Supplementary Material (ESI) for Chemical Communications


– Electronic Supplementary Information (ESI) –

(Experimental Procedures, Characterization Data, and Copies of $^{1}H$ and $^{13}C$ NMR Spectra)

# Noteworthy Observations Accompanying Synthesis of the Apoptolidin Disaccharide

Madduri Srinivasarao, Taesik Park, Yuzhong Chen and Philip L. Fuchs*

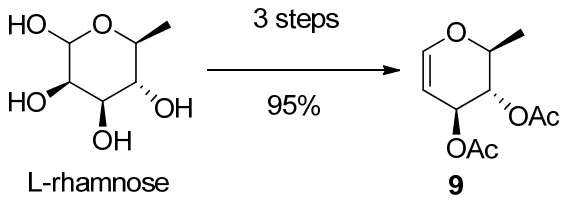
*Department of Chemistry, Purdue University, West Lafayette, Indiana 47907*
*pfuchs@purdue.edu*

## GENERAL PROCEDURES

All reagents purchased were used as received. Tetrahydrofuran (THF) and diethyl ether were distilled from benzophenone ketyl. Benzene, toluene, and methylene chloride ($CH_2Cl_2$) were distilled from calcium hydride. Sodium sulfate ($Na_2SO_4$) was anhydrous. All recrystalization, chromatographic, and workup solvents were distilled. Unless otherwise indicated, all reactions were carried out under in a positive pressure of nitrogen in anhydrous solvents and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Progress of reactions was monitored by thin layer chromatography (TLC) using silica gel 60 F-254 plates (EM reagents, 0.25 mm). The TLC plates were visualized with a UV lamp (254 nm) and/or with TLC visualizing solutions activated with heat. The two commonly employed TLC visualizing solutions were: (i) *p*-anisaldehyde solution (1350mL absolute ethanol, 50mL concentrated $H_2SO_4$, 37mL *p*-anisaldehyde), and (ii) permanganate solution (weight percents of 1% $KMnO_4$ and 2% $Na_2CO_3$ in water).

$^1H$ NMR and $^{13}C$ NMR spectra were recorded on 300 MHz, 400 MHz or 500 MHz. Because of the lability of the allylic hemiacetal and acetals, the NMR spectra were determined in benzene-$d_6$ ($C_6D_6$) solution and are reported in parts per million (ppm) from the residual benzene (7.15ppm and 128.00ppm) standard respectively. Peak multiplicities in $^1H$-NMR spectra, when reported, are abbreviated as s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublet), td (triplet of doublet) and/or quint (quintet). Melting points were obtained on a capillary melting point apparatus or automated melting point system and are uncorrected. Mass spectra were run by the Purdue University campus wide mass spectrometry facility. Because of a stability of the hemiacetal and acetals, the Mass spectra (MS) were determined by ESI technique.

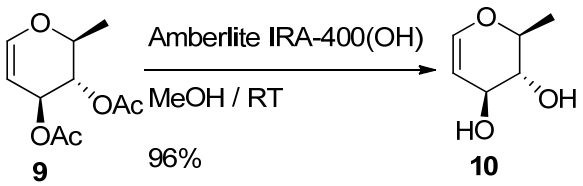
Preparation of Diacetate **9**




L-rhamnose **9**

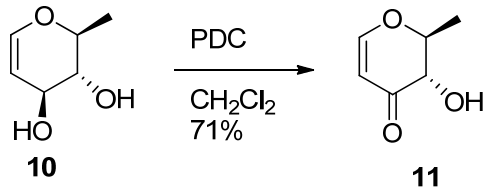
**(2S,3S,4S)-2-Methyl-3,4-dihydro-2H-pyran-3,4-diyl diacetate (9):** Stirred acetic anhydride (200 ml) was treated dropwise with 1.2 mL of 70% perchloric acid. L-rhamnose monohydrate (47.2 g, 0.26 mol) was added in small portions over a period of 1.5 h. During the addition, the reaction mixture was maintained at 40 °C by occasional cooling in an ice-water bath. After addition was complete, the solution was cooled to 23 °C, and 200 mL of 30% HBr in acetic acid was added. After 5h at room temperature, the reaction mixture was diluted with 400 mL of methylene chloride, and washed successively with ice-water (3 X 200 mL) and cold 5% aqueous $NaHCO_3$. The dried (over $Na_2SO_4$) organic phase was concentrated to afford a syrup. This syrup in THF ( 50 mL) was added slowly over a period of 1 h to 120 g of zinc dust in 800 mL of 50% aqueous acetic acid with mechanical stirring while maintaining the temperature at -15 °C to -20 °C (dry ice/acetone bath). After addition was complete, the reaction mixture was stirred for an additional 1h at 0 °C, and then the reaction mixture was filtered. The filtrate was diluted with methylene chloride (250 mL) and extracted with ice-water (3 X 250 mL). The organic extract was washed with cold saturated $NaHCO_3$ (3 X 200 mL), and saturated brine. The dried (over $Na_2SO_4$ and $NaHCO_3$) solution was concentrated below 40 °C to give **9** as a white syrup (53 g. 95%). $^1$H NMR (300 MHz, $CDCl_3$) δ1.30 (d, $J$ = 6.3 Hz, 3H), 2.05 (s, 3H), 2.10 (s, 3H), 4.10 (m, 1H), 4.80 (dd, $J$ = 2.7 and 6.0 Hz, 1H), 5.05 (dd, $J$ = 6.9 Hz, 1H), 5.35 (m, 1H), 6.45 (d, $J$ = 6.3 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 16.46, 20.84, 21.01, 68.21, 71.72, 72.42, 98.67, 145.90, 169.90, 270.66.

Preparation of diol **10**[1]




**(2S,3R,4S)-2-Methyl-3,4-dihydro-2H-pyran-3,4-diol (10):** To a solution of **9** (1 g, 4.67 mmol) in MeOH (15 mL) was added Amberite IRA-400(OH) resin (1 g). After stirring for 2.5 h at room temperature, filtration and concentration gave rhamnal **10** (581 mg, 96% yield). ). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.40 (d, *J* = 6.4 Hz, 3H), 2.40 (s, 1H), 2.75(s, 1H), 3.40 (dd, *J* = 7.6 and 9.9 Hz, 1H), 3.75 (m, 1H), 4.20 (d, *J* = 7.0 Hz, 1H), 4.70 (dd, *J* = 1.7 and 5.8 Hz, 1H), 6.30 (d, *J* = 5.8 Hz, 1H).; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 17.22, 70.14, 74.53, 75.01, 102.74, 144.72.

Preparation of enone **11**

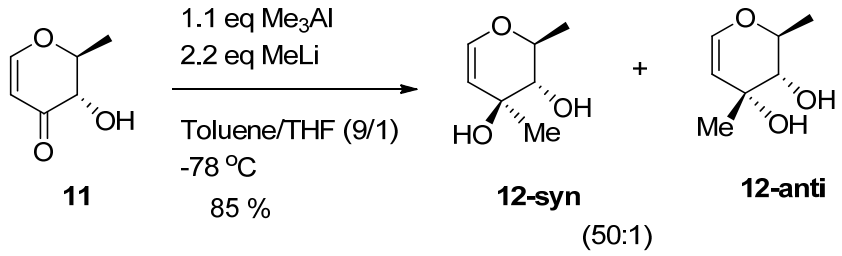



**(2S,3S)-3-Hydroxy-2-methyl-2H-pyran-4(3H)-one (11):** To a solution of **10** (10.11 g, 77.77 mmol) in a mixture of ethyl acetate (500 mL) and acetic acid (5 mL) were added ground PDC (38 g, 100 mmol) at room temperature. After the mixture was stirred with a mechanical stirrer for 2 days, it was diluted with toluene (500 mL) and then filtered through a Celite® pad. Concentration and column chromatography gave **11** (7.1 g, 71% yield) and starting material **10** (2.85 g, 28% recovered yield). ). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.51 (d, *J* = 6.3 Hz, 3H), 3.77 (s,

[1] Compound **10** and **11** were prepared via the procedure reported in *J. Org. Chem.*, **1986**, *51*, 5472.

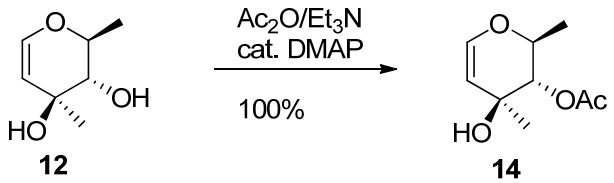
1H), 3.93 (d, *J* = 12.9 Hz, 1H), 4.15 (m, 1H), 5.40 (d, *J* = 5.7 Hz, 1H), 7.34 (d, *J* = 5.7 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 17.76, 72.64, 79.78, 103.40, 164.50, 194.24.

Stereoselective methylation of enone **11**



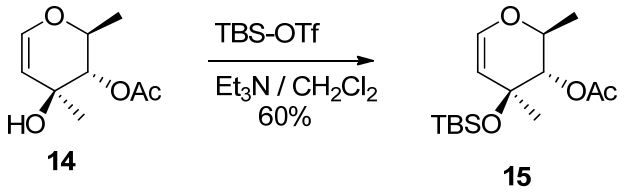

**2,4-Dimethyl-3,4-dihydro-2*H*-pyran-3,4-diol (12)** To a cold (-78 °C) solution of alcohol **11** (234 mg, 1.83 mmol) in toluene (18.0 mL) and THF (2.0 mL) was added a solution of trimethylaluminum (1.0 mL, 2.0 M in heptane) , followed by methyllithium (3.2 mL, 1.2 M in diethyl ether), and the resulting solution was stirred at –78 °C for 20 min, then methanol (0.5 mL), $H_2O$ (0.2 mL), and triethylamine (0.5 mL) was added. The resulting solution was warmed to –20 °C, filtered through a short florisil pad, and eluted with ethyl acetate. The solvent was removed under reduced pressure to afford a white solid, which was purified via recrystallization for a mixture of methylene chloride and hexanes (1:2) to give 224 mg (85%, 50:1 *dr*) diol **12** as needle crystals. $^1$H NMR ($CDCl_3$, 300 MHz) δ 6.18 (d, *J* = 6.0 Hz, 1H), 4.69 (d, *J* = 6.0 Hz, 1H), 3.86 (m, 1H), 3.62 (dd, *J* = 3.3, 10.2 Hz, 1H), 3.05 (d, *J* = 3.3 Hz, 1H), 2.34 (s, 1H), 1.37 (d, *J* = 6.0 Hz, 3H), 1.32 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 142.9, 107.6, 77.8, 73.6, 71.3, 23.8, 17.8. Analytical. Calculated for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.29; H, 8.37.

Preparation of acetate **14**




**(2S,3S,4S)-4-Hydroxy-2,4-dimethyl-3,4-dihydro-2H-pyran-3-yl acetate (14):** To a solution of **12** (0.25 g, 1.73mmol) in methylene chloride (10 mL) were added acetic anhydride (1.06 equiv, 0.175 mL), triethylamine (2 equiv., 0.48 mL) and a catalytic amount of DMAP at room temperature. After stirring for 15 h, concentration and column chromatography with 25% ethyl acetate-hexane gave **14** (0.32 g, 100% yield). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, 3H), 1.32 (s, 3H), 2.15 (s, 3H), 4.00 (m, 1H), 4.76 (d, $J$ = 6.3 Hz, 1H), 4.90 (d, $J$ = 9.9 Hz, 1H), 6.23 (d, $J$ = 6.6 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 17.49, 20.92, 24.85, 69.95, 72.09, 79.35, 108.10, 142.61, 171.49.

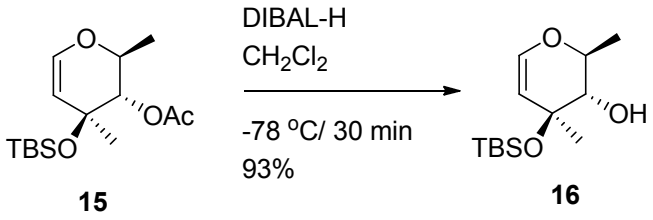
Preparation of acetate **15**




**(2S,3S,4S)-4-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-3,4-dihydro-2H-pyran-3-yl acetate (15):** To a solution of **14** (309 mg, 1.66 mmol) in dry methylene chloride (10 mL) were added 3 equiv. of triethylamine (0.7 mL) and 1.5 equiv. of TBSOTf (0.57 mL) at -78 °C. After the reaction mixture warmed slowly to room temperature for 5 h, it was quenched with water and extracted with methylene chloride. Concentration and column chromatography with 2% ethyl

acetate-hexane gave **15** (296 mg, 60% yield). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 0.10 (d, *J* = 2.9 Hz, 6H), 0.82 (s, 9H), 1.26 (d, *J* = 5.8 Hz, 3H), 1.32 (s, 3H), 2.10 (s, 3H), 3.96 (m, 1H), 4.75 (d, *J* = 5.8 Hz, 1H), 5.08 (d, *J* = 9.3 Hz, 1H), 6.20 (d, *J* = 5.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ -2.65, -2.04, 17.44, 17.89, 20.91, 25.61, 26.26, 71.22, 72.56, 108.19, 142.05, 169.87.

Preparation of alcohol[2] **16**

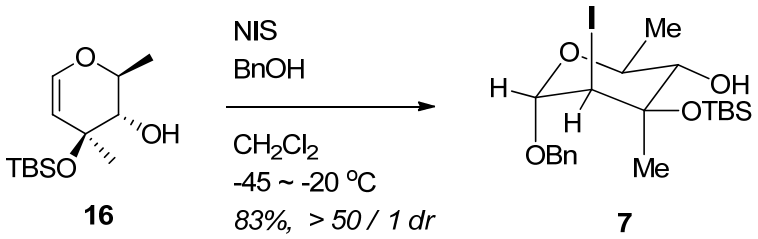



**15** **16**

**(2S,3S,4R,5R,6R)-6-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5-iodo-2,4-dimethyltetrahydro-2H-pyran-3-yl acetate (16):** To a solution of **15** (176 mg, 0.58 mmol) in methylene chloride (5.5 mL) were added DIBAL-H (1M in methylene chloride, 1.2 equiv., 0.66 mL) at -78 °C. After the mixture was stirred for 30 min, it was quenched with aqueous sodium sulfate, and diluted with THF (5 mL). After stirring at room temperature, it was filtered through Celite® pad. The filtrate was concentrated, and column chromatography with 5% ethyl acetate-hexane gave **16** (140 mg, 93% yield). ). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.86 (s, 9H), 1.30 (s, 3H), 1.37 (d, *J* = 6.4 Hz, 3H),1.44 (s, 1H), 2.01 (d, *J* = 2.3 Hz, 1H), 3.60 (dd, *J* = 1.7 and 9.3 Hz, 1H), 3.90 (m, 1H), 4.75 (d, *J* = 5.8 Hz, 1H), 6.15 (d, *J* = 5.8 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ -2.55, -2.18, 17.93, 25.39, 25.72, 73.07, 73.44, 78.22, 108.01, 142.05.

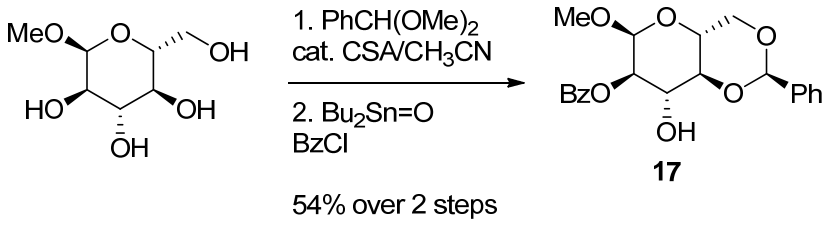
[2] Wehlan, H.; Dauber, M.; Mujica Fernaud, M. T.; Schuppan, J.; Mahrwald, R.; Ziemer, B.; Juarez Garcia, M. E.; Koert, U. *Angew. Chem. Int. Ed.* **2004,** *43*, 4597.

Preparation of alcohol[3] **7**




**(2S,3S,4R,5R,6R)-6-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5-iodo-2,4-dimethyltetrahydro-2H-pyran-3-ol (7):** To a mixture of **16** (62 mg, 0.24 mmol) and benzyl alcohol (3 equiv., 75 μL) in methylene chloride (3 mL) was added NIS (1.5 equiv., 80 mg) at -40 °C. After stirring for 1 h, aqueous sodium sulfite solution was added, and it was extracted with methylene chloride. Column chromatography with 10% ethyl acetate-hexane gave **7** (98 mg, 83% yield, *dr* = 50:1). $^1$H NMR (300 MHz, $CDCl_3$) δ 0.14 (s, 3H), 0.22 (s, 3H), 0.92 (s, 9H), 1.32 (d, *J* = 5.8 Hz, 3H), 1.62 (s, 3H),1.80 (d, *J* = 2.9 Hz, 1H), 3.70 (m, 2H), 4.33 (s, 1H), 4.47-4.60 (ABq, *J* = 11.7 and 68.5 Hz, 2H), 5.40 (d, *J* = 1.7 Hz, 1H), 7.30-7.40 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ -2.06, -1.64, 18.16, 18.58, 22.04, 26.31, 44.06, 68.31, 69.83, 74.63, 76.58, 78.42, 102.54, 127.75, 128.43, 137.38. LRMS(CI) *m/z* 493 $[M + H]^+$; HRMS (EI) calculated for $[C_{20}H_{33}IO_4Si - C_4H_9]^+$, 435.0489; found, 435.0483.

Preparation of **17**



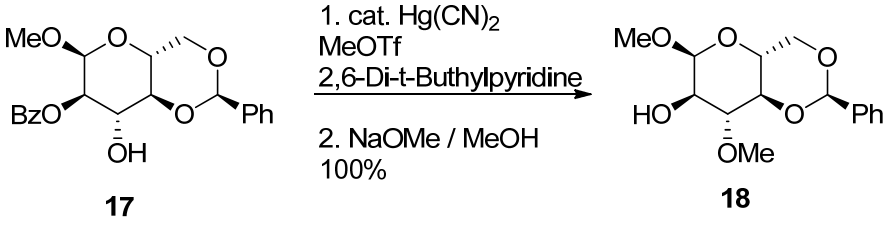

[3] For a related glycosylation, see: Hou, D.; Lowary, T. L. *J. Org. Chem.* **2009**, *74*, 2278.

**(2R,4aR,6S,7R,8S,8aS)-8-Hydroxy-6-methoxy-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-7-yl benzoate (17).** To a solution of methyl D-glucopyranose (10 g, 51.5 mmol) in dry acetonitrile (100 mL) were added benzaldehyde dimethyl acetal (3 equiv., 23 mL) and catalytic p-toluenesulfonic acid monohydrate (1.2 g). The reaction mixture was refluxed for 17 h, and then cooled to room temperature. After neutralized with triethylamine (3.0 mL), it was concentrated to get solidified mixture. Treatment of the solid with hexane, followed by washing with hexane, water, and 5% ethyl acetate-hexane, gave the intermediate diol as crude solid (11 g, 76% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 2.60-2.80 (br s, 1H), 3.20-3.40(br s, 1H), 3.45 (m, 4H), 3.60 (m, 1H), 3.75 (m, 2H), 3.90 (t, *J* = 7.5 Hz, 1H), 4.30 (dd, *J* = 3 and 10.5 Hz, 1H), 4.75(d, *J* = 3 Hz, 1H), 5.50 (s, 1H), 7.35 (m, 3H), 7.50 (m, 2H).; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 55.46, 62.31, 68.85, 71.49, 72.76, 80.93, 99.77, 101.87, 126.27, 128.24, 129.16, 137.00.

To this solid (8.8 g, 31.17 mmol) in a mixture of MeOH (45 mL) and toluene (45 mL) were added dibutyltin oxide (7.76 g, 31.17 mmol). After reflux for 3 h, the mixture was concentrated; 50 mL of toluene was added and then the mixture was concentrated again. 90 mL of dry toluene was added to the mixture in an ice bath, to which a solution of benzoyl chloride (4.38 g, 31.17 mmol) in toluene (20 mL) was added dropwise. After stirring for 30 min in an ice bath, it was the mixture was quenched with MeOH (10 mL) and stirred for 17 h. The mixture was concentrated, and dissolved in 25% ethyl acetate and hexane along with methylene chloride. The mixture was filtered through a silica gel pad with 25% ethyl acetate and hexane. After concentration, it was treated with 10% ethyl acetate and hexane to afford **17** (8.6 g, 72% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 2.50(d, *J* = 2.3 Hz, 1H), 3.40 (s, 3H), 3.65 (t, *J* = 9.3 Hz, 1H), 3.80 (t, *J* = 10.5 Hz, 1H), 3.90 (m, 1H), 4.35 (m, 2H), 5.10 (m, 2H), 5.60 (s, 1H), 7.30-7.60 (m, 8H), 8.10 (d, *J* = 7.5 Hz, 2H).; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 55.49, 62.01, 68.82, 68.90, 74.05,

81.44, 126.30, 128.33, 128.41, 129.28, 129.47, 129.92, 133.35, 136.98, 166.21. LRMS (EI): *m/z* 385 [M –H].

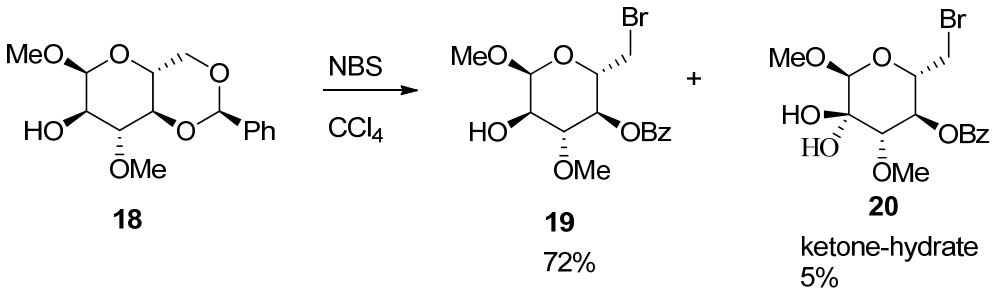
Preparation of **18**




**(2R,4aR,6S,7R,8R,8aR)-6,8-Dimethoxy-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-7-ol (18):** To a solution of **17** (10 g, 25.8 mmol) in methylene chloride (130 mL) were added $Hg(CN)_2$ (130 mg, 0.51 mmol), 2,6-di-*tert*-butylpyridine (23 mL, 0.1 mol), and MeOTf (8.8 mL, 51.6 mmol). After reflux for 1.5 days, normal workup with aqueous sodium bicarbonate and column chromatography with 10% ethyl acetate-hexane gave the crude solid (10.3 g, 100% yield) and recovered 2,6-di-*tert*-butylpyridine (19.5 g, 100%). $^1$H NMR (300 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.60 (s, 3H), 3.68 (t, *J* = 9.3 Hz, 1H), 3.80 (t, *J* = 10.5 Hz, 1H), 3.94 (m, 2H), 4.12 (dd, *J* = 4.1 and 9.3 Hz, 1H), 5.00-5.10 (m, 2H), 5.60 (s, 1H), 7.25-7.60 (m, 8H), 8.10 (d, *J* = 7.5 Hz, 2H).; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 55.36, 61.05, 62.30, 69.94, 73.68, 77.76, 81.90, 97.83, 101.40, 126.07, 128.20, 128.41, 128.96, 129.67, 129.84, 133.24, 137.27, 165.95. To a solution of this product (11 g, 27.47 mmol) in MeOH (137 mL) was added NaOMe (25 wt% in MeOH, 11.86 g, 55 mmol) at room temperature. After stirring for 2 h, the mixture was concentrated. Saturated aqueous $NH_4Cl$ (100 mL) and ethyl acetate (100 mL) were added to the concentrate and it was extracted with ethyl acetate. The extract was dried over $Na_2CO_3$ and concentrated to give **18** as white solid (8.1 g, 100% yield), which was used for next reaction without purification.

$^1$H NMR (300 MHz, $CDCl_3$) δ 2.55 (d, *J* = 6.6 Hz, 1H), 3.45 (s, 3H), 3.56 (m, 2H), 3.65 (m, 1H), 3.66(s, 3H), 3.70-3.90 (m, 2H), 4.29 (dd, *J* = 4.2 and 9.3 Hz, 1H), 4.80 (d, *J* = 3.6 Hz, 1H), 5.54 (s, 1H), 7.30-7.50 (m, 5H).; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 55.35, 61.02, 62.43, 68.91, 72.14, 80.53, 81.94, 99.73, 99.88, 101.19, 125.96, 128.17, 128.90, 137.21.

Preparation of bromide **19**[4]

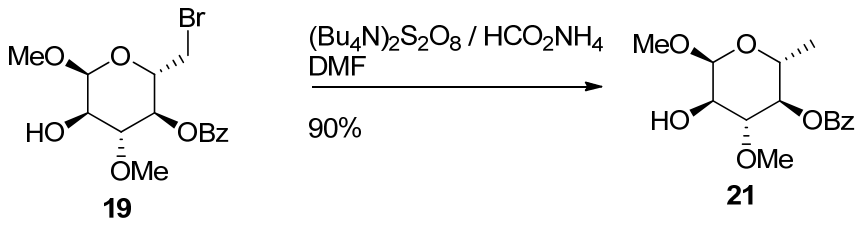



**(2S,3S,4R,5R,6S)-2-(Bromomethyl)-5-hydroxy-4,6-dimethoxytetrahydro-2H-pyran-3-yl benzoate (19):** To a solution of **18** (8.1 g, 27.47 mmol) in $CCl_4$ (270 mL) were added $CaCO_3$ (3.3 g, 33 mmol) and NBS (5.37 g, 30.17 mmol). After reflux for 1 hr, the mixture cooled to room temperature, and filtered through Celite® pad with methylene chloride. Normal workup with aqueous $NaHSO_3$, and column chromatography with 25% ethyl acetate-hexane gave **19** (7.23 g, 72% yield) and ketone hydrate (502 mg, 5 % yield). Compound **19** $[\alpha]^{20}_D$ = +65.4 (c=0.011, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 2.40 (d, *J* = 7.0 Hz, 1H), 3.45 (m, 2H), 3.50 (s, 3H), 3.55 (s, 3H), 3.65 (t, *J* = 9.3 Hz, 1H), 3.75 (m, 1H), 4.05 (dt, *J* = 2.0 and 9.9 Hz, 1H), 4.88 (d, *J* = 3.5 Hz, 1H), 5.10 (t, *J* = 9.3 Hz, 1H), 7.50 (m, 3H), 7.60 (m, 1H), 8.10 (d, *J* = 7.5 Hz, 2H).; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 31.61, 55.60, 60.66, 69.71, 72.01, 72.94, 81.60, 99.01, 128.57, 129.15, 129.80, 133.57, 165.33. **Ketone hydrate (20)**: $^1$H NMR (300 MHz, $CDCl_3$) δ 3.46 (s, 3H), 3.48 (s, 3H), 3.74 (ABq, *J* = 11.7 and 17.5 Hz, 2H), 3.83 (dd, *J* = 1.1 and 5.2 Hz, 1H), 4.78 (d, *J* = 5.2 Hz, 1H), 5.14 (s, 1H), 5.27 (s, 1H), 7.50 (m, 2H), 7.60 (m, 1H), 8.05 (d, *J* = 7.5 Hz, 2H).; $^{13}$C

[4] Tori, K.; That Thang, T.; Sangare, M.; Lukacs, G. *Tet. Lett.* **1977**, *18*, 717.

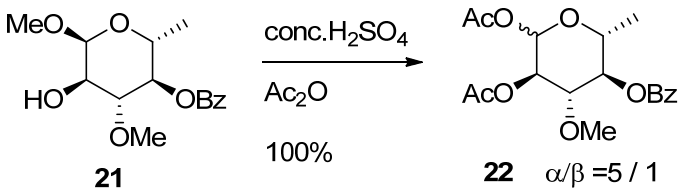
NMR (75 MHz, $CDCl_3$) δ 26.55, 55.34, 59.15, 77.79, 80.02, 85.03, 99.83, 108.93, 128.68, 129.17, 129.85, 133.73, 165.05. LRMS (CI): *m/z* 373, 375 $[M + H - H_2O]^+$.

Preparation of **21**



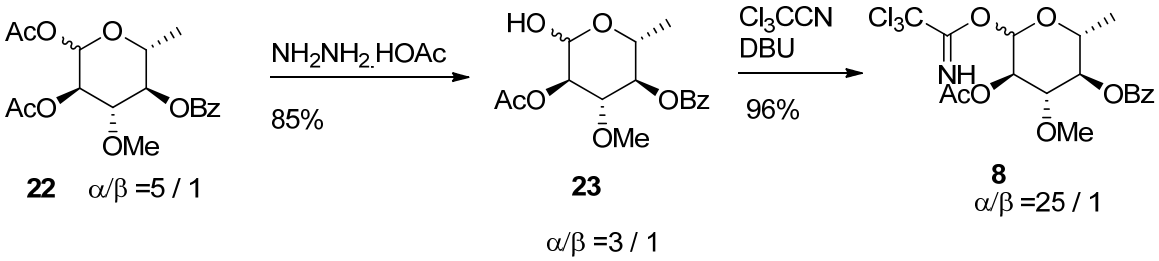

**(2R,3R,4R,5R,6S)-5-Hydroxy-4,6-dimethoxy-2-methyltetrahydro-2H-pyran-3-yl benzoate (21):** A mixture of **19** (978 mg, 2.60 mmol), $(Bu_4N)_2S_2O_8$ (5.3 g, 7.82 mmol), and $NH_4HCO_2$ (1 g, 15.65 mmol) in DMF (52 mL) was stirred at 60 °C for 9 h. After workup with aqueous LiCl solution, the mixture was extracted with ethyl acetate. Column chromatography with 25% ethyl acetate-hexane gave **21** (698 mg, 90% yield). $[\alpha]^{20}_D$ = +90.6 (c=0.015, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.4 Hz, 3H), 3.47 (s, 3H), 3.49 (s, 3H), 3.6 (t, *J* = 9.3 Hz, 1H), 3.70 (m, 1H), 3.92 (m, 1H), 4.80 (d, *J* = 4.1 Hz, 1H), 5.00 (t, *J* = 9.9 Hz, 1H), 7.45 (m, 2H), 7.60 (m, 1H), 8.05 (d, *J* = 7.5 Hz, 2H).; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 17.29, 55.35, 60.44, 65.77, 72.29, 75.55, 81.74, 99.15, 128.46, 129.70, 133.22, 165.48.

Preparation of **22**



**(3R,4S,5R,6R)-5-(Benzoyloxy)-4-methoxy-6-methyltetrahydro-2H-pyran-2,3-diyl diacetate (22):** To a solution of **21** (698 mg, 2.355 mmol) in acetic anhydride (12 mL) was added 3 drops of conc. $H_2SO_4$ in ice bath. After stirring for 2.5 h, 10 drops of $Et_3N$ was added in ice bath, followed by concentration. Column chromatography with 25% ethyl acetate-hexane gave **22** (880 mg, 100% yield, α/β = 5/1). **22 α:** $^1$H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, *J* = 6.4 Hz, 3H), 2.07 (s, 3H), 2.20 (s, 3H), 3.43 (s, 3H), 3.81 (t, *J* = 9.3 Hz, 1H), 4.05 (m, 1H), 5.05 (m, 1H), 6.29 (d, *J* = 3.9Hz, 1H).7.45 (m, 2H), 7.60 (m, 1H), 8.06 (d, *J* = 7.5 Hz, 2H). **22 β:** $^1$H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, *J* = 6.4 Hz, 3H), 2.09 (s, 3H), 2.12 (s, 3H), 3.40 (s, 3H), 3.65 (t, *J* = 9.3 Hz, 1H), 3.78 (m, 1H), 5.00-5.20 (m, 2H), 5.70 (d, *J* = 7.8 Hz, 1H),7.45 (m, 2H), 7.60 (m, 1H), 8.06 (d, *J* = 7.5 Hz, 2H).

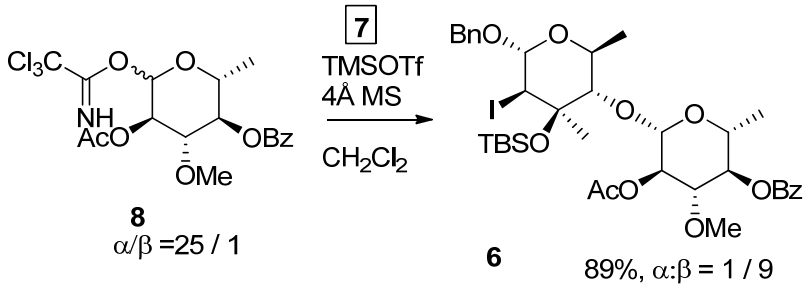
Preparation of chloroacetimidate **8**




**(2R,3R,4S,5R)-5-acetoxy-4-methoxy-2-methyl-6-(2,2,2-trichloro-1-iminoethoxy)tetrahydro-2H-pyran-3-yl benzoate (8)**. To a solution of **22** (95 mg, 0.259 mmol) in anhydrous DMF (2.6 mL) were added $NH_2NH_2$·HOAc (28.6 mg, 0.31 mmol) at room temperature. The mixture was stirred for 1 h, followed by workup with aqueous LiCl and filtration through silica gel pad to afford the crude lactol **23** (71 mg, 85% yield, α/β = 3 /1). This product was taken directly to the next step. To this oil (71 mg, 0.22 mmol) in methylene chloride (2 mL) were added $CCl_3CN$ (44 μL, 0.44 mmol) and a catalytic amount of DBU at room temperature. After stirring for 3 h, the mixture was concentrated, followed by column chromatography with 25% ethyl acetate-hexane to give **8** (99 mg, 96% yield, α/β = 25 /1). $^1$H

NMR (300 MHz, $CDCl_3$) δ 1.25 ( d, *J* = 6.0 Hz, 3H), 2.08 (s, 3H), 3.45 (s, 3H), 3.90 (t, *J* = 11.1 Hz, 1H), 4.15 (m, 1H), 5.05 (dd, *J* = 4.8 and 10.5 Hz, 1H), 5.15 (t, *J* = 10.5 Hz, 1H), 6.50 (d, *J* = 3.9 Hz, 1H), 7.50 (m, 2H), 7.60 (m, 1H), 8.10 (d, J = Hz, 2H), 8.65 (s, 1H).; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 17.33, 20.64, 60.40, 68.63, 72.05, 74.55, 78.34, 91.01, 93.45, 128.49, 129.39, 129.75, 133.40, 160.86, 165.27, 169.90.

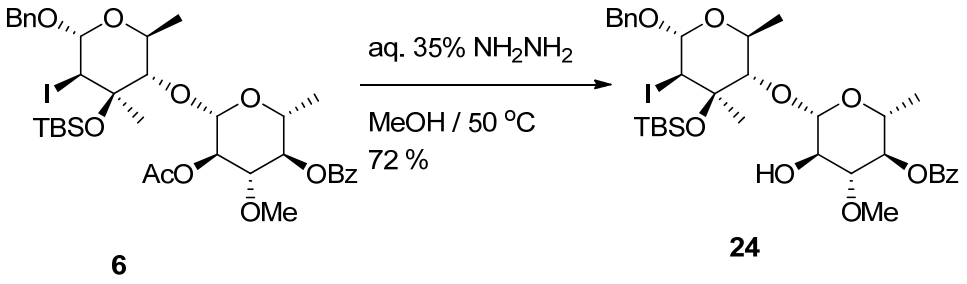
Preparation of sugar **6**




**(2R,3R,4S,5R,6S)-5-Acetoxy-6-((2S,3S,4R,5R,6R)-6-(benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5-iodo-2,4-dimethyltetrahydro-2H-pyran-3-yloxy)-4-methoxy-2-methyltetrahydro-2H-pyran-3-yl benzoate (6):** To a mixture of **7** (296 mg, 0.601 mmol), **8** (334 mg, 0.702 mmol), and 4Å molecular sieves (370 mg) in methylene chloride (6 mL) was added TMSOTf (70 μL, 0.3 mmol) at -70 °C. The mixture was stirred for 2.5 h while the reaction mixture was allowed to warm to -20 °C. After quenching with aqueous $NaHCO_3$, the mixture was extracted with methylene chloride. Column chromatography with 5% ethyl acetate-hexane gave **6** (426 mg, 89% yield, α:β = 1:9). $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.22 (s, 3H), 0.28 (s, 3H), 1.20 (s, 9H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.31 (d, *J* = 6.4 Hz, 3H), 1.60 (s, 3H), 2.11 (s, 3H), 3.36 (s, 3H), 3.45-3.60 (m, 2H), 3.65-3.75 (m, 1H), 3.80 (d, *J* = 8.8 Hz, 1H), 4.28 (d, *J* = 2.3 Hz, 1H), 4.44 (d, *J* = 12.3 Hz, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 4.90-5.05 (m, 1H), 5.09 (t, *J* = 9.9 Hz, 1H), 5.34 (d, *J* = 1.7 Hz, 1H), 7.30-7.40 (m, 5H), 7.47 (m, 2H), 7.60 (m, 1H), 8.06 (m, 2H).; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ -1.73, -0.91, 17.50, 18.46, 18.69, 21.08, 26.93, 44.84, 58.56, 67.61, 69.79, 70.15, 72.62, 74.62, 76.06, 80.61, 81.63, 100.08, 102.21, 127.83, 128.42, 128.47, 129.73, 133.32,

137.30, 165.28, 169.26. LRMS(ESI) *m/z* 821 $[M + Na]^+$; HRMS (ESI) calculated for $C_{36}H_{51}IO_{10}SiNa$, 821.2194; found, 821.2204

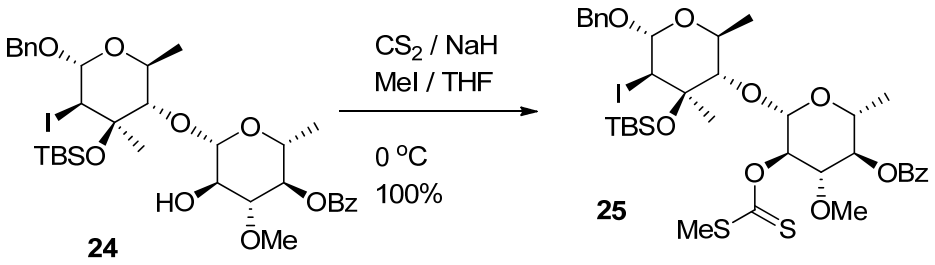
Preparation of alcohol **24**




**6** **24**

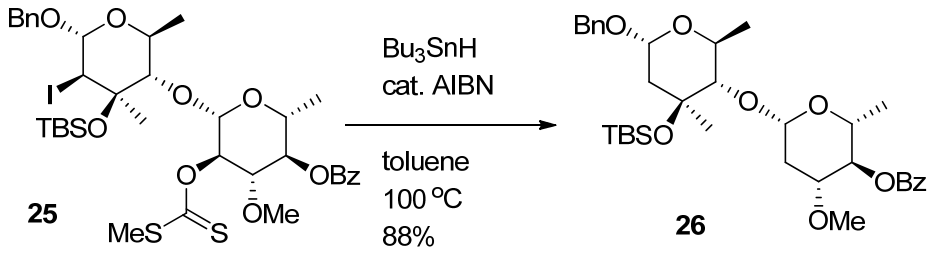
**(2R,3R,4R,5R,6S)-6-(((2S,3S,4R,5R,6R)-6-(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-5-iodo-2,4-dimethyltetrahydro-2H-pyran-3-yl)oxy)-5-hydroxy-4-methoxy-2-methyltetrahydro-2H-pyran-3-yl benzoate (24).** To a solution of **6** (16 mg, 20 μmol) in a 4/1 mixture of MeOH and $Et_2O$ (1 mL) was added aqueous 35% $NH_2NH_2$ solution (0.1 mL). After stirring for 17 h at 50 °C, the mixture was concentrated and filtered through a silica gel pad. Column chromatography with 10% ethyl acetate-hexane gave **24** (11 mg, 72% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 3H), 0.27 (s, 3H), 1.00 (s, 9H), 1.25 (m, 6H), 1.55(m, 2H), 1.72 (s, 3H), 2.41 (s, 1H), 3.36 (t, J = 8.4 Hz, 1H), 3.48 (s, 3H), 3.45-3.63 (m, 3H), 3.80 (d, *J* = 3.6 Hz, 1H), 4.32 (d, *J* = 3.0 Hz, 1H), 4.48 (d, *J* = 12.6 Hz, 1H), 4.70 (d, *J* = 4.5 Hz, 1H), 4.73 (s, 1H), 5.00 (t, *J* = 9.0 Hz, 1H), 5.37 (d, *J* = 2.4 Hz, 1H), 7.30-7.40 (m, 5H), 7.48 (m, 2H), 7.60 (m, 1H), 8.07 (m, 2H). LRMS (ESI) *m/z* 779 $[M + Na]^+$.

Preparation of xanthate **25**



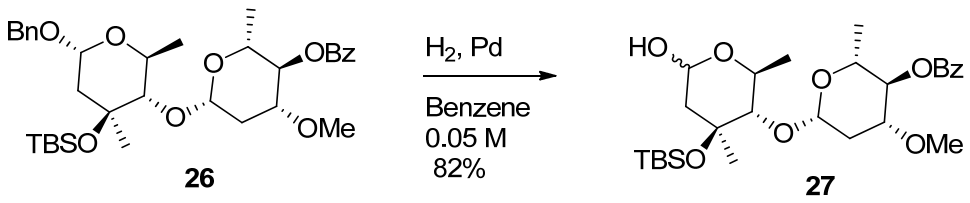

**(2R,3R,4S,5R,6S)-6-((2S,3S,4R,5R,6R)-6-(Benzyloxy)-4-(*tert*-butyldimethylsilyloxy)-5-iodo-2,4-dimethyltetrahydro-2H-pyran-3-yloxy)-4-methoxy-2-methyl-5-(methylthiocarbonothioyloxy)tetrahydro-2H-pyran-3-yl benzoate (25):** To a mixture of **24** (10 mg, 13.2 μmol) and excess $CS_2$ (30 μL) in dry THF (1 mL) cooled in an ice bath was added excess NaH (60% in mineral oil, 10 mg). After stirring for 30 min, excess MeI (10 μL) was added to the mixture. The mixture was stirred for 15 h at room temperature, worked up with aqueous $NaHCO_3$, and extracted with ethyl acetate. Column chromatography with 5% ethyl acetate-hexane gave **25** (11.3 mg, 100% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 0.24 (s, 3H), 0.26 (s, 3H), 1.01 (s, 9H), 1.30 (m, 6H), 1.56 (s, 3H), 2.60 (s, 3H), 3.38 (s, 3H), 3.55-3.70 (m, 2H), 3.75 (m, 2H), 4.25 (d, *J* = 2.9 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.70 (d, *J* = 12.31 Hz, 1H), 5.02 (d, *J* = 8.2 Hz, 1H), 5.10 (t, *J* = 9.3 Hz, 1H), 5.30 (d, *J* = 2.9 Hz, 1H), 5.98 (dd, *J* = 7.6 and 9.3 Hz, 1H), 7.30-7.40 (m, 5H), 7.47 (m, 2H), 7.60 (m, 1H), 8.06 (m, 2H).; $^{13}$C NMR (75 MHz, $CDCl_3$) δ -1.60, -0.84, 17.48, 18.57, 19.75, 26.80, 44.80, 59.84, 67.98, 69.72, 70.29, 74.95, 76.18, 80.98, 82.27, 100.31, 102.23, 127.78, 128.37, 128.51, 129.58, 129.72, 133.34, 137.41, 165.29. LRMS(positive ESI) *m/z* 869 $[M + Na]^+$; HRMS (ESI) calculated for $C_{36}H_{51}IO_9S_2SiNa$, 869.1686; found, 869.1697.

Preparation of sugar **26**



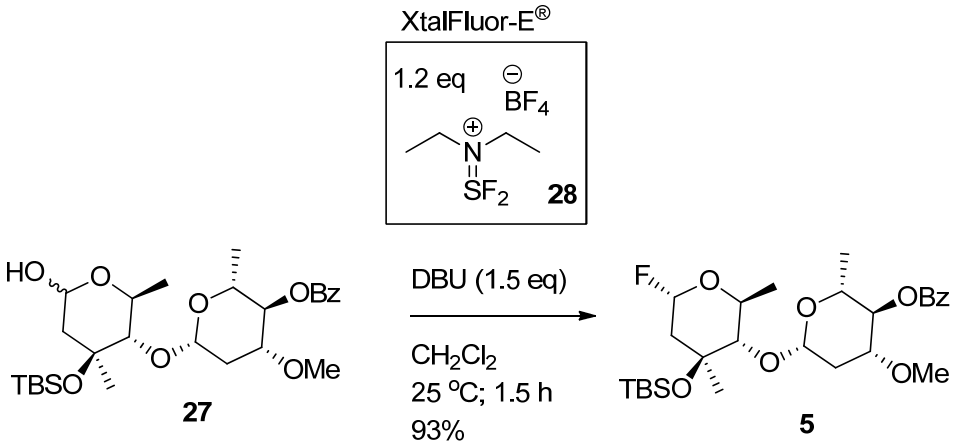

**(2R,3R,4R,6S)-6-((2S,3S,4S,6R)-6-(Benzyloxy)-4-(tert-butyldimethylsilyloxy)-2,4-dimethyltetrahydro-2H-pyran-3-yloxy)-4-methoxy-2-methyltetrahydro-2H-pyran-3-yl benzoate (26):** To a solution of **25** (15.7 mg, 18.5 μmol) in toluene (2 mL) were added a catalytic amount of AIBN and 6 equiv. of $Bu_3SnH$ (25 μL, 93 μmol). After reflux for 2 h in an oil bath, the mixture was cooled to room temperature and treated with 0.1 N NaOH solution followed by extraction with diethyl ether. Chromatography with 5% ethyl acetate/hexane gave disaccharide **26** (10 mg, 88% yield). $^1$H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.92 (s, 9H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.25 (s, 3H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.49 (s, 3H), 1.55-1.70 (m, 2H), 1.90-1.95 (dd, *J* = 3.9 and 13.5 Hz, 1H), 2.07-2.11 (d, *J* = 13.5 Hz, 1H), 2.41-2.46 (m, 1H), 3.30 (s, 3H), 3.36-3.50 (m, 3H), 3.67 (m, 1H), 4.38 (d, *J* = 12.3 Hz, 1H), 4.67 (d, *J* = 12.3 7.30-Hz, 1H), 4.88-4.95 (m, 3H), 7.30 (m, 5H), 7.40-7.60 (m, 3H), 8.05 (d, 2H).; $^{13}$C NMR (100 MHz, $CDCl_3$) δ -1.83, -1.75, 17.70, 18.01, 18.39, 23.37, 25.90, 29.69, 36.01, 44.65, 56.67, 66.01, 68.97, 70.05, 75.71, 76.19, 78.45, 86.30, 96.38, 100.99, 127.49, 127.56, 128.35, 129.72, 130.09, 133.03, 138.02. LRMS (ESI) *m/z* 637 $[M + Na]^+$.

Preparation of lactol **27**



**(2R,3R,4R,6S)-6-(((2S,3S,4S)-4-((tert-butyldimethylsilyl)oxy)-6-hydroxy-2,4-dimethyltetrahydro-2H-pyran-3-yl)oxy)-4-methoxy-2-methyltetrahydro-2H-pyran-3-yl benzoate (27).** To a solution of **26** (100 mg, 163 μmol) in benzene (5 mL) was added Pd/C (10 wt% Aldrich, 8.6 mg, 8 μmol) and the mixture was stirred for 12 h under a hydrogen balloon. The reaction mixture was then passed through Celite and washed with ethyl acetate (25 mL). The solvent was evaporated and the crude product was purified using flash column chromatography with 20% ethyl acetate/hexane to provide **27** (70 mg, 82% yield). $^1$HNMR (300 MHz, $CDCl_3$) δ 8.44 – 7.76 (m, 2H), 7.65 (t, *J* = 7.4 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 3H), 7.52 – 7.26 (m, 1H), 5.41 – 5.16 (m, 1H), 5.09 – 4.73 (m, 1H), 3.57 (m, 1H), 3.55 (m, 3H), 2.99 (d, *J* = 86.3 Hz, 1H), 2.56 – 2.39 (m, 1H), 2.35 – 2.08 (m, 1H), 1.96 (d, *J* = 9.6 Hz, 1H), 1.91 – 1.24 (m, 1H), 1.21 (s, 1H), 1.17 – 0.05 (m, 3H), 0.02 (s, 1H)

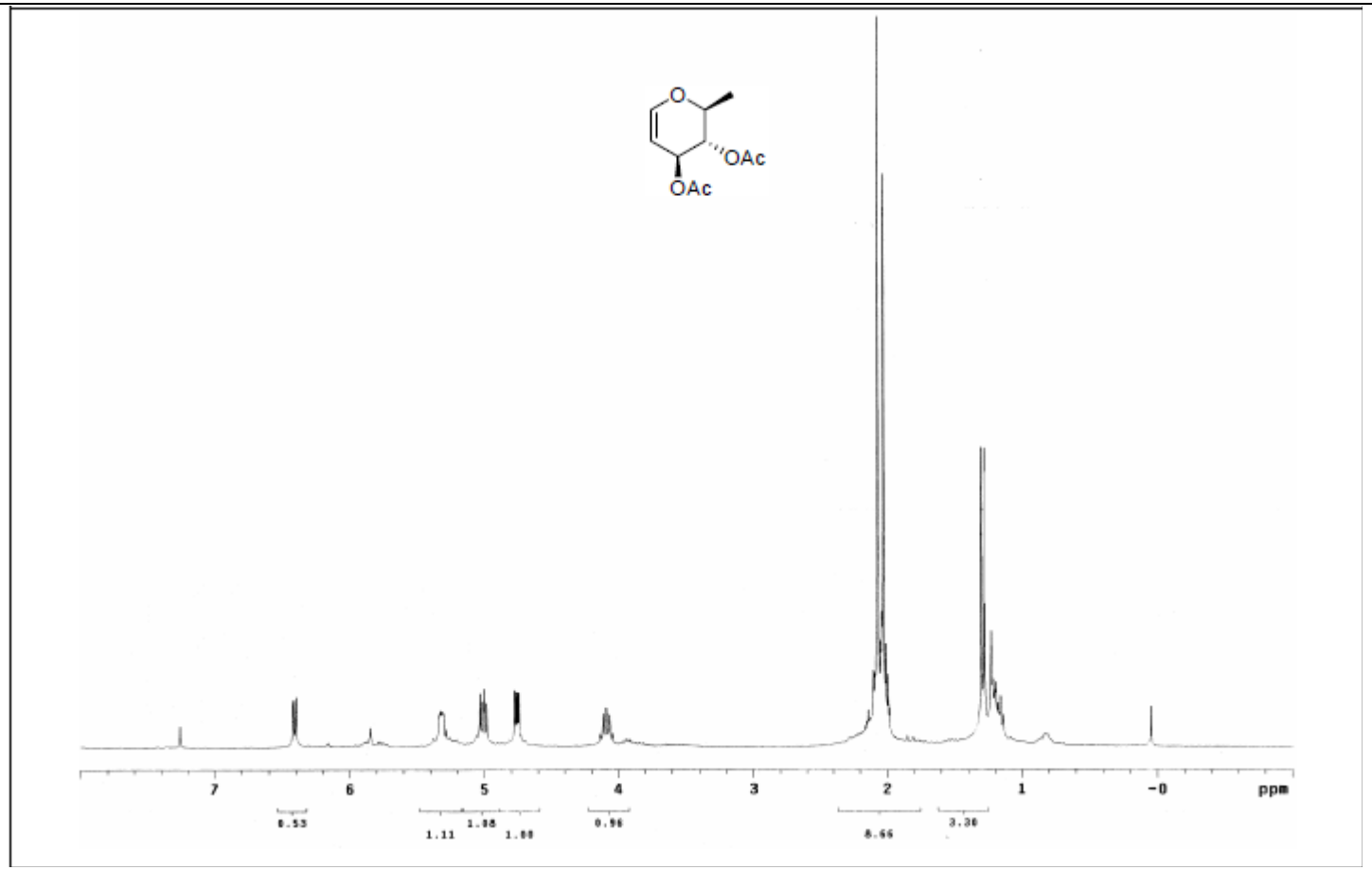
Preparation of fluoride **5**




**(2R,3R,4R,6S)-6-(((2S,3S,4S,6S)-4-((tert-butyldimethylsilyl)oxy)-6-fluoro-2,4-dimethyltetrahydro-2H-pyran-3-yl)oxy)-4-methoxy-2-methyltetrahydro-2H-pyran-3-yl benzoate (5).** To a solution of **27** (50 mg, 0.09 mmol) in dichloromethane (0.9 mL) was added of XtalFluor-E®[5] **28** (25 mg, 0.1 mmol) and DBU (22 mg, 0.14 mmol) at 25 °C. After stirring for 1.5 h, the reaction was quenched with water and extracted with ether. The combined organic

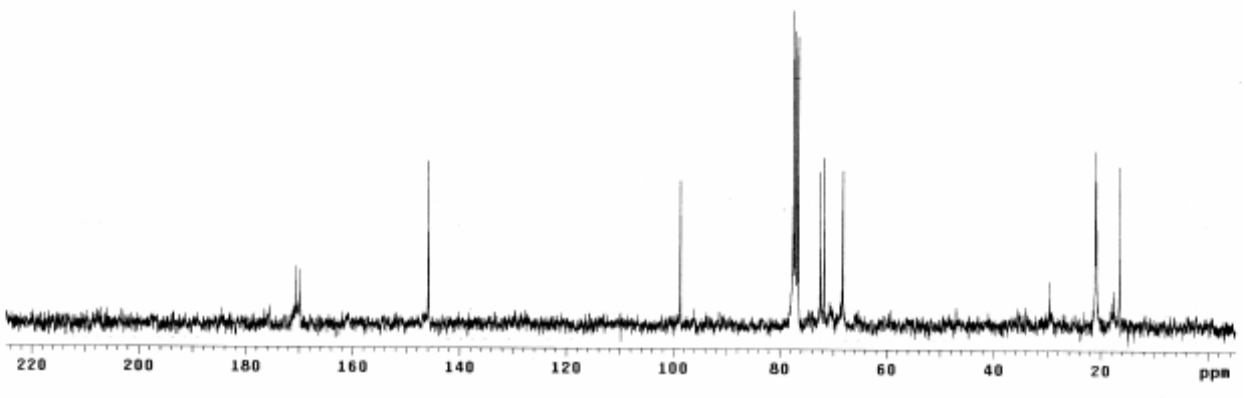
[5] XtalFluor-E® is prepared from commercially available diethylamino sulfur trifluoride (DAST) according to the procedure reported in *J. Org. Chem.* **2010**, *75*, 3401.

layer was washed with brine solution and dried over $MgSO_4$. The solvent was evaporated to provide **5** (53 mg, 93% yield, 10:1 α:β mixture). α- anomer: $^1$HNMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.2 Hz, 2H), 7.74 – 7.58 (m, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 5.77 (d, *J* = 2.1 Hz, 0.5 H), 5.60 (d, *J* = 2.1 Hz, 0.5H), 5.00 (t, *J* = 9.2 Hz, 2H), 4.11 – 3.65 (m, 1H), 3.65 – 3.35 (m, 5H), 3.35 – 2.46 (m, 1H), 2.46 – 2.08 (m, 1H), 2.08 – 1.86 (m, 1H), 2.46 – 0.99 (m, 9H), 0.99 – 0.53 (m, 3H), 0.24 (s, 3H), 0.23 – 0.20 (m, 2H), 0.14 (d, *J* = 7.8 Hz, 3H). $^{13}$CNMR (75 MHz, $CDCl_3$) δ 165.90, 133.14, 130.13, 129.80, 128.45, 107.78, 104.90, 101.07, 85.20, 78.47, 77.53, 77.10, 76.68, 76.19, 74.79, 70.19, 68.72, 56.78, 44.43, 44.09, 36.08, 25.94, 22.84, 18.43, 18.08, 17.77, 1.10, -1.69, -1.80. $^{19}$FNMR (282 MHz, $CDCl_3$) δ -123.54 (ddd, *J* = 6 Hz, *J* = 12 Hz, *J* = 45 Hz).

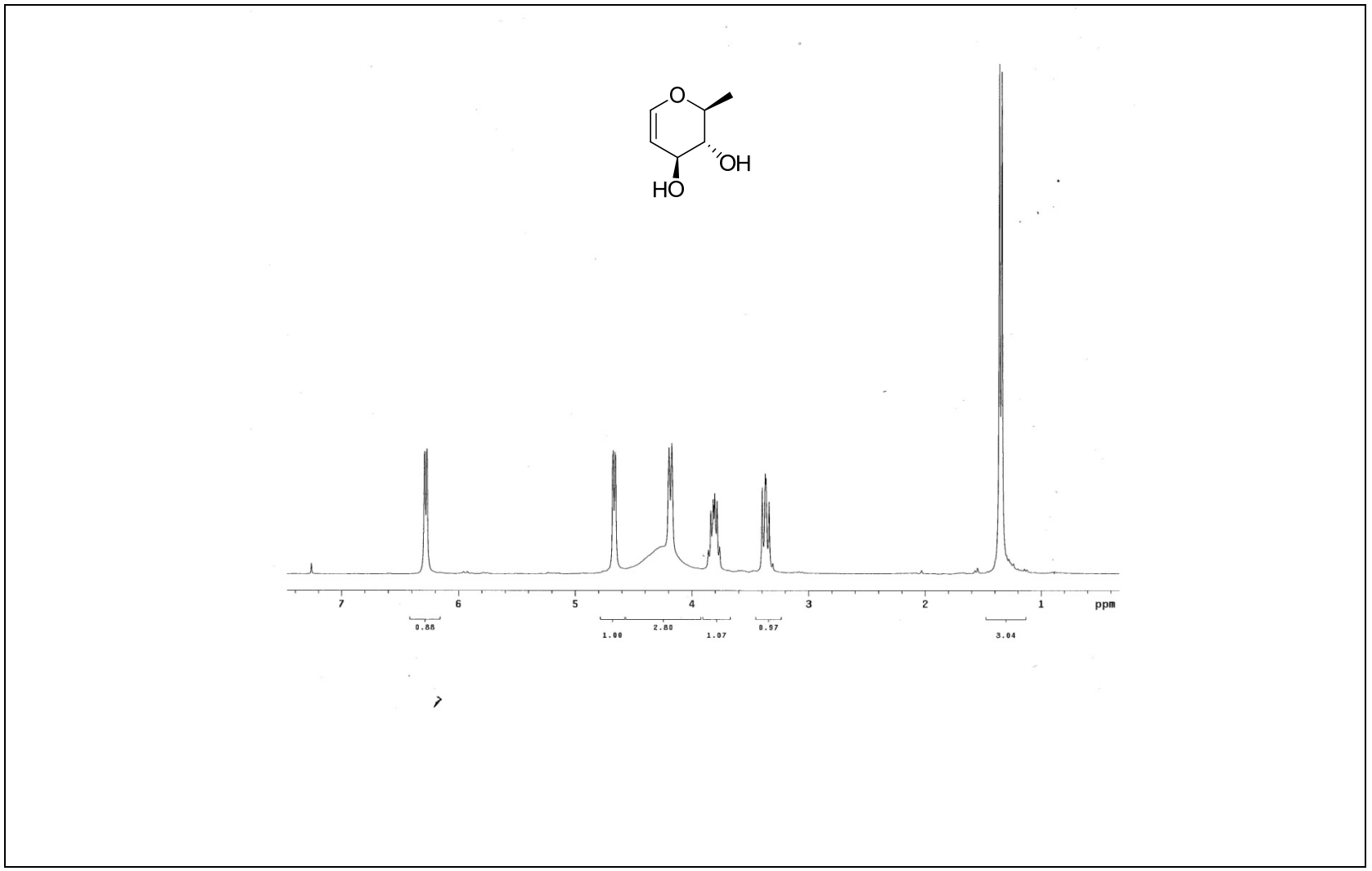



300 MHz $^{1}H$ NMR of compound **9** in $CDCl_3$

| INDEX | FREQUENCY | PPM | HEIGHT |
|---|---|---|---|
| 1 | 12873.467 | 170.667 | 12.0 |
| 2 | 12816.224 | 169.905 | 11.2 |
| 3 | 11085.422 | 145.903 | 33.7 |
| 4 | 7443.119 | 98.676 | 29.9 |
| 5 | 5839.879 | 77.421 | 64.8 |
| 6 | 5808.182 | 77.000 | 69.6 |
| 7 | 5774.215 | 76.551 | 59.4 |
| 8 | 5462.884 | 72.423 | 31.8 |
| 9 | 5409.537 | 71.721 | 34.6 |
| 10 | 5145.200 | 68.212 | 32.8 |
| 11 | 1585.814 | 21.013 | 36.2 |
| 12 | 1572.397 | 20.845 | 30.1 |
| 13 | 1241.915 | 16.464 | 33.1 |

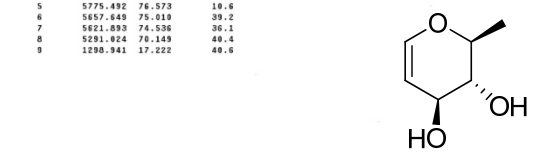



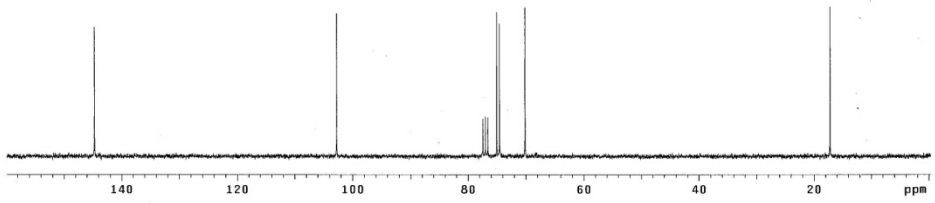

75 MHz $^{13}C$ NMR of compound **9** in $CDCl_3$



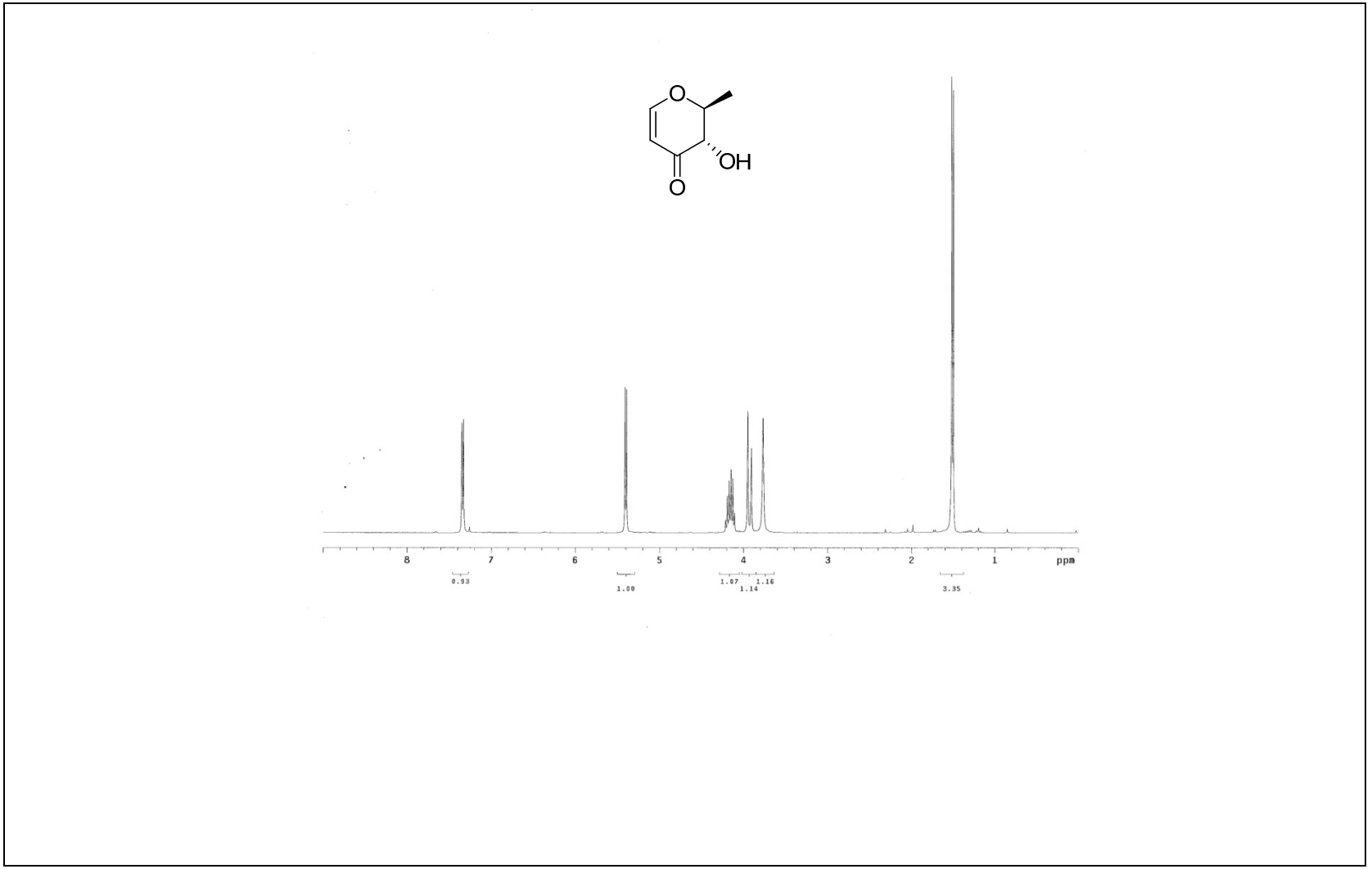

300 MHz $^{1}H$ NMR of compound **10** in $CDCl_3$

| INDEX | FREQUENCY | PPM | HEIGHT |
|---|---|---|---|
| 1 | 10915.797 | 144.724 | 35.2 |
| 2 | 7749.627 | 102.746 | 38.9 |
| 3 | 5839.450 | 77.421 | 10.2 |
| 4 | 5807.723 | 77.000 | 10.9 |
| 5 | 5775.492 | 76.573 | 10.6 |
| 6 | 5657.648 | 75.010 | 39.2 |
| 7 | 5621.893 | 74.536 | 36.1 |
| 8 | 5291.024 | 70.149 | 40.4 |
| 9 | 1298.941 | 17.222 | 40.6 |

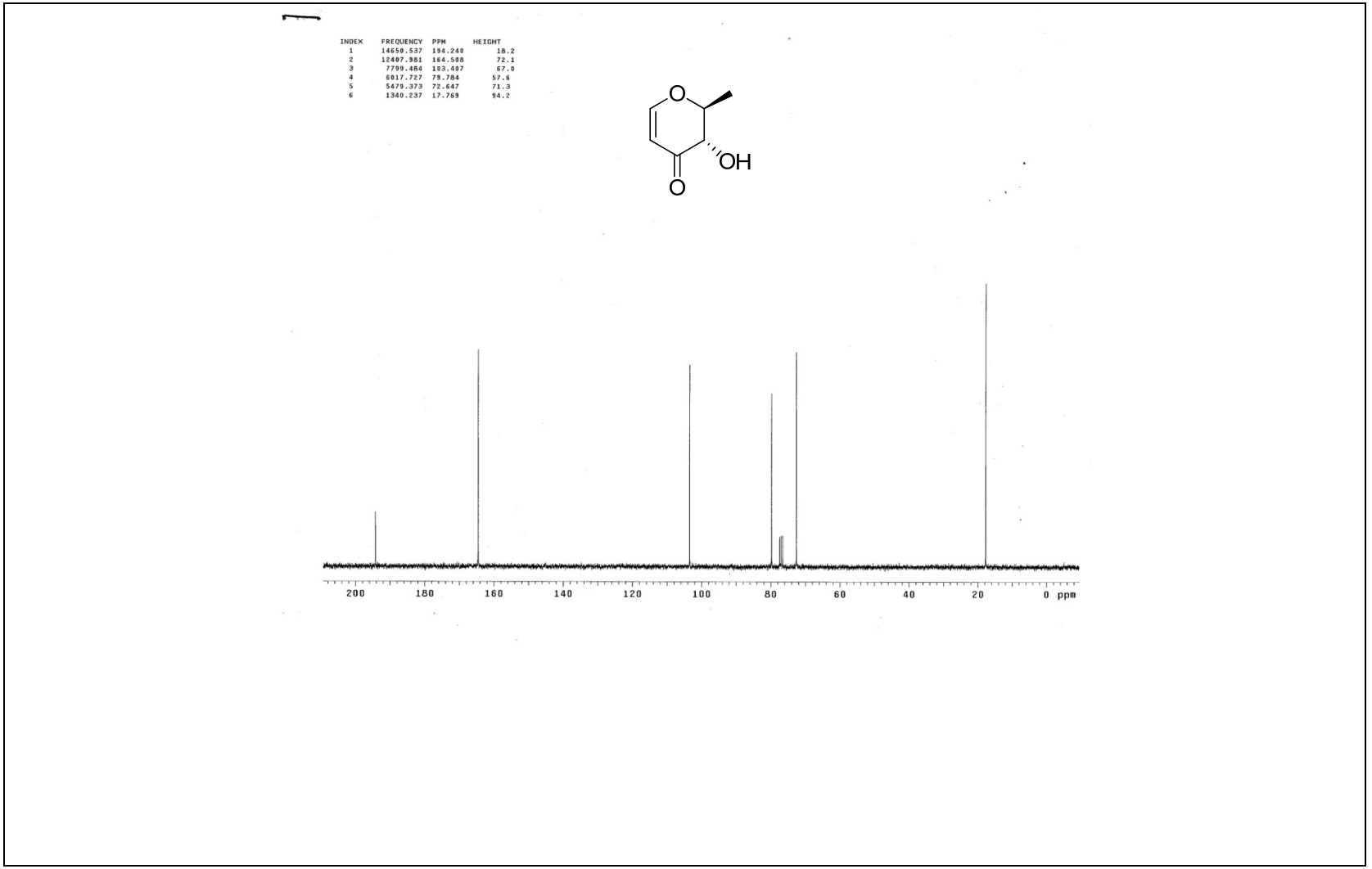


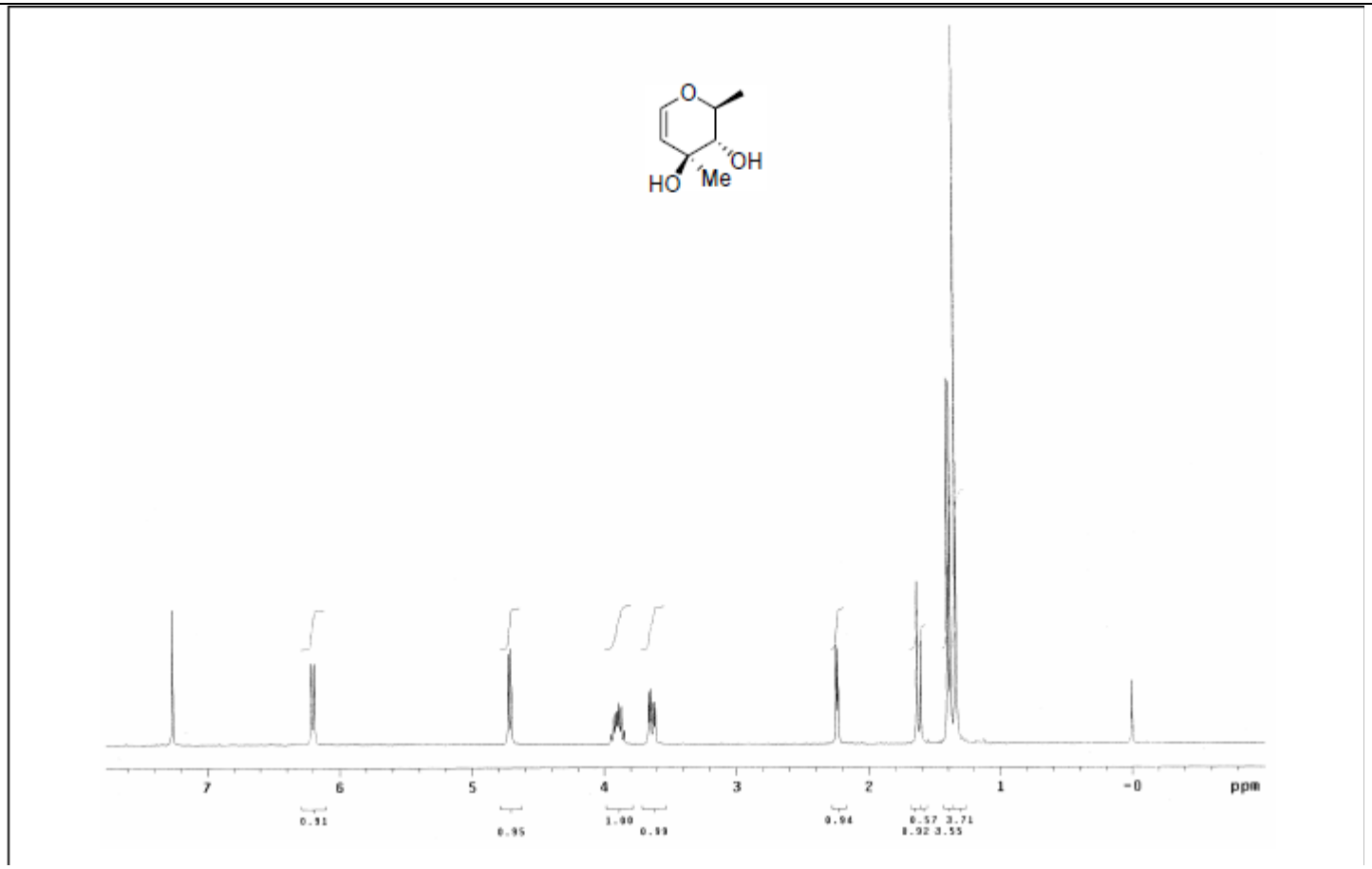

75 MHz $^{13}C$ NMR of compound **10** in $CDCl_3$



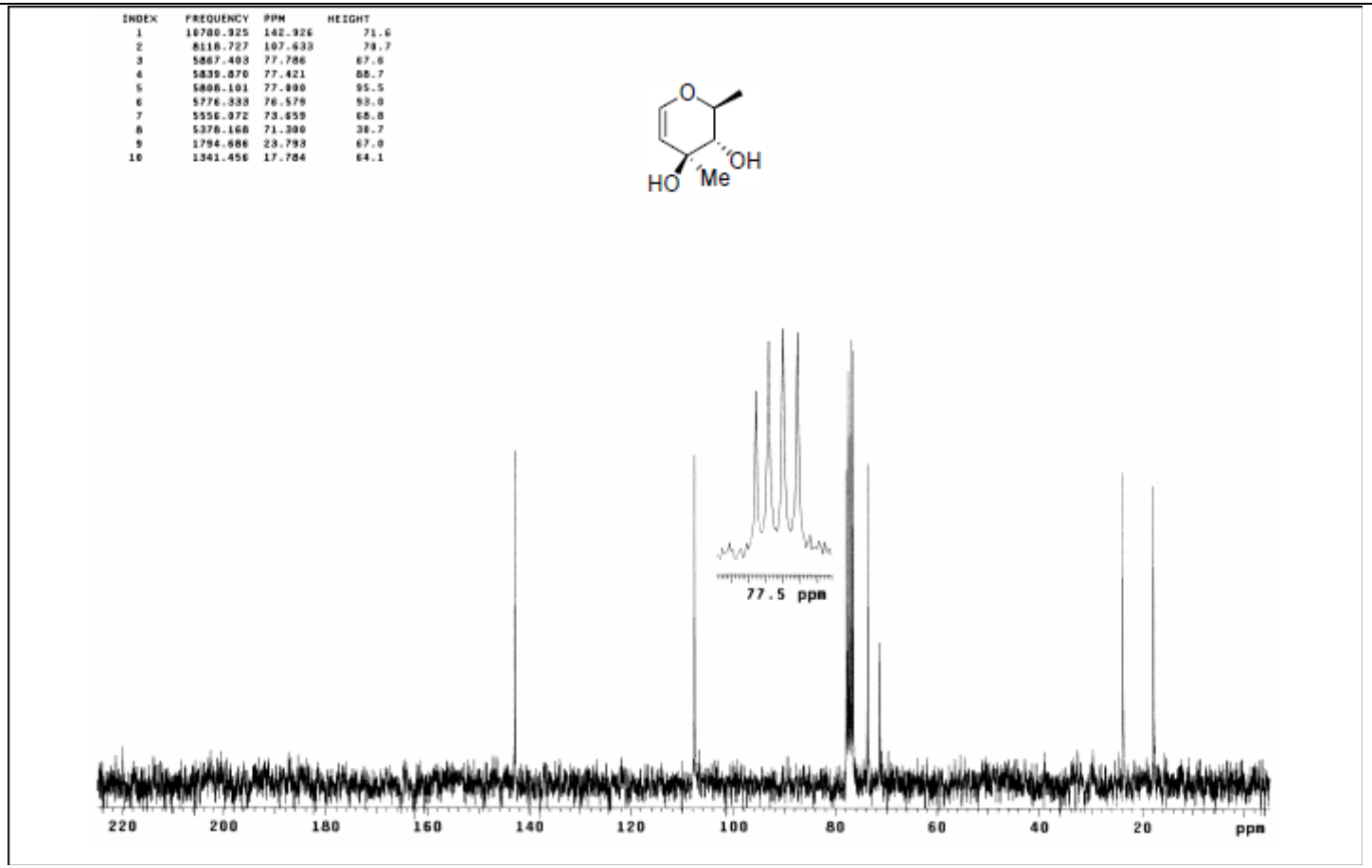

300 MHz $^{1}H$ NMR of compound **11** in $CDCl_3$



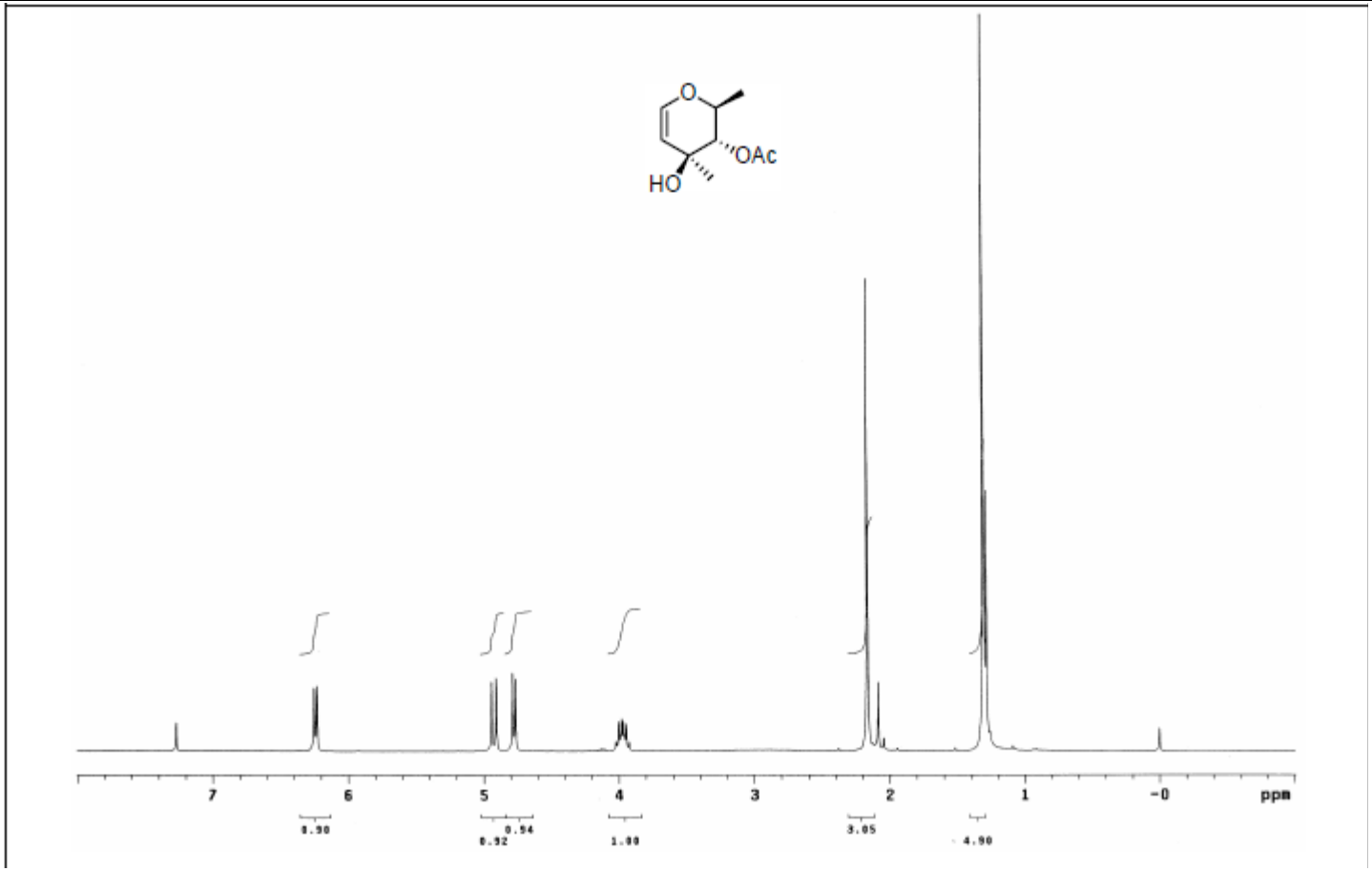

75 MHz $^{13}C$ NMR of compound **11** in $CDCl_3$



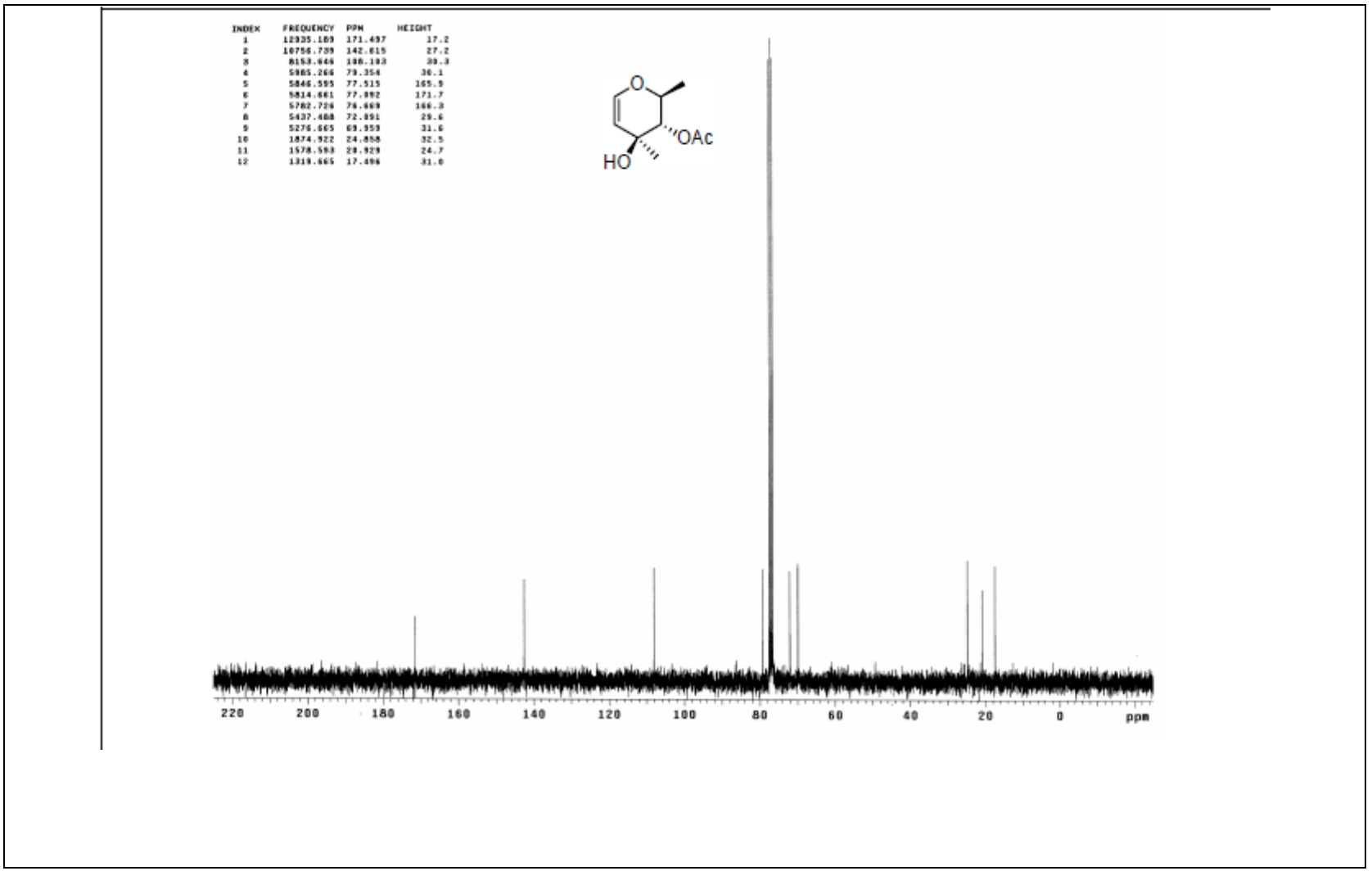

300 MHz $^{1}H$ NMR of compound **12** in $CDCl_3$



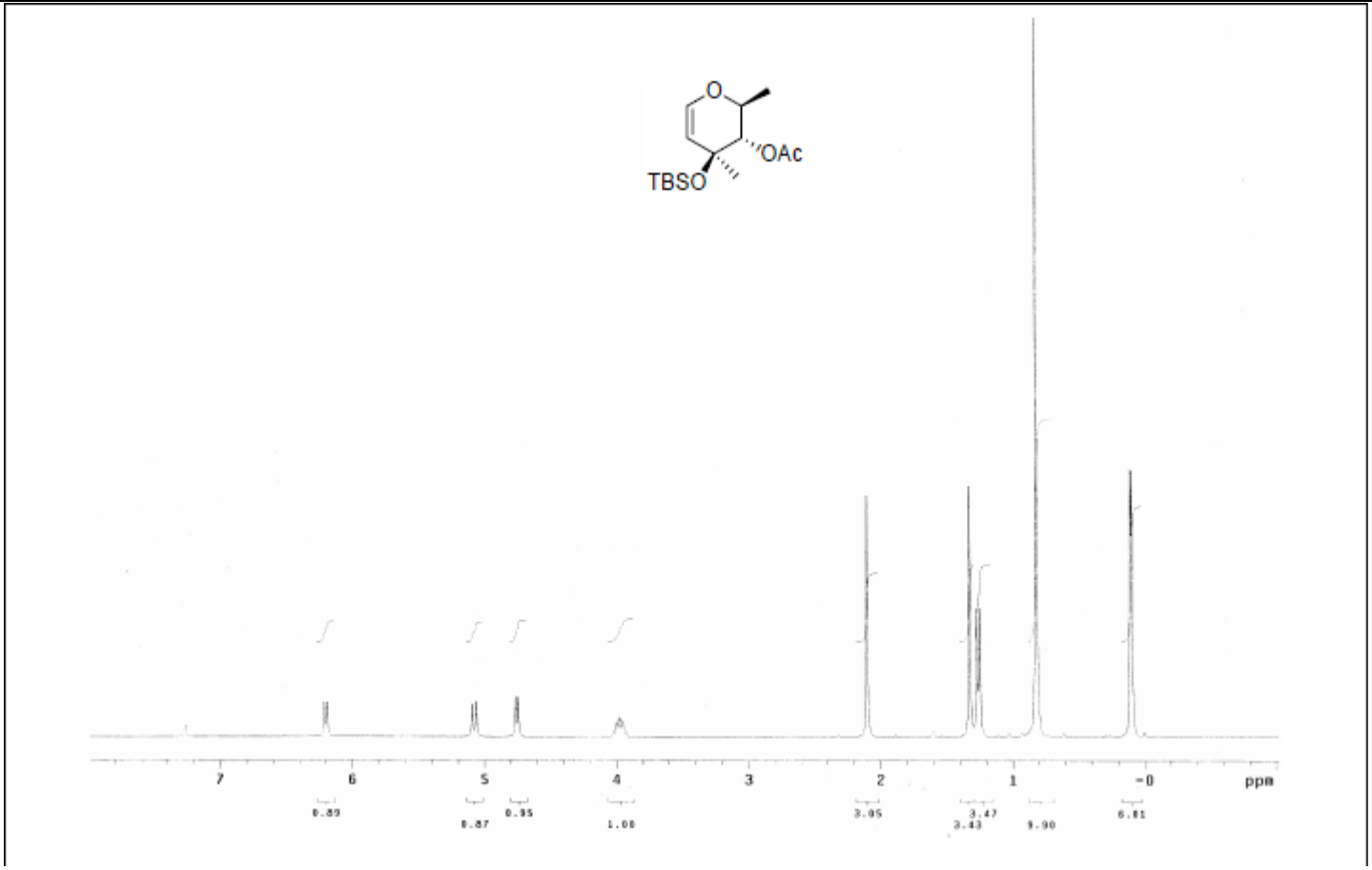

75 MHz $^{13}C$ NMR of compound **12** in $CDCl_3$



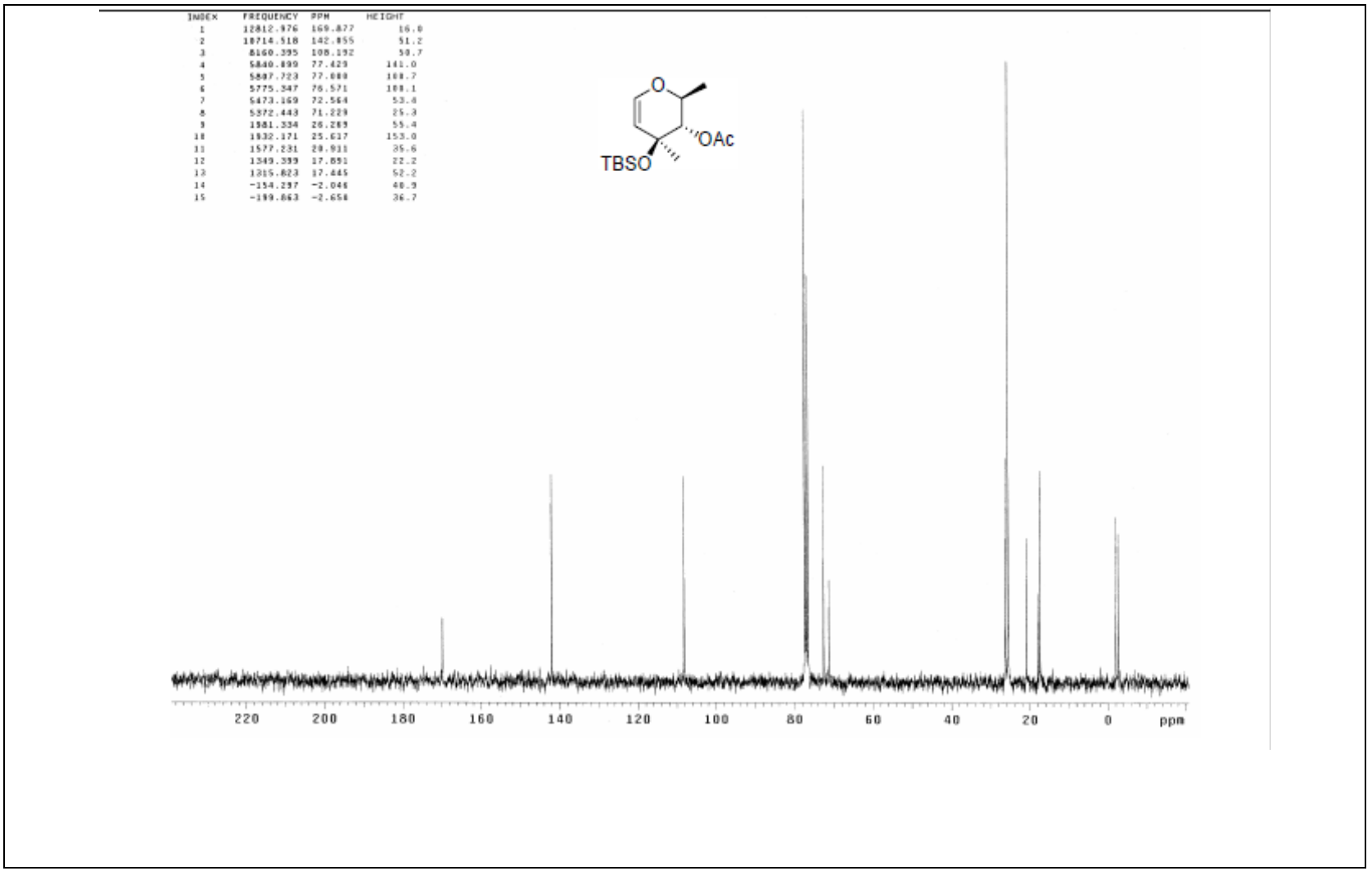

300 MHz $^{1}H$ NMR of compound **14** in $CDCl_3$



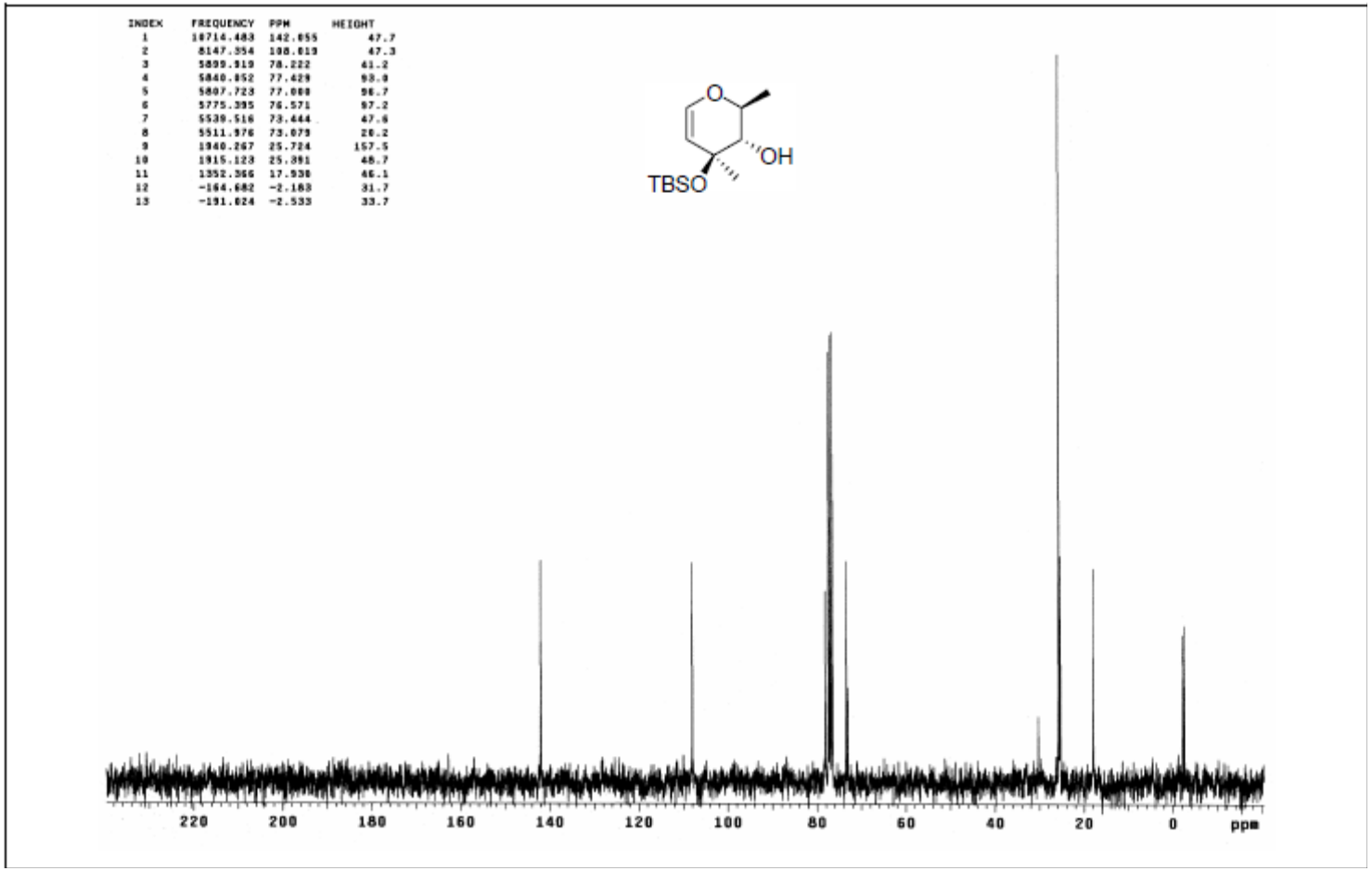

75 MHz $^{13}C$ NMR of compound **14** in $CDCl_3$



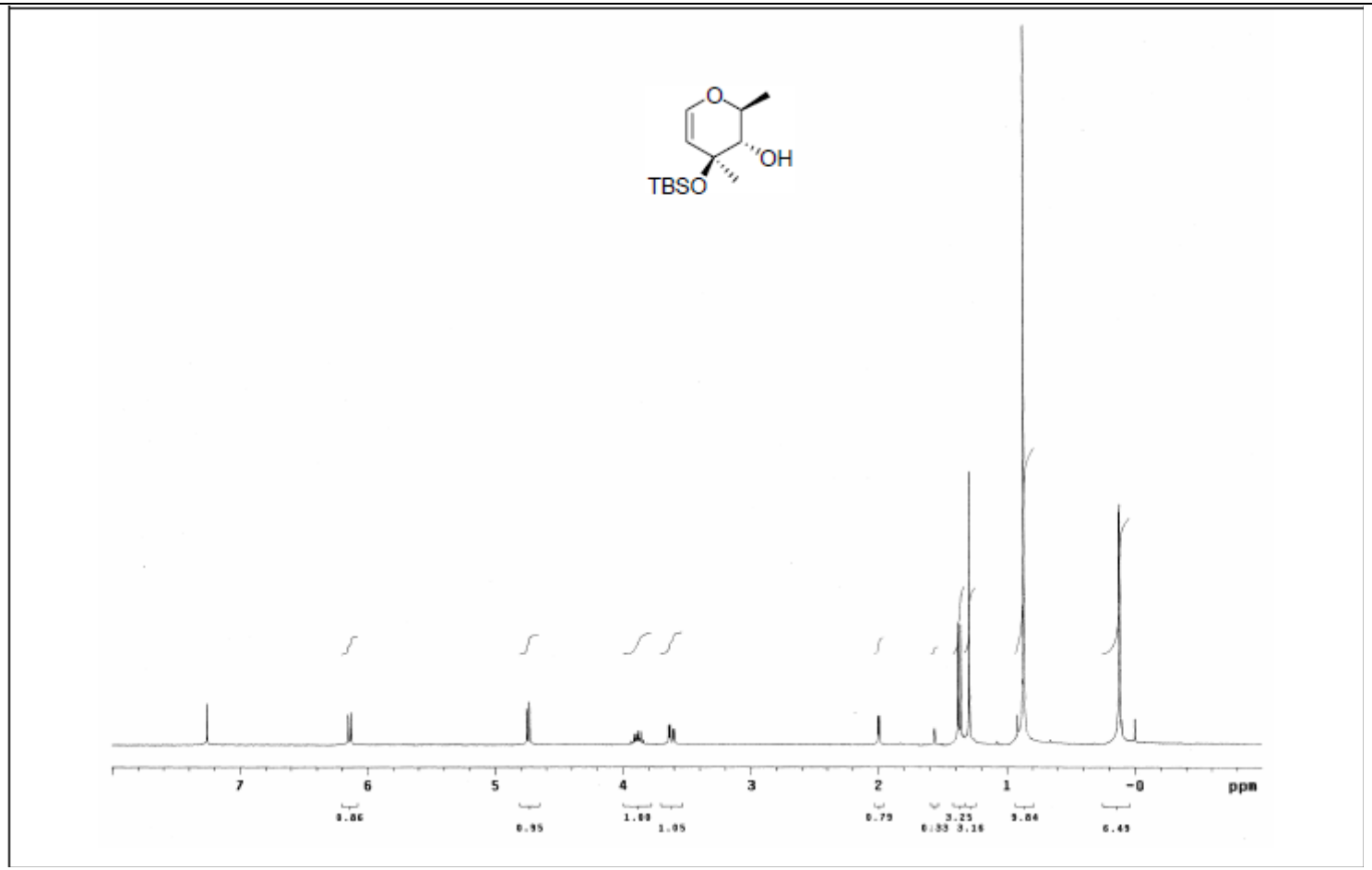

300 MHz $^{1}H$ NMR of compound **15** in $CDCl_3$



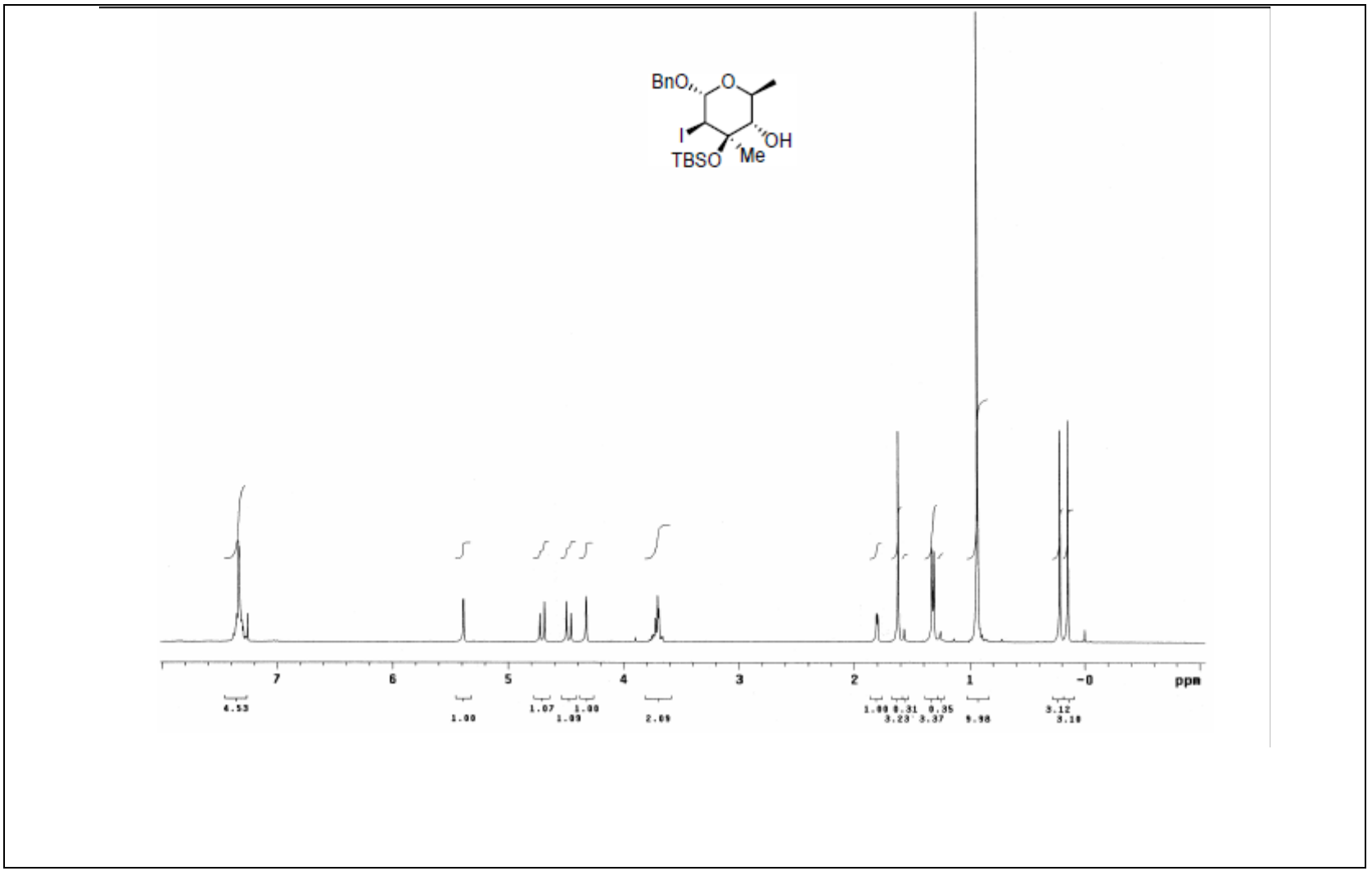

75 MHz $^{13}C$ NMR of compound **15** in $CDCl_3$



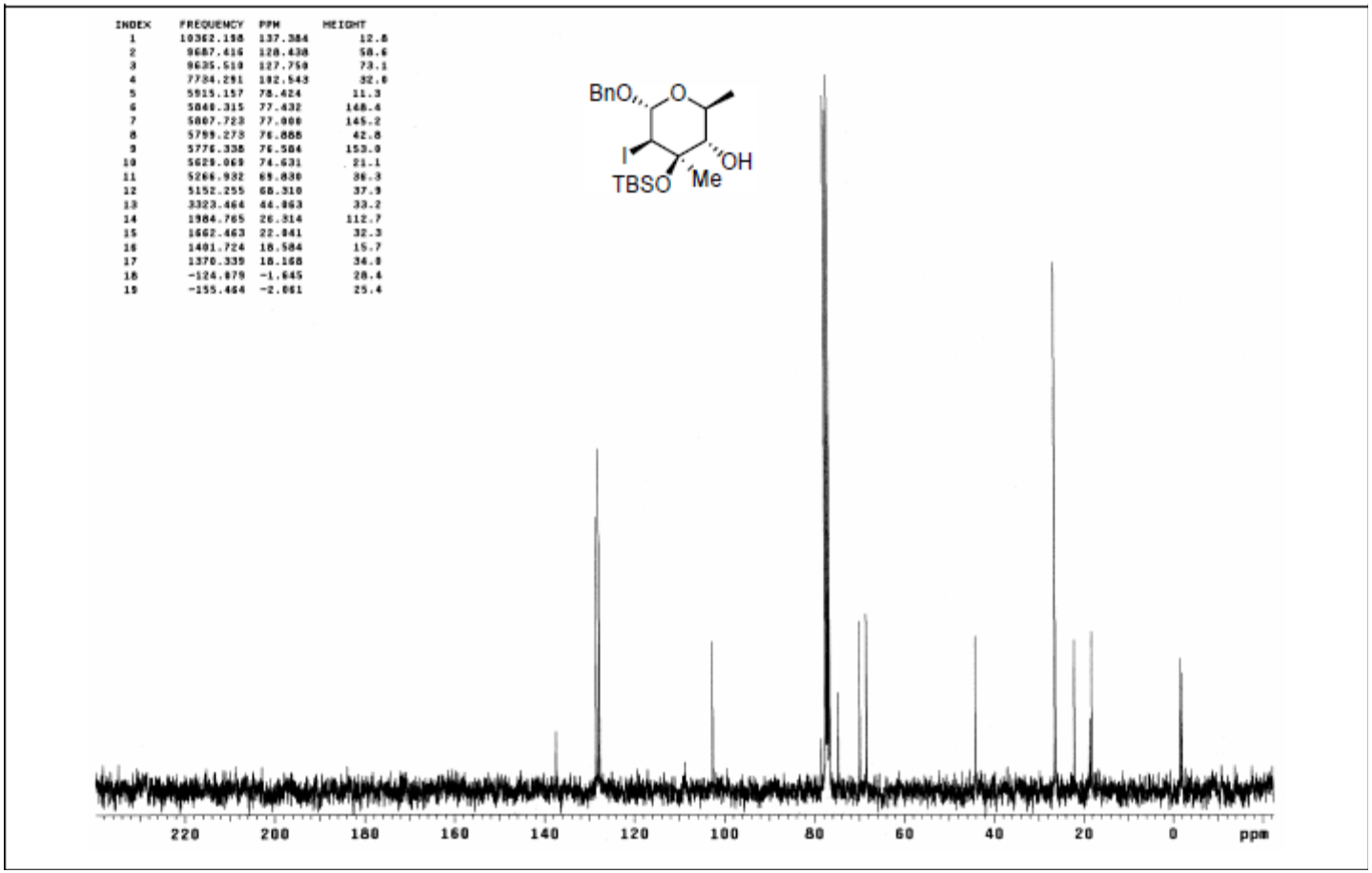

75 MHz $^{13}C$ NMR of compound **16** in $CDCl_3$



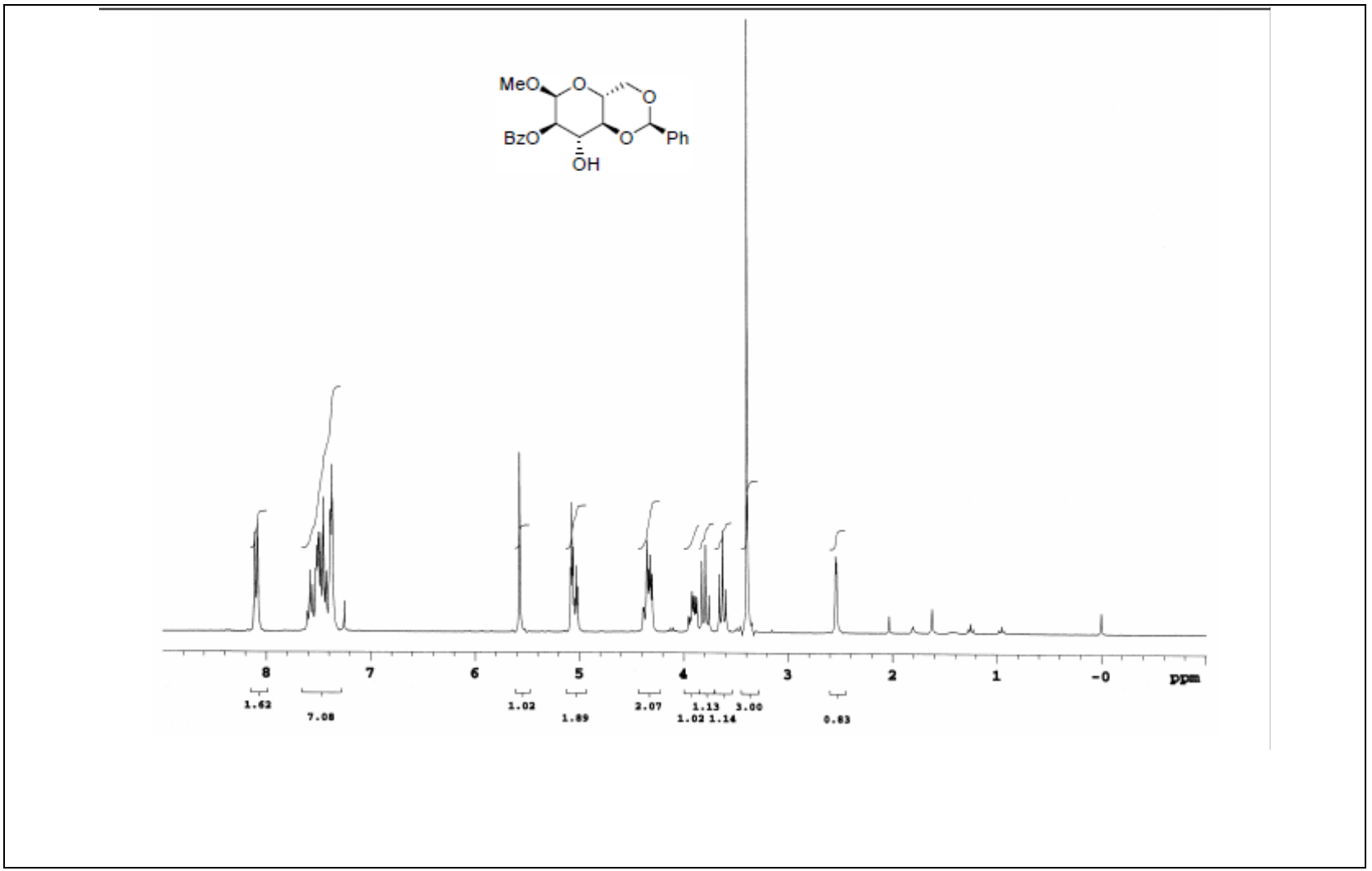

300 MHz $^{1}H$ NMR of compound **16** in $CDCl_3$



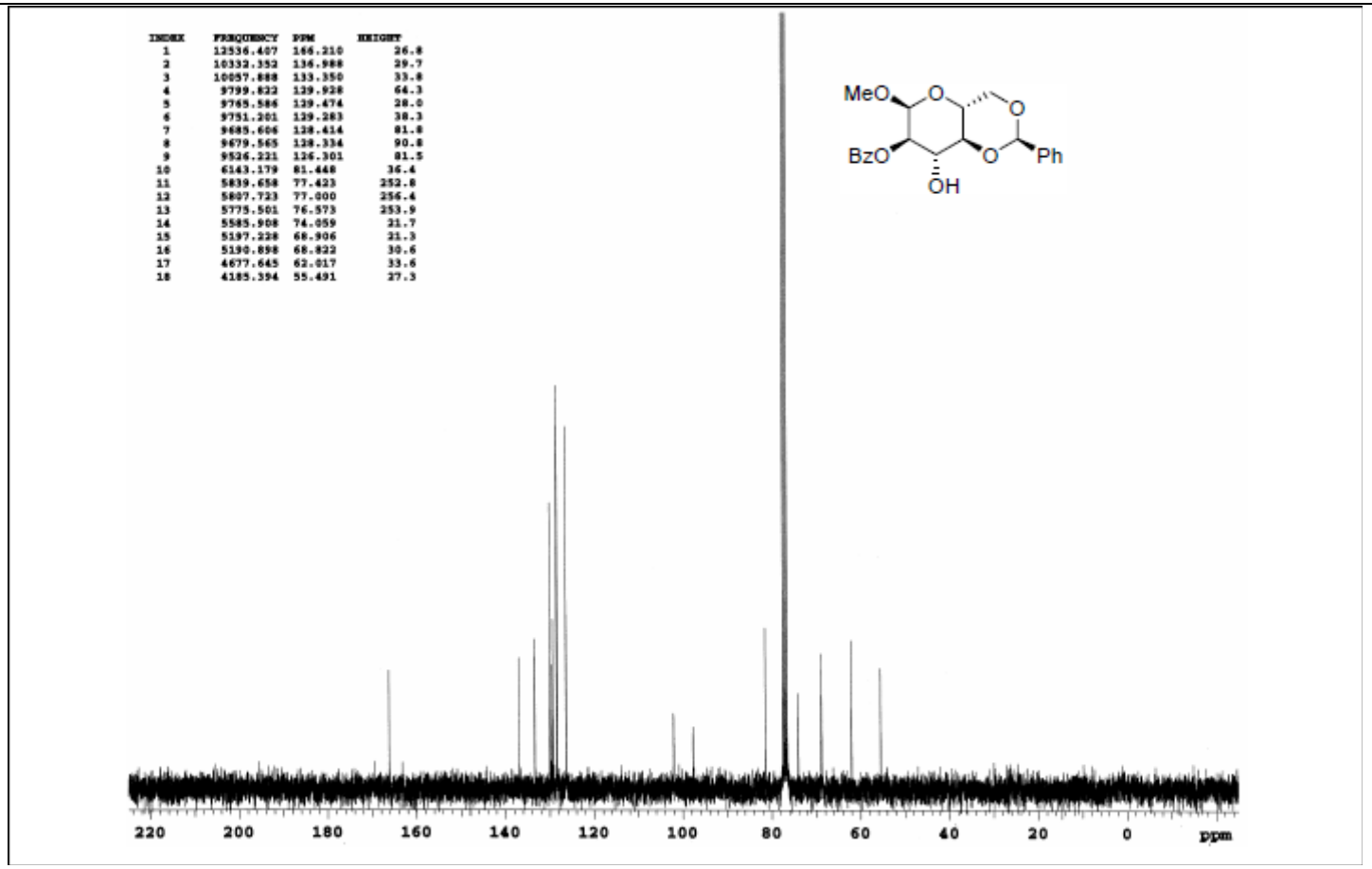

300 MHz $^{1}H$ NMR of compound **7** in $CDCl_3$



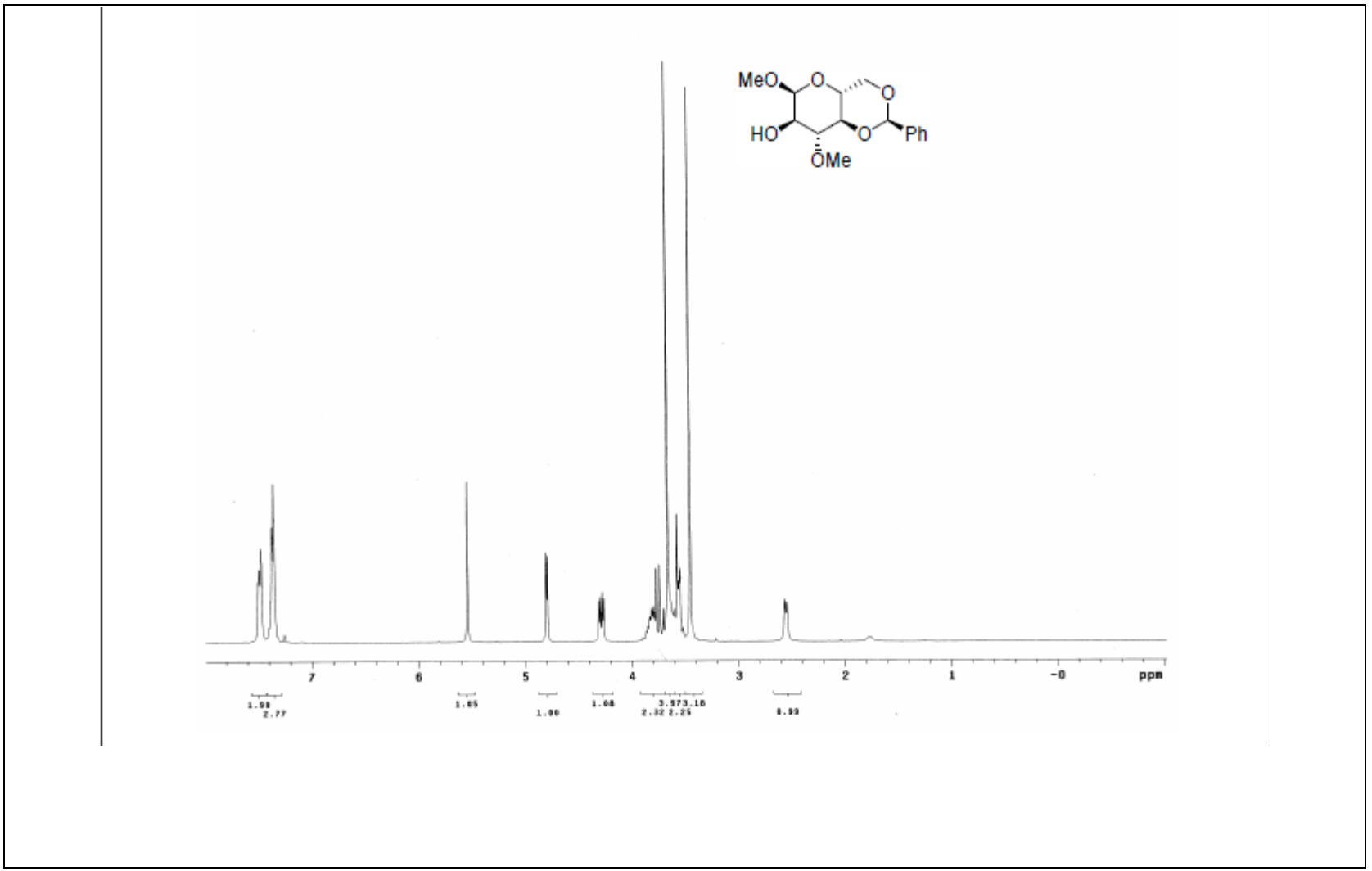

75 MHz $^{13}C$ NMR of compound **7** in $CDCl_3$



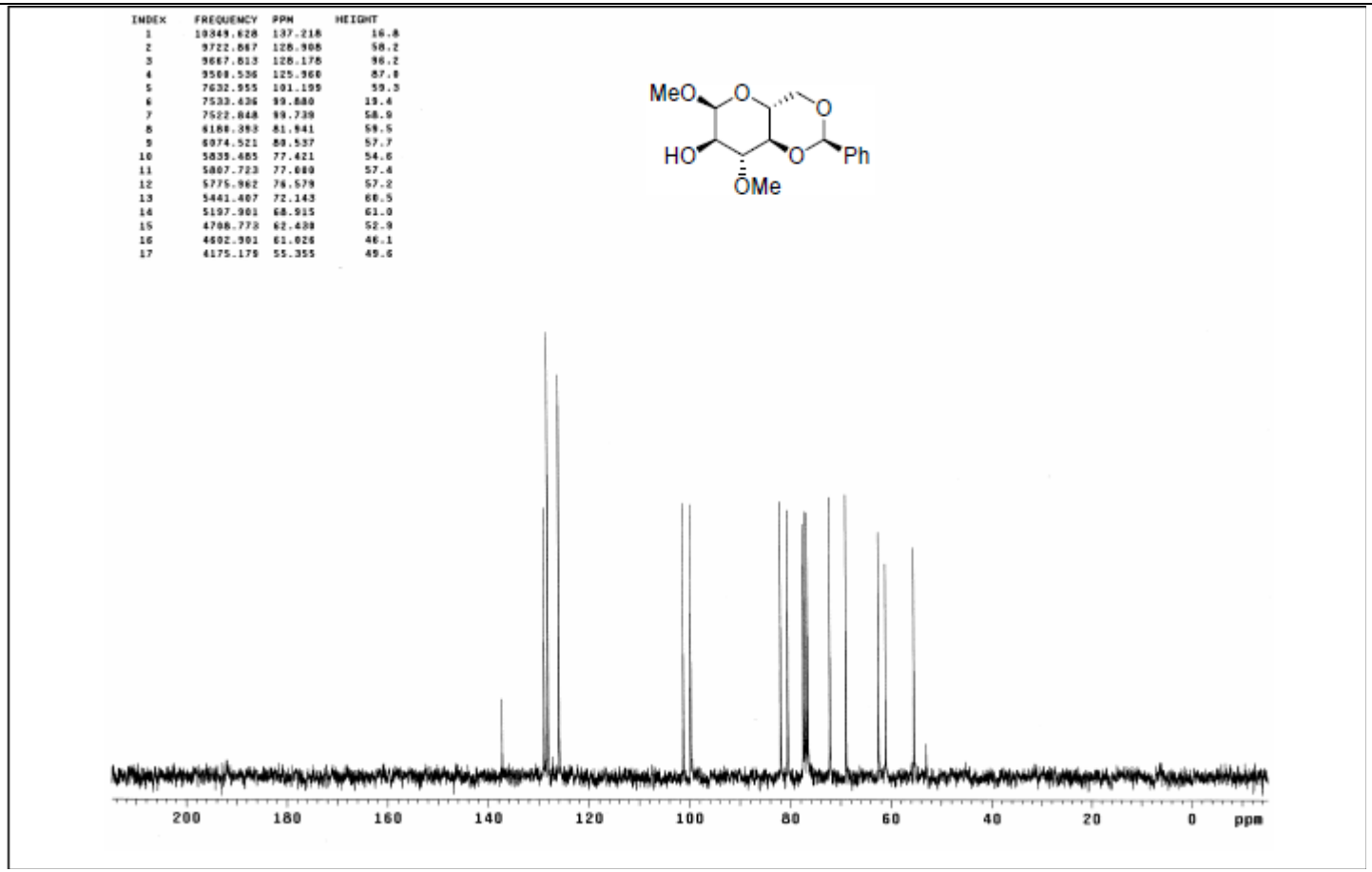

300 MHz $^{1}H$ NMR of compound **17** in $CDCl_3$



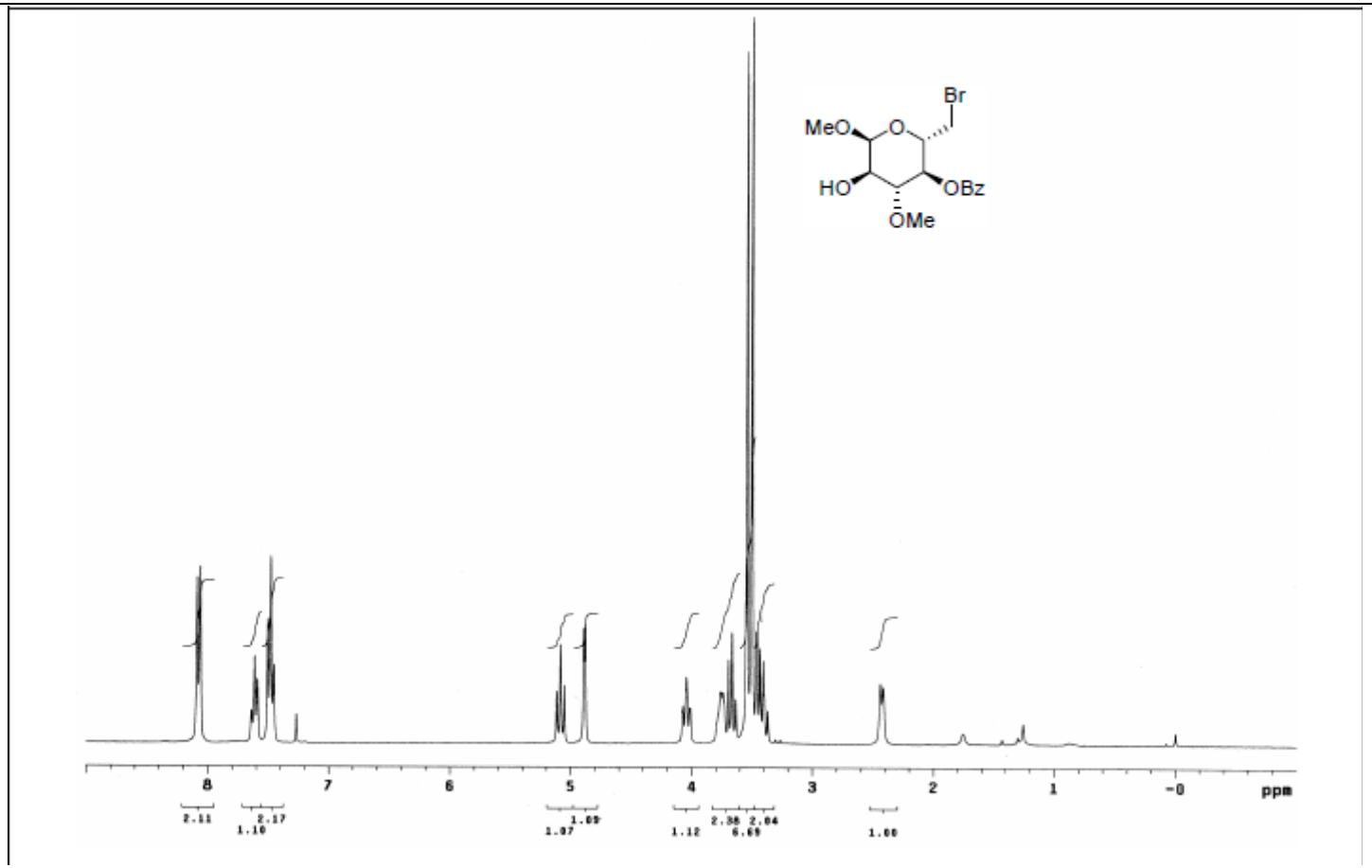

75 MHz $^{13}C$ NMR of compound **17** in $CDCl_3$



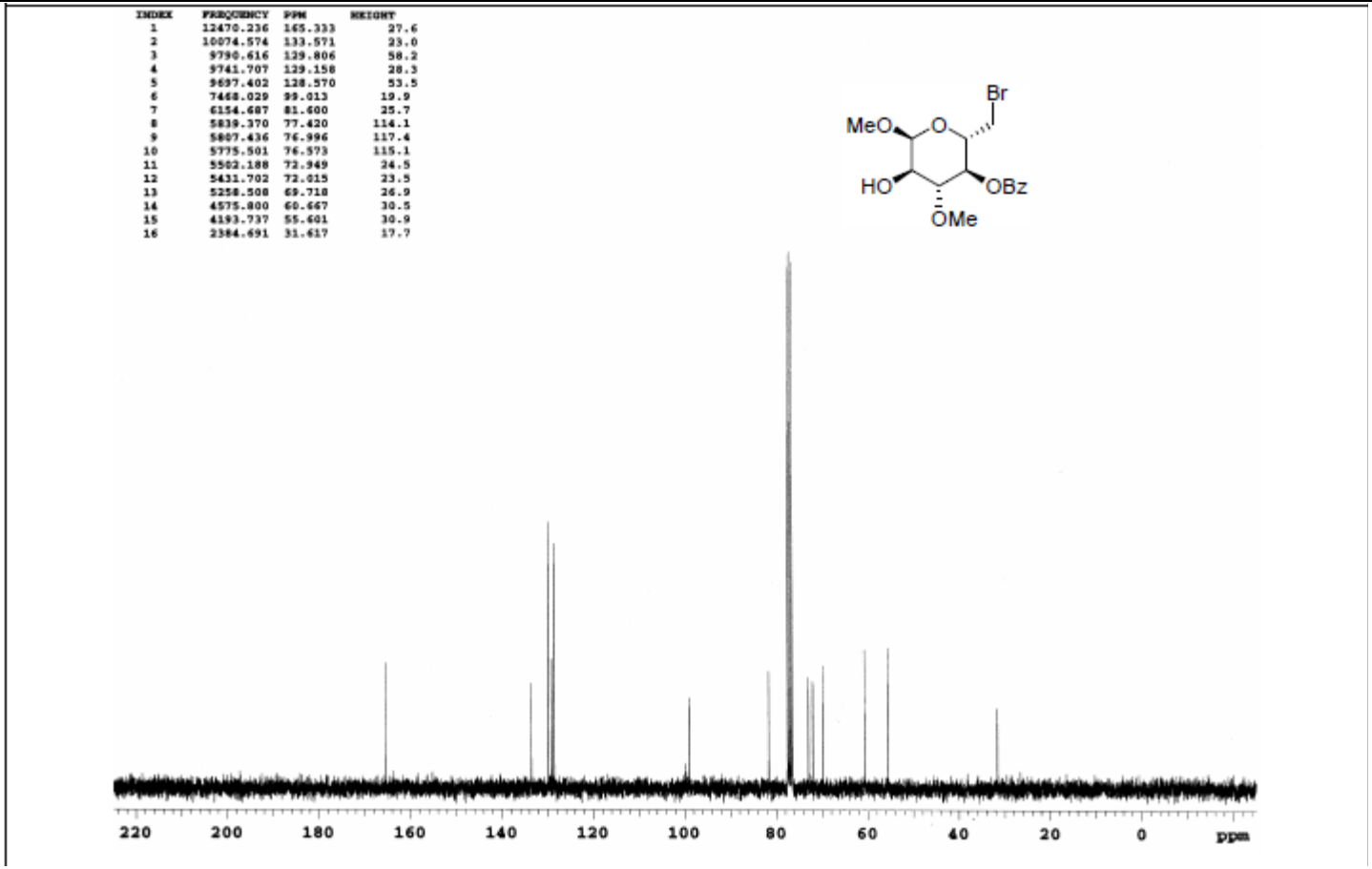

300 MHz $^{1}H$ NMR of compound **18** in $CDCl_3$



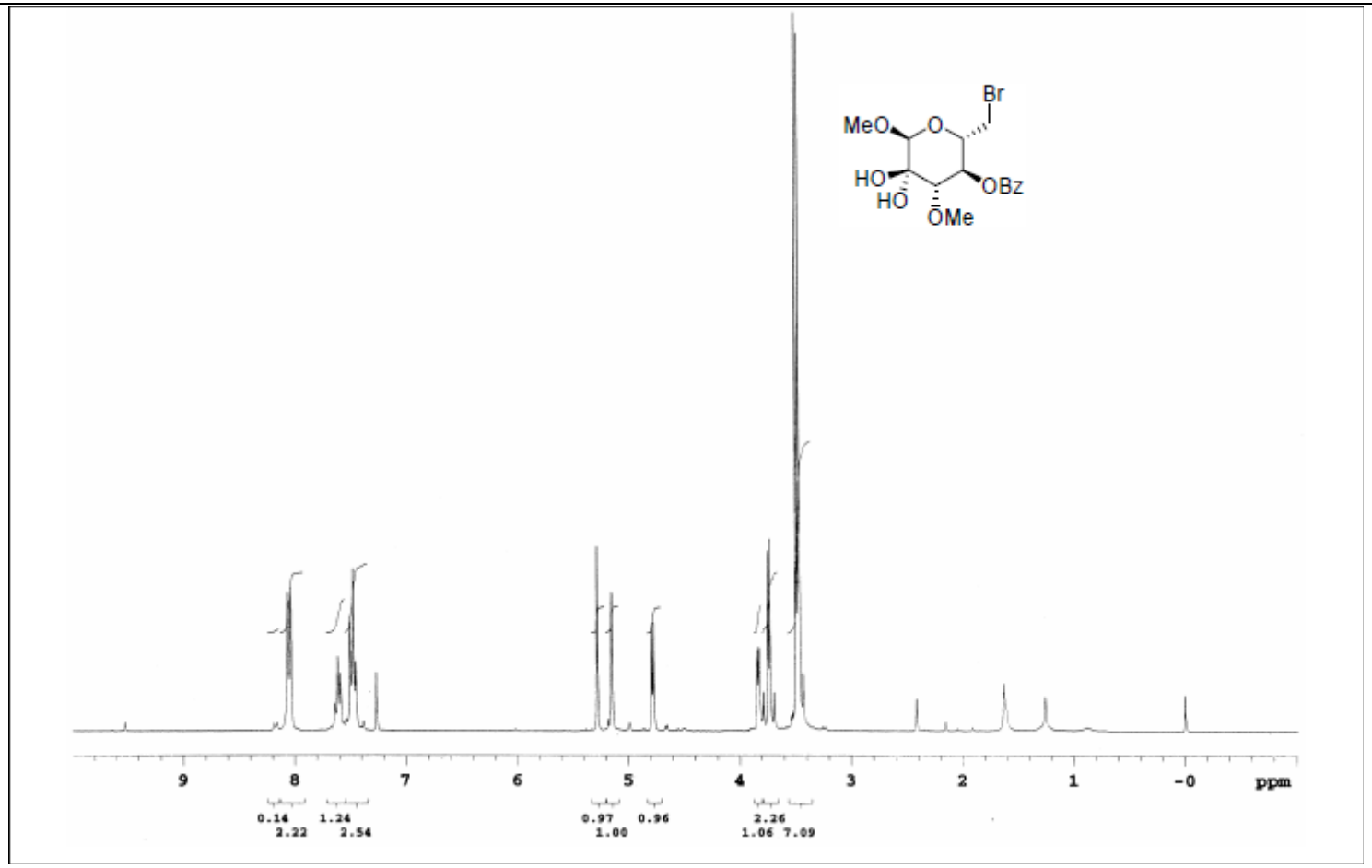

75 MHz $^{13}C$ NMR of compound **18** in $CDCl_3$



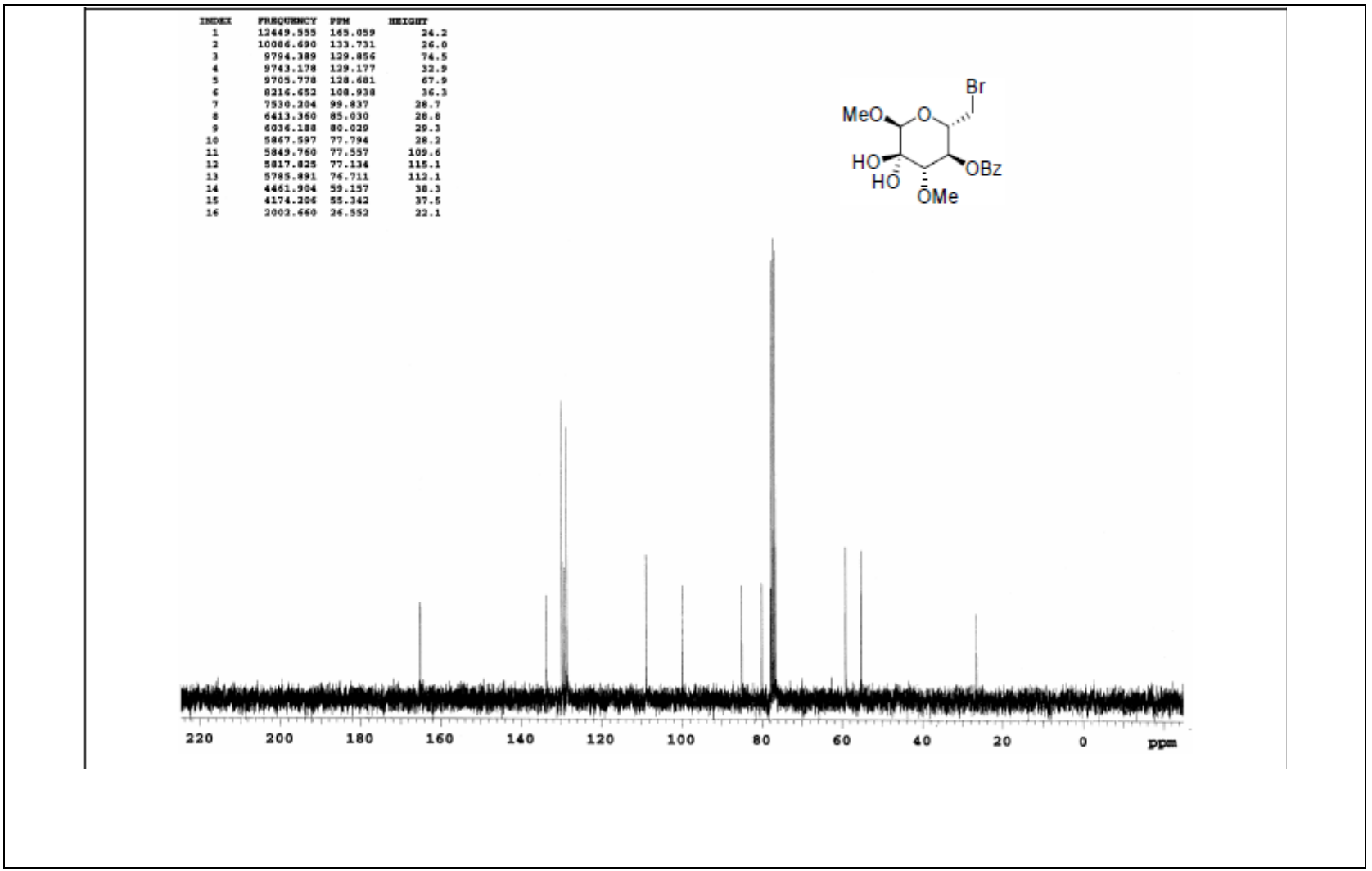

300 MHz $^{1}H$ NMR of compound **19** in $CDCl_3$



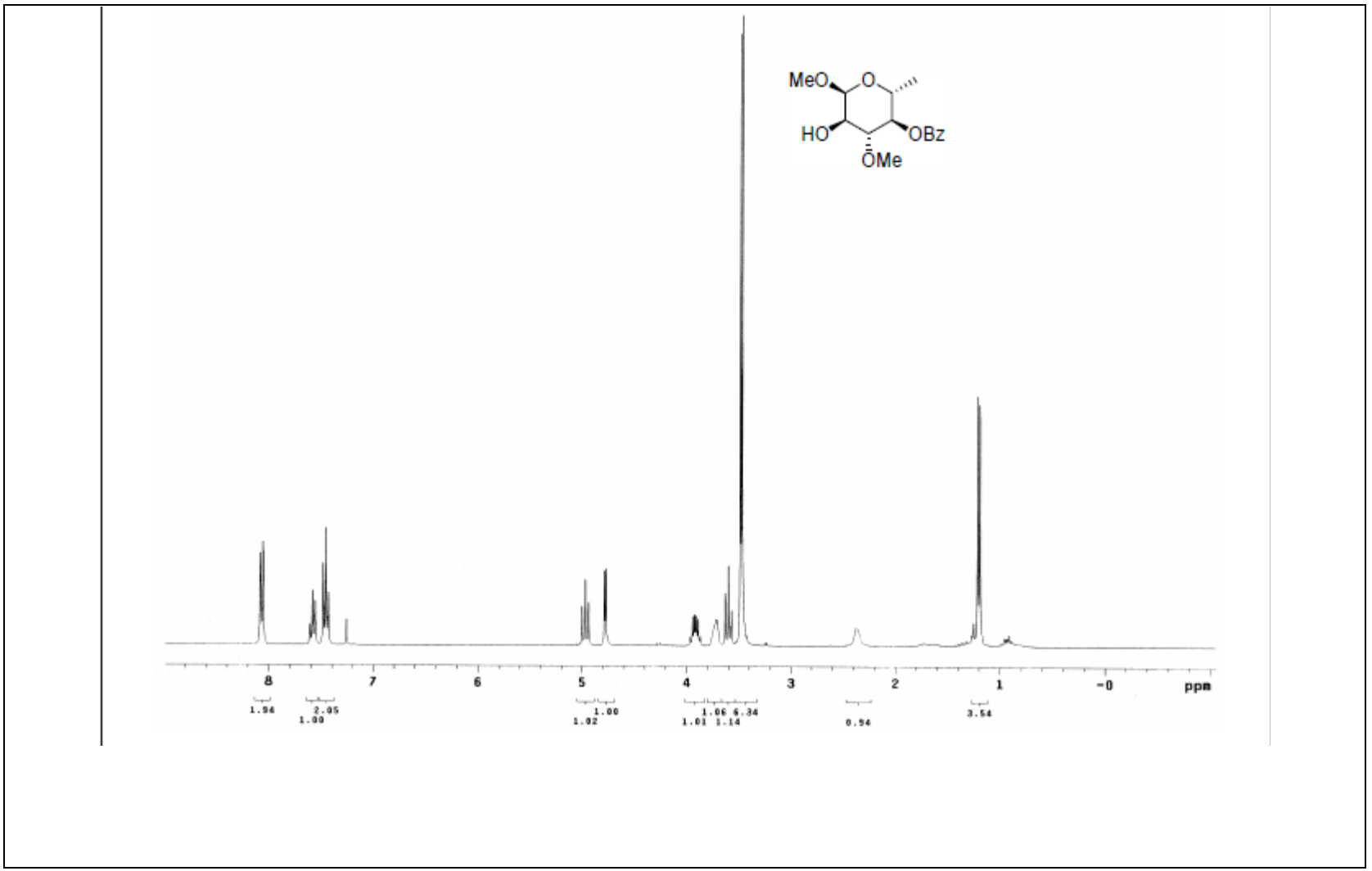

75 MHz $^{13}C$ NMR of compound **19** in $CDCl_3$



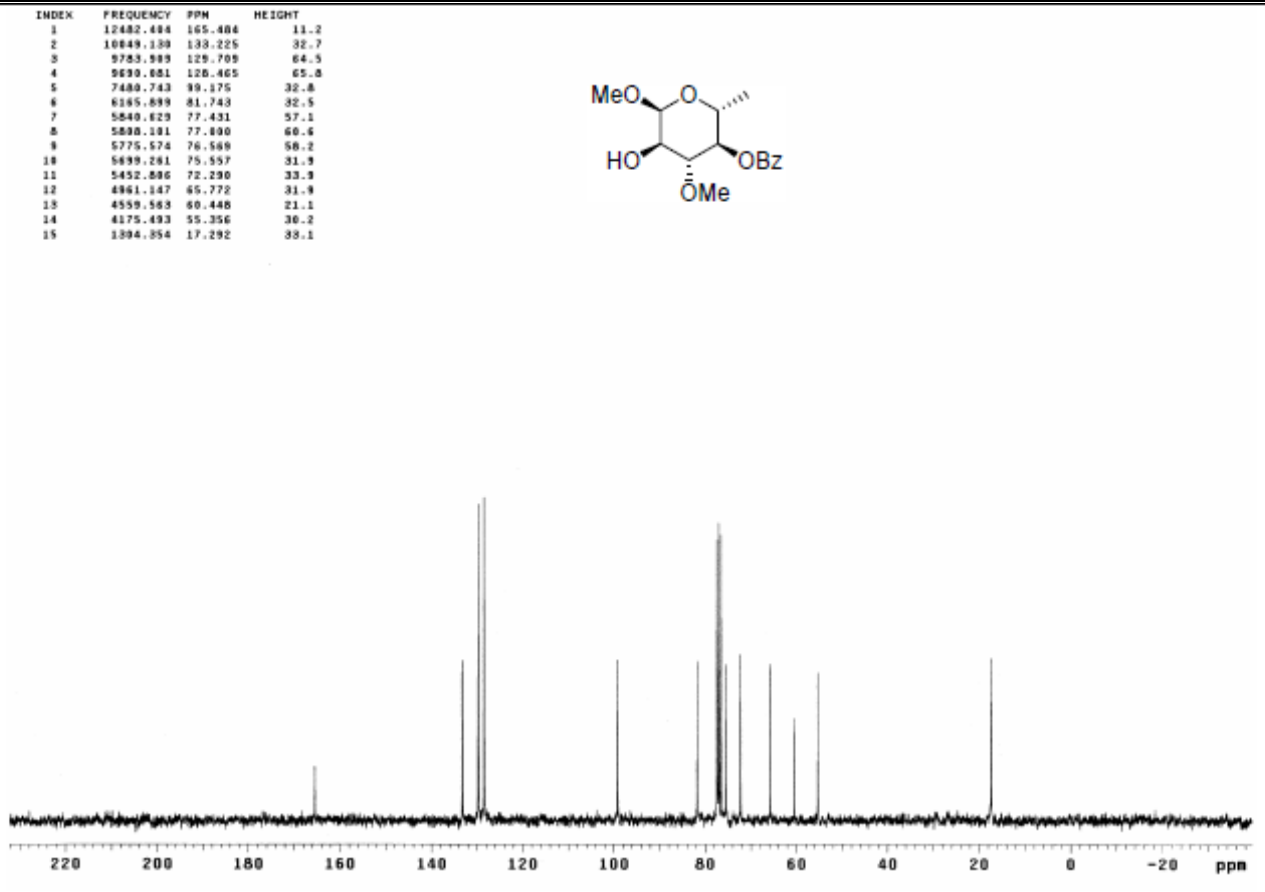

300 MHz $^{1}H$ NMR of compound **20** in $CDCl_3$



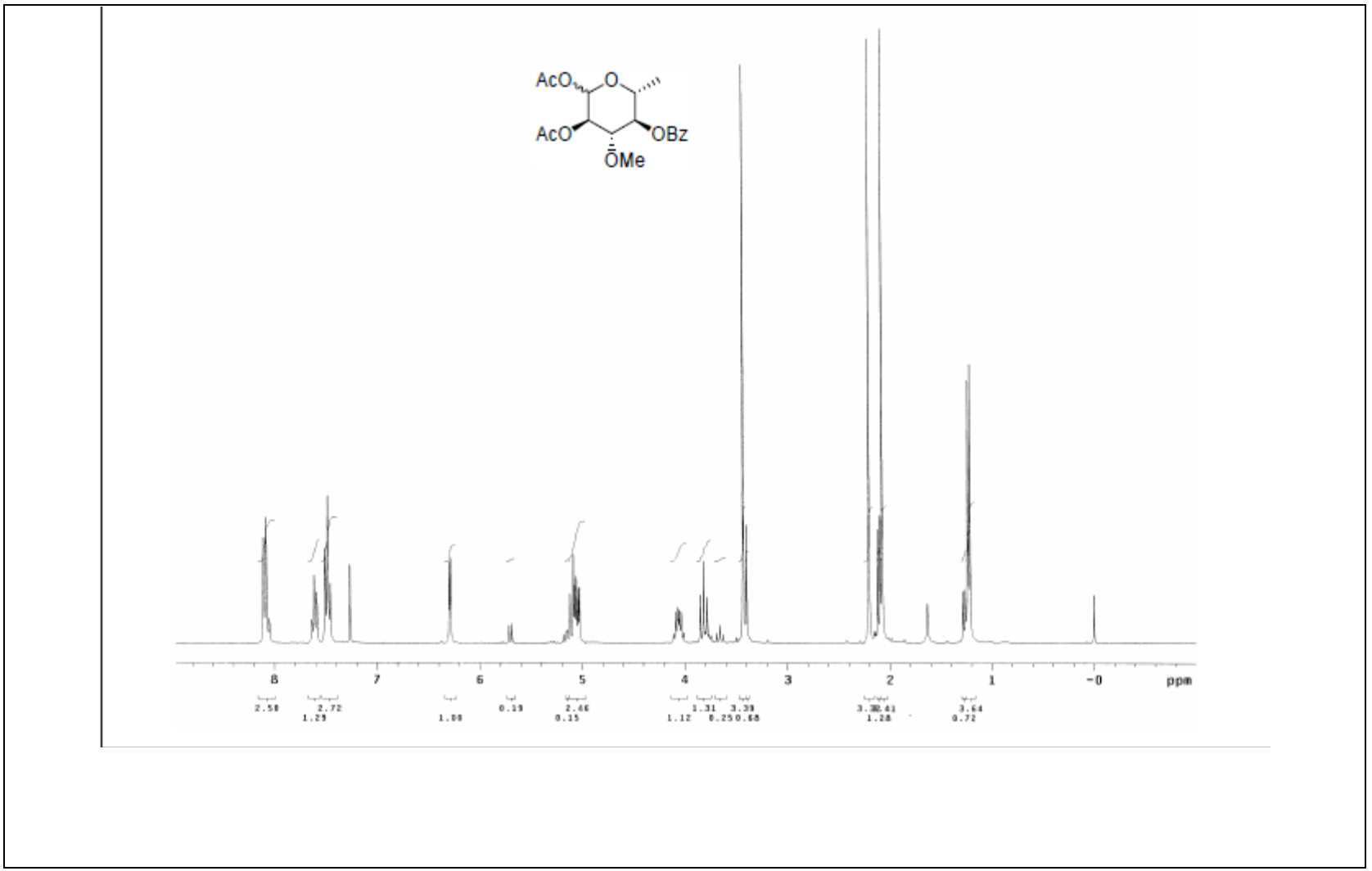

75 MHz $^{13}C$ NMR of compound **20** in $CDCl_3$



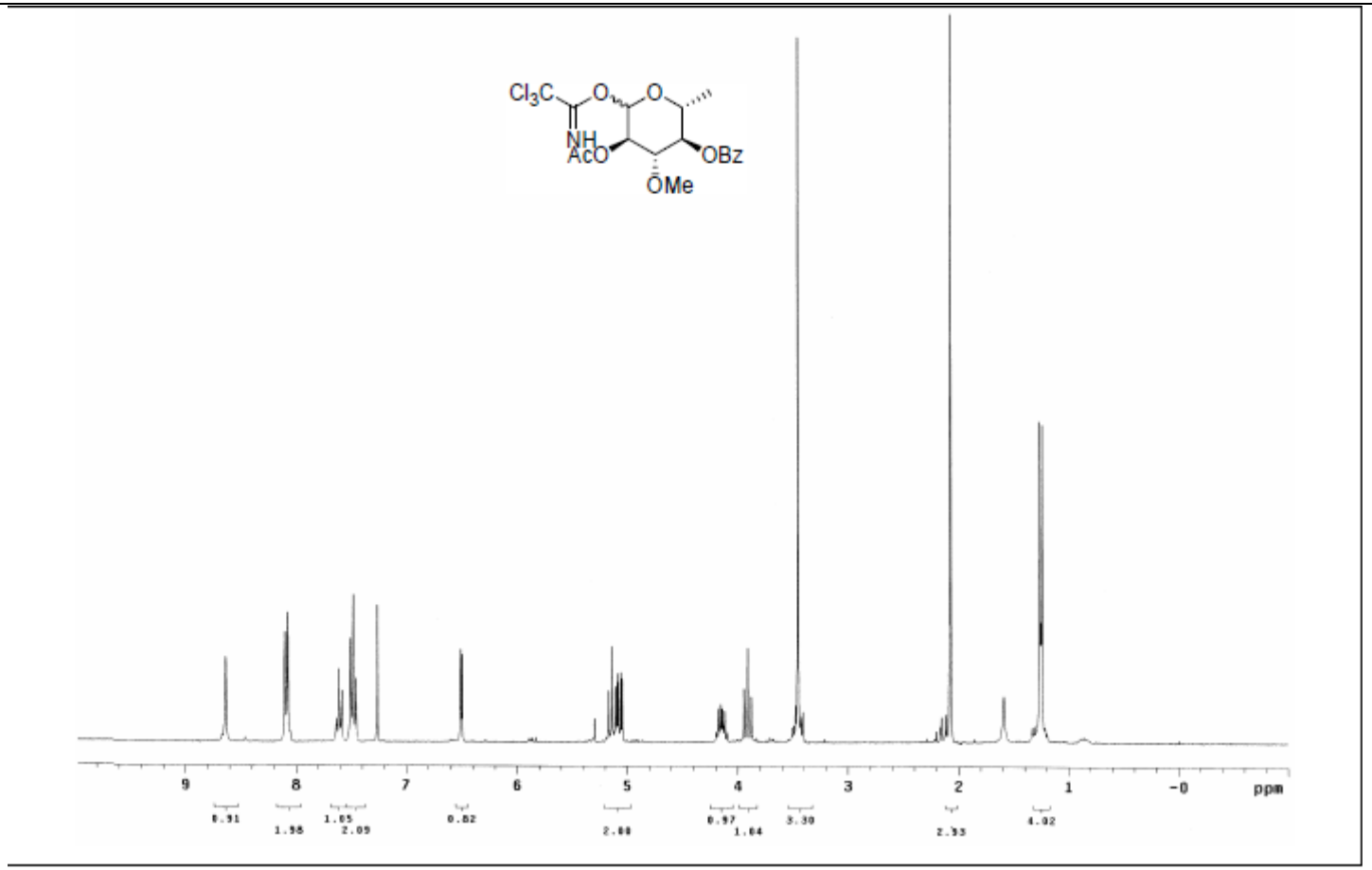

300 MHz $^{1}H$ NMR of compound **21** in $CDCl_3$



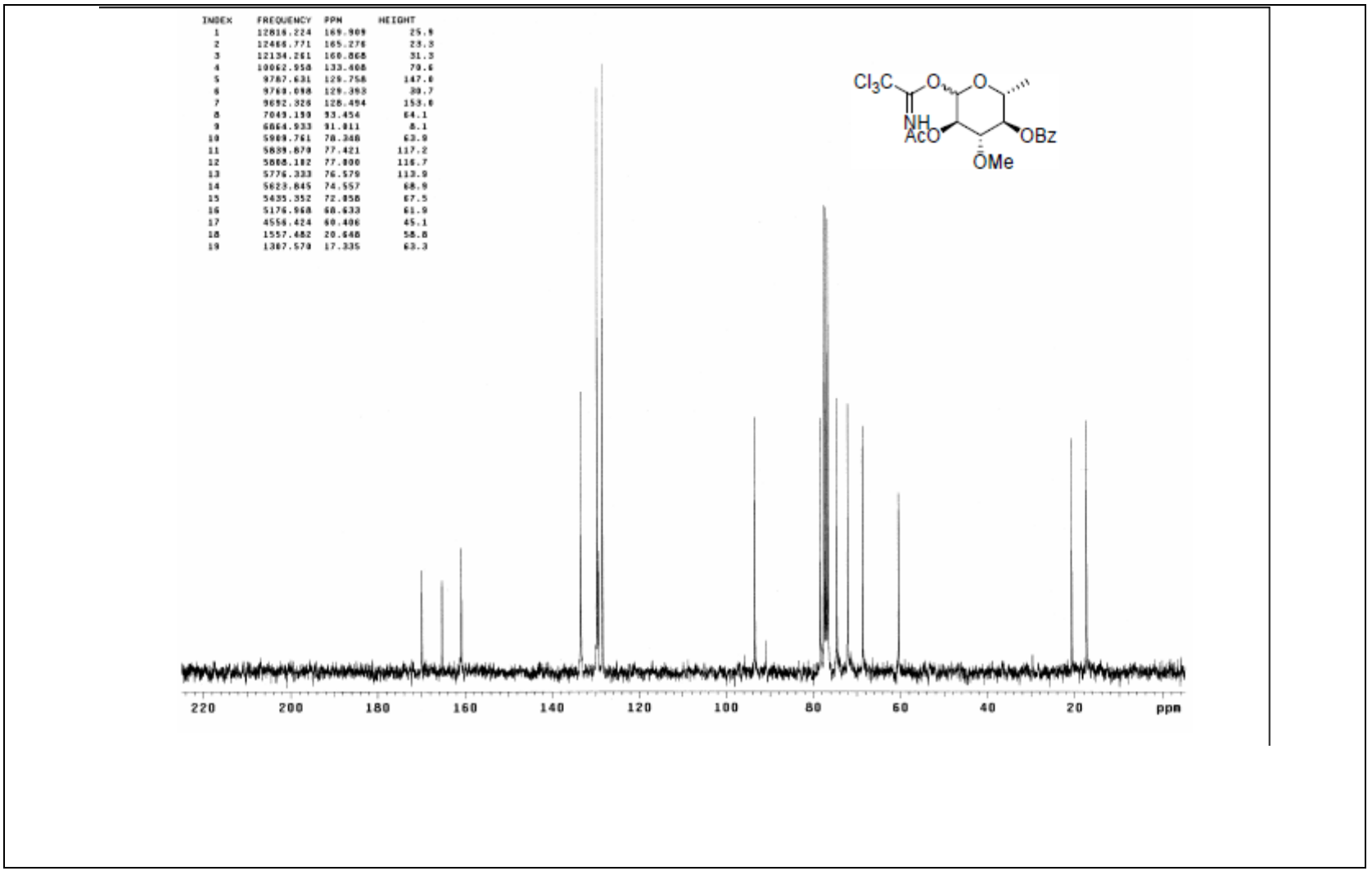

75 MHz $^{13}C$ NMR of compound **21** in $CDCl_3$



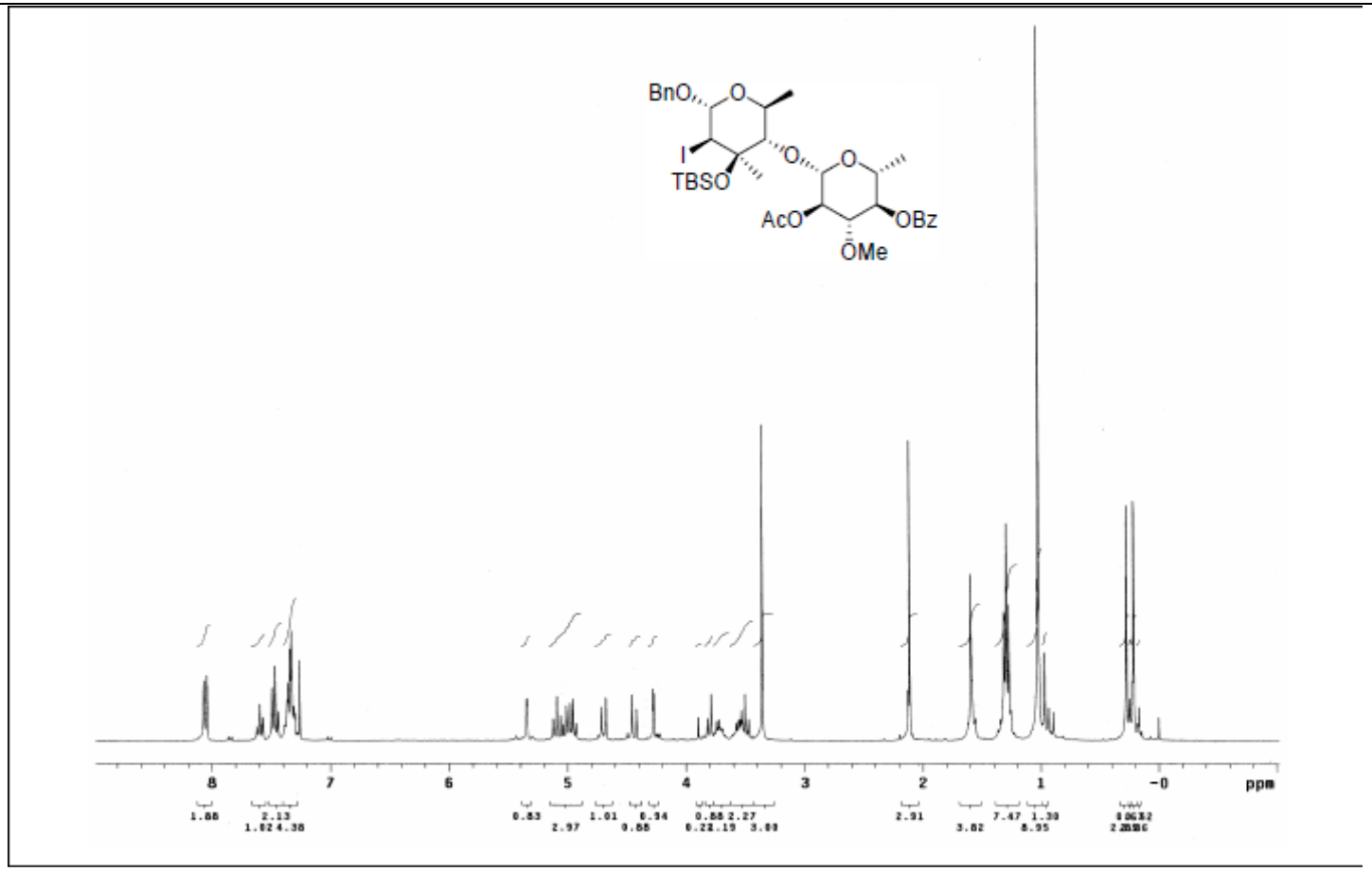

300 MHz $^{1}H$ NMR of compound **22** in $CDCl_3$



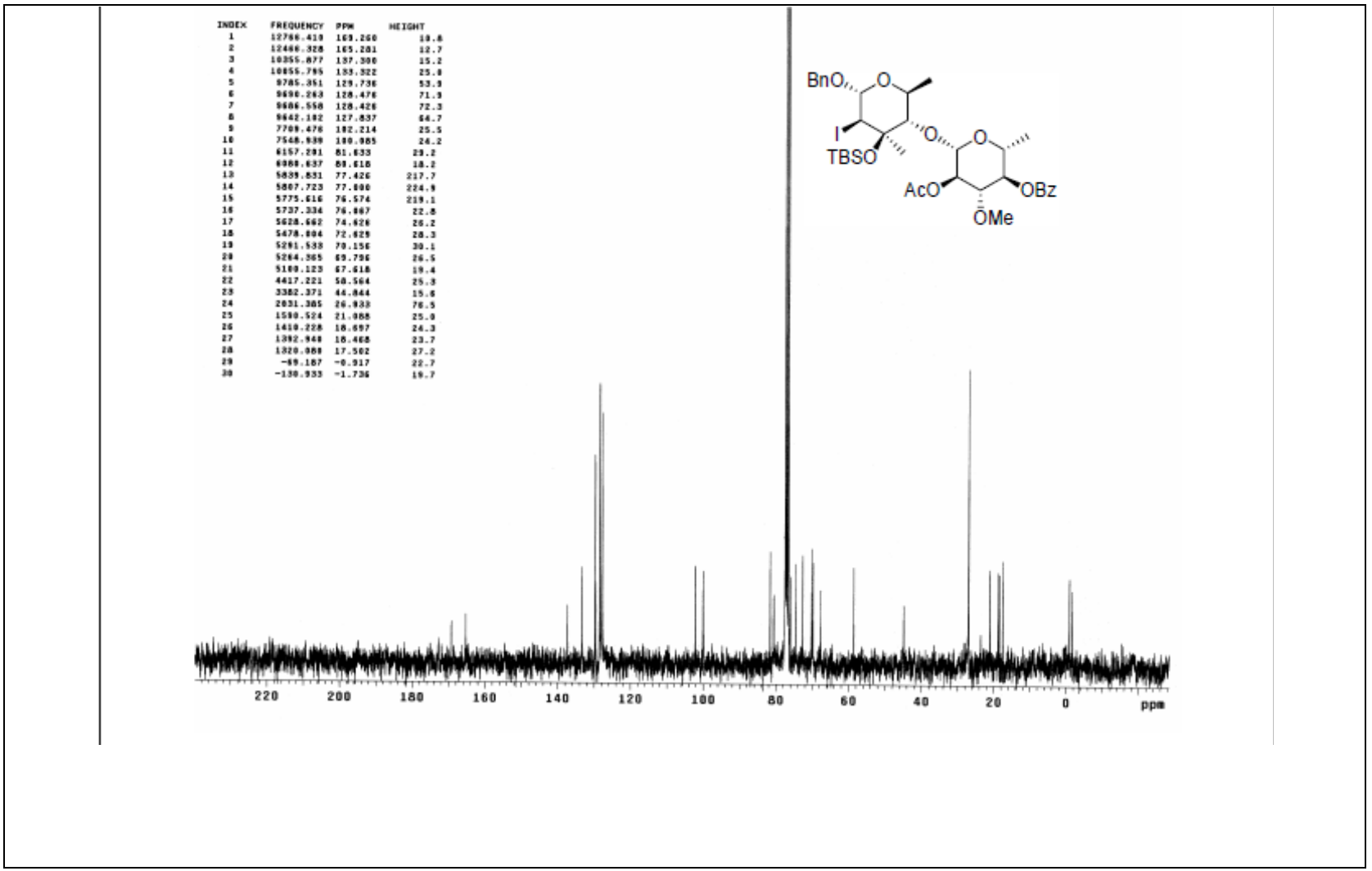

300 MHz $^{1}H$ NMR of compound **8** in $CDCl_3$



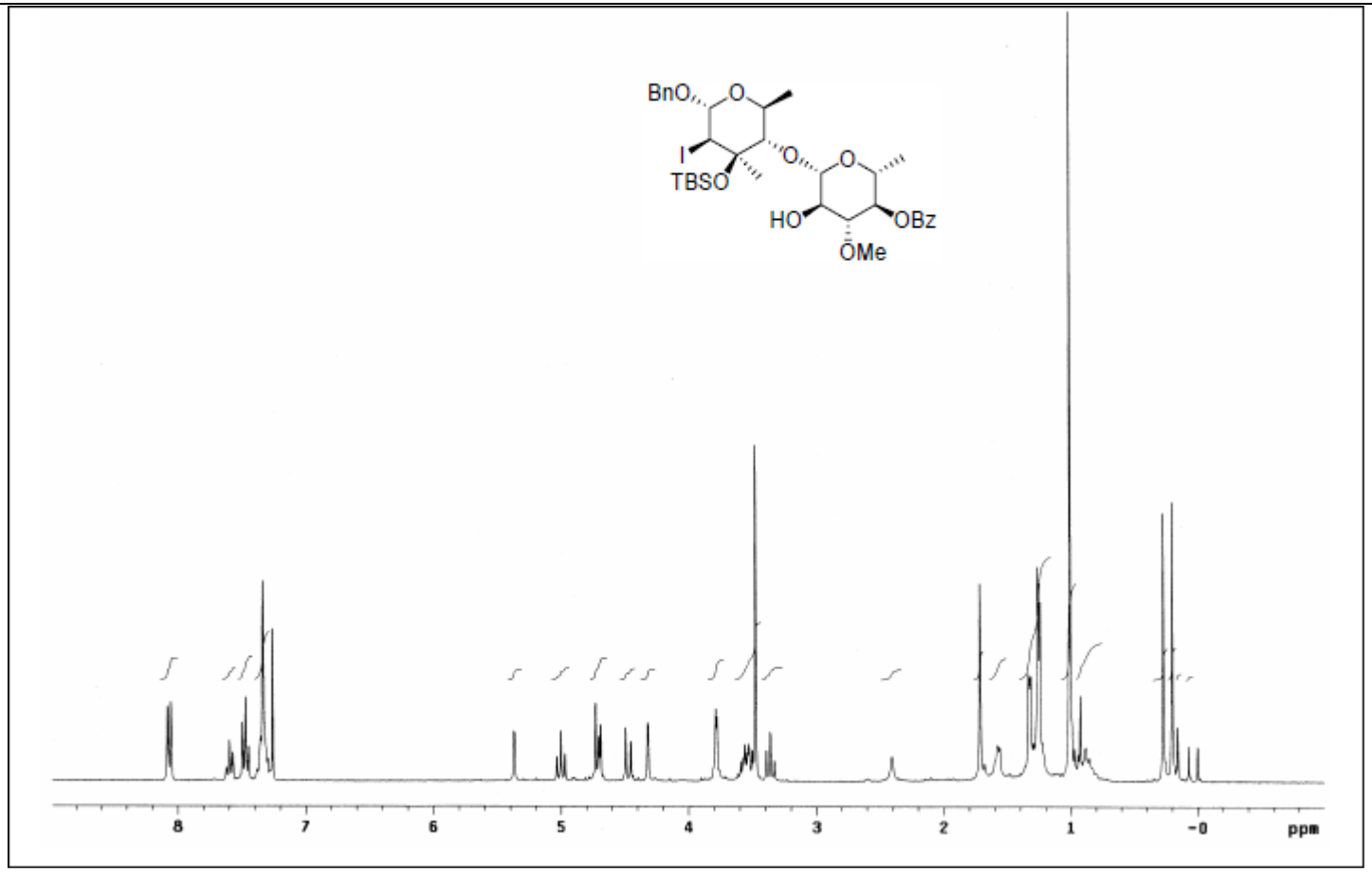

75 MHz $^{13}C$ NMR of compound **8** in $CDCl_3$



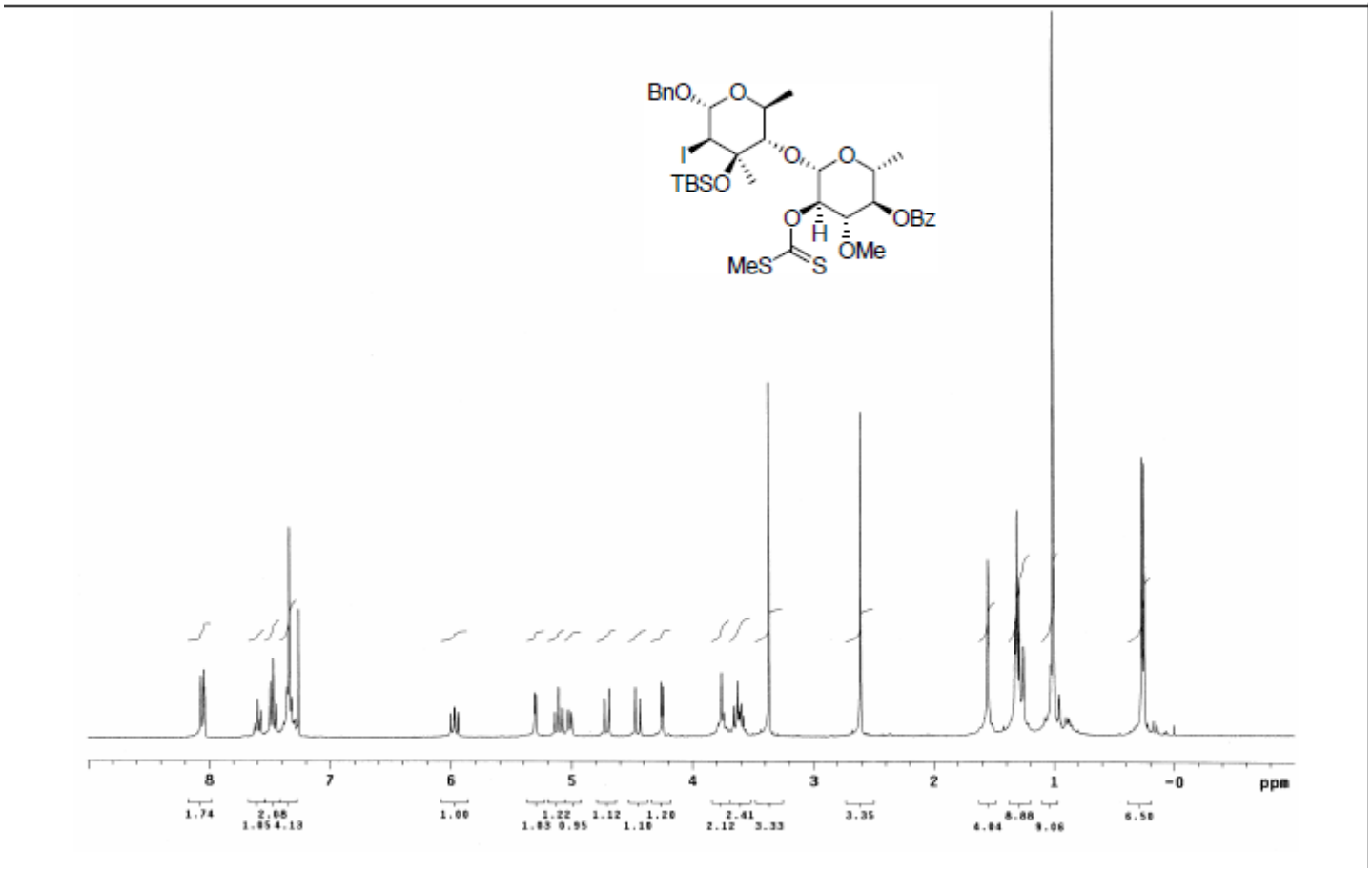

300 MHz $^{1}H$ NMR of compound **6** in $CDCl_3$



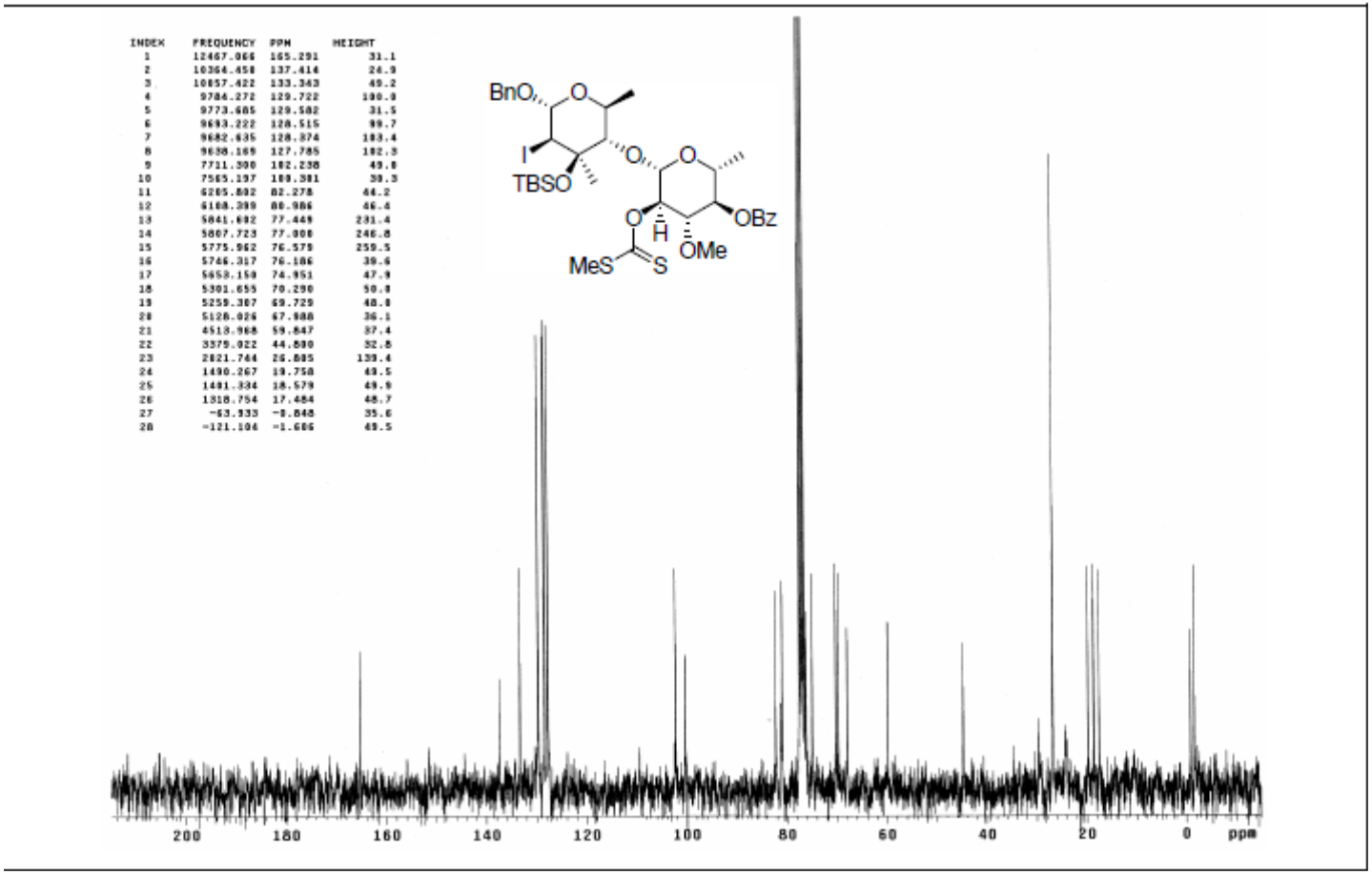

75 MHz $^{13}C$ NMR of compound **6** in $CDCl_3$



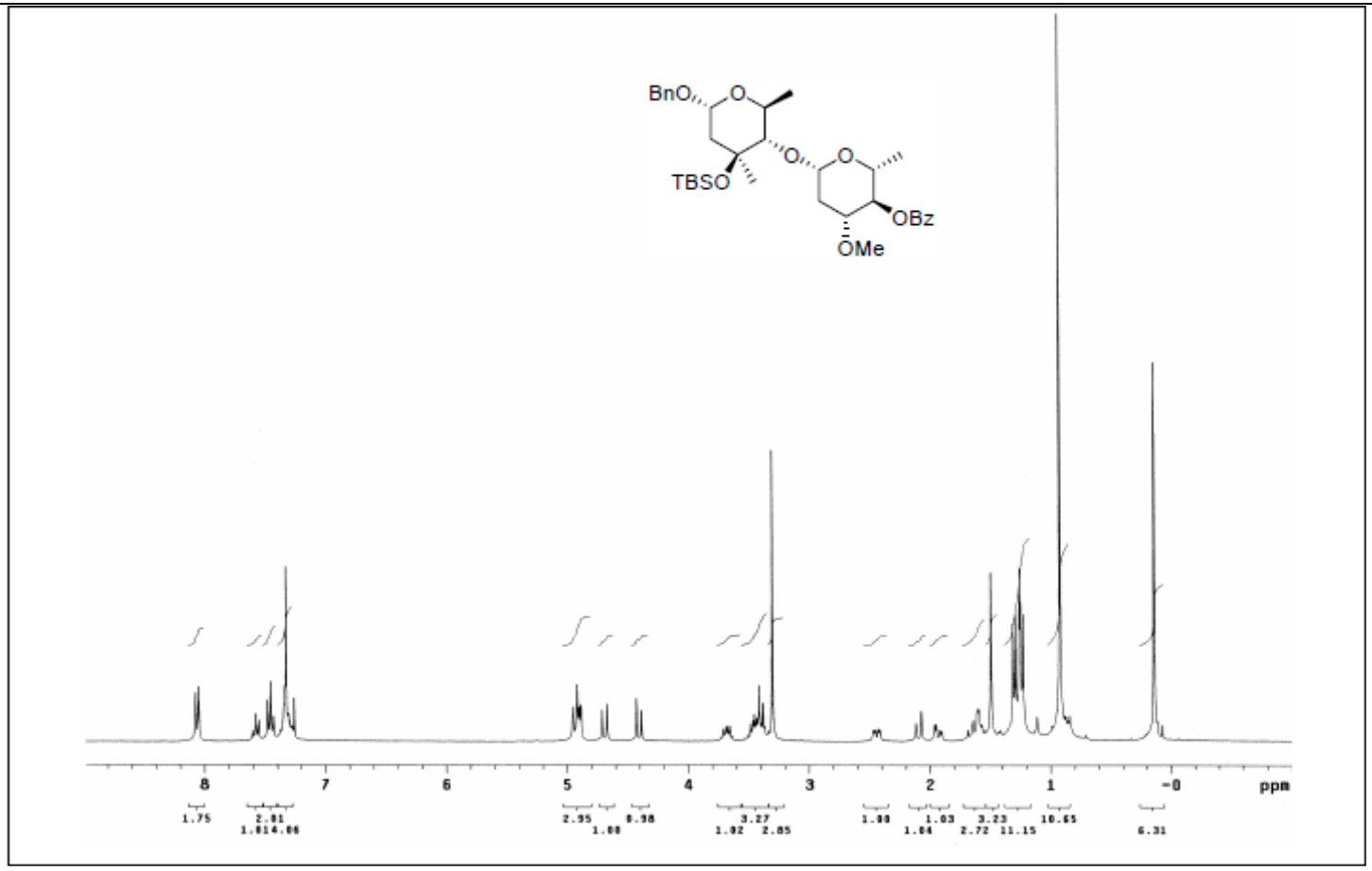

300 MHz $^{1}H$ NMR of compound **24** in $CDCl_3$



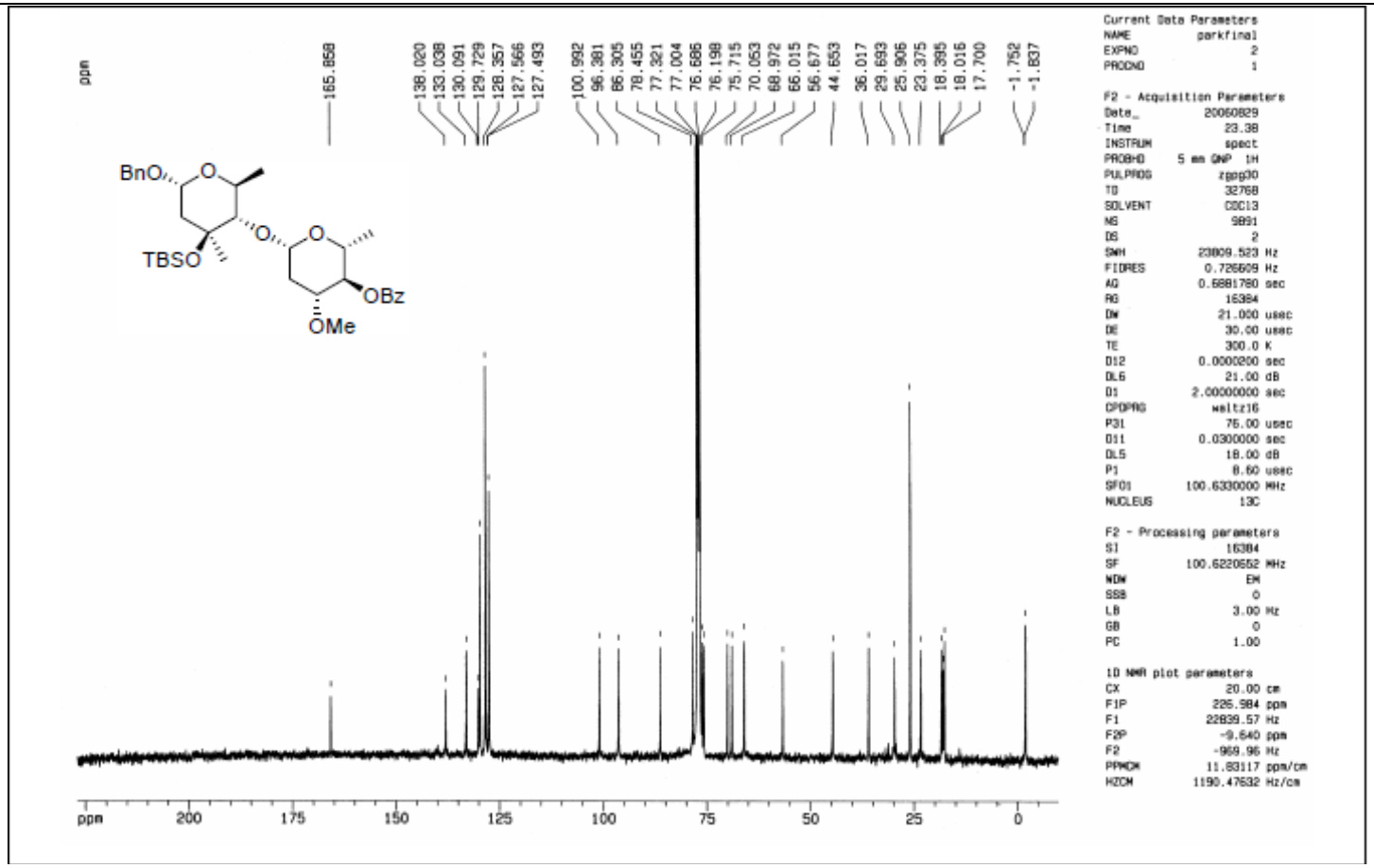

300 MHz $^{1}H$ NMR of compound **25** in $CDCl_3$



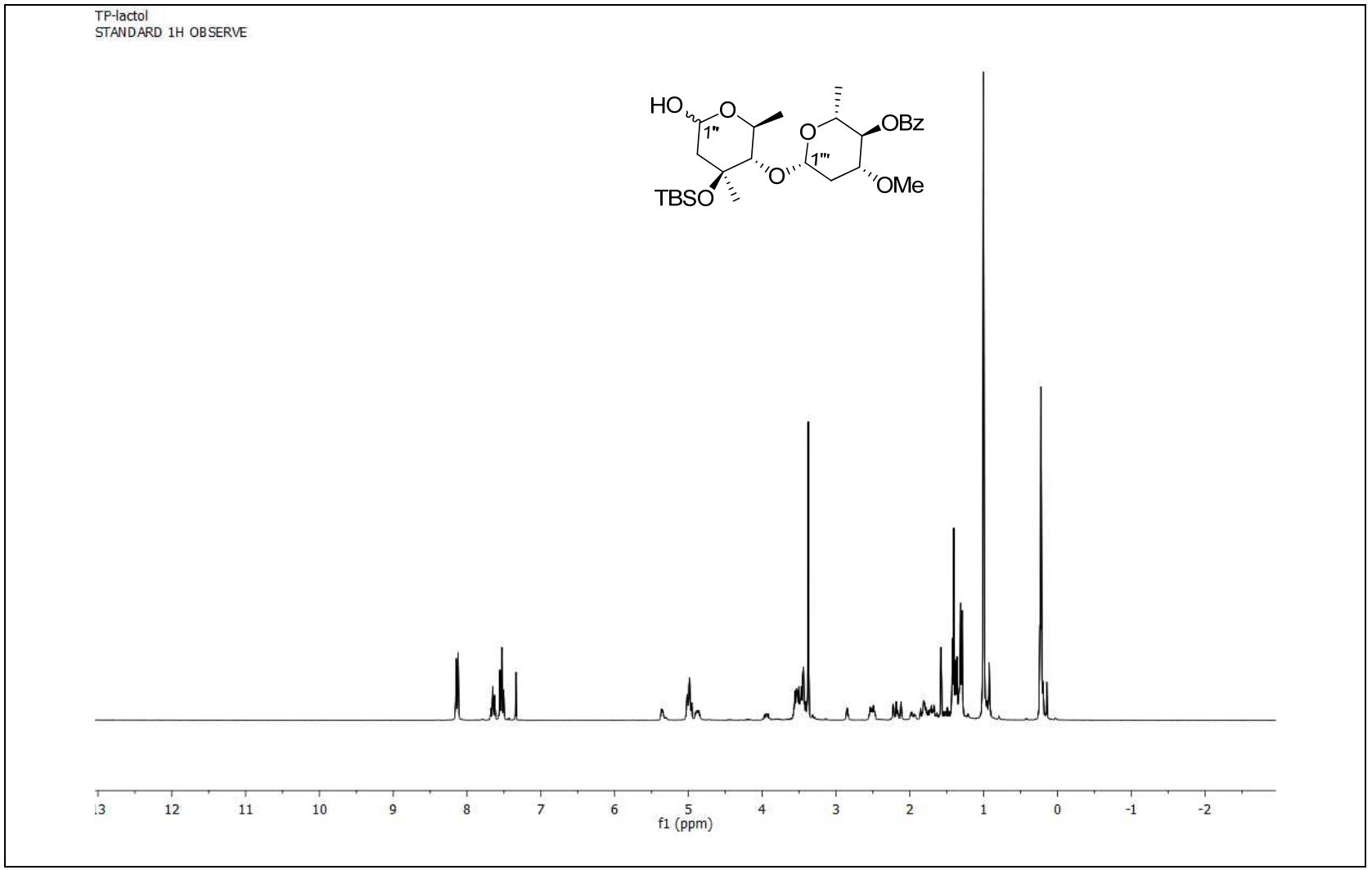

75 MHz $^{13}C$ NMR of compound **25** in $CDCl_3$



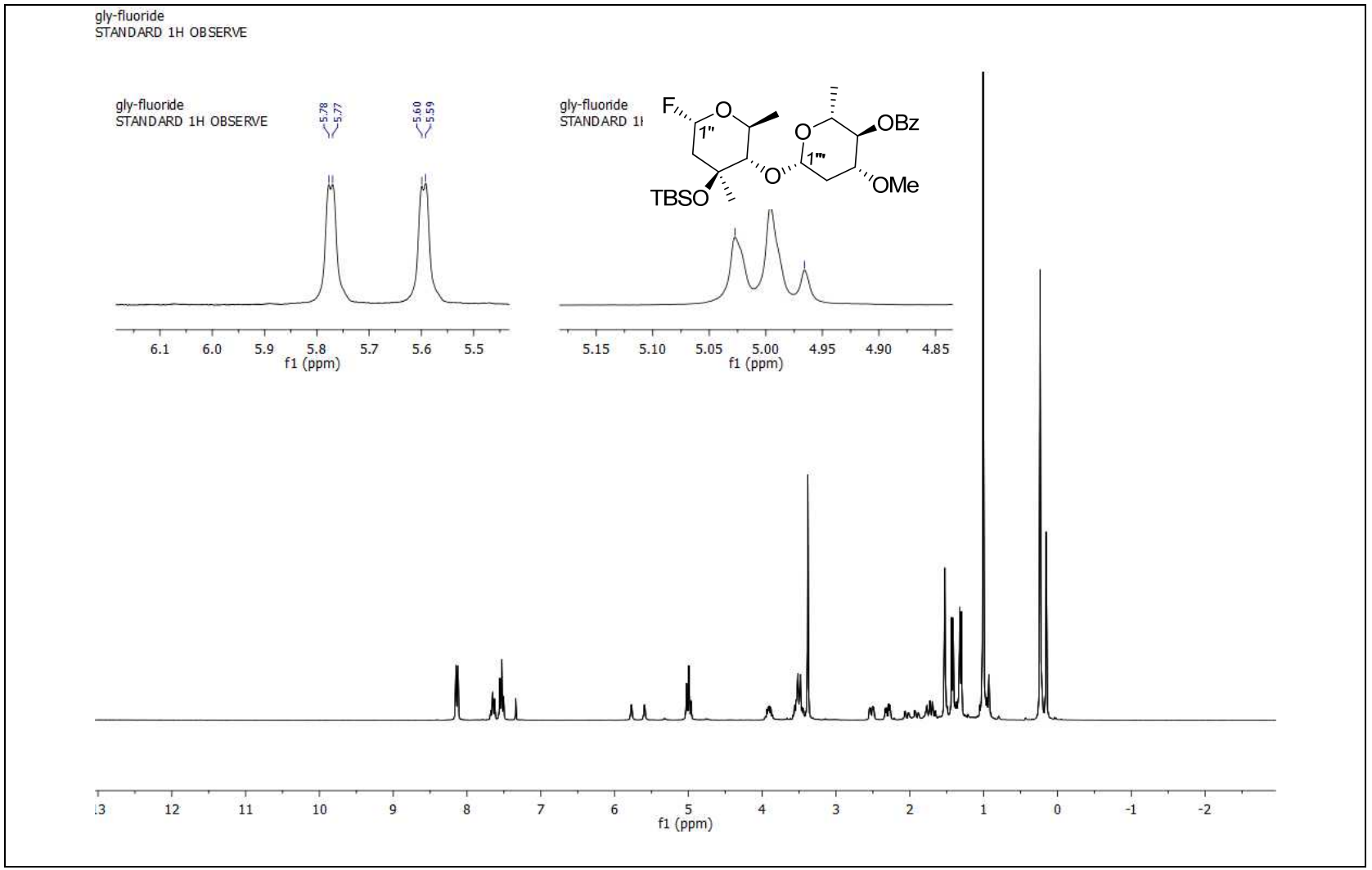

300 MHz $^{1}H$ NMR of compound **26** in $CDCl_3$



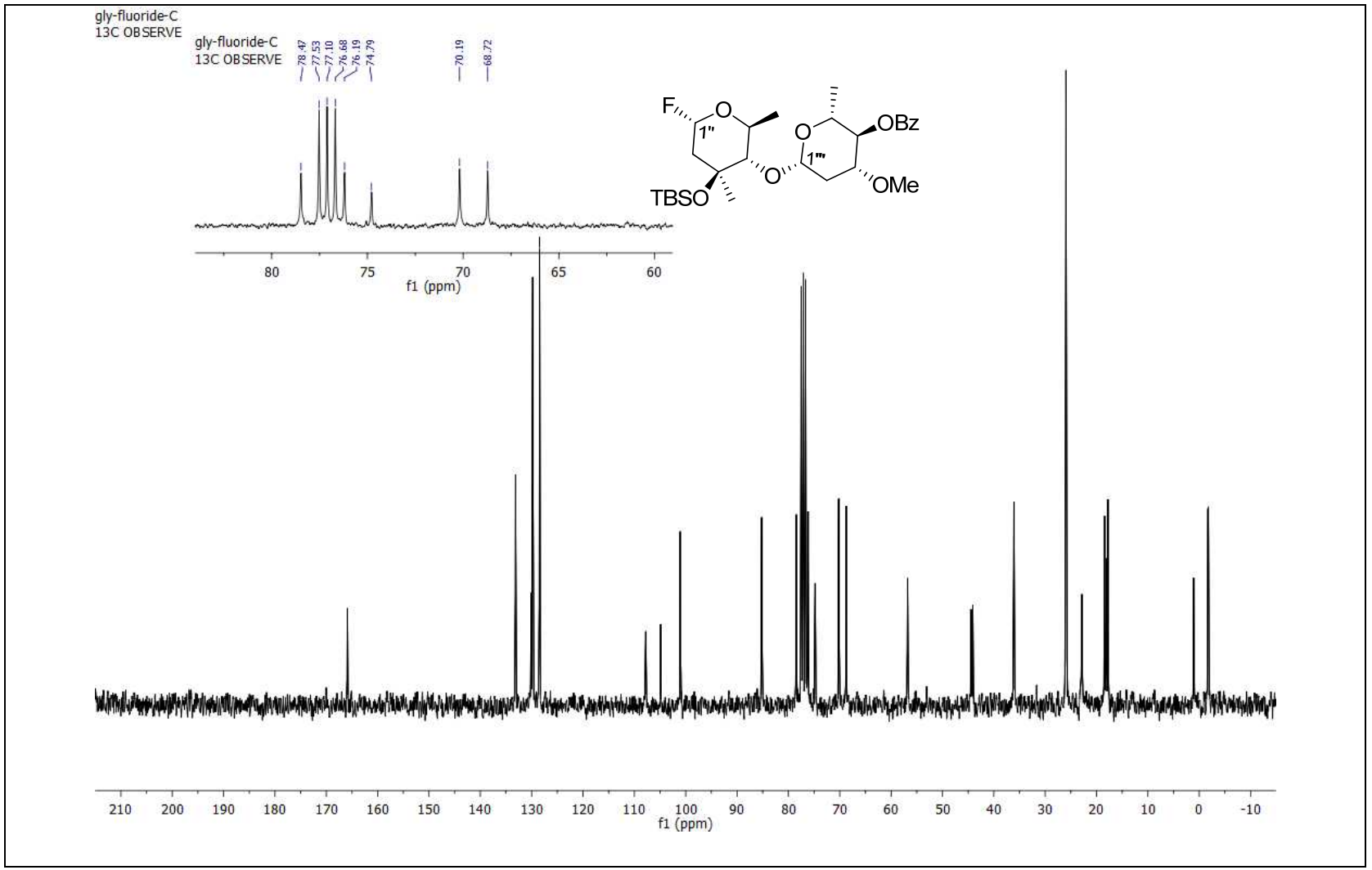

75 MHz $^{13}C$ NMR of compound **26** in $CDCl_3$



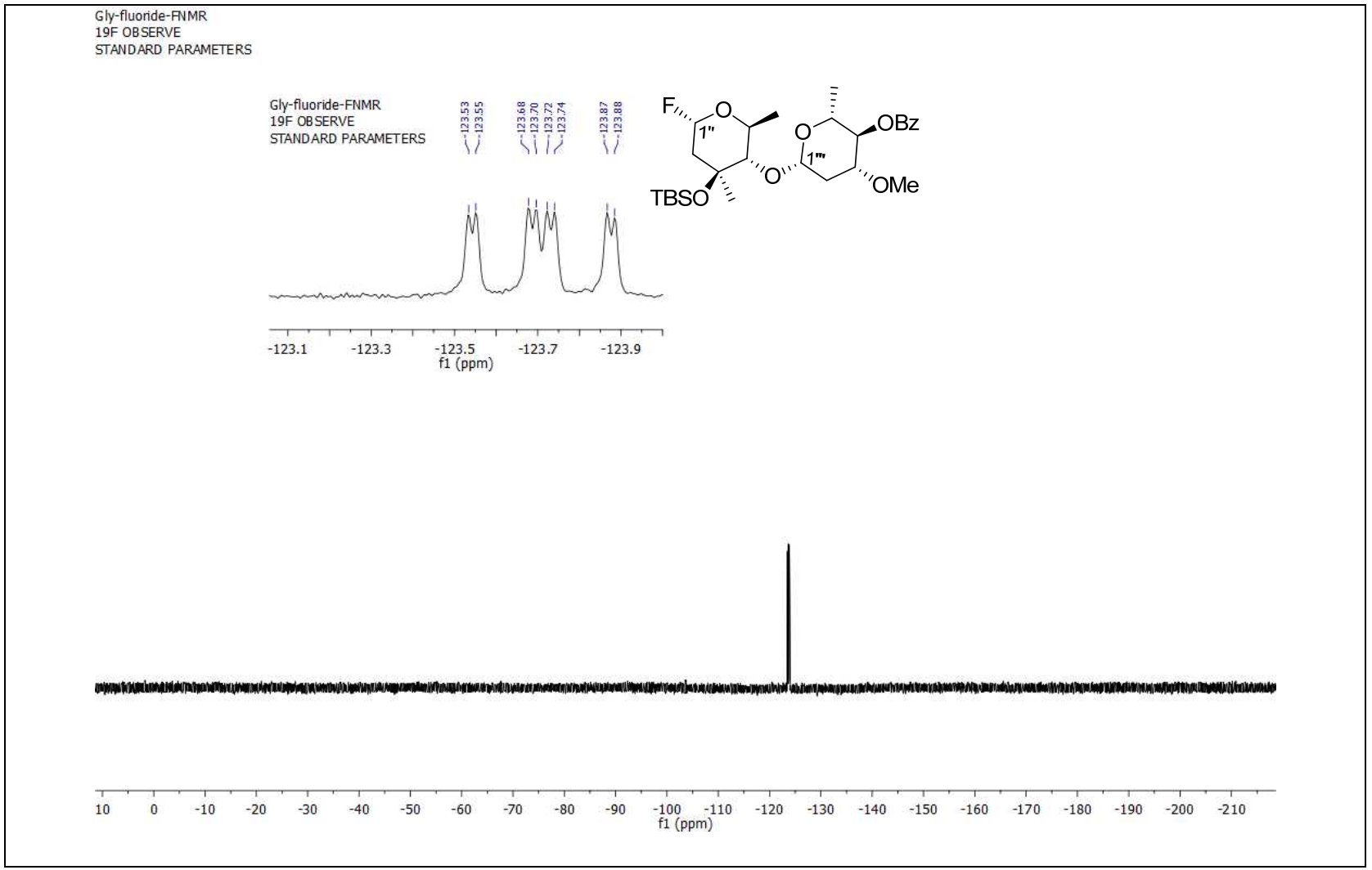

300 MHz $^{1}H$ NMR of compound **27** in $CDCl_3$




300 MHz $^{1}H$ NMR of compound **5** in $CDCl_3$




75 MHz $^{13}C$ NMR of compound **5** in $CDCl_3$




282 MHz $^{19}F$ NMR of compound **5** in $CDCl_3$