Supporting Information For:

C-Glycosides to Fused Polycyclic Ethers. An Efficient Entry into the A-D Ring System of Gambierol

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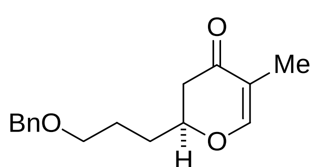
Experimental protocols and spectroscopic data for all new compounds.

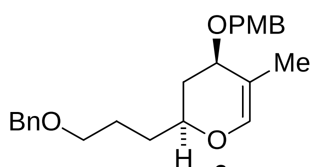
General Information

Ether and THF were distilled from sodium/benzophenone. Benzene, toluene, CH_2Cl_2, CH_3OH, and *i*-Pr_2NEt were distilled from CaH_2. All other reagents were used without purification. Unless otherwise stated, all reactions were run under an atmosphere of argon in flame-dried glassware. NMR spectra were recorded on a Bruker EM-500 or EM-600 spectrophotometer. Chemical shifts were reported in δ, parts per million (ppm), relative to chloroform (δ = 7.24 ppm) or benzene (δ = 7.15 ppm) as an internal standard. Coupling constants, *J*, were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Arizona on a Jeol HX-110A and are reported as % relative intensity to the molecular base peak. IR spectra were recorded on a Nicolet Impact 410.



4

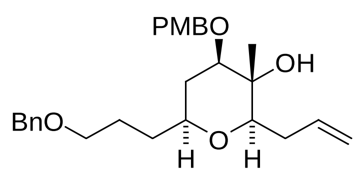
Preparation of (+)-pyrone 4. To a solution of aldehyde **2** (4.81 g, 27 mmol), Cr (III) catalyst **5** (0.399 g, 0.81 mmol), 4Å MS (5.4 g) and acetone (5.4 mL) at rt was added diene **3** (7.55 g, 40.5 mmol). After 52 hours the reaction was diluted with CH_2Cl_2 (30 mL) and cooled to 0°C. Trifluoroacetic acid (3.12 mL, 40.5 mmol) was added and the reaction mixture was stirred for 1 h and filtered. The mother liquor was neutralized with $NaHCO_3$ (sat., 100 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 X 50 ml). The extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexanes/ethyl acetate) afforded 6.34 g (90% yield, 94% ee) of pyrone **4** as a colorless oil. The enantiomeric excess was determined by HPLC (chiracel OD). Conditions: 10% 2-propanol in hexanes, flow rate = 0.5 mL/min; the t_R major isomer = 24.0 min; t_R minor isomer = 34.7 min. $[\alpha]^{27}_D$= +90.16° (c = 0.70, THF); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5 H), 7.24 (s, 1 H), 4.52 (s, 2 H), 4.37 (dddd, *J* = 16.9, 12.1, 7.9, 4.2 Hz, 1 H), 3.54 (ddd, *J* = 15.1, 9.3, 5.9 Hz, 1 H), 3.52 (ddd, *J* = 14.8, 9.4, 5.6 Hz, 1 H), 2.51 (dd *J* = 16.7, 13.2 Hz, 1 H), 2.45 (dd, *J* = 16.7, 4.2 Hz, 1 H), 1.91-1.71 (m, 4 H), 1.68 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 159.6, 138.3, 128.4, 127.6, 113.6, 79.1, 72.9, 69.5, 41.6, 31.3, 25.1, 10.4; IR (neat) 1679, 1107 cm^{-1}; HRMS calcd for $C_{16}H_{21}O_3$ (MH^+) 261.1491, found 261.1494.



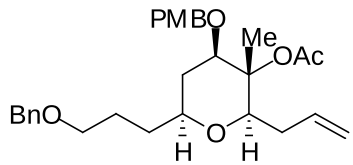
6

Preparation of (+)-PMB ether 6. $CeCl_3 \cdot 7H_2O$ (0.880 g, 2.69 mmol) was added to a solution of **4** (0.50 g, 1.92 mmol) and ethanol (43 mL) at rt. After 0.33 h, the reaction mixture was cooled to –60°C and a solution of $NaBH_4$ (0.172 g, 4.61 mmol) and ethanol (9.5 ml) was added drop wise. The reaction mixture was allowed to warm to rt over 2 h and concentrated. The resulting residue was taken up in H_2O (20 mL) and ether (20 mL). After separation the aqueous phase was extracted with ether (5 X 20 mL), dried (Na_2SO_4), and concentrated to give a yellow oil.

The oil from the reduction was taken up in DMF (9.6 mL) and cooled to 0°C. NaH (0.92 g, 3.84 mmol) was added and the reaction mixture was stirred at 0°C for 0.5 h. 4-Methoxy benzyl chloride (0.52 mL, 3.84 mmol) was added dropwise and the resulting mixture was warmed to rt and stirred for 4 hrs. After cooling to 0°C, the reaction mixture was quenched with NH_4Cl (sat., 15 mL) and extracted with CH_2Cl_2 (3 X 20 mL). The extracts were washed with water (30 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (20:1 hexanes/ethyl acetate) afforded 730 mg (97%) of **6** as a colorless oil. $[\alpha]^{25}_{D}$= +31.70° (c = 2.41, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.36 (m, 4H), 7.33-7.30 (m, 3H), 6.94-6.90 (m, 2H), 6.23 (br s, 1H), 4.58 (d, *J* = 11.4 Hz, 1 H), 4.54 (s, 2H), 4.45 (d, *J* = 11.4 Hz, 1 H), 4.08 (dd, *J* = 7.6, 7.6 Hz, 1H), 3.91-3.86 (m, 1H), 3.83 (s, 3H), 3.54 (ddd, *J* = 15.0, 9.2, 5.8 Hz, 1H), 3.52 (ddd, *J* = 15.2, 9.3, 6.1 Hz, 1H), 2.18 (ddd, *J* = 13.1, 6.5, 2.0 Hz, 1H), 1.82-1.65 (m, 5H), 1.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 140.9, 138.6, 130.9, 129.4, 129.1, 128.3, 127.6, 127.5, 113.7, 110.3, 74.3, 72.8, 72.0, 70.0, 69.8, 55.2, 34.0, 31.6, 25.6, 14.3; IR (neat) 1678, 1103 cm^{-1}; HRMS calcd for $C_{24}H_{31}O_4$ (MH^+) 383.2229, found 383.2222.

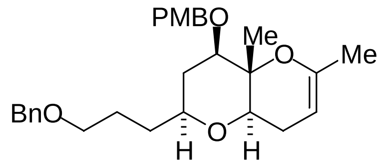


Preparation of (-)-alcohol. To a solution of **6** (0.541 g, 1.79 mmol) and CH_2Cl_2 (28 mL) at –60°C was added dimethyl dioxirane (26.8 mL of a 0.1 M solution in acetone, 2.68 mmol) dropwise. The reaction was warmed slowly to rt and then concentrated. The resulting residue was taken up in THF (28 mL) and cooled to 0°C. Propenylmagnesium chloride (4.5 mL of a 2.0 M solution in THF, 8.94 mmol) was added and the reaction mixture was allowed to warm to rt at which point it was quenched with NH_4Cl (sat., 15 mL). The aqueous phase was extracted with ether (3 X 20 mL), the extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexanes/ethyl acetate) afforded 419 mg (65%) of the alcohol as a colorless oil. $[\alpha]^{24}_{D}$= -6.54° (c = 0.33, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.36 (m, 3 H), 7.35-7.27 (m, 4H), 6.90 (d, *J* = 8.6 Hz, 2 H), 5.95-5.85 (m, 1 H), 5.10 (dd, *J* = 17.2, 1.2 Hz, 1 H), 5.03 (dd, *J*= 10.2, 0.7 Hz, 1 H) 4.65 (d, *J* = 11.5 Hz, 1 H), 4.52 (s, 2 H), 4.45 (d, *J* = 11.5 Hz, 1 H), 3.83 (s, 3 H), 3.52 (ddd, *J*= 15.4, 9.2, 6.2 Hz, 1 H), 3.49 (ddd, *J* = 15.8, 9.2, 6.5 Hz, 1 H), 3.38 (dd, *J* = 11.8, 4.8 Hz, 1 H) 3.38-3.33 (m, 1 H), 3.10 (dd, *J* = 10.1, 2.3 Hz, 1 H), 2.44 (dd, J = 14.5, 7.4 Hz, 1 H), 2.17 (ddd, J = 14.6, 10.0, 6.2 Hz, 1 H), 2.10 (s, 1 H), 1.99 (ddd, J = 12.8, 4.7, 2.1 Hz, 1 H), 1.85-1.77 (m, 1 H), 1.72-1.64 (m, 1 H), 1.63-1.56 (m, 2 H), 1.31 (dd, J = 24.0, 11.8 Hz, 1 H), 1.18 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 138.6, 136.3, 130.6, 129.1, 128.3, 127.6, 127.5, 115.9, 113.9, 82.9, 81.9, 75.8, 73.4, 72.8, 70.8, 70.1, 55.2, 35.2, 32.7, 32.4, 26.0, 15.0; IR (neat) 3479, 1623, 1098 cm^{-1}; HRMS calcd for $C_{27}H_{37}O_5$ (MH^+) 441.2641, found 441.2621.



7

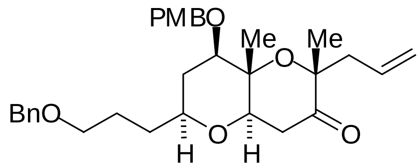
Preparation of (+)-acetate 7. To a solution of the alcohol from above (0.419 g, 1.16 mmol), acetic anhydride (0.868 mL, 9.3 mmol), *i*-Pr_2EtN (2.55 mL, 14.6 mmol), and CH_2Cl_2 (12 mL) was added DMAP (0.284 g, 2.32 mmol) at rt. After 50 hrs the reaction was quenched with $NaHCO_3$ (sat., 20 mL), extracted with CH_2Cl_2 (3 X 20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexanes/ethyl acetate) afforded 352 mg (78%) of acetate **7** as a colorless oil. $[\alpha]^{25}_{D}$= +20.75° (c = 0.08, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.34 (m, 2 H), 7.32-7.25 (m, 5 H), 6.89 (d, J = 8.5 Hz, 2 H), 5.88-5.80 (m, 1 H), 5.08 (d, J = 17.2 Hz, 1 H), 5.03 (d, J = 10.2 Hz, 1 H), 4.63, (dd, J = 11.4, 5.3 Hz, 1 H), 4.53 (d, J = 11.4 Hz, 1 H), 4.52 (s, 2 H), 4.49 (d, J = 11.4 Hz, 1 H), 4.25 (dd, J = 8.2, 4.5 Hz, 1 H), 3.83 (s, 3 H), 3.50 (ddd, J = 15.6, 9.2, 6.4 Hz, 1 H), 3.48 (ddd, J = 15.2, 8.5, 6.0 Hz, 1 H), 3.47-3.41 (partially obscured m, 1 H), 2.25-2.21 (m, 2 H), 1.99 (s, 3 H), 2.00-1.97 (m, 1 H), 1.81-1.76 (m, 1 H), 1.69-1.62 (m, 1 H), 1.59-1.54 (m, 2 H), 1.41 (dd, J= 24.1, 11.9 Hz, 1 H), 1.35 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 159.1, 138.6, 135.3, 130.8, 129.1, 128.3, 127.6, 127.5, 116.3, 113.7, 86.3, 75.9, 75.7, 72.8, 71.2, 70.1, 55.2, 36.9, 32.8, 32.2, 26.0, 22.5, 13.6; IR (neat) 1738, 1103, 1043 cm^{-1}; HRMS calcd for $C_{29}H_{39}O_6$ (MH^+) 483.2747, found 483.2752.



8

Preparation of (-)-bicycle 8. $TiCl_4$ (14.0 mL of a 1.0 M solution in CH_2Cl_2, 14.0 mmol) and TMEDA (12.64 mL, 83.92 mmol) were added sequentially to CH_2Cl_2 (99 mL) and THF (7.4 mL) at 0°C. The resulting brown mixture was warmed to rt and stirred for 10 min. Zn dust (2.05 g, 31.5 mmol), and $PbCl_2$ (0.463 g, 1.66 mmol) were then added. The resulting slurry was stirred for 16 min to reach a blue/green color. To this was added a solution of acetate **7** (0.352 g, 0.874 mmol), CH_2Br_2 (0.982 mL, 14.0 mmol) and CH_2Cl_2 (19 mL). The reaction mixture was heated to reflux for 2 hrs, cooled to 0°C, and quenched with K_2CO_3 (sat., 3.2 mL). After stirring for 30 min., the mixture was filtered. Concentration of the mother liquor and filtration of the residue through a plug of SiO_2 (5:1 hexanes/ethyl acetate) gave a mixture of cyclic and acyclic enol ether as a yellow oil.

To a solution of the mixture of enol ethers and C_6H_6 (87 mL) was added ruthenium catalyst **10** (0.148 g, 174 mmol). After stirring for 16 hrs at rt, the reaction mixture was concentrated. Flash chromatography (20:1 hexanes/ethyl acetate) afforded 214 mg (65%) of bicycle **8** as a yellow oil. $[\alpha]^{25}_{D}$= -5.40° (c = 0.235, THF); ^1H NMR (500 MHz, C_6D_6) δ 7.48 (d, *J* = 8.4 Hz, 2 H), 7.38 (d, *J* = 7.4 Hz, 2 H), 7.29 (d, *J* = 7.3 Hz, 2 H), 7.21 (dd, *J* = 7.4, 7.4 Hz, 1 H), 6.95 (d, *J* = 8.5 Hz, 2 H), 4.98 (d, *J* = 11.7 Hz, 1 H), 4.79 (d, *J* = 11.7 Hz, 1 H), 4.42 (s, 2 H), 4.41 (dd, *J* = 15.2, 4.4 Hz, 1 H), 3.62 (dd, *J* = 11.6, 5.2 Hz, 1 H), 3.46 (s, 3 H), 3.44-3.35 (m, 2 H), 3.30 (dd, *J* = 10.3, 6.2 Hz, 1 H), 3.29-3.24 (m, 1 H), 2.28-2.16 (m, 2 H), 1.89-1.81 (m, 2 H), 1.81 (s, 3 H), 1.75-1.62 (m, 2 H), 1.57-1.44 (m, 2 H), 1.48 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.3, 148.2, 139.2, 131.7, 129.2, 128.3, 127.4, 127.3, 113.7, 92.8, 80.1, 78.6, 75.9, 74.7, 72.6, 72.0, 70.1, 54.6, 36.7, 32.5, 26.1, 24.3, 20.0, 9.8; IR (neat) 1115 cm^{-1}; HRMS calcd for $C_{28}H_{37}O_5$ (MH^+) 453.6406, found 453.6410.



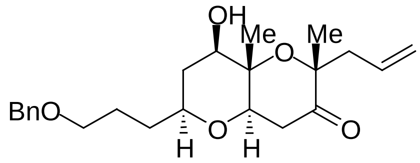
13

Preparation of (-)-Ketone 13.

Preparation of mixed ketal. *m*-CPBA (0.230 g, 1.44 mmol) was added to a solution of bicycle **8** (0.217 g, 0.48 mmol) and MeOH (16 mL) at –60°C. After warming to rt, the reaction was quenched with $NaHCO_3$ (sat., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (5 X 15 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (3:1 hexanes/ethyl acetate) afforded 220 mg (92%) of ketal as a colorless oil.

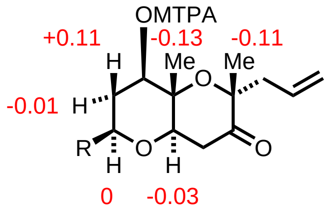
A solution of the mixture of ketals (0.190 g, 0.379 mmol) from above, NaH (45.5 mg, 1.897 mmol), allyl bromide (0.318 mL, 3.79 mmol), tetrabutyl ammonium iodide (ca. 8 mg) and THF (5.4 mL) was heated to reflux for 2 hrs. After cooling to 0°C, the reaction was quenched with NH_4Cl (sat., 15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 X 20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexanes/ethyl acetate) afforded 160 mg (78%) of allyl ether **11** as a colorless oil.

Preparation of (-)-ketone 13. A solution of **11** (160 mg, 0.296 mmol), PPTS (453 mg, 1.81 mmol), pyridine (0.062 mL, 0.77 mmol) and toluene was heated, first to 100°C for 2 hrs and then to reflux for 1 h. After cooling to rt, the reaction mixture was quenched with NaOH (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 X 20 ml), dried (Na_2SO_4), and concentrated. Flash chromatography (3:1 hexanes/ethyl acetate) afforded 146 mg (97%) of ketone **13** as a colorless oil. $[\alpha]^{25}_{D}$= -3.70° (c = 0.12, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.25 (m, 7 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 5.80-5.72 (m, 1 H), 5.08 (d, *J* = 20.1 Hz, 1 H), 5.05 (d, *J* = 27.1 Hz, 1 H), 4.81 (d, *J* = 11.7 Hz, 1 H), 4.62 (d, *J* = 11.7 Hz, 1 H), 4.47 (s, 2 H), 3.79 (s, 3 H), 3.51 (dd, *J* = 11.7, 5.1 Hz, 1 H), 3.49-3.39 (m, 4 H), 2.68 (dd, *J* = 19.1, 7.2 Hz, 1 H), 2.41 (dd, *J* = 19.1, 11.2 Hz, 1H), 2.34 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.23 (dd, *J* = 13.5, 7.2 Hz, 1H), 1.83 (ddd, *J* = 13.5, 5.2, 2.4 Hz, 1 H), 1.75-1.66 (m, 1 H), 1.66-1.57 (m, 1 H), 1.56-1.48 (m, 2 H), 1.40 (dd, *J* = 25.1, 11.7 Hz, 1 H), 1.38 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7, 159.1, 138.5, 132.8, 131.1, 129.3, 128.3, 127.6, 127.5, 119.0, 113.7, 82.9, 80.4, 77.3, 76.3, 74.1, 72.8, 72.5, 70.0, 55.3, 46.6, 39.4, 36.3, 32.2, 26.6, 25.7, 12.1; IR (neat) 1724, 1103 cm^{-1}; HRMS calcd for $C_{31}H_{41}O_6$ (MH^+) 509.2903, found 509.2886.



Preparation of C-6 alcohol. DDQ (0.0984 g, 0.434 mmol) was added to a solution of ketone **15** (0.147 g, 0.289 mmol), CH_2Cl_2 (13.9 mL) and H_2O (0.77 mL) at rt. After stirring for 0.5 h, the reaction mixture was quenched with $NaHCO_3$ (sat., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 X 20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexanes/ethyl acetate) afforded 103 mg (92%) of the alcohol as a colorless oil. $[\alpha]^{25}_{D}$= +10.80° (c = 0.25, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.41 (d, *J* = 7.5 Hz, 2 H), 7.31-7.28 (m, 2 H), 7.23-7.21 (m, 1 H), 5.92-5.84 (m, 1 H), 5.13-5.09 (m, 2 H), 4.44 (s, 2 H), 3.64 (dd, *J* = 11.7, 5.1 Hz, 1 H), 3.42-3.35 (m, 3 H), 3.32-3.27 (m, 1 H), 2.70 (dd, *J* = 18.9, 7.2 Hz, 1 H), 2.49 (dd, *J* = 18.9, 11.2 Hz, 1H), 2.42 (dd, *J* = 13.5, 7.6 Hz, 1 H), 2.26 (dd, *J* = 13.5, 7.1 Hz, 1 H), 2.05 (s, 1 H), 1.87-1.78 (m, 1 H), 1.75 (ddd, *J* = 13.5, 5.1, 2.6 Hz, 1 H), 1.72-1.60 (m, 2 H), 1.57-1.49 (m, 1 H), 1.45 (partially obscured dd, *J* = 24.8, 11.7 Hz, 1 H), 1.41 (s, 3 H), 1.13 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 209.6, 139.4, 133.2, 128.5, 127.6, 118.9, 83.2, 76.5, 76.3, 75.3, 74.1, 73.0, 70.2, 46.8, 39.6, 36.9, 32.6, 26.7, 26.3, 11.4; IR (neat) 3475, 1725, 1101, 1037 cm^{-1}; HRMS calcd for $C_{23}H_{33}O_5$ (MH^+) 389.2328, found 389.2327.

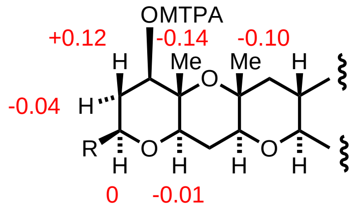
Summary of The Assignment of the Absolute Stereochemistry on the C-6 Mosher's Ester of (13):



Cox, Rainier cmpd.

600 MHz, ^{1}H NMR (CD_2Cl_2)

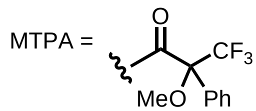
Δ δ (PPM) = δS - δR

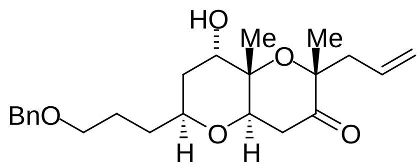


Yasumoto Gambierol C-3 Epimer

600 MHz, ^{1}H NMR (CD_2Cl_2:CD_3OD)

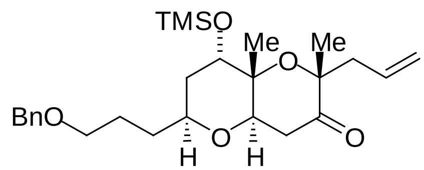
Morohashi, A.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1999**, *40*, 97.





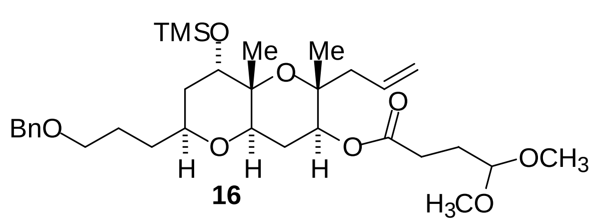
Inversion of the C-6 alcohol. To a solution of the alcohol from **15** (0.053 g, 0.137 mmol), PPh_3 (0.180 g, 0.684 mmol), 4-nitro-benzoic acid (0.103 g, 0.615 mmol) and toluene (4 mL) at rt was added DEAD (0.108 mL, 0.684 mmol). After stirring for 0.33 h, the reaction was heated to reflux for 30 min and then concentrated. The residue was taken up in MeOH (2 mL), THF (2 mL) and NaOH (0.5 mL of a 5% solution in water) and stirred for 2 hours. The mixture was extracted with ether (5 X 10 ml), dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexanes/ethyl acetate) afforded 36.6 mg (70%) of the alcohol as a colorless oil. $[\alpha]^{25}_{D}$= +1.43° (c = 1.83, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.41 (d, *J* = 7.4 Hz, 2 H), 7.31-7.28 (m, 2 H), 7.23-7.21 (m, 1 H), 5.75-5.67 (m, 1 H), 5.06-5.01 (m, 2 H), 4.43 (s, 2 H), 4.24 (dd, *J* = 12.0, 7.0 Hz, 1 H), 4.08-4.03 (m, 1 H), 3.80 (dd, *J* = 2.7, 2.7 Hz, 1 H), 3.42 (ddd, *J* = 15.4, 9.1, 6.4 Hz, 1 H), 3.41 (ddd, *J* = 15.5, 9.1, 6.5 Hz, 1 H), 2.97 (d, *J* = 2.2 Hz, 1 H), 2.74 (dd, *J* = 18.7, 7.0 Hz, 1 H), 2.47 (dd, *J* = 18.7, 12.0 Hz, 1 H), 2.37 (dd, *J* = 13.7, 7.2 Hz, 1 H), 2.13 (dd, *J* = 13.7, 7.5 Hz, 1 H), 1.96-1.88 (m, 1 H), 1.86 (ddd, *J* = 14.4, 2.7, 2.7 Hz, 1 H), 1.80-1.71 (m, 1 H), 1.69-1.61 (m, 1 H), 1.58-1.51 (m, 1 H), 1.48-1.42 (m, 1 H), 1.35 (s, 3 H), 0.99

(s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 208.8, 139.2, 132.9, 128.3, 128.0, 127.5, 118.9, 82.7, 74.0, 72.7, 72.3, 71.4, 70.1, 68.8, 46.3, 39.3, 35.5, 32.4, 26.2, 26.2, 16.6; IR (neat) 3539, 1718,1105 cm^{-1}; HRMS calcd for $C_{23}H_{33}O_5$ (MH^+) 389.2328, found 389.2335.



15

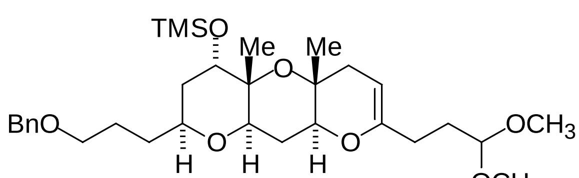
Preparation of ketone 15. To a solution of the alcohol from the Mitsunobu protocol (0.036 g, 0.093 mmol), *i*-Pr_2EtN (0.065 mL, 0.37 mmol) and CH_2Cl_2 (4 mL) at 0°C was added TMSOTf (0.034 mL, 0.19 mmol) dropwise. After stirring for 1h, the reaction was quenched with $NaHCO_3$ (sat., 2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 X 10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexanes/ethyl acetate) afforded 37 mg (87%) of ketone **15** as a colorless oil. $[\alpha]^{25}_{D}$= +9.92º (c = 1.83, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.41 (d, *J* = 7.4 Hz, 2 H), 7.29 (d, *J* = 7.4 Hz, 2 H), 7.21 (dd, *J* = 7.2, 7.2 Hz, 1 H), 6.21-6.13 (m, 1 H), 5.10-5.07 (m, 2 H), 4.46-4.43 (m, 1 H), 4.43 (s, 2 H), 4.02 (br s, 1 H), 3.76 (br s, 1 H), 3.46-3.40 (m, 2 H), 2.80 (dd, *J* = 18.9, 7.4 Hz, 1 H), 2.50 (dd, *J* = 19.1, 11.3 Hz, 1 H), 2.45 (d, *J* = 9.4 Hz, 1 H), 2.40 (dd, *J* = 13.5, 6.1 Hz, 1 H), 1.96-1.90 (m, 1 H), 1.79-1.72 (m, 1 H), 1.70-1.60 (m, 1 H), 1.60-1.50 (m, 3 H), 1.46 (s, 3 H), 1.03 (s, 3 H), 0.29 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 209.8, 139.2, 133.5, 128.3, 127.5, 127.3, 118.1, 83.1, 73.3, 72.7, 71.9, 71.6, 70.2, 68.5, 47.0, 39.8, 38.3, 32.5, 26.8, 26.2, 17.5, 0.1; IR (neat) 1731, 1148, 1113 cm^{-1}; HRMS calcd for $C_{26}H_{41}O_5Si$ (MH^+) 461.2723, found 461.2743.



16

Preparation of (-)-ester 16. To a solution of ketone **15** (0.0367 g, 0.0798 mmol) and EtOH (6 mL) at –60ºC was added a solution of $NaBH_4$ (8 mg, 0.21 mmol) and EtOH (2 ml). The resulting mixture was allowed to warm to rt over 2 hours. The reaction was quenched with acetone (1 ml) and the mixture was then concentrated. The resulting residue was taken up in a 1:1 mixture of water and ether (5 mL). The aqueous phase was extracted with ether (3 X 5 ml), dried (Na_2SO_4), and concentrated.

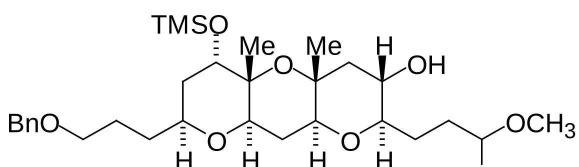
Acid **17** (0.124 g, 0.836 mmol), DMAP (0.0045 mg, 0.037 mmol), and DCC (0.181 g, 0.878 mmol) were added to a solution of the residue from the reduction and CH_2Cl_2 (5.8 mL). After 1 h, the reaction mixture was filtered and the filter cake was washed with CH_2Cl_2 (3 X 2 ml). The extracts were combined and washed with HCl (0.5 M, 2 mL) and $NaHCO_3$ (sat., 2 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexanes/ethyl acetate) afforded 43 mg (91%) of ester **16** as a colorless oil. $[\alpha]^{25}_{D}$= -14.98° (c = 0.185, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.41 (d, *J* = 7.5 Hz, 2 H), 7.32-7.27 (m, 2 H), 7.23-7.20 (m, 1 H), 6.38-6.30 (m, 1 H), 5.30-5.22 (m, 2 H), 4.44 (s, 2 H), 4.36 (dd, *J* = 5.5, 5.5 Hz, 1 H), 4.07 (dd, *J* = 12.7, 3.7 Hz, 1 H), 3.95-3.91 (m, 1 H), 3.78 (br s, 1 H), 3.45 (ddd, *J* = 15.1, 9.1, 6.3 Hz, 1 H), 3.43 (ddd, *J* = 15.1, 9.1, 6.4 Hz, 1 H), 3.19 (s, 3 H), 3.18 (s, 3 H), 2.51 (dd, *J* = 14.1, 6.5 Hz, 1 H), 2.46-2.38 (m, 2 H), 2.37 (d, *J* = 2.2 Hz, 1 H), 2.35 (dd, *J* = 7.1, 21.6 Hz, 1 H), 2.09-1.92 (m, 4 H), 1.83-1.75 (m, 1 H), 1.73-1.64 (m, 2 H), 1.62-1.55 (m, 1 H), 1.50 (dd, *J*= 2.9, 2.9 Hz, 1 H), 1.47 (dd, *J* = 2.8, 2.8 Hz, 1 H), 1.43 (s, 3 H), 1.34 (s, 3 H), 0.29 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.3, 139.3, 134.7, 128.2, 127.3, 117.3, 103.5, 76.0, 74.6, 73.2, 73.0, 72.7, 72.1, 71.1, 70.2, 52.5, 52.5, 47.1, 38.8, 32.6, 29.4, 27.9, 27.7, 26.3, 23.3, 19.2, 0.2; IR (neat) 1743, 1136,1089 cm^{-1}; HRMS calcd for $C_{32}H_{53}O_8Si$ (MH^+) 593.3510, found 593.3502.



18

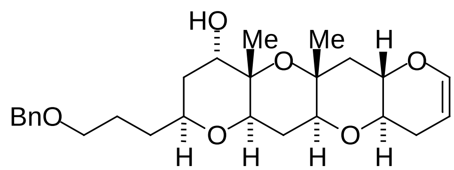
Preparation of (+)-tricycle 18. The acyclic enol ether from **16** was prepared according to the procedure used for the formation of bicycle **8** using **16** (0.037 g, 0.062 mmol), $TiCl_4$ (1.16 mL of a 1.0 M solution in CH_2Cl_2, 1.16 mmol), TMEDA (1.05 mL, 6.96 mmol), Zn (0.170 g, 2.61 mmol), $PbCl_2$ (0.038 g, 0.138 mmol), CH_2Br_2 (0.081 mL, 1.16 mmol), THF (0.612 mL, 6.96 mmol), and CH_2Cl_2 (10.8 mL).

To a solution of acyclic enol ether from above and hexanes (6 ml) in a dry box was added molybdenum catalyst **9** (0.0106 g, 0.0138 mmol). After the reaction mixture was sealed, it was removed from the box and placed in a 60°C bath for 16 hours. After exposure to air and concentration, flash chromatography (20:1 hexanes/ethyl acetate) afforded 27.2 mg (77%, 2 steps) of tricycle **18** as a colorless oil. $[\alpha]^{25}_{D}$= +9.09° (c = 0.15, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.41 (d, *J* = 7.4 Hz, 2 H), 7.31-7.27 (m, 2 H), 7.23-7.20 (m, 1 H), 4.49 (d, *J* = 5.1 Hz, 1 H), 4.46 (dd, *J* = 5.7, 5.7 Hz, 1 H), 4.43 (s, 2 H), 4.02-3.99 (m, 1 H), 4.01 (dd, *J* = 12.3, 3.7 Hz, 1 H), 3.78 (br s, 1 H), 3.66 (dd, *J* = 12.0, 3.7 Hz, 1 H), 3.48-3.41 (m, 2 H), 3.25 (s, 3 H), 3.24 (s, 3 H), 2.38 (d, *J* = 15.6 Hz, 1 H), 2.29 (dd, *J* = 7.6, 7.6 Hz, 1 H), 2.24 (ddd, *J* = 11.3, 3.6, 3.6 Hz, 1 H), 2.10 (dd, *J* = 23.9, 12.1 Hz, 1 H), 2.06-1.94 (m, 4 H), 1.85-1.56 (m, 5 H), 1.52-1.48 (m, 1 H), 1.40 (s, 3 H), 1.36 (s, 3 H), 0.31 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 154.2, 139.3, 128.2, 127.4, 127.3, 103.8, 95.2, 78.5, 75.6, 73.6, 72.7, 72.5, 72.1, 71.8, 70.3, 52.0, 52.0, 39.1, 39.0, 32.6, 30.3, 28.9, 27.3, 26.3, 20.5, 19.8, 0.41; IR (neat) 1678, 1142, 1095, 1060 cm^{-1}; HRMS calcd for $C_{31}H_{51}O_7Si$ (MH^+) 563.3404, found 563.3380.



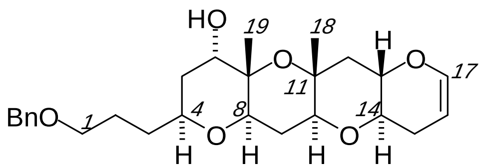
20

Preparation of (-)-alcohol 20. To a solution of **18** (0.009 g, 0.16 mmol) and CH_2Cl_2 (0.5 mL) at –60°C was added dimethyl dioxirane (0.24 mL of a 0.1 M solution in acetone, 0.24 mmol) dropwise. The reaction was warmed to 0°C and concentrated. After taking the residue up in CH_2Cl_2 (1 mL) and cooling to –60°C, DIBAL (0.032 mL of a 1.0 M solution in hexane, 0.032 mmol) was added. After stirring for 10 min, the reaction was quenched with HCl (0.5 M) and the resulting mixture was allowed to warm to rt. The aqueous phase was extracted with CH_2Cl_2 (5 X5 ml), dried (Na_2SO_4), and concentrated. Flash chromatography (3:1 hexanes/ethyl acetate) afforded 6.4 mg (69%) of alcohol **20** as a colorless oil. $[\alpha]^{23}_{D}$= -23.09° (c = 0.210, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.41 (d, *J*= 7.4 Hz, 2H), 7.31-7.27 (m, 2 H), 7.23-7.20 (partially obscured m, 1 H), 4.49 (dd, *J* = 5.6, 5.6 Hz, 1 H), 4.44 (s, 2H), 4.02 (dd, *J* = 12.2, 3.7 Hz, 1 H), 4.04-4.00 (m, 1 H), 3.78 (br s, 1 H), 3.47 (ddd, *J* = 17.0, 9.1, 6.4 Hz, 1 H), 3.44 (ddd, *J* = 16.9, 9.1, 6.4 Hz, 1 H), 3.35 (br s, 1 H), 3.29 (s, 3 H), 3.28 (s, 3 H), 3.15 (dd, *J* = 12.1, 3.1 Hz, 1 H), 3.15-3.11 (partially obscured m, 1 H), 2.22-1.93 (m, 6 H), 1.87-1.78 (m, 2 H), 1.72-1.57 (m, 3 H), 1.50 (ddd, *J* = 11.4, 2.7, 2.7 Hz, 1 H), 1.50-1.47 (partially obscured m, 2 H), 1.35 (s, 3 H), 1.30 (s, 3 H), 0.35 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.3, 128.1, 127.9, 127.7, 104.6, 83.8, 81.5, 75.4, 73.8, 73.8, 73.5, 72.7, 72.1, 70.3, 69.6, 52.2, 51.9, 48.1, 39.1, 32.7, 28.7, 27.5, 27.5, 26.3, 21.5, 20.9, 0.5; IR (neat) 3445, 1136, 1101, 1072 cm^{-1}; HRMS calcd for $C_{31}H_{53}O_8Si$ (MH^+) 581.3510, found 581.3509.



21

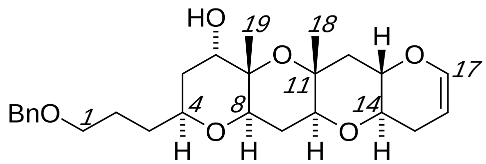
Preparation of (+)-tetracycle 21. A solution of **20** (0.0044 g, 0.0076 mmol), PPTS (0.0116 g, 0.0462 mmol), pyridine (1.6 mL, 0.0197 mmol) and chlorobenzene were heated to reflux for 16 hrs. The reaction was then cooled to rt and quenched with $NaHCO_3$ (1 mL). The aqueous phase was extracted with CH_2Cl_2 (5 X 5 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexanes/ethyl acetate) afforded 3.2 mg (95%) of tetracycle **21** as a colorless oil. $[\alpha]^{23}_D$= +29.94° (c = 0.155, THF); ^{1}H NMR (600 MHz, C_6D_6) δ 7.29 (d, *J* = 7.5 Hz, 2 H), 7.18-7.15 (m, 2 H), 7.10-7.08 (m, 1 H), 6.25 (d, *J* = 5.8 Hz, 1 H), 4.42 (ddd, *J* = 5.7, 5.7, 2.0 Hz, 1 H), 4.31 (s, 2 H), 3.90 (ddd, J = 11.6, 7.7, 4.0 Hz, 1 H), 3.78 (dd, *J* = 12.2, 3.6 Hz, 1 H), 3.66 (br s, 1 H), 3.48 (ddd, *J* = 10.6, 10.6, 5.3 Hz, 1 H), 3.34-3.27 (m, 3 H), 2.95 (dd, *J* = 12.0, 3.4 Hz, 1 H), 2.55 (s, 1 H), 2.17 (dd, *J* = 11.4, 5.3 Hz, 1 H), 2.13 (dd, *J* = 5.5, 5.5 Hz, 1 H), 2.04-1.99 (m, 2 H), 1.85 (dd, *J* = 23.8, 11.9 Hz, 1 H), 1.83-1.77 (m, 1 H), 1.74 (ddd, *J* = 14.6, 2.7, 2.7 Hz, 1 H), 1.69-1.62 (m, 1 H), 1.58-1.40 (m, 4 H), 139.5, 1.13 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (150 MHz, C_6D_6) δ 143.9, 128.3, 128.1, 127.5, 127.3, 98.6, 82.0, 77.2, 76.1, 74.7, 74.6, 73.7, 72.7, 71.1, 70.2, 43.4, 35.8, 32.6, 27.6, 27.4, 26.2, 21.1, 20.2; IR (neat) 1650, 1187, 1107, 1062 cm^{-1}; HRMS calcd for $C_{26}H_{37}O_6$ (MH^+) 445.2590, found 445.2589.



21

Summary of COSY spectrum for 21.

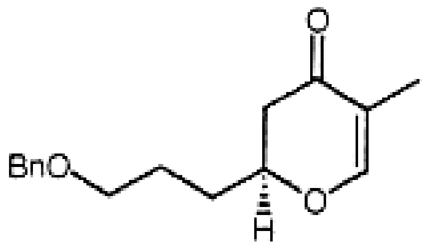
1. Protons at 3.30 ppm (C-1) show cross peaks with protons at 1.80, 1.66 ppm (C-2).
2. Protons at 1.80, 1.66 ppm (C-2) show cross peaks with protons at 1.55 ppm (C-3)
3. Protons at 1.55 ppm (C-3) show cross peaks with protons at 3.89 ppm (C-4).
4. Protons at 3.89 ppm (C-4) show cross peaks with protons at 1.72, 1.48 ppm (C-5).
5. Protons at 1.72, 1.48 ppm (C-5) show cross peaks with protons at 3.66 ppm (C-6).
6. Protons at 3.78 ppm (C-8) show cross peaks with protons at 2.11, 1.87 ppm (C-9).
7. Protons at 2.11, 1.87 ppm (C-1) show cross peaks with protons at 2.95 ppm (C-10).
8. Protons at 1.43, 2.17 ppm (C-12) show cross peaks with protons at 3.48 ppm (C-13).
9. Protons at 3.48 ppm (C-13) show cross peaks with protons at 3.32 ppm (C-14).
10. Protons at 3.32 ppm (C-14) show cross peaks with protons at 2.13, 1.99 ppm (C-15).
11. Protons at 2.13, 1.99 ppm (C-15) show cross peaks with protons at 4.42 ppm (C-16).
12. Protons at 4.42 ppm (C-16) show cross peaks with protons at 6.25 ppm (C-17).



21

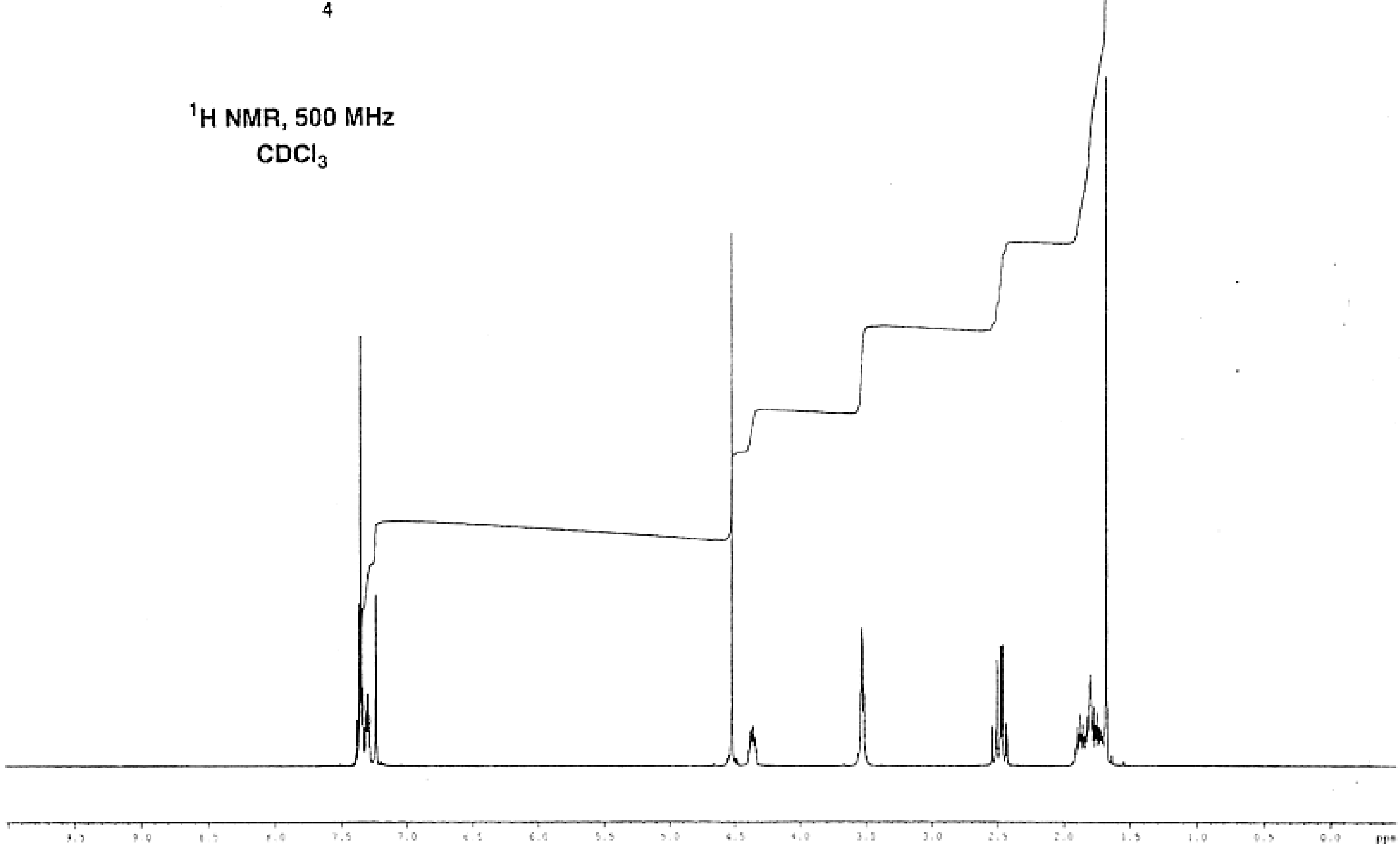
Summary of 1D nOe difference experiments for 21.

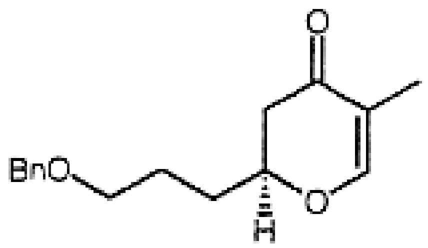
1. Irradiation at 3.89 ppm (C-4) resulted in enhancement at 3.78 (C-8).
2. Irradiation at 3.78 ppm (C-8) resulted in enhancement at 3.89 ppm (C-4), 2.95 ppm (C-10), 2.55 ppm (OH).
3. Irradiation at 3.66 ppm (C-6) resulted in enhancement at 1.13 ppm (C-19).
4. Irradiation at 3.48 ppm (C-13) resulted in enhancement at 1.09 ppm (C-18).
5. Irradiation at 2.95 ppm (C-10) resulted in enhancement at 3.78 ppm (C-8), 3.32 ppm (C-14).



4

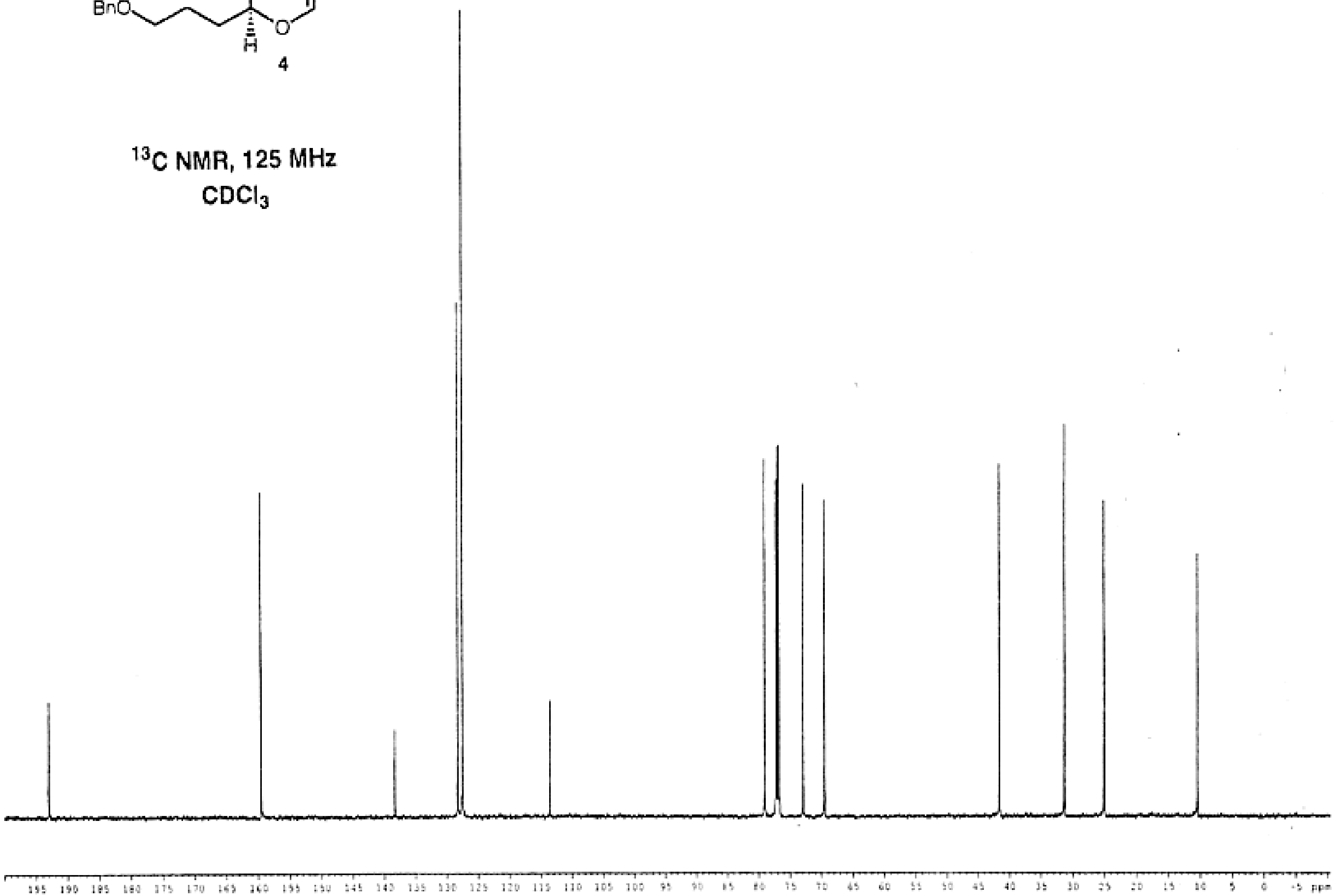
^1H NMR, 500 MHz
$CDCl_3$

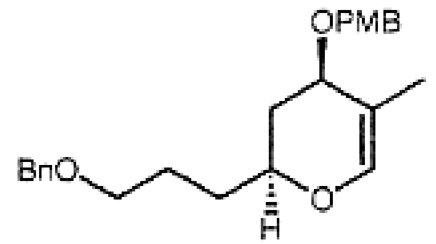




4

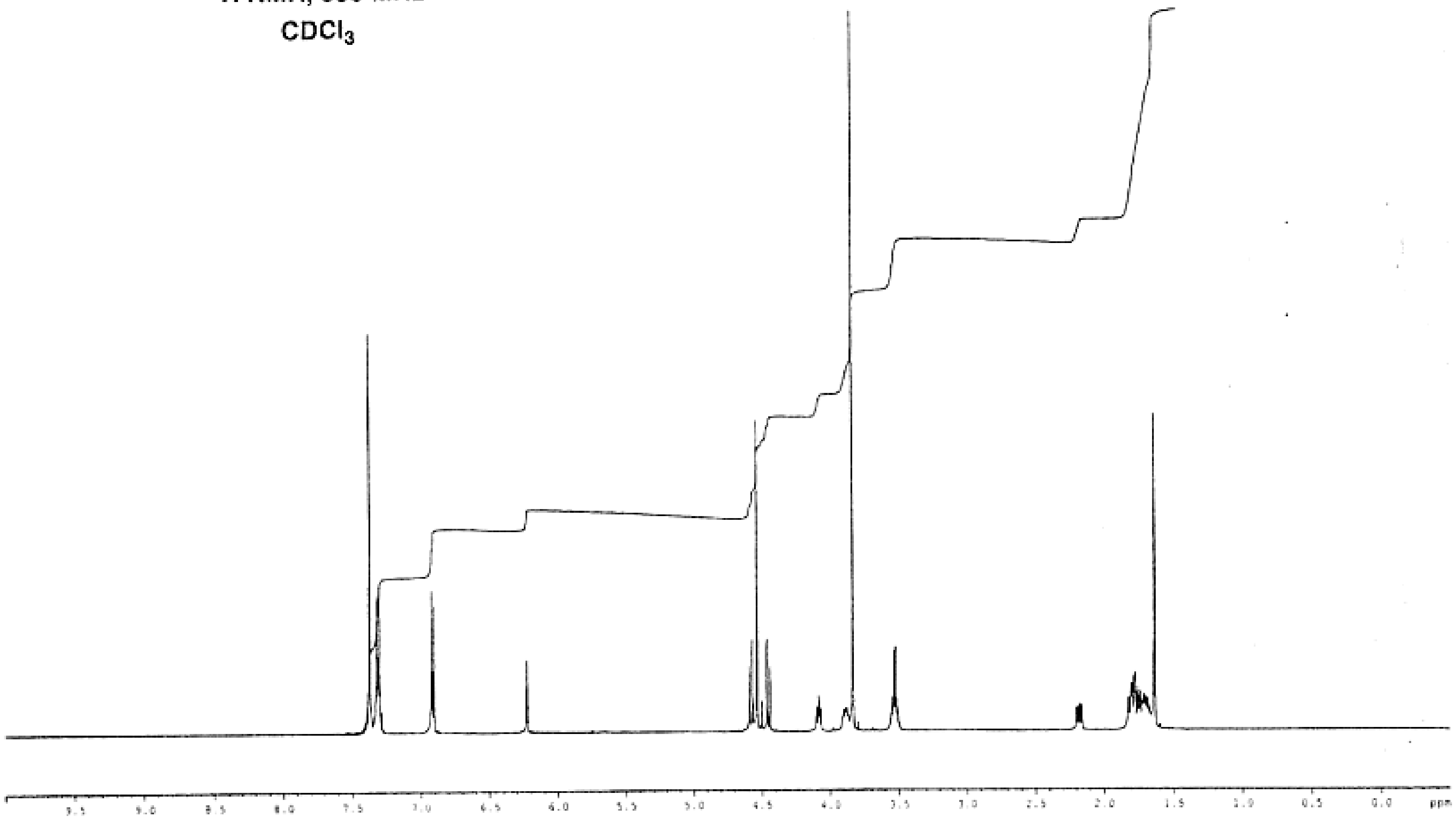
^{13}C NMR, 125 MHz
$CDCl_3$

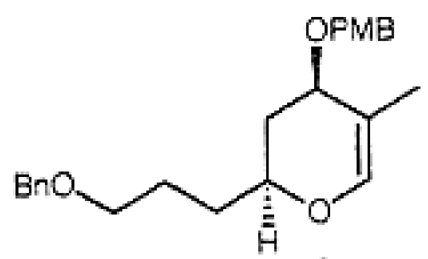




6

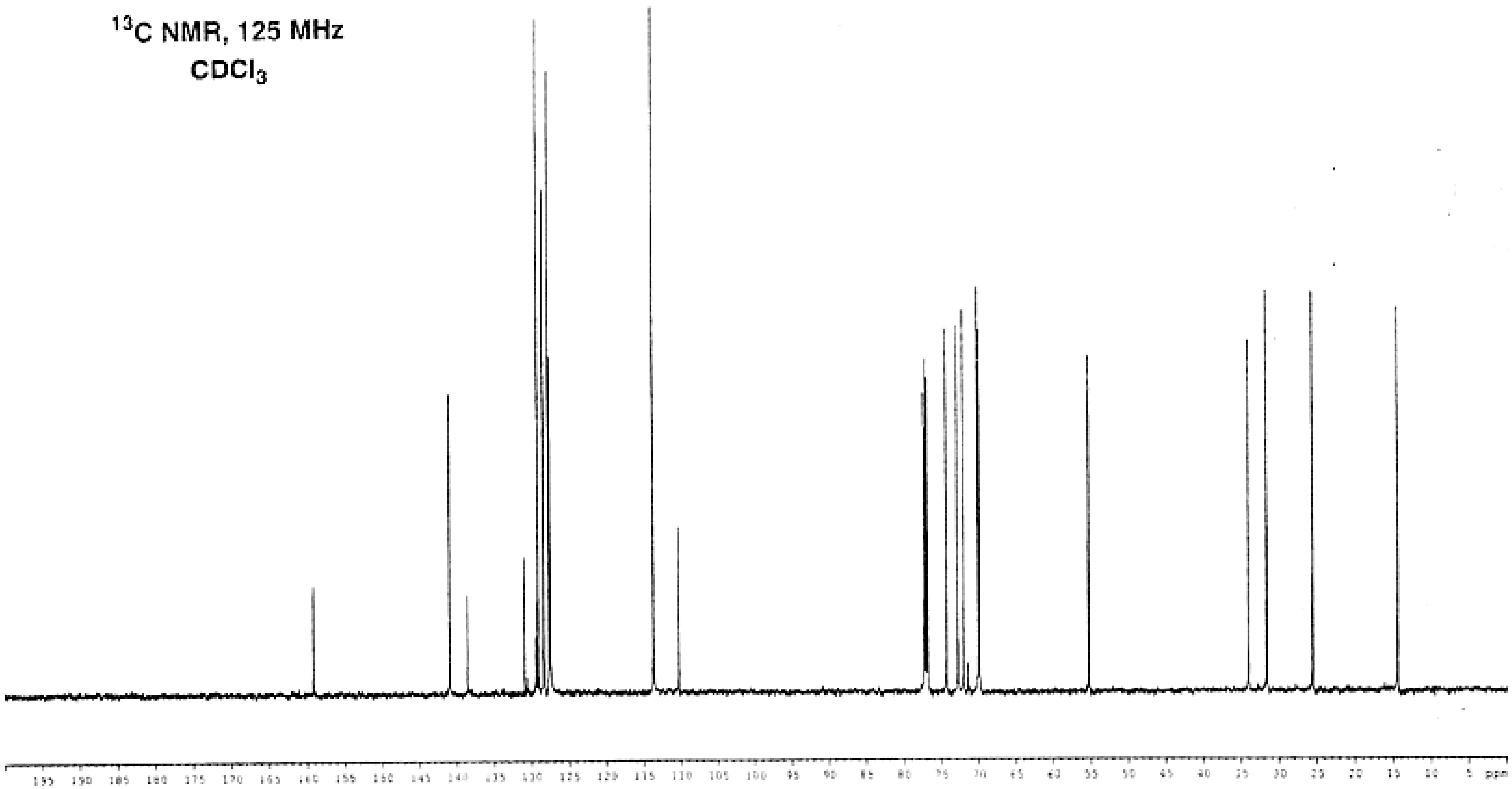
^1H NMR, 500 MHz
$CDCl_3$

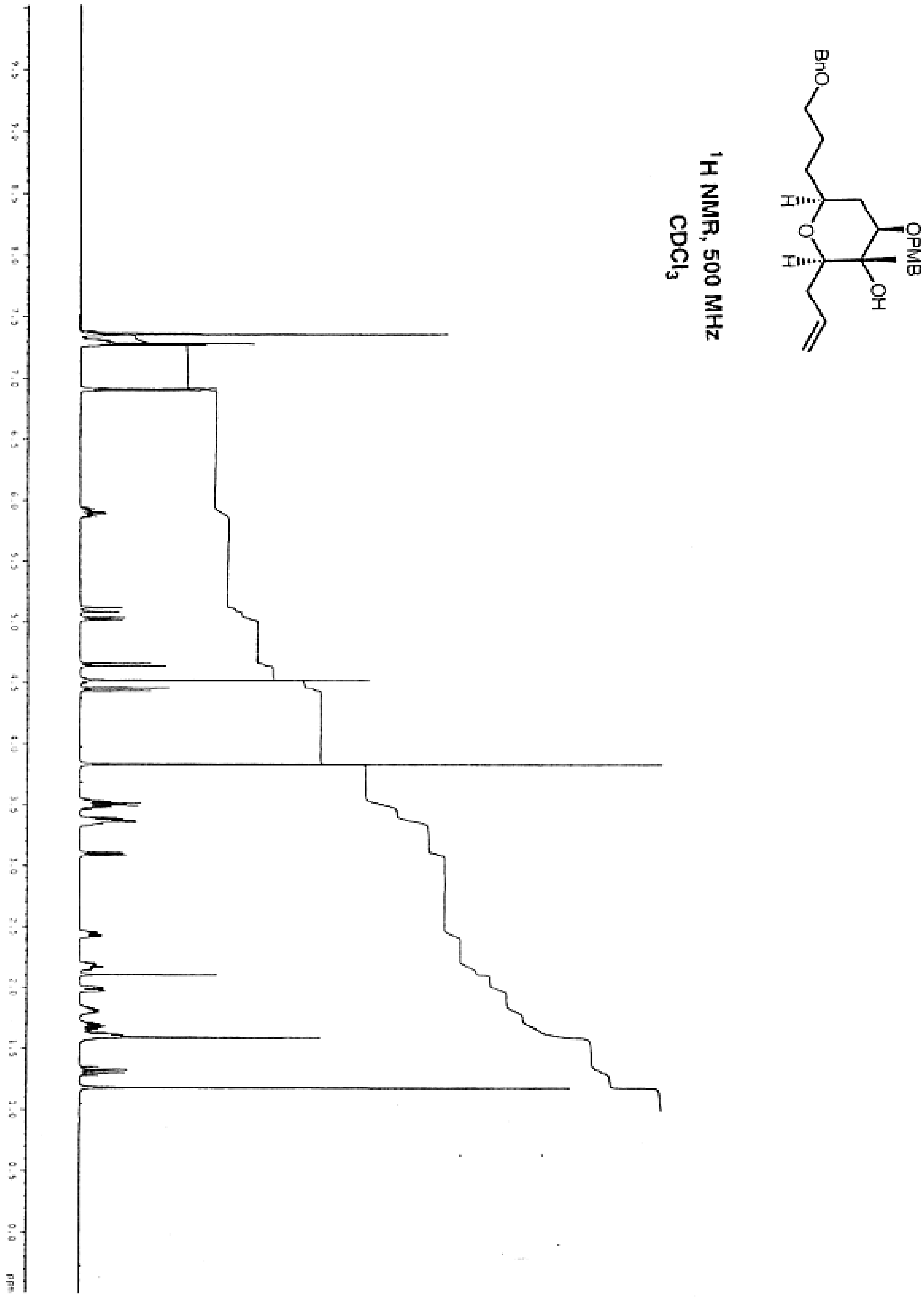


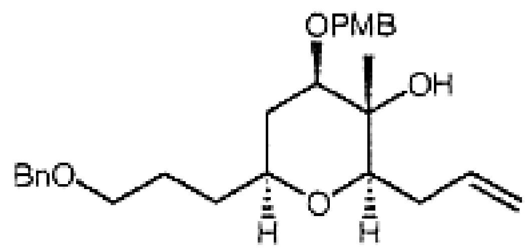


6

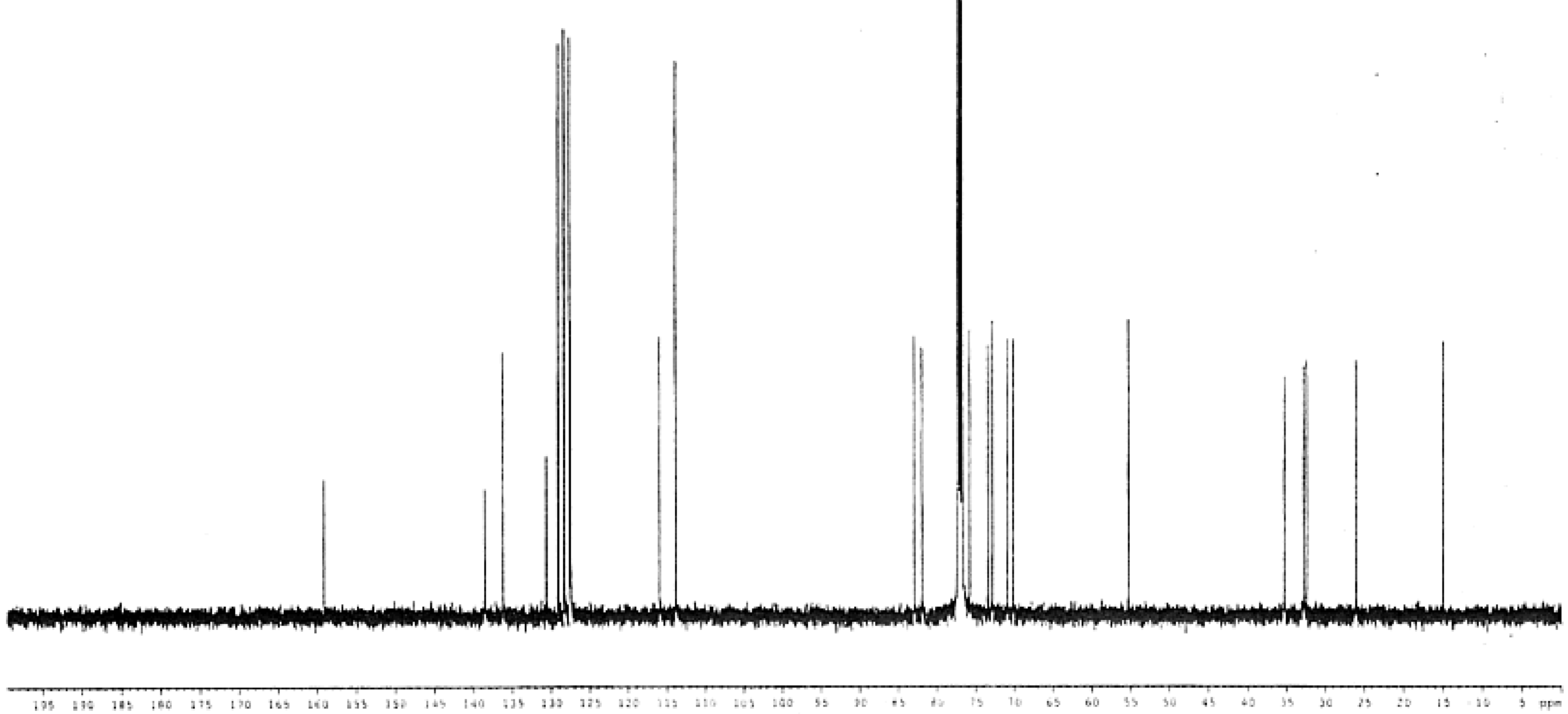
^{13}C NMR, 125 MHz
$CDCl_3$

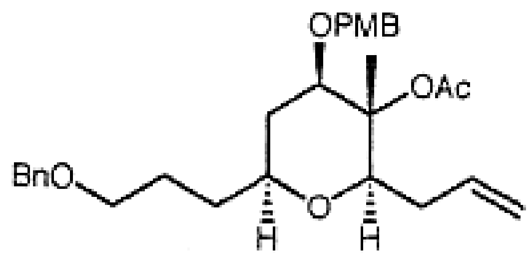



BnO
OPMB
OH
H
O
H
1H NMR, 500 MHz
CDCl3



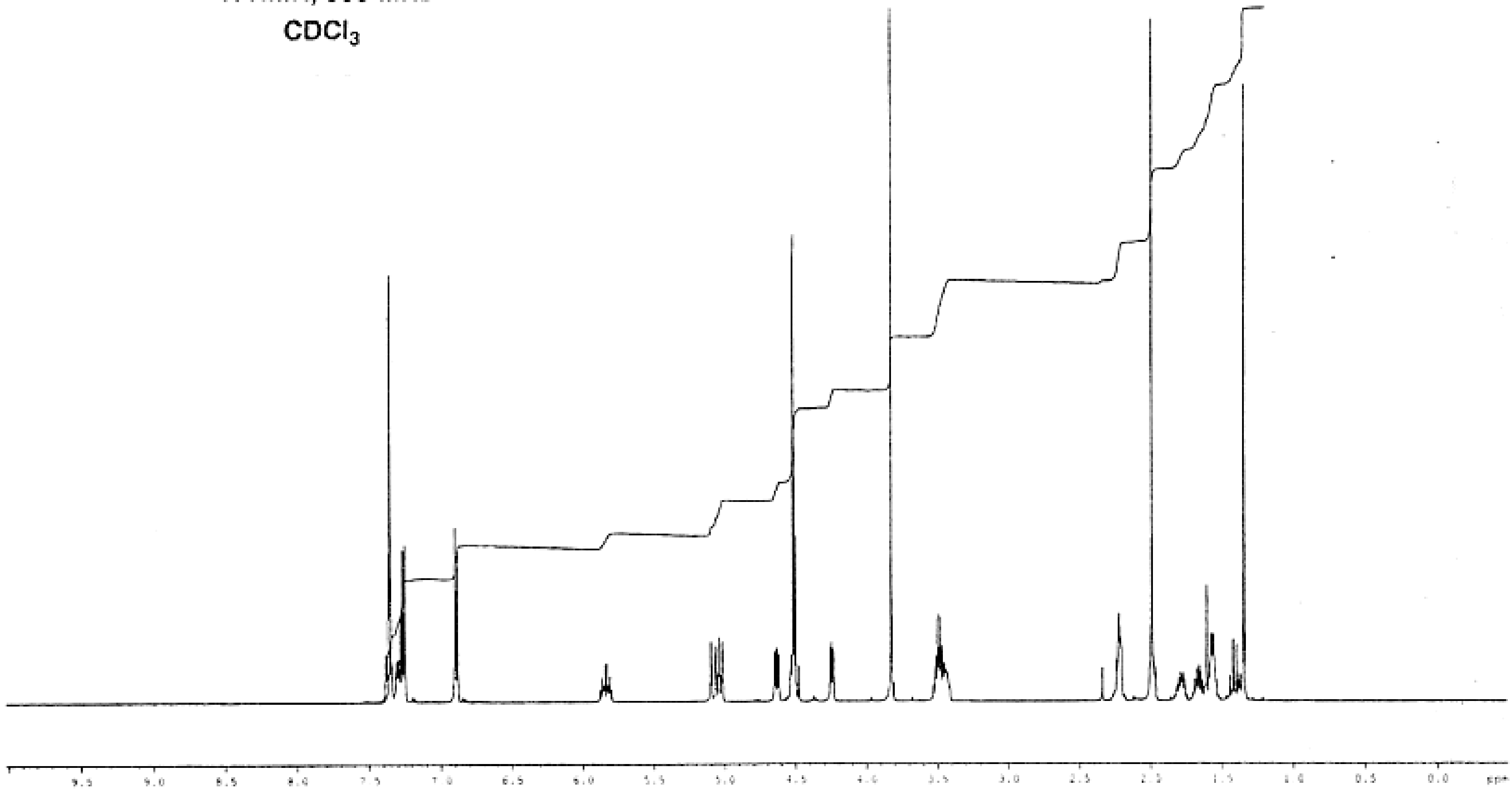
^{13}C NMR, 125 MHz
$CDCl_3$

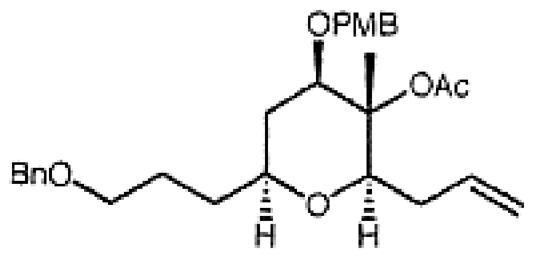




7

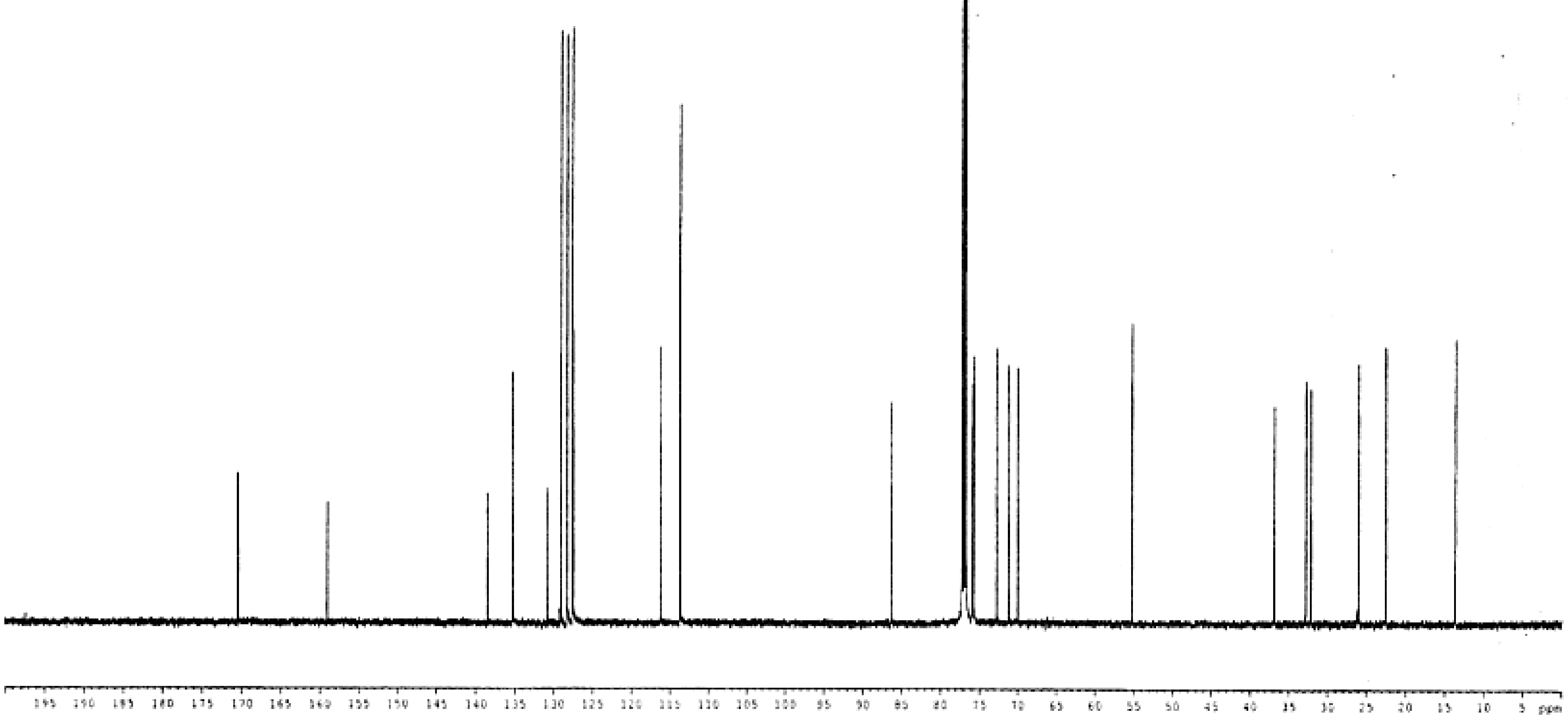
^1H NMR, 500 MHz
$CDCl_3$

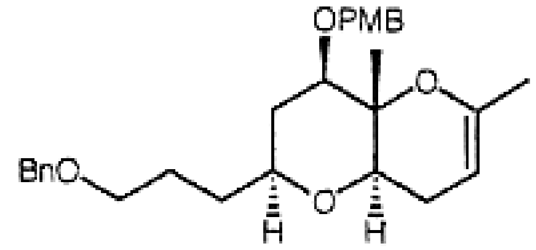




7

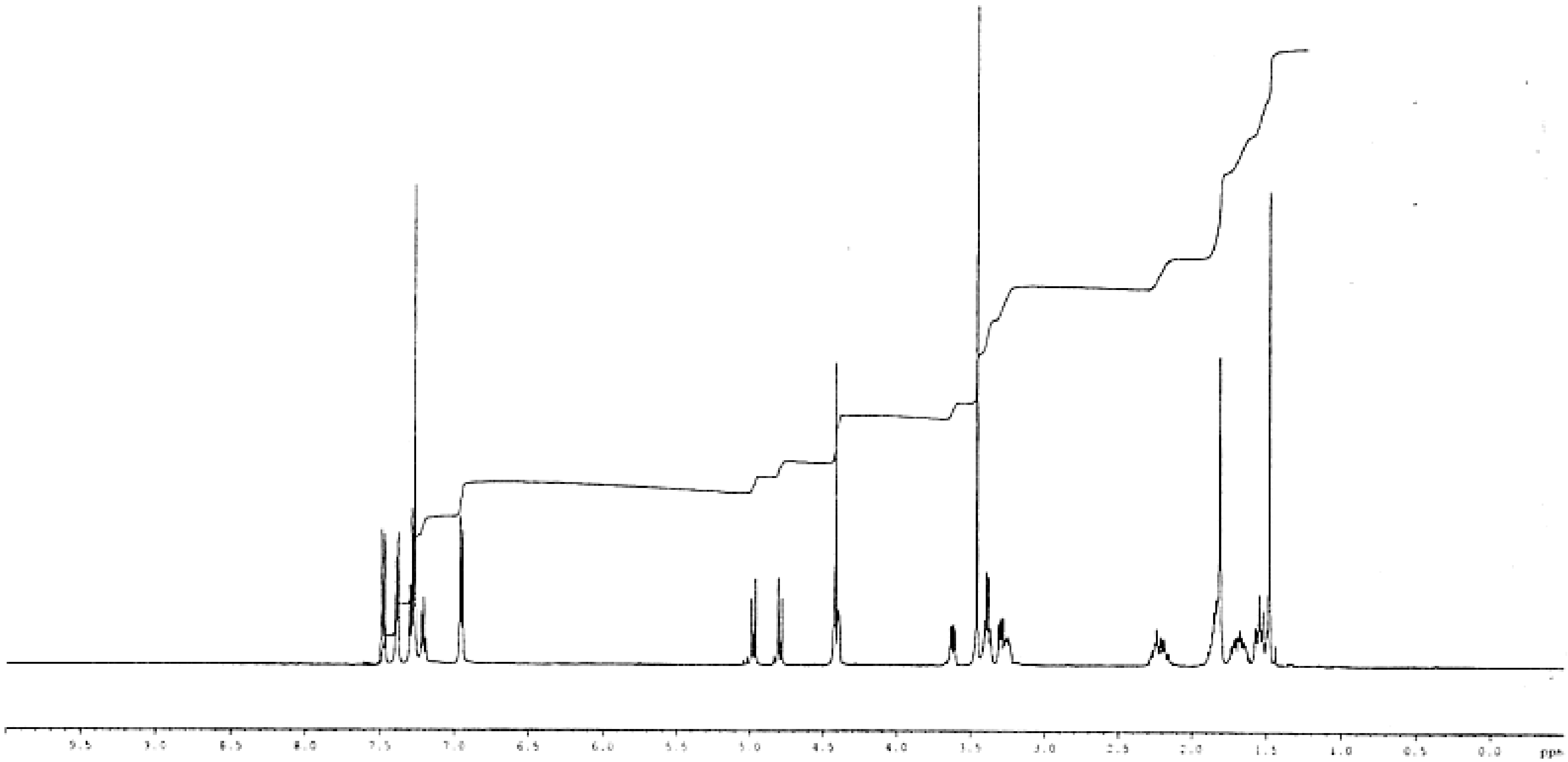
^{13}C NMR, 125 MHz
$CDCl_3$

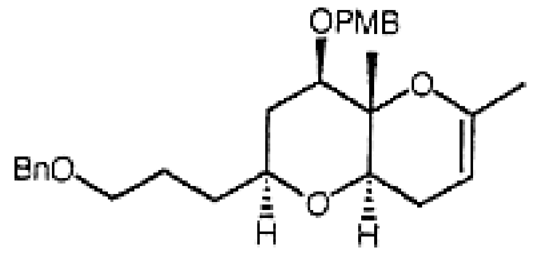




8

¹H NMR, 500 MHz
C_6D_6

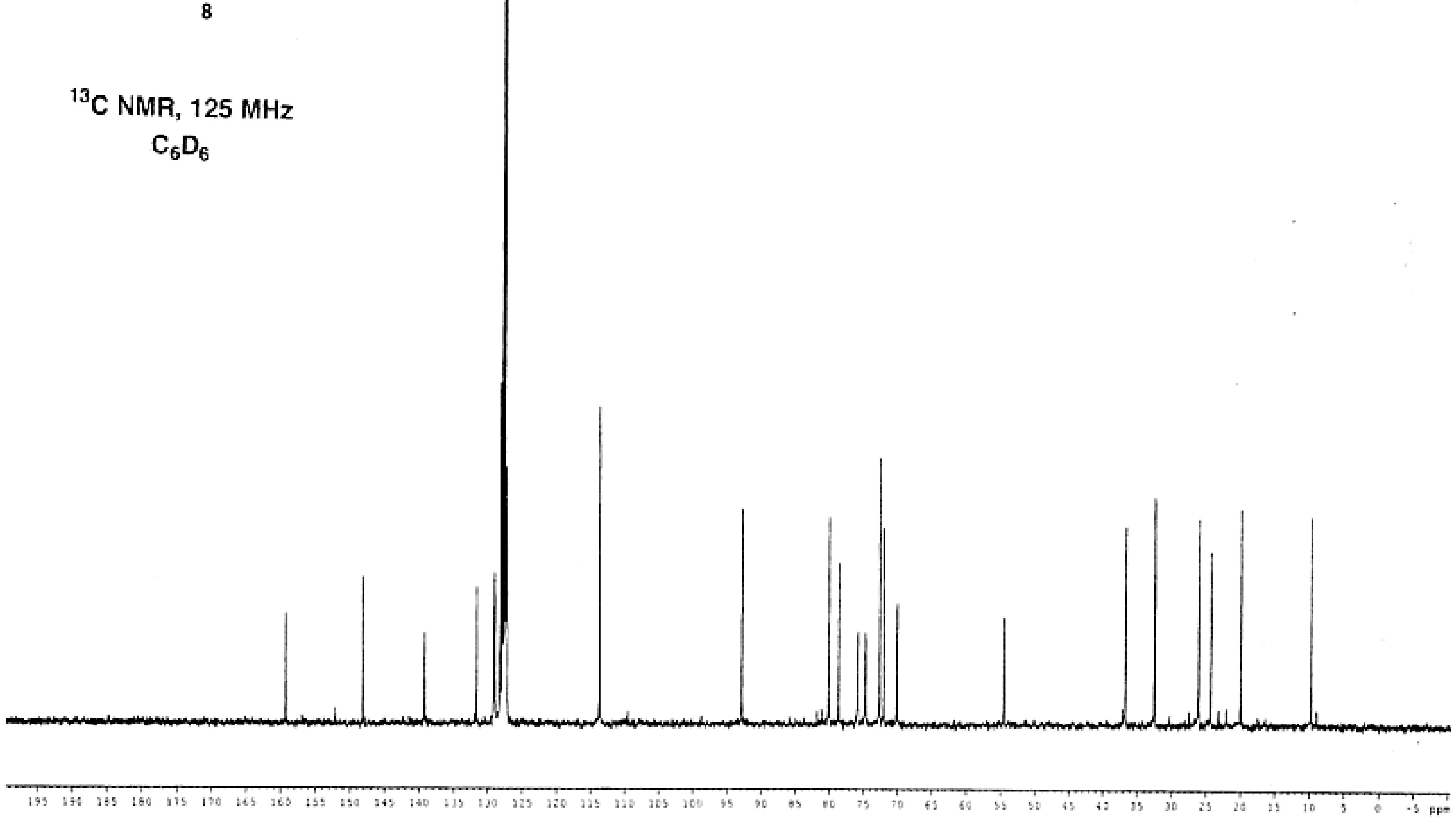


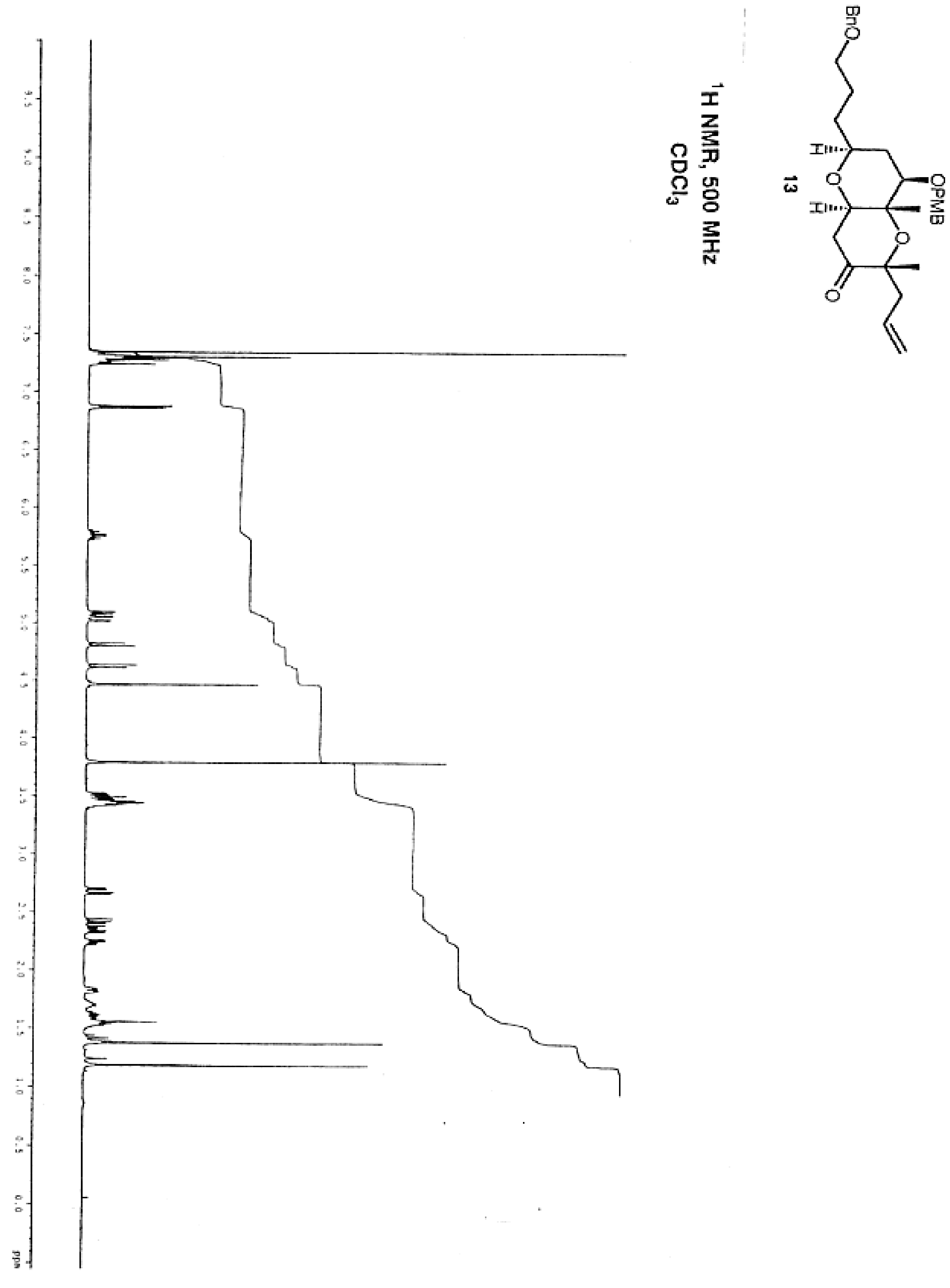


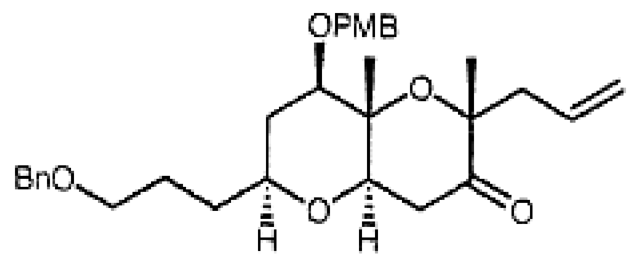
8

^{13}C NMR, 125 MHz

C_6D_6

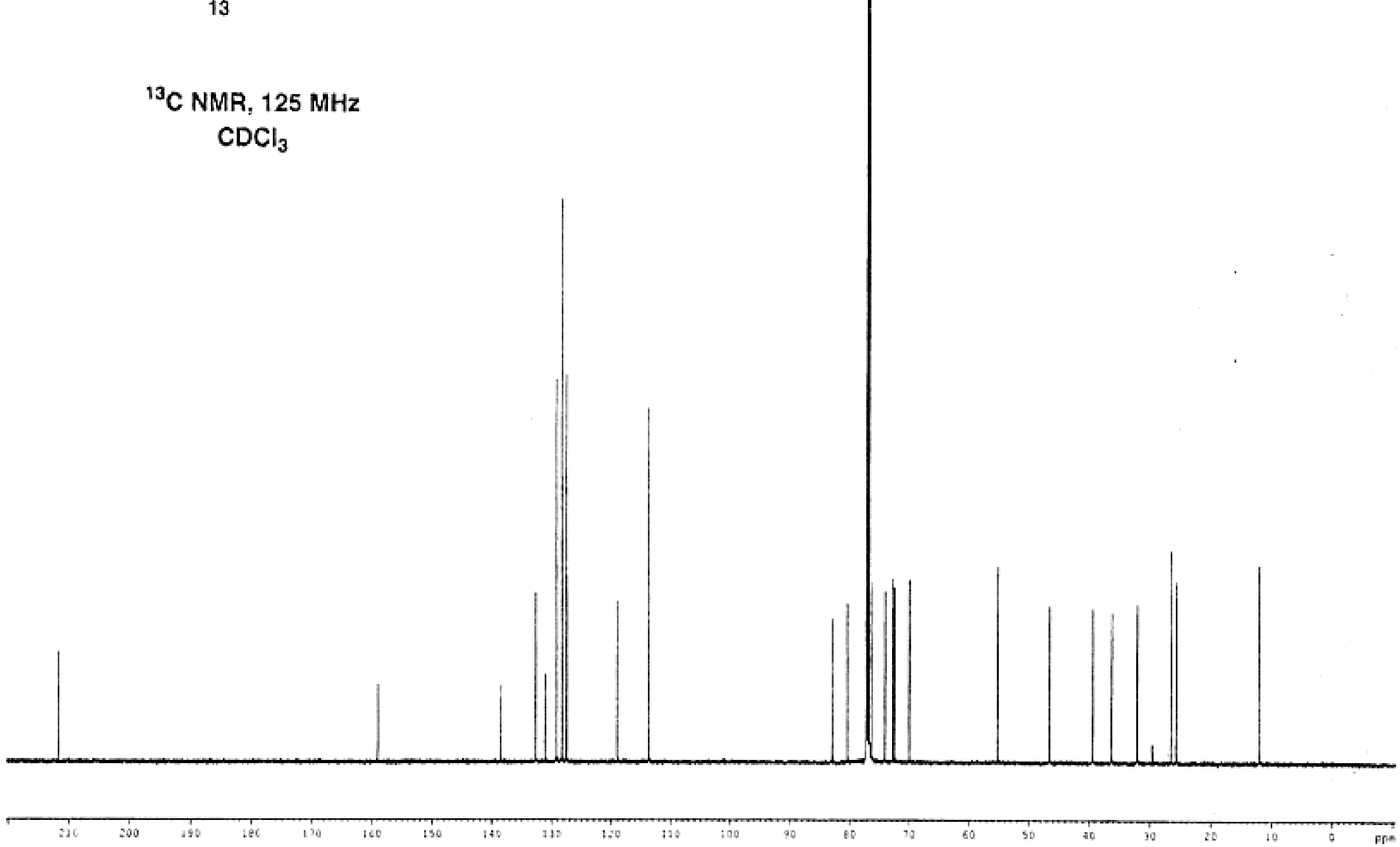


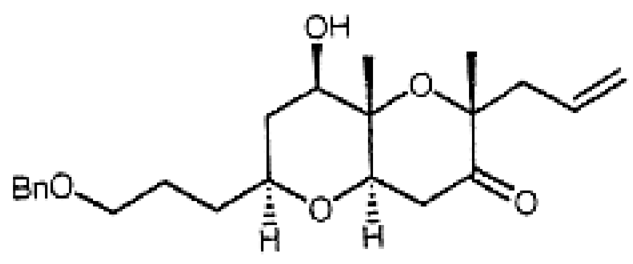

BnO
OPMB
13
1H NMR, 500 MHz
CDCl3



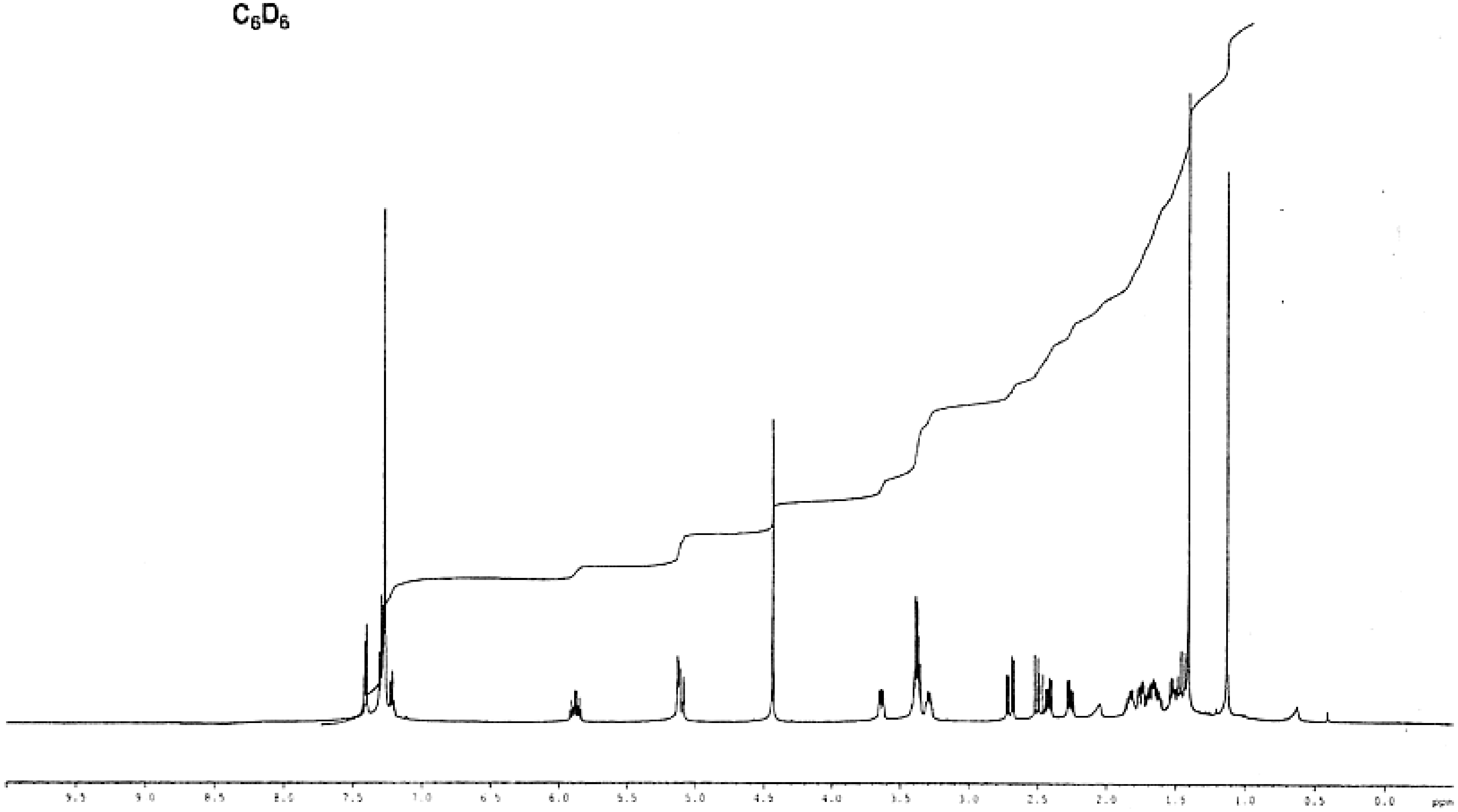
13

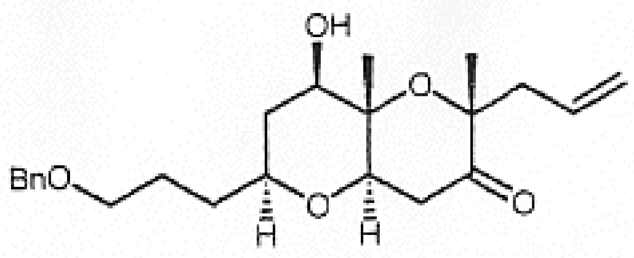
^{13}C NMR, 125 MHz
$CDCl_3$



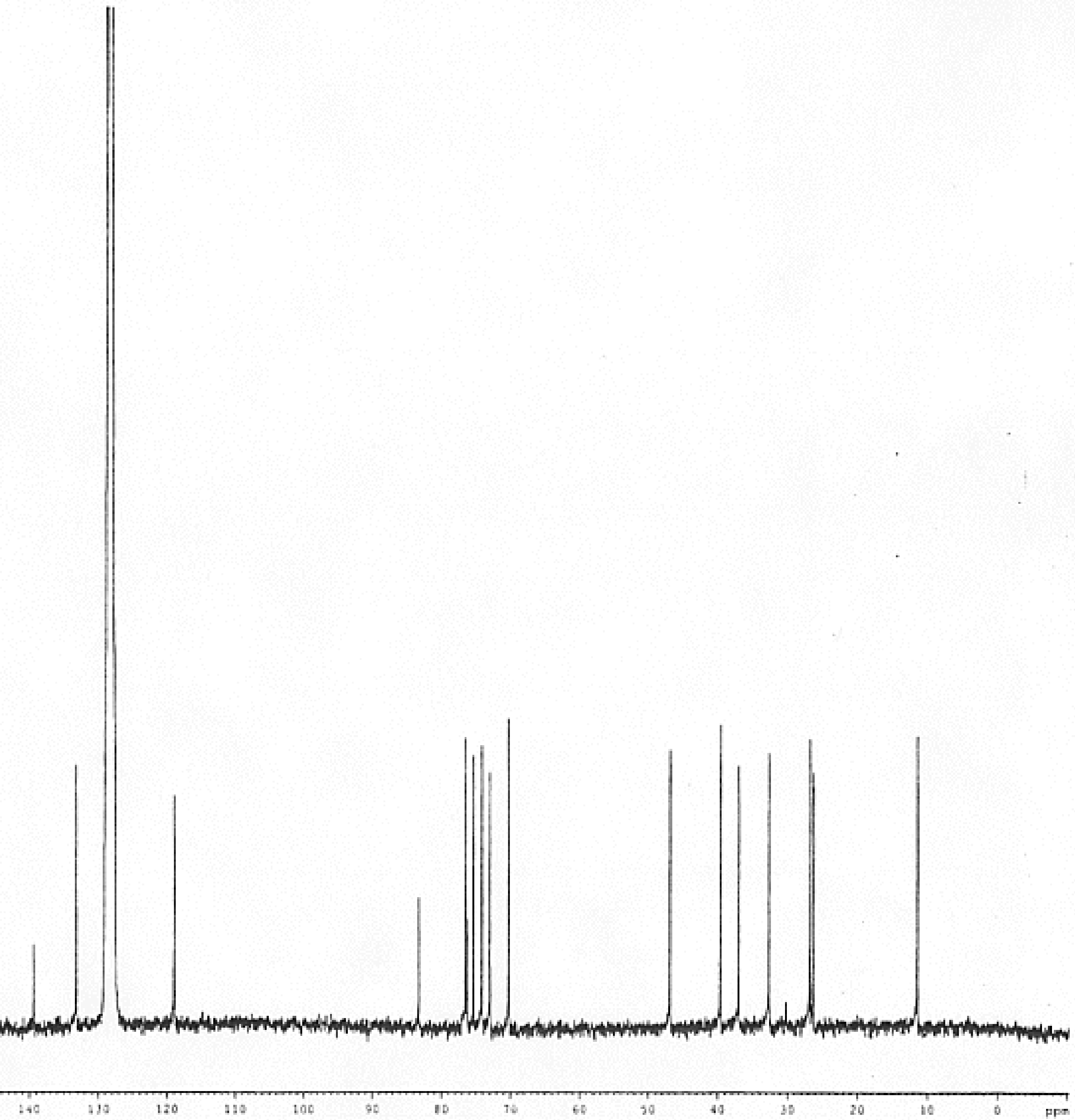


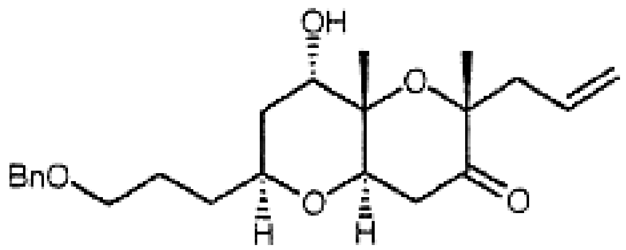
^1H NMR, 500 MHz
C_6D_6



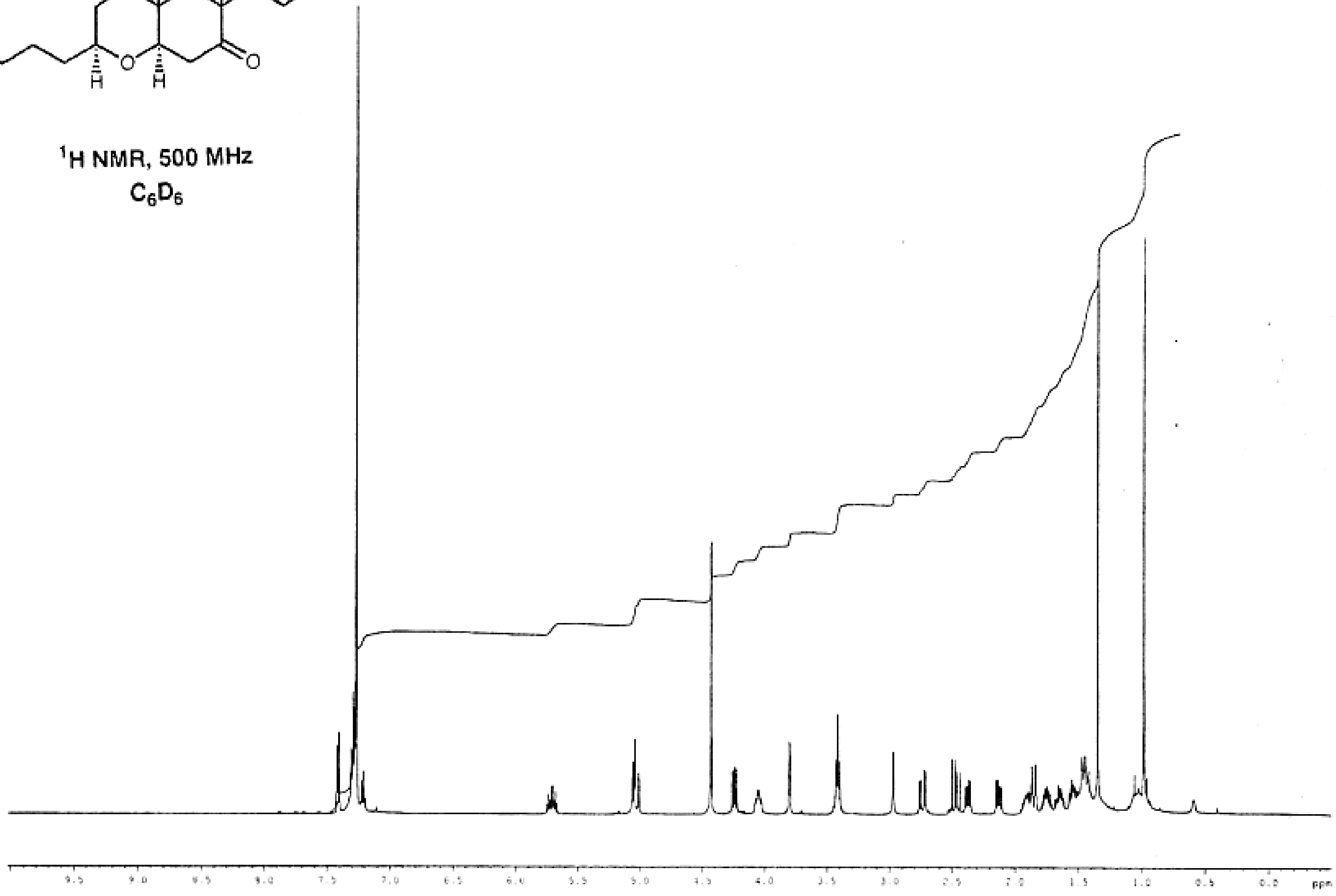


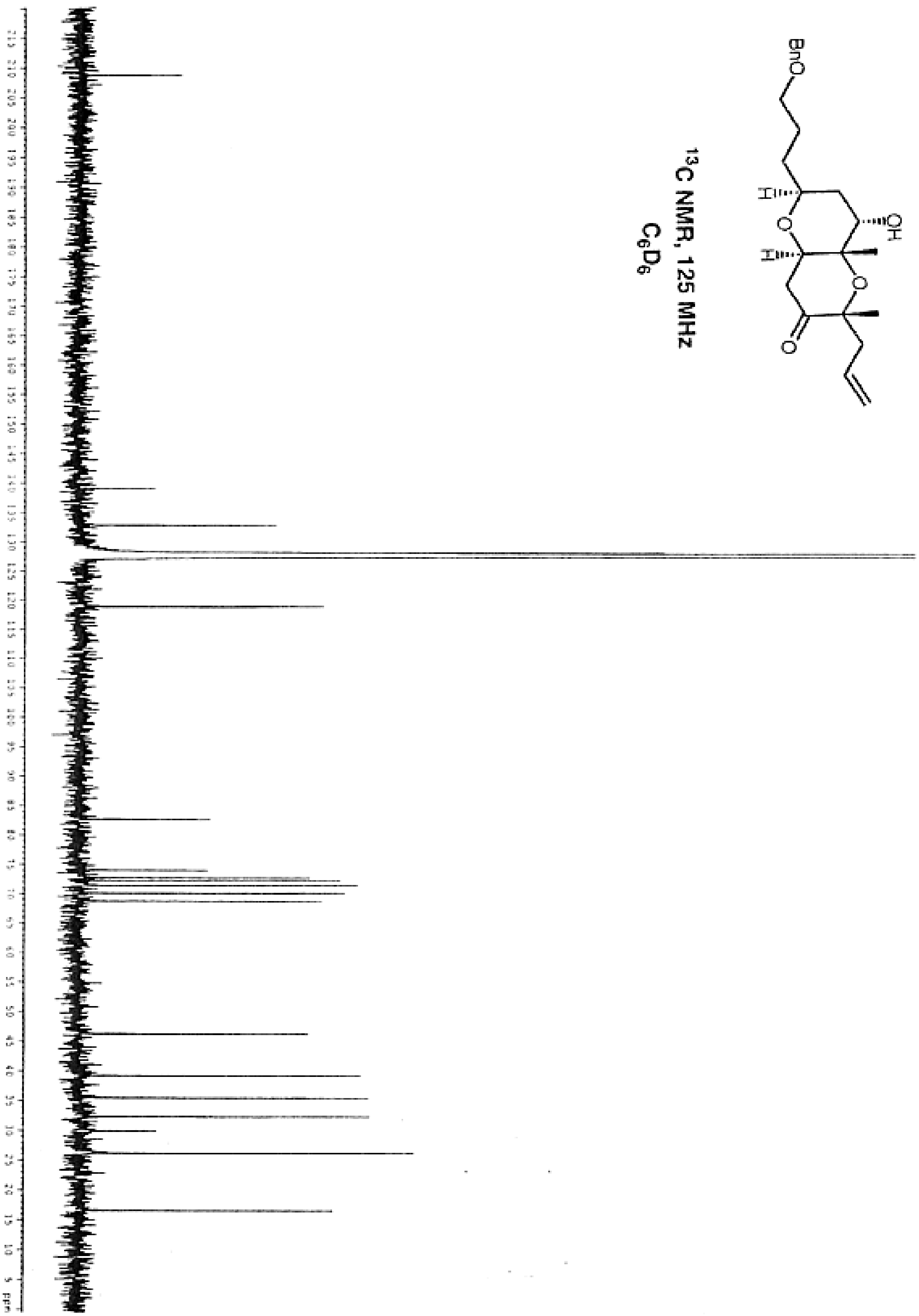
^{13}C NMR, 125 MHz
C_6D_6



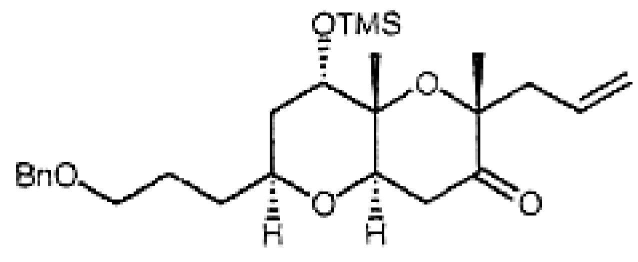


^1H NMR, 500 MHz
C_6D_6





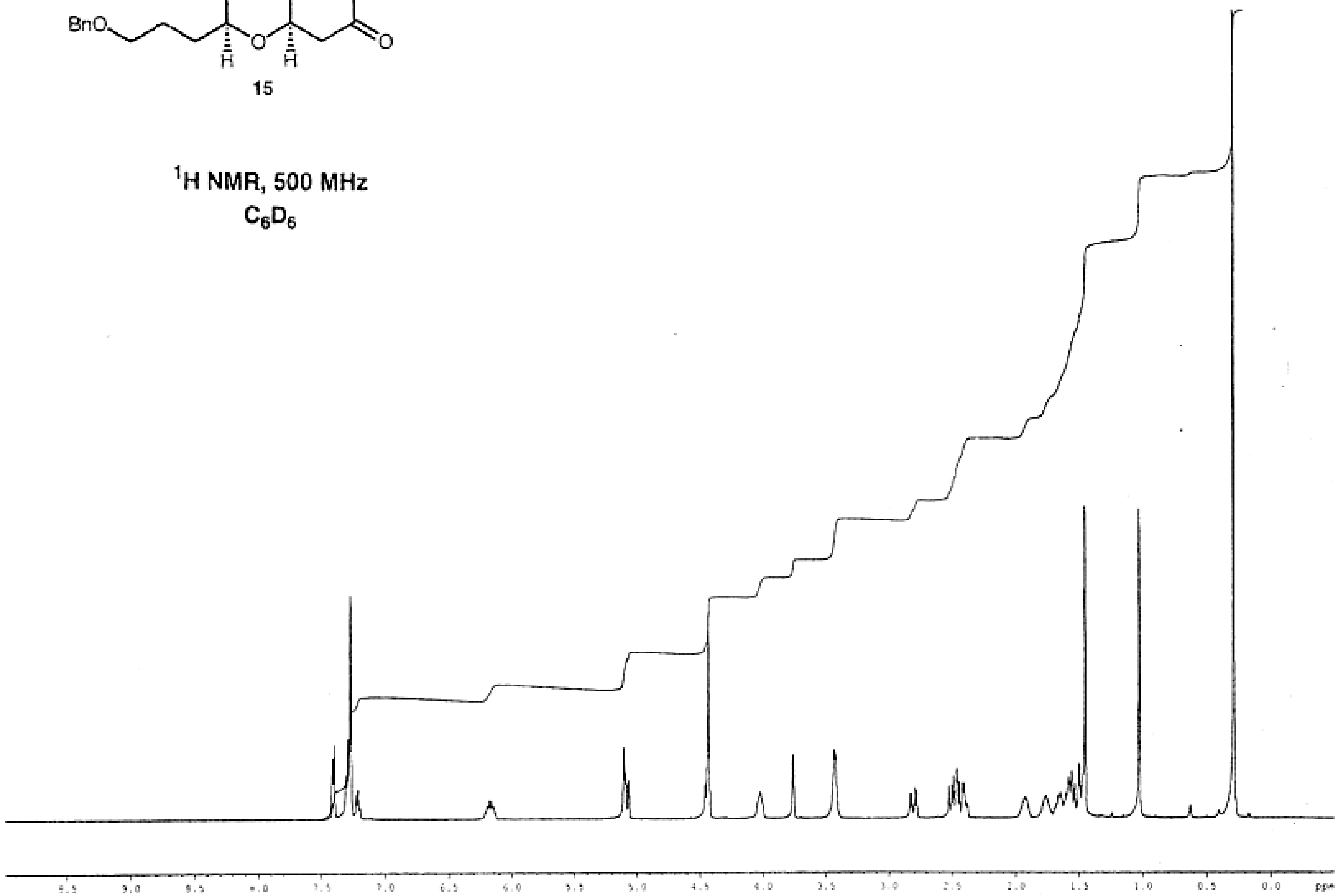
BnO
OH
H
O
H
O
O
^{13}C NMR, 125 MHz
C_6D_6
ppm

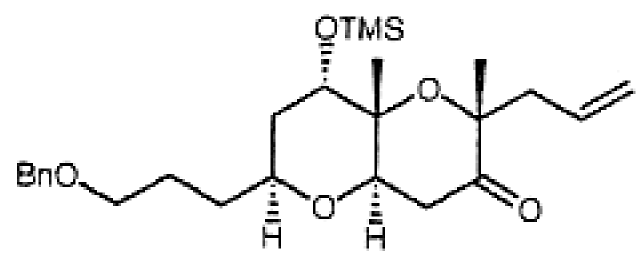


15

^{1}H NMR, 500 MHz

C_6D_6

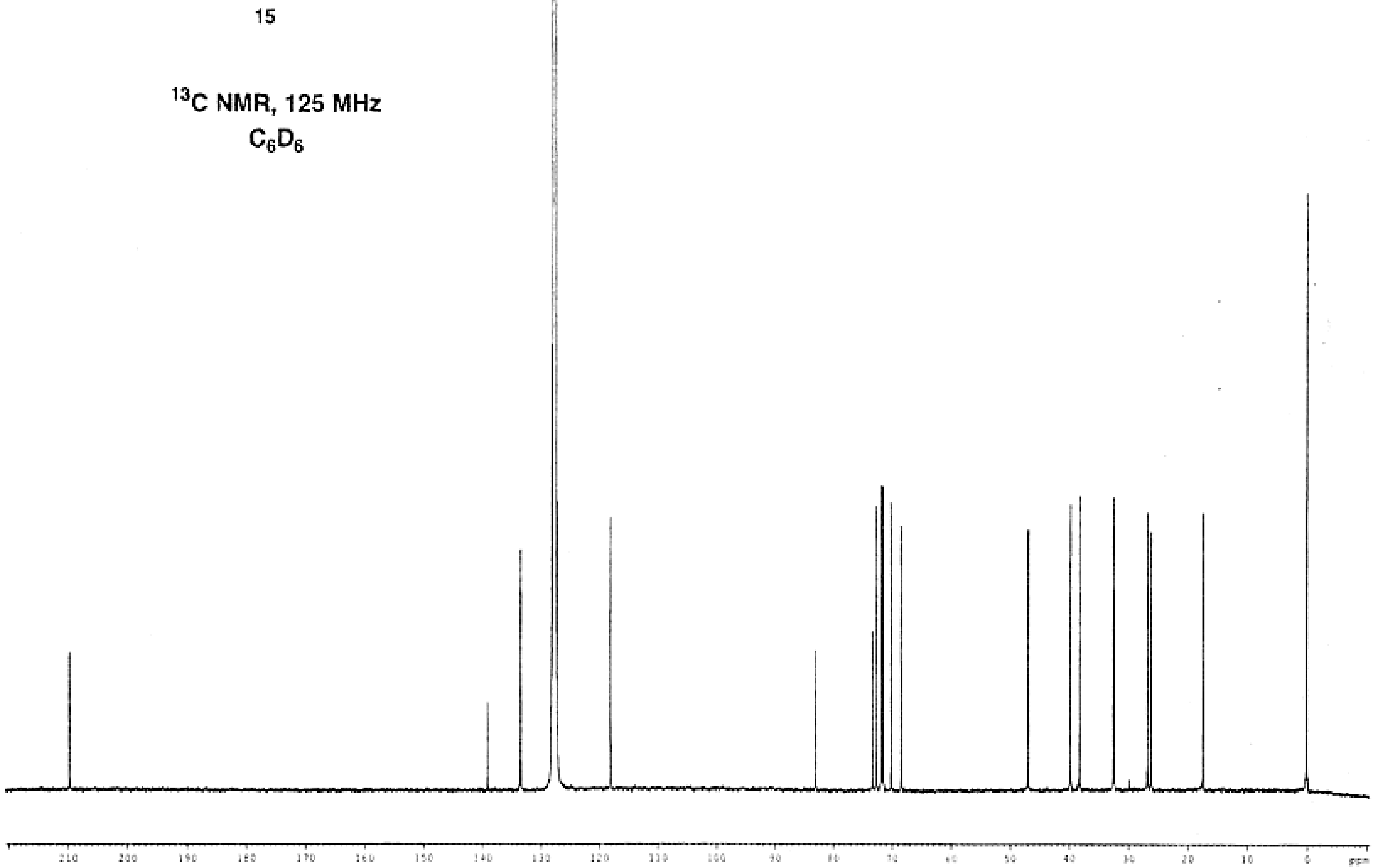


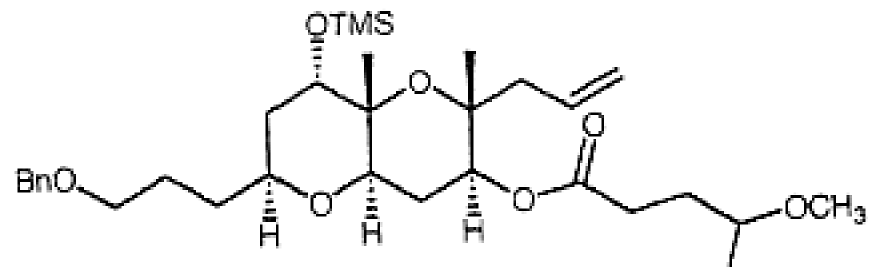


15

¹³C NMR, 125 MHz

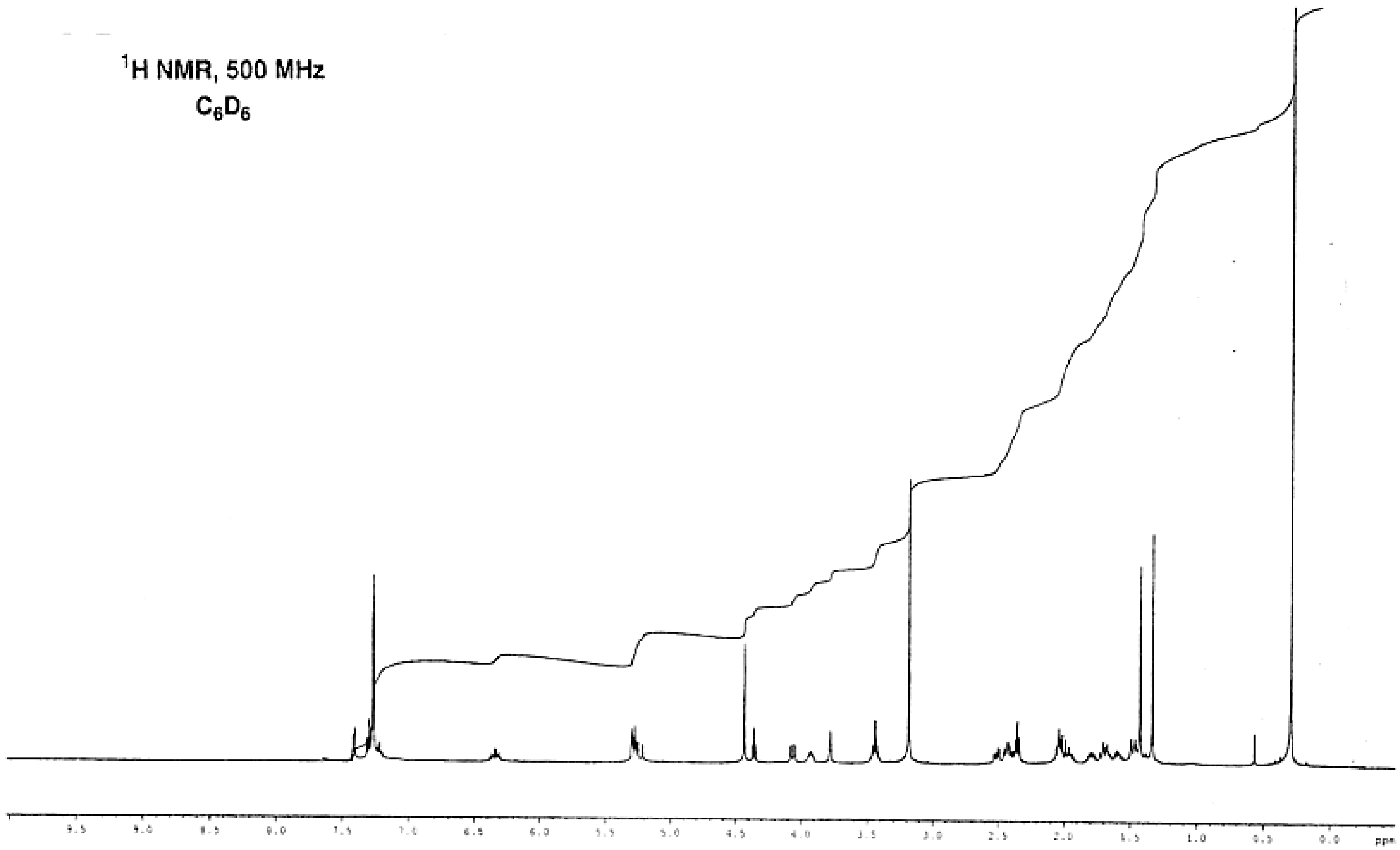
C_6D_6

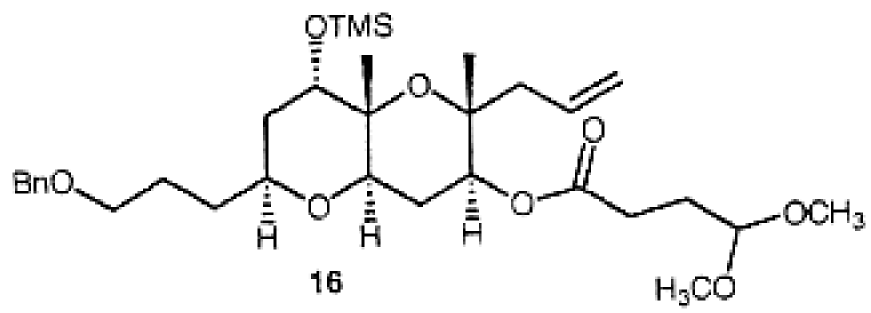




16

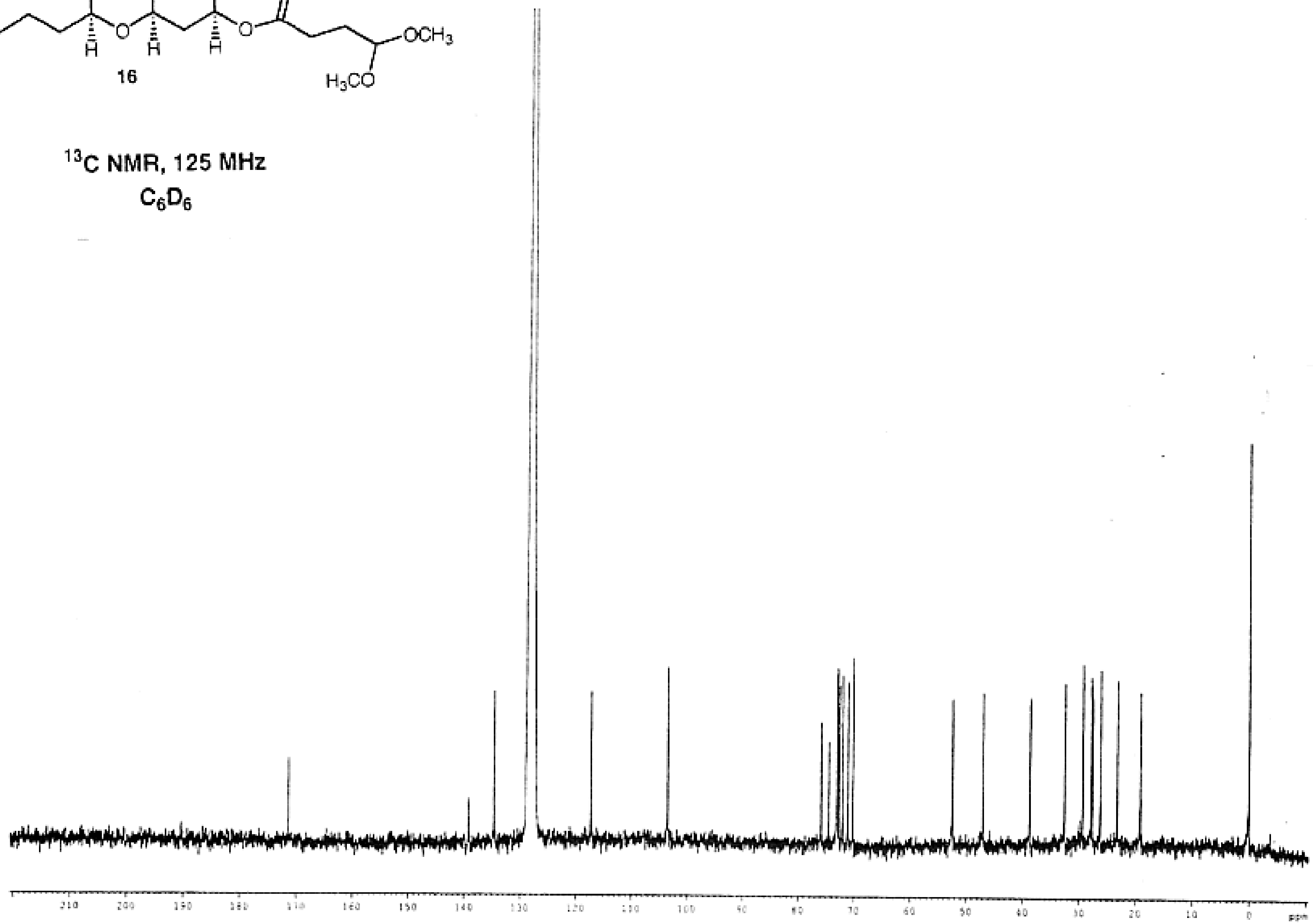
^{1}H NMR, 500 MHz
C_6D_6

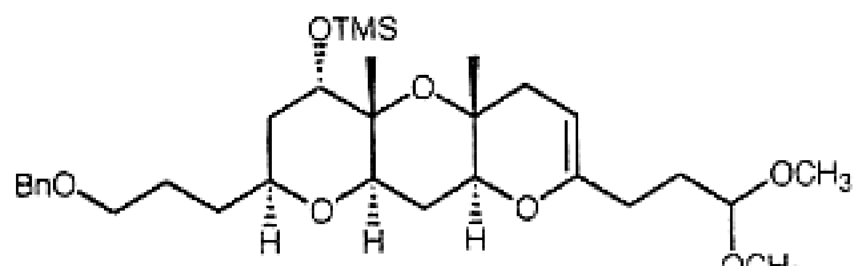




16

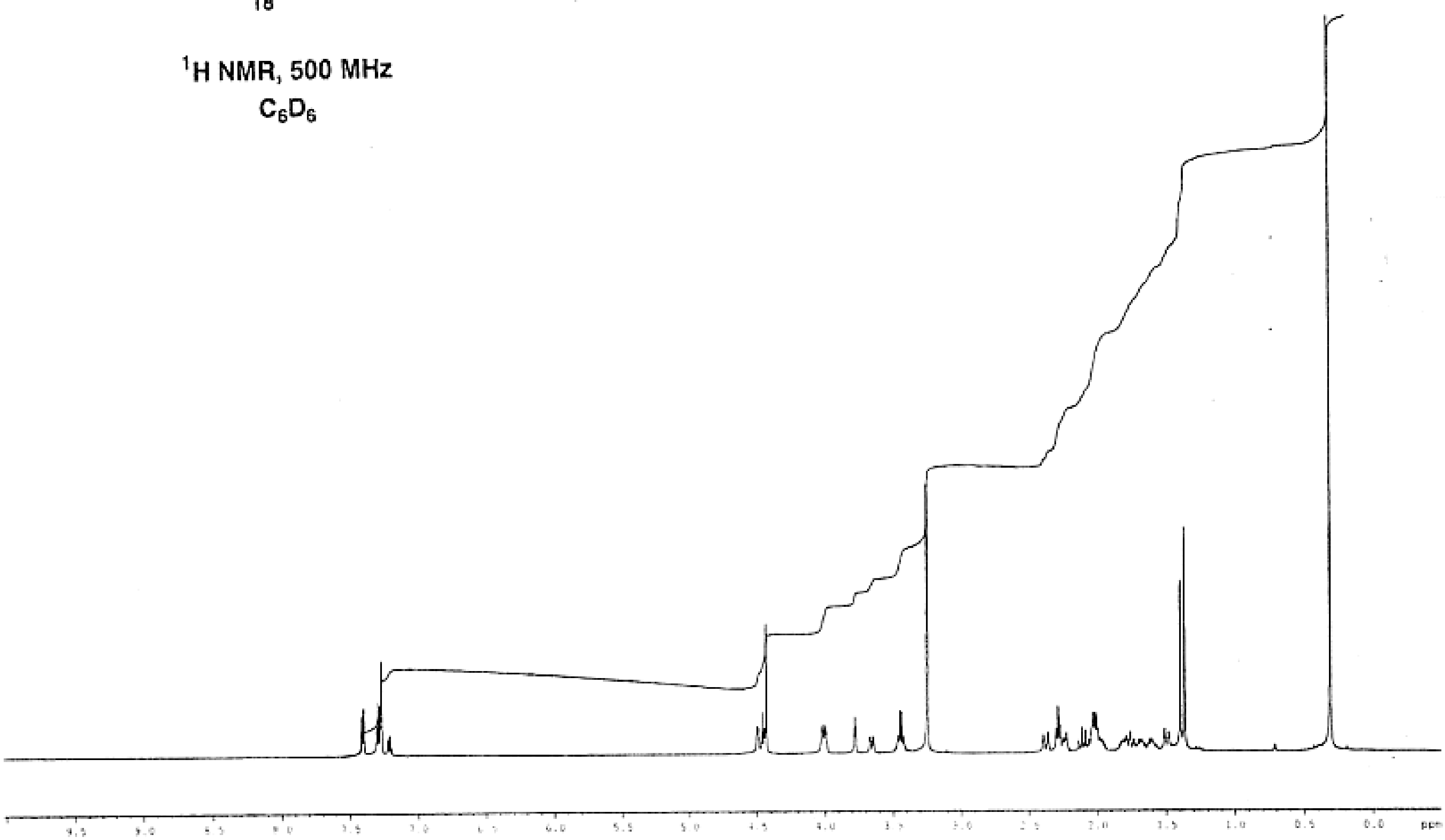
^{13}C NMR, 125 MHz
C_6D_6

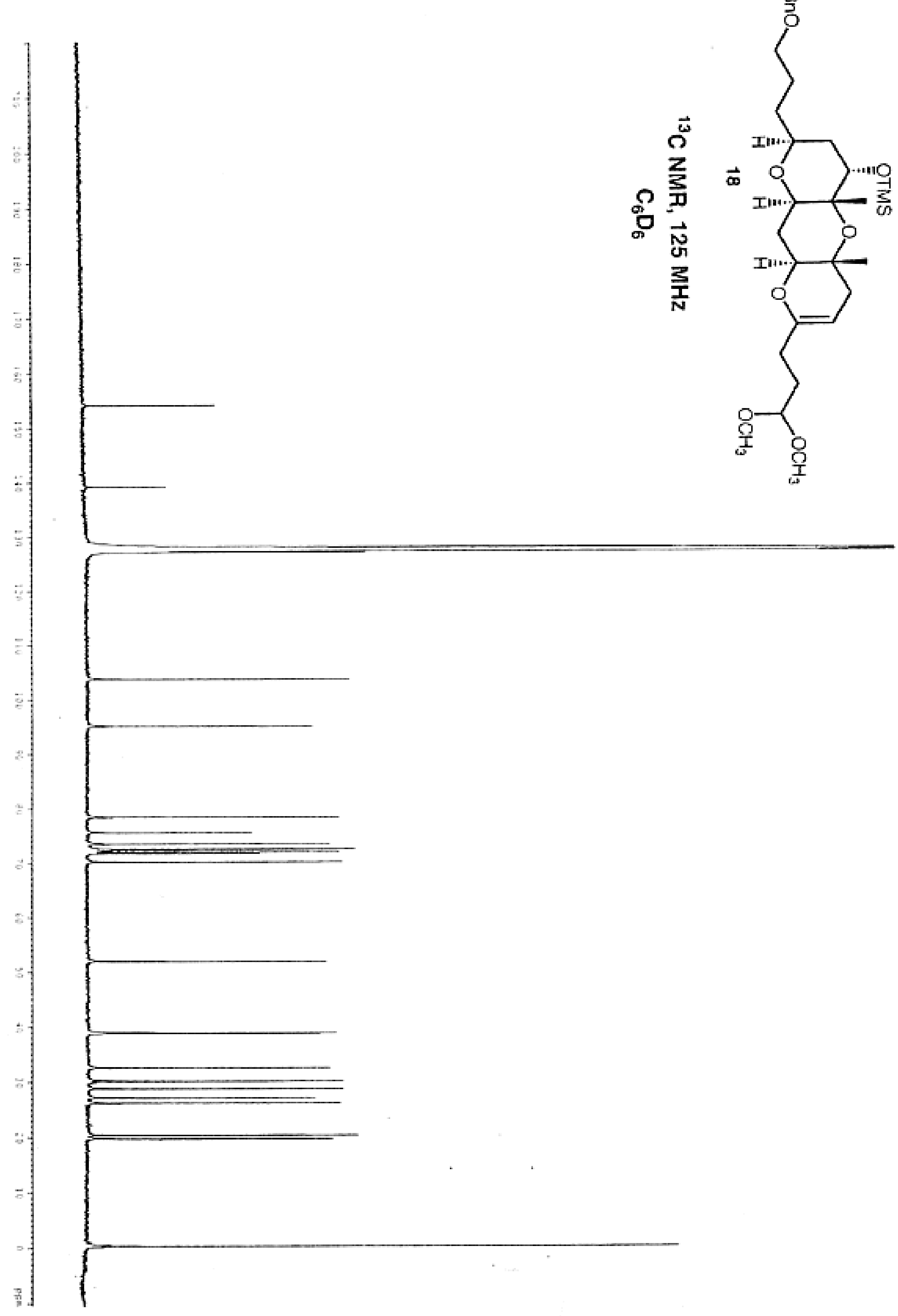




18

^{1}H NMR, 500 MHz
C_6D_6





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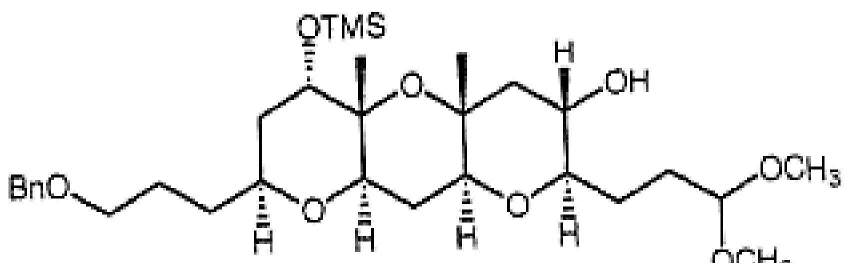
^{13}C NMR, 125 MHz

C_6D_6



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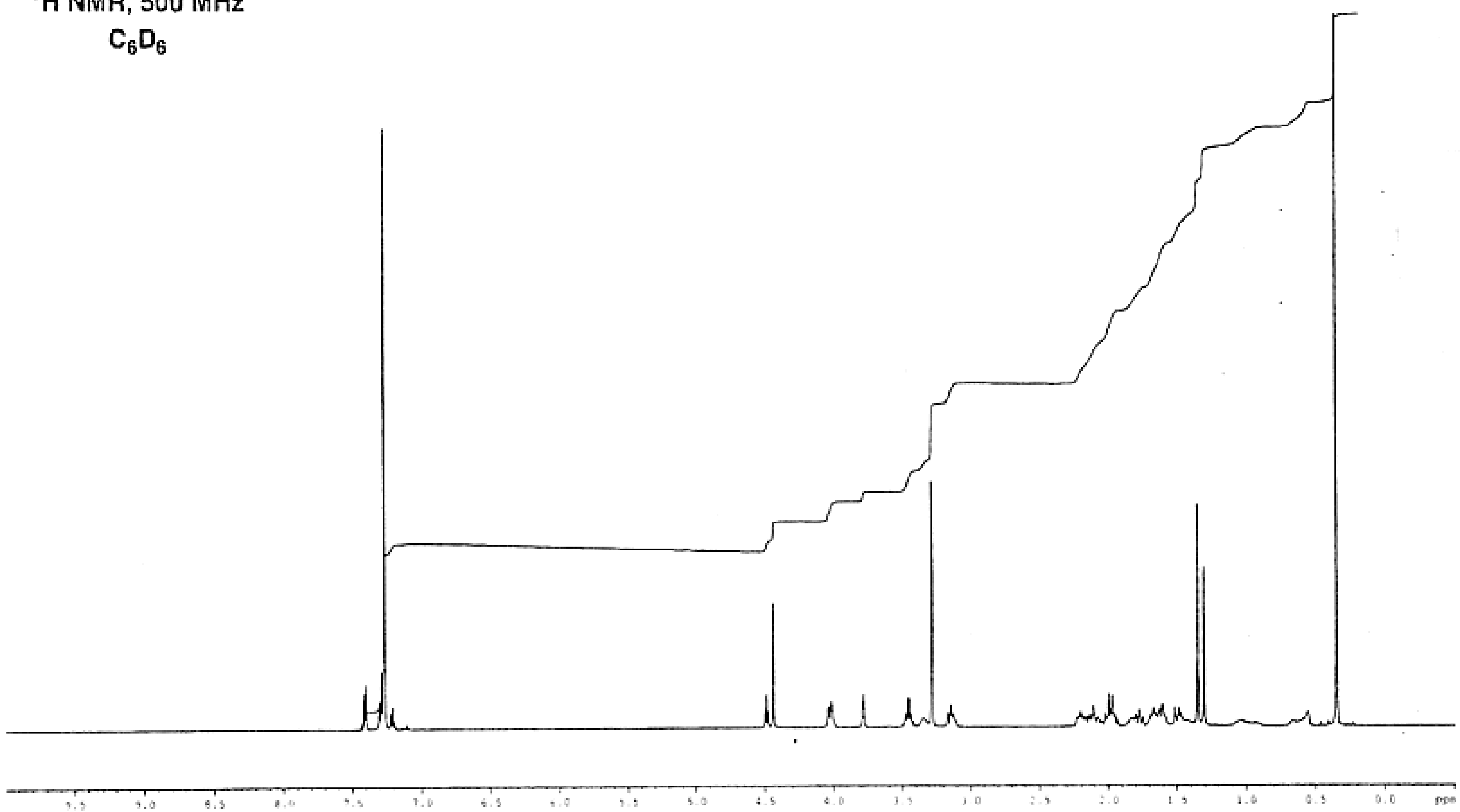
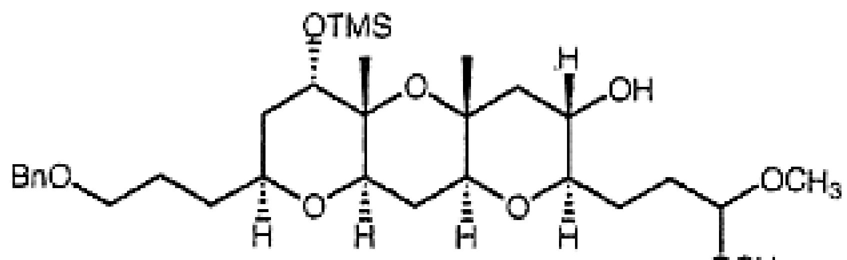
^{1}H NMR, 500 MHz
C_6D_6

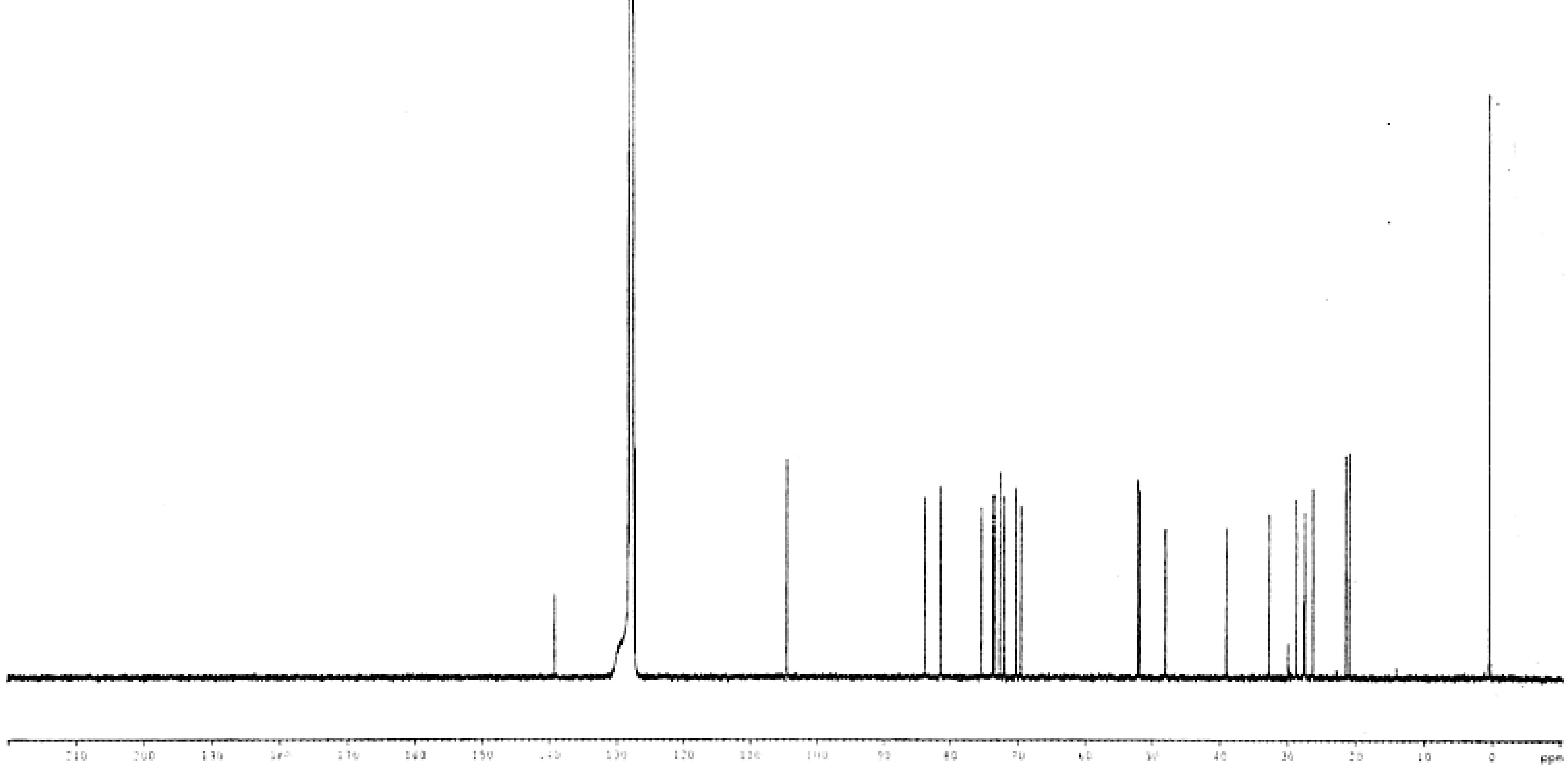


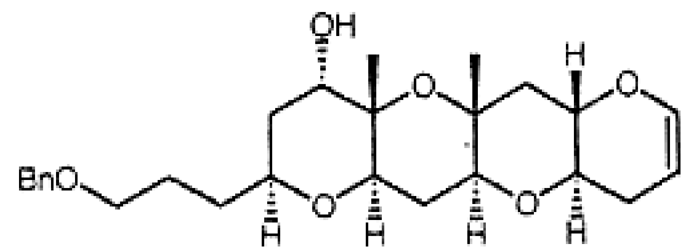


20

^{13}C NMR, 125 MHz

C_6D_6

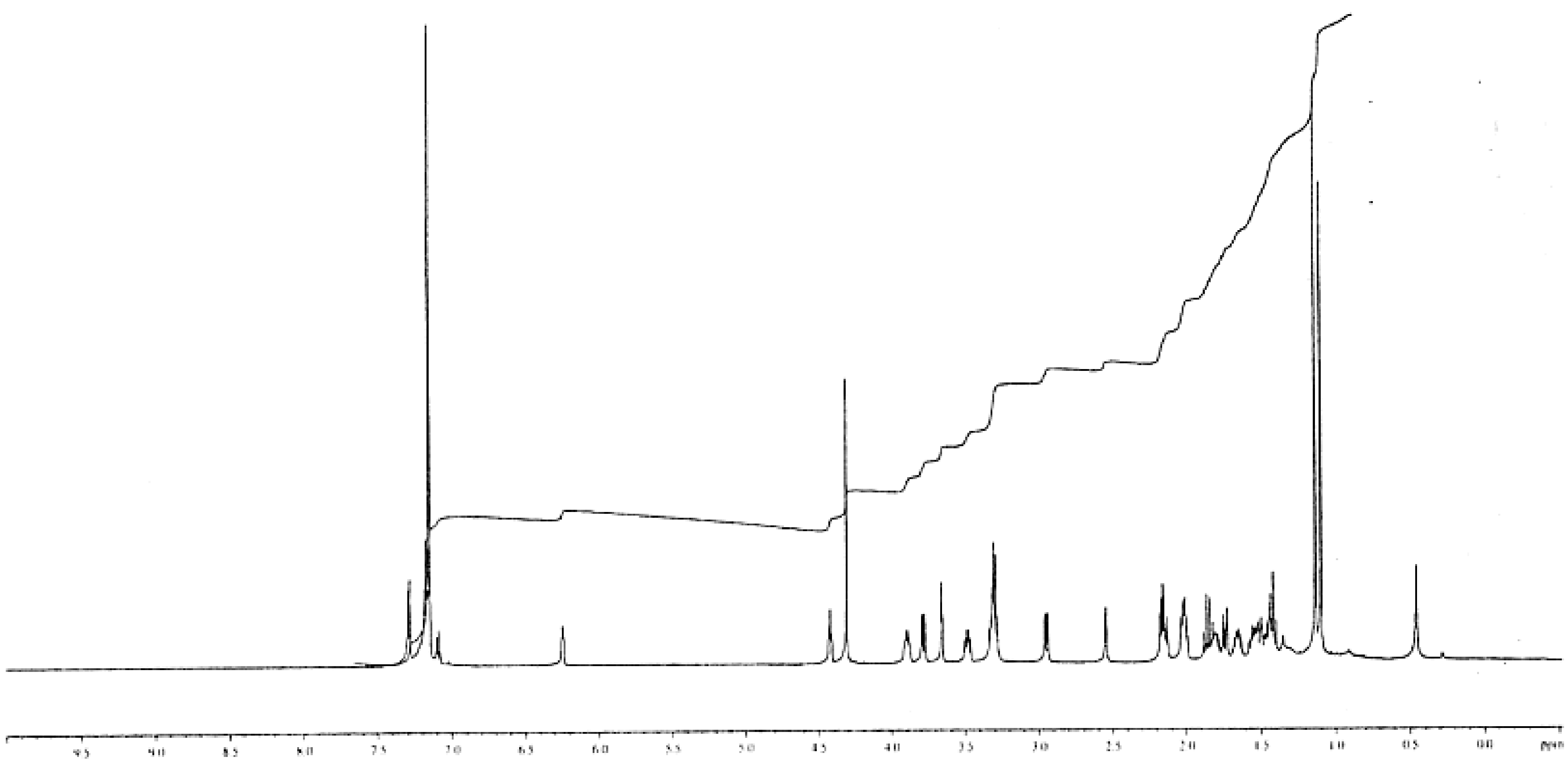


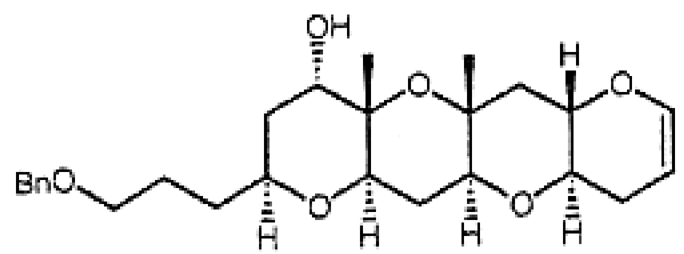


21

^{1}H NMR, 600 MHz

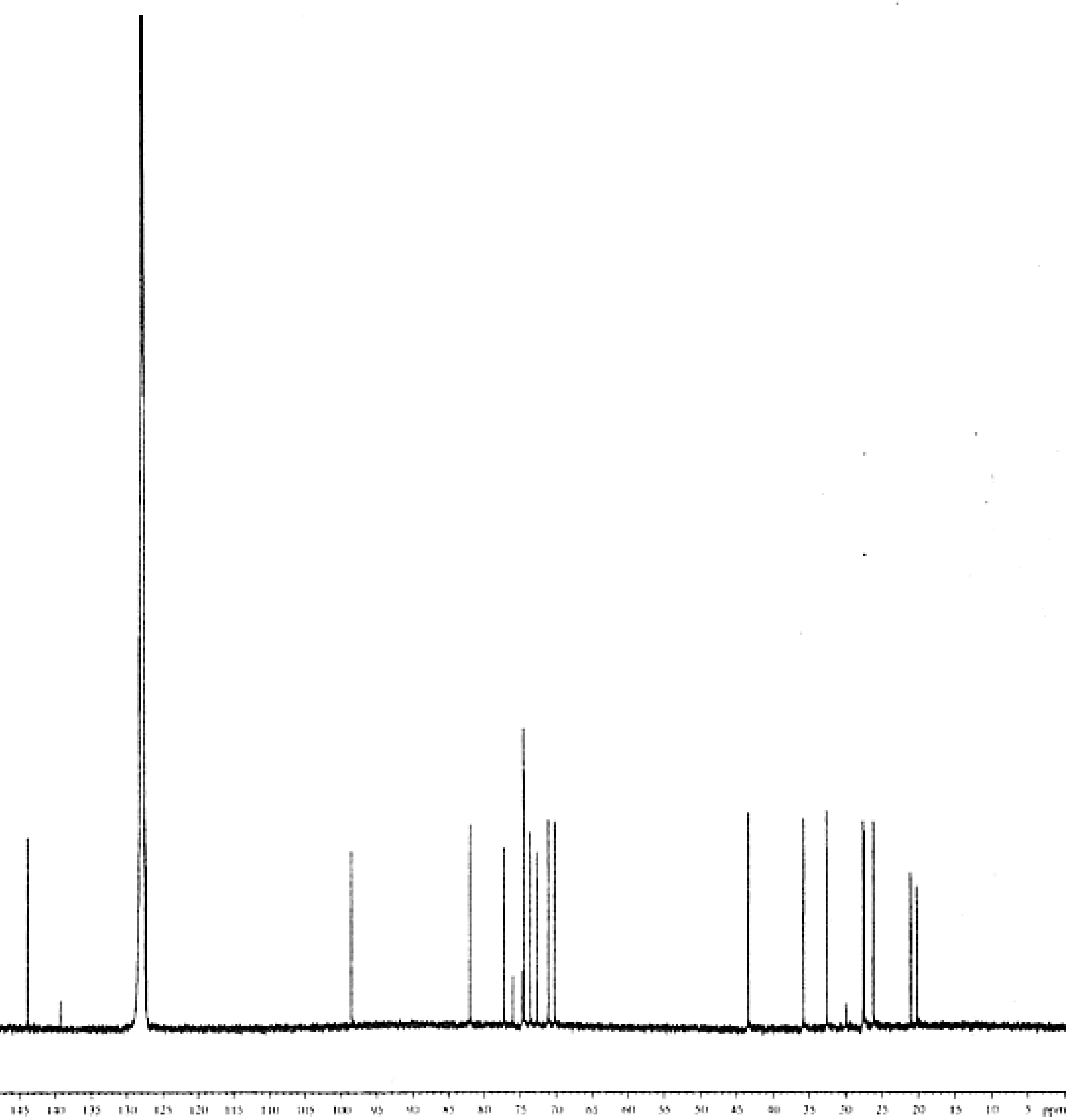
C_6D_6

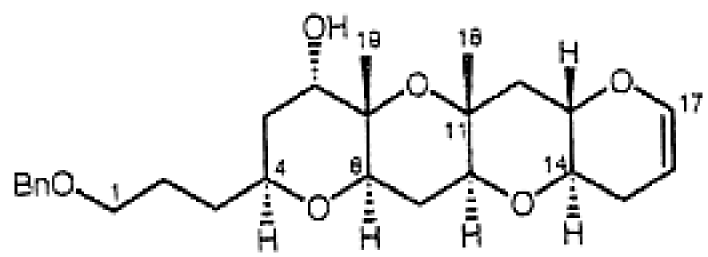




21

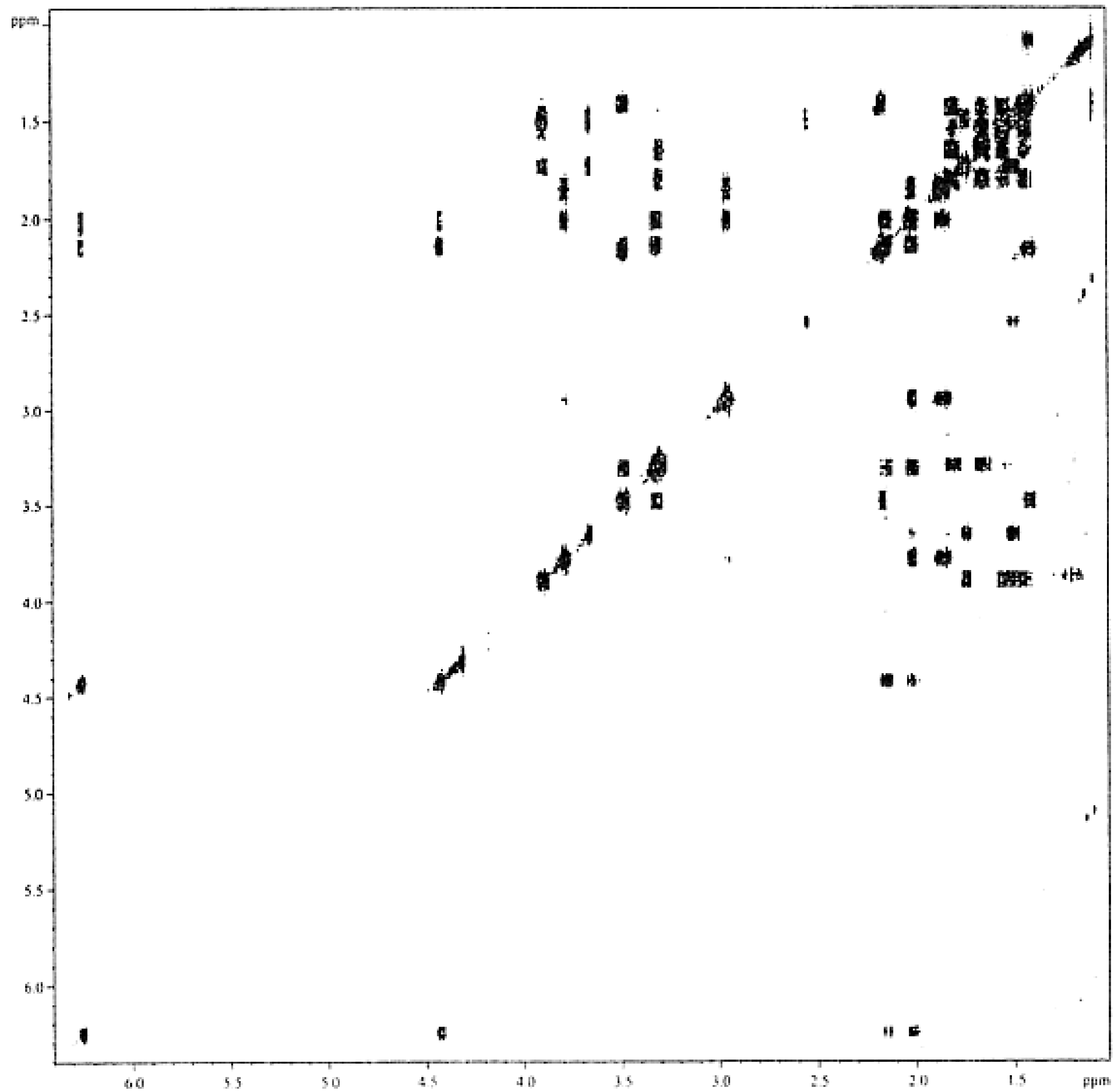
^{13}C NMR, 150 MHz
C_6D_6

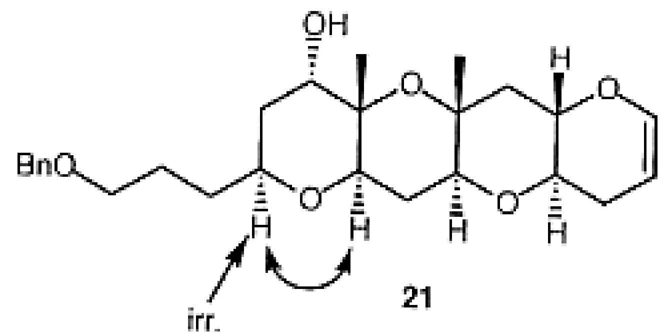




21

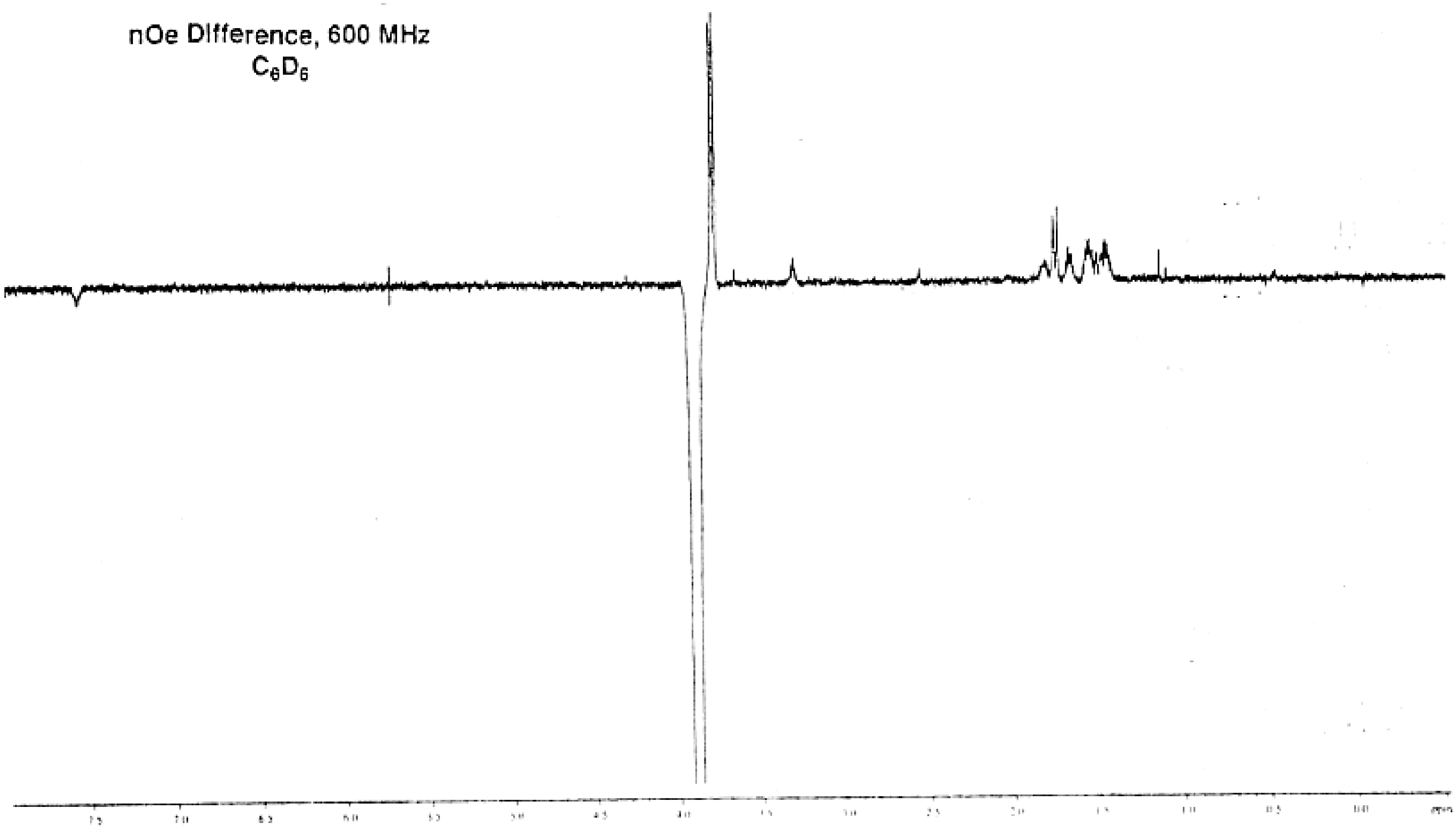
COSY, 600 MHz
C_6D_6

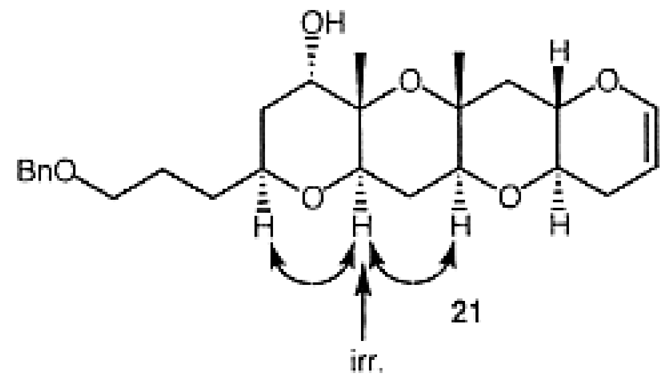




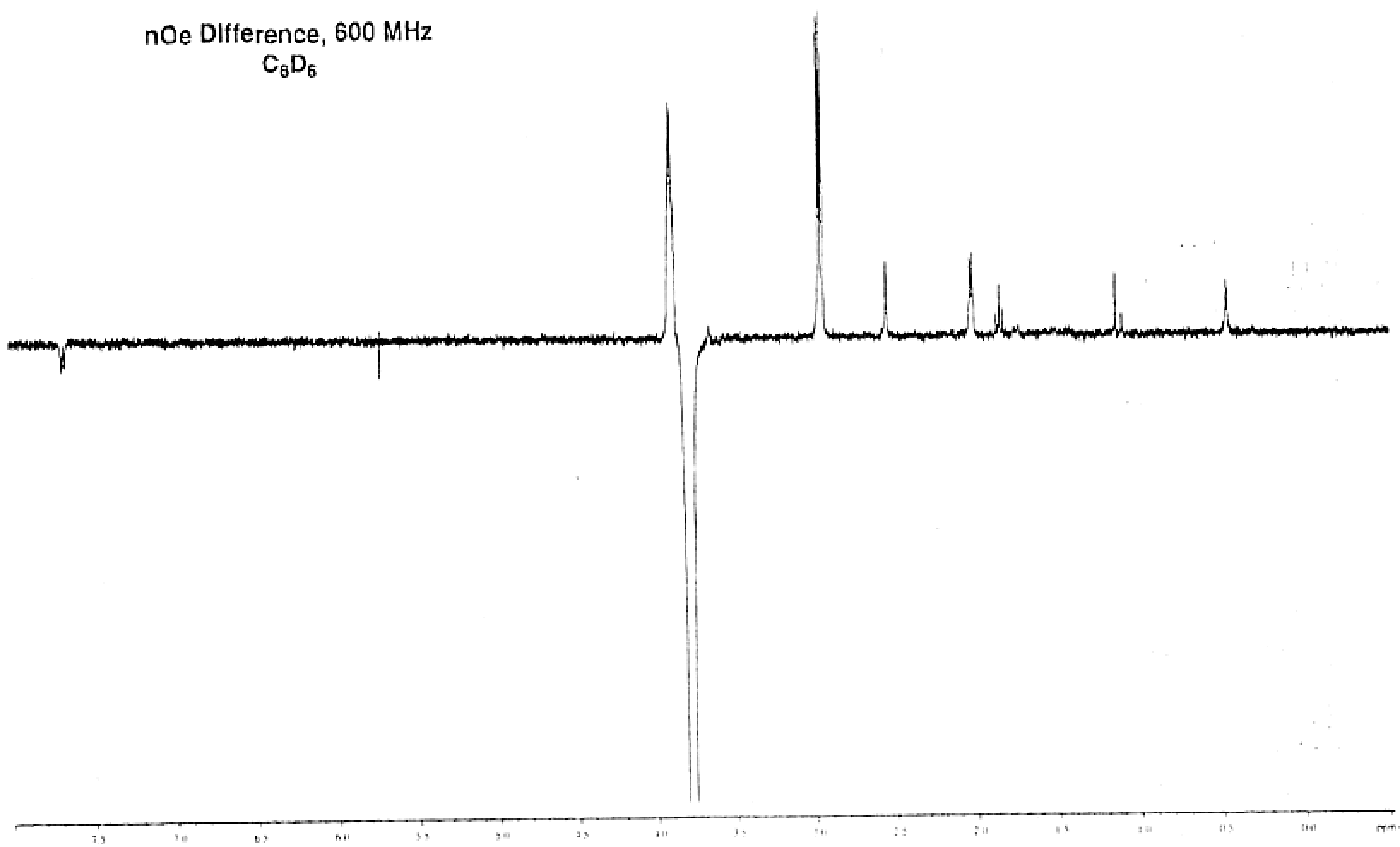
21

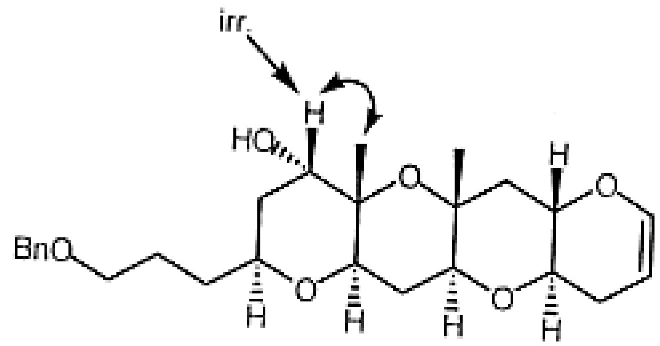
nOe Difference, 600 MHz
C_6D_6





nOe Difference, 600 MHz
C_6D_6





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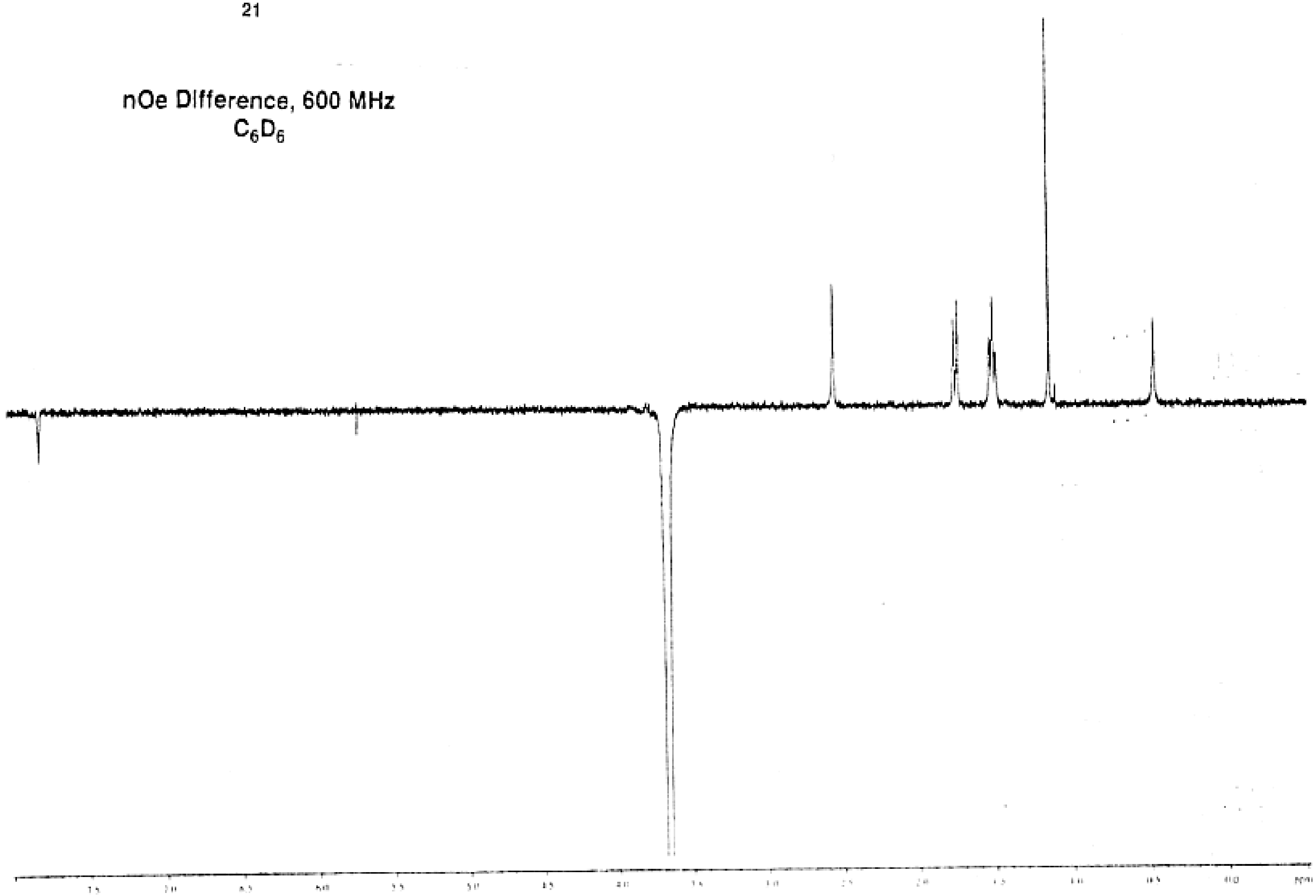
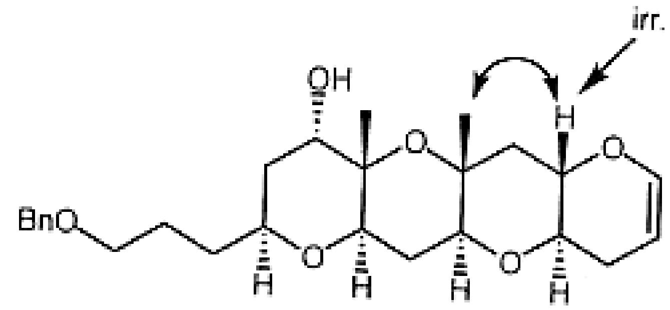
nOe Difference, 600 MHz
C_6D_6





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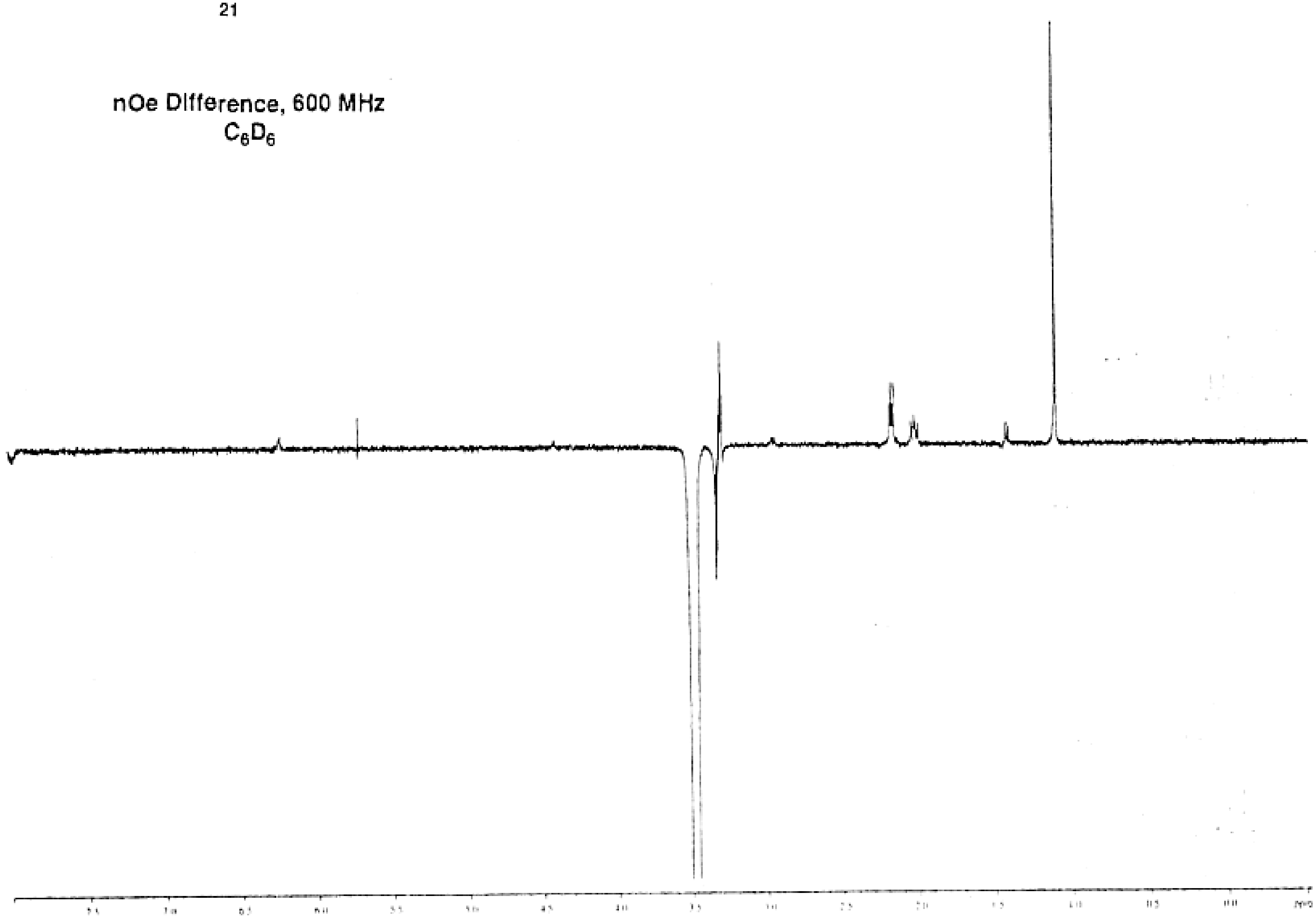
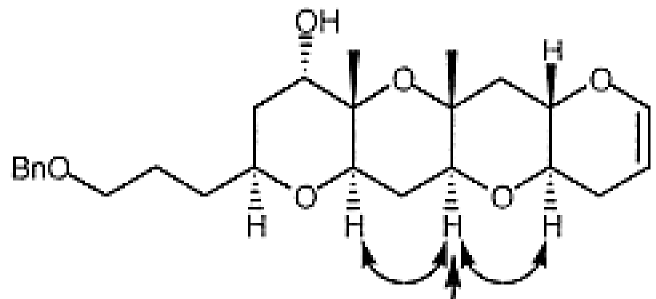
nOe Difference, 600 MHz
C_6D_6





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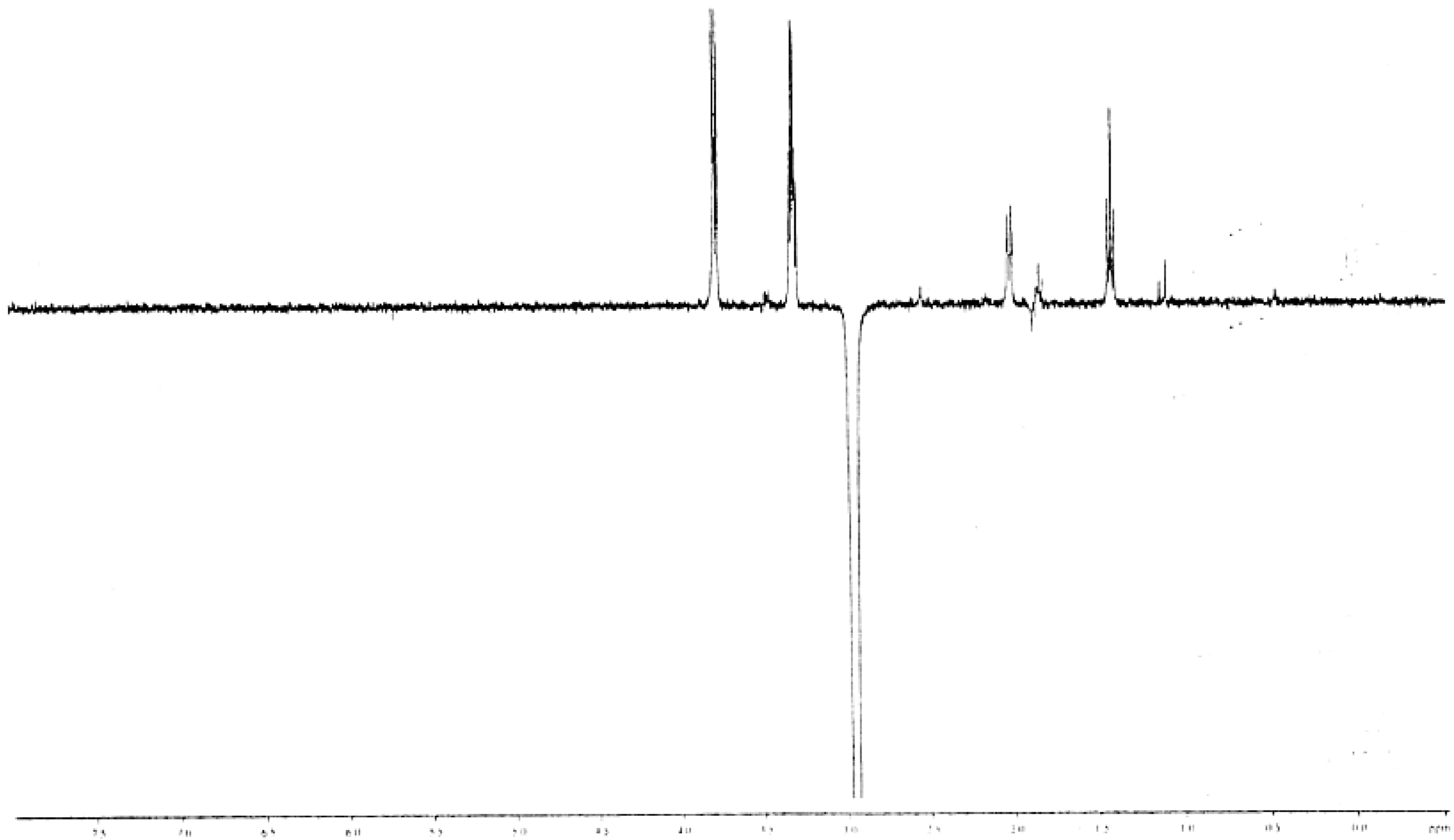
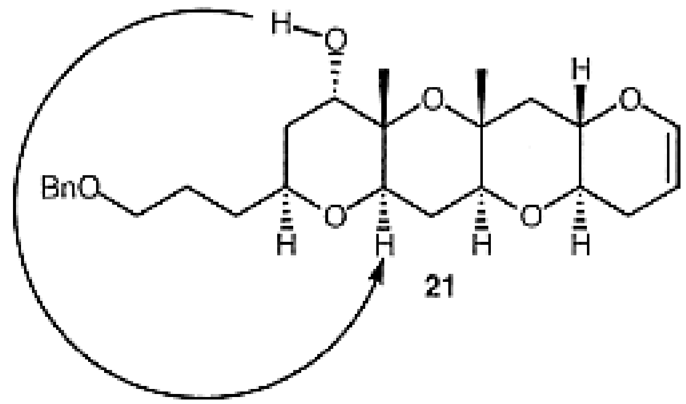
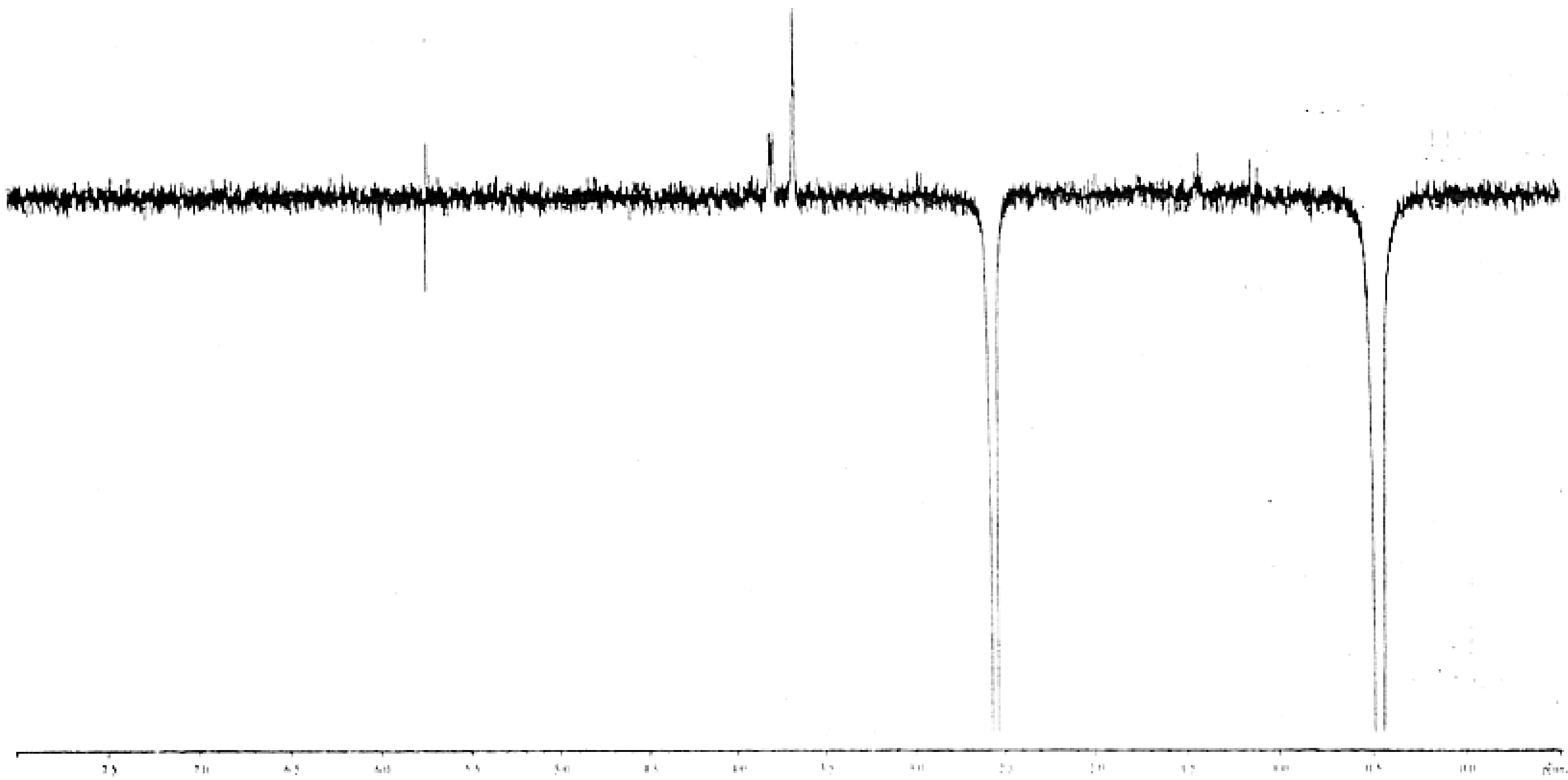
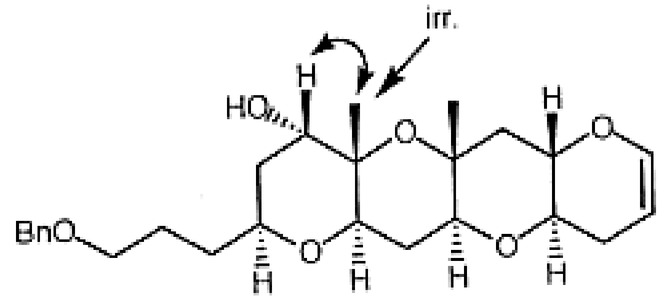
nOe Difference, 600 MHz
C_6D_6





nOe Difference, 600 MHz
C_6D_6





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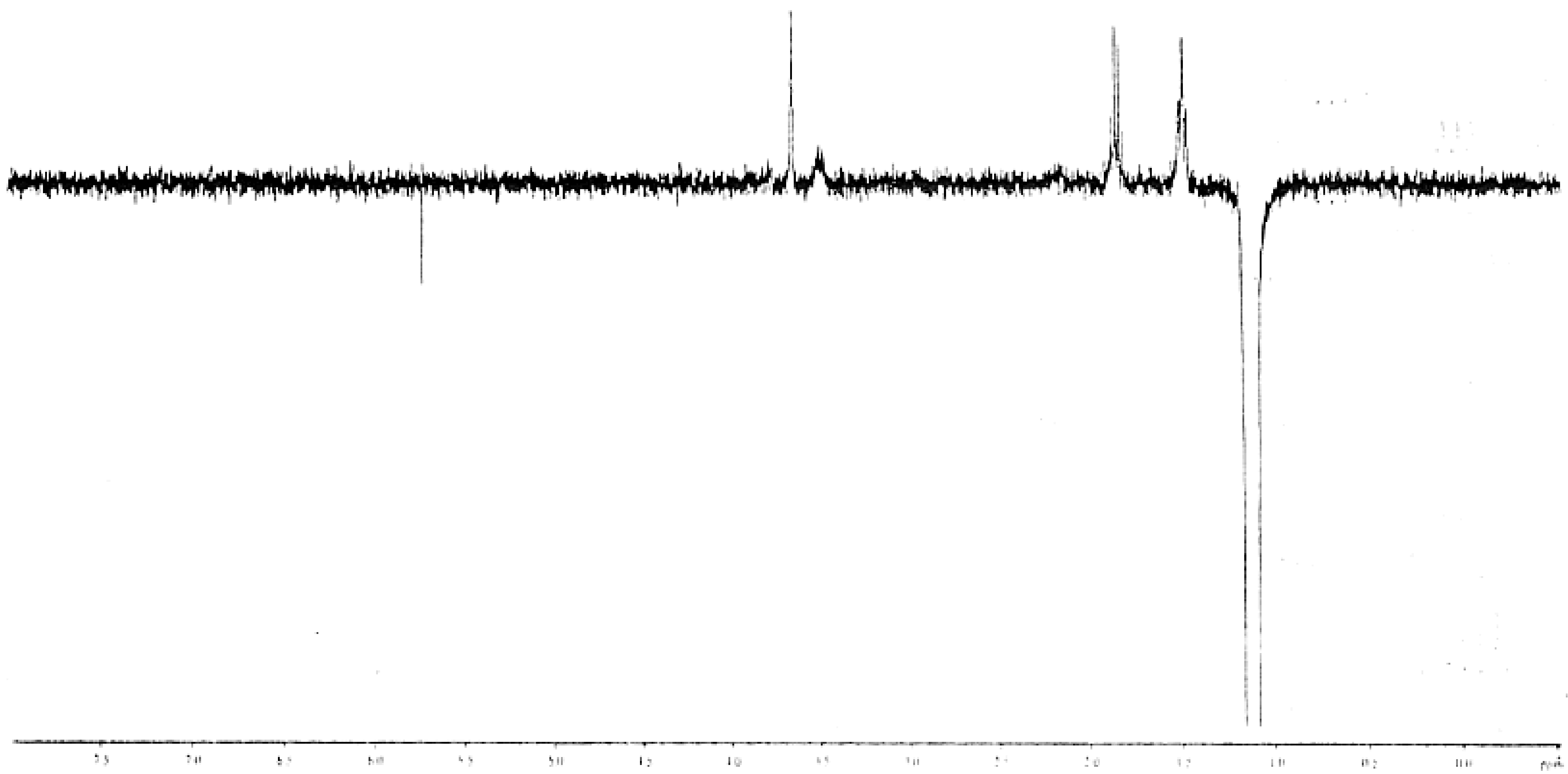
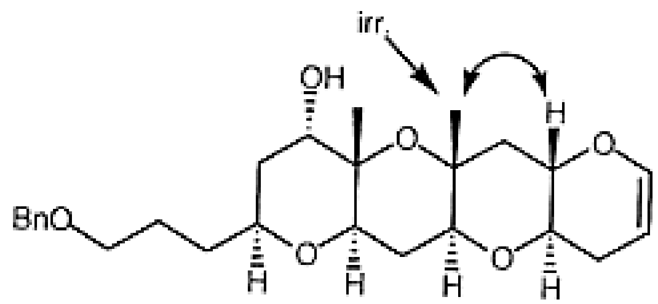
nOe Difference, 600 MHz
C_6D_6





21

nOe Difference, 600 MHz

C_6D_6