Supporting Information

Enantioselective Synthesis of 5-*epi*-Citreoviral Using Ruthenium-Catalyzed Asymmetric Ring-Closing Metathesis

Timothy W. Funk

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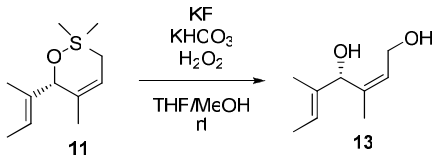
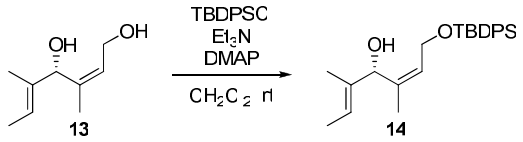
General Information. IR spectra were collected on a Nicolet IR200 attenuated total reflectance FT-IR spectrometer. NMR spectra were recorded on a Bruker 400 MHz FT-NMR spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent for ^{1}H NMR and ^{13}C NMR spectra. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), septet (sept), multiplet (m), and broad (br). Optical rotations were taken on a Jasco P-1010 polarimeter with a wavelength of 589 nm. The concentration "c" has units of g/100 mL (or 10 mg/mL) unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was performed with standard potassium permanganate stain (10 g $KMnO_4$, 20 g Na_2CO_3, 1 L water), standard *p*-anisaldehyde stain (23 mL *p*-anisaldehyde in 500 mL 95% EtOH, cooled to 0 °C, added 9.4 mL cold glacial AcOH and 31.3 mL conc. H_2SO_4, diluted to 1 L with 95% EtOH) or UV light. Flash column chromatography of organic compounds was performed using silica gel 60 (230-400 mesh). All enantiomeric purities were determined by chiral GC (Chiraldex G-TA) or chiral SFC (supercritical CO_2, ADH column, 214 nm UV detection) and were compared to racemic samples.

All glassware was flame dried, and reactions were done under an atmosphere of argon unless otherwise noted. All organic solvents were dried by passage through solvent purification columns containing activated alumina and activated copper (the latter was used for solvents with no heteroatoms). All commercial chemicals were used as obtained. Compounds **2**, **11**, and **12** were synthesized and purified as reported.[1]

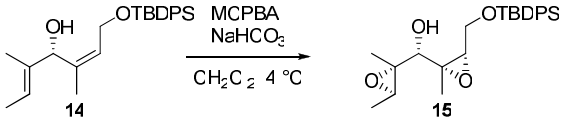


(*S*,2*Z*,5*E*)-3,5-Dimethylhepta-2,5-diene-1,4-diol (13).[2] KF (1.02 g, 17.6 mmol), $KHCO_3$ (0.88 g, 8.8 mmol), and 30% H_2O_2 (4.0 mL, 4.0 g, 35 mmol) were added to a solution of **11** (0.69 g, 3.5 mmol) in THF (35 mL) and MeOH (35 mL), and were stirred at rt for 12 h. The solvents were evaporated until only a small volume remained (~10 mL). Water (25 mL) was added, and the solution was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$, dried over Na_2SO_4, and evaporated to an oil. Purification by flash chromatography (1:1 ethyl acetate/hexanes) afforded 0.40 g (72% yield, 64% yield over two steps) of **13** as a viscous, colorless oil. R_f = 0.37, 60% ethyl acetate in hexanes. $[\alpha]_D^{25.3}$ = –54.7 (c = 0.93). IR (film): ν_{max} 3336, 2918, 1665, 1438, 1378, 1057, 994, 909, 771, 731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 5.58–5.63 (m, 2H), 4.83 (s, 1H), 4.28 (dd, J = 12.4, 8.0 Hz, 1H), 4.09 (ddd, J = 12.4, 6.0, 0.8 Hz, 1H), 3.31 (br s, 2H), 1.64 (dquint with outer peaks not clearly defined, J = 6.8, 0.8 Hz, 3H), 1.62 (s, 3H), 1.51 (s, 3H). ^{13}C NMR

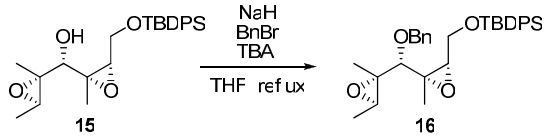
(100 MHz, $CDCl_3$, ppm): δ 139.87, 134.97, 126.63, 119.28, 74.20, 57.92, 18.63, 13.03, 12.80. HRMS (EI) *m/z* calc. for $C_9H_{16}O_2$ (M^+) 156.1150, found 156.1145.



(*S*,2*Z*,5*E*)-1-(*Tert*-butyldiphenylsilyloxy)-3,5-dimethylhepta-2,5-dien-4-ol (14). A solution of N,N-dimethylaminopyridine (DMAP) (16 mg, 0.13 mmol) and **13** (0.40 g, 2.5 mmol) in 25 mL CH_2Cl_2 was cooled to 0 °C. Triethylamine (0.53 mL, 0.38 g, 3.8 mmol) was added to the reaction solution followed by a slow addition of *t*-butyldiphenylsilyl chloride (0.73 mL, 0.77 g, 2.8 mmol) over 3 minutes. After 5 minutes at 0 °C, the solution was allowed to warm to rt and continued stirring for 5.5 h. The solution was quenched with 40 mL of water and was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to a pale yellow oil. Purification by flash chromatography (10% ethyl acetate in hexanes) afforded 0.86 g of **14** as a colorless oil. R_f = 0.35, 10% ethyl acetate in hexanes. $[\alpha]_D^{26.2}$ = –38.9 (c = 1.25). IR (film): ν_{max} 3465, 3068, 2931, 2857, 1471, 1426, 1376, 1245, 1106, 1054, 999, 825, 809, 739, 699, 688 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.68–7.70 (m, 4H), 7.36–7.45 (m, 6H), 5.54–5.58 (m, 1H), 5.51 (q of quint, J = 6.8, 1.6 Hz, 1H), 4.59 (br s, 1H), 4.32 (ddq, J = 12.8, 7.2, 0.8 Hz, 1H), 4.25 (ddq, J = 12.8, 5.6, 1.2 Hz, 1H), 1.70 (d, J = 3.6 Hz, 3H), 1.59 (d, J = 0.8 Hz, 3H), 1.57 (t, J = 1.2 Hz, 3H), 1.43 (s, 3H), 1.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ138.13, 135.70, 135.61, 135.04, 134.84, 133.73, 133.67, 129.72, 129.70, 127.72, 127.67, 127.30, 118.96, 74.31, 60.09, 26.83, 19.15, 18.33, 13.02, 12.89. HRMS (FAB) *m/z* calc. for $C_{25}H_{33}O_2Si$ (M^+ – H) 393.2250, found 393.2280.

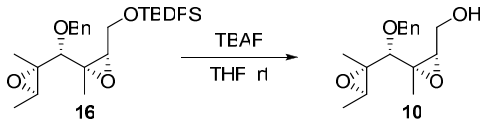


(*S*)-((2*R*,3*S*)-3-((*Tert*-butyldiphenylsilyloxy)methyl)-2-methyloxiran-2-yl)((2*R*,3*R*)-2,3-dimethyloxiran-2-yl)methanol (15). To a solution/suspension of **14** (0.86 g, 2.2 mmol) and $NaHCO_3$ (0.92 g, 11 mmol) in 22 mL of CH_2Cl_2 at 0 °C was added MCPBA (71.7 wt %, 2.10 g, 8.72 mmol). After stirring at 4 °C for 13 h, the mixture was diluted with CH_2Cl_2 (40 mL) and filtered through Celite. A solution of saturated aqueous Na_2CO_3 was added to the filtrate, and it was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$, dried over Na_2SO_4, and evaporated to a pale yellow oil. Purification by flash chromatography (22% ethyl acetate in hexanes) afforded 0.48 g (44% yield over two steps) of **15** as a colorless oil. R_f = 0.37, 25% ethyl acetate in hexanes. $[\alpha]_D^{25.0}$ = –20.7 (c = 0.90). IR (film): ν_{max} 3540, 3071, 2929, 2855, 1471, 1427, 1374, 1207, 1111, 1067, 1025, 993, 875, 822, 784, 737, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.67 (d, J = 1.2 Hz, 4H), 7.37–7.44 (m, 6 H), 3.87 (d, J = 5.6 Hz, 2H), 3.54 (d, J = 1.6 Hz, 1H), 3.32 (q, J = 5.6 Hz, 1H), 3.09 (t, J = 5.6 Hz, 1H), 2.23 (d, J = 2.4 Hz, 1H), 1.30 (d, J = 5.6 Hz, 3H), 1.29 (s, 3H), 1.25 (s, 3H), 1.07 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 135.60, 135.54, 133.05, 132.88, 129.92, 127.84, 72.52, 64.55, 61.83, 60.65, 54.71, 26.78, 19.19, 17.66, 14.32, 13.22. HRMS (FAB) *m/z* calc. for $C_{25}H_{35}O_4Si$ (M^+ + H) 427.2305, found 427.2299.

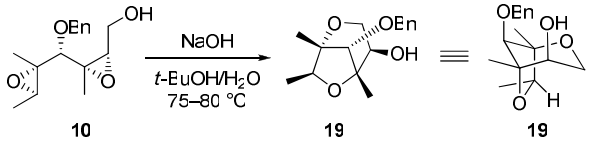


(((2S,3S)-3-((S)-Benzyloxy((2S,3R)-2,3-dimethyloxiran-2-yl)methyl)-3-methyloxiran-2-yl)methoxy)(tert-butyl)diphenylsilane (16). To a suspension of NaH (95%, 41 mg, 1.7 mmol) in THF (8.4 mL) was added **15** (dried by azeotroping from toluene, 0.36 g, 0.84 mmol) at rt. A small amount of bubbling occurred, and the reaction mixture stirred at 65–70 °C. After 10 minutes, the mixture was allowed to cool to rt and tetrabutylammonium iodide (16 mg, 0.042 mmol) and benzyl bromide (filtered through neutral alumina, 0.30 mL, 0.43 g, 2.5 mmol) were added. After 3 h at 65–70 °C, the mixture was carefully quenched with saturated aqueous NH_4Cl (20 mL) and was extracted with Et_2O (4 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to a yellow oil. Purification by flash chromatography (8% ethyl acetate in

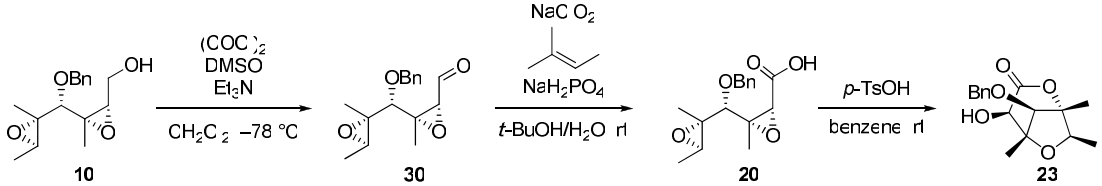
hexanes) gave 309 mg (71% yield) of **16** as a colorless oil. R_f = 0.26, 6% ethyl acetate in hexanes. $[\alpha]_D^{24.6}$ = –5.9 (c = 0.83). IR (film): ν_{max} 3071, 2930, 2857, 1455, 1427, 1383, 1110, 1075, 1028, 909, 882, 822, 733, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.67–7.71 (m, 4H), 7.33–7.43 (m, 6H), 7.23–7.32 (m, 5H), 4.68 (d, J = 11.6 Hz, 1H), 4.51 (d, J = 11.6 Hz, 1H), 3.93 (dd, J = 11.6, 4.0 Hz, 1H), 3.72 (dd, J = 11.6, 6.0 Hz, 1H), 3.23 (s, 1H), 3.16 (q, J = 5.6 Hz, 1H), 3.04 (dd, J = 6.0, 4.4 Hz, 1H), 1.33 (s, 3H), 1.23 (d, J = 5.6 Hz, 3H), 1.22 (s, 3H), 1.07 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 138.58, 135.70, 135.57, 133.29, 133.01, 129.87, 129.85, 128.20, 127.82, 127.79, 127.66, 127.42, 80.88, 73.18, 63.36, 62.29, 61.97, 60.25, 55.69, 26.82, 19.24, 18.34, 14.73, 13.40. HRMS (FAB) *m/z* calc. for $C_{32}H_{41}O_4Si$ (M^+ + H) 517.2774, found 517.2764.



((2*S*,3*S*)-3-((*S*)-Benzyloxy((2*S*,3*R*)-2,3-dimethyloxiran-2-yl)methyl)-3-methyloxiran-2-yl)methanol (10). To a solution of **16** (0.30 g, 0.58 mmol) in THF (11mL) was added tetrabutylammonium fluoride (1M in THF, 1.2 mL, 1.2 mmol). After 2.5 h at rt, the solvent was removed by rotary evaporation, and the residue was dissolved in CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). It was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated to an oil. Purification by flash chromatography (40% ethyl acetate in hexanes) afforded 135 mg (83% yield) of **10** as a colorless oil. R_f = 0.33, 40% ethyl acetate in hexanes. $[\alpha]_D^{24.4}$ = –28.0 (c = 0.86). IR (film): ν_{max} 3427, 2991, 2929, 1454, 1382, 1260, 1213, 1088, 1019, 875, 800, 734, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.26–7.32 (m, 5H), 4.75 (d, J = 12 Hz, 1H), 4.56 (d, J = 12 Hz, 1H), 3.81 (dd, J = 12.4, 5.2 Hz, 1H), 3.46 (dd, J = 12.4, 7.6 Hz, 1H), 3.19 (br s, 1H), 3.06 (s, 1H), 3.01 (dd, J = 7.6, 5.2 Hz, 1H), 2.90 (q, J = 5.6 Hz, 1H), 1.47 (s, 3H), 1.34 (s, 3H), 1.25 (d, J = 5.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 138.12, 128.34, 127.71, 127.68, 82.50, 72.25, 61.85, 61.52, 60.46, 60.45, 19.13, 13.53, 13.20. HRMS (FAB) *m/z* calc. for $C_{16}H_{23}O_4$ (M^+ + H) 279.1596, found 279.1586.

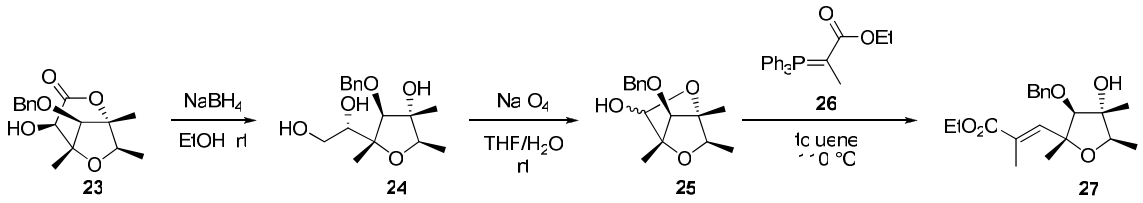


8-(Benzyloxy)-1,5,7-trimethyl-2,6-dioxabicyclo[3.2.1]octan-4-ol (19). To a solution of racemic **10** (50 mg, 0.18 mmol) in *t*-BuOH (0.9 mL) was added NaOH (0.5M in H_2O, 0.90 mL, 0.45 mmol). After stirring at 75–80 °C for 6 h, the solution was quenched with saturated aqueous NH_4Cl (1 mL) and was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layeres were dried over Na_2SO_4 and evaporated to an oil. Purification by flash chromatography (45% ethyl acetate in hexanes) afforded 43.3 mg (87% yield) of **19** as a colorless oil. Copies of the COSY and NOESY spectra are included below as well as peak assignments to all hydrogen atoms on aliphatic carbon atoms. R_f = 0.31, 45% ethyl acetate in hexanes. IR (film): ν_{max} 3426, 2972, 2926, 2863, 1454, 1372, 1277, 1110, 1070, 1043, 1026, 903, 860, 827, 731, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.26–7.39 (m, 5H), 4.62 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.4 Hz, 1H), 4.33 (s, 1H), 4.21 (dd, J = 13.2, 2.4 Hz, 1H), 3.85 (d, J = 13.2 Hz, 1H), 3.65 (m (apparent br d), 1H), 3.49 (q, J = 6.4 Hz, 1H), 2.13 (d, J = 7.2 Hz, 1H), 1.43 (s, 3H), 1.23 (s, 3H), 1.01 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 138.12, 128.40, 127.63, 127.22, 88.94, 86.10, 79.99, 76.02, 75.52, 73.27, 72.05, 19.30, 18.37, 17.05. HRMS (FAB) *m/z* calc. for $C_{16}H_{21}O_4$ (M^+ – H) 277.1440, found 277.1432.

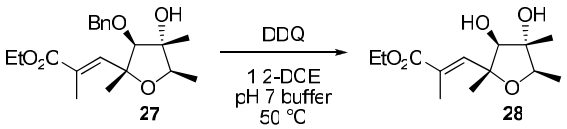


(1*R*,4*R*,5*R*,7*R*,8*R*)-8-(Benzyloxy)-4-hydroxy-1,5,7-trimethyl-2,6-dioxabicyclo[3.2.1]octan-3-one (23). To a solution of oxalyl chloride (0.19 mL, 0.28 g, 2.2 mmol) in CH_2Cl_2 (7 mL) at –78 °C was added DMSO (0.25 mL, 0.28 g, 3.6 mmol). After 10 min at –78 °C, **10** (200 mg, 0.72 mmol) was added. After 20 min at –78 °C, triethylamine (0.70 mL, 0.51 g, 5.0 mmol) was added, and the solution stirred at –78 °C for 30 min before warming

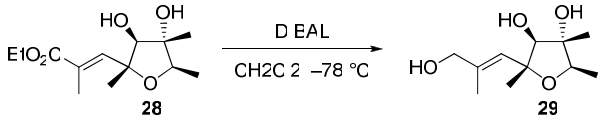
to rt. After 45 min at rt, the reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to a yellow oil (**30**), which was used directly in the next reaction. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 9.38 (d, J = 3.8 Hz, 1H), 7.30–7.39 (m, 5H), 4.64 (d, J = 11.8 Hz, 1H), 4.54 (d, J = 11.8 Hz, 1H), 3.23 (d, J = 3.8 Hz, 1H), 3.15 (s, 1H), 2.81 (q, J = 5.5 Hz, 1H), 1.51 (s, 3H), 1.32 (s, 3H), 1.23 (d, J = 5.5 Hz, 3H). To a solution of crude **30** in *t*-BuOH (5.8 mL) was added 2.9 mL of a pH = 3.8 buffer (NaH_2PO_4, 0.41M in H_2O), 2-methyl-2-butene (0.34 mL, 0.23 g, 3.2 mmol), and $NaClO_2$ (80%, 326 mg, 2.88 mmol). After stirring at rt for 1.5 h, the solution was diluted with pH = 3.8 buffer (10 mL) and was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to an oil (**20**) that was used directly in the next reaction. To a solution of crude **20** in 8 mL of benzene was added *p*-toluenesulfonic acid monohydrate (55 mg, 0.29 mmol). After 2 h at rt, the solution was diluted with water (10 mL) and was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to an oil. Purification by flash chromatography (30% ethyl acetate in hexanes) afforded 157 mg (68% yield over three steps) of **23** as a colorless oil. R_f = 0.36, 30% ethyl acetate in hexanes. Chiral SFC (supercritical CO_2 with 5% MeOH, ADH column, 214 nm UV detection, 4.78 (minor) and 5.27 (major) min retention times of the enantiomers) showed a 92% *ee*. $[\alpha]_D^{24.9}$ = –20.0 (c = 0.96). IR (film): ν_{max} 3434, 2997, 2978, 1720, 1453, 1373, 1283, 1265, 1157, 1127, 1066, 1056, 1028, 949, 845, 830, 740, 722, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.30–7.40 (m, 5H), 4.74 (d, J = 11.6 Hz, 1H), 4.64 (d, J = 11.6 Hz, 1H), 4.10 (q, J = 6.8 Hz, 1H), 4.07 (d, J = 3.6 Hz, 1H), 3.96 (d, J = 3.6 Hz, 1H), 3.85 (s, 1H), 1.45 (s, 6H), 1.27 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 172.63, 137.21, 128.53, 128.09, 127.72, 91.02, 83.07, 82.95, 82.63, 75.55, 74.93, 18.45, 16.33, 15.83. HRMS (EI) *m/z* calc. for $C_{16}H_{20}O_5$ (M^+) 292.1311, found 292.1305.



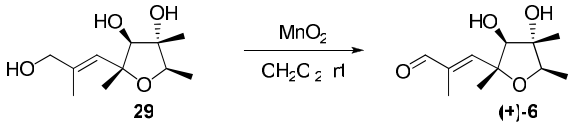
(*E*)-Ethyl-3-((2*R*,3*S*,4*R*,5*R*)-3-(benzyloxy)-4-hydroxy-2,4,5-trimethyltetrahydrofuran-2-yl)-2-methylacrylate (27). To a solution of $NaBH_4$ (91 mg, 2.4 mmol) in ethanol (7 mL) was added **23** (140 mg, 0.48 mmol) as a solution in 4 mL of ethanol. After 4.5 h at rt, the solvent was removed by rotary evaporation, and the remaining residue was dissolved/suspended in ethyl acetate and quenched with 1N aqueous HCl until the pH was <2. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to a sticky oil (**24**) that was used directly in the next step. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.27–7.37 (m, 5H), 4.78 (d, J = 11.8 Hz, 1H), 4.61 (d, J = 11.8 Hz, 1H), 4.07 (s, 1H), 3.88 (q, J = 6.6 Hz, 1H), 3.77–3.82 (m, 1H), 3.56–3.64 (m, 2H), 1.26 (s, 3H), 1.15 (s, 3H), 1.14 (d, J = 6.6 Hz, 3H). To a solution of crude **24** in THF (3 mL) was slowly added $NaIO_4$ (113 mg, 0.53 mmol) as a solution in 3 mL of water. After 1 h at rt, the reaction solution was diluted with water (10 mL) and extracted with ethyl acetate (5 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to a pale yellow oil (**25**) that was used directly in the next step. The ^{1}H NMR spectrum in $CDCl_3$ was unclean and showed no peak corresponding to an aldehyde hydrogen; it is presumably in the lactol form in $CDCl_3$. In DMSO-d_6 an aldehyde peak was present, and the spectrum showed multiple forms of **25** (both diastereomers of the lactol and the aldehyde). ^{1}H NMR (300 MHz, ppm) diagnostic signals: δ 4.70 (s, $CDCl_3$), 3.93 (q, J = 6.9 Hz, $CDCl_3$), 3.46 (s, $CDCl_3$); 9.53 (s, DMSO-d_6). The phosphorus ylide (carbethoxyethylidene)triphenylphosphorane (**26**) (0.52 g, 1.4 mmol) was added to a solution of crude **25** in toluene (5 mL). After 18 h at 110 °C, the solvent was removed by rotary evaporation. The remaining residue was purified by flash chromatography (25% ethyl acetate in hexanes) to afford 136 mg (80% over three steps) of **27** (10:1 *E*/*Z*, *Z* isomer has a peak in the ^{1}H NMR spectrum ($CDCl_3$) at δ 5.33 (d, J = 1.6 Hz, 1H)) as a very pale yellow oil. Data for *E* isomer: R_f = 0.30, 25% ethyl acetate in hexanes. $[\alpha]_D^{25.3}$ = +48.3 (c = 0.99). IR (film): ν_{max} 3468, 2982, 2934, 1708, 1691, 1453, 1370, 1256, 1207, 1131, 1105, 1070, 1023, 748, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.29–7.40 (m, 5H), 6.87 (q, J = 1.2 Hz, 1H), 4.82 (d, J = 11.6 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.189 (q (expected dq), J = 7.2 Hz, 1H), 4.187 (q (expected dq), J = 7.2 Hz, 1H), 3.89 (s, 1H), 3.68 (q, J = 6.4 Hz, 1H), 1.94 (d, J = 1.2 Hz, 3H), 1.44 (s, 1H), 1.32 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.24 (s, 3H), 1.17 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 168.53, 148.49, 138.08, 128.43, 127.74, 127.52, 127.41, 92.02, 81.87, 80.32, 77.16, 72.72, 60.81, 21.79, 16.41, 14.26, 13.54, 12.50. HRMS (FAB) *m/z* calc. for $C_{20}H_{29}O_5$ (M^+ + H) 349.2015, found 349.2026.



(E)-Ethyl 3-((2R,3S,4R,5R)-3-(benzyloxy)-4-hydroxy-2,4,5-trimethyltetrahydrofuran-2-yl)-2-methylacrylate (28).[3] To a solution of **27** (66 mg, 0.19 mmol) in 1,2-dichloroethane (3.1 mL) and pH 7 buffer (0.31 mL) was added DDQ (259 mg, 1.14 mmol). After 13 h at 50 °C, saturated aqueous $NaHCO_3$ (10 mL) and ethyl acetate (10 mL) were added, and the mixture was filtered through Celite. The filtrate was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated to an brown oil. Purification by flash chromatography (55% ethyl acetate in hexanes) afforded 47 mg (95% yield) of **28** (13:1 *E*/*Z*, *Z* isomer has a peak in the ^{1}H NMR spectrum ($CDCl_3$) at δ 6.21 (d, J = 1.6 Hz, 1H)) as a very pale purple solid (mp = 94–96 °C). R_f = 0.34, 55% ethyl acetate in hexanes. $[\alpha]_D^{24.6}$ = +20.2 (c = 0.86). IR (film): ν_{max} 3436, 2982, 2936, 1689, 1644, 1445, 1370, 1259, 1101, 1056, 1020, 965, 949, 913, 748, 732 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.84 (q (apparent d), J = 0.8 Hz, 1H), 4.13 (q, J = 6.8 Hz, 2H), 4.04 (s, 1H), 3.75 (br s, 1H), 3.63 (q, J = 6.4 Hz, 1H), 3.37 (br s, 1H), 1.93 (s, 3H), 1.25 (t, J = 6.8 Hz, 3H), 1.22 (s, 3H), 1.12 (s, 3H), 1.12 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 169.09, 148.60, 127.31, 85.18, 82.09, 80.12, 77.17, 61.04, 21.19, 15.96, 14.15, 13.95, 12.61. HRMS (EI) *m/z* calc. for $C_{13}H_{22}O_5$ (M^+) 258.1467, found 258.1463.



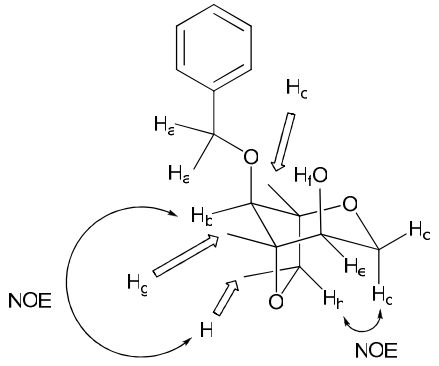
(2*R*,3*S*,4*S*,5*R*)-2-((*E*)-3-Hydroxy-2-methylprop-1-enyl)-2,4,5-trimethyltetrahydrofuran-3,4-diol (29).[3] A solution of diisobutylaluminum hydride (1.5M in toluene, 0.93 mL, 1.4 mmol) was added to a solution of **28** (45 mg, 0.17 mmol) in CH_2Cl_2 (2.3 mL) at –78 °C. The solution became yellow. After 1.5 h at –78 °C, the solution was allowed to warm to 0 °C. After 1 h at 0 °C, the solution was carefully quenched with a saturated aqueous solution of potassium sodium tartrate (Rochelle's salt, 5 mL). Et_2O (5 mL) was added to the solution, and it stirred vigorously at rt for 12 h. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (7 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to an oil. Purification by flash chromatography (ethyl acetate) afforded 31 mg (83% yield) of **29** as a sticky, colorless oil. R_f = 0.25, ethyl acetate. $[\alpha]_D^{24.9}$ = +28.4 (c = 1.09). IR (film): ν_{max} 3349, 2980, 2928, 2360, 1441, 1377, 1183, 1105, 1053, 1017, 948 cm^{-1}. ^{1}H NMR (400 MHz, acetone-d_6, ppm): δ 5.64 (q, J = 1.2 Hz, 1H), 4.25 (d, J = 5.6 Hz, 1H), 4.06 (d, J = 5.6 Hz, 1H), 3.83–3.90 (m, 3H), 3.75 (s, 1H), 3.64 (q, J = 6.4 Hz, 1H), 1.78 (d, J = 1.2 Hz, 3H), 1.17 (s, 3H), 1.10 (s, 3H), 1.08 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6, ppm): δ 135.62, 133.92, 87.11, 82.69, 80.53, 77.70, 68.66, 23.16, 16.49, 14.48, 14.19. HRMS (CI) *m/z* calc. for $C_{11}H_{21}O_4$ (M^+ + H) 217.1440, found 217.1443.



(*E*)-3-((2*R*,3*S*,4*S*,5*R*)-3,4-Dihydroxy-2,4,5-trimethyltetrahydrofuran-2-yl)-2-methylacrylaldehyde ((+)-5-*epi*-citreoviral, (+)-6).[3] To a solution of **29** (17 mg, 0.080 mmol) in 2.7 mL of CH_2Cl_2 was added activated MnO_2 (85%, 81 mg, 0.80 mmol), and the mixture stirred vigorously. After 2 h at rt, the mixture was filtered through Celite, and the Celite was washed with CH_2Cl_2 (3 × 10 mL) and ethyl acetate (3 × 10 mL). The filtrate was evaporated to an oil, which was purified by flash chromatography (60% ethyl acetate in hexanes) to afford 8.7 mg (52% yield) of (+)-**6** as a colorless oil. R_f = 0.25, 60% ethyl acetate in hexanes. $[\alpha]_D^{25.0}$ = +13.2 (c = 1.74). IR (film): ν_{max} 3415, 2983, 2935, 2360, 1677, 1636, 1446, 1380, 1181, 1104, 1061, 1022 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.39 (s, 1H), 6.62 (q, J = 1.2 Hz, 1H), 4.11 (d, J = 6.4 Hz, 1H), 3.75 (q, J = 6.4 Hz, 1H), 1.99 (d, J = 6.4 Hz, 1H), 1.90 (d, J = 1.2 Hz, 3H), 1.35 (s, 3H), 1.24 (s, 3H), 1.21 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 195.55, 160.32, 137.97, 85.21, 82.48, 80.31, 78.23, 20.98, 16.58, 14.50, 9.44. HRMS (EI) *m/z* calc. for $C_{11}H_{18}O_4$ (M^+) 214.1205, found 214.1196.

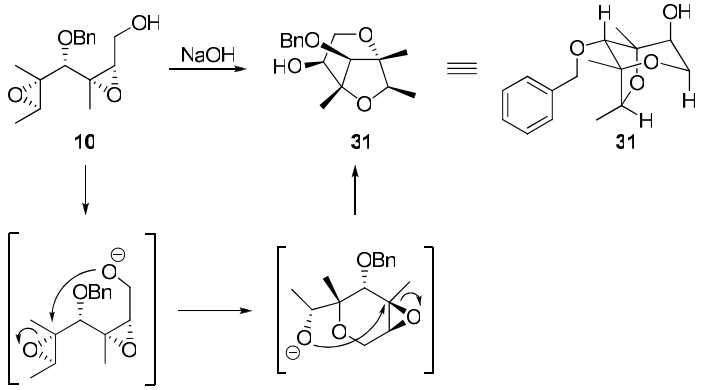
Rationale for Structural Assignment of Compound 19.

Using the ^{1}H NMR, COSY, and NOESY spectra of **19**, the aliphatic hydrogen atoms in the ^{1}H NMR spectrum were assigned as shown on page S18. The chemical shift values, the splitting patterns in the ^{1}H NMR spectrum and the coupling (both J values and COSY data) support the placement of the hydrogen atoms on the carbon skeleton. The NOESY spectrum was used to gain further insight. Diastereotopic H_a and $H_{a'}$ were not differentiated. The diastereotopic H_d and $H_{d'}$ were assigned based on a through-space interaction in the NOESY (which is not observed in the COSY) between the doublet of doublets at 4.21 ppm (the axial $H_{d'}$) and the quartet at 3.49 ppm (H_h). That interaction also supports the proposed bicyclic structure. The equatorial methyl groups were tentatively assigned based on a NOESY crosspeak between the doublet at 1.01 ppm (H_i) and the singlet at 1.23 ppm (H_c), leaving H_g as the singlet at 1.43 ppm. As further support of the bicyclic structure and support for the stereochemistry of the carbon bearing the benzyloxy group, there is a crosspeak in the NOESY spectrum between the singlet at 4.33 ppm (H_b) and the doublet at 1.01 ppm (H_i). This crosspeak is not present in the COSY spectrum.



19

As an alternative to the proposed Payne-rearrangement/epoxide opening sequence yielding **19**, the reaction of **10** with aqueous sodium hydroxide could occur as shown in Scheme S1 to afford compound **31**. This process is similar to the proposed mechanism for the formation of compound **23** but under basic conditions. The possibility of this reaction and therefore the formation of **31** instead of **19** was presented by a reviewer of the original manuscript. The author thanks the reviewer for their important discussion, observations, and contribution to this work and presents the following data in support of the product of the reaction of **10** with NaOH as **19**.

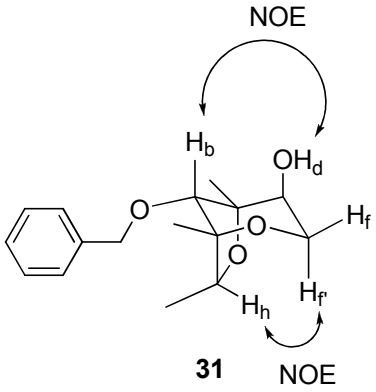


Scheme S1. Alternative to proposed reaction of **10** with sodium hydroxide.

The two differences between **31** and **19** are the absolute stereochemistry of the 2,6-dioxabicyclo[3.2.1]octane ring and the stereochemistry at the carbon bearing the benzyloxy group. The absolute stereochemistry is not relevant in this case because **19** was made as a racemate, so the only difference between them is the stereochemistry at the carbon bearing the benzyloxy group. The NOESY crosspeak mentioned above between H_c and H_i support the structure of the reaction of **10** and NaOH as **19**, but ideally compound **31** could be formed and structurally characterized to differentiate **19** and **31**.

Because compound **31** is structurally identical to **23** but in a lower oxidation state, compound **10** was treated with *p*-toluenesulfonic acid in benzene at room temperature to form **31** (the same way **23** was synthesized). A ^{1}H NMR

spectrum (DMSO-d_6) of the purified material showed a 4:1 ratio of a new compound (proposed structure **31**) to **19**. This spectrum was compared to a spectrum of **19** in DMSO-d_6, and the remaining peaks were assigned to **31** using the ^{1}H NMR, COSY, and NOESY spectra (see page S32). In DMSO-d_6 the alcohol hydrogen atom appears as a doublet at 5.09 ppm (H_d), and there is a crosspeak in the NOESY indicating a through-space interaction with the singlet at 3.60 ppm (H_b). This is consistent with an axial hydrogen atom on the carbon bearing the benzyloxy group as shown in **31**. The bicyclic structure of **31** is supported by a crosspeak between H_h and $H_{f'}$. These data support the structure of the major product of the reaction of **10** with *p*-TsOH to be **31**, which in turn supports the proposition that the product formed by the treatment of **10** with NaOH is not **31**.



31

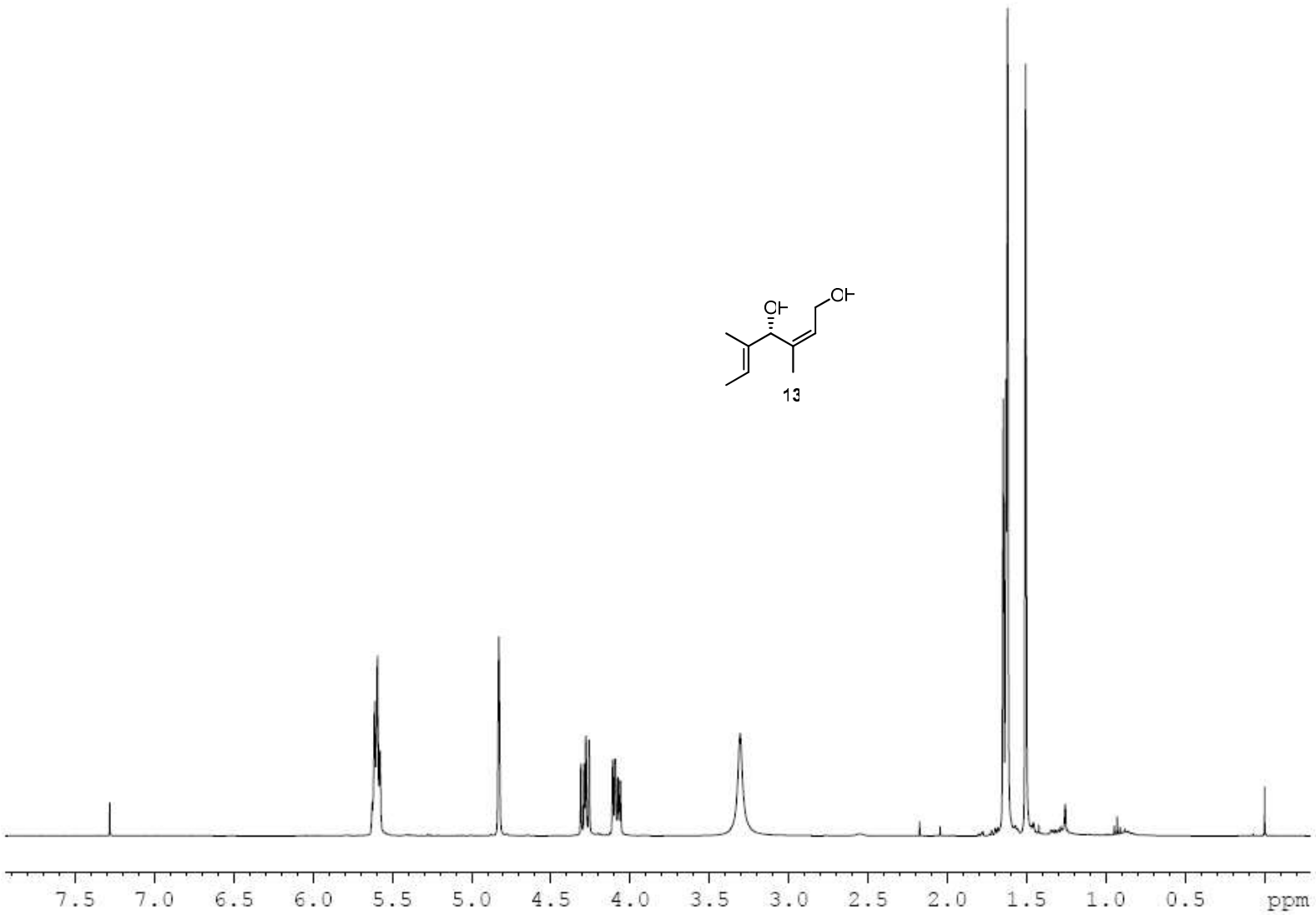
8-(Benzyloxy)-1,5,7-trimethyl-2,6-dioxabicyclo[3.2.1]octan-4-ol (31). To a solution of racemic **10** (20 mg, 0.072 mmol) in 1 mL of benzene was added *p*-toluenesulfonic acid (5.5 mg, 0.029 mmol). After 2 h at room temperature the reaction was diluted with 2 mL of water and was extracted with 3 x 2 mL of ethyl acetate. The organic layers were combined, dried over sodium sulfate, and evaporated to an oil. The oil was purified by flash chromatography (45% ethyl acetate in hexanes) to afford 15 mg (75% total yield) of a 4:1 mixture of **31**:**19** as a colorless oil. R_f = 0.31, 45% ethyl acetate in hexanes. NMR data reported for **31**; copies of the ^{1}H NMR, COSY, and NOESY spectra are below. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 7.25–7.13 (m, 5H), 5.09 (d, J = 4.3 Hz, 1H), 4.44 (d, J = 2.4 Hz, 2H), 3.86 (q, J = 6.8 Hz, 1H), 3.68 (dd, J = 12.4, 2.8 Hz, 1H), 3.60 (s, 1H), 3.30 (dd, J = 4.3, 2.8 Hz, 1H), 3.27 (d, J = 12.4 Hz, 1H), 1.12 (s, 3H), 1.04 (s, 3H), 0.97 (d, J = 6.8 Hz, 3H).

Supporting Information References:

1. Funk, T. W.; Berlin, J. M; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840–1846.

2. Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth*. **1990**, *69*, 96–102.

3. The last 3 steps are slight modifications of Peng and Woerpel's synthesis of (±)-5-*epi*-citreoviral: Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2002**, *4*, 2945–2948.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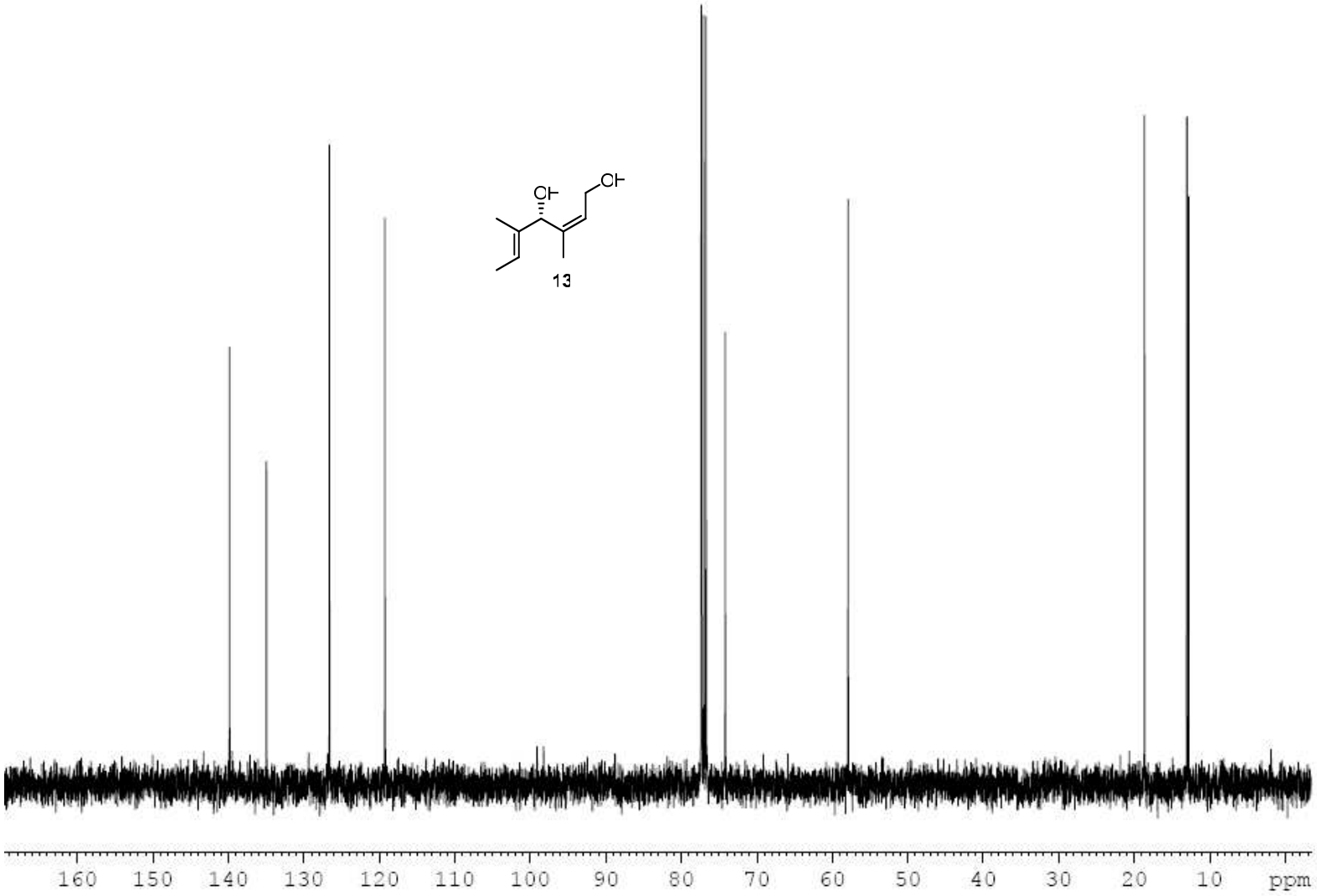
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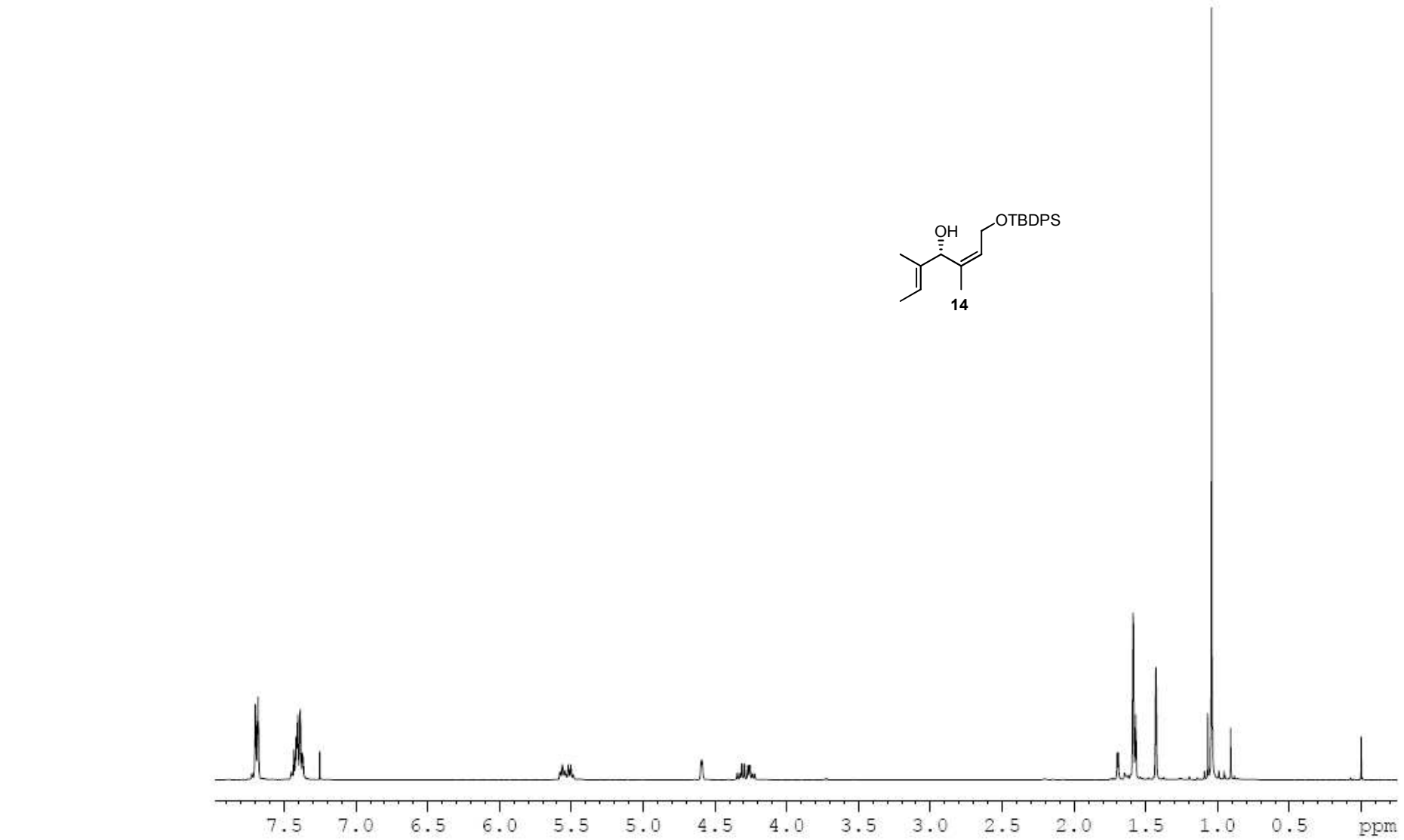
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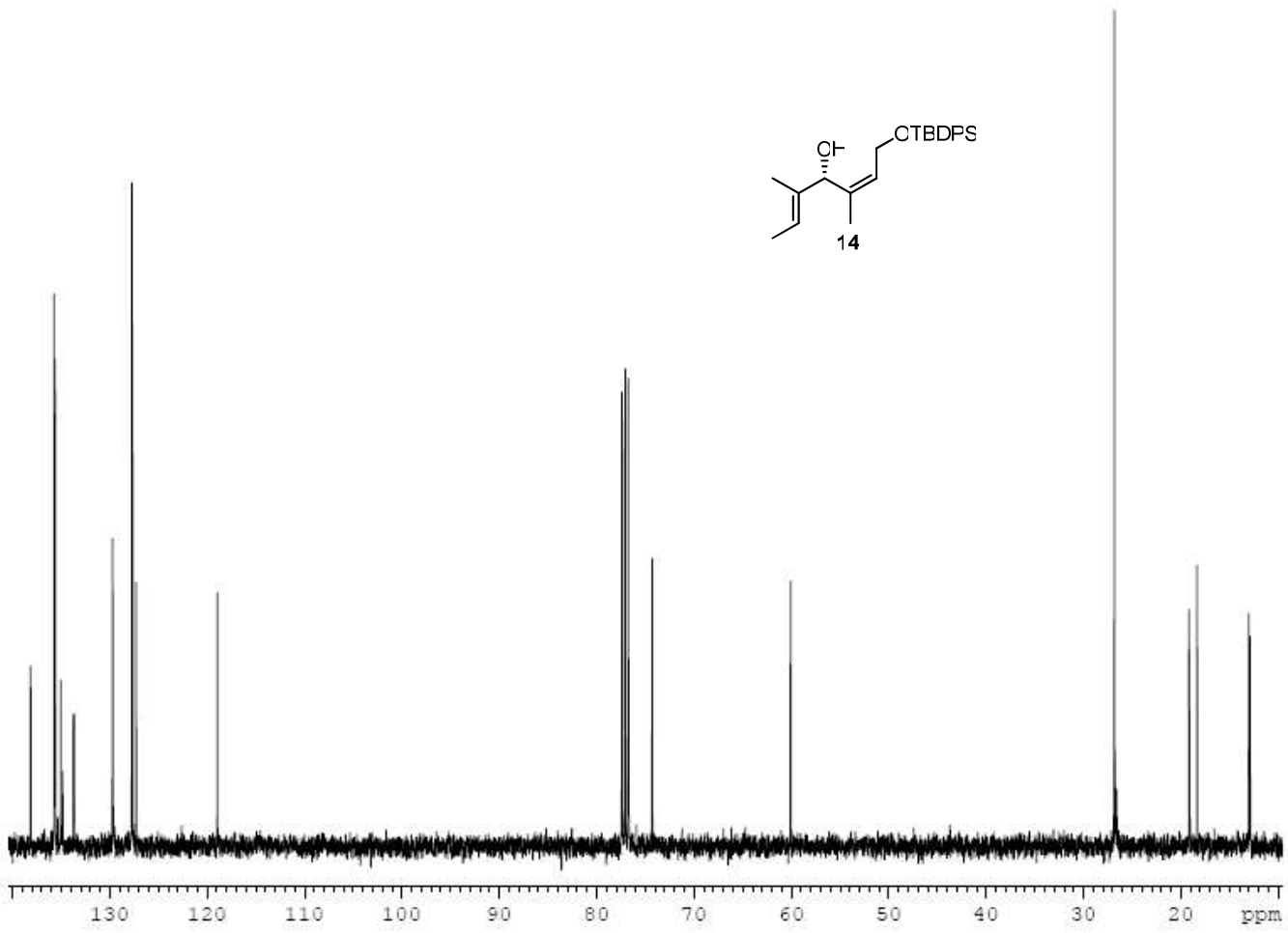
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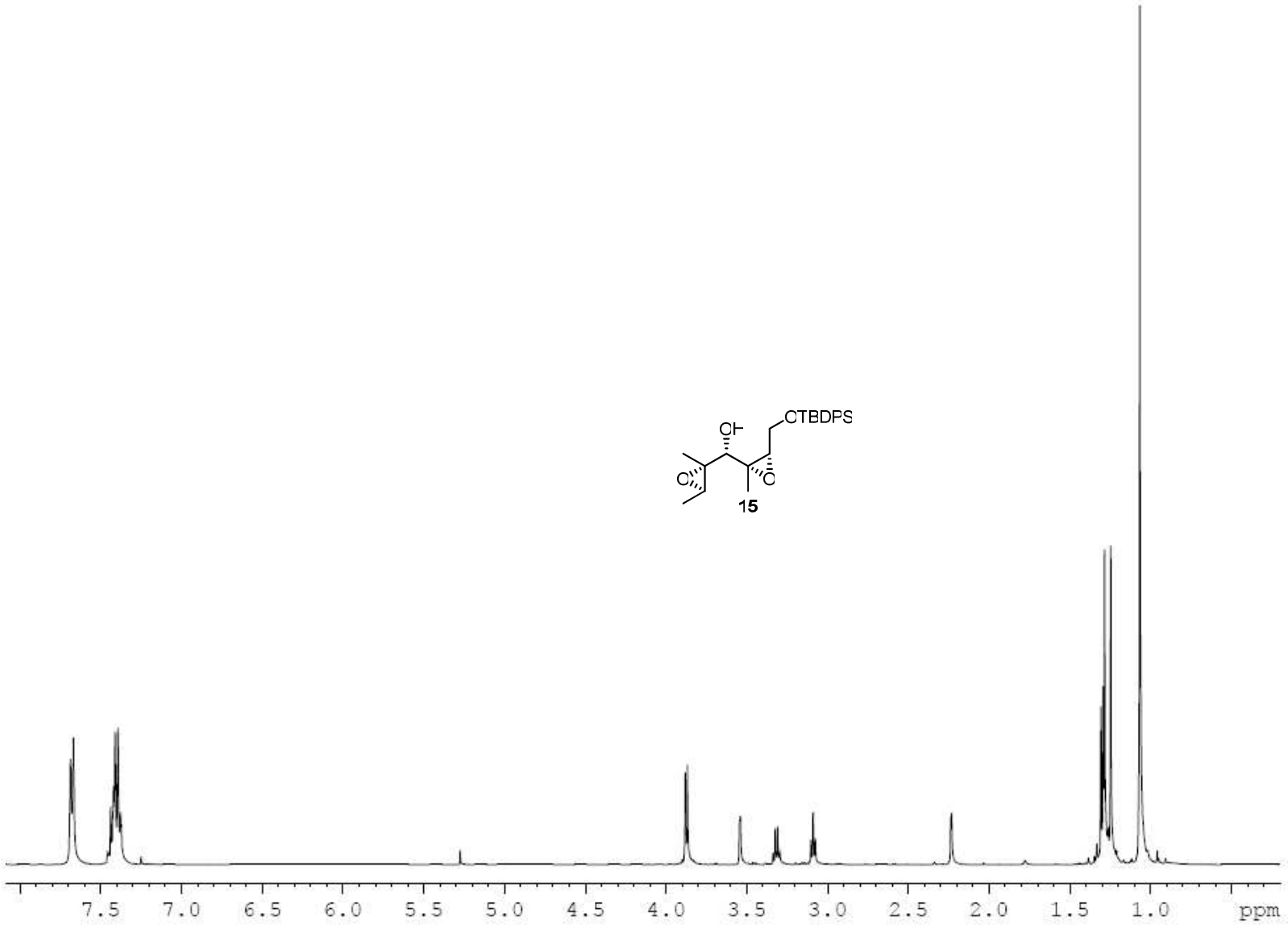
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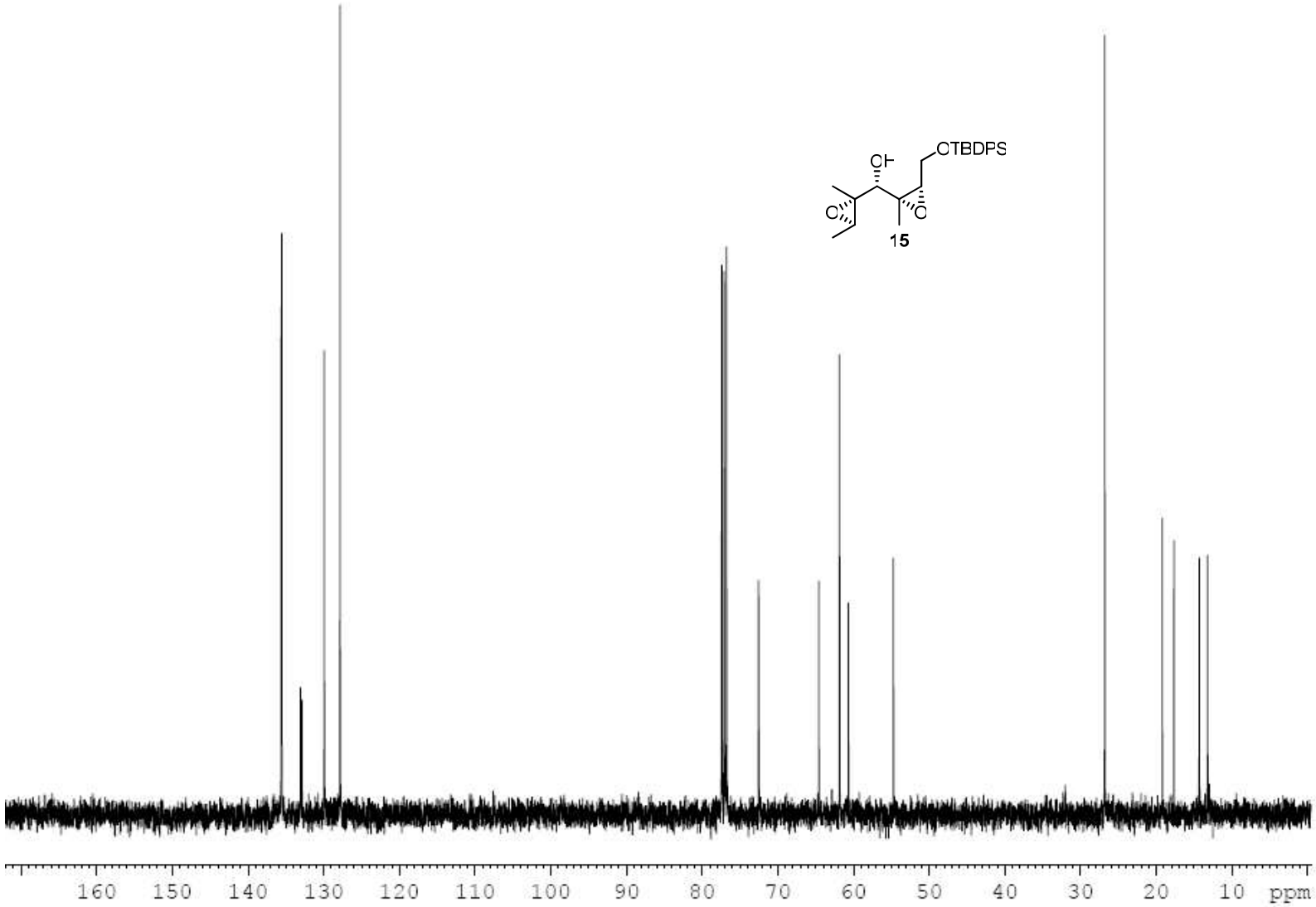
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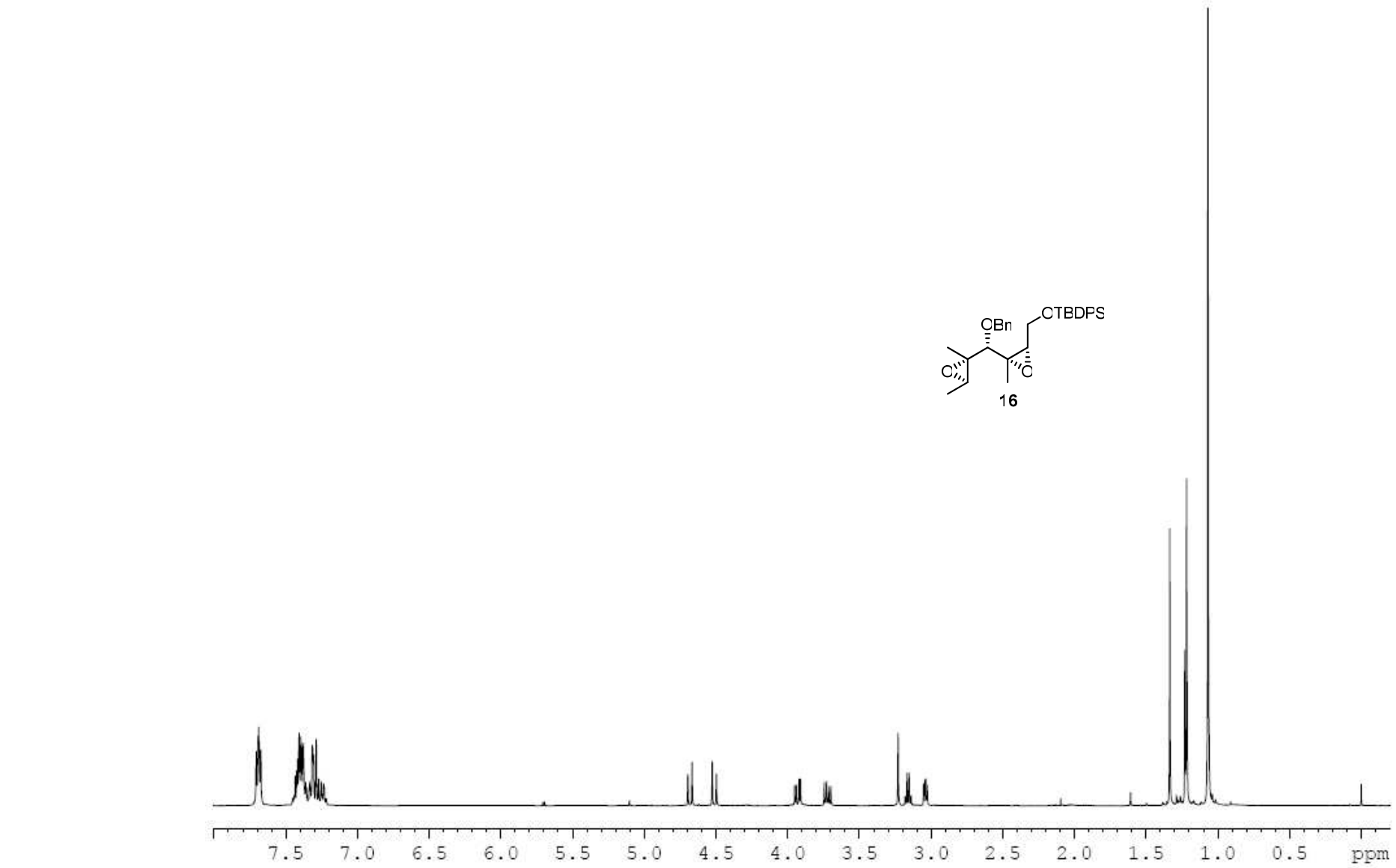
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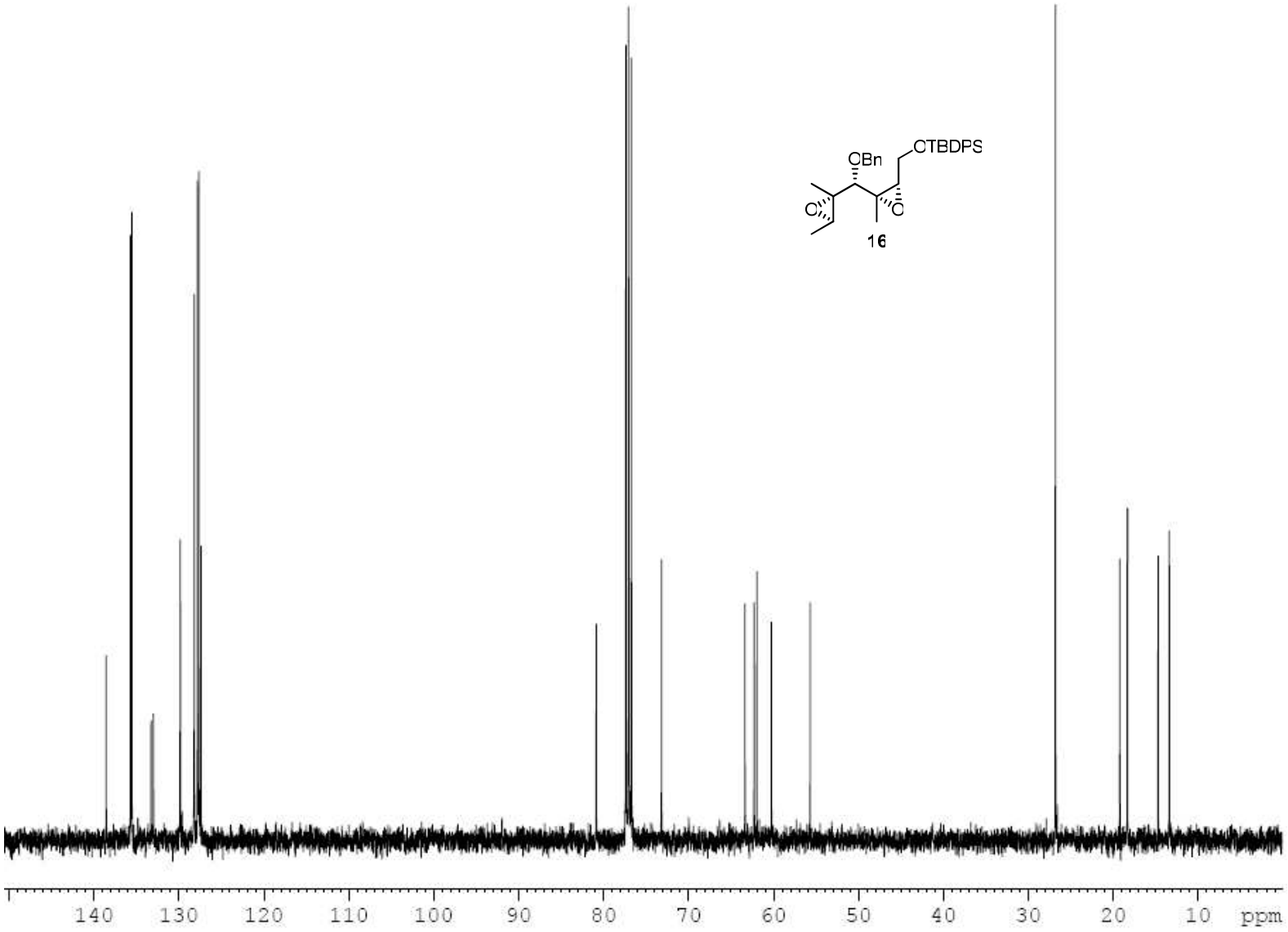
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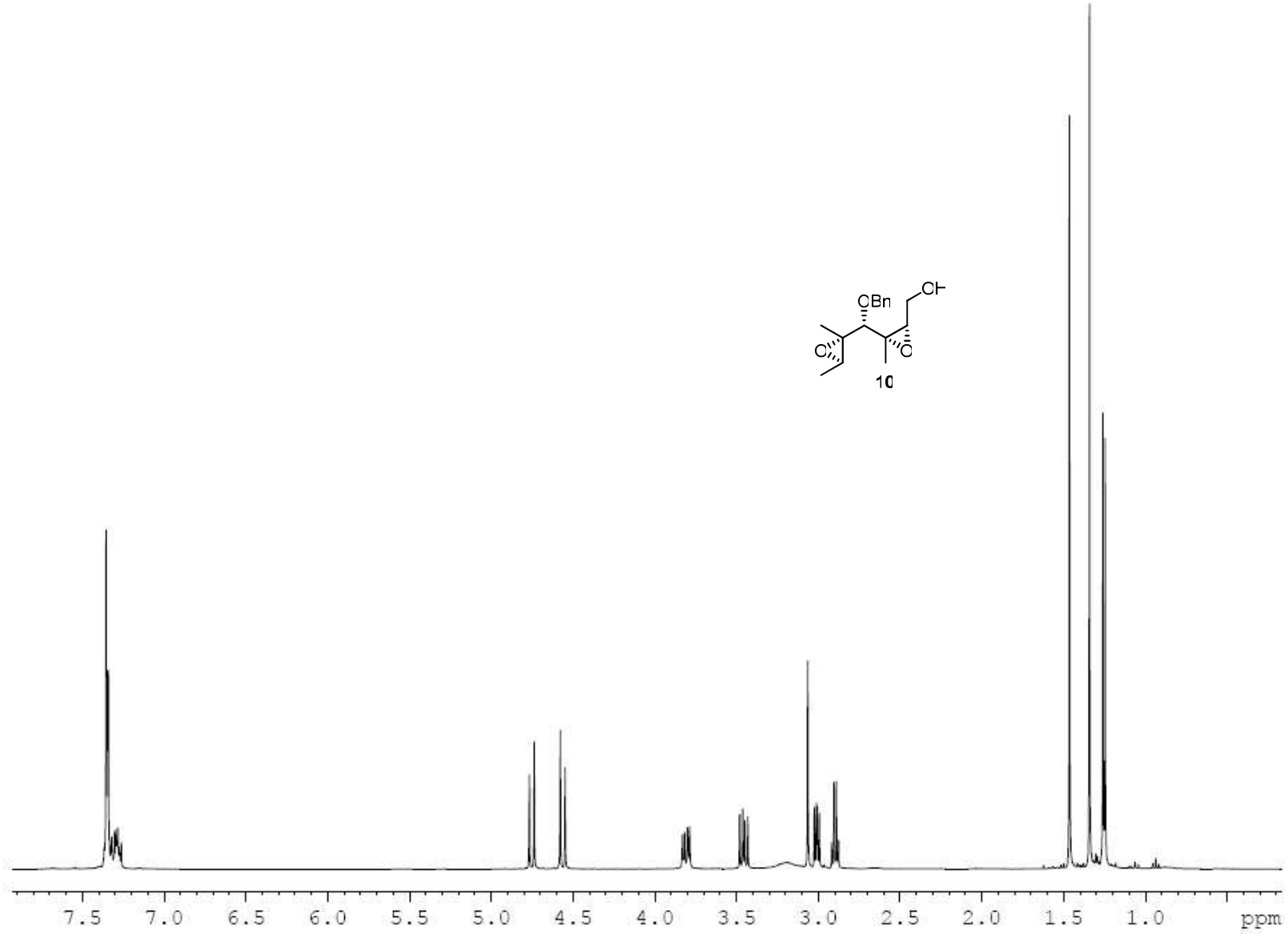
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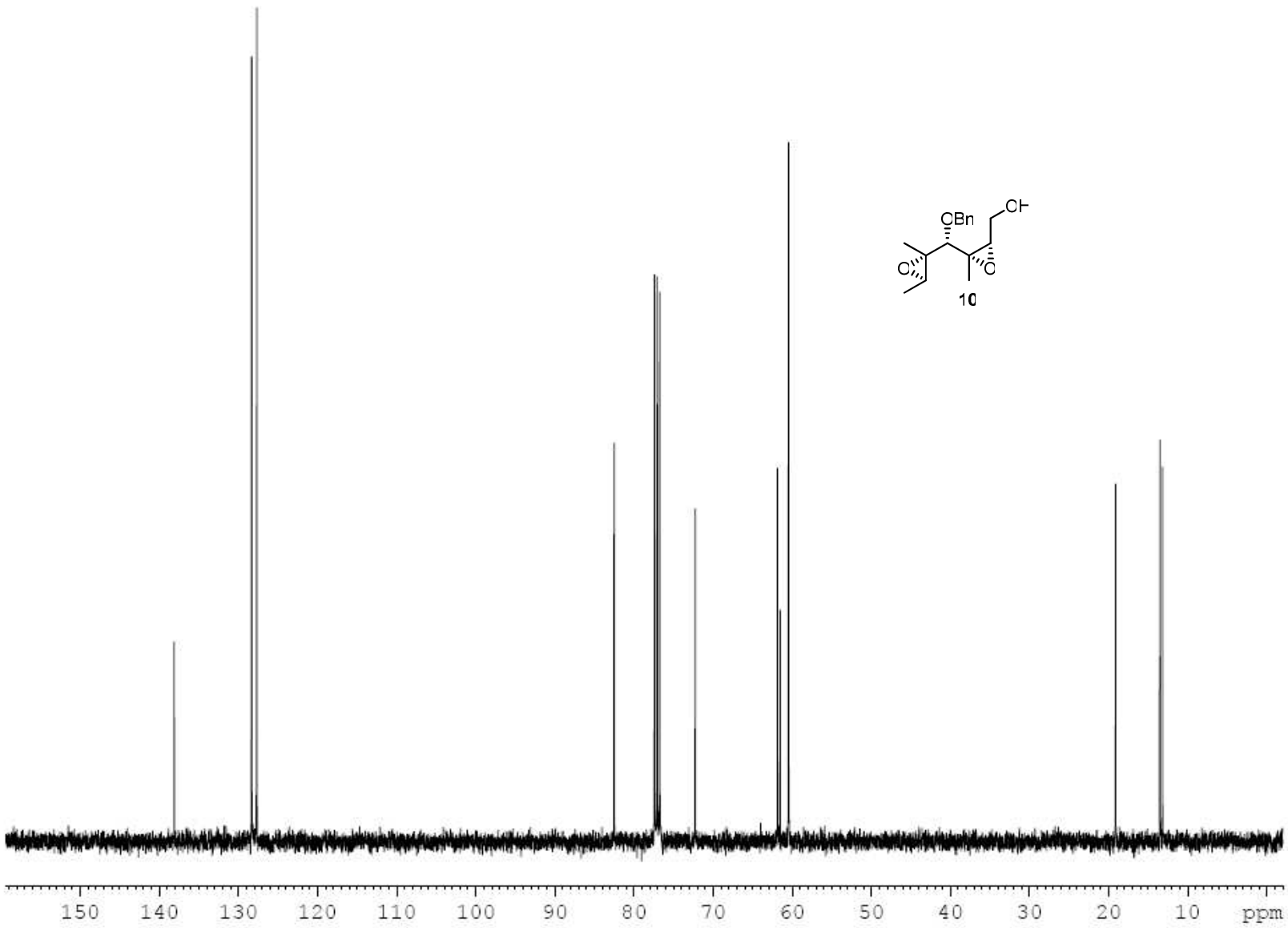
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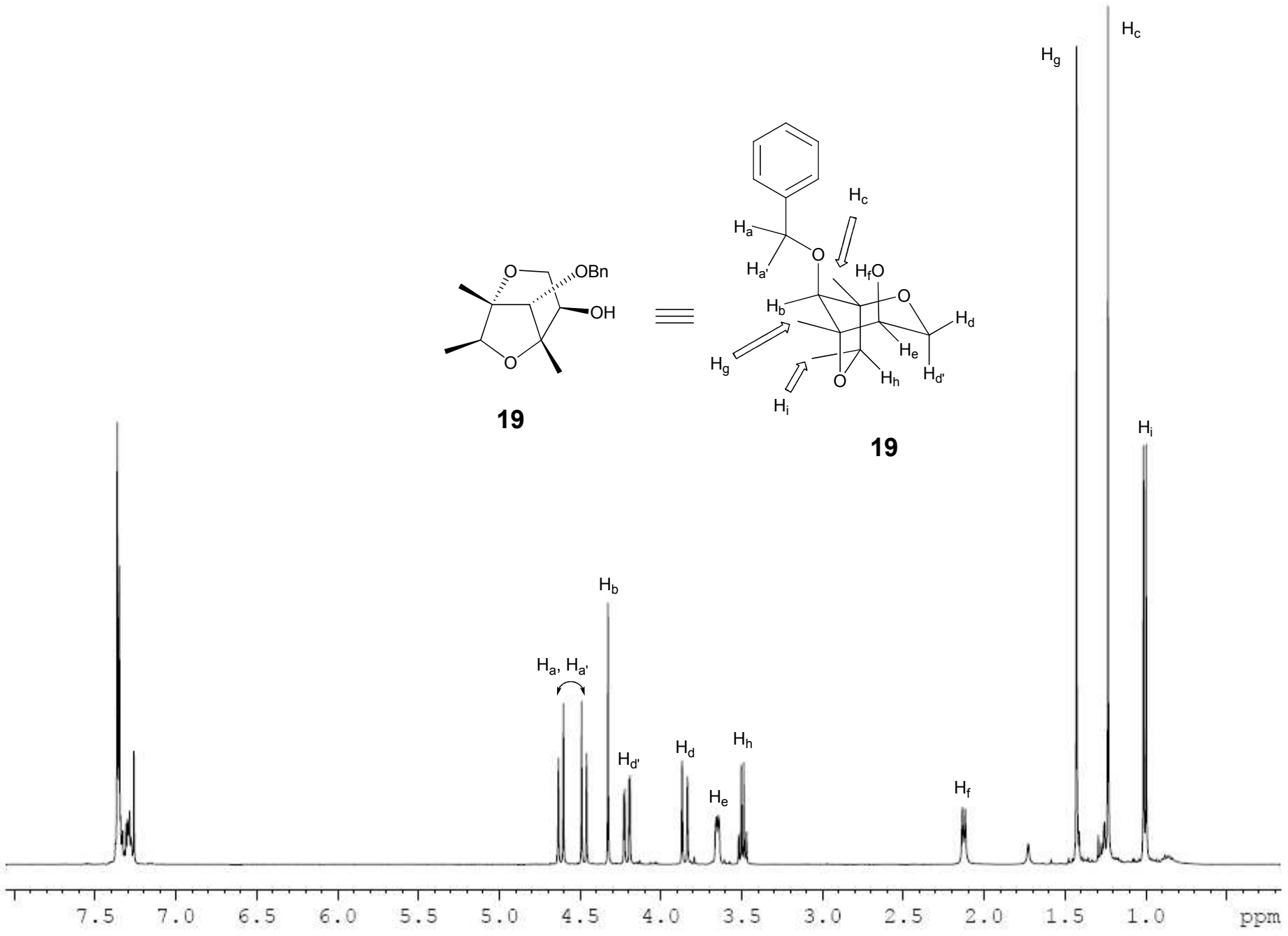
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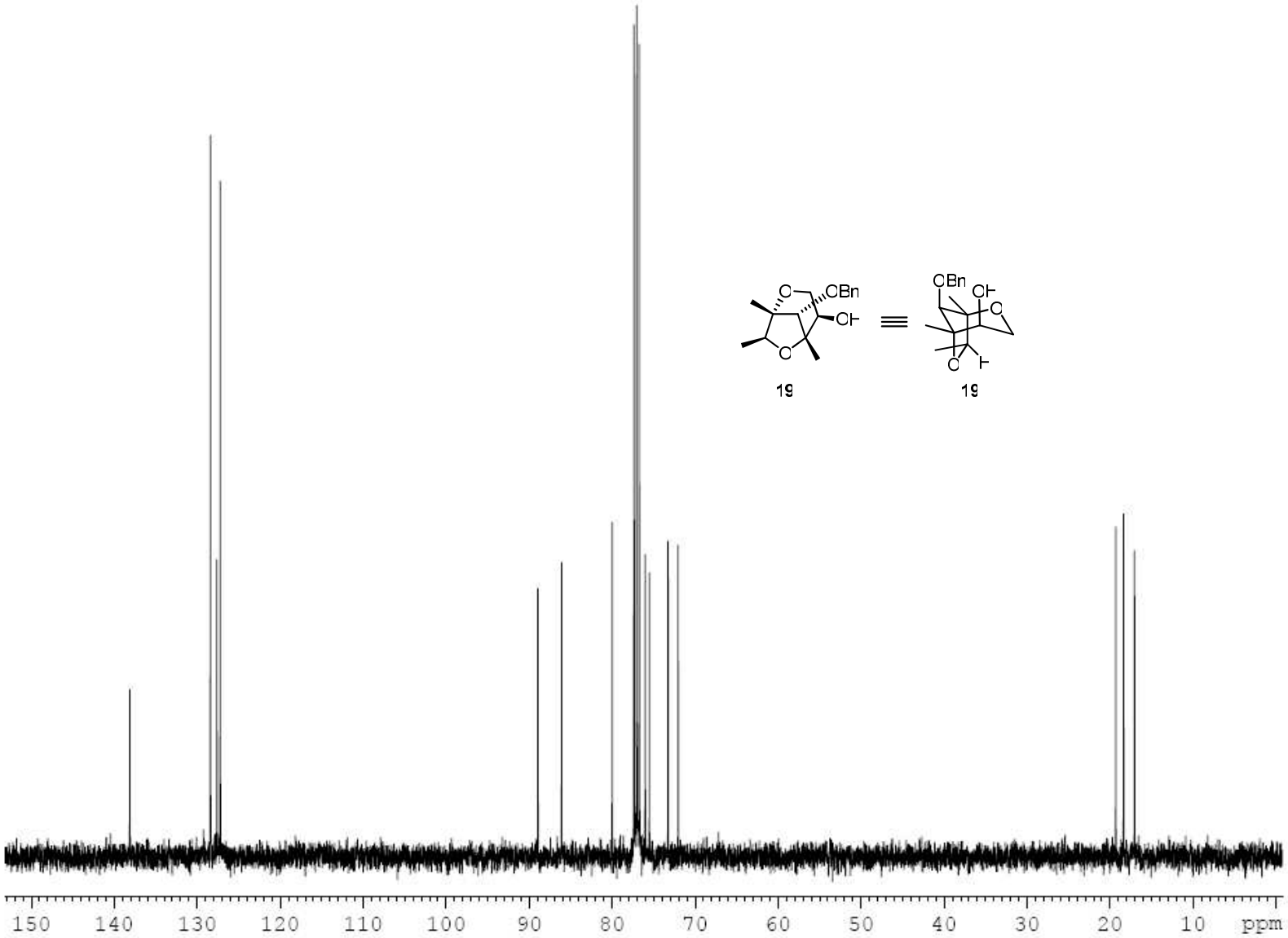
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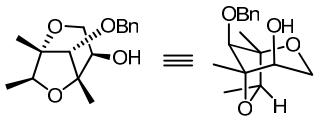
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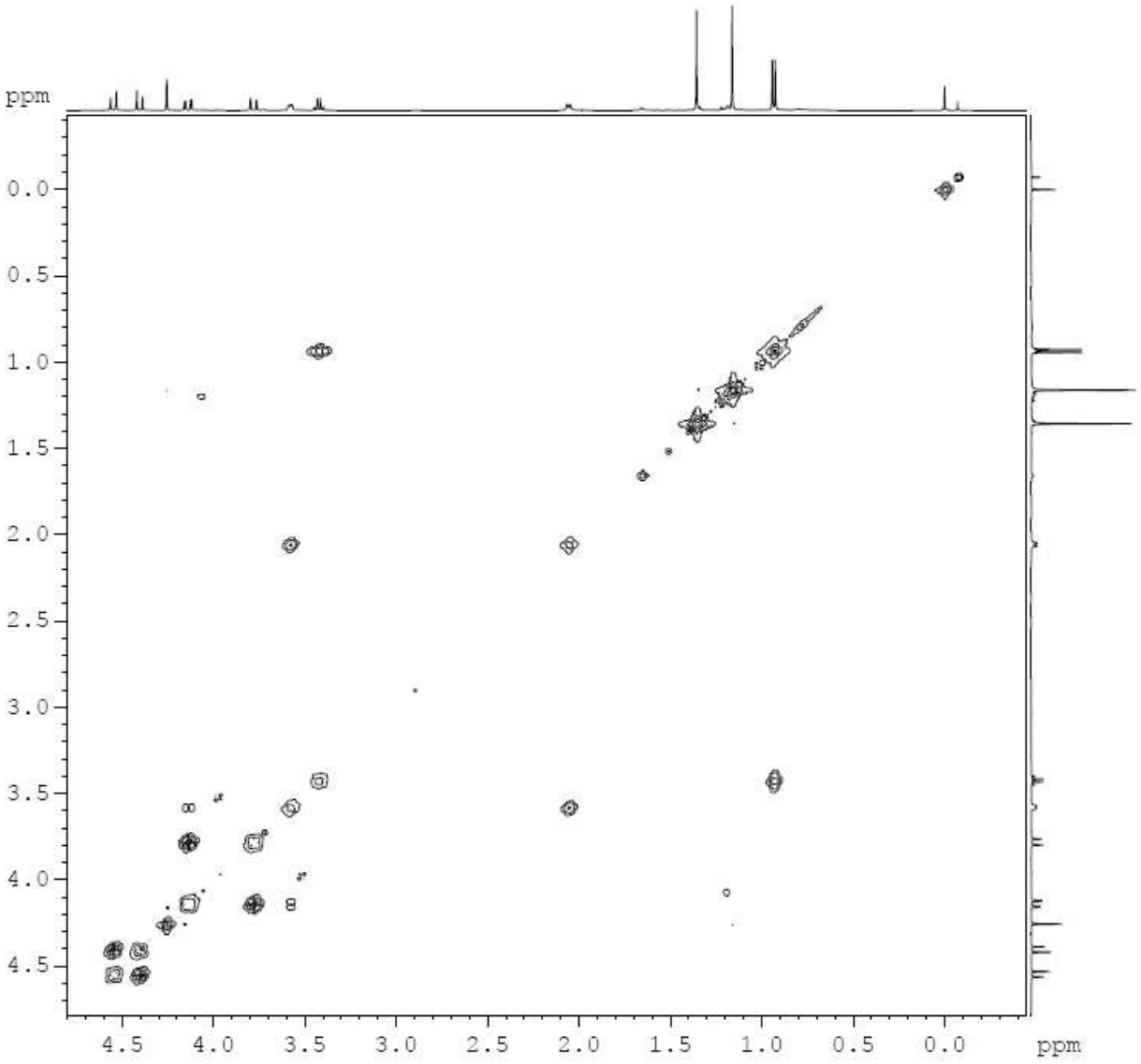
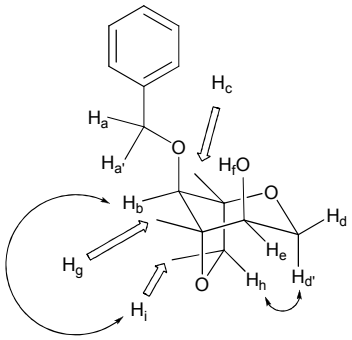
19 19

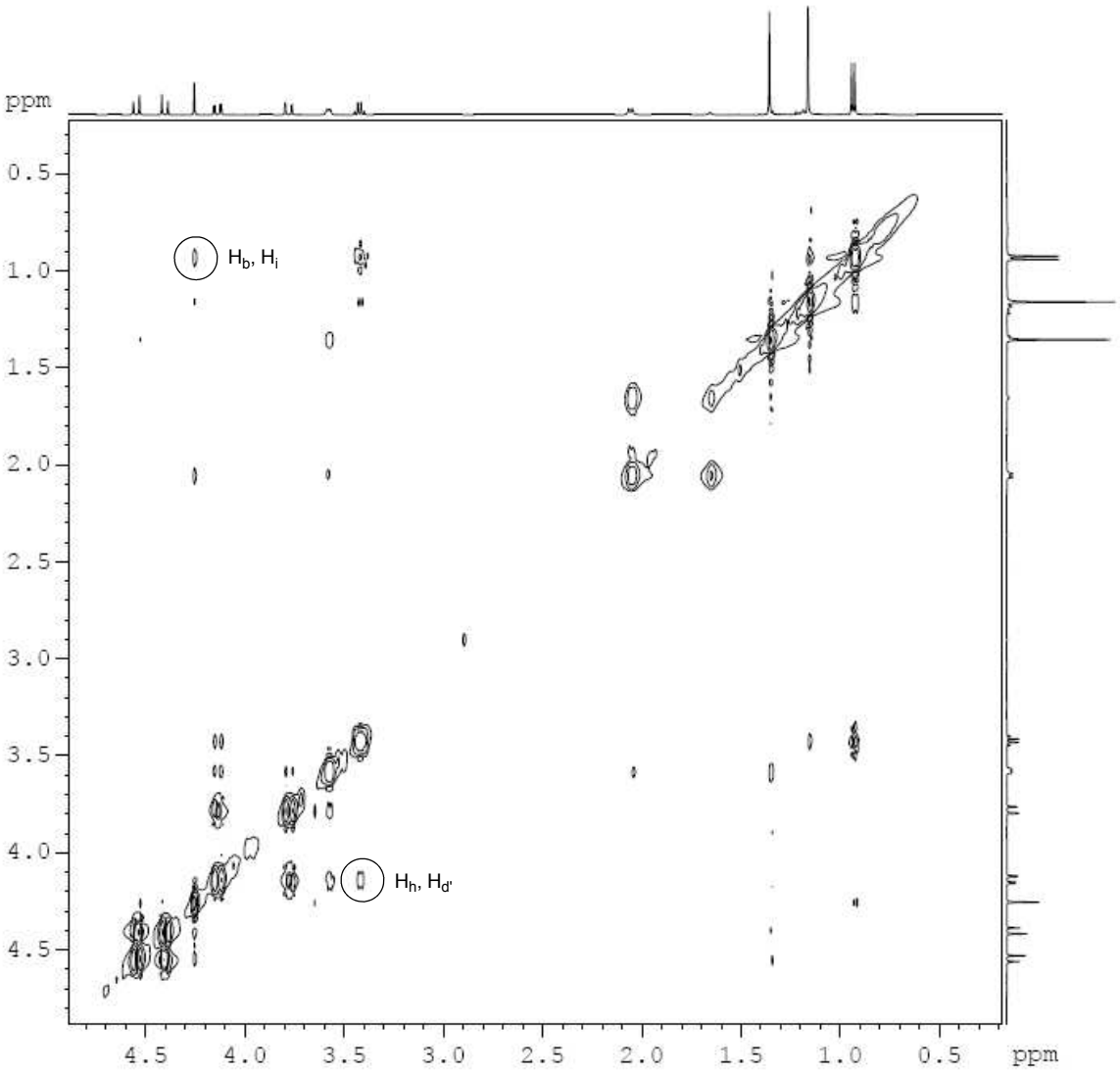
COSY

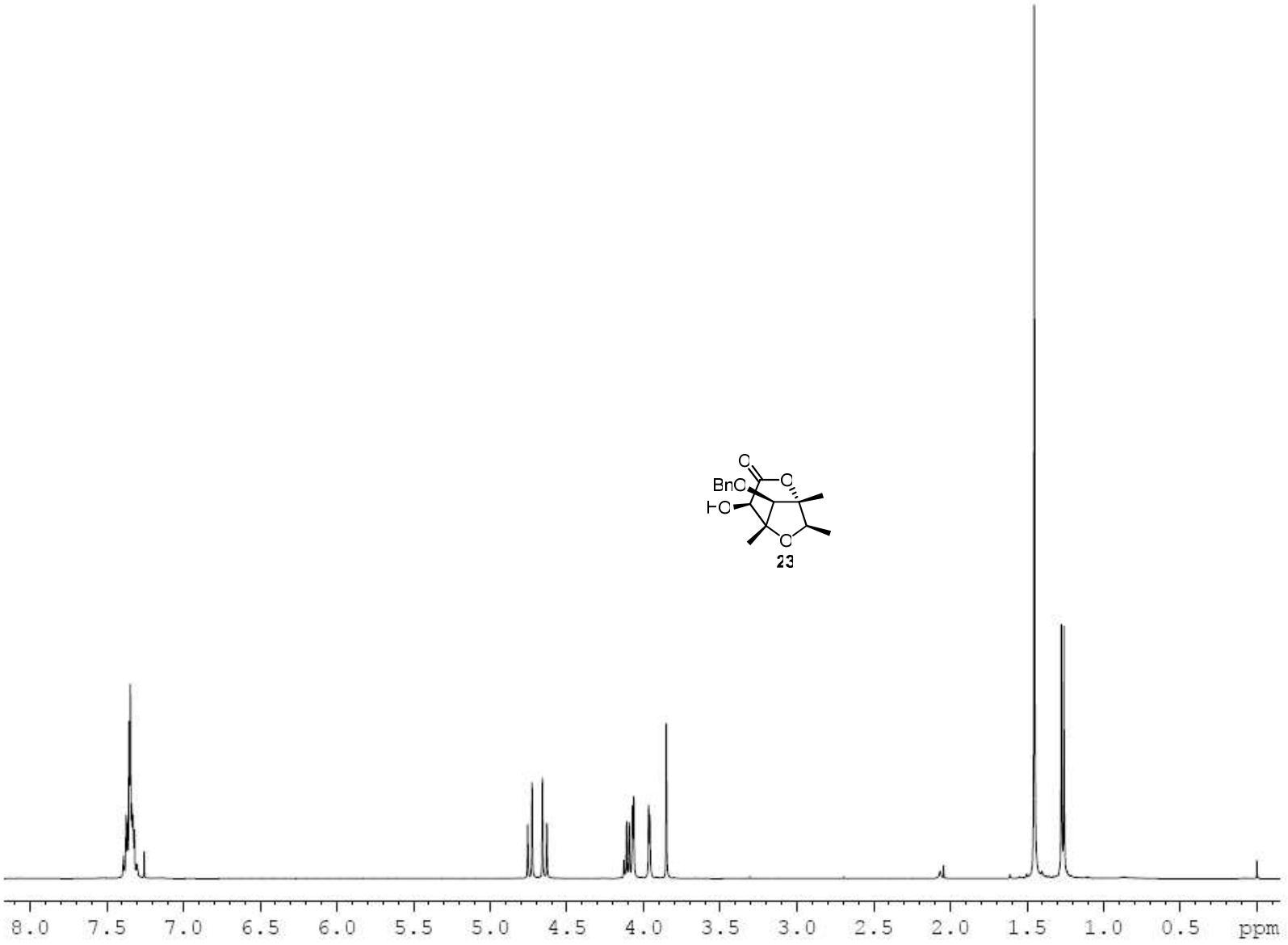

ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

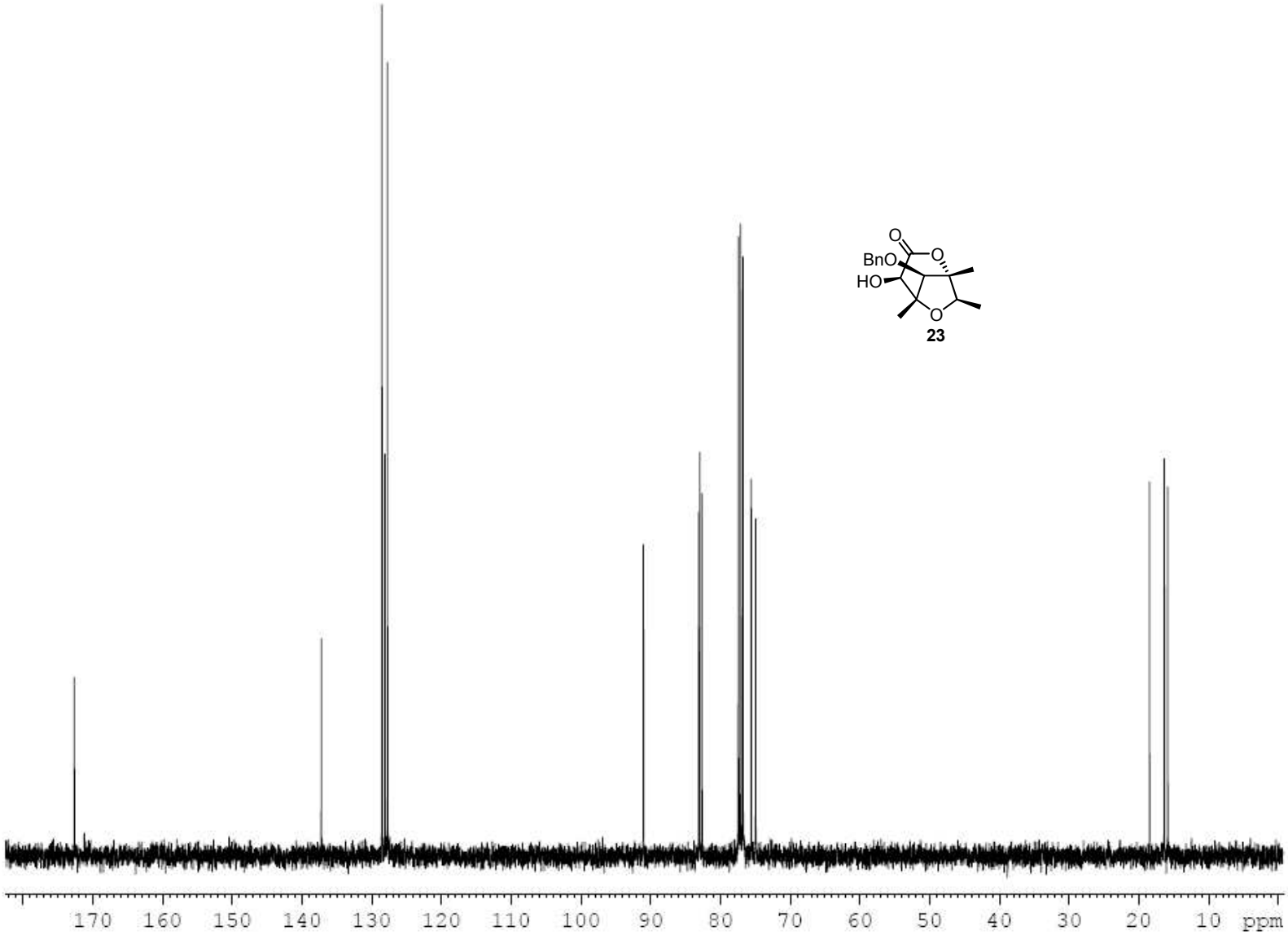

Hc
Ha
O
Ha'
HfO
Hb
O
Hd
He
Hg
O
Hh
Hd'
Hi

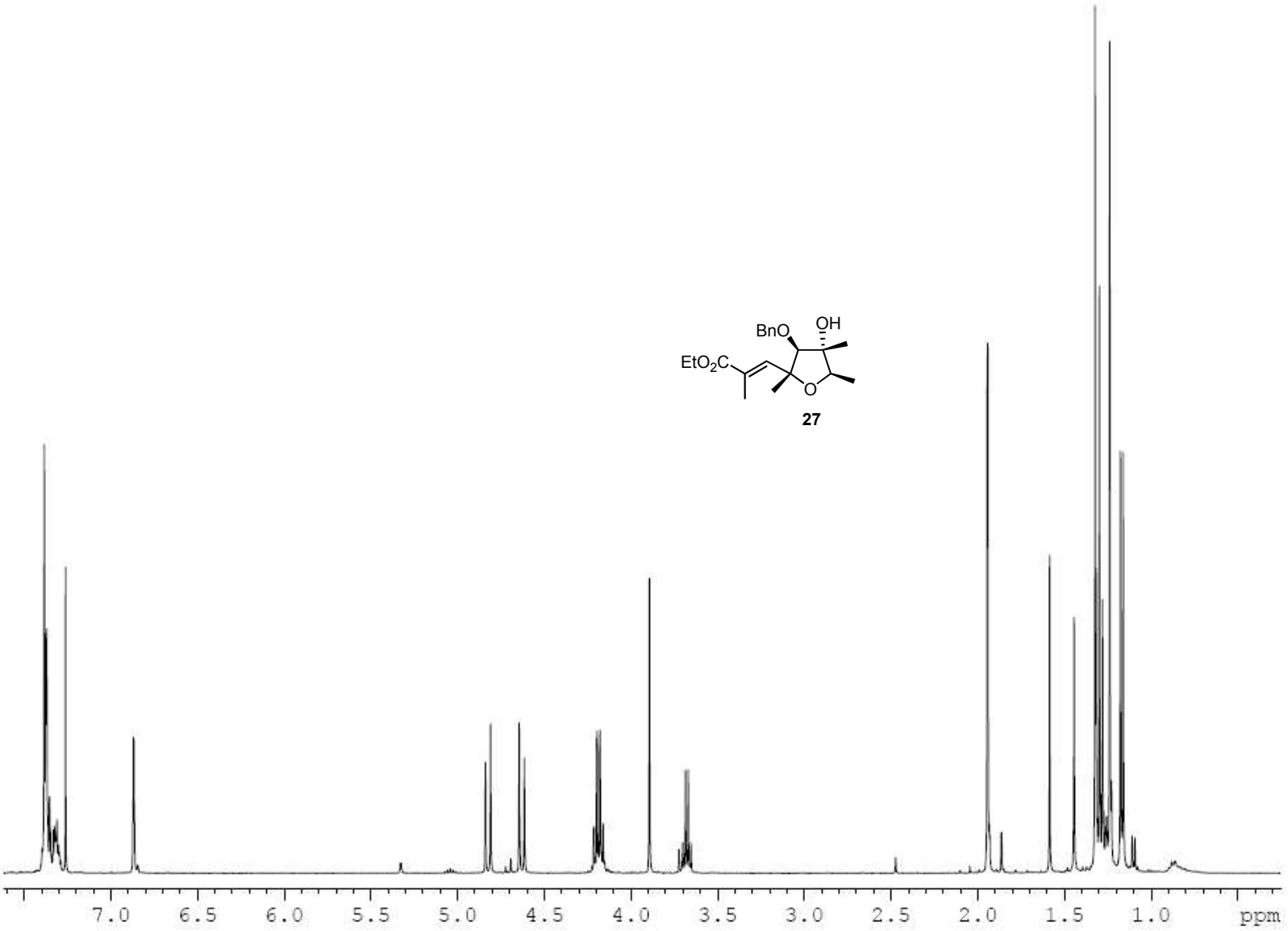
19

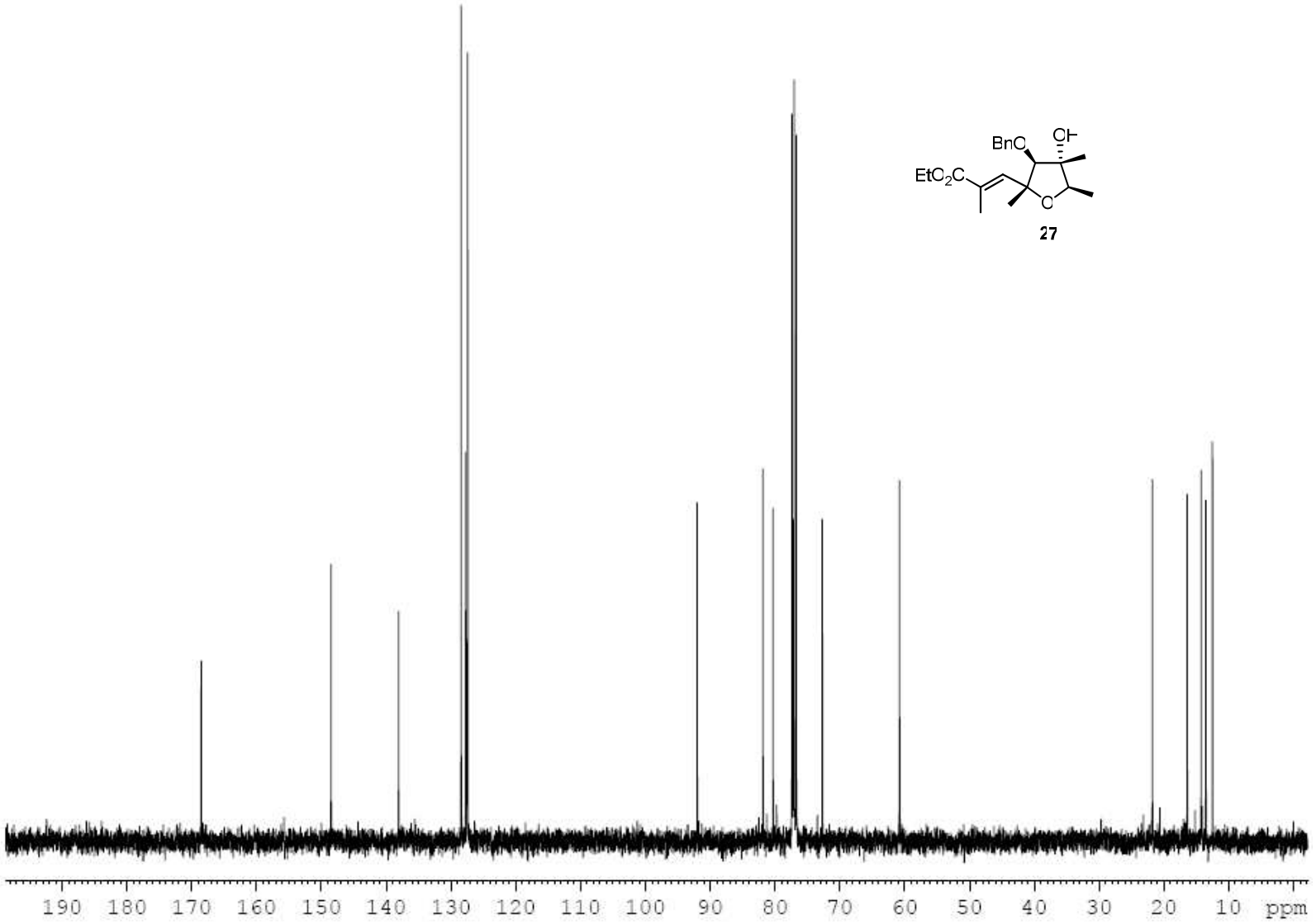
NOESY

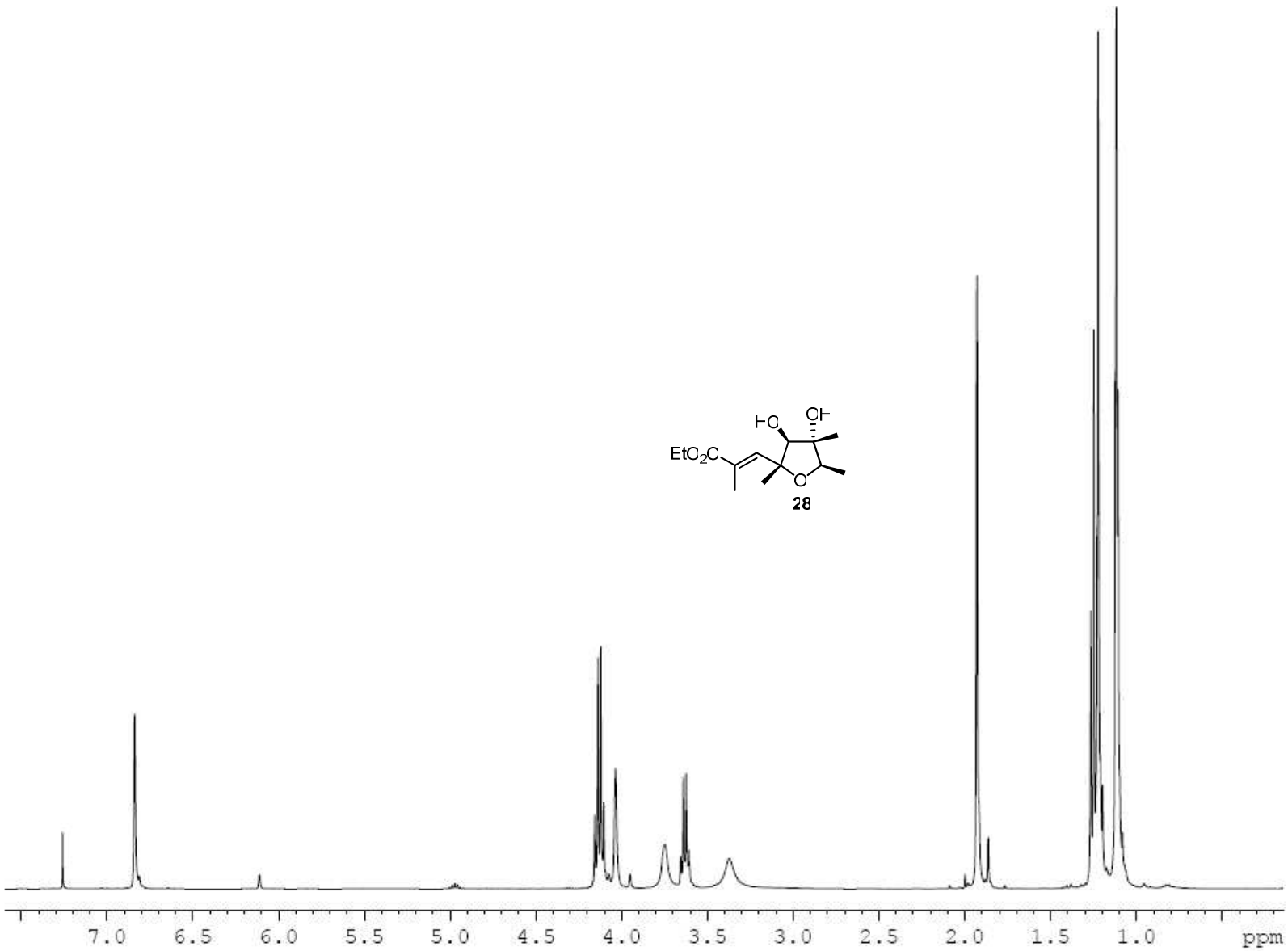

ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
Hb, Hi
Hh, Hd'
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

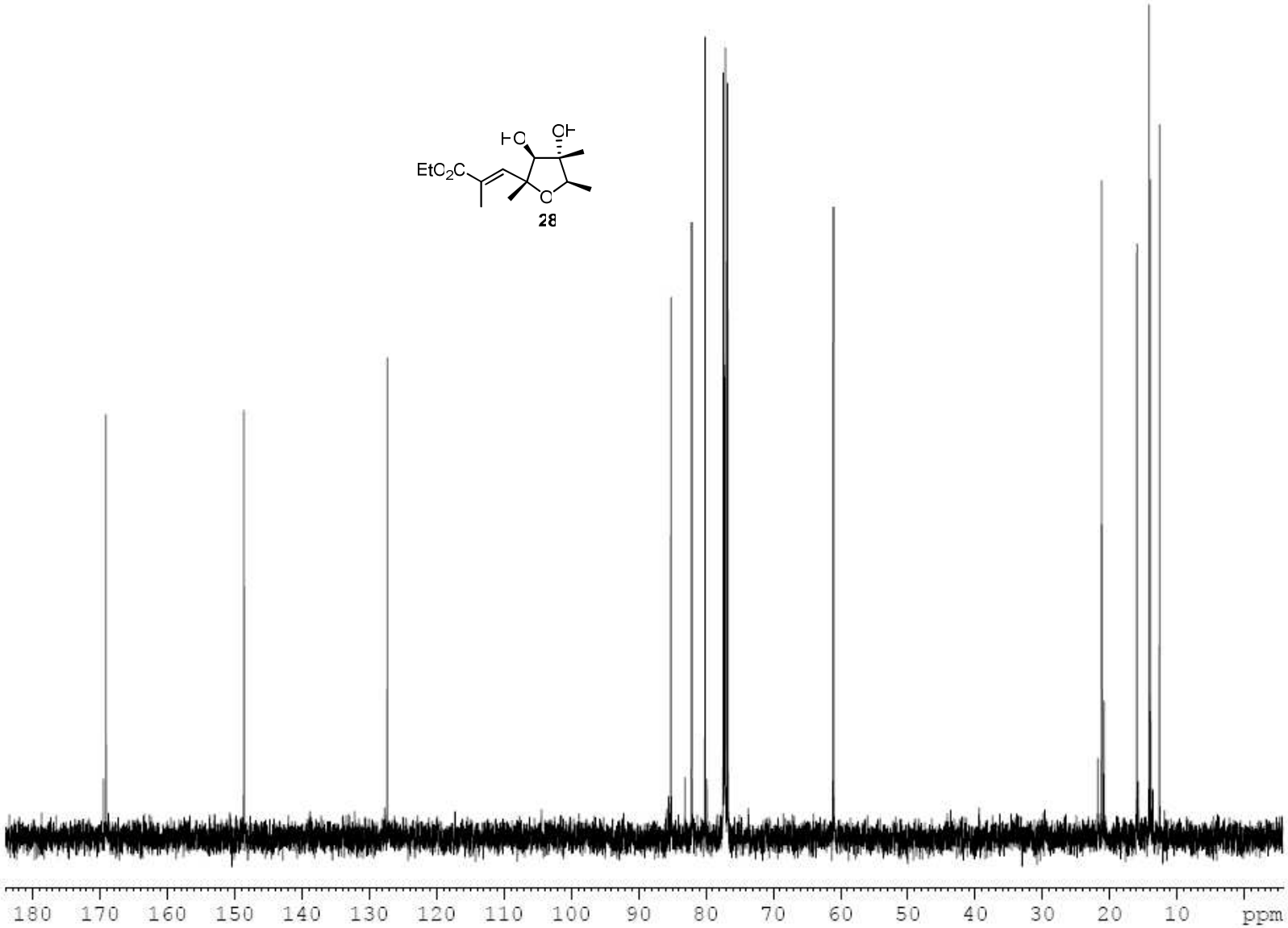

O
BnO
HO
O
23
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

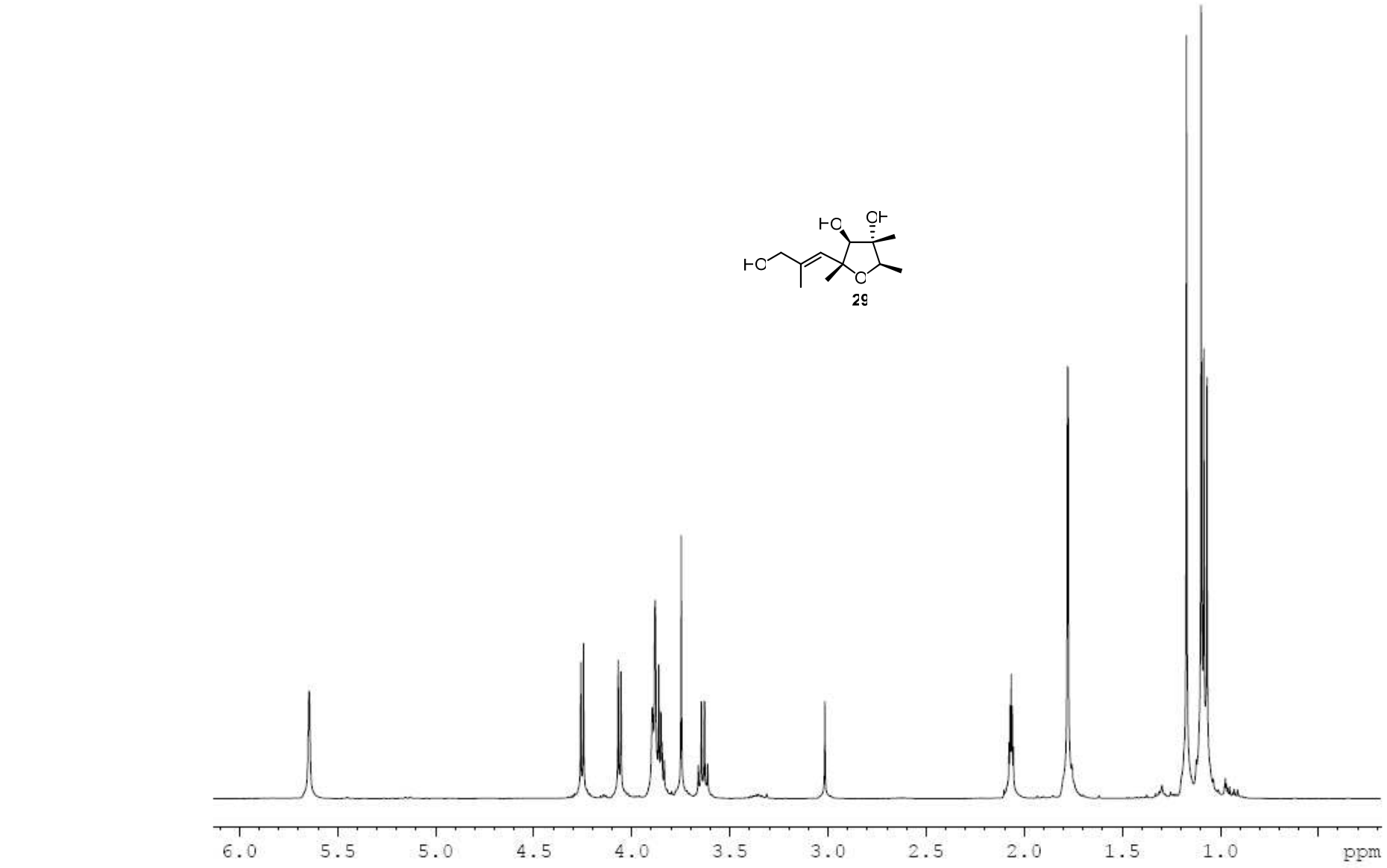

BnO
HO
O
O
O
O
23
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

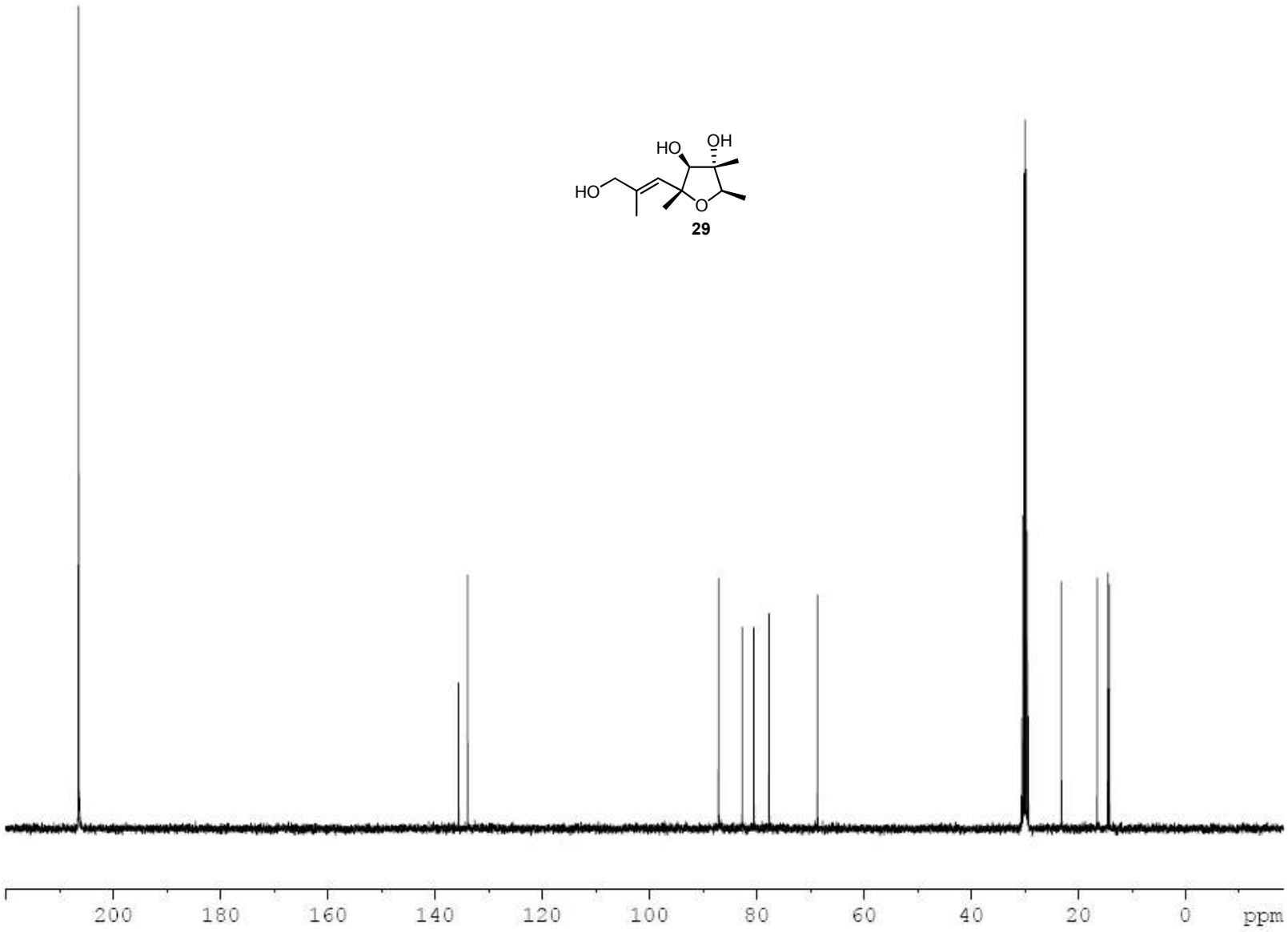

BnO
OH
EtO2C
O
27
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

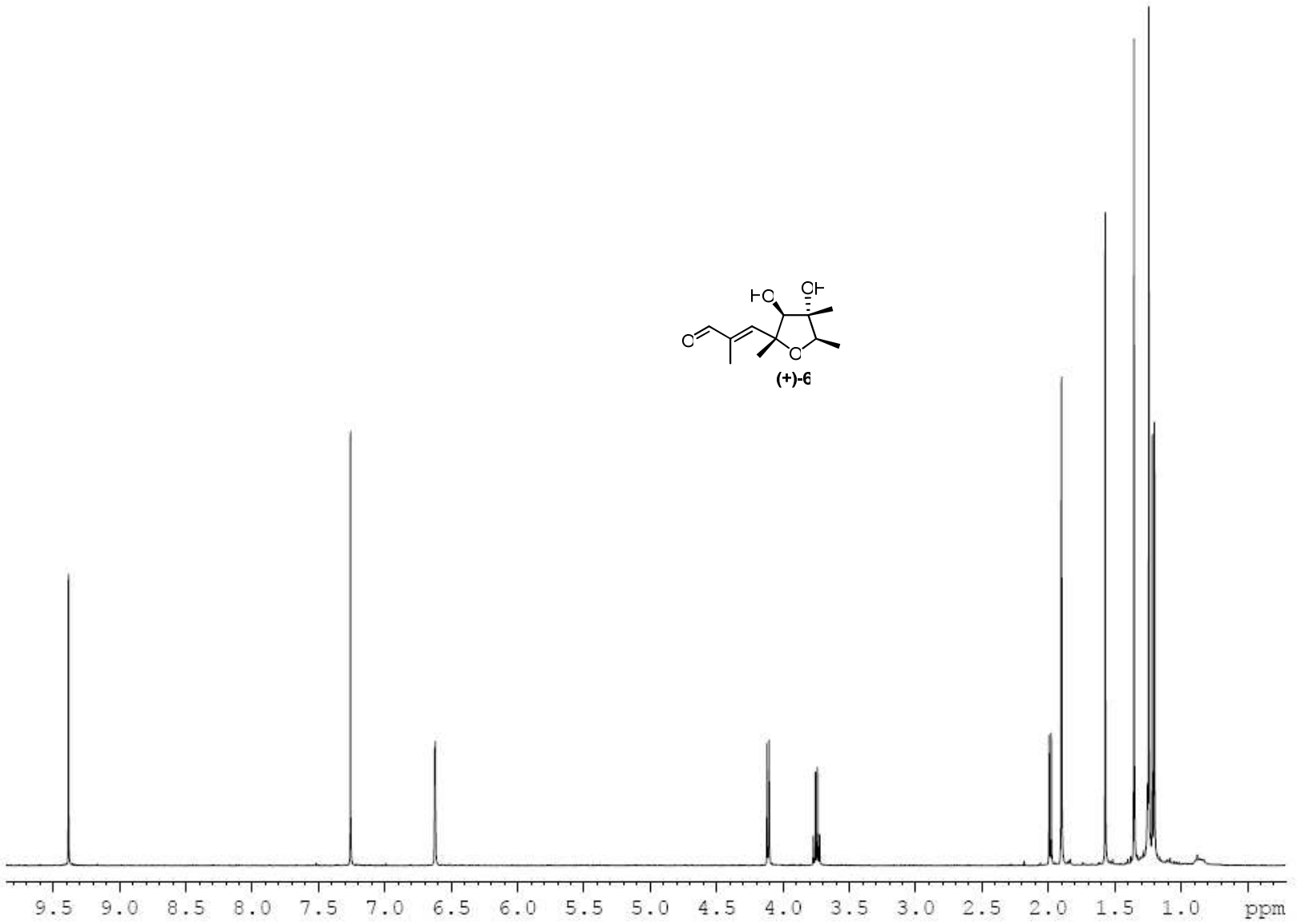

BnO
EtO2C
O
27
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

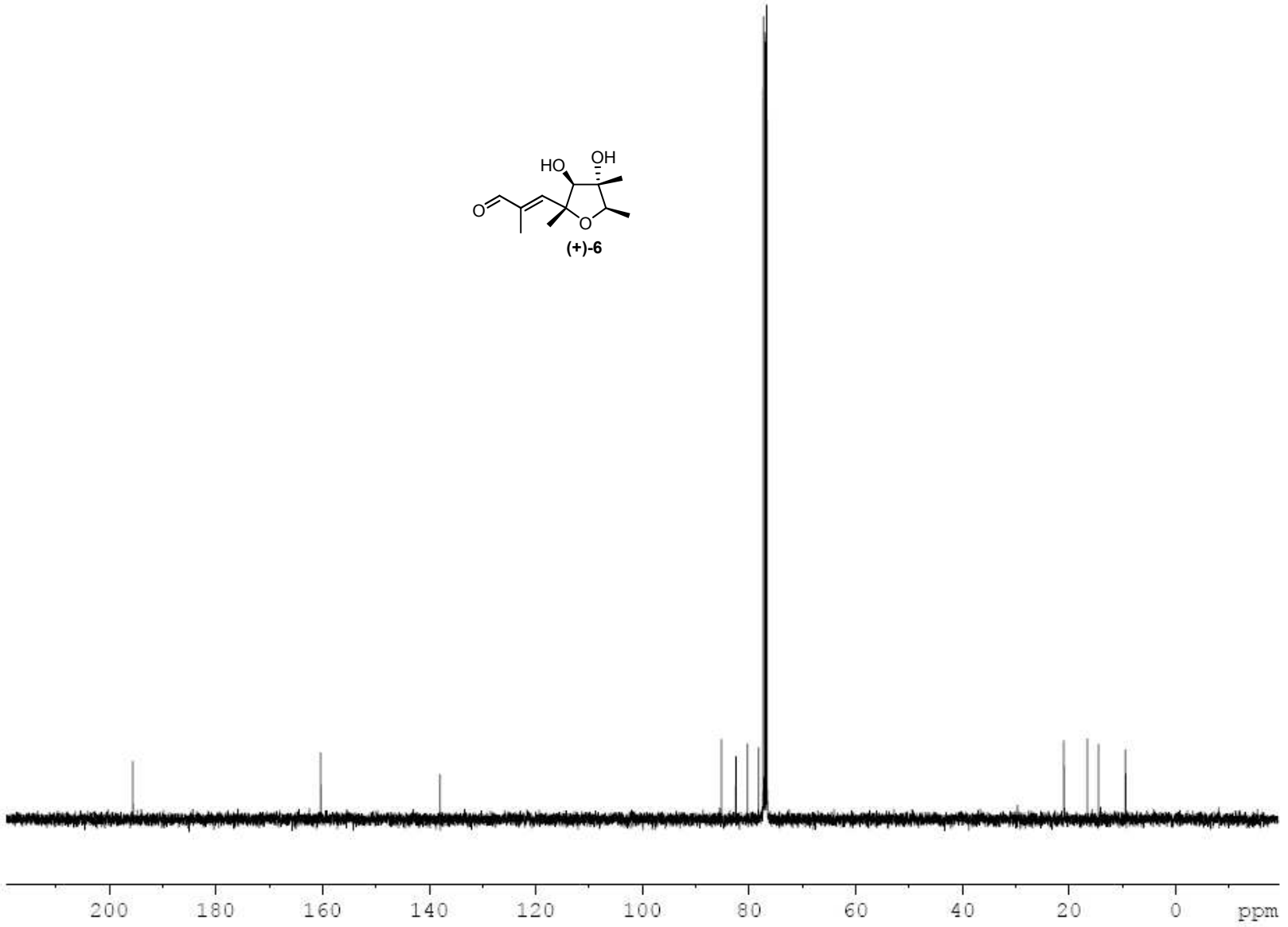

HO
OH
EtO2C
O
28
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

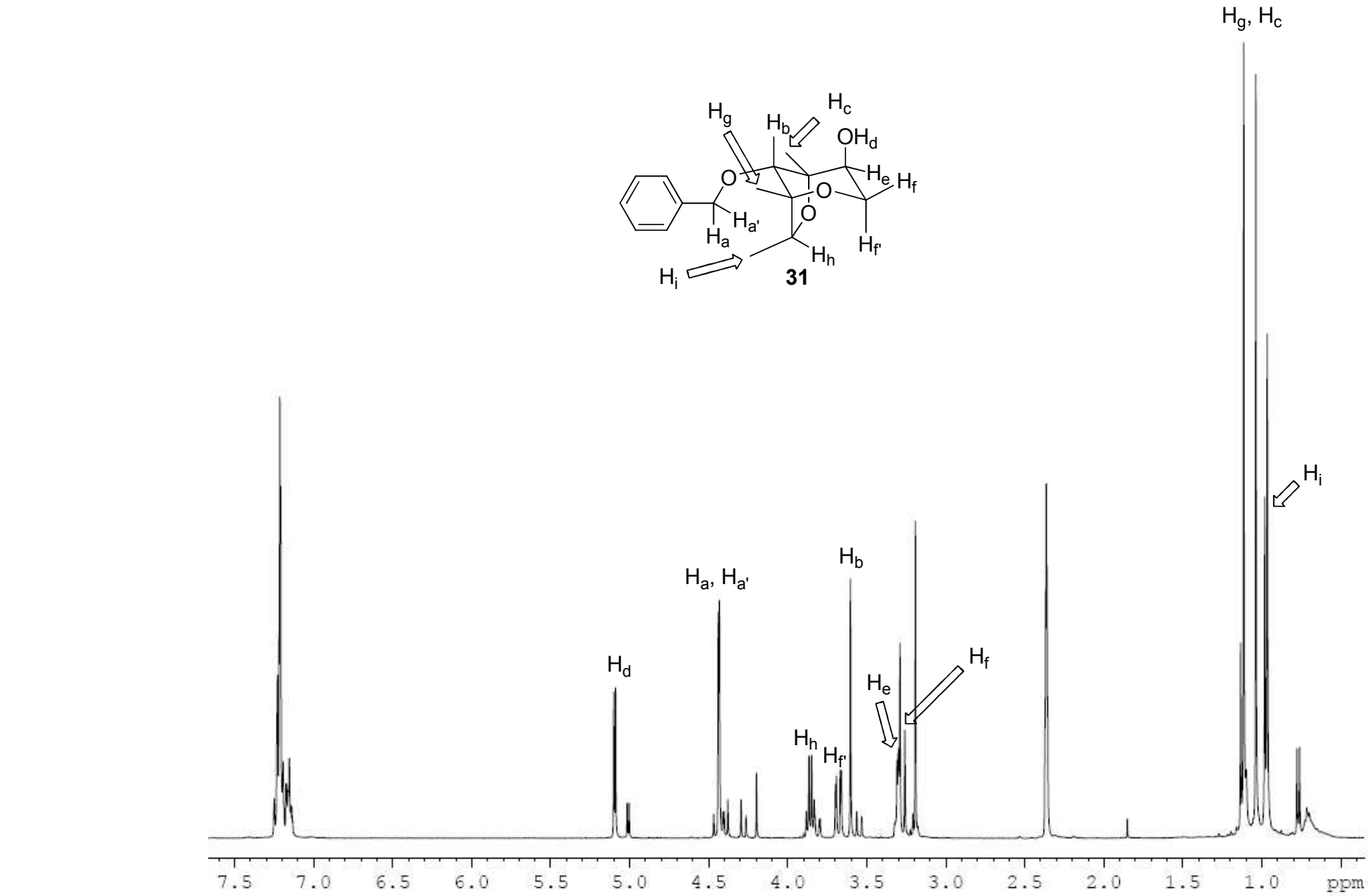

HO
OH
EtO2C
O
28
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

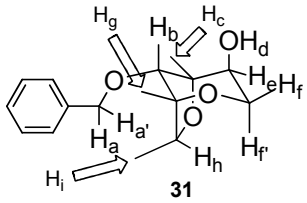

29
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


HO
OH
HO
O
29
200
180
160
140
120
100
80
60
40
20
0
ppm


(+)-6
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

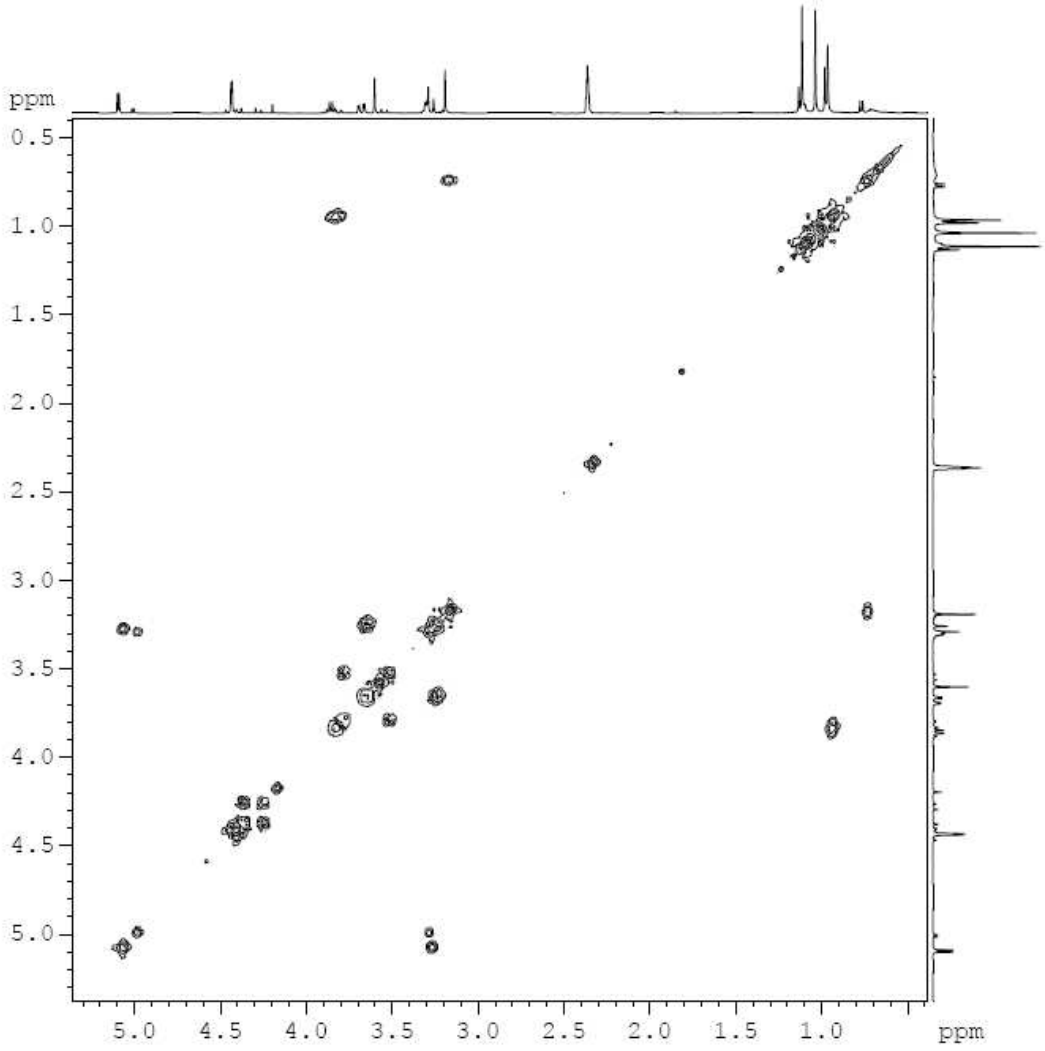

HO
OH
O
O
(+)-6
200
180
160
140
120
100
80
60
40
20
0
ppm

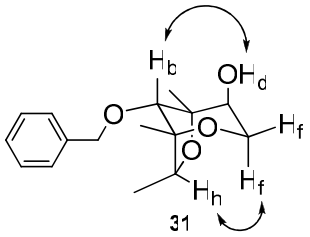

Hg, Hc
Hg
Hb
Hc
OHd
He
Hf
O
O
O
Ha'
Ha
Hf'
Hh
Hi
31
Hi
Ha, Ha'
Hb
Hd
He
Hf
Hh
Hf'
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Hg
Hb
Hc
OHd
O
HeHf
O
Ha'
Ha
O
Hf'
Hh
Hi

31

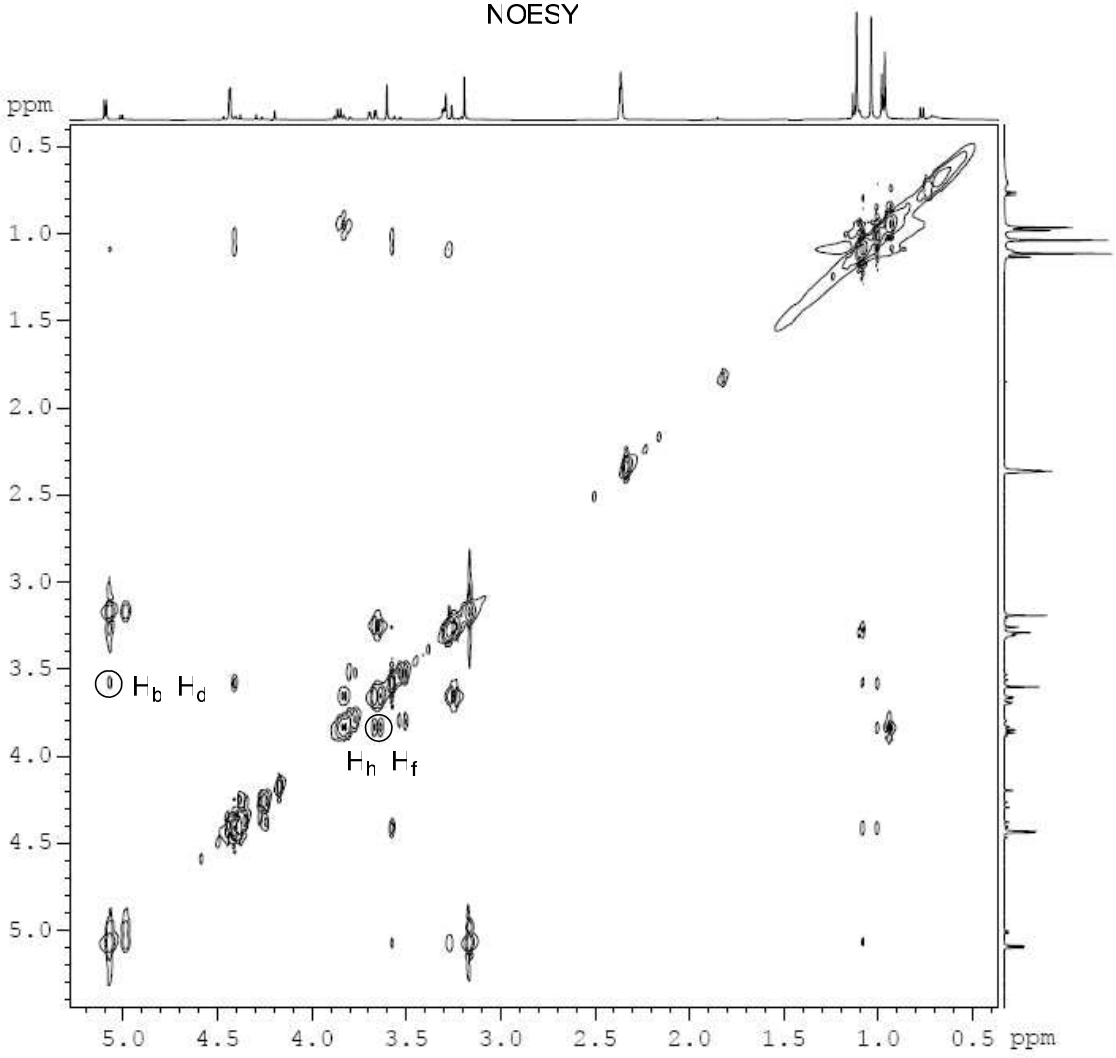
COSY


ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Hb
OHd
O
O
O
Hf
Hh
Hf

31

NOESY


ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
Hb Hd
Hh Hf
5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm