Enantioselective Total Synthesis of (+)-Reserpine

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Supporting Information

A. General Information.

Unless otherwise noted, all reactions were performed under a positive pressure of anhydrous nitrogen or argon in flame- or oven-dried glassware. Moisture- and air-sensitive reagents were dispensed using oven-dried stainless steel syringes or cannulae and were introduced to reaction flasks through rubber septa. Reactions conducted below ambient temperature were cooled by external baths (dry ice/acetone for –78 °C and ice/water for 0 °C). Reactions conducted above ambient temperature were heated by a silicone oil bath.

Analytical thin layer chromatography (TLC) was performed on glass plates pre-coated with silica 60 F_{254} plates, 0.25 mm). Visualization was carried out by exposure to a UV-lamp (short wave 254 nm, long wave 365 nm), and by heating after staining the plate with a ceric ammonium molybdate or a potassium permanganate solution. Extraction and chromatography solvents were reagent or HPLC grade and were used without further purification. Flash chromatography was carried out over silica gel (60 Å, 230–400 mesh) from EM Science or Davisil™. Where indicated, chromatography was conducted on a Biotage Isolera automated chromatography system.

Materials.

Commercial reagents and solvents were used with the following exceptions: tetrahydrofuran, diethyl ether, toluene, dichloromethane, acetonitrile, and methanol employed as reaction solvents were dried by passage through columns of activated alumina. Pyridine and triethylamine were distilled from calcium hydride at 760 torr prior to use. The Dess–Martin Periodinane was prepared according to known procedures.[1] Diazomethane was prepared as a 0.5 M solution in ether according to the known procedure.[2] 2-bromoallyltrimethylsilane was prepared according to the reported procedure.[3] Epoxide **(±)-5** was prepared according to the reported procedure and was distilled from calcium hydride prior to use.[4] Oligomeric cobalt salen catalyst (*R*, *R*)-**8** was prepared according to the reported procedure and stored over calcium sulfate in a –78 °C freezer.[5] Imine **3**, catalyst **10**, and catalyst *ent*-**10**, were prepared according to the reported procedures.[6] Chloroform-d was dried over 3Å MS prior to use. Iridium complex **20** was prepared according to the reported procedure and was stored in a glove box under a N_2 atmosphere.[7]

Instrumentation.

Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Mercury-400 (400MHz), Inova-500 (500MHz), or an Inova-600 (600MHz) spectrometer at 23 °C. Chemical shifts for protons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$:

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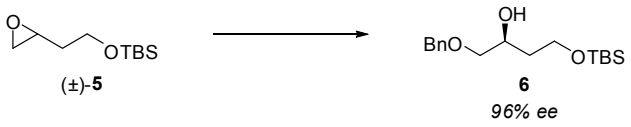
[1] Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. *Org. Synth.* **2000**, *77*, 141–146.
[2] Sigma Aldrich, 2003, "AL-180: Diazald, MNNG and Diazomethane Generators." http://www.sigmaaldrich.com/aldrich/bulletin/AL-180.pdf
[3] Trost, B. M.; Grese, T. A.; Chan, D. M. T. *J. Am. Chem. Soc.* **1991**, *113*, 7350–7362.
[4] Ficini, J.; Barbara, C.; Desmaële, D.; Ourfelli, O. *Heterocycles* **1987**, *25*, 329–332.
[5] White. D. E.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **2003**, *14*, 3633–3638.
[6] Lalonde, M. P.; McGowan, M. A.; Rajapaksa, N. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* In press.
[7] Vazquez-Serrano, L. D.; Owens, B. T.; Buriak, J. M. *Inorg. Chim. Acta* **2006**, *359*, 2786–2797.

7.26 ppm; C_6H_6: 7.16 ppm). Chemical shifts for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the NMR solvent ($CDCl_3$: 77.0 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), integration, and coupling constant (*J*) in Hertz (Hz). Infrared (IR) spectroscopy was performed on the neat compounds on a Brucker Tensor 27 FT-IR Spectrometer using OPUS software. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak). Mass spectra were obtained on an Agilent 1200 series 6120 Quadrupole LC/MS. Optical rotation data were collected using either a 2-mL cell with a 1 dm path length or a 1-mL cell using a 0.5 dm path length on a Jasco P-2000 polarimeter and are reported as $[\alpha]_D^{23}$ (concentration in grams/100 mL solvent). Reported rotations are the average of 3–5 measurements per sample.

B. Experimental procedures and characterization data.

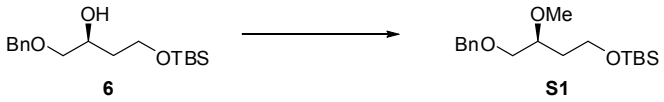


(*S*)-1-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)butan-2-ol (**6**)

A 50-mL round-bottom flask was charged with a stir bar, epoxide (±)-**5** (10.0 g, 49.7 mmol, 1 equiv.), CH_3CN (2.4 mL), and anhydrous BnOH (2.32 mL, 22.4 mmol, 0.45 equiv.). The flask was cooled to 0 ºC, and (*R*,*R*)-**8** (185 mg, 0.227 mmol, 0.45 mol % based on Co) was added in one portion. The flask was sealed with a yellow plastic cap and allowed to stir at 4 ºC for 96 h, at which point pyridinium *para*-toluenesulfonate (PPTS) (60 mg, 0.240 mmol) was added in one portion. The reaction mixture was filtered through a silica gel plug, eluting with Et_2O (400 mL). The filtrate was concentrated in vacuo to provide a dark orange oil which was purified immediately via flash chromatography (silica gel, Biotage, 10% Et_2O in hexanes) to provide the desired secondary alcohol **6** as a clear oil (6.28 g, 20.2 mmol, 41% yield). R*f* = 0.44 (25% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.24 – 7.42 (m, 5 H) 4.58 (d, *J*=12.4 Hz, 1 H) 4.55 (d, *J*=11.9 Hz, 1 H) 4.03 (ddd, *J*=11.40, 6.90, 4.60 Hz, 1 H) 3.86 (m, 1 H) 3.79 (m, 1 H) 3.48 (dd, *J*=9.77, 4.39 Hz, 1 H) 3.43 (dd, *J*=8.79, 6.84 Hz, 1 H) 3.17 (br. s., 1 H) 1.70 (m, 2 H) 0.90 (s, 9 H) 0.06 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 138.13, 128.36 (2C), 127.69 (2C), 127.64, 74.36, 73.32, 69.63, 61.32, 35.42, 25.85 (3C), 18.14, –5.52, –5.55; FTIR (neat, cm^{-1}); 3400(br m), 2953(m), 2928(m), 2857(m), 1497(w), 1471(w), 1463(w), 1389(w), 1362(w), 1253(m), 1205(w), 1090(s), 1005(m), 908(m), 833(s), 775(s), 733(s), 697(s), 663(m); LRMS (APCI) 311.2 $[M + H]^+$; $[\alpha]^{23}_D$ –1.2 (*c* 1.77, $CHCl_3$).

To assess the enantiomeric purity, the epoxide-opened product was elaborated to the corresponding diol in the following manner: Silyl ether **6** (22.7 mg, 0.073 mmol, 1 equiv.) was dissolved in THF (0.47 mL) and TBAF (1 M in THF, 0.152 mL, 2.1 equiv.) was added at 0 ºC. The solution was allowed to come to rt and stir 1 h. The reaction was then diluted with CH_2Cl_2 (5 mL) and the organic layer

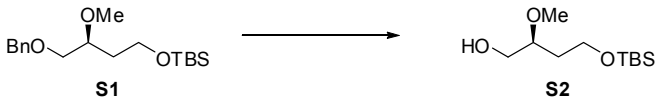
was washed with H_2O (3 x 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to provide the diol as a clear oil. The enantiomeric excess was determined to be 96% by chiral SFC analysis (OD-H, 5% MeOH, 4.0 ml/min) t_R(minor) = 6.88 min, t_R(major) = 7.52 min.



6 **S1**

(*S*)-(4-(benzyloxy)-3-methoxybutoxy)(*tert*-butyl)dimethylsilane (S1)

A 200-mL round-bottomed flask was charged with NaH (105 mg, 16.9 mmol, 1.1 equiv.) in a glove box under N_2. The sealed flask was then removed from the glove box and cooled to 0 ºC under N_2. THF was then added (15 mL) and the suspension was stirred 5 min. Alcohol **6** (4.78 g, 15.3 mmol, 1 equiv.) was then added as a solution in THF (10 mL) via cannula, followed by a THF wash (5 mL). The reaction stirred for 1 h at 0 ºC, after which MeI (1.1 mL, 17.7 mmol, 1.15 equiv.) was added dropwise, and the reaction was allowed to come to rt and stir 16 h. The reaction was quenched with the careful addition of H_2O (30 mL), and the reaction mixture was extracted with Et_2O (3 x 50 mL). The combined organics were washed with $NaHCO_3$ (50 mL) and brine (50 mL), dried over Na_aSO_4, filtered, and concentrated in vacuo to provide the pure methyl ether **S1** as a clear, colorless oil (4.15 g, 12.9 mmol, 84% yield). R*f* = 0.45 (15% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.26 – 7.37 (m, 5 H) 4.56 (s, 2 H) 3.63 – 3.77 (m, 2 H) 3.52 – 3.59 (m, 2 H) 3.44 – 3.50 (m, 1 H) 3.42 (s, 3 H) 1.73 (d, *J*=5.86 Hz, 1 H) 1.71 (d, *J*=6.44 Hz, 1 H) 0.82 – 0.93 (s, 9 H) 0.04 (s, 3 H) 0.03 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 138.37, 128.31 (2C), 127.58 (2C), 127.50, 77.05, 73.30, 72.27, 59.36, 57.67, 34.73, 25.91 (3C), 18.25, –5.39, –5.40; FTIR (neat, cm^{-1}) 2953(m), 2928(m), 2884(w), 2856(m), 1571(w), 1455(w), 1388(w), 1361(w), 1253(m), 1189(w), 1088(s), 1028(w), 1006(w), 985(w), 938(w), 882(w), 833(s), 774(s), 733(m), 697(m), 663(w); LRMS (APCI) 325.2 $[M + H]^+$; $[\alpha]^{23}_D$ –9.4 (*c* 1.98, $CHCl_3$).

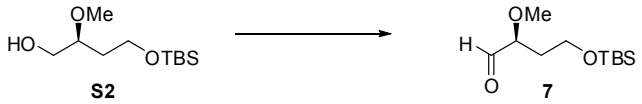


S1 **S2**

(*S*)-4-(*tert*-butyldimethylsilyloxy)-2-methoxybutan-1-ol (S2)

A 500-mL round-bottomed flask was charged with the benzyl ether **S1** (1.83 g, 5.64 mmol, 1 equiv.), which was azeotroped from benzene and dried on high vacuum 30 minutes. Dry, distilled EtOAc (76 mL) was then added under N_2, along with a stir bar. 10 wt% Pd/C (4.83 g, 4.55 mmol, 0.8 equiv.) was then added under a positive stream of nitrogen, and the flask was sealed with a rubber septum. The flask was evacuated and back-filled with H_2 (x 5), after which it was left to stir at rt for 9 h under a balloon of H_2. The reaction mixture was then filtered through a Celite plug with EtOAc. The filtrate was concentrated in

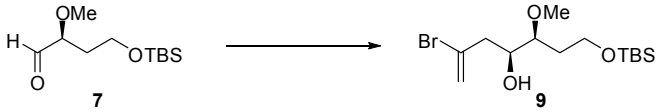
vacuo, and the resultant clear oil was purified by flash chromatography (silica gel, 20% EtOAc in hexanes) to provide the desired product **S2** as a clear oil (1.19 g, 5.07 mmol, 90% yield). R*f* = 0.23 (33% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.73 (m, 2 H) 3.50 – 3.60 (m, 1 H) 3.41 – 3.49 (m, 1 H) 3.40 (s, 3 H) 2.43 (t, *J*=6.30 Hz, 1 H) 1.77 – 1.90 (m, 1 H) 1.64 – 1.76 (m, 1 H) 0.81 – 1.01 (m, 9 H) 0.07 (s, 6 H); ^{13}C NMR (126 MHz, $CHCl_3$) δ: 78.96, 63.64, 59.23, 57.06, 33.84, 25.79 (3C), 18.13, –5.52, –5.54; FTIR (neat, cm^{-1}) 3400 (br m), 2953(m), 2929(m), 2884(w), 2857(m), 1472(m), 1388(w), 1361(w), 1253(m), 1188(w), 1086(s), 1006(w), 975(w), 939(w), 831(s), 774(s), 730(m), 663(m); LRMS (APCI) 235.1 [M + H]$^{+}$; $[\alpha]^{23}_{D}$ + 0.4 (*c* 2.25, $CHCl_3$).



S2 **7**

(*S*)-4-(*tert*-butyldimethylsilyloxy)-2-methoxybutanal (7)

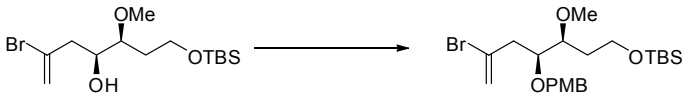
A 200-mL round-bottomed flask with a stir bar was charged with $(COCl)_2$ (950 µl, 11.1 mmol, 1.2 equiv.) and CH_2Cl_2 (12.9 mL). The flask was cooled to –60 ºC, after which a solution of DMSO (1.64 mL, 23.1 mmol, 2.5 equiv.) in CH_2Cl_2 (12.9 mL) was added dropwise. The solution stirred 5 min., after which alcohol **S2** (2.16 g, 9.22 mmol, 1 equiv.) was added in CH_2Cl_2 (11 mL, 2 x 1 mL wash). The reaction was stirred 1 h at –60 ºC, after which NEt_3 (6.4 mL, 45.9 mmol, 5.0 equiv.) was added dropwise, and the reaction was warmed immediately to rt. The solution was diluted with EtOAc (20 mL) and H_2O (20 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organics were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was passed quickly through a plug of Davisil^{TM} (25% EtOAc in hexanes) and the product-containing fractions were concentrated in vacuo to provide the aldehyde **7** as a clear oil (1.99 g, 8.95 mmol, 93% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.68 (d, *J*=1.47 Hz, 1 H) 3.65 – 3.83 (m, 3 H) 3.45 (s, 3 H) 1.94 (ddt, *J*=14.16, 6.96, 5.07, 5.07 Hz, 1 H) 1.82 (dtd, *J*=14.20, 7.00, 7.00, 5.20 Hz, 1 H) 0.89 (s, 9 H) 0.05 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 203.46 , 82.80 , 58.26 , 57.91 , 33.44 , 25.84 (3C), 18.22 , –5.48, –5.55; FTIR (neat, cm^{-1}) 2955(m), 2930(m), 2884(w), 2857(m), 1734(s), 1472(m), 1389(w), 1362(w), 1255(s), 1191(w), 1091(s), 1021(w), 968(w), 938(w), 878(w), 834(s), 808(m), 775(s), 730(m), 663(w); LRMS (APCI) 233.1 [M + H]$^{+}$; $[\alpha]^{24}_{D}$ –42.4 (*c* 1.15, $CHCl_3$).



7 **9**

(4*S*,5*S*)-2-bromo-7-(*tert*-butyldimethylsilyloxy)-5-methoxyhept-1-en-4-ol (9)

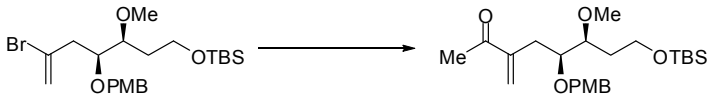
A 100-mL round-bottomed flask with stir bar was charged with CH_2Cl_2 (48 mL) at rt under N_2. $TiCl_4$ (2.4 mL, 21.8 mmol) was then added, followed by Ti(O*i*Pr)$_4$ (2.15 mL, 2.26 mmol), and the solution was allowed to stir for 1 h, to form a 0.6M solution of Ti(O*i*Pr)Cl_3 in CH_2Cl_2. A separate flame-dried, 500-mL round-bottomed flask with a stir bar was charged with aldehyde **7** (1.94 g, 8.35 mmol, 1 equiv.), which had been azeotropically dried with benzene and placed on high vacuum 30 min, and CH_2Cl_2 (190 mL), and was cooled to –78 ºC under N_2. To this was added the freshly-generated Ti(O*i*Pr)Cl_3 complex (30.6 mL, 18.4 mmol, 2.2 equiv.) dropwise over 5 min. The solution was stirred 15 min, after which 2-bromoallyltrimethylsilane (2.17 mL, 12.7 mmol, 1.5 equiv.) was added in CH_2Cl_2 (15 mL, then 5 mL wash) dropwise over 5 min. The reaction stirred at –78 ºC for 16 h, after which it was quenched by the addition of NEt_3 (9 mL) dropwise. Saturated aqueous $NaHCO_3$ (90 mL) was then added, and the flask was warmed immediately to rt. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The resultant oil was purified by flash chromatography (silica gel, 10% EtOAc in hexanes) to provide the product (**9**) as a clear oil (2.70 g, 7.64 mmol, 91% yield). R*f* = 0.27 (15% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.71 (s, 1 H) 5.52 (d, *J*=1.46 Hz, 1 H) 3.89 – 4.01 (m, 1 H) 3.64 - 3.83 (m, 2 H) 3.42 (s, 3 H) 3.33 (td, *J*=5.86, 3.40 Hz, 1 H) 2.77 (d, *J*=5.86 Hz, 1 H) 2.66 (m, *J*=8.30 Hz, 1 H) 1.82 – 1.91 (m, 1 H) 1.73 – 1.82 (m, 1 H) 0.90 (s, 9 H) 0.08 (s, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 131.02, 119.04, 79.74, 70.25, 59.23, 58.14, 45.26, 33.07, 25.86 (3C), 18.18, –5.44, –5.46; IR 3434(m), 2954(m), 2929(m), 2885(m), 2857(m), 2826(w), 1632(m), 1389(w), 1361(w), 1254(m), 1190(w), 1087(s), 1006(w), 938(w), 887(m), 832(s), 774(s), 735(w), 662(w); LRMS (APCI) 353.1 $[M + H]^+$; $[\alpha]^{24}_D$ –7.7 (*c* 1.92, $CHCl_3$).



((3*S*,4*S*)-6-bromo-3-methoxy-4-(4-methoxybenzyloxy)hept-6-enyloxy)(*tert*-butyl)dimethylsilane (S3)

Vinyl bromide **9** (696 mg, 1.97 mmol, 1 equiv.) was azeotroped from benzene and placed on high vacuum 30 min in a 100-mL round-bottomed flask. Et_2O (20.4 mL) was then added, and the flask was cooled to –20 ºC (dry ice/acetone bath). PMB trichloroacetimidate (766 µL, 4.1 mmol, 2.1 equiv.) was then added, followed by a catalytic amount of TfOH (0.52 mL of a 2.5 µl/mL solution in Et_2O). The reaction was allowed to come to 0 ºC over 1.5 h, after which it was stirred 30 min. at rt. The solution was then re-cooled to –20 ºC, and an additional amount of PMB trichloroacetimidate (766 µL, 4.1 mmol, 2.1 equiv.) was added, followed by a catalytic amount of TfOH (0.52 mL of a 2.5 µl/mL solution in Et_2O). The reaction was again allowed to come to 0 ºC over 1.5 h, after which it was allowed to stir 15 min at rt. The reaction

was quenched with saturated aqueous $NaHCO_3$ (30 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 30 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resultant wet solid was purified by flash chromatography (silica gel, 5% EtOAc in hexanes) to provide **S3** as a light yellow oil (699 mg, 1.48 mmol, 75% yield). R*f* = 0.31 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28 (d, *J*=8.79 Hz, 2 H) 6.86 (d, *J*=8.79 Hz, 2 H) 5.70 (d, *J*=0.98 Hz, 1 H) 5.49 (d, *J*=1.46 Hz, 1 H) 4.57 (d, *J*=11.23 Hz, 1 H) 4.52 (d, *J*=11.23 Hz, 1 H) 3.87 (dt, *J*=8.18, 3.97 Hz, 1 H) 3.80 (s, 3 H) 3.62 – 3.69 (m, 1 H) 3.56 – 3.62 (m, 1 H) 3.48 (dt, *J*=8.30, 4.15 Hz, 1 H) 3.38 (s, 3 H) 2.70 (dd, *J*=14.16, 3.91 Hz, 1 H) 2.63 (dd, *J*=14.65, 7.81 Hz, 1 H) 1.78 (dddd, *J*=13.98, 8.24, 5.86, 4.15 Hz, 1 H) 1.52 – 1.62 (m, 1 H) 0.90 (s, 9 H) 0.05 (s, 3 H) 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.21, 131.75, 130.48, 129.75 (2C) 119.12, 113.66 (2C) 77.48, 76.01, 72.40, 59.40, 58.27, 55.24, 42.33, 32.67, 25.92 (3C) 18.23, –5.34, –5.40; IR; 2954(s), 2929(s), 2857(m), 1633(w), 1613(m), 1513(s), 1464(m), 1361(w), 1302(w), 1245(s), 1174(m), 1097(s), 1038(m), 888(w), 835(s), 776(s); LRMS (APCI) 495.1 $[M + Na]^+$; $[\alpha]^{23}_D$ –5.6 (*c* 1.32, $CHCl_3$).

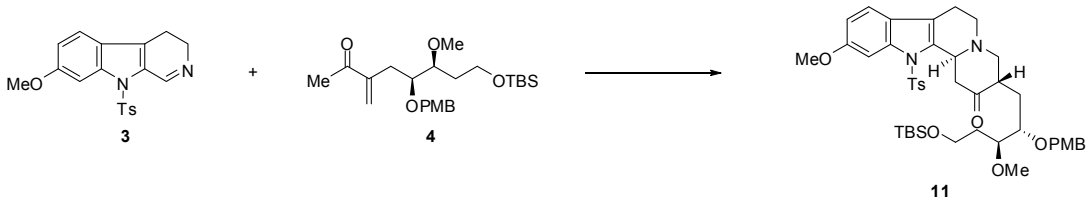


S3 **4**

(5*S*,6*S*)-8-(*tert*-butyldimethylsilyloxy)-6-methoxy-5-(4-methoxybenzyloxy)-3-methyleneoctan-2-one (4)

Vinyl bromide **S3** (286 mg, 0.60 mmol, 1 equiv.) was azeotroped from benzene twice and placed on high vacuum 2 h in a 50-mL round-bottomed flask. Et_2O (12 mL) was then added under N_2, and the flask was cooled to –78 ºC. *Tert*-butyllithium (741 µL of a 1.7 M solution in pentane, 1.26 mmol, 2.1 equiv.) was added dropwise over 5 min. The yellow solution was stirred for 30 min, after which *N*-methoxy-*N*-methylacetamide (138 µL, 0.90 mmol, 1.5 equiv.) was added. The reaction was stirred for an additional 1.5 h at –78 ºC, and was then quenched by addition of H_2O (5 mL) and immediately warmed to rt. The reaction mixture was diluted with H_2O (10 mL), and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resultant oil was purified by flash chromatography (silica gel, 0 to 15% EtOAc in hexanes) to provide **4** as a clear oil (199 mg, 0.46 mmol, 76% yield). R*f* = 0.19 (15% EtOAc in hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.21 (d, *J*=8.49 Hz, 2 H) 6.84 (d, *J*=8.49 Hz, 2 H) 6.03 (s, 1 H) 5.87 (s, 1 H) 4.48 (d, *J*=11.42 Hz, 1 H) 4.40 (d, *J*=11.42 Hz, 1 H) 3.79 (s, 3 H) 3.52 – 3.69 (m, 3 H) 3.43 (dt, *J*=8.42, 4.14 Hz, 1 H) 3.39 (s, 3 H) 2.64 (ddd, *J*=13.55, 4.61, 0.88 Hz, 1 H) 2.37 (dd, *J*=13.62, 8.35 Hz, 1 H) 2.28 (s, 3 H) 1.78 (dddd, *J*=14.06, 8.20, 5.86, 4.10 Hz, 1 H) 1.61 (ddt, *J*=13.79, 8.67, 5.13, 5.13 Hz, 1 H) 0.85 – 0.90 (m, 9 H) 0.03 (s, 3 H) 0.02 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 199.65, 159.10, 146.09, 130.72, 129.71 (2C) 127.52, 113.59 (2C) 77.89, 76.81, 71.90, 59.46, 58.17, 55.22, 32.66, 31.89, 25.91 (3C), 25.85, 18.21, –5.35, –5.41; IR 2949(m), 2929(s), 2856(m), 1678(s), 1613(m), 1586(w), 1464(m), 1441(w), 1362(m), 1324(w), 1032(w), 1247(s),

1090(s), 1036(m), 938(m), 833(s), 775(s), 662(m); LRMS (ESI) 459.2 $[M + Na]^+$; $[\alpha]^{23}_D$ –16.1 (*c* 3.03, $CHCl_3$).

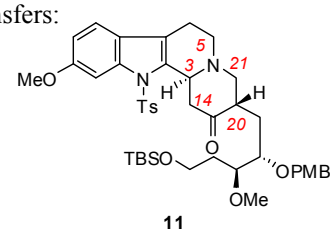


(3*S*,12b*S*)-3-((2*S*,3*S*)-5-(*tert*-butyldimethylsilyloxy)-3-methoxy-2-(4-methoxybenzyloxy)pentyl)-10-methoxy-12-tosyl-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizin-2(12H)-one (11)

An oven-dried 25-mL round-bottom flask with stir-bar was charged with enone **4** (788 mg, 1.80 mmol, 1.2 equiv.), imine **3** (533 mg, 1.50 mmol, 1 equiv.), and aminothiourea **10** (140 mg, 0.30 mmol, 20 mol %). The flask was placed under N_2 and toluene (4.5 mL) was added, followed by AcOH (17.2 µl, 0.30 mmol, 20 mol %) in one portion. The reaction was allowed to stir at rt 4.5 d, and then at 45 °C for 2 h. Analysis of the crude reaction mixture by ^{1}H NMR (comparison of a combination of C3 and PMB Bn signals) showed a 11.5:1.0:1.8:0 diastereomeric ratio of **11**:**12**:**13**:**14**. The crude reaction mixture was directly purified by flash chromatography (silica gel, Biotage, 0 – 50% EtOAc in hexanes gradient) to provide the desired diastereomer as a pale yellow solid (909 mg, 1.15 mmol, 76% yield). R*f* = 0.19 (50% EtOAc in hexanes); ^{1}H NMR (399 MHz, $CDCl_3$) δ: 7.65 (d, *J*=2.20 Hz, 1 H, C12) 7.47 (d, *J*=8.42 Hz, 2 H, Ts) 7.17 – 7.25 (m, 3 H, PMB, C10) 7.10 (d, *J*=7.68 Hz, 2 H, Ts) 6.77 – 6.91 (m, 3 H, PMB, C9) 4.61 (d, *J*=11.34 Hz, 1 H, PMB Bn) 4.51 (dd, *J*=11.34, 2.20 Hz, 1 H, C3) 4.31 (d, *J*=11.34 Hz, 1 H, PMB Bn) 3.87 (s, 3 H, PMB OMe) 3.85 (ddd, *J*=10.61, 4.76, 2.56 Hz, 1 H, C18) 3.75 (dd, *J*=7.87, 4.57 Hz, 2 H, C**H$_2$**OTBS) 3.70 (s, 3 H, **Me**O) 3.54 (ddd, *J*=9.51, 4.57, 2.38 Hz, 1 H, C17) 3.50 (s, 3 H, C17 **Me**O) 3.31 (dd, *J*=13.17, 5.86 Hz, 1 H, C21) 3.10 – 3.20 (m, 2 H, C14, C5) 2.94 (t, *J*=12.44 Hz, 1 H, C21) 2.78 – 2.86 (m, 1 H, C5) 2.68 – 2.78 (m, 3 H, C6(2), C20) 2.39 (t, *J*=12.26 Hz, 1 H, C14) 2.28 (s, 3 H, Ts) 2.05 (ddd, *J*=13.80, 9.15, 2.38 Hz, 1 H, C19) 1.85 (dtd, *J*=14.00, 7.70, 7.70, 2.60 Hz, 1 H, C16) 1.58 (ddt, *J*=14.00, 9.38, 4.62, 4.62 Hz, 1 H, C16) 1.04 (ddd, *J*=13.80, 10.30, 3.40 Hz, 1 H, C19) 0.90 - 0.93 (m, 9 H, TBS) 0.08 (s, 3 H, TBS) 0.08 (s, 3 H, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.55, 159.21, 158.02, 144.63, 138.37, 134.52, 134.41, 130.76, 129.83 (2C), 129.61 (2C), 126.29 (2C), 123.97, 118.92, 118.81, 113.78 (2C), 112.73, 100.33, 78.22, 76.77, 72.43, 61.10, 59.59, 58.95, 58.37, 55.79, 55.17, 45.17, 44.56, 43.00, 32.82, 26.86, 25.94 (3C), 22.25, 21.49, 18.25, –5.29, –5.37; IR 2592(m), 2927(m), 2856(m), 1706(s), 1612(m), 1582(w), 1513(m), 1493(m), 1463(m), 1440(w), 1364(s), 1304(w), 1248(s), 1172(s), 1145(m), 1088(s), 1035(m), 975(m), 834(s), 775(m), 674(s), 626(m); LRMS (APCI) 791.4 $[M + H]^+$; $[\alpha]^{24}_D$ +65.8 ° (*c* 1.11, $CHCl_3$).

The 1-D NOESY spectrum (500 MHz, $CDCl_3$) displayed the following nOe transfers:

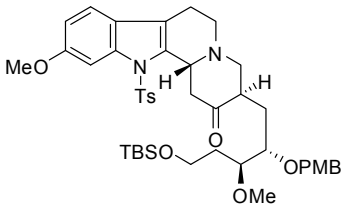
Irradiation of C14 (δ 2.39): 0.3% C3 (δ 4.51), 1.2% C20 (δ 2.75)



Irradiation of C3 (δ 4.51): 0.9% Ts (δ 7.47), 1.7% C14 (δ 3.15), 1.9% C21 (δ 2.94)

Irradiation of C21 (δ 2.94): 1.2% C3 (δ 4.51)

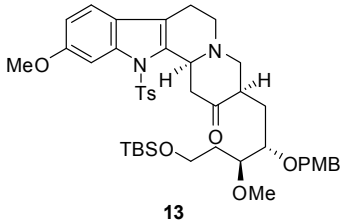
Irradiation of C21 (δ 3.31): 2.6% C5 (δ 2.81), 4.5% C20 (δ 2.74)



12

(3*R*,12b*R*)-3-((2*S*,3*S*)-5-(*tert*-butyldimethylsilyloxy)-3-methoxy-2-(4-methoxybenzyloxy)pentyl)-10-methoxy-12-tosyl-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizin-2(12H)-one (12)

R*f* = 0.28 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.65 (d, *J*=2.29 Hz, 1 H) 7.48 (d, *J*=8.24 Hz, 2 H) 7.30 (d, *J*=8.24 Hz, 2 H) 7.20 (d, *J*=8.24 Hz, 1 H) 7.10 (d, *J*=8.24 Hz, 2 H) 6.88 (d, *J*=8.24 Hz, 2 H) 6.85 (dd, *J*=8.47, 2.06 Hz, 1 H) 4.63 (d, *J*=11.90 Hz, 1 H) 4.49 (m, 2 H) 3.87 (s, 3 H) 3.80 (s, 3 H) 3.69 (td, *J*=9.27, 5.27 Hz, 1 H) 3.62 – 3.66 (m, 1 H) 3.60 (dt, *J*=8.59, 4.64 Hz, 1H) 3.54 (dt, *J*=8.47, 4.01 Hz, 1 H) 3.39 (s, 3 H) 3.21 – 3.34 (m, 2 H) 3.06 – 3.16 (m, 1 H) 2.89 (t, *J*=12.36 Hz, 1 H) 2.65 – 2.83 (m, 4 H) 2.46 – 2.58 (dd, *J*=12.4, 11.8 Hz, 1 H) 2.29 (s, 3 H) 2.17 (ddd, *J*=14.19, 8.70, 5.04 Hz, 1 H) 1.74 – 1.88 (m, 1 H) 1.55 – 1.69 (m, 1 H) 1.32 – 1.46 (m, 1 H) 0.90 (s, 9 H) 0.05 (s, 3 H) 0.04 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 208.31, 159.39, 158.22, 144.78, 138.68, 134.81, 134.53, 130.98, 129.95 (2C), 129.75 (2C), 126.53 (2C), 124.21, 119.37, 119.08, 113.92 (2C), 112.98, 100.62, 78.22, 74.89, 71.33, 60.14, 59.61, 59.00, 58.55, 56.00, 55.41, 45.45, 45.25, 43.22, 32.95, 26.31, 26.10 (3C), 22.49, 21.68, 18.41, –5.15, –5.21; IR 3008 (w), 2928 (m), 2856 (m), 1708 (m), 1613 (m), 1513 (m), 1494 (w), 1367 (s), 1250 (s), 1216 (w), 1173 (s), 1147 (m), 1090 (s), 1037 (m), 836 (s), 759 (s); LRMS (APCI) 791.4 $[M + H]^+$; $[\alpha]^{24}_D$ +16.9 º (*c* 0.29, $CHCl_3$).



13

(3*R*,12b*S*)-3-((2*S*,3*S*)-5-(*tert*-butyldimethylsilyloxy)-3-methoxy-2-(4-methoxybenzyloxy)pentyl)-10-methoxy-12-tosyl-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizin-2(12H)-one (13)

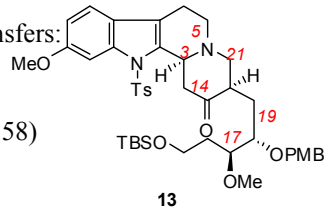
R*f* = 0.36 (50% EtOAc in hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ:7.60 (d, *J*=2.20 Hz, 1 H, C12) 7.44 (d, *J*=8.49 Hz, 2 H, Ts) 7.25 (d, *J*=8.49 Hz, 2 H, PMB) 7.12 (d, *J*=8.49 Hz, 1 H, C10) 7.08 (d, *J*=8.35 Hz, 2 H,

Ts) 6.86 (d, *J*=8.64 Hz, 2 H, PMB) 6.81 (dd, *J*=8.49, 2.34 Hz, 1 H, C9) 4.43 (d, *J*=10.84 Hz, 1 H, PMB Bn) 4.32 (d, *J*=10.69 Hz, 1 H, PMB Bn) 4.04 (dd, *J*=11.10, 2.40 Hz, 1 H, C3) 3.86 (s, 3 H, PMB **Me**O) 3.78 (s, 3 H, **Me**O) 3.62 – 3.73 (m, 2 H, C18, C**H**HOTBS) 3.51 – 3.59 (m, 2 H, CH**H**OTBS, C17) 3.40 (s, 3 H, C17 **Me**O) 3.36 (ddd, *J*=14.57, 2.78, 1.40 Hz, 1 H, C14) 2.98 (m, 2 H, C5, C21) 2.91 (dd, *J*=11.57, 2.78 Hz, 1 H, C5) 2.75 (m, 1 H, C6) 2.54 – 2.64 (m, 3 H, C14, C20, C21) 2.47 (dd, *J*=15.96, 2.30 Hz, 1 H, C6) 2.28 (s, 3 H, Ts) 2.07 (dt, *J*=14.31, 8.80 Hz, 1 H, C19) 1.76 – 1.85 (m, 2 H, C16, C19) 1.56 – 1.44 (m, 1 H, C16) 0.87 – 0.91 (m, 9 H, TBS) 0.04 (s, 3 H, TBS) 0.04 (s, 3 H, TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 210.75, 159.13, 157.97, 144.48, 139.42, 134.90, 133.39, 130.48, 129.97 (2C) 129.23 (2C) 126.59 (2C) 124.57, 122.59, 118.83, 113.69 (2C) 112.92, 101.18, 77.17, 75.89, 71.30, 59.53, 59.33, 58.54, 58.32, 55.81, 55.24, 49.90, 48.26, 46.43, 32.51, 32.03, 25.93 (3C) 22.90, 21.52, 18.25, –5.31, –5.41; IR 2929 (m), 2857 (m), 1709 (m), 1613 (m), 1514 (m), 1368 (s), 1305 (w), 1249 (s), 1216 (s), 1090 (s), 1038 (m), 971 (w), 836 (m), 759 (s); LRMS (APCI) 791.4 $[M + H]^+$; $[\alpha]^{24}_D$ +38.6 º (*c* 1.72, $CHCl_3$).

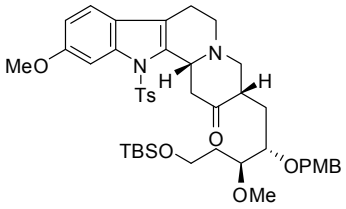
The 1-D NOESY spectrum (500 MHz, $CDCl_3$) displayed the following nOe transfers:

Irradiation of C19 (δ 2.07): 3.0% C14 (δ 2.57), 2.3% C17 (δ 2.57)

Irradiation of C3 (δ 4.04): 3.7% C14 (δ 3.36), 4.7% C5 (δ 2.98), 5.4% C21 (δ 2.58)



13

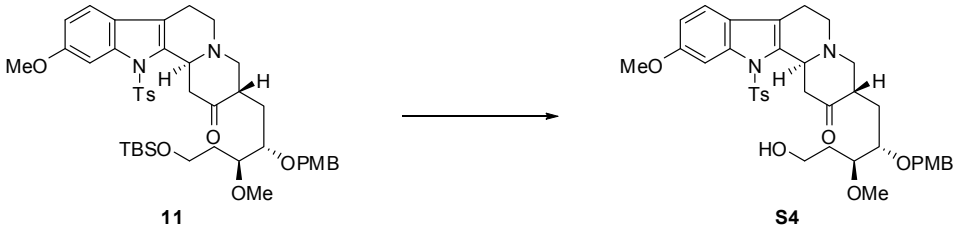


14

(3*S*,12b*R*)-3-((2*S*,3*S*)-5-(*tert*-butyldimethylsilyloxy)-3-methoxy-2-(4-methoxybenzyloxy)pentyl)-10-methoxy-12-tosyl-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizin-2(12H)-one (14)

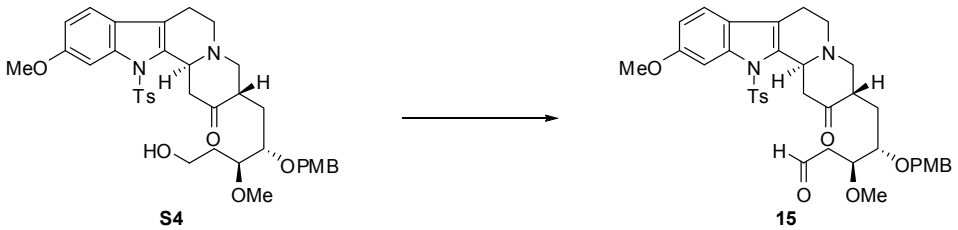
R*f* = 0.61 (50% EtOAc in hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.63 (d, *J*=2.05 Hz, 1 H) 7.45 (d, *J*=8.49 Hz, 2 H) 7.32 (d, *J*=8.79 Hz, 2 H) 7.14 (d, *J*=8.49 Hz, 1 H) 7.08 (d, *J*=8.20 Hz, 2 H) 6.89 (d, *J*=8.49 Hz, 2 H) 6.82 (dd, *J*=8.35, 2.20 Hz, 1 H) 4.58 (d, *J*=10.84 Hz, 1 H) 4.48 (d, *J*=10.54 Hz, 1 H) 4.14 (dd, *J*=10.69, 2.49 Hz, 1 H) 3.87 (s, 3 H) 3.80 (s, 3 H) 3.69 (dd, *J*=7.76, 4.54 Hz, 2 H) 3.60 (ddd, *J*=10.40, 4.25, 2.34 Hz, 1 H) 3.48 – 3.52 (m, 1 H) 3.42 (dd, *J*=15.08, 3.08 Hz, 1 H) 3.33 (s, 3 H) 3.17 (dd, *J*=11.42, 5.86 Hz, 1 H) 3.02 (ddd, *J*=11.00, 4.69, 2.05 Hz, 1 H) 2.96 (dd, *J*=11.42, 3.22 Hz, 1 H) 2.74 – 2.85 (m, 2 H) 2.60 (td, *J*=10.54, 3.51 Hz, 1 H) 2.46 – 2.53 (m, 2 H) 2.29 (s, 3 H) 2.12 – 2.18 (m, 1 H) 1.79 – 1.84 (m, 1 H) 1.47 – 1.58 (m, 2H) 0.90 (s, 9 H) 0.05 (s, 3 H) 0.05 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 210.99, 159.42, 158.24, 144.72, 139.62, 135.01, 133.61, 130.87, 130.04 (2C) 129.44 (2C) 126.75 (2C) 124.75, 122.80, 119.08, 114.00 (2C) 113.18, 101.40, 77.51, 76.45, 72.61, 59.76, 59.54, 59.00, 58.47, 56.01, 55.44, 49.97, 46.52, 32.71, 32.13, 29.86, 26.12, 22.95, 21.69, 18.44, –5.13, –5.22; IR 2929 (m), 2856 (m), 1711

(m), 1613 (m), 1514 (m), 1465 (w), 1369 (m), 1249 (s), 1173 (s), 1144 (m), 1090 (s), 1036 (m), 970 (w), 836 (s), 760 (s). LRMS (APCI) 791.4 $[M + H]^+$; $[\alpha]^{23}_D$ –2.46 º (*c* 0.69, $CHCl_3$).



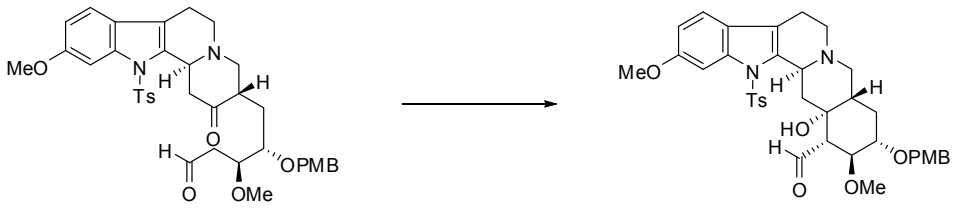
(3*S*,12b*S*)-3-((2*S*,3*S*)-5-hydroxy-3-methoxy-2-(4-methoxybenzyloxy)pentyl)-10-methoxy-12-tosyl-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizin-2(12H)-one (S4)

A solution of 6M HF·pyr in pyr was prepared in a plastic vial: 2 mL pyr, then 300 µl HF·pyr. An aliquot of this solution (2.16 mL, 13.0 mmol, 22 equiv.) was added dropwise to the silyl ether **11** (467 mg, 0.59 mmol, 1 equiv.) in THF (3.2 mL) in a separate plastic vial with a stir bar at 0 ºC. The solution was allowed to gradually warm to rt and was stirred 16 h, after which it was carefully quenched by the slow addition of saturated aqueous $NaHCO_3$ at 0 ºC. The reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, Biotage, 0 to 9% MeOH in CH_2Cl_2) to provide **S4** as a pale yellow solid (370.4 mg, 0.55 mmol, 93%). R*f* = 0.30 (5% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.65 (d, *J*=1.95 Hz, 1 H) 7.47 (d, *J*=8.30 Hz, 2 H) 7.20 (m, 3 H) 7.10 (d, *J*=8.30 Hz, 2 H) 6.80 – 6.89 (m, 3 H) 4.58 (d, *J*=11.23 Hz, 1 H) 4.49 (d, *J*=10.74 Hz, 1 H) 4.34 (d, *J*=11.72 Hz, 1 H) 3.93 (ddd, *J*=10.74, 4.15, 1.95 Hz, 1 H) 3.87 (s, 3 H) 3.76 – 3.83 (m, 2 H) 3.70 (s, 3 H) 3.49 - 3.56 (m, 1 H) 3.52 (s, 3 H) 3.29 (dd, *J*=13.18, 6.35 Hz, 1 H) 3.14 (dd, *J*=13.18, 2.93 Hz, 1 H) 3.10 – 3.19 (m, 1 H) 2.94 (t, *J*=12.45 Hz, 1 H) 2.83 (dt, *J*=10.74, 4.40 Hz, 1 H) 2.65 – 2.78 (m, 3 H) 2.37 (t, *J*=12.45 Hz, 1 H) 2.28 (s, 3 H) 2.02 (ddd, *J*=14.16, 9.77, 2.10 Hz, 1 H) 1.82 – 1.93 (m, 1 H) 1.68 – 1.79 (m, 1 H) 1.05 (ddd, *J*=13.67, 10.74, 2.93 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 208.64, 159.34, 158.02, 144.65, 138.36, 134.39, 134.33, 130.34, 129.89 (2C) 129.59 (2C) 126.27 (2C) 123.94, 118.92, 118.85, 113.85 (2C) 112.71, 100.32, 81.59, 76.09, 72.70, 61.23, 61.03, 58.96, 57.93, 55.78, 55.16, 45.20, 44.61, 42.77, 31.63, 26.73, 22.23, 21.47; IR 3437(m), 2922(m), 2835(m), 1704(s), 1611(m), 1581(w), 1512(m), 1493(w), 1440(w), 1362(s), 1304(m), 1247(s), 1171(s), 1145(s), 1111(m), 1087(s), 1033(s), 975(m), 811(s), 722(m), 675(s), 626(m); LRMS (APCI) 677.3 $[M + H]^+$; $[\alpha]^{24}_D$ +79.6º (*c* 1.0, $CHCl_3$).



(3S,4S)-3-methoxy-5-((3S,12bS)-10-methoxy-2-oxo-12-tosyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-3-yl)-4-(4-methoxybenzyloxy)pentanal (15)

Alcohol **S4** (442 mg, 0.653 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (65 mL) in a 300-mL round-bottom flask at rt. To this was added the Dess–Martin periodinane (305 mg, 0.72 mmol, 1.1 equiv.) in one portion, and the solution stirred 1 h, after which the reaction solution was diluted with Et_2O (60 mL). The reaction mixture was poured into a 500-mL Erlenmeyer flask containing 120 mL of a 1:1 aqueous solution of sat. $NaHCO_3$:10% $Na_2S_2O_3$. The biphasic mixture was stirred vigorously 1 h, after which additional CH_2Cl_2 was added (50 mL) and the layers were separated. The aqueous was extracted with CH_2Cl_2 (2 x 50 mL), and the combined organics were dried over Na_2SO_4, filtered and concentrated in vacuo to provide the crude aldehyde (**15**), which was carried forward without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.81 (t, *J*=1.71 Hz, 1 H) 7.65 (d, *J*=1.95 Hz, 1 H) 7.47 (d, *J*=8.30 Hz, 2 H) 7.16 – 7.23 (m, 3 H) 7.10 (d, *J*=7.81 Hz, 2 H) 6.80 – 6.89 (m, 3 H) 4.54 (d, *J*=11.23 Hz, 1 H) 4.50 (dd, *J*=11.23, 2.44 Hz, 1 H) 4.31 (d, *J*=11.23 Hz, 1 H) 3.90 – 3.98 (m, 2 H) 3.87 (s, 3 H) 3.70 (s, 3 H) 3.48 – 3.50 (m, 3 H) 3.29 (dd, *J*=13.18, 6.35 Hz, 1 H) 3.15 (m, 2 H) 2.94 (t, *J*=12.45 Hz, 1 H) 2.83 (dt, *J*=10.74, 4.64 Hz, 1 H) 2.64 – 2.77 (m, 4 H) 2.59 (ddd, *J*=16.60, 7.81, 1.95 Hz, 1 H) 2.37 (t, *J*=12.20 Hz, 1 H) 2.28 (s, 3 H) 2.04 (ddd, *J*=14.16, 9.28, 2.20 Hz, 1 H) 1.01 (ddd, *J*=13.18, 9.77, 2.93 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 208.50, 201.11, 159.38, 158.04, 144.68, 138.37, 134.36, 134.31, 129.95 (2C), 129.62 (2C), 126.28 (2C), 123.94, 118.94, 118.87, 113.87 (2C), 112.75, 100.31, 76.45, 75.92, 72.59, 60.94, 58.93, 57.99, 55.80, 55.18, 45.18, 44.62, 43.92, 42.77, 29.66, 26.64, 22.24, 21.50; LRMS (APCI) 675.3 $[M + H]^+$



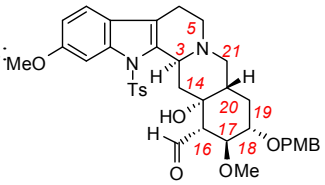
15 **16**

Pentacyclic aldehyde (16)

A flame-dried, 100-mL round-bottom flask was charged with crude aldehyde **15** (0.653 mmol, 1 equiv.), which was azeotroped twice from benzene and placed on high vacuum 30 min. A stir bar was then added under a positive pressure of nitrogen, followed by toluene (21 mL). To a separate 10-mL flask was charged with toluene (2 mL), piperidine (129 μL) and *p*-toluenesulfonic acid (24.8 mg), and 1 mL of this solution was transferred to the first flask (piperidine addition: 65.7 μL, 0.65 mmol, 1 equiv). The reaction was allowed to stir overnight, after which it was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The reaction mixture was extracted with CH_2Cl_2 (3 x 15 mL), and the combined organics were dried

over Na_2SO_4, filtered, and concentrated in vacuo.[8] The residue was azeotroped twice from benzene to aid in the removal of residual piperidine, after which the residue was dissolved in a 1:1 solution of hexanes:EtOAc. The solution was filtered to remove any precipitate, and the filtrate was concentrated in vacuo to provide **16** as a single diastereomer (382 mg, 0.56 mmol, 86% yield). ^{1}H NMR (600 MHz, C_6D_6) δ: 9.83 (d, *J*=2.44 Hz, 1 H) 8.16 (d, *J*=2.44 Hz, 1 H) 7.59 (d, *J*=8.30 Hz, 2 H) 7.33 (d, *J*=8.80 Hz, 2 H) 6.99 (d, *J*=8.30 Hz, 1 H) 6.88 (d, *J*=8.80 Hz, 1 H) 6.88 (d, *J*=8.30 Hz, 2 H) 6.38 (d, *J*=7.81, 2 H) 4.83 (dd, *J*=11.5, 1.5 Hz, 1 H) 4.59 (d, *J*=11.72 Hz, 1 H) 4.51 (d, *J*=11.72 Hz, 1 H) 4.07 (dd, *J*=10.99, 9.03 Hz, 1 H) 3.45 (s, 3H) 3.45 (s, 3 H) 3.38 – 3.51 (m, 1 H) 3.33 (s, 3 H) 3.25 (t, *J*=11.96, 1 H) 3.12 (br. s, 1 H), 2.91 (dd, *J*=13.18, 1.95 Hz, 1 H) 2.69 – 2.81 (m, 1 H) 2.41 – 2.57 (m, 2 H) 2.34 – 2.41 (m, 1 H) 2.29 (dd, *J*=10.99, 2.20, 1 H) 1.83 (ddd, *J*=12.30, 12.30, 12.30, 1 H) 1.53 (s, 3 H) 1.47 – 1.52 (m, 1 H) 1.42 (dd, *J*=13.18, 11.23 Hz, 1 H) 1.33 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 206.34, 159.39, 158.08, 144.80, 139.10, 135.86, 134.26, 130.97, 129.71 (2C), 129.44 (2C), 126.70 (2C), 124.83, 120.42, 118.89, 114.05 (2C), 112.94, 101.09, 82.33, 82.13, 72.51, 71.67, 62.61, 61.21, 56.08, 55.52, 55.39, 53.68, 46.76, 40.03, 38.24, 28.99, 22.68, 21.76; IR 3500 (br m), 2956(m), 2926(s), 2853(m), 1721(m), 1612(m), 1583(w), 1513(m), 1492(m), 1462(m), 1441(w), 1363(s), 1278(m), 1247(s), 1170(s), 1144(m), 1102(s), 1087(s), 1033(s), 973(m), 909(w), 846(w), 810(s), 731(m), 703(w), 657(m), 627(w); LRMS (APCI) 675.3 $[M + H]^+$; $[\alpha]^{24}_D$ +70.8º (*c* 1.00, $CHCl_3$)

The 1-D NOESY spectra (600 MHz, C_6D_6) displayed the following nOe transfers:

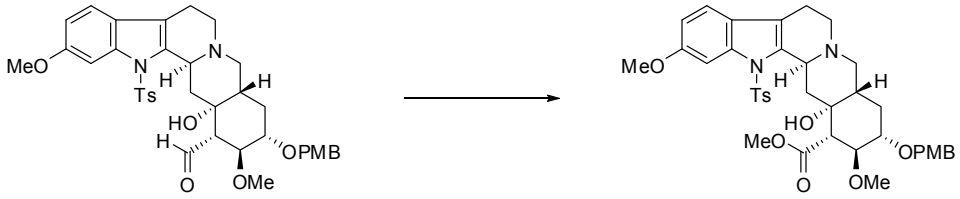


Irradiation of C17 (δ 4.07): 1.79% 19α (δ 1.83)

Irradiation of C16 (δ 2.29): 1.69% CHO (δ 9.83), 3.34% C20 (δ 1.33)

Irradiation of C3 (δ 4.83): 3.31% *o*-CH(Ts) (δ 7.59), 3.63% C21α (δ 3.25), 2.55% C14α (δ 2.91)

Irradiation of C20 (δ 1.33): 2.00% C18 (δ 3.41), 0.75% C5β (δ 2.72). 1.94% C21β (δ 2.44)



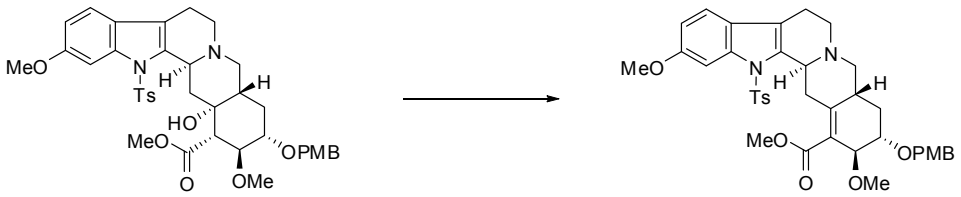
16 **17**

Pentacyclic methyl ester (17)

Aldol adduct **16** (100 mg, 0.148 mmol, 1 equiv.) was dissolved in *t*-BuOH (2.5 mL), H_2O (2.5 mL) and acetone (1.4 mL) in a 25-mL round-bottom flask. 2-methyl-2-butene (58 µL, 0.55 mmol, 3.7 equiv.) was then added via microliter syringe, followed by NaH_2PO_4 (92 mg, 0.67 mmol, 4.5 equiv.) and $NaClO_2$ (80%

[8] The product can be chromatographed on Davisil™, but small amounts of decomposition are observed, and thus the reported workup procedure was devised to provide the pure product without need for flash chromatography.

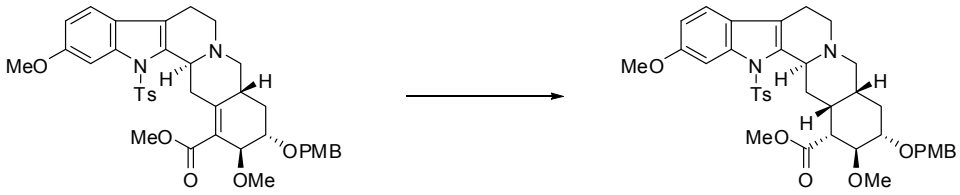
technical grade, 75 mg, 0.67 mmol, 4.5 equiv.) as solids. The biphasic reaction was stirred vigorously 1.5 h, after which saturated aqueous NH_4Cl (5 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resultant yellow solid was suspended in EtOAc (10 mL), to which EtOH was added dropwise until the reaction mixture was homogenous (~ 4 mL). To this was added a solution of CH_2N_2 (1 M in Et_2O) dropwise until a bright yellow color persisted (~200 μL). Excess CH_2N_2 and solvent were removed by evaporation under a steady stream of nitrogen, followed by high vacuum (~5 min). The residue was purified by flash chromatography (silica gel, 20 – 100% EtOAc in hexanes) to provide the ester **17** (74.9 mg, 0.11 mmol, 72% yield). R*f* = 0.44 (100% EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.66 (d, *J*=2.29 Hz, 1 H) 7.48 (d, *J*=8.24 Hz, 2 H) 7.29 (d, *J*=8.70 Hz, 2 H) 7.12 (d, *J*=8.24 Hz, 1 H) 7.08 (d, *J*=8.24 Hz, 2 H) 6.88 (d, *J*=8.70 Hz, 2 H) 6.81 (dd, *J*=8.70, 2.29 Hz, 1 H) 4.63 (d, *J*=11 Hz, 1 H) 4.60 (d, *J*=11.45 Hz, 1 H) 4.54 (d, *J*=10.53 Hz, 1 H) 3.84 – 3.89 (m, 1 H), 3.85 (s, 3 H), 3.81 (s, 3 H) 3.80 (s, 3 H) 3.54 (s, 3 H) 3.39 – 3.48 (m, 1 H) 3.22 (s, 1 H) 3.16 (t, *J*=11.68 Hz, 1 H) 3.02 – 3.11 (m, 1 H) 2.62 – 2.75 (m, 3 H) 2.52 – 2.62 (m, 1 H) 2.37 (dd, *J*=12.36, 1.83 Hz, 1 H) 2.34 (d, *J*=10.99 Hz, 1 H) 2.27 (s, 3 H) 1.61 - 1.76 (m, 3 H) 1.57 (dd, *J*=13.05, 11.22 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 174.09, 159.23, 157.91, 144.66, 138.86, 134.30, 130.98, 129.63 (2C), 129.32 (2C), 126.57 (2C), 124.71, 119.92, 118.75, 113.91 (2C), 112.77, 100.89, 83.52, 81.57, 71.72, 70.98, 61.12, 57.76, 55.95, 55.41, 55.35, 53.54, 52.34, 46.30, 39.62, 37.76, 31.71, 29.23, 22.54, 21.65; IR 3004 (w), 2929 (m), 1717 (m), 1613 (m), 1514 (m), 1493 (m), 1439 (m), 1365 (s), 1280 (m), 1211 (m), 1172 (s), 1147 (m), 1108 (m), 1036 (m), 992 (w), 848 (m), 757 (s), 667 (s) LRMS (APCI) 705.3 $[M + H]^+$; $[\alpha]^{23}_D$ +142.7º (*c* 1.04, $CHCl_3$).



Unsaturated methyl ester (18)

A 25-mL round-bottom flask with stir bar was charged with tertiary alcohol **17** (50.9 mg, 0.072 mmol, 1 equiv.), which had been azeotroped from benzene twice and placed under high vacuum for 30 min. The alcohol was dissolved in THF (3.6 mL), and the flask was cooled to –78 °C under a positive pressure of argon. A 1.3 M *n*-butyllithium solution in hexanes (110 μL, 0.144 mmol, 2 equiv.) was added dropwise, and the solution was stirred 10 min, after which trifluoroacetic anhydride (50.9 μL, 0.36 mmol, 5 equiv.) was added. The reaction mixture was allowed to come to rt over 3 h and was then quenched at 0 °C by slow addition of H_2O. The crude reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organics were washed with a saturated aqueous $NaHCO_3$ solution (1 x 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 60.4 mg of an orange solid. This material consisted of a 3:1

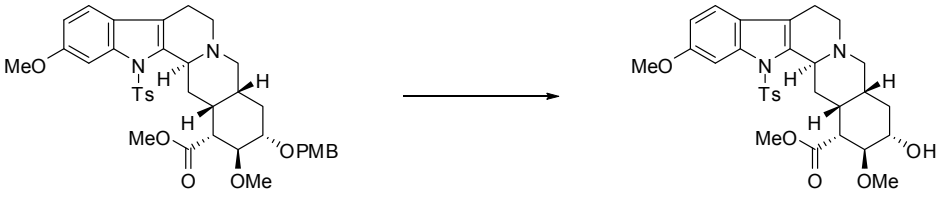
mixture of the tertiary trifluoroacetate to alcohol starting material and was carried forward without further purification. The crude trifluoroacetate, which was azeotroped twice from benzene and placed under high vacuum for 30 min, was transferred to a 25-mL sealed tube and dissolved in 11.5 mL toluene. To this solution was added a stir bar and freshly distilled DBU (86 μL, 10 equiv.) at rt. The flask was then sealed and immersed in a 110 ^{o}C oil bath, and the solution was stirred at this temperature for 15 h. The reaction was removed from the oil bath and the solution was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 1% EtOH/CH_2Cl_2) to provide the unsaturated methyl ester **18** as a pale yellow solid (18.0 mg, 0.026 mmol, 36% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, *J*=1.83 Hz, 1 H) 7.47 (d, *J*=8.42 Hz, 2 H) 7.31 (d, *J*=8.42 Hz, 2 H) 7.16 (d, *J*=8.78 Hz, 1 H) 7.07 (d, *J*=8.05 Hz, 2 H) 6.88 (d, *J*=8.78 Hz, 2 H) 6.82 (dd, *J*=8.42, 2.20 Hz, 1 H) 4.61 (s, 2 H) 4.27 (d, *J*=6.59 Hz, 1 H) 4.08 (d, *J*=11.34 Hz, 1 H) 3.88 (s, 3 H) 3.86 (s, 3 H) 3.80 (s, 3 H) 3.63 – 3.75 (m, 2 H) 3.54 (s, 3 H) 3.06 – 3.25 (m, 1 H) 3.12 (dd, *J*=12.81, 5.12 Hz, 1 H) 2.88 (t, *J*=12.08 Hz, 1 H) 2.67 – 2.79 (m, 2 H) 2.54 – 2.67 (m, 2 H) 2.27 (s, 3 H) 2.16 – 2.25 (m, 1 H) 1.94 – 2.07 (m, 1 H) 1.27 – 1.41 (m, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 168.60, 159.12, 157.87, 144.43, 143.76, 138.52, 135.39, 134.38, 130.71, 129.47, 129.24, 126.60, 126.43, 124.24, 119.22, 118.79, 113.79, 112.59, 100.54, 80.01, 71.10, 61.99, 59.89, 58.96, 55.82, 55.25, 51.72, 45.59, 34.25, 33.71, 29.68, 29.12, 22.31, 21.49; IR 2925(m), 1720 (m), 1613 (w), 1513 (m), 1366 (m), 1248 (m), 1172 (m), 1115 (m), 911 (s), 813 (m), 734 (s), 669 (m); LRMS (APCI) 687.4 $[M + H]^+$; $[\alpha]^{24}_D$ +162.4 (*c* 1.01, $CHCl_3$).



***N*-tosyl, 18-(4-methoxybenzyloxy)-methyl reserpate (19)**

A 2-mL Biotage microwave vial was brought into a glove box and charged with a stir bar and unsaturated ester **18** (5.0 mg, 7.3 μmol, 1 equiv.) which had been azeotroped from benzene (3x) and placed under high vacuum for 30 min. Iridium complex **20** (11.0 mg, 7.3 μmol, 1 equiv.) was added to the vial followed by CH_2Cl_2 (360 μL), which had been degassed through three freeze-pump-thaw cycles. The vial was sealed with a Teflon-lined pressure seal cap and transferred out of the glove box. The vial was evacuated and back-filled with H_2 (4x), after which it was stirred 16 h at rt under a balloon of H_2. The reaction mixture was then concentrated in vacuo. Analysis of the crude reaction mixture by ^{1}HNMR (comparison of the PMB Bn signals) showed a 6:1 diastereomeric ratio of olefin hydrogenation products. The mixture was purified by preparatory thin layer chromatography to provide recovered unsaturated ester **18** (2.3 mg, 3.3 μmol, 46% recovered starting material) and the desired saturated ester **19** as a white solid (2.2 mg, 3.2 μmol, 44% yield, 81% based on recovered starting material). R*f* = 0.51 (EtOAc); ^{1}H NMR (500 MHz,

$CDCl_3$) δ: 7.61 (d, *J*=2.29 Hz, 1 H) 7.32 (d, *J*=8.24 Hz, 2 H), 7.32 (m, 2 H), 7.05 (d, *J*=8.70 Hz, 1 H) 7.02 (d, *J*=8.24 Hz, 2 H) 6.90 (d, *J*=8.70 Hz, 2 H) 6.80 (dd, *J*=8.24, 2.29 Hz, 1 H) 4.64 (d, *J*=10.99 Hz, 1 H) 4.58 (d, *J*=10.99 Hz, 1 H) 4.40 (dd, *J*=5.27, 2.52 Hz, 1 H) 3.89 (s, 3 H) 3.88 (s, 3 H) 3.83 (s, 3 H) 3.72 (dd, *J*=10.99, 9.16 Hz, 1 H) 3.67 (s, 3 H) 3.33 – 3.42 (m, 1 H) 3.12 (dd, *J*=13.28, 5.49 Hz, 1 H) 2.93 – 3.03 (m, 1 H) 2.79 (dd, *J*=11.45, 4.58 Hz, 1 H) 2.85 (ddt, *J*=17.06, 5.72, 2.80, 2.80 Hz, 1 H) 2.64 (dt, *J*=14.54, 3.03 Hz, 1 H) 2.52 (dd, *J*=10.99, 5.04 Hz, 1 H) 2.34 (dd, *J*=11.68, 1.60 Hz, 1 H) 2.27 (s, 3 H) 2.15 – 2.26 (m, 2 H) 2.09 (td, *J*=13.28, 11.90 Hz, 1 H) 1.92 – 2.01 (m, 1 H) 1.87 (dt, *J*=13.16, 3.95 Hz, 1 H) 1.72 (d, *J*=12.36 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 172.51, 159.01, 157.97, 144.23, 140.33, 135.72, 132.38, 131.12, 129.12 (2C), 128.82 (2C), 126.74, 125.65, 123.95, 118.49, 113.72, 113.06, 102.50, 82.88, 79.37, 71.19, 61.13, 56.27, 55.89, 55.26, 52.06, 51.89, 50.66, 50.08, 33.63, 32.33, 30.36, 26.27, 21.49, 18.15.; FTIR (neat, cm^{-1}); 2930 (br m), 1737 (m), 1614 (m), 1514 (m), 1364 (m), 1278 (m), 1171 (s), 1093 (m), 911 (w), 814 (w), 735 (s); LRMS (APCI) 689.3 $[M + H]^+$; $[\alpha]^{23}_D$ + 166.0 (*c* 1.35, $CHCl_3$).

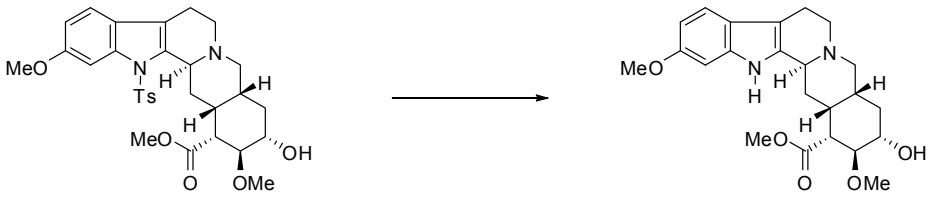


19 **S5**

***N*-tosyl-methyl reserpate (S5)**

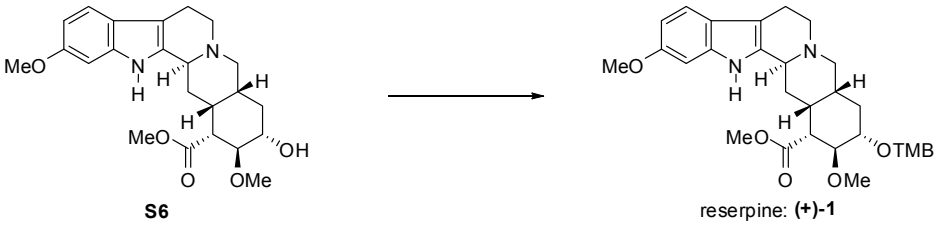
A 2-dram vial with a septum cap and stir bar was charged with PMB ether **19** (11.4 mg, 16.5 μmol, 1 equiv.), followed by CH_2Cl_2 (1.1 mL) and 1,3-dimethoxybenzene (6.5 μL, 49.5 μmol, 3 equiv.). The vial was cooled to 0 °C, and a TfOH solution in CH_2Cl_2 (44 μL of a 50 μL TfOH/1 mL CH_2Cl_2, 24.7 μmol, 1.5 equiv.) was added dropwise via microliter syringe. Consumption of the starting material was monitored using LC/MS (APCI). Upon completion (~30 min after addition of TfOH), the reaction was quenched with a half-saturated aqueous solution of $NaHCO_3$ (1 mL) and diluted with CH_2Cl_2 (0.5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resultant residue was purified (silica gel, 5-10% MeOH/CH_2Cl_2, followed by an eluent of 10:1:1:1 EtOAc:H_2O:MeOH:acetone), to afford alcohol **S5** as a pale yellow solid (8.1 mg, 14.2 μmol, 86% yield). R*f* = 0.28 (10:1:1:1 EtOAc:H_2O:MeOH:acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.60 (d, *J*=1.95 Hz, 1 H) 7.31 (d, *J*=8.30 Hz, 2 H) 7.04 (d, *J*=8.30 Hz, 1 H) 7.01 (d, *J*=7.81 Hz, 2 H) 6.78 (dd, *J*=8.30, 2.44 Hz, 1 H) 4.39 (br. s., 1 H) 3.88 (s, 3 H) 3.87 (s, 3 H) 3.65 (s, 3 H) 3.58 (td, *J*=10.74, 8.79 Hz, 1 H) 3.52 (m, 1 H) 3.11 (dd, *J*=12.94, 5.62 Hz, 1 H) 2.96 (td, *J*=12.33, 4.64 Hz, 1 H) 2.76 – 2.87 (m, 1 H) 2.79 (dd, *J*=11.23, 4.88 Hz, 1 H) 2.64 (dt, *J*=14.41, 3.30 Hz, 1 H) 2.50 (dd, *J*=10.74, 4.88 Hz, 1 H) 2.35 (d, *J*=11.72 Hz, 1 H) 2.26 (s, 3 H) 2.07 – 2.23 (m, 3 H) 1.93 - 2.03 (m, 1 H) 1.71 – 1.84 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 172.57, 157.99, 144.29, 140.33, 135.65, 132.38,

128.86 (2C), 126.74 (2C), 125.64, 123.97, 118.54, 113.07, 102.51, 81.35, 75.30, 61.18, 56.27, 55.90, 51.98, 51.44, 50.65, 50.05, 33.79, 32.79, 32.52, 26.43, 21.50, 18.21; FTIR (neat, cm^{-1}); 1737 (m), 1614 (m), 1493 (w), 1365 (m), 1278 (w), 1254 (w), 1172 (s), 1089 (m), 909 (m), 812 (w), 735 (s); LRMS (APCI) 569.2 $[M + H]^+$; $[\alpha]^{23}_D$ + 211.3 (*c* 0.81, $CHCl_3$).



(+)-Methyl reserpate (S6)

A 20-mL vial was charged with a stir bar, **S5** (10.0 mg, 0.018 mmol, 1 equiv.), and MeOH (3.2 mL) under a positive pressure of N_2. To this was added Na_2HPO_4 (75.1 mg, 0.51 mmol, 30 equiv.) as a solid in one portion, followed by 5%-sodium/mercury amalgam (32 mg, 0.070 mmol, 4 equiv.). The heterogeneous mixture was stirred vigorously at rt and consumption of the **S5** was monitored using LC/MS (APCI). After 4 h, a second portion of Na_2HPO_4 (38 mg, 0.26 mmol, 15 equiv.) was added, followed by 5%-sodium/mercury amalgam (20 mg, 0.043 mmol, 2.7 equiv.). Upon completion (1 h after second addition of reagents), the reaction mixture was transferred away from the bead of mercury that had formed, using CH_2Cl_2 (10 mL) to complete the transfer. The solution was washed with H_2O (2 x 5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resultant residue was purified by flash chromatography (10% MeOH/CH_2Cl_2) to afford, as a white solid, **S6** (5.0 mg, 0.012 mmol, 69%). R*f* = 0.19 (10:1:1:1 EtOAc:H_2O:MeOH:acetone); ^{1}H NMR data were in agreement with literature values.[9] ^{13}C NMR (126 MHz, $CDCl_3$) δ: 173.17, 156.38, 136.78, 128.84, 121.63, 118.51, 109.31, 107.13, 95.24, 80.95, 75.00, 60.93, 55.79, 54.20, 51.97, 51.15, 51.04, 49.00, 33.97, 32.40, 32.12, 23.97, 16.48; FTIR (neat, cm^{-1}); 3372 (m), 2929 (m), 2852 (w), 1723 (m), 1629 (w), 1463 (m), 1279 (w), 910 (s), 732 (s); LRMS (APCI) 415.1 $[M + H]^+$; $[\alpha]^{22}_D$ +96.8 (*c* 0.23, $CHCl_3$).



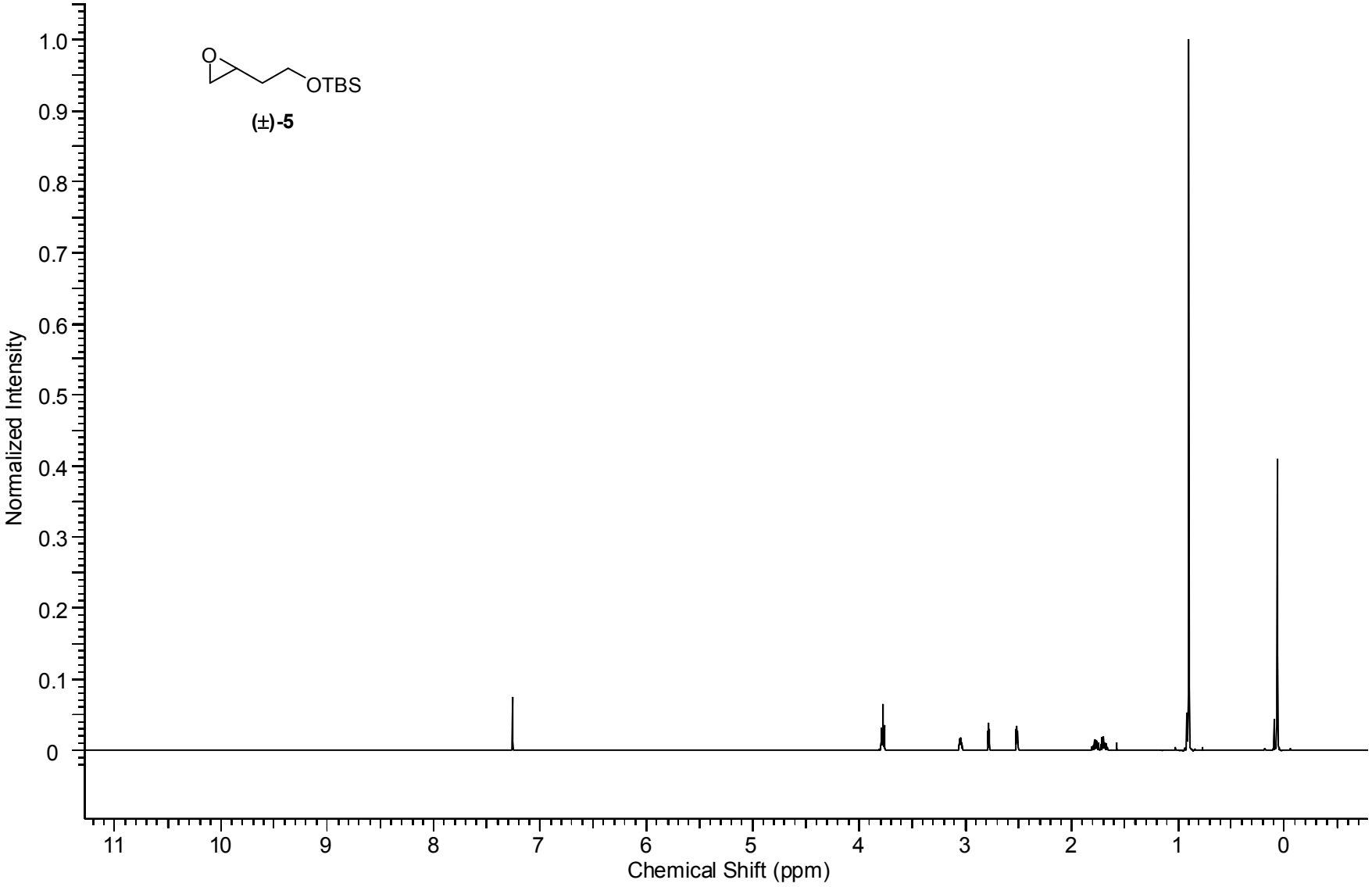
[9] Lounasmaa, M.; Tolvanen, A.; Kan, S.-K. *Heterocycles* **1985**, *23*, 371–375.

Reserpine (+)-(1)[10]

A 1-dram vial with a screw-top septum cap was charged with a stir bar, secondary alcohol **S6** (5.0 mg, 0.012 mmol, 1 equiv.) and 3,4,5-trimethoxybenzoyl chloride (16.7 mg, 0.072 mmol, 5 equiv). Freshly distilled pyridine (300 μL) was added under argon, the vial was wrapped in aluminum foil, and the reaction mixture was allowed to stir at rt 4 d under argon. Upon completion of the reaction, the pyridine was removed in vacuo. The crude residue was cooled to 0 ^{o}C, dissolved in CH_2Cl_2 (2 mL) and treated dropwise with a saturated aqueous solution of Na_2CO_3 (2 mL). The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organics were washed once with deionized water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The resultant solid was purified by flash chromatography (silica gel, 70% EtOAc in hexanes) to provide (+)-reserpine (6.6 mg, 0.011 mmol, 90% yield) as an off-white solid. The synthetic sample of (+)-reserpine gave identical TLC R*f*, ^{1}H NMR, and ^{13}C NMR data to a commercial sample of (–)-reserpine from Aldrich, and were in agreement with literature values (^{1}H NMR, ^{13}C NMR).[9,11] R*f* = 0.21 (EtOAc) ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.48 (br. s, 1 H) 7.34 (d, *J*=8.79 Hz, 1 H) 7.32 (s, 2 H) 6.85 (d, *J*=2.05 Hz, 1 H) 6.78 (dd, *J*=8.64, 2.20 Hz, 1 H) 5.06 (ddd, *J*=11.64, 9.45, 4.98 Hz, 1 H) 4.48 (br. s., 1 H) 3.92 (s, 9 H) 3.91 (m, 1 H) 3.85 (s, 3 H) 3.82 (m, 3 H) 3.51 (s, 3 H) 3.12 – 3.25 (m, 2 H) 3.06 (dd, *J*=12.15, 2.78 Hz, 1 H) 2.96 (m, 1 H) 2.70 (dd, *J*=11.13, 4.69 Hz, 1 H) 2.44 – 2.54 (m, 2 H) 2.28 – 2.41 (m, 2 H) 2.04 – 2.12 (m, 1 H) 2.00 (ddd, *J*=12.67, 4.17, 0.73 Hz, 1 H) 1.92 (d, *J*=11.72 Hz, 1 H) 1.80 (d, *J*=14.64 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 172.79, 165.39, 156.28, 152.98, 142.28, 136.31, 130.36, 125.39, 122.20, 118.59, 109.09, 108.23, 106.78, 95.19, 77.98, 77.82, 60.93, 60.77, 56.27, 55.83, 53.72, 51.84, 51.77, 51.23, 49.06, 34.04, 32.31, 29.75, 24.35, 16.81; IR 3433 (w), 2987 (w), 1730 (m), 1711 (m), 1587 (m), 1499 (m), 1456 (m), 1412 (m), 1331 (s), 1273 (s), 1249 (m), 1225 (s), 1186 (w), 1120 (s), 1062 (m), 1002 (m), 976 (m), 763 (m). LRMS (APCI) 609.2 $[M + H]^+$; $[\alpha]^{22}_{D}$ +114.6 (*c* 0.20, $CHCl_3$).

[10] This procedure was adapted the Stork synthesis of reserpine: Stork, G.; Tang, P. C.; Casey, M.; Goodman, B.; Toyota, M. *J. Am. Chem. Soc.* **2005**, *127*, 16255.

[11] Martin, S. F.; Rüeger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124.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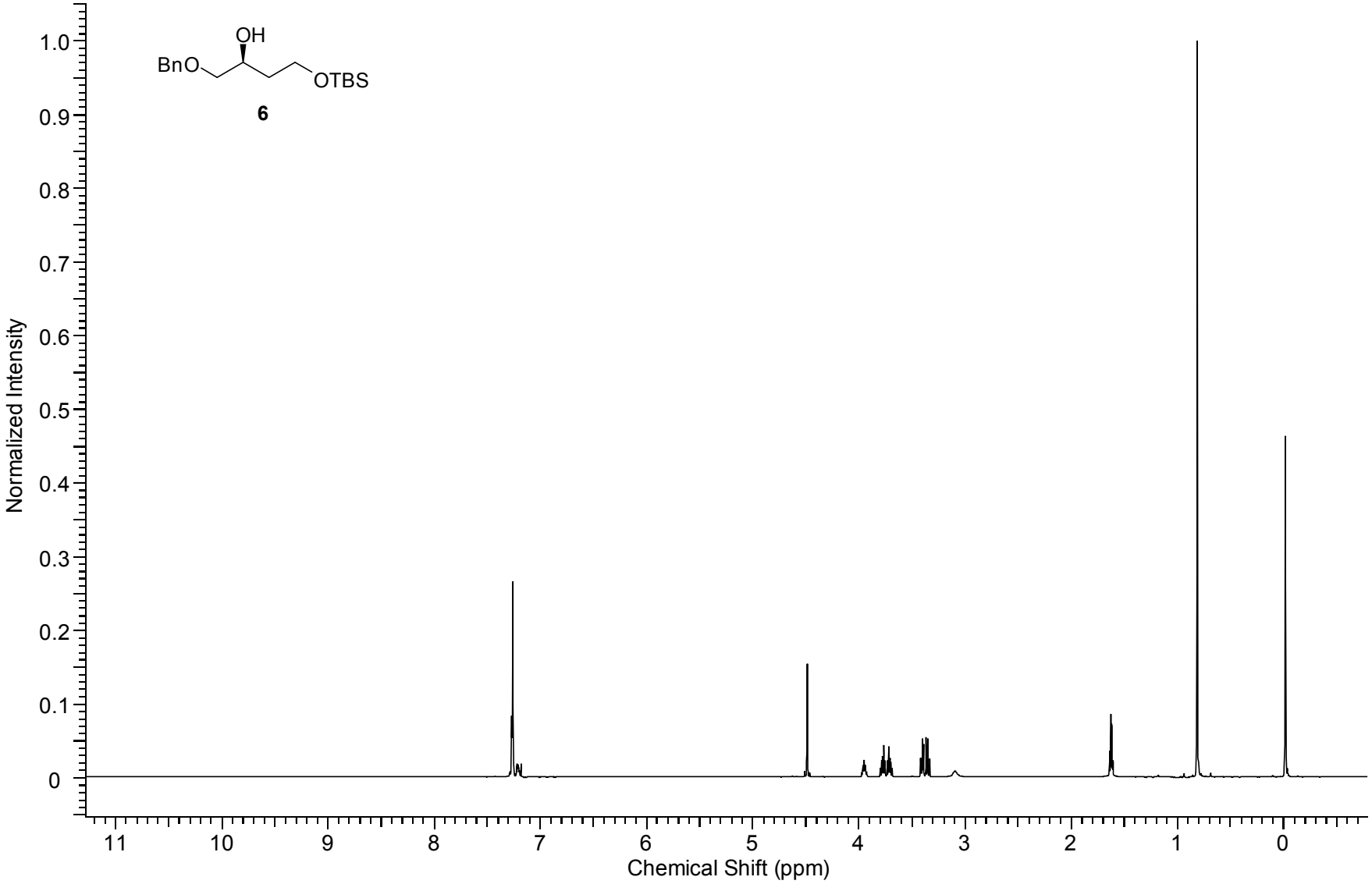
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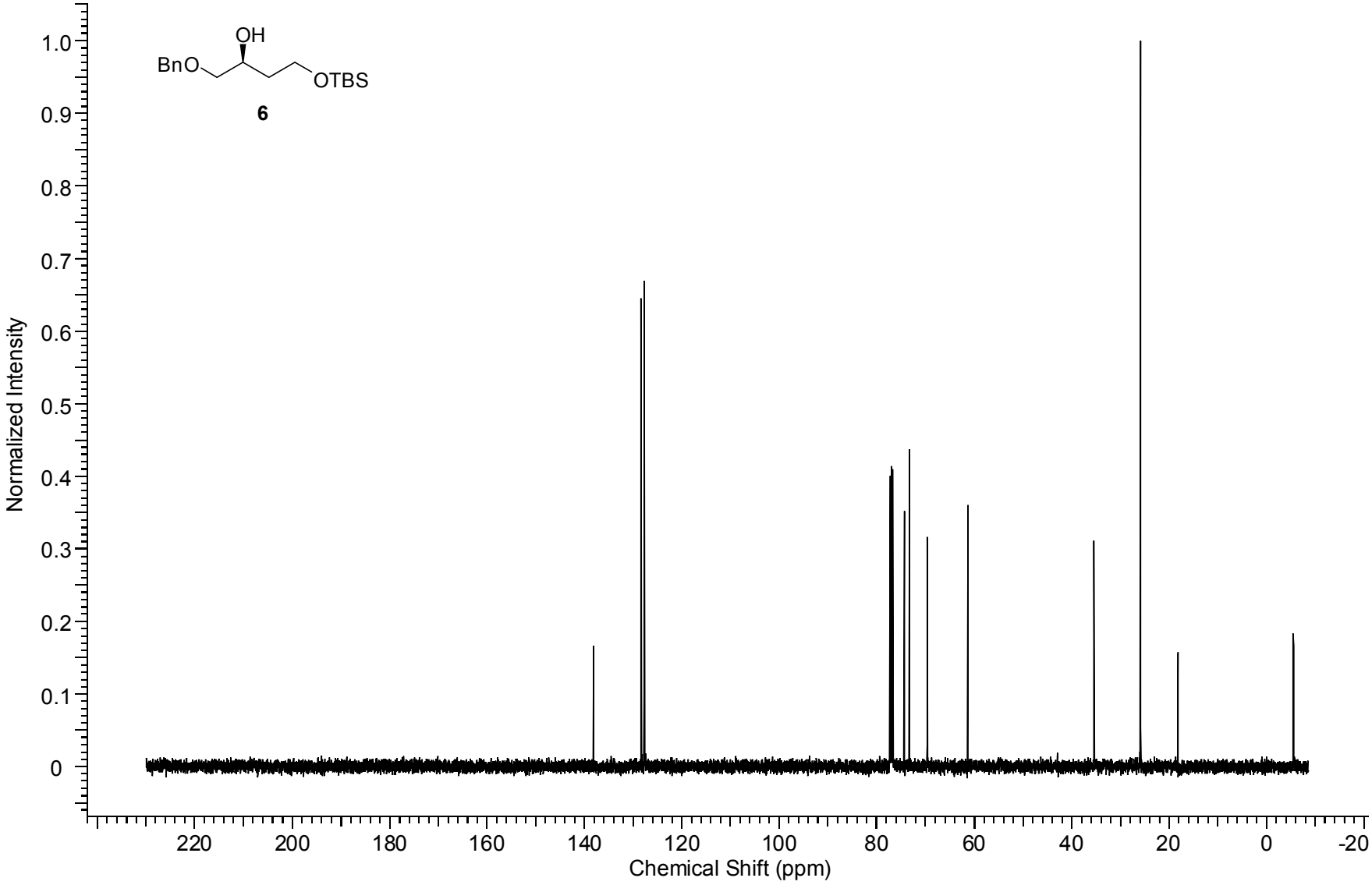
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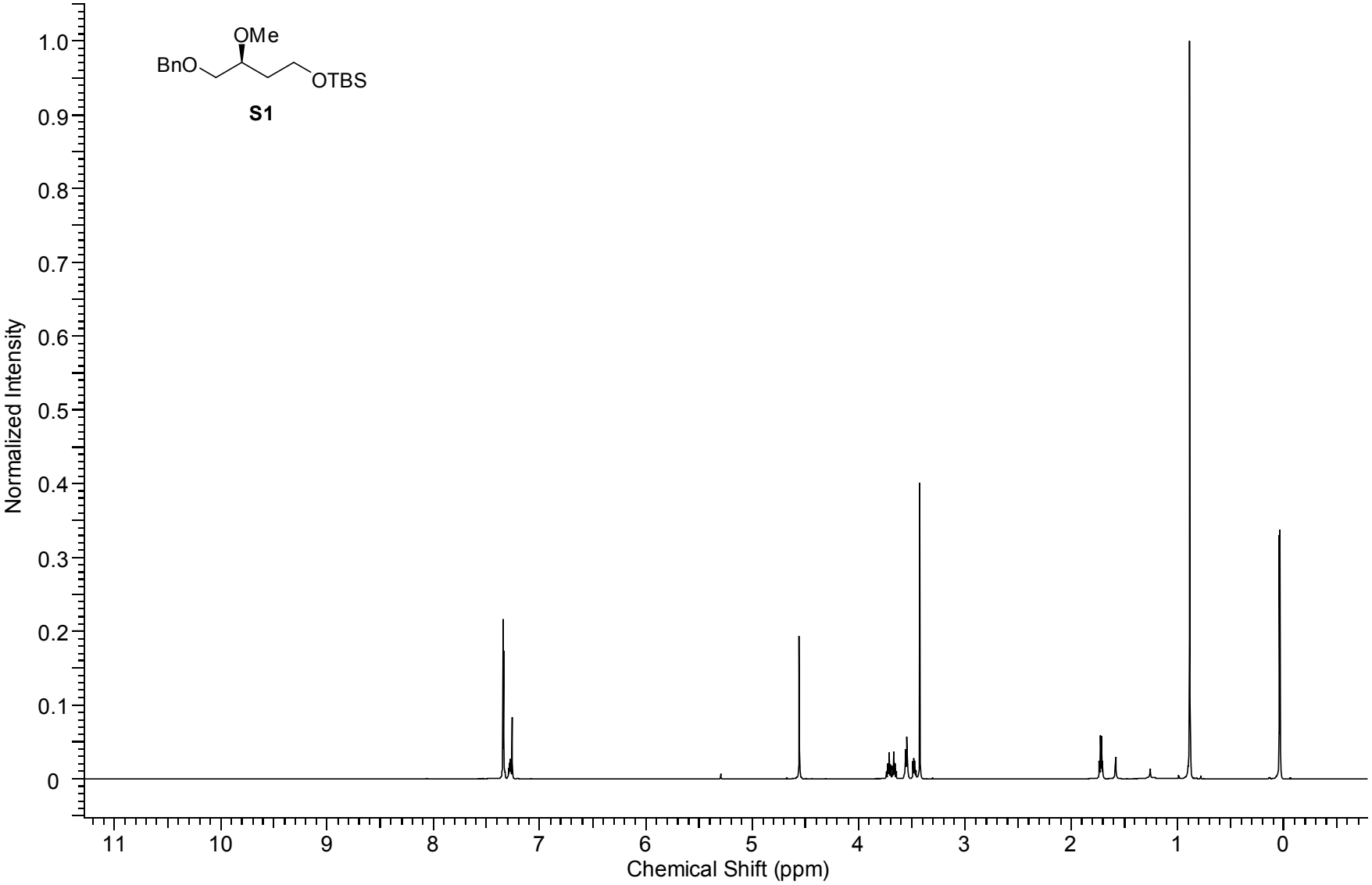
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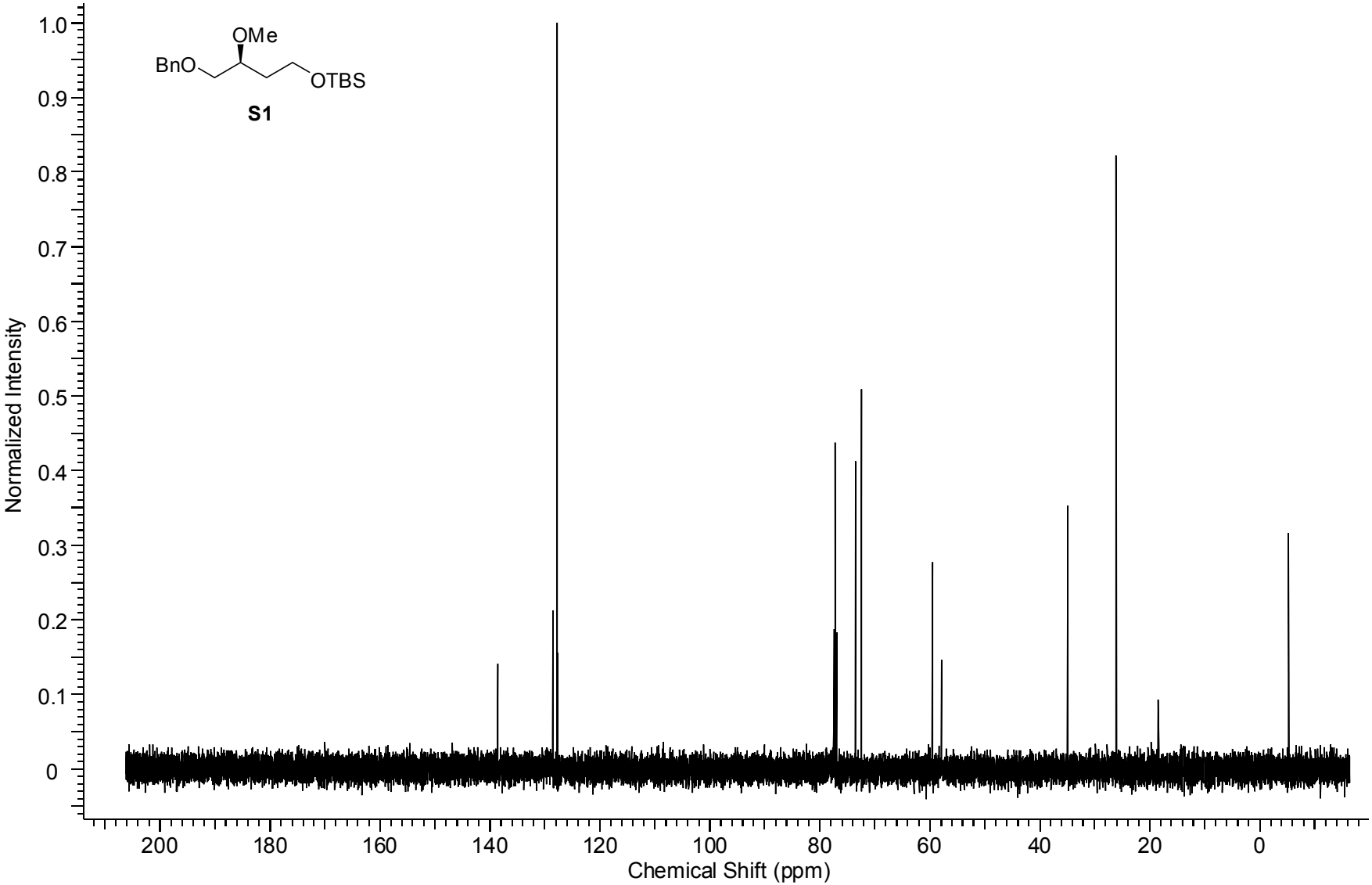
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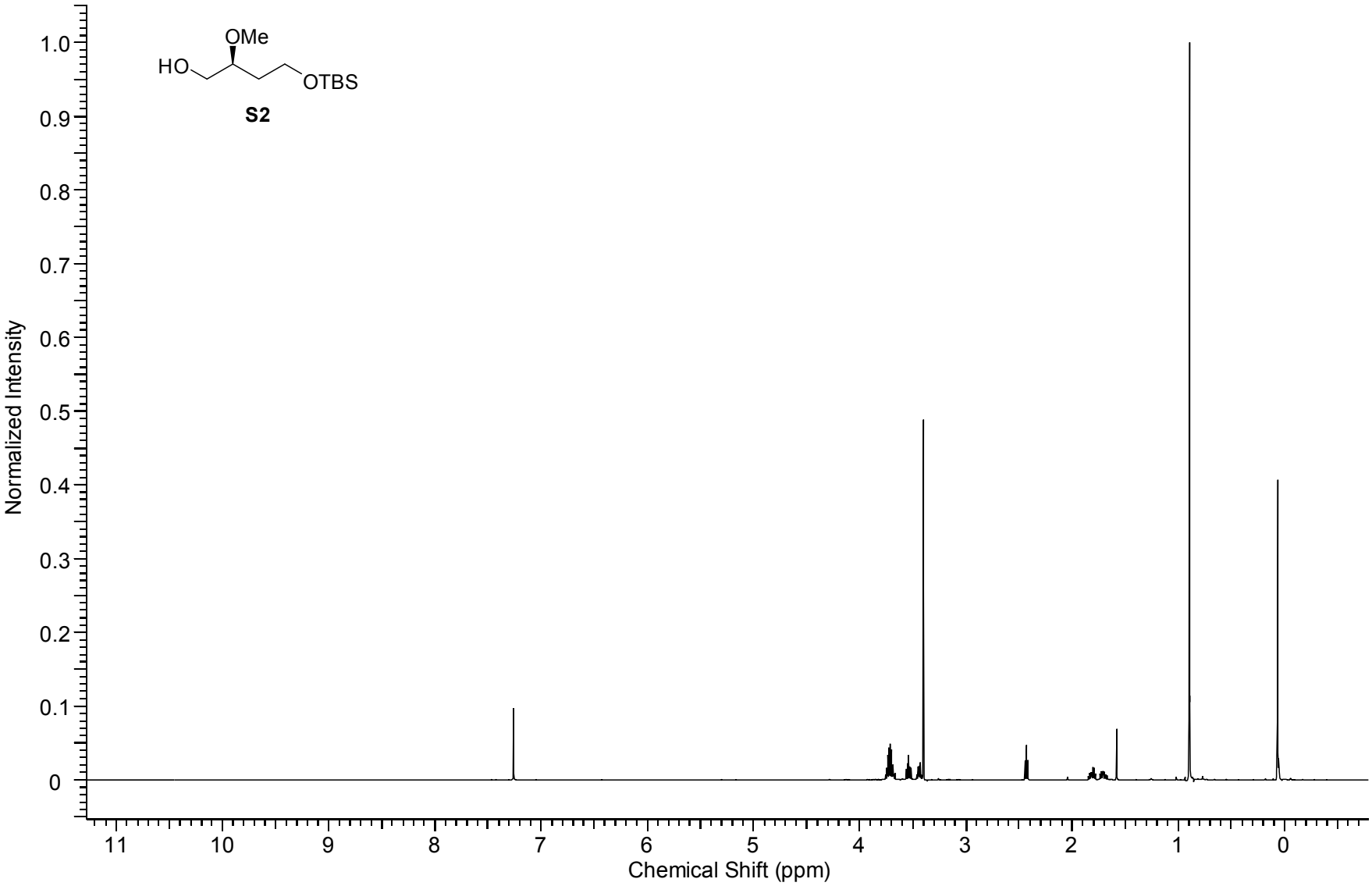
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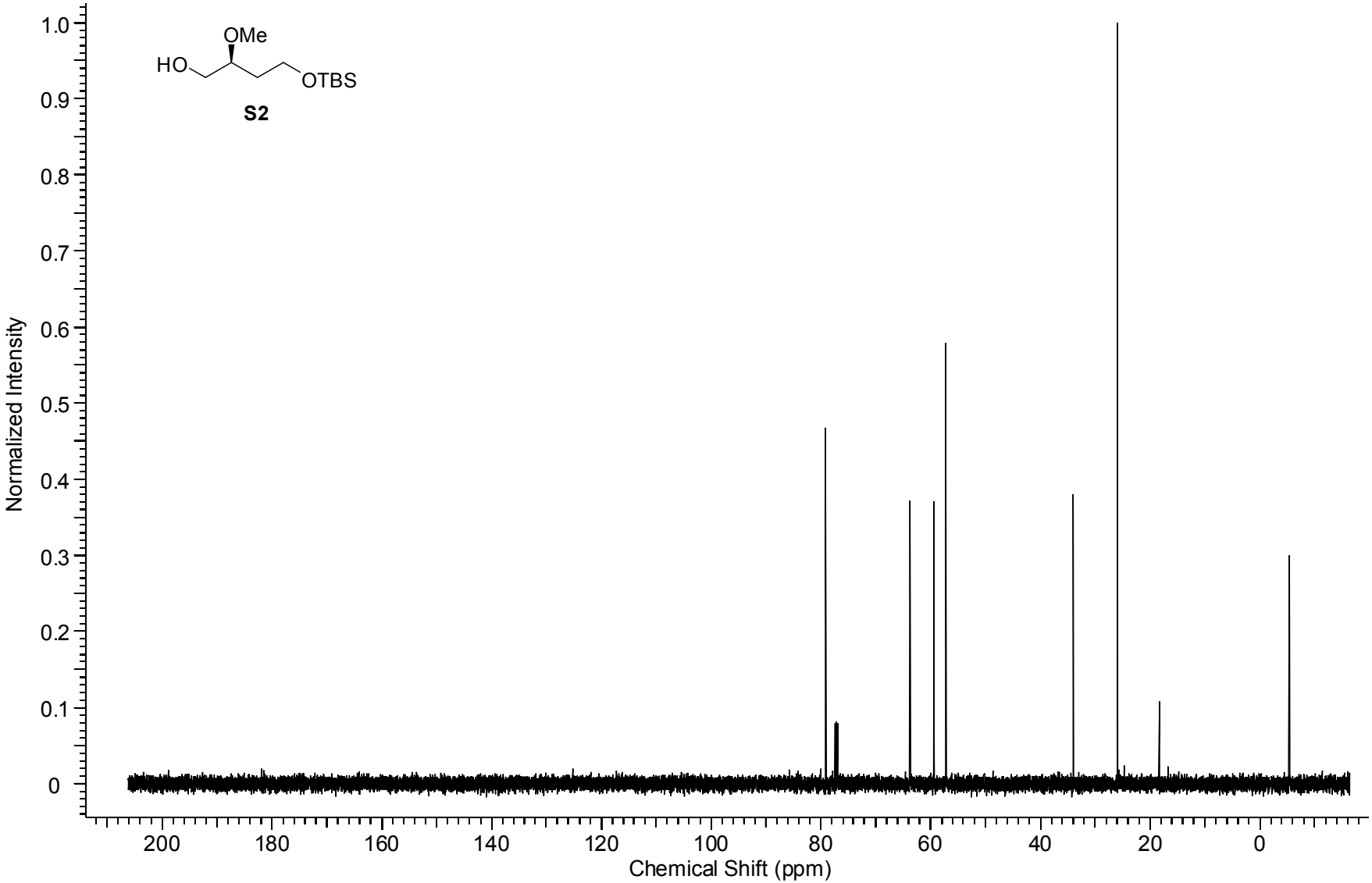
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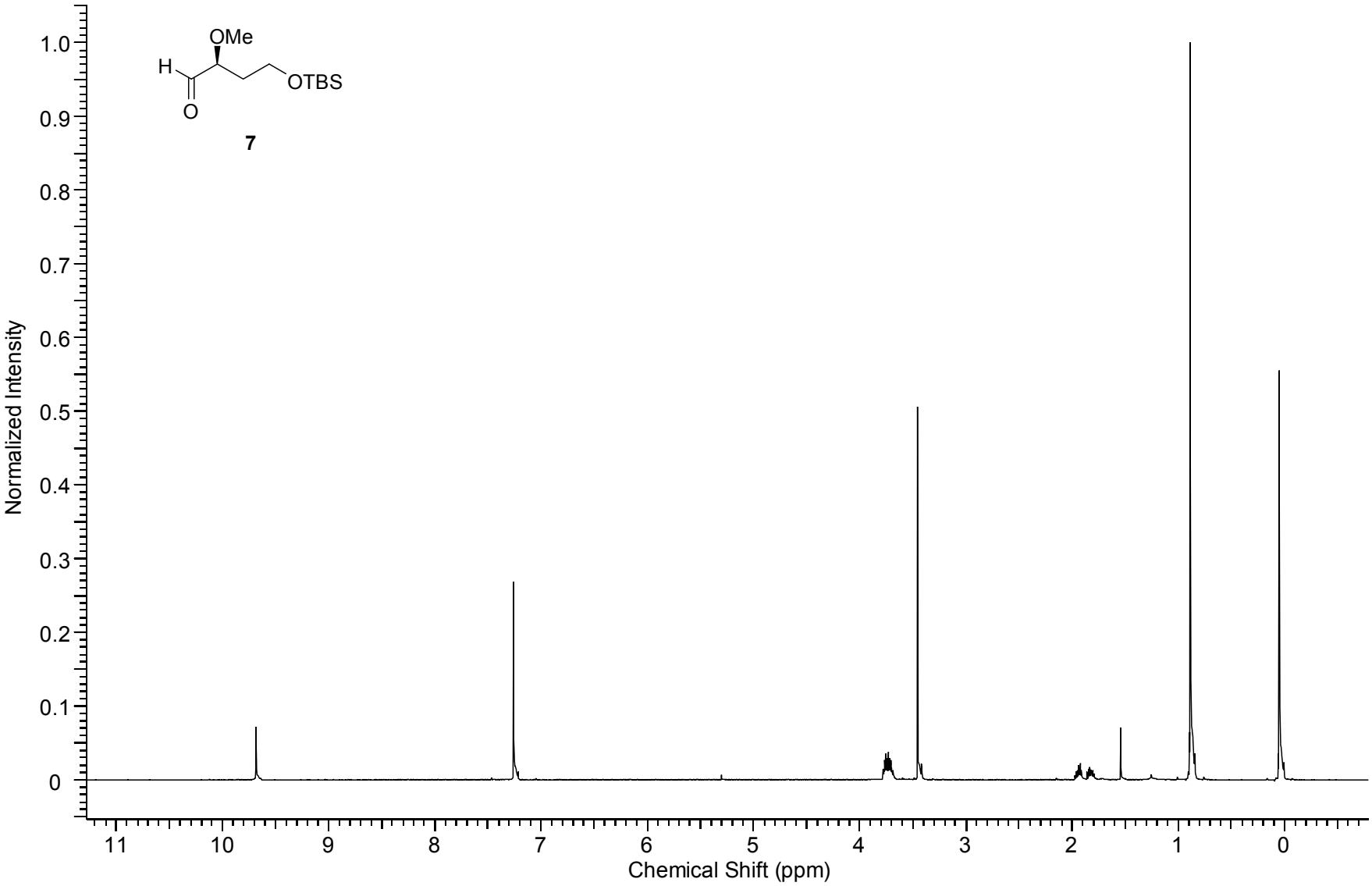
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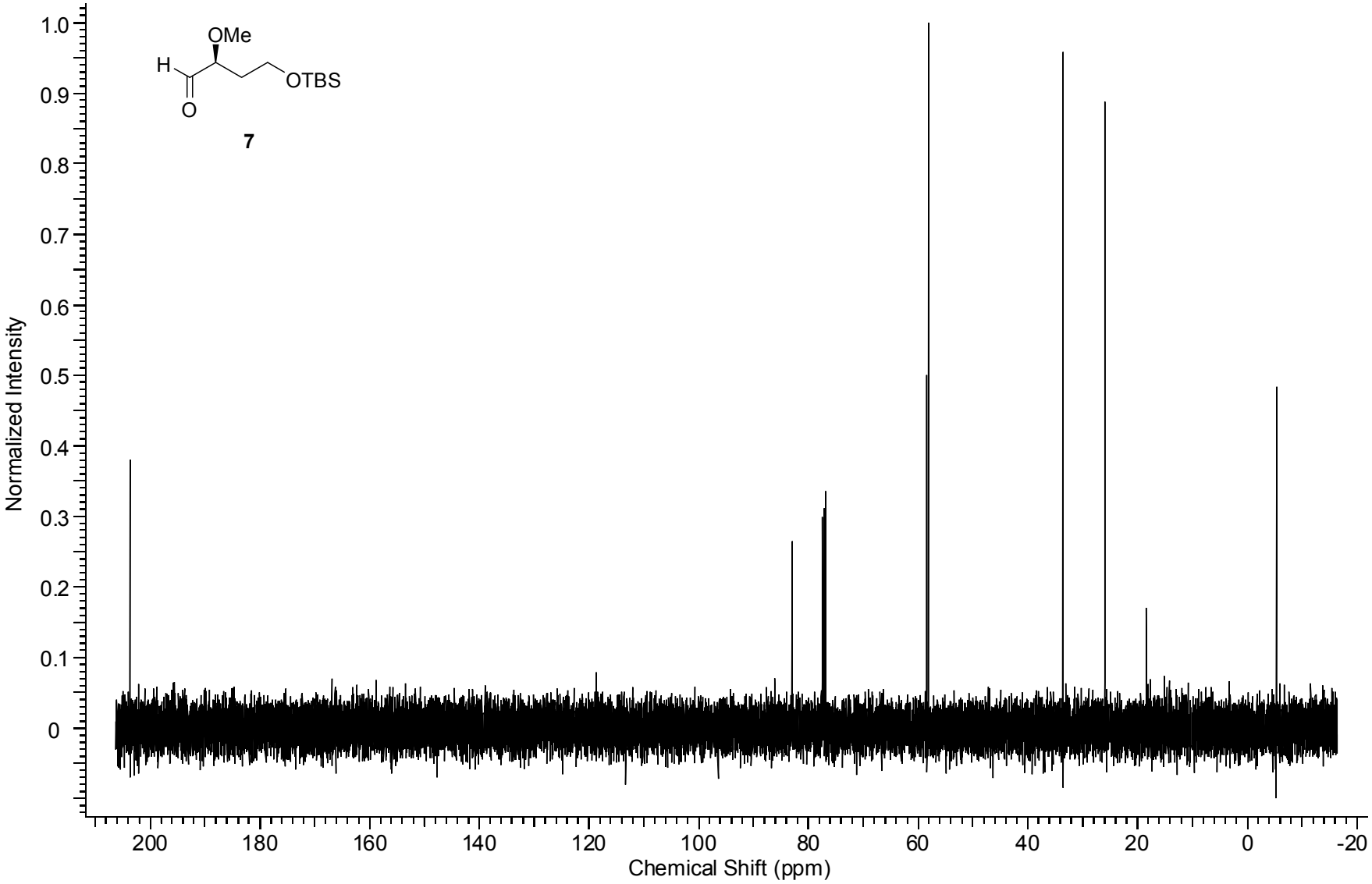
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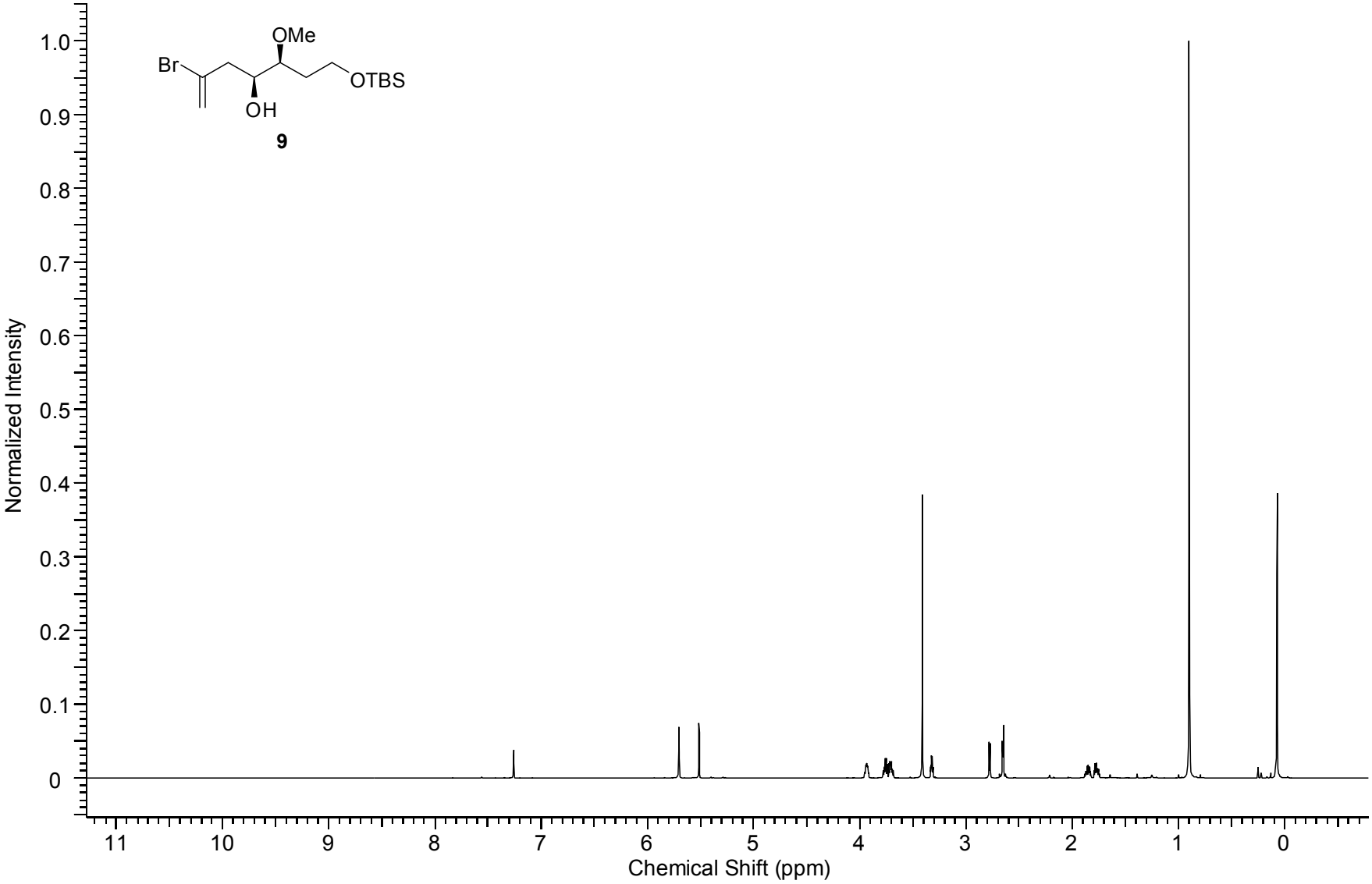
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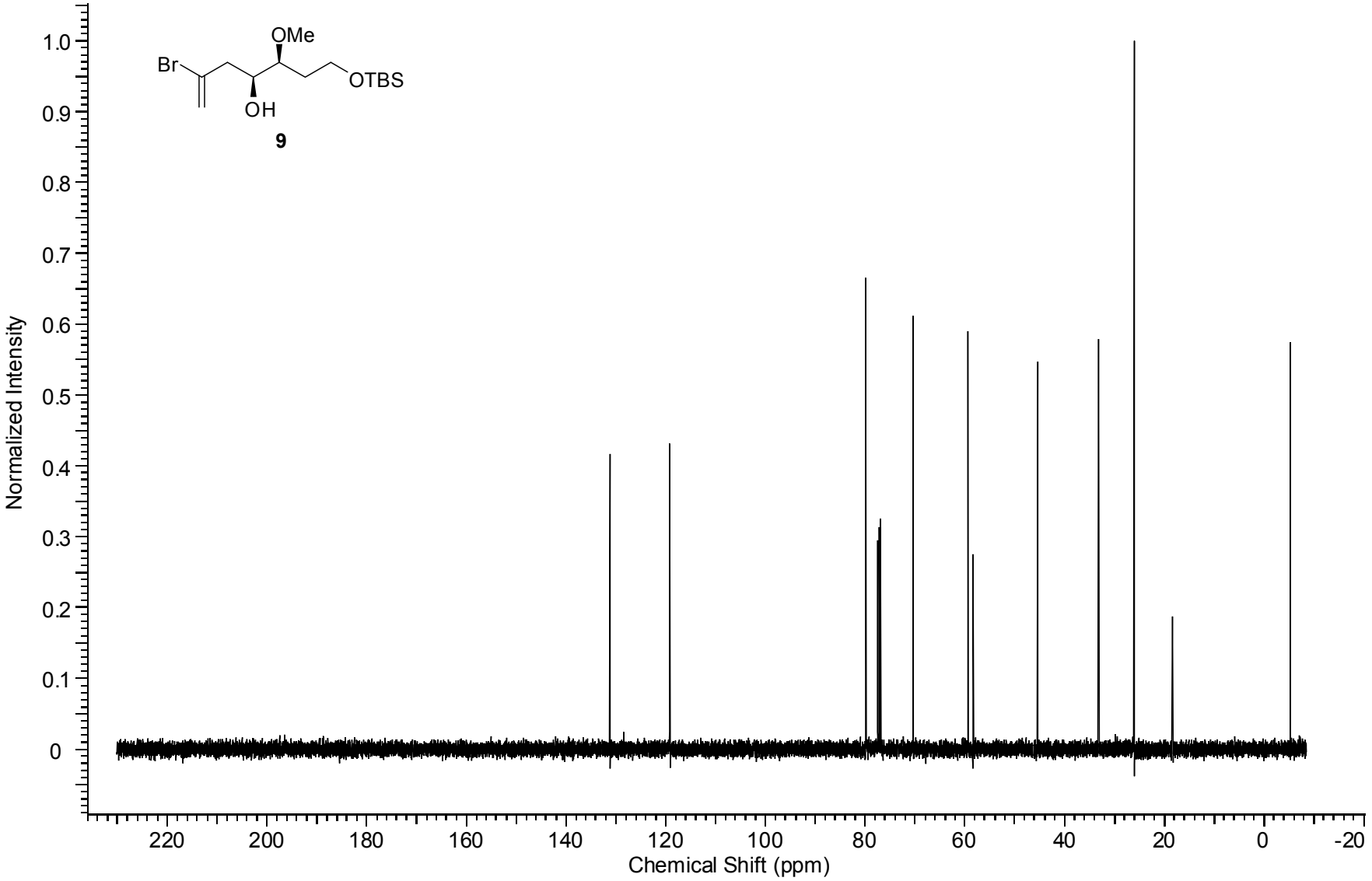
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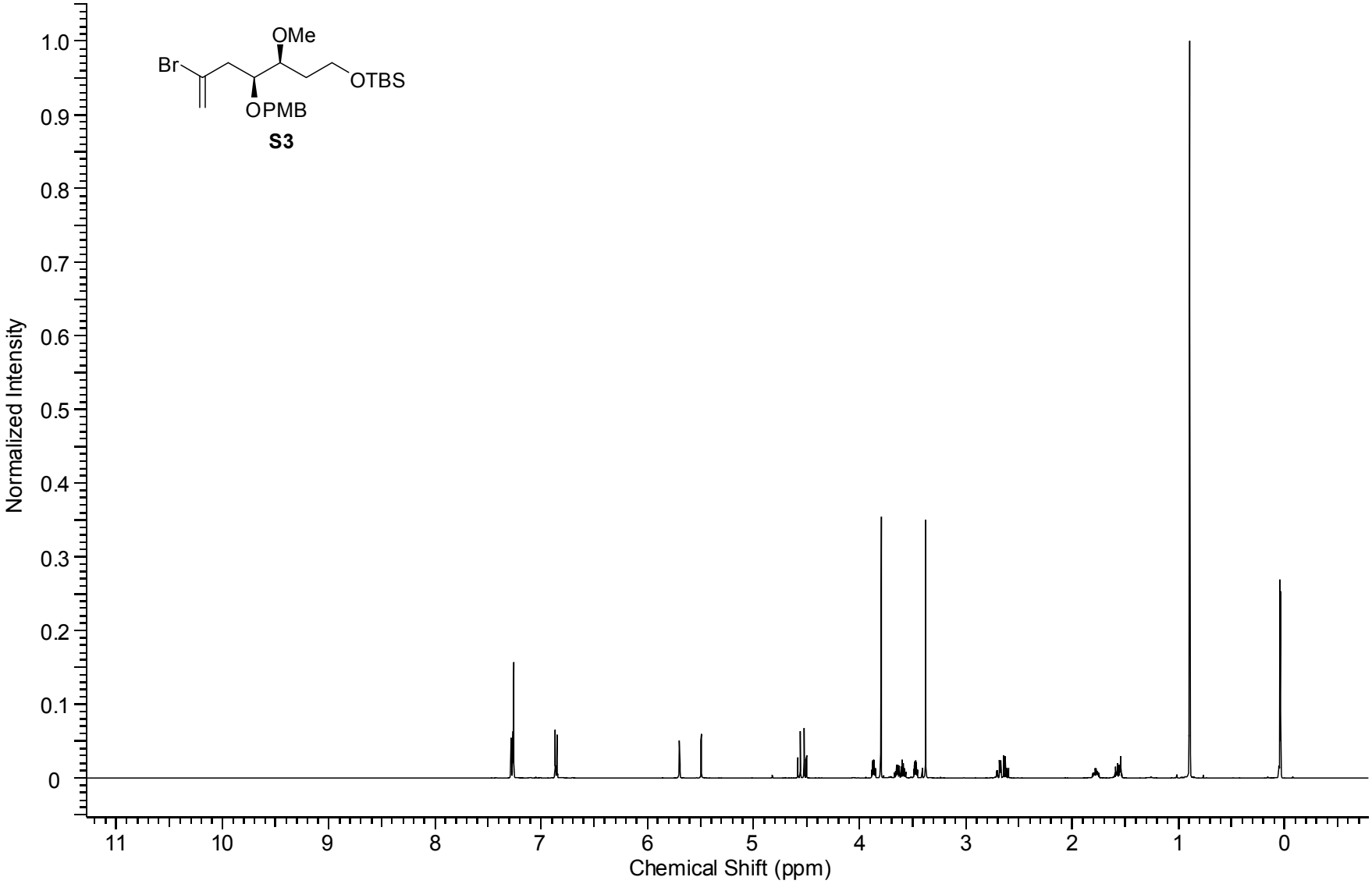
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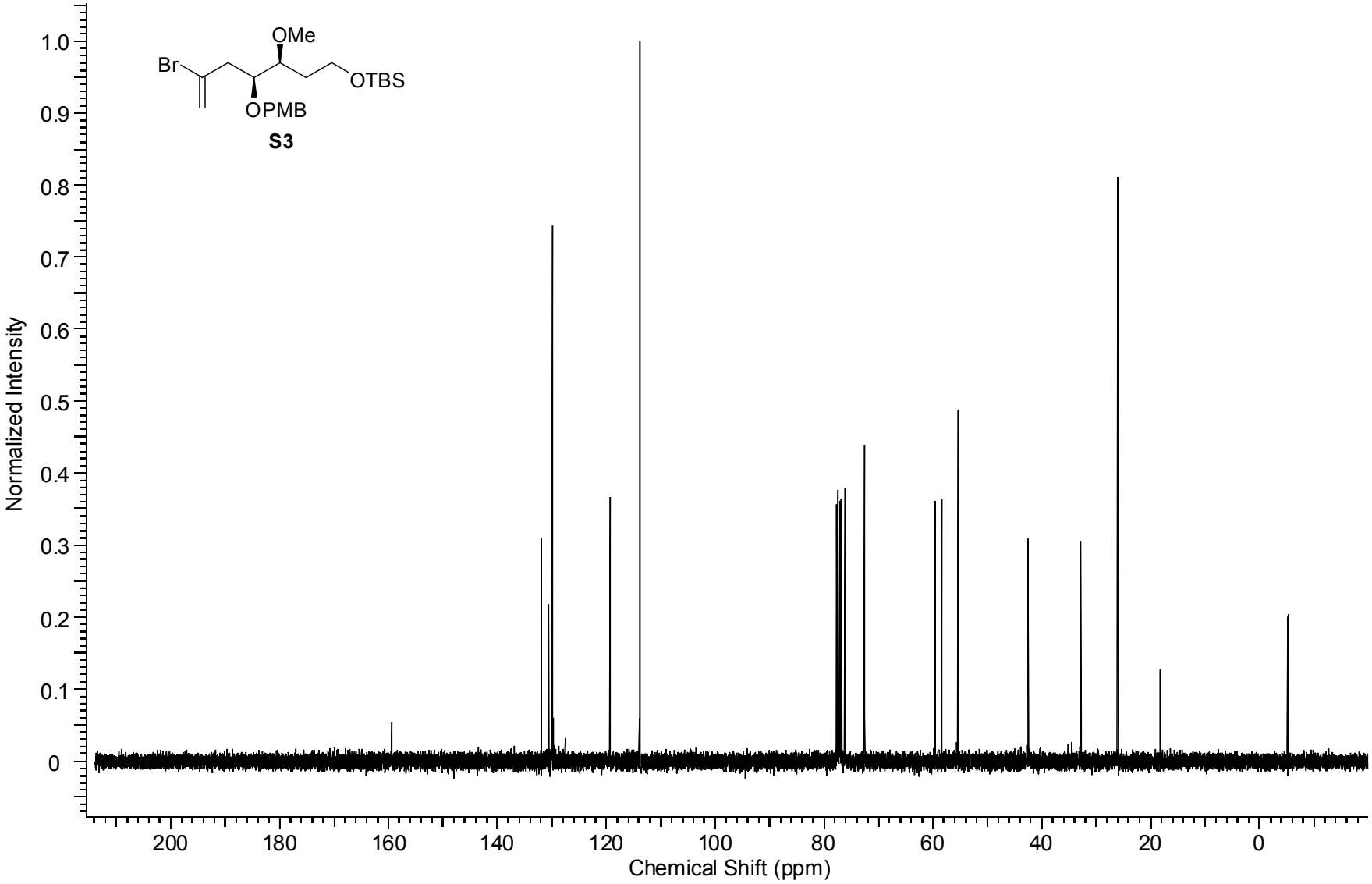
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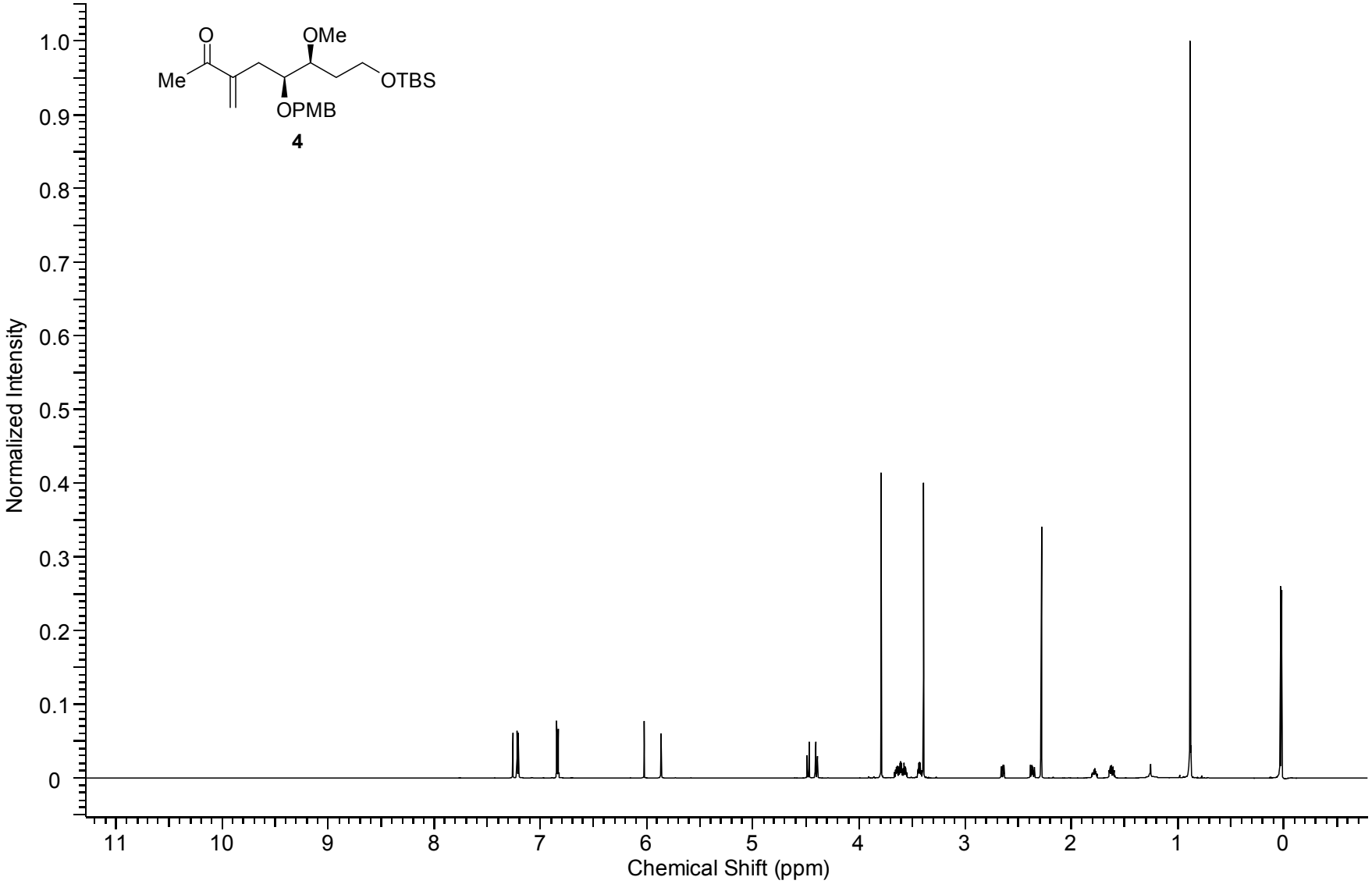
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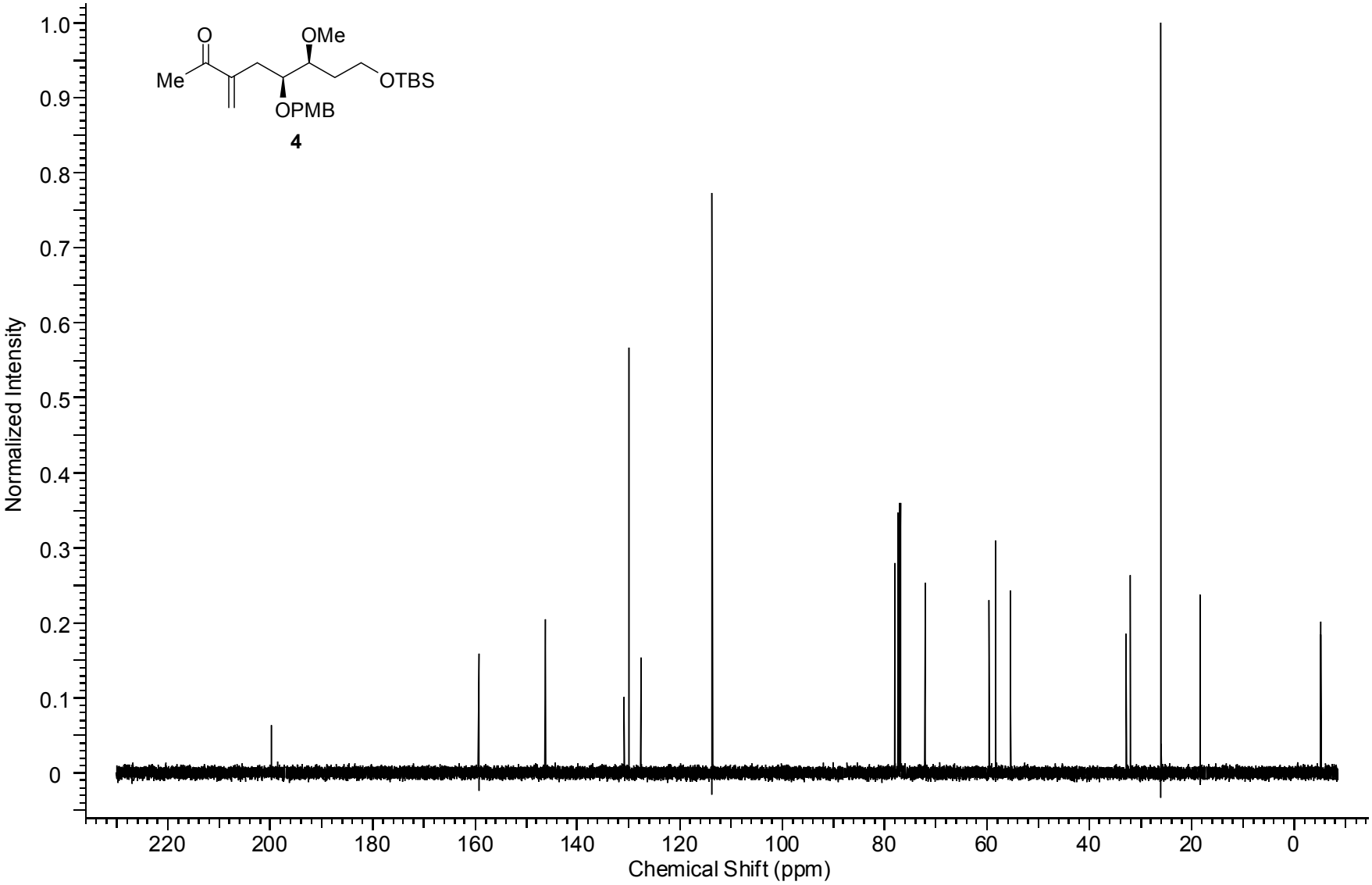
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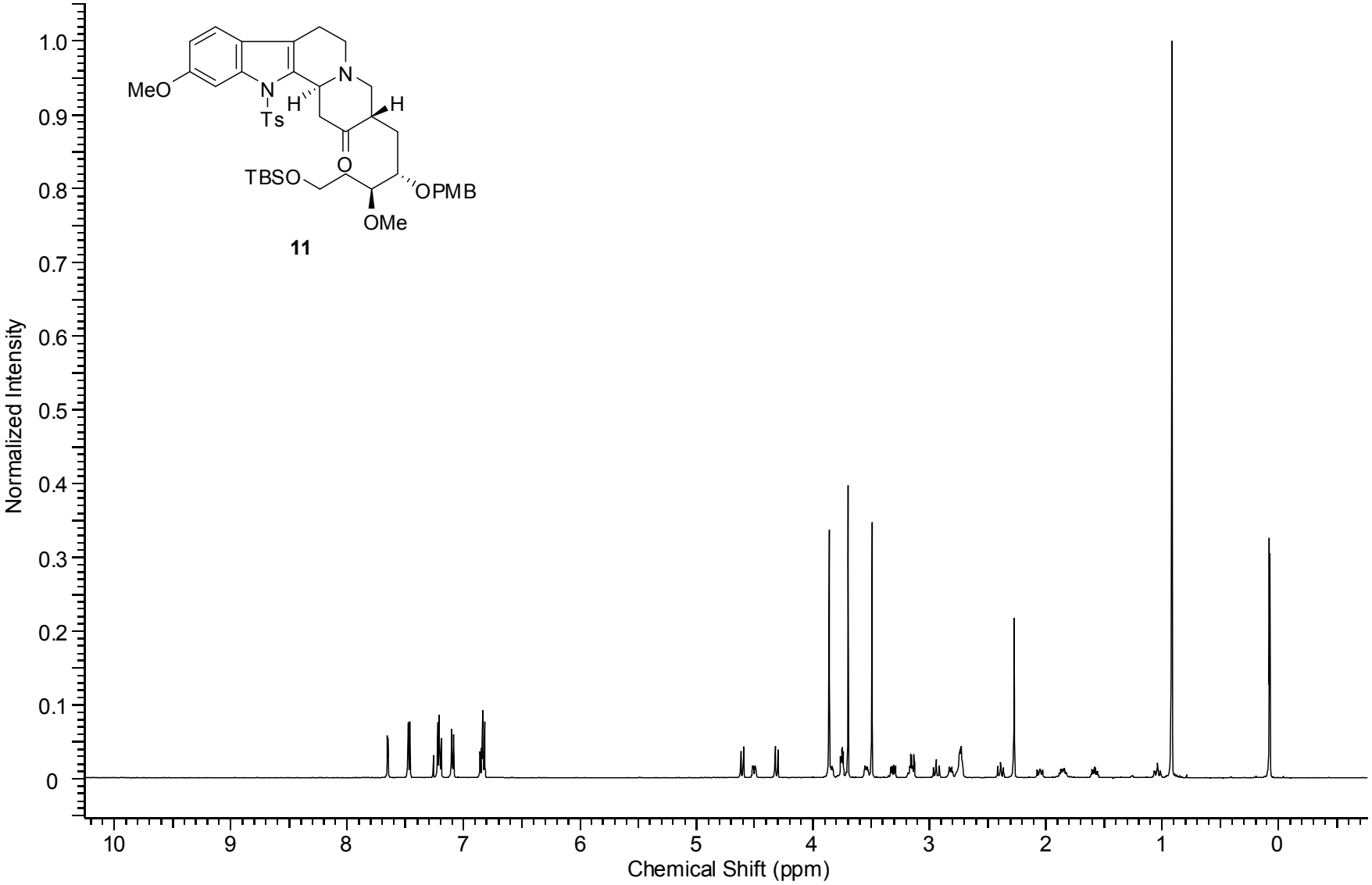
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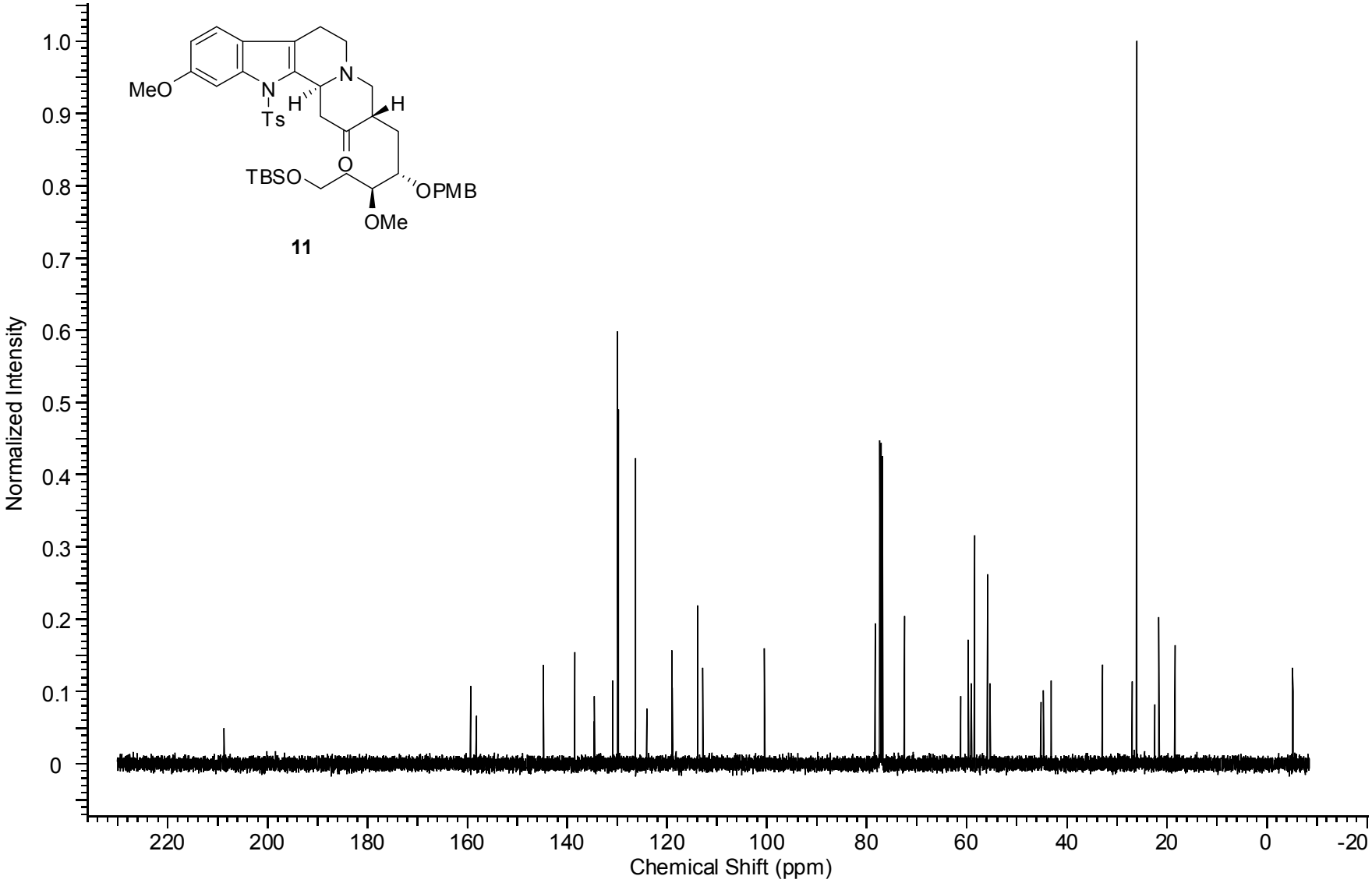
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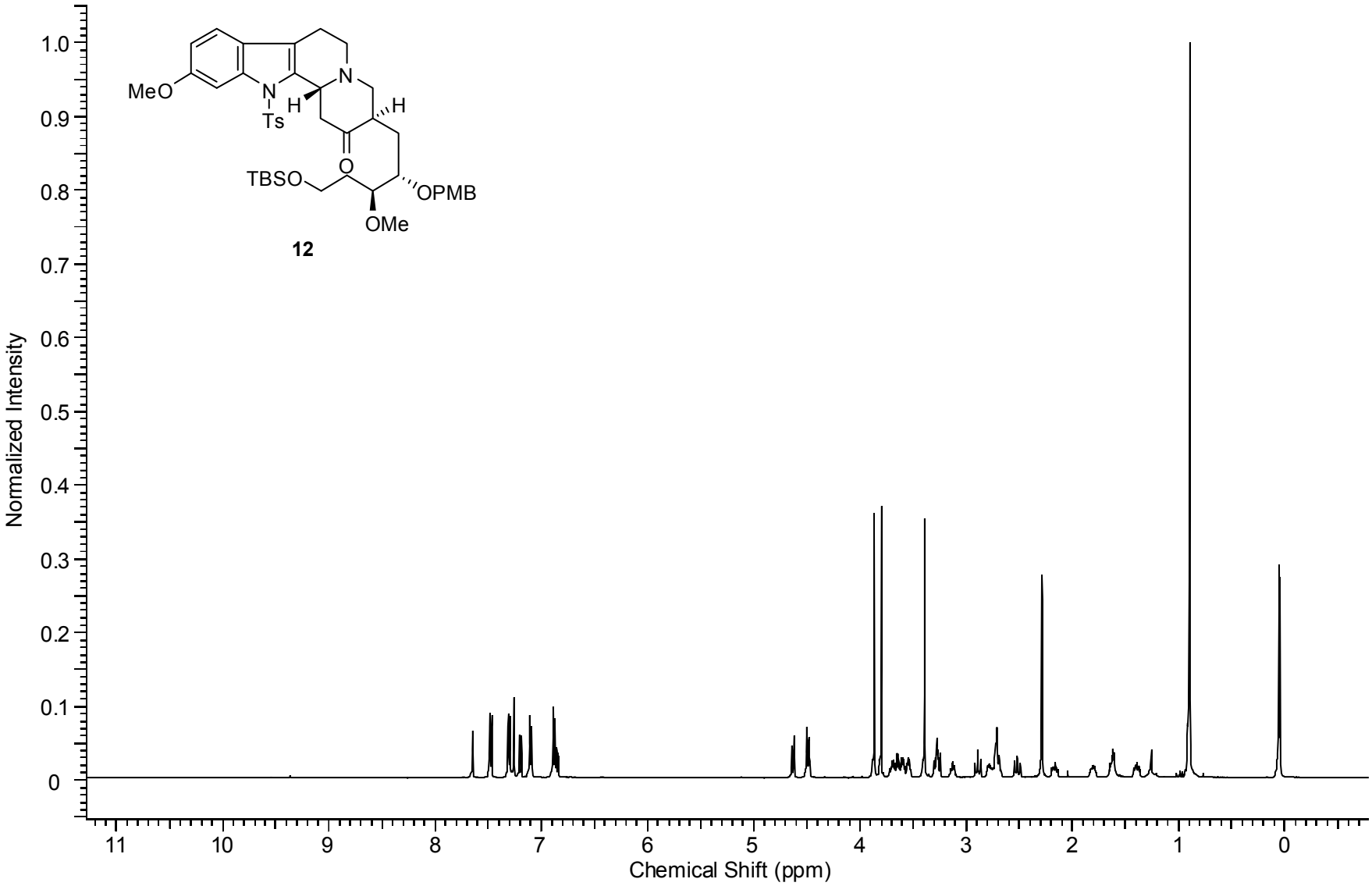
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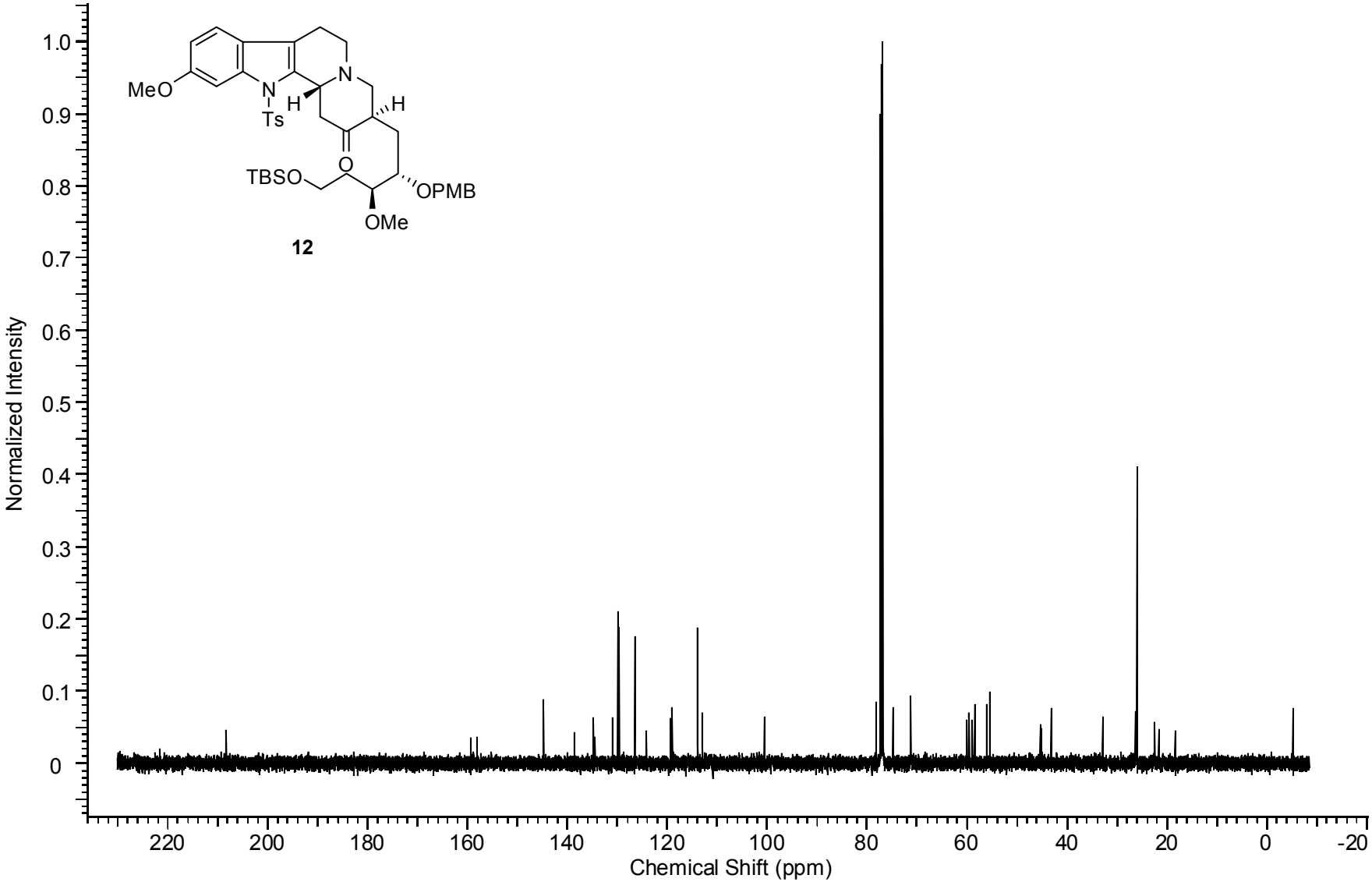
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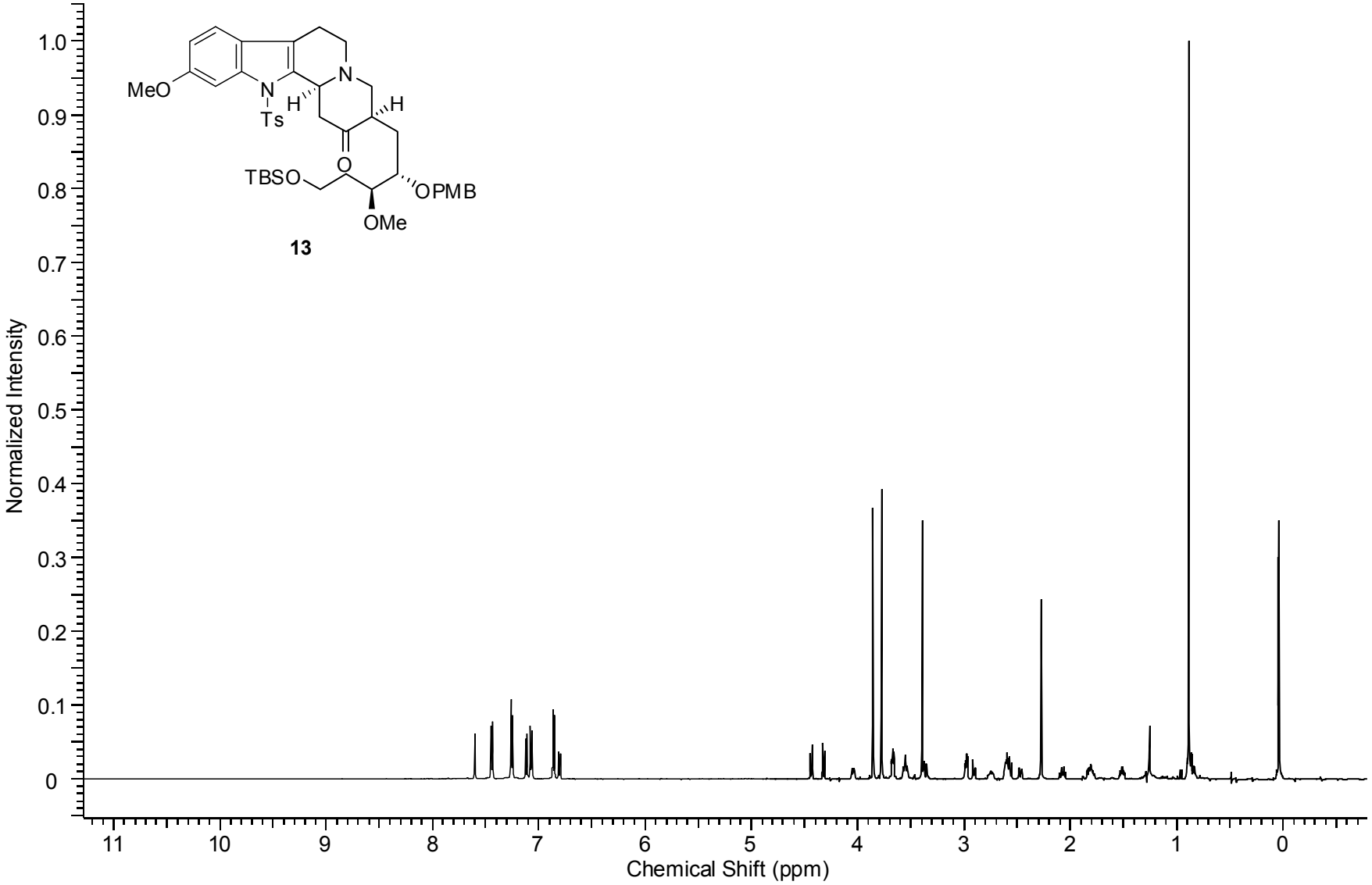
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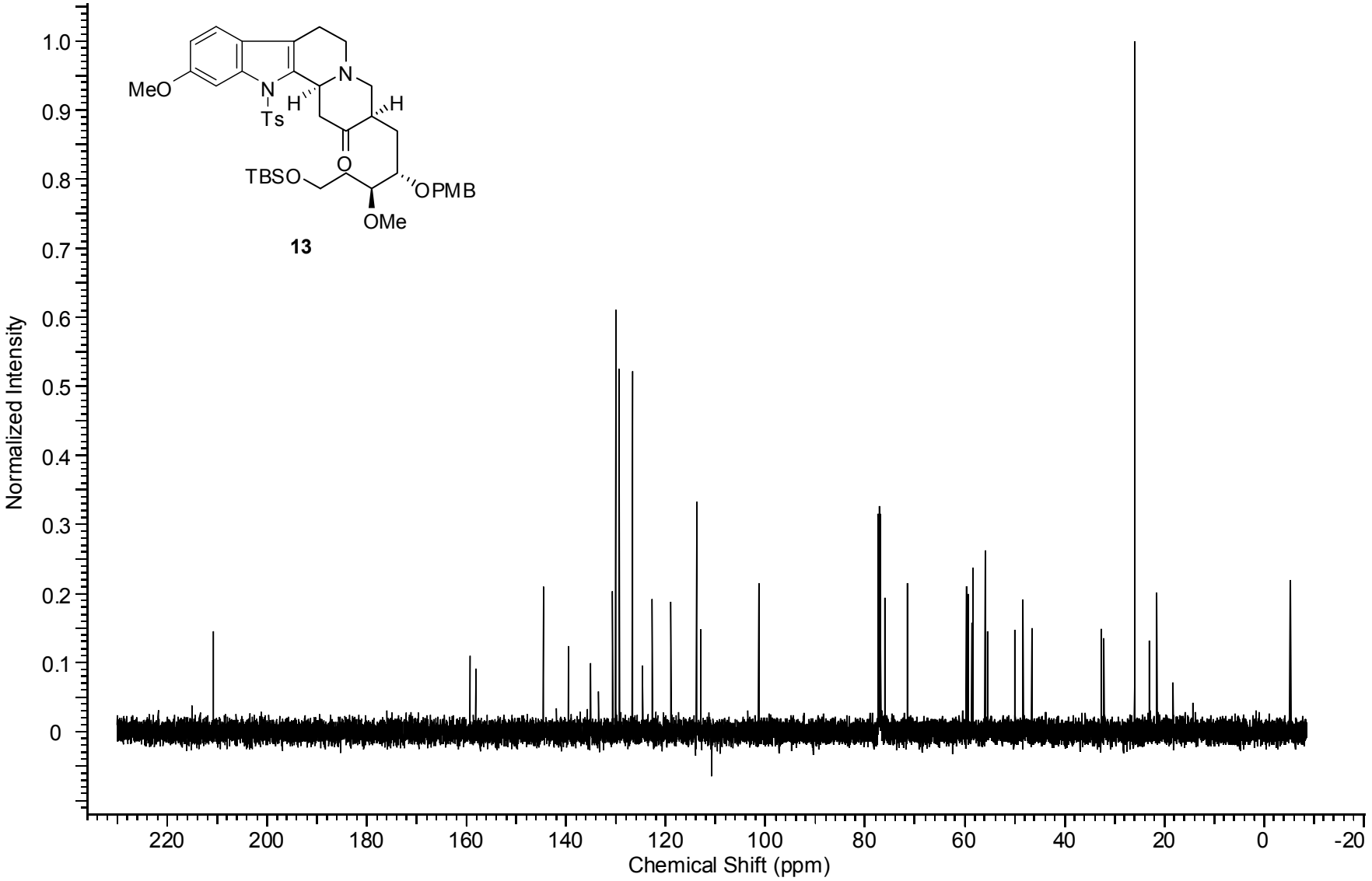
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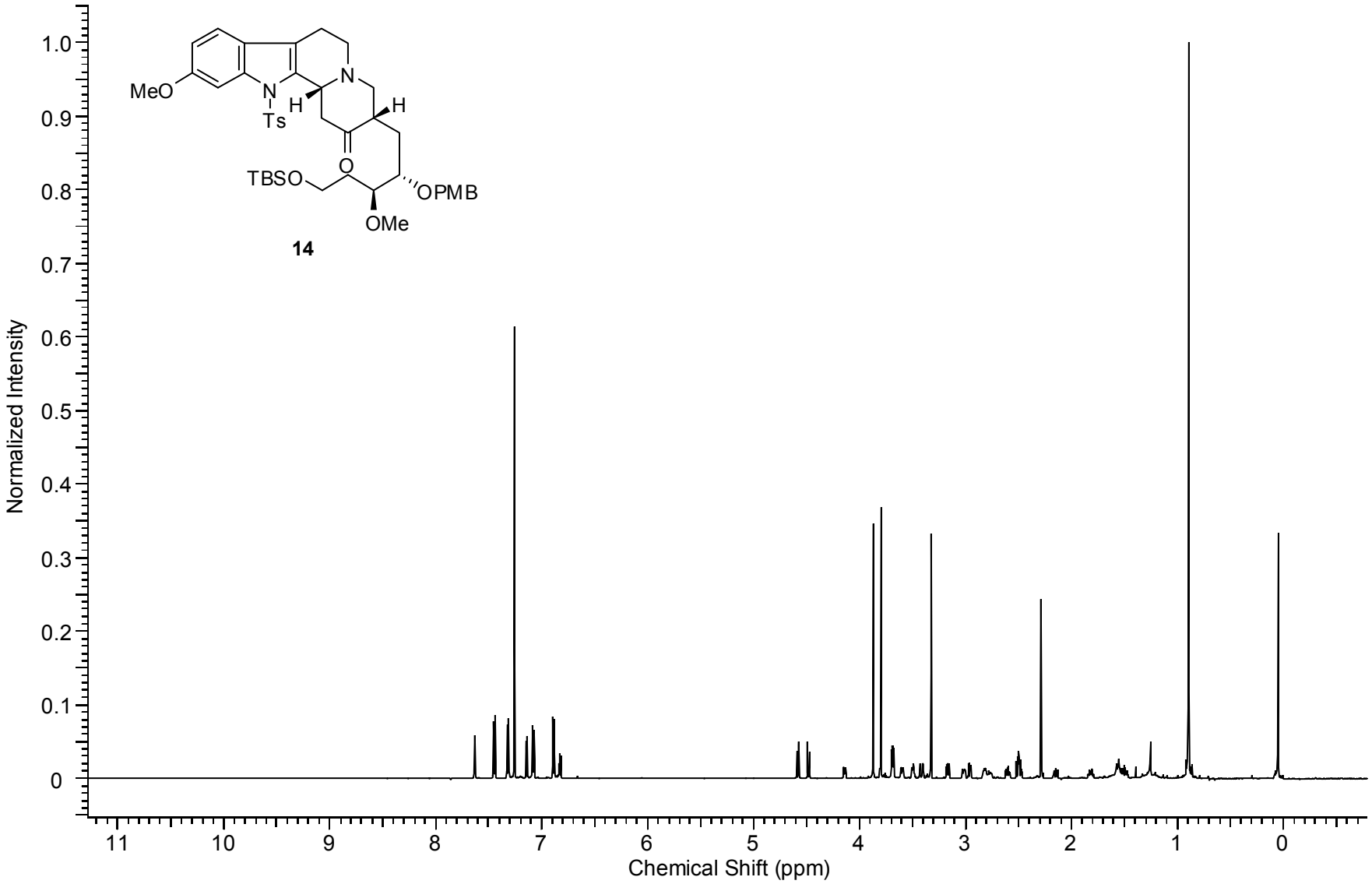
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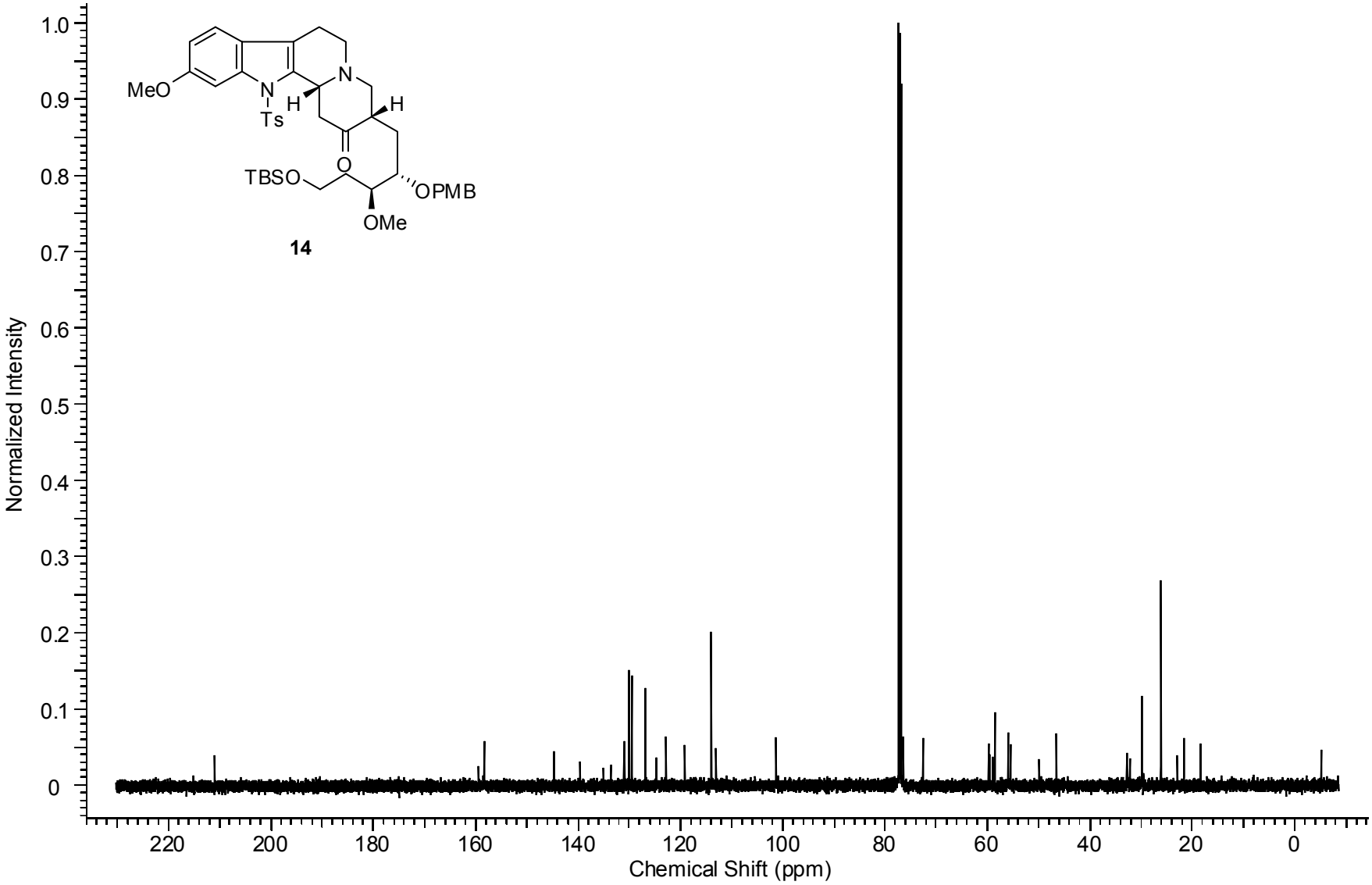
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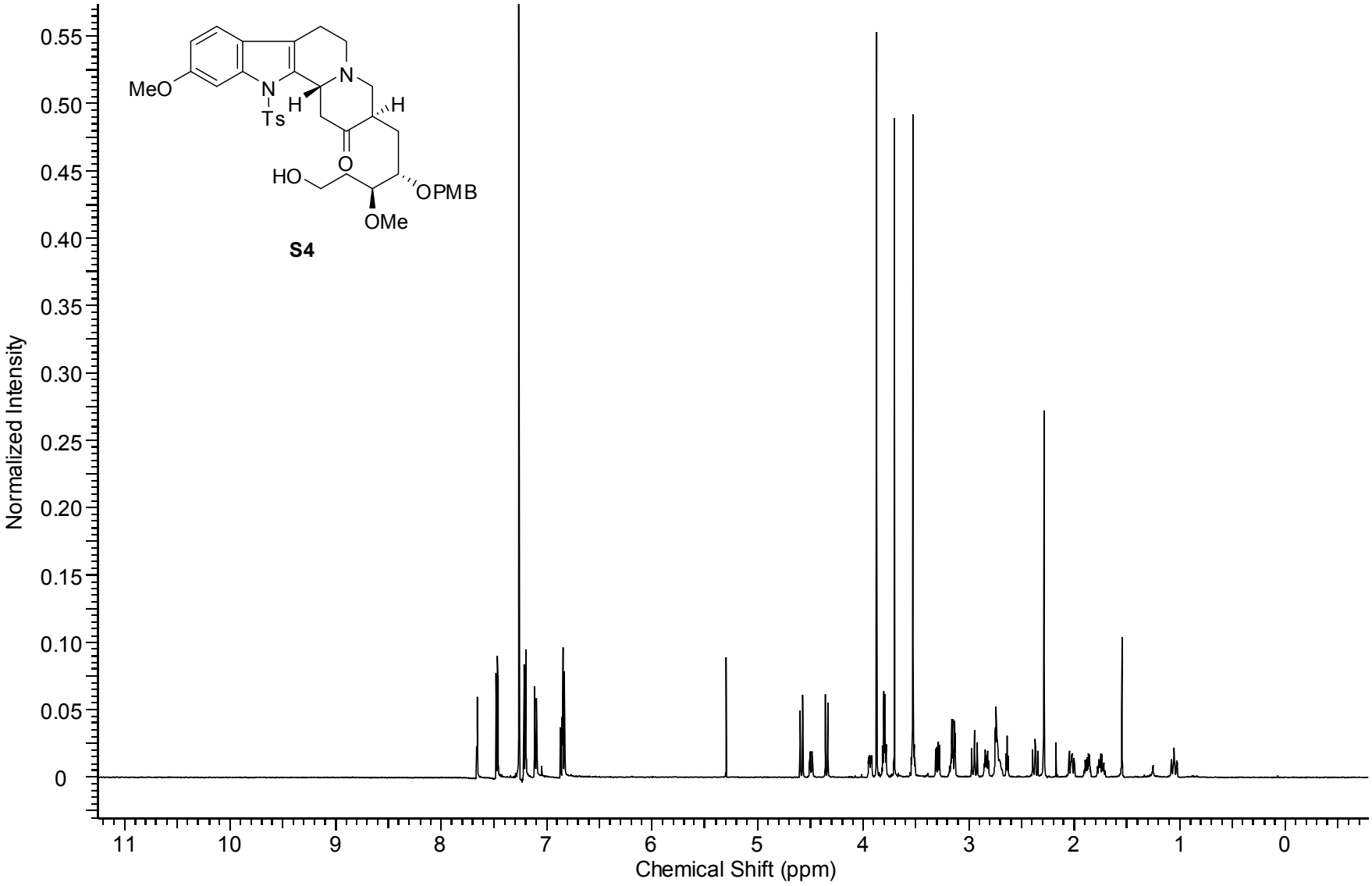
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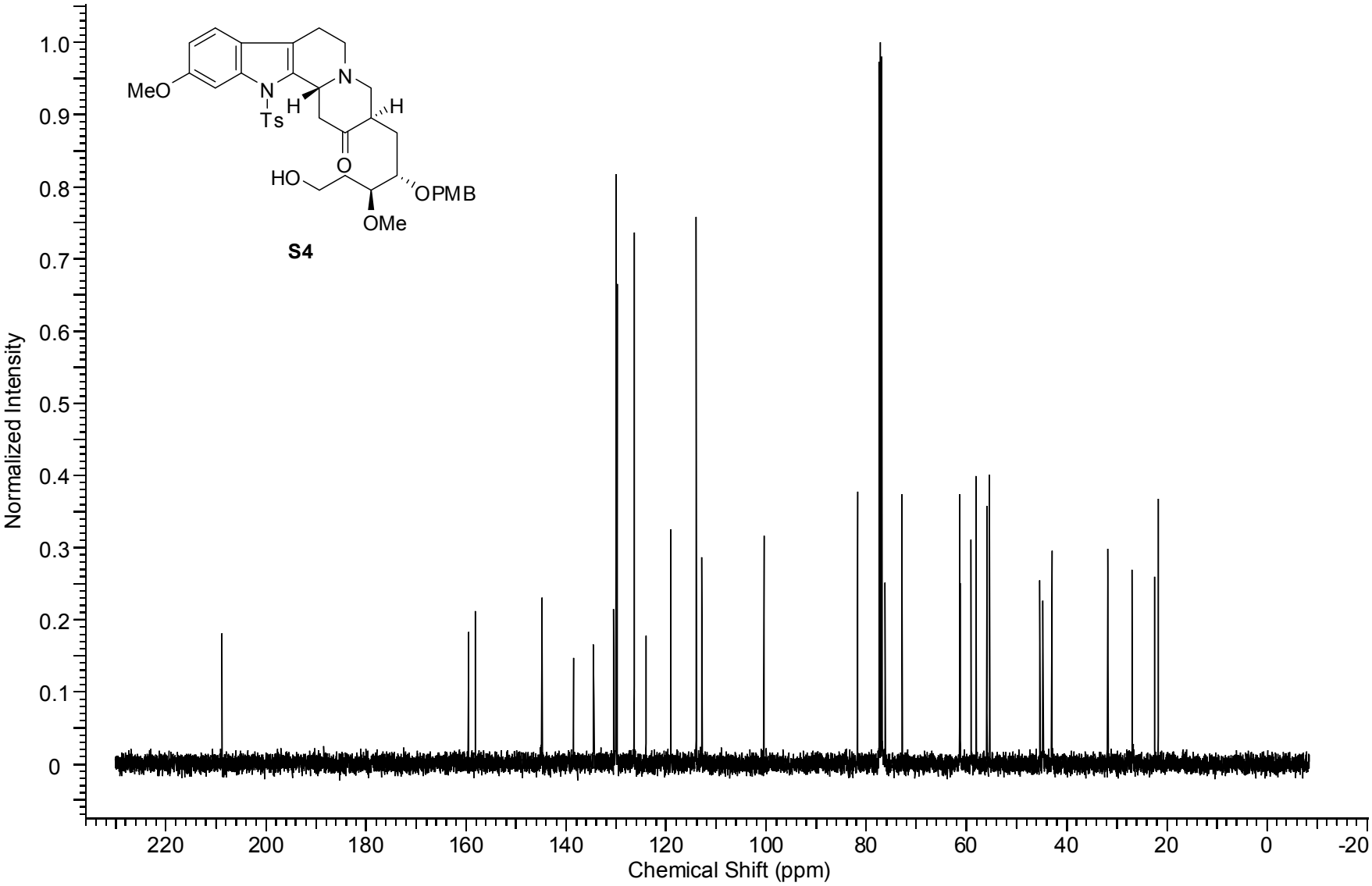
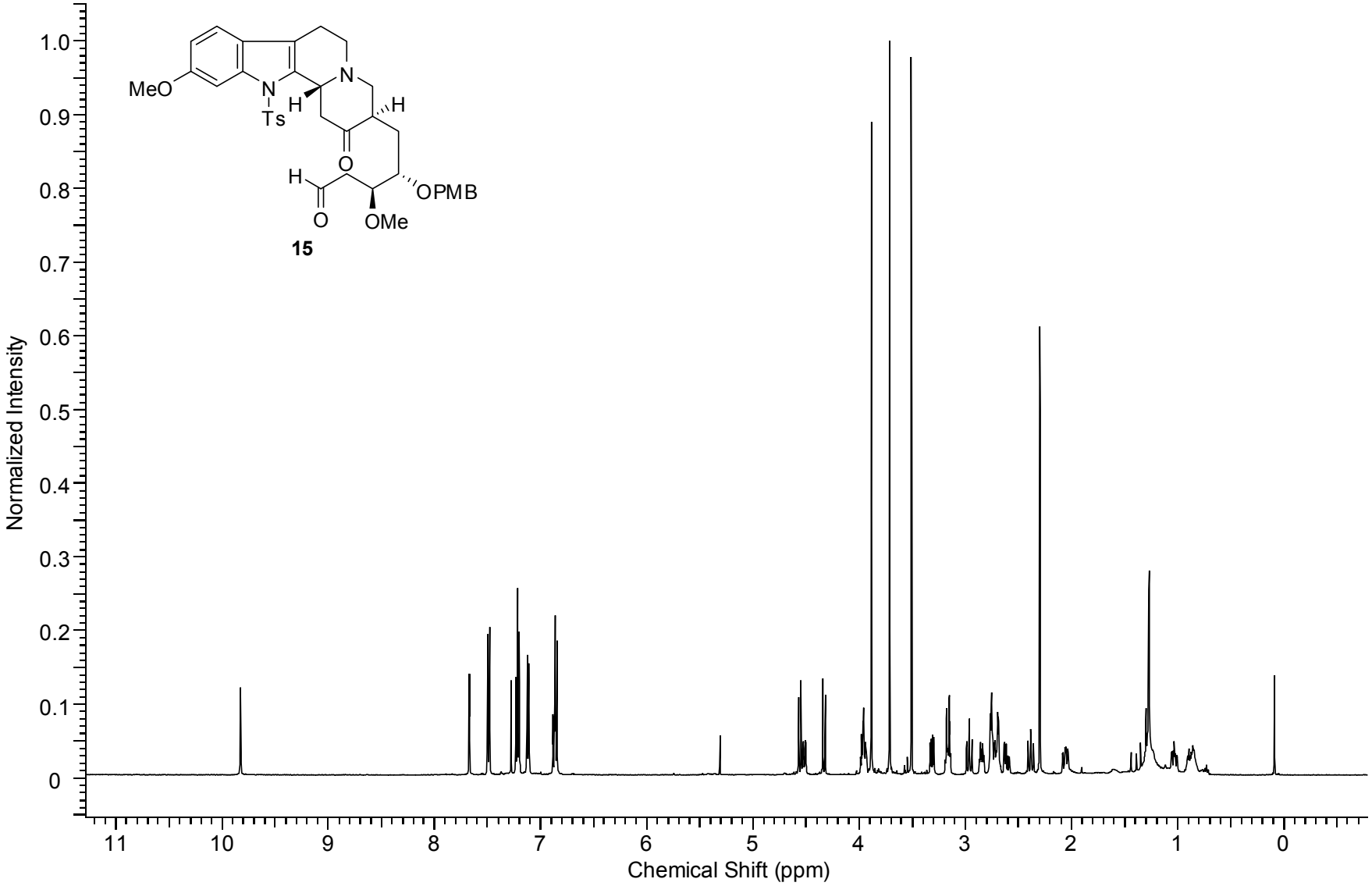
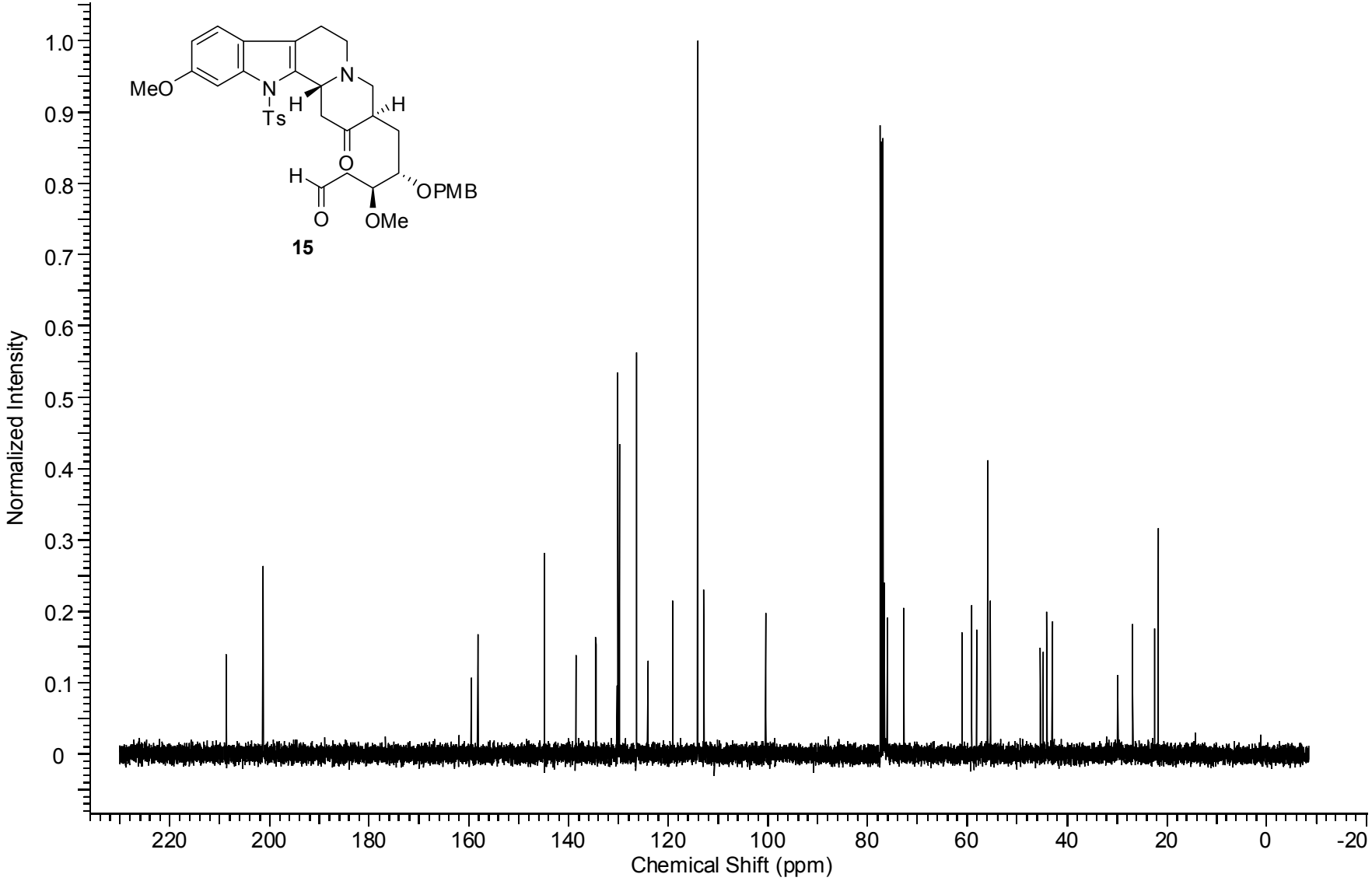
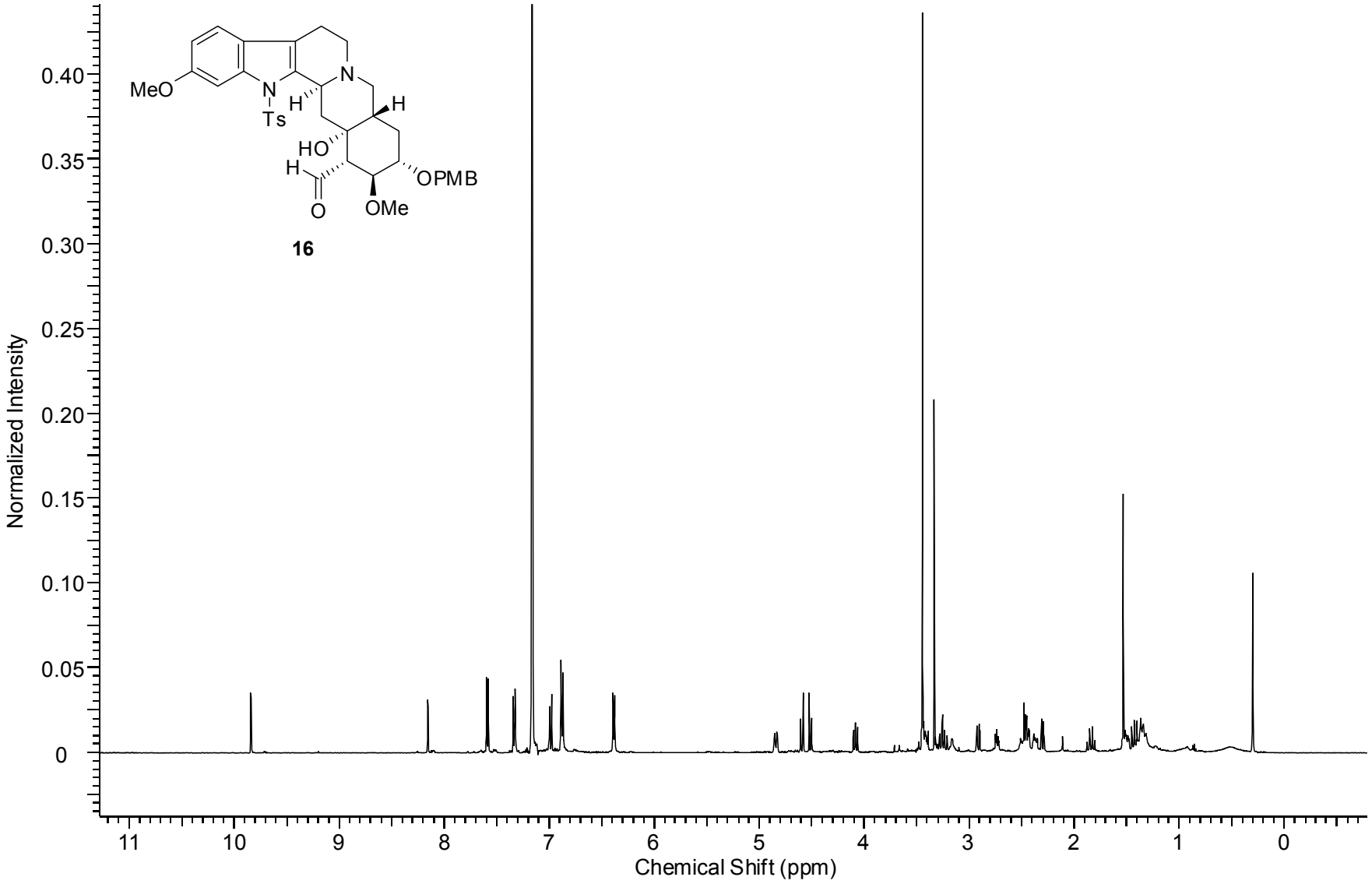
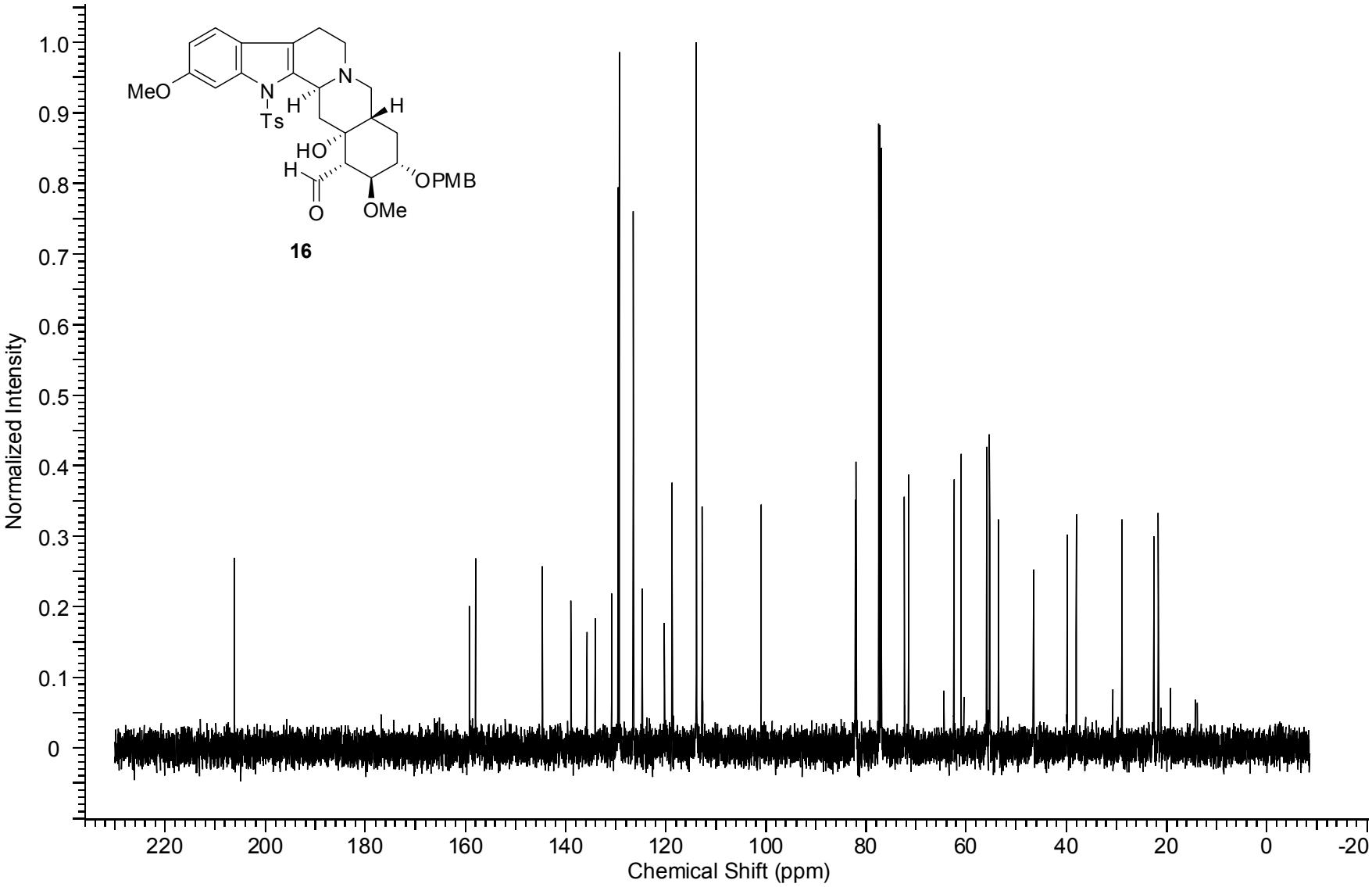
0
Chemical Shift (ppm)

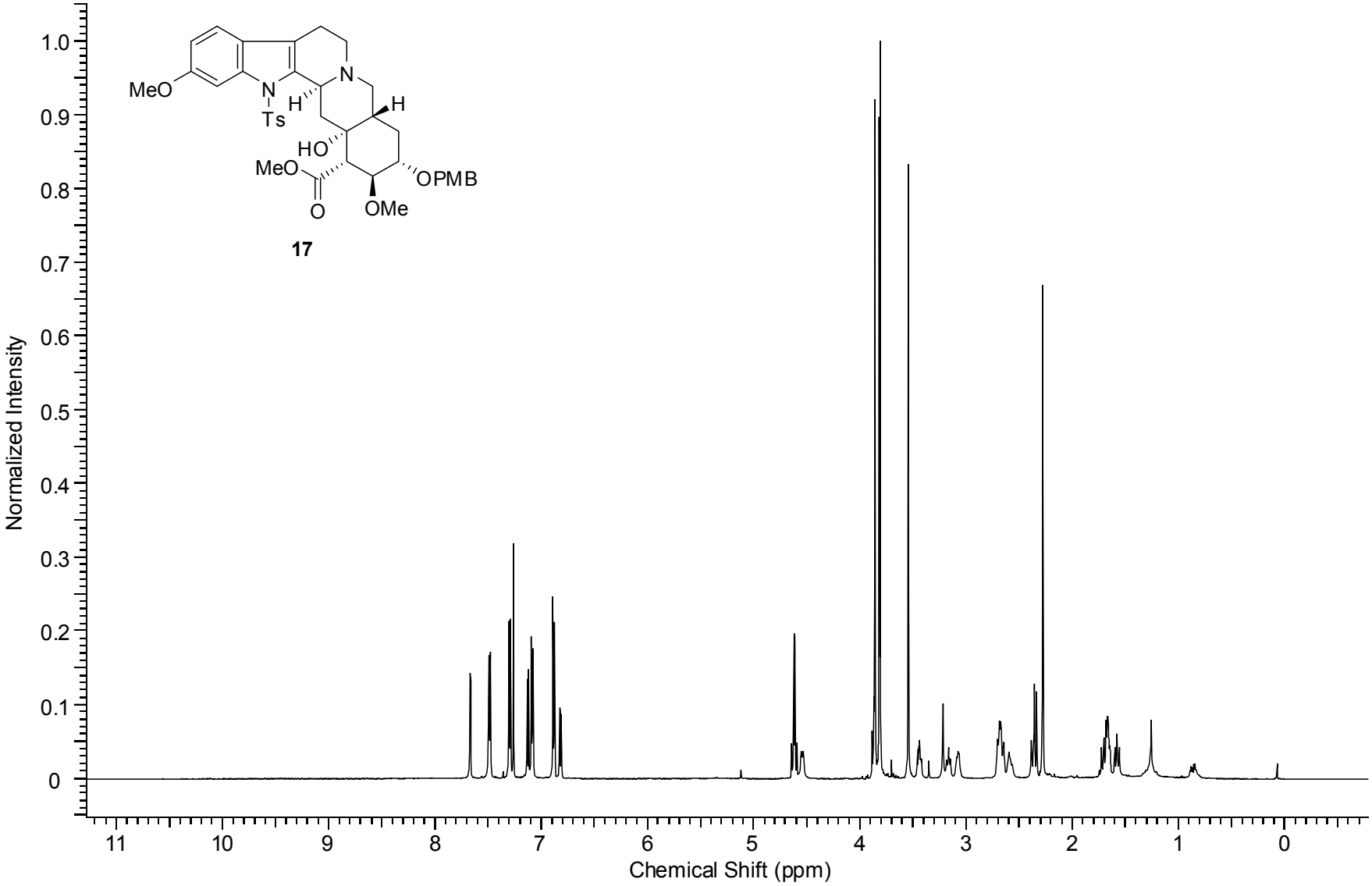

MeO
N
Ts
H
N
H
O
HO
OPMB
OMe
S4
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

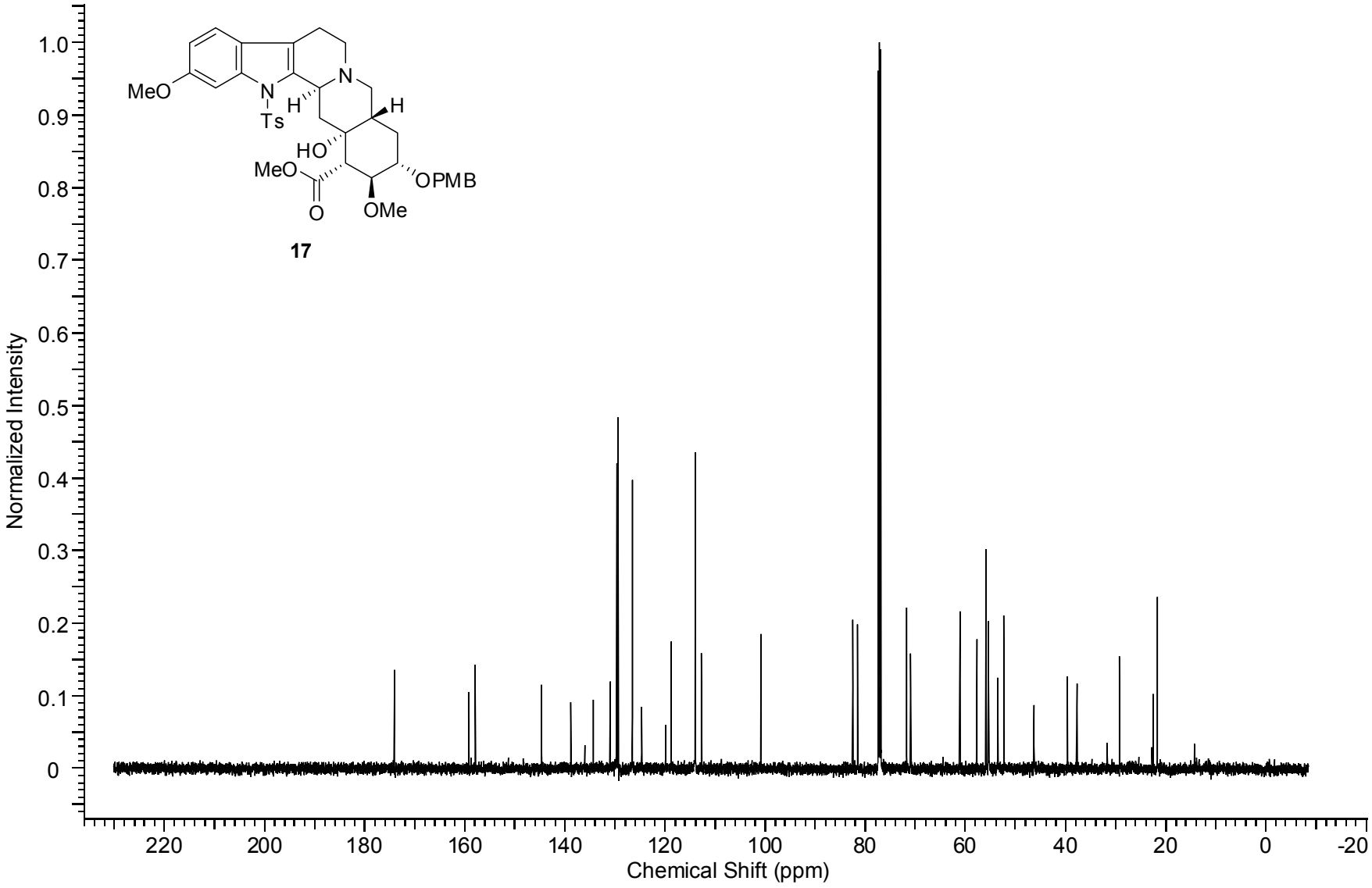

MeO
N
Ts
H
N
H
O
H
O
OMe
OPMB
15
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

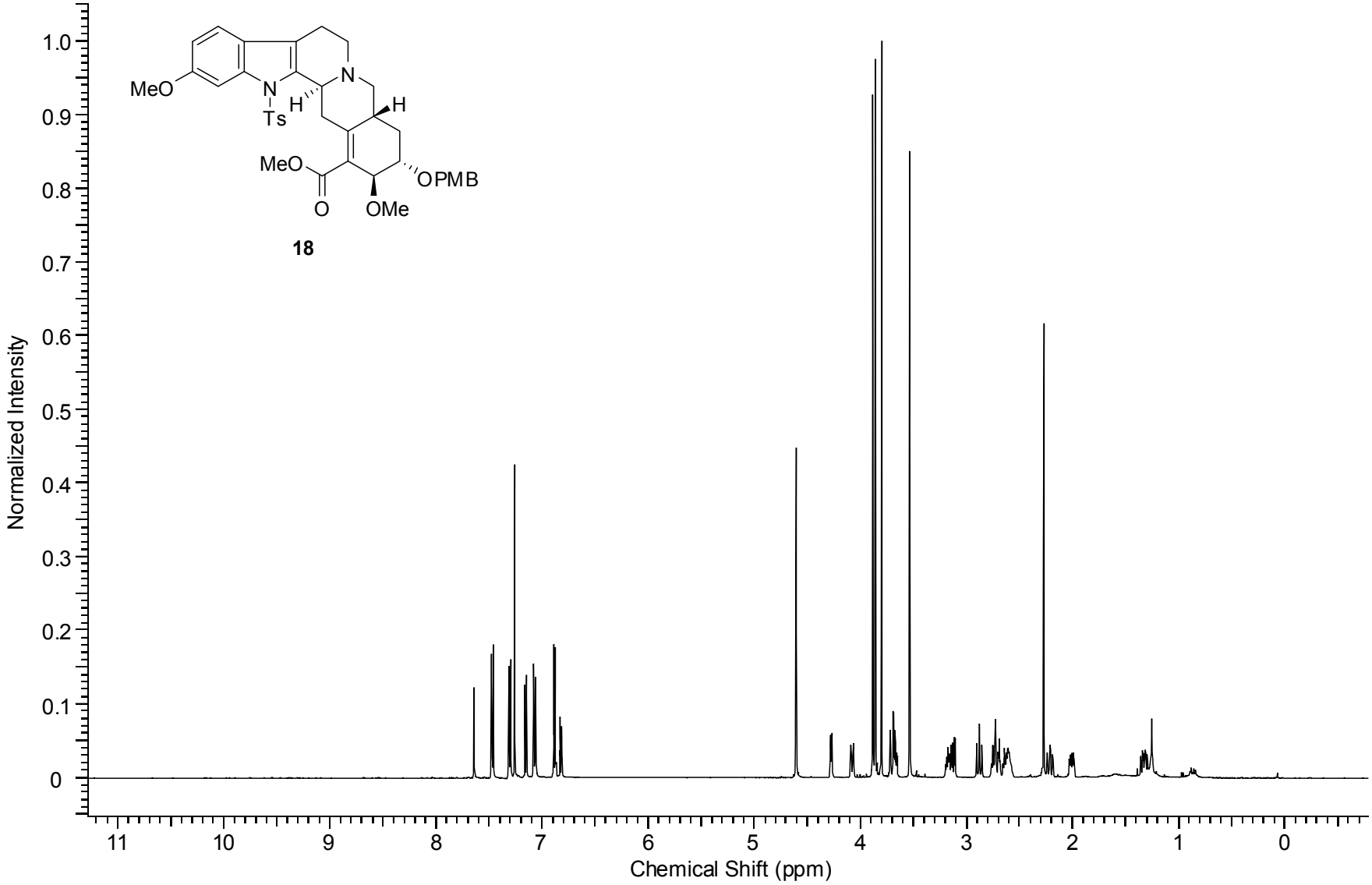

MeO
N
Ts
H
N
H
O
H
O
OPMB
OMe
15
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

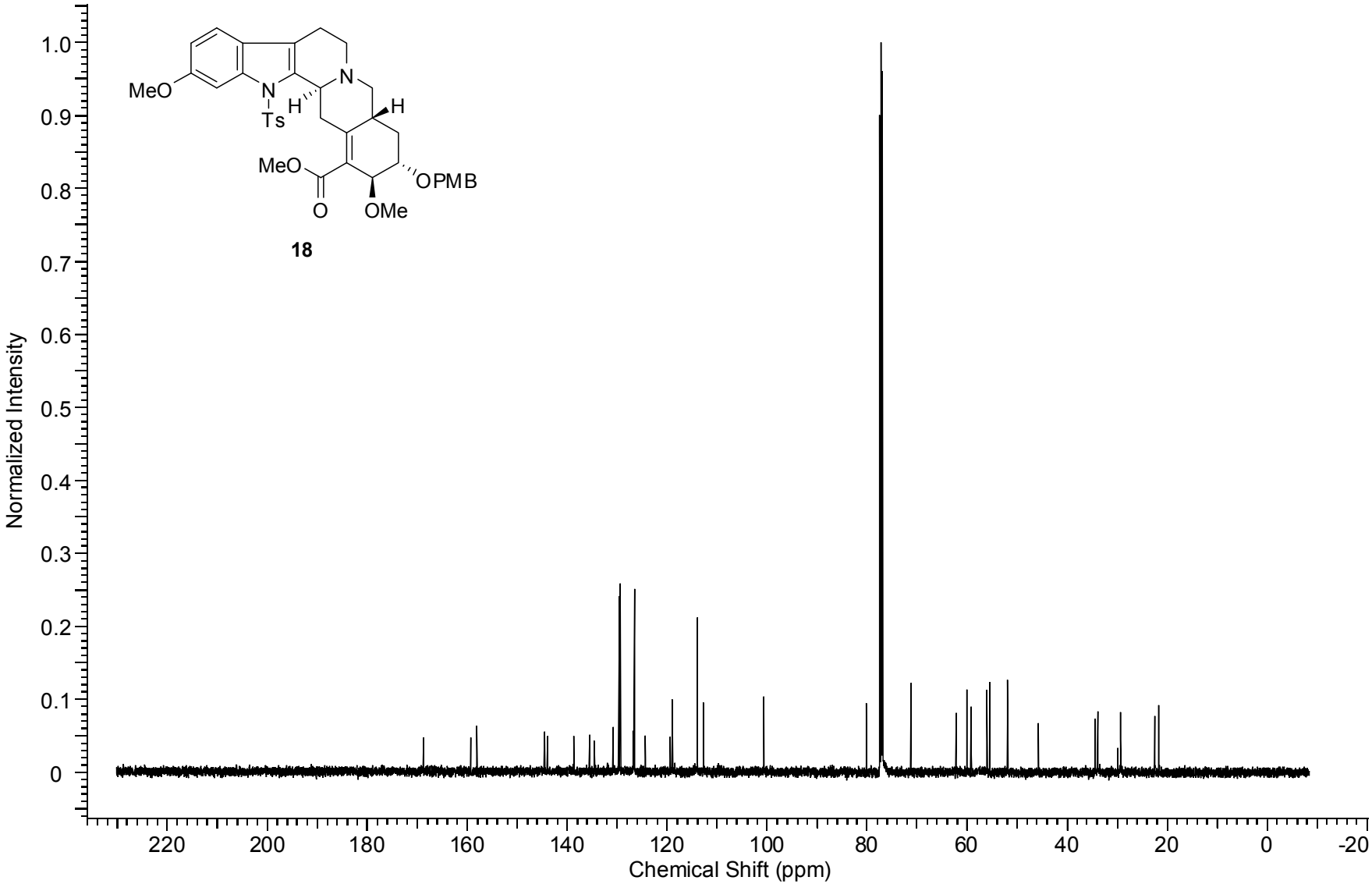

MeO
N
Ts
H
N
H
HO
H
O
OMe
OPMB
16
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

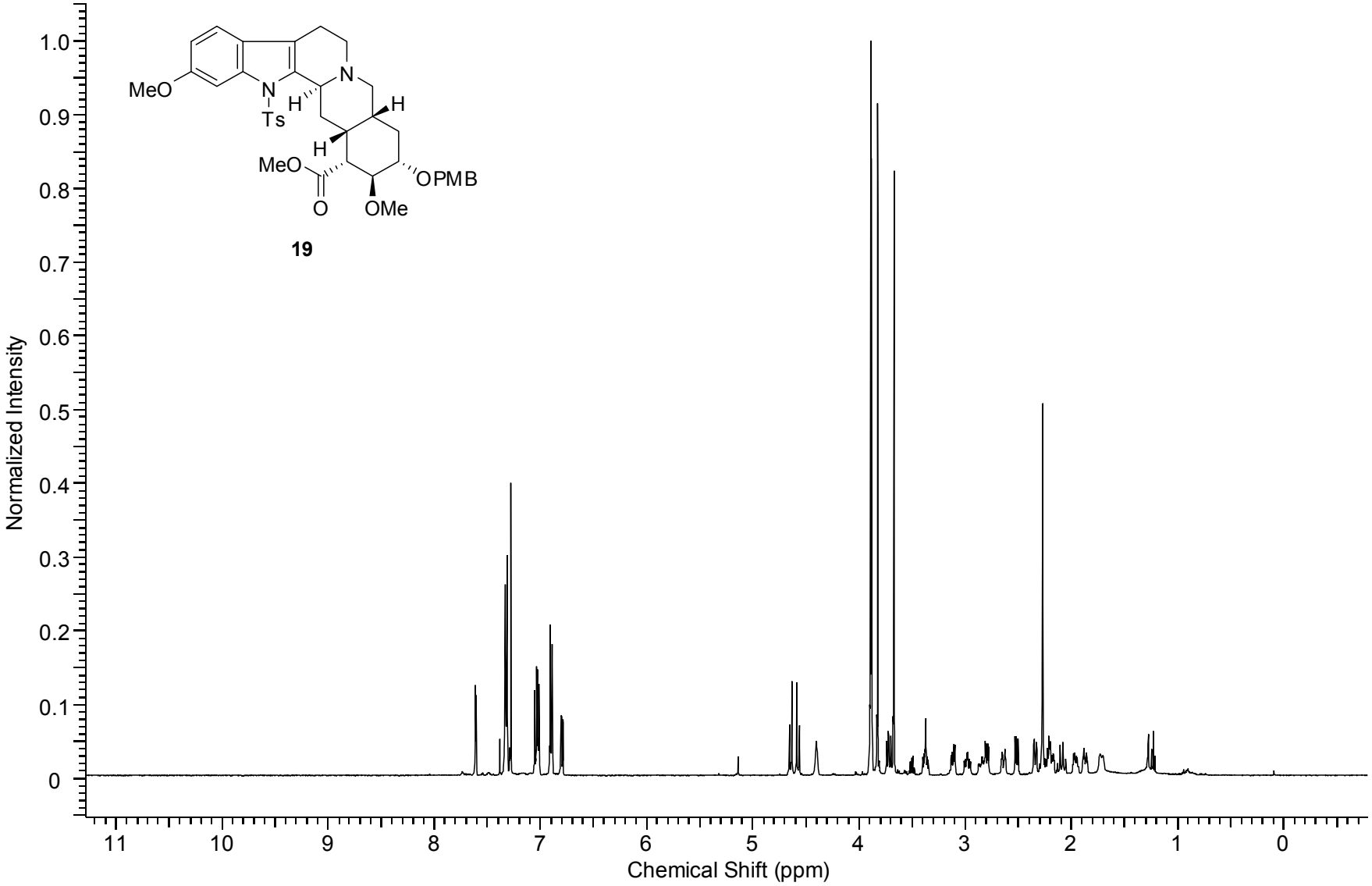

MeO
N
Ts
H
N
H
HO
H
O
OMe
OPMB
16
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

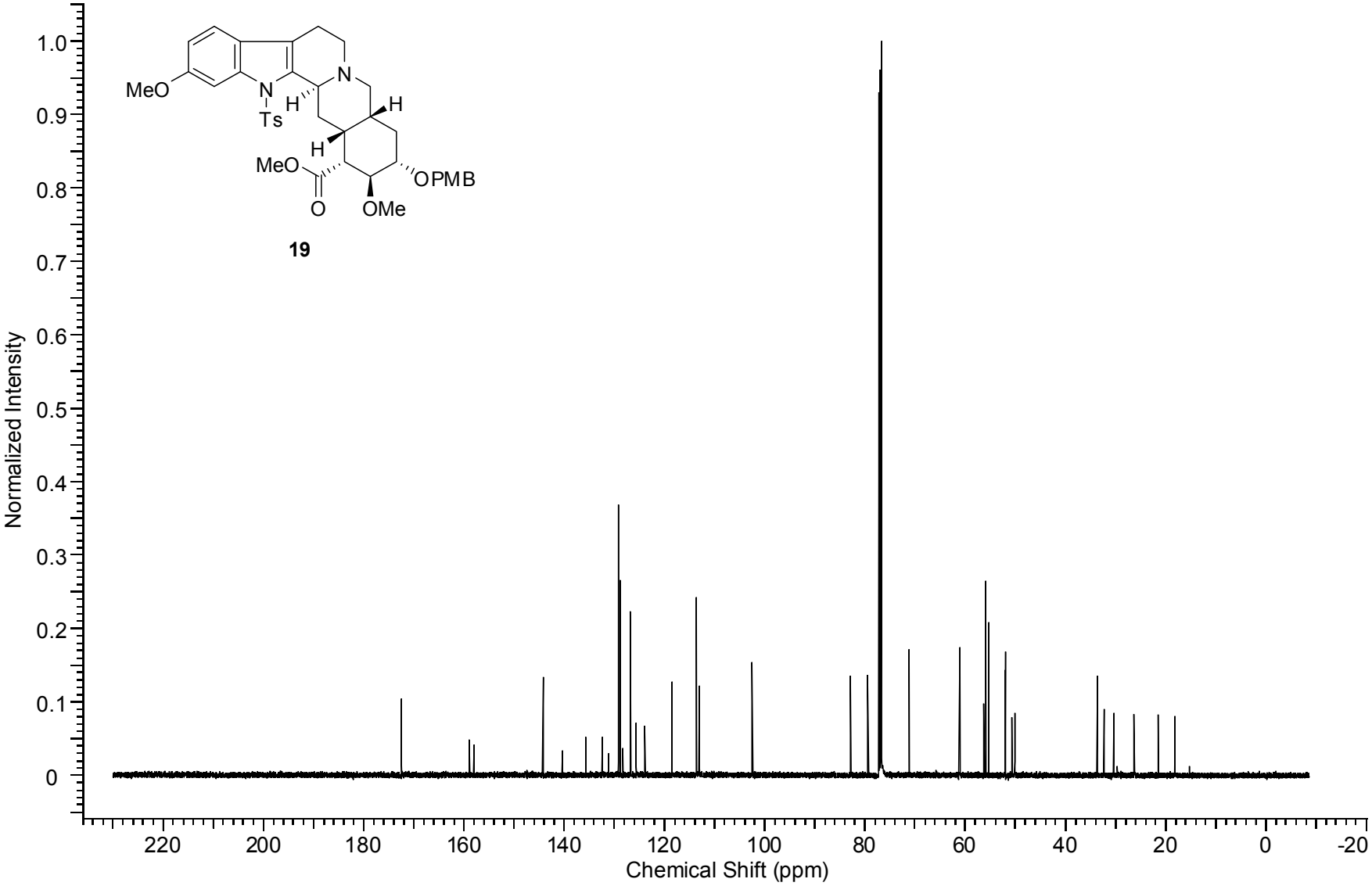

MeO
N
Ts
H
N
H
HO
MeO
O
OMe
OPMB
17
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

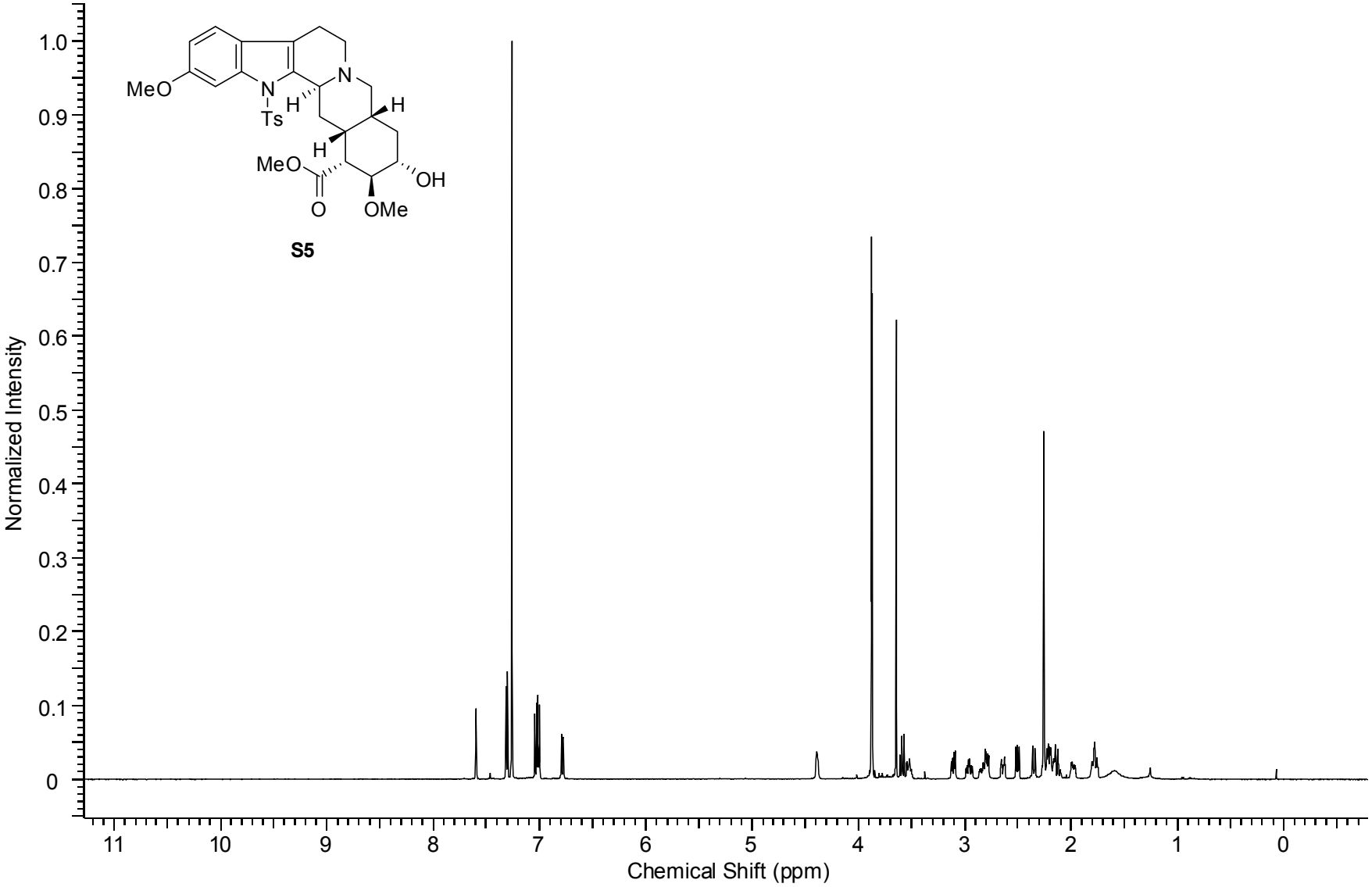

MeO
N
Ts
H
N
H
HO
MeO
O
OMe
OPMB
17
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

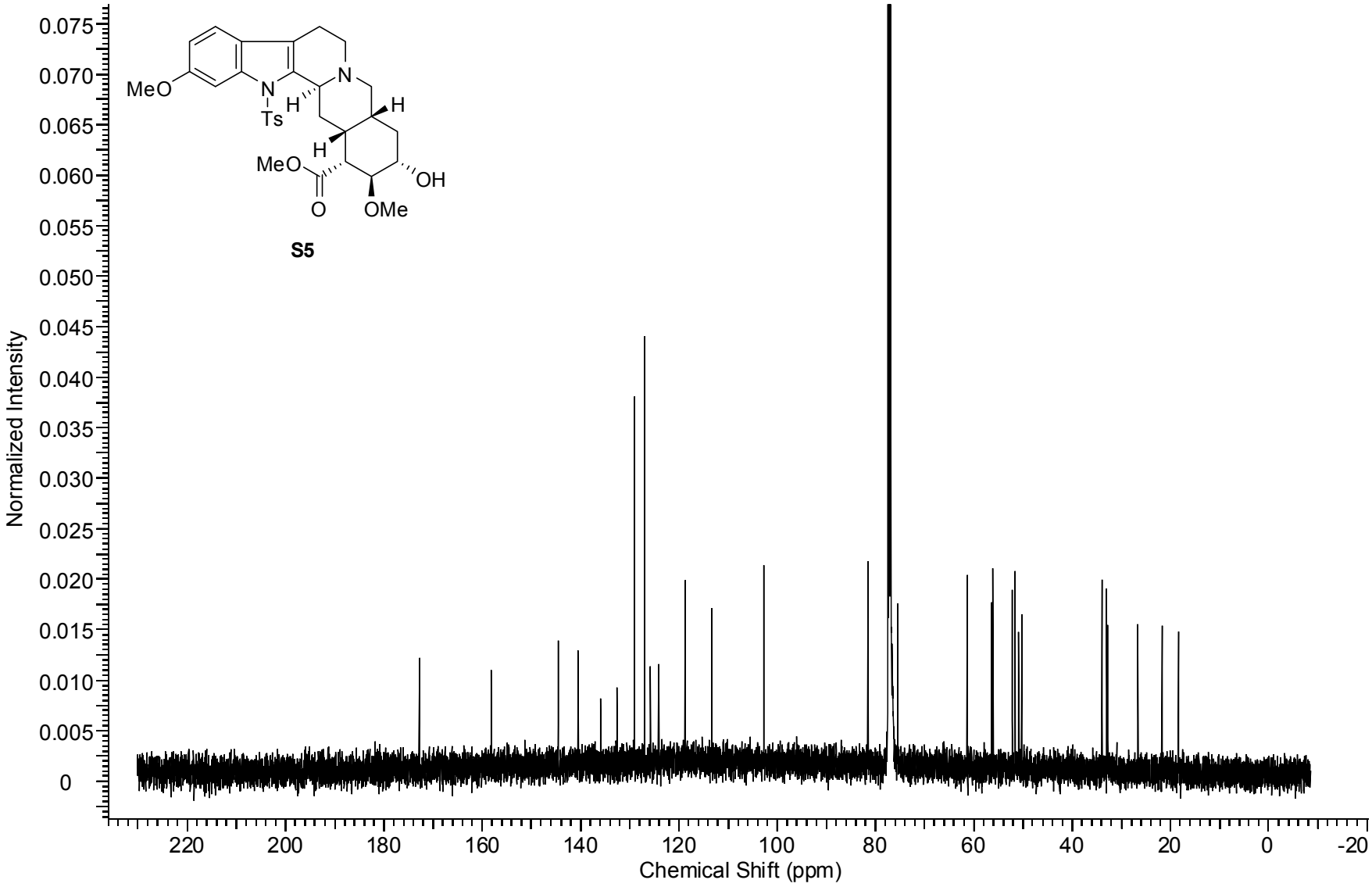

MeO
N
Ts
H
N
H
MeO
O
OMe
OPMB
18
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

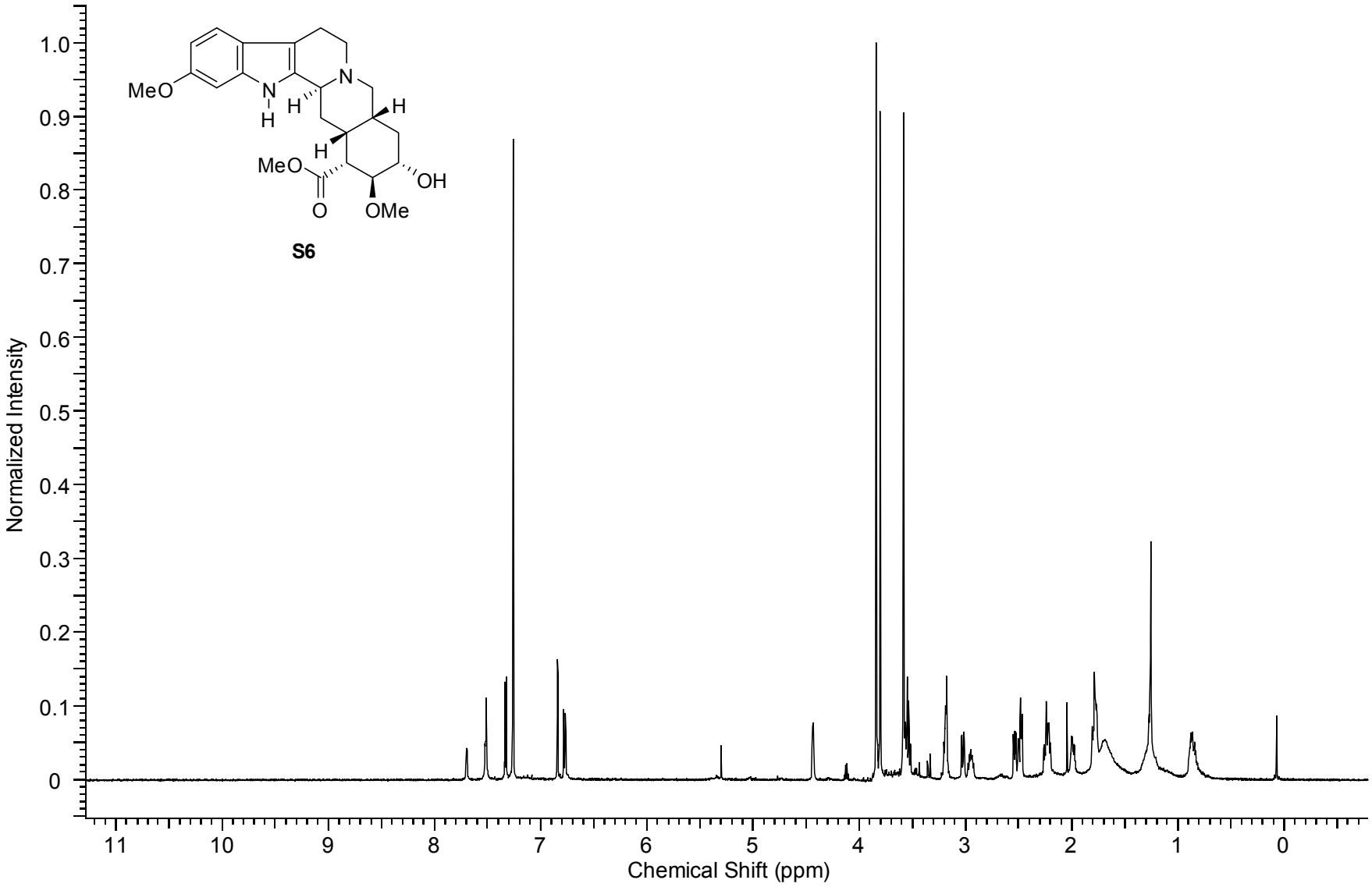

MeO
N
Ts
H
N
H
MeO
O
OMe
OPMB
18
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

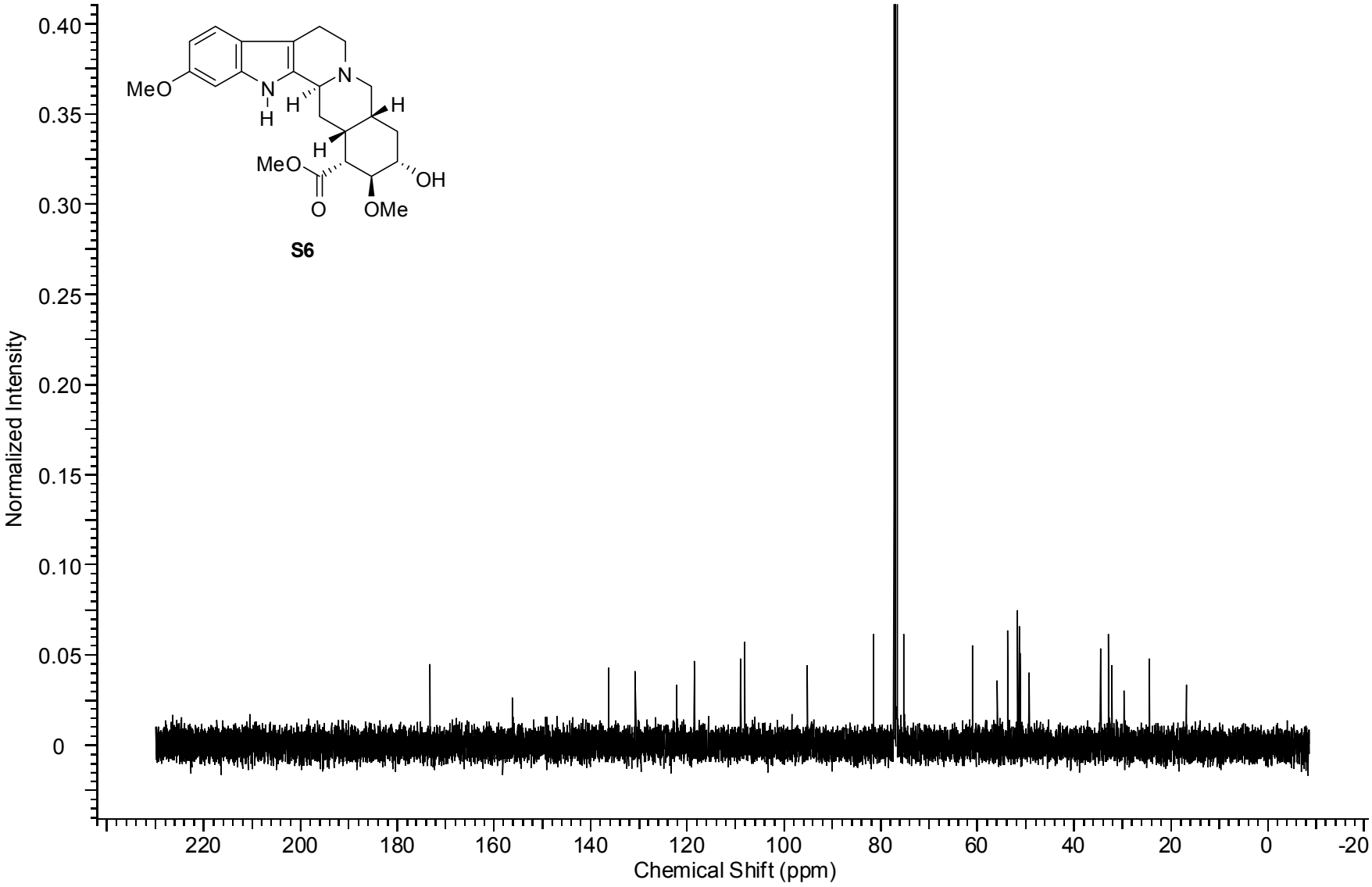

MeO
N
Ts
H
N
H
H
MeO
O
OMe
OPMB
19
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

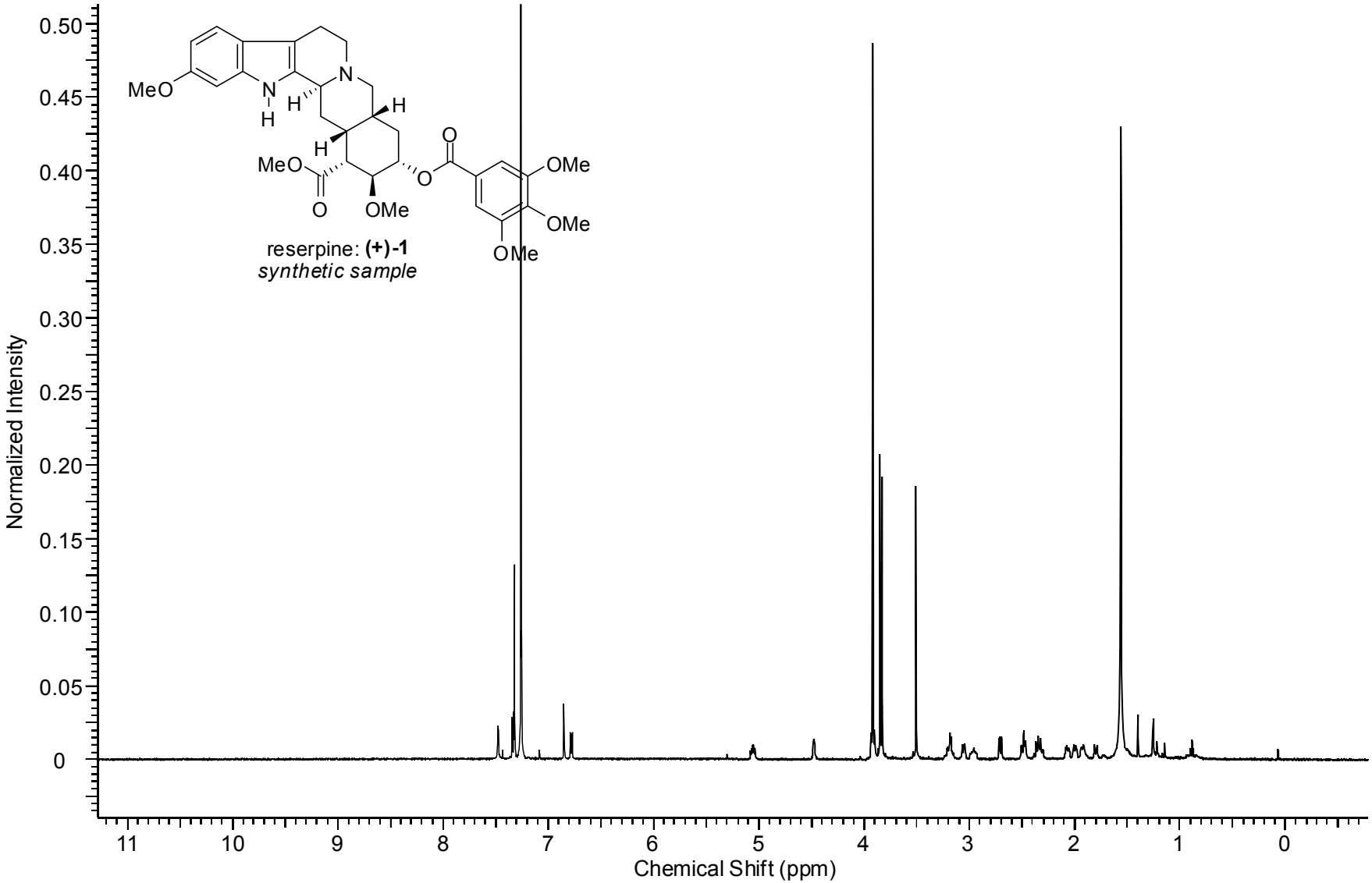

MeO
N
Ts
H
N
H
H
MeO
O
OMe
OPMB
19
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


MeO
N
Ts
H
N
H
H
MeO
O
OMe
OH
S5
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

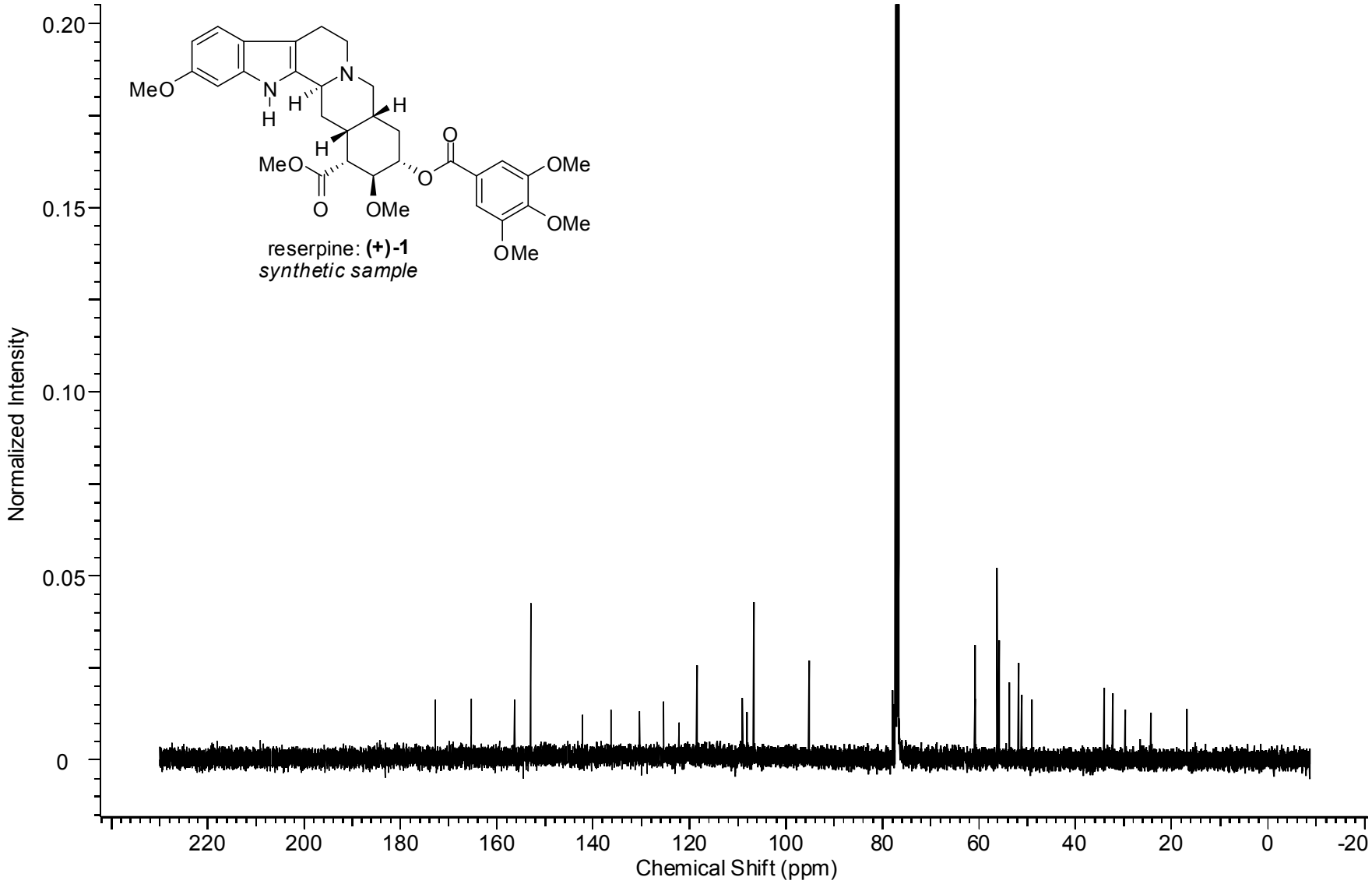

MeO
N
Ts
H
N
H
H
MeO
O
OMe
OH
S5
Normalized Intensity
0.075
0.070
0.065
0.060
0.055
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

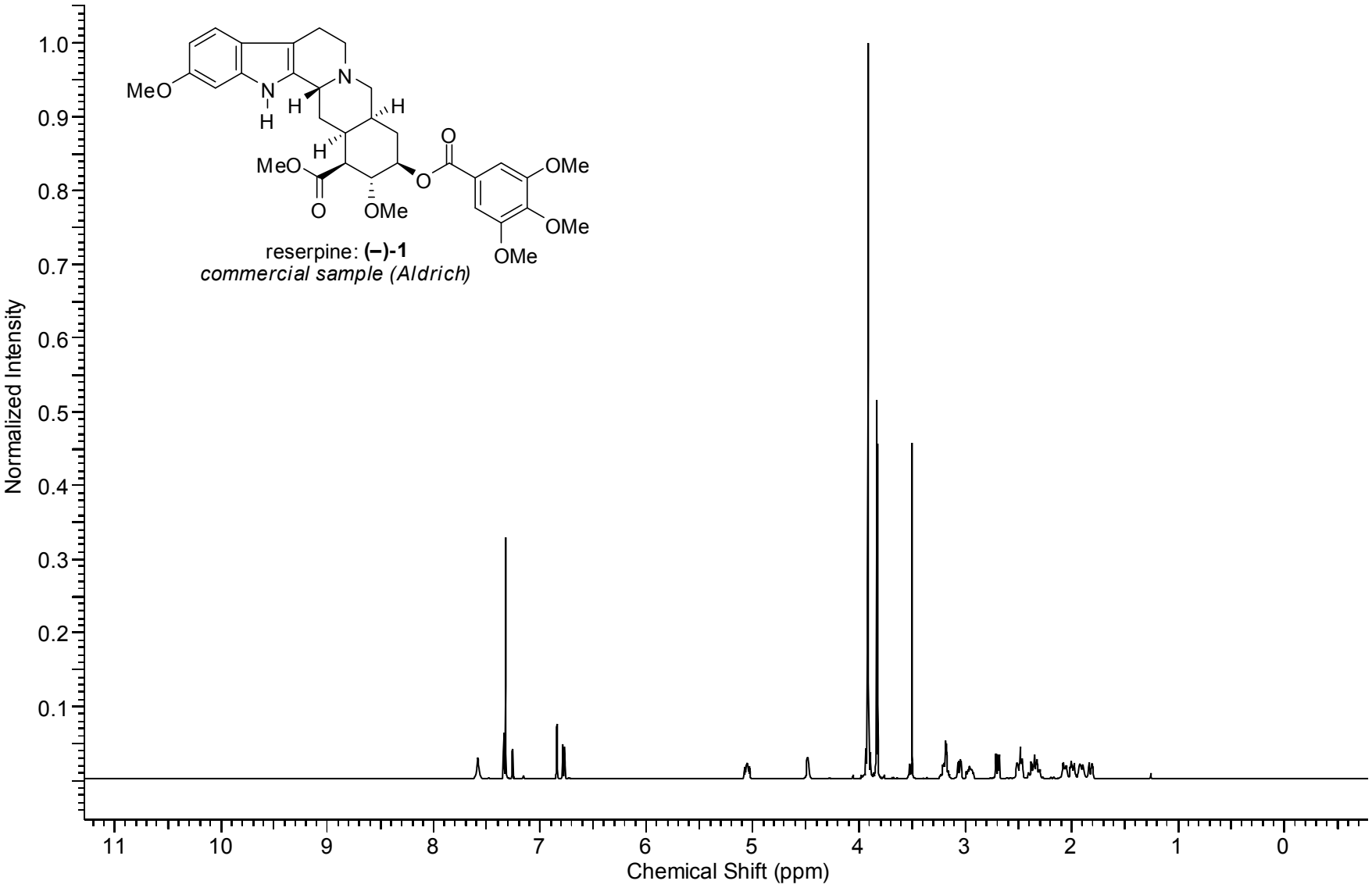

MeO
N
H
N
H
H
H
MeO
OH
O
OMe
S6
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

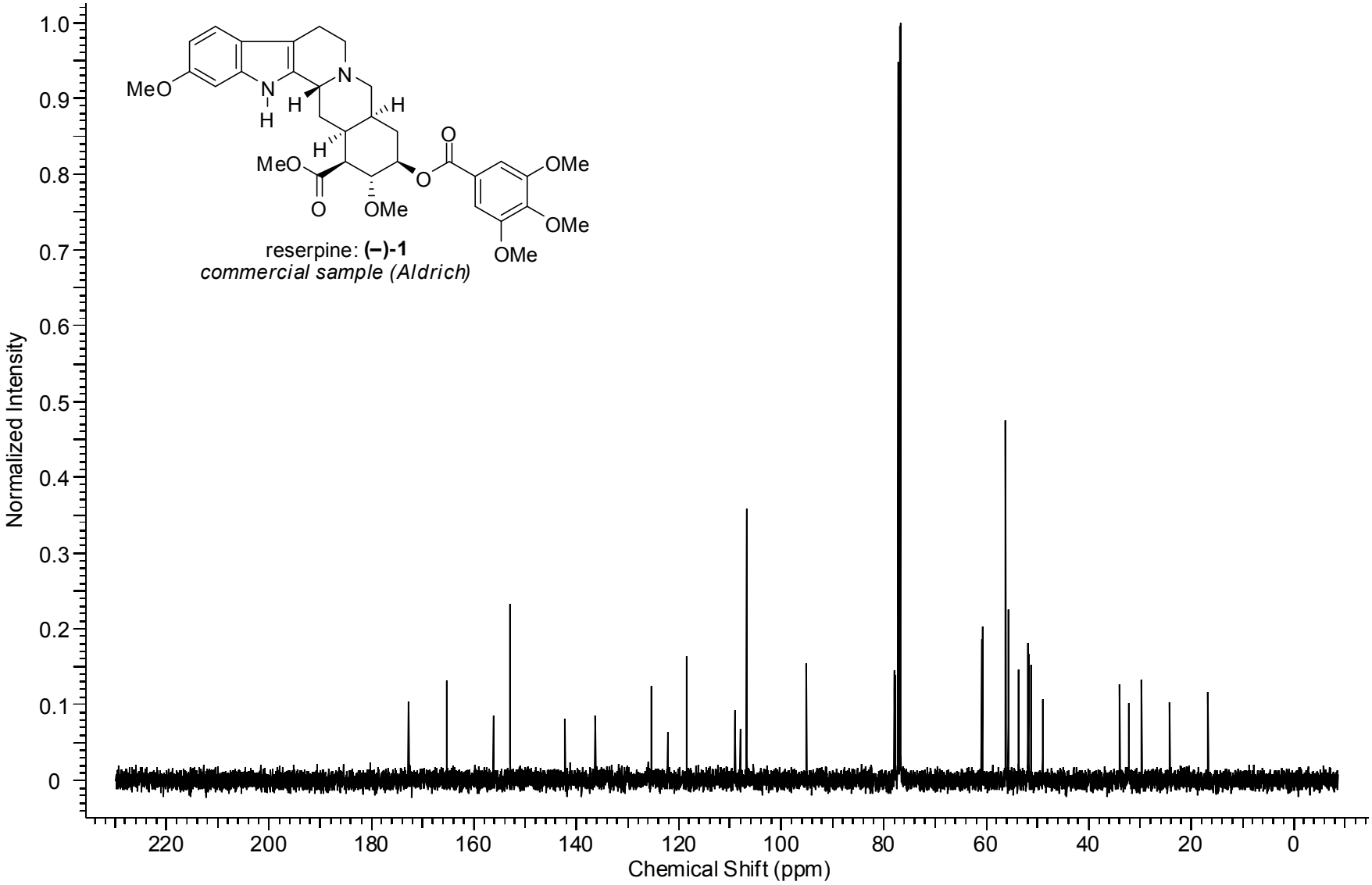

MeO
N
H
N
H
H
H
MeO
O
OMe
OH
S6
Normalized Intensity
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)



The peak at 1.56 ppm is due to residual water that remained after keeping the purified sample under vacuum (< 1 torr) for 3 h


reserpine: (+)-1
synthetic sample
Normalized Intensity
0.20
0.15
0.10
0.05
0
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)


MeO
N
H
N
H
H
H
MeO
O
O
OMe
O
OMe
OMe
OMe
reserpine: (–)-1
commercial sample (Aldrich)
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


reserpine: (–)-1
commercial sample (Aldrich)
Normalized Intensity
Chemical Shift (ppm)