50), 145 (10); HRMS calcd for $C_{15}H_{17}NO_2{\cdot}H^+$ 244.1337, found 244.1345.

4.4.3. N-allyl-5-(4-chlorophenyl)-4-pentynamide (3c). According to the typical procedure, amide **3c** was prepared from amide **1** and 4-chlorophenyl iodide in 54% yield as a white solid. It was purified by column chromatography (hexanes/EtOAc, 2/8) followed by crystallization from Et_2O: mp 196-197 ºC (Et_2O); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.30-7.22 (m, 4H), 5.88-5.77 (m, 2H), 5.23-5.09 (m, 2H), 3.91 (t, *J*=5.7, 2H), 2.75 (t, *J*=7.2, 2H), 2.48 (t, *J*=7.2, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.9, 134.1, 133.8, 132.8, 128.5, 121.9, 116.4, 89.5, 80.5, 42.0, 35.5, 15.9; IR (film) υ (cm^{-1}) 3305, 1631; MS (CI) *m/z* (%) 248 (100), 247 (25), 206 (42), 149 (10); HRMS calculated for $C_{14}H_{14}{}^{35}ClNO{\cdot}H^+$ 248.0842, found 248.0839.

4.4.4. N-allyl-5-(2-thyenyl)-4-pentynamide (3d). According to the typical procedure, amide **3d** was prepared from amide **1** and 2-iodothiophene in 44% yield as a brown solid. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by crystallization from Et_2O: mp 68-69 ºC (Et_2O); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.18-7.10 (m, 2H), 6.93-6.91 (m, 1H), 5.97 (br s, 1H), 5.90-5.77 (m, 1H), 5.23-5.09 (m, 2H), 3.91 (t, *J*=5.5, 2H), 2.77 (t, *J*=7.3, 2H), 2.48 (t, *J*=7.3, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.9, 134.0, 131.4, 126.3, 123.5, 116.4, 92.5, 74.8, 42.0, 35.4, 16.2; IR υ (cm^{-1}) 3305, 1633; MS [CI] *m/z*: 220 (100), 179 (47), 178 (96), 135 (10); HRMS calcd for $C_{12}H_{13}NOS{\cdot}H^+$ 220.0796, found 220.0790.

4.5. Typical procedure for the PIFA-mediated heterocyclization.

4.5.1. (±)-N-allyl-5-cinnamoyl-2-pyrrolidinone (4). A solution of alkynylamide **2** (348 mg, 1.4 mmol) in CF_3CH_2OH (20 mL) was stirred at 0 ºC and a solution of PIFA (940 mg, 2.2 mmol) in 12 mL of the same solvent was added dropwise. The reaction mixture was stirred at that temperature until total consumption of the starting material (tlc, 2 h). For the work up, aqueous Na_2CO_3 (20%) was added (30 mL) and the mixture extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash

chromatography (EtOAc) gave pyrrolidinone **4** as a chromatographically pure yellowish oil (74%): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.70 (d, *J*=15.8, 1H), 7.54-7.39 (m, 5H), 6.76 (d, *J*=15.8, 1H), 5.75-5.62 (m, 1H), 5.15-5.08 (m, 2II), 4.53-4.41 (m, 2II), 3.46-3.38 (m, 1II), 2.48-2.33 (m, 3H), 2.00-1.93 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 197.2, 175.2, 145.2, 133.9, 132.1, 131.2, 129.1, 128.6, 121.4, 118.8, 63.7, 44.5, 29.6, 21.4; IR 1692, 1609; MS [CI] *m/z*: 256 (89), 124 (100); HRMS calcd for $C_{16}H_{17}NO_2{\cdot}H^+$ 256.1338, found 256.1335.

4.5.2. (±)-N-allyl-5-benzoyl-2-pyrrolidinone (5a). According to the typical procedure, pyrrolidinone **5a** was prepared from amide **3a** in 66% yield as a yellowish oil. It was purified by column chromatography (EtOAc): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.91 (d, *J*=7.1, 2H), 7.63-7.45 (m, 3H), 5.78-5.55 (m, 1H), 5.15-5.02 (m, 3H), 4.51-4.45 (m, 1H), 3.39 (dd, *J*=15.0, 7.9, 1H), 2.42-2.39 (m, 3H), 2.01-1.96 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 196.8, 175.0, 134.0, 133.9, 132.3 128.9, 128.2, 118.6, 60.6, 44.2, 29.4, 23.0; IR υ (cm^{-1}) 1690; MS [M] *m/z*: 229 (1), 124 (100), 105 (23); HRMS calcd for $C_{14}H_{15}NO_2$: 229.1103, found 229.1111.

4.5.3. (±)-N-allyl-5-(4-methoxyphenyl)-2-pyrrolidinone (5b). According to the typical procedure, pyrrolidinone **5b** was prepared from amide **3b** in 40% yield as a yellowish solid. It was purified by column chromatography (EtOAc) followed by crystallization from Et_2O: mp 72-73 ºC (Et_2O); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.86 (d, *J*=8.9, 2H), 6.91 (d, *J*=8.9, 2H), 5.72-5.59 (m, 1H), 5.10-4.99 (m, 3H), 4.45-4.38 (m, 1H), 3.82 (s, 3H), 3.37-3.30 (m, 1H), 2.44-2.33 (m, 3H), 1.96-1.90 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 195.4, 175.2, 164.2, 132.5, 130.6 128.9, 118.5, 114.2, 60.4, 55.6, 44.3, 29.6, 23.4; IR υ (cm^{-1}) 1690; MS [CI] *m/z*: 260 (100), 124 (40); HRMS calcd for $C_{15}H_{17}NO_3{\cdot}H^+$ 260.1287, found 270.1277.

4.5.4. (±)-N-allyl-5-(4-chlorophenyl)-2-pyrrolidinone (5c). According to the typical procedure, pyrrolidinone **5c** was prepared from amide **3c** in 54% yield as a yellowish oil. It was purified by column chromatography (EtOAc): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.81 (d, *J*=8.6, 2H), 7.40 (d, *J*=8.6, 2H), 5.66-5.56 (m, 1H), 5.08-4.97 (m, 3H), 4.41-4.35 (m, 1H), 3.37-3.29 (m, 1H), 2.44-2.32 (m, 3H), 1.93-1.87 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 195.8, 175.0, 140.5, 132.5, 132.4, 129.7 129.3, 118.7, 60.7, 44.3, 29.4, 23.1; IR υ (cm^{-1}) 1697; MS [CI] *m/z*: 266 (34), 264 (100), 124 (47); HRMS calcd for $C_{14}H_{14}{}^{35}ClNO_2{\cdot}H^+$ 264.5791, found 264.0785.

4.5.5. (±)-N-allyl-5-(2-thyenyl)-2-pyrrolidinone (5d). According to the typical procedure, pyrrolidinone **5d** was prepared from amide **3d** in 64% yield as a yellowish oil. It was purified by column chromatography (EtOAc): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.71-7.67 (m, 2H), 7.13-7.10 (m, 1H), 5.65-5.56 (m, 1H), 5.06-4.90 (m, 3H), 4.39-4.32 (m, 1H), 3.37-3.29 (m, 1H), 2.46-2.31 (m, 3H), 2.03-1.93 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 190.5, 175.1, 140.9, 135.1, 132.6 132.2, 128.6, 118.8, 61.7, 44.3, 29.5, 23.7; IR υ (cm^{-1}) 1690; MS [CI] *m/z*: 237 (12), 236 (100), 124 (48); HRMS calcd for $C_{12}H_{13}NO_2S{\cdot}H^+$ 236.0745, found 236.0734.

4.6. (±)-(5R,1'R)-N-allyl-5-(1-hydroxy-3-phenylallyl)-pyrrolidin-2-one (syn-6). A solution of L-Selectride® (1.8 mL, 1.0 M in THF) was added dropwise to a cold (-78 ºC) solution of pyrrolidinone **4** (230 mg, 0.9 mmol) in 4.5 mL of the same solvent. After 30 min, temperature was raised to room temperature and 2 mL of an aqueous solution of NaOH (10%) was added. The whole mixture was extracted with CH_2Cl_2 (3x10 mL), the combined organic layers were dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave pyrrolidinone **(syn)-6** as a chromatographically pure yellowish oil (70%): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.30-7.17 (m, 5H), 6.59 (d, *J*=15.9, 1H), 6.10 (dd, *J*=15.9, 6.00, 1H), 5.72-5.65 (m, 1H), 5.14 (d, *J*=4.5, 1H), 5.10 (s, 1H), 4.39-4.25 (m, 2H), 3.76-3.64 (m, 2H), 2.88 (br s, 1H), 2.36-1.98 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 175.9, 136.2, 132.8, 132.3, 128.7, 128.0, 127.5, 126.5, 117.8, 73.4, 61.6, 44.7, 30.2, 20.5; IR υ (cm^{-1}) 3374, 1670; HRMS calculated for $C_{16}H_{19}NO_2{\cdot}H^+$ 258.1494, found 258.1507.

4.7. (±)-(5R,1'S)-N-allyl-5-(1-hydroxy-3-phenylallyl)-pyrrolidin-2-one (anti-6). Solid $NaBH_4$ (68 mg, 1.8 mmol) was added in one portion to a cold (-78 ºC) solution of pyrrolidinone **4** (230 mg, 0.9 mmol) in MeOH (5 mL). After 30 min, H_2O (2 mL) was added and temperature was raised to rt. The whole mixture was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (MeCN) rendered, independently, pyrrolidinones **(syn)-6** and **(anti)-6** as chromatographically pure yellowish oils in a 68:32 ratio (46% combined yield). Only the data for **(anti)-6** is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.40-7.25 (m, 5H), 6.73 (d, *J*=16.0, 1H), 6.14 (dd, *J*=16.0, 5.5, 1H), 5.87-5.74 (m, 1H), 5.27 (d, *J*=9.2, 1H), 5.23 (s, 1H), 4.63 (s, 1H), 4.36 (dd, *J*=15.5, 4.8, 1H), 3.72 (dd, *J*=16.2, 6.9, 2H), 2.92 (br s, 1H), 2.59-2.47 (m, 1H), 2.32-2.26 (m, 1H), 2.14-1.87 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.1, 136.4, 132.8, 132.1, 128.7, 127.3, 126.5, 118.2, 70.7, 61.9, 43.6, 30.6, 18.2.

4.8. Typical procedure for the nucleophilic addition of vinylmagnesium bromide to pyrrolidinones 5 (method A).

4.8.1. Synthesis of (±)-(5R,1'S)-N-allyl-5-(1-hydroxy-1-phenylallyl)-pyrrolidin-2-one (syn-7a). $ZnCl_2$ (30 mg, 0.22 mmol) was added to a solution of pyrrolidinone **5a** (50 mg, 0.2 mmol) in THF (2 mL). After 30 min, the mixture was cold to -20 ºC and vinylmagnesium bromide (0.8 mL, 1.0 M in THF) was added. After 5 h, 4 mL of a saturated solution of NH_4Cl were added, and the whole mixture was extracted with CH_2Cl_2 (3x10 mL). The

combined organic layers were dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave pyrrolidinone **(syn)-7a** as a chromatographically pure yellowish oil (90%): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.26-7.13 (m, 5H), 6.29-6.20 (m, 1H), 5.57-5.51 (m, 1H), 5.45 (d, *J*=17.2, 1H), 5.27 (d, *J*=10.8, 1H), 5.08 (d, *J*=10.2, 1H), 4.90 (d, *J*=17.1, 1H), 4.26-4.19 (m, 1H), 4.09-4.05 (m, 1H), 2.98-3.90 (m, 1H), 2.28-1.86 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.9, 143.4, 140.0, 132.6, 128.5 127.6, 125.7, 117.5, 115.5, 79.3, 64.5, 44.5, 30.0, 21.3; IR υ (cm^{-1}) 3368, 1670; MS [CI] *m/z*: 258 (100), 240 (23), 124 (54); HRMS calculated for $C_{16}H_{19}NO_2{\cdot}H^+$ 258.1494, found 258.1501.

4.8.2. Synthesis of (±)-(5R,1'S)-N-allyl-5-[1-hydroxy-1-(4-methoxyphenyl)allyl]-pyrrolidin-2-one (syn-7b). According to the typical procedure pyrrolidinone **(syn)-7b** was obtained from **5b** in 86% yield. It was purified by column chromatography (EtOAc) as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.34 (d, *J*=8.8, 2H), 6.88 (d, *J*=8.8, 2H), 6.30-6.21 (m, 1H), 5.67-5.54 (m, 1H), 5.45 (d, *J*=17.1, 1H), 5.31 (d, *J*=10.8, 1H), 5.12 (d, *J*=10.2, 1H), 4.99 (d, *J*=17.1, 1H), 4.31-4.27 (m, 1H), 4.05-4.02 (m, 1H), 3.80 (s, 3H), 3.20-3.12 (m, 1H), 2.32-1.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.9, 159.1, 139.3, 135.0, 132.7, 127.0, 117.5, 115.7, 113.9, 79.3, 64.7, 55.3, 44.7, 30.1, 21.3; IR (film) υ (cm^{-1}) 3394, 1668; MS (CI) *m/z* (%) 288 (100), 272 (13), 270 (23), 163 (17); HRMS calculated for $C_{17}H_{21}NO_3{\cdot}H^+$ 288.1599, found 288.1605.

4.8.3. Synthesis of (±)-(5R,1'S)-N-allyl-5-[1-(4-chlorophenyl)-1-hydroxyallyl)]-pyrrolidin-2-one (syn-7c). According to the typical procedure pyrrolidinone **(syn)-7c** was obtained from **5c** in 81% yield. It was purified by column chromatography (EtOAc) as a yellowish oil: ^{1}H NMR (MeOD) δ (ppm) 7.50 (d, *J*=8.7, 2H), 7.35 (d, *J*=8.7, 2H), 6.41-6.31 (m, 1H), 5.65-5.52 (m, 1H), 5.46 (d, *J*=17.2, 1H), 5.31 (d, *J*=10.5, 1H), 5.09 (d, *J*=10.5, 1H), 4.96 (d, *J*=17.2, 1H), 4.21 (br s, 1H), 4.15-4.11 (m, 2H), 3.14-3.04 (m, 1H), 2.10-1.96 (m, 4H); ^{13}C NMR (MeOD) δ (ppm) 179.4, 144.2, 134.3, 141.8, 133.4, 129.3, 129.1, 117.8, 116.0, 80.0, 66.5, 45.8, 30.9, 22.3; IR (film) υ (cm^{-1}) 3354, 1668; MS (M+1, CI) *m/z* (%) 292 (100), 276 (15), 234 (10), 167 (12); HRMS calculated for $C_{16}H_{18}{}^{35}ClNO_2{\cdot}H^+$ 292.1104, found 292.1107.

4.8.4. Synthesis of (±)-(5R,1'S)-N-allyl-5-[1-hydroxy-1-(2-thyenyl)allyl]-pyrrolidin-2-one (syn-7d). According to the typical procedure pyrrolidinone **(syn)-7d** was obtained from **5d** in 61% yield. It was purified by column chromatography (EtOAc) as a brownish oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.28-7.26 (m, 1H), 6.99-6.95 (m, 2H), 6.29-6.20 (m, 1H), 5.76-5.63 (m, 1H), 5.54 (d, *J*=17.2, 1H), 5.37 (d, *J*=10.6, 1H), 5.16 (d, *J*=10.2, 1H), 5.04 (br s, 1H), 4.36 (d, *J*=17.2, 1H), 4.04-3.97 (m, 1H), 3.53-3.41 (m, 1H), 2.92 (s, 1H), 2.22-1.91 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.7, 148.0, 138.6, 132.8, 127.1, 125.4, 124.5, 117.6, 116.8, 79.0, 65.6, 45.0, 29.9, 21.4; IR (film) υ (cm^{-1}) 3339, 1670; MS [EI] *m/z* (%) 246 (20), 124 (93); HRMS calculated for $C_{14}H_{17}{}^{32}SNO_2$ 263.0980, found 263.0957.

4.9. Typical procedure for the nucleophilic addition of vinylmagnesium bromide to pyrrolidinones 5 (method B).

4.9.1. Synthesis of (±)-(5R,1'R)-N-allyl-5-(1-hydroxy-1-phenylallyl)-pyrrolidin-2-one (anti-7a). A vinylmagnesium bromide solution (0.35 mL, 1.0 M in THF) was added to a solution of pyrrolidinone **5a** (50 mg, 0.2 mmol) in THF (2 mL) and the temperature was raised to 40 ºC. After 5 h, 4 mL of a saturated solution of NH_4Cl were added and the whole mixture was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave separated samples of pyrrolidinone **(anti)-7a** and **(syn)-7a** in 67/33 ratio (86% combined yield). Only the data for the **(anti)-7a** isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.46-7.26 (m, 5H), 6.49-6.40 (m, 1H), 5.60-5.44 (m, 1H), 5.47 (d, *J*=17.2, 1H), 5.23 (d, *J*=10.8, 1H), 5.18 (d, *J*=10.2, 1H), 5.07 (d, *J*=17.1, 1H), 4.50-4.45 (m, 1H), 4.12-4.06 (m, 1H), 3.58-3.50 (m, 1H), 2.28-1.80 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 177.2, 143.7, 141.9, 132.8, 128.5, 127.3 125.7, 117.9, 114.1, 78.9, 64.4, 45.1, 30.0, 21.4.

4.9.2. Synthesis of (±)-(5R,1'R)-N-allyl-5-[1-hydroxy-1-(4-methoxyphenyl)allyl]-pyrrolidin-2-one (anti-7b). According to the typical procedure pyrrolidinones **(anti)-7b** and **(syn)-7b** were obtained from **5b** in a 47/53 ratio (80% combined yield) as yellowish oils after purification by column chromatography (EtOAc). Only the data for the **(anti)-7b** isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.34 (d, *J*=8.8, 2H), 6.88 (d, *J*=8.8, 2H), 6.49-6.36 (m, 1H), 5.94-5.80 (m, 1H), 5.45 (d, *J*=17.1, 1H), 5.31 (d, *J*=10.8, 1H), 5.19-5-15 (m, 1H), 4.99 (d, *J*=17.1, 1H), 4.46-4.41 (m, 1H), 4.15-4.10 (m, 1H), 3.79 (s, 3H), 3.56-3.48 (m, 1H), 2.32-1.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 177.2, 159.1, 139.9, 132.7, 126.8, 117.9, 115.7, 113.4, 78.9, 64.6, 55.3, 44.5, 30.1, 21.3.

4.9.3. Synthesis of (±)-(5R,1'R)-N-allyl-5-[1-(4-chlorophenyl)-1-hydroxyallyl]-pyrrolidin-2-one (anti-7c). According to the typical procedure pyrrolidinones **(anti)-7c** and **(syn)-7c** were obtained from **5c** in a 59/41 ratio (73% combined yield) as yellowish oils after purification by column chromatography (EtOAc). Only the data for the **(anti)-7c** isomer is now reported: ^{1}H NMR (MeOD) δ (ppm) 7.51-7.35 (m, 4H), 6.53-6.45 (m, 1H), 5.88-5.72 (m, 1H), 5.47 (d, *J*=17.2, 1H), 5.31 (d, *J*=10.5, 1H), 5.19 (d, *J*=10.5, 1H), 4.96 (d, *J*=17.2, 1H), 4.21 (br s, 1H), 4.40-4.35 (m, 2H), 3.14-3.04 (m, 1H), 2.10-1.96 (m, 4H); ^{13}C NMR (MeOD) δ (ppm) 179.4, 142.6, 142.1, 134.3, 134.0, 129.3, 129.1, 117.4, 116.0, 80.0, 65.3, 45.1, 30.8, 23.4.

4.9.4. Synthesis of (±)-(5R,1'R)-N-allyl-5-[1-hydroxy-1-(2-thyenyl)allyl]-pyrrolidin-2-one (anti-7d). According

to the typical procedure pyrrolidinones **(anti)-7d** and **(syn)-7d** were obtained from **5d** in a 38/62 ratio (83% combined yield) as yellowish oils after purification by column chromatography (EtOAc). Only the data for the **(anti)-7c** isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.28-7.26 (m, 1H), 6.99-6.95 (m, 2H), 6.44-6.35 (m, 1H), 5.80-5.62 (m, 1H), 5.58 (d, *J*=17.2, 1H), 5.34 (d, *J*=10.6, 1H), 5.16 (d, *J*=10.2, 1H), 5.04 (br s, 1H), 4.46 (d, *J*=17.2, 1H), 4.04-3.97 (m, 1H), 3.53-3.41 (m, 1H), 2.95 (s, 1H), 2.22-1.91 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.7, 148.0, 140.0, 135.8, 126.9, 125.6, 124.7, 117.4, 116.9, 68.2, 65.6, 45.2, 29.8, 21.4.

4.10. Typical procedure for the olefin metathesis reaction on pyrrolidinones 7.

4.10.1. Synthesis of (±)-(8S,8aR)-8-hydroxy-8-phenyl-1,2,8,8a-tetrahydroindolizin-3(5H)-one (syn)-9a. Grubbs II catalyst (5 mg, 10% wt) was added in one portion onto a solution of pyrrolidinone **(syn)-7a** (50 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) at rt. After 12 h, the solvent was eliminated under vacuum and the resulting residue was column chromatographed (EtOAc) to afford indolizidinone **(syn)-9a** as a white solid that was triturated in Et_2O (65%): mp 162-165 ºC (Et_2O); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.41-7.26 (m, 5H), 5.97 (d, *J*=10.3, 1H), 5.82 (d, *J*=10.3, 1H), 4.48 (d, *J*=18.8, 1H), 3.79 (d, *J*=7.7, 1H), 3.63 (d, *J*=18.8, 1H), 2.79 (br s, 1H), 2.02-1.75 (m, 3H), 1.41-1.27 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.9, 139.0, 133.5, 128.2 127.8, 126.5, 123.7, 73.9, 63.0, 40.0, 29.2, 18.8; IR (film) υ (cm^{-1}) 3359, 1670; MS (CI) *m/z* (%) 230 (100), 212 (83), 211 (53), 146 (34); HRMS calculated for $C_{14}H_{15}NO_2{\cdot}H^+$ 230.1181, found 230.1191.

4.10.2. Synthesis of (±)-(8S,8aR)-8-hydroxy-8-(4-methoxyphenyl)-1,2,8,8a-tetrahydroindolizin-3(5H)-one (syn)-9b. According to the typical procedure indolizidinone **(syn)-9b** was obtained from **(syn)-7b** in 65% yield. It was purified by column chromatography (EtOAc) as a brown oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.23 (d, *J*=8.7, 2H), 6.85 (d, *J*=8.7, 2H), 5.94 (d, *J*=10.2, 1H), 5.79 (d, *J*=10.2, 1H), 4.46 (d, *J*=18.9, 1H), 3.77 (br s, 4H), 3.61 (d, *J*=18.9, 1H), 2.57 (br s, 1H), 1.97-1.77 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.8, 159.3, 133.7, 133.5, 131.4, 127.7, 123.5, 73.6, 63.0, 55.2, 39.9, 29.2, 18.8; IR (film) υ (cm^{-1}) 3389, 1670; MS (CI) *m/z* (%) 260 (100), 242 (99), 241 (77), 240 (41), 223 (11), 176 (53); HRMS calculated for $C_{15}H_{17}NO_3{\cdot}H^+$ 260.1286, found 260.1285.

4.10.3. Synthesis of (±)-(8S,8aR)-8-(4-chlorophenyl)-8-hydroxy-1,2,8,8a-tetrahydroindolizin-3(5H)-one (syn)-9c. According to the typical procedure indolizidinone **(syn)-9c** was obtained from **(syn)-7c** in 58% yield. It was purified by column chromatography (EtOAc) as a brown oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.36-7.27 (m, 4H), 6.00 (d, *J*=10.6, 1H), 5.80 (d, *J*=10.6, 1H), 4.51 (d, *J*=19.2, 1H), 3.78 (d, *J*=8.3, 1H), 3.63 (d, *J*=19.2, 1H), 2.33 (br s, 1H), 1.98-1.54 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.6, 159.3, 133.1, 131.4, 128.3, 128.0, 124.3, 63.0, 40.0, 29.1, 18.7; IR (film) υ (cm^{-1}) 3387, 1670; MS (CI) *m/z* (%) 264 (100), 248 (36), 246 (40); HRMS calculated for $C_{14}H_{14}{}^{35}ClNO_2{\cdot}H^+$ 264.0791, found 264.0804.

4.10.4. Synthesis of (±)-(8S,8aR)-8-hydroxy-8-thyenyl-1,2,8,8a-tetrahydroindolizin-3(5H)-one (syn)-9d. According to the typical procedure indolizidinone **(syn)-9d** was obtained from **(syn)-7d** in 60% yield. It was purified by column chromatography (EtOAc) as a brown oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.31-7.25 (m, 1H), 7.00-6.93 (m, 1H), 6.81-6.77 (m, 1H) 6.04-5.88 (m, 2H), 4.45 (d, *J*=19.3, 1H), 3.87-3.82 (m, 1H), 3.61 (d, *J*=19.3, 1H), 3.12 (br s, 1H), 2.11-2.00 (m, 3H), 1.41-1.31 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 175.0, 144.8, 133.7, 127.3, 126.2, 125.4, 123.6, 73.3, 62.6, 39.9, 29.0, 19.0; IR (film) υ (cm^{-1}) 3330, 1670; MS (CI) *m/z* (%) 236 (100), 218 (89), 217 (64), 152 (60); HRMS calculated for $C_{12}H_{13}NO_2S{\cdot}H^+$ 236.0745, found 236.0741.

4.10.5. Synthesis of (±)-(8R,8aR)-8-hydroxy-8-phenyl-1,2,8,8a-tetrahydroindolizin-3(5H)-one (anti)-9a. According to the typical procedure indolizidinone **(anti)-9a** and **(syn)-9a** were obtained from a syn/anti (33/67) mixture of **7a** in 66% combined yield. It was purified by column chromatography (EtOAc) as a brown oil. Only the data for the **(anti)-9a** isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.43-7.30 (m, 5H), 6.01 (s, 2H), 3.79 (d, *J*=7.7, 1H), 3.73-3.69 (dd, *J*=3.7, 2H), 3.42 (br s, 1H), 2.58-2.14 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 175.5, 142.8, 132.6, 128.0 127.6, 126.6, 123.3, 71.6, 64.0, 40.1, 30.3, 17.3.

4.10.6. Synthesis of (±)-(8R,8aR)-8-hydroxy-8-(4-methoxyphenyl)-1,2,8,8a-tetrahydroindolizin-3(5H)-one (anti)-9b. According to the typical procedure indolizidinone **(anti)-9b** and **(syn)-9b** were obtained from a syn/anti (53/47) mixture of **7b** in 60% combined yield. It was purified by column chromatography (EtOAc) as a brown oil. Only the data for the **(anti)-9b** isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.23 (d, *J*=8.7, 2H), 6.85 (d, *J*=8.7, 2H), 5.98 (s, 2H), 4.46 (d, *J*=18.9, 1H), 3.80 (br s, 4H), 3.61 (d, *J*=18.9, 1H), 2.57 (br s, 1H), 1.97-1.77 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 175.4, 158.8, 134.9, 133.7, 132.9, 126.8, 126.5, 71.5, 63.9, 55.3, 40.0, 30.3, 17.4.

4.10.7. Synthesis of (±)-(8R,8aR)-8-(4-chlorophenyl)-8-hydroxy-1,2,8,8a-tetrahydroindolizin-3(5H)-one (anti)-9c. According to the typical procedure indolizidinone **(anti)-9c** and **(syn)-9c** were obtained from a syn/anti (41/49) mixture of **7c** in 65% combined yield. It was purified by column chromatography (EtOAc) as a brown oil. Only the data for the **(anti)-9c** isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.36-7.27 (m, 4H), 6.09 (s, 2H), 4.51 (d, *J*=19.2, 1H), 3.78 (d, *J*=8.3, 1H), 3.63 (d, *J*=19.2, 1H), 2.33 (br s, 1H,), 1.98-1.54 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 175.4, 159.6, 134.9, 133.6, 132.9, 129.1, 128.3, 123.2, 63.9, 40.0, 30.2, 18.7.

4.10.8. Synthesis of (±)-(8R,8aR)-8-hydroxy-8-thyenyl-1,2,8,8a-tetrahydroindolizin-3(5H)-one (anti)-9d. According to the typical procedure indolizidinone **(anti)-9d** and **(syn)-9d** were obtained from a syn/anti (38/62) mixture of **7c** in 69% combined yield. It was purified by column chromatography (EtOAc) as a brown oil. Only the data for the **(anti)-9d** isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.31-7.25 (m, 1H), 7.00-6.93 (m, 1H), 6.81-6.77 (m, 1H) 6.92 (s, 2H), 4.45 (d, *J*=19.3, 1H), 3.87-3.82 (m, 1H), 3.61 (d, *J*=19.3, 1H), 3.12 (br s, 1H), 2.11-2.00 (m, 3H), 1.41-1.31 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 175.4, 147.4 132.71, 127.1, 126.8, 125.1, 123.4, 71.3, 63.7, 40.0, 29.5, 18.0.

4.11. Typical procedure for the olefin metathesis reaction on pyrrolidinones 6.

4.11.1. Synthesis of (±)-(8R,8aR)-8-hydroxy-1,2,8,8a-tetrahydroindolizin-3(5H)-one (syn)-8. Grubbs II catalyst (3 mg, 10% wt) was added in one portion onto a solution of pyrrolidinone **(syn)-6** (90 mg, 0.35 mmol) in toluene (10 mL) and temperature was raised to reflux. After 4 h, the mixture was cooled to rt and solvent was eliminated under vacuum. The resulting residue was column chromatographed (EtOAc) to afford indolizidinone **(syn)-8** as a white solid that was triturated in hexanes (71%): mp 111-113 ºC (hexanes); ^{1}H NMR ($CDCl_3$) δ (ppm) 6.83 (d, *J*=7.0, 1H), 4.96 (dd, *J*=11.9, 5.9, 1H), 3.98 (s, 1H), 3.76 (dd, *J*=16.1, 8.0, 1H), 2.51-1.95 (m, 7H); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.7, 121.8, 105.0, 63.4, 58.9, 31.6, 30.7, 20.1; IR υ (cm^{-1}) 3359, 1670; MS [CI] *m/z* (%) 154 (100), 153 (37), 136 (12); HRMS calculated for $C_8H_{11}NO_2{\cdot}H^+$ 154.0868, found 154.0866.

4.11.2. Synthesis of (±)-(8S,8aR)-8-hydroxy-1,2,8,8a-tetrahydroindolizin-3(5H)-one (anti)-8. According to the typical procedure indolizidinone **(anti)-8** was obtained from **(anti)-6** in 86% combined yield. It was purified by column chromatography (EtOAc) as a brown oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 6.72 (d, *J*=7.5, 1H), 5.05-5.00 (m, 1H), 3.68-3.60 (m, 1H), 3.54-3.45 (m, 1H), 2.97 (br s, 1H), 2.45-1.39 (m, 4H), 2.20-2.11 (m, 1H), 1.83-1.76 (m, 1H).; ^{13}C NMR ($CDCl_3$) δ (ppm) 171.9, 121.2, 107.2, 70.4, 60.4, 32.5, 31.1, 24.3.

4.12. Typical procedure for the hydrogenation reaction.

4.12.1. Synthesis of (±)-(8R,8aR)-8-hydroxy-hexahydroindolizin-3(5H)-one (syn)-10. A solution of indolizidine (**syn**)**-8** (37 mg, 0.24 mmol) in MeOH (5 mL) was hydrogenated (70 psi) in the presence of Pd/C (4 mg, 10% weight) until total consumption of the starting material (tlc, 8 h). Then, the mixture was filtered through celite, the solvent evaporated, and the resulting residue was column chromatographed (EtOAc) to yield indolizidinone (**syn**)**-10** as a colorless oil (46%): ^{1}H NMR (MeOD) δ (ppm) 4.11 (d, *J*=12.6, 1H), 3.81 (s, 1H), 3.53 (t, *J*=12.6, 6.3, 1H), 2.65 (t, *J*=22.9, 10.2, 1H), 2.40-1.24 (m, 9H); ^{13}C NMR (MeOD) δ (ppm) 174.7, 66.5, 60.9, 39.9, 30.8, 30.4, 19.3, 17.7; IR υ (cm^{-1}) 3379, 1660; MS [CI] *m/z*: 156 (100), 155 (17), 138 (13); HRMS calculated for $C_8H_{13}NO_2{\cdot}H^+$ 156.1025, found 156.1024.

4.12.2. Synthesis of (±)-(8R,8aR)-8-hydroxy-8-phenyl-hexahydroindolizin-3(5H)-one (syn)-11a. According to the typical procedure indolizidinone **(syn)-11a** was obtained from **(syn)-9a** in 60% yield. It was purified as a white solid by column chromatography (MeOH) followed by crystallization from Et_2O: mp 144-148 ºC (Et_2O): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.47 (d, *J*=7.4, 2H), 7.35-7.26 (m, 3H), 4.22 (d, *J*=13.1, 1H), 3.71 (t, *J*=8.3, 1H), 2.85-2.77 (m, 1H), 2.74 (s, 1H), 2.41-2.04 (m, 4H), 1.92-1.64 (m, 4H); ^{13}C NMR (MeOD) δ (ppm) 184.5, 143.7, 128.0, 127.9, 126.3, 73.6, 67.4, 40.8, 40.4, 31.1, 21.4, 19.8; IR (film) υ (cm^{-1}) 3379, 1663; MS (CI) *m/z* (%) 232 (100), 214 (47), 213 (28); HRMS calculated for $C_{14}H_{17}NO_2{\cdot}H^+$ 232.1337, found 232.1343.

4.12.3. Synthesis of (±)-(8R,8aR)-8-hydroxy-8-(4-methoxyphenyl)-hexahydroindolizin-3(5H)-one (syn)-11b. According to the typical procedure indolizidinone **(syn)-11b** was obtained from **(syn)-9b** in 63% yield. It was purified as a yellowish oil by column chromatography (EtOAc): ^{1}H NMR (MeOD) δ (ppm) 7.37 (d, *J*=8.9, 2H), 6.88 (d, *J*=8.9, 2H), 4.10 (d, *J*=13.2, 1H), 3.77-3.71 (m, 4H), 2.91-2.81 (m, 1H), 2.40-1.69 (m, 8H); ^{13}C NMR (MeOD) δ (ppm) 176.6, 160.0, 136.6, 128.8, 114.4, 73.7, 67.7, 56.7, 41.0, 40.5, 31.1, 21.6, 19.7; IR (film) υ (cm^{-1}) 3379, 1660; MS (CI) *m/z* (%) 262 (67), 244 (100), 243 (49); HRMS calculated for $C_{15}H_{19}NO_3{\cdot}H^+$ 262.1443, found 262.1455.

4.12.4. Synthesis of (±)-(8R,8aR)-8-(4-chlorophenyl)-8-hydroxy-hexahydroindolizin-3(5H)-one (syn)-11c. According to the typical procedure indolizidinone **(syn)-11c** was obtained from **(syn)-9c** in 53% yield. It was purified as a brownish oil by column chromatography (EtOAc): ^{1}H NMR (MeOD) δ (ppm) 7.44 (d, *J*=8.7, 2H), 7.33 (d, *J*=8.7, 2H), 4.14-4.10 (m, 1H), 3.80-3.73 (m, 1H), 2.90-2.83 (m, 1H), 2.39-1.69 (m, 8H); ^{13}C NMR (MeOD) δ (ppm) 176.7, 144.8, 134.0, 129.4, 129.1, 73.6, 67.4, 40.8, 40.5, 31.1, 21.4, 19.8; IR (film) υ (cm^{-1}) 3379, 1660; MS (CI) *m/z* (%) 266 (100), 250 (10), 248 (19); HRMS calculated for $C_{14}H_{16}{}^{35}ClNO_2{\cdot}H^+$ 266.0948, found 266.0948.

4.12.5. Synthesis of (±)-(8R,8aR)-8-hydroxy-8-(2-thyenyl)-hexahydroindolizin-3(5H)-one (syn)-11d. According to the typical procedure indolizidinone **(syn)-11d** was obtained from **(syn)-11d** in 56% yield. It was purified as a yellowish oil by column chromatography (EtOAc): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.26-7.18 (m, 1H), 6.95-6.87 (m, 1H), 4.17-4.13 (m, 1H), 3.61-3.56 (m, 1H), 3.75-2.67 (m, 1H), 2.28-1.66 (m, 9H); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.8, 146.3, 126.8, 124.3, 123.7, 73.9, 66.0, 39.4, 39.1, 30.1, 21.0, 18.1; IR (film) υ (cm^{-1}) 3334, 1660;

MS (CI) *m/z* (%) 238 (100), 222 (14), 220 (48), 219 (23); HRMS calculated for $C_{12}H_{15}{}^{32}SNO{\cdot}H^+$ 238.0902, found 238.0913.

4.12.6. Synthesis of (±)-(8S,8aR)-8-hydroxy-8-phenyl-hexahydroindolizin-3(5H)-one (anti)-11a. According to the typical procedure indolizidinone **11a** was obtained as a diastereomeric mixture from (33/67) **(syn/anti)-9a** in 69% combined yield. It was purified as a yellowish oil by column chromatography (EtOAc). Data for the anti isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.47 (d, *J*=7.4, 2H), 7.33-7.25 (m, 3H), 4.21 (d, *J*=13.1, 1H), 3.70 (t, *J*=8.3, 1H), 2.86-2.76, 2.74 (s, 2H), 2.41-2.04 (m, 4H), 1.90-1.63 (m, 4H); ^{13}C NMR (MeOD) δ (ppm) 184.4, 143.7, 128.1, 127.9, 126.8, 73.6, 67.5, 40.9, 40.3, 31.3, 21.4, 19.8.

4.12.7. Synthesis of (±)-(8S,8aR)-8-hydroxy-8-(4-methoxyphenyl)-hexahydroindolizin-3(5H)-one (anti)-11b. According to the typical procedure indolizidinone **11b** was obtained as a diastereomeric mixture from (53/47) **(syn/anti)-9b** in 67% combined yield. It was purified as a yellowish oil by column chromatography (EtOAc). Data for the anti isomer is now reported: ^{1}H NMR (MeOD) δ (ppm) 7.36 (d, *J*=8.9, 2H), 6.89 (d, *J*=8.9, 2H), 4.11 (d, *J*=13.2, 1H), 3.75-3.71 (m, 4H), 2.91-2.83 (m, 1H), 2.38-1.65 (m, 8H); ^{13}C NMR (MeOD) δ (ppm) 176.5, 160.0, 135.6, 128.8, 114.3, 73.6, 67.5, 56.7, 40.9, 40.5, 32.1, 21.6, 19.7.

4.12.8. Synthesis of (±)-(8S,8aR)-8-(4-chlorophenyl)-8-hydroxy-hexahydroindolizin-3(5H)-one (anti)-11c. According to the typical procedure indolizidinone **11c** was obtained as a diastereomeric mixture from (41/59) **(syn/anti)-9c** in 65% combined yield. It was purified as a yellowish oil by column chromatography (EtOAc). Data for the anti isomer is now reported: ^{1}H NMR (MeOD) δ (ppm) 7.44 (d, *J*=8.7, 2H), 7.33 (d, *J*=8.7, 2H), 4.14-4.10 (m, 1H), 3.80-3.73 (m, 1H), 2.90-2.83 (m, 1H), 2.39-1.69 (m, 8H); ^{13}C NMR (MeOD) δ (ppm) 176.7, 143.7, 134.0, 129.3, 128.1, 73.8, 67.5, 40.9, 40.4, 31.1, 21.4, 19.8.

4.12.9. Synthesis of (±)-(8S,8aR)-8-hydroxy-8-(2-thyenyl)-hexahydroindolizin-3(5H)-one (anti)-11d. According to the typical procedure indolizidinone **11d** was obtained as a diastereomeric mixture from (38/62) **(syn/anti)-9c** in 68% combined yield. It was purified as a yellowish oil by column chromatography (EtOAc). Data for the anti isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.40-7.37 (m, 1H), 6.93-6.90 (m, 1H), 6.87-6.83 (m, 1H), 3.85-3.80 (m, 1H), 3.39-3.23 (m, 2H), 2.23-1.43 (m, 9H); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.8, 146.2, 126.6, 124.3, 123.7, 74.0, 66.1, 39.3, 39.2, 30.1, 21.0, 18.1.

4.13. Typical procedure for the dihydroxylation reaction.

4.13.1. Synthesis of (±)-(6S,7S,8R,8aR)-6,7,8-trihydroxy-hexahydroindolizidin-3-one (syn-12). $K_2OsO_4{\cdot}2H_2O$ (7 mg, 0.015 mmol) and N-methylmorpholine-N-oxide (70 mg, 0.6 mmol) were sequentially added to 2 mL of an acetone/water (1/1) solution of indolizidinone (**syn**)-**8** (50 mg, 0.3 mmol). The mixture was stirred at room temperature for 18 hours, and then filtered through celite. The volatiles were eliminated and the residue was column chromatographed (EtOAc) to render trihydroxyindolizidinone (**syn**)-**12** as a colorless oil (93%): ^{1}H NMR (MeOD) δ (ppm) 5.48 (d, *J*=3.7, 1H), 3.94-3.64 (m, 3H), 2.49-2.29 (m, 2H), 2.11-1.87 (m, 4H); ^{13}C NMR (MeOD) δ (ppm) 177.5, 74.5, 68.2, 65.0, 57.2, 35.2, 32.5, 19.6; IR υ (cm^{-1}) 3408, 1660; HRMS calculated for $C_8H_{13}NO_4{\cdot}H^+$: 188.0923, found: 188.0915.

4.13.2. Synthesis of (±)-(6R,7S,8S,8aR)-6,7,8-trihydroxy-8-phenyl-hexahydroindolizidin-3-one (anti-13a). According to the typical procedure, indolizidine **(anti)-13a** was obtained from a 0.5/1.0 diastereomeric mixture of **(syn/anti)-9a** in 57% yield. It was purified by column chromatography (EtOAc) followed by crystallization from Et_2O: mp 183-184 ºC (Et_2O); ^{1}H NMR (MeOD) δ (ppm) 7.50-7.47 (m, 2H), 7.37-7.27 (m, 3H), 4.21-4.17 (m, 1H), 4.04-3.98 (m, 1H), 3.89-3.83 (m, 1H), 3.71 (s, 1H), 3.06-2.99 (m, 1H), 2.55-2.09 (m, 3H), 1.87-1.75 (m, 1H); ^{13}C NMR (MeOD) δ (ppm) 176.6, 142.7, 129.2, 128.5, 128.3, 78.0, 76.3, 65.4, 60.8, 40.9, 31.7, 18.6; IR (film) υ (cm^{-1}) 3408, 1658; MS (CI) *m/z* (%) 264 (100), 246 (33), 230 (33), 228 (61), 212 (26), 210 (17), 190 (12), 140 (17), 115 (13), 84 (11); HRMS calculated for $C_{14}H_{17}NO_4{\cdot}H^+$ 264.1236, found 264.1244.

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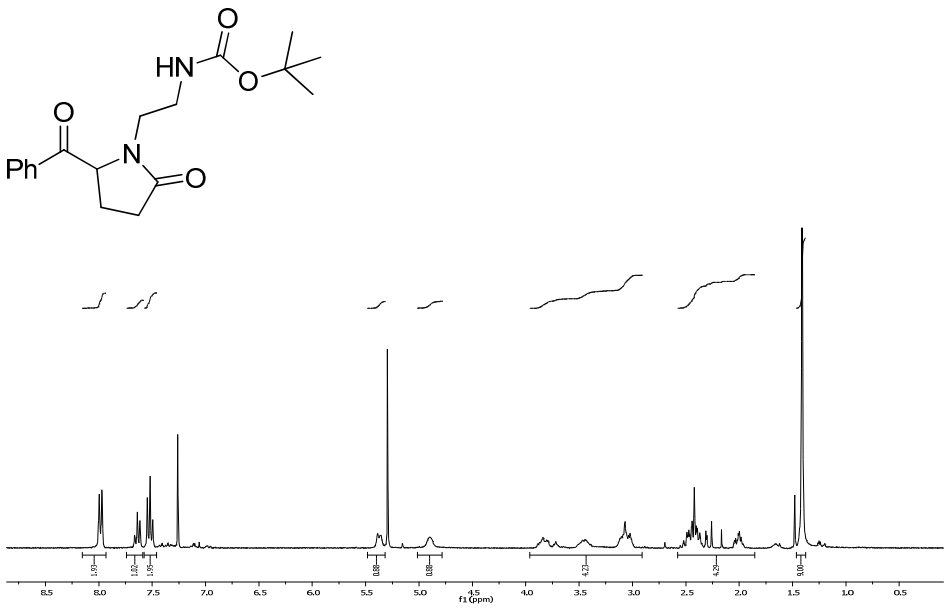
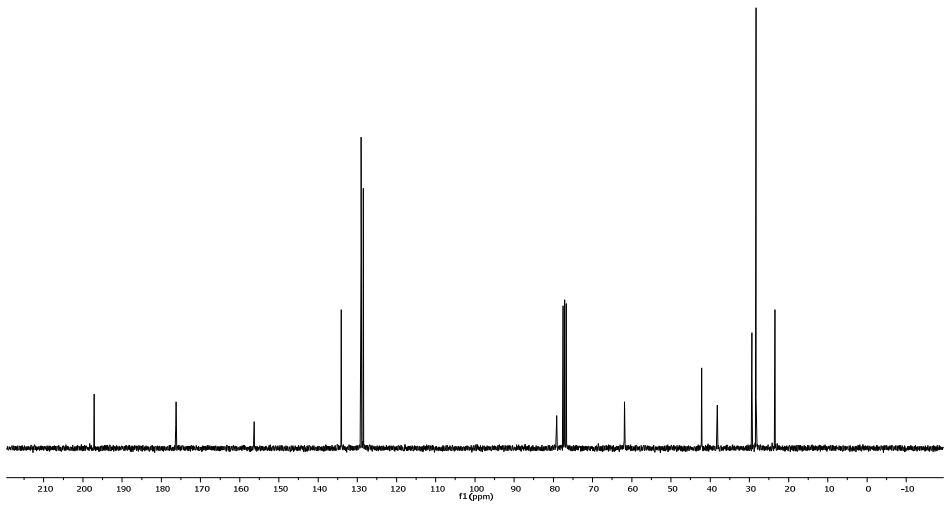
Anexo II

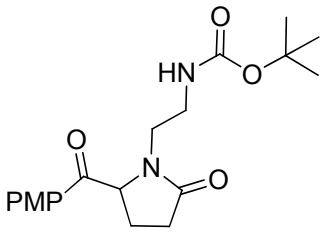
Selección de espectros representativos

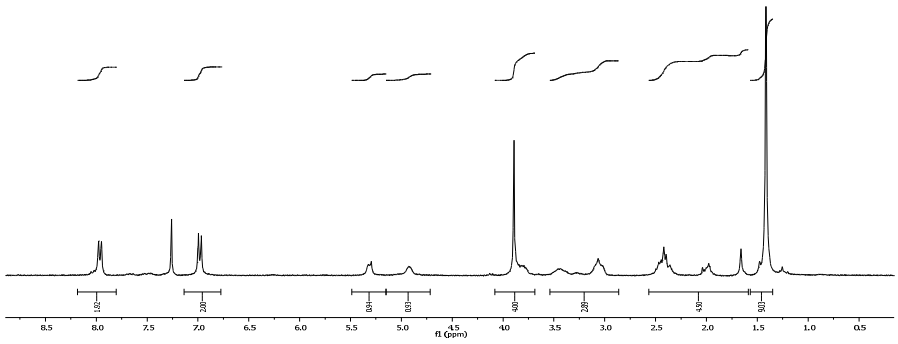
5-benzoyl-N-(2-N'-tert-butoxycarbonylaminoethyl)pyrrolidin-2-one (**9a**).

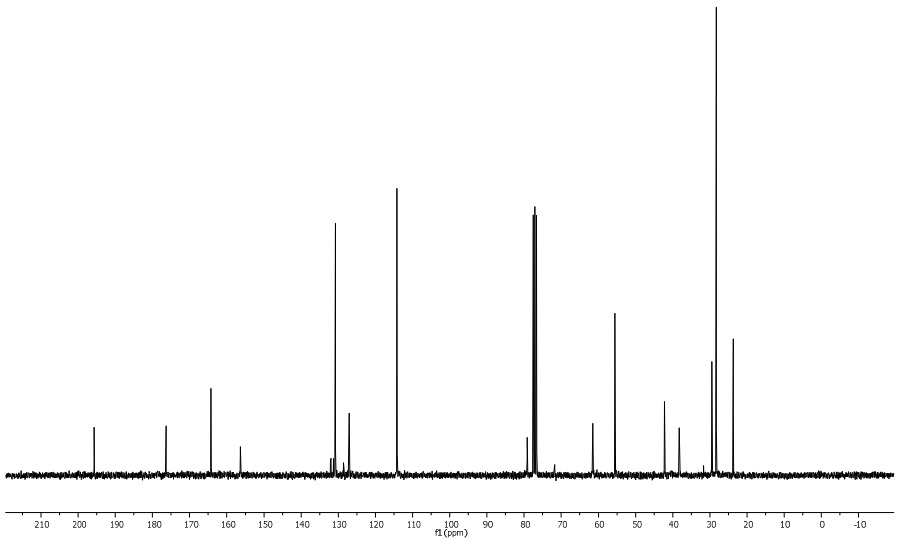




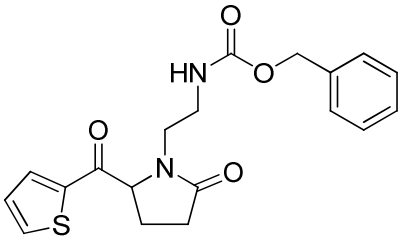
N-(2-N'-tert-butoxycarbonylaminoethyl)-5-(p-methoxybenzoyl)pyrrolidin-2-one (**10a**).

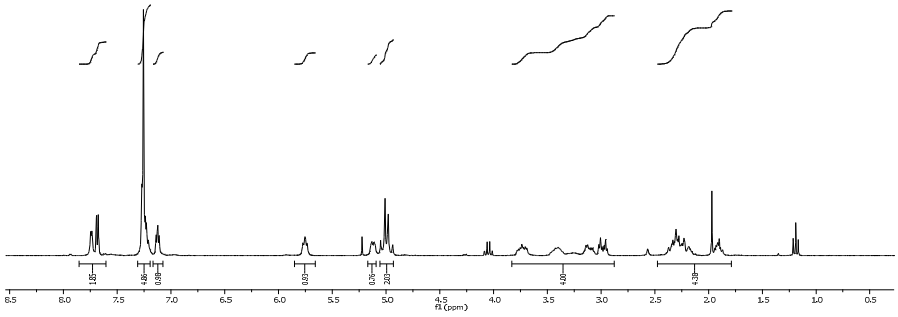


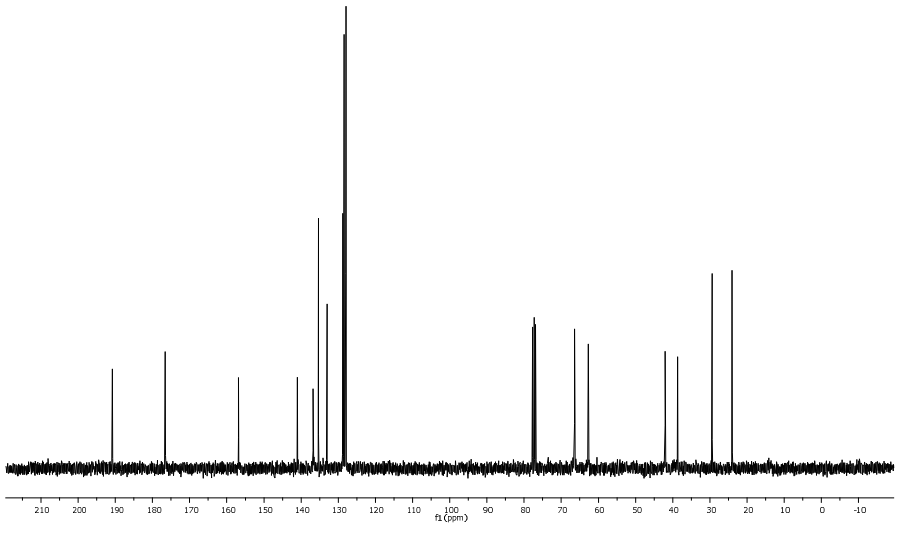




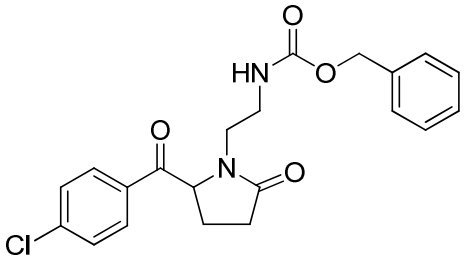
N-(2-N'-benzyloxycarbonylaminoethyl)-5-(2-thienylcarbonyl)pyrrolidin-2-one (**11b**).

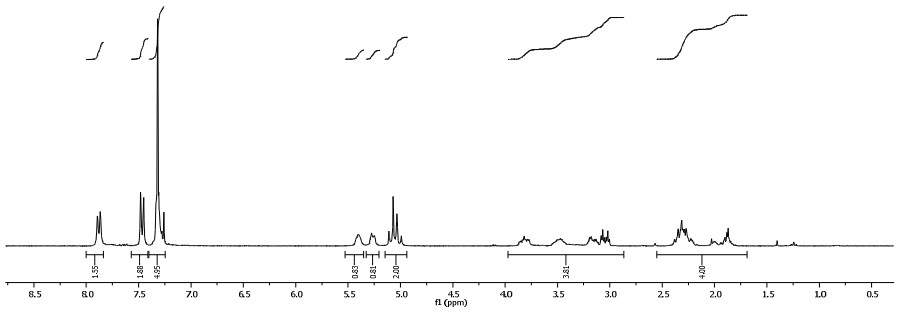


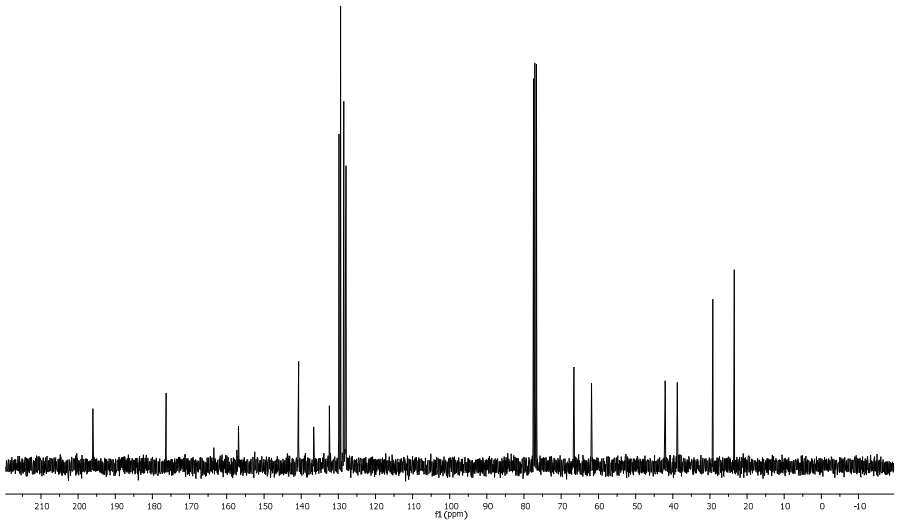




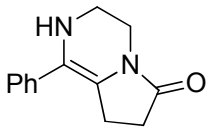
N-(2-N'-benzyloxycarbonylaminoethyl)-5-(p-chlorobenzoyl)pyrrolidin-2-one (**12b**).

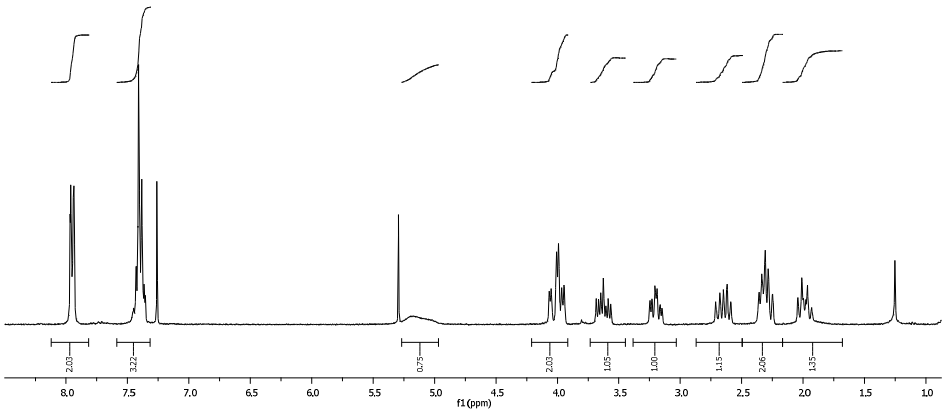


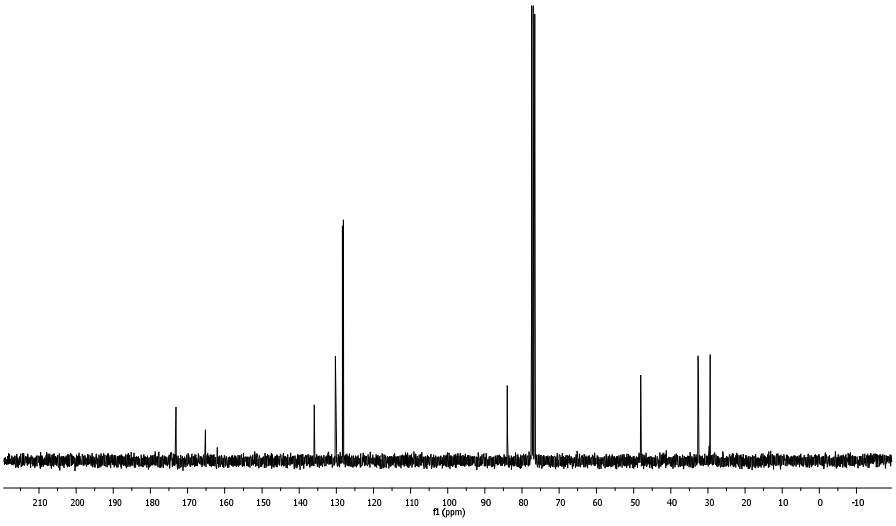




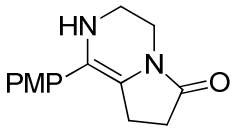
1-phenyl-3,4,7,8-tetrahydropyrrolo[1,2-a]pyrazin-6(2H)-one (**13a**).

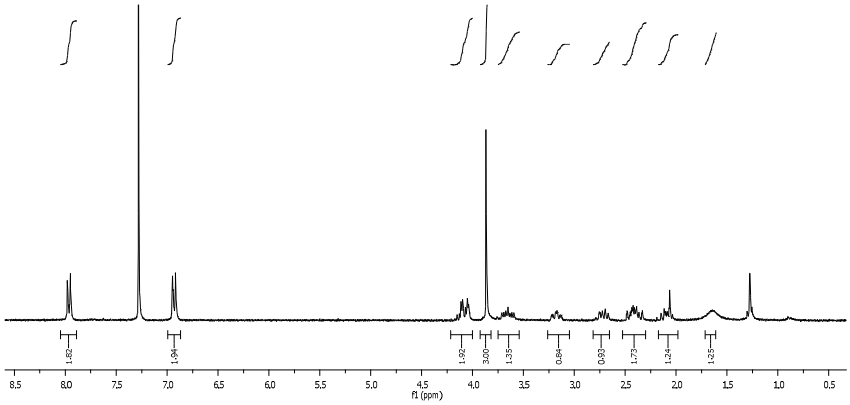


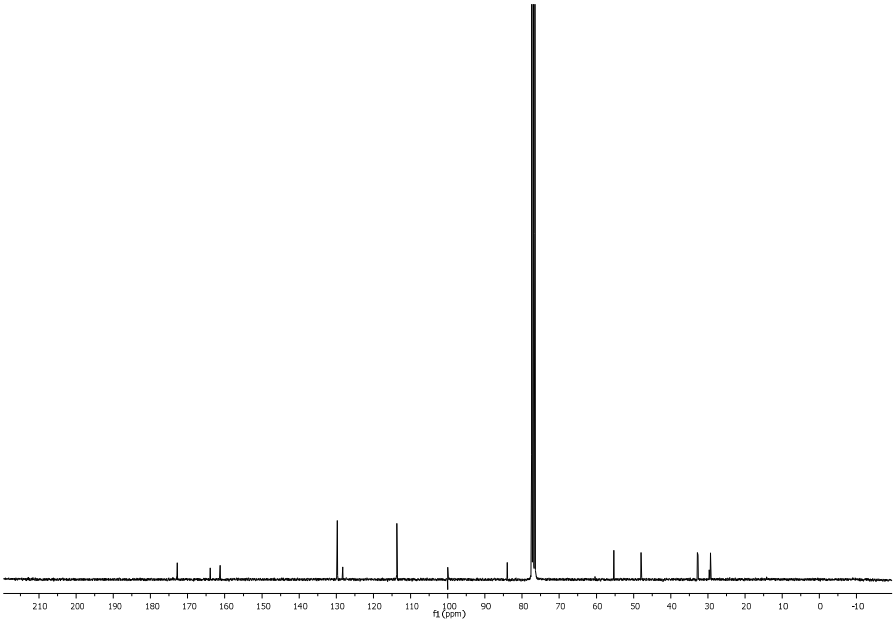




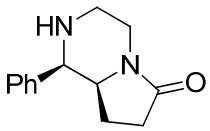
1-(4-methoxyphenyl)-3,4,7,8-tetrahydropyrrolo[1,2-a]pyrazin-6(2H)-one (**13b**).

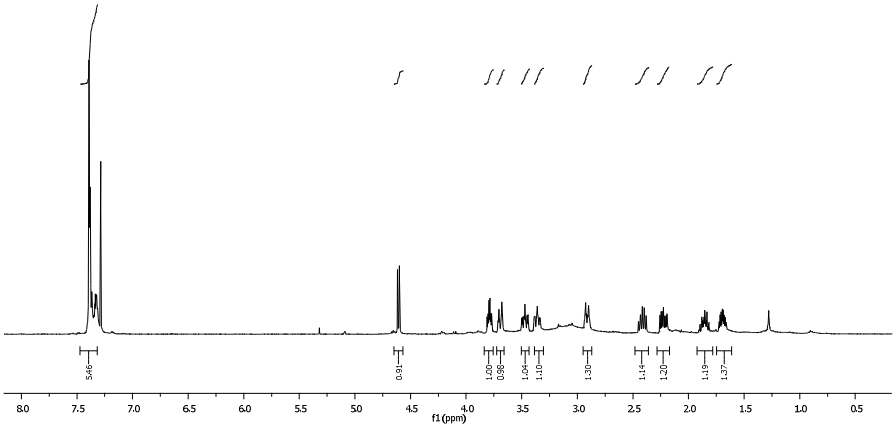


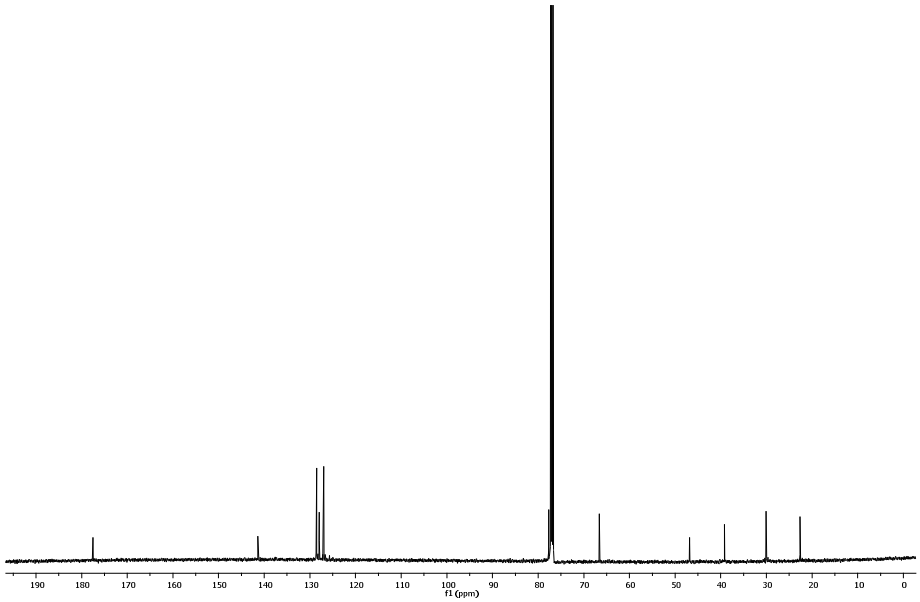




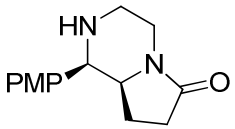
(+/-)-(1R,8aS)-1-phenylhexahydropyrrolo[1,2-a]pyrazin-6-one (**14a**).

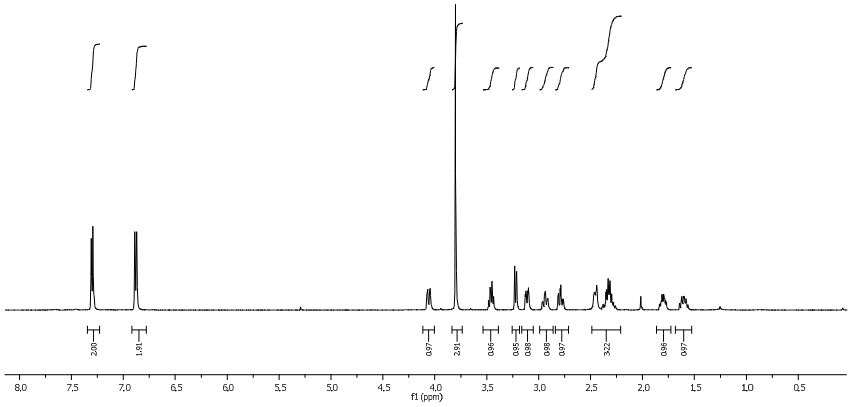


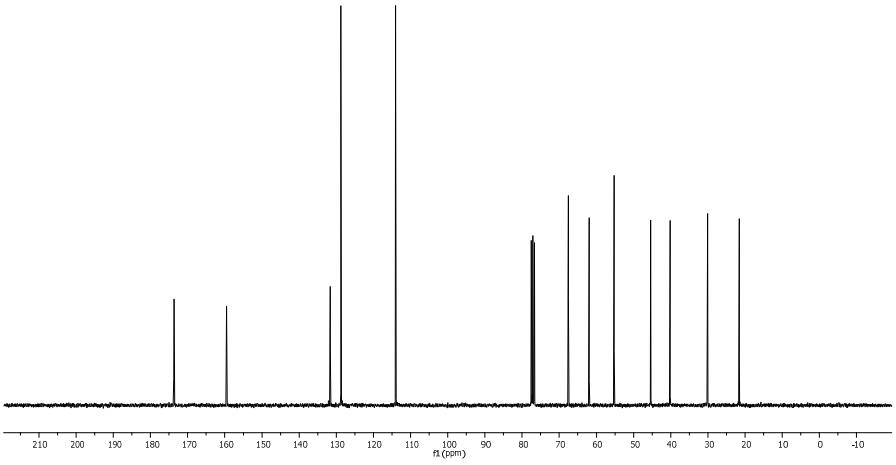




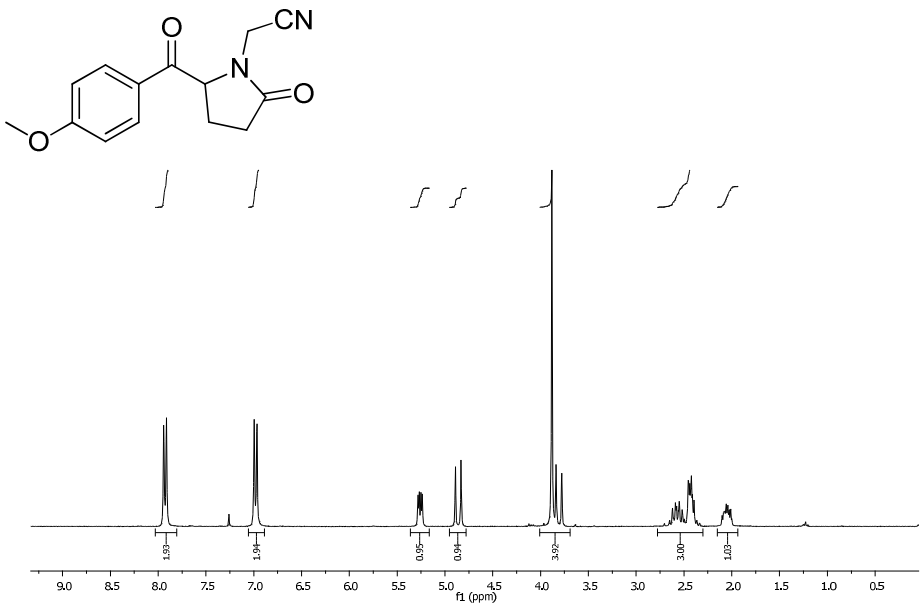
(+/-)-(1R,8aS)-1-(p-methoxyphenyl)hexahydropyrrolo[1,2-a]pyrazin-6-one (**14b**).

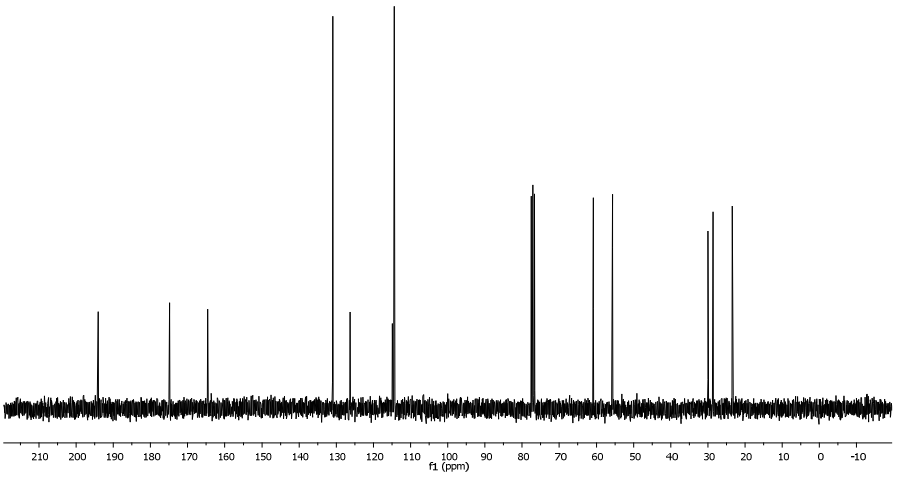




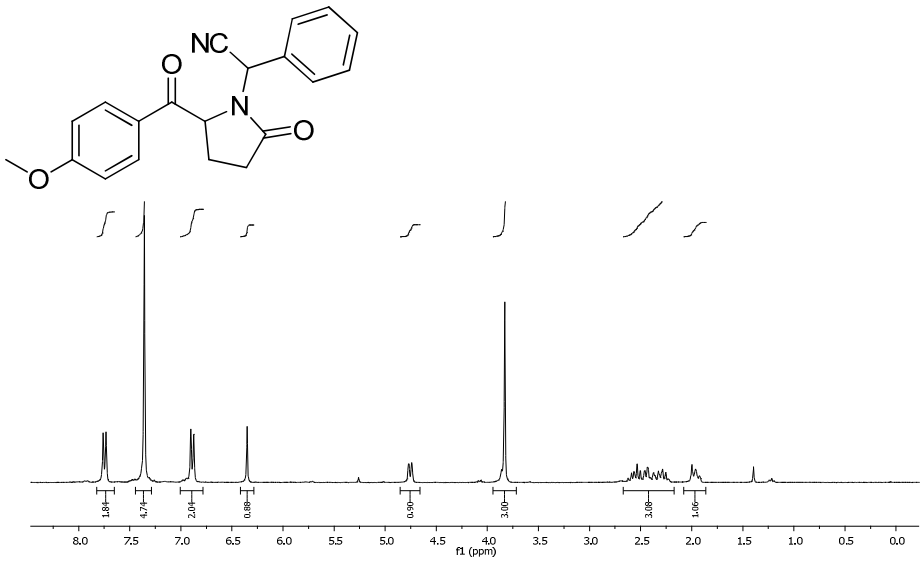


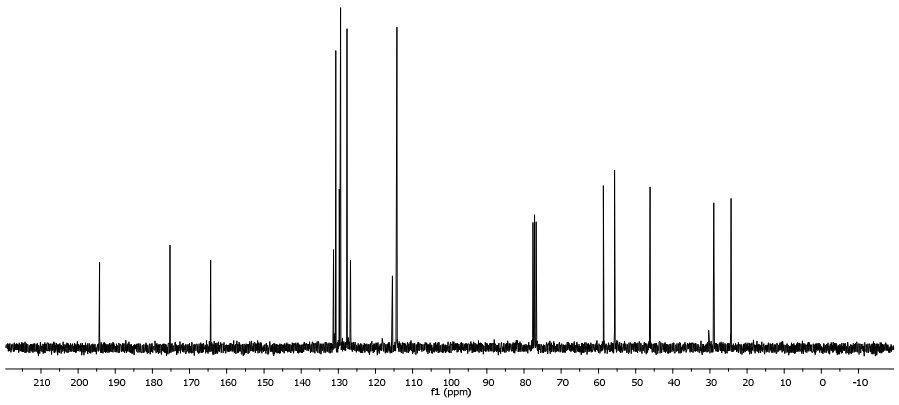
N-cyanomethyl-5-p-methoxyphenylpyrrolidinone (**18a**).



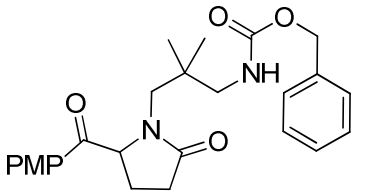


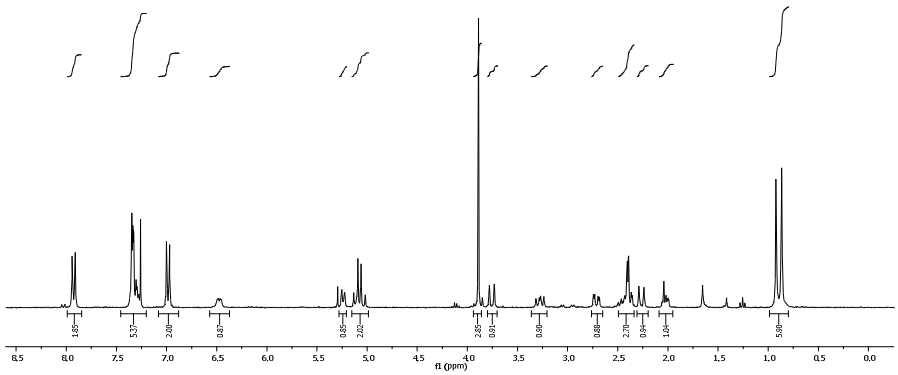
5-p-methoxyphenyl-N-(1-phenylcyanomethyl)pyrrolidin-2-one (**18b, 18c**).

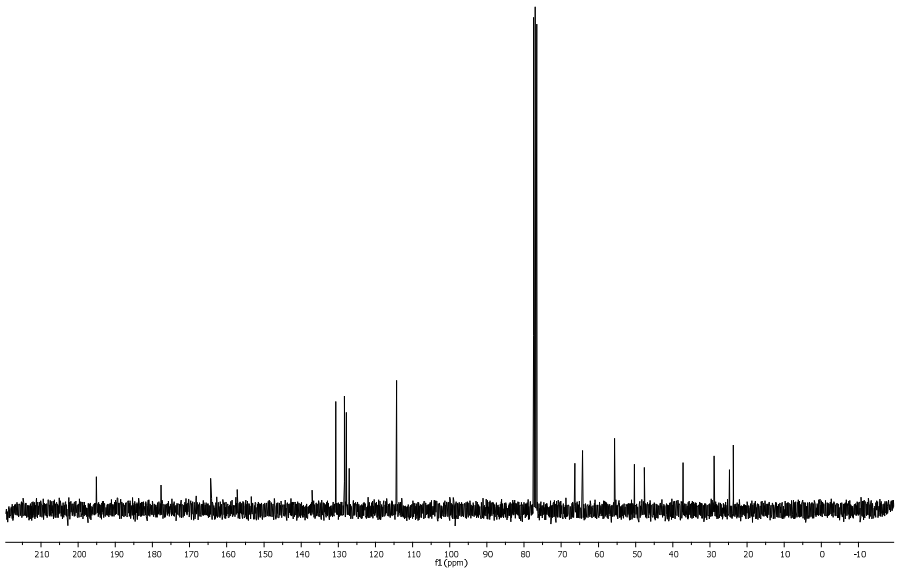




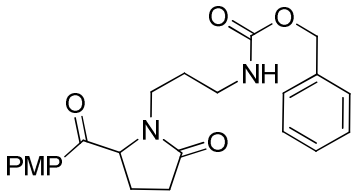
N-(3-benzyloxycarbonylamino-2,2-dimethylpropyl)-5-(4´-methoxybenzoyl)-2-pyrrolidinone (**29b**).

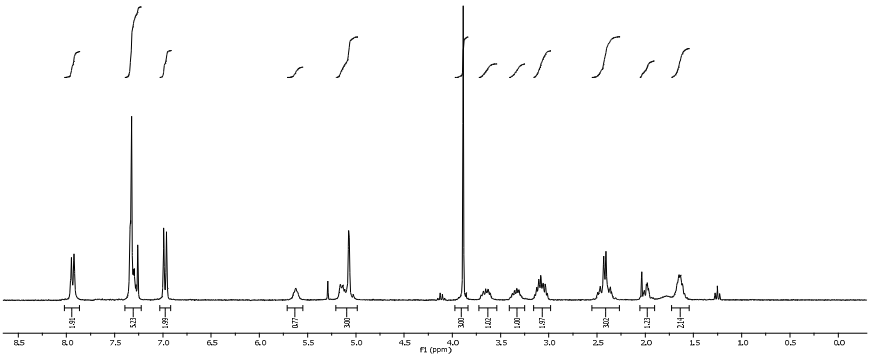


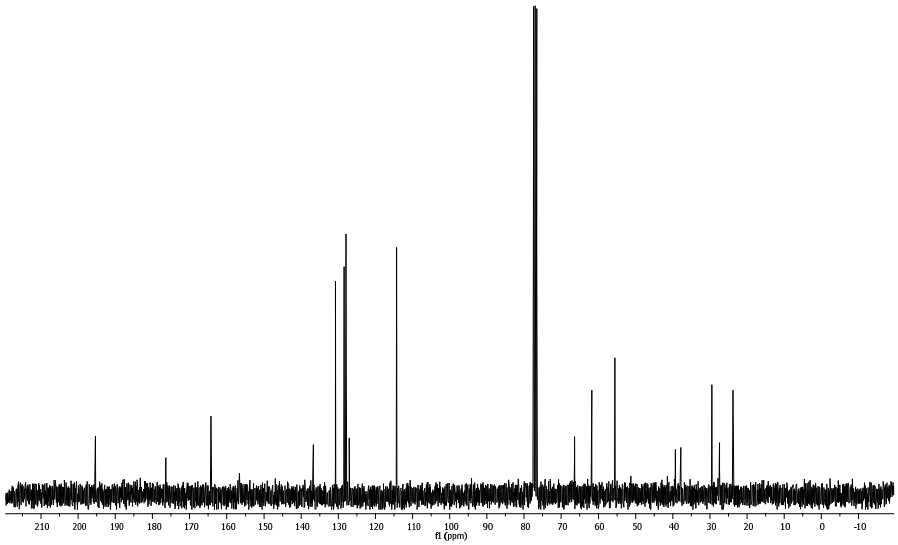




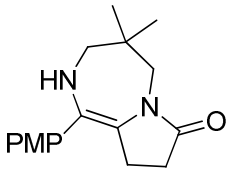
N-(3-benzyloxycarbonylaminopropyl)-5-(4´-methoxybenzoyl)-2-pyrrolidinone (**30**).

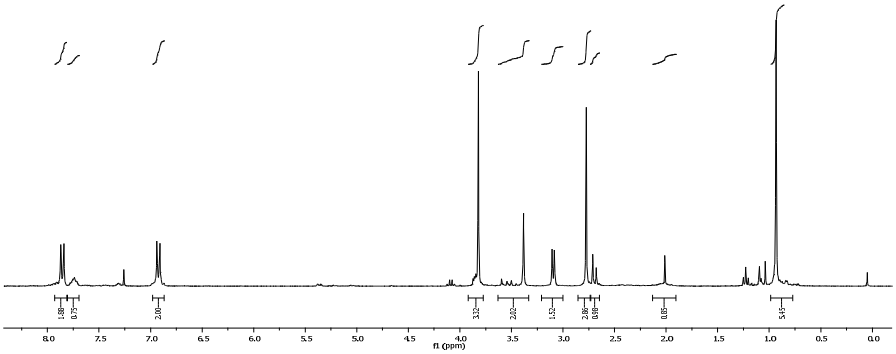


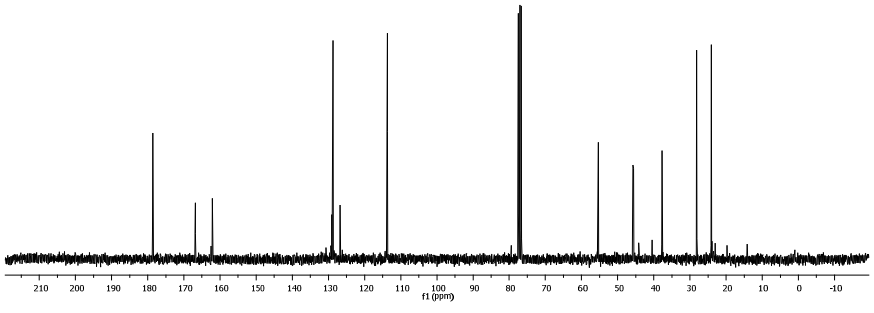




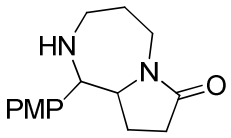
1-(4-methoxyphenyl)-4,5,8,9-tetrahydro-2H-pyrrolo[1,2-a][1,4]diazepin-7(3H)-one (**31**).

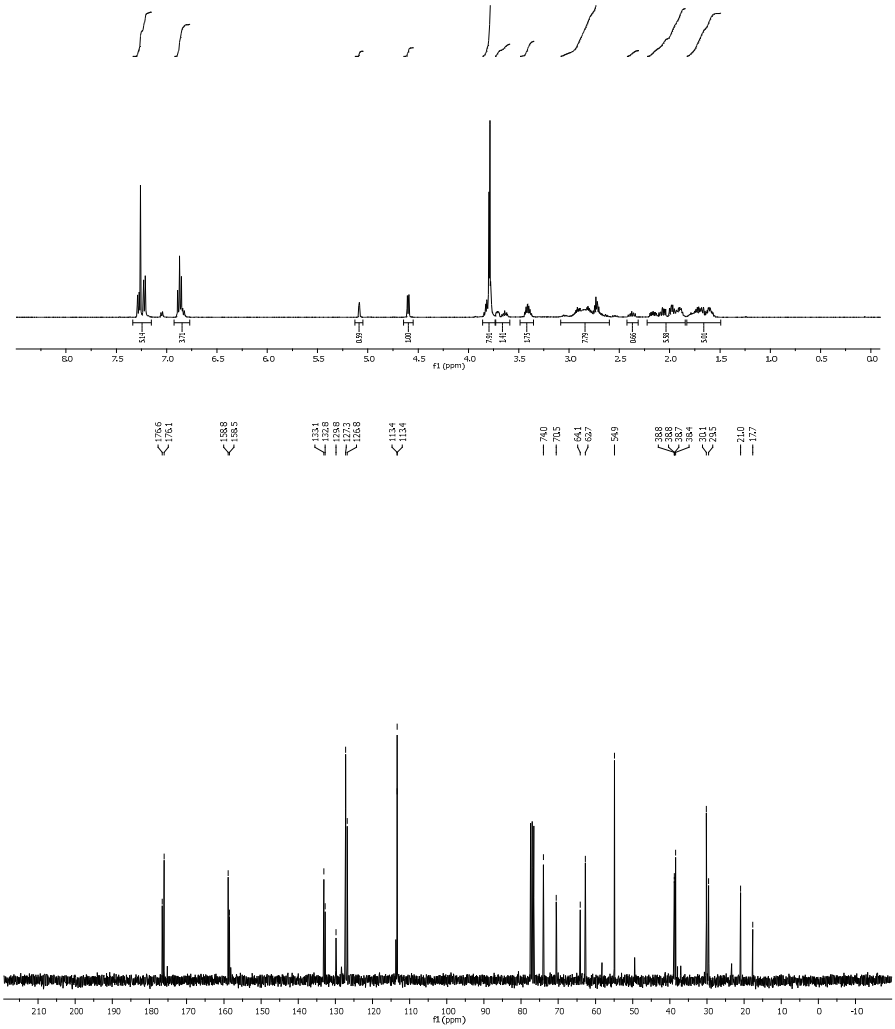




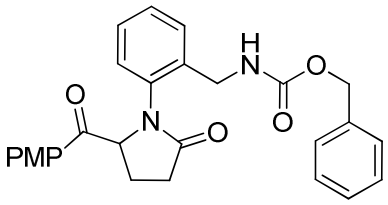


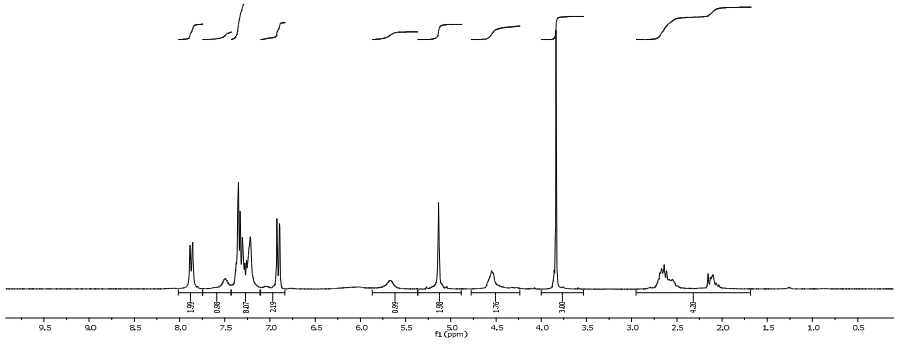
1-(4-methoxyphenyl)-octahydro-pyrrolo[1,2-a][1,4]diazepin-7-one (**33**).

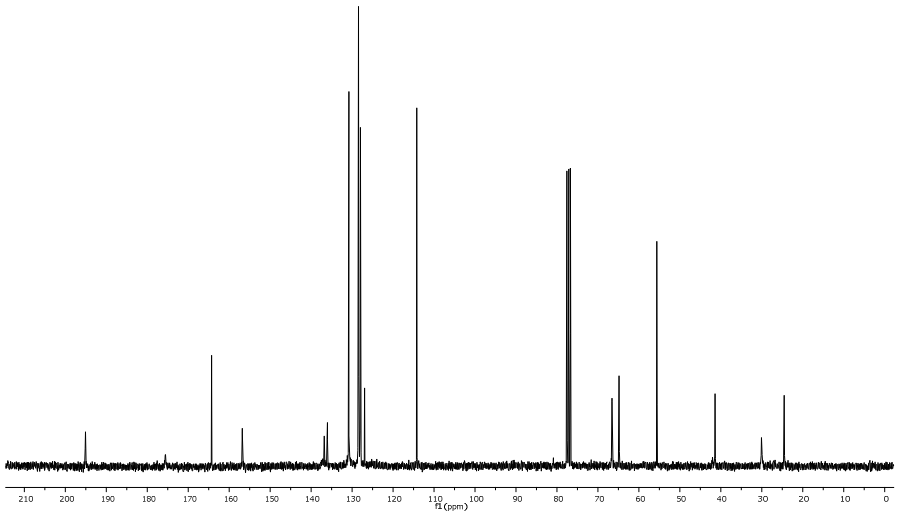




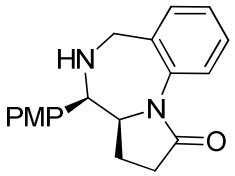
N-[(2-benzyloxycarbonylaminomethyl)phenyl]-5-(4´-methoxybenzoyl)-2-pyrrolidinone (**41**).

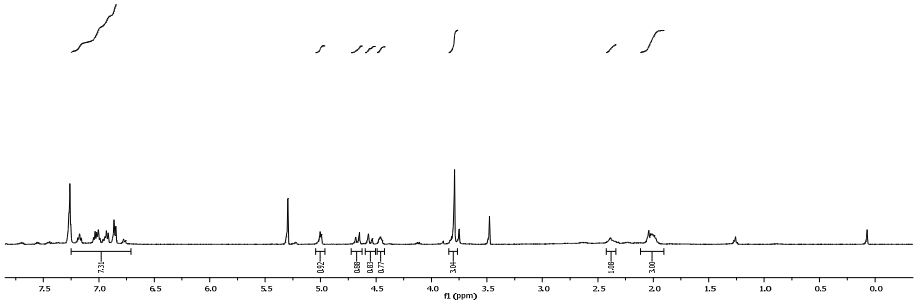


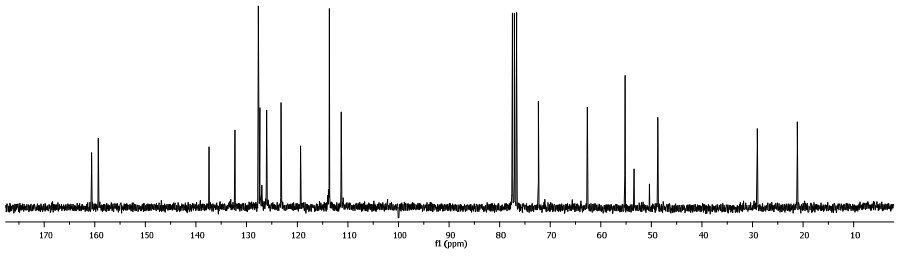




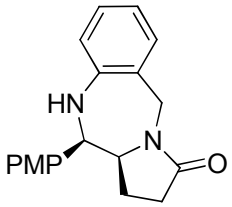
(+/-)-(4R,3aR)-(4-methoxyphenyl)-2,3,3a,4,5,6-hexahydro-benzo[f]pyrrolo[1,2-a][1,4]diazepin-1-one (**43**).

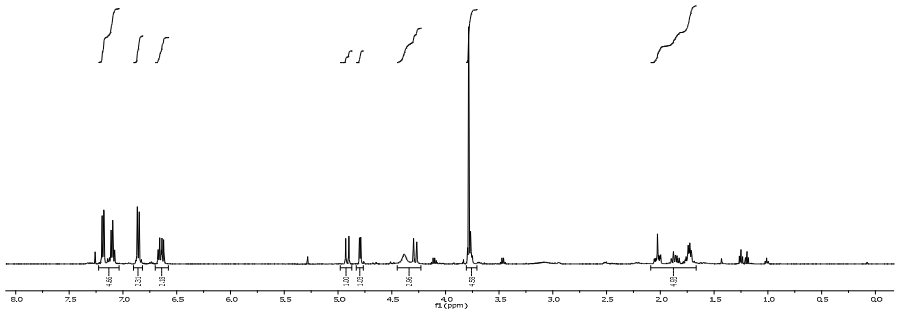


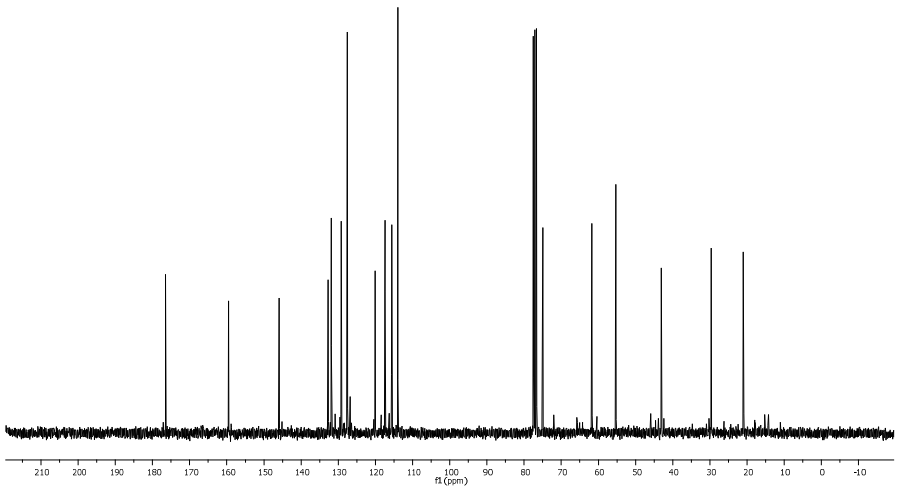




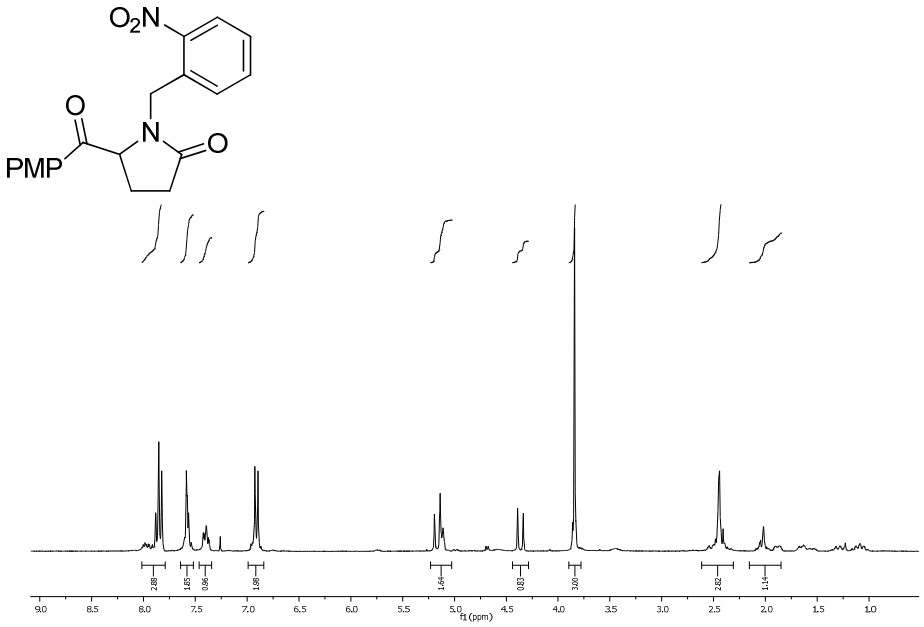
(+/-)-(11R,11aR)-11-(4-methoxyphenyl)-1,2,5,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-3-one (**44**).

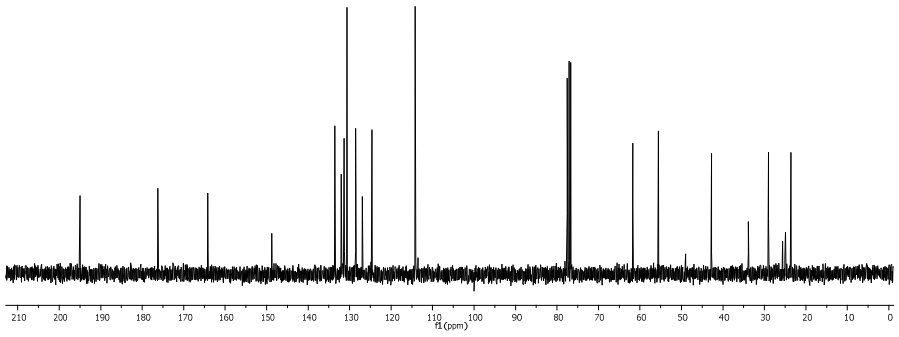




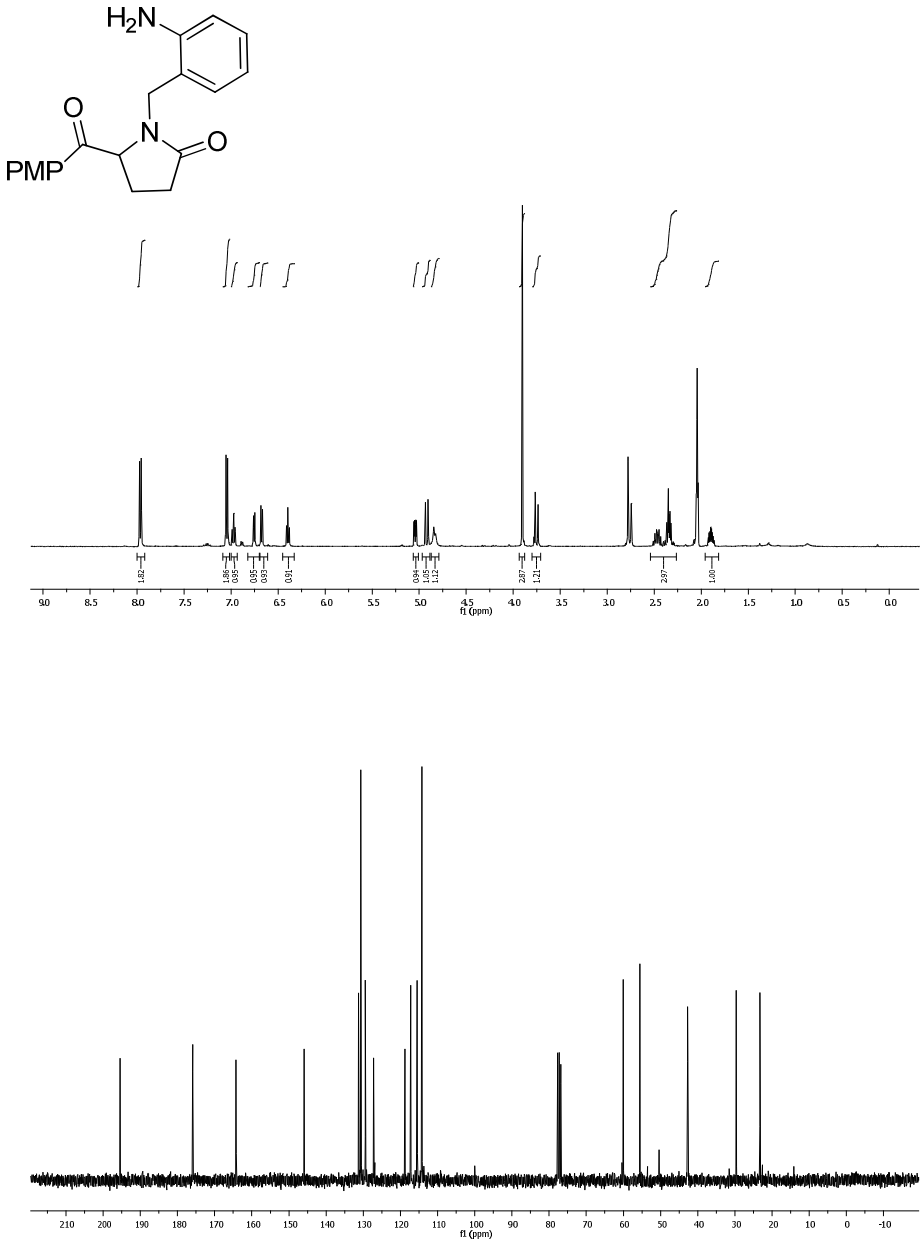


5-(4-methoxybenzoyl)-N-(2-nitrobenzyl)-2-pyrrolidinone (**48b**).

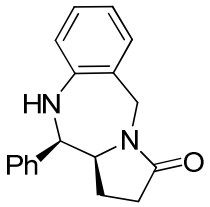


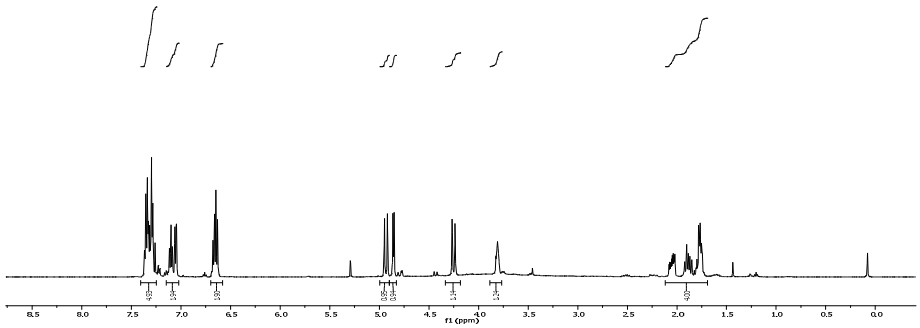


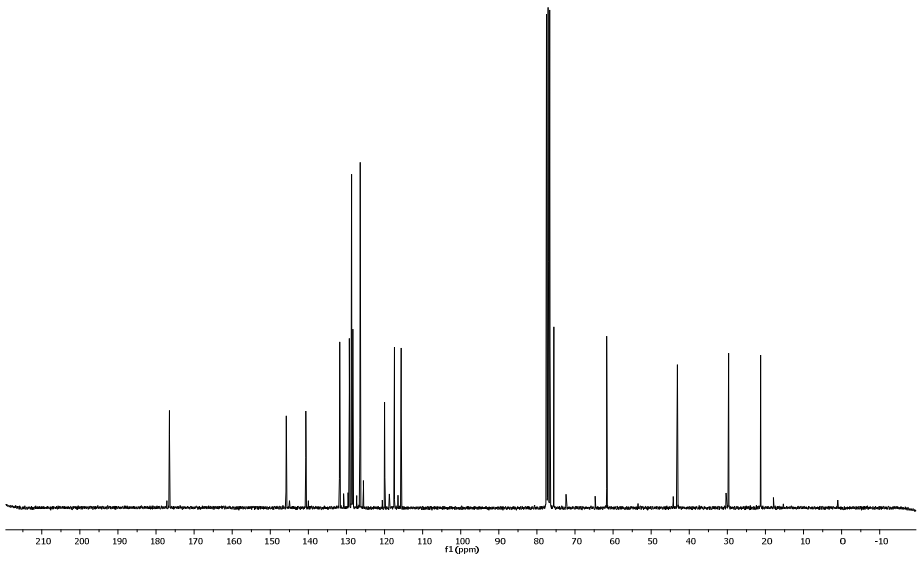
N-(2´-aminobenzyl)-5-(4-methoxybenzoyl)-2-pyrrolidinone (**49**).



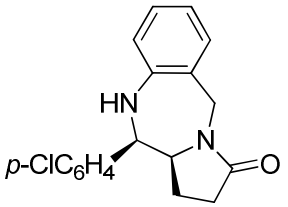
(+/-)-(11R,11aR)-11-phenyl-1,2,5,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-3-one (**50**).

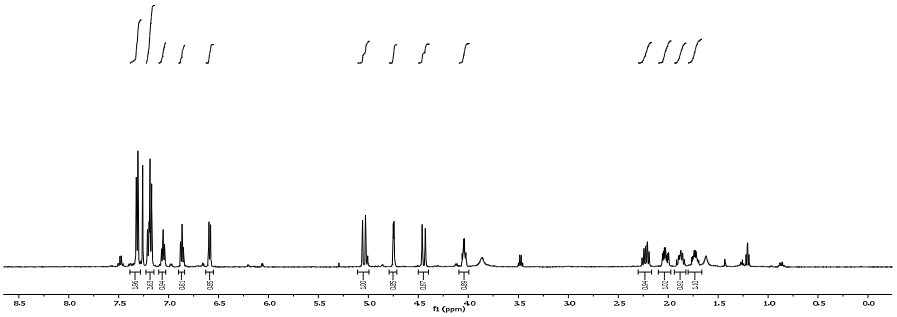


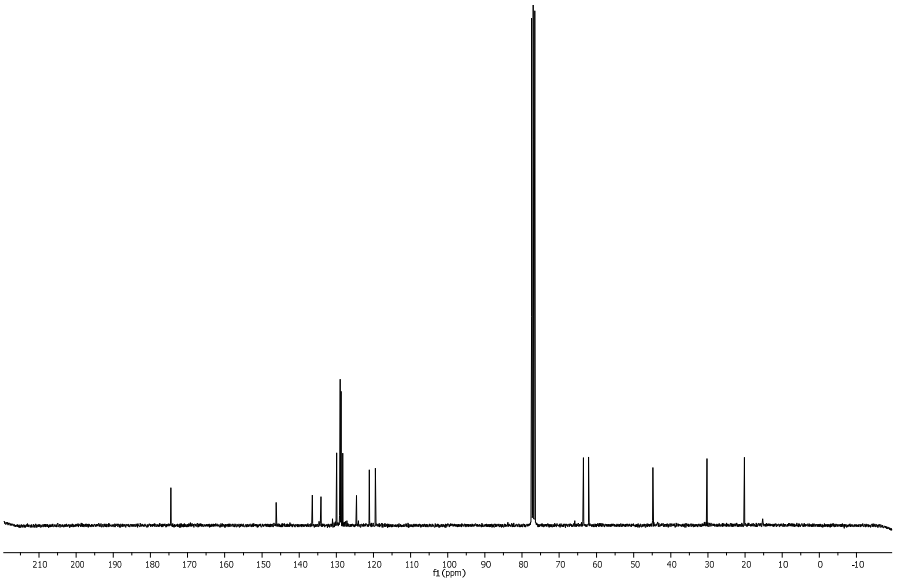




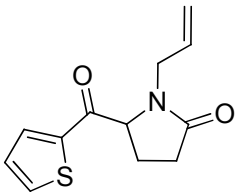
(+/-)-(11R,11aR)-11-(4-chlorophenyl)-1,2,5,10,11,11a-hexahydro-benzo[e]pyrrolo[1,2-a][1,4]diazepin-3-one (**52**).

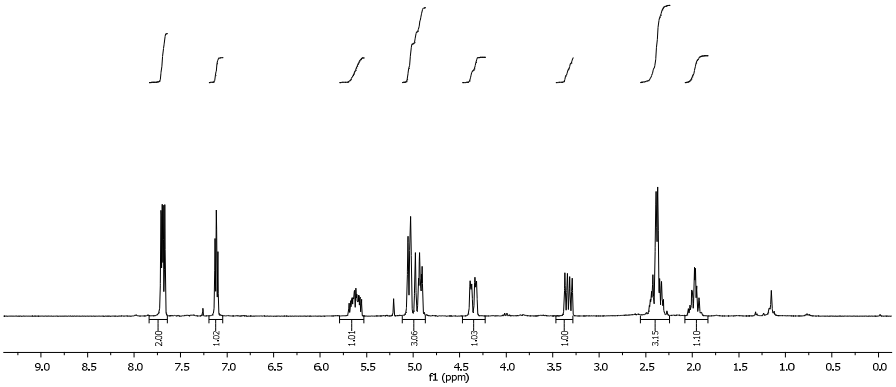


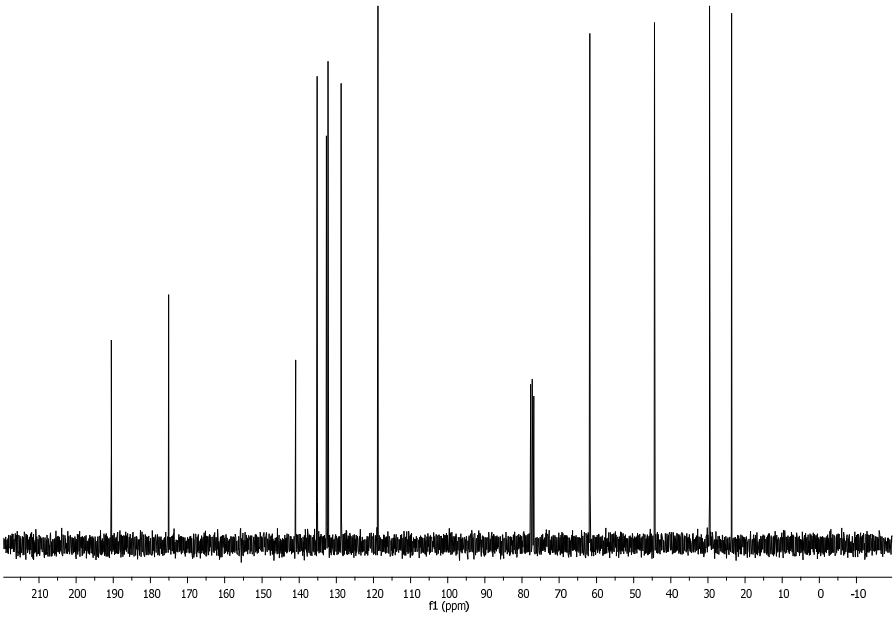




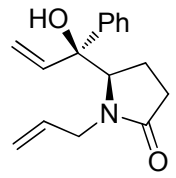
N-allyl-5-(2-thiophenecarbonyl)pyrrolidin-2-one (**58c**).

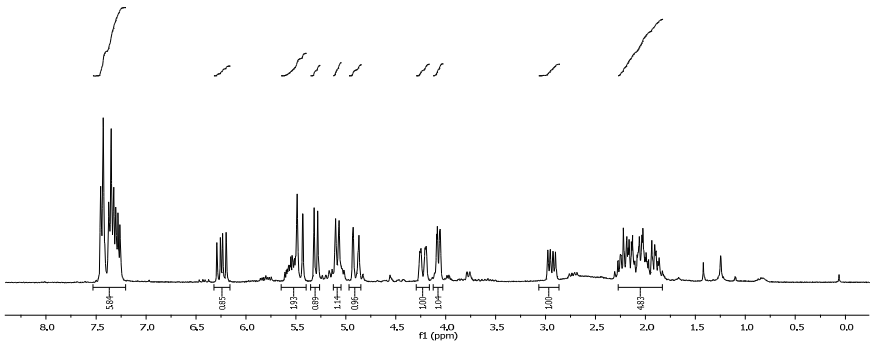


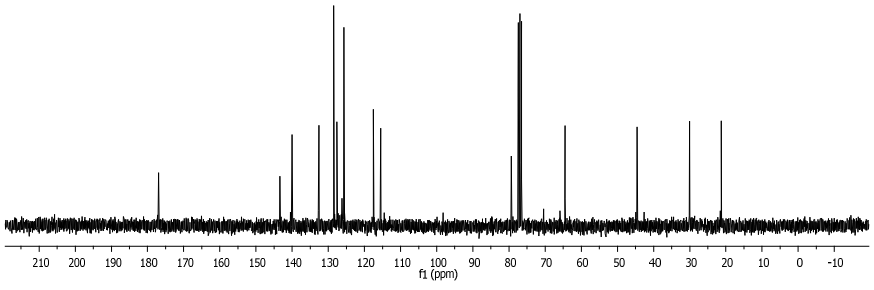




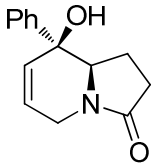
(+/-)-(5R,1'S)-1-allyl-5-(1-hydroxy-1-phenylallyl)pyrrolidin-2-one (**60a syn**).

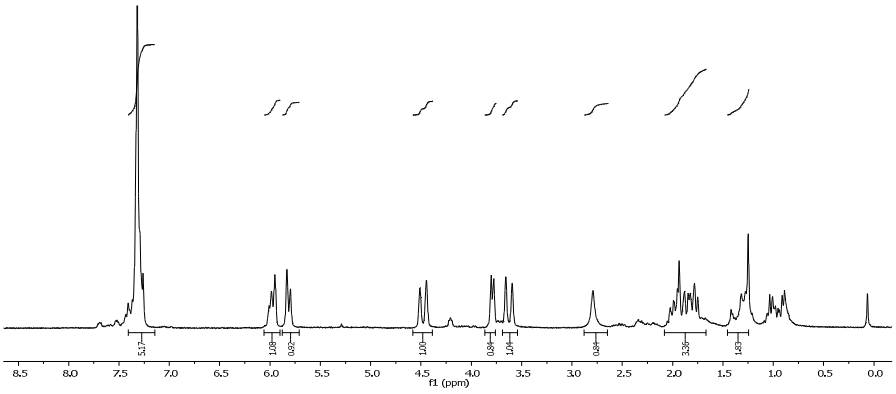


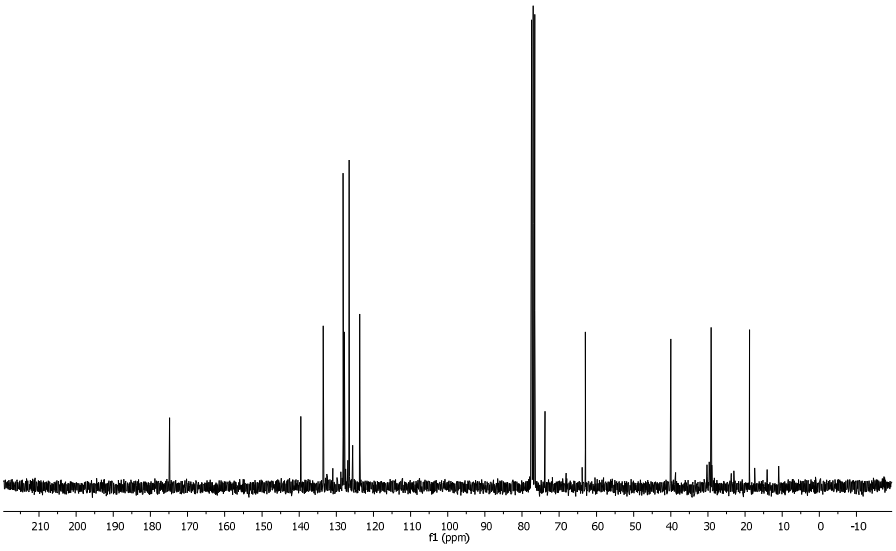




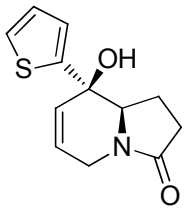
(+/-)-(8S,8aR)-8-hydroxy-8-phenyl-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**61a syn**).

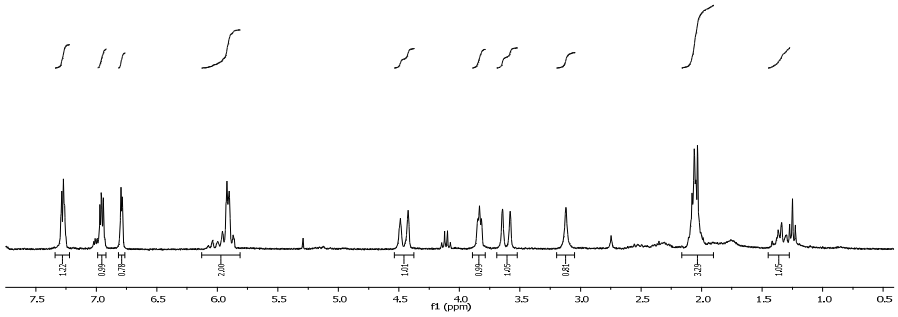


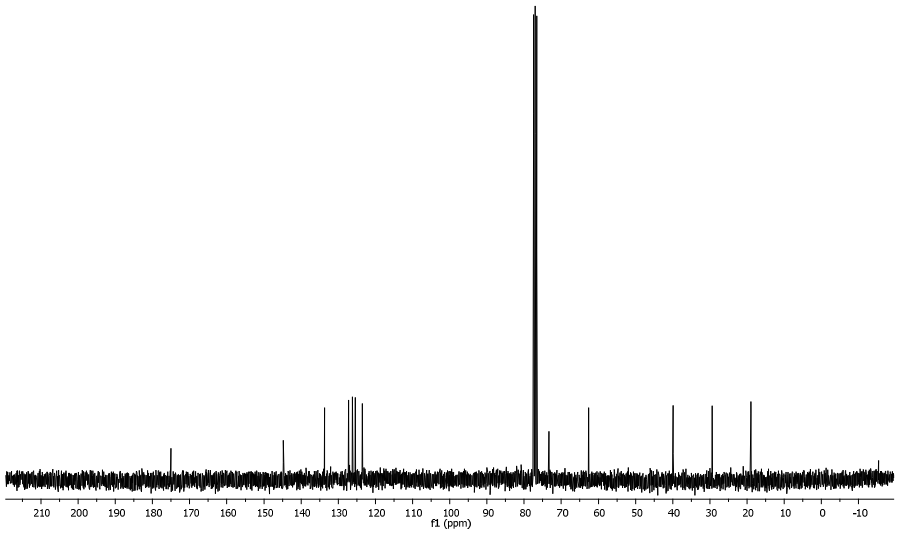




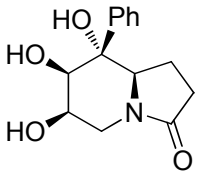
(+/-)-(8R,8aR)-8-hydroxy-8-(thien-2-yl)-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**61c syn**).

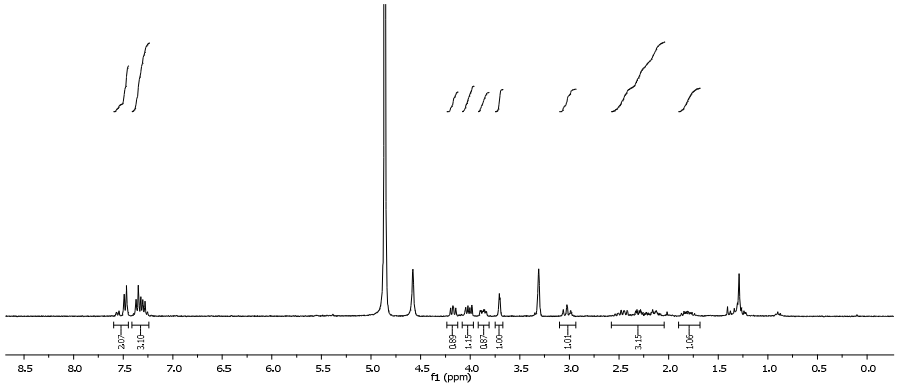


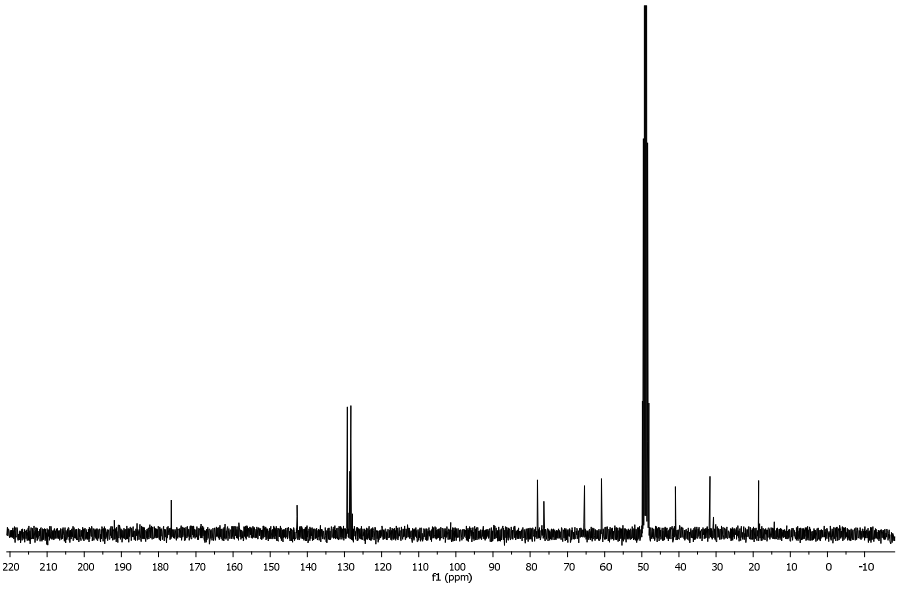




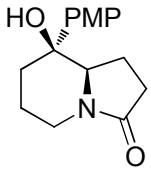
(+/-)-(6R,7R,8R,8aR)-6,7,8-trihydroxy-8-phenylhexahydroindolizin-3(2H)-one (**62a anti**).

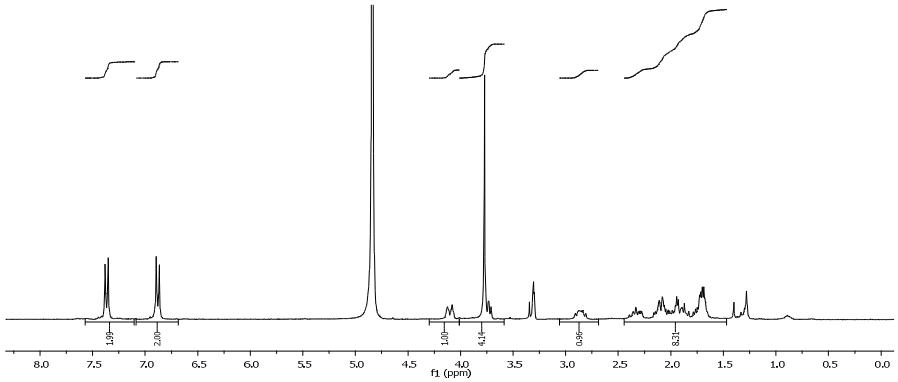


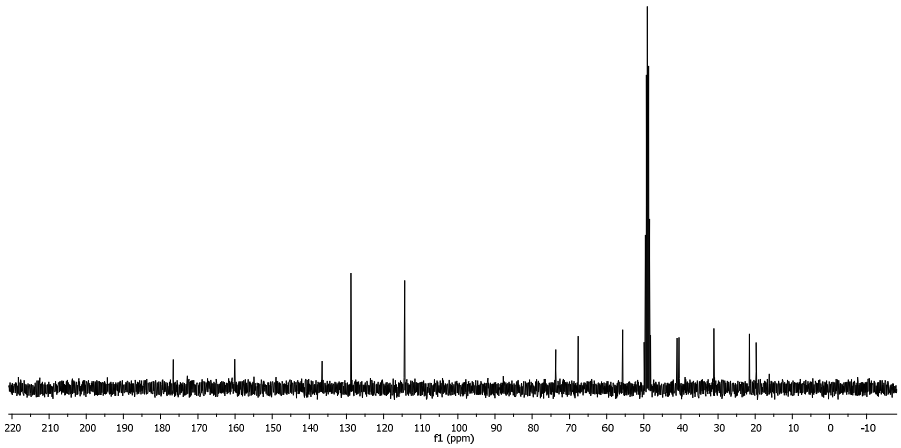




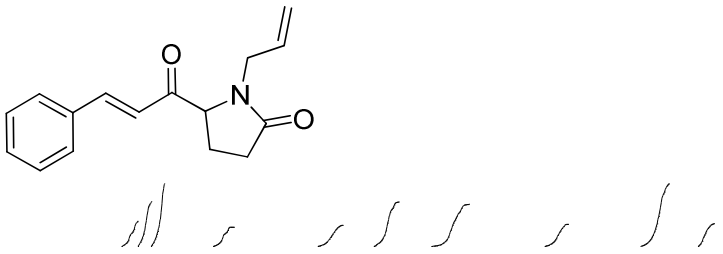
(+/-)-(8S,8aR)-8-hydroxy-8-(4-methoxyphenyl)hexahydroindolizin-3(2H)-one (**64b syn**).

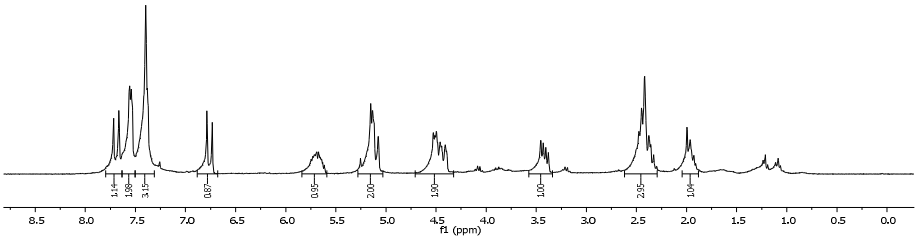


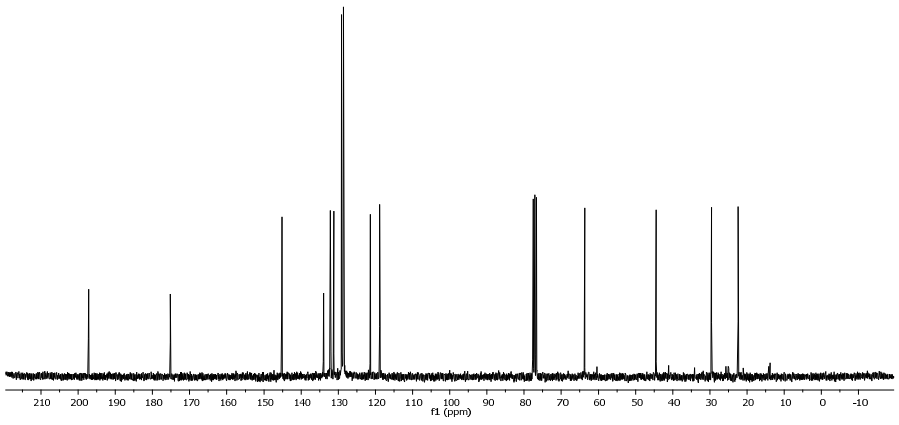




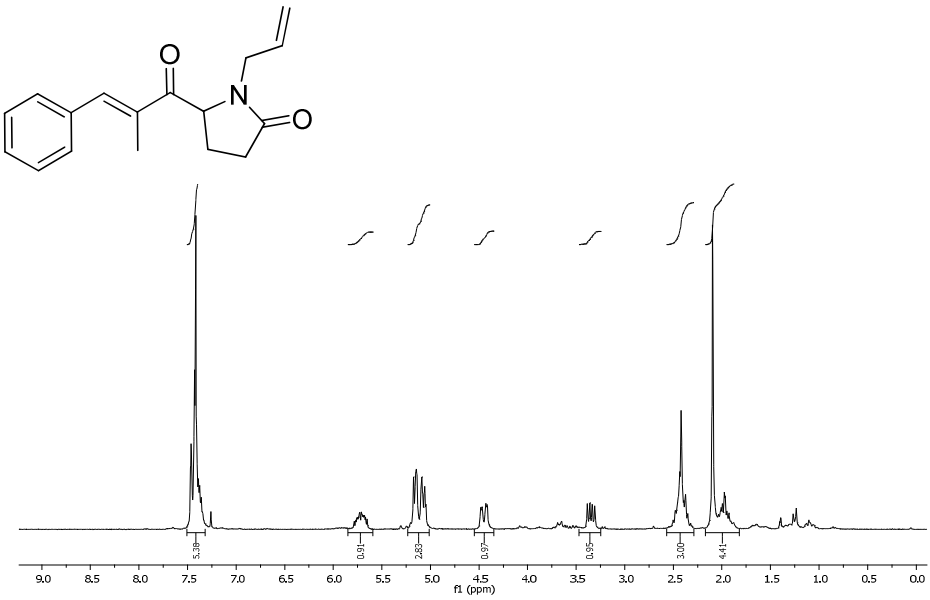
N-Allyl-5-(3-phenylacryloyl)-pyrrolidin-2-one (**68a**).

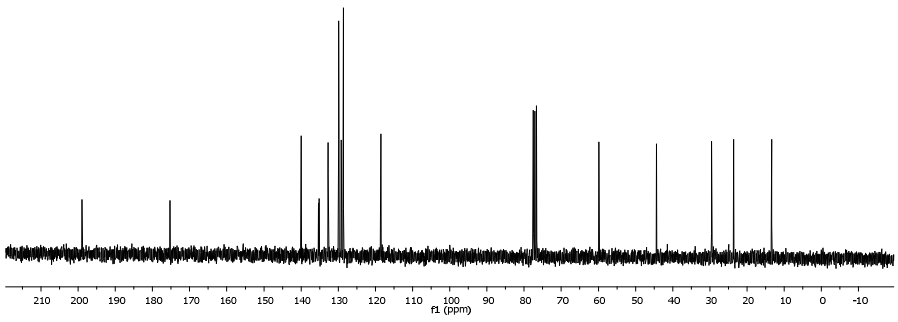




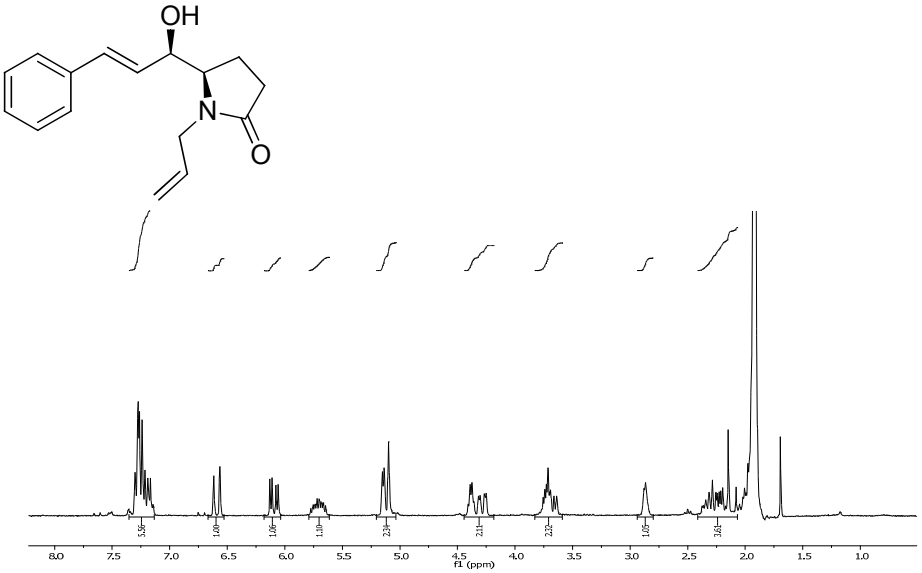


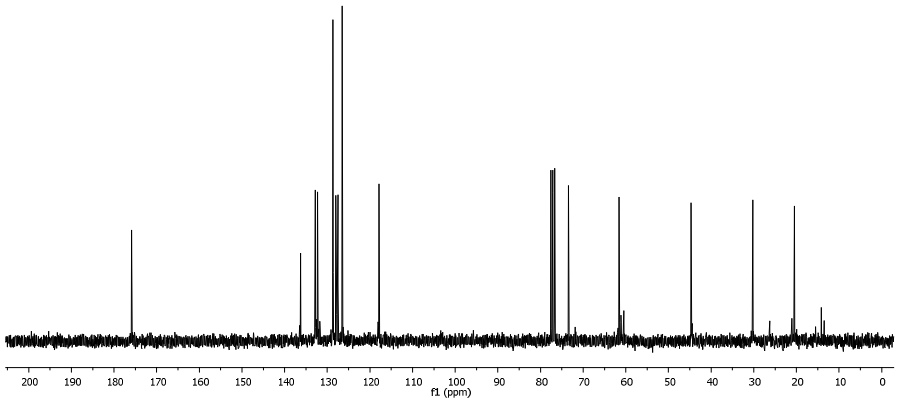
(E)-1-allyl-5-(2-methyl-3-phenylacryloyl)pyrrolidin-2-one (**68b**).



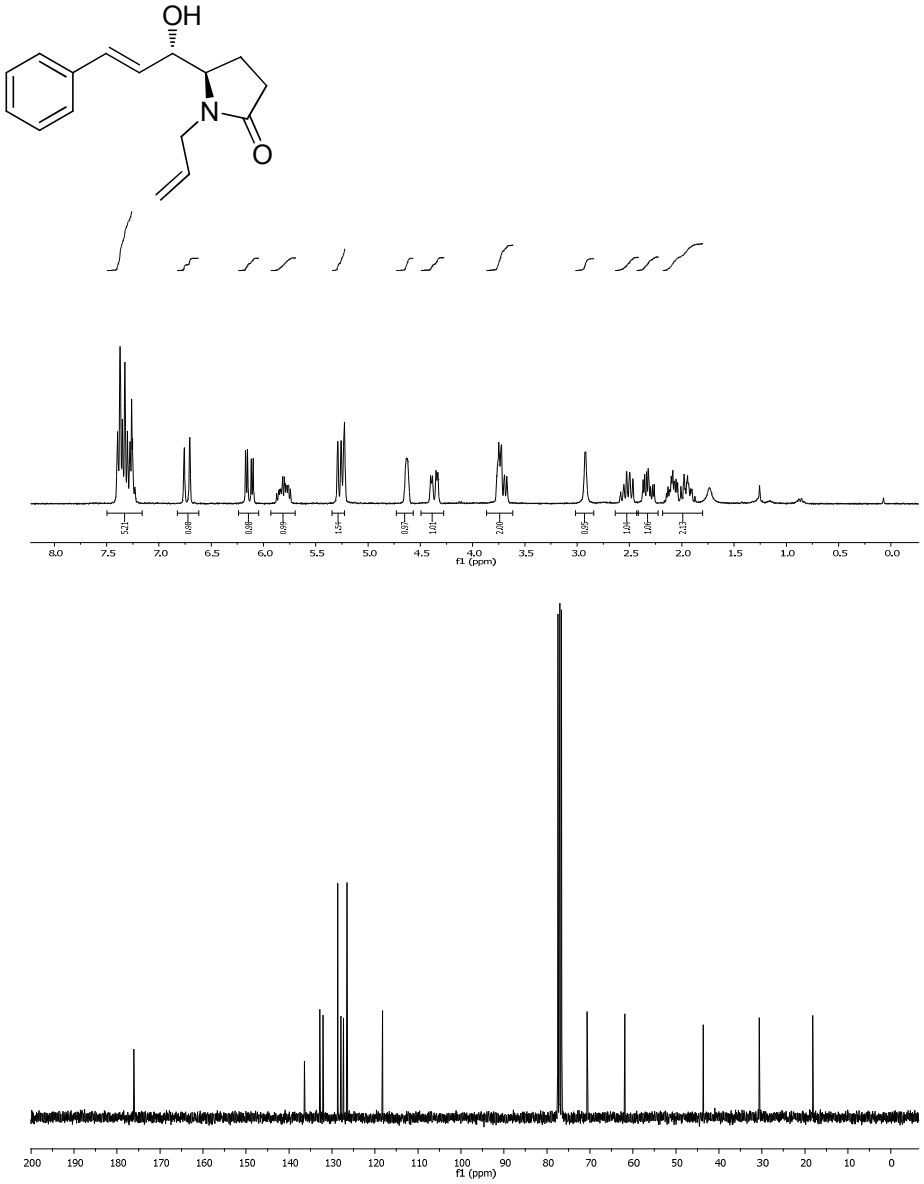


(+/-)-(5R,1'R)-N-allyl-5-(1-hydroxy-3-phenylallyl)-pyrrolidin-2-one (**69a syn**).

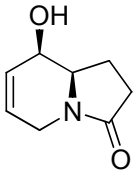


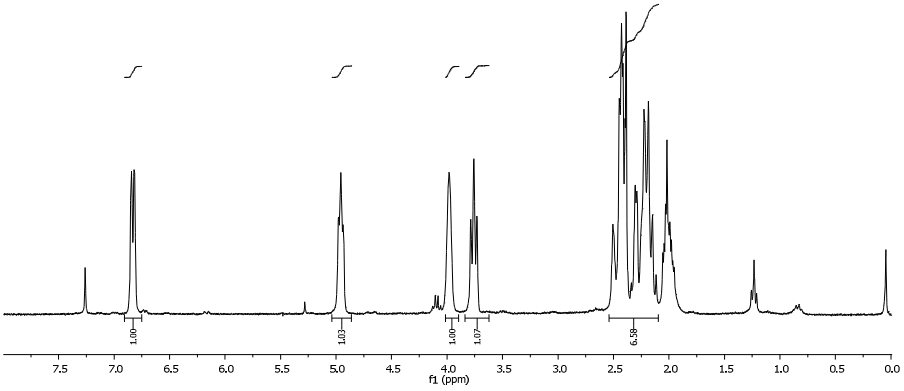


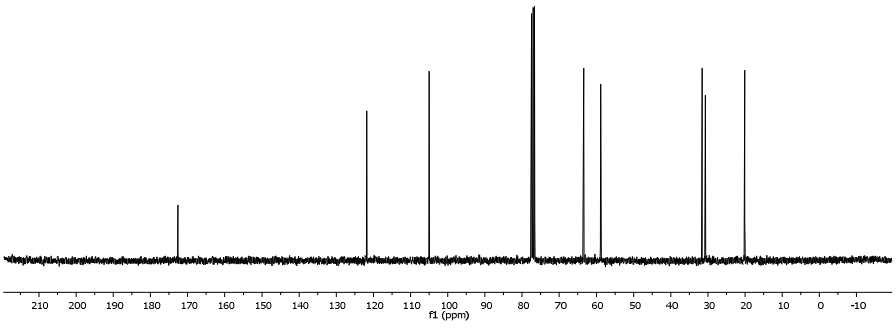
(+/-)-(5R,1'S,2'E)-N-allyl-5-(1-hydroxy-3-phenylallyl)-pyrrolidin-2-one (**69a anti**).



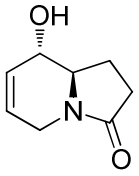
(+/-)-(8R,8aR)-8-hydroxy-1,5,8,8a-tetrahydro-2H-indolizidin-3-one (**70a syn**).

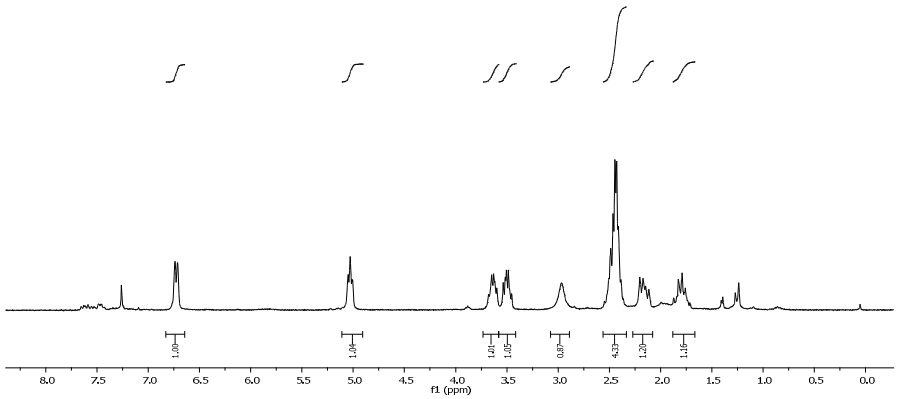


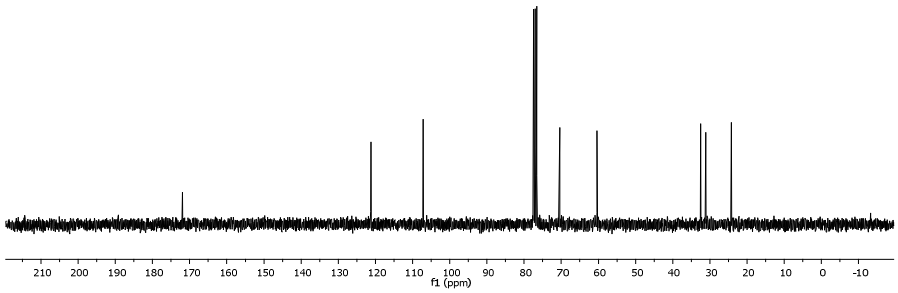




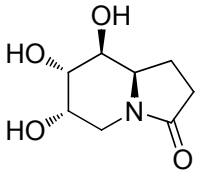
(+/-)-(8S,8aR)-8-hydroxy-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**70a anti**).

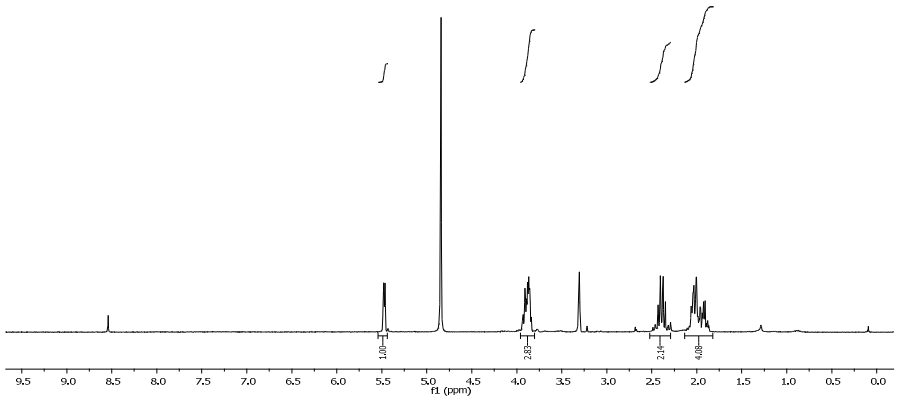


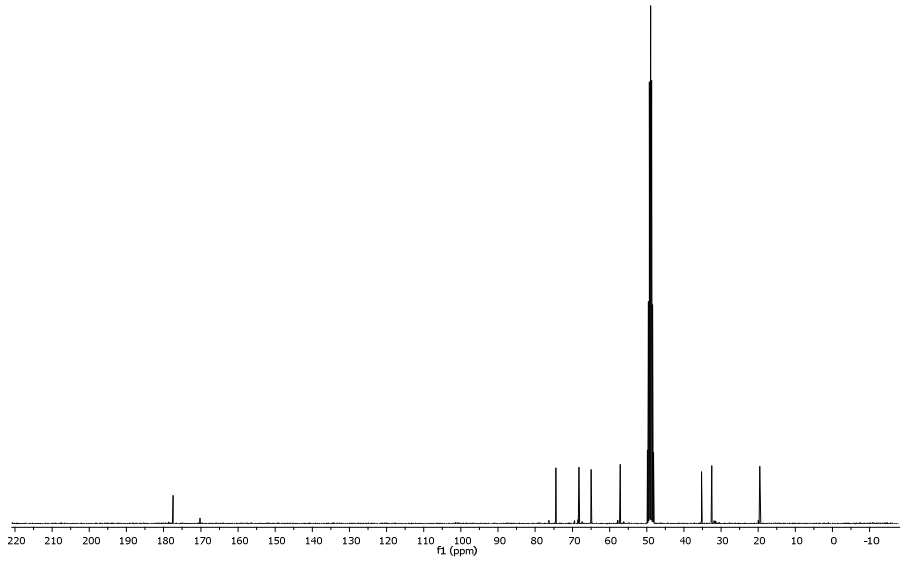




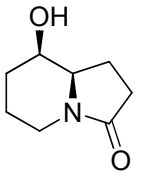
(+/-)-(6S,7S,8S,8aR)-6,7,8-trihydroxy-hexahydro-indolizidin-3-one (**72a syn**).

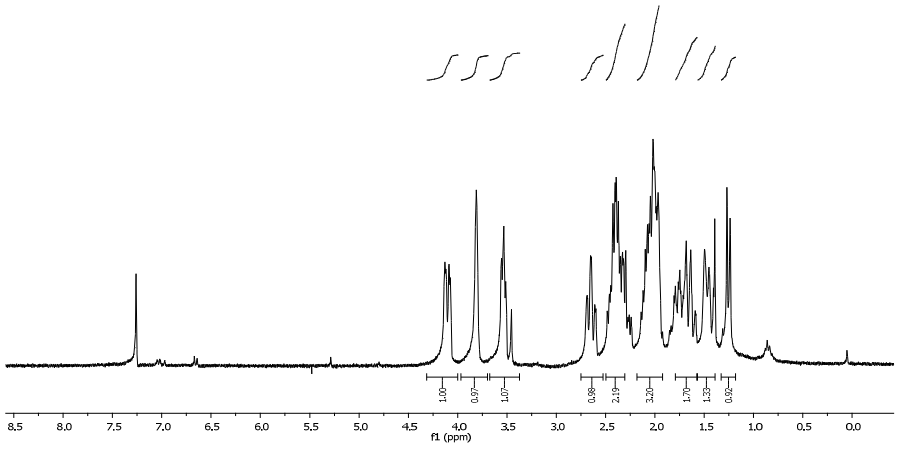


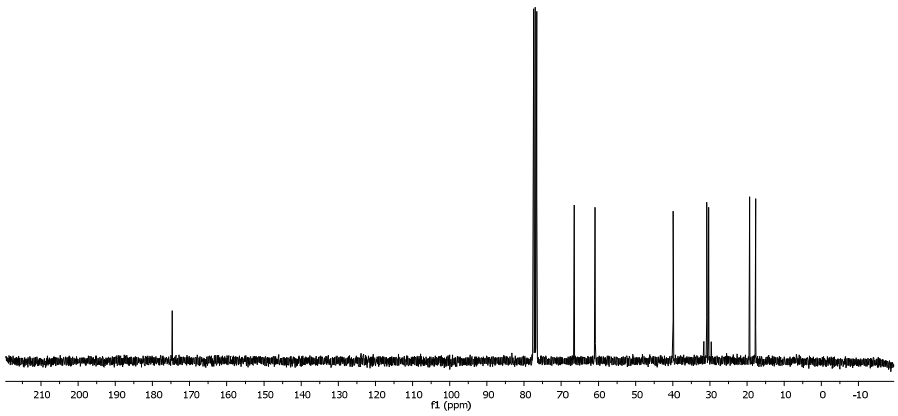




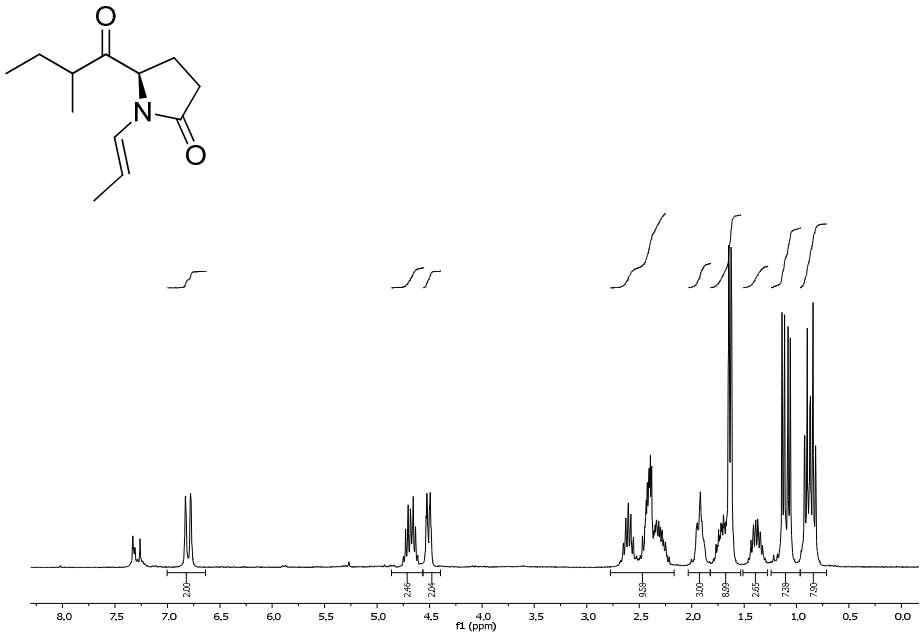
(+/-)-(8R,8aR)-8-hydroxyhexahydroindolizin-3(2H)-one (**73a syn**).

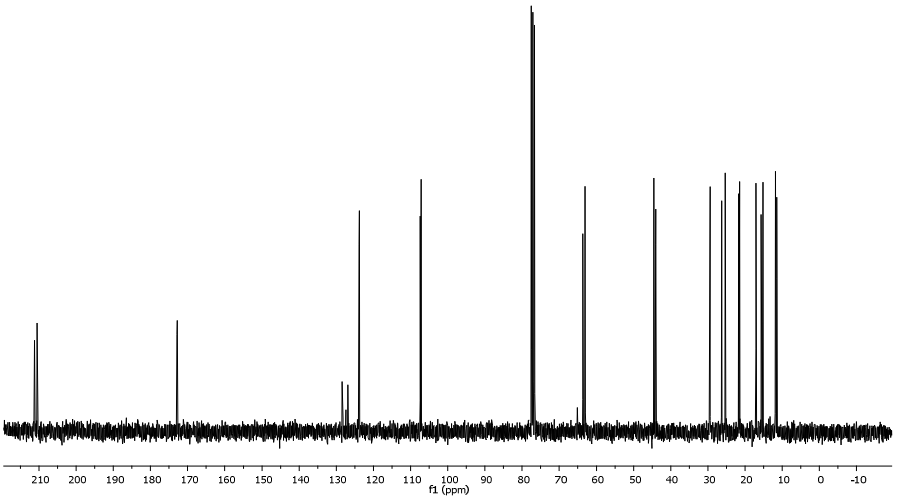




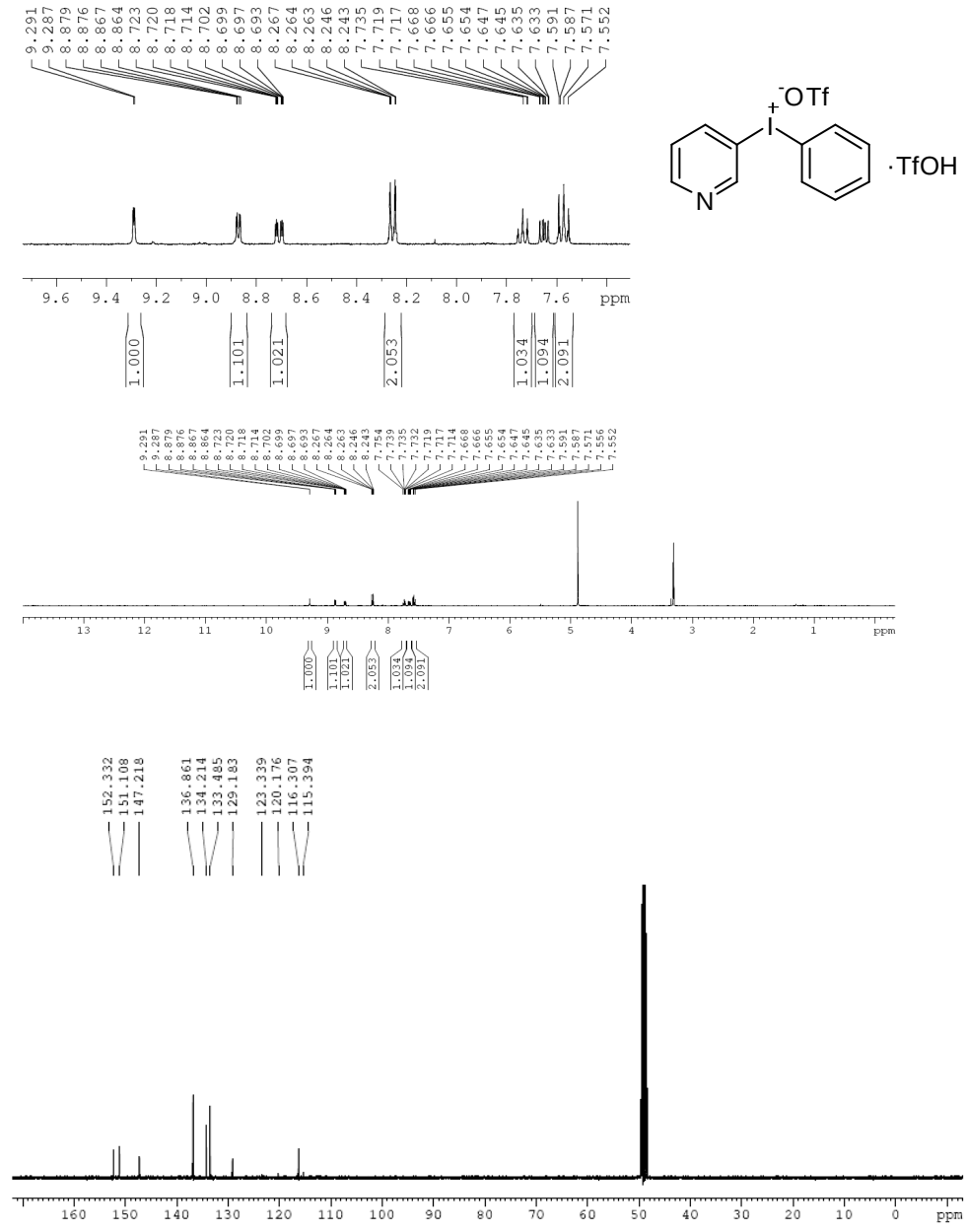


N-(1-propenyl)-5-(2-methylbutanoyl)-pyrrolidin-2-one (**81**).

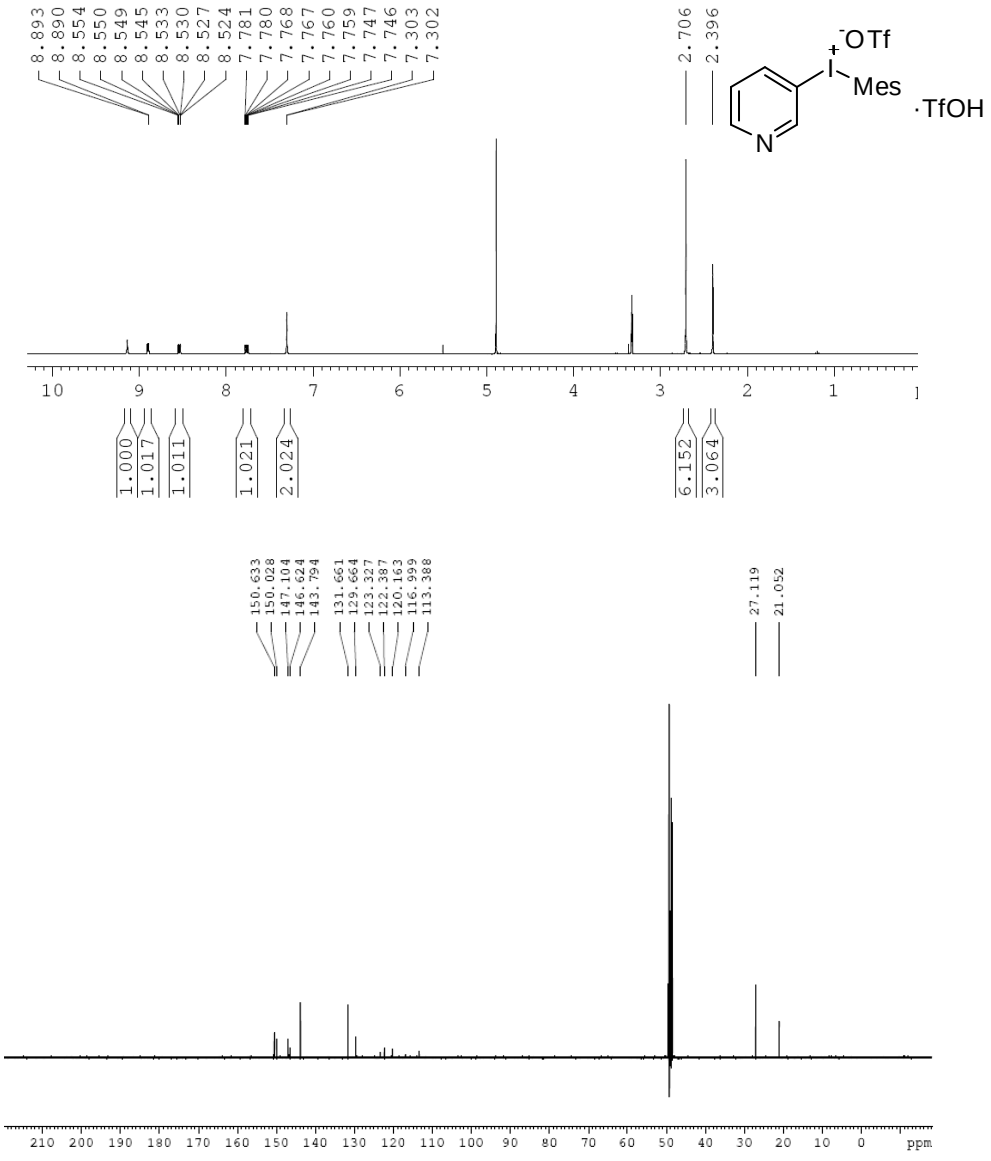




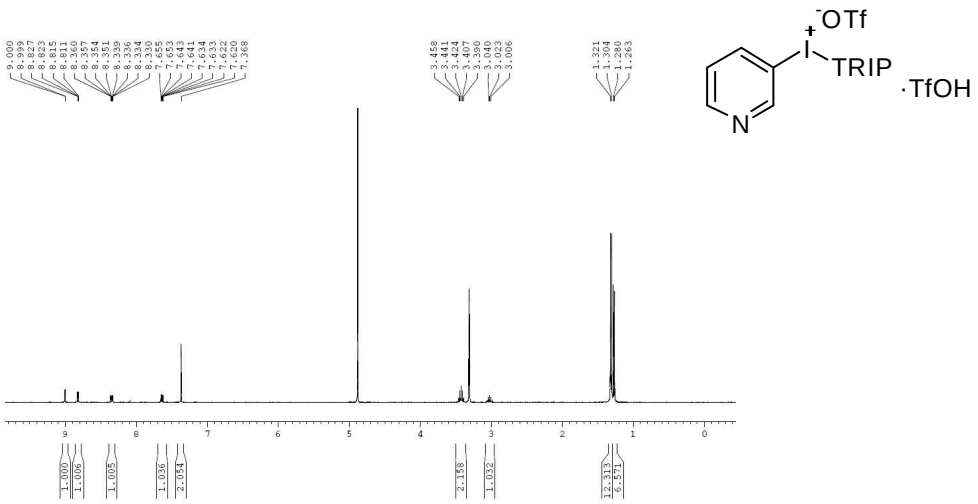
3-(phenyliodonio)pyridinium triflate (**85**).

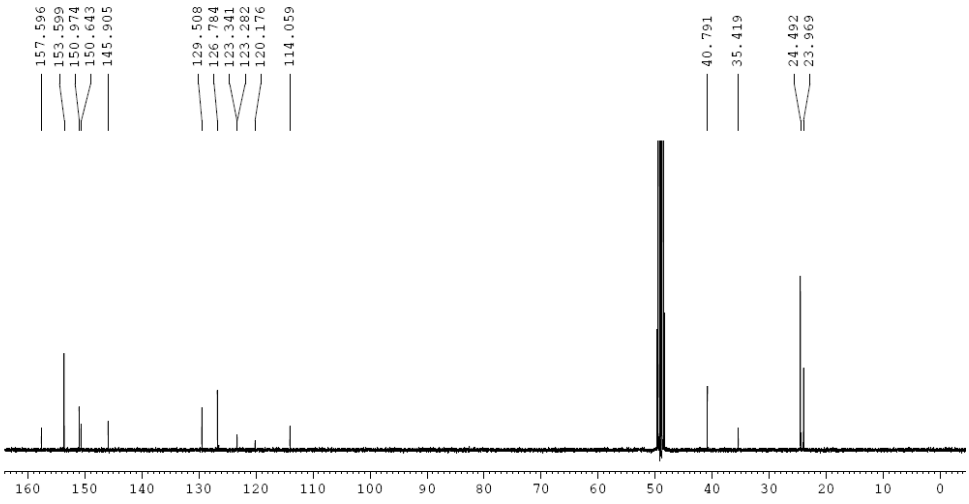


3-(mesityliodonio)pyridinium triflate (**86**).

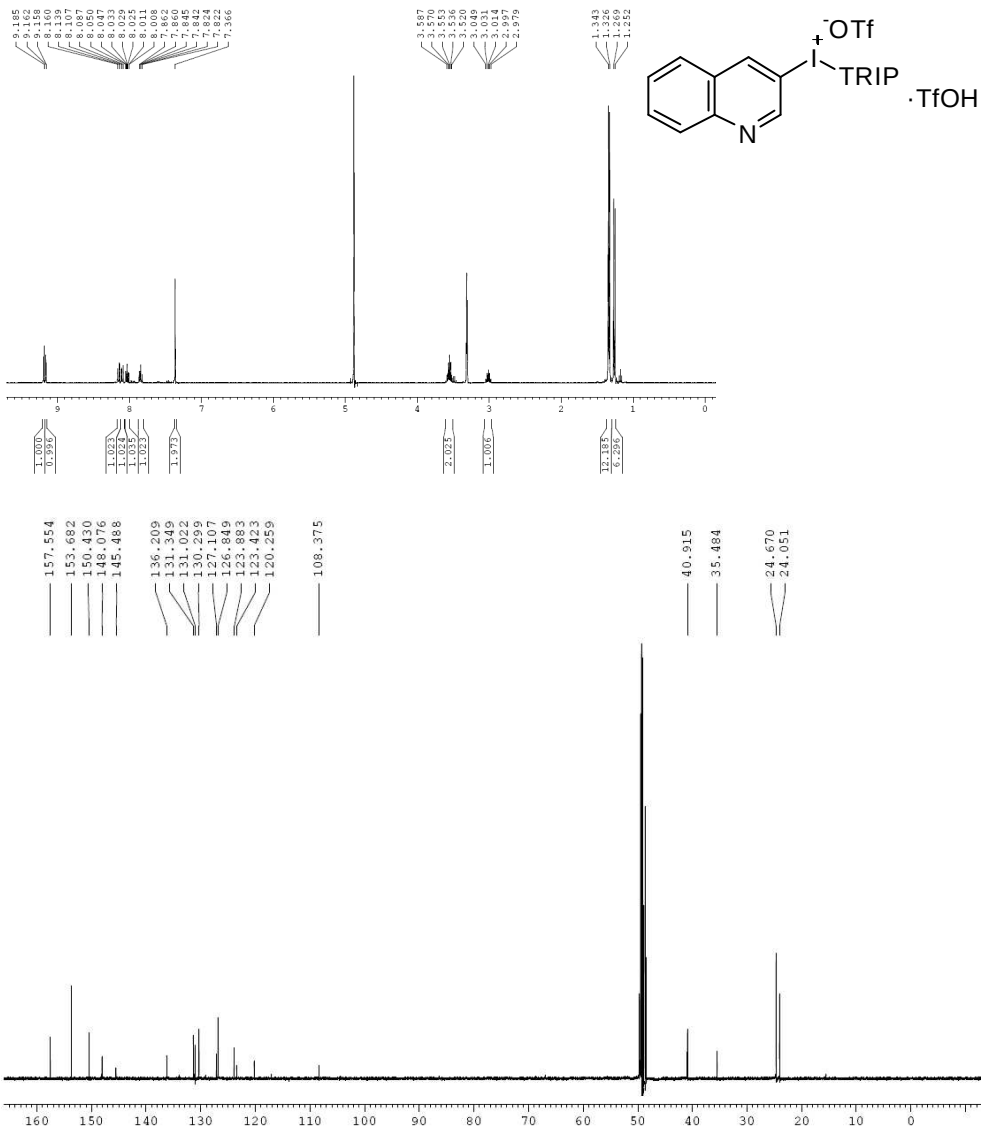


3-[(2,4,6-triisopropylphenyl)iodonil]pyridinium triflate (**87**).

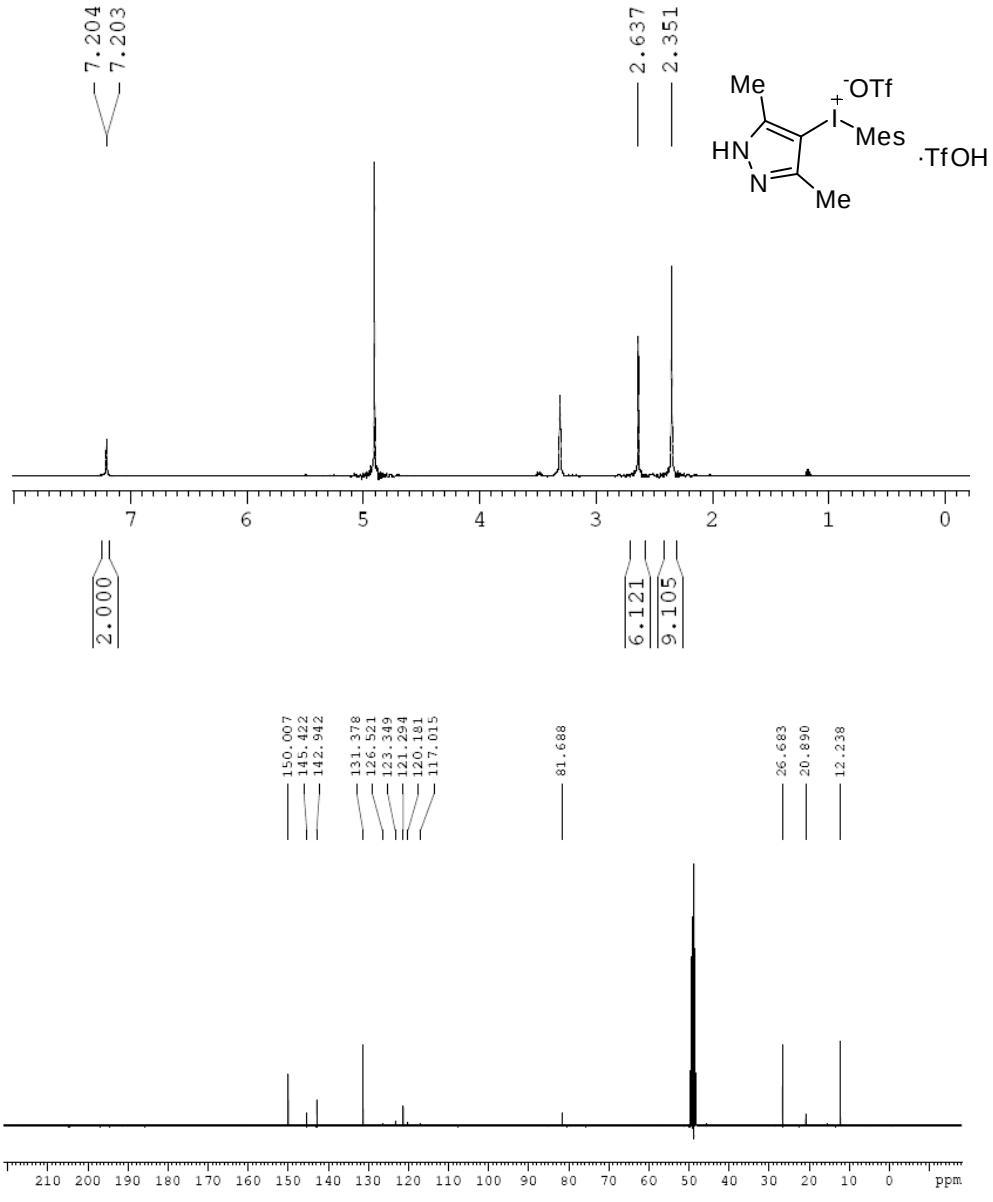




3-[(2,4,6-triisopropylphenyl)iodonio]quinolinium triflate (**90**).



4-(mesityliodonio)-3,5-dimethyl-1H-pyrazol-2-ium triflate (**91**).



4-[(2,4,6-triisopropylphenyl)iodonio]-1H-pyrazol-2-ium triflate (**94**).