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A Model Steroid Glycoside Synthesis via A Glycosyl Transfer Mediated by Heterocycloaddition

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Supplementary Material

EXPERIMENTAL SECTION

Pulsed Fourier transform 300 MHz 1H and 75 MHz 13C spectra were obtained with deuterated chloroform (99.8%, 0.03% v/v TMS). Chemical shifts are in δ or ppm units downfield from Me_4Si as internal reference. Coupling constants are reported in Hertz units (J value). The assignment of the ^{13}C was confirmed by single frequency off resonance decoupled and proton coupled spectra. TLC analyses were done on silica gel 60 F254 plates available from EM Science, and visualized by dipping them in a cerium sulfate or polymolybdic acid solution. All regular and flash column chromatography separations were performed using 230-400 mesh, 60 Å silica gel . Optical rotations were recorded on an automatic polarimeter using a 1 dm cell at the reported temperatures and concentrations.

5α-Cholest-1-en 3-one (6). Three steps from 3β-cholestanol. To five grams (12.9 mmol) of3β-cholestanol in dry acetone (180 mL) and diethyl ether (45 mL) was added to 11 mL of CrO_3-H_2SO_4 solution (4.0 g of CrO_3 was added into 3.5 mL of cooled H_2SO_4, followed by dilution to 15 mL with distilled water) via a dropping funnel, at 15 °C. The reaction mixture was stirred mechanically. Within 10 min, the reaction color turned from orange to green. The mixture was diluted with 200 mL of distilled water. The cloudy, green suspension was rotary evaporated to remove acetone and ether. The residue was extracted with ether : chloroform (9:1) (6 x 100 mL). The combined extracts were washed with water (3 x 150 mL), dried over Na_2SO_4 and evaporated in vacuo to give 4.8 g (97%) of **5α-cholestan-3-one** . : mp 128-130 °C (lit. 128-130 °C)[1]; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.68 (s, 3H.), 0.86 (d, 6H, J=6.6), 0.90 (d, 3H, J=6.5), 1.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.6, 12.2, 18.9, 21.6, 22.7, 23.0, 24.0, 24.4, 28.2, 28.4, 29.2, 31.9, 35.6, 35.8, 36.0, 36.3, 38.3, 38.7, 39.7, 40.1, 42.8, 44.9, 46.9, 54.0, 56.5 (two carbons), 212.0.

2α-Bromo-5a-cholestan-3-one . The copper(II) bromide was ground, without drying, in a mortar and pestle to ensure a large surface area for reaction. Copper(II) bromide (4.3 g, 19.2 mmol) in dry ethyl acetate (96 mL) was refluxed. A solution of 5α-cholestan-3-one (3.7 g, 9.6 mmol) in hot chloroform (100 mL) was then added into the above refluxed solution. [2] The reaction mixture was refluxed with vigorous stirring to ensure complete exposure of the copper(II) bromide to the reaction medium until the reaction color changed from green to amber. The

mixture was then filtered in order to remove copper(I) bromide, and washed well with ethyl acetate. The organic solution was washed first with 6% aqueous sodium metabisulfite solution (2 x 150 mL), secondly with saturated aqueous sodium bicarbonate solution (2 x 150 mL), finally with brine (2 x 150 mL), dried over Na_2SO_4 and evaporated in vacuo to give 4.2 g (92%) of the title compound: mp 168-170 °C (lit. 169-170 °C)[1]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.67 (s, 3H), 0.85 (d, 6H, J=6.6,), 0.90 (d, 3H, J=6.5), 1.08 (s, 3H), 2.42 (d, 1H, J=6.4), 2.62 (dd, 1H, J=12.9, 6.4), 4.74 (dd, 1H, J=13.4, 6.3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.3, 18.9, 21.7, 22.7, 22.9, 24.0, 24.4, 28.2, 28.4, 28.6, 31.7, 35.1, 35.9, 36.3, 39.2, 39.7, 39.9, 42.8, 44.1, 47.7, 51.9, 53.8, 54.7, 56.3, 56.4, 201.2. MS m/z (%) 466 (9.3), 386 (31.30, 311 (24.4), 231 (100), 163 (26.7), 121 (58.6).

5α-Cholest-1-en 3-one (6). 2α-Bromo-5α-cholestan 3-one (2.5 g, 5.4 mmol) was added portionwise to a boiling suspension of calcium carbonate (2.4 g, 24 mmol) in *N,N*-dimethylacetamide (25 mL). After refluxing the pale yellow suspension for 15 min., most of the solvent was removed in vacuo. The residue was extracted with ether (4 x 150 mL). The combined ether extracts were washed first with 2N-HCl solution (3 x100 mL), secondly with brine (3 x 150 mL), finally with water (3 x100 mL), dried over Na_2SO_4 and evaporated in vacuo to give 2.0 g of crude solid product. Purification by flash chromatography over silica gel, eluting with 90% benzene-ether, gave **5α-cholest-1-en 3-one (6)** (Rf = 0.39), mp 96-98 °C (lit. 96-99 °C)[3], in 71% (1.5 g) and cholest 4-en 3-one (Rf = 0.24) in 20% (0.4 g). Spectroscopic data for **(6)**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.70 (s, 3H), 0.87 (d, 6H, J=6.6), 0.90(d, 3H, J=6.5), 1.01 (s, 3H), 5.85 (d, 1H, J=10.2), 7.16 (d, 1H, J=10.2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.3, 13.1, 18.8, 21.4, 22.7, 23.0, 24.0, 24.2, 27.8, 28.1, 28.4, 31.5, 35.8, 35.9, 36.3, 39.1, 39.6, 39.9, 41.1, 42.8, 44.5, 50.1, 56.4, 56.5, 127.5, 158.6, 200.1. MS m/z (%) 384 (21.7), 342 (12.9), 271 (10.3), 229 (14.5), 187 (6.5), 134 (41.1), 122 (100). Anal. Calcd for C27H44 O: C 84.31, H 11.53. Found: C 84.22, H 11.56. Spectroscopic data for cholest 4-en 3-one: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.71 (s, 3H), 0.87 (d, 6H, J=6.6), 0.90(d, 3H, J=6.5), 1.18(s, 3H), 5.72 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.1, 17.6, 18.8, 21.2, 22.7, 23.0, 24.0, 24.4, 28.2, 28.4, 32.3, 33.1, 34.2, 35.8, 35.9, 36.3, 38.8, 39.7, 39.8, 42.6, 54.0, 56.1, 56.3, 123.9, 171.8, 199.7.

5α-Cholestan-1,2-epoxy-3-one (7). To an ice-cooled solution of 1.5 g (3.9 mmol) of 5α-cholest-1-en 3-one **(6)** in 20 mL of dry dichloromethane was added 2.4 mL of triton-B (40 wt.% solution in methanol) followed by 6 mL of tert-butyl hydroperoxide (4.1 M solution in dichloromethane).[4] After stirring at 0 °C for 20 min, the reaction mixture was allowed to stir at rt for 36 h. After removing the solvent in vacuo, the residue was mixed with water (100 mL) and the product was isolated by extraction with ethyl acetate (4 x 50 mL). The combined extracts were

washed with brine (2 x 150 mL), dried over Na_2SO_4, evaporated in vacuo and purified by column chromatography (silica gel, 100% benzene) to afford 850 mg (53% yield) of **5α-Cholestan-1,2-epoxy-3-one** (**7**) (Rf = 0.76) and 10 mg (~1%) of 5α-cholestan-3-one (Rf = 0.59). Spectroscopic data for (**7**): ^1H NMR ($CDCl_3$, 300 MHz) δ 0.62 (s, 3H), 0.80 (d, 6H, J=7.8), 0.81 (s, 3H), 0.85 (d, 3H, J=6.6), 3.13 (d, 1H, J=4.1), 3.42 (d, 1H, J=4.1). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.0, 12.1, 18.7, 21.6, 22.6, 22.9, 23.9, 24.2, 27.3, 28.0, 28.2, 31.2, 34.1, 35.5, 35.8, 36.2, 36.6, 39.5, 39.7, 40.1, 42.6, 48.8, 56.0, 56.2, 56.3, 61.0, 205.4. MS m/z (%) 400 (43.3), 245 (100), 109 (28.3), 81 (39.8), 55.1 (48.9).

5α-Cholestan-1,3-dione (**4**) Two steps from epoxyketone **7**. A solution of 1,2-epoxy-3-one **7** (1 g, 2.5 mmol) in 12.5 mL of dry diethyl ether was added dropwise to a suspension of lithium aluminum hydride (500 mg, 13.2 mmol) in 50 mL of dry diethyl ether at room temperature. After refluxing for 3 h 45 min, the reaction mixture was cooled to room temperature and then in an ice-bath. The excess hydride was decomposed by the dropwise addition of ice water (0.5 mL) followed by aqueous 6N-NaOH solution (0.5 mL) and water (1.5 mL) in succession. After vigorous stirring for another 20 min, the mixture was filtered and washed thoroughly with ether. The white precipitate was repeatedly extracted with warm diethyl ether. The combined ethereal solutions were evaporated, and the cooled residue was treated with aqueous 2N-HCl solution (150 mL). The acid solution was extracted with diethyl ether (3 x150 mL). In order to remove the acid and neutral products, the ether extracts were washed with cooled aqueous 6N-NaOH solution (75 mL). Then, the ethereal solution was dried over Na_2SO_4 and evaporated in vacuo to give **5α-cholestan-1,3-diol** as a mixture of OH epimers at C-1 and C-3 in 99% yield (1.0 g)[5]: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.65 (s, 3H), 0.80 (s, 3H), 0.85 (d, 6H, J=6.6), 0.89 (d, 3H, J=6.5), 3.73(m, 1H), 4.01 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.2, 13.2, 18.9, 20.9, 22.8, 23.0, 24.1, 24.5, 28.2, 28.4, 28.8, 31.9, 35.7, 36.0, 36.4, 37.6, 38.2, 38.5, 39.7, 40.0, 42.8, 47.0, 56.55, 56.59, 66.7, 73.3. MS (M+NH4) m/z (%) 422 (100), 404 (15.2), 368 (3.6), 196 (10.1), 136 (25.8).

5α-Cholestan-1,3-dione (**4**). Into a solution of 5α-cholestan-1,3-diol (500 mg, 1.2 mmol) in dry acetone (100 mL) and dry diethyl ether (17 mL) was added 1.1 mL of CrO_3-H_2SO_4 solution (2.7 g of CrO_3 was added into 2.3 mL of cooled H_2SO_4, followed by dilution to 10 mL with distilled water) via a dropping funnel, at 15 °C. After the mixture was stirred for 10 min, the reaction color turned from orange to green. The mixture was diluted with 100 mL of distilled water. The cloudy, green suspension was rotary evaporated to remove acetone and ether. The residue was extracted with ether : chloroform (9:1) (6 x 50 mL). The combined extracts were washed with water (3 x75 mL), dried over Na_2SO_4 and evaporated in vacuo to give

400 mg (81% yield) of the title compound[6]: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.68 (s, 3H,). 0.86 (d, 6H, J=6.6), 0.92 (d, 3H, J=6.5), 1.23 (s, 3H), 3.23 (d, 1H, J=16.5), 3.68 (d, 1H, J=16.8). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.3, 12.4, 18.8, 22.7, 23.0, 24.0, 24.4, 27.8, 28.2, 28.3, 30.8, 35.9, 36.0, 36.3, 39.4, 39.7, 40.0, 42.8, 44.4, 46.9, 50.4, 56.3, 56.5, 203.8, 206.7. MS (M+NH4) m/z (%) 418 (100), 400 (5.7), 196 (40.7), 136 (53.5), 94 (36.1).

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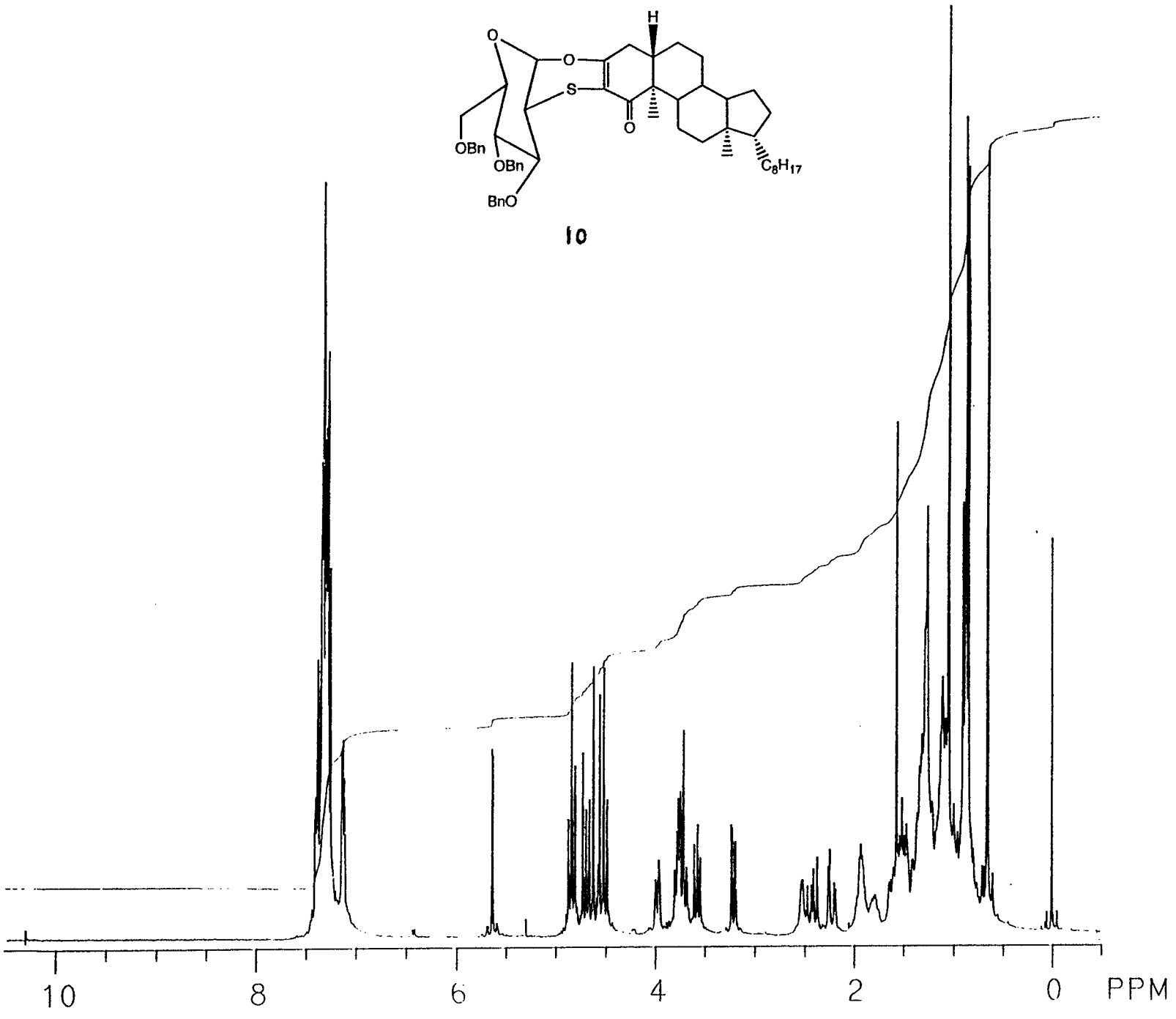

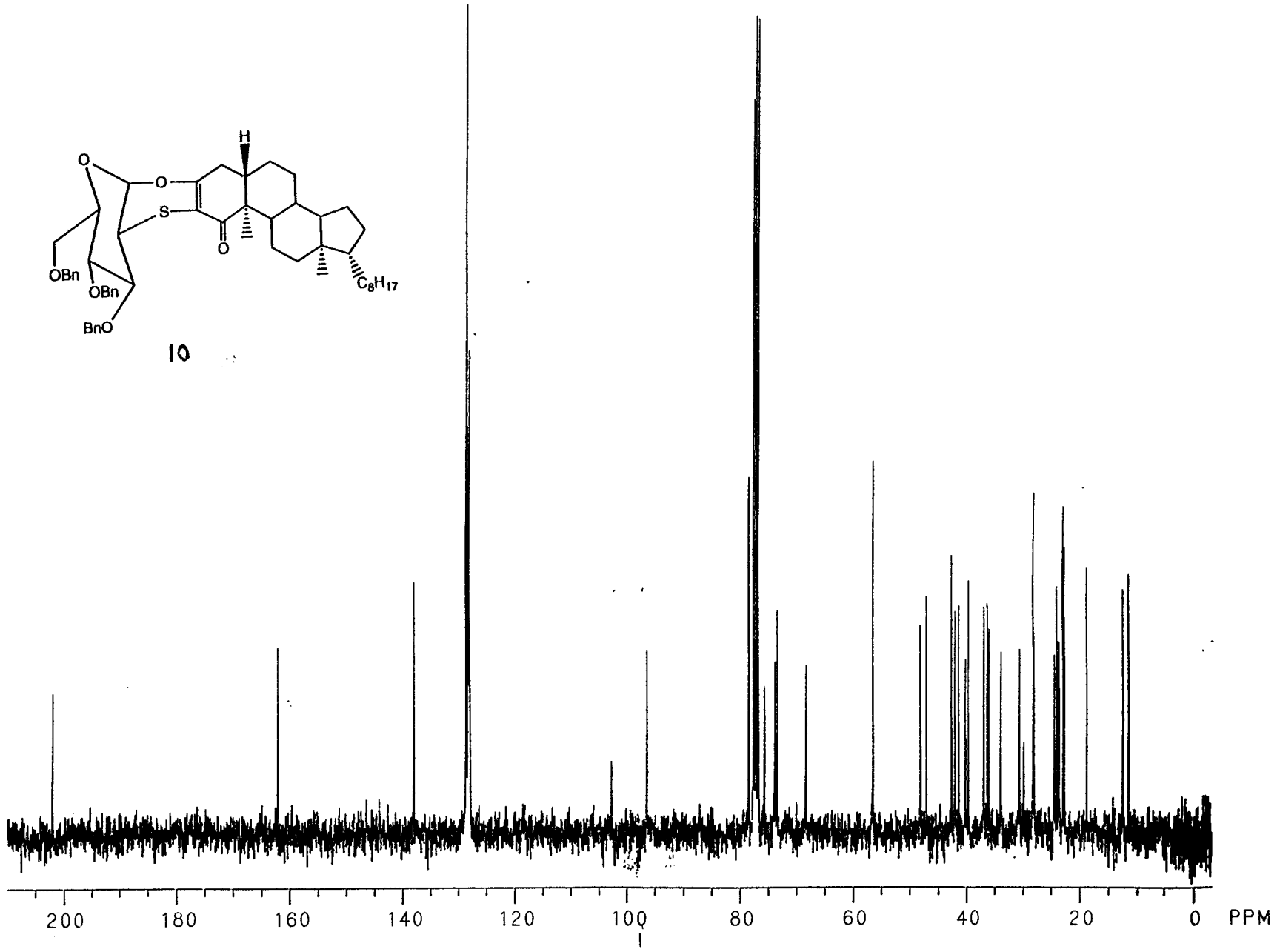

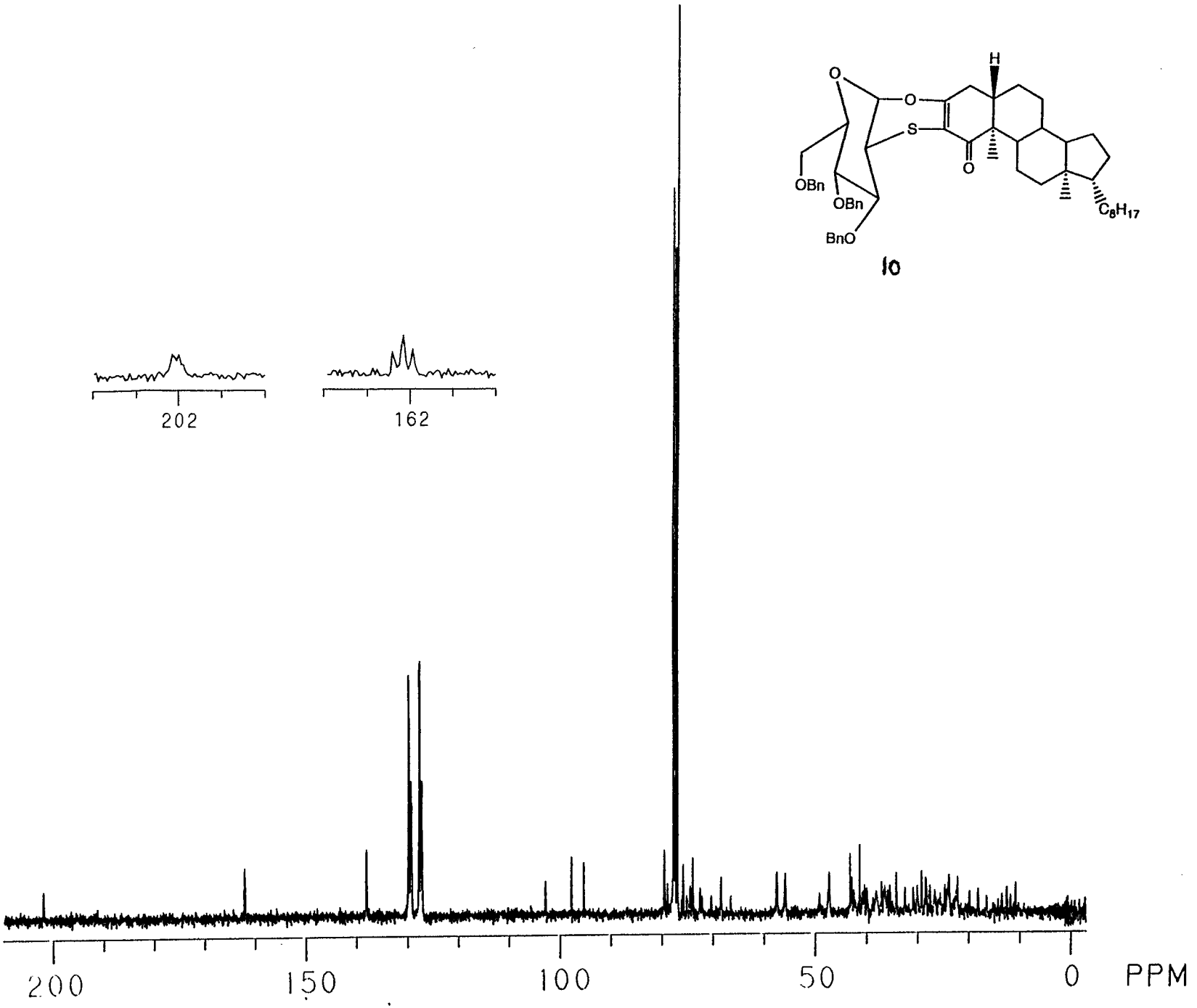

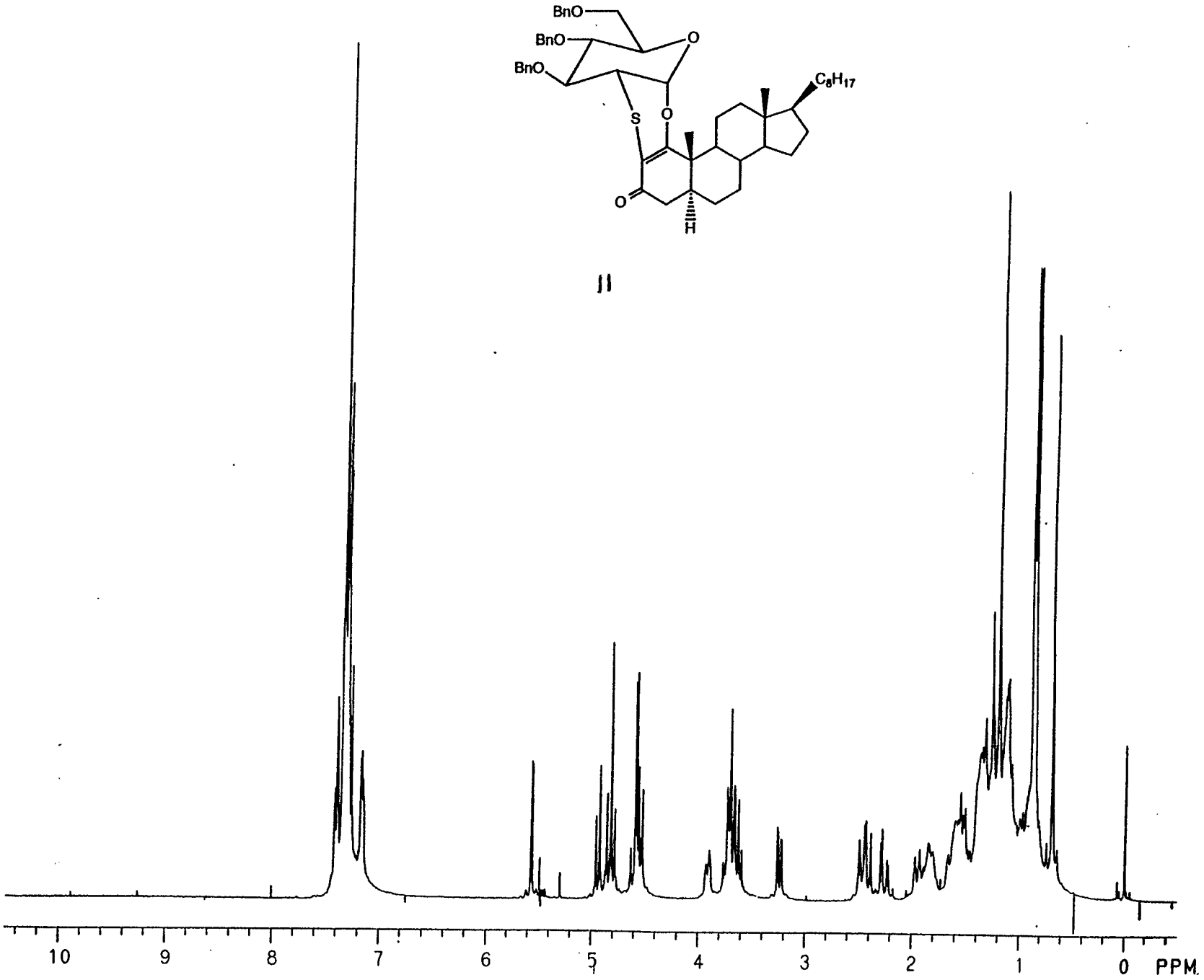

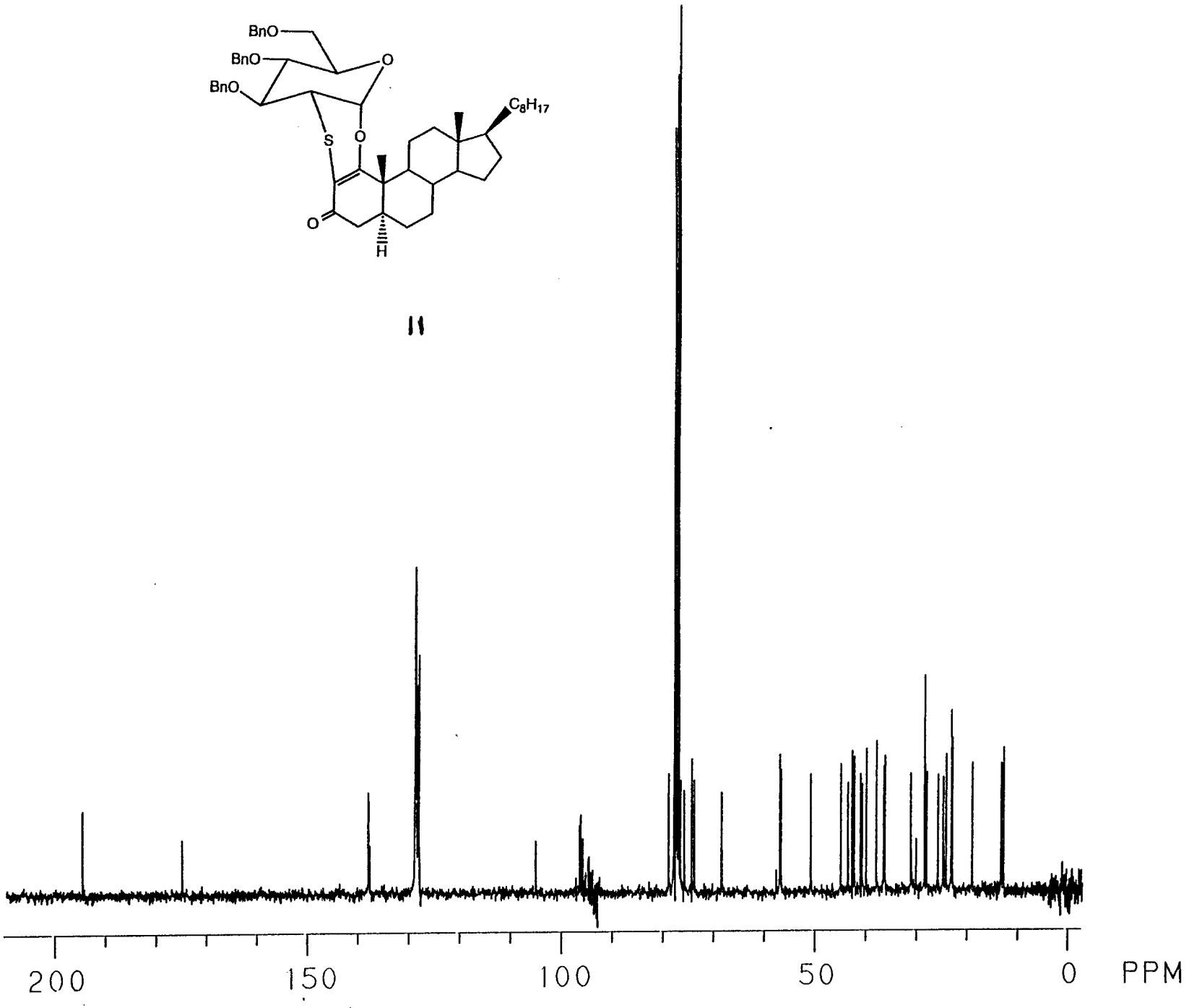

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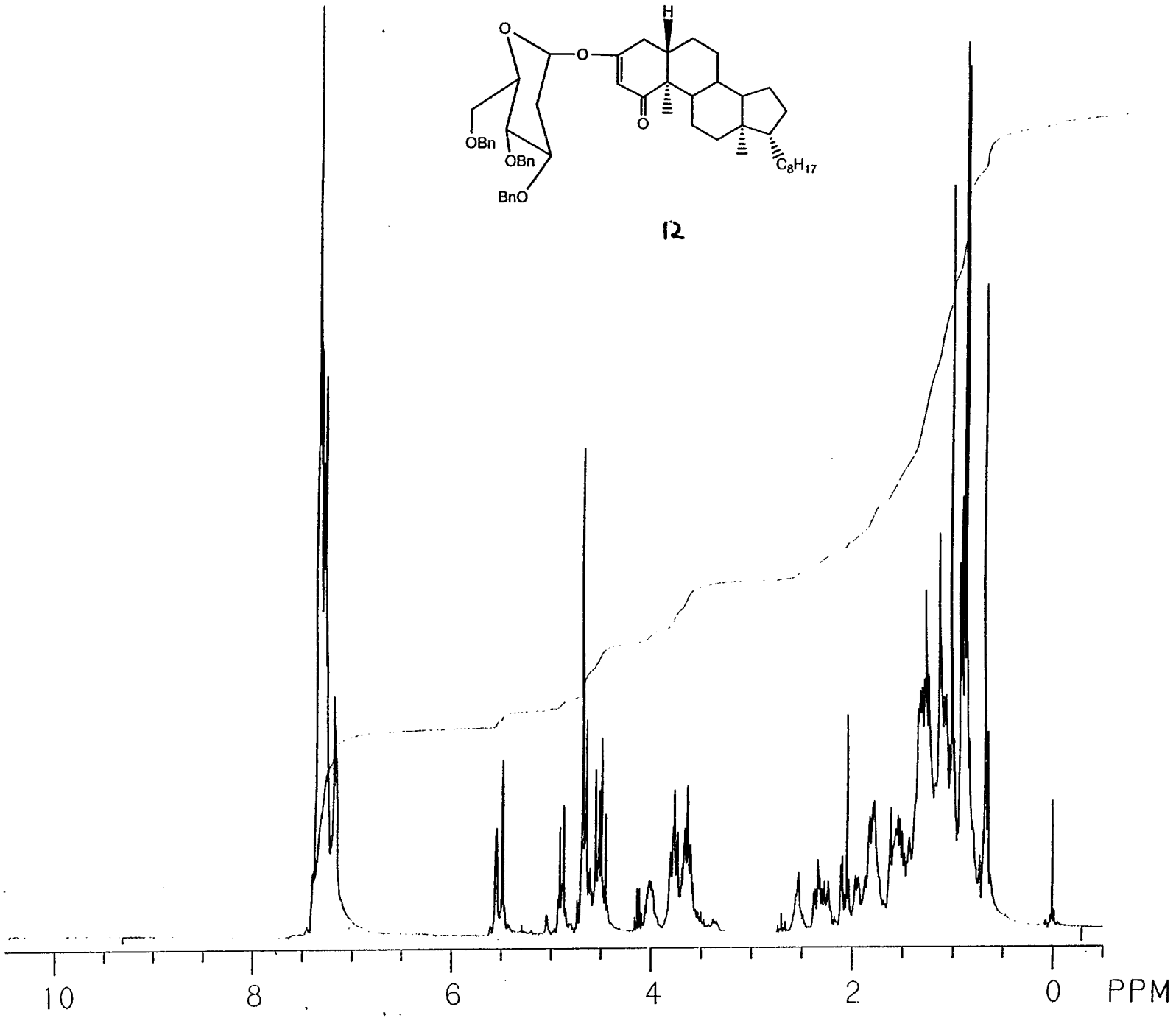

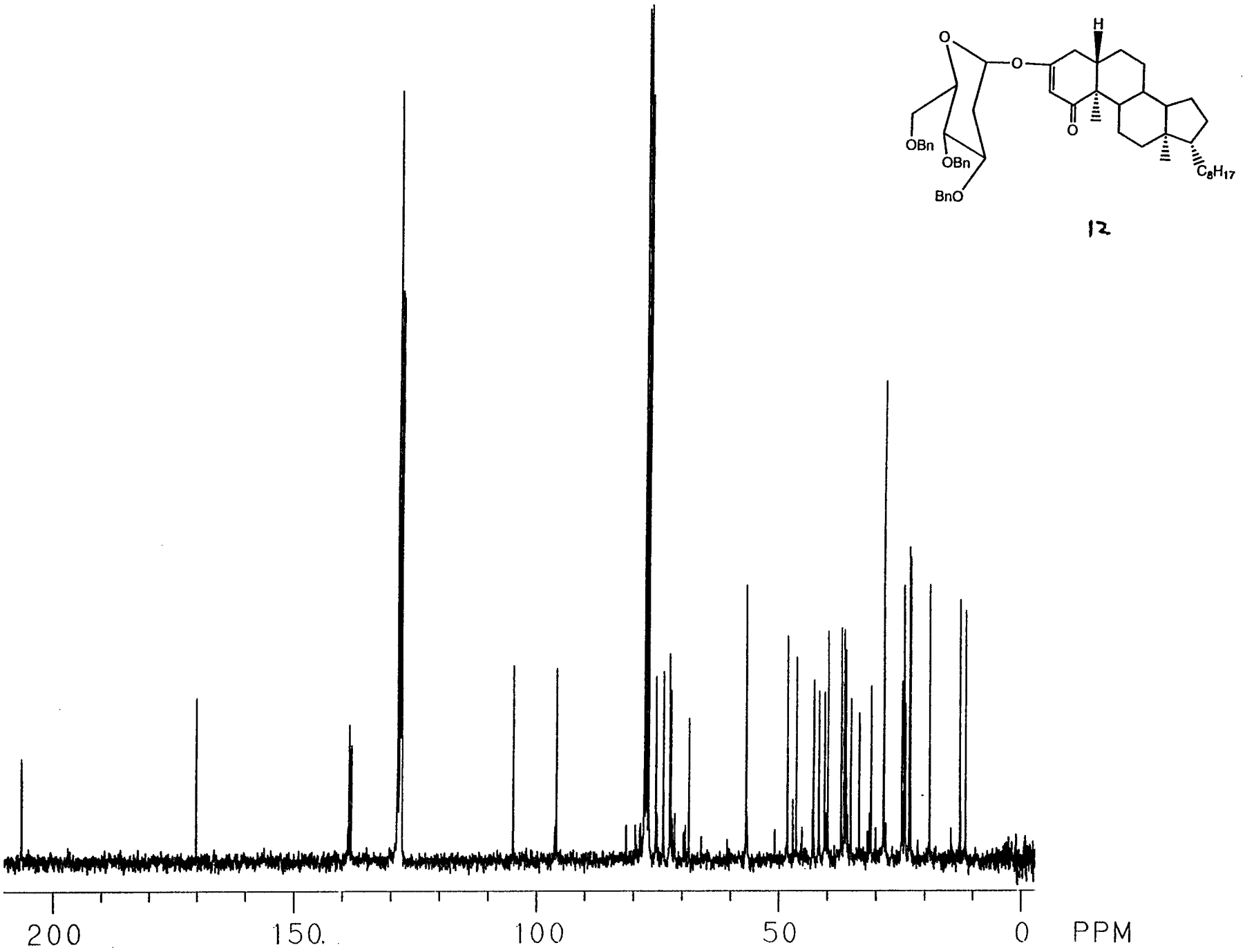

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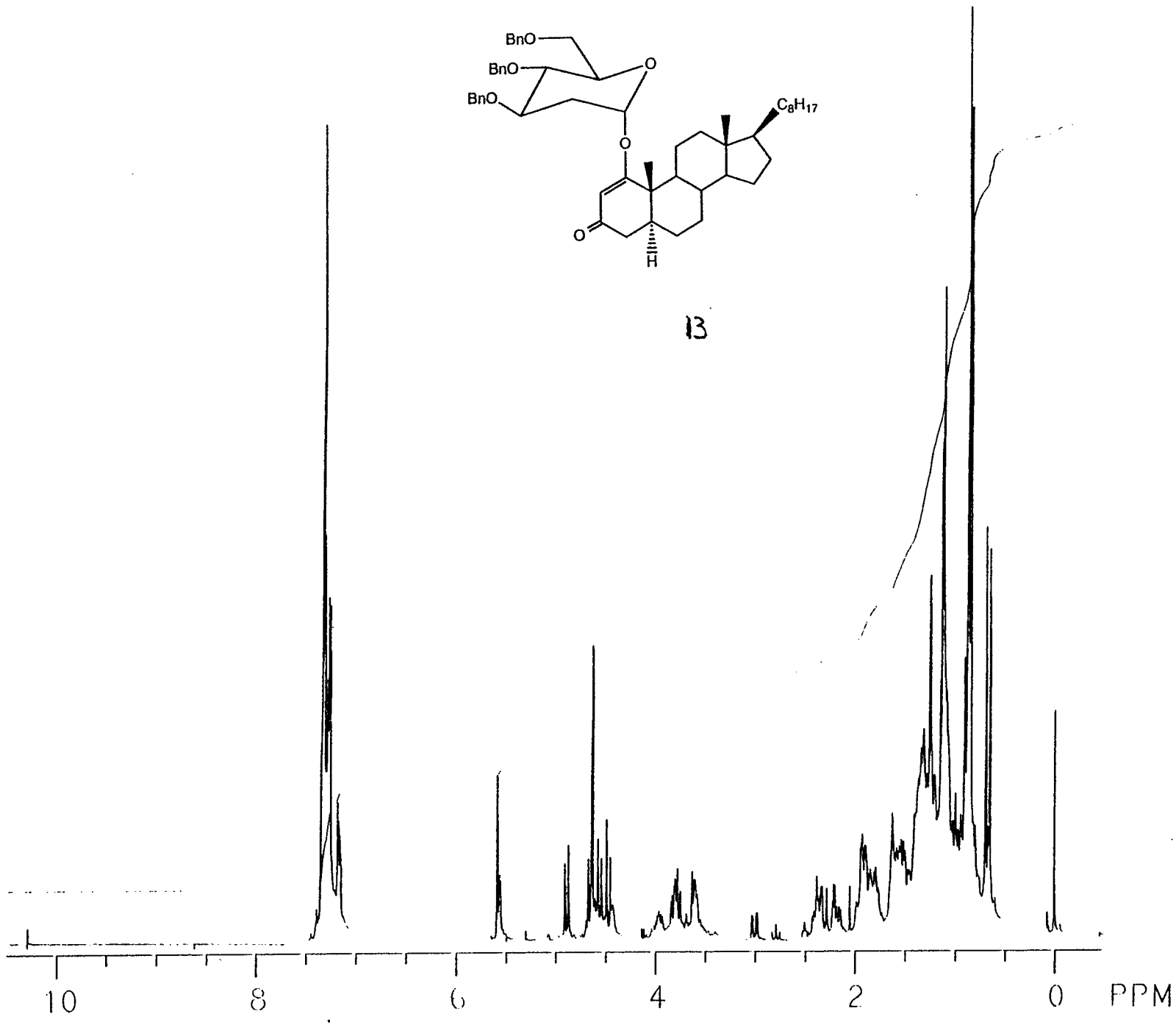

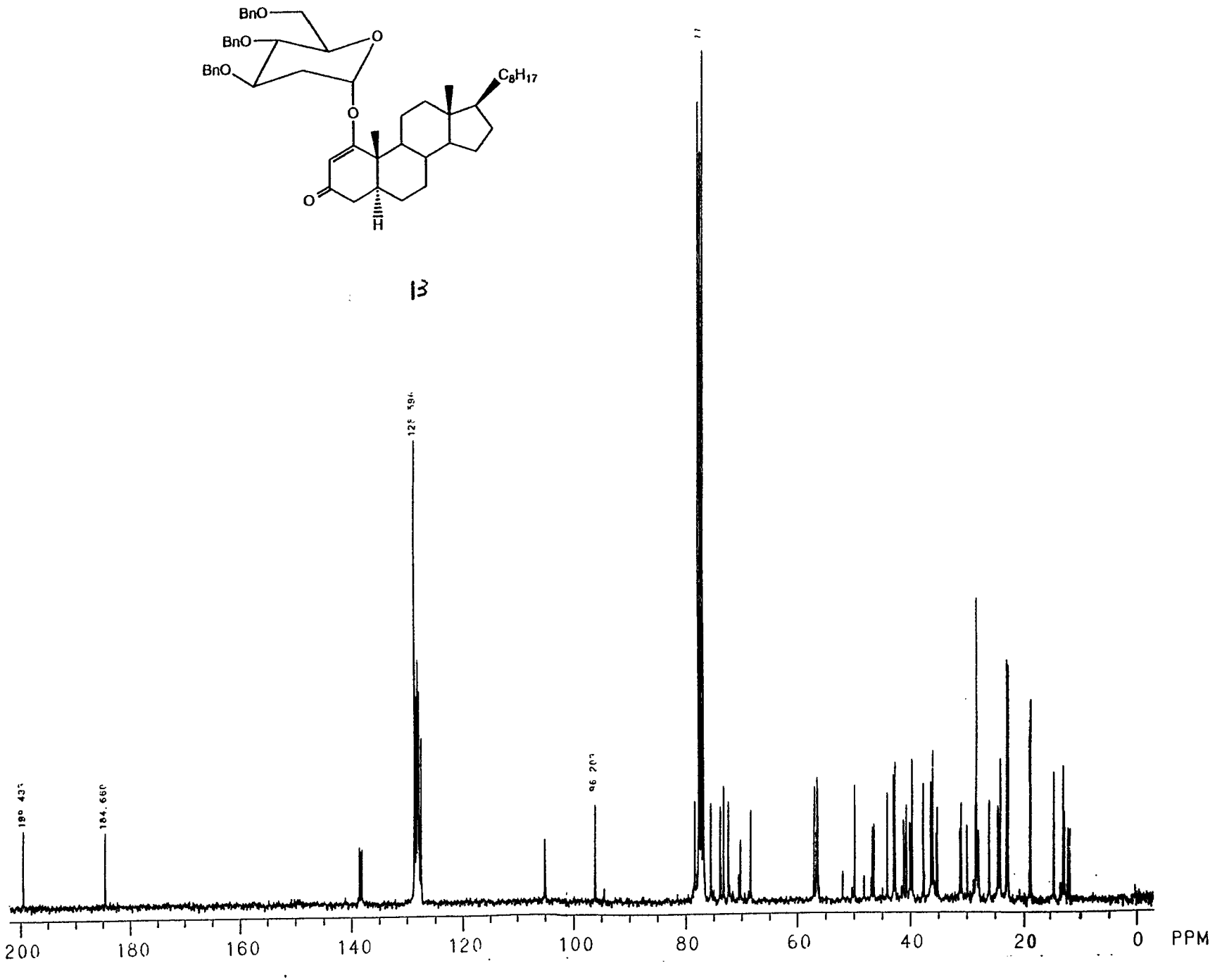

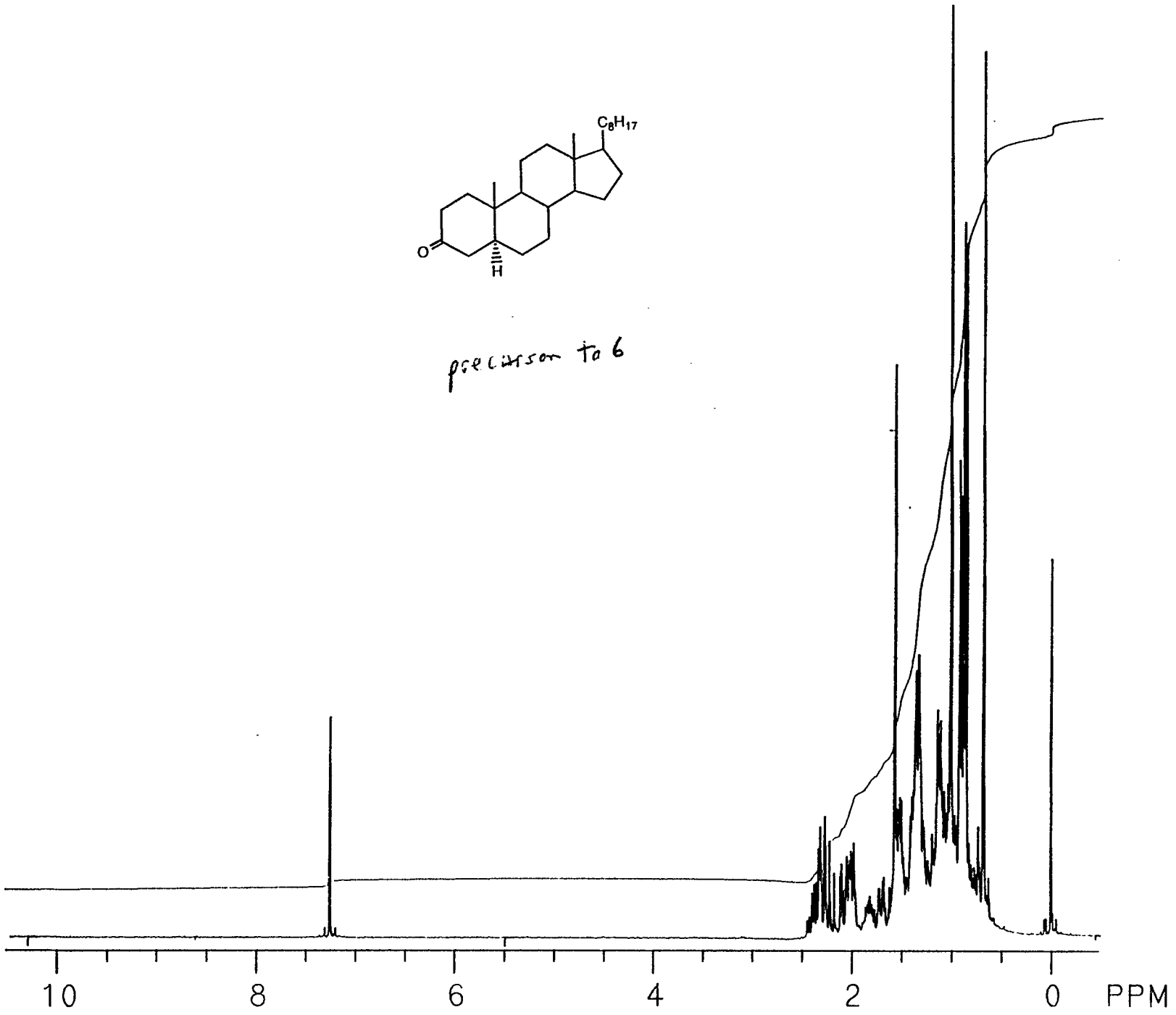

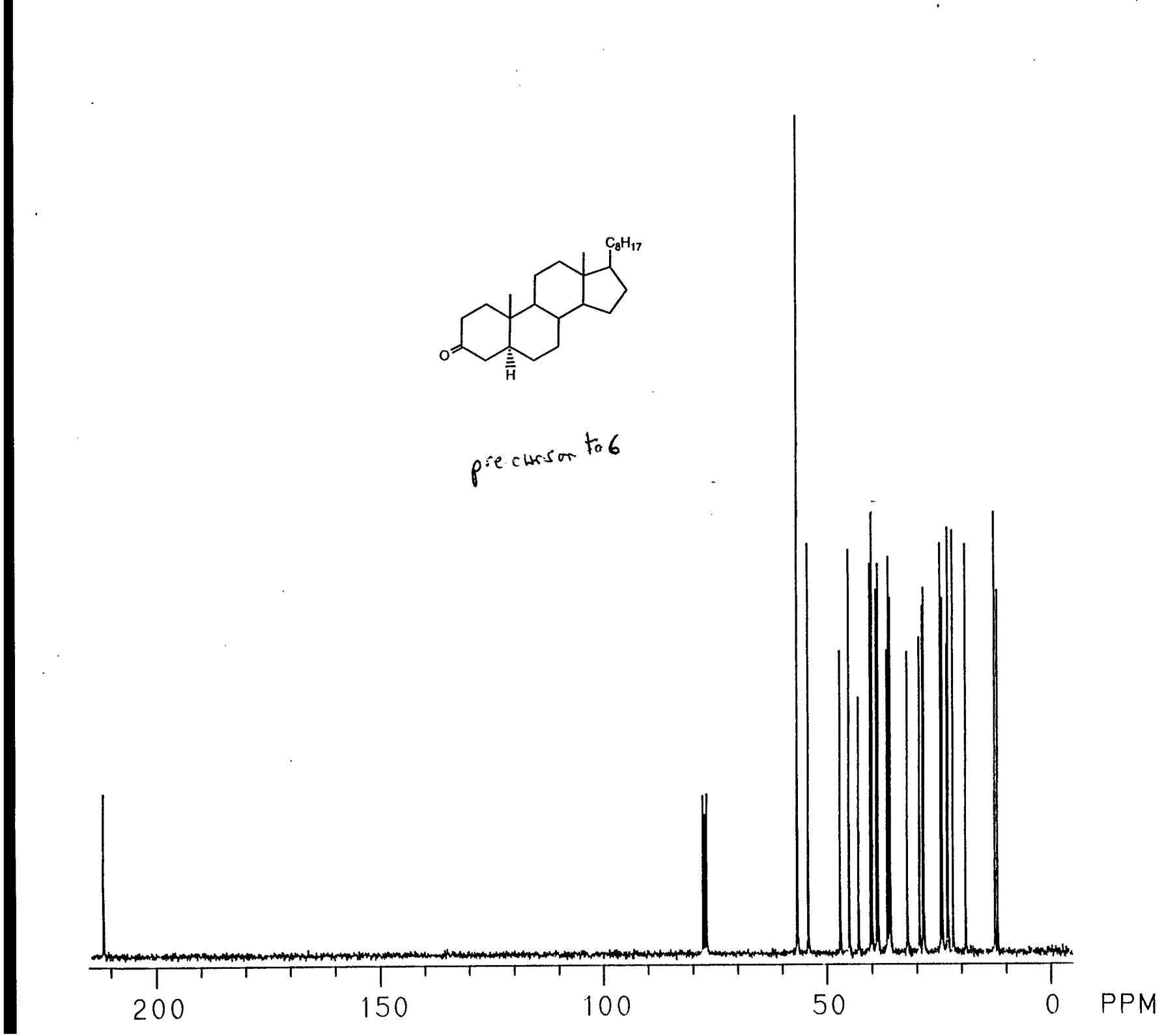

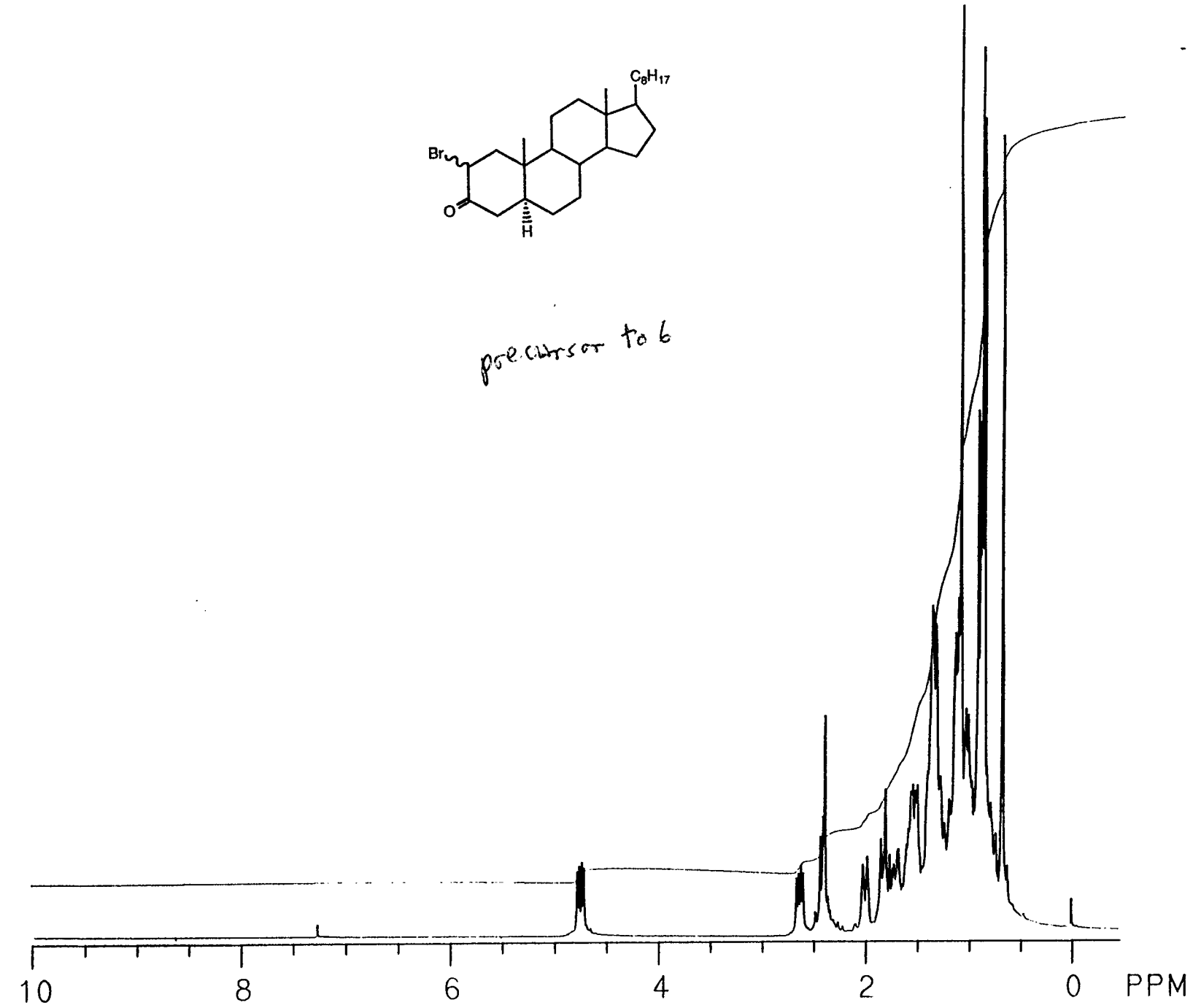

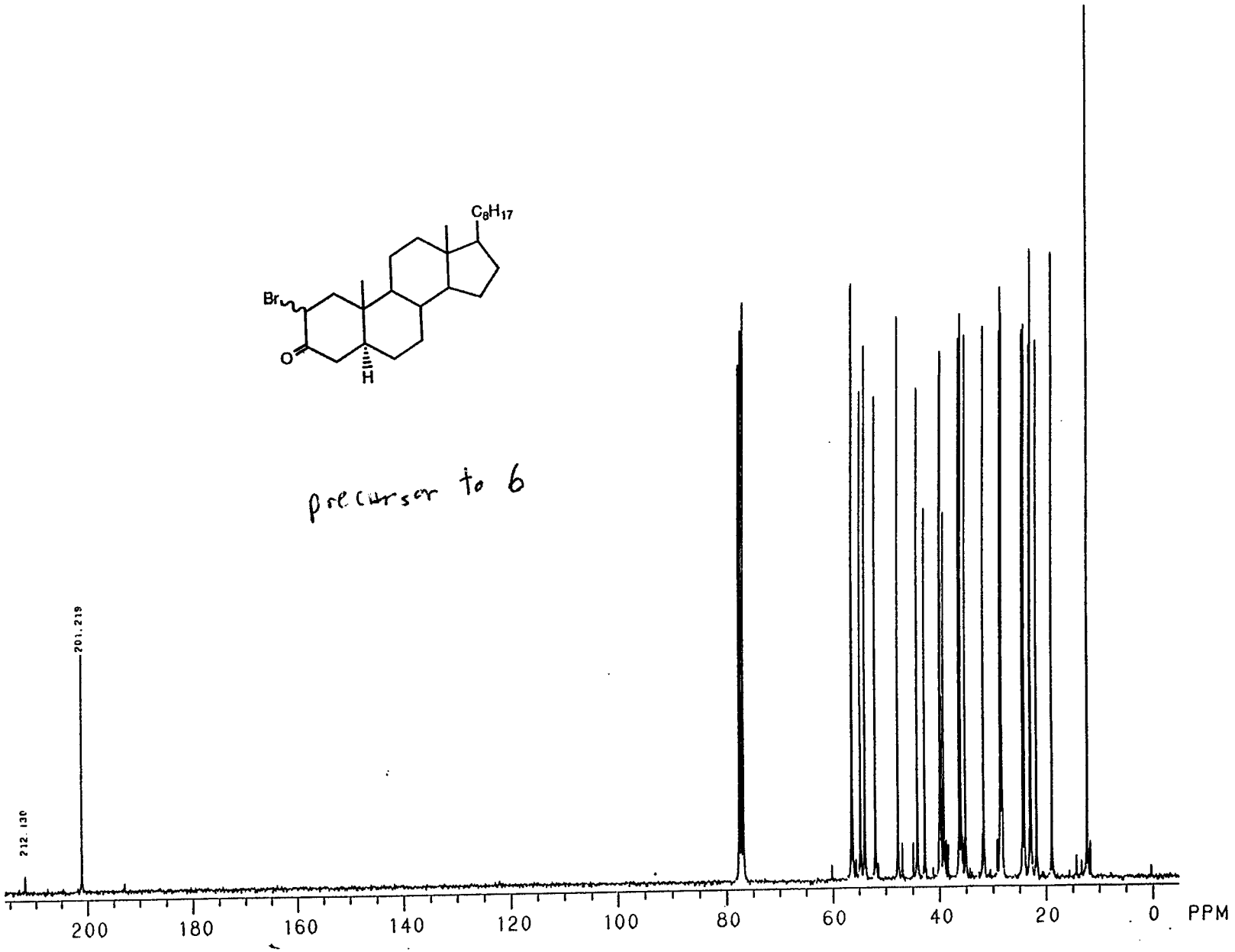

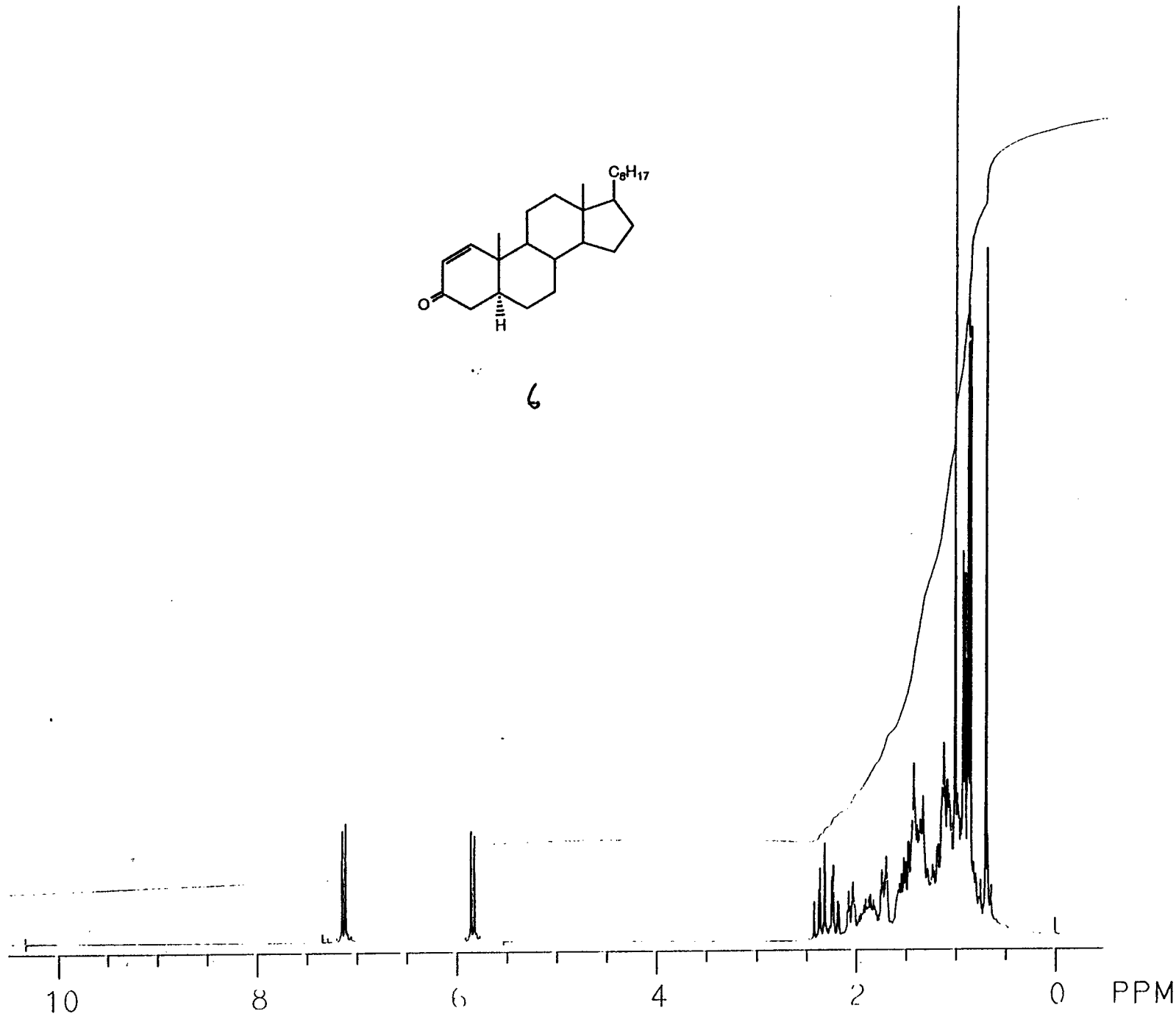

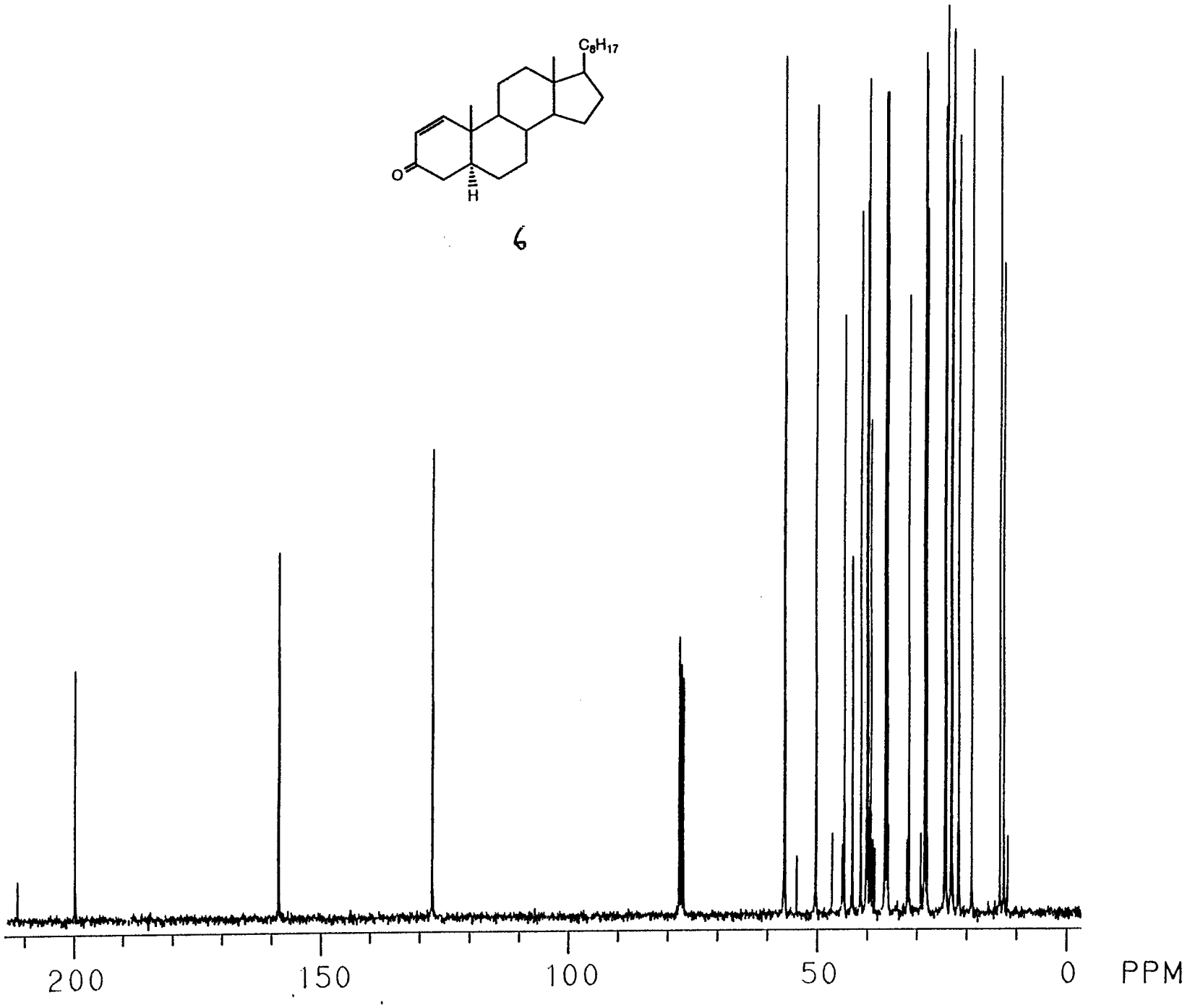

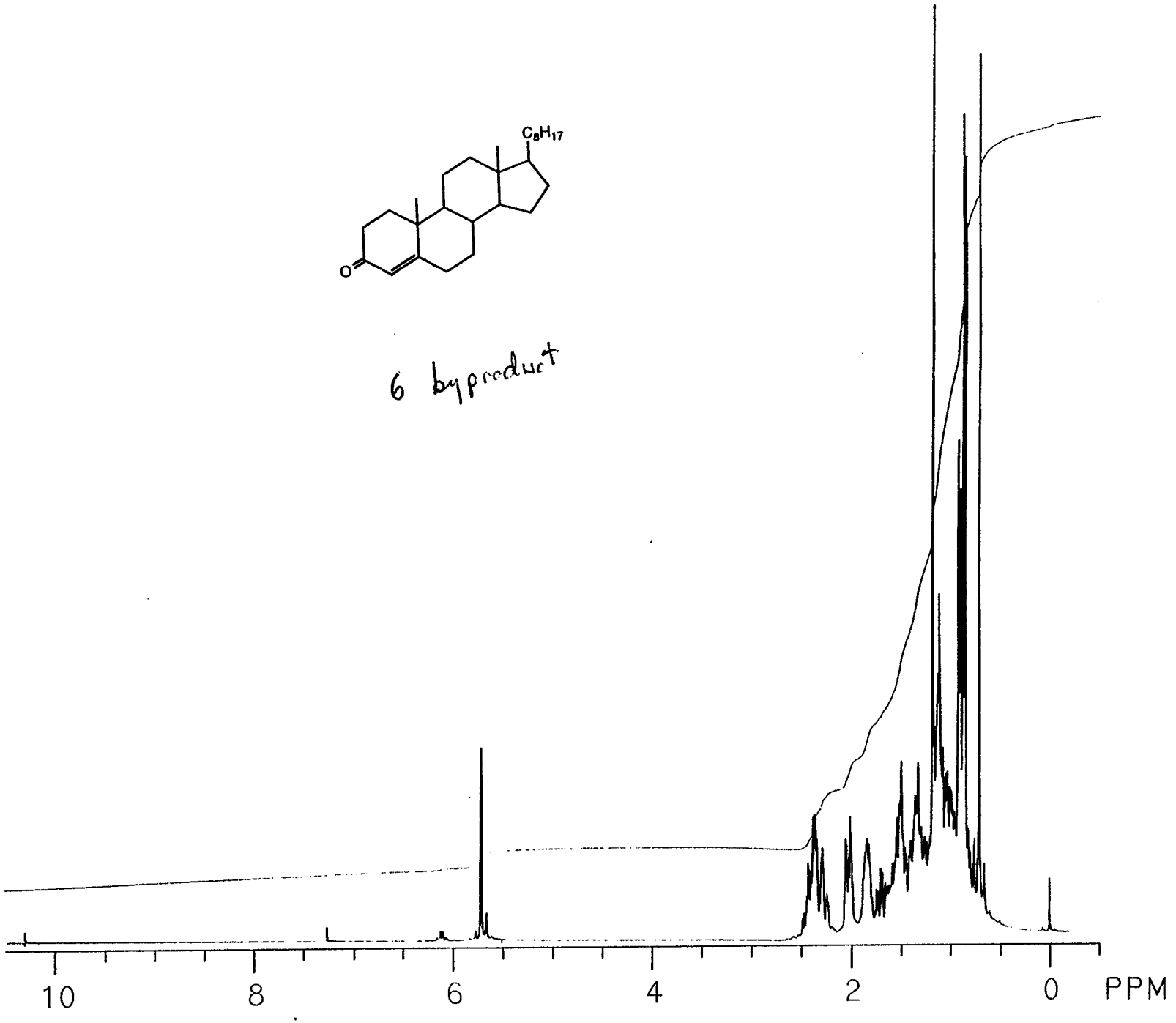

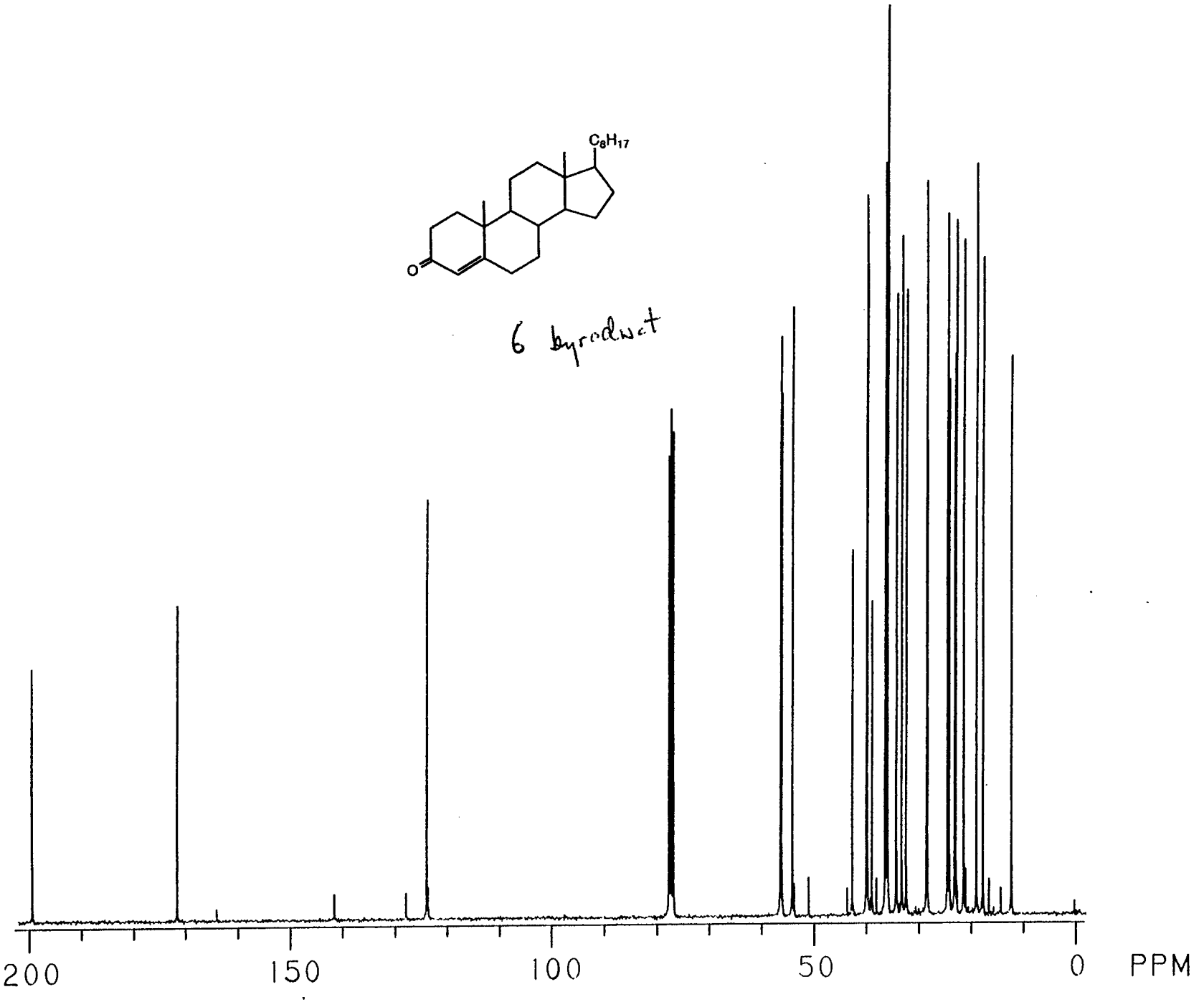

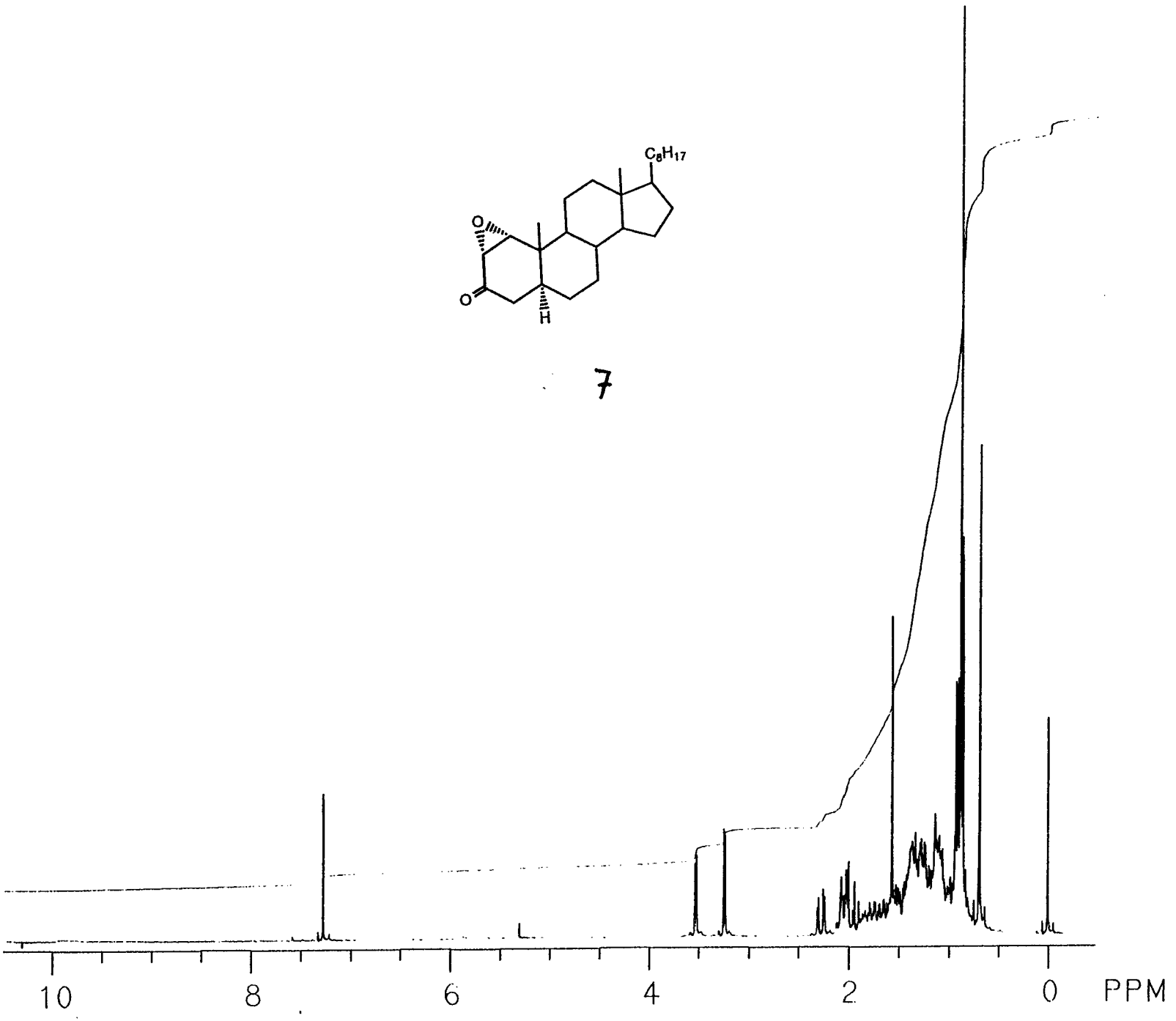

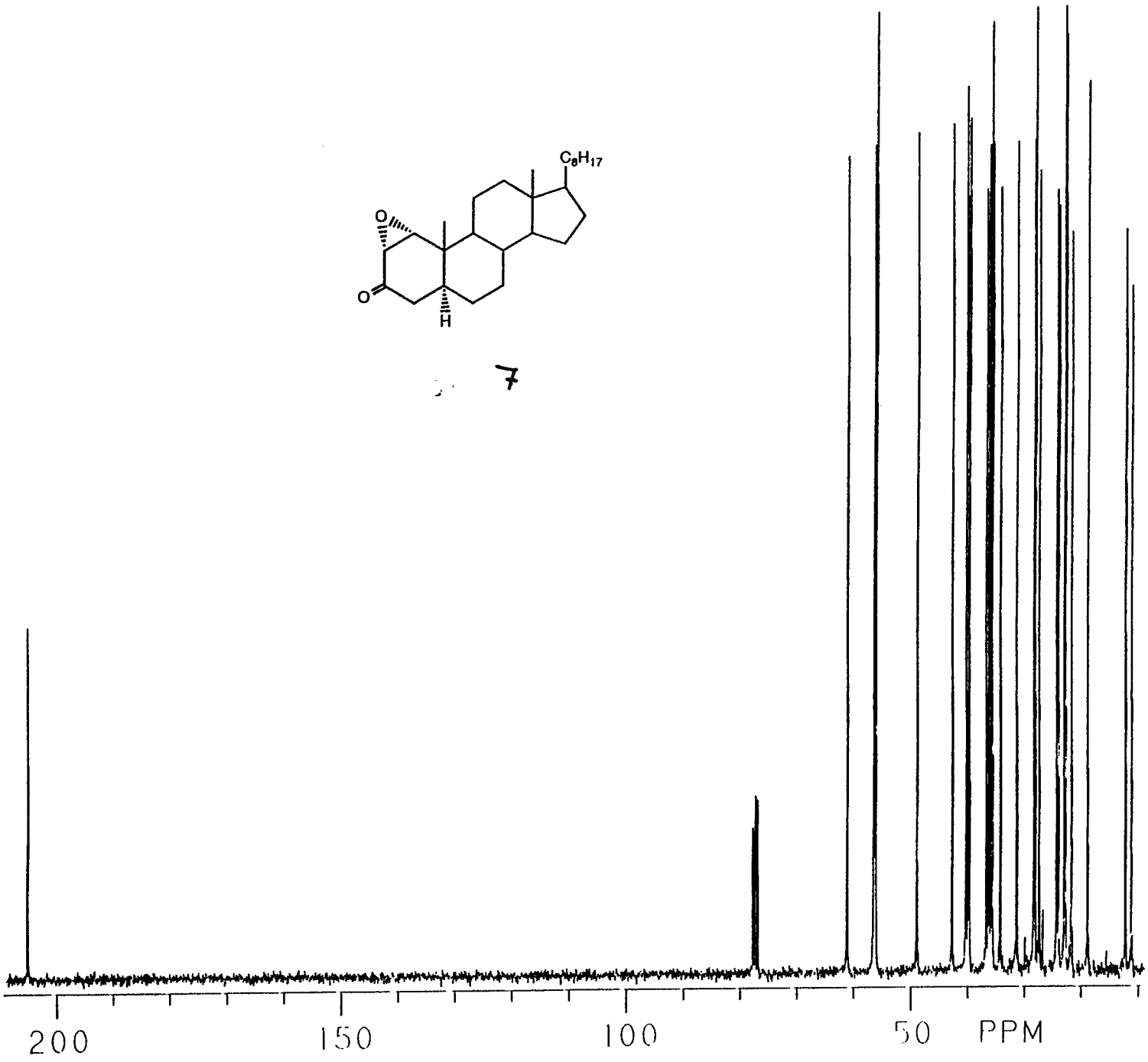

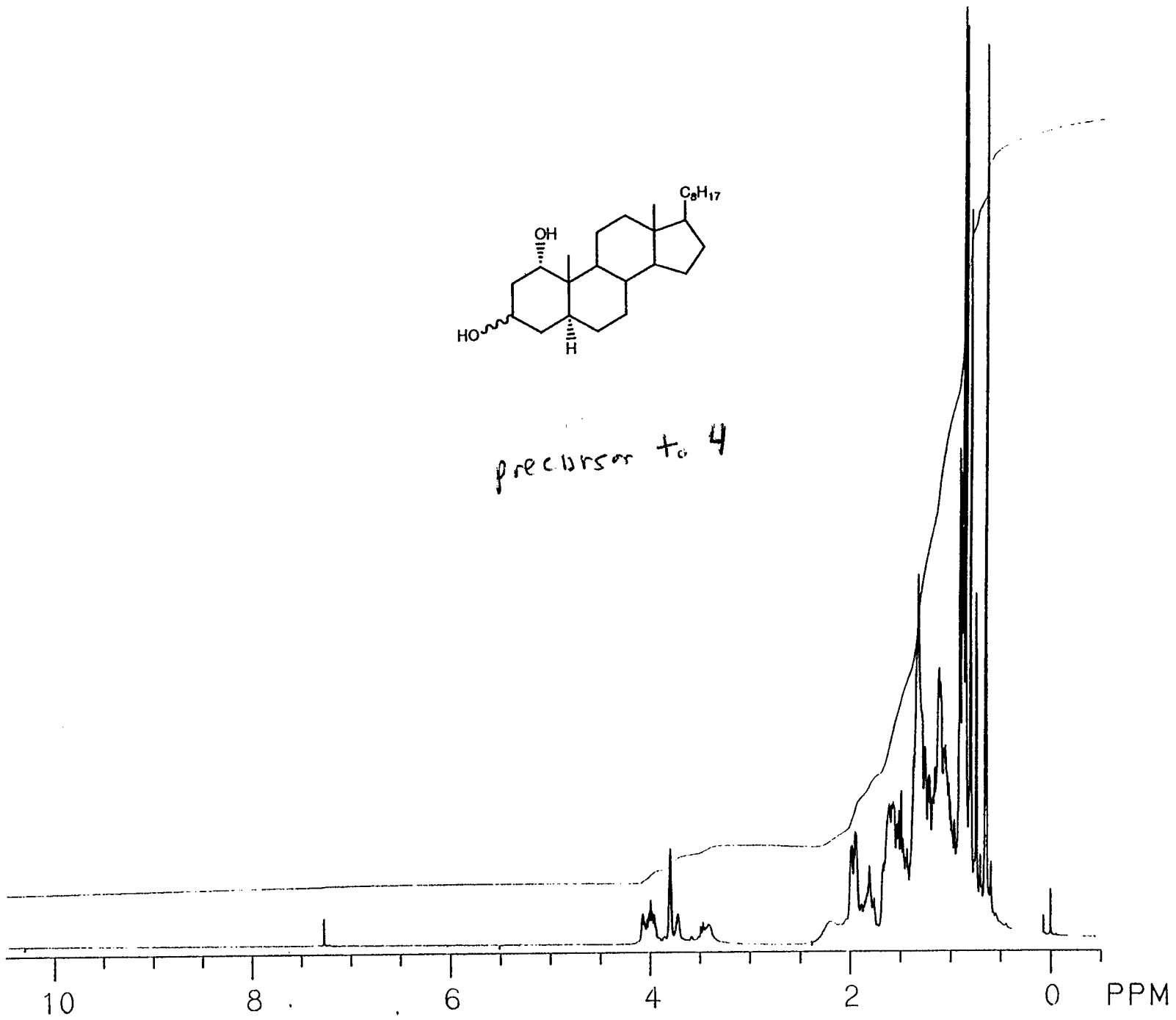

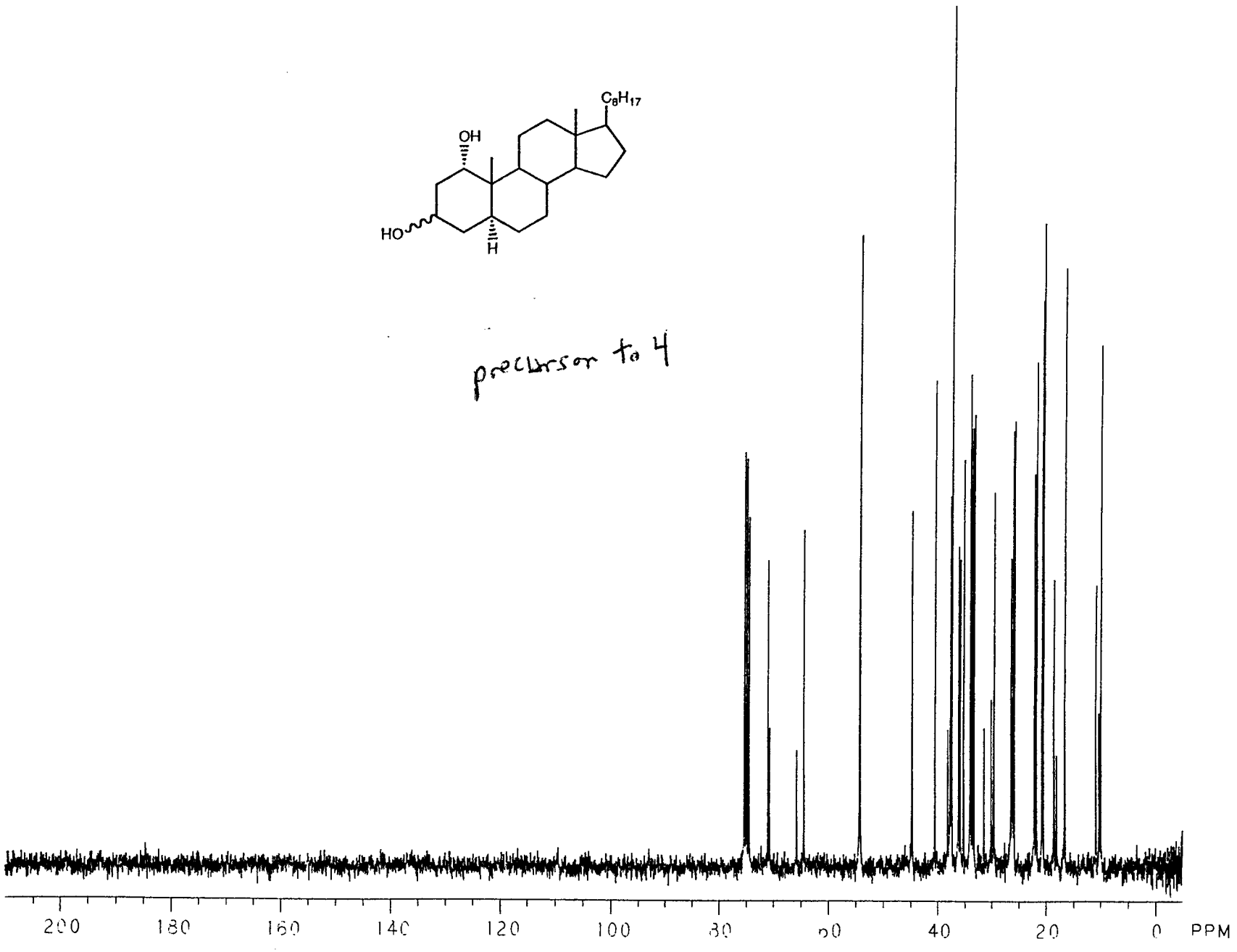

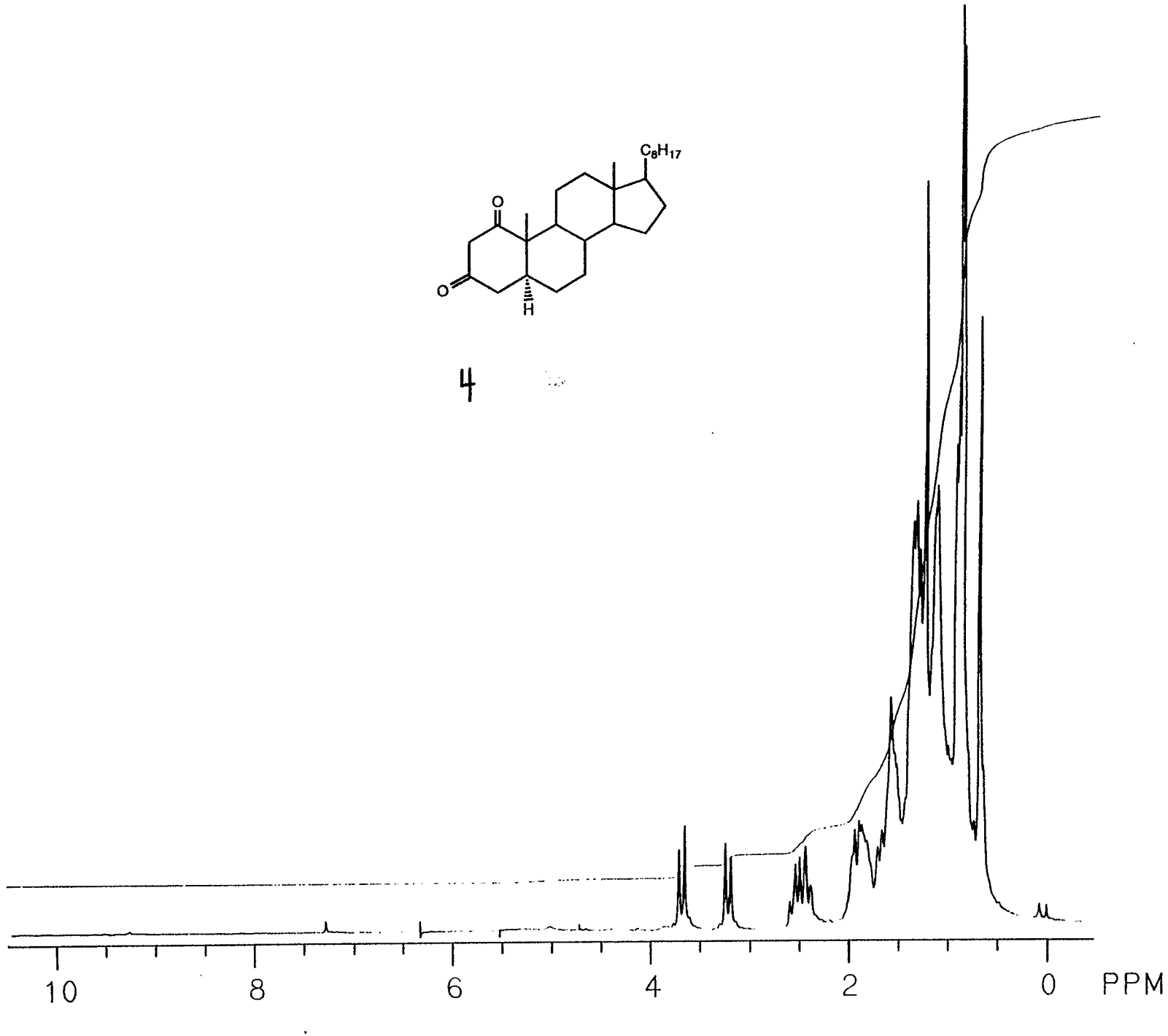

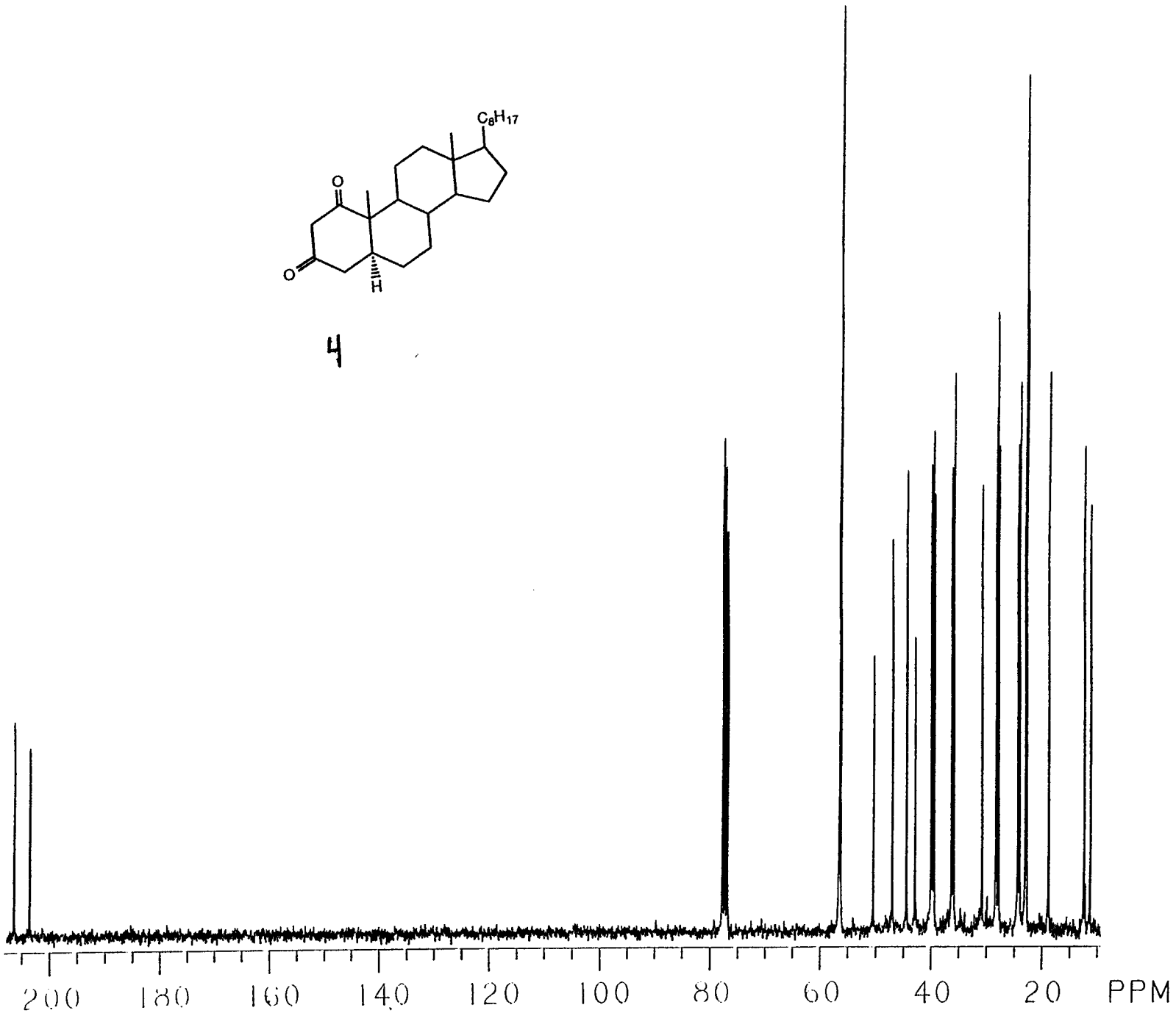

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