Supplementary Information

General information: Reactions were performed in oven-dried round bottom flasks fitted with rubber septa under an atmosphere of argon unless otherwise stated. Analytical thin layer chromatography (TLC) was performed on pre-coated aluminium sheets of silica (60 F_{254}, Merck) and visualised by short-wave UV light and potassium permanganate or cerium ammonium molybdate dips. Flash column chromatography was carried out using Merck silica gel 60 (0.015-0.040 mm).

Materials: All anhydrous solvents and reagents were obtained from commercial suppliers and used without any further purification with the following exceptions: allyl bromide was distilled at atmospheric pressure (bp 71°C). Zinc powder was purified according to Purification of Laboratory Chemicals (4th Ed).[1] Zinc bromide was dried under vacuum at 150 °C for four hours. The molarity of solutions of *tert*-butyllithium was determined by titration against diphenyl acetic acid as an indicator. Where noted, solvents were degassed by bubbling with argon for 30 minutes before use.

Instrumentation: All melting points were determined on a Sanford Research Systems EZ-Melt apparatus and are uncorrected.

Infrared spectra were recorded on a Bruker alpha-p FT-IR and are recorded as frequency of absorption cm^{-1}.

^{1}H-nuclear magnetic resonance spectra were recorded at 500 MHz on Bruker Avance 500 spectrometers using an internal deuterium lock. Chemical shifts were measured in parts per million (ppm) relative to tetramethylsilane (δ = 0) using the following internal references for residual protons in the solvent: $CDCl_3$ (δ 7.26), CD_3OD (δ 3.32), and DMSO-*d6* (δ 2.50). Data is presented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), coupling constant (*J*) in Hz

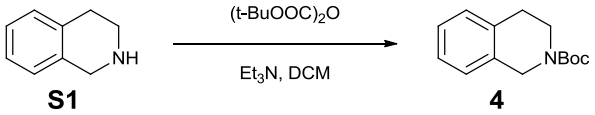
^{13}C-nuclear magnetic resonance spectra were recorded at 126 MHz on Bruker Avance spectrometers using an internal deuterium lock. All chemical shift values were reported in ppm relative to tetramethylsilane (δ = 0). The following internal references were used: $CDCl_3$ (δ_C 77.0), CD_3OD (δ 49.0) and DMSO-*d6* (δ 39.5).

LC-MS analyses were performed on a Micromass LCT / Water's Alliance 2795 HPLC system using using a Waters 2487 Dual λ Absorbance UV Detector; Column = Phenomenex Gemini 3u C18 (3cm x 4.6mm i.d); Solvents: aqueous (0.1% Formic Acid) and methanol. UV detection was at 254nm and ionisation was positive or negative ion electrospray.

High resolution mass spectrometry data was collected using a Agilent 6210 Time Of Flight Mass Spectrometer; Column = Merck Chromolith SpeedROD RP-18e 50x4.6mm; solvents: methanol, aqueous (0.1% Formic Acid)**;** Reference Masses: Caffeine $[M+H]^+$ = 195.087652, Reserpine $[M+H]^+$ = 609.280657, (1H,1H,3H-tetrafluoropentoxy)phosphazene $[M+H]^+$ = 922.009798; UV detection was at 254nm and ionisation was positive or negative ion electrospray. Molecular weight scan range was 50-1000. Samples were supplied as 1 mg/mL in methanol or DMSO with 3 μL injected on a partial loop fill.

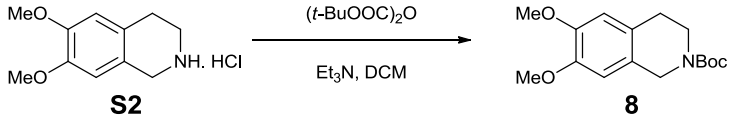
Synthetic procedures:

***tert*-Butyl 3,4-dihydroisoquinoline-2(1*H*)-carboxylate (4)**[2]



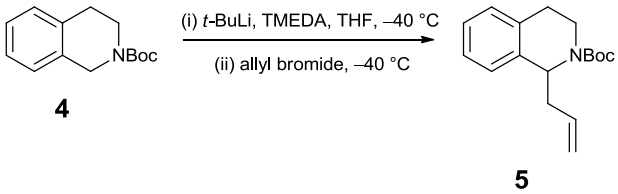
1,2,3,4-Tetrahydroisoquinoline (2.82 mL, 26.5 mmol) was added to a solution of di-*tert*-butyldicarbonate (5.78 g, 26.5 mmol) in DCM (30 mL) followed by addition of triethylamine (4.06 mL, 29.2 mmol) and the solution stirred at room temperature for 60 hours. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (20 mL), dried over $MgSO_4$ and solvent removed under reduced pressure. The residue was purified by flash column chromatography (1:6 EtOAc – petroleum ether 60–80; R_f 0.60) to give the title compound **4** as a colourless solid (3.93 g, 64%); mp 36 – 38 °C (lit. 35 – 38 °C)[2]; ν_{max} 1635 (C=O); δ_H (500 MHz; $CDCl_3$) 1.49 (9H, s), 2.76 (2H, t, *J* 5.8), 3.60 (2H, t, *J* 5.8), 4.54 (2H, s), 7.02–7.12 (4H, m); δ_C (126 MHz; $CDCl_3$) 28.6, 29.1, 40.9 (broad), 45.5 (broad), 79.8, 126.3, 126.5, 128.8, 133.9, 134.9, 146.9, 155.0; *m/z* 256 (70%, $[M+Na]^+$), 134 (100%, $[M– COOC(CH_3)_3]^+$); Found $[M+Na]^+$ 256.1309, $C_{14}H_{19}NO_2Na$ requires 256.1308.

***tert*-Butyl 6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (8)**[2]



Triethylamine (2.55 mL, 18.2 mmol) was added to a suspension of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (2.00 g, 8.71 mmol) in DCM (30 mL) followed by addition of a solution of di-*tert*-butyldicarbonate (1.90 g, 8.71 mmol) in DCM (10 mL). The resulting mixture was stirred at room temperature for 48 hours. The solution was washed with saturated aqueous $NaHCO_3$ solution (30 mL), dried over $MgSO_4$ and solvent removed under reduced pressure. The residue was purified by flash column chromatography (1:4 EtOAc – petroleum ether 60–80; R_f 0.40) to give the title compound **8** as a colourless solid (1.93 g, 76%); mp 128 – 130 °C (lit. 123 – 126 °C)[2]; ν_{max} 1684 (C=O); δ_H (500 MHz; $CDCl_3$) 1.51 (9H, s), 2.76 (2H, t, *J* 6.6), 3.64 (2H, t, *J* 6.6), 3.87 (6H, s), 4.51 (2H, s), 6.60 (1H, s), 6.63 (1H, s); δ_C (126 MHz; $CDCl_3$) 28.7, 29.0, 41.0 (broad), 45.5, 56.2, 56.2, 79.9 109.5, 111.8, 125.8, 126.8, 147.8, 147.9, 155.1; *m/z* 316 (55%, $[M+Na]^+$), 194 (100%, $[M–COOC(CH_3)_3]^+$); Found $[M+Na]^+$ 316.1511, $C_{16}H_{23}NO_4Na$ requires 316.1519; Found: C 65.45%; H 7.97%, N 4.71%; $C_{16}H_{23}NO_4$ requires: C 65.51%, H 7.90%, N 4.77%.

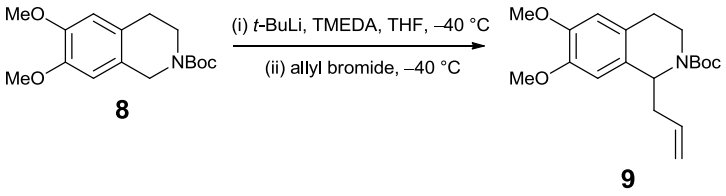
tert-Butyl 1-allyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (5)



4 **5**

tert–Butyllithium (2.93 mL of a 1.3 M solution in pentanes, 3.85 mmol) was added dropwise to a solution of *N*-Boc-tetrahydroisoquinoline **4** (300 mg, 1.28 mmol) and TMEDA (580 μL, 3.85 mmol) in THF (20 mL) at –40 °C. The resulting deep red solution was stirred at –40 °C for 40 minutes before addition of allyl bromide (1.12 mL, 12.8 mmol). The pale orange solution was allowed to stir at 0 °C for 30 minutes and then for 16 hours at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL), extracted into DCM (2 x 20 mL) and dried over $MgSO_4$. Solvent was removed under reduced pressure and the residue purified by flash column chromatography (1:19 EtOAc – petroleum ether 60–80; R_f 0.35) to give the title compound **5** as a pale yellow oil (220 mg, 62%); ν_{max} 1698 (C=O); a 2:3 mixture of amide rotamers was observed by ^{1}H NMR in $CDCl_3$ at room temperature; δ_H (500 MHz; $CDCl_3$) 1.45 (9H, s), 2.40 – 2.60 (2H, m), 2.72 (1H, dt, *J* 16.2, 3.8), 2.79– 3.00 (1H, m), 3.11– 3.20 (0.6H, m), 3.23 – 3.36 (0.4H, m), 3.88 – 4.04 (0.4H, m), 4.12 – 4.28 (0.6H, m), 4.93 – 5.11 (2.6H, m), 5.23 (0.4H, t, *J* 7.1), 5.66 – 5.95 (1H, m), 7.06 – 7.23 (4H, m); δ_C (126 MHz; $CDCl_3$) 28.5, 28.6, 28.7 36.8, 38.5, 41.3, 41.6, 53.7, 54.6, 79.5, 79.83, 117.0, 117.30, 126.0, 126.5, 126.6, 127.0, 127.3, 128.7, 129.1, 134.3, 134.6, 135.1, 135.2, 137.2, 137.4, 154.7, 154.8; *m/z* 296 (80%, $[M+Na]^+$), 176 (100%, M^+); Found M^+ 274.1800, $C_{17}H_{23}NO_2$ requires 274.1082.

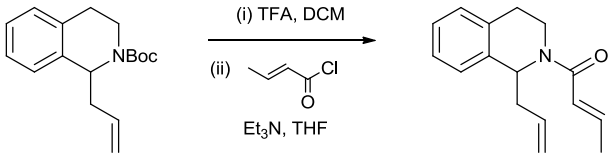
tert-Butyl-1-allyl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (9)[3]



8 **9**

tert–Butyllithium (2.36 mL of a 1.3 M solution in pentanes, 3.07 mmol) was added dropwise to a solution of *N*-Boc-tetrahydroisoquinoline **8** (300 mg, 1.03 mmol) and TMEDA (460 µL, 3.07 mmol) in THF (20 mL) at –40 °C. The resulting deep orange solution was stirred at –40 °C for 40 minutes before addition of allyl bromide (890 µL, 10.3 mmol). The pale orange solution was allowed to stir at 0 °C for 30 minutes and then for 16 hours at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL), extracted into DCM (2 x 20 mL) and dried over $MgSO_4$. Solvent was removed under reduced pressure and the residue purified by flash column chromatography (1:4 EtOAc – petroleum ether 60–80; R_f 0.35) to give the title compound **9** as a pale yellow oil (211 mg, 62%); ν_{max} 1682 (C=O); a 2:3 mixture of amide rotamers was observed by ^{1}H NMR in $CDCl_3$ at room temperature; δ_H (500 MHz; $CDCl_3$) 1.35 – 1.55 (9H, m), 2.37 – 2.52 (2H, m), 2.63 (1H, dt, *J* 15.9, 3.3) 2.71 – 2.92 (1H, m), 3.02 – 3.16 (0.6H, m), 3.17 – 3.32 (0.4H, m), 3.83 (3H, s), 3.84 (3H, s), 3.89 – 4.02 (0.4H, m), 4.20 (0.6H, dd, *J* 13.2, 3.3), 4.90 – 5.08 (2.6H, m), 5.14 (0.4H, t, *J* 6.5), 5.64 – 5.99 (1H, m), 6.56 (1H, s), 6.58 (1H, s); δ_C (126 MHz; $CDCl_3$) 28.3, 28.5, 28.7, 36.9, 38.57, 41.4, 41.7, 53.42, 54.3, 56.1, 56.2, 79.6, 80.0, 110.1, 110.4, 111.5, 111.7, 117.1, 117.5, 126.3, 126.7, 129.2, 129.6, 135.4, 135.5, 147.4, 147.5, 147.7, 147.9, 154.9, 155.0; *m/z* 356 (45% $[M+Na]^+$), 236 (100%, $[M– COOC(CH_3)_3]^+$); Found M^+ 334.2007, $C_{19}H_{27}NO_4$ requires 334.2013.

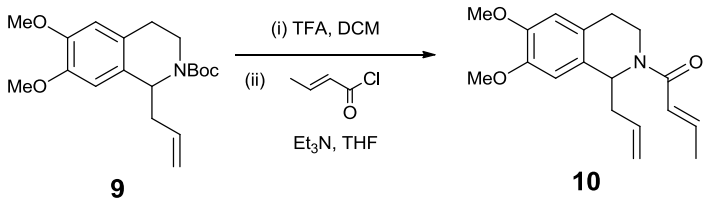
(*E*)-1-(1-Allyl-3,4-dihydroisoquinolin-2(1*H*)-yl)but-2-en-1-one (6)



5 **6**

Trifluoroacetic acid (370 μL, 4.87 mmol) was added to a solution of **5** (190 mg, 0.70 mmol) in DCM (3 mL) and the pale orange solution was stirred at room temperature for 5 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and saturated aqueous $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and solvent removed under reduced pressure. The crude residue (100 mg) was dissolved in THF (3 mL) and triethylamine (90 μL, 0.64 mmol) was added followed by dropwise addition of crotonoyl chloride (60 μL, 0.59 mmol) and the solution was stirred at room temperature for 15 hours. The reaction mixture was partitioned between DCM (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL), dried over $MgSO_4$ and solvent removed under reduced pressure. The residue was purified by flash column chromatography (1:2 EtOAc–petroleum ether 60–80; R_f 0.32) to give the title compound **6** as a yellow oil (111 mg, 70% over 2 steps); ν_{max} 1660 (C=O); a 2:3 mixture of amide rotamers was observed by ^{1}H NMR in $CDCl_3$ at room temperature; δ_H (500 MHz; $CDCl_3$) 1.86 (3H, app td, *J* 6.6, 1.6), 2.50 – 2.68 (2H, m, 2.68 – 2.85 (1H, m), 2.85 – 2.98 (1H, m), 3.13 (0.4H, ddd, *J* 13.3, 11.0, 4.5), 3.56 (0.6H, ddd, *J* 13.3, 11.0, 4.5), 3.80 – 4.02 (0.6H, m), 4.63 (0.4H, ddd, *J* 13.3, 5.9, 2.4), 4.93 – 5.14 (2.4H, m), 5.73 (0.6H, dd, 5.75 – 5.89 (1H, m), 6.31 (1H, dd, *J* 15.0, 1.6), 6.73 – 6.92 (1H, m), 6.97 – 7.18 (4H, m); δ_C (126 MHz; $CDCl_3$) 18.4, 28.2, 29.4, 35.9, 40.2, 41.2, 41.7, 52.4, 56.4, 117.2, 118.6, 122.0, 122.4, 126.2, 126.4, 126.7, 127.0, 127.1, 127.5, 128.6, 129.3, 133.6, 134.1, 135.1, 136.6, 137.2, 141.7, 141.7, 166.0, 166.2 (C=O); *m/z* 264 (40%, $[M+Na]^+$), 242 (100%, M^+); Found M^+ 242.1548, $C_{16}H_{19}NO$ requires 242.1539.

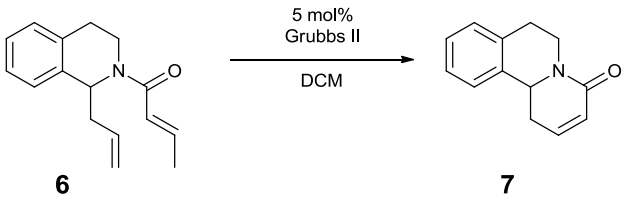
(*E*)-1-(1-Allyl-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)but-2-en-1-one (10)



9 **10**

Trifluoroacetic acid (1.05 mL, 13.6 mmol) was added to a solution of **9** (650 mg, 1.95 mmol) in DCM (10 mL) and the yellow solution was stirred at room temperature for 2 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM (10 mL) and saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was dried over $MgSO_4$ and solvent removed under reduced pressure. The residue (400 mg) was dissolved in THF (10 mL) and triethylamine (260 μL, 1.89 mmol) was added followed by dropwise addition of crotonoyl chloride (160 μL, 1.71 mmol) and the solution was stirred for 15 hours at room temperature. The reaction mixture was partitioned between DCM and saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and solvent removed under reduced pressure. The residue was purified by flash column chromatography (1:2 EtOAc–petroleum ether 60–80; R_f 0.32) to give the title compound **10** as a yellow oil (441 mg, 75% over 2 steps); ν_{max} 1659 (C=O); a 2:3 mixture of amide rotamers was observed by ^{1}H NMR in $CDCl_3$ at room temperature; δ_H (500 MHz; $CDCl_3$) 1.71 – 1.85 (3H, m), 2.42 – 2.60 (2.4H, m), 2.61 – 2.69 (0.6H, m), 2.71 – 2.84 (1H, m), 3.02 (0.4H, ddd, *J* 12.5, 12.5, 4.1), 3.38 – 3.55 (0.6H, m), 3.74 (3H, s), 3.76 (3H, s,), 3.82 – 3.92 (0.6H, m,), 4.57 (0.4H, dd, *J* 13.1, 4.0), 4.86 (0.4H, dd, *J* 8.6, 5.2), 4.88 – 4.96 (1H, m), 4.96 – 5.08 (1H, m,), 5.58 (0.6H, t, *J* 7.0), 5.65 – 5.81 (1H, m), 6.25 (1H, dd, *J* 14.9, 5.3), 6.43 – 6.60 (2H, m), 6.77 (1H, dq, *J* 13.8, 6.8); δ_C (126 MHz, $CDCl_3$) 18.1, 27.7, 28.8, 35.7, 40.0, 41.0, 41.5, 51.8, 55.8, 55.9, 55.9, 109.9, 110.4, 111.3, 111.7, 117.0, 118.4, 121.9, 122.4, 125.4, 126.6, 128.3, 129.1, 134.0, 135.0, 141.2, 141.4, 147.4, 147.5, 147.7, 148.0, 165.8, 166.0; *m/z* 302 (100%, M^+); Found M^+ 302.1751, $C_{18}H_{23}NO_3$ requires 302.1750.

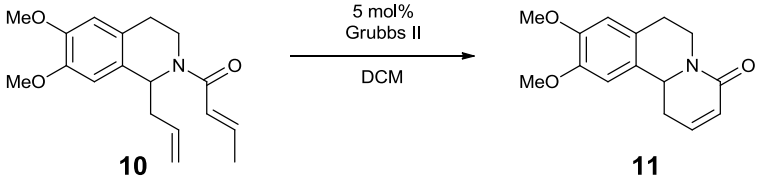
6,7-Dihydro-1H-pyrido[2,1-*a*]isoquinolin-4(11b*H*)-one (7)



6 **7**

Grubbs type II catalyst (16 mg, 5 mol%) was added to a solution of amide **6** (90 mg, 0.37 mmol) in degassed DCM (5 mL) and the purple solution was stirred at room temperature for five hours. The resulting brown solution was concentrated under reduced pressure and subsequently purified by flash column chromatography (1:1 EtOAc–petroleum ether 60–80; R_f 0.26) to give the title compound **7** as pale brown solid (60 mg, 85%); mp 62 – 68 °C; ν_{max} 1652 (C=O); δ_H (500 MHz; $CDCl_3$) 2.25 – 2.36 (1H, m), 2.68 – 2.81 (2H, m), 2.81 – 2.99 (2H, m), 4.70–4.75 (1H, m), 4.78 (1H, dd, *J* 13.9, 4.6), 6.05 (1H, dd, *J* 9.8, 2.9), 6.65 (1H, ddd, *J* 9.8, 6.3, 2.1), 7.04 – 7.29 (4H, m); δ_C (126 MHz; $CDCl_3$) 29.7, 33.6, 38.1, 54.8, 125.8, 125.8, 126.9, 127.0, 129.2, 135.1, 136.1, 139.1, 164.9; *m/z* 200 (100%, M^+); Found M^+ 200.1072, $C_{13}H_{13}NO$ requires 200.1069; Found: C 78.51%; H 6.62%, N 6.84%; $C_{13}H_{12}NO$ requires: C 78.36%, H 6.58%, N 7.03%.

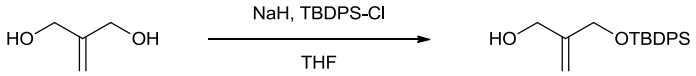
9,10-Dimethoxy-6,7-dihydro-1H-pyrido[2,1-*a*]isoquinolin-4(11b*H*)-one (11)[4]



10 **11**

$Ti(O^iPr)_4$ (220 µL, 30 mol %) was added to a solution of **10** (749 mg, 2.49 mmol) in DCM (30 mL) and the solution was stirred at room temperature for one hour before the addition of Grubbs type II catalyst (105 mg, 5 mol%). The resulting brown solution was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and the residue purified by flash column chromatography (4:1 EtOAc–petroleum ether 60–80; R_f 0.20) to give the title compound **11** as a pale brown solid (555 mg, 86%); mp 124 – 126 °C (lit. 128 – 130 °C)[4]; ν_{max} 1656 (C=O); δ_H (500 MHz; $CDCl_3$) 2.16 – 2.29 (1H, m), 2.56 – 2.72 (2H, m), 2.72 – 2.91 (2H, m), 3.79 (3H, s), 3.80 (3H, s), 4.57– 4.79 (2H, m), 5.99 (1H, dd, *J* 9.8, 2.8), 6.36 – 6.77 (3H, m); δ_C (126 MHz; $CDCl_3$) 29.0, 33.7, 38.0, 54.4, 55.9, 56.1, 108.8, 111.6, 125.6, 127.2, 127.6, 138.8, 148.0, 148.0, 164.8; *m/z* 260 (100%, M^+); Found M^+ 260.1282, $C_{15}H_{17}NO_3$ requires 260.1281; Found: C 69.50%; H 6.62%, N 5.34%; $C_{15}H_{17}NO_3$ requires: C 69.48%, H 6.61%, N 5.40%.

2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)prop-2-en-1-ol (S4)



S3 **S4**

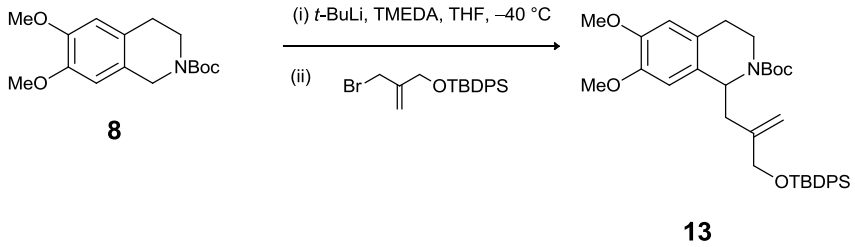
2-Methylene-1,3-propane diol **S3** (2.0 mL, 24.5 mmol) was added to a solution of NaH (648 mg, 27.0 mmol) in THF (50 mL) and the resulting solution was stirred for 30 minutes before addition of TBDPS-Cl (6.28 mL, 24.5 mmol). The resulting solution was stirred for 15 hours at room temperature. The reaction mixture was partitioned between DCM (50 mL) and saturated aqueous NH_4Cl solution (50 mL), dried over Na_2SO_4 and solvent removed under reduced pressure. The residue was purified by flash column chromatography (1:4 EtOAc – petroleum ether 60–80; R_f 0.35) to give the title compound **S4** as a colourless oil (6.10 g, 76%); ν_{max} 3333 (OH); δ_H (500 MHz; $CDCl_3$) 1.05 (9H, s), 1.85 (1H, t, *J* 6.1), 4.16 (2H, d, *J* 6.1), 4.24 (2H, s), 5.08 – 5.12 (1H, m), 5.12 – 5.17 (1H, m), 7.34 – 7.46 (6H, m), 7.64 – 7.71 (4H, m); δ_C (126 MHz; $CDCl_3$) 19.2, 26.8, 64.5, 65.6, 111.2, 127.8, 129.8, 133.2, 135.6, 147.1; Mass spectrometry data could not be obtained.

((2-(Bromomethyl)allyl)oxy)(tert-butyl)diphenylsilane (12)

S4 **12**

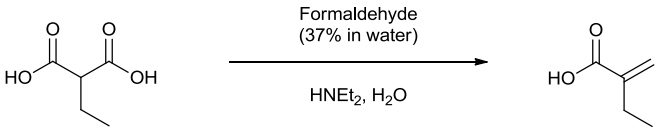
N-Bromo succinimide (4.20 g, 23.6 mmol) was added to a solution of PPh_3 (6.19 g, 23.6 mmol) in DCM (100 mL) at −78 °C and the mixture was stirred at −78 °C for 15 minutes before addition of alcohol **S4** (5.92 g, 18.1 mmol). The resulting mixture was stirred at −60 °C for 1 hour and allowed to warm to −20 °C over 2 hours. The mixture was washed with saturated aqueous $NaHCO_3$ solution (100 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (petroleum ether 60–80; R_f 0.30) to give the title compound **12** as a colourless oil (5.53 g, 78%); ν_{max} 1428 (C=C); δ_H (500 MHz; $CDCl_3$) 1.10 (9H, s), 4.05 (2H, s), 4.34 (2H, s), 5.29 – 5.33 (1H, m), 5.33 – 5.35 (1H, m), 7.33 – 7.56 (6H, m), 7.60 – 7.97 (4H, m); δ_C (126 MHz; $CDCl_3$) 19.3, 26.8, 32.8, 64.2, 115.0, 127.8, 129.8, 133.3, 135.5, 144.4; Mass spectrometry data could not be obtained.

***tert*-Butyl-1-(2-(((tert-butyldiphenylsilyl)oxy)methyl)allyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (13)**



tert–Butyllithium (6.82 mL of a 1.5 M solution in pentanes, 10.2 mmol) was added to a solution of *N*-Boc-6,7 dimethoxytetrahydroisoquinoline (1.00 g, 3.41 mmol) and TMEDA (1.53 mL, 10.2 mmol) in THF (50 mL) at −40 °C. The red solution was stirred for 40 minutes at −40 °C before addition of bromide **12** (5.31 g, 13.6 mmol). The pale yellow solution was stirred for 30 minutes at 0 °C and then 4 hours at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (50 mL), extracted into DCM (2 x 50 mL) and dried over $MgSO_4$. Solvent was removed under reduced pressure and the residue purified by flash column chromatography (1:4 EtOAc–petroleum ether 60–80; R_f 0.45) to give the title compound **13** as a colourless oil (1.39 g, 68%); ν_{max} 1691 (C=O); a 2:3 mixture of amide rotamers was observed by ^1H NMR in $CDCl_3$ at room temperature; δ_H (500 MHz; $CDCl_3$) 1.00 – 1.09 (9H, m), 1.35 (9H, s), 2.40 – 2.53 (2H, m), 2.53 – 2.65 (1H, m), 2.69 – 2.92 (1H, m), 3.05 – 3.18 (0.6H, m), 3.23 (0.4H, ddd, *J* 13.0, 11.5, 4.1), 3.76 (3H, s), 3.83 (3H, s), 3.96 (0.4H, ddd, *J* 13.0, 5.6, 2.4), 4.10 – 4.16 (1H, m), 4.20 (0.6H, ddd, *J* 13.0, 5.6, 2.4), 4.23 – 4.30 (1H, m), 4.87 (1H, s), 4.99 (0.6H, t, *J* 7.1), 5.13 (0.4H, s), 5.21 (0.6H, s), 5.25 (0.4H, dd, *J* 9.1, 5.5), 6.46 – 6.62 (2H, m), 7.30 – 7.46 (6H, m), 7.57 – 7.73 (4H, m); δ_C (126 MHz; $CDCl_3$) 19.1, 19.4, 26.6, 26.9, 27.8, 28.1, 28.4, 28.5, 36.5, 38.0, 39.6, 39.8, 52.5, 53.3, 55.9, 56.0, 66.2, 66.4, 79.3, 80.0, 110.0, 110.2, 111.4, 111.6, 112.1, 113.0, 126.0, 126.5, 127.7, 127.8, 129.3, 129.3, 129.6, 129.6, 129.8, 133.5, 133.7, 134.9, 135.5, 135.5, 135.6, 135.6, 136.2, 144.4, 145.2, 147.3, 147.6, 147.8, 154.7; *m/z* 602 (100%, M^+); Found M^+ 602.3298, $C_{36}H_{47}NO_5Si$ requires 602.3296.

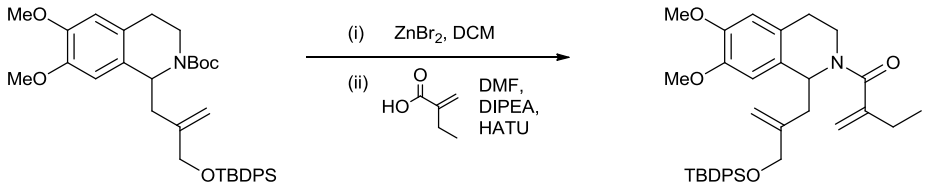
Ethyl acrylic acid (S6)[5]



S5 **S6**

Formaldehyde (1.87 mL of a 37% solution in water, 1.02 mmol) and diethylamine (2.41 mL, 1.02 mmol) were added to a solution of ethylmalonic acid 239 (3.0 g, 1.02 mmol) in water (25 mL) and the solution was stirred under reflux for five hours before cooling to room temperature. HCl (20 mL of a 1.0 M solution) was added and the mixture was extracted into DCM and dried over Na2SO4. The solvent was removed under reduced pressure to give the title compound **S6** as a colourless oil (1.77g, 78%) which was used without further purification; δ_H (500 MHz; $CDCl_3$) 1.10 (3H, t, *J* 7.4), 2.33 (2H, q, *J* 7.4), 5.66 (1H, m), 6.29 (1H, s).

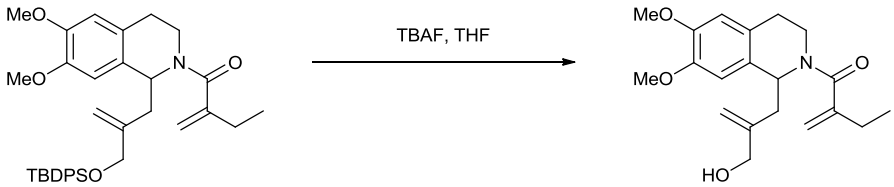
1-(1-(2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)allyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-methylenebutan-1-one (14)



13 **14**

$ZnBr_2$ (7.13 g, 31.6 mmol) was dried under vacuum at 150 °C for four hours and then allowed to cool to room temperature under argon. DCM (50 mL) was added followed by a solution of **13** (3.8 g, 6.31 mmol) in DCM (50 mL). The resulting suspension was stirred at room temperature for 24 hours. Saturated aqueous $NaHCO_3$ (50 mL) was added and the mixture extracted into DCM (50 mL) and dried over $MgSO_4$. Solvent was removed under reduced pressure to give a yellow oil (3.16 g) which was dissolved in DMF (40 mL). Ethyl acrylic acid (959 µL, 9.45 mmol) was added followed by DIPEA (2.74 mL, 15.7 mmol) and HATU (3.59 g, 9.45 mmol). The solution was stirred at room temperature for three hours. Saturated aqueous $NaHCO_3$ (40 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL), washed with brine (2 x 20 mL) and dried over $MgSO_4$. Solvent was removed under reduced pressure and the residue purified by flash column chromatography (1:2 EtOAc–petroleum ether 60–80; R_f 0.45) to give the title compound **14** as a colourless oil (2.7g, 75%); ν_{max} 1614 (C=O); a 1:4 mixture of amide rotamers was observed by ^1H NMR in $CDCl_3$ at room temperature; δ_H (500 MHz; $CDCl_3$) 1.02 – 1.17 (12H, m), 2.14 (0.2H, m), 2.29 (2H, q, *J* 7.4), 2.51–2.58 (1H, dd, *J* 14.0, 10.0), 2.60 – 2.70 (1H, m), 2.74 – 2.90 (1.6H, m), 2.90 – 3.00 (0.2H, m), 3.11 – 3.22 (0.2H, m), 3.42 – 3.51 (0.8H, m), 3.75 (0.6H, s), 3.79 (2.4H, s), 3.85 (3H, s), 3.98 – 4.08 (1H, m), 4.13 (0.2H, d, *J* 13.6), 4.20 (0.8H, d, *J* 13.6), 4.46 (0.8H, d, *J* 13.6), 4.68 (0.2H, dd, *J* 13.2, 6.3), 4.88 (0.8H, s), 4.90 – 4.97 (0.6H, m), 5.0 0 (0.8H, s), 5.04 (0.2H, m), 5.10 – 5.13 (1.6H, m), 5.33 (0.2H, s), 5.76 (0.8H, dd, *J* 10.0, 4.4), 6.49 (0.2H, s), 6.55 (0.8H, s), 6.60 (0.2H, s), 6.66 (0.8H, s), 7.41 (6H, m), 7.64 – 7.75 (4H, m); δ_C (126 MHz; $CDCl_3$); 11.6, 11.7, 19.4, 26.8, 26.9, 27.0, 27.3, 27.6, 29.1, 34.9, 39.9, 40.0, 40.0, 49.3, 55.9, 56.6, 66.2, 66.5, 109.6, 110.0, 111.3, 111.6, 112.1, 112.6, 113.0, 113.9, 124.9, 126.0, 127.6, 127.7, 127.8, 127.8, 128.7, 129.2, 129.6, 129.8, 133.3, 133.4, 133.7, 133.7, 135.5, 135.6, 143.8, 145.2, 146.5, 147.0, 147.2, 147.6, 147.7, 148.0, 171.3, 171.9; m/z 584 (100%, M^+); Found 606.3010, $C_{36}H_{45}NO_4SiNa$ requires 606.3000.

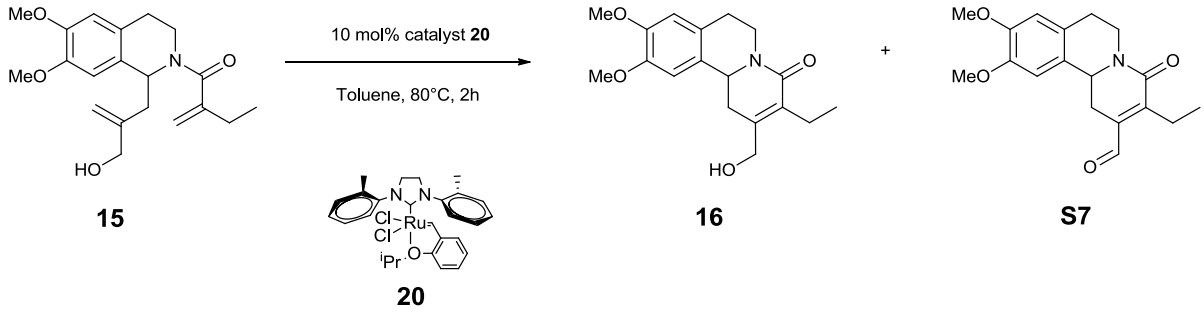
1-(1-(2-(Hydroxymethyl)allyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-methylenebutan-1-one (15)



14 **15**

TBAF (13.6 mL of a 1.0 M solution in THF, 13.6 mmol) was added to a solution of **14** (1.55 g, 2.72 mmol) in THF (30 mL) and the solution was stirred for 15 hours at room temperature. Water (20 mL) was added and the mixture extracted into DCM (2 x 20 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure and the residue purified by flash column chromatography (1:1 EtOAc−petroleum ether 60–80; R_f 0.35) to give the title compound **15** as a colourless oil (720 mg, 80%); ν_{max} 3390 (OH), 1609 (C=O); δ_H (500 MHz; $CDCl_3$) 1.12 (3H, t, *J* 7.4), 2.22 – 2.39 (2H, m), 2.58 (1H, dd, *J* 13.4, 11.0), 2.66 – 2.78 (2H, m), 2.82 – 2.93 (1H, m), 3.47 (1H, app td, *J* 12.9, 4.1,), 3.86 (3H, s), 3.89 (3H, s), 4.09 (1H, app dd, *J* 13.5, 5.6), 4.21 – 4.32 (2H, m), 4.77 (1H, s), 5.05 (1H, s), 5.08 (1H, s), 5.18 (1H, s), 5.74 (1H, dd, *J* 11.0, 4.3), 6.59 (1H, s), 6.74 (1H, s); δ_C (126 MHz; $CDCl_3$) 11.7, 27.2, 29.0, 40.2, 41.6, 51.4, 55.9, 56.2, 67.8, 109.9, 111.2, 112.6, 115.0, 124.3, 128.7, 145.8, 146.5, 147.9, 172.3; *m/z* 368 (100%, $[M+Na]^+$); Found M^+ 346.2019, $C_{20}H_{27}NO_4$ requires 346.2013.

3-Ethyl-2-(hydroxymethyl)-9,10-dimethoxy-6,7-dihydro-1*H*-pyrido[2,1-a]isoquinolin-4(11b*H*)-one (16) and 3-ethyl-9,10-dimethoxy-4-oxo-4,6,7,11b-tetrahydro-1H-pyrido[2,1-a]isoquinoline-2-carbaldehyde (S7)

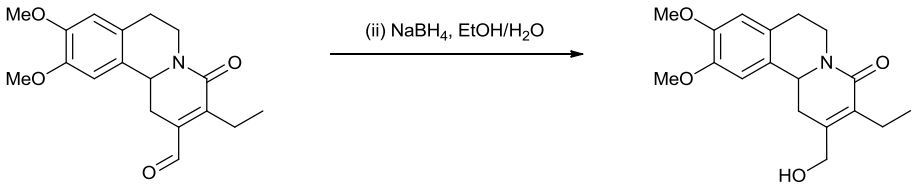


15 **16** **S7**

20

Catalyst **20** (8 mg, 0.14 mmol) was added to a solution of alcohol **15** (50 mg, 0.01 mmol) in degassed toluene (2 mL) and the resulting brown solution was stirred at 80 ºC for 2 hours. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (1:1 EtOAc: petroleum ether 60–80; R_f 0.25) to give the title compound **16** as a colourless solid (20 mg, 44%); mp 129 – 131 °C; ν_{max} 3381 (OH), 1606 (C=O); δ_H (500 MHz; $CDCl_3$) 1.03 (3H, t, *J* 7.5), 2.18 (1H, app d, *J* 2.9), 2.19 – 2.29 (1H, m), 2.35 (1H, dq, *J* 15.0, 7.5), 2.51 (1H, dq, *J* 15.0, 7.5), 2.62 – 2.70 (1H, m), 2.77 – 2.85 (2H, m), 2.94 (1H, dd, *J* 17.1, 4.3), 3.87 (6H, s), 4.34 (1H, d, *J* 13.3), 4.48 (1H, d, *J* 13.3), 4.61 (1H, dd, *J* 14.2, 4.3), 4.71 – 4.81 (1H, m), 6.63 (1H, s), 6.66 (1H, s); δ_C (126 MHz; $CDCl_3$) 14.9, 19.7, 29.1, 34.6, 38.4, 53.8, 55.9, 56.1, 61.5, 108.6, 111.3, 126.9, 127.9, 132.3, 143.7, 147.8, 147.9, 165.8; *m/z* 318 (100%, M^+); Found M^+ 318.1726, $C_{18}H_{24}NO_4$ requires 318.1700; Found: C 68.29%; H 7.37%, N 4.32%; $C_{18}H_{23}NO_4$ requires: C 68.12%, H 7.30%, N 4.41%. In addition to recovered starting material **15** (3 mg, 3%), aldehyde **S7** was also isolated (20 mg, 44%); ν_{max} 1695 (CH=O), 1622 (NC=O); δ_H (500 MHz; $CDCl_3$) 1.25 (3H, t, *J* 7.5), 2.07 – 2.15 (1H, m), 2.72 – 2.78 (1H, m), 2.83 – 3.03 (4H, m), 3.20 (1H, dd, *J* 17.0, 4.2), 3.89 (3H, s), 3.90 (3H, s), 4.61 (1H, dd, *J* 14.1, 4.2), 4.77 – 4.87 (1H, m), 6.67 (2H, s), 10.34 (1H, s); δ_C (126 MHz; $CDCl_3$) 16.1, 18.7, 29.0, 29.9, 39.0, 53.6, 56.0, 56.2, 108.7, 111.5, 126.8, 127.1, 137.6, 148.2, 148.3, 149.3, 164.8, 191.3; *m/z* 316 (100%, M^+); Found M^+ 316.1544, $C_{18}H_{22}NO_4$ requires 316.1543. The aldehyde could be reduced to the required alcohol (see below).

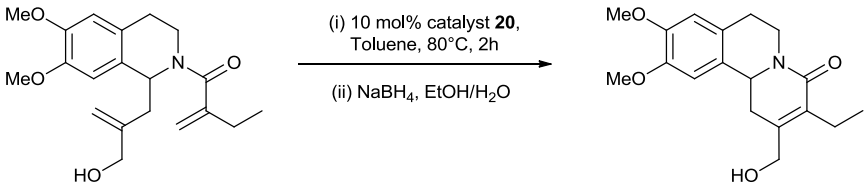
3-Ethyl-2-(hydroxymethyl)-9,10-dimethoxy-6,7-dihydro-1*H*-pyrido[2,1-a]isoquinolin-4(11b*H*)-one (16) from reduction of aldehyde (S7)



S7 **16**

Sodium borohydride (12 mg, 0.32 mmol) was added to a solution of aldehyde **S7** (20 mg, 0.06 mmol) in EtOH (2 mL) and water (1 mL) at 0 °C and the reaction was stirred at 0 °C for 2 hours. Water (3 mL) was added and the mixture extracted into EtOAc (3 mL) and dried over $MgSO_4$. Solvent was removed under reduced pressure and the residue was purified by flash column chromatography (1:1 EtOAc: petroleum ether 60–80; R_f 0.50) to give the alcohol (15 mg) as a colourless solid. The total yield of alcohol **16** from diene **15** over two steps was 75%.

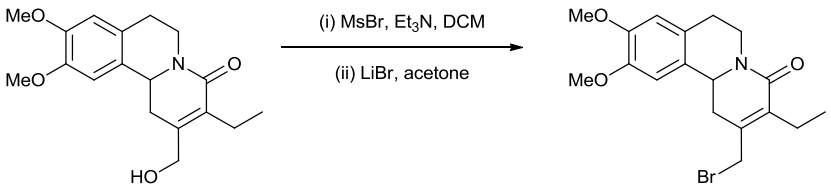
Alternative synthesis of 3-Ethyl-2-(hydroxymethyl)-9,10-dimethoxy-6,7-dihydro-1*H*-pyrido[2,1-a]isoquinolin-4(11b*H*)-one (16)



15 **16**

Catalyst **20** (247 mg, 0.43 mmol) was added to a solution of alcohol **15** (1.5 g, 4.34 mmol) in degassed toluene (60 mL) and the resulting brown solution was stirred at 80 ºC for 2 hours. The solvent was removed under reduced pressure and the residue dissolved in EtOH (20 mL) and water (10 mL). $NaBH_4$ (162 mg, 4.34 mmol) was added at 0 °C and the solution stirred for 2 hours at 0 °C. Water (20 mL) was added and the mixture was extracted into EtOAc (20 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was passed through a plug of silica (1:1 EtOAc− petroleum ether 60–80) and the solvent removed under reduced pressure to give a brown oil. Trituration with ether gave a colourless solid which was isolated by filtration to give the title compound **16** (735 mg, 53%).

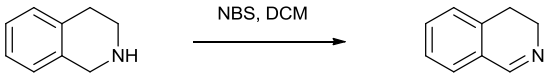
2-(Bromomethyl)-3-ethyl-9,10-dimethoxy-6,7-dihydro-1*H*-pyrido[2,1-a]isoquinolin-4(11b*H*)-one (17)



16 **17**

Mesyl bromide (40 µL, 0.52 mmol) was added to a solution of alcohol **16** (140 mg, 0.44 mmol) and triethylamine (307 µL, 2.21 mmol) in DCM (10 mL) at 0 ºC and the resulting solution was allowed to stir at room temperature for 2 hours. Solvent was removed under reduced pressure to give a mixture of the corresponding mesylate and bromide **17** (1:4). The residue was dissolved in acetone (10 mL) and lithium bromide (191 mg, 2.21 mmol) was added. The solution was stirred at reflux for one hour and after cooling to room temperature excess lithium bromide was removed by filtration. The solvent was removed under reduced pressure and the residue purified by flash column chromatography (1:2 EtOAc: petroleum ether 60–80; R_f 0.50) to give the title compound **17** as a colourless oil (120 mg, 72%); ν_{max} 1621 (C=O); δ_H (500 MHz; $CDCl_3$) 1.14 (3H, t, *J* 7.5), 2.41 – 2.52 (2H, m,), 2.55 – 2.64 (1H, m), 2.68 – 2.79 (2H, m), 2.82 – 2.94 (2H, m), 3.89 (3H, s), 3.91 (3H, s), 4.07 (1H, d, *J* 9.9), 4.25 (1H, d, *J* 9.9), 4.68 (1H, dd, *J* 13.9, 4.3), 4.77 – 4.83 (1H, m), 6.66 (1H, s), 6.67 (1H, s,); δ_C (126 MHz; $CDCl_3$) 14.1, 20.3, 29.1, 31.3, 36.6, 38.5, 53.7, 55.9, 56.3, 108.8, 111.6, 127.2, 127.6, 135.6, 139.4, 148.1, 164.9; one quaternary carbon not observed; *m/z* 380 (100%, M^+); Found M^+ 380.0829, $C_{18}H_{23}BrNO_3$ requires 380.0856.

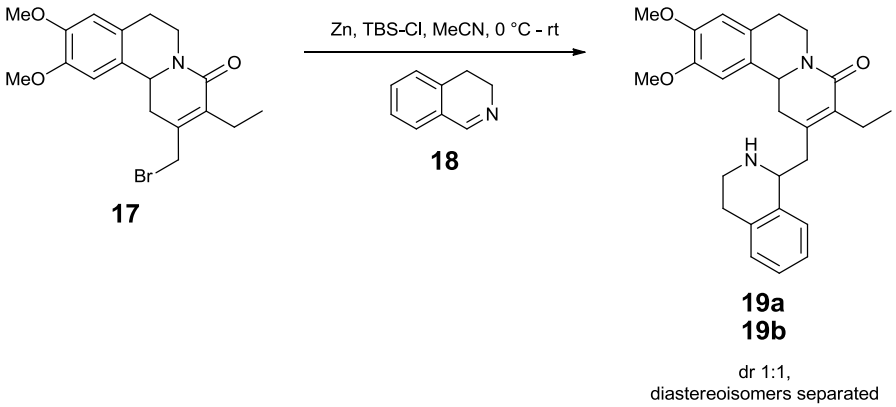
3,4-Dihydroisoquinoline (18)[6]



S1 **18**

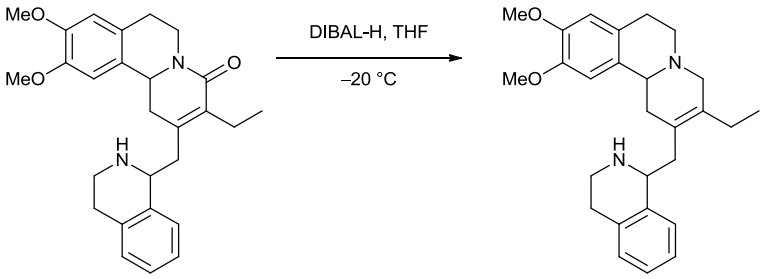
N-Bromosuccinimide (1.00 g, 5.62 mmol) was added to a solution of tetrahydroisoquinoline **S1** (703 µL, 5.62 mmol) in DCM (10 mL) and the resulting solution was stirred at room temperature for 15 hours. The solution was washed with saturated aqueous $NaHCO_3$ solution (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography (100% EtOAc; R_f 0.40) to give the title compound **18** as a colourless solid (385 mg, 52%); m.p. 39 – 42 °C (lit. 42 – 45 °C);[6] δ_H (500 MHz; $CDCl_3$) 2.77 (2H, t, *J* 7.5), 3.77 – 3.82 (2H, m), 7.17 (1H, d, *J* 7.4), 7.27 – 7.34 (2H, m), 7.37 (1H, app td, *J* 7.3, 1.8), 8.35 (1H, t, *J* 2.1); δ_C (126 MHz; $CDCl_3$) 25.0, 47.4, 127.1, 127.2, 127.4, 128.5, 131.1, 136.4, 160.4.

3-Ethyl-9,10-dimethoxy-2-((1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-6,7-dihydro-1*H*-pyrido[2,1-a]isoquinolin-4(11b*H*)-one (19a and 19b)



TBS-Cl (87 mg, 0.58 mmol) was added to a solution of **18** (76 mg, 0.58 mmol) in MeCN (8 mL) at 0 °C and the solution was stirred at 0 °C for 10 minutes before the addition of bromide **17** (200 mg, 0.53 mmol) and zinc powder (172 mg, 2.63 mmol). The resulting suspension was stirred at room temperature for 5 hours. Saturated aqueous $NaHCO_3$ was added (8 mL) and the mixture filtered to remove zinc, extracted into EtOAc (2 x 5 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by flash column chromatography (5-10% MeOH in EtOAc; R_f 0.15 and 0.30) to give two diastereoisomers of the title compound **19** as a colourless oils. Diastereoisomer 1 (**19a**): (22 mg, 10%); ν_{max} 1616 (C=O); δ_H (500 MHz, $CDCl_3$) 1.07 (3H, t, *J* 7.4), 2.33 – 2.46 (2H, m), 2.58 – 2.65 (2H, m), 2.68 – 2.74 (1H, m), 2.75 – 2.93 (6H, m), 2.96 – 3.02 (1H, m), 3.23 (1H, ddd, *J* 11.9, 6.5, 5.2), 3.89 (3H, s), 3.89 (3H, s), 4.24 (1H, dd, *J* 9.6, 4.3), 4.65 (1H, dd, *J* 14.0, 4.0), 4.84 (1H, ddd, *J* 12.1, 4.0, 2.4,), 6.56 (1H, s,), 6.67 (1H, s), 7.08 – 7.25 (4H, m); δ_C (126 MHz; $CDCl_3$) 14.5, 20.3, 29.3, 30.0, 38.3, 38.3, 40.4, 40.8, 53.6, 53.9, 55.9, 56.3, 108.9, 111.6, 125.9, 126.1, 126.3, 127.4, 128.0, 129.5, 134.1, 135.5, 138.7, 142.7, 148.0, 148.0, 165.6; *m/z* 433 (100%, M^+); Found M^+ 433.2494 $C_{27}H_{33}N_2O_3$ requires 433.2486; Diastereoisomer 2 (**19b**): (22 mg, 10%); ν_{max} 1617 (C=O); δ_H (500 MHz; $CDCl_3$) 1.11 (3H, t, *J* 7.4), 2.23 – 2.33 (1H, m), 2.40 – 2.50 (2H, m), 2.52 – 2.61 (1H, m), 2.65 – 2.73 (2H, m), 2.77 – 2.93 (5H, m), 3.07 (1H, dt, *J* 12.5, 5.7), 3.28 (1H, dt, *J* 12.5, 6.1), 3.85 (3H, s), 3.88 (3H, s), 4.30 (1H, dd, *J* 8.4, 5.6), 4.56 (1H, dd, *J* 14.0, 4.1), 4.73 – 4.86 (1H, m), 6.44 (1H, s), 6.66 (1H, s), 7.09 – 7.22 (4H, m); δ_C (126 MHz; $CDCl_3$) 14.4, 20.5, 29.3, 29.7, 38.3, 38.6, 40.3, 40.6, 53.6, 54.8, 55.9, 56.2, 108.8, 111.5, 125.8, 126.5, 126.5, 127.2, 128.0, 129.5, 134.2, 135.3, 138.4, 142.9, 147.9, 148.0, 165.6; *m/z* 433 (100%, M^+); Found M^+ 433.2498 $C_{27}H_{33}N_2O_3$ requires 433.2486.

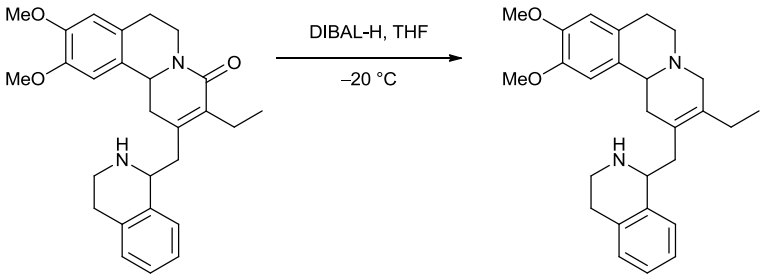
3-Ethyl-9,10-dimethoxy-2-((1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-4,6,7,11b-tetrahydro-1*H*-pyrido[2,1-a]isoquinoline (Diastereoisomer 1, 3a)



19a **3a**

Diisobutylaluminium hydride (231 µL of a 1.0 M solution in THF, 0.23 mmol) was added dropwise to a solution of **19a** (20 mg, 0.05 mmol) in THF (1 mL) at −20 °C. The solution was stirred at −20 °C for 1 hour and then warmed to 0 °C. EtOAc (1 mL) was added at 0 °C followed by 1M NaOH (1 mL). The mixture was extracted into EtOAc (2 x 2 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure and the residue purified by flash column chromatography (10% 2M NH_3 in MeOH, 90% EtOAc; R_f 0.50) to give the title compound **3a** as a colourless oil. However, a pink solution was obtained on dissolving in methanol (12 mg, 52%); ν_{max} 1554 (O-CH_3); δ_H (500 MHz; MeOD) 1.03 (3H, t, *J* 7.6), 2.01 – 2.11 (1H, m), 2.11 – 2.28 (2H, m), 2.55 (1H, ddd, *J* 11.3, 10.8, 3.6), 2.66 – 2.80 (4H, m,), 2.86 – 2.93 (2H, m), 2.96 – 3.02 (1H, m), 3.04 – 3.17 (3H, m), 3.25 (1H, ddd, *J* 12.0, 6.8, 5.3), 3.34 (1H, app d, *J* 15.5), 3.50 (1H, dd, *J* 10.7, 4.0), 3.81 (3H, s), 3.82 (3H, s), 4.24 (1H, dd, *J* 9.1, 5.2), 6.71 (1H, s), 6.79 (1H, s), 7.05 – 7.21 (3H, m), 7.21 – 7.31 (1H, m); δ_C (126 MHz; MeOD) 13.4, 24.8, 29.4, 29.8, 37.4, 39.0, 41.3, 52.3, 54.5, 56.5, 56.8, 59.4, 60.4, 110.5, 113.1, 126.2, 126.9, 127.5, 127.7, 130.2, 131.0, 135.4, 135.7, 139.2, 149.2, 149.3; *m/z* 419 (100%, M^+); Found $[M+Na]^+$ 441.2469 $C_{27}H_{34}N_2O_2Na$ requires 441.2512.

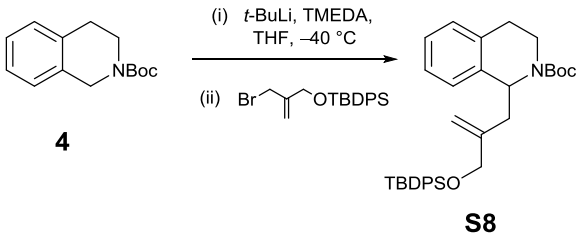
3-Ethyl-9,10-dimethoxy-2-((1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-4,6,7,11b-tetrahydro-1*H*-pyrido[2,1-a]isoquinoline (Diastereoisomer 2, 3b)



19b **3b**

Diisobutyl aluminium hydride (197 µL of a 1.0M solution in THF, 0.19 mmol) was added dropwise to a solution of **19b** (17 mg, 0.04 mmol) in THF (1 mL) at −20 °C. The solution was stirred at −20 °C for 1 hour and then warmed to 0 °C. EtOAc (1 mL) was added at 0 °C followed by 1M NaOH (1 mL) and the mixture was extracted into EtOAc (2x 2 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure and the residue purified by flash column chromatography (10% 2M NH_3 in MeOH, 90% EtOAc; R_f 0.48) to give the title compound **3b** as a colourless oil. However, a pink solution was obtained on dissolving in methanol (6 mg, 37%); δ_H (500 MHz; MeOD) 1.07 (3H, t, *J* 7.6), 2.03 – 2.11 (1H, m), 2.12 – 2.20 (1H, m), 2.27 (1H, dq, *J* 15.5, 7.6), 2.44 – 2.50 (1H, m,), 2.54 (1H, dd, *J* 11.3, 4.0), 2.60 (1H, dd, *J* 13.9, 8.2), 2.69 (1H, dd, *J* 14.1, 3.1), 2.75 (1H, dd, *J* 13.9, 6.3), 2.82 – 2.95 (2H, m), 3.01 (1H, dt, *J* 12.1, 5.9), 3.04 – 3.16 (3H, m), 3.29 (1H, dd, *J* 6.9, 5.3), 3.34 – 3.39 (1H, m), 3.41 (1H, dd, *J* 10.7, 3.8), 3.76 (3H, s), 3.80 (3H, s), 4.21 – 4.25 (1H, m), 6.58 (1H, s), 6.68 (1H, s), 7.09 – 7.19 (3H, m), 7.22 – 7.28 (1H, m); δ_C (126 MHz; MeOD) 13.3, 24.7, 29.2, 29.8, 38.6, 39.4, 41.1, 52.3, 55.6, 56.5, 56.7, 59.1, 60.44, 110.3, 113.1, 126.8, 126.9, 127.5, 127.6, 127.8, 130.2, 130.9, 134.6, 135.9, 139.4, 149.1, 149.2; *m/z* 419 (100%, M^+); Found M^+ 419.2699 $C_{27}H_{34}N_2O_2$ requires 419.2693.

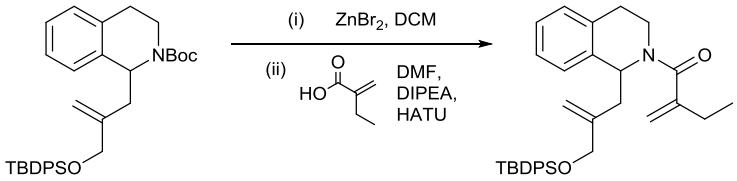
tert-Butyl-1-(2-(((tert-butyldiphenylsilyl)oxy)methyl)allyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (S8)



4 **S8**

tert-Butyllithium (15.8 mL of a 1.3 M solution in hexane, 20.6 mmol) was added dropwise to a solution of *N*-Boc tetrahydroisoquinoline (4.0 g, 17.1 mmol) in THF (150 mL) at − 40 °C. The deep red solution was stirred at − 40 °C for 10 minutes and then cooled to − 78 °C for 30 minutes. Bromide **12** (8.6 g, 22.3 mmol) was added and the solution stirred at − 78 °C for 30 minutes before being allowed to warm to room temperature. The reaction was stirred at room temperature for 15 hours. Saturated aqueous NH_4Cl (150 mL) was added and the mixture extracted into DCM (2 x 75 mL) and dried over $MgSO_4$. Solvent was removed under reduced pressure and the residue purified by flash column chromatography (2:3 petroleum ether 60–80 – DCM; R_f 0.35) to give the title compound **S8** as a colourless oil (4.0 g, 43%); ν_{max} 1692 (C=O); a 7:3 mixture of amide rotamers was observed by ^{1}H NMR in $CDCl_3$ at room temperature; δ_H (500 MHz; $CDCl_3$) 1.06 – 1.12 (9H, app m), 1.39 (6.3H, s), 1.45 (2.7H, s), 2.43 – 2.58 (2H, m), 2.71 (0.3H, s), 2.74 (0.7H, s), 2.82 – 2.99 (1H, m), 3.23 (0.7H, app td, *J* 13.8, 4.0), 3.32 (0.3H, t, *J* 13.8), 3.96 (0.3H, br d, *J* 14.1), 4.13 – 4.22 (1.7H, m), 4.25 (1H, d, *J* 14.0,), 4.90 (1H, s), 5.08 (0.7H, dd, *J* 8.1, 5.5), 5.19 (0.3H, s), 5.25 (0.7H, s), 5.30 – 5.35 (0.3H, m), 7.02 – 7.19 (4H, m), 7.37 – 7.47 (6H, m), 7.67 – 7.73 (4H, m, ArCH) δ_C (126 MHz; $CDCl_3$); 19.3, 26.8, 28.3, 28.4, 36.6, 38.2, 39.7, 40.0, 52.9, 53.7, 66.1, 66.3, 79.9, 112.1, 112.9, 125.9, 125.9, 126.4, 126.5, 127.2, 127.4, 127.6, 127.7, 128.7, 129.1, 129.5, 129.7, 133.6, 134.5, 135.5, 135.6, 137.4, 144.2, 145.0, 154.7. m/z 542 (100% M^+) Found $[M+Na]^+$ 564.2904 $C_{34}H_{43}NO_3SiNa$ requires 564.2950.

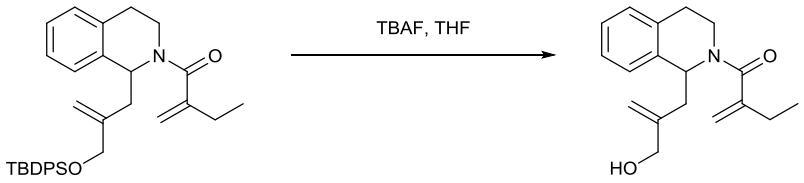
1-(1-(2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)allyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-methylenebutan-1-one (S9)



S8 **S9**

$ZnBr_2$ (5.6 g, 24.9 mmol) was dried under vacuum at 150 °C for four hours and then allowed to cool to room temperature under argon. DCM (20 mL) was added followed by a solution of **S8** (2.7 g, 4.98 mmol) in DCM (20 mL). The resulting suspension was stirred at room temperature for 24 hours. Saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture extracted into DCM (2 x 20 mL) and dried over $MgSO_4$. Solvent was removed under reduced pressure to give a yellow oil (2.2 g) which was dissolved in DMF (25 mL). Ethyl acrylic acid (618 µL, 4.98 mmol) was added followed by DIPEA (1.77 mL, 10.2 mmol) and HATU (2.31 g, 6.09 mmol). The solution was stirred at room temperature for two hours. Saturated aqueous $NaHCO_3$ (25 mL) was added and the mixture was extracted into EtOAc (2 x 25 mL), washed with brine (2 x 20 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure and the residue purified by flash column chromatography (1:4 EtOAc–petroleum ether 60–80; R_f 0.40) to give the title compound **S9** as a colourless oil (2.0 g, 76%); ν_{max} 1621 (C=O); a 1:3 mixture of amide rotamers was observed by ^1H NMR in $CDCl_3$ at room temperature; δ_H (500 MHz; $CDCl_3$) 1.10 (12H, s), 2.10 – 2.19 (0.25H, m), 2.19 – 2.26 (0.25H, m), 2.30 (1.5H, q, *J* 7.3), 2.47 (0.25H, dd, *J* 14.2, 5.3), 2.53 – 2.63 (1H, m), 2.70 – 2.82 (1.75H, m), 2.83 – 2.94 (0.75H, m), 2.97 – 3.08 (0.25H, m), 3.18 – 3.28 (0.25H, m), 3.48 (0.75H, td, *J* 13.4, 4.2), 4.01 (0.75H, dd, *J* 13.7, 5.5), 4.06 – 4.14 (0.5H, m), 4.21 (0.75H, d, *J* 13.6), 4.39 (0.75H, d, *J* 13.6), 4.64 (0.25H, dd, *J* 13.8, 5.7), 4.87 – 4.91 (1H, m), 4.95 – 5.05 (1.5H, m), 5.12 – 5.15 (1.5H, m), 5.33 (0.25H, s), 5.80 (0.75H, dd, *J* 9.6, 4.6), 7.05 – 7.20 (4H, m), 7.35 – 7.48 (6H, m), 7.65 – 7.74 (4H, m); δ_C (126 MHz; $CDCl_3$) 11.5, 11.7, 19.4, 26.8, 26.9, 27.3, 29.5, 29.7, 35.1, 40.0, 40.1, 49.8, 56.9, 66.1, 66.4, 112.1, 112.7, 113.1, 113.4, 126.3, 126.5, 126.8, 127.0, 127.5, 127.6, 127.6, 127.7, 128.8, 129.3, 129.6, 129.8, 133.0, 133.8, 133.9, 135.5, 135.6, 137.3, 145.0, 147.0, 171.3; quaternary carbons for minor rotamer not observed; *m/z* 524 (100%, M^+); Found M^+ 546.2789 $C_{34}H_{41}NO_2SiNa$ requires 546.2799.

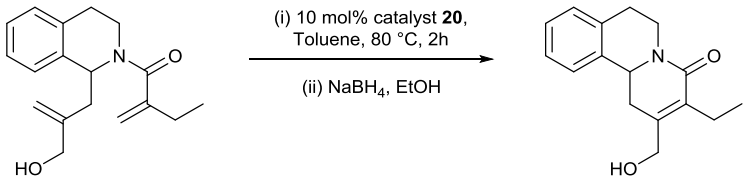
1-(1-(2-(Hydroxymethyl)allyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-methylenebutan-1-one (S10)



S9 **S10**

TBAF (11.4 mL of a 1.0 M solution in THF, 11.4 mmol) was added to a solution of **S9** (2.0 g, 3.81 mmol) in THF (40 mL) and the solution was stirred for 15 hours at room temperature. Water (40 mL) was added and the mixture was extracted into DCM (2 x 30 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure and the residue purified by flash column chromatography (1:1 EtOAc−petroleum ether 60–80; R_f 0.40) to give the title compound **S10** as a colourless oil (971 mg, 90%); ν_{max} 3381 (OH), 1600 (C=O); δ_H (500 MHz; $CDCl_3$) 1.12 (3H, t, *J* 7.4), 2.23 – 2.38 (2H, m), 2.60 (1H, dd, *J* 13.5, 11.0), 2.70 (1H, dd, *J* 13.5, 4.4), 2.81 (1H, ddd, *J* 16.3, 3.9, 1.8), 2.90 – 3.01 (1H, m), 3.44 – 3.55 (1H, m), 4.03 (1H, dd, *J* 8.1, 4.4), 4.10 (1H, dddd, *J* 13.5, 5.9, 1.8, 1.0), 4.21 – 4.33 (2H, m), 4.78 (1H, m), 5.06 (1H, app q, *J* 1.0,), 5.09 (1H, app q, *J* 1.3), 5.18 – 5.19 (1H, m), 5.83 (1H, dd, *J* 11.0, 4.4), 7.10 – 7.31 (4H, m); δ_C (126 MHz; $CDCl_3$) 11.7, 27.2, 29.4, 40.2, 41.7, 51.5, 67.4, 112.5, 114.7, 126.6, 126.7, 127.5, 128.9, 132.6, 136.8, 145.9, 146.6, 172.3; *m/z* 286 (100%, M^+); Found $[M+Na]^+$ 308.1618 $C_{18}H_{23}NO_2Na$ requires 308.1621.

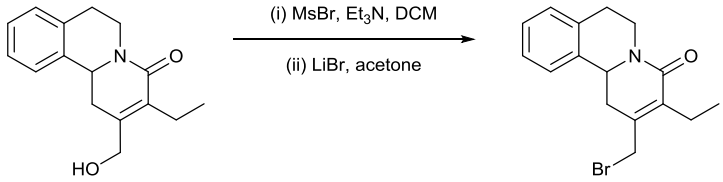
3-Ethyl-2-(hydroxymethyl)-6,7-dihydro-1*H*-pyrido[2,1-a]isoquinolin-4(11b*H*)-one (S11)



S10 **S11**

Catalyst **20** (240 mg, 0.42 mmol) was added to a solution of alcohol **S10** (1.20 g, 4.20 mmol) in degassed toluene (30 mL) and the resulting brown solution was stirred at 80 ºC for 4 hours. Solvent was removed under reduced pressure and the residue dissolved in EtOH (20 mL) and water (10 mL). Sodium borohydride (157 mg, 4.2 mmol) was added at 0 °C and the mixture stirred at 0 °C for 1 hour until the aldehyde side product had been consumed as indicated by TLC. Water (20 mL) was added and the mixture was extracted into DCM (2 x 20 mL) and dried over $MgSO_4$. Solvent was removed under reduced pressure and the residue purified by flash column chromatography (1−2% MeOH in DCM; R_f 0.35) followed by recrystallisation from EtOAc/hexane to give the title compound **S11** as a pale brown solid (550 mg, 51%); mp 115 – 117 °C; ν_{max} 3376 (OH), 1637 (C=O) δ_H (500 MHz; $CDCl_3$) 1.08 (3H, t, *J* 7.5), 1.57 – 1.60 (1H, m), 2.27 – 2.35 (1H, m), 2.40 (1H, dq, *J* 14.3, 7.5), 2.49 – 2.58 (1H, m), 2.79 – 2.85 (1H, m), 2.88 – 3.02 (3H, m), 4.33 (1H, dd, *J* 13.1, 5.6), 4.53 (1H, dd, *J* 13.1, 4.7), 4.72 (1H, dd, *J* 14.1, 4.4), 4.77 – 4.81 (1H, m), 7.14 – 7.31 (4H, m); δ_C (126 MHz; $CDCl_3$) 14.9, 19.7, 29.7, 34.5, 38.4, 54.0, 61.6, 125.8, 126.6, 126.7, 128.9, 132.7, 134.9, 136.2, 143.1, 165.5; *m/z* 258 (100%, M^+); Found M^+ 258.1492, $C_{16}H_{19}NO_2$ requires 258.1489; Found: C 74.73%; H 7.49%, N 5.38%; $C_{16}H_{18}NO_2$ requires: C 74.68%, H 7.44%, N 5.44%.

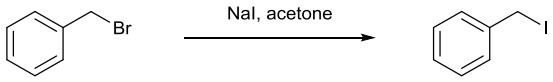
2-(Bromomethyl)-3-ethyl-6,7-dihydro-1*H*-pyrido[2,1-a]isoquinolin-4(11b*H*)-one (22)



S11 **22**

Mesyl bromide (120 µL, 1.47 mmol) was added to a solution of alcohol **S11** (315 mg, 1.22 mmol) and triethylamine (853 µL, 6.12 mmol) in DCM (20 mL) at 0 ºC and the resulting solution was allowed to stir at room temperature for 2 hours. Solvent was removed under reduced pressure to give a mixture of the corresponding mesylate and bromide **22** (1:4). The residue was dissolved in acetone (20 mL) and lithium bromide (531 mg, 6.12 mmol) was added. The solution was stirred at reflux for one hour and excess lithium bromide was removed by filtration. Solvent was removed under reduced pressure and the residue purified by flash column chromatography (1:4 EtOAc − petroleum ether 60–80; R_f 0.40) to give the title compound **22** as a colourless solid (330 mg, 84%); mp 83 – 84 °C; ν_{max} 1625 (C=O); δ_H (500 MHz; $CDCl_3$) 1.14 (3H, t, *J* 7.5), 2.38 – 2.53 (2H, m), 2.54 – 2.65 (1H, m), 2.72 – 2.87 (2H, m), 2.87 – 3.03 (2H, m,), 4.07 (1H, dd, *J* 9.9, 0.7), 4.25 (1H, d, *J* 9.9), 4.68 – 4.85 (2H, m), 7.15 – 7.31 (4H, m); δ_C (126 MHz; $CDCl_3$) 14.1, 20.3, 29.6, 31.2, 36.4, 38.5, 53.9, 125.8, 126.7, 126.9, 129.0, 134.9, 135.5, 135.8, 139.5, 164.8; *m/z* 320 (100%, M^+); Found M^+ 320.0650, $C_{16}H_{19}BrNO$ requires 320.0645; Found: C 60.10%; H 5.51%, N 4.27%; $C_{16}H_{18}BrNO$ requires: C 60.01%, H 5.67%, N 4.37%.

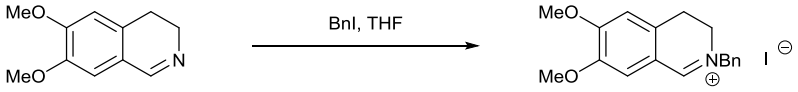
Benzyl iodide (S13)[7]



S12 **S13**

Sodium iodide (3.78 g, 25.2 mmol) was added to a solution of benzyl bromide (1.00 mL, 8.41 mmol) in acetone (20 mL) and the solution was stirred for 20 hours at room temperature in the dark. The resulting suspension was diluted with Et_2O (20 mL), washed with 10% aqueous sodium thiosulfate (20 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure to give the title compound **S13** as a pale brown solid (1.80 g, 89%) which was used directly without further purification; δ_H (500 MHz; $CDCl_3$) 4.48 (2 H, s), 7.24 – 7.29 (1 H, m), 7.29 – 7.35 (2 H, m), 7.38 – 7.42 (2 H, m).

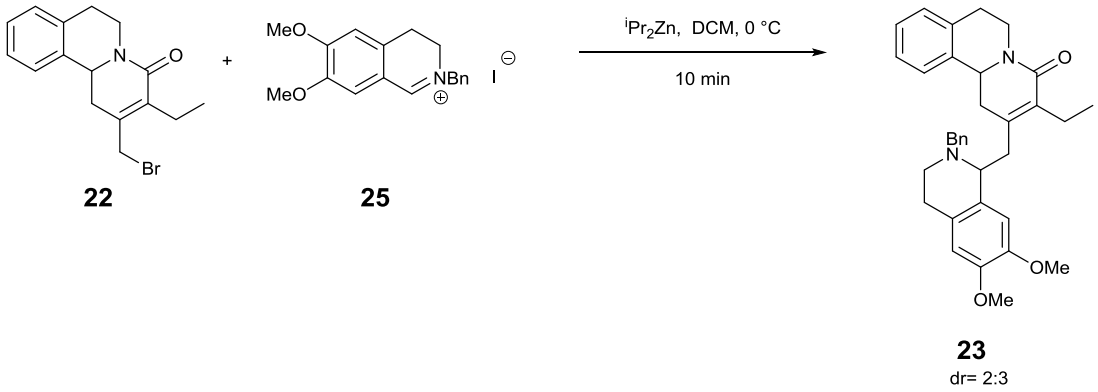
***N*-(Benzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline iodide (25)**



24 **25**

Freshly prepared benzyl iodide (351 mg, 1.61 mmol) was added to a solution of 6,7-dimethoxy dihydroisoquinoline **24** (280 mg, 1.46 mmol) in THF (6 mL). The solution was stirred at room temperature for 45 minutes and a yellow precipitate formed. The solid was isolated by filtration and washed with Et_2O (2 x 10 mL) to give the title compound **25** as a yellow solid (495 mg, 83%); mp 168 – 169 °C; δ_H (500 MHz; MeOD) 3.19 (2H, t, *J* 8.3), 3.88 – 3.95 (5H, m), 4.00 (3H, s), 5.18 (2H, s), 7.11 (1H, s), 7.45 (1H, s), 7.47 – 7.54 (3H, m), 7.54 – 7.58 (2H, m), 9.09 (1H, s); δ_C (126 MHz; MeOD) 24.9, 47.4, 55.5, 55.9, 63.0, 110.9, 115.2, 117.0, 129.0, 129.2, 129.4, 131.6, 133.2, 149.0, 158.3, 164.6; *m/z* 282 (100%, M^+); Found M^+ 282.1492, $C_{18}H_{20}NO_2$ requires 282.1489; Found: C 52.97%; H 5.05%, N 3.30%; $C_{18}H_{20}NO_3I$ requires: C 52.83%, H 4.93%, N 3.42%.

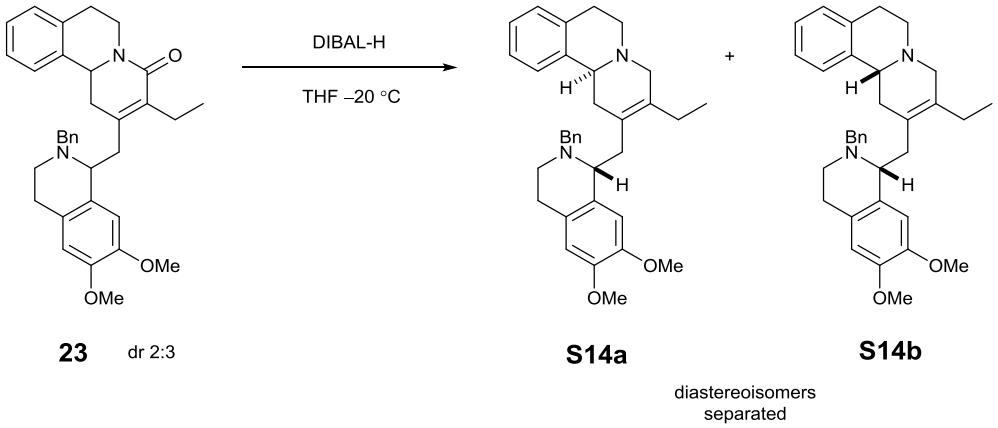
2-((2-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-3-ethyl-6,7-dihydro-1*H*-pyrido[2,1-a]isoquinolin-4(11b*H*)-one (23)



22 **25** **23**
dr= 2:3

Diisopropyl Zinc (172 µL of a 1.0 M solution in toluene, 0.17 mmol) was added to a solution of bromide **22** (50 mg, 0.16 mmol) and iodide salt **25** (83 mg, 0.20 mmol) in DCM (8 mL) at 0 °C and the solution was stirred for 10 minutes at 0 °C. Saturated aqueous NH_4Cl (8 mL) was added and the solution extracted into DCM (2 x 4 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by flash column chromatography (2:3 EtOAc–petroleum ether 60–80; R_f 0.30) to give the title compound **23** as a colourless oil as a 5:3 mixture of diastereoisomers (50 mg, 61%); ν_{max} 1622 (C=O); δ_H (500 MHz; $CDCl_3$) 0.97 – 1.08 (7.8H, m), 1.86 – 1.98 (1.6H, m), 2.20 – 2.62 (13H, m), 2.71 – 3.08 (16.6H, m), 3.31 – 3.42 (2.6H, m) 3.64 (1.6H, m), 3.71 – 3.84 (9.2H, m), 3.88 (5H, s), 3.90 (5H, s), 3.91 (3H, s), 4.41 (1H, dd, *J* 13.5, 4.8), 4.65 (1.6H, dd, *J* 14.2, 4.2), 4.78 – 4.87 (2.6H, m), 6.47 (1H, s), 6.55 (1.6H, s), 6.65 (1.6H, s), 6.67 (1H, s), 6.80 – 6.86 (1H, m), 7.02 – 7.07 (1.6H, m), 7.08 – 7.14 (1.6H, m), 7.17 – 7.38 (19.2H, m); δ_C (126 MHz; $CDCl_3$) 14.3, 14.4, 20.3, 20.4, 22.7, 23.5, 29.8, 38.1, 38.2, 38.2, 38.4, 40.0, 40.4, 43.1, 43.5, 53.5, 53.7, 55.9, 55.9, 56.0, 56.1, 57.6, 57.8, 58.8, 58.8, 110.8, 110.9, 111.7, 111.8, 125.7, 125.8, 126.2, 126.4, 126.5, 126.5, 127.1, 127.2, 128.2, 128.3, 128.9, 129.0, 129.1, 129.2, 129.2, 132.5, 132.9, 135.0, 135.0, 136.4, 139.2, 139.3, 143.8, 144.4, 147.2, 147.4, 147.8, 147.8, 165.7, 165.9 ; *m/z* 523 (100%, M^+); Found M^+ 523.2909, $C_{34}H_{39}N_2O_3$ requires 523.2955.

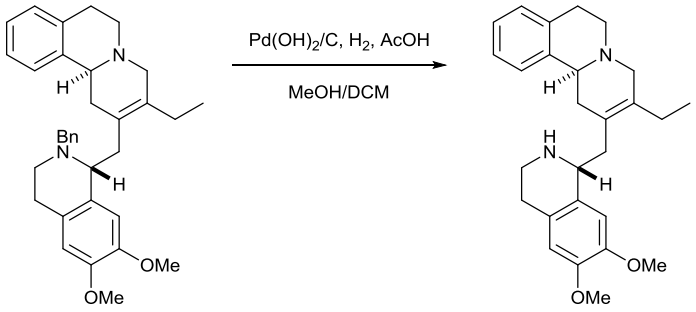
2-((2-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-3-ethyl-4,6,7,11b-tetrahydro-1*H*-pyrido[2,1-a]isoquinoline (S14a and S14b)



Diisobutyl aluminium hydride (430 µL of a 1M solution in THF, 0.43 mmol) was added dropwise to a solution of **23** (45 mg, 0.09 mmol) in THF (2 mL) at −20 °C. The solution was stirred at −20 °C for 1 hour. The reaction mixture was diluted with EtOAc (2 mL) and 1M NaOH (2 mL) was added. The resulting mixture was stirred for 2 hours at room temperature and the mixture extracted into EtOAc (2 x 2 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure and the residue purified by flash column chromatography (2% 2M NH_3 in MeOH, 98% DCM; R_f 0.13 and 0.19) to give two diastereoisomers of the title compound. Diastereisomer 1 (**S14a**) (5 mg, 11 %); ν_{max} 1515 (O-CH_3); δ_H (500 MHz; $CDCl_3$) 0.90 (3H, t, *J* 7.6), 1.90 (1H, dq, *J* 14.8, 7.6), 1.96 – 2.11 (2H, m) 2.16 (1H, dd, *J* 14.2, 6.2), 2.23 – 2.30 (1H, m), 2.44 – 2.54 (2H, m), 2.66 – 2.76 (2H, m), 2.89 – 3.08 (4H, m), 3.13 (1H, ddd, *J* 15.4, 11.2, 5.2), 3.24 (1H, d, *J* 15.4), 3.29 – 3.40 (2H, m), 3.69 – 3.76 (2H, m), 3.77 – 3.82 (4H, m), 3.87 (3H, s), 6.49 (1H, s), 6.62 (1H, s), 6.85 – 6.90 (1H, m), 7.05 – 7.14 (3H, m), 7.22 (1H, app t, *J* 7.5), 7.30 (2H, app t, *J* 7.5), 7.37 (2H, d, *J* 7.5); δ_C (126 MHz; $CDCl_3$) 12.9, 23.8, 24.1, 29.6, 37.4, 38.5, 43.6, 51.1, 56.0, 57.9, 58.2, 58.8, 59.6, 111.4, 111.6, 125.6, 125.8, 125.9, 126.2, 126.6, 127.0, 128.3, 128.8, 129.1, 130.2, 132.4, 134.5, 138.6, 139.9, 147.1, 147.6; *m/z* 419 (100%, $[M\text{-}Bn]^+$); Found M^+ 509.3152, $C_{34}H_{41}N_2O_3$ requires 509.3163. Diastereoisomer 2 (**S14b**) (13 mg, 30%); ν_{max} 1515 (O-CH_3) ;δ_H (500 MHz; $CDCl_3$) 0.85 (3H, t, *J* 7.6), 1.70 (1H, dq, *J* 14.8, 7.6), 1.85 (1H, dq, *J* 14.8, 7.6,), 2.02 – 2.12 (1 H, m), 2.36 (1 H, dd, *J* 13.8, 7.0), 2.48 – 2.57 (3H, m), 2.74 (1H, app d, *J* 15.9), 2.82 (1H, app d, *J* 16.5), 2.89 – 3.05 (3H, m), 3.09 (1H, ddd, *J* 11.0, 5.4, 1.5), 3.20 (1H, ddd, *J* 16.1, 11.1, 5.3), 3.30 (1H, d, *J* 15.5), 3.34 – 3.41 (1H, m), 3.47 (1H, dd, *J* 10.8, 3.6,), 3.71 (1H, t, *J* 7.0), 3.75 (1H, d, *J* 13.4), 3.81 – 3.85 (4H, m), 3.88 (3H, s), 6.49 (1H, s), 6.63 (1H, s), 7.09 – 7.14 (2H, m), 7.14 – 7.21 (2H, m), 7.22 – 7.27 (1H, m), 7.28 – 7.32 (2H, m), 7.38 – 7.41 (2H, m); δ_C (126 MHz; $CDCl_3$) 12.5, 23.5, 23.7, 29.4, 37.5, 37.7, 43.2, 51.1, 55.8, 56.0, 57.8, 58.5, 59.1, 59.8, 111.2, 111.5, 125.4, 125.8, 125.9, 126.9, 126.9, 128.2, 128.8, 129.0, 130.2, 131.8, 134.4, 138.3, 139.6, 146.8,

147.4; one quaternary carbon not observed; *m/z* 419 (100%, $[M\text{-}Bn]^+$); Found M^+ 509.3172, $C_{34}H_{41}N_2O_3$ requires 509.3163.

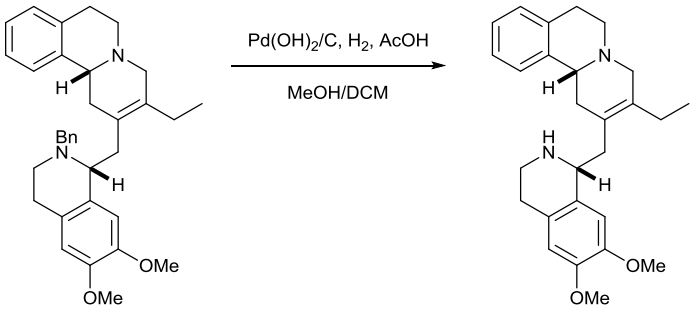
2-((6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-3-ethyl-4,6,7,11b-tetrahydro-1*H*-pyrido[2,1-a]isoquinoline (21a)



S14a **21a**

$Pd(OH)_2$ (15 mg) was added to a solution of **S14a** (15 mg, 0.03 mmol) in MeOH (2.7 mL) and DCM (0.45 mL) and AcOH (4 µL) was added. The flask was placed under an atmosphere of H_2 and stirred at 30 °C for 1.5 hours. The mixture was filtered through Celite and the solvent was removed under reduced pressure. The residue was dissolved in DCM (2 mL), washed with saturated aqueous $NaHCO_3$ (2 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure to give the title compound **21a** as a colourless oil. However, an orange solution was obtained on dissolving in MeOH (9 mg, 73 %); ν_{max} 1515 (O-CH_3); δ_H (500 MHz; MeOD) 1.05 (3H, t, *J* 7.6), 2.09 – 2.18 (2H, m), 2.26 (1H, m), 2.50 – 2.60 (2H, m), 2.63 (1H, br d, *J* 16.7), 2.70 (1H, dd, *J* 13.8, 5.5), 2.74 – 2.84 (3H, m), 2.92 – 3.00 (1H, m), 3.05 – 3.17 (3H, m), 3.20 – 3.28 (1H, m), 3.35 (1H, d, *J* 15.8), 3.49 (1H, dd, *J* 10.7, 3.9), 3.79 (3H, s), 3.80 (3H, s), 4.15 (1H, dd, *J* 8.8, 5.5), 6.70 (1H, s), 6.78 (1H, s), 7.06 – 7.15 (4H, m); δ_C (126 MHz; MeOD); 13.3, 24.8, 29.2, 29.7, 38.3, 39.3, 41.0, 52.1, 55.0, 56.5, 56.7, 59.1, 60.7, 111.6, 113.5, 126.4, 126.8, 127.2, 127.4, 128.2, 129.8, 131.3, 134.7, 135.0, 138.7, 148.7, 149.4; *m/z* 419 (100%, M^+); Found M^+ 419.2680, $C_{27}H_{35}N_2O_2$ requires 419.2693.

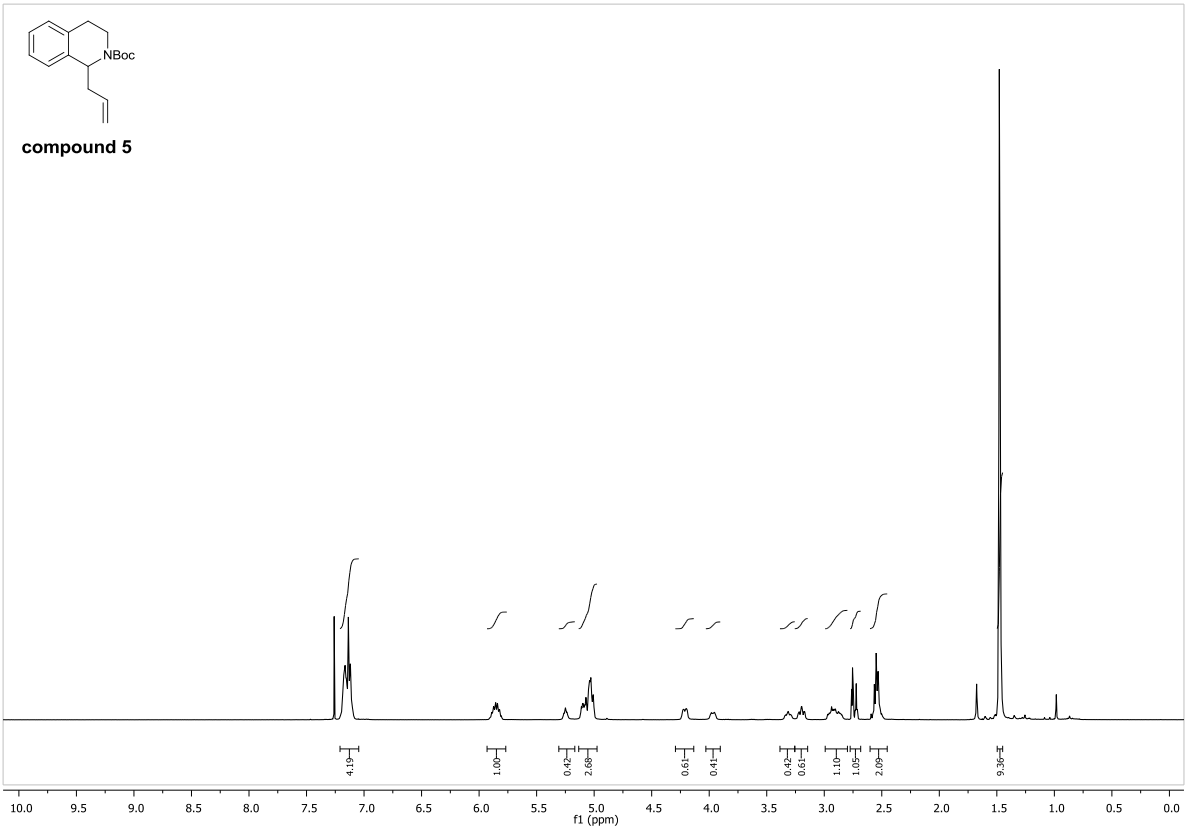
2-((6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-3-ethyl-4,6,7,11b-tetrahydro-1*H*-pyrido[2,1-a]isoquinoline (21b)



S14b **21b**

$Pd(OH)_2$ (10 mg) was added to a solution of **S14b** (10 mg, 0.02 mmol) in MeOH (1.8 mL) and DCM (0.3 mL) and AcOH (3 µL) was added. The flask was placed under an atmosphere of H_2 and stirred at 30 °C for 1.5 hours. The mixture was filtered through Celite and the solvent was removed under reduced pressure. The residue was dissolved in DCM (2 mL), washed with saturated aqueous $NaHCO_3$ (2 mL) and dried over Na_2SO_4. Solvent was removed under reduced pressure to give the title compound **21b** as a colourless oil. However, an orange solution was obtained on dissolving in MeOH (5 mg, 61%); ν_{max} 1515 (O-CH_3); δ_H (500 MHz; MeOD) 1.01 (3H, t, *J* 7.6), 2.04 (1H, dq, *J* 15.2, 7.6), 2.15 (1H, dq, *J* 15.2, 7.6,), 2.21 – 2.29 (1H, m), 2.51 – 2.60 (1H, m), 2.64 (1H, dd, *J* 13.8, 5.3), 2.70 (1H, dd, *J* 13.8, 9.1), 2.76 – 2.89 (4H, m), 2.96 (1H, dt, *J* 11.8, 5.7), 3.05 – 3.24 (4H, m), 3.36 (1H, d, *J* 15.6), 3.57 (1H, dd, *J* 10.7, 4.1), 3.80 (3H, s), 3.82 (3H, s), 4.15 (1H, dd, *J* 9.1, 5.3), 6.71 (1H, s), 6.79 (1H, s), 7.09 – 7.21 (3H, m), 7.29 (1H, br d, *J* 7.5); δ_C (126 MHz; MeOD) 13.5, 24.8, 29.1, 29.8, 37.2, 39.1, 40.9, 52.1, 53.9, 56.4, 56.7, 59.4, 60.8, 111.5, 113.4, 126.3, 126.5, 127.3, 127.5, 127.9, 129.8, 131.1, 135.0, 135.3, 138.6, 148.7, 149.3; *m/z* 419 (100%, M^+); Found M^+ 419.2663, $C_{27}H_{35}N_2O_2$ requires 419.2693.

NMR Data: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0.61
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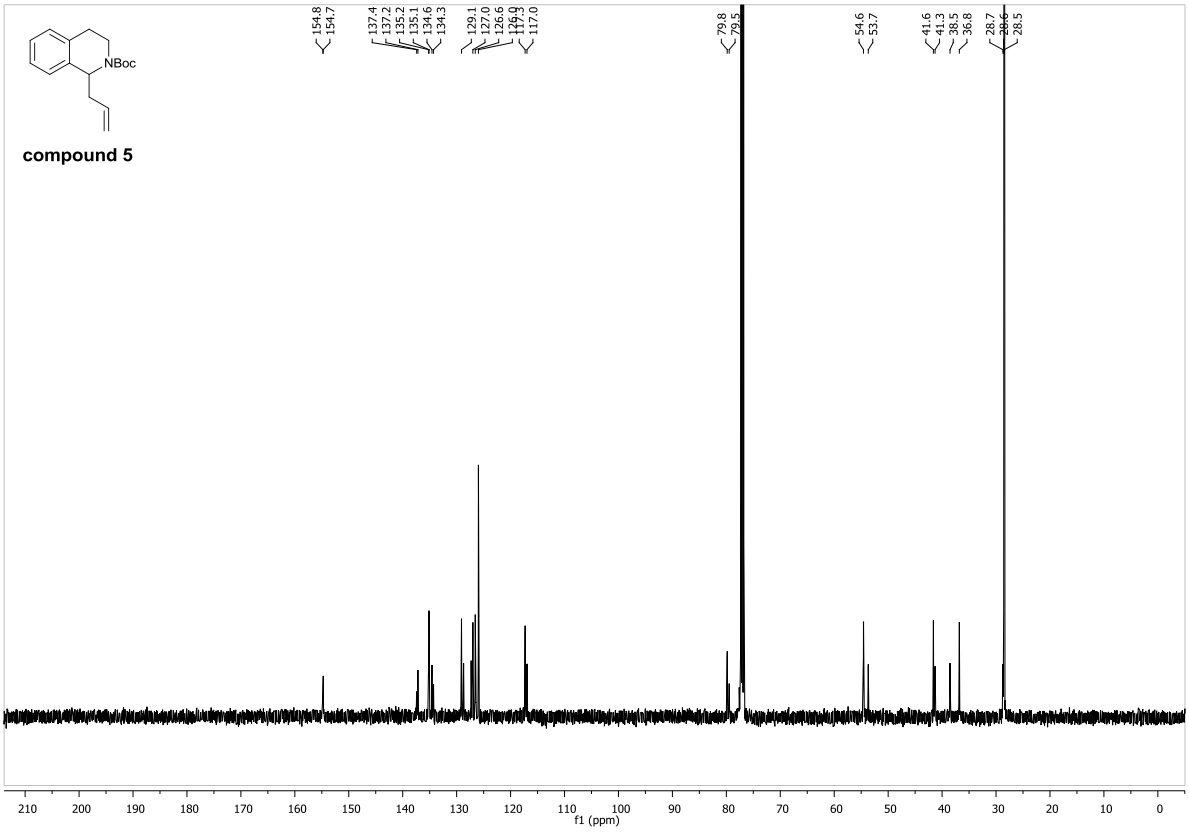
1.05
2.09
9.36
f1 (ppm)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compound 5
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154.7
137.4
137.2
135.2
135.1
134.6
134.3
129.1
127.0
126.6
126.0
117.3
117.0
79.8
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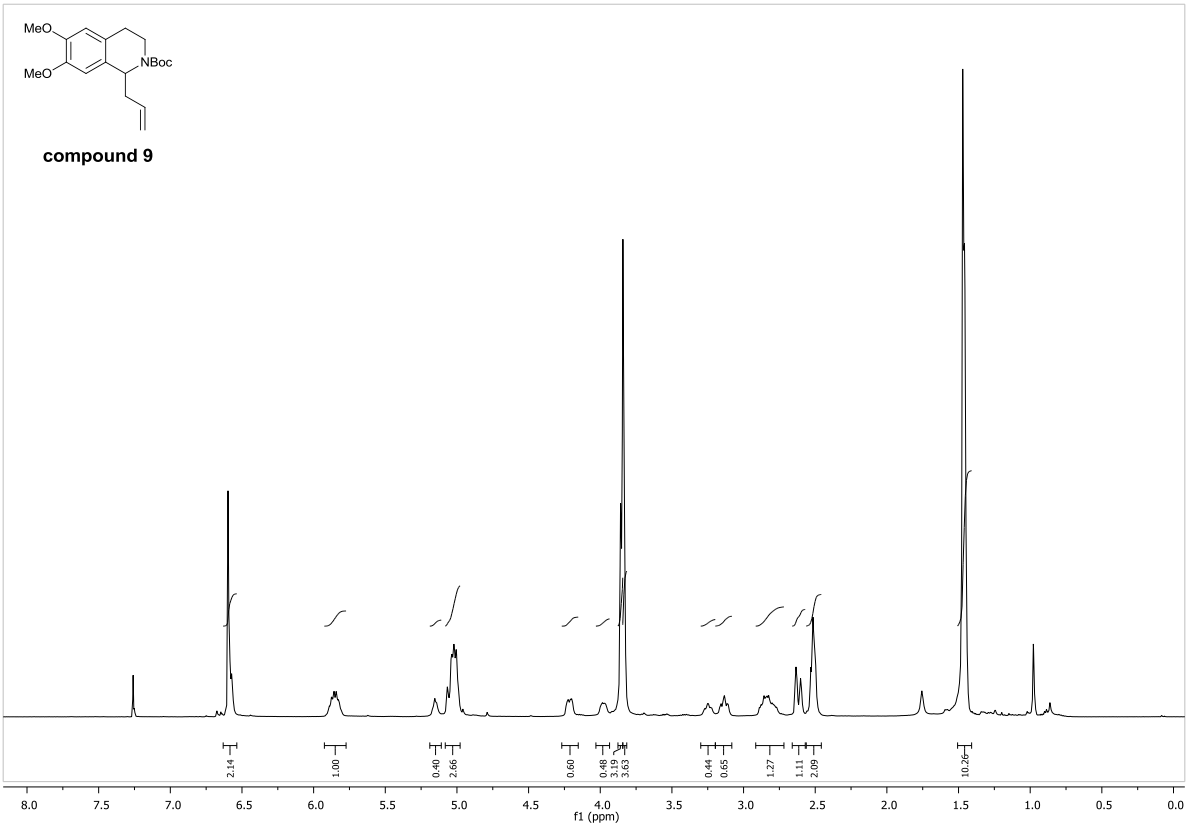
53.7
41.6
41.3
38.5
36.8
28.7
28.6
28.5
f1 (ppm)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MeO
NBoc
compound 9
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0.60
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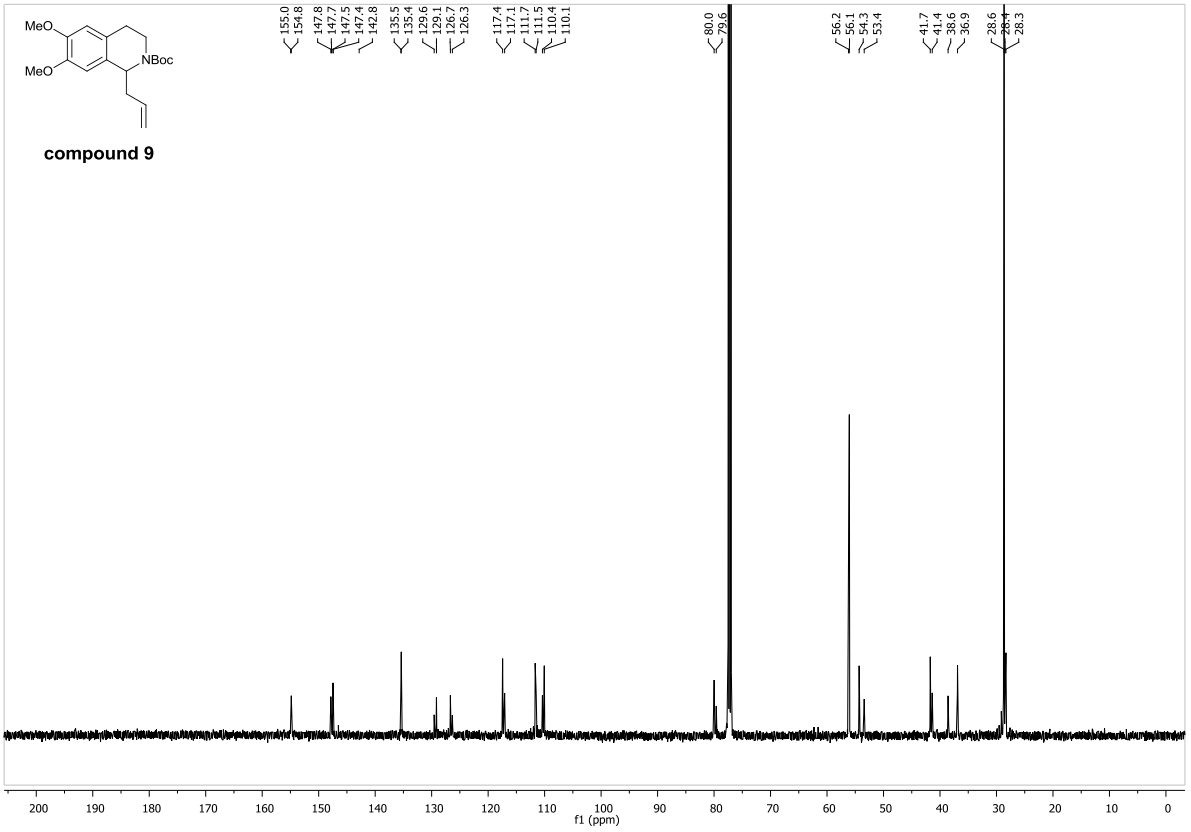
3.19
3.83
0.44
0.65
1.27
1.11
2.09
10.26
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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MeO
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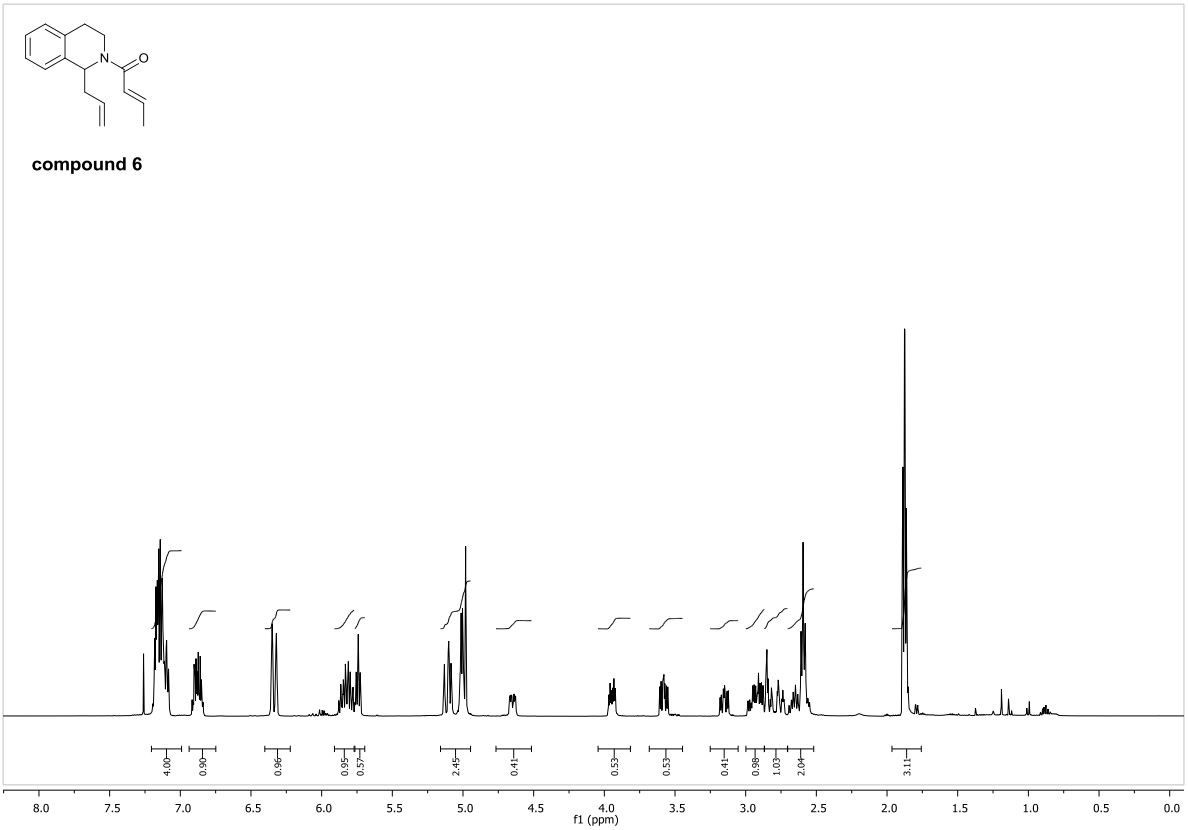
147.5
147.4
142.8
135.5
135.4
129.6
129.1
126.7
126.3
117.4
117.1
111.7
111.5
110.4
110.1
80.0
79.6
56.2
56.1
54.3
53.4
41.7
41.4
38.6
36.9
28.6
28.4
28.3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


compound 6
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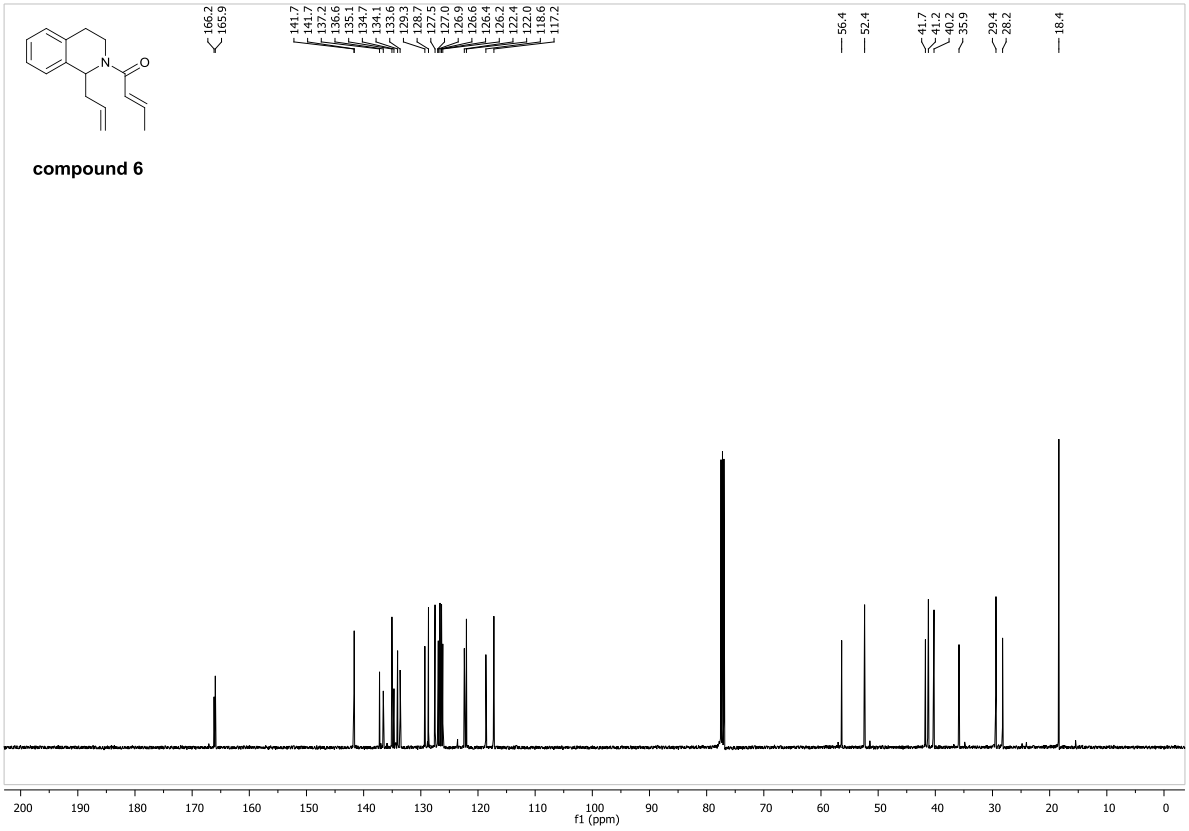
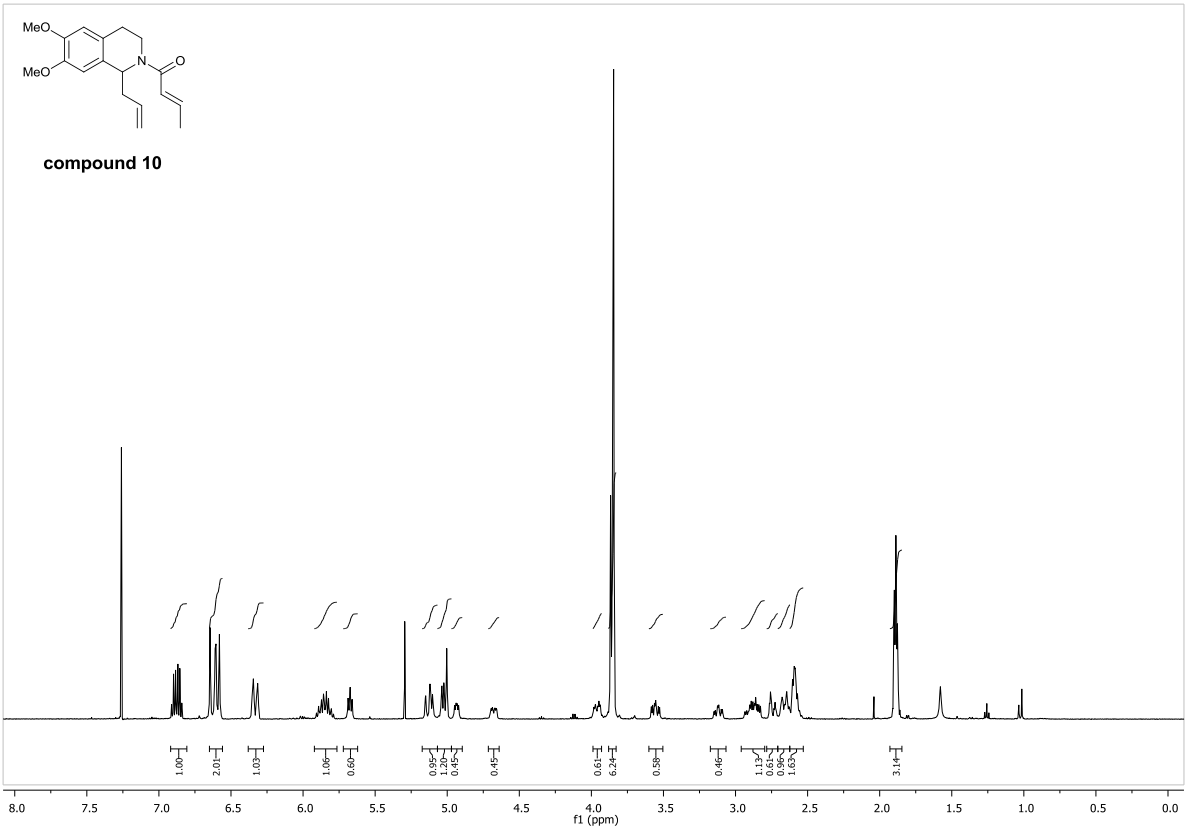
0.96
0.95
0.57
2.45
0.41
0.53
0.53
0.41
0.98
1.03
2.04
3.11
f1 (ppm)


compound 6
166.2
165.9
141.7
141.7
137.2
136.6
135.1
134.7
134.1
133.6
129.3
128.7
127.5
127.0
126.9
126.6
126.4
126.2
122.4
122.0
118.6
117.2
56.4
52.4
41.7
41.2
40.2
35.9
29.4
28.2
18.4
f1 (ppm)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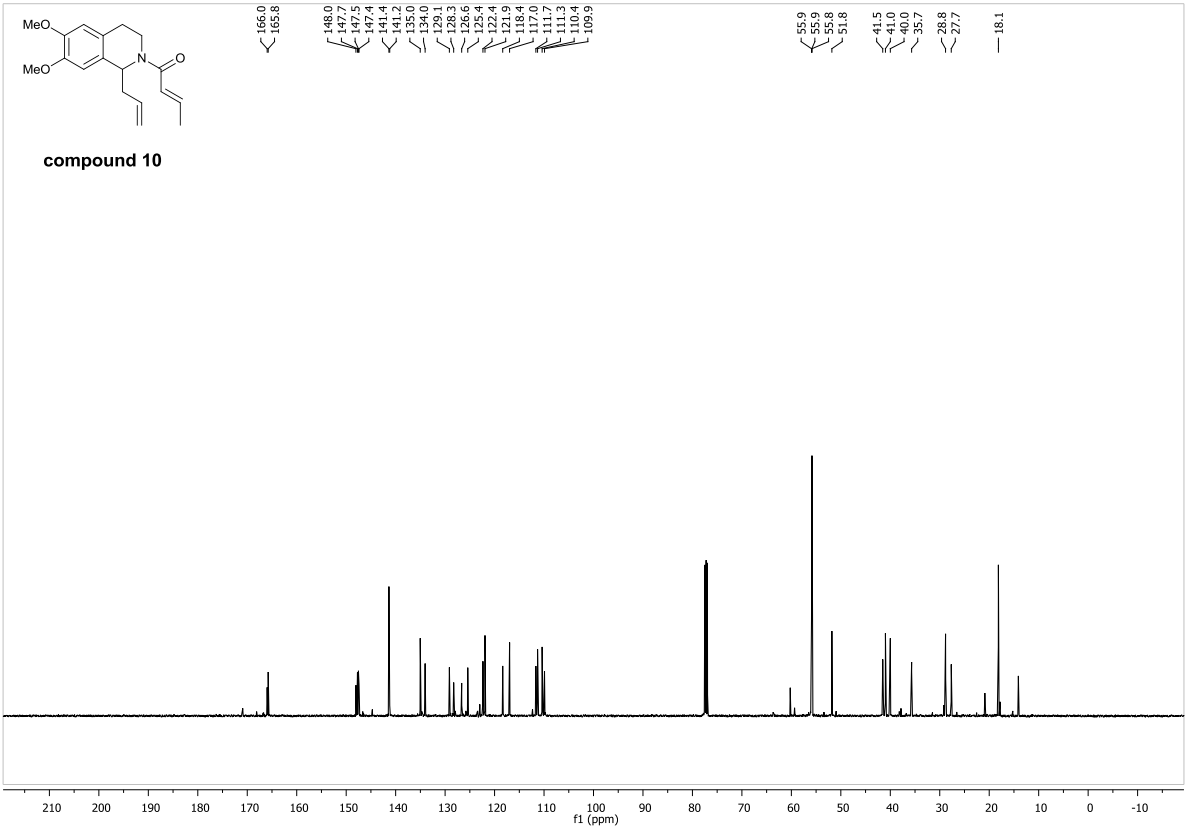
MeO
N
O
compound 10
1.00
2.01
1.03
1.06
0.60
0.95
1.26
0.45
0.45
0.61
6.24
0.58
0.46
1.13
0.61
0.66
1.65
3.14
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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MeO
N
O
compound 10
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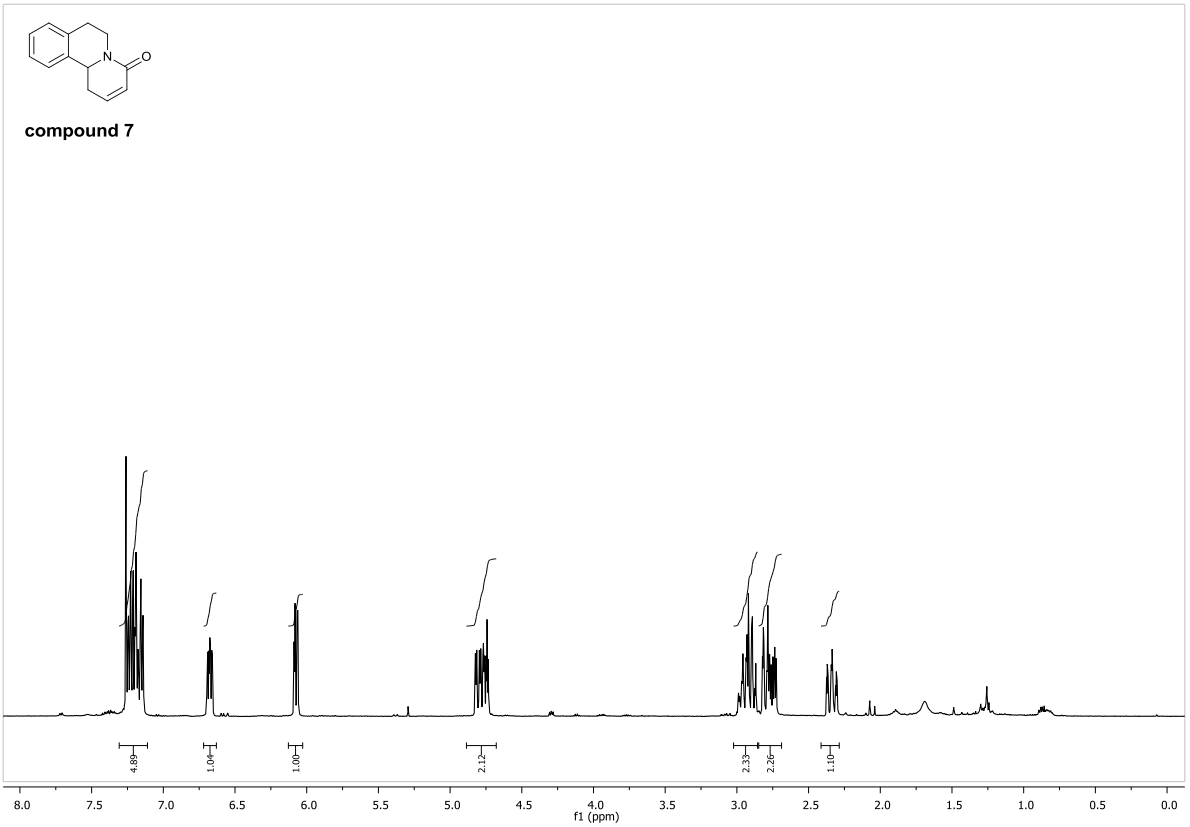
165.8
148.0
147.7
147.5
147.4
141.4
141.2
135.0
134.0
129.1
128.3
126.6
125.4
122.4
121.9
118.4
117.0
111.7
111.3
110.4
109.9
55.9
55.9
55.8
51.8
41.5
41.0
40.0
35.7
28.8
27.7
18.1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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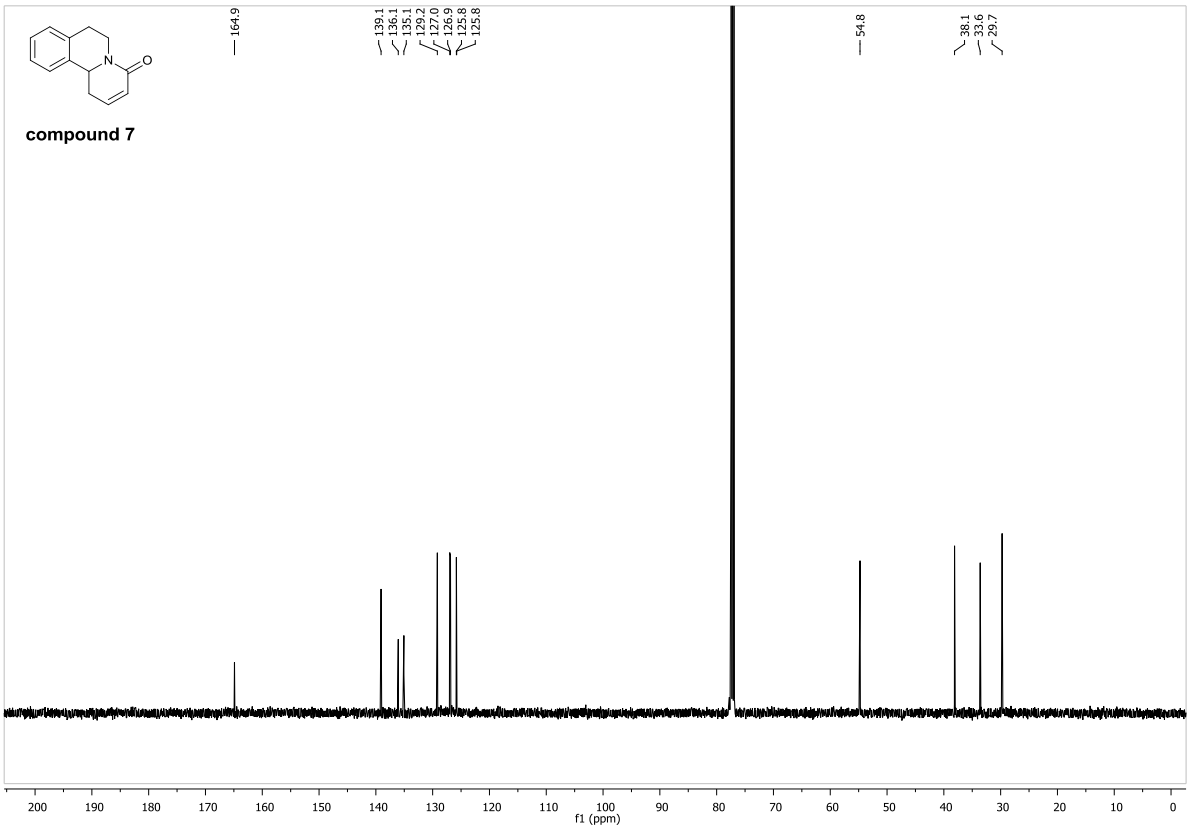
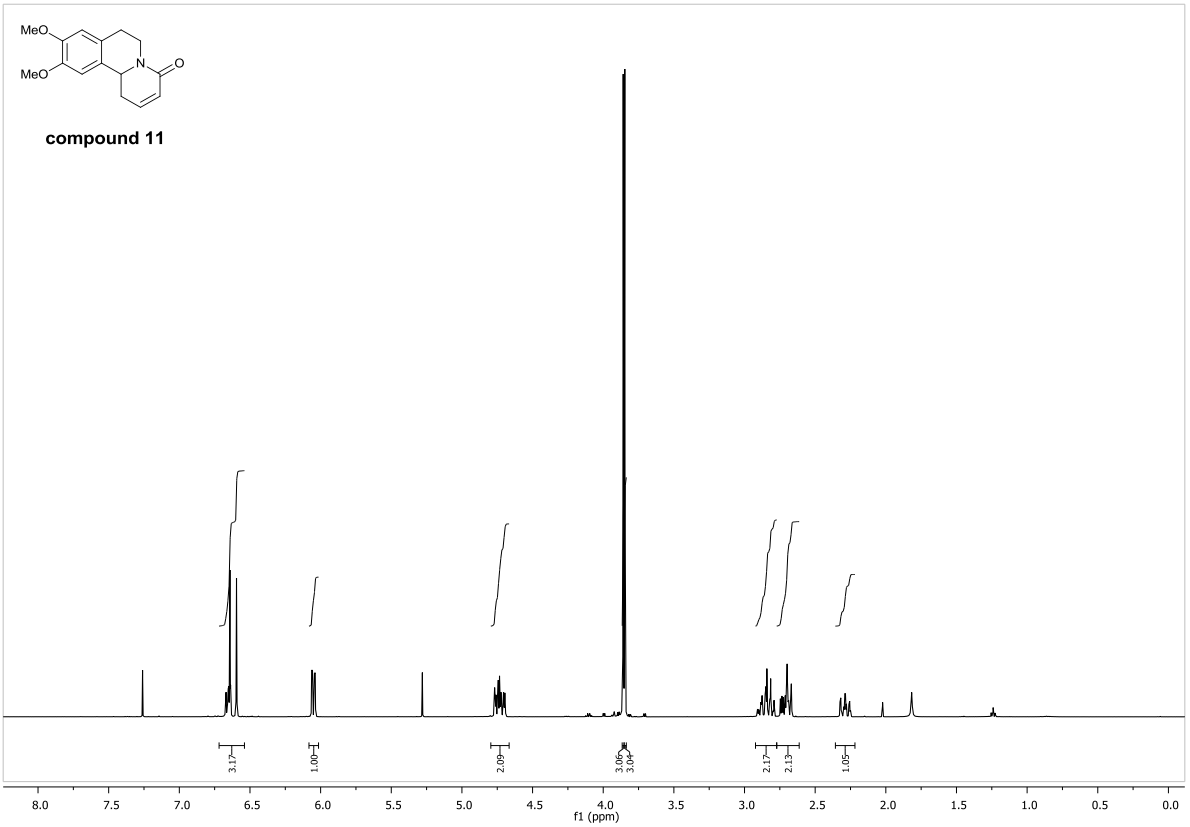
1.00
2.12
2.33
2.26
1.10
f1 (ppm)


compound 7
164.9
139.1
136.1
135.1
129.2
127.0
126.9
125.8
125.8
54.8
38.1
33.6
29.7
f1 (ppm)


MeO
MeO
N
O
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3.17
1.00
2.09
3.06
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2.17
2.13
1.05
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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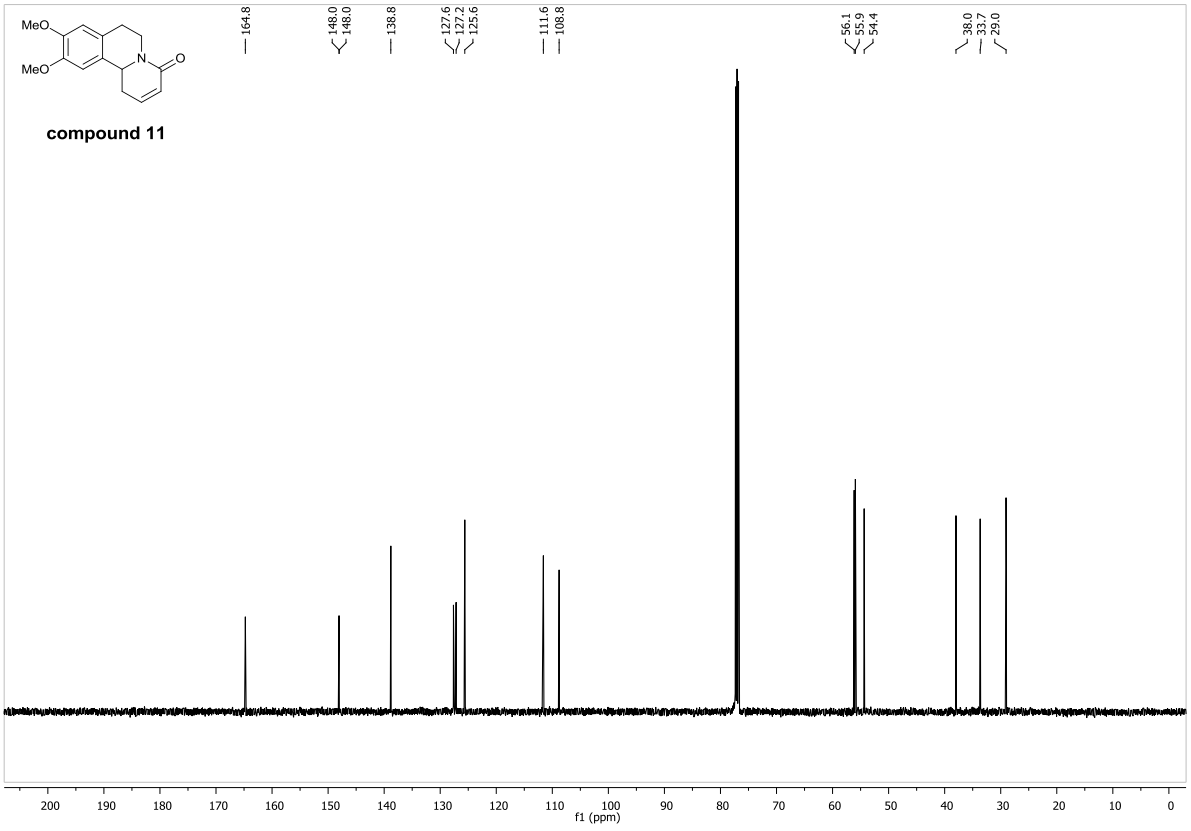
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


MeO
MeO
N
O
compound 11
164.8
148.0
148.0
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127.6
127.2
125.6
111.6
108.8
56.1
55.9
54.4
38.0
33.7
29.0
200
190
180
170
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120
110
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90
80
70
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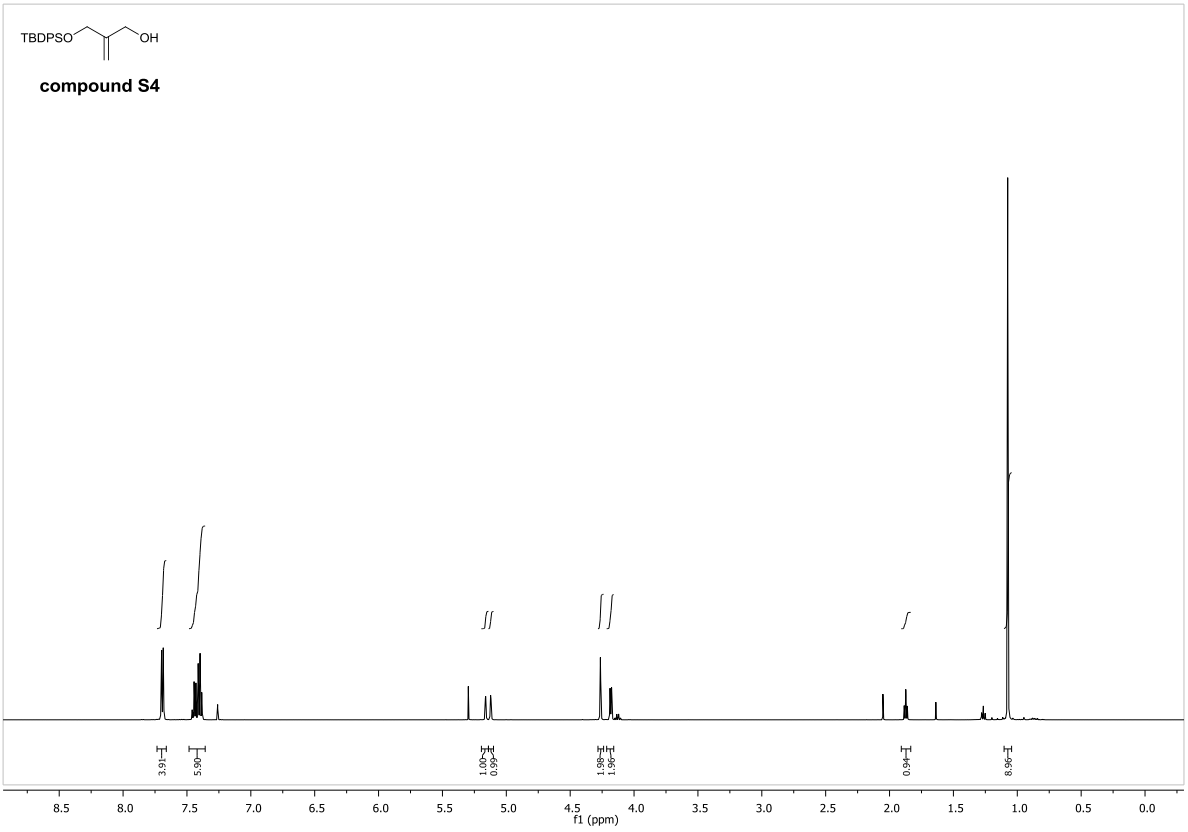
50
40
30
20
10
0
f1 (ppm)


TBDPSO
OH
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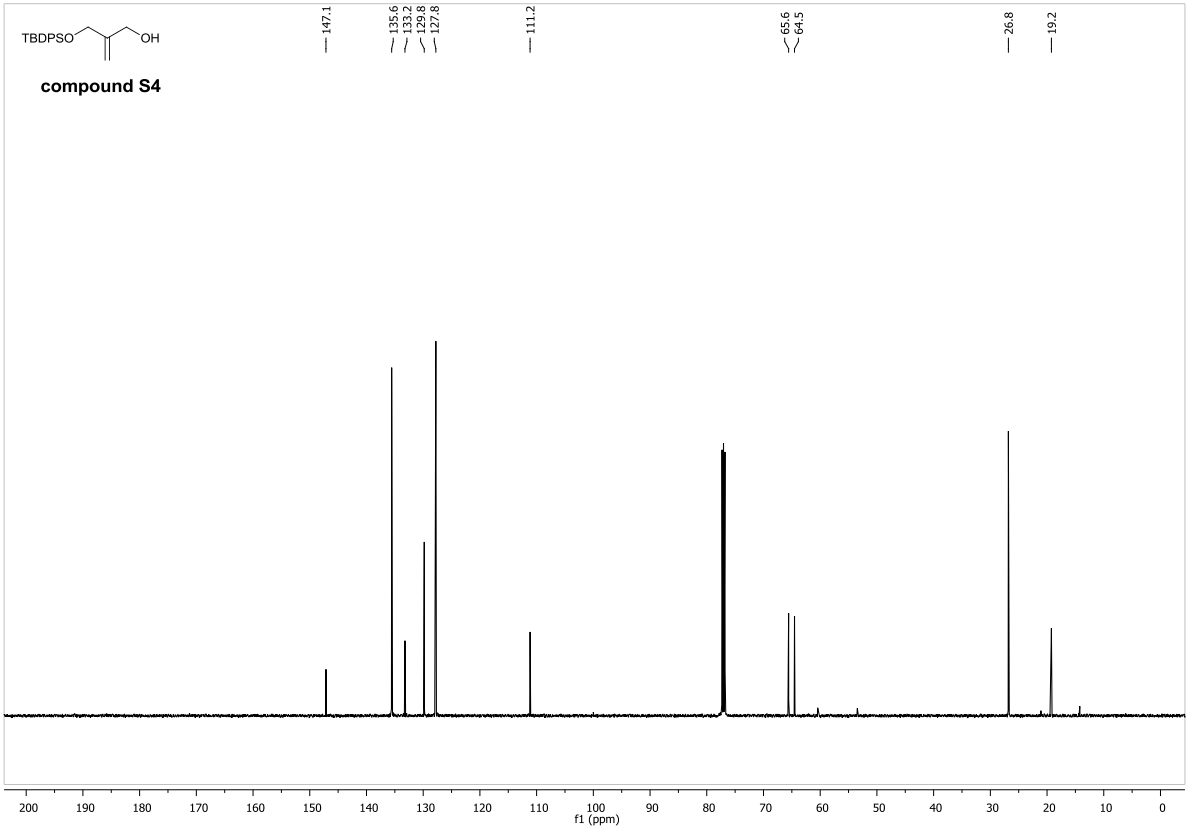
0.99
1.98
1.96
0.94
8.96
f1 (ppm)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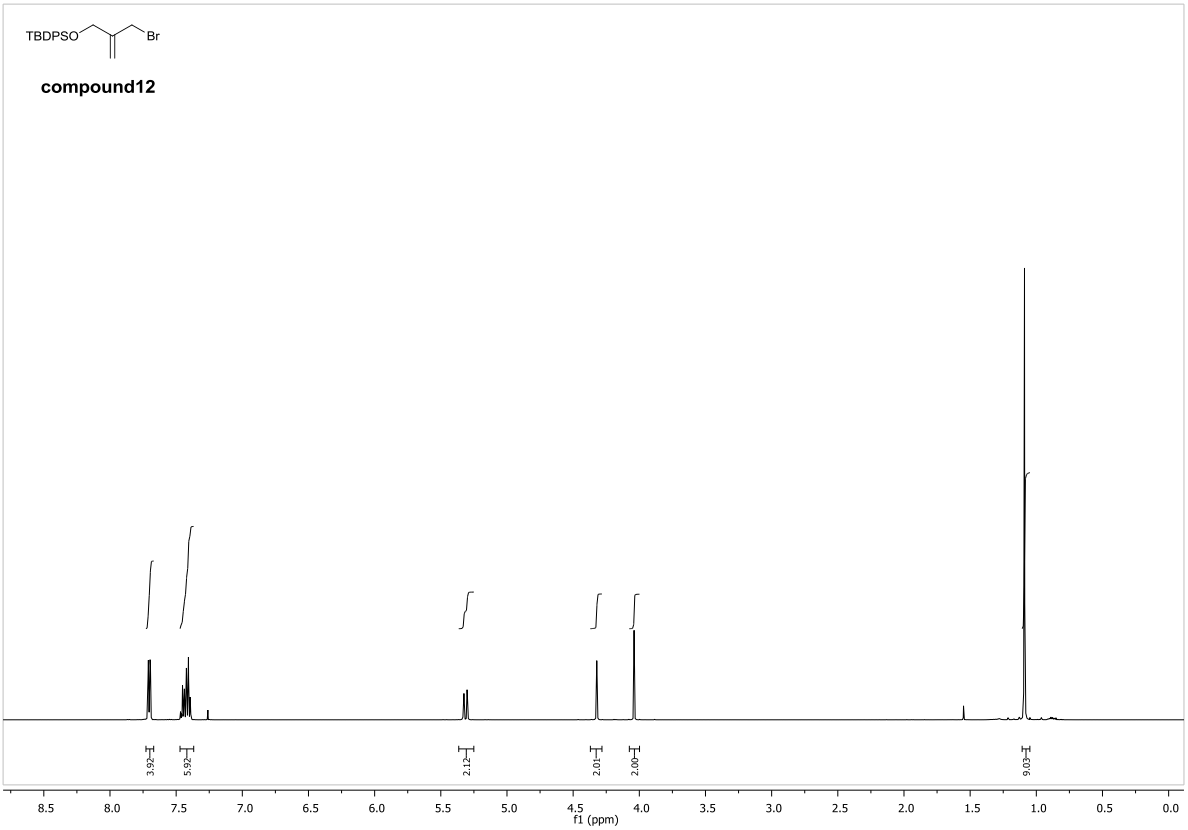
127.8
111.2
65.6
64.5
26.8
19.2
f1 (ppm)


TBDPSO
Br
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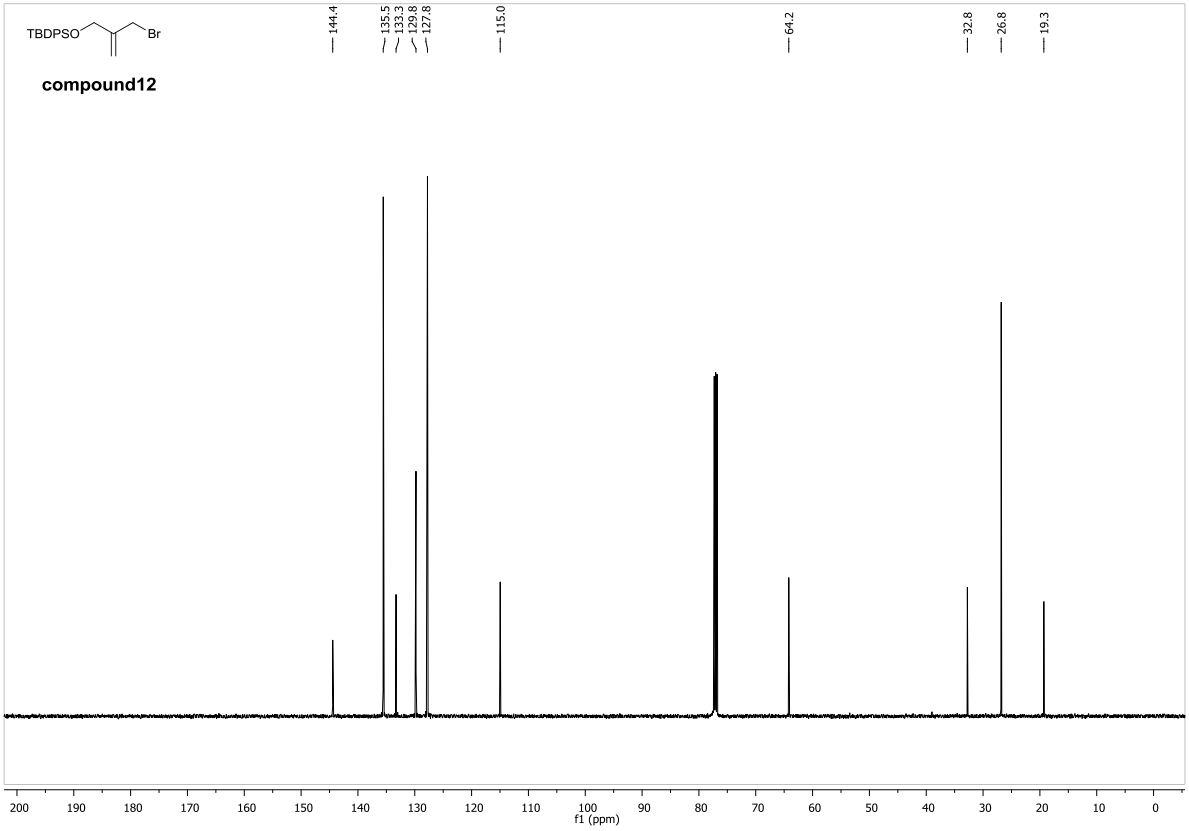
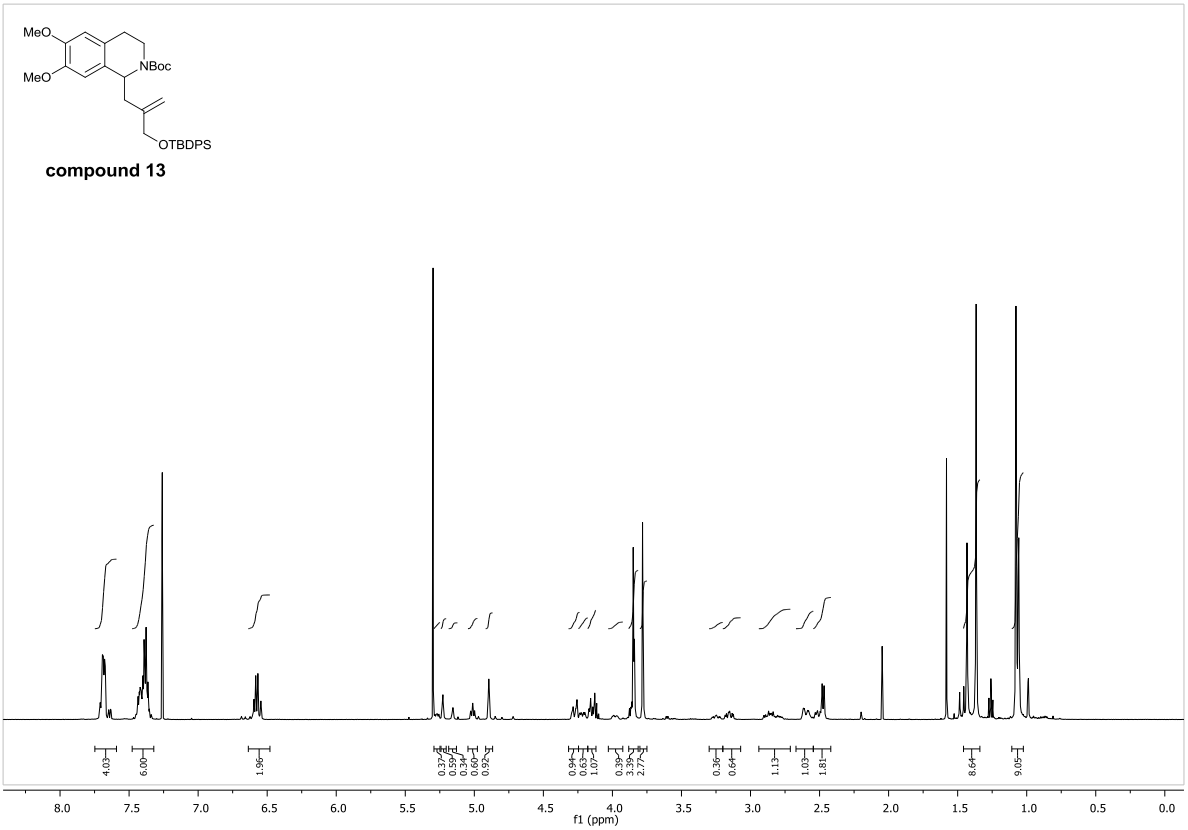
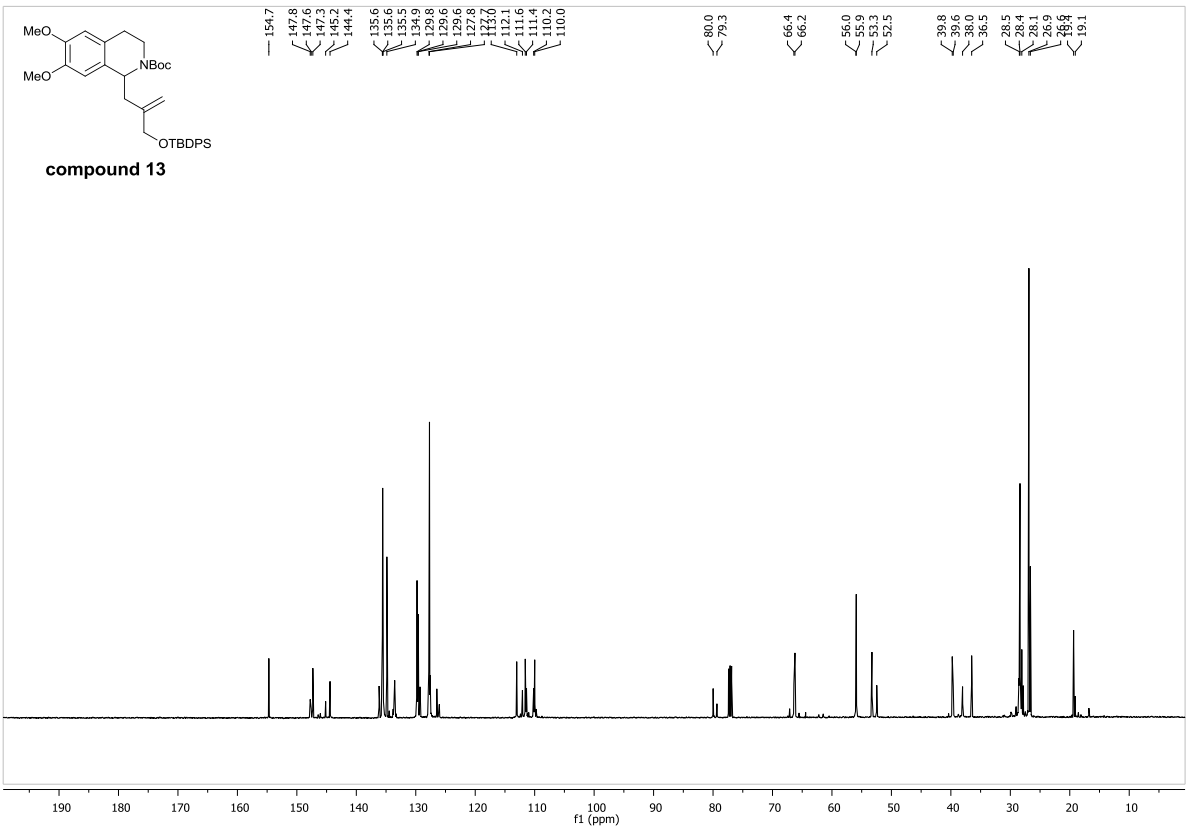
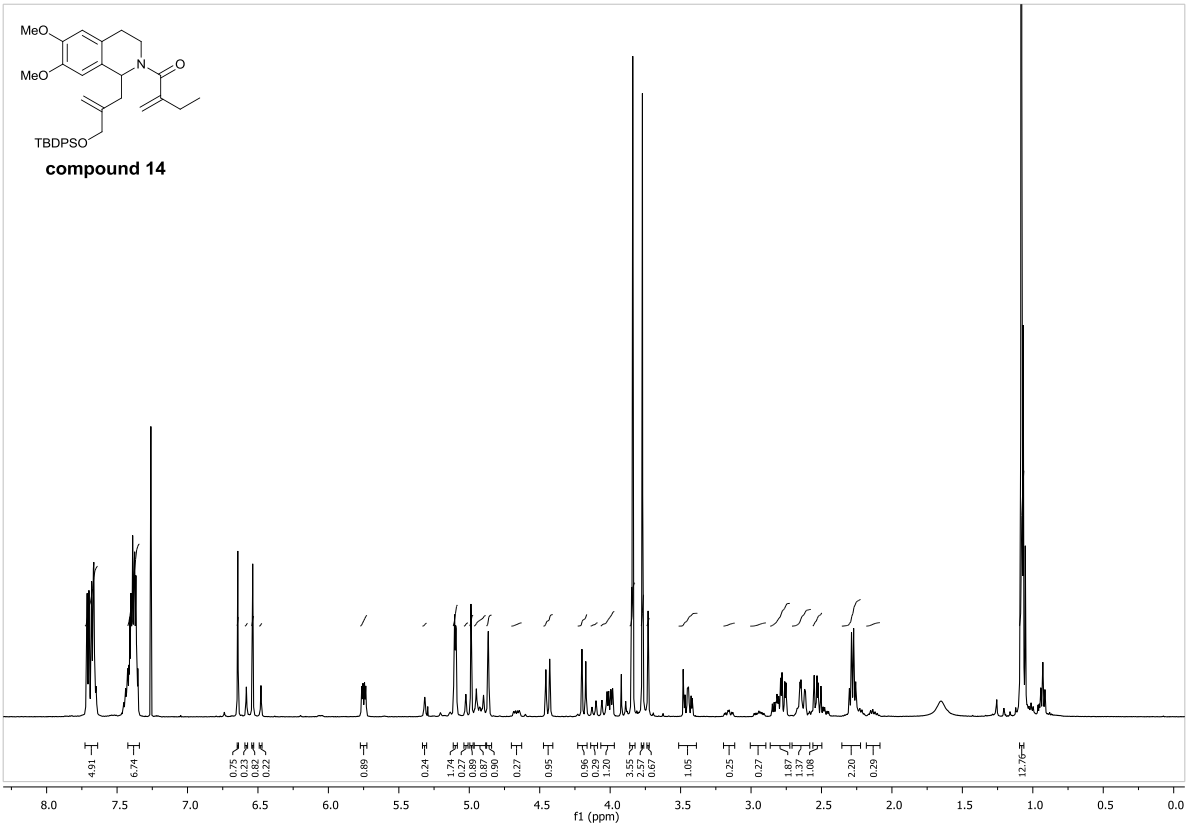
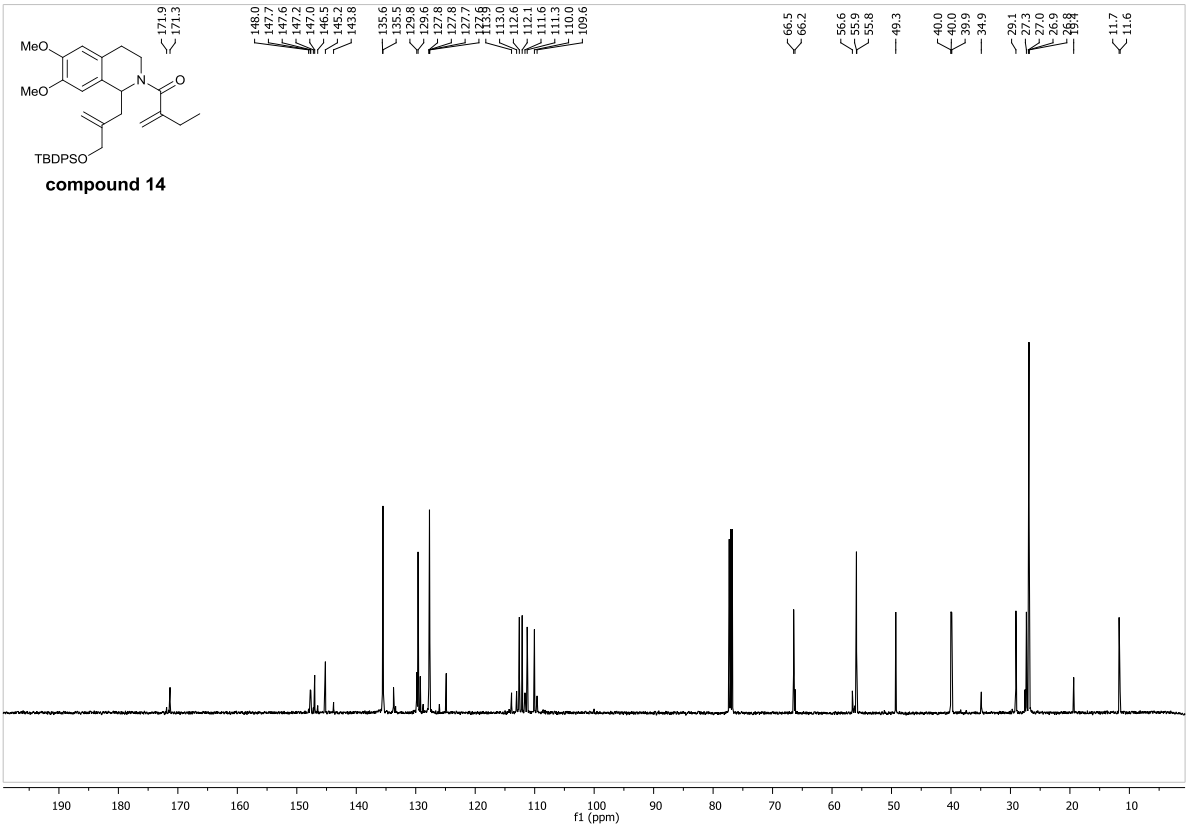
2.12
2.01
2.00
9.03
f1 (ppm)

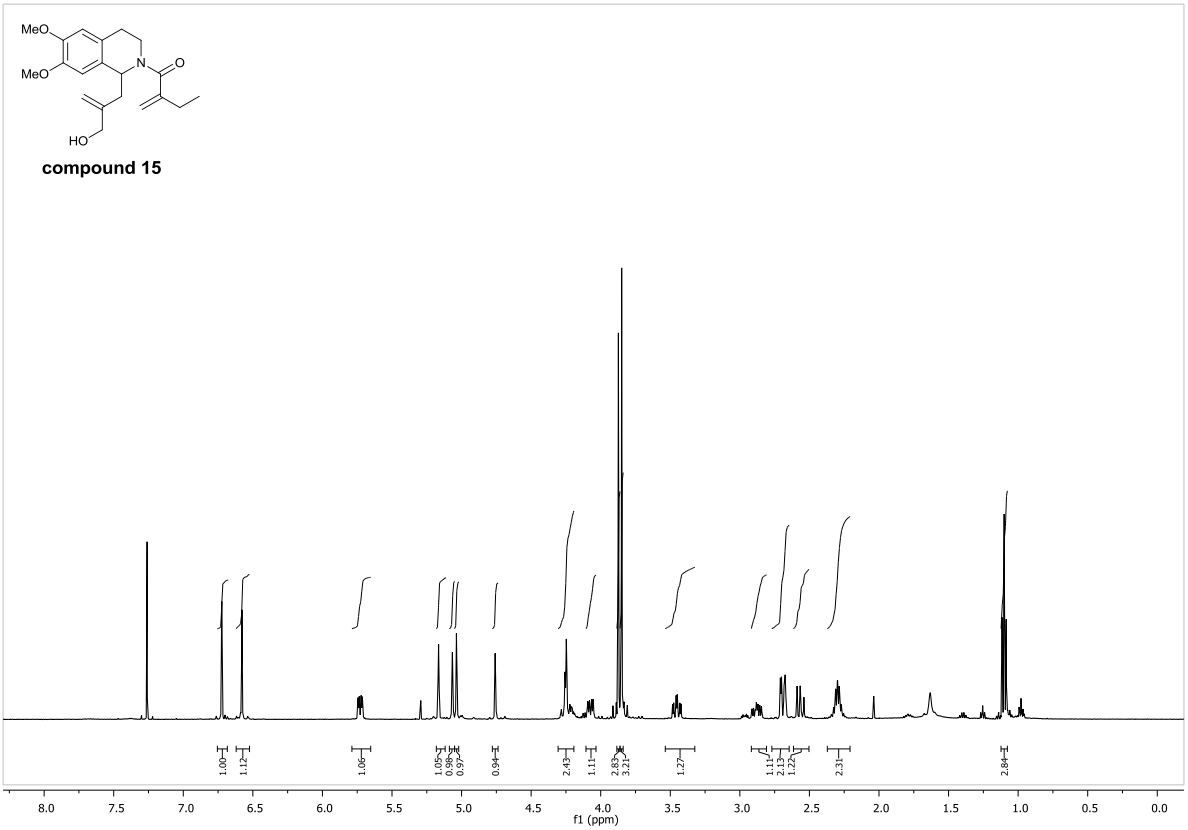

TBDPSO
Br
compound12
144.4
135.5
133.3
129.8
127.8
115.0
64.2
32.8
26.8
19.3
f1 (ppm)

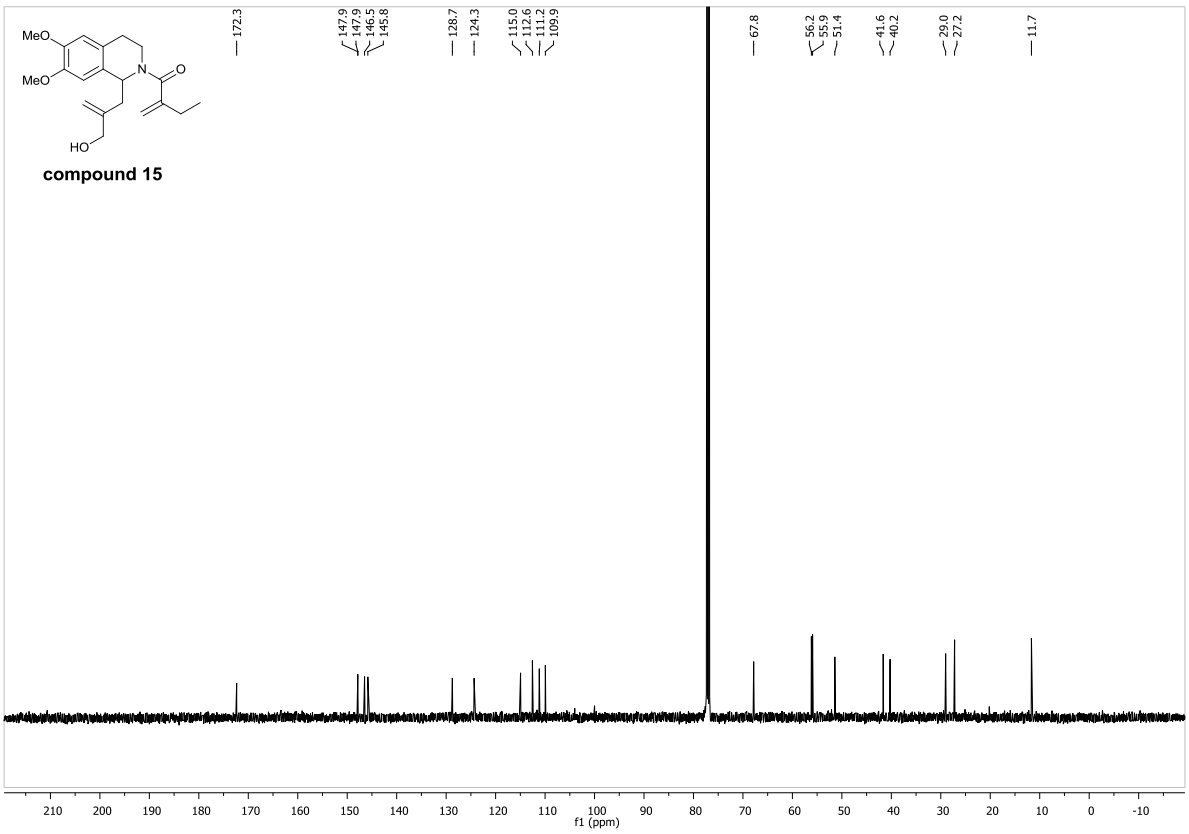

MeO
MeO
NBoc
OTBDPS
compound 13
4.03
6.00
1.96
0.37
0.59
0.34
0.60
0.92
0.84
0.85
1.07
0.39
3.39
2.77
0.36
0.64
1.13
1.03
1.81
8.64
9.05
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

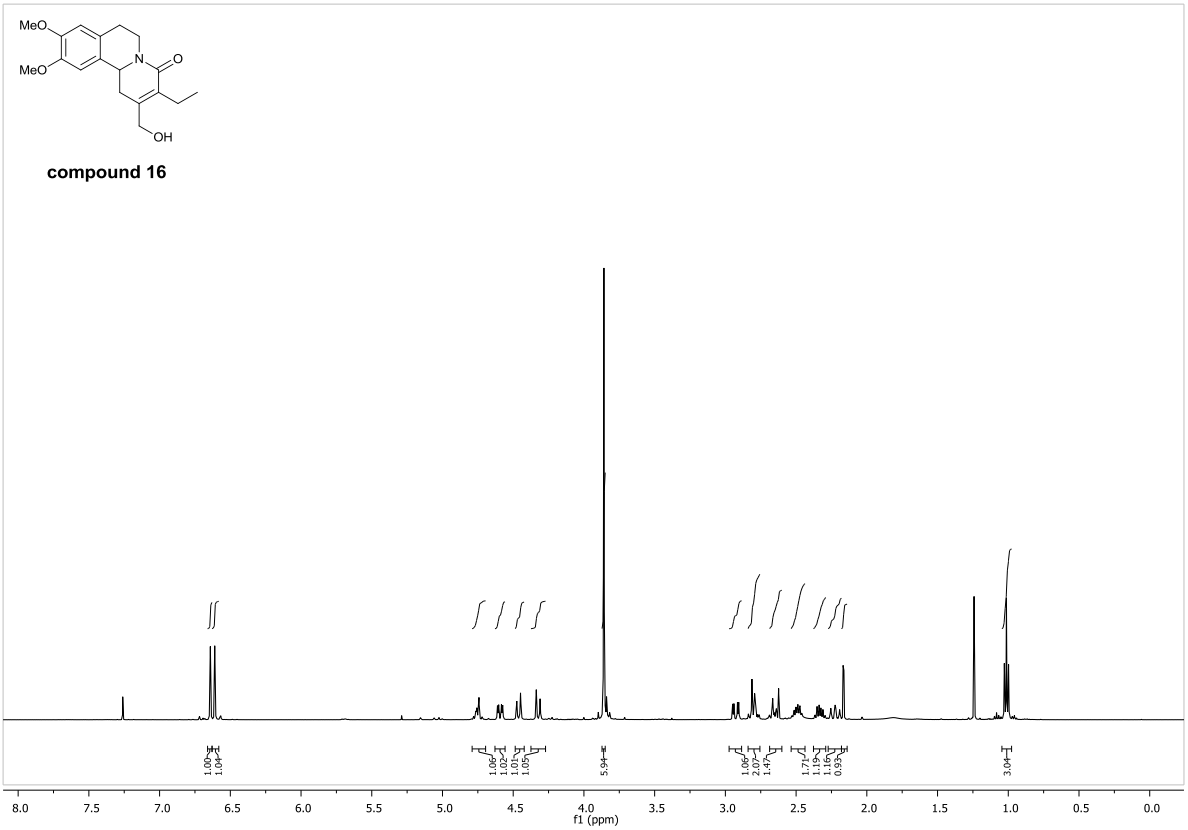

MeO
MeO
NBoc
OTBDPS
compound 13
154.7
147.8
147.6
147.3
145.2
144.4
135.6
135.6
135.5
134.9
129.8
129.6
129.6
127.8
127.7
113.0
112.1
111.6
111.4
110.2
110.0
80.0
79.3
66.4
66.2
56.0
55.9
53.3
52.5
39.8
39.6
38.0
36.5
28.5
28.4
28.1
26.9
19.6
19.1
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

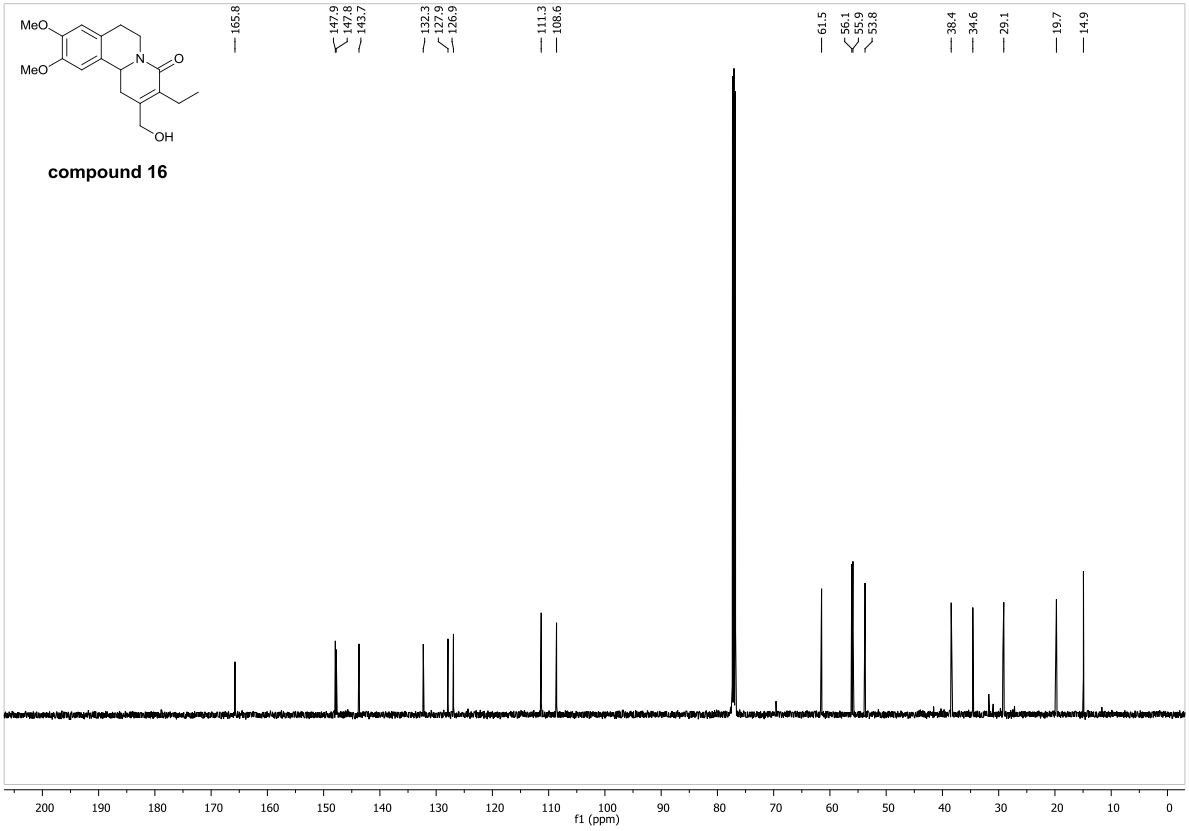

MeO
MeO
N
O
TBDPSO
compound 14
4.91
6.74
0.75
0.23
0.82
0.22
0.89
0.24
1.74
0.27
0.89
0.87
0.90
0.27
0.95
0.96
0.29
1.20
3.55
2.57
0.67
1.05
0.25
0.27
1.87
1.37
1.08
2.20
0.29
12.76
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

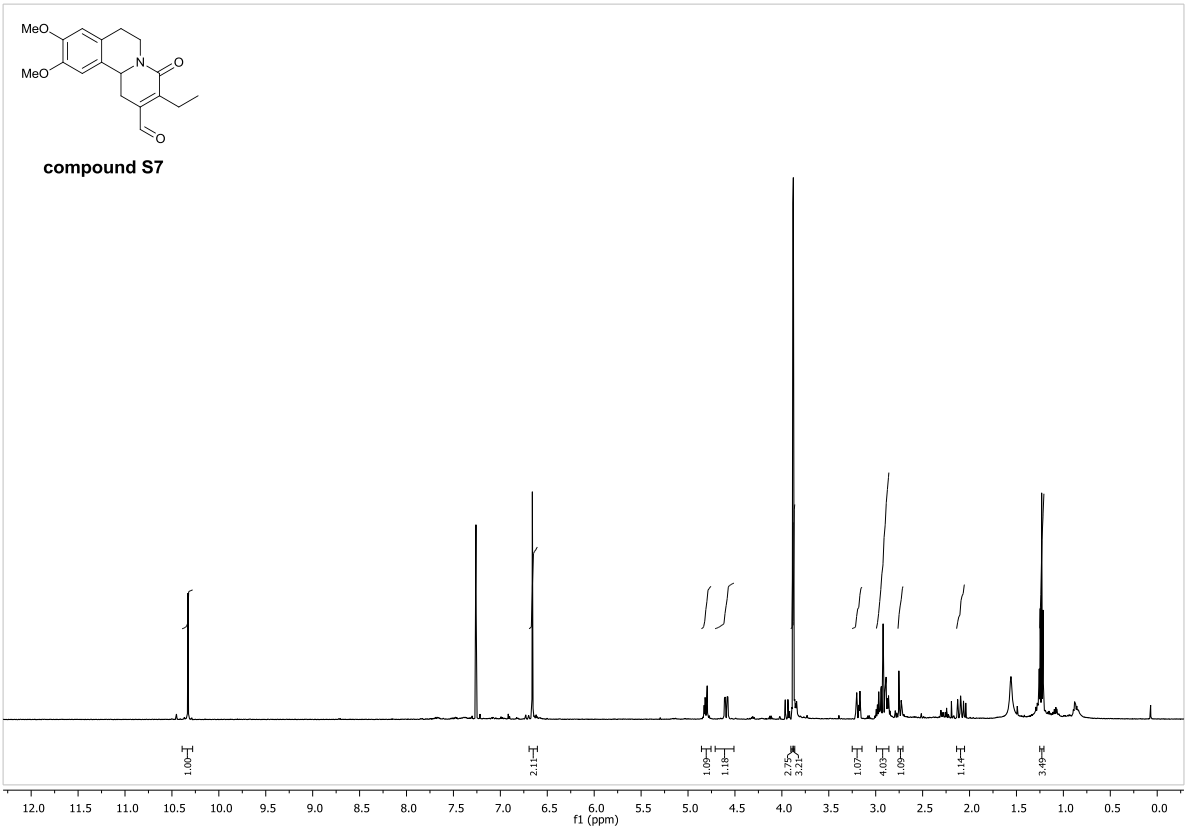

MeO
MeO
N
O
TBDPSO
compound 14
171.9
171.3
148.0
147.7
147.6
147.2
147.0
146.5
145.2
143.8
135.6
135.5
129.8
129.6
127.8
127.8
127.7
113.0
112.6
112.1
111.6
111.3
110.0
109.6
66.5
66.2
56.6
55.9
55.8
49.3
40.0
40.0
39.9
34.9
29.1
27.3
27.0
26.9
19.4
11.7
11.6
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

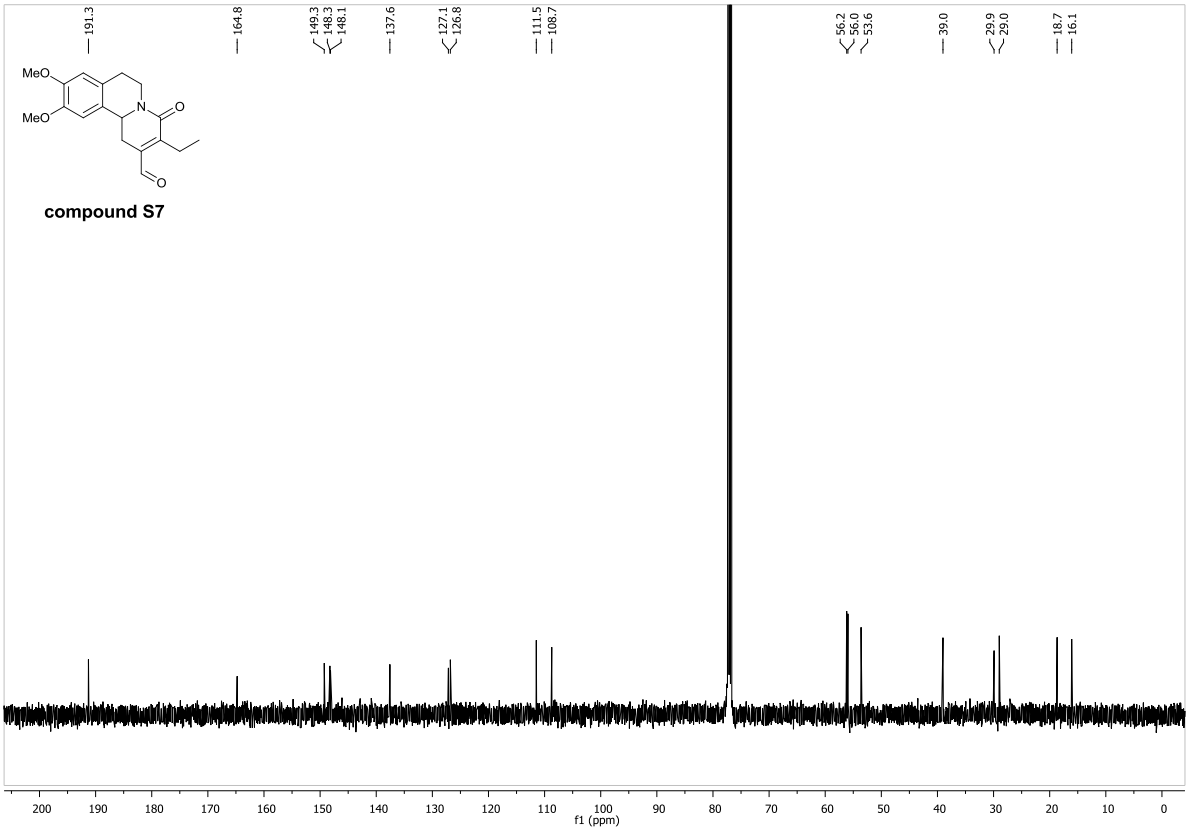

MeO
MeO
N
O
HO
compound 15
1.00
1.12
1.06
1.05
0.98
0.97
0.94
2.43
1.11
2.85
3.21
1.27
1.11
2.15
1.20
2.31
2.84
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

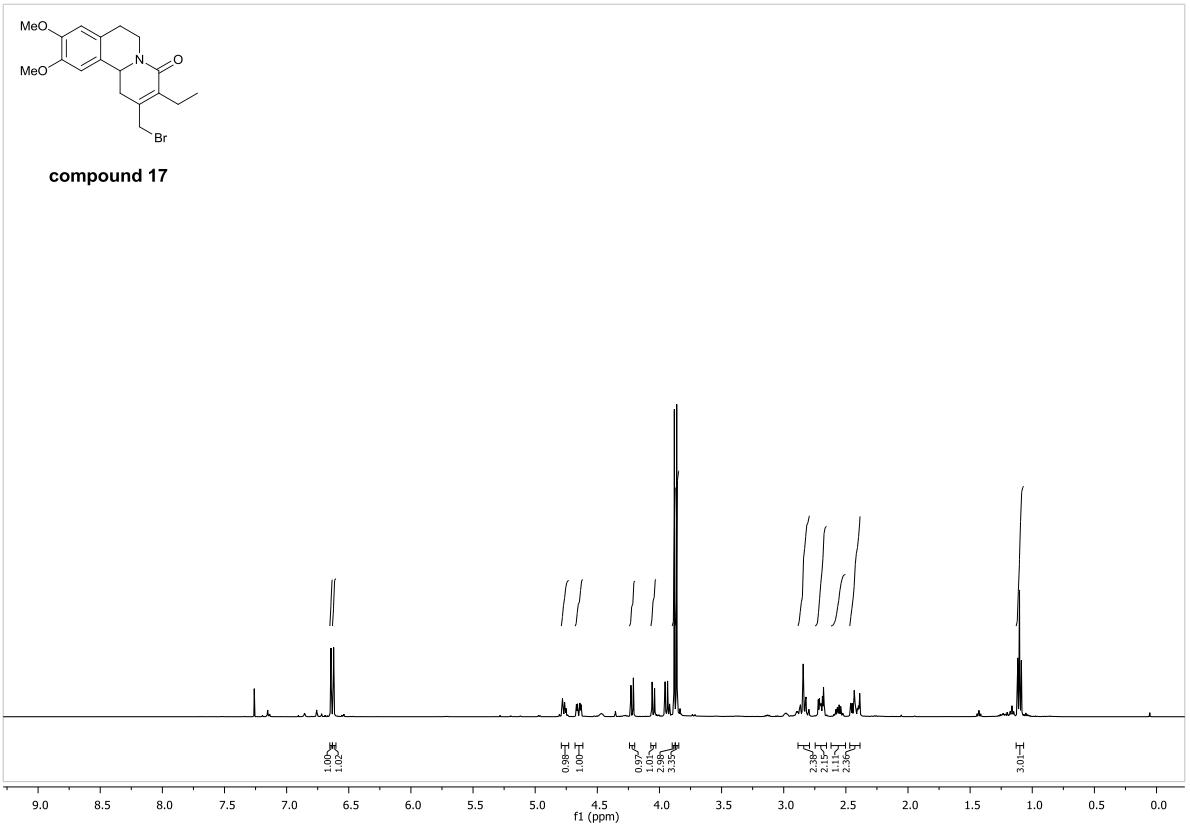

MeO
MeO
N
O
HO
compound 15
172.3
147.9
147.9
146.5
145.8
128.7
124.3
115.0
112.6
111.2
109.9
67.8
56.2
55.9
51.4
41.6
40.2
29.0
27.2
11.7
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

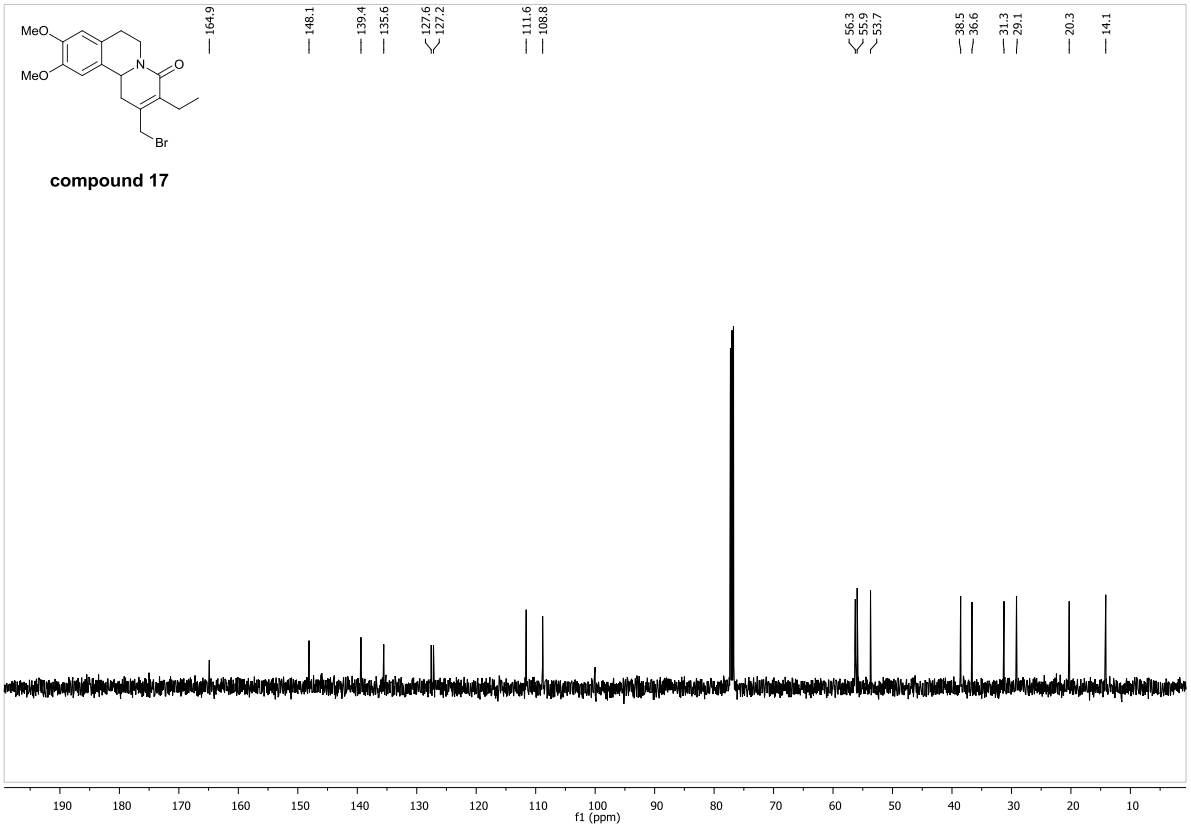

MeO
MeO
N
O
OH
compound 16
1.00
1.04
1.06
1.02
1.05
1.05
5.94
1.06
2.07
1.47
1.71
1.19
1.16
0.95
3.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

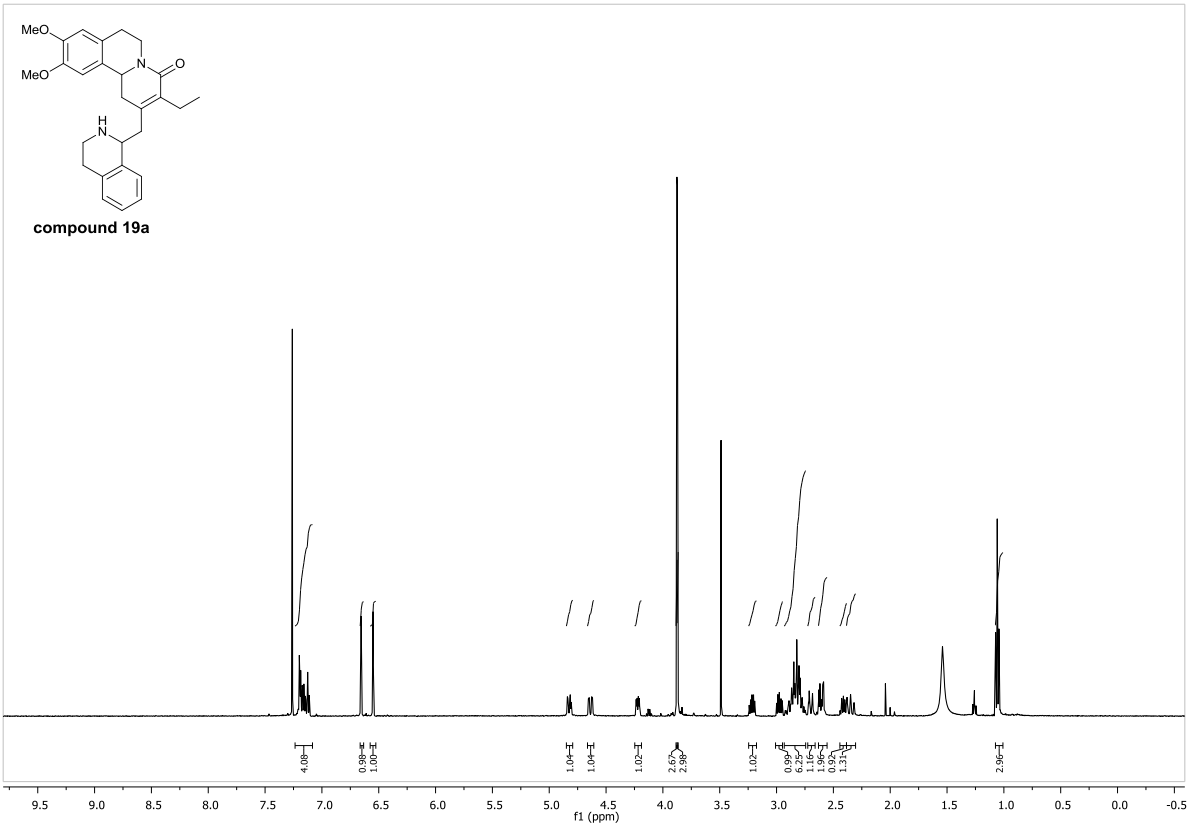

MeO
MeO
N
O
OH
compound 16
165.8
147.9
147.8
143.7
132.3
127.9
126.9
111.3
108.6
61.5
56.1
55.9
53.8
38.4
34.6
29.1
19.7
14.9
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

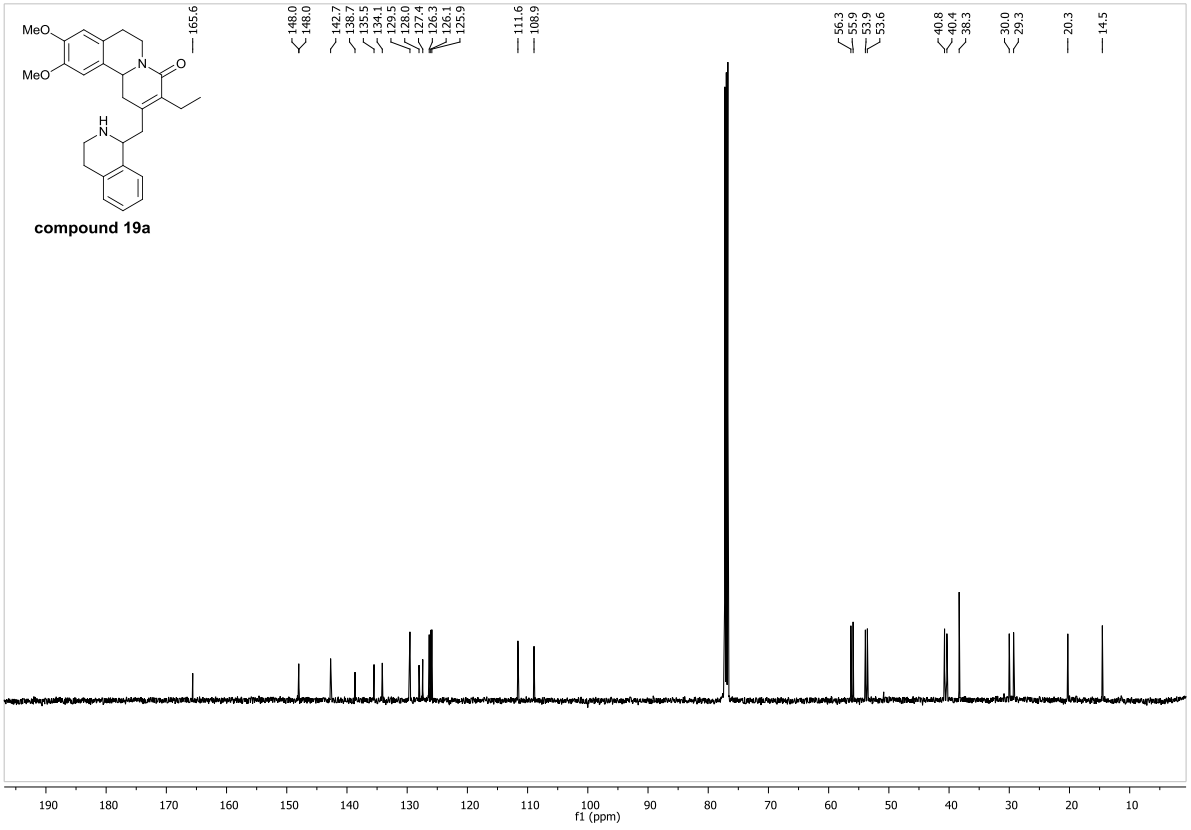

MeO
MeO
N
O
O
compound S7
1.00
2.11
1.09
1.18
2.75
3.21
1.07
4.03
1.09
1.14
3.49
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

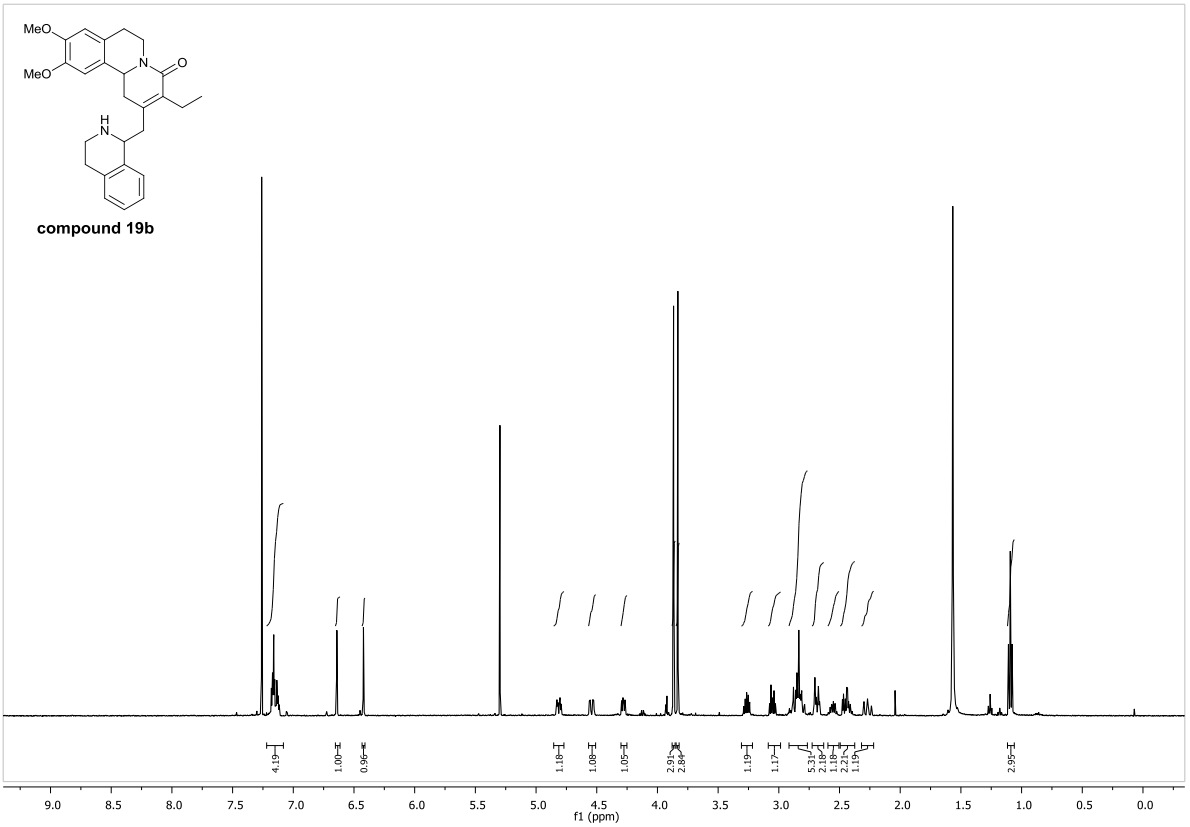

191.3
164.8
149.3
148.3
148.1
137.6
127.1
126.8
111.5
108.7
56.2
56.0
53.6
39.0
29.9
29.0
18.7
16.1
MeO
MeO
N
O
O
compound S7
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

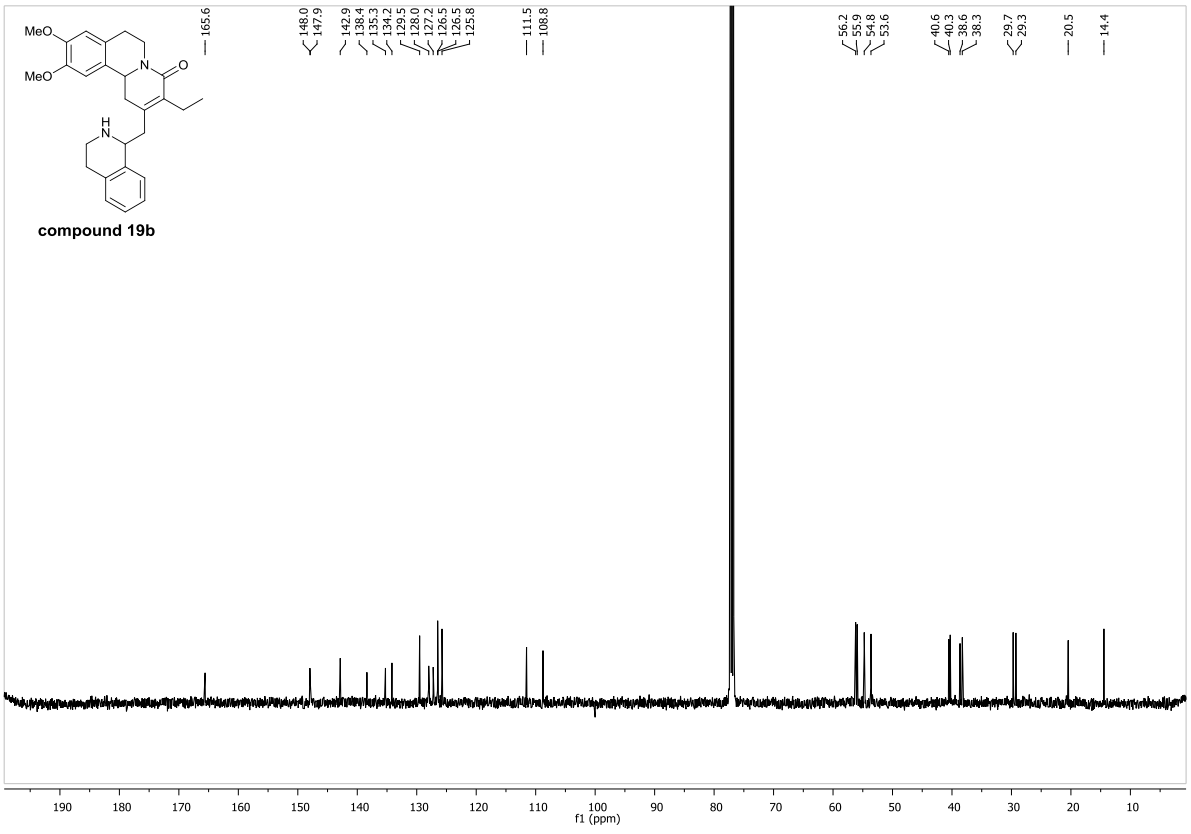

MeO
MeO
N
O
Br
compound 17
1.00
1.02
0.98
1.00
0.97
1.01
2.99
3.35
2.38
2.15
1.15
2.36
3.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

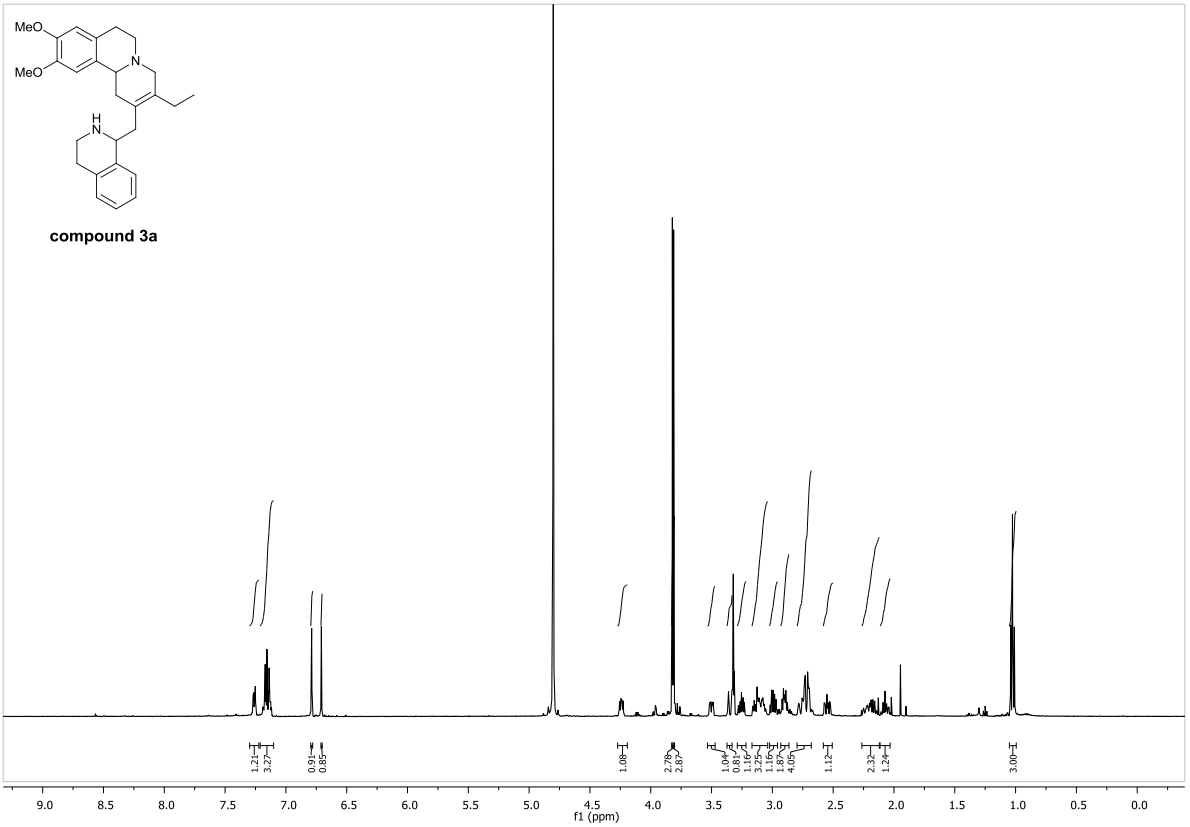

MeO
MeO
N
O
Br
compound 17
164.9
148.1
139.4
135.6
127.6
127.2
111.6
108.8
56.3
55.9
53.7
38.5
36.6
31.3
29.1
20.3
14.1
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

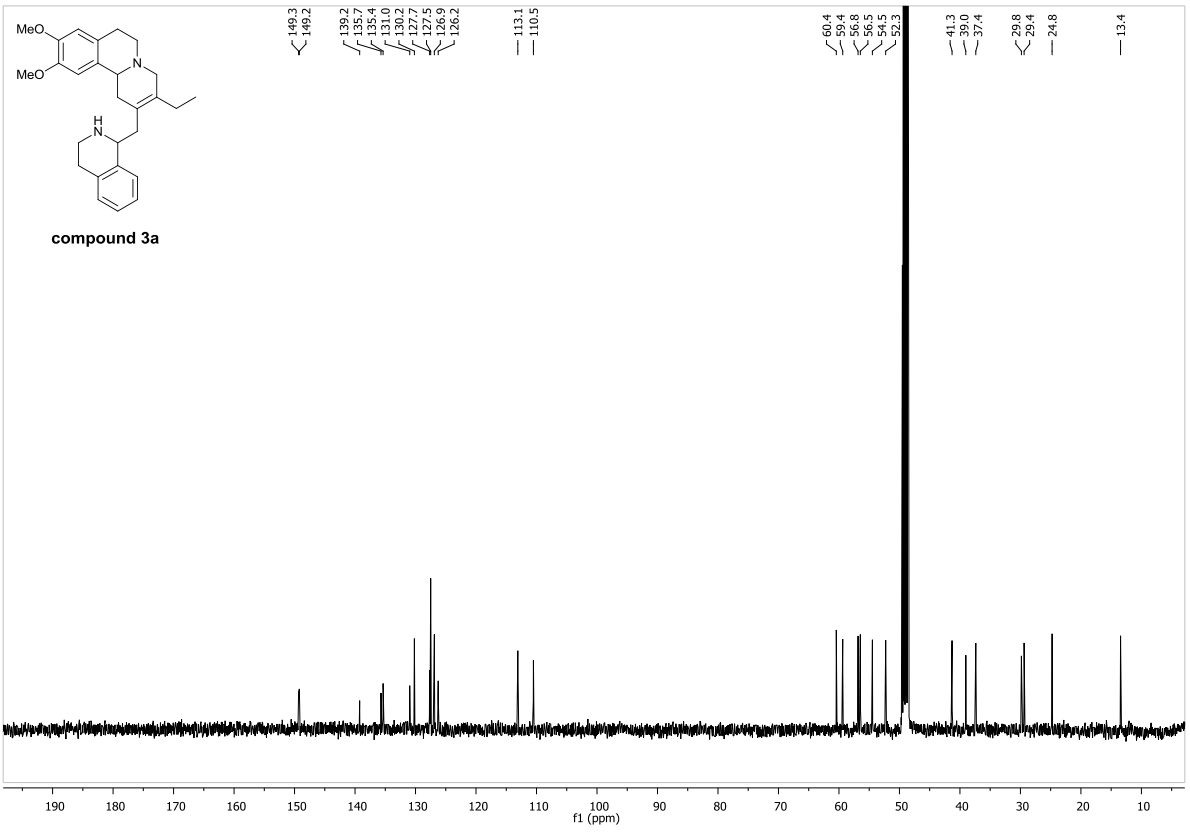

MeO
MeO
N
O
H
N
compound 19a
4.08
0.98
1.00
1.04
1.04
1.02
2.67
2.90
1.02
0.99
6.25
1.16
1.96
0.92
1.31
2.96
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

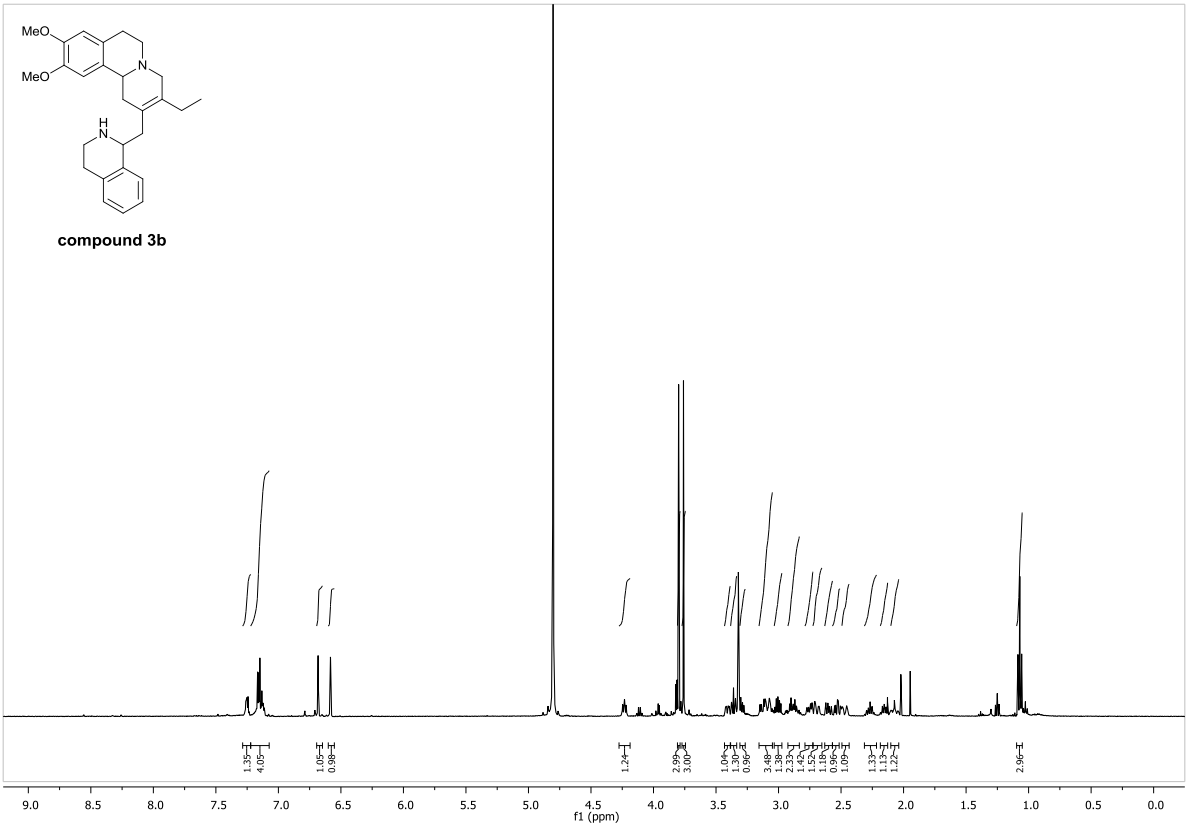

MeO
MeO
N
O
H
N
compound 19a
165.6
148.0
148.0
142.7
138.7
135.5
134.1
129.5
128.0
127.4
126.3
126.1
125.9
111.6
108.9
56.3
55.9
53.9
53.6
40.8
40.4
38.3
30.0
29.3
20.3
14.5
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

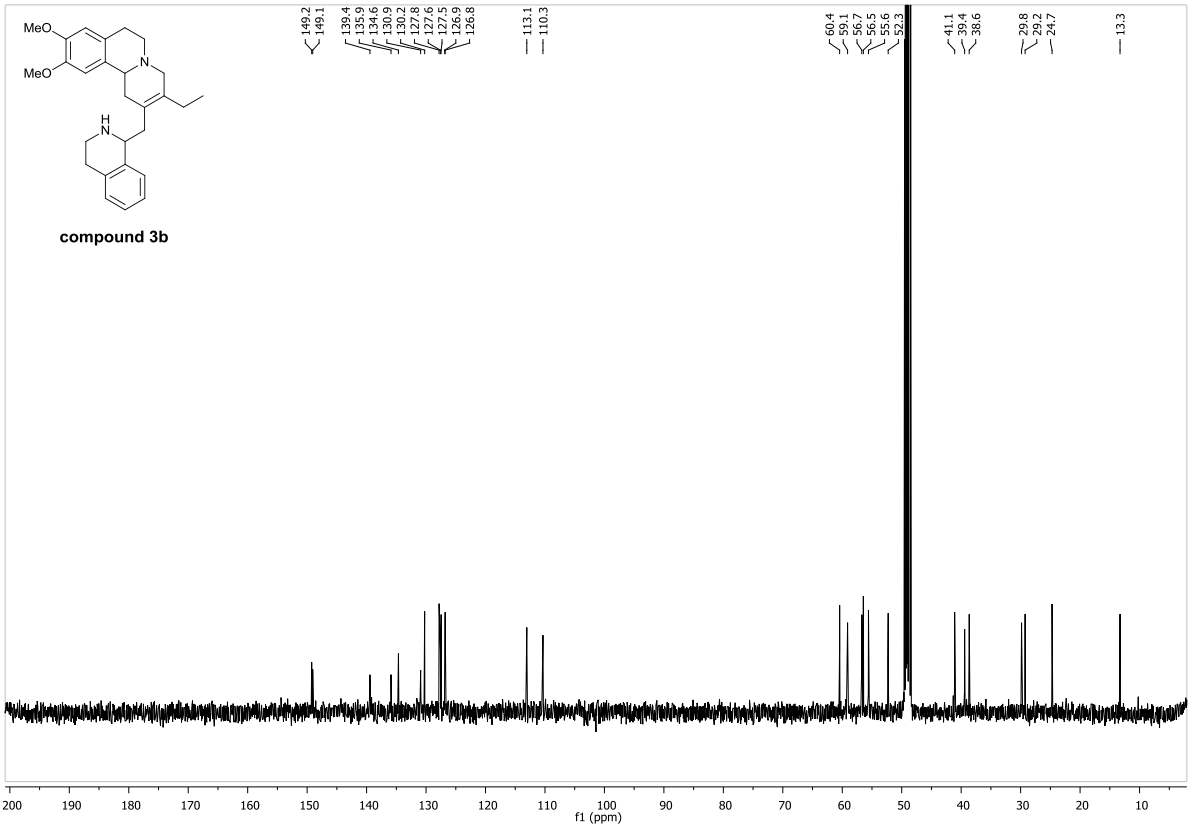

MeO
MeO
N
O
H
N
compound 19b
4.19
1.00
0.96
1.18
1.08
1.05
2.91
2.04
1.19
1.17
5.31
2.16
1.18
2.21
1.19
2.95
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

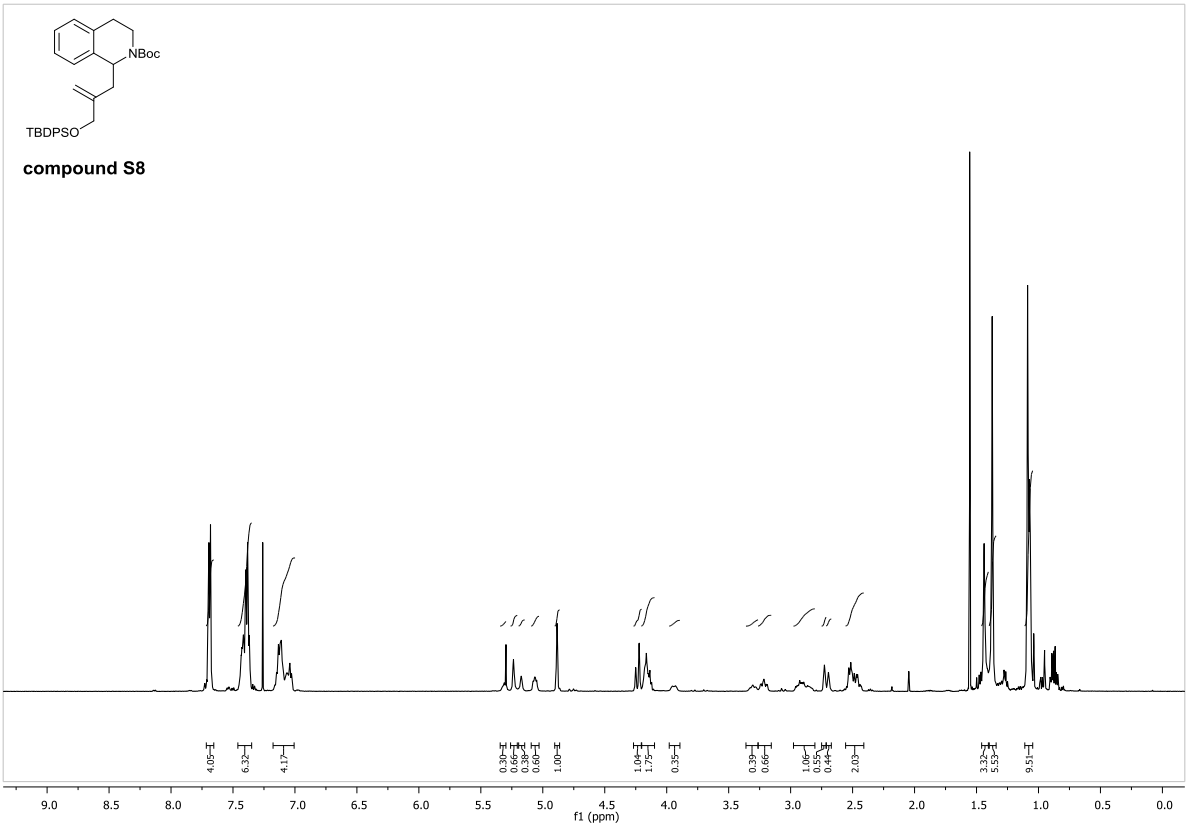

MeO
MeO
N
O
H
N
compound 19b
165.6
148.0
147.9
142.9
138.4
135.3
134.2
129.5
128.0
127.2
126.5
126.5
125.8
111.5
108.8
56.2
55.9
54.8
53.6
40.6
40.3
38.6
38.3
29.7
29.3
20.5
14.4
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

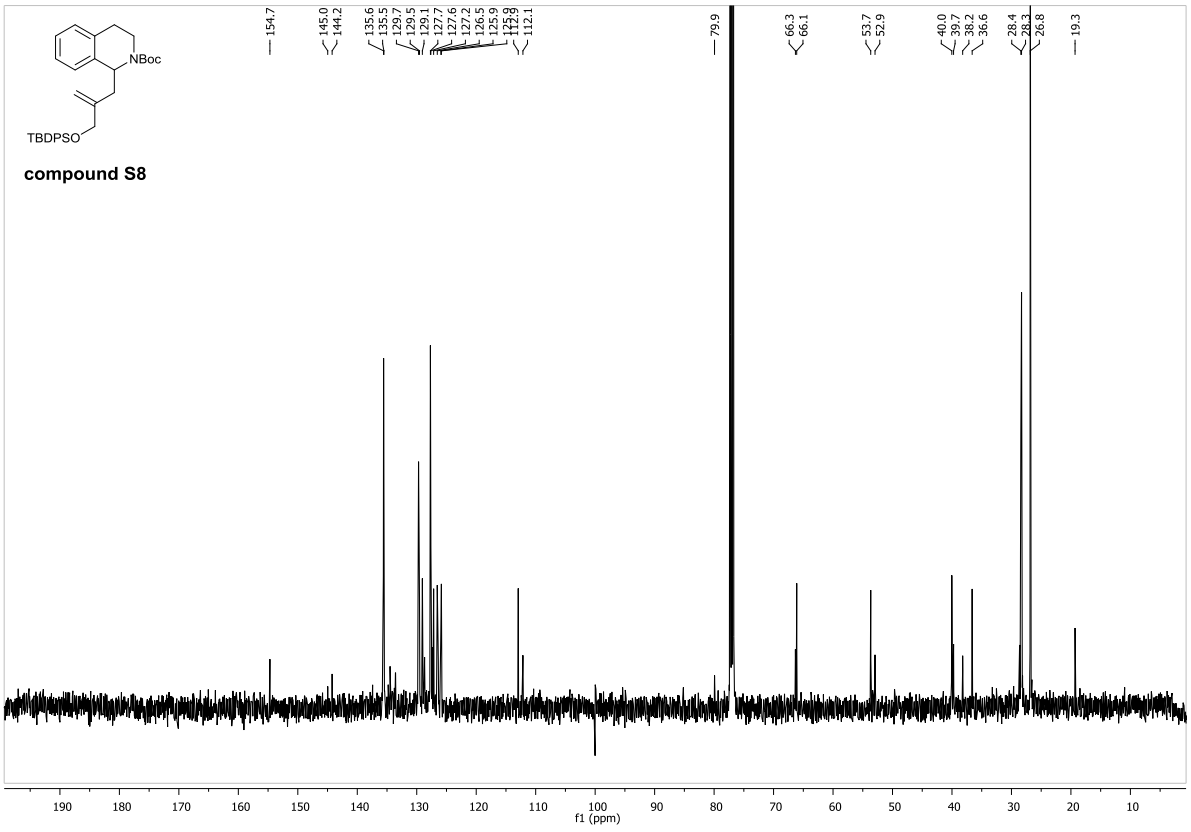

MeO
MeO
N
H
N
compound 3a
1.21
3.27
0.91
0.85
1.08
2.79
2.87
1.04
0.87
1.16
3.25
1.16
1.05
4.05
1.12
2.32
1.24
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

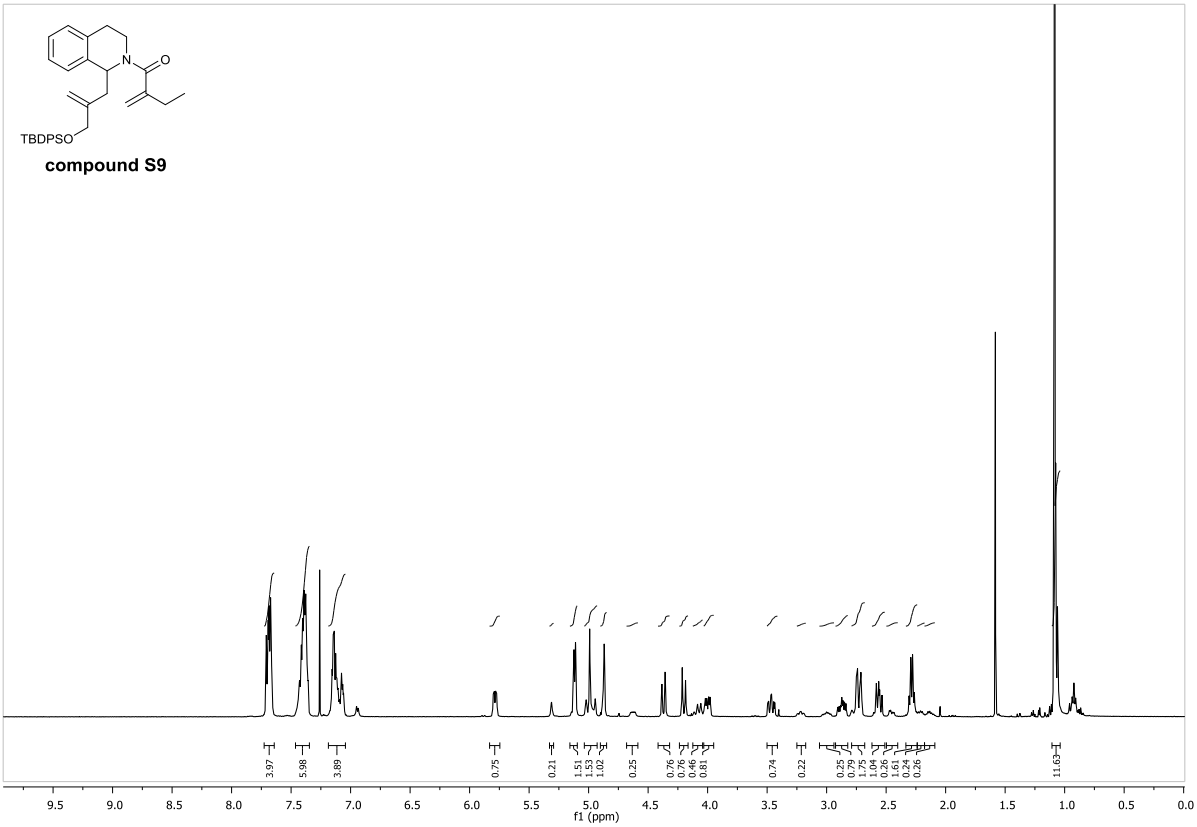

MeO
MeO
N
H
N
compound 3a
149.3
149.2
139.2
135.7
135.4
131.0
130.2
127.7
127.5
126.9
126.2
113.1
110.5
60.4
59.4
56.8
56.5
54.5
52.3
41.3
39.0
37.4
29.8
29.4
24.8
13.4
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

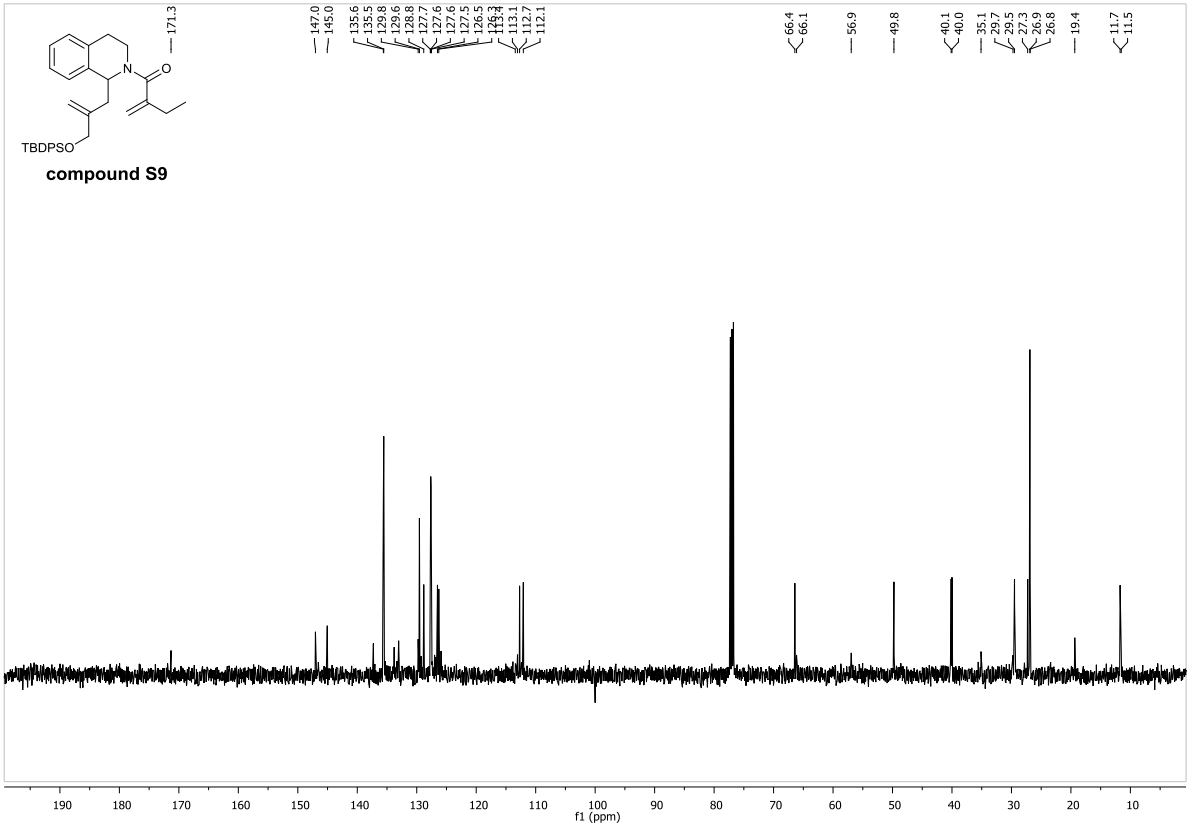

MeO
MeO
N
H
N
compound 3b
1.35
4.05
1.05
0.98
1.24
2.99
3.00
1.04
1.30
0.96
3.48
1.38
2.33
1.42
1.52
1.46
0.96
1.09
1.33
1.13
1.22
2.96
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

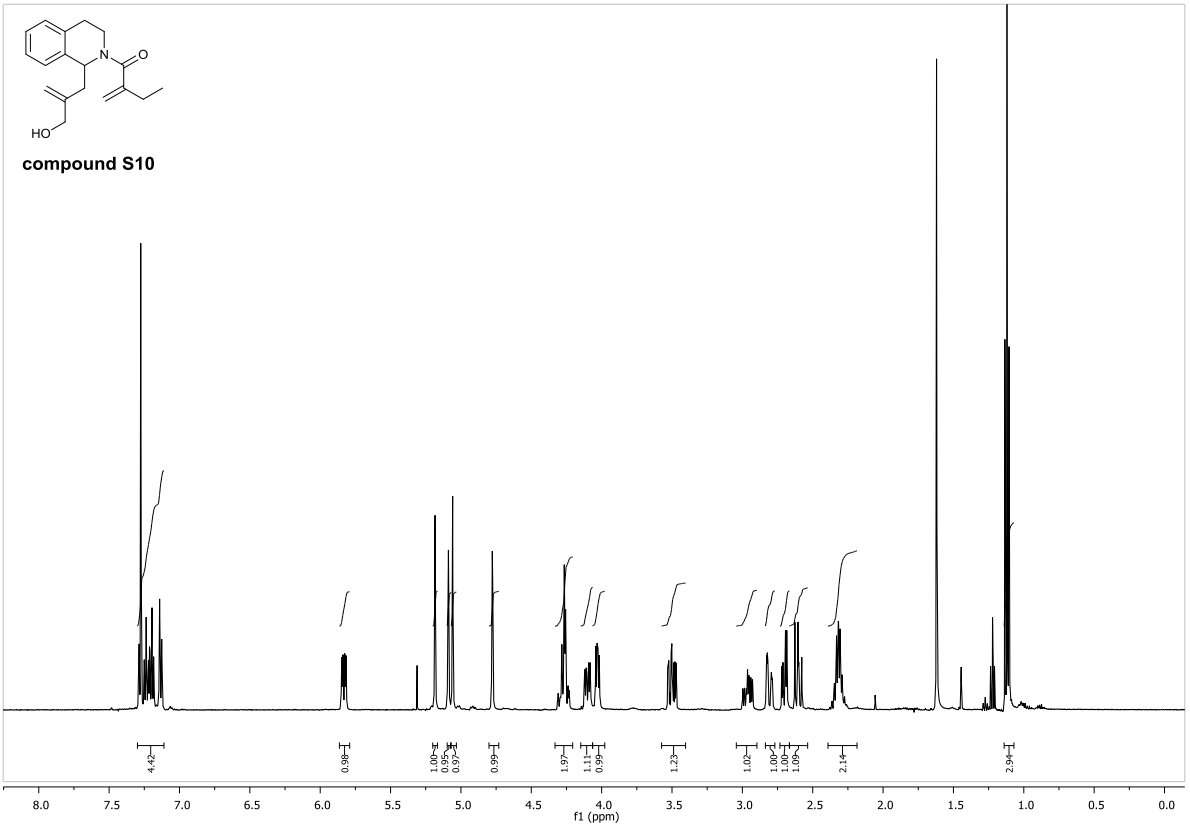

MeO
MeO
N
H
N
compound 3b
149.2
149.1
139.4
135.9
134.6
130.9
130.2
127.8
127.6
127.5
126.9
126.8
113.1
110.3
60.4
59.1
56.7
56.5
55.6
52.3
41.1
39.4
38.6
29.8
29.2
24.7
13.3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

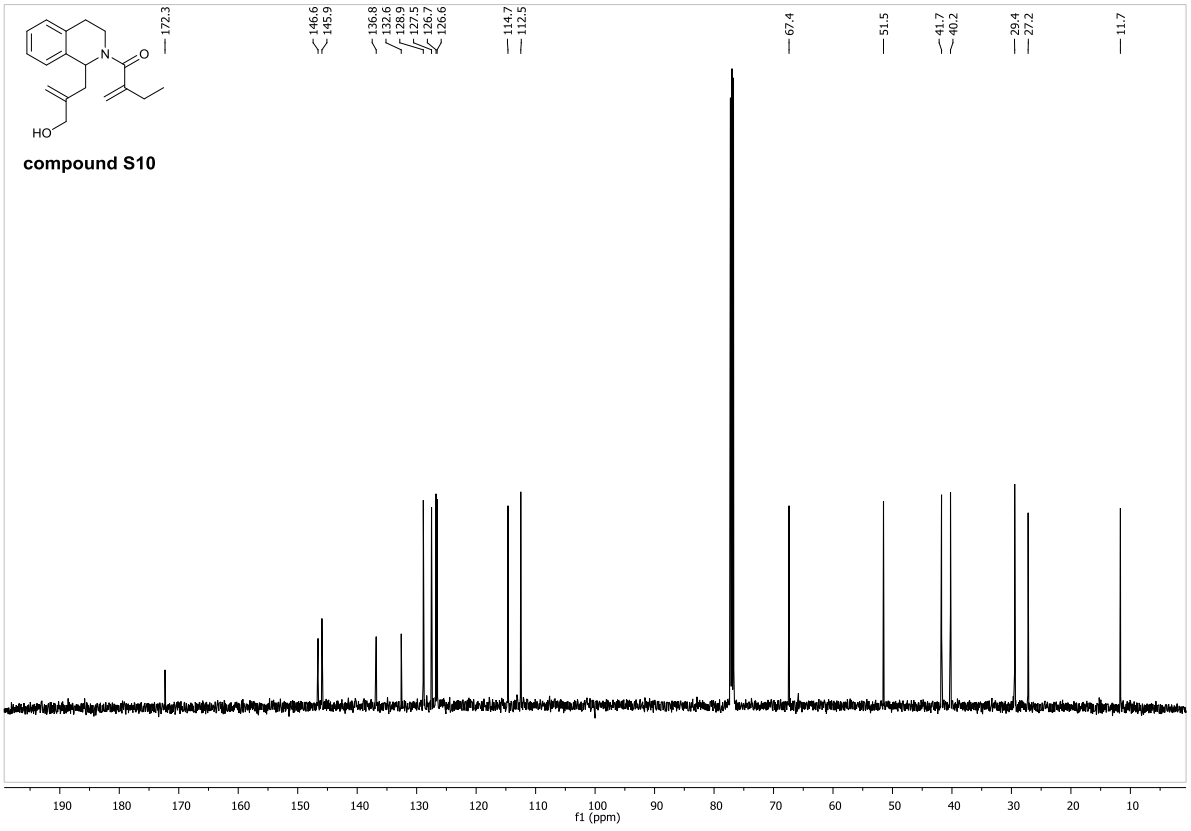

NBoc
TBDPSO
compound S8
f1 (ppm)

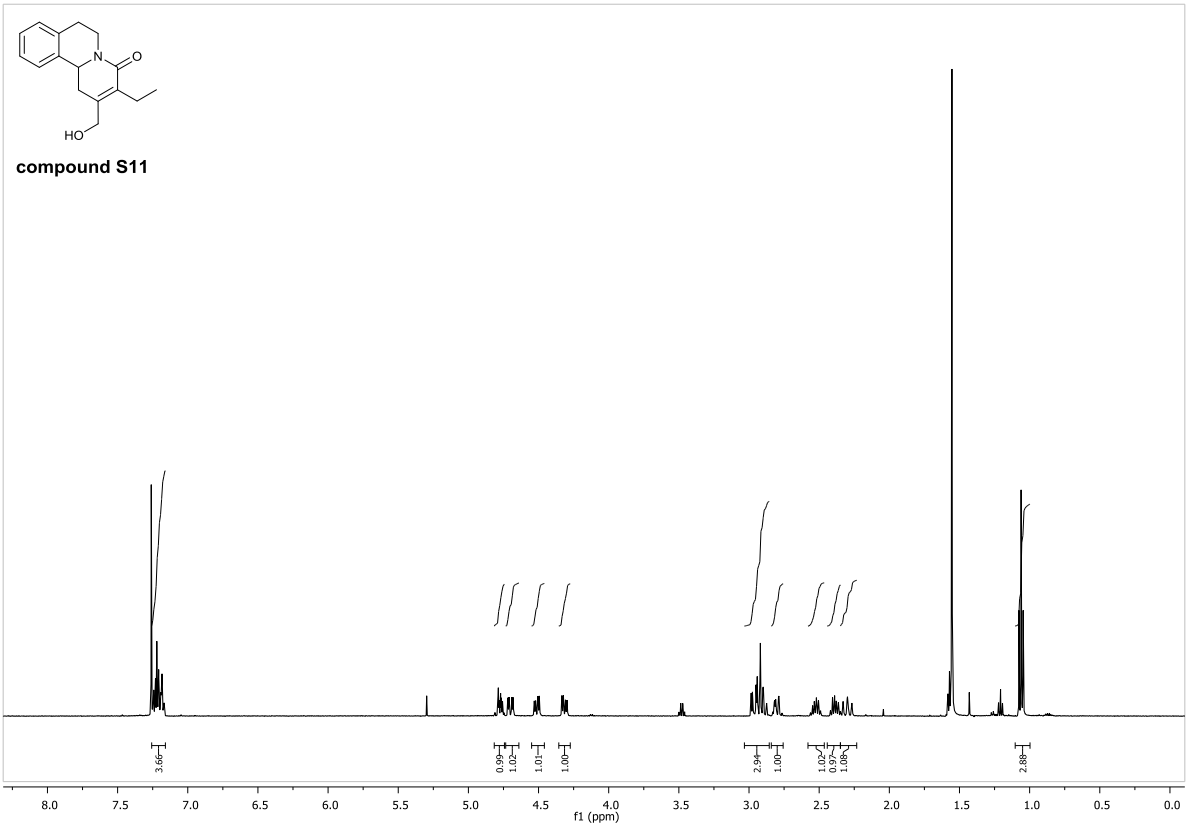

NBoc
TBDPSO
compound S8
154.7
145.0
144.2
135.6
135.5
129.7
129.5
129.1
127.7
127.6
127.2
126.5
125.9
112.1
79.9
66.3
66.1
53.7
52.9
40.0
39.7
38.2
36.6
28.4
28.3
26.8
19.3
f1 (ppm)

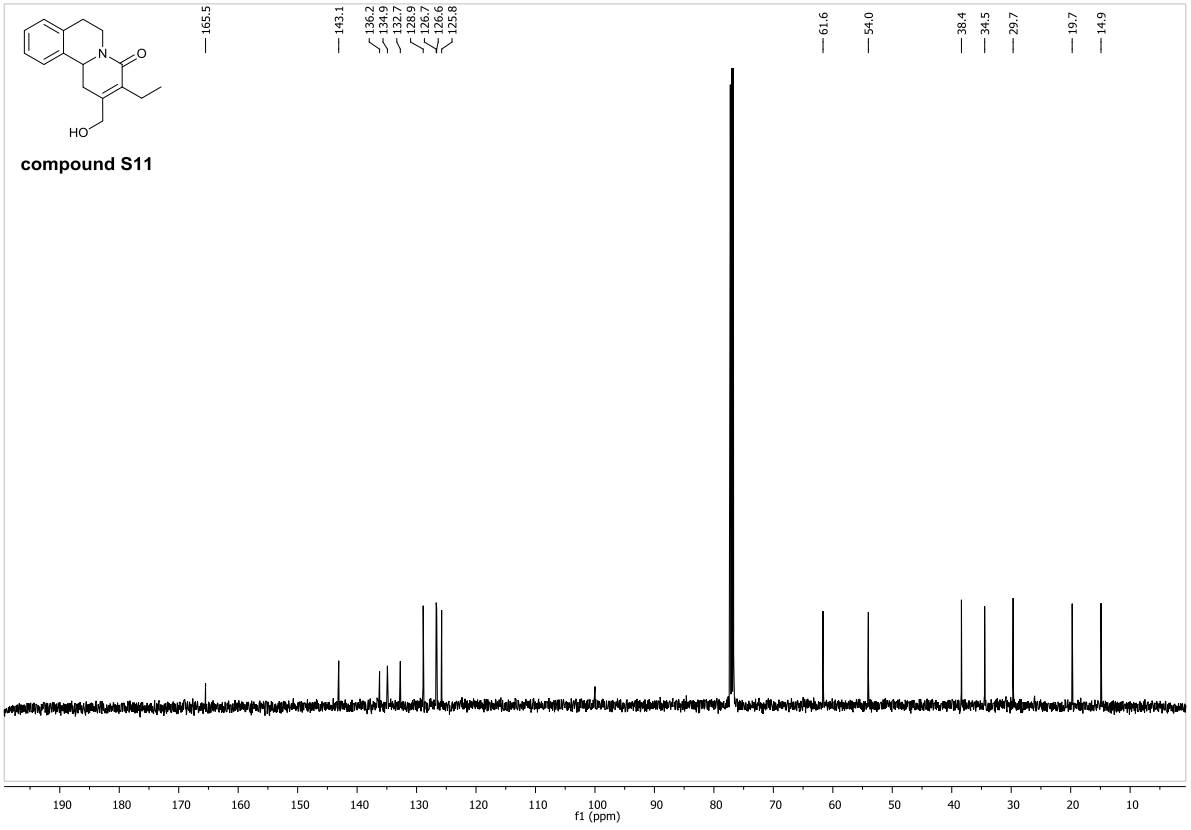

TBDPSO
compound S9
f1 (ppm)

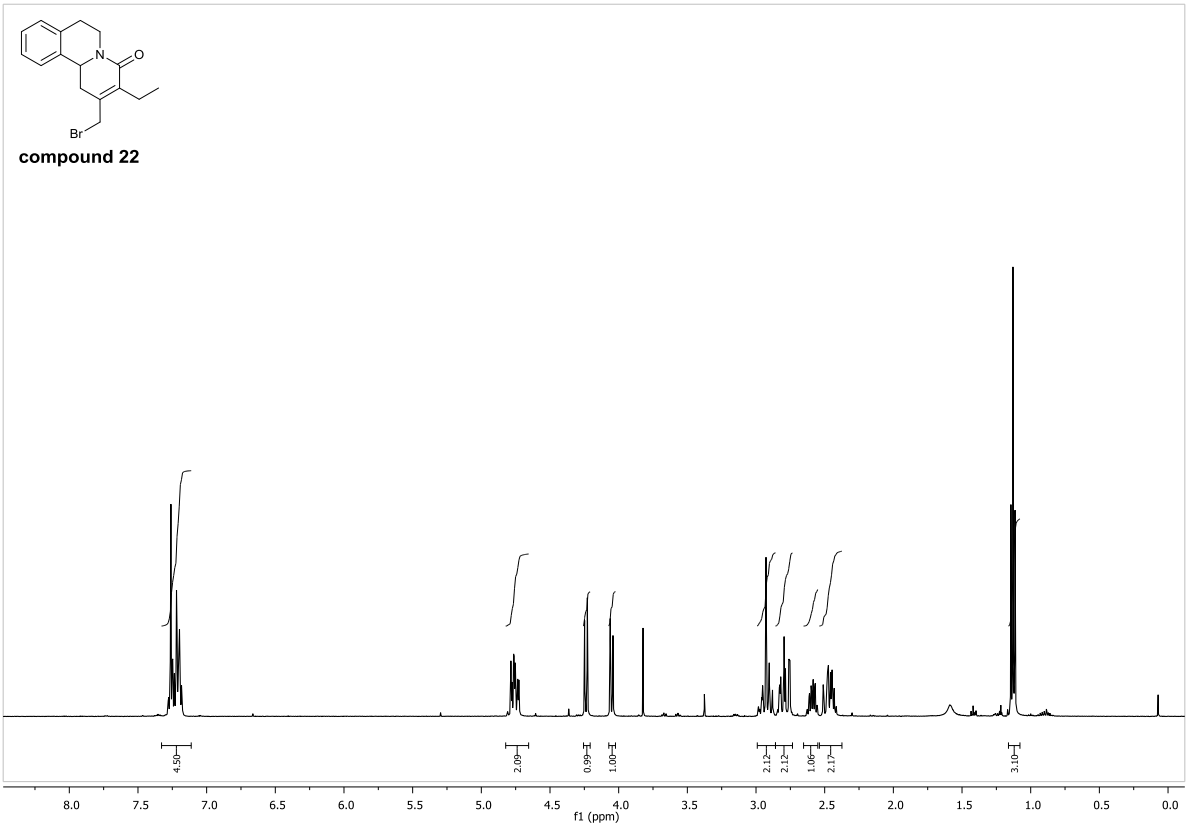

TBDPSO
compound S9
f1 (ppm)

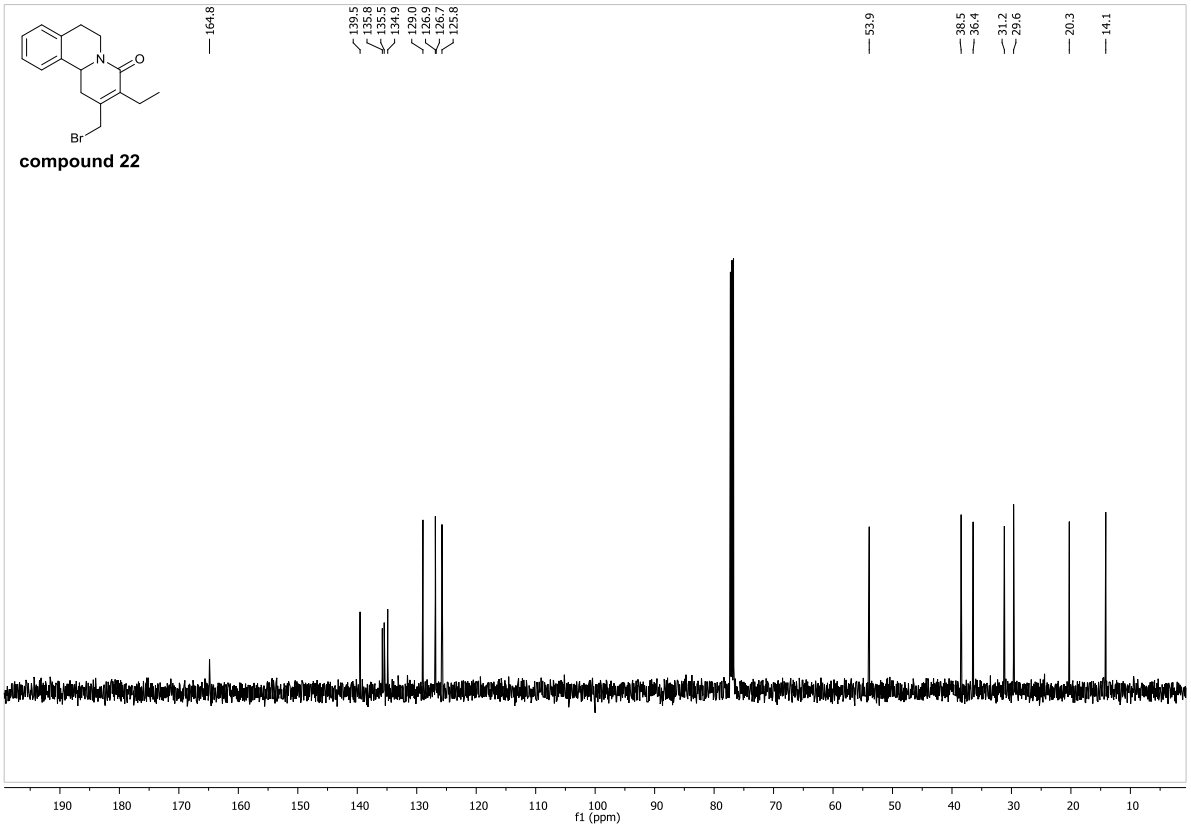

compound S10
f1 (ppm)

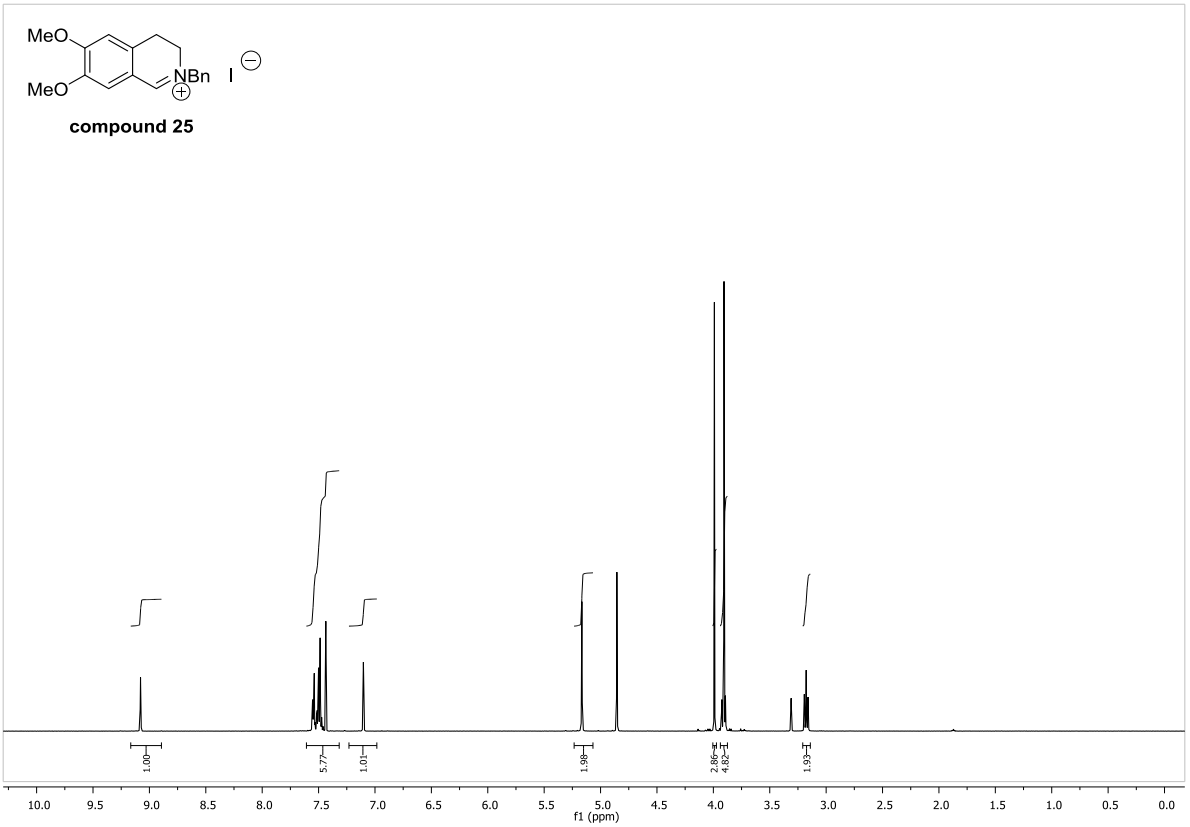

compound S10
f1 (ppm)

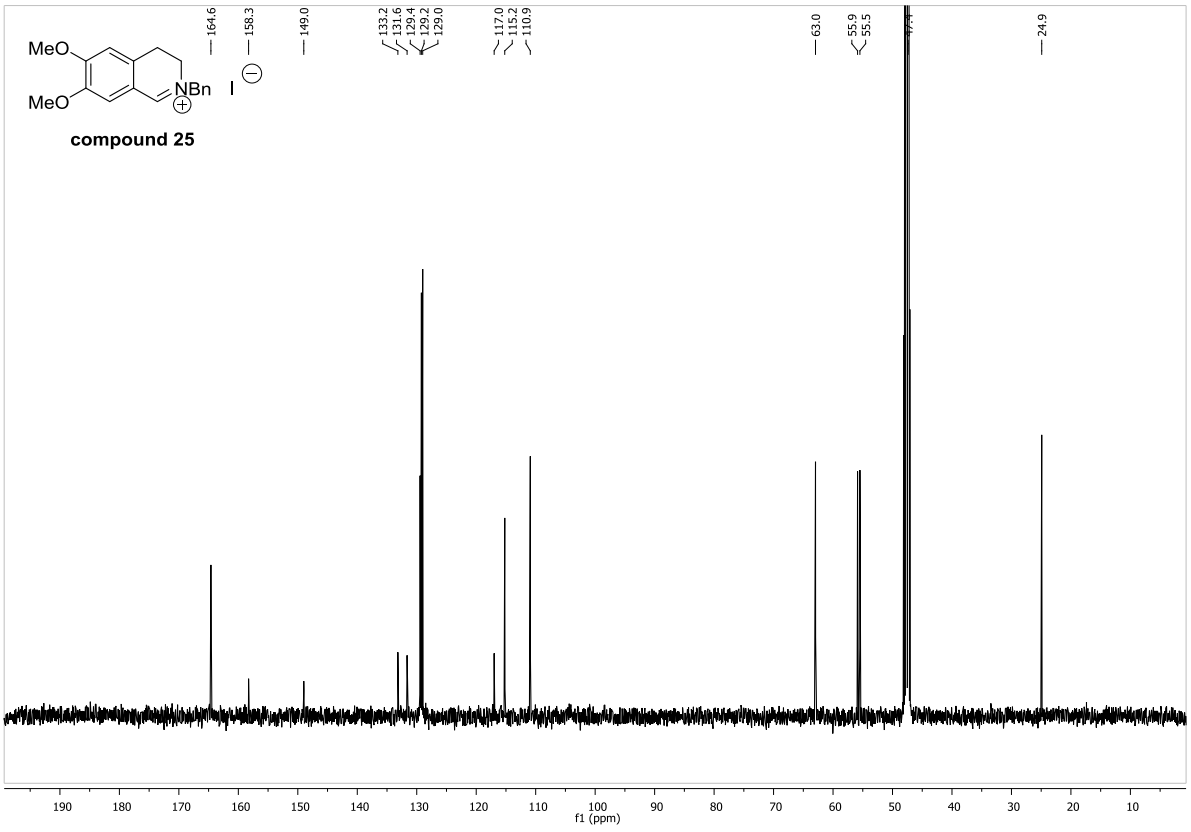

compound S11
f1 (ppm)

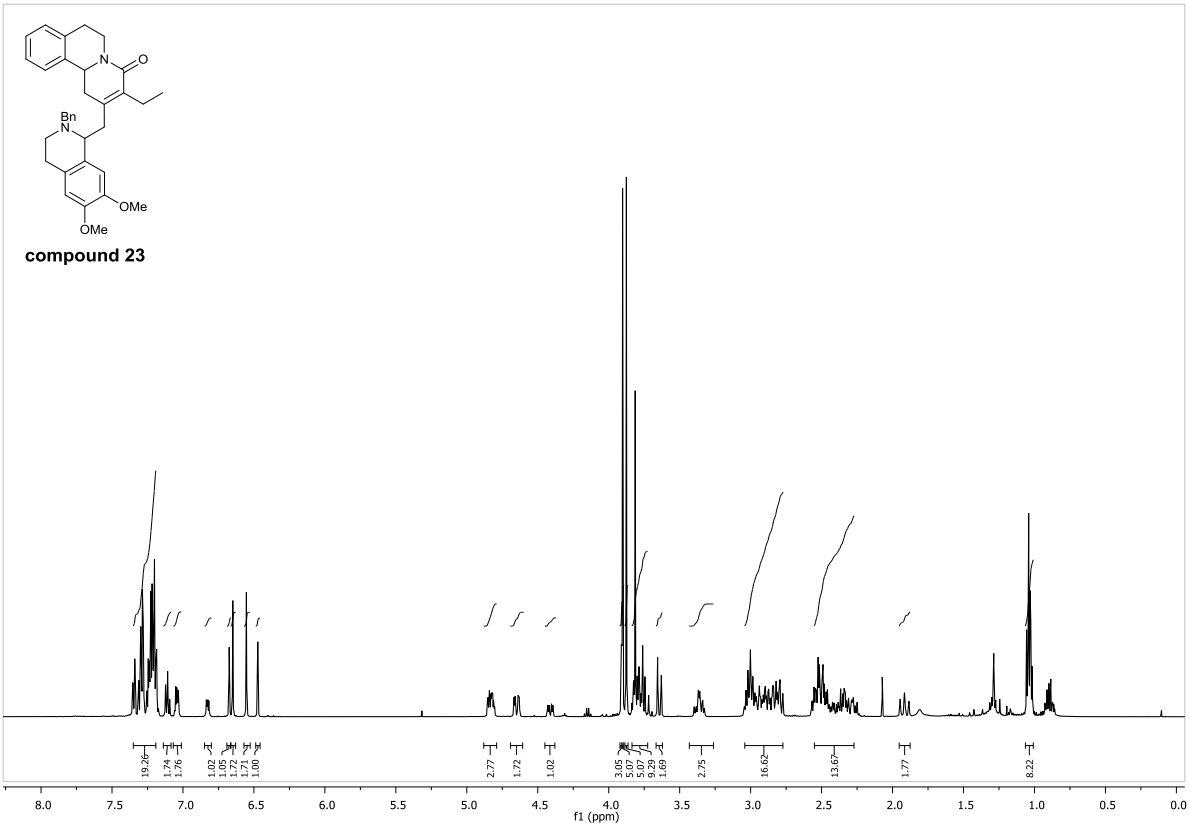

compound S11
165.5
143.1
136.2
134.9
132.7
128.9
126.7
126.6
125.8
61.6
54.0
38.4
34.5
29.7
19.7
14.9
f1 (ppm)

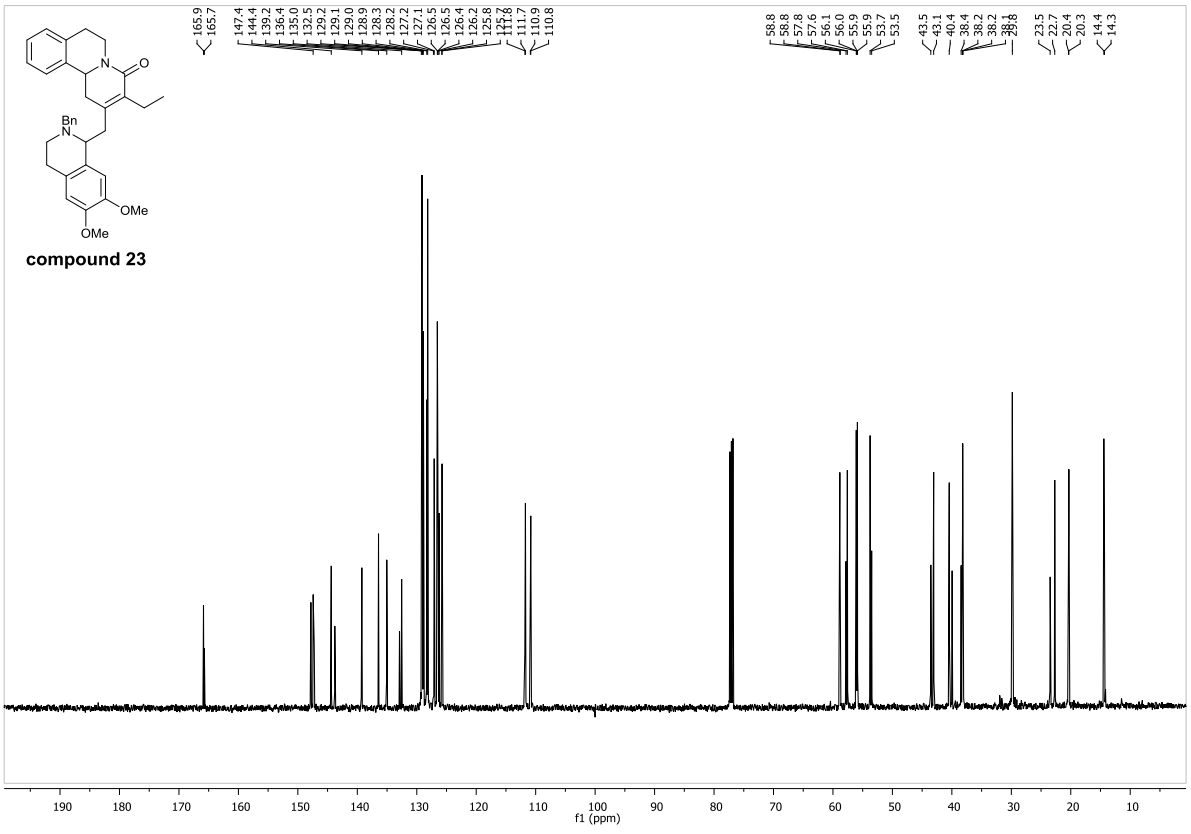

compound 22
f1 (ppm)

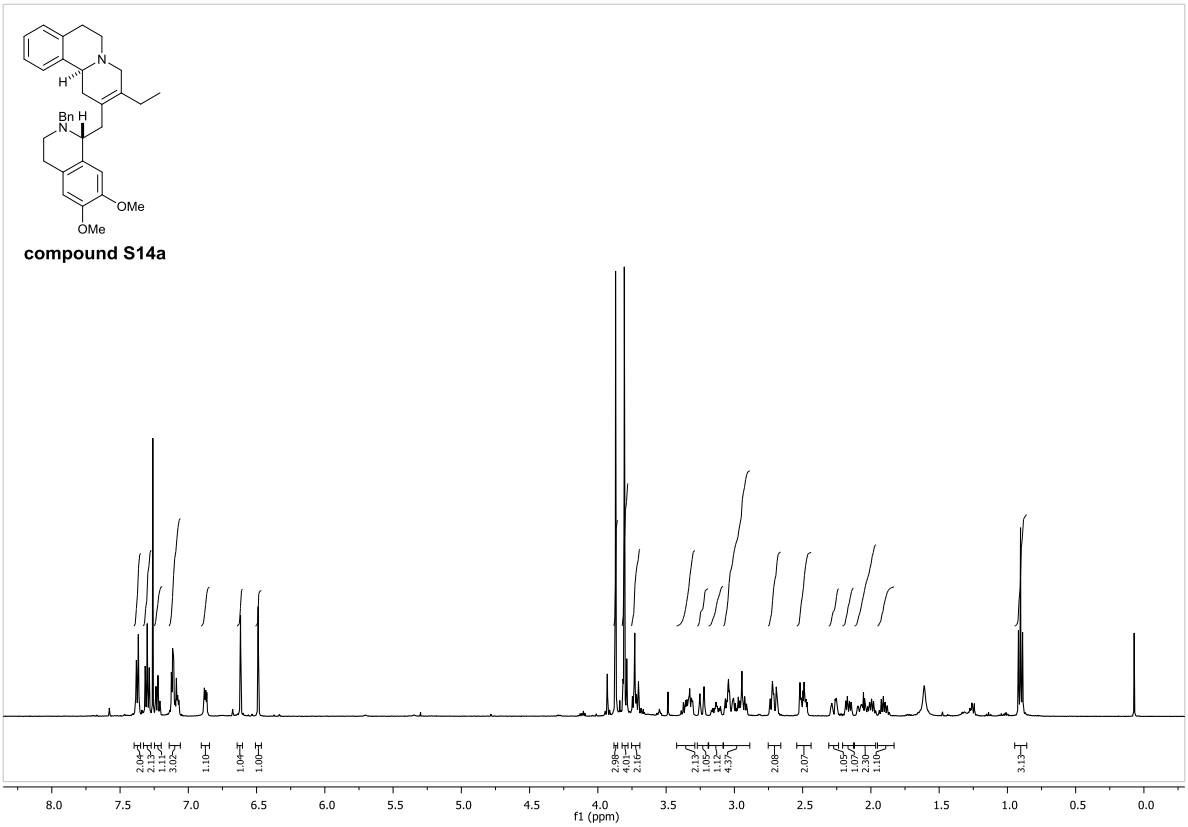

compound 22
164.8
139.5
135.8
135.5
134.9
129.0
126.9
126.7
125.8
53.9
38.5
36.4
31.2
29.6
20.3
14.1
f1 (ppm)

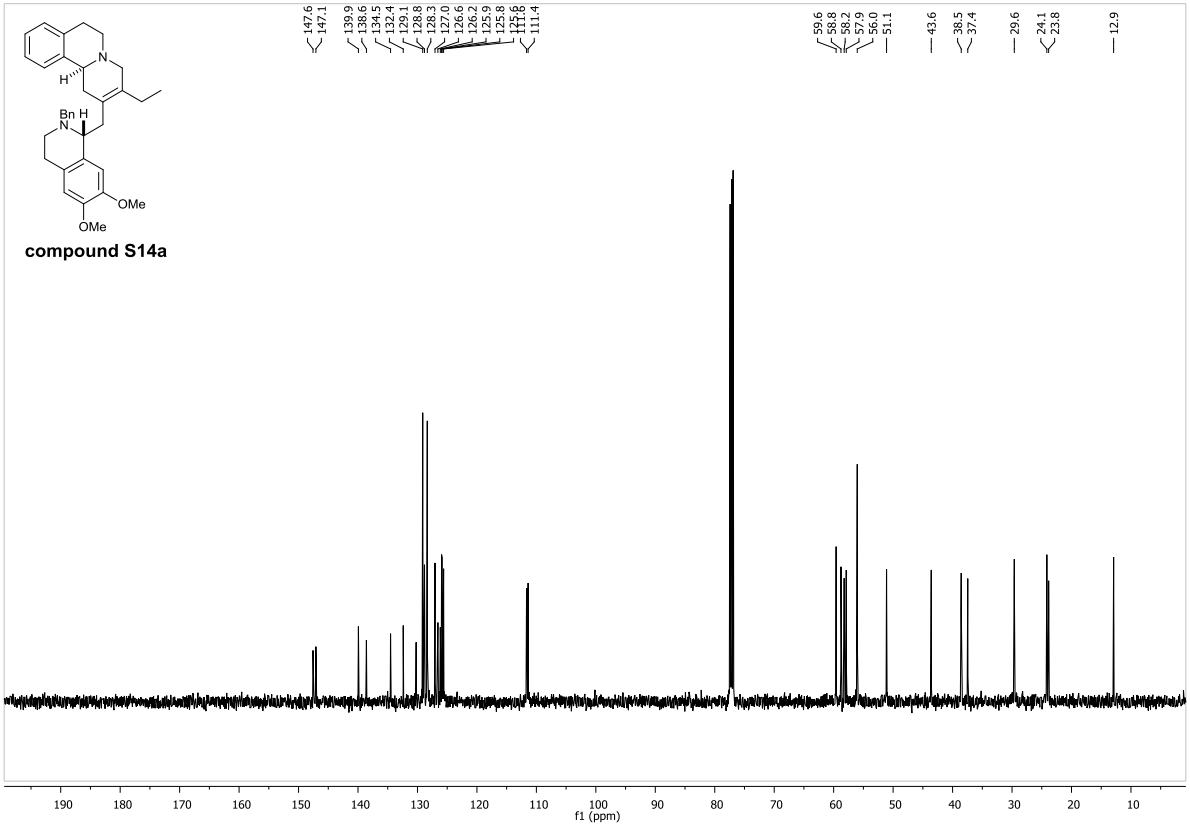

MeO
MeO
NBn
I
compound 25
1.00
5.77
1.01
1.98
2.86
4.82
1.93
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

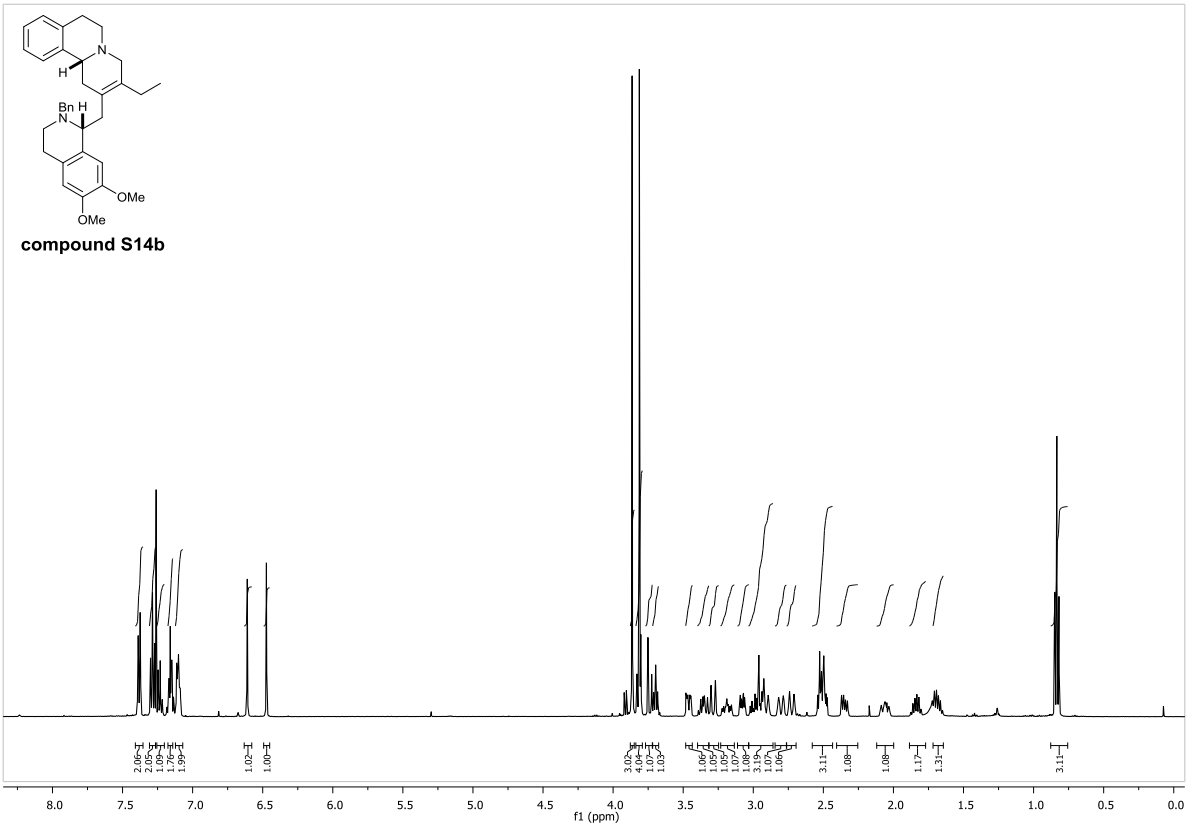

164.6
158.3
149.0
133.2
131.6
129.4
129.2
129.0
117.0
115.2
110.9
63.0
55.9
55.5
47.4
24.9
MeO
MeO
NBn
I
compound 25
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

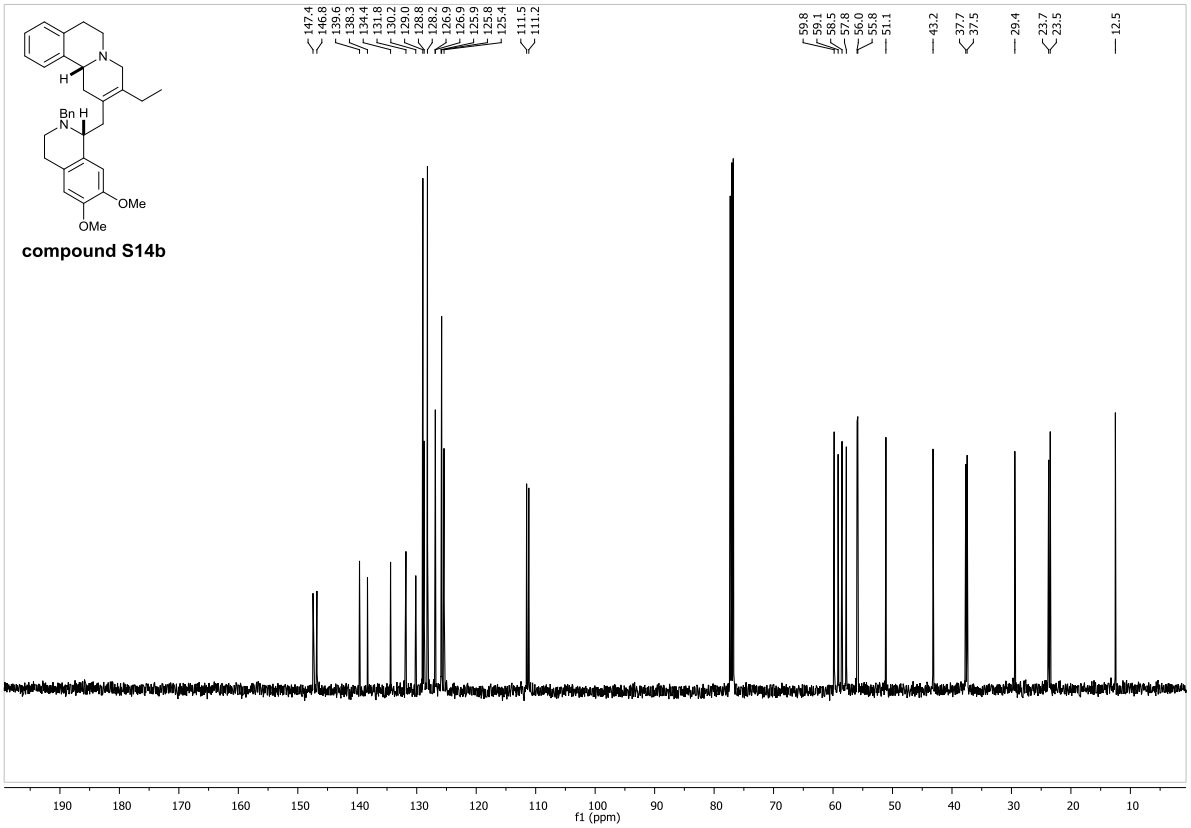

Bn
N
O
OMe
OMe
compound 23
19.26
1.74
1.76
1.02
1.05
1.72
1.71
1.00
2.77
1.72
1.02
3.05
5.07
9.29
1.69
2.75
16.62
13.67
1.77
8.22
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

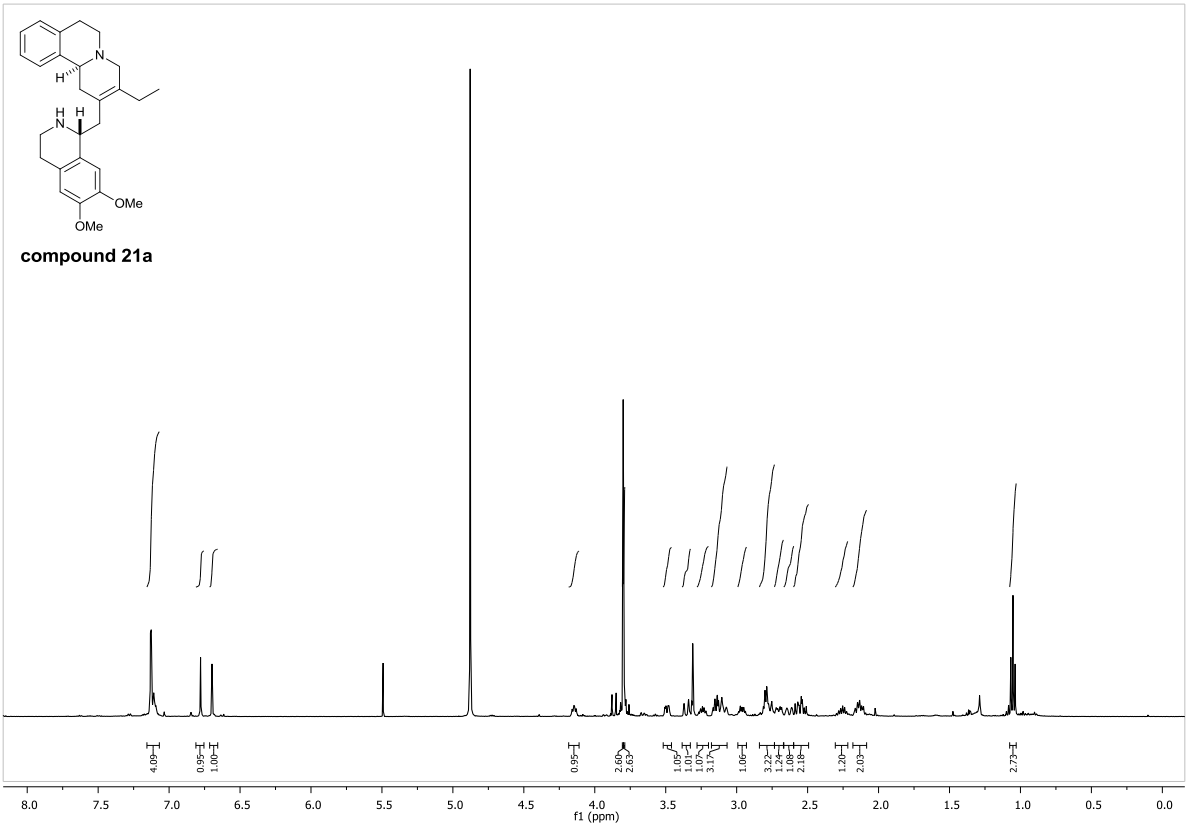

Bn
N
O
OMe
OMe
compound 23
165.9
165.7
147.4
144.4
139.2
136.4
135.0
132.5
129.2
129.1
129.0
128.9
128.3
128.2
127.2
127.1
126.5
126.4
126.2
125.8
111.7
110.9
110.8
58.8
58.8
57.8
57.6
56.1
56.0
55.9
55.9
53.7
53.5
43.5
43.1
40.4
38.4
38.2
38.2
23.5
22.7
20.4
20.3
14.4
14.3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

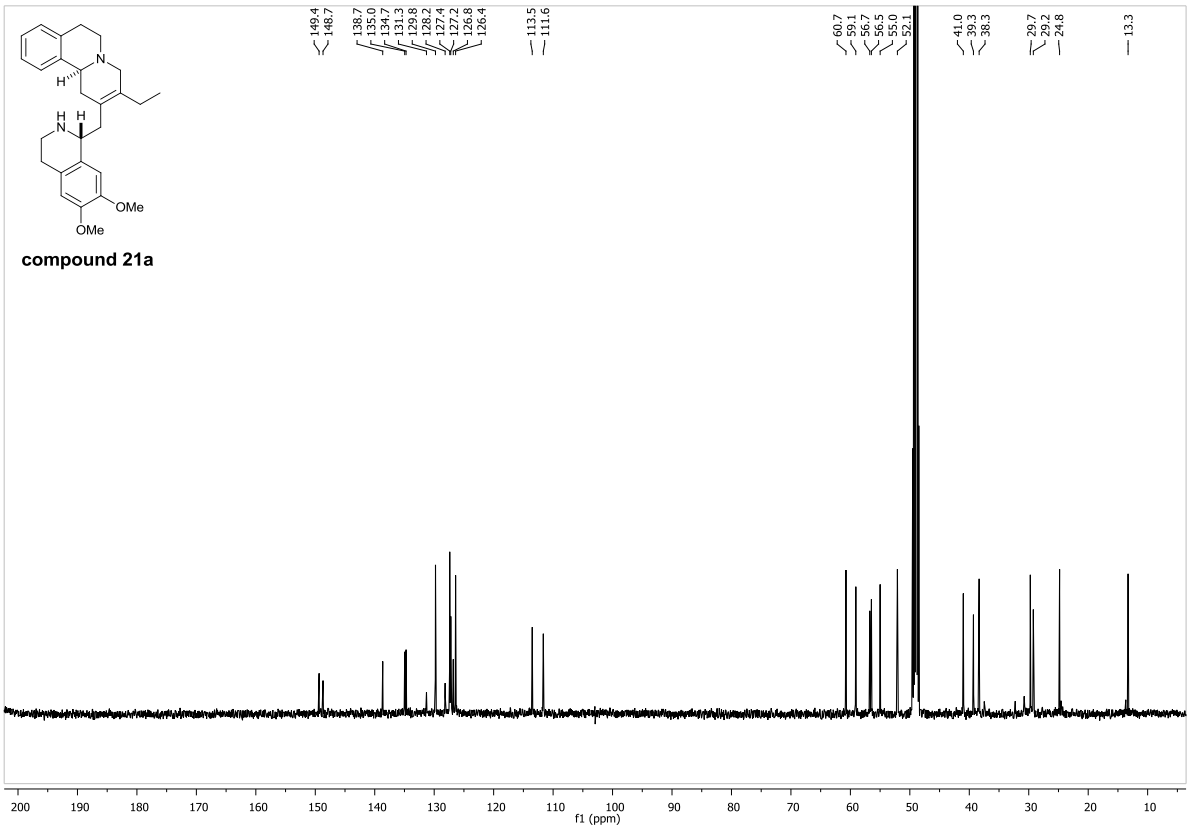

Bn H
N
OMe
OMe
compound S14a
f1 (ppm)

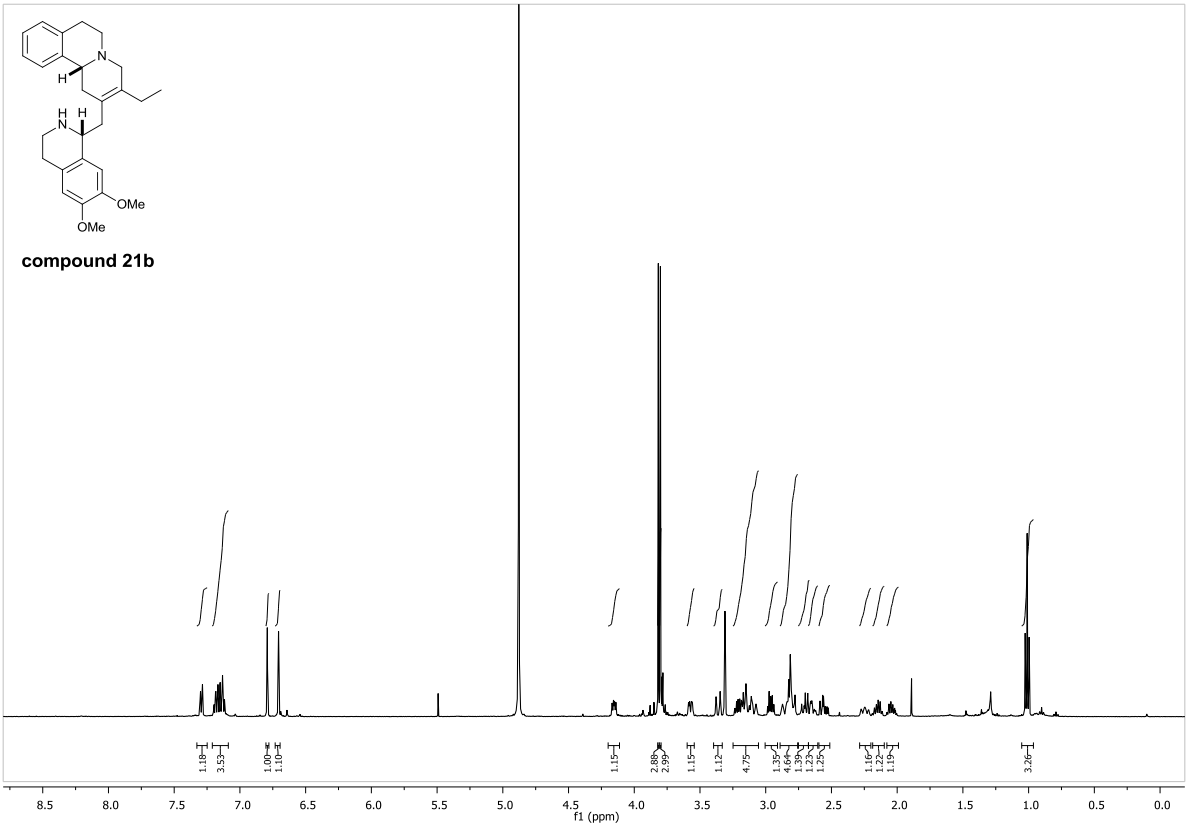

Bn H
N
OMe
OMe
compound S14a
f1 (ppm)

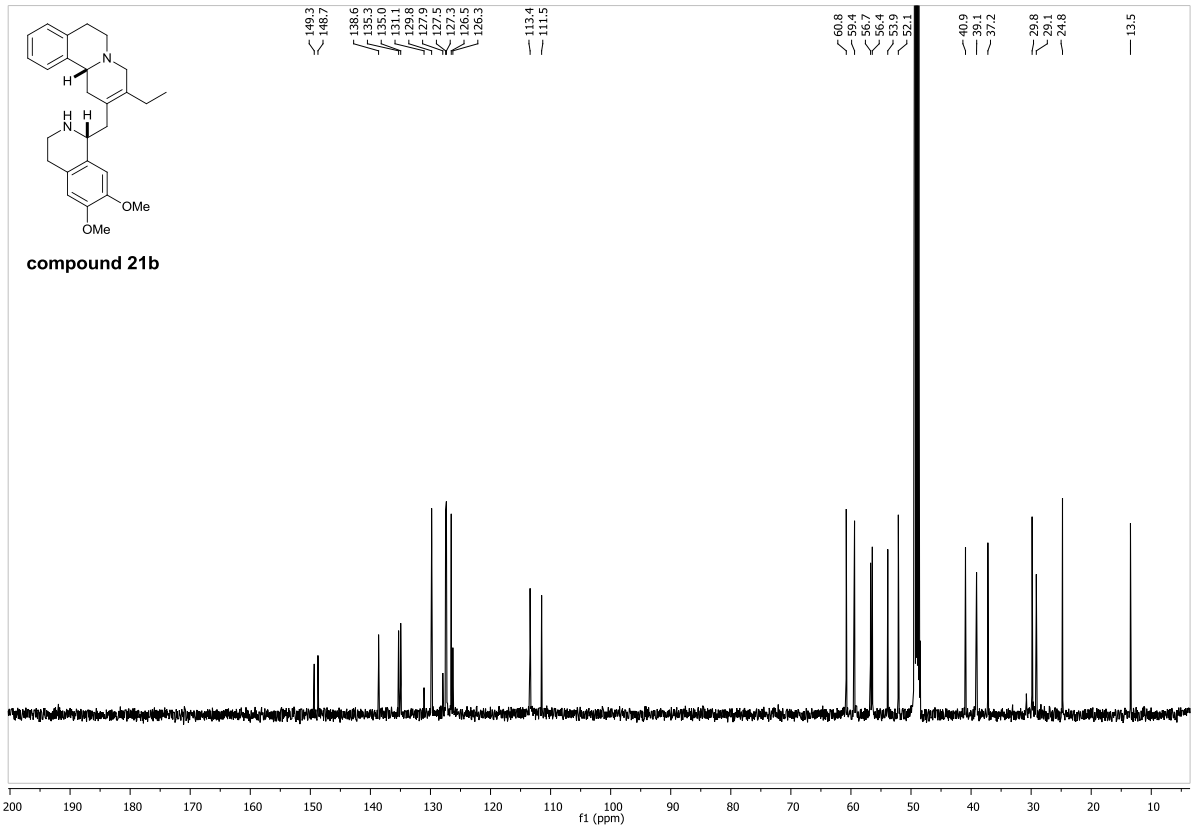

Bn H
N
H
N
OMe
OMe
compound S14b
f1 (ppm)

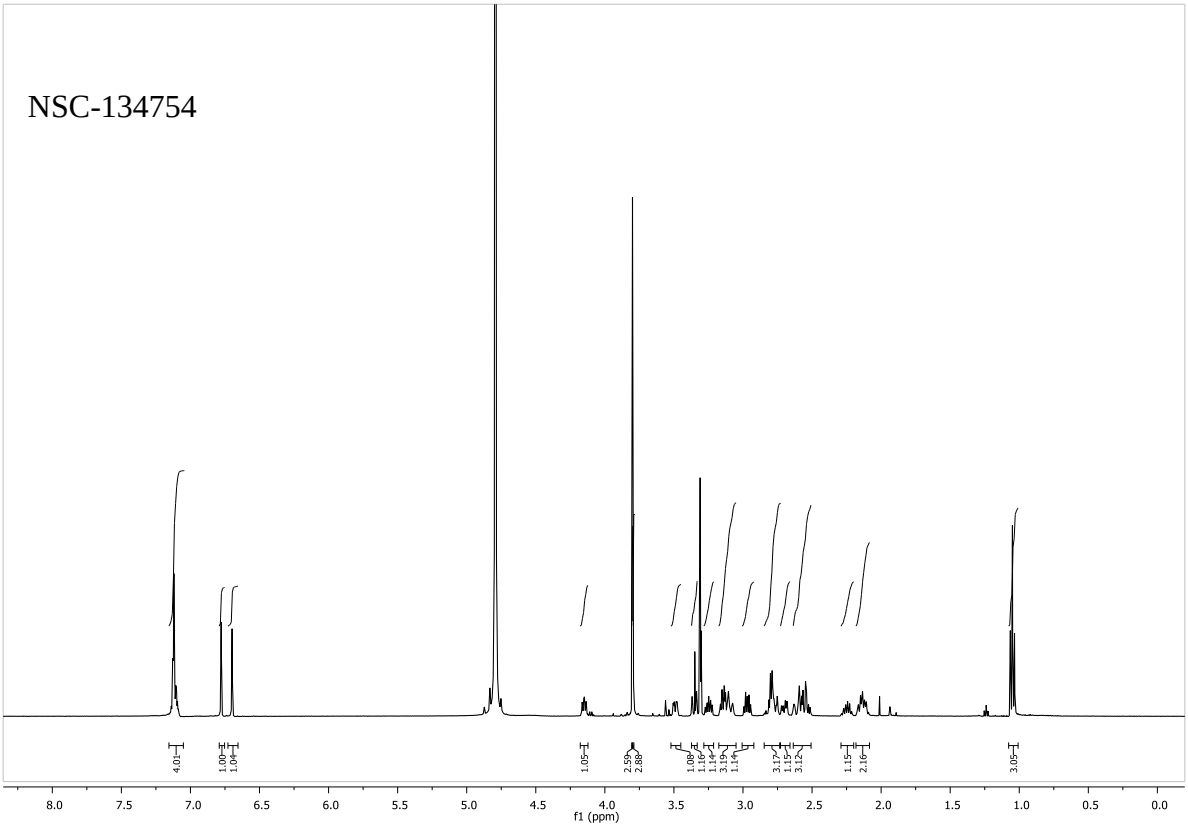

Bn H
N
H
N
OMe
OMe
compound S14b
147.4
146.8
139.6
138.3
134.4
131.8
130.2
129.0
128.8
128.2
126.9
126.9
125.9
125.8
125.4
111.5
111.2
59.8
59.1
58.5
57.8
56.0
55.8
51.1
43.2
37.7
37.5
29.4
23.7
23.5
12.5
f1 (ppm)


OMe
OMe
compound 21a
4.09
0.95
1.00
0.95
2.60
2.63
1.05
1.01
1.07
3.17
1.06
3.22
1.24
1.08
2.18
1.20
2.03
2.73
f1 (ppm)


OMe
OMe
compound 21a
149.4
148.7
138.7
135.0
134.7
131.3
129.8
128.2
127.4
127.2
126.8
126.4
113.5
111.6
60.7
59.1
56.7
56.5
55.0
52.1
41.0
39.3
38.3
29.7
29.2
24.8
13.3
f1 (ppm)


OMe
OMe
compound 21b
f1 (ppm)


OMe
OMe
compound 21b
149.3
148.7
138.6
135.3
135.0
131.1
129.8
127.9
127.5
127.3
126.5
126.3
113.4
111.5
60.8
59.4
56.7
56.4
53.9
52.1
40.9
39.1
37.2
29.8
29.1
24.8
13.5
f1 (ppm)


NSC-134754
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1.00
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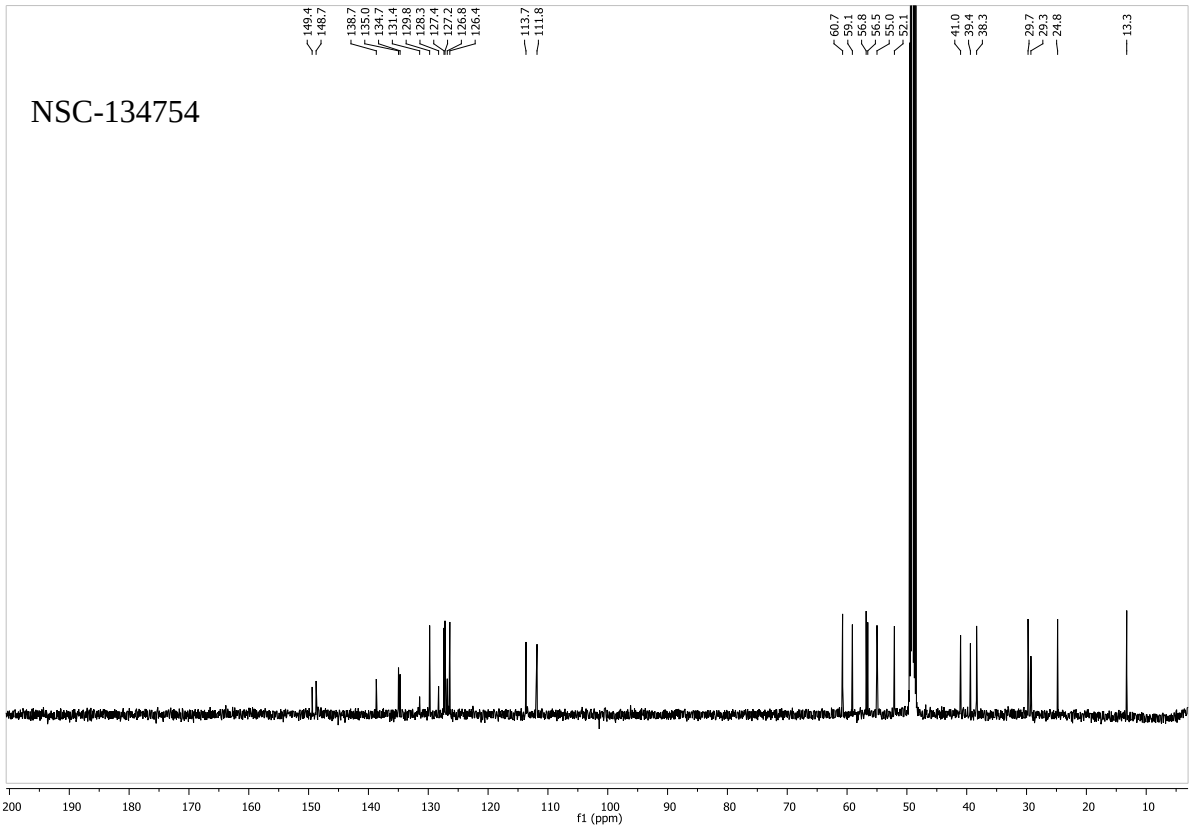
1.14
3.16
1.14
3.17
1.15
3.12
1.15
2.16
3.05
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


149.4
148.7
138.7
135.0
134.7
131.4
129.8
128.3
127.4
127.2
126.8
126.4
113.7
111.8
60.7
59.1
56.8
56.5
55.0
52.1
41.0
39.4
38.3
29.7
29.3
24.8
13.3
NSC-134754
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

Luciferase reporter assay conditions:

U2OS human osteosarcoma cells were used (as described previously)[8] expressing a luciferase reporter gene fused to a triple tandem repeat of a HRE (U2OS-HRE-Luc). Cells were treated with the compounds at 10 μM or 5 μM in hypoxia (1% O_2, 5% CO_2 and 94% N_2) in an LEEC dual gas incubator at 37°C for 16 hours. Following incubation cells were immediately washed twice with ice cold PBS buffer. Passive lysis buffer (100 μL, Promega) was added and the lysates were incubated for 10 minutes at room temperature and then centrifuged. Cell lysate (20μL) was pipetted into a 96 well plate and the relative light unit (RLU) recorded immediately after the addition of luciferase reagent (100μl, Promega) using a luminometer (Dynex Technologies. Worthing, United Kingdom). All compounds were prepared and stored in DMSO (2%) and DMSO was added to untreated cells as a control.

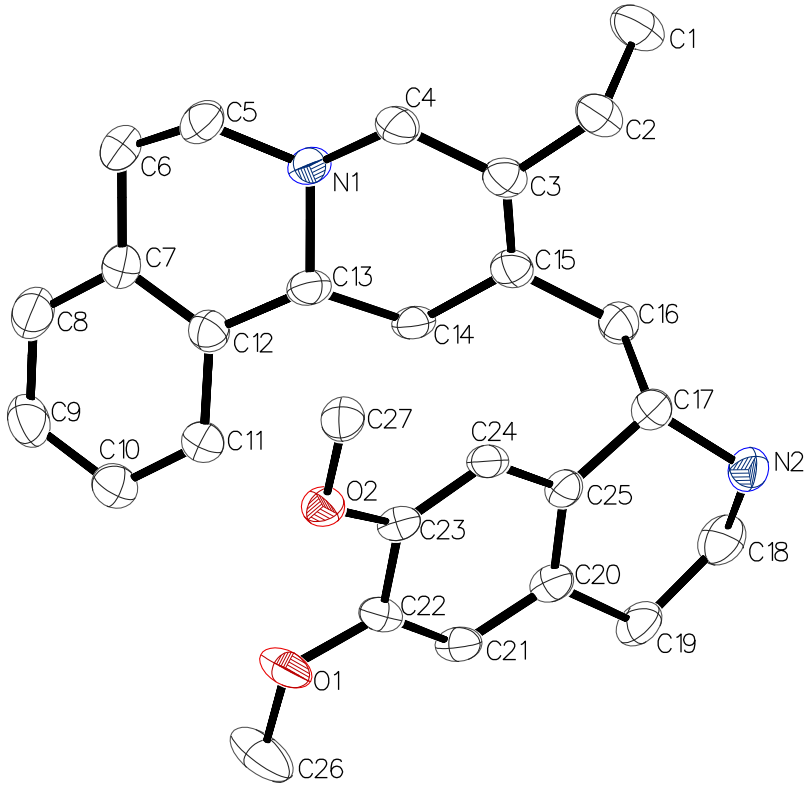
Collection of X-Ray data:

Single crystals of $C_{27}H_{39}N_2O_9S_{1.5}$ were selected and mounted on a MiTeGen sample holder on a Bruker SMART CCD 6000 diffractometer. The crystal was kept at 120 K during data collection. Using Olex2[9], the structure was solved with the olex2.solve[10] structure solution program using Charge Flipping and refined with the olex2.refine[11] refinement package using Gauss-Newton minimisation.

Table S1. X-ray crystallographic data for the structure of **21**

Parameter	**21**
Formula	$C_{27}H_{36}N_2O_2$ x H_2O x HSO_4 x 0.5 SO_4
Mr	1167.38
Crystal system	Monoclinic
Space group	C2/*c*
T (K)	120
a (Å)	31.44(2)
b (Å)	8.720(5)
c (Å)	22.886(12)
α (°)	90
β (°)	117.22(4)
γ (°)	90
V (Å^3)	5580(6)
Z	4
density (calc, g/cm^{-3})	1.3897
wavelength (Å)	0.71073
abs. coef (mm^{-1})	0.210
F(000)	2491
crystal size (mm^3)	0.36 x 0.21 x 0.19
theta range for data collection	2.45 – 26.00
index ranges	-31 < h < 43 -11 < k < 11 -31 < l < 31
reflections collected	19949
independent reflections	5459
refinement method	full-matrix least-squares on F^2
data/restraints/parameters	5459/62/377
goodness of fit on F^2	0.9214
final R indices	R_1 = 0.0775 wR_2 = 0.2142
largest diff peak and hole [eÅ^{-3}]	1.0669 and -1.0170

Figure S1 ORTEP drawing of the molecular structure of the cation of **21** as determined by X-ray diffraction experiments.



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