Supporting information

A general approach to the aza-diketomorpholine scaffold

Matheo Berthet, Baptiste Legrand, Jean Martinez, Isabelle Parrot *

Institut des Biomolécules Max Mousseron, IBMM UMR-5247 CNRS, Université de Montpellier, ENSCM, CC 17-03, Pl. E. Bataillon, 34095 Montpellier Cedex 5 (France)

Contents

- **Nuclear Magnetic resonance (NMR)**

NMR spectra were recorded at ambient temperature on a Bruker Avance AM-300, Bruker Avance 400 MHz, Bruker Avance III 500 MHz (BBO) or Bruker Avance III 600 MHz spectrometers. ^{1}H NMR data are reported as followed: chemical shift (δ) in *ppm*, multiplicity (s = singlet, d = doublet, t = triplet, b = broad, m = multiplet), coupling constants *J* in *Hz*, integration, and assignment. ^{13}C NMR data are reported as followed: chemical shift (δ) in *ppm* and assignment. The reported ^{1}H and ^{13}C NMR signals were assigned using standard 2D-NMR techniques (COSY, HSQC, NOESY and HMBC).

- **Mass spectrometry**

LC/MS system consisted of a Waters Alliance 2690 HPLC, coupled to a ZQ spectrometer (Manchester, UK) fitted with an electrospray source operated in the positive ionization mode (ESI+). All the analyses were carried out using a C18 Chromolith Flash 25 x 4.6 mm column operated at a flow rate of 3.0 mL.min^{-1}. A gradient of 0 to 100% solvent B was developed over 3 min. Positive-ion electrospray mass spectra were acquired at a solvent flow rate of 100-200 µL/min. Nitrogen was used for both the nebulizing and drying gas. The data were obtained in a scan mode ranging from 200 to 1700 m/z in 0.1 s intervals. A total of 10 scans were summed up to get the final spectrum. High resolution mass spectra (**HRMS**) were performed by the "Laboratoire de Mesures Physiques" of Montpellier University on a Micromass Q-Tof spectrometer equipped with electrospray source ionization (ESI), using phosphoric acid as an internal standard.

- **HPLC chiral system**

Chiral HPLC analyses were performed on a chromatograph equipped with a variable detector at λ=214 nm and λ=254 nm using Chiralcel columns OD-H (0.46 x 25 cm). An isocratic gradient of *n*-hexane/*i*PrOH 95:5 was applied over 30 min at a flow rate of 1.0 mL.min^{-1}.

- **Polarimeter**

The optical rotations were obtained at 20°C in a 1.0mL glass cell on a JASCO P2000 Polarimeter with a sodium lamp at 589 nm and reported as follows : $[\alpha]_D^{20}$ (C = g.dL^{-1}, solvent), with [α] in 10^{-1} deg.cm^2.g^{-1}.

- **Solvents and reagents**

Unless otherwise specified, started reagents were purchased from commercial sources and used without further purification (Sigma-Aldrich®, Bachem®, IRIS Biotech®, TCI®). Unless otherwise specified, absolute configuration of amino acids used is "L". All solvents were dried and freshly distilled before use.

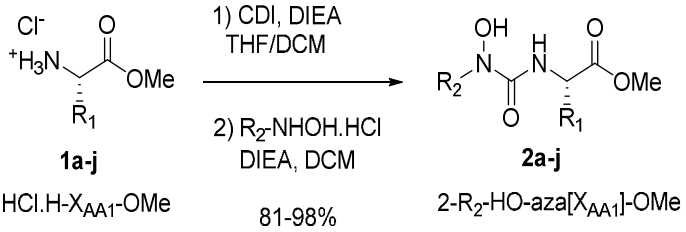
Reactions were magnetically stirred and monitored by thin layer chromatography using Merck-Kieselgel 60 F254 plates. Visualization was accomplished with UV light and exposure to a 10% solution of ninhydrin in ethanol followed by heating. When required, **flash**

chromatography columns were performed on Isolera™ Four Biotage® using Biotage® Snap cartridges KP-Sil.

Synthesis of 2-R_2,HO-aza[X_{AA1}]-OMe 2a-j

General experimental procedure A

To a cold (0°C) suspension of carbonyldiimidazole (3.45 mmol, 1.5 equiv.) in anhydrous THF (0.9 M) was added a solution of HCl.H-X_{AA1}-OR (2.30 mmol, 1.0 equiv.) and DIEA (9.20 mmol, 4.0 equiv.) in DCM (2.5 mL). After stirring at 0°C for 15 minutes, a solution of HCl.R_2-NHOH (1.2 equiv.) and DIEA (4.0 equiv.) in DCM (1.0 M) was added. After stirring at 0°C for 30 minutes, the reaction mixture was quenched with a 1.0 M aqueous solution of HCl and extracted with DCM (x3). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to afford the desired product in 81-98% yields.



2-Me,HO-aza[Phe]-OMe 2a

According to the general procedure A and starting with HCl.H-Phe-OMe and HCl.Me-NHOH, the title compound **2a** was obtained as a white solid in 95% yield (551.2 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.05 (s, 3H), 3.07 (d, 2H, *J*=6.3 Hz), 3.67 (s, 3H), 4.66 (dd, 1H, *J*=6.3 Hz, *J*=14.2 Hz), 6.37 (d, 1H, *J*=7.9 Hz), 7.12-7.14 (m, 2H), 7.20-7.30 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.2, 52.4, 54.3, 127.2, 128.7, 129.2, 136.0, 160.7, 173.2; LC/MS r_t=1.21; ESI-MS$^+$ *m/z* 253.0 [M+H$^+$]; HRMS (ESI+) *m/z*: Calcd for $C_{12}H_{16}N_2O_4$ [M+H]$^+$: 253.1188, found: 253.1188; R_f=0.49 (cHx/EtOAc 7:3).

2-Me,HO-aza[Ser(Bn)]-OMe 2b

According to the general procedure A and starting with HCl.H-Ser(Bn)-OMe and HCl.Me-NHOH, the title compound **2b** was obtained as a white solid in 90% yield (584.4 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.11 (s, 3H), 3.68 (s, 3H), 3.68 (dd, 1H, *J*=3.6 Hz, *J*=9.3 Hz), 3.87 (dd, 1H, *J*=3.6 Hz, *J*=9.6 Hz), 4.48 (d, 2H, *J*=12.2 Hz, *J*=34.3 Hz), 4.55-4.59 (m, 1H), 6.76 (d, 1H, *J*=8.4 Hz), 7.24-7.27 (m, 3H), 7.29-7.33 (m, 2H), 8.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.2, 52.5, 53.6, 69.9, 73.1, 127.6, 127.9, 128.4, 137.5, 160.8, 171.4; LC/MS r_t=1.30; ESI-MS$^+$ *m/z* 283.0 [M+H]$^+$, 305.1 [M+Na$^+$]; HRMS (ESI+) *m/z*: Calcd for $C_{13}H_{18}N_2O_5$ [M+H]$^+$: 283.0312, found: 283.0314; R_f=0.58 (cHx/EtOAc 6:4).

2-Me,HO-aza[Tyr(Bn)]-OMe 2c

According to the general procedure A and starting with HCl.H-Tyr(Bn)-OMe and HCl.Me-NHOH, the title compound **2c** was obtained as a white solid in 90% yield (741.9 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.03 (d, 2H, J=6.1 Hz), 3.09 (s, 3H), 3.69 (s, 3H), 4.60-4.68 (m, 1H), 5.01 (s, 2H), 6.31 (b, 1H), 6.89 (d, 2H, J=8.6 Hz), 7.04 (d, 2H), 7.30-7.34 (m, 1H), 7.36-7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.5, 38.6, 52.5, 54.4, 70.1, 115.1, 127.6, 128.1, 128.3, 128.7, 130.4, 137.1, 158.1, 160.6, 173.3; LC/MS r_t=1.63 ; ESI-MS$^+$ *m/z* 358.9 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{19}H_{22}N_2O_5$ $[M+H]^+$: 359.1607, found: 359.1608; R_f=0.50 (cHx/EtOAc 8:2).

2-Me,HO-aza[Cys(Bn)]-OMe 2d

According to the general procedure A and starting with HCl.H-Cys(Bn)-OMe and HCl.Me-NHOH, the title compound **2d** was obtained as a white solid in 81% yield (555.8 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.73-2.82 (m, 2H), 3.07 (s, 3H), 3.63 (s, 2H), 3.64 (s, 3H), 4.54 (dd, 1H, J=5.9 Hz, J=13.2 Hz), 6.54 (d, 1H, J=7.8 Hz), 7.13-7.25 (m, 5H), 7.95 (b, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.4, 36.5, 38.3, 52.7, 52.71, 127.3, 128.6, 128.9, 137.6, 160.5, 172.3; LC/MS r_t=1.41; ESI-MS$^+$ *m/z* 299.1 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{13}H_{18}N_2O_4S$ $[M+H]^+$: 299.1521, found: 299.1522; R_f=0.52 (cHx/EtOAc 8:2).

2-Me,HO-aza[Ile]-OMe 2e

According to the general procedure A and starting with HCl.H-Ile-OMe and HCl.Me-NHOH, the title compound **2e** was obtained as a white solid in 90% yield (451.8 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, 3H, J=7.5 Hz), 0.93 (d, 3H, J=7.5 Hz), 1.14-1.26 (m, 1H), 1.39-1.50 (m, 1H), 1.86-1.95(m, 1H), 3.17 (s, 3H), 3.74 (s, 3H), 4.36 (dd, 1H, J=5.3 Hz, J=8.2 Hz), 5.92 (b, 1H), 6.39 (d, 1H, J=8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.6, 15.7, 25.3, 37.8, 38.7, 52.4, 57.8, 161.2, 173.7; LC/MS r_t=1.15; ESI-MS$^+$ *m/z* 219.0 $[M+H]^+$ HRMS (ESI+) *m/z*: Calcd for $C_9H_{18}N_2O_4$ $[M+H]^+$: 219.0212, found: 219.0212; R_f=0.37 (cHx/EtOAc 7:3).

2-Bn,HO-aza[Val]-OMe 2f

According to the general procedure A and starting with HCl.H-Val-OMe and HCl.Bn-NHOH, the title compound **2f** was obtained as a white solid in 97% yield (625.4 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (d, 3H, J=6.9 Hz), 0.94 (d, 3H, J=6.8 Hz), 2.10-2.18 (m, 1H), 3.70 (s, 3H), 4.37 (dd, 1H, J=5.2 Hz, J=8.9 Hz), 4.64 (d, 2H, J=2.0 Hz), 6.38 (d, 1H, J=8.8 Hz), 6.70 (b, 1H), 7.27-7.33 (m, 5H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.0, 19.1, 31.3, 52.3, 54.8, 58.4, 127.8, 128.62, 129.0, 136.7, 160.3, 173.5; LC/MS r_t =1.45; ESI-MS$^+$ *m/z* 281.1 $[M+H]^+$, 303.1 $[M+Na]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{14}H_{20}N_2O_4$ $[M+H]^+$: 281.1212, found: 281.1212; R_f=0.46 (cHx/EtOAc).

2-Bn,HO-aza[Trp]-OMe 2g

According to the general procedure A and starting with HCl.H-Trp-OMe and HCl.Bn-NHOH, the title compound **2g** was obtained as a white solid in 92% yield (777.4 mg). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.15-3.26 (m, 2H), 3.61 (s, 3H), 4.48-4.58 (m, 1H), 4.52 (s, 2H), 6.86 (d, 1H, *J*=8.0 Hz), 6.99 (t, 1H, *J*=7.7 Hz), 7.08 (t, 1H, *J*=7.5 Hz), 7.13 (d, 1H, *J*=2.0 Hz), 7.22-7.31 (m, 5H), 7.35 (d, 1H, *J*=8.1 Hz), 7.47 (d, 1H, *J*=7.8 Hz), 9.55 (s, 1H), 10.92 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 27.2, 51.9, 53.6, 109.3, 111.5, 118.1, 118.6, 121.1, 123.8, 127.0, 127.2, 128.1, 128.1, 136.2, 137.8, 159.9, 172.8; LC/MS r_t=1.59 ; ESI-MS$^+$: *m/z* 368.1 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{20}H_{21}N_3O_4$ $[M+H]^+$: 368.1610, found: 368.1606; R_f=0.58 (cHx/EtOAc 8:2).

2-*i*Pr,HO-aza[Phe]-OMe 2h

According to the general procedure A and starting with HCl.H-Phe-OMe and HCl.*i*Pr-NHOH, the title compound **2h** was obtained as a white solid in 98% yield (631.8 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (d, 3H, *J*=6.6 Hz), 1.11 (d, 3H, *J*=6.7 Hz), 3.08-3.09 (m, 2H), 3.68 (s, 3H), 4.29-4.36 (m, 1H), 4.73 (dd, 1H, *J*=7.1 Hz, *J*=13.5 Hz), 6.37 (d, 1H, *J*=8.0 Hz), 7.11-7.13 (m, 2H), 7.19-7.25 (m, 2H), 7.27-7.29 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2, 18.7, 38.4, 50.5, 52.4, 54.1, 127.1, 128.7, 129.4, 136.2, 160.3, 173.1; LC/MS r_t=1.21; ESI-MS$^+$: *m/z* 281.3 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{14}H_{20}N_2O_4$ $[M+H]^+$: 281.1501, found: 281.1499; R_f=0.45 (cHx/EtOAc 8:2).

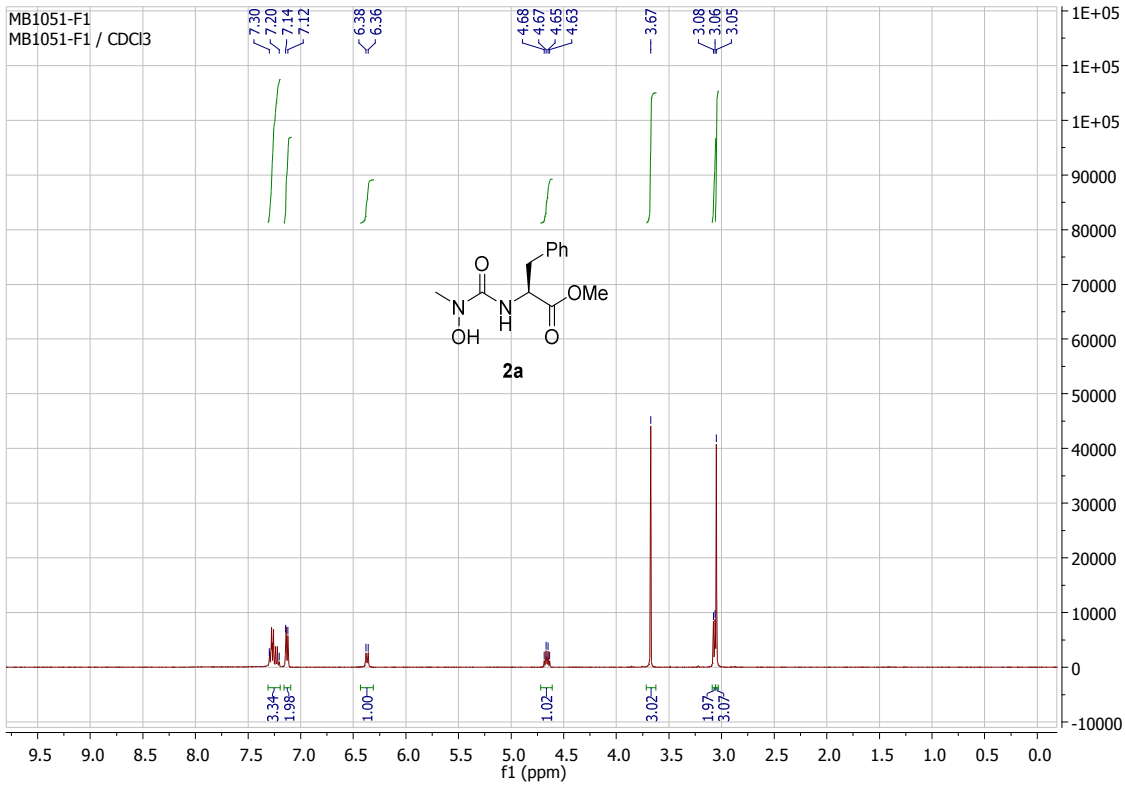
2-*i*Pr,HO-aza[(D)-Phe]-OMe 2i

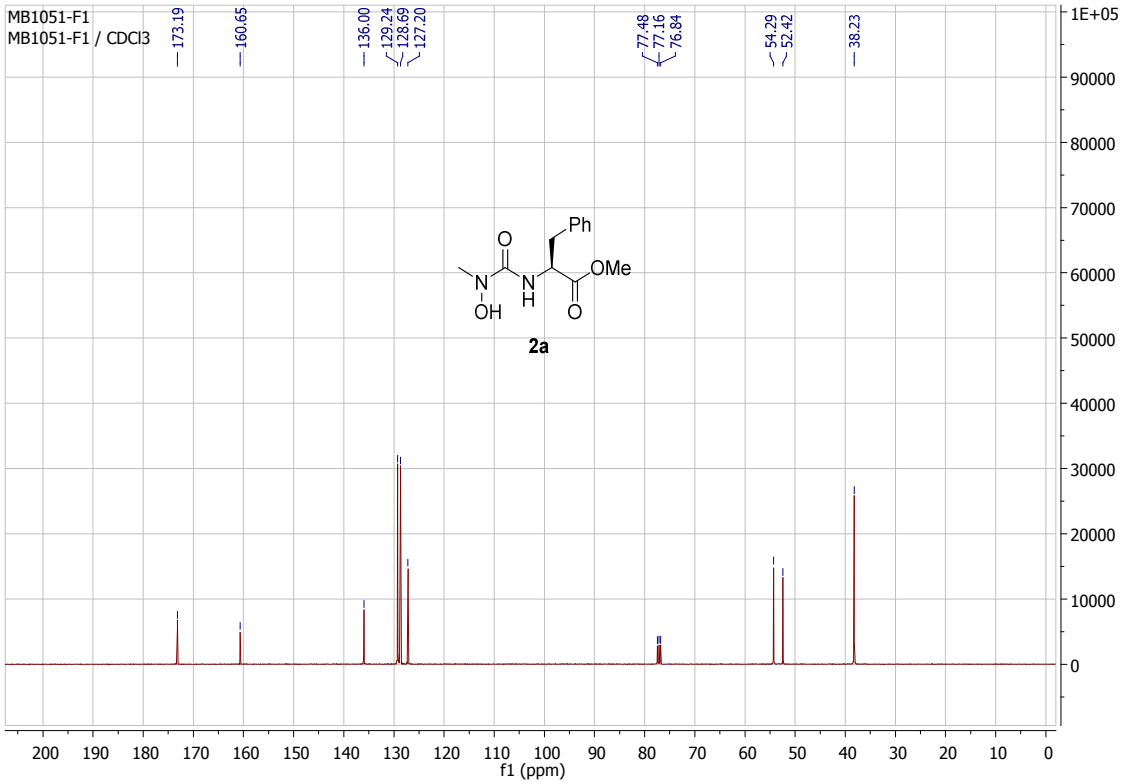
According to the general procedure A and starting with (D)-HCl.H-Phe-OMe and HCl.*i*Pr-NHOH, the title compound **2i** was obtained as a white solid in 98% yield (631.8 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (d, 3H, *J*=6.7 Hz), 1.11 (d, 3H, *J*=6.7 Hz), 3.05-3.12 (m, 2H), 3.68 (s, 3H), 4.30-4.35 (m, 1H), 4.73 (dd, 1H, *J*=6.3 Hz, *J*=14.3 Hz), 6.36 (d, 1H, *J*=8.0 Hz), 6.41-6.49 (b, 1H), 7.11-7.13 (m, 2H), 7.20-7.23 (m, 2H), 7.25-7.28 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.1, 18.5, 38.4, 50.4, 52.4, 54.1, 127.1, 128.7, 129.3, 136.2, 160.3, 173.2; LC/MS r_t=1.21; ESI-MS$^+$: *m/z* 281.3 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{14}H_{20}N_2O_4$ $[M+H]^+$: 281.1501, found: 281.1499; R_f=0.45 (cHx/EtOAc 8:2).

2-*i*Pr,HO-aza[Leu]-OMe 2j

According to the general procedure A and starting with HCl.H-Leu-OMe and HCl.*i*Pr-NHOH, the title compound **2j** was obtained as a white solid in 96% yield (543.9 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (d, 3H, *J*=1.9 Hz), 0.94 (d, 3H, *J*=1.9 Hz), 1.10 (d, 3H, *J*=6.6 Hz), 1.13 (d, 3H, *J*=6.7 Hz), 1.52-1.59 (m, 1H), 1.60-1.63 (m, 1H), 1.65-1.75 (m, 1H), 3.72 (s, 3H), 4.33-4.40 (m, 1H), 4.43-4.49 (m, 1H), 6.30 (d, 1H, *J*=8.2 Hz), 6.75 (b, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.2, 18.7, 21.9, 23.0, 25.0, 41.5, 50.4, 51.7, 52.4, 160.7, 175.0; LC/MS r_t=1.14; ESI-MS$^+$: *m/z* 247.2 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{11}H_{22}N_2O_4$ $[M+H]^+$: 247.1658, found: 247.1662; R_f=0.43 (cHx/EtOAc 7:3).

^{1}H and ^{13}C NMR spectra of HO-aza[X_{AA1}]-OMe

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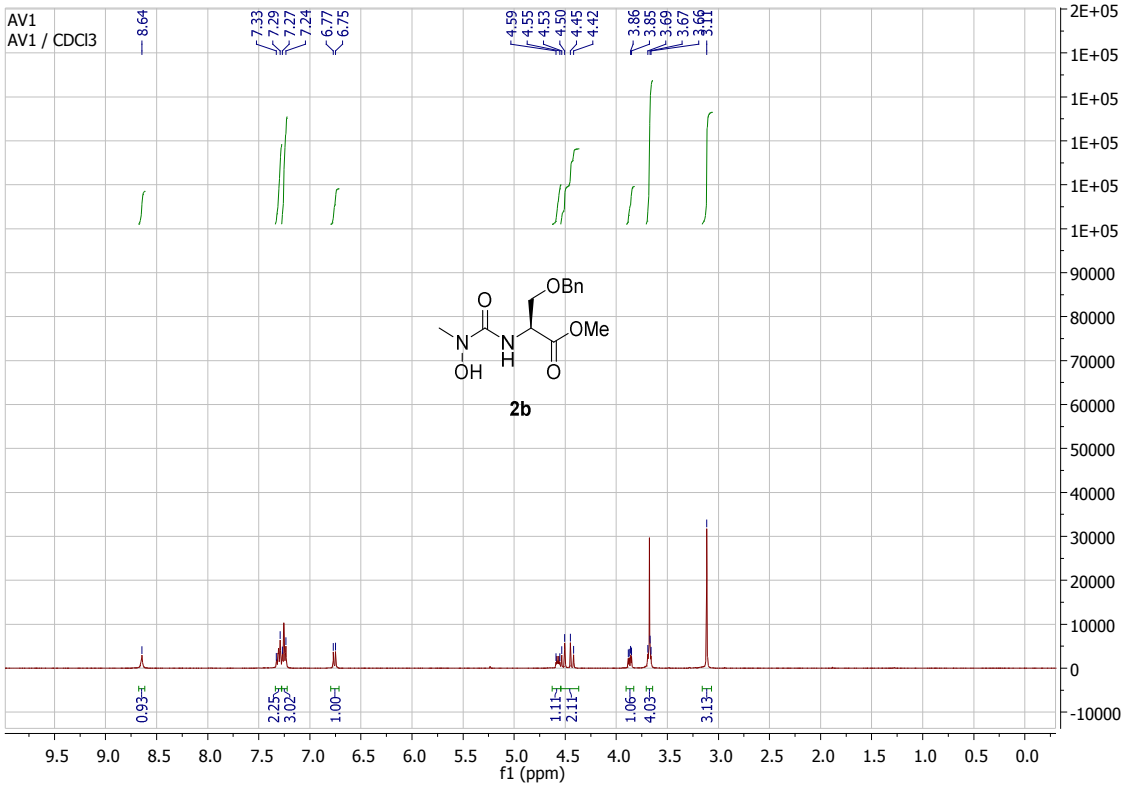
N
H
OMe
O
2a
f1 (ppm)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H
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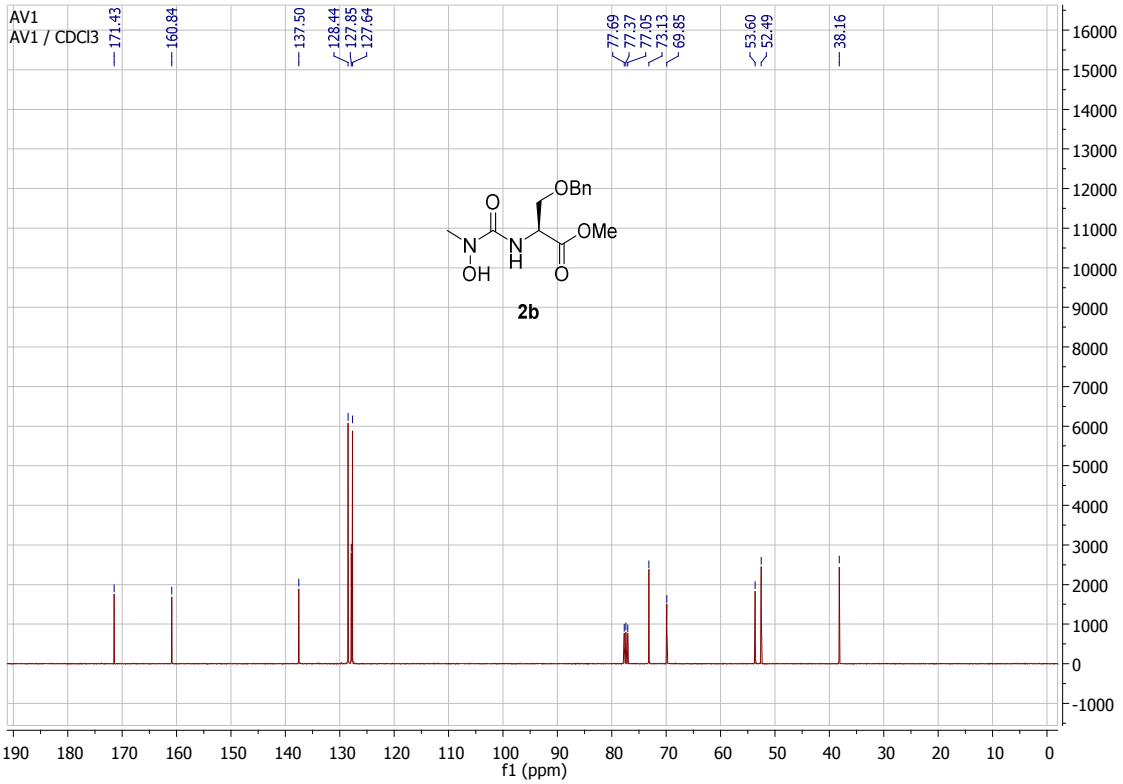
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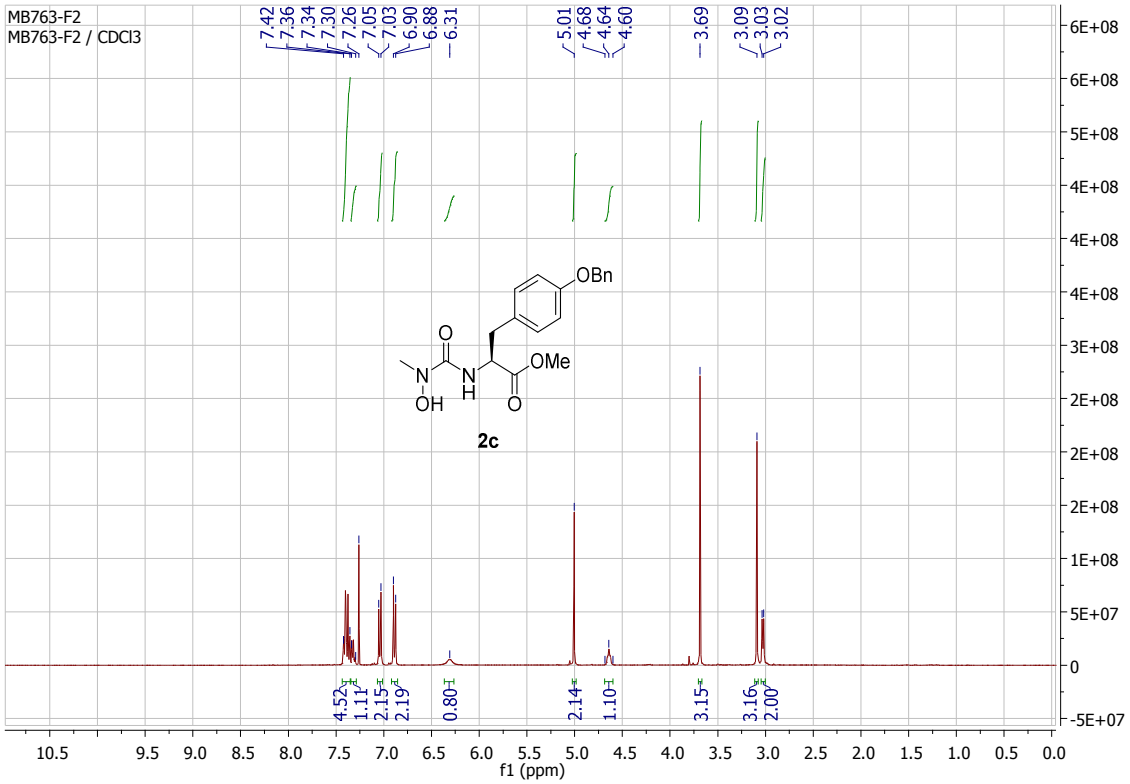
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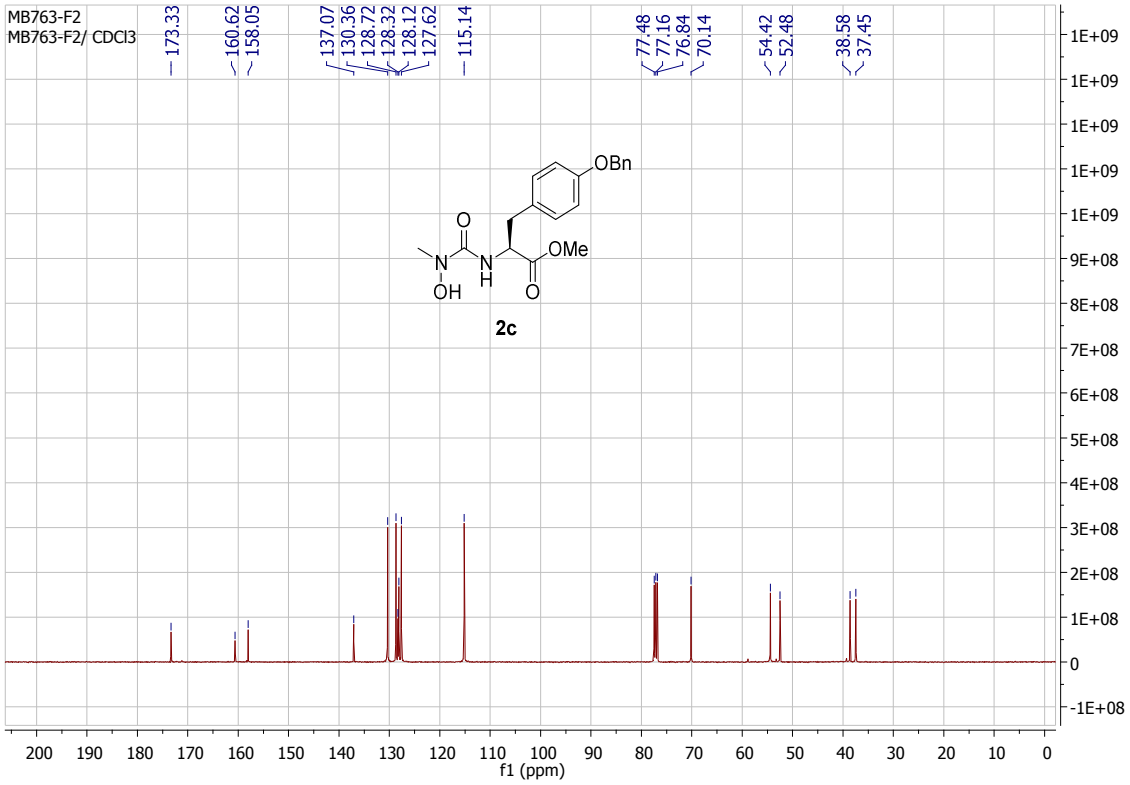
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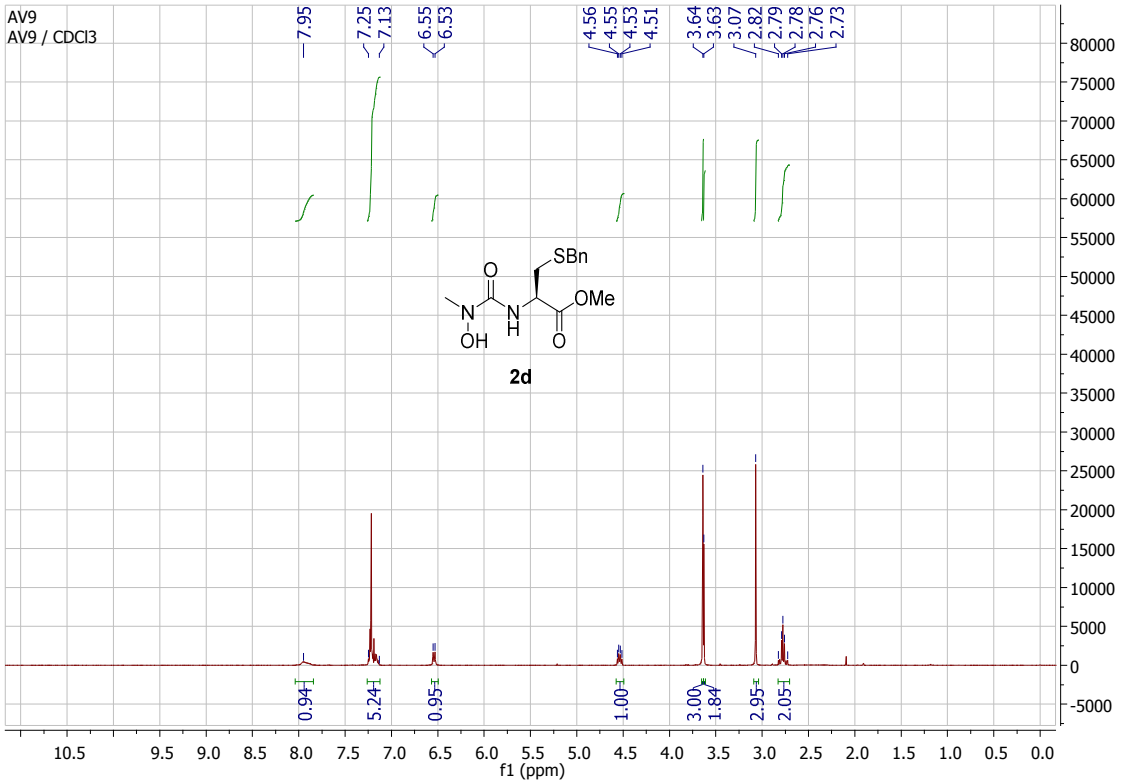
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AV9 / CDCl3
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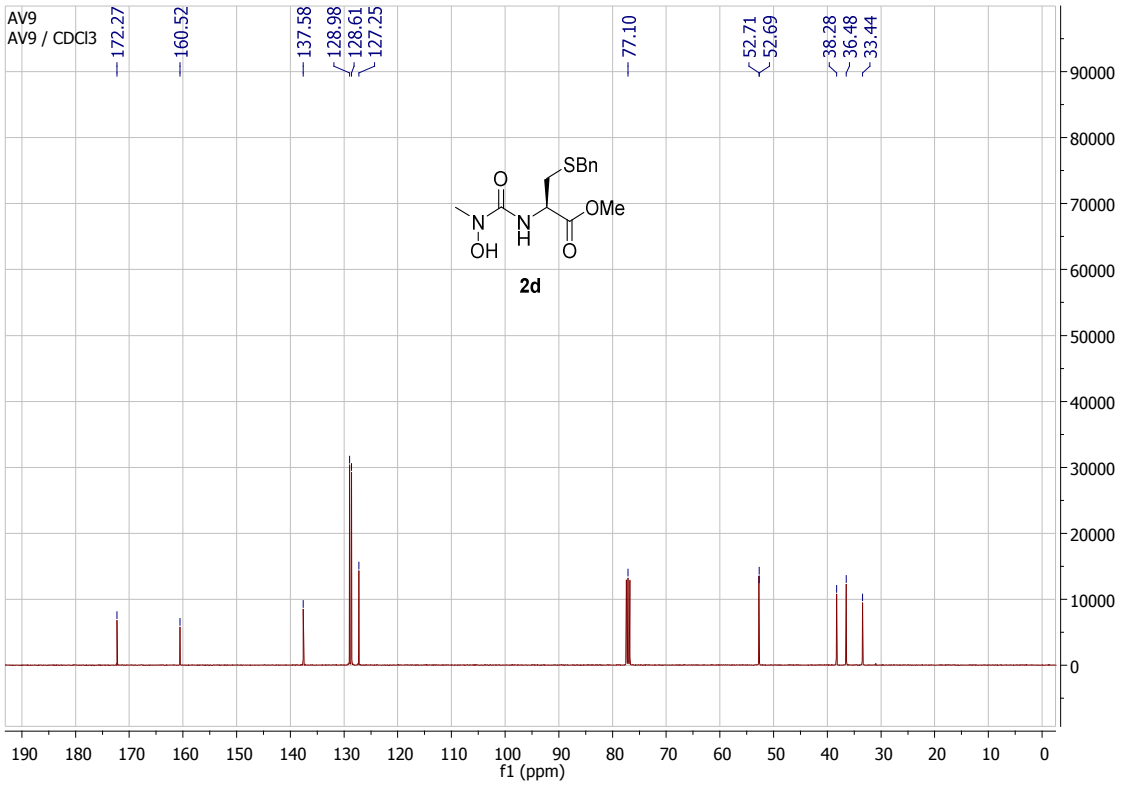
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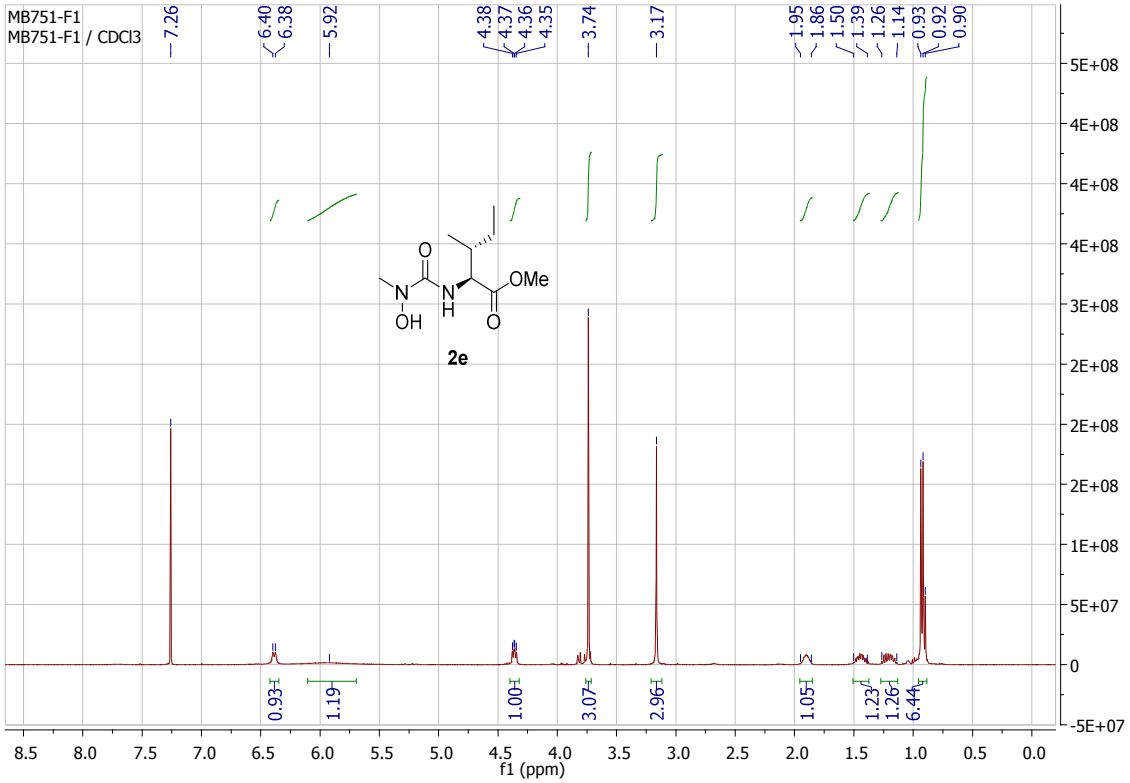
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0.92
0.90
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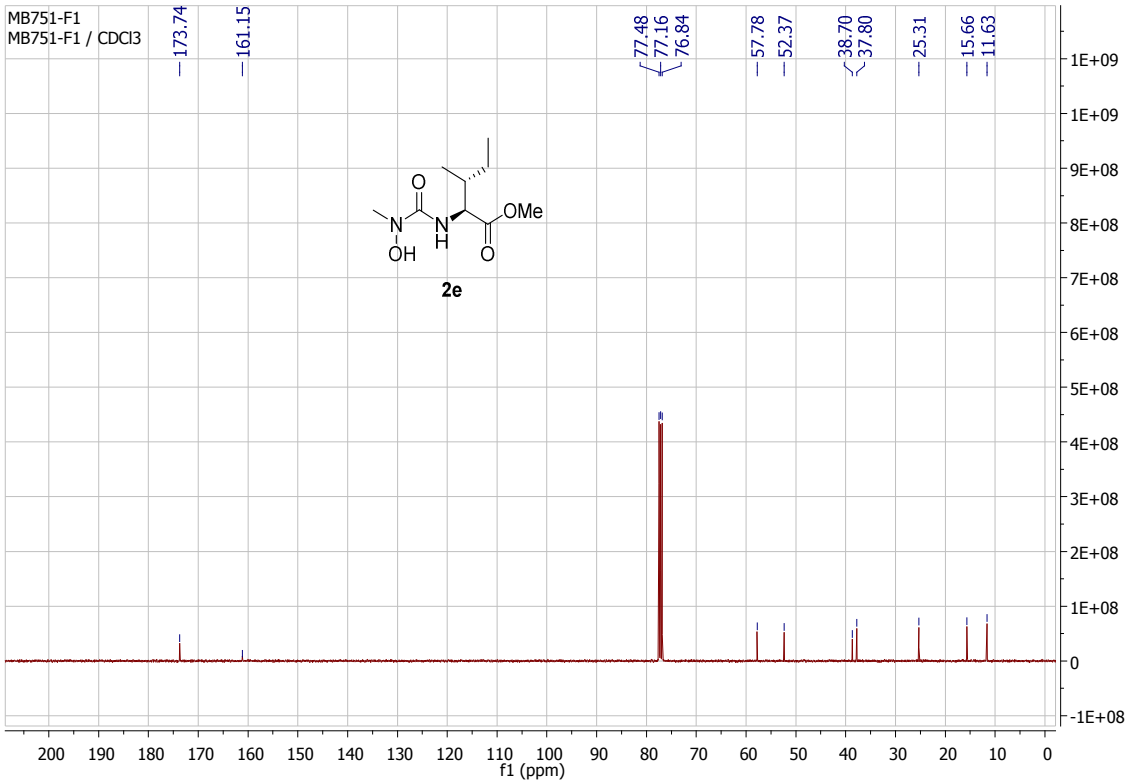
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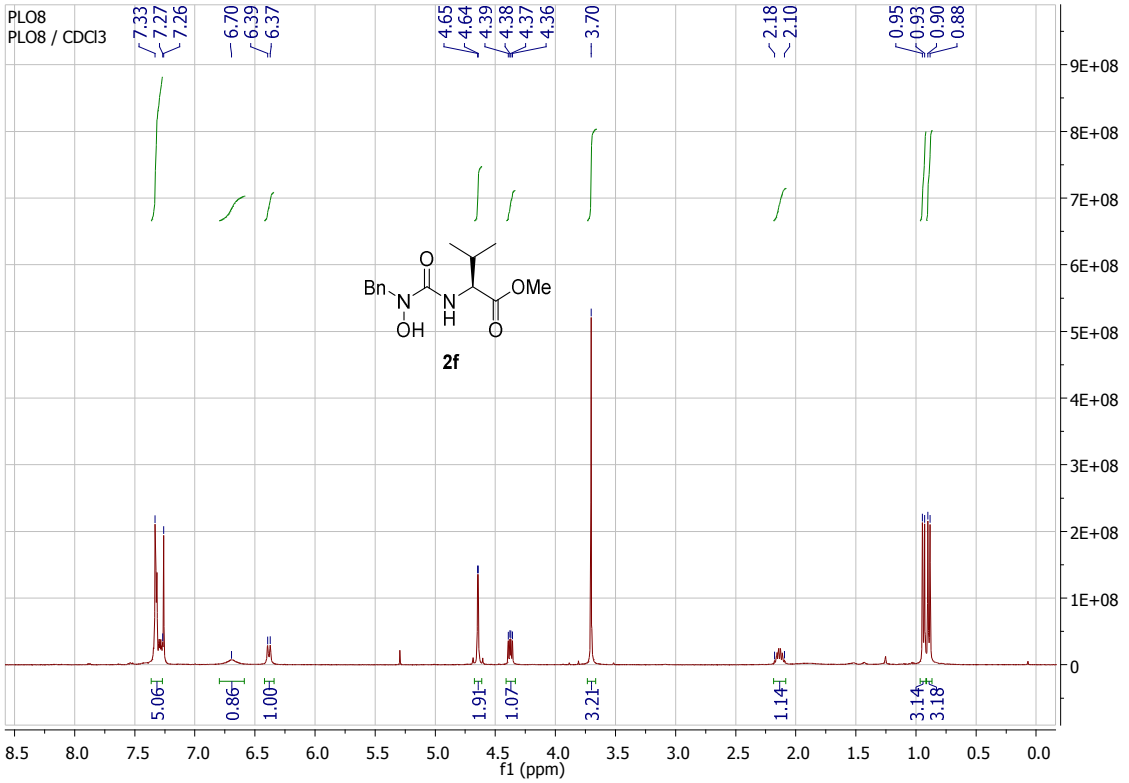
f1 (ppm)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4.37
4.36
3.70
2.18
2.10
0.95
0.93
0.90
0.88
Bn
N
O
OH
N
H
O
OMe
O
2f
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0.86
1.00
1.91
1.07
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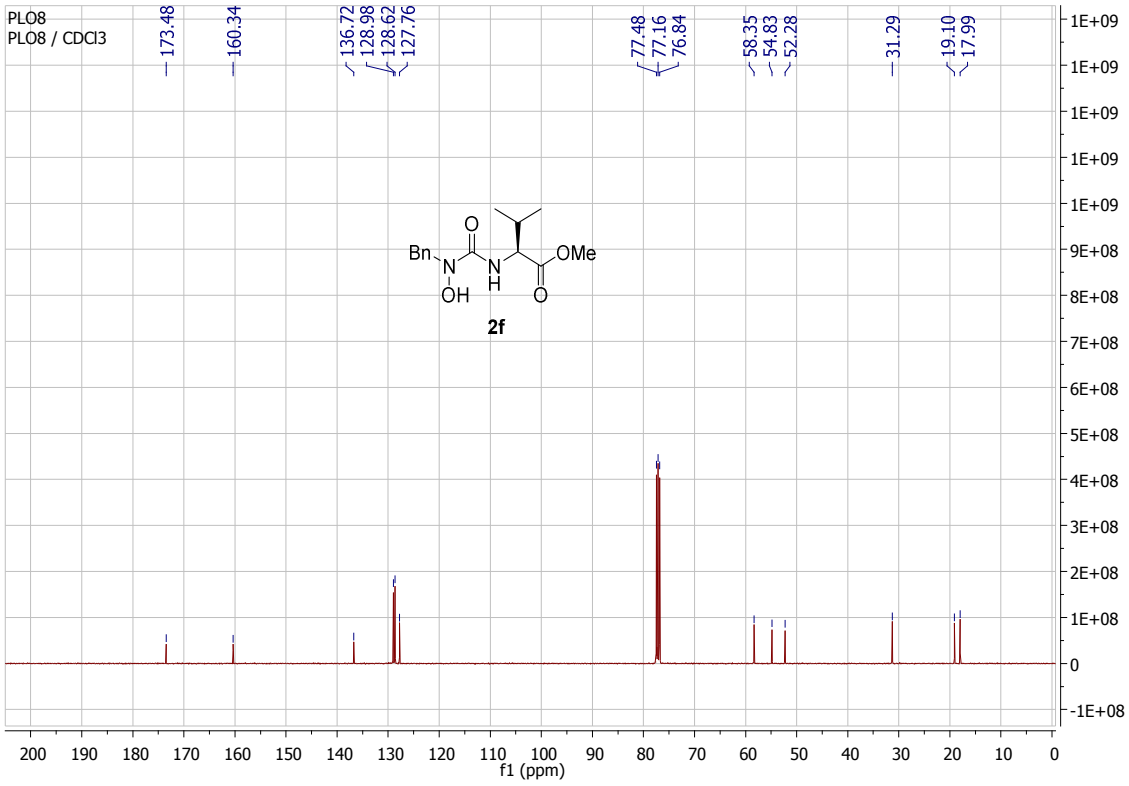
1.14
3.14
3.18
f1 (ppm)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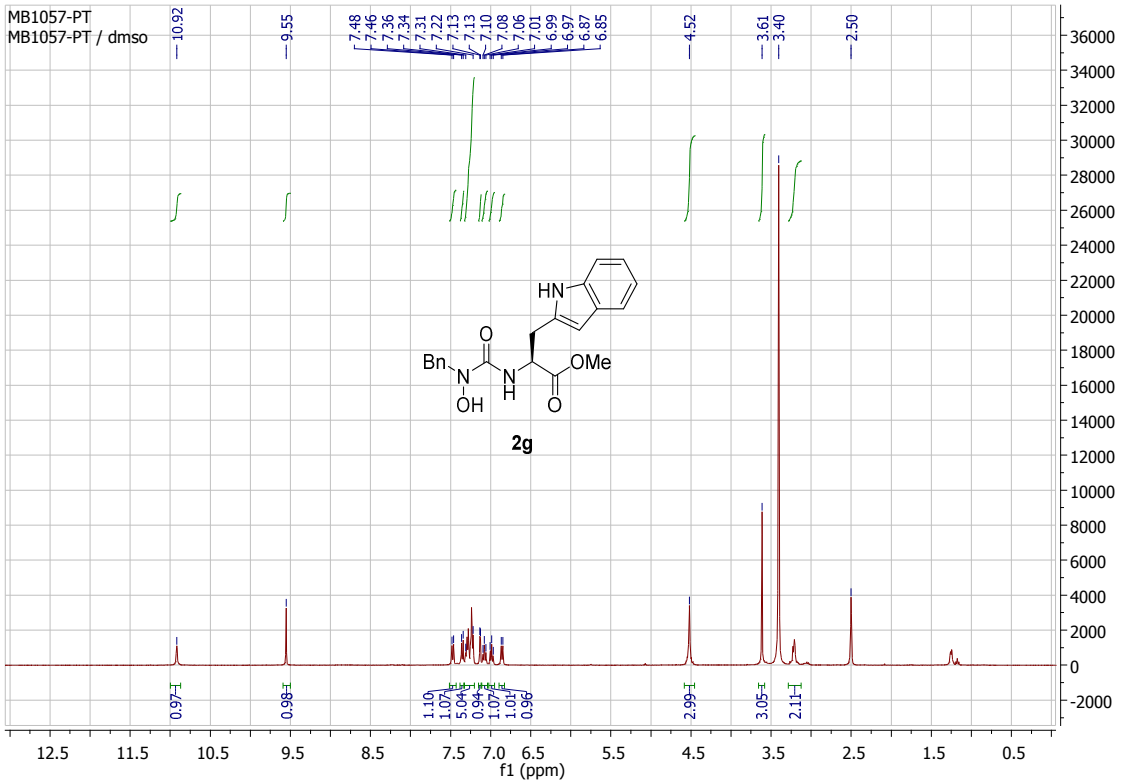
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MB1057-PT / dmso
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3.40
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O
Bn
N
N
H
OMe
OH
O
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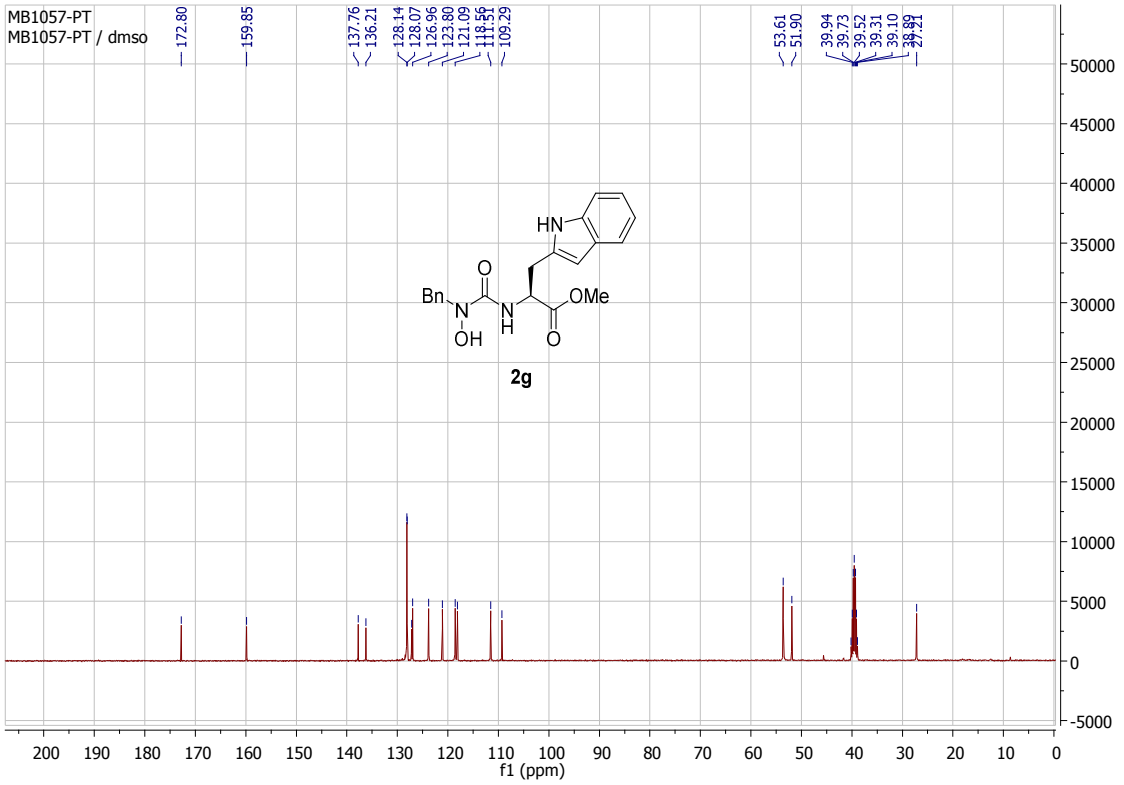
f1 (ppm)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MB1057-PT / dmso
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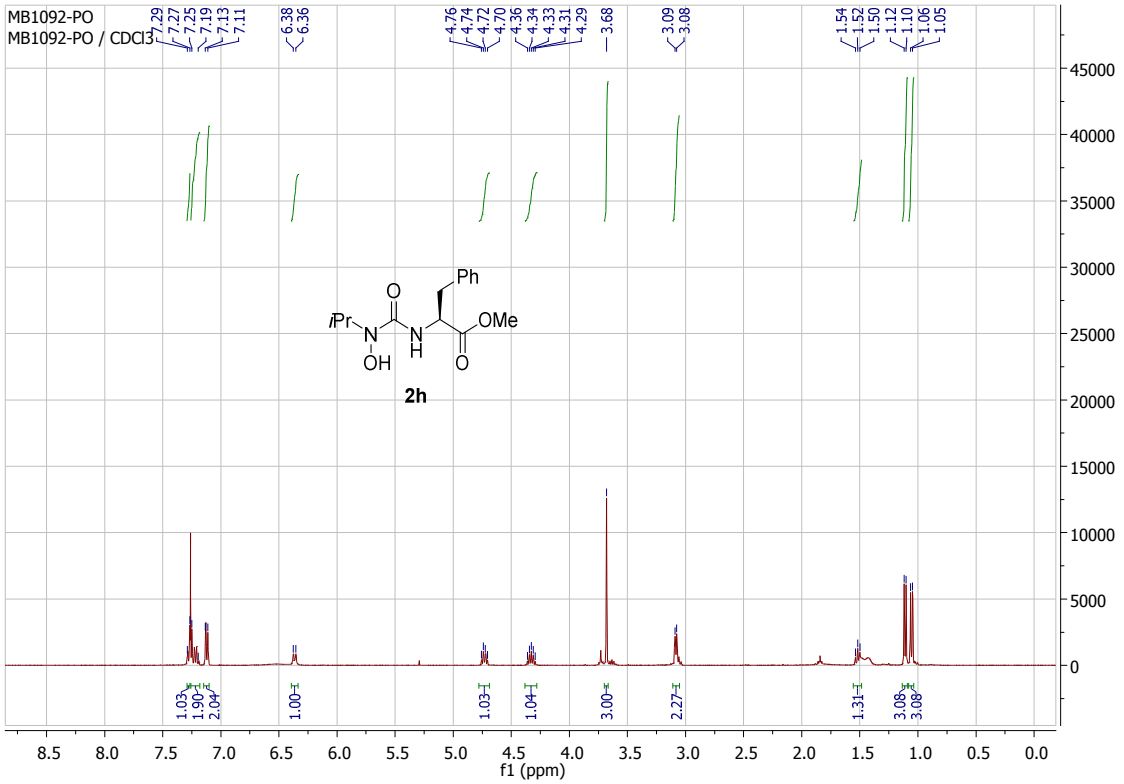
f1 (ppm)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4.31
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1.12
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H
OMe
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2h
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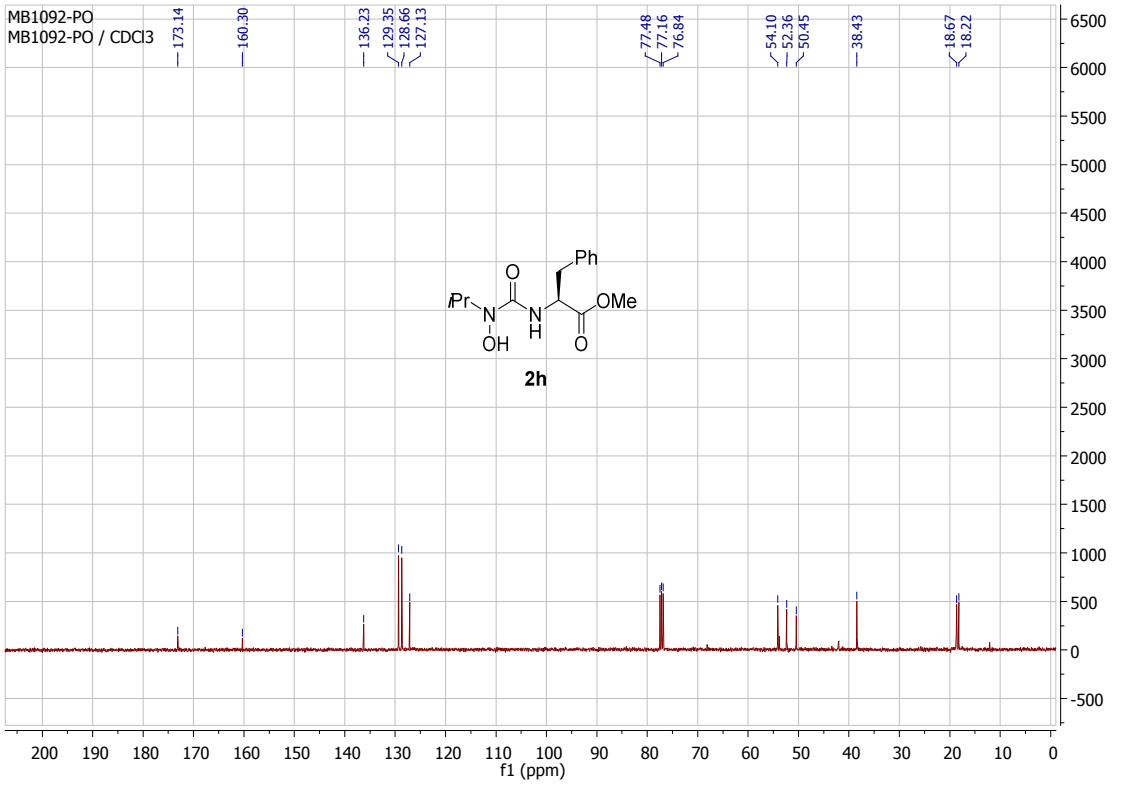
f1 (ppm)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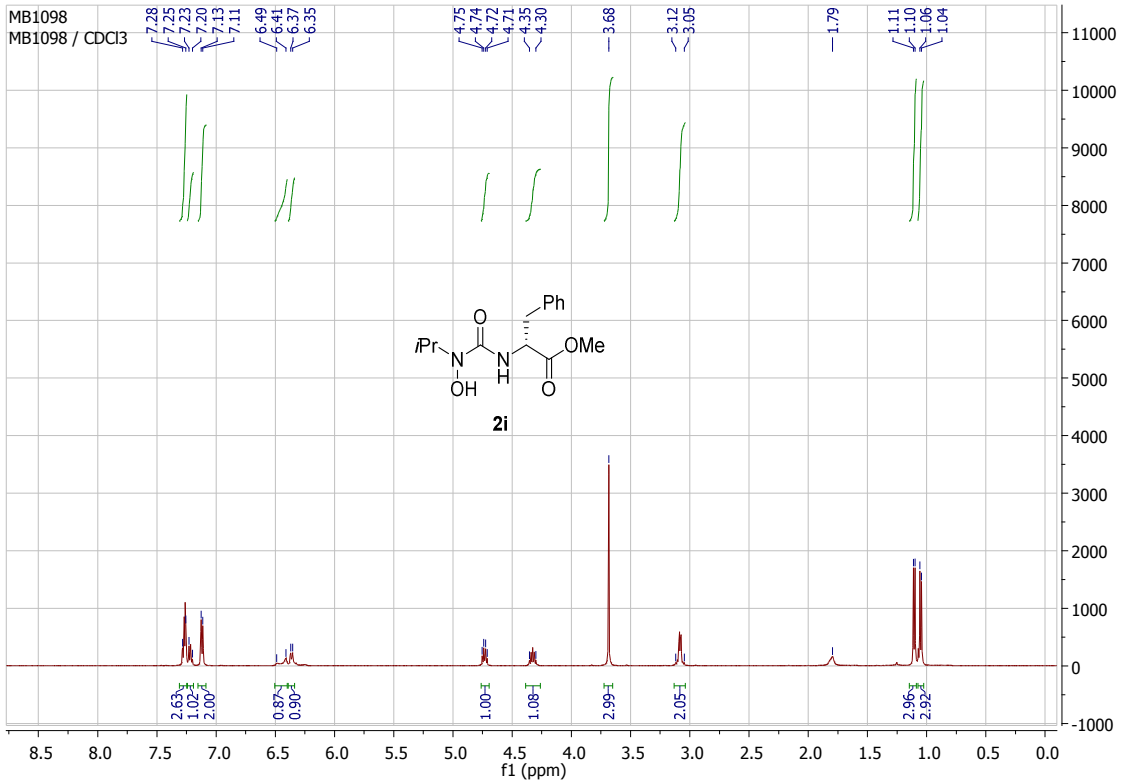
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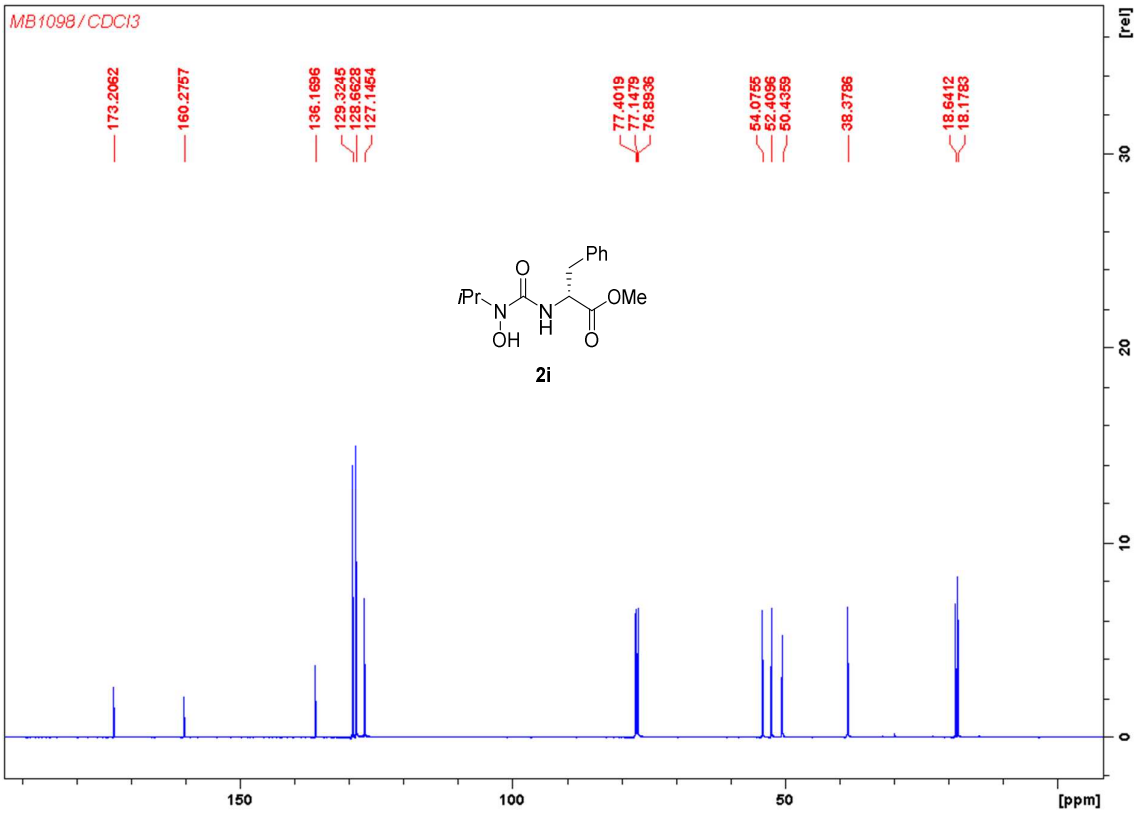
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Ph
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OMe
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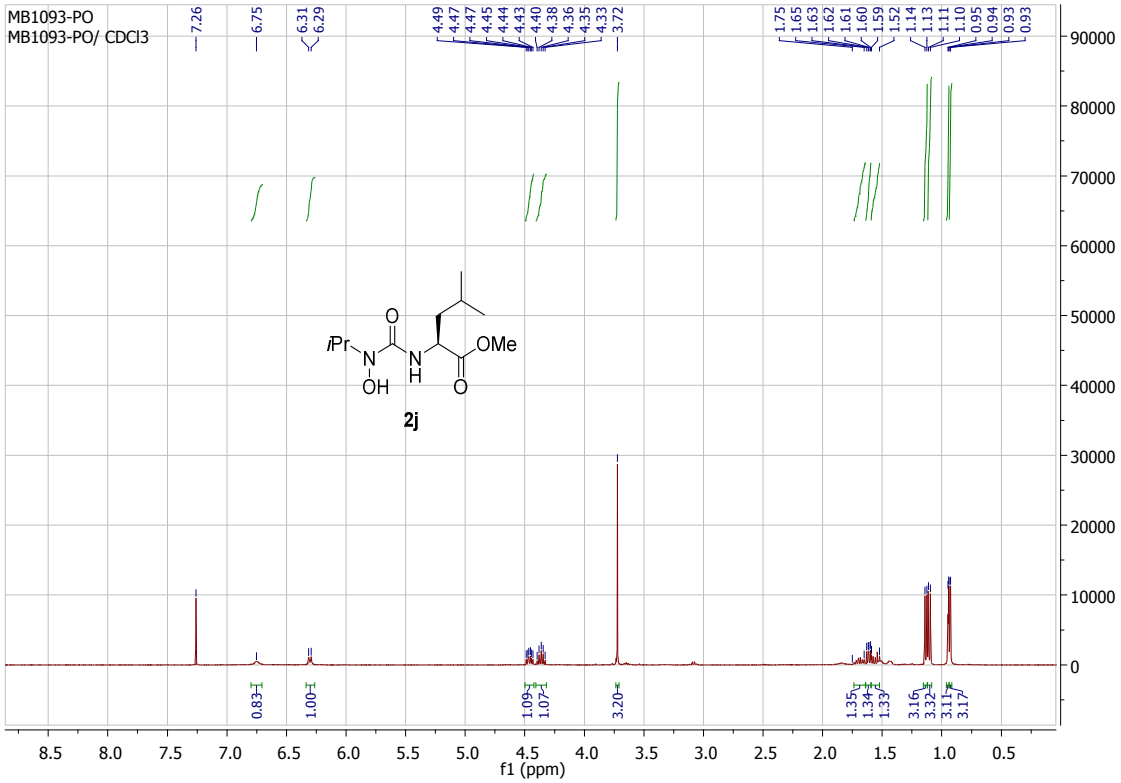
[ppm]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1.10
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N
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OMe
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2j
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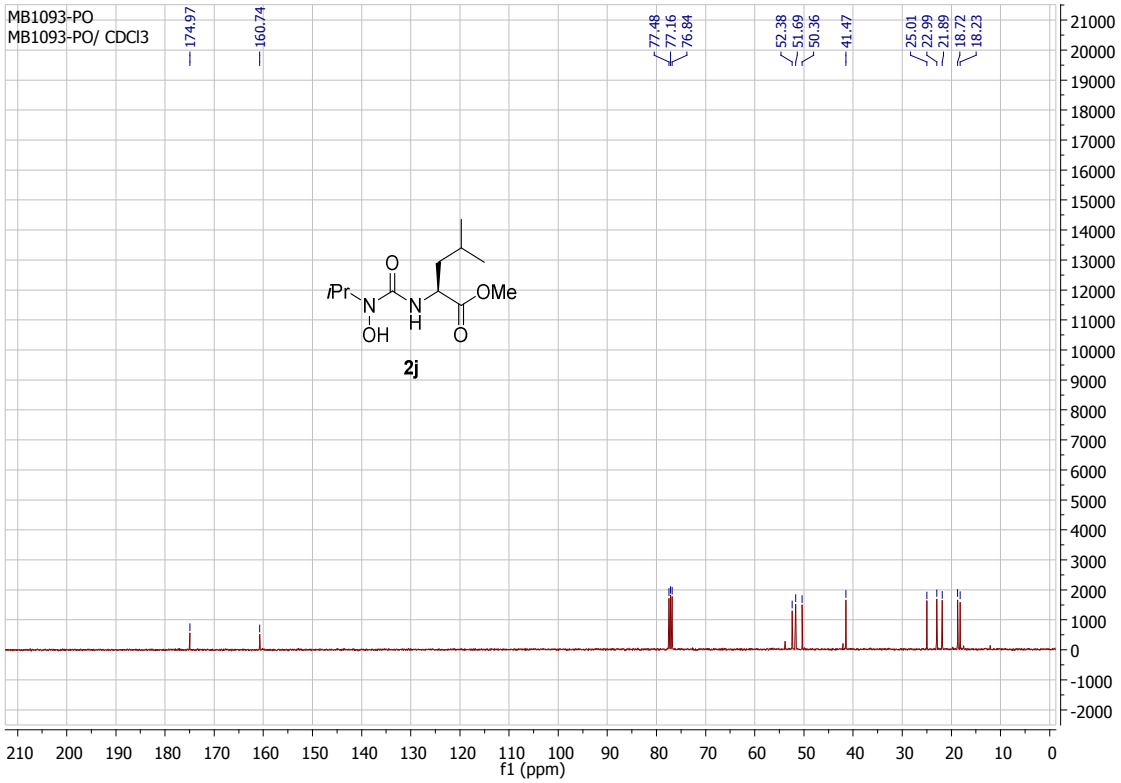
f1 (ppm)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MB1093-PO/ CDCl3
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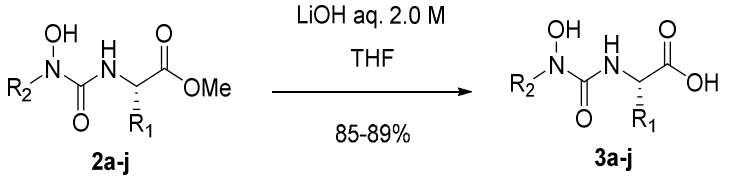
22.99
21.89
18.72
18.23
iPr
N
OH
O
N
H
OMe
O
2j
f1 (ppm)

Synthesis of 2-R_2,HO-aza[X_{AA1}]-OH 3a-j

General experimental procedure B

To a solution of 2-R_2,HO-aza[X_{AA1}]-OMe **2a-j** (1.90 mmol, 1.0 equiv.) in THF (15 mL) was slowly added a 2.0 M aqueous solution of LiOH (2.0 eq). After stirring at room temperature for 2h, the mixture was quenched with a 1.0 M aqueous solution of HCl and extracted with EtOAc (x3). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to afford the desired product in 85-89% yields.



2-Me,HO-aza[Phe]-OH 3a

According to the general procedure B and starting with 2-Me,HO-aza[Phe]-OMe **2a**, the title compound **3a** was obtained as a colorless oil in 90% yield (407.4 mg). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.94 (s, 3H), 3.01-3.11 (m, 2H), 4.40 (dt, 1H, *J*=5.3 Hz, *J*=7.9 Hz), 6.69 (d, 1H, *J*=8.3 Hz), 7.20-7.22 (m, 3H), 7.26-7.30 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 37.1, 38.7, 54.1, 126.7, 128.5, 129.4, 137.7, 160.7, 173.6 ; LC/MS r_t=1.07; ESI-MS$^+$ *m/z* 239.1 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{11}H_{14}N_2O_4$ $[M+H]^+$: 239.1032, found: 239.1033.

2-Me,HO-aza[Ser(Bn)]-OH 3b

According to the general procedure B and starting with 2-Me,HO-aza[Ser(Bn)]-OMe **2b**, the title compound **3b** was obtained as a colourless oil in 90% yield (458.7 mg). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.98 (s, 3H), 3.68 (dd, 1H, *J*=3.4 Hz, *J*=9.5 Hz), 3.81 (dd, 1H, *J*=4.1 Hz, *J*=9.5 Hz), 4.19-4.28 (m, 1H), 4.47 (s, 2H), 6.74 (d, 1H, *J*=7.8 Hz), 7.26-7.36 (m, 5H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 38.9, 54.1, 70.8, 72.6, 127.9, 128.7, 138.7, 160.9, 172.9; LC/MS r_t=1.15; ESI-MS$^+$ *m/z* 269.1 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{12}H_{16}N_2O_5$ $[M+H]^+$: 269.2142, found: 269.2144.

2-Me,HO-aza[Tyr(Bn)]-OH 3c

According to the general procedure B and starting with 2-Me,HO-aza[Tyr(Bn)]-OMe **2c**, the title compound **3c** was obtained as a white solid in 90% yield (588.9 mg). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.92 (s, 3H), 2.97 (dd, 2H, *J*=4.2 Hz, *J*=6.1 Hz), 4.30 (td, 1H, *J*=5.6 Hz, *J*=7.6 Hz), 5.05 (s, 2H), 6.62 (d, 1H, *J*=8.2 Hz), 6.91 (d, 2H, *J*=8.6 Hz), 7.11 (d, 2H, *J*=8.6 Hz), 7.32-7.34 (m, 1H), 7.36-7.40 (m, 2H), 7.43-7.45 (m, 2H), 9.52 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 36.0, 38.5, 54.1, 69.2, 114.6, 127.8, 127.9, 128.5, 129.6, 130.3, 137.2, 157.1, 160.4,

173.5; LC/MS r_t=1.52; ESI-MS$^+$ *m/z* 345.1 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{18}H_{20}N_2O_5$ $[M+H]^+$: 345.1450, found: 345.1453.

2-Me,HO-aza[Cys(Bn)]-OH 3d

According to the general procedure B and starting with 2-Me,HO-aza[Cys(Bn)]-OMe **2d**, the title compound **3d** was obtained as a white solid in 87% yield (470.0 mg). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.84 (dd, 2H, *J*=2.9 Hz, *J*=5.8 Hz), 2.98 (s, 3H), 3.74 (d, 2H, *J*=0.9 Hz), 4.30 (dd, 1H, *J*=6.4 Hz, *J*=13.0 Hz), 6.90 (d, 1H, *J*=7.9 Hz), 7.23-7.34 (m, 5H), 9.59 (b, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 33.9, 36.3, 39.3, 53.5, 127.7, 129.2, 129.8, 139.3, 161.2, 173.5; LC/MS r_t=1.25; ESI-MS$^+$ *m/z* 285.1 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{12}H_{16}N_2O_4S$ $[M+H]^+$: 285.1284, found: 285.1286.

2-Me,HO-aza[Ile]-OH 3e

According to the general procedure B and starting with 2-Me,HO-aza[Ile]-OMe **2e**, the title compound **3e** was obtained as a white solid in 85% yield (329.8 mg). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.84-0.87 (m, 6H), 1.07-1.18 (m, 1H), 1.35-1.43 (m, 1H), 1.74-1.84 (m, 1H), 2.96 (s, 3H), 4.06 (dd, 1H, *J*=5.4 Hz, *J*=8.6 Hz), 6.41 (d, 1H, *J*=8.7 Hz), 9.63 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 11.4, 15.5, 24.8, 37.0, 38.5, 56.9, 160.5, 173.4; LC/MS r_t=0.99; ESI-MS$^+$ *m/z* 205.1 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_8H_{16}N_2O_4$ $[M+H]^+$: 205.1188, found: 205.1190.

2-Bn,HO-aza[Val]-OH 3f

According to the general procedure B and starting with 2-Bn,HO-aza[Val]-OMe **2f**, the title compound **3f** was obtained as a colourless oil in 85% yield (430.1 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (d, 3H, *J*=6.9 Hz), 0.94 (d, 3H, *J*=6.8 Hz), 2.10-2.18 (m, 1H), 3.70 (s, 3H), 4.37 (dd, 1H, *J*=5.2 Hz, *J*=8.9 Hz), 4.64 (d, 2H, *J*=2.0 Hz), 6.38 (d, 1H, *J*=8.8 Hz), 6.70 (b, 1H), 7.27-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.5, 36.0, 36.9, 53.6, 127.5, 128.9, 129.4, 138.6, 159.2, 168.7; LC/MS r_t=1.28; ESI-MS$^+$ *m/z* 267.2 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{13}H_{18}N_2O_4$ $[M+H]^+$: 267.1345, found: 267.1344.

2-Bn,HO-aza[Trp]-OH 3g

According to the general procedure B and starting with 2-Bn,HO-aza[Trp]-OMe **2g**, the title compound **3g** was obtained as a white solid in 91% yield (611.0 mg). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.20 (d, 2H, *J*=5.9 Hz), 4.46 (dd, 1H, *J*=6.1 Hz, *J*=13.8 Hz), 4.52 (s, 2H), 6.70 (d, 1H, *J*=8.0 Hz), 6.97 (t, 1H, *J*=7.4 Hz), 7.06 (t, 1H, *J*=7.5 Hz), 7.10 (d, 1H, *J*=1.8 Hz), 7.20-7.30 (m, 5H), 7.34 (d, 1H, *J*=8.0 Hz), 7.52 (d, 1H, *J*=7.8 Hz), 9.50 (s, 1H), 10.88 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 27.3, 53.4, 53.7, 109.6, 111.4, 118.4, 118.5, 121.0, 123.7, 126.9, 127.4, 128.1, 128.1, 136.2, 137.9, 159.9, 173.8; LC/MS r_t=1.43; ESI-MS$^+$: m/z 354.2 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{19}H_{19}N_3O_4$ $[M+H]^+$: 354.1454, found: 354.1454.

2-*i*Pr,HO-aza[Phe]-OH 3h

According to the general procedure B and starting with 2-*i*Pr,HO-aza[Phe]-OMe **2h**, the title compound **3h** was obtained as a white solid in 87% yield (440.2 mg). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.93 (d, 3H, *J*=6.6 Hz), 0.98 (d, 3H, *J*=6.6 Hz), 2.99-3.10 (m, 2H), 4.09-4.16 (m, 1H), 4.36-4.41 (m, 1H), 6.70 (d, 1H, *J*=8.3 Hz), 7.18-.7.21 (m, 3H), 7.25-7.28 (m, 2H), 8.95 (b, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.3, 18.5, 36.9, 49.1, 53.8, 126.4, 128.2, 129.2, 137.6, 160.3, 173.4; LC/MS r_t=1.17; ESI-MS$^+$: m/z 266.9 $[M+H]^+$, 289.1 $[M+Na]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{13}H_{18}N_2O_4$ $[M+H]^+$: 267.1345, found: 267.1344.

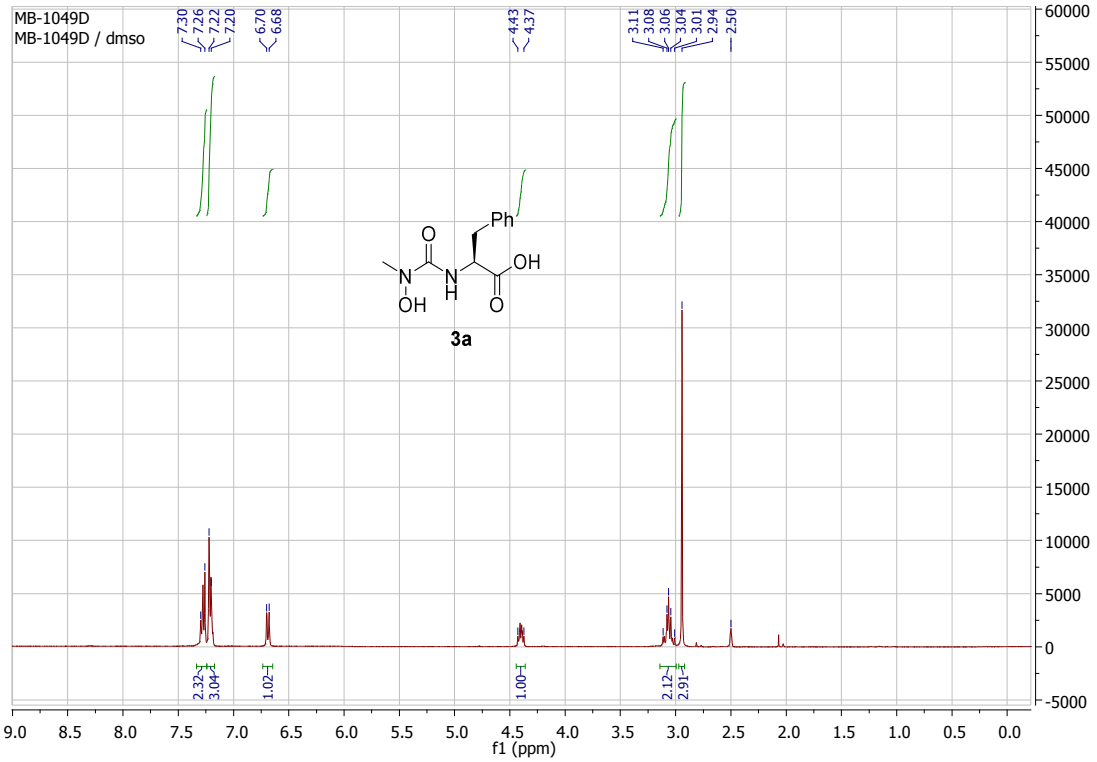
2-*i*Pr,HO-aza[Phe]-OH 3i

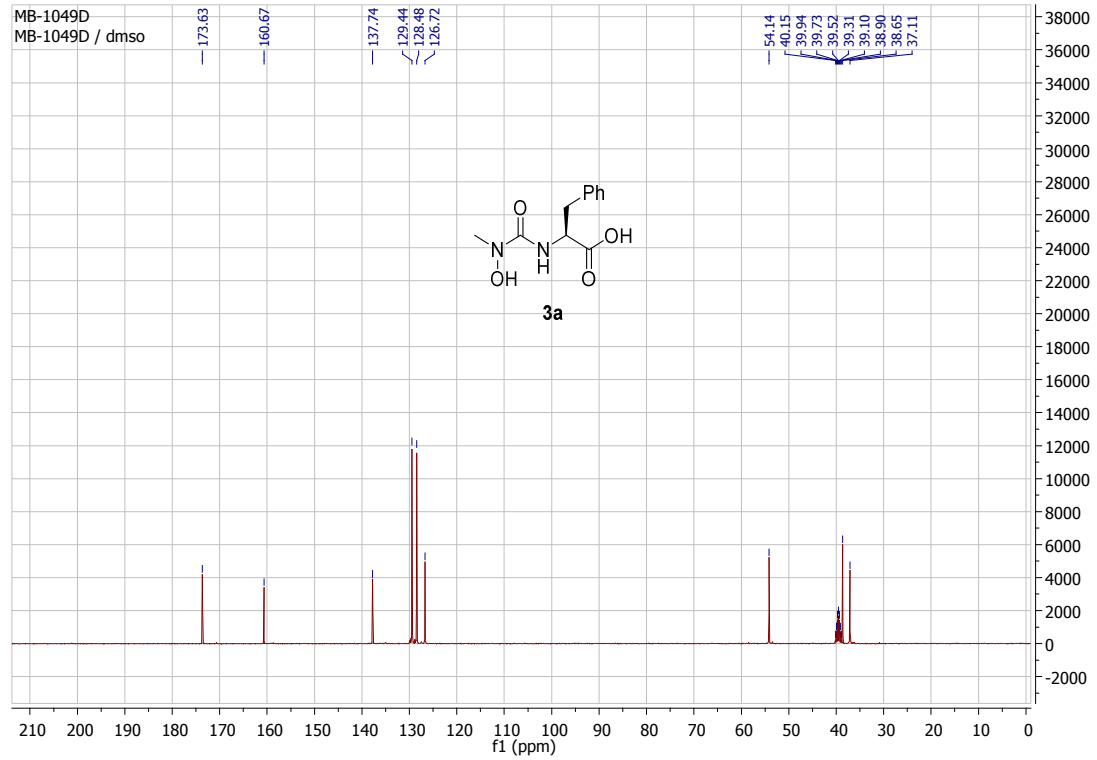
According to the general procedure B and starting with 2-*i*Pr,HO-aza[(D)-Phe]-OMe **2i**, the title compound **3i** was obtained as a white solid in 87% yield (440.2 mg). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.93 (d, 3H, *J*=6.6 Hz), 0.98 (d, 3H, *J*=6.6 Hz), 3.00-3.10 (m, 2H), 4.09-4.16 (m, 1H), 4.36-4.42 (m, 1H), 6.70 (d, 1H, *J*=8.4 Hz), 7.18-.7.21 (m, 3H), 7.25-7.29 (m, 2H), 8.94 (b, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.3, 18.5, 36.8, 49.1, 53.7, 126.4, 128.2, 129.2, 137.6, 160.3, 173.4; LC/MS r_t=1.17; ESI-MS$^+$: m/z 266.9 $[M+H]^+$, 289.1 $[M+Na]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{13}H_{18}N_2O_4$ $[M+H]^+$: 267.1345, found: 267.1344.

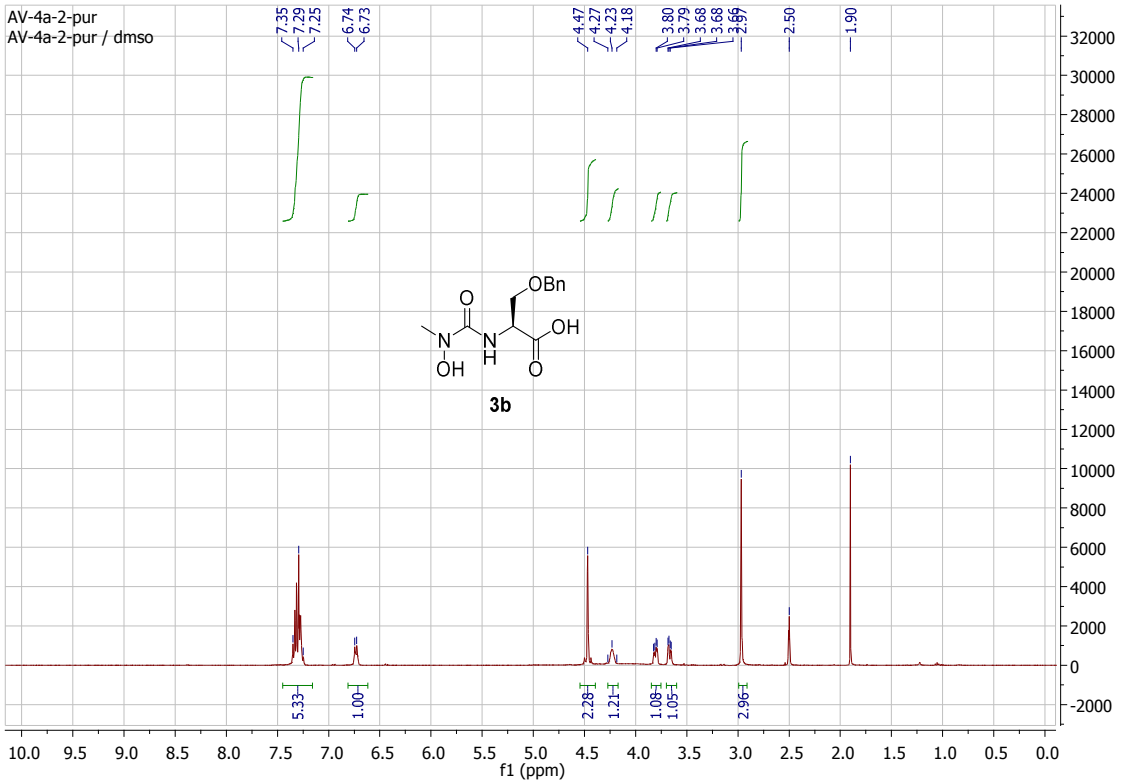
2-*i*Pr,HO-aza[Leu]-OH 3j

According to the general procedure B and starting with 2-*i*Pr,HO-aza[Leu]-OMe **2j**, the title compound **3j** was obtained as a white solid in 92% yield (406.0 mg). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.86 (d, 3H, *J*=6.4 Hz), 0.88 (d, 3H, *J*=6.3 Hz), 0.99 (d, 3H, *J*=2.2 Hz), 1.00 (d, 3H, *J*=2.2 Hz), 1.45-1.53 (m, 1H), 1.59-1.66 (m, 1H), 4.12-4.20 (m, 2H), 6.71 (d, 1H, *J*=8.6 Hz), 8.95 (b, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.3, 18.5, 21.4, 22.9, 24.4, 40.4, 49.1, 50.9, 160.5, 174.6; LC/MS r_t=1.11; ESI-MS$^+$: *m/z* 232.8 $[M+H]^+$, 255.1 $[M+Na]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{20}H_{20}N_2O_4$ $[M+H]^+$: 233.1501, found: 233.1502.

^{1}H and ^{13}C NMR spectra of HO-aza[X_{AA1}]-OH



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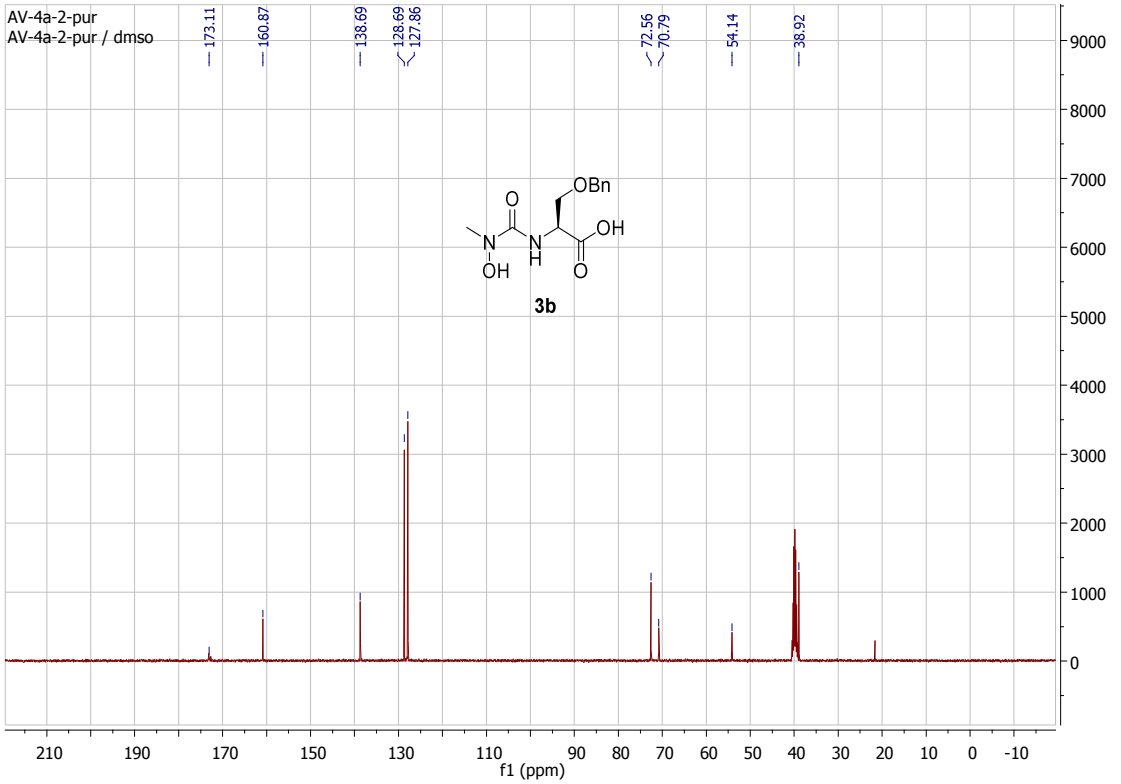
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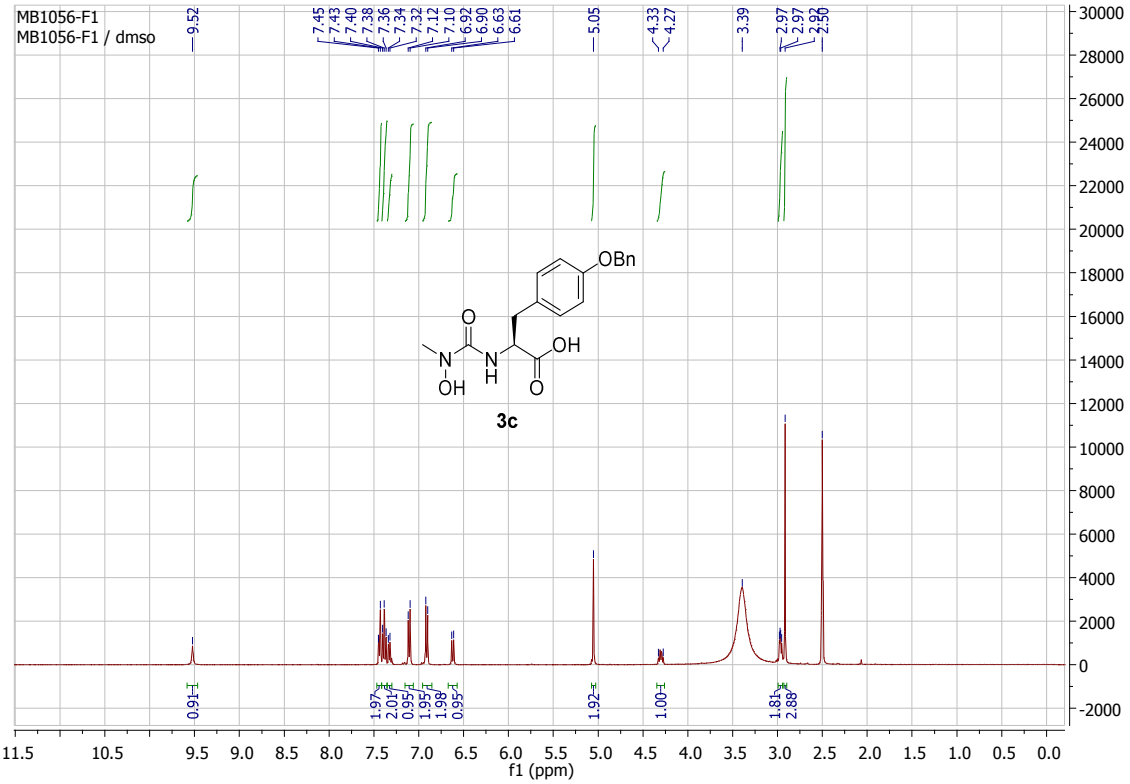
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MB1056-F1 / dmso
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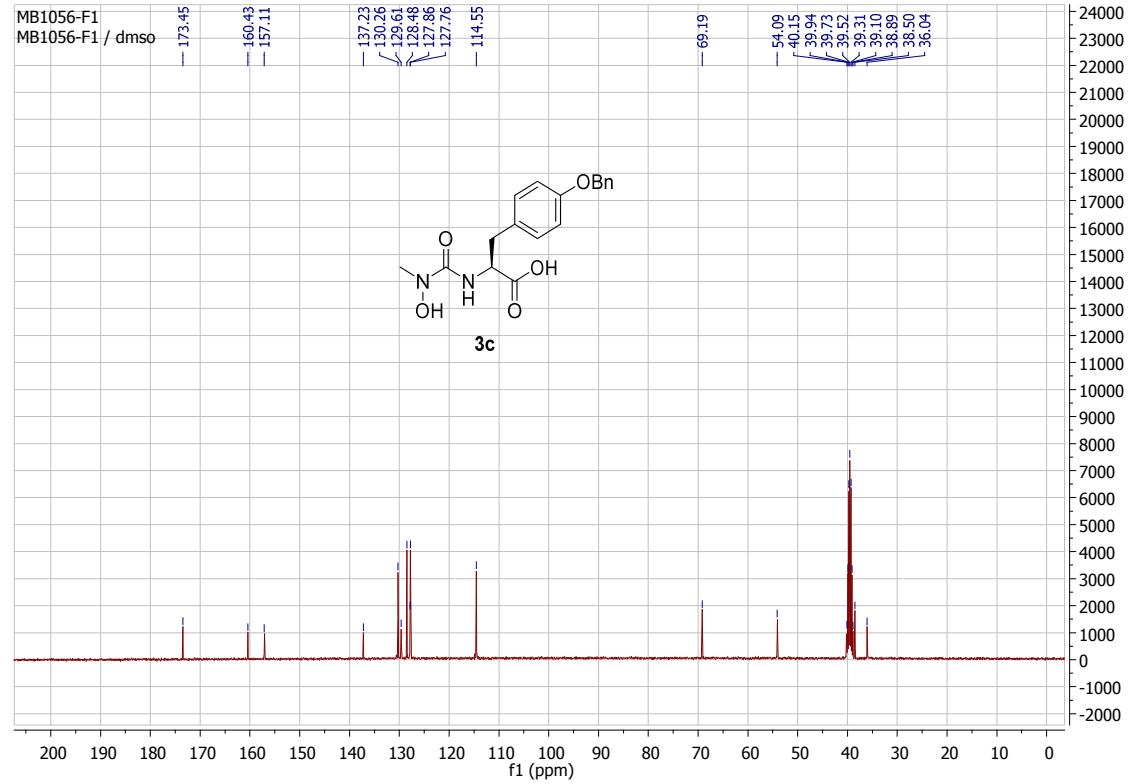
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MB1056-F1 / dmso
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40.15
39.94
39.73
39.52
39.31
39.10
38.89
38.50
36.04
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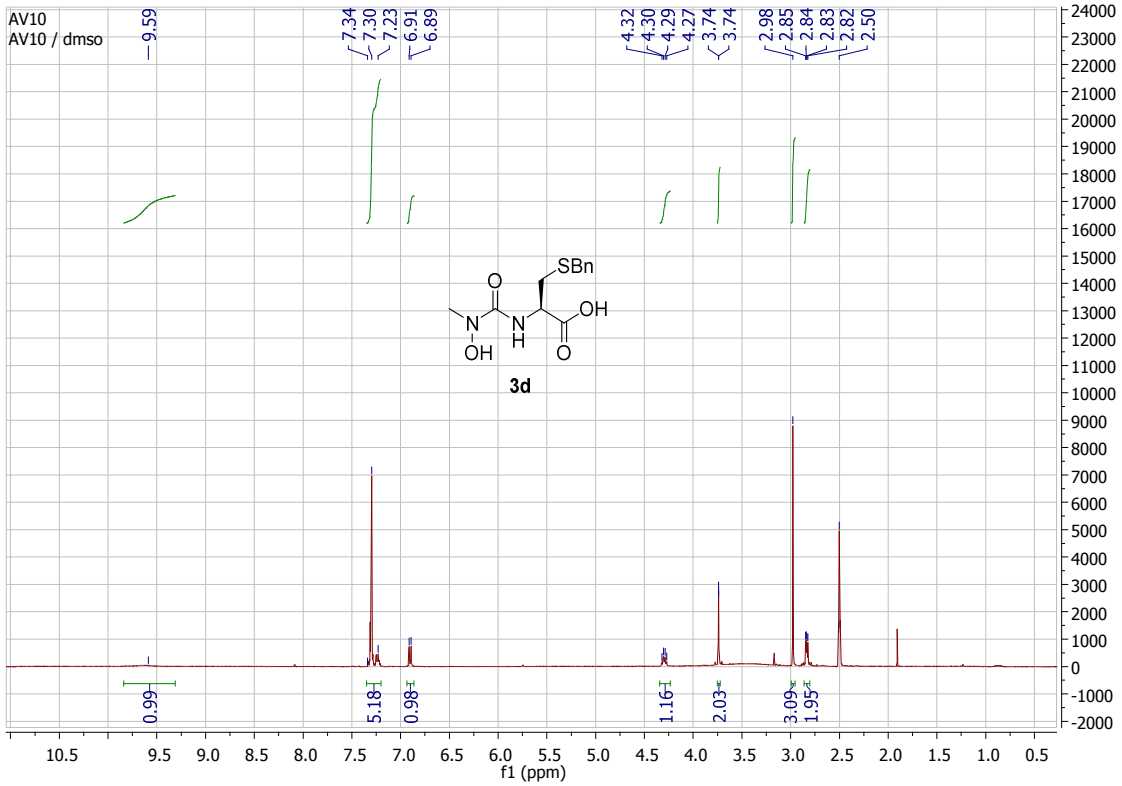
O
N
OH
N
H
OH
O
3c
f1 (ppm)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AV10 / dmso
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7.34
7.30
7.23
6.91
6.89
4.32
4.30
4.29
4.27
3.74
3.74
2.98
2.85
2.84
2.83
2.82
2.50
SBn
OH
N
H
N
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O
O
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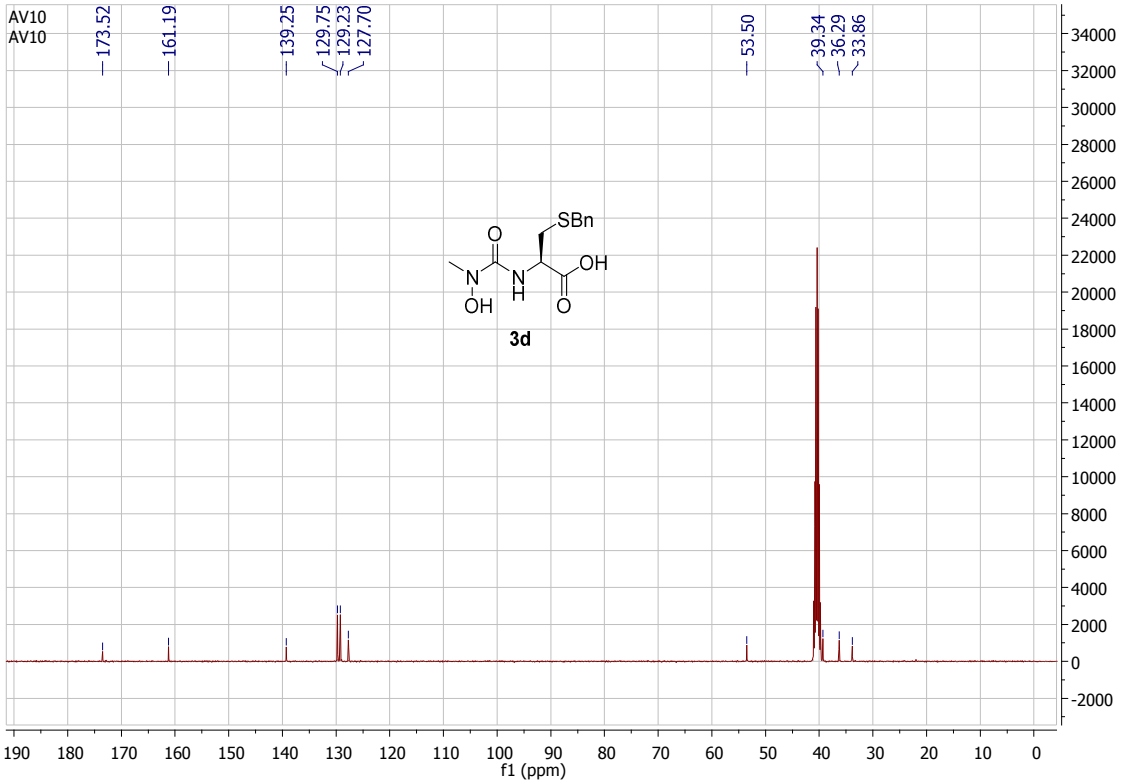
1.16
2.03
3.09
1.95
f1 (ppm)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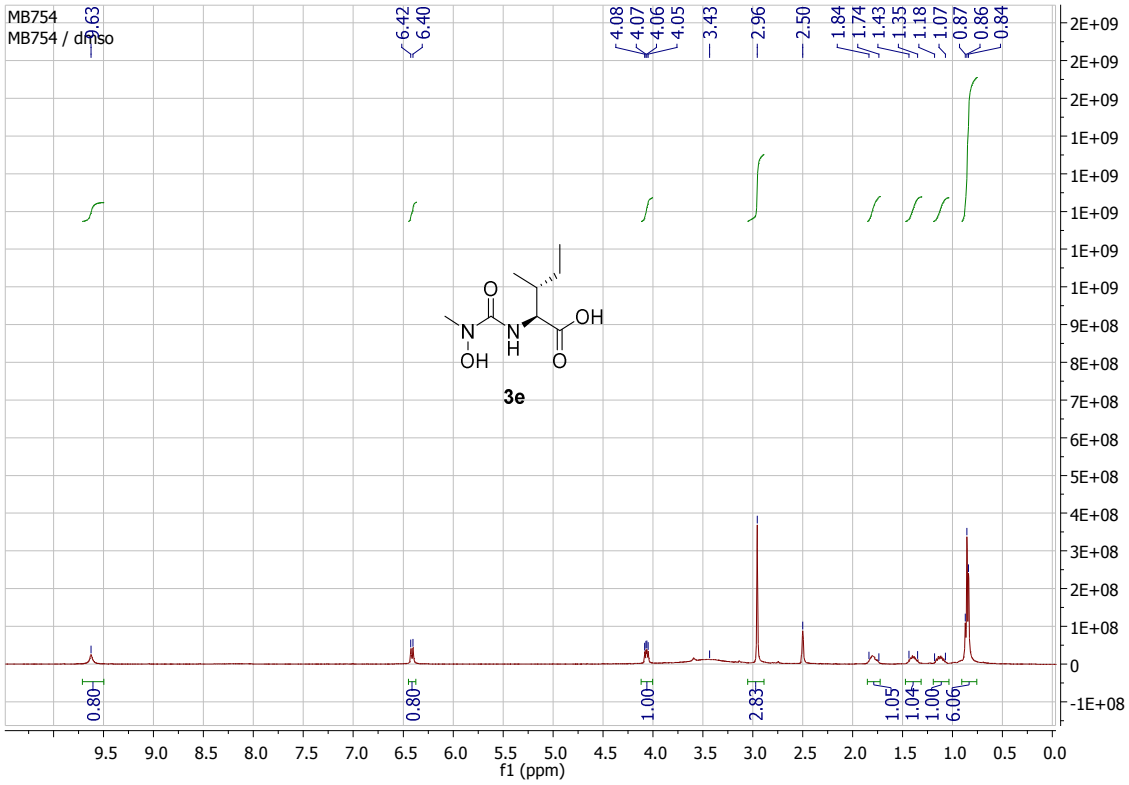
N
H
N
OH
O
O
3d
f1 (ppm)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4.07
4.06
4.05
3.43
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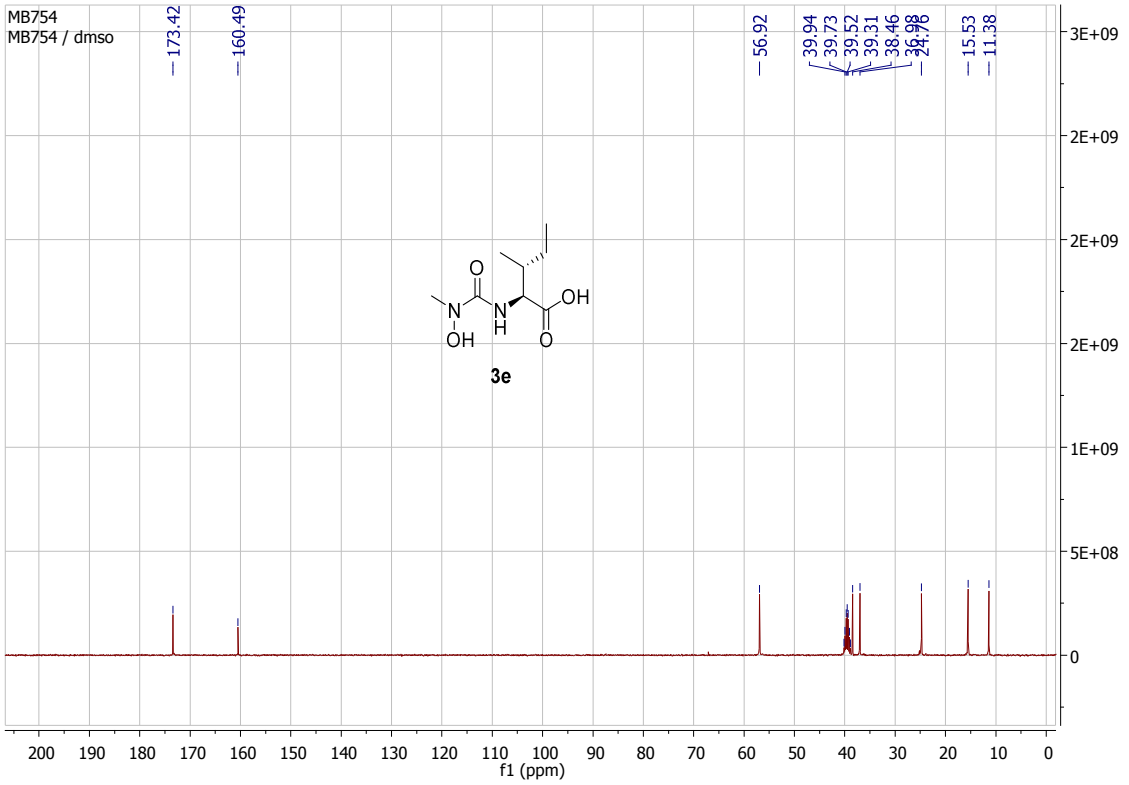
2.50
1.84
1.74
1.43
1.35
1.18
1.07
0.87
0.86
0.84
0.80
0.80
1.00
2.83
1.05
1.04
1.00
6.06
f1 (ppm)

3e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MB754 / dmso
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39.52
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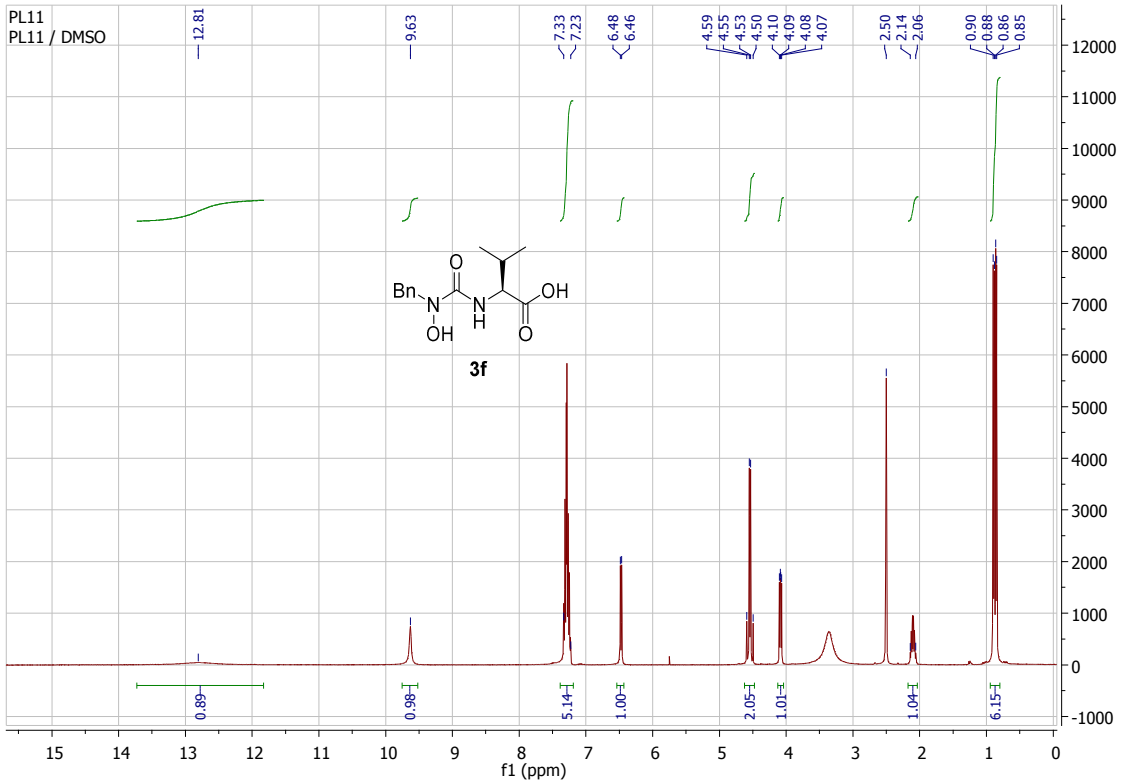
38.46
15.53
11.38
f1 (ppm)

3e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PL11 / DMSO
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7.23
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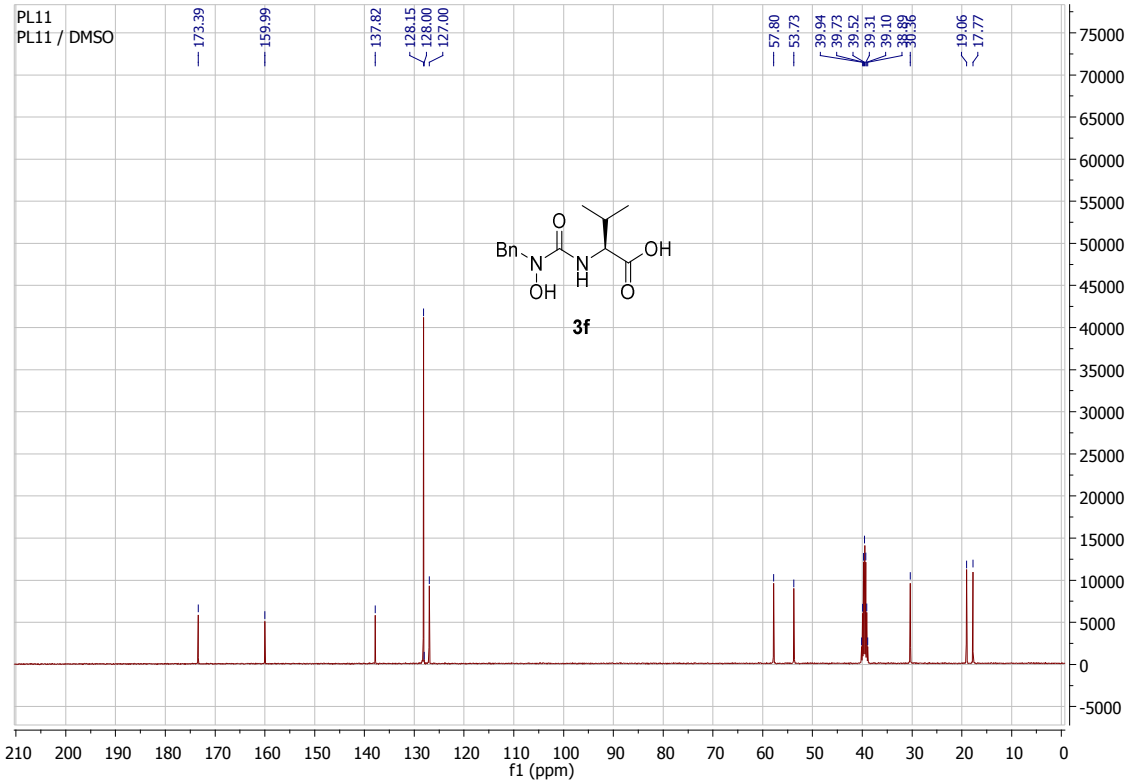
6.46
4.59
4.55
4.53
4.50
4.10
4.09
4.08
4.07
2.50
2.14
2.06
0.90
0.88
0.86
0.85
0.89
0.98
5.14
1.00
2.05
1.01
1.04
6.15
Bn
N
OH
O
N
H
OH
O
3f
f1 (ppm)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PL11 / DMSO
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137.82
128.15
128.00
127.00
57.80
53.73
39.94
39.73
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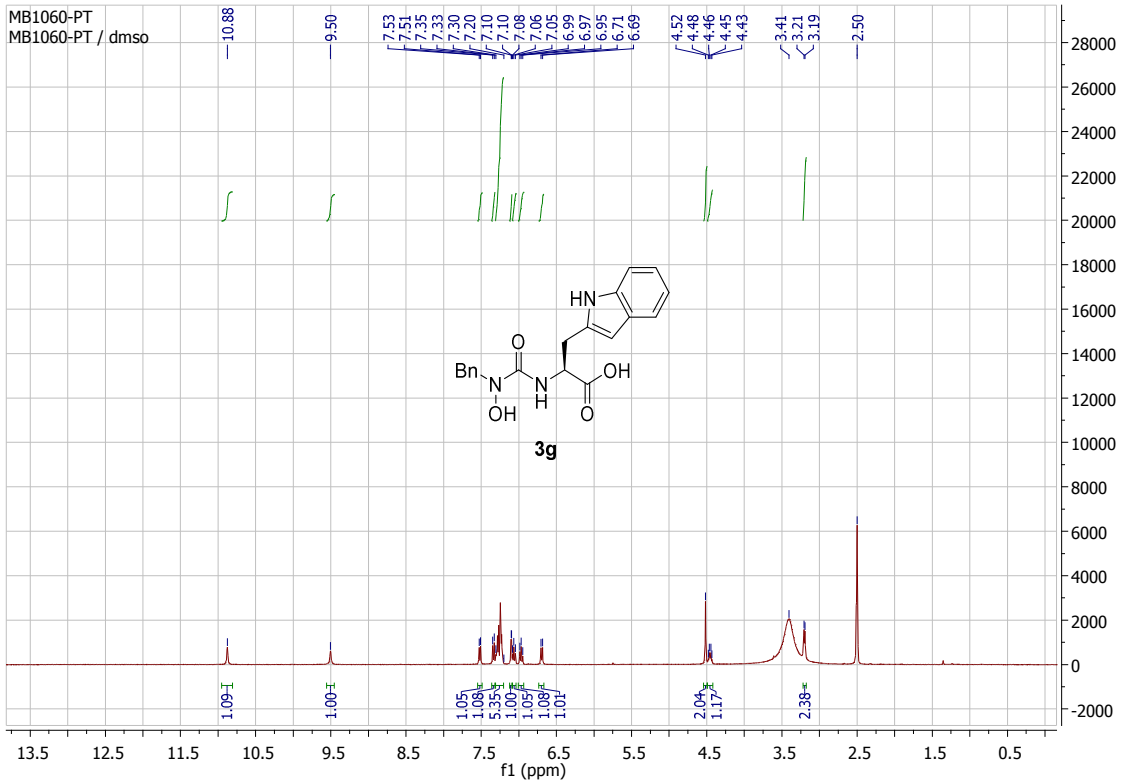
OH
O
N
H
OH
O
3f
f1 (ppm)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MB1060-PT / dmso
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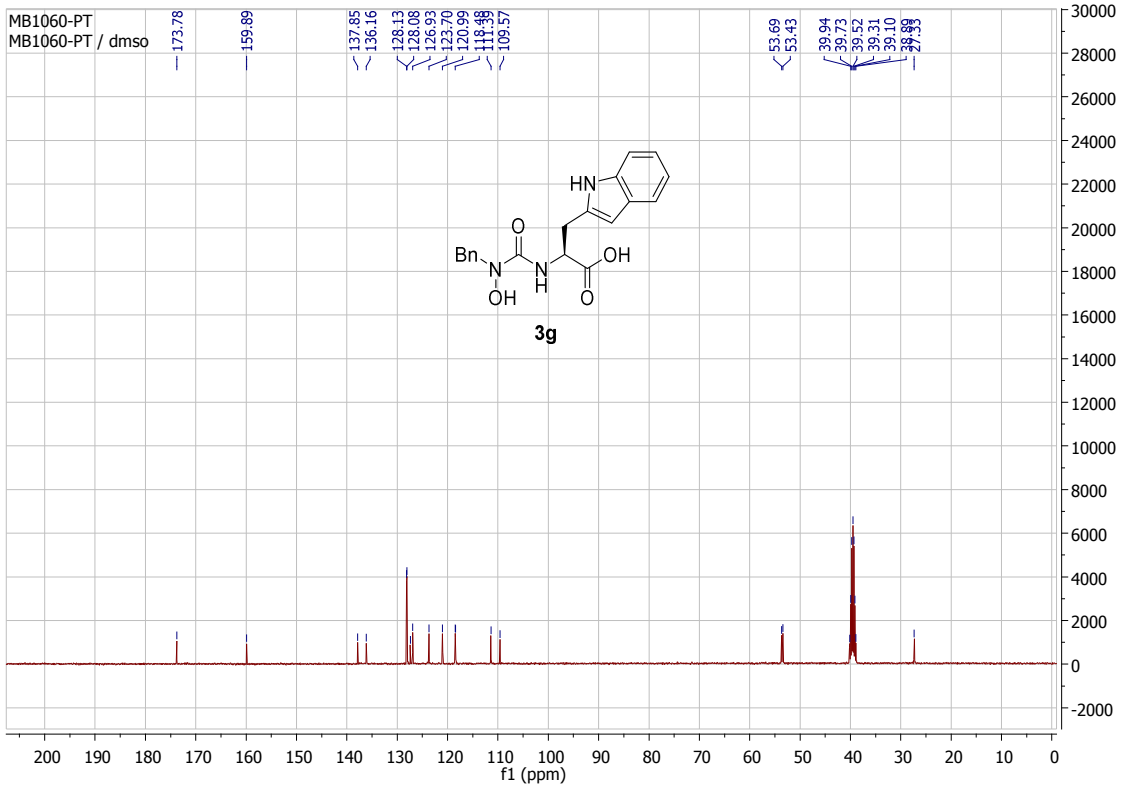
9.50
7.53
7.51
7.35
7.33
7.30
7.20
7.10
7.08
7.06
7.05
6.99
6.97
6.95
6.71
6.69
4.52
4.48
4.46
4.45
4.43
3.41
3.21
3.19
2.50
HN
O
Bn
N
OH
N
H
OH
O
3g
1.09
1.00
1.05
1.08
5.35
1.00
1.05
1.09
1.01
2.04
1.17
2.38
f1 (ppm)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MB1060-PT / dmso
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137.85
136.16
128.13
128.08
126.93
123.70
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53.69
53.43
39.94
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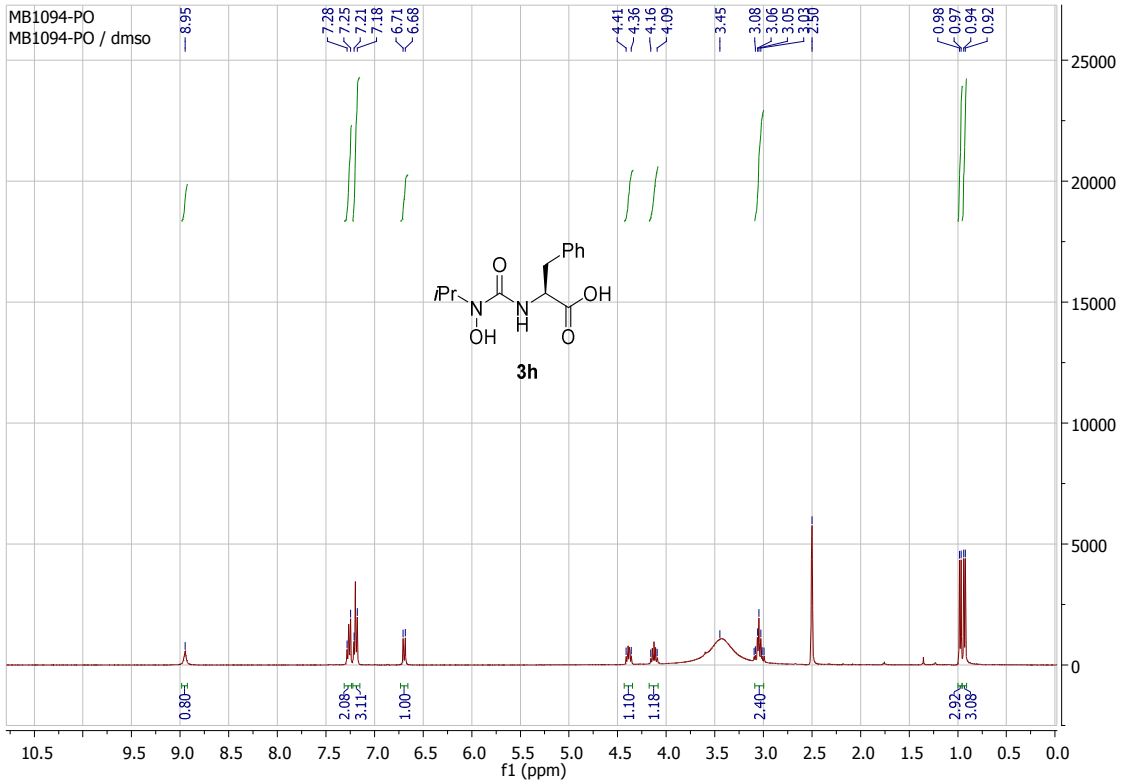
N
OH
N
H
OH
O
3g
f1 (ppm)


MB1094-PO
MB1094-PO / dmso
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7.28
7.25
7.21
7.18
6.71
6.68
4.41
4.36
4.16
4.09
3.45
3.08
3.06
3.05
3.03
2.50
0.98
0.97
0.94
0.92
Ph
O
iPr
N
OH
N
H
OH
O
3h
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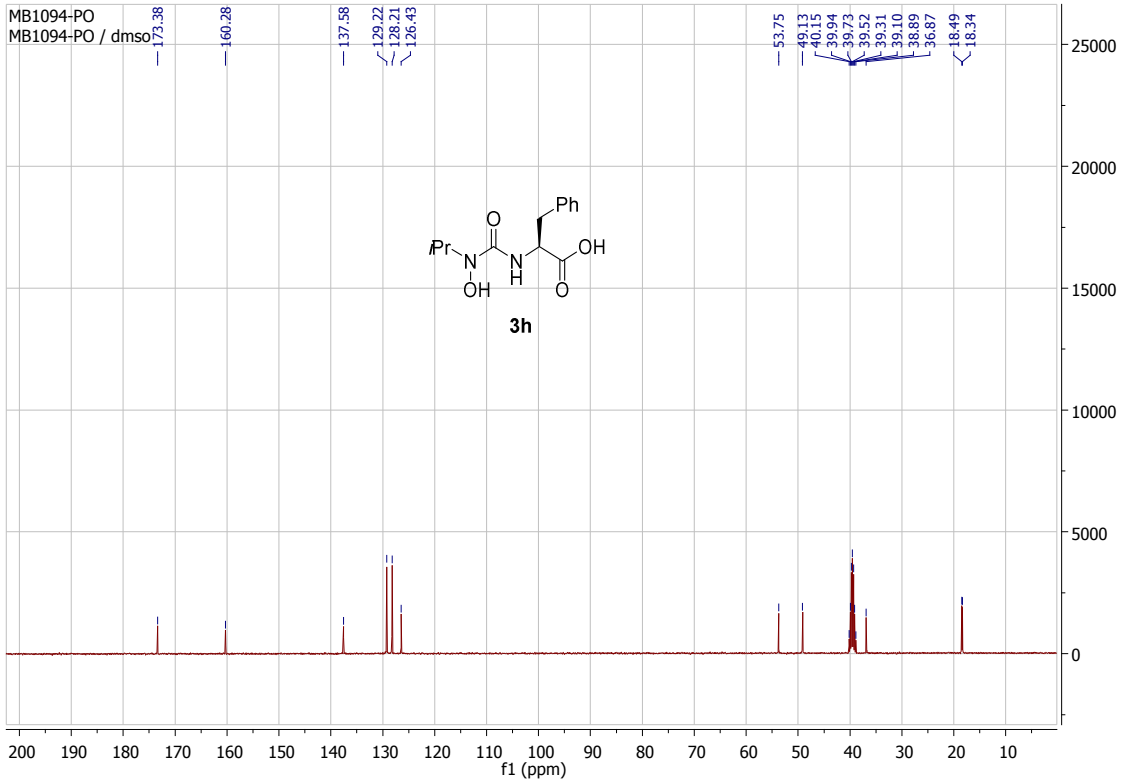
2.08
3.11
1.00
1.10
1.18
2.40
2.92
3.08
f1 (ppm)


MB1094-PO
MB1094-PO / dmso
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137.58
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128.21
126.43
53.75
49.13
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39.73
39.52
39.31
39.10
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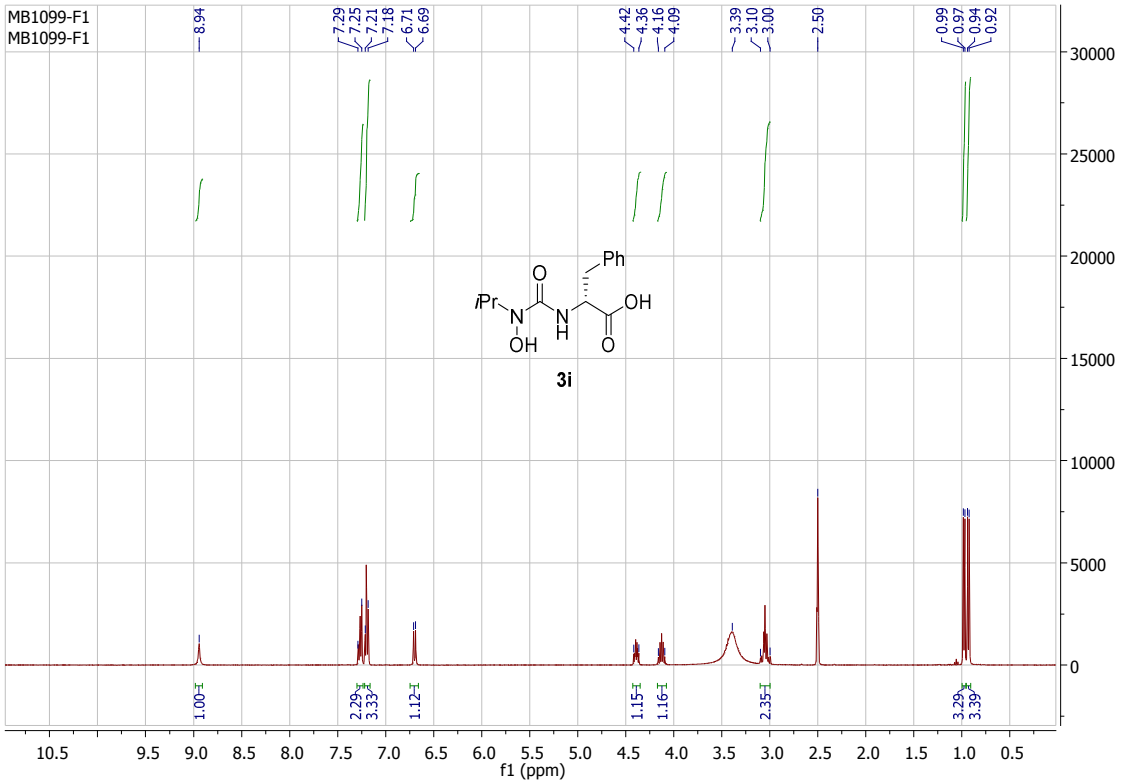
N
OH
N
H
OH
O
3h
f1 (ppm)


MB1099-F1
MB1099-F1
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7.29
7.25
7.21
7.18
6.71
6.69
4.42
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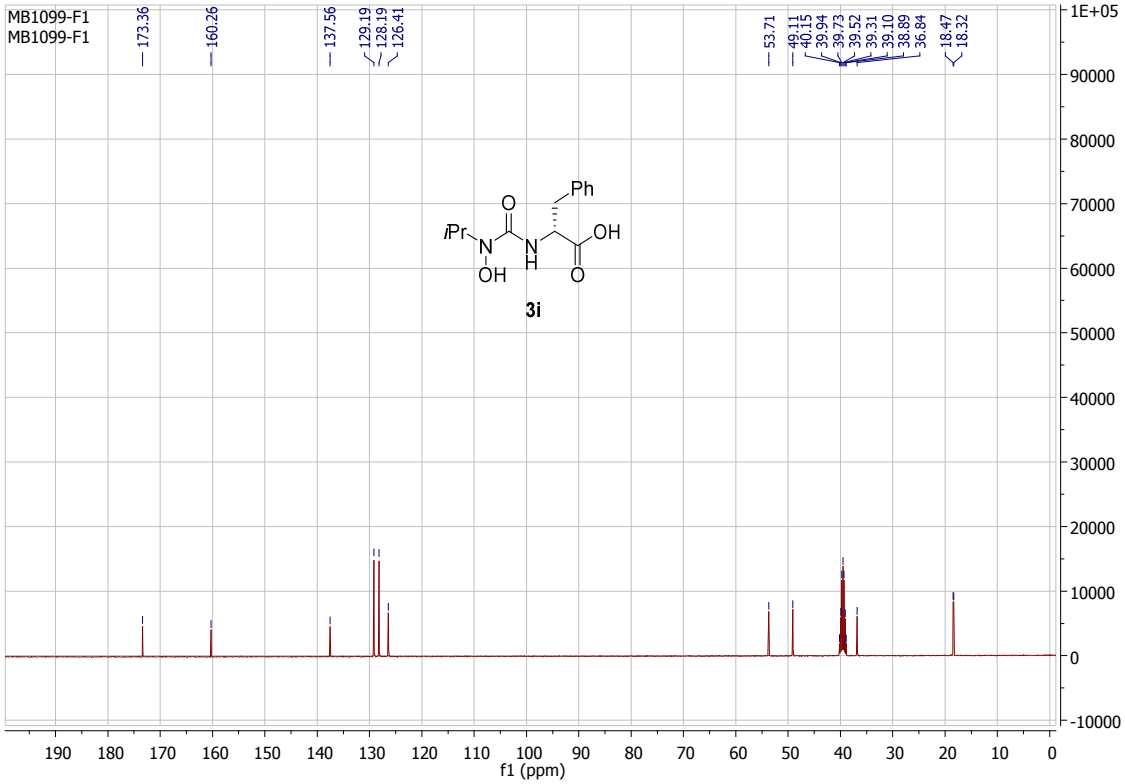
4.16
4.09
3.39
3.10
3.00
2.50
0.99
0.97
0.94
0.92
Ph
O
iPr
N
OH
N
H
OH
O
3i
1.00
2.29
3.33
1.12
1.15
1.16
2.35
3.29
3.39
f1 (ppm)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MB1099-F1
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160.26
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126.41
53.71
49.11
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39.73
39.52
39.31
39.10
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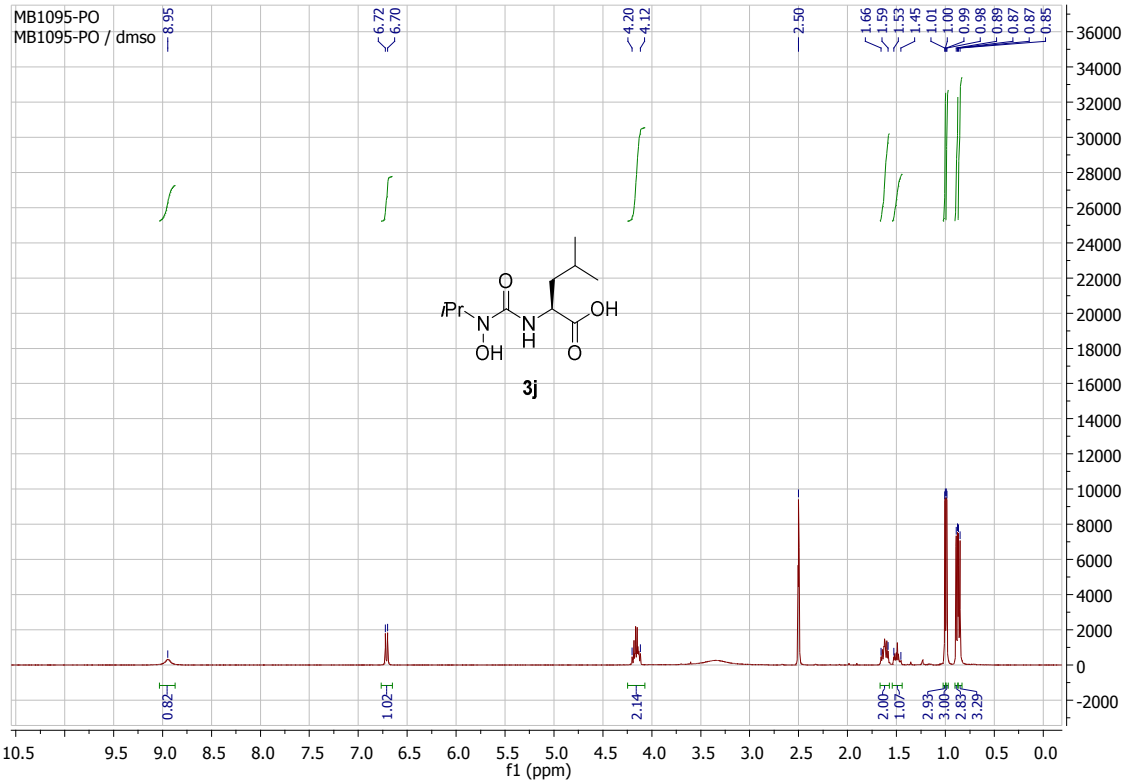
N
OH
N
H
OH
O
3i
f1 (ppm)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MB1095-PO / dmso
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4.20
4.12
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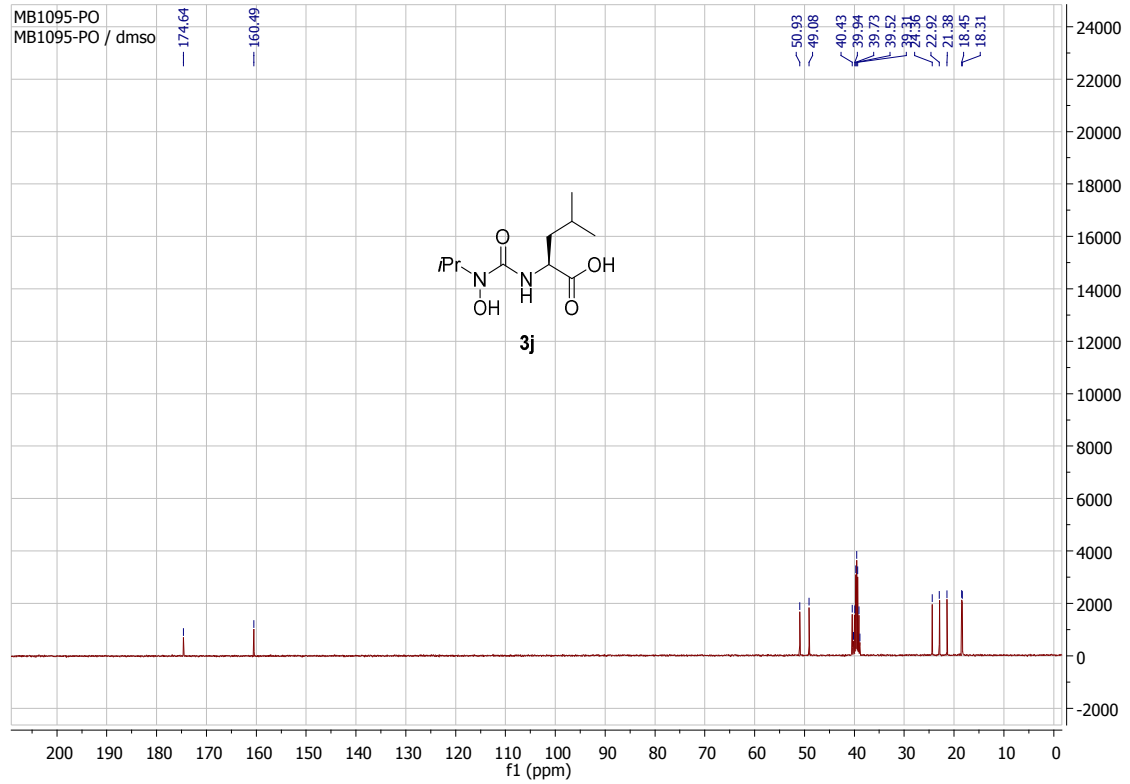
1.66
1.59
1.53
1.45
1.01
1.00
0.99
0.98
0.89
0.87
0.87
0.85
0.82
1.02
2.14
2.00
1.07
2.93
3.00
2.83
3.29
iPr
N
OH
O
N
H
OH
O
3j
f1 (ppm)


MB1095-PO
MB1095-PO / dmso
174.64
160.49
50.93
49.08
40.43
39.94
39.73
39.52
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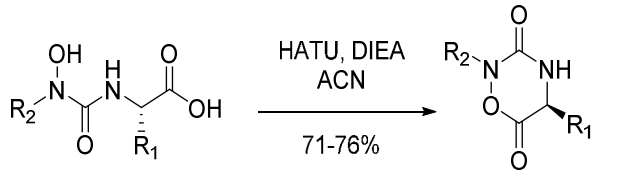
39.10
38.89
38.68
38.47
38.26
22.92
21.38
18.45
18.31
iPr
N
OH
O
N
H
OH
O
3j
f1 (ppm)

Synthesis of 1,2-R_2,4-Oxd[X_{AA1}] 4a-j

General experimental procedure C

To a solution of 2-R_2,HO-aza[X_{AA1}]-OH **3a-j** (1.60 mmol, 1.0 equiv.) in anhydrous ACN (20 mL) were added DIEA (4.80 mmol, 3.0 equiv.) and then solid HATU (1.92 mmol, 1.2 equiv.). After stirring at room temperature for 1h, the mixture was concentrated under reduced pressure and directly purified by flash chromatography (cHx:EtOAc 1:0 → 1:1) to afford the desired product in 71-76% yields.



3a-j
2-R_2-HO-aza[X_{AA1}]-OH

4a-j
1,2-R_2,4-Oxd[X_{AA1}]

1,2-Me,4-Oxd[Phe] 4a

According to the general procedure C and starting with 2-Me,HO-aza[Phe]-OH **3a**, the title compound **4a** was obtained as a white solid in 73% yield (257.2 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 2.97 (dd, 1H, *J*=10.4 Hz, *J*=14.2 Hz), 3.18 (s, 3H), 3.37 (dd, 1H, *J*=4.1 Hz, *J*=14.3 Hz), 4.22 (ddd, 1H, *J*=1.5 Hz, *J*=4.1 Hz, *J*=10.4 Hz), 5.53 (s, 1H), 7.21-7.22 (m, 2H), 7.30-7.38 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 35.7, 36.6, 54.7, 128.0, 129.3, 129.4, 134.8, 159.3, 168.4 ; LC/MS r_t=1.34; ESI-MS$^+$ *m/z* 221.2 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{11}H_{12}N_2O_3$ $[M+H]^+$: 221.0926, found: 221.0927; R_f=0.46 (cHx/EtOAc 7:3); $[\alpha]_D^{20}$= +12.8 (C=1, Acetonitrile).

1,2-Me,4-Oxd[Ser(Bn)] 4b

According to the general procedure C and starting with 2-Me,HO-aza[Ser(Bn)]-OH **3b**, the title compound **4b** was obtained as a white solid in 73% yield (292.3 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 3.20 (s, 3H), 3.73 (t, 1H, *J*=9.5 Hz), 3.93 (dd, 1H, *J*=3.9 Hz, *J*=9.9 Hz), 4.28 (dd, 1H, *J*=3.8 Hz, *J*=9.0 Hz), 4.58 (s, 2H), 5.88 (b, 1H), 7.30–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 36.6, 52.9, 66.8, 73.8, 128.0, 128.3, 128.7, 136.7, 159.2, 166.9; LC/MS r_t=1.41; ESI-MS$^+$ *m/z* 251.1 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{12}H_{14}N_2O_4$ $[M+H]^+$: 251.1226, found: 251.1227; R_f = 0,42 (cHx/EtOAc 6:4); $[\alpha]_D^{20}$= -26.1 (C=1, Acetonitrile).

1,2-Me,4-Oxd[Tyr(Bn)] 4c

According to the general procedure C and starting with 2-Me,HO-aza[Tyr(Bn)]-OH **3c**, the title compound **4c** was obtained as a white solid in 76% yield (396.7 mg). ^{1}H NMR (DMSO-d_6, 300 MHz) *δ* 2.91 (dd, 1H, *J*=10.3 Hz, *J*=14.4 Hz), 3.19 (s, 3H), 3.30 (dd, 1H, *J*=4.1 Hz,

J=14.4 Hz), 4.16 (ddd, 1H, *J*=1.4 Hz, *J*=4.2 Hz, *J*=10.3 Hz), 5.06 (s, 2H), 5.38-5.50 (m, 1H), 6.95 (d, 2H, *J*=8.6 Hz), 7.12 (d, 2H, *J*=8.6 Hz), 7.31-7.35 (m, 1H), 7.37-7.44 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 34.9, 36.6, 54.7, 70.2, 115.8, 126.8, 127.6, 128.2, 128.8, 130.4, 136.9, 158.5, 159.3, 168.4; LC/MS r_t=1.78; ESI-MS$^+$ *m/z* 327.1 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{18}H_{18}N_2O_4$ $[M+H]^+$: 327.1345, found: 327.1346; R_f=0.45 (cHx/EtOAc 7:3); $[\alpha]_D^{20}$=-21.0 (C = 1, Acetonitrile).

1,2-Me,4-Oxd[Cys(Bn)] 4d

According to the general procedure C and starting with 2-Me,HO-aza[Cys(Bn)]-OH **3d**, the title compound **4d** was obtained as a white solid in 72% yield (306.8 mg). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.77 (dd, 1H, *J*=6.6 Hz, *J*=14.2 Hz), 2.84 (dd, 1H, *J*=5.5 Hz, *J*=14.2 Hz), 3.06 (s, 3H), 3.83 (s, 2H), 4.37-4.40 (m, 1H), 7.26-7.34 (m, 5H), 8.45 (d, 1H, *J*=1.3 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 30.5, 36.0, 36.9, 53.6, 127.5, 128.9, 129.4, 138.6, 159.2, 168.7; LC/MS r_t=1.58 ; ESI-MS$^+$ *m/z* 267.1 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{12}H_{14}N_2O_3S$ $[M+H]^+$: 267.1371, found: 267.1373; R_f=0.39 (cHx/EtOAc 6:4); $[\alpha]_D^{20}$= - 32.7 (C=1, Acetonitrile).

1,2-Me,4-Oxd[Ile] 4e

According to the general procedure C and starting with 2-Me,HO-aza[Ile]-OH **3e**, the title compound **4e** was obtained as a colourless oil in 71% yield (211.5 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 3H, *J*=7.4 Hz,), 1.01 (d, 3H, *J*=7.0 Hz), 1.19-1.30 (m, 1H), 1.49-1.59 (m, 1H), 1.98-2.07 (m, 1H), 3.11 (s, 3H), 3.81 (dd, 1H, *J*=2.5 Hz, *J*=6.1 Hz), 7.45 (b, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.2, 15.1, 24.8, 35.2, 36.4, 58.5, 160.3, 167.9 ; LC/MS r_t=1.25; ESI-MS$^+$ *m/z* 187.1 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_8H_{14}N_2O_3$ $[M+H]^+$: 187.4112, found: 187.4112; R_f=0.50 (cHx/EtOAc 1:1); $[\alpha]_D^{20}$= + 41.3 (C=1, Acetonitrile).

1,2-Bn,4-Oxd[Val] 4f

According to the general procedure C and starting with 2-Bn,HO-aza[Val]-OH **3f**, the title compound **4f** was obtained as a white solid in 73% yield (290.0 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (d, 3H, *J*=6.8 Hz), 1.09 (d, 3H, *J*=7.0 Hz), 2.32-2.40 (m, 1H), 3.81 (dd, 1H, *J*=2.0 Hz, *J*=5.5 Hz), 4.70 (d, 2H, *J*=15.4 Hz), 4.78 (d, 2H, *J*=15.4 Hz), 6.46 (s, 1H), 7.31-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.8, 19.0, 29.2, 52.8, 59.4, 128.2, 128.7, 129.1, 135.0, 158.9, 167.6; LC/MS r_t=1.57; ESI-MS+ *m/z* 249.2 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{13}H_{16}N_2O_3$ $[M+H]^+$: 249.1239, found: 249.1239; R_f=0.55 (cHx/EtOAc 1:1); $[\alpha]_D^{20}$= -52.1 (C=1, Acetonitrile).

1,2-Bn,4-Oxd[Trp] 4g

According to the general procedure C and starting with 2-Bn,HO-aza[Trp]-OH **3g**, the title compound **4g** was obtained as a white solid in 73% yield (391.7 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.12 (dd, 1H, *J*=10.6 Hz, *J*=14.9 Hz), 3.54 (dd, 1H, *J*=4.2 Hz, *J*=14.5 Hz), 4.30 (ddd,

1H, *J*=1.0 Hz, *J*=3.9 Hz, *J*=10.6 Hz), 4.64 (d, 1H, *J*=15.5 Hz), 4.83 (d, 1H, *J*=15.5 Hz), 5.19 (b, 1H), 7.11 (d, 1H, *J*=2.2 Hz), 7.15-7.19 (m, 1H), 7.31-7.42 (m, 6H), 7.55 (d, 1H, *J*=8.0 Hz), 8.18 (b, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 26.0, 52.8, 53.2, 108.8, 111.8, 118.3, 120.4, 123.1, 123.6, 126.7, 128.2, 128.7, 129.2, 134.9, 136.7, 158.3, 168.6; LC/MS r_t=1.70; ESI-MS$^+$ *m/z* : 336.2 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{19}H_{17}N_3O_3$ $[M+H]^+$: 336.1348, found: 336.1347; R_f=0.39 (cHx/EtOAc 7:3); $[\alpha]_D^{20}$= -13.0 (C=1, Acetonitrile).

1,2-*i*Pr,4-Oxd[Phe] 4h

According to the general procedure C and starting with 2-*i*Pr,HO-aza[Phe]-OH **3h**, the title compound **4h** was obtained as a white solid in 75% yield (297.9 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 1.27 (d, 3H, *J*=6.6 Hz), 1.29 (d, 3H, *J*=6.8 Hz), 2.93 (dd, 1H, *J*=10.5 Hz, *J*=14.3 Hz), 3.38 (dd, 1H, *J*=4.0 Hz, *J*=14.3 Hz), 4.17 (dd, 1H, *J*=4.7 Hz, *J*=9.9 Hz), 4.30-4.36 (m, 1H), 5.17 (b, 1H), 7.21-7.23 (m, 2H), 7.29-7.38 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 18.2, 18.8, 35.9, 50.7, 54.3, 128.0, 129.2, 129.5, 134.8, 158.2, 168.8; LC/MS r_t=1.45; ESI-MS+ *m/z* 249.0 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{13}H_{16}N_2O_3$ $[M+H]^+$: 249.1239, found: 249.1237; R_f=0.52 (cHx/EtOAc 7:3); $[\alpha]_D^{20}$= -15.7 (C=1, Acetonitrile).

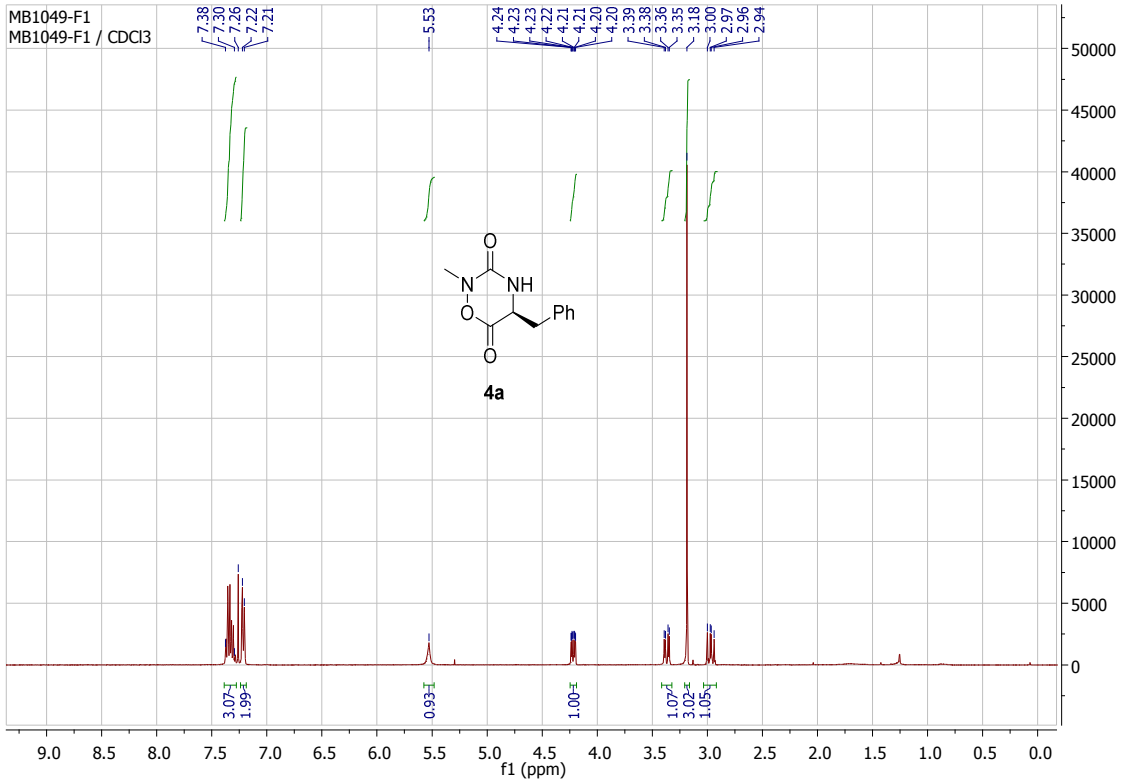
1,2-*i*Pr,4-Oxd[(D)-Phe] 4i

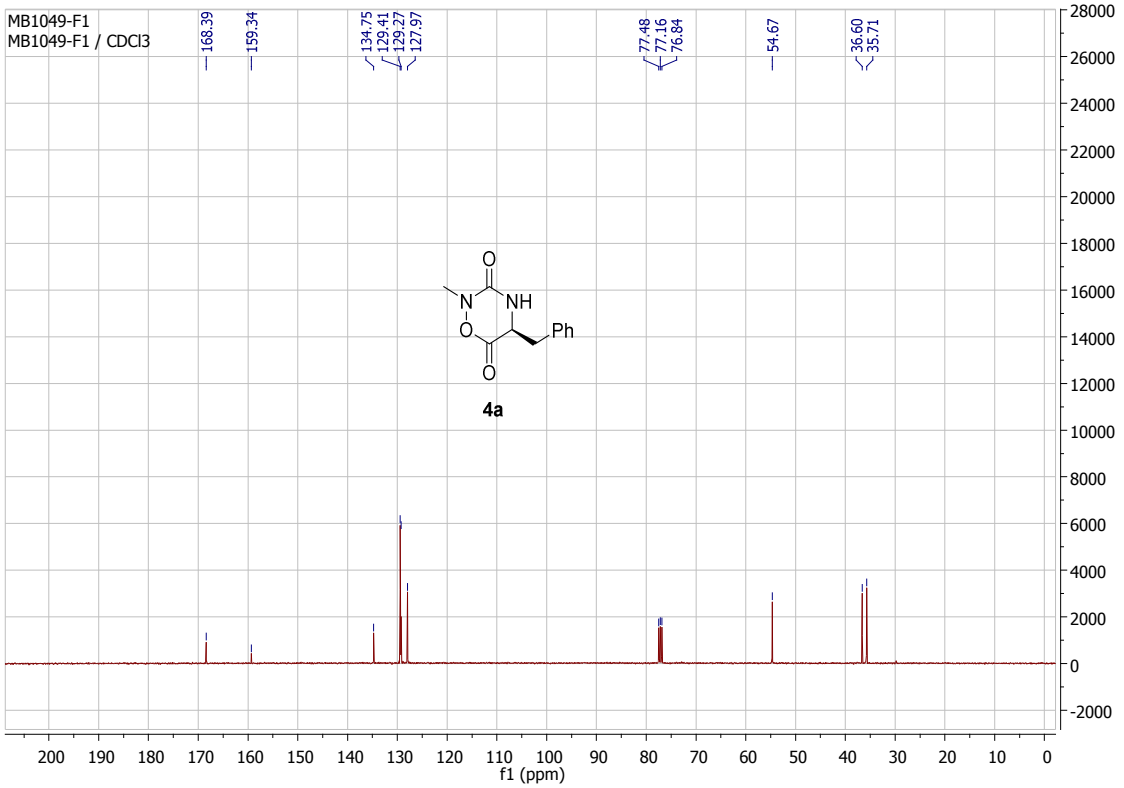
According to the general procedure C and starting with 2-*i*Pr,HO-aza[(D)-Phe]-OH **3i**, the title compound **4i** was obtained as a white solid in 75% yield (297.9 mg). ^{1}H NMR ($CDCl_3$, 500 MHz) *δ* 1.28 (d, 3H, *J*=6.6 Hz), 1.30 (d, 3H, *J*=6.8 Hz), 2.93 (dd, 1H, *J*=10.7 Hz, *J*=14.2 Hz), 3.39 (dd, 1H, *J*=3.9 Hz, *J*=14.3 Hz), 4.17 (dd, 1H, *J*=3.4 Hz, *J*=11.3 Hz), 4.31-4.36 (m, 1H), 5.04 (b, 1H), 7.21-7.22 (m, 2H), 7.30-7.38 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) *δ* 18.0, 18.7, 35.8, 50.6, 54.2, 127.9, 129.1, 129.4, 134.6, 158.0, 168.6; LC/MS r_t=1.45; ESI-MS+ *m/z* 249.0 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{13}H_{16}N_2O_3$ $[M+H]^+$: 249.1239, found: 249.1237; R_f=0.52 (cHx/EtOAc 7:3); $[\alpha]_D^{20}$= +15.7 (C=1, Acetonitrile).

1,2-*i*Pr,4-Oxd[Leu] 4j

According to the general procedure C and starting with 2-*i*Pr,HO-aza[Leu]-OH **3j**, the title compound **4j** was obtained as a white solid in 76% yield (260.6 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 0.95 (d, 3H, *J*=6.2 Hz), 1.00 (d, 3H, *J*=6.3 Hz), 1.28 (d, 3H, *J*=3.1 Hz), 1.30 (d, 3H, *J*=3.2 Hz), 1.61-1.72 (m, 1H), 1.76-1.85 (m, 2H), 3.96-4.00 (m, 1H), 4.29-4.36 (m, 1H), 5.99 (b, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 18.3, 18.7, 21.5, 23.1, 24.6, 50.7, 51.7, 158.8, 169.5; LC/MS r_t=1.44; ESI-MS+ *m/z* 214.8 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{10}H_{18}N_2O_3$ $[M+H]^+$: 215.1396, found: 215.1394; R_f=0.49 (cHx/EtOAc 7:3); $[\alpha]_D^{20}$= -5.3 (C=1, Acetonitrile).

^{1}H and ^{13}C NMR analysis of 1,2,4-Oxd[X_{AA1}]

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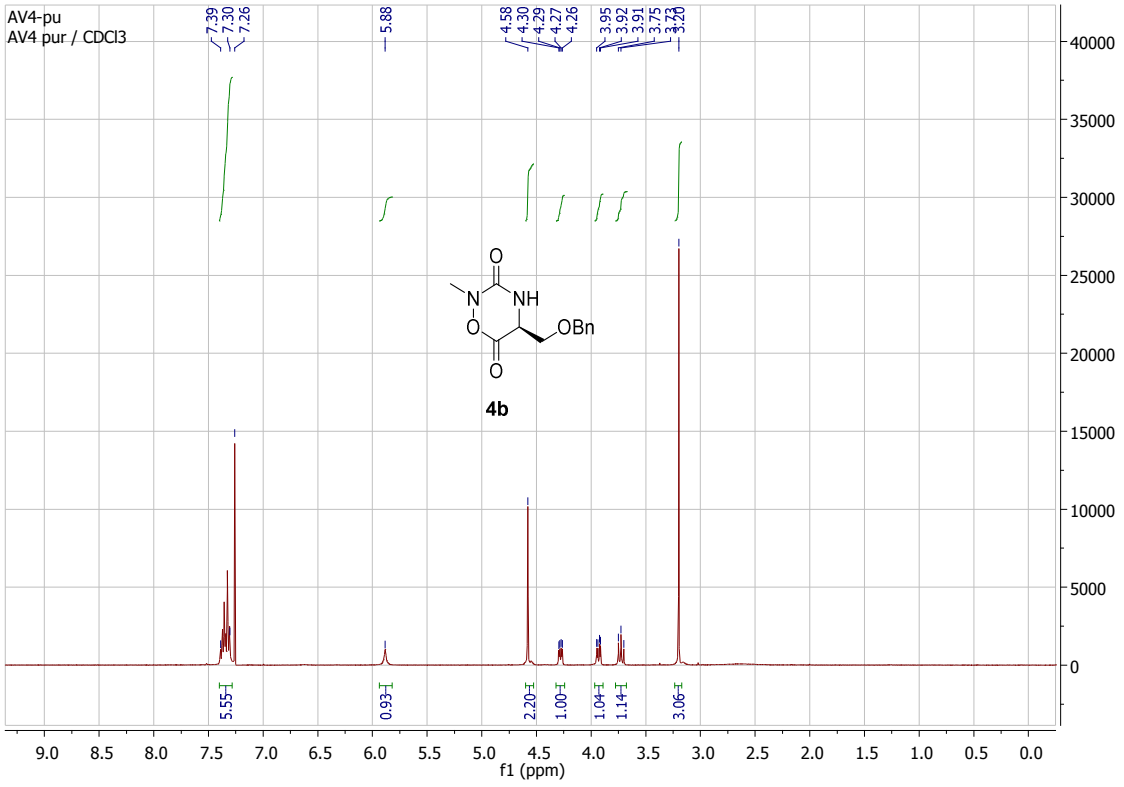
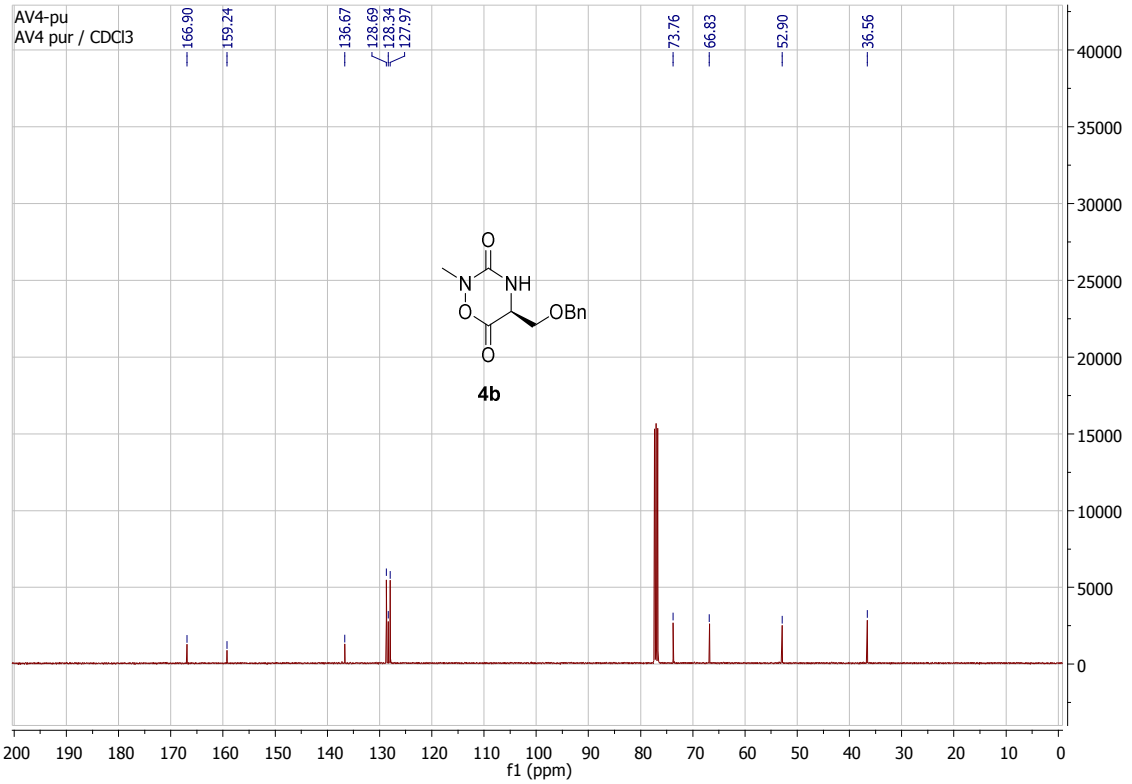
MB1049-F1 / CDCl3
168.39
159.34
134.75
129.41
129.27
127.97
77.48
77.16
76.84
54.67
36.60
35.71
Ph
4a
f1 (ppm)


AV4-pu
AV4 pur / CDCl3
7.39
7.30
7.26
5.88
4.58
4.30
4.29
4.27
4.26
3.95
3.92
3.91
3.75
3.73
3.20
OBn
4b
5.55
0.93
2.20
1.00
1.04
1.14
3.06
f1 (ppm)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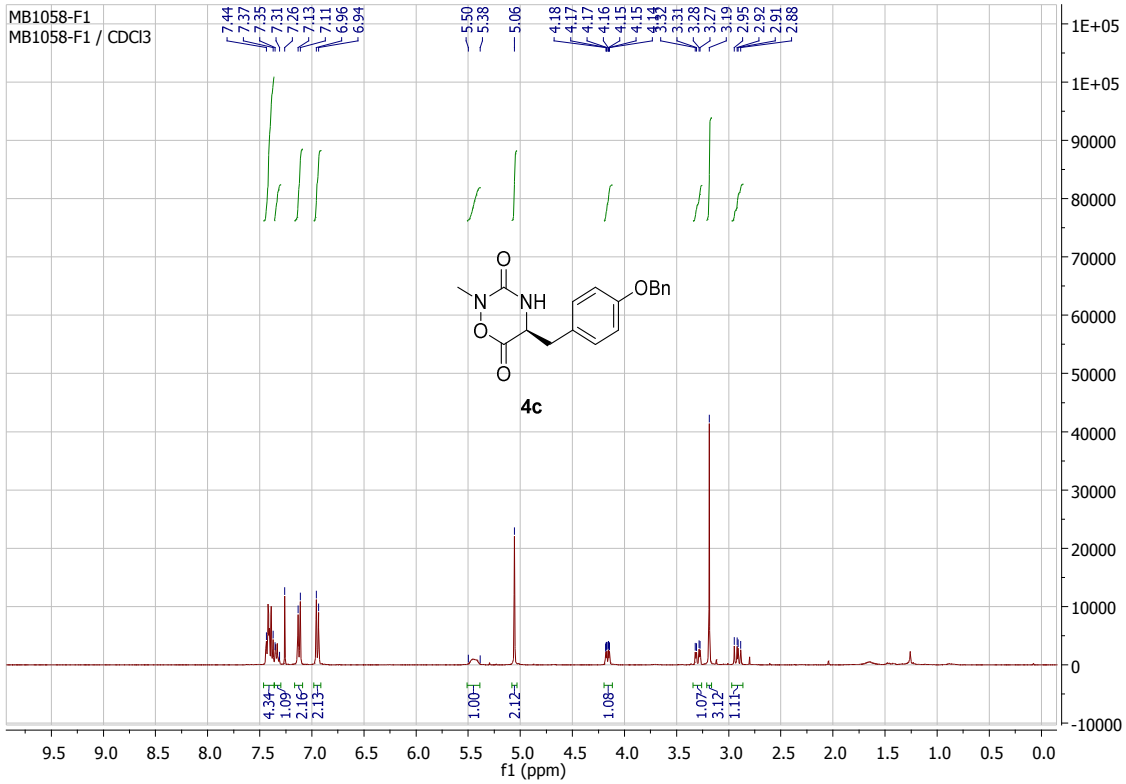
AV4 pur / CDCl3
166.90
159.24
136.67
128.69
128.34
127.97
73.76
66.83
52.90
36.56
O
N
NH
O
OBn
O
4b
f1 (ppm)


MB1058-F1
MB1058-F1 / CDCl3
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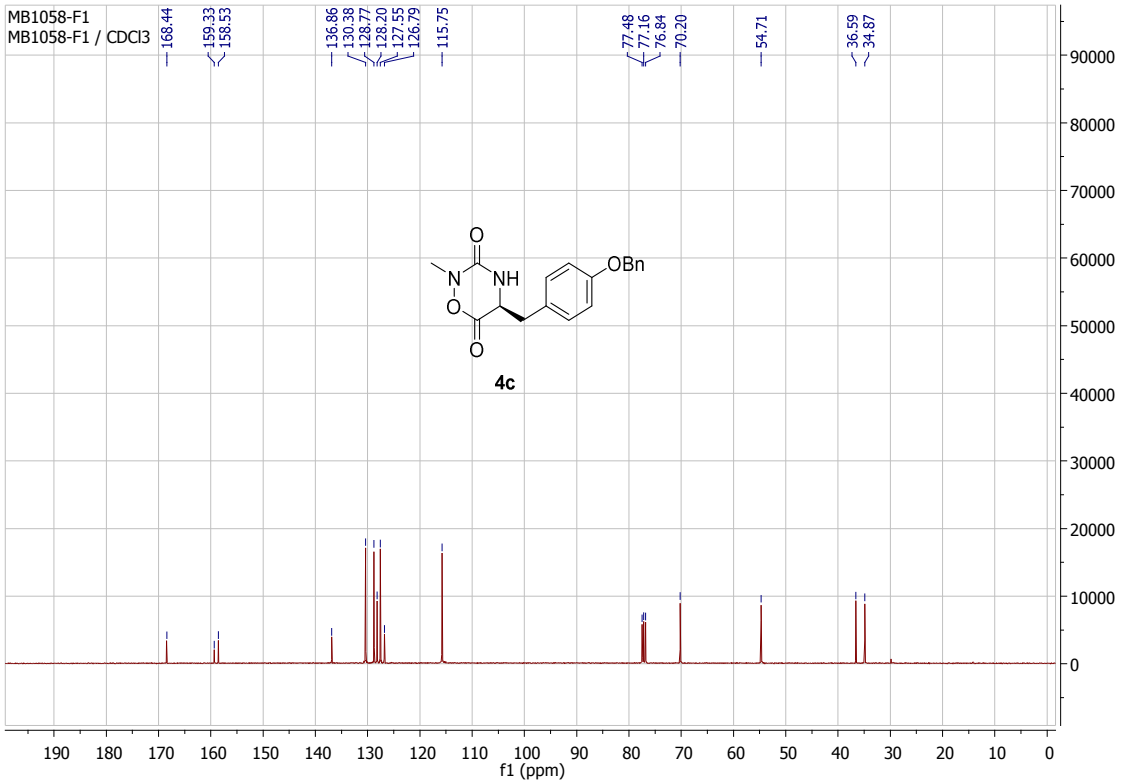
7.37
7.35
7.31
7.26
7.13
7.11
6.96
6.94
5.50
5.38
5.06
4.18
4.17
4.17
4.16
4.15
4.15
3.31
3.28
3.27
3.19
2.95
2.92
2.91
2.88
O
N
NH
O
OBn
O
4c
4.34
1.09
2.16
2.13
1.00
2.12
1.08
1.07
3.12
1.11
f1 (ppm)


MB1058-F1
MB1058-F1 / CDCl3
168.44
159.33
158.53
136.86
130.38
128.77
128.20
127.55
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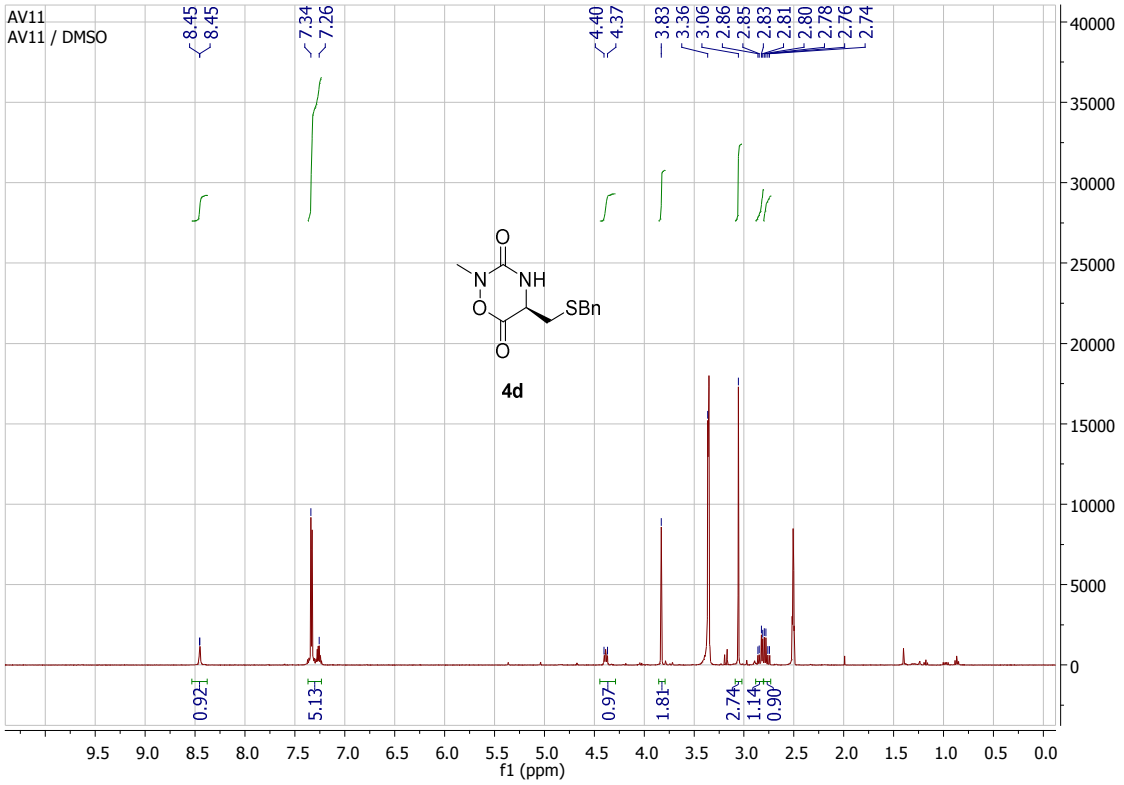
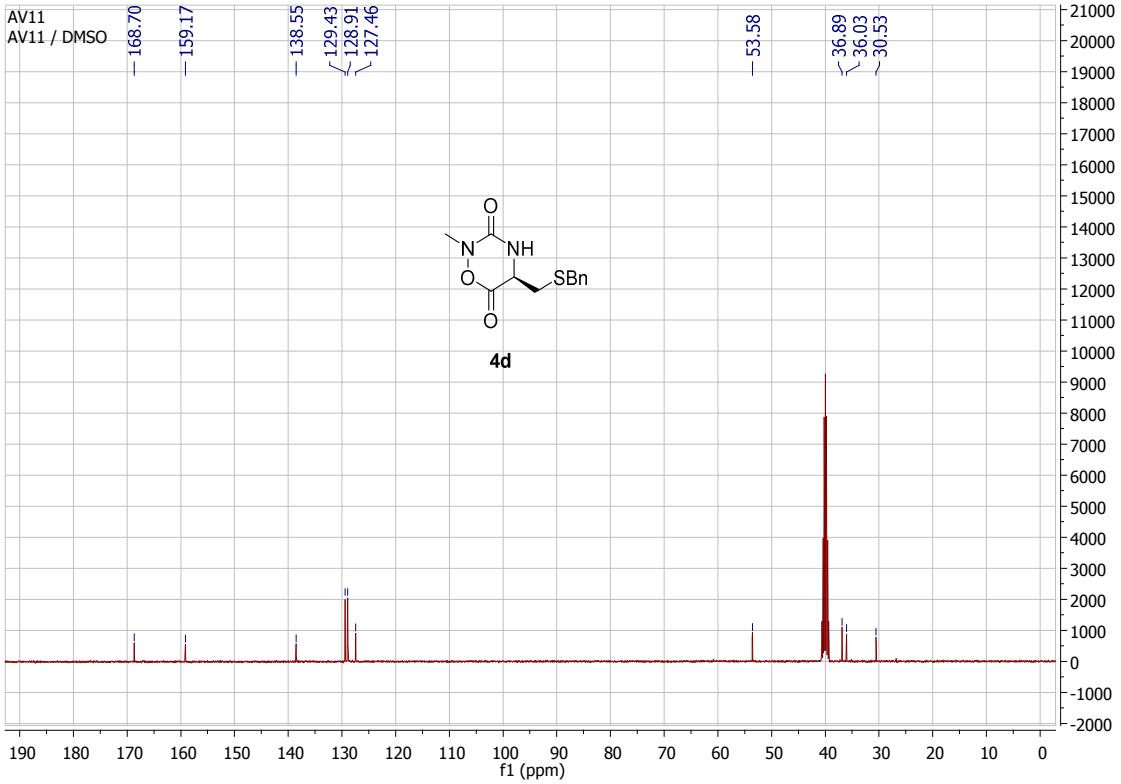
54.71
36.59
34.87
OBn
4c
f1 (ppm)


AV11
AV11 / DMSO
8.45
8.45
7.34
7.26
4.40
4.37
3.83
3.36
3.06
2.86
2.85
2.83
2.81
2.80
2.78
2.76
2.74
SBn
4d
0.92
5.13
0.97
1.81
2.74
1.14
0.90
f1 (ppm)


AV11
AV11 / DMSO
168.70
159.17
138.55
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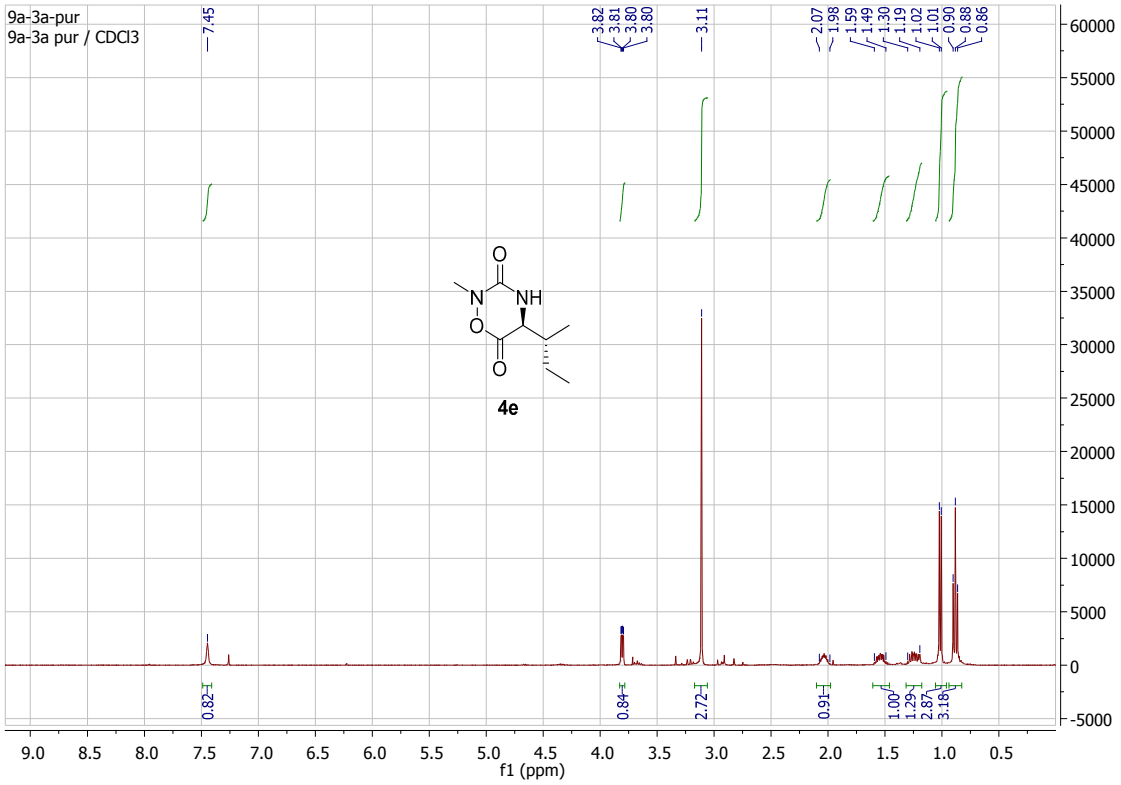
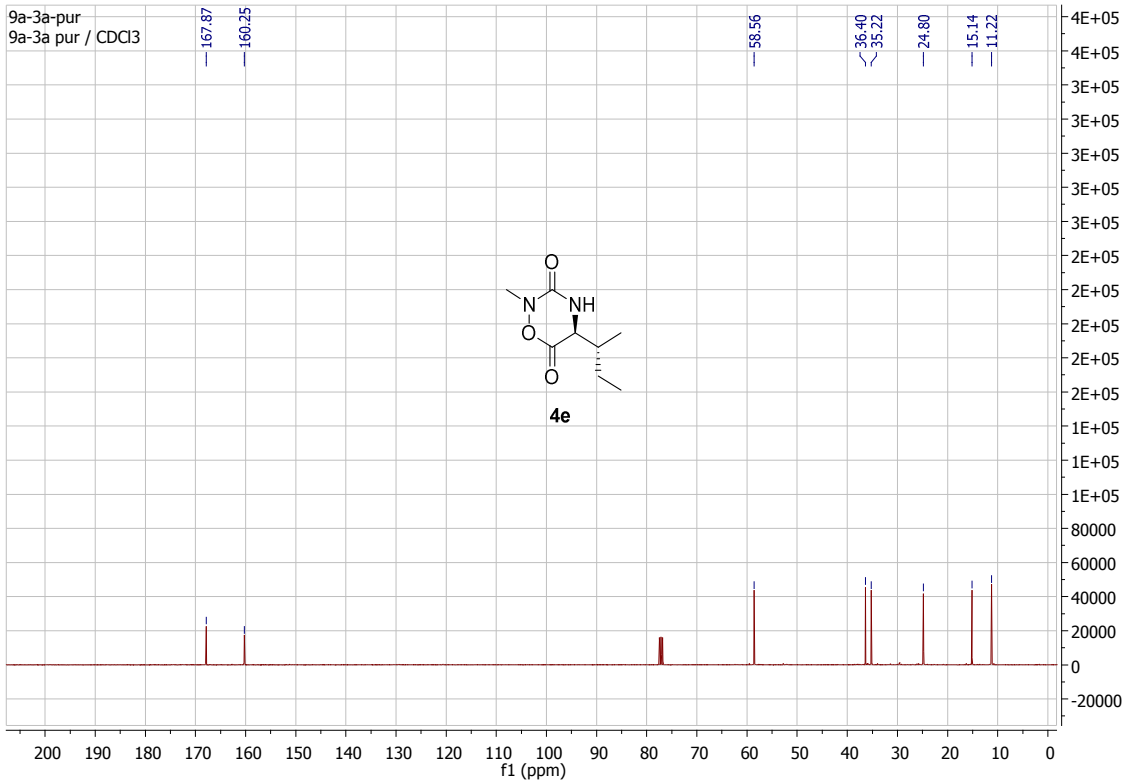
128.91
127.46
53.58
36.89
36.03
30.53
NH
SBn
4d
f1 (ppm)


9a-3a-pur
9a-3a pur / CDCl3
7.45
3.82
3.81
3.80
3.80
3.11
2.07
1.98
1.59
1.49
1.30
1.19
1.02
1.01
0.90
0.88
0.86
NH
4e
0.82
0.84
2.72
0.91
1.00
1.29
2.87
3.18
f1 (ppm)


9a-3a-pur
9a-3a pur / CDCl3
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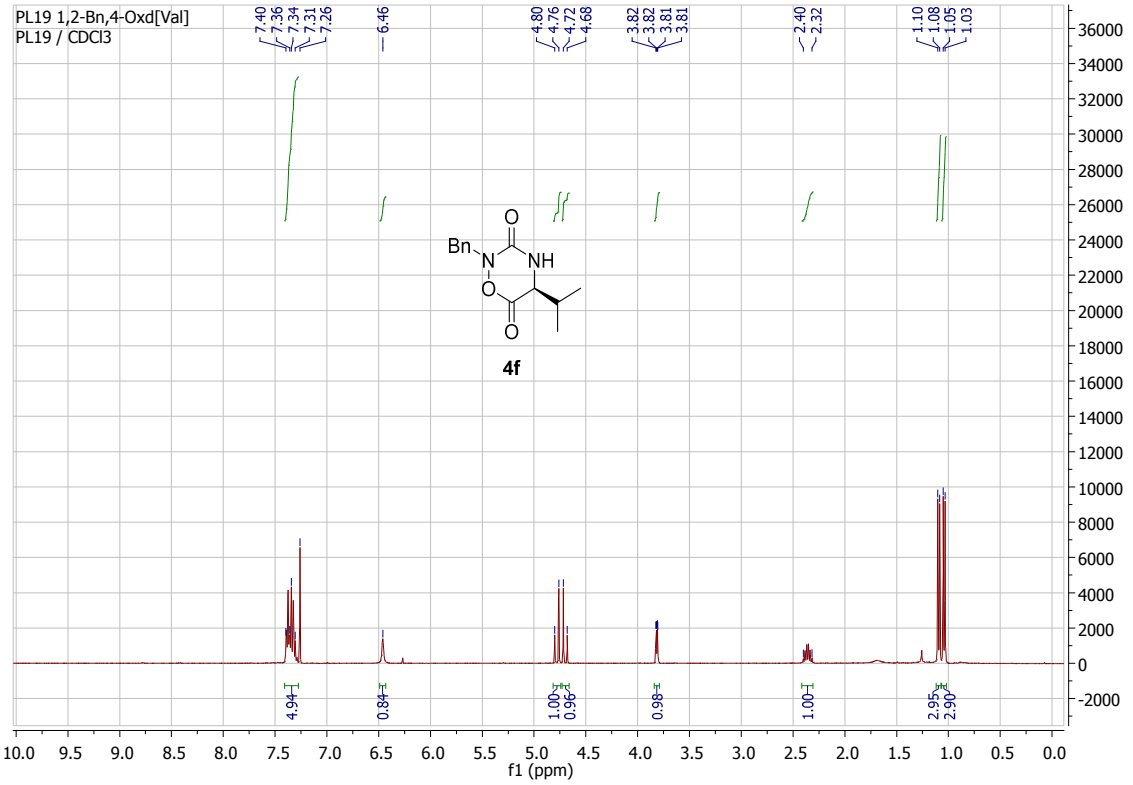
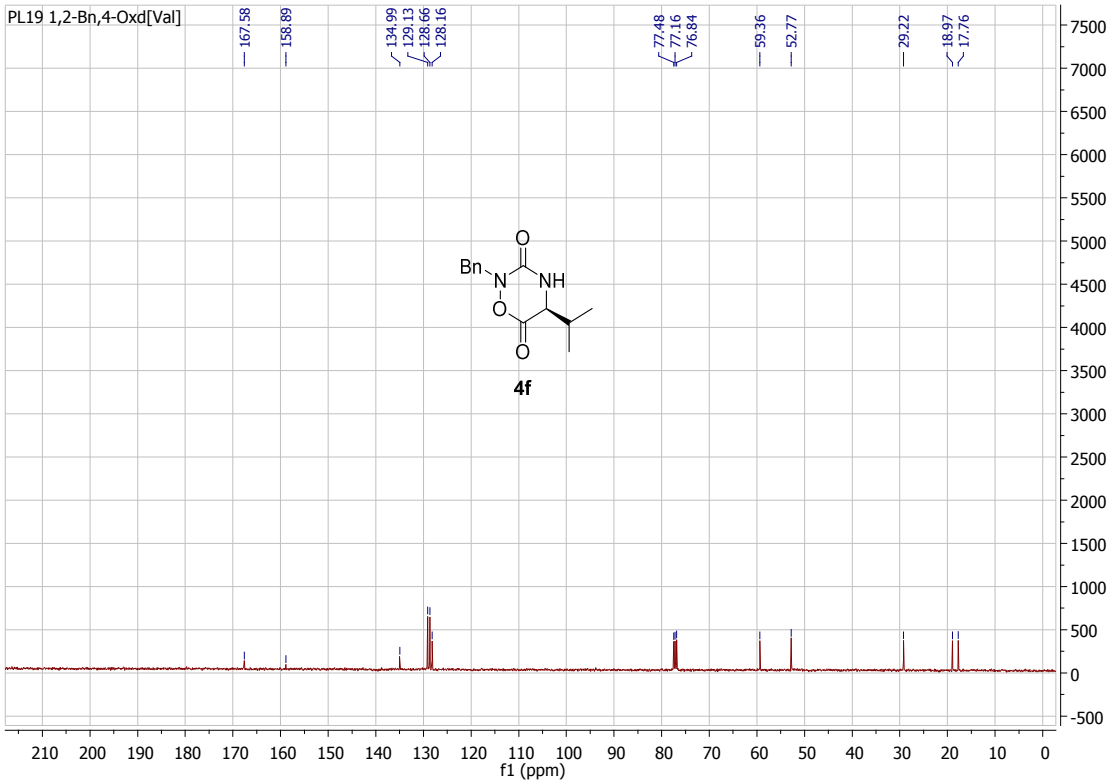
160.25
58.56
36.40
35.22
24.80
15.14
11.22
4e
f1 (ppm)


PL19 1,2-Bn,4-Oxd[Val]
PL19 / CDCl3
7.40
7.36
7.34
7.31
7.26
6.46
4.80
4.76
4.72
4.68
3.82
3.82
3.81
3.81
2.40
2.32
1.10
1.08
1.05
1.03
4.94
0.84
1.00
0.96
0.98
1.00
2.95
2.90
4f
f1 (ppm)


PL19 1,2-Bn,4-Oxd[Val]
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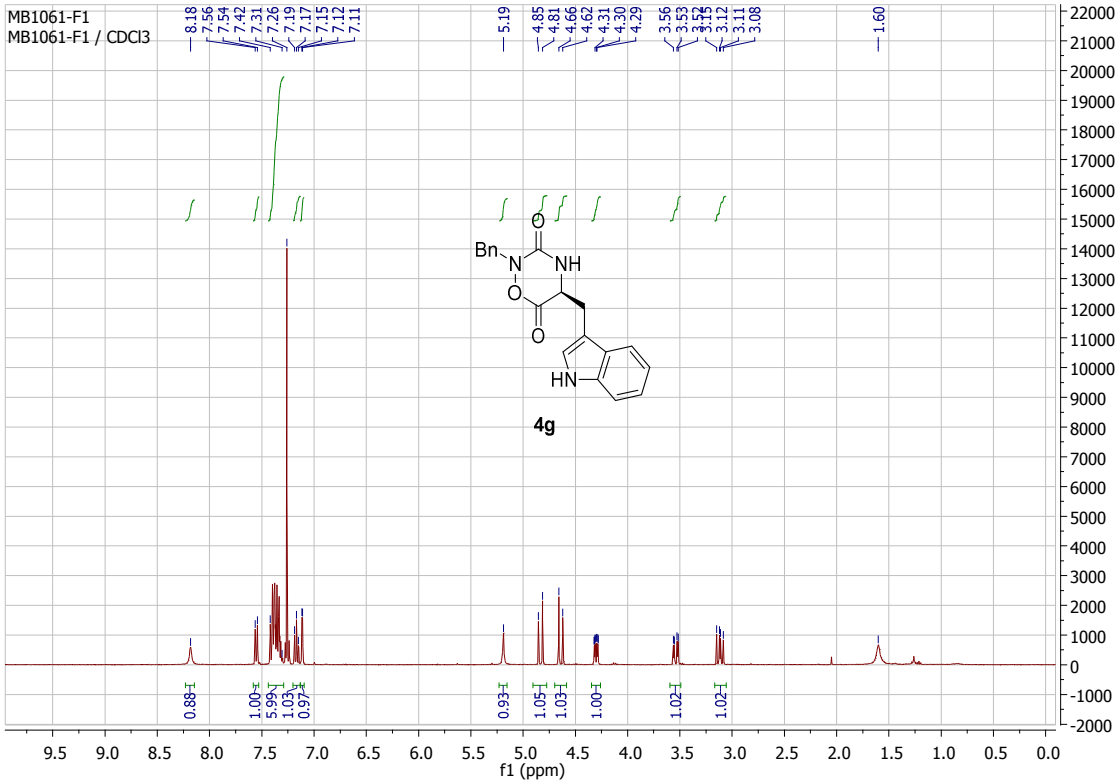
158.89
134.99
129.13
128.66
128.16
77.48
77.16
76.84
59.36
52.77
29.22
18.97
17.76
Bn
N
NH
O
O
O
4f
f1 (ppm)


MB1061-F1
MB1061-F1 / CDCl3
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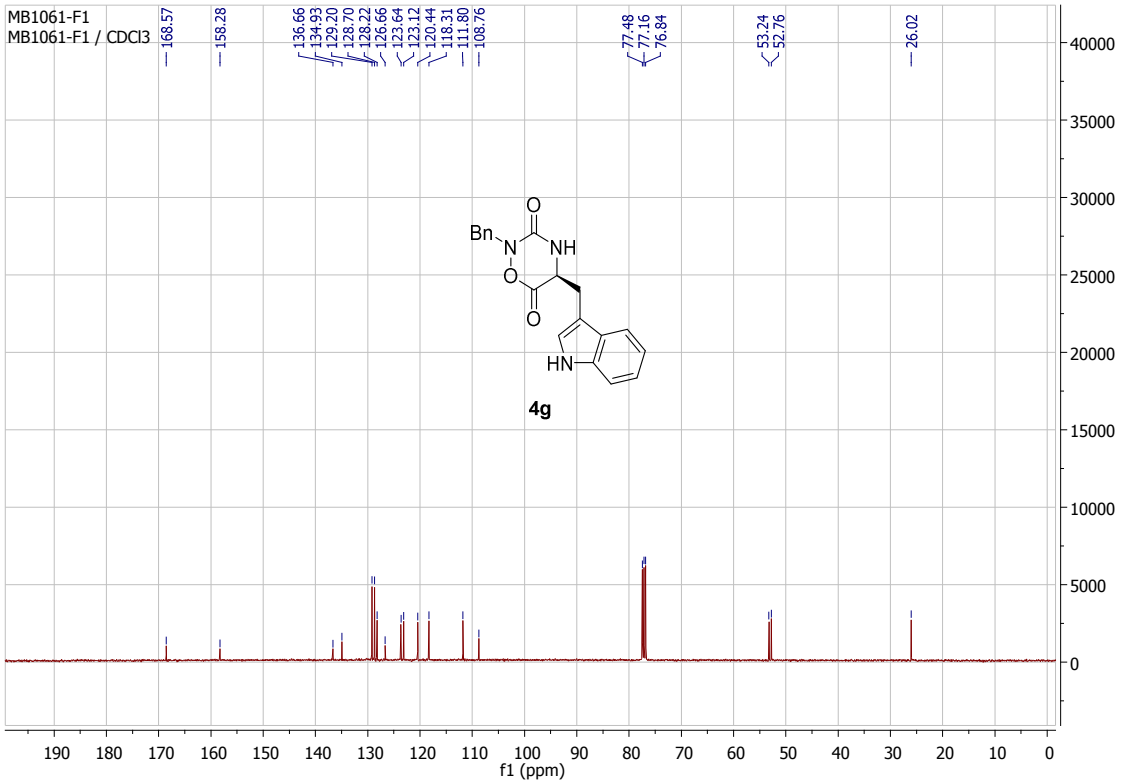
7.56
7.54
7.42
7.31
7.26
7.19
7.17
7.15
7.12
7.11
5.19
4.85
4.81
4.66
4.62
4.31
4.30
4.29
3.56
3.53
3.12
3.11
3.08
1.60
Bn
N
NH
O
O
O
HN
4g
f1 (ppm)


MB1061-F1
MB1061-F1 / CDCl3
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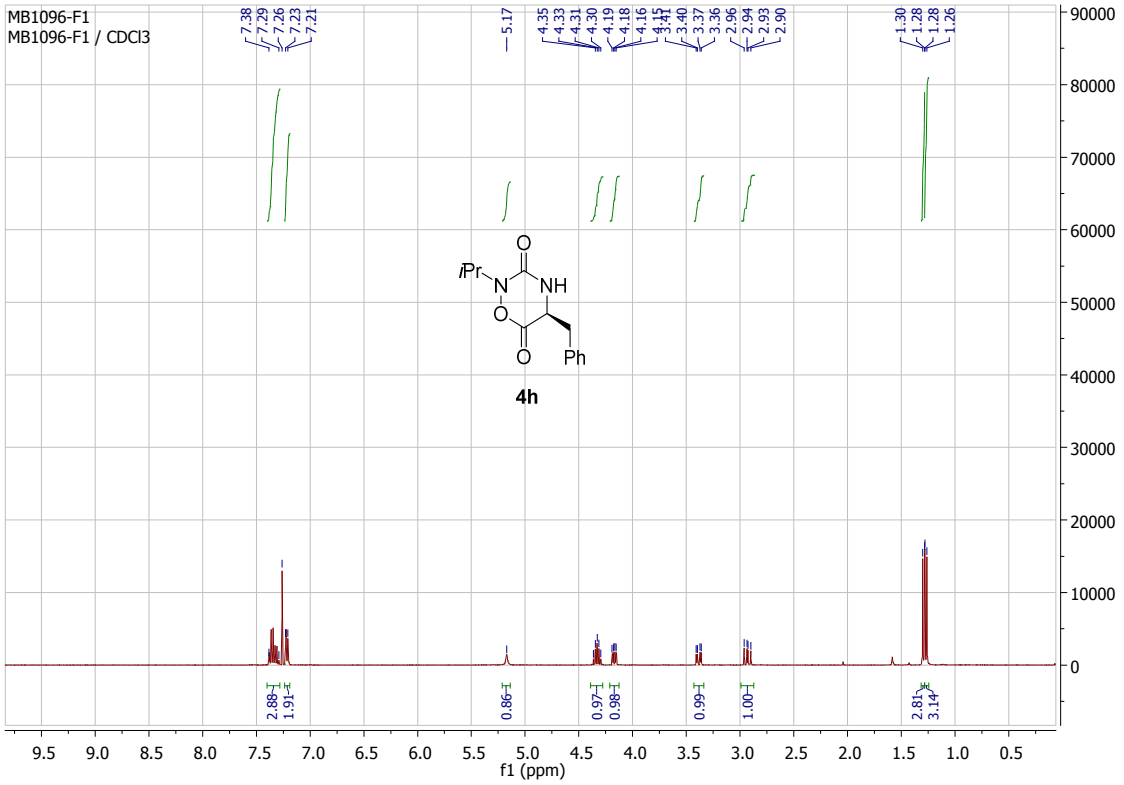
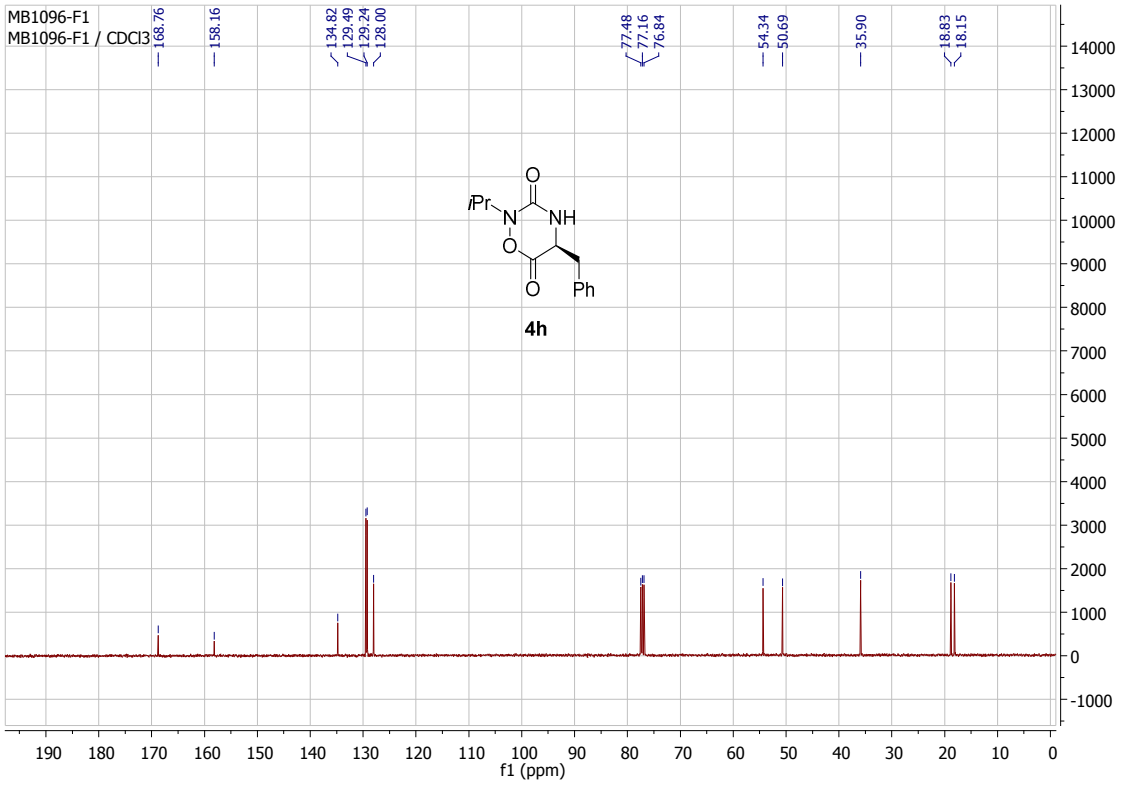
158.28
136.66
134.93
129.20
128.70
128.22
126.66
123.64
123.12
120.44
118.31
111.80
108.76
77.48
77.16
76.84
53.24
52.76
26.02
Bn
N
O
NH
O
O
HN
4g
f1 (ppm)


MB1096-F1
MB1096-F1 / CDCl3
7.38
7.29
7.26
7.23
7.21
5.17
4.35
4.33
4.31
4.30
4.19
4.18
4.16
4.15
3.40
3.37
3.36
2.96
2.94
2.93
2.90
1.30
1.28
1.28
1.26
iPr
N
O
NH
O
O
Ph
4h
2.88
1.91
0.86
0.97
0.98
0.99
1.00
2.81
3.14
f1 (ppm)


MB1096-F1
MB1096-F1 / CDCl3
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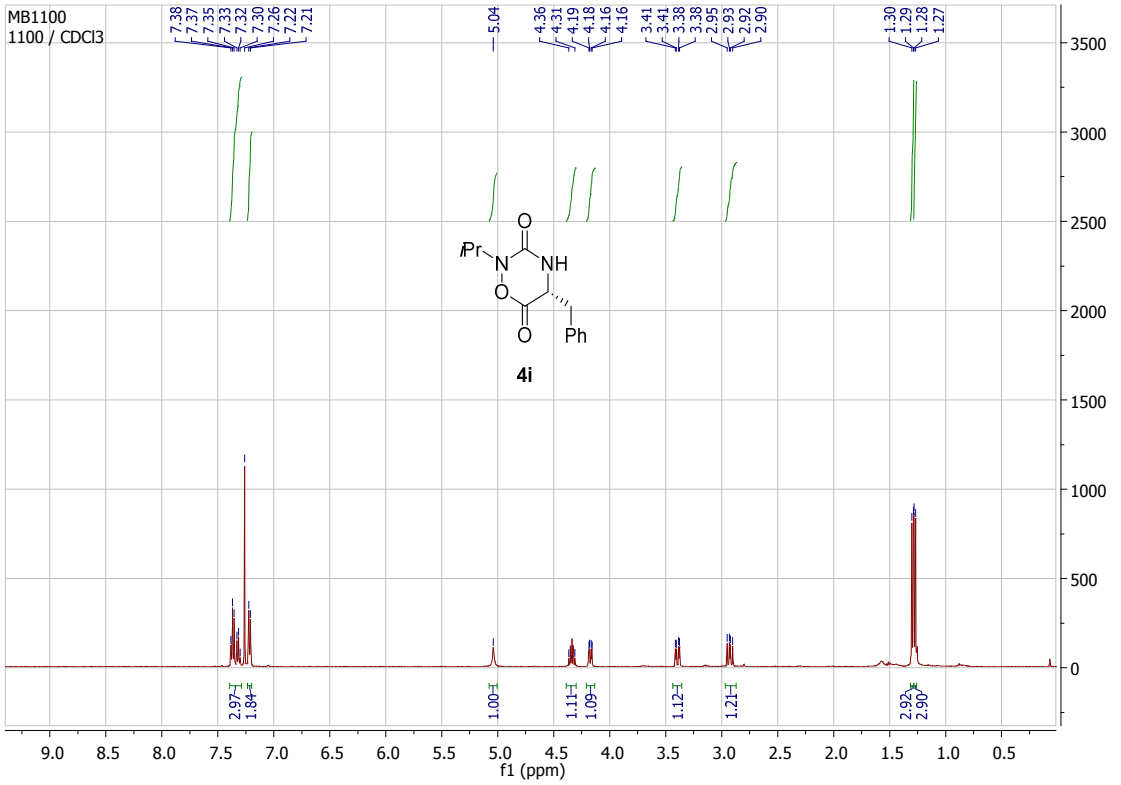
158.16
134.82
129.49
129.24
128.00
77.48
77.16
76.84
54.34
50.69
35.90
18.83
18.15
iPr
N
O
NH
O
O
Ph
4h
f1 (ppm)


MB1100
1100 / CDCl3
7.38
7.37
7.35
7.33
7.32
7.30
7.26
7.22
7.21
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4.36
4.31
4.19
4.18
4.16
4.16
3.41
3.41
3.38
3.38
2.95
2.93
2.92
2.90
1.30
1.29
1.28
1.27
2.97
1.84
1.00
1.11
1.09
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1.21
2.92
2.90
iPr
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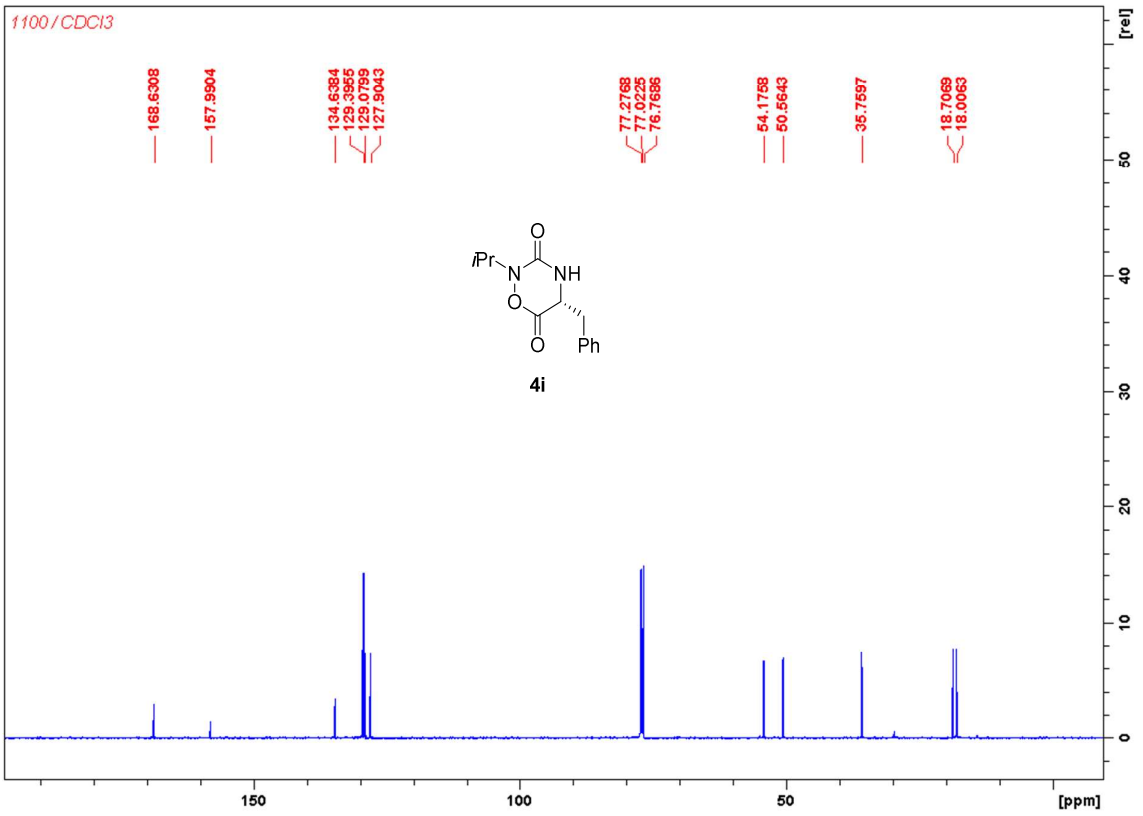
O
NH
O
O
Ph
4i
f1 (ppm)


1100 / CDCl3
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129.0799
127.9043
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77.0225
76.7686
54.1758
50.5643
35.7597
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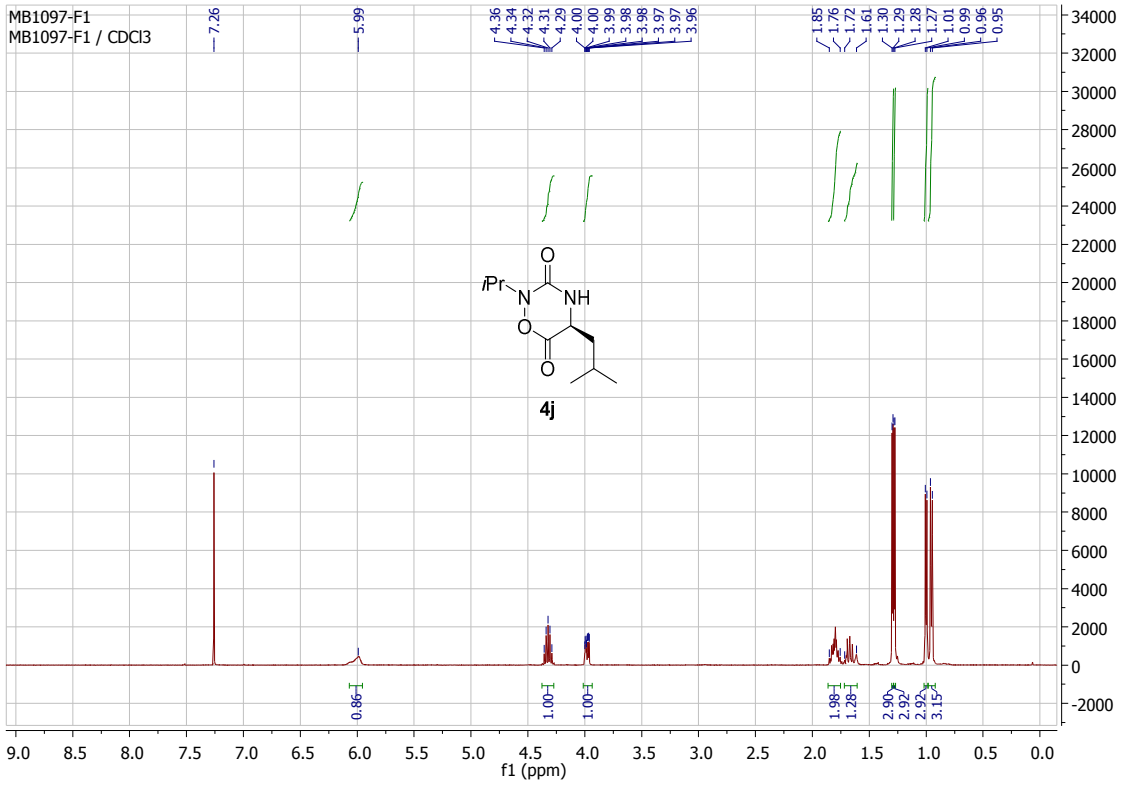
N
O
NH
O
O
Ph
4i
150
100
50
[ppm]


MB1097-F1
MB1097-F1 / CDCl3
7.26
5.99
4.36
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4.32
4.31
4.29
4.00
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3.99
3.98
3.98
3.97
3.97
3.96
1.85
1.76
1.72
1.61
1.30
1.29
1.28
1.27
1.01
0.99
0.96
0.95
iPr
N
O
NH
O
O
4j
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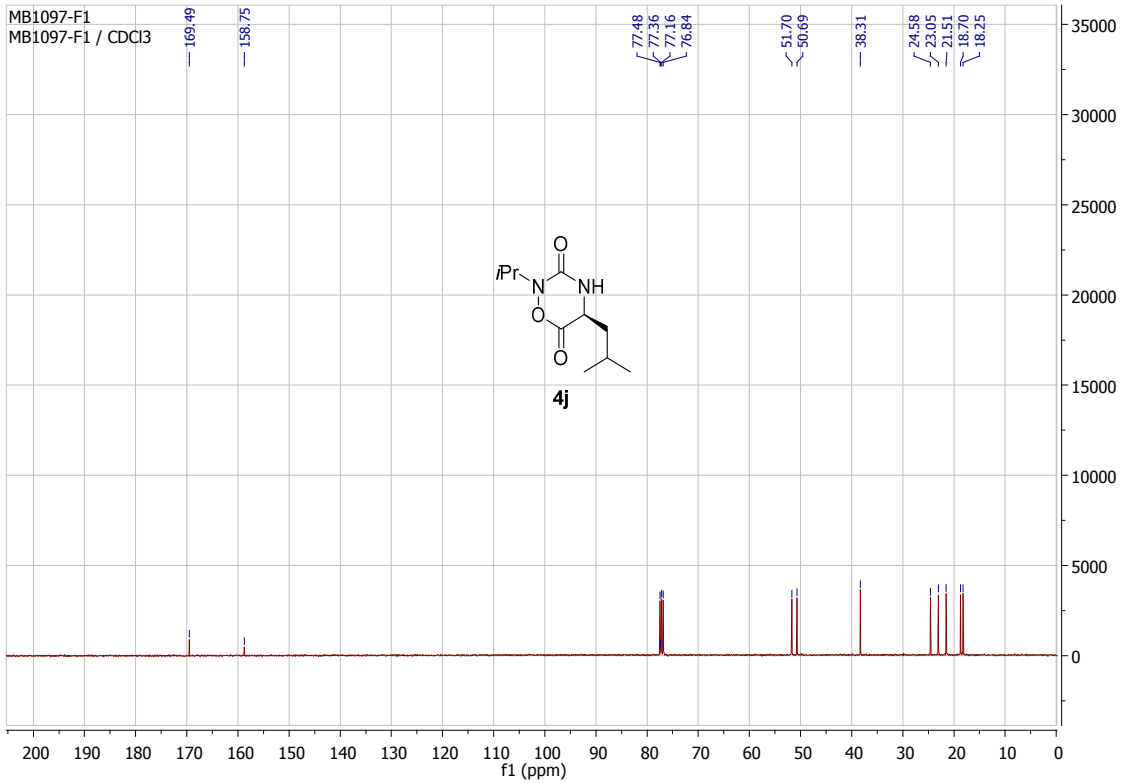
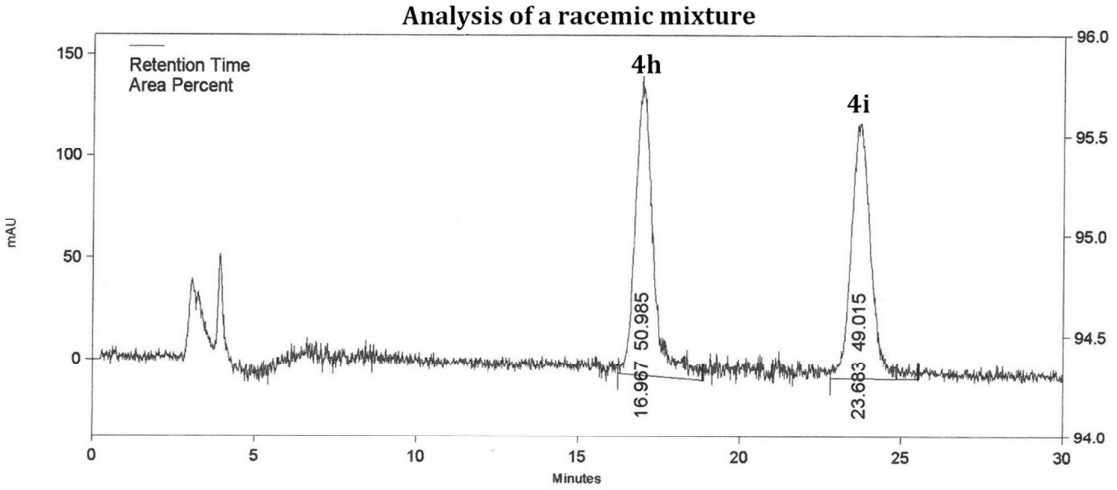
1.00
1.00
1.98
1.28
2.90
2.92
2.92
3.15
f1 (ppm)



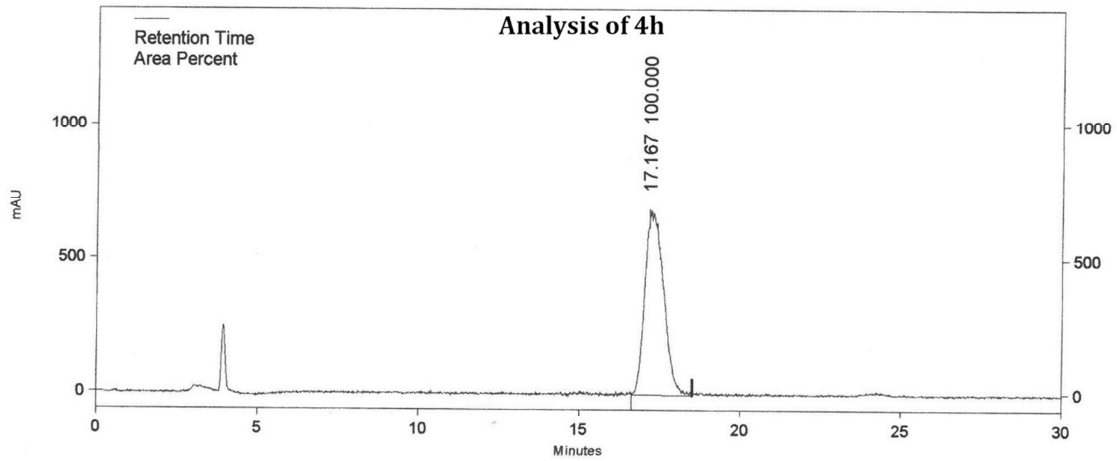
Racemization studies for the cyclisation of oxyazadipeptides 4h and 4i

To a solution of 2-R_2,HO-aza[X_{AA1}]-OH **3h** or **3i** (1.60 mmol, 1.0 equiv.) in anhydrous ACN (20 mL) were added DIEA (4.80 mmol, 3.0 equiv.) and then solid HATU (1.92 mmol, 1.2 equiv.). After stirring at room temperature for 1h, the mixture was concentrated under reduced pressure and directly purified by flash chromatography (cHx:EtOAc 1:0 → 1:1) to afford the desired product **4h** or **4i** in 75% yields (297.9 mg), respectively.

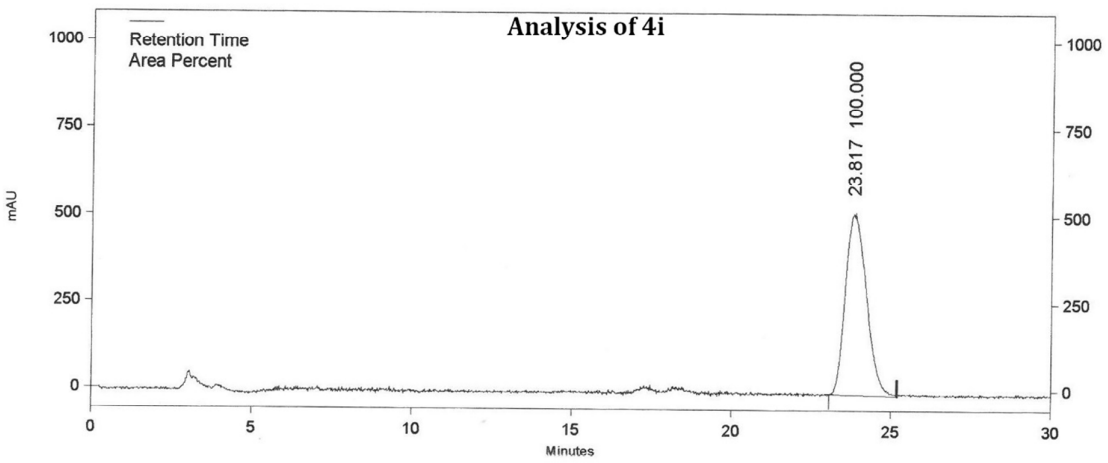
A 0.05 M mixture of **4h** and **4i** (1:1) in *n*-hexane/*i*-PrOH 98:2 was analyzed by chiral analytic HPLC in *n*-hexane: *i*PrOH 95:5; 1.0 mL.min^{-1}; λ=214 nm; 25°C; r_t (**4h**)=17.2 min; r_t (**4i**)=23.8 min.



For **4h**: enantiomeric excess > 99 % was determined by analyzing a solution of **4h** in *n*-hexane/*i*-PrOH 98:2 by chiral analytic HPLC in *n*-hexane: *i*PrOH 95:5; 1.0 mL.min^{-1}; λ=214 nm; 25°C; r_t (**4h**)=17.2 min.



For **4i**: enantiomeric excess > 99 % was determined by analyzing a solution of **4i** in *n*-hexane/*i*PrOH 98:2 by chiral analytic HPLC in *n*-hexane: *i*PrOH 95:5; 1.0 mL.min^{-1}; λ=214 nm; 25°C; r_t (**4i**)=23.8 min.



Synthesis of 1,2,4-Oxd[PG-X_{AA2}-X_{AA1}] 5a-c

General experimental procedure D

To a solution of PG-X_{AA2}-OH (1.00 mmol, 1.0 equiv.) in ACN (5.0 mL) were added DIEA (3.00 mmol, 3.0 equiv.), solid HATU (1.20 mmol, 1.2 equiv.) and then 1,2,4-Oxd[X_{AA2}] **4a**, **4f** or **4g** (1.00 mmol, 1.0 equiv.). After stirring at room temperature for 1h, the mixture was concentrated under reduced pressure and directly purified by flash chromatography (cHx/EtOAc 1:0 → 3:7) to afford the desired product **5a-c** in 51-56% yields.

General experimental procedure E

To a solution of 2-R_2,HO-aza[X_{AA1}]-OH **3a**, **3f** or **3g** (1.00 mmol, 1.0 equiv.) in ACN (12.5 mL) was sequentially added DIEA (3.00 mmol, 3.0 equiv.) and solid HATU (1.20 mmol, 1.2 equiv.). After stirring at room temperature for 1h, the reaction mixture was directly added to a solution of PG-X_{AA2}-OH (1.00 mmol, 1.0 equiv.), DIEA (3.00 mmol, 3.0 equiv.) and HATU (1.20 mmol, 1.2 equiv.) in ACN (5.0 mL). After stirring for 1h at room temperature, the mixture was purified by flash chromatography (cHx/EtOAc 1:0 → 3:7) to afford the desired 1,2,4-Oxd[PG-X_{AA2}-X_{AA1}] **5a-c** in 64-69% yields.

1,2-Me,4-Oxd[Cbz-Ser(*t*Bu)-Phe] 5a

According to the general procedure D and starting with 1,2-Me,4-Oxd[Phe] **4a**, the title compound **5a** was obtained as a white solid in 51% yield (253.8 mg).

According to the general procedure E and starting with 2-Me,HO-aza[Phe]-OH **3a**, the title compound **5a** was obtained as a white solid in 70% yield (348.3 mg).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9H), 3.08 (s, 3H), 3.18-3.21 (m, 2H), 3.43 (dd, 1H, *J*=5.5 Hz, *J*=9.3 Hz), 3.59-3.66 (m, 1H), 5.14 (s, 2H), 5.44 (t, 1H, *J*=6.6 Hz), 5.79-5.84 (m, 1H), 7.16-7.24 (m, 2H), 7.29-7.35 (m, 5H), 7.38-7.39 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.2, 35.6, 36.5, 55.3, 56.4, 62.8, 67.2, 73.8, 127.9, 128.3, 128.7, 129.0, 129.1, 129.5, 134.2, 136.5, 152.9, 155.8, 166.5, 172.0; LC/MS r_t=2.14; ESI-MS$^+$ *m/z*: 498.1 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{26}H_{31}N_3O_7$ $[M+H]^+$: 498.2240, found: 498.2241; R_f=0.46 (cHx/EtOAc 8:2); $[\alpha]_D^{20}$= - 2.3 (C=1, Acetonitrile).

1,2-Bn,4-Oxd[Cbz-Phe-Val] 5b

According to the general procedure D and starting with 1,2-Bn,4-Oxd[Val] **4f**, the title compound **5b** was obtained as a white solid in 56% yield (296.6 mg).

According to the general procedure E and starting with 2-Bn,HO-aza[Val]-OH **3f**, the title compound **5b** was obtained as a white solid in 72% yield (381.3 mg).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (d, 3H, *J*=6.2 Hz), 0.95 (d, 3H, *J*=6.7 Hz), 1.92-2.03 (m, 1H), 2.83 (dd, 1H, *J*=7.6 Hz, *J*=13.4 Hz), 2.94 (dd, 1H, *J*=6.5 Hz, *J*=13.7 Hz) 4.57 (d, 1H, *J*=15.3 Hz), 4.76 (d, 1H, *J*=10.0 Hz), 4.82 (d, 1H, *J*=15.3 Hz), 5.12 (s, 2H), 5.47 (d, 1H, *J*=6.8 Hz), 5.98 (dd, 1H, *J*=7.4 Hz, *J*=14.8 Hz), 6.97-6.99 (m, 2H), 7.13-7.22 (m, 3H), 7.35-7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 19.3, 29.3, 40.1, 52.3, 55.5, 59.6, 67.2, 127.6, 128.3, 128.7, 128.8, 129.0, 129.4, 133.8, 135.1, 152.0, 165.6; LC/MS r_t=2.24; ESI-MS$^+$ *m/z*

530.2 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{30}H_{31}N_3O_6$ $[M+H]^+$: 530.2291, found: 530.2288; R_f=0.35 (cHx/EtOAc 8:2); $[\alpha]_D^{20}$= +69.7 (C=1, Acetonitrile).

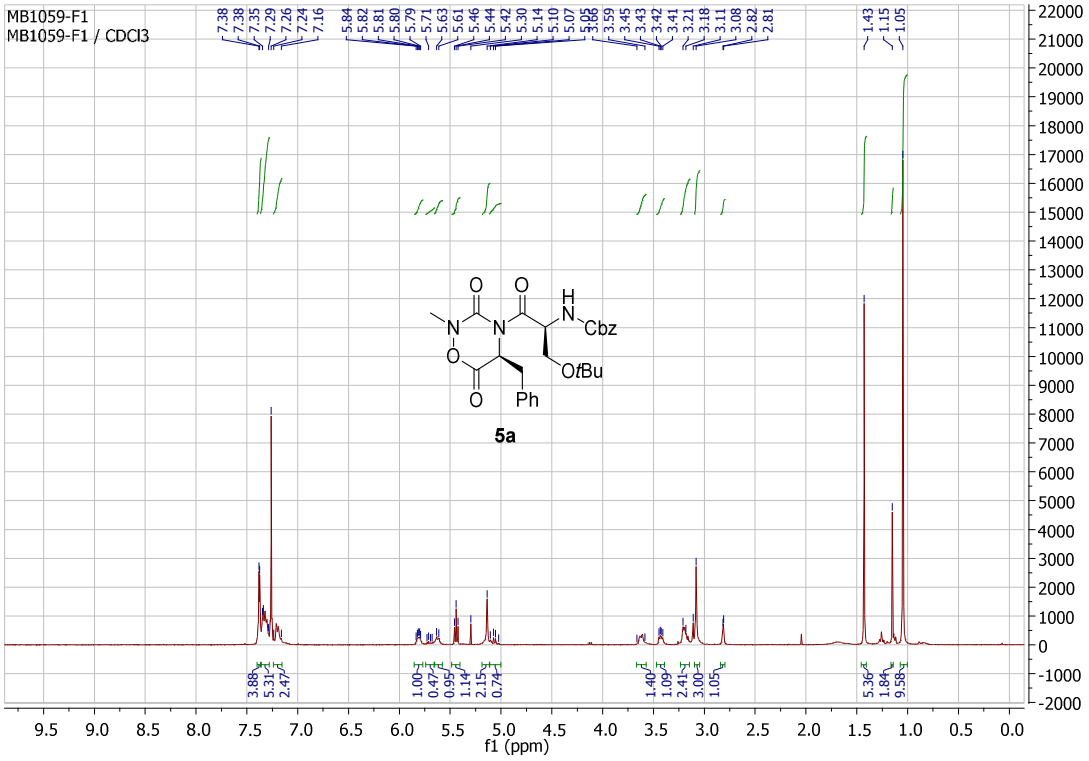
1,2-Bn,4-Oxd[Boc-Ala-Trp] 5c

According to the general procedure D and starting with 1,2-Bn,4-Oxd[Trp] **4g**, the title compound **5c** was obtained as a white solid in 52% yield (263.4 mg).

According to the general procedure E and starting with 2-Bn,HO-aza[Phe]-OH **3g**, the title compound **5c** was obtained as a white solid in 70% yield (354.6 mg).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 3H, *J*=7.1 Hz), 1.46 (s, 9H), 3.33 (dd, 1H, *J*=7.5 Hz, *J*=14.7 Hz), 3.41 (dd, 1H, *J*=5.1 Hz, *J*=14.6 Hz), 3.93 (d, 1H, *J*=16.0 Hz), 4.44 (d, 1H, *J*=15.3 Hz), 5.15 (d, 1H, *J*=9.1 Hz), 5.49 (dd, 1H, *J*=5.2 Hz, *J*=7.4 Hz), 5.54-5.64 (m, 1H), 7.04 (b, 1H), 7.13-7.25 (m, 4H), 7.30-7.32 (m, 3H), 7.34-7.36 (m, 1H), 7.55 (d, 1H, *J*=7.8 Hz), 8.14 (b, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.9, 26.8, 28.5, 50.8, 51.9, 55.4, 108.1, 111.5, 118.7, 120.2, 122.7, 124.5, 126.9, 128.6, 128.9, 129.1, 134.1, 136.4, 151.2, 155.3, 167.3, 174.9; LC/MS r_t=2.08; ESI-MS^+ *m/z* 507.2 $[M+H]^+$; HRMS (ESI+) *m/z*: Calcd for $C_{27}H_{30}N_4O_6$ $[M+H]^+$: 507.2244, found: 507.2244; R_f=0.29 (cHx/EtOAc 6:4); $[\alpha]_D^{20}$= -8.7 (C=1, Acetonitrile).

^{1}H and ^{13}C NMR spectra of 1,2,4-Oxd[PG-X_{AA2}-X_{AA1}]


MB1059-F1
MB1059-F1 / CDCl3
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7.38
7.35
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5.84
5.82
5.81
5.80
5.79
5.71
5.63
5.61
5.46
5.44
5.42
5.30
5.14
5.10
5.07
3.59
3.45
3.43
3.42
3.41
3.21
3.18
3.11
3.08
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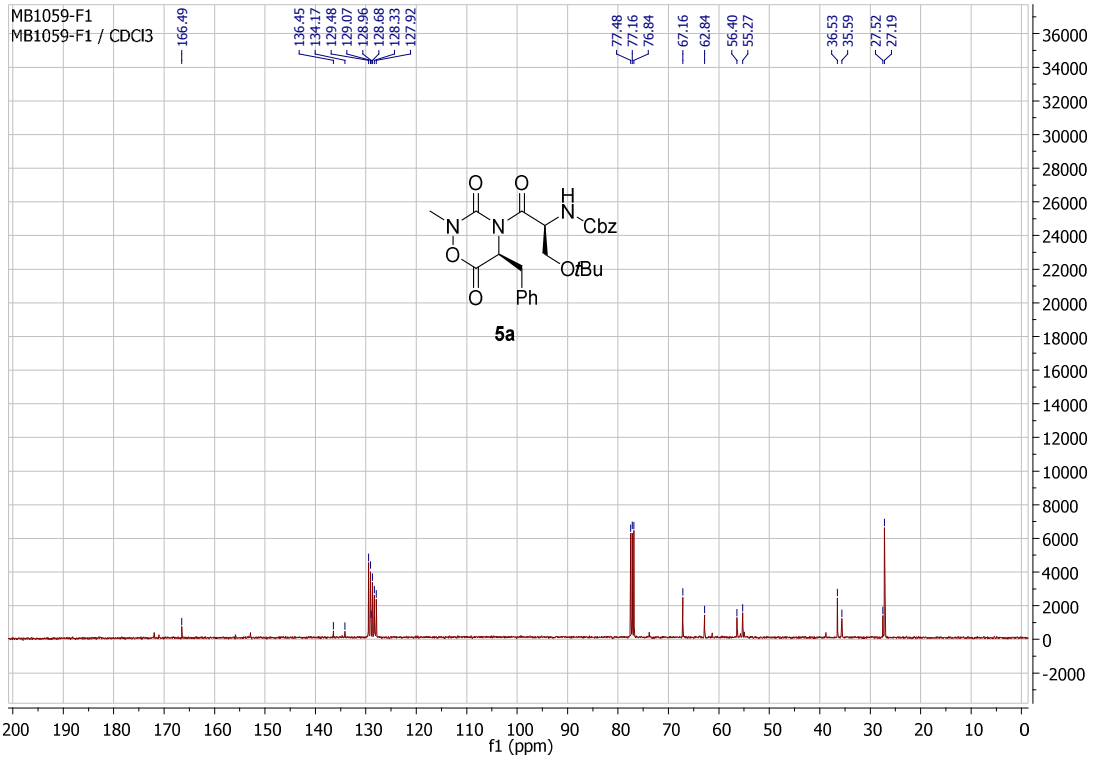
1.15
1.05
O
O
H
N
Cbz
N
N
O
OtBu
O
Ph
5a
3.88
5.31
2.47
1.00
0.47
0.95
1.14
2.15
0.74
1.40
1.09
2.41
3.00
1.05
5.36
1.84
9.58
f1 (ppm)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MB1059-F1 / CDCl3
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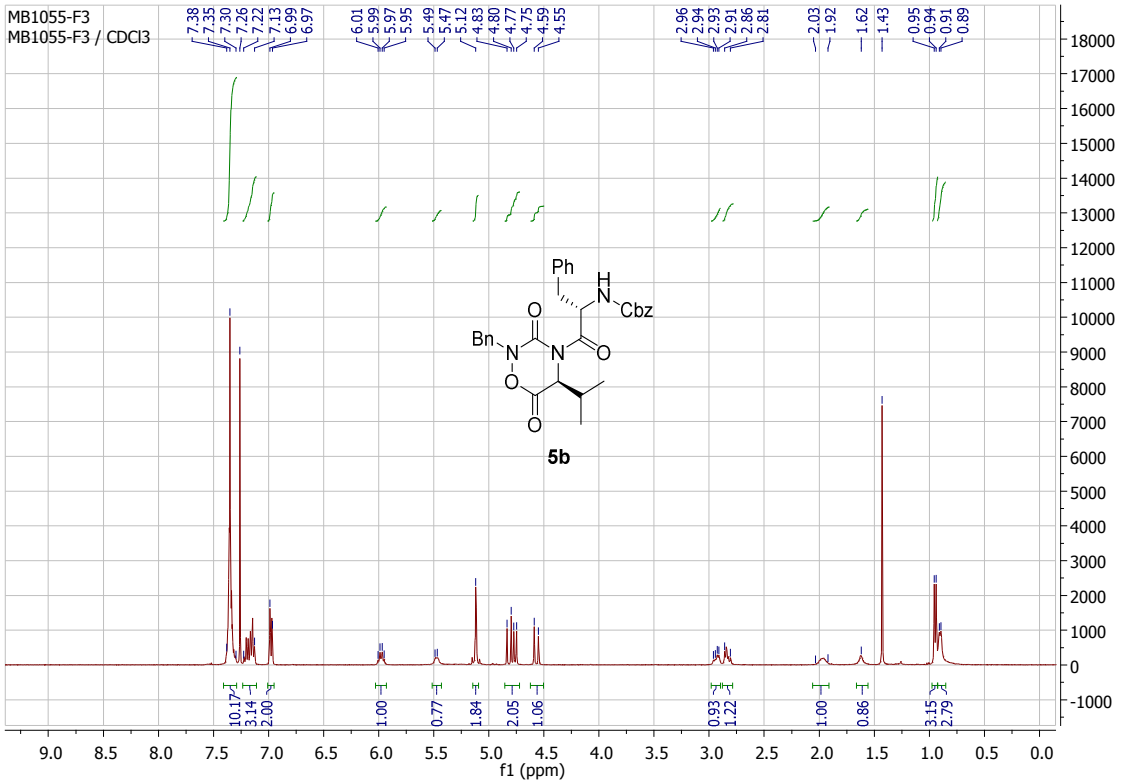
134.17
129.48
129.07
128.96
128.68
128.33
127.92
77.48
77.16
76.84
67.16
62.84
56.40
55.27
36.53
35.59
27.52
27.19
O
O
H
N
Cbz
N
N
O
OtBu
O
Ph
5a
f1 (ppm)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MB1055-F3 / CDCl3
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7.35
7.30
7.26
7.22
7.13
6.99
6.97
6.01
5.99
5.97
5.95
5.49
5.47
5.12
4.83
4.80
4.77
4.75
4.59
4.55
2.96
2.94
2.93
2.91
2.86
2.81
2.03
1.92
1.62
1.43
0.95
0.94
0.91
0.89
Ph
H
N
Cbz
Bn
N
O
N
O
O
O
5b
10.17
3.14
2.00
1.00
0.77
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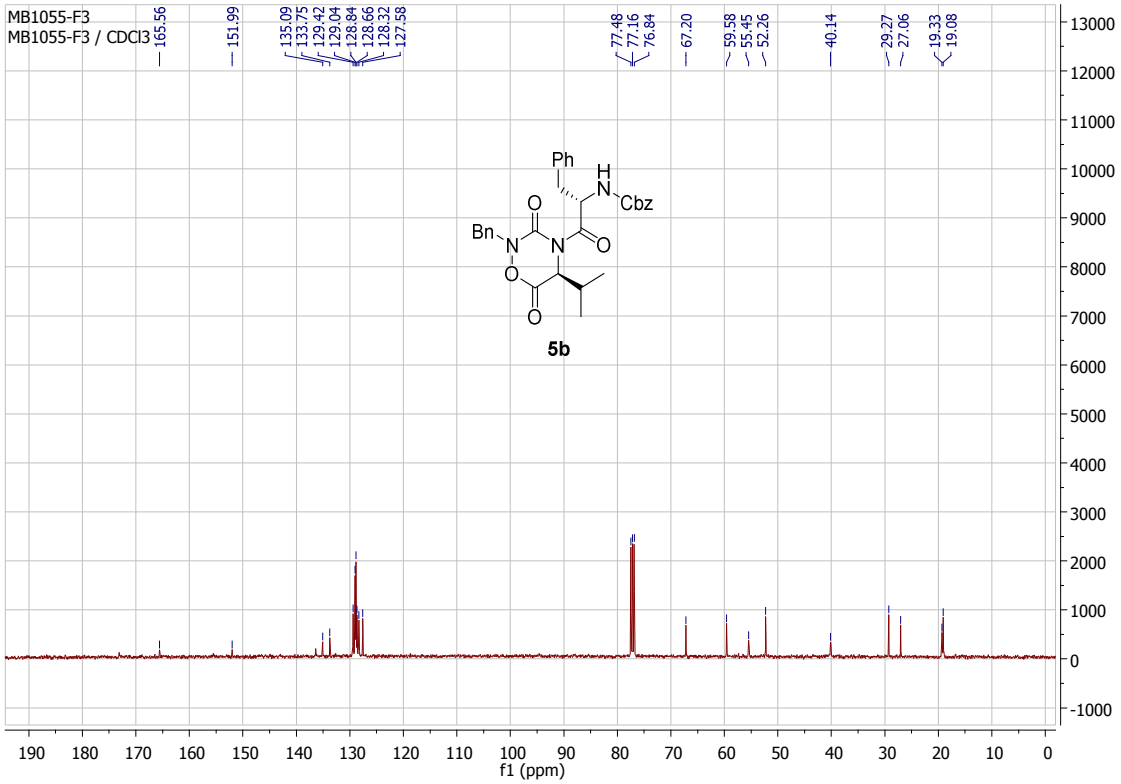
2.05
1.06
0.93
1.22
1.00
0.86
3.15
2.79
f1 (ppm)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MB1055-F3 / CDCl3
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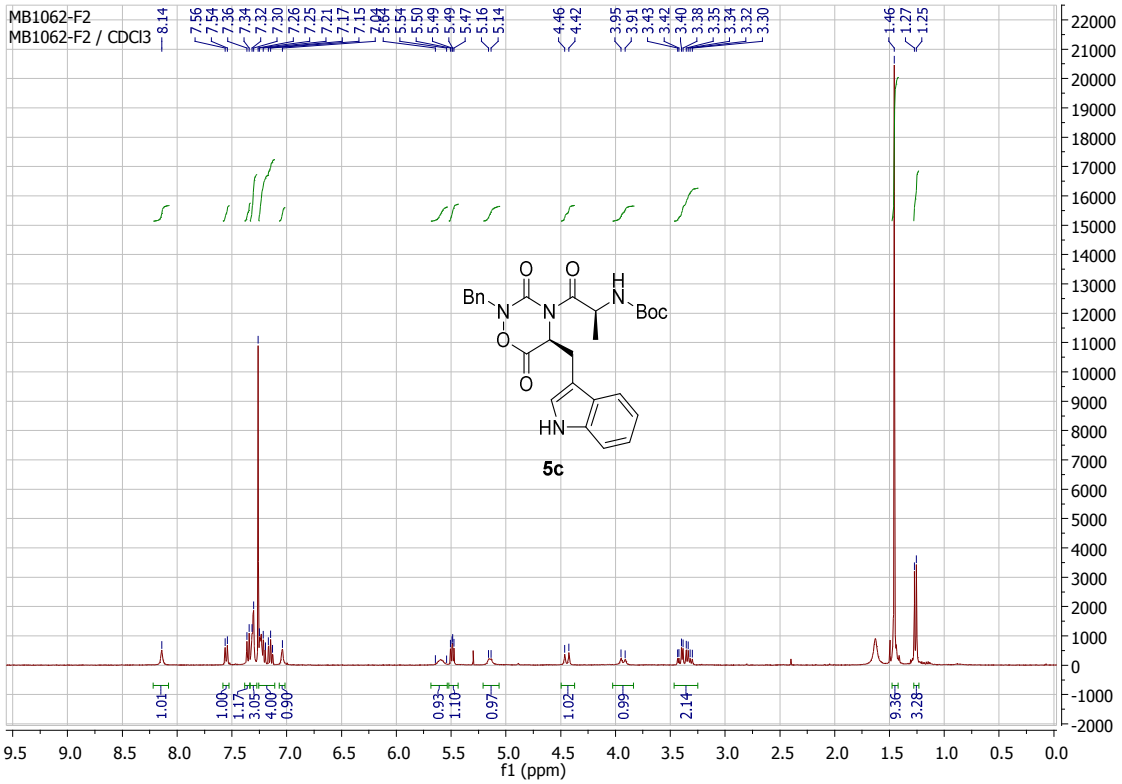
135.09
133.75
129.42
129.04
128.84
128.66
128.32
127.58
77.48
77.16
76.84
67.20
59.58
55.45
52.26
40.14
29.27
27.06
19.33
19.08
Ph
H
N
Cbz
Bn
N
O
N
O
O
O
5b
f1 (ppm)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MB1062-F2 / CDCl3
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7.54
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7.32
7.30
7.26
7.25
7.21
7.17
7.15
7.04
5.84
5.54
5.50
5.49
5.49
5.47
5.16
5.14
4.46
4.42
3.95
3.91
3.43
3.42
3.40
3.38
3.35
3.34
3.32
3.30
1.46
1.27
1.25
Bn
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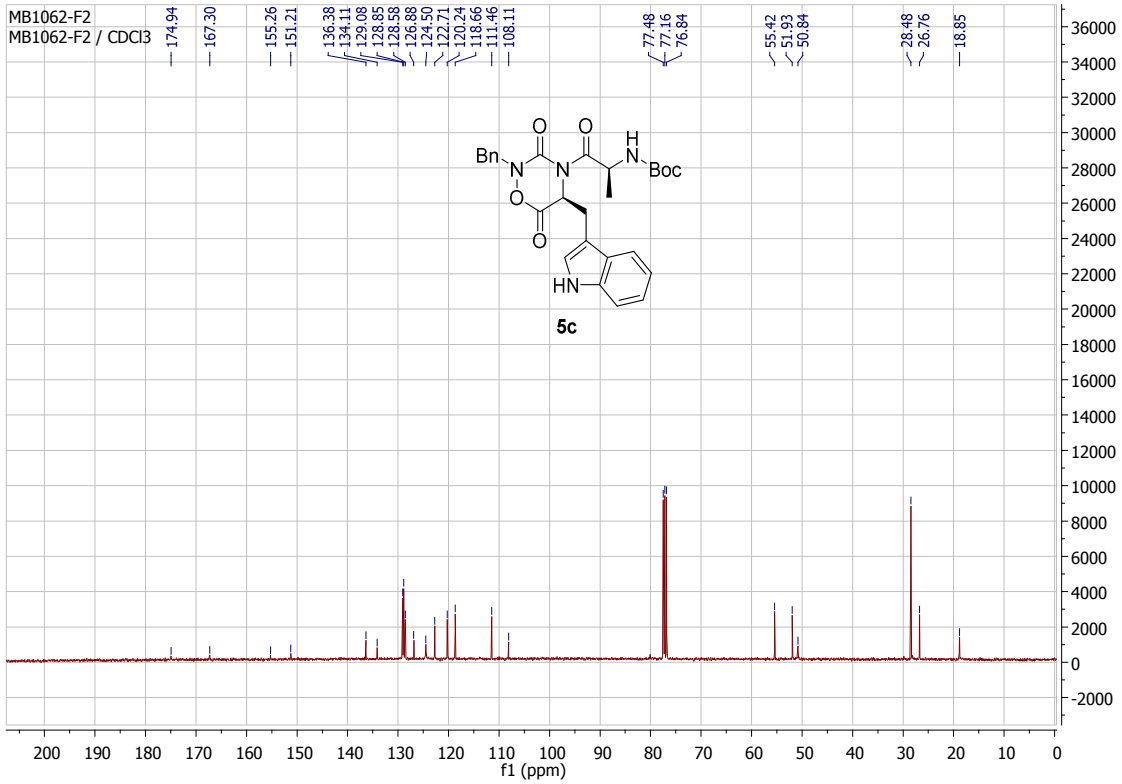
O
N
O
O
O
H
N
Boc
HN
5c
1.01
1.00
1.17
3.05
4.00
0.90
0.93
1.10
0.97
1.02
0.99
2.14
9.36
3.28
f1 (ppm)


MB1062-F2
MB1062-F2 / CDCl3
174.94
167.30
155.26
151.21
136.38
134.11
129.08
128.85
128.58
126.88
124.50
122.71
120.24
118.66
111.46
108.11
77.48
77.16
76.84
55.42
51.93
50.84
28.48
26.76
18.85
Bn
N
O
N
O
O
O
H
N
Boc
HN
5c
f1 (ppm)

Crystallographic data of 4c and 5a

For **4c**:
The crystal was placed in the cold stream of an Oxford Cryosystems open-flow nitrogen cryostat [1] with a nominal stability of 0.1K. X-ray data were collected on a Gemini-S (Agilent Technologie) diffractometer equipped with a copper microsource (λ = 1.5418). Diffraction data were processed using CrysAlisPro.

For **5a**:

Crystals were selected under polarizing optical microscope and mounted on MicroMount needles (MiTiGen) for single-crystal X-ray diffraction experiments. X-ray intensity data were collected on a Bruker APEX II Quazar diffractometer (4 circle Kappa goniometer, CCD detector) using Iμs microfocus source (Mo-K_α radiation with λ = 0.71073 Å) at 296 K. The structure solutions were obtained by direct methods, developed by successive difference Fourier syntheses, and refined by full-matrix least-squares on all F^2 data using SHELX program suite in Bruker APEX2 interface.[2]

Details of each structure determinations are given in Table S1.

The crystal structures of DKP, DKM and aza-DKM were superimposed on the heterocycles using MOLMOL.[3] The representation and quantitative analysis were carried out using MOLMOL and Pymol (Delano scientific).

Table S1: Selected crystallographic data for 4c and 5a.

	4c	**5a**
Molecular fomula	$C_{18}H_{18}N_2O_4$	$C_{26}H_{31}N_3O_7$
M (g.mol^{-1})	326.34	497.54
Space group	$P2_1$	$C2/c$
a (Å)	15.1202(7)	20.2258(12)
b (Å)	5.6812(3)	9.7315(6)
c (Å)	19.0459(8)	28.7120(16)
beta (°)	97.578(4)	108.254(2)
Volume	1621.77(7)	5366.9(6)
Dx (g.cm^{-3})	1.337	1.232
Z	4	8
F(000)	687.996	2112.0
Nref(measured)	17075	4931
R_{int}	0.064	0.090
Data completeness	98.88	0.999
Theta (max)	68.0610	25.350
$R_1(F^2 > 2\,\sigma(F^2))$	0.051 (5750)	0.0588 (2619)
wR2 (all data)	0.057 (4615)	0.1959 (4927)
S	1.0953	1.013
Npar	440	330

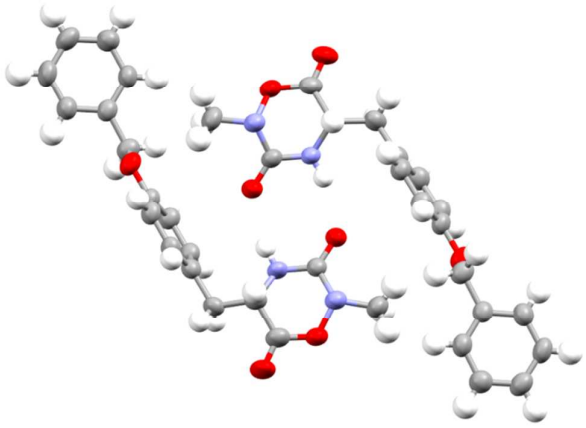


Figure S1: X-ray crystal structures of the aza-DKM **4c**.

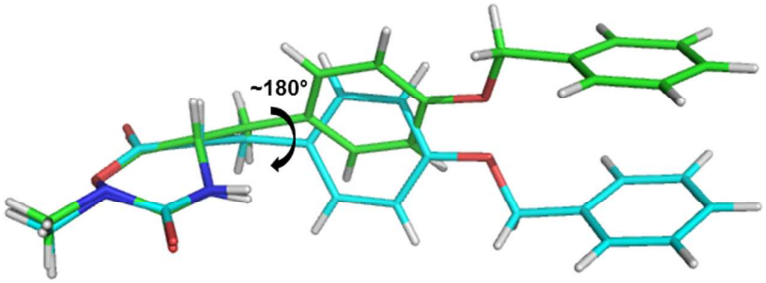


Figure S2: superimposition of the two independent molecules of **4c**

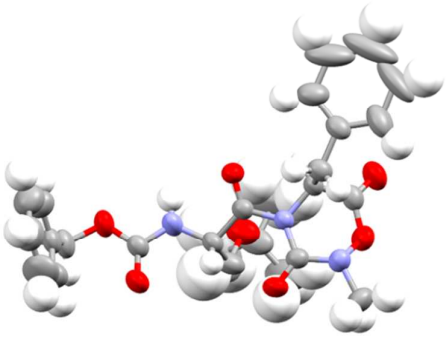


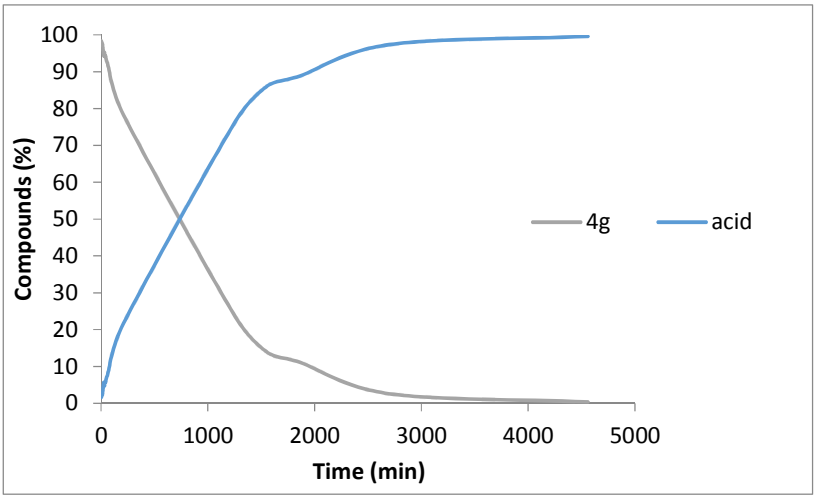
Figure S3: X-ray crystal structures of the aza-DKM **5a**.

(1) Cosier, J. & Glazer, A.M., 1986. J. Appl. Cryst. 105-107.
(2) G.M. Sheldrick, " SHELXL-2014 ", Program for crystal structure determination, Göttingen Univ., Germany (2014).
(3) R. Koradi, M. Billeter, K. Wuthrich, J. Mol. Graph. 1996, 14, 51-55, 29-32.

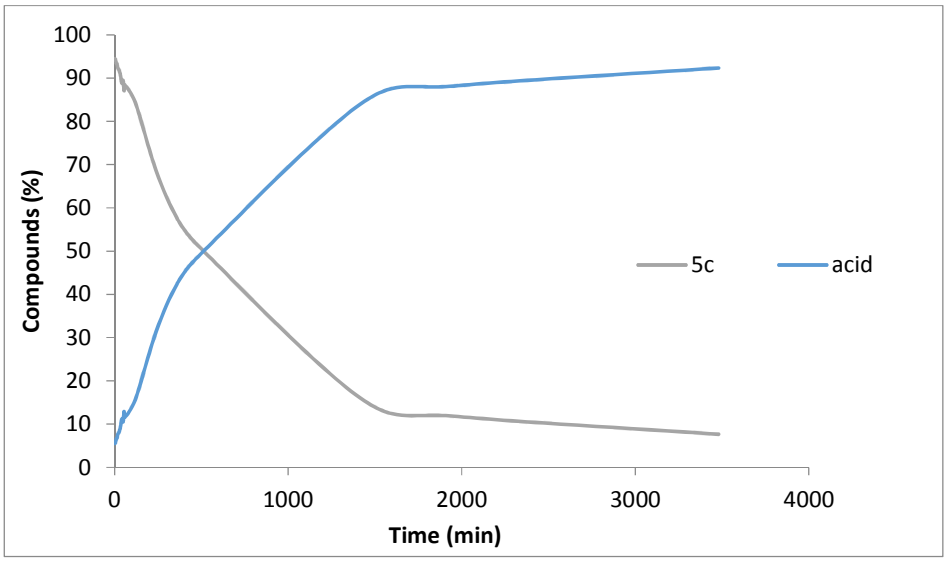
Evaluation of the aqueous stability by LC/MS analysis of 4g and 5c

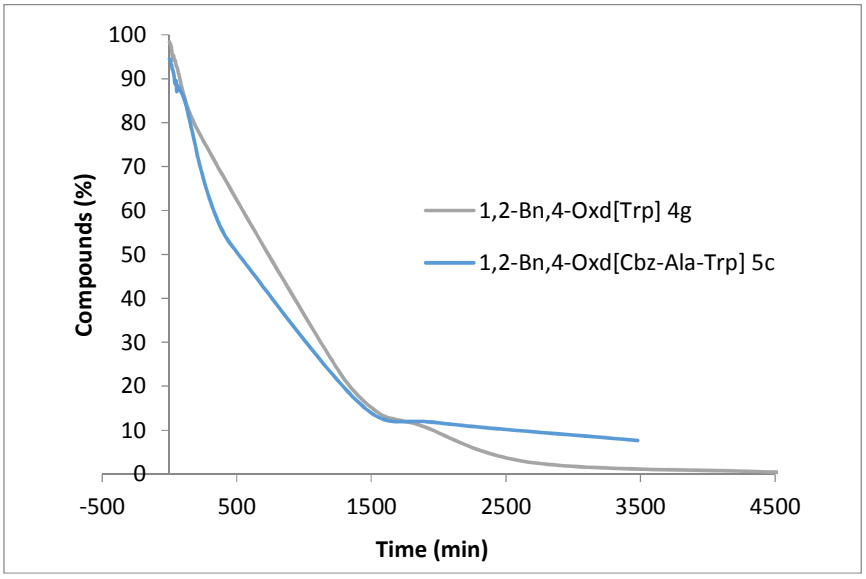
Compound **4g** and **5c** are diluted into water and directly analyzed by LC/MS.

t (min)	4g (%)	Acid (%)
0	98,4	1,6
5	98,05	1,95
10	97,7	2,3
15	96,9	3,1
20	95,4	4,6
25	94,3	5,7
30	95,3	4,7
35	94,25	5,75
40	94,3	5,7
45	93,69	6,31
50	92,95	7,05
55	92,66	7,34
60	92,26	7,74
210	78,25	21,75
1260	23,37	76,63
1560	13,81	86,19
1860	11,16	88,84
2700	2,61	97,39
4560	0,39	99,61



t (min)	5c (%)	Acid (%)
0	94,5	5,5
5	94,37	5,63
10	93,48	6,52
15	93,18	6,82
20	92,26	7,74
25	91,99	8,01
30	91,37	8,63
35	90,52	9,48
40	89,15	10,85
45	88,78	11,22
50	89,45	10,55
55	87,1	12,9
60	88,38	11,62
120	84,37	15,63
240	68,59	31,41
360	57,6	42,4
480	51,33	48,67
1440	15,36	84,64
1980	11,75	88,25
3480	7,65	92,35




100
90
80
70
60
50
40
30
20
10
0
Compounds (%)
-500
500
1500
2500
3500
4500
Time (min)
1,2-Bn,4-Oxd[Trp] 4g
1,2-Bn,4-Oxd[Cbz-Ala-Trp] 5c