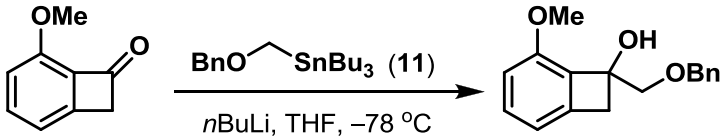
Supporting Information Available

I) Experimental Procedures and Physical Data for Compounds

General Procedures. Reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), and toluene were dried and distilled according to the standard protocols. Methanol (MeOH), *N*,*N*'-dimethylformamide (DMF), dimethylsulfoxide (DMSO), acetonitrile (CH_3CN), and acetone were purchased in anhydrous form and used without further purification. Ethyl acetate (EtOAc), Et_2O, CH_2Cl_2, hexanes and water (H_2O) were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layers chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60 F_{254}) using UV light as visualizing agent and an ethanolic solution of ammonium molybdate or potassium permanganate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on an Agilent 400-MR DD2 or Agilent vrms-500 Magnetic Resonance System

and calibrated using residue undeuterated solvent as internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on an IRTracer-100 spectrometer and Bruker TENSOR27 spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker (compact) Ultra High Resolution ESI Q-TOF mass spectrometer. Optical rotation ([α]) was recorded on a Jasco P-1030 polarimeter.

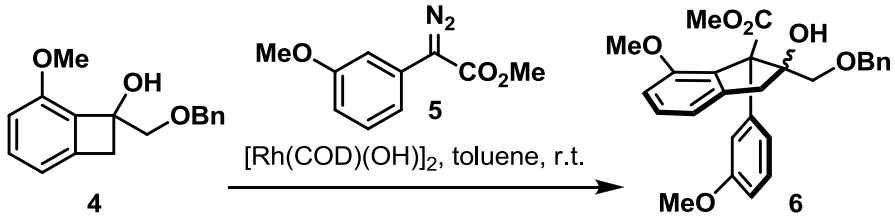
Tertiary Alcohol 4



10 **4**

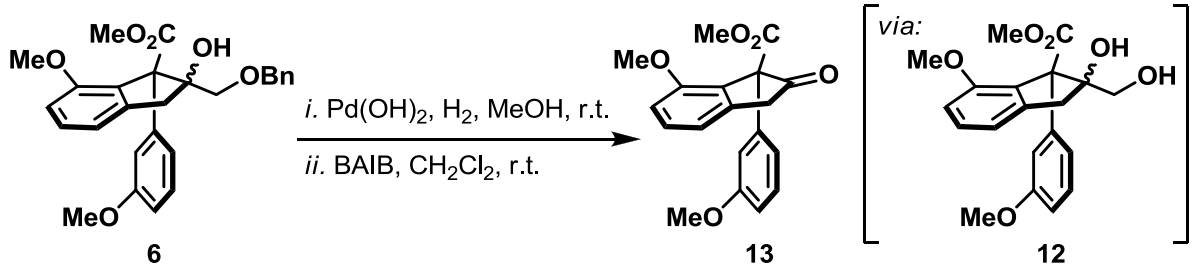
To a stirred solution of (benzyloxymethyl)tri-*n*-butylstannane[1] (**11**, 6.42 g, 15.60 mmol) in THF (45.0 mL) at –78 °C was added *n*-butyllithium (2.5 M in hexanes, 6.24 mL, 15.60 mmol). The resulting mixture was stirred for 30 min before a solution of ketone **10**[2] (2.20 g, 14.86 mmol) in THF (22.0 mL) was added. The resulting mixture was stirred for 20 min before it was quenched with NH_4Cl (30 mL, sat. aq.), extracted with EtOAc (3 × 30 mL), combined organic layer washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 9:1) to afford tertiary alcohol **4** (3.62 g, 90%) as a yellow oil. **4**: R_f = 0.21 (silica gel, hexanes:EtOAc 9:1); IR (film) ν_{max} 3427, 2928, 2864, 1707, 1608, 1478, 1259, 1071, 772, 735, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 4.4 Hz, 4H), 7.25–7.18 (m, 1H), 7.18–7.11 (dd, 1H), 6.66 (d, *J* = 7.1 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.1 Hz, 1H), 3.80 (d, *J* = 9.5, 1.2 Hz, 1H), 3.78 (s, 3H), 3.58 (d, *J* = 9.4 Hz, 1H), 3.27 (d, *J* = 14.0 Hz, 1H), 3.19–3.15 (m, 1H), 3.08 ppm (dd, *J* = 14.0, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 143.9, 138.1, 131.4, 131.1, 128.6, 127.9, 127.9, 116.2, 112.5, 78.6, 75.7, 73.7, 56.7, 44.4 ppm; HRMS calcd. For $C_{17}H_{18}O_3Na^+$ $[M + Na]^+$ 293.1154, found 293.1151.

Tertiary Alcohol 6



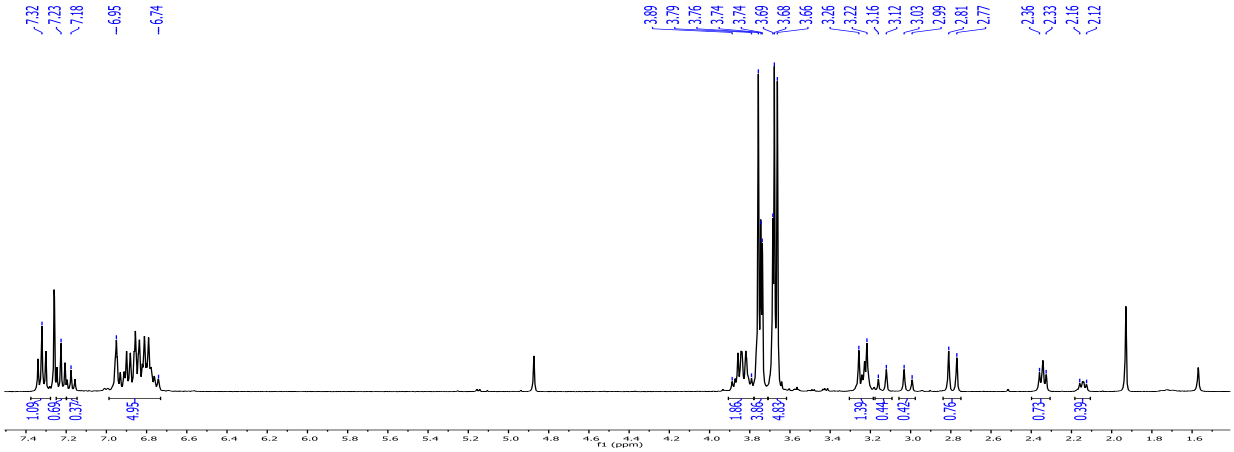
To a stirred solution of tertiary alcohol **4** (4.31 g, 15.9 mmol) and diazoester **5**[3] (3.45 g, 16.76 mmol) in toluene (25.0 mL) at 0 °C was added $[Rh(COD)(OH)]_2$ (61.0 mg, 0.13 mmol). The resulting mixture was stirred for 10 min then warmed to room temperature and stirred for 3 h before it was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 4:1) to afford tertiary alcohol **6** (*ca.* 3:1 mixture of diastereoisomers, 5.5 g, 77%) as a yellow foam. **6**: R_f = 0.34 (silica gel, hexanes:EtOAc 7:3); IR (film) ν_{max} 3544, 2951, 2836, 1735, 1590, 1480, 1266, 1218, 1082, 735, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, *ca.* 3:1 mixture of diastereoisomers): δ 7.37–7.27 (m, 5H), 7.17 (t, *J* = 8.1 Hz, 0.7H), 7.12 (t, *J* = 8.0 Hz, 0.3H), 6.98 (t, *J* = 2.2 Hz, 0.7H), 6.92 (d, *J* = 7.5 Hz, 0.3H), 6.90–6.85 (m, 2H), 6.84–6.75 (m, 3H), 4.64–4.57 (m, 1H), 4.51 (d, *J* = 12.2 Hz, 0.7H), 4.40 (d, *J* = 11.9 Hz, 0.3H), 3.89 (d, *J* = 9.4 Hz, 0.7H), 3.73–3.71 (m, 2H), 3.70 (s, 2H), 3.68 (s, 2H), 3.66 (s, 2H), 3.57 (s, 2H), 3.30 (d, *J* = 9.6 Hz, 0.3H), 3.19 (d, *J* = 16.4 Hz, 1H), 3.12 (d, *J* = 16.0 Hz, 0.3H), 3.06 (d, *J* = 15.8 Hz, 0.3H), 2.95 (d, *J* = 16.1 Hz, 0.7H), 2.41 ppm (s, 0.7H); ^{13}C NMR (100 MHz, $CDCl_3$, *ca.* 3:1 mixture of diastereoisomers): δ 174.1, 172.4, 159.0, 158.6, 157.0, 156.7, 143.8, 142.8, 138.3, 137.8, 137.2, 130.6, 130.0, 129.9, 128.5, 128.3, 127.8, 127.8, 127.5, 127.3, 123.0, 121.4, 117.8, 117.3, 116.9, 115.3, 112.5, 112.3, 110.1, 109.5, 86.6, 85.1, 74.5, 73.9, 73.6, 73.3, 68.0, 67.6, 55.5, 55.3, 55.1, 52.5, 52.1, 43.3, 42.8 ppm; HRMS calcd. For $C_{27}H_{28}O_6Na^+$ $[M + Na]^+$ 471.1778, found 471.1778.

Keto Ester 13



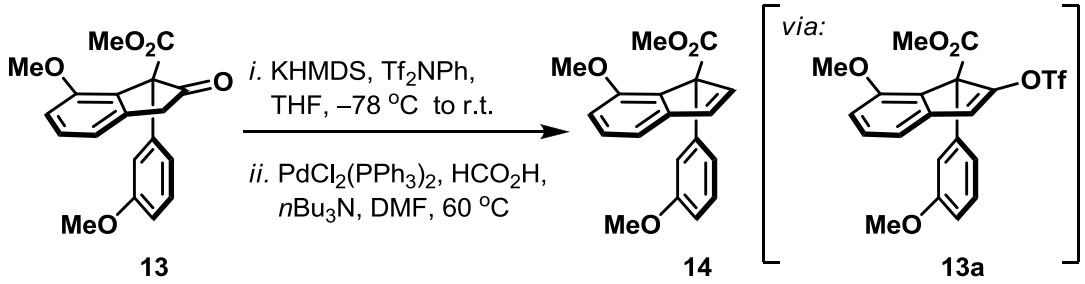
(i) To a stirred solution of benzyl ether **6** (5.5 g, 12.3 mmol) in MeOH (50.0 mL) at room temperature was added $Pd(OH)_2$ on carbon (5 wt% on carbon, 18% wt/wt, 1.0 g). The resulting mixture was purged with hydrogen gas (balloon bubbling) for 10 min then stirred under an atmosphere of hydrogen (balloon) for 15 h. The resulting mixture was filtered through a pad of Celite® and eluted with MeOH (50 mL), and concentrated under reduced pressure to afford crude diol **12** which was used directly in the subsequent reaction.

Representative ^{1}H NMR (400 MHz, $CDCl_3$, crude) of diol 12



(ii) To a stirred solution of diol **12** (obtained above) in CH_2Cl_2 (40.0 mL) at room temperature was added BAIB (3.96 g, 12.3 mmol). The resulting mixture was stirred for 3.5 h before it was transferred to a separatory funnel and washed with pH7 phosphate buffer (50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 8:2→6:4) to afford keto ester **13** (3.8 g, 94% over two steps) as a colorless oil. **13**: R_f = 0.70 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 2931, 1741, 1261, 1121, 1045, 786, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (t, *J* = 7.9 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 1H), 7.01 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.89 (t, *J* = 2.2 Hz, 1H), 6.87–6.80 (m, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 3.69 (s, 3H), 3.61 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.6, 169.7, 159.4, 156.7, 138.4, 135.5, 130.4, 129.0, 128.6, 121.0, 117.4, 114.9, 113.4, 109.9, 69.0, 55.7, 55.3, 53.0, 42.5 ppm; HRMS calcd. For $C_{19}H_{18}O_5Na^+$ [M + Na]$^+$ 349.1052, found 349.1049.

Indene Methyl Ester 14

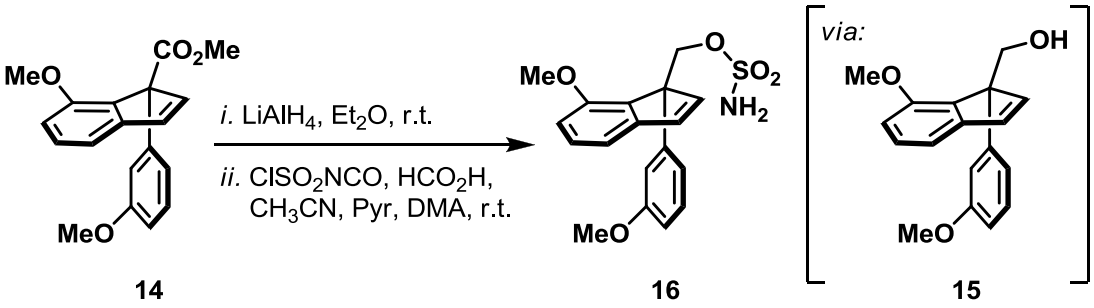


(i) To a stirred solution of ketone **13** (3.8 g, 11.6 mmol) in THF (100.0 mL) at –78 °C was added KHMDS (0.7 M in toluene, 18.2 mL, 12.8 mmol). The resulting mixture was stirred for 30 min before a solution of Tf_2NPh (5.4 g, 15.1 mmol) in THF (30.0 mL) was added. The resulting mixture was stirred for 15 min then warmed to room temperature and stirred for 2 h before it was quenched with NH_4Cl (200 mL, sat. aq.), extracted with EtOAc (3 × 50 mL), combined organic layer washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 9.5:1) to afford triflate **13a** (5.3 g, 99%) as a yellow oil. **13a**: R_f = 0.30 (silica gel, hexanes:EtOAc 8:2); IR (film) ν_{max} 2955, 2844, 1426, 1209, 1137, 827, 734, 603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (ddd, J = 8.4, 7.4, 0.6 Hz, 1H), 7.22 (t, 1H), 7.02 (dd, J = 7.5, 0.8 Hz, 1H), 6.89–6.79 (m, 4H), 6.66 (s, 1H), 3.76 (s, 3H), 3.74 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 159.5, 155.4, 154.6, 140.9, 134.4, 130.8, 129.7, 129.3, 127.4, 127.1, 123.4, 120.3, 120.1, 118.5 (q, $J_{C\text{-}F}$ = 320.8 Hz), 117.5, 116.9, 115.8, 114.3, 113.5, 111.1, 66.5, 55.7, 55.3, 53.2 ppm; HRMS calcd. For $C_{20}H_{17}F_3O_7SNa^+$ $[M + Na]^+$ 481.0545, found 481.0541.

(ii) To a stirred solution of triflate **13a** (obtained above) in DMF (23.0 mL) at room temperature was added $PdCl_2(PPh_3)_2$ (0.41 g, 0.58 mmol) and nBu$_3$N (8.78 mL, 34.8 mmol). The resulting mixture was purged with argon (balloon bubbling) for 5 min before HCO_2H (0.91 mL, 23.2 mmol) was added. The resulting mixture was placed into a pre-heated (60 °C) oil bath and stirred for 1.5 h before it was cooled to room temperature, diluted with HCl (1 N aq., 150 mL), extracted with EtOAc (3 × 50 mL), combined organic layer washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 9:1) to afford indene methyl ester **14** (3.5 g, 96%) as a colorless oil. **14**: R_f = 0.65 (silica gel,

hexanes:EtOAc 7:3); IR (film) ν_{max} 2948, 2835, 1733, 1475, 1265, 1017, 811, 722, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (t, 1H), 7.19 (t, 1H), 7.99 (d, 1H), 6.97–6.89 (m, 2H), 6.85 (dd, *J* = 5.4, 1.3 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 2H), 6.58 (d, *J* = 5.4 Hz, 1H), 3.76 (d, *J* = 1.4 Hz, 6H), 3.71 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 159.3, 156.0, 145.4, 140.2, 138.1, 133.0, 132.4, 130.1, 128.9, 120.5, 115.0, 114.2, 112.4, 110.2, 68.4, 55.7, 55.3, 52.7 ppm; HRMS calcd. For $C_{19}H_{18}O_4Na^+$ $[M + Na]^+$ 333.1103, found 333.1096.

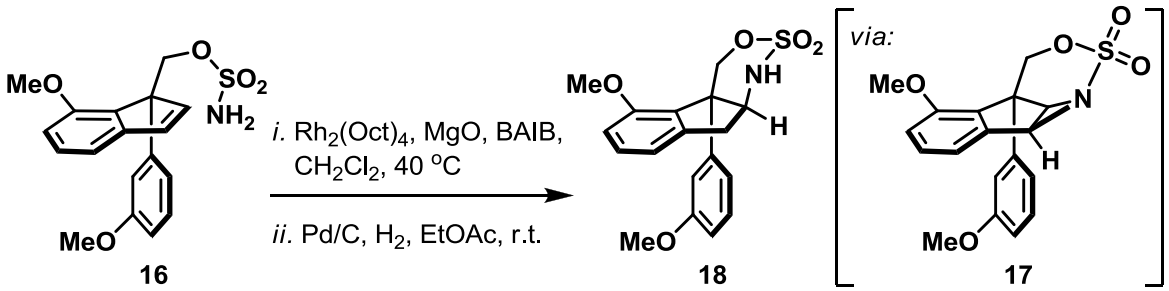
Sulfamate 16



(i) To a stirred suspension of $LiAlH_4$ (0.45 g, 12.2 mmol) in Et_2O (40.0 mL) at 0 °C was added a solution of methyl ester **14** (3.5 g, 11.1 mmol) in Et_2O (40.0 mL). The resulting mixture was stirred for 5 min then warmed to room temperature and stirred for 1.5 h before it was cooled to 0 °C and quenched sequentially with H_2O (5.5 mL), NaOH (15% aq., 5.5 mL) and H_2O (6 mL). The resulting mixture was warmed to room temperature and stirred for 5 min before it was filtered through a pad of Celite®, eluted with EtOAc (100 mL), and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 8:2) to afford alcohol **15** (3.03 g, 97%) as a colorless oil. **15**: R_f = 0.50 (silica gel, hexanes:EtOAc 6:4); IR (film) ν_{max} 3464, 2941, 2835, 1596, 1473, 1259, 1052, 808, 729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 8.3, 7.4 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.03 (dd, *J* = 7.4, 0.8 Hz, 1H), 6.88 (ddd, *J* = 7.8, 1.8, 1.0 Hz, 1H), 6.84 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.77–6.73 (m, 1H), 6.69 (d, *J* = 5.4 Hz, 1H), 6.40 (d, *J* = 5.4 Hz, 1H), 4.43 (d, *J* = 10.9 Hz, 1H), 3.98 (d, *J* = 10.8 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 2.93 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 155.2, 146.7, 143.4, 139.7, 135.0, 130.3, 129.7, 129.4, 119.6, 115.6, 113.6, 111.6, 109.3, 65.7, 65.0, 55.7, 55.2 ppm; HRMS calcd. For $C_{18}H_{18}O_3Na^+$ $[M + Na]^+$ 305.1154, found 305.1149.

(ii) To a stirring solution of chlorosulfonyl isocyanate (2.34 mL, 26.6 mmol) at 0 °C was added formic acid (1.42 mL, 26.6 mmol) with rapid stirring. The resulting mixture was stirred for 5 min before CH_3CN (7.0 mL) was added and the resulting mixture was stirred at room temperature for 6 h. The resulting mixture was cooled to 0 °C before a solution of alcohol **15** (obtained above) and pyridine (2.14 mL, 26.6 mmol) in DMA (9.0 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred for 1.5 h before it was transferred to a separatory funnel containing water (100 mL). The resulting mixture was extracted with EtOAc (3 × 150 mL), combined organic layer washed with $NaHCO_3$ (100 mL, sat. aq.), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 7:3) to afford sulfamate **16** (2.59 g, 67%) as a colorless oil. **16**: R_f = 0.35 (silica gel, hexanes:EtOAc 7:3); IR (film) ν_{max} 3308, 3240, 2936, 2839, 1360, 1263, 1167, 955, 799, 540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 8.3, 7.4 Hz, 1H), 7.17 (t, 1H), 6.98 (d, 1H), 6.90–6.88 (m, 2H), 6.80 (d, *J* = 5.5 Hz, 1H), 6.78–6.73 (m, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 6.63 (d, *J* = 5.5 Hz, 1H), 5.32 (d, *J* = 9.5 Hz, 1H), 4.65 (s, 2H), 4.47 (d, *J* = 9.5 Hz, 1H), 3.74 (s, 3H), 3.71 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 155.8, 145.8, 142.3, 138.3, 133.0, 131.7, 130.2, 129.3, 119.5, 115.1, 113.5, 112.1, 109.5, 72.2, 60.9, 55.5, 55.3 ppm; HRMS calcd. For $C_{18}H_{19}NO_5SNa^+$ $[M + Na]^+$ 384.0882, found 384.0879.

Cyclic Sulfamate 18

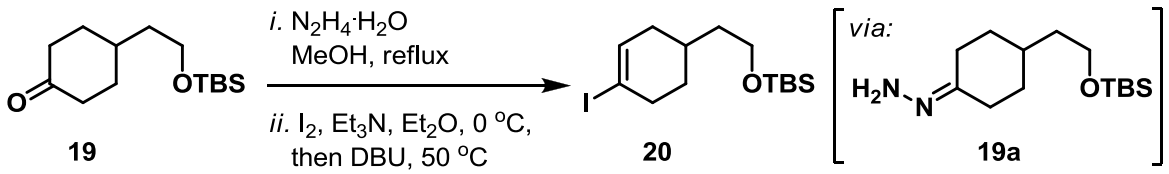


(i) To a stirred solution of sulfamate **16** (2.59 g, 7.17 mmol) in CH_2Cl_2 (70.0 mL) at room temperature was added MgO (0.65 g, 16.5 mmol), $Rh_2(Oct)_4$ (55.0 mg, 0.14 mmol) and BAIB (2.77 g, 8.6 mmol) sequentially. The resulting mixture was warmed to 40 °C and stirred for 4 h before it was cooled to room temperature, filtered through a pad of Celite® and eluted with CH_2Cl_2 (30 mL), and concentrated under reduced pressure. The resulting residue was purified

by flash column chromatography (silica gel, hexanes:EtOAc 8:2) to afford aziridine **17** (2.25 g, 87%) as a white amorphous solid. **17**: R_f = 0.35 (silica gel, hexanes:EtOAc 7:3); IR (film) ν_{max} 2943, 2839, 1737, 1584, 1487, 1375, 1266, 1185, 957, 780, 695, 452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 8.3, 7.5 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.26 (dd, *J* = 7.5, 0.8 Hz, 1H), 6.94 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.88 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 6.78 (ddd, *J* = 7.7, 1.8, 0.9 Hz, 1H), 6.71 (dd, *J* = 2.6, 1.7 Hz, 1H), 5.37 (d, *J* = 10.4 Hz, 1H), 4.97 (d, *J* = 10.4 Hz, 1H), 4.23 (d, *J* = 3.6 Hz, 1H), 4.05 (d, *J* = 3.6 Hz, 1H), 3.79 (s, 3H), 3.67 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 155.9, 139.4, 137.2, 132.3, 131.2, 130.2, 119.3, 118.8, 113.4, 112.8, 112.7, 74.2, 58.0, 55.4, 52.6, 49.7 ppm; HRMS calcd. For $C_{18}H_{17}NO_5SNa^+$ $[M + Na]^+$ 382.0725, found 382.0727.

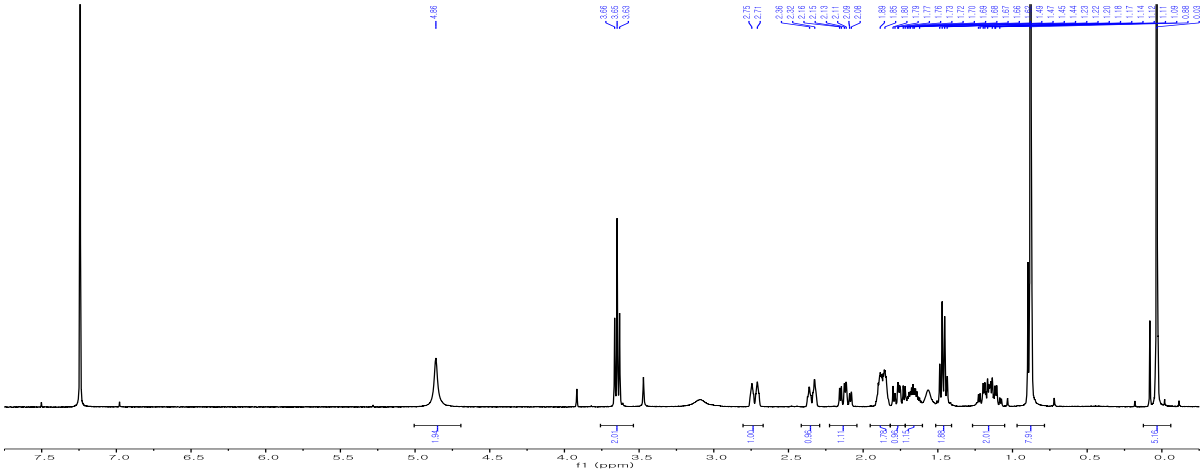
(ii) To a stirred solution of aziridine **17** (obtained above) in EtOAc (20.0 mL) at room temperature was added palladium on carbon (10 wt% on carbon, 1.00 g, 0.94 mmol). The resulting mixture was purged with hydrogen gas (balloon bubbling) for 1 min then stirred under an atmosphere of hydrogen (balloon) for 3 h. The resulting mixture was filtered through a pad of Celite® and eluted with acetone (100 mL), and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 4:1) to afford cyclic sulfamate **18** (2.12 g, 94%) as a white foam. **18**: R_f = 0.50 (silica gel, hexanes:EtOAc 7:3); IR (film) ν_{max} 3256, 2945, 2842, 1730, 1584, 1424, 1363, 1182, 957, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (t, *J* = 7.9 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.79 (ddd, *J* = 7.8, 5.9, 2.1 Hz, 2H), 6.63 (t, *J* = 2.2 Hz, 1H), 5.43 (d, *J* = 12.2 Hz, 1H), 5.14 (d, *J* = 12.3 Hz, 1H), 4.53 (dd, *J* = 10.2, 5.2 Hz, 1H), 4.24 (d, *J* = 10.2 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.04 (dd, *J* = 16.4, 5.4 Hz, 1H), 2.67 ppm (d, *J* = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 158.7, 142.5, 140.4, 130.9, 129.9, 127.3, 119.7, 118.8, 114.1, 112.5, 110.6, 76.8, 67.5, 55.6, 55.6, 55.3, 36.6 ppm; HRMS calcd. For $C_{18}H_{19}NO_5SNa^+$ $[M + Na]^+$ 384.0882, found 384.0877.

Vinyl Iodide 20



(i) To a stirred solution of ketone **19**[4] (0.56 g, 2.18 mmol) in MeOH (3.0 mL) at room temperature was added hydrazine hydrate (0.40 mL, 8.73 mmol). The resulting mixture was warmed to reflux and stirred for 14 h before it was cooled to room temperature and concentrated under reduced pressure to afford crude hydrazone **19a**, which was used directly in the subsequent reaction.

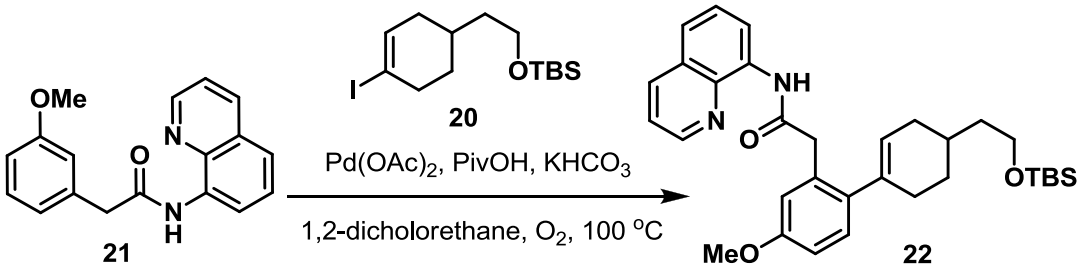
Representative ^{1}H NMR (400 MHz, $CDCl_3$, crude) of hydrazone 19a



(ii) To a stirred solution of hydrazone **19a** (crude, 0.52 g, 1.92 mmol) in Et_2O (18.0 mL) at 0 °C was added Et_3N (2.70 mL, 19.4 mmol) and I_2 (0.97 g, 3.82 mmol). The resulting mixture was stirred for 25 min before it was warmed to room temperature, diluted with Et_2O (15 mL) and quenched with $Na_2S_2O_3$ (20 mL, sat. aq.), and stirred for 45 min before it was extracted with Et_2O (3 × 10 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was dissolved in THF (3.0 mL) and treated with DBU (0.70 mL, 4.69 mmol) at room temperature, and warmed to 50 °C and stirred for 4 h before it was cooled to room temperature and concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (10 mL) and washed with HCl (1 N aq., 10 mL), organic layer separated and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:Et_2O 20:1) to afford vinyl iodide **20** (0.38 g, 48% over two steps) as a yellow amorphous solid. **20**: R_f = 0.80 (silica gel, hexanes:Et_2O 20:1); IR (film) ν_{max} 2927, 2857, 1472, 1256, 1104, 835, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.26 (ddd, J = 6.0, 3.3, 1.9 Hz, 1H), 3.63 (t, J = 6.5 Hz, 2H), 2.56–2.46 (m, 2H), 2.20–2.07 (m, 1H), 1.84–1.66 (m,

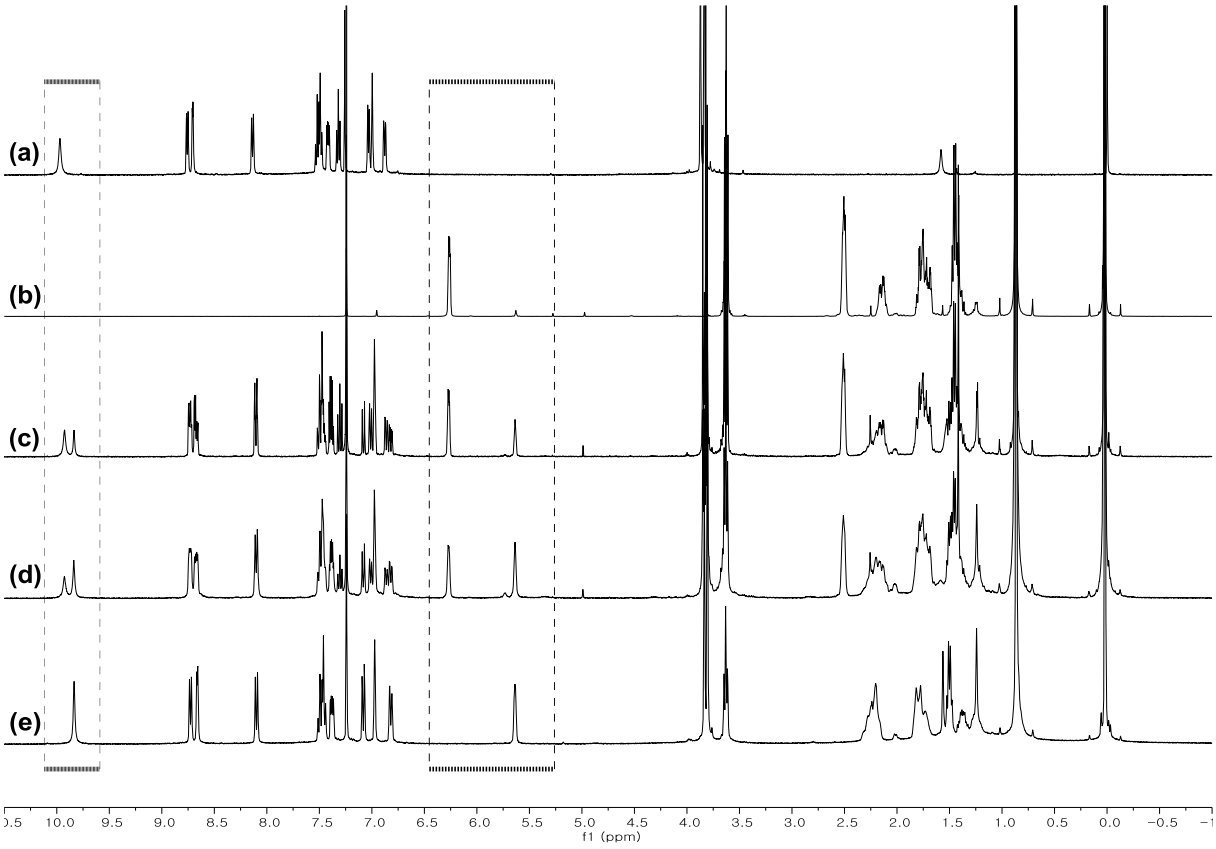
3H), 1.55–1.35 (m, 3H), 0.87 (s, 9H), 0.02 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.8, 96.4, 60.8, 39.2, 38.7, 35.5, 31.4, 28.7, 25.9, 18.3, –5.3 ppm.

Quinolinamide 22

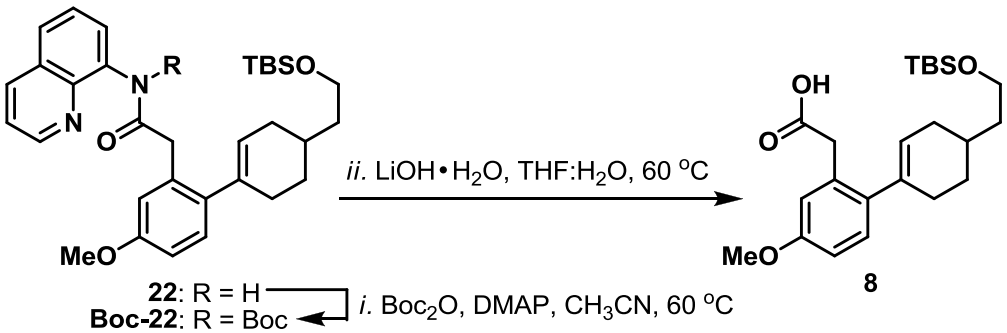


To a stirred solution of quinolinamide **21**[5] (0.16 g, 0.55 mmol) and vinyl iodide **20** (0.30 g, 0.82 mmol) in 1,2-dicholoroethane (6.0 mL) at room temperature was added $Pd(OAc)_2$ (12.3 mg, 55 μmol), PivOH (11.2 mg, 0.11 mmol) and $KHCO_3$ (0.11 g, 1.09 mmol). The resulting mixture was evacuated and filled with oxygen (3 ×) before it was placed into a pre-heated (100 °C) oil bath and stirred for 14 h. The resulting mixture was cooled to room temperature, filtered through a pad of silica gel and eluted with hexane:EtOAc (1:1, 150 mL), and concentrated under reduced pressure. The resulting residue was resubjected to the identical aerobic CH-alkenylation condition [$Pd(OAc)_2$ (12.3 mg, 55 μmol), PivOH (11.2 mg, 0.11 mmol) and $KHCO_3$ (0.11 g, 1.09 mmol), 1,2-dichloroethane (6.0 mL), O_2, 100 °C, 14 h] and the resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 10:1→1:1) to afford quinolinamide **22** (0.15 g, 53%) as a yellow amorphous solid. **22**: R_f = 0.40 (silica gel, hexanes:Et_2O 1:1); IR (film) ν_{max} 3352, 2927, 2856, 1687, 1525, 1485, 1255, 1100, 834 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 8.73 (d, *J* = 7.3 Hz, 1H), 8.66 (d, *J* = 4.3 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.54–7.45 (m, 2H), 7.45–7.37 (m, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.97 (s, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 5.63 (d, *J* = 4.3 Hz, 1H), 3.83 (s, 2H), 3.81 (d, *J* = 1.6 Hz, 3H), 3.63 (t, *J* = 6.9 Hz, 2H), 2.36–2.14 (m, 3H), 1.84–1.75 (m, 3H), 1.59–1.45 (m, 2H), 1.38 (tt, *J* = 16.2, 7.8 Hz, 1H), 0.87 (s, 9H), 0.06 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 158.5, 148.0, 138.5, 137.4, 136.1, 134.5, 133.1, 130.0, 127.8, 127.3, 126.7, 121.5, 121.4, 116.3, 115.2, 113.4, 77.2, 61.3, 55.3, 43.1, 39.3, 32.1, 31.0, 29.8, 29.3, 26.0, 18.3, –5.3 ppm; HRMS calcd. For $C_{32}H_{43}N_2O_3SiNa^+$ $[M + H]^+$ 531.3037, found 531.3041.

Representative ^{1}H NMR (400 MHz, $CDCl_3$) analysis illustrating the progression of aerobic CH-alkenylation reaction leading to the formation quinolinamide 22 [vinyl iodide (20):quinolinamide (21) = 1.5:1 at the beginning of reaction]: (a) quinolinamide 21; (b) vinyl iodide 20; (c) crude reaction mixture after 14 hours; (d) crude reaction mixture after 28 hours; (e) quinolinamide 22



Carboxylic Acid 8

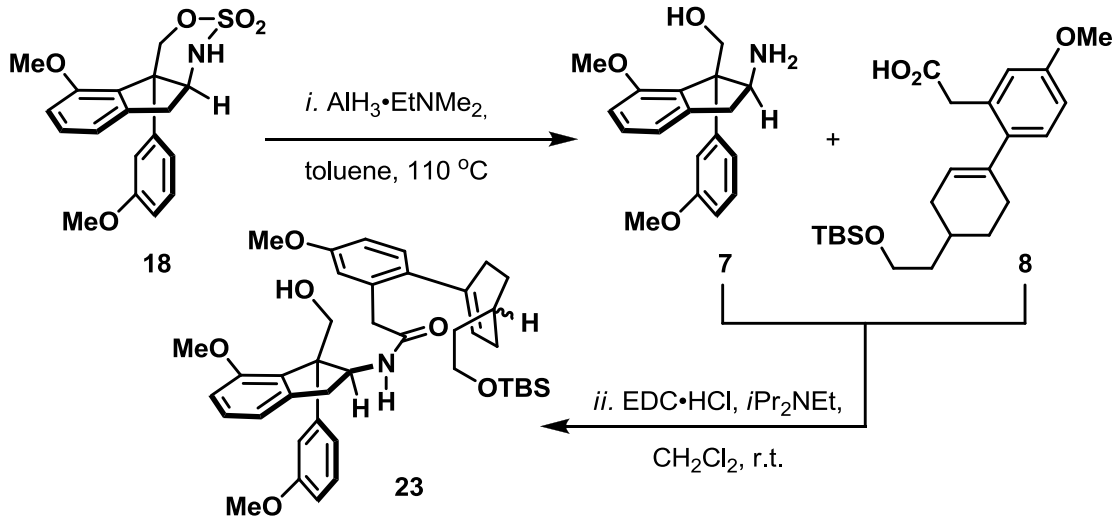


(i) To a stirred solution of quinolinamide **22** (0.24 g, 0.45 mmol) in CH_3CN (4.5 mL) at room temperature was added Boc_2O (0.30 g, 1.34 mmol) and DMAP (27.4 mg, 0.23 mmol). The resulting mixture was warmed to 60 ℃ and stirred for 16 h before it was cooled to room

temperature, filtered through a pad of silica gel and eluted with hexane:EtOAc (2:1, 150 mL), and concentrated under reduced pressure to afford Boc-carbamate **Boc-22**, which was used directly in the subsequent reaction.

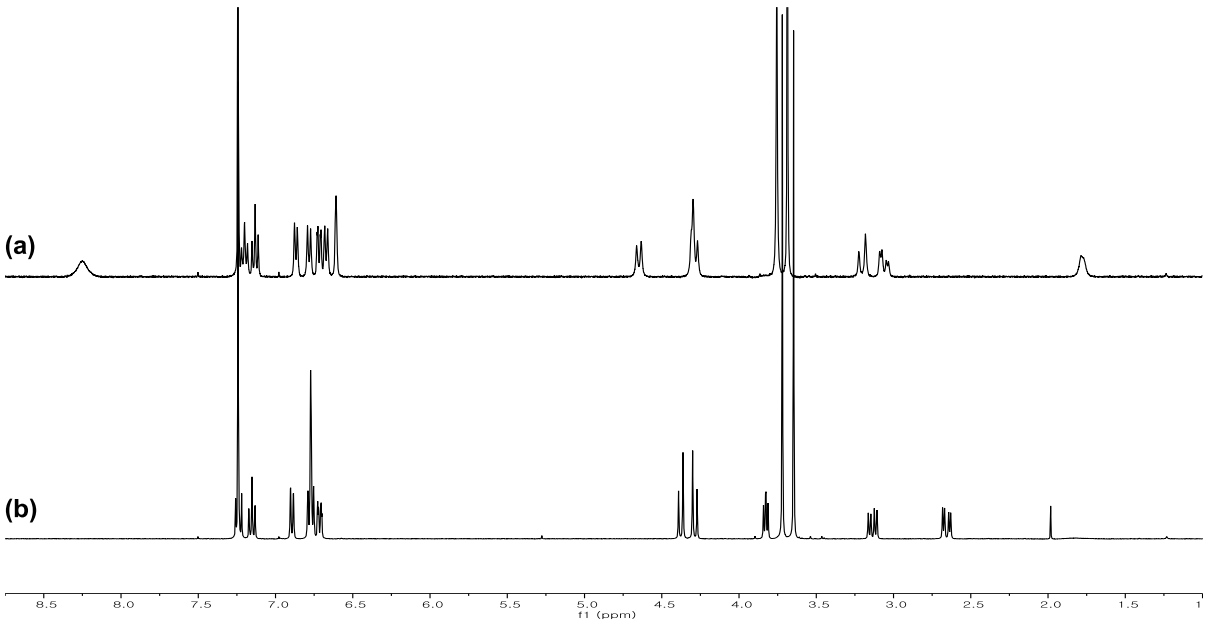
(ii) To a stirred solution of Boc-carbamate **Boc-22** in THF/H_2O (4.0 mL, 3:1) at room temperature was added LiOH•H_2O (0.16 g, 3.81 mmol). The resulting mixture was warmed to 60 ℃ and stirred for 2 h before it was cooled to room temperature, diluted with HCl (1 N aq., 20 mL) and extracted with EtOAc (3 × 15 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 8:1→1:6) to afford carboxylic acid **8** (0.14 g, 78% over two steps) as a yellow amorphous solid and recovered Boc-8-aminoquinoline (82.0 mg, 75% over two steps). **8**: R_f = 0.59 (silica gel, hexanes:EtOAc 1:2); IR (film) ν_{max} 2927, 1709, 1608, 1257, 1101, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.03 (d, *J* = 8.1 Hz, 1H), 6.86–6.71 (m, 2H), 5.49 (br s, 1H), 3.77 (s, 3H), 3.70 (t, *J* = 6.8 Hz, 2H), 3.64 (s, 2H), 2.34–2.11 (m, 3H), 1.90–1.66 (m, 3H), 1.63–1.49 (m, 2H), 1.43–1.29 (m, 1H), 0.90 (s, 9H), 0.06 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.9, 158.1, 137.2, 137.0, 131.8, 129.6, 126.5, 115.5, 112.8, 61.3, 55.2, 39.2, 38.6, 32.1, 30.7, 29.7, 29.3, 26.0, 18.4, –5.3 ppm; HRMS calcd. For $C_{23}H_{36}O_4SiNa^+$ $[M + Na]^+$ 427.2275, found 427.2280.

Hydroxy Amide 23

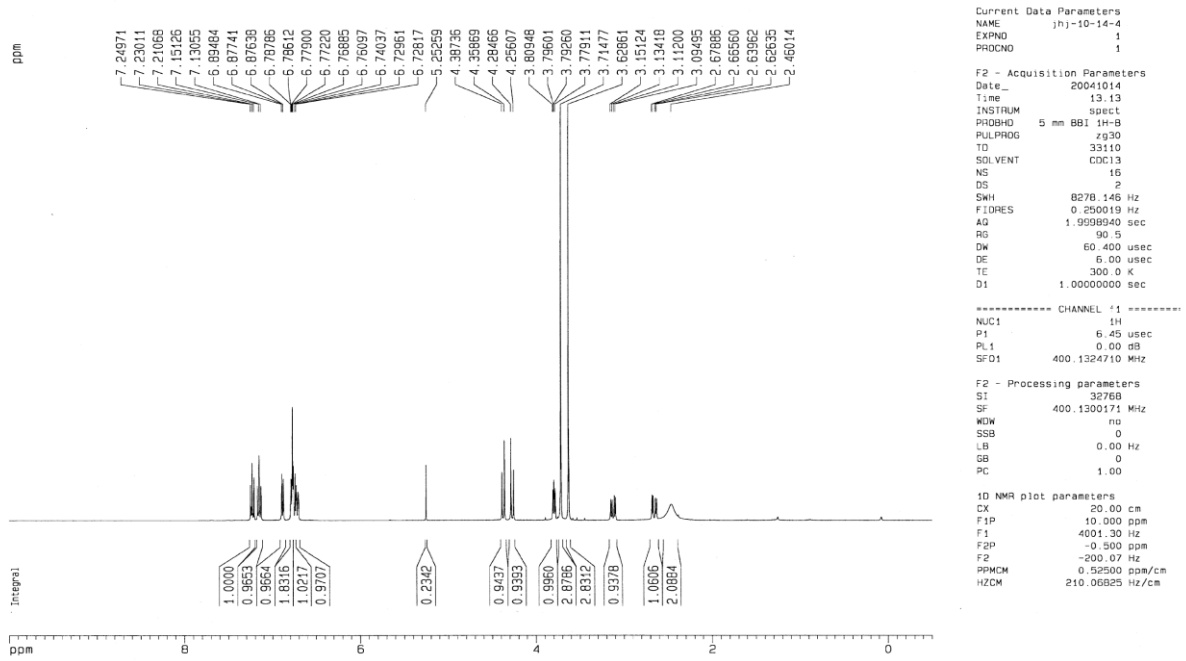


(i) To a stirred solution of cyclic sulfamate **18** (1.0 g, 2.77 mmol) in toluene (30 mL) at room temperature was added AlH_3•$EtNMe_2$ (0.5 M in toluene, 33 mL, 16.6 mmol). The resulting mixture was warmed to 110 ℃ and stirred for 6 h before it was cooled to 0 ℃ and quenched with sodium potassium tartrate (100 mL, sat. aq.). The resulting mixture was warmed to room temperature and stirred for 30 min before it was extracted with EtOAc (3 × 100 mL), combined organic layer washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude amino-alcohol **7** (809 mg, 98%) as a yellow oil.[6,7] Trituation of crude amino-alcohol **7** with CH_3CN afforded a white powdery solid to facilitate transfer and storage. **7**: R_f = 0.17 (silica gel, CH_2Cl_2:MeOH 10:1); IR (film) ν_{max} 3344, 2998, 2938, 2835, 1591, 1481, 1264, 1064, 774 cm^{-1}; ^1H NMR [400 MHz, $CDCl_3$ + 1.0 % NH_4OH(aq.)]: δ 7.24 (t, *J* = 8.3, 1H), 7.15 (t, *J* = 8.3, 1H), 6.89 (dq, *J* = 7.5, 1.0 Hz, 1H), 6.81–6.74 (m, 3H), 6.74–6.68 (m, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 4.29 (d, *J* = 11.5 Hz, 1H), 3.83 (dd, *J* = 6.8, 5.2 Hz, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 3.14 (dd, *J* = 15.7, 6.8 Hz, 1H), 2.66 ppm (dd, *J* = 15.7, 5.2 Hz, 1H); ^{13}C NMR [101 MHz, $CDCl_3$ + 1.0 % NH_4OH(aq.)]: δ 159.4, 157.2, 146.5, 144.2, 131.7, 129.2, 128.9, 119.2, 117.9, 113.2, 110.9, 109.6, 65.9, 65.1, 61.0, 55.3, 55.1, 41.3 ppm; HRMS calcd. For $C_{18}H_{22}NO_3^+$ $[M + H]^+$ 300.1594, found 300.1597.

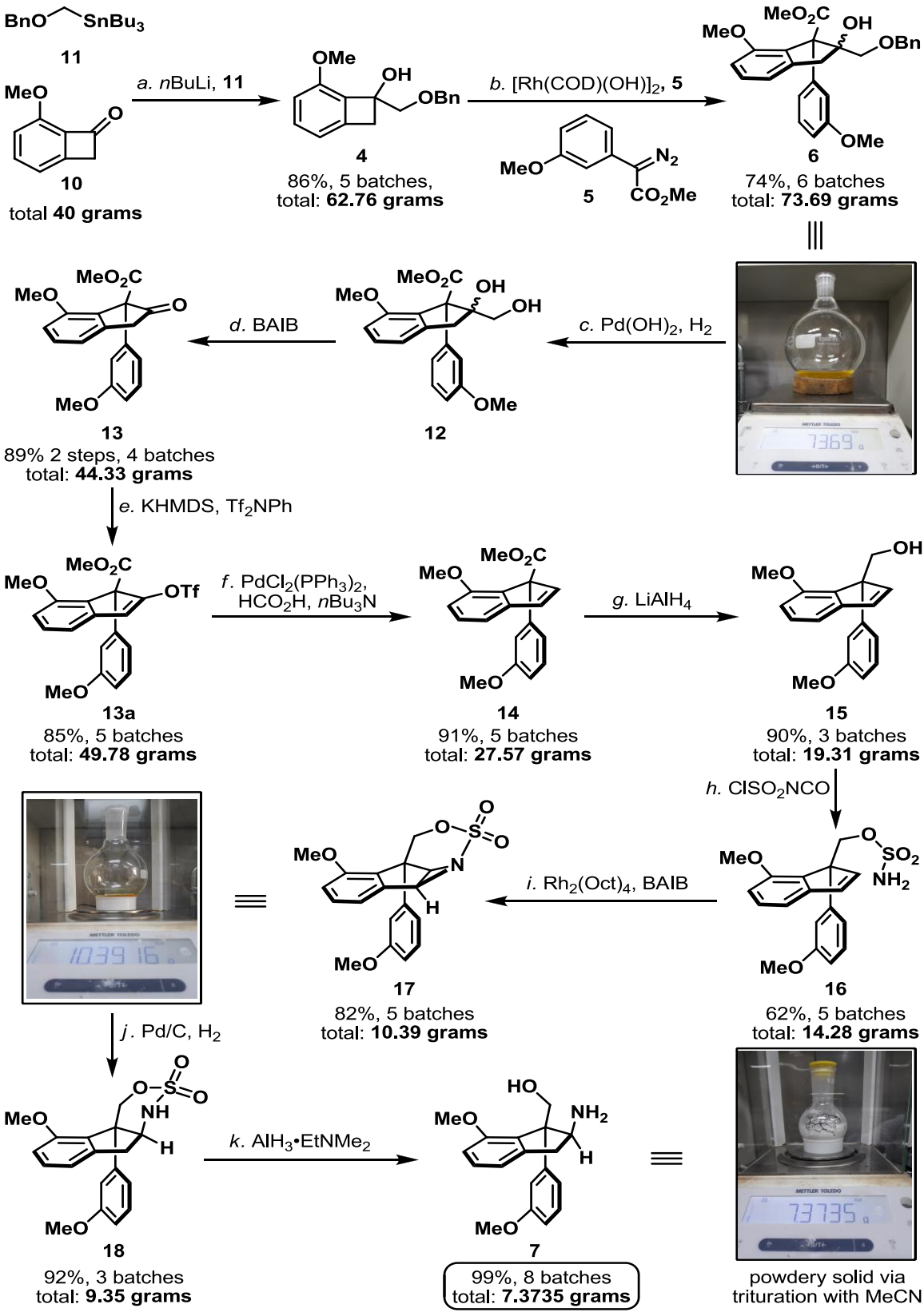
*[Note: ^1H NMR of amino alcohol **7** in deuterated chloroform exhibited significant differences depending on the acid content of the deuterated solvent: ^1H NMR (400 MHz) of amino alcohol **7** in (a) $CDCl_3$; (b) $CDCl_3$ with 1.0 % of NH_4OH(aq.)*



^1H NMR (400 MHz, $CDCl_3$) of amino-alcohol 7 reported by Weinreb and co-worker[6]



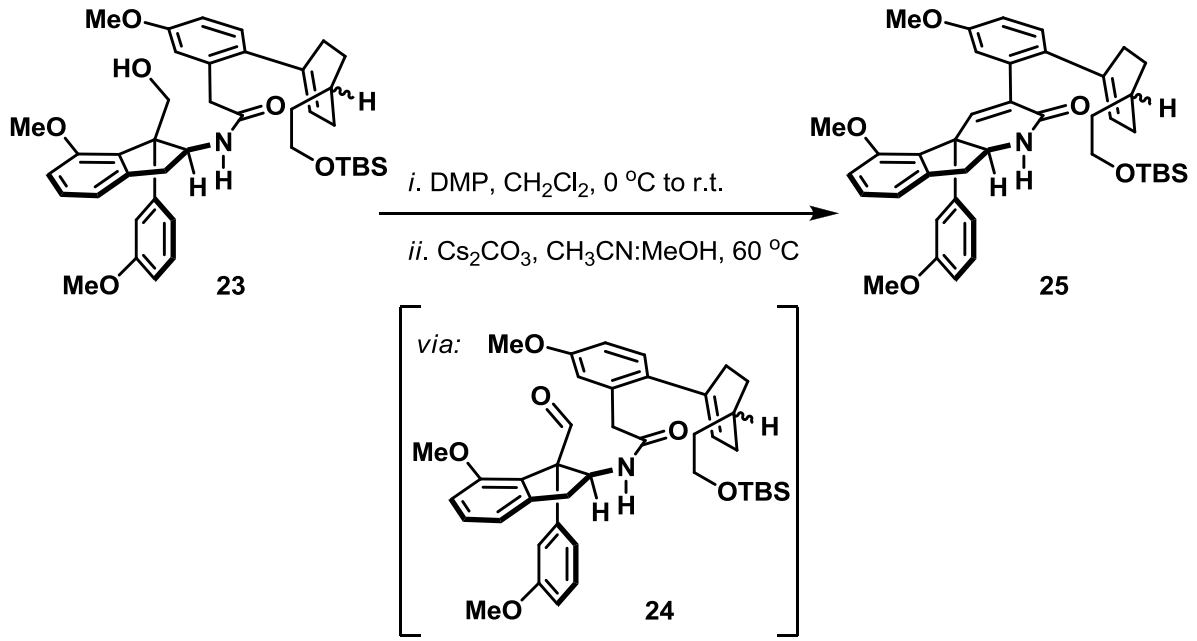
Schematic summary for the gram-scale synthesis of amino-alcohol 7



* % yield represent average yield over the indicated batches

(ii) To a stirred solution of crude amino-alcohol **7** (0.23 g, 0.78 mmol) in CH_2Cl_2 (8.2 mL) at room temperature was added carboxylic acid **8** (0.33 g, 0.82 mmol), EDC•HCl (0.16 mg, 0.84 mmol) and *i*Pr_2NEt (0.3 mL, 1.7 mmol). The resulting mixture was stirred for 14 h before it was quenched with NH_4Cl (10 mL, sat. aq.), extracted with CH_2Cl_2 (3 × 10 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 4:1→1:3) to afford hydroxy amide **23** (0.29 g, 54% over two steps) as a brown amorphous solid. **23**: R_f = 0.50 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 3334, 2927, 2856, 1729, 1648, 1479, 1258, 1099, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 7.31–7.22 (m, 1H), 7.20–7.12 (m, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.94 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.87 (d, *J* = 7.4 Hz, 1H), 6.85–6.77 (m, 2H), 6.75–6.66 (m, 2H), 6.61–6.54 (m, 1H), 6.46 (br t, *J* = 2.2 Hz, 1H), 5.30 (br s, 1H), 4.79–4.86 (m, 1H), 4.21–4.05 (m, 2H), 3.77–3.72 (m, 6H), 3.70–3.65 (m, 5H), 3.49 (s, 2H), 2.99 (dd, *J* = 16.3, 5.9 Hz, 1H), 2.65 (dd, *J* = 16.3, 6.2 Hz, 1H), 2.48 (td, *J* = 9.6, 4.9 Hz, 1H), 2.21–1.98 (m, 2H), 1.72–1.58 (m, 2H), 1.56–1.42 (m, 2H), 1.36–1.22 (m, 2H), 0.90 (s, 9H), 0.07 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 171.7, 159.5, 158.3, 156.7, 156.7, 145.2, 145.1, 144.0, 137.4, 137.4, 137.2, 133.2, 129.8, 129.7, 129.7, 129.5, 129.2, 126.3, 126.3, 119.1, 118.7, 118.6, 114.9, 114.9, 113.2, 113.1, 111.5, 109.2, 109.2, 66.1, 66.0, 62.4, 62.4, 62.1, 62.1, 61.3, 61.3, 55.4, 55.3, 55.0, 41.6, 39.4, 39.3, 38.7, 32.0, 30.9, 30.8, 29.6, 29.4, 29.3, 26.0, 18.4, –5.2, –5.2 ppm; HRMS calcd. For $C_{41}H_{55}NO_6SiNa^+$ $[M + Na]^+$ 708.3691, found 708.3692.

Lactam 25

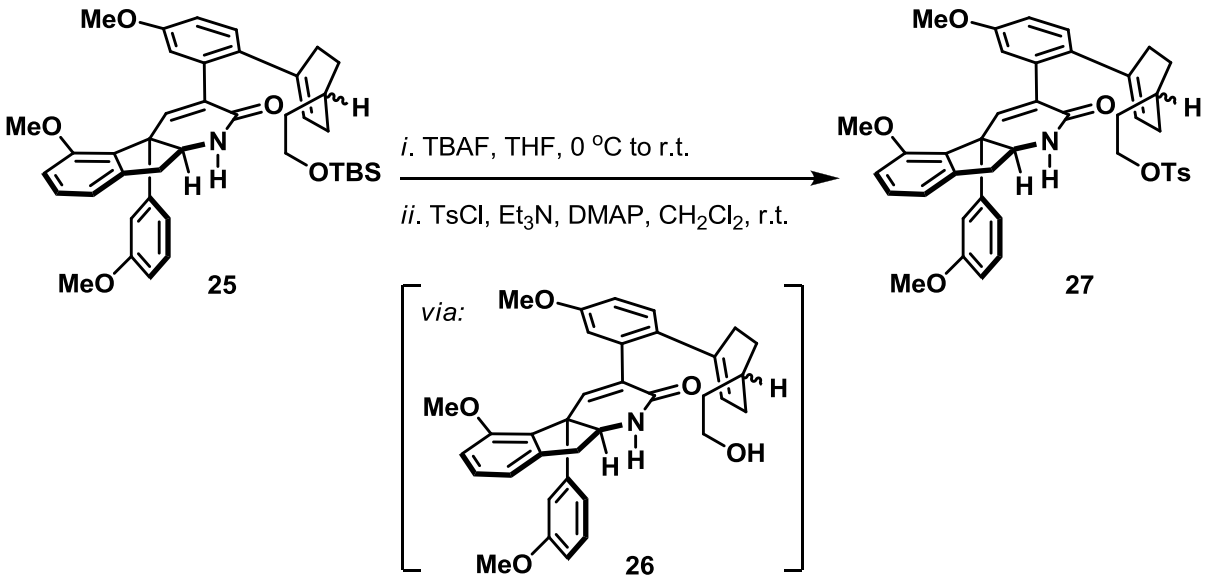


(i) To a stirred solution of alcohol **23** (0.22 g, 0.32 mmol) in CH_2Cl_2 (6.0 mL) at 0 °C was added Dess-Martin periodinane (0.19 g, 0.45 mmol). The resulting mixture was warmed to room temperature and stirred for 4 h before it was quenched with $Na_2S_2O_3$ (5 mL, sat. aq.), extracted with CH_2Cl_2 (3 × 10 mL), combined organic layer washed with $NaHCO_3$ (20 mL, sat. aq.), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 3:1) to afford aldehyde **24** (0.20 g, 93%) as a white amorphous solid. **24**: R_f = 0.54 (silica gel, hexanes:EtOAc 2:1); IR (film) ν_{max} 3406, 2927, 1709, 1605, 1481, 1267, 1087, 834, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 9.66 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 2H), 6.84–6.74 (m, 4H), 6.62–6.54 (m, 2H), 5.46 (s, 1H), 4.75 (dtd, *J* = 9.2, 7.6, 1.6 Hz, 1H), 3.78 (s, 3H), 3.74–3.67 (m, 5H), 3.59 (s, 3H), 3.55–3.39 (m, 2H), 3.31–3.20 (dd, 15.8, 7.2 Hz, 1H), 2.67 (ddd, *J* = 15.8, 7.5, 2.7 Hz, 1H), 2.24–2.06 (m, 3H), 1.86–1.69 (m, 3H), 1.59–1.49 (m, 2H), 1.38 (dq, *J* = 11.1, 5.2 Hz, 1H), 0.90 (s, 9H), 0.06 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 198.6, 198.6, 171.4, 159.8, 158.4, 156.6, 144.5, 139.9, 139.9, 137.4, 137.4, 137.2, 137.2, 133.0, 133.0, 130.8, 130.0, 130.0, 129.4, 126.5, 126.5, 126.2, 126.2, 119.5, 119.5, 117.8, 115.0, 113.4, 113.4, 113.3, 113.2, 112.5, 112.5, 109.9, 69.7, 69.7, 61.4, 61.3, 61.3, 61.3, 55.3, 55.2, 55.1, 41.5, 41.4, 39.4, 39.4,

37.9, 32.1, 32.1, 30.9, 30.9, 29.8, 29.7, 29.3, 29.3, 26.0, 18.4, –5.2 ppm; HRMS calcd. For $C_{41}H_{53}NO_6SiNa^+$ $[M + Na]^+$ 706.3534, found 706.3539.

(ii) To a stirred solution of aldehyde **24** (0.16 g, 0.24 mmol) in CH_3CN/MeOH (10:1, 11 mL) at room temperature was added Cs_2CO_3 (0.31 g, 0.95 mmol). The resulting mixture was placed into a pre-heated (60 ^oC) oil bath and stirred for 8 h before it was cooled to room temperature and concentrated under reduced pressure. The resulting residue was diluted with H_2O/CH_2Cl_2 (1:1, 10 mL), extracted with CH_2Cl_2 (3 × 10 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 4:1→1:3) to afford lactam **25** (99.7 mg, 63%) as an orange foam. *[Note: Intramolecular aldol condensation of aldehyde **24** under the conditions described by Weinreb[6] and Wipf[7] groups (K_2CO_3, MeOH, 60 ^oC) afforded lactam **25** in significantly lower yield]*. **25**: R_f = 0.17 (silica gel, hexanes:EtOAc 2:1); IR (film) ν_{max} 3200, 2927, 1676, 1480, 1255, 1079, 834, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 7.31–7.16 (m, 2H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.91 (dt, *J* = 7.8, 2.2 Hz, 2H), 6.84–6.64 (m, 6H), 5.83 (br s, 1H), 5.41–5.33 (m, 1H), 4.15 (tq, *J* = 6.4, 3.0 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.64 (td, *J* = 6.7, 3.2 Hz, 2H), 3.59 (s, 3H), 3.33 (ddd, *J* = 15.7, 7.1, 4.4 Hz, 1H), 2.92 (dd, *J* = 15.7, 6.5 Hz, 1H), 2.37–2.24 (m, 0.5H), 2.18 (s, 1H), 2.22–2.13 (m, 0.5H), 2.11–1.96 (m, 1H), 1.72–1.60 (m, 1H), 1.60–1.50 (m, 1H), 1.49–1.39 (m, 2H), 1.29–1.21 (m, 1H), 1.14–0.98 (m, 1H), 0.90 (d, *J* = 2.2 Hz, 9H), 0.06 ppm (d, *J* = 2.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 164.4, 164.3, 159.7, 157.7, 157.7, 156.5, 145.6, 145.5, 143.0, 139.9, 139.6, 138.2, 138.1, 136.6, 136.1, 135.9, 134.4, 134.0, 130.5, 130.4, 129.7, 129.3, 128.8, 128.7, 126.0, 125.9, 119.1, 117.4, 117.3, 115.8, 115.7, 113.1, 112.9, 111.7, 110.0, 64.2, 64.2, 61.4, 61.4, 55.7, 55.3, 55.1, 55.1, 41.3, 41.1, 39.4, 32.3, 30.0, 29.9, 29.6, 29.6, 29.1, 26.0, 18.4, –5.2, –5.2 ppm; HRMS calcd. For $C_{41}H_{51}NO_5SiNa^+$ $[M + Na]^+$ 688.3429, found 688.3431.

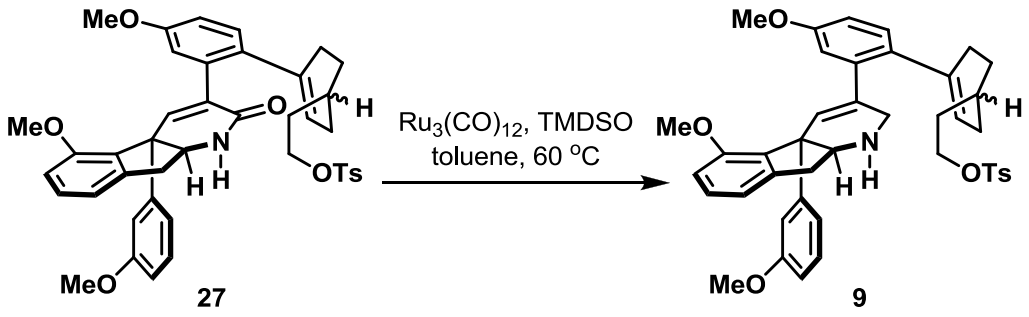
Tosylate 27



(i) To a stirred solution of TBS ether **25** (58 mg, 87 μmol) in THF (1.0 mL) at 0 ℃ was added TBAF (1.0 M in THF, 0.17 mL, 0.17 mmol). The resulting mixture was warmed to room temperature and stirred for 14 h before it was quenched with NH_4Cl (5 mL, sat. aq.), extracted with EtOAc (3 × 5 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 2:1→1:5) to afford alcohol **26** (40 mg, 83%) as a white foam. **26**: R_f = 0.35 (silica gel, hexanes:EtOAc 1:3); IR (film) ν_{max} 3279, 2919, 1672, 1601, 1480, 1265, 1051, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 7.32–7.11 (m, 2H), 7.05 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.98–6.87 (m, 2H), 6.87–6.60 (m, 6H), 6.48 (s, 0.5H), 6.39 (s, 0.5H), 5.37 (s, 1H), 4.19–4.10 (m, 1H), 3.79 (d, *J* = 1.8 Hz, 3H), 3.72 (s, 3H), 3.61 (d, *J* = 5.3 Hz, 3H), 3.67–3.60 (m, 2H), 3.29 (dt, *J* = 14.8, 6.8 Hz, 1H), 2.90 (ddd, *J* = 15.7, 6.3, 2.8 Hz, 1H), 2.36–2.24 (m, 0.5H), 2.23–2.14 (m, 1.5H), 2.12–1.96 (m, 1H), 1.72–1.37 (m, 5H), 1.37–1.24 (m, 1H), 1.19–1.07 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 164.6, 159.6, 157.7, 157.7, 156.5, 145.6, 145.5, 143.1, 134.0, 139.9, 138.2, 138.1, 136.4, 136.1, 136.0, 134.4, 134.2, 130.5, 130.4, 129.6, 129.3, 128.7, 128.6, 125.8, 125.7, 119.1, 117.3, 115.8, 115.7, 113.0, 112.9, 111.8, 109.9, 64.2, 60.9, 55.7, 55.6, 55.3, 55.1, 41.0, 40.9, 38.8, 38.6, 32.1, 32.0, 29.5, 29.4, 29.3, 29.2, 28.9, 28.8 ppm; HRMS calcd. For $C_{35}H_{37}NO_5Na^+$ $[M + Na]^+$ 574.2564, found 574.2566.

(ii) To a stirred solution of alcohol **26** (40 mg, 73 μmol) in CH_2Cl_2 (1.0 mL) at room temperature was added TsCl (28 mg, 0.15 mmol), DMAP (1.8 mg, 15 μmol), and Et_3N (50 μL, 0.36 mmol). The resulting mixture was stirred for 4 h before it was diluted with brine (3 mL), extracted with CH_2Cl_2 (3 × 5 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 3:1→1:2) to afford tosylate **27** (45 mg, 88%) as a yellow amorphous solid. **27**: R_f = 0.5 (silica gel, hexanes:EtOAc 1:2); IR (film) ν_{max} 3201, 2925, 1674, 1601, 1480, 1358, 1260, 1175, 1077, 810 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 7.79 (dd, *J* = 8.2, 3.2 Hz, 2H), 7.34 (dd, *J* = 8.3, 3.4 Hz, 2H), 7.28–7.16 (m, 2H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.95–6.86 (m, 2H), 6.83–6.63 (m, 6H), 6.03 (d, *J* = 11.0 Hz, 0.4H), 5.87 (br s, 0.6H), 5.45–5.23 (m, 1H), 4.21–4.11 (m, 1H), 4.10–3.99 (m, 2H), 3.79 (s, 3H), 3.72 (d, *J* = 1.6 Hz, 3H), 3.59 (d, *J* = 2.7 Hz, 3H), 3.33 (td, *J* = 15.3, 6.9 Hz, 1H), 2.88 (dt, *J* = 15.8, 5.7 Hz, 1H), 2.43 (s, 3H), 2.31–2.18 (m, 1H), 2.15 (s, 2H), 2.06–1.93 (m, 1H), 1.61–1.47 (m, 4H), 1.14–0.95 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 164.4, 164.3, 159.7, 157.8, 157.8, 156.5, 145.6, 145.5, 144.7, 143.0, 143.0, 140.1, 139.8, 138.3, 138.2, 136.2, 136.1, 136.1, 136.0, 134.3, 134.0, 133.2, 130.5, 130.4, 129.9, 129.8, 129.7, 129.3, 128.7, 128.6, 127.9, 125.2, 125.2, 119.0, 117.4, 117.4, 115.8, 113.1, 112.9, 111.7, 110.0, 68.9, 64.2, 64.2, 55.7, 55.3, 55.1, 41.1, 41.0, 34.8, 34.6, 31.5, 31.4, 29.5, 29.0, 28.9, 28.6, 28.5, 21.6 ppm; HRMS calcd. For $C_{42}H_{43}NO_7SNa^+$ $[M + Na]^+$ 728.2652, found 728.2655.

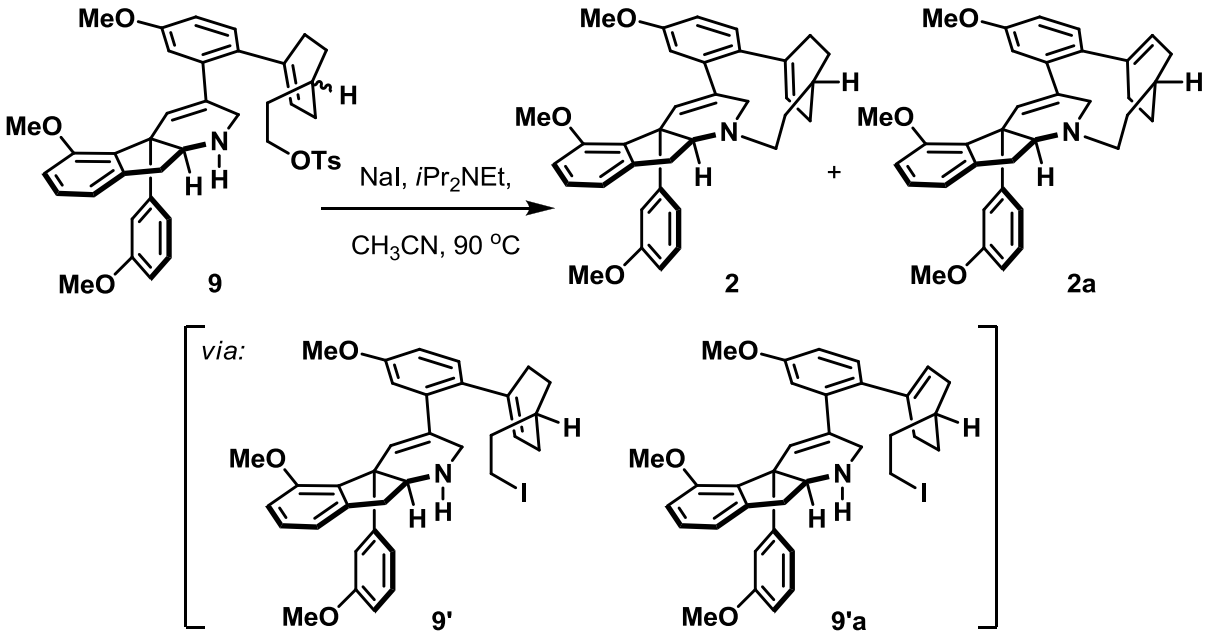
Amine 9



To a stirred solution of amide **27** (79.0 mg, 0.11 mmol) in toluene (2.0 mL) at room temperature was added $Ru_3(CO)_{12}$ (7.2 mg, 11 μmol) and TMDSO (0.20 mL, 1.12 mmol).

The resulting mixture was evacuated and filled with argon (3 ×) before it was placed into a pre-heated (60 ^{o}C) oil bath and stirred for 14 h. The resulting mixture was cooled to room temperature before it was quenched with NaOH (1.0 M aq)/CH_2Cl_2 (1:1, 5 mL) and stirred for 30 min. The resulting mixture was diluted with H_2O/CH_2Cl_2 (1:1, 5 mL), extracted with CH_2Cl_2 (3 × 8 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was filtered through a pad of silica gel and eluted with hexane:EtOAc (1:2, 100 mL), and concentrated under reduced pressure. The resulting residue was resubjected to the identical amide reduction condition [$Ru_3(CO)_{12}$ (7.2 mg, 11 μmol), TMDSO (0.20 mL, 1.12 mmol), toluene (2.0 mL), 60 ^{o}C, 14 h] and the resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 3:1→1:5) to afford amine **9** (44 mg, 57%) and lactam **27** (10 mg, 13%) as yellow foams. **9**: R_f = 0.20 (silica gel, hexanes:EtOAc 1:2); IR (film) ν_{max} 2925, 2835, 1599, 1479, 1358, 1261, 1175, 1080, 912, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.21–7.13 (m, 2H), 6.98 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.88 (d, *J* = 7.4 Hz, 1H), 6.79–6.66 (m, 6H), 6.27 (d, *J* = 15.6 Hz, 1H), 5.44 (d, *J* = 4.8 Hz, 1H), 4.05 (t, *J* = 6.5 Hz, 2H), 3.79 (d, *J* = 1.0 Hz, 3H), 3.72 (d, *J* = 2.5 Hz, 3H), 3.66–3.61 (m, 1H), 3.58 (d, *J* = 3.6 Hz, 3H), 3.54–3.43 (m, 1H), 3.10 (dd, *J* = 16.0, 7.2 Hz, 1H), 2.89 (dd, *J* = 16.0, 5.7 Hz, 1H), 2.44 (s, 3H), 2.21–2.05 (m, 2H), 2.01–1.90 (m, 1H), 1.77 (s, 1H), 1.60–1.42 (m, 5H), 1.11–0.83 ppm (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 159.5, 158.1, 158.1, 157.3, 148.2, 148.2, 144.7, 143.5, 143.5, 141.3, 141.2, 139.5, 139.2, 138.3, 138.0, 135.1, 135.0, 133.2, 132.9, 132.8, 129.9, 129.7, 129.5, 129.0, 128.9, 128.8, 128.5, 127.9, 124.7, 124.7, 119.3, 117.8, 117.7, 114.6, 114.5, 113.3, 111.9, 110.6, 109.5, 77.3, 68.8, 66.5, 55.3, 55.2, 55.1, 55.1, 45.4, 35.6, 35.6, 35.2, 35.1, 31.7, 31.6, 30.2, 29.9, 29.3, 29.3, 28.7, 28.6, 21.6 ppm; HRMS calcd. For $C_{42}H_{46}NO_6S^+$ [M + H]$^+$ 692.3040, found 692.3044.

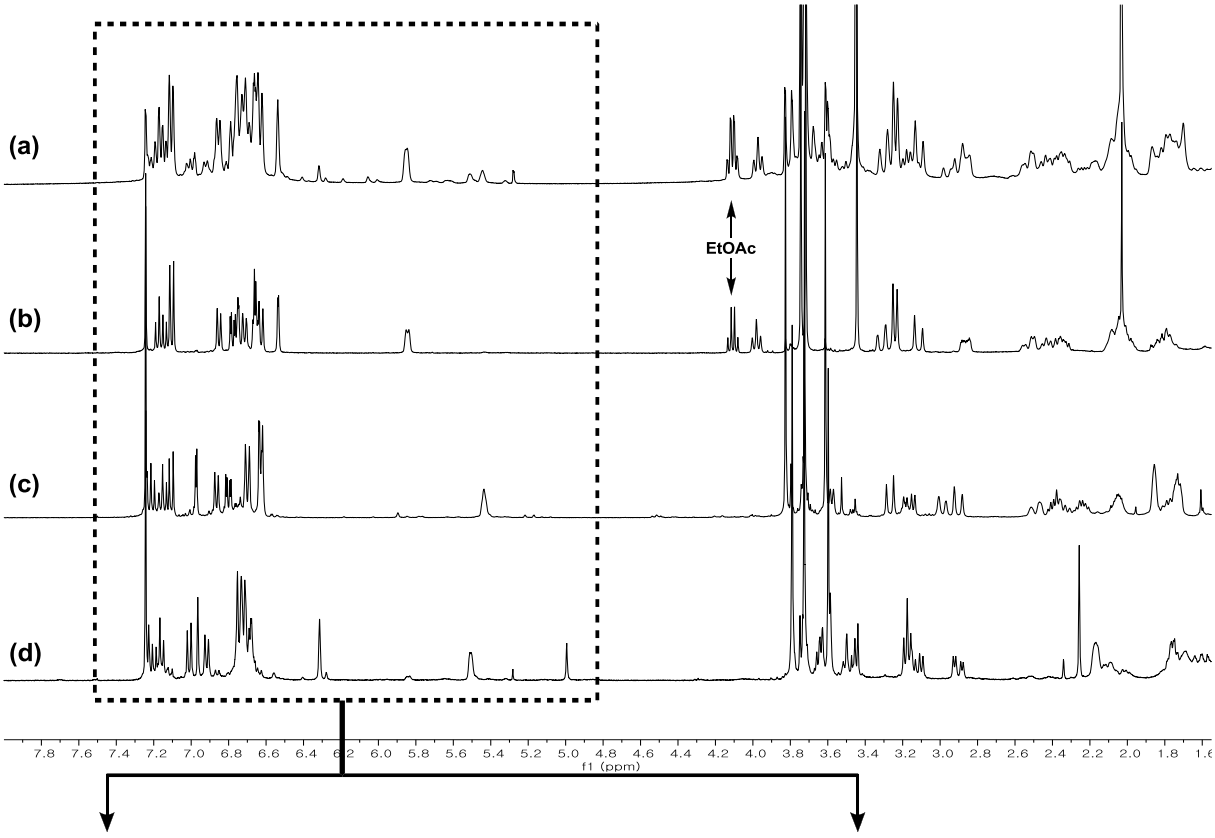
Macrocycle 2/2a

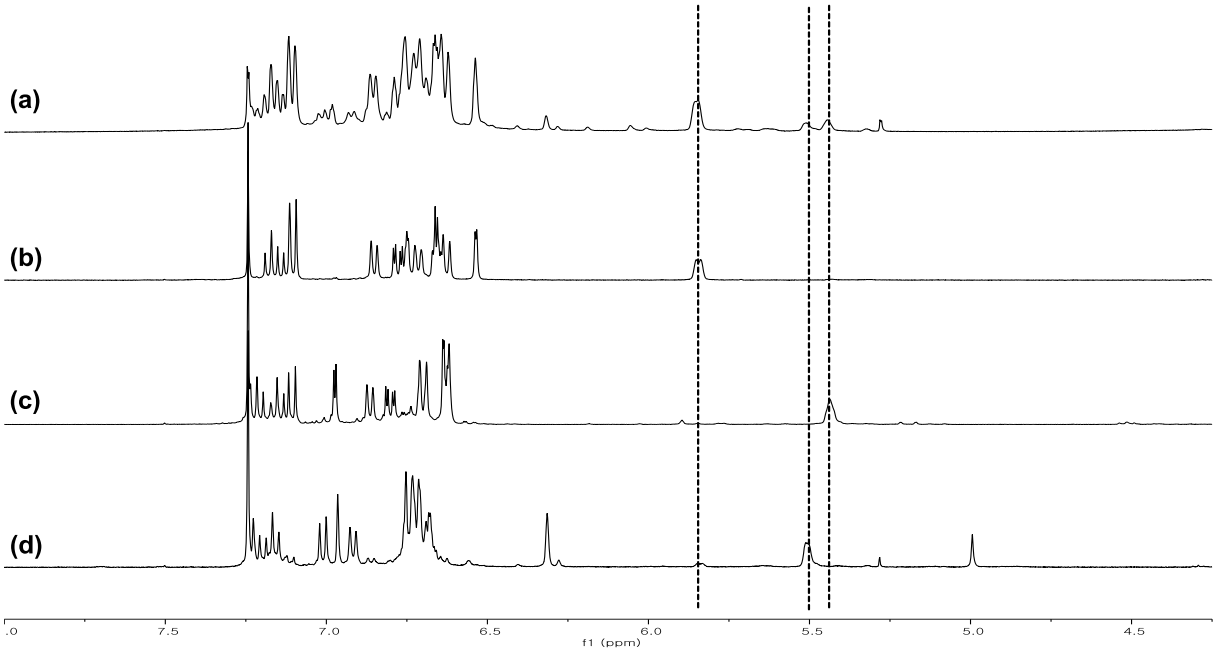


To a stirred solution of amino tosylate **9** (0.27 g, 0.39 mmol) in CH_3CN (200 mL) at room temperature was added NaI (0.58 mg, 3.9 mmol) and *i*Pr_2NEt (0.68 mL, 3.9 mmol). The resulting mixture was evacuated and filled with argon (3 ×) before it was placed into a pre-heated (90 °C) oil bath and stirred for 16 h. The resulting mixture was cooled to room temperature and concentrated under reduced pressure, and the resulting residue was diluted with H_2O (15 mL), extracted with CH_2Cl_2 (3 × 10 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 10:1→1:3) to afford: fraction A: macrocycle **2**/**2a** (**2**:**2a** ~ 1:0.36, 120 mg, 59%); fraction B: macrocycle **2**/**2a** and iodide **9′**/**9′a** (43.0 mg); and fraction C: iodide **9′**/**9′a** (37.0 mg, 14%) as yellow amorphous solids. The mixture of macrocycle **2**/**2a** and iodide **9′**/**9′a** (fractions B and C) was resubjected under the identical macrocyclization condition (with the exclusion of NaI) followed by chromatographic purification to afford additional macrocycle **2**/**2a** (55.0 mg, 27%). *[Alternatively, macrocyclization could be carried out with continuous heating without the isolation of iodide itermediates to afford macrocycle **2**/**2a** with similar result]*. **2**/**2a**: R_f = 0.43 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 2921, 2852, 1599, 1478, 1464, 1377, 1288, 1262, 1122, 874 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 7.24–7.09 (m, 3H), 7.03–6.96 (m, 1H), 6.90–6.84 (m, 2H), 6.83–6.62 (m, 4H), 6.57–6.50 (m,

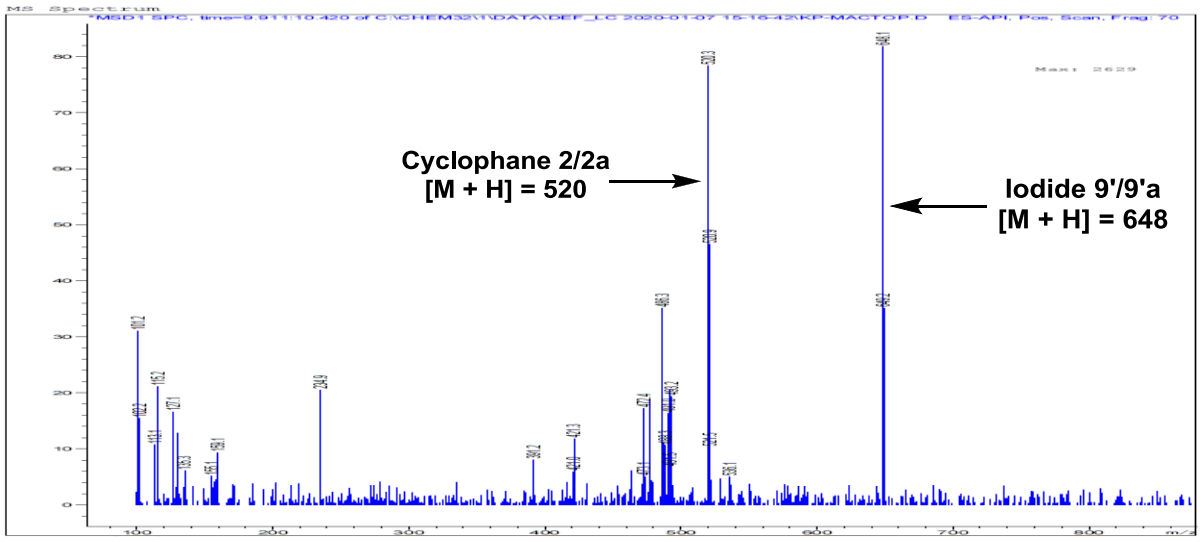
1H), 5.86 (d, *J* = 5.9 Hz, 0.6H), 5.45 (s, 0.4H), 3.98 (t, *J* = 8.9 Hz, 1H), 3.83 (s, 1.5H), 3.77–3.69 (m, 6H), 3.62 (s, 1.5H), 3.45 (s, 3H), 3.34–3.24 (m, 2H), 3.24–3.09 (m, 1H), 3.02–2.83 (m, 1H), 2.60–2.46 (m, 1H), 2.45–2.20 (m, 2H), 2.16–1.95 (m, 2H), 1.91–1.71 (m, 2H), 1.15–0.99 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 159.6, 159.2, 158.1, 156.7, 156.3, 153.1, 144.5, 143.5, 142.9, 139.0, 136.1, 135.5, 135.2, 135.1, 132.9, 131.7, 130.1, 129.1, 129.0, 128.5, 128.4, 127.6, 119.4, 119.3, 117.0, 116.5, 115.1, 113.2, 112.7, 111.9, 111.7, 110.7, 110.4, 109.8, 109.4, 74.7, 74.6, 58.0, 55.4, 55.2, 55.0, 52.7, 51.2, 50.0, 45.8, 43.3, 35.9, 35.2, 30.0, 29.7, 28.9, 28.4, 26.7, 26.5, 26.3, 26.0. ppm; HRMS calcd. For $C_{35}H_{38}NO_3^+$ $[M + H]^+$ 520.2846, found 520.2849.

Representative ^{1}H NMR (400 MHz, $CDCl_3$) analysis illustrating the rate difference in the formation of macrocycle 2 and 2a after 16 hours at 90 °C: (a) semi-purified reaction mixture containing macrocycle 2/2a and iodide 9′/9′a; (b) macrocycle 2 obtained from preparative thin-layer-chromatography purification; (c) macrocycle 2a obtained from preparative thin-layer-chromatography purification; (d) diastereoisomerically enriched iodide 9′/9′a

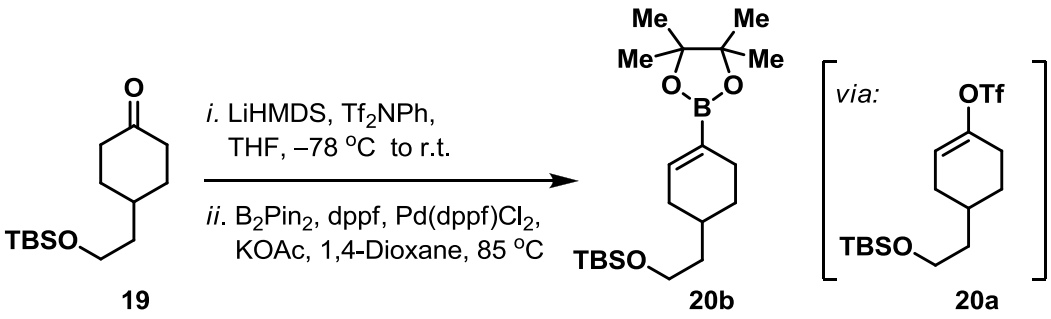




Representative LCMS analysis of macrocycle formation (crude, 90 °C, 16 hours)



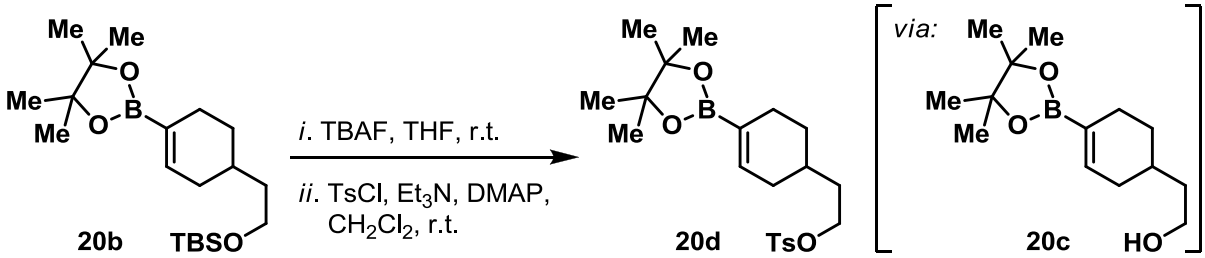
Boronic Ester 20b



(i) To a stirred solution of ketone **19**[4] (0.69 g, 2.7 mmol) in THF (26.0 mL) at room temperature was added Tf_2NPh (1.4 g, 4.0 mmol). The resulting mixture was cooled to –78 °C before LiHMDS (1.0 M in THF, 3.8 mL, 3.8 mmol) was added. The resulting mixture was stirred for 45 min then warmed to room temperature and stirred for 1 h before it was diluted with brine (40 mL), extracted with EtOAc (3 × 30 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:Et_2O 95:5) to afford triflate **20a** (0.99 g, 96%) as a yellow oil. **20a**: R_f = 0.75 (silica gel, hexanes:EtOAc 6:1); IR (film) ν_{max} 2930, 1417, 1205, 834, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.70 (br s, 1H), 3.65 (t, *J* = 6.4 Hz, 2H), 2.46–2.20 (m, 3H), 1.95–1.81 (m, 2H), 1.80–1.69 (m, 1H), 1.56–1.38 (m, 3H), 0.87 (s, 9H), 0.03 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.1, 117.7, 60.9, 37.9, 30.3, 30.1, 29.1, 28.5, 27.1, 25.9, 18.3, –5.4 ppm; HRMS calcd. For $C_{15}H_{27}F_3O_4SSiNa^+$ $[M + Na]^+$ 411.1244, found 411.1247.

(ii) To a stirred solution of triflate **20a** (0.99 g, 2.6 mmol) in 1,4-dioxane (12.8 mL) at room temperature was added B_2Pin_2 (0.71g, 2.8 mmol), dppf (0.14 g, 0.25 mmol) and KOAc (0.50 g, 5.1 mmol). The resulting mixture was evacuated and filled with argon (3 ×) before $Pd(dppf)Cl_2$ (43.1 mg, 59 μmol) was added and placed into a pre-heated (85 °C) oil bath. The resulting mixture was stirred for 16 h before it was cooled to room temperature, filtered through a pad of Celite® and eluted with CH_2Cl_2 (30 mL), and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:Et_2O 10:1) to afford boronic ester **20b** (1.87 g, 67%) as a yellow amorphous solid. **20b**: R_f = 0.67 (silica gel, hexanes: Et_2O 4:1); IR (film) ν_{max} 2927, 1634, 1387, 1330, 1146, 833, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.50 (br s, 1H), 3.63 (t, *J* = 6.7 Hz, 2H), 2.25–2.11 (m, 2H), 2.11–2.01 (m, 1H), 1.81–1.59 (m, 3H), 1.45 (qd, *J* = 6.6, 1.8 Hz, 2H), 1.22 (s, 12H), 1.20–1.06 (m, 1H), 0.85 (s, 9H), –0.01 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 142.2, 82.9, 61.0, 39.6, 33.4, 29. 7, 28.8, 26.1, 25.9, 24.8, 24.8, 18.3, –5.3 ppm; HRMS calcd. For $C_{20}H_{39}BO_3SiNa^+$ $[M + Na]^+$ 389.2658, found 389.2656.

Tosylate 20d

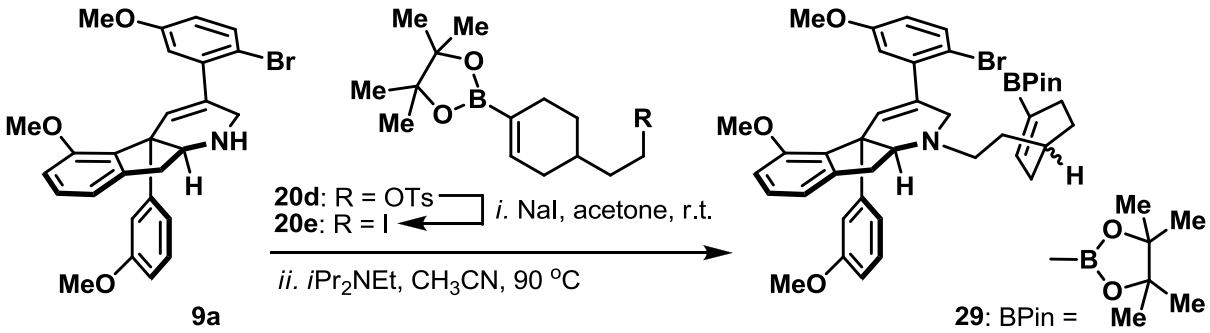


(i) To a stirred solution of TBS ether **20b** (0.29 g, 0.75 mmol) in THF (7.0 mL) at 0 ℃ was added TBAF (1.0 M in THF, 1.5 mL, 1.5 mmol). The resulting mixture was warmed to room temperature and stirred for 14 h before it was cooled to 0 ℃ and treated with additional TBAF (1.0 M in THF, 1.5 mL, 1.5 mmol). The resulting mixture was warmed to room temperature and stirred for 6 h before it was quenched with NH_4Cl (5 mL, sat. aq.), extracted with EtOAc (3 × 10 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:Et_2O 10:1→1:1) to afford alcohol **20c** (0.14 g, 74%) as a white amorphous solid. **20c**: R_f = 0.35 (silica gel, hexanes: Et_2O 1:1); IR (film) ν_{max} 3368, 2978, 2919, 1634, 1387, 1145, 857 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.51 (br s, 1H), 3.69 (t, *J* = 6.8 Hz, 2H), 2.27–2.16 (m, 2H), 2.12–2.02 (m, 1H), 1.80–1.65 (m, 3H), 1.53 (qd, *J* = 6.7, 4.8 Hz, 2H), 1.33–1.13 (s, 13H), 0.93–0.84 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.9, 83.0, 60.8, 39.5, 33.3, 29.7, 28.8, 26.0, 24.8, 24.8 ppm; HRMS calcd. For $C_{14}H_{25}BO_3Na^+$ $[M + Na]^+$ 275.1792, found 275.1795.

(ii) To a stirred solution of alcohol **20c** (0.12 g, 0.49 mmol) in CH_2Cl_2 (5.0 mL) at room temperature was added TsCl (0.18 g, 0.96 mmol), DMAP (11.9 mg, 97 μmol), and Et_3N (0.27 mL, 1.94 mmol). The resulting mixture was stirred for 12 h before it was diluted with brine (5 mL), extracted with CH_2Cl_2 (3 × 8 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes: Et_2O 3:1→1:2) to afford tosylate **20d** (0.11 g, 57%) as a yellow amorphous solid. **20d**: R_f = 0.5 (silica gel, hexanes: Et_2O 2:1); IR (film) ν_{max} 2941, 1663, 1361, 1168, 815, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.7 Hz, 2H), 7.32 (d, *J* = 7.7 Hz, 2H), 6.44 (br s, 1H), 4.07 (t, *J* = 6.2 Hz, 2H), 2.43 (s, 3H), 2.18–1.94 (m, 3H), 1.70–1.53 (m, 5H), 1.27–1.21 (m, 12H), 1.10 ppm (m, 1H); ^{13}C NMR (101 MHz,

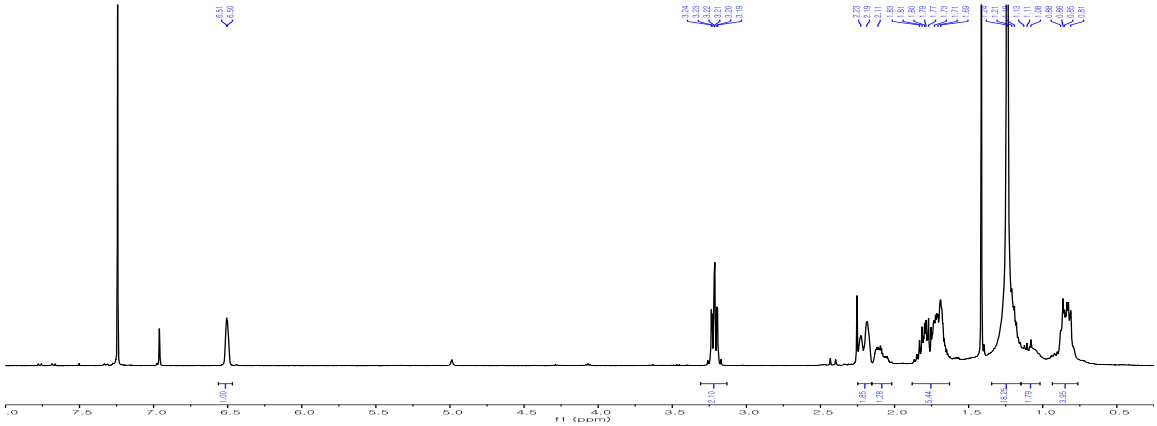
$CDCl_3$): δ 144.7, 141.2, 133.1, 129.8, 127.9, 83.1, 68.6, 35.2, 32.7, 29.3, 28.3, 25.7, 24.8, 24.8, 21.6 ppm; HRMS calcd. For $C_{21}H_{31}BO_5SNa^+$ $[M + Na]^+$ 429.1881, found 429.1883.

Aryl Bromide-Boronic Ester 29



(i) To a stirred solution of tosylate **20d** (36.8 mg, 90.6 μmol) in acetone (2.0 mL) at room temperature was added NaI (0.14 g, 0.91 mmol). The resulting mixture was stirred for 12 h before it was concentrated under reduced pressure, diluted with H_2O (5 mL) and extracted with Et_2O (3 × 5 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Crude iodide **20e** which was used directly in the subsequent reaction.

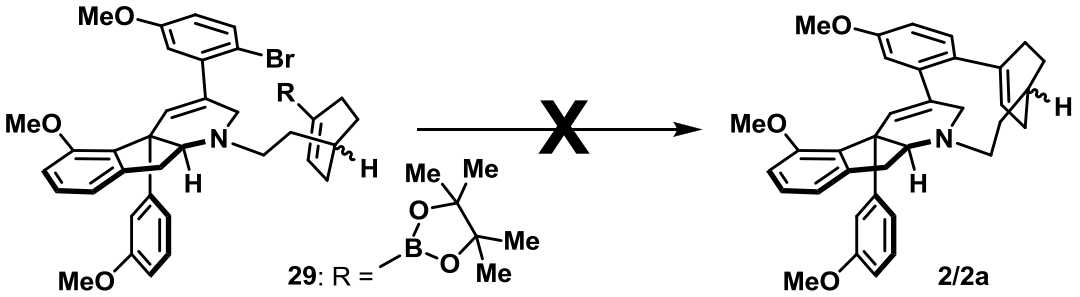
Representative ^{1}H NMR (400 MHz, $CDCl_3$, crude) of iodide 20e



(ii) To a stirred solution of amine **9a**[6] (60.0 mg, 0.12 mmol) and iodide **20e** (43.0 mg, 0.12 mmol) in CH_3CN (1.5 mL) at room temperature was added *i*Pr_2NEt (0.16 mL, 0.92 mmol). The resulting mixture was evacuated and filled with argon (3 ×) before it was placed into a pre-heated (90 °C) oil bath and stirred for 36 h. The resulting mixture was cooled to room temperature, concentrated under reduced pressure, diluted with H_2O (3 mL) and extracted with CH_2Cl_2 (3 × 3 mL), combined organic layer dried over anhydrous Na_2SO_4 and

concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 8:1→1:2) to afford aryl bromide-boronic ester **29** (48.0 mg, 73% over two steps) as a brown foam. **29**: R_f = 0.50 (silica gel, hexanes:EtOAc 1:1); IR (film) ν_{max} 2976, 2928, 2836, 1633, 1588, 1479, 1387, 1289, 1145 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 7.40 (d, *J* = 8.7 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 7.9 Hz, 1H), 7.02 (s, 1H), 6.92–6.85 (m, 2H), 6.77–6.64 (m, 4H), 6.48 (s, 0.5H), 6.41 (s, 0.5H), 5.92 (d, *J* = 3.0 Hz, 1H), 3.75 (d, *J* = 1.7 Hz, 6H), 3.69 (t, *J* = 8.6 Hz, 1H), 3.55–3.44 (m, 4H), 3.33 (d, *J* = 16.8 Hz, 1H), 3.15 (dd, *J* = 15.4, 9.5 Hz, 1H), 2.82 (dd, *J* = 15.3, 7.7 Hz, 1H), 2.57 (t, *J* = 6.9 Hz, 2H), 2.20–2.07 (m, 1H), 2.07–1.96 (m, 1H), 1.94–1.82 (m, 1H), 1.69–1.59 (m, 2H), 1.58–1.40 (m, 2H), 1.33 (t, *J* = 6.7 Hz, 1H), 1.27–1.21 (m, 12H), 1.14–0.93 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 159.0, 158.7, 156.3, 148.9, 148.9, 143.4, 143.3, 142.6, 142.3, 136.9, 133.2, 132.8, 132.8, 128.6, 128.2, 128.1, 127.8, 119.6, 119.5, 117.8, 116.4, 116.3, 114.2, 114.2, 113.3, 113.2, 111.0, 111.0, 109.4, 82.9, 77.2, 70.9, 70.4, 56.2, 55.6, 55.2, 55.2, 55.0, 52.7, 52.4, 50.2, 49.9, 33.9, 33.9, 33.2, 33.2, 30.7, 30.5, 28.9, 27.8, 27.7, 26.2, 26.1, 24.9, 24.8, 24.8 ppm; HRMS calcd. For $C_{41}H_{50}NO_5^+$ $[M + H]^+$ 726.2967, found 726.2963.

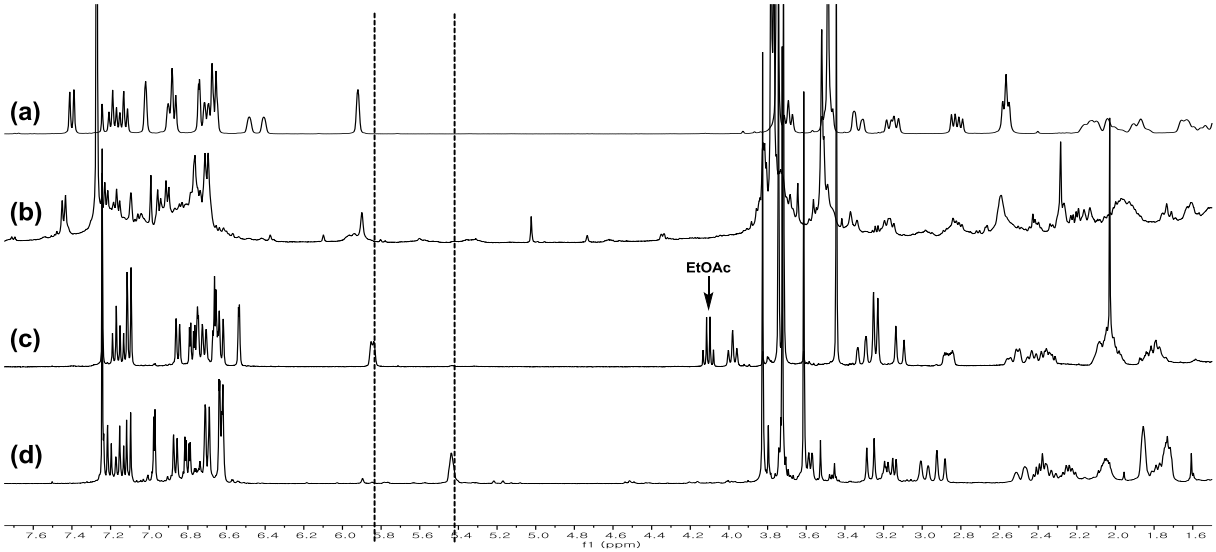
Attempted preparation of macrocycle 2/2a *via* intramolecular Suzuki reaction of 29:



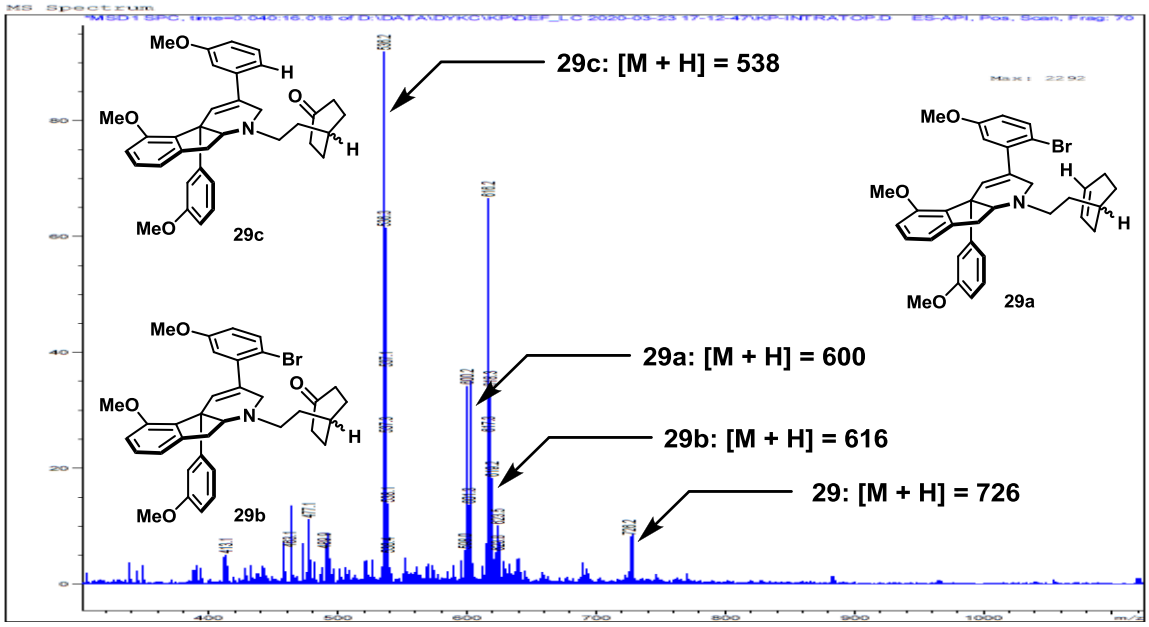
Representative procedure: To a stirred solution of aryl bromide-boronic ester **29** (19.0 mg, 26 μmol) in CH_3CN/H_2O (1:1, 3.0 mL) at room temperature was added K_2CO_3 (7.23 mg, 52 μmol) and Pd(dppf)Cl_2 (1.90 mg, 2.6 μmol). The resulting mixture was evacuated and filled with argon (3 ×) before it was placed into a pre-heated (90 ^oC) oil bath and stirred for 8 h. The resulting mixture was cooled to room temperature and diluted with H_2O/CH_2Cl_2 (1:1, 10 mL), extracted with CH_2Cl_2 (3 × 10 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was filtered through a pad of

silica gel and eluted with hexane:EtOAc 1:2 (25 mL), concentrated under reduced pressure, and the resulting residue was subjected to ^{1}H NMR and LCMS analysis.

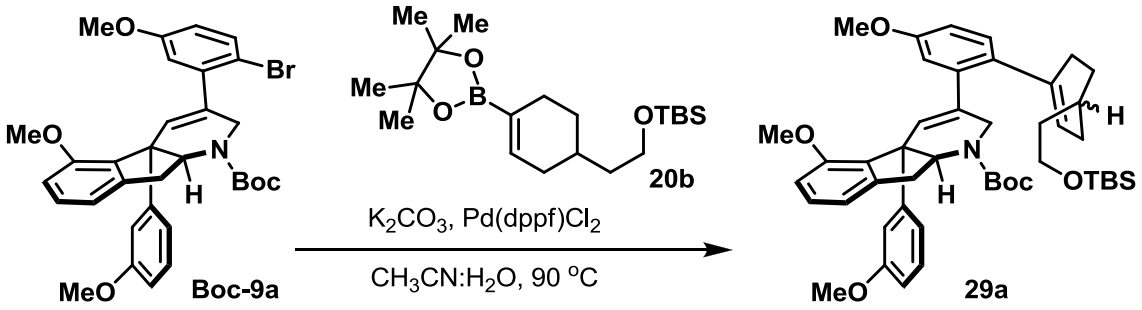
Representative ^{1}H NMR ($CDCl_3$) analysis illustrating the outcome of intramolecular Suzuki reaction of substrate 29: (a) aryl bromide-boronic ester 29; (b) semi-purified reaction mixture; (c) macrocycle 2 obtained from preparative thin-layer-chromatography purification; (d) macrocycle 2a obtained from preparative thin-layer-chromatography purification



Representative LCMS analysis of of attempted intramolecule Suzuki reaction of substrate 29 (Speculated components by LCMS, macrocycle 2/2a was not detected):

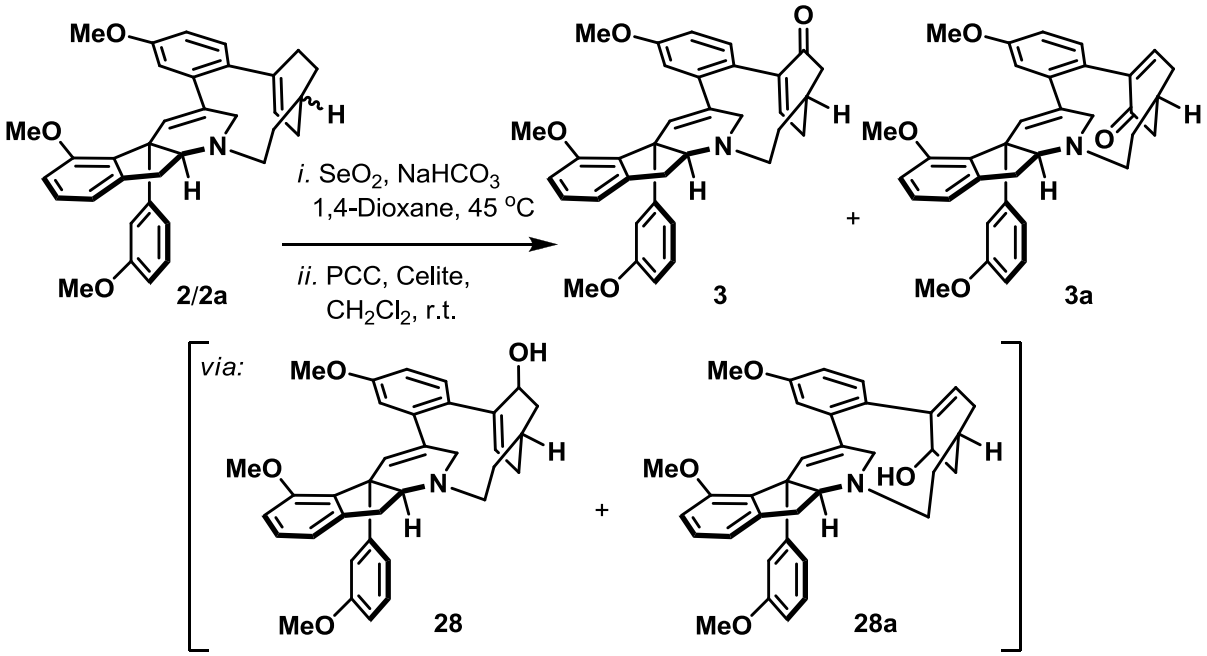


Intermolecular Suzuki Product 29a



To a stirred solution of aryl bromide **Boc-9a** (0.45 g, 0.76 mmol) in CH_3CN/H_2O (1:1, 8.0 mL) at room temperature was added K_2CO_3 (0.21 g, 1.53 mmol) and $Pd(dppf)Cl_2$ (55.8 mg, 76 μmol). The resulting mixture was evacuated and filled with argon (3 ×) before it was placed into a pre-heated (90 °C) oil bath and stirred for 14 h. The resulting mixture was cooled to room temperature and diluted with H_2O/CH_2Cl_2 (1:1, 15 mL), extracted with CH_2Cl_2 (3 × 10 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 8:1→1:2) to afford biaryl **29a** (0.43 g, 75%) as a brown foam. **29a**: ^{1}H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.11 (m, 2H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 7.3 Hz, 1H), 6.86–6.65 (m, 6H), 5.93 (s, 0.5H), 5.88 (s, 0.5H), 5.46 (s, 0.5H), 5.43 (s, 0.5H), 5.10–4.75 (m, 2H), 3.80 (s, 3H), 3.73 (s, 3H), 3.72–3.63 (m, 2H), 3.51 (s, 3H), 3.23–2.91 (m, 2H), 2.28–1.97 (m, 3H), 1.68–1.32 (m, 7H), 1.13 (s, 8H), 0.93 (s, 10H), 0.09 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, 1:1 mixture of diastereoisomers): δ 159.4, 158.1, 158.0, 156.2, 154.7, 154.6, 147.8, 142.4, 139.8, 139.6, 138.0, 137.6, 136.3, 135.9, 135.8, 132.0, 129.9, 129.6, 129.0, 128.6, 126.4, 126.0, 125.6, 125.5, 119.2, 117.5, 117.4, 114.9, 112.7, 112.6, 112.5, 112.4, 111.1, 111.0, 109.8, 79.4, 77.3, 63.2, 61.5, 61.4, 55.4, 55.3, 55.2, 55.1, 55.0, 55.0, 42.0, 41.8, 39.6, 39.5, 33.1, 33.0, 32.2, 32.1, 30.7, 30.6, 29.7, 29.6, 28.9, 28.4, 27.9, 26.0, 18.4, –5.2, –5.2 ppm.

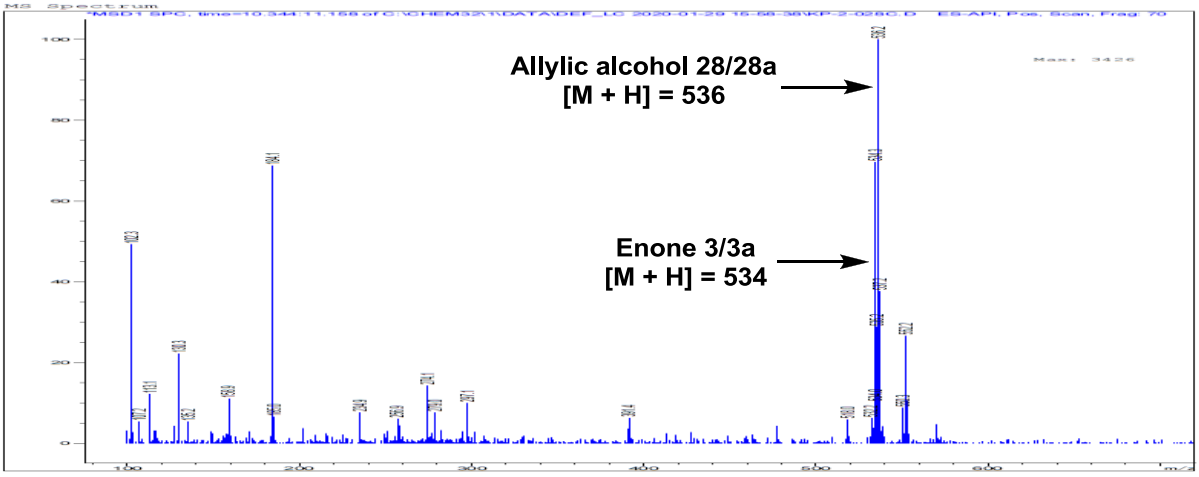
Enones 3 and 3a



(i) To a stirred solution of macrocycle **2**/**2a** (**2**:**2a** ~ 2:1, 15.0 mg, 29 μmol) in 1,4-dioxane (1.0 mL) at room temperature was added SeO_2 (5.7 mg, 52 μmol) and $NaHCO_3$ (12.1 mg, 0.14 mmol). The resulting mixture was evacuated and filled with argon (3 ×) before it was placed into a pre-heated (45 °C) oil bath and stirred for 5 h. The resulting mixture was cooled to room temperature before it was quenched with $NaHCO_3$ (3 mL, sat. aq.), extracted with CH_2Cl_2 (3 × 3 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 3:1→1:6) to afford allylic alcohol **28**/**28a** (10.6 mg, 69%) as a brown foam. *[Note: a "diastereoisomerically enriched" mixture of **2** and **2a** was used for SeO_2-mediated allylic oxidation and conversion to enones **3** and **3a** to facilitate assignment of ^{1}H NMR signals correspond to allylic alcohols **28** and **28a**, and macrocycle **2** and **2a**, based on the ratio of enone **3** and **3a** obtained]*. **28**/**28a**: R_f = 0.15 (silica gel, hexanes:EtOAc 1:2); IR (film) ν_{max} 3414, 2926, 2853, 1601, 1479, 1262, 1082, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, *ca.* 2:1 mixture of diastereoisomers): δ 7.57 (d, *J* = 8.5 Hz, 0.3H), 7.51 (d, *J* = 8.5 Hz, 0.7H), 7.23–7.07 (m, 3H), 6.86 (dd, *J* = 7.6, 3.4 Hz, 1H), 6.79 (ddt, *J* = 11.4, 8.4, 3.0 Hz, 1H), 6.75–6.57 (m, 4H), 6.54 (d, *J* = 2.2 Hz, 1H), 5.99 (d, *J* = 6.6 Hz, 0.7H), 5.60 (d, *J* = 6.5 Hz, 0.3H), 4.72 (t, *J* = 7.9 Hz, 0.7H), 4.66 (t, *J* = 7.9 Hz, 0.3H), 3.97 (t, *J* = 8.8 Hz, 0.7H), 3.91 (t, *J* = 8.8 Hz, 0.3H), 3.83 (d, *J* = 2.0 Hz, 2H), 3.79–3.67 (m, 6H), 3.60 (d, *J* = 10.7 Hz, 2H),

3.52 (s, 1H), 3.44 (s, 2H), 3.43–3.31 (m, 1H), 3.31–3.15 (m, 1H), 3.15–3.00 (m, 1H), 2.98–2.86 (m, 1H), 2.50–2.17 (m, 2H), 2.17–1.94 (m, 2H), 1.77 (td, *J* = 9.3, 4.4 Hz, 0.7H), 1.67 (td, *J* = 9.3, 4.4 Hz, 0.3H), 1.08 ppm (d, *J* = 16.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$, *ca.* 2:1 mixture of diastereoisomers): δ 159.7, 159.5, 159.3, 158.9, 158.4, 156.5, 156.4, 152.2, 151.9, 144.0, 143.9, 143.4, 142.3, 137.5, 137.2, 135.6, 135.4, 134.7, 133.6, 133.5, 132.5, 132.3, 131.0, 130.9, 130.3, 129.9, 129.5, 129.4, 129.0, 128.7, 128.4, 128.3, 119.3, 118.7, 117.1, 116.8, 116.7, 116.5, 115.7, 115.5, 113.3, 112.9, 112.1, 111.6, 111.0, 110.4, 109.9, 109.6, 74.0, 73.6, 68.6, 68.4, 57.5, 55.4, 55.2, 55.0, 52.8, 51.7, 50.8, 49.8, 45.5, 43.3, 41.2, 41.0, 36.5, 36.0, 35.1, 34.5, 29.8, 29.0, 28.6, 27.2, 26.5 ppm; HRMS calcd. For $C_{35}H_{38}NO_4^+$ $[M + H]^+$ 536.2795, found 536.2800.

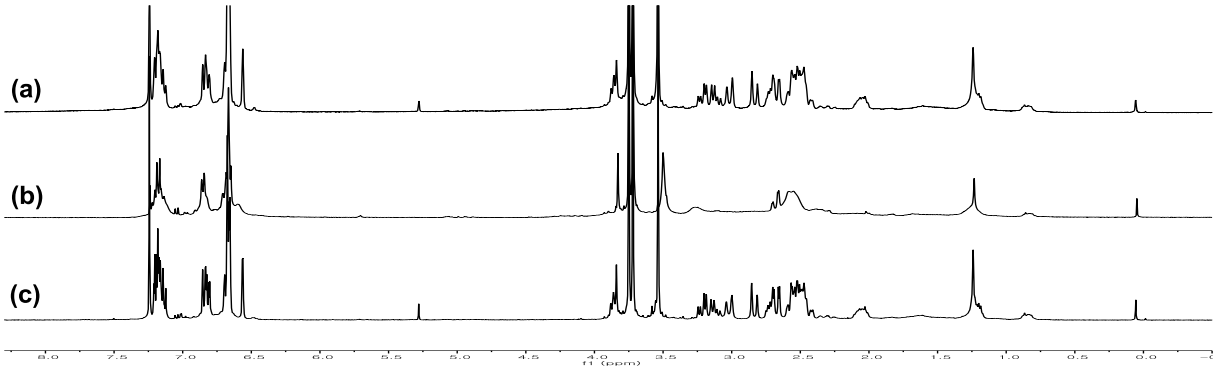
Representative LCMS analysis of SeO_2-mediated allylic oxidation at 100 °C for 4 h



(ii) To a stirred solution of allylic alcohol **28**/**28a** (15.7 mg, 29 μmol) in CH_2Cl_2 (1.5 mL) at room temperature was added PCC (12.4 mg, 57 μmol) and Celite® (33 mg). The resulting mixture was stirred for 4 h before it was filtered through a pad of Celite® and eluted with CH_2Cl_2 (10 mL). The resulting filtrate was diluted with $NaHCO_3$ (10 mL, sat. aq.), extracted with CH_2Cl_2 (3 × 10 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 3:1→1:4) to afford enone **3** (9.0 mg, 58%) and enone **3a** (4.4 mg, 28%) as yellow amorphous solids. **3**: R_f = 0.40 (silica gel, hexanes:EtOAc 1:2); IR (film) ν_{max} 2932, 2836, 1668, 1598, 1478, 1464, 1262, 1081, 1041, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.11 (m, 4H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.82 (dd, *J* = 8.4, 3.0

Hz, 1H), 6.71–6.64 (m, 5H), 6.56 (d, *J* = 1.9 Hz, 1H), 3.91–3.82 (m, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.54 (s, 3H), 3.22 (dd, *J* = 17.2, 6.9 Hz, 1H), 3.12 (dd, *J* = 17.0, 8.9 Hz, 1H), 3.02 (d, *J* = 16.1 Hz, 1H), 2.84 (d, *J* = 16.0 Hz, 1H), 2.78–2.63 (m, 2H), 2.62–2.39 (m, 5H), 2.13–1.99 (m, 1H), 1.32–1.15 ppm (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.7, 159.4, 158.8, 156.5, 152.4, 149.4, 144.1, 143.4, 139.4, 136.8, 134.9, 131.3, 131.2, 128.8, 128.7, 126.2, 118.9, 116.9, 114.8, 112.8, 111.8, 110.2, 109.6, 73.7, 55.3, 55.2, 55.0, 55.0, 50.5, 47.6, 43.1, 33.3, 30.7, 30.0, 27.4 ppm; HRMS calcd. For $C_{35}H_{36}NO_4^+$ [M + H] 534.2639, found 534.2643.

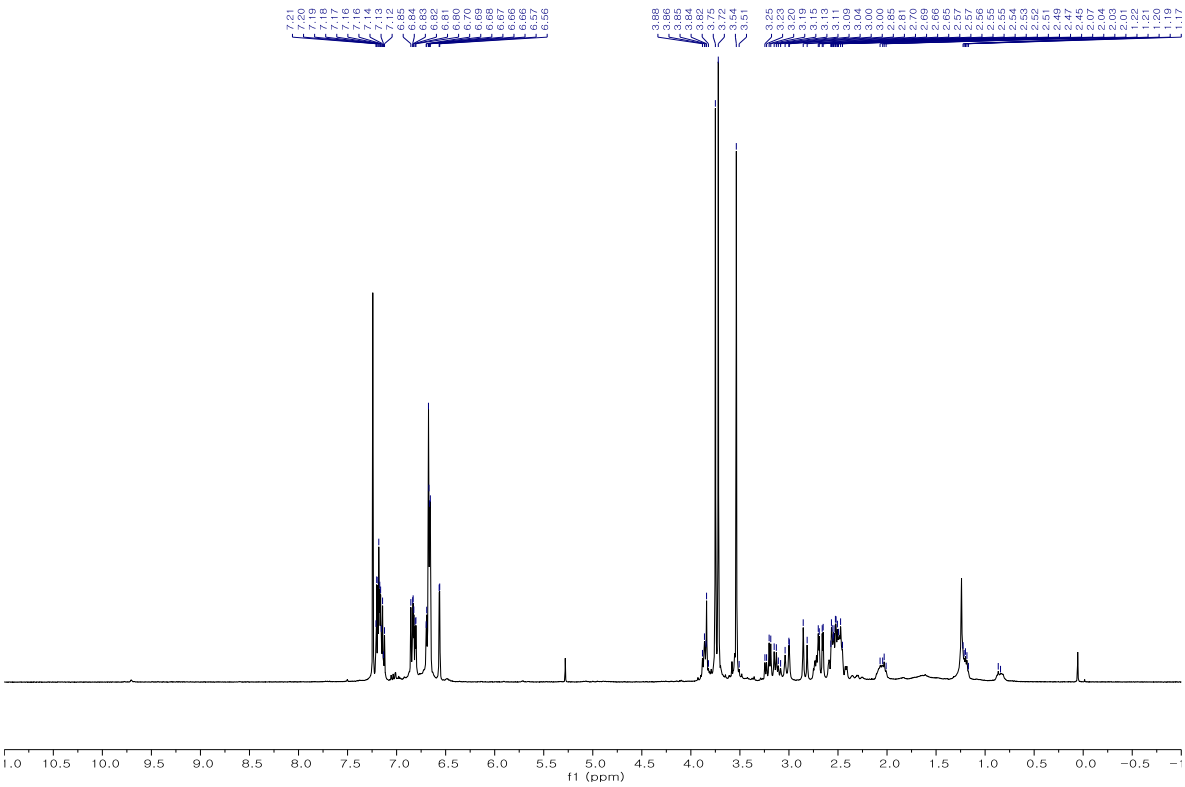
*[Note: ^{1}H NMR of enone **3** in deuterated chloroform: (a) K_2CO_3 treated $CDCl_3$; (b) untreated $CDCl_3$; (c) untreated $CDCl_3$ with 0.5% of NH_4OH(aq.)]*



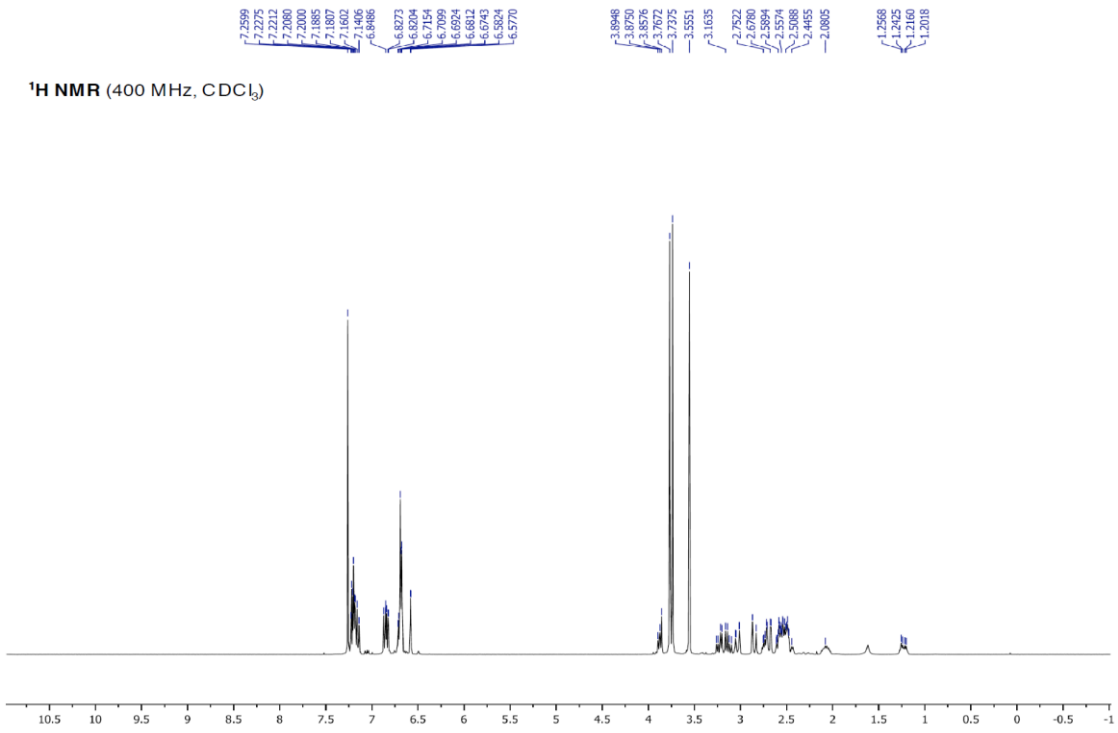
3a: R_f = 0.50 (silica gel, hexanes:EtOAc 1:2); IR (film) ν_{max} 2936, 2834, 1664, 1598, 1478, 1261, 1082, 1041, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 7.3 Hz, 1H), 7.20(d, *J* = 5.4 Hz, 1H), 7.15 (t, *J* = 8.2 Hz, 1H), 7.01 (d, *J* = 2.9 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.84 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.78–6.73 (m, 1H), 6.72–6.61 (m, 5H), 3.84 (s, 3H), 3.72 (s, 3H), 3.58 (s, 3H), 3.36 (dd, *J* = 7.4, 2.7 Hz, 1H), 3.26 (dd, *J* = 16.5, 7.5 Hz, 1H), 3.09 (d, *J* = 14.2 Hz, 1H), 3.01 (dd, *J* = 16.5, 2.7 Hz, 1H), 2.78–2.69 (m, 1H), 2.64–2.54 (m, 2H), 2.52–2.45 (m, 2H), 2.36 (q, *J* = 3.4 Hz, 2H), 2.15 (dt, *J* = 13.0, 4.7 Hz, 1H), 1.84 (td, *J* = 10.5, 9.5, 4.8 Hz, 1H), 1.44 ppm (qd, *J* = 11.1, 4.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.0, 195.1, 159.7, 159.6, 158.7, 156.6, 156.2, 152.0, 151.3, 148.7, 144.9, 144.4, 144.0, 143.8, 143.6, 143.4, 141.0, 135.3, 134.5, 133.6, 132.7, 131.7, 131.5, 130.0, 129.2, 129.0, 128.7, 128.5, 128.4, 126.1, 119.2, 118.9, 116.6, 116.4, 114.8, 114.5, 113.1, 111.9, 111.9, 111.4, 110.6, 109.5, 109.4, 75.6, 72.8, 60.3, 55.7, 55.4, 55.2, 55.1 55.0, 50.1, 49.7, 48.0, 47.3, 42.1, 36.6, 34.0, 33.2, 31.0, 30.8, 30.1, 29.9, 26.7 ppm; HRMS calcd. For $C_{35}H_{36}NO_4^+$ [M + H] 534.2639, found 534.2642.

^{1}H NMR comparison between enone 3 synthesized in this work [(a), 400 MHz, $CDCl_3$] and from Baran and co-workers [(b), 400 MHz, $CDCl_3$][8]

(a)

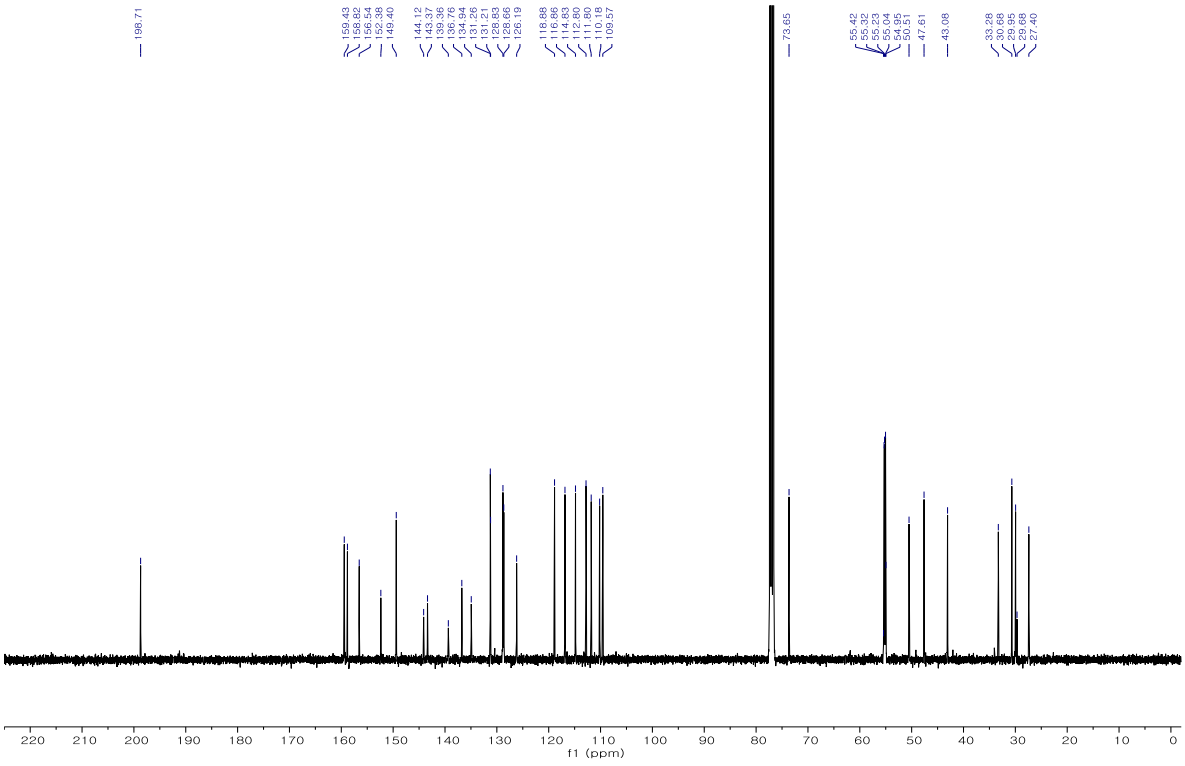


(b)

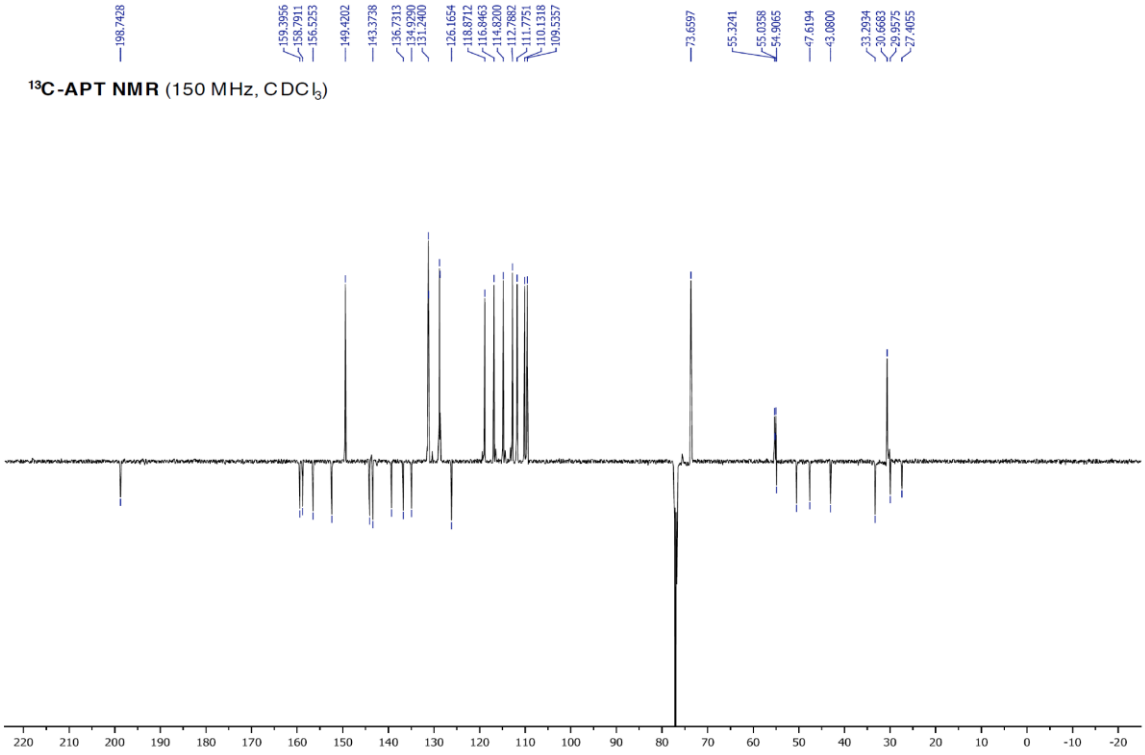


^{13}C NMR comparison between enone 3 synthesized in this work [(a), 101 MHz, $CDCl_3$] and from Baran and co-workers [(b), ^{13}C-APT, 150 MHz, $CDCl_3$][8]

(a)

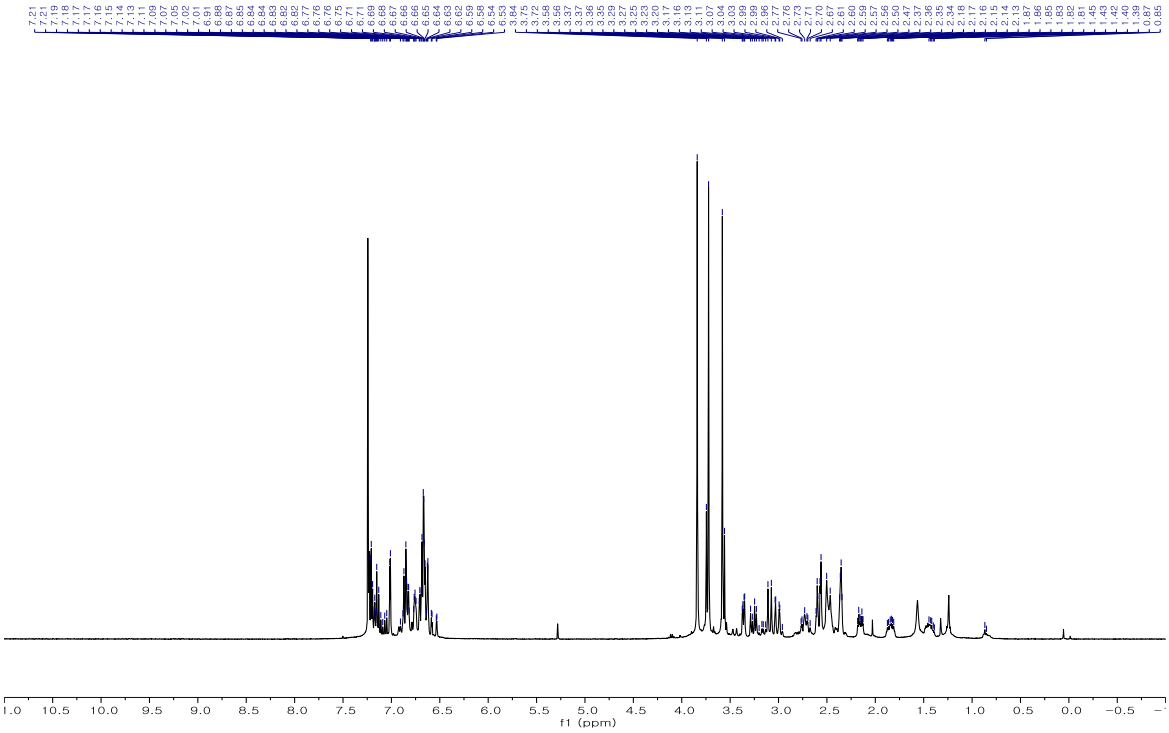


(b)

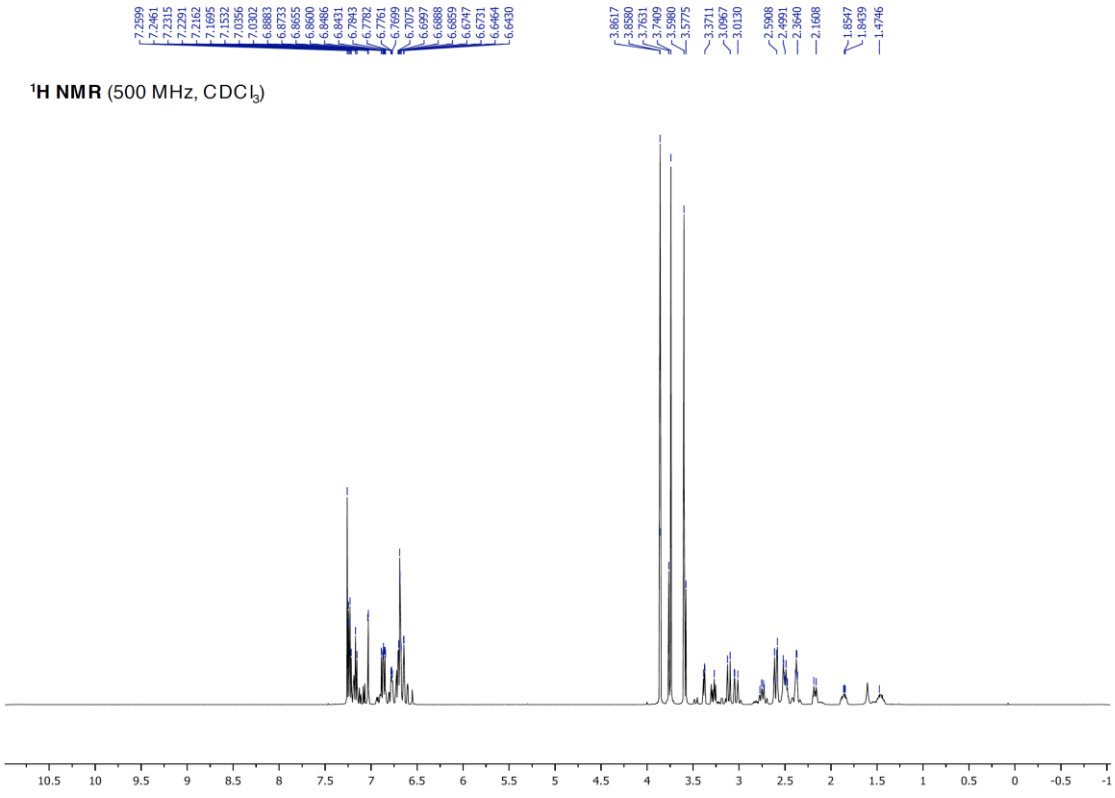


^{1}H NMR comparison between enone 3a synthesized in this work [(a), 400 MHz, $CDCl_3$] and from Baran and co-workers [(b), 500 MHz, $CDCl_3$][8]

(a)

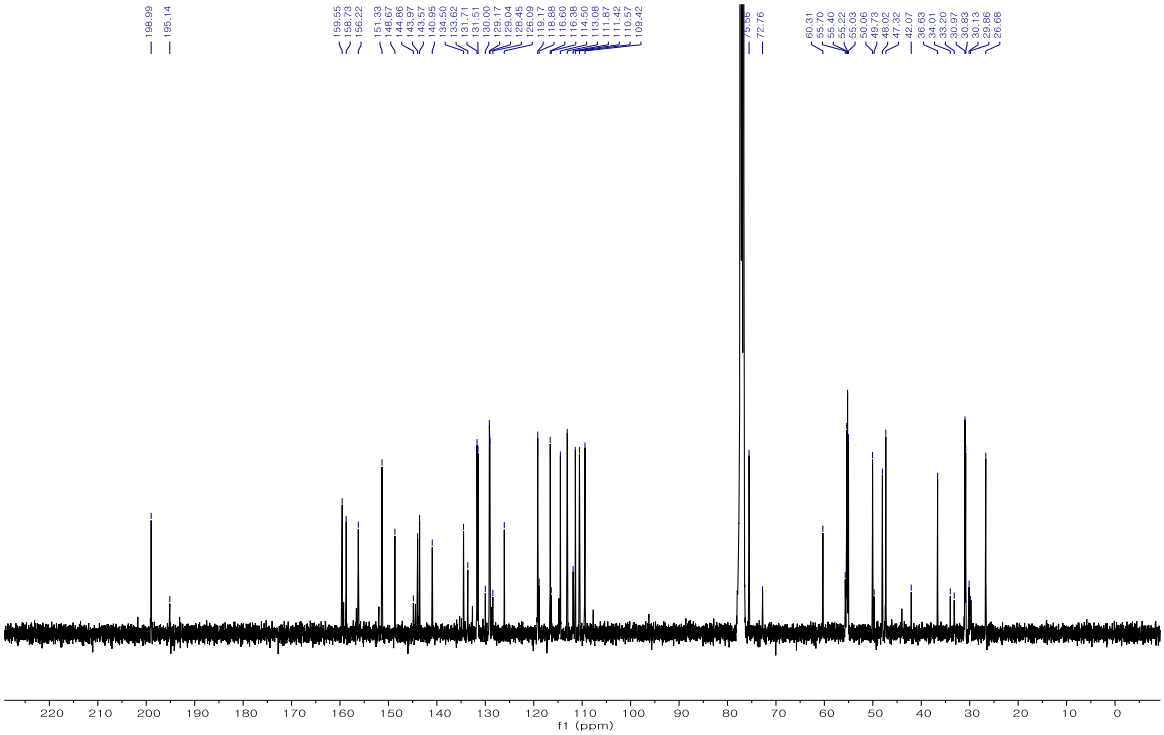


(b)

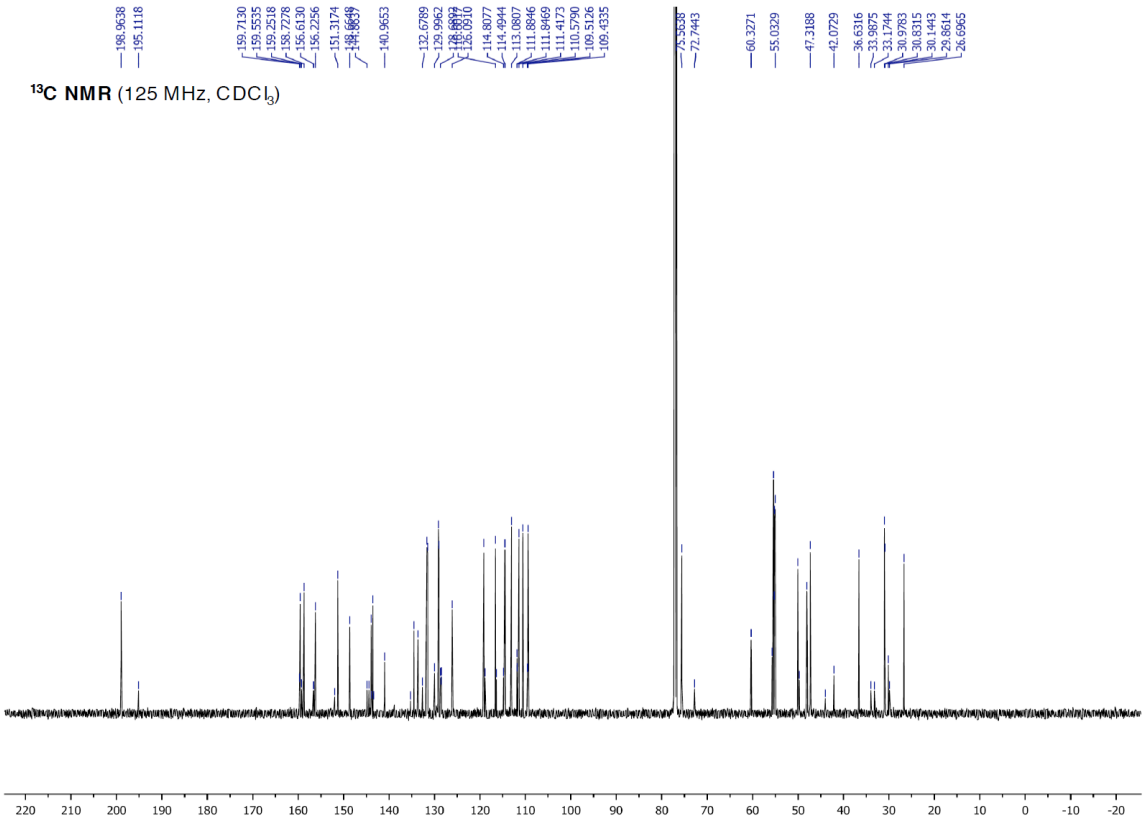


^{13}C NMR comparison between enone 3a synthesized in this work [(a), 101 MHz, $CDCl_3$] and from Baran and co-workers [(b), 125 MHz, $CDCl_3$][8]

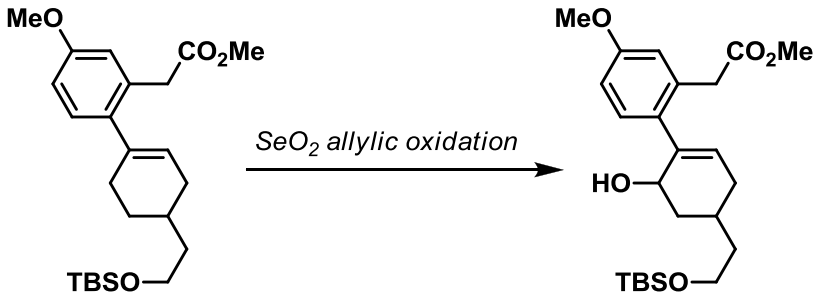
(a)



(b)



SeO_2-mediated allylic oxidation of bicyclic alkene model substrate 22a:



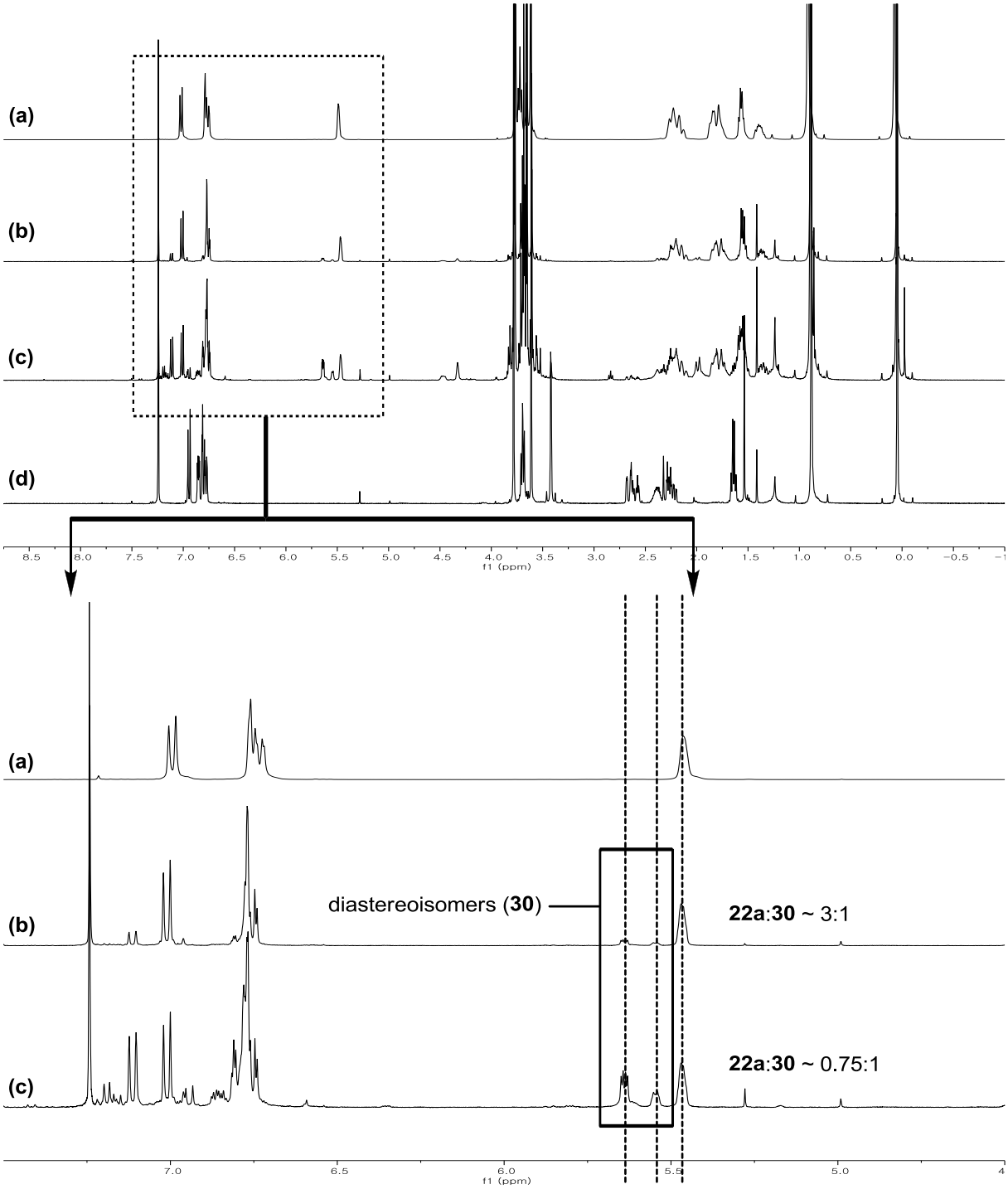
22a **30**

Bicyclic alkene model substrate **22a** [prepared from carboxylic acid **8**: MeI (2.0 equiv), K_2CO_3 (3.0 equiv), acetone, 25 °C, 16 h, 79%] was subjected to SeO_2-mediated allylic oxidation conditions and reaction progress was followed by ^{1}H NMR analysis.

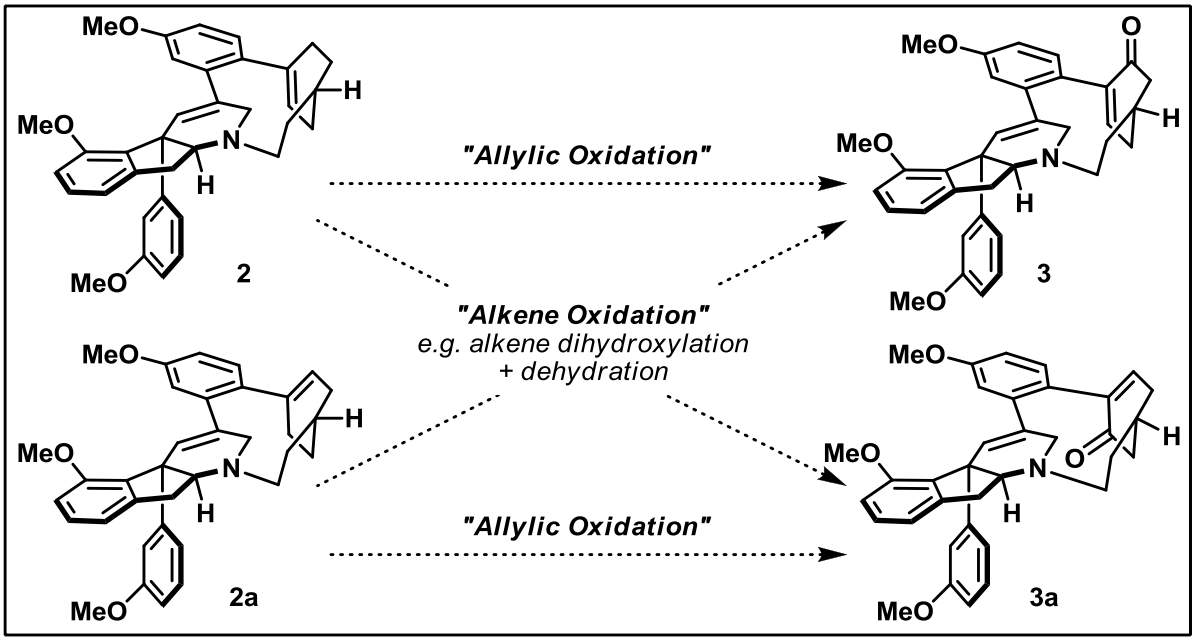
Methyl Ester 22a: R_f = 0.50 (silica gel, hexanes:Et_2O 4:1); IR (film) ν_{max} 2927, 2806, 1740, 1607, 1463, 1254, 1100, 834, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (d, *J* = 8.3 Hz, 1H), 6.82–6.72 (m, 2H), 5.49 (br s, 1H), 3.77 (s, 3H), 3.72 (t, *J* = 6.7 Hz, 2H), 3.66 (s, 3H), 3.62 (s, 2H), 2.30–2.18 (m, 2H), 2.18–2.09 (m, 1H), 1.91–1.70 (m, 3H), 1.63–1.52 (m, 2H), 1.39 (m, 1H), 0.92 (s, 9H), 0.08 ppm (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.3, 158.1, 137.2, 137.1, 132.6, 129.5, 126.2, 115.5, 112.5, 77.4, 77.1, 76.8, 61.2, 55.1, 51.8, 39.3, 38.9, 32.2, 30.7, 29.7, 29.3, 26.0, 18.4, –5.3 ppm; HRMS calcd. For $C_{24}H_{38}O_4SiNa^+$ $[M + Na]^+$ 441.2432, found 441.2435.

Allylic Alcohol 30: R_f = 0.25 (silica gel, hexanes:Et_2O 4:1); IR (film) ν_{max} 3484, 2953, 2857, 1737, 1608, 1501, 1255, 1095, 837, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, *ca.* 3:1 mixture of diastereoisomers): δ 7.11 (d, *J* = 8.1 Hz, 1H), 6.84–6.71 (m, 2H), 5.70–5.58 (m, 0.7H), 5.53 (br s, 0.3H), 4.46 (br s, 0.3H), 4.32 (s, 0.7H), 3.84–3.75 (m, 3H), 3.77 (s, 2H), 3.74–3.68 (m, 2H), 3.67 (s, 1H), 3.65 (s, 2H), 3.62–3.51 (m, 1H), 2.43–2.14 (m, 1H), 2.08–1.88 (m, 2H), 1.87–1.70 (m, 1H), 1.66–1.42 (m, 2H), 0.89 (s, 9H), 0.05 ppm (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$, *ca.* 3:1 mixture of diastereoisomers): δ 173.0, 158.5, 140.7, 138.1, 134.2, 133.6, 132.6, 130.5, 130.1, 128.5, 115.9, 115.7, 112.8, 69.5 68.0, 61.4, 60.8, 55.2, 52.2, 39.4, 39.1, 38.9, 38.9, 38.8, 38.0, 32.7, 32.5, 29.8, 26.0, 25.0, 18.4, –5.3; HRMS calcd. For $C_{24}H_{38}O_5SiNa^+$ $[M + Na]^+$ 457.2381, found 457.2384.

Representative ^{1}H NMR (400 MHz, $CDCl_3$) analysis of SeO_2-mediated allylic oxidation of bicyclic substrate 22a: (a) bicyclic substrate 22a; (b) SeO_2 (1.8 equiv), $NaHCO_3$ (5.0 equiv), 1,4-dioxane, 45 °C, 5 hours. 22a:30(*ca.* 3:1 mixture of diastereoisomers) ~ 3:1; (c) SeO_2 (1.8 equiv), $NaHCO_3$ (5.0 equiv), 1,4-dioxane, 75 °C, 5 hours. 22a:30(*ca.* 3:1 mixture of diastereoisomers) ~ 0.75:1; (d) PCC oxidation [PCC (2.0 equiv), Celite®, CH_2Cl_2, 25 °C, 4 hours] of allylic alcohol 30 leading to a single enone.



Oxidation Studies on Macrocycle 2/2a:



At the outset of our oxidation studies, we envisaged macrocycle **2**/**2a** could be used inter-exchangeably, as shown in the schematic diagram above, depending on the reaction conditions and the outcome of the reactions, to afford enones **3** and **3a**.

Reaction conditions for model (22a) and real system (2/2a):

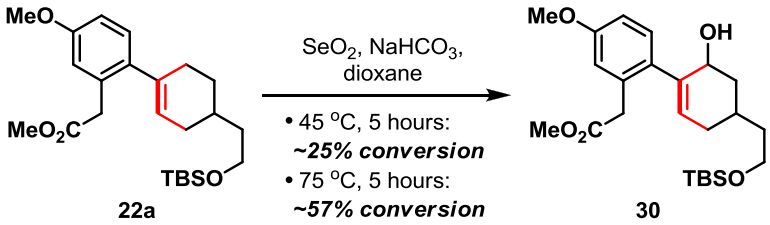
Allylic Oxidation:	***Alkene Oxidation:***
SeO_2, TBHP, CH_2Cl_2	OsO_4 (cat.), NMO, THF/H_2O
SeO_2, HCO_2H, dioxane	OsO_4 (cat.), NMO, pyridine
SeO_2, dioxane	OsO_4 (cat.), $K_3Fe(CN)_6$, *t*BuOH
Ph_2Se_2, $PhIO_2$, chlorobenzene	OsO_4 (1.0 equiv), THF/H_2O
CrO_3, 3,5-dimethylpyrazole	
PCC, benzene	*m*CPBA, CH_2Cl_2
PDC, TBHP	*m*CPBA, TFA, CH_2Cl_2
$Pd(OH)_2$/C, TBHP, CH_2Cl_2	*m*CPBA, TsOH, CH_2Cl_2
$Mn(OAc)_3$, O_2, TBHP, EtOAc	
CuBr, TBHP, benzene	BH_3•THF, THF
$Rh(cap)_4$, TBHP, CH_2Cl_2	BH_3•DMS, THF

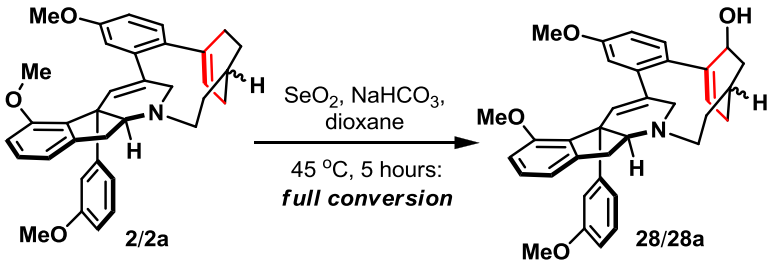
Summary:

- OsO_4-mediated dihydroxylation reactions largely afforded starting material.
- Hydroboration also largely afforded unreacted starting material
- *m*CPBA-mediated epoxidations reactions afforded a mixture of recovered starting material, or multiple products under forcing conditions. These reactions overall proved irreproducible.
- Allylic oxidation: SeO_2-based reagent system showed most promise and was further optimized for substrate **2**/**2a**
- All reactions monitored by tlc, NMR and LCMS analysis.

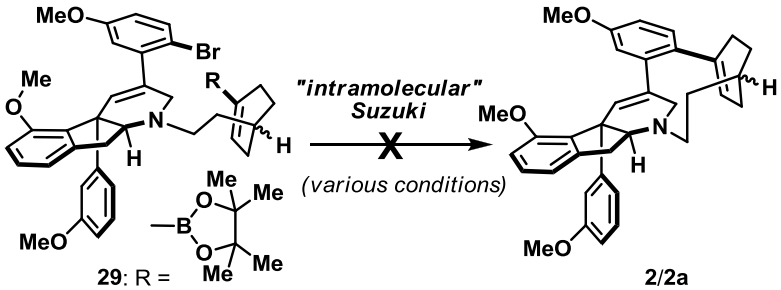
Evidences in Support of the Strained Alkene in Substrate 2/2a:

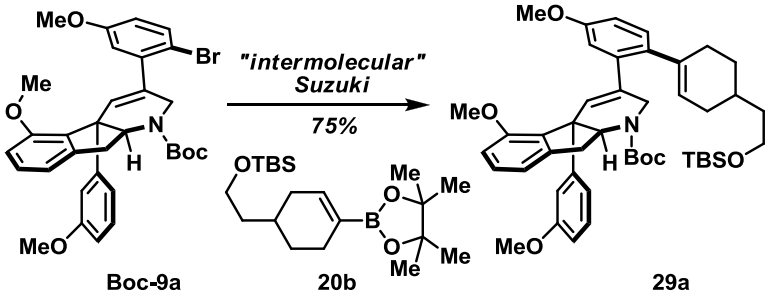
Experimentally *(i. allylic oxidation):*





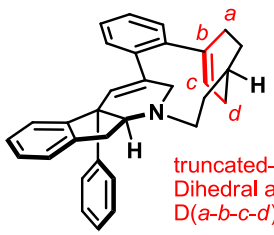
Experimentally *(ii. Suzuki cross-coupling):*

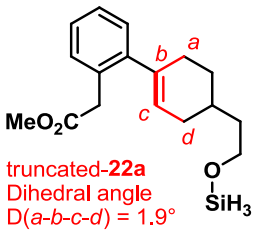




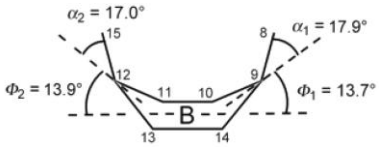
Computationally:

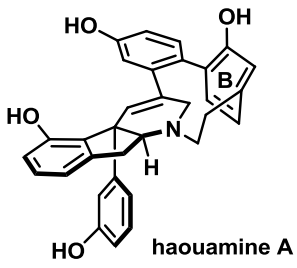
Geometric optimization (at B3LYP/def2-SVP level of theory) performed on truncated **2** and **22a**:



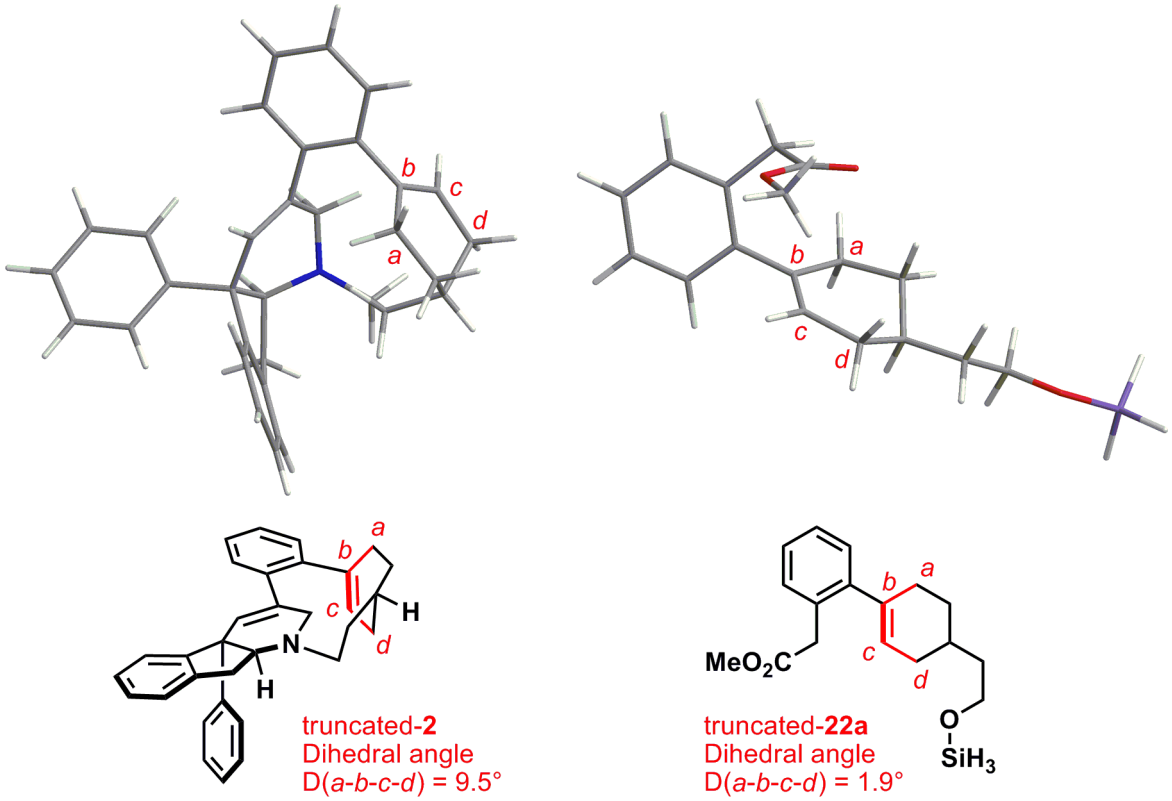


Pictorial showing distorted B-ring of Haouamine. Courtesy of:
Org. Lett. **2006**, *8*, 1901 (Wipf)





The computations were performed with Gaussian16 package.* The geometries of truncated molecules were optimized using B3LYP functional** in gas phase. The def2-SVP basis sets*** were employed for all atoms. Frequency analysis were performed to confirm each structure being a local minimum (no imaginary frequency).

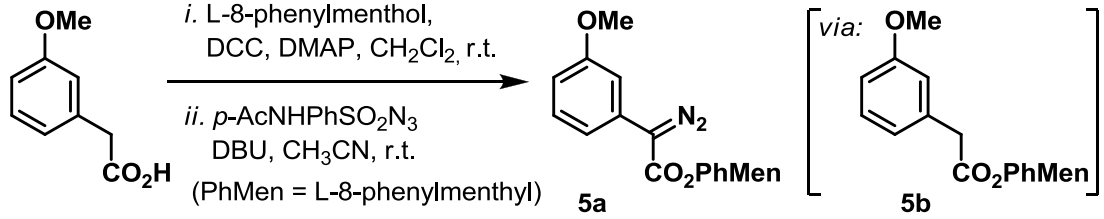


*Frisch, M. J. et al. Gaussian 16, revision A.03; Gaussian, Inc.: Wallingford, CT, 2016.

(a) Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* **1993, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlationenergy formula into a functional of the electron density. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785. (c) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. Ab Initio Calculation of Vibrational Absorption and Circular Dichroism Spectra Using Density Functional Force Fields. *J. Phys. Chem.* **1994**, *98*, 11623.

***Weigend, F.; Ahlrichs, R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. *Phys. Chem. Chem. Phys.*, **2005**, *7*, 3297.

Diazoester 5a

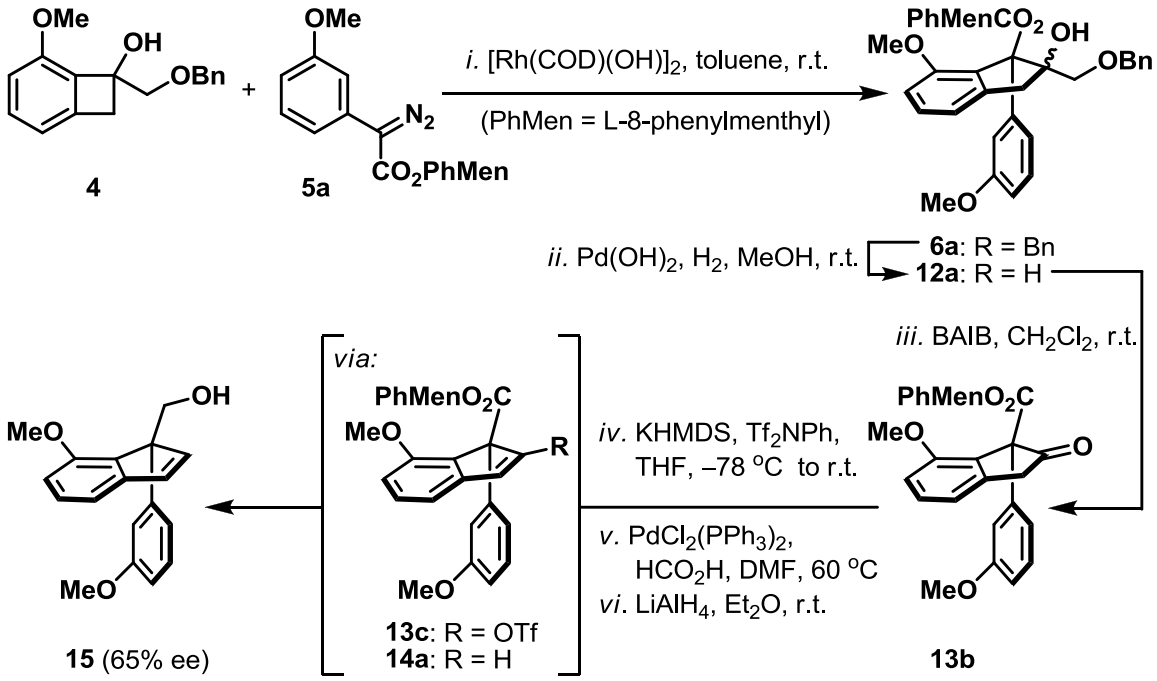


(i) To a stirred solution of 3-methoxyphenylacetic acid (0.80 g, 4.84 mmol) in CH_2Cl_2 (48.0 mL) at room temperature was added L-8-phenylmenthol[9] (1.35 g, 5.81 mmol), DCC (1.20 g, 5.81 mmol) and DMAP (60.0 mg, 0.48 mmol). The resulting mixture was stirred for 16 h before it was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 8:2) to afford ester **5b** (1.75 g, 95%) as a colorless oil.

(ii) To a stirred solution of ester **5b** (obtained above, 1.75 g, 4.60 mmol) in CH_3CN (23.0 mL) at room temperature was added DBU (0.98 g, 6.43 mmol) and *p*-$AcNHPhSO_2N_3$ (1.32 g, 5.51 mmol). The resulting mixture was stirred for 16 h before it was concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (25 mL) and diluted with H_2O (40 mL), the aqueous layer extracted with CH_2Cl_2 (3 × 25 mL), combined organic layer washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 9:1) to afford diazoester **5a** (1.74 g, 93%) as a red oil. **5a**: R_f = 0.64 (silica gel, hexanes:EtOAc 9:1); IR (film) ν_{max} 2955, 2920, 2083, 1739, 1689, 1494, 1234, 1150, 1025, 767, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29–7.23 (m, 4H), 7.20 (dd, *J* = 8.4, 6.6 Hz, 1H), 7.15–7.11 (m, 1H), 7.09 (t, *J* = 2.2 Hz, 1H), 6.86 (ddd, *J* = 7.8, 1.8, 0.9 Hz, 1H), 6.70 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 5.07 (td, *J* = 10.8, 4.5 Hz, 1H), 3.83 (s, 3H), 2.05 (ddd, *J* = 12.2, 10.4, 3.6 Hz, 1H), 1.98–1.89 (m, 1H), 1.77 (dd, *J* = 13.5, 3.5 Hz, 1H), 1.67 (dt, *J* = 13.0, 3.1 Hz, 1H), 1.55 (s, 1H), 1.50 (tq, *J* = 5.6, 2.6 Hz, 1H), 1.35 (s, 3H), 1.24 (s, 3H), 1.16 (qd, *J* = 13.1, 3.4 Hz, 1H), 1.05 (q, *J* = 11.9 Hz, 1H), 0.89 ppm (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 160.1, 151.5, 129.8, 128.0, 127.6, 125.4, 125.2, 115.9, 111.4, 109.5, 74.5, 74.5, 55.4, 55.4, 51.1, 42.5, 39.8, 34.6, 31.7, 28.4, 26.8, 24.7, 21.9 ppm; HRMS calcd. For $C_{25}H_{30}N_2O_3Na^+$ $[M + Na]^+$ 429.2149, found 429.2150.

Synthesis of Optically Active Primary Alcohol 15:

***a.* Chiral Auxiliary Approach:**

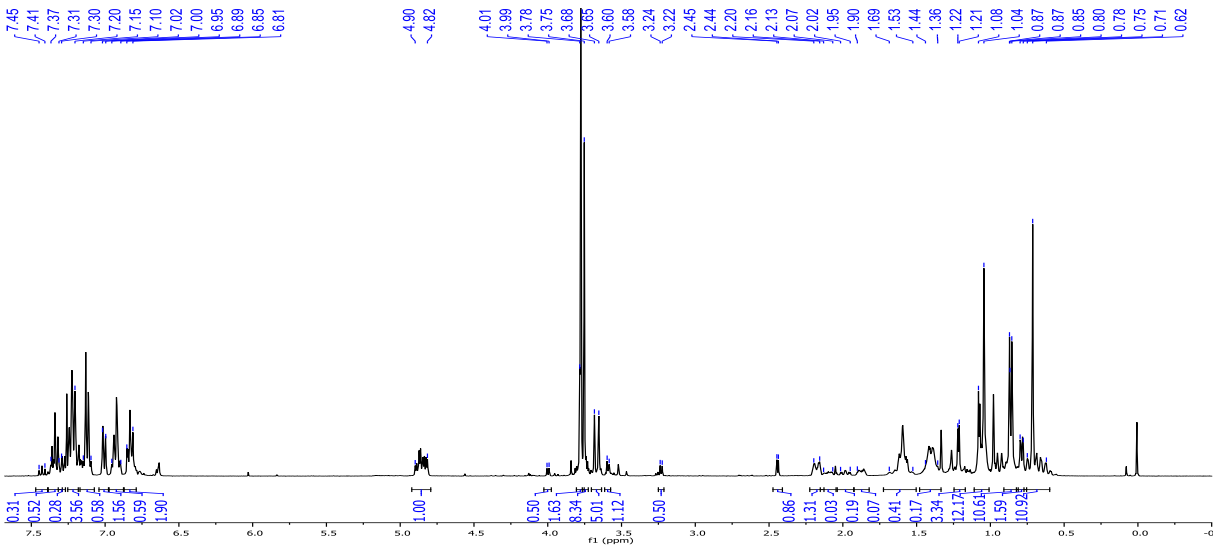


(i) To a stirred solution of tertiary alcohol **4** (78.0 mg, 0.28 mmol) in toluene (1.4 mL) at 0 °C was added diazoester **5a** (0.13 g, 0.31 mmol) followed by $[Rh(COD)(OH)]_2$ (5.0 mg, 11.0 μmol). The resulting mixture was stirred for 10 min before it was warmed to room temperature and stirred for 4 h. The resulting mixture was treated with additional $[Rh(COD)(OH)]_2$ (5.0 mg, 11.0 μmol) and stirred for 12 h before it was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 9.5:1→9:1) to afford tertiary alcohol **6a** (66.0 mg, 36%, unoptimized, complex mixture of 4 diastereoisomers) as a yellow oil. **6a**: R_f = 0.5, 0.6 (silica gel, hexanes:EtOAc 8:2); IR (film) ν_{max} 3474, 3033, 2957, 2866, 1726, 1599, 1454, 1260, 1089, 735, 698 cm^{-1}; HRMS calcd. For $C_{42}H_{48}O_6Na^+$ $[M + Na]^+$ 671.3343, found 671.3345.

(ii) To a stirred solution of benzyl ether **6a** (65.0 mg, 0.10 mmol) in MeOH (2.5 mL) at room temperature was added $Pd(OH)_2$ on carbon (5 wt% on carbon, 106% wt/wt, 69.0 mg). The resulting mixture was purged with hydrogen gas (balloon bubbling) for 10 min then stirred under an atmosphere of hydrogen (balloon) for 2 h. The resulting mixture was filtered through a pad of silica gel and eluted with EtOAc (5 mL), and concentrated under reduced pressure to afford crude diol **12a** which was used directly in the subsequent reaction.

(iii) To a stirred solution of diol **12a** (obtained above) in CH_2Cl_2 (2.0 mL) at room temperature was added BAIB (38.6 mg, 0.12 mmol). The resulting mixture was stirred for 1 h before it was washed with pH7 phosphate buffer (3 mL), the organic layer separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 9.5:1) to afford keto ester **13b** (28.5 mg, 54% over two steps) as a colorless oil. **13b**: R_f = 0.70 (silica gel, hexanes:EtOAc 6:4); IR (film) ν_{max} 2960, 2920, 2871, 1736, 1588, 1484, 1212, 1046, 768, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, mixture of 2 diastereoisomers): δ 7.43 (t, *J* = 7.9 Hz, 0.1H), 7.35 (td, *J* = 7.9, 7.4, 4.5 Hz, 0.9H), 7.30–7.17 (m, 4H), 7.17–7.08 (m, 2H), 7.01 (dd, *J* = 7.7, 1.2 Hz, 1H), 6.97–6.88 (m, 2H), 6.87–6.77 (m, 2H), 4.93–4.79 (m, 1H), 4.0 (d, *J* = 5.6 Hz, 0.2H), 3.76 (s, 3H), 3.75 (s, 2H), 3.67 (s, 0.5H), 3.66 (s, 0.5H), 3.59 (d, *J* = 5.1 Hz, 0.3H), 3.26 (d, *J* = 6.4 Hz, 0.2H), 3.23 (d, *J* = 5.4 Hz, 0.3H), 2.18 (dq, *J* = 12.4, 3.1 Hz, 0.5H), 2.14–1.94 (m, 0.3H), 1.92–1.82 (m, 0.2H), 1.69–1.52 (m, 2H), 1.47–1.36 (m, 2H), 1.29–1.13 (m, 2H), 1.14–1.01 (m, 3H), 1.01–0.88 (m, 2H), 0.86 (dd, *J* = 6.4, 1.4 Hz, 2H), 0.82–0.74 (m, 1.5H), 0.73–0.59 ppm (m, 2.5H); HRMS calcd. For $C_{34}H_{38}O_5Na^+$ $[M + Na]^+$ 549.2611, found 549.2612.

Representative ^1H NMR (400 MHz, $CDCl_3$, mixture of 2 diastereoisomers) of 13b

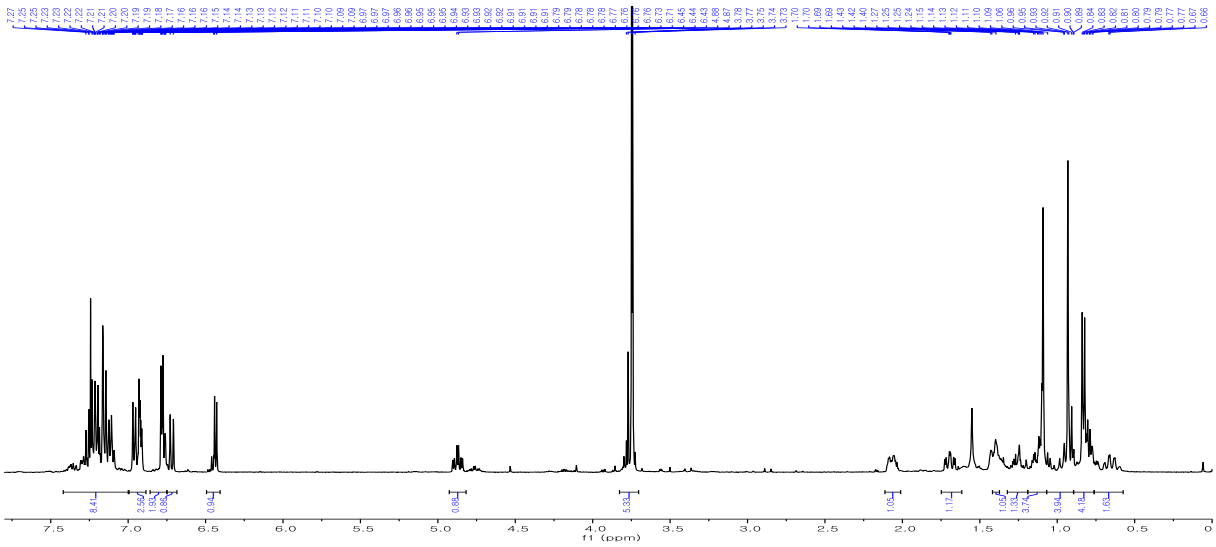


(iv) To a stirred solution of ketone **13b** (28.0 mg, 54.0 μmol) in THF (2.0 mL) at −78 °C was added KHMDS (0.7 M in toluene, 80 μL, 59.4 μmol). The resulting mixture was stirred for 30 min before a solution of Tf_2NPh (25.0 mg, 70.0 μmol) in THF (1.0 mL) was added. The

resulting mixture was stirred for 15 min then warmed to room temperature and stirred for 2 h before it was quenched with NH_4Cl (3 mL, sat. aq.), extracted with EtOAc (3 × 3 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 9:1) to afford triflate **13c** (35.0 mg, 99%) as a yellow oil. **13c**: R_f = 0.56 (silica gel, hexanes:EtOAc 8:2).

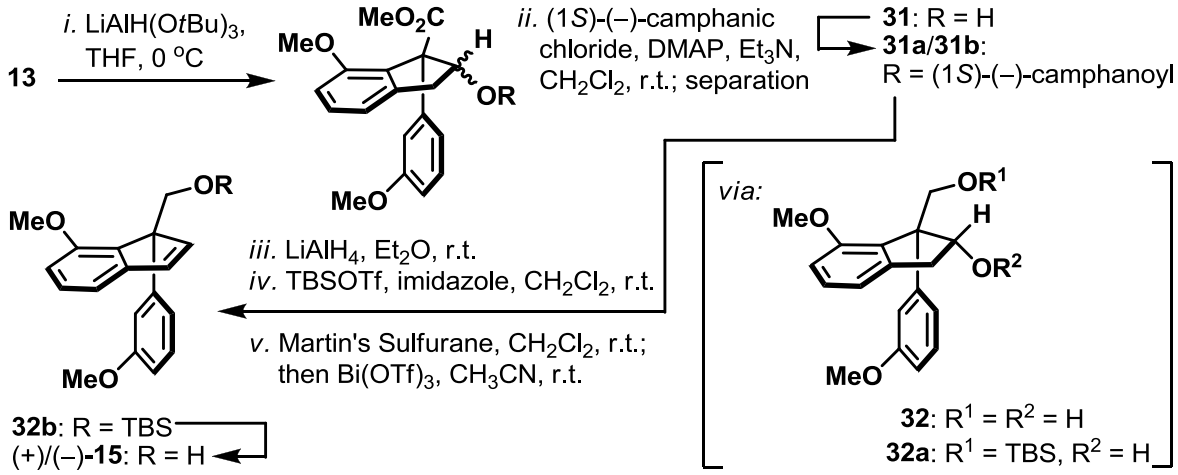
(v) To a stirred solution of triflate **13c** (obtained above) in DMF (2.0 mL) at room temperature was added $PdCl_2(PPh_3)_2$ (1.9 mg, 2.7 μmol) and *n*Bu_3N (0.04 mL, 0.16 mmol). The resulting mixture was purged with argon (balloon bubbling) for 5 min before HCO_2H (5.1 μL, 0.14 mmol) was added. The resulting mixture was placed into a pre-heated (60 ^oC) oil bath and stirred for 1.5 h before it was cooled to room temperature, diluted with HCl (1 N aq., 5 mL), extracted with EtOAc (3 × 2 mL), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 9:1) to afford alkenyl ester **14a** (21.6 mg, 78%) as a colorless oil. **14a**: R_f = 0.60 (silica gel, hexanes:EtOAc 8:2); ^1H NMR (400 MHz, $CDCl_3$, mixture of 2 diastereoisomers): δ 7.42–7.00 (m, 8H), 6.99–6.89 (m, 3H), 6.86–6.75 (m, 2H), 6.72 (d, *J* = 8.3 Hz, 1H), 6.44 (dd, *J* = 7.6, 5.3 Hz, 1H), 4.87 (td, *J* = 10.6, 4.3 Hz, 1H), 3.83–3.70 (m, 5H), 2.11–2.01 (m, 1H), 1.69 (ddd, *J* = 12.1, 10.4, 3.5 Hz, 1H), 1.40 (s, 1H), 1.32–1.19 (m, 1H), 1.19–1.07 (m, 4H), 1.07–0.89 (m, 4H), 0.89–0.76 (m, 4H), 0.76–0.57 ppm (m, 1H).

Representative ^1H NMR (400 MHz, $CDCl_3$, mixture of 2 diastereoisomers) of 14a



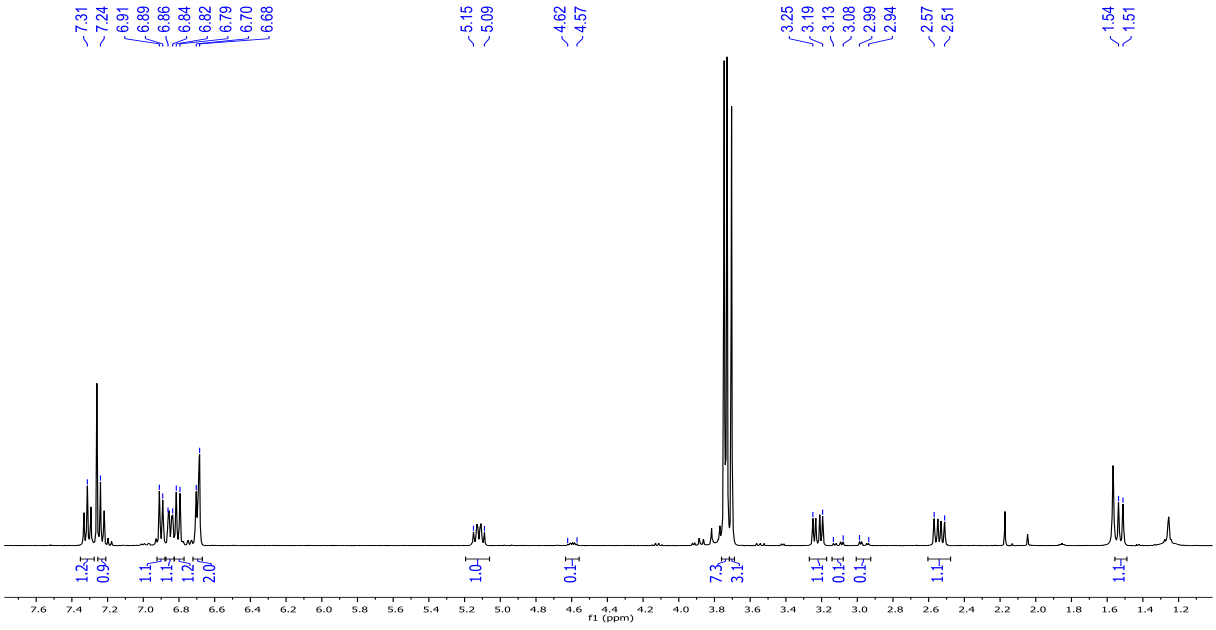
(vi) To a stirred suspension of $LiAlH_4$ (2.0 mg, 46.0 μmol) in Et_2O (0.3 mL) at 0 °C was added a solution of alkenyl ester **14a** (21.6 mg, 42.0 μmol) in Et_2O (0.3 mL). The resulting mixture was stirred for 5 min then warmed to room temperature and stirred for 0.5 h before it was cooled to 0 °C and quenched sequentially with H_2O (50 μL), NaOH (15% aq., 50 μL) and H_2O (0.1 mL). The resulting mixture was warmed to room temperature and stirred for 5 min before it was filtered through a pad of Celite®, eluted with EtOAc (5 mL), and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 4:1) to afford optically active alcohol **15** (9.7 mg, 81%) as a colorless oil with characterization data identical to those obtained for the racemic compound.

***b.* Resolution Approach:**



(i) To a stirred solution of keto ester **13** (1.0 equiv) in THF at −78 °C was added $LiAlH(OtBu)_3$ (1.0 M in THF, 1.5 equiv). The resulting mixture was warmed to 0 °C and stirred for 3 h before it was quenched with NH_4Cl (sat. aq.), extracted with EtOAc (3 ×), combined organic layer washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was filtered through a pad of silica gel and eluted with (hexanes:EtOAc 4:1), and concentrated under reduced pressure to afford alcohol **31** (92%, *ca.* 10:1 mixture of diastereoisomers) as an amorphous white solid. **31**: ^{1}H NMR (400 MHz, $CDCl_3$, *ca.* 10:1 mixture of diastereoisomers): δ 7.31 (t, *J* = 7.6, 1H), 7.24 (t, *J* = 7.6, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 10.5 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.72–6.67 (m, 2H), 5.19–5.06 (m, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.22 (dd, *J* = 15.3, 6.5 Hz, 1H), 2.54 (dd, *J* = 15.3, 8.1 Hz, 1H), 1.52 ppm (d, *J* = 10.2 Hz, 1H).

Representative ^{1}H NMR (400 MHz, $CDCl_3$, crude) of alcohol 31



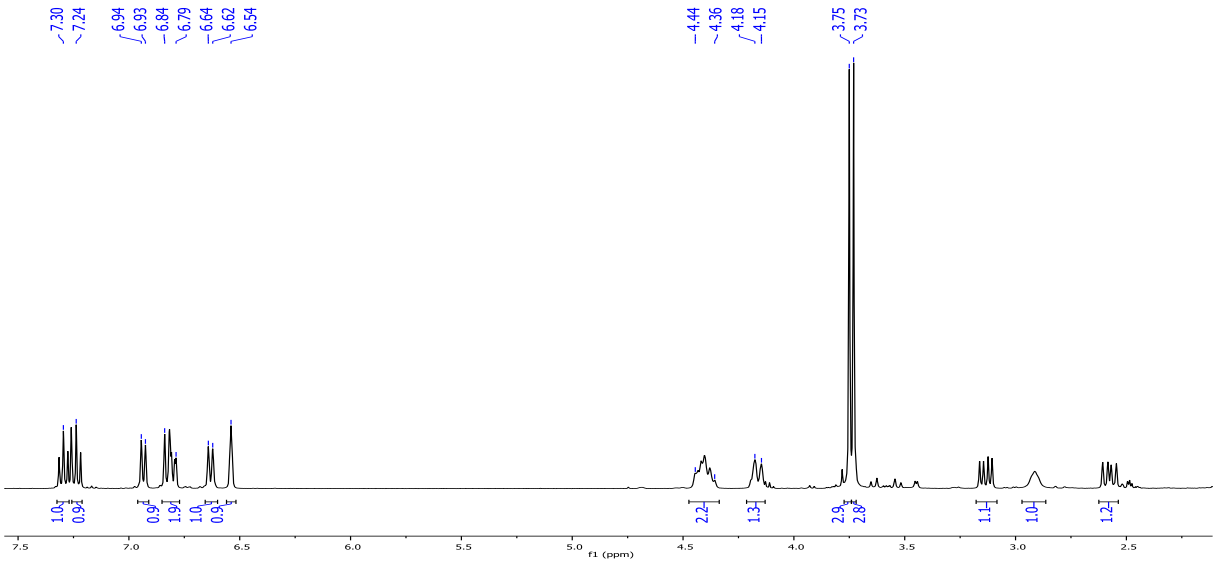
(ii) To a stirred solution of alcohol **31** (1.0 equiv) in CH_2Cl_2 at room temperature was added DMAP (1.0 equiv), Et_3N (4.0 equiv) and (1*S*)-(–)-camphanic chloride (2.0 equiv). The resulting mixture was stirred for 1 h before it was quenched with NH_4Cl (sat. aq.), extracted with EtOAc (3 ×), combined organic layer dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, CH_2Cl_2:acetone 99.3:0.7) to afford diastereomeric camphanic ester **31a** (less polar isomer, 49%) as a white foam and **31b** (more polar isomer, 48%) as a colorless oil. **31a** and **31b**: IR (film) ν_{max} 2962, 2837, 1789, 1734, 1591, 1483, 1267, 1233, 1059, 733 cm^{-1}; HRMS calcd. For $C_{29}H_{32}O_8Na^+$ $[M + Na]^+$ 531.1989, found 531.1988.

Less polar camphanic ester 31a: R_f = 0.3 (silica gel, CH_2Cl_2:acetone 99:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.30 (m, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.77 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.69 (ddd, *J* = 7.8, 1.8, 0.9 Hz, 1H), 6.64 (dd, *J* = 2.6, 1.7 Hz, 1H), 6.14 (t, *J* = 6.3 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H), 3.45 (dd, *J* = 16.0, 6.6 Hz, 1H), 2.88 (dd, *J* = 16.0, 6.1 Hz, 1H), 2.19–2.10 (m, 1H), 1.80 (ddd, *J* = 12.6, 10.5, 4.4 Hz, 1H), 1.75–1.66 (m, 1H), 1.57 (ddt, *J* = 12.8, 8.9, 5.0 Hz, 1H), 1.04 (s, 3H), 0.87 (s, 3H), 0.78 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.4, 173.2, 167.0, 158.9, 156.8, 142.0, 136.0, 130.6, 128.8, 128.3, 122.1, 117.4, 116.1, 112.6, 110.3, 90.9, 80.9, 65.6, 55.6, 55.3, 54.8, 54.2, 52.9, 37.4, 30.4, 28.9, 16.6, 16.6, 9.8 ppm.

More polar camphanic ester 31b: R_f = 0.2 (silica gel, CH_2Cl_2:acetone 99:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (t, *J* = 7.9 Hz, 1H), 7.17 (t, *J* = 8.1 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.80–6.76 (m, 1H), 6.67 (d, *J* = 7.1 Hz, 2H), 6.15 (t, *J* = 6.2 Hz, 1H), 3.73 (s, 6H), 3.70 (s, 3H), 3.47 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.86 (dd, *J* = 16.0, 5.9 Hz, 1H), 1.95 (dd, *J* = 12.4, 8.8 Hz, 1H), 1.74 (ddt, *J* = 12.8, 8.4, 4.3 Hz, 2H), 1.64–1.52 (m, 1H), 1.02 (s, 3H), 0.74 ppm (d, *J* = 2.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 177.9, 172.9, 166.8, 159.0, 156.8, 141.9, 136.2, 130.6, 128.7, 128.4, 121.9, 117.3, 116.2, 112.5, 110.4, 91.0, 81.0, 65.5, 55.6, 55.3, 54.8, 54.1, 52.9, 37.9, 30.3, 29.1, 16.8, 16.6, 9.7 ppm.

(iii) To a stirred suspension of $LiAlH_4$ (2.0 equiv) in Et_2O at 0 °C was added a solution of camphanic ester **31a** (1.0 equiv) in Et_2O. The resulting mixture was stirred for 5 min then warmed to room temperature and stirred for 1 h before it was cooled to 0 °C and quenched sequentially with H_2O, NaOH (15% aq.) and H_2O. The resulting mixture was warmed to room temperature and stirred for 5 min before it was filtered through a pad of Celite®, eluted with EtOAc, and concentrated under reduced pressure to afford the corresponding diol **32** (95%) as a colorless oil. **32**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.85–6.77 (m, 2H), 6.63 (d, *J* = 7.9 Hz, 1H), 6.54 (s, 1H), 4.47–4.34 (m, 2H), 4.16 (d, *J* = 11.9 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.13 (dd, *J* = 15.3, 7.2 Hz, 1H), 2.91 (br s, 1H), 2.58 ppm (dd, *J* = 15.3, 9.4 Hz, 1H).

Representative ^{1}H NMR (400 MHz, $CDCl_3$, crude) of diol 32

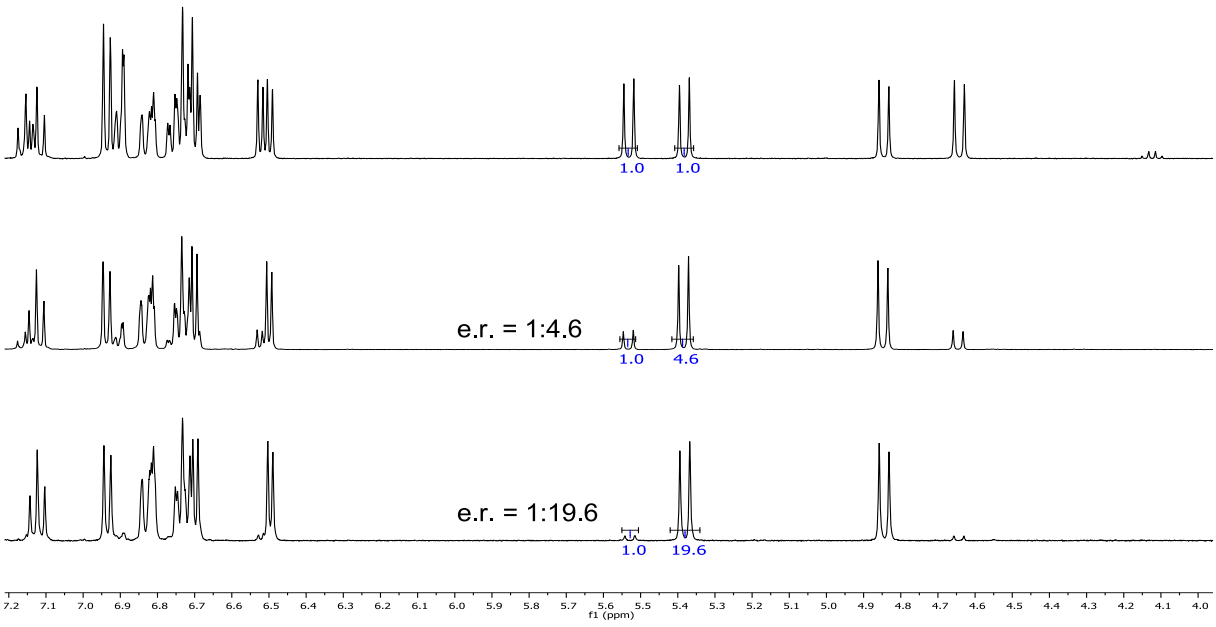


(iv) To a stirred solution of diol **32** (1.0 equiv) in CH_2Cl_2 at room temperature was added imidazole (4.0 equiv) and TBSOTf (2.0 equiv). The resulting mixture was stirred for 3 h before it was passed through a pad of silica gel and eluted with (hexanes:EtOAc 9:1), and concentrated under reduced pressure to afford primary mono-silyl ether **32a** (81%) as a colorless oil.

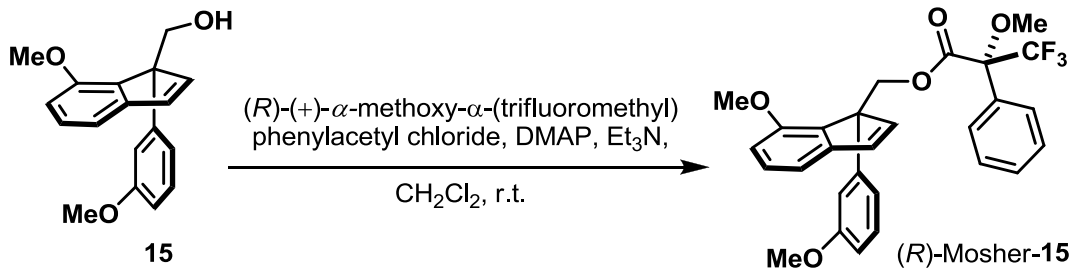
(v) To a stirred solution of secondary alcohol **32a** (1.0 equiv) in CH_2Cl_2 at room temperature was added Martin's sulfurane (1.5 equiv). The resulting mixture was stirred for 3 h before it was filtered through a pad of silica gel and eluted with (hexanes:EtOAc 95:5), and concentrated under reduced pressure to afford indene **32b** as a colorless oil. **32b**: R_f = 0.65 (silica gel, hexanes:EtOAc 2:1); IR (film) ν_{max} 2953, 2929, 2856, 1599, 1473, 1261, 1098, 850, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25–7.19 (m, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 7.01–6.97 (m, 1H), 6.94 (d, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.75–6.62 (m, 4H), 4.77 (d, *J* = 9.6 Hz, 1H), 3.77–3.73 (m, 1H), 3.73 (s, 3H), 3.66 (s, 3H), 0.80 (s, 9H), 0.00 (s, 3H), –0.08 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.2, 155.6, 146.3, 145.1, 140.9, 135.1, 129.6, 129.0, 128.5, 120.0, 114.4, 113.7, 111.4, 108.8, 65.5, 63.9, 55.2, 55.1, 25.7, 18.1, –5.4, –5.6 ppm; HRMS calcd. For $C_{24}H_{32}O_3SiNa^+$ $[M + Na]^+$ 419.2013, found 419.2016.

To a stirred solution silyl ether **32b** (obtained above) in CH_3CN/H_2O (98:2) at room temperature was added $Bi(OTf)_3$ (1.5 equiv). The resulting mixture was stirred for 2 h before it was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 4:1) to afford alkenyl alcohol **15** (70% over two steps) as a colorless oil. All characterization data for optically active alcohol **15** are identical to those obtained for the racemic compound [(+)-**15**: $[\alpha]_D^{24}$ = +255 (*c* = 0.29, $CHCl_3$); (–)-**15**: $[\alpha]_D^{24}$ = –261 (*c* = 0.59, $CHCl_3$)]. The reaction sequence developed for the conversion of racemic **15** to racemic amino-alcohol 7 is directly applicable for optically active **(+)-15** and **(–)-15** [(+)-**7**: $[\alpha]_D^{24}$ = +77.1 (*c* = 1.27, $CHCl_3$); (–)-**7**: $[\alpha]_D^{24}$ = –76.3 (*c* = 1.11, $CHCl_3$)].

Representative ^{1}H NMR (400 MHz, $CDCl_3$): mixture of diastereomeric Mosher esters derived from racemic alkenyl alcohol 15 (top); mixture of diastereomeric Mosher esters derived from optically active alkenyl alcohol 15 (chiral auxiliary approach, middle); mixture of diastereomeric Mosher esters derived from optically active alkenyl alcohol 15 (resolution approach, bottom)

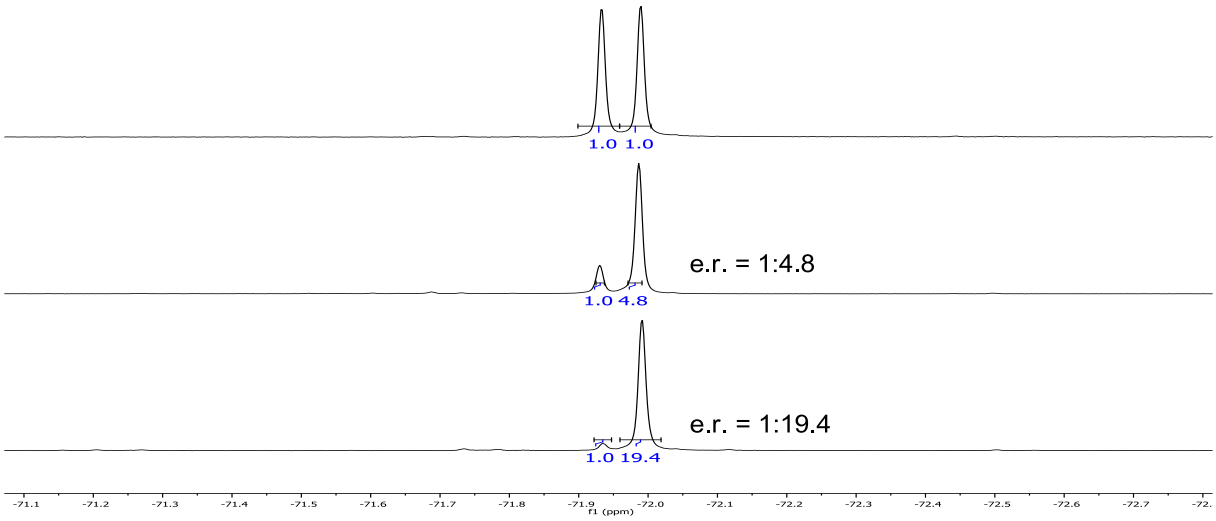


Preparation of Mosher Ester Derivative of Alkenyl Alcohol 15:



To a stirred solution of alkenyl alcohol **15** (1.0 equiv.) in CH_2Cl_2 (0.1 M) at room temperature was added DMAP (0.1 equiv.), Et_3N (4.0 equiv.) and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (1.2 equiv.). The resulting mixture was stirred for 2 h before it was quenched with NH_4Cl (sat. aq.), extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (silica gel, hexanes:EtOAc 9.5:1) to afford (*R*)-Mosher-**15** as a colorless oil.

Representative ^{19}F NMR (376 MHz, $CDCl_3$): mixture of diastereomeric Mosher esters derived from racemic alkenyl alcohol 15 (top); mixture of diastereomeric Mosher esters derived from optically active alkenyl alcohol 15 (chiral auxiliary approach, middle); mixture of diastereomeric Mosher esters derived from optically active alkenyl alcohol 15 (resolution approach, bottom)



II) Abbreviations

BAIB = diacetoxyiodo)benzene

Bn = benzyl

Boc_2O = di-*tert*-butyl dicarbonate

Boc = *tert*-butoxycarbonyl

B_2Pin_2 = bis(pinacolato)diboron

COD = cyclooctadienyl

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

DCC = *N*,*N*'-dicyclohexylcarbodiimide

DMA = *N*,*N*'-dimethylacetamide

DMAP = 4-dimethylaminopyridine

DMF = *N*,*N*'-dimethylformamide

DMP = Dess-Martin periodinane

dppf = 1,1′-Bis(diphenylphosphino)ferrocene

EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide

KHMDS = potassium bis(trimethylsilyl)amide

PCC = pyridinium chlorochromate

$Pd(dppf)Cl_2$ = [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)

PivOH = 2,2-dimethylpropionic acid

PPh_3 = triphenylphosphine

$Rh_2(Oct)_4$ = rhodium(II) octanoate, dimer

TBAF = tetra-*n*-butylammonium fluoride

TBS = *tert*-butyldimethylsilyl

TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate

TMDSO = 1,1,3,3-tetramethyldisiloxane

Tf_2NPh = *N*-phenyl-bis(trifluoromethanesulfonimide)

Tf = trifluoromethansulfonyl

Ts = *p*-toluenesulfonyl

TsCl = *p*-toluenesulfonyl chloride

III) References

1. For preparation of (benzyloxymethyl)tri-*n*-butylstannane, see: Di Bussolo, V.; Fiasella, A.; Romano Maria, R.; Favero, L.; Pineschi, M.; Crotti, P. *Org. Lett.* **2007**, *9*, 4479.
2. For preparation of ketone **10**, see: Chen, P. H.; Savage, N. A.; Dong, G. *Tetrahedron* **2014**, *70*, 4135.
3. For preparation of diazoester **5**, see: Chan, W.; Yeung, S.; Zhou, Z.; Chan, A. S. C.; Yu, W. *Org. Lett.* **2010**, *12*, 604.
4. For preparation of ketone **19**, see: (a) Desrat, S.; Remeur, C.; Roussi, F. *Org. Biomol. Chem.* **2015**, *13*, 5520; (b) Ihara, M.; Taniguchi, T.; Makita, K.; Takano, M.; Ohnishi, M.; Taniguchi, N.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1993**, *115*, 8107.
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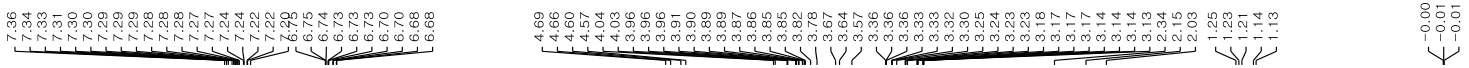
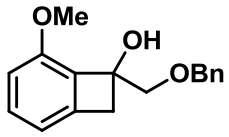
9. For preparation of L-8-phenylmenthol, see: Ort, O. *Org. Synth.* **1987**, *65*, 203.

IV) ^{1}H and ^{13}C NMR Spectra for Compounds

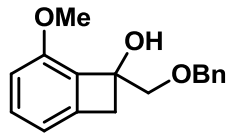


^{1}H NMR (400 MHz, $CDCl_3$)

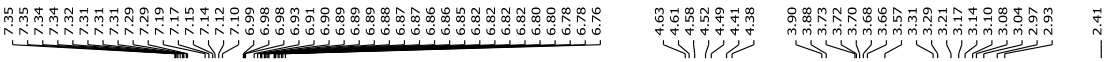


4

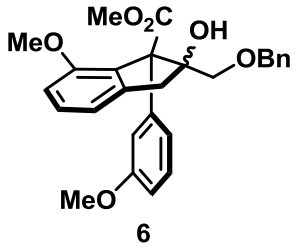
^{13}C NMR (101 MHz, $CDCl_3$)



4



^{1}H NMR (400 MHz, $CDCl_3$)



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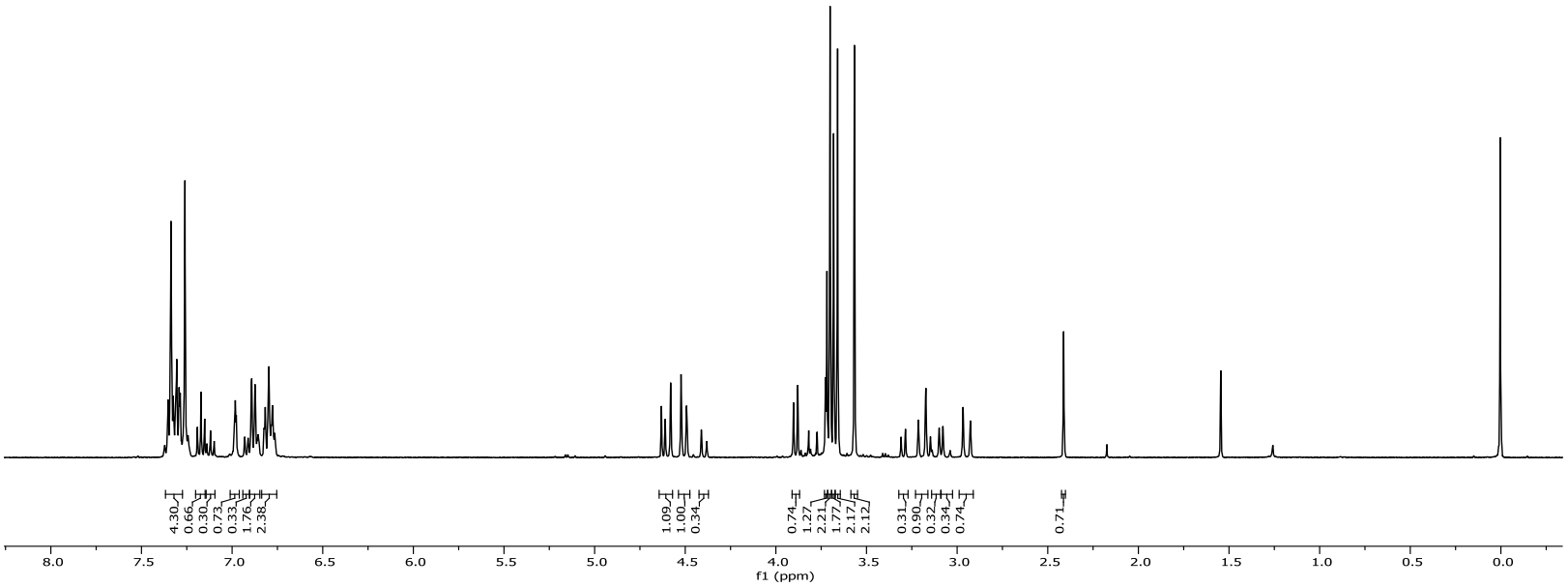
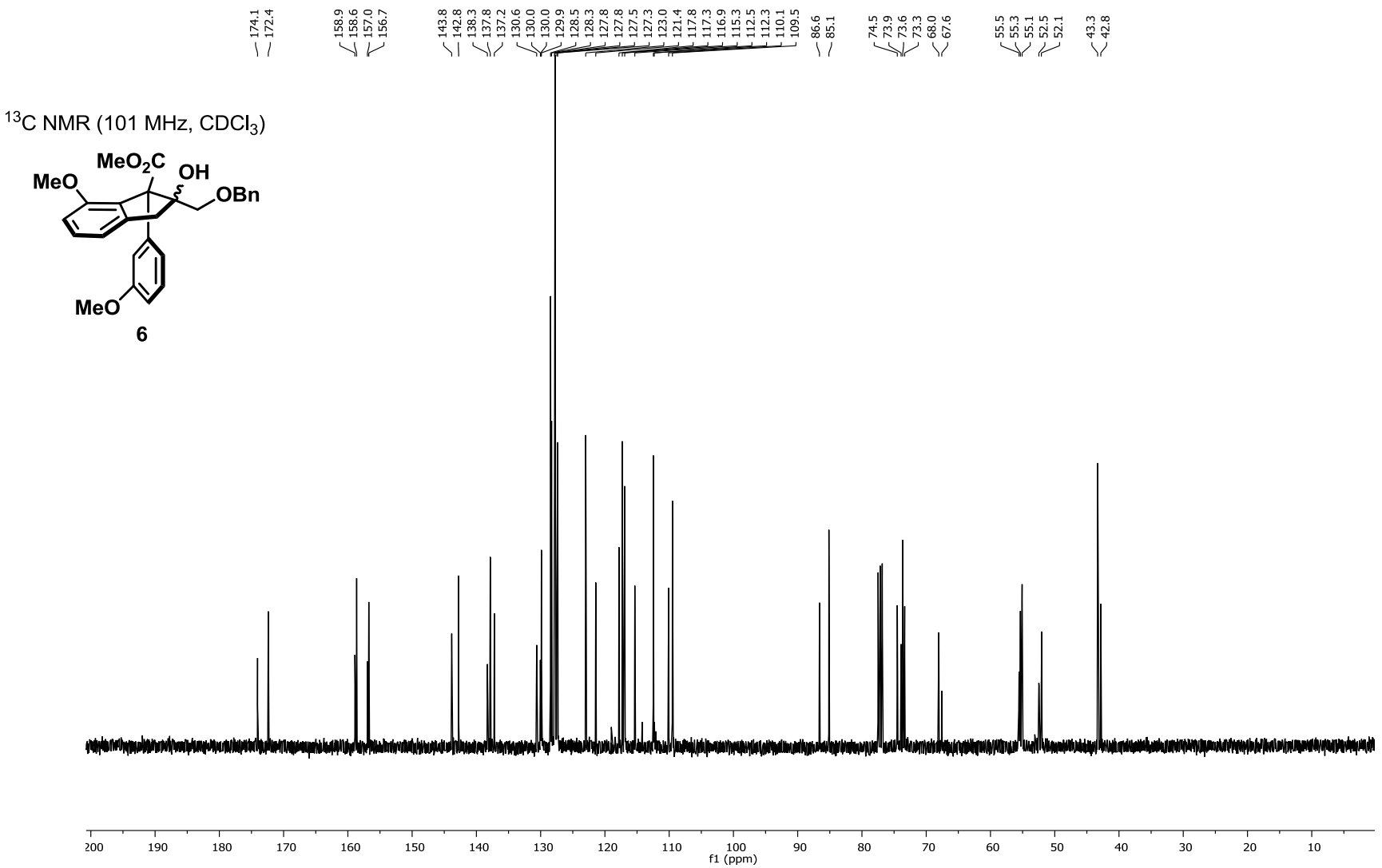
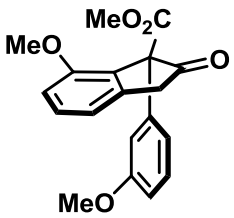
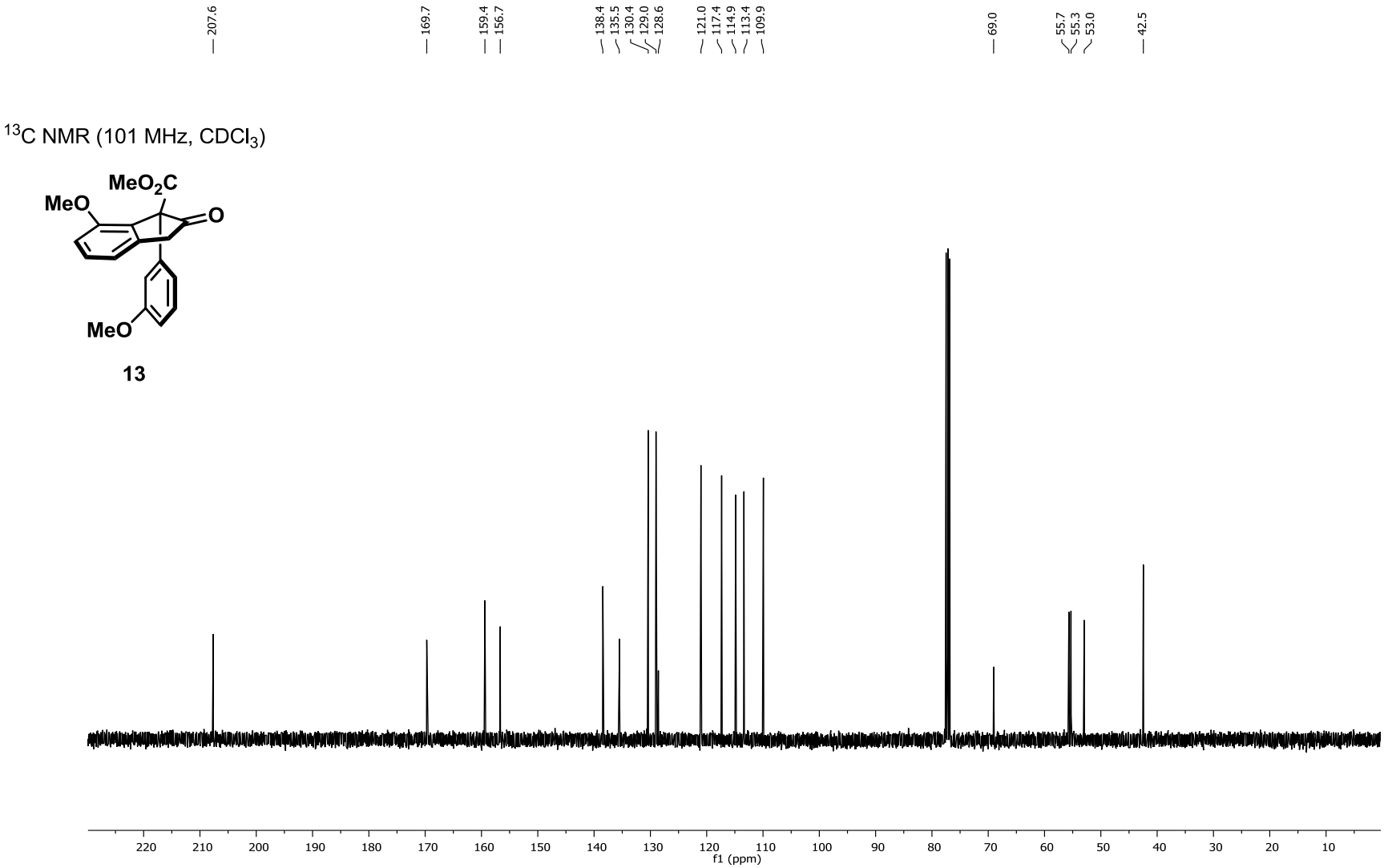



174.1
172.4
158.9
158.6
157.0
156.7
143.8
142.8
138.3
137.8
137.2
130.6
130.0
130.0
129.9
128.5
128.3
127.8
127.8
127.5
127.3
123.0
121.4
117.8
117.3
116.9
115.3
112.5
112.3
110.1
109.5
86.6
85.1
74.5
73.9
73.6
73.3
68.0
67.6
55.5
55.3
55.1
52.5
52.1
43.3
42.8
13C NMR (101 MHz, CDCl3)
MeO2C
OH
MeO
OBn
MeO
6
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)



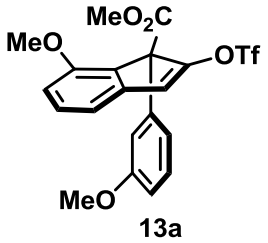
13



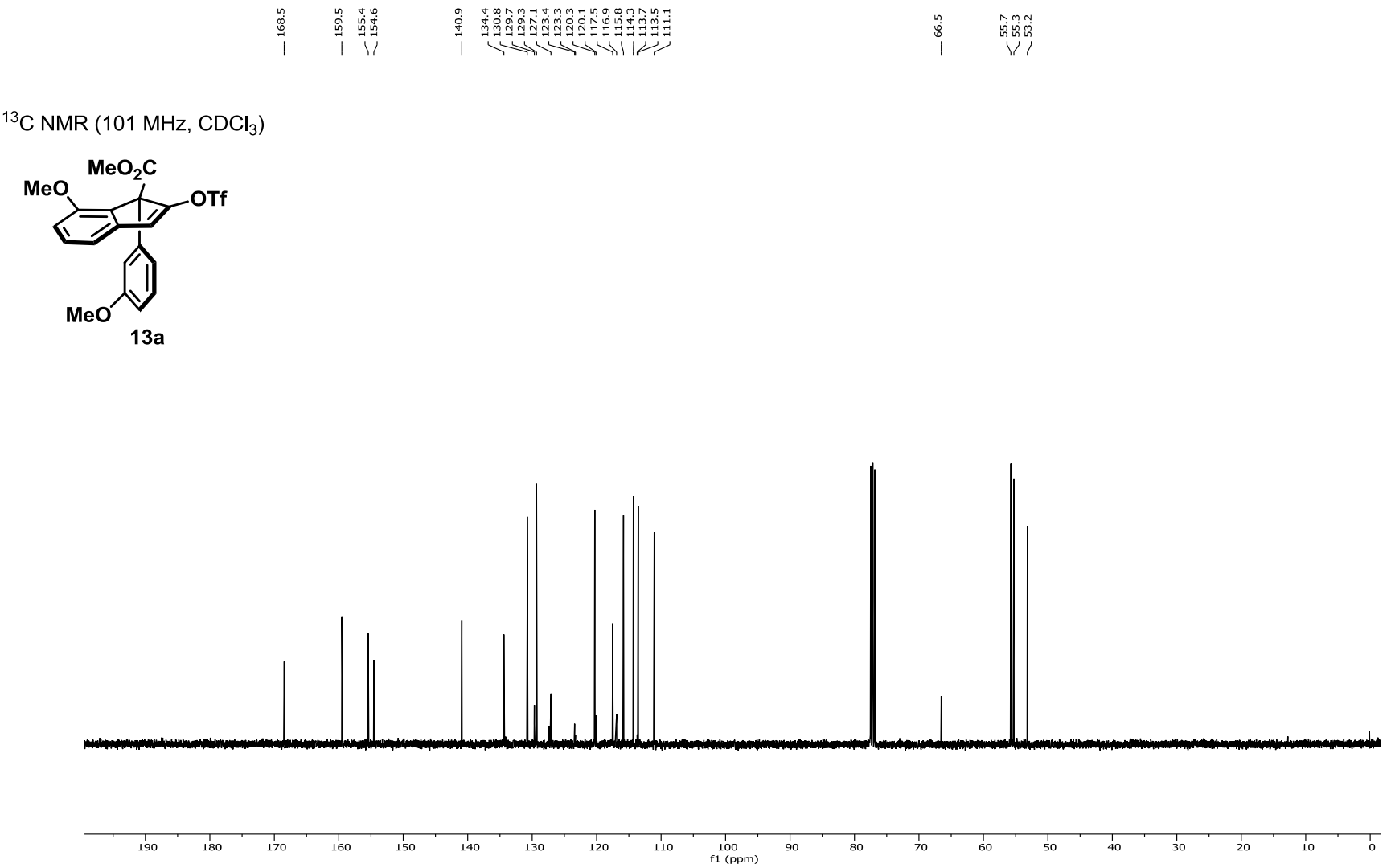
^{13}C NMR (101 MHz, $CDCl_3$)

13

^{1}H NMR (400 MHz, $CDCl_3$)

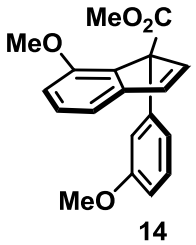


13a



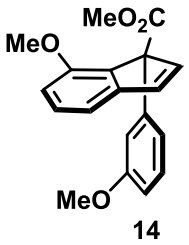
^{13}C NMR (101 MHz, $CDCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$)

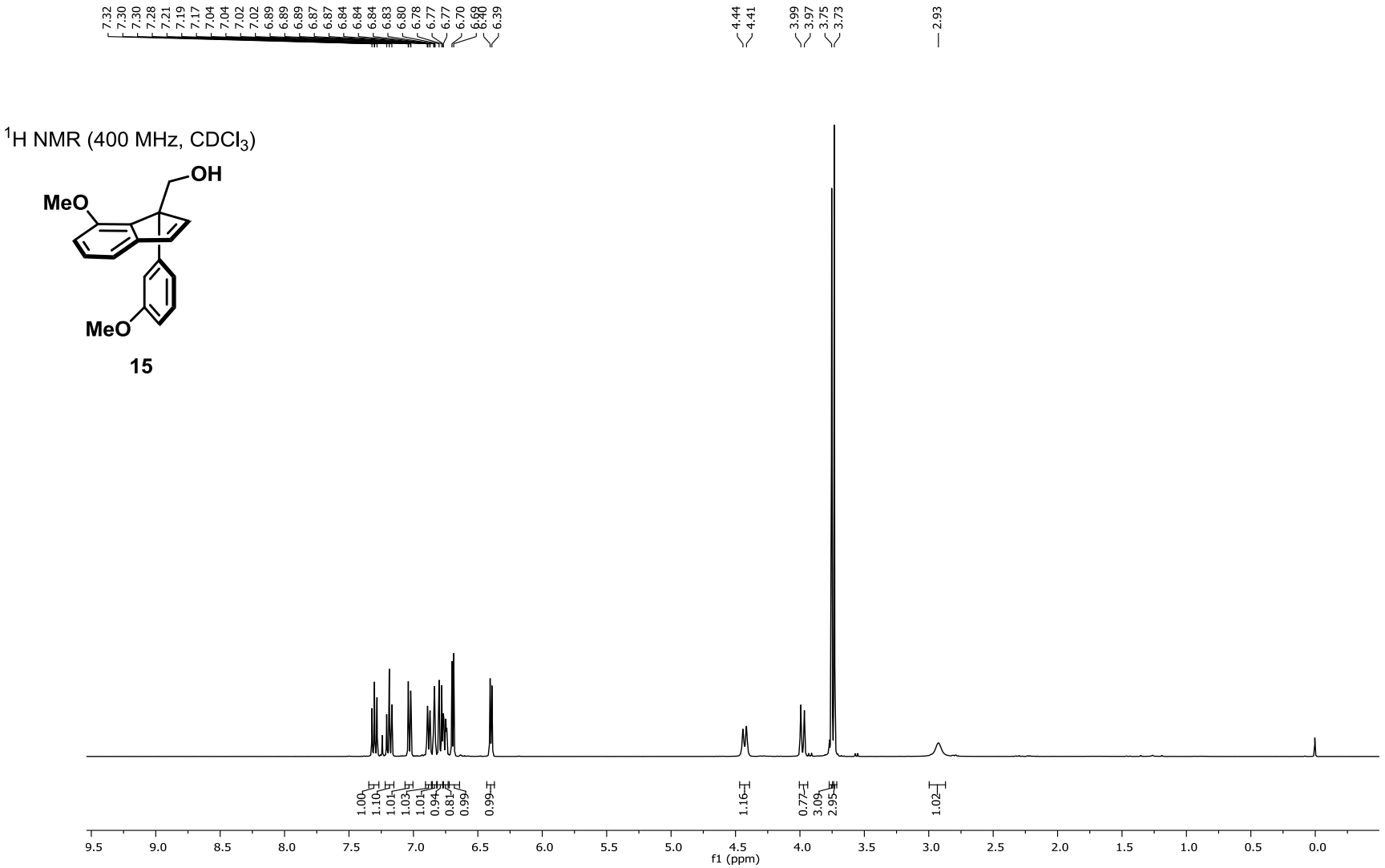


14

^{13}C NMR (101 MHz, $CDCl_3$)



14


7.32
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7.30
7.28
7.21
7.19
7.17
7.04
7.04
7.02
7.02
6.89
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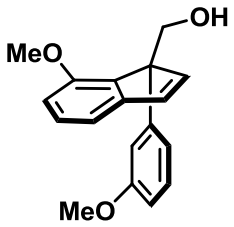
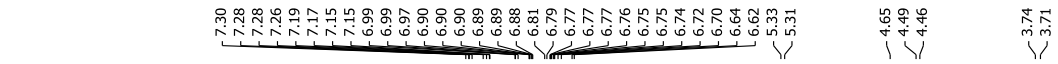
6.87
6.87
6.84
6.84
6.84
6.83
6.80
6.78
6.77
6.77
6.70
6.69
6.40
6.39
4.44
4.41
3.99
3.97
3.75
3.73
2.93
1H NMR (400 MHz, CDCl3)
OH
MeO
MeO
15
1.00
1.10
1.01
1.03
1.01
0.94
0.81
0.99
0.99
1.16
0.77
3.09
2.95
1.02
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

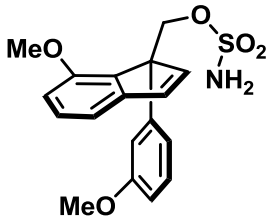
^{13}C NMR (101 MHz, $CDCl_3$)



15

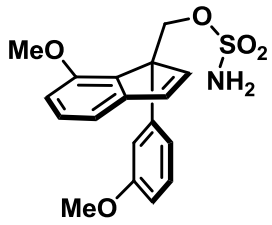


^{1}H NMR (400 MHz, $CDCl_3$)

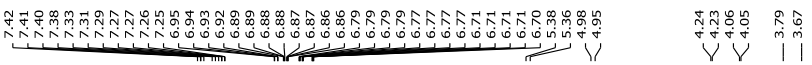


16

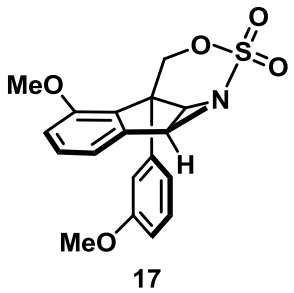
^{13}C NMR (101 MHz, $CDCl_3$)



16

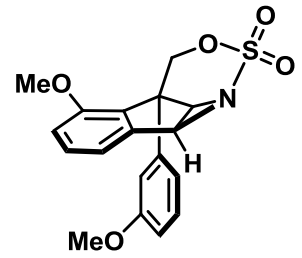


^{1}H NMR (400 MHz, $CDCl_3$)



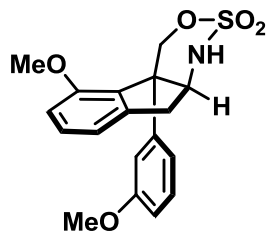
17

^{13}C NMR (101 MHz, $CDCl_3$)



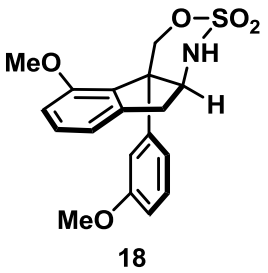
17

^{1}H NMR (400 MHz, $CDCl_3$)



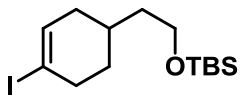
18

^{13}C NMR (101 MHz, $CDCl_3$)



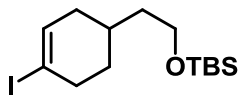
18

^{1}H NMR (400 MHz, $CDCl_3$)



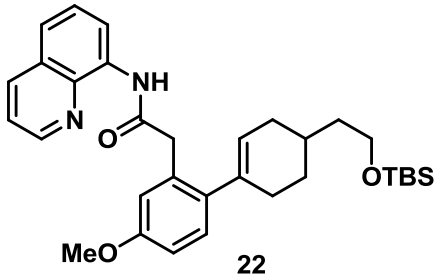
20

^{13}C NMR (101 MHz, $CDCl_3$)

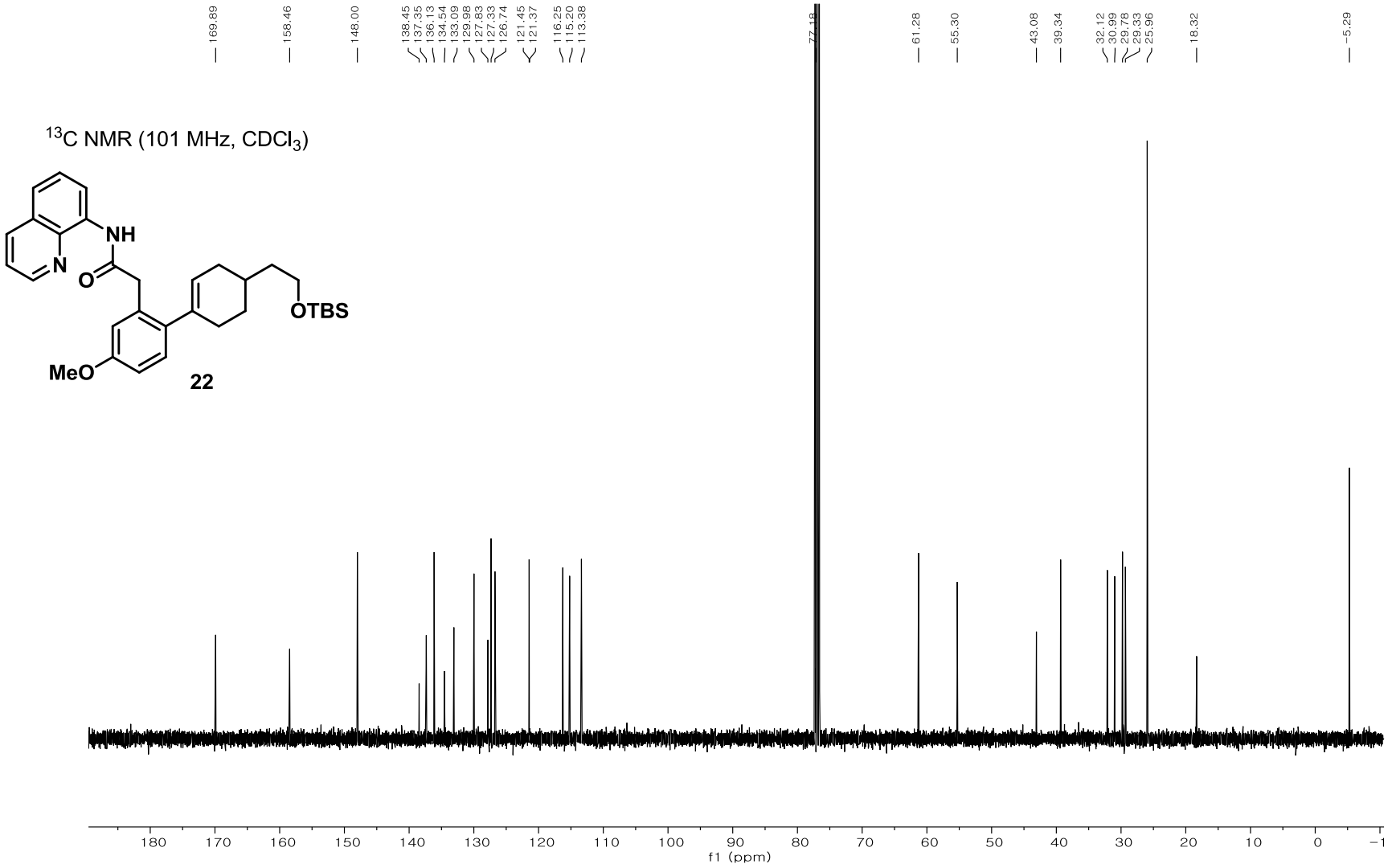


20

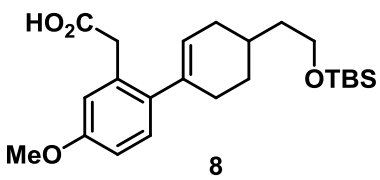
^{1}H NMR (400 MHz, $CDCl_3$)



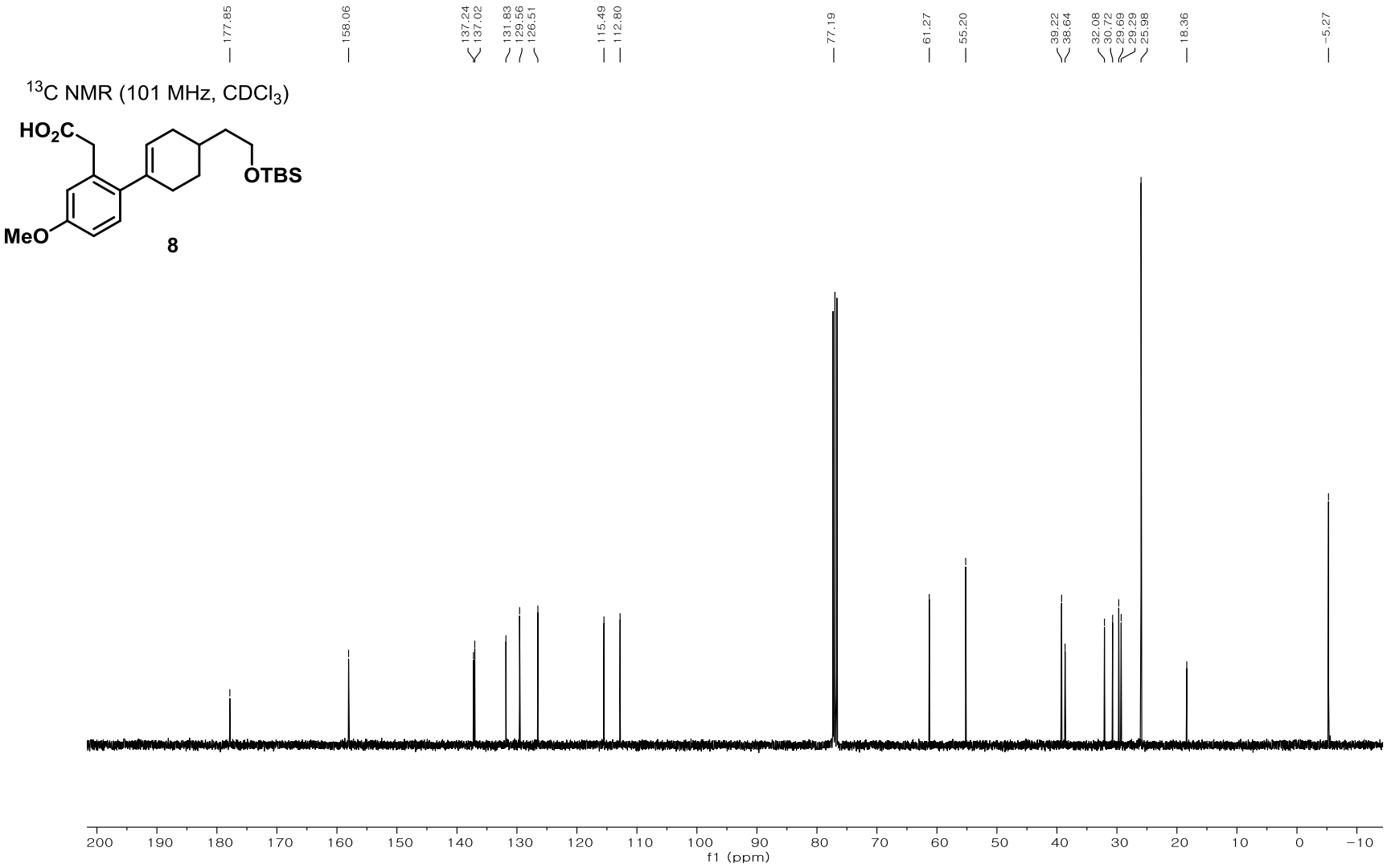
22

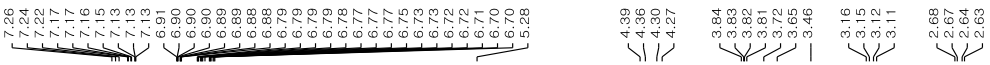

169.89
158.46
148.00
138.45
137.35
136.13
134.54
133.09
129.98
127.83
127.33
126.74
121.45
121.37
116.25
115.20
113.38
77.18
61.28
55.30
43.08
39.34
32.12
30.99
29.78
29.33
25.96
18.32
-5.29
13C NMR (101 MHz, CDCl3)
NH
N
O
OTBS
MeO
22
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)

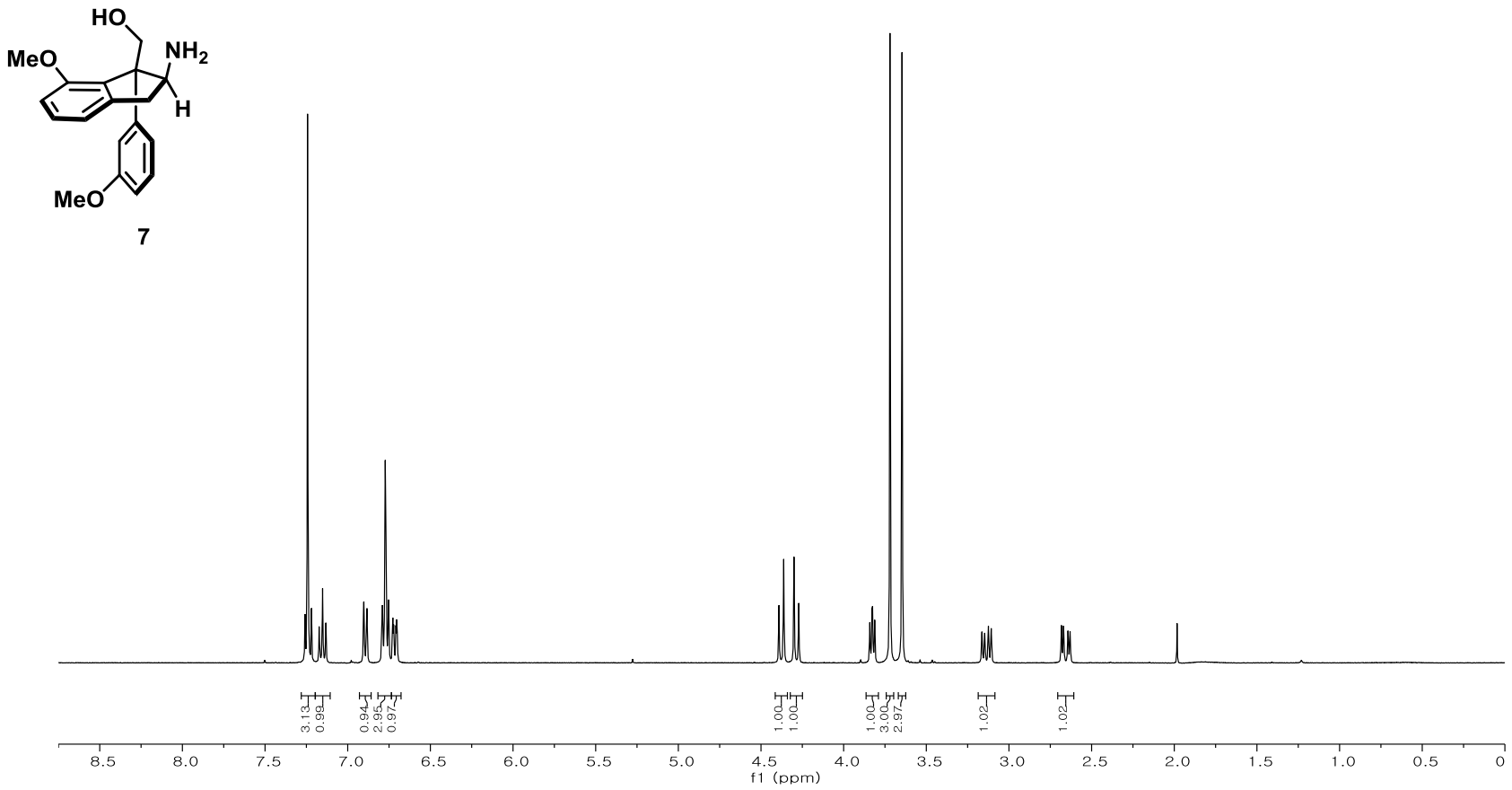


8

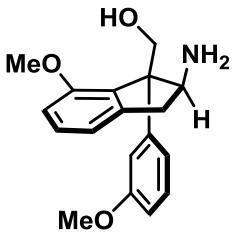

177.85
158.06
137.24
137.02
131.83
129.56
126.51
115.49
112.80
77.19
61.27
55.20
39.22
38.64
32.08
30.72
29.69
29.29
25.98
18.36
-5.27
^{13}C NMR (101 MHz, $CDCl_3$)
HO_2C
OTBS
MeO
8
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



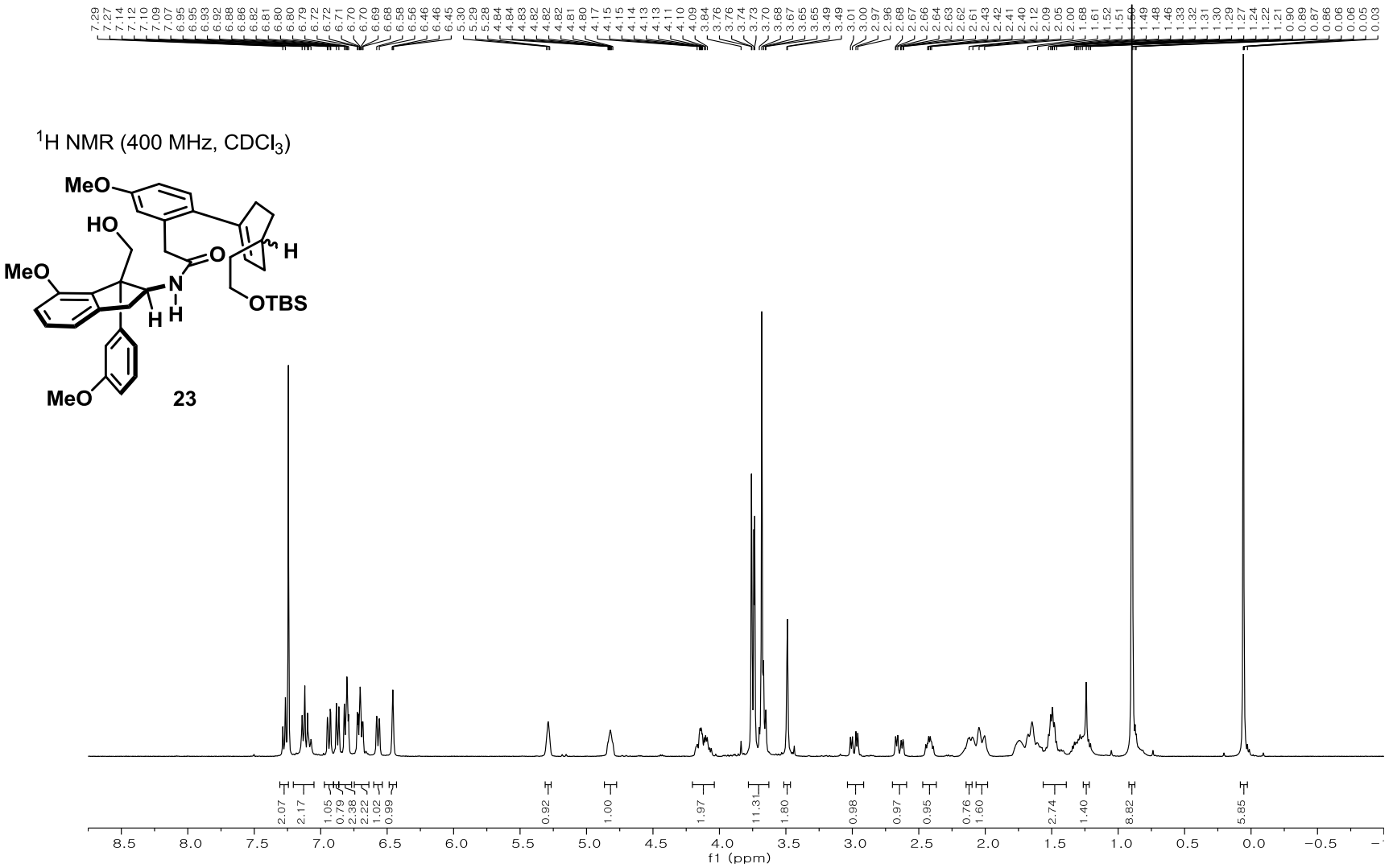
^{1}H NMR (400 MHz, $CDCl_3$)

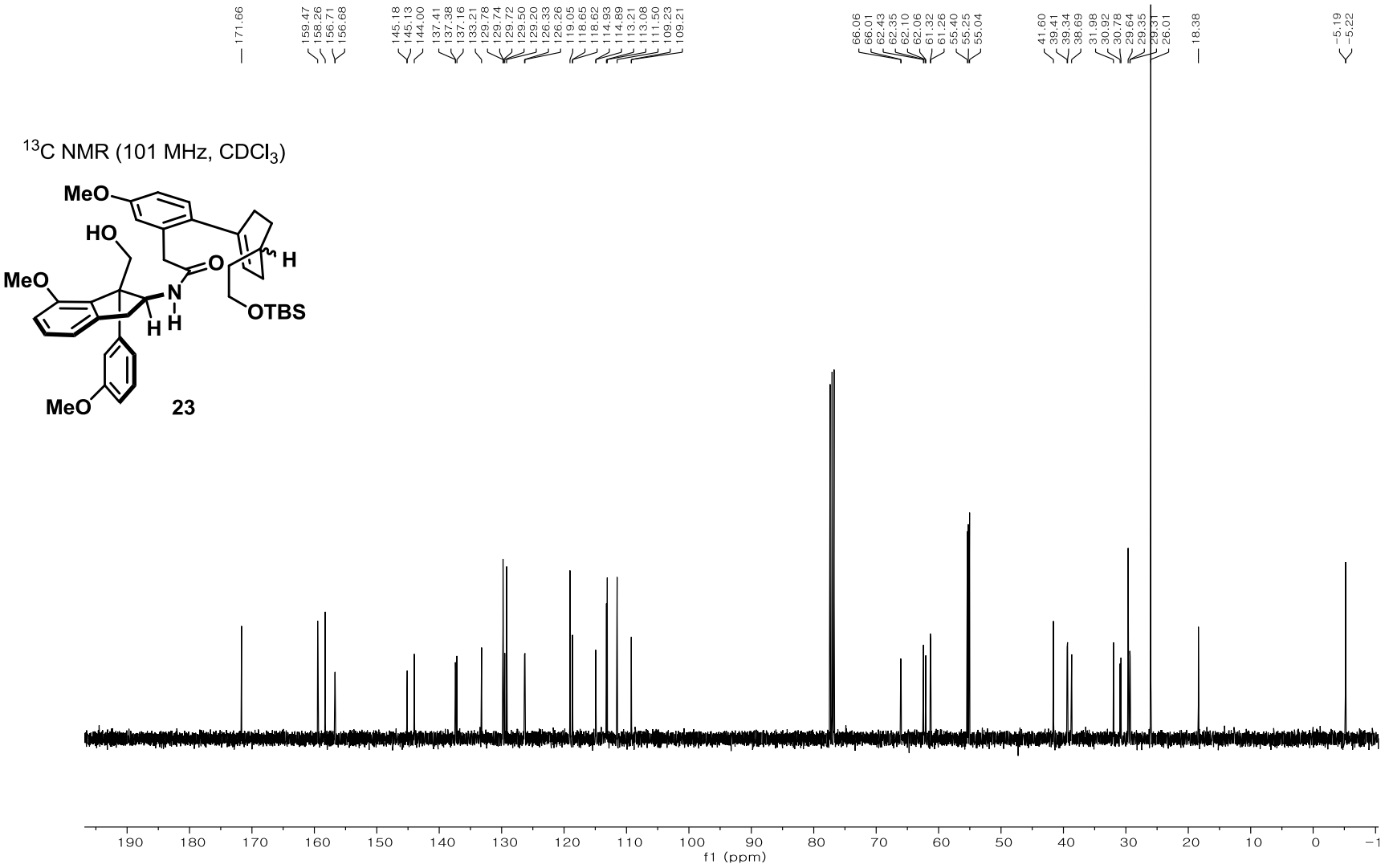


^{13}C NMR (101 MHz, $CDCl_3$)

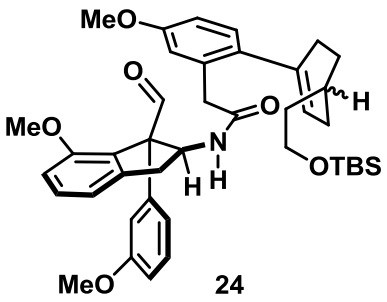


7

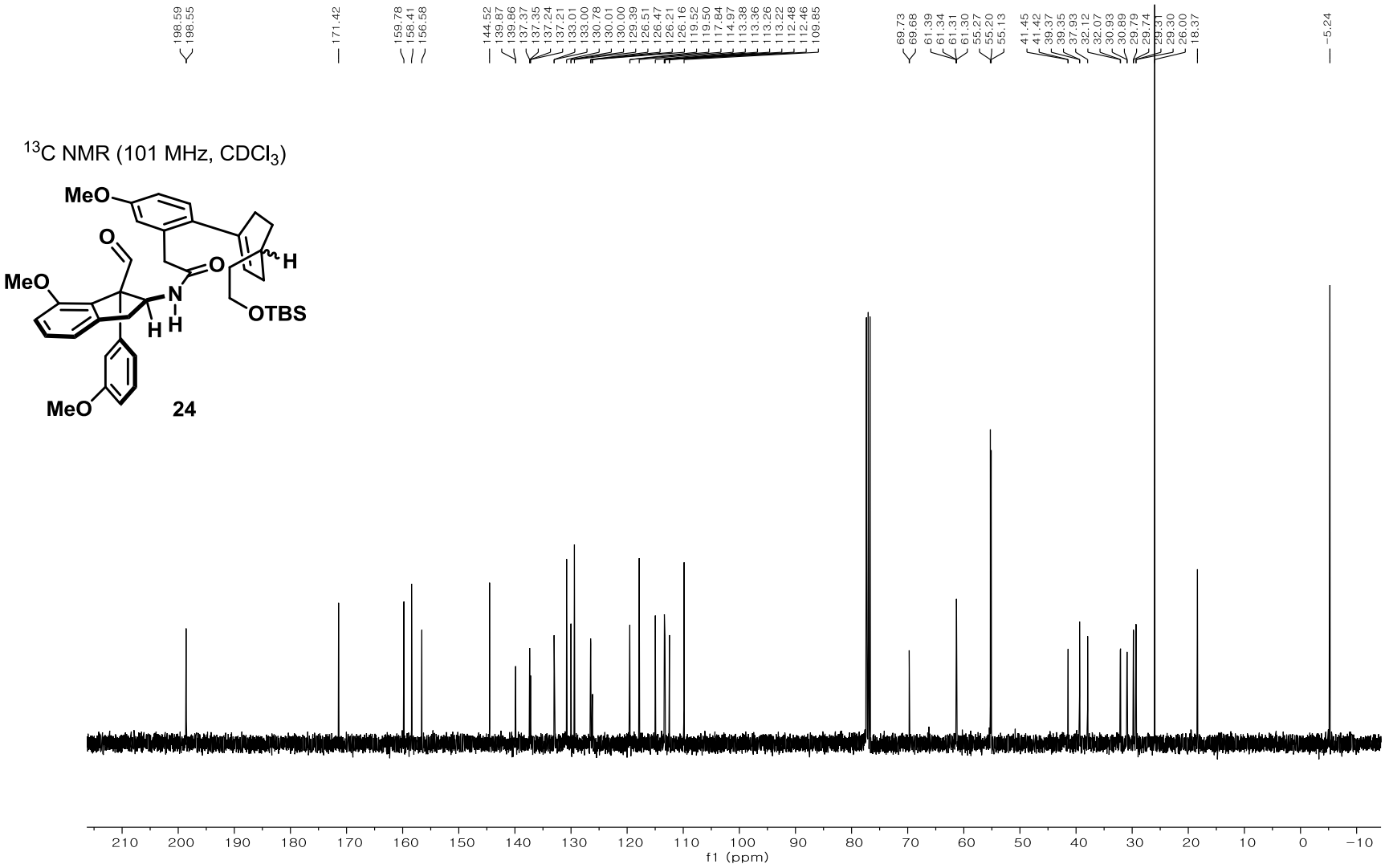

^{1}H NMR (400 MHz, CDCl$_3$)
MeO
HO
MeO
O
H
N
H
H
OTBS
MeO
23
f1 (ppm)


171.66
159.47
158.26
156.71
156.68
145.18
145.13
144.00
137.41
137.38
137.16
133.21
129.78
129.74
129.72
129.50
129.20
126.33
126.26
119.05
118.65
118.62
114.93
114.89
113.21
113.08
111.50
109.23
109.21
66.06
66.01
62.43
62.35
62.10
62.06
61.32
61.26
55.40
55.25
55.04
41.60
39.41
39.34
38.69
31.98
30.92
30.78
29.64
29.35
29.31
26.01
18.38
-5.19
-5.22
13C NMR (101 MHz, CDCl3)
MeO
HO
MeO
O
H
N
H
H
OTBS
MeO
23
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)

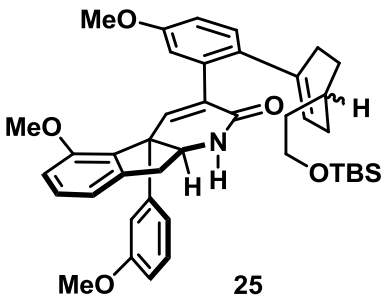
^{1}H NMR (400 MHz, $CDCl_3$)



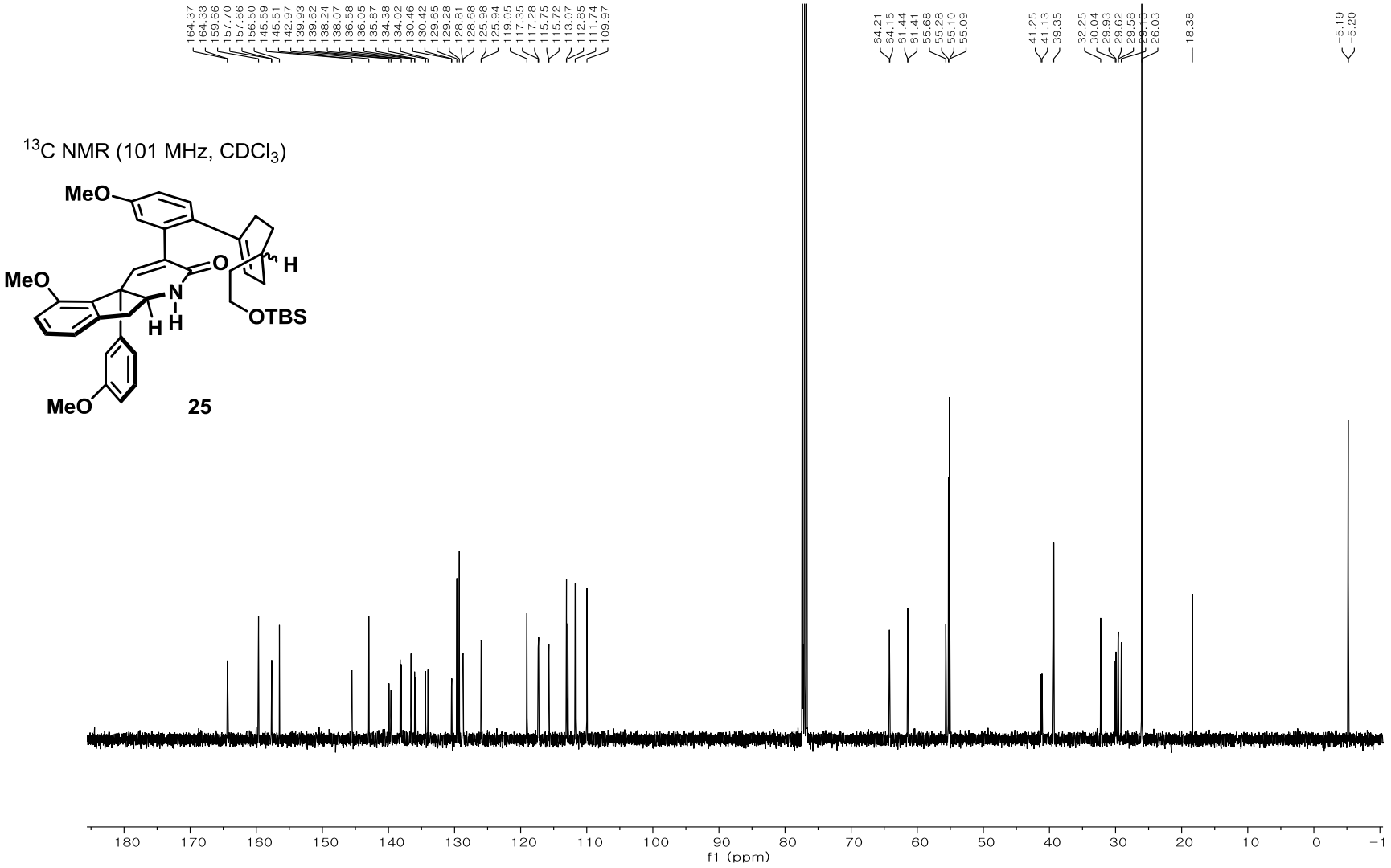
24

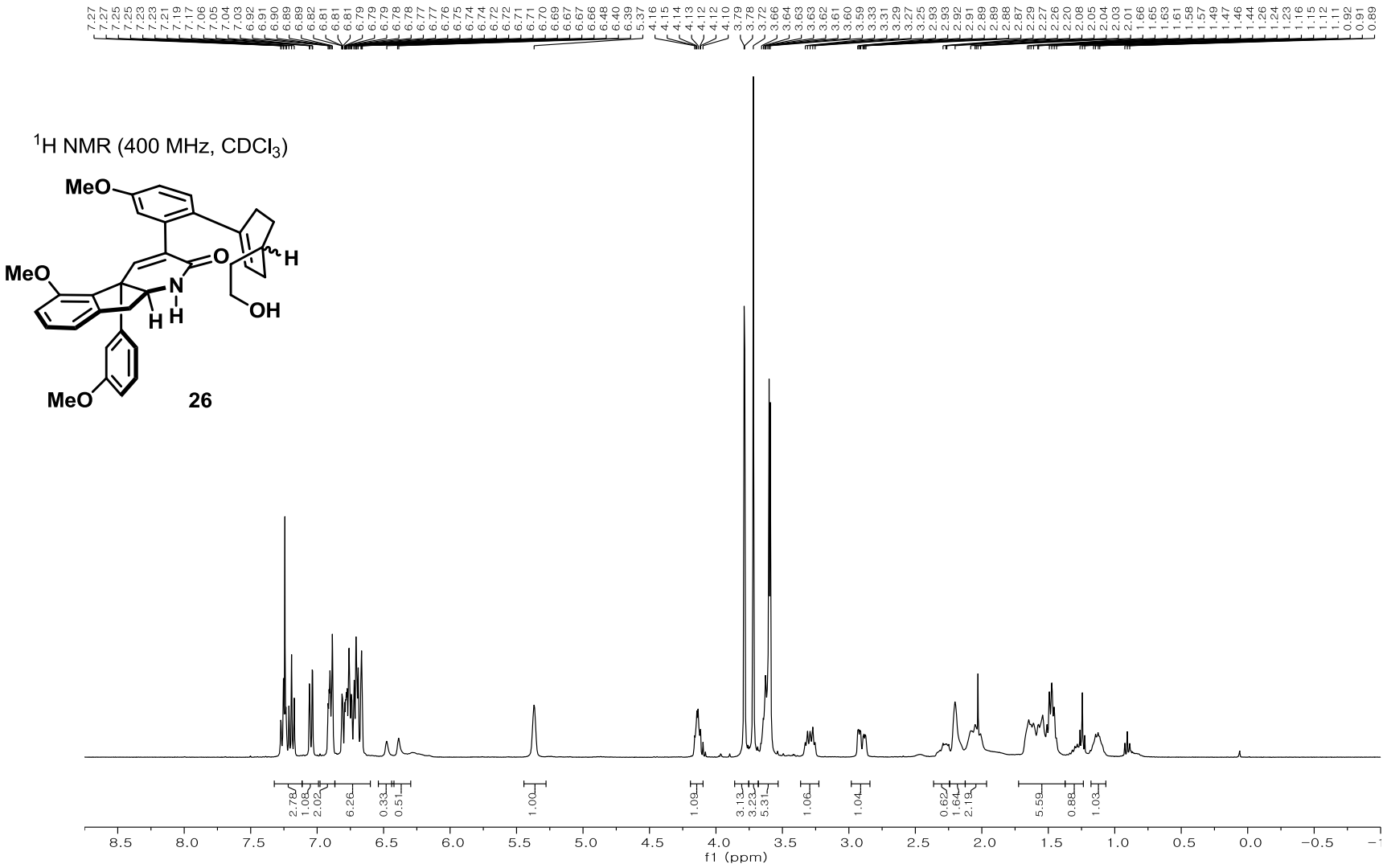

198.59
198.55
171.42
159.78
158.41
156.58
144.52
139.87
139.86
137.37
137.35
137.24
137.21
133.01
133.00
130.78
130.01
130.00
129.39
126.51
126.47
126.21
126.16
119.52
119.50
117.84
114.97
113.38
113.36
113.26
113.22
112.48
112.46
109.85
69.73
69.68
61.39
61.34
61.31
61.30
55.27
55.20
55.13
41.45
41.42
39.37
39.35
37.93
32.12
32.07
30.93
30.89
29.79
29.74
29.31
29.30
26.00
18.37
-5.24
13C NMR (101 MHz, CDCl3)
MeO
O
O
H
MeO
N
H
H
OTBS
MeO
24
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)

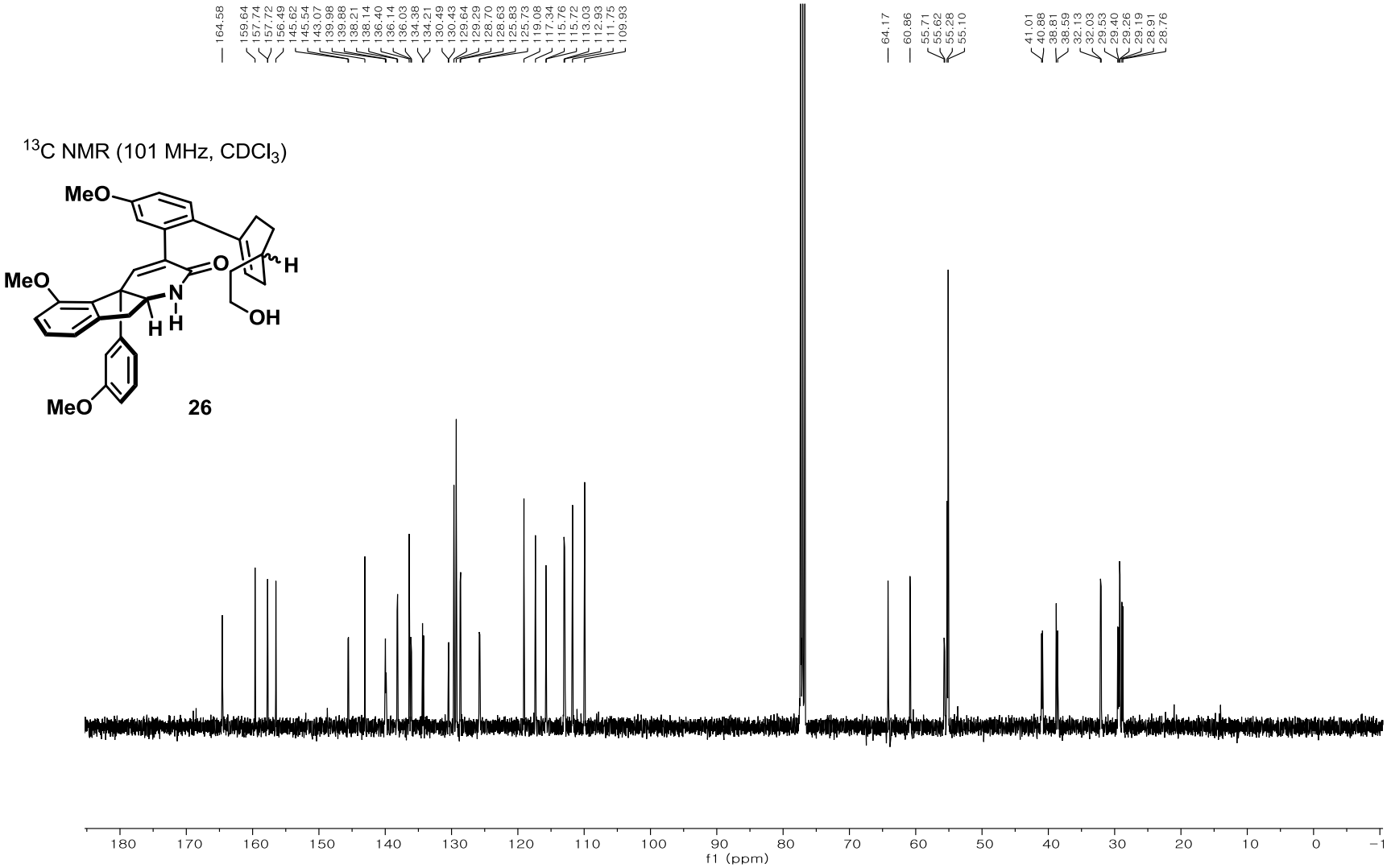
^{1}H NMR (400 MHz, $CDCl_3$)

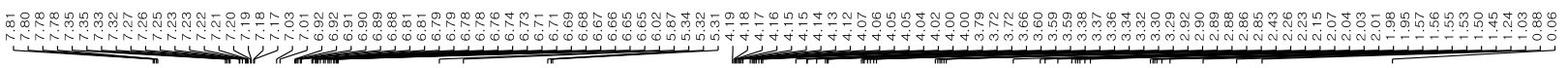


25

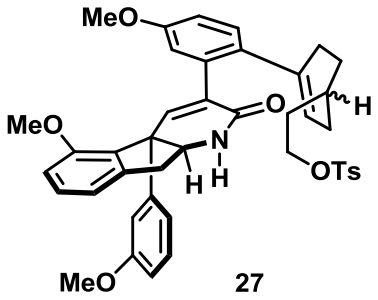

164.37
164.33
159.66
157.70
157.66
156.50
145.59
145.51
142.97
139.93
139.62
138.24
138.07
136.58
136.05
135.87
134.38
134.02
130.46
130.42
129.65
129.28
128.81
128.68
125.98
125.94
119.05
117.35
117.28
115.75
115.72
113.07
112.85
111.74
109.97
64.21
64.15
61.44
61.41
55.68
55.28
55.10
55.09
41.25
41.13
39.35
32.25
30.04
29.93
29.62
29.58
29.18
26.03
18.38
-5.19
-5.20
^{13}C NMR (101 MHz, CDCl$_3$)
MeO
MeO
MeO
O
H
N
H
H
OTBS
25
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (ppm)


^{1}H NMR (400 MHz, CDCl$_3$)
MeO
MeO
MeO
O
N
H
H
H
OH
26
f1 (ppm)

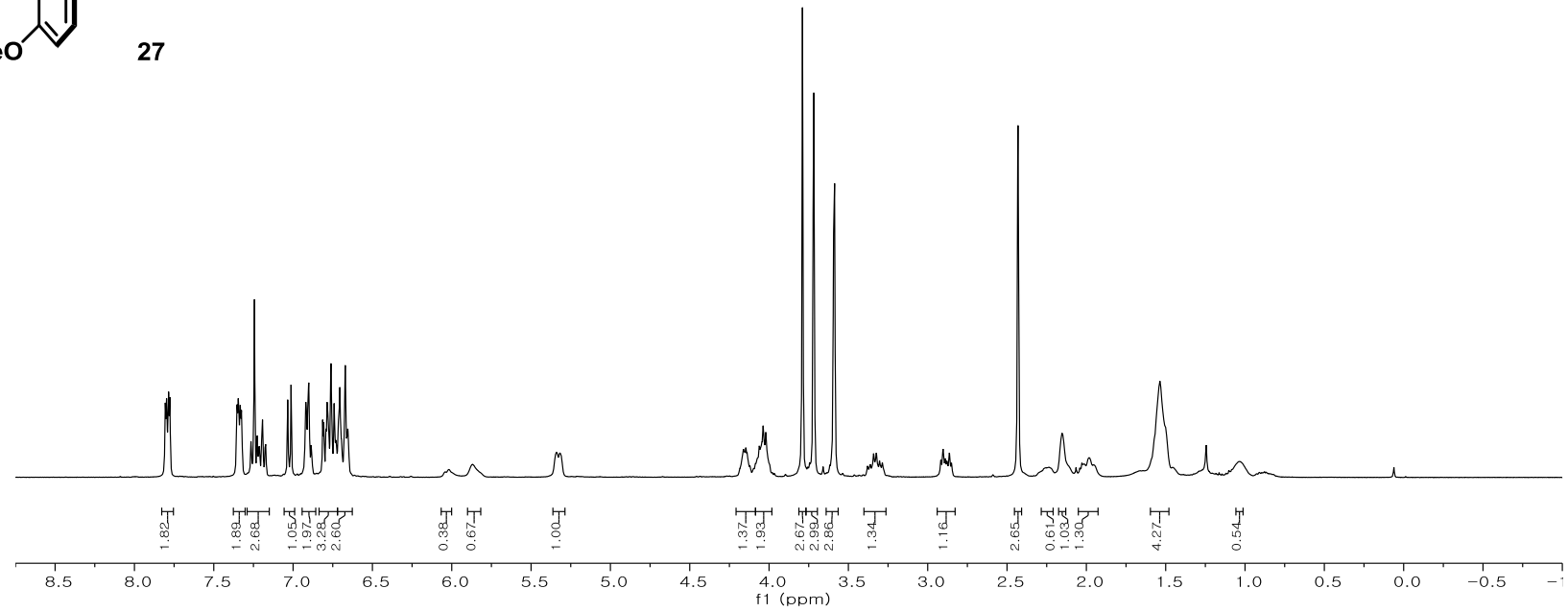

164.58
159.64
157.74
157.72
156.49
145.62
145.54
143.07
139.98
139.88
138.21
138.14
136.40
136.14
136.03
134.38
134.21
130.49
130.43
129.64
129.29
128.70
128.63
125.83
125.73
119.08
117.34
115.76
115.72
113.03
112.93
111.75
109.93
64.17
60.86
55.71
55.62
55.28
55.10
41.01
40.88
38.81
38.59
32.13
32.03
29.53
29.40
29.26
29.19
28.91
28.76
^{13}C NMR (101 MHz, CDCl$_3$)
MeO
MeO
MeO
O
N
H
H
H
OH
26
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−1
f1 (ppm)

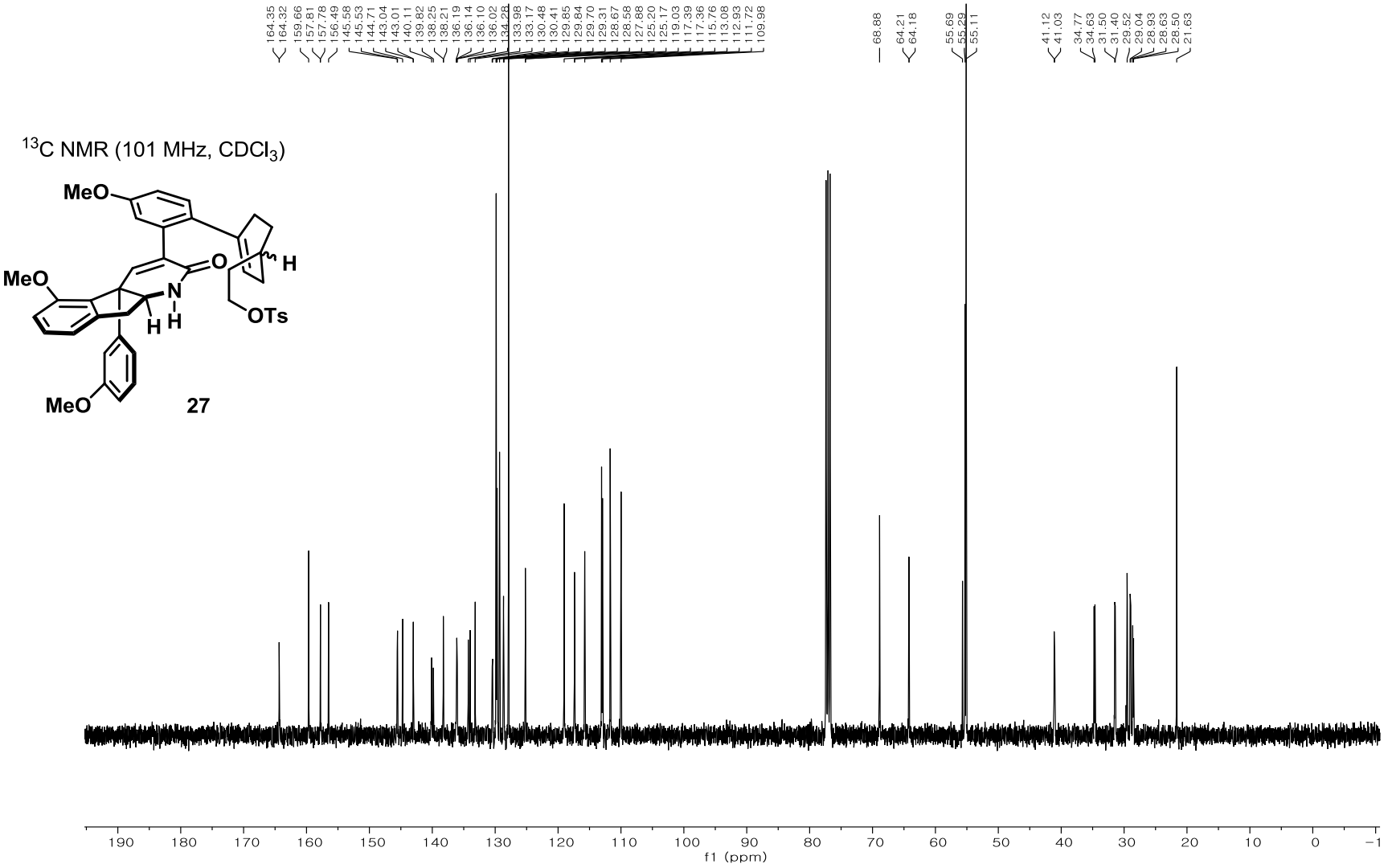


^{1}H NMR (400 MHz, $CDCl_3$)

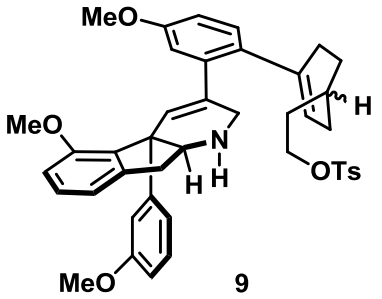


27

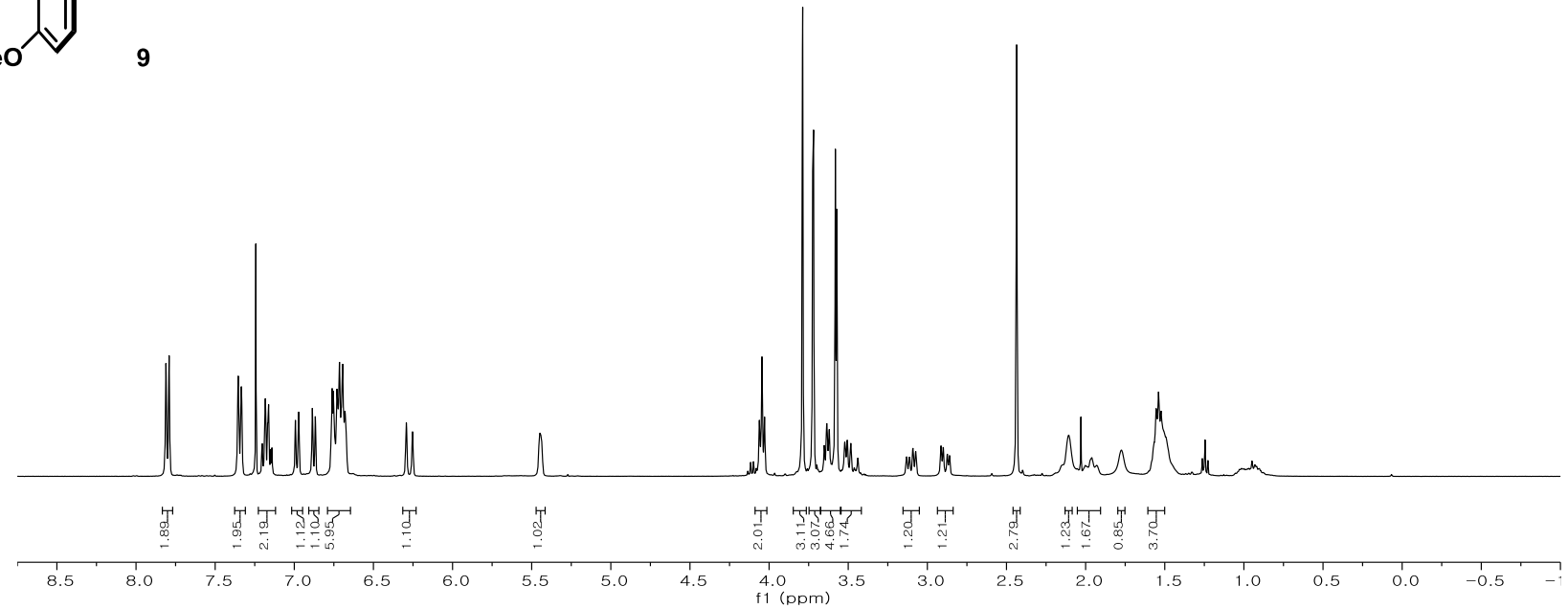


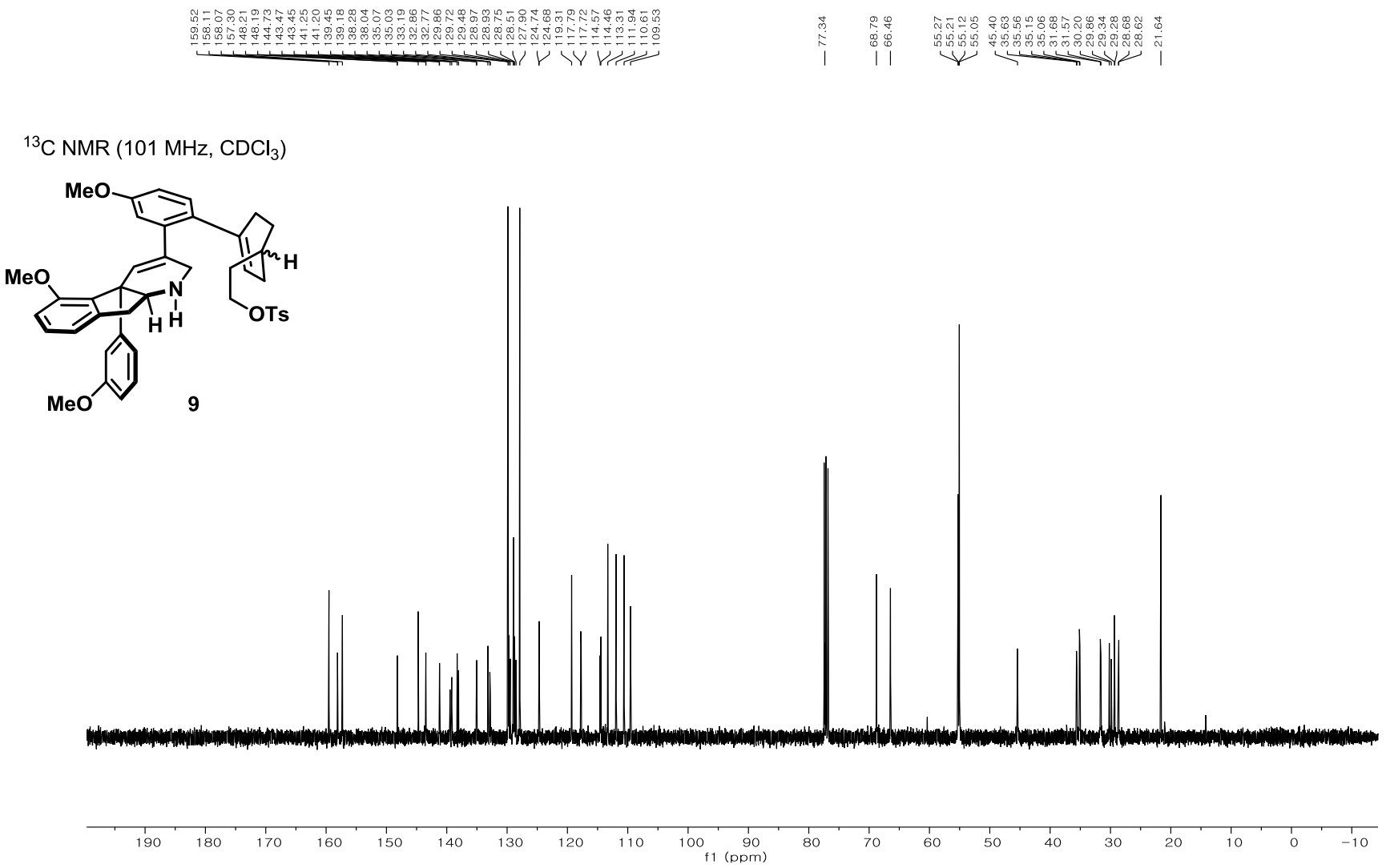

164.35
164.32
159.66
157.81
157.78
156.49
145.58
145.53
144.71
143.04
143.01
140.11
139.82
138.25
138.21
136.19
136.14
136.10
136.02
134.28
133.98
133.17
130.48
130.41
129.85
129.84
129.70
129.31
128.67
128.58
127.88
125.20
125.17
119.03
117.39
117.36
115.76
113.08
112.93
111.72
109.98
68.88
64.21
64.18
55.69
55.29
55.11
41.12
41.03
34.77
34.63
31.50
31.40
29.52
29.04
28.93
28.63
28.50
21.63
^{13}C NMR (101 MHz, CDCl$_3$)
MeO
MeO
MeO
O
H
N
H
H
OTs
27
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−1
f1 (ppm)

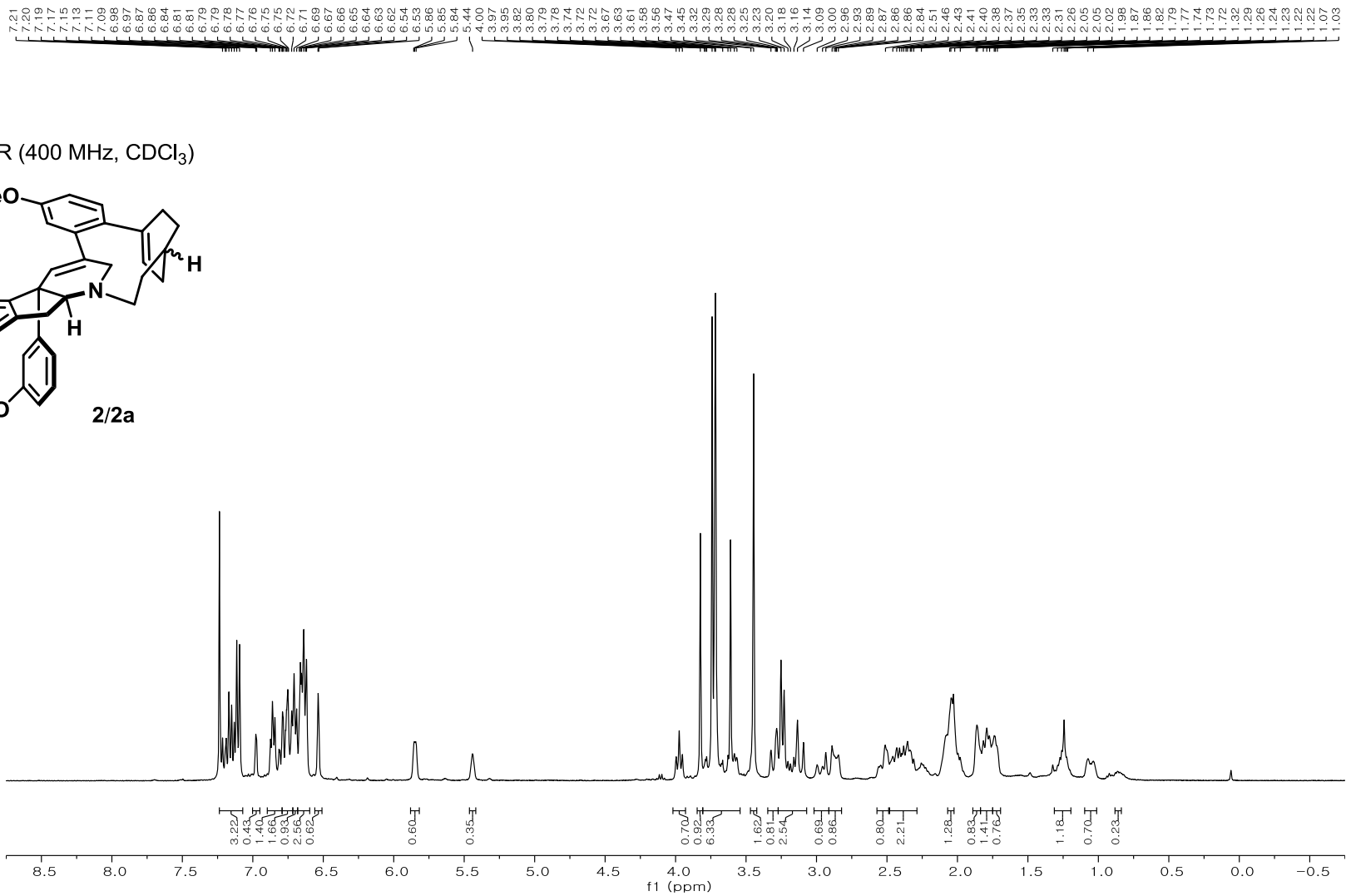
^{1}H NMR (400 MHz, $CDCl_3$)

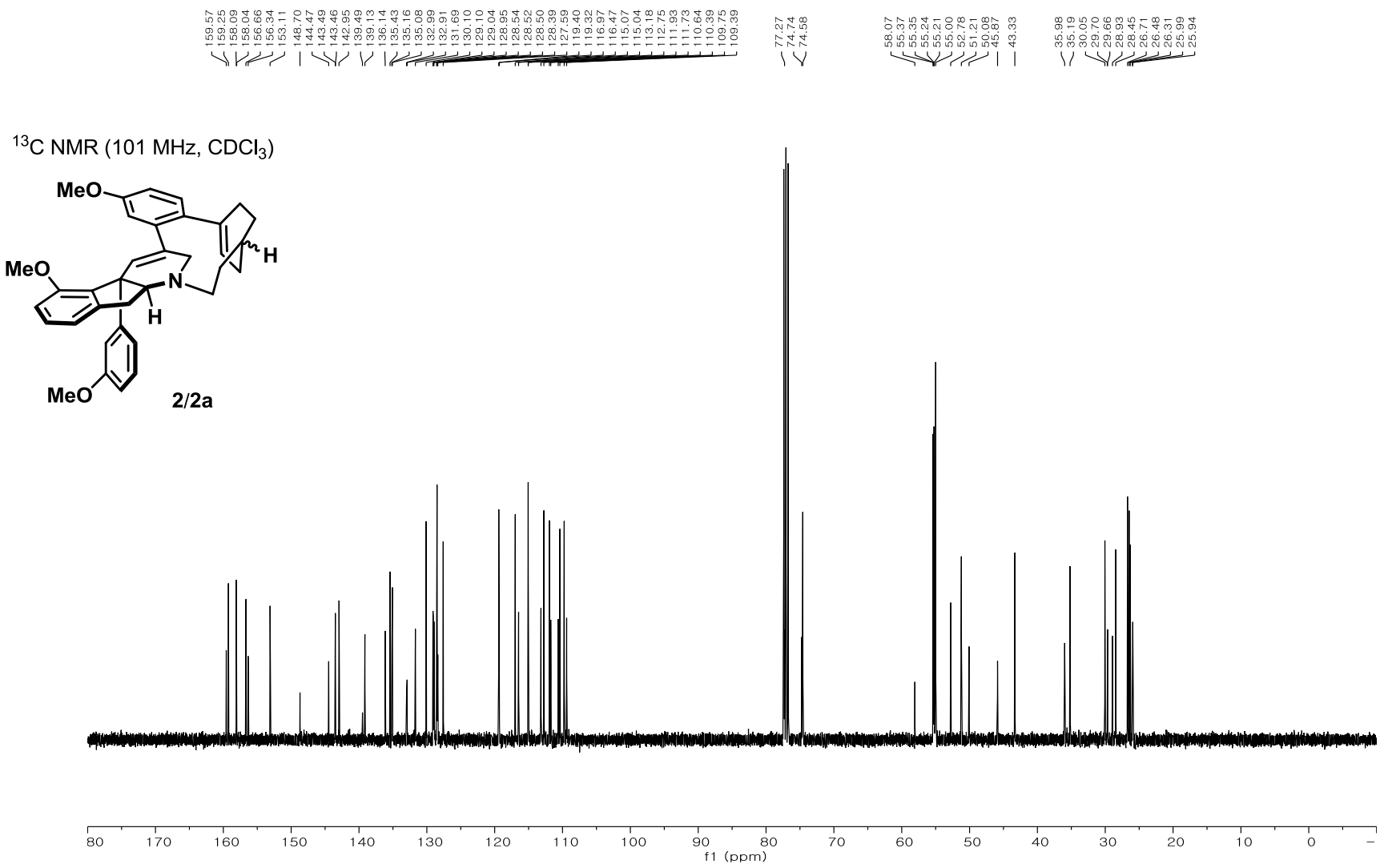


9

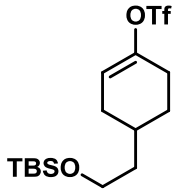



159.52
158.11
158.07
157.30
148.21
148.19
144.73
143.47
143.45
141.25
141.20
139.45
139.18
138.28
138.04
135.07
135.03
133.19
132.86
132.77
129.86
129.72
129.48
128.97
128.93
128.75
128.51
127.90
124.74
124.68
119.31
117.79
117.72
114.57
114.46
113.31
111.94
110.61
109.53
77.34
68.79
66.46
55.27
55.21
55.12
55.05
45.40
35.63
35.56
35.15
35.06
31.68
31.57
30.20
29.86
29.34
29.28
28.68
28.62
21.64
^{13}C NMR (101 MHz, CDCl$_3$)
MeO
MeO
MeO
N
H
H
H
OTs
9
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)


7.21 7.20 7.19 7.17 7.15 7.13 7.11 7.09 6.98 6.97 6.87 6.86 6.84 6.81 6.81 6.79 6.79 6.78 6.77 6.76 6.75 6.75 6.72 6.71 6.69 6.67 6.66 6.65 6.64 6.63 6.62 6.54 6.53 5.86 5.85 5.84 5.44 4.00 3.97 3.95 3.82 3.80 3.79 3.78 3.74 3.72 3.72 3.67 3.63 3.61 3.58 3.56 3.47 3.45 3.32 3.29 3.28 3.28 3.25 3.23 3.20 3.18 3.16 3.14 3.09 3.00 2.96 2.93 2.89 2.87 2.86 2.86 2.84 2.51 2.46 2.43 2.41 2.40 2.38 2.37 2.35 2.33 2.31 2.26 2.05 2.05 2.02 1.98 1.87 1.86 1.82 1.79 1.77 1.74 1.73 1.72 1.32 1.29 1.26 1.24 1.23 1.22 1.22 1.07 1.03
^{1}H NMR (400 MHz, $CDCl_3$)
MeO
MeO
MeO
N
H
H
2/2a
3.22 0.43 1.40 1.66 0.93 2.56 0.62 0.60 0.35 0.70 0.92 6.33 1.62 0.81 2.54 0.69 0.86 0.80 2.21 1.28 0.83 1.41 0.76 1.18 0.70 0.23
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)

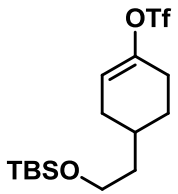

159.57
159.25
158.09
158.04
156.66
156.34
153.11
148.70
144.47
143.49
143.46
142.95
139.49
139.13
136.14
135.43
135.16
135.08
132.99
132.91
131.69
130.10
129.10
129.04
128.95
128.54
128.52
128.50
128.39
127.59
119.40
119.32
116.97
116.47
115.07
115.04
113.18
112.75
111.93
111.73
110.64
110.39
109.75
109.39
77.27
74.74
74.58
58.07
55.37
55.35
55.24
55.21
55.00
52.78
51.21
50.08
45.87
43.33
35.98
35.19
30.05
29.70
29.66
28.93
28.45
26.71
26.48
26.31
25.99
25.94
13C NMR (101 MHz, CDCl3)
MeO
MeO
MeO
N
H
H
2/2a
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)



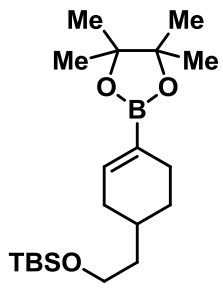
20a

^{13}C NMR (101 MHz, $CDCl_3$)



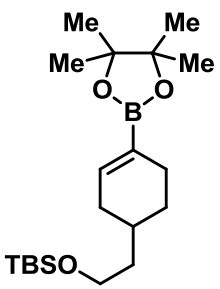
20a

^{1}H NMR (400 MHz, $CDCl_3$)



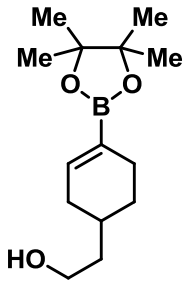
20b

^{13}C NMR (101 MHz, $CDCl_3$)



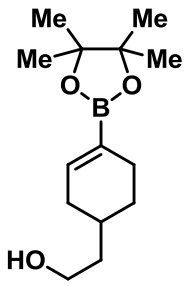
20b

^{1}H NMR (400 MHz, $CDCl_3$)



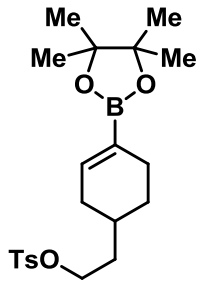
20c

^{13}C NMR (101 MHz, $CDCl_3$)

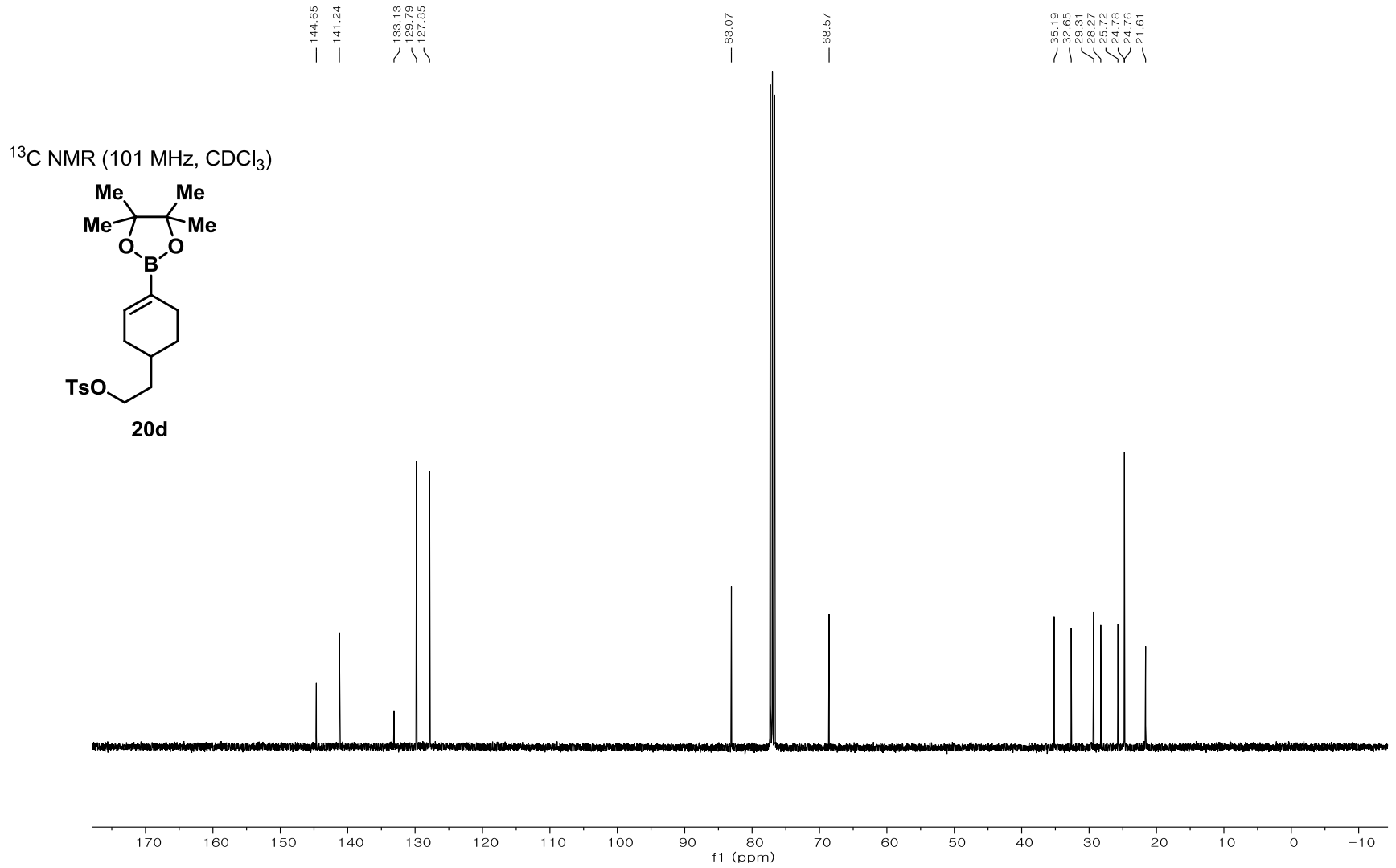


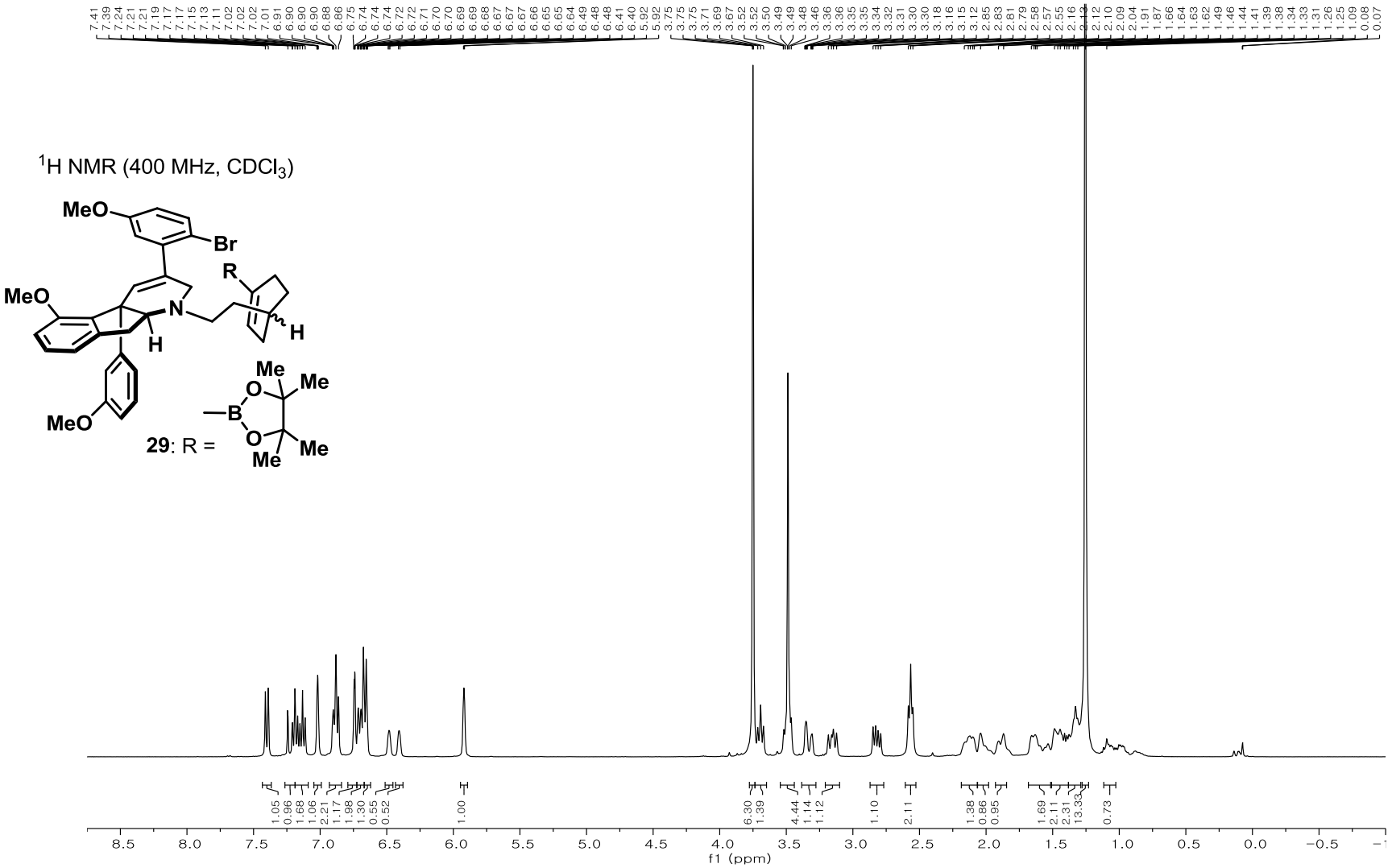
20c

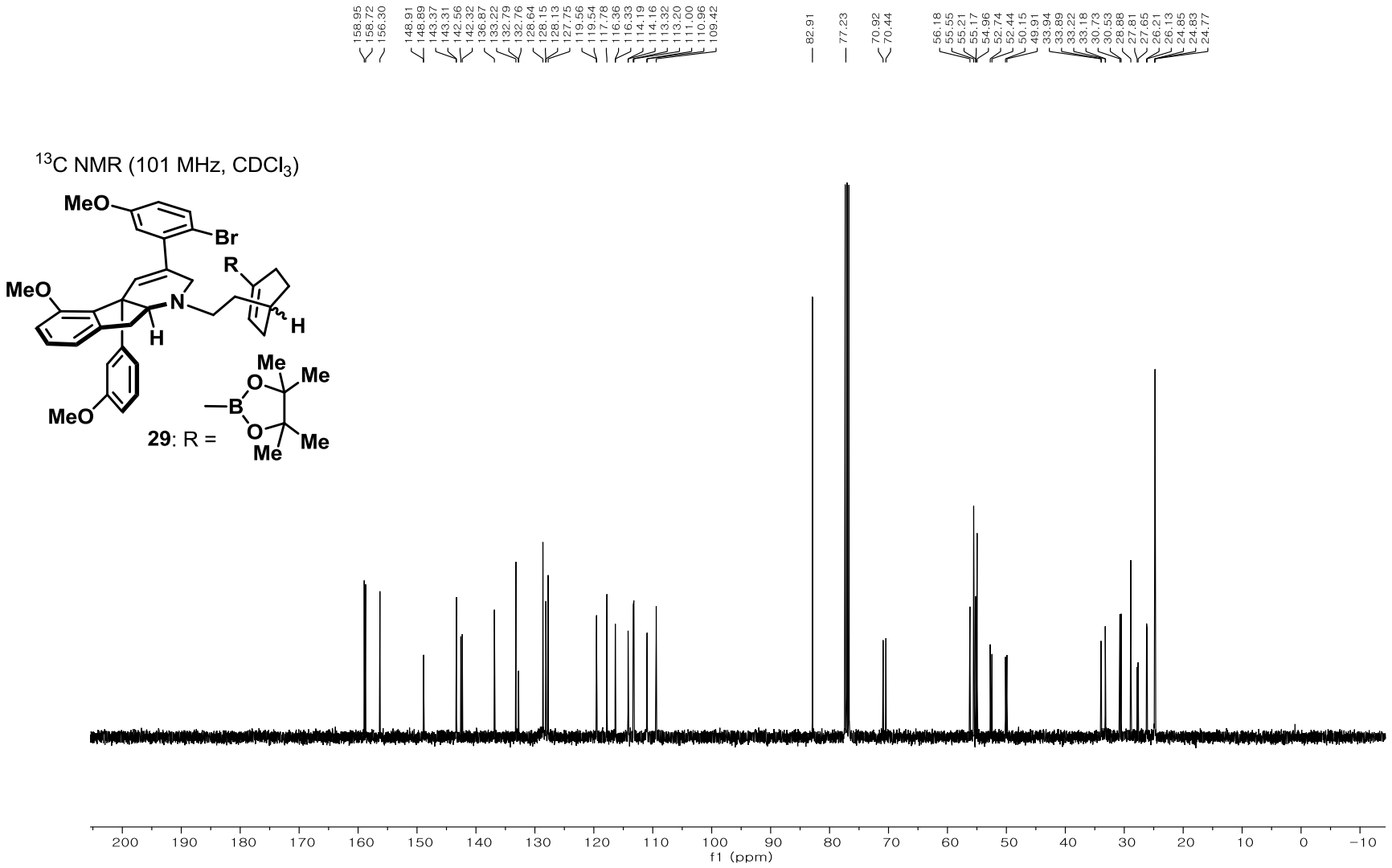
^{1}H NMR (400 MHz, $CDCl_3$)

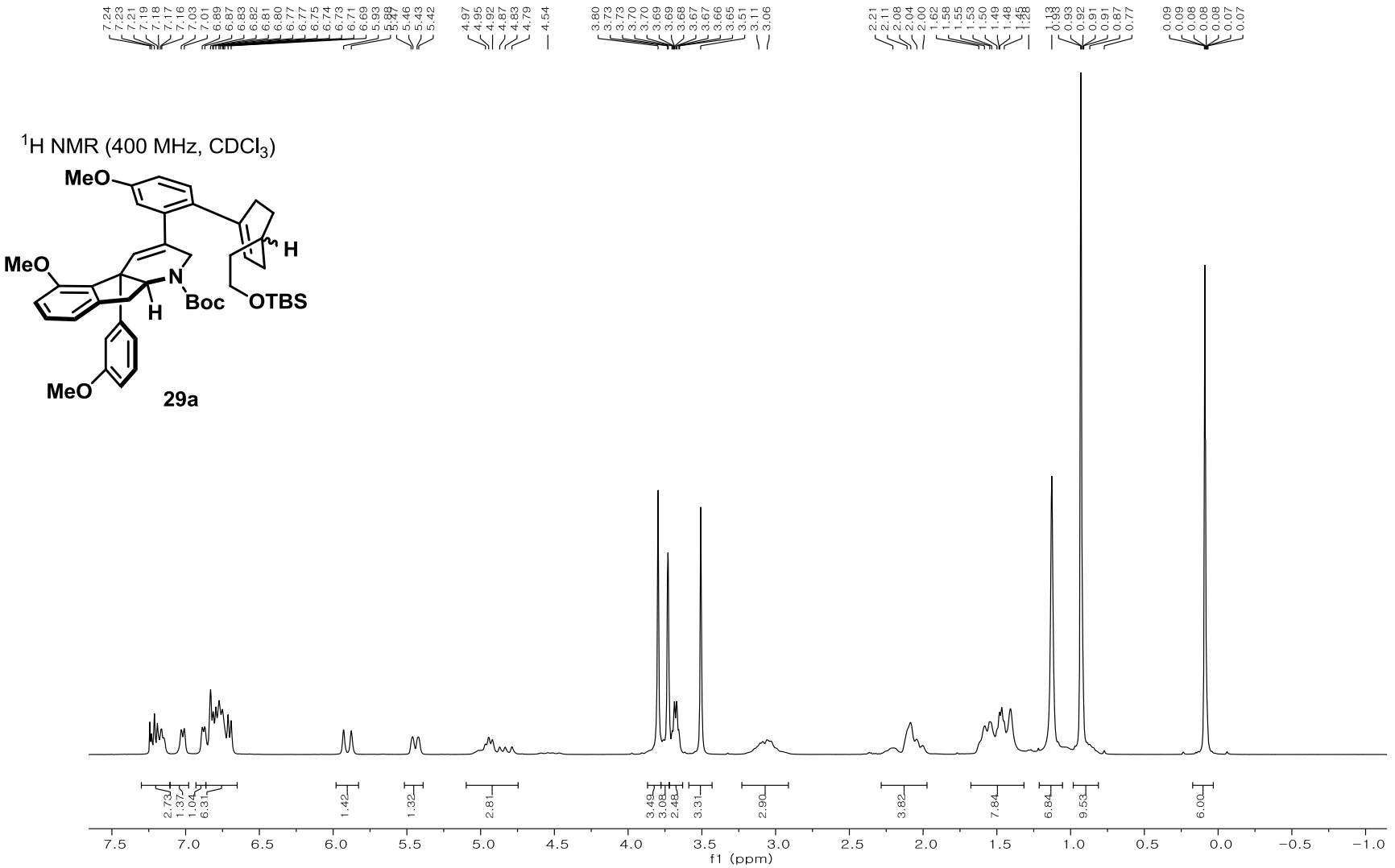


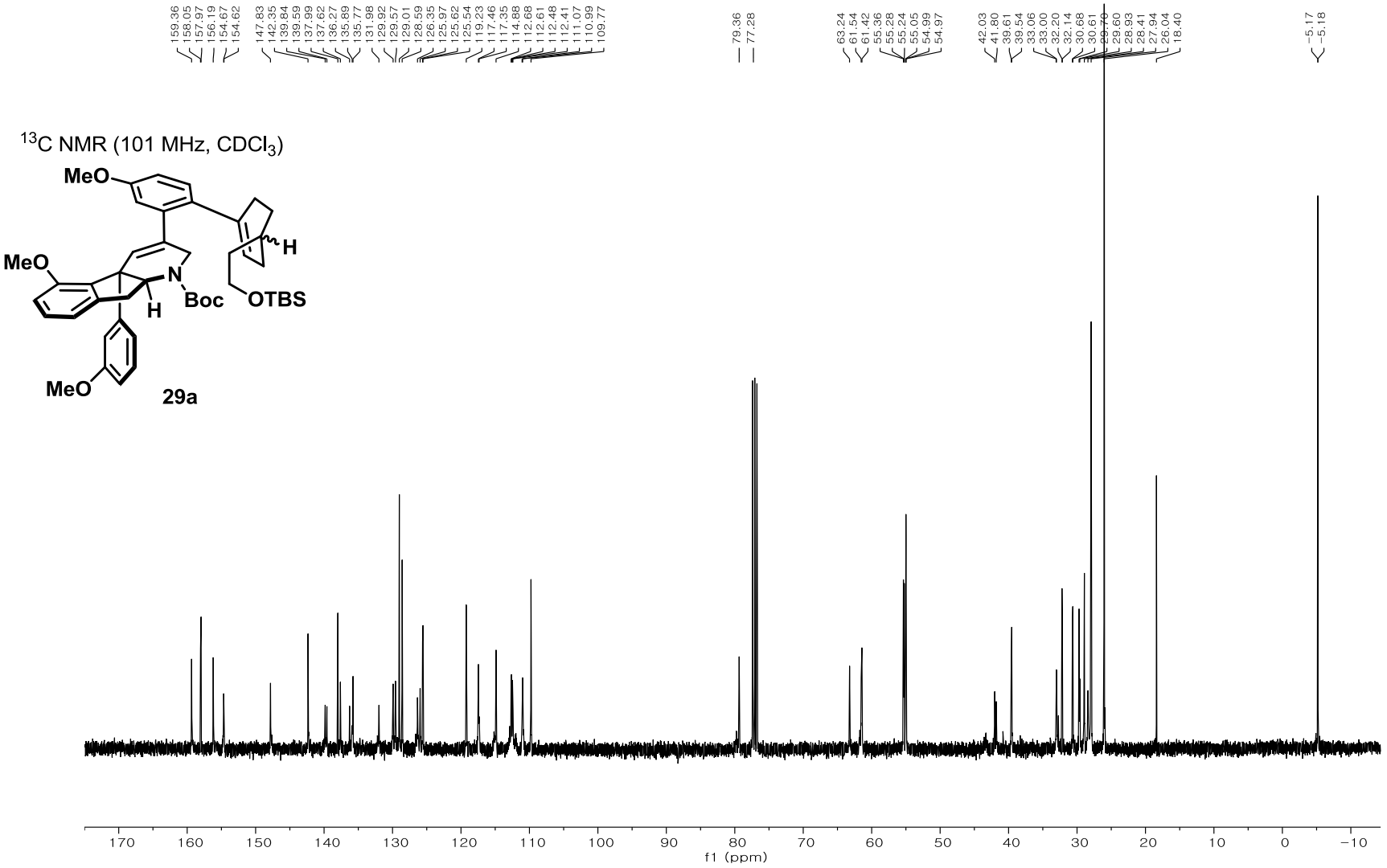
20d

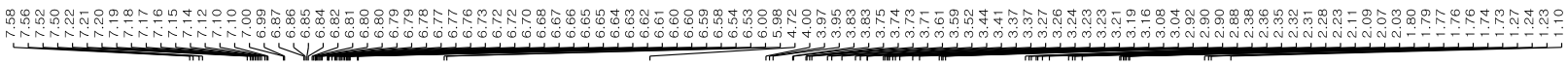

144.65
141.24
133.13
129.79
127.85
83.07
68.57
35.19
32.65
29.31
28.27
25.72
24.78
24.76
21.61
13C NMR (101 MHz, CDCl3)
Me
Me
Me
Me
O
O
B
TsO
20d
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)


1H NMR (400 MHz, CDCl3)
MeO
Br
R
MeO
N
H
H
MeO
Me
Me
O
B
O
Me
Me
29: R =
f1 (ppm)

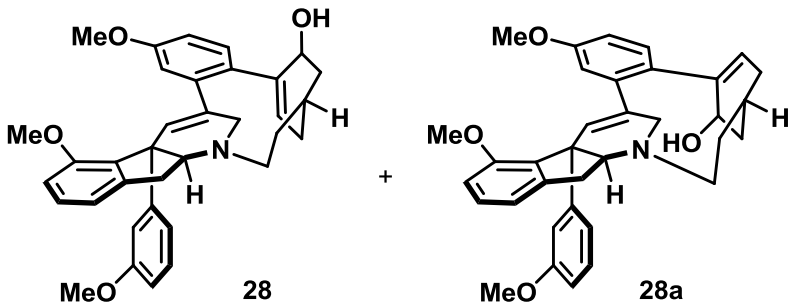

158.95
158.72
156.30
148.91
148.89
143.37
143.31
142.56
142.32
136.87
133.22
132.79
132.76
128.64
128.15
128.13
127.75
119.56
119.54
117.78
116.36
116.33
114.19
114.16
113.32
113.20
111.00
110.96
109.42
82.91
77.23
70.92
70.44
56.18
55.55
55.21
55.17
54.96
52.74
52.44
50.15
49.91
33.94
33.89
33.22
33.18
30.73
30.53
28.88
27.81
27.65
26.21
26.13
24.85
24.83
24.77
13C NMR (101 MHz, CDCl3)
MeO
Br
R
MeO
N
H
H
MeO
Me
Me
O
B
O
Me
Me
29: R =
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

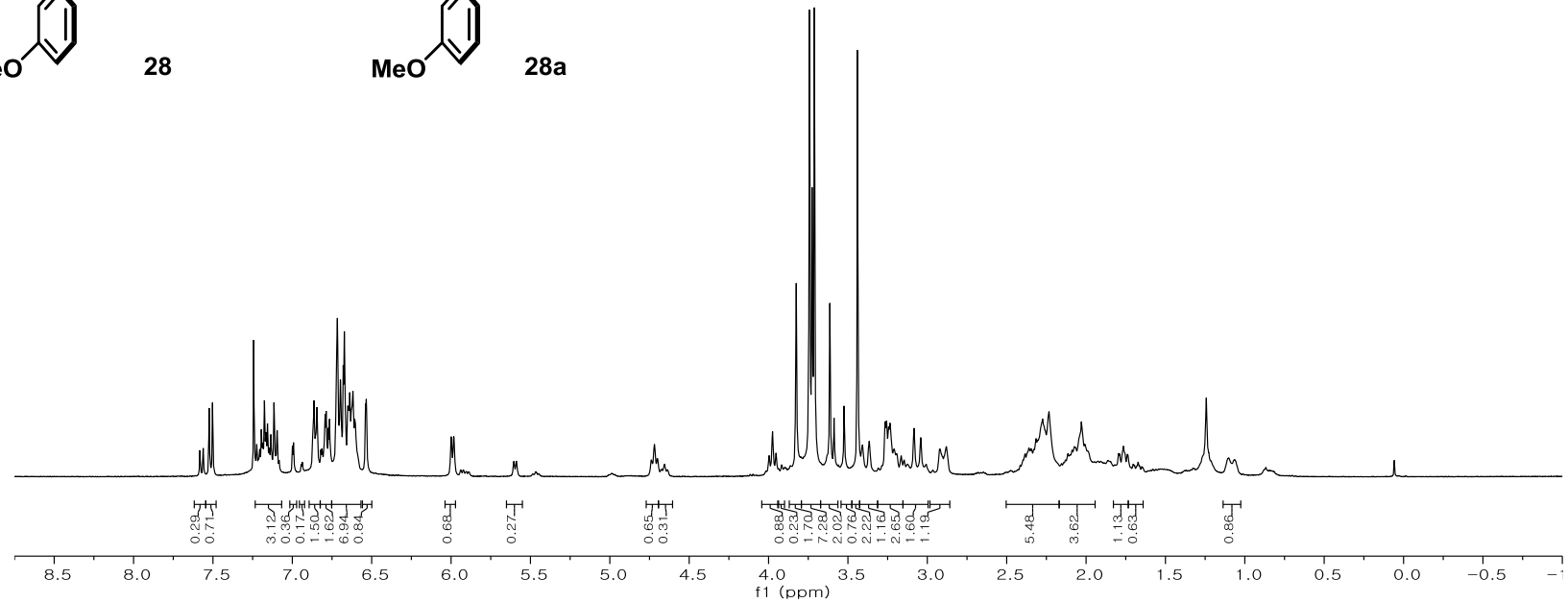

^{1}H NMR (400 MHz, $CDCl_3$)
MeO
MeO
MeO
H
N
Boc
H
OTBS
29a
f1 (ppm)

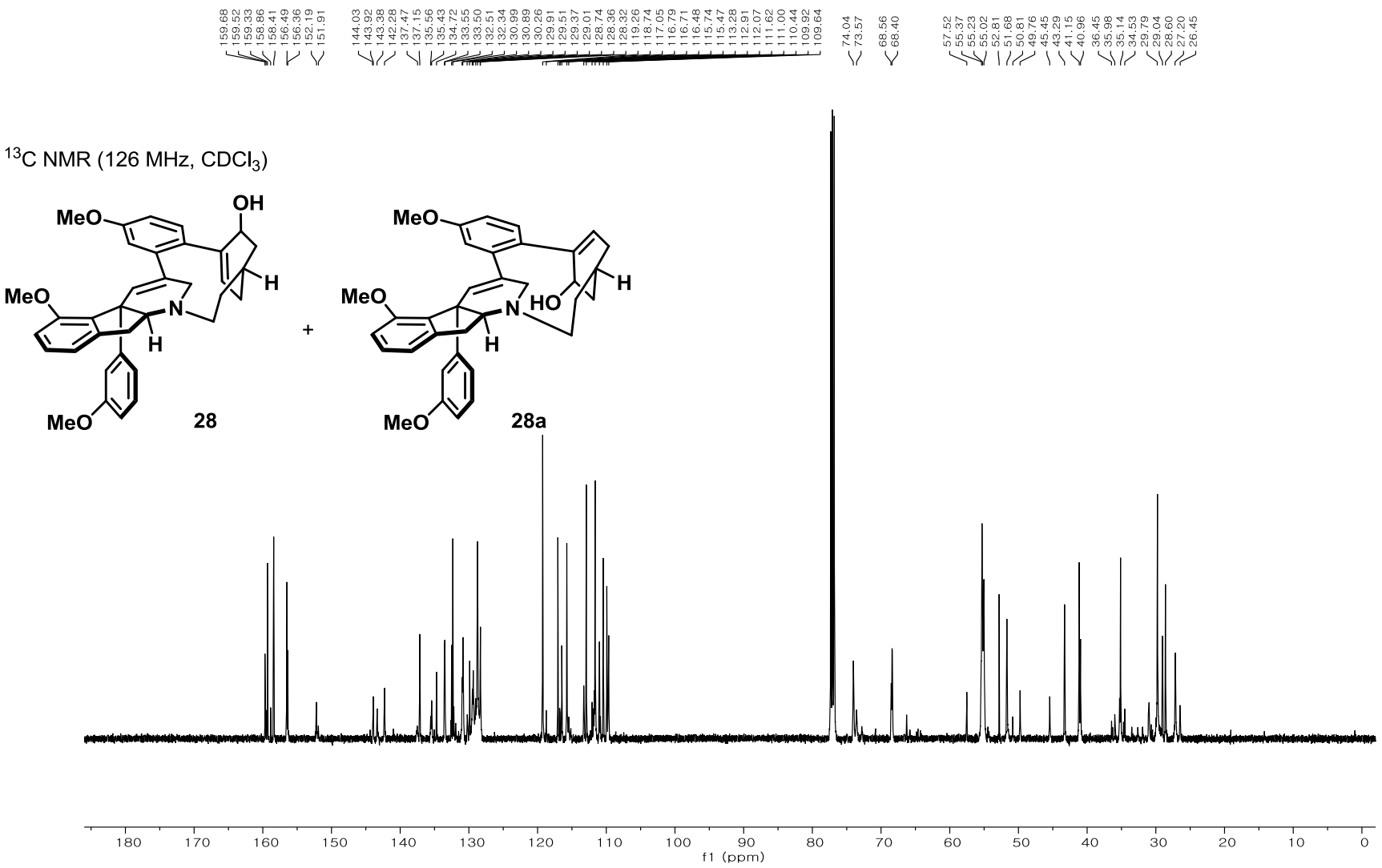

159.36
158.05
157.97
156.19
154.67
154.62
147.83
142.35
139.84
139.59
137.99
137.62
136.27
135.89
135.77
131.98
129.92
129.57
129.01
128.59
126.35
125.97
125.62
125.54
119.23
117.46
117.35
114.88
112.68
112.61
112.48
112.41
111.07
110.99
109.77
79.36
77.28
63.24
61.54
61.42
55.36
55.28
55.24
55.05
54.99
54.97
42.03
41.80
39.61
39.54
33.06
33.00
32.20
32.14
30.68
30.61
29.70
29.60
28.93
28.41
27.94
26.04
18.40
-5.17
-5.18
13C NMR (101 MHz, CDCl3)
MeO
MeO
MeO
N
Boc
H
H
OTBS
29a
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

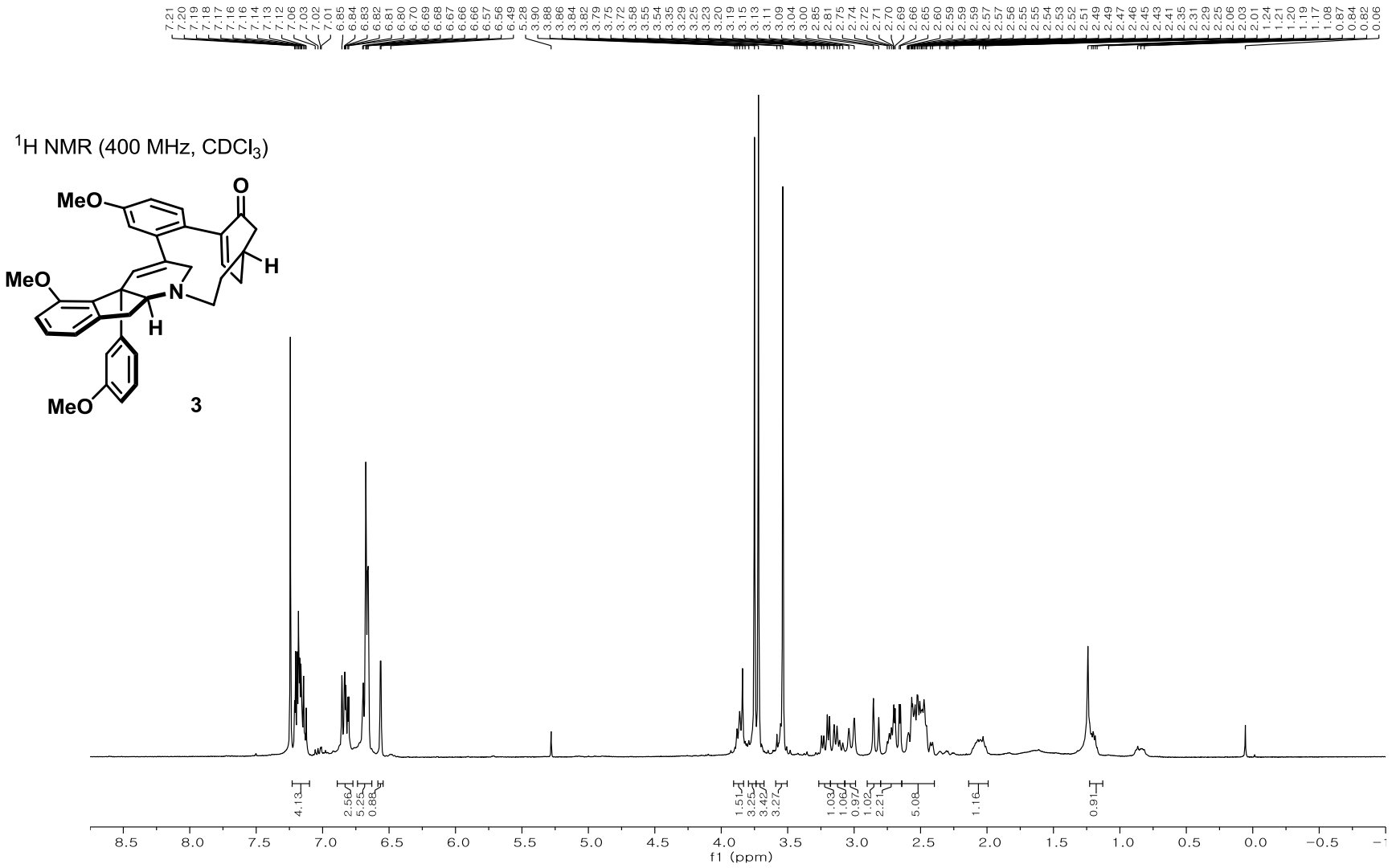


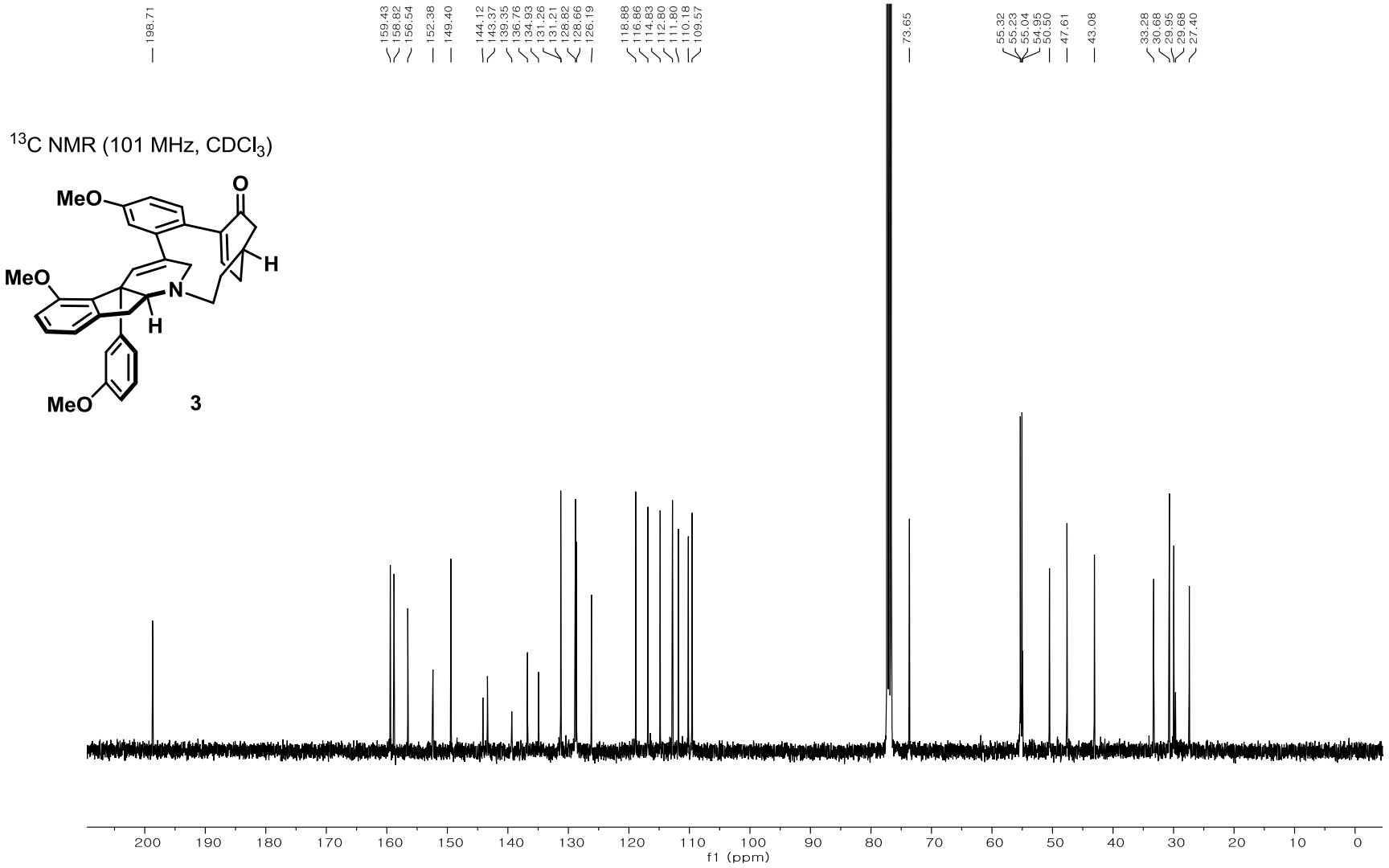
^{1}H NMR (400 MHz, $CDCl_3$)

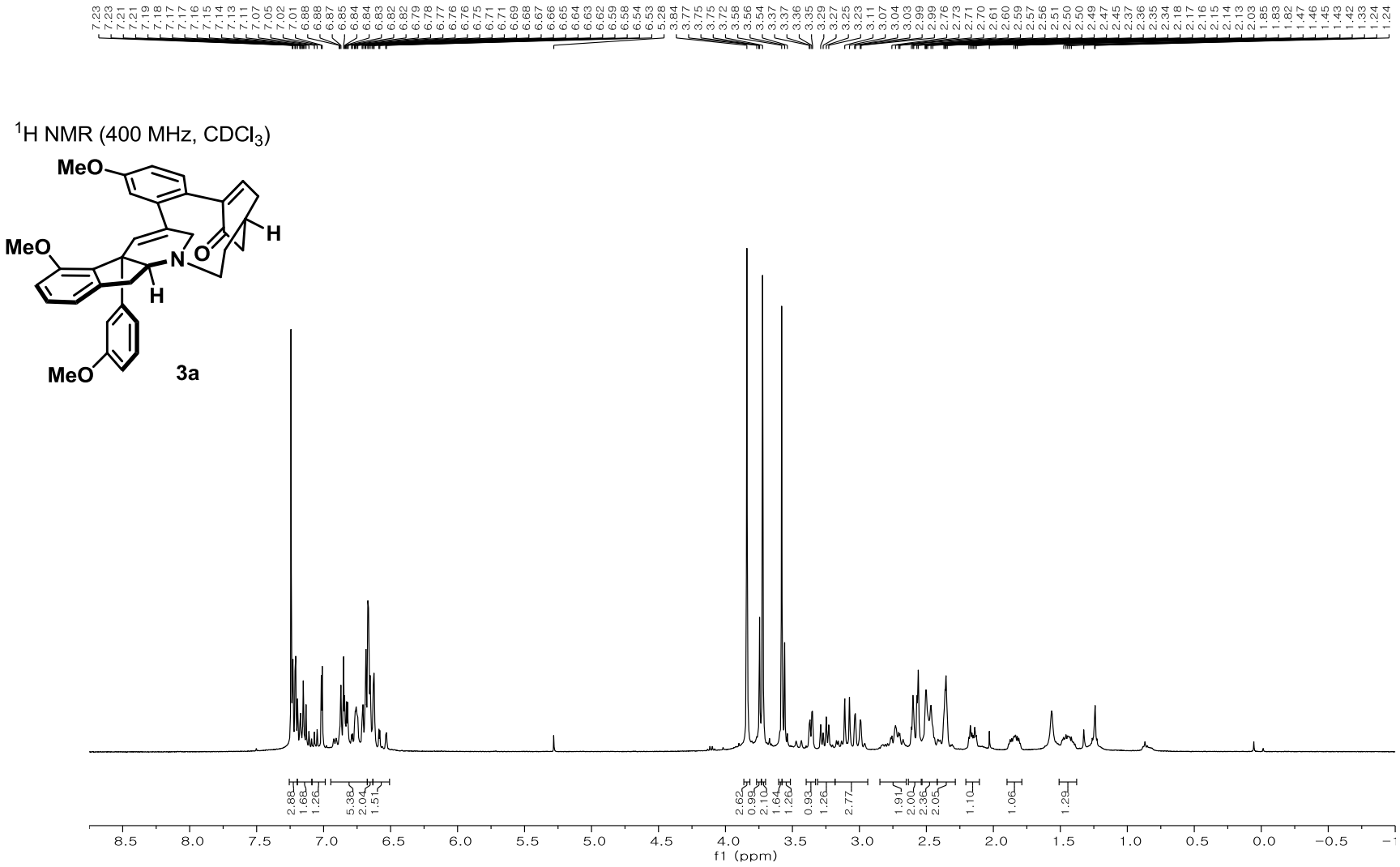


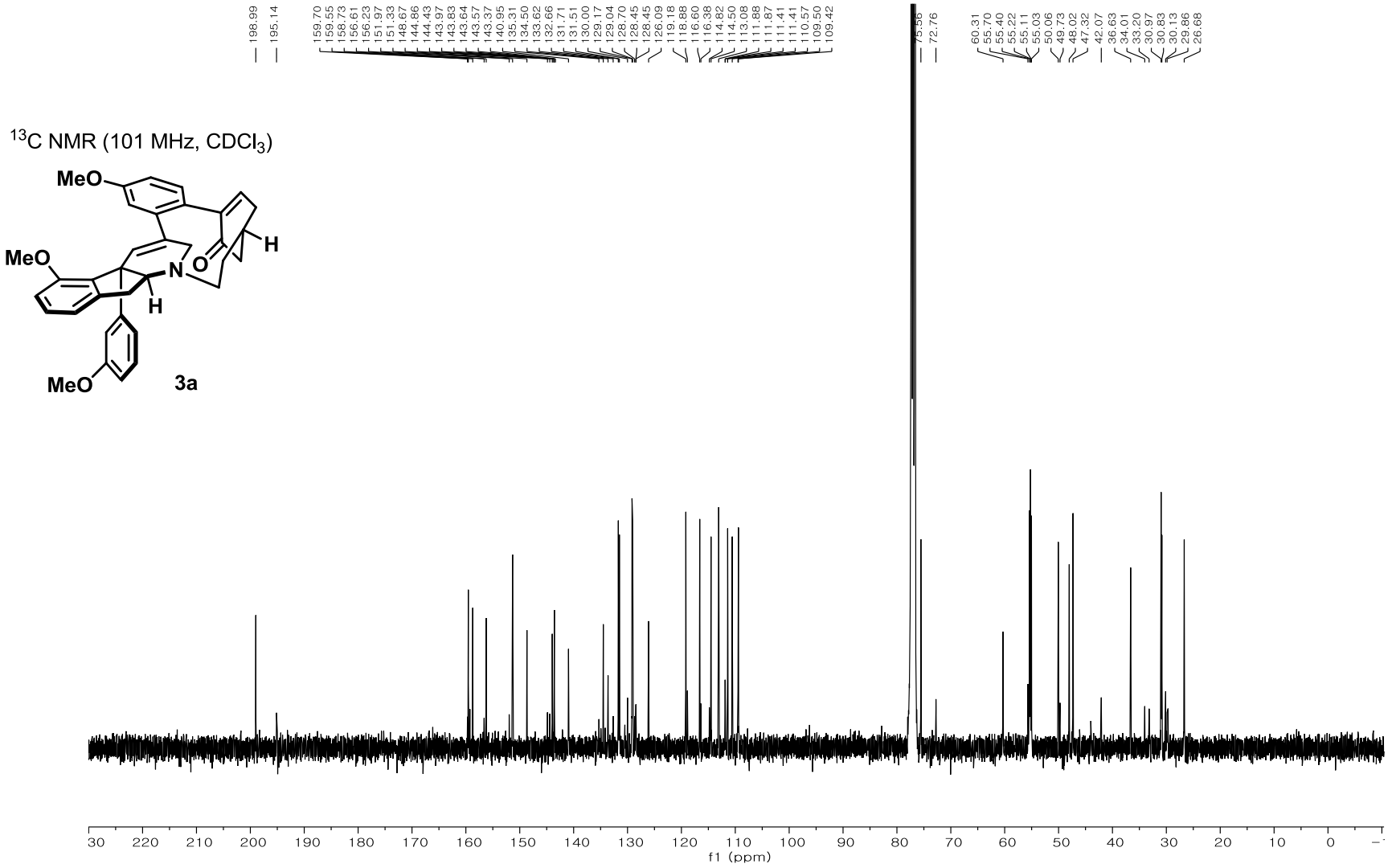


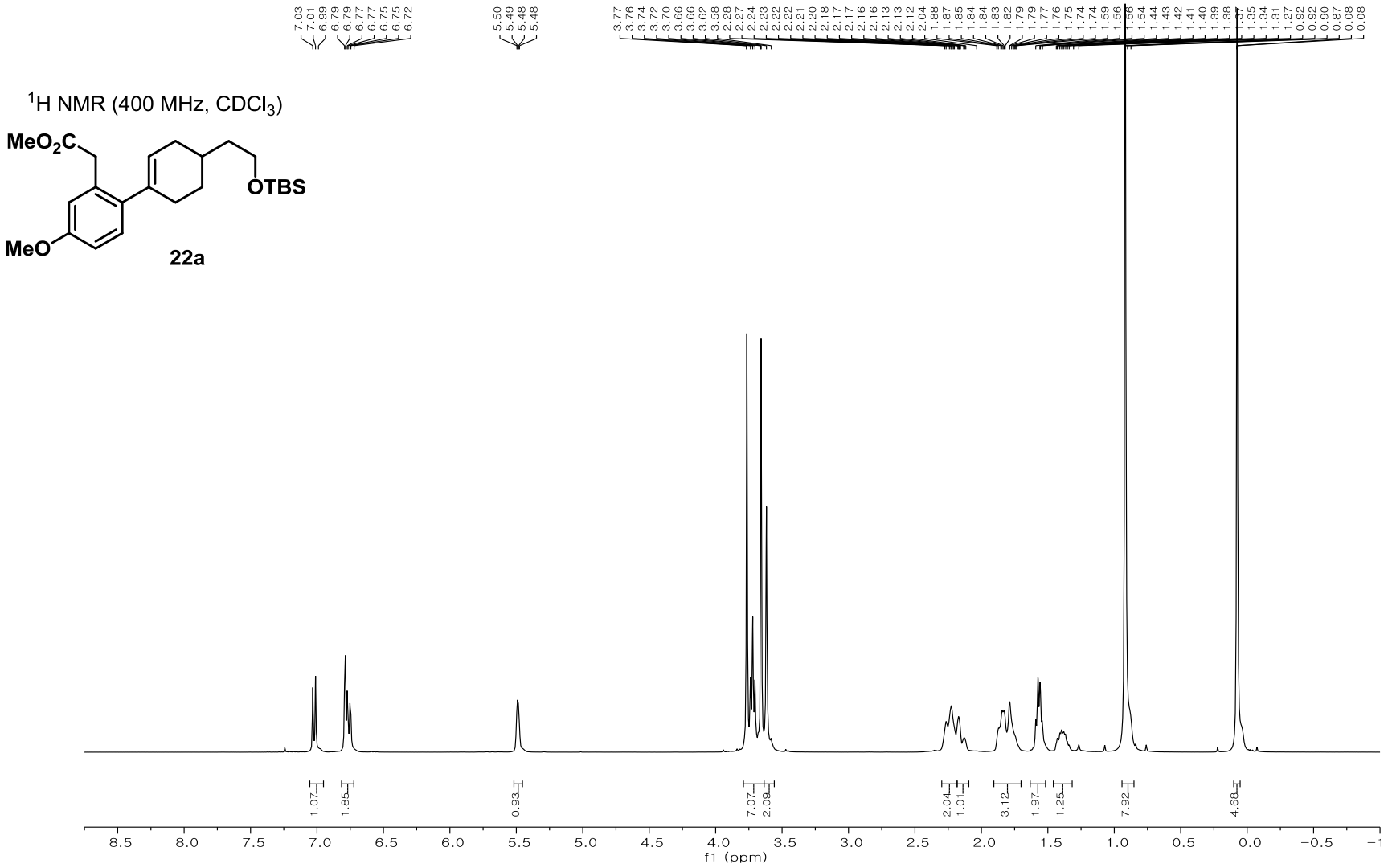

159.68
159.52
159.33
158.86
158.41
156.49
156.36
152.19
151.91
144.03
143.92
143.38
142.28
137.47
137.15
135.56
135.43
134.72
133.55
133.50
132.51
132.34
130.99
130.89
130.26
129.91
129.51
129.37
129.01
128.74
128.36
128.32
119.26
118.74
117.05
116.79
116.71
116.48
115.74
115.47
113.28
112.91
112.07
111.62
111.00
110.44
109.92
109.64
74.04
73.57
68.56
68.40
57.52
55.37
55.23
55.02
52.81
51.68
50.81
49.76
45.45
43.29
41.15
40.96
36.45
35.98
35.14
34.53
29.79
29.04
28.60
27.20
26.45
13C NMR (126 MHz, CDCl3)
MeO
OH
H
MeO
N
H
MeO
28
+
MeO
MeO
N
HO
H
H
MeO
28a
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

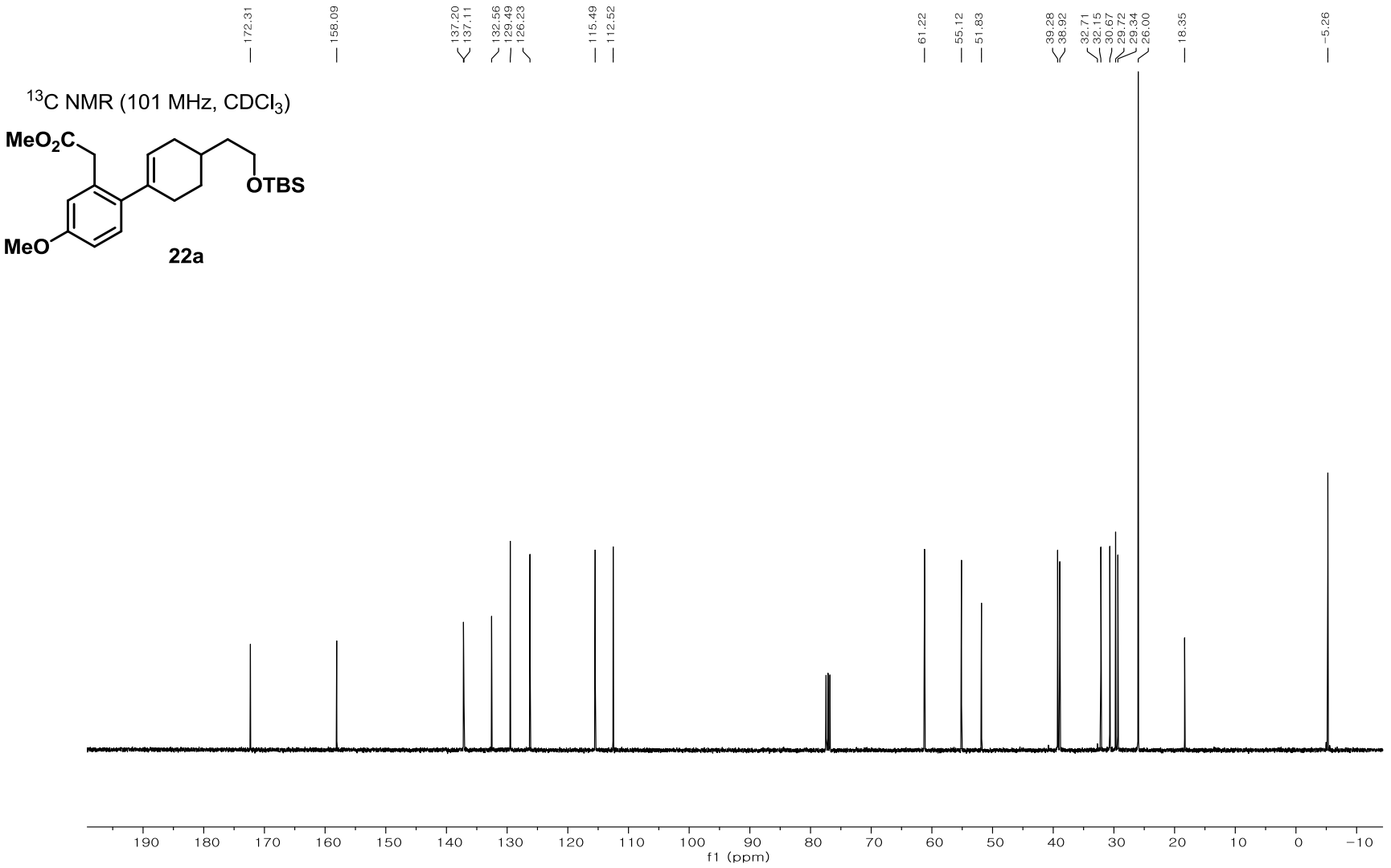

^{1}H NMR (400 MHz, CDCl$_3$)
MeO
O
H
MeO
N
H
MeO
3
f1 (ppm)


198.71
159.43
158.82
156.54
152.38
149.40
144.12
143.37
139.35
136.76
134.93
131.26
131.21
128.82
128.66
126.19
118.88
116.86
114.83
112.80
111.80
110.18
109.57
73.65
55.32
55.23
55.04
54.95
50.50
47.61
43.08
33.28
30.68
29.95
29.68
27.40
^{13}C NMR (101 MHz, CDCl$_3$)
MeO
MeO
MeO
O
H
N
H
3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

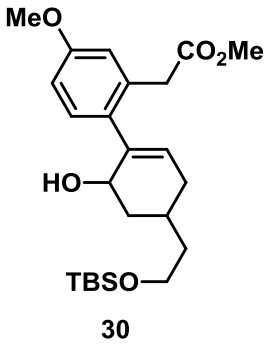

^{1}H NMR (400 MHz, $CDCl_3$)
MeO
MeO
MeO
H
N
O
H
3a
f1 (ppm)


198.99
195.14
159.70
159.55
158.73
156.61
156.23
151.97
151.33
148.67
144.86
144.43
143.97
143.83
143.64
143.57
143.37
140.95
135.31
134.50
133.62
132.66
131.71
131.51
130.00
129.17
129.04
128.70
128.45
128.45
126.09
119.18
118.88
116.60
116.38
114.82
114.50
113.08
111.88
111.87
111.41
111.41
110.57
109.50
109.42
77.56
72.76
60.31
55.70
55.40
55.22
55.11
55.03
50.06
49.73
48.02
47.32
42.07
36.63
34.01
33.20
30.97
30.83
30.13
29.86
26.68
^{13}C NMR (101 MHz, CDCl$_3$)
MeO
MeO
MeO
H
N
O
H
3a
f1 (ppm)

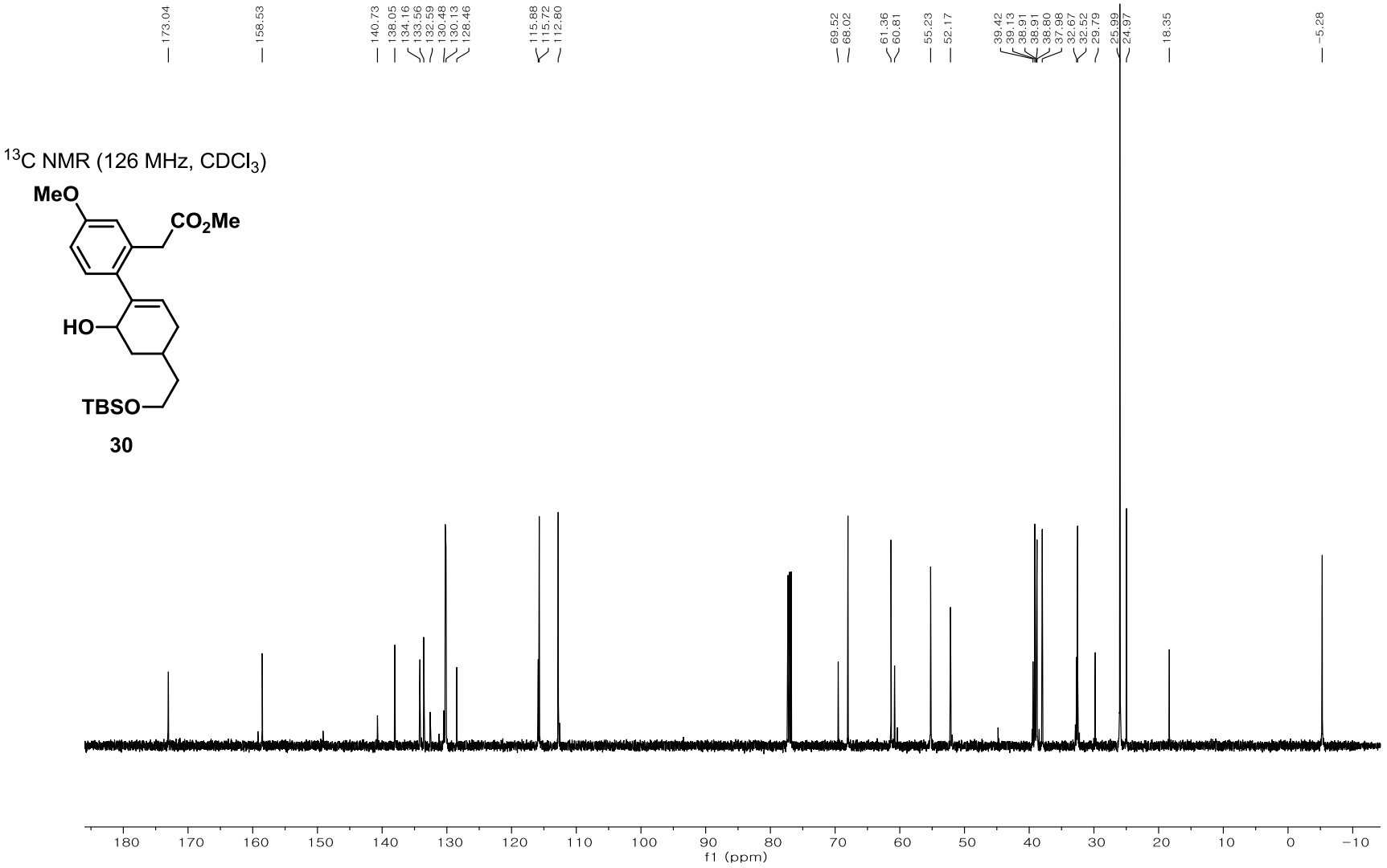

^{1}H NMR (400 MHz, $CDCl_3$)
MeO_2C
OTBS
MeO
22a
f1 (ppm)


172.31
158.09
137.20
137.11
132.56
129.49
126.23
115.49
112.52
61.22
55.12
51.83
39.28
38.92
32.71
32.15
30.67
29.72
29.34
26.00
18.35
-5.26
13C NMR (101 MHz, CDCl3)
MeO2C
OTBS
MeO
22a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

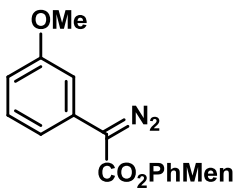
^{1}H NMR (400 MHz, $CDCl_3$)



30

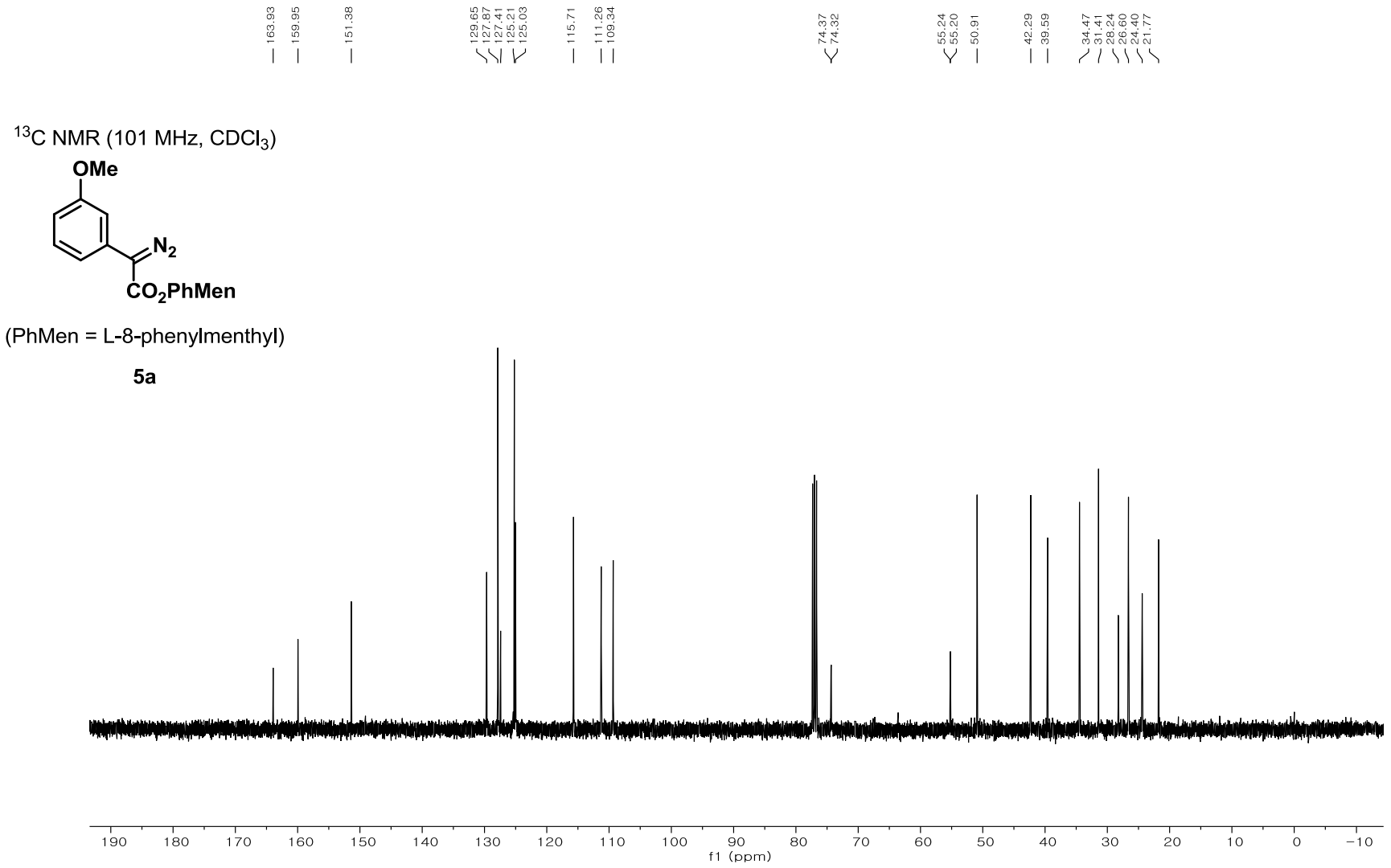

173.04
158.53
140.73
138.05
134.16
133.56
132.59
130.48
130.13
128.46
115.88
115.72
112.80
69.52
68.02
61.36
60.81
55.23
52.17
39.42
39.13
38.91
38.91
38.80
37.98
32.67
32.52
29.79
25.99
24.97
18.35
-5.28
^{13}C NMR (126 MHz, CDCl$_3$)
MeO
CO$_2$Me
HO
TBSO
30
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)

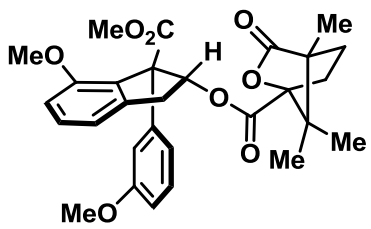


(PhMen = L-8-phenylmenthyl)

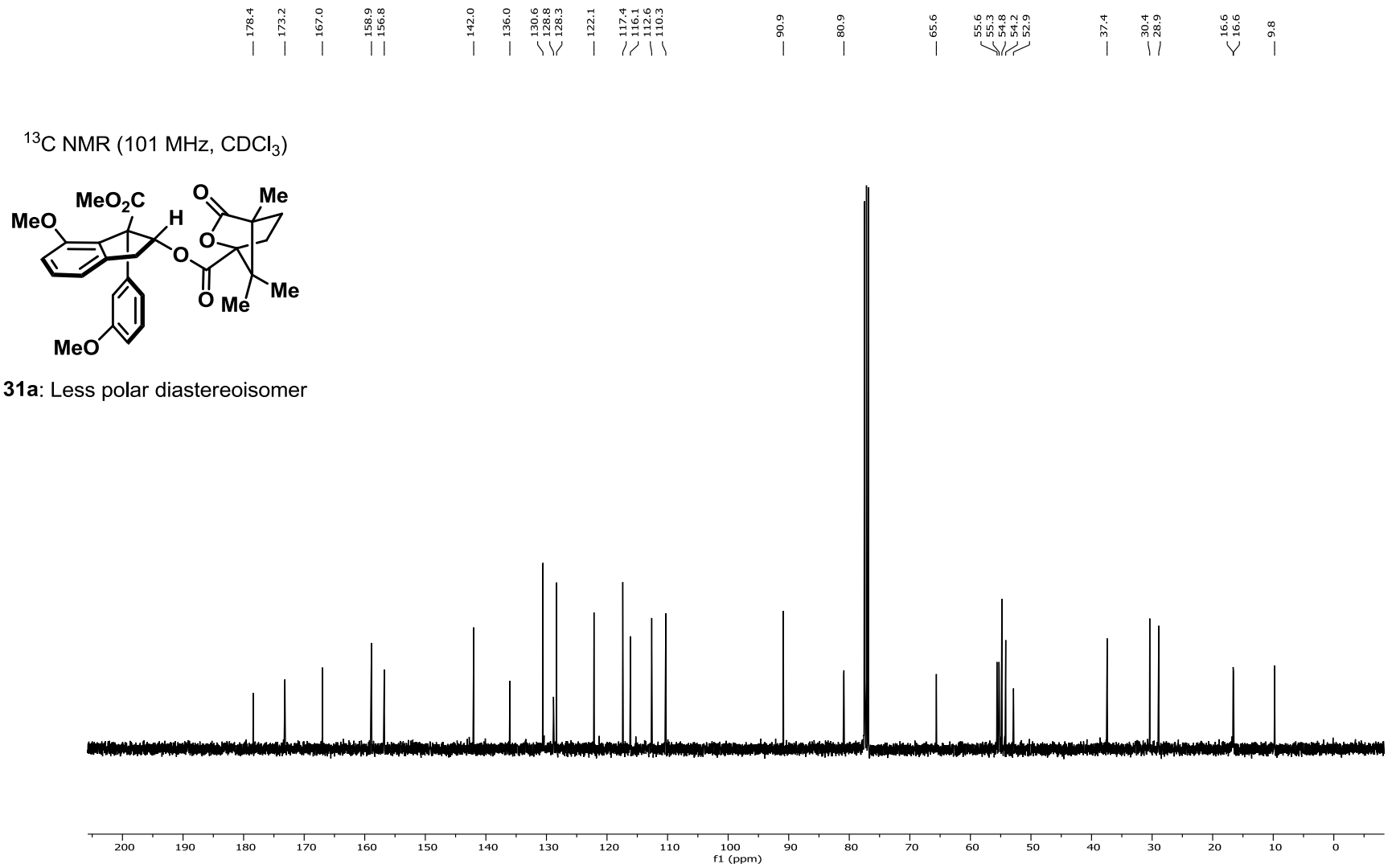
5a


163.93
159.95
151.38
129.65
127.87
127.41
125.21
125.03
115.71
111.26
109.34
74.37
74.32
55.24
55.20
50.91
42.29
39.59
34.47
31.41
28.24
26.60
24.40
21.77
^{13}C NMR (101 MHz, $CDCl_3$)
OMe
N_2
CO_2PhMen
(PhMen = L-8-phenylmenthyl)
5a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

^{1}H NMR (400 MHz, $CDCl_3$)



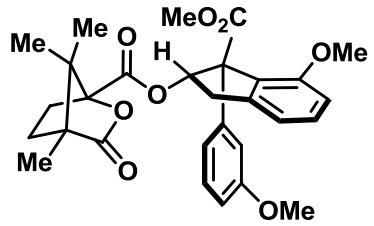
31a: Less polar diastereoisomer



^{13}C NMR (101 MHz, $CDCl_3$)

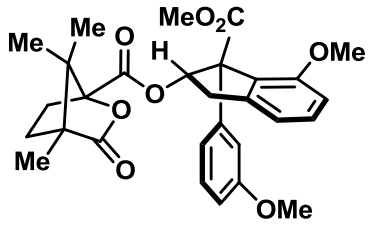
31a: Less polar diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$)



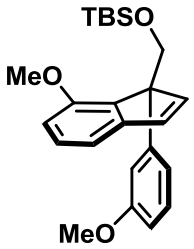
31b: More polar diastereoisomer

^{13}C NMR (101 MHz, $CDCl_3$)



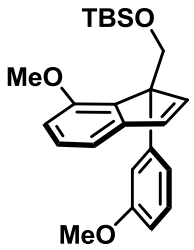
31b: More polar diastereoisomer

^{1}H NMR (400 MHz, $CDCl_3$)



32b

^{13}C NMR (101 MHz, $CDCl_3$)



32b