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SUPPORTING INFORMATION

Title: Palladium-Catalyzed Intramolecular C–O Bond Formation: An Approach to the Synthesis of Chiral Benzodioxocines
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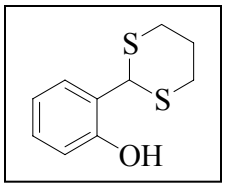
Ref. No.: O200700762

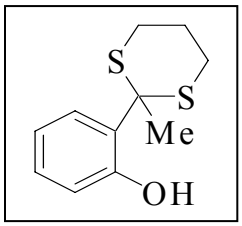
Experimental Section

General

Melting points are uncorrected. ^{1}H (300 MHz, 600 MHz) and ^{13}C (75 MHz, 150 MHz) NMR spectra were recorded with DPX-300 and Bruker AVANCE-600 spectrometers using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded in JEOL AX-500/Micromass Q-Tof micro^{TM} instrument. Elemental analyses were carried out with a C, H, N analyzer. Specific rotations were measured at 589 nm with a JASCO P-10 polarimeter. TLC was performed on pre-coated plates (0.25 nm, silica gel 60 F_{254}). Organic extracts were dried over anhydrous sodium sulfate. Solvents were distilled and dried immediately prior to use. Column chromatography and flash chromatography were carried out using commercial-grade silica gel (60-120 mesh or 230-400 mesh). PS, EA stand for petroleum spirit (60-80 °C) and ethyl acetate.



2-[1,3]Dithian-2-yl-phenol (I): To a solution of salicylaldehyde (610 mg, 5 mmol) and 1,3-propanedithiol (0.5-0.6 mL, 5-6 mmol) in dry CH_2Cl_2 (20 mL) was added iodine (127 mg, 0.5 mmol), and the resulting mixture was stirred at room temperature for 20 min. The reaction was then quenched with saturated aqueous solution of $Na_2S_2O_3$. The organic layer was extracted with CH_2Cl_2 (4×25 mL). The combined organic layer was washed with water (3 × 25 mL), dried (Na_2SO_4) and evaporated to furnish the crude thioacetal. The solid on recrystallization from EA: Petroleum spirit (40-60 °C) furnished the pure thioacetal derivative as a white crystalline solid. Mp 119°C. Yield 1.04 g (98%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.90-2.00 (m, 1 H), 2.15-2.20 (m, 1 H), 2.88-2.93 (m, 2 H), 3.02-3.11 (m, 2 H), 5.41 (s, 1 H), 6.35 (brs, 1 H), 6.86-6.90 (m, 2 H), 7.17-7.30 (m, 2 H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 25.0, 31.6, 47.1, 117.2, 121.0, 123.6 129.1, 130.0, 154.3. ESIMS, *m/z*: 235 (MNa^+). $C_{10}H_{12}OS_2$ (212.33): calcd C 56.57, H 5.70; found: C 56.33, H 5.44.

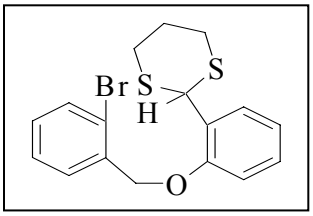


2-(2-Methyl-[1,3]dithian-2-yl)phenol (II): To a solution of *o*-hydroxy acetophenone (340 mg, 2.5 mmol) and 1,3-propanedithiol (2.75 mmol) in dry CH_2Cl_2 (20 mL) were added PTSA (*p*-Toluenesulfonic acid) (10-15 mg) and silica gel (60-120, 4 g), and the

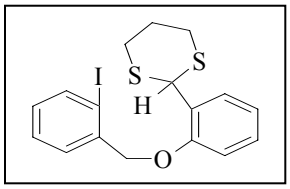
resulting heterogeneous mixture was refluxed for 3 h. The reaction mixture was filtered through a sintered-glass funnel. The solid residue was washed with CH_2Cl_2 (3x20 mL). The solvent was evaporated from the combined filtrate under vacuum to isolate the crude product, which on column chromatography over silica gel furnished the pure thioketal derivative. Pale pink liquid. Yield 509 mg (90%) (eluent PS-EA 19:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.97-2.02 (m, 2 H), 2.64 (s, 3 H), 2.80-2.86 (m, 4 H), 6.88-6.99 (m, 2 H), 7.47 (t-like, 1 H), 7.79 (dd-like, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 24.0, 28.0, 29.4, 52.6, 118.1, 119.0, 119.5, 130.6, 136.3, 156.0. ESIMS, *m/z*: 249 (MNa^+). $C_{11}H_{14}OS_2$ (226.36): calcd C 58.37, H 6.23; found: C 58.05, H 5.99.

General Procedure for the Arylation of Thioacetal/ketal (Preparation of III-V):

To a magnetically stirred solution of the thioacetal/ketal (1 mmol) and the appropriate 2-bromo/iodobenzyl bromide (1.2 mmol) in CH_2Cl_2 (20 mL) was added Bu_4NBr (50 mg) followed by aqueous NaOH (50%, 20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. The aques part was extracted with CH_2Cl_2 (4×20 mL). The combined organic layer was washed with H_2O (3×25 mL), dried (Na_2SO_4) and evaporated to afford a syrup, which on column chromatography over silica gel yielded the corresponding bromo/iodobenzyl derivatives.

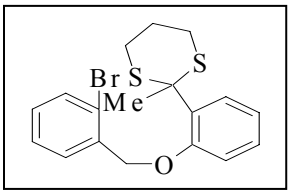


2-[2-(2-Bromobenzyloxy)-phenyl]-[1,3]dithiane (III): White crystalline solid. Mp 130°C. Yield 286 mg (75%) (eluent PS-EA 19:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.92-2.04 (m, 1 H), 2.15-2.20 (m, 1 H), 2.88-2.93 (m, 2 H), 3.07-3.16 (m, 2 H), 5.21 (s, 2 H), 5.80 (s, 1 H), 6.87 (d, *J* = 8.2 Hz, 1 H), 6.99 (t-like, 1 H), 7.16-7.26 (m, 2 H), 7.33 (t-like, 1 H), 7.59 (m, 3 H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 25.3, 32.4, 44.1, 70.0, 112.6, 121.7, 122.0, 127.6, 128.0, 128.7, 129.1, 129.2, 129.4, 132.6, 136.2, 154.2. ESIMS, *m/z*: 403, 405 (MNa^+ for Br^{79}, Br^{81}). $C_{17}H_{17}BrOS_2$ (381.35): calcd C 53.54, H 4.49; found: C 53.29, H 4.25.



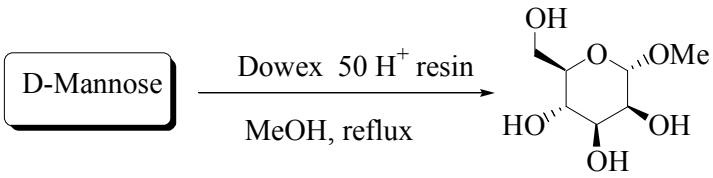
2-[2-(2-Iodobenzyloxy)-phenyl]-[1,3]dithiane (IV): White crystalline solid. Mp 125°C. Yield 299 mg (70%) (eluent PS-EA 24:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.88-2.01 (m, 1 H), 2.18 (d, *J* = 14.0 Hz, 1 H), 2.91 (d, *J* = 14.1 Hz, 2 H), 3.11 (t, *J* = 12.6 Hz, 2 H), 5.12 (s, 2 H), 5.80 (s, 1 H), 6.86 (d, *J* = 8.2 Hz, 1 H), 7.01 (dd-like, 2 H), 7.23 (t-like, 1 H), 7.37 (t, *J* = 7.5 Hz, 1 H), 7.51 (d, *J* = 7.5 Hz, 1 H), 7.61 (d, *J* = 6.7 Hz, 1 H), 7.88 (d, *J* = 7.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.2, 32.2, 44.0, 74.2, 97.0, 112.5, 121.5,

127.8, 128.4, 128.5, 129.1, 129.2, 138.8, 139.0, 154.3. ESIMS, *m/z*: 451 (MNa^+). $C_{17}H_{17}IOS_2$ (428.35): calcd C 47.67, H 4.00; found: C 47.39, H 4.22.



2-[2-(2-Bromobenzyloxy)-phenyl]-2-methyl-[1,3]dithiane (V): White crystalline solid. Mp 113°C. Yield 257 (65%) (eluent PS-EA 24:1). ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.93-2.01 (m, 2 H), 2.05 (s, 3 H), 2.74-2.90 (m, 4 H), 5.23 (s, 2 H), 7.00 (t-like, 1 H), 7.18 (t-like, 1 H), 7.24-7.29 (m, 2 H), 7.36 (t-like, 1 H), 7.57 (d, *J* = 7.9 Hz, 1 H), 7.84 (d, *J* = 7.6 Hz, 1 H), 7.98 (d, *J* = 7.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 24.7, 28.5, 29.1, 52.0, 70.3, 114.4, 120.6, 121.4, 127.5, 129.0, 131.0, 131.5, 132.3, 136.5, 156.6. ESIMS, *m/z*: 417, 419 (MNa^+ for Br^{79}, Br^{81}). $C_{18}H_{19}BrOS_2$ (395.38): calcd C 54.68, H 4.84; found: C 54.39, H 4.57.

Procedure for the Synthesis of Methyl-α-D-mannopyranoside

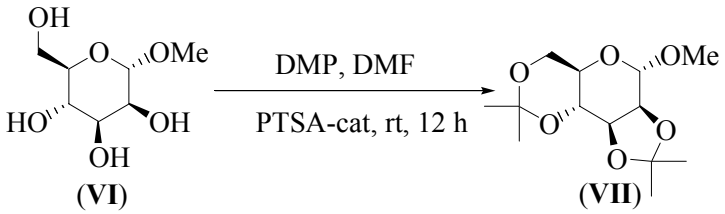


(**VI**)

A mixture of D-mannose (10 g) and methanol (50 mL) was heated under reflux for 30 min. The mixture was cooled to room temperature and Dowex-50 H^+ resin (3 g) was added to it. After 2 hours of heating under reflux the mixture was hot filtered and washed

with hot methanol. The combined filtrate and washings were concentrated and kept overnight for complete precipitation of colorless crystals. The crystals were filtrated off and washed with cold isopropanol. Finally, drying over steam bath afforded the methyl ether (**VI**) (7.6 g, 70%), m.p.189-190 °C.

Procedure for the Synthesis of Methyl 2,3:4,6-di-*O*-isopropylidene-α-D mannopyranoside (VII)

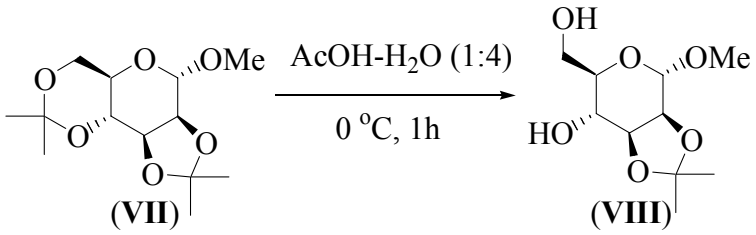


(**VI**) (**VII**)

A mixture of methyl-α-D-mannopyranoside (**VI**) (4 g), DMP (16 mL), DMF (16 mL) and PTSA (0.04 g) was stirred vigorously for 12 h at room temperature. After the completion of the reaction (as revealed by TLC), 10 mL of a saturated $NaHCO_3$ solution and 30 mL of water were added successively to the reaction mixture, which was then extracted with CH_2Cl_2 (4×20 mL). The combined organic extract was washed with water, dried (Na_2SO_4) and concentrated. Removal of the residual DMF under reduced pressure by azeotropic distillation with CCl_4 afforded the alcohol as a syrupy liquid, which on column chromatography over silica gel furnished (**VII**).

Crystalline solid. M.p. 75 °C. Yield 70% (eluent PS-EA 19:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.35 (s, 3 H), 1.42 (s, 3 H), 1.52 (s, 3 H), 1.55 (s, 3 H), 3.31 (s, 3 H), 3.51-3.59 (m, 1 H), 3.71-3.80 (m, 2 H), 3.86-3.91 (dd, *J* = 10.8, 5.7 Hz, 1 H), 4.10-4.17 (m, 2 H), 4.90 (s, 1 H).

Synthesis of Methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside

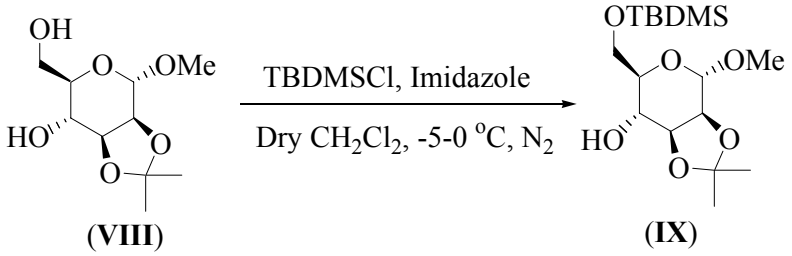


(**VII**) (**VIII**)

A solution of methyl 2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranoside (**VII**) (4 g) in 30 mL acetic acid: water (1:4 v/v) was stirred at 0 °C for 1h. After completion of reaction as indicated by TLC, the solution was neutralized with saturated $NaHCO_3$ solution at 0 °C. The mixture was then evaporated under reduced pressure to obtain a solid mass, which was extracted with CH_2Cl_2 (4×20 mL). The combined organic extract was dried (Na_2SO_4), concentrated under reduced pressure, and then subjected to column chromatographic purification to furnish the requisite compound as a crystalline solid (**VIII**).

Crystalline solid. M.p. 105 °C. Yield 60% (eluent PS-EA 4:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.35 (s, 3 H), 1.55 (s, 3 H), 2.96-3.15 (brs, 1 H), 3.31 (s, 3 H), 3.54-3.57 (dt, *J* = 6.0, 3.0 Hz, 1 H), 3.69-3.74 (dd, *J* = 9.6, 6.3 Hz, 1 H), 3.84 (d, *J* = 3.0 Hz, 1 H), 4.13-4.16 (m, 2 H), 4.92 (s, 1 H).

Synthesis of Methyl-6-*O*-*t*-butyldimethylsilyl-2,3-*O*-isopropylidene-α-D-mannopyranoside

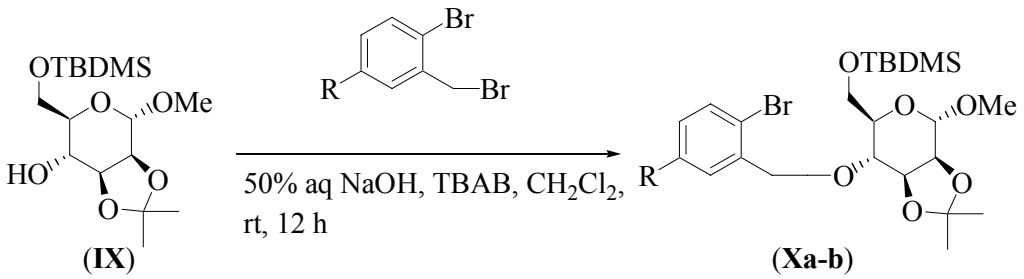


(**VIII**) (**IX**)

A mixture of methyl-2,3-*O*-isopropylidene-α-D-mannopyranoside (**VIII**) (2.43 g, 10 mmol), TBDMSCl (1.5 g, 10 mmol), and imidazole (2.04 g, 30 mmol) in CH_2Cl_2 (15 mL) was stirred at –5-0 °C for 1h. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (4×20 mL). The combined organic extract was washed with water and dried (Na_2SO_4); the solvent was evaporated under reduced pressure to furnish a pale yellow liquid, which on column chromatographic purification gave the pure alcohol (**IX**).

Colorless liquid. Yield 78% (eluent PS-EA 19:1). ^{1}H NMR ($CDCl_3$, 300 MHz): 0.1 (s, 6 H, $SiMe_2$), 0.9 (s, 9 H, CMe_3), 1.35 (s, 3 H), 1.57 (s, 3 H), 3.39 (s, 3 H), 3.54-3.60 (m, 1 H), 3.69-3.74 (dd, *J* = 9.1, 6.3 Hz, 1 H), 3.85-3.87 (dd, *J* = 5.0, 1.5 Hz, 2 H), 4.09-4.15 (m, 2 H), 4.92 (s, 1 H).

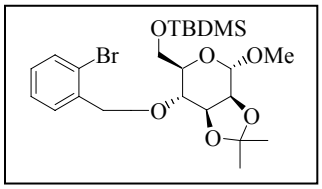
General Procedure for the Synthesis of Methyl-6-O-(t-butyldimethylsilyl)-4-O-(2-bromobenzyl)-2,3-*O*-isopropylidene-α-D-mannopyranoside Derivatives



To a magnetically stirred solution of methyl 6-t-butyldimethylsilyl-2,3-*O*-isopropylidene-α-D-mannopyranoside **(IX)** (1 mol eqv.) and appropriate 2-bromobenzylbromide **(62)** (1.1 mol eqv) in CH_2Cl_2 was added Bu_4NBr (TBAB) (100 mg) followed by 20 mL of aq. NaOH (50% v/v) at 0 °C. The stirring was continued at room temperature for 12 h. The organic layer was separated and the aqueous part was extracted with CH_2Cl_2 (4×20 mL). The combined organic extract was washed with water and dried (Na_2SO_4); the solvent was evaporated under reduced pressure to furnish a crude oil, which on column chromatographic purification yielded **(Xa-b)**.

Methyl-6-*O*-(*t*-butyldimethylsilyl)-4-*O*-(2-bromobenzyl)-2,3-*O*-isopropylidene-α-D-mannopyranoside (Xa)

Colorless liquid. Yield 76% (eluent PS-EA 19:1).



$[\alpha]^{25}_{,D}$ +25.8 (*c* 0.32, $CHCl_3$).

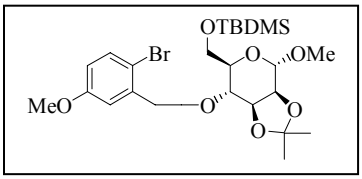
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.07 (s, 6 H, $SiMe_2$), 0.92 (s, 9 H, CMe_3), 1.37 (s, 3 H), 1.57 (s, 3 H), 3.36 (s, 3 H), 3.46-3.65 (m, 2 H), 3.75-3.82 (dd, *J* = 12.0, 6.0 Hz, 1 H),

3.88-3.92 (d, *J* = 12.0 Hz, 1 H), 4.11-4.13 (d, *J* = 6.0 Hz, 1 H), 4.20-4.23 (dd, *J* = 6.0, 3.0 Hz, 1 H), 4.66-4.70 (d, *J* = 12.0 Hz, 1 H), 4.93-4.97 (d, *J* = 12.0 Hz, 1 H), 4.97 (s, 1 H), 6.68-7.40 (m, 4 H).

Methyl-6-*O*-(*t*-butyldimethylsilyl)-4-*O*-(2-bromo-5-methoxybenzyl)-2,3-

-*O*-isopropylidene-α-D-mannopyranoside (Xb)

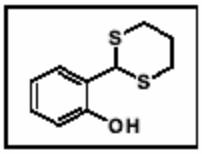
Colorless liquid. Yield 80% (eluent PS-EA 19:1).

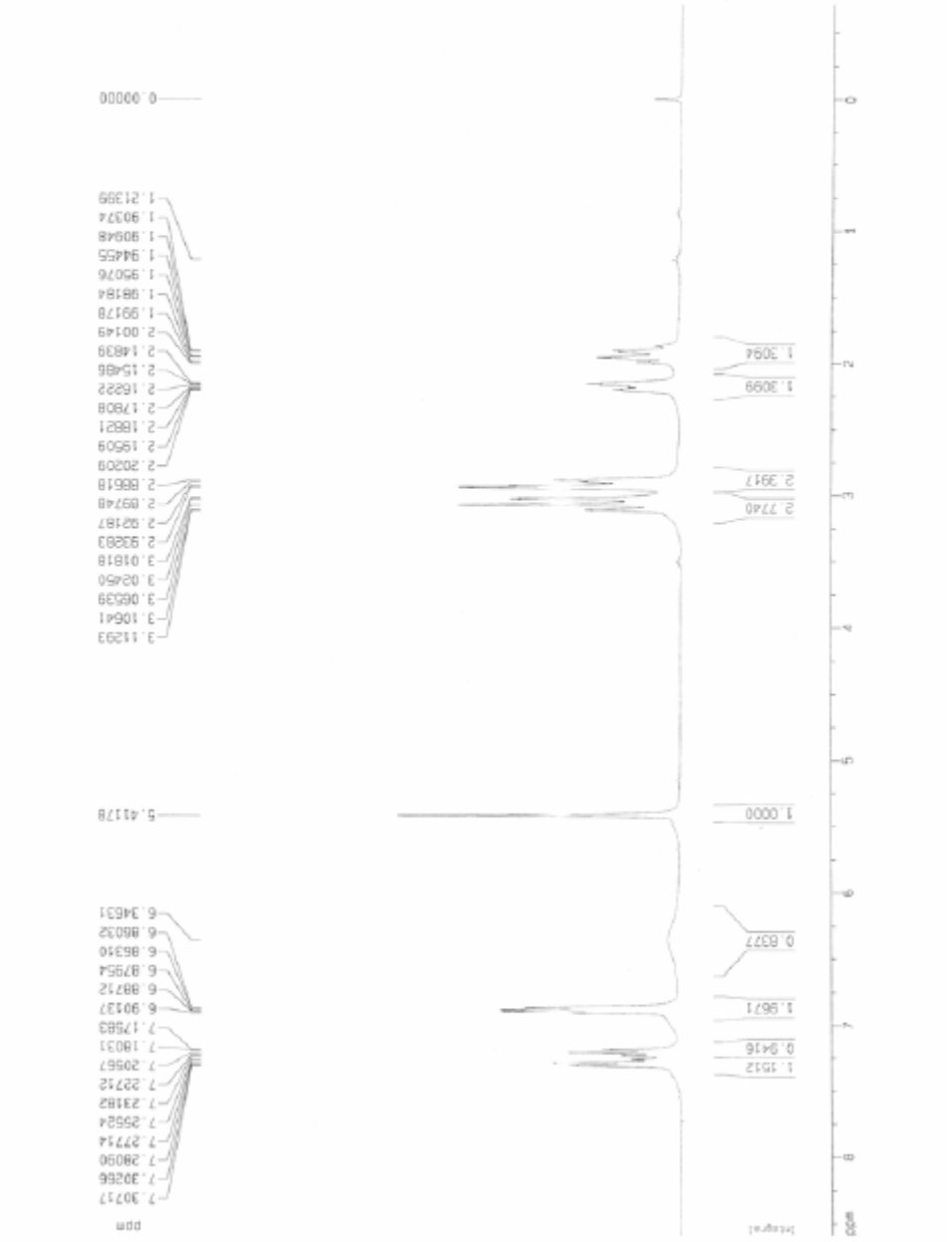


$[\alpha]^{25}_{,D}$ +34.5 (*c* 0.23, $CHCl_3$).

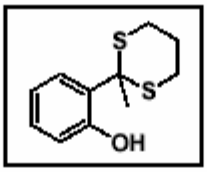
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.05 (s, 6 H, $SiMe_2$), 0.88 (s, 9 H, CMe_3), 1.37 (s, 3 H), 1.55 (s, 3 H), 3.37 (s, 3 H), 3.56-3.60 (m, 2 H), 3.73-3.75 (d, *J* = 6.0 Hz, 1 H), 3.79 (s, 3 H), 3.91-3.95 (dd, *J* = 12.0, 1.5 Hz, 1 H), 4.11-4.13 (d, *J* = 6.0 Hz, 1 H), 4.29-4.31 (d, *J* = 6.0 Hz, 1 H), 4.60-4.64 (d, *J* = 12.0 Hz, 1 H), 4.86-4.90 (d, *J* = 12.0 Hz, 1 H), 5.03 (s, 1 H), 6.67-6.71 (dd, *J* = 9.0, 3.0 Hz, 1 H), 7.06 (d, *J* = 3.0 Hz, 1 H), 7.40-7.43 (d, *J* = 9.0 Hz, 1 H).

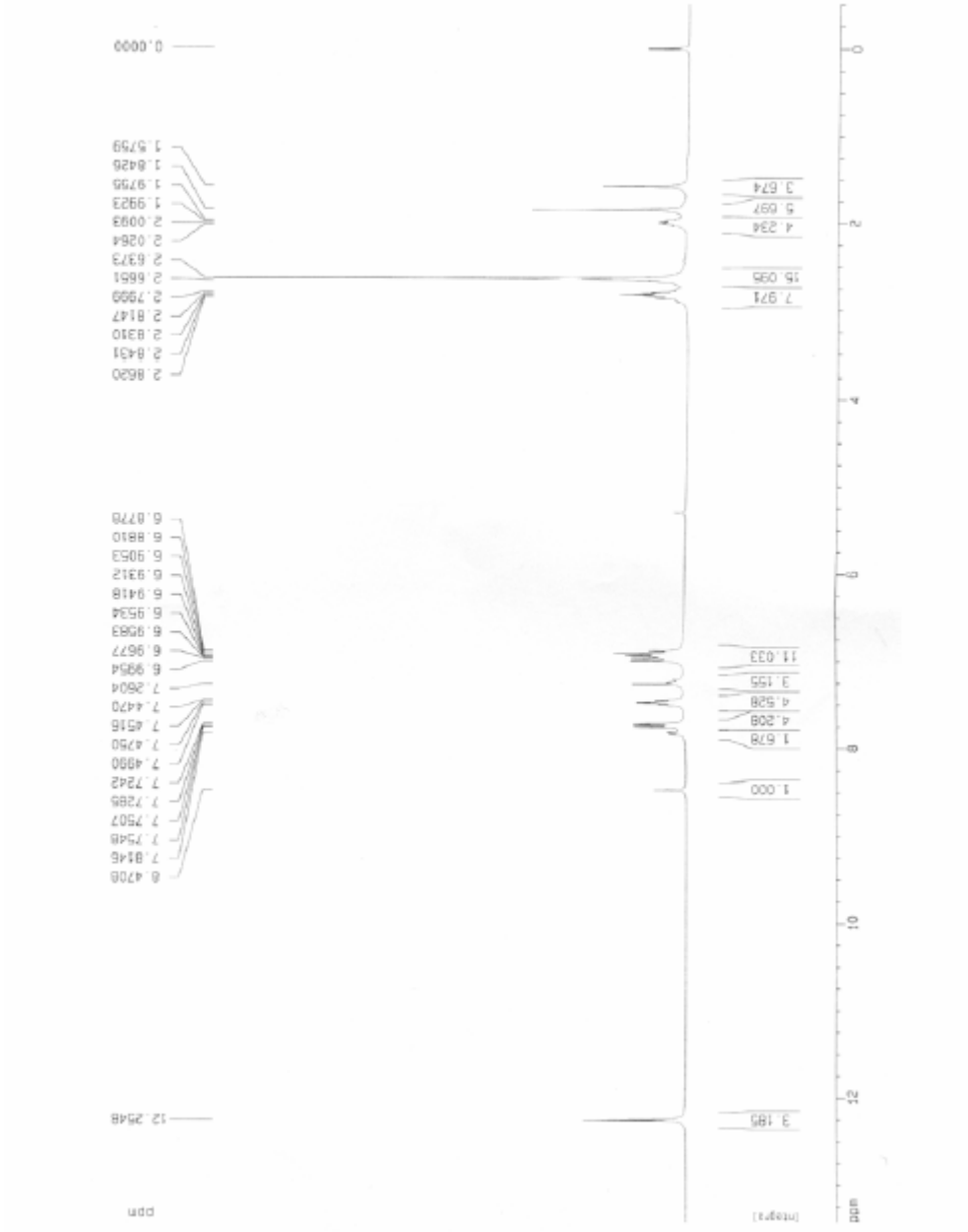
^{1}H NMR: $CDCl_3$ and 300 MHz



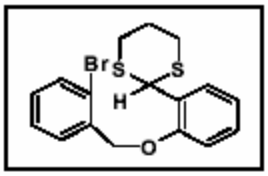


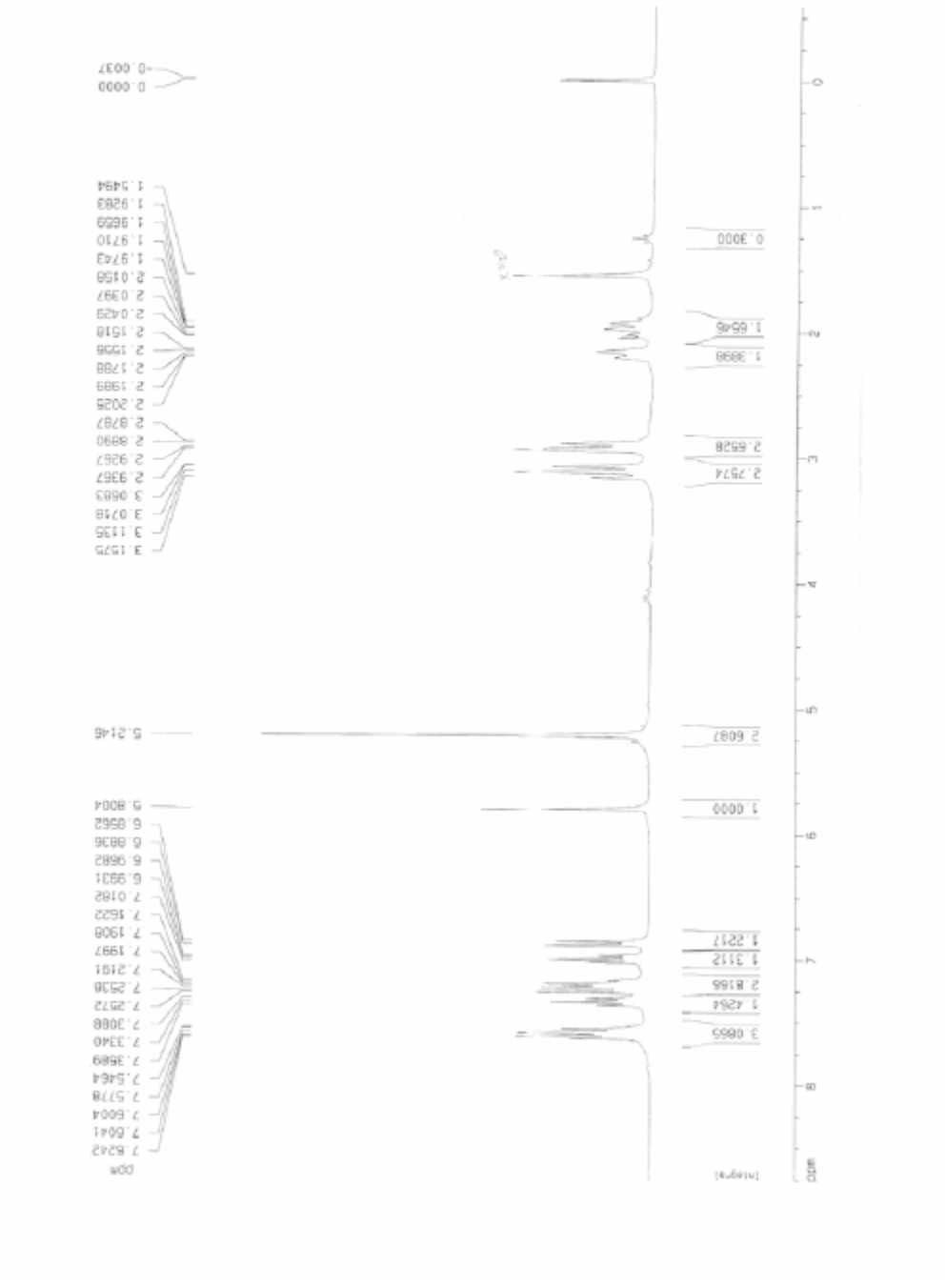
^{1}H NMR: $CDCl_3$ and 300 MHz



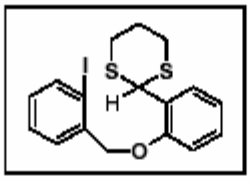


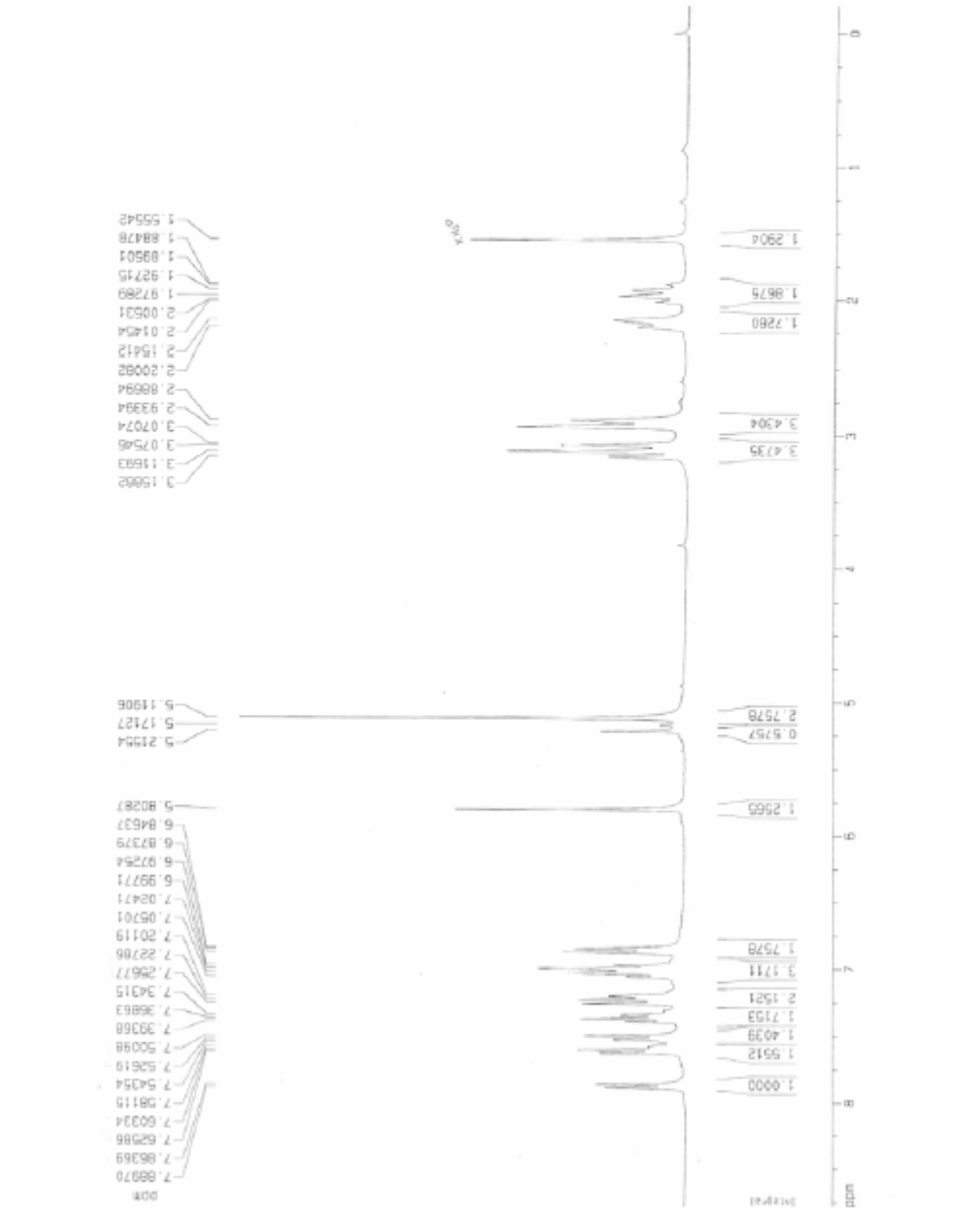
^{1}H NMR: $CDCl_3$ and 300 MHz



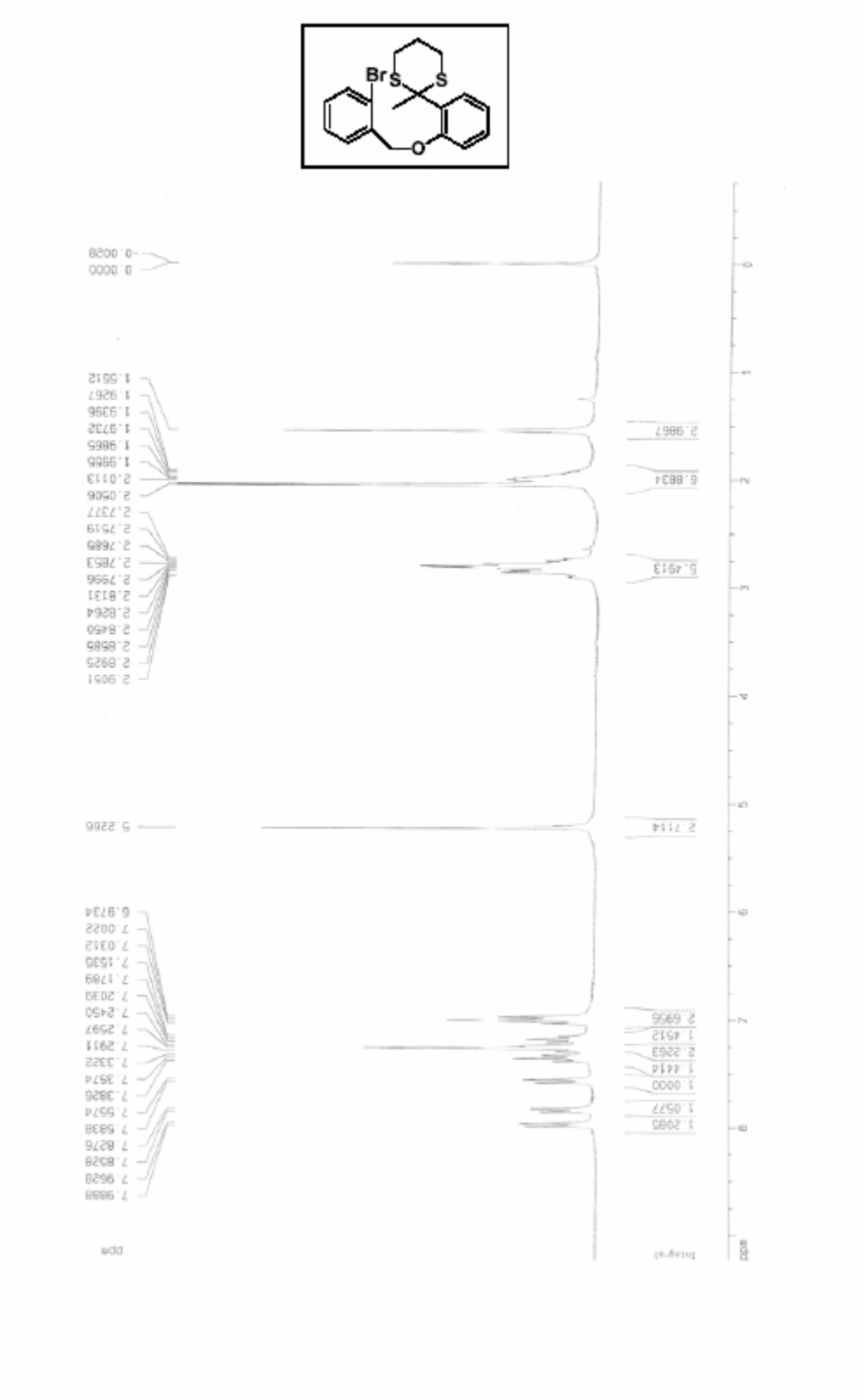


^{1}H NMR: $CDCl_3$ and 300 MHz

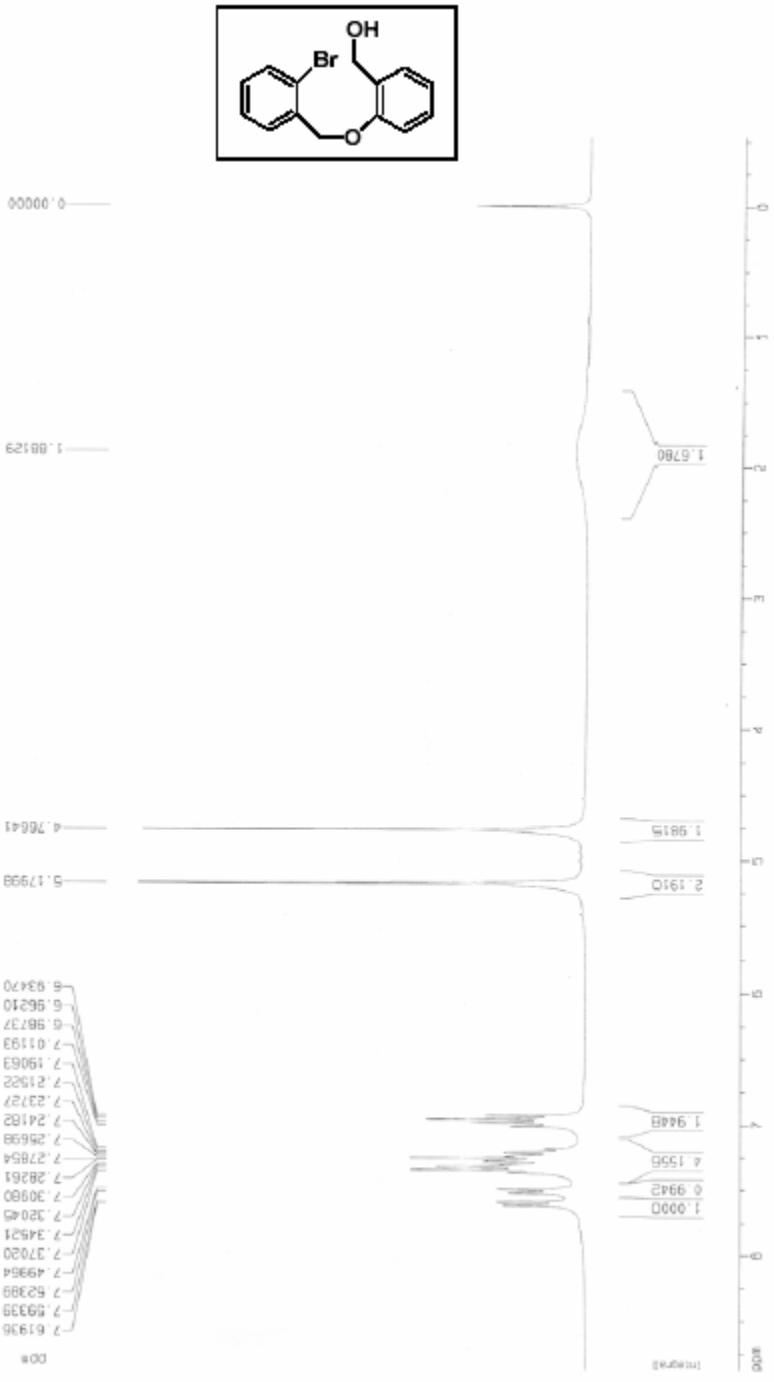




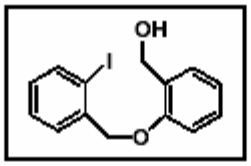
^{1}H NMR: $CDCl_3$ and 300 MHz

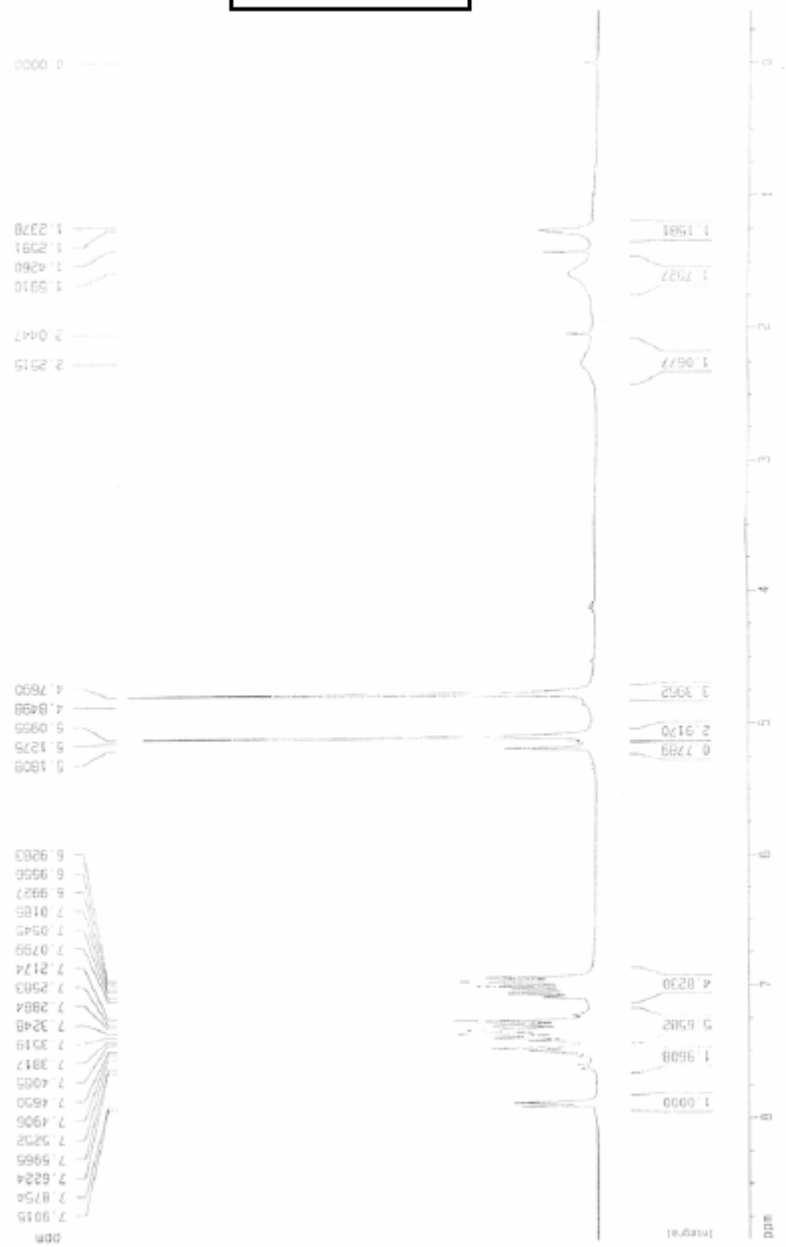


^{1}H NMR of 1a: $CDCl_3$ and 300 MHz

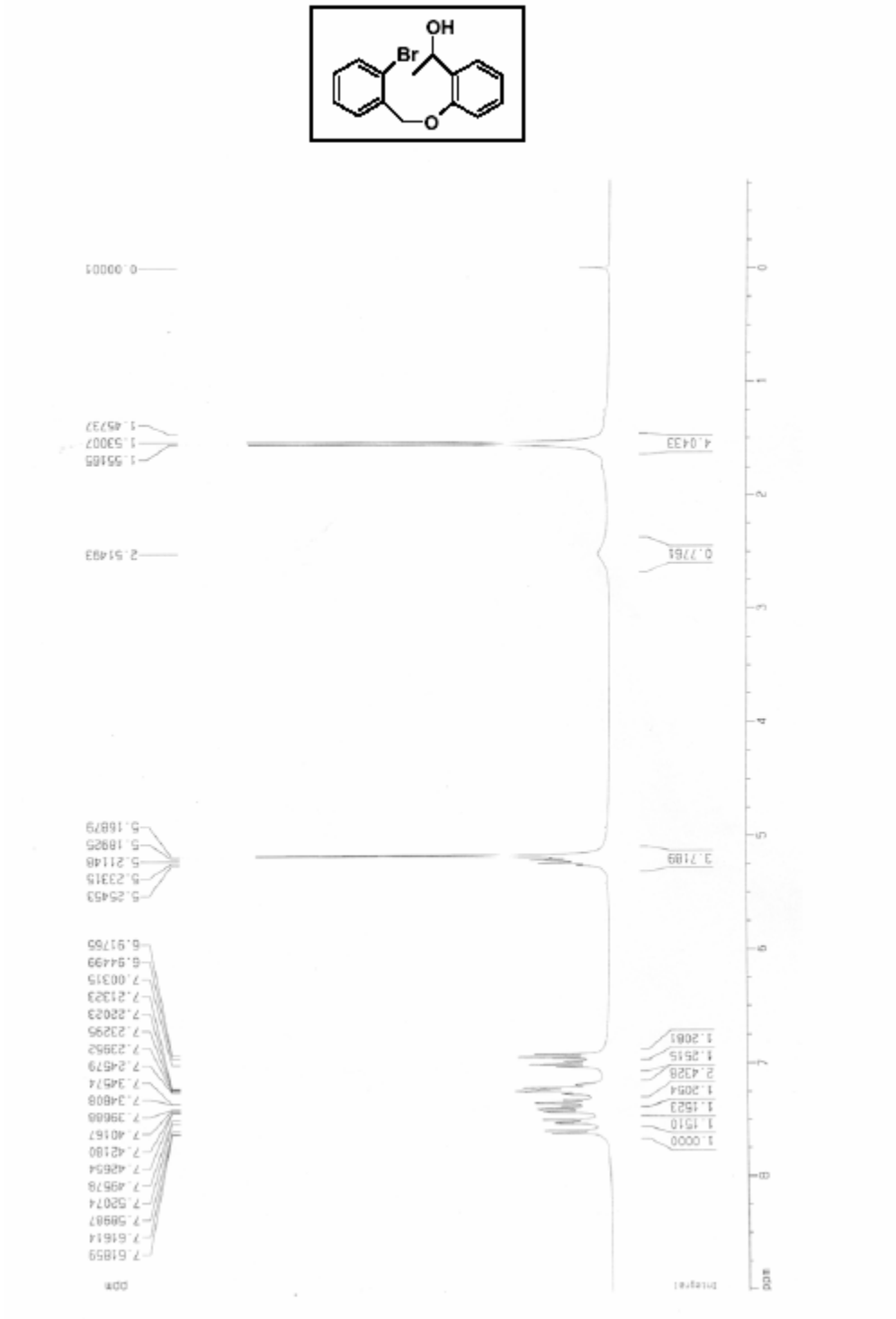


^{1}H NMR of 1b: $CDCl_3$ and 300 MHz

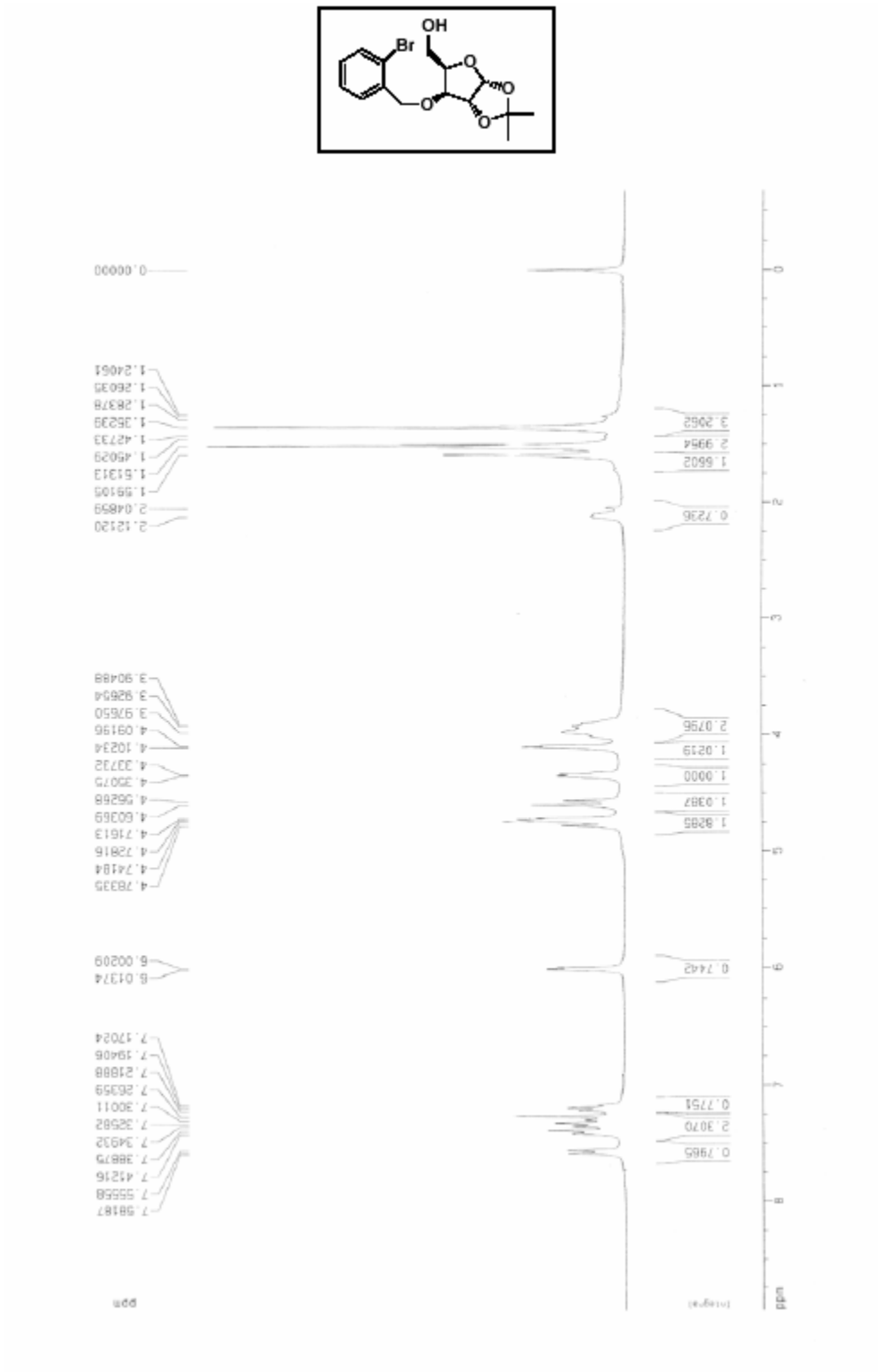




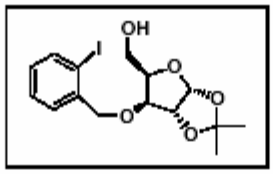
^{1}H NMR of 1c: $CDCl_3$ and 300 MHz

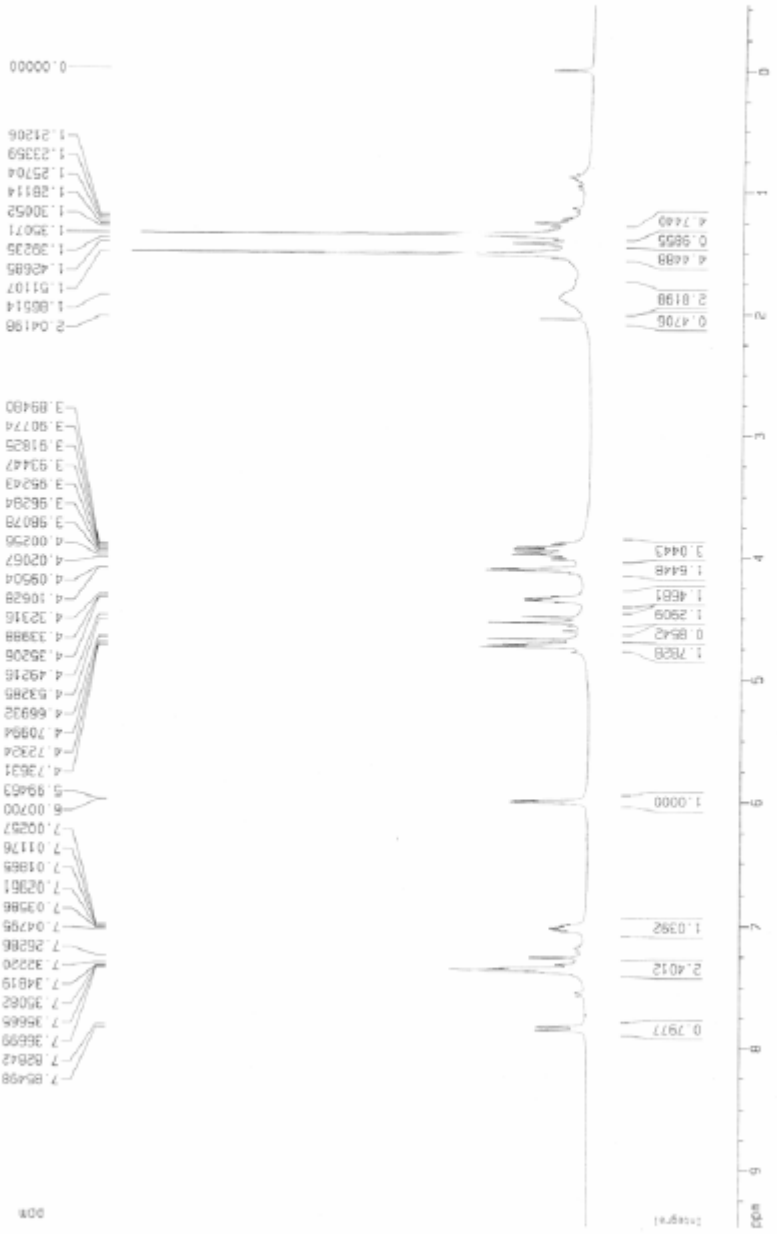


^{1}H NMR of 4a: $CDCl_3$ and 300 MHz

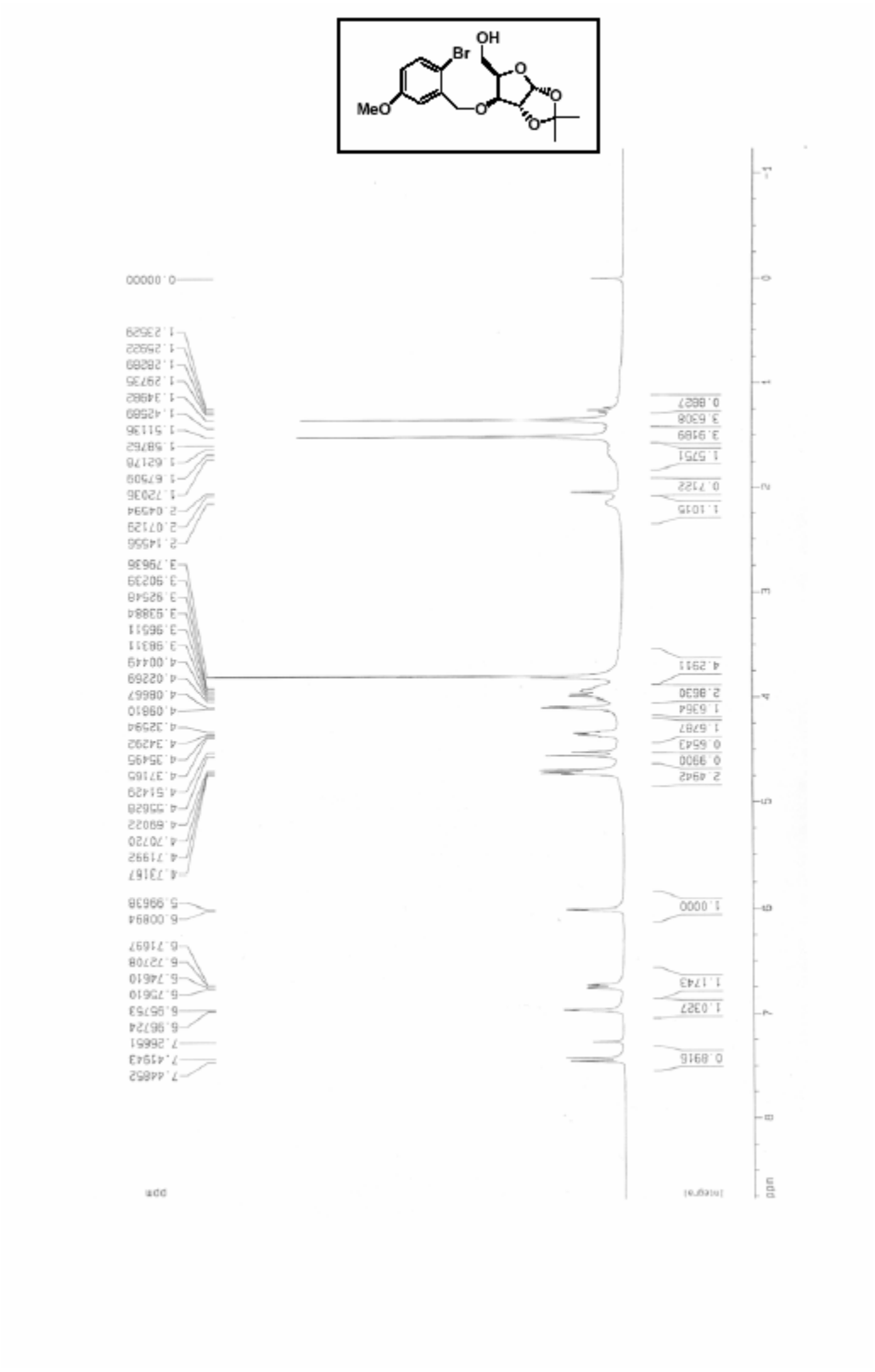


^{1}H NMR of 4b: $CDCl_3$ and 300 MHz

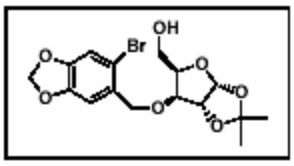


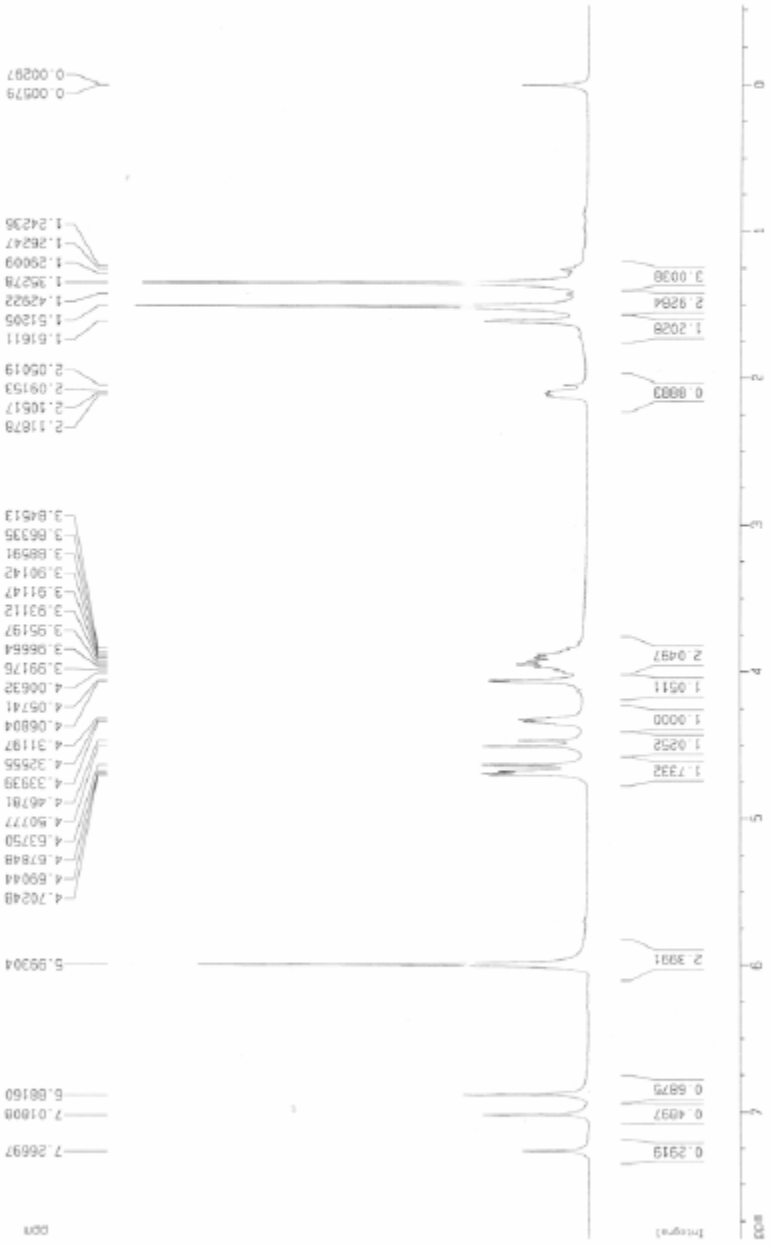


^{1}H NMR of 4c: $CDCl_3$ and 300 MHz

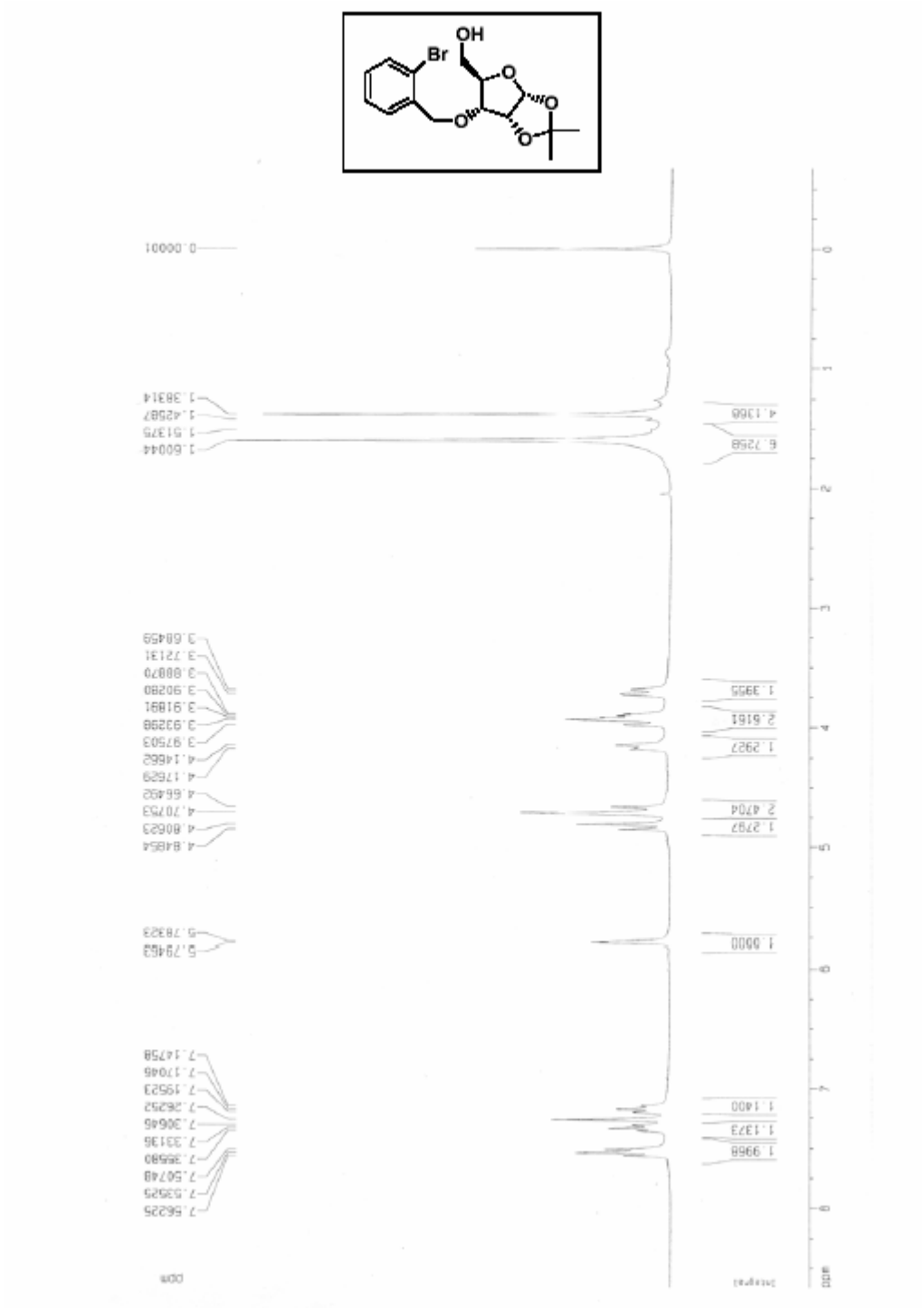


^{1}H NMR of 4d: $CDCl_3$ and 300 MHz

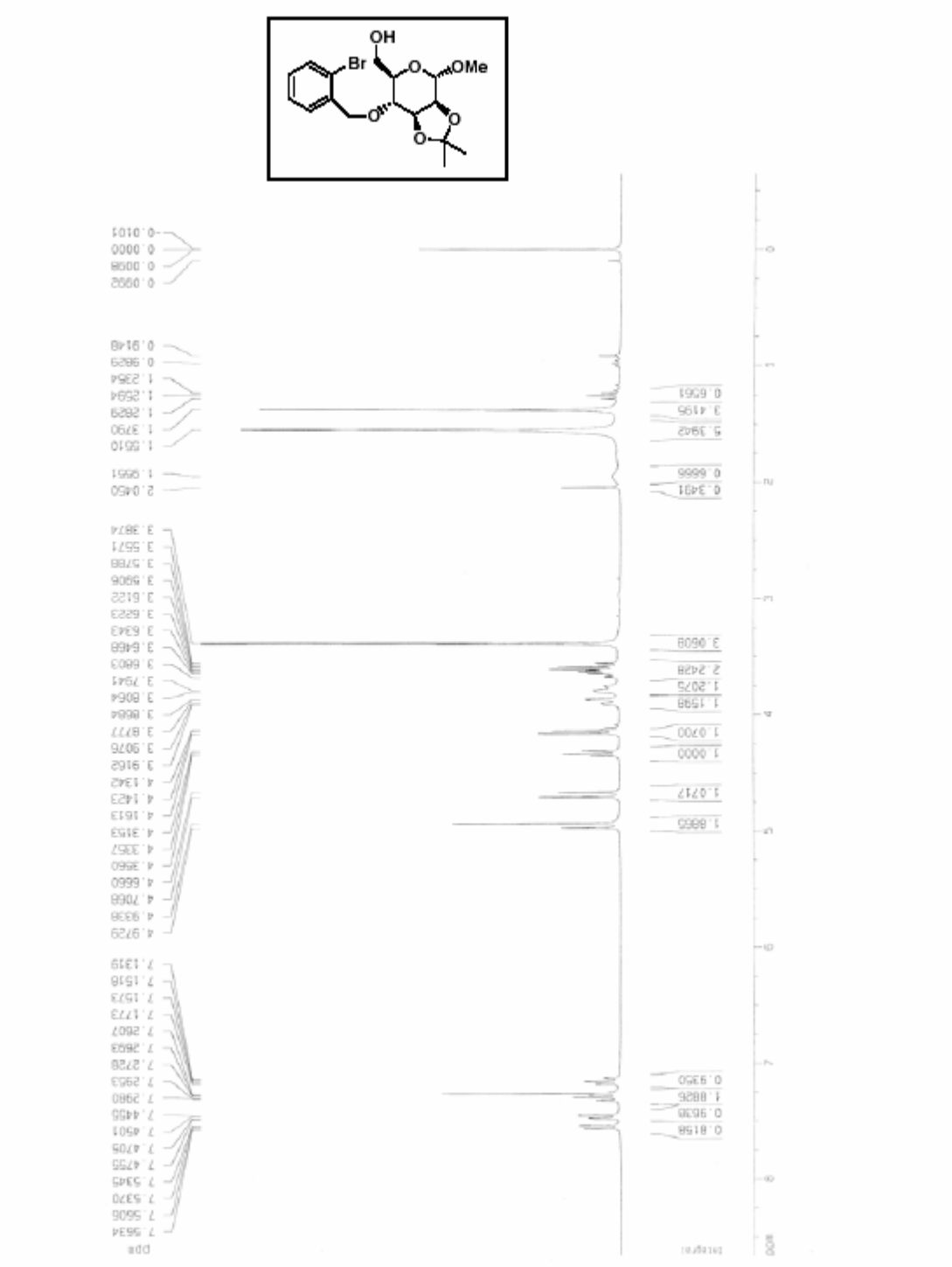




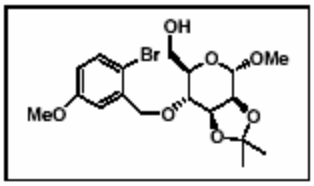
^{1}H NMR of 4e: $CDCl_3$ and 300 MHz

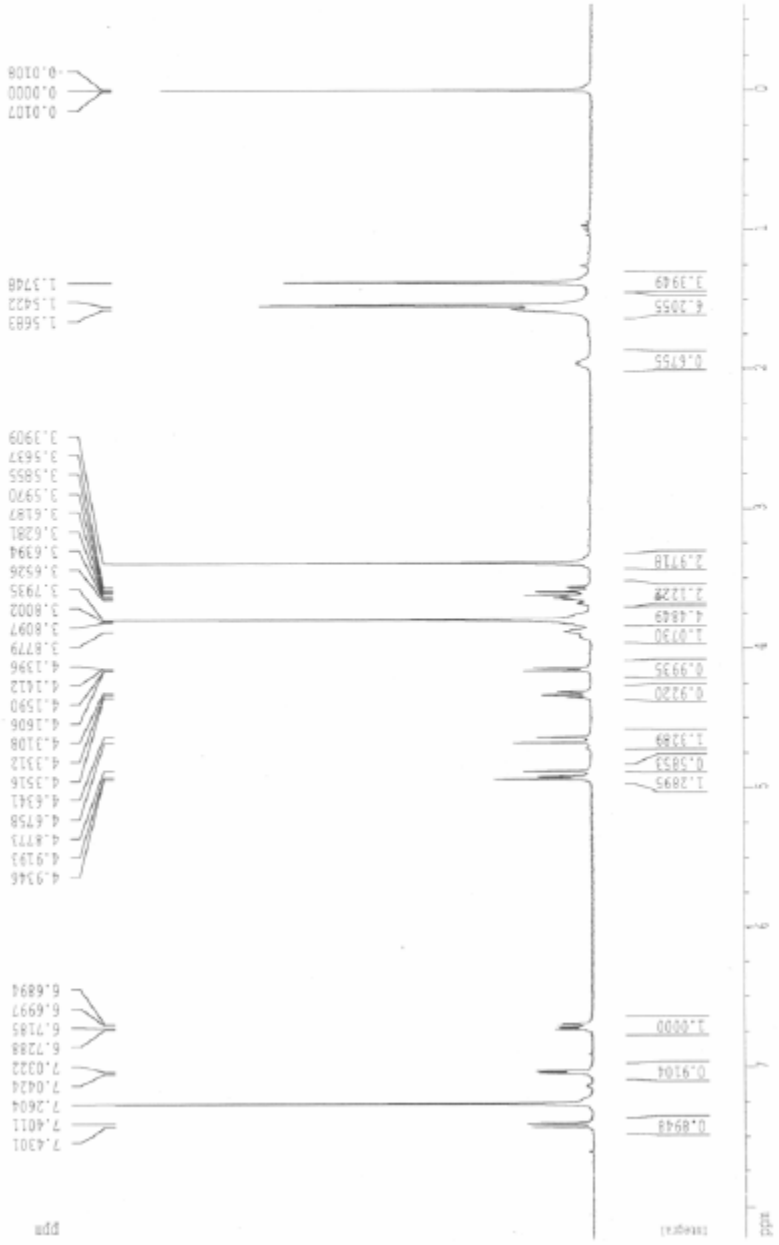


^{1}H NMR of 6a: $CDCl_3$ and 300 MHz

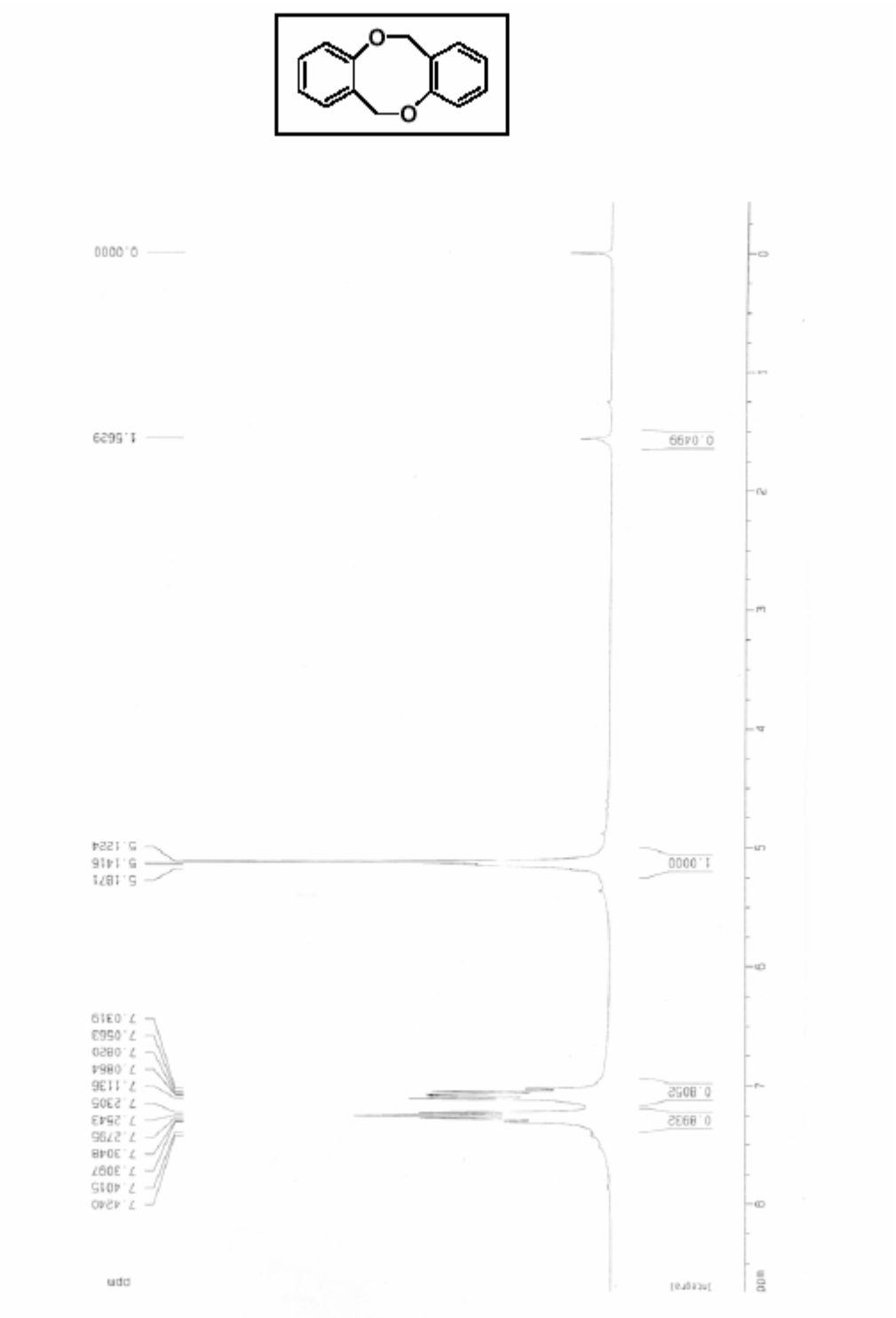


[1]H NMR of 6b: $CDCl_3$ and 300 MHz

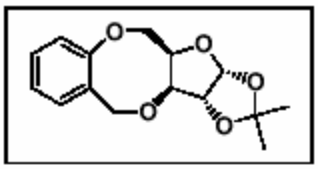


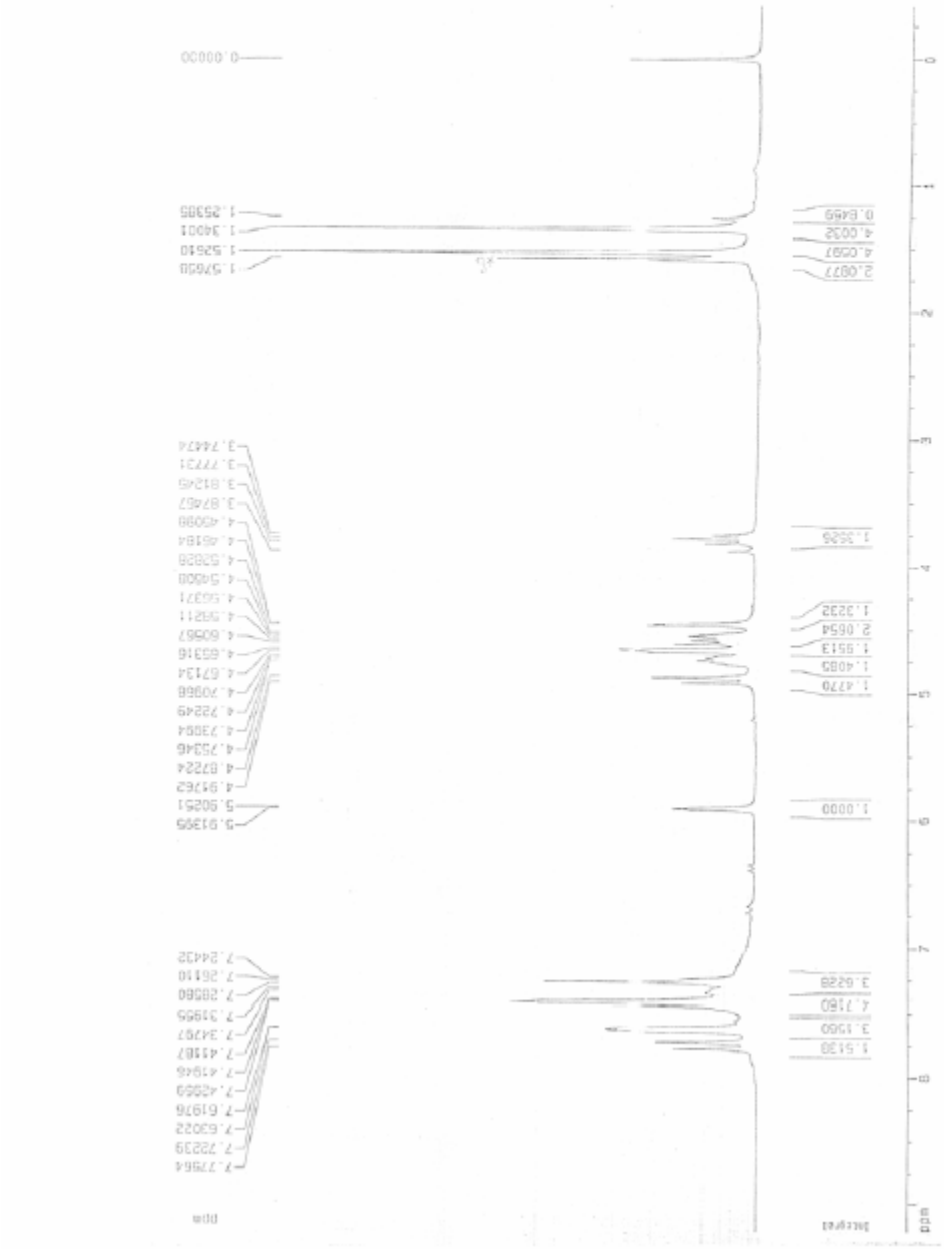


^{1}H NMR of 2: $CDCl_3$ and 300 MHz

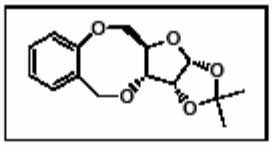


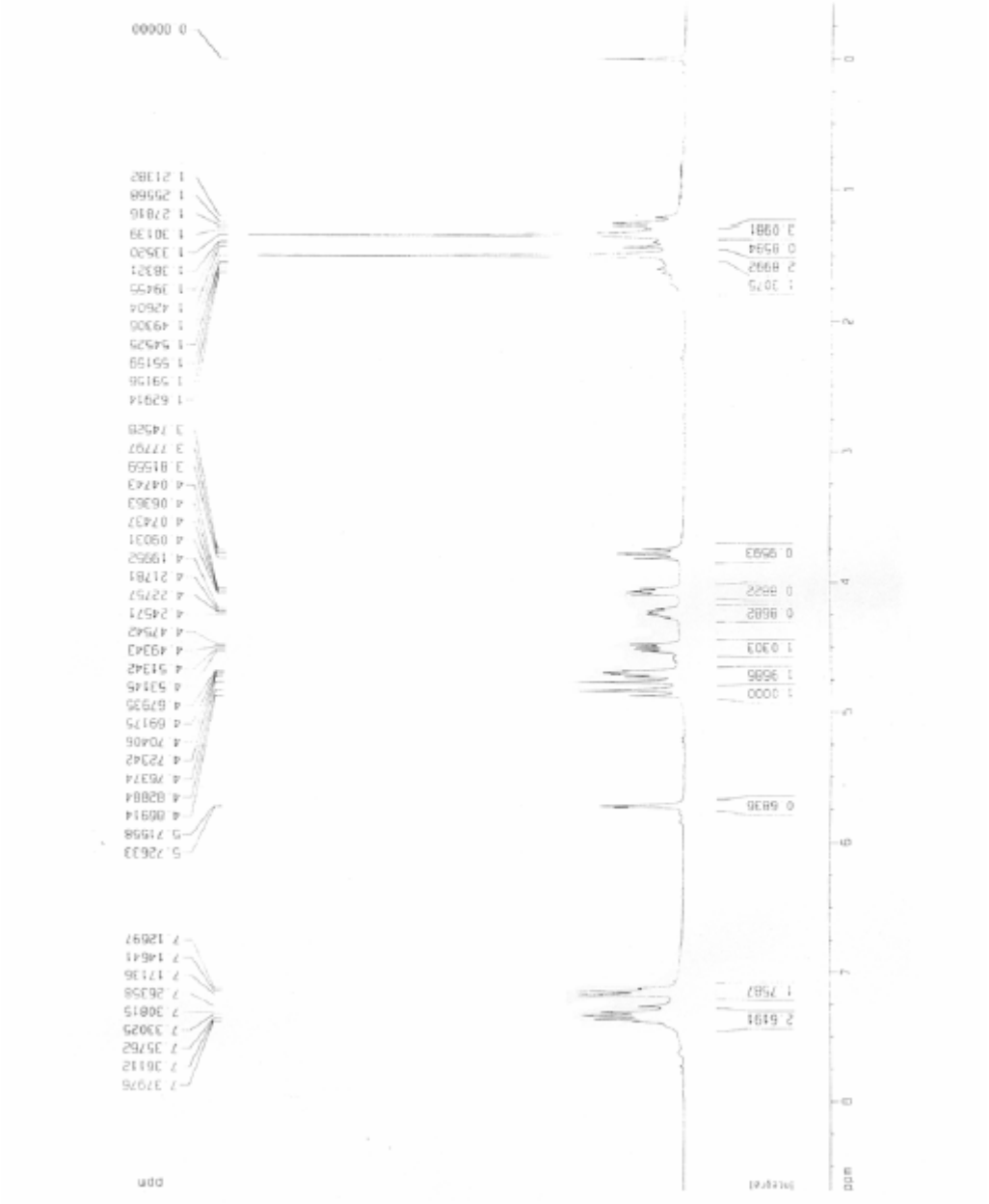
^{1}H NMR of 5a: $CDCl_3$ and 300 MHz



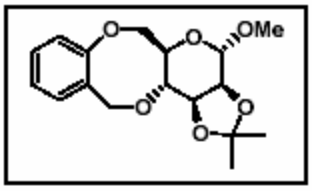


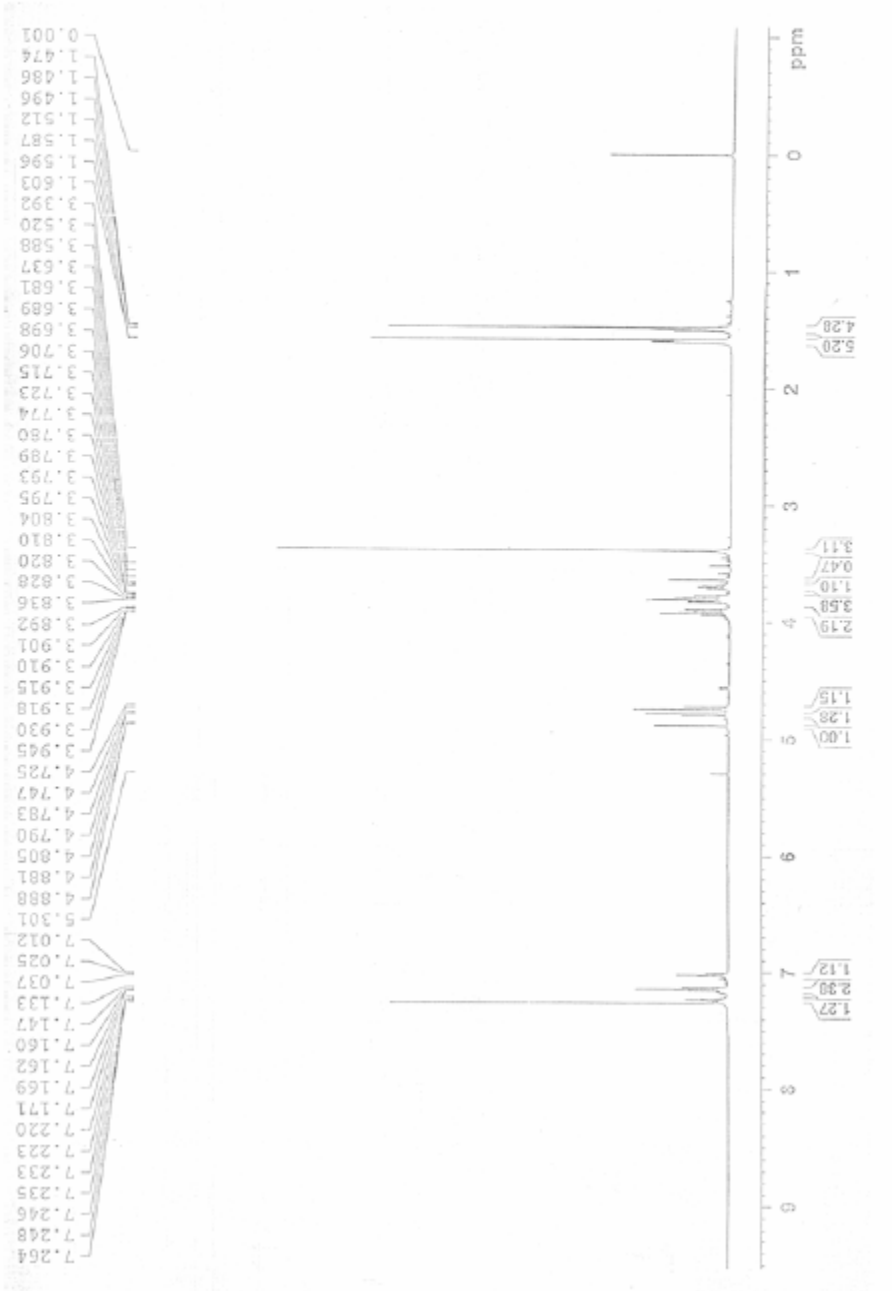
^{1}H NMR of 5b: $CDCl_3$ and 300 MHz



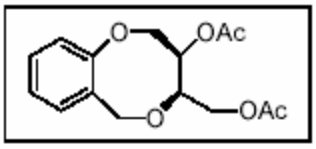


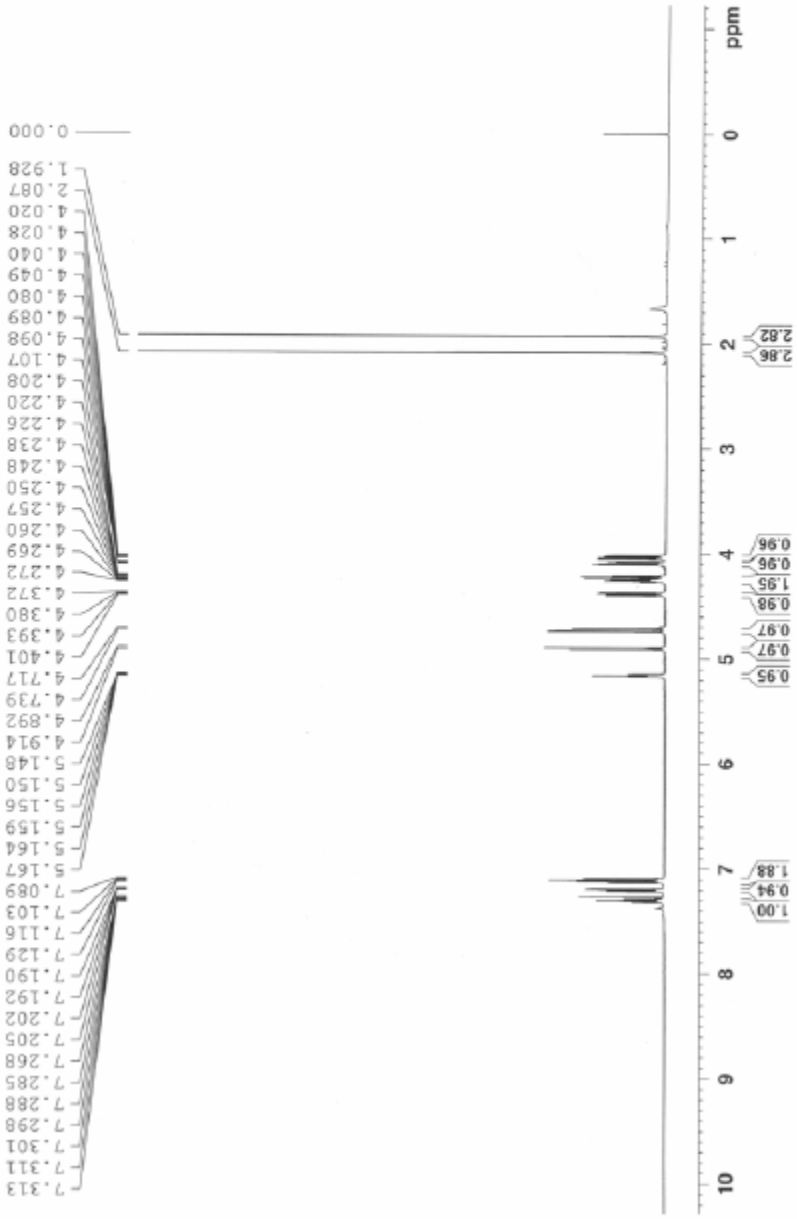
^{1}H NMR of 7: $CDCl_3$ and 600 MHz



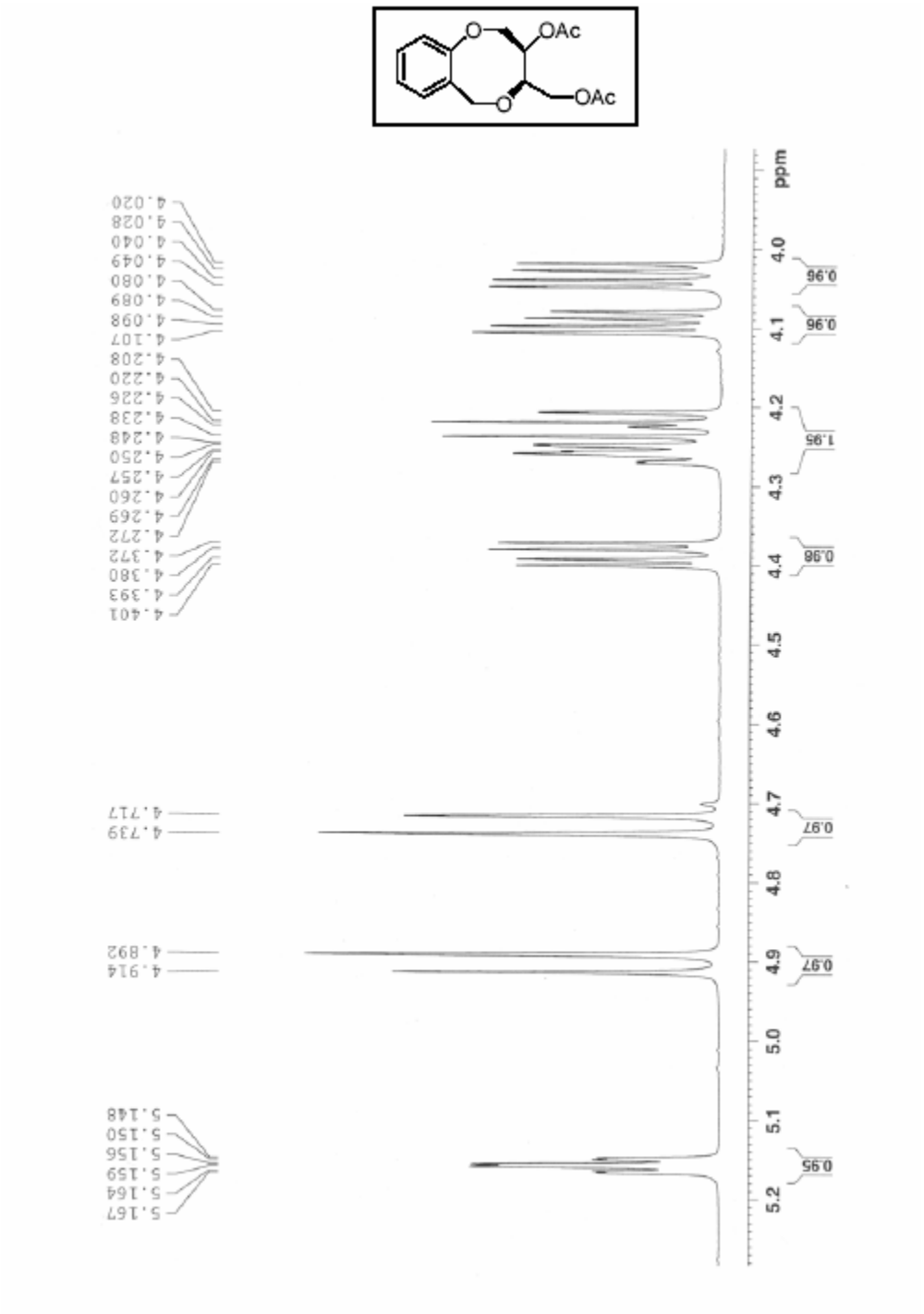


^{1}H NMR of 8: $CDCl_3$ and 600 MHz

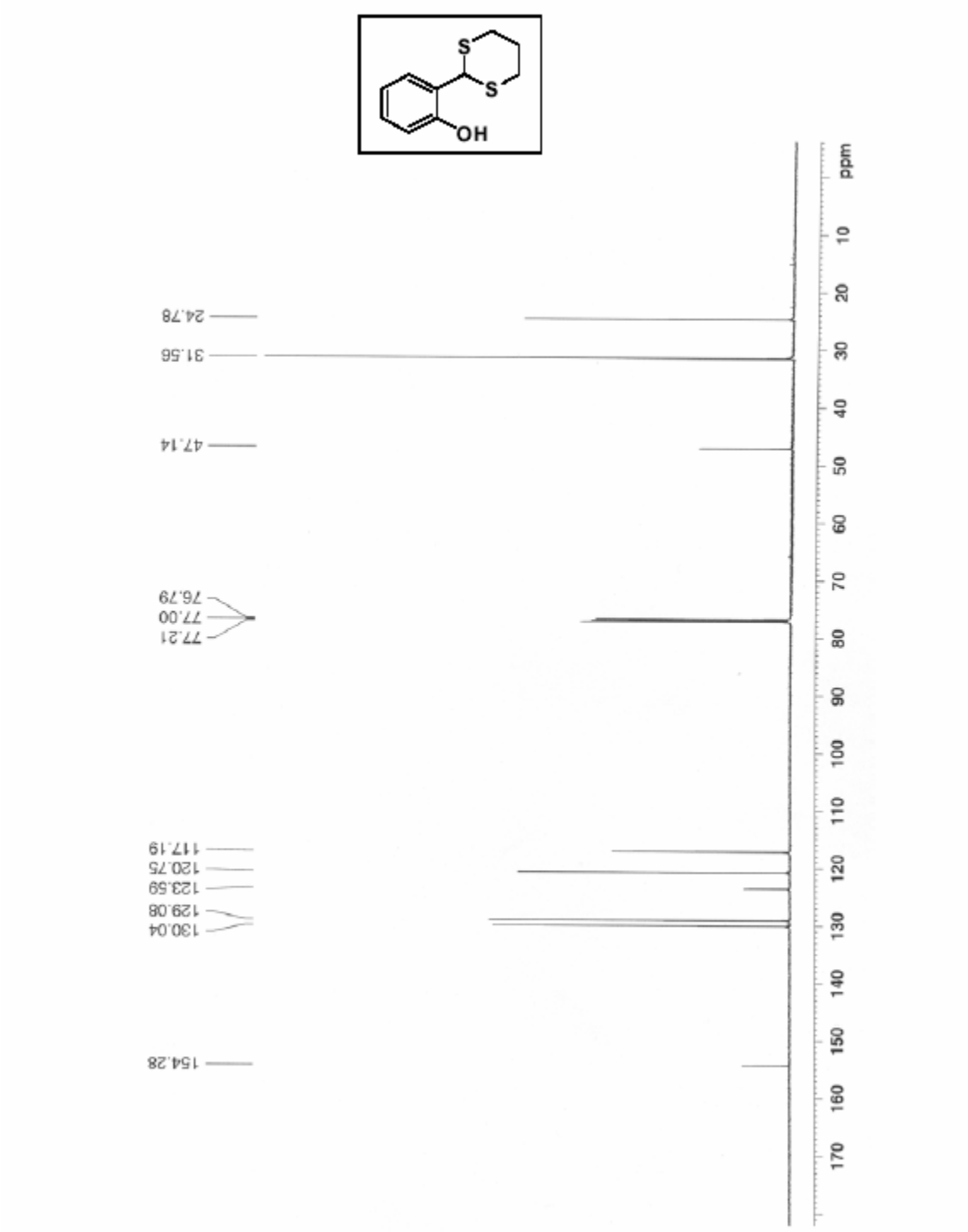




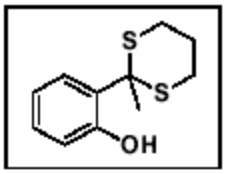
^{1}H NMR of 8: Expansion: $CDCl_3$ and 600 MHz

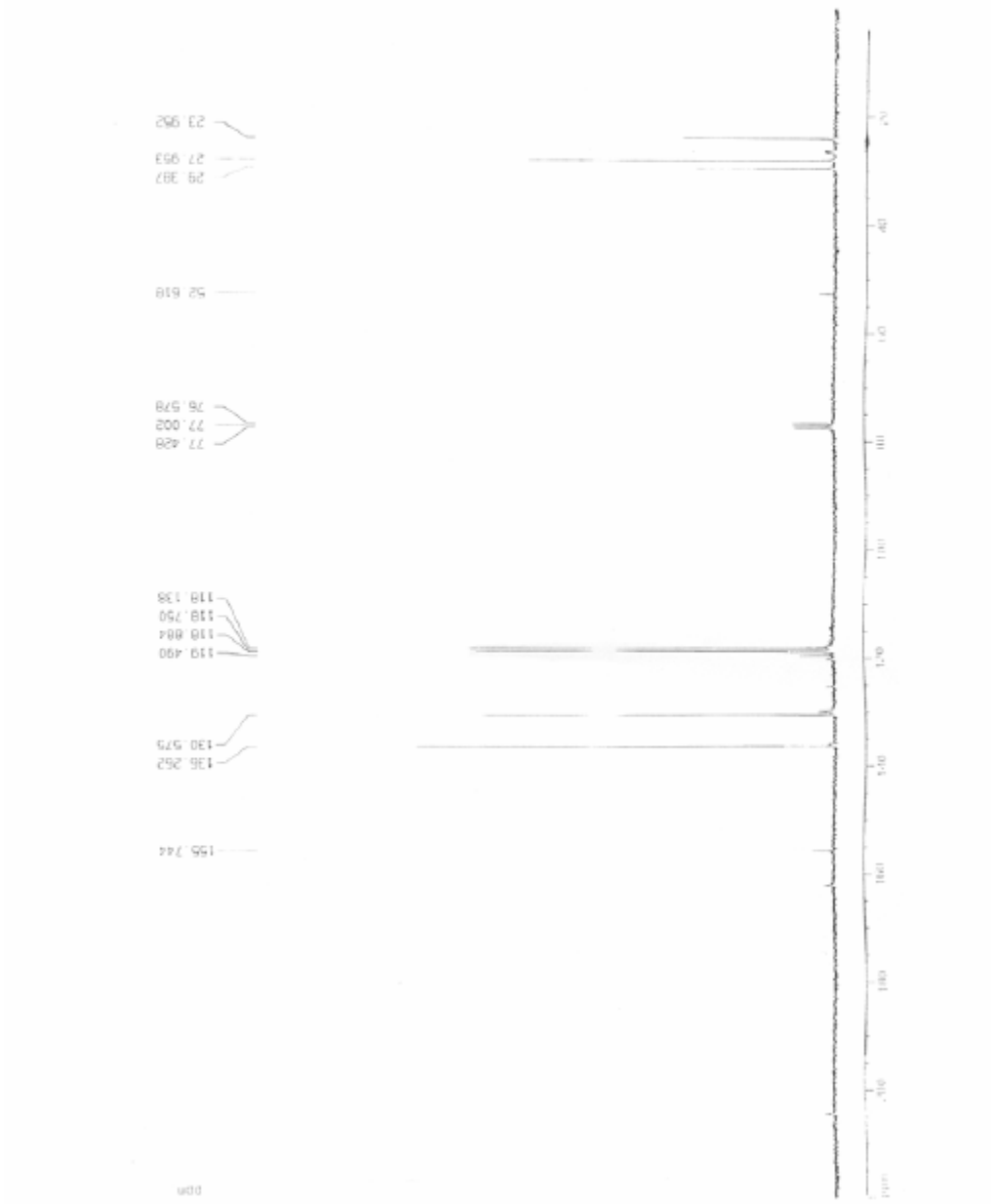


^{13}C NMR: $CDCl_3$ and 150 MHz

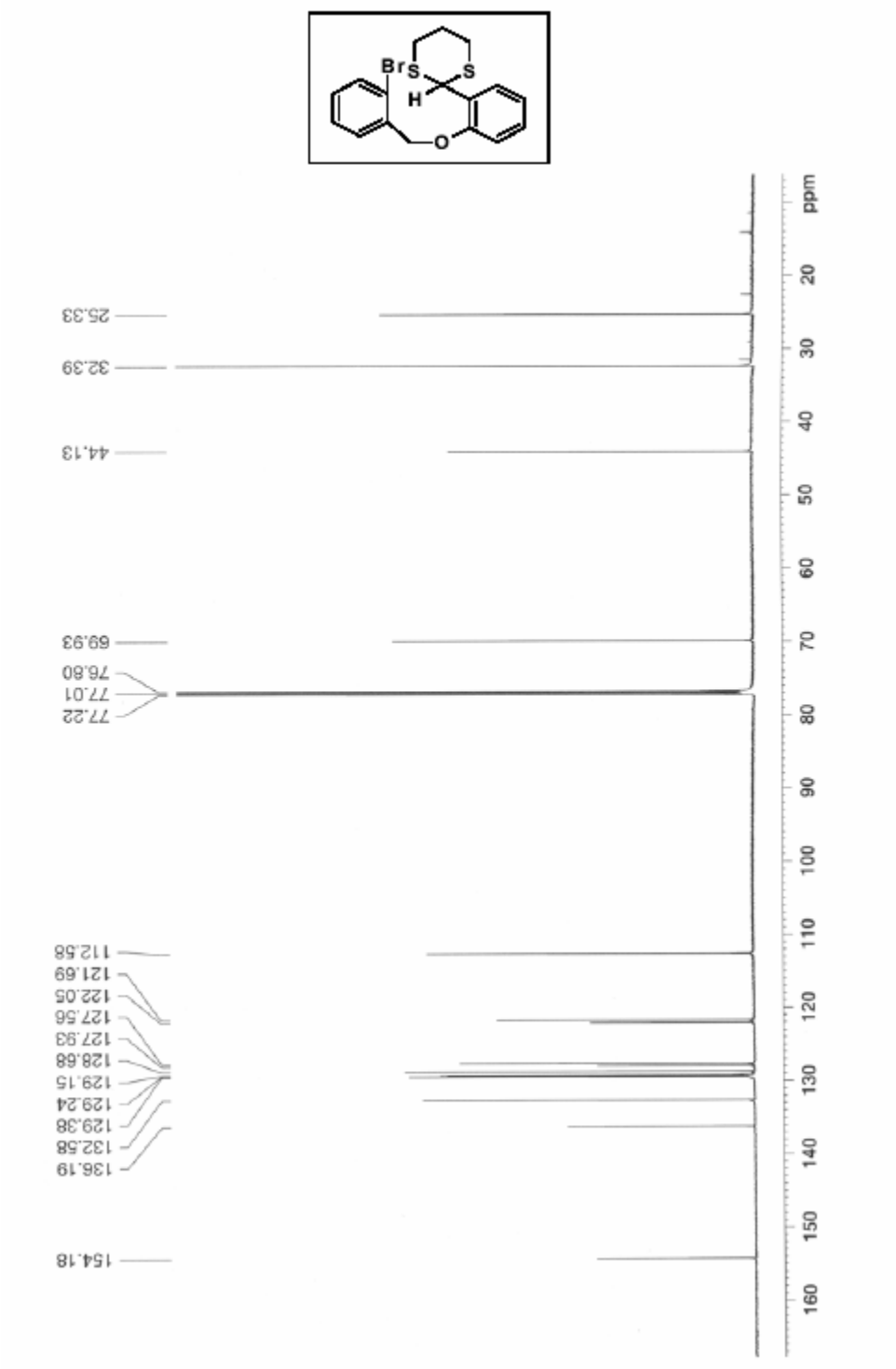


^{13}C NMR: $CDCl_3$ and 75 MHz

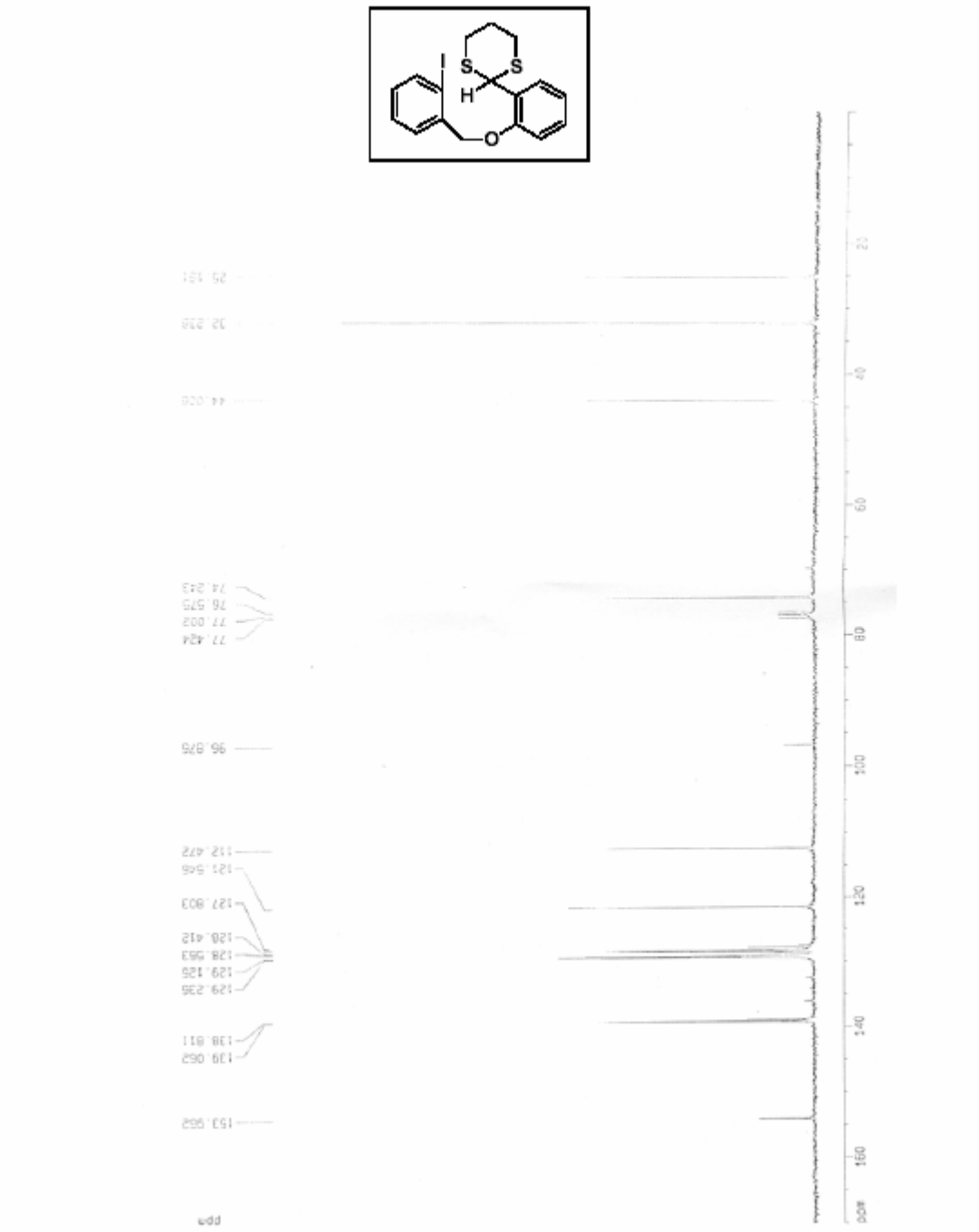




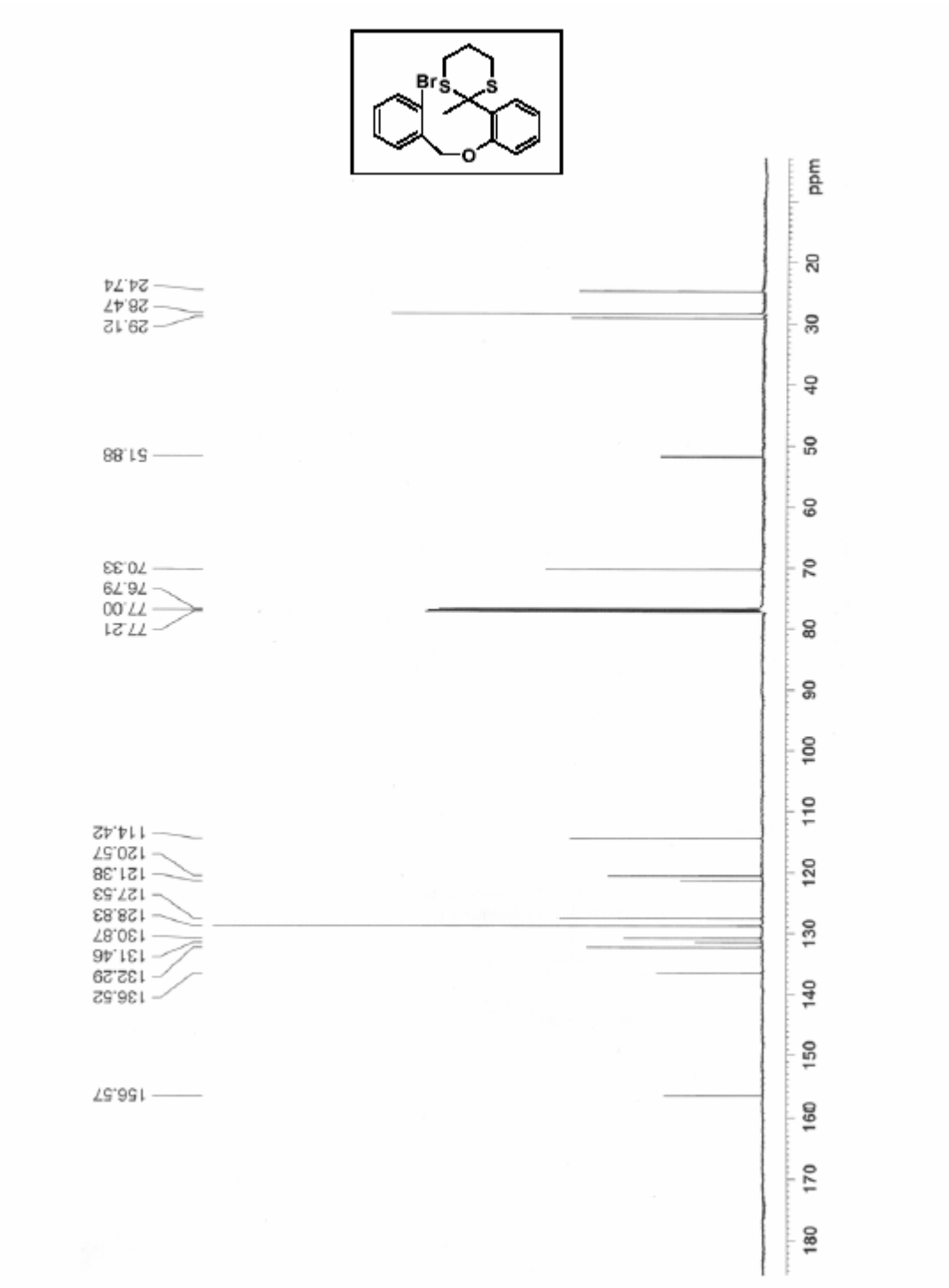
^{13}C NMR: $CDCl_3$ and 150 MHz



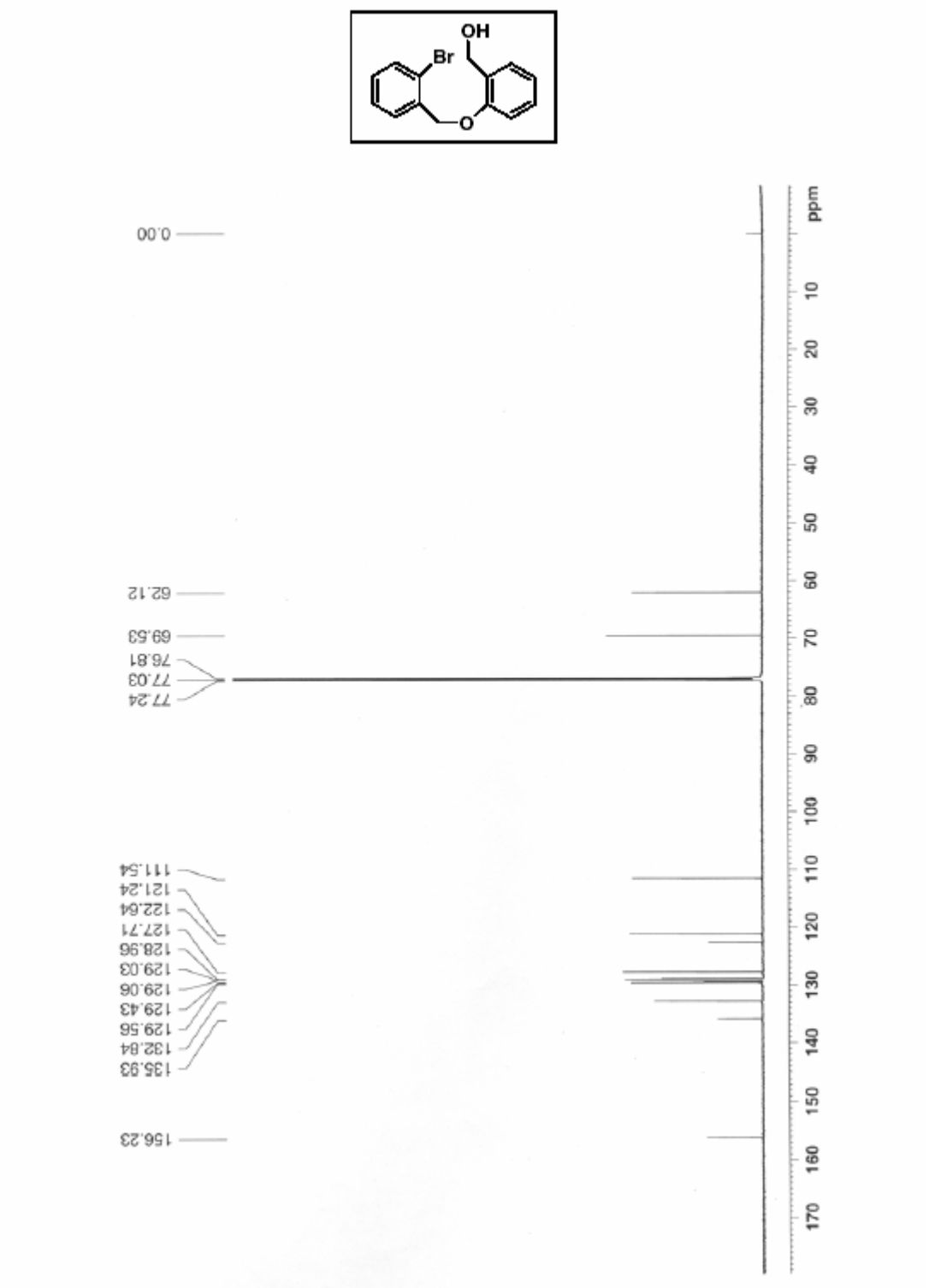
^{13}C NMR: $CDCl_3$ and 75 MHz



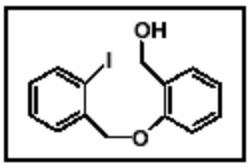
^{13}C NMR: $CDCl_3$ and 150 MHz

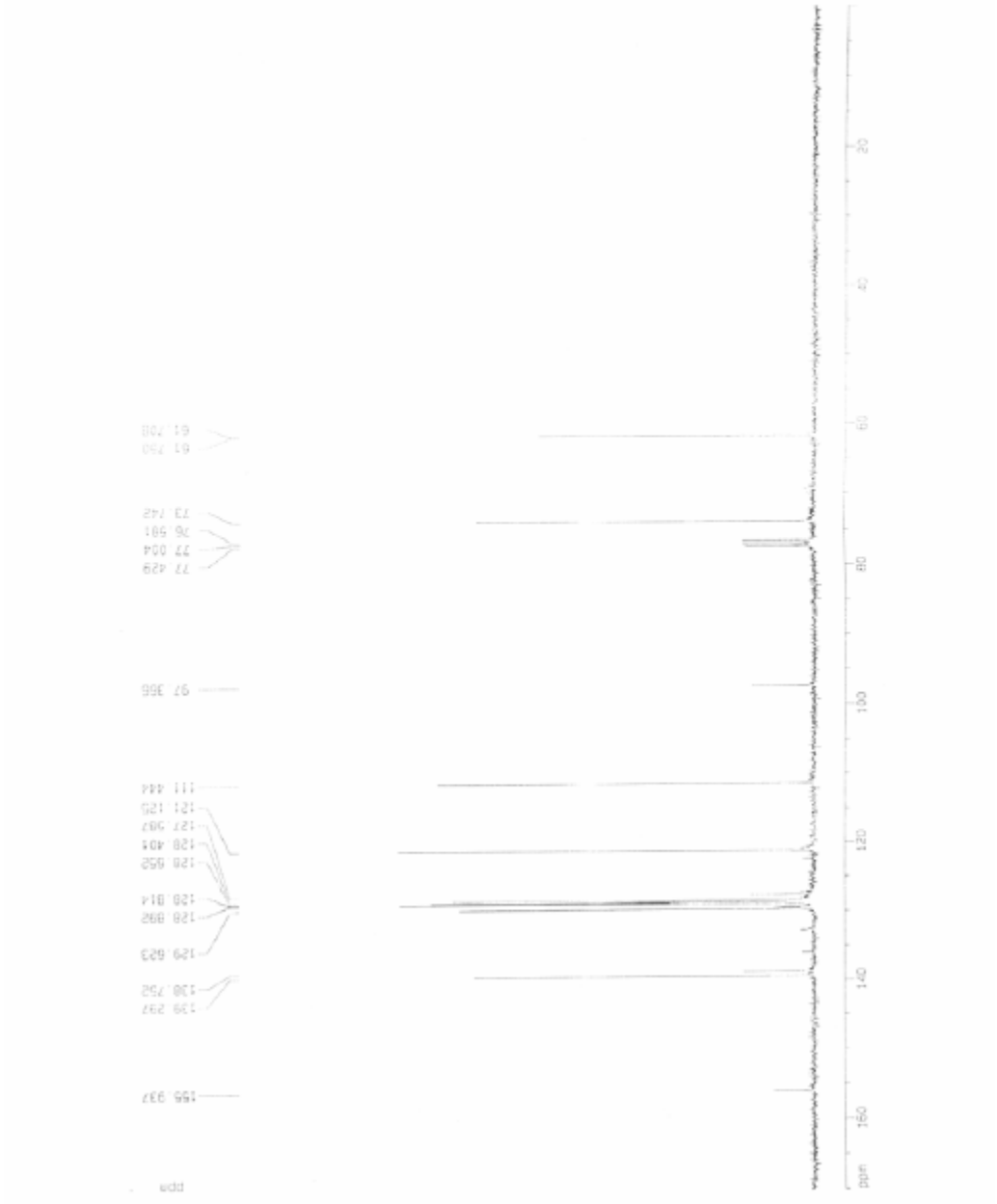


^{13}C NMR of 1a: $CDCl_3$ and 150 MHz

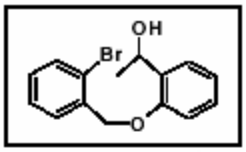


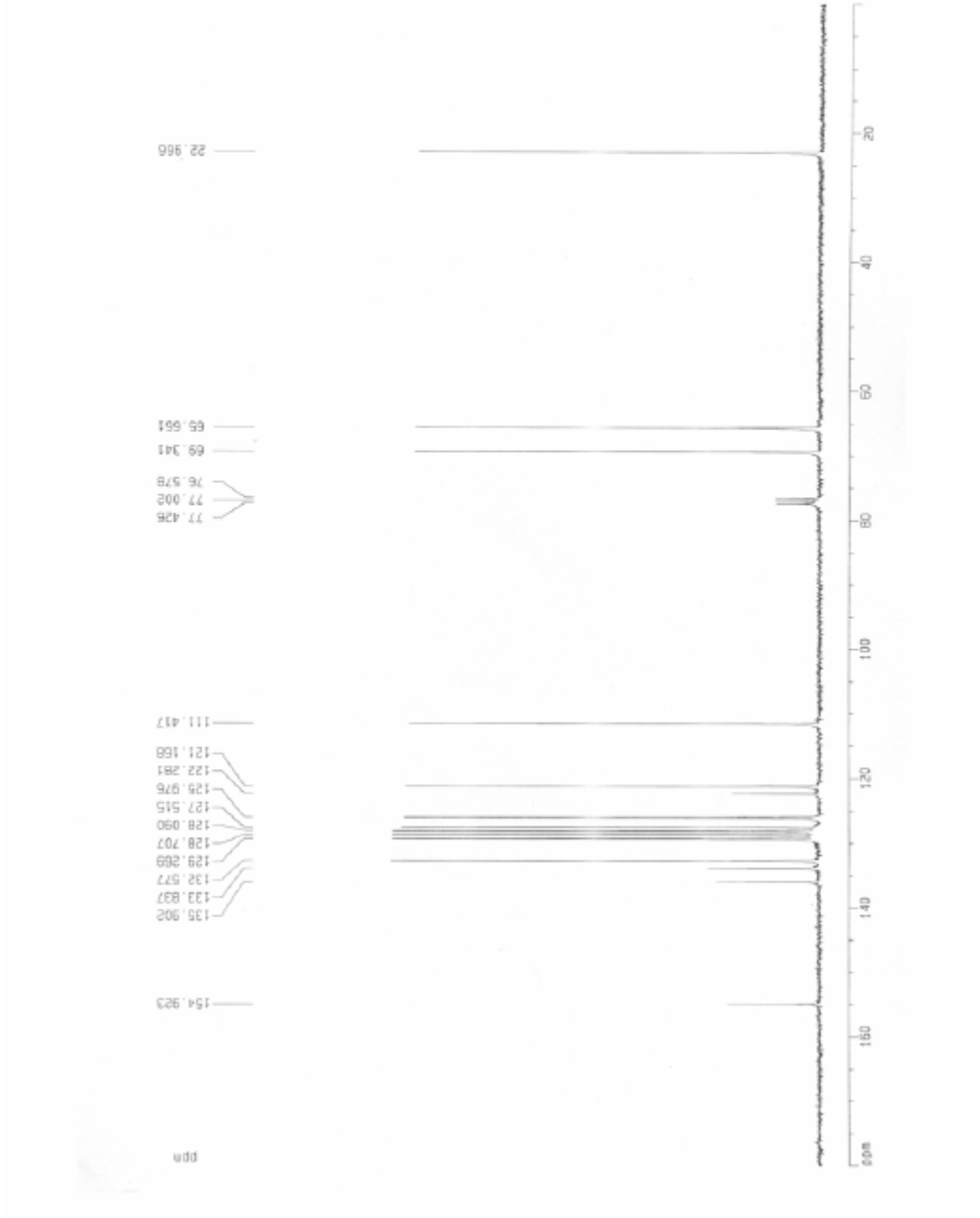
^{13}C NMR of 1b: $CDCl_3$ and 75 MHz



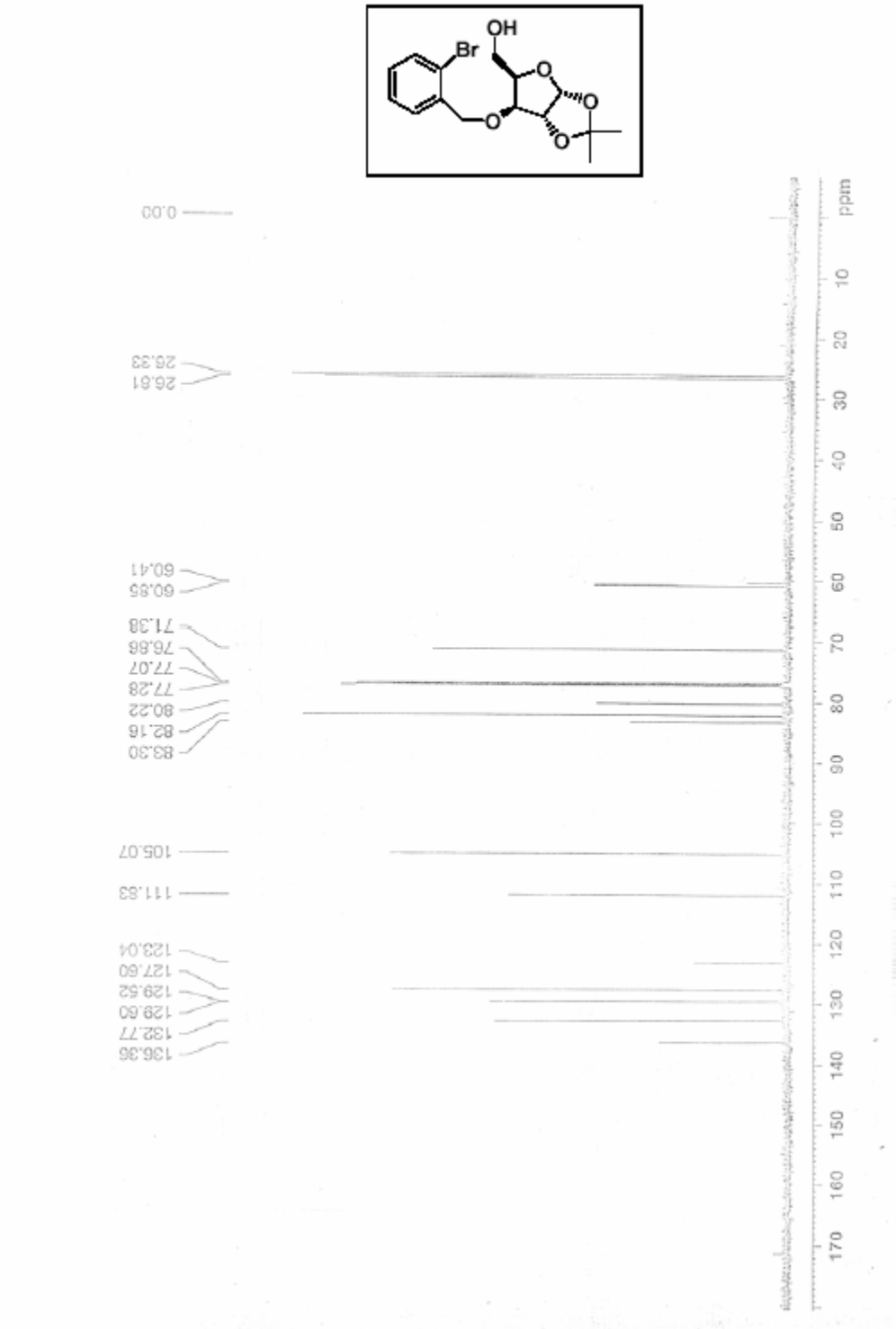


^{13}C NMR of 1c: $CDCl_3$ and 150 MHz

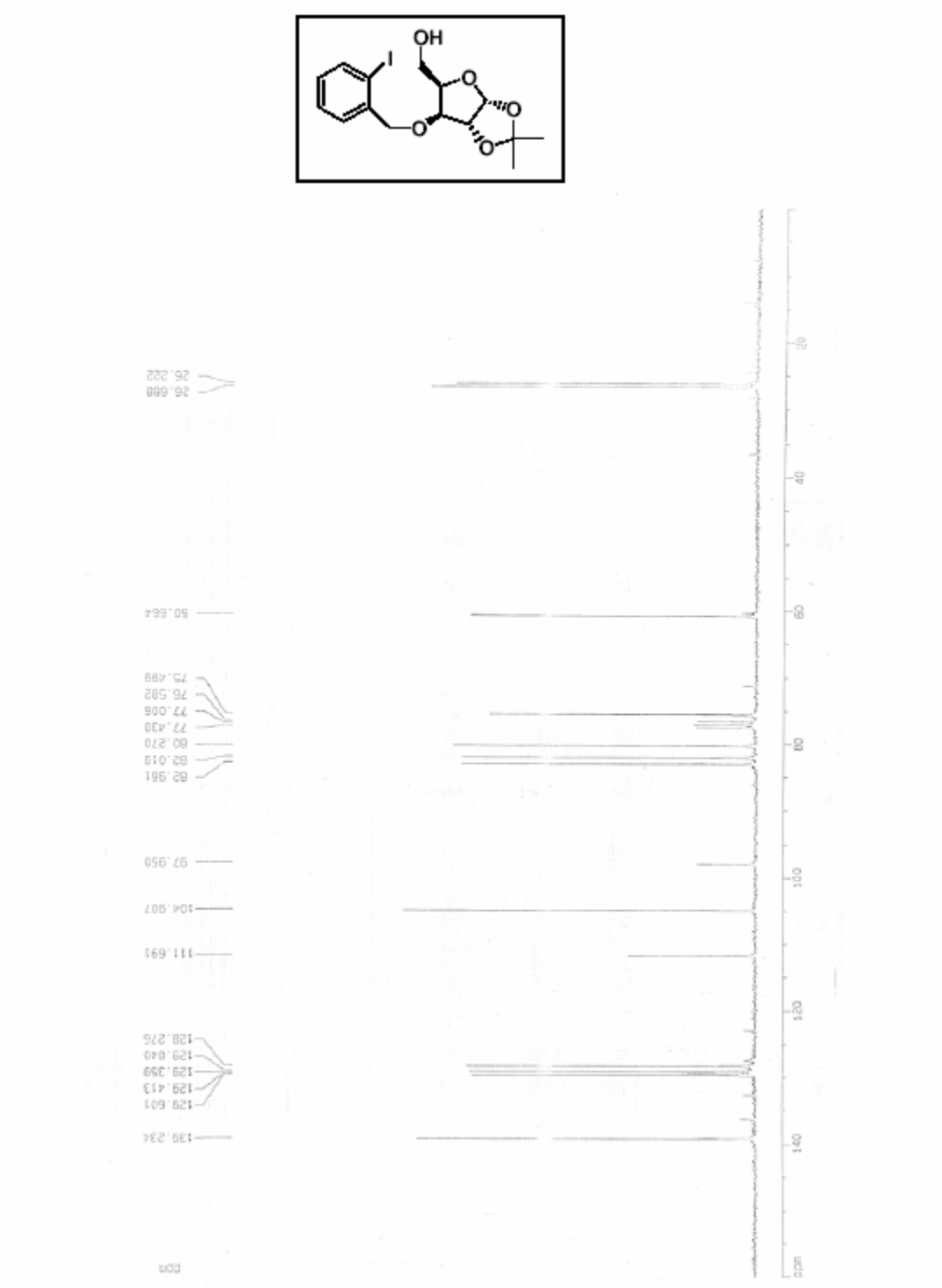




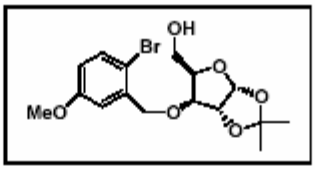
^{13}C NMR of 4a: $CDCl_3$ and 150 MHz

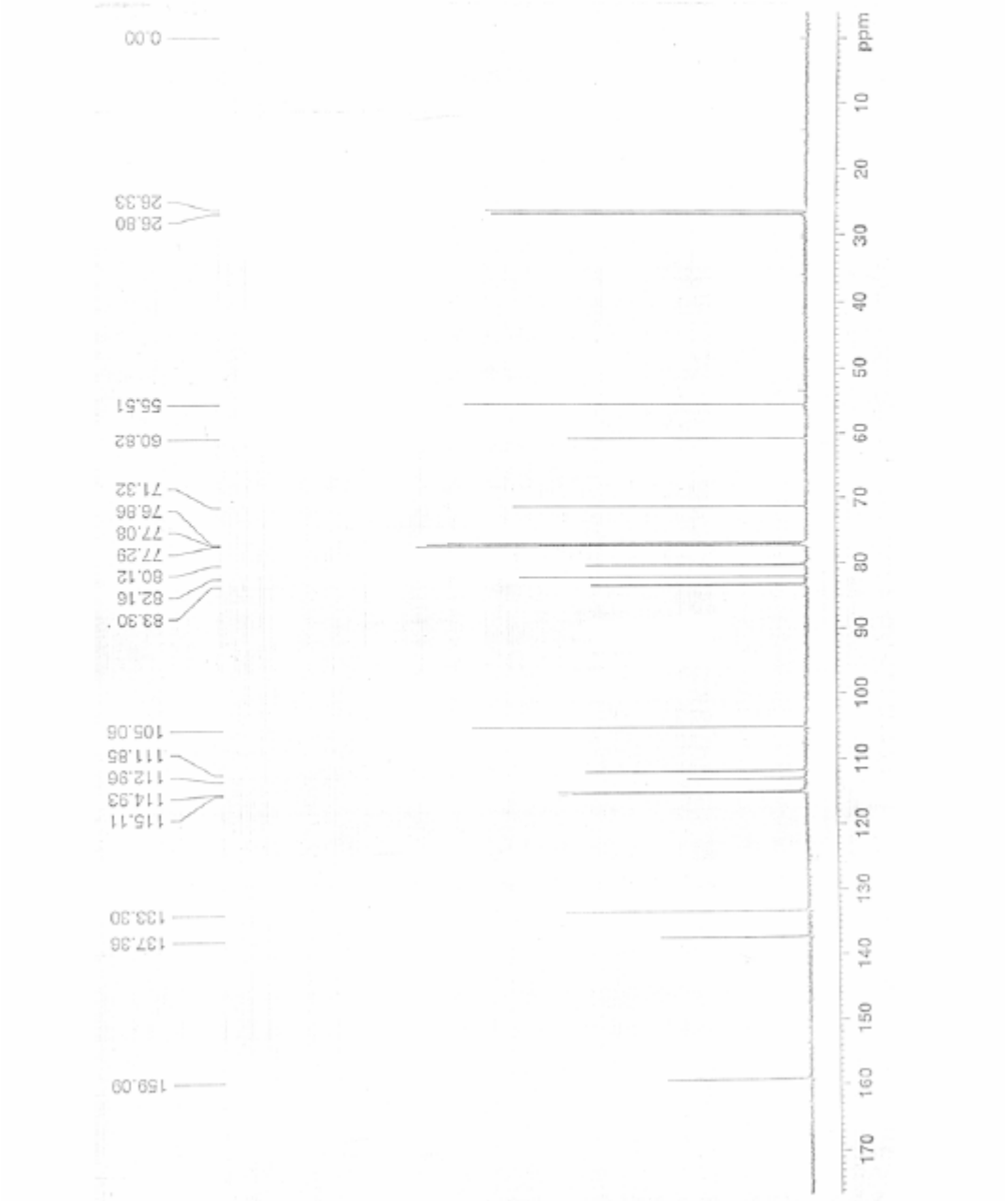


^{13}C NMR of 4b: $CDCl_3$ and 75 MHz

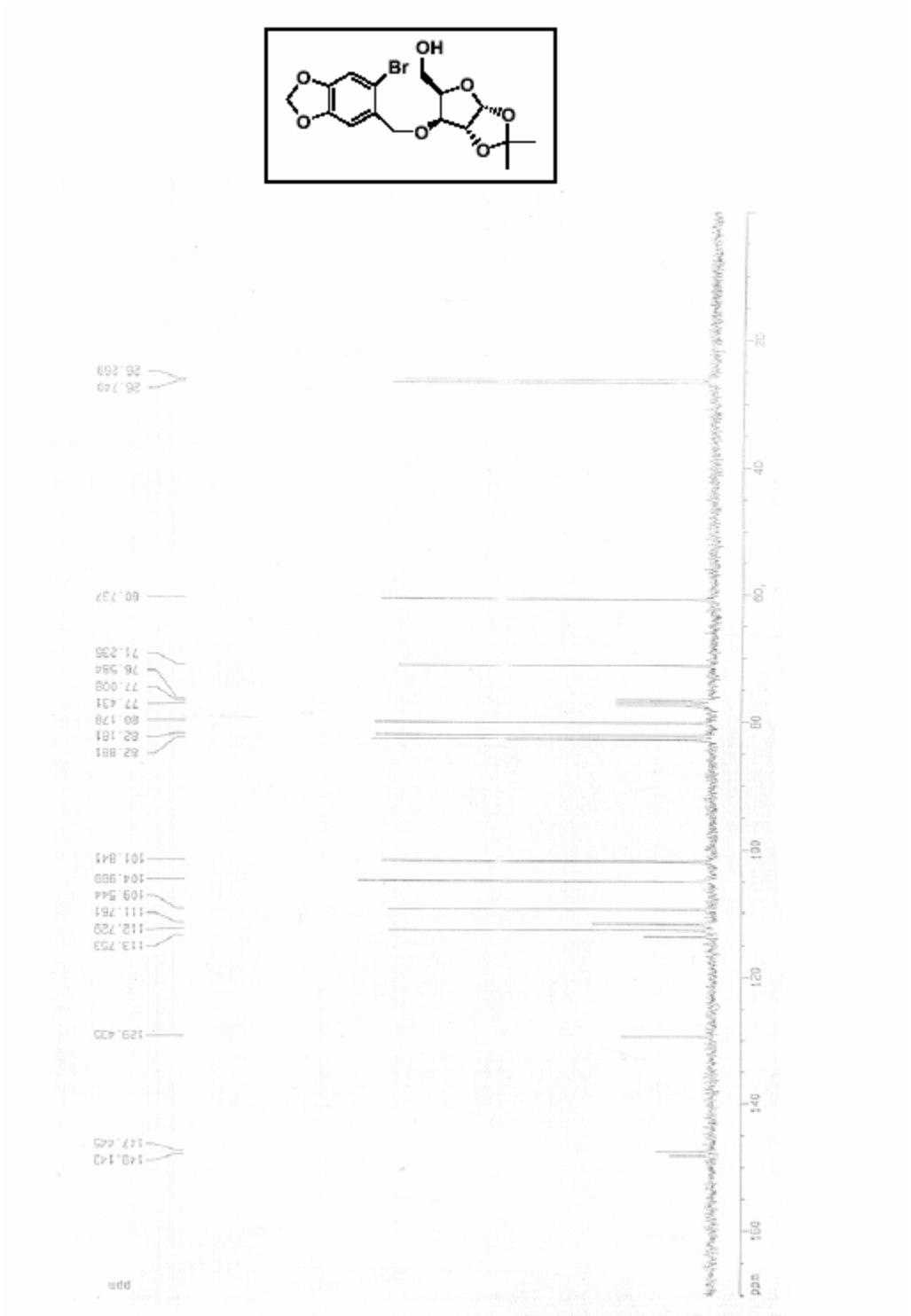


^{13}C NMR of 4c: $CDCl_3$ and 150 MHz

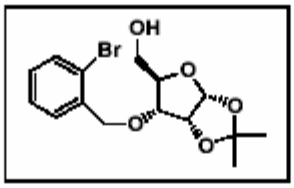


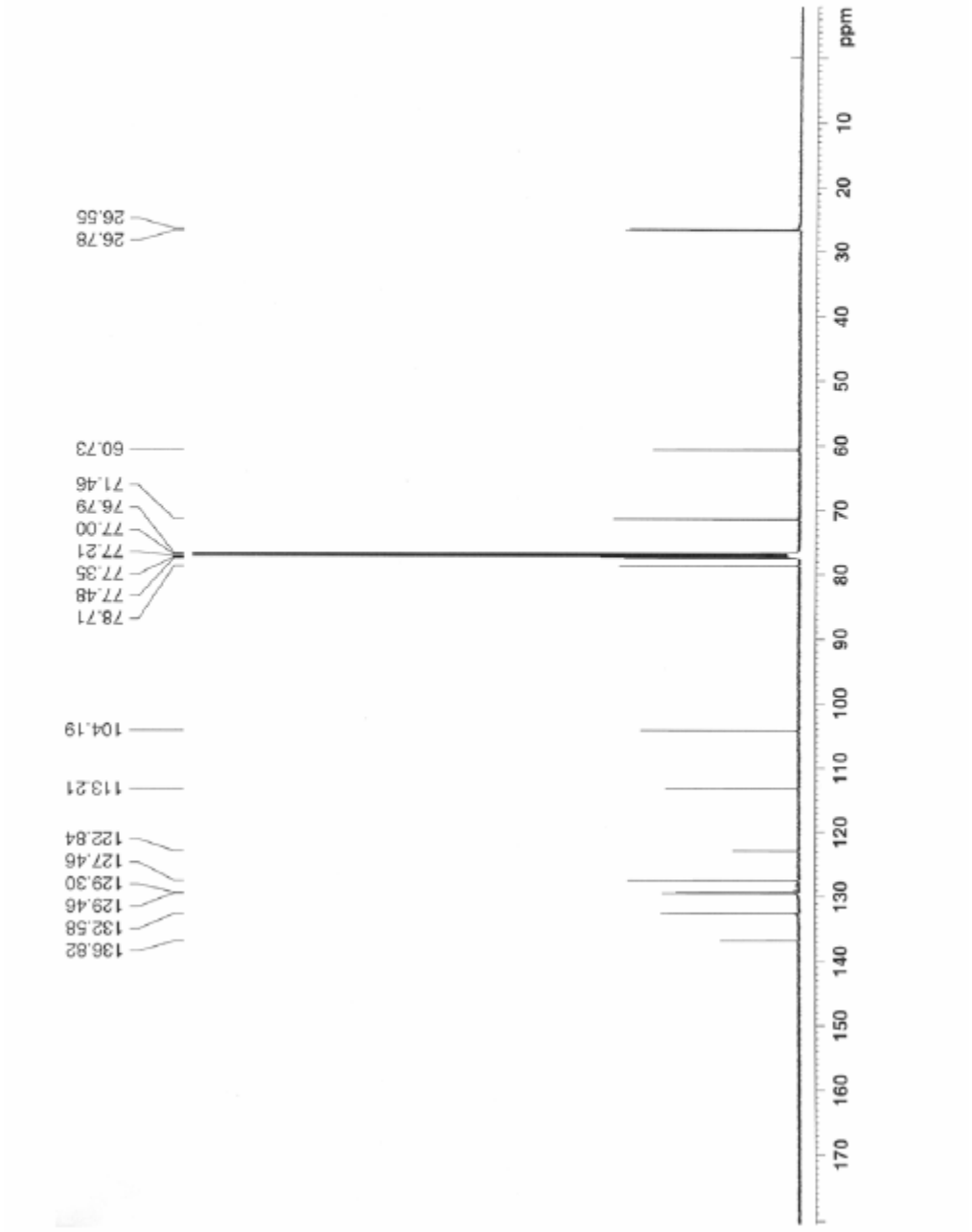


^{13}C NMR of 4d: $CDCl_3$ and 75 MHz

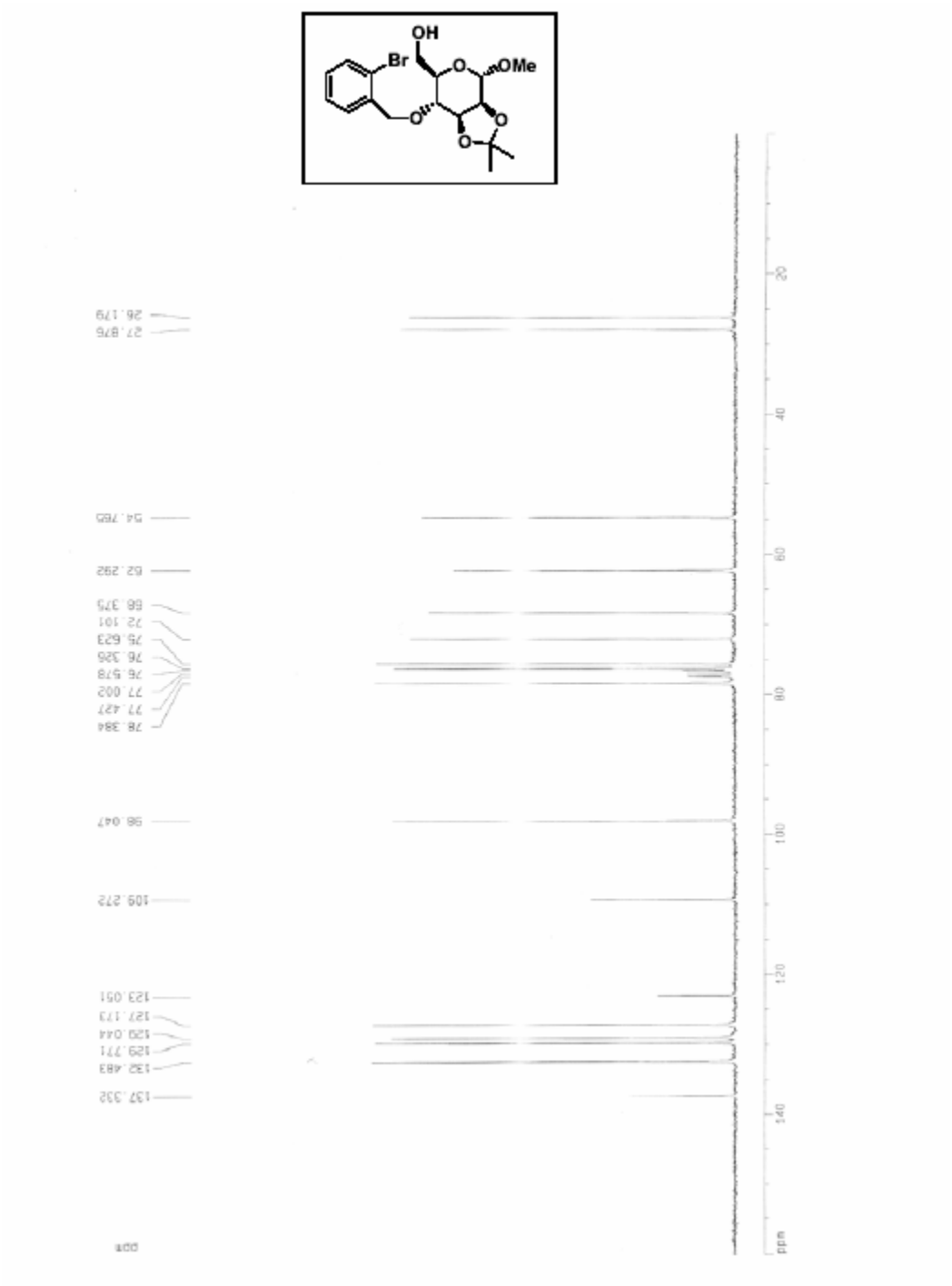


^{13}C NMR of 4e: $CDCl_3$ and 150 MHz

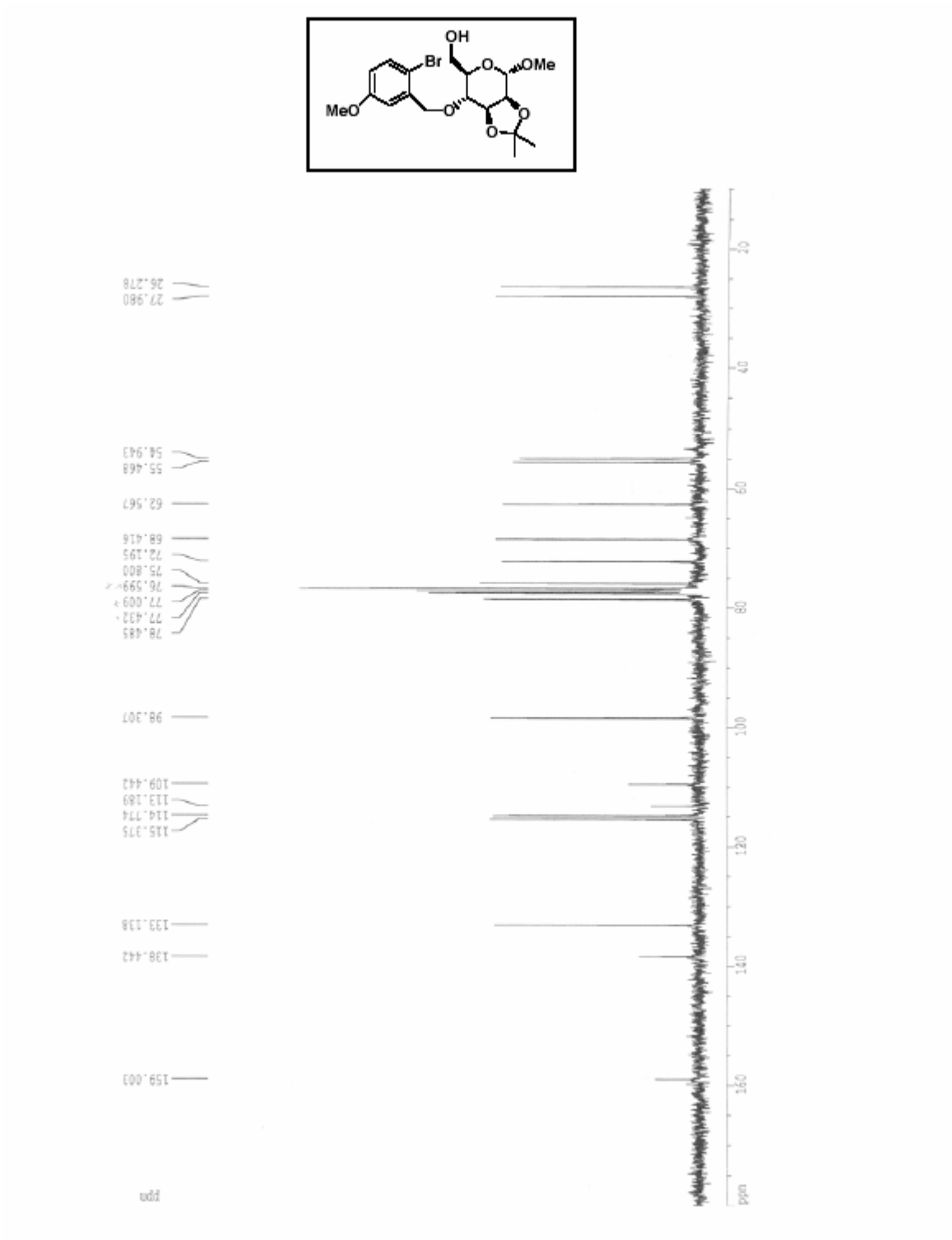




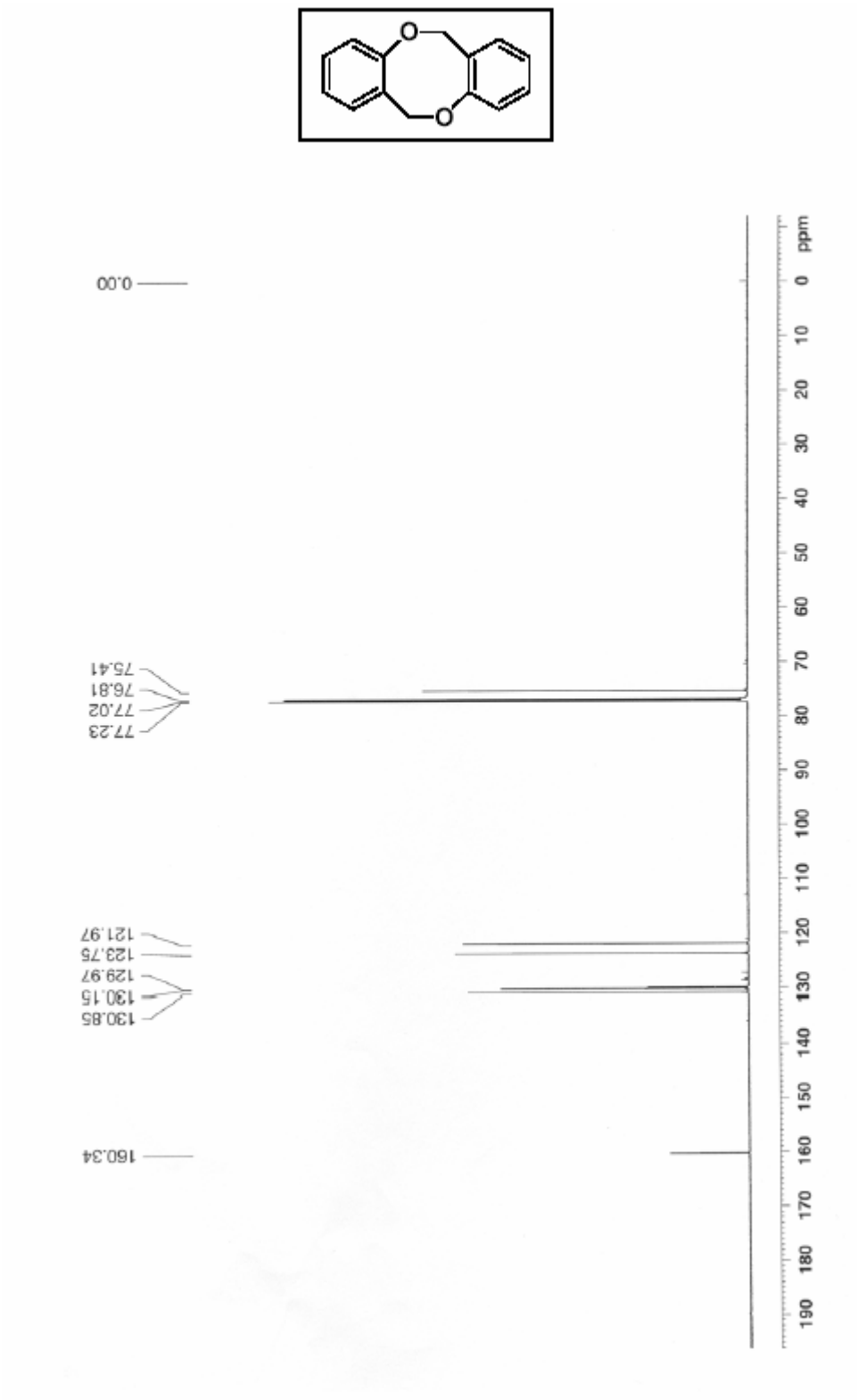
^{13}C NMR of 6a: $CDCl_3$ and 75 MHz



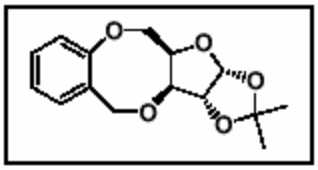
^{13}C NMR of 6b: $CDCl_3$ and 75 MHz

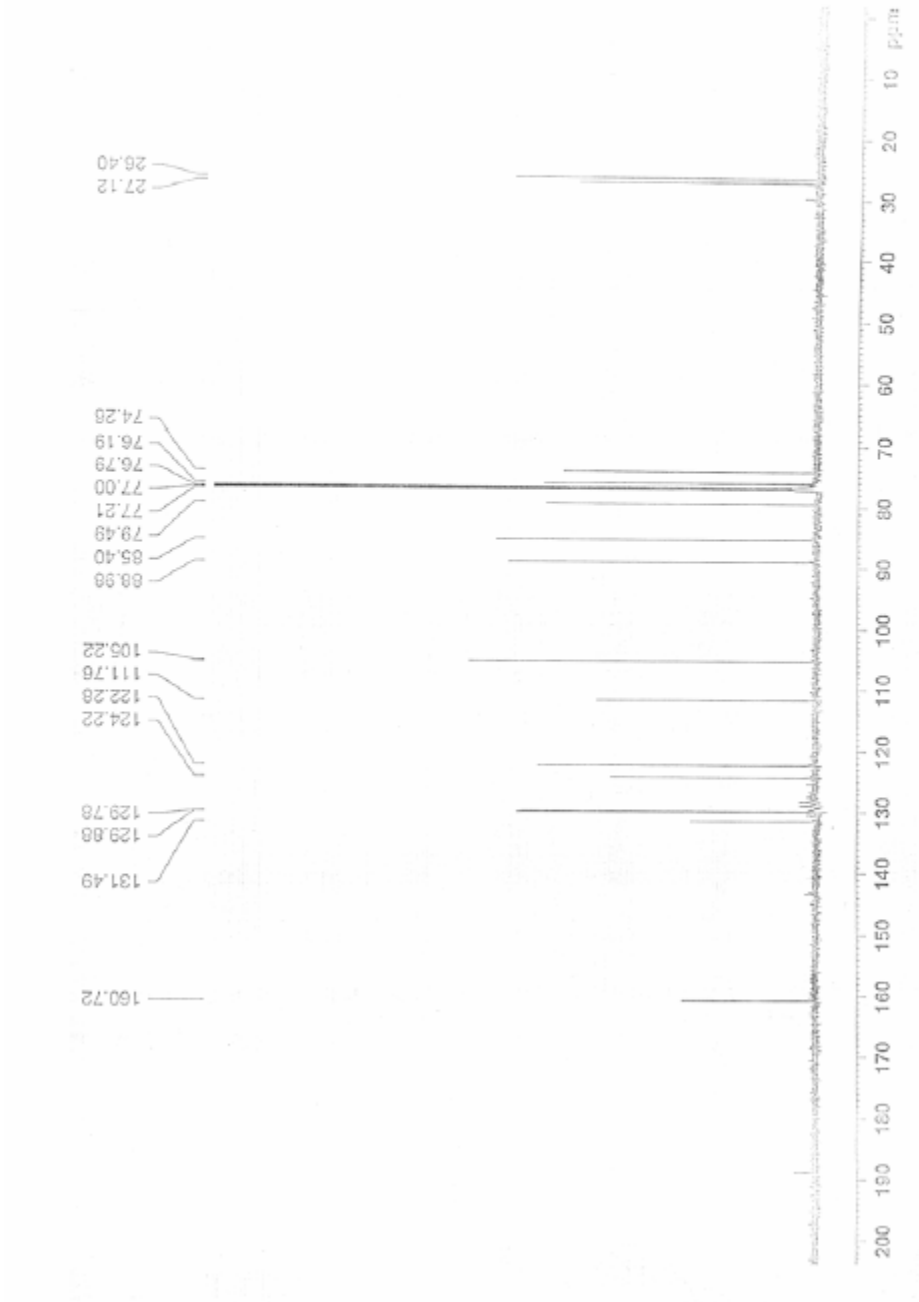


^{13}C NMR of 2: $CDCl_3$ and 150 MHz

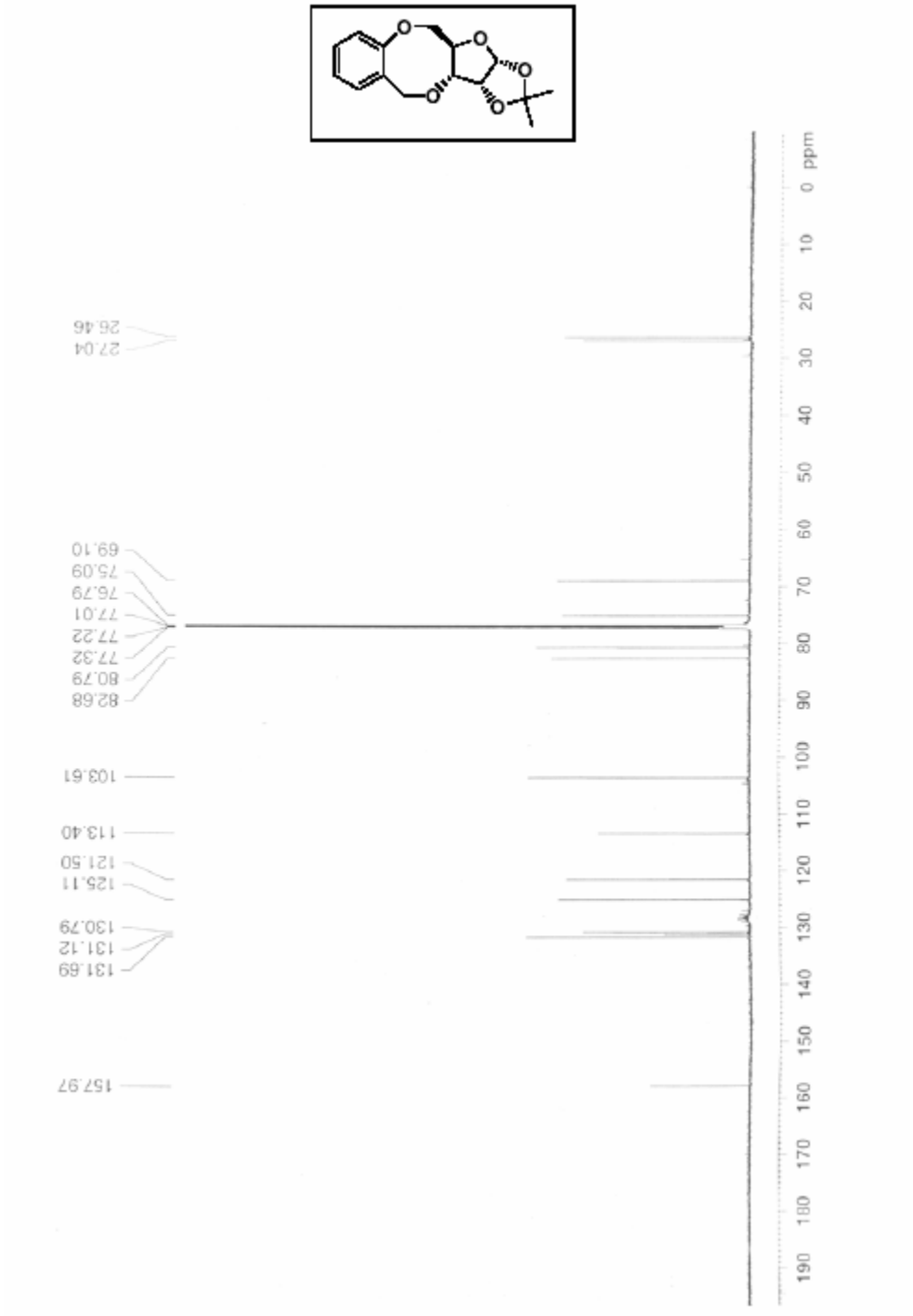


^{13}C NMR of 5a: $CDCl_3$ and 150 MHz

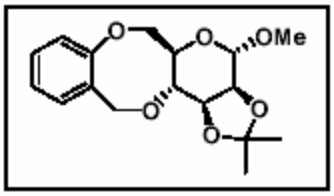


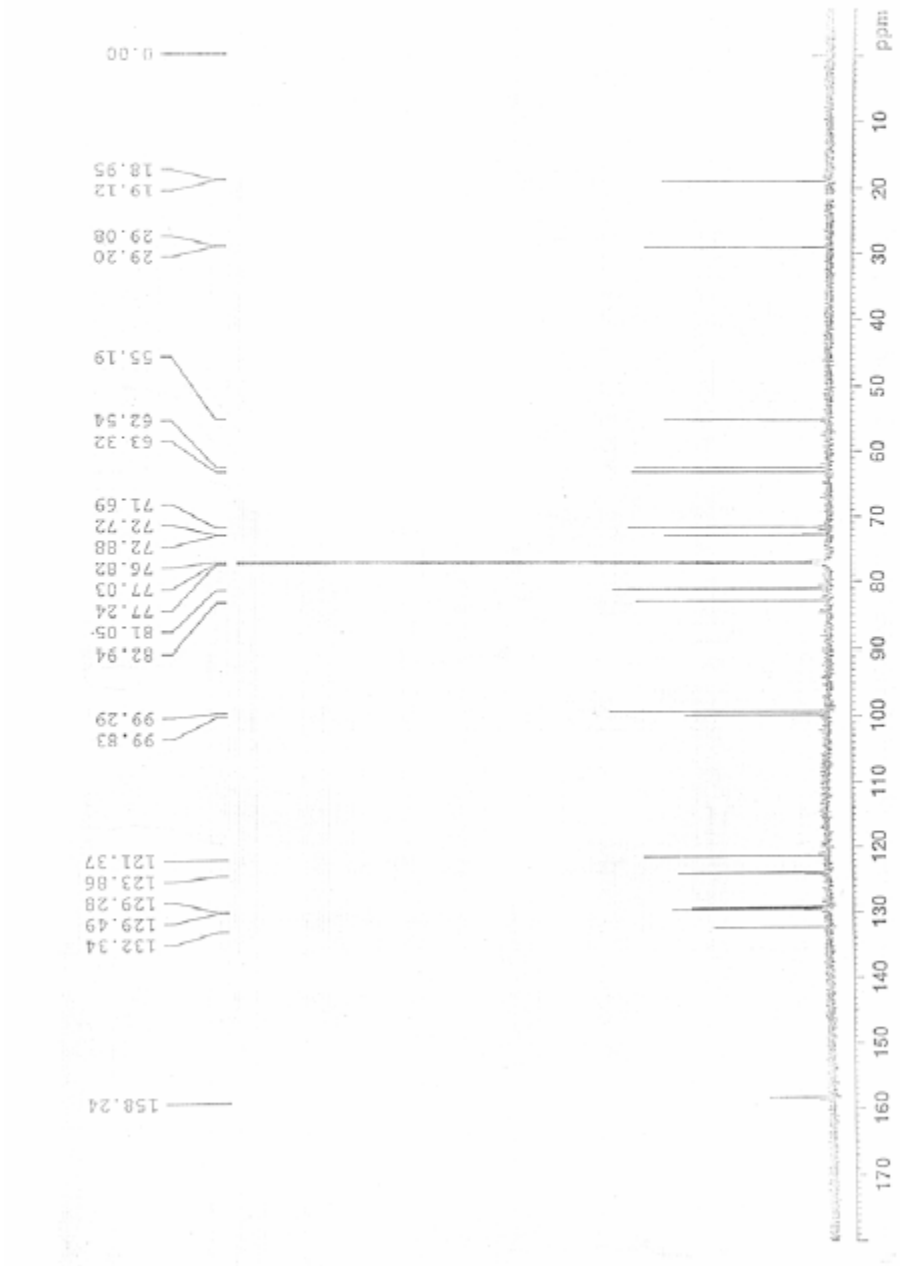


^{13}C NMR of 5b: $CDCl_3$ and 150 MHz

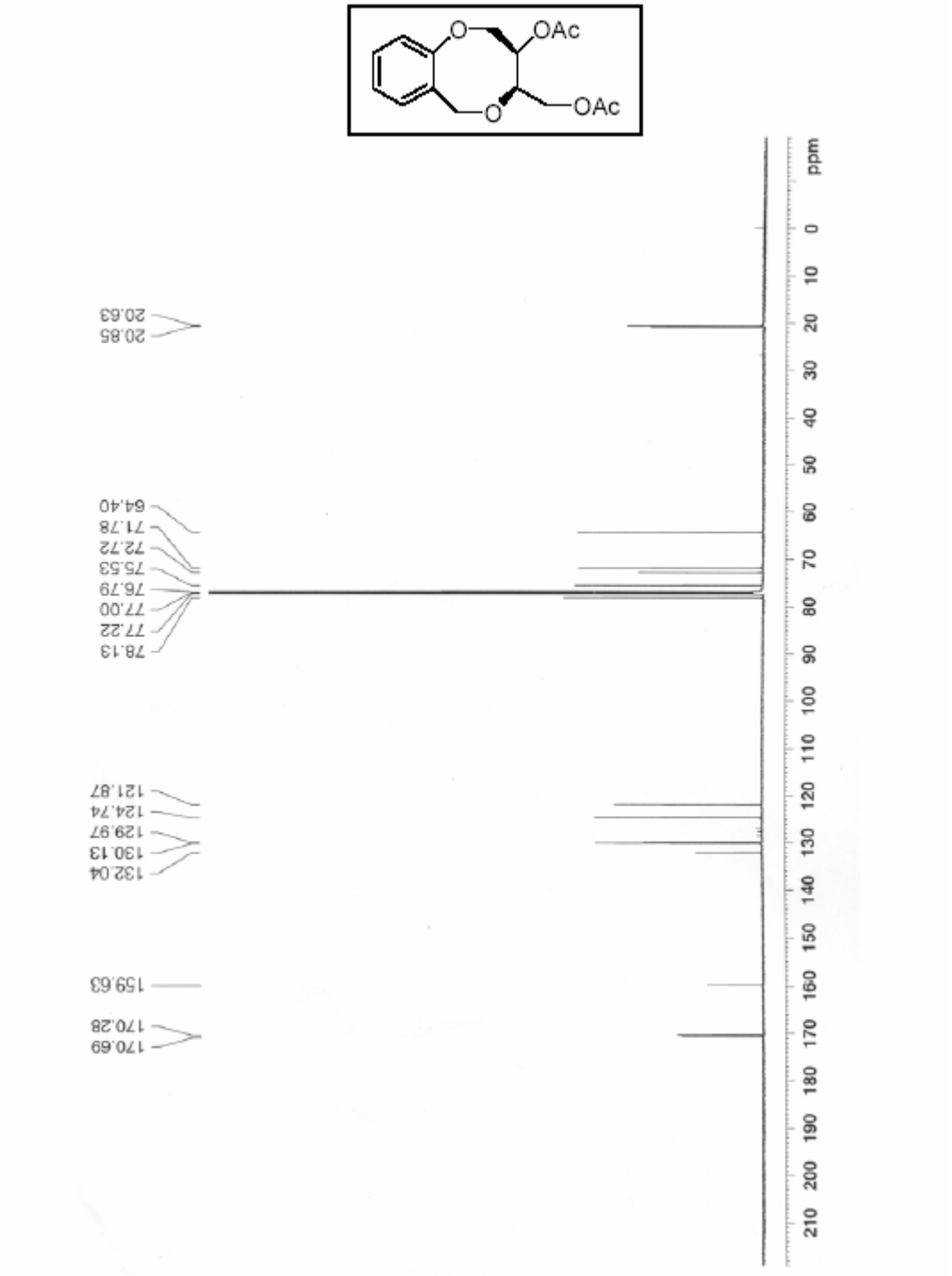


^{13}C NMR of 7: $CDCl_3$ and 150 MHz

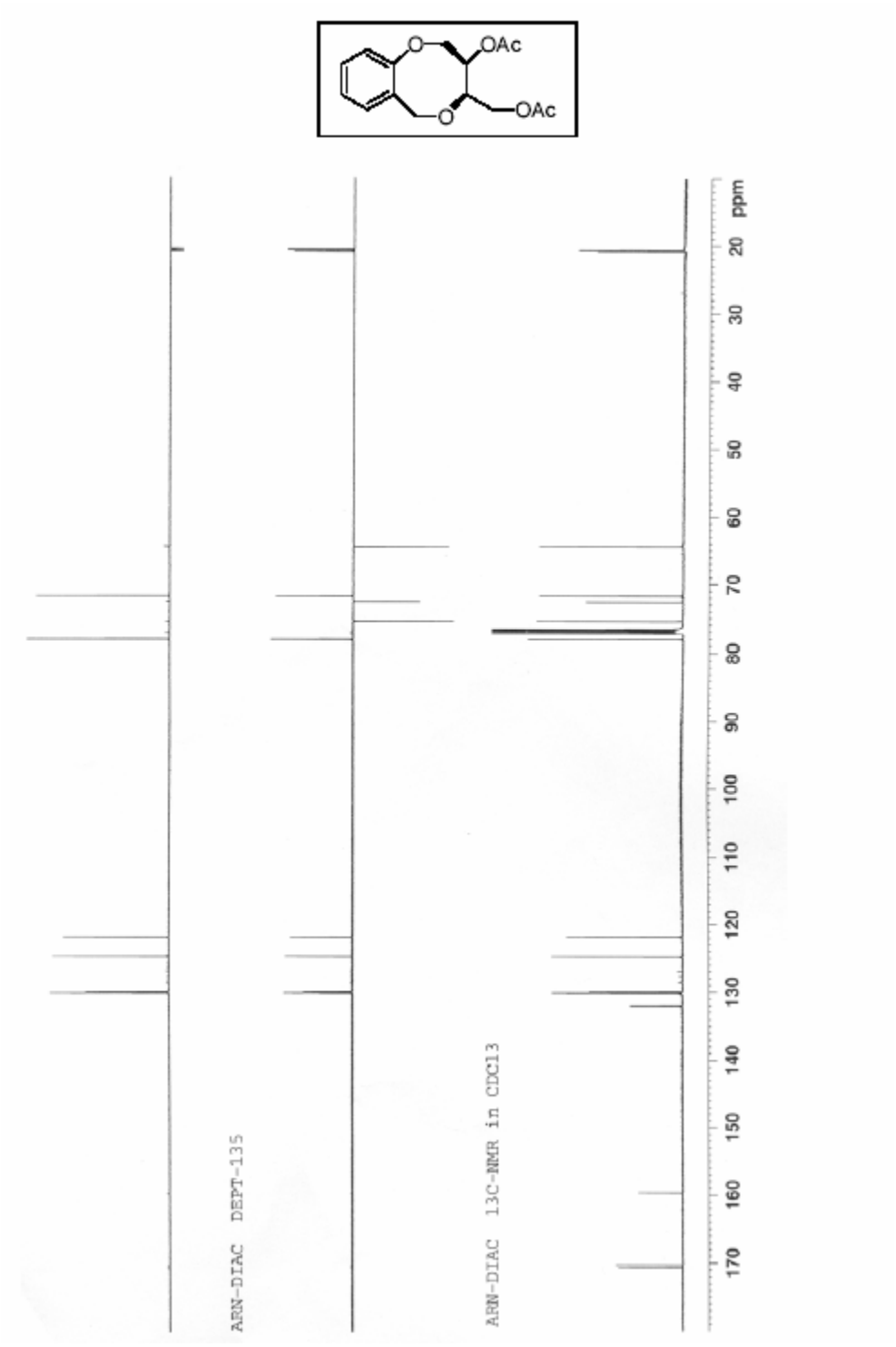




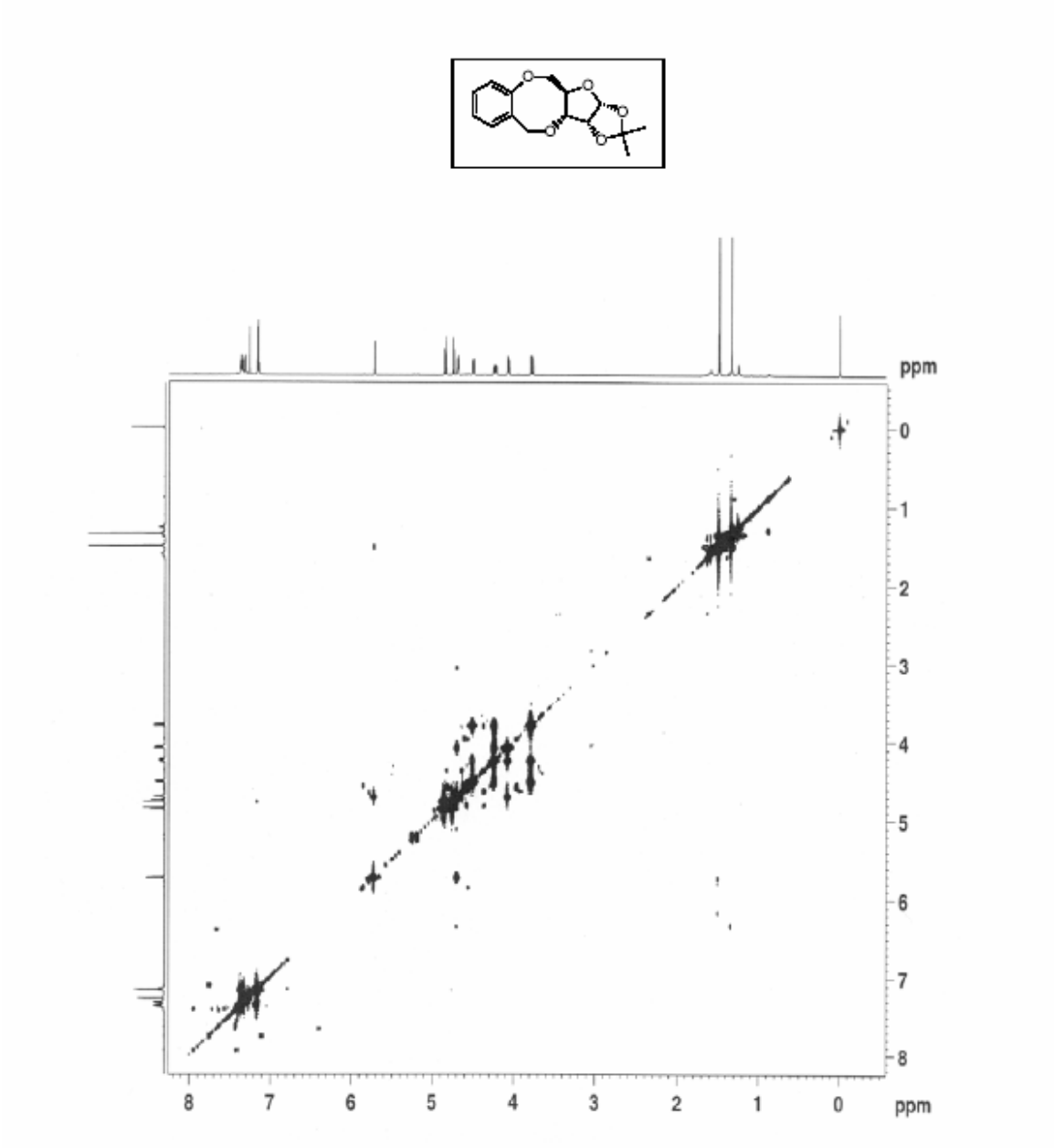
^{13}C NMR of 8: $CDCl_3$ and 150 MHz



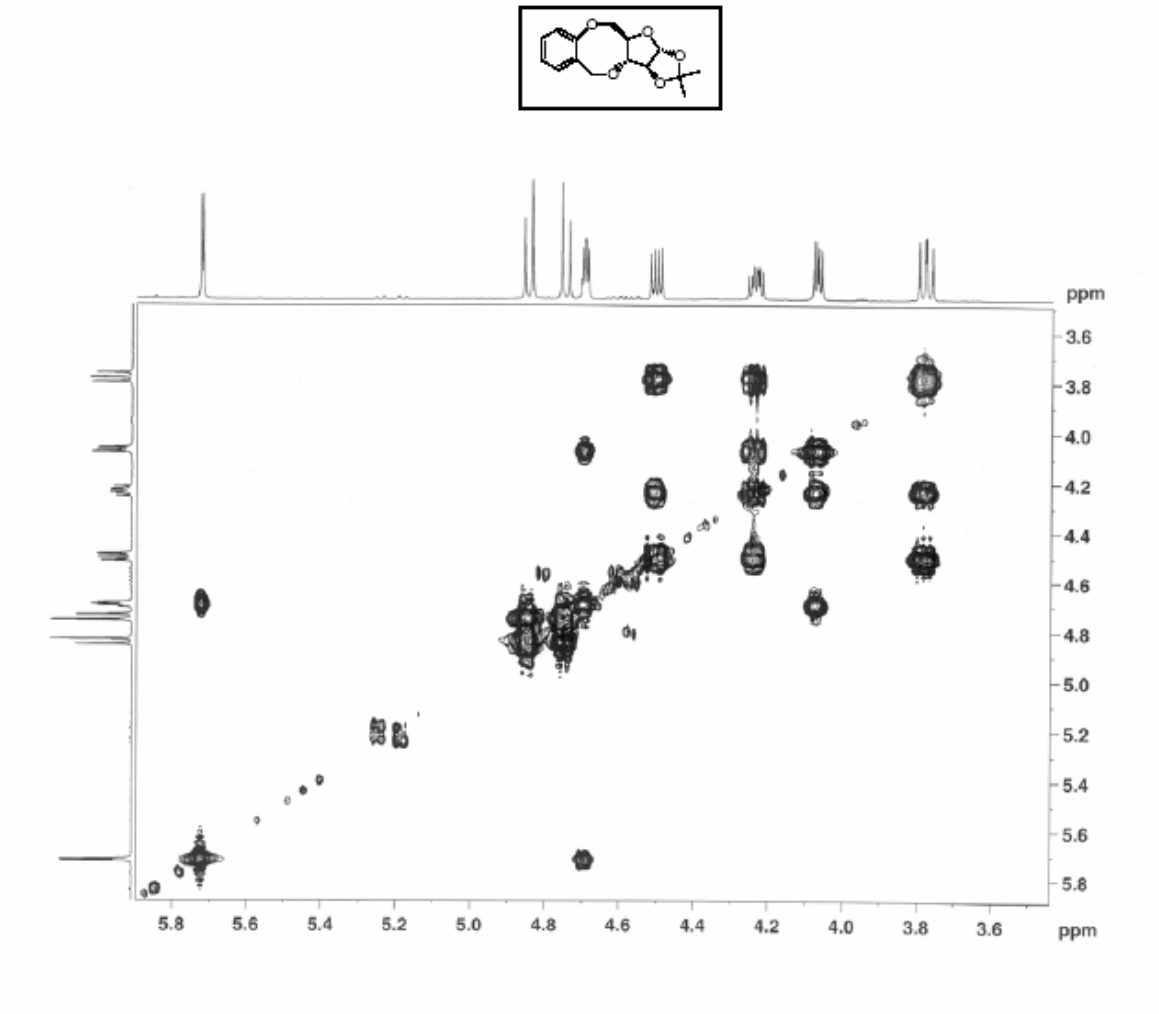
^{13}C NMR of 8: **DEPT** *Spectra $CDCl_3$ and 150 MHz*



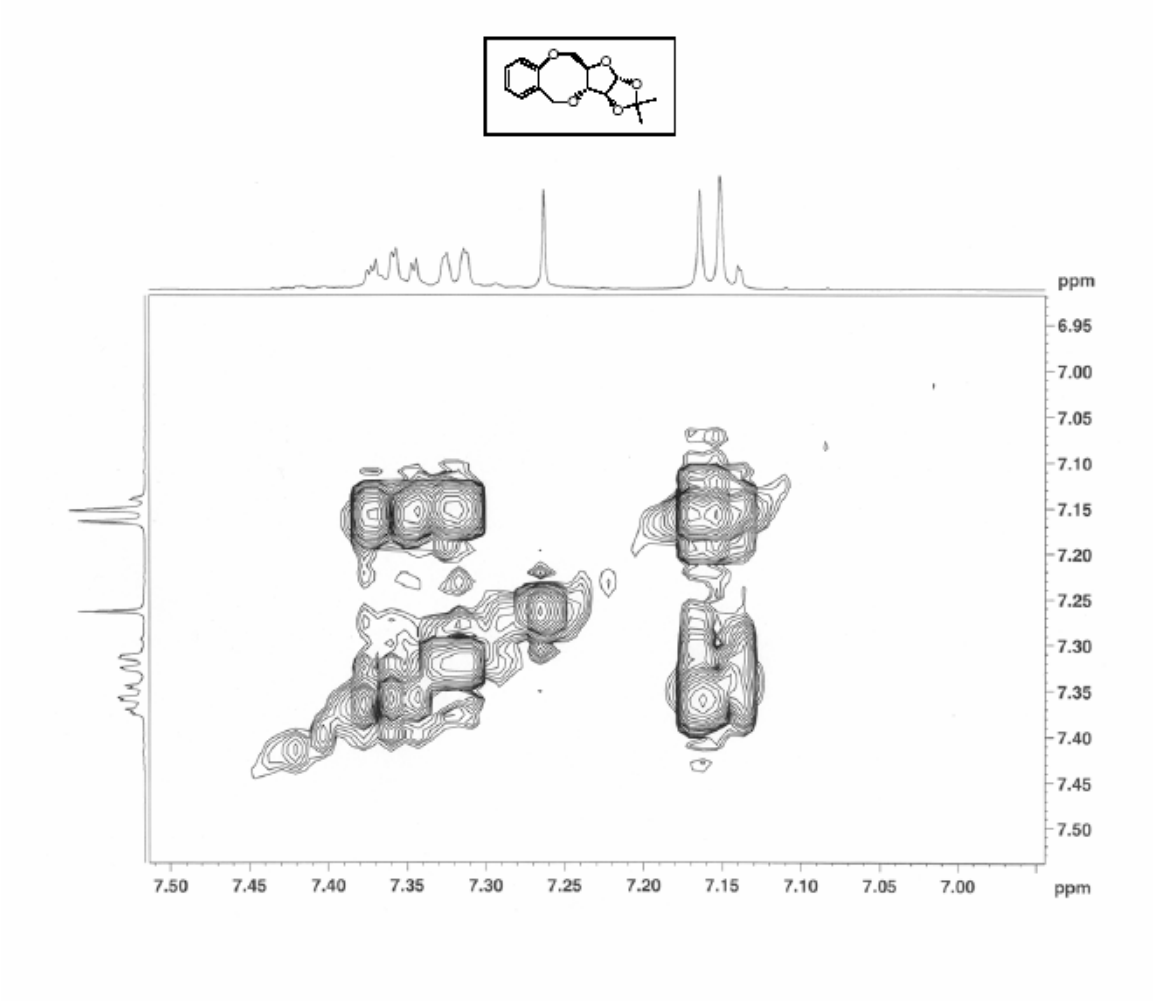
^{1}H-^{1}H COSY Spectra of 5b: $CDCl_3$ and 600 MHz



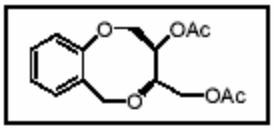
^{1}H-^{1}H COSY Spectra of 5b: Expansion $CDCl_3$ and 600 MHz

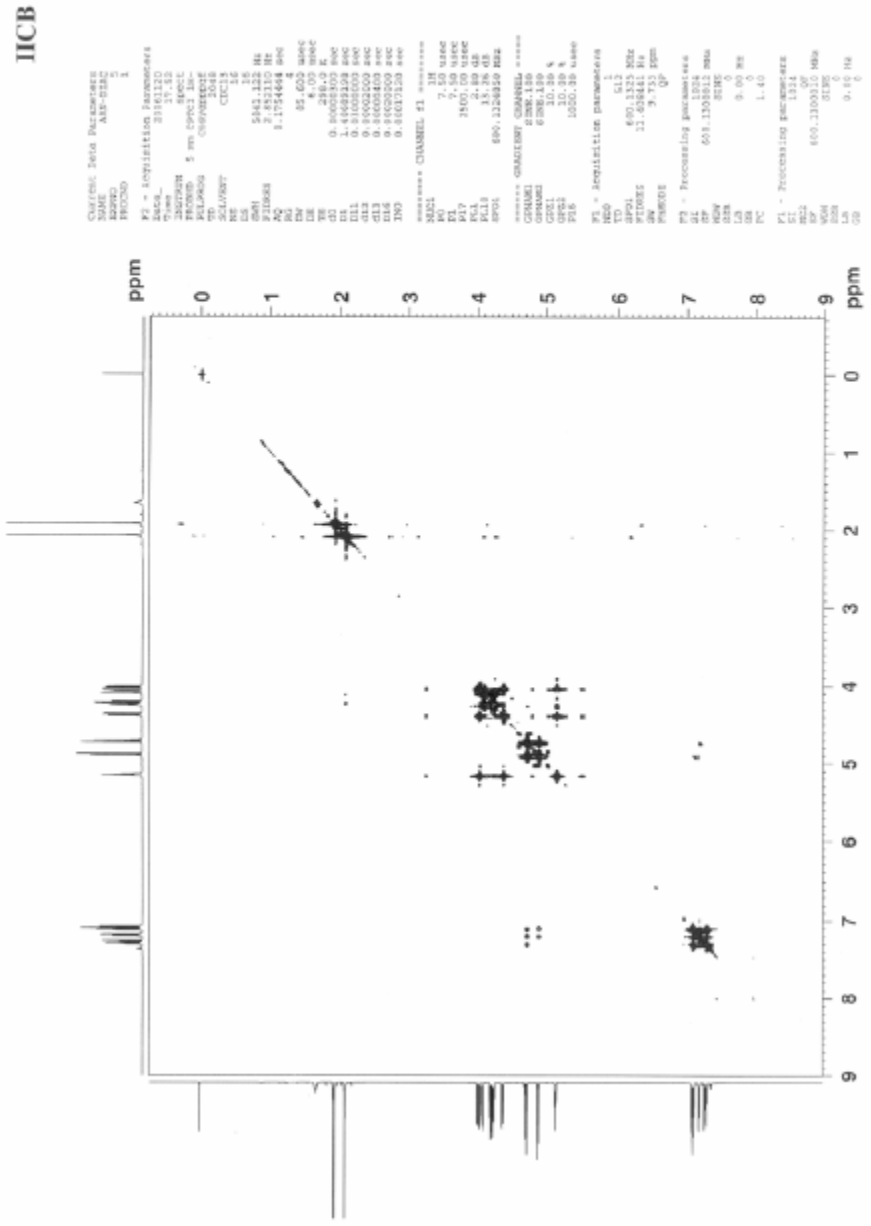


^{1}H-^{1}H COSY Spectra of 5b:Expansion $CDCl_3$ and 600 MHz

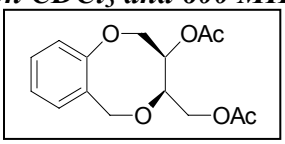


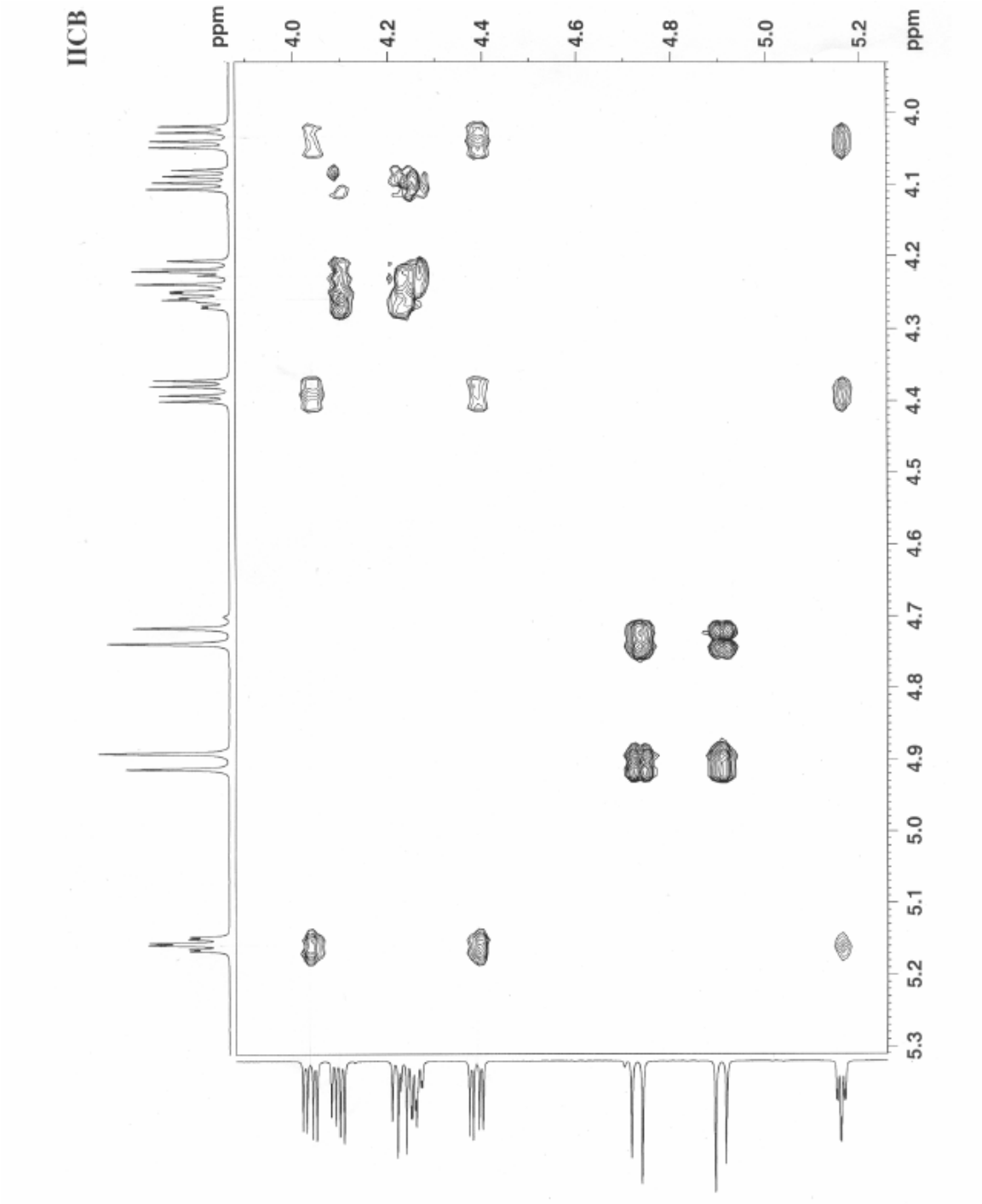
^{1}H-^{1}H COSY Spectra of 8: $CDCl_3$ and 600 MHz





^{1}H-^{1}H COSY Spectra of 8: Expansion $CDCl_3$ and 600 MHz





^{1}H-^{1}H COSY Spectra of 8: Expansion $CDCl_3$ and 300 MHz