Electronic Supplementary Material (ESI) for Chemical Communications.

Modular synthesis of thirty lead-like scaffolds suitable for CNS drug discovery programmes

Joan Mayol-Llinàs, William Farnaby* and Adam Nelson*

Supporting Information

Contents

General Experimental

Commercially available starting materials were obtained from Sigma−Aldrich, Fluorochem and Alfa Aesar. All non-aqueous reactions were performed under nitrogen atmosphere unless otherwise stated. Water-sensitive reactions were performed in anhydrous solvents in oven-dried glassware cooled under nitrogen before use. Anhydrous dichloromethane (DCM), anhydrous tetrahydrofuran (THF), anhydrous toluene, anhydrous diethyl ether, anhydrous ethanol, anhydrous methanol and anhydrous acetonitrile were obtained from a PureSolv MD5 Purification System. Anhydrous dimethylsulfoxide (DMSO) and anhydrous 1,4-dioxane were obtained from SureSeal bottles from Sigma−Aldrich. All other solvents used were of chromatography or analytical grade. Petrol refers to petroleum spirit (b.p. 40-60 °C). An IKA RV 10 rotary evaporator was used to remove the solvents under reduced pressure.

Thin layer chromatography (TLC) was performed using aluminium backed silica (Merck silica gel 60 F254) plates obtained from Merck. Ultraviolet lamp (λ_{max} = 254 nm) and $KMnO_4$ were used for visualization. Flash column chromatography was performed using silica gel 60 (35-70 μm particles) supplied by Merck. A Bruker Daltonics micrOTOF spectrometer with electrospray (ES) ionisation source was used for high-resolution mass spectrometry (HRMS). Perkin-Elmer One FT-IR spectrometer was used to analyse the infrared spectra. Melting points (m.p.) were determined using Stuart melting point apparatus SMP3. X-ray measurements were carried out at 120 K on an Agilent SuperNova diffractometer equipped with an Atlas CCD detector and connected to an Oxford Cryostream low temperature device using mirror monochromated Cu K_α radiation (λ = 1.54184 Å) from a Microfocus X-ray source. The structure was solved by intrinsic phasing using SHELXT[1] and refined by a full matrix least squares technique based on F^2 using SHELXL2014.[2]

Proton (^{1}H) and carbon (^{13}C) NMR data was collected on a Bruker 300, 400 or 500 MHz spectrometer. Data was collected at 300 K unless otherwise stated. Chemical shifts (δ) are given in parts per million (ppm) and they are referenced to the residual solvent peak. Coupling constants (*J*) are reported in Hertz (Hz) and splitting patterns are reported in an abbreviated manner: app. (apparent), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br. (broad). Assignments were made using COSY, DEPT, HMQC and NOESY experiments.

Preparation of Cyclisation Precursors 1a–g

Building blocks 4-benzoylmorpholin-3-one, **8** and **10** were prepared following literature procedures,[3–5] respectively.

General Procedure A

By modification of an existing procedure,[6] LiHMDS (2.20 eq of a 1.0 M solution in toluene or THF) was added to a solution of the carbonyl derivative (1.00 eq) in toluene (0.17 M) at −78 °C. After stirring the mixture for 1.5 h at −78 °C, a solution of the imidazole derivative **8** (1.20 eq) in toluene (2.50 M) was added dropwise and the reaction mixture was stirred at −78 °C for 3 h. Then, the reaction was allowed to warm to rt and a saturated aqueous solution of NH_4Cl (5 mL per 1.00 mmol of the carbonyl derivative) was added. The phases were separated and the aqueous phase was extracted with Et_2O or EtOAc (3 × (2 mL per 1.00 mmol of the carbonyl derivative)). Then, the organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure B

By modification of an existing procedure,[7] LiHMDS (2.20 eq of a 1.0 M solution in toluene) was added to a solution of the carbonyl derivative (1.00 eq) in the specified amount of toluene at 0 °C. After stirring for 15 min, allyl chloroformate (1.20 eq) was added and the reaction mixture was allowed to warm to rt and stirred for 1 h. Then, a saturated aqueous solution of NH_4Cl (3 mL per 1.00 mmol of the carbonyl derivative) was added, the mixture was stirred for 15 min, the phases were separated and the aqueous phase was extracted with EtOAc (3 × (1 mL per 1.00 mmol of the carbonyl derivative)). The organic phases were combined, washed with brine (2 mL per 1.00 mmol of the carbonyl derivative), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure C

According to a procedure,[8] the sulfone derivative **10** (1.20 eq) was added to a solution of the allyl ester derivative (1.00 eq) in DCM (0.10 M) at rt. After stirring the mixture for 5 min, Cs_2CO_3 (2.50 eq) was added and the reaction was stirred for the specified time at rt. Then, a

saturated aqueous solution of NH_4Cl (10 mL per 1.00 mmol of the allyl ester derivative) was added and the mixture was stirred for 30 min at rt. The phases were separated and the organic phase was extracted with DCM (3 × (5 mL per 1.00 mmol of the allyl ester derivative)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

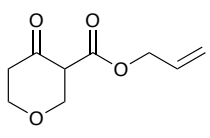
General Procedure D

By modification of an existing procedure,[9] the specified amount of K_2CO_3 was added to a solution of the allyl ester derivative **S1** (1.00 eq) in acetone (0.26 M). After stirring for 15 min at rt, the specified amount of the arylmethyl bromide derivative was added dropwise and the reaction mixture was stirred at 70 °C for 2 h. Then, the mixture was allowed to cool to rt, a saturated aqueous solution of NH_4Cl (9 mL per 1.00 mmol of the allyl ester derivative **S1**) was added and the mixture was stirred for 30 min. Subsequently, EtOAc (6 mL per 1.00 mmol of the allyl ester derivative **S1**) was added, the phases were separated and the aqueous phase was extracted with EtOAc (3 × (5 mL per 1.00 mmol of the allyl ester derivative **S1**)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure E

According to a procedure,[10] PPh_3 (0.20 eq) and $Pd(OAc)_2$ (0.05 eq) were added to a solution of the quaternary allyl ester derivative (1.00 eq) in THF (0.10 M) and the reaction mixture was stirred for 1 h at 70 °C. Then, the solution was allowed to cool to rt, filtered through celite and concentrated under reduced pressure to give a crude material.

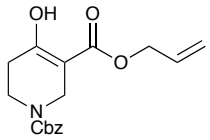
Prop-2-en-1-yl 4-oxooxane-3-carboxylate



9

According to General Procedure A, tetrahydro-4*H*-pyran-4-one (3.84 mL, 41.6 mmol) and LiHMDS (91.6 mL, 91.6 mmol of a 1.0 M solution in toluene) gave a crude material. The crude material was extracted with EtOAc and purified by flash column chromatography eluting with 5:95 EtOAc−hexane to yield the *allyl ester derivative* ***9*** (3.48 g, 45%, *keto:enol* 24:76 by ^{1}H-NMR in $CDCl_3$) as a colourless oil, R_f 0.72 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2968, 2856, 1741, 1718, 1663, 1624, 1395, 1305, 1216, 1101, 1047; δ_H (500 MHz, $CDCl_3$) 5.92 (2H, ddt, *J* 17.3, 10.5 and 5.6, propenyl 2-H), 5.34 (1H, app. q, *J* 1.5, 3-H_{trans}^{keto}), 5.31 (1H, app. dq, *J* 17.3 and 1.5, propenyl 3-H_{trans}^{enol}), 5.26 (1H, app. dd, *J* 10.5 and 1.2, propenyl 3-H_{cis}^{keto}), 5.25 (1H, app. dq, *J* 10.5 and 1.5, propenyl 3-H_{cis}^{enol}), 4.65 (4H, dt, *J* 5.6 and 1.5, propenyl 1-H_2), 4.29 (2H, app. t, *J* 1.7, 2-H_2^{enol}), 4.23 (1H, dd, *J* 11.6 and 7.1, 2-H_A^{keto}), 4.11 (1H, ddd, *J* 11.6, 5.1 and 0.9, 2-H_B^{keto}), 4.05-3.93 (2H, m, 6-H_2^{keto}), 3.84 (2H, t, *J* 5.7, 6-H_2^{enol}), 3.50 (1H, app. ddd, *J* 6.8, 5.1 and 1.3, 3-H^{keto}), 2.67 (1H, ddd, *J* 14.5, 6.2 and 5.1, 5-H_A^{keto}), 2.55 (1H, dddd, *J* 14.5, 7.1, 5.5 and 1.3, 5-H_B^{keto}), 2.39 (2H, tt, *J* 5.7 and 1.7, 5-H_2^{enol}); δ_C (75 MHz, $CDCl_3$) 201.2 (C-4^{keto}), 169.7 (carboxylate C=O^{enol}), 169.3 (C-4^{enol}), 167.5 (carboxylate C=O^{keto}), 131.9 (propenyl C-2^{enol}), 131.5 (propenyl C-2^{keto}), 118.8 (propenyl C-3^{keto}), 118.3 (propenyl C-3^{enol}), 97.3 (C-3^{enol}), 69.6 (C-2^{keto}), 68.2 (C-6^{keto}), 66.0 (propenyl C-1^{keto}), 64.8 (propenyl C-1^{enol}), 63.9 (C-6^{enol}), 63.0 (C-2^{enol}), 57.8 (C-3^{keto}), 42.0 (C-5^{keto}), 28.8 (C-5^{enol}); HRMS found MNa^+, 207.0627. $C_9H_{12}O_4$ requires *MNa*, 207.0627. Compound **9** existed as a mixture of keto and enol tautomers.

1-Benzyl 3-prop-2-en-1-yl 4-hydroxy-1,2,5,6-tetrahydropyridine-1,3-dicarboxylate

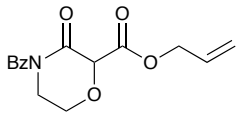


S1

According to General Procedure B, 1-(benzyloxycarbonyl)-4-piperidinone (10.6 g, 45.45 mmol) in toluene (68.0 mL) gave a crude material. The crude material was purified by flash column chromatography, eluting with 10:90 EtOAc−hexane to yield the *allyl ester derivative* ***S1*** (5.77 g, 40%, >98% enol by ^{1}H-NMR in $CDCl_3$) as a colourless oil, R_f 0.60 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3032, 2945, 1697, 1662, 1620, 1422, 1305, 1227, 1193, 1111,

1056; δ_H (400 MHz, $CDCl_3$) 7.39-7.31 (5H, m, phenyl), 5.94 (1H, ddt, *J* 17.2, 10.5 and 5.6, propenyl 2-H), 5.34 (1H, dd, *J* 17.2 and 1.4, propenyl 3-H_{trans}), 5.26 (1H, app. dq, *J* 10.5 and 1.4, propenyl 3-H_{cis}), 5.17 (2H, s, arylmethyl 1-H_2), 4.69 (2H, app. dt, *J* 5.6 and 1.4, propenyl 1-H_2), 4.18 (2H, s, 2-H_2), 3.65 (2H, t, *J* 5.9, 6-H_2), 2.40 (2H, app. br. s, 5-H_2); δ_C (100 MHz, $CDCl_3$) 170.6 (carboxylate C=O), 170.3 (C-4), 155.3 (Cbz C=O), 136.7 (phenyl C-1), 131.8 (propenyl C-2), 128.6 (phenyl C_2-3,5), 128.2 (phenyl C_2-2,6), 128.1 (phenyl C-4), 118.6 (propenyl C-3), 95.8 (C-3), 67.4 (arylmethyl C-1), 65.2 (propenyl C-1), 40.6 (C-2), 40.0 (C-6), 28.8 (C-5); HRMS found MH^+, 318.1330. $C_{17}H_{19}NO_5$ requires *MH*, 318.1335. Compound **S1** existed exclusively as the enol tautomer.

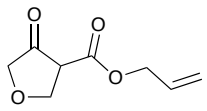
Prop-2-en-1-yl-4-benzoyl-3-oxomorpholine-2-carboxylate



S2

According to General Procedure A, 4-benzoylmorpholin-3-one (9.32 g, 45.4 mmol) and LiHMDS (100 mL, 100 mmol of a 1.0 M solution in THF) gave a crude material. The crude material was extracted with Et_2O and purified by flash column chromatography eluting with DCM to yield the allyl ester derivative[6] **S2** (5.00 g, 41%) as a light yellow oil, R_f 0.62 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2950, 2893, 1745, 1685, 1449, 1373, 1274, 1227, 1155, 1139; δ_H (500 MHz, $CDCl_3$) 7.65-7.61 (2H, m, phenyl 2,6-H_2), 7.51 (1H, tt, *J* 7.1 and 1.2, phenyl 4-H), 7.42-7.36 (2H, m, phenyl 3,5-H_2), 5.94 (1H, ddt, *J* 17.3, 10.5 and 5.9, propenyl 2-H), 5.38 (1H, app. dq, *J* 17.3 and 1.3, propenyl 3-H_{trans}), 5.30 (1H, app. dq, *J* 10.5 and 1.3, propenyl 3-H_{cis}), 4.83 (1H, s, 2-H), 4.74 (2H, app. dt, *J* 5.9 and 1.3, propenyl 1-H_2), 4.35 (1H, ddd, *J* 12.0, 7.9 and 3.7, 6-H_A), 4.07 (1H, ddd, *J* 12.0, 5.4 and 3.8, 6-H_B), 4.00 (1H, ddd, *J* 13.3, 7.9 and 3.8, 5-H_B), 3.93 (1H, ddd, *J* 13.3, 5.4 and 3.7, 5-H_A); δ_C (125 MHz, $CDCl_3$) 172.6 (C-3), 166.5 (benzoyl C=O), 165.6 (carboxylate C=O), 134.6 (phenyl C-1), 132.4 (phenyl C-4), 131.0 (propenyl C-2), 128.5 (phenyl C_2-2,6), 128.2 (phenyl C_2-3,5), 119.7 (propenyl C-3), 77.1 (under signal for residual solvent, C-2), 66.9 (propenyl C-1), 62.4 (C-6), 44.7 (C-5); HRMS found MH^+, 290.1024. $C_{15}H_{15}NO_5$ requires *MH*, 290.1022.

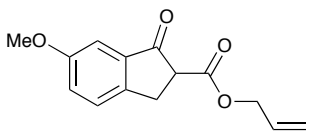
Prop-2-en-1-yl 4-oxooxolane-3-carboxylate



S3

According to a procedure for a related compound,[11] methyl glycolate (8.57 mL, 111 mmol) was added dropwise to a suspension of NaH (4.88 g, 122 mmol of a 60% dispersion in mineral oil) in Et_2O (370 mL). After stirring for 4 h, the solvent was removed under reduced pressure and the crude material was dissolved in DMSO (222 mL). The solution was cooled to 0 °C and allyl acrylate (16.3 mL, 122 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred overnight. An aqueous solution of 10% HCl (70 mL) and Et_2O (200 mL) were added and the mixture was stirred for 30 min. Water (70 mL) was added, the phases were separated and the aqueous phase was extracted with Et_2O (4 × 100 mL). The organic phases were combined, washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material. The crude material was purified by flash column chromatography, eluting with 10:90→20:80 EtOAc−hexane to yield the *allyl ester derivative* ***S3*** (5.45 g, 29%) as a pink oil, R_f 0.43 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 2951, 2883, 1770, 1725; δ_H (400 MHz, $CDCl_3$) 5.90 (1H, ddt, *J* 17.2, 10.3 and 5.7, propenyl 2-H), 5.34 (1H, dd, *J* 17.2 and 1.4, propenyl 3-H_{trans}), 5.26 (1H, dd, *J* 10.3 and 1.4, propenyl 3-H_{cis}), 4.71-4.60 (2H, m, propenyl 1-H_2), 4.49 (1H, dd, *J* 9.7 and 8.3, 2-H_A), 4.44 (1H, dd, *J* 9.7 and 8.3, 2-H_B), 4.02 (1H, d, *J* 17.1, 5-H_A), 3.94 (1H, d, *J* 17.1, 5-H_B), 3.53 (1H, t, *J* 8.3, 3-H); δ_C (100 MHz, $CDCl_3$) 207.3 (C-4), 166.3 (carboxylate C=O), 131.4 (propenyl C-2), 119.1 (propenyl C-3), 70.8 (C-5), 69.5 (C-2), 66.5 (propenyl C-1), 53.4 (C-3); HRMS found MNa^+, 193.0467. $C_8H_{10}O_4$ requires *MNa*, 193.0471.

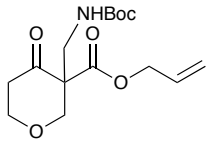
Prop-2-en-1-yl 6-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate



S4

According to General Procedure B, 6-methoxy-1-indanone (7.37 g, 45.45 mmol) in toluene (100 mL) gave a crude material. The crude material was purified by flash column chromatography, eluting with 10:90 EtOAc−hexane to yield the allyl ester derivative[12] **S4** (5.23 g, 47%) as a brown oil, R_f 0.56 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 2940, 2837, 1736, 1704, 1571, 1491, 1432, 1317, 1296, 1273, 1204, 1184, 1148, 1024; δ_H (400 MHz, $CDCl_3$) 7.39 (1H, dd, *J* 8.3 and 0.8, 4-H), 7.22 (1H, dd, *J* 8.3 and 2.5, 5-H), 7.19 (1H, d, *J* 2.5, 7-H), 5.94 (1H, ddt, *J* 17.2, 10.5 and 5.7, propenyl 2-H), 5.37 (1H, app. dq, *J* 17.2 and 1.4, propenyl 3-H_{trans}), 5.26 (1H, app. dq, *J* 10.5 and 1.4, propenyl 3-H_{cis}), 4.69 (2H, app. tt, *J* 5.7 and 1.4, propenyl 1-H_2), 3.83 (3H, s, methoxy), 3.78 (1H, dd, *J* 8.1 and 3.9, 2-H), 3.47 (1H, dd, *J* 16.9 and 3.9, 3-H_A), 3.32 (1H, dd, *J* 16.9 and 8.1, 3-H_B); δ_C (100 MHz, $CDCl_3$) 199.3 (C-1), 168.9 (carboxylate C=O), 159.8 (C-6), 146.5 (C-3a), 136.5 (C-7a), 131.7 (propenyl C-2), 127.2 (C-4), 125.0 (C-5), 118.6 (propenyl C-3), 105.7 (C-7), 66.2 (propenyl C-1), 55.7 (methoxy), 54.0 (C-2), 29.7 (C-3); HRMS found MNa^+, 269.0782. $C_{14}H_{14}O_4$ requires *MNa*, 269.0784.

Prop-2-en-1-yl 3-({[(*tert*-butoxy)carbonyl]amino}methyl)-4-oxooxane-3-carboxylate

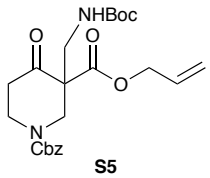


11

According to General Procedure C, the allyl ester derivative **9** (7.00 g, 38.0 mmol) was stirred overnight to give a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *quaternary allyl ester derivative **11*** (10.1 g, 85%) as a colourless oil, R_f 0.67 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3403, 2976, 2934, 2868, 1709, 1501, 1366, 1249, 1225, 1212, 1163, 1135, 1112; δ_H (400 MHz, $CDCl_3$) 5.88 (1H, ddt, *J* 17.3, 10.4 and 5.8, propenyl 2-H), 5.31 (1H, app. dq, *J* 17.3 and 1.4, propenyl 3-H_{trans}), 5.24 (1H, app. dq, *J* 10.4 and 1.4, propenyl 3-H_{cis}), 5.09 (1H, app. t, *J* 5.6, NH), 4.65 (1H, app. t, *J* 1.4, propenyl 1-H_A), 4.64 (1H, app. t, *J* 1.4, propenyl 1-H_B), 4.44 (1H, d, *J* 11.8, 2-H_A), 4.14-4.05 (1H, m, 6-H_A), 3.87-3.76 (1H, m, 6-H_B), 3.60 (1H, dd, *J* 14.1 and 6.8, methylcarbamate 1-H_A), 3.58 (1H, d, *J* 11.8, 2-H_B), 3.50 (1H, dd, *J* 14.1 and 6.8,

methylcarbamate 1-H_B), 2.76 (1H, ddd, *J* 15.4, 9.3 and 6.4, 5-H_A), 2.59 (1H, app. dt, *J* 14.9 and 4.4, 5-H_B), 1.38 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 204.1 (C-4), 169.4 (carboxylate C=O), 155.8 (Boc C=O), 131.3 (propenyl C-2), 119.2 (propenyl C-3), 79.7 (^{t}Bu C_1), 72.3 (C-2), 68.4 (C-6), 66.5 (propenyl C-1), 64.0 (C-3), 41.0 (C-5 and methylcarbamate C-1), 28.3 (^{t}Bu C_3); HRMS found MH^+, 314.1601. $C_{15}H_{23}NO_6$ requires *MH*, 314.1598.

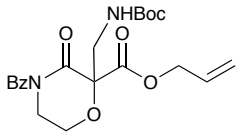
1-Benzyl 3-prop-2-en-1-yl 3-({[(*tert*-butoxy)carbonyl]amino}methyl)-4-oxopiperidine-1,3-dicarboxylate



S5

According to General Procedure C, the allyl ester derivative **S1** (6.47 g, 20.4 mmol) was stirred overnight to give a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *quaternary allyl ester derivative* ***S5*** (7.69 g, 84%) as a colourless oil, R_f 0.63 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3398, 2977, 1697, 1499, 1423, 1365, 1234, 1138; δ_H (500 MHz, CD_3OD, 333 K) 7.42-7.28 (5H, m, phenyl), 5.86 (1H, ddt, *J* 17.3, 10.5 and 5.8, propenyl 2-H), 5.28 (1H, app. dq, *J* 17.3 and 1.4, propenyl 3-H_{trans}), 5.19 (1H, app. dq, *J* 10.5 and 1.4, propenyl 3-H_{cis}), 5.16 (1H, app. s, arylmethyl 1-H_A), 5.15 (1H, app. s, arylmethyl 1-H_B), 4.61 (1H, d, *J* 13.9, 2-H_A), 4.57-4.52 (2H, m, propenyl 1-H_2), 4.18-4.09 (1H, m, 6-H_A), 3.61 (1H, d, *J* 14.4, methylcarbamate 1-H_A), 3.46 (1H, d, *J* 14.4, methylcarbamate 1-H_B), 3.46-3.39 (1H, m, 6-H_B), 3.35 (1H, d, *J* 13.9, 2-H_B), 2.68 (1H, ddd, *J* 15.2, 9.9 and 6.5, 5-H_A), 2.53 (1H, app. dt, *J* 15.2 and 4.7, 5-H_B), 1.41 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 205.1 (C-4), 170.3 (carboxylate C=O), 157.9 (Boc C=O), 156.8 (Cbz C=O), 137.9 (phenyl C-1), 132.8 (propenyl C-2), 129.5 (phenyl C_2-3,5), 129.2 (phenyl C-4), 129.0 (phenyl C_2-2,6), 119.3 (propenyl C-3), 80.7 (^{t}Bu C_1), 68.9 (arylmethyl C-1), 67.6 (propenyl C-1), 63.2 (C-3), 49.5 (C-2), 44.2 (C-6), 42.9 (methylcarbamate C-1), 40.4 (C-5), 28.7 (^{t}Bu C_3); HRMS found MNa^+, 469.1936. $C_{23}H_{30}N_2O_7$ requires *MNa*, 469.1945.

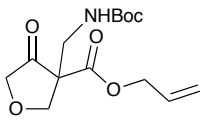
Prop-2-ene-1-yl-4-benzoyl-2-({[(*tert*-butoxy)carbonyl]amino}methyl)-3-oxomorpholine-2-carboxylate



S6

According to General Procedure C, the allyl ester derivative **S2** (5.00 g, 17.3 mmol) was stirred overnight to give a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the quaternary allyl ester derivative[8] **S6** (6.00 g, 83%) as a colourless oil, R_f 0.70 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3390, 2977, 1687, 1504, 1366, 1275, 1228, 1143, 1064; δ_H (500 MHz, $CDCl_3$) 7.69-7.62 (2H, m, phenyl 2,6-H_2), 7.52 (1H, tt, *J* 7.1 and 1.2, phenyl 4-H), 7.42-7.37 (2H, m, phenyl 3,5-H_2), 5.96 (1H, ddt, *J* 17.2, 10.4 and 5.8, propenyl 2-H), 5.40 (1H, app. dq, *J* 17.2 and 1.3, propenyl 3-H_{trans}), 5.32 (1H, app. dq, *J* 10.4 and 1.3, propenyl 3-H_{cis}), 5.00 (1H, br. s, NH), 4.74 (2H, app. d, *J* 5.8, propenyl 1-H_2), 4.30-4.23 (1H, m, 6-H_A), 4.19 (1H, dt, *J* 12.3 and 4.0, 6-H_B), 4.00 (1H, ddd, *J* 13.4, 9.3 and 4.0, 5-H_A), 3.92 (1H, dt, *J* 13.4 and 3.6, 5-H_B), 3.82 (1H, dd, *J* 14.3 and 7.4, methylcarbamate 1-H_A), 3.74 (1H, dd, *J* 14.3 and 5.8, methylcarbamate 1-H_B), 1.42 (9H, s, ^{t}Bu); δ_C (125 MHz, $CDCl_3$) 172.7 (C-3), 167.7 (benzoyl C=O), 167.5 (carboxylate C=O), 155.7 (Boc C=O), 134.7 (phenyl C-1), 134.4 (phenyl C-4), 131.0 (propenyl C-3), 128.5 (phenyl C_2-2,6), 128.3 (phenyl C_2-3,5), 119.9 (propenyl C-2), 83.0 (C-2), 79.8 (^{t}Bu C_1), 67.1 (propenyl C-1), 62.1 (C-6), 44.9 (C-5), 44.7 (methylcarbamate C-1), 28.4 (^{t}Bu C_3); HRMS found MH^+, 419.1814. $C_{21}H_{26}N_2O_7$ requires *MH*, 419.1812.

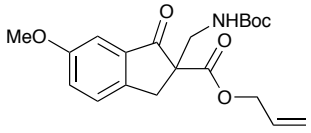
Prop-2-en-1-yl 3-({[(*tert*-butoxy)carbonyl]amino}methyl)-4-oxooxolane-3-carboxylate



S7

According to General Procedure C, the allyl ester derivative **S3** (9.60 g, 56.4 mmol) was stirred for 3 h to give a crude material. The crude material was purified by flash column chromatography, eluting with 10:90→15:85 EtOAc−petrol to yield the *quaternary allyl ester derivative* ***S7*** (14.7 g, 87%) as a colourless oil, R_f 0.41 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3367, 2978, 1770, 1710, 1504, 1366; δ_H (400 MHz, $CDCl_3$) 5.86 (1H, ddt, *J* 17.2, 10.5 and 5.7, propenyl 2-H), 5.30 (1H, app. dq, *J* 17.2 and 1.3, propenyl 3-H_{trans}), 5.25 (1H, app. dq, *J* 10.5 and 1.3, propenyl 3-H_{cis}), 5.11 (1H, app. t, *J* 5.3, NH), 4.65 (1H, app. t, *J* 1.4, propenyl 1-H_A), 4.64 (1H, app. t, *J* 1.4, propenyl 1-H_B), 4.49 (1H, d, *J* 9.9, 2-H_A), 4.21 (1H, d, *J* 9.9, 2-H_B), 4.11 (1H, d, *J* 17.2, 5-H_A), 4.05 (1H, d, *J* 17.2, 5-H_B), 3.72-3.55 (2H, m, methylcarbamate 1-H_2), 1.40 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 208.8 (C-4), 168.6 (carboxylate C=O), 156.2 (Boc C=O), 131.1 (propenyl C-2), 119.2 (propenyl C-3), 80.1 (^{t}Bu C_1), 73.3 (C-2), 71.2 (C-5), 66.7 (propenyl C-1), 61.0 (C-3), 41.4 (methylcarbamate C-1), 28.4 (^{t}Bu C_3); HRMS found MNa^+, 322.1256. $C_{14}H_{21}NO_6$ requires *MNa*, 322.1261.

Prop-2-en-1-yl 2-({[(*tert*-butoxy)carbonyl]amino}methyl)-6-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate

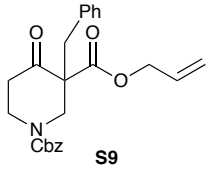


S8

According to General Procedure C, the allyl ester derivative **S4** (5.12 g, 20.8 mmol) was stirred overnight to give a crude material. The crude material was purified by flash column chromatography, eluting with 15:85 EtOAc−hexane to yield the *quaternary allyl ester derivative* ***S8*** (7.80 g, >99%) as an amorphous colourless solid, R_f 0.50 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3377, 2974, 2940, 1727, 1697, 1514, 1492, 1280, 1241, 1189, 1161, 1134; δ_H (300 MHz, $CDCl_3$) 7.37 (1H, d, *J* 8.3, 4-H), 7.21 (1H, dd, *J* 8.3 and 2.6, 5-H), 7.17 (1H, d, *J* 2.6, 7-H), 5.81 (1H, ddt, *J* 17.2, 10.6 and 5.6, propenyl 2-H), 5.20 (1H, dd, *J* 17.2 and 1.3, propenyl 3-H_{trans}), 5.18 (1H, br. s, NH), 5.17 (1H, dd, *J* 10.6 and 1.3, propenyl 3-H_{cis}), 4.59 (2H, app. dt, *J* 5.6 and 1.5, propenyl 1-H_2), 3.82 (3H, s, methoxy), 3.67 (1H, d, *J* 6.6, methylcarbamate 1-H_A), 3.65 (1H, d, *J* 6.6, methylcarbamate 1-H_B), 3.45 (1H, d, *J* 17.2,

3-H_A), 3.24 (1H, d, *J* 17.2, 3-H_B), 1.40 (9H, s, ^{t}Bu); δ_C (75 MHz, $CDCl_3$) 201.0 (C-1), 170.8 (carboxylate C=O), 159.9 (C-6), 156.4 (Boc C=O), 146.4 (C-3a), 136.2 (C-7a), 131.5 (propenyl C-2), 127.4 (C-4), 125.3 (C-5), 118.6 (propenyl C-3), 105.9 (C-7), 79.7 (^{t}Bu C_1), 66.2 (propenyl C-1), 62.4 (C-2), 55.7 (methoxy), 44.0 (methylcarbamate C-1), 35.0 (C-3), 28.4 (^{t}Bu, C_3); HRMS found MNa^+, 398.1572. $C_{20}H_{25}NO_6$ requires *MNa*, 398.1574.

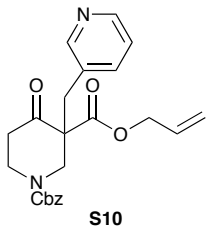
1-Benzyl 3-prop-2-en-1-yl 3-benzyl-4-oxopiperidine-1,3-dicarboxylate



S9

According to General Procedure D, the allyl ester derivative **S1** (0.75 g. 2.36 mmol), K_2CO_3 (1.30 g, 9.44 mmol) and (bromomethyl)benzene (0.56 mL, 4.72 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *quaternary allyl ester derivative* ***S9*** (0.86 g, 89%) as a colourless oil, R_f 0.38 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3063, 3030, 2936, 1698, 1427, 1266, 1239, 1217, 1178, 1121; δ_H (500 MHz, $CDCl_3$, 323 K) 7.41-7.15 (10H, phenyl), 5.77 (1H, ddt, *J* 16.9, 10.7 and 5.6, propenyl 2-H), 5.26 (1H, dd, *J* 16.9 and 1.3, propenyl 3-H_{trans}), 5.21 (1H, app. dq, *J* 10.7 and 1.3, propenyl 3-H_{cis}), 5.17 (1H, app. s, Cbz arylmethyl 1-H_A), 5.16 (1H, app. s, Cbz arylmethyl 1-H_B), 4.72 (1H, dd, *J* 13.8 and 2.1, 2-H_A), 4.50 (2H, d, *J* 5.6, propenyl 1-H_2), 4.25 (1H, app. br. s, 6-H_A), 3.31 (1H, d, *J* 13.9, arylmethyl 1-H_A), 3.31-3.25 (1H, m, 6-H_B), 3.17 (1H, d, *J* 13.9, arylmethyl 1-H_B), 3.14 (1H, d, *J* 13.8, 2-H_B), 2.75 (1H, ddd, *J* 14.9, 10.4 and 6.6, 5-H_A), 2.49 (1H, app. dt, *J* 14.9 and 4.4, 5-H_B); δ_C (125 MHz, $CDCl_3$, 323 K) 203.5 (C-4), 169.5 (carboxylate C=O), 155.2 (Cbz C=O), 136.6 (Cbz phenyl C-1), 135.6 (phenyl C-1), 131.4 (propenyl C-2), 130.6 (phenyl C_2-2,6), 128.6 (Cbz phenyl C_2-3,5), 128.5 (phenyl C_2-3,5), 128.2 (Cbz phenyl C_2-2,6), 128.0 (Cbz phenyl C-4), 127.2 (phenyl C-4), 119.3 (propenyl C-3), 67.7 (Cbz arylmethyl C-1), 66.4 (propenyl C-1), 62.3 (C-3), 50.1 (C-2), 43.5 (C-6), 40.0 (C-5), 37.6 (arylmethyl C-1); HRMS found MNa^+, 430.1624. $C_{24}H_{25}NO_5$ requires *MNa*, 430.1630.

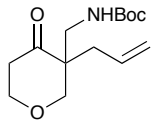
1-Benzyl 3-prop-2-en-1-yl 4-oxo-3-[(pyridin-3-yl)methyl]piperidine-1,3-dicarboxylate



S10

According to General Procedure D, the allyl ester derivative **S1** (1.00 g. 3.15 mmol), K_2CO_3 (2.17 g, 15.7 mmol) and 3-(bromomethyl)pyridine hydrobromide (1.03 g, 4.10 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 60:40 EtOAc−hexane to yield the *quaternary allyl ester derivative* ***S10*** (0.63 g, 49%) as a yellow oil, R_f 0.50 (EtOAc); ν_{max}/cm^{-1} 3031, 2946, 1697, 1423, 1235, 1215, 1177, 1125; δ_H (500 MHz, CD_3OD, 333 K) 7.23 (2H, d, *J* 6.3, pyridine 2,6-H_2), 6.51 (1H, d, *J* 7.9, pyridine 4-H), 6.20-6.14 (5H, m, phenyl), 6.14-6.11 (1H, m, pyridine 5-H), 4.58 (1H, ddt, *J* 16.9, 10.1 and 6.0, propenyl 2-H), 4.05 (1H, dd, *J* 16.9 and 1.4, propenyl 3-H_{trans}), 4.01 (1H, dd, *J* 10.1 and 1.4, propenyl 3-H_{cis}), 3.97 (1H, app. s, Cbz arylmethyl 1-H_A), 3.96 (1H, app. s, Cbz arylmethyl 1-H_B), 3.50 (1H, dd, *J* 13.6 and 2.2, 2-H_A), 3.30-3.27 (1H, m, propenyl 1-H_A), 3.10-3.04 (1H, m, 6-H_A), 2.18 (1H, d, *J* 14.3, pyridinylmethyl, 1-H_A), 2.18-2.15 (2H, m, 6-H_B and propenyl 1-H_B), 2.12 (1H, d, *J* 13.6, 2-H_B), 1.82 (1H, d, *J* 14.3, pyridinylmethyl 1-H_B), 1.63-1.52 (1H, m, 5-H_A), 1.35 (1H, app. dt, *J* 14.9 and 4.1, 5-H_B); δ_C (125 MHz, CD_3OD, 333 K) 204.6 (C-4), 170.5 (carboxylate C=O), 156.6 (Cbz C=O), 151.9 (pyridine 2-C), 148.7 (pyridine C-6), 140.1 (pyridine C-4), 137.8 (phenyl C-1), 133.8 (pyridine C-3), 132.5 (propenyl C-2), 129.5 (phenyl C_2-3,5), 129.1 (phenyl C-4), 128.9 (phenyl C_2-2,6), 124.7 (pyridine C-5), 119.8 (propenyl C-3), 68.8 (Cbz arylmethyl C-1), 67.5 (propenyl C-1), 63.3 (C-3), 51.2 (C-2), 44.5 (C-6), 40.6 (C-5), 35.4 (pyridinylmethyl C-1); HRMS found MH^+, 409.1755. $C_{23}H_{24}N_2O_5$ requires *MH*, 409.1763.

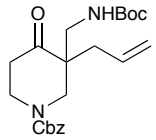
***tert*-Butyl *N*-{[4-oxo-3-(prop-2-en-1-yl)oxan-3-yl]methyl}carbamate**



1a

According to General Procedure E, the quaternary allyl ester derivative **11** (10.1 g, 32.2 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 10:90 EtOAc−hexane to yield the *ketone derivative **1a*** (6.60 g, 76%) as a brown oil, R_f 0.39 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3351, 2975, 2932, 2861, 1702, 1504, 1365, 1246, 1214, 1163, 1115; δ_H (400 MHz, $CDCl_3$) 5.66 (1H, app. dq, *J* 16.8 and 7.5, propenyl 2-H), 5.15-5.10 (2H, m, propenyl 3-H_2), 4.83 (1H, br. s, NH), 4.14-4.07 (1H, m, 6-H_A), 3.83 (1H, d, *J* 11.8, 2-H_A), 3.80-3.77 (1H, m, 6-H_B), 3.59 (1H, d, *J* 11.8, 2-H_B), 3.35 (1H, dd, *J* 14.3 and 7.9, methylcarbamate 1-H_A), 3.26 (1H, dd, *J* 14.3 and 5.5, methylcarbamate 1-H_B), 2.65 (1H, ddd, *J* 15.1, 9.8 and 6.5, 5-H_A), 2.53 (1H, dd, *J* 14.3 and 7.5, propenyl 1-H_A), 2.47 (1H, app. dt, *J* 15.1 and 4.1, 5-H_B), 2.34 (1H, dd, *J* 14.3 and 7.5, propenyl 1-H_B), 1.41 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 210.1 (C-4), 156.0 (Boc C=O), 131.9 (propenyl C-2), 119.3 (propenyl C-3), 79.4 (^{t}Bu C_1), 73.1 (C-2), 68.2 (C-6), 55.1 (C-3), 42.0 (methylcarbamate C-1), 40.1 (C-5), 36.9 (propenyl C-1), 28.3 (^{t}Bu C_3); HRMS found MH^+, 270.1701. $C_{14}H_{23}NO_4$ requires *MH*, 270.1699.

Benzyl 3-({[(*tert*-butoxy)carbonyl]amino}methyl)-4-oxo-3-(prop-2-en-1-yl)piperidine-1-carboxylate

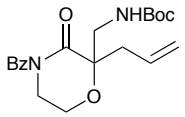


1b

According to General Procedure E, the quaternary allyl ester derivative **S5** (7.56 g, 16.9 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *ketone derivative **1b*** (5.93 g, 87%) as a yellow oil, R_f 0.74 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3366, 2976, 2931, 1689, 1429, 1365, 1273, 1157; δ_H (500 MHz, CD_3OD, 333 K) 7.42-7.27 (5H, m, phenyl), 5.67 (1H, app.

dq, *J* 16.9 and 8.0, propenyl 2-H), 5.18 (2H, s, arylmethyl 1-H_2), 5.06 (1H, app. d, *J* 10.8, propenyl 3-H_{cis}), 5.05 (1H, app. d, *J* 18.8, propenyl 3-H_{trans}), 3.93-3.83 (1H, m, 6-H_A), 3.75 (1H, d, *J* 14.0, 2-H_A), 3.67 (1H, app. br. s, 6-H_B), 3.52 (1H, d, *J* 14.0, 2-H_B), 3.37 (1H, d, *J* 14.7, methylcarbamate 1-H_A), 3.15 (1H, d, *J* 14.7, methylcarbamate 1-H_B), 2.63-2.53 (1H, m, 5-H_A), 2.53-2.45 (1H, m, 5-H_B), 2.34 (1H, dd, *J* 14.2 and 7.0, propenyl 1-H_A), 2.24 (1H, dd, *J* 14.2 and 8.0, propenyl 1-H_B), 1.41 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD) 211.1 (4-C), 158.2 (Boc C=O), 157.2 (Cbz C=O), 137.9 (phenyl C-1), 133.6 (propenyl C-2), 129.6 (phenyl C_2-3,5), 129.2 (phenyl C_2-2,6), 129.0 (phenyl C-4), 119.4 (propenyl C-3), 80.5 (^{t}Bu C_1), 68.8 (arylmethyl C-1), 55.2 (C-3), 50.3 (C-2), 44.2 (C-6 and methylcarbamate C-1), 39.6 (C-5), 37.7 (propenyl C-1), 28.7 (^{t}Bu C_3); HRMS found MNa^+, 425.2043. $C_{22}H_{30}N_2O_5$ requires *MNa*, 425.2046.

***tert*-Butyl *N*-{[4-benzoyl-3-oxo-2-(prop-2-en-1-yl)morpholin-2-yl]methyl}carbamate**

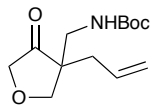


1c

According to General Procedure E, the quaternary allyl ester derivative **S6** (6.00 g, 14.3 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the lactam derivative[8] **1c** (4.30 g, 80%) as a brown oil, R_f 0.65 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3379, 2977, 2933, 1682, 1505, 1366, 1277, 1246, 1221, 1140, 1116, 1087; δ_H (400 MHz, $CDCl_3$) 7.55 (2H, d, *J* 7.6, phenyl 2,6-H_2), 7.50 (1H, t, *J* 7.6, phenyl 4-H), 7.39 (2H, t, *J* 7.6, phenyl 3,5-H_2), 5.88 (1H, ddt, *J* 16.0, 11.1 and 7.3, propenyl 2-H), 5.20 (1H, app. d, *J* 10.5, propenyl 3-H_{cis}), 5.19 (1H, app. d, *J* 16.8, propenyl 3-H_{trans}), 4.90 (1H, br. s, NH), 4.10-4.04 (2H, m, 6-H_2), 3.98 (1H, app. dt, *J* 9.9 and 4.8, 5-H_A), 3.90 (1H, app. dt, *J* 13.1 and 4.8, 5-H_B), 3,62 (1H, dd, *J* 14.0 and 7.1, methylcarbamate 1-H_A), 3.39 (1H, dd, *J* 14.0 and 5.6, methylcarbamate 1-H_B), 2.67 (1H, dd, *J* 14.3 and 7.3, propenyl 1-H_A), 2.51 (1H, dd, *J* 14.3 and 7.0, propenyl 1-H_B), 1.43 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 172.9 (C-3), 172.6 (benzoyl C=O), 155.8 (Boc C=O), 135.4 (phenyl C-1), 132.0 (phenyl C-4), 131.6 (propenyl C-2), 128.2 (phenyl C_2-3,5), 128.0 (phenyl

C_2-2,6), 119.8 (propenyl C-3), 82.1 (C-2), 79.7 (^{t}Bu C_1), 60.4 (C-6), 45.7 (methylcarbamate C-1), 45.4 (C-5), 39.7 (propenyl C-1), 28.4 (^{t}Bu C_3); HRMS found MH^+, 375.1919. $C_{20}H_{26}N_2O_5$ requires *MH*, 375.1914

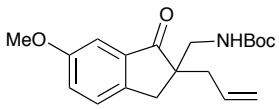
***tert*-Butyl *N*-{[4-oxo-3-(prop-2-en-1-yl)oxolan-3-yl]methyl}carbamate**



1d

According to General Procedure E, the quaternary allyl ester derivative **S7** (14.7 g, 49.1 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *ketone derivative* ***1d*** (11.0 g, 88%) as a light-brown oil, R_f 0.42 (85:15 petrol−EtOAc); ν_{max}/cm^{-1} 3357, 2977, 2933, 1697, 1515, 1392, 1366, 1248, 1158, 1059; δ_H (400 MHz, $CDCl_3$) 5.70 (1H, ddt, *J* 16.6, 10.5 and 7.4, propenyl 2-H), 5.14-5.10 (1H, m, propenyl 3-H_{trans}), 5.12-5.08 (1H, m, propenyl 3-H_{cis}), 4.84 (1H, app. t, *J* 5.3, NH), 4.10 (1H, d, *J* 9.9, 2-H_A), 3.99 (1H, d, *J* 9.9, 2-H_B), 3.94 (2H, app. s, 5-H_2), 3.31 (1H, app. s, methylcarbamate 1-H_A), 3.29 (1H, app. s, methylcarbamate 1-H_B), 2.27 (1H, app. d, *J* 1.2, propenyl 1-H_A), 2.25 (1H, app. d, *J* 1.2, propenyl 1-H_B), 1.40 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 217.6 (C-4), 156.2 (Boc C=O), 131.9 (propenyl C-2), 119.8 (propenyl C-3), 79.9 (^{t}Bu C_1), 73.8 (C-2), 71.5 (C-5), 52.5 (C-3), 42.4 (methylcarbamate C-1), 36.3 (propenyl C-1), 28.4 (^{t}Bu C_3); HRMS found MNa^+, 278.1363. $C_{13}H_{21}NO_4$ requires *MNa*, 278.1362.

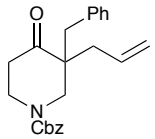
***tert*-Butyl *N*-{[6-methoxy-1-oxo-2-(prop-2-en-1-yl)-2,3-dihydro-1*H*-inden-2-yl]methyl} carbamate**



1e

According to General Procedure E, the quaternary allyl ester derivative **S8** (7.80 g, 20.8 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 10:90 EtOAc−hexane to yield the *ketone derivative **1e*** (5.58 g, 81%) as an amorphous brown solid, R_f 0.57 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3359, 2975, 2928, 1694, 1490, 1274, 1245, 1161; δ_H (400 MHz, $CDCl_3$) 7.31 (1H, d, *J* 8.4, 4-H), 7.18 (1H, dd, *J* 8.4 and 2.6, 5-H), 7.13 (1H, d, *J* 2.6, 7-H), 5.60 (1H, ddt, *J* 17.0, 10.1 and 7.4, propenyl 2-H), 5.07 (1H, dd, *J* 17.0 and 1.9, propenyl 3-H_{trans}), 5.00 (1H, dd, *J* 10.1 and 1.9, propenyl 3-H_{cis}), 4.90 (1H, app. t, *J* 5.4, NH), 3.80 (3H, s, methoxy), 3.46 (1H, dd, *J* 13.7 and 6.6, methylcarbamate 1-H_A), 3.29 (1H, dd, *J* 13.7 and 6.1, methylcarbamate 1-H_B), 3.00 (1H, d, *J* 17.2, 3-H_A), 2.93 (1H, d, *J* 17.2, 3-H_B), 2.45-2.27 (2H, m, propenyl 1-H_2), 1.38 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 209.9 (C-1), 159.6 (C-6), 156.4 (Boc C=O), 146.5 (C-3a), 137.4 (C-7a), 132.9 (propenyl C-2), 127.4 (C-4), 124.8 (C-5), 119.1 (propenyl C-3), 105.2 (C-7), 79.5 (Boc C_1), 55.7 (methoxy), 54.0 (C-2), 45.7 (methylcarbamate C-1), 39.4 (propenyl C-1), 34.9 (C-3), 28.4 (Boc C_3); HRMS found MNa^+, 354.1679. $C_{19}H_{25}NO_4$ requires *MNa*, 354.1675.

Benzyl 3-benzyl-4-oxo-3-(prop-2-en-1-yl)piperidine-1-carboxylate

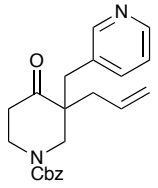


1f

According to General Procedure E, the quaternary allyl ester derivative **S9** (0.83 g, 2.03 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *ketone derivative **1f*** (0.66 g, 89%) as a brown oil, R_f 0.45 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3063, 3029, 2916, 1694, 1430, 1231; δ_H (500 MHz, CD_3OD, 333 K) 7.36-7.04 (10H, m, phenyl), 5.70 (1H, ddt, *J* 17.6, 10.4

and 7.3, propenyl 2-H), 5.13 (2H, s, Cbz arylmethyl 1-H_2), 5.05 (1H, app. d, *J* 10.4, propenyl 3-H_{cis}), 5.03 (1H, app. d, *J* 17.6, propenyl 3-H_{trans}), 3.77 (1H, app. dt, *J* 13.0 and 6.5, 6-H_A), 3.68 (1H, d, *J* 13.8, 2-H_A), 3.58 (1H, d, *J* 13.8, 2-H_B), 3.56-3.51 (1H, m, 6-H_B), 2.93 (1H, d, *J* 13.9, arylmethyl 1-H_A), 2.80 (1H, d, *J* 13.9, arylmethyl 1-H_B), 2.55-2.40 (2H, m, 5-H_2), 2.31 (1H, dd, *J* 14.3 and 6.8, propenyl 1-H_A), 2.16 (1H, dd, *J* 14.3 and 7.8, propenyl 1-H_B); δ_C (125 MHz, CD_3OD, 333 K) 212.0 (C-4), 157.2 (Cbz C=O), 137.9 (Cbz phenyl C-1), 137.8 (phenyl C-1), 134.0 (propenyl C-2), 131.5 (phenyl C_2-3,5), 129.5 (Cbz phenyl C_2-3,5), 129.2 (phenyl C_2-2,6 and Cbz phenyl C_2-2,6), 129.0 (Cbz phenyl C-4), 127.7 (phenyl C-4), 119.3 (propenyl C-3), 68.7 (Cbz arylmethyl C-1), 54.6 (C-3), 51.0 (C-2), 43.8 (C-6), 40.7 (arylmethyl C-1), 39.7 (C-5), 39.6 (propenyl C-1); HRMS found MNa^+, 386.1717. $C_{23}H_{25}NO_3$ requires *MNa*, 386.1732.

Benzyl 4-oxo-3-(prop-2-en-1-yl)-3-[(pyridin-3-yl)methyl]piperidine-1-carboxylate



1g

According to General Procedure E, the quaternary allyl ester derivative **S10** (0.60 g, 1.47 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 60:40 EtOAc−hexane to yield the *ketone derivative **1g*** (0.43 g, 80%) as a yellow oil, R_f 0.48 (EtOAc); ν_{max}/cm^{-1} 3030, 2915, 1693, 1422, 1230; δ_H (500 MHz, CD_3OD, 333 K) 8.37 (1H, dd, *J* 4.9 and 1.7, pyridine 6-H), 8.32 (1H, d, *J* 2.3, pyridine 2-H), 7.58 (1H, d, *J* 7.9, pyridine 4-H), 7.37-7.24 (6H, m, phenyl and pyridine 5-H), 5.69 (1H, ddt, *J* 17.1, 10.3 and 7.3, propenyl 2-H), 5.15 (2H, s, phenylmethyl 1-H_2), 5.09 (1H, app. dt, *J* 10.3 and 1.6, propenyl 3-H_{cis}), 5.05 (1H, dd, *J* 17.1 and 1.6, propenyl 3-H_{trans}), 3.87-3.81 (1H, m, 6-H_A), 3.74 (1H, dd, *J* 13.8 and 1.2, 2-H_A), 3.57 (1H, d, *J* 13.8, 2-H_B), 3.56-3.51 (1H, m, 6-H_B), 2.98 (1H, d, *J* 14.2, pyridinylmethyl 1-H_A), 2.84 (1H, d, *J* 14.2, pyridinylmethyl 1-H_B), 2.56 (1H, ddd, *J* 15.6, 8.3 and 6.1, 5-H_A), 2.48 (1H, app. dt, *J* 15.6 and 6.1, 5-H_B), 2.29 (1H, dd, *J* 14.6 and 6.8, propenyl 1-H_A), 2.20 (1H, dd, *J* 14.6 and 7.7, propenyl 1-H_B); δ_C (125 MHz, CD_3OD, 333 K) 211.3 (C-4), 157.2 (Cbz C=O), 151.8 (pyridine C-2), 148.4 (pyridine C-6), 140.0 (pyridine C-4), 137.9 (phenyl C-1), 134.5 (pyridine C-3), 133.5

(propenyl C-2), 129.5 (phenyl C_2-3,5), 129.2 (phenyl C_2-2,6), 129.1 (phenyl C-4), 124.7 (pyridine C-5), 119.7 (propenyl C-3), 68.7 (Cbz arylmethyl C-1), 54.5 (C-3), 51.0 (C-2), 43.9 (C-6), 39.6 (propenyl C-1), 39.5 (C-5), 37.5 (pyridinylmethyl C-1); HRMS found MH^+, 365.1862. $C_{22}H_{24}N_2O_3$ requires *MH*, 365.1865.

Synthesis of Scaffolds

General Procedure F (Method A in main text)

By modification of an existing procedure,[13] 2-methyl-2-butene (7.50 eq) was added dropwise to BH_3•THF (3.50 eq of a 1.0 M solution in THF) at 0 °C. The mixture was stirred for 2 h at 0 °C. Then, a solution of the alkene derivative (1.00 eq) in THF (0.35 M) at 0 °C was added dropwise. The reaction mixture was stirred for 45 min at 0 °C and subsequently it was stirred for 1 h at rt. Then, $NaBO_3$•$4H_2O$ (7.50 eq) and water (3 mL per 1.00 mmol of the alkene derivative) were added. After stirring the mixture vigorously for 18 h at rt, EtOAc (3 mL per 1.00 mmol of the alkene derivative) was added, the phases were separated and the aqueous phase was extracted with EtOAc (4 × (3 mL per 1.00 mmol of the alkene derivative)). Then, the organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure G (Method B in main text)

Trifluoroacetic acid (20.0 eq) and Et_3SiH (1.50 eq) were added to a solution of the hemiacetal derivative (1.00 eq) in DCM (0.10 M) at rt. The reaction mixture was stirred for 18 h at rt. After removing the solvent and trifluoroacetic acid under reduced pressure, the crude material was dissolved in DCM (0.10 M), and Et_3N (10.0 eq) and Boc_2O (1.20 eq) were added. After stirring the reaction mixture for 18 h at rt, a saturated aqueous solution of $NaHCO_3$ (10 mL per 1.00 mmol of the hemiacetal derivative) was added, the phases were separated and the aqueous phase was extracted with DCM (3 × (4 mL per 1.00 mmol of the hemiacetal derivative)). Then, the organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure H (Variation of Method B in main text)

By modification of an existing procedure,[14] Et_3SiH (16.0 eq) was added dropwise to a solution of the hemiacetal derivative (1.00 eq) in DCM (16.0 mM) at rt. The mixture was cooled to −78 °C and BF_3•Et_2O (4.00 eq) was added dropwise. After stirring the reaction mixture at −78 °C for 2 h, it was allowed to warm to rt and stirred overnight. The solvent was removed under reduced pressure and the crude material was dissolved in DCM (0.10 M). Then, Et_3N (5.00 eq) and Boc_2O (1.20 eq) were added and the reaction mixture was stirred overnight at rt. A saturated aqueous solution of NH_4Cl (10 mL per 1.00 mmol of the hemiacetal derivative) was added, the phases were separated and the aqueous phase was extracted with DCM (3 × (3 mL per 1.00 mmol of the hemiacetal derivative)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure I (Variation of Method B in main text)

Trifluoroacetic acid (20.0 eq) and Et_3SiH (1.50 eq) were added to a solution of the hemiacetal derivative (1.00 eq) in DCM (0.10 M) at rt. The reaction mixture was stirred for 18 h at rt. A saturated aqueous solution of $NaHCO_3$ (10 mL per 1.00 mmol of the hemiacetal derivative) was added, the phases were separated and the aqueous phase was extracted with DCM (3 × (4 mL per 1.00 mmol of the hemiacetal derivative)). Then, the organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure J (Method C in main text)

Ozonized oxygen gas was passed through a solution of the alkene derivative (1.00 eq) in DCM (0.10 M) at −78 °C until the solution became blue in colour. Then, the solution was purged with oxygen gas until the blue colour disappeared and dimethyl sulfide (20.0 eq) was added dropwise. After stirring the reaction mixture for 30 min at −78 °C, it was allowed to warm to rt. Then, it was stirred at rt for 18 h and the solvent was removed under reduced pressure to yield a crude material.

General Procedure K (Method E in main text)

According to a procedure,[8] the specified amount of a solution of diisobutylaluminium hydride 1.0 M in DCM was added dropwise to a solution of the ketone derivative (1.00 eq) in DCM

(0.18 M) at −78 °C. After stirring the reaction mixture for 1 h at −78 °C, the mixture was allowed to warm to rt and a saturated aqueous solution of potassium sodium tartrate tetrahydrate (5 mL per 1.00 mmol of the ketone derivative) was added dropwise. Then, the mixture was stirred for 18 h at rt, the phases were separated and the aqueous phase was extracted with DCM (5 × (3 mL per 1.00 mmol of the ketone derivative). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure L (Method F in main text)

According to a procedure,[15] $NaHCO_3$ (2.00 eq) and I_2 (1.10 eq) were added to a solution of the alkene derivative (1.00 eq) in acetonitrile (0.10 M) at 0 °C. The reaction mixture was stirred at rt for 3 days. Then, a saturated aqueous solution of $Na_2S_2O_3$ (7 mL per 1.00 mmol of the alkene derivative) was added, the phases were separated and the aqueous phase was extracted with EtOAc (3 × (7 mL per 1.00 mmol of the alkene derivative)). The organic phases were combined, washed with brine (3 mL per 1.00 mmol of the alkene derivative), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure M (Method G in main text)

^{t}BuOK (3.00 eq) was added to a solution of the alcohol derivative (1.00 eq) in THF (75.0 mM) at 0 °C. After stirring the reaction mixture for the specified time at rt, a saturated aqueous solution of NH_4Cl (10 mL per 1.00 mmol of the alcohol derivative) and EtOAc (10 mL per 1.00 mmol of the alcohol derivative) were added. The phases were separated and the aqueous phase was extracted with EtOAc (4 × (5 mL per 1.00 mmol of the alcohol derivative)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a crude material.

General Procedure N (Method H or Method I in main text)

The respective aldehyde (1.50 eq) and trifluoroacetic acid (35.0 eq) were added dropwise to a solution of the ketone derivative (1.00 eq) in MeOH (0.18 M). The reaction mixture was stirred at 65 °C for four days. Then, the mixture was allowed to cool to rt and the solvent and trifluroroacetic acid were removed under reduced pressure to give a crude material.

General Procedure O (Method L in main text)

By modification of an existing procedure,[8] pyridine (31.0 eq) was added to a solution of the alcohol derivative (1.00 eq) in Ac_2O (26.4 eq) at rt. Then, the reaction mixture was stirred for 18 h at rt and the solvent was removed under reduced pressure. The crude material was dissolved in DCM (3 mL per 1.00 mmol of the alcohol derivative) and an aqueous solution of 10% $CuSO_4$ (3 mL per 1.00 mmol of the alcohol derivative) was added. After stirring the mixture for 5 min at rt, the phases were separated and the aqueous phase was extracted with DCM (3 × (2 mL per 1.00 mmol of the alcohol derivative)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the specified acetate derivative.

General Procedure P (Method M in main text)

By modification of an existing procedure,[16] triethylamine (2.00 eq) and methanesulfonyl chloride (1.20 eq) were added to a solution of the alcohol derivative (1.00 eq) in DCM (0.20 M) at 0 °C. The reaction mixture was stirred for 2 h at rt. Then, trifluoroacetic acid (65.0 eq) was added dropwise and the mixture was stirred for a further 5 h at rt. Subsequently, the solvent and trifluoroacetic acid were removed under reduced pressure. After dissolving the crude product in DCM (0.20 M), triethylamine (35.0 eq) was added and the resulting mixture was stirred for 18 h at rt. Then, Boc_2O (1.20 eq) was added and the reaction was stirred for a further 18 h at rt. A saturated aqueous solution of $NaHCO_3$ (5 mL per 1.00 mmol of the alcohol derivative) was added, the phases were separated and the aqueous phase was extracted with DCM (3 × (3 mL per 1.00 mmol of the alcohol derivative)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

General Procedure Q (Method C followed by Method N in main text)

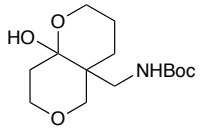
Ozonized oxygen gas was passed through a solution of the alkene derivative (1.00 eq) in DCM (0.10 M) at −78 °C until the solution became blue in colour. Then, the solution was purged with oxygen gas until the blue colour disappeared and dimethyl sulfide (20.0 eq) was added dropwise. After stirring the reaction mixture for 30 min at −78 °C, it was allowed to warm to rt. Then, it was stirred at rt for 18 h and the solvent was removed under reduced

pressure. The crude material was dissolved in DCM (0.10 M) and pyridinium dichromate (2.00 eq) and celite (0.4 g per 1.00 mmol of the alkene derivative) were added. The reaction mixture was stirred for 1 week at rt. Then, the mixture was filtered through celite and concentrated under reduced pressure to give a crude material.

General Procedure R (Method C followed by Method O in main text)

Ozonized oxygen gas was passed through a solution of the alkene derivative (1.00 eq) in DCM (0.10 M) at −78 °C until the solution became blue in colour. Then, the solution was purged with oxygen gas until the blue colour disappeared and dimethyl sulfide (20.0 eq) was added dropwise. After stirring the reaction mixture for 30 min at −78 °C, it was allowed to warm to rt. Then, it was stirred at rt for 18 h and the solvent was removed under reduced pressure. The crude material was dissolved in acetic acid (0.20 M) and $NaBH(OAc)_3$ (7.00 eq) was added. The reaction mixture was stirred for 2 h at rt. Then, a saturated aqueous solution of $NaHCO_3$ (50 mL per 1.00 mmol of the alkene) and DCM (20 mL per 1.00 mmol of the alkene) were added. The mixture was stirred for 1 h at rt, the phases were separated and the aqueous phase was extracted with DCM (4 × (10 mL per 1.00 mmol of the alkene)). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude material.

***tert*-Butyl *N*-({8a-hydroxy-octahydropyrano[4,3-*b*]pyran-4a-yl}methyl)carbamate**

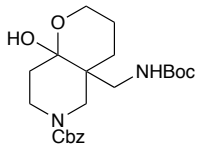


12

According to General Procedure F, the alkene derivative **1a** (0.50 g, 1.85 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 50:50 EtOAc−hexane to yield the *hemiacetal derivative* ***12*** (0.41 g, 76%, *dr* >95:<5 by ^{1}H-NMR) as an amorphous colourless solid, R_f 0.25 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3301, 2960, 2880, 1692, 1594, 1365, 1283, 1273, 1254, 1170, 1109, 1068; δ_H (400 MHz, CD_3OD)

6.32 (1H, app.t, *J* 5.1, NH), 4.06 (1H, ddd, *J* 12.4, 11.2 and 3.0, 2-H_A), 3.85 (1H, d, *J* 11.6, 5-H_A), 3.80 (1H, app. tt, *J* 5.5 and 1.2, 7-H_A), 3.69-3.60 (2H, m, 2-H_B and 7-H_B), 3.44 (1H, d, *J* 11.6, 5-H_B), 3.40-3.32 (3H, m, OH and methylcarbamate 1-H_2), 2.02 (1H, td, *J* 13.1 and 5.5, 8-H_A), 1.92 (1H, app. td, *J* 13.3 and 4.9, 3-H_A), 1.79 (1H, app. qt, *J* 13.3 and 4.6, 3-H_B), 1.57 (1H, app. d, *J* 13.5, 8-H_B), 1.47 (9H, s, ^{t}Bu), 1.46-1.39 (1H, m, 4-H_A), 1.25 (1H, app. d, *J* 13.7, 4-H_B); δ_C (100 MHz, CD_3OD) 158.7 (Boc C=O), 96.0 (C-8a), 79.8 (^{t}Bu C_1), 70.5 (C-5), 66.7 (C-7), 60.8 (C-2), 45.0 (methylcarbamate C-1), 41.9 (C-4a), 36.9 (C-8), 28.7 (^{t}Bu C_3), 24.6 (C-4), 22.3 (C-3); HRMS found MNa^+, 310.1628. $C_{14}H_{25}NO_5$ requires *MNa*, 310.1624.

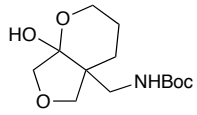
Benzyl 4a-({[(*tert*-butoxy)carbonyl]amino}methyl)-8a-hydroxy-octahydro-2*H*-pyrano[3,2-*c*]pyridine-6-carboxylate



S11

According to General Procedure F, the alkene derivative **1b** (0.20 g, 0.49 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 30:70 EtOAc−hexane to yield the *hemiacetal derivative* ***S11*** (0.12 g, 58%, *dr* >95:<5 by ^{1}H-NMR) as an amorphous colourless solid, R_f 0.37 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3317, 2957, 2889, 2472, 1672, 1432, 1363, 1250, 1164, 1142, 1089, 1065; δ_H (500 MHz, CD_3OD, 333 K) 7.42-7.26 (5H, m, phenyl), 5.14 (1H, d, *J* 12.4, arylmethyl 1-H_A), 5.11 (1H, d, *J* 12.4, arylmethyl 1-H_B), 4.02 (1H, td, *J* 11.9 and 3.2, 2-H_A), 3.95 (1H, app. dt, *J* 13.1 and 2.6, 7-H_A), 3.66-3.57 (2H, m, 2-H_B and 5-H_A), 3.40-3.33 (3H, m, 5-H_B and methylcarbamate 1-H_2), 3.08 (1H, td, *J* 13.1 and 3.4, 7-H_B), 2.93 (1H, br. s, OH), 1.95 (1H, td, *J* 13.5 and 5.0, 4-H_A), 1.83-1.71 (2H, m, 8-H_A and 3-H_A), 1.65-1.51 (1H, m, 8-H_B), 1.42 (10H, s, ^{t}Bu and 3-H_B), 1.30 (1H, app. d, *J* 13.5, 4-H_B); δ_C (125 MHz, CD_3OD, 333 K) 158.4 (Boc C=O), 157.3 (Cbz C=O), 138.1 (phenyl C-1), 129.6 (phenyl C_2-3,5), 129.1 (phenyl C_2-2,6), 129.0 (phenyl C-4), 96.6 (C-8a), 80.1 (^{t}Bu C_1), 68.6 (arylmethyl C-1), 61.0 (C-2), 49.0 (C-5), 47.3 (C-4a), 44.6 (methylcarbamate C-1), 42.9 (C-7), 35.7 (C-8), 28.8 (^{t}Bu C_3), 25.8 (C-4), 22.1 (C-3); HRMS found MNa^+, 443.2147. $C_{22}H_{32}N_2O_6$ requires *MNa*, 443.2152.

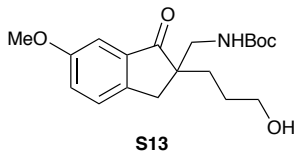
***tert*-Butyl *N*-({7a-hydroxy-hexahydro-2*H*-furo[3,4-b]pyran-4a-yl}methyl)carbamate**



S12

According to General Procedure F, the alkene derivative **1d** (1.00 g, 3.91 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 40:60 EtOAc−hexane to yield the *hemiacetal derivative* ***S12*** (0.78 g, 73%, *hemiacetal:alcohol* 67:33 by ^{1}H-NMR in $CDCl_3$) as a colourless oil, R_f 0.19 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3342, 2936, 2881, 1688, 1510,1365, 1248, 1164, 1049, 1008; δ_H (400 MHz, $CDCl_3$) 5.30 (1H, s, $NH^{alcohol}$), 4.94 (1H, app. t, *J* 6.6, $NH^{hemiacetal}$), 4.05 (1H, d, *J* 8.7, 5-$H_A^{alcohol}$), 3.89-3.80 (2H, m, 2-$H_A^{hemiacetal}$ and hydroxypropyl 3-$H_A^{alcohol}$), 3.79-3.73 (4H, m, 2-$H_2^{alcohol}$, 5-$H_2^{hemiacetal}$), 3.73-3.66 (2H, m, 2-$H_B^{hemiacetal}$ and hydroxypropyl 3-$H_B^{alcohol}$), 3.63 (1H, d *J* 8.7, 5-$H_B^{alcohol}$), 3.61-3.57 (2H, m, 7-$H_2^{hemiacetal}$), 3.37-3.25 (3H, m, methylcarbamate 1-$H_2^{alcohol}$ and methylcarbamate 1-$H_A^{hemiacetal}$), 3.30 (1H, dd, *J* 14.4 and 4.5, methylcarbamate 1-$H_B^{hemiacetal}$), 1.85-1.67 (2H, m, 3-$H_A^{hemiacetal}$ and hydroxypropyl 2-$H_A^{alcohol}$), 1.66-1.57 (2H, m, 4-$H_A^{hemiacetal}$ and hydroxypropyl 1-$H_A^{alcohol}$), 1.54-1.45 (2H, m, 3-$H_B^{hemiacetal}$ and hydroxypropyl 2-$H_B^{alcohol}$), 1.46-1.36 (20H, m, 4-$H_B^{hemiacetal}$, hydroxypropyl 1-$H_B^{alcohol}$, ^{t}Bu^{hemiaceta}l and ^{t}Bu^{alcohol}); δ_C (100 MHz, $CDCl_3$) 218.1 (C-4^{alcohol}), 157.0 (Boc C=O^{hemiacetal}), 156.4 (Boc C=O^{alcohol}), 103.4 (C-7a^{hemiacetal}), 80.0 (^{t}Bu $C_1^{alcohol}$), 79.7 (^{t}Bu $C_1^{hemiacetal}$), 77.2 (C-5^{hemiacetal}), 74.5 (C-2^{alcohol}), 73.9 (C-7^{hemiacetal}), 71.5 (C-5^{alcohol}), 62.5 (hydroxypropyl C-3^{alcohol}), 61.2 (C-2^{hemiacetal}), 52.2 (C-3^{alcohol}), 46.3 (methylcarbamate C-1^{hemiacetal}), 44.9 (C-4a^{hemiacetal}), 42.3 (methylcarbamate C-1^{alcohol}), 28.5 (^{t}Bu $C_3^{hemiacetal}$), 28.4 (^{t}Bu $C_3^{alcohol}$), 28.1 (hydroxypropyl C-1^{alcohol}), 27.1 (hydroxypropyl C-2^{alcohol}), 22.5 (C-4^{hemiacetal}), 21.1 (C-3^{hemiacetal}); HRMS found MNa^+, 296.1463. $C_{13}H_{23}NO_5$ requires *MNa*, 296.1468. Compound **S12** existed as a mixture of the hemiacetal and alcohol.

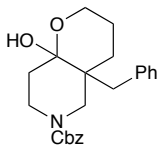
***tert*-Butyl *N*-{[2-(3-hydroxypropyl)-6-methoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl]methyl} carbamate**



S13

According to General Procedure F, the alkene derivative **1e** (0.50 g, 1.50 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 50:50 EtOAc−hexane to yield the *alcohol derivative* ***S13*** (0.32 g, 61%, >98% alcohol by ^{1}H-NMR in $CDCl_3$) as a pale-yellow oil, R_f 0.40 (30:70 petrol−EtOAc); ν_{max}/cm^{-1} 3368, 2931, 2870, 1687, 1490, 1365, 1274, 1245, 1161, 1054, 1024; δ_H (400 MHz, $CDCl_3$) 7.32 (1H, d, *J* 8.4, 4-H), 7.18 (1H, dd, *J* 8.4 and 2.6, 5-H), 7.13 (1H, d, *J* 2.6, 7-H), 4.95 (1H, app. t, *J* 5.0, NH), 3.82 (3H, s, methoxy), 3.54 (2H, t, *J* 6.3, hydroxypropyl 3-H_2), 3.45 (1H, dd, *J* 13.5 and 7.0, methylcarbamate 1-H_A), 3.25 (1H, dd, *J* 13.5 and 5.9, methylcarbamate 1-H_B), 2.98 (1H, d, *J* 17.1, 3-H_A), 2.93 (1H, d, *J* 17.1, 3-H_B), 1.81 (1H, br. s, OH), 1.74-1.64 (2H, m, hydroxypropyl 1-H_2), 1.56-1.44 (1H, m, hydroxypropyl 2-H_A), 1.37 (9H, s, ^{t}Bu), 1.36-1.28 (1H, m, hydroxypropyl 2-H_B); δ_C (100 MHz, $CDCl_3$) 210.5 (C-1), 159.6 (C-6), 156.5 (Boc C=O), 146.5 (C-3a), 137.5 (C-7a), 127.4 (C-4), 124.9 (C-5), 105.2 (C-7), 79.6 (Boc C_1), 62.8 (hydroxypropyl C-3), 55.7 (methoxy), 54.0 (C-2), 45.8 (methylcarbamate C-1), 35.6 (C-3), 31.0 (hydroxypropyl C-1), 28.4 (^{t}Bu C_3), 27.5 (hydroxypropyl C-2); HRMS found MNa^+, 372.1784. $C_{19}H_{27}NO_5$ requires *MNa*, 372.1781. Compound **S13** existed exclusively as the alcohol.

Benzyl 4a-benzyl-8a-hydroxy-octahydro-2*H*-pyrano[3,2-*c*]pyridine-6-carboxylate

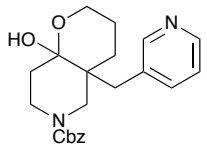


S14

According to General Procedure F, the alkene derivative **1f** (0.60 g, 1.65 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 30:70 EtOAc−hexane to yield the *hemiacetal derivative* ***S14*** (0.52 g, 83%) as colourless oil, R_f 0.39 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3399, 2943, 2877, 2523, 2068, 1672, 1431, 1269,

1248, 1138, 1071; δ_H (500 MHz, CD_3OD, 333 K) 7.44-7.25 (5H, m, Cbz phenyl), 7.17-7.06 (5H, m, phenyl), 5.16 (2H, s, Cbz arylmethyl 1-H_2), 4.12-3.95 (2H, m, 2-H_A and 7-H_A), 3.64-3.59 (1H, m, 5-H_A), 3.59-3.56 (1H, m, 2-H_B), 3.27 (1H, d, *J* 13.3, 5-H_B), 3.14 (1H, t, *J* 12.9, 7-H_B), 2.79 (2H, s, arylmethyl 1-H_2), 1.97 (1H, td, *J* 13.1 and 5.2, 8-H_A), 1.82 (1H, td, *J* 13.5 and 5.0, 4-H_A), 1.74-1.66 (1H, m, 3-H_A), 1.66-1.60 (1H, m, 8-H_B), 1.37-1.24 (1H, m, 3-H_B), 0.77 (1H, app. d, *J* 13.5, 4-H_B); δ_C (125 MHz, CD_3OD, 333 K) 157.7 (Cbz C=O), 138.9 (Cbz phenyl C-1 and phenyl C-1), 132.2 (phenyl C_2-3,5), 129.5 (Cbz phenyl C_2-3,5), 129.1 (phenyl C_2-2,6 and Cbz phenyl C_2-2,6), 128.7 (Cbz phenyl C-4), 126.9 (phenyl C-4), 96.9 (C-8a), 68.5 (Cbz arylmethyl C-1), 60.7 (C-2), 46.9 (C-5), 42.7 (C-7), 41.5 (C-4a), 39.1 (arylmethyl C-1), 35.1 (C-8), 27.3 (C-4), 22.2 (C-3); HRMS found MNa^+, 404.1830. $C_{23}H_{27}NO_4$ requires *MNa*, 404.1837.

Benzyl 8a-hydroxy-4a-[(pyridin-3-yl)methyl]-octahydro-2*H*-pyrano[3,2-*c*]pyridine-6-carboxylate

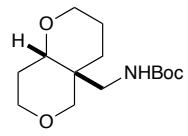


S15

According to General Procedure F, the alkene derivative **1g** (0.20 g, 0.55 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 80:20→100:0 EtOAc−hexane to yield the *hemiacetal derivative* ***S15*** (0.15 g, 70%) as a colourless oil, R_f 0.26 (EtOAc); ν_{max}/cm^{-1} 3339, 2943, 2877, 2519, 2065, 1692, 1426, 1351, 1270, 1247, 1212, 1138, 1072, 1024; δ_H (500 MHz, CD_3OD, 333 K) 8.37 (1H, app. s, pyridine 6-H), 8.31 (1H, d, *J* 4.9, pyridine 2-H), 7.70-7.57 (1H, m, pyridine 4-H), 7.51-7.23 (5H, m, phenyl), 7.15 (1H, br. s, pyridine 5-H), 5.18 (2H, s, phenylmethyl 1-H_2), 4.15-3.98 (2H, m, 7-H_A and 2-H_A), 3.60 (1H, ddd, *J* 11.3, 5.4 and 1.6, 2-H_B), 3.55 (1H, d, *J* 13.5, 5-H_A), 3.31 (1H, d, *J* 13.5, 5-H_B), 3.13 (1H, td, *J* 12.9 and 3.3, 7-H_B), 2.85 (1H, d, *J* 13.7, pyridinylmethyl 1-H_A), 2.80 (1H, d, *J* 13.7, pyridinylmethyl 1-H_B), 1.98 (1H, td, *J* 13.3 and 5.4, 8-H_A), 1.85 (1H, td, *J* 13.4 and 4.9, 4-H_A), 1.77-1.67 (1H, m, 3-H_A), 1.64 (1H, app. d, *J* 14.1, 8-H_B), 1.34 (1H, app. d, *J* 13.7, 3-H_B), 0.77 (1H, app. d, *J* 13.4, 4-H_B); δ_C (125 MHz,

CD_3OD, 333 K) 157.5 (Cbz C=O), 152.3 (pyridine C-2), 147.7 (pyridine C-6), 140.6 (pyridine C-4), 138.1 (phenyl C-1), 135.5 (pyridine C-3), 129.6 (phenyl C_2-3,5), 129.2 (phenyl C_2-2,6), 129.0 (phenyl C-4), 124.4 (pyridine C-5), 96.7 (C-8a), 68.6 (phenylmethyl C-1), 60.6 (C-2), 46.9 (C-5), 42.7 (C-7), 41.6 (C-4a), 36.5 (pyridinylmethyl C-1), 35.3 (C-8), 27.4 (C-4), 22.1 (C-3); HRMS found MH^+, 383.1961. $C_{22}H_{26}N_2O_4$ requires *MH*, 383.1965.

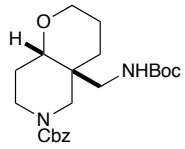
tert-Butyl _N_-{[(4a_R_*,8a_R_*)-octahydropyrano[4,3-_b_]pyran-4a-yl]methyl}carbamate



13

According to General Procedure G, the hemiacetal derivative **12** (0.16 g, 0.55 mmol) gave a crude material. The crude material (*dr* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 30:70 EtOAc−hexane to yield the *ether derivative **13*** (0.15 g, 99%, *dr* >95:<5 by ^{1}H-NMR) as colourless blocks, m.p. ($CHCl_3$/Et_2O), 98-102 °C; R_f 0.50 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3318, 2959, 2932, 2873, 2858, 2824, 1710, 1546, 1365, 1249, 1169, 1094, 1073, 1057; δ_H (400 MHz, $CDCl_3$) 4.73 (1H, br. s, NH), 3.97 (1H, app. dd, *J* 11.6 and 4.9, 2-H_A), 3.85 (1H, d, *J* 11.6, 5-H_A), 3.72-3.64 (2H, m, 7-H_2), 3.42 (1H, app. t, *J* 3.8, 8a-H_A), 3.37 (1H, td, *J* 11.6 and 2.3, 2-H_B), 3.30-3.23 (3H, m, 5-H_B and methylcarbamate 1-H_2), 2.08 (1H, dddd, *J* 14.4, 10.6, 7.2 and 3.3, 8-H_A), 1.78-1.64 (1H, m, 3-H_A), 1.54 (1H, app. dd, *J* 14.4 and 2.8, 8-H_B), 1.48-1.37 (3H, m, 3-H_B and 4-H_2), 1.43 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 156.4 (Boc C=O), 79.4 (^{t}Bu C_1), 74.6 (C-8a), 67.9 (C-5), 67.7 (C-2), 63.4 (C-7), 45.7 (methylcarbamate C-1), 36.8 (C-4a), 28.6 (C-4), 28.5 (^{t}Bu C_3), 28.3 (C-8), 22.3 (C-3); HRMS found MH^+, 272.1856. $C_{14}H_{25}NO_4$ requires *MH*, 272.1856. The relative configuration was determined using X-ray crystallography and NOESY (500 MHz, $CDCl_3$), nOe observed between 8a-H and 8-H_A, 8a-H and 8-H_B, 8a-H and NH.

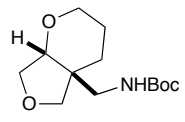
Benzyl (4a_R_*,8a_R_*)-4a-({[(_tert_-butoxy)carbonyl]amino}methyl)-octahydro-2_H_-pyrano[3,2-_c_]pyridine-6-carboxylate



2

According to General Procedure G, the hemiacetal derivative **S11** (0.10 g, 0.24 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *ether derivative **2*** (49.0 mg, 51%, *dr* >95:<5 by ^{1}H-NMR) as colourless oil, R_f 0.45 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3320, 2925, 2874, 2851, 1711, 1672, 1534, 1445, 1432, 1360, 1281, 1246, 1220, 1163, 1149, 1131, 1086; δ_H (500 MHz, CD_3OD, 333 K) 7.40-7.25 (5H, m, phenyl), 5.12 (2H, s, arylmethyl 1-H_2), 3.94 (1H, app. dt, *J* 11.1 and 2.4, 2-H_A), 3.87 (1H, app. dt, *J* 13.1 and 3.0, 7-H_A), 3.51 (1H, d, *J* 13.5, 5-H_A), 3.42-3.33 (3H, m, 2-H_B, 5-H_B and 8a-H), 3.16 (1H, d, *J* 14.3, methylcarbamate 1-H_A), 3.12 (1H, app. dt, *J* 13.1 and 3.3, 7-H_B), 2.84 (1H, d, *J* 14.3, methylcarbamate 1-H_B), 2.01-1.91 (1H, m, 8-H_A), 1.82-1.69 (1H, m, 3-H_A), 1.63-1.52 (2H, m, 8-H_B and 4-H_A), 1.50-1.44 (1H, m, 3-H_B), 1.43 (10H, s, ^{t}Bu and 4-H_B); δ_C (125 MHz, CD_3OD, 333 K) 158.5 (Boc C=O), 157.5 (Cbz C=O), 138.2 (phenyl C-1), 129.5 (phenyl C_2-3,5), 129.1 (phenyl C_2-2,6), 128.9 (phenyl C-4), 80.3 (^{t}Bu C_1), 76.2 (C-8a), 68.6 (C-2), 68.4 (arylmethyl C-1), 46.1 (C-5), 45.9 (methylcarbamate C-1), 40.5 (C-7), 38.8 (C-4a), 30.0 (C-4), 28.8 (^{t}Bu C_3), 28.3 (C-8), 23.1 (C-3); HRMS found MNa^+, 427.2202. $C_{22}H_{32}N_2O_5$ requires *MNa*, 427.2203. The relative configuration was determined using NOESY (500 MHz, CD_3OD, 333 K), nOe observed between 8a-H and 8-H_A, 8a-H and 8-H_B, 8a-H and methylcarbamate 1-H_A, 8a-H and methylcarbamate 1-H_B.

tert-Butyl _N_-{[(4a_R_*,7a_S_*)-hexahydro-2_H_-furo[3,4-_b_]pyran-4a-yl]methyl}carbamate

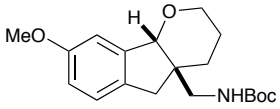


35

According to General Procedure H, the hemiacetal derivative **S12** (0.74 g, 2.70 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting

with 20:80 EtOAc−hexane to yield the *ether derivative* ***35*** (0.30 g, 43%, *dr* >95:<5 by ^{1}H-NMR) as colourless oil, R_f 0.35 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3318, 2949, 2928, 2875, 2855, 1677, 1540, 1365, 1276, 1250, 1160, 1135, 1093, 1081, 1059, 1034; δ_H (500 MHz, $CDCl_3$) 4.76 (1H, app. t, *J* 5.1, NH), 4.11 (1H, dd, *J* 10.1 and 4.0, 7-H_A), 3.92-3.86 (1H, m, 2-H_A), 3.87 (1H, d, *J* 8.4, 5-H_A), 3.79 (1H, app. d, *J* 10.1, 7-H_B), 3.73 (1H, app. d, *J* 4.0, 7a-H), 3.51 (1H, d, *J* 8.4, 5-H_B), 3.31 (1H, td, *J* 11.4 and 2.3, 2-H_B), 3.15 (1H, dd, *J* 14.1 and 6.8, methylcarbamate 1-H_A), 2.98 (1H, dd, *J* 14.1 and 6.5, methylcarbamate 1-H_B), 1.80-1.69 (1H, m, 3-H_A), 1.69-1.64 (2H, m, 4-H_2), 1.53-1.46 (1H, m, 3-H_B), 1.43 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 156.5 (Boc C=O), 80.3 (C-7a), 79.7 (^{t}Bu C_1), 74.2 (C-7), 71.2 (C-5), 66.2 (C-2), 46.5 (methylcarbamate C-1), 45.9 (C-4a), 28.5 (^{t}Bu C_3), 24.3 (C-4), 21.7 (C-3); HRMS found MNa^+, 280.1517. $C_{13}H_{23}NO_4$ requires *MNa*, 280.1519. The relative configuration was determined using NOESY (500 MHz, $CDCl_3$), nOe observed between 7a-H and methylcarbamate 1-H_A, 7a-H and methylcarbamate 1-H_B, 7a-H and NH.

***tert*-Butyl *N*-{[(4a*R**,9b*S**)-8-methoxy-2*H*,3*H*,4*H*,4a*H*,5*H*,9b*H*-indeno[1,2-*b*]pyran-4a-yl]methyl}carbamate**

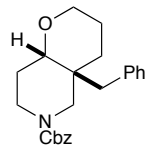


38

According to General Procedure H, the alcohol derivative **S13** (0.10 g, 0.28 mmol) gave a crude material. The crude material (*dr* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *ether derivative* ***38*** (62.0 mg, 65%, *dr* >95:<5 by ^{1}H-NMR) as a colourless oil, R_f 0.48 (60:40 petrol−EtOAc); ν_{max}/cm^{-1} 3336, 2929, 2856, 1696, 1513, 1488, 1451, 1364, 1275, 1264, 1244, 1166, 1152, 1079, 1029; δ_H (400 MHz, $CDCl_3$) 7.09 (1H, d, *J* 8.2, 6-H), 6.89 (1H, d, *J* 2.4, 9-H), 6.77 (1H, dd, *J* 8.2 and 2.4, 7-H), 4.76 (1H, app. t, *J* 6.3, NH), 4.74 (1H, s, 9b-H), 3.78 (3H, s, methoxy), 3.60 (2H, app. t, *J* 4.3, 2-H_2), 3.37 (1H, dd, *J* 14.0 and 6.9, methylcarbamate 1-H_A), 3.25 (1H, dd, *J* 14.0 and 6.3, methylcarbamate 1-H_B), 2.60 (2H, app. s, 5-H_2), 1.79-1.67 (1H, m, 3-H_A), 1.67-1.58 (1H, m, 4-H_A), 1.57-1.47 (1H, m, 4-H_B), 1.43 (10H, s, ^{t}Bu and 3-H_B); δ_C (100 MHz, $CDCl_3$) 159.1 (C-8), 156.3 (Boc C=O), 143.0 (C-9a), 133.1 (C-5a), 126.4 (C-6), 114.6 (C-7), 109.5 (C-9), 82.8 (C-9b), 79.3 (^{t}Bu C_1), 63.1 (C-2), 55.5 (methoxy), 46.2

(methylcarbamate C-1), 39.0 (C-5), 28.5 (^{t}Bu C_3), 28.0 (C-4), 22.0 (C-3); HRMS found MNa^+, 356.1838. $C_{19}H_{27}NO_4$ requires *MNa*, 356.1832. The relative configuration was determined using NOESY (500 MHz, CD_3OD), nOe observed between 9b-H and methylcarbamate 1-H_A, 9b-H and methylcarbamate 1-H_B.

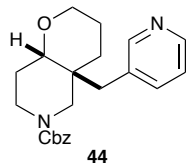
Benzyl (4a*R,8a*R**)-4a-benzyl-octahydro-2*H*-pyrano[3,2-*c*]pyridine-6-carboxylate**



43

According to General Procedure I, the hemiacetal derivative **S14** (0.45 g, 1.18 mmol) gave a crude material. The crude material (*dr* 93:7 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 10:90 EtOAc−hexane to yield the *ether derivative **43*** (0.27 g, 63%, *dr* >95:<5 by ^{1}H-NMR) as colourless oil, R_f 0.40 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3061, 3028, 2932, 2851, 1692, 1427, 1265, 1243, 1210, 1129, 1086, 1074, 1025; δ_H (500 MHz, CD_3OD, 333 K) 7.35-7.25 (5H, m, Cbz phenyl), 7.15 (5H, app. br. s, phenyl), 5.19 (1H, d, *J* 12.4, Cbz arylmethyl 1-H_A), 5.15 (1H, d, *J* 12.4, Cbz arylmethyl 1-H_B), 3.97 (1H, app. ddt, *J* 13.0, 5.5 and 2.0, 7-H_A), 3.92 (1H, app. ddt, *J* 11.3, 4.7 and 1.8, 2-H_A), 3.60 (1H, d, *J* 13.3, 5-H_A), 3.38-3.29 (3H, m, 5-H_B, 8a-H and 2-H_B), 3.15 (1H, td, *J* 13.0 and 3.2, 7-H_B), 2.75 (1H, d, *J* 13.4, arylmethyl 1-H_A), 2.40 (1H, d, *J* 13.4, arylmethyl 1-H_B), 2.10 (1H, dddd, *J* 14.4, 13.0, 5.5 and 3.2, 8-H_A), 1.76-1.69 (1H, m, 3-H_A), 1.69-1.63 (1H, m, 8-H_B), 1.48 (1H, td, *J* 13.8 and 4.7, 4-H_A), 1.37 (1H, app. ddt, *J* 13.2, 4.7 and 2.4, 3-H_B), 1.10 (1H, app. dt, *J* 13.8 and 3.6, 4-H_B); δ_C (125 MHz, CD_3OD, 333 K) 157.7 (Cbz C=O), 138.2 (phenyl C-1 and Cbz phenyl C-1), 131.9 (phenyl C_2-3,5), 129.5 (Cbz phenyl C_2-3,5), 129.1 (phenyl C_2-2,6 and Cbz phenyl C_2-2,6), 128.9 (Cbz phenyl C-4), 127.2 (phenyl C-4), 78.7 (C-8a), 68.7 (Cbz arylmethyl C-1), 68.5 (C-2), 46.4 (C-5), 42.3 (arylmethyl C-1), 40.2 (C-7), 37.7 (C-4a), 31.7 (C-4), 28.0 (C-8), 23.3 (C-3); HRMS found MNa^+, 388.1880. $C_{23}H_{27}NO_3$ requires *MNa*, 388.1888. The relative configuration was determined using NOESY (500 MHz, CD_3OD, 333 K), nOe observed between 8a-H and arylmethyl 1-H_A, 8a-H and arylmethyl 1-H_B, 8a-H and 8-H_A, 8a-H and 8-H_B.

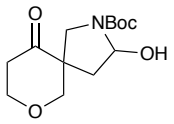
Benzyl (4a*R,8a*R**)-4a-[(pyridin-3-yl)methyl]-octahydro-2*H*-pyrano[3,2-*c*]pyridine-6-carboxylate**



44

According to General Procedure I, the hemiacetal derivative **S15** (0.13 g, 0.34 mmol) gave a crude material. The crude material (*dr* 91:9 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 70:30 EtOAc−hexane to yield the *ether derivative **44*** (0.11 g, 88%, *dr* 91:9 by ^{1}H-NMR) as colourless oil, R_f 0.32 (EtOAc); ν_{max}/cm^{-1} 3030, 2934, 2851, 1690, 1424, 1266, 1243, 1207, 1130, 1085, 1025; δ_H (500 MHz, CD_3OD, 333 K) 8.36 (1H, d, *J* 6.8, pyridine 6-H), 8.35 (1H, s, pyridine 2-H), 7.76-7.57 (1H, m, pyridine 4-H), 7.39 (2H, d, *J* 7.9, phenyl 2,6-H_2), 7.34 (2H, t, *J* 7.9, phenyl 3,5-H_2), 7.28 (1H, t, *J* 7.9, phenyl 4-H), 7.20 (1H, app. br. s, pyridine 5-H), 5.18 (2H, s, phenylmethyl, 1-H_2), 3.99 (1H, ddd, *J* 13.0, 3.0 and 1.3, 7-H_A), 3.96-3.91 (1H, m, 2-H_A), 3.55 (1H, d, *J* 13.4, 5-H_A), 3.40-3.33 (3H, m, 5-H_B, 8a-H and 2-H_B), 3.14 (1H, td, *J* 13.0 and 3.3, 7-H_B), 2.81 (1H, d, *J* 13.5, pyridinylmethyl 1-H_A), 2.40 (1H, d, *J* 13.5, pyridinylmethyl 1-H_B), 2.13-2.02 (1H, m, 8-H_A), 1.74-1.68 (1H, m, 8-H_B), 1.68-1.63 (1H, m, 3-H_A), 1.45 (1H, td, *J* 13.4 and 3.0, 4-H_A), 1.41-1.36 (1H, m, 3-H_B), 1.07 (1H, app. d, *J* 13.4, 4-H_B); δ_C (125 MHz, CD_3OD, 333 K) 157.6 (Cbz C=O), 152.0 (pyridine C-2), 148.0 (pyridine C-6), 140.3 (pyridine C-4), 138.2 (phenyl C-1), 134.7 (pyridine C-3), 129.6 (phenyl C_2-3,5), 129.1 (phenyl C_2-2,6), 129.0 (phenyl C-4), 124.5 (pyridine C-5), 78.7 (C-8a), 68.7 (Cbz arylmethyl C-1), 68.5 (C-2), 45.8 (C-5), 40.2 (C-7), 39.1 (pyridinylmethyl C-1), 37.6 (C-4a), 31.7 (C-4), 28.0 (C-8), 23.2 (C-3); HRMS found MH^+, 367.2015. $C_{22}H_{26}N_2O_3$ requires *MH*, 367.2021. The relative configuration was determined using NOESY (500 MHz, CD_3OD, 333 K), nOe observed between 8a-H and pyridinylmethyl 1-H_A, 8a-H and 8-H_A, 8a-H and 8-H_B.

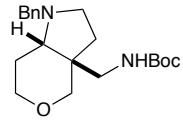
***tert*-Butyl 3-hydroxy-10-oxo-7-oxa-2-azaspiro[4.5]decane-2-carboxylate**



14

According to General Procedure J, the alkene derivative **1a** (0.25 g, 0.93 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 50:50 EtOAc−hexane to yield the *hemiaminals **14*** (0.19 g, 75%, *dr* 66:34 by ^{1}H-NMR) as an amorphous colourless solid, R_f 0.23 and 0.34 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3432, 2956, 2923, 2852, 1697, 1382, 1365, 1255, 1223, 1169, 1149, 1115, 1097; δ_H (400 MHz, $CDCl_3$) 5.53 (1H, app. d, *J* 6.5, 3-H^{maj}), 2.46 (1H, app. d, *J* 4.9 3-H^{min}), 4.11 (4H, app. d, *J* 11.6, 8-H$_A$ and 6-H$_A$), 3.89 (2H, ddd, *J* 11.6, 8.8 and 4.5, 8-H$_B$), 3.76 (1H, d, *J* 11.6, 6-H$_B^{maj}$), 3.72-3.60 (4H, m, 6-H$_B^{min}$, 1-H$_A$ and 1H$_B^{min}$), 3.50 (1H, d, *J* 11.2, 1-H$_B^{maj}$), 2.93 (1H, br. s, OH^{min}), 2.70-2.43 (6H, m, 9-H$_2$ and 4-H$_A$), 1.75 (2H, app. d, *J* 14.1, 4-H$_B$), 1.64 (1H, br. s, OH^{maj}), 1.48 (18H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 206.2 (C$_2$-10), 154.8 (Boc 2C=O), 81.7 (C$_2$-3), 80.9 (^{t}Bu 2C$_1$), 75.5 (C$_2$-6), 68.5 (C$_2$-8), 56.6 (C-5^{maj}), 55.8 (C-5^{min}), 51.1 (C-1^{min}), 50.9 (C-1^{maj}), 40.9 (C$_2$-9), 36.6 (C-4^{min}), 36.0 (C-4^{maj}), 28.5 (^{t}Bu 2C$_3$); HRMS found MNa$^+$, 294.1314. $C_{13}H_{21}NO_5$ requires *MNa*, 294.1311.

tert-Butyl _N_-{[(3a_R_,7a_S_)-1-benzyl-octahydropyrano[4,3-_b_]pyrrol-3a-yl]methyl} carbamate

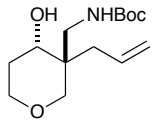


15

Benzylamine (12.9 μL, 117 μmol), acetic acid (12.2 μL, 214 μmol) and $NaBH(OAc)_3$ (56.7 mg, 267 μmol) were added to a solution of the hemiaminals **14** (29.0 mg, 107 μmol) in DCM (1.00 mL) at rt. The reaction mixture was stirred for 18 h at rt. Then, a saturated aqueous solution of $NaHCO_3$ (1 mL) was added and the solution was stirred for 5 min. The phases were separated and the aqueous phase was extracted with DCM (3 × 1 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to

give a crude product. The crude product was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *amine derivative* ***15*** (11.0 mg, 30%, *dr* 83:17 by ^{1}H-NMR) as an amorphous colourless solid, R_f 0.53 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3323, 2965, 2924, 2792, 1712, 1537, 1452, 1388, 1268, 1247, 1165, 1131, 1085; δ_H (400 MHz, $CDCl_3$) 7.35-7.21 (5H, m, phenyl), 5.22 (1H, br. s, NH), 3.96 (1H, d, *J* 13.3, arylmethyl 1-H_A), 3.80 (1H, td, *J* 10.9 and 3.1, 6-H_A), 3.66-3.61 (1H, m, 6-H_B), 3.59 (1H, d, *J* 11.8, 4-H_A), 3.45 (1H, d, *J* 11.8, 4-H_B), 3.39-3.30 (1H, m, methylcarbamate 1-H_A), 3.29-3.20 (2H, m, arylmethyl 1-H_B and methylcarbamate 1-H_B), 2.92 (1H, td, *J* 9.4 and 4.5, 2-H_A), 2.50 (1H, app. s, 7a-H), 2.39-2.27 (1H, m, 2-H_B), 1.91-1.78 (1H, m, 7-H_A), 1.70 (1H, app. dq, *J* 14.6 and 3.6, 7-H_B), 1.63-1.51 (1H, m, 3-H_A), 1.45 (9H, s, ^{t}Bu), 1.39-1.28 (1H, m, 3-H_B); δ_C (100 MHz, $CDCl_3$) 156.5 (C=O), 139.7 (phenyl C-1), 128.5 (phenyl C_2-3,5), 128.3 (phenyl C_2-2,6), 127.0 (phenyl C-4), 79.2 (^{t}Bu C_1), 71.2 (C-4), 64.0 (C-6), 63.0 (C-7a), 57.1 (arylmethyl C-1), 51.2 (C-2), 46.3 (methylcarbamate C-1), 44.1 (C-3a), 29.4 (C-3), 28.5 (^{t}Bu C_3), 24.0 (C-7); HRMS found MH^+, 347.2337. $C_{20}H_{30}N_2O_3$ requires *MH*, 347.2329. The relative configuration was determined using NOESY (500 MHz, $CDCl_3$), nOe observed between 7a-H and methylcarbamate 1-H_A, 7a-H and methylcarbamate 1-H_B, 7a-H and 7-H_A, 7a-H and 7-H_B.

tert-Butyl _N_-{[(3_R_*, 4_R_*)-4-hydroxy-3-(prop-2-en-1-yl)oxan-3-yl]methyl}carbamate

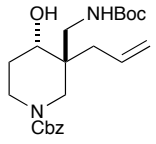


16a

According to General Procedure K, the ketone derivative **1a** (0.50 g, 1.85 mmol) and diisobutylaluminium hydride (4.08 mL, 4.08 mmol of a 1.0 M solution in DCM) gave a crude material. The crude material (*dr* 86:14 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 50:50 EtOAc−hexane to yield the *alcohol derivative* ***16a*** (0.47 g, 93%, *dr* 86:14 by ^{1}H-NMR) as a yellow oil, R_f 0.31 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3340, 2975, 2932, 2856, 1682, 1512, 1365, 1274, 1248, 1163, 1083; δ_H (400 MHz, $CDCl_3$) 5.83 (1H, ddt, *J* 15.3, 9.5 and 7.7, propenyl 2-H), 5.13 (1H, app. d, *J* 15.3, propenyl 3-H_{trans}), 5.10

(1H, app. d, *J* 9.5, propenyl 3-H_{cis}), 4.80 (1H, app. t, *J* 7.0, NH), 3.97 (1H, app. dd, *J* 11.6 and 4.0, 6-H_A), 3.68 (1H, dd, *J* 11.1 and 4.8, 4-H), 3.61 (1H, d, *J* 11.4, 2-H_A), 3.39 (1H, td, *J* 11.6 and 2.9, 6-H_B), 3.35-3.33 (1H, app. d, *J* 8.0, methylcarbamate 1-H_A), 2.98 (1H, d, *J* 11.4, 2-H_B), 2.70 (1H, dd, *J* 14.9 and 5.4, methylcarbamate 1-H_B), 2.43 (1H, dd, *J* 14.0 and 7.2, propenyl 1-H_A), 2.26 (1H, dd, *J* 14.0 and 8.1, propenyl 1-H_B), 1.85 (1H, app. qd, *J* 11.9 and 4.8, 5-H_A), 1.70 (1H, app. dt, *J* 13.1 and 1.84, 5-H_B), 1.45 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 157.8 (Boc C=O), 134.0 (propenyl C-2), 118.6 (propenyl C-3), 80.3 (^{t}Bu C_1), 70.3 (C-2), 70.1 (C-4), 67.2 (C-6), 43.7 (methylcarbamate C-1), 42.9 (C-3), 31.6 (propenyl C-1), 29.5 (C-5), 28.4 (^{t}Bu C_3); HRMS found MH^+, 272.1855. $C_{14}H_{25}NO_4$ requires *MH*, 272.1856. The relative configuration was determined by analogy with the carbocyclic analogue[8] and using NOESY (500 MHz, $CDCl_3$), nOe observed between 4-H and methylcarbamate 1-H_A.

Benzyl (3*R,4*R**)-3-({[(*tert*-butoxy)carbonyl]amino}methyl)-4-hydroxy-3-(prop-2-en-1-yl)piperidine-1-carboxylate**

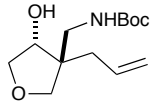


16b

According to General Procedure K, the ketone derivative **1b** (0.50 g, 1.24 mmol) and diisobutylaluminium hydride (1.36 mL, 1.36 mmol of a 1.0 M solution in DCM) gave a crude material. The crude material (*dr* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 30:70 EtOAc−hexane to yield the *alcohol derivative* ***16b*** (0.39 g, 78%, *dr* >95:<5 by ^{1}H-NMR) as a colourless oil, R_f 0.55 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3367, 2975, 2935, 2870, 2492, 1672, 1428, 1364, 1234, 1155, 1079; δ_H (500 MHz, CD_3OD, 333 K) 7.37-7.27 (5H, m, phenyl), 5.87 (1H, app. dd, *J* 13.3 and 7.0, propenyl 2-H), 5.11 (2H, s, arylmethyl 1-H_2), 5.03 (1H, app. d, *J* 17.0 propenyl 3-H_{trans}), 5.00 (1H, app. d, *J* 10.2, propenyl 3-H_{cis}), 3.95 (1H, app. d, *J* 13.3, 6-H_A), 3.72 (1H, d, *J* 13.7, 2-H_A), 3.63 (1H, dd, *J* 9.7 and 4.4, 4-H), 3.15 (1H, d, *J* 14.3, methylcarbamate 1-H_A), 3.06 (1H, app. br. s, 6-H_B), 2.95 (1H, d, *J* 14.3, methylcarbamate 1-H_B), 2.78 (1H, d, *J* 13.7, 2-H_B), 2.18 (1H, dd, *J* 14.2 and 7.9, propenyl 1-H_A), 2.09 (1H, dd, *J* 14.2 and 7.0, propenyl 1-H_B), 1.78-1.71 (1H, m, 5-

H_A), 1.70-1.60 (1H, m, 5-H_B), 1.43 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 158.9 (Boc C=O), 157.3 (Cbz C=O), 138.1 (phenyl C-1), 135.2 (propenyl C-2), 129.5 (phenyl C_2-3,5), 129.1 (phenyl C_2-2,6), 129.0 (phenyl C-4), 118.6 (propenyl C-3), 80.5 (^{t}Bu C_1), 71.8 (C-4), 68.5 (arylmethyl C-1), 48.3 (C-2), 45.0 (methylcarbamate C-1), 43.6 (C-3), 43.0 (C-6), 33.3 (propenyl C-1), 29.8 (C-5), 28.8 (^{t}Bu C_3); HRMS found MNa^+, 427.2205. $C_{22}H_{32}N_2O_5$ requires *MNa*, 427.2203. The relative configuration was determined by analogy with the carbocyclic analogue[8] and using NOESY (500 MHz, CD_3OD), nOe observed between 4-H and methylcarbamate 1-H_A, 4-H and methylcarbamate 1-H_B.

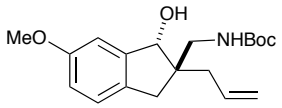
tert-Butyl _N_-{[(3_R_*,4_S_*)-4-hydroxy-3-(prop-2-en-1-yl)oxolan-3-yl]methyl}carbamate



16d

According to General Procedure K, the ketone derivative **1d** (2.00 g, 7.83 mmol) and diisobutylaluminium hydride (17.2 mL, 17.2 mmol of a 1.0 M solution in DCM) gave a crude material. The crude material (*dr* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 20:80→40:60 EtOAc−hexane to yield the *alcohol derivative* ***16d*** (1.85 g, 92%, *dr* >95:<5 by ^{1}H-NMR) as a light-yellow oil, R_f 0.29 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3341, 2976, 2930, 2872, 1686, 1516, 1365, 1272, 1248, 1162, 1068, 1046; δ_H (400 MHz, $CDCl_3$) 5.83 (1H, ddt, *J* 17.2, 10.1 and 7.5, propenyl 2-H), 5.17 (1H, dd, *J* 17.2 and 1.8, propenyl 3-H_{trans}), 5.12 (1H, dd, *J* 10.1 and 1.8, propenyl 3-H_{cis}), 4.84 (1H, app. t, *J* 5.0, NH), 4.24-4.10 (2H, m, 5-H_A and 4-H), 3.71-3.67 (1H, m, 5-H_B), 3.66 (1H, d, *J* 8.9, 2-H_A), 3.54 (1H, d, *J* 8.9, 2-H_B), 3.17-3.02 (2H, m, methylcarbamate, 1-H_2), 2.60 (1H, br. s, OH), 2.33 (1H, dd, *J* 14.3 and 7.7, propenyl 1-H_A), 2.26 (1H, dd, *J* 14.3 and 7.1, propenyl 1-H_B), 1.43 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 156.9 (Boc C=O), 134.7 (propenyl C-2), 118.5 (propenyl C-3), 79.9 (^{t}Bu C_1), 75.6 (C-4), 74.3 (C-5), 73.9 (C-2), 50.2 (C-3), 44.1 (methylcarbamate C-1), 33.5 (propenyl C-1), 28.5 (^{t}Bu C_3); HRMS found MNa^+, 280.1514. $C_{13}H_{23}NO_4$ requires *MNa*, 280.1519. The relative configuration was determined from compound **3**.

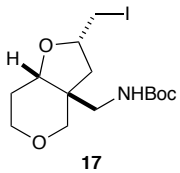
***tert*-Butyl *N*-{[(1*R**,2*S**)-1-hydroxy-6-methoxy-2-(prop-2-en-1-yl)-2,3-dihydro-1*H*-inden-2-yl]methyl}carbamate**



16e

According to General Procedure K, the ketone derivative **1e** (1.00 g, 3.01 mmol) and diisobutylaluminium hydride (6.63 mL, 6.63 mmol of a 1.0 M solution in DCM) gave a crude material. The crude material (*dr* >90:<10 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *alcohol derivative* ***16e*** (0.63 g, 63%, *dr* >95:<5 by ^{1}H-NMR) as a yellow oil, R_f 0.37 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3368, 2976, 2931, 2835, 1685, 1512, 1490, 1435, 1365, 1272, 1245, 1159, 1029; δ_H (400 MHz, $CDCl_3$) 7.03 (1H, d, *J* 8.2, 4-H), 6.91 (1H, d, *J* 2.4, 7-H), 6.75 (1H, dd, *J* 8.2 and 2.4, 5-H), 5.85-5.68 (1H, m, propenyl 2-H), 5.03 (1H, app. d, *J* 19.7, propenyl 3-H$_{trans}$), 5.04 (1H, app. d, *J* 11.7, propenyl 3-H$_{cis}$), 4.94 (1H, app. t, *J* 6.3, NH), 3.79 (3H, s, methoxy), 3.29 (1H, dd, *J* 14.2 and 6.9, methylcarbamate 1-H$_A$), 3.20 (1H, dd, *J* 14.2 and 5.8, methylcarbamate 1-H$_B$), 2.73 (1H, d, *J* 15.4, 3-H$_A$), 2.51 (1H, d, *J* 15.4, 3-H$_B$), 2.34 (1H, dd, *J* 14.2 and 7.4, propenyl 1-H$_A$), 2.05 (1H, dd, *J* 14.2 and 7.3, propenyl 1-H$_B$), 1.44 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 159.2 (C-6), 157.1 (Boc C=O), 145.5 (C-7a), 135.2 (propenyl C-2), 131.4 (C-3a), 125.6 (C-4), 118.0 (propenyl C-3), 114.5 (C-5), 108.9 (C-7), 80.7 (C-1), 79.8 (^{t}Bu C_1), 55.6 (methoxy), 52.7 (C-2), 46.5 (methylcarbamate C-1), 36.8 (C-3), 34.6 (propenyl C-1), 28.5 (^{t}Bu C_3); HRMS found MNa^+, 356.1838. $C_{19}H_{27}NO_4$ requires *MNa*, 356.1832. The relative configuration was determined from compound **39** and **22e**.

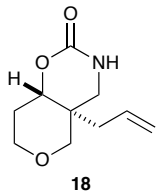
***tert*-Butyl *N*-{[(2*R**,3a*R**,7a*R**)-2-(iodomethyl)-hexahydro-2*H*-furo[3,2-*c*]pyran-3a-yl]methyl}carbamate**



17

According General Procedure L, the alkene derivative **16a** (0.10 g, 0.37 mmol) gave a crude material. The crude material (*dr* 80:20 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 15:85 EtOAc−hexane to yield the *tetrahydrofuran derivative **17*** (57.0 mg, 39%, *dr* >95:<5 by ^{1}H-NMR) as an amorphous colourless solid, R_f 0.50 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3323, 2975, 2950, 2923, 2895, 2868, 2848, 1703, 1547, 1349, 1273, 1252, 1235, 1164, 1139, 1069; δ_H (500 MHz, $CDCl_3$, 323 K) 4.85 (1H, br. s, NH), 4.06 (1H, app. dtd, *J* 8.5, 6.9 and 5.3, 2-H), 3.78 (1H, app. t, *J* 3.8, 7a-H), 3.71 (1H, ddd, *J* 11.4, 5.7 and 2.7, 6-H$_A$), 3.63 (1H, td, *J* 11.4 and 3.1, 6-H$_B$), 3.56 (1H, d, *J* 11.9, 4-H$_A$), 3.48 (1H, d, *J* 11,9, 4-H$_B$), 3.35-3.29 (3H, m, methylcarbamate 1-H$_2$ and iodomethyl 1-H$_A$), 3.24 (1H, dd, *J* 10.0 and 6.9, iodomethyl 1-H$_B$), 1.98 (1H, dd, *J* 13.4 and 8.5, 3-H$_A$), 1.95-1.91 (1H, m, 7-H$_A$), 1.82 (1H, app. dq, *J* 14.9 and 3.0, 7-H$_B$), 1.45 (9H, s, ^{t}Bu), 1.29 (1H, dd, *J* 13.4 and 6.9, 3-H$_B$); δ_C (125 MHz, $CDCl_3$) 156.3 (C=O), 79.5 (^{t}Bu C$_1$), 77.9 (C-7a), 77.0 (C-2), 71.0 (C-4), 64.0 (C-6), 44.8 (methylcarbamate C-1), 44.6 (C-3a), 38.9 (C-3), 28.5 (^{t}Bu C$_3$), 26.9 (C-7), 9.43 (iodomethyl C-1); HRMS found MH$^+$, 398.0823. $C_{14}H_{24}INO_4$ requires *MH*, 398.0822. The relative configuration was determined by NOESY NMR (500 MHz, $CDCl_3$) nOe observed between methylcarbamate 1-H$_A$ and 2-H, 2-H and 7a-H.

(4a*R, 8a*R**)-4a-(Prop-2-en-1-yl)-octahydropyrano[3,4-*e*][1,3]oxazin-2-one**

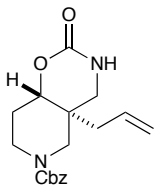


18

According to General Procedure M, the alcohol derivative **16a** (20.0 mg, 73.7 μmol) was stirred for 1 h to yield the crude *carbamate derivative **18*** (14.0 mg, 96%) as an amorphous colourless solid, R_f 0.20 (EtOAc); ν_{max}/cm^{-1} 3277, 2964, 2922, 2852, 1707, 1660, 1471, 1442, 1366, 1312, 1256, 1179, 1101, 1081, 1059; δ_H (400 MHz, $CDCl_3$) 5.91 (1H, br. s, NH), 5.87-5.72 (1H, m, propenyl 2-H), 5.22 (1H, app. d, *J* 2.5, propenyl 3-H$_A$), 5.18 (1H, app. s, propenyl 3-H$_B$), 4.25 (1H, dd, *J* 12.0 and 4.9, 8a-H), 4.11 (1H, app. dd, *J* 12.1 and 5.3, 7-H$_A$), 3.88 (1H, dd, *J* 11.6 and 1.2, 5-H$_A$), 3.46 (1H, td, *J* 12.1 and 2.7, 7-H$_B$), 3.14 (1H, dd, *J* 11.3

and 4.4, 4-H_A), 2.94 (1H, dd, *J* 11.6 and 1.7, 5-H_B), 2.81 (1H, dd, *J* 11.3 and 1.4, 4-H_B), 2.61 (1H, dd, *J* 13.9 and 6.7, propenyl 1-H_A), 2.18 (1H, dd, *J* 13.9 and 8.2, propenyl 1-H_B), 2.03 (1H, app. qd, *J* 12.6 and 5.3, 8-H_A), 1.87-1.77 (1H, m, 8-H_B); δ_C (100 MHz, $CDCl_3$) 154.0 (C-2), 132.1 (propenyl C-2), 120.3 (propenyl C-3), 78.9 (C-8a), 70.4 (C-5), 66.7 (C-7), 45.2 (C-4), 35.5 (C-4a), 28.6 (propenyl C-1), 26.8 (C-8); HRMS found MH^+, 198.1124. $C_{10}H_{15}NO_3$ requires *MH*, 198.1124.

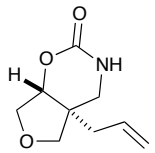
Benzyl (4a*R,8a*R**)-2-oxo-4a-(prop-2-en-1-yl)-octahydro-2*H*-pyrido[3,4-*e*][1,3]oxazine-6-carboxylate**



30

According to General Procedure M, the alcohol derivative **16b** (0.12 g, 0.30 mmol) was stirred for 1 h to yield a crude material. The crude material was purified by flash column chromatography, eluting with 80:20 EtOAc−hexane to yield the *carbamate derivative **30*** (62.0 mg, 63%) as a colourless oil, R_f 0.42 (10:90 MeOH−EtOAc); ν_{max}/cm^{-1} 3480, 3376, 3215, 3133, 2938, 2874, 1671, 1437, 1311, 1267, 1236, 1215, 1157, 1112, 1086, 1054; δ_H (500 MHz, CD_3OD, 333 K) 7.38-7.25 (5H, m, phenyl), 5.81 (1H, app. br. s, propenyl 2-H), 5.13 (2H, s, arylmethyl 1-H_2), 5.12-5.04 (2H, m, propenyl 3-H_2), 4.34 (1H, app. dt, *J* 13.0 and 2.1, 7-H_A), 4.28 (1H, dd, *J* 10.0 and 6.8, 8a-H), 4.20 (1H, d, *J* 13.7, 5-H_A), 3.15 (1H, d, *J* 11.7, 4-H_A), 2.96-2.90 (1H, m, 7-H_B), 2.87 (1H, d, *J* 11.7, 4-H_B), 2.51 (1H, d, *J* 13.7, 5-H_B), 2.20 (1H, dd, *J* 14.3 and 6.4, propenyl 1-H_A), 2.03 (1H, dd, *J* 14.3 and 8.6, propenyl 1-H_B), 1.86-1.75 (2H, m, 8-H_2); δ_C (125 MHz, CD_3OD, 333 K) 157.0 (C-2), 156.3 (Cbz C=O), 137.9 (phenyl C-1), 133.6 (propenyl C-2), 129.5 (phenyl C_2-3,5), 129.2 (phenyl C_2-2,6), 129.1 (phenyl C-4), 120.2 (propenyl C-3), 81.0 (C-8a), 68.7 (arylmethyl C-1), 48.6 (C-5), 46.6 (C-4), 43.2 (C-7), 36.1 (C-4a), 29.8 (propenyl C-1), 26.6 (C-8); HRMS found MNa^+, 353.1473. $C_{18}H_{22}N_2O_4$ requires *MNa*, 353.1477.

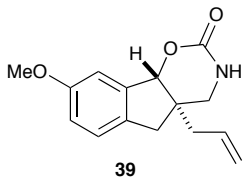
(4a*R,7a*S**)-4a-(Prop-2-en-1-yl)-hexahydro-2*H*-furo[3,4-*e*][1,3]oxazin-2-one**



3

According to General Procedure M, the alcohol derivative **16d** (0.56 g, 2.17 mmol) was stirred for 18 h to yield a crude material. The crude material was purified by flash column chromatography, eluting with EtOAc to yield the *carbamate derivative **3*** (0.26 g, 65%) as colourless blocks, m.p. (DCM), 138-142 °C; R_f 0.20 (EtOAc); ν_{max}/cm^{-1} 3254, 3132, 2979, 2950, 2929, 2895, 1700, 1384, 1301, 1257, 1132, 1104, 1076, 1014; δ_H (400 MHz, $CDCl_3$) 6.57 (1H, br. s, NH), 5.78 (1H, ddt, *J* 17.1, 9.8 and 7.4, propenyl 2-H), 5.27-5.12 (2H, m, propenyl 3-H_2), 4.58 (1H, dd, *J* 10.1 and 8.0, 7a-H), 4.05 (1H, dd, *J* 10.1 and 8.0, 7-H_A), 4.01 (1H, d, *J* 8.6, 5-H_A), 3.70 (1H, dd, *J* 10.1 and 8.0, 7-H_B), 3.46 (1H, d, *J* 8.6, 5-H_B), 3.38 (1H, dd, *J* 11.1 and 4.3, 4-H_A), 3.18 (1H, d, *J* 11.1, 4-H_B), 2.34-2.17 (2H, m, propenyl 1-H_2); δ_C (100 MHz, $CDCl_3$) 154.9 (C-2), 132.0 (propenyl C-2), 120.4 (propenyl C-3), 80.5 (C-7a), 71.7 (C-5), 64.9 (C-7), 46.7 (C-4), 40.5 (C-4a), 29.9 (propenyl C-1); HRMS found MH^+, 184.0964. $C_9H_{13}NO_3$ requires *MH*, 184.0968. The relative configuration was determined using X-ray crystallography.

(4a*R,9b*S**)-8-Methoxy-4a-(prop-2-en-1-yl)-2*H*,3*H*,4*H*,4a*H*,5*H*,9b*H*-indeno[2,1-*e*][1,3] oxazin-2-one**

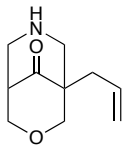


39

According to General Procedure M, the alcohol derivative **16e** (20.0 mg, 60.0 μmol) was stirred for 18 h to yield a crude material. The crude material was purified by flash column

chromatography, eluting with 70:30 EtOAc−hexane to yield the *carbamate derivative* ***39*** (9.00 mg, 58%) as colourless blocks, m.p. ($CHCl_3$/pentane), 180-185 °C; R_f 0.46 (EtOAc); ν_{max}/cm^{-1} 3231, 3122, 2935, 2354, 1691, 1481, 1434, 1295, 1242, 1081; δ_H (400 MHz, $CDCl_3$) 7.13 (1H, d, *J* 8.2, 6-H), 7.00 (1H, d, *J* 2.5, 9-H), 6.79 (1H, dd, *J* 8.2 and 2.5, 7-H), 5.84 (1H, br. s, NH), 5.72 (1H, ddt, *J* 17.0, 10.1 and 7.5, propenyl 2-H), 5.39 (1H, s, 9b-H), 5.12 (1H, ddt, *J* 10.1, 1.7 and 0.9, propenyl 3-H_{cis}), 5.03 (1H, app. dq, *J* 17.0 and 1.7, propenyl 3-H_{trans}), 3.80 (3H, s, methoxy), 3.54-3.41 (2H, m, 4-H_2), 2.95 (1H, d, *J* 14.7, 5-H_A), 2.45 (1H, d, *J* 14.7, 5-H_B), 2.20 (1H, dd, *J* 14.5 and 7.5, propenyl 1-H_A), 1.84 (1H, dd, *J* 14.5 and 7.0, propenyl 1-H_B); δ_C (100 MHz, $CDCl_3$) 159.4 (C-8), 155.1 (C-2), 139.6 (C-9a), 133.1 (propenyl C-2), 131.3 (C-5b), 126.5 (C-6), 119.6 (propenyl C-3), 114.5 (C-7), 108.2 (C-9), 85.8 (C-9b), 55.6 (methoxy), 49.0 (C-4), 45.3 (C-4a), 35.6 (C-5), 31.2 (propenyl C-1); HRMS found MH^+, 260.1275. $C_{15}H_{17}NO_3$ requires *MH*, 260.1281. The relative configuration was determined using X-ray crystallography.

(1*R, 5*S**)-1-(Prop-2-en-1-yl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one**

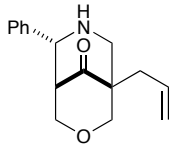


19

According to General Procedure N, paraformaldehyde (16.8 mg, 0.56 mmol) and the ketone derivative **1a** (0.10 g, 0.37 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 95.4:4.1:0.5 DCM−EtOH−NH_4OH to yield the *bridged bicyclic derivative* ***19*** (20.0 mg, 30%) as a yellow oil, R_f 0.40 (92.4:6.8:0.8 DCM−EtOH−NH_4OH); ν_{max}/cm^{-1} 3362, 3074, 2922, 2848, 1709, 1674, 1638, 1455, 1435, 1375, 1234, 1211, 1082; δ_H (400 MHz, CD_3OD) 5.86 (1H, ddt, *J* 15.4, 11.0 and 7.5, propenyl 2-H), 5.09 (1H, dd, *J* 10.5 and 1.5, propenyl 3-H_{cis}), 5.08 (1H, dd, *J* 16.7 and 1.5, propenyl 3-H_{trans}), 4.43 (1H, app. dt, *J* 11.3 and 1.6, 4-H_A), 4.26 (1H, dd, *J* 11.3 and 1.6, 2-H_A), 3.97 (1H, app. dt, *J* 11.3 and 2.5, 4-H_B), 3.73 (1H, dd, *J* 11.3 and 3.1, 2-H_B), 3.63 (1H, app. dt, *J* 13.8 and 2.2, 6-H_A), 3.49 (1H, dd, *J* 13.7 and 2.4, 8-H_A), 3.13 (1H, app. dt, *J* 13.8 and 2.9, 6-H_B), 2.89 (1H, dd, *J* 13.7 and 3.1, 8-H_B), 2.37 (1H, app. s, 5-H), 2.15 (2H, app. d, *J* 7.5, propenyl

1-H_2); δ_C (100 MHz, CD_3OD) 213.7 (C-9), 134.0 (propenyl C-2), 118.7 (propenyl C-3), 79.3 (C-2), 75.9 (C-4), 60.3 (C-8), 55.8 (C-6), 53.9 (C-1), 52.7 (C-5), 35.3 (propenyl C-1). HRMS found MH^+, 182.1179. $C_{10}H_{15}NO_2$ requires *MH*, 182.1175.

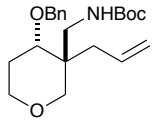
(1*R,5*S**,6*R**)-6-phenyl-1-(prop-2-en-1-yl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-one**



4

According to General Procedure N, benzaldehyde (57.6 μL, 0.56 mmol) and the ketone derivative **1a** (0.10 g, 0.37 mmol) gave a crude material. The crude material (*dr* >95:<5 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 97:2.7:0.3 DCM−EtOH−NH_4OH to yield the *bridged bicyclic derivative **4*** (32.0 mg, 33%, *dr* >95:<5 by ^{1}H-NMR) as an amorphous yellow solid, R_f 0.40 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3337, 3059, 3030, 2921, 2851, 1708, 1470, 1372, 1225, 1210, 1088; δ_H (500 MHz, $CDCl_3$) 7.34-7.18 (5H, m, phenyl), 5.75 (1H, ddt, *J* 17.3, 10.0 and 7.5, propenyl 2-H), 5.03 (1H, dd, *J* 10.0 and 1.9, propenyl 3-H_{cis}), 5.00 (1H, dd, *J* 17.3 and 1.9, propenyl 3-H_{trans}), 4.27 (1H, app. s, 6-H), 4.16 (1H, dd, *J* 11.4 and 1.6, 2-H_A), 4.06 (1H, app. d, *J* 11.7, 4-H_A), 3.69 (1H, dd, *J* 11.4 and 3.1, 2-H_B), 3.61 (1H, app. dt, *J* 11.7 and 2.1, 4-H_B), 3.54 (1H, d, *J* 13.8, 8-H_A), 2.97 (1H, dd, *J* 13.8 and 3.2, 8-H_B), 2.82 (1H, br. s, NH), 2.51 (1H, app. s, 5-H), 2.18 (1H, dd, *J* 14.4 and 7.3, propenyl 1-H_A), 2.11 (1H, dd, *J* 14.4 and 7.7, propenyl 1-H_B); δ_C (125 MHz, $CDCl_3$) 212.0 (C-9), 139.1 (phenyl C-1), 132.4 (propenyl C-2), 128.8 (phenyl C_2-3,5), 127.6 (phenyl C-4), 126.2 (phenyl C_2-2,6), 118.7 (propenyl C-3), 78.4 (C-2), 70.1 (C-4), 66.9 (C-6), 58.8 (C-8), 56.6 (C-5), 52.2 (C-1), 34.3 (propenyl C-1); HRMS found MH^+, 258.1491. $C_{16}H_{19}NO_2$ requires *MH*, 258.1488. The relative configuration was determined using NOESY (500 MHz, $CDCl_3$), nOe observed between phenyl and 4-H_A, 6-H and 8-H_A, 5-H and 6-H.

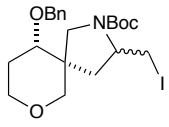
***tert*-Butyl *N*-{[(3*R**,4*R**)-4-(benzyloxy)-3-(prop-2-en-1-yl)oxan-3-yl]methyl}carbamate**



20

By modification of an existing procedure,[17] NaH (37.0 mg, 0.92 mmol of a 60% dispersion in mineral oil) was added to a mixture of the alcohol derivative **16a** (0.23 g, 0.84 mmol), benzyl bromide (0.12 mL, 1.00 mmol) and tetrabutylammonium iodide (62.0 mg, 0.17 mmol) in THF (5.00 mL) at 0 °C. The reaction mixture was stirred for 18 h at rt. Then, a saturated aqueous solution of $NaHCO_3$ (5 mL) was added, the phases were separated and the aqueous phase was extracted with EtOAc (4 × 5 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 10:90 EtOAc−hexane to yield the *benzyl derivative* ***20*** (0.26 g, 86%) as a colourless oil, R_f 0.75 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3426, 3344, 2973, 2930, 2859, 1712, 1504, 1453, 1365, 1243, 1165, 1088; δ_H (400 MHz, $CDCl_3$) 7.40-7.27 (5H, m, phenyl), 5.81 (1H, ddt, *J* 15.2, 10.1 and 7.5, propenyl 2-H), 5.17-5.01 (2H, m, propenyl 3-H_2), 4.87 (1H, app. t, *J* 4.8, NH), 4.66 (1H, d, *J* 11.6, arylmethyl 1-H_A), 4.39 (1H, d, *J* 11.6, arylmethyl 1-H_B), 4.05-3.90 (1H, m, 6-H_A), 3.67 (1H, d, *J* 11.8, 2-H_A), 3.48 (1H, app. td, *J* 7.9 and 3.8, 4-H), 3.45-3.38 (1H, m, 6-H_B), 3.18-3.09 (1H, m, methylcarbamate 1-H_A), 3.01 (1H, d, *J* 11.8, 2-H_B), 3.00 (1H, d, *J* 13.5, methylcarbamate 1-H_B), 2.33 (2H, app. d, *J* 7.6, propenyl 1-H_2), 2.00-1.90 (1H, m, 5-H_A), 1.78 (1H, app. dtd, *J* 13.7, 9.5 and 4.5, 5-H_B), 1.41 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 156.1 (C=O), 138.4 (phenyl C-1), 133.8 (propenyl C-2), 128.6 (phenyl C_2-3,5), 127.8 (phenyl C_2-2,6), 126.2 (phenyl C-4), 118.6 (propenyl C-3), 81.3 (^{t}Bu C_1), 78.9 (C-4), 70.6 (C-2), 70.3 (arylmethyl C-1), 66.0 (C-6), 44.3 (methylcarbamate C-1), 42.1 (C-3), 32.1 (propenyl C-1), 28.5 (^{t}Bu C_3), 26.3 (C-5); HRMS found MH^+, 362.2328. $C_{21}H_{31}NO_4$ requires *MH*, 362.2325.

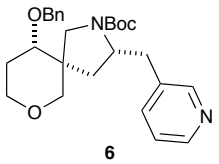
tert-Butyl (5*R,10*R**)-10-(benzyloxy)-3-(iodomethyl)-7-oxa-2-azaspiro[4.5]decane-2-carboxylate**



21

According General Procedure L, the alkene derivative **20** (0.10 g, 0.28 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 15:85 EtOAc−hexane to yield the *pyrrolidine derivative **21*** (41.0 mg, 30%, *dr* 77:23 by ^{1}H-NMR) as a yellow oil, R_f 0.63 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2928, 2857, 1687, 1391, 1364, 1157, 1087; δ_H (500 MHz, $CDCl_3$, 323 K) 7.37-7.26 (10H, m, phenyl), 4.67 (1H, d, *J* 11.8, arylmethyl 1-H_A^{maj}), 4.64 (1H, d, *J* 11.9, arylmethyl 1-H_A^{min}), 4.45 (1H, d, *J* 11.8, arylmethyl 1-H_B^{maj}), 4.42 (1H, d, *J* 11.9, arylmethyl 1-H_B^{min}), 3.92-3.82 (2H, m, 8-H_A), 3.79-3.75 (2H, m, 3-H) 3.73 (2H, d, *J* 11.1, 6-H_A), 3.61 (2H, d, *J* 11,3, 1-H_A), 3.58-3.49 (4H, m, 8-H_B and iodomethyl 1-H_A), 3.44-3.40 (4H, m, 10-H and iodomethyl 1-H_B), 3.33 (2H, d, *J* 11.1, 6-H_B), 3.21 (2H, d, *J* 11.3, 1-H_B), 2.20-2.08 (2H, m, 9-H_A), 1.93-1.65 (6H, m, 9-H_B and 4-H_2), 1.47 (9H, s, $^{t}Bu^{maj}$), 1.45 (9H, s, $^{t}Bu^{min}$); δ_C (125 MHz, $CDCl_3$, 323 K) 154.3 (2C=O), 138.5 (phenyl C-1^{maj}), 138.4 (phenyl C-1^{min}), 128.6 (phenyl C_2-3,5^{min}), 128.5 (phenyl C_2-3,5^{maj}), 127.8 (phenyl C-4^{min}), 127.7 (phenyl C-4^{maj}), 127.6 (phenyl C_4-2,6), 80.1 (^{t}Bu C_1^{min}), 80.0 (^{t}Bu C_1^{maj}), 78.0 (C-10^{min}), 77.1 (C-10^{maj}), 73.0 (C_2-6), 71.1 (arylmethyl C-1^{min}), 70.9 (arylmethyl C-1^{maj}), 64.9 (C-8^{maj}), 63.2 (C-8^{min}), 56.3 (C-3^{maj}), 55.2 (C-3^{min}), 52.3 (C-1^{min}), 51.6 (C-1^{maj}), 46.3 (C-5^{maj}), 45.8 (C-5^{min}), 36.6 (C_2-4), 28.6 (^{t}Bu $2C_3$), 27.4 (C-9^{maj}), 26.3 (C-9^{min}), 13.7 (iodomethyl C-1^{maj}), 12.9 (iodomethyl C-1^{min}); HRMS found MH^+, 488.1295. $C_{21}H_{30}INO_4$ requires *MH*, 488.1292.

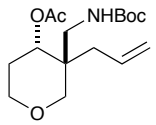
tert-Butyl (3*R,5*S**,10*S**)-10-(benzyloxy)-3-[(pyridin-3-yl)methyl]-7-oxa-2-azaspiro[4.5] decane-2-carboxylate**



6

According to a procedure,[18] a solution of the alkene **20** (0.10 g, 0.28 mmol) and 3-bromopyridine (31.8 μL, 0.33 mmol) in 1,4-dioxane (1.62 mL) was added to a mixture of $Pd(OAc)_2$ (3.09 mg, 13.8 μmols), DPE-Phos (14.9 mg, 27.0 μmols) and Cs_2CO_3 (0.22 g, 0.67 mmols). The reaction mixture was stirred vigorously at 105 °C for 18 h. Then, it was allowed to cool to rt, filtered through celite and concentrated under reduced pressure to give a crude product. The crude product (*dr* 67:33 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 70:30→50:50 hexane−EtOAc to yield the *pyrrolidine derivative* ***6*** (38.0 mg, 31%, *dr* >95:<5 by ^{1}H-NMR) as a grey oil, R_f 0.56 (EtOAc); ν_{max}/cm^{-1} 2928, 2858, 1685, 1393, 1364, 1155, 1085; δ_H (500 MHz, $CDCl_3$, 323 K) 8.44 (1H, d, *J* 1.7, pyridine 2-H), 8.40 (1H, app. s, pyridine 6-H), 7.43 (1H, d, *J* 4.5, pyridine 4-H), 7.38-7.25 (5H, m, phenyl), 7.13 (1H, dd, *J* 7.7 and 4.5, pyridine 5-H), 4.61 (1H, d, *J* 11.7, phenylmethyl 1-H_A), 4.36 (1H, d, *J* 11.7, phenylmethyl 1-H_B), 4.04 (1H, app. br. s, 3-H), 3.83 (1H, m, 8-H_A), 3.54 (1H, d, *J* 11.4, 6-H_A), 3.50-3.43 (2H, m, 1-H_A and 8-H_B), 3.26 (1H, app. br. s, 10-H), 3.15 (1H, d, *J* 11.4, 6-H_B), 3.13-2.87 (2H, m, 1-H_B and pyridinylmethyl 1-H_A), 2.72 (1H, app. br. s, pyridinylmethyl 1-H_B), 1.99 (1H, dd, *J* 13.6 and 8.0, 4-H_A), 1.78-1.71 (2H, m, 4-H_B and 9-H_A), 1.66-1.56 (1H, m, 9-H_B), 1.48 (9H, s, ^{t}Bu); δ_C (125 MHz, $CDCl_3$, 323 K) 154.7 (C=O), 151.0 (pyridine C-2), 147.8 (pyridine C-6), 138.5 (pyridine C-3), 137.0 (pyridine C-4), 134.0 (phenyl C-1), 128.5 (phenyl C_2-3,5), 127.8 (phenyl C-4), 127.7 (phenyl C_2-2,6), 123.2 (pyridine C-5), 79.7 (^{t}Bu C_1), 76.7 (C-10), 71.7 (C-6), 70.7 (phenylmethyl C-1), 64.9 (C-8), 57.1 (C-3), 51.1 (C-1), 46.5 (C-5), 37.7 (C-4), 34.1 (pyridinylmethyl C-1), 28.6 (C-9 and ^{t}Bu C_3); HRMS found MH^+, 439.2604. $C_{26}H_{34}N_2O_4$ requires *MH*, 439.2596. The relative stereochemistry was determined using NOESY (500 MHz, $CDCl_3$, 323 K) nOe not observed between 3-H and 6-H_A.

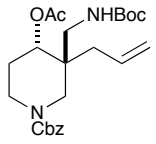
(3*R, 4*R**)-3-({[(*tert*-Butoxy)carbonyl]amino}methyl)-3-(prop-2-en-1-yl)oxan-4-yl acetate**



22a

According to General Procedure O, the alcohol derivative **16a** (0.36 g, 1.35 mmol) gave the *acetyl derivative* ***22a*** (0.40 g, 95%) as a yellow oil, R_f 0.71 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3355, 2973, 2933, 2859, 1739, 1714, 1508, 1365, 1236, 1164, 1089; δ_H (400 MHz, $CDCl_3$) 5.88-5.73 (1H, m, propenyl 2-H), 5.11 (1H, app. s, propenyl 3-H_{trans}), 5.08 (1H, app. d, *J* 2.5, propenyl 3-H_{cis}), 5.00 (1H, app. t, *J* 6.9, 4-H), 4.95 (1H, br. s, NH), 3.86 (1H, app. dt, *J* 11.6 and 4.6, 6-H_A), 3.68 (1H, d, *J* 12.0, 2-H_A), 3.55-3.46 (1H, m, 6-H_B), 3.28 (1H, dd, *J* 14.6 and 8.2, methylcarbamate 1-H_A), 3.18 (1H, d, *J* 12.0, 2-H_B), 2.87 (1H, dd, *J* 14.6 and 5.5, methylcarbamate 1-H_B), 2.35 (1H, dd, *J* 14.1 and 7.5, propenyl 1-H_A), 2.13-2.04 (1H, m, propenyl 1-H_B), 2.08 (3H, s, acetyl), 1.87-1.79 (2H, m, 5-H_2), 1.41 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 170.9 (acetyl C=O), 156.2 (Boc C=O), 133.1 (propenyl C-2), 118.8 (propenyl C-3), 79.4 (^{t}Bu C_1), 71.5 (C-4), 70.4 (C-2), 65.8 (C-6), 42.3 (methylcarbamate C-1), 42.0 (C-3), 33.5 (propenyl C-1), 28.4 (^{t}Bu C_3), 27.6 (C-5), 21.2 (acetyl CH_3). HRMS found MNa^+, 336.1791. $C_{16}H_{27}NO_5$ requires *MNa*, 336.1786.

Benzyl (3*R,4*R**)-4-(acetyloxy)-3-({[(*tert*-butoxy)carbonyl]amino}methyl)-3-(prop-2-en-1-yl)piperidine-1-carboxylate**

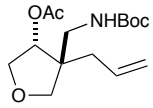


22b

According to General Procedure O, the alcohol derivative **16b** (0.34 g, 0.84 mmol) gave the *acetyl derivative* ***22b*** (0.36 g, 95%) as a colourless oil, R_f 0.70 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3367, 2976, 2936, 1738, 1697, 1510, 1434, 1365, 1232, 1160, 1036; δ_H (500 MHz, CD_3OD, 333 K) 7.38-7.26 (5H, m, phenyl), 5.93-5.78 (1H, m, propenyl 2-H), 5.12 (2H, s, arylmethyl 1-H_2), 5.05 (1H, app. d, *J* 10.2, propenyl 3-H_{cis}), 5.04 (1H, app. d, *J* 17.2, propenyl 3-H_{trans}), 4.85 (1H, dd, *J* 8.3 and 4.0, 4-H), 3.71 (1H, app. br. s, 6-H_A), 3.57 (1H, d, *J* 13.9, 2-H_A), 3.35 (1H, app. br. s, 6-H_B), 3.16 (1H, d, *J* 13.9, 2-H_B), 3.13 (1H, d, *J* 15.1, methylcarbamate 1-H_A), 3.03 (1H, d, *J* 15.1, methylcarbamate 1-H_B), 2.22-2.08 (2H, m, propenyl 1-H_2), 2.05 (3H, s, acetyl), 1.96-1.86 (1H, m, 5-H_A), 1.75-1.66 (1H, m, 5-H_B), 1.42 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 172.1 (acetyl C=O), 158.2 (Boc C=O), 157.2 (Cbz C=O), 138.0 (phenyl C-1), 134.5 (propenyl C-2), 129.5 (phenyl C_2-3,5), 129.1 (phenyl

C_2-2,6), 129.0 (phenyl C-4), 118.8 (propenyl C-3), 80.3 (^{t}Bu C_1), 73.2 (C-4), 68.6 (arylmethyl C-1), 48.6 (C-2), 43.6 (C-6), 42.9 (C-3), 42.2 (methylcarbamate C-1), 35.3 (propenyl C-1), 28.8 (^{t}Bu C_3), 27.1 (C-5), 21.0 (acetyl CH_3); HRMS found MNa^+, 469.2304. $C_{24}H_{34}N_2O_6$ requires *MNa*, 469.2309.

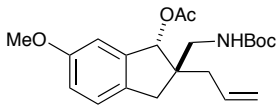
(3*R,4*S**)-4-({[(*tert*-Butoxy)carbonyl]amino}methyl)-4-(prop-2-en-1-yl)oxolan-3-yl acetate**



22d

According to General Procedure O, the alcohol derivative **16d** (1.76 g, 6.83 mmol) gave the *acetyl derivative* ***22d*** (1.95 g, 95%) as a yellow oil, R_f 0.52 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3254, 3139, 2974, 2938, 2874, 1737, 1704, 1449, 1395, 1366, 1352, 1249, 1233, 1223, 1162, 1131, 1082, 1020; δ_H (400 MHz, $CDCl_3$) 5.72 (1H, ddt, *J* 17.3, 10.0 and 7.4, propenyl 2-H), 5.18-5.04 (3H, m, 3-H and propenyl 3-H_2), 4.91 (1H, app. t, *J* 5.0, NH), 4.25 (1H, dd, *J* 10.6 and 5.6, 2-H_A), 3.71 (1H, dd, *J* 10.6 and 2.9, 2-H_B), 3.68 (1H, d, *J* 9.0, 5-H_A), 3.61 (1H, d, *J* 9.0, 5-H_B), 3.21 (1H, dd, *J* 14.2 and 6.4, methylcarbamate 1-H_A), 3.13 (1H, dd, *J* 14.2 and 6.4, methylcarbamate 1-H_B), 2.30-2.14 (2H, m, propenyl 1-H_2), 2.08 (3H, s, acetyl), 1.43 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 170.7 (acetyl C=O), 156.4 (Boc C=O), 133.9 (propenyl C-2), 118.7 (propenyl C-3), 79.7 (^{t}Bu C_1), 77.2 (C-3), 74.7 (C-5), 73.4 (C-2), 50.1 (C-4), 43.9 (methylcarbamate C-1), 34.0 (propenyl C-1), 28.5 (^{t}Bu C_3), 21.0 (acetyl CH_3); HRMS found MNa^+, 322.1621. $C_{15}H_{25}NO_5$ requires *MNa*, 322.1624.

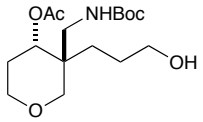
(1*R,2*S**)-2-({[(*tert*-Butoxy)carbonyl]amino}methyl)-6-methoxy-2-(prop-2-en-1-yl)-2,3-dihydro-1*H*-inden-1-yl acetate**



22e

According to General Procedure O, the alcohol derivative **16e** (0.50 g, 1.50 mmol) gave the *acetyl derivative* ***22e*** (0.55 g, 98%) as a pale-yellow oil, R_f 0.50 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 3376, 2976, 2930, 1712, 1493, 1366, 1233, 1163, 1029; δ_H (400 MHz, $CDCl_3$) 7.08 (1H, d, *J* 8.9, 4-H), 6.81 (2H, app. d, *J* 6.3, 5-H and 7-H), 6.04 (1H, s, 1-H), 5.86 (1H, ddt, *J* 16.6, 10.4 and 7.4, propenyl 2-H), 5.06 (1H, d, *J* 16.6, propenyl 3-H_{trans}), 5.05 (1H, d, *J* 10.4, propenyl 3-H_{cis}), 4.96 (1H, app. t, *J* 7.5, NH), 3.78 (3H, s, methoxy), 3.27 (1H, dd, *J* 14.2 and 6.9, methylcarbamate 1-H_A), 3.11 (1H, dd, *J* 14.2 and 6.2, methylcarbamate 1-H_B), 2.86 (1H, d, *J* 15.9, 3-H_A), 2.67 (1H, d, *J* 15.9, 3-H_B), 2.21 (2H, app. d, *J* 7.4, propenyl 1-H_2), 2.13 (3H, s, acetyl), 1.42 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 171.4 (acetyl C=O), 159.1 (C-6), 156.3 (Boc C=O), 141.5 (C-7a), 134.4 (propenyl C-2), 133.5 (C-3a), 125.7 (C-4), 118.2 (propenyl C-3), 115.5 (C-5), 110.1 (C-7), 80.5 (C-1), 79.4 (^{t}Bu C_1), 55.6 (methoxy), 51.8 (C-2), 45.5 (methylcarbamate C-1), 38.2 (C-3), 36.5 (propenyl C-1), 28.5 (^{t}Bu C_3), 21.2 (acetyl CH_3); HRMS found MNa^+, 398.1934. $C_{21}H_{29}NO_5$ requires *MNa*, 398.1937. The relative stereochemistry was determined using NOESY (500 MHz, $CDCl_3$) nOe observed between 1-H and methylcarbamate 1-H_A, 1-H and methylcarbamate 1-H_B.

(3*R,4*R**)-3-({[(*tert*-Butoxy)carbonyl]amino}methyl)-3-(3-hydroxypropyl)oxan-4-yl acetate**

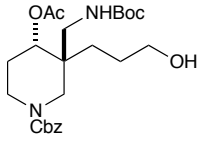


23

According to General Procedure F, the alkene derivative **22a** (0.22 g, 0.69 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 60:40 EtOAc−hexane to yield the *alcohol derivative* ***23*** (0.17 g, 73%) as a light-yellow oil, R_f 0.13 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3364, 2960, 2865, 1712, 1514, 1365, 1237, 1165, 1083, 1048, 1027; δ_H (400 MHz, $CDCl_3$) 5.05 (1H, app. t, *J* 6.9, NH), 4.95 (1H, app. t,

J 6.4, 4-H), 3.81 (1H, app. dt, *J* 10.7 and 5.0, 6-H_A), 3.67-3.58 (3H, m, 2-H_A and hydroxypropyl 3-H_2), 3.54 (1H, app. dt, *J* 12.0 and 6.3, 6-H_B), 3.28 (1H, dd, *J* 14.4 and 7.9, methylcarbamate 1-H_A), 3.21 (1H, d, *J* 12.0, 2-H_B), 2.94 (1H, dd, *J* 14.4 and 5.6, methylcarbamate 1-H_B), 2.07 (3H, s, acetyl), 1.98 (1H, br. s, OH), 1.82 (2H, app. q, *J* 5.9, 5-H_2), 1.65-1.32 (4H, m, hydroxypropyl 1,2-H_4), 1.41 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 170.9 (acetyl C=O), 156.5 (Boc C=O), 79.5 (^{t}Bu C_1), 71.5 (C-4), 70.1 (C-2), 65.4 (C-6), 62.9 (hydroxypropyl C-3), 41.7 (methylcarbamate C-1), 41.3 (C-3), 28.4 (^{t}Bu C_3), 27.4 (C-5), 25.7 (hydroxypropyl C-2), 24.6 (hydroxypropyl C-1), 21.2 (acetyl CH_3); HRMS found MH^+, 332.2072. $C_{16}H_{29}NO_6$ requires *MH*, 332.2067.

Benzyl (3*R,4*R**)-4-(acetyloxy)-3-({[(*tert*-butoxy)carbonyl]amino}methyl)-3-(3-hydroxypropyl)piperidine-1-carboxylate**

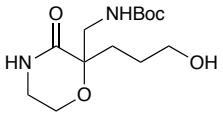


S16

According to General Procedure F, the alkene derivative **22b** (0.25 g, 0.55 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 60:40 EtOAc−hexane to yield the *alcohol derivative* ***S16*** (0.22 g, 86%) as a colourless oil, R_f 0.38 (20:80 petrol−EtOAc); ν_{max}/cm^{-1} 3400, 2937, 2872, 2508, 1681, 1433, 1365, 1235, 1157, 1035; δ_H (500 MHz, CD_3OD, 333 K) 7.38-7.28 (5H, m, phenyl), 5.12 (2H, s, arylmethyl 1-H_2), 4.87 (1H, dd, *J* 8.1 and 3.8, 4-H), 3.68 (1H, app. br. s, 6-H_A), 3.53 (1H, app. br. s, 2-H_A), 3.53-3.40 (2H, m, hydroxypropyl 3-H_2), 3.38 (1H, app. br. s, 6-H_B), 3.18 (2H, d, *J* 14.7, 2-H_B and methylcarbamate 1-H_A), 3.03 (1H, d, *J* 14.7, methylcarbamate 1-H_B), 2.05 (3H, s, acetyl), 1.95-1.86 (1H, m, 5-H_A), 1.76-1.63 (1H, m, 5-H_B), 1.61-1.53 (1H, m, hydroxypropyl 2-H_A), 1.53-1.44 (2H, m, hydroxypropyl 2-H_B and hydroxypropyl 1-H_A), 1.42 (9H, s, ^{t}Bu), 1.40-1.32 (1H, m, hydroxypropyl 1-H_B); δ_C (125 MHz, CD_3OD, 333 K) 172.2 (acetyl C=O), 158.3 (Boc C=O), 157.2 (Cbz C=O), 138.1 (phenyl C-1), 129.5 (phenyl C_2-3,5), 129.1 (phenyl C_2-2,6), 129.0 (phenyl C-4), 80.3 (^{t}Bu C_1), 73.5 (C-4), 68.5 (arylmethyl C-1), 63.6 (hydroxypropyl C-3), 48.7 (C-2), 43.1 (methylcarbamate C-1), 42.5

(C-6), 42.2 (C-3), 28.8 (^{t}Bu C_3), 27.2 (hydroxypropyl C-1), 27.0 (hydroxypropyl C-2), 21.0 (acetyl CH_3); HRMS found MNa^+, 487.2411. $C_{24}H_{36}N_2O_7$ requires *MNa*, 487.2420.

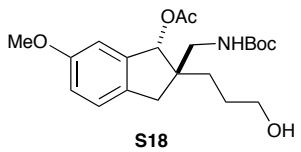
tert-Butyl _N_-{[2-(3-hydroxypropyl)-3-oxomorpholin-2-yl]methyl}carbamate



S17

According to General Procedure F, the alkene derivative **1c** (0.20 g, 0.53 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with EtOAc to yield the *alcohol derivative* ***S17*** (0.11 g, 71%) as a pale oil, R_f 0.20 (10:90 MeOH−EtOAc); ν_{max}/cm^{-1} 3307, 2974, 2932, 2876, 1696, 1660, 1509, 1484, 1365, 1340, 1269, 1248, 1163, 1124, 1063; δ_H (400 MHz, $CDCl_3$) 7.20 (1H, br. s, 4-H), 5.12 (1H, app. t, *J* 5.0, methylcarbamate NH), 3.96-3.78 (2H, m, 6-H_2), 3.65-3.49 (3H, m, hydroxypropyl 3-H_2 and methylcarbamate 1-H_A), 3.49-3.40 (1H, m, 5-H_A), 3.40-3.28 (2H, m, 5-H_B and methylcarbamate 1-H_B), 2.54 (1H, br. s, OH), 2.00-1.85 (1H, m, hydroxypropyl 1-H_A), 1.79-1.64 (2H, m, hydroxypropyl 1-H_B and hydroxypropyl 2-H_A), 1.63-1.51 (1H, m, hydroxypropyl 2-H_B), 1.42 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 172.8 (C-3), 156.2 (Boc C=O), 80.9 (^{t}Bu C_1), 79.5 (C-2), 62.5 (hydroxypropyl C-3), 59.5 (C-6), 44.9 (C-5), 42.2 (methylcarbamate C-1), 31.3 (hydroxypropyl C-2), 28.5 (^{t}Bu C_3), 26.6 (hydroxypropyl C-1); HRMS found MNa^+, 311.1574. $C_{13}H_{24}N_2O_5$ requires *MNa*, 311.1577.

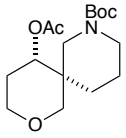
(1*R,2*S**)-2-({[(*tert*-Butoxy)carbonyl]amino}methyl)-2-(3-hydroxypropyl)-6-methoxy-2,3-dihydro-1*H*-inden-1-yl acetate**



S18

According to General Procedure F, the alkene derivative **22e** (0.20 g, 0.53 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 50:50 EtOAc−hexane to yield the *alcohol derivative* ***S18*** (0.17 g, 83%) as a colourless oil, R_f 0.36 (30:70 petrol−EtOAc); ν_{max}/cm^{-1} 3376, 3270, 3145, 2937, 2873, 1705, 1493, 1394, 1368, 1234, 1167, 1144, 1121, 1008; δ_H (400 MHz, $CDCl_3$) 7.08 (1H, d, *J* 8.1, 4-H), 6.81 (2H, app. d, *J* 7.6, 5-H and 7-H), 5.97 (1H, s, 1-H), 5.06 (1H, app. t, *J* 7.0, NH), 3.77 (3H, s, methoxy), 3.67-3.51 (2H, m, hydroxypropyl 3-H_2), 3.24-3.04 (2H, m, methylcarbamate 1-H_2), 2.83 (1H, d, *J* 15.8, 3-H_A), 2.65 (1H, d, *J* 15.8, 3-H_B), 2.11 (3H, s, acetyl), 1.87 (1H, br. s, OH), 1.63-1.49 (4H, m, hydroxypropyl 1,2-H_4), 1.41 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$) 171.5 (acetyl C=O), 159.1 (C-6), 156.7 (Boc C=O), 141.6 (C-7a), 133.7 (C-3a), 125.7 (C-4), 115.6 (C-5), 110.3 (C-7), 80.6 (C-1), 79.6 (^{t}Bu C_1), 63.2 (hydroxypropyl C-3), 55.6 (methoxy), 51.7 (C-2), 45.0 (methylcarbamate C-1), 38.7 (C-3), 28.5 (^{t}Bu C_3), 27.6 (hydroxypropyl C-1), 27.3 (hydroxypropyl C-2), 21.3 (acetyl CH_3); HRMS found MNa^+, 416.2049. $C_{21}H_{31}NO_6$ requires *MNa*, 416.2043.

tert-Butyl (5*R, 6*R**)-5-(acetyloxy)-2-oxa-8-azaspiro[5.5]undecane-8-carboxylate**

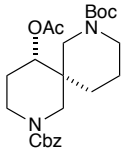


24

According to General Procedure P, the alcohol derivative **23** (0.10 g, 0.30 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *piperidine derivative* ***24*** (54.0 mg, 57%) as a colourless oil, R_f 0.59 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2936, 2857, 1737, 1687, 1423, 1365, 1274, 1234, 1160, 1141, 1090, 1040; δ_H (500 MHz, $CDCl_3$, 323 K) 4.89 (1H, dd, *J* 6.2 and 3.7, 5-H), 3.71 (1H, ddd, *J* 12.1, 8.7 and 3.6, 3-H_A), 3.65 (1H, app. t, *J* 5.1, 3-H_B), 3.62 (1H, d, *J* 12.0, 1-H_A), 3.50 (1H, d, *J* 13.7, 7-H_A), 3.42-3.34 (1H, m, 9-H_A), 3.32-3.28 (1H, m, 9-H_B), 3.25 (1H, d, *J* 12.0, 1-H_B), 3.24 (1H, d, *J* 13.7, 7-H_B), 2.05 (3H, s, acetyl), 2.03-1.98 (1H, m, 4-H_A), 1.69-1.60 (1H, m, 4-H_B), 1.53-1.48 (3H, m, 10-H_2 and 11-H_A), 1.43 (9H, s, ^{t}Bu), 1.42-1.38 (1H, m, 11-H_B); δ_C (125 MHz, $CDCl_3$, 323 K) 170.1 (acetyl C=O), 154.9 (Boc C=O), 79.7 (^{t}Bu C_1), 71.1 (C-5), 70.8 (C-1), 64.7 (C-3), 49.4 (C-7), 44.5 (C-9), 37.5 (C-

6), 28.5 (^{t}Bu C_3), 27.4 (C-4), 26.6 (C-10), 21.0 (acetyl CH_3), 20.5 (C-11); HRMS found MNa^+, 336.1789. $C_{16}H_{27}NO_5$ requires *MNa*, 336.1786.

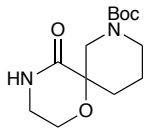
2-Benzyl 8-*tert*-butyl (5*R,6*S**)-5-(acetyloxy)-2,8-diazaspiro[5.5]undecane-2,8-dicarboxylate**



5

According to General Procedure P, the alcohol derivative **S16** (50.0 mg, 0.12 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 30:70 EtOAc−hexane to yield the *piperidine derivative **5*** (19.0 mg, 40%) as a colourless oil, R_f 0.60 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2936, 2866, 1737, 1686, 1425, 1364, 1273, 1232, 1205, 1154, 1108, 1038; δ_H (500 MHz, CD_3OD, 333 K) 7.37-7.27 (5H, m, phenyl), 5.14 (1H, d, *J* 12.4, arylmethyl 1-H_A), 5.11 (1H, d, *J* 12.4, arylmethyl 1-H_B), 4.89 (1H, dd, *J* 6.8 and 3.6, 5-H), 3.63-3.44 (3H, m, 3-H_2 and 1-H_A), 3.44-3.33 (4H, m, 9-H_2, 1-H_B and 7-H_A), 3.19 (1H, d, *J* 12.9, 7-H_B), 2.06 (3H, s, acetyl), 1.99-1.90 (1H, m, 4-H_A), 1.74-1.65 (1H, m, 4-H_B), 1.64-1.58 (1H, m, 11-H_A), 1.57-1.47 (2H, m, 10-H_2), 1.43 (9H, s, ^{t}Bu), 1.41-1.36 (1H, m, 11-H_B); δ_C (125 MHz, CD_3OD, 333 K) 171.9 (acetyl C=O), 157.1 (Boc C=O), 156.5 (Cbz C=O), 138.1 (phenyl C-1), 129.5 (phenyl C_2-3,5), 129.1 (phenyl C_2-2,6), 129.0 (phenyl C-4), 81.3 (^{t}Bu C_1), 72.7 (C-5), 68.5 (arylmethyl C-1), 50.2 (C-7), 49.0 (C-1), 45.5 (C-9), 41.7 (C-3), 39.3 (C-6), 28.7 (^{t}Bu C_3), 28.0 (C-10), 27.2 (C-4), 21.7 (C-11), 20.8 (acetyl CH_3); HRMS found MNa^+, 469.2306. $C_{24}H_{34}N_2O_6$ requires *MNa*, 469.2314.

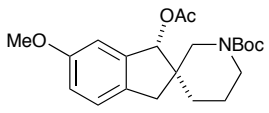
***tert*-Butyl 5-oxo-1-oxa-4,8-diazaspiro[5.5]undecane-8-carboxylate**



33

According to General Procedure P, the alcohol derivative **S17** (78.0 mg, 0.27 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 60:40 EtOAc−hexane to yield the *piperidine derivative* ***33*** (42.0 mg, 57%) as a colourless oil, R_f 0.44 (EtOAc); ν_{max}/cm^{-1} 3192, 3071, 2954, 2925, 1687, 1667, 1421, 1364, 1335, 1276, 1243, 1175, 1150, 1107, 1086; δ_H (500 MHz, CD_3OD, 333 K) 4.37 (1H, br. s, 4-H), 4.16 (1H, d, *J* 13.9, 7-H_A), 3.95 (1H, app. d, *J* 12.3, 9-H_A), 3.79 (1H, ddd, *J* 12.1, 8.5 and 3.5, 2-H_A), 3.72 (1H, app. br. s, 2-H_B), 3.32 (1H, ddd, *J* 12.5, 8.5 and 4.2, 3-H_A), 3.26-3.15 (1H, m, 3-H_B), 3.00 (1H, app. br. s, 7-H_B), 2.69 (1H, app. br. s, 9-H_B), 1.93 (1H, app. td, *J* 13.5 and 4.5, 10-H_A), 1.86-1.76 (1H, m, 10-H_B), 1.75-1.62 (1H, m, 11-H_A), 1.36 (10H, s, 11-H_B and ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 173.9 (C-5), 157.1 (Boc C=O), 81.1 (^{t}Bu C_1), 77.6 (C-6), 60.1 (C-2), 45.0 (C-7), 43.1 (C-9), 43.0 (C-3), 32.8 (C-10), 28.7 (^{t}Bu C_3), 20.6 (C-11); HRMS found MNa^+, 293.1466. $C_{13}H_{22}N_2O_4$ requires *MNa*, 293.1471.

tert-Butyl (2*R,3*S**)-3-(acetyloxy)-5-methoxy-1,3-dihydrospiro[indene-2,3'-piperidine]-1'-carboxylate**

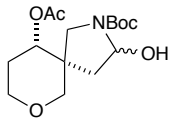


40

According to General Procedure P, the alcohol derivative **S18** (50.0 mg, 0.13 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 10:90 EtOAc−hexane to yield the *piperidine derivative* ***40*** (6.00 mg, 13%) as a colourless oil, R_f 0.50 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 2928, 2851, 1732, 1689, 1493, 1426, 1365, 1285, 1234, 1152, 1018; δ_H (500 MHz, $CDCl_3$, 323 K) 7.10 (1H, d, *J* 8.3, 7-H), 6.98 (1H, d, *J* 2.5, 4-H), 6.84 (1H, dd, *J* 8.3 and 2.5, 6-H), 5.83 (1H, s, 3-H), 3.78 (3H, s,

methoxy), 3.60-3.48 (1H, m, 6'-H_A), 3.32 (1H, ddd, *J* 12.8, 7.0 and 5.1, 6'-H_B), 3.25 (1H, d, *J* 13.2, 2'-H_A), 3.15 (1H, d, *J* 13.2, 2'-H_B), 2.81 (1H, d, *J* 15.6, 1-H_A), 2.66 (1H, d, *J* 15.6, 1-H_B), 2.04 (3H, s, acetyl), 1.87-1.78 (1H, m, 4'-H_A), 1.69 (1H, app. dt, *J* 13.0 and 5.6, 4'-H_B), 1.61-1.54 (2H, m, 5'-H_2), 1.40 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$, 323 K) 170.8 (acetyl C=O), 159.3 (C-5), 155.0 (Boc C=O), 141.7 (C-3a), 135.2 (C-7a), 125.9 (C-7), 116.3 (C-6), 111.7 (C-4), 80.6 (C-3), 79.7 (^{t}Bu C_1), 55.7 (methoxy), 51.8 (C-2'), 47.4 (C-2), 44.3 (C-6'), 39.8 (C-1), 30.4 (C-4'), 28.6 (^{t}Bu C_3), 22.9 (C-5'), 21.2 (acetyl CH_3); HRMS found MNa^+, 398.1935. $C_{21}H_{29}NO_5$ requires *MNa*, 398.1937.

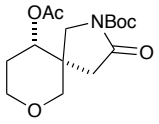
tert-Butyl (5*R,10*R**)-10-(acetyloxy)-3-hydroxy-7-oxa-2-azaspiro[4.5]decane-2-carboxylate**



25

According to General Procedure J, the alkene derivative **22a** (69.0 mg, 0.22 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 30:70→50:50 EtOAc−hexane to yield *hemiaminals **25*** (51.0 mg, 74%, *dr* 58:42 by ^{1}H-NMR) as an amorphous colourless solid, R_f 0.53 and 0.33 (50:50 EtOAc−petrol); ν_{max}/cm^{-1} 3451, 2973, 2861, 1739, 1694, 1389, 1365, 1233, 1160; δ_H (500 MHz, CD_3OD, 333 K) 5.08-4.99 (1H, m, 3-H^{maj}), 4.95-4.86 (1H, m, 3-H^{min}) 4.79-4.68 (2H, m, 10-H), 3.81-3.63 (2H, m, 8-H_A), 3.54-3.36 (6H, m, 8-H_B, 6-H_A and 1-H_A), 3.30-3.09 (4H, m, 6-H_B and 1-H_B), 2.02-1.91 (8H, m, acetyl and 4-H_A), 1.83-1.68 (4H, m, 4-H_B and 9-H_A), 1.64-1.54 (2H, m, 9-H_B), 1.38 (18H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 171.9 (acetyl 2C=O), 156.0 (Boc C=O^{maj}), 155.7 (Boc C=O^{min}), 90.5 (C-3^{maj}), 89.8 (C-3^{min}), 81.8 (^{t}Bu $C_1{}^{maj}$), 81.7 (^{t}Bu $C_1{}^{min}$), 74.5 (C-10^{maj}), 73.4 (C-8^{maj}), 72.9 (C-10^{min}), 72.4 (C-8^{min}) 65.4 (C-6^{maj}), 64.7 (C-6^{min}) 52.3 (C-1^{maj}), 50.6 (C-1^{min}), 46.1 (C_2-5), 39.0 (C-4^{min}), 37.4 (C-4^{maj}), 30.1 (C-9^{maj}), 29.5 (C-9^{min}), 28.6 (^{t}Bu $2C_3$), 20.8 (acetyl $2CH_3$); HRMS found MNa^+, 338.1575. $C_{15}H_{25}NO_6$ requires *MNa*, 338.1579.

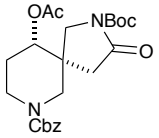
***tert*-Butyl (5*R**, 10*R**)-10-(acetyloxy)-3-oxo-7-oxa-2-azaspiro[4.5]decane-2-carboxylate**



26

Pyridinium dichromate (47.4 mg, 0.126 mmol) and celite (20 mg) were added to a solution of the hemiaminals **25** (20.0 mg, 63.4 μmol) in DCM (1.00 mL) at rt. The reaction mixture was stirred for 1 week at rt. Then, the mixture was filtered through celite and concentrated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 40:60 EtOAc−hexane to yield the *pyrrolidine derivative* ***26*** (13.0 mg, 65%) as a colourless oil, R_f 0.30 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2975, 2933, 2857, 1785, 1738, 1711, 1367, 1310, 1230, 1147, 1093, 1044, 1025; δ_H (500 MHz, $CDCl_3$) 4.90 (1H, dd, *J* 8.8 and 4.2, 10-H), 3.88 (1H, app. dt, *J* 12.0 and 4.7, 8-H_A), 3.70 (1H, d, *J* 11.6, 6-H_A), 3.57 (1H, ddd, *J* 12.0, 9.0 and 3.3, 8-H_B), 3.49 (2H, app. s, 1-H_2), 3.36 (1H, d, *J* 11.6, 6-H_B), 2.68 (1H, d, *J* 17.9, 4-H_A), 2.49 (1H, d, *J* 17.9, 4-H_B), 2.09 (3H, s, acetyl), 1.90 (1H, app. dq, *J* 13.0 and 4.0, 9-H_A), 1.68 (1H, app dtd, *J* 13.9, 9.3 and 4.5, 9-H_B), 1.52 (9H, s, ^{t}Bu); δ_C (125 MHz, $CDCl_3$) 171.9 (C-3), 170.3 (acetyl C=O), 149.9 (Boc C=O), 83.5 (^{t}Bu C_1), 72.3 (C_2-6,10), 65.3 (C-8), 51.0 (C-1), 38.6 (C-5), 37.9 (C-4), 28.7 (C-9), 28.1 (^{t}Bu C_3), 21.1 (acetyl CH_3); HRMS found MH^+, 314.1598. $C_{15}H_{23}NO_6$ requires *MH*, 314.1598.

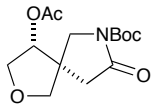
7-Benzyl 2-*tert*-butyl (5*R,10*S**)-10-(acetyloxy)-3-oxo-2,7-diazaspiro[4.5]decane-2,7-dicarboxylate**



31

According to General Procedure Q, the alkene derivative **22b** (0.20 g, 0.45 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 35:65 EtOAc−hexane to yield the *pyrrolidine derivative **31*** (0.12 g, 60%) as a colourless oil, R_f 0.42 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2978, 1785, 1738, 1696, 1432, 1367, 1315, 1229, 1148, 1104, 1041; δ_H (500 MHz, CD_3OD, 333 K) 7.37-7.27 (5H, m, phenyl), 5.15 (1H, d, *J* 12.3, arylmethyl 1-H_A), 5.12 (1H, d, *J* 12.3, arylmethyl 1-H_B), 4.97 (1H, dd, *J* 8.4 and 3.9, 10-H), 3.80-3.75 (1H, m, 8-H_A), 3.73 (1H, dd, *J* 13.6 and 1.5, 6-H_A), 3.58 (1H, d, *J* 11.2, 1-H_A), 3.53 (1H, d, *J* 11.2, 1-H_B), 3.39-3.34 (1H, m, 8-H_B), 3.32 (1H, d, *J* 13.6, 6-H_B), 2.63 (1H, d, *J* 17.7, 4-H_A), 2.33 (1H, d, *J* 17.7, 4-H_B), 2.04 (3H, s, acetyl), 1.83 (1H, app. ddt, *J* 14.0, 6.4 and 3.9, 9-H_A), 1.67 (1H, dtd, *J* 14.0, 8.4 and 4.4, 9-H_B), 1.49 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 174.1 (C-3), 171.7 (acetyl C=O), 157.1 (Boc C=O), 151.3 (Cbz C=O), 137.9 (phenyl C-1), 129.6 (phenyl C_2-3,5), 129.2 (phenyl C-4), 128.9 (phenyl C_2-2,6), 84.5 (^{t}Bu C_1), 74.7 (C-10), 68.7 (arylmethyl C-1), 53.3 (C-1), 50.2 (C-6), 41.9 (C-8), 40.3 (C-5), 39.4 (C-4), 28.3 (C-9), 28.2 (^{t}Bu C_3) 20.7 (acetyl CH_3); HRMS found MNa^+, 469.1942. $C_{23}H_{30}N_2O_7$ requires *MNa*, 469.1945.

tert-Butyl (4*R,5*S**)-4-(acetyloxy)-8-oxo-2-oxa-7-azaspiro[4.4]nonane-7-carboxylate**

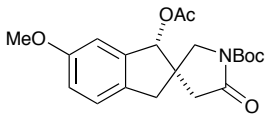


36

According to General Procedure Q, the alkene derivative **22d** (0.25 g, 0.83 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 40:60→60:40 EtOAc−hexane to yield the *pyrrolidine derivative **36*** (0.19 g, 76%) as a yellow oil, R_f 0.34 (40:60 petrol−EtOAc); ν_{max}/cm^{-1} 2977, 2933, 2873, 1786, 1737, 1699, 1389, 1366, 1311, 1230, 1151, 1104, 1062, 1047, 1023; δ_H (500 MHz, CD_3OD, 333 K) 5.15 (1H, dd, *J* 5.3 and 2.7, 4-H), 4.20 (1H, dd, *J* 10.8 and 5.3, 3-H_A), 3.86 (1H, d, *J* 8.7, 1-H_A), 3.75 (1H, dd, *J* 10.8 and 2.7, 3-H_B), 3.73 (1H, d, *J* 11.0, 6-H_A), 3.72 (1H, d, *J* 8.7, 1-H_B), 3.68 (1H, d, *J* 11.0, 6-H_B), 2.78 (1H, d, *J* 17.8, 9-H_A), 2.48 (1H, d, *J* 17.8, 9-H_B), 2.08 (3H, s, acetyl), 1.52 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 174.1 (C-8), 172.0 (acetyl C=O), 151.3 (Boc C=O), 84.5 (^{t}Bu C_1), 79.4 (C-4), 76.2 (C-1), 73.7 (C-3), 55.7 (C-6), 46.7 (C-5),

37.2 (C-9), 28.3 (^{t}Bu C_3), 20.6 (acetyl CH_3); HRMS found MNa^+, 322.1257. $C_{14}H_{21}NO_6$ requires *MNa*, 322.1261.

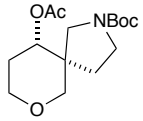
***tert*-Butyl (2*R**,3*R**)-3-(acetyloxy)-5-methoxy-5'-oxo-1,3-dihydrospiro[indene-2,3'-pyrrolidine]-1'-carboxylate**



41

According to General Procedure Q, the alkene derivative **22e** (0.10 g, 0.26 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 25:75 EtOAc−hexane to yield the *pyrrolidine derivative **41*** (37.0 mg, 37%) as a colourless oil, R_f 0.48 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2978, 2934, 1784, 1737, 1715, 1492, 1367, 1310, 1224, 1150, 1022; δ_H (400 MHz, $CDCl_3$, 323 K) 7.13 (1H, d, *J* 8.3, 7-H), 6.91 (1H, d, *J* 2.6, 4-H), 6.85 (1H, dd, *J* 8.3 and 2.6, 6-H), 6.00 (1H, s, 3-H), 3.78 (3H, s, methoxy), 3.76 (1H, d, *J* 11.0, 2'-H_A), 3.57 (1H, d, *J* 11.0, 2'-H_B), 3.06 (1H, d, *J* 15.3, 1-H_A), 2.90 (1H, d, *J* 15.3, 1-H_B), 2.83 (1H, d, *J* 17.4, 4'-H_A), 2.44 (1H, d, *J* 17.4, 4'-H_B), 2.08 (3H, s, acetyl), 1.51 (9H, s, ^{t}Bu); δ_C (100 MHz, $CDCl_3$, 323 K) 172.1 (C-5'), 170.7 (acetyl C=O), 159.7 (C-5), 150.0 (Boc C=O), 141.1 (C-3a), 133.1 (C-7a), 125.9 (C-7), 116.2 (C-6), 111.1 (C-4), 83.2 (^{t}Bu C_1), 81.1 (C-3), 56.2 (C-2'), 55.7 (methoxy), 47.5 (C-2), 41.8 (C-1), 40.4 (C-4'), 28.2 (^{t}Bu C_3), 20.9 (acetyl CH_3); HRMS found MNa^+, 398.1583. $C_{20}H_{25}NO_6$ requires *MNa*, 398.1574.

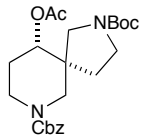
***tert*-Butyl (5*R**, 10*R**)-10-(acetyloxy)-7-oxa-2-azaspiro[4.5]decane-2-carboxylate**



27

By modification of an existing procedure,[19] $NaBH(OAc)_3$ (93.0 mg, 441 μmol) was added to a solution of the hemiaminals **25** (20.0 mg, 63.4 μmol) in AcOH (0.30 mL) at rt. The reaction mixture was stirred for 3 h at rt. Then, a saturated aqueous solution of $NaHCO_3$ (1 mL) and DCM (1 mL) were added. The phases were separated and the aqueous phase was extracted with DCM (4 × 1 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 25:75 EtOAc−hexane to yield the *pyrrolidine derivative **27*** (15.0 mg, 79%) as a colourless oil, R_f 0.47 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2971, 2863, 1738, 1691, 1398, 1364, 1234, 1172, 1145, 1103, 1090, 1071; δ_H (500 MHz, $CDCl_3$, 323 K) 4.91 (1H, dd, *J* 7.5 and 3.8, 10-H), 3.81 (1H, ddd, *J* 11.2, 7.0 and 3.9, 8-H_A), 3.65 (1H, d, *J* 11.5, 6-H_A), 3.61 (1H, ddd, *J* 11.2, 7.4 and 3.7, 8-H_B), 3.48-3.45 (1H, m, 3-H_A), 3.37-3.26 (1H, m, 3-H_B), 3.34 (1H, d, *J* 11.5, 6-H_B), 3.29 (1H, d, *J* 11.3, 1-H_A), 3.16 (1H, m, 1-H_B), 2.08 (3H, s, acetyl), 1.94-1.86 (2H, m, 9-H_A and 4-H_A), 1.84-1.78 (1H, m, 4-H_B), 1.75-1.67 (1H, m, 9-H_B), 1.46 (9H, s, ^{t}Bu); δ_C (125 MHz, $CDCl_3$, 323 K) 170.3 (acetyl C=O), 154.6 (Boc C=O), 79.6 (^{t}Bu C_1), 72.2 (C-10), 71.4 (C-6), 65.0 (C-8), 51.3 (C-1), 44.4 (C_2-3,5), 29.2 (C-9), 28.7 (C-4 and ^{t}Bu C_3), 21.1 (acetyl CH_3); HRMS found MH^+, 300.1805. $C_{15}H_{25}NO_5$ requires *MH*, 300.1805.

7-Benzyl 2-*tert*-butyl (5*R,10*S**)-10-(acetyloxy)-2,7-diazaspiro[4.5]decane-2,7-dicarboxylate**

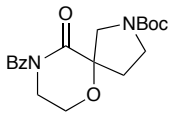


32

According to General Procedure R, the alkene derivative **22b** (0.10 g, 0.23 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 30:70 EtOAc−hexane to yield the *pyrrolidine derivative **32*** (61.0 mg, 61%) as a colourless oil, R_f 0.41 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2974, 2876, 1737, 1688, 1430, 1398, 1364, 1233, 1211, 1145, 1101, 1059, 1041; δ_H (500 MHz, CD_3OD, 333 K) 7.38-7.26 (5H, m,

phenyl), 5.16 (1H, d, *J* 12.4, arylmethyl 1-H_A), 5.09 (1H, d, *J* 12.4, arylmethyl 1-H_B), 4.90 (1H, dd, *J* 7.1 and 3.7, 10-H), 3.61 (1H, ddd, *J* 12.5, 7.7 and 4.2, 8-H_A), 3.53 (1H, d, *J* 13.4, 6-H_A), 3.52-3.47 (1H, m, 8-H_B), 3.45-3.40 (1H, m, 3-H_A), 3.38 (1H, d, *J* 13.4, 6-H_B), 3.35-3.27 (1H, m, 3-H_B), 3.22 (1H, d, *J* 11.2, 1-H_A), 3.12 (1H, d, *J* 11.2, 1-H_B), 2.06 (3H, s, acetyl), 1.93-1.84 (1H, m, 4-H_A), 1.82-1.74 (1H, m, 9-H_A), 1.73-1.63 (2H, m, 4-H_B and 9-H_B), 1.43 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 171.9 (acetyl C=O), 157.1 (Boc C=O), 156.3 (Cbz C=O), 138.0 (phenyl C-1), 129.6 (phenyl C_2-3,5), 129.1 (phenyl C-4), 128.9 (phenyl C_2-2,6), 81.1 (^{t}Bu C_1), 73.9 (C-10), 68.6 (arylmethyl C-1), 52.6 (C-1), 49.2 (C-6), 47.5 (C-5), 45.4 (C-3), 41.6 (C-8), 30.2 (C-4), 28.9 (C-9), 28.8 (^{t}Bu C_3), 20.8 (acetyl CH_3); HRMS found MNa^+, 455.2147. $C_{23}H_{32}N_2O_6$ requires *MNa*, 455.2152.

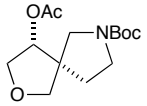
***tert*-Butyl 9-benzoyl-10-oxo-6-oxa-2,9-diazaspiro[4.5]decane-2-carboxylate**



34

According to General Procedure R, the alkene derivative **1c** (0.20 g, 0.53 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *pyrrolidine derivative **34*** (94.0 mg, 49%) as a colourless oil, R_f 0.63 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2974, 2888, 1682, 1394, 1366, 1313, 1279, 1234, 1172, 1132, 1100, 1082; δ_H (500 MHz, CD_3OD, 333 K) 7.57-7.53 (2H, m, phenyl 2,6-H_2), 7.50 (1H, tt, *J* 7.2 and 1.6, phenyl 4-H), 7.41 (2H, td, *J* 7.2 and 1.6, phenyl 3,5-H_2), 4.13-4.01 (2H, m, 7-H_2), 3.99-3.86 (2H, m, 8-H_2), 3.69 (2H, app. s, 1-H_2), 3.54 (1H, ddd, *J* 10.5, 8.5 and 3.5, 3-H_A), 3.47 (1H, ddd, *J* 10.5, 8.9 and 7.5, 3-H_B), 2.43-2.35 (1H, m, 4-H_A), 2.35-2.26 (1H, m, 4-H_B), 1.46 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 174.6 (C-10), 173.3 (benzoyl C=O), 156.2 (Boc C=O), 136.9 (phenyl C-1), 132.9 (phenyl C-4), 129.3 (phenyl C_2-3,5), 129.0 (phenyl C_2-2,6), 81.3 (C-5), 81.1 (^{t}Bu C_1), 61.4 (C-7), 56.6 (C-1), 46.8 (C-8), 45.9 (C-3), 36.6 (C-4), 28.8 (^{t}Bu C_3); HRMS found MNa^+, 383.1575. $C_{19}H_{24}N_2O_5$ requires *MNa*, 383.1577.

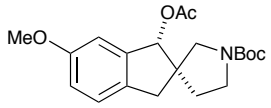
***tert*-Butyl (4*R**,5*S**)-4-(acetyloxy)-2-oxa-7-azaspiro[4.4]nonane-7-carboxylate**



37

According to General Procedure R, the alkene derivative **22d** (0.25 g, 0.83 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 30:70 EtOAc−hexane to yield the *pyrrolidine derivative **37*** (0.18 g, 76%) as a colourless oil, R_f 0.42 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2975, 2934, 2873, 1738, 1693, 1400, 1366, 1236, 1161, 1122; δ_H (500 MHz, CD_3OD, 333 K) 5.04 (1H, dd, *J* 4.9 and 2.1, 4-H), 4.09 (1H, dd, *J* 10.7 and 4.9, 3-H_A), 3.71 (1H, dd, *J* 10.7 and 2.1, 3-H_B), 3.70 (1H, d, *J* 8.6, 1-H_A), 3.67 (1H, d, *J* 8.6, 1-H_B), 3.40-3.34 (1H, m, 8-H_A), 3.34-3.28 (1H, m, 8-H_B), 3.28-3.22 (2H, m, 6-H_2), 2.04 (3H, s, acetyl), 2.03-2.01 (1H, m, 9-H_A), 1.81 (1H, ddd, *J* 13.6, 8.0 and 6.1, 9-H_B), 1.42 (9H, s, ^{t}Bu); δ_C (125 MHz, CD_3OD, 333 K) 172.1 (acetyl C=O), 156.3 (Boc C=O), 81.1 (^{t}Bu C_1), 78.9 (C-4), 75.9 (C-1), 74.2 (C-3), 55.5 (C-6), 54.0 (C-5), 46.1 (C-8), 28.8 (C-9 and ^{t}Bu C_3), 20.6 (acetyl CH_3); HRMS found MNa^+, 308.1465. $C_{14}H_{23}NO_5$ requires *MNa*, 308.1468.

***tert*-Butyl (2*R**,3*R**)-3-(acetyloxy)-5-methoxy-1,3-dihydrospiro[indene-2,3'-pyrrolidine]-1'-carboxylate**

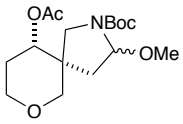


42

According to General Procedure R, the alkene derivative **22e** (0.10 g, 0.26 mmol) gave a crude material. The crude material was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *pyrrolidine derivative **42*** (49.0 mg, 51%) as a colourless oil, R_f 0.38 (70:30 petrol−EtOAc); ν_{max}/cm^{-1} 2974, 2933, 1733, 1689, 1492, 1395, 1365, 1227, 1163, 1144, 1118, 1100, 1020; δ_H (500 MHz, CD_3OD, 333 K) 7.14 (1H, d, *J* 8.3, 7-H), 6.92 (1H, d, *J* 2.5, 4-H), 6.86 (1H, dd, *J* 8.3 and 2.5, 6-H), 5.92 (1H, s, 3-H), 3.76 (3H,

s, methoxy), 3.50-3.37 (2H, m, 5'-H_2), 3.33 (1H, d, *J* 11.0, 2'-H_A), 3.16 (1H, d, *J* 11.0, 2'-H_B), 3.01 (1H, d, *J* 15.3, 1-H_A), 2.77 (1H, d, *J* 15.3, 1-H_B), 2.15 (1H, app. dt, *J* 13.0 and 7.4, 4'-H_A), 2.06 (3H, s, acetyl), 1.89 (1H, app. dt, *J* 13.0 and 6.8, 4'-H_B), 1.44 (9H, s, ^{t}Bu); δ_C (100 MHz, CD_3OD, 333 K) 172.5 (acetyl C=O), 160.7 (C-5), 156.5 (Boc C=O), 142.9 (C-3a), 136.1 (C-7a), 126.6 (C-7), 116.9 (C-6), 112.2 (C-4), 82.1 (C-3), 81.0 (^{t}Bu C_1), 57.2 (C-2'), 56.0 (methoxy), 55.0 (C-2), 46.3 (C-5'), 41.5 (C-1), 32.1 (C-4'), 28.8 (^{t}Bu C_3), 20.8 (acetyl CH_3); HRMS found MNa^+, 384.1779. $C_{20}H_{27}NO_5$ requires *MNa*, 384.1781.

tert-Butyl (5*R,10*R**)-10-(acetyloxy)-3-methoxy-7-oxa-2-azaspiro[4.5]decane-2-carboxylate**

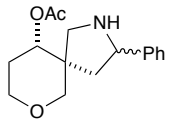


28

TsOH•H_2O (2.74 mg, 14.4 μmol) was added to a solution of the hemiaminals **25** (0.15 g, 0.48 mmol) in MeOH (1.20 mL) at rt. The reaction mixture was stirred for 18 h at rt. Then, the solvent was removed under reduced pressure to give a crude product. The crude product was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *aminals* ***28*** (0.12 g, 77%, *dr* 77:23 by ^{1}H-NMR) as a colourless oil, R_f 0.33 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 2973, 2934, 2859, 1740, 1697, 1390, 1366, 1234, 1164, 1068; δ_H (500 MHz, CD_3OD, 333 K) 5.16 (1H, app. d, *J* 6.3, 3-H^{min}), 5.13 (1H, app. d, *J* 5.7, 3-H^{maj}), 4.99 (1H, dd, *J* 5.5 and 3.5, 10-H^{min}), 4.85 (1H, dd, *J* 7.6 and 3.8, 10-H^{maj}), 3.94 (1H, d, *J* 11.5, 6-$H_A{}^{min}$) 3.83 (1H, d, *J* 11.5, 6-$H_A{}^{maj}$), 3.79 (2H, ddd, *J* 11.2, 7.0 and 3.9, 8-H_A), 3.62-3.59 (2H, m, 8-H_B), 3.57 (1H, d, *J* 11.5, 6-$H_B{}^{maj}$), 3.54 (2H, d, *J* 11.6, 1-H_A), 3.47 (1H, d, *J* 11.5, 6-$H_B{}^{min}$), 3.33-3.27 (8H, m, 1-H_B and methoxy 1-H_3), 2.08 (3H, s, acetyl 1-$H_3{}^{min}$), 2.05 (3H, s, acetyl 1-$H_3{}^{maj}$), 2.00 (2H, dd, *J* 13.8 and 5.7, 4-H_A), 1.91 (2H, app. d, *J* 13.8, 4-H_B), 1.86-1.80 (2H, m, 9-H_A), 1.73-1.64 (2H, m, 9-H_B), 1.49 (9H, s, ^{t}Bu^{min}), 1.48 (9H, s, ^{t}Bu^{maj}); δ_C (125 MHz, CD_3OD, 333 K) 172.0 (acetyl C=O^{maj}), 171.9 (acetyl C=O^{min}) 156.0 (Boc 2C=O), 90.7 (C-3^{maj}), 89.9 (C-3^{min}), 81.8 (^{t}Bu 2C_1), 74.5 (C-10^{maj}), 73.4 (C-6^{maj}), 72.9 (C-10^{min}), 72.4 (C-6^{min}), 65.4 (C-8^{maj}), 64.6 (C-8^{min}), 56.0 (methoxy C-1^{maj}), 55.7 (methoxy C-

1[min]), 52.4 (C_2-1), 46.3 (C_2-5), 37.3 (C_2-4), 30.1 (C-9[maj]), 29.5 (C-9[min]), 28.6 (^{t}Bu 2C_3), 20.8 (acetyl 2CH_3); HRMS found MNa^+, 352.1740. $C_{16}H_{27}NO_6$ requires *MNa*, 352.1730.

tert-Butyl (5*R,10*R**)-10-(acetyloxy)-3-phenyl-7-oxa-2-azaspiro[4.5]decane-2-carboxylate**



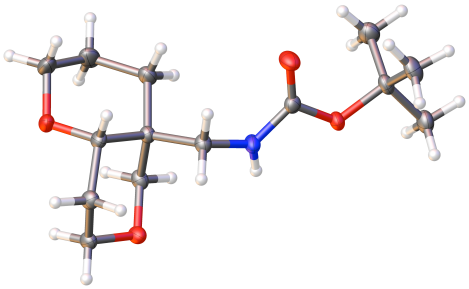
29

According to a procedure,[20] PhMgBr (0.75 mL, 0.75 mmol of a 1.0 M solution in THF) was added dropwise to a suspension of CuBr•Me_2S (0.15 g, 0.75 mmol) in Et_2O (1.50 mL) at –40 °C. The suspension was stirred at –40 °C for 1 h and then it was cooled to –78 °C. Subsequently, Et_2O•BF_3 (92.6 μL, 0.75 mmol) and a solution of the aminals **28** (0.10 g, 0,30 mmol) in Et_2O (0.50 mL) were added and the reaction mixture was warmed to 0 °C. The reaction was stirred at 0 °C for 18 h. Then, it was warmed to rt, a saturated aqueous solution of NH_4Cl (2 mL) and EtOAc (2 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (4 × 2 mL). The organic phases were combined, washed with brine (4 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a crude product. The crude product (*dr* 50:50 by ^{1}H-NMR) was purified by flash column chromatography, eluting with 20:80 EtOAc−hexane to yield the *phenyl derivative **29*** (0.10 g, 88%, *dr* 57:43 by ^{1}H-NMR) as a colourless oil, R_f 0.56 (50:50 petrol−EtOAc); ν_{max}/cm^{-1} 3504, 2972, 2930, 2859, 1738, 1688, 1392, 1363, 1234, 1159, 1090, 1070; δ_H (500 MHz, CD_3OD, 333 K) 7.24-7.16 (5H, m, phenyl[min]), 7.14-7.05 (5H, m phenyl[maj]), 4.91 (1H, dd, *J* 7.4 and 3.9, 10-H[min]), 4.87-4.78 (1H, m, 10-H[maj]), 4.80-4.73 (1H, m, 3-H[min]) 4.66 (1H, app. t, *J* 8.4, 3-H[maj]), 3.70 (2H, ddd, *J* 11.3, 7.5 and 3.7, 8-H_A), 3.60 (2H, d, *J* 11.5, 6-H_A), 3.56 (2H, ddd, *J* 11.3, 6.7 and 4.1, 8-H_B), 3.45 (2H, d, *J* 12.0, 1-H_A), 3.35 (2H, d, *J* 12.0, 1-H_B), 3.29 (2H, *J* 11.5, 6-H_B), 2.46 (1H, app. dd, *J* 13.5 and 8.5, 4-H_A[min]), 2.28 (1H, ddd, *J* 13.5, 8.0 and 1.3, 4-H_A[maj]), 2.00 (3H, s, acetyl[min]), 1.91 (3H, s, acetyl[maj]), 1.86-1.79 (1H, m, 9-H_A[min]), 1.79-1.71 (2H, m, 4-H_B[maj] and 9-H_A[maj]), 1.70-1.62 (2H, m, 4-H_B[min] and 9-H_B[min]), 1.58 (1H, app. dtd, *J* 13.8, 6.7 and 3.7, 9-H_B[maj]); δ_C (125 MHz, CD_3OD, 333 K) 172.0 (C=O[min]), 171.8

(C=O^{maj}), 156.3 (phenyl C-1^{maj}), 156.1 (phenyl C-1^{min}), 129.4 (phenyl C_2-4), 127.8 (phenyl C_2-3,5^{maj}), 127.7 (phenyl C_2-3,5^{min}), 126.6 (phenyl C_2-2,6^{min}), 126.5 (phenyl C_2-2,6^{maj}), 73.5 (C-6^{min}), 73.1 (C_2-10), 71.4 (C-6^{maj}), 65.7 (C-8^{min}), 65.5 (C-8^{maj}), 62.4 (C-3^{maj}), 61.6 (C-3^{min}), 55.3 (C-1^{maj}), 53.1 (C-10^{min}), 46.9 (C-5^{maj}), 46.6 (C-5^{min}), 41.4 (C-4^{maj}), 41.2 (C-4^{min}), 30.2 (C-9^{maj}), 29.7 (C-9^{min}), 20.9 (acetyl CH_3^{min}) 20.7 (acetyl CH_3^{maj}); HRMS found MH^+, 276.1594. $C_{16}H_{21}NO_3$ requires *MH*, 276.1594.

X-Ray Structures

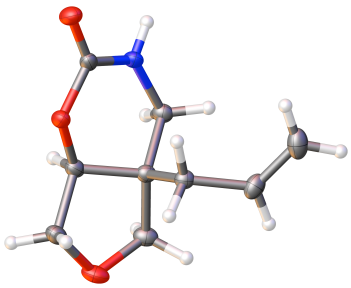
ORTEP diagram of 13



Crystal data and structure refinement for 13	
Empirical formula	$C_{14}H_{25}NO_4$
Formula weight	271.35
Temperature/K	120.01(19)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.04739(18)
b/Å	12.2038(2)
c/Å	10.96322(18)
α/°	90.00
β/°	91.7913(16)
γ/°	90.00
Volume/Å^3	1477.35(4)
Z	4

ρ_{calc}g/cm^3	1.220
μ/mm^{-1}	0.721
F(000)	592.0
Crystal size/mm^3	0.21 × 0.12 × 0.09
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8 to 147.5
Index ranges	-9 ≤ h ≤ 13, -14 ≤ k ≤ 14, -13 ≤ l ≤ 13
Reflections collected	6401
Independent reflections	2882 [R_{int} = 0.0214, R_{sigma} = 0.0256]
Data/restraints/parameters	2882/0/175
Goodness-of-fit on F^2	1.052
Final R indexes [I>=2σ (I)]	R_1 = 0.0374, wR_2 = 0.0880
Final R indexes [all data]	R_1 = 0.0435, wR_2 = 0.0918
Largest diff. peak/hole / e Å^{-3}	0.29/-0.19

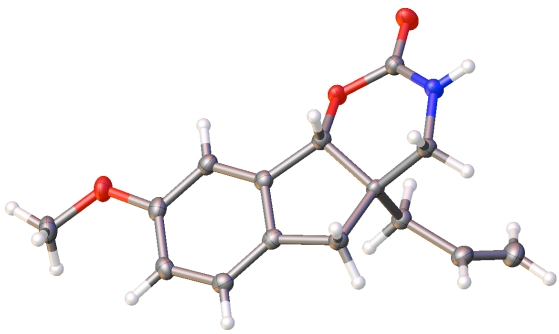
ORTEP diagram of 3



Crystal data and structure refinement for 3	
Empirical formula	$C_9H_{13}NO_3$
Formula weight	183.20
Temperature/K	120.01(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	7.65800(10)

b/Å	9.53160(10)
c/Å	12.1849(2)
α/°	90
β/°	94.8050(10)
γ/°	90
Volume/Å^3	886.29(2)
Z	4
ρ_{calc}g/cm^3	1.373
μ/mm^{-1}	0.859
F(000)	444.0
Crystal size/mm^3	0.48 × 0.28 × 0.26
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	11.596 to 147.354
Index ranges	-8 ≤ h ≤ 9, -8 ≤ k ≤ 11, -14 ≤ l ≤ 15
Reflections collected	4943
Independent reflections	1726 [R_{int} = 0.0130, R_{sigma} = 0.0130]
Data/restraints/parameters	1726/0/118
Goodness-of-fit on F^2	1.072
Final R indexes [I>=2σ (I)]	R_1 = 0.0315, wR_2 = 0.0799
Final R indexes [all data]	R_1 = 0.0339, wR_2 = 0.0817
Largest diff. peak/hole / e Å^{-3}	0.31/-0.19

ORTEP diagram of 39



Crystal data and structure refinement for 39	
Empirical formula	$C_{15}H_{17}NO_3$
Formula weight	259.29
Temperature/K	119.97(16)
Crystal system	triclinic
Space group	P-1
a/Å	6.7483(5)
b/Å	9.9314(7)
c/Å	11.0967(8)
α/°	63.764(7)
β/°	79.148(6)
γ/°	74.800(6)
Volume/Å^3	641.49(9)
Z	2
ρ_{calc}g/cm^3	1.342
μ/mm^{-1}	0.762
F(000)	276.0
Crystal size/mm^3	0.15 × 0.08 × 0.06
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.916 to 147.94
Index ranges	$-8 \leq h \leq 7$, $-12 \leq k \leq 10$, $-13 \leq l \leq 12$
Reflections collected	4223
Independent reflections	2397 [R_{int} = 0.0277, R_{sigma} = 0.0391]
Data/restraints/parameters	2397/0/173
Goodness-of-fit on F^2	1.028
Final R indexes [I>=2σ (I)]	R_1 = 0.0379, wR_2 = 0.0941
Final R indexes [all data]	R_1 = 0.0450, wR_2 = 0.0996
Largest diff. peak/hole / e Å^{-3}	0.35/-0.22

Assessment of the CNS Lead-Likeness of the Prepared Scaffolds

In order to assess the CNS lead-likeness of the 30 prepared scaffolds, corresponding virtual scaffolds without protecting groups, iodines, ketones and alkenes were generated (Fig. 1). Subsequently, a previously described protocol was used for virtual library generation and scoring to obtain the mean CNS Lead MPO score per scaffold.[21] See Table 1 and Table 2 for reactions and aspects of medicinal chemistry capping groups used for virtual decoration.

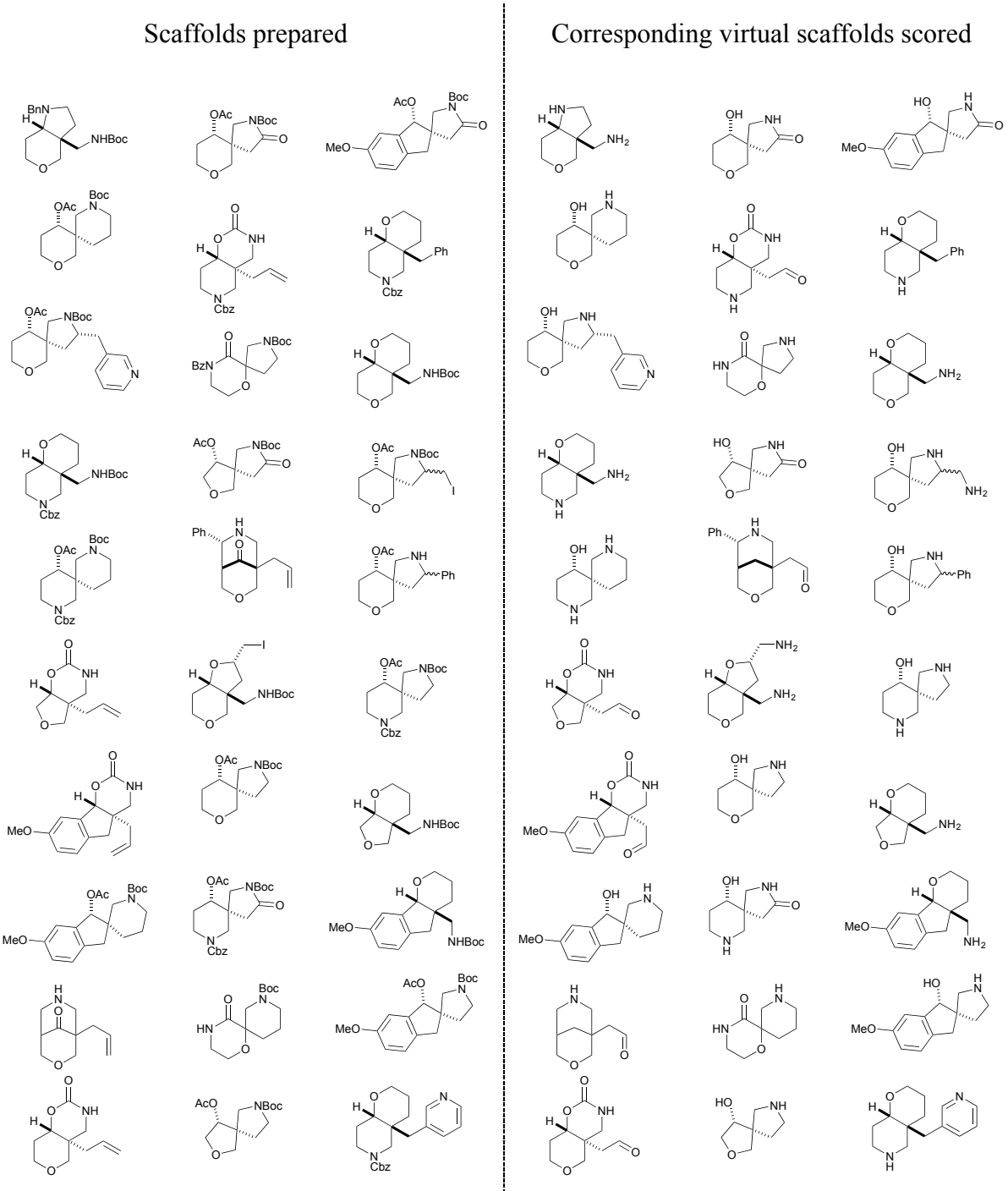


Figure 1: Generation of virtual scaffolds from the 30 scaffolds prepared. Virtual scaffolds containing aldehydes were converted to alcohols prior to decoration or were decorated with a reductive amination reaction.

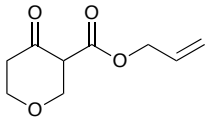
Type of decoration reaction	Functionality in the scaffold	Functionality in the reagent
Amidation	Amines	Carboxylic acid
Sulfonylation	Amines	Sulfonyl chlorides
O-alkylation/arylation	Alcohols	Halides
N-alkylation/arylation	Amines, amides	Halides
Reductive amination	Amines	Ketones, aldehydes
Reductive amination	aldehydes	Amines
Urea formation	Amines	Isocyanates

Table 1: Reactions used for virtual library generation. Scaffolds with one point of decoration were decorated once. Scaffolds with two or more points of decoration were decorated twice. Primary amines serve as two points of decoration.

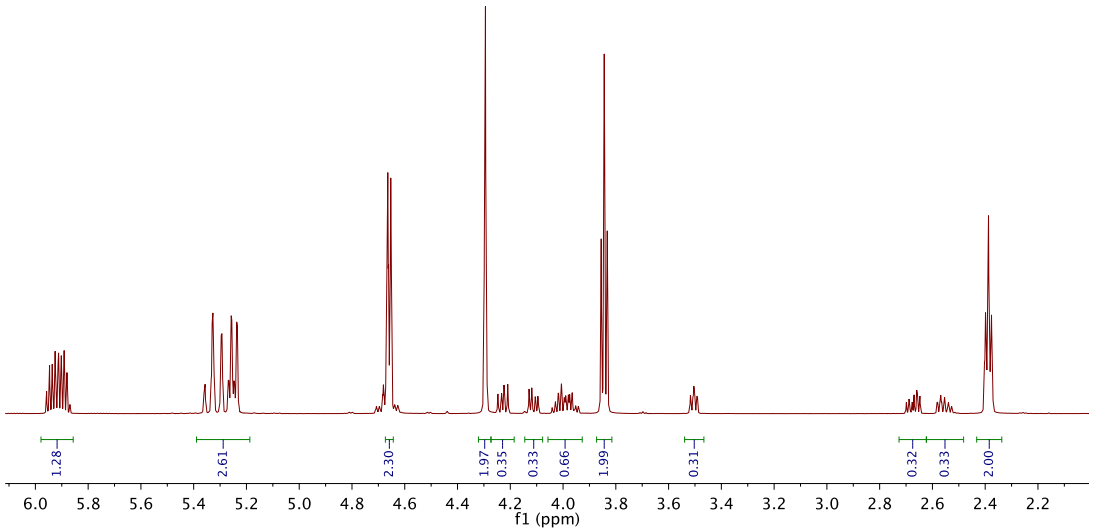
Substituent type	Number	Mean MW	Range MW	Mean cLogP	Range cLogP
Carboxylic acids	20	118.6	60.0 – 156.6	0.71	-0.49 – 2.12
Sulfonyl chlorides	15	173.2	114.5 – 211.1	1.24	0.00 – 2.40
Halides	30	163.3	94.9 – 205.5	1.88	0.68 – 3.24
Ketones	3	76.7	58.1 – 100.1	-0.32	-0.68 – -0.10
Aldehydes	15	102.4	44.0 – 140.6	0.93	-0.44 – 2.25
Isocyanates	15	119.9	71.1 – 167.6	1.01	-0.05 – 2.36

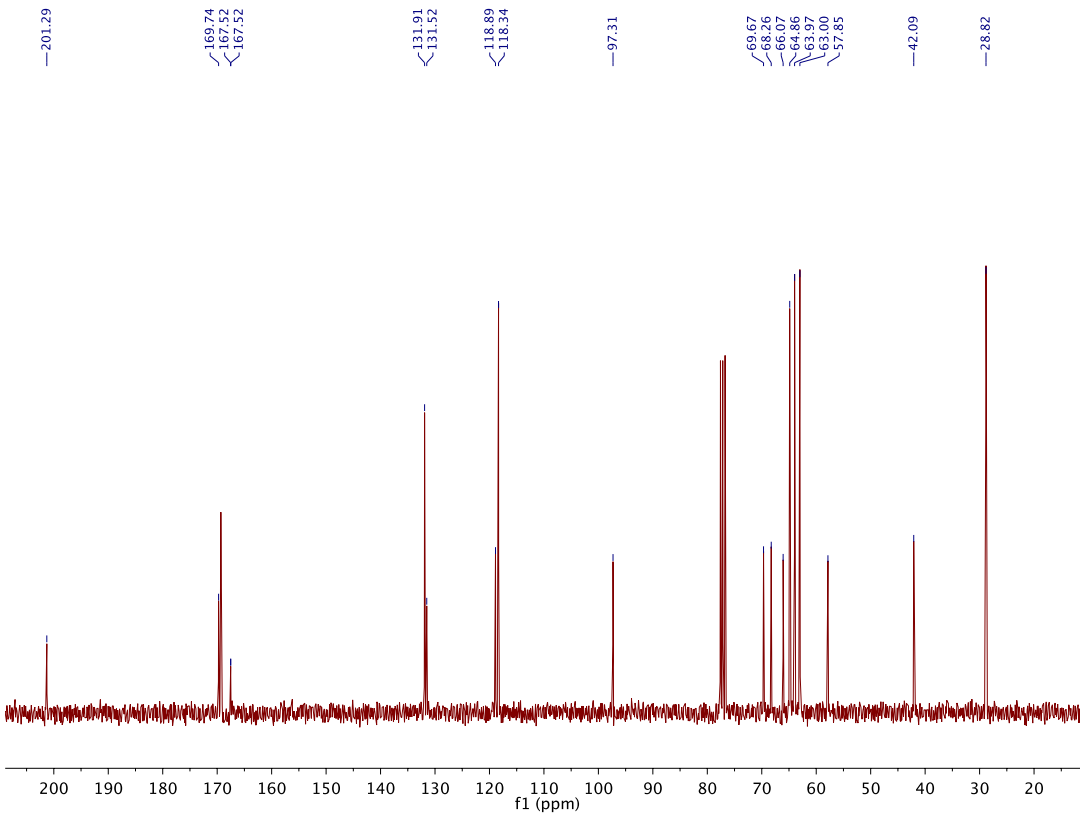
Table 2: Aspects of the 98 medicinal chemistry capping groups used for the decoration of the virtual scaffolds. More features of these medicinal chemistry capping groups can be found in a previously published set.[18]

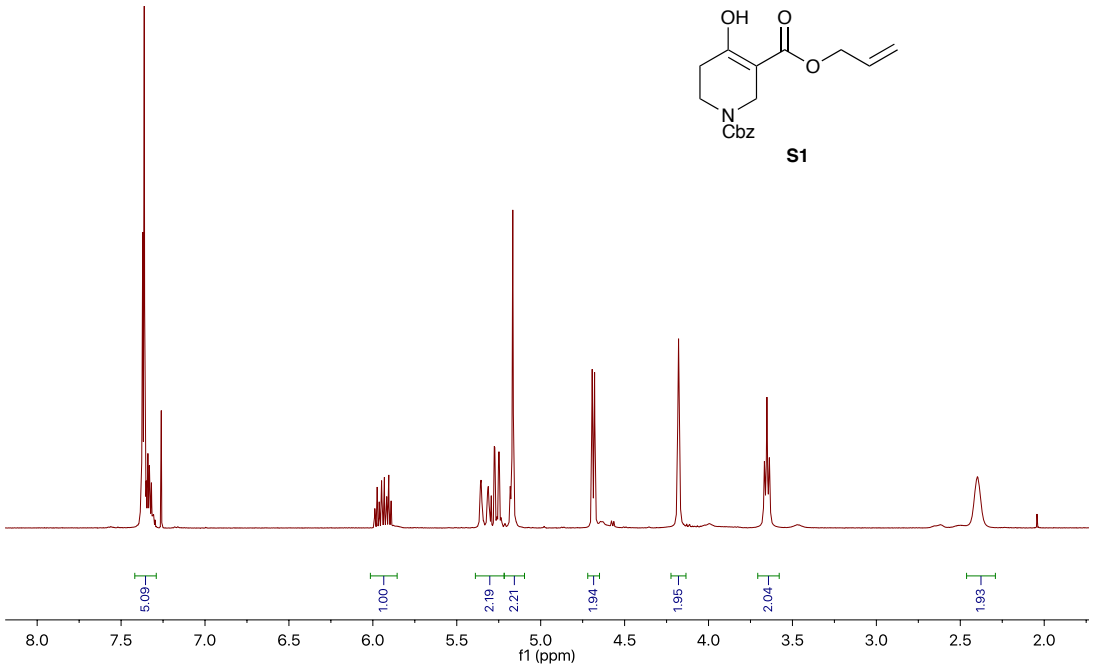
^{1}H and ^{13}C NMR Spectra



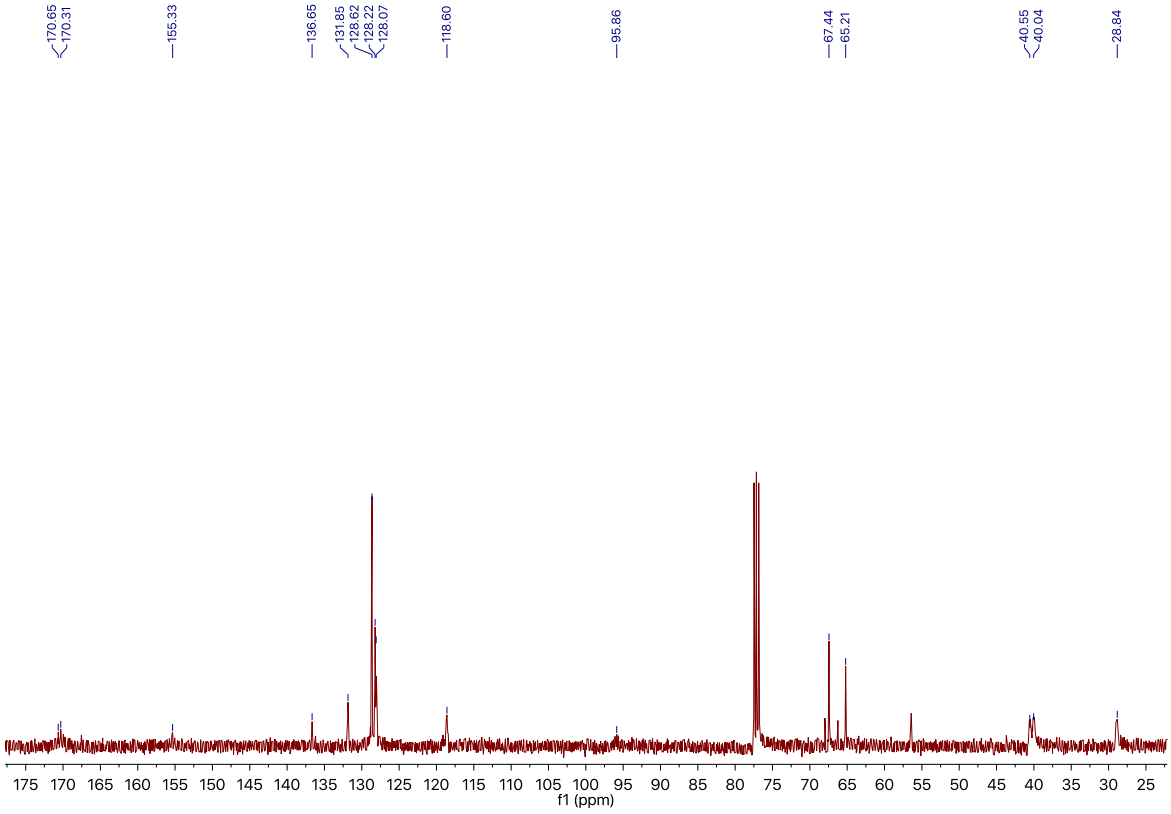
9

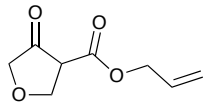




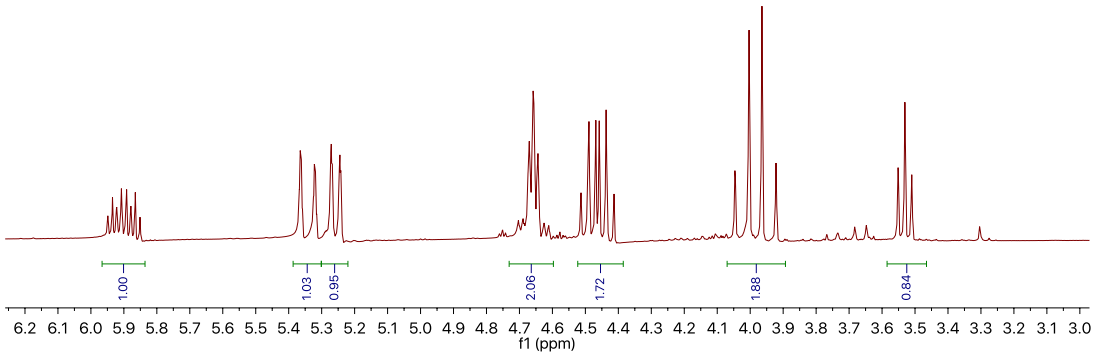

OH
O
O
N
Cbz
5.09
1.00
2.19
2.21
1.94
1.95
2.04
1.93
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

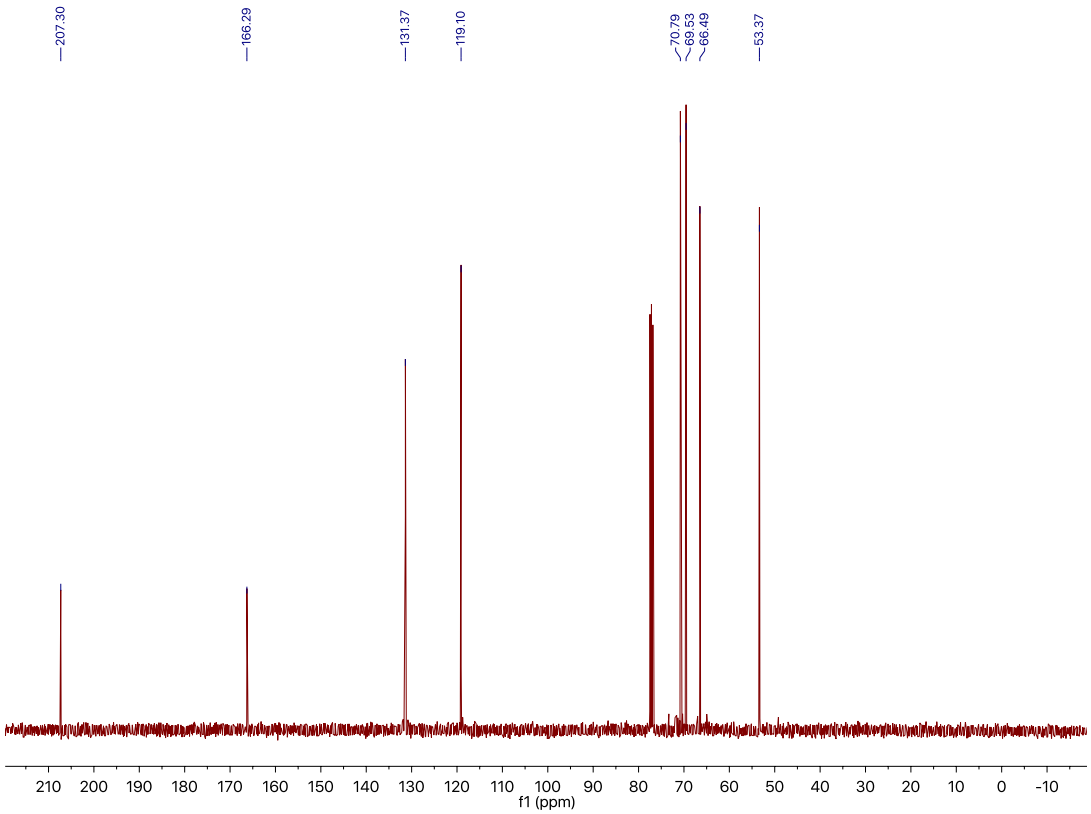
S1

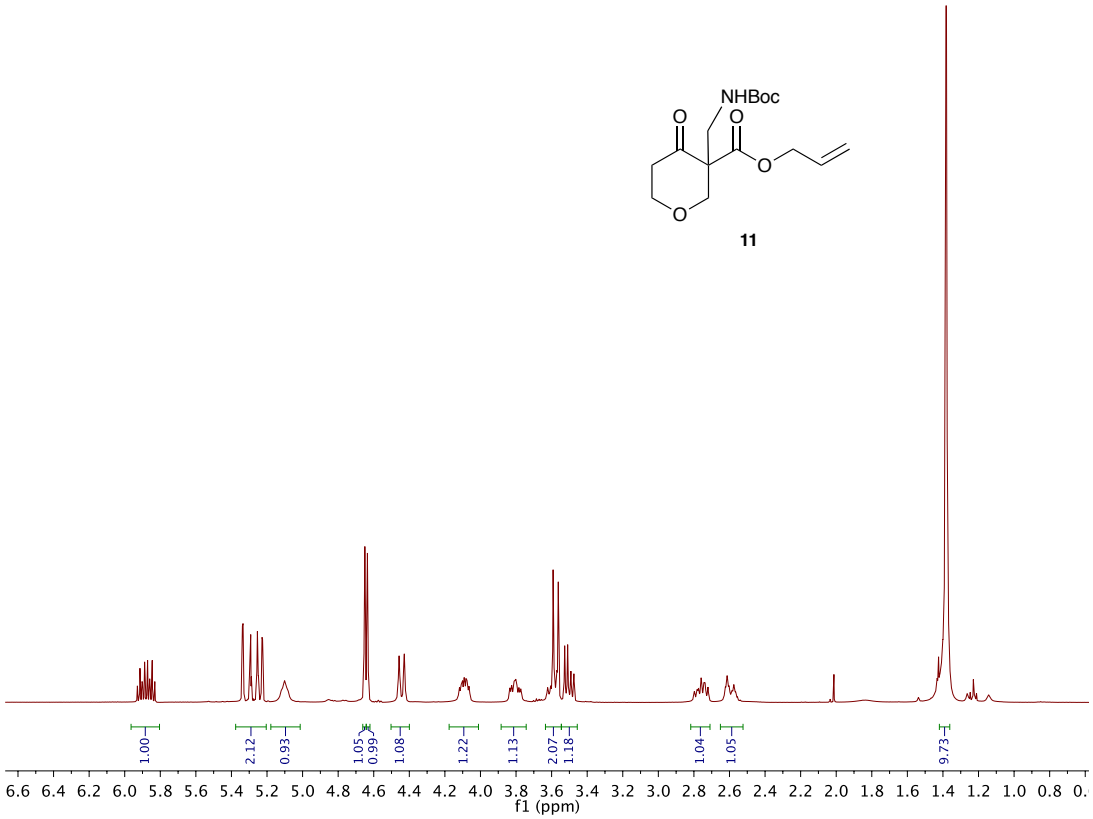

170.65
170.31
155.33
136.65
131.85
128.62
128.22
128.07
118.60
95.86
67.44
65.21
40.55
40.04
28.84
175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25
f1 (ppm)

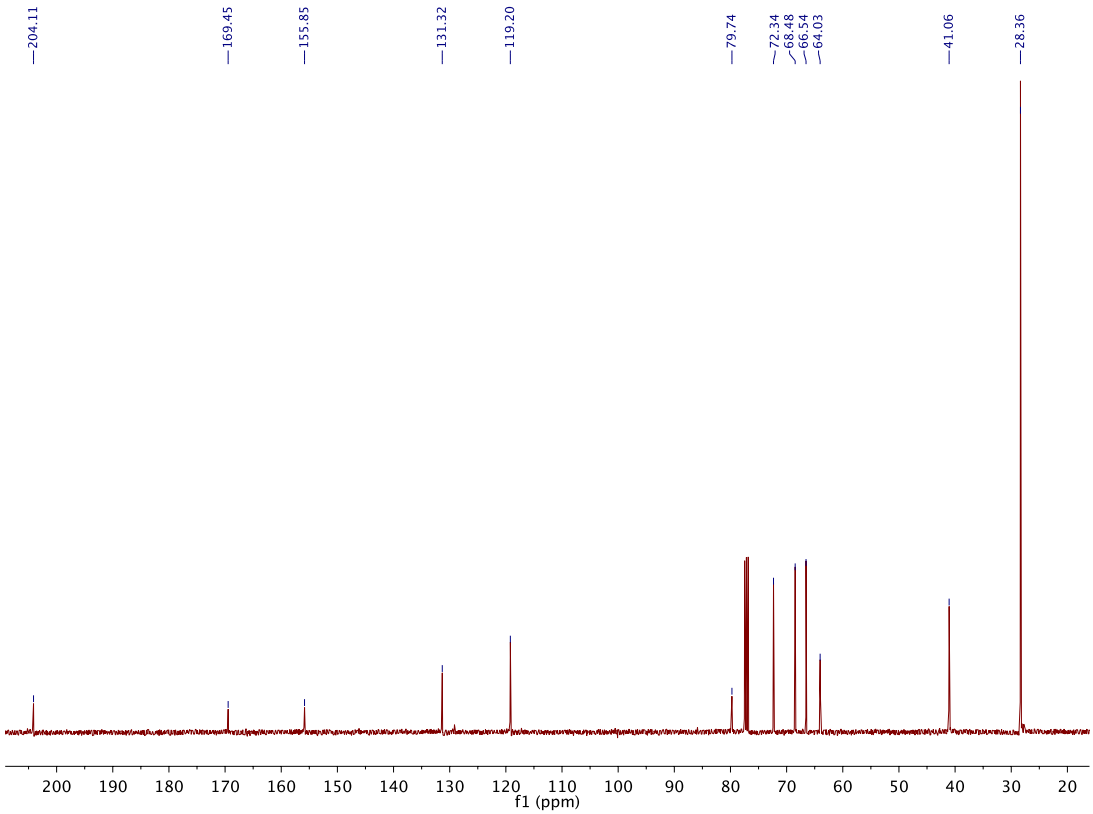


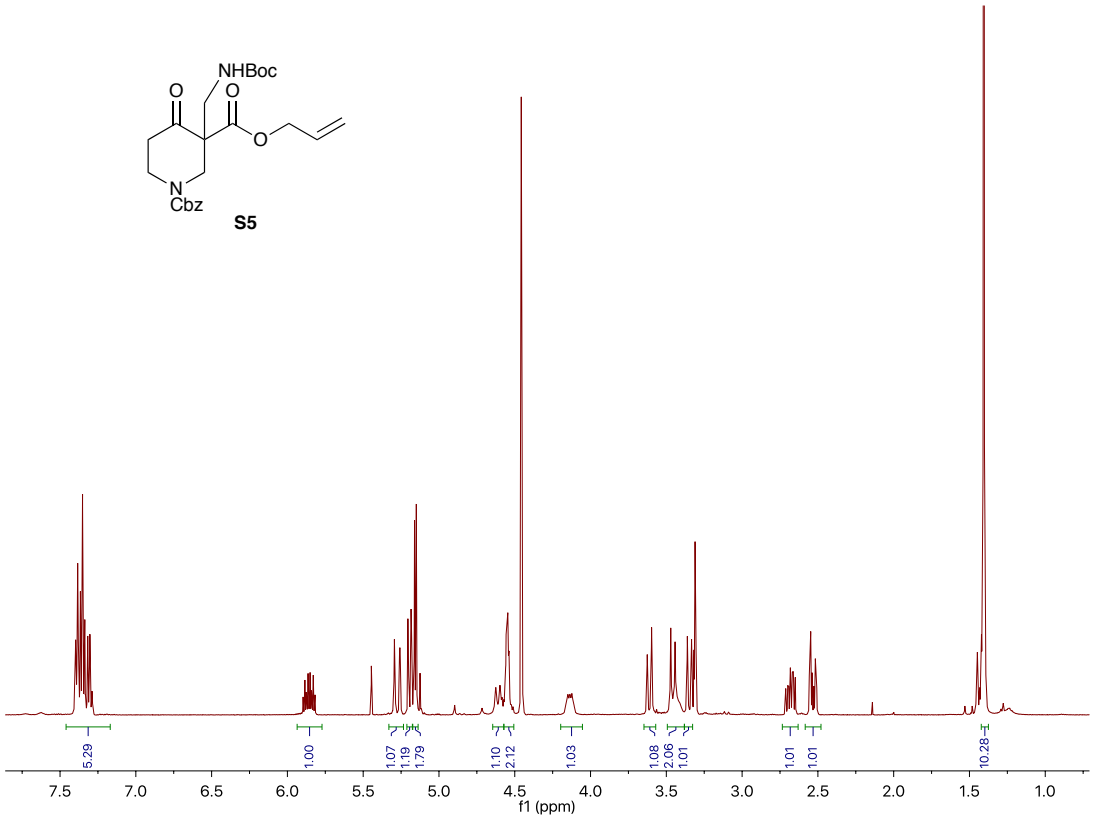
S3

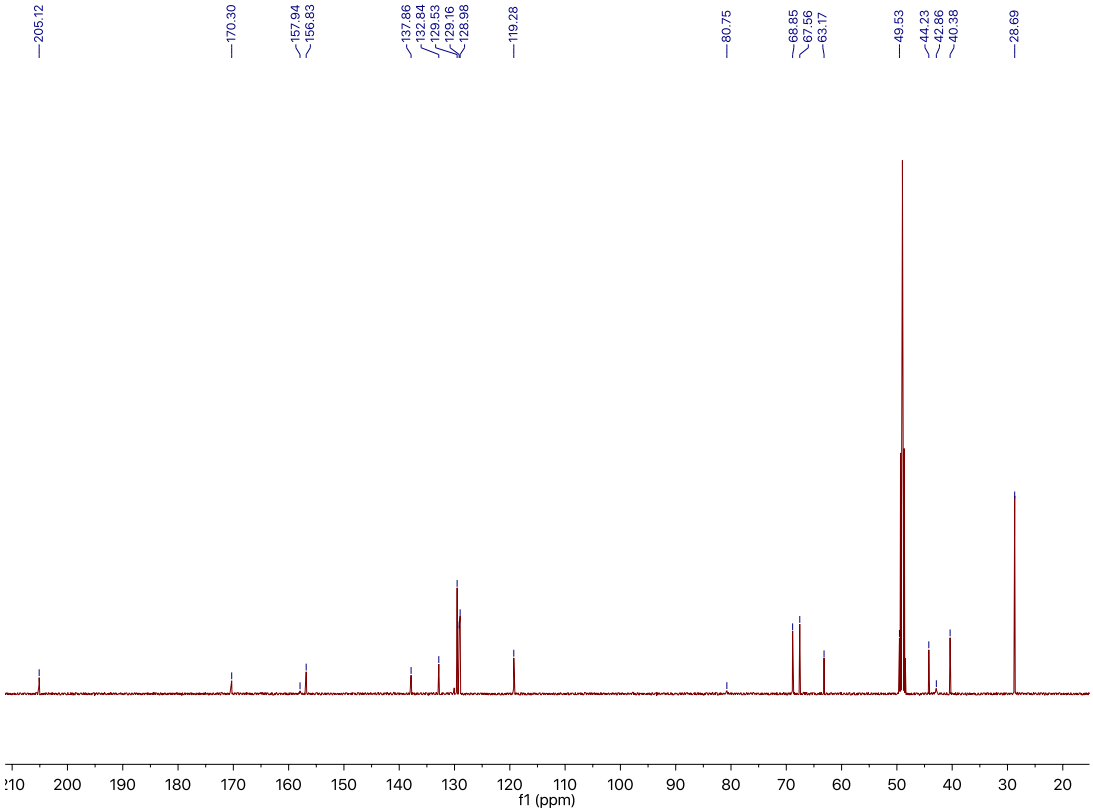

1.00
1.03
0.95
2.06
1.72
1.88
0.84
6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0
f1 (ppm)

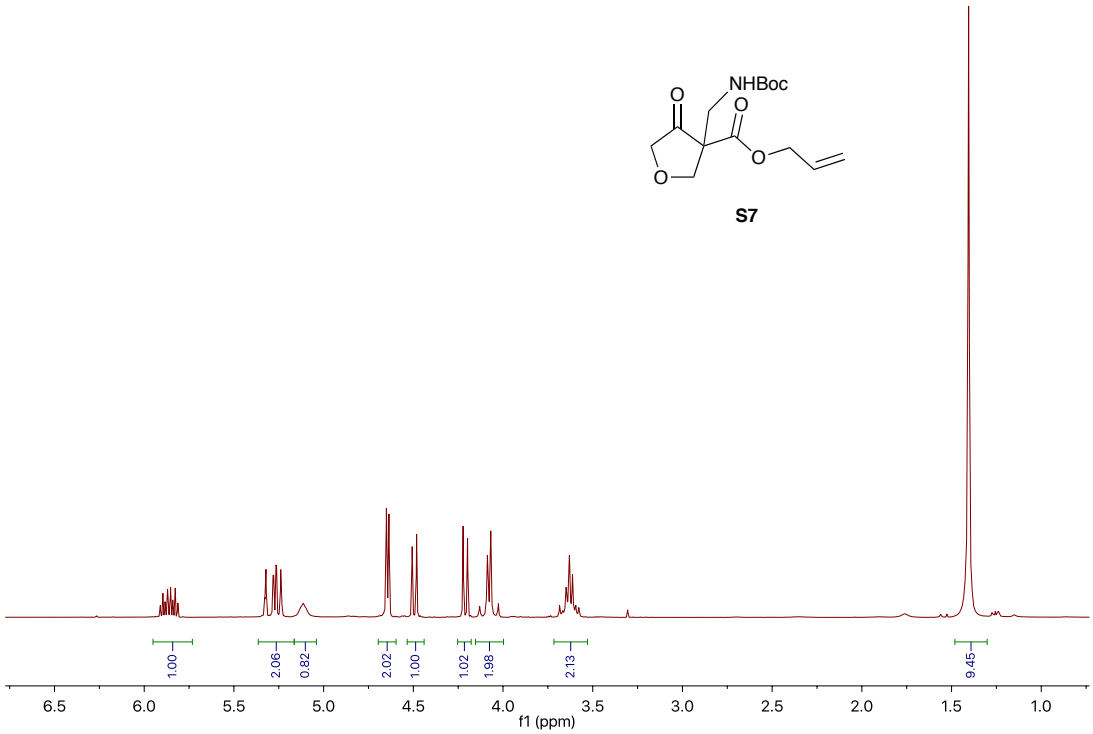

207.30
166.29
131.37
119.10
70.79
69.53
68.49
53.37
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


NHBoc
O
O
O
O
O
11
1.00
2.12
0.93
1.05
0.99
1.08
1.22
1.13
2.07
1.18
1.04
1.05
9.73
6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.
f1 (ppm)

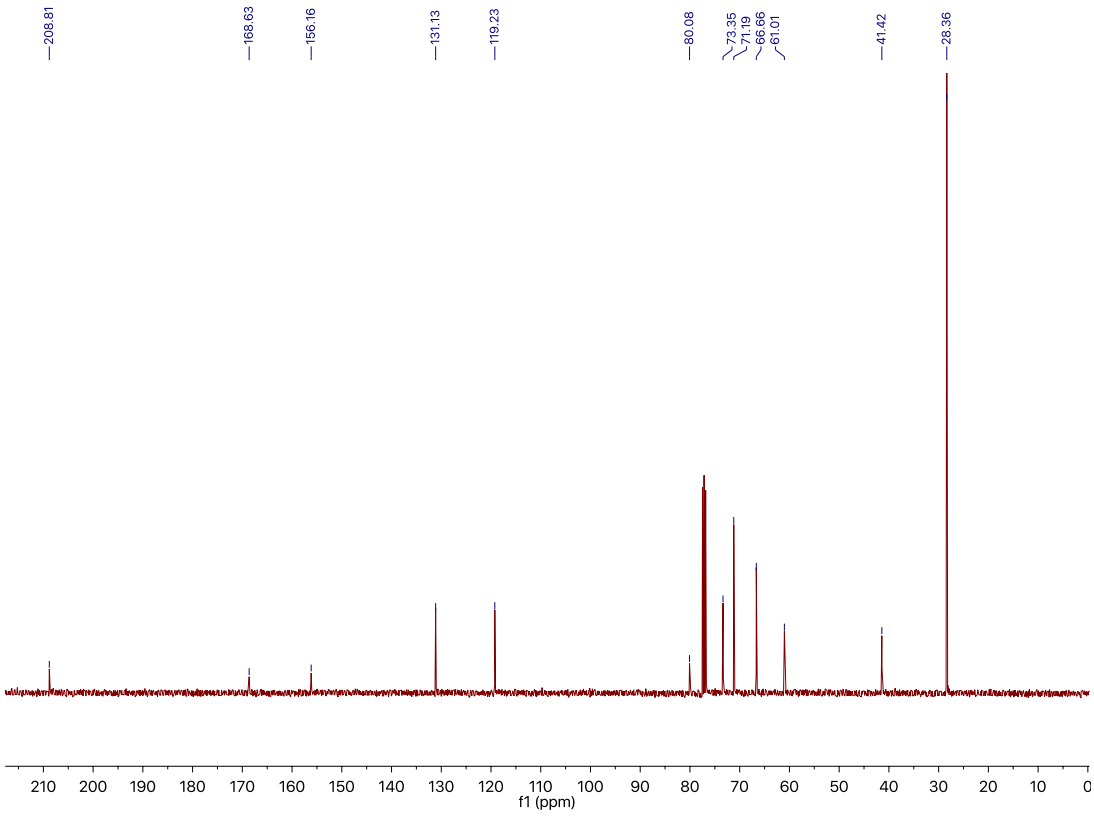

204.11
169.45
155.85
131.32
119.20
79.74
72.34
68.48
66.54
64.03
41.06
28.36
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

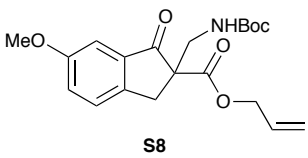

NHBoc
O
O
O
N
Cbz
S5
5.29
1.00
1.07
1.19
1.79
1.10
2.12
1.03
1.08
2.06
1.01
1.01
1.01
10.28
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


205.12
170.30
157.94
156.83
137.86
132.84
129.53
129.16
128.98
119.28
80.75
68.85
67.56
63.17
49.53
44.23
42.86
40.38
28.69
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)


NHBoc
O
O
O
O
O
1.00
2.06
0.82
2.02
1.00
1.02
1.98
2.13
9.45
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

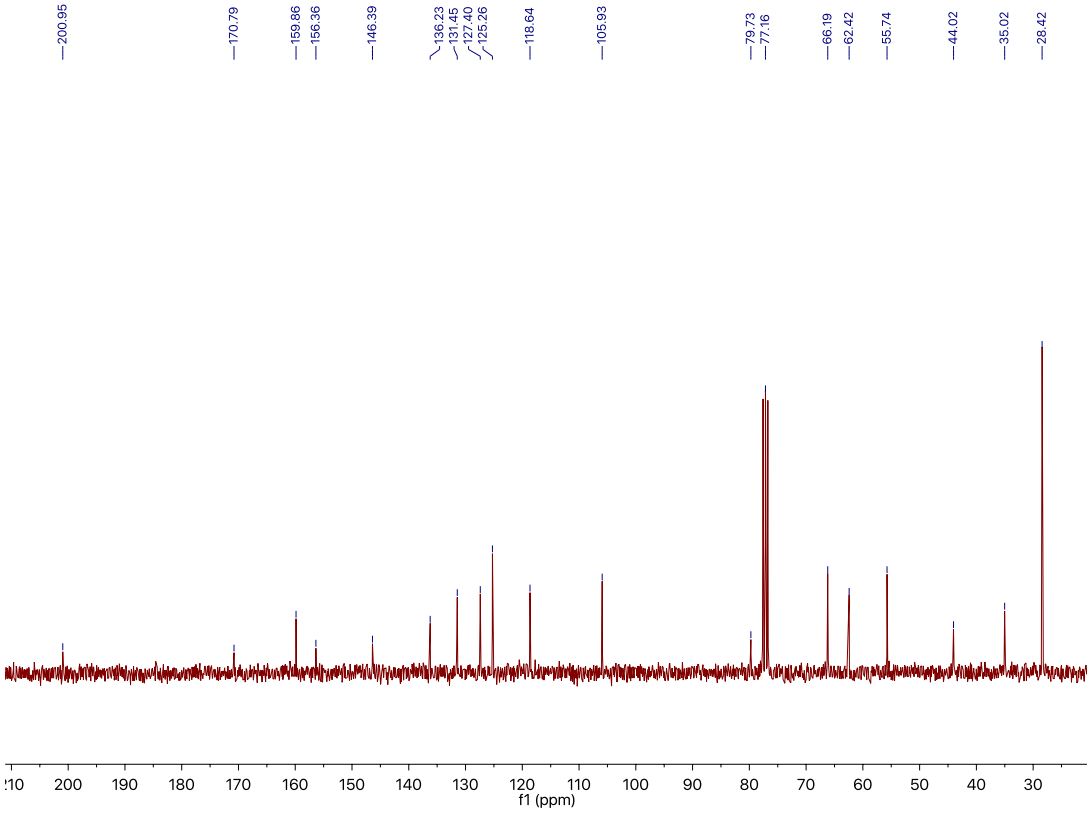
S7

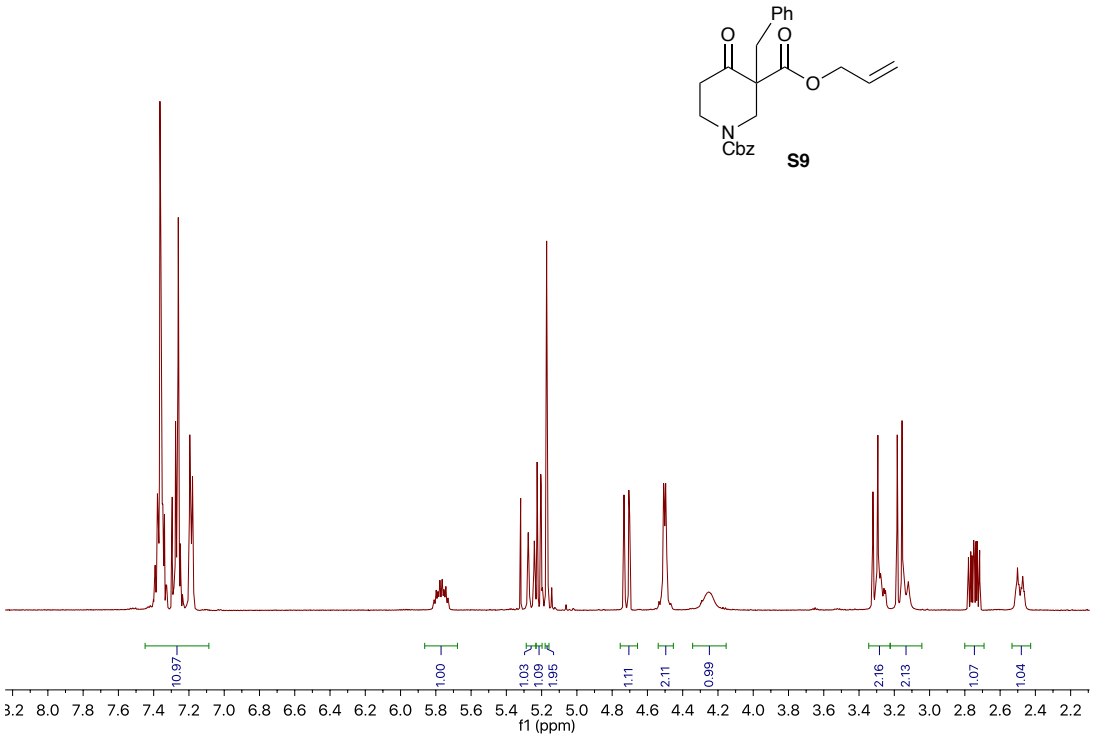

208.81
168.63
156.16
131.13
119.23
80.08
73.35
71.19
66.66
61.01
41.42
28.36
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MeO
O
NHBoc
O
O

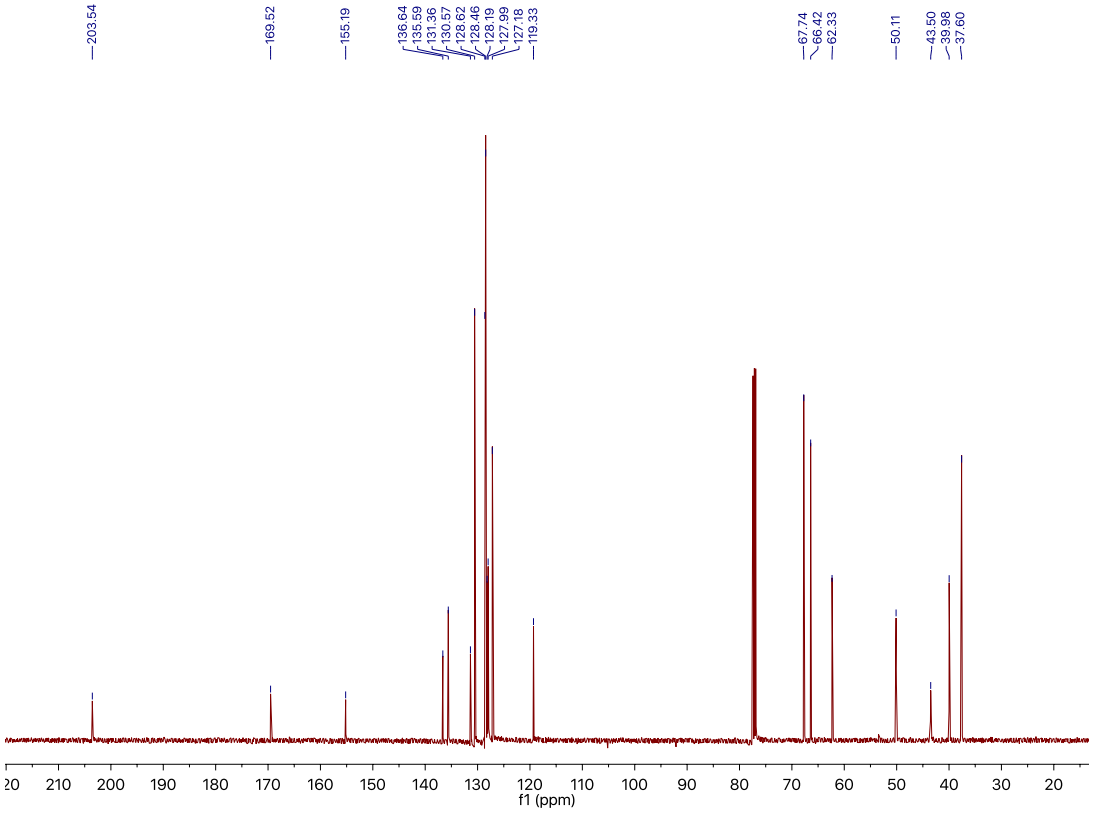
S8

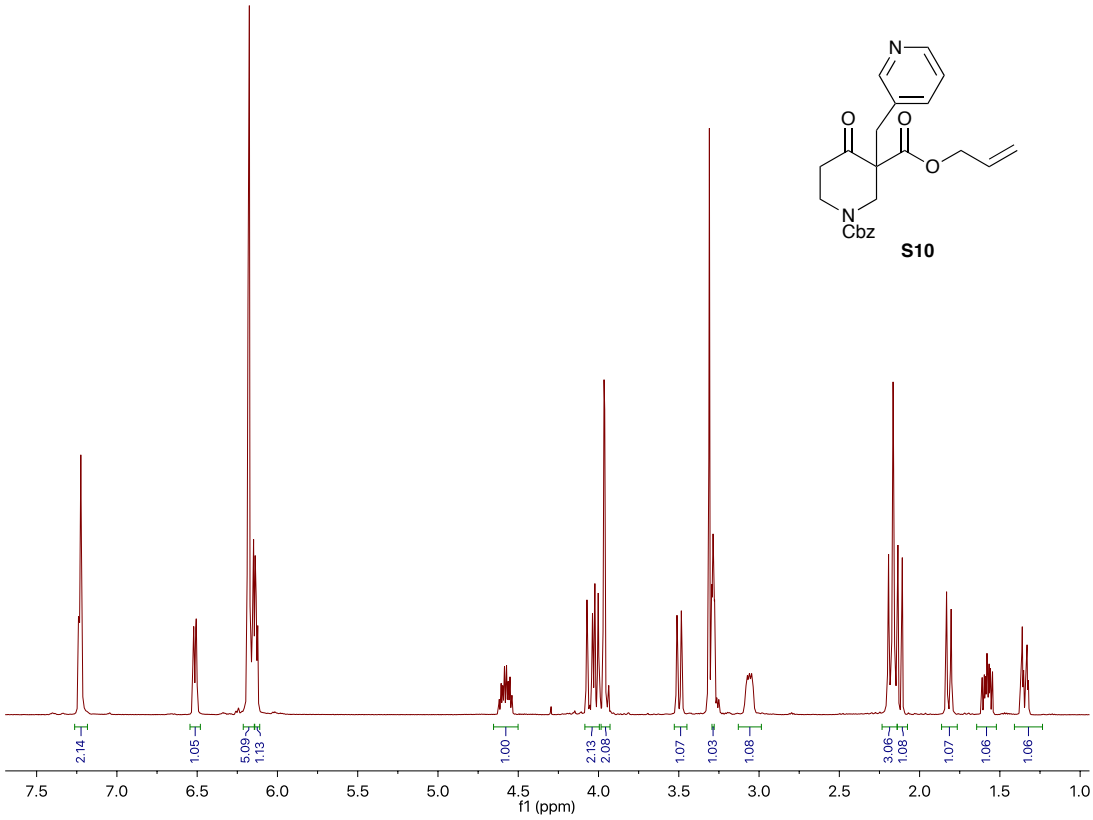
1.01
1.12
0.99
1.00
2.95
2.07
3.11
2.09
1.03
0.99
9.52
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


200.95
170.79
159.86
156.36
146.39
136.23
131.45
127.40
125.26
118.64
105.93
79.73
77.16
66.19
62.42
55.74
44.02
35.02
28.42
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)

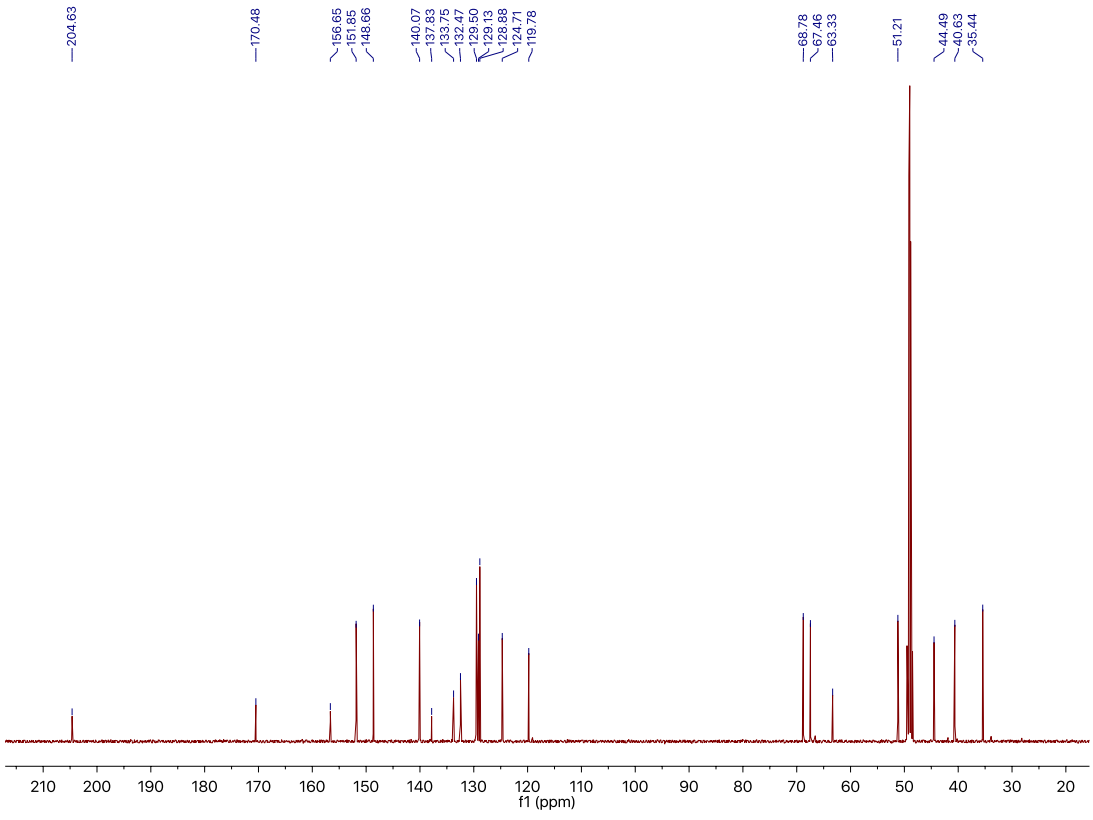

Ph
O
O
O
N
Cbz
10.97
1.00
1.03
1.09
1.95
1.11
2.11
0.99
2.16
2.13
1.07
1.04
f1 (ppm)

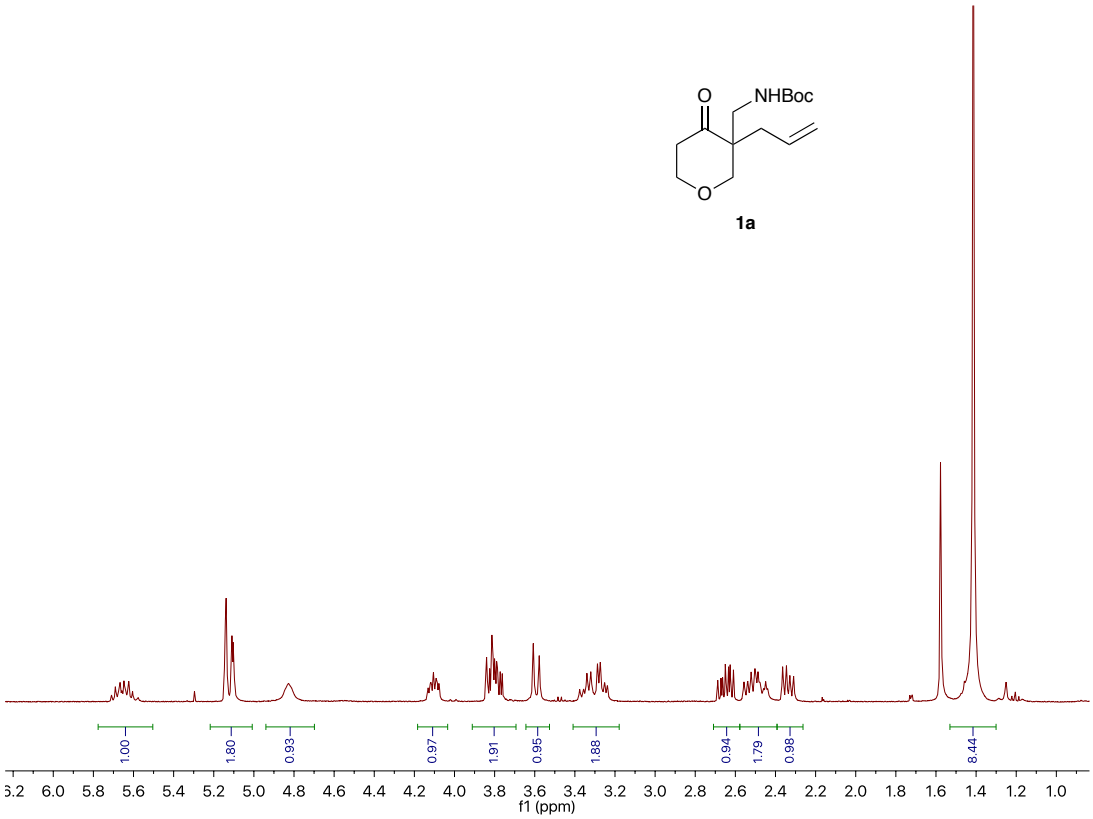
S9

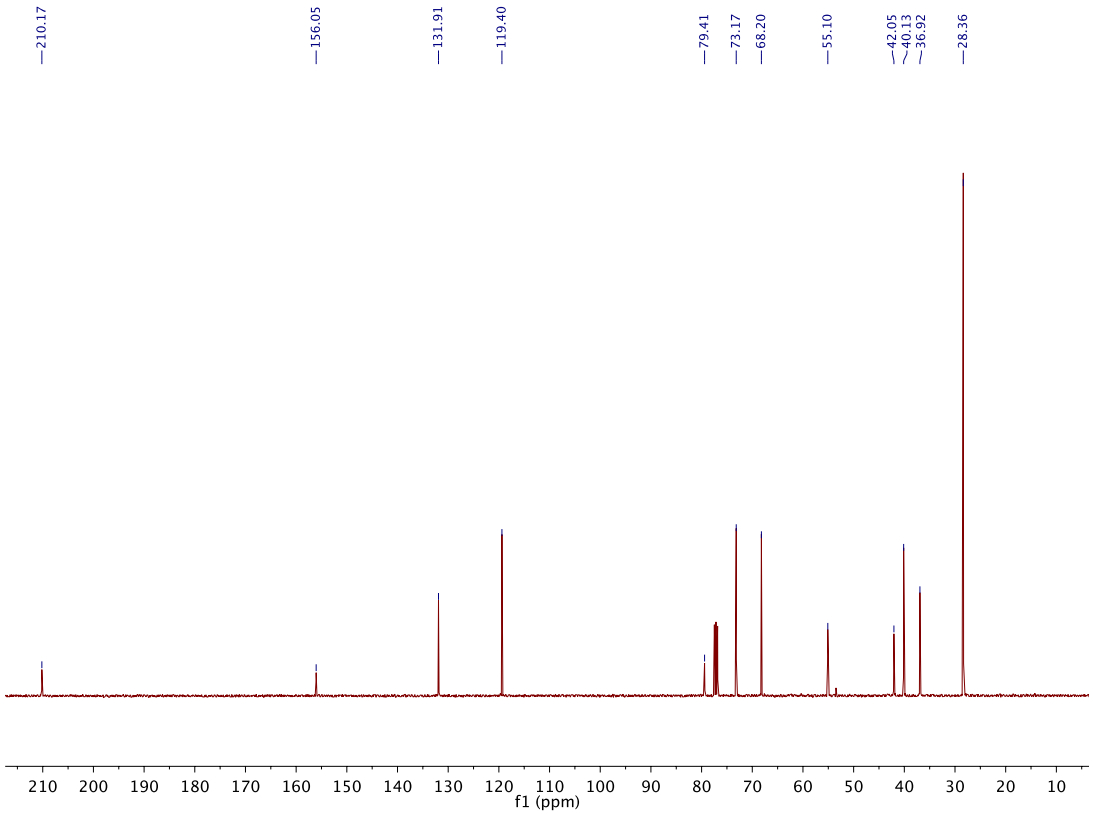

203.54
169.52
155.19
136.64
135.59
131.36
130.57
128.62
128.46
128.19
127.99
127.18
119.33
67.74
66.42
62.33
50.11
43.50
39.98
37.60
f1 (ppm)

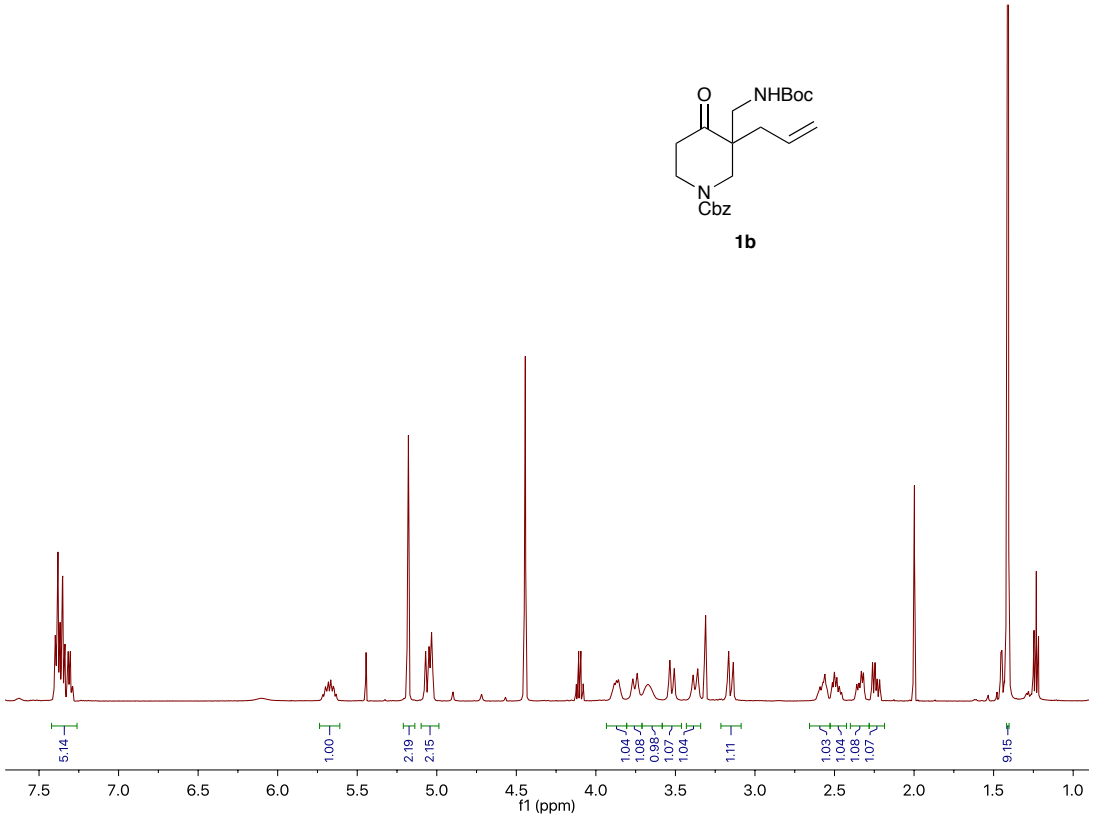

N
O
O
O
N
Cbz
2.14
1.05
5.09
1.13
1.00
2.13
2.08
1.07
1.03
1.08
3.06
1.08
1.07
1.06
1.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

S10

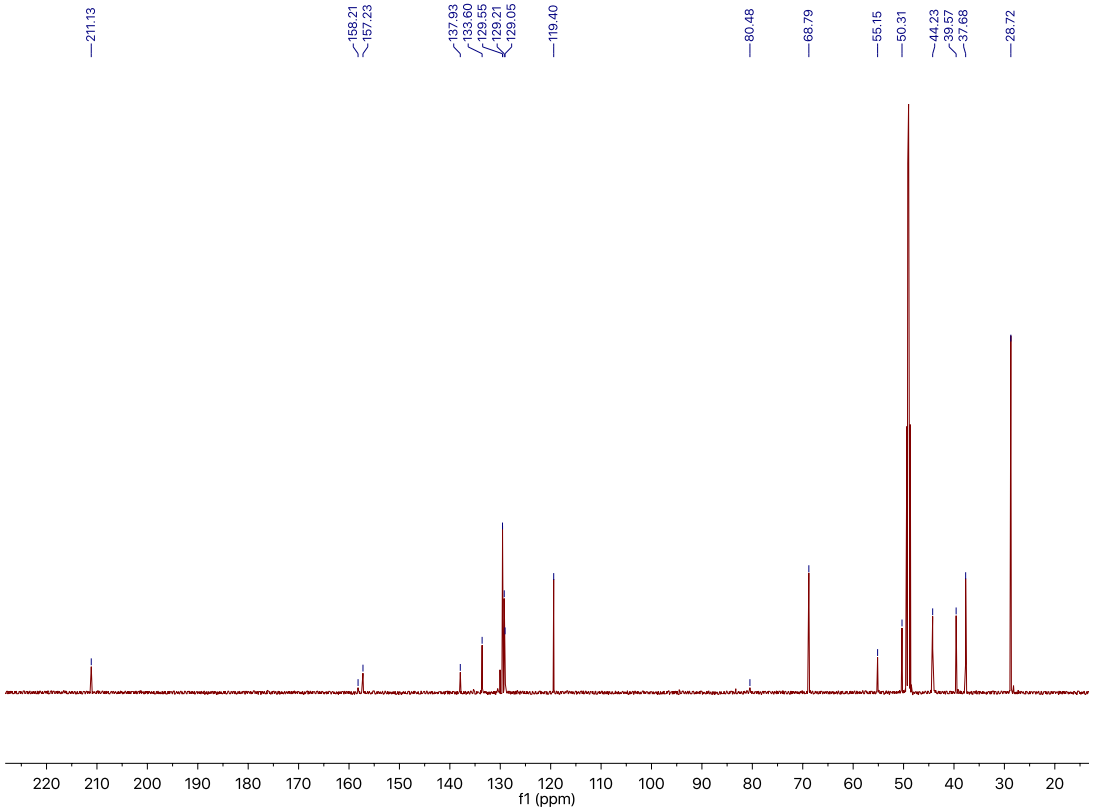

204.63
170.48
156.65
151.85
148.66
140.07
137.83
133.75
132.47
129.50
129.13
128.88
124.71
119.78
68.78
67.46
63.33
51.21
44.49
40.63
35.44
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

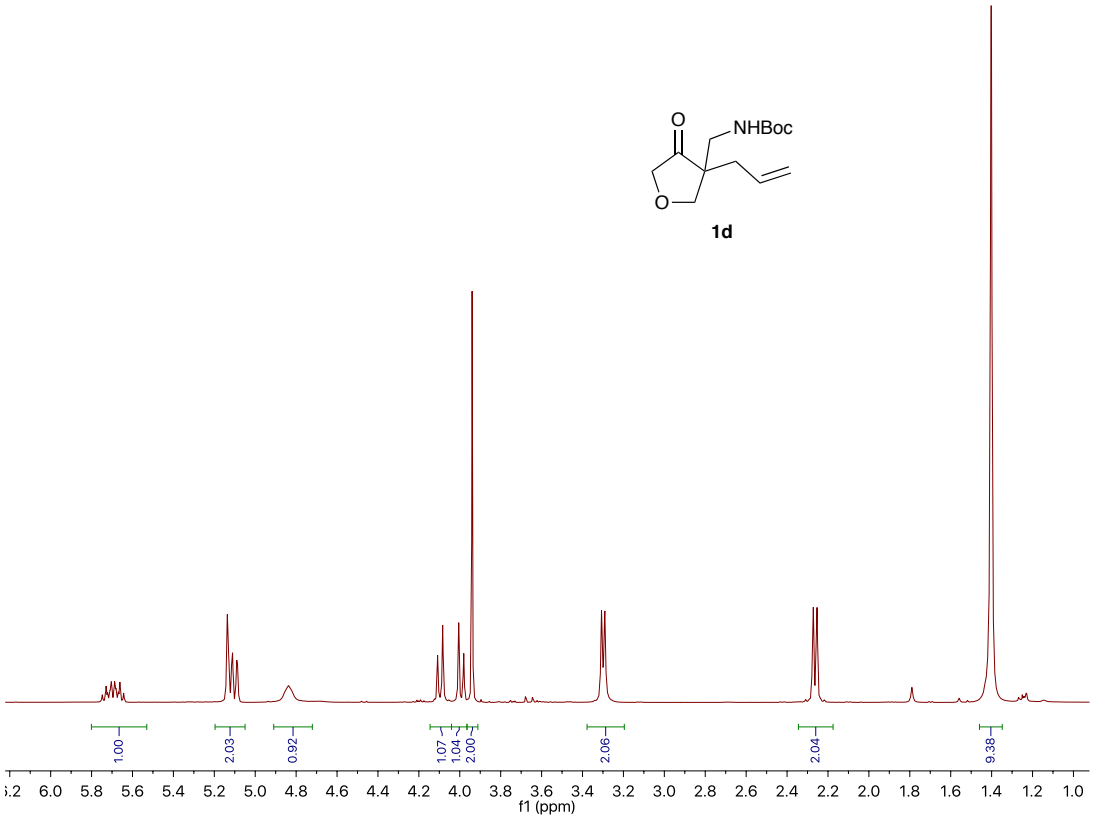

O
NHBoc
O
1a
1.00
1.80
0.93
0.97
1.91
0.95
1.88
0.94
1.79
0.98
8.44
f1 (ppm)

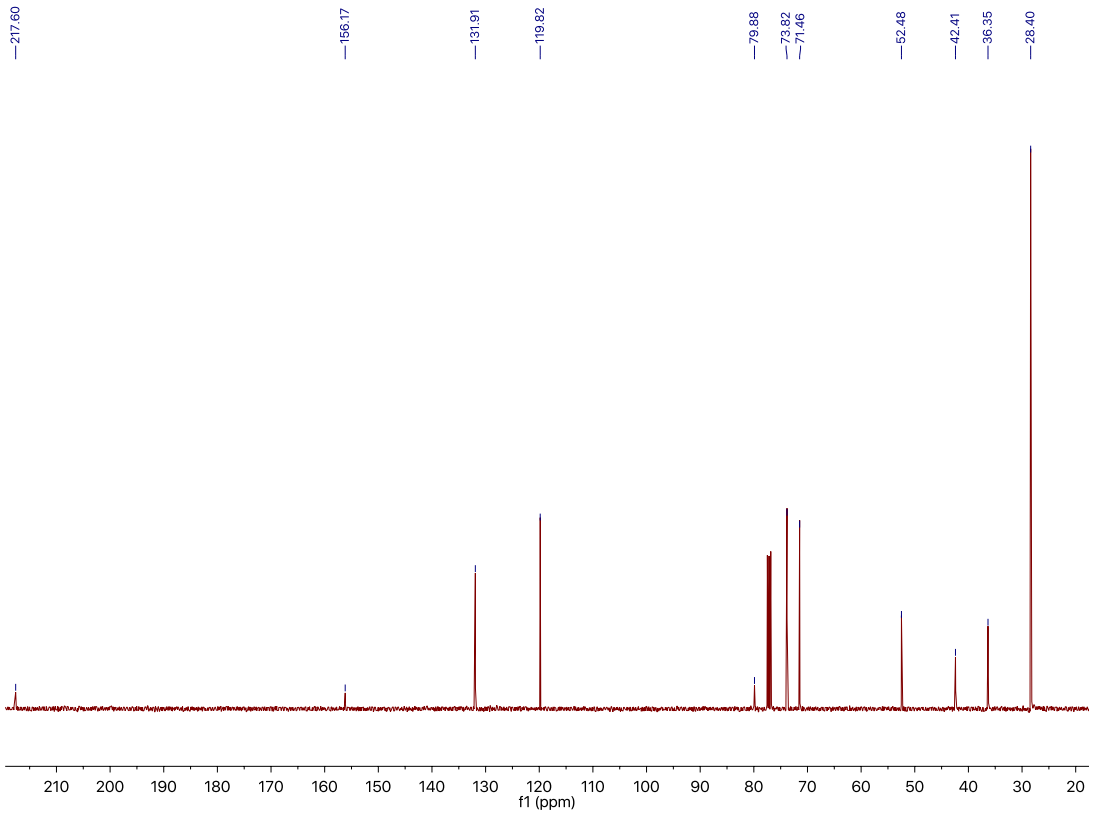

210.17
156.05
131.91
119.40
79.41
73.17
68.20
55.10
42.05
40.13
36.92
28.36
f1 (ppm)

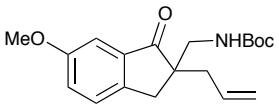

O
NHBoc
N
Cbz
5.14
1.00
2.19
2.15
1.04
1.08
0.98
1.07
1.04
1.11
1.03
1.04
1.08
1.07
9.15
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

1b


211.13
158.21
157.23
137.93
133.60
129.55
129.21
129.05
119.40
80.48
68.79
55.15
50.31
44.23
39.57
37.68
28.72
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

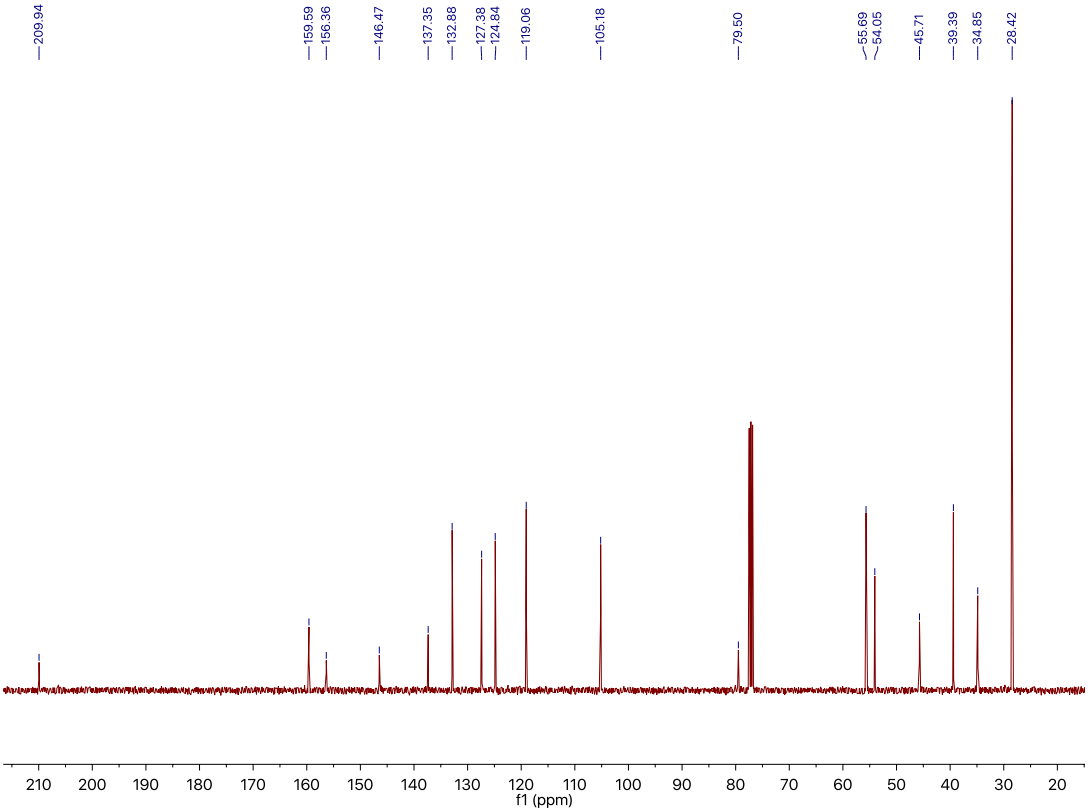

O
NHBoc
O
1d
1.00
2.03
0.92
1.07
1.04
2.00
2.06
2.04
9.38
f1 (ppm)

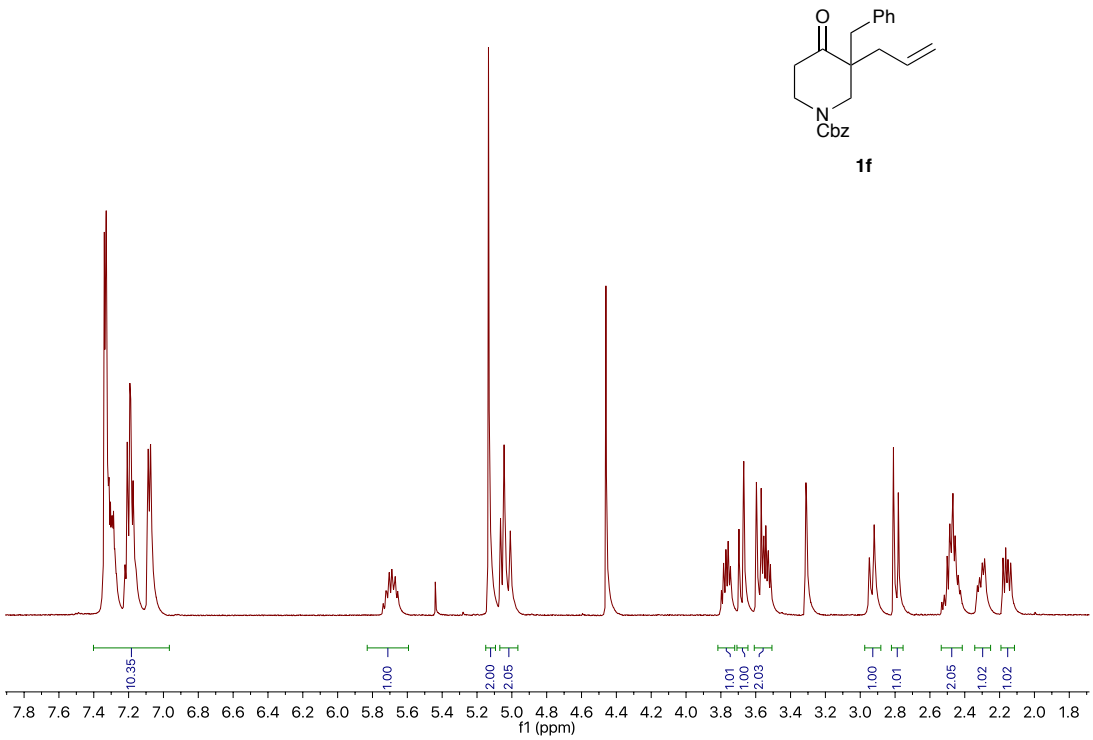

217.60
156.17
131.91
119.82
79.88
73.82
71.46
52.48
42.41
36.35
28.40
f1 (ppm)


MeO
O
NHBoc

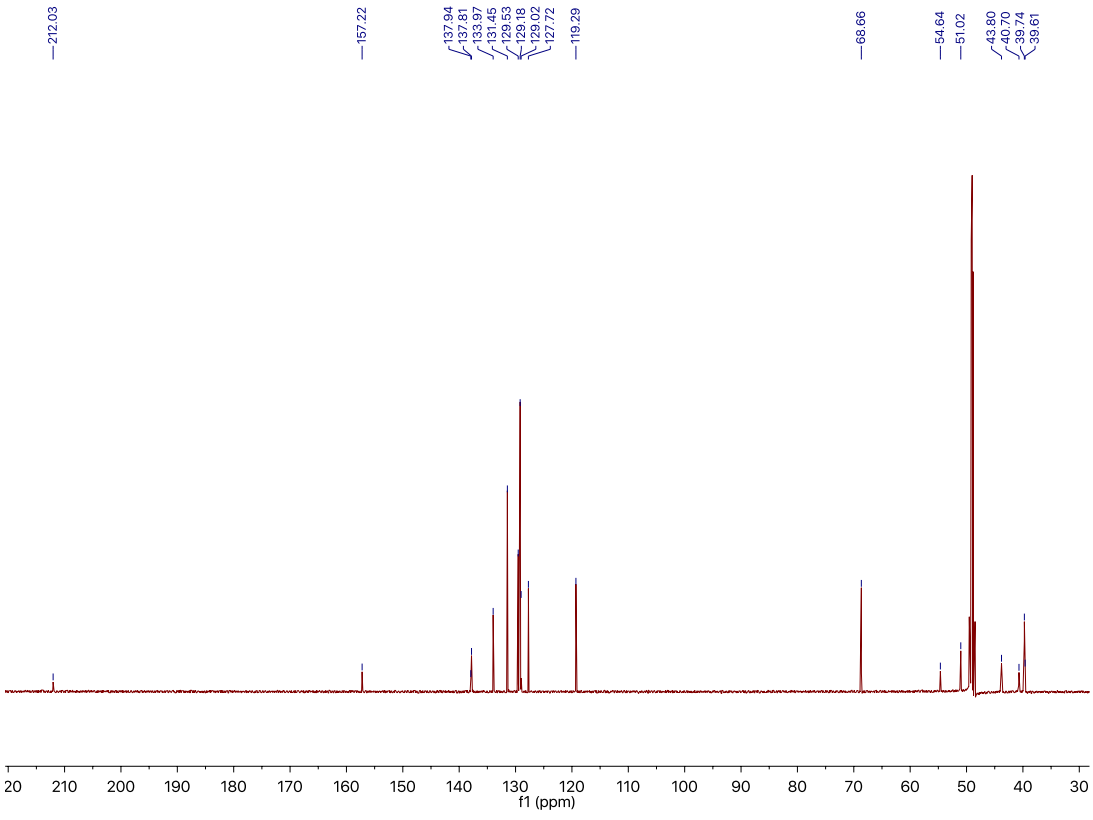
1e

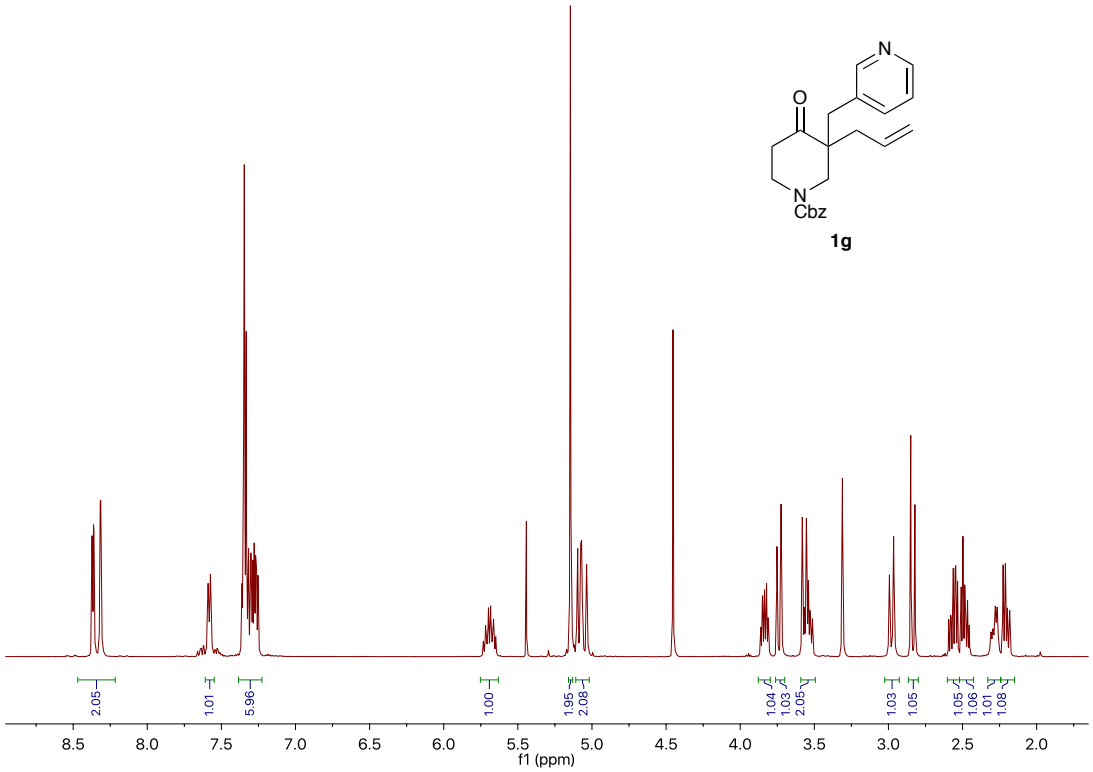
1.00
1.00
0.97
1.02
2.11
0.96
3.18
1.05
1.09
2.12
2.12
9.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

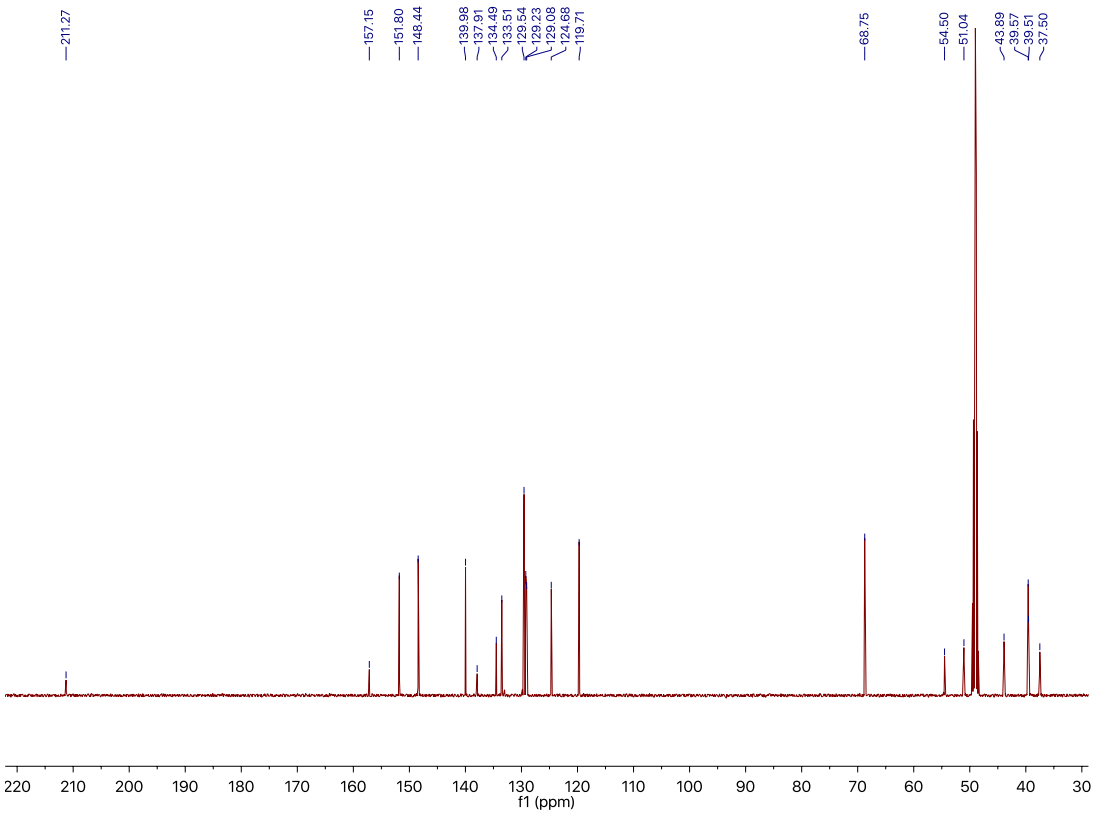

209.94
159.59
156.36
146.47
137.35
132.88
127.38
124.84
119.06
105.18
79.50
55.69
54.05
45.71
39.39
34.85
28.42
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

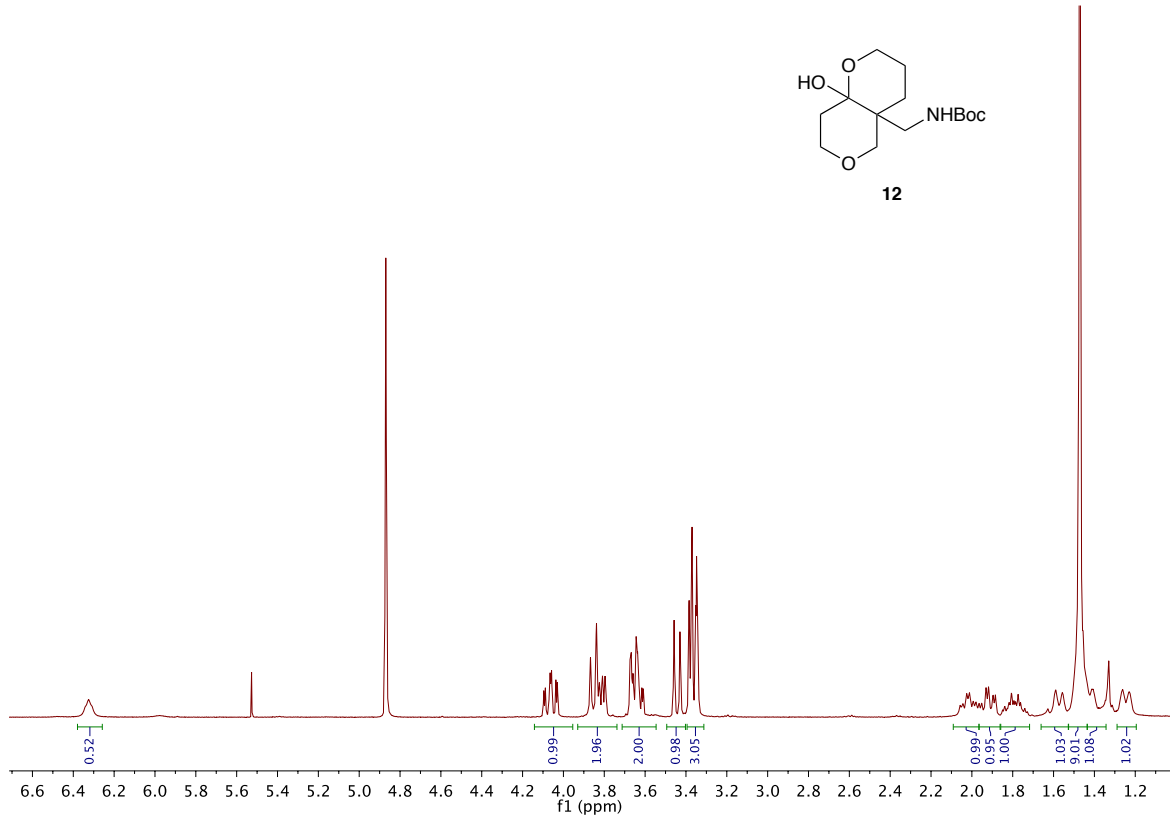

O
Ph
N
Cbz
10.35
1.00
2.00
2.05
1.01
1.00
2.03
1.00
1.01
2.05
1.02
1.02
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8
f1 (ppm)

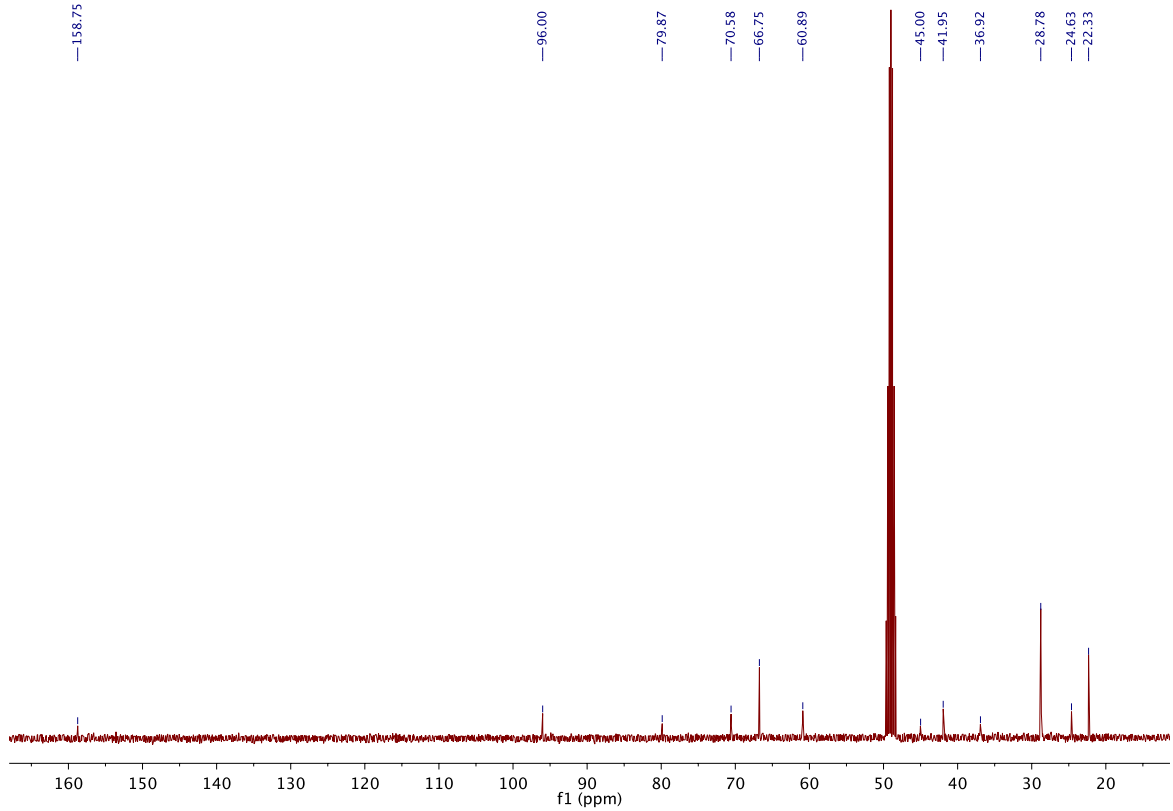
1f

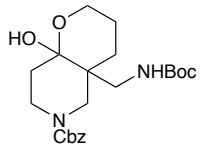

212.03
157.22
137.94
137.81
133.97
131.45
129.53
129.18
129.02
127.72
119.29
68.66
54.64
51.02
43.80
40.70
39.74
39.61
20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30
f1 (ppm)


N
O
N
Cbz
1g
2.05
1.01
5.96
1.00
1.95
2.08
1.04
1.03
2.05
1.03
1.05
1.05
1.06
1.01
1.08
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)


211.27
157.15
151.80
148.44
139.98
137.91
134.49
133.51
129.54
129.23
129.08
124.68
119.71
68.75
54.50
51.04
43.89
39.57
39.51
37.50
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)

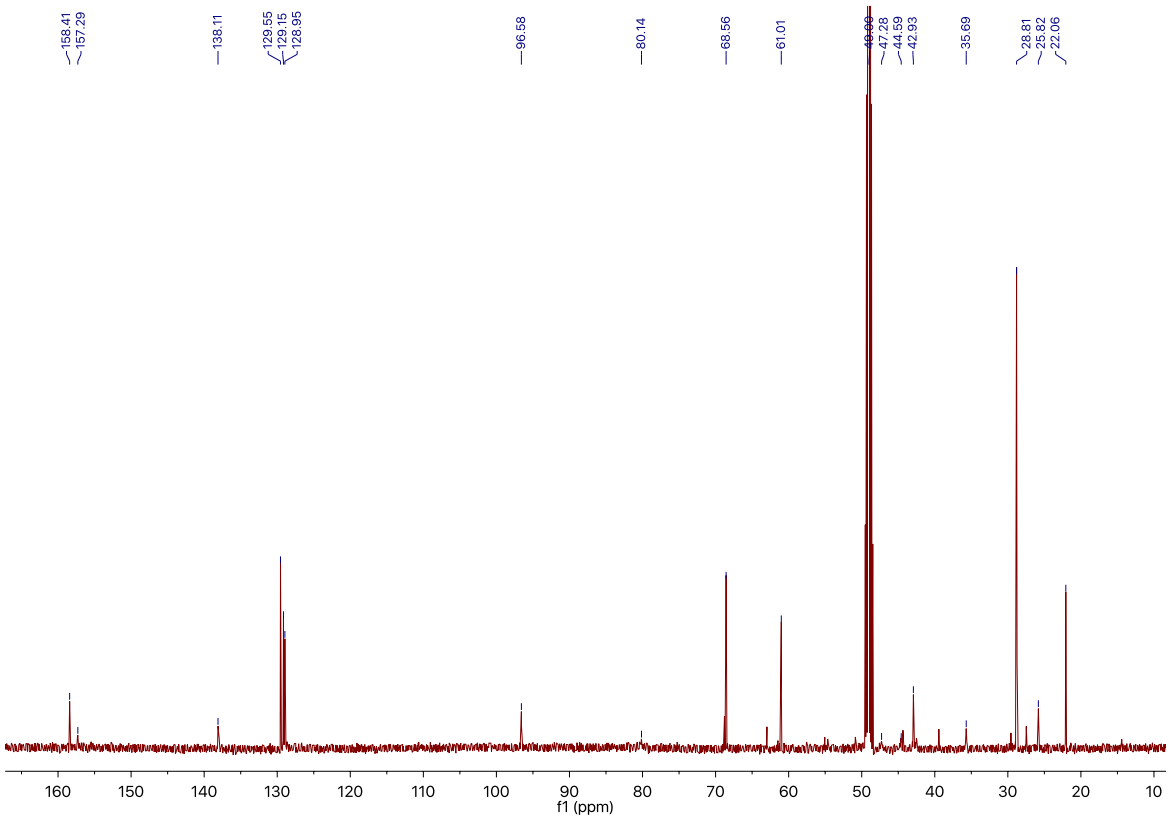

HO
O
NHBoc
O
12
0.52
0.99
1.96
2.00
0.98
3.05
0.99
0.95
1.00
1.03
9.01
1.08
1.02
f1 (ppm)

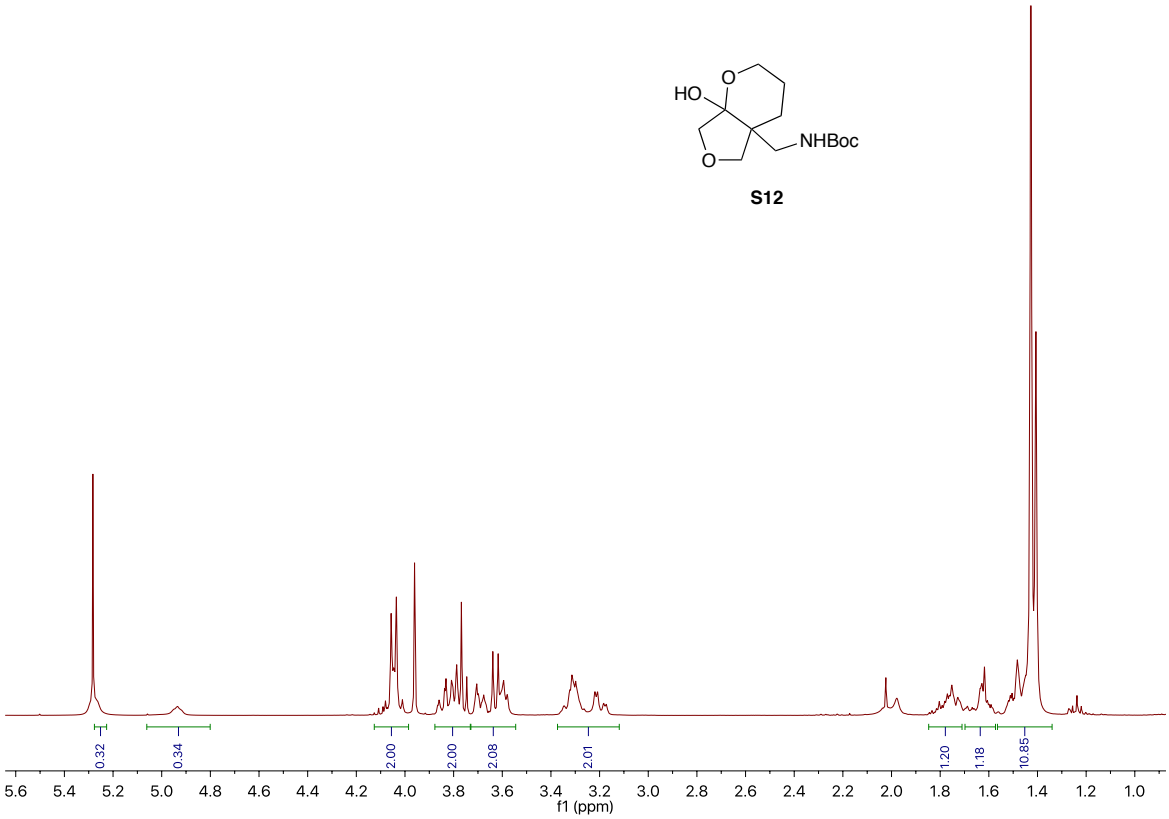

158.75
96.00
79.87
70.58
66.75
60.89
45.00
41.95
36.92
28.78
24.63
22.33
f1 (ppm)


HO
O
NHBoc
N
Cbz

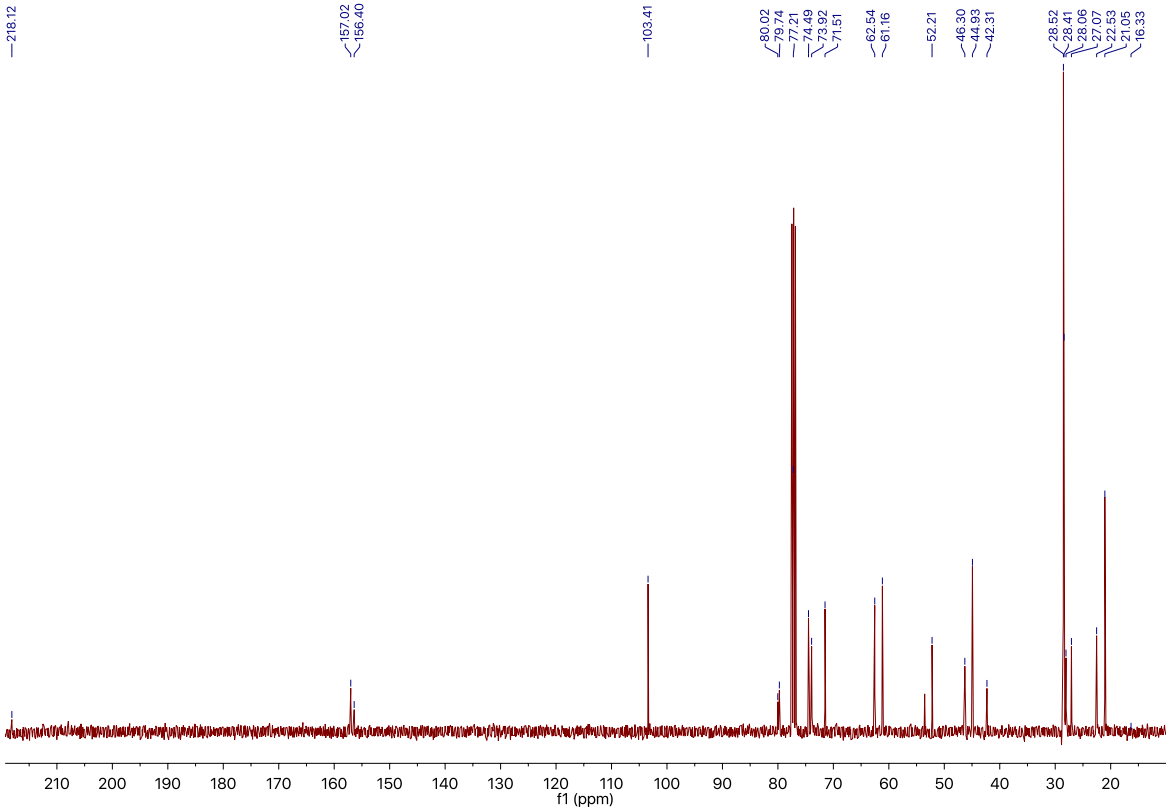
S11

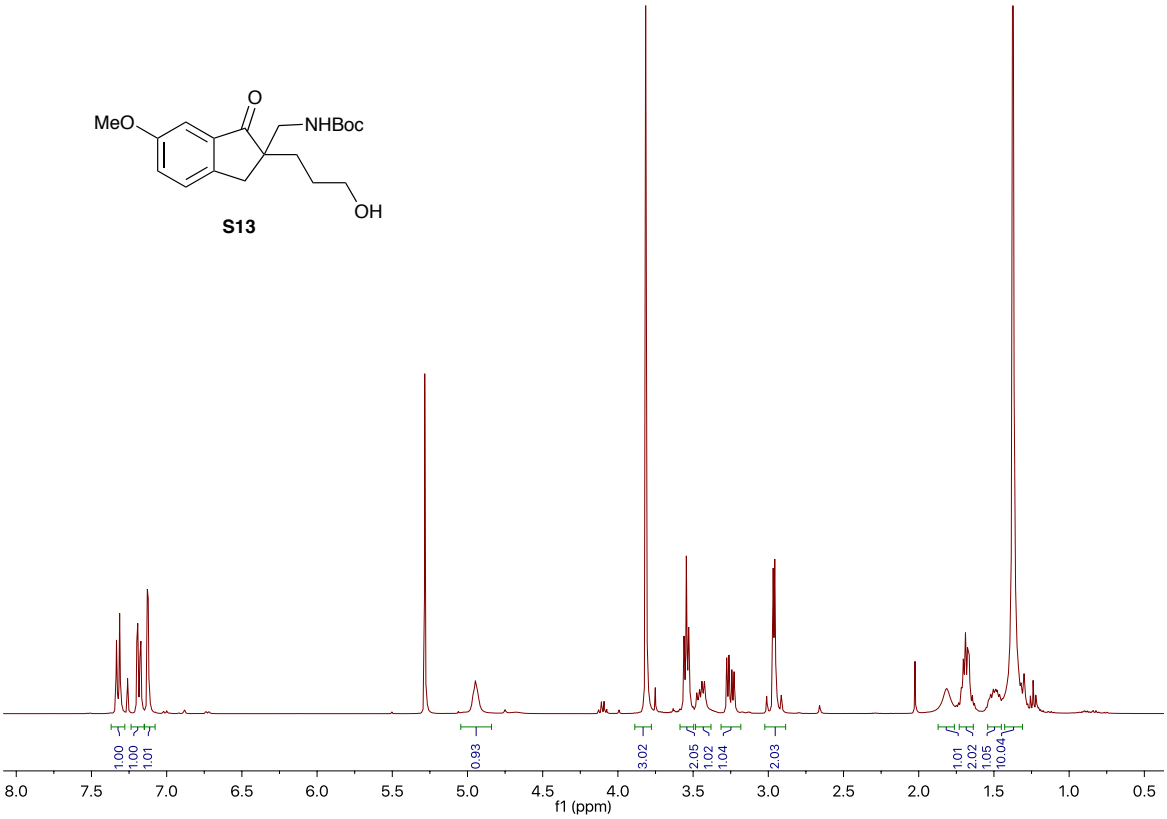
5.46
2.21
1.96
1.97
3.06
1.00
0.82
0.89
1.89
1.27
9.36
1.24
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


158.41
157.29
138.11
129.55
129.15
128.95
96.58
80.14
68.56
61.01
49.00
47.28
44.59
42.93
35.69
28.81
25.82
22.06
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

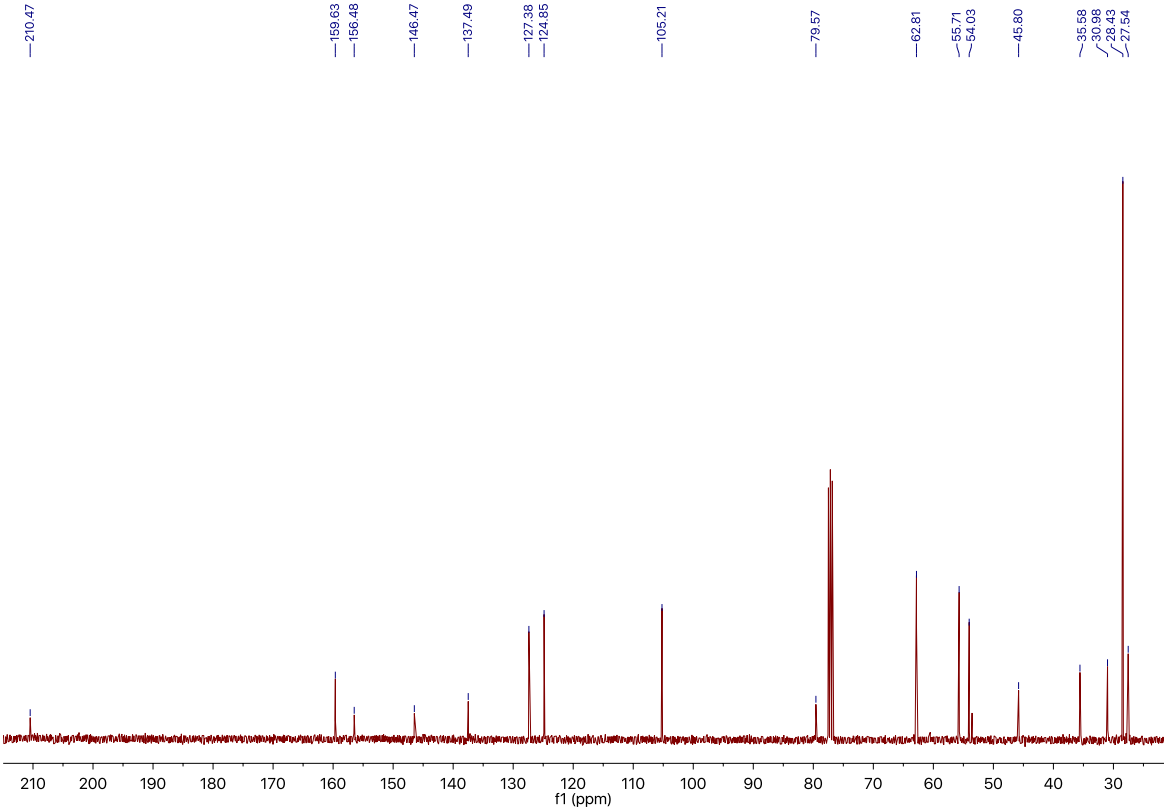

HO
O
O
NHBoc
0.32
0.34
2.00
2.00
2.08
2.01
1.20
1.18
10.85
f1 (ppm)

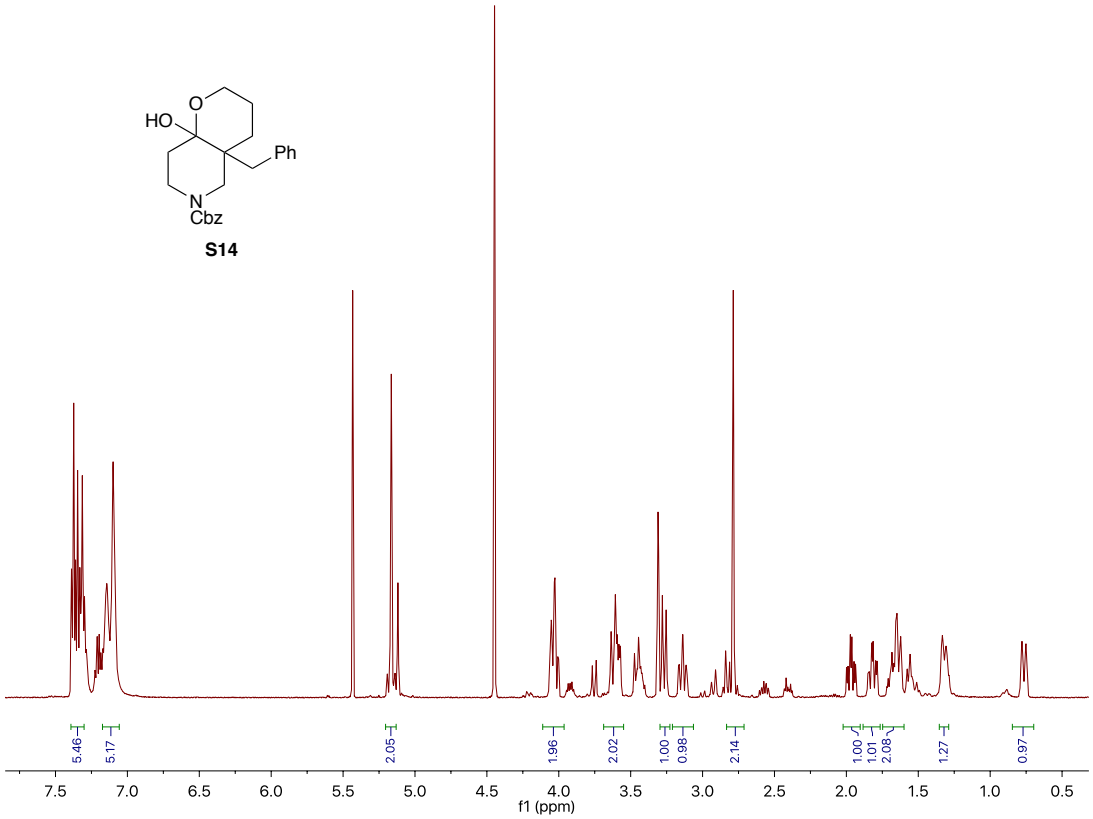
S12

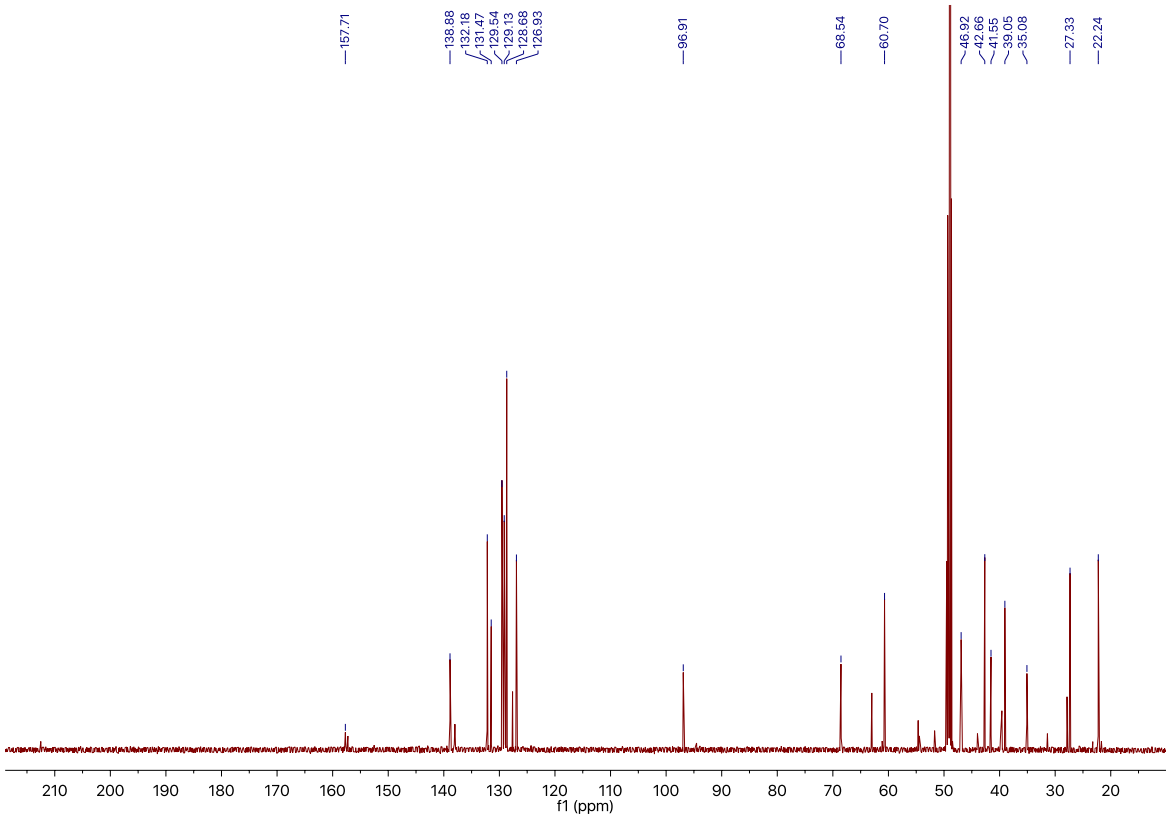

218.12
157.02
156.40
103.41
80.02
79.74
77.21
74.49
73.92
71.51
62.54
61.16
52.21
46.30
44.93
42.31
28.52
28.41
28.06
27.07
22.53
21.05
16.33
f1 (ppm)

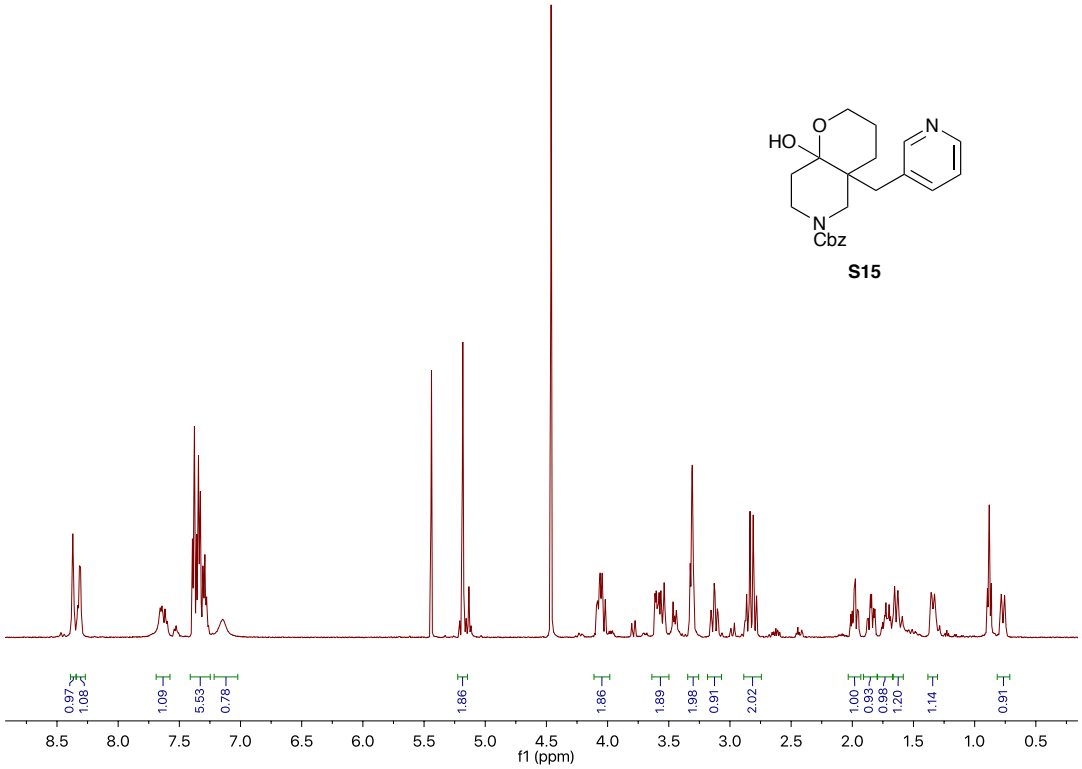

MeO
O
NHBoc
OH
1.00
1.00
1.01
0.93
3.02
2.05
1.02
1.04
2.03
1.01
2.02
1.05
10.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

S13

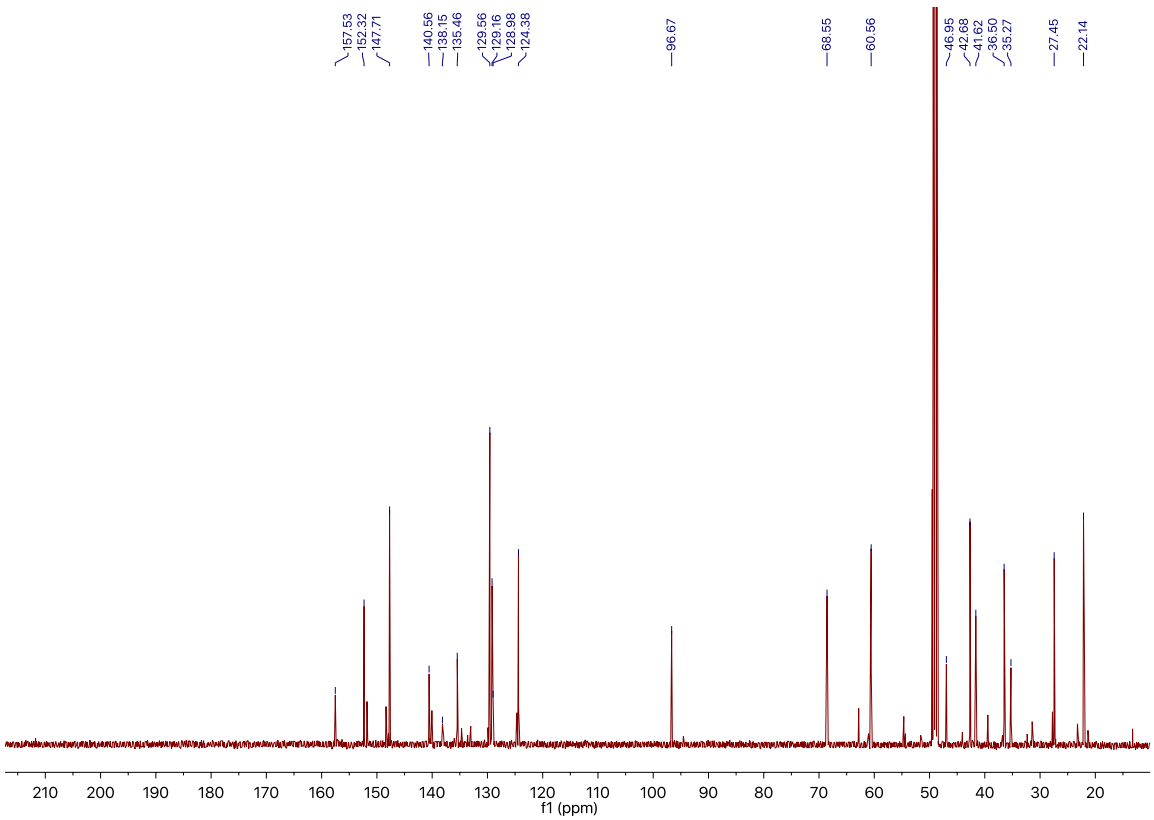

210.47
159.63
156.48
146.47
137.49
127.38
124.85
105.21
79.57
62.81
55.71
54.03
45.80
35.58
30.98
28.43
27.54
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)

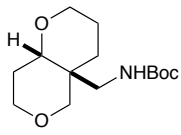

HO
O
Ph
N
Cbz
S14
5.46
5.17
2.05
1.96
2.02
1.00
0.98
2.14
1.00
1.01
2.08
1.27
0.97
f1 (ppm)


157.71
138.88
132.18
131.47
129.54
129.13
128.68
126.93
96.91
68.54
60.70
46.92
42.66
41.55
39.05
35.08
27.33
22.24
f1 (ppm)


HO
O
N
N
Cbz
0.97
1.08
1.09
5.53
0.78
1.86
1.86
1.89
1.98
0.91
2.02
1.00
0.93
0.98
1.20
1.14
0.91
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

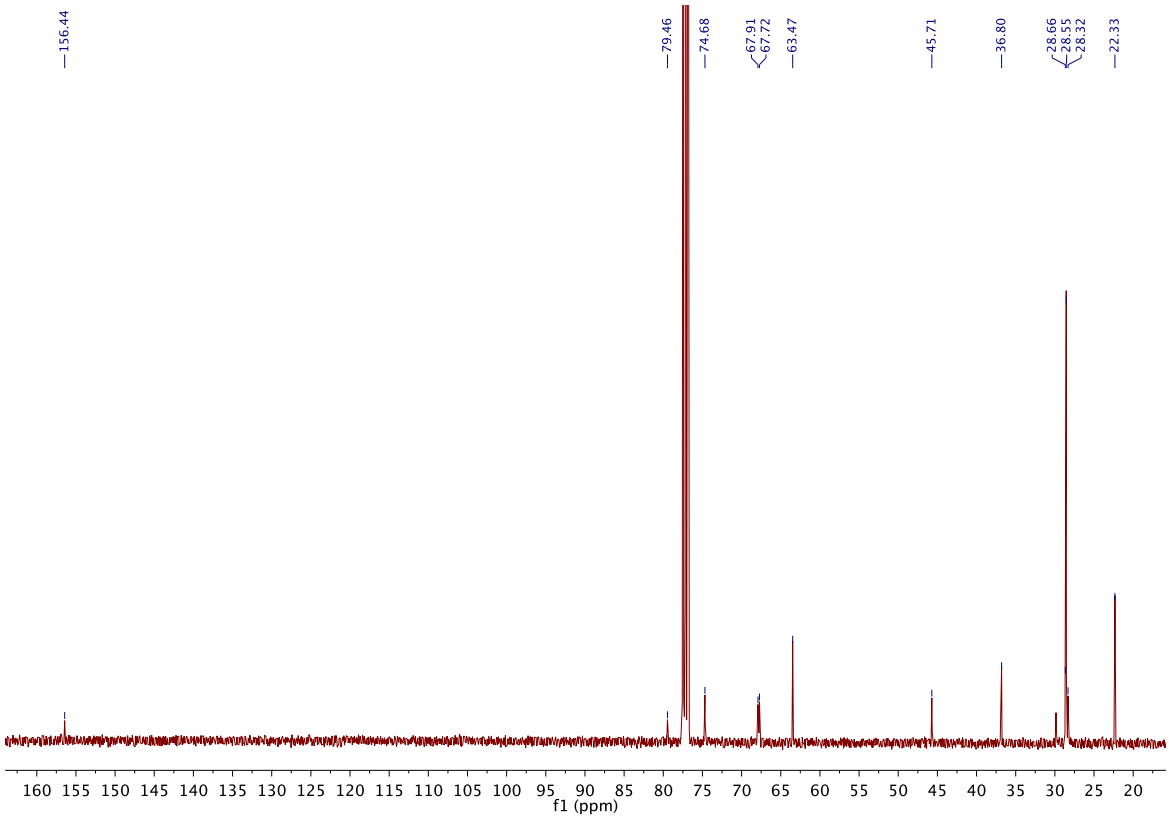
S15

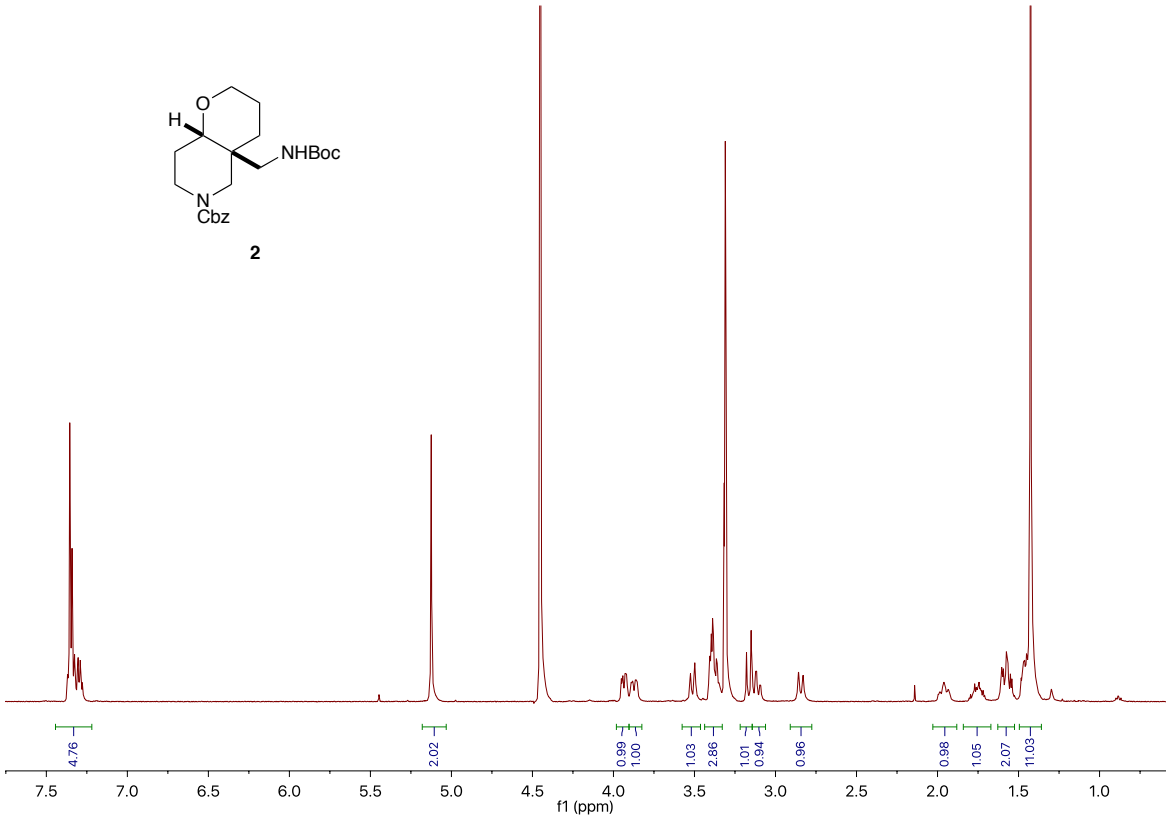

157.53
152.32
147.71
140.56
138.15
135.46
129.56
129.16
128.98
124.38
96.67
68.55
60.56
46.95
42.68
41.62
36.50
35.27
27.45
22.14
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)


O
H
NHBoc
O

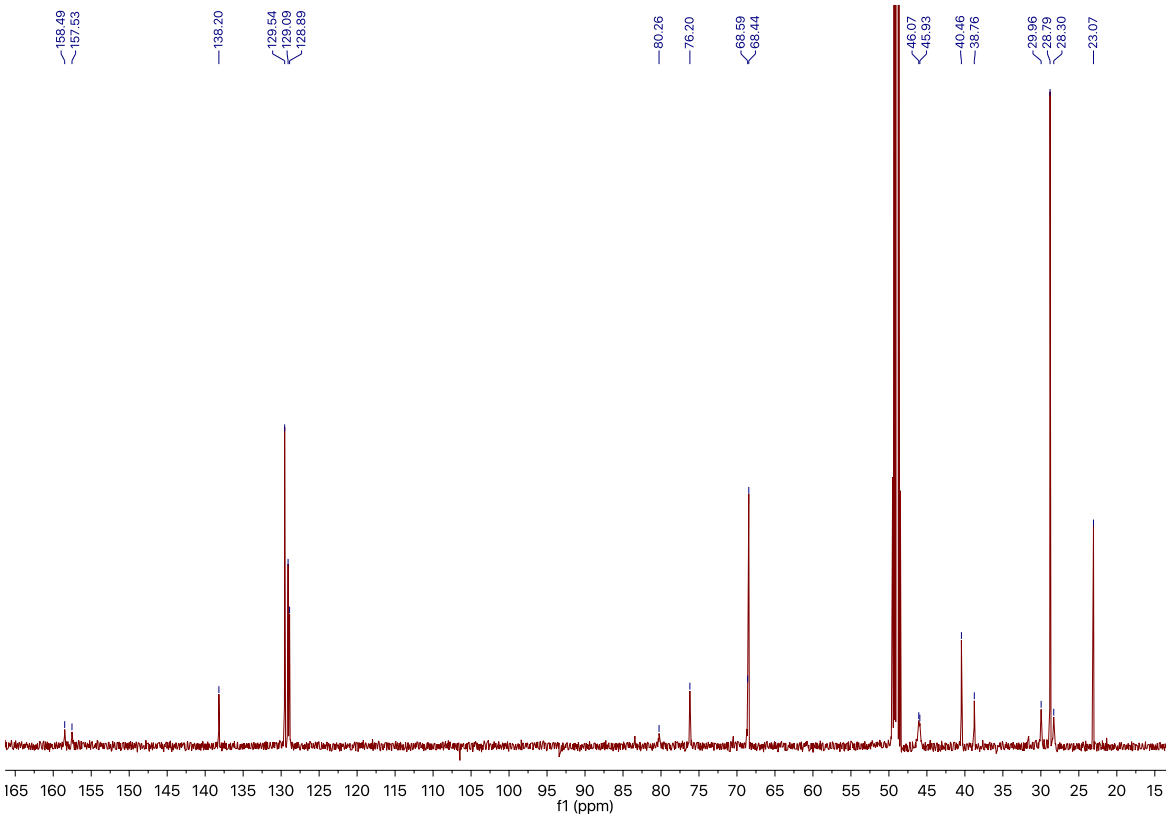
13

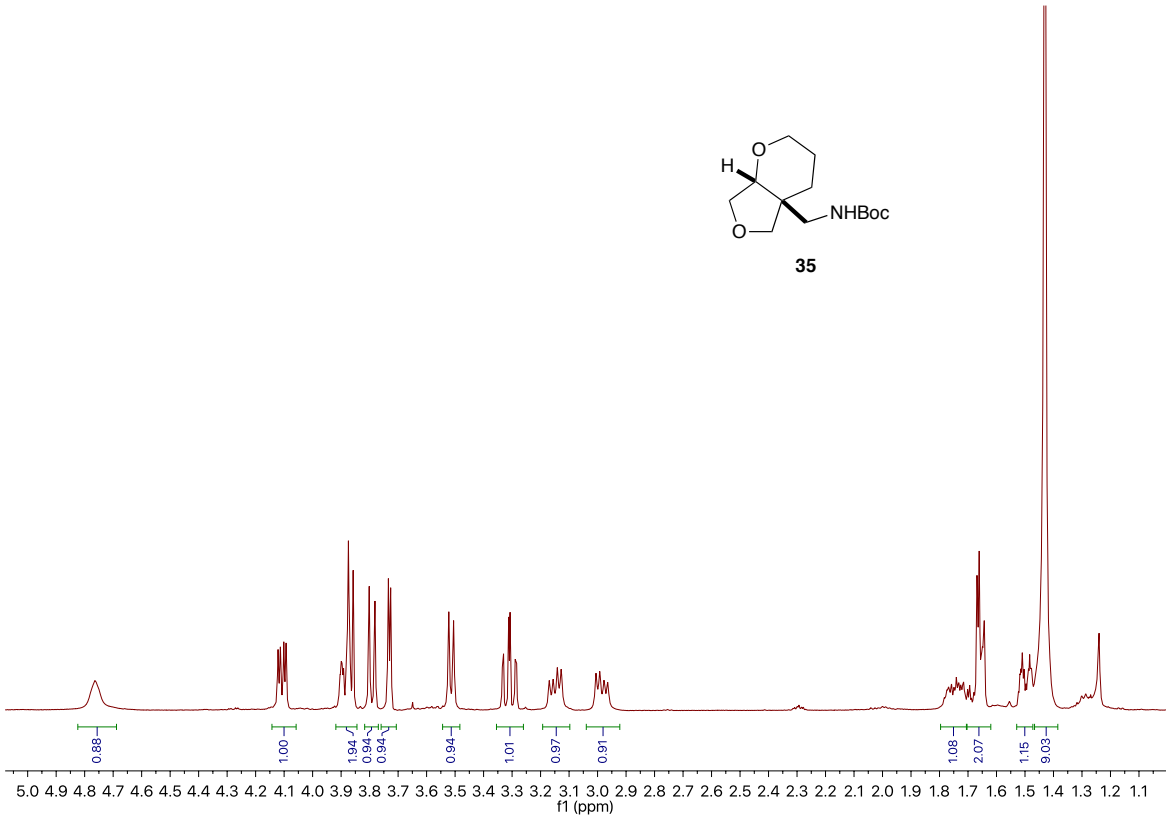
0.83
1.00
1.03
2.02
1.00
1.00
3.00
1.04
1.14
1.07
12.07
f1 (ppm)

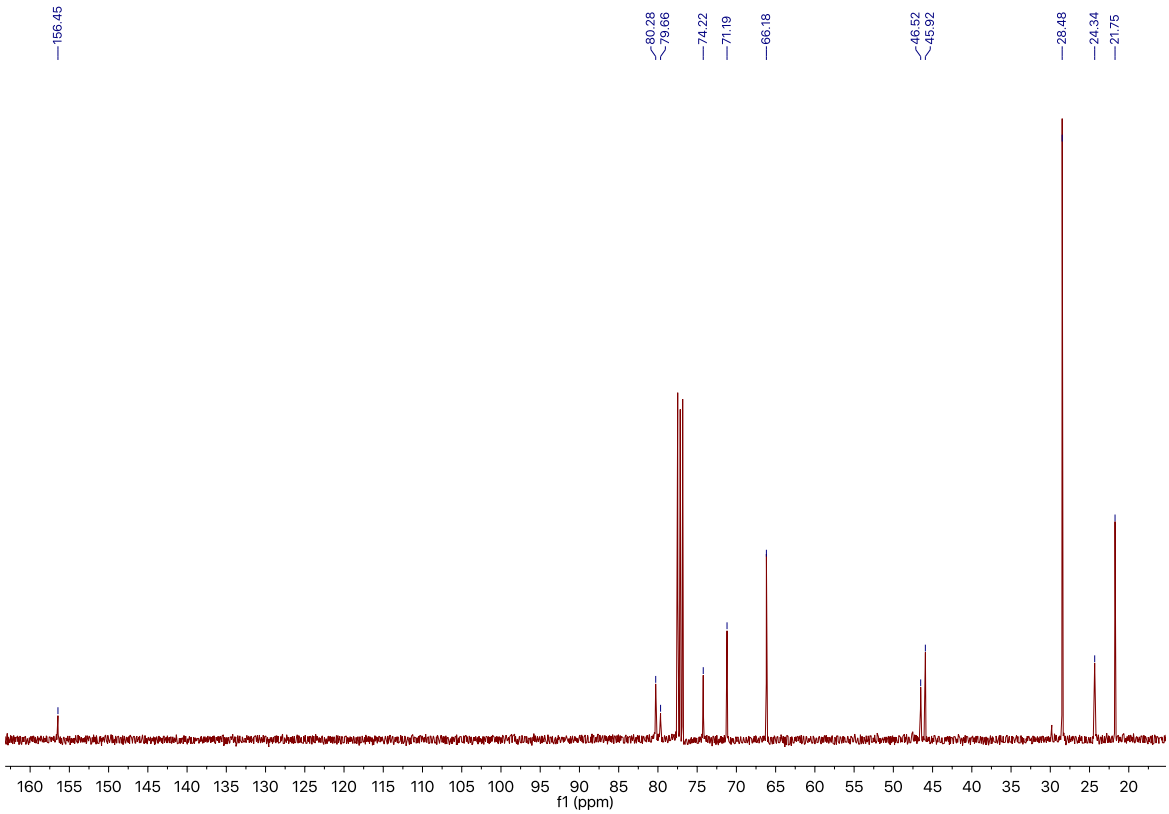

156.44
79.46
74.68
67.91
67.72
63.47
45.71
36.80
28.66
28.55
28.32
22.33
f1 (ppm)

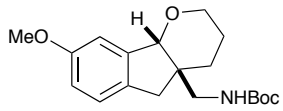

O
H
NHBoc
N
Cbz
4.76
2.02
0.99
1.00
1.03
2.86
1.01
0.94
0.96
0.98
1.05
2.07
11.03
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

2


158.49
157.53
138.20
129.54
129.09
128.89
80.26
76.20
68.59
68.44
46.07
45.93
40.46
38.76
29.96
28.79
28.30
23.07
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15
f1 (ppm)

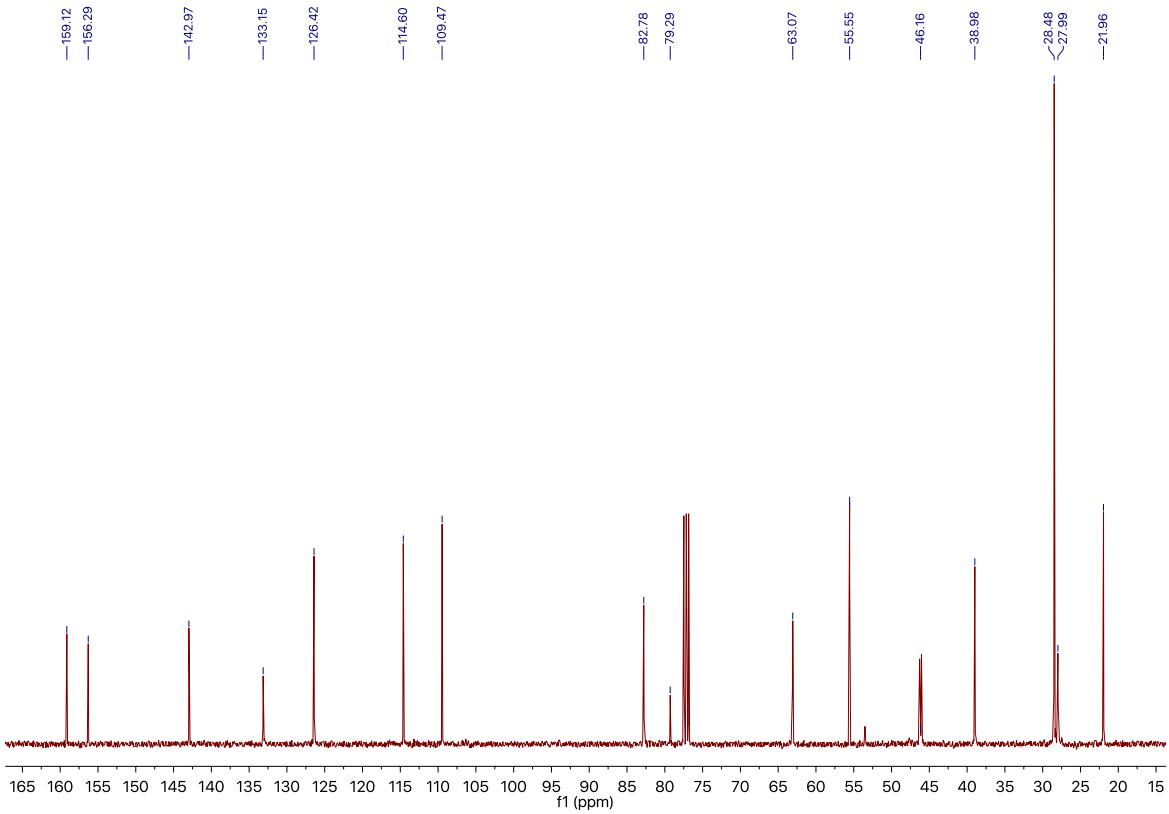

O
H
O
NHBoc
35
0.88
1.00
1.94
0.94
0.94
0.94
1.01
0.97
0.91
1.08
2.07
1.15
9.03
5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1
f1 (ppm)

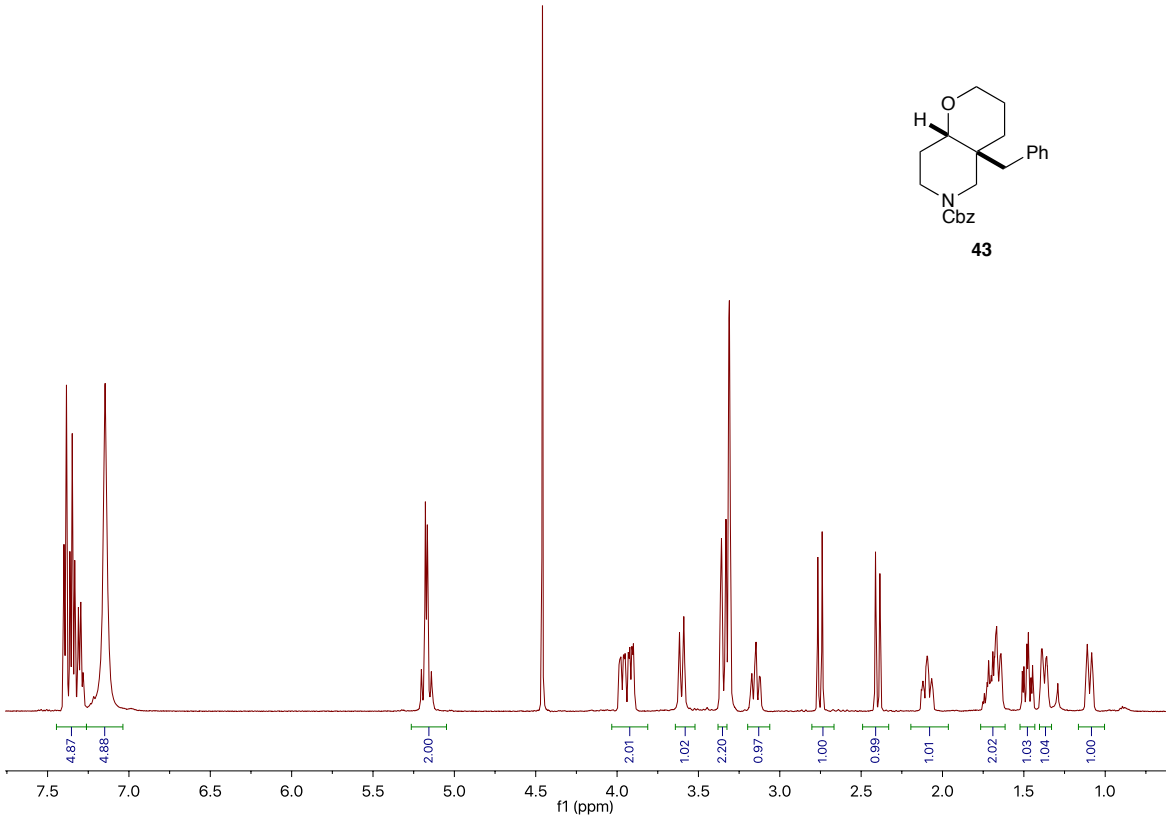

156.45
80.28
79.66
74.22
71.19
66.18
46.52
45.92
28.48
24.34
21.75
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)

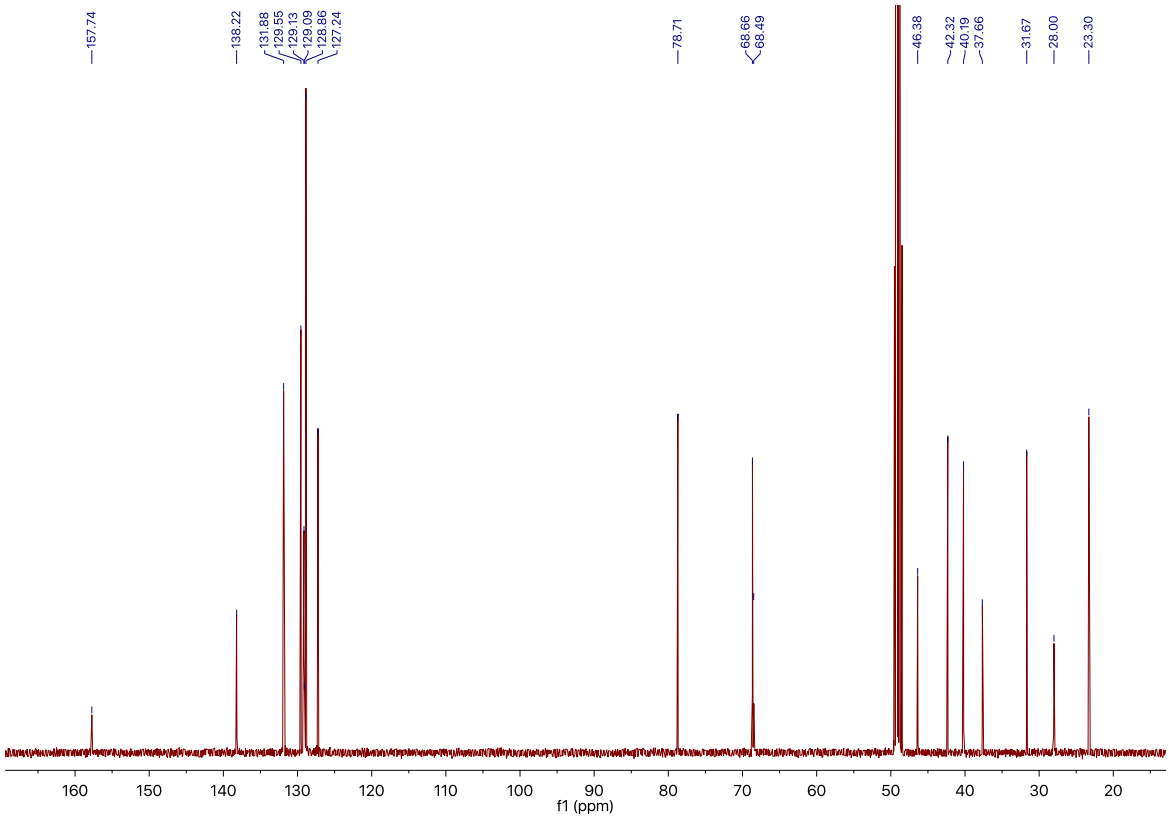

MeO
H
O
NHBoc

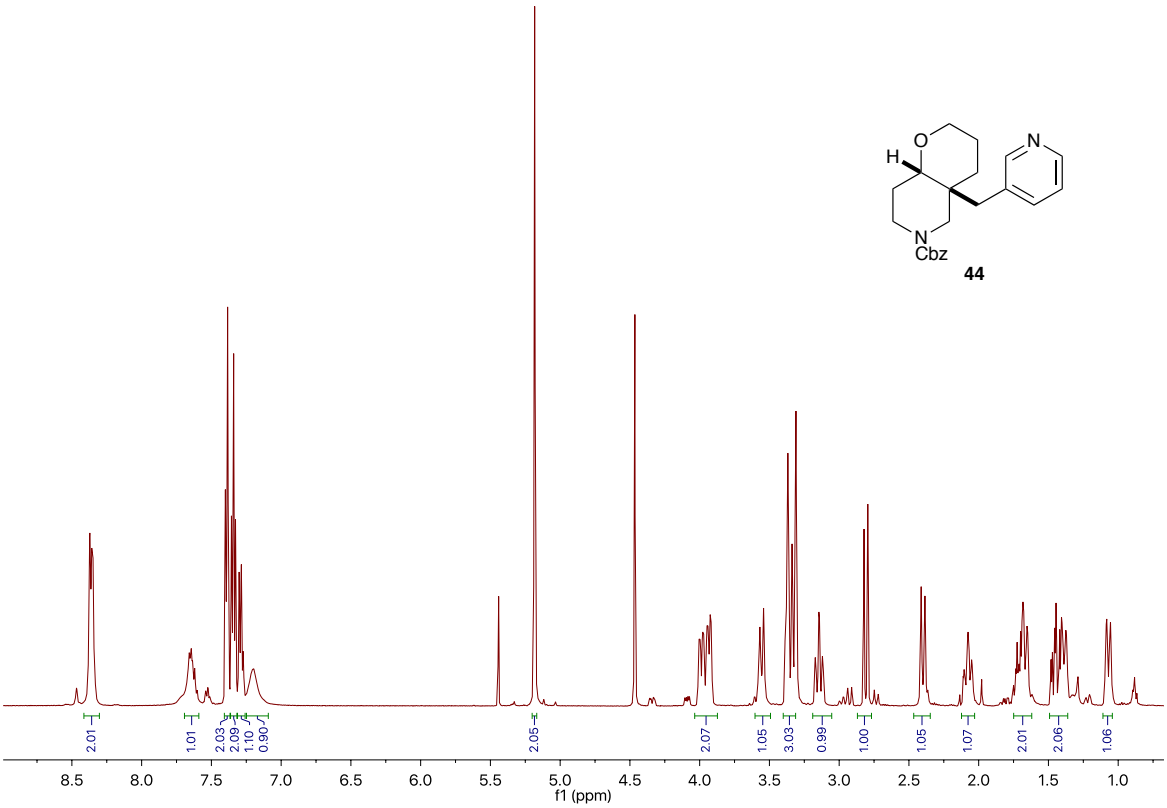
38

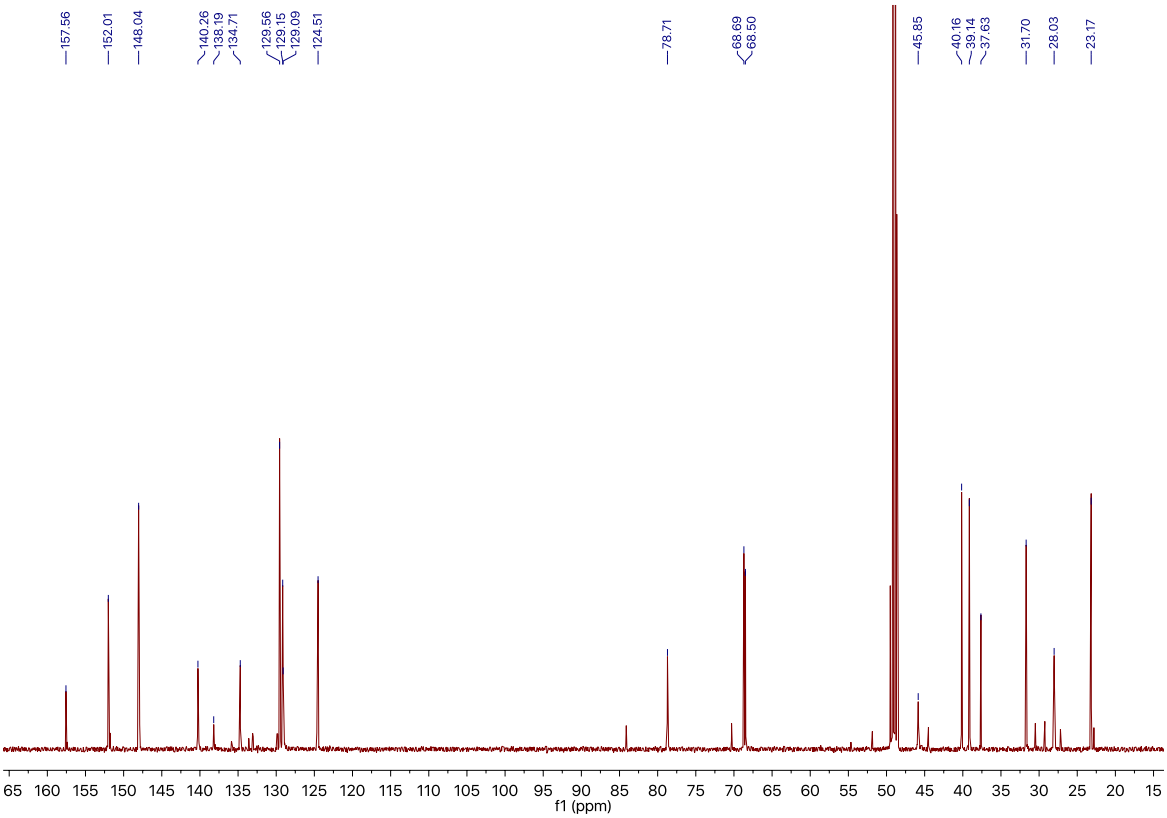
1.00
0.98
1.04
1.98
3.00
2.02
1.00
0.96
2.01
1.07
1.08
1.04
10.36
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

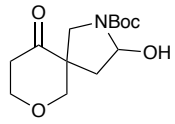

159.12
156.29
142.97
133.15
126.42
114.60
109.47
82.78
79.29
63.07
55.55
46.16
38.98
28.48
27.99
21.96
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15
f1 (ppm)


O
H
Ph
N
Cbz
43
4.87
4.88
2.00
2.01
1.02
2.20
0.97
1.00
0.99
1.01
2.02
1.03
1.04
1.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


157.74
138.22
131.88
129.55
129.13
129.09
128.86
127.24
78.71
68.66
68.49
46.38
42.32
40.19
37.66
31.67
28.00
23.30
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

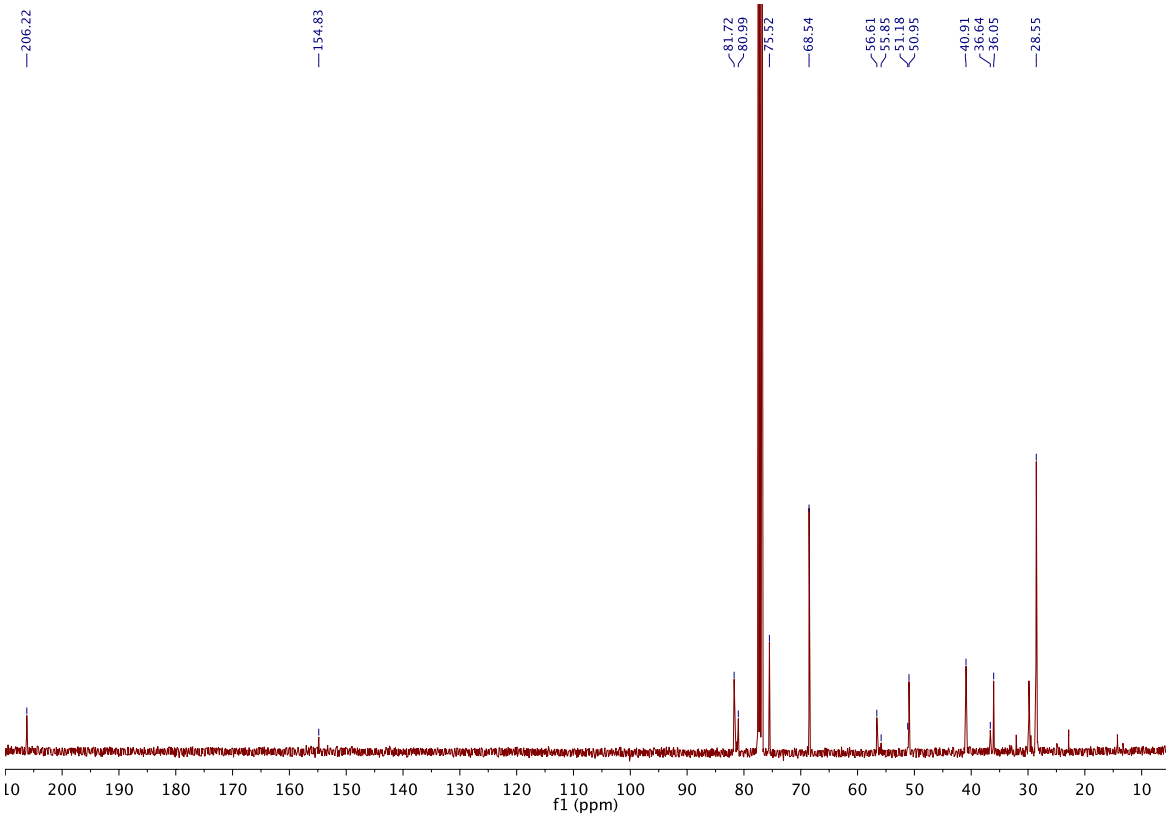

O
H
N
N
Cbz
44
2.01
1.01
2.03
2.09
1.10
0.90
2.05
2.07
1.05
3.03
0.99
1.00
1.05
1.07
2.01
2.06
1.06
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

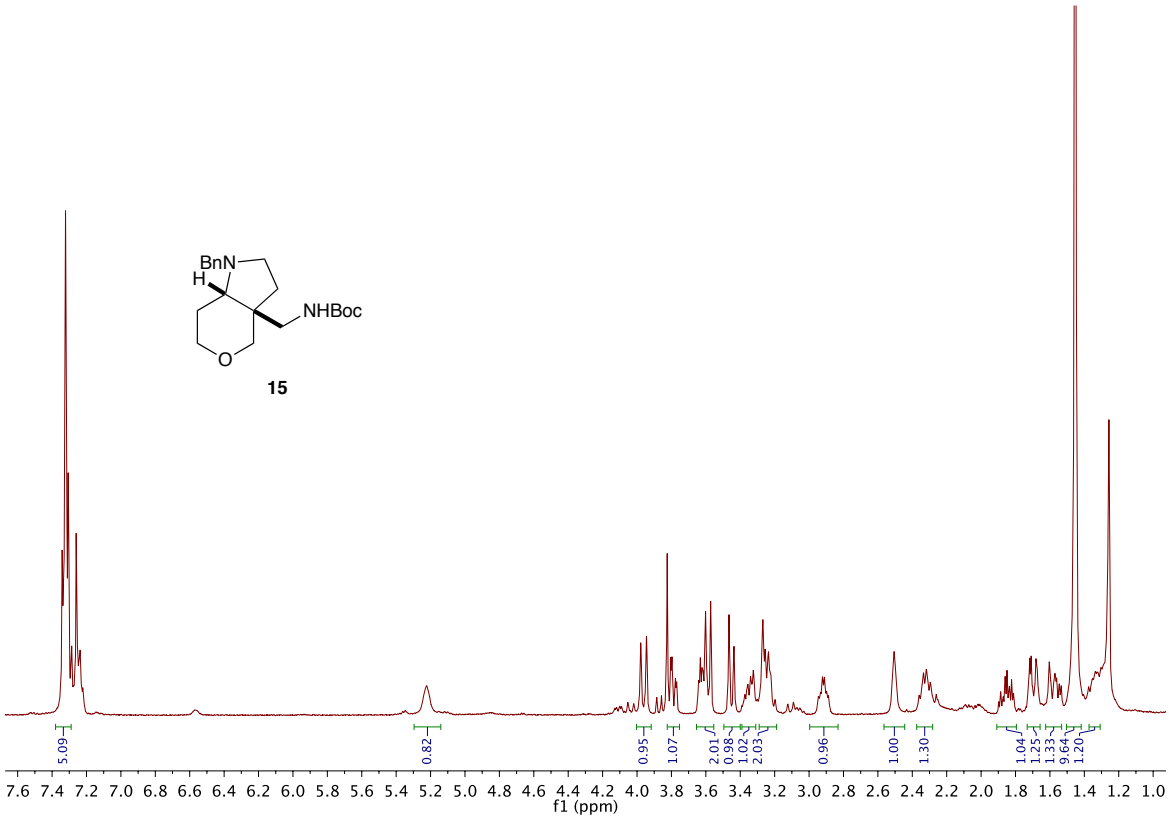

157.56
152.01
148.04
140.26
138.19
134.71
129.56
129.15
129.09
124.51
78.71
68.89
68.50
45.85
40.16
39.14
37.63
31.70
28.03
23.17
65 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15
f1 (ppm)


O
NBoc
OH
O

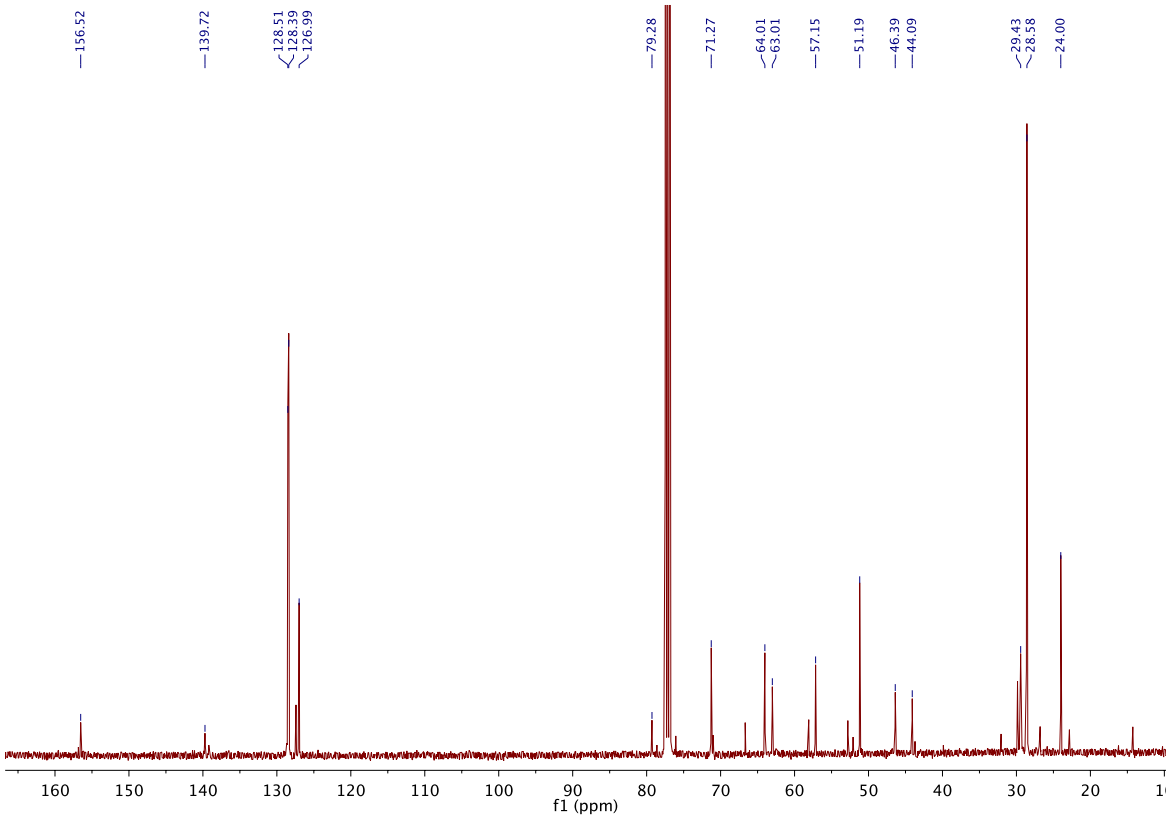
14

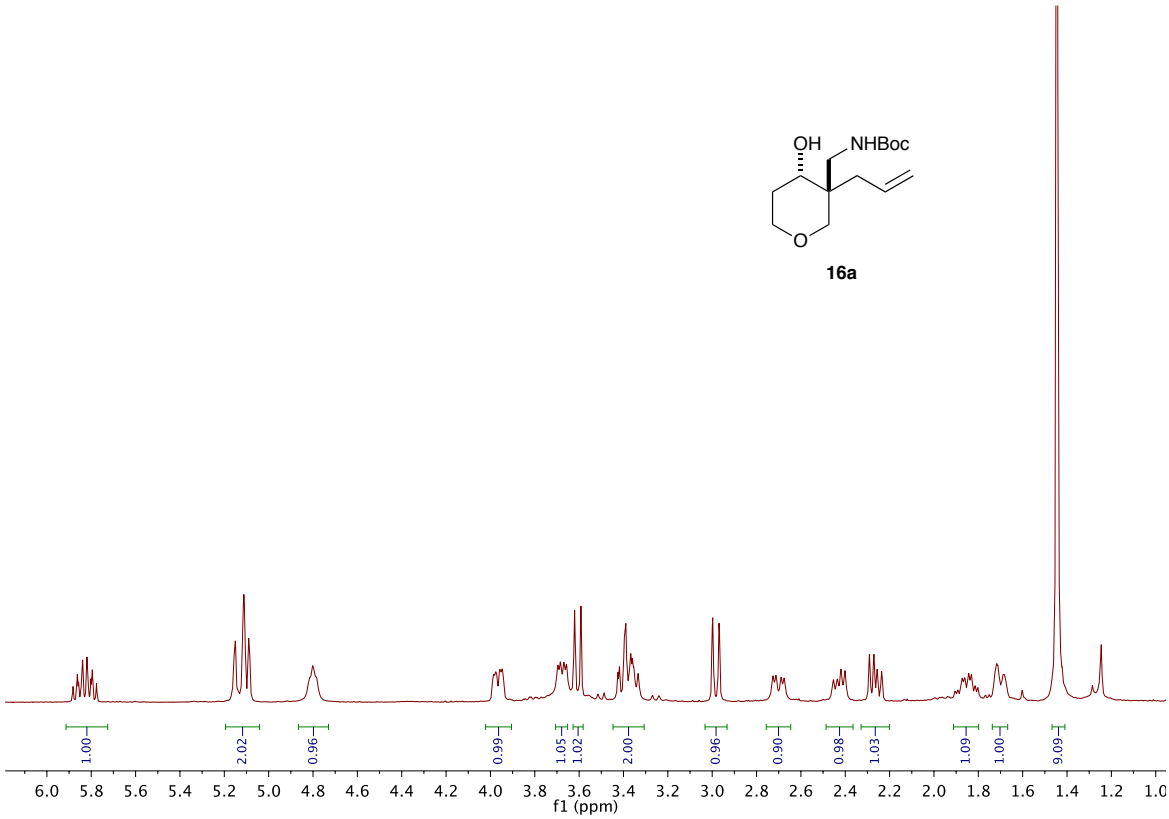
1.00
0.52
3.15
1.56
1.54
1.38
2.46
1.29
0.53
5.42
2.00
2.06
16.74
6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f1 (ppm)

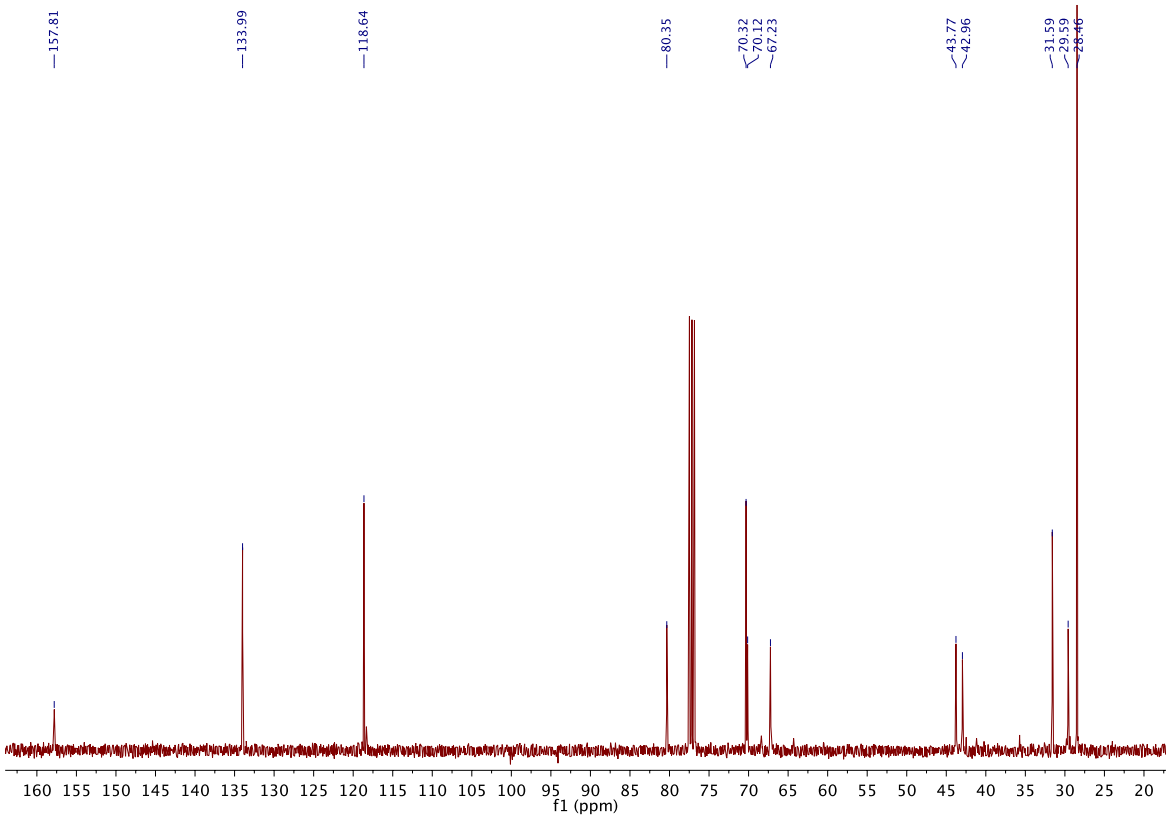

206.22
154.83
81.72
80.99
75.52
68.54
56.61
55.85
51.18
50.95
40.91
36.64
36.05
28.55
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

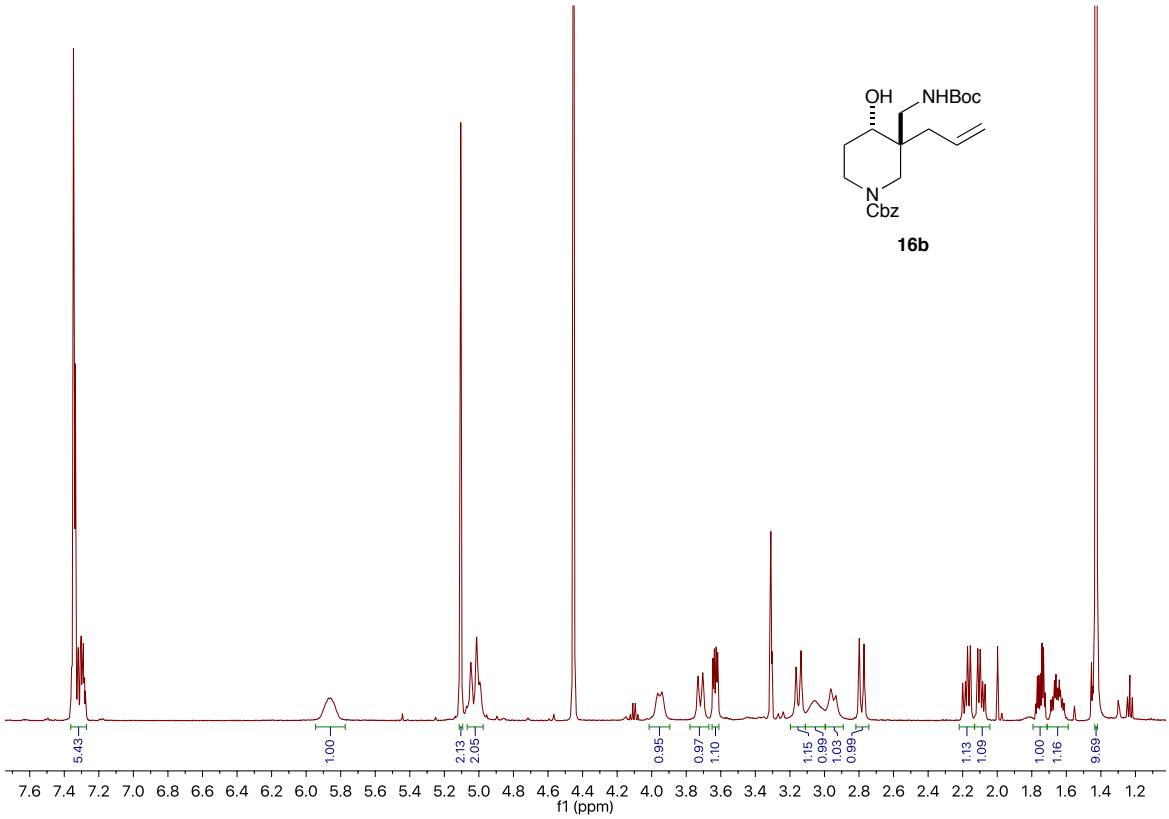

BnN
H
NHBoc
O
5.09
0.82
0.95
1.07
2.01
0.98
1.02
2.03
0.96
1.00
1.30
1.04
1.25
1.33
9.64
1.20
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0
f1 (ppm)

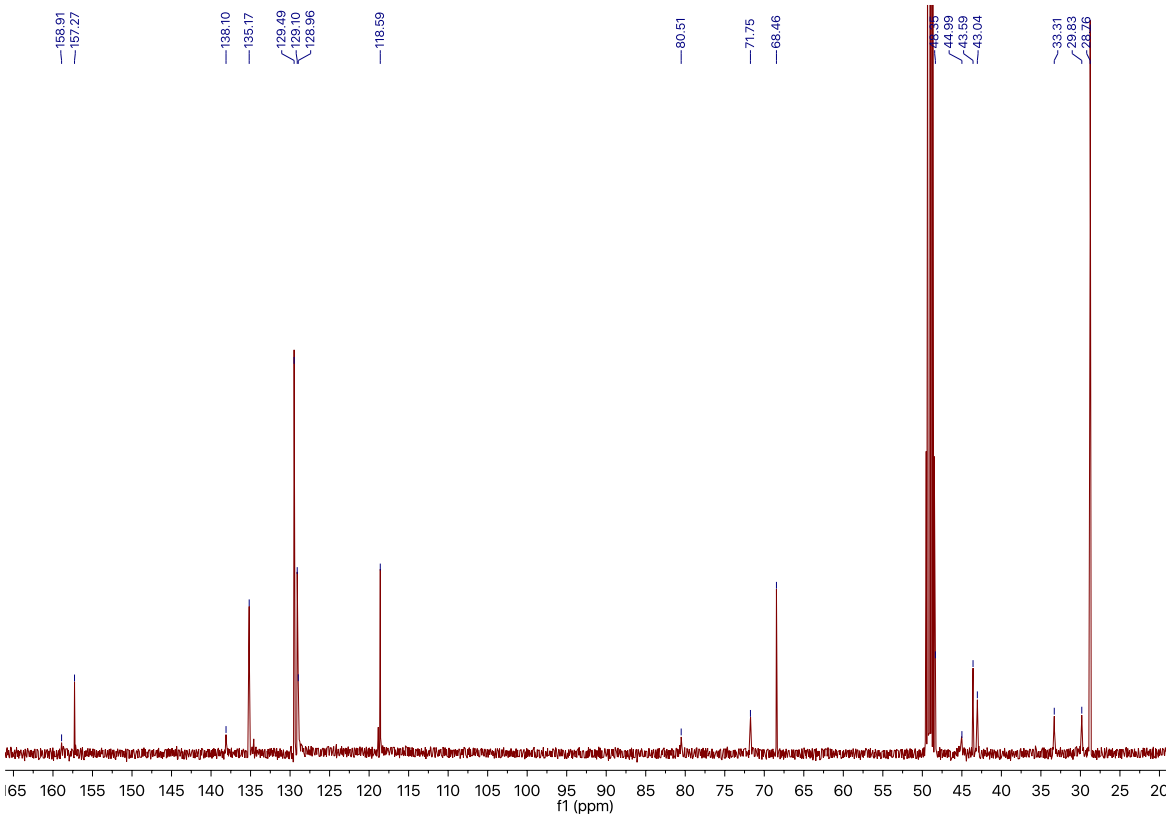
15

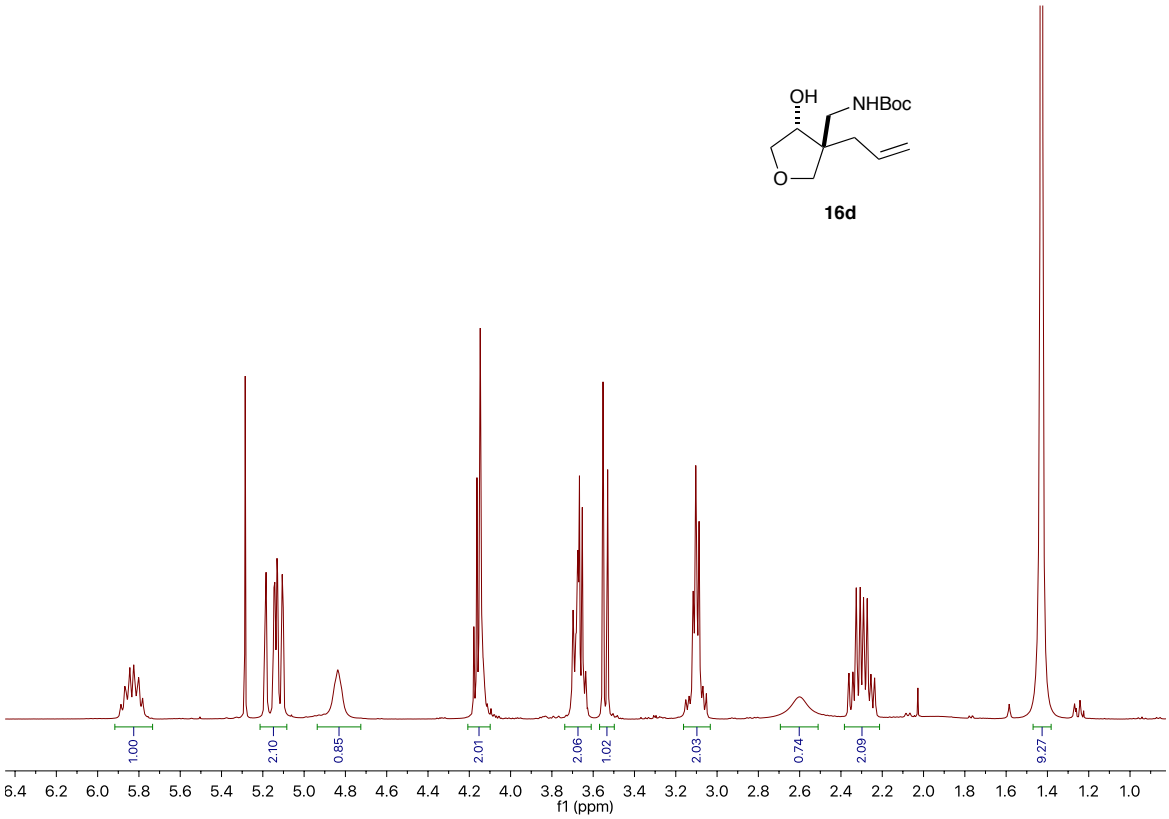

156.52
139.72
128.51
128.39
126.99
79.28
71.27
64.01
63.01
57.15
51.19
46.39
44.09
29.43
28.58
24.00
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

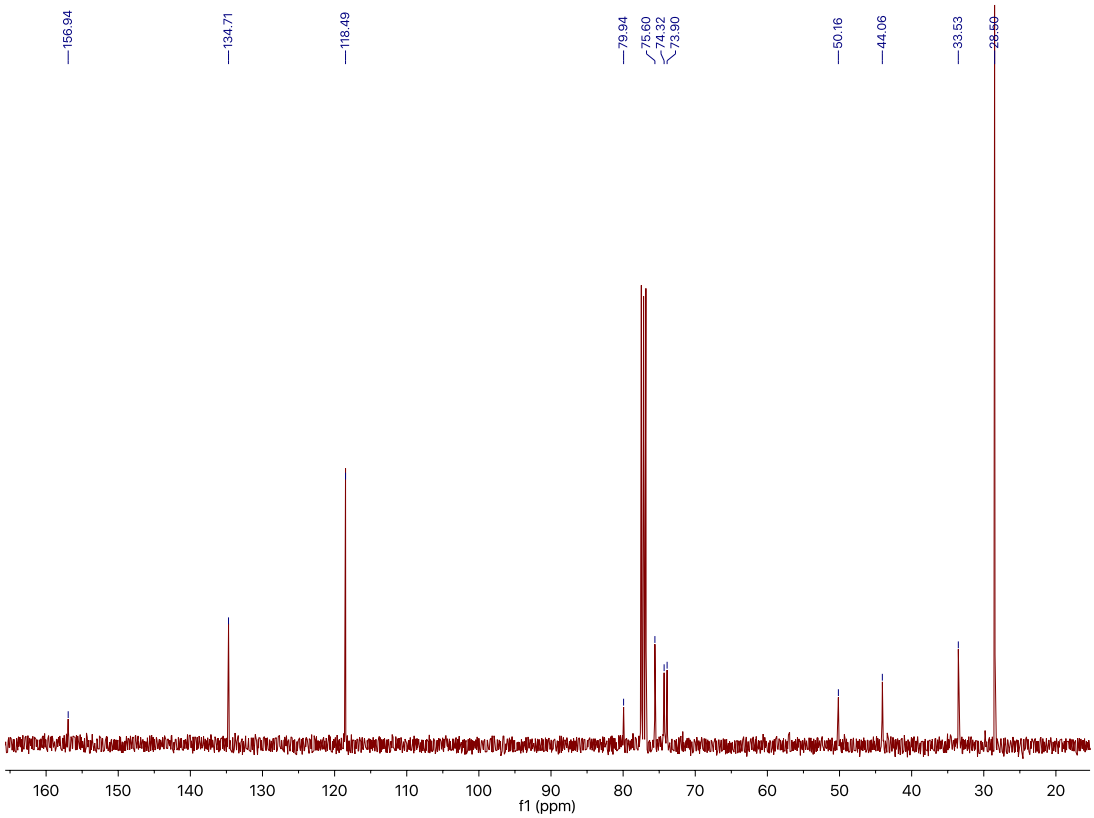

OH
NHBoc
O
16a
1.00
2.02
0.96
0.99
1.05
1.02
2.00
0.96
0.90
0.98
1.03
1.09
1.00
9.09
f1 (ppm)

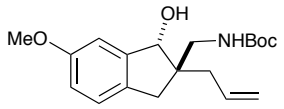

157.81
133.99
118.64
80.35
70.32
70.12
67.23
43.77
42.96
31.59
29.59
28.46
f1 (ppm)


OH
NHBoc
N
Cbz
16b
5.43
1.00
2.13
2.05
0.95
0.97
1.10
1.15
0.99
1.03
0.99
1.13
1.09
1.00
1.16
9.69
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
f1 (ppm)


158.91
157.27
138.10
135.17
129.49
129.10
128.96
118.59
80.51
71.75
68.46
44.99
43.59
43.04
33.31
29.83
28.26
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
f1 (ppm)

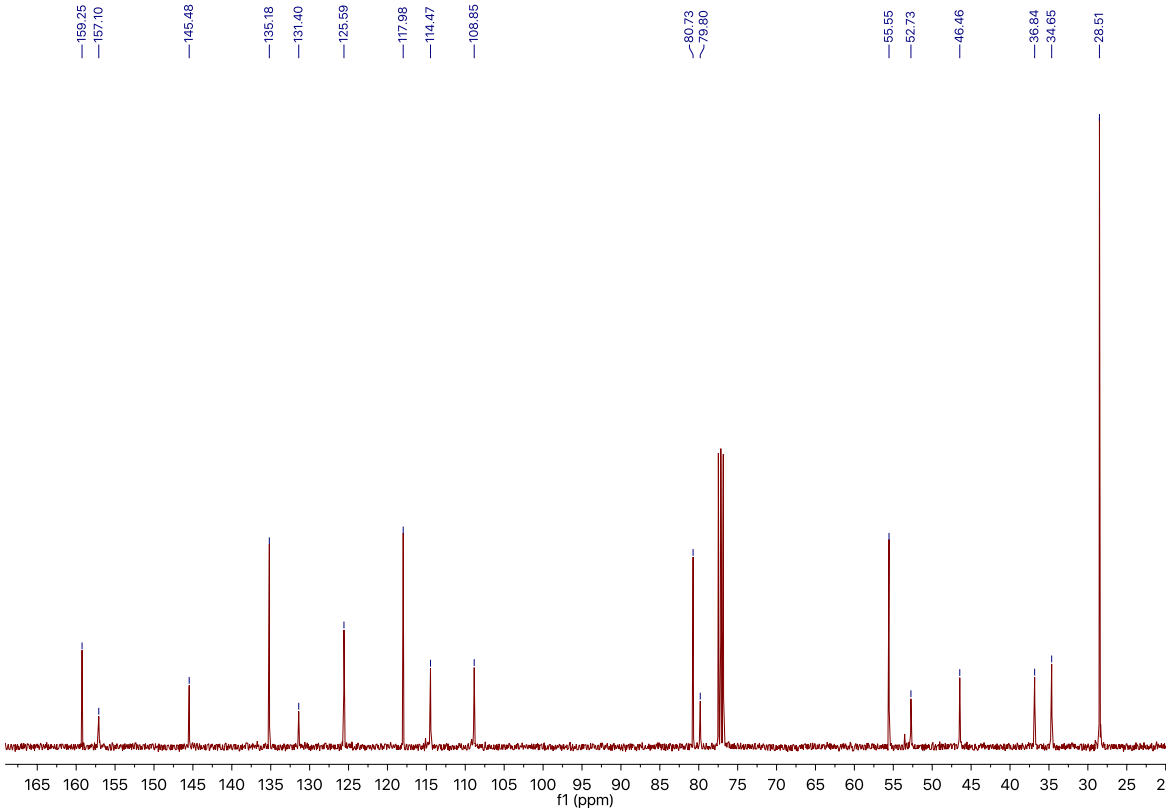

OH
NHBoc
O
16d
1.00
2.10
0.85
2.01
2.06
1.02
2.03
0.74
2.09
9.27
f1 (ppm)

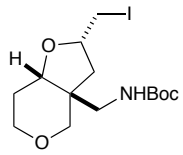

156.94
134.71
118.49
79.94
75.60
74.32
73.90
50.16
44.06
33.53
28.60
f1 (ppm)


OH
MeO
NHBoc

16e

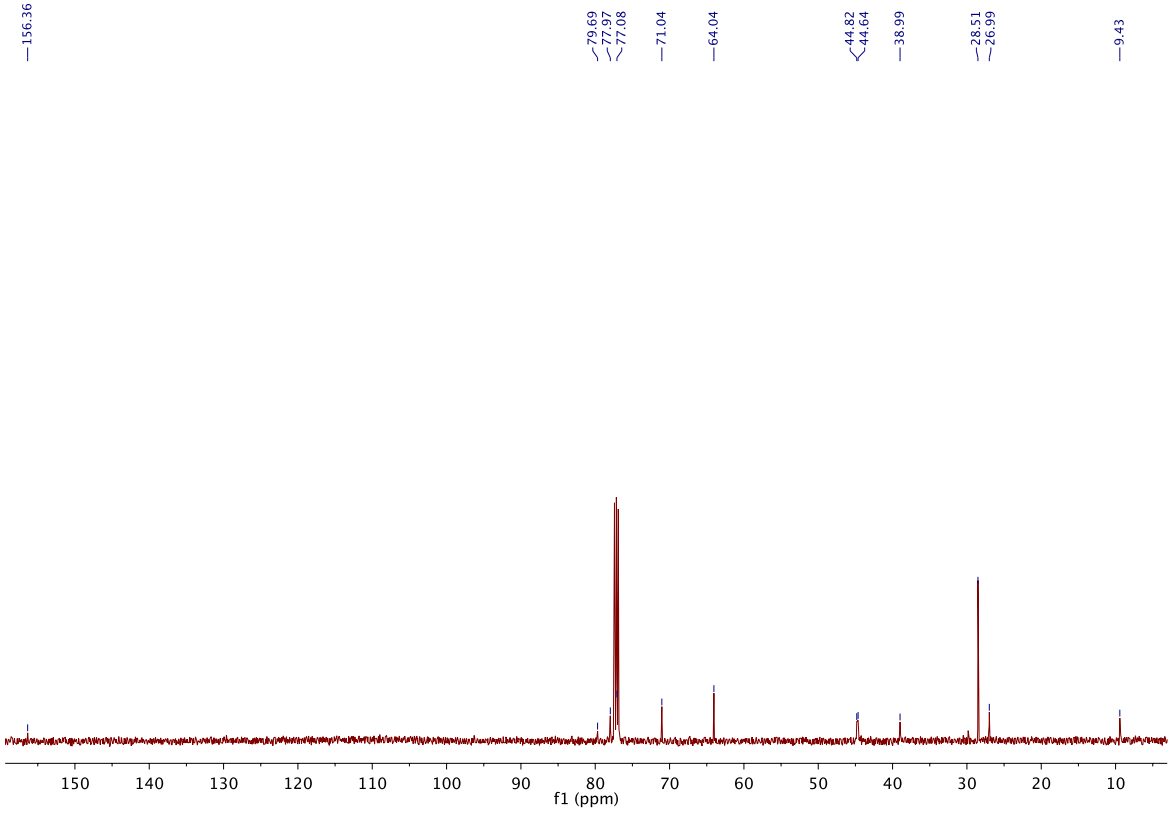
1.00
1.00
1.02
0.97
2.36
1.04
3.03
0.99
1.07
1.12
1.10
1.07
1.03
8.98
f1 (ppm)

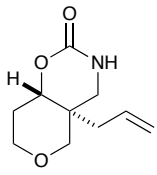

159.25
157.10
145.48
135.18
131.40
125.59
117.98
114.47
108.85
80.73
79.80
55.55
52.73
46.46
36.84
34.65
28.51
f1 (ppm)


I
O
H
NHBoc
O

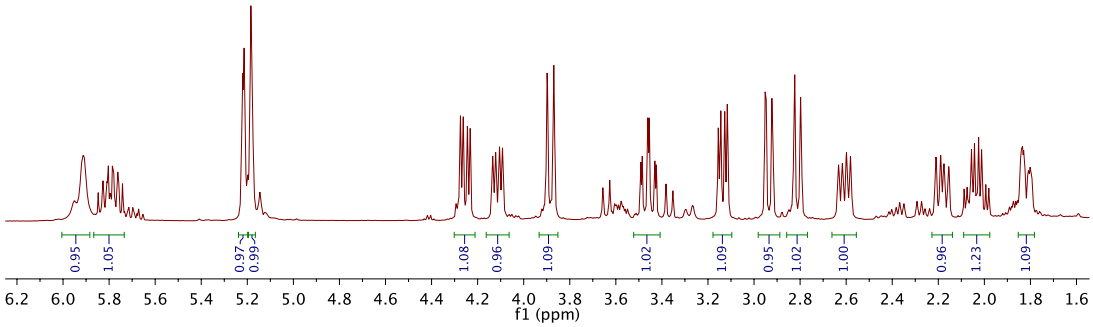
17

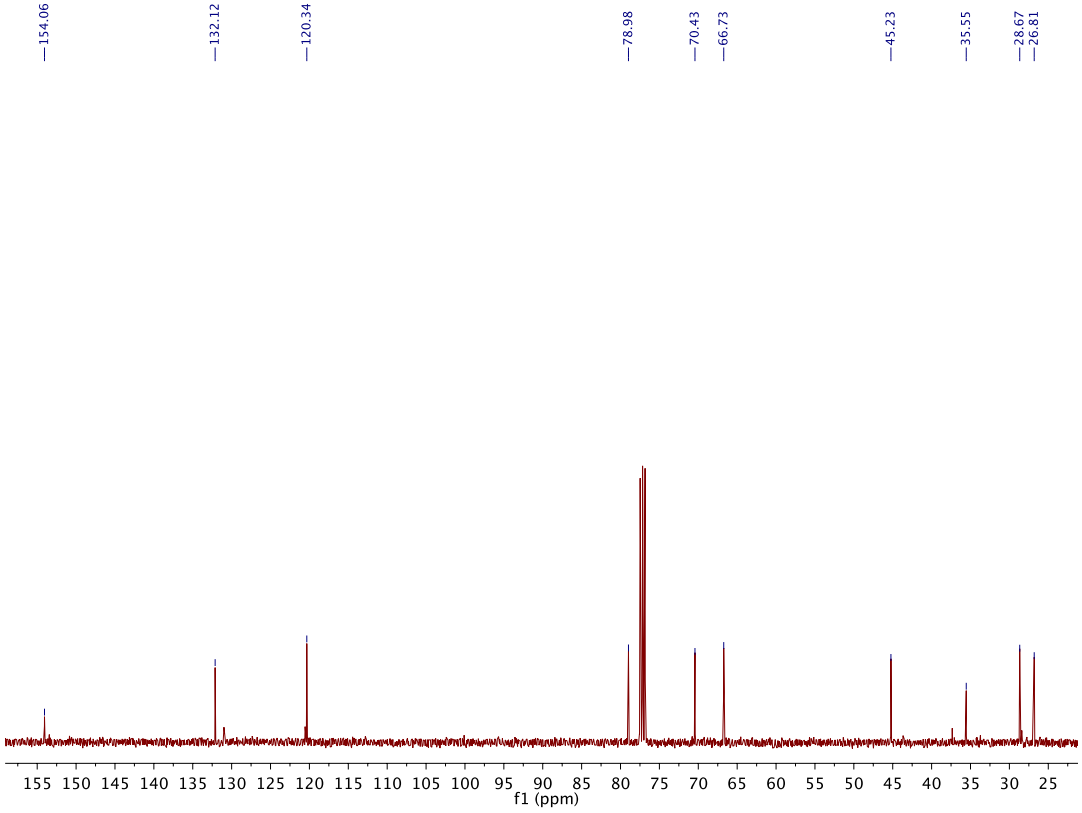
0.88
1.00
1.02
1.04
1.07
1.04
1.00
3.06
0.99
2.04
1.10
9.23
0.99
5.1 4.9 4.7 4.5 4.3 4.1 3.9 3.7 3.5 3.3 3.1 2.9 2.7 2.5 2.3 2.1 1.9 1.7 1.5 1.3 1.1
f1 (ppm)

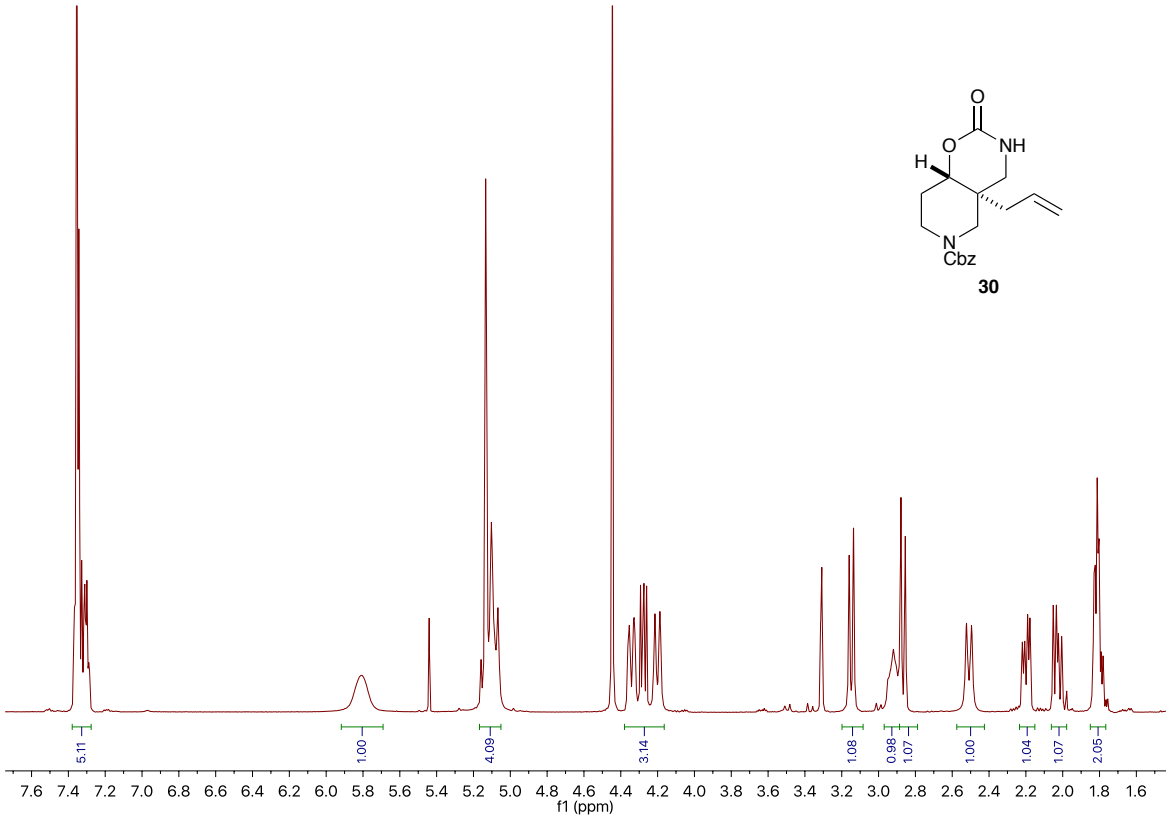

156.36
79.69
77.97
77.08
71.04
64.04
44.82
44.64
38.99
28.51
26.99
9.43
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

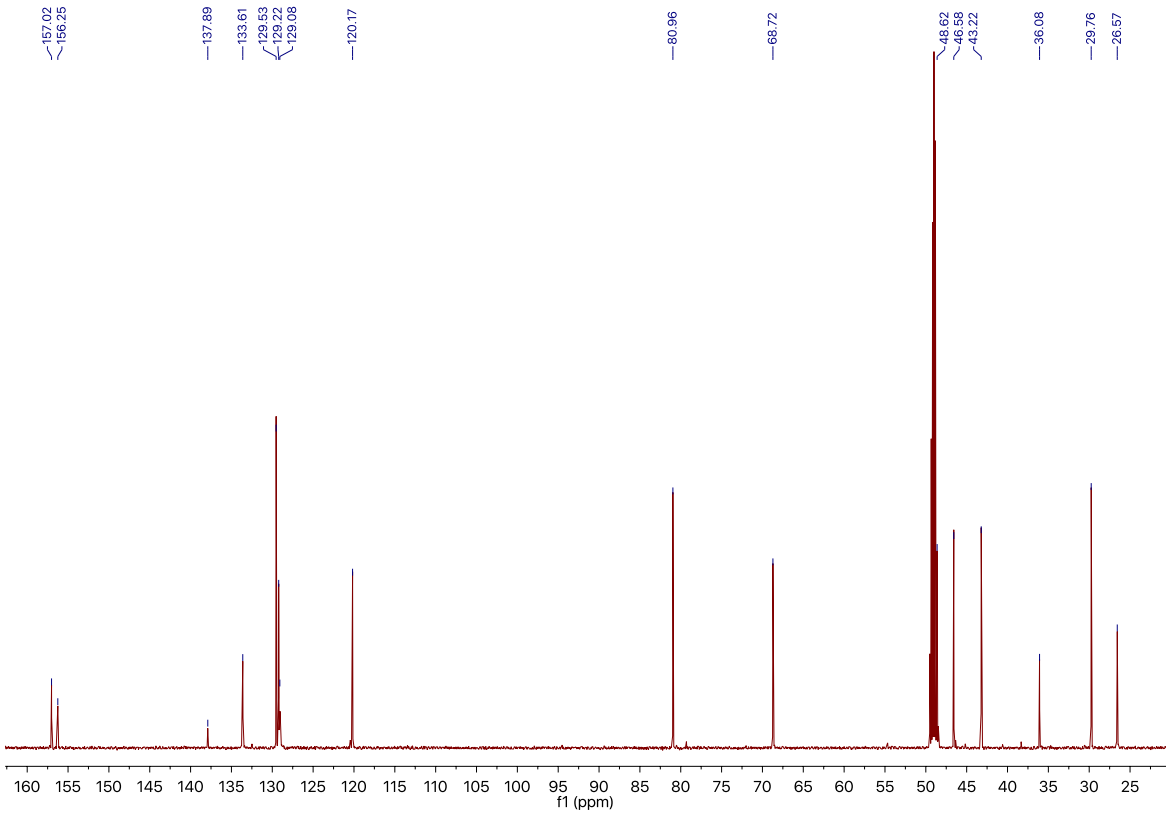

O
O
NH
H
O

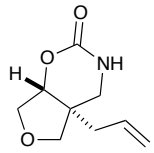
18


0.95
1.05
0.97
0.99
1.08
0.96
1.09
1.02
1.09
0.95
1.02
1.00
0.96
1.23
1.09
6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
f1 (ppm)

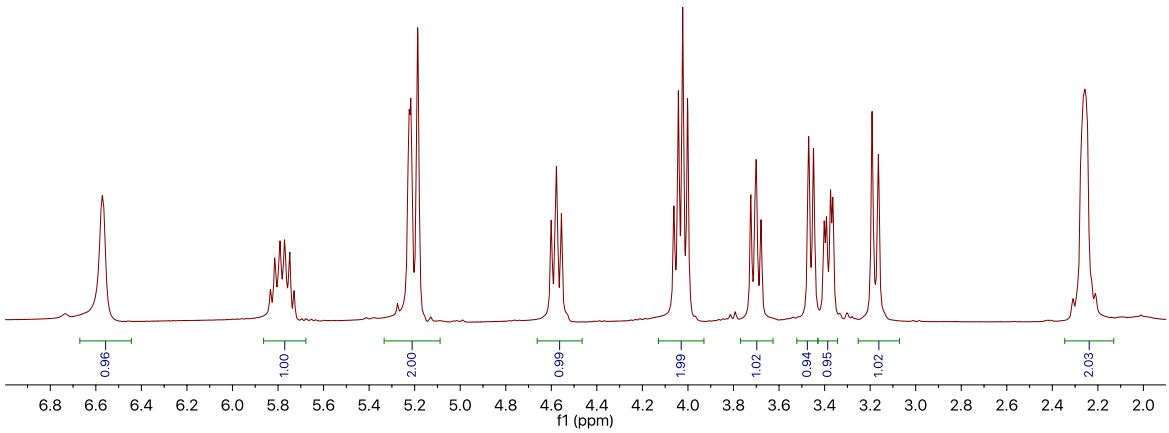

154.06
132.12
120.34
78.98
70.43
66.73
45.23
35.55
28.67
26.81
155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25
f1 (ppm)

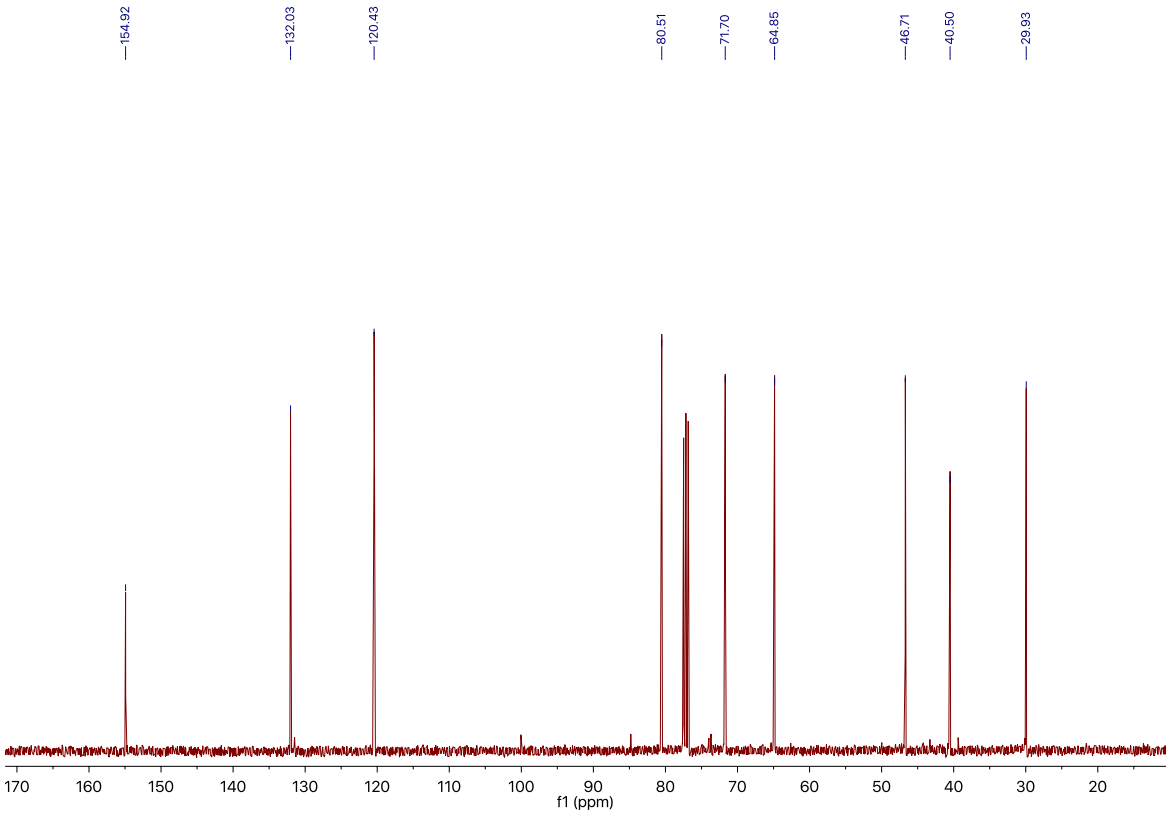

O
O
NH
H
N
Cbz
30
5.11
1.00
4.09
3.14
1.08
0.98
1.07
1.00
1.04
1.07
2.05
f1 (ppm)

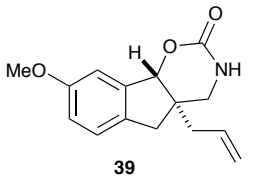

157.02
156.25
137.89
133.61
129.53
129.22
129.08
120.17
80.96
68.72
48.62
46.58
43.22
36.08
29.76
26.57
f1 (ppm)


O
O
NH
H
O

3

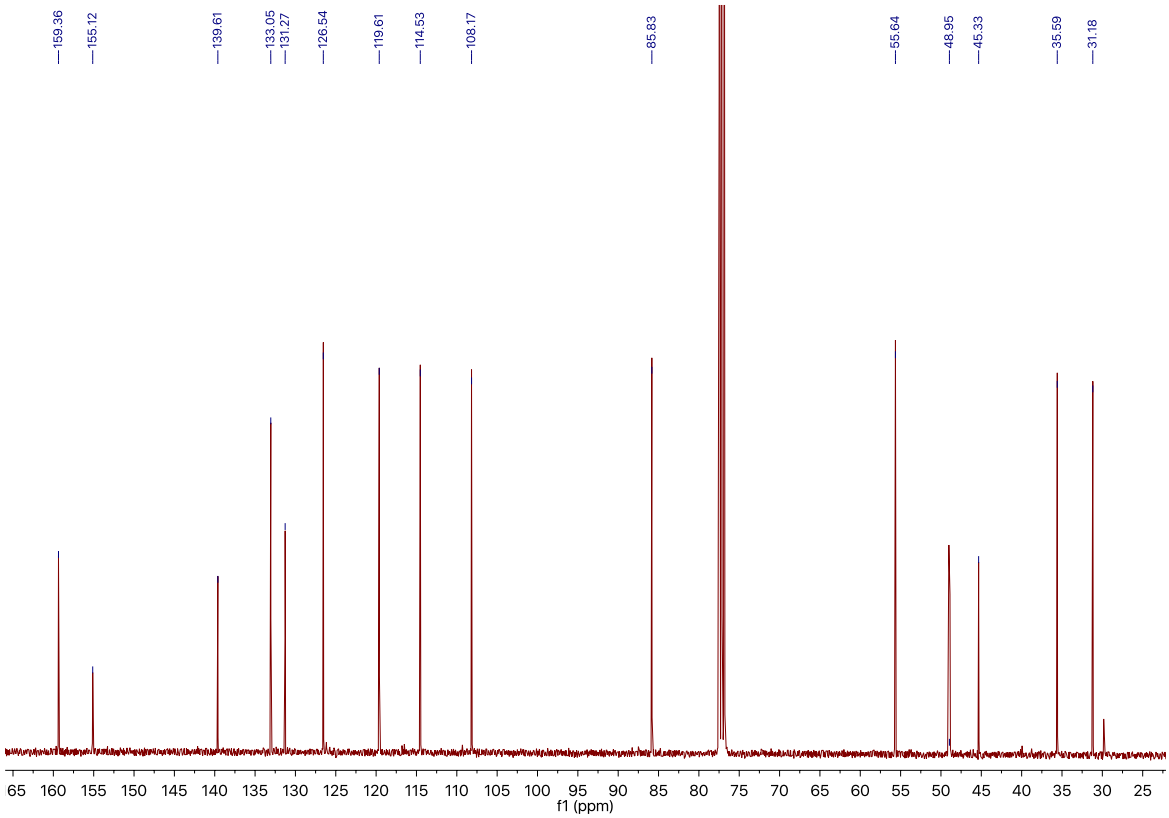

0.96
1.00
2.00
0.99
1.99
1.02
0.94
0.95
1.02
2.03
6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0
f1 (ppm)

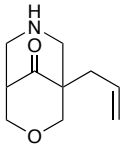

154.92
132.03
120.43
80.51
71.70
64.85
46.71
40.50
29.93
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)


O
H
O
NH
MeO

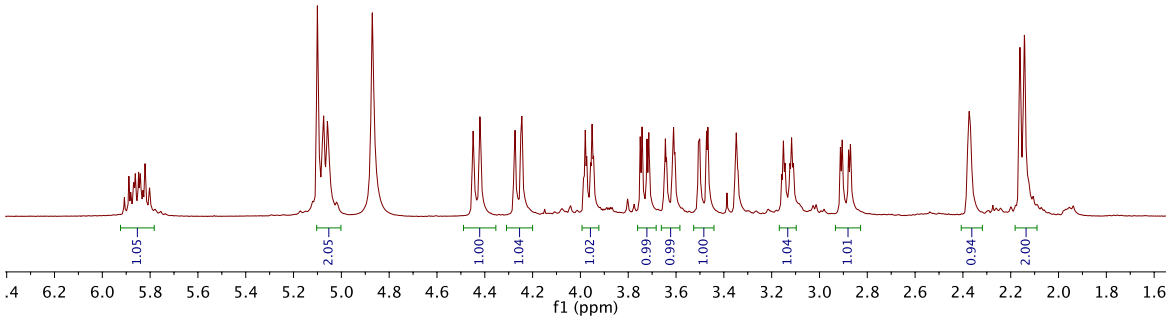
39

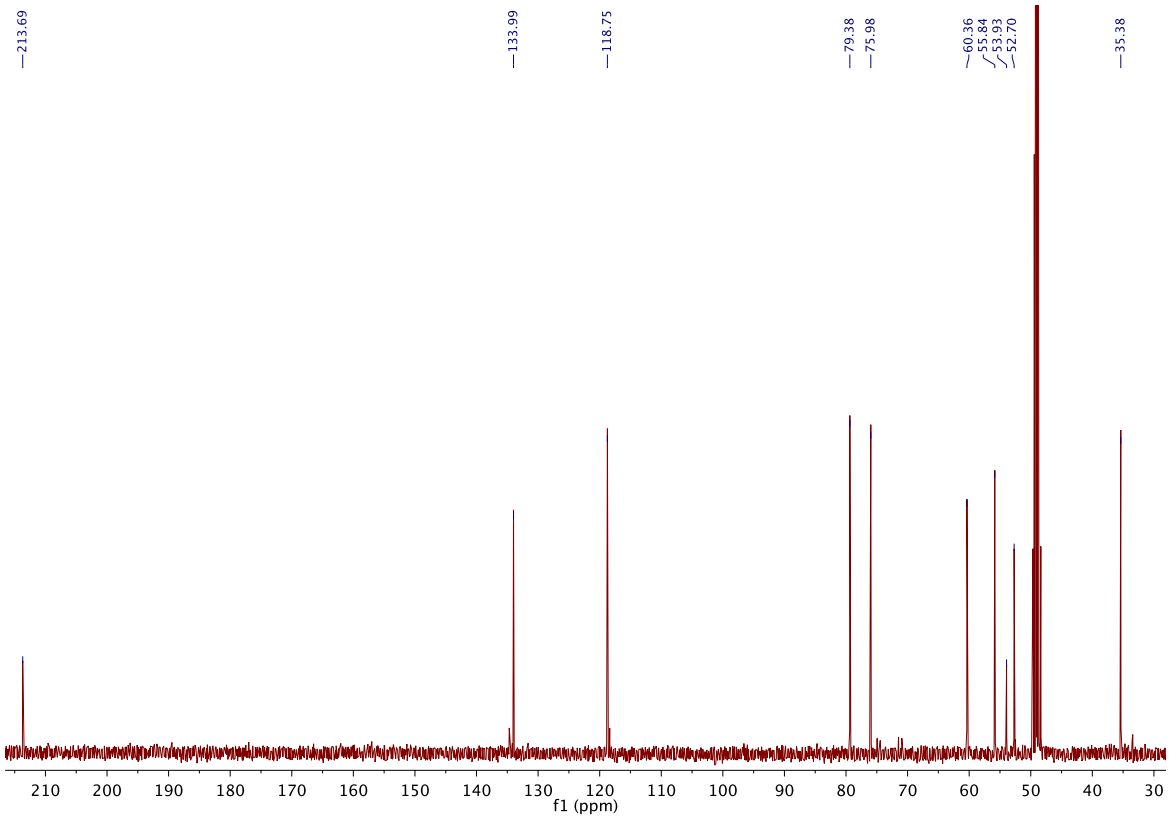
1.00
0.98
0.99
0.53
1.03
0.98
1.99
3.04
1.97
1.01
1.01
0.99
0.99
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

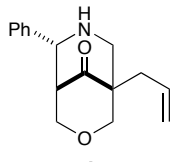

159.36
155.12
139.61
133.05
131.27
126.54
119.61
114.53
108.17
85.83
55.64
48.95
45.33
35.59
31.18
65 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25
f1 (ppm)


H
N
O
O

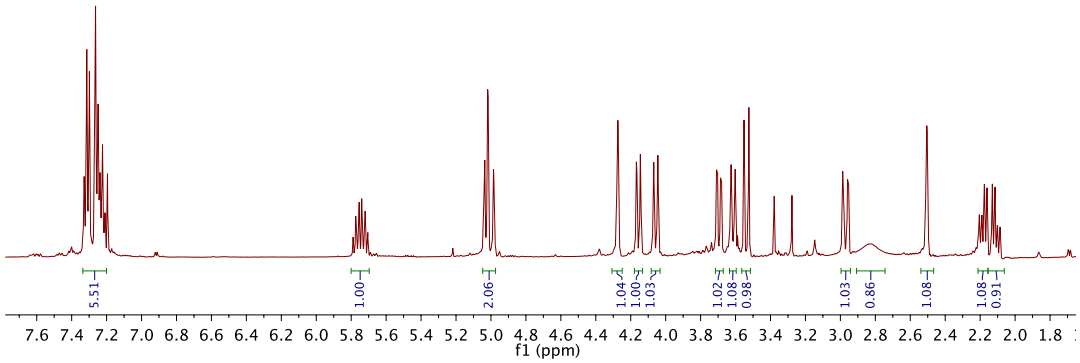
19

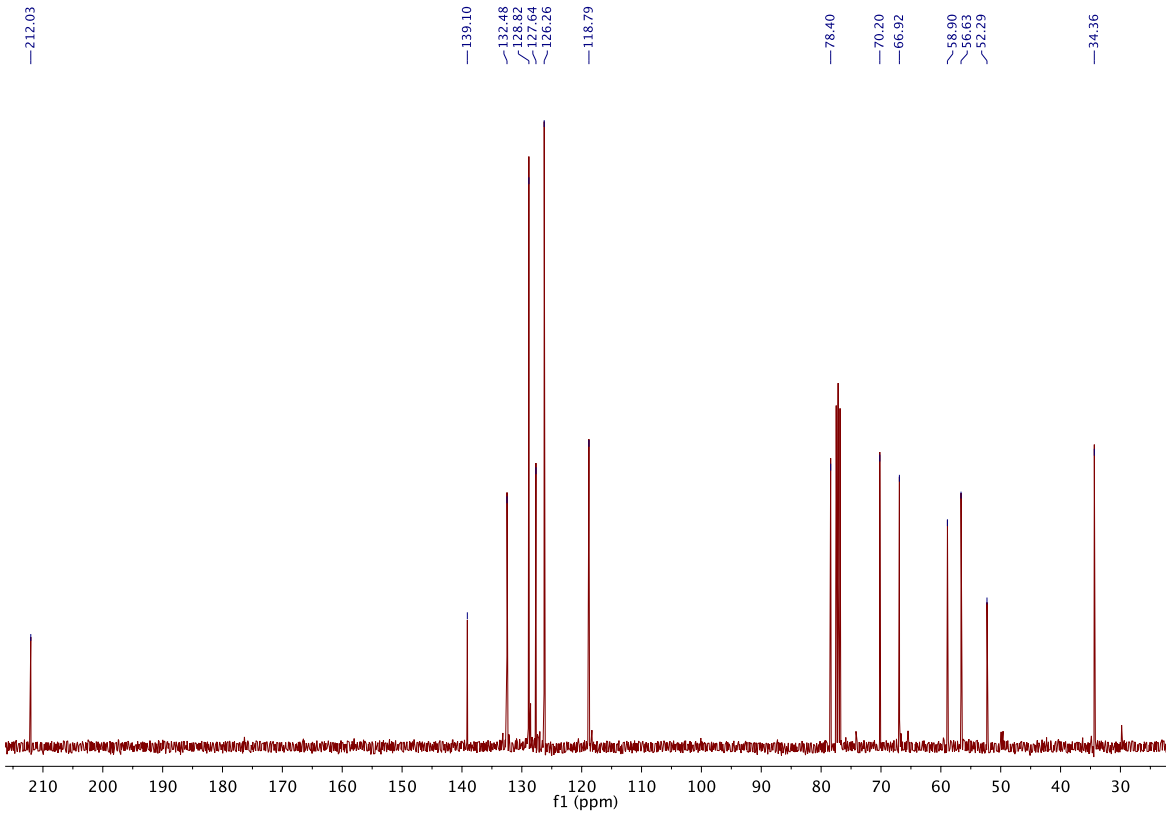

1.05
2.05
1.00
1.04
1.02
0.99
0.99
1.00
1.04
1.01
0.94
2.00
.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
f1 (ppm)

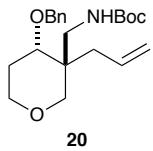

213.69
133.99
118.75
79.38
75.98
60.36
55.84
53.93
52.70
35.38
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30
f1 (ppm)


Ph
H
N
O
O

4

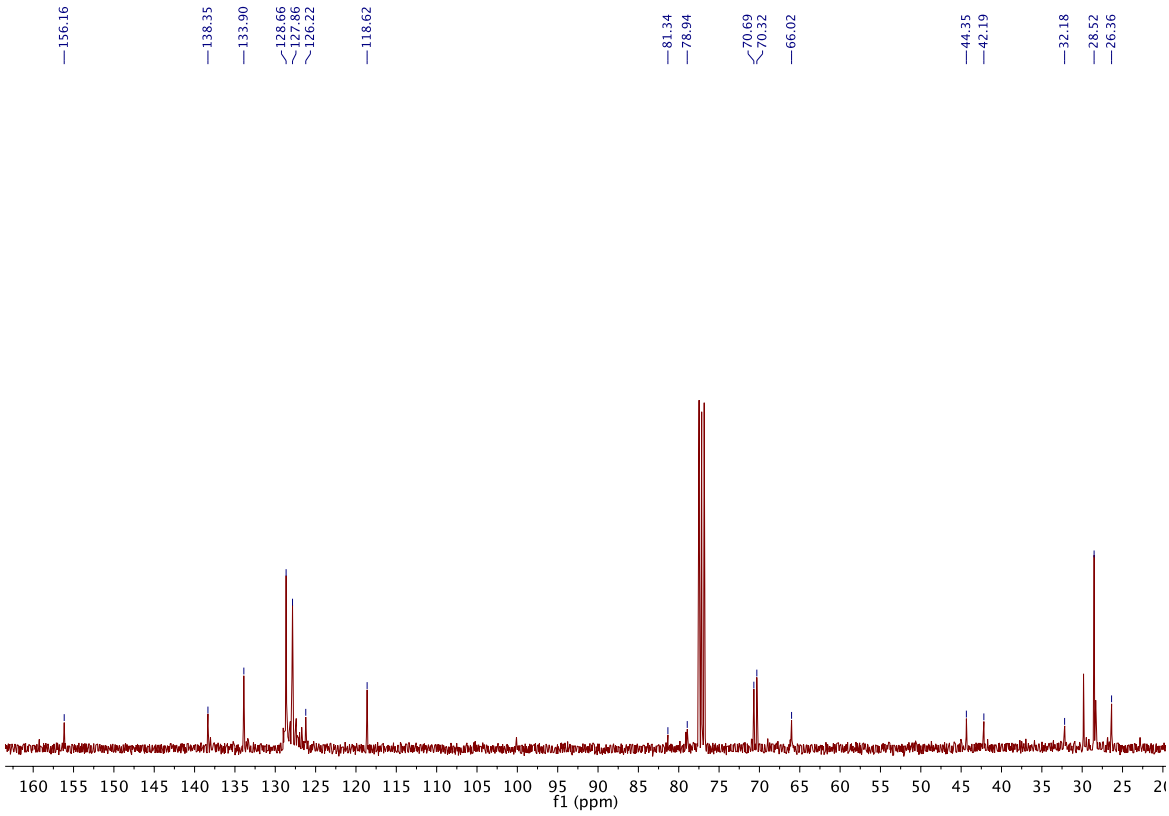

5.51
1.00
2.06
1.04
1.00
1.03
1.02
1.08
0.98
1.03
0.86
1.08
1.08
0.91
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8
f1 (ppm)

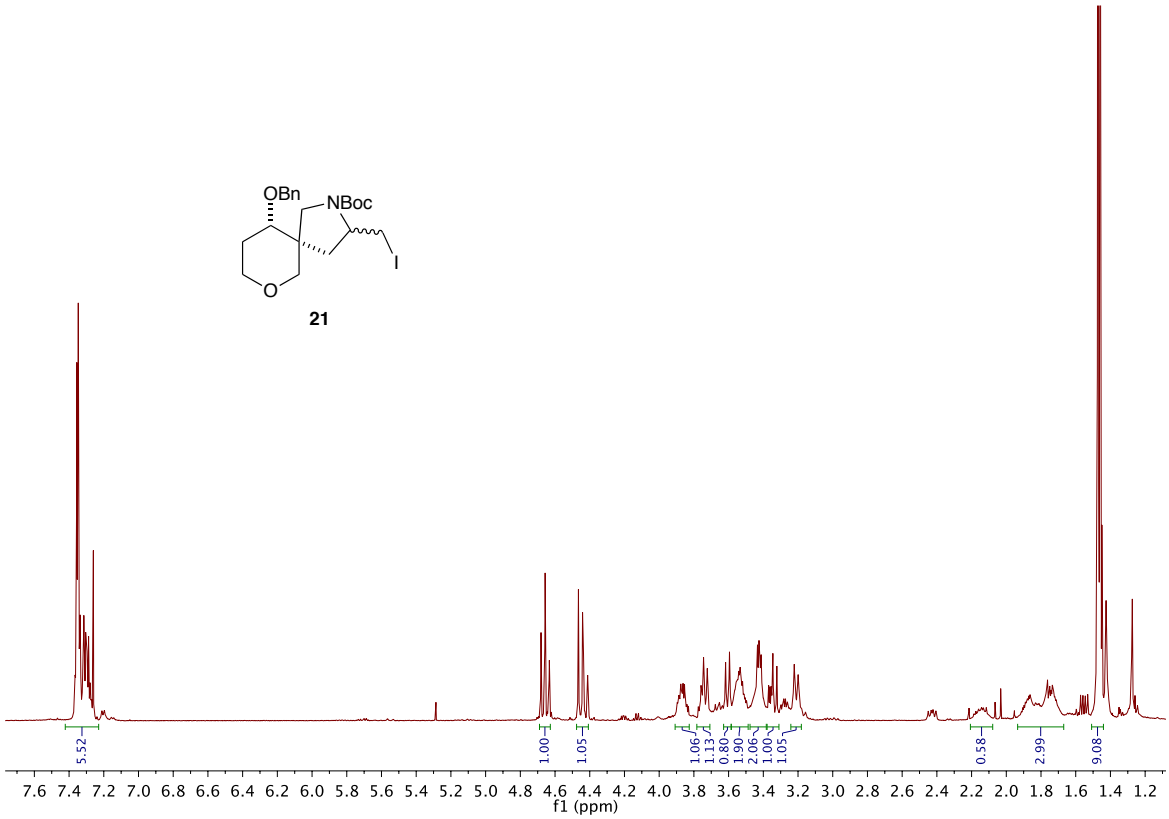

212.03
139.10
132.48
128.82
127.64
126.26
118.79
78.40
70.20
66.92
58.90
56.63
52.29
34.36
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30
f1 (ppm)

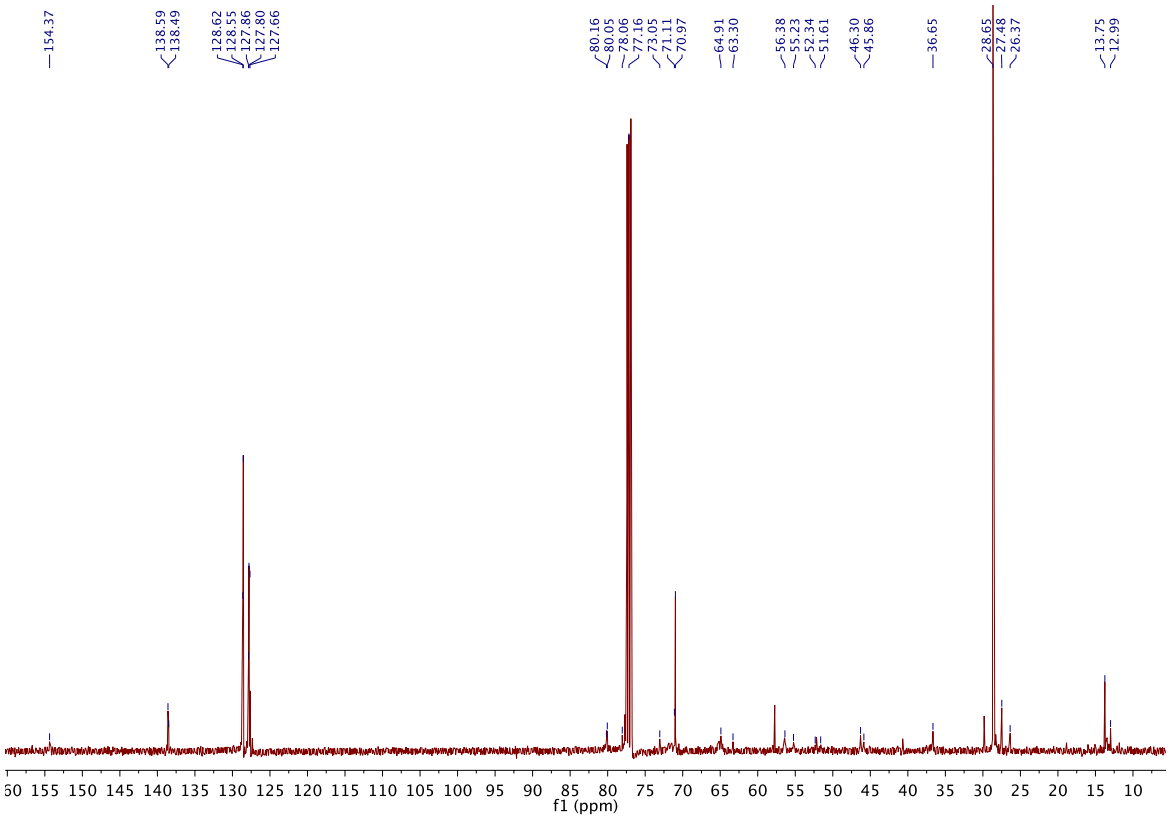

OBn
NHBoc
O

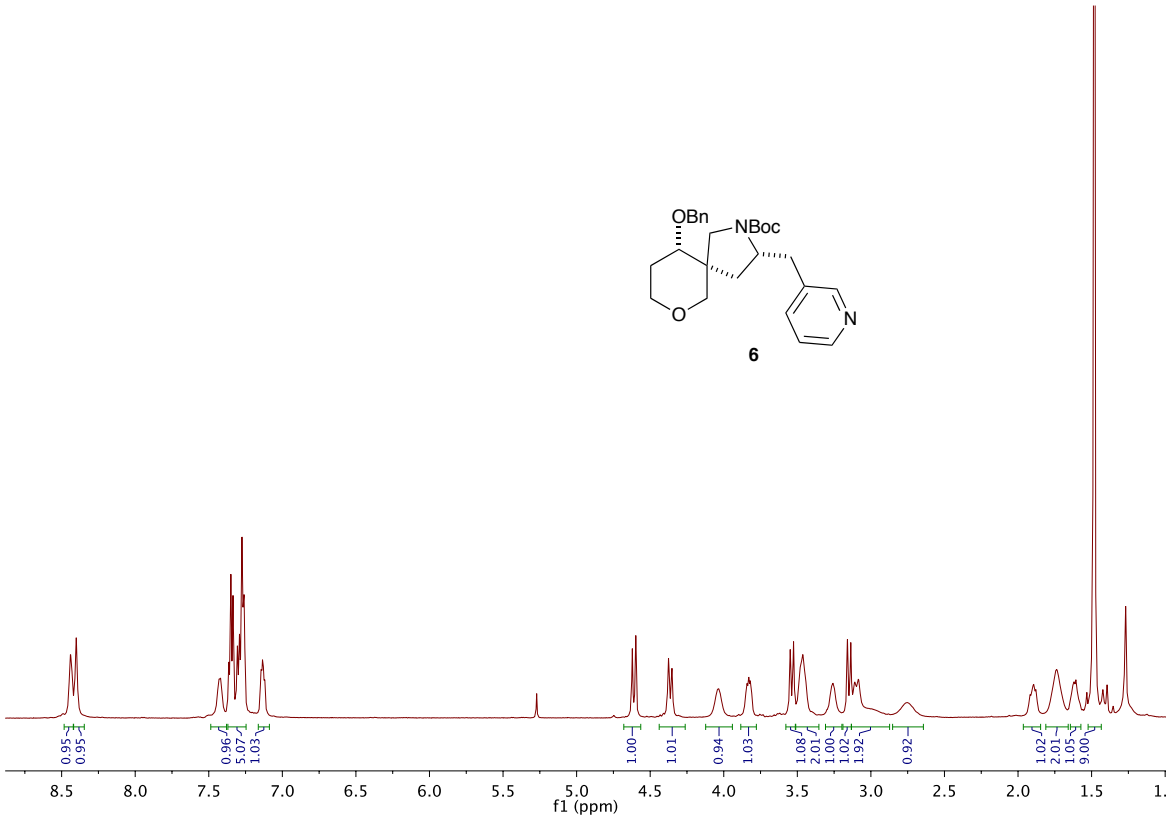
20

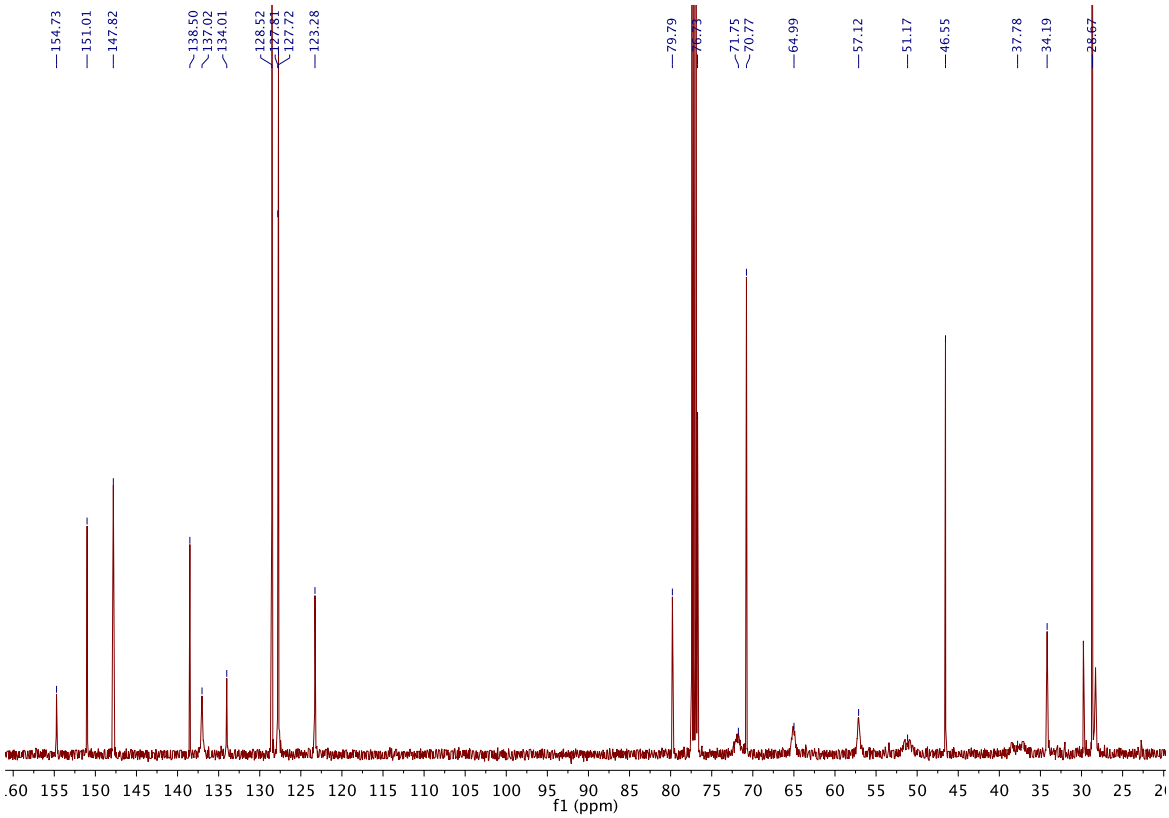
5.02
1.00
1.99
0.64
0.98
0.90
1.05
1.04
1.97
0.98
1.48
1.49
1.07
1.06
9.09
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
f1 (ppm)

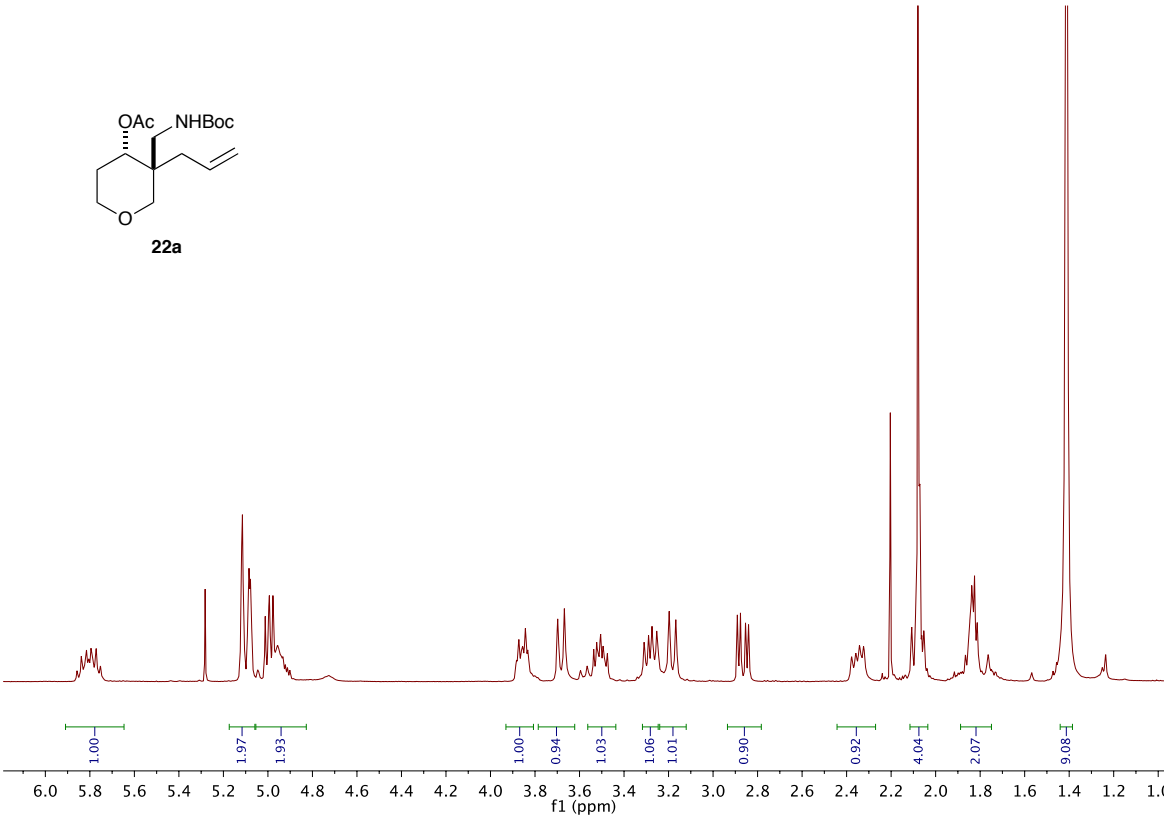

156.16
138.35
133.90
128.66
127.86
126.22
118.62
81.34
78.94
70.69
70.32
66.02
44.35
42.19
32.18
28.52
26.36
160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25
f1 (ppm)

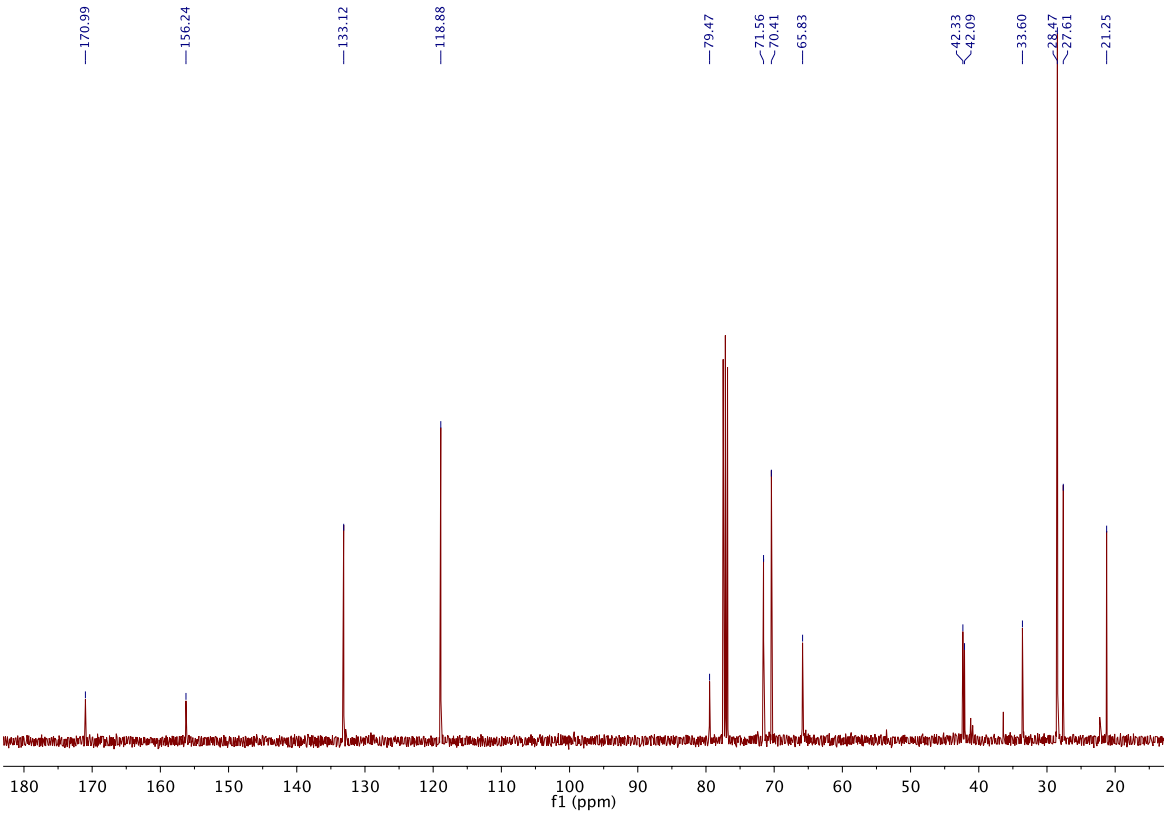

OBn
NBoc
I
O
21
5.52
1.00
1.05
1.06
1.13
0.80
1.90
2.06
1.00
1.05
0.58
2.99
9.08
f1 (ppm)

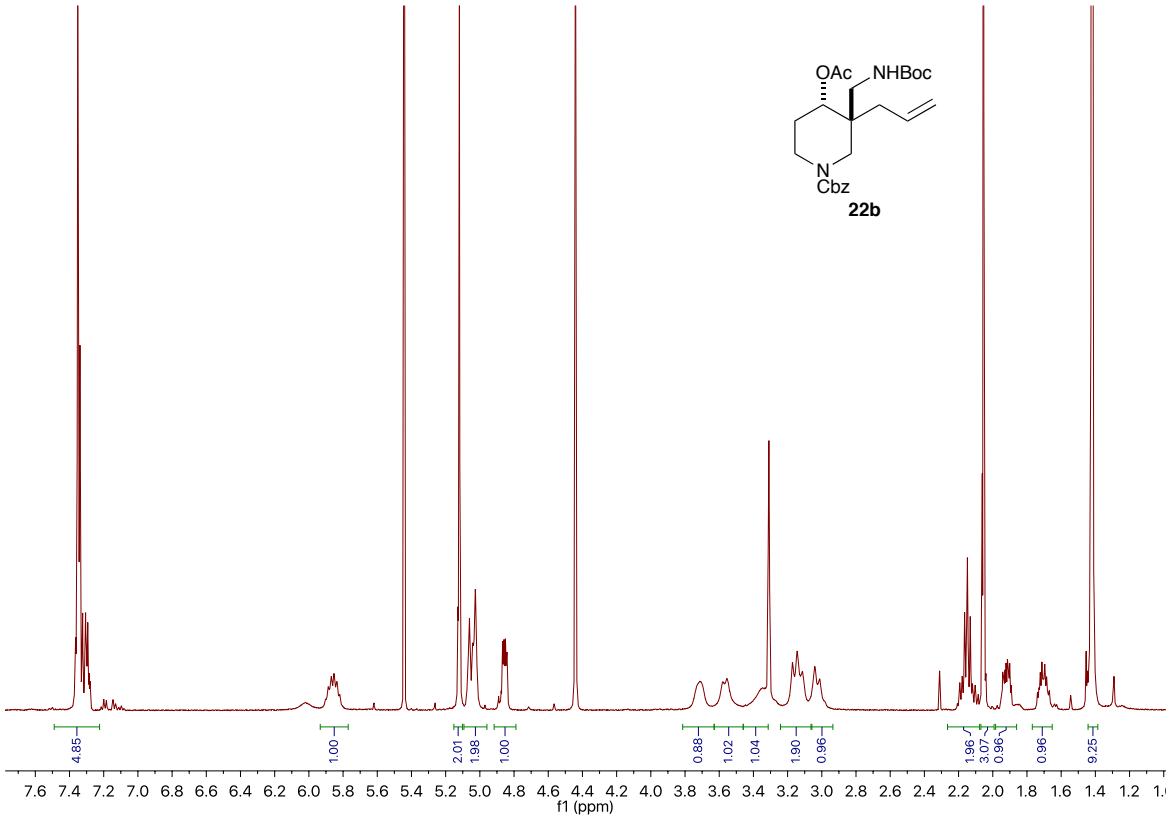

154.37
138.59
138.49
128.62
128.55
127.86
127.80
127.66
80.16
80.05
78.06
77.16
73.05
71.11
70.97
64.91
63.30
56.38
55.23
52.34
51.61
46.30
45.86
36.65
28.65
27.48
26.37
13.75
12.99
f1 (ppm)

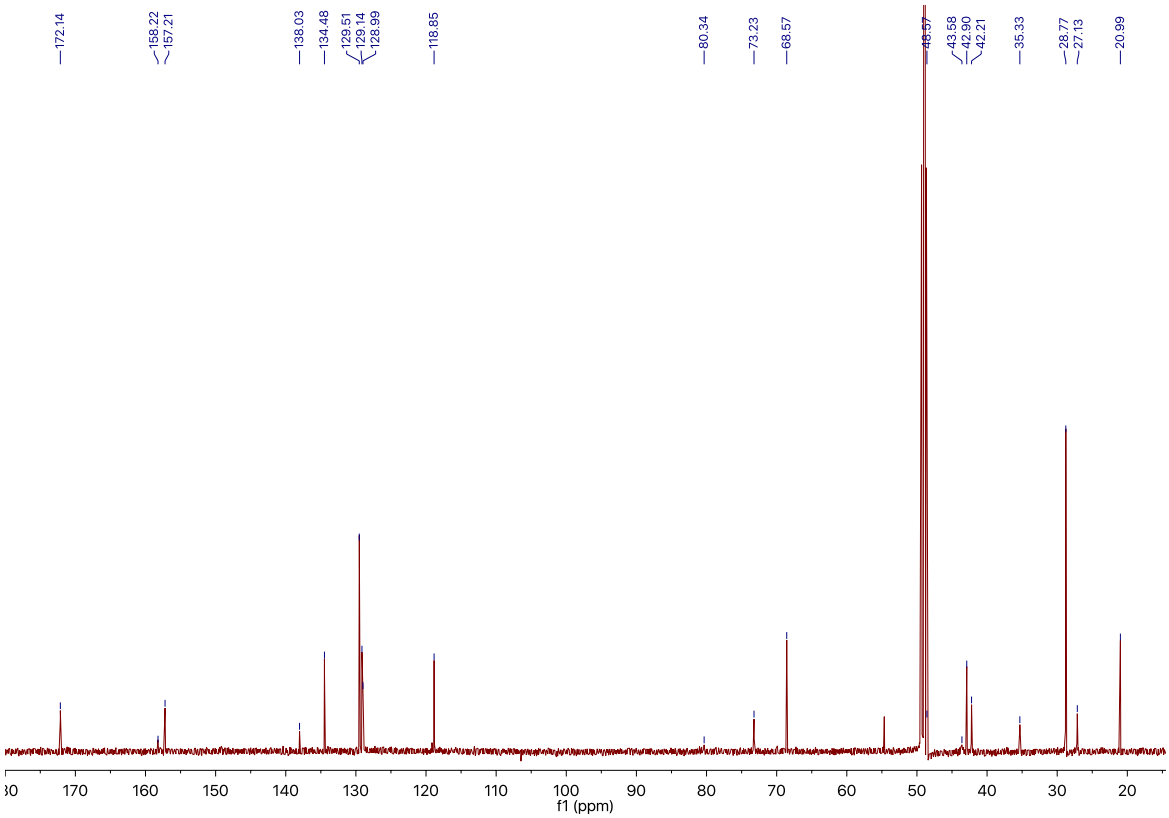

OBn
NBoc
O
N
6
f1 (ppm)

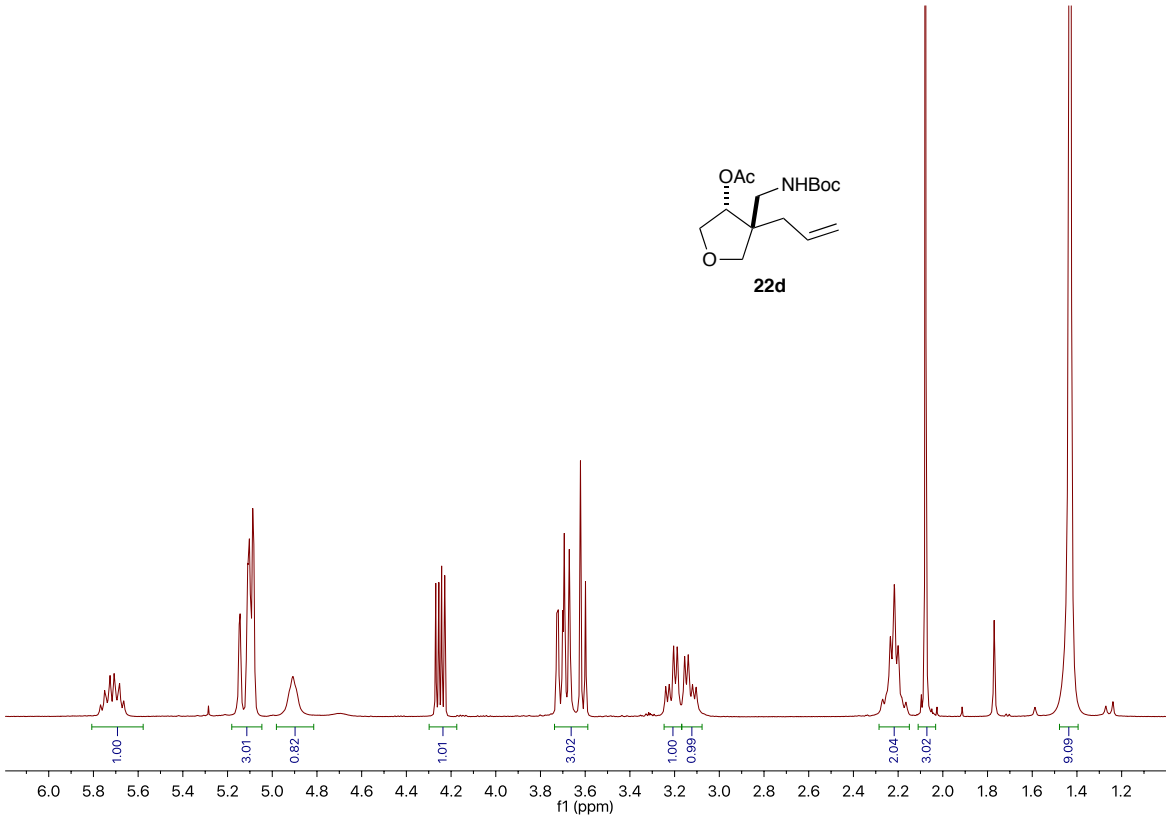

154.73
151.01
147.82
138.50
137.02
134.01
128.52
127.81
127.72
123.28
79.79
78.73
71.75
70.77
64.99
57.12
51.17
46.55
37.78
34.19
28.67
f1 (ppm)

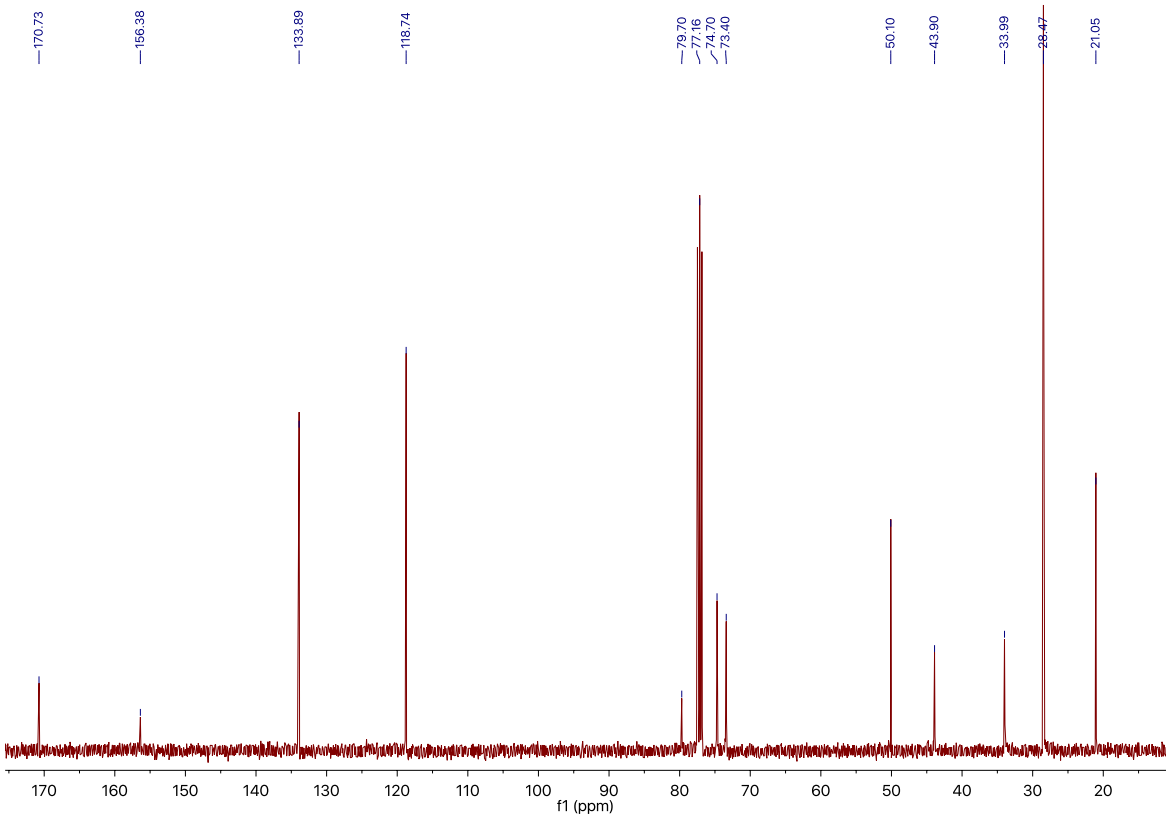

OAc
NHBoc
O
22a
1.00
1.97
1.93
1.00
0.94
1.03
1.06
1.01
0.90
0.92
4.04
2.07
9.08
f1 (ppm)

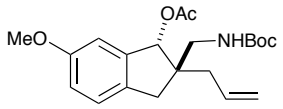

170.99
156.24
133.12
118.88
79.47
71.56
70.41
65.83
42.33
42.09
33.60
28.47
27.61
21.25
f1 (ppm)


OAc
NHBoc
N
Cbz
22b
4.85
1.00
2.01
1.98
1.00
0.88
1.02
1.04
1.90
0.96
1.96
3.07
0.96
0.96
9.25
f1 (ppm)


172.14
158.22
157.21
138.03
134.48
129.51
129.14
128.99
118.85
80.34
73.23
68.57
49.57
43.58
42.90
42.21
35.33
28.77
27.13
20.99
f1 (ppm)

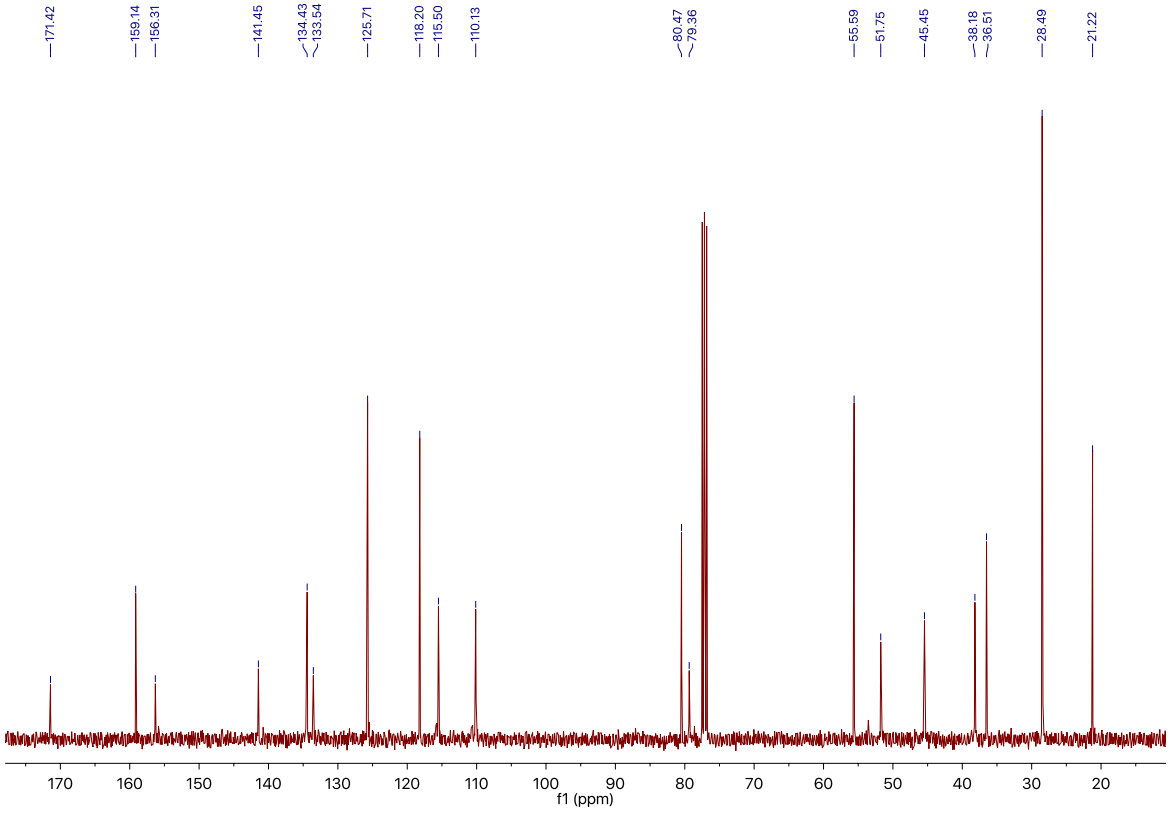

OAc
NHBoc
O
22d
1.00
3.01
0.82
1.01
3.02
1.00
0.99
2.04
3.02
9.09
f1 (ppm)

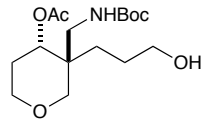

170.73
156.38
133.89
118.74
79.70
77.16
74.70
73.40
50.10
43.90
33.99
28.47
21.05
f1 (ppm)


OAc
MeO
NHBoc

22e

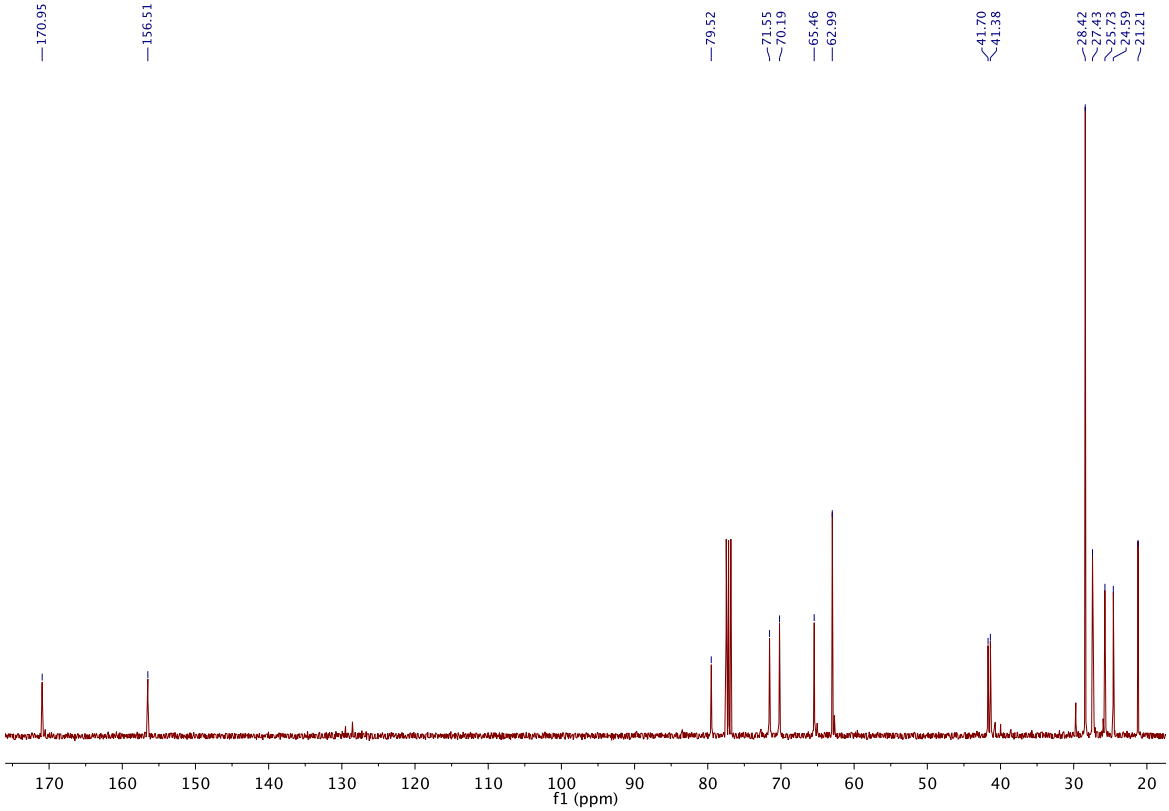
1.00
2.03
0.99
0.99
2.01
0.82
3.01
0.88
1.05
1.03
1.01
1.88
3.01
9.08
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
f1 (ppm)

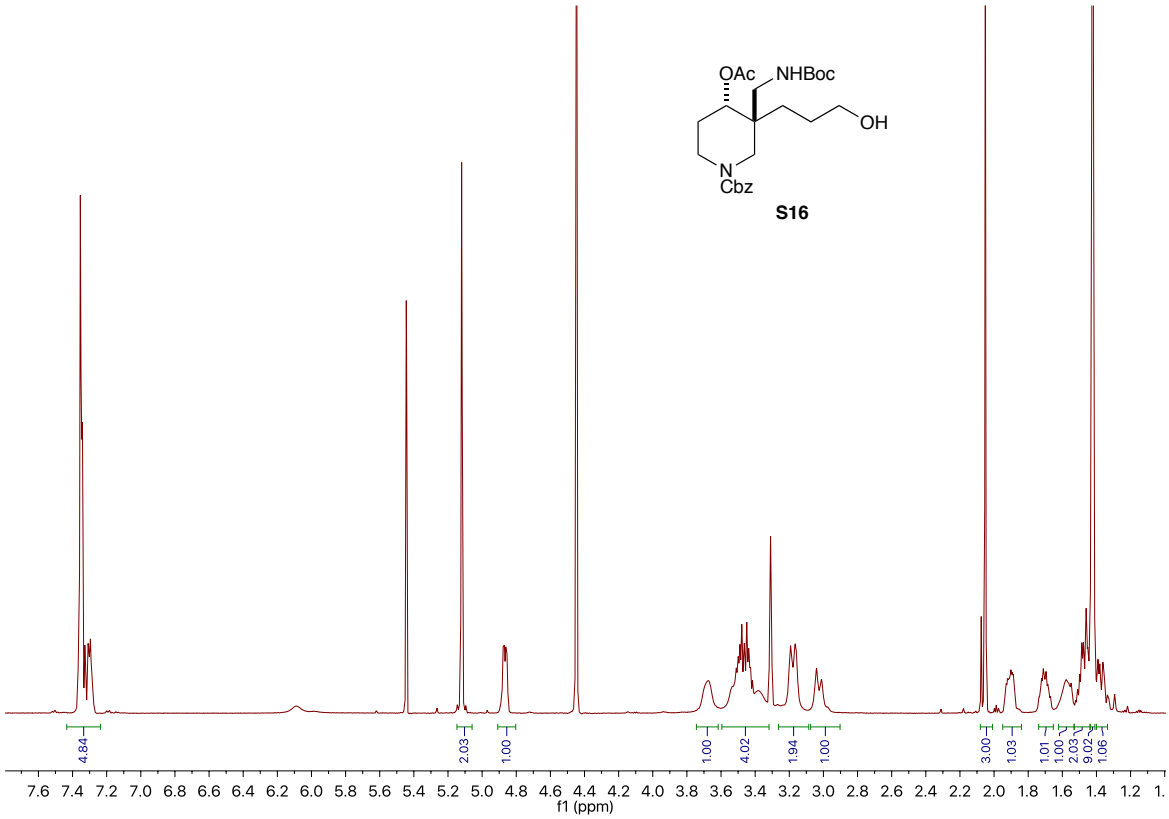

171.42
159.14
156.31
141.45
134.43
133.54
125.71
118.20
115.50
110.13
80.47
79.36
55.59
51.75
45.45
38.18
36.51
28.49
21.22
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)


OAc
NHBoc
OH
O

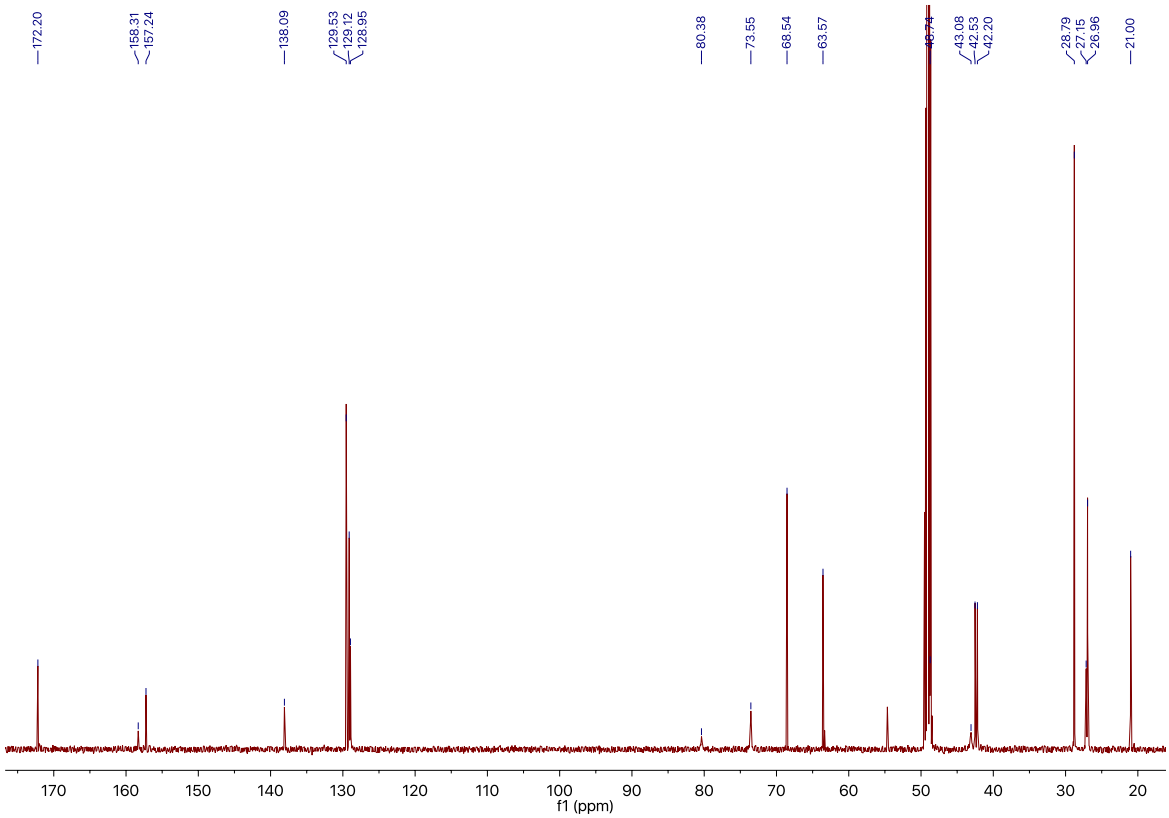
23

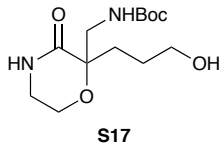
0.96
1.05
1.06
3.06
1.05
2.09
1.00
3.04
1.02
2.04
2.03
1.97
9.10
5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
f1 (ppm)


170.95
156.51
79.52
71.55
70.19
65.46
62.99
41.70
41.38
28.42
27.43
25.73
24.59
21.21
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)


OAc
NHBoc
OH
N
Cbz
4.84
2.03
1.00
1.00
4.02
1.94
1.00
3.00
1.03
1.01
1.00
2.03
9.02
1.06
f1 (ppm)

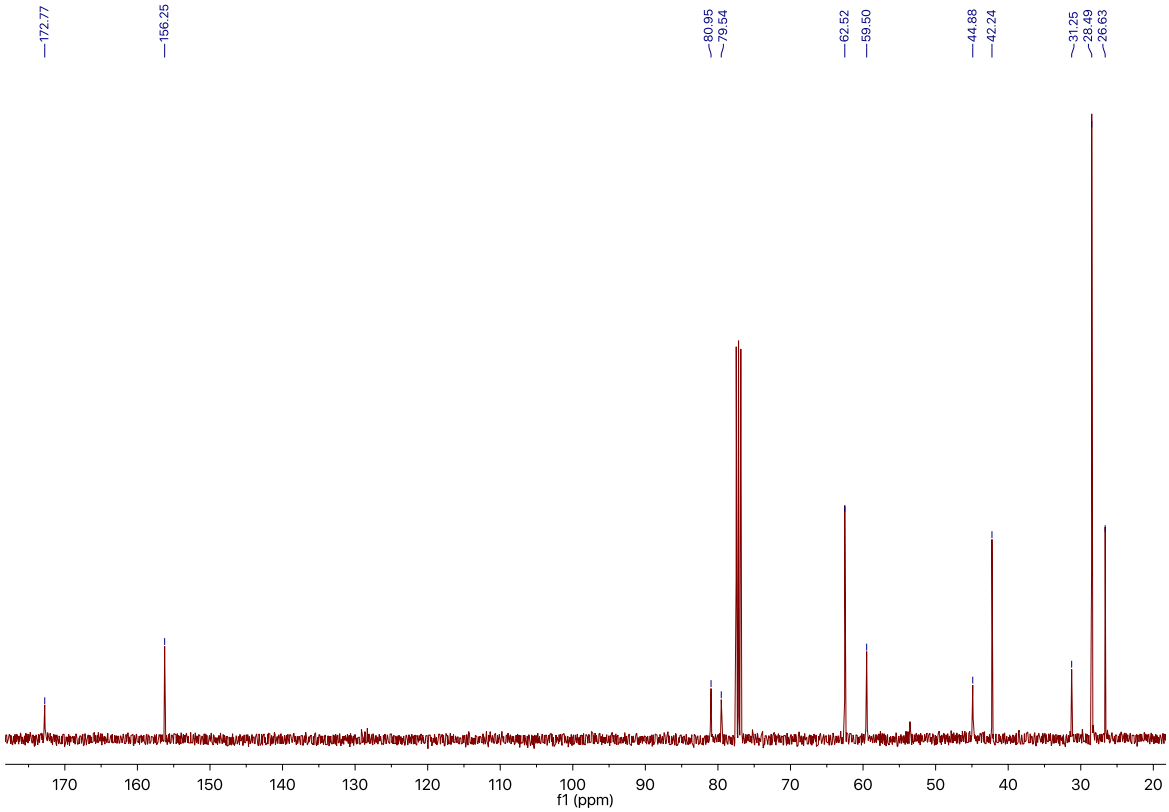
S16

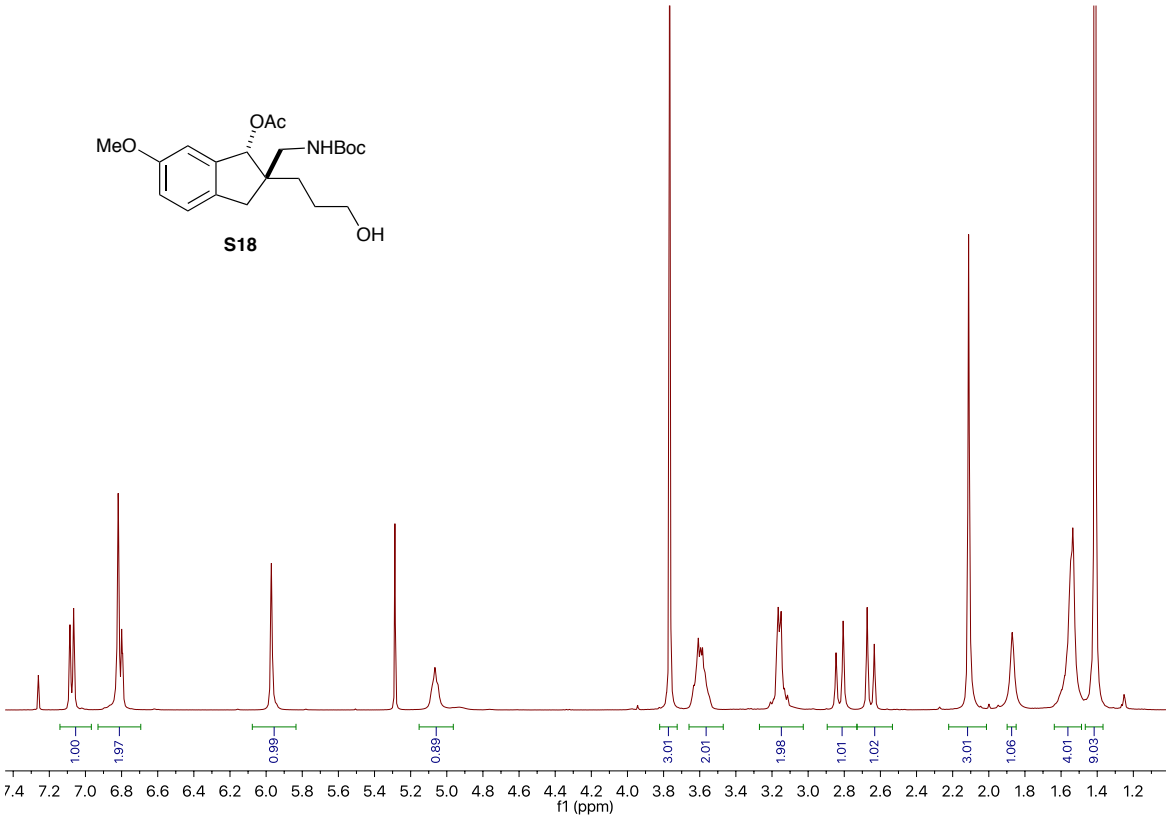

172.20
158.31
157.24
138.09
129.53
129.12
128.95
80.38
73.55
68.54
63.57
48.74
43.08
42.53
42.20
28.79
27.15
26.96
21.00
f1 (ppm)

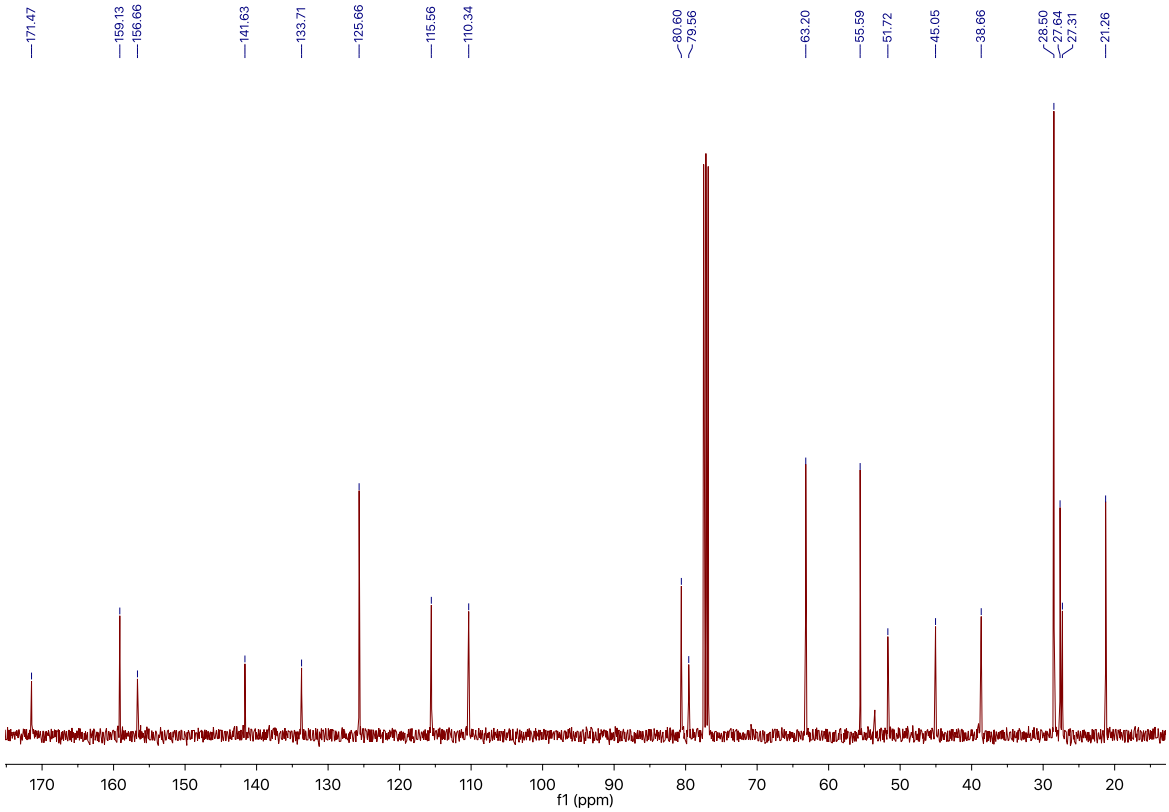

O
NHBoc
HN
OH
O

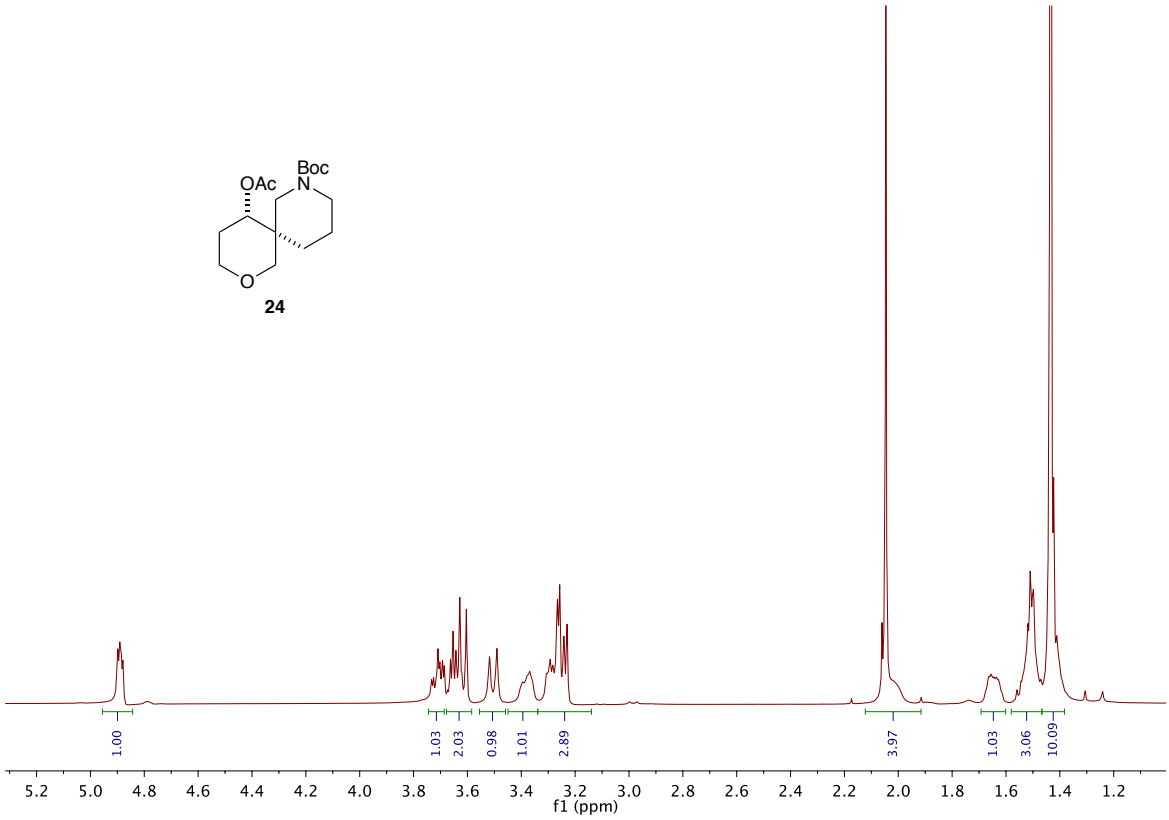
S17

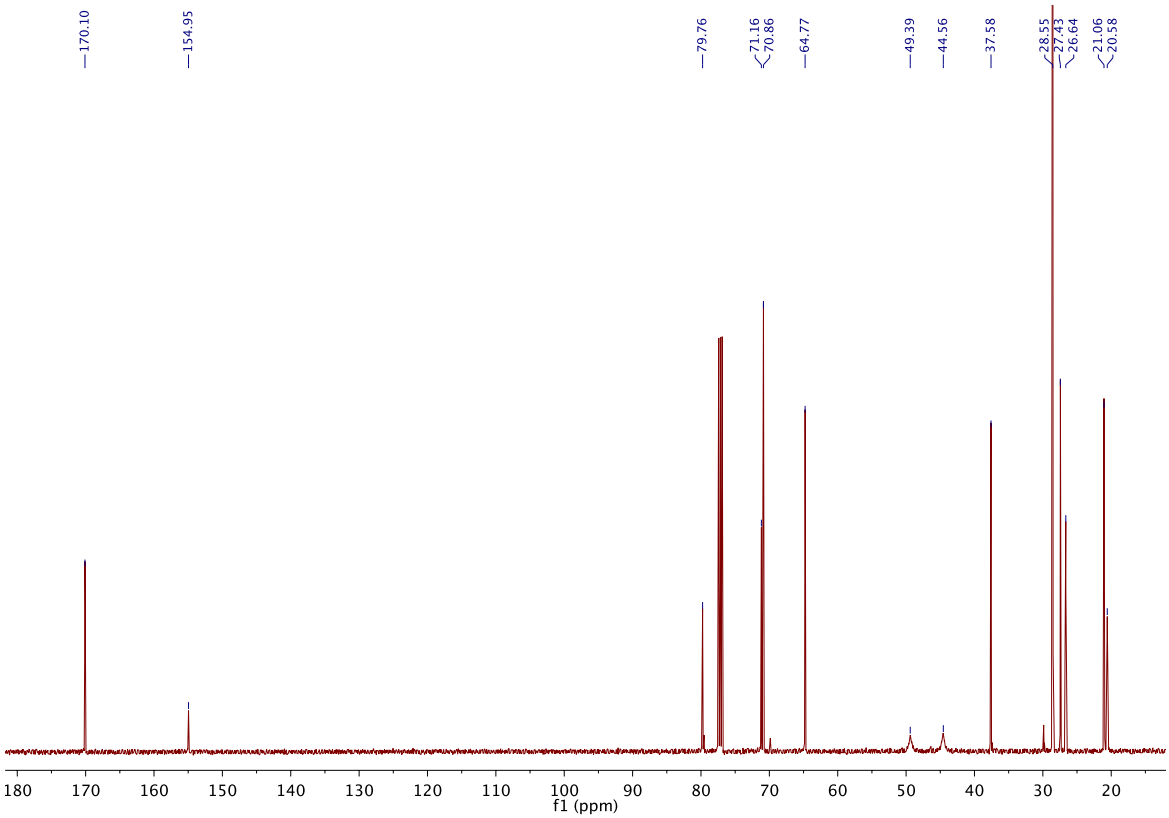
1.05
0.99
2.04
3.01
1.00
1.94
1.03
1.00
2.00
1.03
8.97
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0
f1 (ppm)

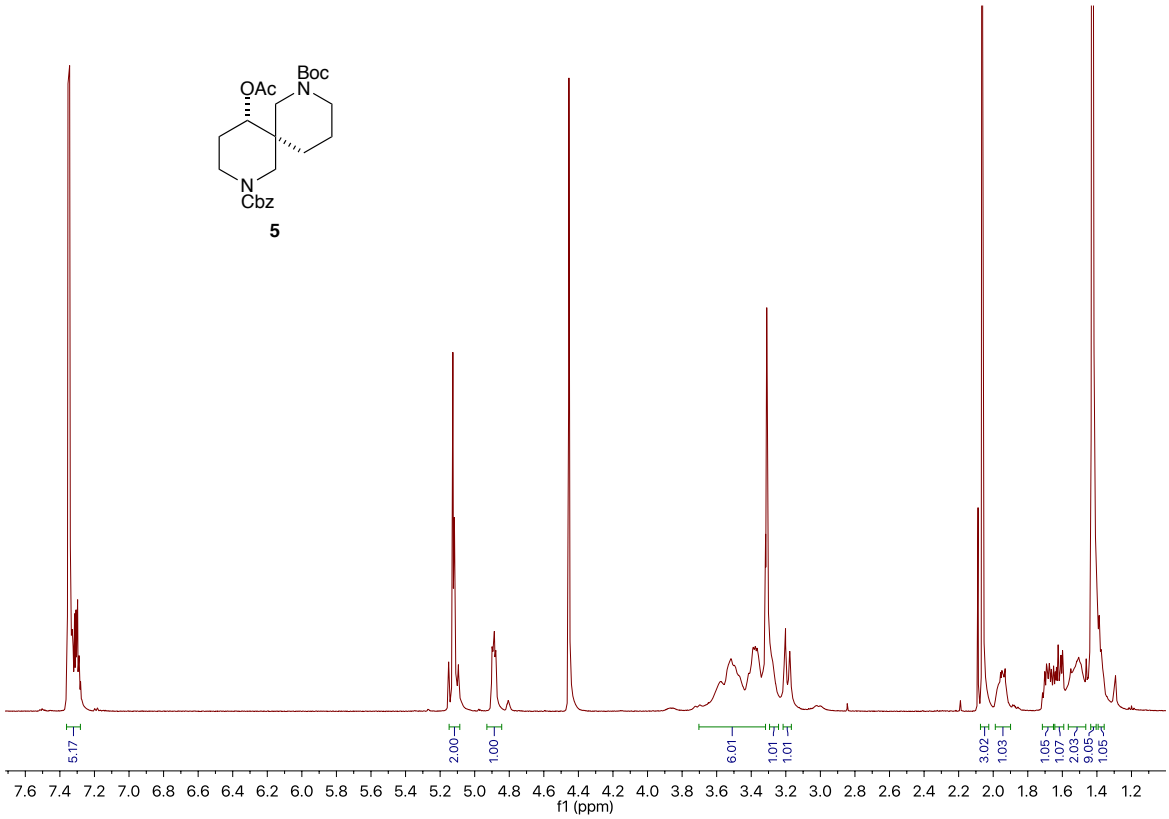

172.77
156.25
80.95
79.54
62.52
59.50
44.88
42.24
31.25
28.49
26.63
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

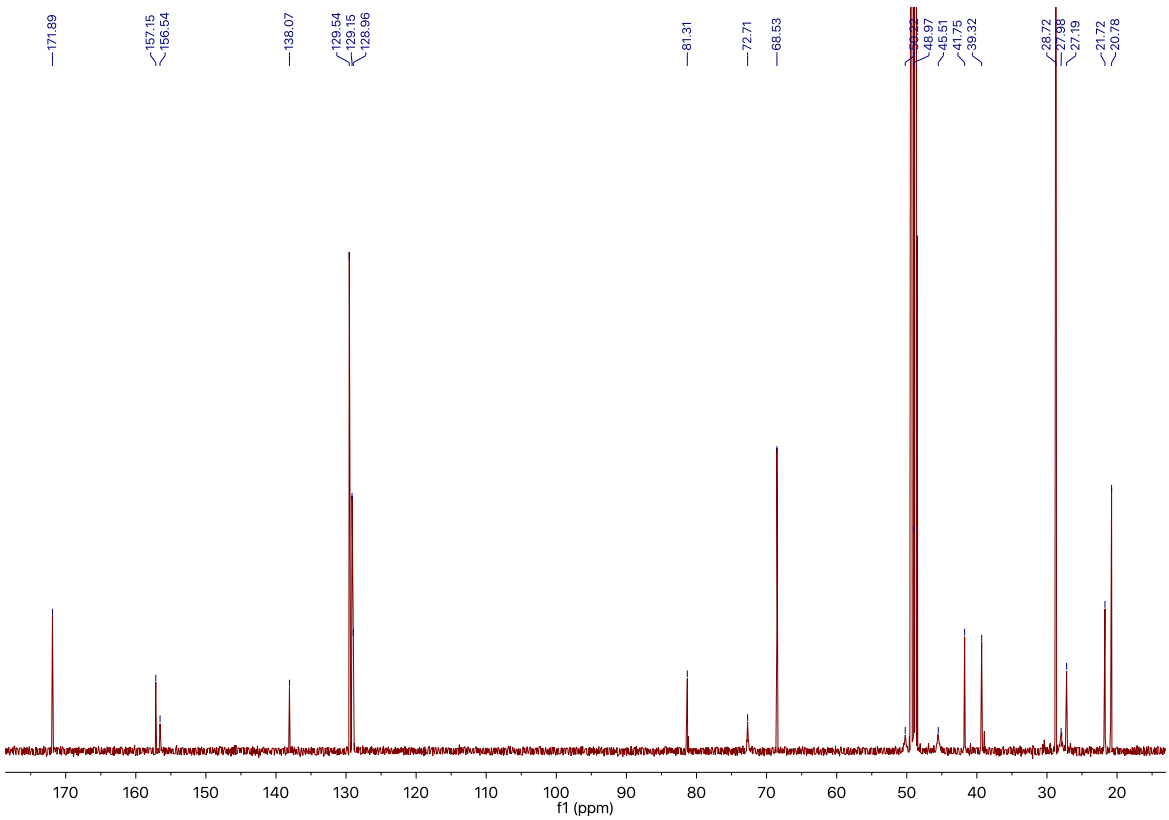

OAc
MeO
NHBoc
OH
S18
1.00
1.97
0.99
0.89
3.01
2.01
1.98
1.01
1.02
3.01
1.06
4.01
9.03
f1 (ppm)

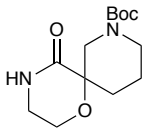

171.47
159.13
156.66
141.63
133.71
125.66
115.56
110.34
80.60
79.56
63.20
55.59
51.72
45.05
38.66
28.50
27.64
27.31
21.26
f1 (ppm)


OAc
Boc
N
O
24
1.00
1.03
2.03
0.98
1.01
2.89
3.97
1.03
3.06
10.09
f1 (ppm)


170.10
154.95
79.76
71.16
70.86
64.77
49.39
44.56
37.58
28.55
27.43
26.64
21.06
20.58
f1 (ppm)

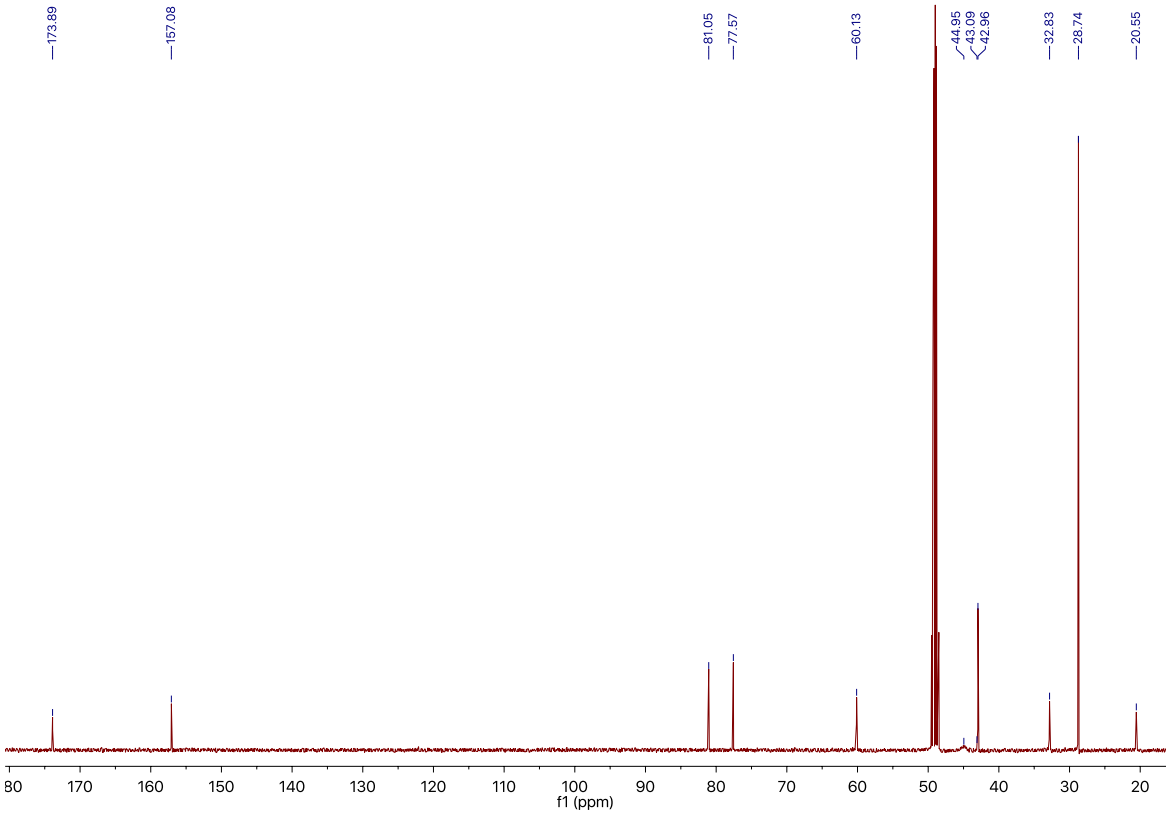

OAc
Boc
N
N
Cbz
5
5.17
2.00
1.00
6.01
1.01
1.01
3.02
1.03
1.05
1.07
2.03
9.05
1.05
f1 (ppm)

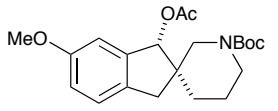

171.89
157.15
156.54
138.07
129.54
129.15
128.96
81.31
72.71
68.53
48.97
45.51
41.75
39.32
28.72
27.98
27.19
21.72
20.78
f1 (ppm)


Boc
N
O
HN
O

33

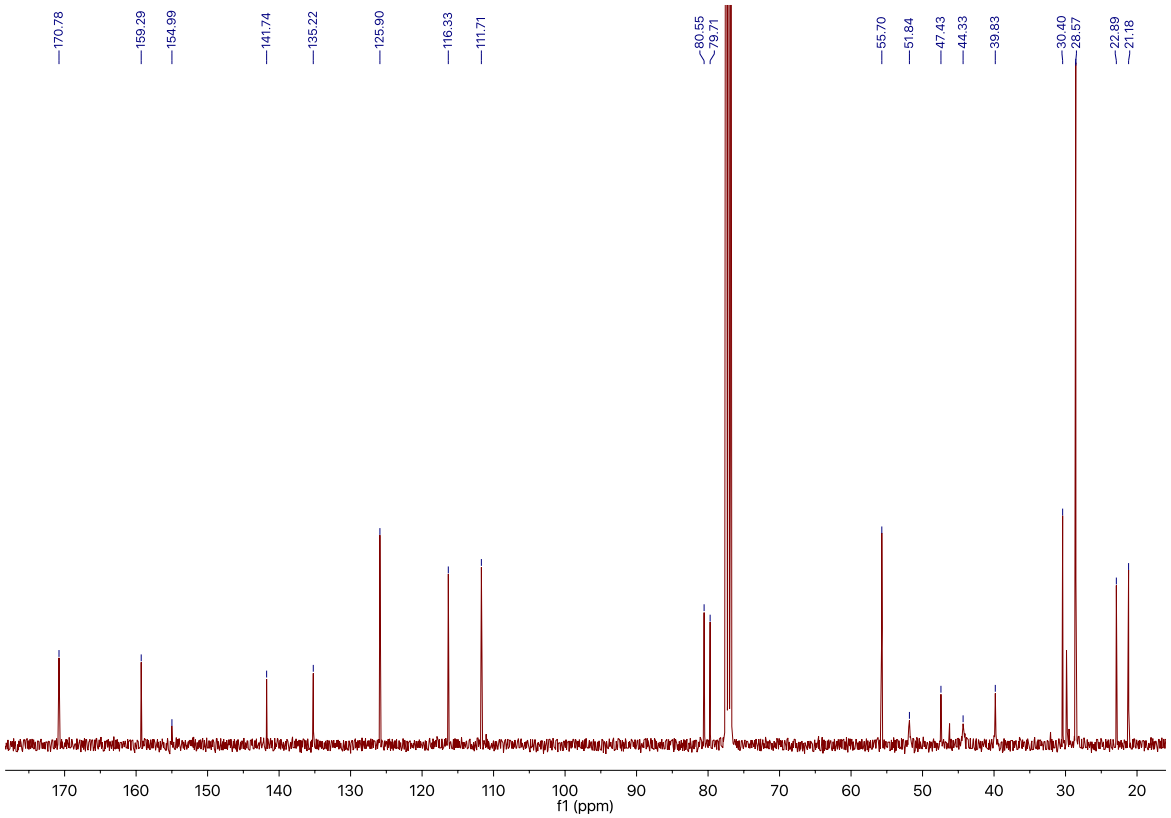
1.00
0.95
0.96
1.00
0.88
1.03
1.10
0.89
0.92
1.09
1.01
0.94
9.82
4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1
f1 (ppm)

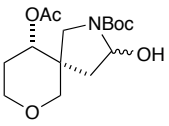

173.89
157.08
81.05
77.57
60.13
44.95
43.09
42.96
32.83
28.74
20.55
80 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)


OAc
MeO
NBoc

40

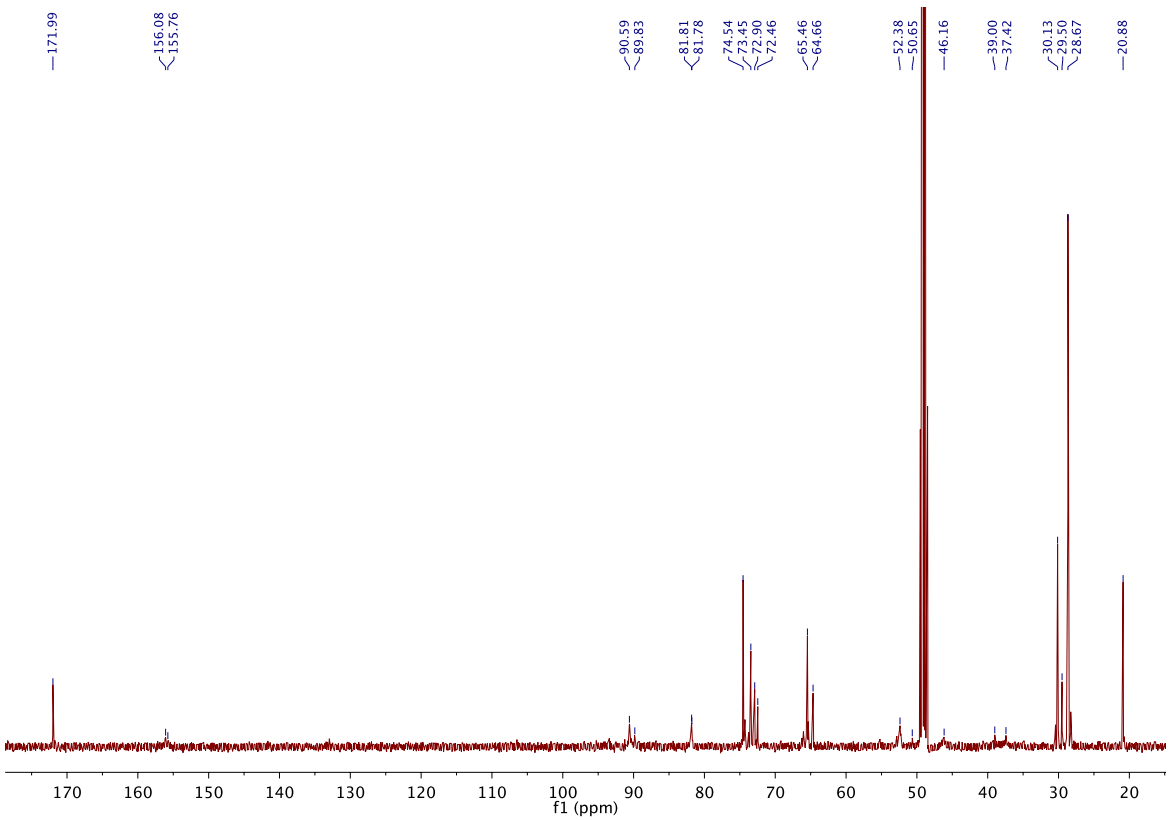
1.00
0.97
0.99
0.94
3.02
0.94
0.99
1.00
1.04
0.99
0.97
2.90
1.03
1.03
2.00
9.06
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

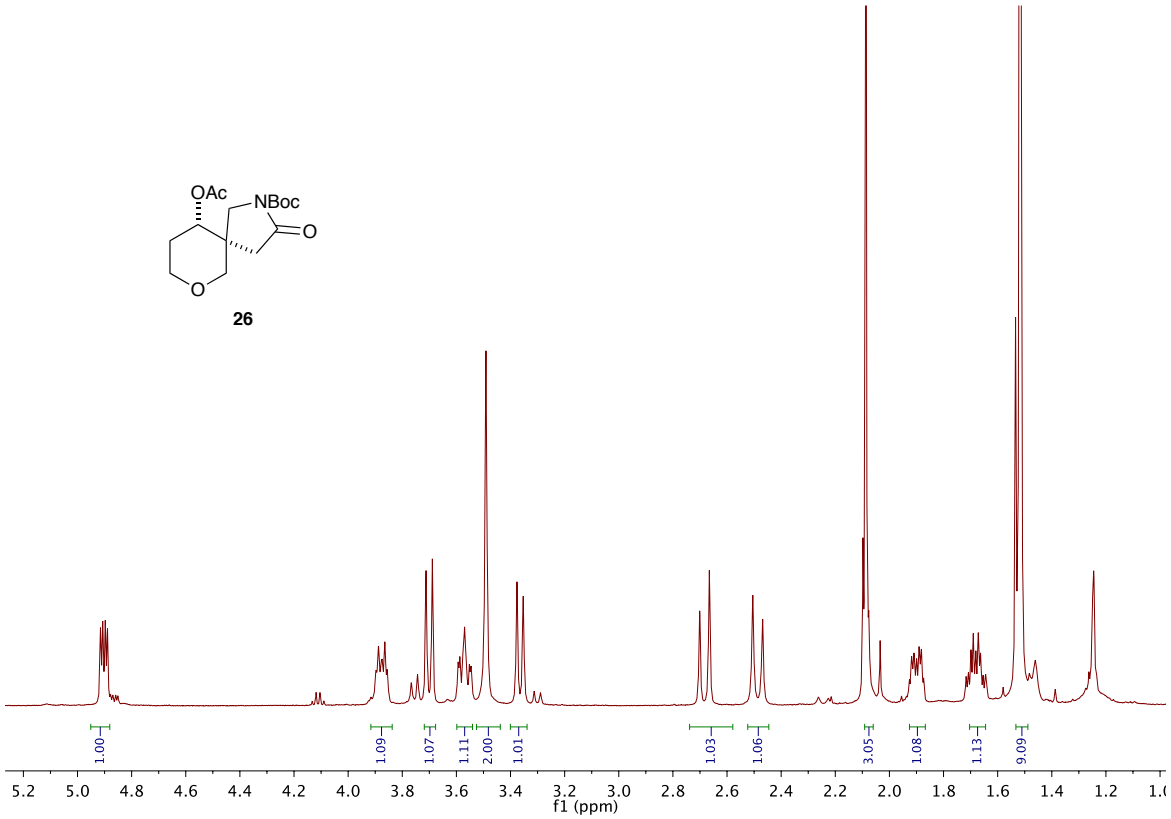

170.78
159.29
154.99
141.74
135.22
125.90
116.33
111.71
80.55
79.71
55.70
51.84
47.43
44.33
39.83
30.40
28.57
22.89
21.18
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

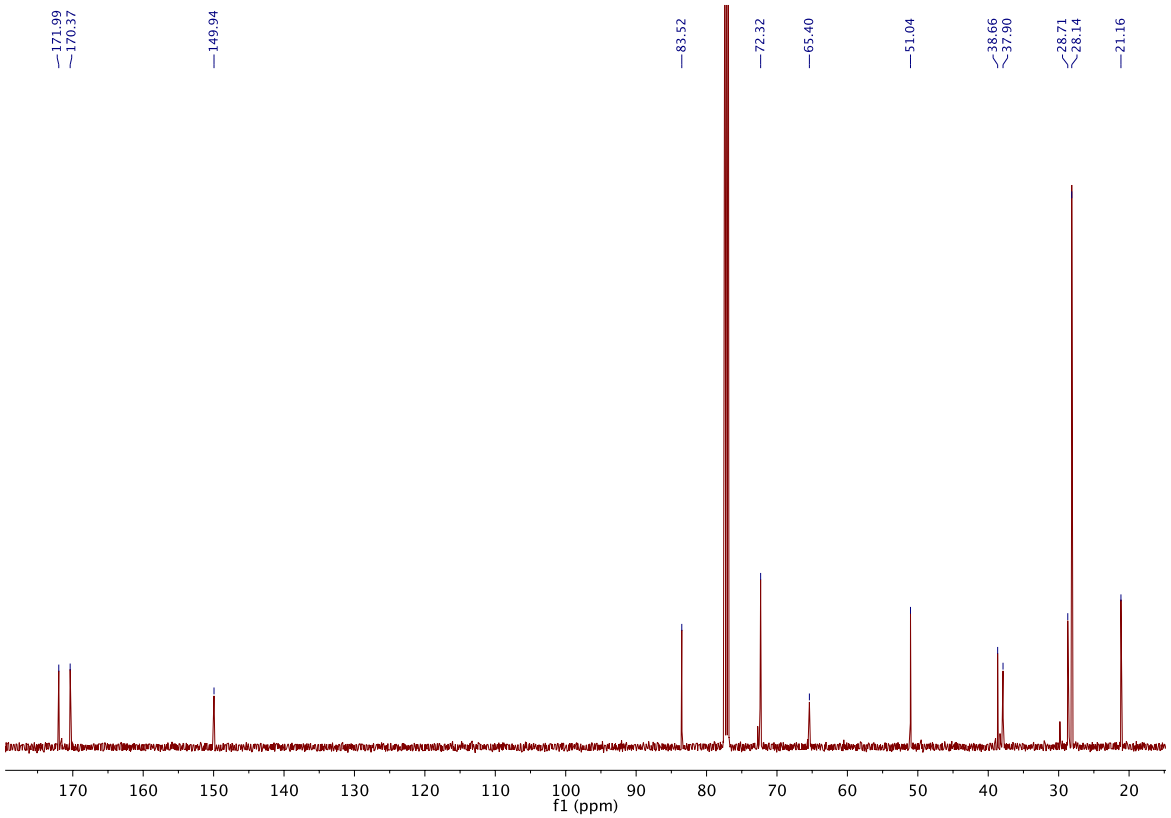

OAc
NBoc
OH
O

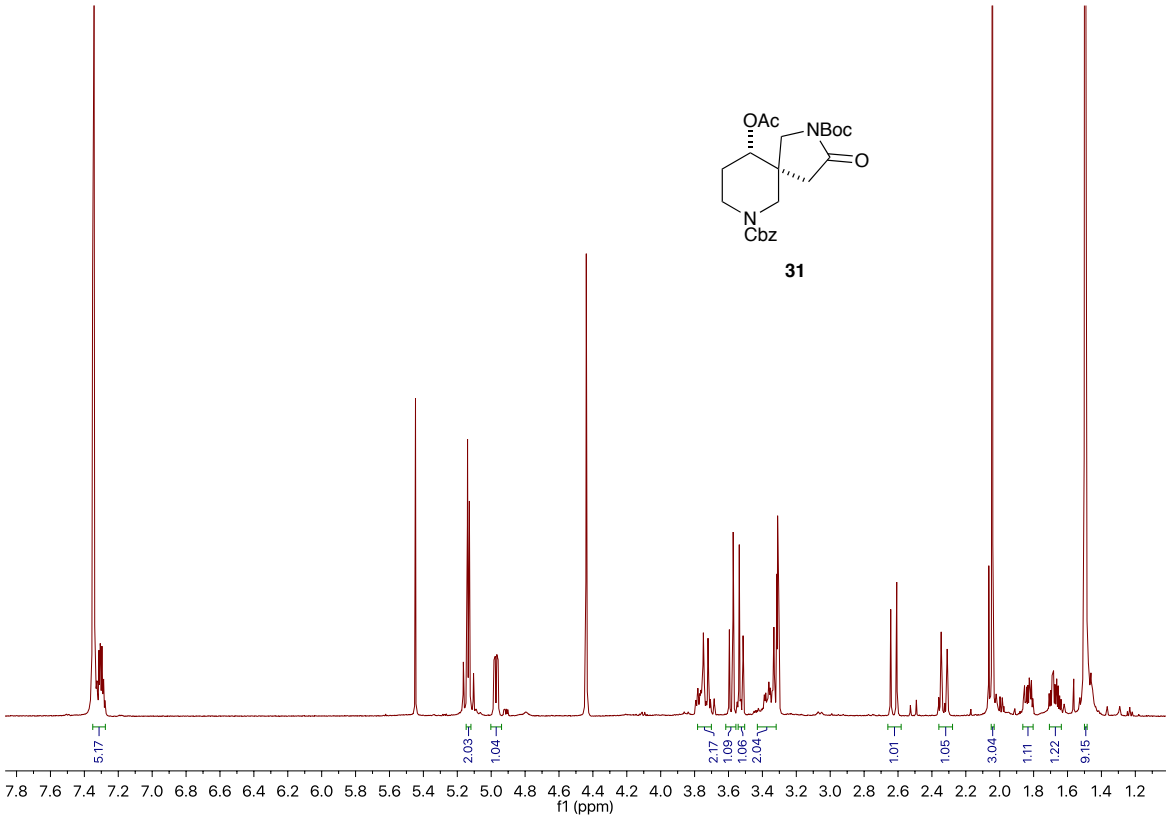
25

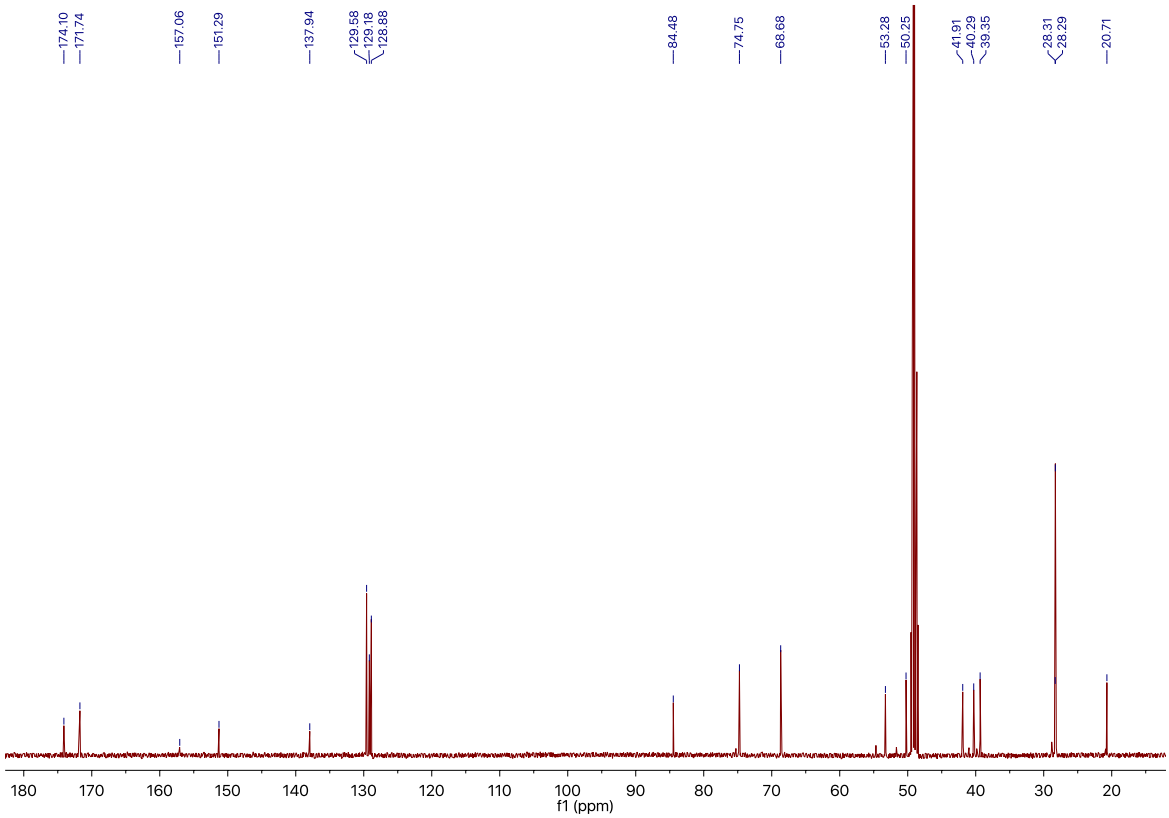
0.49
0.48
1.00
1.74
3.03
2.79
4.28
2.36
1.19
10.84
5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0
f1 (ppm)

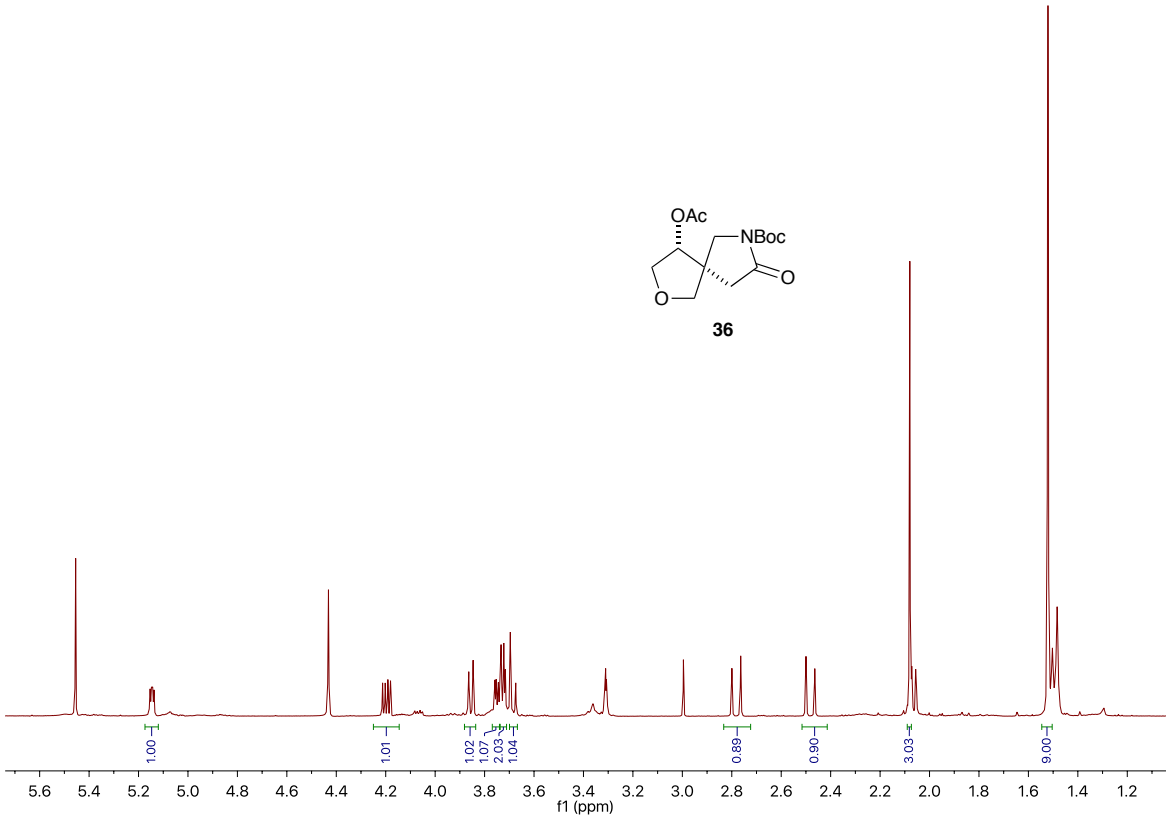

171.99
156.08
155.76
90.59
89.83
81.81
81.78
74.54
73.45
72.90
72.46
65.46
64.66
52.38
50.65
46.16
39.00
37.42
30.13
29.50
28.67
20.88
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

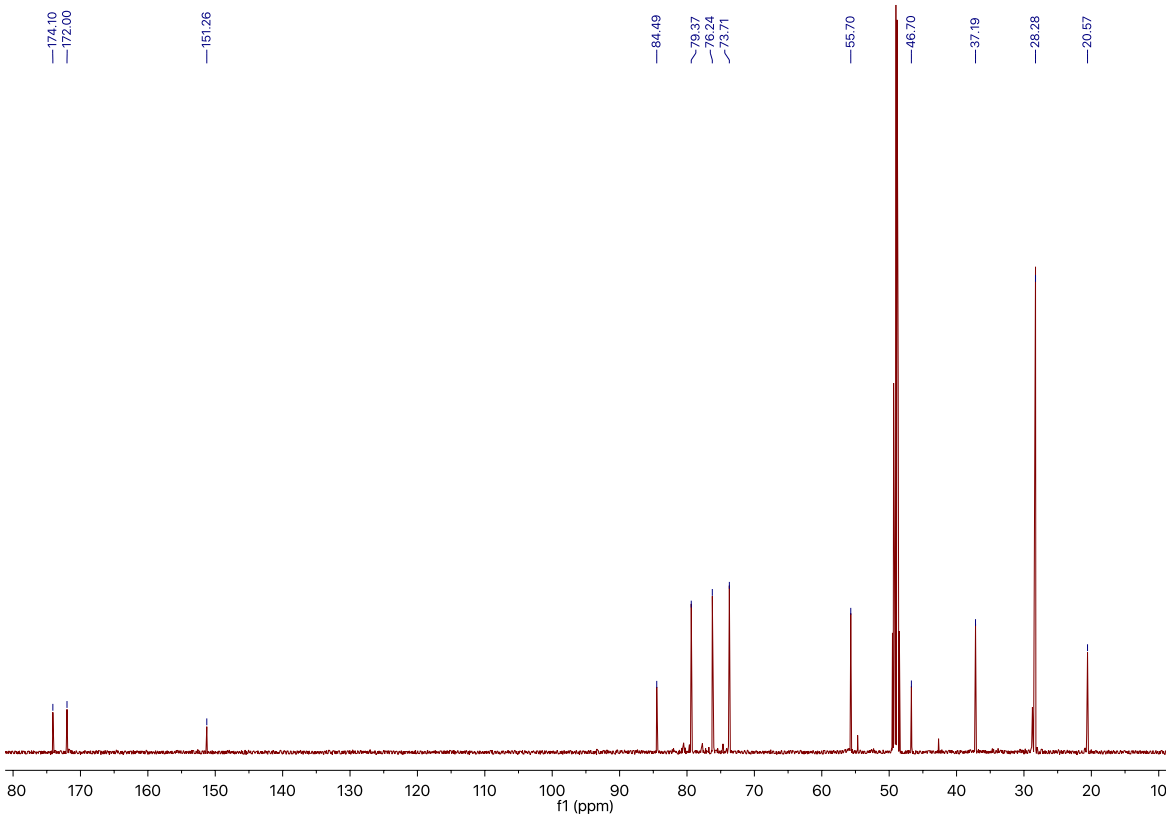

OAc
NBoc
O
O
26
1.00
1.09
1.07
1.11
2.00
1.01
1.03
1.06
3.05
1.08
1.13
9.09
f1 (ppm)

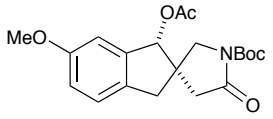

171.99
170.37
149.94
83.52
72.32
65.40
51.04
38.66
37.90
28.71
28.14
21.16
f1 (ppm)


OAc
NBoc
O
N
Cbz
31
5.17
2.03
1.04
2.17
1.09
1.06
2.04
1.01
1.05
3.04
1.11
1.22
9.15
f1 (ppm)


174.10
171.74
157.06
151.29
137.94
129.58
129.18
128.88
84.48
74.75
68.68
53.28
50.25
41.91
40.29
39.35
28.31
28.29
20.71
f1 (ppm)

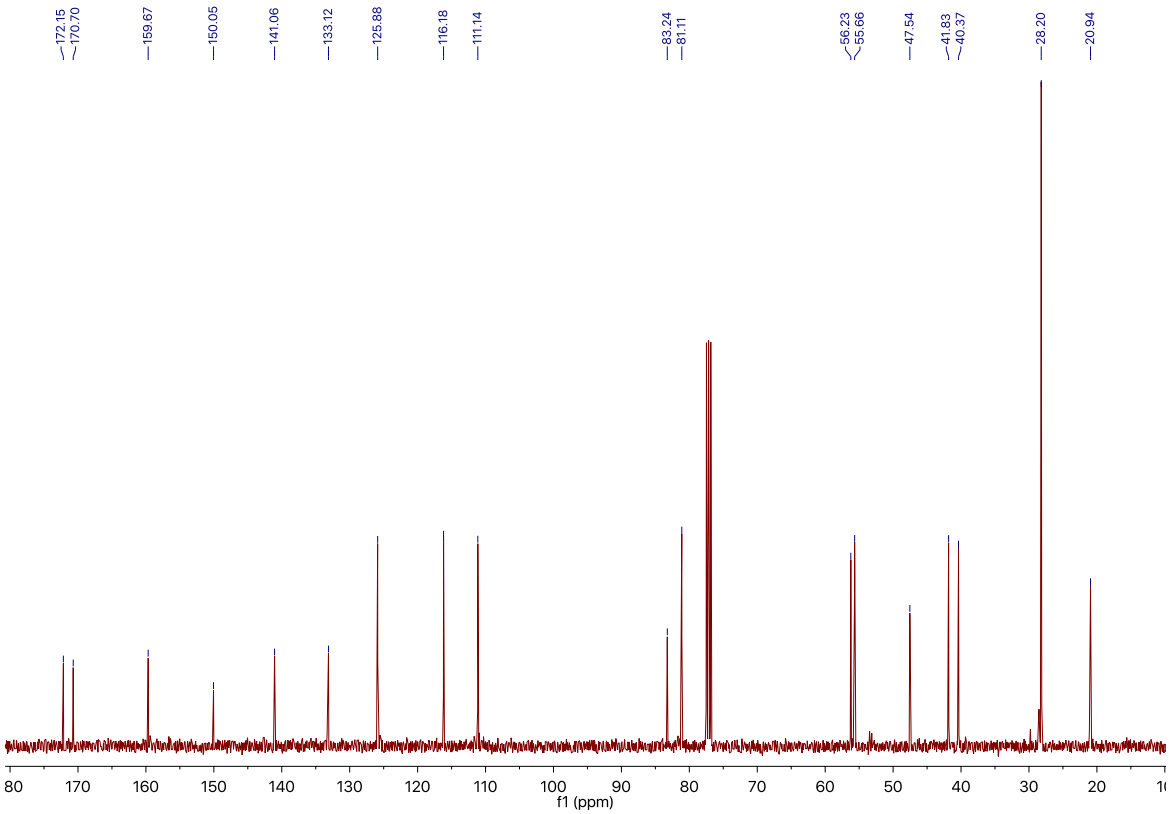

OAc
NBoc
O
O
36
1.00
1.01
1.02
1.07
2.03
1.04
0.89
0.90
3.03
9.00
f1 (ppm)

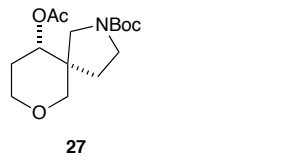

174.10
172.00
151.26
84.49
79.37
76.24
73.71
55.70
46.70
37.19
28.28
20.57
f1 (ppm)


OAc
MeO
NBoc
O

41

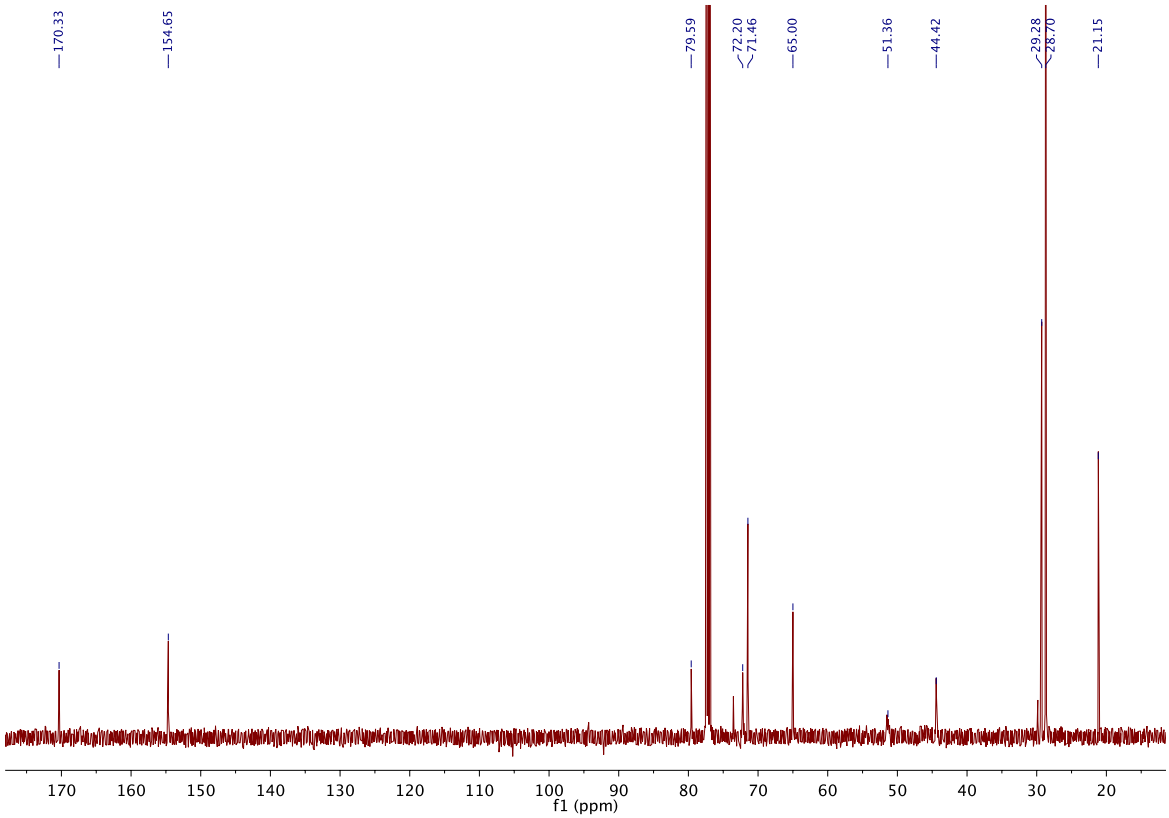
1.08
1.01
1.07
1.04
3.11
1.05
1.00
1.07
1.06
1.04
1.00
3.00
9.09
f1 (ppm)

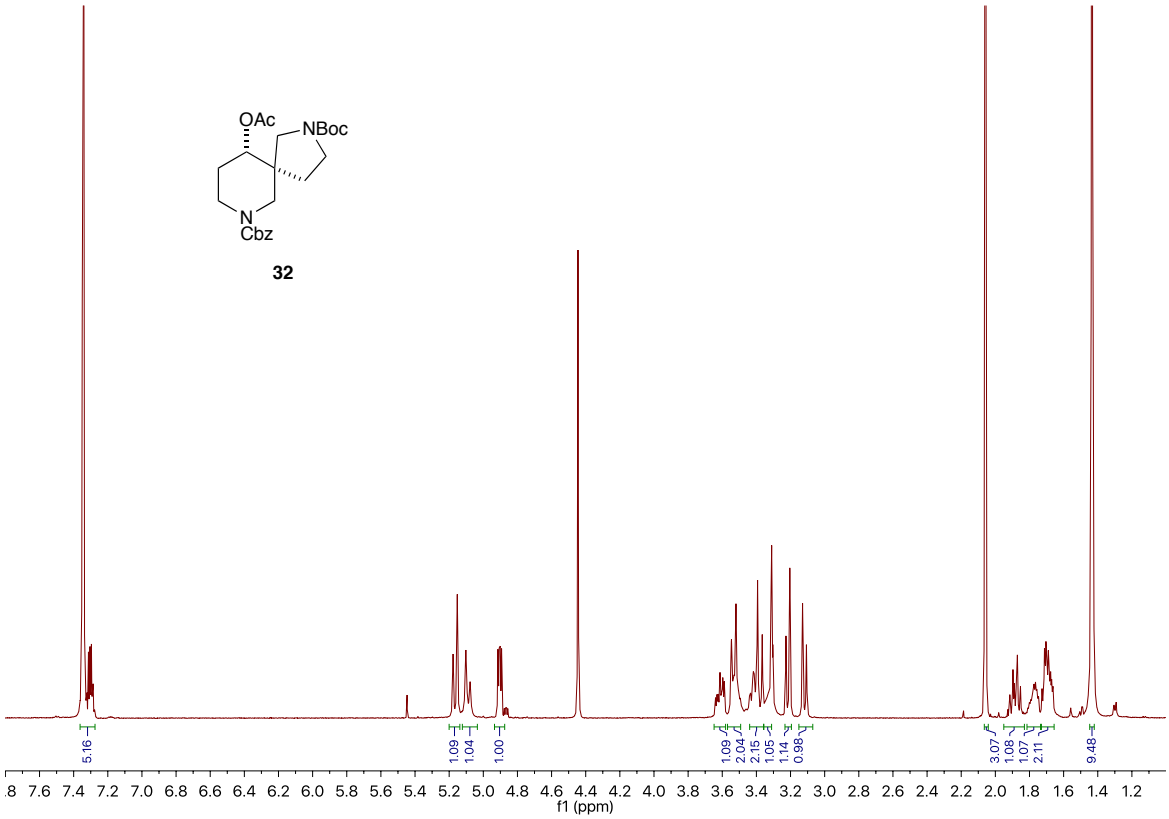

172.15
170.70
159.67
150.05
141.06
133.12
125.88
116.18
111.14
83.24
81.11
56.23
55.66
47.54
41.83
40.37
28.20
20.94
f1 (ppm)

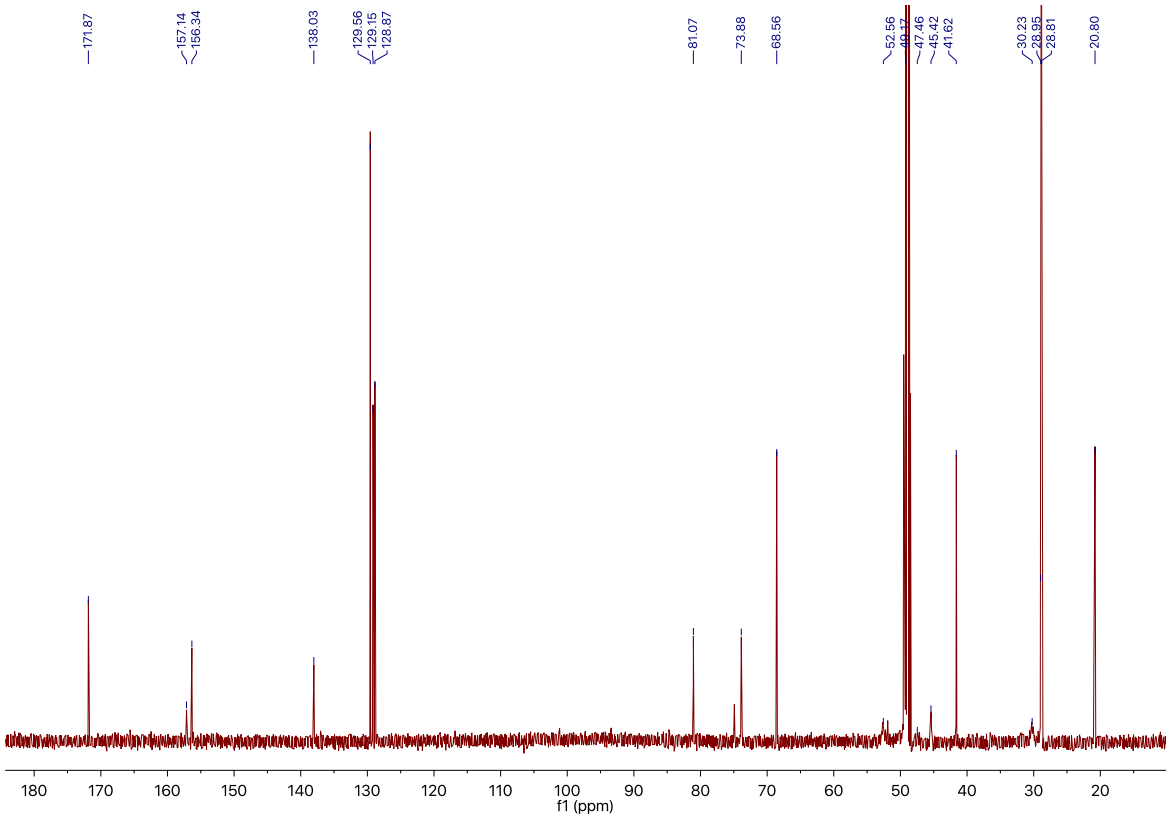

OAc
NBoc
O

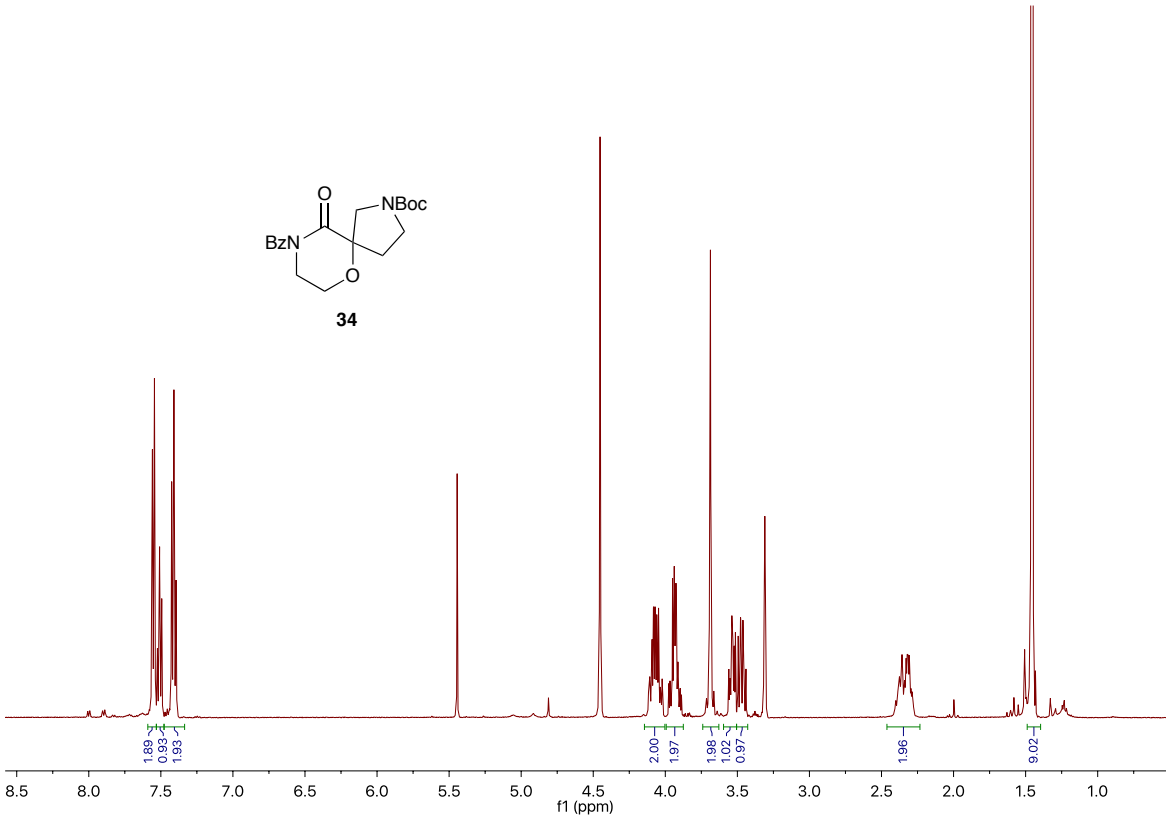
27

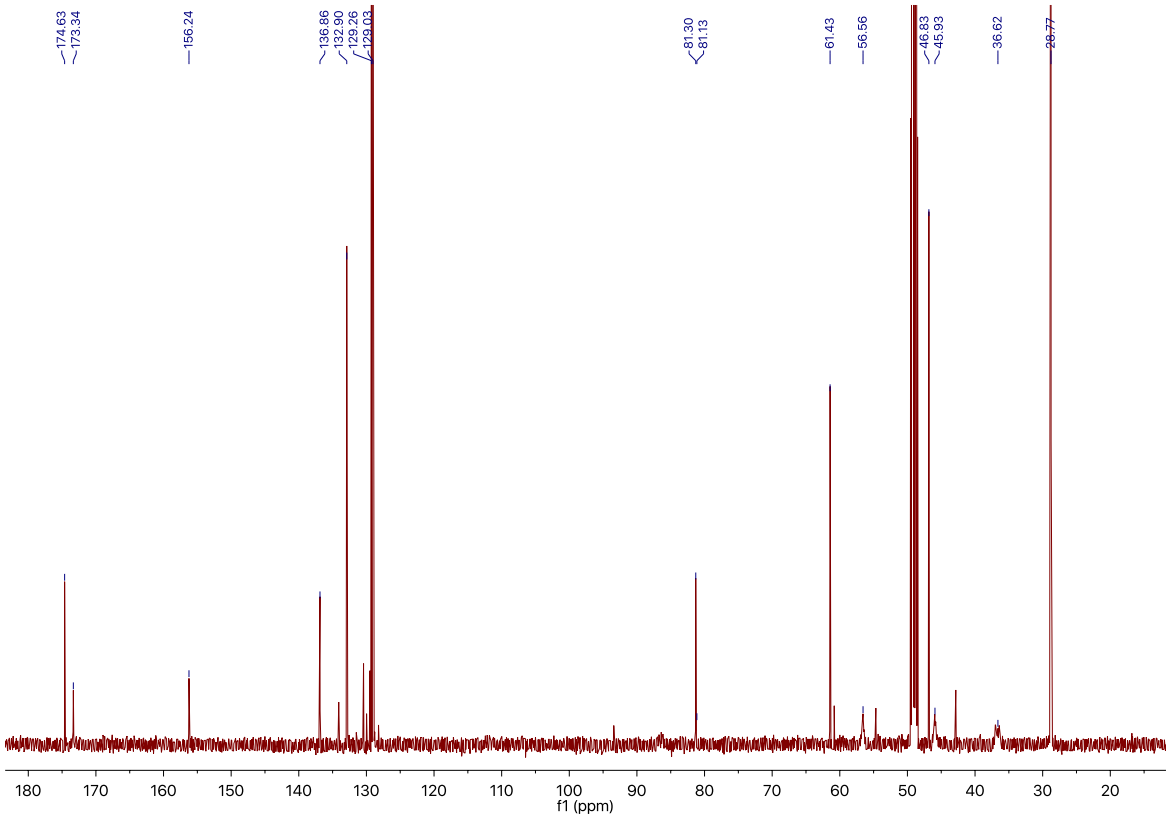
0.91
1.00
2.04
1.02
3.05
0.92
3.01
2.99
1.03
9.07
5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
f1 (ppm)

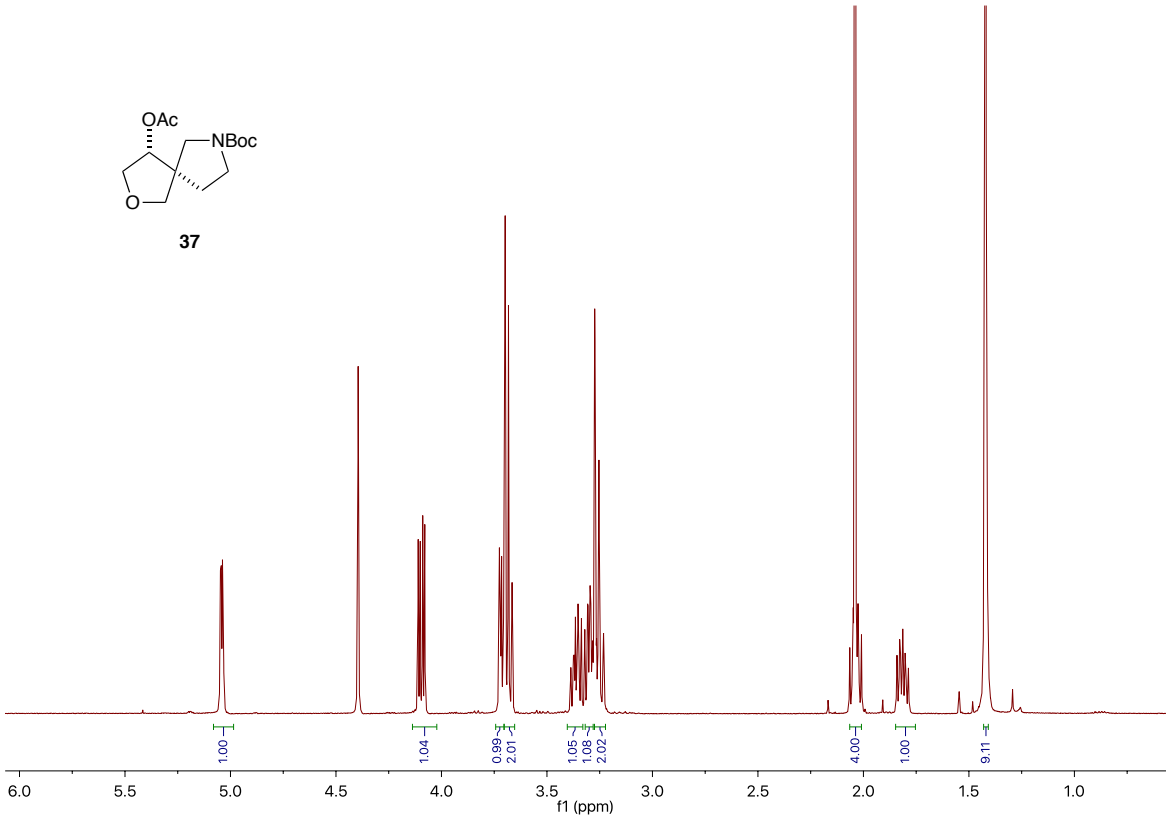

170.33
154.65
79.59
72.20
71.46
65.00
51.36
44.42
29.28
28.70
21.15
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

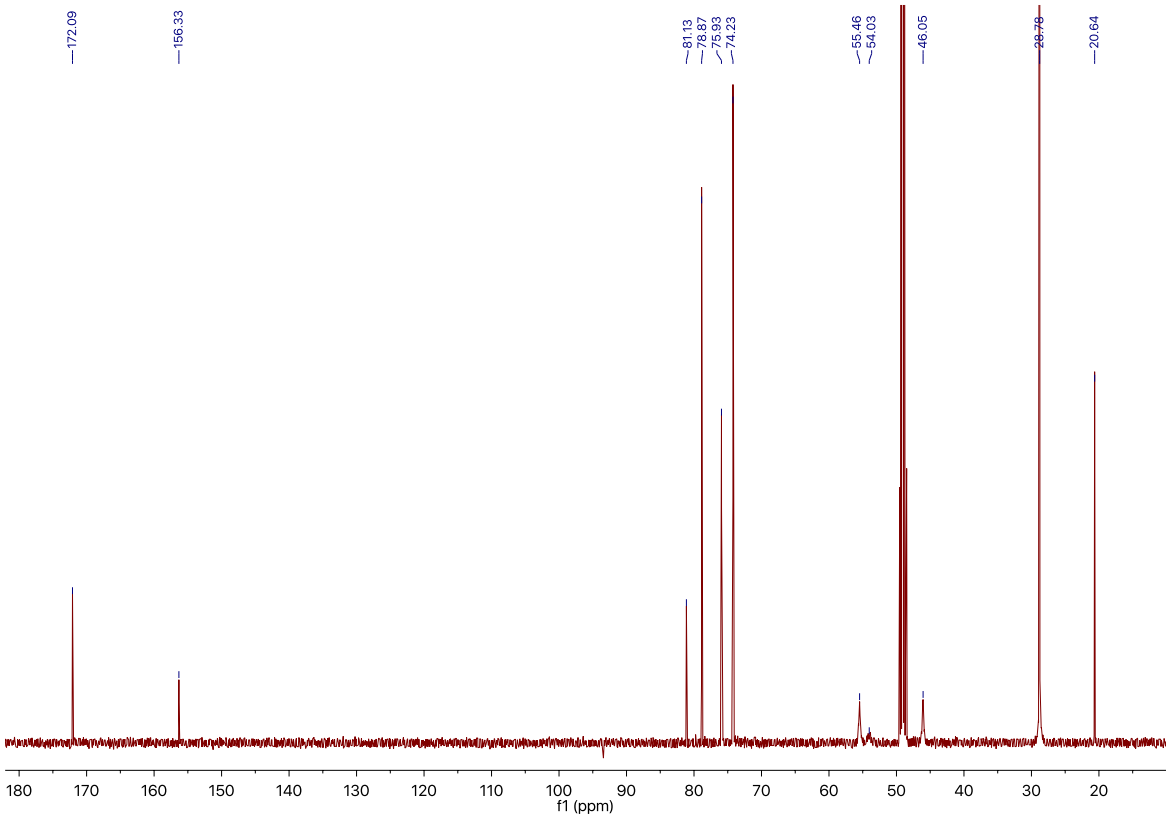

OAc
NBoc
N
Cbz
32
5.16
1.09
1.04
1.00
1.09
2.04
2.15
1.05
1.14
0.98
3.07
1.08
1.07
2.11
9.48
f1 (ppm)

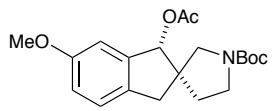

171.87
157.14
156.34
138.03
129.56
129.15
128.87
81.07
73.88
68.56
52.56
49.17
47.46
45.42
41.62
30.23
28.95
28.81
20.80
f1 (ppm)


O
NBoc
BzN
O
34
1.89
0.93
1.93
2.00
1.97
1.98
1.02
0.97
1.96
9.02
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


174.63
173.34
156.24
136.86
132.90
129.26
129.03
81.30
81.13
61.43
56.56
46.83
45.93
36.62
28.77
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

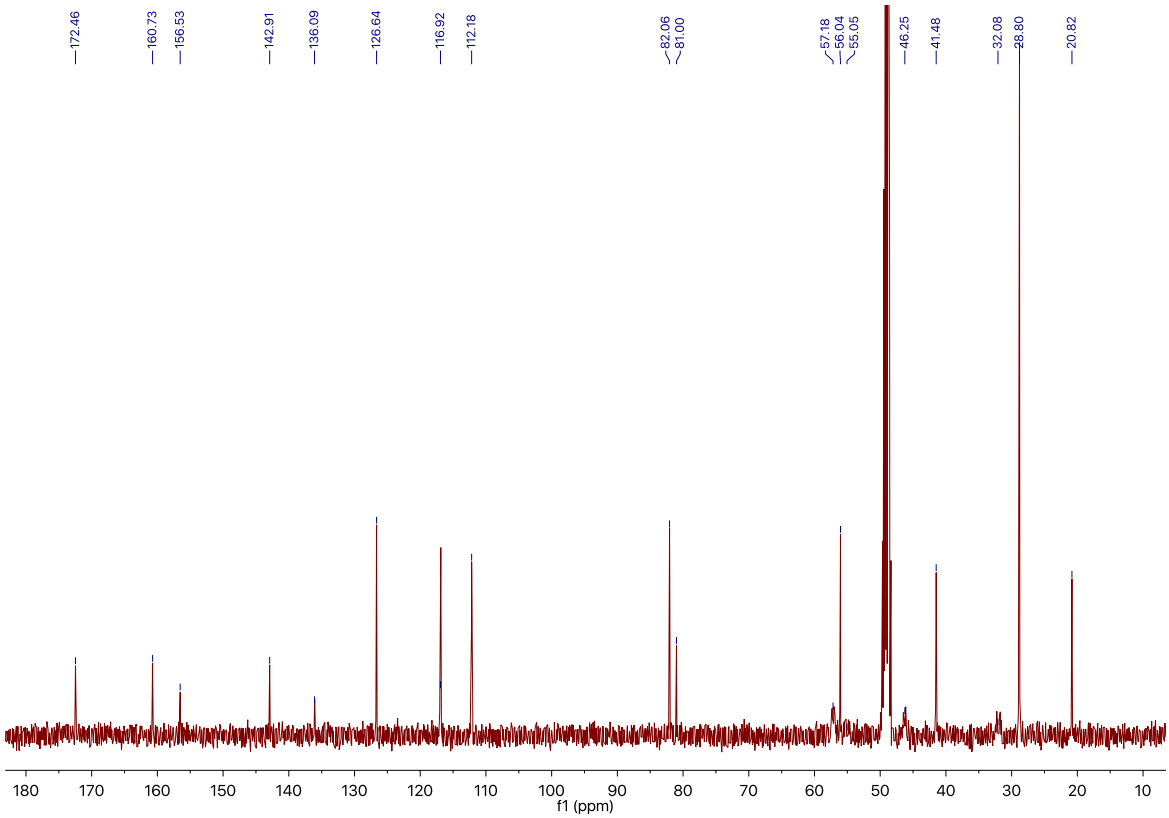

OAc
NBoc
O
37
1.00
1.04
0.99
2.01
1.05
1.08
2.02
4.00
1.00
9.11
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

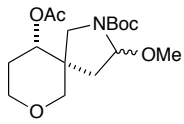

172.09
156.33
81.13
78.87
75.93
74.23
55.46
54.03
46.05
28.78
20.64
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)


OAc
MeO
NBoc

42

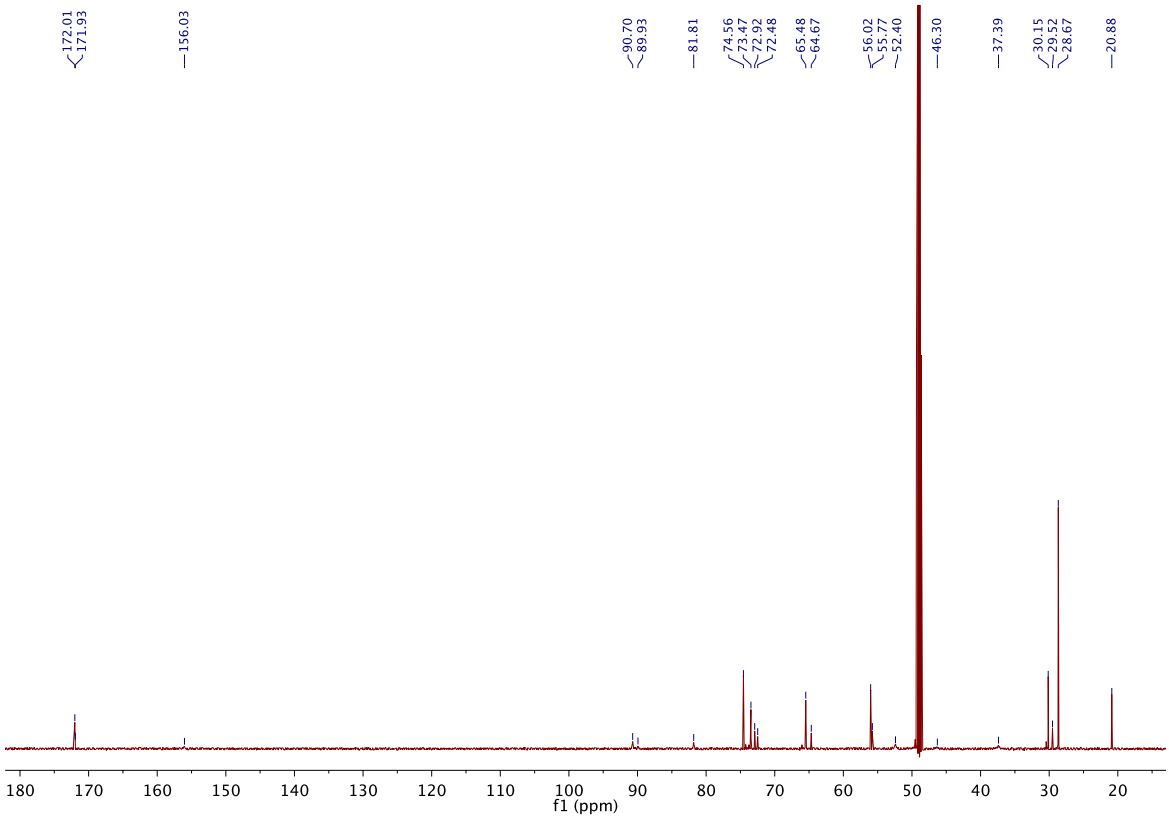
1.00
0.95
1.01
0.99
3.00
2.07
1.04
1.04
1.03
1.03
1.07
3.04
1.05
9.03
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

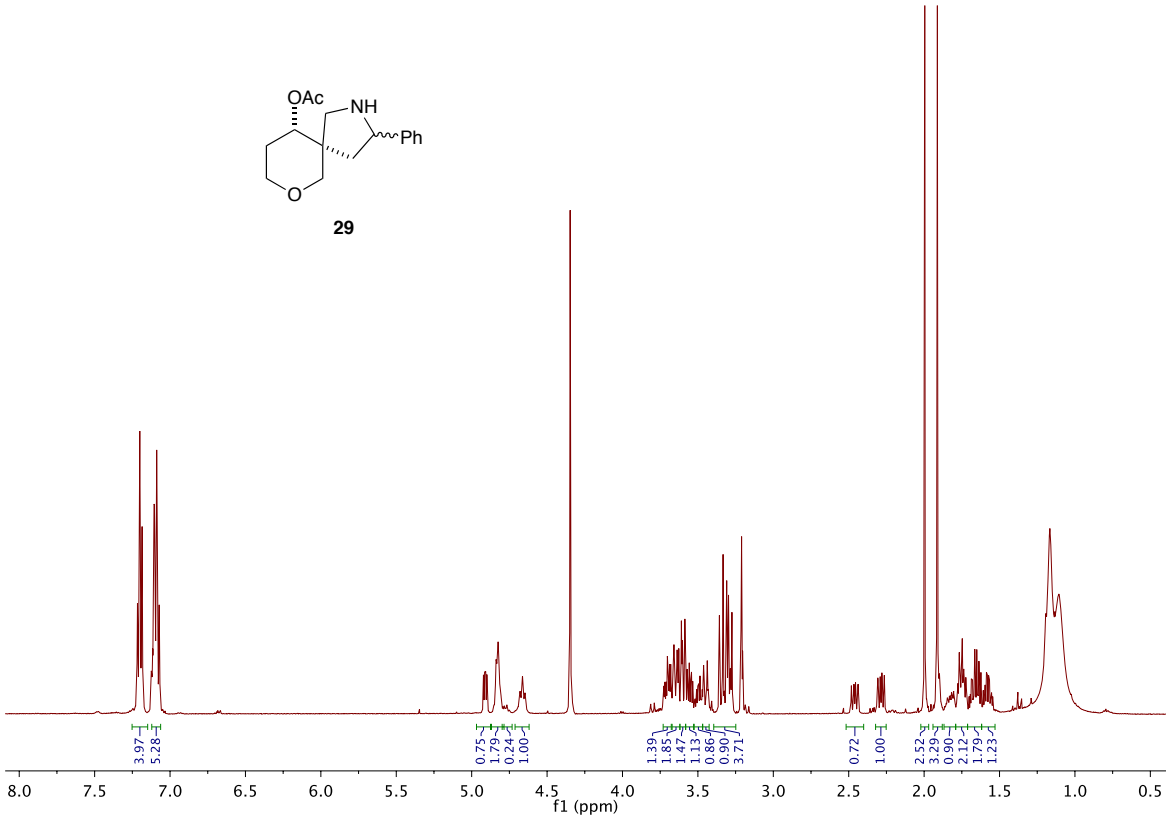

172.46
160.73
156.53
142.91
136.09
126.64
116.92
112.18
82.06
81.00
57.18
56.04
55.05
46.25
41.48
32.08
28.80
20.82
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


OAc
NBoc
OMe
O

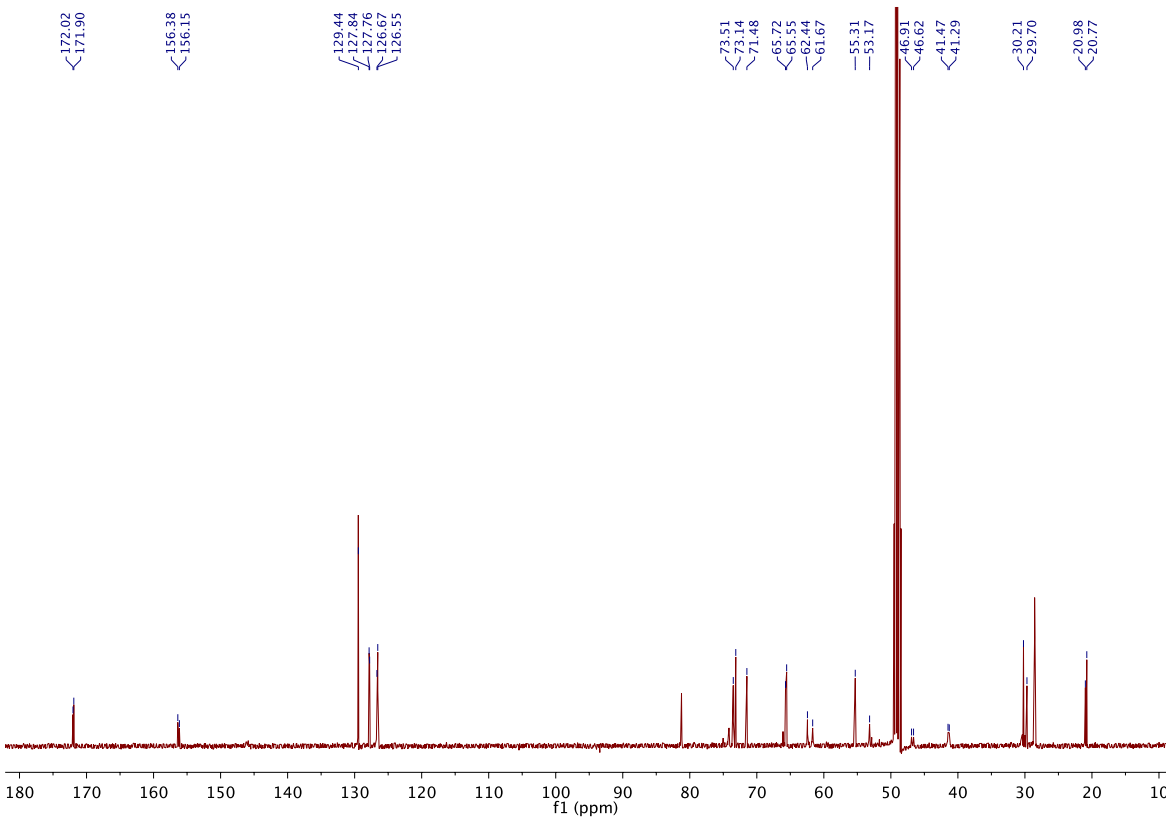
28

0.30
1.00
0.31
1.00
0.16
0.10
1.09
1.17
0.32
0.37
1.05
0.96
1.13
7.84
0.96
3.75
1.06
1.91
1.42
1.49
14.48
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
f1 (ppm)

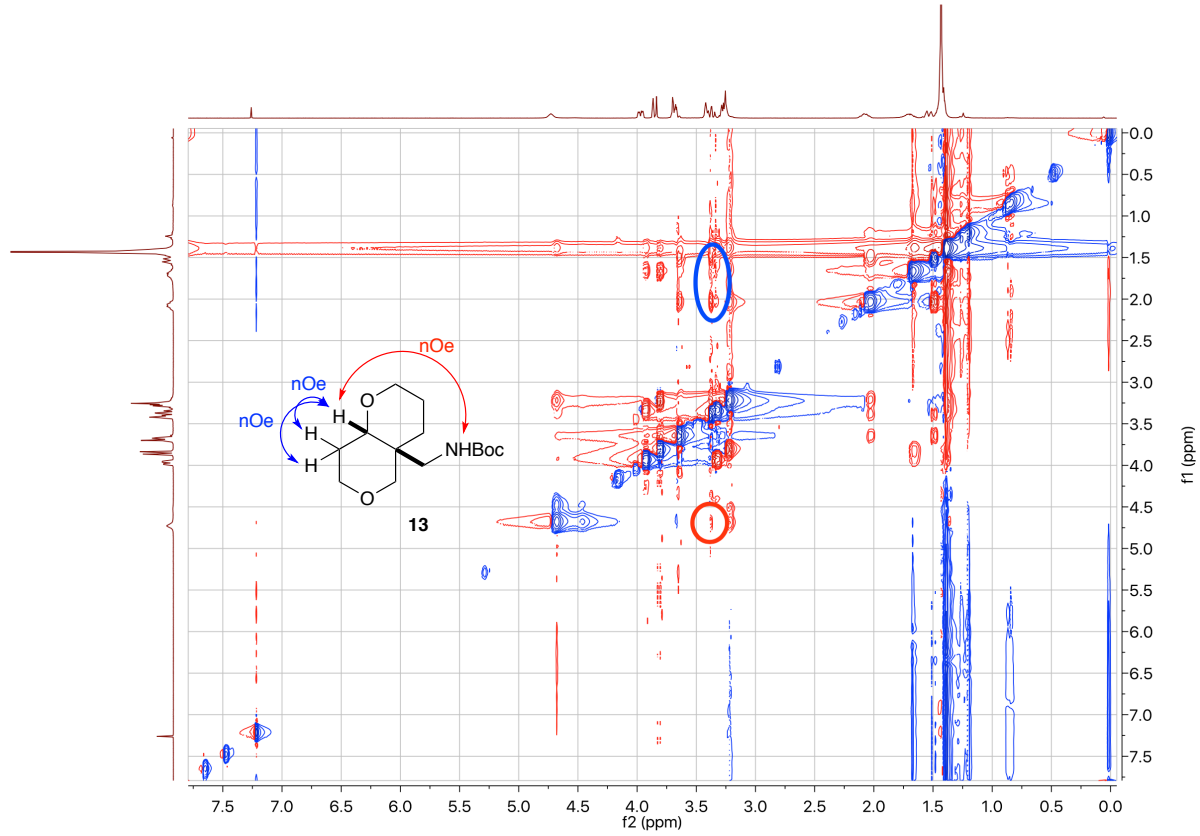

172.01
171.93
156.03
90.70
89.93
81.81
74.56
73.47
72.92
72.48
65.48
64.67
56.02
55.77
52.40
46.30
37.39
30.15
29.52
28.67
20.88
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

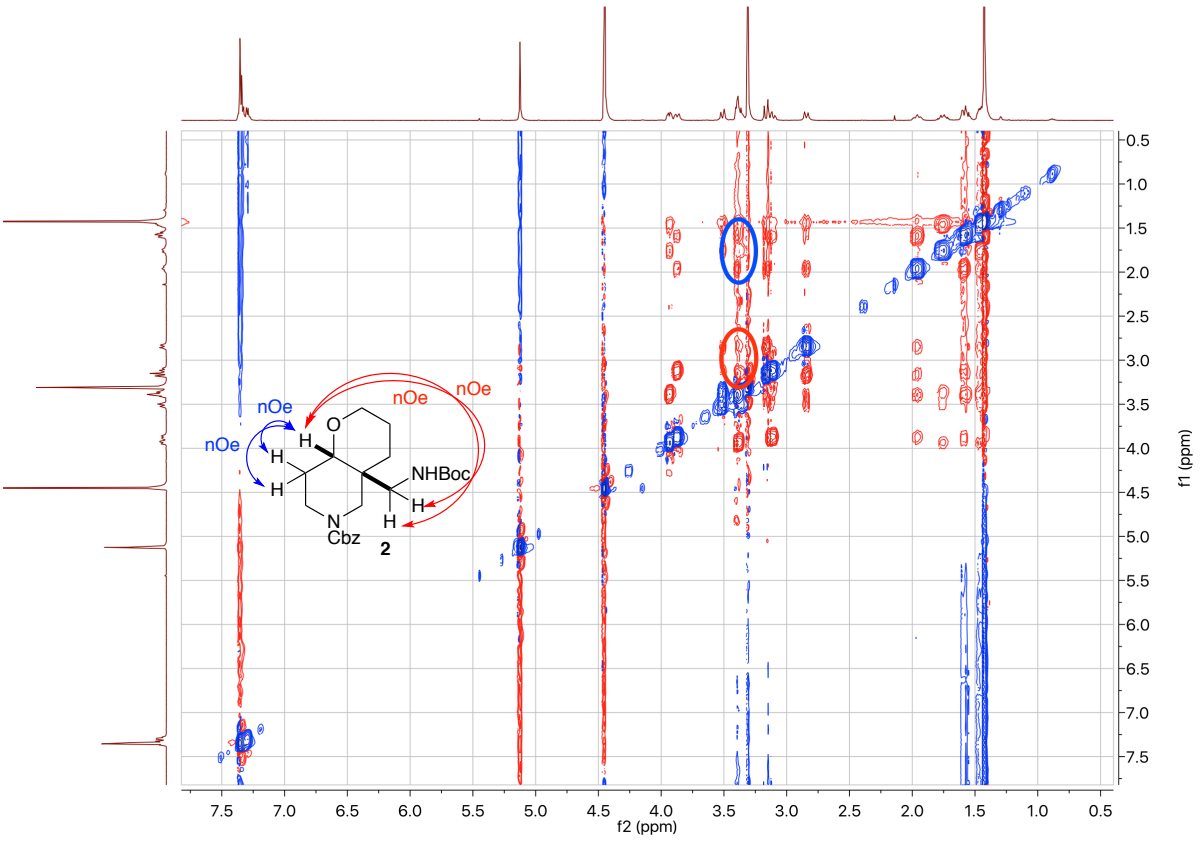

OAc
NH
Ph
O
3.97
5.28
0.75
1.79
0.24
1.00
1.39
1.85
1.47
1.13
0.86
0.90
3.71
0.72
1.00
2.52
3.29
0.90
2.12
1.79
1.23
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

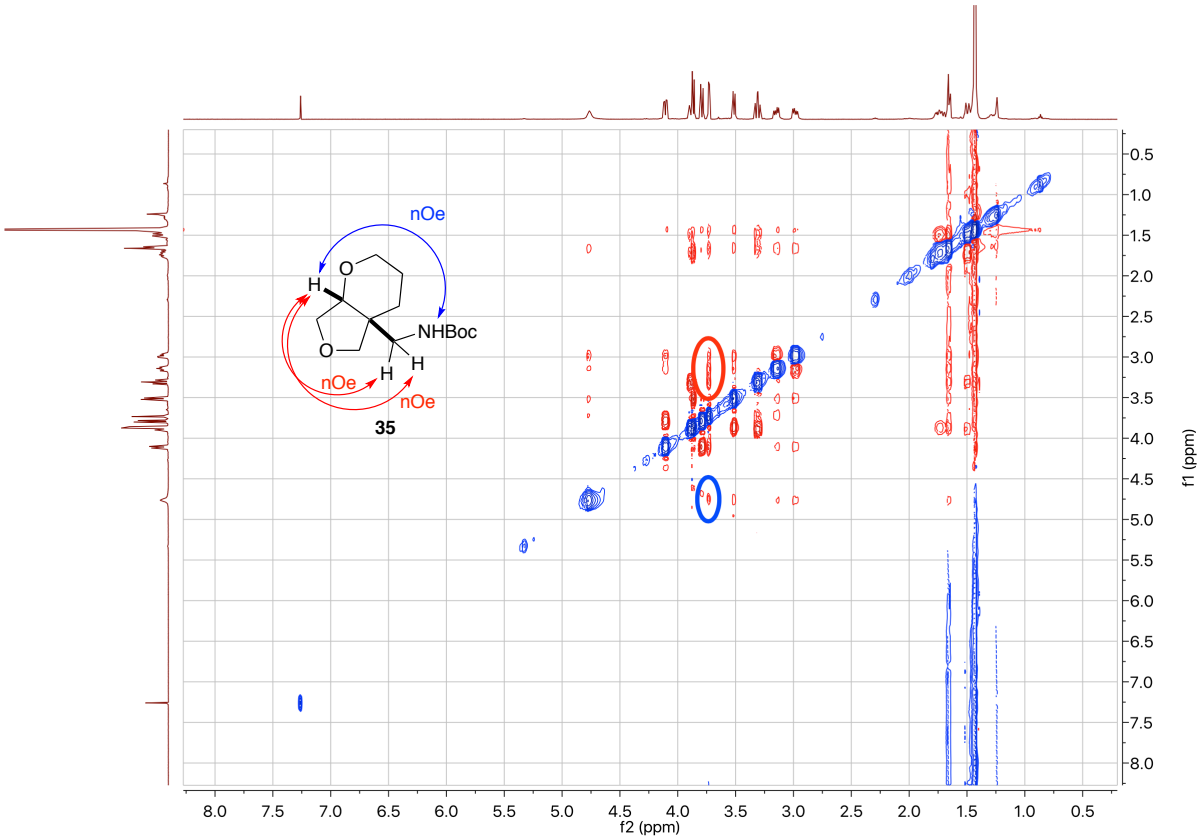
29

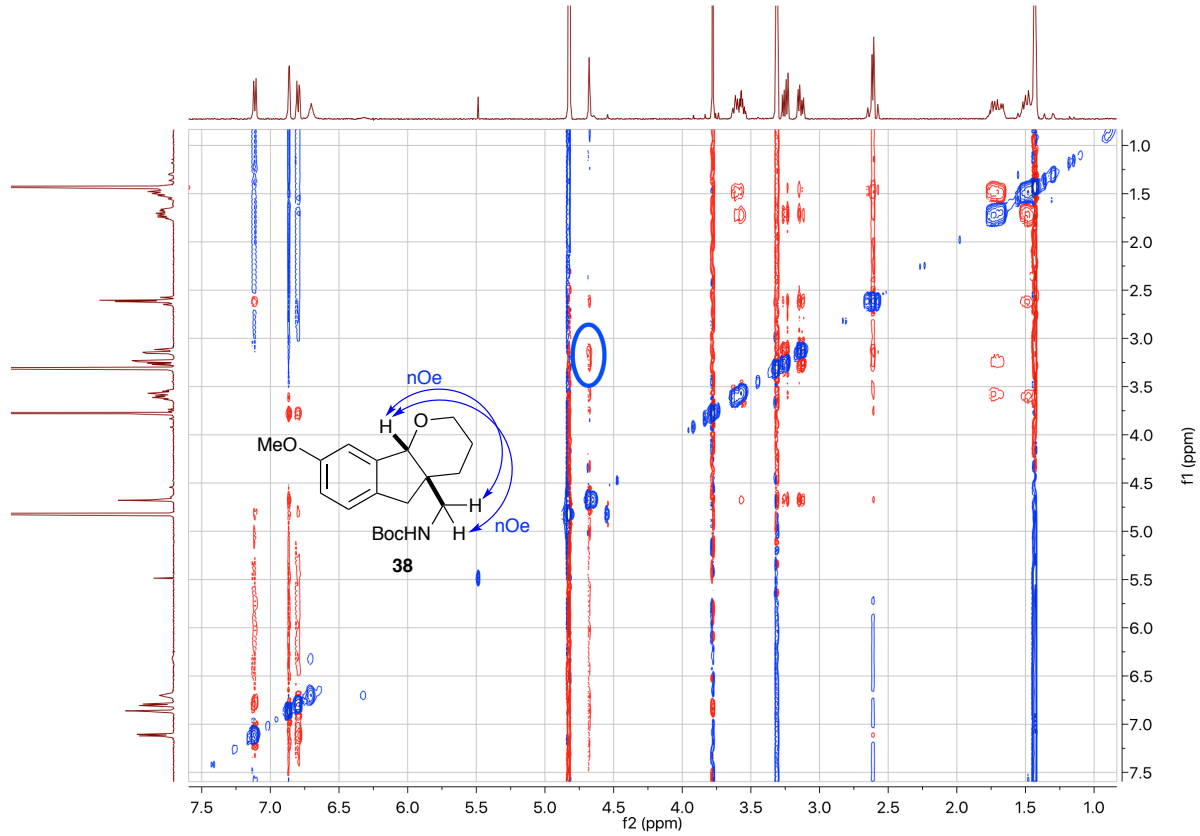

172.02
171.90
156.38
156.15
129.44
127.84
127.76
126.67
126.55
73.51
73.14
71.48
65.72
65.55
62.44
61.67
55.31
53.17
46.91
46.62
41.47
41.29
30.21
29.70
20.98
20.77
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

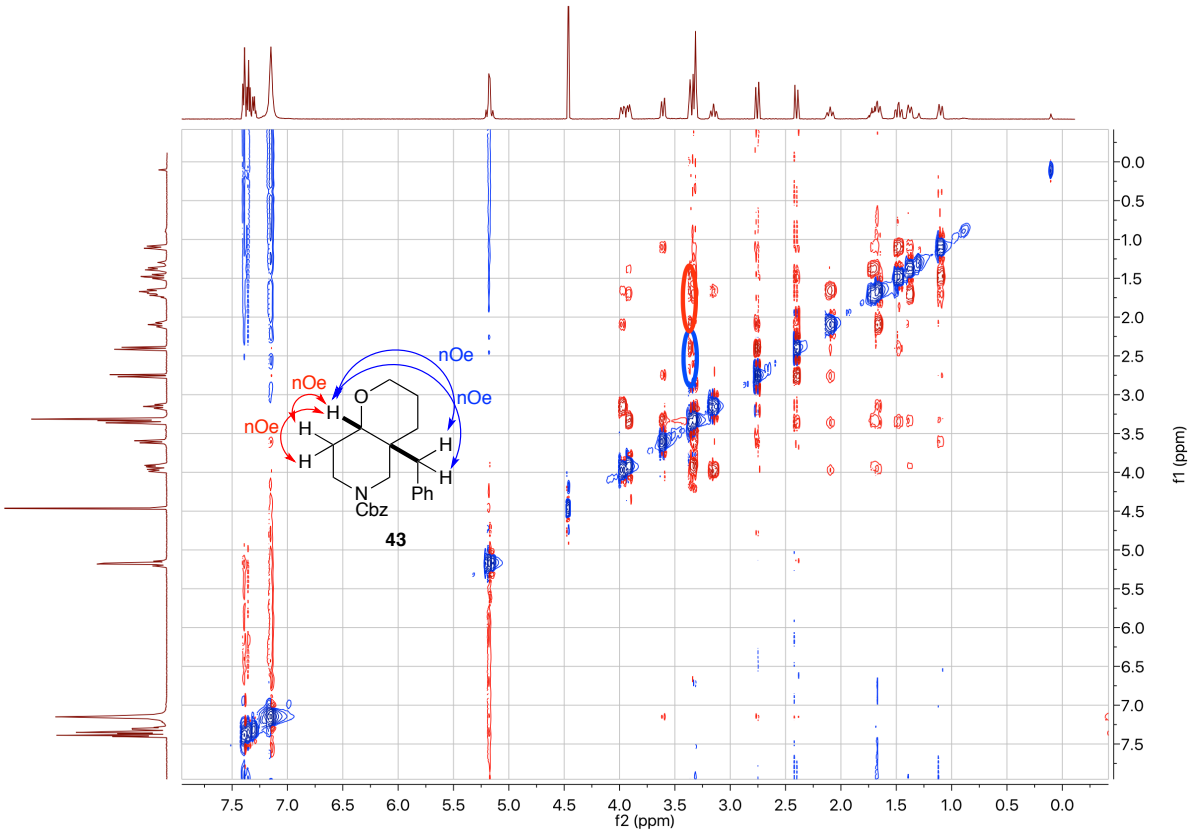
NOESY Spectra

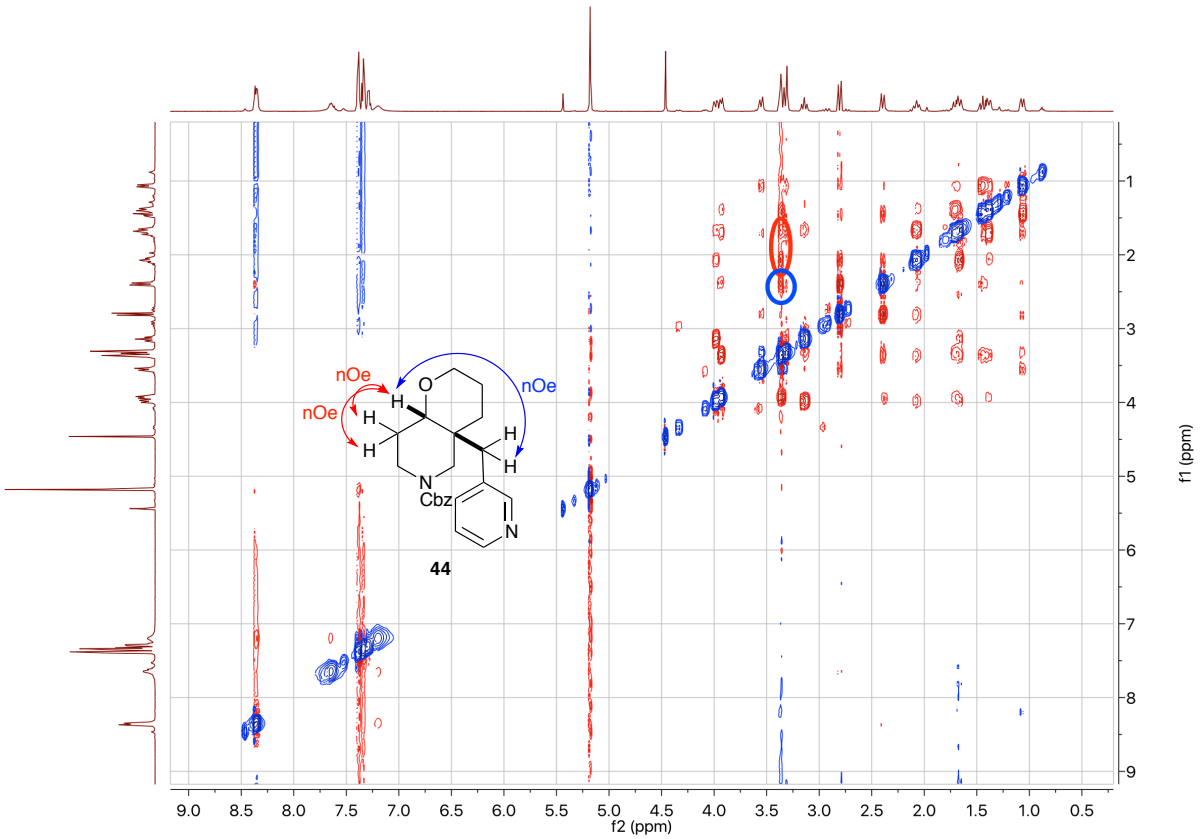


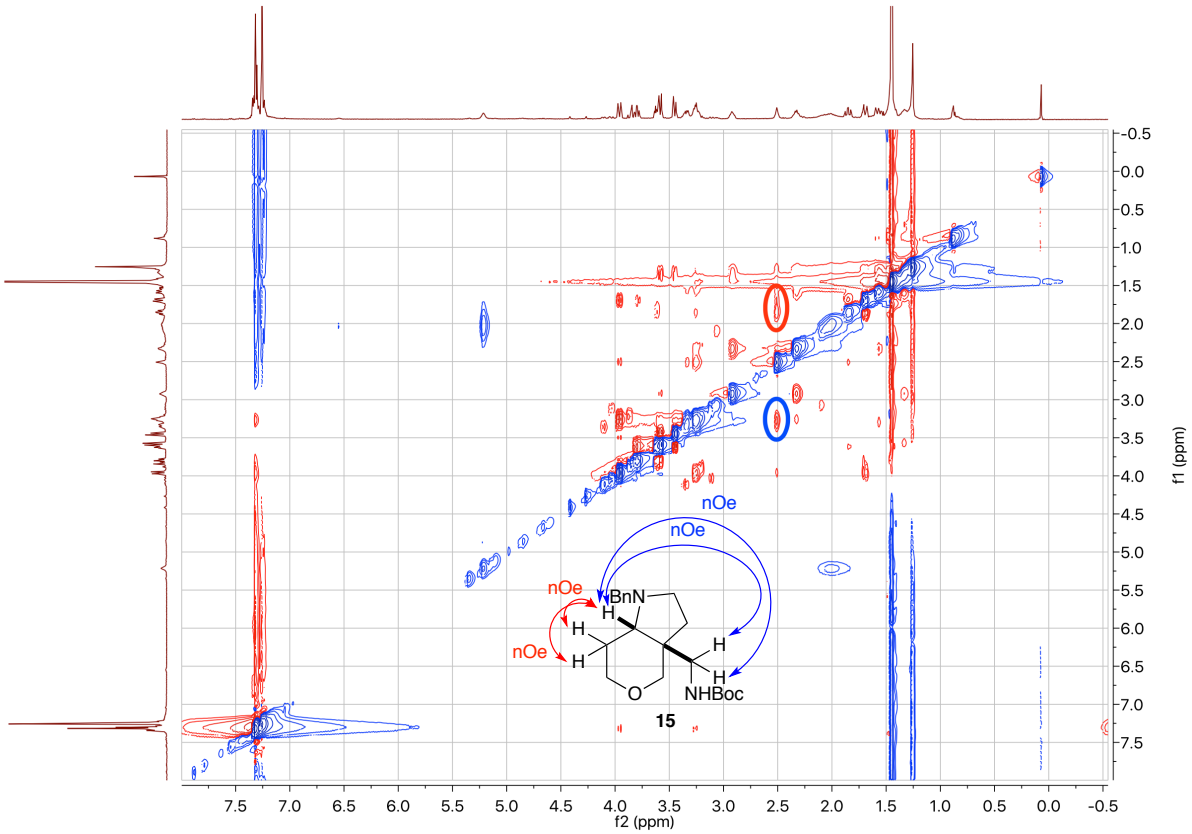


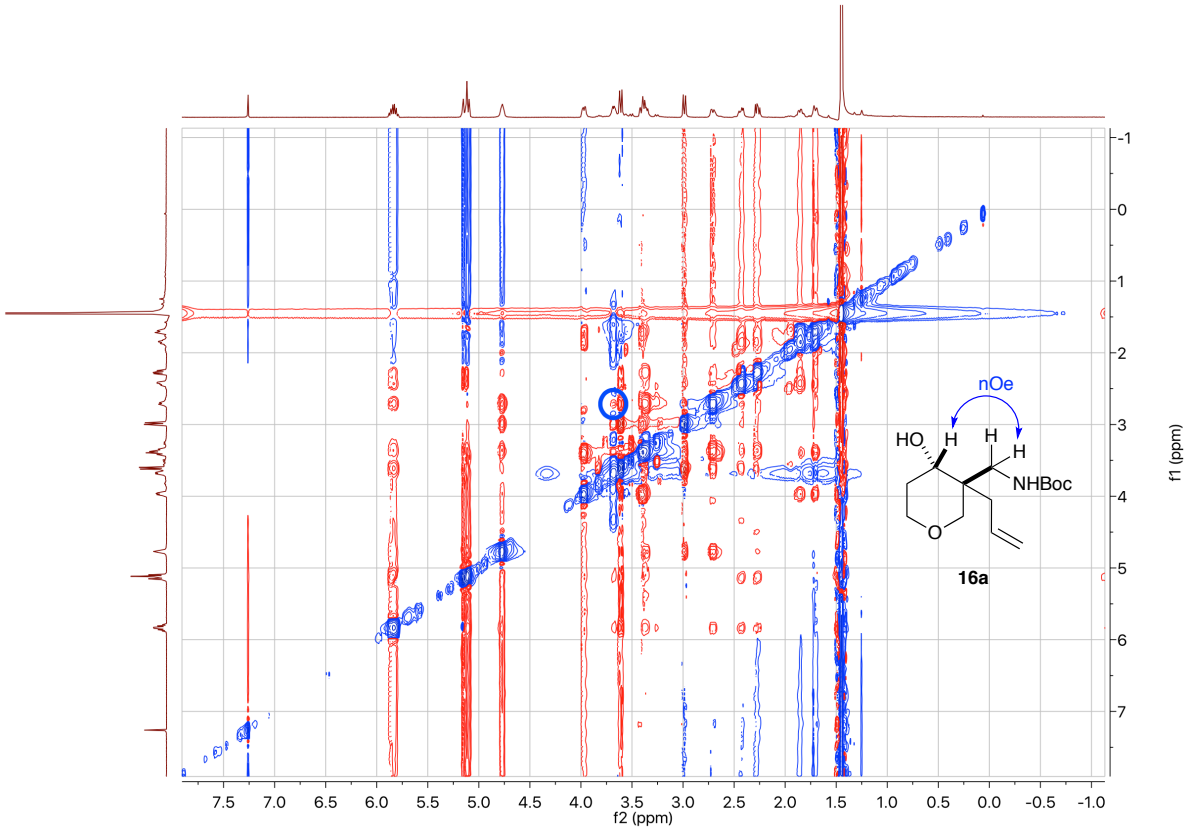

nOe
H
O
NHBoc
O
H
H
nOe
nOe
35
f2 (ppm)
f1 (ppm)

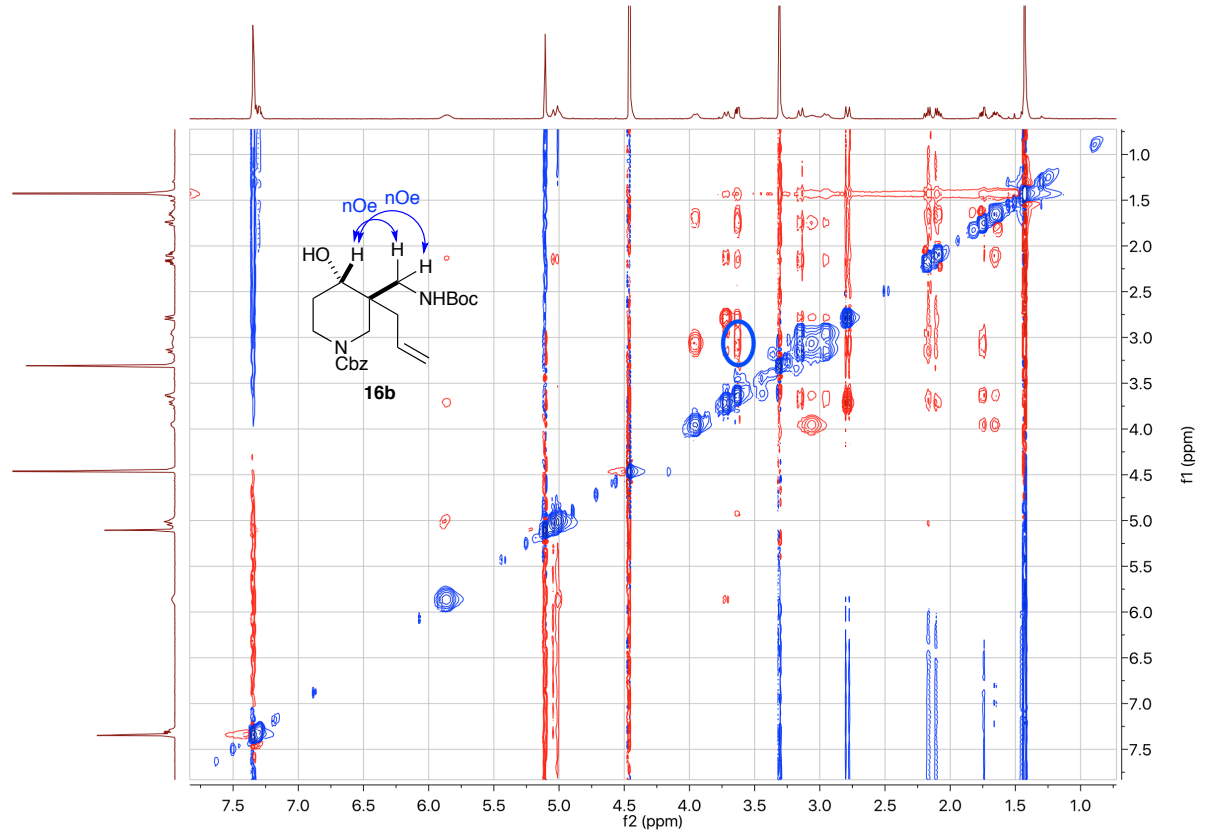

nOe
H
O
MeO
H
BocHN
H
nOe
38
f2 (ppm)
f1 (ppm)

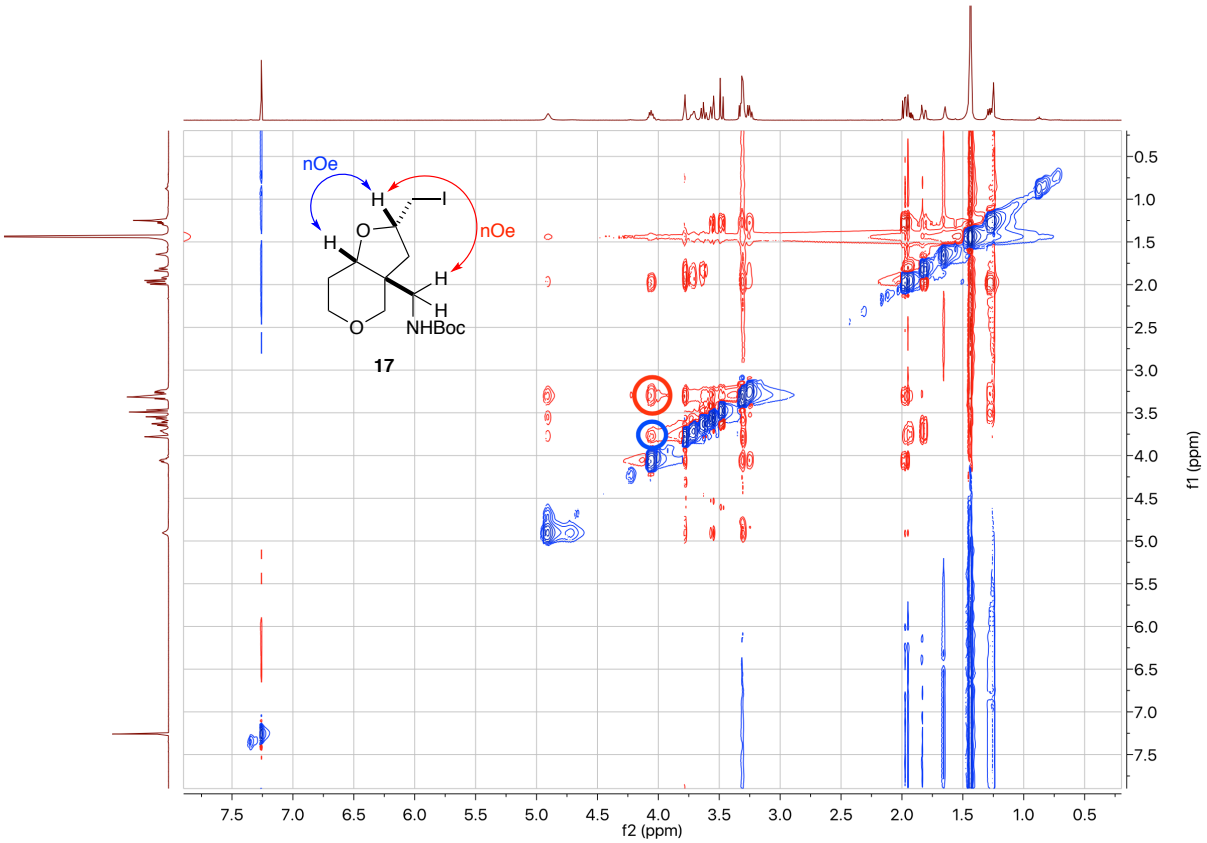

nOe
nOe
nOe
nOe
O
H
H
H
H
H
N
Cbz
Ph
43
f2 (ppm)
f1 (ppm)

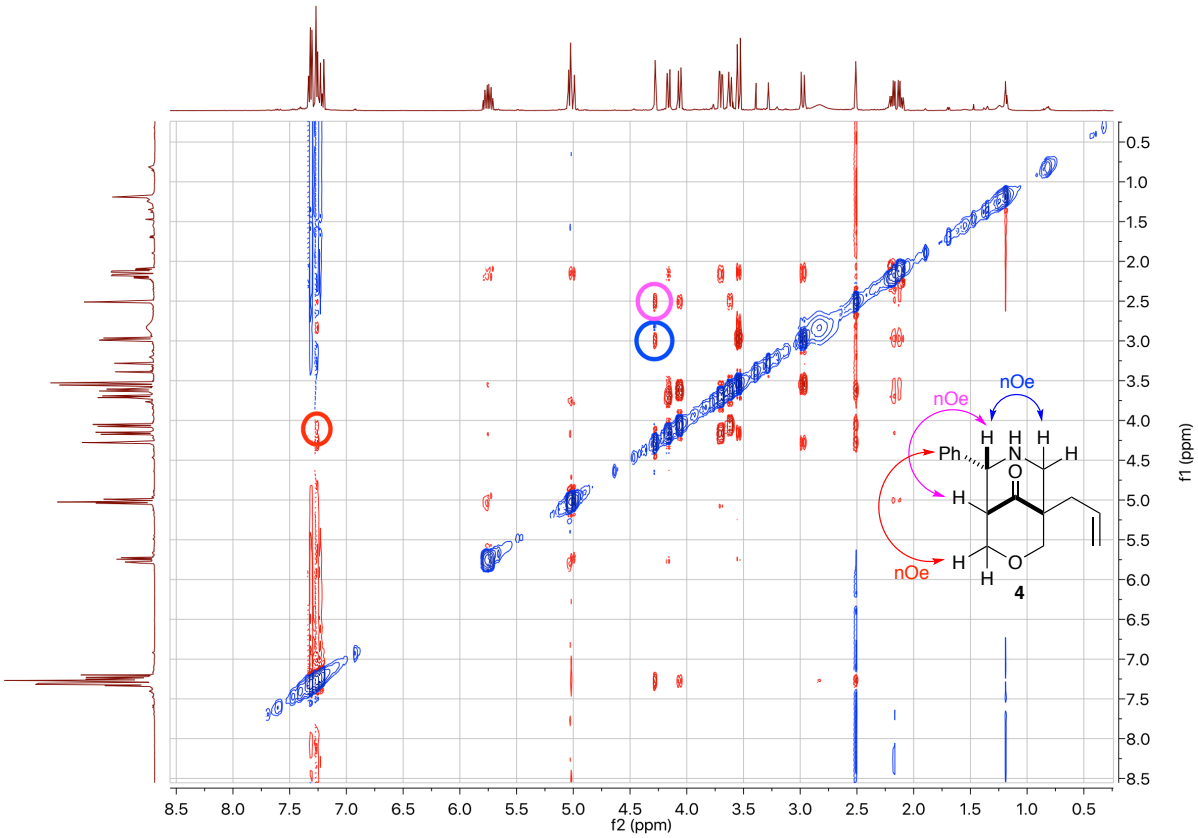

nOe
nOe
nOe
O
H
H
H
H
N
Cbz
N
44
f2 (ppm)
f1 (ppm)

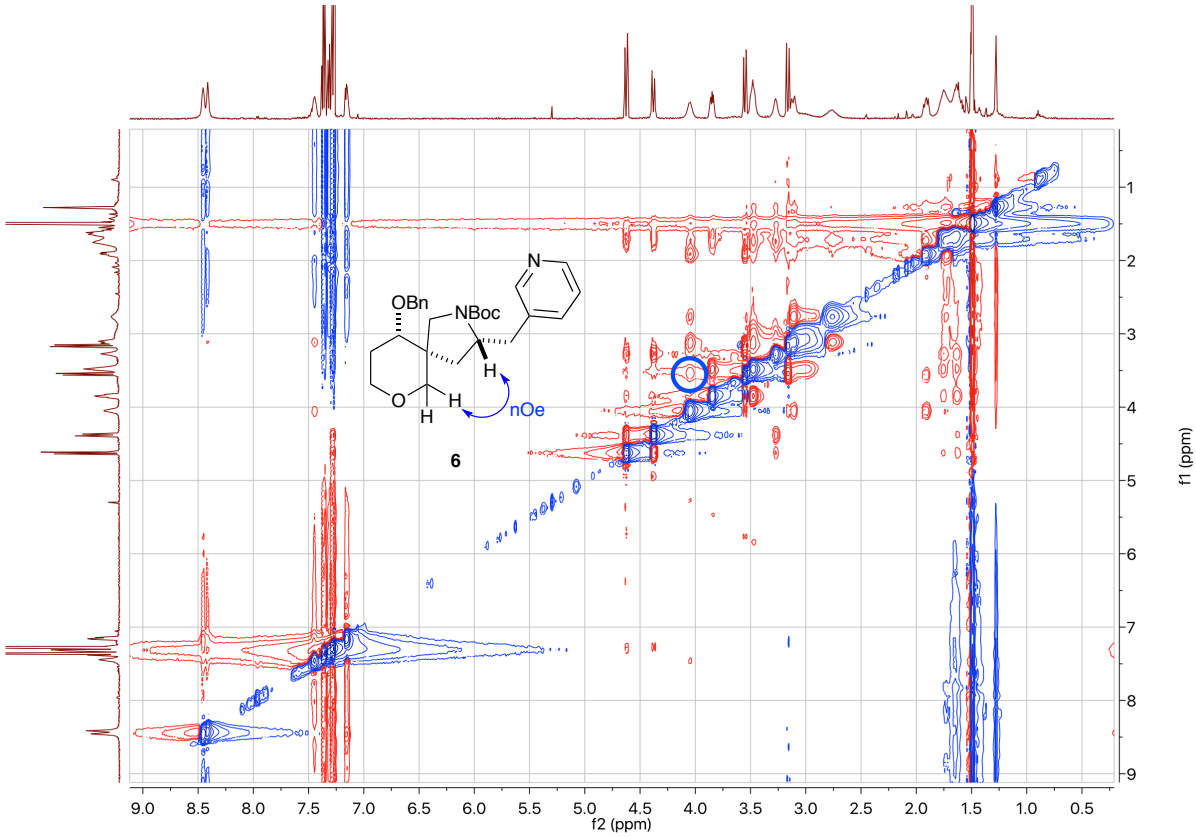

nOe
nOe
nOe
nOe
BnN
H
H
H
H
H
O
NHBoc
15
f2 (ppm)
f1 (ppm)

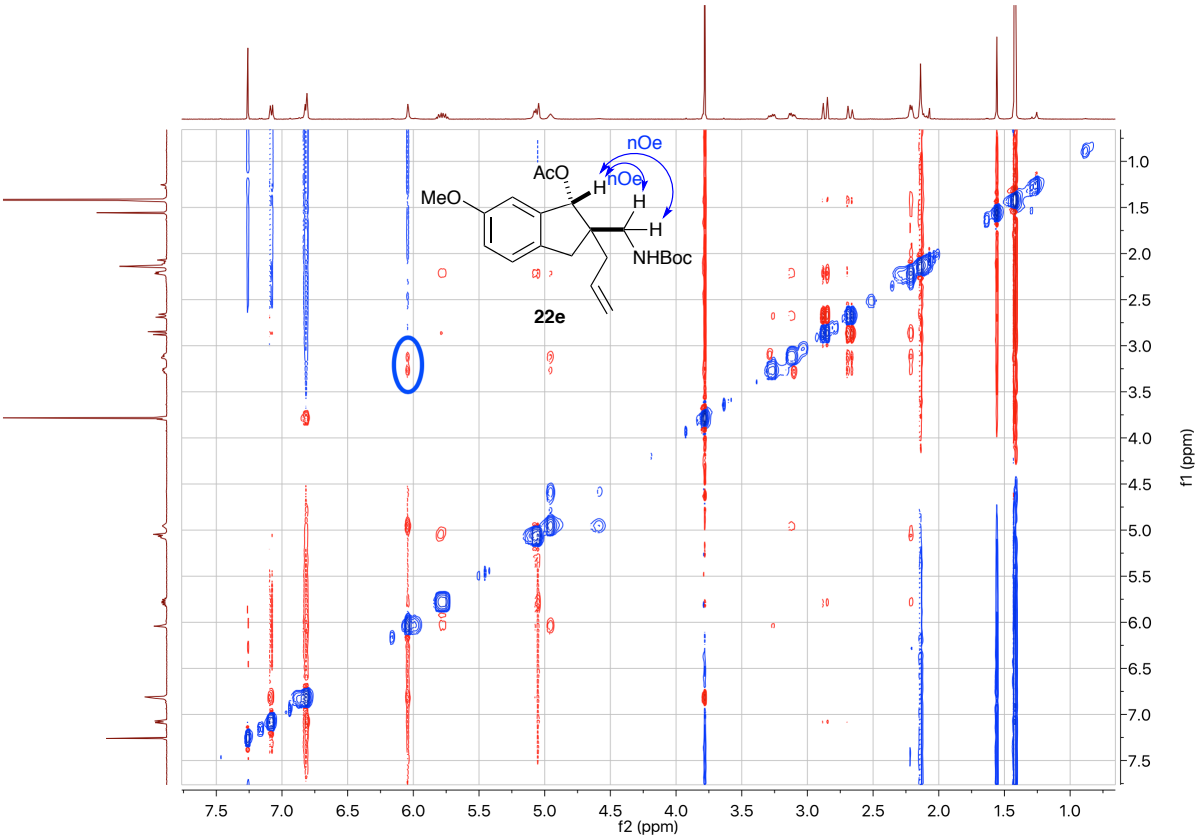

nOe
HO
H
H
H
NHBoc
O
16a
f2 (ppm)
f1 (ppm)


nOe
nOe
HO
H
H
H
NHBoc
N
Cbz
16b
f2 (ppm)
f1 (ppm)


nOe
H
I
O
H
nOe
H
H
O
NHBoc
17
f2 (ppm)
f1 (ppm)


nOe
nOe
nOe
Ph
H
N
O
4
f2 (ppm)
f1 (ppm)


OBn
NBoc
N
H
O
nOe
6
f2 (ppm)
f1 (ppm)



References

1 G. M. Sheldrick, *Acta Crystallogr. A*, 2015, **71**, 3.

2 G. M. Sheldrick, *Acta Crystallogr. C*, 2015, **71**, 3.

3 *US Pat.*, US005635103A, 1997.

4 B. M. Trost and J. Xu, *J. Org. Chem.*, 2007, **72**, 9372.

5 D. Sikriwal, R. Kant, P. R. Maulik and D. K. Dikshit, *Tetrahedron*, 2010, **66**, 6167.

6 Y. Numajiri, G. Jime, B. Wang, K. N. Houk and B. M. Stoltz, *Org. Lett.*, 2015, **17**, 1082.

7 R. Ragavan, K. Kumar, V. Vijayakumar, S. Sarveswari, S. Ramaiah, A. Anbarasu, S. Karthikeyan, P. Giridharan and N. Kumari, *Org. Med. Chem. Lett.*, 2013, **3**, 1.

8 Y. Numajiri, B. P. Pritchett, K. Chiyoda and B. M. Stoltz, *J. Am. Chem. Soc.*, 2015, **137**, 1040.

9 L. H. P. Teixeira, E. J. Barreiro and C. A. M. Fraga, *Synth. Commun.*, 1997, **27**, 3241.

10 I. Shimizu, T. Yamada and J. Tsuji, *Tetrahedron Lett.*, 1980, **21**, 3199.

11 M. A. Gianturco, P. Friedel and A. S. Giammarino, *Tetrahedron*, 1964, **20**, 1763.

12 K. Matsuzaki, K. Okuyama, E. Tokunaga, M. Shiro and N. Shibata, *ChemistryOpen*, 2014, **3**, 233.

13 Z. Xu, Q. Wang and J. Zhu, *J. Am. Chem. Soc.*, 2015, **137**, 6712.

14 Y. H. Zhu, M. Zhang, Q. Y. Li, Q. Liu, J. Zhang, Y. Y. Yuan, F. J. Nan and M. W. Wang, *Chin. Chem. Lett.*, 2014, **25**, 693.

15 I. Colomer, C. J. Empson, P. Craven, Z. Owen, R. G. Doveston, I. Churcher, S. P. Marsden and A. Nelson, *Chem. Commun.*, 2016, **52**, 7209.

16 X. Wu, J. Huang, B. Guo, L. Zhao, Y. Liu, J. Chen and W. Cao, *Adv. Synth. Catal.*, 2014, **356**, 3377.

17 G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, P. Melchiorre and L. Sambri, *Org. Lett.*, 2004, **6**, 3973.

18 R. G. Doveston, P. Tosatti, M. Dow, D. J. Foley, H. Y. Li, A. J. Campbell, D. House, I. Churcher, S. P. Marsden and A. Nelson, *Org. Biomol. Chem.*, 2015, **13**, 859.

19 N. Langlois and F. Rakotondradany, *Tetrahedron*, 2000, **56**, 2437.

20 B. M. Trost and F. Miege, *J. Am. Chem. Soc.*, 2014, **136**, 3016.

21 J. Mayol-Llinàs, A. Nelson, W. Farnaby and A. Ayscough, *Drug Discov. Today*, 2017, **22**, 965.