SUPPORTING INFORMATION

Pyrrolinone-pyrrolidine Oligomers As Universal Peptidomimietics

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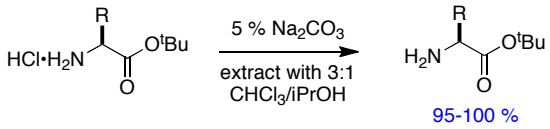
A. General Experimental Methods

All reactions were carried out under an inert atmosphere (nitrogen or argon where stated) with dry solvents under anhydrous conditions. Glassware for anhydrous reactions were dried in an oven at 140 ºC for minimum 6 h prior to use. Dry solvents were obtained by passing the previously degassed solvents through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at a high commercial quality (typically 97 % or higher) and used without further purification, unless otherwise stated. Analytical thin layer chromatography (TLC) was carried out on Merck silica gel plates with QF-254 indicator and visualized by UV, ceric ammonium molybdate, and/or potassium permanganate stains. Flash column chromatography was performed using silica gel 60 (Silicycle, 230-400 mesh) as per the Still protocol.[1] ^{1}H and ^{13}C spectra were recorded on a Varian Mercury or Inova spectrometer (300 MHz ^{1}H; 75 MHz ^{13}C) and were calibrated using residual non-deuterated solvent as an internal reference ($CDCl_3$: ^{1}H-NMR = 7.26, ^{13}C-NMR = 77.16, DMSO-d*6*: ^{13}C-NMR = 39.52, CD_3OD: ^{1}H-NMR = 3.31, ^{13}C-NMR = 49.00) The following abbreviations or combinations thereof were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, p = pentet, br = broad, app = apparent. IR spectra were recorded on an IRAffinity-1 Shimadzu spectrophotometer using NaCl plates. Melting points were recorded on an automated melting point apparatus (EZ-Melt, Stanford Research Systems) and are uncorrected. Optical rotations were obtained on a Jasco DIP-360 digital polarimeter at the D-line of sodium.

Note: Compounds (*R*)-pyrrolidin-3-ol and **7a**, **7d** and **7g** have been previously characterized; see the references section.

B. General Procedures for Synthesis

Procedure for generating α-amino esters from corresponding hydrochloride salts in high yields under mild conditions



The HCl salt (20 mmol) was suspended in 100 mL of 3:1 chloroform/isopropanol and transferred to a 500 mL separatory funnel. Sodium carbonate solution (5 %, 250 mL) was added and the organic layer is separated after extraction. The aqueous layer was extracted with three 50 mL portions of 3:1 chloroform/isopropanol. The combined organic layers was washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated to afford the α-amino ester as a colorless liquid (> 95 %).

Note: The free α-amino acids were prone to racemization when stored at 25 ºC for several days. This can be avoided by freshly preparing them before the reaction.

C. General Procedure for X-Ray Structure Determination

A Leica MZ 75 microscope was used to identify a suitable colorless multi-faceted crystal with very well defined faces with dimensions (max, intermediate, and min) 0.05 mm x 0.03 mm x 0.01 mm from a representative sample of crystals of the same habit. The crystal mounted on a nylon loop was then placed in a cold nitrogen stream maintained at 110 K.

A BRUKER D8-GADDS X-ray (three-circle) diffractometer was employed for crystal screening, unit cell determination, and data collection. The goniometer was controlled using the FRAMBO software suite.[ϕ] The sample was optically centered with the aid of a video camera such that no translations were observed as the crystal was rotated through all positions. The detector was set at 6.0 cm from the crystal sample (MWPC Hi-Star Detector, 512x512 pixel). The X-ray radiation employed was generated from a Cu sealed X-ray tube (K_α = 1.54184Å

[ϕ] APEX2 “Program for Data Collection on Area Detectors” BRUKER AXS Inc., 5465 East Cheryl Parkway, Madison, WI 53711-5373 USA

with a potential of 40 kV and a current of 40 mA) fitted with a graphite monochromator in the parallel mode (175 mm collimator with 0.5 mm mono-capillary optics).

The rotation exposure indicated acceptable crystal quality and the unit cell determination was undertaken. 2100 data frames were taken at widths of 0.5° with an exposure time of 10 seconds. Over 6000 reflections were centered and their positions were determined. These reflections were used in the auto-indexing procedure to determine the unit cell. A suitable cell was found and refined by nonlinear least squares and Bravais lattice procedures and reported here in Table 1. No super-cell or erroneous reflections were observed.

After careful examination of the unit cell, a standard data collection procedure was initiated. This procedure consists of collection of one hemisphere of data collected using omega scans, involving the collection 0.5° frames at fixed angles for ϕ, 2θ, and χ (2θ = -28°, χ = 54.73°, 2θ = -90°, χ = 54.73°), while varying omega. Addition data frames were collected to complete the data set. Each frame was exposed for 10 sec. The total data collection was performed for duration of approximately 24 hours at 110K. No significant intensity fluctuations of equivalent reflections were observed.

Data Reduction, Structure Solution, and Refinement

Integrated intensity information for each reflection was obtained by reduction of the data frames with the program SAINT.* The integration method employed a three dimensional profiling algorithm and all data were corrected for Lorentz and polarization factors, as well as for crystal decay effects. Finally the data was merged and scaled to produce a suitable data set. The absorption correction program SADABS** was employed to correct the data for absorption effects.

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* SAINT, “Program for Data Reduction from Area Detectors” ” BRUKER AXS Inc., 5465 East Cheryl Parkway, Madison, WI 53711-5373 USA

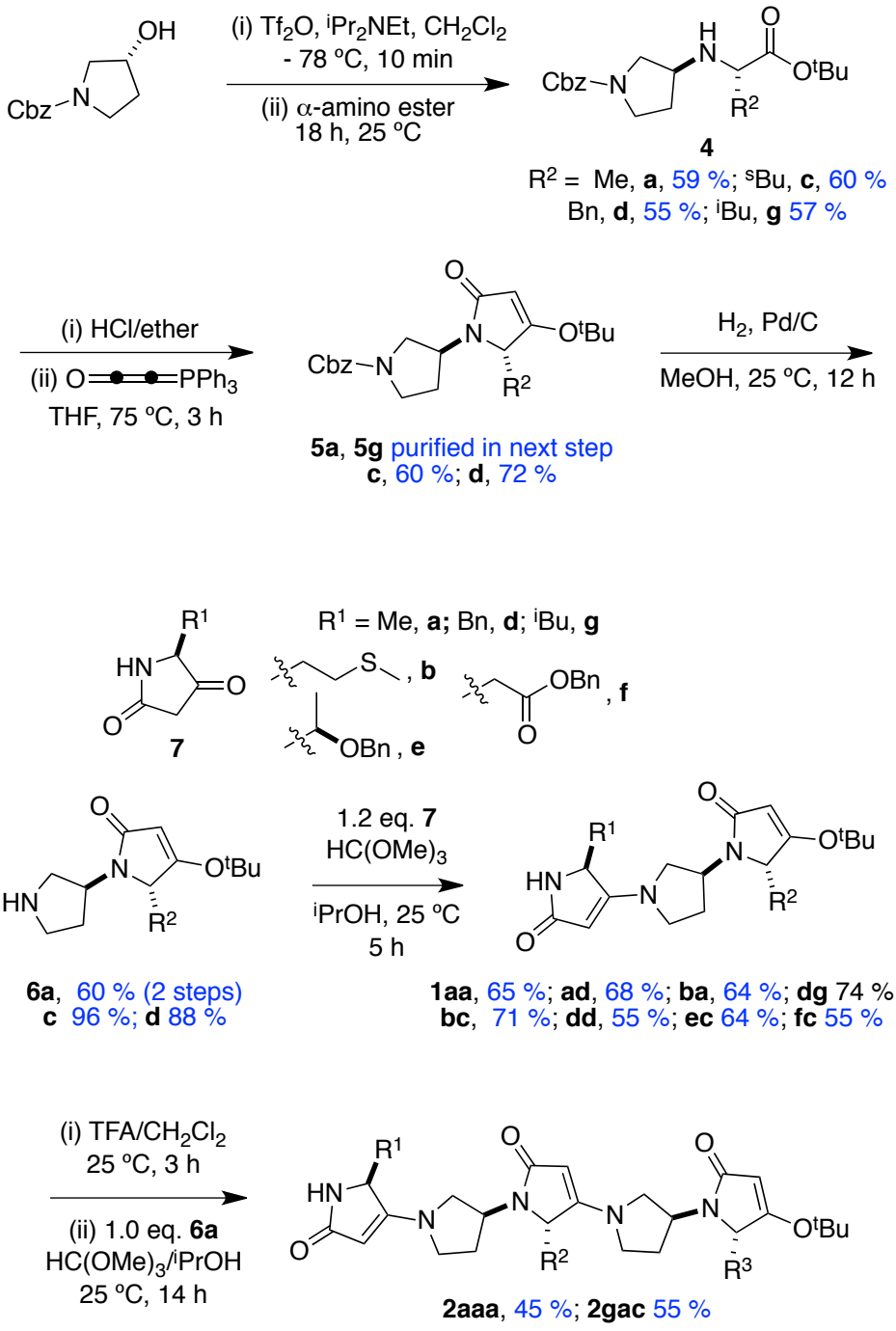
** SADABS, Sheldrick, G.M. “Program for Absorption Correction of Area Detector Frames”, BRUKER AXS Inc., 5465 East Cheryl Parkway, Madison, WI 53711-5373 USA

Systematic reflection conditions and statistical tests for the data suggested the space group $P2_1$. A solution was obtained readily using SHELXTL (SHELXS).* All non-hydrogen atoms were refined with anisotropic thermal parameters. The Hydrogen atoms bound to carbon were placed in idealized positions [C–H = 0.96 Å, $U_{iso}(H) = 1.2 \times U_{iso}(C)$]. The structure was refined (weighted least squares refinement on F^2) to convergence. X-seed was employed for the final data presentation and structure plots.**

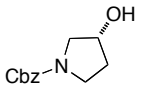
* SHELXTL, Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122

** Barbour, L.J.,(2001) "X-Seed - A software tool for supramolecular crystallography" *J. Supramol. Chem.* **2001**, *1,* 189-191.

Scheme S1


(i) Tf2O, iPr2NEt, CH2Cl2
- 78 °C, 10 min
(ii) α-amino ester
18 h, 25 °C
4
R2 = Me, a, 59 %; sBu, c, 60 %
Bn, d, 55 %; iBu, g 57 %
(i) HCl/ether
(ii) PPh3
THF, 75 °C, 3 h
5a, 5g purified in next step
c, 60 %; d, 72 %
H2, Pd/C
MeOH, 25 °C, 12 h
R1 = Me, a; Bn, d; iBu, g
7
b
e
f
1.2 eq. 7
HC(OMe)3
iPrOH, 25 °C
5 h
6a, 60 % (2 steps)
c 96 %; d 88 %
1aa, 65 %; ad, 68 %; ba, 64 %; dg 74 %
bc, 71 %; dd, 55 %; ec 64 %; fc 55 %
(i) TFA/CH2Cl2
25 °C, 3 h
(ii) 1.0 eq. 6a
HC(OMe)3/iPrOH
25 °C, 14 h
2aaa, 45 %; 2gac 55 %

(*R*)-benzyl 3-hydroxypyrrolidine-1-carboxylate



Procedure: To a stirred solution of (*R*)-pyrrolidin-3-ol maleate salt[2] (18.0 g, 88.3 mmol) in water (75 mL) was added sodium carbonate (47 g, 442 mmol, 5.0 equiv) portion-wise at 0 ºC. Benzyl chloroformate (15 mL, 106 mmol, 1.2 equiv) was added dropwise over 30 minutes using a syringe pump. The reaction was stirred at 25 ºC for 4 h. Dichloromethane (250 mL) was added and the aqueous layer was separated. The organic layer was extracted once with water (50 mL) and brine (75 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (SiO_2, 1:1 EtOAc/CH_2Cl_2) to afford the Cbz-protected pyrrolidin-3-ol in 78 % yield.

Physical state: colorless oil

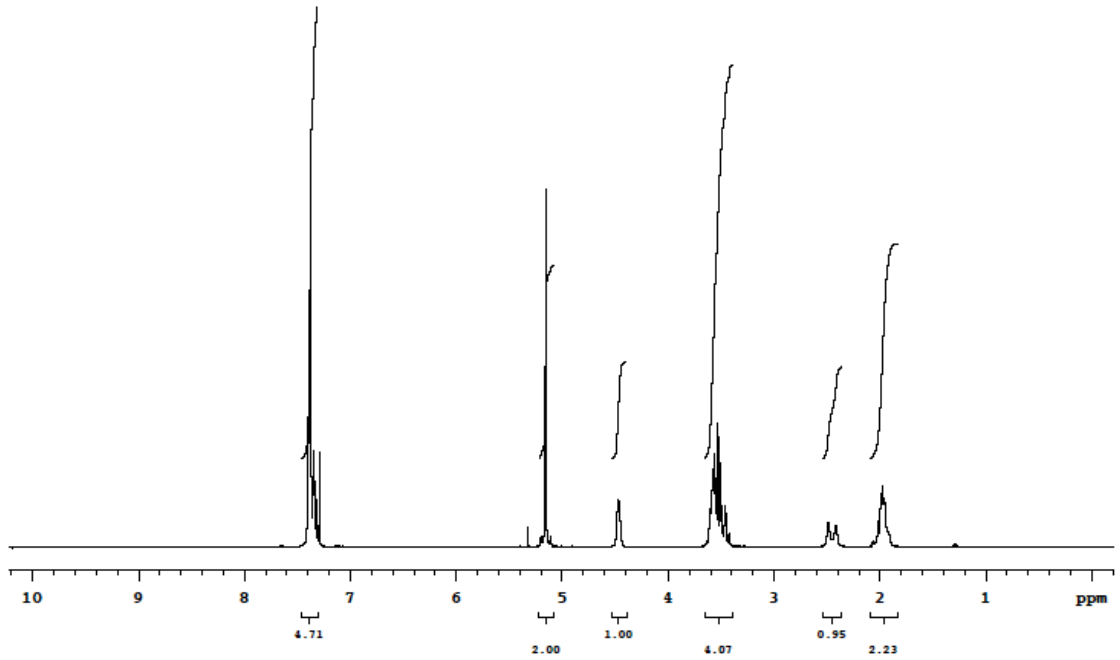
$[\alpha]^{20}$ -19.7 (*c* 1.0, MeOH)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39-2.29 (m, 5H), 5.18 (app s, 2H), 4.46 (br s, 1H), 3.61-3.42 (m, 4H), 2.45 (d, *J* = 19.2 Hz, 1H), 2.02-1.95 (m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 154.5, 136.9, 128.4, 128.0, 127.9, 71.0 and 70.1, 66.8, 54.7 and 54.2, 44.1 and 43.8, 34.1 and 33.6

IR (film, cm^{-1}) 3427 (br), 2951, 1703, 1692, 1688, 1435, 1361, 1201, 1120, 977, 768, 696

MS (ESI) m/z calcd for $(M+H)^+$ $C_{12}H_{16}NO_3$ 222.11; found 222.15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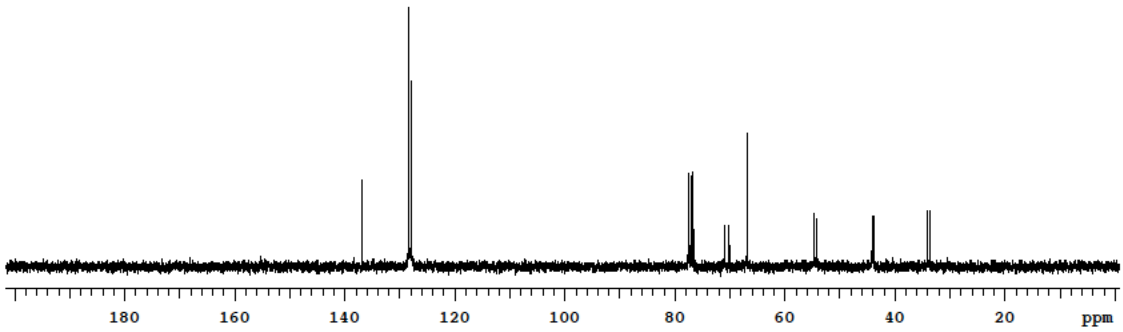
2.23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120
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80
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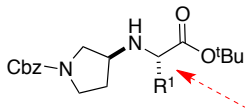
ppm

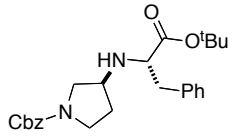
Note on epimerization and purification by crystallization of **4**



Variable amount of epimerization at the indicated center was found to occur during the reaction. This was difficult to control and could depend on rate of warming up to room temperature, scale of reaction and duration of storage of the free amine. Nevertheless, the epimer was completely removed by crystallization of **4.HCl** from EtOH or MeCN as described below. Since the NMR spectra of derivatives containing the Cbz group reveals rotamers, hydrogenation of the crystallized products was also carried out to confirm stereochemical purity (page S26).

Compound **4d**

(*S*)-benzyl 3-(((*S*)-1-(*tert*-butoxy)-1-oxo-3-phenylpropan-2-yl)amino)pyrrolidine-1-carboxylate



Procedure: To a solution of Cbz-protected pyrrolidin-3-ol (2.58 g, 11.7 mmol) in dry dichloromethane (15 mL) at -78 ºC was added diisopropylethyl amine (2.2 mL, 12.9 mmol, 1.1 equiv), dropwise. Freshly distilled (P_2O_5) triflic anyhydride (2.1 mL, 12.2 mmol, 1.05 equiv) was added using a syringe pump at rate of 4 mL/hr ensuring that the bath temperature does not exceed -70 ºC. The reaction mixture turned pink. On complete addition of triflic anyhydride, the reaction was stirred for 10 min. A solution of phenylalanine *tert*-butyl ester (3.89 g, 17.6 mmol, 1.5 equiv) in dichloromethane (15 mL) was then added at a rate of 30 mL/hr. The reaction was stirred for 10 minutes at -78 ºC, and allowed to warm to 25 ºC. During this time the reaction assumed an orange hue. After 18 h, the reaction mixture was transferred to a separatory funnel and diluted with dichloromethane (125 mL). The organic layer was extracted with saturated sodium bicarbonate (2 X 150 mL) and brine (1 X 100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (SiO_2, 1:5 ethyl acetate/dichloromethane; cerric ammonium molybdate stain and UV for visualization) to afford the product in 55 % yield.

Note: NMR spectra show two conformers due to restricted rotation about the N-C=O bond of the Cbz group.

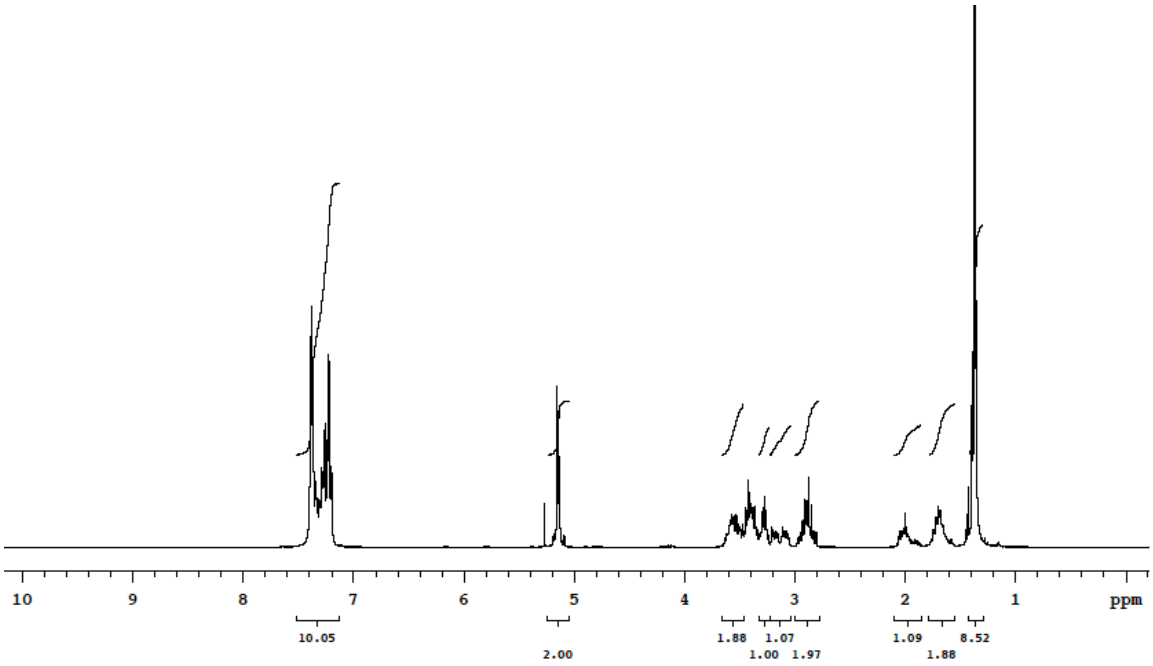
Physical state: colorless oil

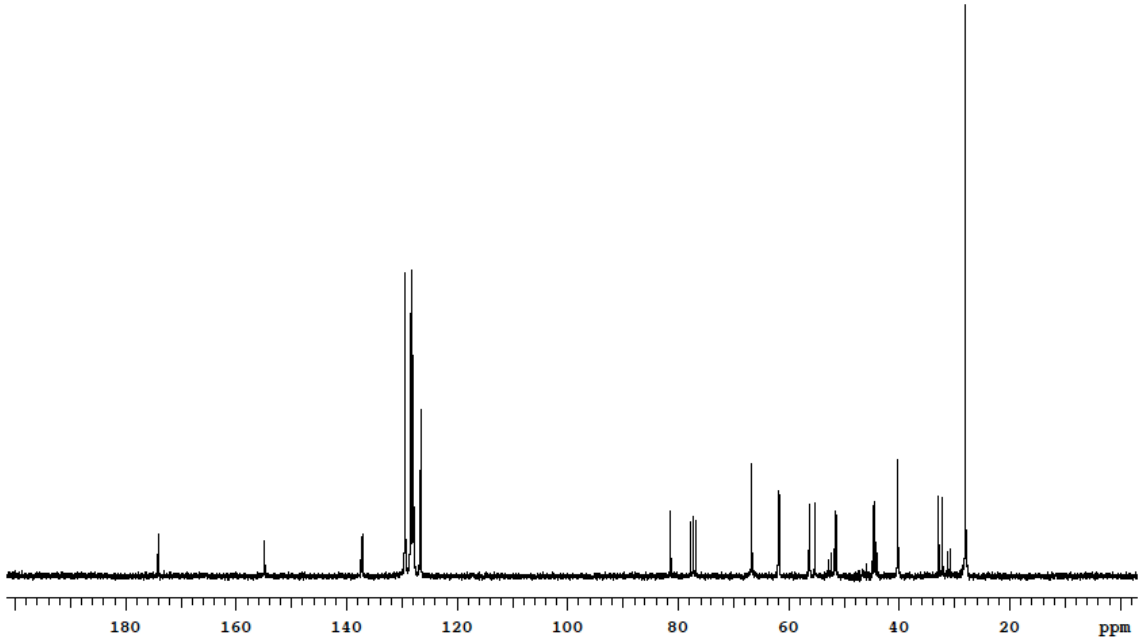
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42-7.18 (m, 10 H), 5.16-5.12 (m, 2H), 3.62-3.48 (m, 2H), 3.46-3.34 (m, 2H), 3.32-3.24 (m, 1H), 3.22-3.04 (m, 2H), 2.98-2.80 (m, 2H), 2.08-1.88 (m, 1H), 1.78-1.60 (m, 1H), 1.40-1.34 (m, 9H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 174.1, 154.9, 137.3, 137.0, 129.4, 128.5, 128.3, 127.94, 127.86, 126.6, 81.3, 66.7, 61.8, 56.3 and 55.3, 51.7 and 51.4, 44.8 and 44.4, 40.3, 32.9 and 32.1, 28.0

IR (film, cm^{-1}) 3324, 2978, 2882, 1722, 1703, 1682, 1454, 1417, 1361, 1152, 1113

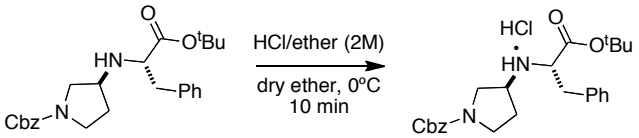
MS (ESI) m/z calcd for $(M+H)^+$ $C_{25}H_{33}N_2O_4$ 425.24; found 425.26





Compound **4d.HCl**

(*S*)-benzyl 3-(((*S*)-1-(*tert*-butoxy)-1-oxo-3-phenylpropan-2-yl)amino)pyrrolidine-1-carboxylate hydrochloride



Procedure: The amine was dissolved in dry ether (0.05 M) and cooled to 0 ºC. A solution of HCl(g)/ether (2 M, 1.1 equiv) was added drop wise. Upon complete precipitation, the solution was stirred for 5 min, and filtered. The precipitate was washed with dry ether to afford the pure product in > 90 % yield, which was recrystallized from ethanol.

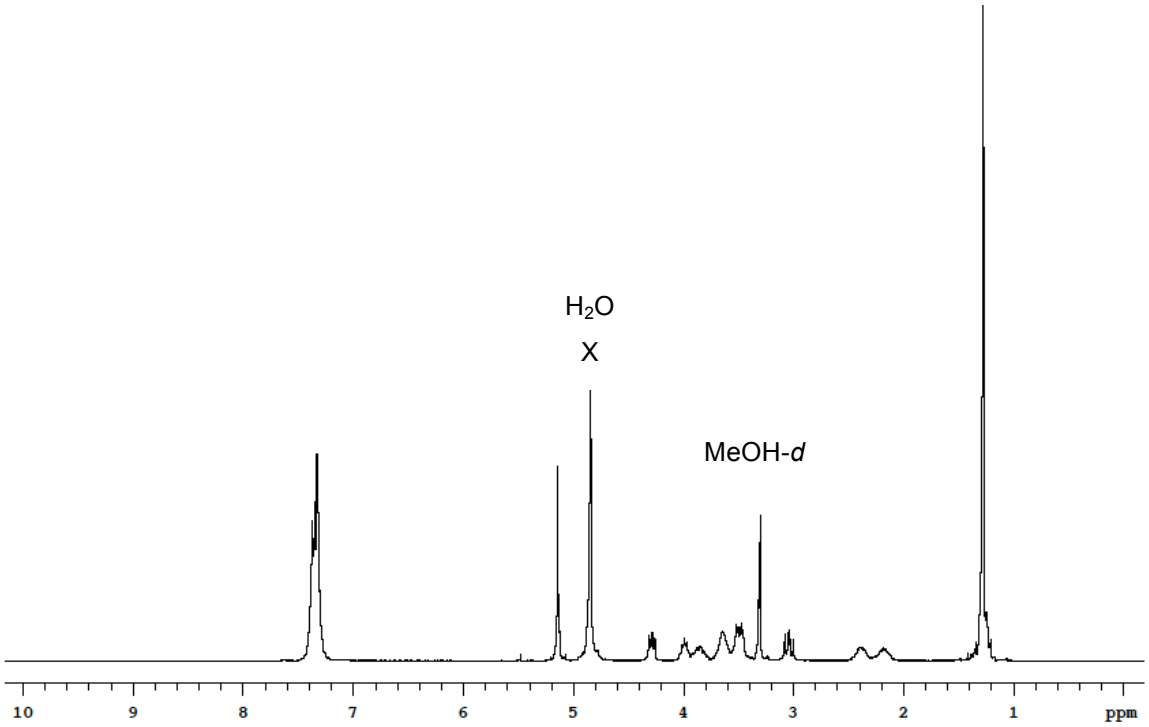
Note: NMR spectra show two conformers due to restricted rotation about the N-C=O bond of the Cbz group.

Physical state: White cubic crystals (hot ethanol, ~ 23 mL/gram), m.p = 180-181 ºC

$[\alpha]^{20}$+ 26.1 (*c* 0.5, MeOH)

^{1}H-NMR (300 MHz, CD_3OD) δ 7.41-7.20 (m, 10H), 5.14 (s, 2H), 4.28 (dd, *J* = 9.9, 5.1 Hz, 1H), 4.04-3.94 (m, 1H), 3.92-3.78 (m, 1H), 3.72-3.58 (m, 2H), 3.51 (d, *J* = 5.4 Hz, 1H), 3.46 (d, *J* = 5.1 Hz, 1H), 3.04 (dd, *J* = 13.8, 9.9 Hz, 1H), 2.48-2.32 (m, 1H), 2.28-208 (m, 1H), 1.28 (s, 9H)

^{13}C-NMR (75 MHz, CD_3OD) δ 167.3, 154.7, 136.5, 133.6, 129.4, 128.5, 128.2, 127.9, 127.7, 127.5, 84.5, 67.0, 60.3, 56.3 and 55.5, 48.1 and 47.7, 43.8 and 43.6, 37.8, 28.2 and 27.4, 26.5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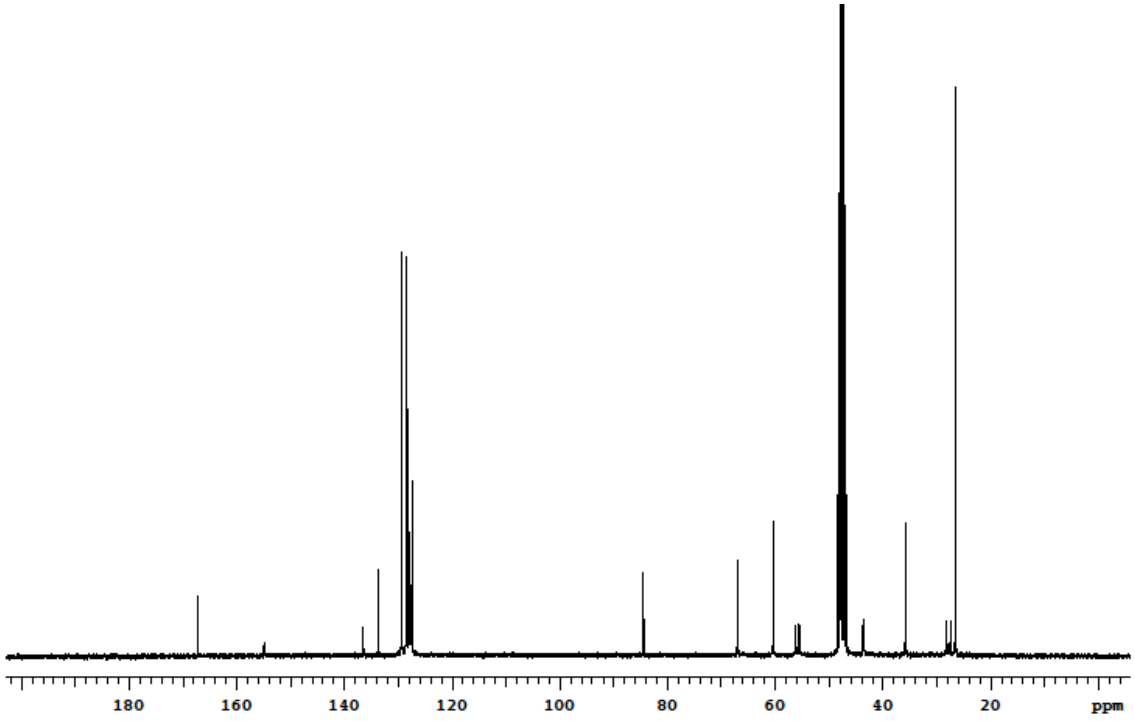
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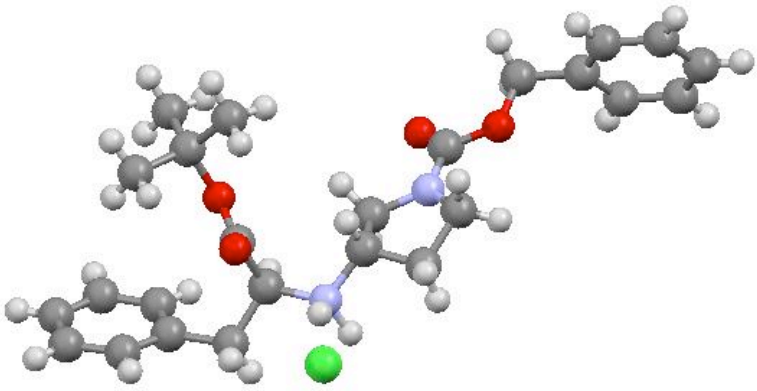
X-Ray for compound **4d.HCl**



Crystal data and structure refinement details

Empirical formula C25 H33 Cl N2 O4

Formula weight 460.98

Temperature 110(2) K

Wavelength 1.54178 Å

Crystal system Monoclinic

Space group P2(1)

Unit cell dimensions a = 5.4168(8) Å a= 90°.

b = 9.5940(15) Å b= 93.420(11)°.

c = 23.395(4) Å g = 90°.

Volume 1213.6(3) $Å^3$

Z 2

Density (calculated) 1.261 Mg/m^3

Absorption coefficient 1.660 mm^{-1}

F(000)492

Crystal size 0.05 x 0.03 x 0.01 mm^3

Theta range for data collection 3.79 to 59.95°.

Index ranges -5<=h<=6, -10<=k<=10, -26<=l<=26

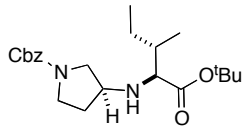
Reflections collected 10759

Independent reflections 3162 [R(int) = 0.0697]

Completeness to theta = 59.95°	94.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9836 and 0.9216
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3162 / 1 / 290
Goodness-of-fit on F^2	1.009
Final R indices [I>2sigma(I)]	R1 = 0.0604, wR2 = 0.1347
R indices (all data)	R1 = 0.0865, wR2 = 0.1492
Absolute structure parameter	0.00(4)
Largest diff. peak and hole	0.379 and -0.230 e.$Å^{-3}$

Compound **4c**

S)-benzyl 3-(((2*S*,3*S*)-1-(*tert*-butoxy)-3-methyl-1-oxopentan-2-yl)amino)pyrrolidine-1-carboxylate



Procedure: As described before for (*S*)-benzyl 3-(((*S*)-1-(*tert*-butoxy)-1-oxo-3-phenylpropan-2-yl)amino)pyrrolidine-1-carboxylate. Column chromatography was performed using 10 % ethyl acetate in dichloromethane to afford the product in 60 % yield.

Note: NMR spectra show two conformers due to restricted rotation about the N-C=O bond of the Cbz group.

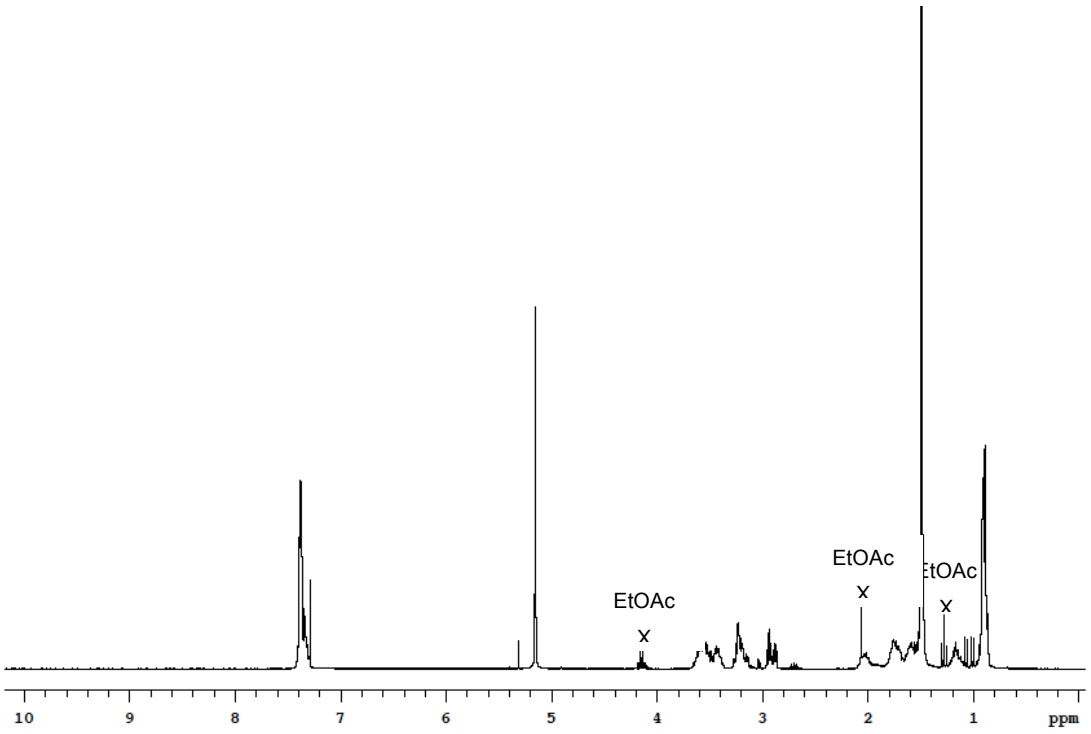
Physical state: colorless oil

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42-7.30 (m, 5H), 5.12 (s, 2H), 3.66-3.48 (m, 2H), 3.48-3.39 (m, 1H), 3.27-3.14 (m, 2H), 2.97-2.85 (m, 1H), 2.08-1.98 (m, 1H), 1.80-1.66 (m, 2H), 1.64-1.52 (m, 1H), 1.47 (m, 9H), 1.22-1.10 (m, 1H), 0.93-0.89 (m, 6H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 174.7, 157.9, 155.0, 137.1, 128.4, 127.9, 81.1, 66.7, 64.9, 56.6 and 55.6, 51.9 and 51.5, 44.8 and 44.5, 38.6, 33.0 and 32.3, 28.9, 25.4, 15.6, 11.5

IR (film, cm^{-1}) 2967, 2876, 1715, 1454, 1418, 1339, 1252, 1209, 1148, 1117, 698

MS (ESI) m/z calcd for $(M+H)^+$ $C_{22}H_{35}N_2O_4$ 391.25; found 391.26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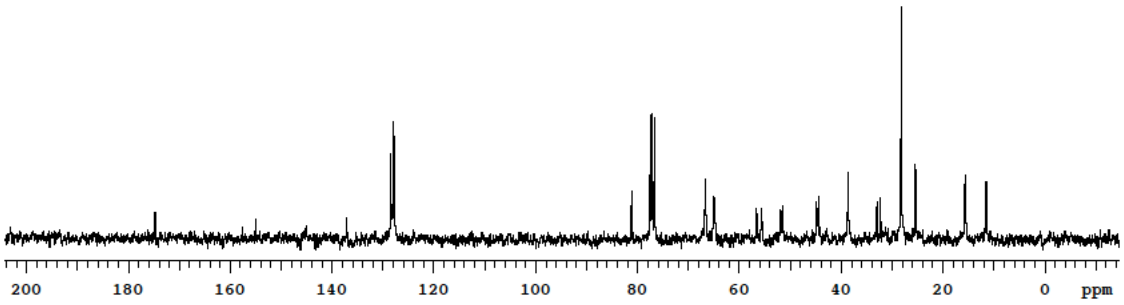
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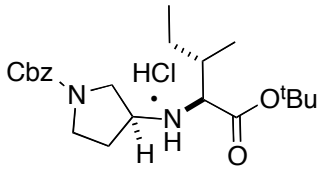
180
160
140
120
100
80
60
40
20
0
ppm

Compound **4c.HCl**

Characterization of the hydrochloride salt



Procedure: As described before for compound **4d.HCl**. The product was re-crystallized from hot MeCN (~28 mL/gram).

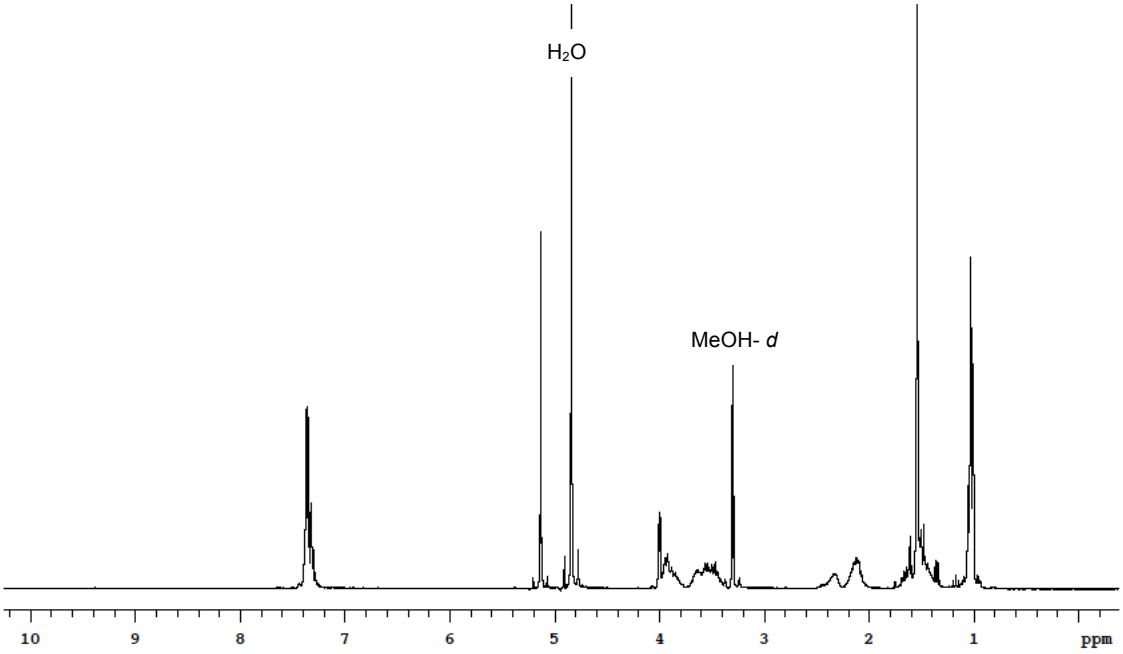
Note: NMR spectra show two conformers due to restricted rotation about the N-C=O bond of the Cbz group.

Physical state: White crystals (MeCN), mp =176-177 ºC

$[\alpha]^{20}$ + 24.4 (*c* 0.5, MeOH)

^{1}H-NMR (300 MHz, CD_3OD) δ 7.37-7.28 (m, 5H), 5.14 (s, 2H), 4.00 (m, 1H), 3.98-3.78 (m, 2H), 3.72-3.60 (m, 1H), 3.60-3.40 (m, 2H), 2.45-2.28 (m, 1H), 2.22-2.06 (m, 1H), 1.72-1.60 (m, 1H), 1.54 (s, 9H), 1.50-1.36 (m, 2H), 1.08-0.98 (m, 6H)

^{13}C-NMR (75 MHz, CD_3OD) δ 166.8, 154.8, 136.5, 128.1, 127.8, 127.7, 84.8, 67.0, 63.6, 57.1 and 56.4, 48.0 and 47.7, 43.8 and 43.6, 36.1, 28.0 and 27.2, 26.8, 26.6, 12.9, 10.8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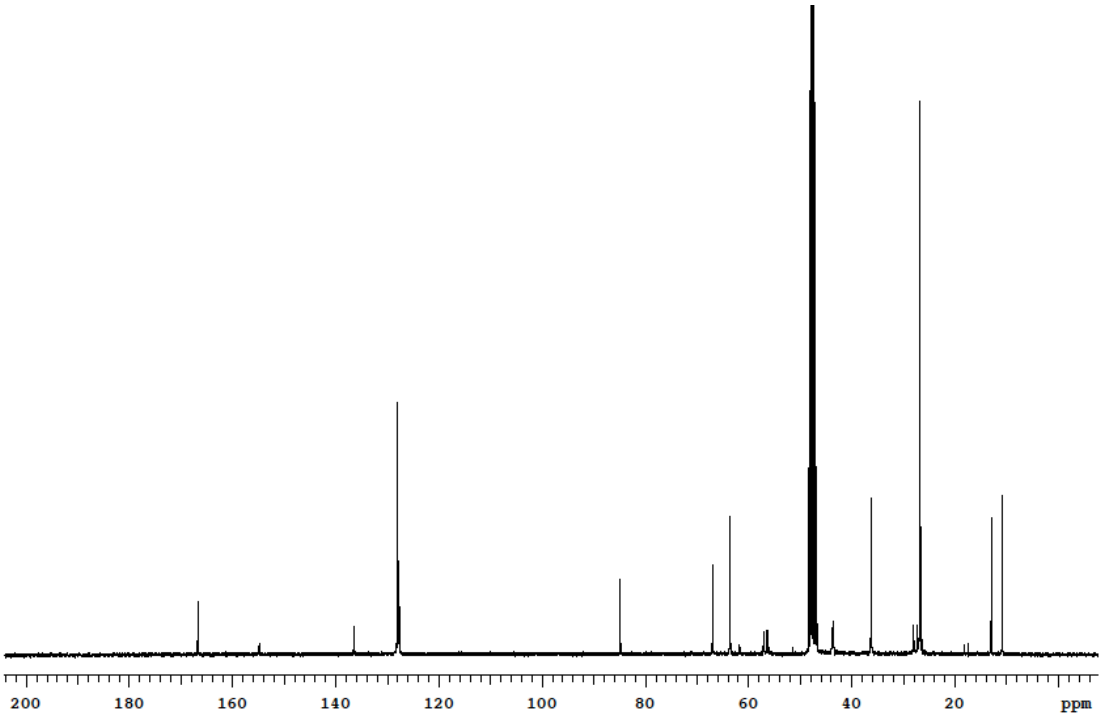
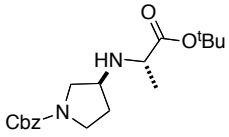
MeOH- d
10
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
ppm

Compound **4a**

(*S*)-benzyl 3-(((*S*)-1-(*tert*-butoxy)-1-oxopropan-2-yl)amino)pyrrolidine-1-carboxylate



Procedure: As described before for (*S*)-benzyl 3-(((*S*)-1-(*tert*-butoxy)-1-oxo-3-phenylpropan-2-yl)amino)pyrrolidine-1-carboxylate. The residue was purified by column chromatography (SiO_2, 1:2 ethyl acetate/dichloromethane; Cerric ammonium molybdate stain and UV for visualization) to afford the product in 59 % yield.

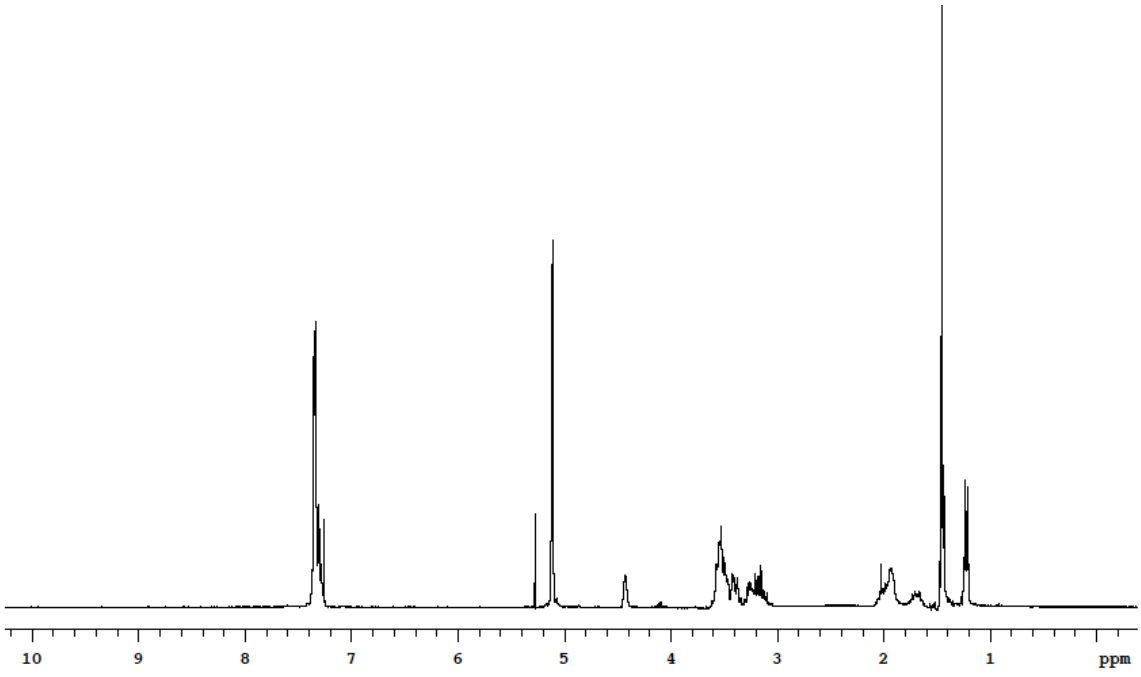
Note: NMR spectra show two conformers due to restricted rotation about the N-C=O bond of the Cbz group.

Physical state: colorless oil

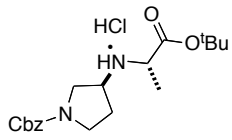
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.26 (m, 5H), 5.11 (m, 2H), 4.40 (br s, 1H), 3.66-3.45 (m, 3H), 3.44-3.33 (m, 1H), 3.31-3.05 (m, 2H), 2.02-1.84 (m, 1H), 1.78-1.58 (m, 1H), 1.48 (s, 9H), 1.22 (d, *J* = 6.0 Hz, 3H*)*

IR (film, cm^{-1}) 3435 (br), 2976, 2949, 2890, 1675, 1456, 1448, 1420, 1363, 1340, 1212, 1150, 1117, 770, 699

MS (ESI) m/z calcd for $C_{19}H_{29}N_2O_4$ $(M+H)^+$ 349.20; found 349.20


10
9
8
7
6
5
4
3
2
1
ppm

Compound **4a.HCl**



Procedure: As described before for compound **4d.HCl**. The product was re-crystallized from hot MeCN (~ 10 mL/gram).

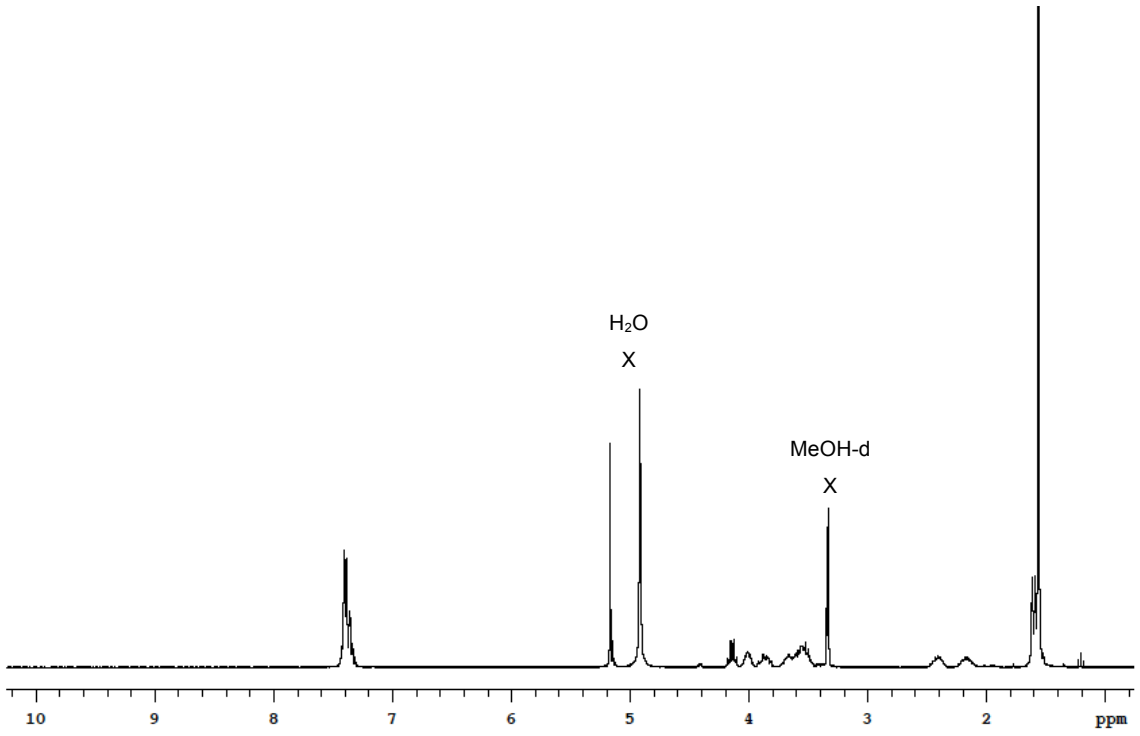
Note: NMR spectra show two conformers due to restricted rotation about the N-C=O bond of the Cbz group.

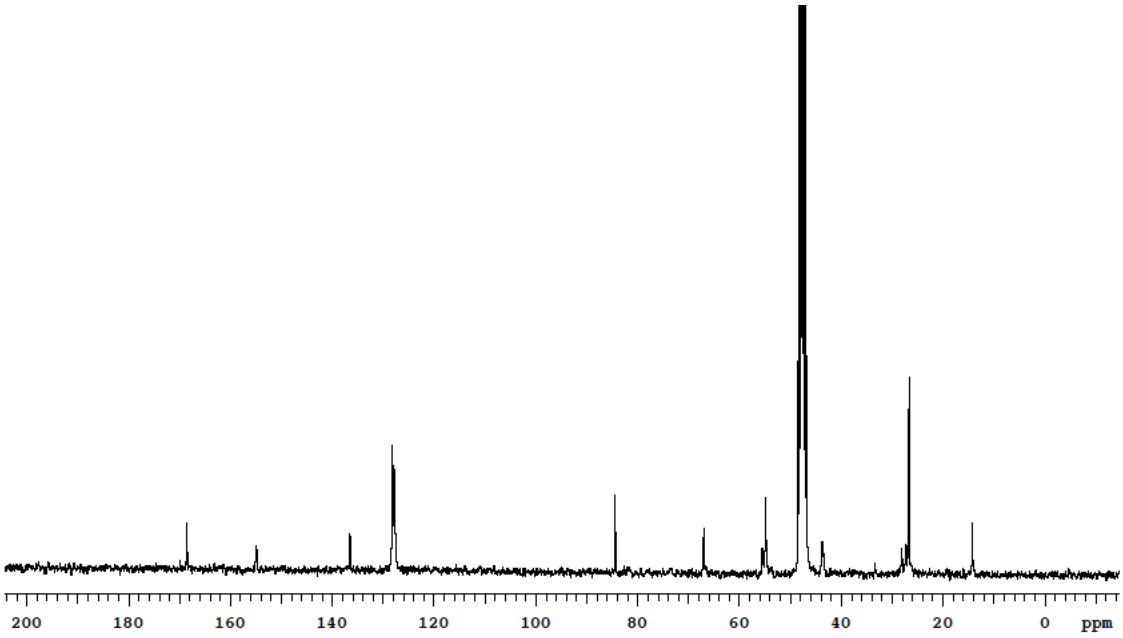
Physical state: White needles (MeCN), mp = 154-155 ºC

$[\alpha]^{20}$ – 1.8 (*c* 0.5, MeOH)

^{1}H-NMR (300 MHz, CD_3OD) δ 7.44-7.31 (m, 5H), 5.19 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 1H), 4.08-3.94 (m, 1H), 3.94-3.78 (m, 1H), 3.75-3.43 (m, 3H), 2.51-2.34 (m, 1H), 2.27-2.08 (m, 1H), 1.60 (d, *J* = 7.5 Hz, 3H), 1.56 (s, 9H)

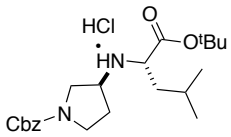
^{13}C-NMR (75 MHz, CD_3OD) δ 168.6, 155.0, 136.5, 128.2, 127.9, 127.6, 84.4, 67.0, 54.9, 55.4 and 54.6, 43.8 and 43.5, 28.0 and 27.2, 26.7, 14.2 (one of the pyrrolidine ring carbons overlap with methanol solvent multiplet)


H2O
X
MeOH-d
X
10
9
8
7
6
5
4
3
2
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm

Compound **4g.HCl**

(*S*)-benzyl 3-(((*S*)-1-(*tert*-butoxy)-4-methyl-1-oxopentan-2-yl)amino)pyrrolidine-1-carboxylate

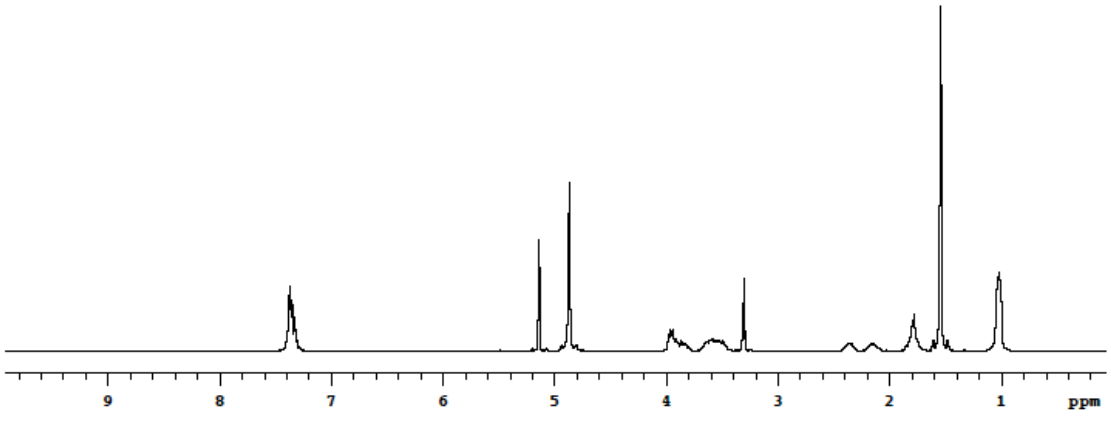


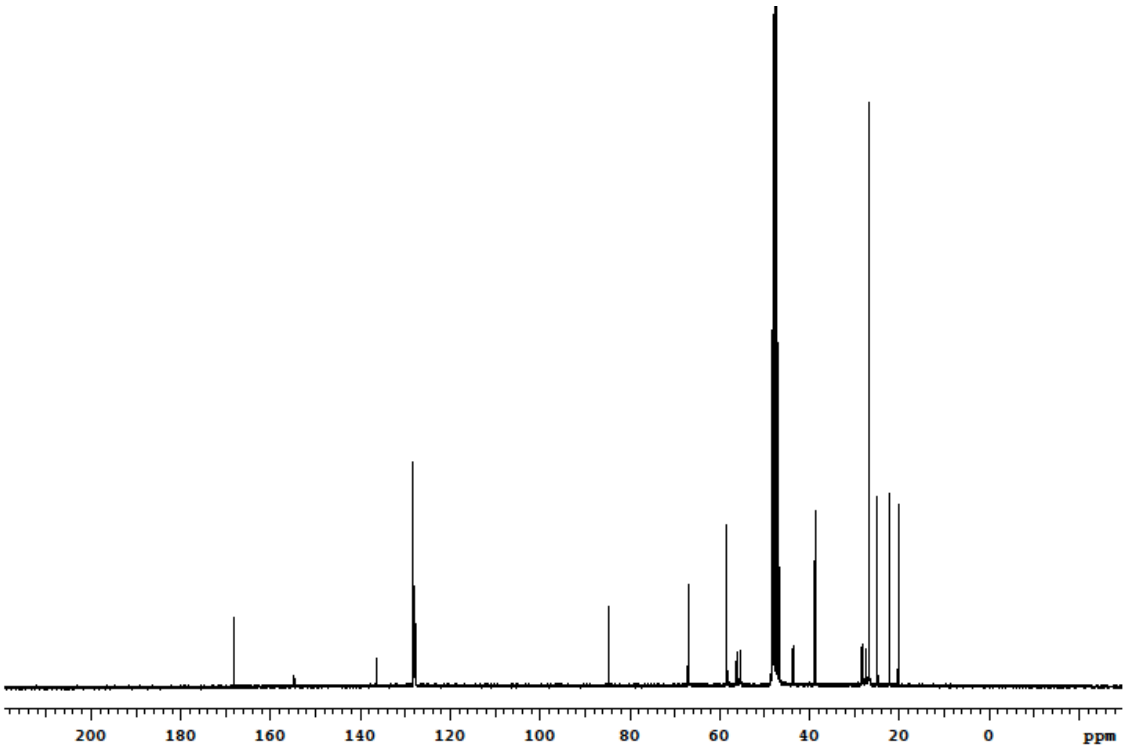
Procedure: As described before for compound **4d.HCl**. The product was re-crystallized from hot MeCN (70 mL/gram)

Physical state: White needles (MeCN)

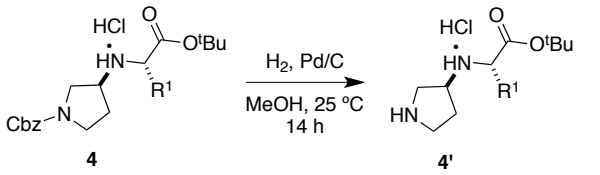
^{1}H-NMR (300 MHz, CD_3OD) δ 7.43-7.27 (m, 5H), 5.14 (app s, 2H), 4.02-3.74 (m, 3H), 3.68-3.40 (m, 3H), 2.44-2.27 (m, 1H), 2.23-2.03 (m, 1H), 1.88-1.70 (m, 3H), 1.54 (s, 9H), 1.07-0.98 (m, 6H)

^{13}C-NMR (75 MHz, CD_3OD) δ 168.1, 154.9 and 154.7, 136.5, 128.2, 127.8, 127.7, 84.8, 67.0, 58.3, 56.2 and 55.4, 48.1 and 47.7, 43.8 and 43.5, 38.7, 28.2 and 27.4, 26.7, 24.8, 22.2, 20.2




200
180
160
140
120
100
80
60
40
20
0
ppm

General procedure for hydrogenation of substrates **4.HCl** to afford diamine derivatives **4'**



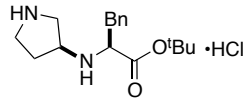
1 conformer, 1 diastereomer

> 97 %

To a stirred solution of the starting material (**4.HCl**, 0.07 mmol) in MeOH (1 mL) was added 10 % palladium on carbon (15 mg, 0.2 eq Pd) under a stream of N_2. The reaction was evacuated and re-filled with N2 and placed under an atmosphere of H_2 (balloon) for 14 h. The reaction was filtered using a small pipet plug of SiO_2. The plug was washed with MeOH (4 mL) and the combined eluent was concentrated to afford the pure products (**4'**) in > 97 % yield

Compound **4'd**

(*S*)-*tert*-butyl 3-phenyl-2-((*S*)-pyrrolidin-3-ylamino)propanoate hydrochloride

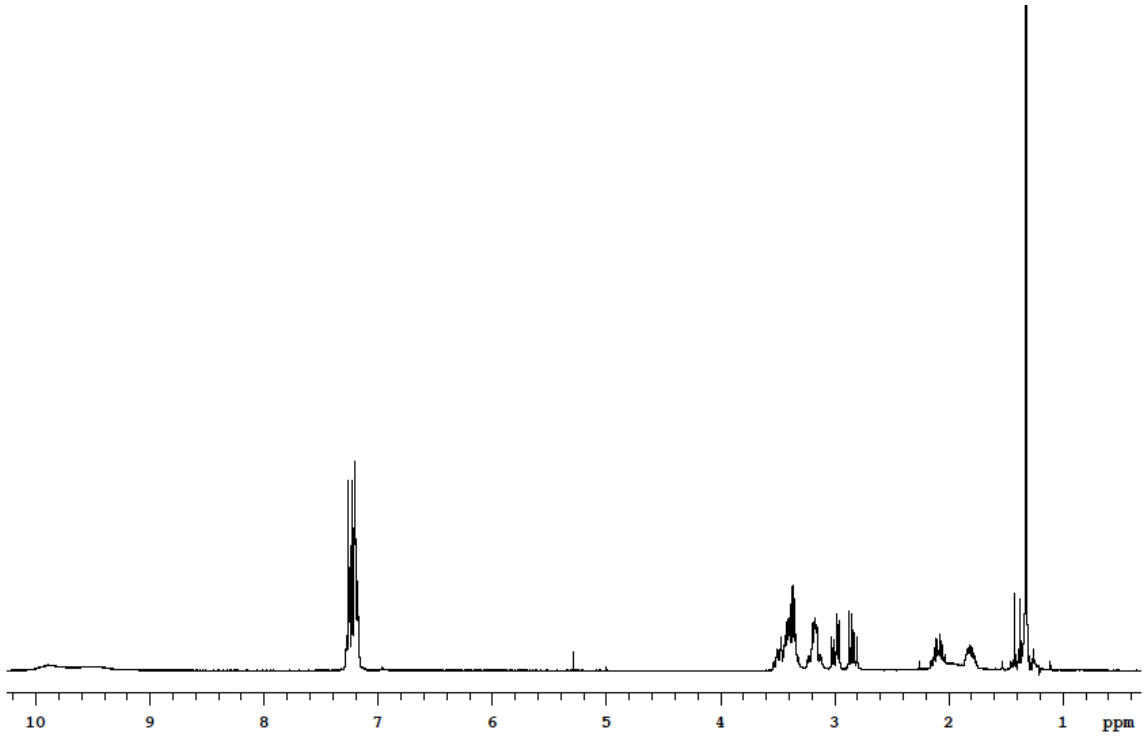


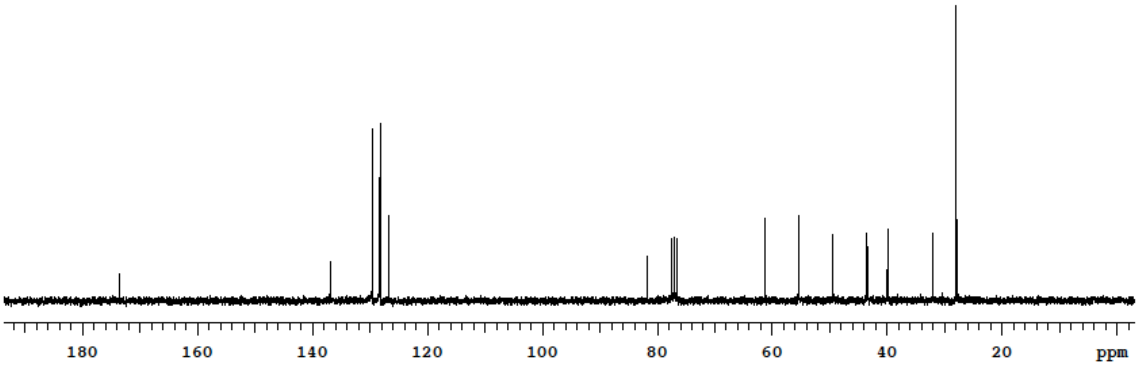
Physical state: White solid

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31-7.13 (m, 5H), 3.37-3.27 (m, 4H), 3.24-3.10 (m, 2H), 2.99 (dd, *J* = 13.4, 5.9 Hz, 1H), 2.84 (dd, *J* = 13.2, 7.8 Hz, 1H), 2.16-2.02 (m, 1H), 1.88-1.73 (m, 1H), 1.32 (s, 9H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.5, 136.9, 129.6, 128.3, 126.7, 81.8, 61.2, 55.4, 49.4, 43.5, 39.9, 32.0, 28.0

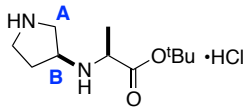
HRMS (ESI) m/z calcd for $C_{17}H_{27}N_2O_2$ $(M+H)^+$ 291.2072; found 291.2079 (2.2 ppm)




180
160
140
120
100
80
60
40
20
ppm

Compound **4'a**

(*S*)-*tert*-butyl 2-((*S*)-pyrrolidin-3-ylamino)propanoate hydrochloride



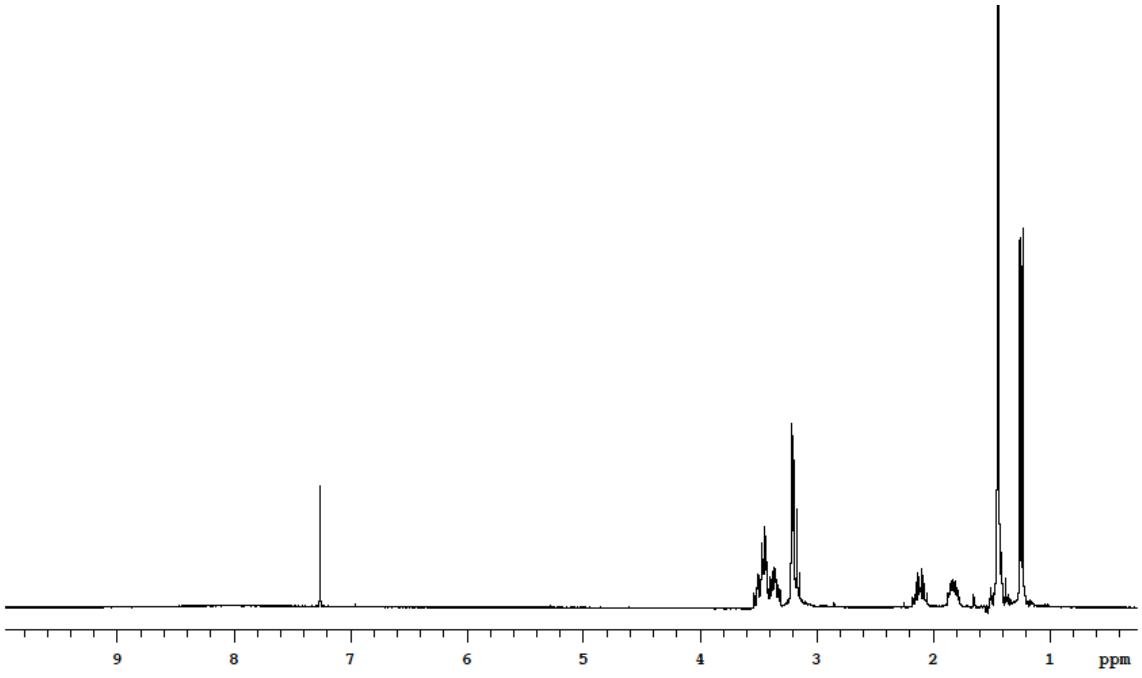
Procedure: As per the general procedure for hydrogenation of **4.HCl** (page S26)

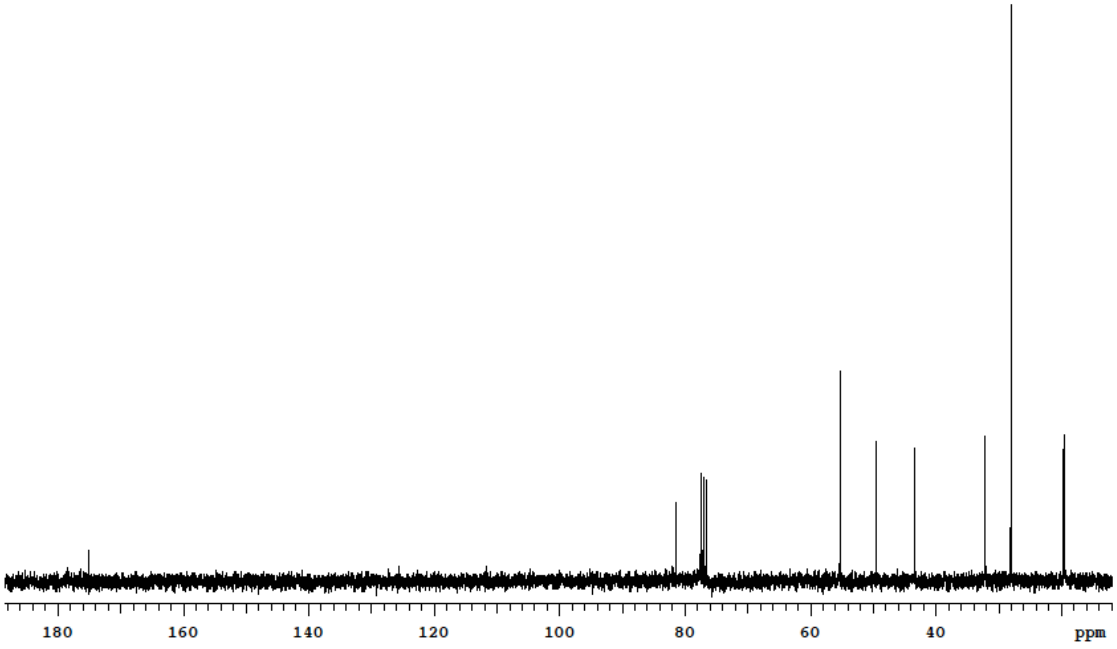
Physical state: White solid

^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.58-3.42 (m, 2H), 3.42-3.30 (m, 1H), 3.27-3.11 (m, 3H), 2.21-2.02 (m, 1H), 1.90-1.75 (m, 1H), 1.44 (s, 9H), 1.24 (d, *J* = 6.9 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 175.0, 81.4, 55.2, 49.5, 43.5, 32.1, 28.0, 19.6

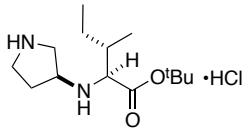
Note: Carbons **A** and **B** overlap at 55.2 ppm.




180
160
140
120
100
80
60
40
ppm

Compound **4'c**

(2*S*,3*S*)-*tert*-butyl 3-methyl-2-((*S*)-pyrrolidin-3-ylamino)pentanoate hydrochloride

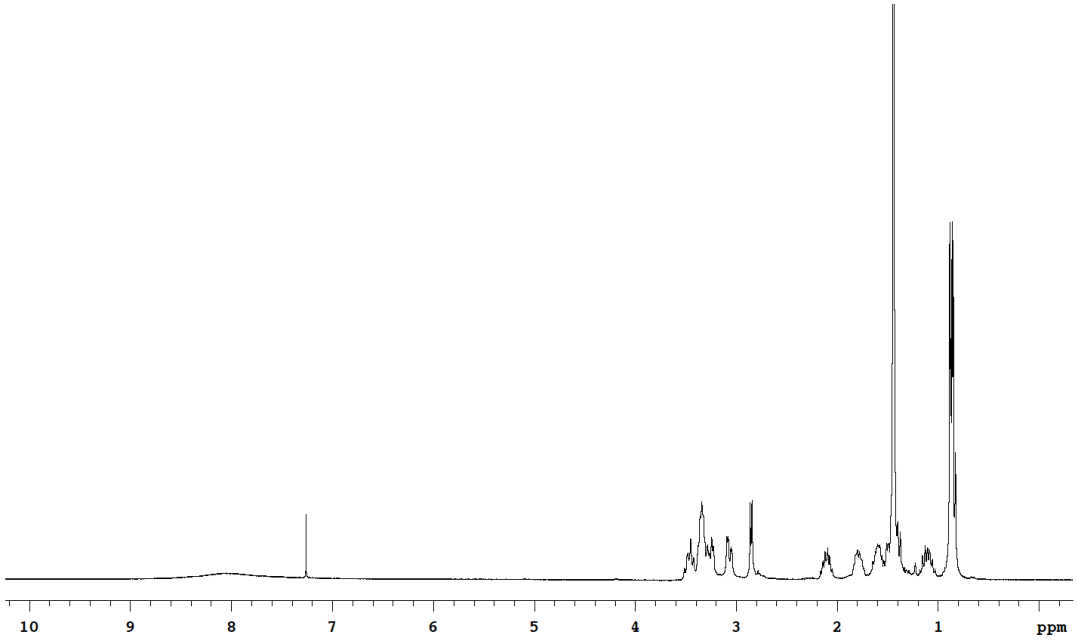


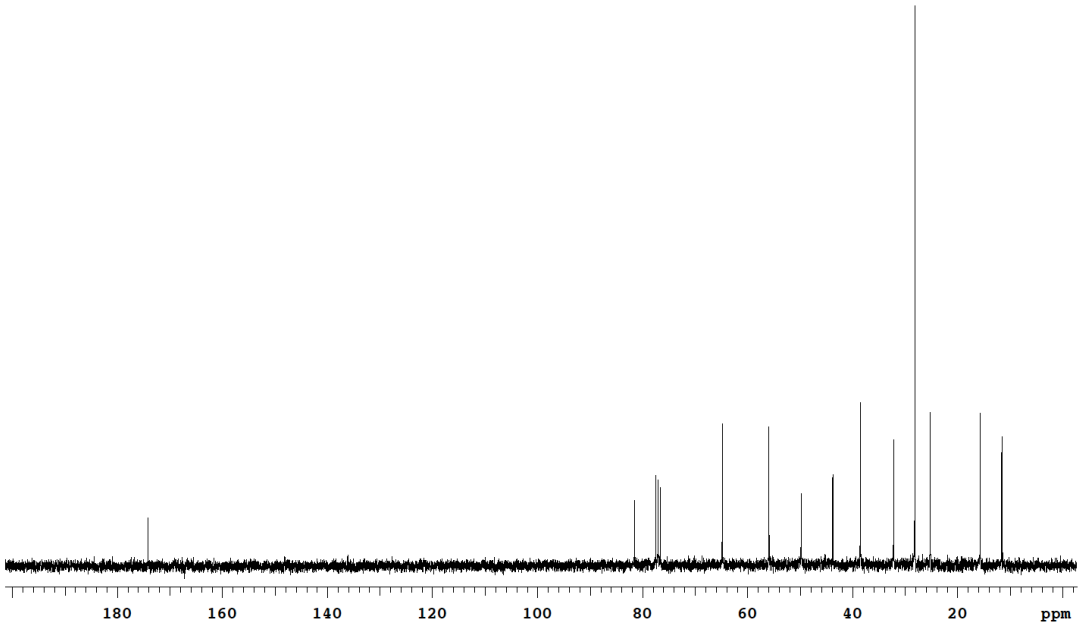
Procedure: As per the general procedure for hydrogenation of **4.HCl** (page S26)

Physical state: White solid

^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.52-3.19 (m, 4H), 3.07 (dd, *J* = 11.6, 3.8 Hz, 1H), 2.85 (d, *J* = 5.4 Hz, 1H), 2.18-2.02 (m, 1H), 1.85-1.72 (m, 1H), 1.65-1.43 (m, 1H), 1.42-1.36 (m, 10H), 1.19-1.02 (m, 1H), 0.90-1.82 (m, 6H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 174.2, 81.5, 64.8, 56.0, 49.8, 43.8, 38.5, 32.2, 28.1, 25.3, 15.7, 11.6



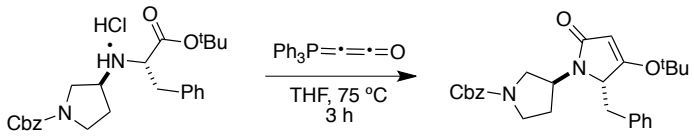

180
160
140
120
100
80
60
40
20
ppm

Note on cyclizations with Bestmann's ylide

The by-product of the following reaction is Ph_3PO and can be difficult to separate from the product. For sidechains Bn (Phe) and ^{s}Bu (Ile) complete separation is possible on small scales (typically 100-500 mg). However for many other sidechains little to no separation is possible. A general solution to this problem is to separate only excess Bestmann's ylide at this stage by passing through a short column of silica gel. The mixture of Ph_3PO and product is subject to hydrogenolysis, which allows efficient separation of Ph_3PO from the more polar amine product. The procedure corresponding to **6a** is a representative example.

Compound **5d**

(*S*)-benzyl 3-((*S*)-2-benzyl-3-(*tert*-butoxy)-5-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)pyrrolidine-1-carboxylate



Procedure: The re-crystallized hydrochloride salt (2.8 g, 6.1 mmol) was suspended in dry THF (50 mL) and heated to 75 ºC under an Argon atmosphere. Bestmann's ylide (2X re-crystallized from PhMe, 2.21 g, 7.32 mmol, 1.2 equiv) was added in one portion. After 30 min, a second portion of Bestmann's ylide (368 mg, 1.22 mmol, 0.2 equiv) was added, and this process was repeated four additional times at 15 min intervals to complete the addition of 2.2 equiv of ylide. The reaction was monitored by NMR spectroscopy. After completion of reaction (~ 3 h), the solvent was evaporated. Ether (150 mL) was added to the residue and stirred for 3 h. The ether layer was decanted, and concentrated to obtain the crude product contaminated with Ph_3PO. The product was isolated by flash chromatography (5-10 % acetone/dichlromethane) in 72 % yield.

Note: NMR spectra show two conformers due to restricted rotation about the N-C=O bond of the Cbz group.

Physical state: Colorless oil

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40-7.12 (m, 10 H), 5,18-5.12 (m, 2H), 4.90 (app s), 4.18-4.02 (m, 2H), 3.84-3.74 (m, 1H), 3.74-3.58 (m, 2H), 3.42-3.28 (m, 1H), 3.16-2.96 (m, 2H), 2.62-2.38 (m, 1H), 2.18-2.02 (m, 1H), 1.38-1.34 (s, 9H)

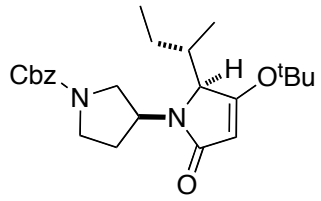
^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.7, 170.2, 155.0, 137.0, 135.0, 129.4, 128.5, 128.3, 128.0, 127.9, 126.9, 97.2, 82.0, 66.8, 63.1 and 62.7, 52.9 and 52.3, 47.5 and 47.1, 44.5, 36.8 and 36.6, 28.2, 27.7

IR (film, cm^{-1}) 3564, 1701, 1618, 1454, 1417, 1360, 1338, 1258, 1167, 1119, 1078, 810, 698

HRMS (ESI) m/z calcd for $(M+H)^+$ $C_{27}H_{33}N_2O_4$ 449.2455; found 449.2440 (3.3 ppm)

Compound **5c**

(*S*)-benzyl 3-((*S*)-3-(*tert*-butoxy)-2-((*S*)-*sec*-butyl)-5-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)pyrrolidine-1-carboxylate



Procedure: As described for compound **5d** (in this case the reaction is slower due to steric hindrance and was complete after 24 h; slightly higher yields were obtained by carrying out the reaction in dioxane at 100 ºC). Column chromatography using 5 % acetone in dichloromethane as eluent afforded the product in 60 % yield.

Physical state: pale yellow oil

$[\alpha]^{20}$ + 42.1 (*c* 0.8, MeOH)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30-7.18 (m, 5H), 5.09 (s, 2H), 4.96 (s, 1H), 4.02-3.92 (m, 1H), 3.77 (d, *J* = 2.4 Hz, 1H), 3.70-3.52 (m, 3H), 3.32-3.21 (m, 1H), 2.54-2.33 (m, 1H), 2.02-1.90 (m, 1H), 1.80-1.69 (m, 1H), 1.58-1.40 (m, 1H), 1.39 (s, 9H), 1.24-1.18 (m, 1H), 0.94-0.84 (m, 3H), 0.71-0.6 (m, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.2, 170.3, 154.8, 136.9, 128.4, 127.92, 127.86, 97.4, 81.8, 66.7, 65.9 and 65.6, 52.6 and 51.9, 47.1 and 46.7, 44.5 and 44.3, 36.4, 28.2, 27.4, 26.2, 12.6, 12.4

IR (film, cm^{-1}) 2965, 2876, 1672, 1614, 1418, 1360, 1332, 1211, 1169, 1119

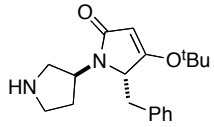
HRMS (ESI) m/z calcd for $(M+H)^+$ $C_{24}H_{34}N_2O_4$ 415.2597; found 415.2580 (4.1 ppm)

Note on physical state of cyclic amines 6

The pure free amines are colorless oils; however the basic pyrrolidine ring gets protonated in the presence of traces of water and solidifies. The anion is chloride that arises from either the starting material or glass as revealed by X-Ray analysis of **6d**.

Compound **6d**

(*S*)-5-benzyl-4-(*tert*-butoxy)-1-((*S*)-pyrrolidin-3-yl)-1*H*-pyrrol-2(5*H*)-one



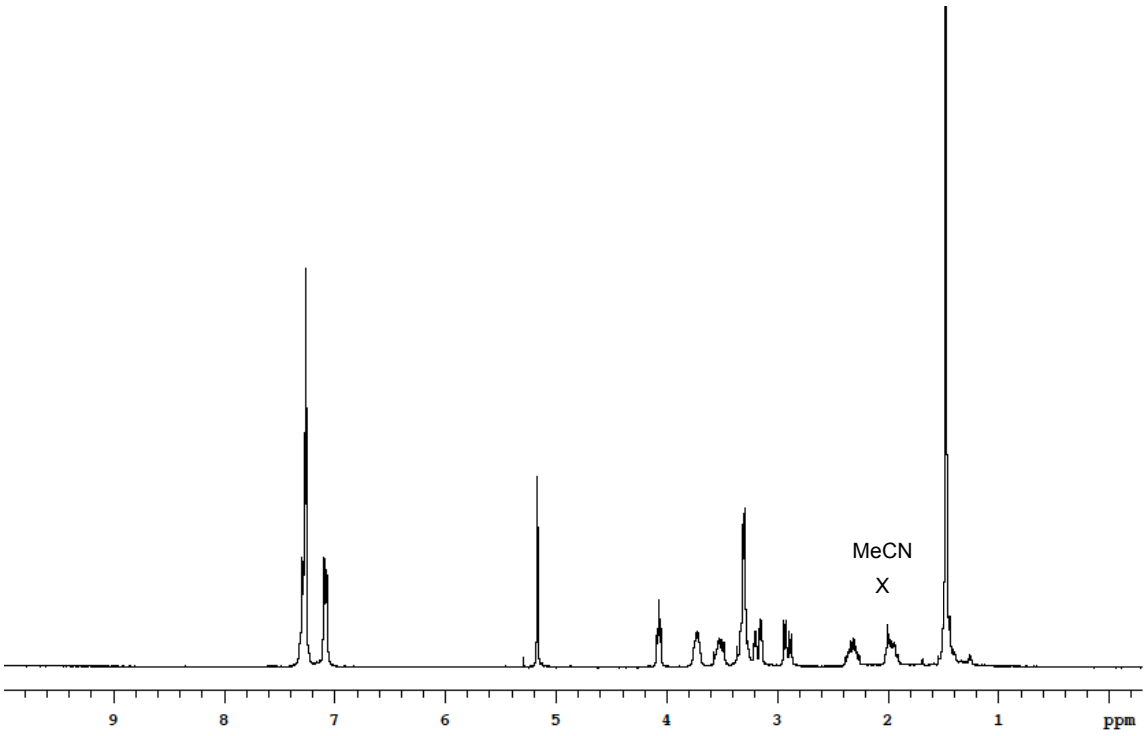
Procedure: To a stirred solution of **5d** (410 mg, 0.91 mmol) in methanol (9 mL) under nitrogen was carefully added 10 wt % Pd/C (195 mg, 0.2 equiv Pd) at 25 ºC. The reaction was evacuated, refilled with N_2, and placed under an atmosphere of H_2 (1 atm, balloon) for 12 h. The reaction mixture was purged with N_2, and filtered over a pad of celite under a gentle vacuum (**SAFETY NOTE:** Do not let the pad run dry). The celite pad was washed with methanol (2 X 25 mL), and the combined filtrates were concentrated. Dichloromethane (2 X 5 mL) was added and the residue was re-concentrated to remove residual methanol. The residue was placed under a high vacuum (< 5 mm Hg) for 2 h to afford the product, which was crystallized from MeCN in 88 % yield.

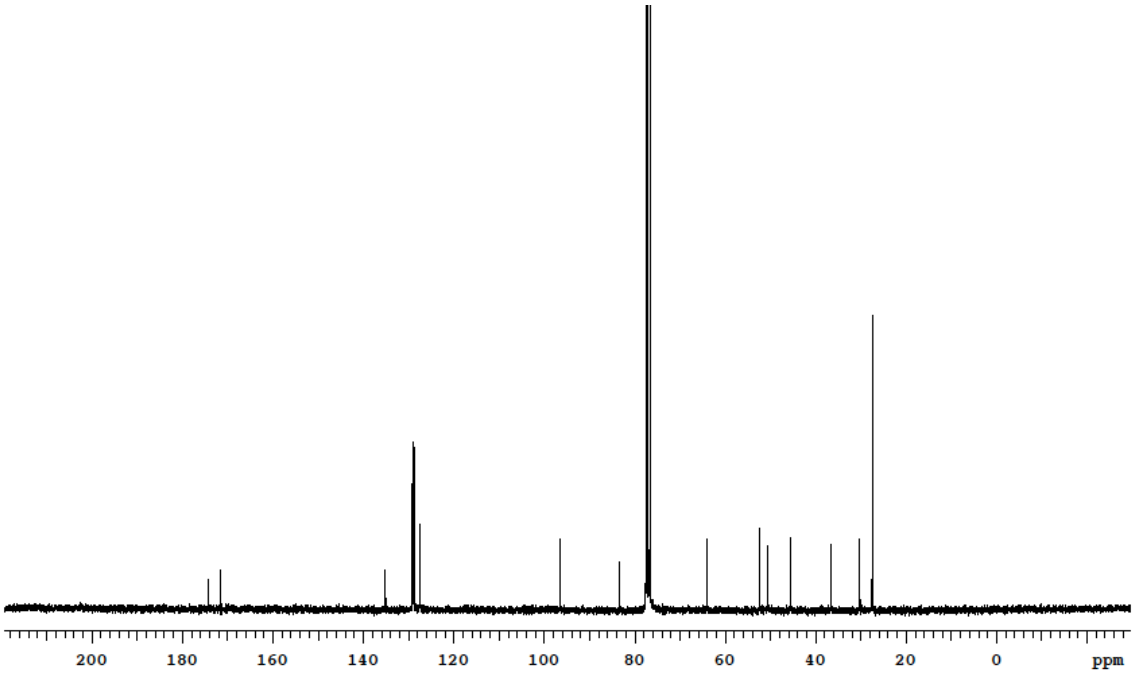
Physical state: white solid

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32-7.24 (m, 3H), 7.12-7.06 (m, 2H), 5.17 (app s, 1H), 4.07 (t, *J* = 5.4 Hz, 1H), 3.77-3.69 (m, 1H), 3.57-3.46 (m, 1H), 3.34-3.28 (m, 3H), 3.18 (dd, *J* = 14.6, 4.7 Hz, 1H), 2.91 (dd, *J* = 14.4, 6.0 Hz, 1H), 2.38-2.26 (m, 1H), 2.02-1.90 (m, 1H), 1.48 (s, 9H)

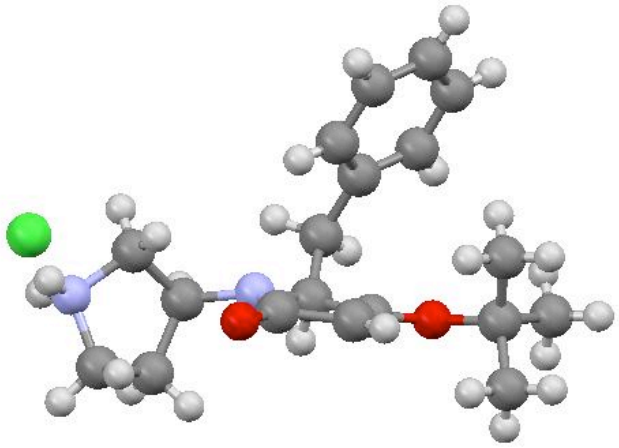
^{13}C-NMR (75 MHz, $CDCl_3$) δ 174.3, 171.5, 135.1, 129.1, 128.8, 127.6, 96.5, 83.3, 64.0, 52.4, 50.6, 45.5, 36.6, 30.2, 27.5

HRMS (ESI) m/z calcd for $(M+H)^+$ $C_{19}H_{27}N_2O_2$ 315.2073; found 315.2062 (3.5 ppm)


MeCN
X
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm

X-Ray for compound **6d.HCl**



Crystal data and structure refinement details

Empirical formula C19 H27 Cl N2 O2

Formula weight 350.88

Temperature 110(2) K

Wavelength 1.54178 Å

Crystal system Monoclinic

Space group P2(1)

Unit cell dimensions a = 11.8906(6) Å a= 90°.

b = 5.7704(3) Å b= 106.185(4)°.

c = 13.5908(7) Å g = 90°.

Volume 895.55(8) $Å^3$

Z 2

Density (calculated) 1.301 Mg/m^3

Absorption coefficient 1.992 mm^{-1}

F(000)376

Crystal size 0.20 x 0.15 x 0.02 mm^3

Theta range for data collection 3.39 to 62.33°.

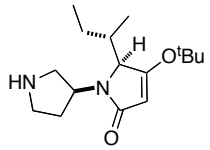
Index ranges -13<=h<=13, -6<=k<=6, -15<=l<=15

Reflections collected 18976

Independent reflections	2697 [R(int) = 0.0497]
Completeness to theta = 62.33°	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9612 and 0.6914
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2697 / 1 / 220
Goodness-of-fit on F^2	1.008
Final R indices [I>2sigma(I)]	R1 = 0.0634, wR2 = 0.1608
R indices (all data)	R1 = 0.0723, wR2 = 0.1691
Absolute structure parameter	0.01(3)
Largest diff. peak and hole	0.949 and -0.295 e.$Å^{-3}$

Compound **6c**

(*S*)-4-(*tert*-butoxy)-5-((*S*)-*sec*-butyl)-1-((*S*)-pyrrolidin-3-yl)-1*H*-pyrrol-2(5*H*)-one



Procedure: To a stirred solution of the starting material **5c** (180 mg, 0.43 mmol) in methanol (5 mL) under nitrogen was carefully added 10 wt % Pd/C (92 mg, 0.2 equiv Pd) at 25 ºC. The reaction was evacuated, refilled with N_2, and placed under an atmosphere of H_2 (1 atm, balloon) for 12 h. The reaction mixture was purged with N_2, and filtered over a pad of celite under a gentle vacuum (SAFETY NOTE: Do not let the pad run dry). The celite pad was washed with methanol (2 X 15 mL), and the combined filtrates were concentrated. The residue was purified by column chromatography (SiO_2, 5 % MeOH/CH_2Cl_2 → 5 % MeOH/ CH_2Cl_2 containing 1 % Et_3N) to afford the product in 96 % yield.

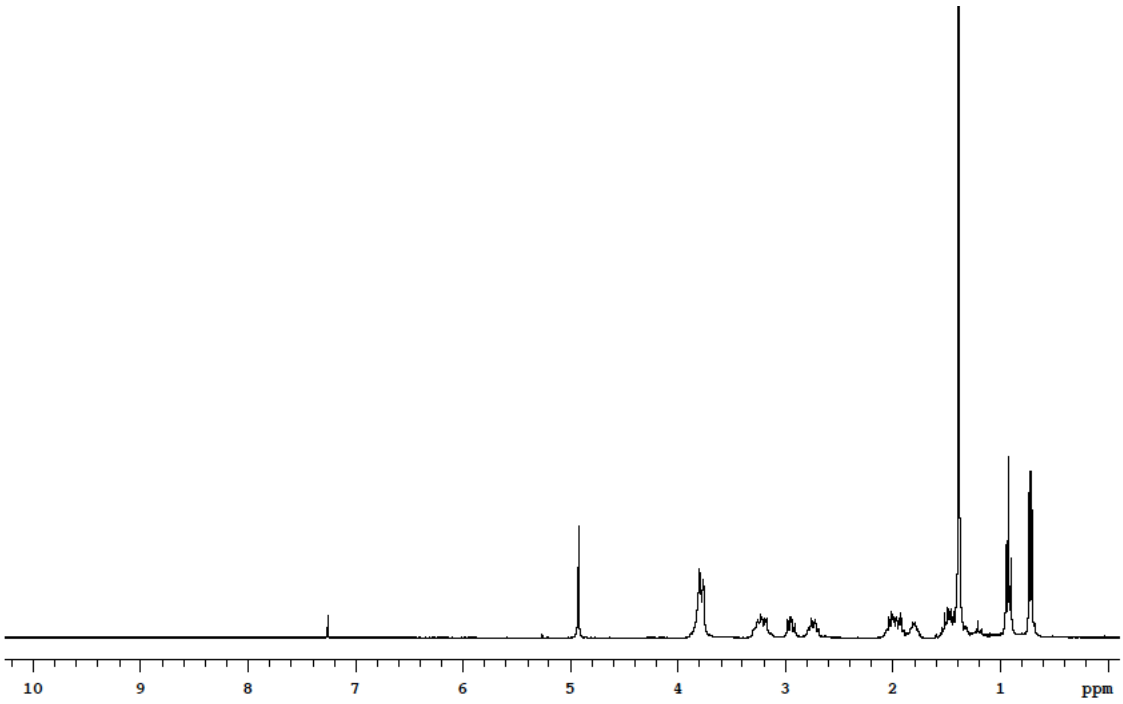
Physical state: colorless oil

^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.92 (app s, 1H), 3.80 (m, 1H), 3.76 (d, *J* = 2.4 Hz, 1H), 3.26-3.18 (m, 2H), 2.94 (dd, *J* = 11.9 and 8.3 Hz, 1H), 2.76-2.72 (m, 1H), 2.04-1.96 (m, 2H), 1.84-1.74 (m, 1H), 1.54-1.41 (m, 2H), 1.39 (s, 9H), 0.92 (t, *J* = 7.5 Hz, 3H), 0.72 (d, *J* = 6.9 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.8, 170.1, 97.6, 81.6, 66.7, 54.3, 51.7, 47.6, 36.2 31.1, 27.4, 25.9, 12.6, 12.5

IR (film, cm^{-1}) 2965, 2936, 2874, 1647, 1611, 1396, 1333, 1254, 1206, 1169, 858, 808

HRMS (ESI) m/z calcd for $C_{14}H_{29}N_2O_2$ $(M+H)^+$281.2229; found 281.2222 (2.5 ppm)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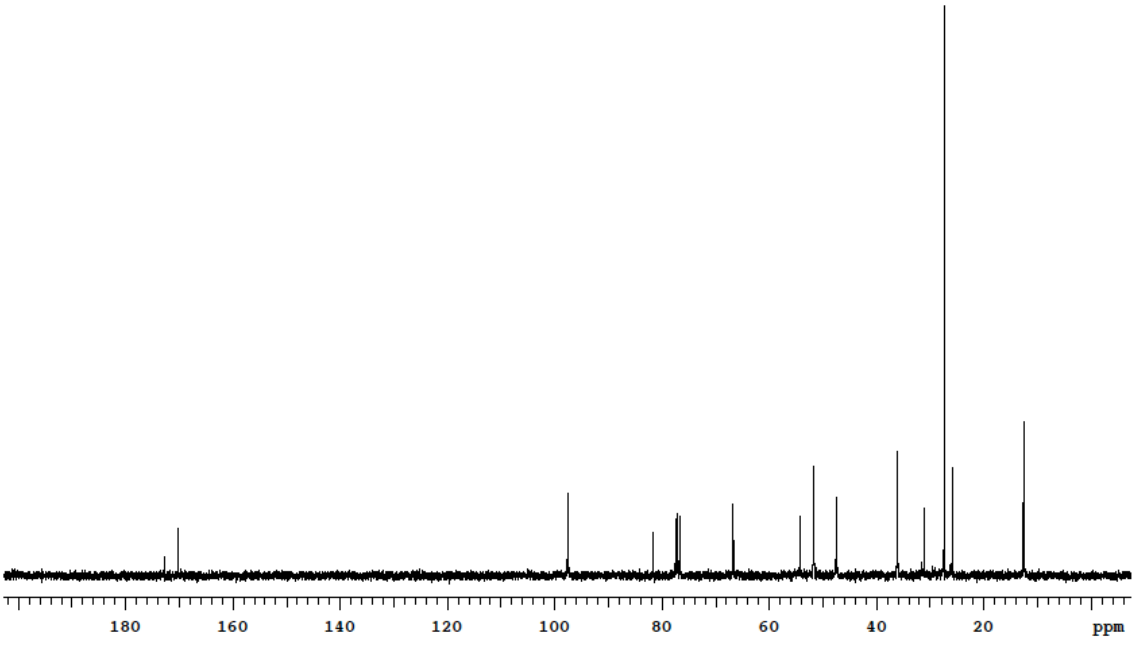
180
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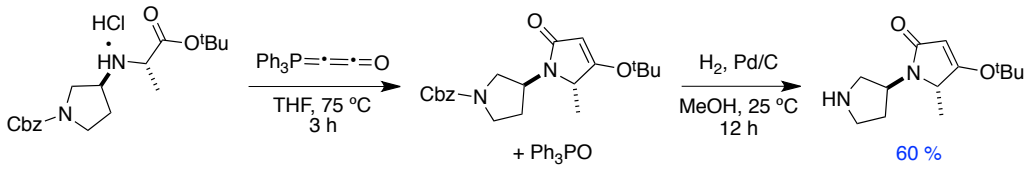
ppm

Compound **6a**

(*S*)-4-(*tert*-butoxy)-5-methyl-1-((*S*)-pyrrolidin-3-yl)-1*H*-pyrrol-2(5*H*)-one



Procedure: The same procedure for cyclization to obtain **5d** was used here. The reaction was complete in 3 h. Upon cooling, the THF was removed *in vacuo* and the residue was loaded onto a short SiO_2 column. Elution with 5 % EtOAc/CH_2Cl_2 (to remove traces of unreacted starting material) followed by 100 % EtOAc, afforded a mixture of the cyclized product and triphenylphosphine oxide. The mixture was directly utilized in the next step.

To a stirred solution of the above mixture (1.4 g) in methanol (30 mL) under nitrogen was carefully added 10 wt % Pd/C (729 mg, 0.2 equiv Pd) at 25 ºC. The reaction was evacuated, refilled with N_2, and placed under an atmosphere of H_2 (1 atm, balloon) for 12 h. The reaction mixture was purged with N_2, and filtered over a pad of celite under a gentle vacuum (**SAFETY NOTE**: Do not let the pad run dry). The celite pad was washed with methanol (2 X 40 mL), and the combined filtrates were concentrated. The residue was purified by column chromatography (SiO_2, 5 % MeOH/CH_2Cl_2 → 5 % MeOH/ CH_2Cl_2 containing 1 % Et_3N → 10 % MeOH/ CH_2Cl_2 containing 1 % TEA) to afford the product (490 mg, 60 % yield).

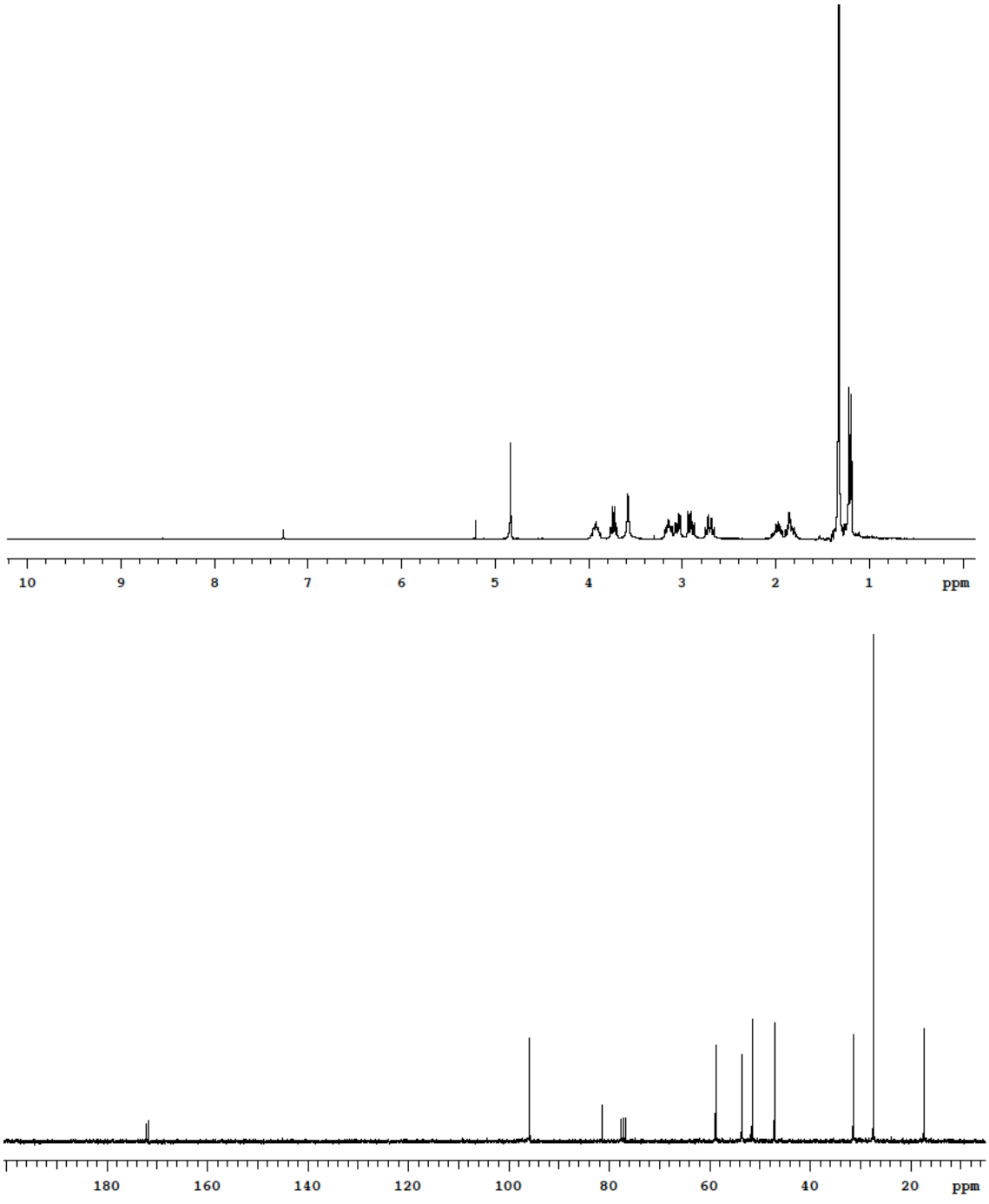
Physical state: colorless oil

^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.83 (app s, 1H), 4.00-3.84 (m, 1H), 3.73 (q, *J* = 6.6 Hz, 1H), 3.58 (br s, 1H), 3.21-3.09 (m, 1H), 3.05 (dd, *J* = 11.6, 5.0 Hz, 1H), 2.90 (dd, *J* = 11.7, 7.7 Hz, 1H), 2.77-2.61 (m, 1H), 2.06-1.91 (m, 1H), 1.90-1.74 (m, 1H), 1.32 (s, 9H), 1.20 (d, *J* = 6.6 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.1, 171.6, 95.8, 81.3, 58.7, 53.6, 51.5, 47.1, 31.4, 27.4, 17.3

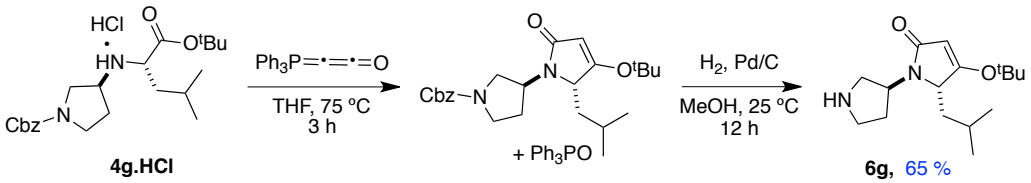
IR (film, cm^{-1}) 2978, 2936, 2874, 1611, 1373, 1340, 1258, 1167, 876, 839, 808, 682

HRMS (ESI) m/z calcd for $C_{13}H_{23}N_2O_2$ $(M+H)^+$ 239.1760; found 239.1752 (3.3 ppm)



Compound **6g**

(*S*)-4-(*tert*-butoxy)-5-isobutyl-1-((*S*)-pyrrolidin-3-yl)-1*H*-pyrrol-2(5*H*)-one



4g.HCl **6g,** 65 %

Procedure: As described for **6a**.

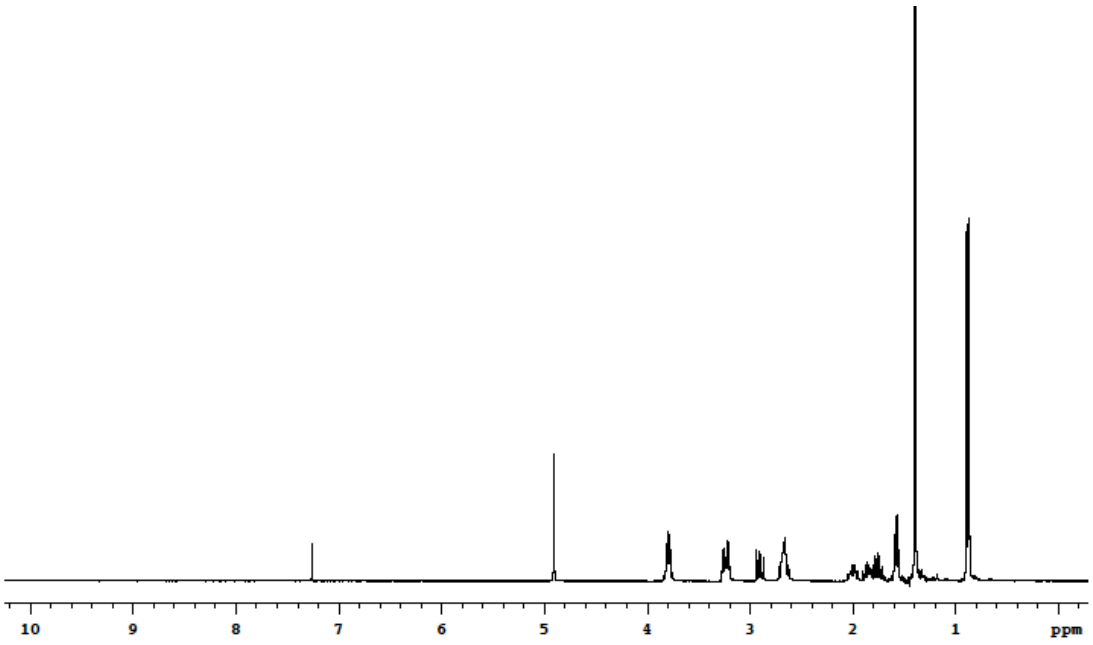
Physical state: Colorless oil

^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.91 (s, 1H), 3.87-3.71 (m, 2H), 3.30-3.14 (m, 2H), 2.90 (dd, *J* = 12.0, 8.1 Hz, 1H), 2.75-2.56 (m, 2H), 2.08-1.92 (m, 1H), 1.92-1.81 (m, 1H), 1.81-1.68 (m, 1H), 1.62-1.52 (m, 2H), 1.39 (s, 9H), 0.88 (d, *J* = 6.6 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.6, 171.3, 96.7, 81.4, 62.2, 54.7, 52.1, 47.9, 39.2, 31.7, 27.4, 24.0, 23.8, 23.0

IR (film, cm^{-1}) 2955, 2870, 1670, 1647, 1616, 1541, 1458, 1419, 1373, 1339, 1169, 858, 808

HRMS (ESI) m/z calcd for $C_{16}H_{29}N_2O_2$ $(M+H)^+$ 281.2229; found 281.2222 (2.5 ppm)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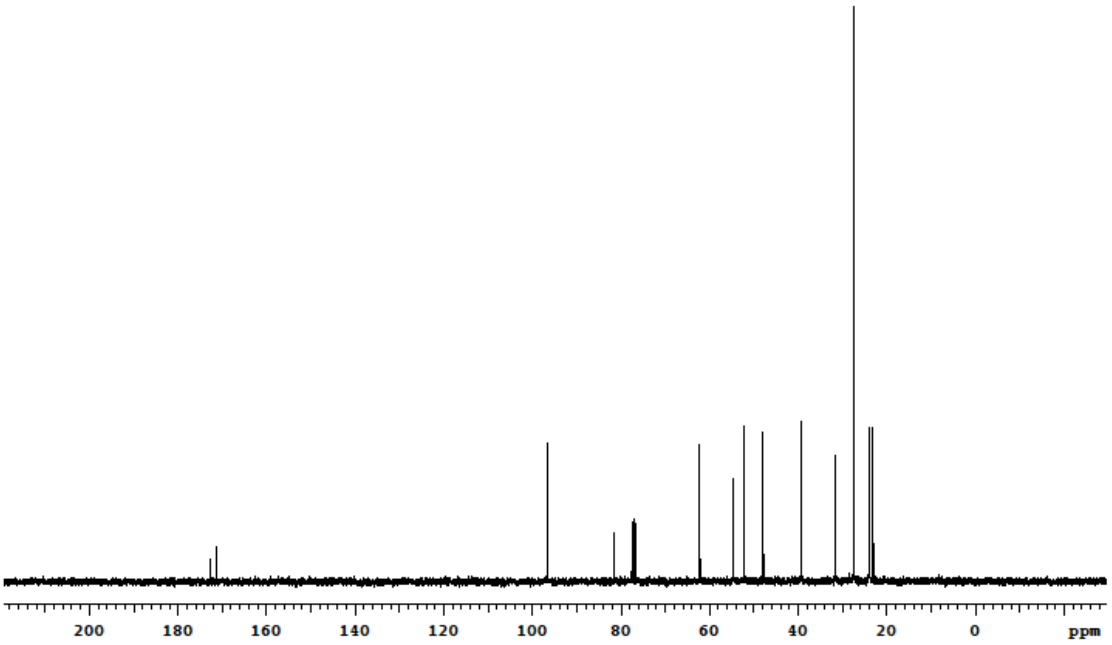
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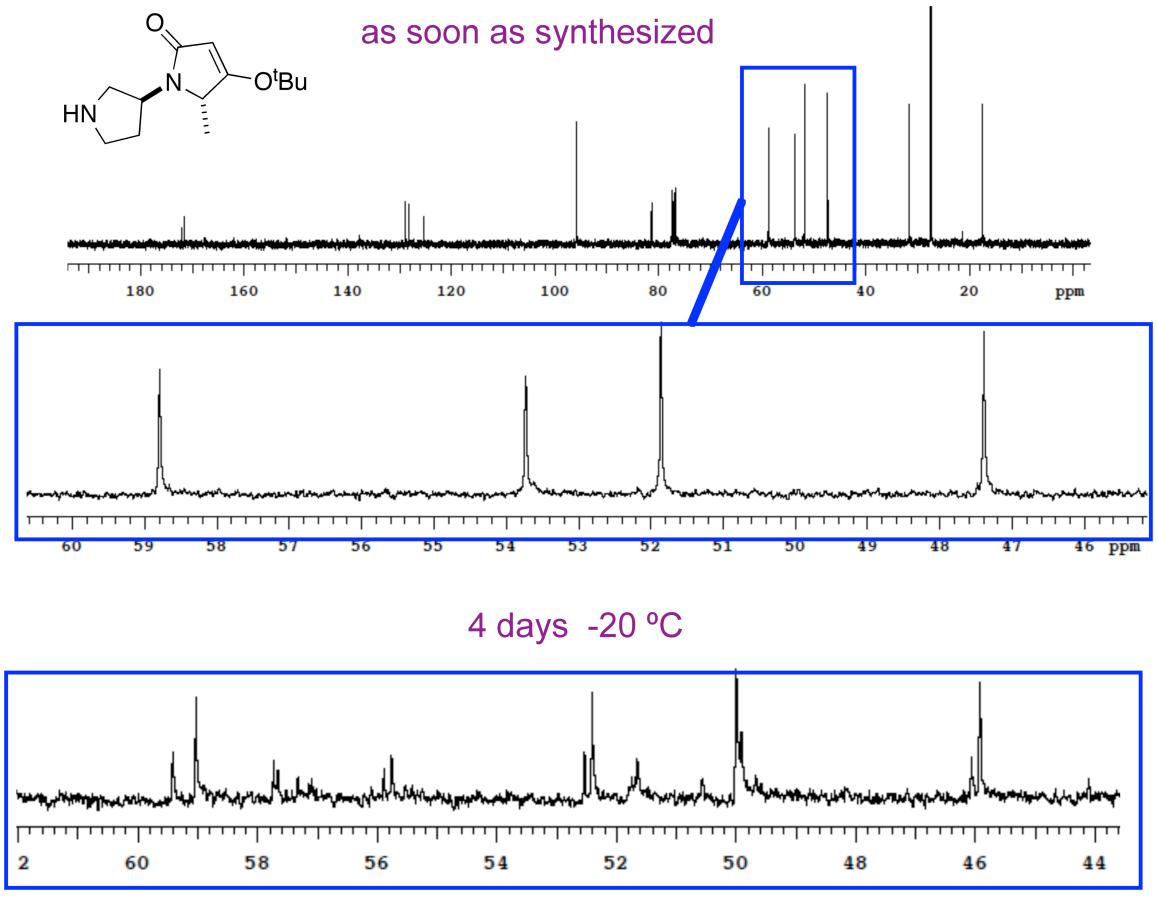
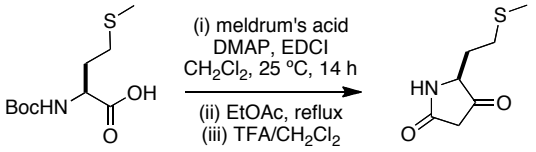
Note on storage of cyclic amines 6

Amines **6** are prone to epimerization of the Cα center even when stored at – 20 ºC. The propensity to epimerize is greater for smaller sidechains such as Me (Ala). It is best to plan the synthesis so that the amines are used up as soon as they are purified and characterized. Epimerization is not a problem for trimers **1** and pentamer **2** due to lack of a basic group.



Compound **7b**

(*S*)-5-(2-(methylthio)ethyl)pyrrolidine-2,4-dione



Procedure: A modified literature procedure was used.[3] To a stirred solution of meldrum's acid (476 mg, 3.3 mmol, 1.1 equiv) and DMAP (550 mg, 4.5 mmol, 1.5 equiv) at 0 ºC in dichloromethane (30 mL) was added *N*-Boc-Met-OH (748 mg, 3.0 mmol, 1.0 equiv) in one portion. EDCI (1.2 g, 7.2 mmol, 2.4 equiv) was added in one portion and the reaction mixture was stirred at 25 ºC for 14 h. The yellow reaction mixture was transferred to a separatory funnel and diluted with ACS reagent grade EtOAc (80 mL) and washed with cold 5 % $KHSO_4$ (3 X 50 mL) and brine (75 mL). The organic layer was dried over $MgSO_4$ and filtered. The filtrate was refluxed for 30 min under N_2. Upon concentration, the residue was dissolved in dichloromethane (8 mL) and cooled to 0 ºC. TFA (8 mL) was added and the reaction was stirred for 30 min. Toluene (25 mL) was added and the solution was concentrated. Residual TFA was azeotroped 3 times with toluene (25 mL ea) and the residue was placed under high vacuum for 3 h. A small portion of dichloromethane was added to obtain a concentrated solution and few drops of hexanes were added to afford crystals at – 20 ºC. The crystals were collected by filtration and washed with cold hexanes to obtain the pure product (333 mg, 64 %). **NOTE:** The crystals are stable at room temperature for several weeks but assume a yellow coloration. It is best stored at – 20 ºC under N_2.

Physical state: White needles (dichloromethane/hexanes), mp = 83–85 ºC

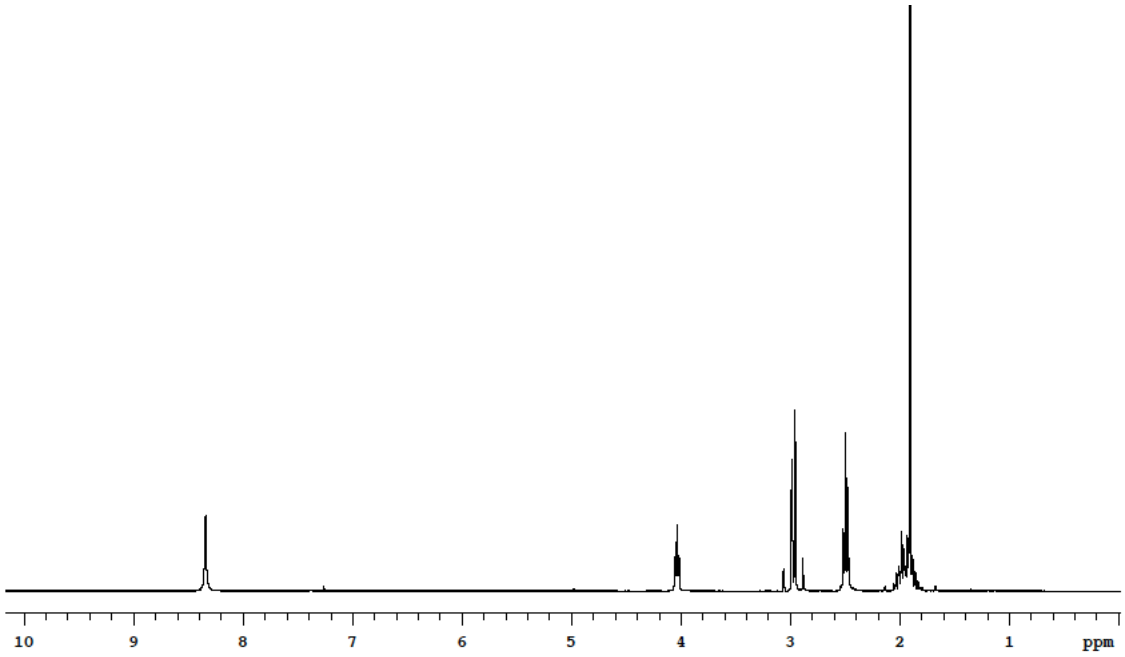
$[\alpha]^{20}$ + 1.9 (*c* 1.0, MeOH)

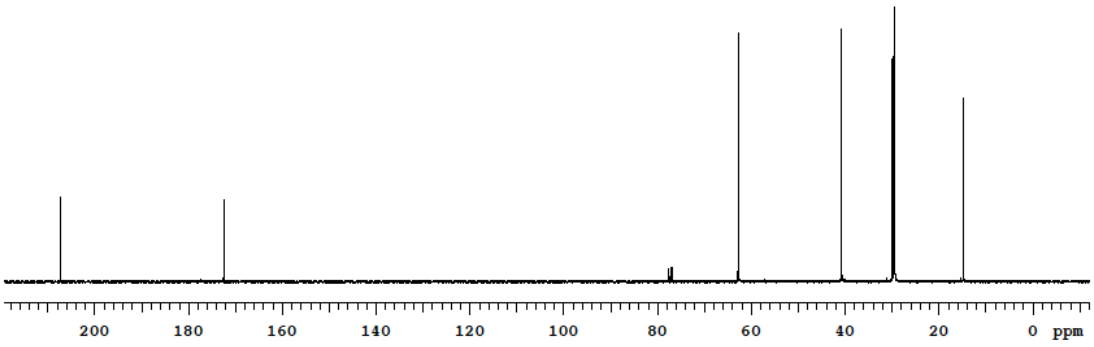
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 4.04 (t, *J* = 5.5 Hz, 1H), 3.02 (d, *J* = 22.1 Hz, 1H), 2.92 (d, *J* = 22.1 Hz, 1H), 2.49 (t, *J* = 6.7 Hz, 2H), 2.02-1.88 (m, 2H), 1.91 (s, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 207.3, 172.5, 62.8, 40.8, 29.9, 29.5, 14.7

IR (film, cm^{-1}) 3213 (br), 3101, 2918, 1770, 1699, 1684, 1636, 1364, 1307, 1265, 1159, 912, 739

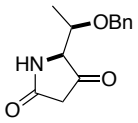
MS (ESI) m/z calcd for $(M+H)^+$ $C_7H_{12}NO_2S$ 174.05; found 174.07





Compound **7e**

(*S*)-5-((*R*)-1-(benzyloxy)ethyl)pyrrolidine-2,4-dione



Procedure: As per the procedure used for **7b**.

$[\alpha]^{21}$ – 53.1 (*c* 0.5, MeOH)

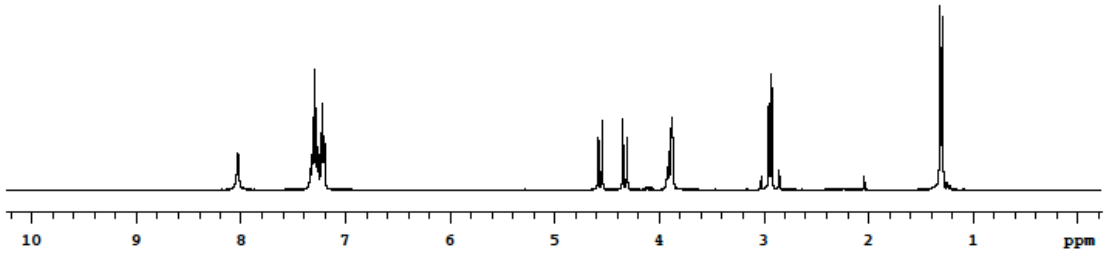
Physical state: White flaky crystals (dichloromethane/hexanes)

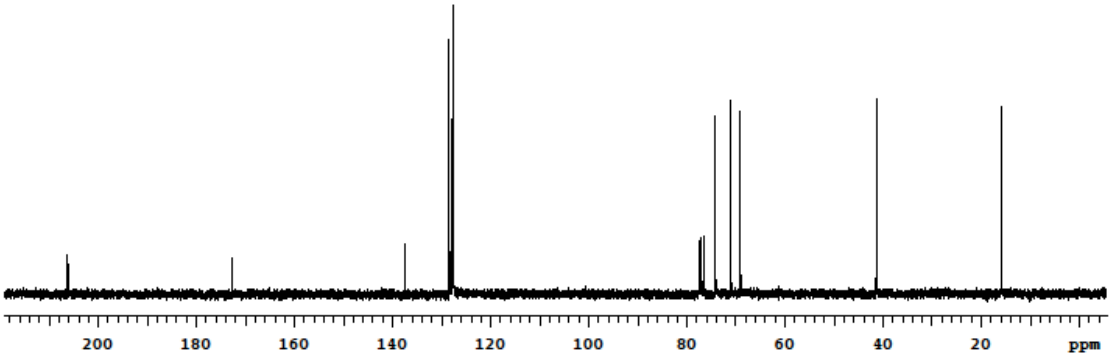
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.1 (br s, 1H), 7.36-7.25 (m, 3H), 7.25-7.18 (m, 2H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.33 (d, *J* = 11.7 Hz, 1H), 3.98-3.83 (m, 2H), 2.99 (d, *J* = 21.9 Hz, 1H), 2.89 (d, *J* = 21.9 Hz, 1H), 1.30 (d, *J* = 6.0 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 206.2, 172.6, 137.5, 128.4, 127.8, 127.6, 74.1, 71.0, 69.1, 41.3, 15.8

IR (film, cm^{-1}) 3227 (br), 3105, 2978, 2879, 1771, 1697, 1379, 1361, 1321, 1090, 1047, 735, 698

HRMS (ESI) m/z calcd for $C_{13}H_{16}NO_3$ $(M+H)^+$ 234.1130; found 234.1139 (3.8 ppm)

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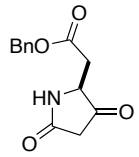
ppm

Compound **7f**

(*S*)-benzyl 2-(3,5-dioxopyrrolidin-2-yl)acetate



Procedure: As per the procedure used for **7b**.

$[\alpha]^{21}$ – 33.4 (*c* 0.5, MeOH)

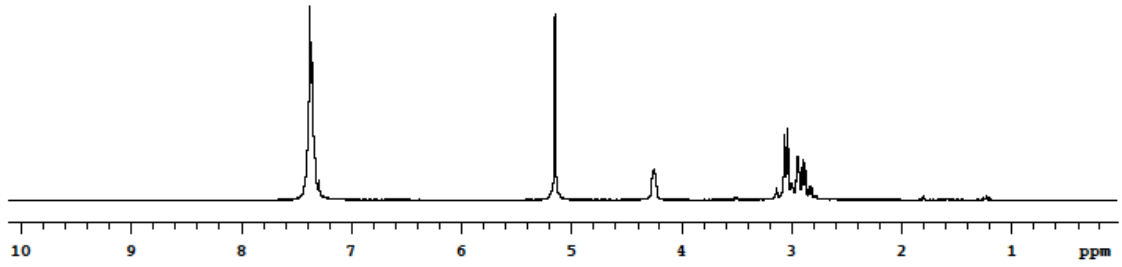
Physical state: pale yellow solid

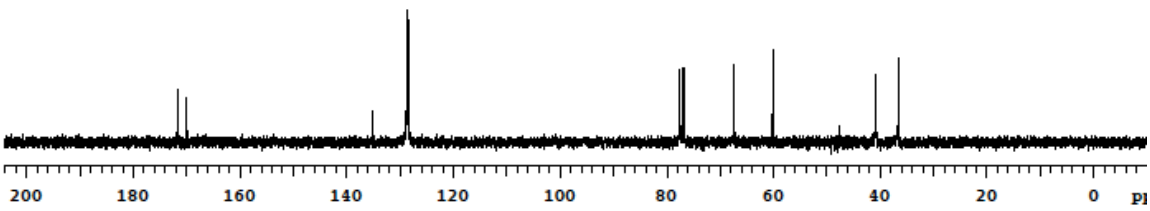
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.44-7.28 (m, 5H), 5.15 (s, 2H), 4.30-4.19 (m, 1H), 3.17-2.98 (m, 2H), 2.98-2.78 (m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.7, 169.9, 134.9, 128.74, 128.69, 128.5, 67.4, 60.1, 40.7, 36.6

IR (film, cm^{-1}) 3240 (br), 1773, 1730, 1701, 1358, 1246, 1184, 741, 700

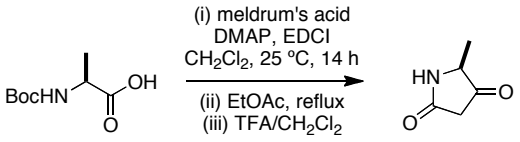
HRMS (ESI) m/z calcd for $C_{13}H_{14}NO_4$ $(M+H)^+$ 248.0922; found 248.0926 (1.3 ppm)





Compound **7a**

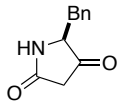
(*S*)-5-methylpyrrolidine-2,4-dione



Procedure: As described above for (*S*)-5-(2-(methylthio)ethyl)pyrrolidine-2,4-dione, **7b**. The product (white solid) was obtained by addition of dry ether to the crude residue (brown oil), and stirring for 14 h (890 mg, 92 %). The spectra match (^{1}H and ^{13}C-NMR) the reported spectra.[3]

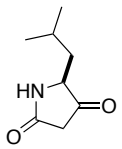
Compound **7d**

(*S*)-5-benzylpyrrolidine-2,4-dione



Procedure: As described above for (*S*)-5-(2-(methylthio)ethyl)pyrrolidine-2,4-dione, **7b**. The product (white solid) was obtained by addition of dry ether and hexanes to the crude residue (brown oil), and stirring for 2 h (75 %). The spectra match (^{1}H and ^{13}C-NMR) the reported spectra.[3]

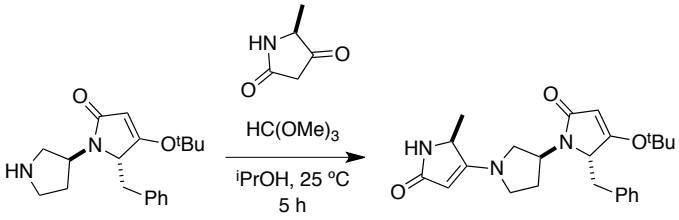
Compound **7g**



Procedure: As described above for (*S*)-5-(2-(methylthio)ethyl)pyrrolidine-2,4-dione, **7b**. The product (white solid) was obtained by addition of dry ether and hexanes to the crude residue (brown oil), and stirring for 2 h (70 %). The spectra match (^{1}H and ^{13}C-NMR) the reported spectra.[3]

Compound **1ad**

(*S*)-5-benzyl-4-(*tert*-butoxy)-1-((*S*)-1-((*S*)-2-methyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)pyrrolidin-3-yl)-1*H*-pyrrol-2(5*H*)-one



Procedure: To a stirred solution of the amine (1 mmol) and tetramic acid (1.2 mmol) in ^{i}PrOH (0.1 M) was added trimethylorthoformate (1.5 mmol, 164 µL) at 25 ºC under Argon. The reaction mixture was stirred for 5 h and concentrated at 25 ºC. The residue was purified by flash chromatography (4-5 % MeOH/CH_2Cl_2) to afford the product in 68 % yield.

Physical state: white solid

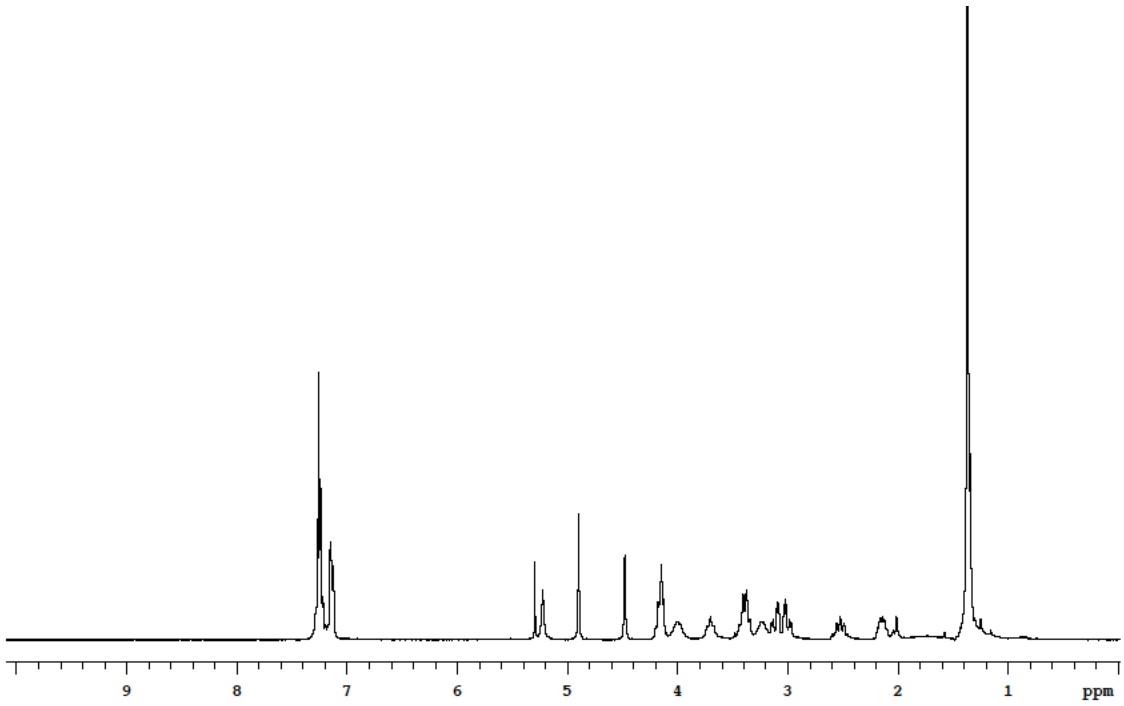
$[\alpha]^{20}$ + 56.1 (*c* 0.7, MeOH)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31-7.20 (m, 3H), 7.17-7.09 (m, 2H), 5.23 (br s, 1H), 4.90 (app s, 1H), 4.48 (app s, 1H), 4.25-4.08 (m, 2H), 4.07-.88 (m, 1H), 3.70 (t, *J* = 8.9 Hz, 1H), 3.49-3.32 (m, 2H), 3.30-3.18 (m, 1H), 3.12 (dd, *J* = 14.4, 4.6 Hz, 1H), 3.00 (dd, *J* = 14.5, 4.7 Hz, 1H), 2.52 (p, *J* = 10.2 Hz, 1H), 2.24-2.05 (m, 1H), 1.37 (s, 9H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.0, 173.5, 170.3, 167.1, 135.5, 129.3, 128.3, 127.1, 97.1, 87.8, 82.2, 77.2, 62.8, 53.0, 52.8, 49.9, 47.5, 36.8, 27.4, 19.1

IR (film, cm^{-1}) 3250 (br), 2978, 1652, 1557, 1454, 1397, 1372, 1337, 1258, 1219, 1163, 733, 700

HRMS (ESI) m/z calcd for $C_{24}H_{32}N_3O_3$ $(M+H)^+$ 410.2444; found 410.2462 (4.4 ppm)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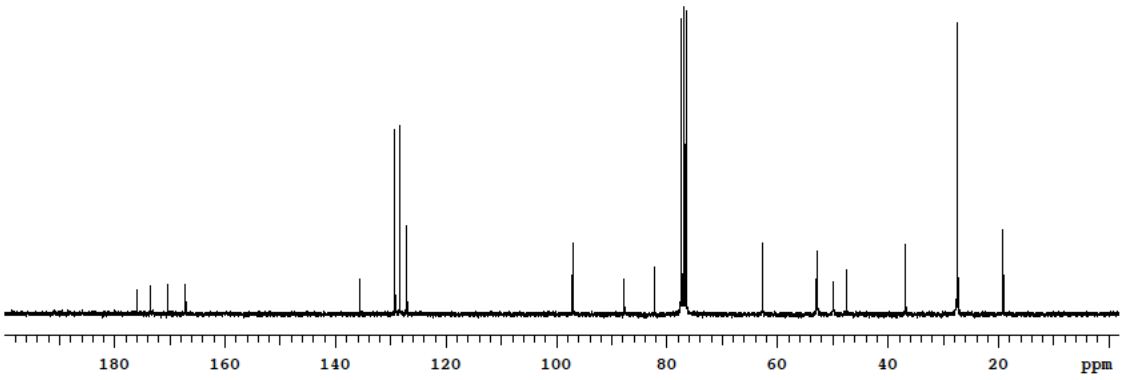
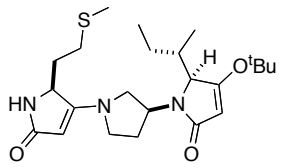

180
160
140
120
100
80
60
40
20
ppm

Compound **1bc**

(*S*)-4-(*tert*-butoxy)-5-((*S*)-*sec*-butyl)-1-((*S*)-1-((*S*)-2-(2-(methylthio)ethyl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)pyrrolidin-3-yl)-1*H*-pyrrol-2(5*H*)-one



Procedure: As described for compound **1ad.** 71 % yield

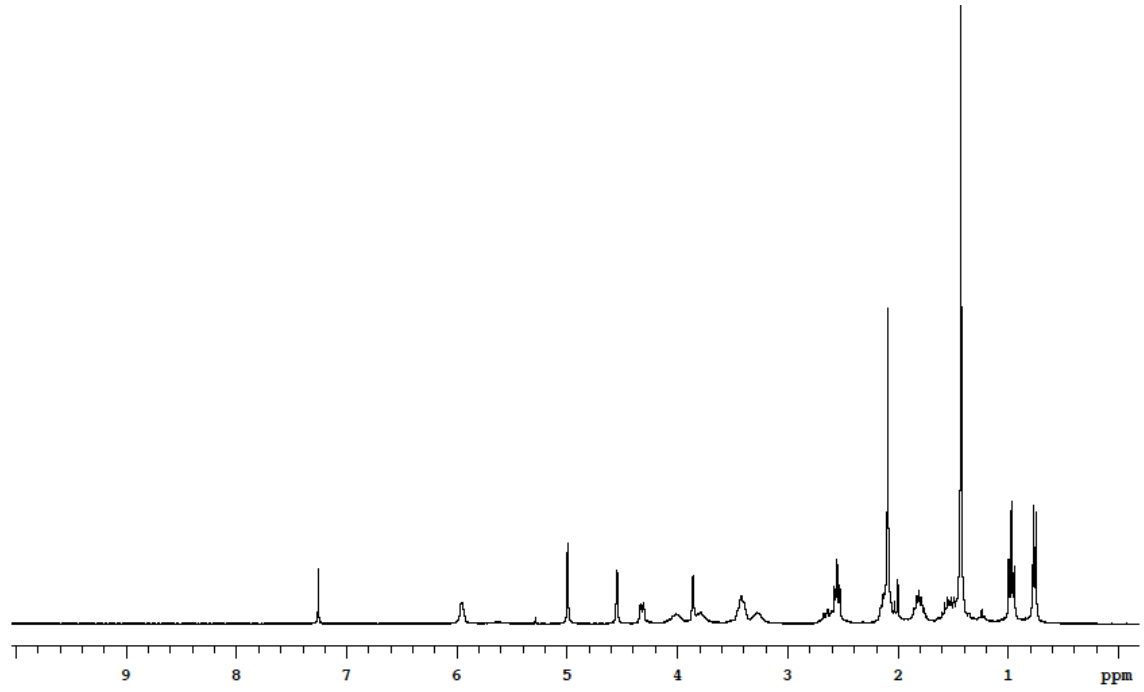
Physical state: White solid

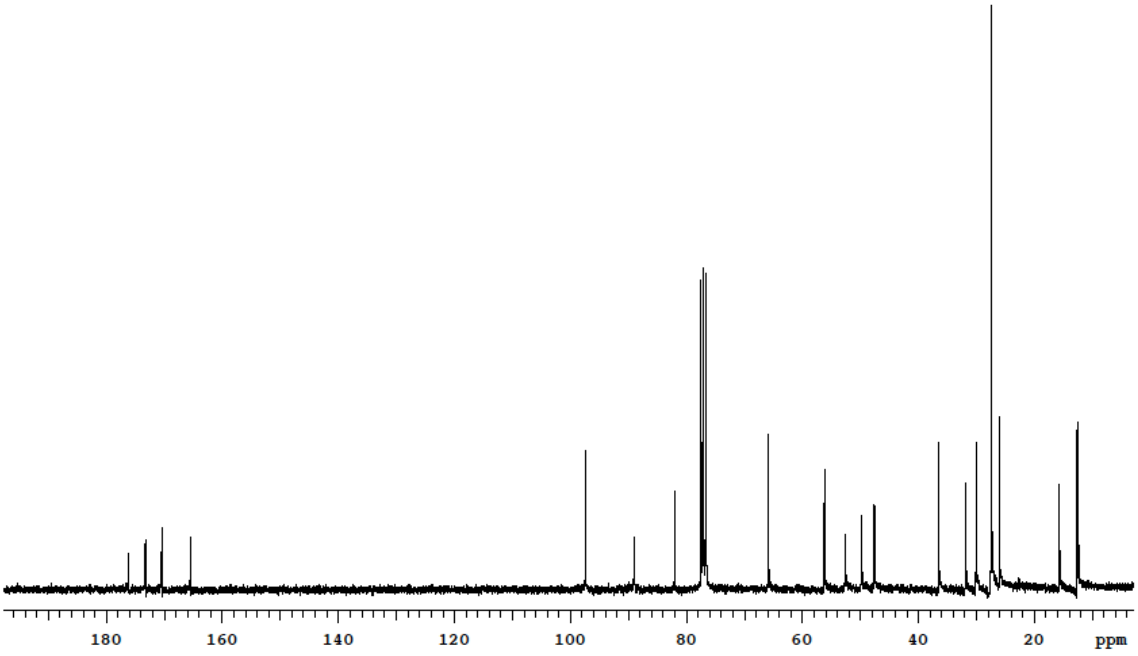
^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.96 (br s, 1H), 5.00 (app s, 1H), 4.55 (app s, 1H), 4.32 (d, *J* = 7.2 Hz, 1H), 4.09-3.94 (m, 1H), 3.86 (d, *J* = 2.1 Hz, 1H), 3.84-3.70 (m, 1H), 3.49-3.34 (m, 2H), 3.32-3.18 (m, 1H), 2.72-2.59 (m, 1H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.17-2.05 (m, 2H), 2.09 (s, 3H), 1.89-1.72 (m, 2H), 1.63-1.47 (m, 2H), 1.43 (s, 9H), 0.97 (app t, *J* = 7.4 Hz, 3H), 0.76 (d, *J* = 6.9 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.2, 173.3, 170.4, 165.5, 97.4, 89.0, 82.0, 77.2, 65.8, 56.2, 52.6, 49.8, 47.6, 36.5, 31.8, 30.1, 27.4, 26.0, 15.6, 12.6, 12.4

IR (film, cm^{-1}) 3247 (br), 2965, 2936, 2873, 1669, 1663, 1653, 1648, 1599, 1399, 1375, 1333, 1254, 1166, 858, 779

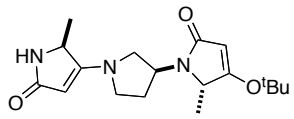
HRMS (ESI) m/z calcd for $(M+H)^+$ 436.2634; found 436.2624 (2.3 ppm)


9
8
7
6
5
4
3
2
1
ppm


180
160
140
120
100
80
60
40
20
ppm

Compound **1aa**

(*S*)-4-(*tert*-butoxy)-5-methyl-1-((*S*)-1-((*S*)-2-methyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)pyrrolidin-3-yl)-1*H*-pyrrol-2(5*H*)-one



Procedure: As described for compound **1ad**. 65 % yield.

Physical state: White solid

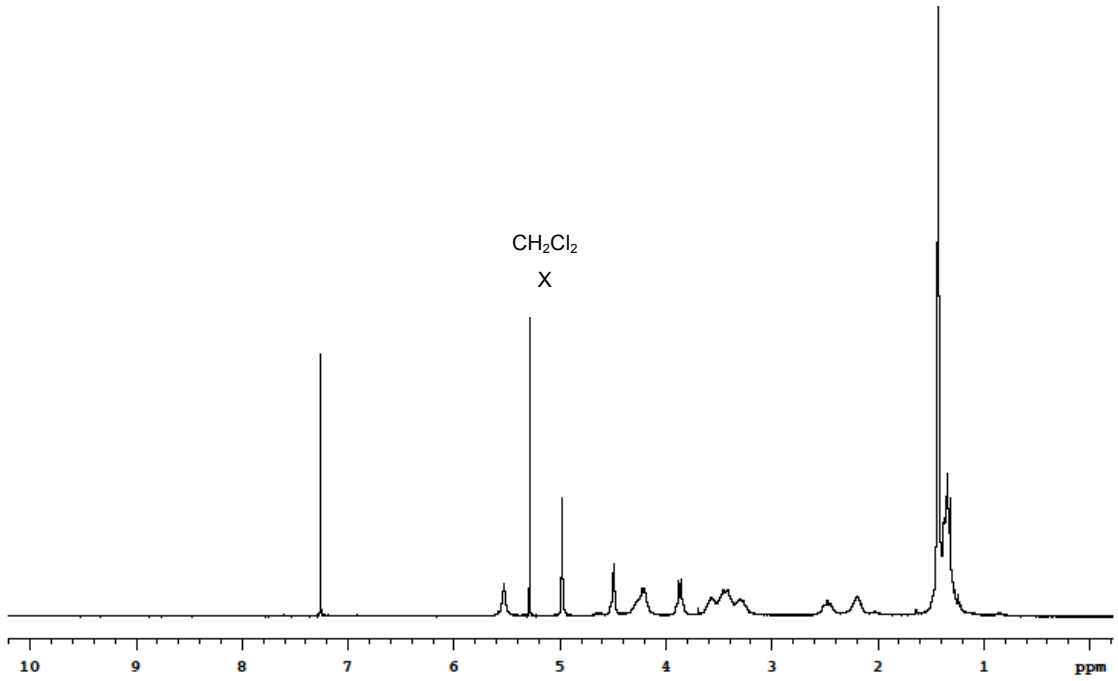
$[\alpha]^{20}$ +12.5 (*c* 1.0, MeOH)

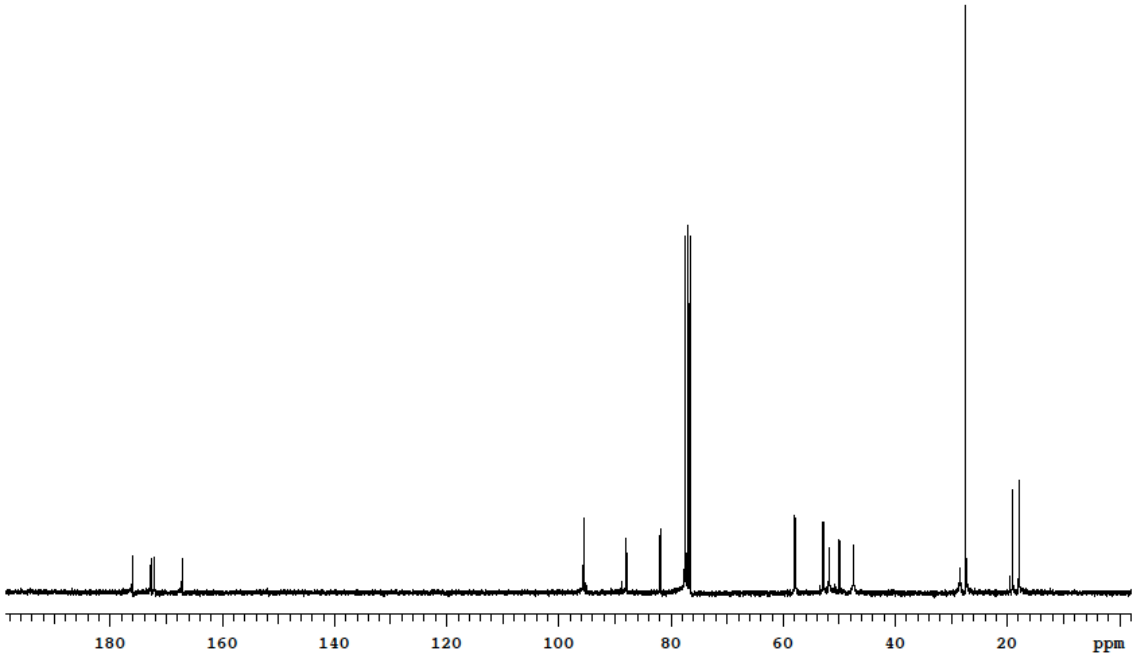
^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.55 (br s, 1H), 4.98 (app s, 1H), 4.49 (app s, 1H), 4.34-4.18 (m, 2H), 3.91-3.82 (m, 1H), 3.64-3.52 (m, 1H), 3.51-3.36 (m, 2H), 3.34-3.25 (m, 1H), 2.54-2.42 (m, 1H), 2.26-2.14 (m, 1H), 1.43 (s, 9H), 1.38-1.30 (m, 6H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.0, 172.4, 172.1, 167.2, 95.6, 87.9, 81.9, 57.9, 52.9, 51.8, 49.9, 47.4, 28.5, 27.4, 19.1, 17.9

IR (film, cm^{-1}) 3442 (br), 2980, 2933, 1645, 1599, 1396, 1373, 1339, 1260, 1219, 1167, 723

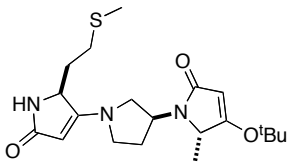
HRMS (ESI) m/z calcd for $C_{18}H_{27}N_3O_3$ 334.2131 $(M+H)^+$; found 334.2136 (1.5 ppm)


CH_2Cl_2
X
10
9
8
7
6
5
4
3
2
1
ppm


180
160
140
120
100
80
60
40
20
ppm

Compound **1ba**

(*S*)-4-(*tert*-butoxy)-5-methyl-1-((*S*)-1-((*S*)-2-(2-(methylthio)ethyl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)pyrrolidin-3-yl)-1*H*-pyrrol-2(5*H*)-one



Procedure: As described for compound **1ad**. 64 % yield.

Physical state: pale yellow oil

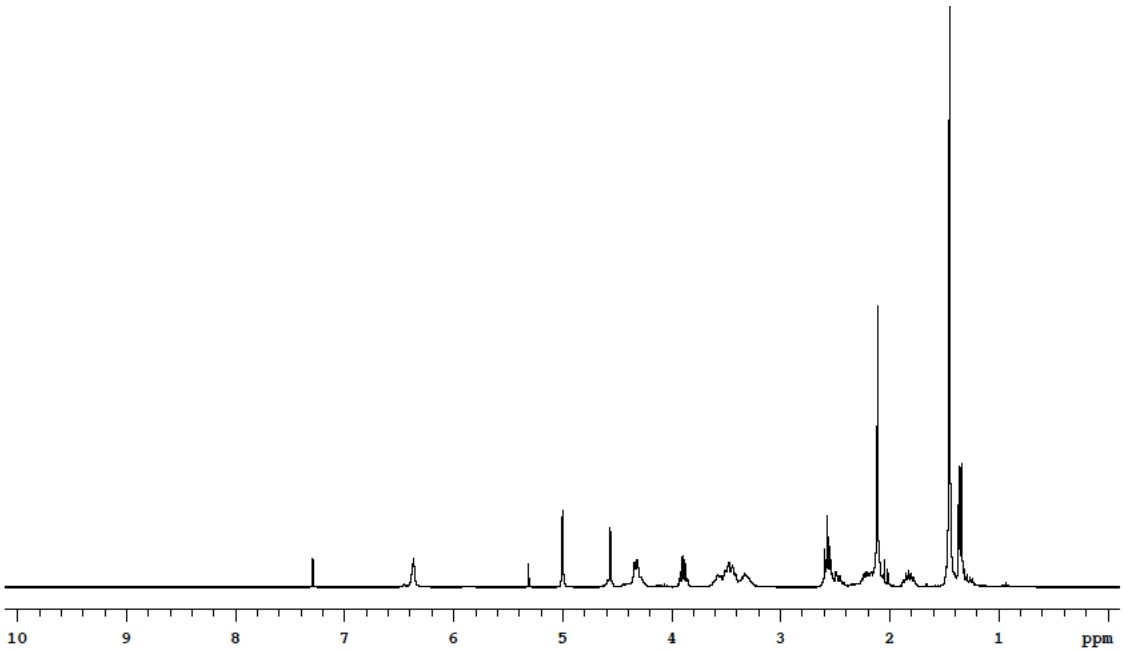
$[\alpha]^{20}$ +15.0 (*c* 0.7, MeOH)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.37 (br s, 1H), 5.00 (app s, 1H), 4.56 (d, *J* = 1.2 Hz, 1H), 4.37-4.25 (m, 2H), 3.94-3.82 (m, 1H), 3.64-3.52 (m, 1H), 3.53-3.38 (m, 2H), 3.38-3.30 (m, 1H), 2.57 (t, *J* = 7.3 Hz, 2H), 2.53-2.40 (m, 1H), 2.28-2.13 (m, 2H), 2.11 (s, 3H), 1.90-1.75 (m, 1H), 1.45 (s, 9H), 1.35 (d, *J* = 6.6 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.2, 172.7, 172.1, 165.4, 95.5, 89.2, 81.9, 77.3, 57.9, 56.3, 51.7, 50.1, 47.6, 31.9, 29.9, 27.4, 18.0, 15.7

IR (film, cm^{-1}) 3214 (br), 2958, 2873, 1653, 1599, 1480, 1456, 1399, 1373, 1339, 1302, 1259, 1214, 1168, 1096, 880, 840, 781, 757

HRMS (ESI) m/z calcd for $(M+H)^+$ $C_{20}H_{32}N_3O_3S$ 394.2164; found 394.2175 (2.7 ppm)


10
9
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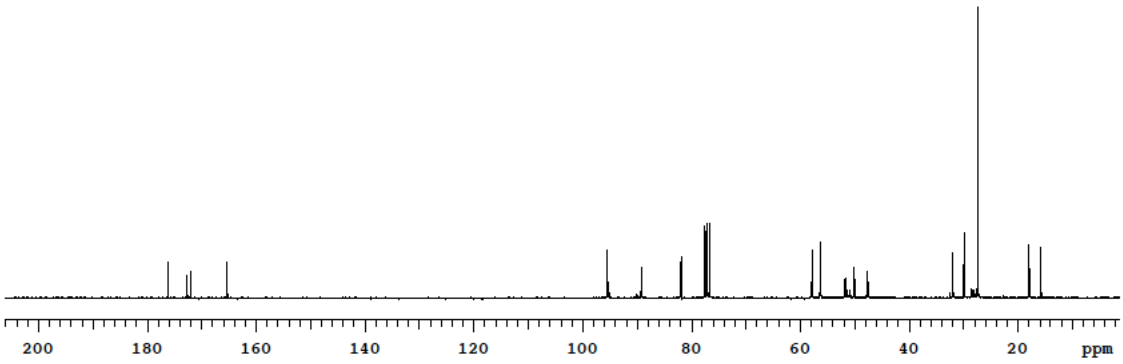
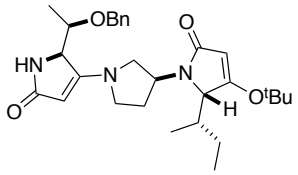
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
ppm

Compound **1ec**

(*S*)-1-((*S*)-1-((*R*)-2-((*R*)-1-(benzyloxy)ethyl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)pyrrolidin-3-yl)-4-(*tert*-butoxy)-5-((*S*)-*sec*-butyl)-1*H*-pyrrol-2(5*H*)-one



Procedure: As described for compound **1ad**. 64 % yield.

Physical state: white solid

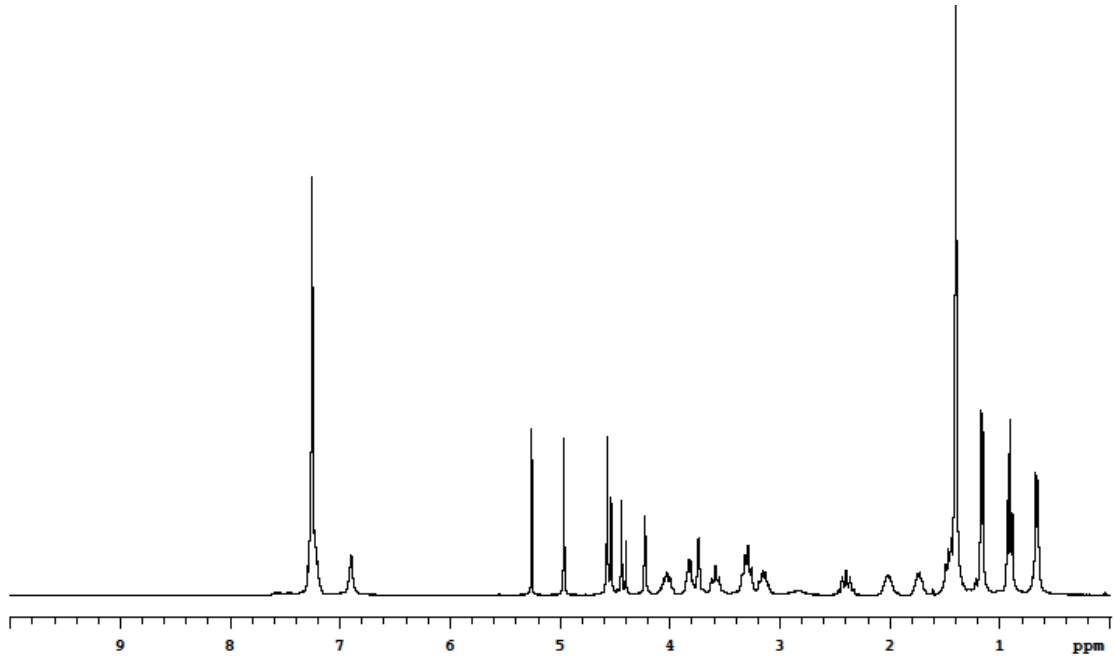
$[\alpha]^{21}$ + 27.9 (*c* 1.7, MeOH)

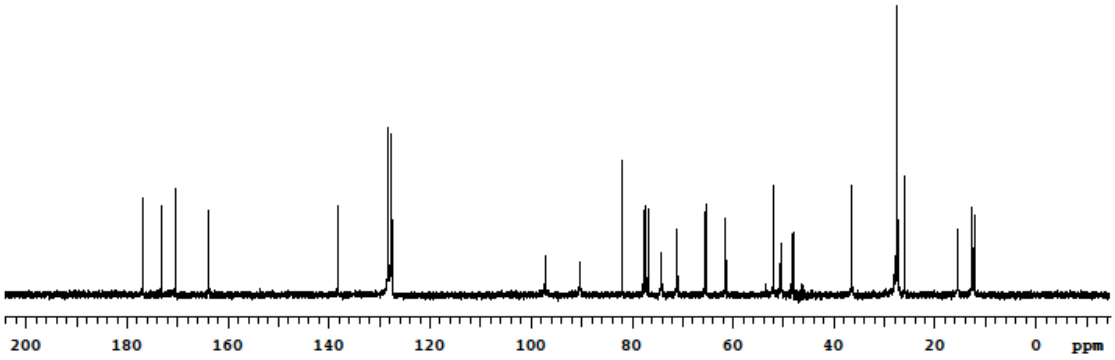
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35-7.15 (m, 5H), 6.90 (br s, 1H), 4.96 (s, 1H), 4.63-4.50 (m, 2H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.23 (d, *J* = 1.8 Hz, 1H), 4.10-3.93 (m, 1H), 3.87-3.77 (m, 1H), 3.77-3.69 (m, 1H), 3.64-3.51 (m, 1H), 3.39-3.22 (m, 2H), 3.22-3.10 (m, 1H), 2.50-2.31 (m, 1H), 2.10-1.92 (m, 1H), 1.81-1.64 (m, 1H), 1.52-1.33 (m, 11 H), 1.16 (d, *J* = 6.0 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.66 (d, *J* = 6.6 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.9, 173.2, 170.4, 163.9, 138.3, 128.3, 127.7, 127.5, 97.2, 97.1, 90.3, 81.9, 74.1, 71.1, 65.4, 61.5, 52.0, 50.6, 48.1, 36.5, 27.4, 26.0, 15.5, 12.6, 12.2

IR (film, cm^{-1}) 3271 (br), 2967, 2933, 1668, 1597, 1396, 1253, 1167, 1098, 856, 779, 736, 698

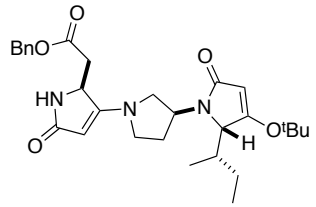
HRMS (ESI) m/z calcd for $C_{29}H_{42}N_3O_4$ $(M+H)^+$ 496.3175; found 496.3158 (3.5 ppm)


9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm

Compound **1fc**

benzyl 2-((*S*)-3-((*S*)-3-((*S*)-3-(*tert*-butoxy)-2-((*S*)-*sec*-butyl)-5-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)pyrrolidin-1-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)acetate



Procedure: As described for compound **1ad**; the reaction was run for 8 h to afford **1fc** in 55 % yield.

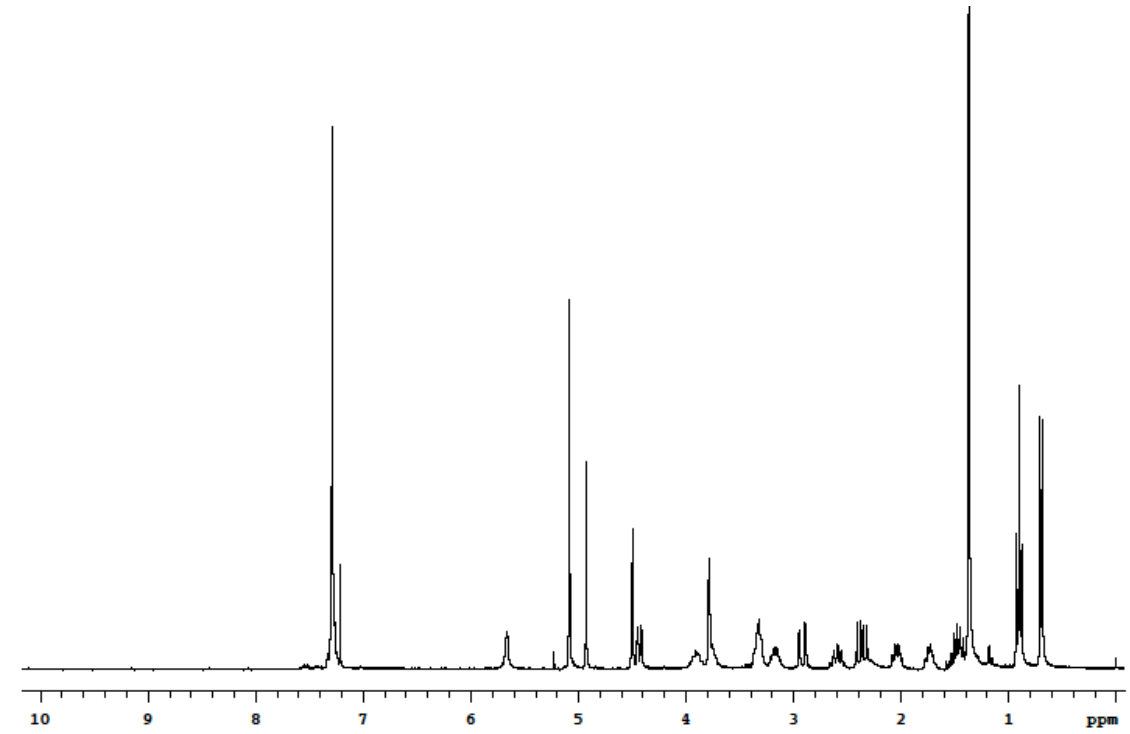
Physical state: white solid

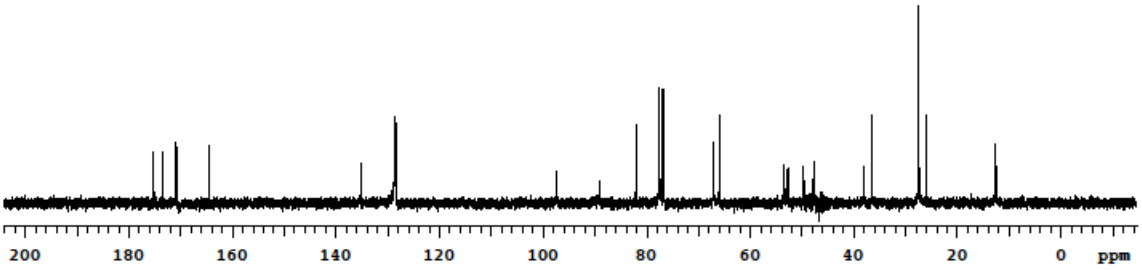
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35-7.23 (m, 5H), 5.67 (br s, 1H), 5.08 (s, 2H), 4.93 (s, 1H), 4.49 (s, 1H), 4.43 (dd, *J* = 10.8, 2.1 Hz, 1H), 3.97-3.83 (m, 1H), 3.78 (d, *J* = 2.4 Hz, 1H), 3.79-3.70 (m, 1H), 3.41-3.25 (m, 2H), 3.25-3.08 (m, 1H), 2.92 (dd, *J* = 17.0, 2.6 Hz, 1H), 2.68-2.49 (m, 1H), 2.36 (dd, *J* = 16.9, 11.0 Hz, 1H), 2.11-1.93 (m, 1H), 1.81-1.64 (m, 1H), 1.60-1.39 (m, 2H), 1.37 (s, 9H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.70 (d, *J* = 6.9 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 175.2, 173.4, 170.9, 170.6, 164.5, 135.2, 128.7, 128.6, 128.5, 97.5, 97.4, 89.1, 67.1, 66.0, 53.4, 52.7, 49.7, 47.8, 47.7, 38.1, 36.4, 27.5, 26.0, 12.7, 12.5

IR (film, cm^{-1}) 3270 (br), 2962, 2934, 2874, 1734, 1676, 1603, 1165, 856, 698

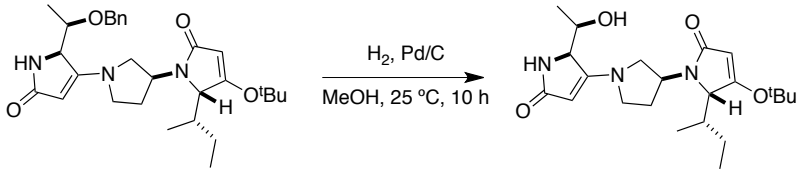
HRMS (ESI) m/z calcd for $C_{29}H_{40}N_3O_5$ $(M+H)^+$ 510.2967; found 510.2960 (1.6 ppm)


10
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm

Compound **1ec-deprotected**

(*S*)-1-((*S*)-1-((*R*)-2-((*R*)-1-(benzyloxy)ethyl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)pyrrolidin-3-yl)-4-(*tert*-butoxy)-5-((*S*)-*sec*-butyl)-1*H*-pyrrol-2(5*H*)-one



1ec **1ec-deprotected**

40 %

Procedure: Compound **1ec** (0.22 mmol) in MeOH (2 mL) was subject to hydrogenloysis using 10 % Pd/C (47 mg, 0.2 eq Pd) for 10 h. The reaction was purges with N_2 for a few minutes and filtered over Celite. The filtrate was concentrated and purified by flash chromatography (5-7 % MeOH/CH_2Cl_2) to afford the product in 40 % yield.

Physical state: white solid

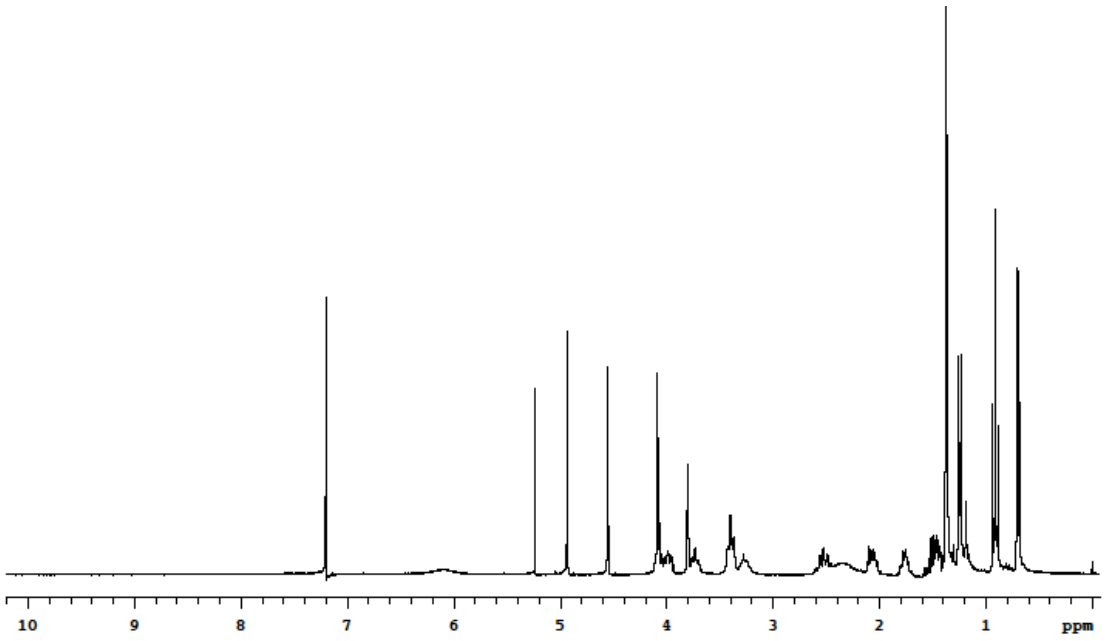
$[\alpha]^{21}$ – 2.2 (*c* 1.2, MeOH)

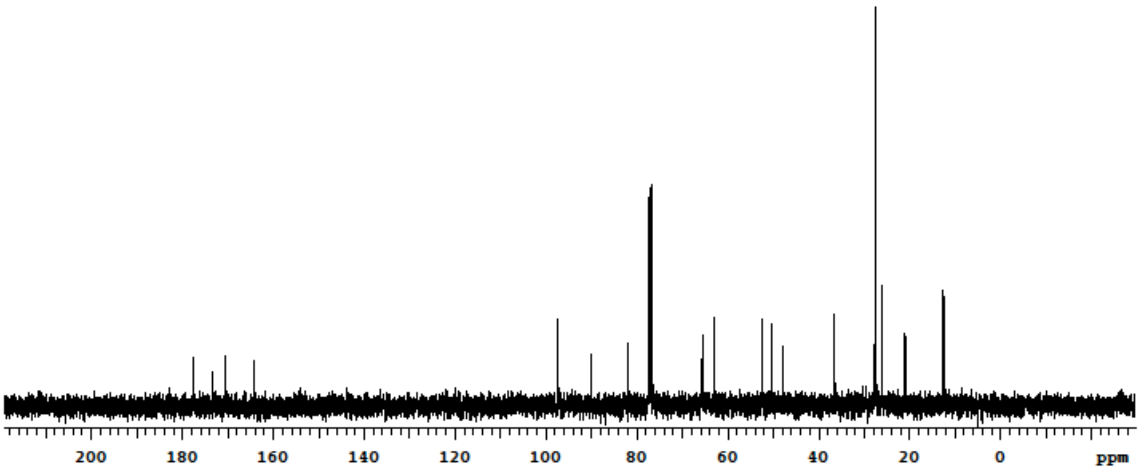
^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.93 (s, 1H), 4.55 (s, 1H), 4.13-3.92 (m, 3H), 3.80 (d, *J* = 2.7 Hz, 1H), 3.78-3.66 (m, 1H), 3.45-3.34 (m, 2H), 3.34-3.18 (m, 1H), 2.63-2.42 (m, 1H), 2.14-1.99 (m, 1H), 1.83-1.69 (m, 1H), 1.61-1.41 (m, 2H), 1.37 (s, 9H), 1.25 (d, *J* = 9.0 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.70 (d, *J* = 6.6 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 177.6, 173.4, 170.5, 164.3, 97.4, 90.0, 82.0, 65.8, 65.4, 62.9, 52.4, 50.3, 47.9, 36.5, 27.8, 27.4, 26.0, 21.0, 12.6, 12.4

IR (film, cm^{-1}) 3302 (br), 2968, 2874, 1653, 1595, 1396, 1375, 1253, 1167, 779, 735

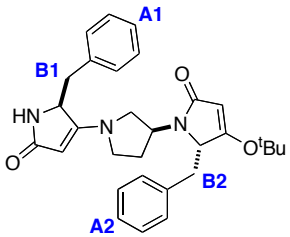
HRMS (ESI) m/z calcd for $C_{22}H_{36}N_3O_4$ $(M+H)^+$ 406.2705; found 406.2692 (3.4 ppm)


10
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm

Compound **1dd**

(*S*)-5-benzyl-1-((*S*)-1-((*S*)-2-benzyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)pyrrolidin-3-yl)-4-(*tert*-butoxy)-1*H*-pyrrol-2(5*H*)-one



Procedure: As described for compound **1ad**. 55 % yield.

Physical state: White solid.

$[\alpha]^{20}$ -1.5 (*c* 1.0, MeOH)

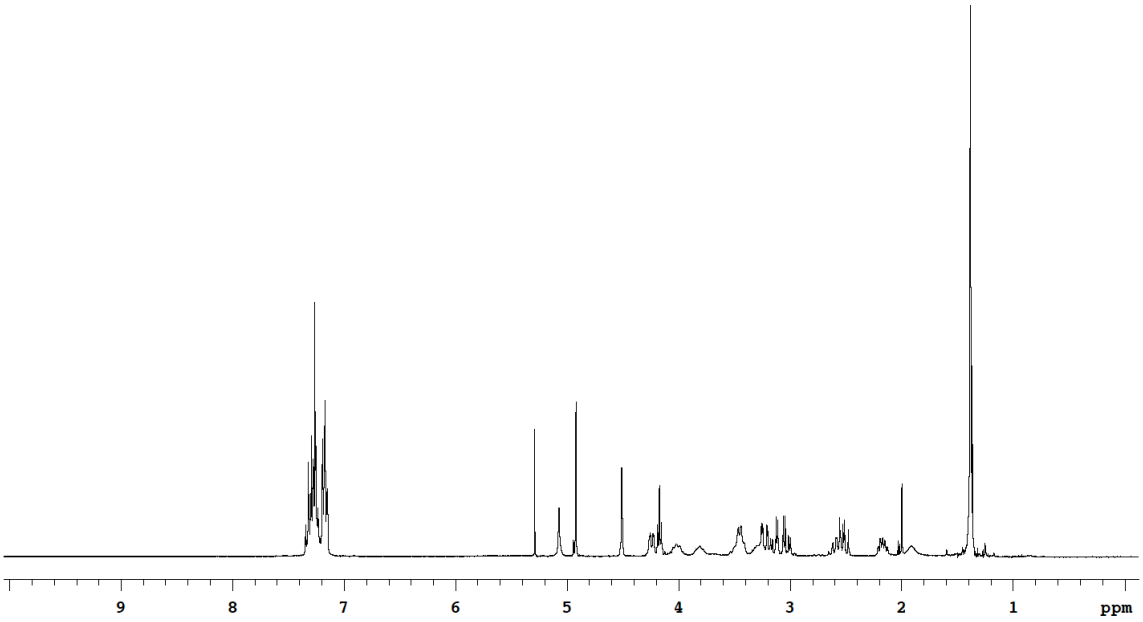
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37-7.22 (m, 6H), 7.21-7.12 (m, 4H), 5.07 (br s, 1H), 4.92 (app s, 1H), 4.51 (d, *J* = 1.5 Hz, 1H), 4.24 (dd, *J* = 9.6, 2.7 Hz, 1H), 4.17 (t, *J* = 4.9 Hz, 1H), 4.10-3.94 (m, 1H), 3.89-3.73 (m, 1H), 3.54-3.36 (m, 2H), 3.34-3.26 (m, 1H), 3.23 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.14 (dd, *J* = 14.6, 5.0 Hz, 1H), 3.03 (dd, *J* = 14.8, 5.0 Hz, 1H), 2.68-2.45 (m, 2H), 2.25-2.09 (m, 1H), 1.38 (s, 9H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 175.5, 173.5, 170.3, 165.4, 137.0, 135.5, 129.3, 129.1, 128.8, 128.4, 127.1, 97.1, 88.8, 82.3, 62.8, 58.4, 53.0, 50.0, 47.6, 39.5, 36.7, 27.4

Note: Carbons A1 and A2 overlap; carbons B1 and B2 overlap.

IR (film, cm^{-1}) 3273 (br), 2978, 2932, 2876, 1668, 1600, 1396, 1372, 1339, 1165, 729, 700

HRMS (ESI) m/z calcd for $(M+H)^+$ $C_{30}H_{36}N_3O_3$ 486.2756; 486.2778 found (4.4 ppm)


9
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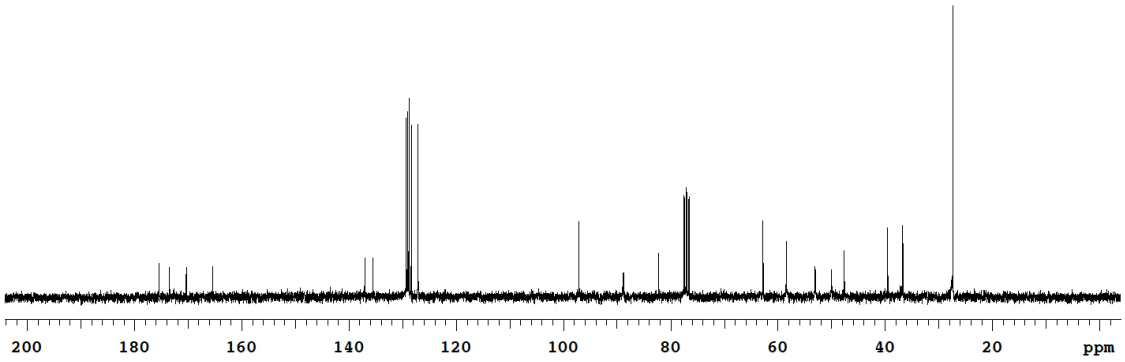
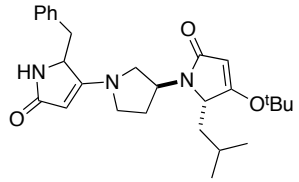
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
ppm

Compound **1dg**

(5*S*)-1-((3*S*)-1-(2-benzyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)pyrrolidin-3-yl)-4-(*tert*-butoxy)-5-isobutyl-1*H*-pyrrol-2(5*H*)-one



Procedure: As described for compound **1ad**. 74 % yield.

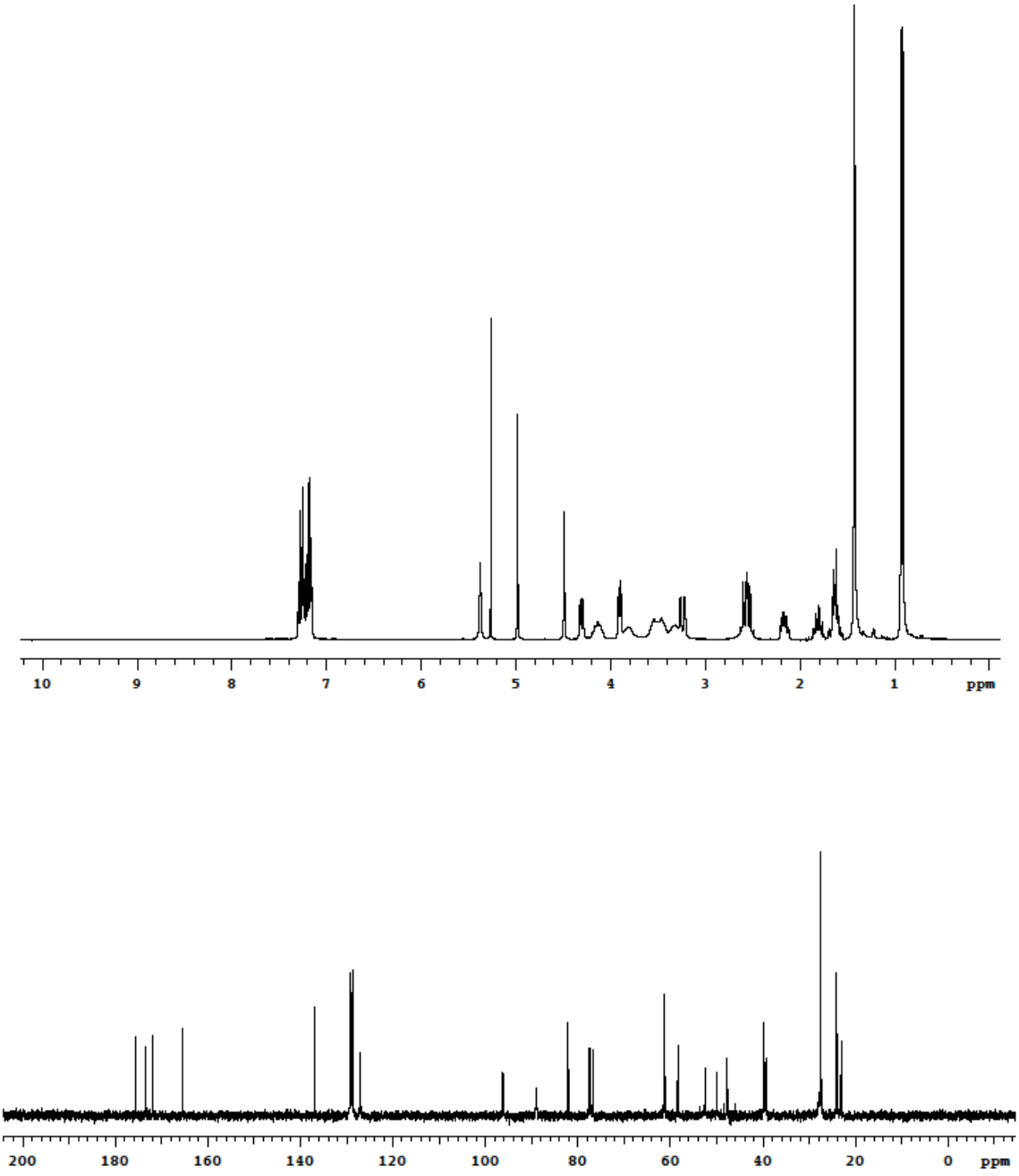
Physical state: White foam

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35-7.08 (m, 5H), 5.17 (br s, 1H), 4.98 (s, 1H), 4.51 (d, *J* = 1.5 Hz, 1H), 4.30 (dd, *J* = 9.6, 2.7 Hz, 1H), 4.21-4.00 (m, 1H), 3.90 (dd, *J* = 6.3, 3.9 Hz, 1H), 3.86-3.72 (m, 1H), 3.62-3.40 (m, 2H), 3.40-3.29 (m, 1H), 3.25 (dd, *J* = 13.6, 2.9 Hz, 1H), 2.66-2.47 (m, 2H), 2.24-2.10 (m, 1H), 1.89-1.74 (m, 1H), 1.68-1.55 (m, 2H), 1.43 (s, 9H), 0.93 (d, *J* = 6.6 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 175.5, 173.3, 171.9, 165.4, 136.9, 129.1, 128.8, 127.1, 96.2, 88.9, 82.1, 61.2, 58.4, 52.5, 50.0, 47.6, 39.7, 39.5, 27.8, 27.4, 24.1, 24.0, 23.0

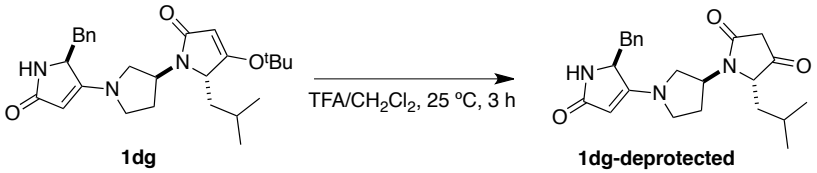
IR (film, cm^{-1}) 3213 (br), 2955, 2870, 1673, 1601, 1396, 1371, 1341, 1258, 1167, 922, 858, 731

HRMS (ESI) m/z calcd for $C_{27}H_{38}N_3O_3$ $(M+H)^+$ 452.2913; found 452.2906 (1.5 ppm)


10
9
8
7
6
5
4
3
2
1
ppm
200
180
160
140
120
100
80
60
40
20
0
ppm

Compound **1dg-deprotected**

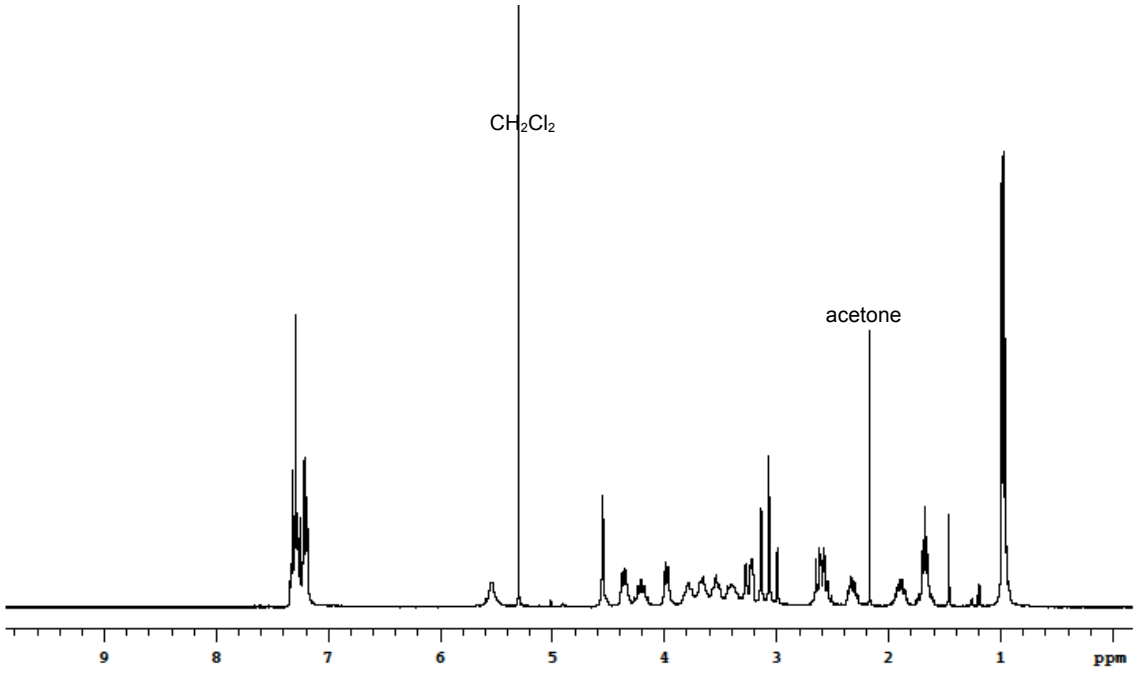
(3'*S*,5*S*)-1'-(2-benzyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)-5-isobutyl-[1,3'-bipyrrolidine]-2,4-dione



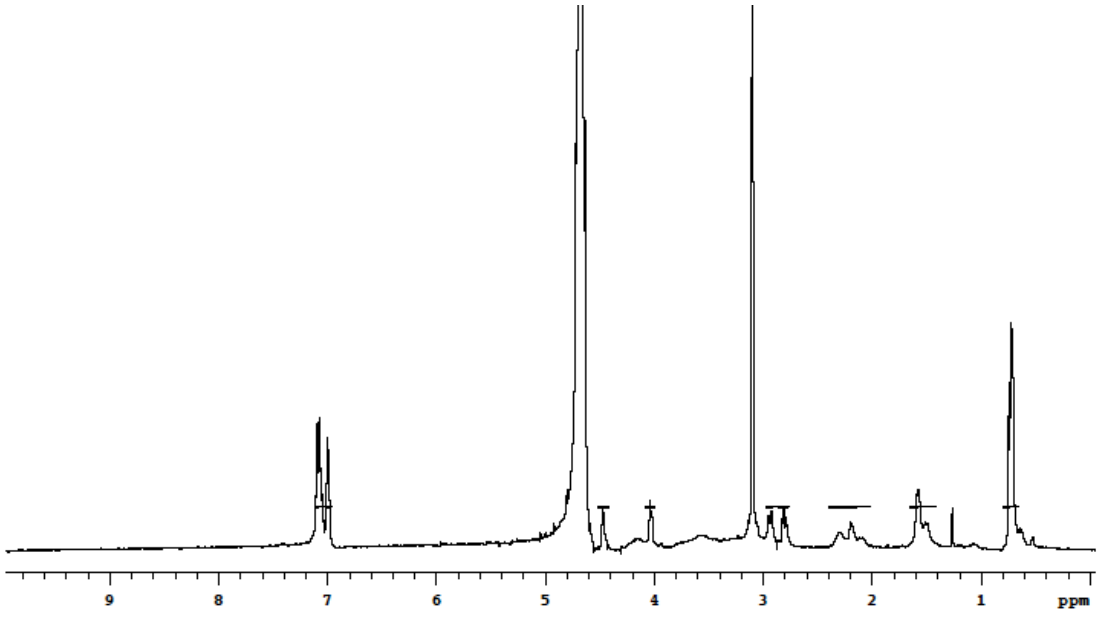
1dg **1dg-deprotected**

Procedure: As described below for **1aa-deprotected**.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36-7.17 (m, 5H), 5.54 (br s, 1H), 4.55 (s, 1H), 4.39-4.33 (m, 1H), 4.28-4.12 (m, 1H), 4.02-3.94 (m, 1H), 3.84-3.72 (m, 1H), 3.71-3.61 (m, 1H), 3.60-3.48 (m, 1H), 3.30-3.27 (m, 2H), 3.16-2.98 (m, 2H), 2.69-2.49 (m, 2H), 2.39-2.26 (m, 1H), 1.98-1.81 (m, 1H), 1.74-1.61 (m, 2H), 0.99 (d, *J* = 2.1 Hz, 3H), 0.97 (d, *J* = 2.1 Hz, 3H)

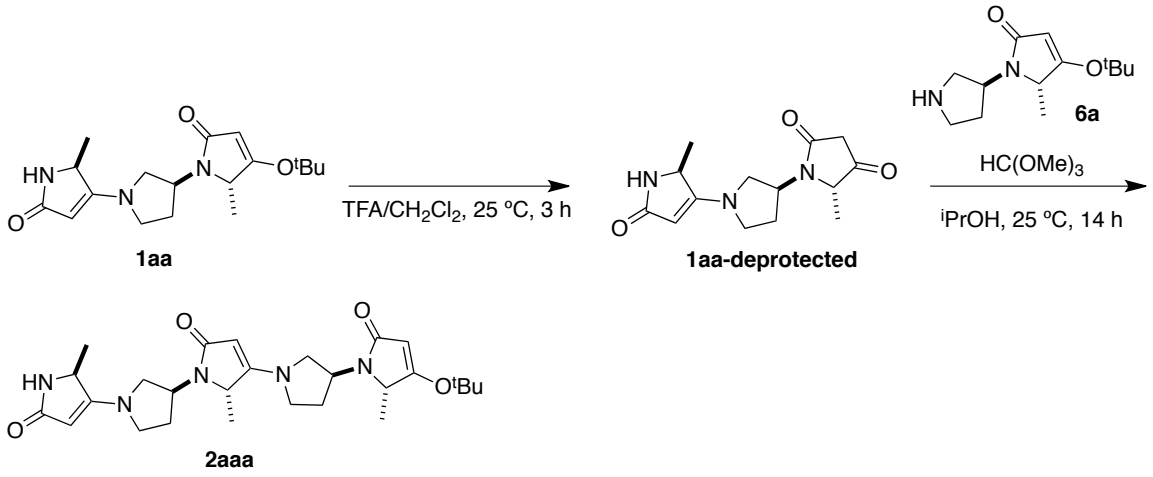


Compounds **1** and **2** tend to have some degree of water solubility. For instance, it was possible to record the ^{1}H NMR spectrum of deprotected **1dg** in 65 % D-$_2$O/CD_3OD at 10 mM (see below) despite the presence of non-polar side-chains.



Compound **2aaa**

(*S*)-4-(*tert*-butoxy)-5-methyl-1-((*S*)-1-((*S*)-2-methyl-1-((*S*)-1-((*S*)-2-methyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)pyrrolidin-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)pyrrolidin-3-yl)-1*H*-pyrrol-2(5*H*)-one



Procedure: Trimer **1aa** (0.8 mmol) was treated with TFA/CH_2Cl_2 (1:1, 1.5 mL) at 25 ºC. The reaction was stirred in a vented teflon-capped flask until complete disappearance of starting material (monitored by NMR spectroscopy, ~ 3 h).. Toluene (5 mL) was added and the reaction mixture was concentrated *in vacuo*. Toluene (2 X 5 mL) was used to azeotrope residual TFA, and the residue was stirred with dry Et_2O (10 mL). After 2 h, the ether was decanted and the residue was dried under high vacuum to afford **1aa-deprotected** as a white solid in quantitative yield.

The tetramic acid **1aa-deprotected** (0.8 mmol) and amine **6a** (0.8 mmol) were stirred in ^{i}PrOH (8 mL) under Argon. Trimethylorthoformate (1.2 mmol, 131 µL) was added and the reaction was allowed to proceed for 14 h. The reaction mixture was concentrated at 25 ºC to obtain a yellow foam. The product was purified by flash chromatography (4-7 % MeOH/CH_2Cl_2) to afford the pentamer **2aaa** in 45 % yield.

Physical state: White solid.

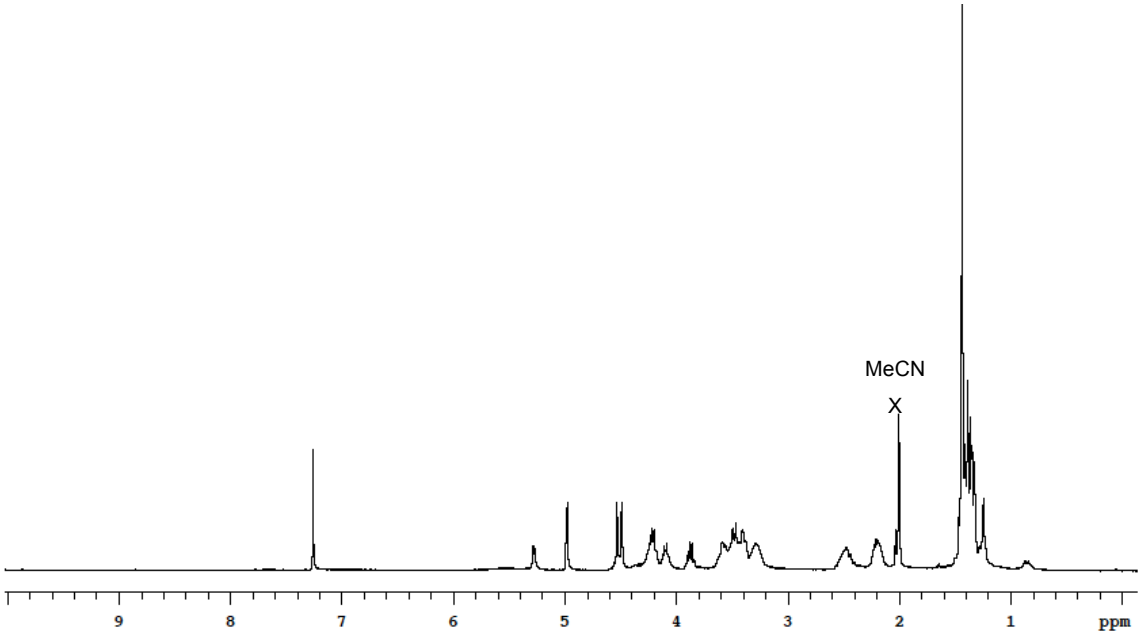
$[\alpha]^{20}$ +17.8 (*c* 0.9, MeOH)

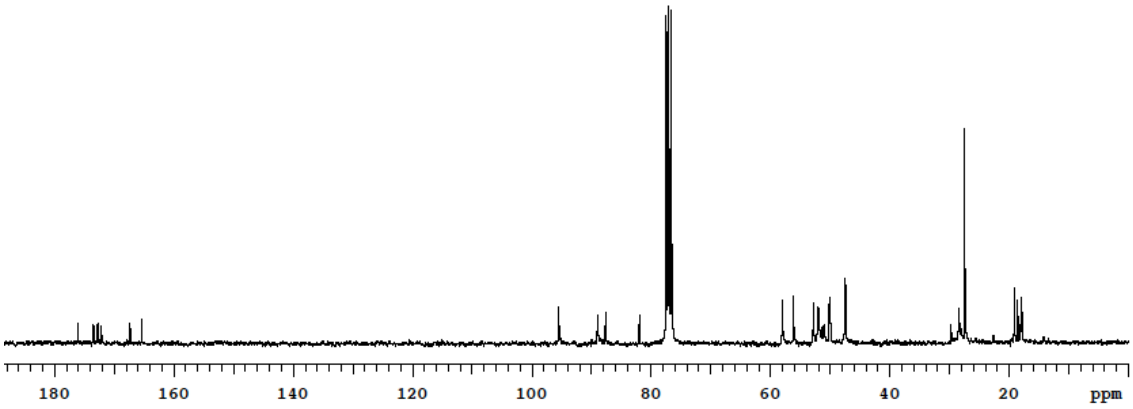
^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.27 (br s, 1H), 4.98 (app s, 1H), 4.53 (app s, 1H), 4.49 (app s, 1H), 4.30-4.14 (m, 3H), 4.13-4.03 (m, 1H), 3.92-3.81 (m, 1H), 3.66-3.54 (m, 2H), 3.53-3.35 (m, 4H), 3.35-3.17 (m, 2H), 2.60-2.38 (m, 2H), 2.28-2.09 (m, 2H), 1.44 (s, 9H), 1.42-1.32 (m, 9H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.0, 173.5, 172.8, 172.1, 167.3, 165.3, 95.5, 95.3, 88.9, 87.6, 82.0, 77.2, 58.0, 56.1, 52.8, 52.0, 51.8, 50.1, 50.0, 47.5, 29.7, 27.4, 19.1, 18.6, 17.9

IR (film, cm^{-1}) 3310 (br), 2978, 2932, 2870, 1669, 1664, 1647, 1636, 1595, 1340, 1260, 1166, 779, 725

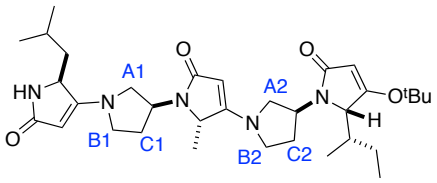
HRMS (MALDI) m/z calcd for $(M+H)^+$ $C_{27}H_{40}N_5O_4$ 498.3080; found 498.3079 (1.0 ppm)




180
160
140
120
100
80
60
40
20
ppm

Compound **2gac**

(*S*)-4-(*tert*-butoxy)-5-((*S*)-*sec*-butyl)-1-((*S*)-1-((*S*)-1-((*S*)-1-((*S*)-2-isobutyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)pyrrolidin-3-yl)-2-methyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)pyrrolidin-3-yl)-1*H*-pyrrol-2(5*H*)-one



Procedure: As reported above for compound **2aaa**. 55 % yield.

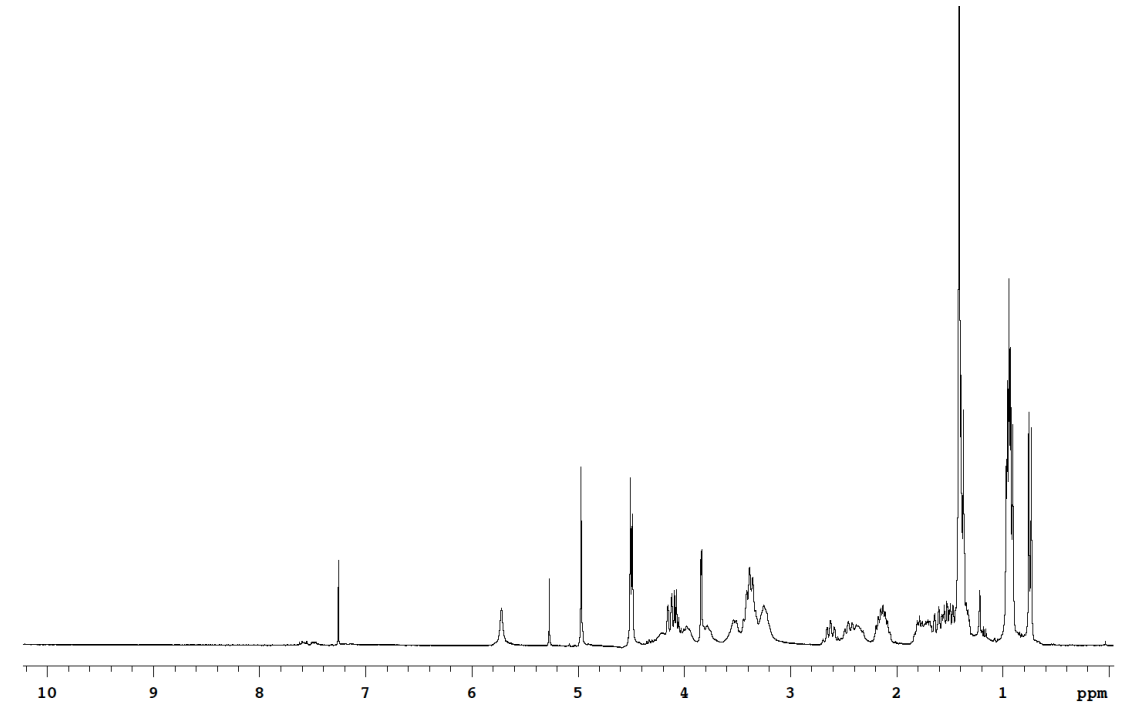
Physical state: White solid.

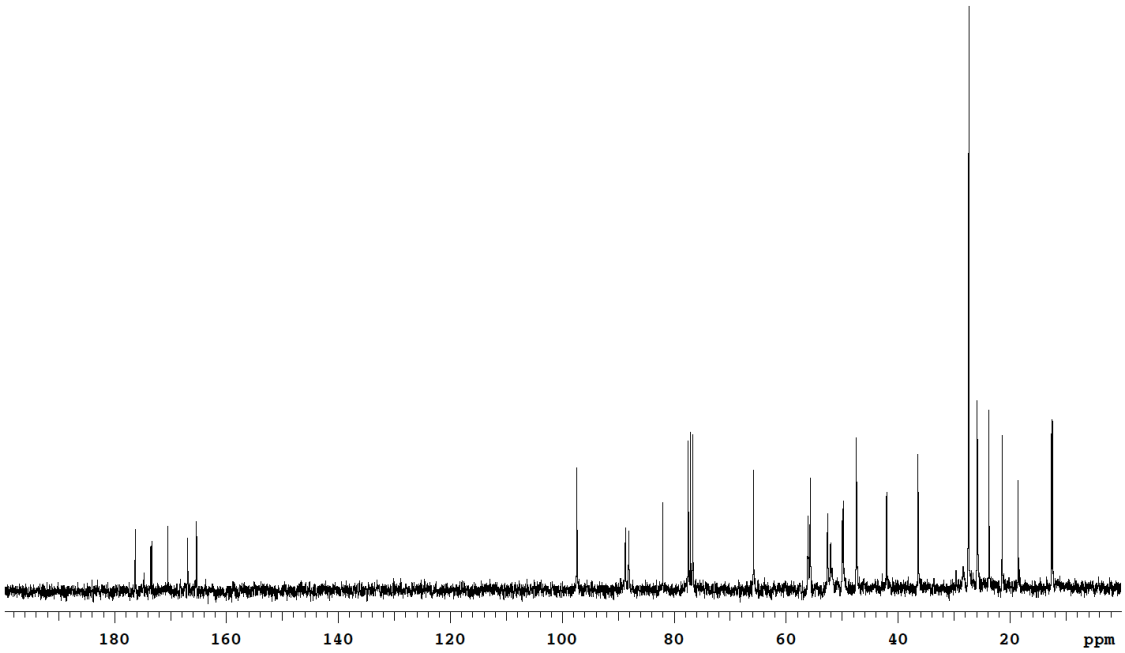
^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.72 (br s, 1H), 4.97 (s, 1H), 4.51 (s, 1H), 4.49 (s, 1H), 4.29-3.90 (m, 4H), 3.84 (d, *J* = 2.4 Hz, 1H), 3.82-3.71 (m, 1H), 3.62-3.46 (m, 1H), 3.46-3.32 (m, 4H), 3.30-3.15 (m, 2H), 2.73-2.52 (m, 1H), 2.50-2.29 (m, 2H), 2.26-2.02 (m, 2H), 1.84-1.44 (m, 5H), 1.40 (s, 9H), 1.42-1.34 (m, 3H), 1.02-0.87 (m, 9H), 0.74 (d, *J* = 6.9 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.3, 173.5, 173.3, 170.5, 166.9, 165.3, 97.4, 88.7, 88.1, 82.1, 65.8, 56.1, 55.7, 52.6, 52.0, 50.0, 49.8, 47.5, 42.0, 36.4, 27.4, 25.9, 25.8, 23.7, 21.4, 18.6, 12.6, 12.4

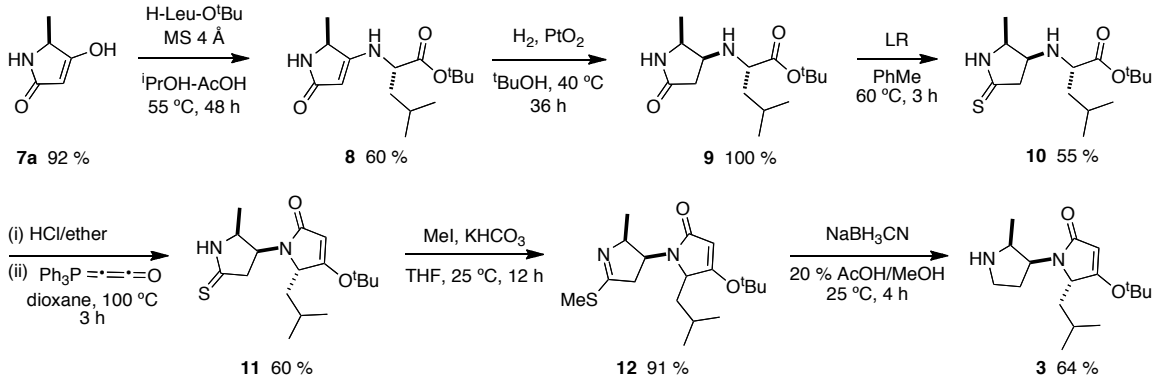
Note: Carbons A1 and A2, B1 and B2, and C1 and C2 overlap at 56.1, 50.0 and 36.4 ppm, respectively.

HRMS (ESI) m/z calcd for $(M+H)^+$ $C_{30}H_{36}N_3O_3$ 582.4019; found 582.4029 (1.5 ppm)


10
9
8
7
6
5
4
3
2
1
ppm

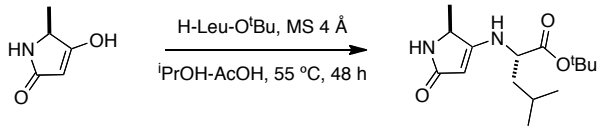

180
160
140
120
100
80
60
40
20
ppm

Scheme S2


H-Leu-OtBu
MS 4 Å
iPrOH-AcOH
55 °C, 48 h
H2, PtO2
tBuOH, 40 °C
36 h
LR
PhMe
60 °C, 3 h
(i) HCl/ether
(ii) Ph3P =•=•=O
dioxane, 100 °C
3 h
MeI, KHCO3
THF, 25 °C, 12 h
NaBH3CN
20 % AcOH/MeOH
25 °C, 4 h
7a 92 %
8 60 %
9 100 %
10 55 %
11 60 %
12 91 %
3 64 %

Compound **8**

((*S*)-*tert*-butyl 4-methyl-2-(((*S*)-2-methyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)amino)pentanoate



7a **8** 60 %

Procedure: A modified procedure was used.[4] The tetramic acid **7a** (1.85 g, 16.4 mmol, 1.5 equiv) and leucine *tert*-butyl ester (2.51 g, 11 mmol, 1 equiv) was stirred in 9:1 ^{i}PrOH/AcOH (55 mL, 0.2 M with respect to leucine *tert*-butyl ester) in the presence of 4 Å molecular sieves. The reaction was purged with N_2 and heated to 55 ºC for 48 h. Upon cooling, the reaction mixture was filtered over Celite. Toluene (50 mL) was added and the solution was concentrated. Residual AcOH was azeotroped with PhMe (3 X 50 mL) to obtain a brown residue. Purification by flash chromatography (1-2 % MeOH/EtOAc) afforded the product as a brown solid, which was further purified by crystallization from hot EtOAc to obtain **8** in 60 % yield.

Physical state: White needles (ethyl acetate), mp = 206 ºC (decomposes)

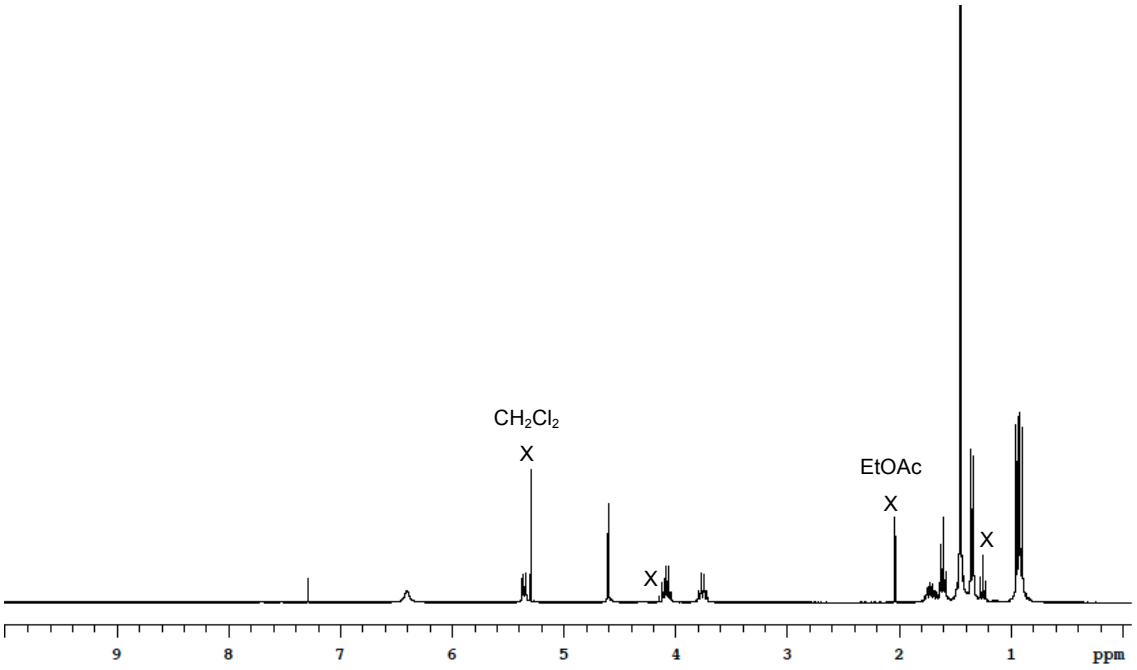
$[\alpha]^{20}$ – 93.1 (*c* 1.0, MeOH)

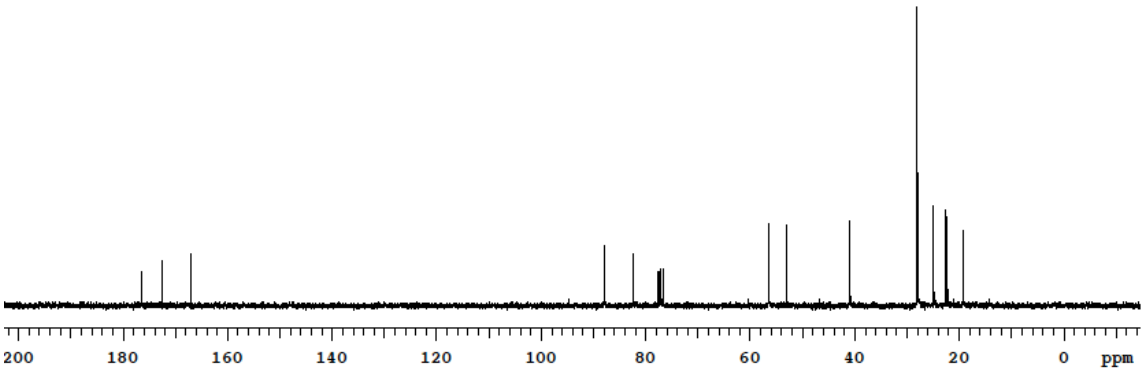
^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.40 (br s, 1H), 5.36 (d, *J* =8.1 Hz, 1H), 4.60 (s, 1H), 4.09 (m, 1H), 3.76 (q, *J* = 7.5 Hz, 1H), 1.72 (m, 1H), 1.61 (t, *J* = 6.7 Hz, 2H), 1.45 (s, 9H), 1.35 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.5, 172.5, 166.9, 87.8, 82.3, 56.4, 53.1, 40.9, 28.0, 24.9, 22.6, 22.3, 19.2

IR (film, cm^{-1}) 3217 (br), 3048, 2959, 2870, 1744, 1645, 1601, 1557, 1368, 1207, 1146, 845, 783, 704

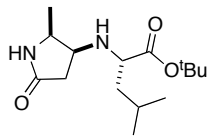
MS (ESI) m/z calcd for $(M+H)^+$ $C_{15}H_{27}N_2O_3$ 283.19; found 283.19


CH2Cl2
X
EtOAc
X
X
X
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm

Compound **9**

(*S*)-*tert*-butyl 4-methyl-2-(((2*S*,3*S*)-2-methyl-5-oxopyrrolidin-3-yl)amino)pentanoate



Procedure: As described in the literature.[4]

Physical state: Colorless oil

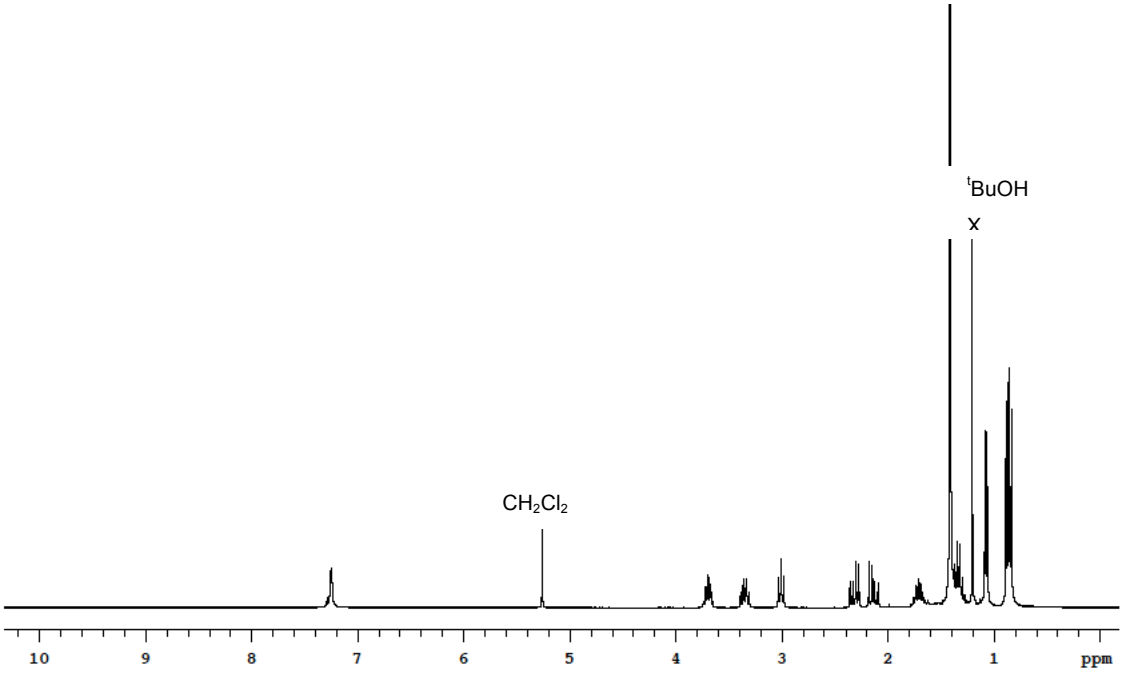
$[\alpha]^{20}$ -10.0 (*c* 1.0, MeOH)

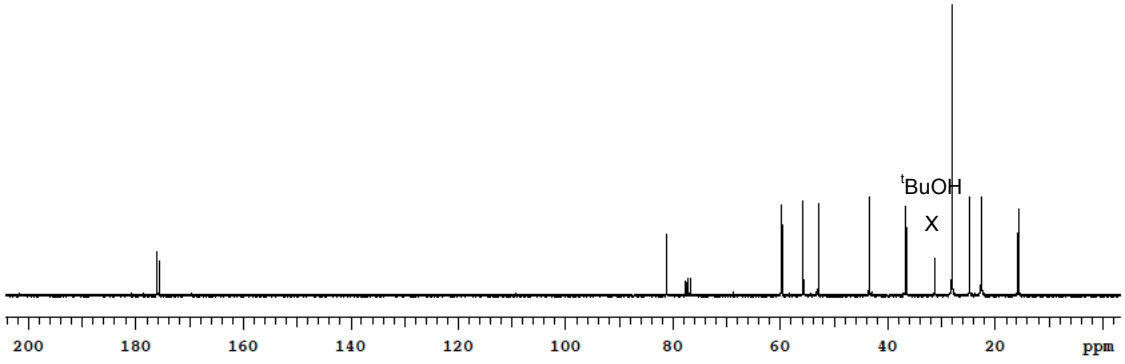
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.20 (br s, 1H), 3.70 (m, 1H), 3.35 (m, 1H), 3.01 (app t, *J* = 7.3 Hz, 1H), 2.32 (dd, *J* = 16.4, 7.7 Hz, 1H), 2.14 (dd, *J* = 16.4, 9.6 Hz, 1H), 1.72 (m, 1H), 1.41 (s, 9H), 1.34 (m, 2H), 1.08 (d, *J* = 6.3 Hz, 3H), 0.88 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.1, 175.6, 81.2, 59.7, 55.7, 52.9, 43.4, 36.5, 28.0, 24.7, 22.6, 22.5, 15.7

IR (film, cm^{-1}) 3273 (br), 2960, 2932, 1732, 1697, 1682, 1472, 1456, 1435, 1368, 1152, 941, 849

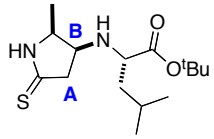
MS (ESI) m/z calcd for $(M+H)^+$ $C_{15}H_{29}N_2O_3$ 285.21; found 285.19


tBuOH
x
CH2Cl2
10
9
8
7
6
5
4
3
2
1
ppm


tBuOH
X
200
180
160
140
120
100
80
60
40
20
ppm

Compound **10**

(*S*)-*tert*-butyl 4-methyl-2-(((2*S*,3*S*)-2-methyl-5-thioxopyrrolidin-3-yl)amino)pentanoate



Procedure: The amine **9** (440 mg, 1.55 mmol, 1 equiv) was dissolved in dry toluene (16 mL) and the reaction flask was evacuated and re-filled with N_2. Lawesson's reagent (314 mg, 0.78 mmol, 0.5 equiv) was added under a stream of N_2 and the reaction was heated to 60 ºC. Upon heating the reaction became clear. After 3 h, the reaction mixture was concentrated in a fume hood. Ether (40 mL) was added to the residue and stirred vigorously for 4 h. The ether layer was decanted and concentrated to obtain the crude product. The pure product was obtained by flash chromatography (SiO_2, PhMe then 20 % EtOAc/Hexanes) in 55 % yield.

Physical state: yellow oil that crystallizes on standing at -20 ºC

$[\alpha]^{20}$ +13.1 (*c* 0.5, MeOH)

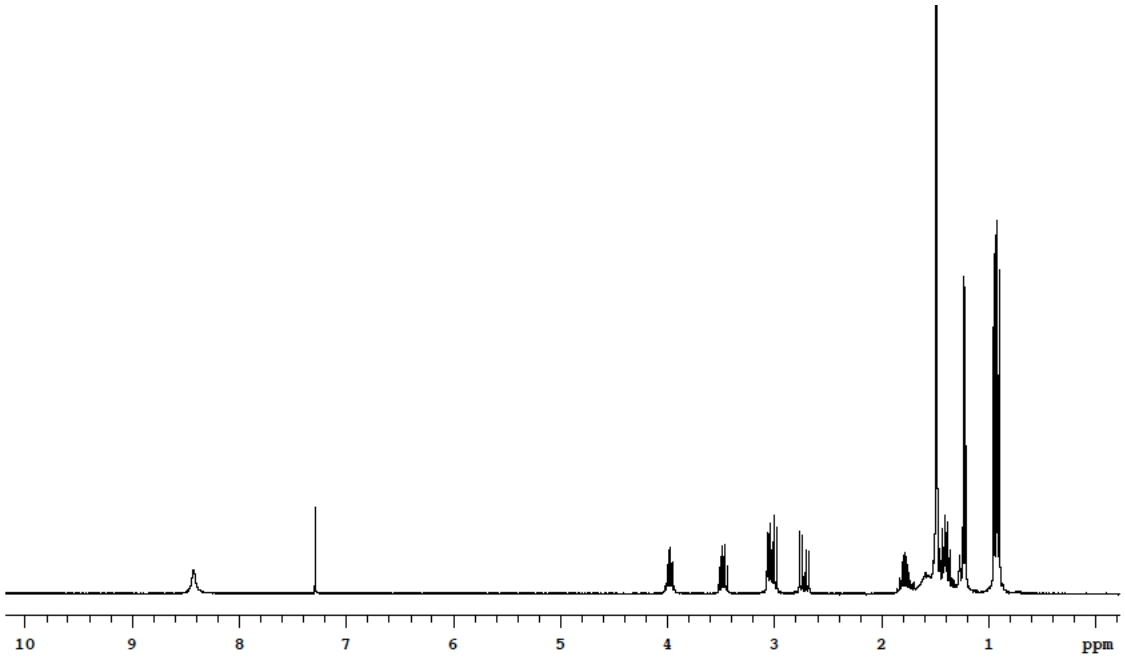
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.4 (br s, 1H), 3.98 (m, 1H), 3.48 (app q, *J* = 7.5 Hz, 1H), 3.08-2.98 (m, 2H), 2.72 (dd, *J* = 17.9, 8.5 Hz, 1H), 1.79 (m, 1H), 1.46 (s, 9H), 1.40 (m, 2H), 1.23 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H)

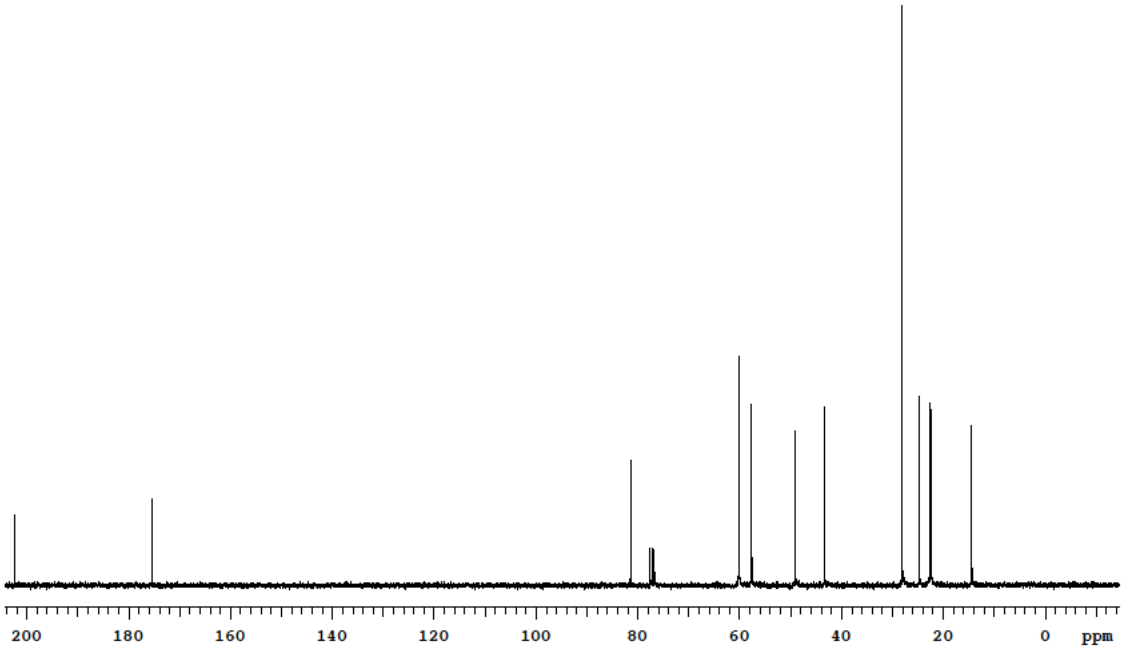
^{13}C-NMR (75 MHz, $CDCl_3$) δ 202.5, 175.4, 81.4, 60.1, 57.7, 49.1, 43.3, 28.1, 24.7, 22.7, 22.4, 14.4

Note: Carbons A and B overlap at 57.7

IR (film, cm^{-1}) 3283, 3175, 2959, 2930, 1732, 1717, 1539, 1531, 1520, 1506, 1497, 1456, 1149, 1069, 845

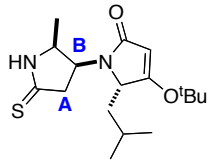
MS (ESI) m/z calcd for $(M+H)^+$ $C_{15}H_{29}N_2O_2S$ 301.19; found 301.17


10
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm

Compound **11**

(*S*)-4-(*tert*-butoxy)-5-isobutyl-1-((2*S*,3*S*)-2-methyl-5-thioxopyrrolidin-3-yl)-1*H*-pyrrol-2(5*H*)-one



Procedure: The amine **10** (200 mg, 0.67 mmol) was dissolved in dry ether (15 mL) and cooled to 0 ºC. HCl/ether (2M, 0.37 mL) was added dropwise to precipitate the hydrochloride salt. After 10 min, the solution was filtered using a sintered glass funnel and washed with cold Et_2O (10 mL). Since the hydrochloride salt was hygroscopic, MeOH (10 mL) was added to the funnel to dissolve the salt. The MeOH filtrate was concentrated to obtain **10.HCl**.
To a solution of **10.HCl** (206 mg, 0.61 mmol) in dioxane (7 mL) at 100 ºC under an Argon atmosphere was added Bestmann's ylide (2X re-crystallized from PhMe, 221 mg, 0.73 mmol, 1.2 equiv) in one portion. After 30 min, a second portion of Bestmann's ylide (37mg, 0.12 mmol, 0.2 equiv) was added, and this process was repeated three additional times at 15 min intervals to complete the addition of 2 equiv of ylide. The reaction was monitored by NMR spectroscopy. After completion of reaction (~ 3 h), the solvent was removed. The product was isolated by flash chromatography (5-10 % acetone/dichlromethane). Further purification was achieved by crystallization to obtain 130 mg of **11** 60 % yield.

Physical state: White prisms (dichloromethane/hexanes), mp = 210 ºC decomposes

$[\alpha]^{20}$ -58.5 (*c* 1.0, MeOH)

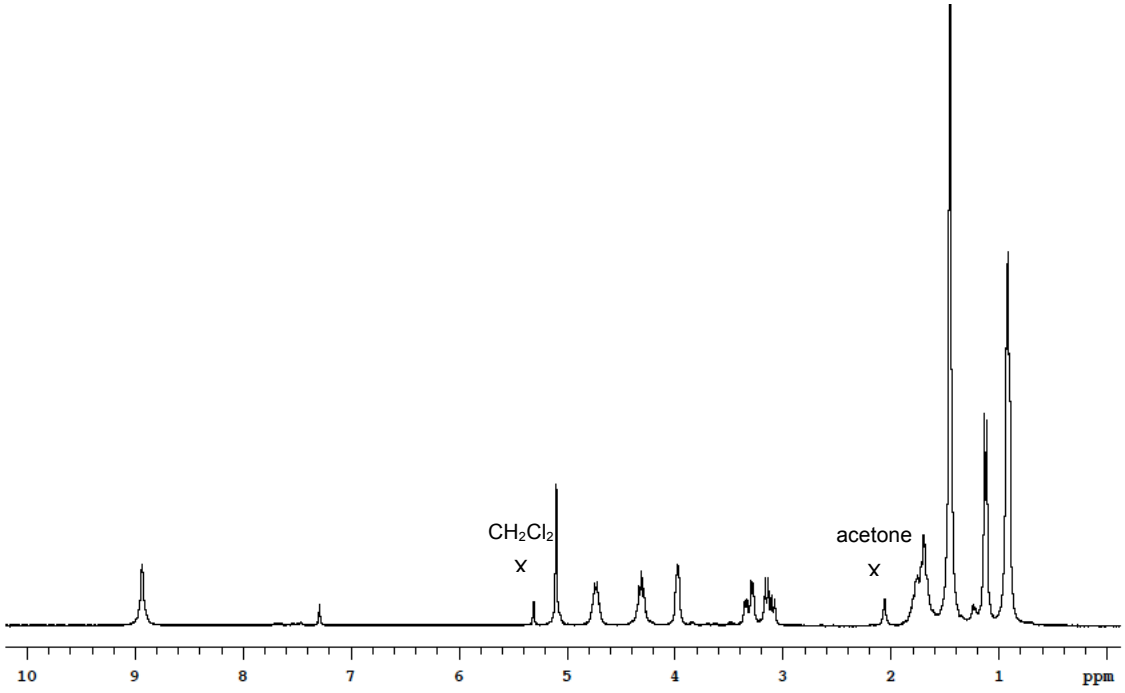
^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.0 (s, 1H), 5.09 (s, 1H), 4.82-4.66 (m, 1H), 4.37-4.24 (m, 1H), 4.01-3.94 (m, 1H), 3.31 (dd, *J* = 17.4, 6.0 Hz, 1H), 3.12 (dd, *J* = 17.6, 8.3 Hz, 1H), 1.81-1.64 (m, 3H), 1.45 (s, 9H), 1.12 (d, *J* = 6.6 Hz, 3H), 0.98-0.85 (m, 6H)

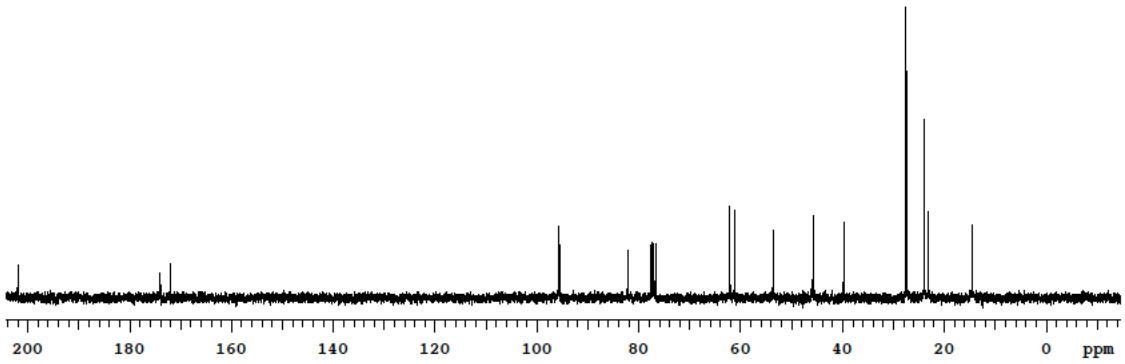
^{13}C-NMR (75 MHz, $CDCl_3$) δ 202.0, 174.0, 171.9, 95.6, 82.2, 62.1, 61.2, 53.6, 45.8, 39.7, 27.5, 23.9, 23.2, 14.5

Note: Carbons A and B overlap at 53.6

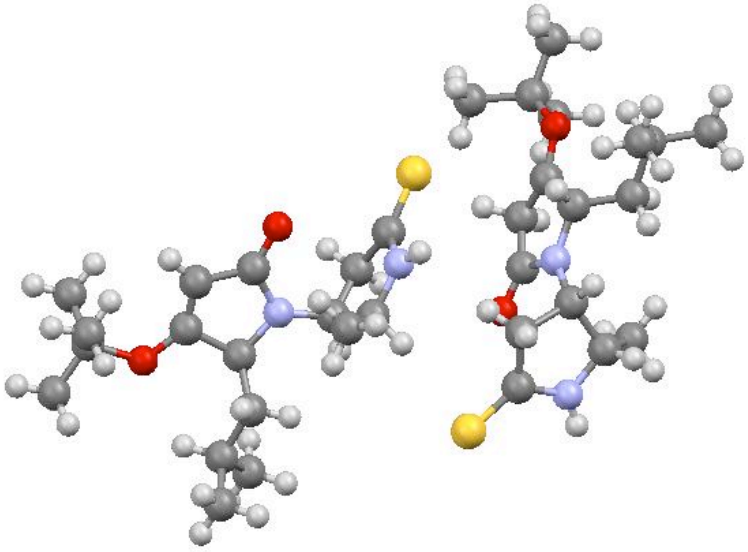
IR (film, cm^{-1}) 3134 (br), 2954, 2866, 2359, 1653, 1622, 1539, 1435, 1350, 1317, 1258, 1238, 1171, 1093, 870, 845, 689

MS (ESI) m/z calcd for $(M+H)^+$ $C_{17}H_{29}N_2O_2S$ 325.19; found 325.20




200
180
160
140
120
100
80
60
40
20
0
ppm

X-Ray for compound **11**



Crystal data and structure refinement details

Empirical formula C17 H28.50 N2 O2 S

Formula weight 324.98

Temperature 110(2) K

Wavelength 1.54178 Å

Crystal system Monoclinic

Space group P2(1)

Unit cell dimensions a = 9.080(3) Å a= 90°.

b = 6.0442(11) Å b= 95.46(2)°.

c = 33.842(9) Å g = 90°.

Volume 1848.9(8) $Å^3$

Z 4

Density (calculated) 1.167 Mg/m^3

Absorption coefficient 1.616 mm^{-1}

F(000)706

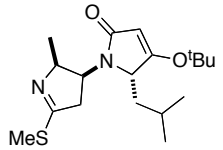
Crystal size 0.10 x 0.10 x 0.01 mm^3

Theta range for data collection 1.31 to 60.00°.

Index ranges	-9<=h<=10, -6<=k<=6, -37<=l<=37
Reflections collected	21923
Independent reflections	4733 [R(int) = 0.0950]
Completeness to theta = 60.00°	90.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9840 and 0.8551
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4733 / 277 / 399
Goodness-of-fit on F^2	1.009
Final R indices [I>2sigma(I)]	R1 = 0.1036, wR2 = 0.2324
R indices (all data)	R1 = 0.1248, wR2 = 0.2477
Absolute structure parameter	0.13(6)
Extinction coefficient	0.0008(4)
Largest diff. peak and hole	0.582 and -0.369 e.$Å^{-3}$

Compound **12**

(2'*S*,3'*S*,5*S*)-4-(*tert*-butoxy)-5-isobutyl-2'-methyl-5'-(methylthio)-3',4'-dihydro-2'*H*-[1,3'-bipyrrol]-2(5*H*)-one



Procedure: To a solution of **11** (98 mg, 0.3 mmol, 1equiv) in THF (3 mL) was added potassium bicarbonate (45 mg, 0.45 mmol, 1.5 equiv) followed by methyl iodide (28 µL, 0.45 mmol, 1.5 equiv) dropwise. The reaction was stirred at 25 ºC for 12 h during the course of which a white precipitate formed. The precipitate was filtered and the filtrate was evaporated to obtain the pure product in 91 % yield.

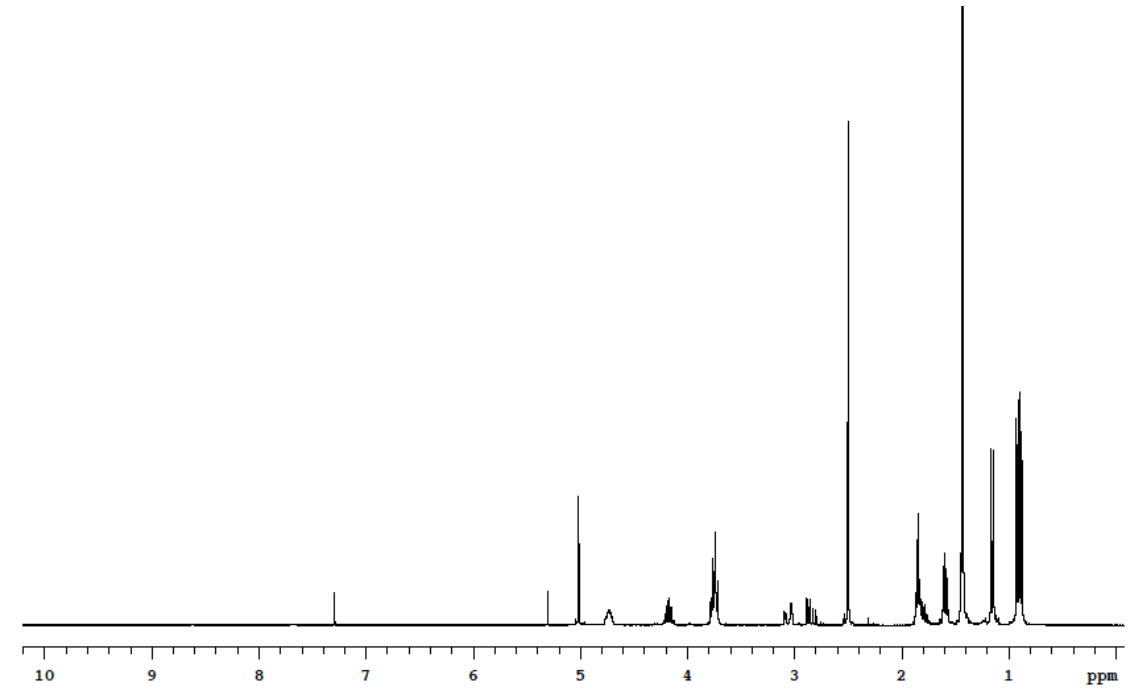
Physical state: Colorless oil

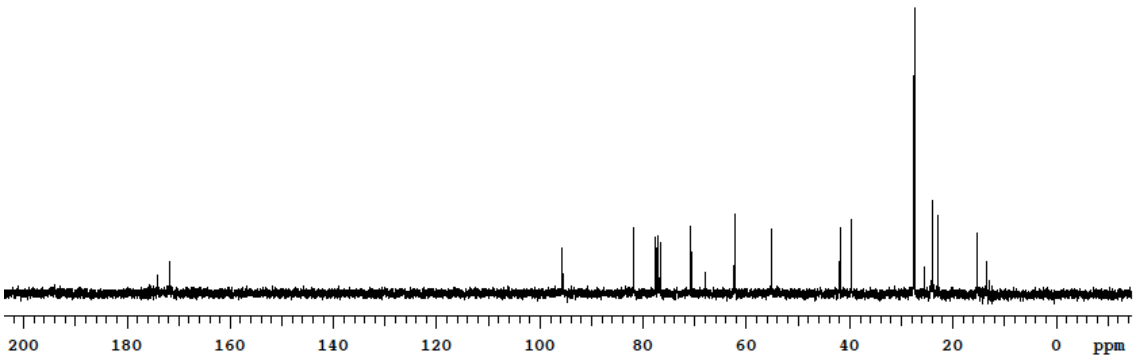
^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.79-4.69 (m, 1H), 4.18 (p, *J* = 6.6 Hz, 1H), 3.81-3.72 (m, 1H), 3.06 (dd, *J* = 16.8, 3.9 Hz, 1H), 2.84 (dd, *J* = 16.8, 8.7 Hz, 1H), 2.50 (s, 3H), 1.89-1.78 (m, 1H), 1.64-1.58 (m, 2H), 1.43 (s, 9H), 1.15 (d, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 174.0, 171.8, 171.6, 95.6, 81.9, 70.7, 62.3, 55.2, 41.9, 39.6, 27.4, 24.0, 23.9, 22.9, 15.2, 13.9

IR (film, cm^{-1}) 3107, 2930, 2868, 1682, 1616, 1575, 1456, 1394, 1371, 1339, 1258, 1167, 1089, 1030, 808, 733

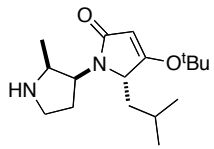
HRMS (ESI) m/z calcd for $(M+H)^+$ 339.2106; found 339.2102 (1.3 ppm)


10
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm

Compound **3**

(*S*)-4-(*tert*-butoxy)-5-isobutyl-1-((2*S*,3*S*)-2-methylpyrrolidin-3-yl)-1*H*-pyrrol-2(5*H*)-one



Procedure: To a solution of **12** (43 mg, 0.13 mmol, 1 equiv) in 20 % AcOH/MeOH (1.3 mL) at 25 ºC was added sodium cyanoborohydride (32 mg, 0.5 mmol, 4 equiv in one portion. This process was repeated 3 additional times every 1 hour. After 4 h, the reaction was brought 0 ºC and carefully neutralized with 2 N NaOH (2.5 mL). Ether (10 mL) was added and extracted with saturated $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in a fume hood. The residue was purified by flash chromatography to afford 23 mg of the product as a white solid.

Physical state: White solid

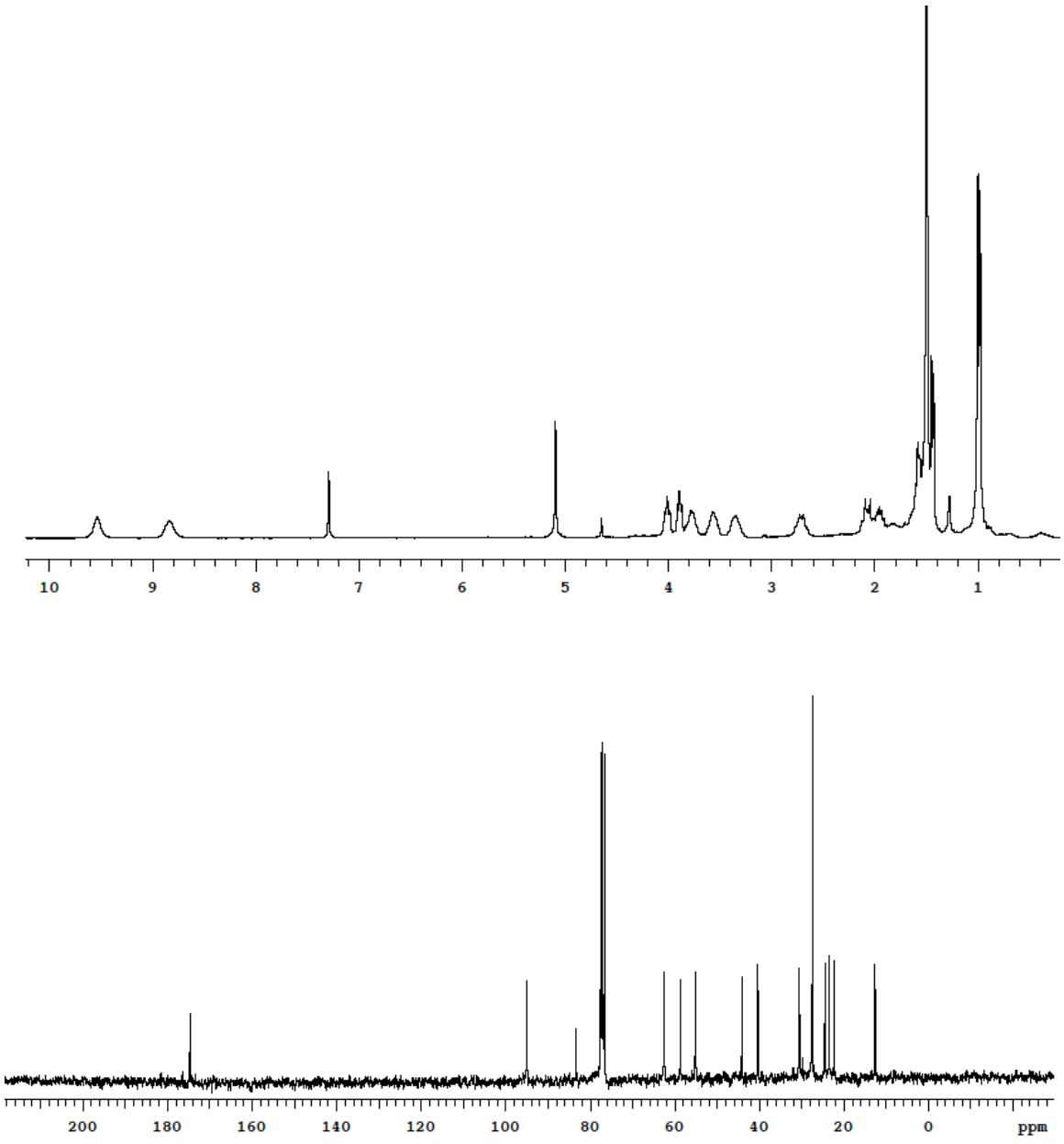
^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.6 (br, 1H), 8.8 (br, 1H), 5.09 (s, 1H), 4.01 (t, *J* = 7.2 Hz, 1H), 3.89 (dd, *J* = 7.5, 4.8 Hz, 1H), 3.84-3.70 (m, 1H), 3.62-3.50 (m, 1H), 3.51-3.28 (m, 1H), 2.78-2.64 (m, 1H), 2.11-1.90 (m, 2H), 1.61-1.54 (m, 2H), 1.50 (s, 9H), 1.44 (d, *J* = 6.6 Hz, 3H), 0.99 (app d, 6H)

Note: Extra proton at 9.6 is due to protonation of the pyrrolidine *N* by residual water.

^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.0, 174.7, 94.5, 83.3, 62.5, 58.6, 55.1, 44.1, 40.3, 30.5, 27.4, 24.5, 23.4, 22.2, 12.6

IR (film, cm^{-1}) 3117, 2957, 2871, 1609, 1558, 1521, 1373, 1340, 1259, 1163, 1120, 851, 637

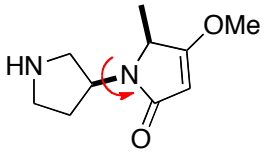
MS (ESI) m/z calcd for $(M+H)^+$ $C_{17}H_{31}N_2O_2$ 295.23; found 295.24


10
9
8
7
6
5
4
3
2
1
200
180
160
140
120
100
80
60
40
20
0
ppm

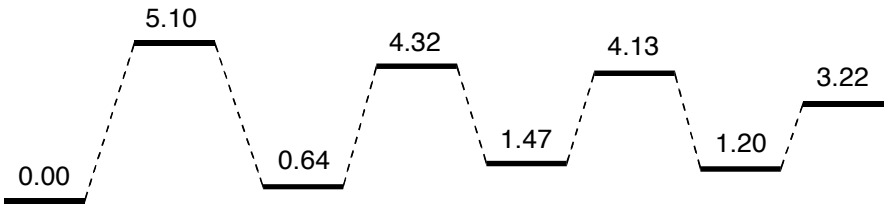
D. Molecular Modeling

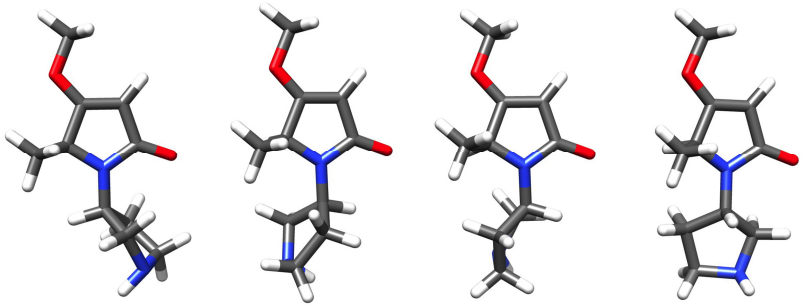
DFT Calculation

Reaction path calculations were performed at the B3LYP level of theory with the 6-31G(d') basis set, and a polarized continuum solvation model with a dielectric of H_2O (ε=78.3553). All B3LYP calculations were performed using Gaussian 03.[5] The energy barriers for the compounds **6a'** and **6d** were calculated as rotations of the bonds (red arrows). ΔG^{o} values were shown in kcal/mol. For **6a'**, DFT calculations showed one more low energy conformer, **B'** as a minor conformer.

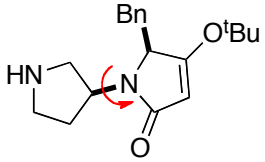


6a'

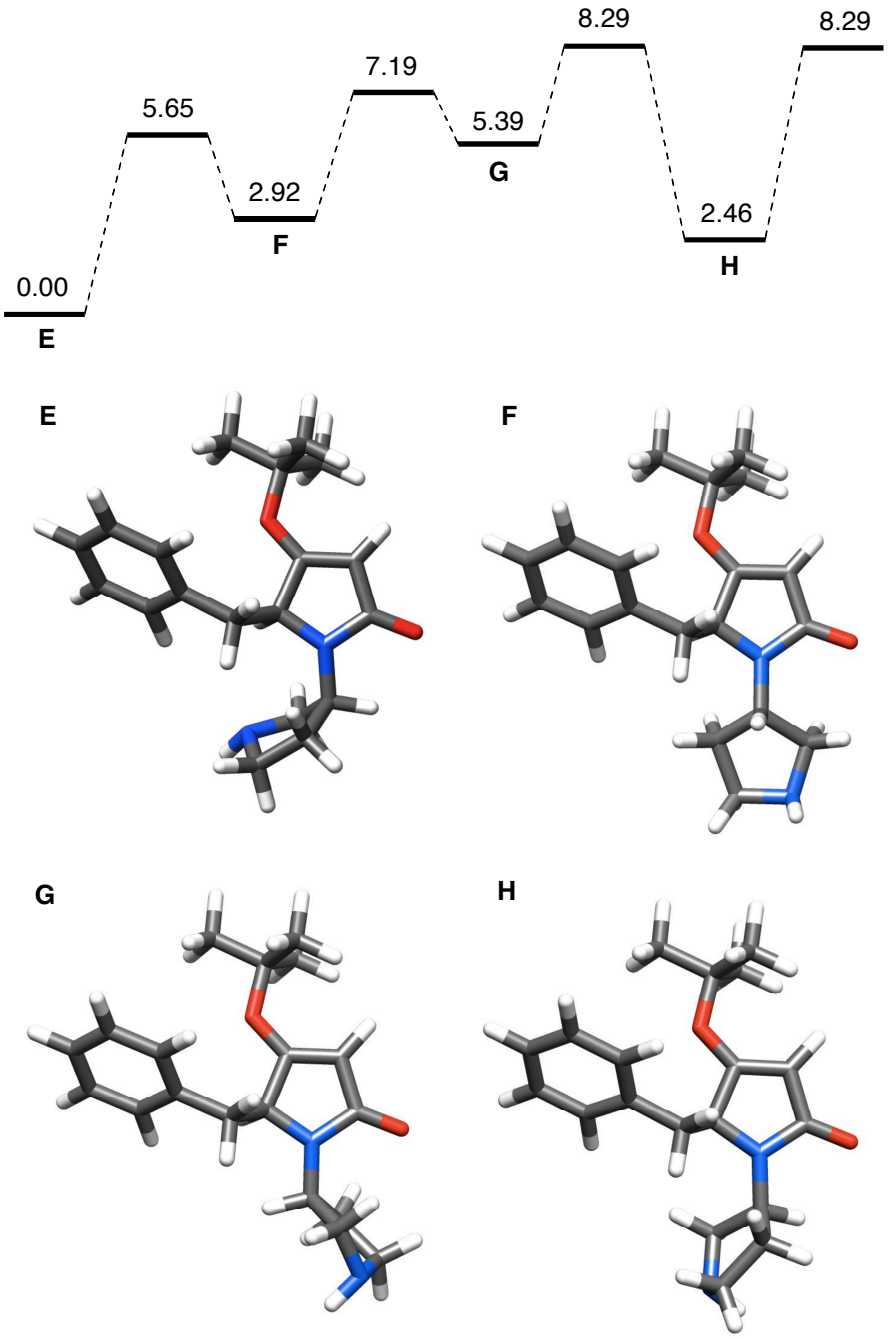




A **B** **B'** **C**



6d



Quenched Molecular Dynamics (QMD)

NAMD[6] was used for the molecular simulations performed in this work. Explicit atom representations were used throughout the study. The protein structure files (PSF) for all the peptidomimetics were built using Discovery Studio 2.5 (Accelrys Inc) using the CHARMm force field.[7]

Quenched molecular dynamics simulations were performed using the CHARMm force field as implemented in Discovery Studio 2.5. All four molecules were modeled as neutral compounds in a dielectric continuum of 80 (simulating H_2O). Thus, the starting conformers were minimized using 3000 steps of conjugate gradient. The minimized structures were then subjected to heating, equilibration, and dynamics simulation. Throughout, the equations of motions were integrated using the Verlet algorithm with a time step 1 fs. Each peptidomimetic was heated to 1000 K over 10 ps and equilibrated for another 10 ps at 1000 K, then molecular dynamics runs were performed for a total time of 600 ps with trajectories saved every 1 ps. The resulting 600 structures were thoroughly minimized using 1000 steps of SD followed by 3000 steps of conjugate gradient. Structures with energies less than 3.0 kcal mol^{-1} relative to the global minimum were selected for further analysis.

The VMD[7] package was used to display, overlay, and classify the selected structures into conformational groups. The best clustering was obtained using a grouping method based on calculation of RMS deviation of a subset of atoms, in this study these were the C^{α}- and C^{β}- atoms. Thus, threshold cutoff values 0.3 Å were selected to obtain families with reasonable homogeneity. The lowest energy conformation from each family was considered to be a typical representative of the family as a whole.

Procedure For Overlays

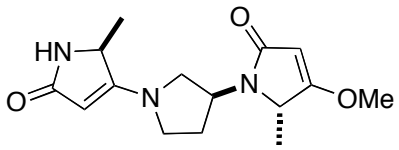
After minimization in the QMD process, the conformers were grouped into families base on their Cα-Cβ coordinates. The process of systematically matching preferred conformers with secondary structures was performed in the following way. All the conformers within 3.0 kcal/mol were considered to be "preferred". **1aa** has 582 conformers (18 families) and **2aaa** has 490 conformers (166 families) within 3.0 kcal/mol and 0.5 Å RMSD. Each of these was overlaid on ideal secondary structures using an in house generated algorithm that compared Cα-Cβ coordinates of the side chains which generates a list of structures ranked in terms of the RMSD for the overlay process. The lowest

energy structures from each family were each overlaid on the ideal secondary structures shown in Figure 1.

Templates For Secondary Structures

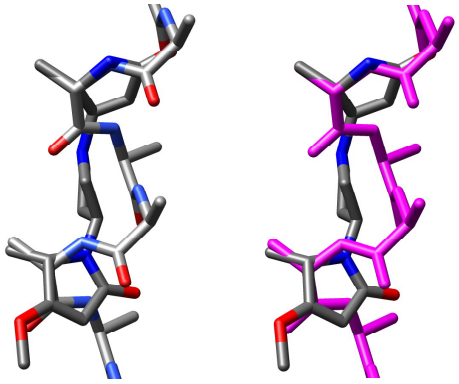
Standard template for overlays with 3_{10}-helix, α-helix, π-helix, and β-strand were obtained from Discovery Studio 2.5.[8] Parallel β-sheet and sheet/turn/sheet templates were obtained by modified β-sheet builder (http://www-lbit.iro.umontreal.ca/bBuilder/index.html).[9]

Overlays Of Compound 1aa Conformers On The Secondary Structures

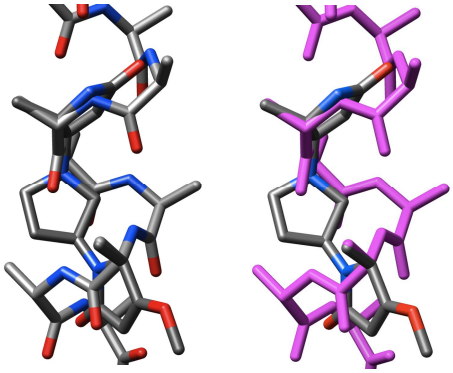


1aa

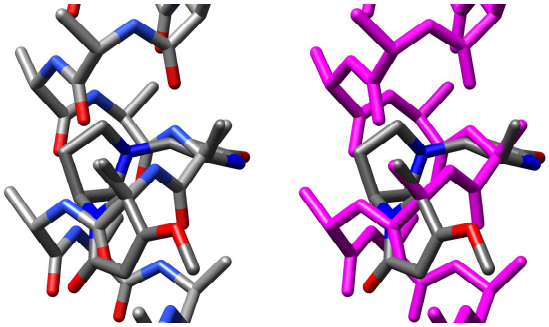
overlay on 3_{10}-helix



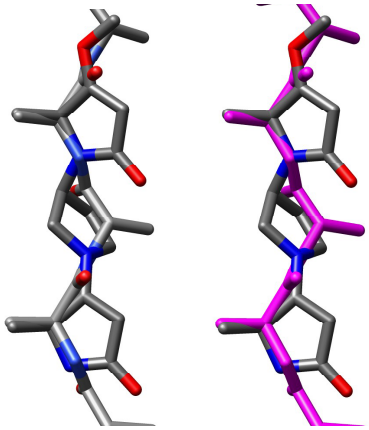
overlay on α-helix



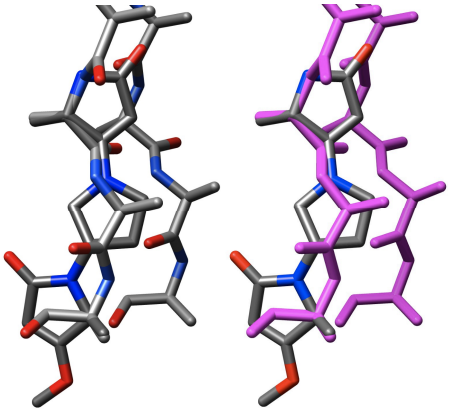
overlay on π-helix



overlay on β-strand



overlay on parallel β-sheet



overlay on sheet/β-turn/sheet

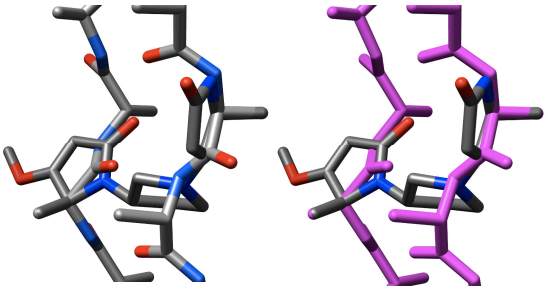
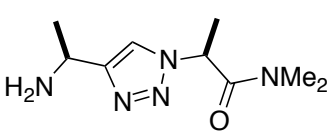
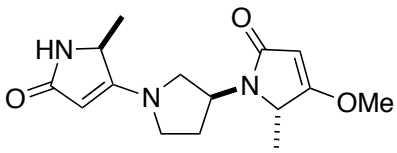


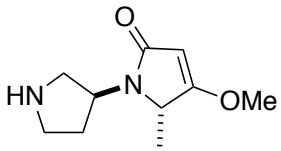
Table S1. Comparison Of Fits Of A, 1, 3, B And C On Secondary Structures Bases On QMD Analyses (less than 0.3 Å RMSD highlighted)



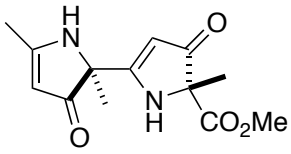
A



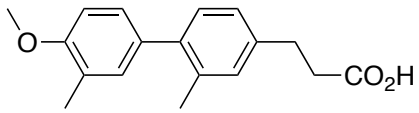
1



3



B

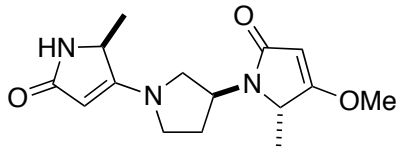


C

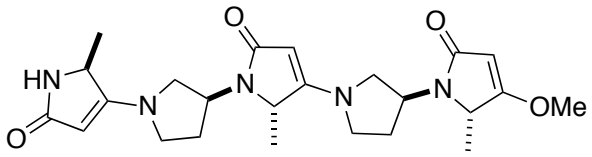
structure	seq.	A		1		3		B		C[a]	
		ΔG	rmsd	ΔG	rmsd	ΔG	rmsd	ΔG	rmsd	ΔG	rmsd
3_{10}-helix	*i*-*i*+1			**2.55**	**0.22**	2.09	0.55	**0.28**	**0.13**	0.95	0.47
	i-*i*+2	**1.66**	**0.28**	**2.43**	**0.25**					**0.12**	**0.23**
	i-*i*+3			1.27	0.49						
α-helix	*i*-*i*+1			2.00	0.47	2.09	0.50	**0.23**	**0.30**	0.95	0.33
	i-*i*+2	**1.62**	**0.25**	**2.55**	**0.30**					0.78	0.34
	i-*i*+3			**0.73**	**0.14**					0.78	0.39
	i-*i*+4			**1.27**	**0.18**						
π-helix	*i*-*i*+1			**2.55**	**0.14**	2.09	0.54	0.83	0.37	**0.53**	**0.29**
	i-*i*+2	1.63	0.33	**2.99**	**0.30**						
	i-*i*+3			**2.43**	**0.31**					0.90	0.38
	i-*i*+4			0.85	0.35			0.0051	0.81	0.78	0.36
	i-*i*+5			**1.27**	**0.27**						
β-strand	*i*-*i*+1					2.24	0.46	**0.079**	**0.29**	0.12	0.61
	i-*i*+2			**1.19**	**0.19**						
β-sheet (parallel)	*i*-*i*+1			**1.01**	**0.10**			**0.079**	**0.15**	1.58	0.37
	i-*i*+2			**2.55**	**0.20**						
sheet/ β-turn/ sheet	*i*-*i*+1	**0.19**	**0.23**			2.25	0.49	**0.17**	**0.18**		
	i-*i*+2			**1.19**	**0.12**						
	i-*i*'			**2.74**	**0.27**						
	i-*i*'+1			**0.59**	**0.08**						
	i-*i*'+2			**0.81**	**0.18**						
	i'-*i*+1			**1.38**	**0.09**						
	i-*i*''	**0.14**	**0.06**	**0.75**	**0.25**						
	i'- *i*''+1			1.00	0.42						
	i'- *i*''							**0.28**	**0.29**	0.93	0.54
	i-*i*'							**1.05**	**0.10**	0.87	0.39
	i+1-*i*'+1									**1.58**	**0.24**
	i''-*i*'									0.69	0.37

[a] Hamilton's original helical mimics were terphenyls, but biphenyls were used in this modeling study to represent two amino acid side-chains, [b]ΔG (kcal/mol), and RMSD (Å)

Overlay Examples Of Compound 1aa Conformers And 2aaa Conformers On EDA-A1, Mcl-1/Bim And RAD52 Crystal Structures

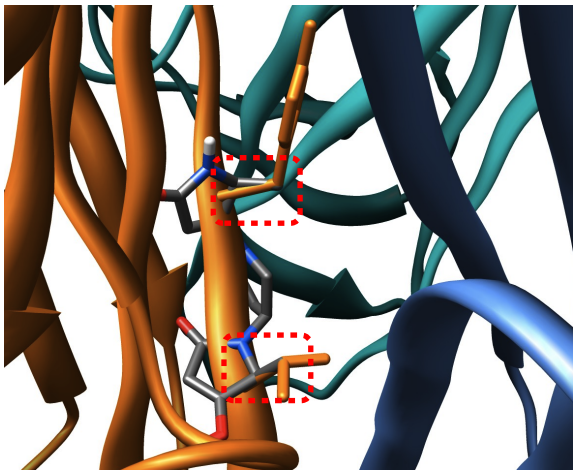


1aa

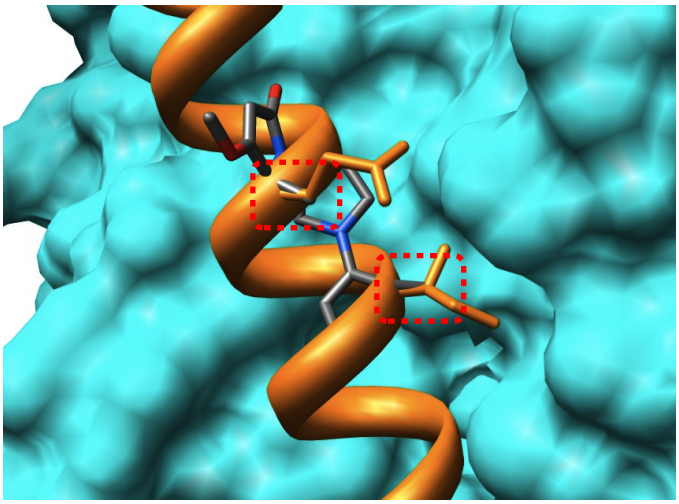


2aaa

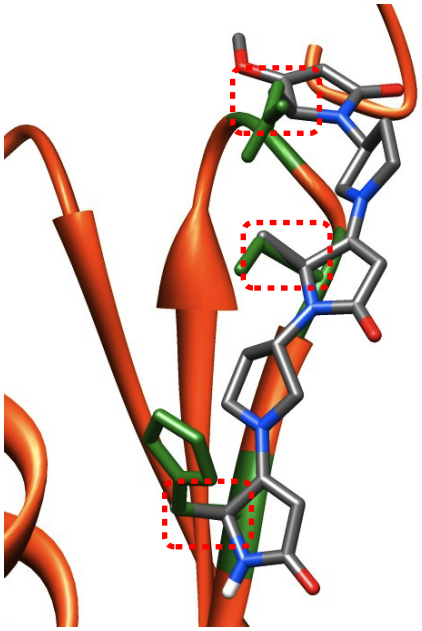
a. **1aa** on *i*-*i*+2 residues of anti-parallel β-sheet on EDA-A1 (PDB: 1RJ7, Ectodysplasin-A1) (ΔG= 1.20 kcal/mol, RMSD = 0.11 Å)



b. **1aa** on *i*-*i*+3 residues of α-helix on Mcl-1/Bim complex (PDB: 2NL9) (ΔG= 1.63 kcal/mol, RMSD = 0.12 Å)



c. **2aaa** on *i*-*i*'-*i*'+2 residues of sheet/β-turn/sheet on RAD52 (PDB: 1KN0) (ΔG= 1.04 kcal/mol, RMSD = 0.14 Å)



E. References

The full citation[10] in the text is given here (a partial one was used in the text).

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