SUPPORTING INFORMATION

Omegatides: Constrained Analogs Of Peptide Primary Sequence

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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, cerric ammonium molybdate, and/or potassium permanganate stains. Flash column chromatography was performed using silica gel 60 (Silicycle, 230-400 mesh). ^{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 undeuterated 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. 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.

B. Literature procedures used in synthesis

Compounds **1** {a-c} and **5** {a-c} were synthesized using a literature procedure.[1, 2] (*S*)-5-methylpyrrolidine-2,4-dione (pyrrolinone **A**) was obtained by a known procedure in 90 % yield, and the spectra match (^{1}H and ^{13}C-NMR) the reported spectra.[1] Compounds **2** {a-c} were prepared accordingly original procedure.[2]

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 = 1.54184 Å 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

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

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. 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.**

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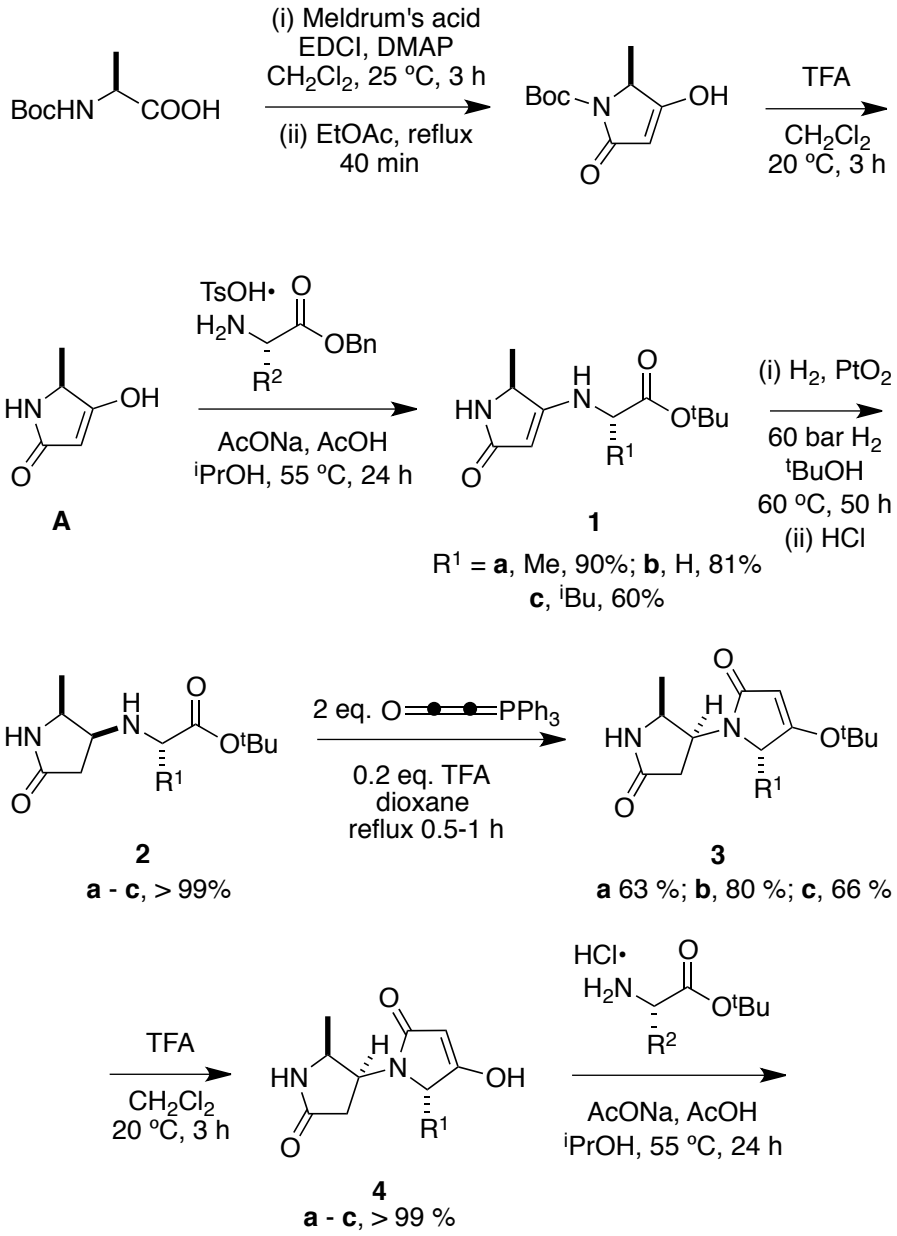
* SAINT, “Program for Data Reduction from Area Detectors” ” BRUKER AXS Inc., 5465 East Cheryl Parkway, Madison, WI 53711-5373 USA

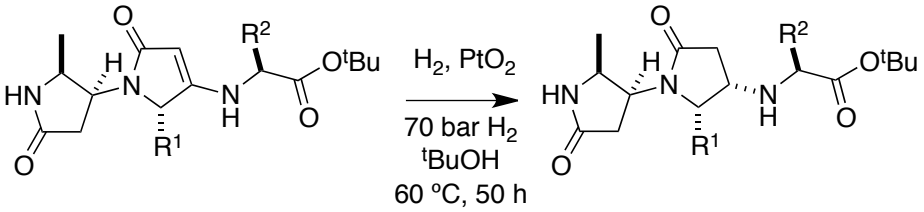
** SADABS, Sheldrick, G.M. “Program for Absorption Correction of Area Detector Frames”, BRUKER AXS Inc., 5465 East Cheryl Parkway, Madison, WI 53711-5373 USA

* 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.

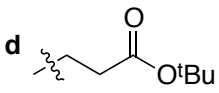
Scheme S1

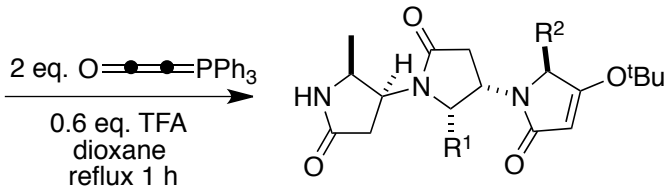

BocHN
COOH
(i) Meldrum's acid
EDCI, DMAP
CH2Cl2, 25 °C, 3 h
(ii) EtOAc, reflux
40 min
Boc
N
OH
O
TFA
CH2Cl2
20 °C, 3 h
HN
OH
O
A
TsOH•
H2N
O
OBn
R2
AcONa, AcOH
iPrOH, 55 °C, 24 h
H
N
OtBu
R1
1
(i) H2, PtO2
60 bar H2
tBuOH
60 °C, 50 h
(ii) HCl
R1 = a, Me, 90%; b, H, 81%
c, iBu, 60%
2
a - c, > 99%
2 eq. O=C=C=PPh3
0.2 eq. TFA
dioxane
reflux 0.5-1 h
3
a 63 %; b, 80 %; c, 66 %
TFA
CH2Cl2
20 °C, 3 h
4
a - c, > 99 %
HCl•
AcONa, AcOH
iPrOH, 55 °C, 24 h



5
aa, 50 %; **cd**, 40 %

6
aa; **cd**, > 99 %

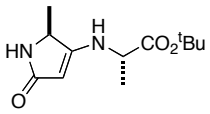




7aa, 80 %

Compound **1a**

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

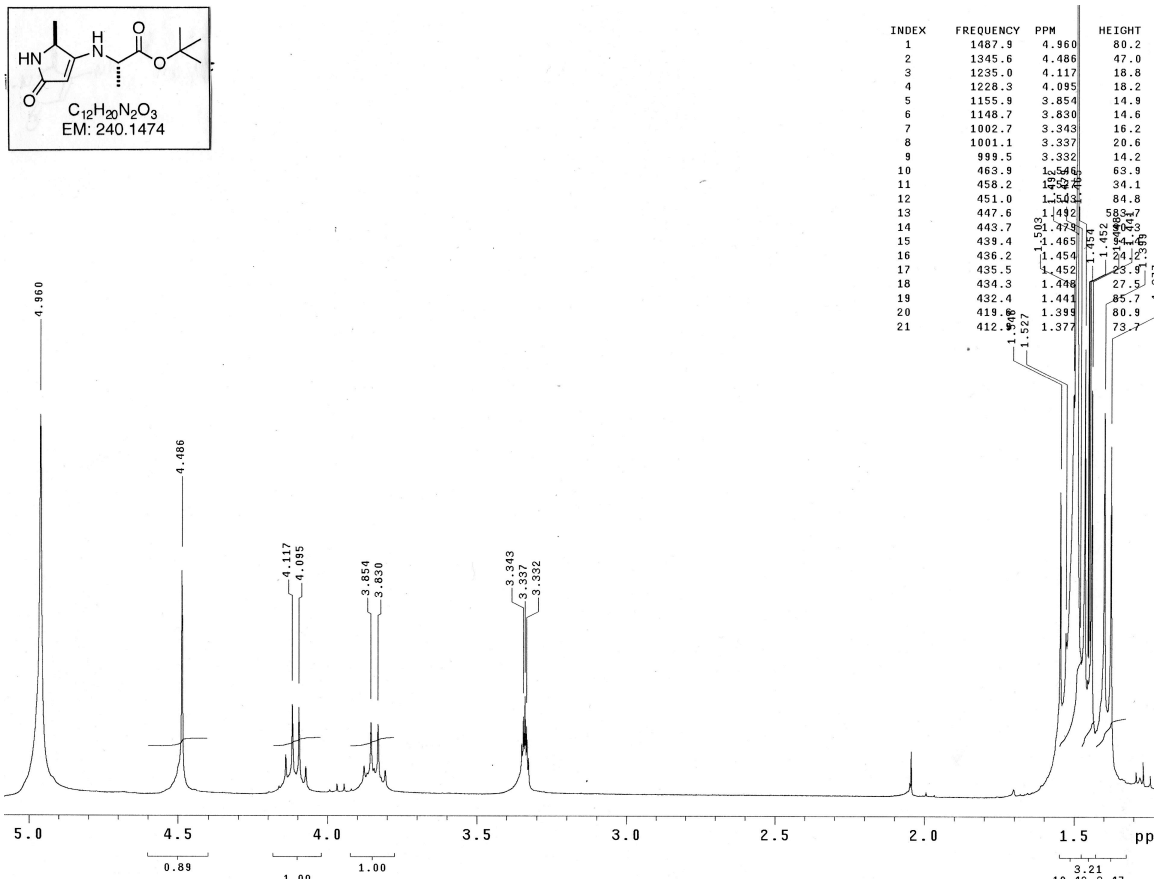


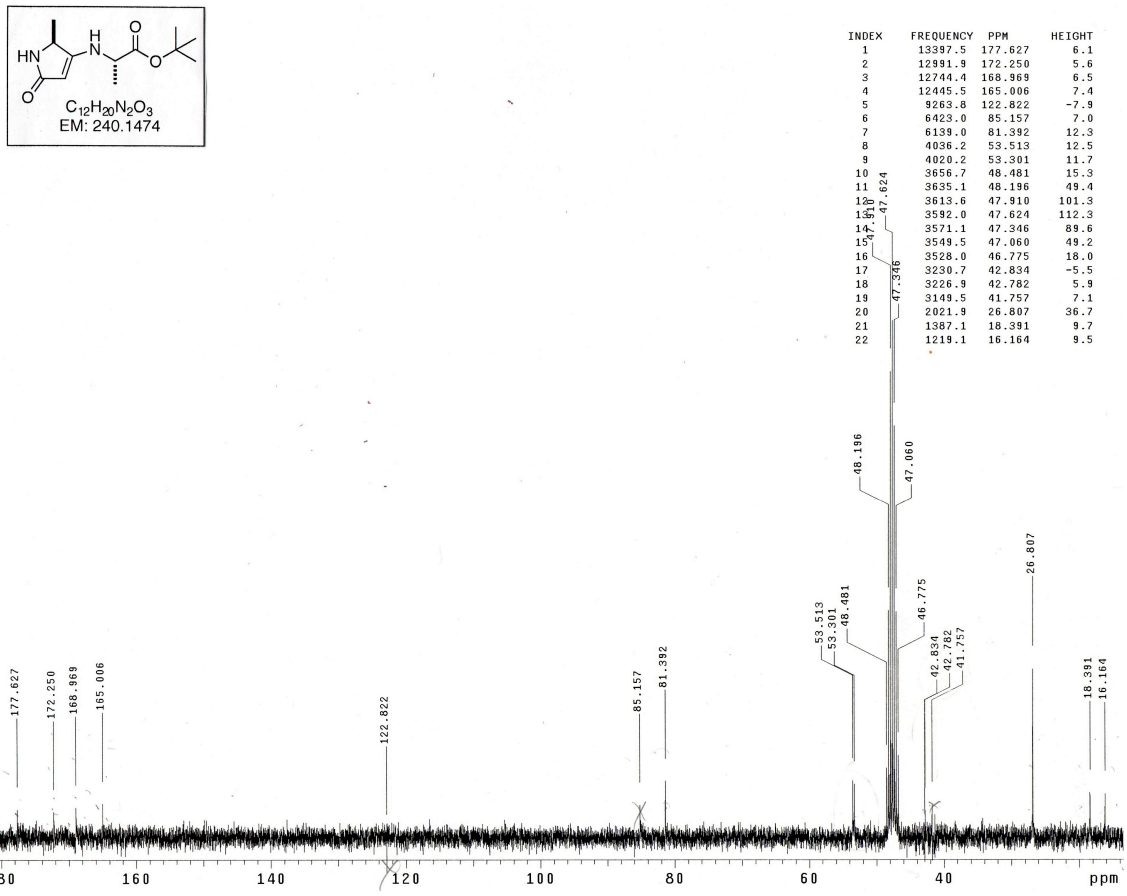
Physical state: solid, 60% mp = 158 – 160 °C, cryst. dichloromethane/hexanes.

^{1}H-NMR (300 MHz, CD_3OD): 4.49 (s, 1H), 4.11 (q, J = 6.6 Hz, 1H), 3.84 (q, J = 7.2 Hz, 1H), 1.49 (s, 9H), 1.45 (d, J = 7.2 Hz, 3H), 1.39 (d, J = 6.0 Hz, 3H)

^{13}C-NMR (75 MHz, CD_3OD): 177.6, 172.3, 169.0, 165.0, 81.4, 53.5, 53.3, 26.8, 18.4, 16.2

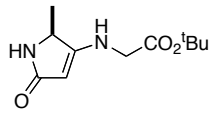
MS: (ESI, m/z): calculated for $C_{12}H_{20}N_2O_3$ 240.15, found 241.18 (H^+)





Compound **1b**

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

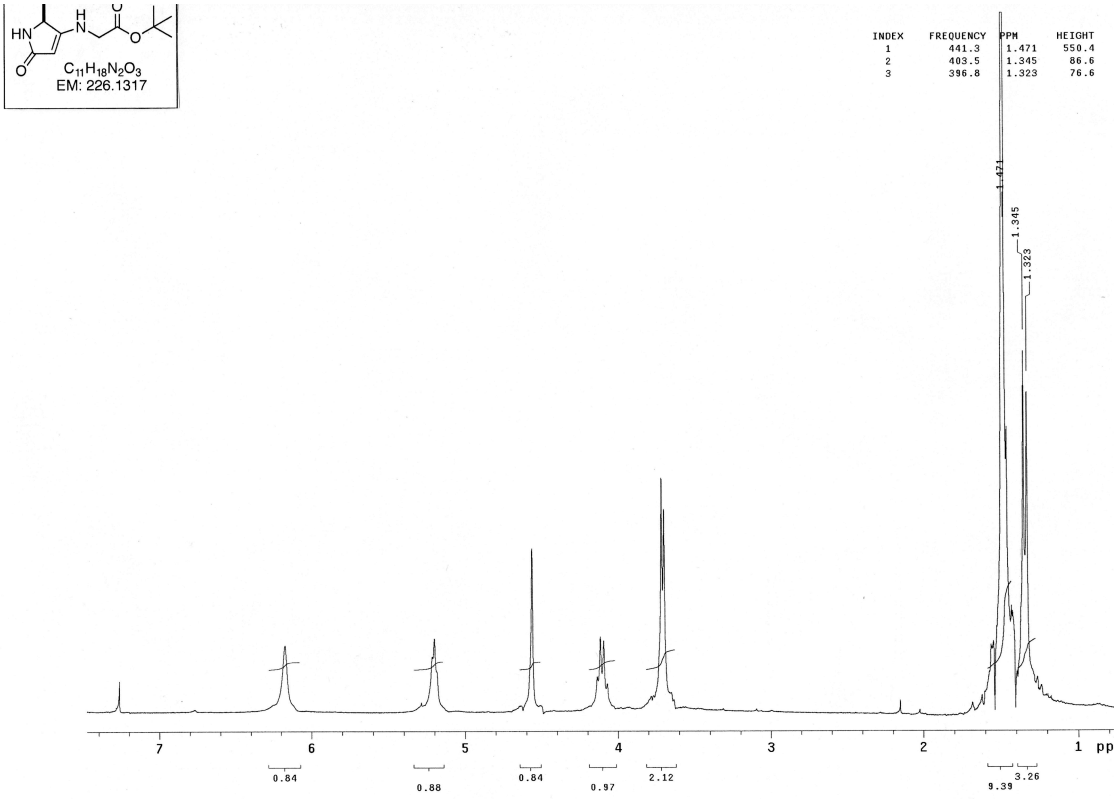


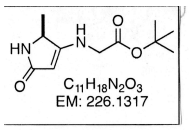
Physical state: oil, 81 %.

^{1}H-NMR (300 MHz, $CDCl_3$): 6.18 (br s, 1H), 5.21 (br s, 1H), 4.50 (s, 1H), 4.16 (q, J = 6.6 Hz, 1H), 3.80 (s, 2H), 1.51 (s, 9H), 1.37 (d, J = 6.9 Hz, 3H)

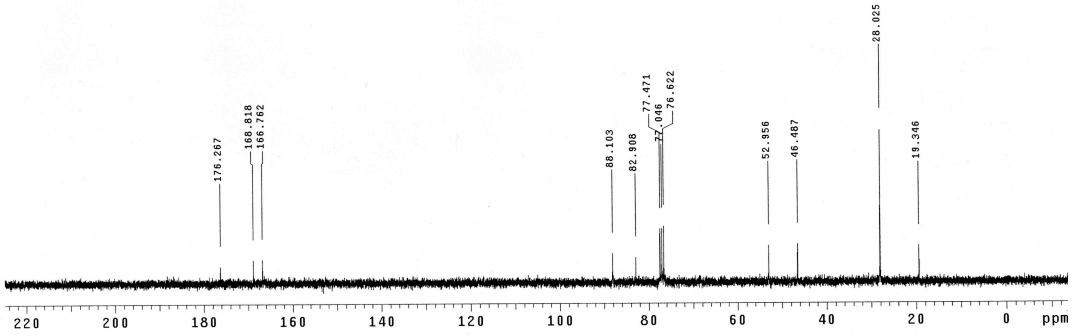
^{13}C-NMR (75 MHz, $CDCl_3$): 177.3, 168.8, 166.8, 88.1, 82.9, 52.9, 48.5, 28.0, 19.3

MS: (ESI, m/z): calculated for $C_{11}H_{18}N_2O_3$ 226.13, found 227.14 (H^+)

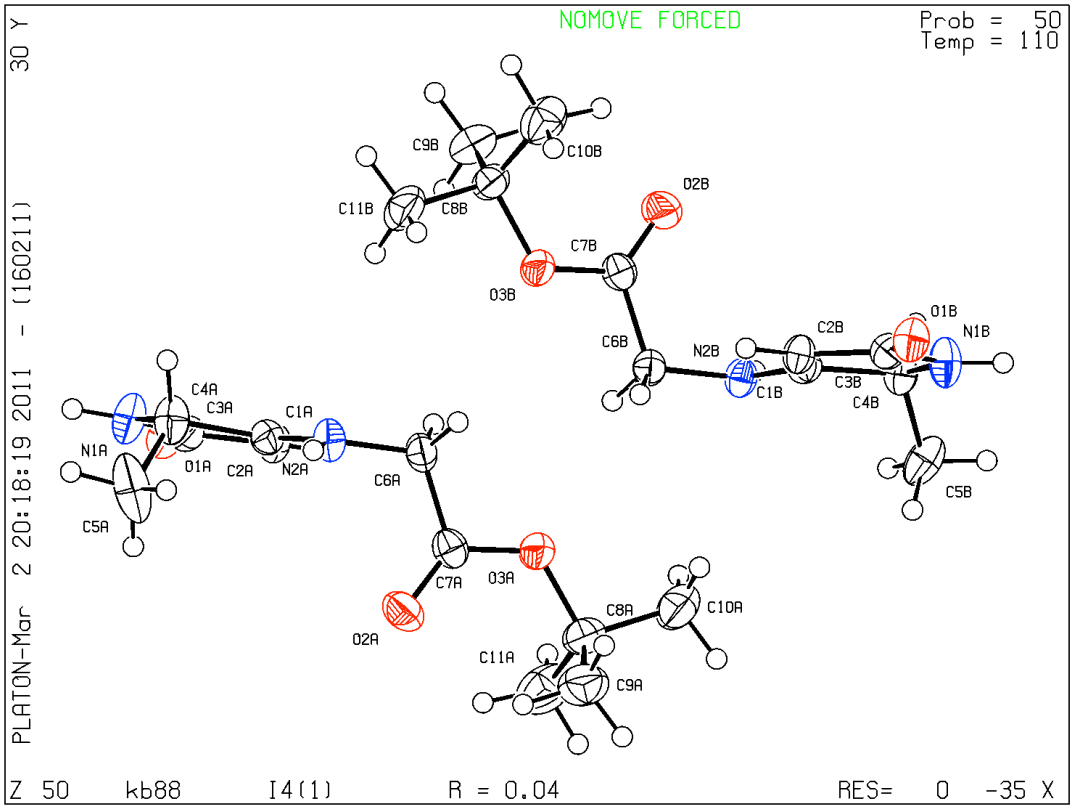




INDEX	FREQUENCY	PPM	HEIGHT
1	13292.9	176.267	3.9
2	12731.1	168.818	5.4
3	12576.1	166.762	5.6
4	6644.2	88.103	6.9
5	6252.4	82.908	6.0
6	5842.3	77.471	12.8
7	5810.3	77.046	12.9
8	5778.3	76.622	13.5
9	3993.6	52.956	8.7
10	3505.8	46.487	9.1
11	2113.5	28.025	36.0
12	1459.0	19.346	8.6

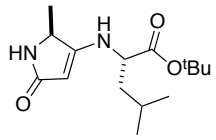


X-Ray **1b**


NOMOVE FORCED
Prob = 50
Temp = 110
PLATON-Mar 2 20:18:19 2011 - (160211)
30 Y
Z 50 kb88 I4(1) R = 0.04 RES= 0 -35 X
C9B
C10B
C11B
C8B
O2B
C7B
O3B
C6B
N2B
C2B
O1B
N1B
C1B
C3B
C4B
C5B
C4A
C3A
C1A
N1A
O1A
C2A
N2A
C6A
C5A
C7A
O3A
O2A
C8A
C10A
C11A
C9A

Compound **1c**

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



Physical state: White needles (ethyl acetate), mp = 206 ºC (decomposes), 60%.

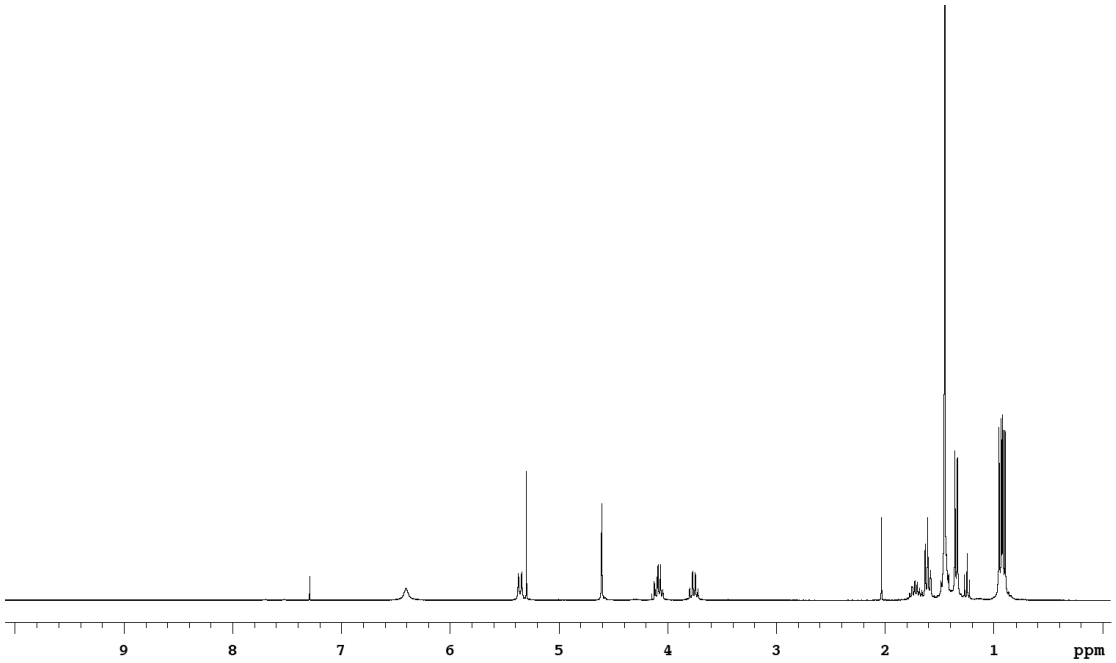
$[\alpha]^{20}_{D}$ – 93.1 (*c* 1.0, MeOH)

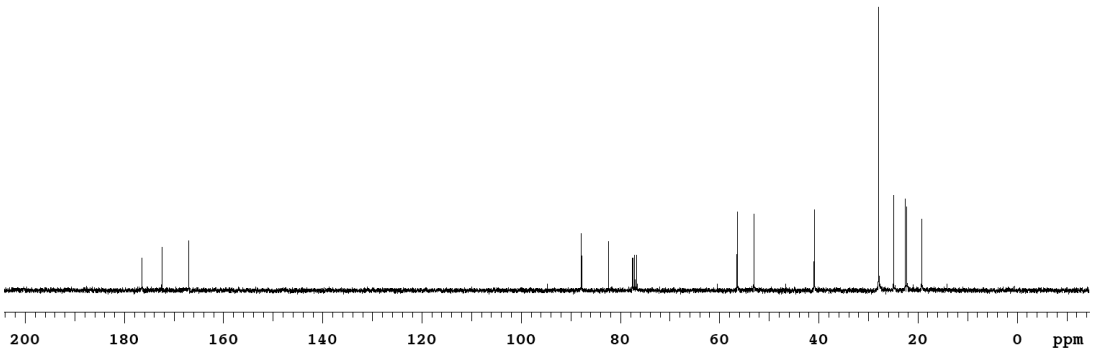
^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 6.40 (br s, 1H), 5.36 (d, *J* =8.1 Hz, 1H), 4.60 (s, 1H), 4.09 (m, 1H), 3.76 (q, *J* = 7.5 Hz, 1H), 1.72 (m, 1H), 1.61 (t, *J* = 6.7 Hz, 2H), 1.45 (s, 9H), 1.35 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) ∂ 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

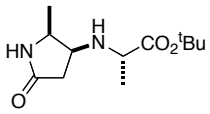
MS (ESI) m/z calcd for $(M+H)^+$ $C_{15}H_{27}N_2O_3$ 283.19; found 283.19





Compound **2a**

(S)-tert-butyl 2-(((2S, 3S)-2-methyl-5-oxopyrrolidin-3-yl) amino) propanoate

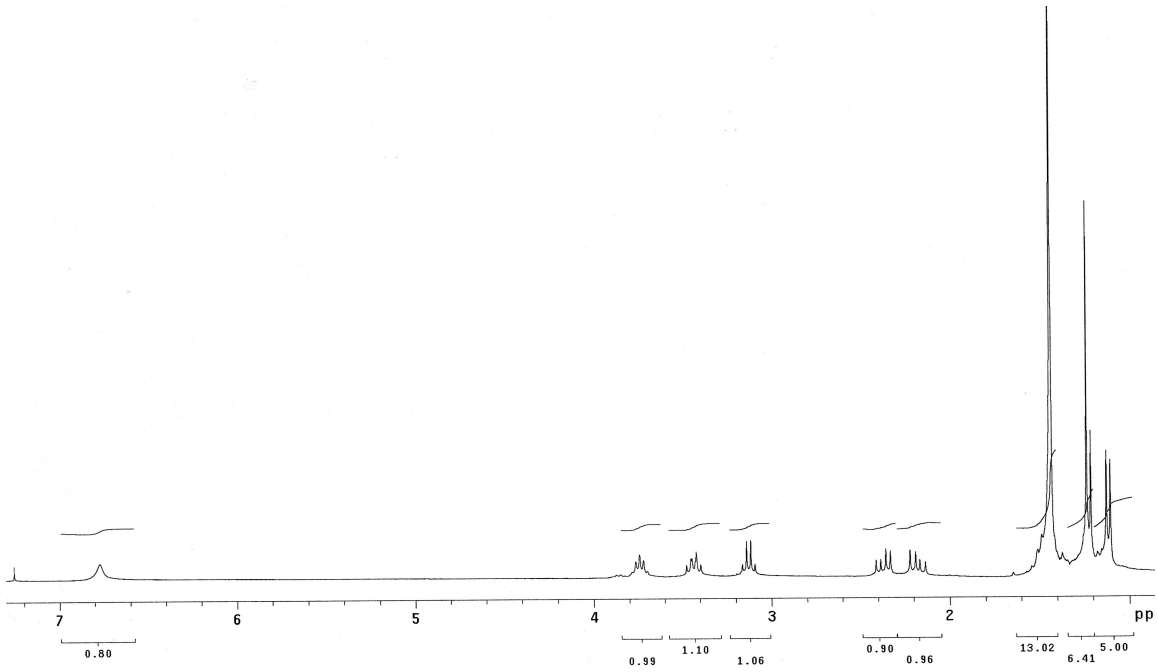


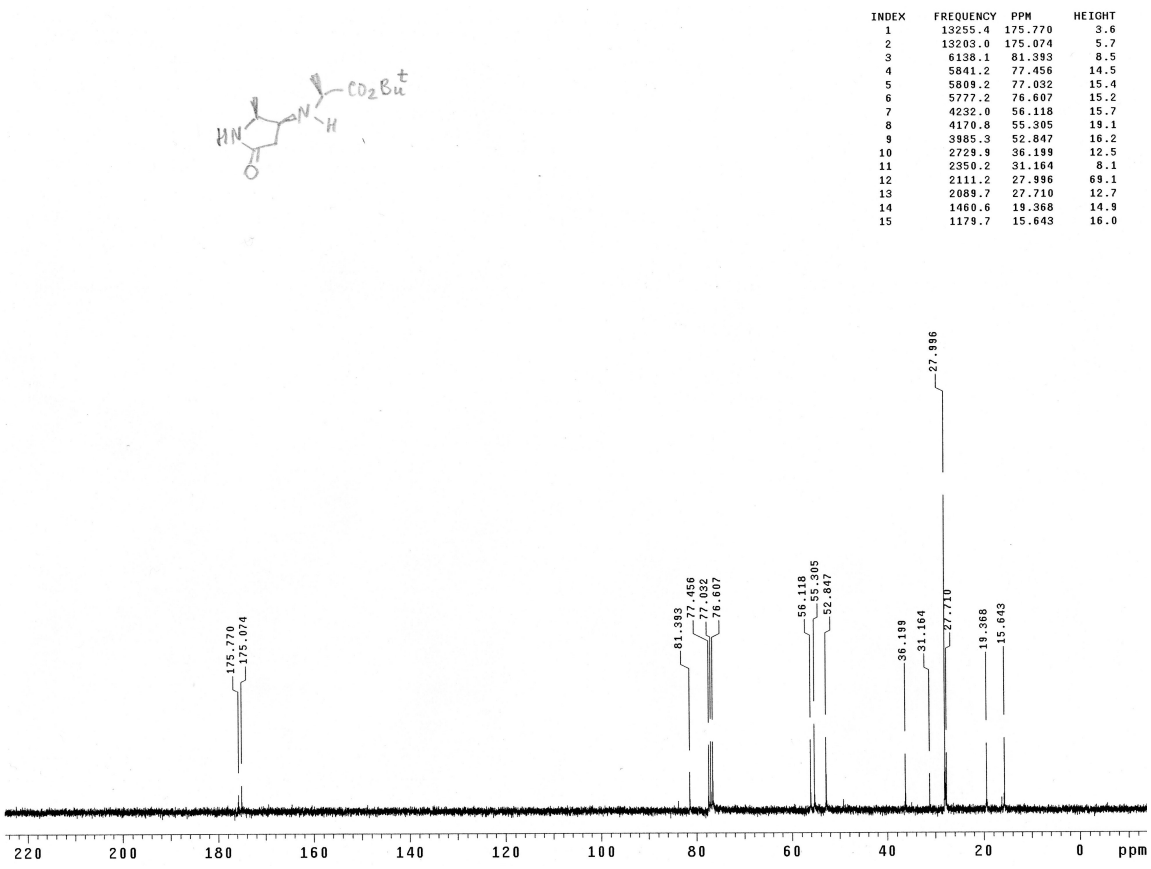
^{t}BuOH
X

^{1}H-NMR (300 MHz, $CDCl_3$): 6.77 (bs, 1H), 3.80 – 3.65 (m, 1H), 3.55 – 3.35 (m, 1H), 3.13 (q, J = 7.2 Hz, 1H), 2.37 (dd, J = 16.2, J = 7.8 Hz, 1H), 2.18 (dd, J = 16.4, J = 9.5 Hz, 1H), 1.44 (s, 9H), 1.22 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 6.3 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$): 175.8, 175.1, 81.4, 56.1, 52.8, 36.2, 28.0, 27.7, 19.4, 15.6

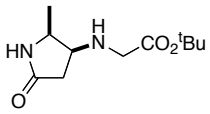
MS: (ESI, m/z): calculated for $C_{12}H_{22}N_2O_3$ 242.16, found 243.17 (H+)





Compound **2b**

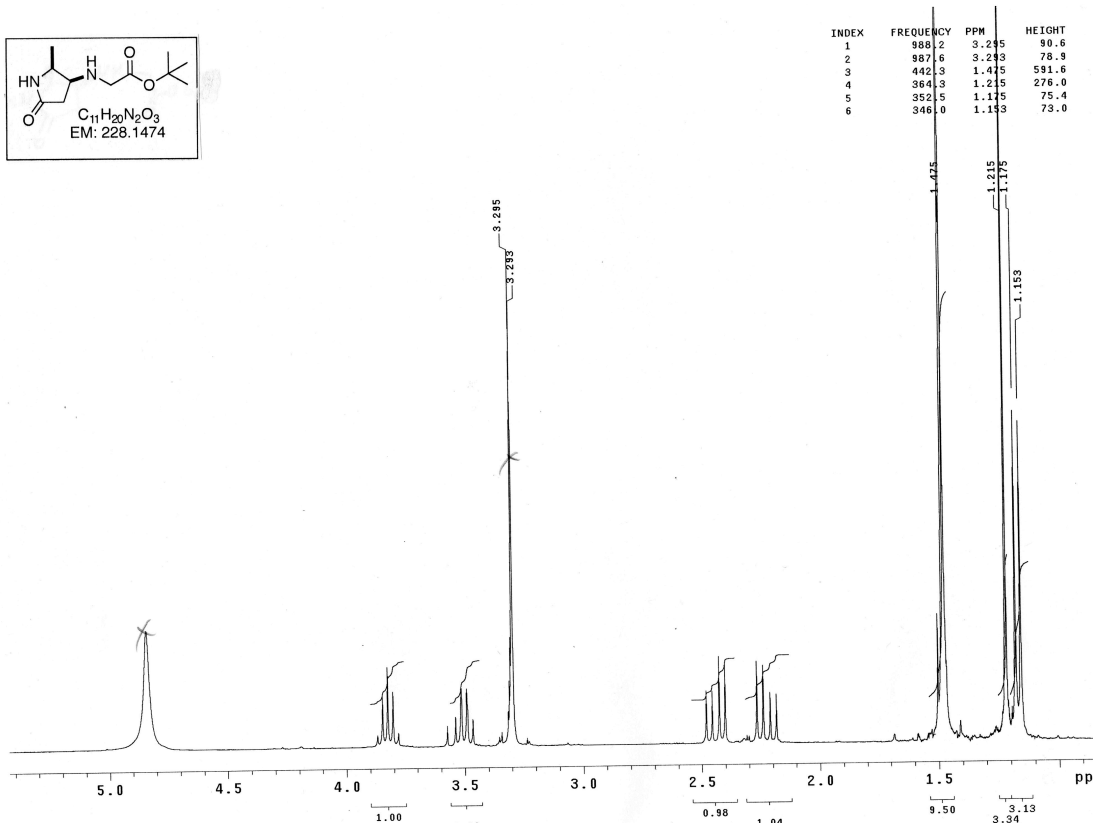
tert-butyl 2-(((2S,3S)-2-methyl-5-oxopyrrolidin-3-yl)amino)acetate

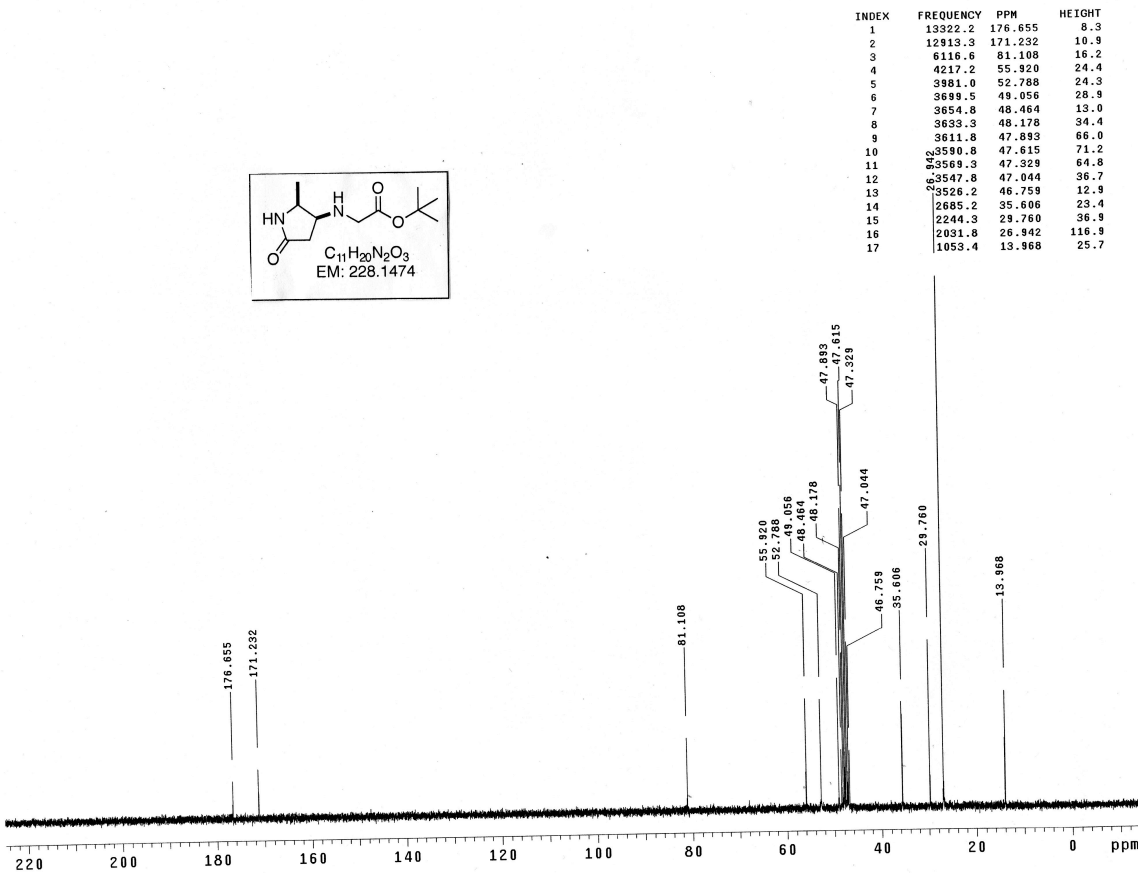


^{1}H-NMR (300 MHz, $CDCl_3$): 4.84 (s, 1H), 3.88-3.75 (m, 1H), 3.46 – 3.40 (m, 1H), 3.29 (s, 2H), 2.32 (dd, J = 16.5, J = 7.5 Hz, 1H), 2.09 (dd, J = 16.5, J = 7.5 Hz, 1H), 1.35 (s, 9H), 1.05 (d, J = 6.3 Hz, 3H)

^{13}C-NMR (75 MHz, CD_3OD): 176.7, 171.2, 81.1, 56.0, 52.8, 35.6, 29.8, 27.0, 14.0

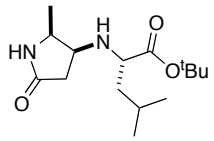
MS: (ESI, m/z): calculated for $C_{11}H_{20}N_2O_3$ 228.15, found 229.15 (H^+), 251.11 (Na+)





Compound **2c**

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



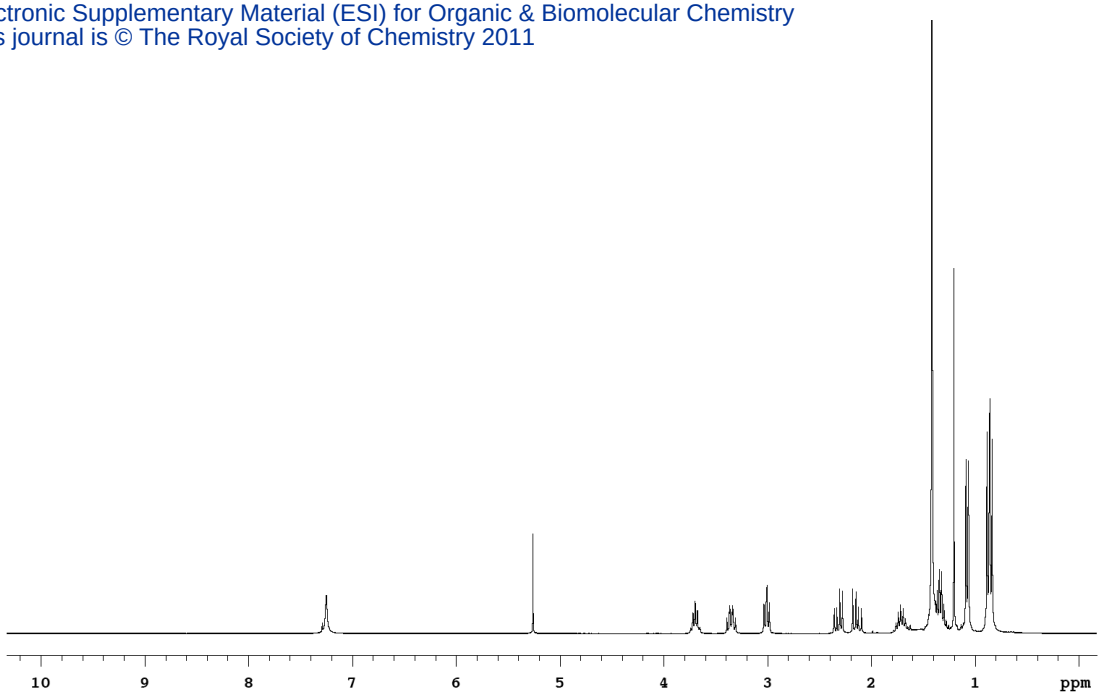
$[\alpha]^{20}$ -10.0 (*c* 1.0, MeOH)

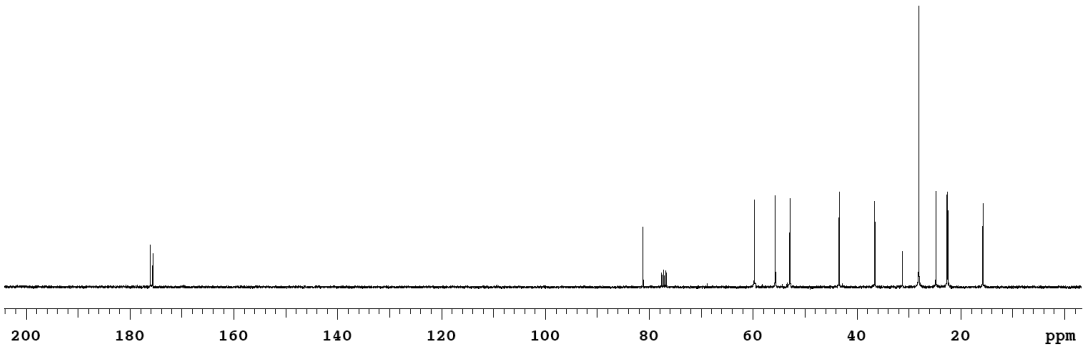
^{1}H-NMR (300 MHz, $CDCl_3$) ∂ 7.20 (br s, 1H), 3.70 (m, 1H), 3.35 (m, 1H), 3.01 (app t, *J* = 7.3 Hz, 1H), 2.32 (dd, *J* = 16.4, 7.7 Hz, 1H), 2.14 (dd, *J* = 16.4, 9.6 Hz, 1H), 1.72 (m, 1H), 1.41 (s, 9H), 1.34 (m, 2H), 1.08 (d, *J* = 6.3 Hz, 3H), 0.88 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H)

^{13}C-NMR (75 MHz, $CDCl_3$) ∂ 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 calculated for $(M+H)^+$ $C_{15}H_{29}N_2O_3$ 285.21; found 285.19





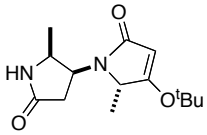
General procedure to prepare compound **3**

A mixture of enamine **2a** (4 mmol), (triphenylphosphoranyllidene)ketene (8 mmol) and TFA (2.6 mmol) in 5 mL dioxane was heated at 105 – 110^{o}C for 1 h. Upon completion (analysis by NMR), the solvent was removed at reduced pressure, Purification was carried out by flash column chromatography (eluent ethylacetate/methanol).

Note: 3 a-c products are hygroscopic solids and soluble in the water. Isolation could be done by simple extraction of the crude mixture with warm water (50 ^{o}C), followed by extraction of the impurity triphenylphosphoxide with ether. The water layer contains pure product and triphenylmethylphosphonium ylide as a salt with TFA. Further separation could be done on a SiO_2 column eluting with ethylacetate – methanol mixture 20:1 – 10:1.

Compound **3a**

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



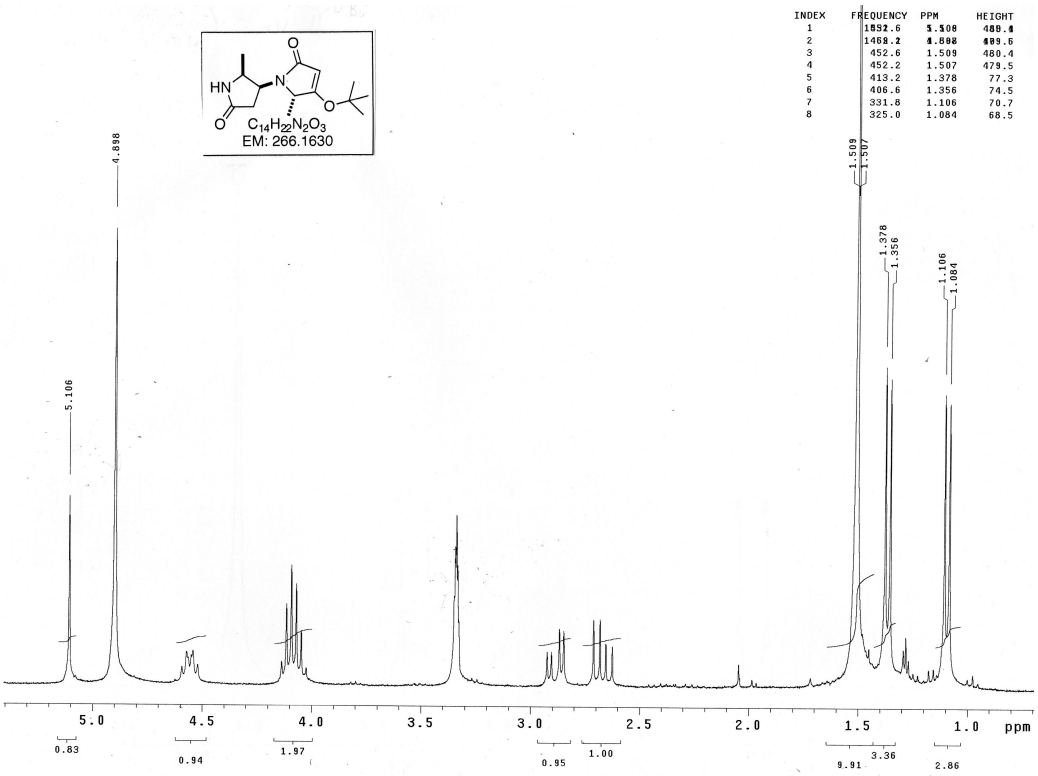
Hygroscopic white solid, mp = 174 – 178 °C, 63%.

$[\alpha]^{20}_{D}$ – 79.7 (*c* 1.0, MeOH)

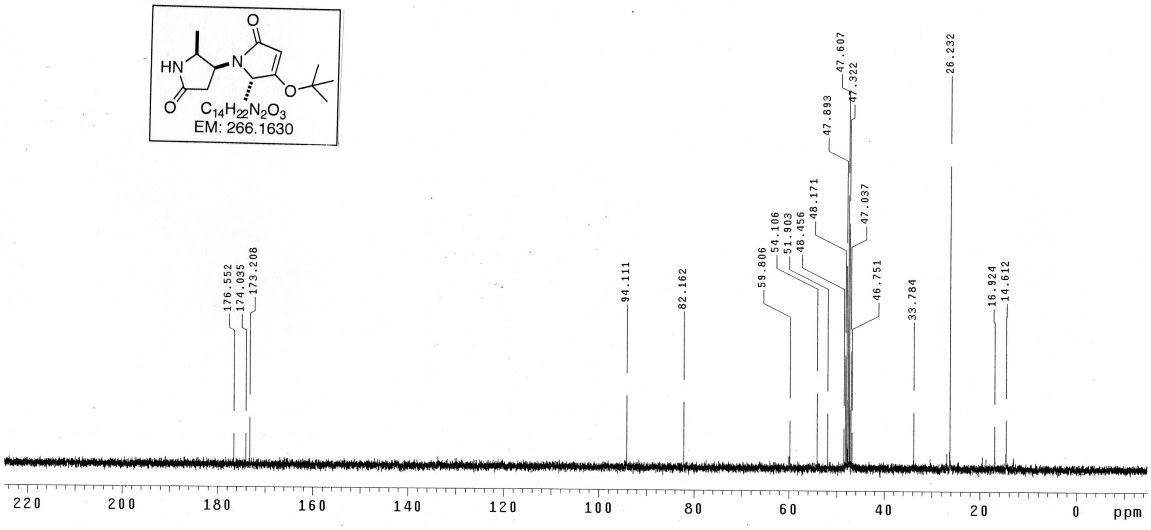
^{1}H-NMR (CD_3OD): 5.11 (s, 1H), 4.60 – 4.45 (m, 1H), 4.16 – 3.96 (m, 3H), 2.89 (dd, J = 16.8, J = 6.0 Hz, 1H), 2.67 (dd, J = 17.1, J = 9.0 Hz, 1H), 1.51 (s, 9H), 1.37 (d, J = 6.6 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H)

^{13}C-NMR (75 MHz, CD_3OD): 176.6, 174.0, 173.2, 94.1, 82.2, 59.8, 54.1, 51.9, 33.8, 26.2, 16.9, 14.6

MS: (ESI, m/z): calculated for $C_{14}H_{22}N_2O_3$ 266.16, found 267.15 (H+), 289.13 (Na+)

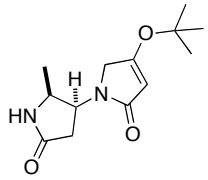


3	13062.3	173.208	10.5
4	7097.3	94.111	15.9
5	6196.1	82.162	14.6
6	4510.2	59.806	10.6
7	4080.3	54.106	16.7
8	3914.2	51.903	12.2
9	3654.3	48.456	9.0
10	3632.7	48.171	25.2
11	3611.8	47.893	44.8
12	3590.3	47.607	60.2
13	3568.7	47.322	54.0
14	3547.2	47.037	26.0
15	3525.7	46.751	8.0
16	2547.8	33.784	12.5
17	1978.3	26.232	66.8
18	1276.3	16.924	9.6
19	1101.9	14.612	10.9



Compound **3b**

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



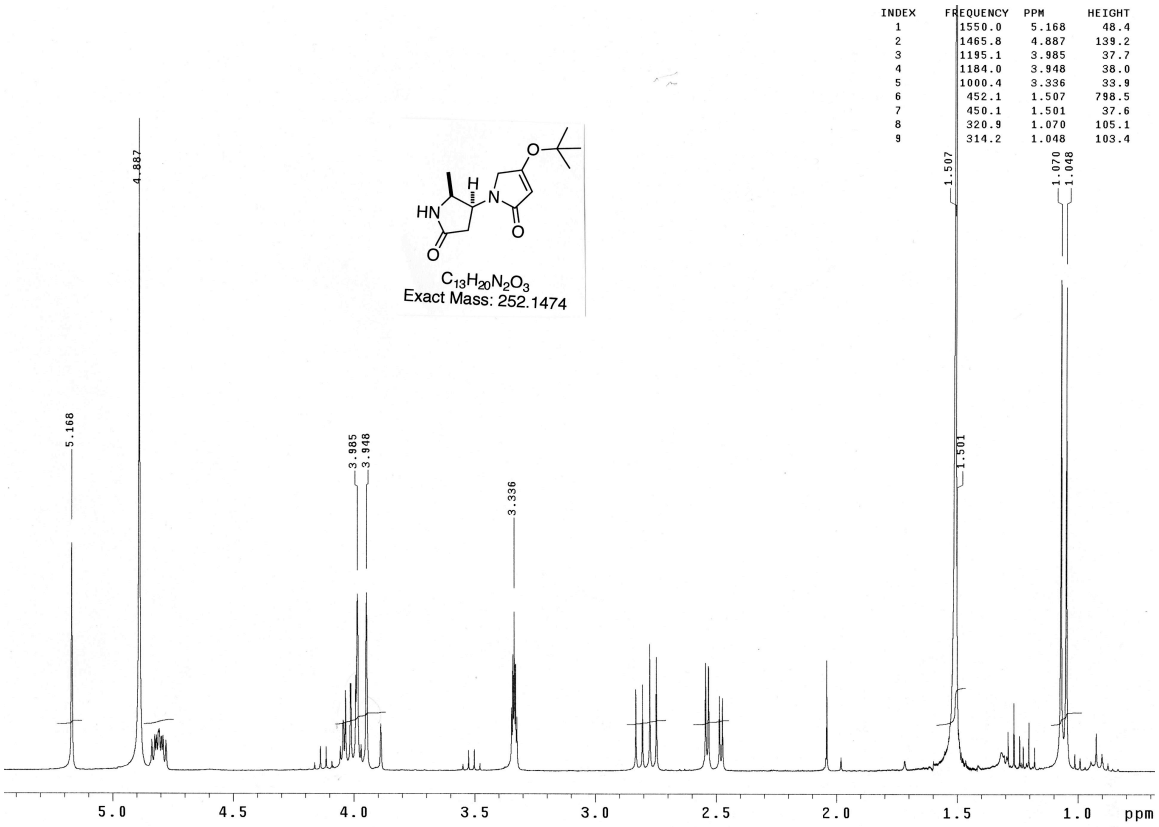
Physical state: Hygroscopic solid, mp = 75 – 80 ^{o}C, 80%.

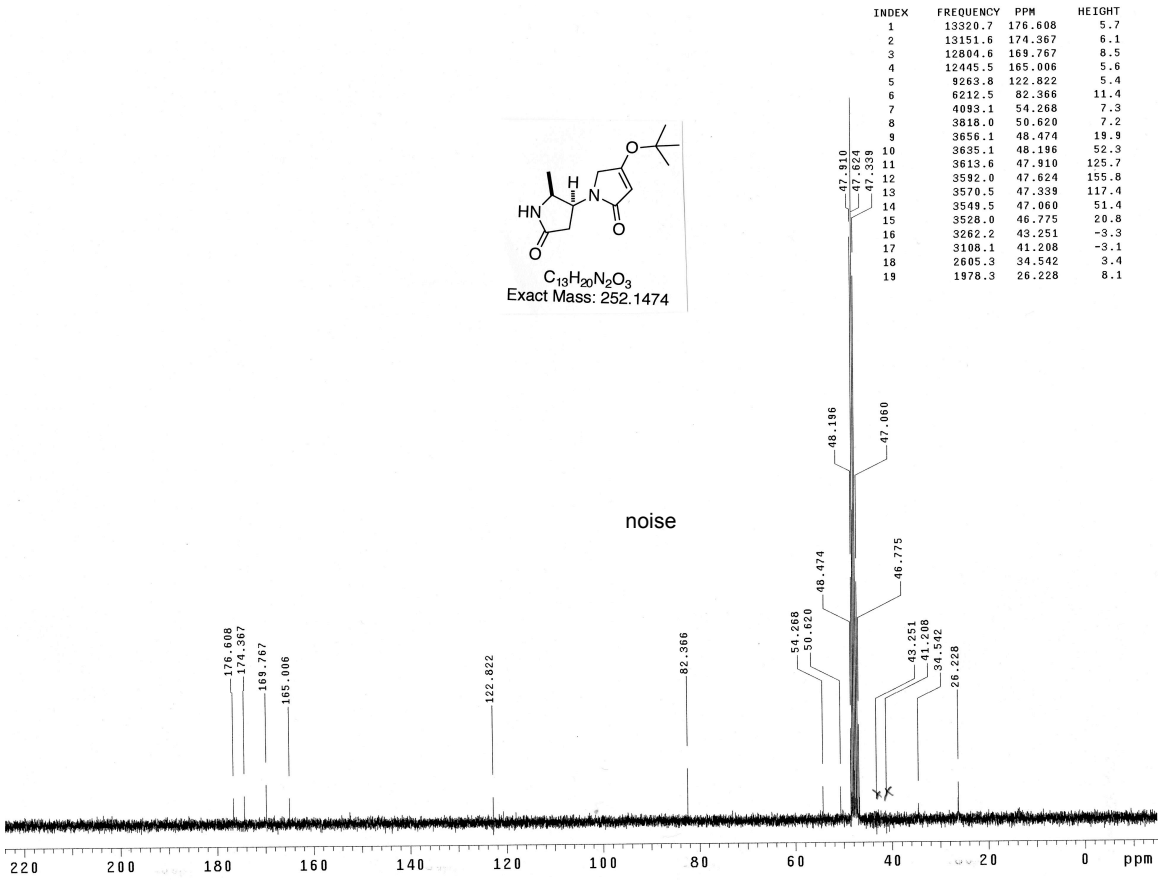
$[\alpha]^{20}_{D}$ – 55.6 (*c* 1.0, MeOH)

^{1}H-NMR (CD_3OD): 4.85 – 4.76 (m, 1H), 4.08 – 3.88 (m, 3H), 2.79 (dd, J = 17.2, J = 8.2Hz, 1H), 2.51 (dd, J = 17.2, J = 3.8 Hz, 1H), 1.51 (s, 9H), 1.06 (d, J = 6.6 Hz, 3H)

^{13}C-NMR (75 MHz, CD_3OD): 176.6, 174.4, 169.8, 165.0, 122.8, 82.4, 54.3, 50.6, 43.3, 41.2

MS: (ESI, m/z): calculated for $C_{13}H_{20}N_2O_3$ 252.15, found 253.18 (H^+)

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3 12804.6 169.767 8.5
4 12445.5 165.006 5.6
5 9263.8 122.822 5.4
6 6212.5 82.366 11.4
7 4093.1 54.268 7.3
8 3818.0 50.620 7.2
9 3656.1 48.474 19.9
10 3635.1 48.196 52.3
11 3613.6 47.910 125.7
12 3592.0 47.624 155.8
13 3570.5 47.339 117.4
14 3549.5 47.060 51.4
15 3528.0 46.775 20.8
16 3262.2 43.251 -3.3
17 3108.1 41.208 -3.1
18 2605.3 34.542 3.4
19 1978.3 26.228 8.1
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Exact Mass: 252.1474
noise
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46.775
43.251
41.208
34.542
26.228
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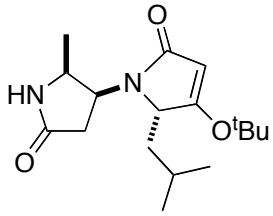
180
160
140
120
100
80
60
40
20
0
ppm

Compound **3c**

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

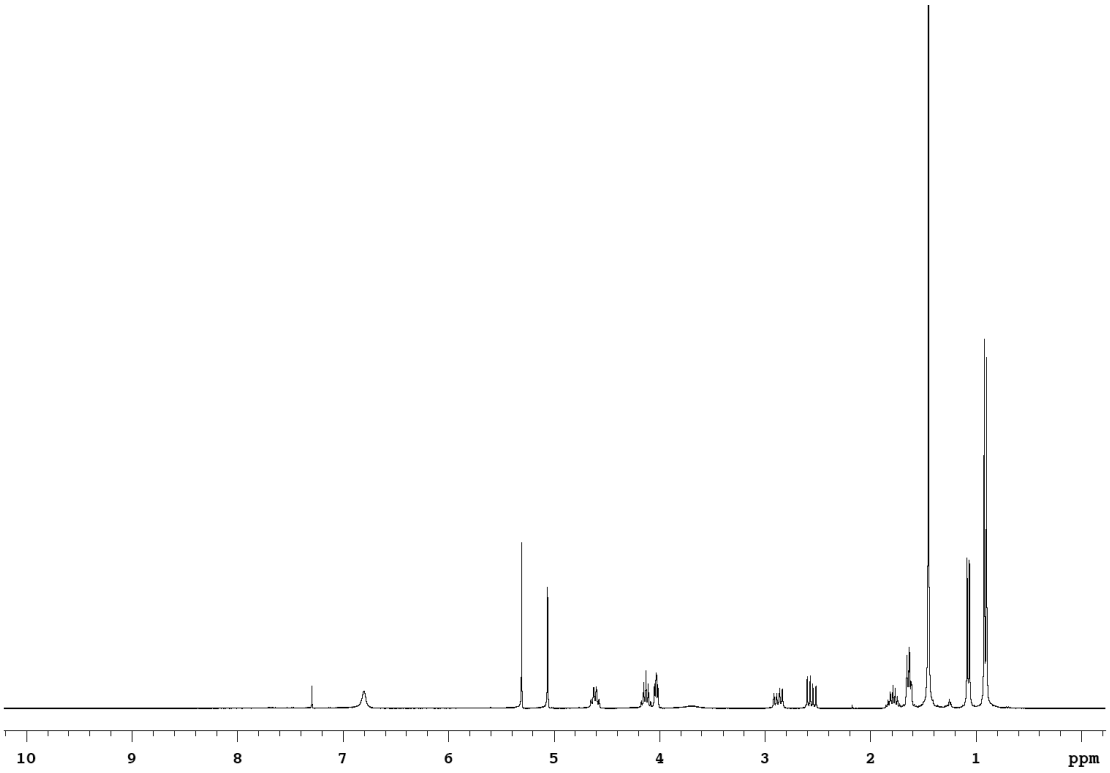


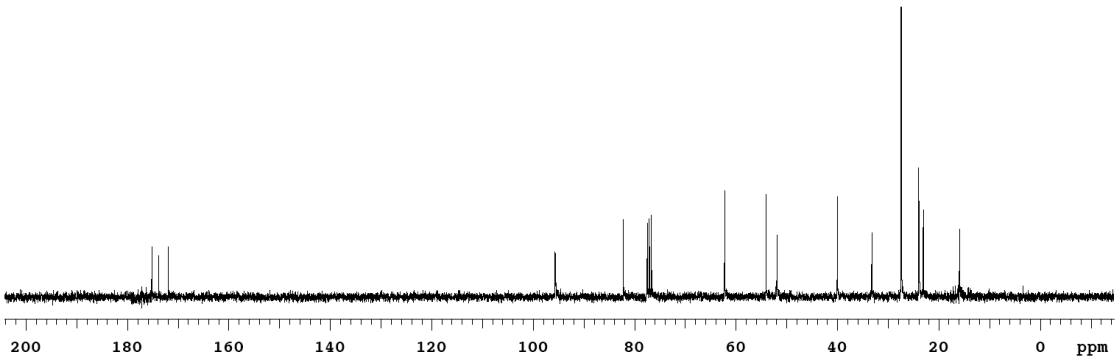
White crystals, 60 %

$[\alpha]^{20}_D$ – 61.0 (*c* 1.0, MeOH)

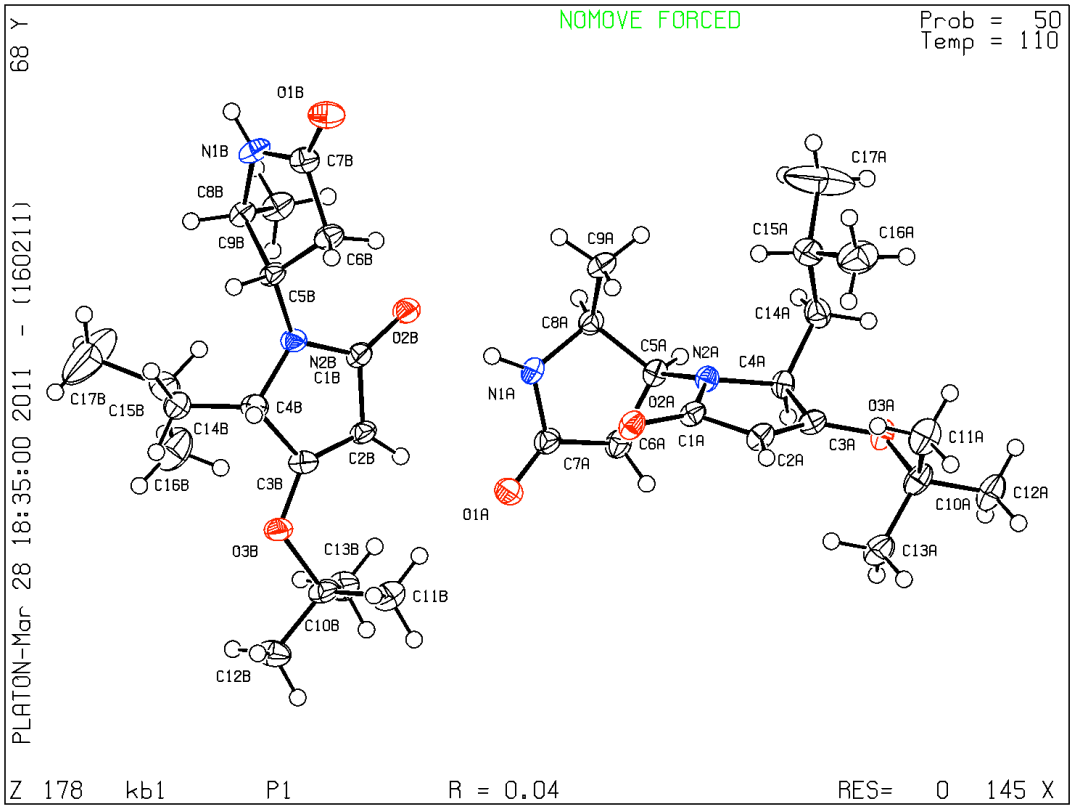
^{1}H-NMR (CDCl$_3$): 6.80 (br s, 1H), 5.06 (s, 1H), 4.61 (q, *J* = 7.6 Hz, 1H), 4.13 (p, *J* = 6.7 Hz, 1H), 4.03 (t, *J* = 5.1 Hz, 1H), 2.88 (dd, *J* = 16.7, 8.1 Hz, 1H), 2.56 (dd, *J* = 16.5, 8.7 Hz, 1H), 1.87-1.70 (m, 1H), 1.68-1.59 (m, 2H), 1.45 (s, 9H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.91 (app d, *J* = 6.6 Hz, 6H)

^{13}C-NMR (CDCl$_3$): 175.2, 173.8, 172.0, 95.6, 82.2, 62.2, 54.1, 51.9, 40.0, 33.2, 27.5, 24.0, 23.9, 23.1, 15.9





X-Ray **3c**


NOMOVE FORCED
Prob = 50
Temp = 110
PLATON-Mar 28 18:35:00 2011 - (160211)
68 Y
Z 178 kb1 P1 R = 0.04 RES= 0 145 X
O1B
N1B
C7B
C8B
C9B
C6B
C5B
O2B
N2B
C1B
C17B
C15B
C4B
C14B
C2B
C16B
C3B
O3B
C13B
C11B
C10B
C12B
C17A
C15A
C16A
C9A
C14A
C8A
C5A
N2A
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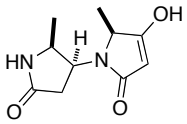
O2A
O3A
C11A
C6A
C1A
C3A
C7A
C2A
C10A
C12A
O1A
C13A

General procedure for compounds **4 a-c**

Compounds **4** were prepared by acid elimination of *tert*-butyl group from **3 a-c** in a mixture 2:2:0.1 of CH_2Cl_2/TFA/Et_3SiH at room temperature for 3 h in quantitative yields. These are hygroscopic white solids unstable during storage at room temperature. NMR revealed two or more conformers. The products were immediately carried to the next step.

Compound **4a**

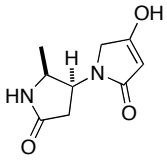
(S)-4-hydroxy-5-methyl-1-((2S,3S)-2-methyl-5-oxopyrrolidin-3-yl)-1H-pyrrol-2(5H)-one



^{1}H-NMR (CD_3OD) two forms: 4.60 – 4.50 (m, 0.57H), 4.50 – 4.35 (m, 0.43H), 4.20 – 3.90 (m, 2H), 3.48 (q, J = 6.9 Hz, 1H), 3.02 – 2.75 (m, 1H), 2.74 – 2.55 (m, 1H), 1.37 (d, J = 6.6 Hz, 3H), 1.23 – 1.10 (d, J = 6.6 Hz, 3H), 1.06 (m, 6H)
^{13}C-NMR (75 MHz, CD_3OD) two forms: 177.6, 177.1, 176.7, 174.8, 65.6, 65.5, 58.6, 54.2, 53.5, 53.2, 51.9, 34.0, 33.7, 26.2, 16.6, 15.8, 15.0, 14.5
MS: (ESI, m/z): calculated for $C_{10}H_{14}N_2O_3$ 210.10, found 211.11 (H+)

Compound **4b**

4-hydroxy-1-((2S,3S)-2-methyl-5-oxopyrrolidin-3-yl)-1H-pyrrol-2(5H)-one



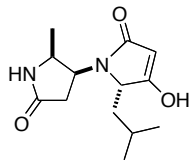
^{1}H-NMR (CD_3OD) two forms: 4.85 – 4.70 (m, 1H), 4.20 – 3.80 (m, 2H), 3.65 – 3.40 (m, 1H), 2.80 – 2.65 (m, 1H), 2.60 – 2.30 (m, 1H), 1.30 – 0.95 (m, 3H)

^{13}C-NMR (75 MHz, CD_3OD) two forms: 203.1, 176.6, 173.4, 98.8, 56.3, 56.0, 55.4, 54.3, 54.2, 53.9, 53.7, 53.5, 50.5, 50.3, 50.1, 49.2, 34.6, 34.1, 33.9, 33.7, 13.7, 13.6, 13.4, 13.4

MS: (ESI, m/z): calculated for $C_9H_{12}N_2O_3$ 196.08, found 197.09 (H+)

Compound **4c**

(*S*)-4-hydroxy-5-isobutyl-1-((2*S*,3*S*)-2-methyl-5-oxopyrrolidin-3-yl)-1*H*-pyrrol-2(5*H*)-one



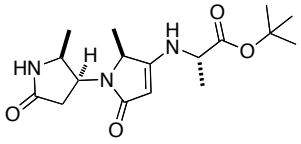
^{1}H-NMR (CD_3OD) two forms: 4.50 (q, J = 7.8 Hz, 1H), 4.36 (q, J = 7.3 Hz, 1H), 4.19 (t, J = 10.3 Hz, 1H), 4.15 – 4.00 (m, 3H), 3.00 – 2.75 (m, 2H), 2.75 – 2.55 (m, 2H), 2.00 – 1.75 (m, 2H), 1.75 – 1.60 (m, 3H), 1.60 -1.50 (m, 1H), 1.18 (d, J = 6.6 Hz, 3H), 1.33 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.3 Hz, 3H), 1.02 – 0.90 (m, 12 H)

^{13}C-NMR (75 MHz, CD_3OD) two forms: 177.2, 176.4, 176.1, 175.4, 171.2, 67.7, 61.5, 54.2, 53.5, 53.4, 52.2, 40.4, 39.3, 33.6, 33.5, 26.2, 23.9, 23.6, 22.7, 22.4, 21.8, 20.5, 15.2, 14.6

MS: (ESI, m/z): calculated for $C_{13}H_{20}N_2O_3$ 252.1474, found 253.1559 (H+), 275,1333 (Na+)

Compound **5aa**

(S)-tert-butyl 2-(((S)-2-methyl-1-((2S,3S)-2-methyl-5-oxopyrrolidin-3-yl)-5-oxo-2,5-dihydro-1H-pyrrol-3-yl)amino)propanoate

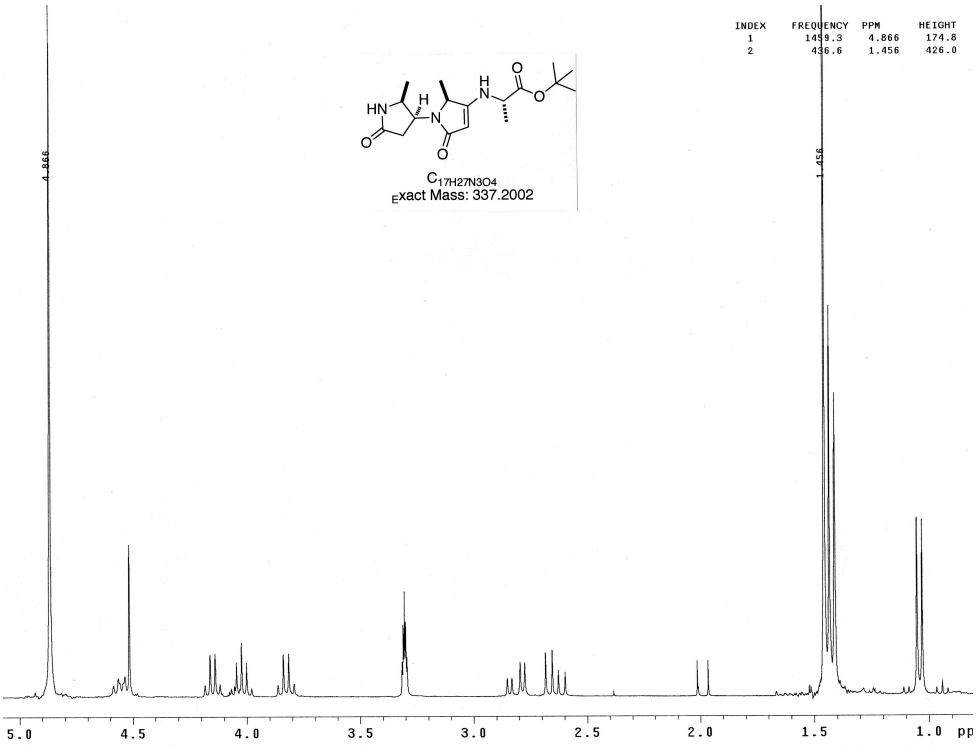


Procedure: As described before for **1 a-c**. White solid, mp = 199 – 200 ^{o}C (dichloromethane/hexanes), 50% .

^{1}H-NMR (CD_3OD): 4.60 – 4.50 (m, 1H), 4.52 (s, 1H), 4.15 (q, J = 6.6 Hz, 1H), 4.10 – 3.96 (m, 1H), 3.83 (q, J = 7.2 Hz, 1H), 2.81 (dd, J = 16.8, J = 6.0 Hz, 1H), 2.64 (dd, J = 17.0, J = 8.8 Hz, 1H), 1.46 (s, 9H), 1.42 (d, J = 6.6 Hz, 6H), 1.04 (d, J = 6.6 Hz, 3H)

^{13}C-NMR (75 MHz, CD_3OD): 176.7, 175.5, 172.1, 166.5, 85.6, 81.4, 58.0, 54.4, 53.3, 51.8, 34.0, 26.8, 18.9, 16.1, 14.4

MS: (ESI, m/z): calculated for $C_{17}H_{27}N_3O_4$ 337.20, found 338.23 (H+)


INDEX FREQUENCY PPM HEIGHT
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1.456
C17H27N3O4
Exact Mass: 337.2002
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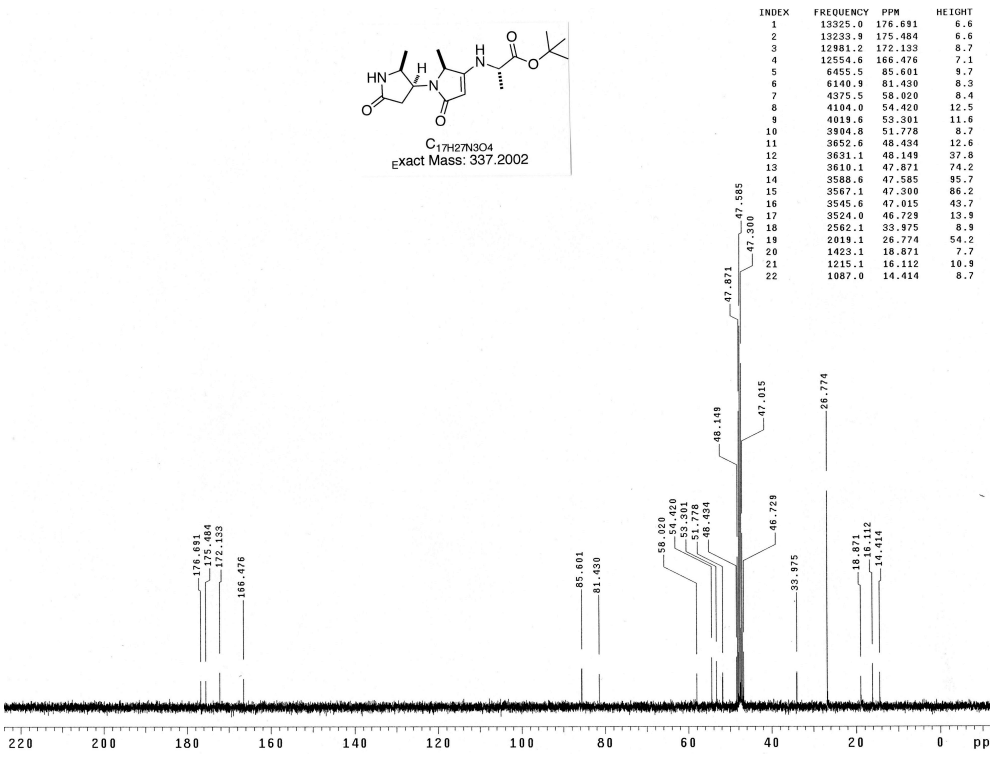
4.0
3.5
3.0
2.5
2.0
1.5
1.0
pp


INDEX FREQUENCY PPM HEIGHT
1 13325.0 176.691 6.6
2 13233.9 175.484 6.6
3 12981.2 172.133 8.7
4 12554.6 166.476 7.1
5 6455.5 85.601 9.7
6 6140.9 81.430 8.3
7 4375.5 58.020 8.4
8 4104.0 54.420 12.5
9 4019.6 53.301 11.6
10 3904.8 51.778 8.7
11 3652.6 48.434 12.6
12 3631.1 48.149 37.8
13 3610.1 47.871 74.2
14 3588.6 47.585 95.7
15 3567.1 47.300 86.2
16 3545.6 47.015 43.7
17 3524.0 46.729 13.9
18 2562.1 33.975 8.9
19 2019.1 26.774 54.2
20 1423.1 18.871 7.7
21 1215.1 16.112 10.9
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C17H27N3O4
Exact Mass: 337.2002
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140
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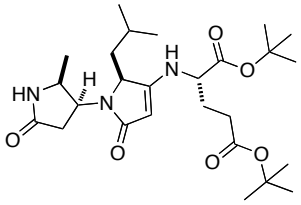
100
80
60
40
20
0
pp

Compound **5cd**

(S)-di-tert-butyl 2-(((S)-2-isobutyl-1-((2S,3S)-2-methyl-5-oxopyrrolidin-3-yl)-5-oxo-2,5-dihydro-1H-pyrrol-3-yl)amino)pentanedioate

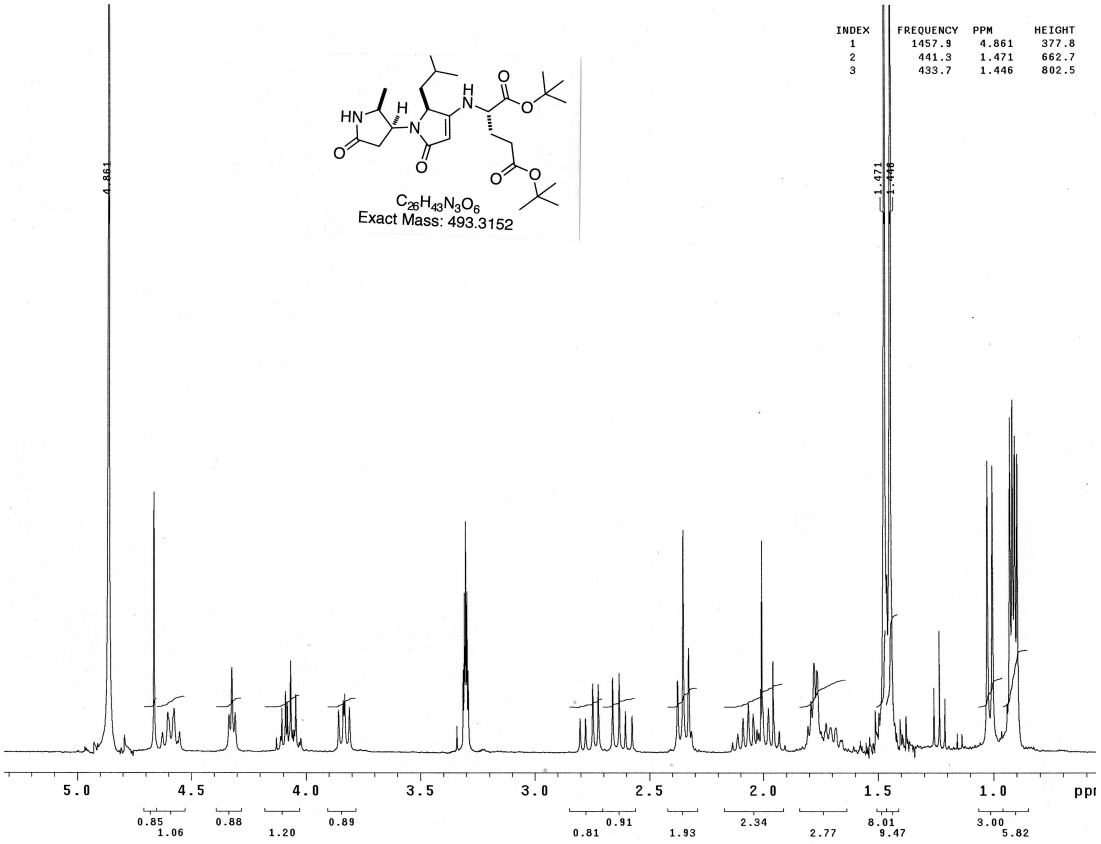


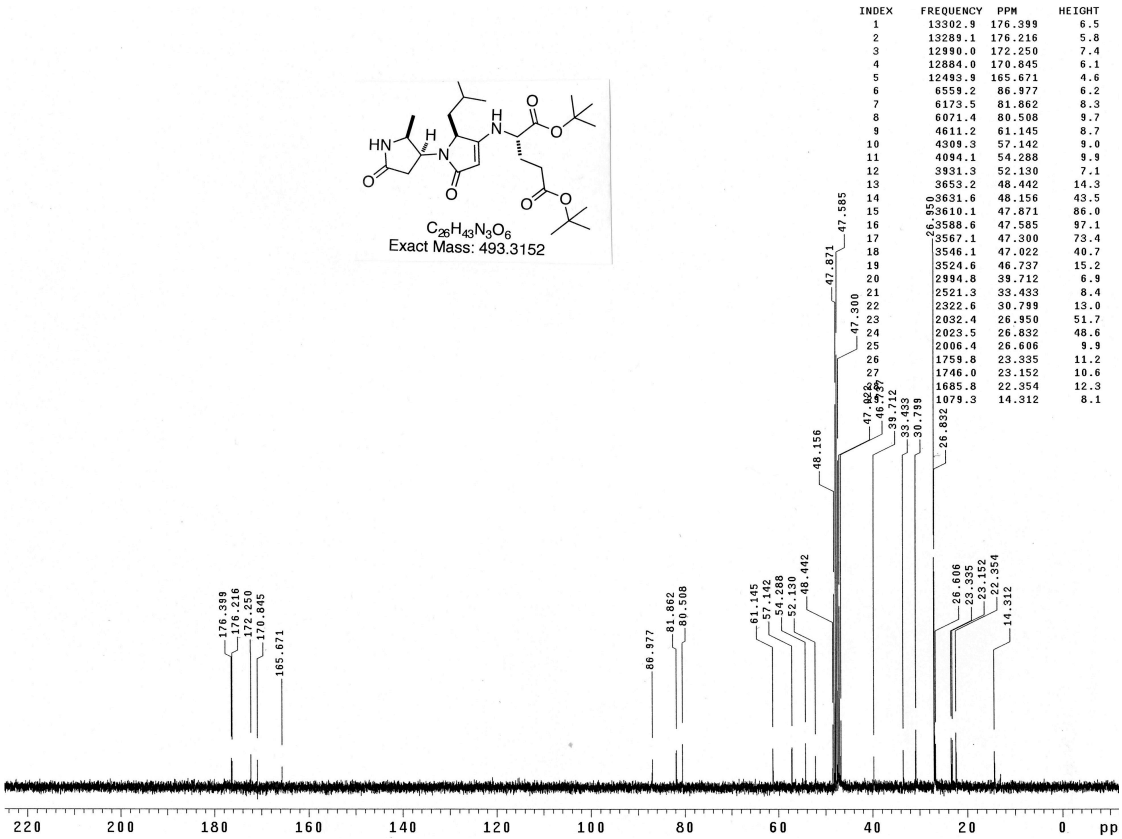
Procedure: As described before for **1 a-c**. White solid, mp = 51 – 55 ^{o}C, eluent ethylacetate/methanol 10:1 – 5:1, 40%.

^{1}H-NMR (CD_3OD): 4.66 (s, 1H), 4.64 – 4.54 (m, 1H), 4.32 (t, J = 4.0 Hz, 2H), 4.12 – 4.01 (m, 1H), 3.83 (dd, J = 8.1, J = 6.0 Hz, 1H), 2.76 (dd, J = 16.5, J = 7.2 Hz, 1H), 2.62 (dd, J = 16.8, J = 8.7 Hz, 1H), 2.40 – 2.30 (m, 2H), 2.15 – 1.90 (m, 2H), 1.83 – 1.65 (m, 3H), 1.47 (s, 9H), 1.45 (s, 9H), 1.01 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 3.3 Hz, 3H), 0.90 (d, J = 3.3 Hz, 3H)

^{13}C-NMR (75 MHz, CD_3OD): 176.4, 176.2, 172.3, 170.8, 165.7, 87.0, 81.9, 80.5, 61.1, 57.1, 54.3, 52.1, 39.7, 33.4, 30.8, 27.0, 26.8, 26.6, 23.3, 23.2, 22.4, 14.3

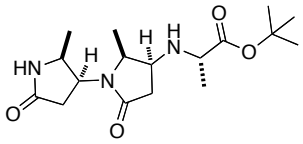
MS: (ESI, m/z): calculated for $C_{26}H_{43}N_3O_6$, 493.31, found 494.32 (H+)





Compound **6aa**

(2'S,3'S,4S,5S)-4-((S)-3-(tert-butoxy)-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)-2',5-dimethyl-[1,3'-bipyrrolidine]-2,5'-dione



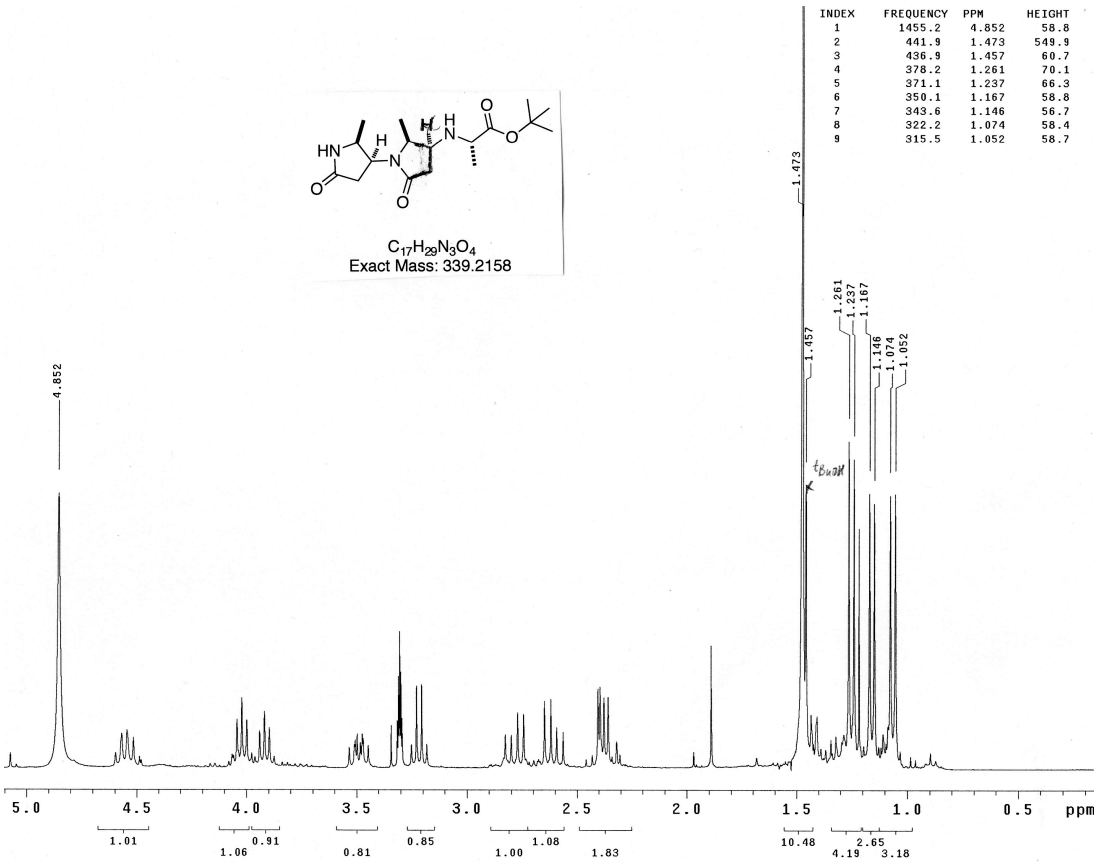
Procedure: As described before for **2 a-c**.

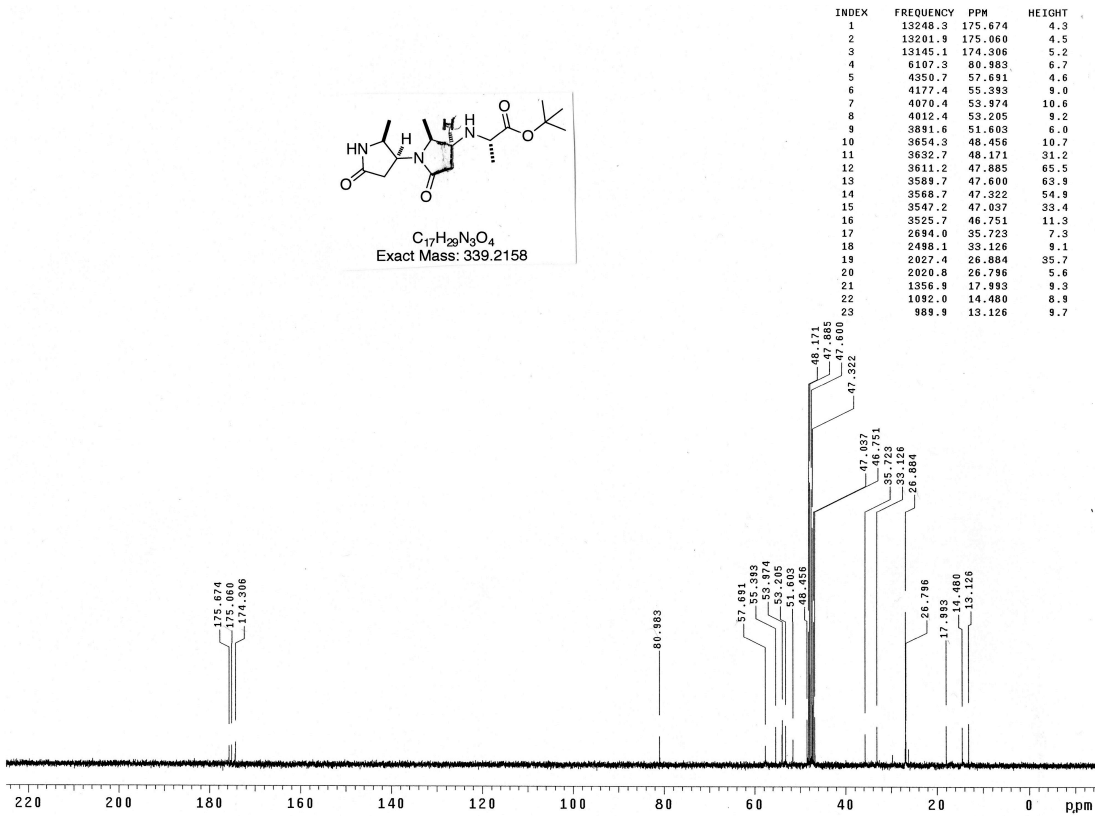
Physical state: sticky oil, yield quantitative.

^{1}H-NMR (CD_3OD): 4.60 – 4.48 (m, 1H), 4.08 – 3.97 (m, 1H), 3.96 – 3.87 (m, 1H), 3.54 – 3.42 (m, 1H), 3.22 (q, J = 7.0 Hz, 1H), 2.79 (dd, J = 16.5, J = 8.1 Hz, 1H), 2.61 (dd, J = 16.8, J = 8.7 Hz, 1H), 2.48 – 2.30 (m, 2H), 1.47 (s, 9H), 1.25 (d, J = 7.2 Hz, 3H), 1.04 – 0.95 (m, 6H)

^{13}C-NMR (75 MHz, CD_3OD): 175.7, 175.1, 174.3, 81.0, 57.7, 55.4, 54.0, 53.2, 51.6, 35.7, 33.1, 26.9, 26.8, 18.0, 14.5, 13.1

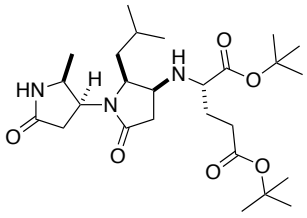
MS: (ESI, m/z): calculated for $C_{17}H_{27}N_3O_4$ 339.22, found 340.22 (H+)


INDEX FREQUENCY PPM HEIGHT
1 1455.2 4.852 58.8
2 441.9 1.473 549.9
3 436.9 1.457 60.7
4 378.2 1.261 70.1
5 371.1 1.237 66.3
6 350.1 1.167 58.8
7 343.6 1.146 56.7
8 322.2 1.074 58.4
9 315.5 1.052 58.7
C17H29N3O4
Exact Mass: 339.2158
4.852
1.473
1.457
1.261
1.237
1.167
1.146
1.074
1.052
tBu
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.01 1.06 0.91 0.81 0.85 1.00 1.08 1.83 10.48 2.65 4.19 3.18


INDEX FREQUENCY PPM HEIGHT
1 13248.3 175.674 4.3
2 13201.9 175.060 4.5
3 13145.1 174.306 5.2
4 6107.3 80.983 6.7
5 4350.7 57.691 4.6
6 4177.4 55.393 9.0
7 4070.4 53.974 10.6
8 4012.4 53.205 9.2
9 3891.6 51.603 6.0
10 3654.3 48.456 10.7
11 3632.7 48.171 31.2
12 3611.2 47.885 65.5
13 3589.7 47.600 63.9
14 3568.7 47.322 54.9
15 3547.2 47.037 33.4
16 3525.7 46.751 11.3
17 2694.0 35.723 7.3
18 2498.1 33.126 9.1
19 2027.4 26.884 35.7
20 2020.8 26.796 5.6
21 1356.9 17.993 9.3
22 1092.0 14.480 8.9
23 989.9 13.126 9.7
C17H29N3O4
Exact Mass: 339.2158
175.674
175.060
174.306
80.983
57.691
55.393
53.974
53.205
51.603
48.456
48.171
47.885
47.600
47.322
47.037
46.751
35.723
33.126
26.884
26.786
17.993
14.480
13.126
220 200 180 160 140 120 100 80 60 40 20 0 ppm

Compound **6cd**

(*S*)-di-*tert*-butyl 2-(((2*S*,2'*S*,3*S*,3'*S*)-2-isobutyl-2'-methyl-5,5'-dioxo-[1,3'-bipyrrolidin]-3-yl)amino)pentanedioate, oil, yield quantitative.

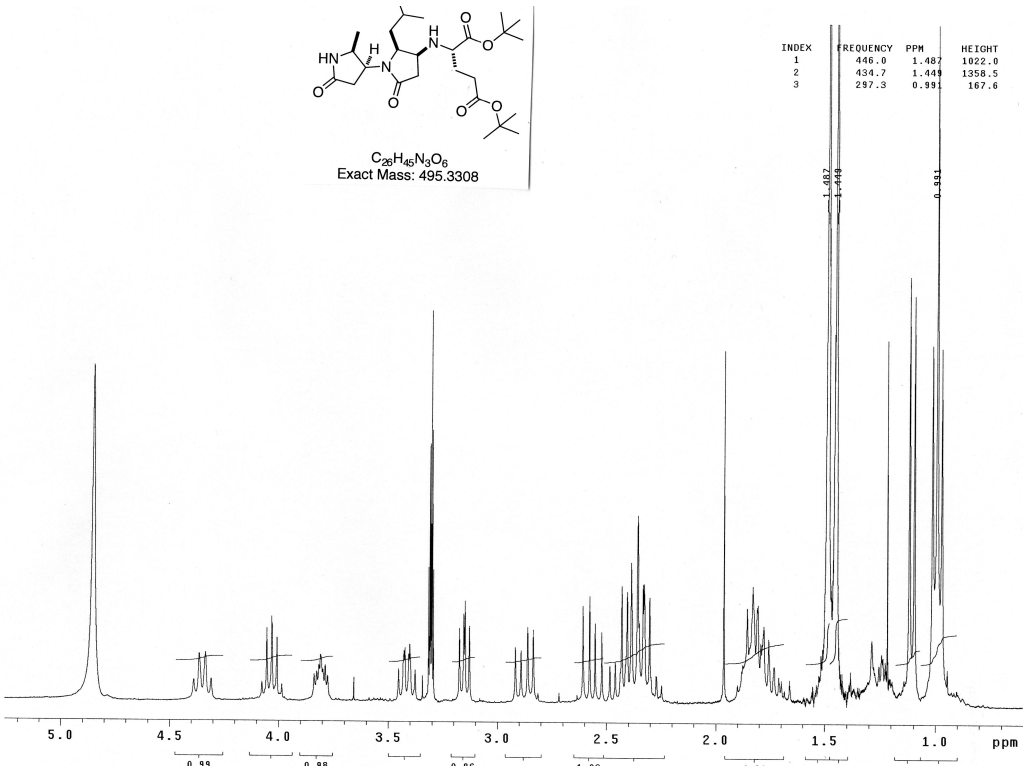


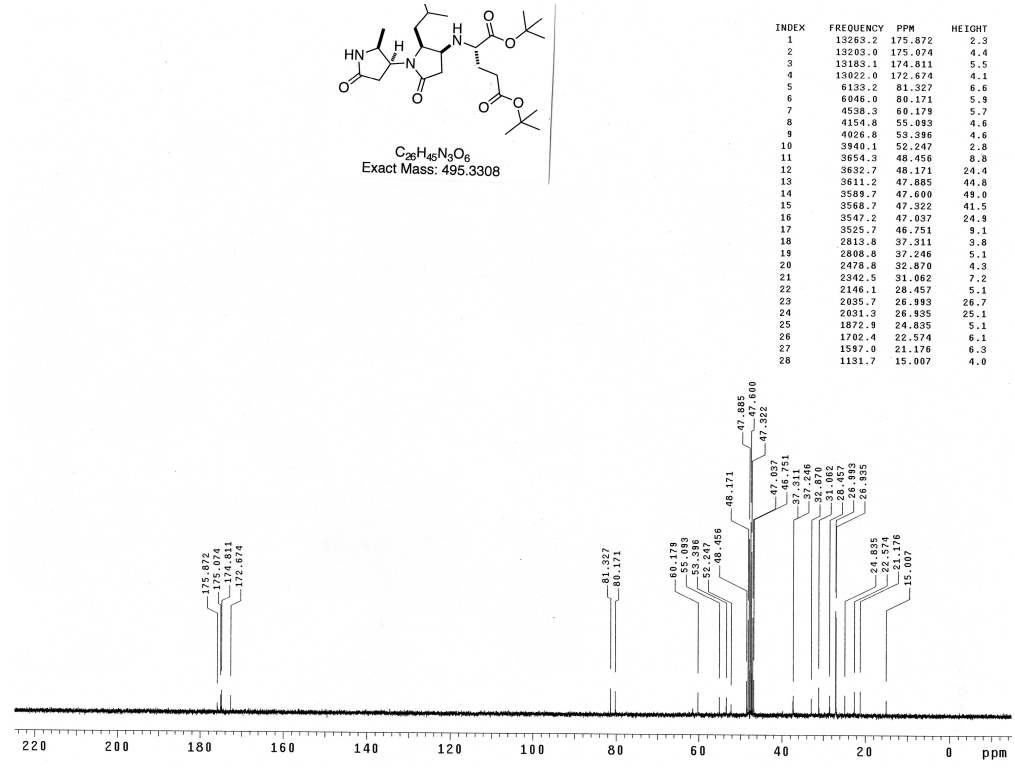
Procedure: Similar to that described before for **2 a-c**, except that hydrogenation was performed at elevated hydrogen pressure (70 bar) and temperature (70 ^{o}C) for 30 h with catalytic acetic acid.

^{1}H-NMR (CD_3OD): 4.35 (q, J = 9.0 Hz, 1H), 4.10 – 3.96 (m, 1H), 3.86 -3.75 (m, 1H), 3.47 – 3.35 (m, 1H), 3.15 (dd, J = 7.5, J = 6.0 Hz, 1H), 2.88 (dd, J = 16.8, J = 7.5 Hz, 1H), 2.56 (dd, J = 16.8, J = 9.3 Hz, 1H), 2.50 – 2.23 (m, 4H), 1.90 – 1.70 (m, 4H), 1.49 (s, 9H), 1.45 (s, 9H), 1.11 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 3.3 Hz, 3H), 0.90 (d, J = 3.3 Hz, 3H)

^{13}C-NMR (75 MHz, CD_3OD): 175.9, 175.1, 174.8, 172.7, 81.3, 80.2, 60.2, 55.1, 53.4, 52.2, 37.3, 37.2, 32.9, 31.1, 28.5, 27.0, 26.9, 24.8, 22.6, 21.2, 15.0

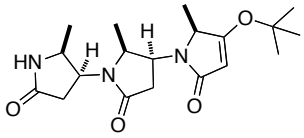
MS: (ESI, m/z): calculated for $C_{26}H_{45}N_3O_6$, 495.33, found 496.34 (H+)


$C_{26}H_{45}N_3O_6$
Exact Mass: 495.3308
INDEX FREQUENCY PPM HEIGHT
1 446.0 1.487 1022.0
2 434.7 1.449 1358.5
3 297.3 0.991 167.6
1.487
1.449
0.991
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


$C_{26}H_{45}N_3O_6$
Exact Mass: 495.3308
INDEX FREQUENCY PPM HEIGHT
1 13263.2 175.872 2.3
2 13203.0 175.074 4.4
3 13183.1 174.811 5.5
4 13022.0 172.674 4.1
5 6133.2 81.327 6.6
6 6046.0 80.171 5.9
7 4538.3 60.179 5.7
8 4154.8 55.093 4.6
9 4026.8 53.396 4.6
10 3940.1 52.247 2.8
11 3654.3 48.456 8.8
12 3632.7 48.171 24.4
13 3611.2 47.885 44.8
14 3589.7 47.600 49.0
15 3568.7 47.322 41.5
16 3547.2 47.037 24.9
17 3525.7 46.751 9.1
18 2813.8 37.311 3.8
19 2808.8 37.246 5.1
20 2478.8 32.870 4.3
21 2342.5 31.062 7.2
22 2146.1 28.457 5.1
23 2035.7 26.993 26.7
24 2031.3 26.935 25.1
25 1872.9 24.835 5.1
26 1702.4 22.574 6.1
27 1597.0 21.176 6.3
28 1131.7 15.007 4.0
175.872
175.074
174.811
172.674
81.327
80.171
60.179
55.093
53.396
52.247
48.456
48.171
47.885
47.600
47.322
47.037
46.751
37.311
37.246
32.870
31.062
28.457
26.993
26.935
24.835
22.574
21.176
15.007
220
200
180
160
140
120
100
80
60
40
20
0
ppm

Compound **7aa**

(2'S,3'S,4S,5S)-4-((S)-3-(tert-butoxy)-2-methyl-5-oxo-2,5-dihydro-1H-pyrrol-1-yl)-2',5-dimethyl-[1,3'-bipyrrolidine]-2,5'-dione



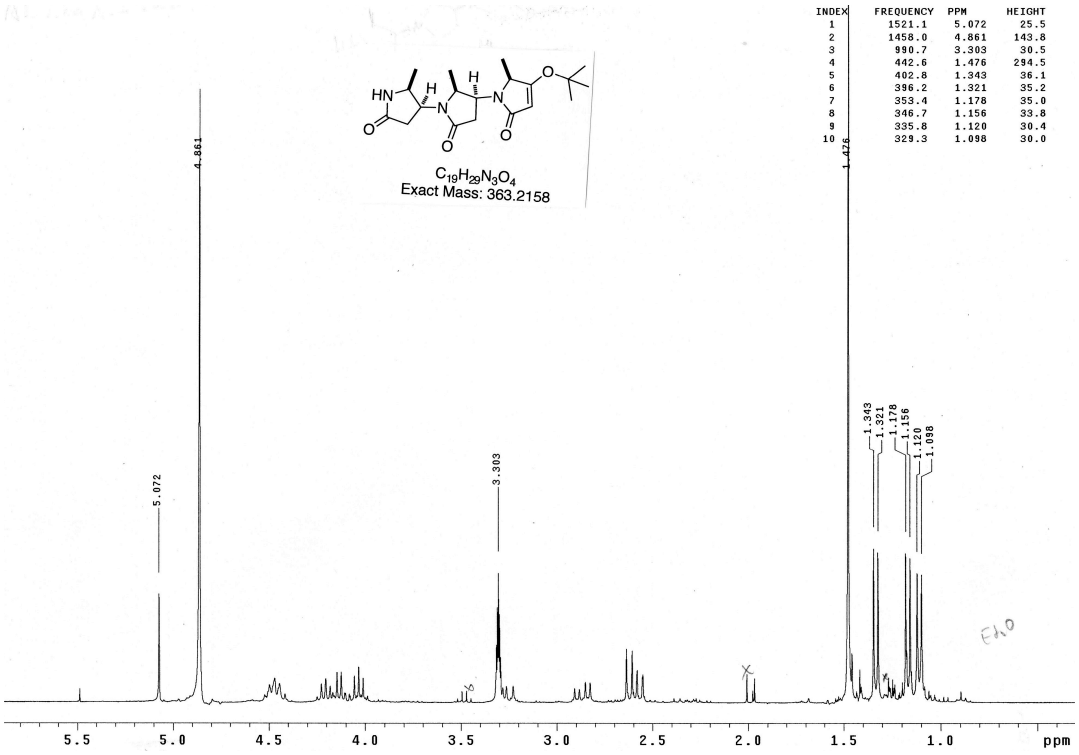
Procedure: As described for **3 a-c** preparation. White crystals, mp = 229 – 230 ^{o}C (chloroform/hexanes), yield 80%.

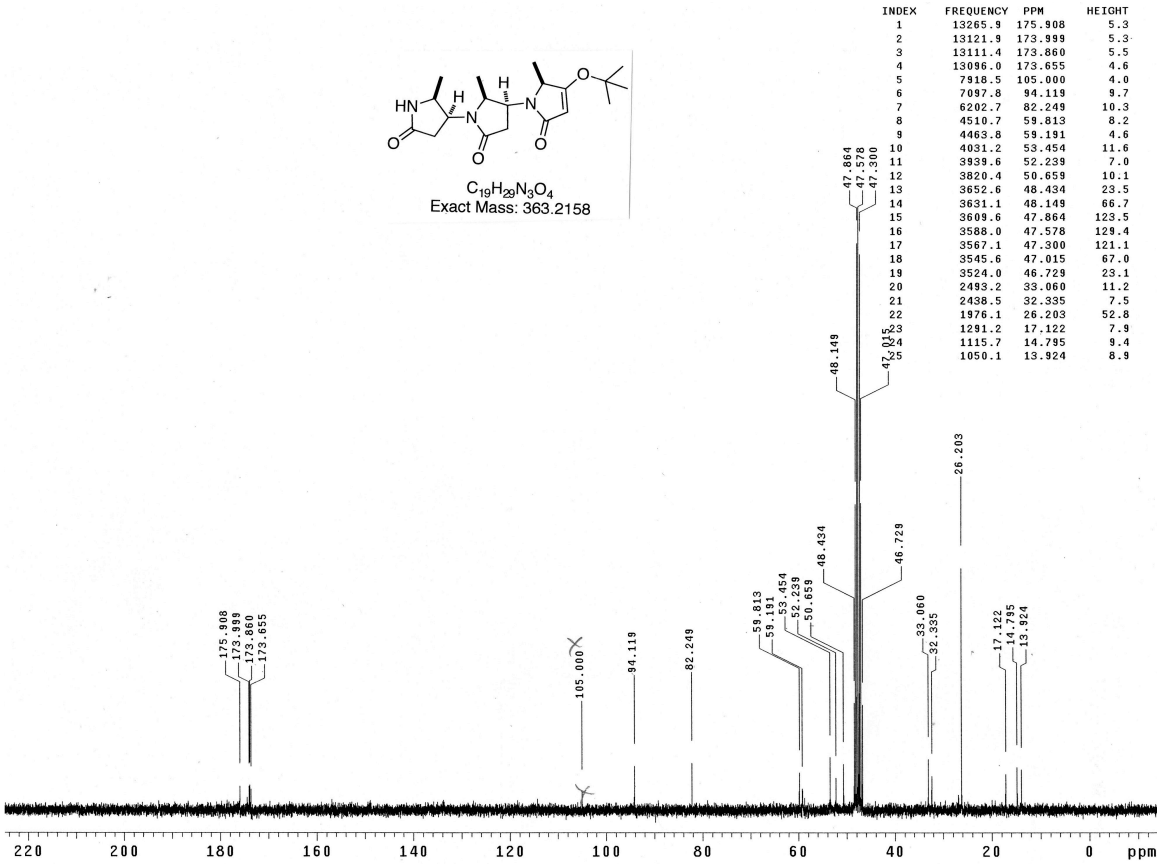
$[\alpha]^{20}_{D}$ – 115.1 (*c* 1.0, MeOH)

^{1}H-NMR (CD_3OD): 5.07 (s, 1H), 4.53 – 4.40 (m, 2H), 4.26 – 3.98 (m, 3H), 3.27 (dd, J = 16.5, J = 11.1 Hz, 1 H), 2.87 (dd, J = 16.8, J = 7.2 Hz, 1H), 2.62 (d, J = 8.7 Hz, 1H), 2.57 (dd, J = 9.0, J = 0.9 Hz, 1H), 1.48 (s, 9H), 1.33 (d, J = 6.6 Hz, 3H), 1.17 (d, J = 6.6 Hz, 3H), 1.11 (d, J = 6.6 Hz, 3H)

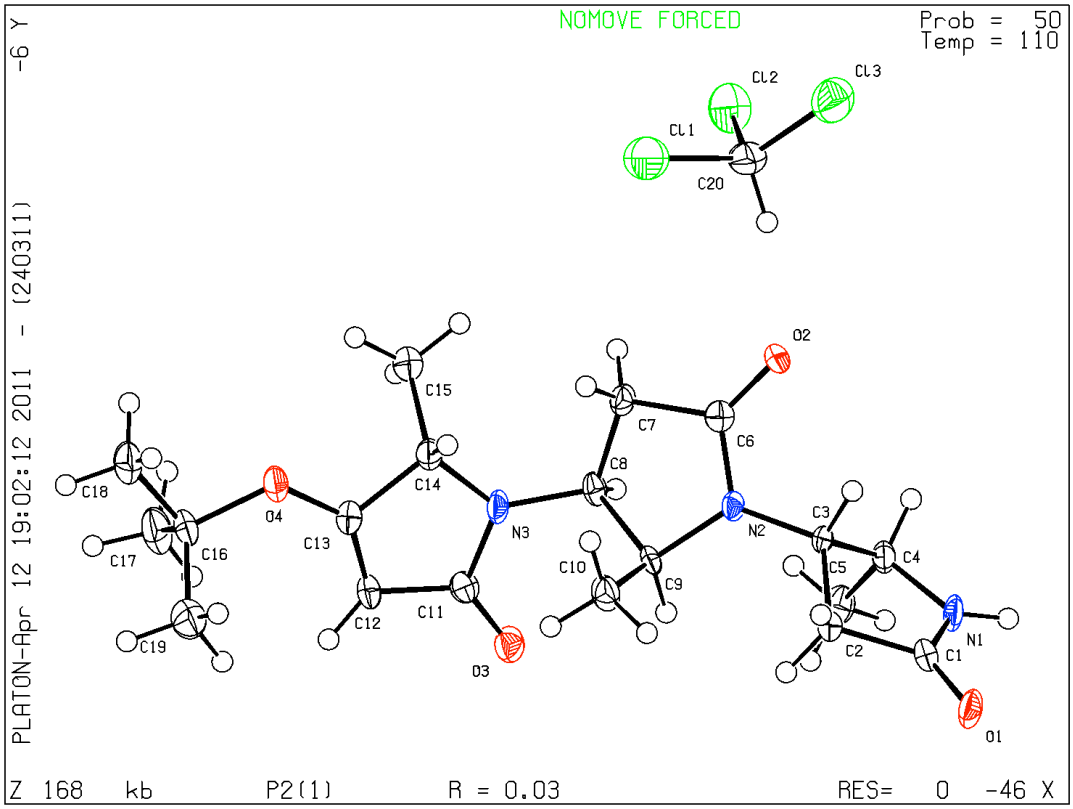
^{13}C-NMR (75 MHz, CD_3OD): 176.0, 174.0, 173.9, 173.0, 94.1, 82.2, 59.8, 59.2, 53.5, 52.2, 50.7, 33.1, 32.3, 26.2, 17.1, 14.8, 13.9

MS: (ESI, m/z): calculated for $C_{19}H_{29}N_3O_4$ (+Na) exact mass 386.2061 (Na+), found 386.2056


INDEX FREQUENCY PPM HEIGHT
1 1521.1 5.072 25.5
2 1458.0 4.861 143.8
3 990.7 3.303 30.5
4 442.6 1.476 294.5
5 402.8 1.343 36.1
6 396.2 1.321 35.2
7 353.4 1.178 35.0
8 346.7 1.156 33.8
9 335.8 1.120 30.4
10 329.3 1.098 30.0
C19H29N3O4
Exact Mass: 363.2158
5.072
4.861
3.303
1.476
1.343
1.321
1.178
1.156
1.120
1.098
5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm


INDEX FREQUENCY PPM HEIGHT
1 13265.9 175.908 5.3
2 13121.9 173.999 5.3
3 13111.4 173.860 5.5
4 13096.0 173.655 4.6
5 7918.5 105.000 4.0
6 7097.8 94.119 9.7
7 6202.7 82.249 10.3
8 4510.7 59.813 8.2
9 4463.8 59.191 4.6
10 4031.2 53.454 11.6
11 3939.6 52.239 7.0
12 3820.4 50.659 10.1
13 3652.6 48.434 23.5
14 3631.1 48.149 66.7
15 3609.6 47.864 123.5
16 3588.0 47.578 129.4
17 3567.1 47.300 121.1
18 3545.6 47.015 67.0
19 3524.0 46.729 23.1
20 2493.2 33.060 11.2
21 2438.5 32.335 7.5
22 1976.1 26.203 52.8
23 1291.2 17.122 7.9
24 1115.7 14.795 9.4
25 1050.1 13.924 8.9
C19H29N3O4
Exact Mass: 363.2158
220 200 180 160 140 120 100 80 60 40 20 0 ppm

X-Ray 7aa


NOMOVE FORCED
Prob = 50
Temp = 110
-6 Y
PLATON-Apr 12 19:02:12 2011 - (240311)
Cl2
Cl3
Cl1
C20
C15
O2
C7
C6
C18
C14
C8
O4
N3
N2
C3
C13
C10
C9
C5
C4
C17
C16
C12
C11
C2
N1
C19
O3
C1
O1
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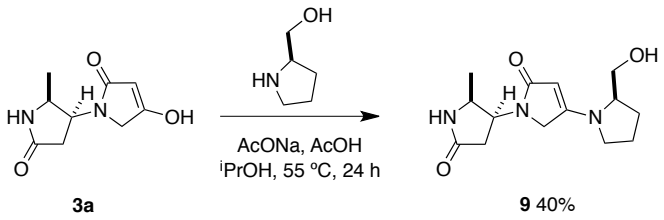
P2(1)
R = 0.03
RES= 0 -46 X

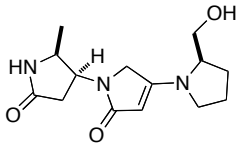
Scheme S3



3a **9** 40%

Compound **9**

4-((*R*)-2-(Hydroxymethyl)pyrrolidin-1-yl)-1-((2*S*,3*S*)-2-methyl-5-oxopyrrolidin-3-yl)-1H-pyrrol-2(5H)-one



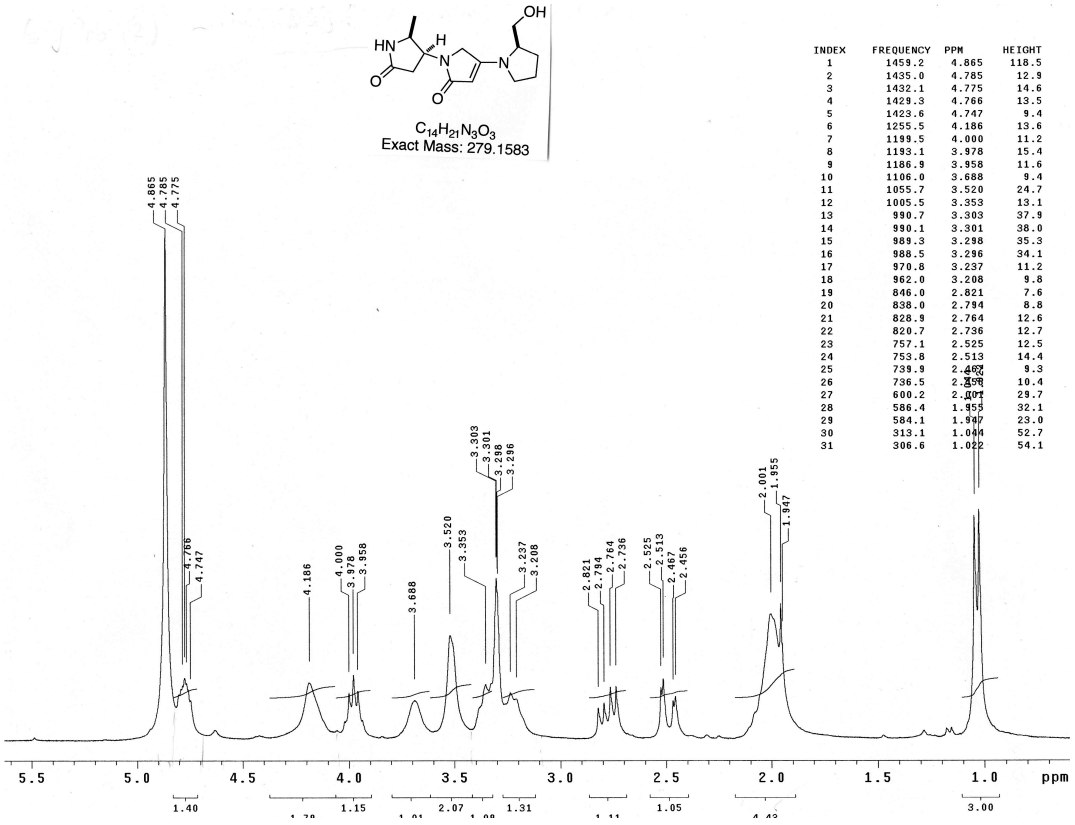
Procedure: As described for **1 a-c**, except that no sodium acetate was added. White sticky oil, 40%, was eluted with ethylacetate/methanol 5:1 – 5:4 mixtures on SiO_2.

$[\alpha]^{20}_D$ – 189.40 ± 1.14 (*c* 1.0, MeOH)

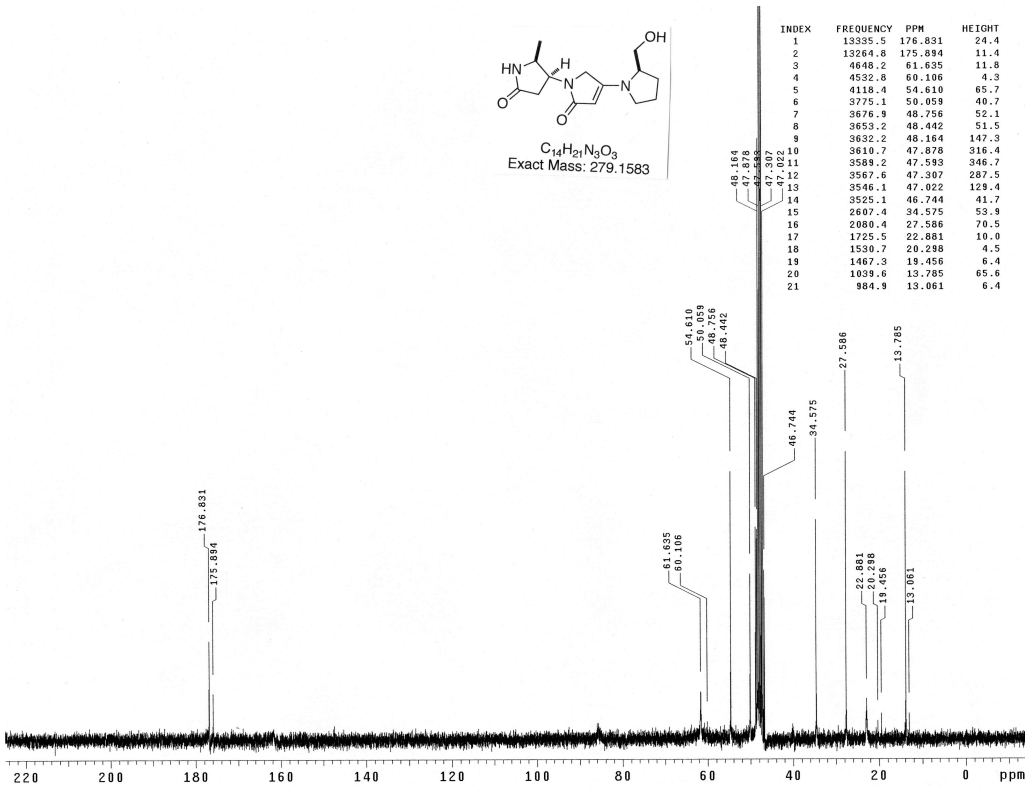
^{1}H-NMR (CD_3OD): 4.85 – 4.70 (m, 2H), 4.19 (bs, 2H), 4.05 – 3.90 (m, 1H), 3.69 (bs, 1H), 3.52 (bs, 2H), 3.40 – 3.20 (m, 3H), 2.78 (dd, J = 17.3, J = 8.2 Hz, 1H), 2.49 (dd, J = 17.3, J = 3.4 Hz, 1H), 2.00 (bs, 3H), 1.03 (d, J = 6.6 Hz, 3H)

^{13}C-NMR (75 MHz, CD_3OD): 176.9, 175.9, 61.6, 54.6, 50.1, 48.8, 34.6, 27.6, 22.9, 20.0, 19.5, 13.8, 13.1

MS: (ESI, m/z): calculated for $C_{14}H_{21}N_3O_3$ exact mass: 279.1583, found 280.1753 (H+)



INDEX	FREQUENCY	PPM	HEIGHT
1	1459.2	4.865	118.5
2	1435.0	4.785	12.9
3	1432.1	4.775	14.6
4	1429.3	4.766	13.5
5	1423.6	4.747	9.4
6	1255.5	4.186	13.6
7	1199.5	4.000	11.2
8	1193.1	3.978	15.4
9	1186.9	3.958	11.6
10	1106.0	3.688	9.4
11	1055.7	3.520	24.7
12	1005.5	3.353	13.1
13	990.7	3.303	37.9
14	990.1	3.301	38.0
15	989.3	3.298	35.3
16	988.5	3.296	34.1
17	970.8	3.237	11.2
18	962.0	3.208	9.8
19	846.0	2.821	7.6
20	838.0	2.794	8.8
21	828.9	2.764	12.6
22	820.7	2.736	12.7
23	757.1	2.525	12.5
24	753.8	2.513	14.4
25	739.9	2.467	9.3
26	736.5	2.456	10.4
27	600.2	2.001	29.7
28	586.4	1.955	32.1
29	584.1	1.947	23.0
30	313.1	1.044	52.7
31	306.6	1.022	54.1

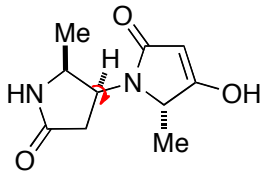


INDEX	FREQUENCY	PPM	HEIGHT
1	13335.5	176.831	24.4
2	13264.8	175.894	11.4
3	4648.2	61.635	11.8
4	4532.8	60.106	4.3
5	4118.4	54.610	65.7
6	3775.1	50.059	40.7
7	3676.9	48.756	52.1
8	3653.2	48.442	51.5
9	3632.2	48.164	147.3
10	3610.7	47.878	316.4
11	3589.2	47.593	346.7
12	3567.6	47.307	287.5
13	3546.1	47.022	129.4
14	3525.1	46.744	41.7
15	2607.4	34.575	53.9
16	2080.4	27.586	70.5
17	1725.5	22.881	10.0
18	1530.7	20.298	4.5
19	1467.3	19.456	6.4
20	1039.6	13.785	65.6
21	984.9	13.061	6.4

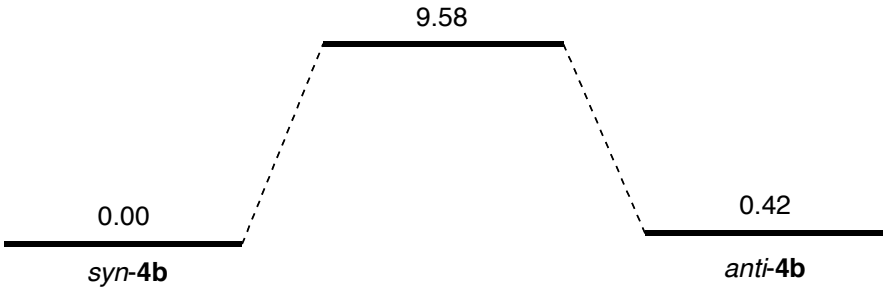
D. Modeling Procedures

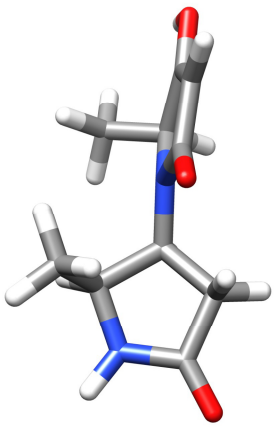
DFT Calculation

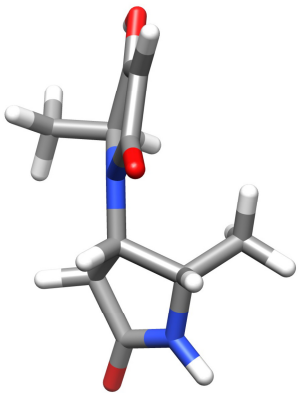
Reaction path calculations were performed at the B3LYP level of theory with the 6-31G(d') basis set, and a polarized continuum solvation model with a dielectric of H_2O (ε=78.3553). All B3LYP calculations were performed using Gaussian 03[3]. The energy barriers for the compound **4b** were calculated as rotation of the bond (red arrows). ΔG^{o} values were shown in kcal/mol. The population ratio of two conformers is *syn*-**4b**: *anti*-**4b** = 1.00: 0.48.



4b







Quenched Molecular Dynamics (QMD)

NAMD[4] 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. [5]

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[6] 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

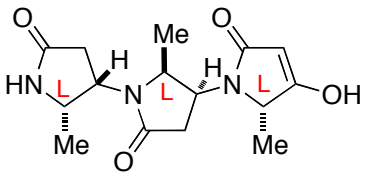
After minimization in the QMD process, the conformers were grouped into families base on their Cα-Cβ coordinates. The process of systematically matching preferred conformers with secondary structures was performed in the

following way. All the conformers within 3.0 kcal/mol were considered to be "preferred". 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 conformers within 3.0 kcal/mol were each overlaid on the ideal secondary structures.

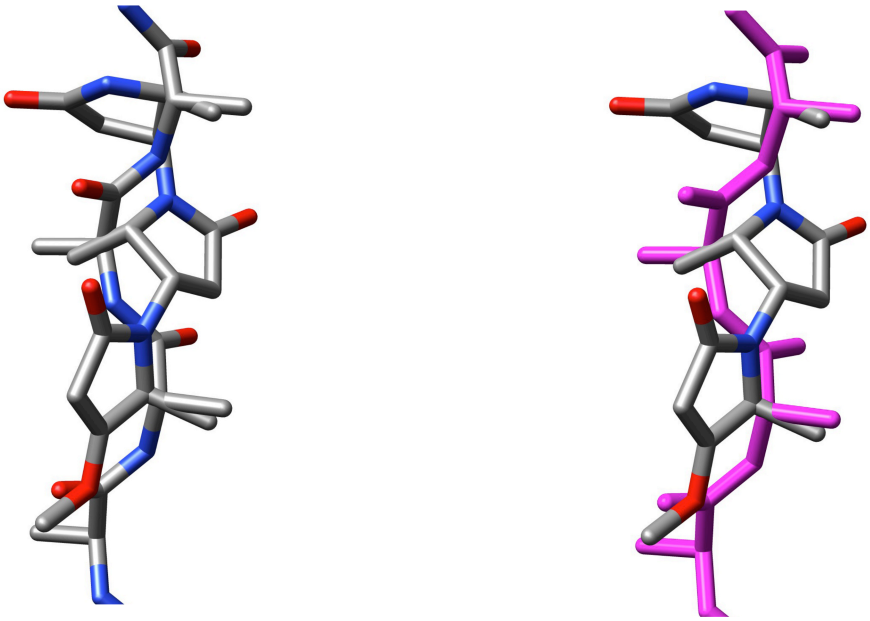
Templates for Secondary Structures

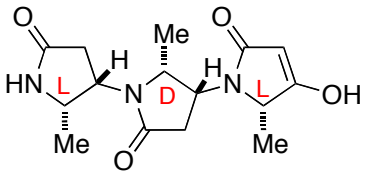
Standard template for overlays with β-strand was obtained from Discovery Studio 2.5.[5]

Overlays of compound 8 conformers with different stereochemistry on the β-strand



8a





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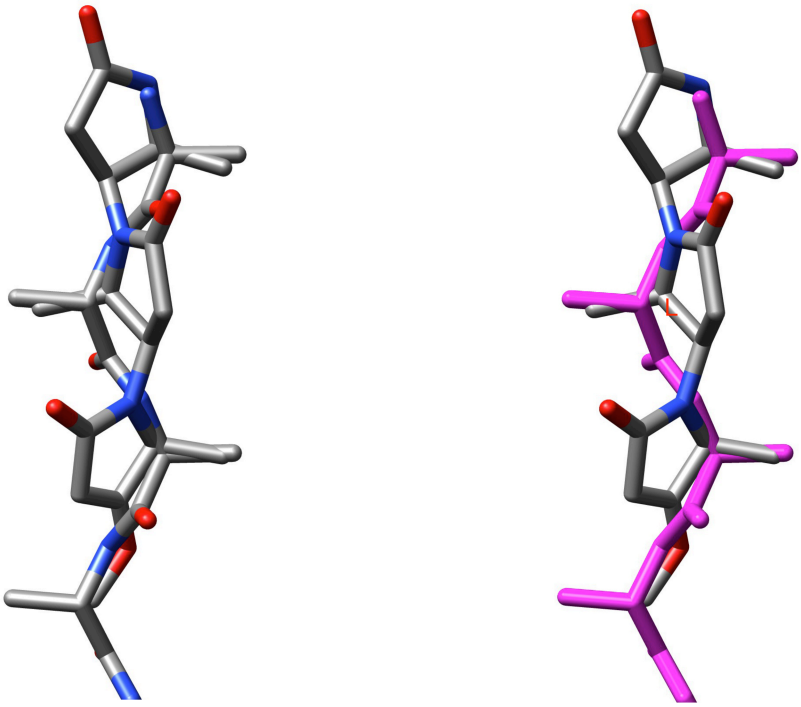
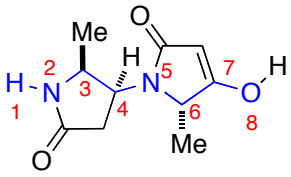


Procedure for Ramanchandran Plot



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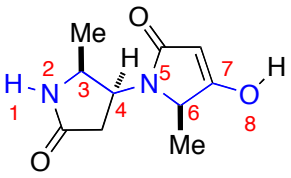

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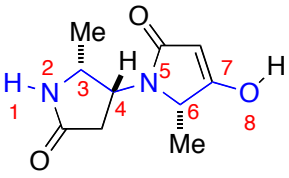

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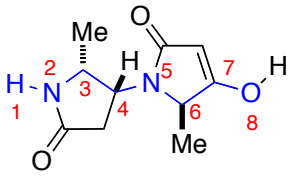

DD

Definition of torsional angles: ϕ (H^1-N^2-C^3-C^4), ψ (N^2-C^3-C^4-N^5), ϕ' (C^4-N^5-C^6-C^7) and ψ' (N^5-C^6-C^7-O^8)

For each compound, 600 conformers within 3.0 kcal/mol were obtained by QMD. Ramanchandran plot for the conformers was obtained from UCSF Chimera 1.5.2. www.cgl.ucsf.edu/chimera/

E. References

1. Hosseini, M.; Kringelum, H.; Murray, A.; Tonder, J. E., Dipeptide Analogues Containing 4-Ethoxy-3-pyrrolin-2-ones. *Organic Letters* **2006,** *8*, 2103-2106.
2. Hosseini, M.; Grau Jakob, S.; Sorensen Kasper, K.; Sotofte, I.; Tanner, D.; Murray, A.; Tonder Janne, E., Short and efficient diastereoselective synthesis of pyrrolidinone-containing dipeptide analogues. *Org. Biomol. Chem.* **2007,** *5*, 2207-10.
3. Frisch, M. J. T., G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A. *Gaussian 03, Revision E.01*, Gaussian, Inc.: Wallingford, CT, 2004.
4. Phillips, J. C.; Braun, R.; Wang, W.; Gumbart, J.; Tajkhorshid, E.; Villa, E.; Chipot, C.; Skeel, R. D.; Kale, L.; Schulten, K., Scalable molecular dynamics with NAMD. *J. Comput. Chem.* **2005,** *26*, 1781-1802.
5. Accelrys, I. *CHARMm module in Discovery Studio 2.1*, 2010.
6. Humphrey, W.; Dalke, A.; Schulten, K., VMD: visual molecular dynamics. *J. Mol. Graph.* **1996,** *14*, 33-8, 27-8.