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An approach to the Synthesis of a Hepatitis C Virus Inhibitor through a Proline Catalyzed 1,3-Dipolar Cycloaddition using Acrolein

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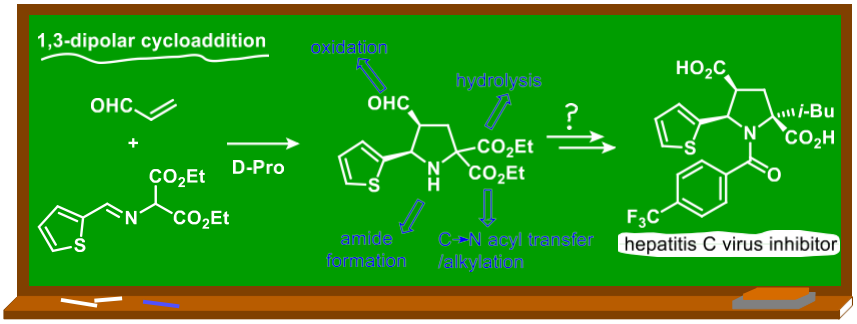

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Abstract An efficient and easy protocol for performing 1,3-dipolar cycloaddition using azomethine ylides and acrolein is presented. The reaction catalyzed by D-proline allows the synthesis of C-3 unsubstituted pyrrolidines. The application of this methodology to the synthesis of an advanced intermediate in the preparation of a Hepatitis C virus Inhibitor is presented. Final attempts to complete the synthesis of the target inhibitor results in the preparation of its C-4 epimer in good overall yield.

Key words prolinol, cycloaddition, dipole, pyrrolidine, aminomalonate, acrolein, ylides

The 1,3-dipolar cycloaddition also known as the Huisgen reaction,[1-3] is one of the most versatile tools for the preparation of five membered heterocycles. This reaction first described by Buchner during the preparation of pyrazoles[4] and later on studied in detail by Huisgen[5] have been employed extensively during the synthesis of different types of five membered heterocycles by the use of an 1,3-dipole and a dipolarophile. The versatility of this reaction has been clearly demonstrated by the great variety of dipoles that can be used in the cycloaddition (the so-called allyl-type and propargyl/allenyl-type anions),[6] in combination with a broad number of alkenes and alkynes. Importantly, while other reactions are restricted to functional groups with specific stereoelectronic properties, 1,3-dipolar cycloadditions have been carryed out with a wide range of substrates of different nature. Between them, azomethine ylides[7] stand out as stable dipoles that give access to pyrrolidines (Figure 1), a class of heterocycles present in many natural products[8] and pharmaceuticals[9] and which plays an important role as organocatalyst[10] and as a ligand in metal catalyst.[11]

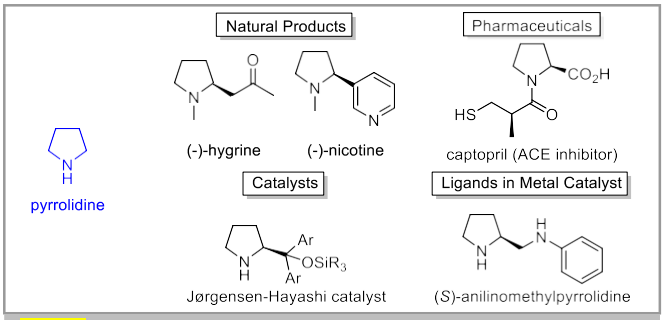
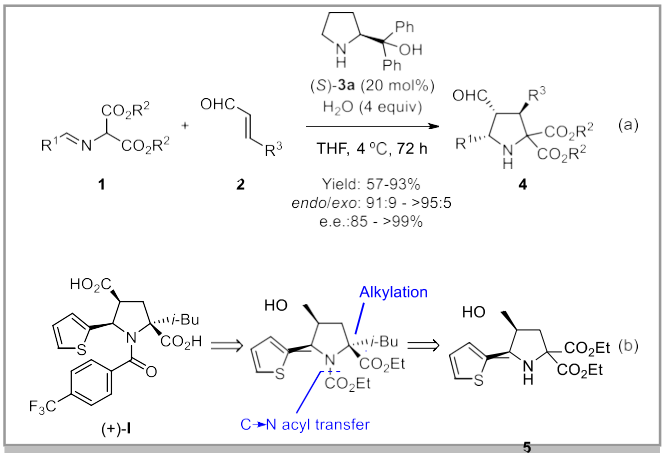


Figure 1 Structure of pyrrolidine and examples of pyrrolidine-containing molecules

In 2007 we presented an organocatalytic approach topyrrolidine heterocycles through a dipolar cycloaddition between α,β-unsaturated aldehydes **2** and azomethine ylides derived from **1,** under (*S*)-diphenylprolinol **3a** catalysis (Scheme 1a).[12,13] This reaction provides expedited access to fully substituted pyrrolidines **4** in a methodology that tolerates a wide range of substitution patterns in both the aldehyde and theazomethine ylide . With this protocol at hand, we decided to demonstrate the utility of the methodology towards the synthesis of the hepatitis C virus RNA-dependent RNA polymerase inhibitors (+)-**I** developed by Burton *et al.* from GlaxoSmithKline Pharmaceuticals.[14,15] In this sense, an analysis of the structure of the projected inhibitor (2*S*,4*S*,5*R*)-(+)-**I** (Scheme 1b), indicates that this can be obtained from an *N*- protected tetrasubstitued pyrrolidine **5** using standard functional group interconversions. Access to this intermediate isprojected by a C→N acyl transfer followed by a fully diastereoselective alkylation. This trisubsituted pyrrolidine with opposite stereochemistry compared to **4** could be obtained with the aforementioned 1,3-dipolar cycloaddition methodology, however requiring the use of acrolein **2a** as unsaturatedaldehyde and (*R*)-**3a** as catalyst.

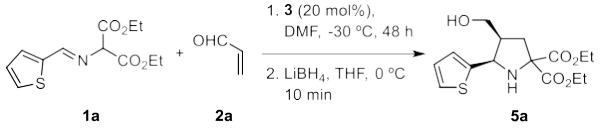


Scheme 1 Organocatalytic asymmetric 1,3-dipolar cycloaddition developed in our group and retrosynthetic analysis of hepatitis C virus inhibitor I

At the outset of the investigation acrolein **2a** and imine **1a** were used as substrates, which would give access to the desired pyrrolidine,. Unfortunately, reaction using THF as solvent and (*R*)-**3a** as catalyst only promoted the dimerization of imine **1**,[16] whereas other solvents such as DMF provided racemic pyrrolidine **5a** (e.e. <5%). This result can be justified by a possible uncatalyzed background reaction that may occur in the absence of the catalyst.[17] At this point, we decided to reassess a suitable catalyst for this reaction observing that other substituted pyrrolidines were ineffective in this cycloaddition in terms of enantioselectivity. To our delight, D-proline afforded, after *in* situ reduction of the formyl group (at C-3) to prevent observed epimerization,[18] the desired adduct **5a** in a promising 35% yield with excellent *endo*/*exo* selectivity and in a 70% e.e. with DMF as solvent.

Observing a promising stereoselectivity, efforts were aimed to improve the yield of the transformation by altering the rate of reactants imine **1a** and aldehyde **2a** (in order to hasten formation of the desired pyrrolidines whereas reducing aforementioned dimerization side reactions) (Table 1). The use of increasing ammounts of **1a** resulted in a maximum yield of 45% when 1.3 equivalents of **1a** were used, observing growing quantities of the dimer derived from imine **1a** for higher imine equivalents (entries 2-5). The use of further D-aminoacids as catalyst was also evaluated, which under identical reaction conditions afforded the final adduct in lower yield or with lower *endo*/*exo* selectivity (entries 6-8). Finally, it was found that using acrolein from a stock solution (entry 9) and under inert atmosphere (entry 10) improved the enantioselectivity of the process while also increasing the yield up to 52%. The use of additives, such as molecular sieves, did not further improve the yield (entry 11).

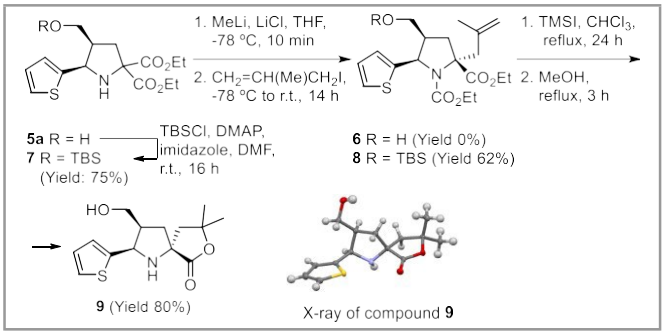
Table 1 Optimization of the Reaction Conditions



Entry	Catalyst 3	1a:2a	Yield (%)[a]	*endo*/*exo*	e.e. (*endo*) (%)[b]
1	(*R*)-3a	1.1:1	23	>95:5	<5
2	D-Pro (3b)	1.1:1	35	>95:5	70
3	D-Pro (3b)	1.3:1	45	>95:5	70
4	D-Pro (3b)	1.5:1	43	>95:5	70
5	D-Pro (3b)	3.0:1	40	>95:5	70
6	D-Ala (3c)	1.3:1	23	90:10	n.d.[c]
7	D-Ser (3d)	1.3:1	34	>95:5	n.d.[c]
8	D-Val (3e)	1.3:1	34	>95:5	n.d.[c]
9[d]	D-Pro (3b)	1.3:1	45	>95:5	80
10[d,e]	D-Pro (3b)	1.3:1	52	>95:5	80
11[d,e,f]	D-Pro (3b)	1.3:1	48	>95:5	80

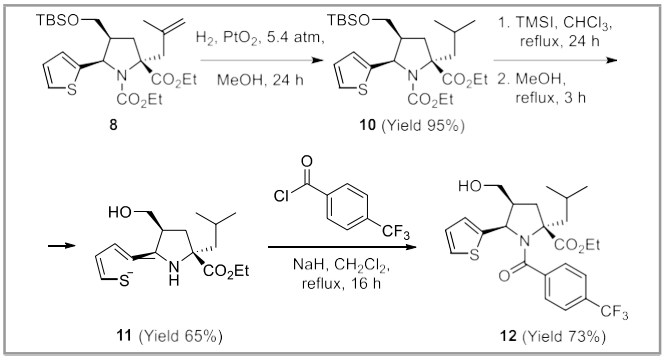
[a] Isolated yield after reduction to alcohol 5a
[b] Calculated by HPLC
[c] n.d. not determined
[d] Acrolein 2a was added from a stock solution in DMF
[e] Anhydrous conditions
[f] MS 3Å was added to the reaction

Following the projected retrosynthetic analysis, we proceeded to evaluate the diastereoselective C→N acyl transfer reactionwhich would give access to *N*-protected pyrrolidine. This particular rearrangement was previously studied in our group[19] directed to the synthesis of α-aminoacids starting from aminomalonates or derivatives such as **5a** (Scheme 2). With this precedent, we treated the pyrrolidine-2,2-dicarboxylate **5a** with methyllihium in the presence of lithium chloride at low temperature and, after 10 minutes we treated the formed intermediate with isobuthenyl iodide. Unfortunately, the formation of compound **6** was not observed most probably due the interfering presence of the hydroxymethyl substituent at C-
4. At this point, we decided to protect the alcohol by its derivatization to silyl ether **7**, transformation that proceeded in 75% yield. The C→N acyl transfer/alkylation protocol applied to this substrate yielded the desired pyrrolidine derivative **8** in a satisfactory 62% yield. *N*-Deprotection of the pyrrolidine with TMSI followed by heating the crude product in refluxing MeOH afforded the spirocyclic compound **9** in 80% yield (two steps). This compound in which a double *N*- an *O*-deprotection and an addition to the double bond has occurred, allowed us to confirm the absolute configuration in all stereocenters by X-ray crystallography.[20] It is observed that the alkylation after the C→N ethoxycarbonyl migration in **7** is performed from the less hindered face, thus maintaining the necessary stereochemistry of the projected virus inhibitor (+)-**I**.



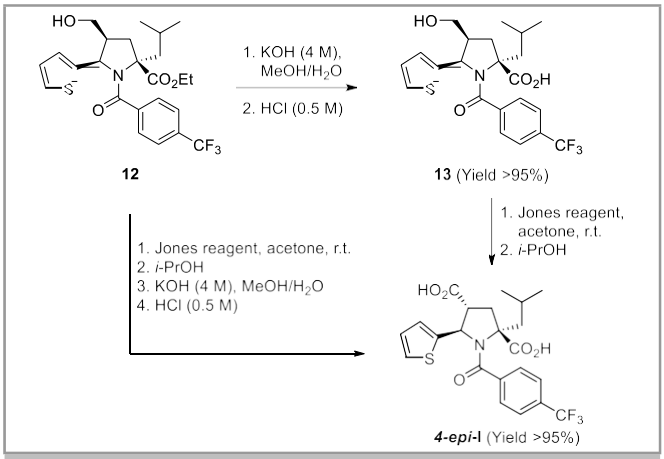
Scheme 2 C→N acyl transfer/alkylation protocol and deprotection for obtaining spirocyclic compound 9

In order to continue with the synthesis of compound (+)-**I**, we proceeded with the hydrogenation of the double bond at the isobutenyl moiety in pyrrolidine **8** before performing the projected *N*-deprotection (Schem 3). Therefore, hydrogenation in the presence of PtO_2 at 5.4 atm (80 psi) furnished compound **10** in an excellent 95% yield. Double *N*- and *O*- deprotection transferring the conditions applied to compound **8** yielded pyrrolidine **11** in 65% yield. Directed *N*-acylation using trifluormehylbenzoyl chloride under standard conditions furnished **12** in 73% yield, an advanced intermediate of virus inhibitor (+)-**I**. Thes pyrrolidine **12** displays the right stereochemistry and contains the substituents needed for completing the synthesis of the target (+)-**I**.



Scheme 3 Preparation of the advanced intermediate 12

The last steps of the synthesis consist on a hydrolysis of the ester moiety present at C-2 in pyrrolidine **12** and an oxidation ofthe hydroxymethyl moiety at C-4 (Scheme 4). We started first with the hydrolysis in basic media followed with a treatment in HCl observing complete conversion into proline derivative **13**. Oxidation reaction performed with Jones reagent under standard conditions furnished the pyrrolidine-2,4-dicarboxylic acid ***4-epi*-I** in excellent yield. Unfortunately, an epimerization at C-4 had occurred as indicated by NMR resonance of H-4 (3.32 ppm in ***4-epi*-I** *vs.* 3.87 in **I**). Other oxidation protocol such as $KMnO_4$ or PCC reagents, or Swern reaction to provide the aldehyde intermediate did not produce the desired compound. At this point, in order to avoid epimerization at C-4 we tried to invert the order of the transformations by firts oxidating the hydroxymethyl chain before proceeding with the hydrolysis in basic conditions. However, in this case again the final pyrrolidine was obtained as the C-4 epimer of the virus inhibitor**I** in comparable yields.



Scheme 4 Attempts to the synthesis of virus inhibitor (+)-I; synthesis of 4-*epi*-I

In conclusion, a straightforward method for obtaining C-3 unsubstituted pyrrolidines by a 1,3-dipolar cycloaddition using acrolein as dipolarophile has been developed. The resulting pyrrolidine **5a** is a suitable compound to perform the synthesis of and advanced intermediate **12** in the synthesis of hepatitis C virus inhibitor **I** developed by GlaxoSmithKline Pharmaceuticals. Thus, C→N acyl transfer/alkylation protocol applied to pyrrolidine **7** followed by functional group manipulation provided the aforementioned intermediate. Final hydrolysis and oxidation furnished the C-4 epimer of the virus inhibitor **4-*epi*-I.**

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Monodimensional and/or bidimensional nuclear magnetic resonance proton and carbon spectra (^{1}H NMR, ^{13}C NMR) were acquired at 25 °C on a Bruker AC-300 spectrometer or a Bruker AC-500 spectrometer. Infrared spectra (IR) were measured in a Jasco FT/IR 4100 (ATR) in the interval between 4000 and 400 cm^{-1} with a 4 cm^{-1} resolution. Mass spectra (MS) were recorded on an Agilent 7890A gas chromatograph Coupled to an Agilent 5975 quadrupole mass spectrometer under electronic impact ionization (EI) 70 eV. High-resolution mass spectra (HRMS) were recorded on an Acquity UPLC Coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using electrospray ionization (ESI^+ or ESI^-). Melting points (M.p.) were measured in a Stuart SMP30 apparatus in open capillary tubes and are uncorrected. The enantiomeric excess (e.e.) of the products was determined by High Performance Liquid Chromatography on a chiral stationary phase in a Waters chromatograph Coupled to a Waters photodiode array detector. Specific optical rotations($[\alpha]_D^{20}$) were measured at 20 °C on a Jasco P-2000 polarimeter with sodium lamp at 589 nm and a path of length of 1 dm. X-ray data collections were performed in an Agilent Supernova diffractometer equipped with an Atlas CCD area detector, and a CuKα micro-focus source with multilayer optics (λ = 1.54184 Å, 250 µm FWHM beam size). The sample was kept at 150 K with an Oxford Cryosystems Cryostream 700 cooler. Analytical grade solvents and reagents of the highest commercial quality grade were used without further purification. Anhydrous solvents were purified and dried with activated molecular sieves prior to use.[21] Reactions at reduced temperatures were carried out using a Thermo Haake EK90 refrigerator. Reactions were monitored using analytical thin layer chromatography (TLC), in pre-coated silica- backed plates (Merck Kiesegel 60 F254). These were visualized by ultraviolet irradiation, *p*-anisaldehyde, phosphomolybdic acid or potassium permanganate stains.[22] For flash chromatography Silicycle 40-63, 230-400 mesh silica gel was used.[23] For the removal of the solvents under reduced pressure Büchi R-2 series rotatory evaporators were used. For precision weighing Sartorius Analytical Balance Practum 224-1S was used (± 0.1 mg).

(*E*)-Diethyl 2-[(thiophen-2-yl)methyleneamino]malonate (1a).[12a]

To a solution of diethyl aminomalonate hydrochloride (2.00 g, 9.45 mmol) in CH_2Cl_2 (20 mL) triethylamine (1.3 mL, 9.45 mmol) was added and then 2-thiophenecarboxaldehyde (0.87 mL, 9.45 mmol), as well as anhydrous Na_2SO_4. The reaction was stirred at room temperature for a period of 3 days. After this time, the reaction mixture was filtered andthe solvent removed under reduced pressure. Imine **1a** (2.00 g, 7.56 mmol) was obtained in 80% yield as a yellow oil and was used without further purification in the next step. This imine could be stored at -30 °C for a period of 2-3 weeks without any decomposition.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.20 (s, 1H, CH=N), 6.57-7.50 (m, 3H, C_{arom}-H), 4.60 (s, 1H, CHCO), 4.15-4.35 (m, 4H, 2 × CH_2), 0.85-0.95 (m, 6H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.6 (C=O), 160.1 (CH=N), 143.7 (C_{arom}-C), 132.7, 130.5, 127.4 (C_{arom}-H), 73.7 (CHCO), 61.4 (2 × CH_2), 13.6 (2 × CH_3).

(4*S*,5*R*)-Diethyl 4-(hydroxymethyl)-5-(thiophen-2-yl)pyrrolidine-2,2-dicarboxylate (5a).

To a solution of D-proline (6.6 mg, 0.057 mmol) in DMF (7 mL) at -30 °C, acrolein (0.28 mL of a 1M solution in DMF, 0.29 mmol) was added. After subjecting the reaction mixture to stir for a period of 30 minutes at this temperature, the corresponding imine (0.100 g, 0.37 mmol) was added. After stirring for 48 hours at -30 °C, H_2O was added, the phases separated, the aqueous layer extracted with Et_2O (3 × 15 mL), and the combined organic layers washed with Na_2CO_3 (1 × 10 mL), Brine (2 × 10 mL) and H_2O (2 × 10 mL). Finally, the organic layer was dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The crude was reduced using $LiBH_4$ (0.041 g, 1.88 mmol) in THF at 0 °C. After stirring for 15 minutes at this temperature, saturated NH_4Cl (aq.) solution was added, the phases separated, the aqueous layer extracted with EtOAc (3 x 10 mL), the combined organic layers dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc 6:4) to afford the alcohol **5a** (0.048 g, 0.14 mmol, in two steps) in 52% yield as a colourless oil. Spectral properties (except specific rotation $[\alpha]_D^{20}$) match with those described for the enantiomer.[12b]

$[\alpha]_D^{20}$: + 44.5 (*c* 1.00, CH_2Cl_2).

IR (neat): 3630-3310 (OH + NH), 1730 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.20 (dd, *J* = 4.6, 1.7 Hz, 1H, C_{arom}-H), 7.07-6.94 (m, 2H, C_{arom}-H), 4.86 (d, *J* = 6.5 Hz, 1H, H-5), 4.20-4.30 (m, 4H, 2 × CH_2CH_3), 3.40 (d, *J* = 6.1 Hz, 2H, CH_2OH), 2.65-2.43 (m, 2H, 2 × H-3), 2.41 (m, 1H, H-4), 1.32-1.23 (m, 6H, 2 × CH_2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.4, 170.4 (2 × C=O), 144.8 (C_{arom}-C), 126.9, 124.3, 123.9 (C_{arom}-H), 70.7 (C-2), 62.4 (CH_2OH), 62.1, 61.9 (2 × CH_2CH_3), 59.7 (C-5), 44.9 (C-4), 34.3 (C-3), 14.1, 14.0 (2 × CH_2CH_3).

MS (70 eV) m/z (%): 328 [$(M+H)^+$, 17)], 310 (13), 282 (100), 254 (59), 237 (43), 236 (14), 163 (18).

HRMS: Calculated for $[C_{15}H_{22}NO_5S]^+$: 328.1219 [$(M+H)^+$]; found: 328.1223.

HPLC: Chiralcel OZ-3 column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min; Major diastereoisomer: τ_{major} = 64.1 min; τ_{minor} = 30.2 min (e.e.: 80%); Minor diastereoisomer: τ_{major} = 20.2 min; τ_{minor} = 36.6 min (e.e.: 65%).

(4*S*,5*R*)-Diethyl 4-((*tert*-butyldimethylsilyl)oxymethyl)-5-(thiophen-2-yl)pyrrolidine-2,2-dicarboxylate (7).

To a solution of alcohol **5a** (0.35 g, 1.06 mmol) dissolved in anhydrous DMF (17 mL) under inert atmosphere at room temperature, firstly, TBDMSCl (0.40 g, 2.66 mmol) was added and then imidazole (0.22 g, 3.19 mmol) and catalytic amount of DMAP (13 mg, 0.106 mmol) were added. After stirring for 14 hours at room temperature, NH_4Cl (aq.) was added, the phases separated, the aqueous layer extracted with Et_2O (3 × 15 mL), and the combined organic layers washed with Na_2CO_3 (1 × 10 mL), Brine (2 × 10 mL) and H_2O (2 × 10 mL). Finally, the organic layer was dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc 9:1) to afford the pyrrolidine **7** (0.33 g, 0.080 mmol) in 75% yield as a colourless oil. Spectral properties (except specific rotation $[\alpha]_D^{20}$) match with those described for the enantiomer.[12c]

$[\alpha]_D^{20}$: + 13.9 (*c* 1.25, CH_2Cl_2).

IR (neat): 3984-3462 (NH), 1733 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.15 (dd, *J* = 4.7, 1.5 Hz, 1H, C_{arom}-H), 6.95-6.82 (m, 2H, C_{arom}-H), 4.83 (d, *J* = 6.9 Hz, 1H, H-5), 4.36-4.11 (m, 4H, 2 × CH_2CH_3), 3.37 (bs, 1H, NH), 3.27 (d, *J* = 6.8 Hz, 2H, CH_2OSi), 2.63-2.33 (m, 3H, 2 × H-3 + H-4), 1.31-1.21 (m, 6H, 2 × CH_2CH_3), 0.83 (s, 9H, $(CH_3)_3C$), -0.06 (s, 3H, CH_3Si), -0.08 (s, 3H, CH_3Si).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.4, 170.4 (2 × C=O), 145.8 (C_{arom}-C), 126.6, 124.1, 123.9 (C_{arom}-H), 71.2 (C-2), 62.8 (CH_2OSi), 61.9, 61.7 (2 × CH_2CH_3), 59.2 (C-5), 45.4 (C-4), 34.4 (C-3), 25.9 ($(CH_3)_3C$), 18.1 ($(CH_3)_3C$), 14.0, 14.0 (2 × CH_2CH_3), -5.5 (CH_3Si), -5.6 (CH_3Si).

MS (70 eV) m/z (%): 442 [$(M+H)^+$, 100)], 426 (28), 384 (30), 368 (55), 356 (20), 236 (20).

HRMS: Calculated for $[C_{21}H_{36}NO_5SSi]^+$: 442.2083 [$(M+H)^+$]; found: 442.2067.

(2*S*,4*S*,5*R*)-Diethyl 4-((*tert*-butyldimethylsilyl)oxymethyl)-2-(2-methylallyl)-5-(thiophen-2-yl)pyrrolidine-1,2-dicarboxylate (8).

MeLi (0.18 mL of a 1.47 M solution in diethyl ether, 0.26 mmol) was added to a solution of the amine **7** (0.108 g, 0.26 mmol) and LiCl (0.044 g, 1.05 mmol) in THF (15.0 mL) at -78 °C under inert atmosphere and vigorous stirring. The reaction mixture was stirred at - 78 °C for 10 min and 3-iodo-2-methylpropene (0.11 mL, 1.05 mmol) was added and the reaction was stirred overnight at room temperature. Once the reaction was finished, HCl (1 M) and brine were added and the phases were separated. The aqueous layer was extracted with EtOAc (3 × 15 mL), the combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexanes/EtOAc 8:2) to afford pure N-alkoxycarbonyl-α-amino ester **8** (0.080 g, 0.16 mmol) in 62% yield as a colourless oil. Spectral properties (except specific rotation $[\alpha]_D^{20}$) match with those described for the enantiomer.[12c]

$[\alpha]_D^{20}$: + 14.3 (*c* 1.00, CH_2Cl_2).

HPLC: Chiralpak IA column, *n*-hexane/*i*-PrOH 95:5, flow rate 1.0 mL/min; τ_{major} = 3.96 min; τ_{minor} = 4.21 min (e.e.: 80%).

IR (neat): 1737 (C=O), 1704 (NC=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) (1:0.75 rotamer ratio, * denotes minor rotamer resonances) δ = 7.22-7.14 (m, 2H, C_{arom}-H), 6.95-6.88 (m, 1H, C_{arom}-H), 5.34* (d, *J* = 8.5 Hz, 1H, H-5), 5.22 (d, *J* = 8.5 Hz, 1H, H-5), 4.94* (s, 2H, C=CH_2), 4.83 (s, 2H, C=CH_2), 4.37-4.20 (m, 4H, 2 × CH_2CH_3), 4.13-4.05* (m, 2H, CH_2CH_3), 4.04-3.88* (m, 2H, CH_2CH_3), 3.40-3.22 (m, 1H, CH^aH^bOH), 3.16 (d, *J* = 13.8 Hz, 1H, C-2CH^aH^bC), 3.11-2.96 (m, 1H,CH^aH^bOH), 2.94-2.82 (m, 1H, H-4), 2.78-2.64 (m, 1H, C-2CH^aH^bC), 2.35-2.17 (m, 1H, H-3a), 2.16-2.03 (m, 1H, H- 3b), 1.83 (s, 6H, CCH_3), 1.37-1.29 (t, *J* = 7.1 Hz, 6H, 2 × CH_2CH_3), 1.19* (t, *J* = 7.1 Hz, 2H, $CH_2CH^aH^bHc$), 0.96* (t, *J* = 7.1 Hz, 4H, $CH_2CH^aH^bH^c$), 0.83 (s, 9H, $(CH_3)3C$), -0.10 (s, 6H, 2 × CH_3Si).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.8*, 173.6 (C-2CO_2Et), 153.8, 153.6* (NCO_2Et), 142.9*, 142.4 (C=CH_2), 142.3*, 141.9 (C_{arom}-C), 126.4*, 126.2, 126.1, 124.2*, 123.9 (C_{arom}-H), 116.4*, 116.1 (C=CH_2), 68.8, 68.3* (C-2), 62.8*, 61.4 (CH_2OSi), 61.2*, 61.1 (2 × CH_2CH_3), 60.8*, 60.1 (C-5), 44.1, 43.1* (C-4), 42.5*, 40.9 (C-2CH_2C), 39.2*, 37.9 (C-3), 25.7 ($(CH_3)3C$), 24.1*, 24.0 (CH_3CCH_2), 18.1 ($(CH_3)_3C$), 14.5*, 14.3, 14.2 (2 × CH_2CH_3), -5.5 (CH_3Si), -5.7 (CH_3Si).

MS (70 eV) m/z (%): 496 [$(M+H)^+$, 90)], 480 (24), 440 (45), 422 (25), 412 (19), 364 (16), 354 (21), 308 (100), 262 (30).

HRMS: Calculated for $[C_{25}H_{42}NO_5SSi]^+$: 496.2553 [$(M+H)^+$]; found: 496.2638.

(2*R*,4*S*,5*R*)-3-Hydroxymethyl-8,8-dimethyl-2-(thiophen-2-yl)-7-oxa-1-azaspiro[4.4]nonan-6-one (9).

TMSI (10.00 mmol) was added to a solution of the corresponding *N*-protected pyrrolidine **8** (0.097 g, 0.19 mmol) in $CHCl_3$ (16 mL) at room

temperature under inert atmosphere. The reaction mixture was refluxed 24 h, then MeOH (9.5 mL) was added and the reaction was refluxed 3 h more. After this time, the solvent was removed under reduced pressure and NH_3/H_2O (15.0 mL) was added. Once the phases were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by flash column chromatography (hexanes/EtOAc 7:3) to afford pure spirocyclic **9** (0.040 g, 0.14 mmol) in 74% yield as an orange oil. Spectral properties (except specific rotation $[\alpha]_D^{20}$) match with those described for the enantiomer.[12c]

$[\alpha]_D^{20}$: -2.0 (*c* 1.00, CH_2Cl_2).

IR (neat): 3560-3356 (NH + OH), 1728 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ = 7.24-7.15 (m, 2H, C_{arom}-H), 6.98 (dd, *J* = 5.0, 3.6 Hz, 1H, C_{arom}-H), 4.70 (d, *J* = 7.2 Hz, 1H, H-5), 3.56-3.36 (m, 2H, CH_2OH), 2.71-2.58 (m, 1H, H-4), 2.39-2.29 (m, 1H, H-3a), 2.28-2.18 (m, 2H, C-2CH_2C), 2.10 (dd, *J* = 12.8, 6.8 Hz, H-3b), 1.49 (s, 3H, CH_3), 1.46 (s, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 179.8 (C=O), 143.9 (C_{arom}-C), 127.1, 124.9, 124.4 (C_{arom}-H), 81.9 ($C(CH_3)_2$), 66.6 (C-2), 62.5 (CH_2OH), 60.2 (C-5), 51.2 (C-2CH_2C), 46.4 (C-4), 41.3 (C-3), 29.7, 28.6 (2 × CH_3).

MS (70 eV) m/z (%): 282 [$(M+H)^+$, 62)], 264 (20), 254 (46), 238 (20), 237 (64), 226 (100), 223 (22), 222 (80), 208 (52), 180 (21), 168 (34), 155 (48).

HRMS: Calculated for $[C_{14}H_{20}NO_3S]^+$: 282.1164 [$(M+H)^+$]; found: 282.1157.

HPLC: Chiralpak AD-H column, *n*-hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min; τ_{major} = 23.5 min; τ_{minor} = 32.6 min (e.e.: 65%).

(2*S*,4*S*,5*R*)-Diethyl 4-((*tert*-butyldimethylsilyl)oxymethyl)-2-(2-methylallyl)-5-(thiophen-2-yl)pyrrolidine-1,2-dicarboxylate (10).

A catalytic amount of PtO_2 was added to a solution of the *N*-protected pyrrolidine **8** (0,120 g, 0.24 mmol) in MeOH (14 mL) at room temperature, under H_2 atmosphere and at 80 psi for 48 hours. After this time, the reaction mixture was filtered through a small pad of silica and the solvent was removed under reduced pressure to afford pyrrolidine **10** (0.114 g, 0.23 mmol) in 95% yield as a colourless oil.

$[\alpha]_D^{20}$: + 2.0 (*c* 1.0, CH_2Cl_2).

IR (neat): 1738 (C=O), 1706 (NC=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) (1:0.70 rotamer ratio, * denotes minor rotamer resonances) δ = 7.23-7.06 (m, 2H, C_{arom}-H), 6.94-6.85 (m, 1H, C_{arom}-H), 5.36* (d, *J* = 8.5 Hz, 1H, H-5), 5.24 (d, *J* = 8.5 Hz, 1H, H-5), 4.31-4.16 (m, 4H, 2 × CH_2CH_3), 4.08-3.79* (m, 4H, 2 × CH_2CH_3), 3.40-3.28 (m, 1H, CH^aH^bOSi), 3.14-3.01 (m, 1H, CH^aH^bOSi), 2.87-2.71 (m, 1H, H-4), 2.26-2.05 (m, 3H, $CH(CH_3)2$ + 2 × H-3), 1.95-1.76 (m, 2H, C-2CH_2), 1.29 (t, *J* = 7.1 Hz, 6H, 2 × CH_2CH_3), 1.14* (t, *J* = 7.1 Hz, 2H, $CH_2CH^aH^bHc$), 0.98 (d, *J* = 6.0 Hz, 3H, $CH(CH_3)$), 0.93 (d, *J* = 6.0 Hz, 3H, $CH(CH_3)$), 0.90-0.84* (m, 4H, $CH_2CH^aH^bHc$), 0.81 (s, 9H, $(CH_3)3C$), -0.12 (s, 6H, 2 × CH_3Si).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.0*, 173.8 (C-2CO_2Et), 153.8, 153.6* (NCO_2Et), 142.9*, 142.3 (C_{aro} -C), 126.3*, 126.2, 126.1, 126.0*, 124.2*, 123.8 (C_{arom}-H), 68.8, 68.5* (C-2), 62.8, 61.7* (CH_2OSi), 61.2*, 61.0, 60.9 (2 × CH_2CH_3), 60.5*, 59.8 (C-5), 44.5, 43.6* (C-4), 42.5 (C-3), 38.3*, 37.0 (C-2CH_2CH), 25.8, 25.2* ($(CH_3)3C$), 24.8 ($CH(CH_3)_2$), 24.0, 24.0 ($CH(CH_3)_2$), 18.1 ($(CH_3)3C$), 14.4*, 14.2, 14.2 (2 × CH_2CH_3), -5.6 (CH_3Si), -5.7 (CH_3Si).

MS (70 eV) m/z (%): 498 [$(M+H)^+$, 33)], 482 (21), 441 (22), 440 (100), 424 (83), 414 (45), 366 (65), 292 (46), 282 (21).

HRMS: Calculated for $[C_{25}H_{44}NO_5SSi]^+$: 498.2709 [$(M+H)^+$]; found: 498.2714.

(2*S*,4*S*,5*R*)-Ethyl 4-hydroxymethyl-2-isobutyl-5-(thiophen-2-yl)pyrrolidine-2-carboxylate (11).

TMSI (10.00 mmol) was added to a solution of the *N*-protected pyrrolidine **10** (0.125 g, 0.25 mmol) in $CHCl_3$ (20.5 mL) at room temperature under inert atmosphere. The reaction mixture was refluxed 24 h, then MeOH (12 mL) was added and the reaction was refluxed 3 h more. After this time, the solvent was removed under reduced pressure and $NH3/H_2O$ (15.0 mL) was added. Once the phases were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by flash column chromatography (hexanes/EtOAc 7:3) to afford pure pyrrolidine **11** (0.051 g, 0.16 mmol) in 65% yield as a colourless oil.
$[\alpha]^{20}$: -25.2 (*c* 1.00, CH Cl).

D 2 2

IR (neat): 3673-3203 (OH), 1721 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ = 7.22-7.16 (m, 1H, C_{arom}-H), 6.93-6.90 (m, 2H, C -H), 4.29 (d, *J* = 8.0 Hz, 1H, H-5), 4.24–4.14 (m, 2H, CH CH), 3.66 (dd, *J* = 10.9, 4.3 Hz, 1H, CH^aH^bOH), 3.54 (dd, *J* = 10.9, 5.3 Hz, 1H, CH^aH^bOH), 2.28-2.05 (m, 3H, H-4 + 2 × H-3), 1.86-1.63 (m, 3H, $CH_2CH(CH_3)_2$ + $CH(CH_3)_2$), 1.29 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 0 96 (d, *J* = 6.3 Hz, 3H, $CH(CH_3)$), 0 87 (d, *J* = 6.3 Hz, 3H, $CH(CH_3)$).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.9 (C=O), 149.3 (C_{arom}-C), 126.5, 124.1, 123.3 (C_{arom}-H), 67.6 (C-2), 63.2 (CH_2OH), 61.2 (CH_2CH_3), 59.8 (C-5), 49.8 (C-4), 49.6 ($CH_2CH(CH_3)_2$), 39.4 (C-2CH_2CH), 25.1, 24.3 ($CH(CH_3)_2$), 23.2 ($CH(CH_3)_2$), 14.2 (CH_2CH_3).

MS (70 eV) m/z (%): 312 [$(M+H)^+$, 24)], 294 (13), 266 (74), 239 (14), 238 (100), 221 (19), 220 (17).

HRMS: Calculated for $[C_{16}H_{26}NO_3S]^+$: 312.1633 [$(M+H)^+$]; found: 312.1626.

(2*S*,4*S*,5*R*)-Ethyl 4-hydroxymethyl-2-isobutyl-5-(thiophen-2 yl)-1- (trifluromethyl)benzoyl)pyrrolidine-2-carboxylate (12).

To a solution of pyrrolidine **11** (0.050 g, 0.16 mmol) in CH_2Cl_2 (9 mL) at 0 °C and under inert atmosphere, NaH (0.013 g, 0.32 mmol) and after 15 minutes, 4-(trifluoromethyl)benzoyl chloride (45 μL, 0.32 mmol) were added and then the mixture was refluxed overnight. Once the reaction was finished, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexanes/EtOAc 6:4) to afford pirrolidine **12** (0.057 g, 0.012 mmol) in 73% yield as a colourless oil.

$[\alpha]_D^{20}$: -18.2 (*c* 1.00, CH_2Cl_2).

IR (neat): 3580-3285 (OH), 1729 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ = 7.40 (d, *J* = 8.0 Hz, 2H, C_{arom}-H), 7.17 (d, *J* = 8.0 Hz, 2H, C_{arom}-H), 7.07 (d, *J* = 5.0, 1H, C_{arom}-H), 6.55 (dd, *J* = 5.0 3.5 Hz, 1H, C_{arom}-H), 6.13 (d, *J* = 3.5 Hz, 1H, C_{arom}-H), 4.98 (d, *J* = 9.2 Hz, 1H, H- 5), 3.34-3.19 (m, 2H, CH_2CH_3), 3.69 (dd, *J* = 11.0, 4.0 Hz, 1H, CH^aH^bOH), 3.56 (dd, *J* = 11.0, 5.3 Hz, 1H, CH^aH^bOH), 2.73, 2.55 (m, 1H, H-4), 2.52-2.21 (m, 3H, $CH(CH_3)$2 + 2 × H-3), 2.17-2.02 (m, 2H, $CH_2CH(CH_3)_2$), 1.32 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.12 (d, *J* = 7.8 Hz, 3H, $CH(CH_3)$), 1.10 (d, *J* = 7.8 Hz, 3H, $CH(CH_3)$).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.4 (CO_2Et), 169.8 (NCO), 145.2, 145.2, 140.8 (C_{arom}-C), 126.5, 126.4, 125.7, 125.1, 124.9 (C_{arom}-H), 71.1 (C-2), 62.8 (C-5), 61.5, 61.5 (CH_2OH + CH_2CH_3), 50.7 (H-4), 44.2 ($CH_2CH(CH_3)_2$), 37.4 ($CHCH_2C$), 25.4, 25.3, 25.2 ($CH(CH_3)_2$ + $CH(CH_3)_2$), 14.2 (CH_2CH_3).

MS (70 eV) m/z (%): 484 [$(M+H)^+$, 10)], 466 (56), 464 (33), 438 (88), 418 (52), 410 (100), 393 (47), 173 (28).

HRMS: Calculated for $[C_{24}H_{29}F_3NO_4S]^+$: 484.1769 [$(M+H)^+$]; found: 484.1754.

(2*S*,4*S*,5*R*)-4-hydroxymethyl-2-isobutyl-5-(thiophen-2-yl)-1-(4- (trifluoromethyl)benzoyl)pyrrolidine-2-carboxylic acid (13).

To a solution of the pyrrolidine **12** (0.034 g, 0.070 mmol) in MeOH/H_2O (4:1) (2 mL) a solution of KOH (1 M) (2 mL) was added and then the mixture was refluxed overnight. Once the reaction was finished the MeOH was removed under reduced pressure and HCl was added until the formation of a white precipitate. Then the phases were separated, the aqueous layer was extracted with EtOAc (2 × 15 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and removing the solvent under reduced pressure to afford acid **13** (0.032 mg, 0.070 mmol) in > 99% yield as a yellow oil.

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$[\alpha]_D^{20}$: -39.2 (*c* 1.00 , CH_2Cl_2).

IR (neat): 3507-3091 (OH), 1724 (C=O), 1616 (NC=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ = 7.45 (d, *J* = 8.1 Hz, 2H, C_{arom}-H), 7.16 (d, *J* = 8.1 Hz, 2H, C_{arom}-H), 7.12 (d, *J* = 5.1 Hz, 1H, C_{arom}-H), 6.64 (dd, *J* = 5.0, 3.5 Hz, 1H, C_{arom}-H), 6.16 (d, *J* = 3.0 Hz, 1H, C_{arom}-H), 4.97 (d, *J* = 4.4 Hz, 1H, H-5), 3.68 (dd, *J* = 11.3, 5.6 Hz, 1H, CH^aH^bOH), 3.54 (dd, *J* = 11.3, 6.2 Hz, 1H, CH^aH^bOH), 2.95-2.73 (m, 2H, H-4 + H-3a), 2.53-2.31 (m, 2H, H-3b + $CH^aH^bCH(CH_3)_2$), 2.12-1.84 (m, 2H, $CH^aH^bCH(CH_3)_2$ + $CH(CH_3)_2$), 1.09 (d, *J* = 6.4 Hz, 3H, $CH(CH_3)$), 1.08 (d, *J* = 6.4 Hz, 3H, $CH(CH_3)$).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 174.7 (CO_2Et), 172.7 (NCO), 144.5, 144.5, 139.8 (C_{arom}-C), 126.6, 126.1, 125.8, 125.2, 125.1 (C_{arom}-H), 73.3 (C- 2), 64.0 (C-5), 61.8 (CH_2OH), 49.2 (C-4), 44.6 ($CH_2CH(CH_3)_2$), 36.1 (C-3), 25.2, 24.8 ($CH(CH_3)_2$), 24.1 ($CH(CH_3)_2$).

HRMS: Calculated for $[C_{22}H_{25}F_3NO_4S]^+$: 456.1456; found: 456.1459.

(2*S*,4*R*,5*R*)-2-Isobutyl-5-(thiophen-2-yl)-1-((4-trifluoromethyl)benzoyl)pyrrolidine-2,4-dicarboxylic acid (4-*epi*-I).

To a solution of the pyrrolidine **12** (0.028 g, 0.064 mmol) in acetone (0.8 mL) Jones reagent (24 μL, 0.15 mmol) was added and then the mixture was stirred 30 minutes. Once the reaction was finished *i*-PrOH was added and the phases were separated, the aqueous layer was extracted with EtOAc (3 × 15 mL) and the combined organic layers were dried over Na_2SO_4. After removing the solvent under reduced pressure to afford acid 27 (0.029 mg, 0.061 mmol) in >99% yield as a white solid.

^1H NMR (300 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 8.1 Hz, 2H, C_{arom}-H), 7.34 (d, *J* = 8.1 Hz, 2H, C_{arom}-H), 7.27 (d, *J* = 5.1 Hz, 1H, C_{arom}-H), 6.73-6.62 (m, 1H, C_{arom}-H), 6.41 (d, *J* = 3.2 Hz, 1H, C_{arom}-H), 5.63 (d, *J* = 5.3 Hz, 1H, H-5), 3.46-3.19 (m, 1H, H-4), 2.75-2.31 (m, 1H, H-3a), 2.47-2.40 (m, 1H, H-3b), 2.23-2.07 (m, 2H, $CH_2CH(CH_3)_2$), 1.65-1.60 (m, 1H, $CH(CH_3)_2$), 1.29-1.09 (m, 6H, $CH(CH_3)_2$).

HRMS: Calculated for $[C_{22}H_{23}F_3NO_5S]^+$: 470.1249; found: 470.1258.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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(20) CCDC 2115906 (**9**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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