Intermolecular Radical Addition to *N*-Acylhydrazones as a Stereocontrol Strategy for Alkaloid Synthesis: Formal Synthesis of Quinine

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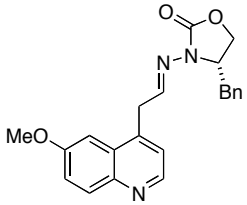
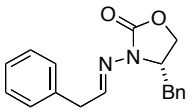
Supplementary Information.

Materials and Methods. Reactions employed oven- or flame-dried glassware under nitrogen unless otherwise noted. THF, diethyl ether, benzene and toluene were distilled from sodium/benzophenone ketyl under argon. CH_2Cl_2 was distilled from CaH_2 under argon or nitrogen. Alternatively, these solvents were purchased inhibitor-free and were sparged with argon and passed through columns of activated alumina prior to use (dropwise addition of blue benzophenone ketyl solution revealed the THF purified in this manner sustained the blue color more readily than the control sample purified by distillation). Nitrogen was passed successively through columns of anhydrous $CaSO_4$ and R3-11 catalyst for removal of water and oxygen, respectively. All other materials were used as received from commercial sources unless otherwise noted. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates with UV indicator. Flash chromatography columns were packed with 230-400 mesh silica gel as a slurry in the initial elution solvent. Gradient flash chromatography was conducted by adsorption of product mixtures on silica gel, packing over a short pad of clean silica gel as a slurry in hexane, and eluting with a continuous gradient from hexane to the indicated solvent. Radial chromatography refers to centrifugally accelerated thin-layer chromatography performed with a Chromatotron using commercially supplied rotors. Melting points are uncorrected. Nuclear magnetic resonance (NMR) data were obtained at operating frequencies indicated in the text, and are reported in units of ppm. Infrared spectra were recorded using a single beam FT-IR spectrophotometer by standard transmission methods or by use of an attenuated total reflectance (ATR) probe. Optical rotations were determined using a digital polarimeter operating at ambient temperature. Low resolution mass spectra were obtained using sample introduction by dip, liquid chromatography or gas chromatography. High resolution mass spectra and combustion analyses were obtained from external commercial and institutional services. Chromatographic diastereomer ratio analyses employed GCMS with 15 m x 0.25 mm x 0.25 μm (l x i.d. x f.t.) 5%-phenyl-95%-dimethylsiloxane column and helium as mobile phase or HPLC with Microsorb-MV Si 8um 100A or Chiralcel OD columns (2-propanol/hexane as mobile phase) or Chirex 3014 column (chloroform/hexane as mobile phase).

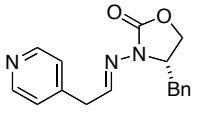


***N*-Acylhydrazone 1.** A solution of 6-methoxy-4-methylquinoline (600 mg, 3.47 mmol) and *tert*-butoxybis(dimethylamino)methane (1.79 mL, 8.68 mmol) in DMF (5.5 mL) was heated at 130 °C under N_2 for 12 h. The oil residue after removal of solvent by vacuum distillation was heated at reflux with **2** (573 mg, 2.98 mmol) in EtOH (10 mL) and 5N HCl (3.5 mL) for 4 h. The mixture was neutralized with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried with Na_2SO_4. Concentration and gradient flash chromatography (hexane/EtOAc 1:1 to 1:4) afforded **1** (800 mg, 2.13 mmol, 62%) as light brown oil. $[\alpha]_D^{23}$ +8.6 (*c* 1.0, $CHCl_3$); IR (film) 3007, 2930, 1769, 1620, 1591, 1508, 1403, 1365, 1241, 1216, 1081, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 4.9, 4.9 Hz, 1H), 8.05 (d, *J* = 9.8 Hz, 1H), 7.05 (d, *J* = 6.4 Hz, 2H), 7.43-7.16 (m, 7H), 4.37-4.27 (m, 1H), 4.22 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.13-4.02 (m, 3H), 3.93 (s, 3H), 3.13 (dd, *J* = 13.9, 3.8 Hz, 1H), 2.77 (dd, *J* = 13.9, 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 154.1, 151.2, 147.2, 147.0, 143.9, 141.1, 134.9, 131.2, 129.1, 128.9, 128.5, 127.3, 122.1, 121.9, 101.9, 65.8, 57.6, 55.6, 37.3, 36.9; MS (CI) *m/z* (relative intensity) 376 ($[M+H]^+$, 100%); HRMS (EI) calcd for $C_{22}H_{21}N_3O_3$: 375.1583. Found: 375.1587.

Preparation of Hydrazones (General Procedure A). To a solution of 3-amino-4-phenylmethyl-2-oxazolidone in CH_2Cl_2 was added $TsOH•H_2O$ (5 mol%) and the appropriate aldehyde at room temperature. When the reaction was complete (TLC), concentration and flash chromatography (e.g., hexane/EtOAc 4:1 to 1:1) furnished the hydrazone. Only the (*E*)-isomer was detected.

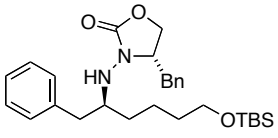


***N*-Acylhydrazone 6a**. From (*S*)-aminooxazolidinone **4** (120 mg, 0.625 mmol) and phenylacetaldehyde (74 μL, 0.625 mmol) by General Procedure A was obtained **6a** (150 mg, 0.51 mmol, 82% yield) as a colorless oil. $[\alpha]_D^{27}$ –3.3 (*c* 2.7, $CHCl_3$); IR (film) 3062, 3028, 2917, 1769, 1603, 1496, 1454, 1402, 1290, 1213, 1083, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 6.0, 6.0 Hz, 1H), 7.44-7.21 (m, 8H), 7.15 (d, *J* = 6.8 Hz, 2H), 4.42-4.33 (m, 1H), 4.24 (dd, *J* = 8.3, 8.3 Hz, 1H), 4.10 (dd, *J* = 9.0, 5.3 Hz, 1H), 3.72 (d, *J* = 5.7 Hz, 2H), 3.23 (dd, *J* = 13.6, 3.8 Hz, 1H), 2.83 (dd, *J* = 13.6, 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 153.9, 136.2, 135.2, 129.3, 128.9, 128.9, 128.8, 127.2, 126.9, 65.7, 57.6, 39.9, 37.2; MS (CI) *m/z* (relative intensity) 295 ($[M+H]^+$, 100%); Anal. Calcd for: $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.32; H, 6.19; N, 9.53.

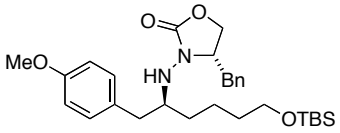


***N*-Acylhydrazone 6c.** A solution of 4-picoline (0.5 mL, 5.16 mmol) and *tert*-butoxybis(dimethylamino)methane (2.14 mL, 10.32 mmol) in DMF (2 mL) was heated at 130 °C under N_2 for 12 h. Removal of solvent by vacuum distillation afforded enamine product (740 mg, 5 mmol, 93% yield) as yellow solid. A solution of enamine product (72 mg, 0.49 mmol) and **4** (80 mg, 0.42 mmol) in EtOH (2 mL) and 5N HCl (0.42 mL) was heated at reflux for 4 h. The mixture was neutralized with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried with Na_2SO_4. Concentration and gradient flash chromatography (EtOAc to EtOAc/MeOH 20:1) afforded **6c** (80 mg, 0.271 mmol, 65%) as colorless oil; $[\alpha]_D^{25}$ +5.3 (*c* 6.0, $CHCl_3$); IR (film) 3028, 2921, 1768, 1600, 1497, 1403, 1216, 1091, 1069, 994 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 6.0 Hz, 2H), 8.15 (dd, *J* = 6.4, 6.4 Hz, 1H), 7.30-7.19 (m, 3H), 7.16 (d, *J* = 5.7 Hz, 2H), 7.10 (d, *J* = 6.8 Hz, 2H), 4.37-4.29 (m, 1H), 4.21 (dd, *J* = 7.9, 7.9 Hz, 1H), 4.05 (dd, *J* = 9.1, 5.3 Hz, 1H), 3.66 (d, *J* = 5.7 Hz, 2H), 3.17 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.79 (dd, *J* = 13.94, 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 151.7, 150.1, 149.9, 145.4, 135.1, 129.2, 128.8, 127.2, 124.2, 65.8, 57.8, 39.0, 37.4; MS (CI) *m/z* (relative intensity) 296 ($[M+H]^+$, 100%); HRMS (EI) calcd for $C_{17}H_{17}N_3O_2$: 295.1321. Found: 295.1327.

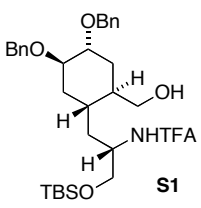
Radical Addition (General Procedure B): Using standard pyrex glassware, a solution of the hydrazone in CH_2Cl_2 (0.02 M) or in benzene/CH_3CN (10:1 *v*/*v*, 0.1 M) was deoxygenated (N_2 or Ar was bubbled through the solution via a syringe needle for ca. 30 min); then $InCl_3$ (dried for ca. 12 h at 0.1 mmHg prior to use, 2.2 equiv) was added. After 40 min at room temperature, the appropriate alkyl iodide (passed through basic alumina prior to use, 1.2–10 equiv) and $Mn_2(CO)_{10}$ (1.2 eq) were added and the mixture was irradiated (Rayonet photochemical reactor, 300 nm) for 10–20 h. Triethylamine (5 equiv) was added, and the mixture was stirred for 40 min and concentrated. Flash chromatography (hexane/EtOAc 9:1 to 1:1) afforded *N*-acylhydrazines. Unless otherwise noted, the minor diastereomers were not detected.



Hydrazine 8a. From phenylacetaldehyde hydrazone **6a** (97 mg, 0.33 mmol) and iodide **7** (0.13 mL, 0.50 mmol) according to General Procedure B in benzene/CH_3CN was obtained hydrazine **8a** (63 mg, 0.130 mmol, 40% yield, >98:2 dr, ^{1}H NMR analysis) as colorless oil; $[\alpha]_D^{29}$ +18.5 (*c* 2.8, $CHCl_3$); IR (film) 3286, 3063, 3028, 2929, 2857, 1760, 1472, 1497, 1396, 1251, 1097 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.17 (m, 8H), 7.07 (d, *J* = 7.5 Hz, 2H), 4.05-3.99 (br s, 1H), 3.94 (d, *J* = 6.4 Hz, 2H), 3.70-3.56 (m, 3H), 3.41-3.32 (m, 1H), 3.11 (dd, *J* = 13.6, 3.8 Hz, 1H), 2.85-2.70 (m, 2H), 2.48 (dd, *J* = 13.2, 10.2 Hz, 1H), 1.61-1.39 (m, 6H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 139.3, 135.9, 129.2, 129.1, 128.9, 128.5, 127.0, 126.3, 65.7, 62.9, 60.6, 59.2, 39.9, 36.8, 33.0, 32.7, 26.0, 22.0, 18.3, -5.2; MS (CI) *m*/*z* (relative intensity) 484 ([M+H]$^+$, 100%); Anal. Calcd for $C_{28}H_{42}N_2O_3Si$: C, 69.67; H, 8.77; N, 5.80. Found: C, 69.69; H, 8.84; N, 5.81.



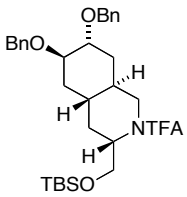
Hydrazine 8b. From (*S*)-aminooxazolidinone **4** (120 mg, 0.63 mmol) and *p*-methoxyphenylacetaldehyde (189 mg, 1.26 mmol) by General Procedure A, with rapid elution through silica gel, was obtained a partially purified sample of **6b** (204 mg, ca. 70% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (t, *J* = 5.9 Hz, 1H), 7.33-7.13 (m, 7H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.40-4.33 (m, 1H), 4.26-4.20 (m, 1H), 4.10-4.03 (m, 1H), 3.80 (s, 3H), 3.65 (d, *J* = 5.8 Hz, 2H), 3.23 (dd, *J* = 8.3, 3.5 Hz, 1H), 2.81 (dd, *J* = 8.2, 5.3 Hz, 1H). Despite numerous attempts, this material could not be further purified without extensive decomposition. From hydrazone **6b** (65 mg, 0.20 mmol) and iodide **7** (80 μL, 0.30 mmol) according to General Procedure B in benzene/CH_3CN was obtained hydrazine **8b** (40 mg, 0.078 mmol, 39% yield, 2.9:1 dr, ^{1}H NMR analysis) as colorless oil; IR (film) 3492, 3028, 2932, 2857, 1758, 1612, 1513, 1410, 1248, 1097 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) major isomer: δ 7.30 (dd, *J* = 8.3, 8.3 Hz, 2H), 7.24 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 7.2 Hz, 2H), 6.85 (dd, *J* = 8.7, 2.3 Hz, 2H), 4.03-3.92 (m, 2H), 3.80-3.55 (br s, 1H), 3.77 (s, 3H), 3.74-3.55 (m, 3H), 3.35-3.25 (m, 1H), 3.13 (dd, *J* = 13.6, 3.4 Hz, 1H), 2.80-2.64 (m, 2H), 2.49 (dd, *J* = 13.2, 10.2 Hz, 1H), 1.63-1.38 (m, 6H), 0.89 (s, 9H), 0.04 (s, 6H); minor isomer: 0.91 (s, 9H), 0.10 (s, 6H), some resonances not reported due to overlap with major isomer; ^{13}C NMR (125 MHz, $CDCl_3$) major isomer: δ 158.5, 158.1, 135.9, 131.0, 130.0, 129.0, 128.8, 127.0, 113.9, 65.7, 62.9, 60.5, 59.0, 55.2, 38.8, 36.8, 32.9, 32.5, 25.9, 21.9, 18.3, -5.3; minor isomer: δ 135.8, 130.9, 62.4, 60.4, 58.8, 38.9, 36.7, 32.6, 32.3, 25.6, 21.5, -3.6, some resonances not reported due to overlap with major isomer; MS (CI) *m*/*z* (relative intensity) 514 ([M+H]$^+$, 100%); Anal. Calcd for $C_{29}H_{44}N_2O_4Si$: C, 67.93; H, 8.65; N, 5.46. Found: C, 67.81; H, 8.55; N, 5.39.



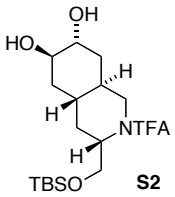
S1

***N*-((*S*)-1-((1*R*,2*R*,4*R*,5*R*)-4,5-Bis(benzyloxy)-2-(hydroxymethyl)cyclohexyl)-3-(tert-butyldimethylsilyloxy)propan-2-yl)-2,2,2-trifluoroacetamide (S1).** To a solution of **11**[1] (104 mg, 0.17 mmol) in THF (1.7 mL), was added *n*-BuLi (1.7 M in hexanes, 0.22 mL, 0.38 mmol) at –78 °C. After 1 h, trifluoroacetic anhydride (0.21

mL, 1.51 mmol) was added at –78 °C, and the mixture was allowed to warm to ambient temperature overnight. The reaction was quenched by saturated NH_4Cl solution and the organic phase was washed with water, saturated $NaHCO_3$ solution and brine, then dried (Na_2SO_4) and concentrated to afford the trifluoroacetohydrazide. This material was taken up in MeOH (1 mL) and a solution of SmI_2 in THF (0.3 M, 4.33 mL) was added dropwise until the blue color remained. After 1 h, the reaction mixture was opened to the air. Concentration and flash chromatography (hexane/EtOAc 10:1 to 3:1) afforded **S1** (66 mg, 72% yield) as a pale yellow oil; $[\alpha]_D^{24.1}$ –50.1 (*c* 0.9, $CHCl_3$); IR (film) 3424, 3317, 3088, 3063, 3030, 2925, 2855, 1711, 1551, 1462, 1253, 1182, 1161, 1095, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 10H), 6.94 (d, J = 8.4 Hz, 1H), 4.50 (ABq, Δν = 19.6 Hz, J_{AB} = 12.0 Hz, 2H), 4.48 (ABq, Δν = 54.2 Hz, J_{AB} = 12.0 Hz, 2H), 4.16-4.08 (m, 1H), 3.75 (dd, J = 11.2, 4.4 Hz, 1H), 3.68 (dd, J = 10.2, 4.4 Hz, 1H), 3.68-3.62 (m, 2H), 3.61 (dd, J = 10.2, 3.4 Hz, 1H), 3.51 (dd, J = 11.0, 3.0 Hz, 1H), 2.03-1.94 (m, 2H), 1.85-1.78 (m, 2H), 1.76-1.57 (m, 3H), 1.47 (ddd, J = 13.9, 11.7, 2.5 Hz, 1H), 1.29 (ddd, J = 13.9, 9.2, 4.3 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1 ($^2J_{CF}$ = 36.4 Hz), 138.7, 138.6, 128.33, 128.27, 127.49, 127.46, 127.41, 127.36, 116.0 ($^1J_{CF}$ = 286.3 Hz), 75.0, 74.1, 70.8, 70.5, 64.9, 64.7, 49.5, 38.4, 33.9, 30.3, 28.9, 28.1, 25.8, 18.2, –5.5, –5.6; MS (ESI) *m/z* (relative intensity) 610.01 ([M+H]$^+$, 13%), 632.29 ([M+Na]$^+$, 100%); HRMS (ESI) *m/z* calcd. for $C_{32}H_{47}F_3NO_5Si$ ([M+H]$^+$) 610.3176; Found 610.3180.

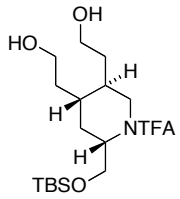


1-((3*S*,4a*R*,6*R*,7*R*,8a*R*)-6,7-Bis(benzyloxy)-3-((tert-butyldimethylsilyloxy)-methyl)octahydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone (12). To a solution of trifluoroacetamide **S1** (53 mg, 0.087 mmol) and PPh_3 (47 mg, 0.18 mmol) in THF (4.5 mL) at 0 °C was added diisopropyl azodicarboxylate (0.036 mL, 0.18 mmol). The mixture was allowed to warm to ambient temperature and stirred overnight. Concentration and flash chromatography (hexane to 5:1 hexane/EtOAc) afforded **12** (49 mg, 95% yield) as a pale yellow oil; $[\alpha]_D^{23.3}$ –52.0 (*c* 1.0, $CHCl_3$); IR (film) 3064, 3031, 2928, 2857, 1685, 1454, 1253, 1205, 1171, 1141, 1090, 1073 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 10H), 4.51 (ABq, Δν = 23.7 Hz, J_{AB} = 12.0 Hz, 2H), 4.50 (ABq, Δν = 24.9 Hz, J_{AB} = 12.0 Hz, 2H), 4.02-3.65 (br m, 6H), 3.17 (br s, 1H), 1.90-1.77 (m, 4H), 1.64-1.48 (m, 3H), 1.40-1.25 (m, 1H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 138.5, 138.4, 128.4 (2C), 127.6, 127.41, 127.39 (2C), 116.6 ($^1J_{CF}$ = 286.6 Hz), 74.2, 74.1, 70.8 (2C), 64.0, 31.9, 30.4, 25.8, 18.2, –5.51, –5.53, some peaks not observed due to line broadening related to TFA rotamers; MS (ESI) *m/z* (relative intensity) 592.00 ([M+H]$^+$, 52%), 614.19 ([M+Na]$^+$, 100%); HRMS (ESI) *m/z* calcd. for $C_{32}H_{45}F_3NO_4Si$ ([M+H]$^+$) 592.3070; Found 592.3073.

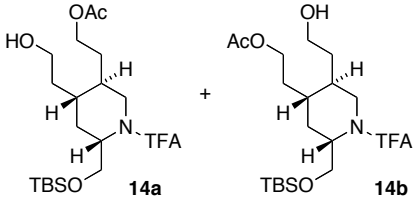


S2

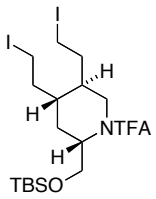
1-((3*S*,4a*R*,6*R*,7*R*,8a*R*)-3-((*tert*-Butyldimethylsilyloxy)methyl)-6,7-dihydroxy-octahydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone (S2). To a solution of bis-benzyl ether **12** (49 mg, 0.083 mmol) in EtOAc (2 mL) was added Pd/C (10% *w/w*, 0.21 mmol). The mixture was stirred under H_2 (balloon) for 2 days. Filtration, concentration and flash chromatography (hexane/EtOAc 3:1 to 1:1) afforded **S2** (32 mg, 93% yield) as a colorless oil; $[\alpha]_D^{24.0}$ –53.3 (*c* 0.7, $CHCl_3$); IR (film) 3429, 2930, 2859, 1683, 1464, 1255, 1205, 1147, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.94-3.80 (m, 6H), 3.20 (br s, 1H), 1.92-1.53 (m, 9H), 1.29 (br s, 1H), 0.87 (s, 9H), 0.039 (s, 3H), 0.038 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 116.5 ($^1J_{CF}$ = 286.6 Hz), 69.5, 63.9, 34.1, 32.9, 31.6, 25.8, 18.1, –5.5, –5.6, some peaks exhibited line broadening related to TFA rotamers; MS (ESI) *m/z* (relative intensity) 411.92 ([M+H]$^+$, 100%), 280.20 ([M–OTBS]$^+$, 58%); HRMS (ESI) *m/z* calcd. for $C_{18}H_{33}F_3NO_4Si$ ([M+H]$^+$) 412.2131; Found 412.2138.



1-((2*S*,4*R*,5*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-4,5-bis(2-hydroxyethyl)-piperidin-1-yl)-2,2,2-trifluoroethanone (13). To a solution of vicinal diol **S2** (144 mg, 0.35 mmol) in CH_2Cl_2 (3.5 mL) was added silica gel-supported $NaIO_4$ (0.667 mmol/g, 577 mg, 0.385 mmol). After the mixture was stirred overnight, filtration and concentration afforded an unstable dialdehyde. This material was taken up in MeOH (35 mL), and to this solution was added $NaBH_4$ (26 mg, 0.69 mmol) at 0 °C. After 1 h the solution was concentrated and partitioned between CH_2Cl_2 and water, and the organic phase was washed with saturated aqueous $NaHCO_3$ and brine. Concentration and flash chromatography (hexane/EtOAc 1:1 to EtOAc) afforded diol **13** (133 mg, 92% yield) as a colorless oil; $[\alpha]_D^{25.0}$ –54.9 (*c* 0.5, $CHCl_3$); IR (film) 3366, 2930, 2859, 1683, 1472, 1451, 1256, 1202, 1143, 1114, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.13-4.05 (m, 1H), 3.98 (dd, *J* = 10.4, 3.9 Hz, 1H), 3.78-3.53 (m, 7H), 1.80-1.77 (m, 6H), 1.66-1.52 (m, 3H), 1.39-1.33 (m, 1H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 156.6 ($^2J_{CF}$ = 34.9 Hz), 116.4 ($^1J_{CF}$ = 288.5 Hz), 62.1, 60.6, 60.0, 55.4, 43.9, 38.0, 36.1, 34.9, 33.8, 27.8, 25.8, 18.1, –5.7 (2C); MS (ESI) *m/z* (relative intensity) 414.02 ($[M+H]^+$, 100%), 436.15 ($[M+Na]^+$, 30%); HRMS (ESI) *m/z* calcd. for $C_{18}H_{35}F_3NO_4Si$ ($[M+H]^+$) 414.2287; Found 414.2287.

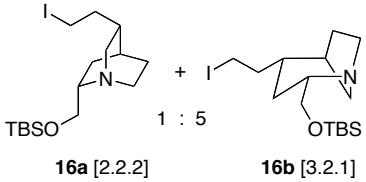


2-((3*R*,4*R*,6*S*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-4-(2-hydroxyethyl)-1-(2,2,2-trifluoroacetyl)piperidin-3-yl)ethyl acetate (14a) and 2-((2*S*,4*R*,5*R*)-2-((*tert*-butyldimethylsilyloxy)methyl)-5-(2-hydroxyethyl)-1-(2,2,2-trifluoroacetyl)piperidin-4-yl)ethyl acetate (14b). To a solution of diol **13** (155 mg, 0.38 mmol) in CH_2Cl_2 (16 mL) was added vinyl acetate (0.038 mL, 0.41 mmol) and lipase acrylic resin (*Candida antarctica*, 31 mg, 0.012 mmol). After 7 days, filtration, concentration and radial chromatography (hexane/EtOAc 10:1 to 1:1) afforded starting material (49 mg, 32%), which can be reused, **14b** (60 mg, 35%) and **14a** (50 mg, 29%) as colorless oils. **14b:** $[\alpha]_D^{24.0}$ –50.7 (c 0.6, $CHCl_3$); IR (film) 3466, 2955, 2929, 2861, 1739, 1683, 1471, 1367, 1252, 1193, 1143, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.19-4.01 (m, 3H), 3.99 (dd, *J* = 10.3, 3.7 Hz, 1H), 3.73 (ddd, *J* = 10.8, 5.5, 5.5 Hz, 1H), 3.69-3.53 (m, 4H), 2.05 (s, 3H), 1.92-1.86 (m, 1H), 1.82-1.76 (m, 1H), 1.70-1.45 (m, 6H), 1.28-1.20 (m, 1H), 0.87 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 156.7 ($^2J_{CF}$ = 35.2 Hz), 116.4 ($^1J_{CF}$ = 286.0 Hz), 62.2, 62.1, 59.9, 55.5, 43.8, 36.2, 34.8, 34.1, 33.7, 27.4, 25.8, 21.0, 18.1, –5.7 (2C); HRMS (ESI) *m/z* calcd. for $C_{20}H_{37}F_3NO_5Si$ ($[M+H]^+$) 456.2393; Found 456.2396. **14a:** $[\alpha]_D^{23.1}$ –42.4 (c 0.5, $CHCl_3$); IR (film) 3469, 2949, 2928, 2857, 1741, 1678, 1462, 1366, 1249, 1202, 1142, 1110, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.15-4.02 (m, 3H), 3.99 (dd, *J* = 10.0, 3.4 Hz, 1H), 3.77-3.51 (m, 5H), 2.05 (s, 3H), 1.81-1.45 (m, 8H), 1.33-1.27 (m, 1H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 156.5 ($^2J_{CF}$ = 34.0 Hz), 116.4 ($^1J_{CF}$ = 285.9 Hz), 62.1, 60.5, 55.5, 43.7, 37.9, 37.2, 33.9, 30.9, 27.6, 25.8, 20.9, 18.1, –5.7 (2C?); MS (ESI) *m/z* (relative intensity) 456.05 ($[M+H]^+$, 41%), 478.26 ($[M+Na]^+$, 100%); HRMS (ESI) *m/z* calcd. for $C_{20}H_{37}F_3NO_5Si$ ($[M+H]^+$) 456.2393; Found 456.2402.

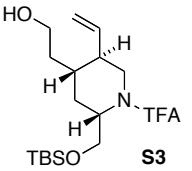


1-((2*S*,4*R*,5*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-4,5-bis(2-iodoethyl)-piperidin-1-yl)-2,2,2-trifluoroethanone (15). To a solution of diol **13** (68 mg, 0.16 mmol), PPh_3 (173 mg, 0.66 mmol) and imidazole (56 mg, 0.82 mmol) in THF (10 mL) at 0 °C was added I_2 (168 mg, 0.66 mmol) in two portions over 15 min. After 1 h the mixture was quenched with sat. $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic phase was washed with brine and dried with Na_2SO_4. Concentration and flash chromatography afforded the diiodide **15** (105 mg, quantitative) as a colorless oil; $[\alpha]_D^{24.2}$ –5.3 (*c* 0.4, $CHCl_3$); IR (film)

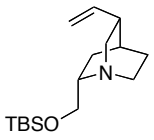
2953, 2928, 2857, 1679, 1449, 1198, 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.13-4.07 (m, 1H), 4.02 (br d, *J* = 8.5 Hz, 1H), 3.67 (br, 1H), 3.58-3.52 (m, 2H), 3.38-3.30 (m, 2H), 3.18-3.05 (m, 2H), 2.14-2.06 (m, 1H), 1.88-1.72 (m, 5H), 1.66-1.58 (m, 1H), 1.34-1.25 (m, 1H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.1, 55.3, 42.9, 40.1, 38.4, 37.4, 35.5, 26.5, 25.8, 18.2, 3.9, 3.6, –5.6 (2C); HRMS (ESI) *m/z* calcd. for $C_{18}H_{33}F_3I_2NO_2Si$ ($[M+H]^+$) 634.0322; Found 634.0336.



(2*S*,4*S*,8*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl-8-(2-iodoethyl)-quinuclidine (16a) and (2*S*,4*R*,5*R*)-2-((*tert*-butyldimethylsilyloxy)-methyl)-4-(2-iodoethyl)-1-azabicyclo[3.2.1]octane (16b). To a solution of diiodide **15** (32 mg, 0.051 mmol) in MeOH (2 mL) was added NH_3/MeOH (7N, 2 mL). After ca. 12 h, the mixture was concentrated and purified by flash chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 10:1) to provide the tertiary amines **16a** and **16b** as an inseparable mixture of isomers (21 mg, quantitative, ratio 5:1) as colorless oil; IR (film) 2952, 2927, 2855, 1467, 1255, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) major isomer: δ 4.08 (dd, *J* = 11.1, 5.8 Hz, 1H), 3.99-3.92 (m, 2H), 3.50-3.53 (m, 2H), 3.48-3.40 (m, 1H), 3.22-3.10 (m, 2H), 3.08 (dd, *J* = 11.6, 4.0 Hz, 1H), 2.55-2.50 (m, 1H), 2.36 (dddd, *J* = 13.2, 12.4, 6.8, 5.2 Hz, 1H), 2.11 (ddd, *J* = 15.6, 7.6. 7.2 Hz, 1H), 2.02-1.88 (m, 4H), 1.61 (ddd, *J* = 15.6, 3.6, 2.8 Hz, 1H), 0.91 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: δ 63.8, 62.8, 53.8, 48.9, 38.4, 38.0, 36.3, 28.3, 26.1, 21.6, 18.4, 3.2, –5.0, –5.2; minor isomer: δ 62.1, 58.5, 54.7, 43.0, 36.5, 33.8, 25.8, 24.5, 24.3, 21.0, 18.1, 2.4, –5.3, –5.5; MS (ESI) *m/z* (relative intensity) 410.10 ($[M+H]^+$, 100%); HRMS (ESI) *m/z* calcd. for $C_{16}H_{33}NOISi$ ($[M+H]^+$) 410.1376; Found 410.1386.

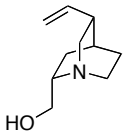


1-((2*S*,4*R*,5*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-4-(2-hydroxyethyl)-5-vinylpiperidin-1-yl)-2,2,2-trifluoroethanone (S3). To a solution of monoester alcohol **14b** (22 mg, 0.048 mmol) in THF (0.48 mL) was added 2-$O_2NC_6H_5SeCN$ (22 mg, 0.096 mmol) and Bu_3P (24 μL, 0.096 mmol). The reaction mixture was heated at 60 °C overnight. The mixture was concentrated and the residue was dissolved in THF (1 mL). To this solution was added aqueous H_2O_2 (30% *w/w*, 0.09 mL, 0.82 mmol). After ca. 12 h, the mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. Concentration and flash chromatography afforded an olefinic ester (21 mg, quantitative). To a solution of the olefinic ester (10 mg, 0.023 mmol) in MeOH (1 mL) was added NaOMe/MeOH solution (0.1 M, 0.23 mL, 0.023 mmol) in five portions over 5 h with TLC monitoring. Concentration and flash chromatography (hexane/EtOAc 10:1 to 3:1) afforded **S3** (8.3 mg, 92%) as a colorless oil; $[\alpha]_D^{25.5}$ –60.3 (c 0.4, $CHCl_3$); IR (film) 3448, 2954, 2929, 2858, 1685, 1463, 1255, 1204, 1145, 1117, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 17.1, 9.7, 9.2 Hz, 1H), 5.09-5.04 (m, 2H), 4.13-4.08 (m, 1H), 3.99-3.91 (m, 1H), 3.76-3.60 (m, 5H), 2.10 (m, apparent q, *J* = 8.2 Hz, 1H), 1.89 (dd, *J* = 11.4, 4.0 Hz, 1H), 1.83-1.67 (m, 2H), 1.53-1.46 (m, 2H), 1.26-1.20 (m, 1H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 116.5 ($^1J_{CF}$ = 286.6 Hz), 116.1, 63.0 (br), 60.9, 56.1, 46.3 (br), 46.0, 37.2, 33.1, 28.0, 26.1, 18.3, –5.5 (2C); HRMS (ESI) *m/z* calcd. for $C_{18}H_{33}F_3NO_3Si$ ($[M+H]^+$) 396.2182; Found 396.2188.

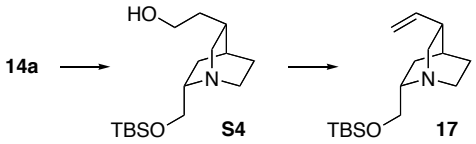


***O*-(*tert*-Butyldimethylsilyl)quincorine (17).** To a solution of alcohol **S3** (5.2 mg, 0.013 mmol) was added PPh_3 (6.8 mg, 0.026 mmol) and imidazole (2.2 mg, 0.032 mmol) in THF (0.5 mL) at 0 °C was added I_2 (7 mg, 0.028 mmol) in two portions over 15 min. The mixture was stirred for 1 h, quenched with sat. $Na_2S_2O_3$, and extracted with CH_2Cl_2. The organic phase was washed with brine and dried with Na_2SO_4. Concentration and flash chromatography afforded the iodide, which was dissolved in MeOH (0.4 mL). To this solution was added NH_3/MeOH (7N, 0.4 mL). After ca. 12 h, concentration and flash chromatography (CH_2Cl_2 to

CH_2Cl_2/MeOH 10:1) afforded *O*-TBS-quincorine (**17**, 3 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.24 (d, *J* = 10.8 Hz, 1H), 5.19 (d, *J* = 17.2 Hz, 1H), 4.37 (br d, *J* = 10.4 Hz, 1H), 3.76 (dd, *J* = 12.0, 4.5 Hz, 1H), 3.72-3.62 (m, 1H), 3.45 (dd, *J* = 13.3, 10.8 Hz, 1H), 3.36-3.28 (m, 1H), 3.18-3.03 (m, 2H), 2.72-2.64 (m, 1H), 2.13-2.09 (m, 1H), 2.03-1.90 (m, 2H), 1.90-1.79 (m, 1H), 0.92 (s, 9H), 0.90-0.84 (m, 1H), 0.15 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 117.3, 62.3, 58.3, 53.9, 43.1, 36.9, 27.1, 25.9, 24.5, 21.0, 18.2, –5.3, –5.6; HRMS (ESI) *m/z* calcd. for $C_{16}H_{32}NOSi$ ([M+H]$^+$) 282.2253; Found 282.2266.



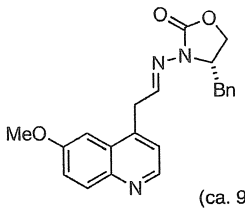
Quincorine (18). To a solution of **17** (8 mg, 0.028 mmol) in THF (1 mL) was added TBAF (1 M in THF, 37 μL, 0.037 mmol) at 0 °C. The solution was allowed to warm to ambient temperature. After ca. 12 h, concentration and preparative TLC (CH_2Cl_2/MeOH 2:1) afforded quincorine (**18**, 5.1 mg, 78%) as a colorless oil; $[\alpha]_D^{22.5}$ +38 (*c* 0.3, MeOH) [lit. $[\alpha]_D^{20}$ +39 (*c* 1.0, MeOH)[2]]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddd, *J* = 17.3, 10.4, 7.6 Hz, 1H), 5.07-5.01 (m, 2H), 3.46-3.43 (m, 2H), 3.17 (dd, *J* = 14.0 Hz, *J* = 6.0 Hz, 1H), 2.98-2.90 (m, 3H), 2.70-2.57 (m, 2H), 2.34-2.29 (m, 1H), 1.85-1.79 (m, 1H), 1.75-1.71 (m, 1H), 1.57-1.41 (m, 2H), 0.80-0.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 114.4, 63.0, 57.2, 55.7, 40.3, 40.1, 28.0, 27.3, 24.7; HRMS (ESI) *m/z* calcd. for $C_{10}H_{18}NO$ ([M+H]$^+$) 168.1388; Found 168.1388.



Alternative Preparation of 17. To a solution of alcohol **14a** (18 mg, 0.053 mmol), PPh_3 (28 mg, 0.11 mmol) and imidazole (9 mg, 0.13 mmol) in THF (0.5 mL) at 0 °C was added I_2 (27 mg, 0.11 mmol) in two portions over 15 min. After 1 h the mixture was quenched with sat. $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic phase was washed with brine and dried with Na_2SO_4. Concentration and flash chromatography afforded the iodide. This material was dissolved in MeOH (1.5 mL). To this solution was added NH_3/MeOH (7N, 1.5 mL). After ca. 12 h, the mixture was concentrated to provide the tertiary amine (18 mg). To a solution of the tertiary amine (13 mg) in MeOH/H_2O (5:1, 0.6 mL) was added $Ba(OH)_2$•$8H_2O$ (60 mg, 0.19 mmol) at 0 °C. The mixture was allowed to warm to ambient temperature. After 2 h, the mixture was diluted with CH_2Cl_2, filtered and purified by flash chromatography (CH_2Cl_2/MeOH 3:1 to 1:1) to afford **S4** (11 mg, 85% over 3 steps) as a colorless oil; $[\alpha]_D^{25.4}$ +5.8 (*c* 0.3, $CHCl_3$); IR (film) 3352, 2950, 2927, 2857, 1463, 1254, 1117, 1089 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (dd, *J* = 10.8, 6.0, 1H), 3.72-3.66 (m, 3H), 3.33 (dd, *J* = 13.6, 10.8 Hz, 1H), 3.27-3.17 (m, 1H), 3.12-3.04 (m, 1H), 2.88-2.78 (m, 1H), 2.68 (ddd, *J* = 13.2, 5.2, 2.4 Hz, 1H), 2.5 (br, 1H), 1.93-1.81 (m, 2H), 1.69 (m, apparent q, *J* = 6.8 Hz, 2H), 1.66-1.53 (m, 1H), 1.40 (br dd, *J* = 13.2, 6.8 Hz, 1H), 1.33-1.28 (br, 1H), 0.93-0.88 (m, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.7, 60.8, 57.7, 57.1, 42.3, 37.3, 31.5, 27.0, 26.0, 23.5, 18.4, –5.2, –5.3, one carbon is not resolved; ^{13}C NMR (100 MHz, C_6D_6) δ 65.5, 61.0, 57.6, 57.4, 42.2, 37.1, 32.2, 30.2, 26.7, 26.2, 24.4, 18.6, –5.1, –5.3; MS (ESI) *m/z* (relative intensity) 300.30 ([M+H]$^+$, 100%); HRMS (ESI) *m/z* calcd. for $C_{16}H_{34}NO_2Si$ ([M+H]$^+$) 300.2359; Found 300.2369. To a solution of alcohol (10 mg, 0.034 mmol) in THF (0.34 mL) was added 2-$O_2NC_6H_5SeCN$ (15 mg, 0.068 mmol) and Bu_3P (16 μL, 0.068 mmol). The reaction mixture was heated at 60 °C overnight. The mixture was concentrated and the residue (11 mg, 0.023 mmol) was dissolved in CH_2Cl_2 (0.6 mL). To this solution was added aq. K_2HPO_4 (2.4 M, 30 μL) and mCPBA (6 mg, 0.024 mmol). After ca. 12 h, the mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. Concentration and flash chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 10:1) afforded *O*-TBS-quincorine (**17**, 5.4 mg, 84%) as a colorless oil. This material was identical to that produced as described above.

References and Notes

1. Korapala, C. S.; Qin, J.; Friestad, G. K. *Org. Lett.* **2007**, *9*, 4243-4246.
2. http://www.tciamerica.com/catalog/Q0074.html, accessed February 4, 2011.



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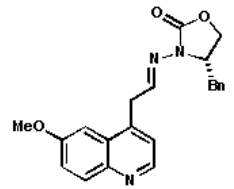
(ca. 90% purity)



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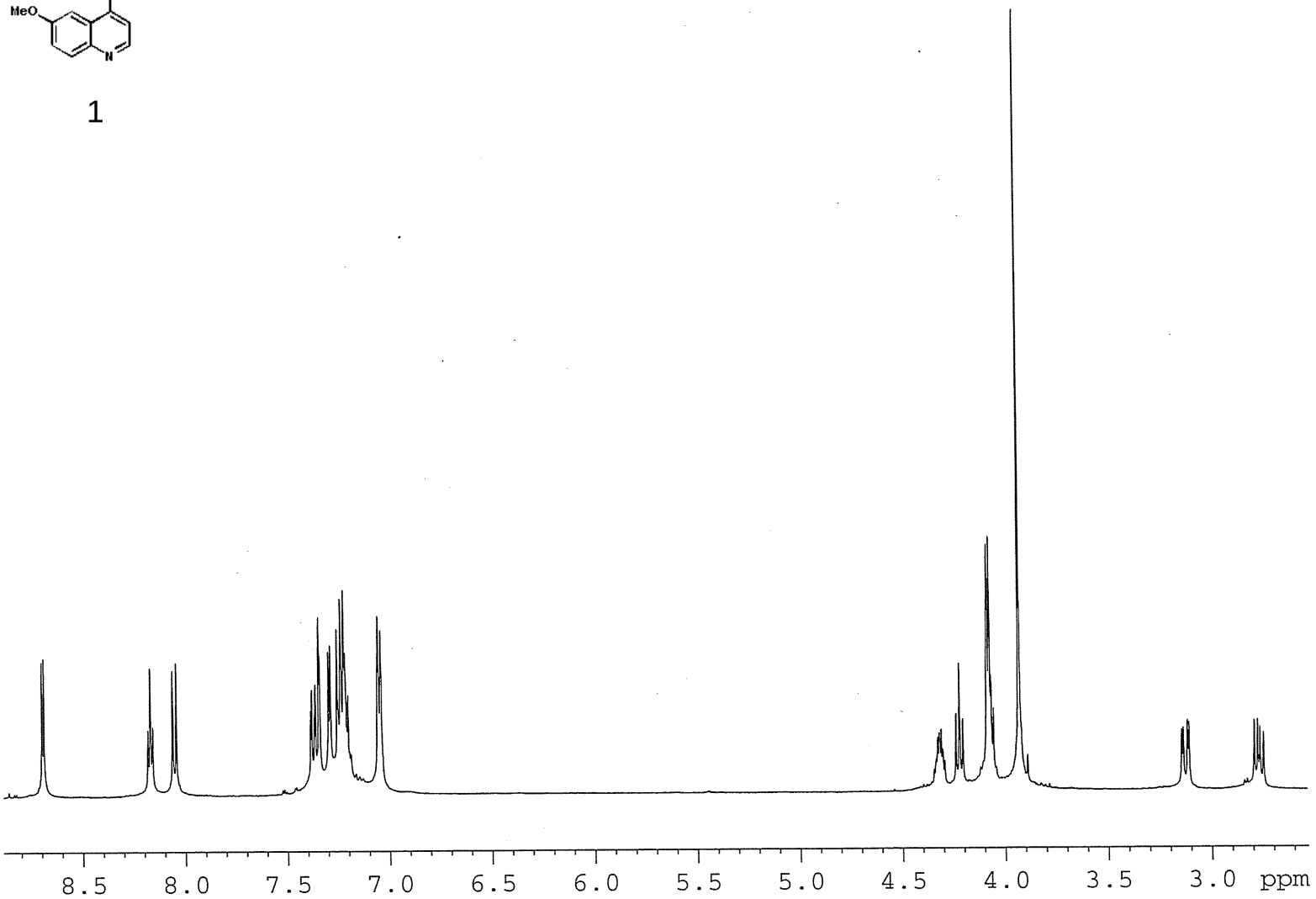
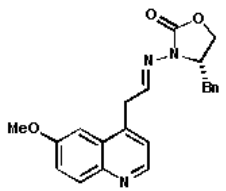
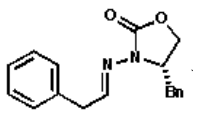
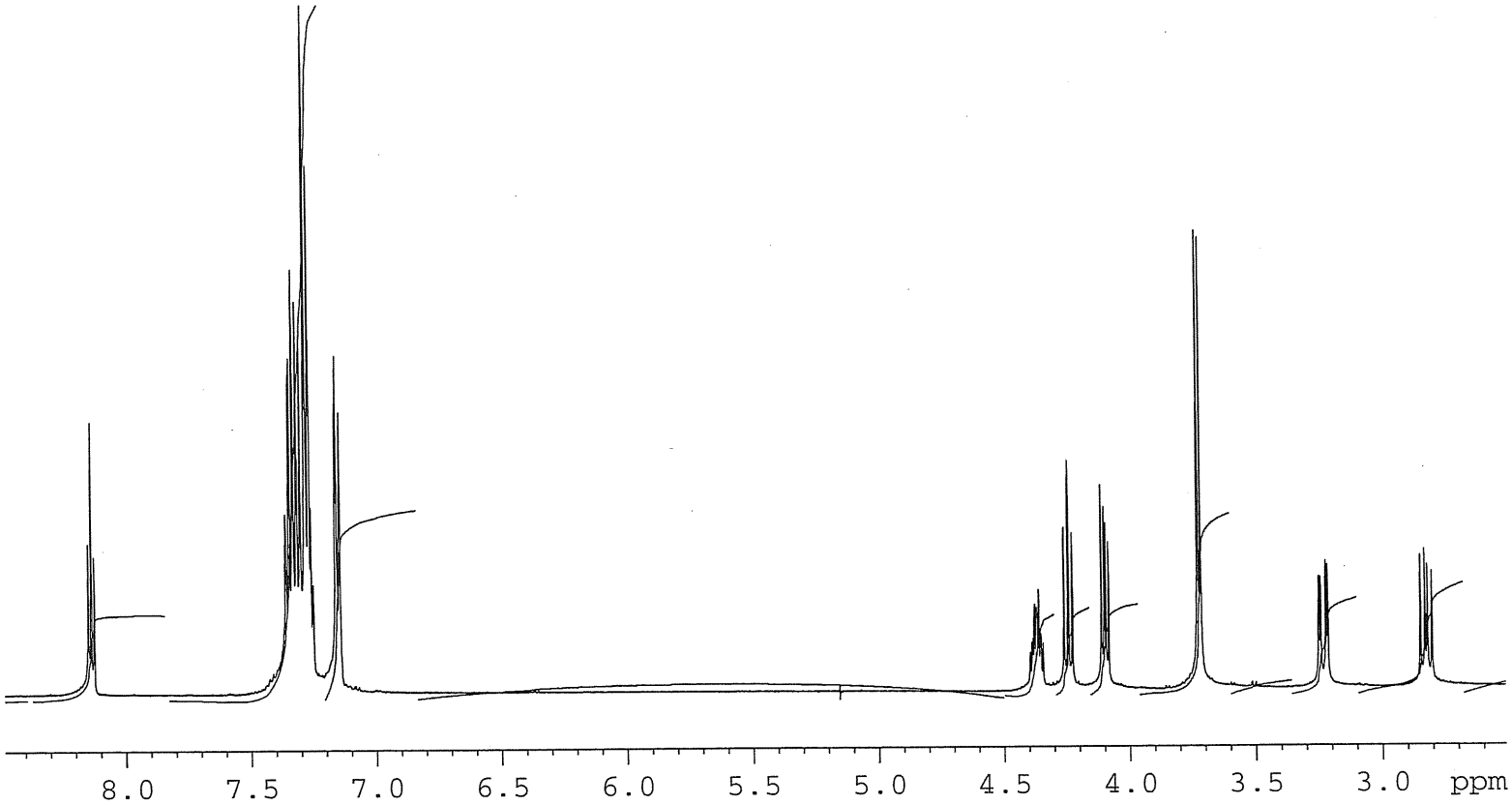


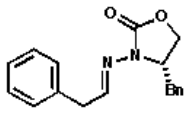


1

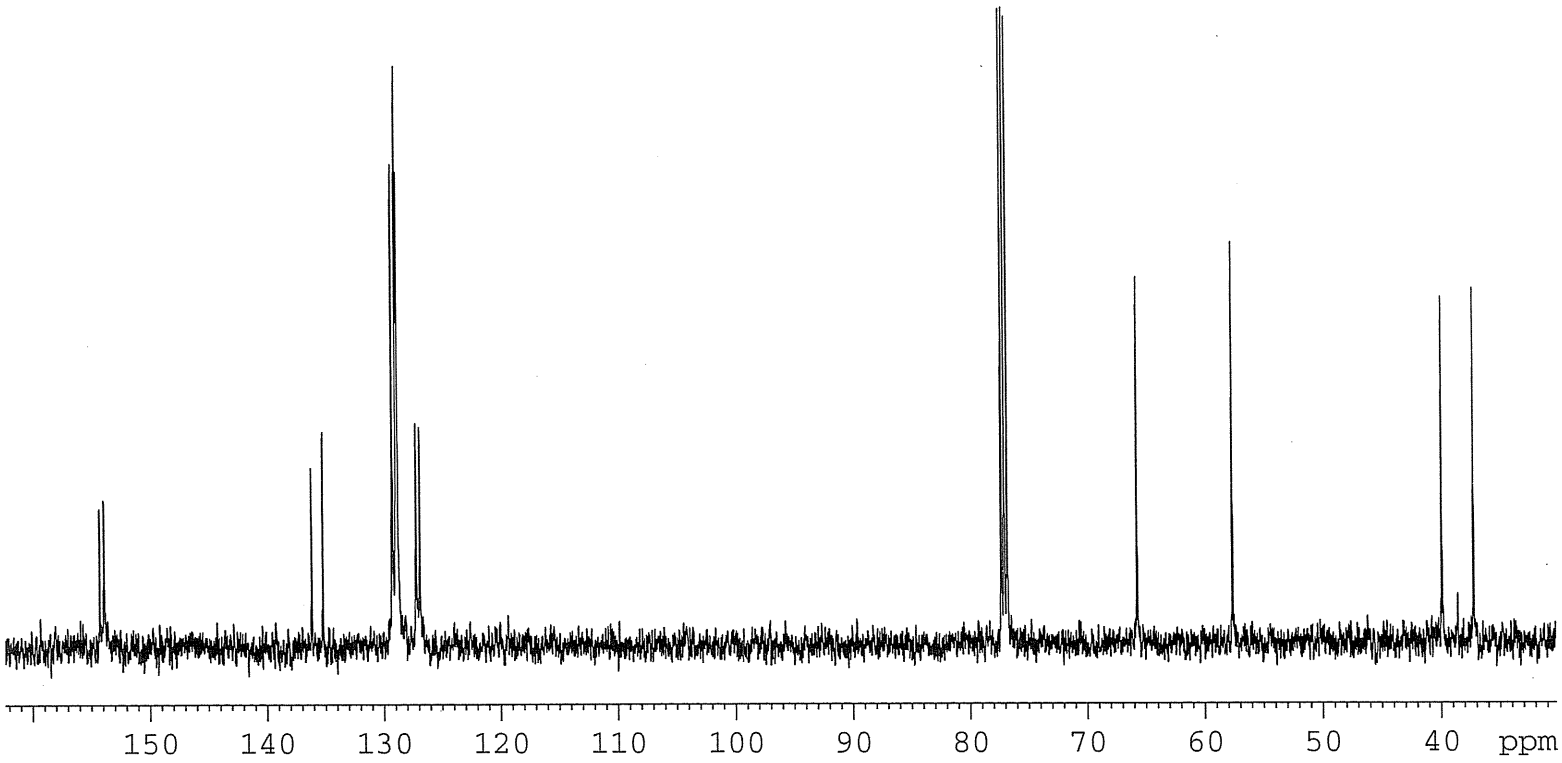


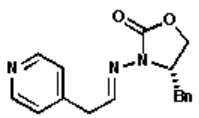
6a



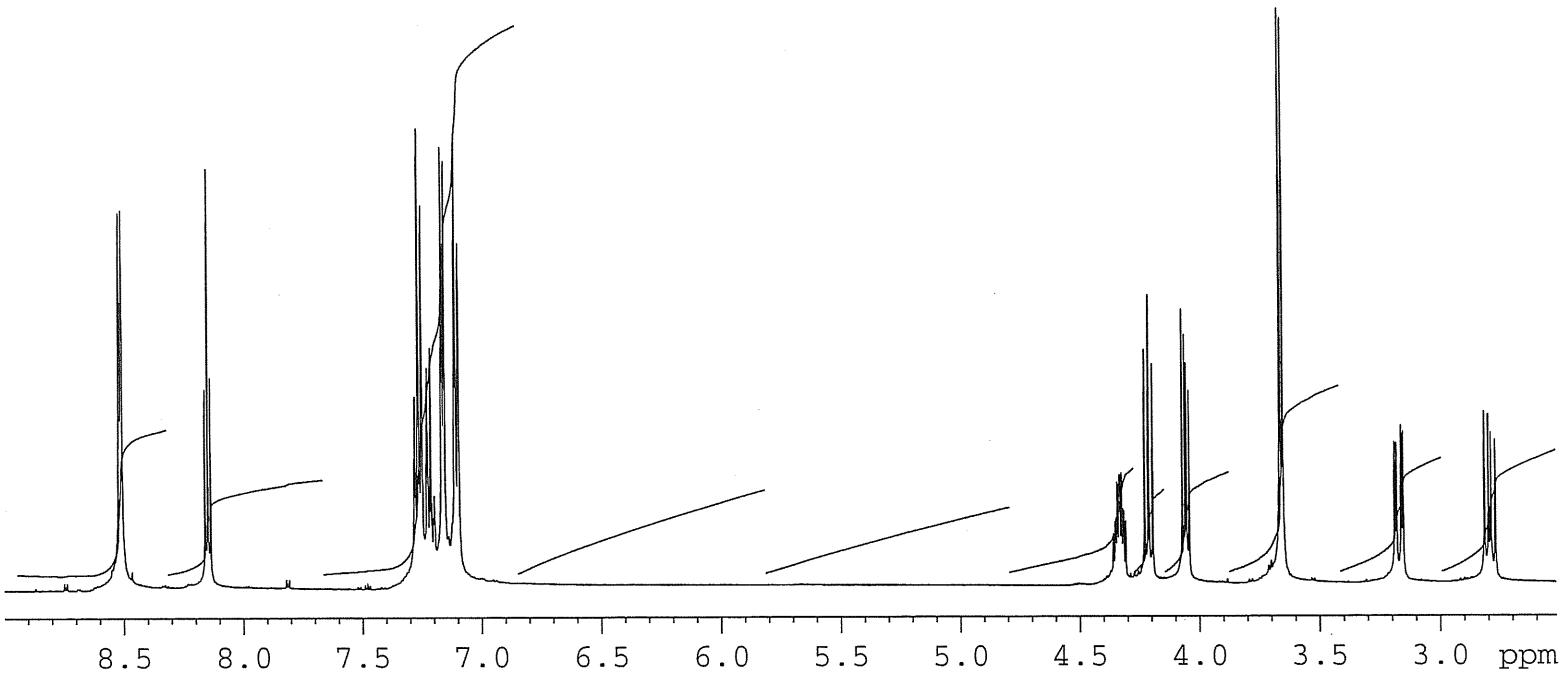


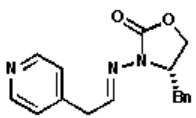
6a



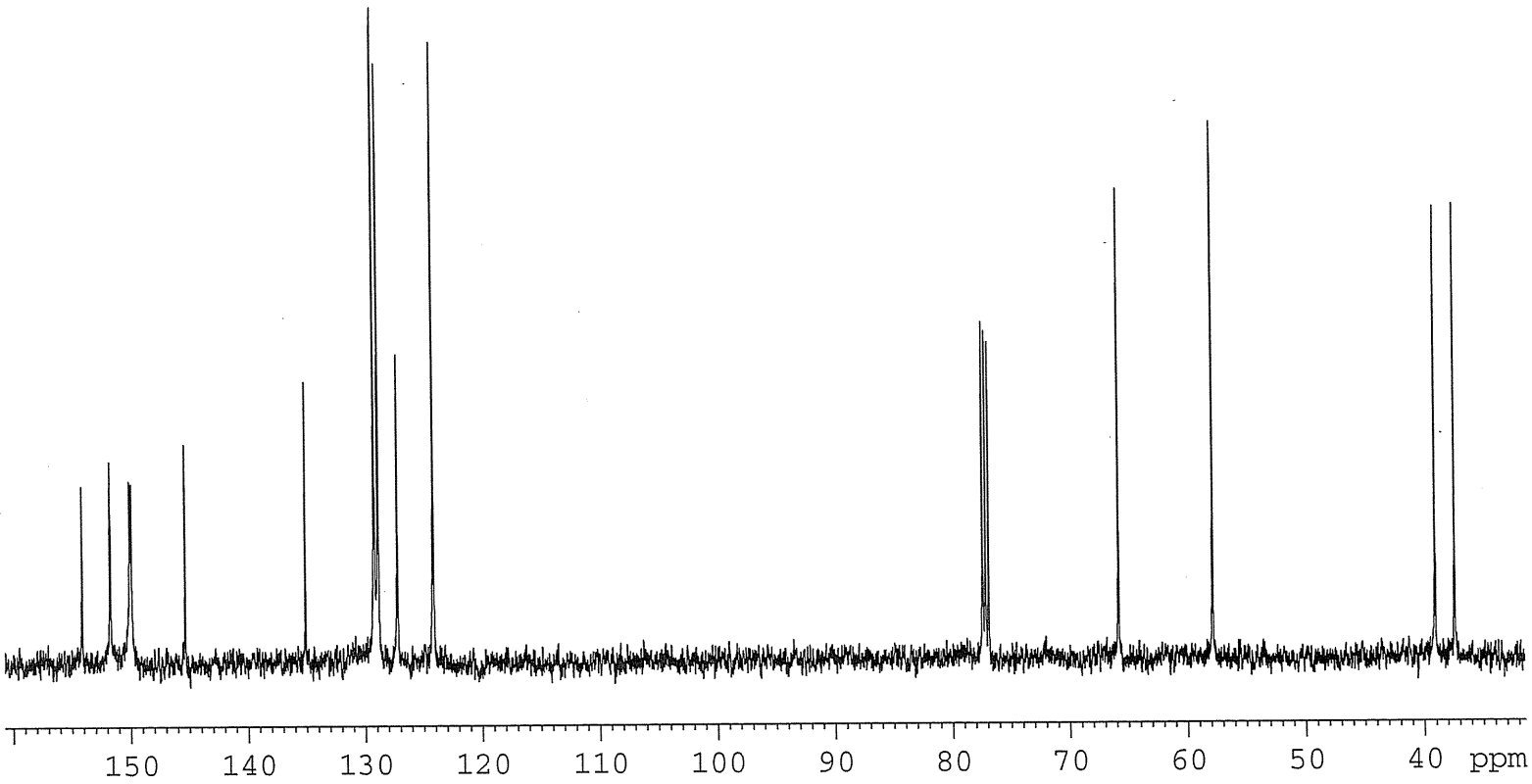


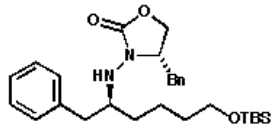
6c



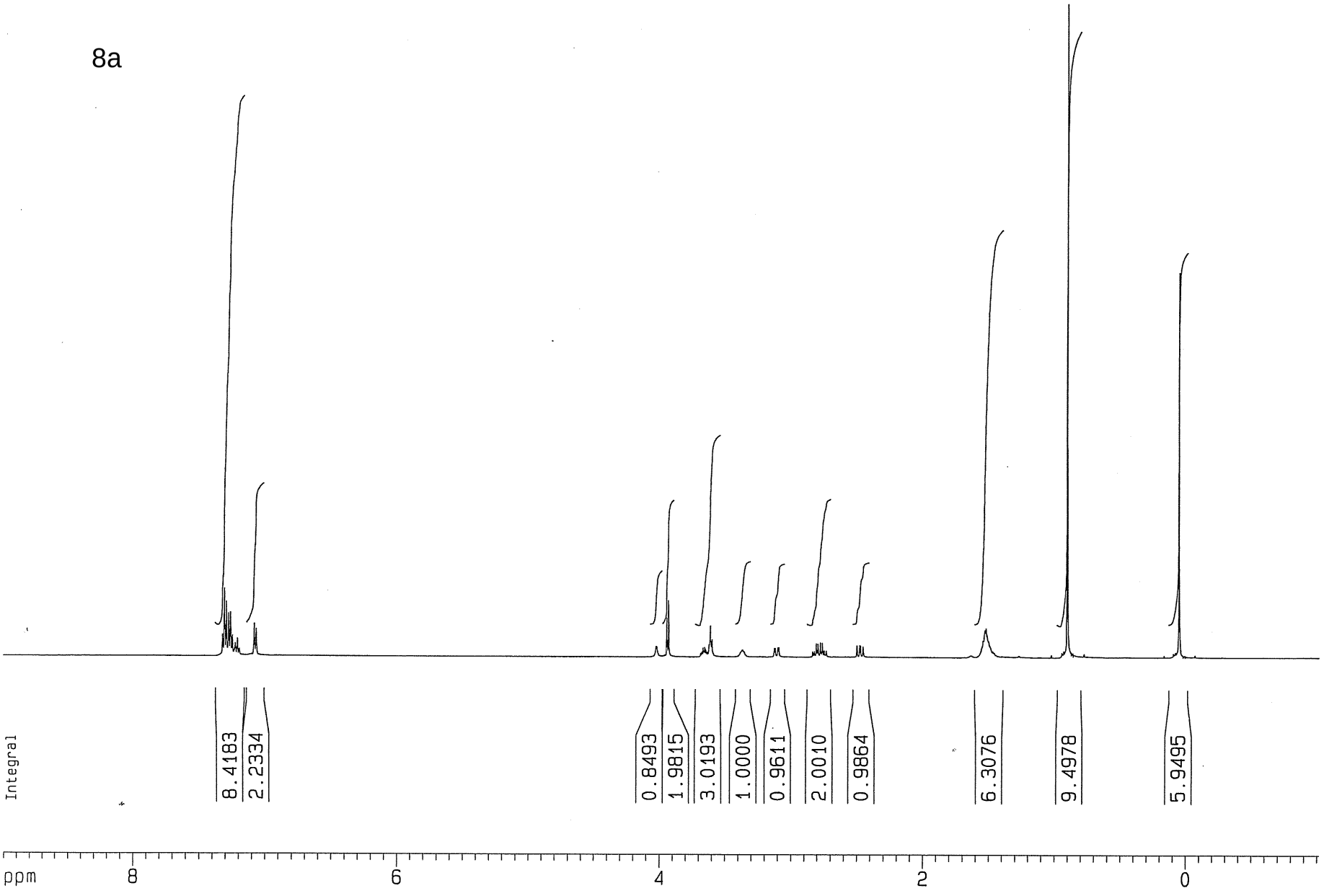


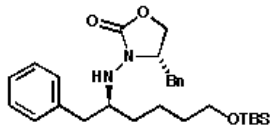
6c



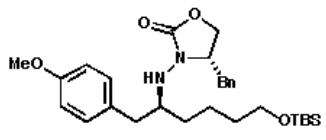

O
O
N
HN
Bn
OTBS

8a


Integral
8.4183
2.2334
0.8493
1.9815
3.0193
1.0000
0.9611
2.0010
0.9864
6.3076
9.4978
5.9495
ppm
8
6
4
2
0

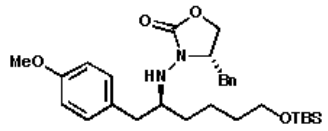


8a

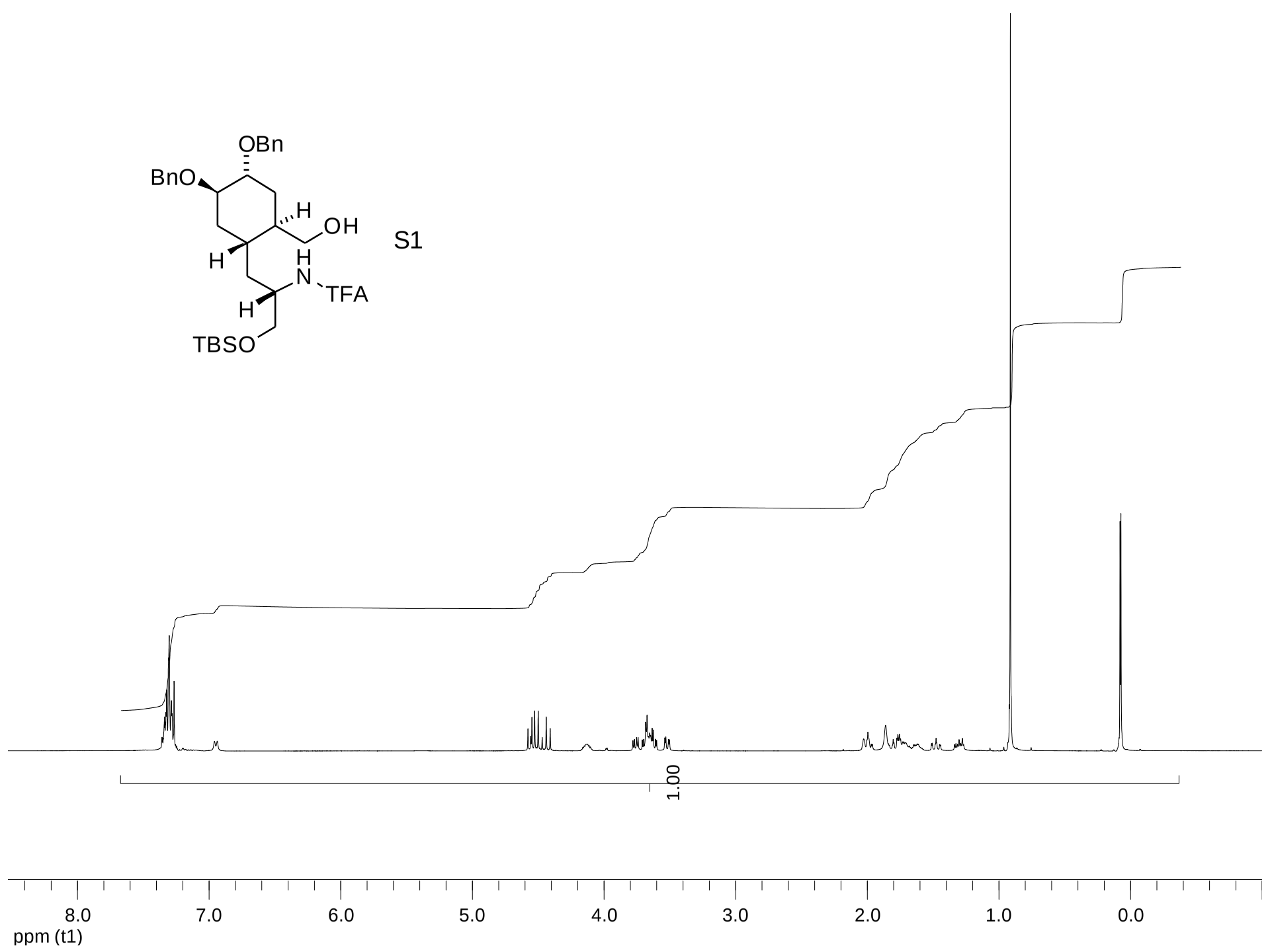

MeO
HN
N
O
O
Bn
OTBS

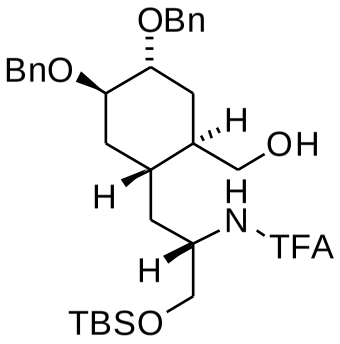
8b

Integral
2.1749
1.4690
2.2099
2.1808
2.1635
2.1520
3.3037
1.2261
2.3228
1.1548
1.1132
2.2370
1.1745
6.7200
9.7854
6.0000
ppm
8
6
4
2
0

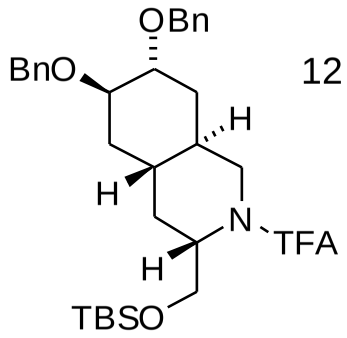


8b


OBn
BnO
H
OH
H
H
N
TFA
H
TBSO
S1
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)



S1

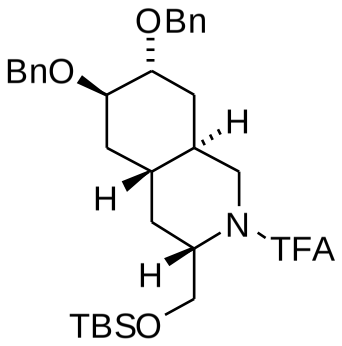


12

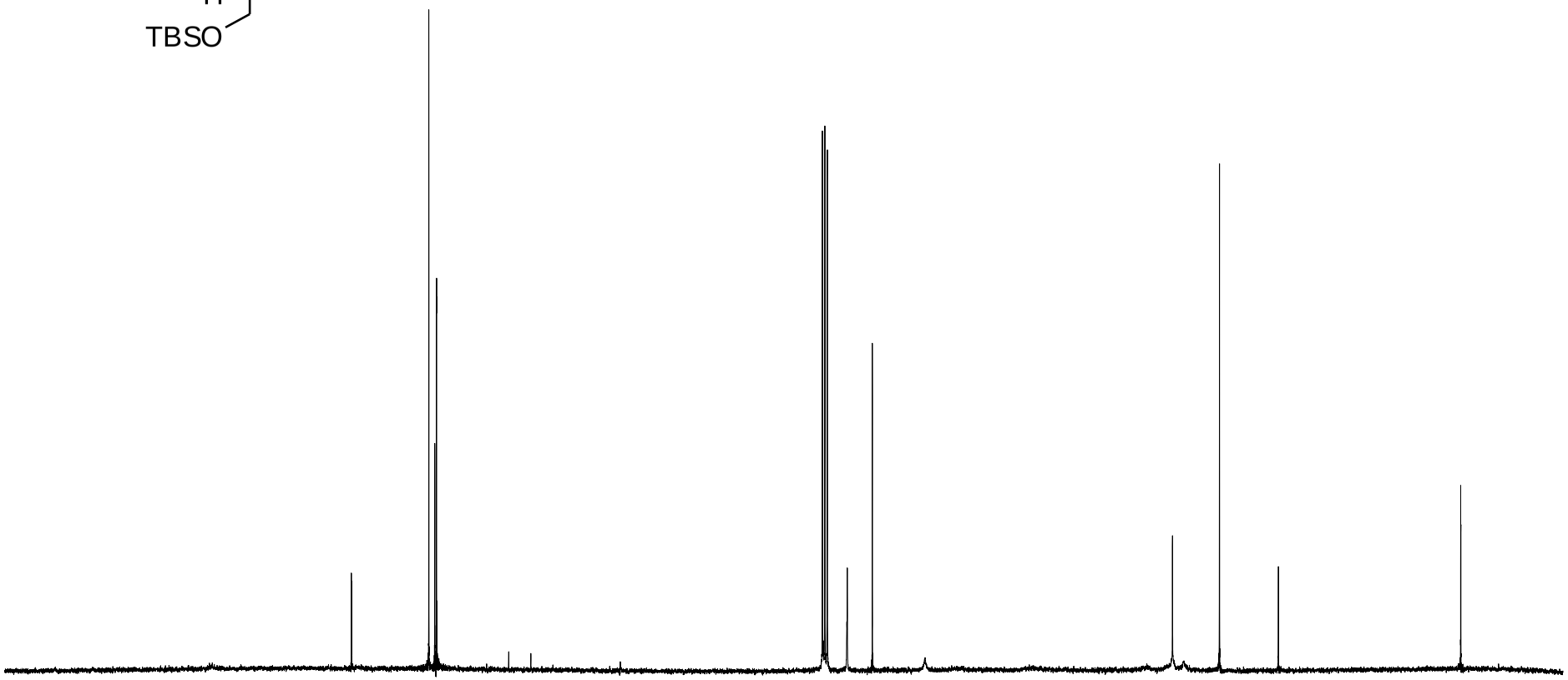
1.00

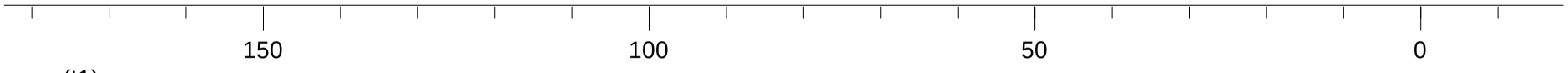
7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0 -1.0

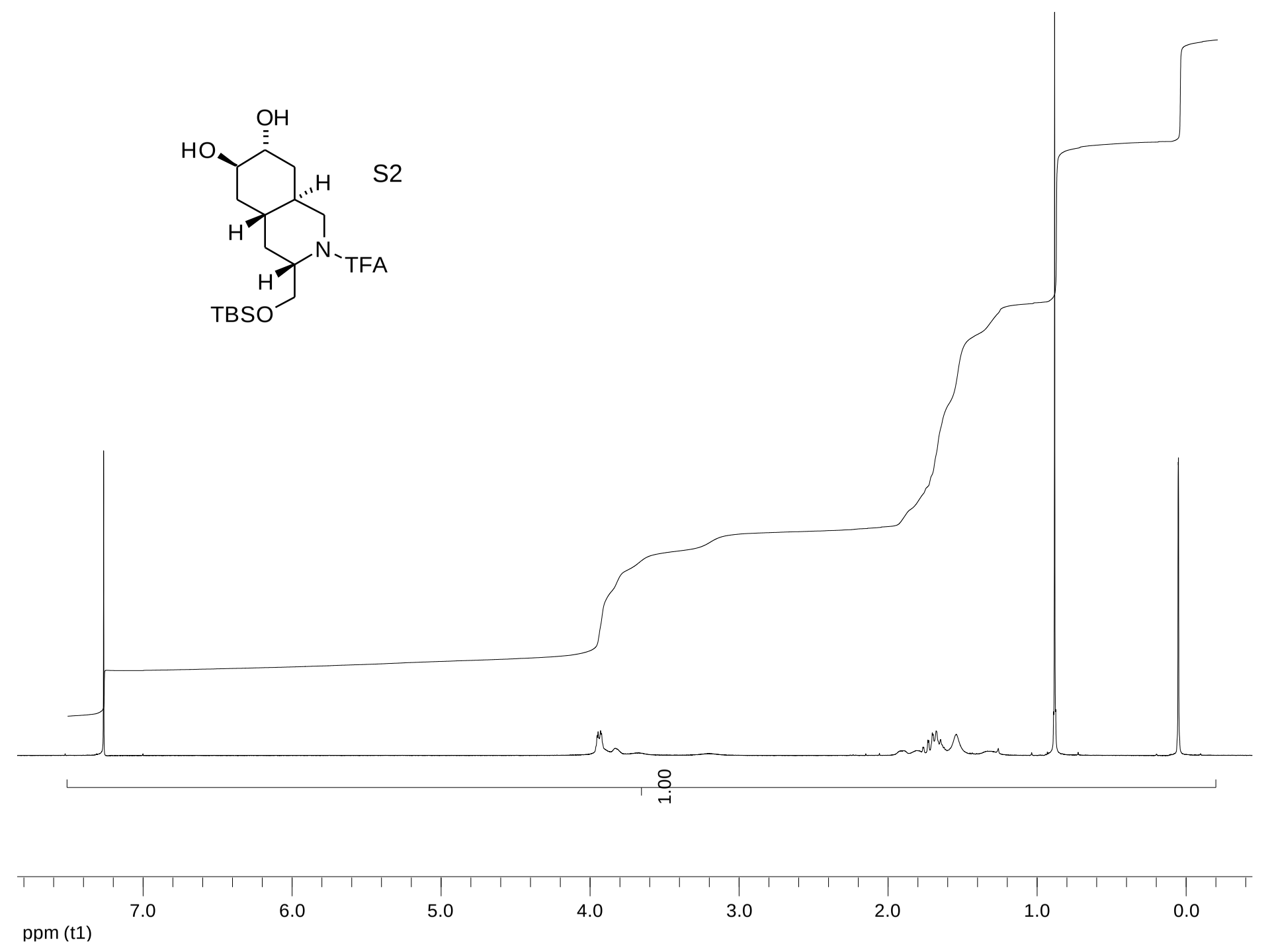
ppm (t1)

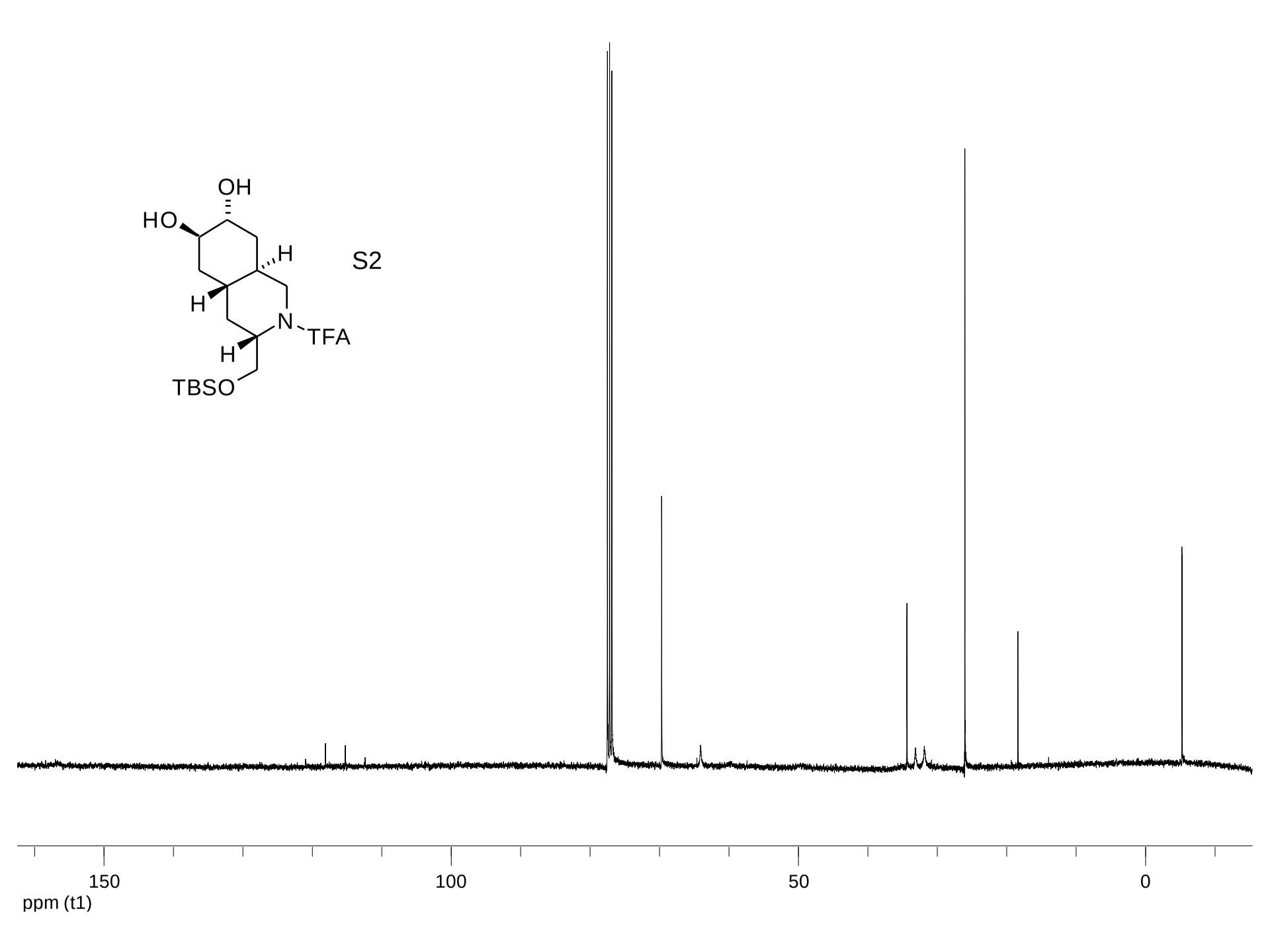


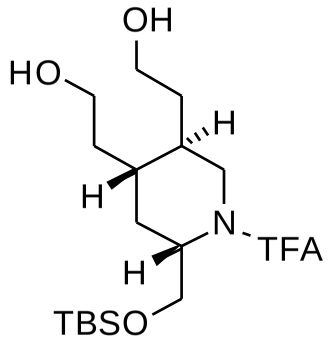
12



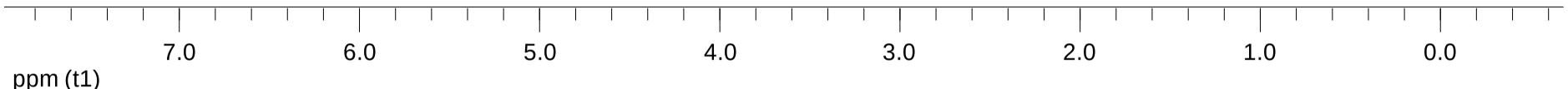


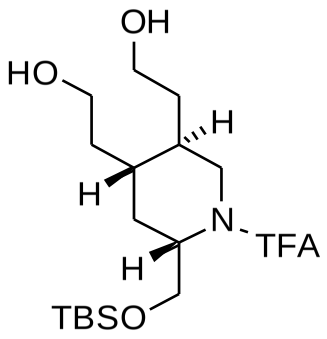

OH
HO
H
S2
H
N
TFA
H
TBSO
1.00
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


OH
HO
H
H
N
TFA
H
TBSO
S2
150
100
50
0
ppm (t1)

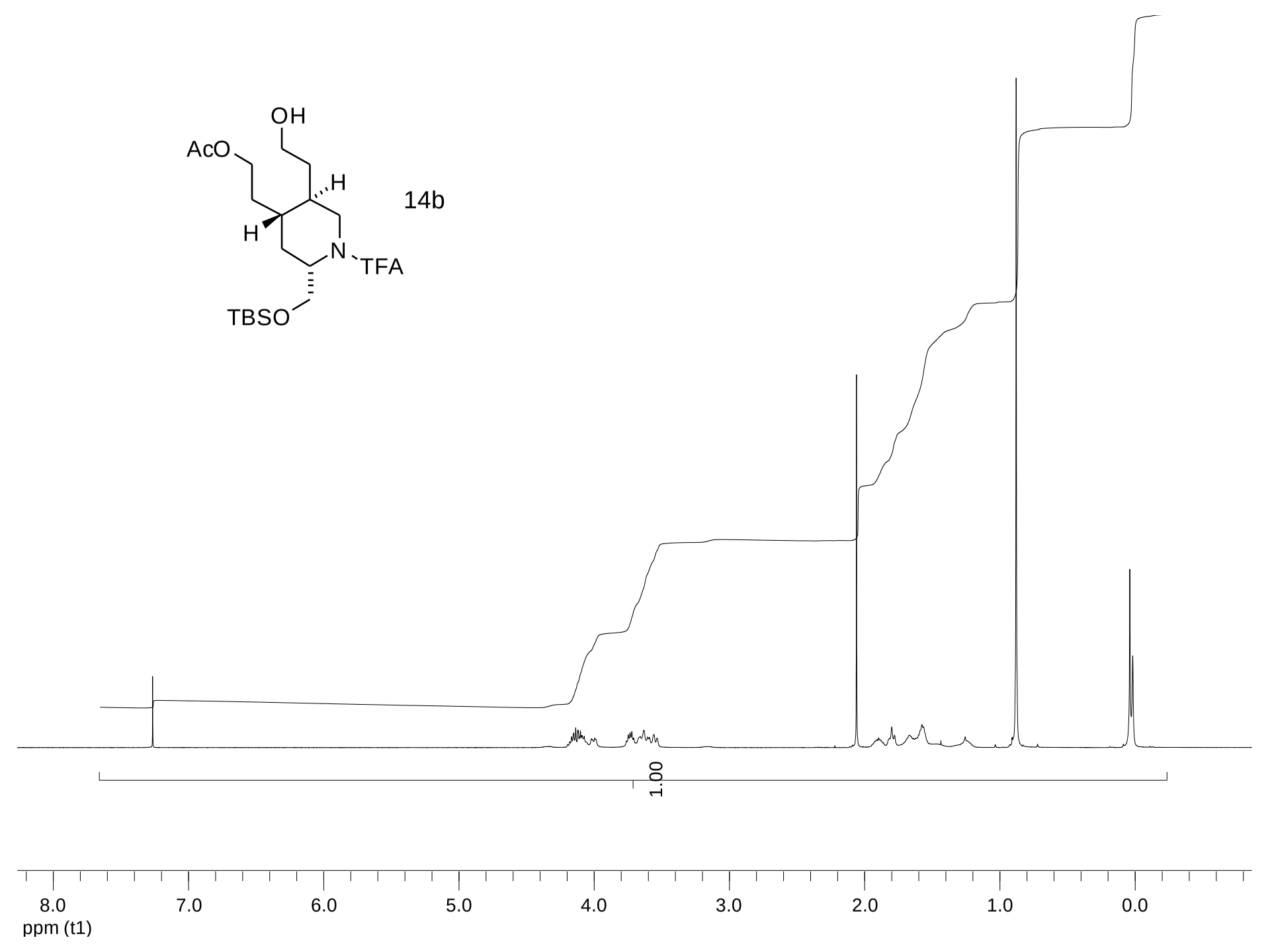


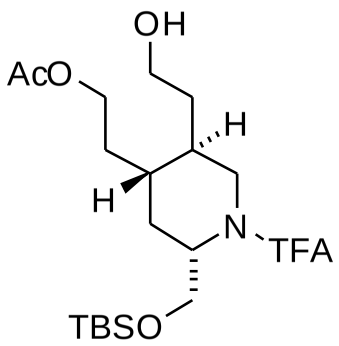
13





13


OH
AcO
H
H
N
TFA
TBSO
14b
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)



14b

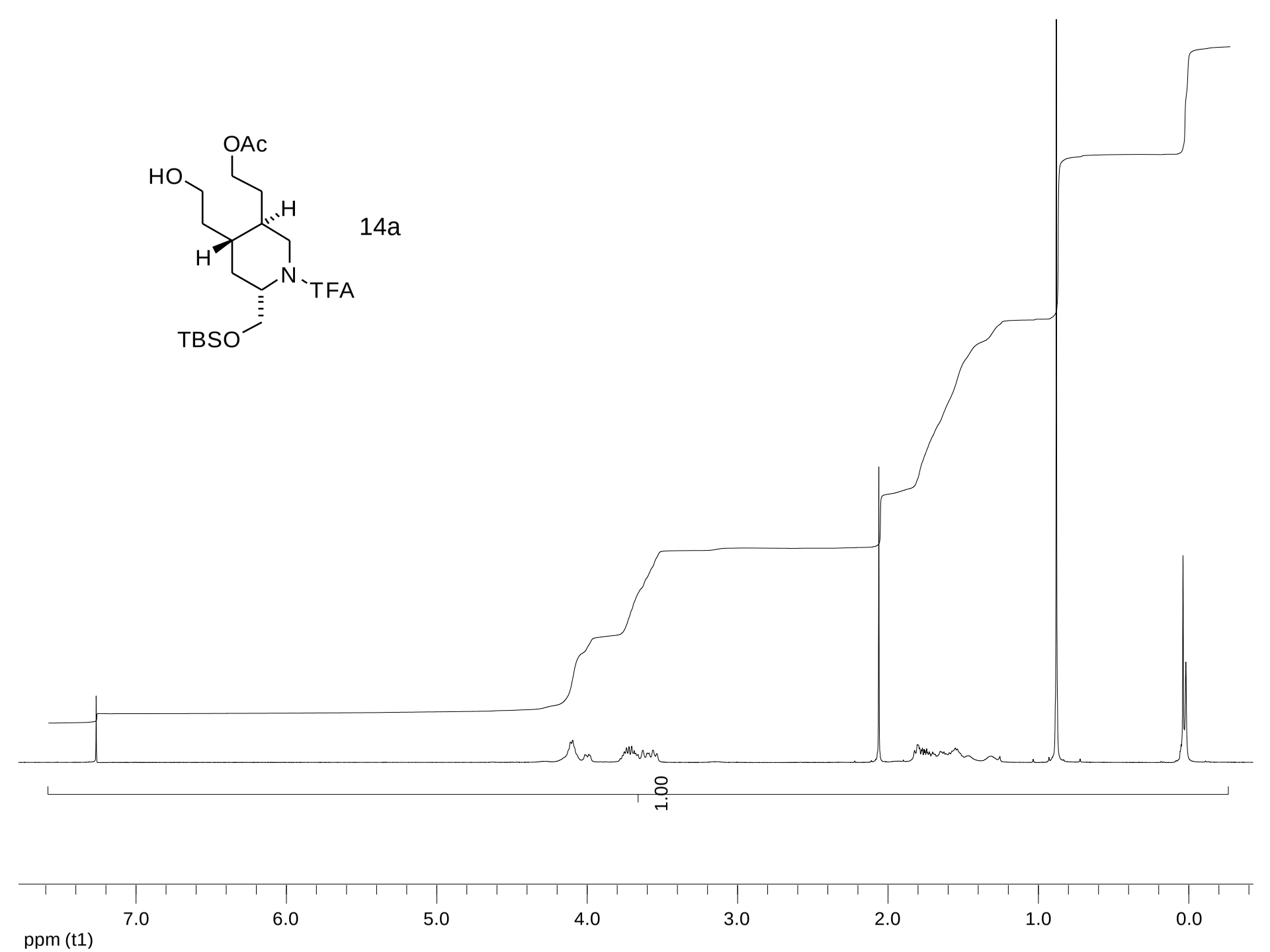
150

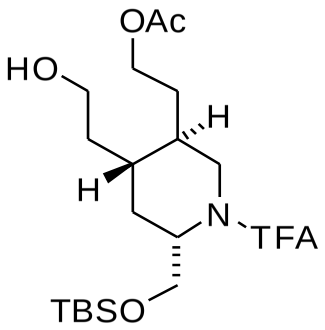
100

50

0

ppm (t1)


OAc
HO
H
H
N
TFA
TBSO
14a
1.00
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)



14a

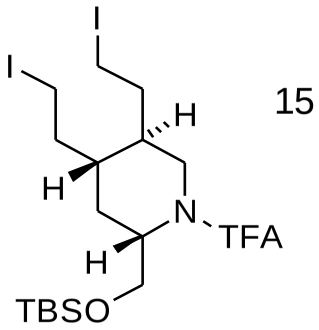
150

100

50

0

ppm (t1)

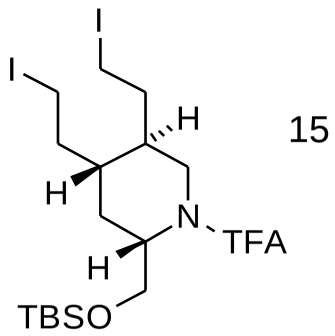


15

1.00

7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

ppm (t1)



15

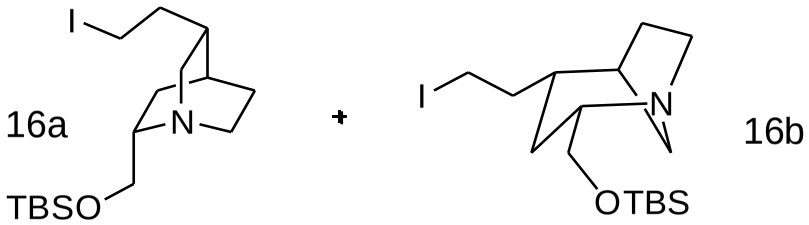
150

100

50

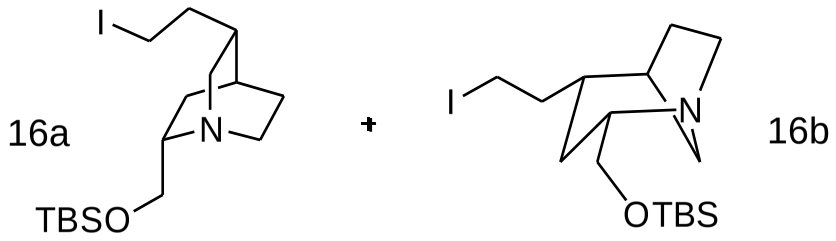
0

ppm (t1)



16a + 16b

1 : 5

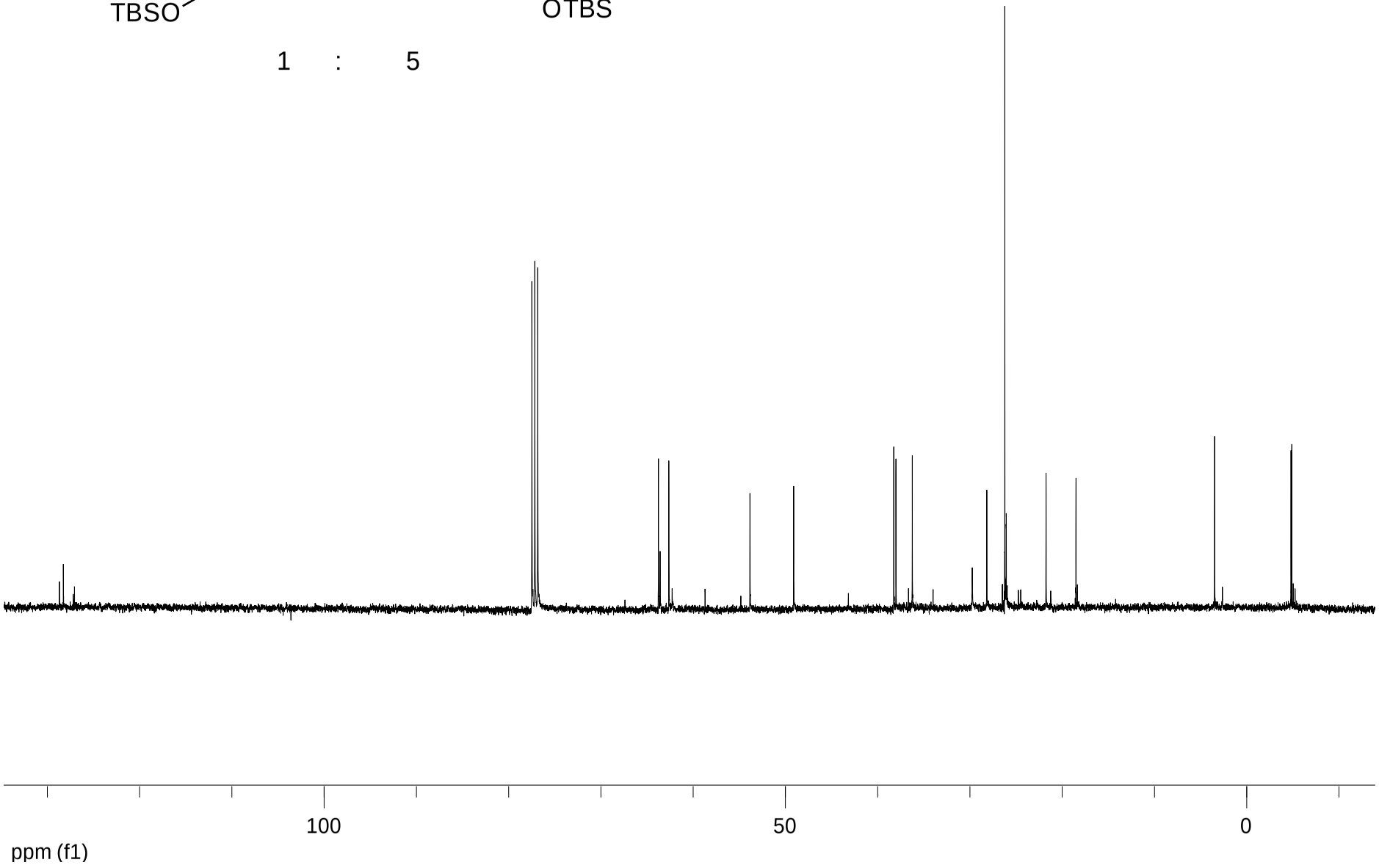


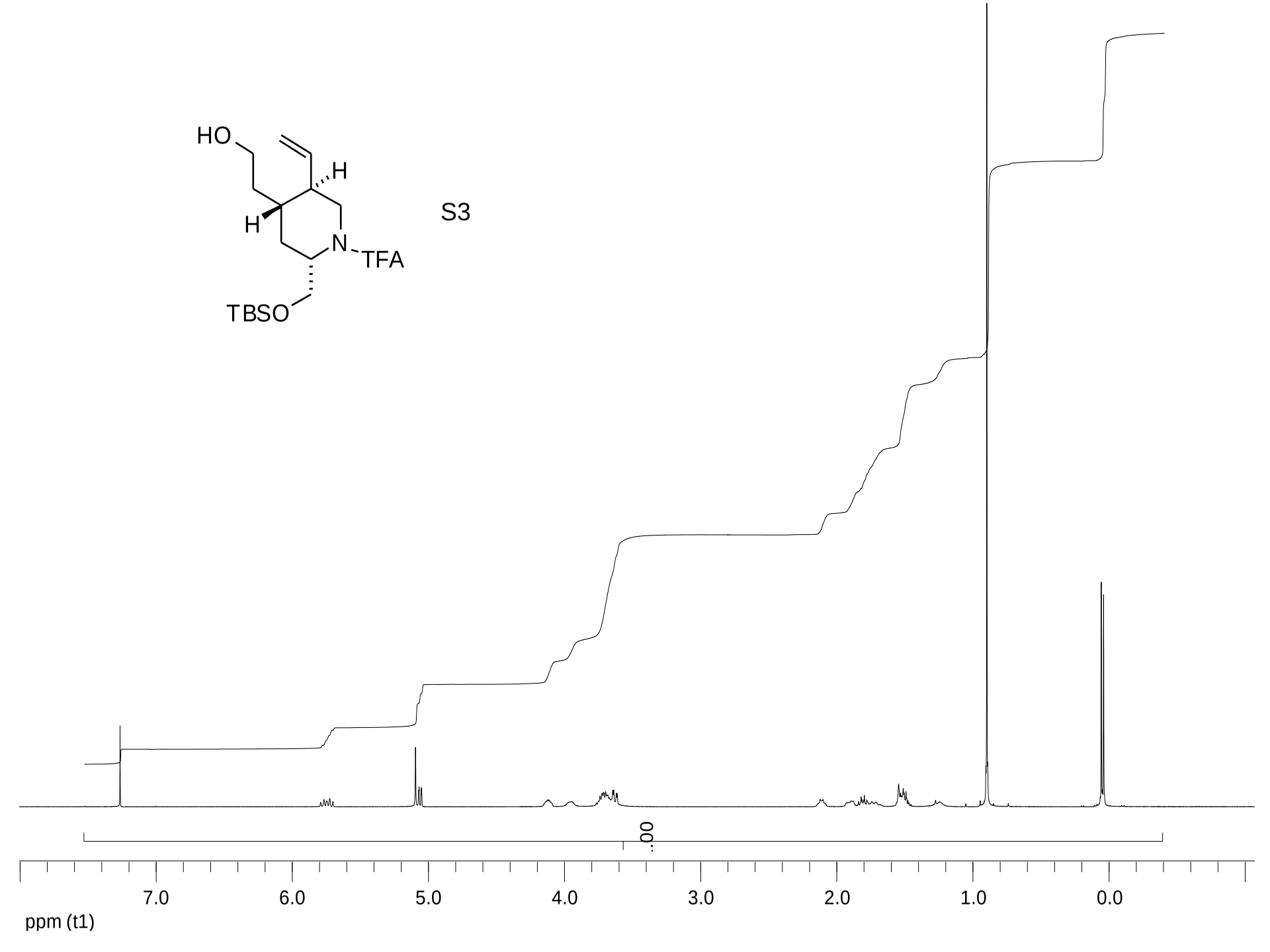
16a

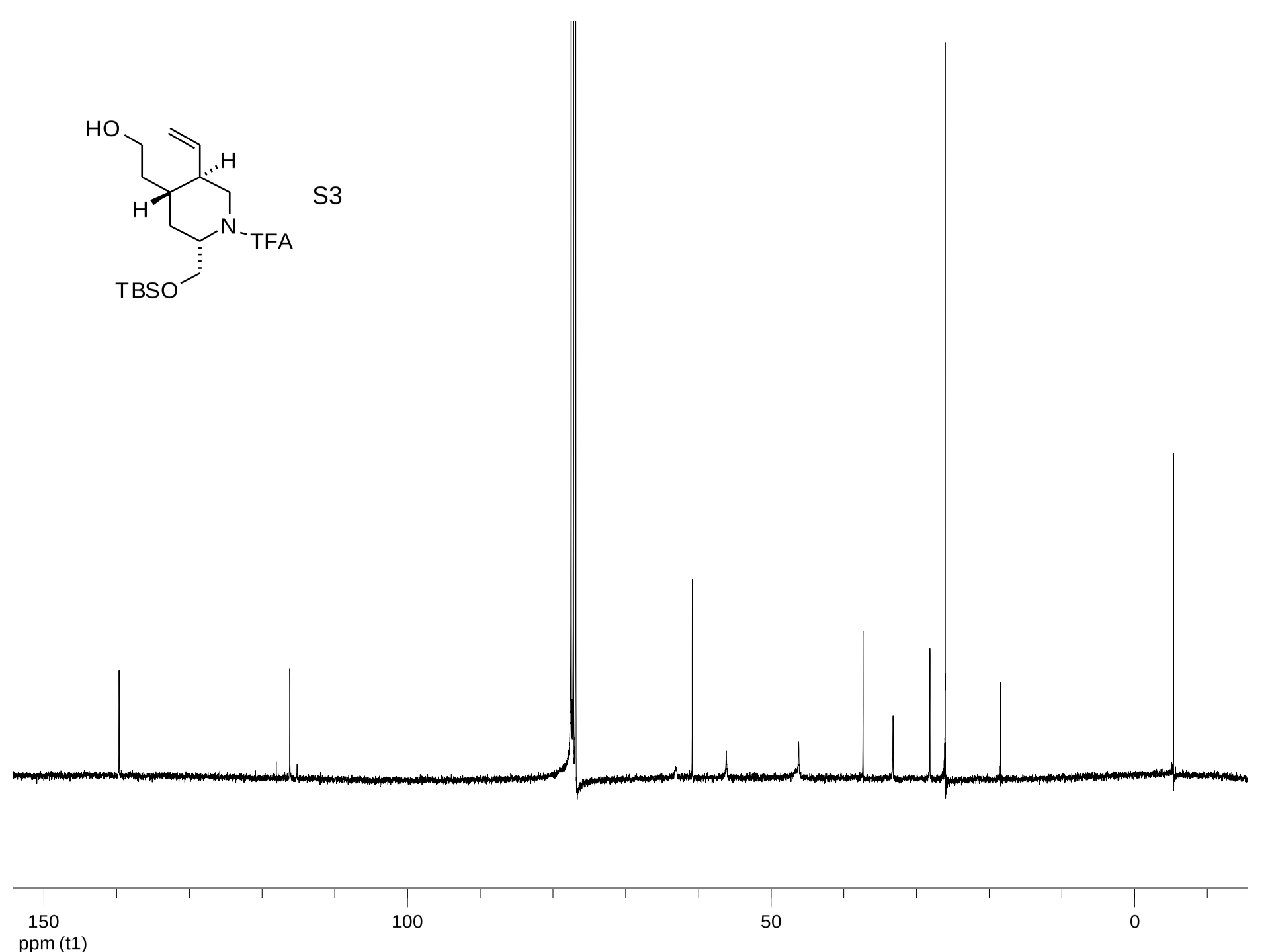
+

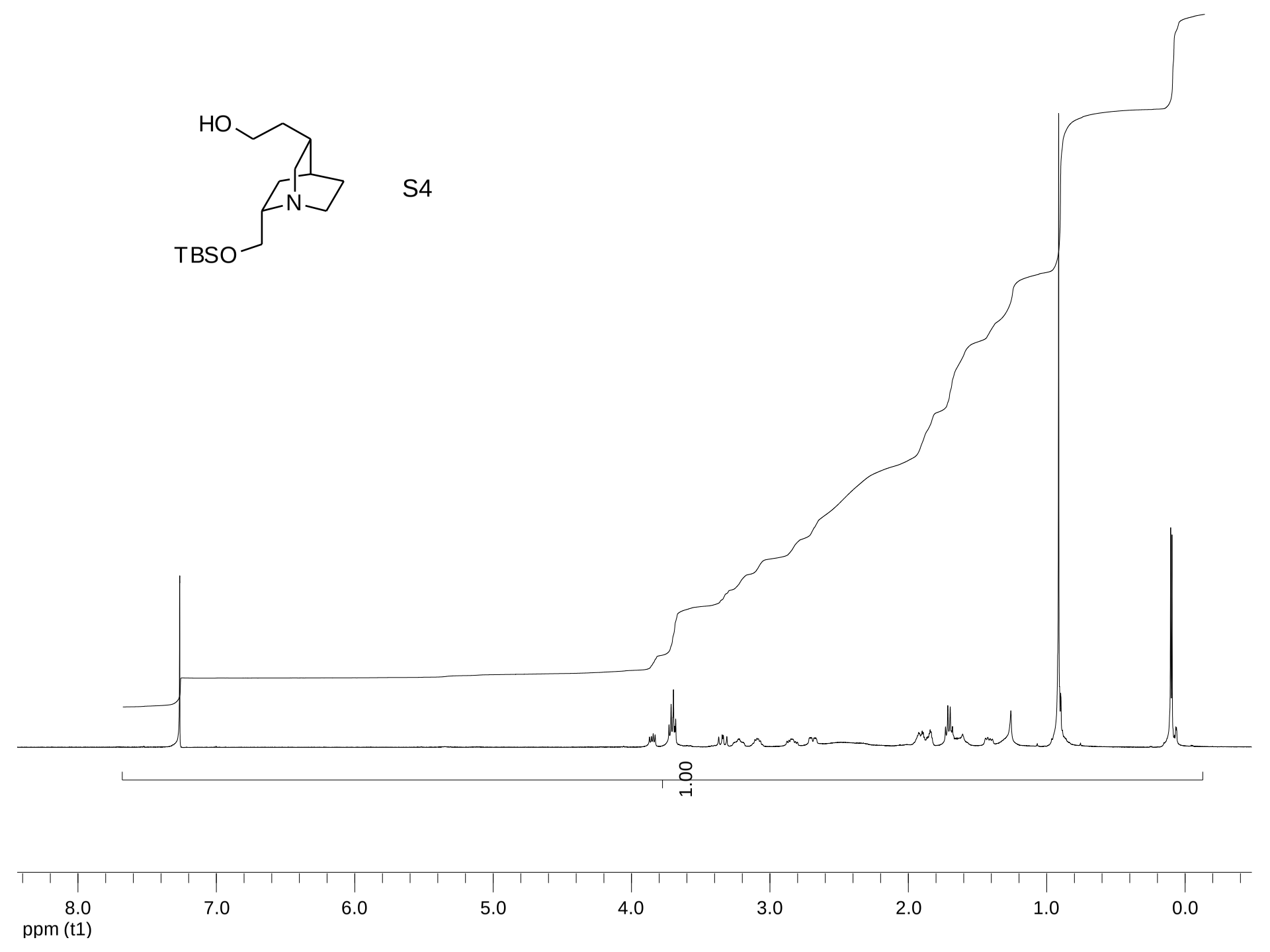
16b

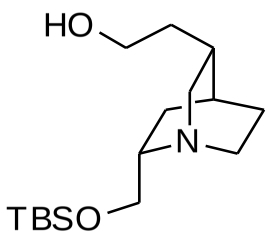
1 : 5



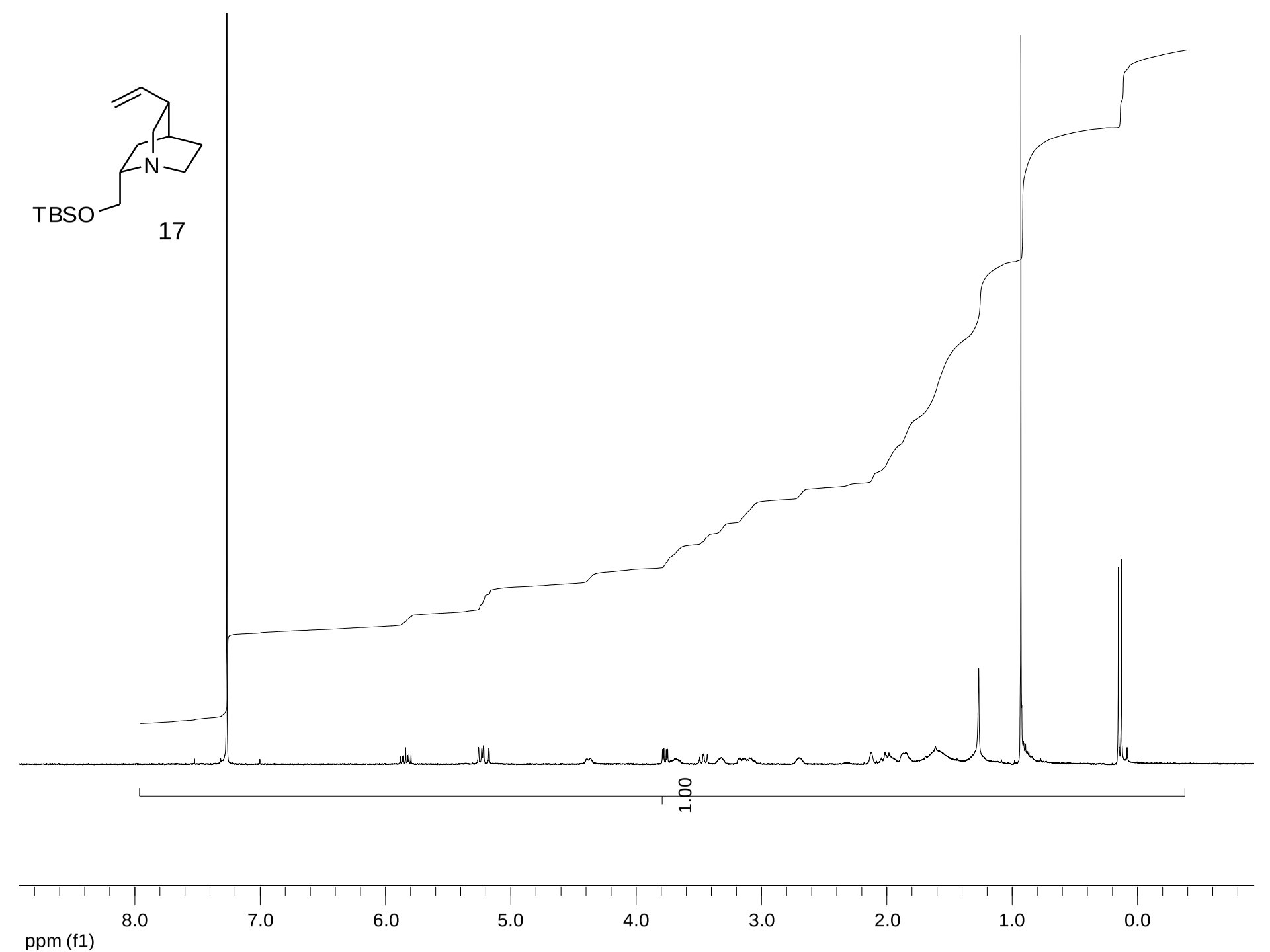

HO
H
H
N
TFA
TBSO
S3
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

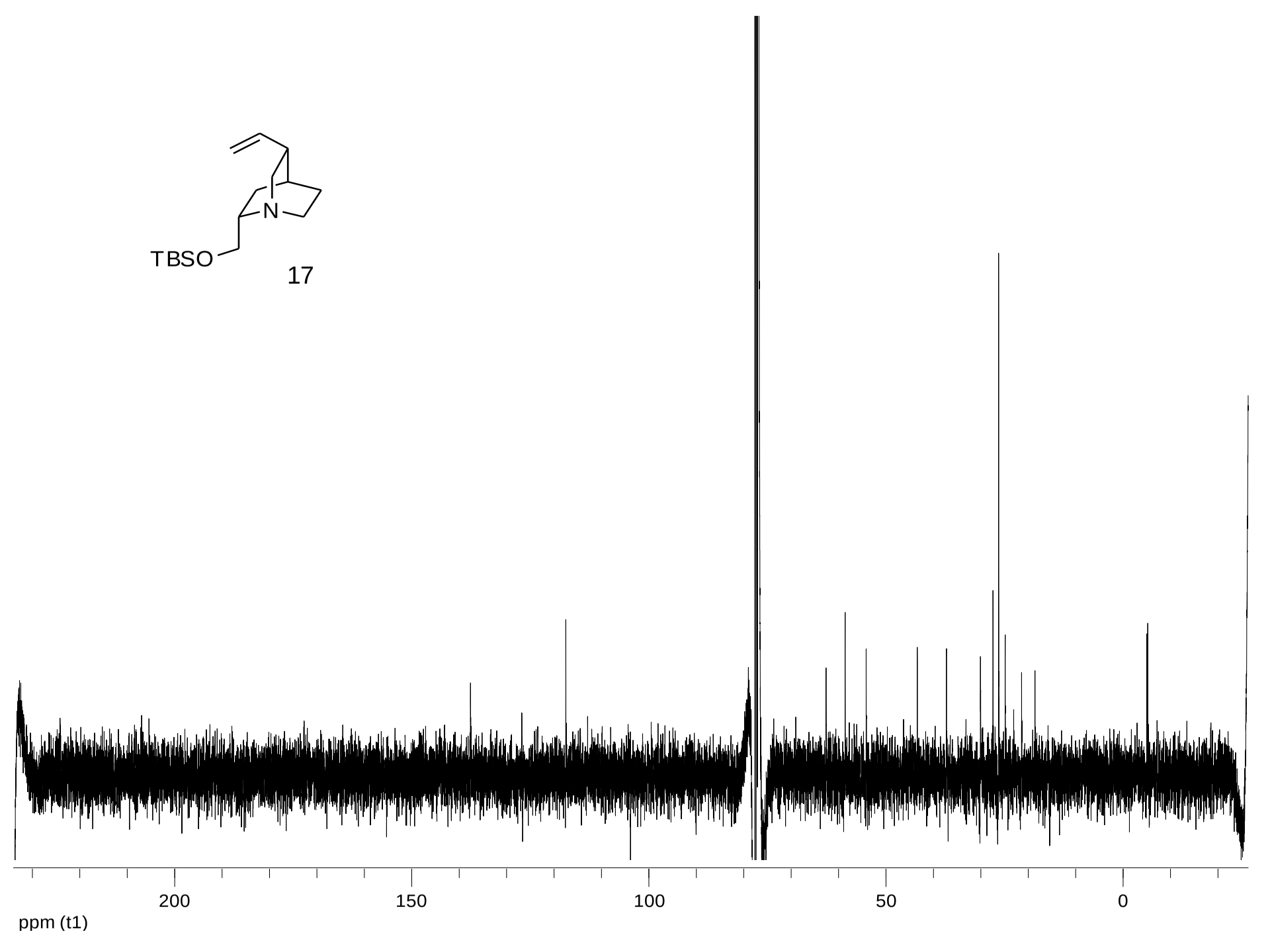

HO
H
H
N
TFA
TBSO
S3
150
100
50
0
ppm (t1)

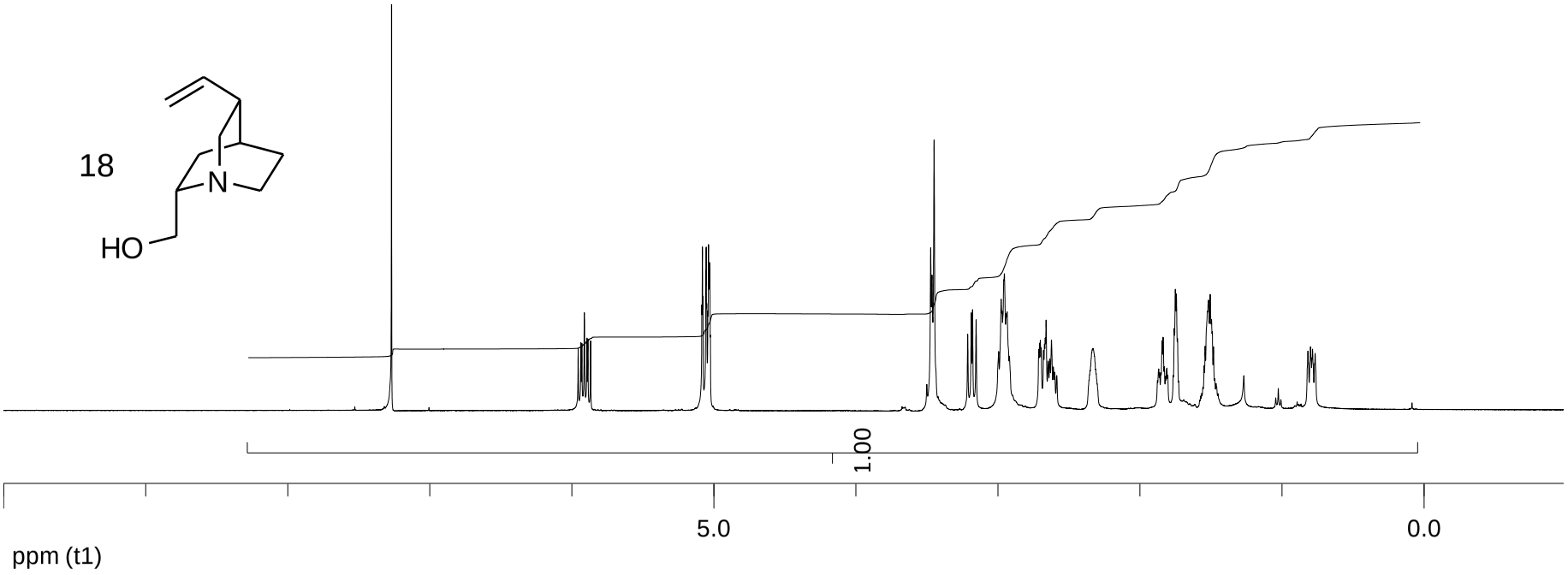

HO
N
TBSO
S4
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)



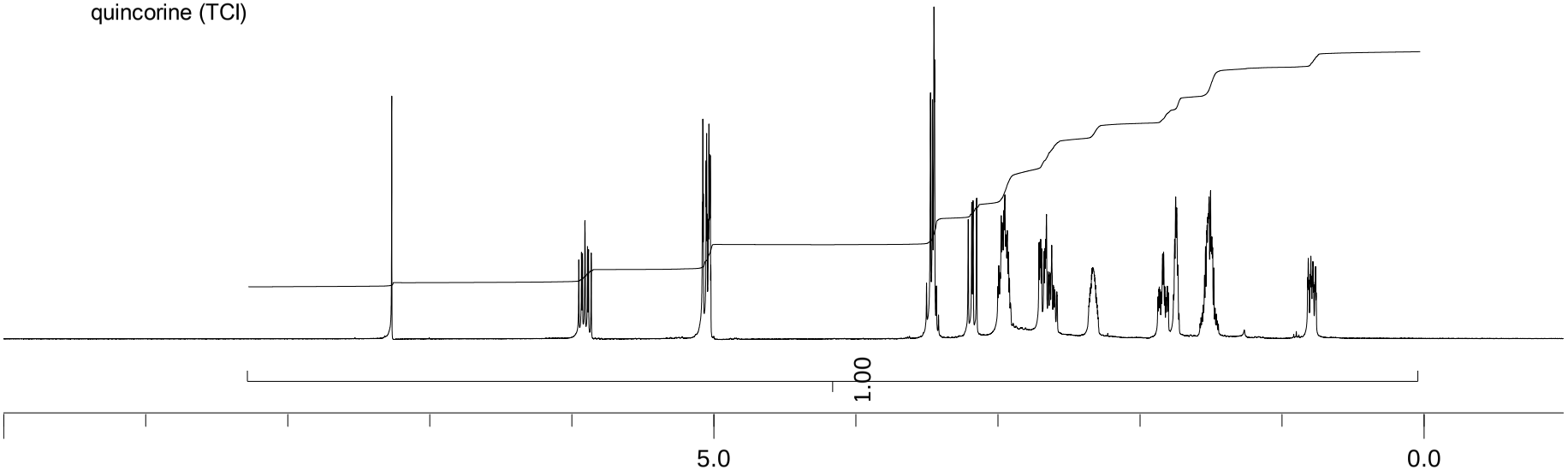
S4

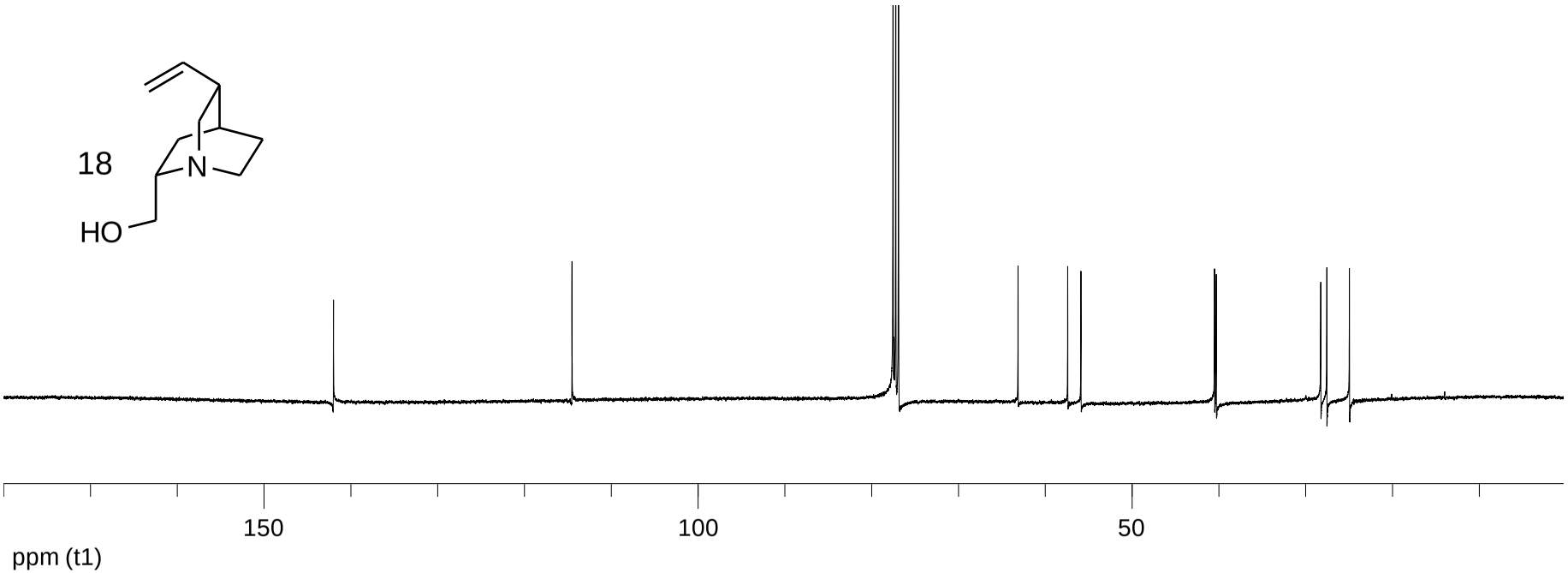

N
TBSO
17
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


N
TBSO
17
200
150
100
50
0
ppm (t1)



quincorine (TCI)





qincorine (TCI)