The First Locked Side Chain Analogs of Calcitriol (1α,25-Dihydroxyvitamin D_3 Induce Vitamin D Receptor Transcriptional Activity.

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Experimental Protocols

Transactivation Assays. Nearly confluent cells were transfected in triplicate P-60 dishes using LipofectAMINE^{TM} Reagent (Life Technologies) following the manufacturer guidelines. The 4xVDRE-DR3-tk-Luc construct containing four copies in tandem of a consensus DR3 response element for vitamin D cloned upstream of the herpes virus simplex thymidine kinase gene promoter and luciferase reporter gene was provided by Dr. C. Carlberg, Kuopio, Finland.

Chemical Protocols. All reactions involving oxygen- or moisture-sensitive compounds were carried out under a dry argon atmosphere. Reaction temperatures refer to external bath temperatures. All dry solvents were distilled under argon immediately prior to use. Tetrahydrofuran (THF) was distilled from Na/benzophenone. DMF was distilled from CaH_2. Diisopropylamine (*i*-Pr_2NH) and pyrrolydine were distilled from CaH_2. Dicloromethane (CH_2CI_2) was distilled from P_2O_5. The analytical grade cation exchange resin AG50 WX40 was supplied by BioRad and was washed with MeOH prior to use. Liquid reagents or solutions of reagents were added by syringe or cannula. Organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated using a rotary evaporator at aspirator pressure (20-30 mm Hg). Reactions were monitored by thin-layer chromatography (TLC) using aluminium-backed Merck 60 silica gel plates (0.2 mm thickness); the chromatograms were visualized first with ultraviolet light (254 nm) and then by immersion in a solution of phosphomolybdic acid in MeOH (5%), followed by heating. Flash column chromatography was performed with Merck 60 (230-400 mesh) silica gel. All NMR spectra were measured using solutions in $CDCI_3$ sunless otherwise stated. Chemical shifts are reported on the 5 scale (ppm) downfield from tetramethylsilane (δ= 0.0) using the residual solvent signal at 7.26 (^{1}H) or 77.0 triplet (^{13}C) as internal standard, and coupling constants are reported in hertz (Hz). NMR spectra were recorded at 250 (^{1}H) and 63 (^{13}C) MHz, unless otherwise stated. Distortion less Enhancement by Polarization Transfer (DEPT) was used to assign carbon types. Mass spectra were obtained using electron-impact ionisation at 70 eV.

(1S,4aS,5S,7aR)-1-[*tert*-butyl-dimethylsiliyl]oxi-4a-methyl-5-([1-trifluoromethano-sulfonyloxi]vinyl)-octahydro-indene (10). *n*-Hexyllithium (7 mL, 17.8 mmol, 2.6 M in Hexanes) was added dropwise to dry diisopropylamine (2.7 mL, 19.3 mmol) in THF (30 mL) at –78 °C. The cooling bath was removed and the mixture was stirred for 30 min. The

resulting solution of LDA was cooled to –78 °C and a solution of methyl ketone **8** (5 g, 16.12 mmol) in dry THF (30 mL) was added dropwise. After the mixture was stirred for 30 min, a solution of *N*-(5-chloro-2-pyridyl)-triflimide (5.9 g, 17.77 mmol) in THF (30 mL) was added. The cooling bath was removed and the resulting mixture was stirred for 1h. The reaction was quenched with brine (80 mL). The mixture was extracted with Et_2O. The organic layer was dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (5% Et_2O/Hexanes) to give 4.62 g of triflate **10** [64%, R_f 0.94, 5% EtOAc/Hexanes, white solid]. **^{1}H RMN** δ (ppm): 5.19 (1H, d, *J*=3.7 Hz), 4.96 (1H, dd, *J*=1.2 y 3.7 Hz), 4.04 (1H, s), 2.3-1.2 (12H, m), 0.9 (3H, s), 0.89 (9H, s), 0.02 (3H, s), 0.01 (3H, s). **^{13}C RMN** δ (ppm): 158.7(C), 118.4 (C), 104.7 (CH2), 69.2 (CH), 55.7 (CH), 52.3 (CH), 43.4 (C), 39.1 (CH_2), 34.1 (CH_2), 26.1 (CH_3), 24.6 (CH_2), 23.0 (CH_2), 17.9 (C), 17.4 (CH_2), 14.8 (CH_3), -4.8 (CH_3). -5.,2 (CH_3). **IR (KBr, ν cm^{-1}):** 2951, 2858, 1663, 1419, 775. **EMBR (IQ):** 442 (1), 440 (3), 384 (9), 292 (23), 161 (17), 160 (100). **EMAR (IQ):** Calcd for $C_{19}H_{32}F_3O_4SSi$ 441.1742, found 441.1734.

(1S,4aS,5R,7aR)-1-(*tert*-Butyl-dimethylsilyl)oxy-5-ethynyl-4a-methyl-octahydro-indene (7). *n*-HexLi (7.2 mL, 18.0 mmol, 2.6 M) was added to dry diisopropylamine (2.7 mL, 19.3 mmol) at - 78 °C. After the mixture was stirred for 30 min, dry THF (30 mL) was added. The cooling bath was removed and the mixture was stirred for 30 min. The resulting solution of LDA was cooled to – 78 °C, and a solution of triflate **10** (4 g, 9.0 mmol) in dry THF (50 mL) was added dropwise. The cooling bath was removed, and the mixture was stirred at room temperature for 1h. The reaction was quenched with brine (80 mL) and the mixture was extracted with Et_2O. The combined organic layers was dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (5% Et_2O/Hexanes) to give 2.5 g of alkyne **7**. [98%, R_f 0.9, 5% EtOAc/Hexanes, viscous oil]. **^{1}H RMN** δ (ppm): 4.03 (1H, s), 2.07 (1H, s), 2.15-1.06 (12H, m), 1.02 (3H, s), 0.88 (9H, s), 0.01 (3H, s), 0.0 (3H, s). **^{13}C RMN** δ (ppm): 85.7 (C), 70.2 (CH), 68.7 (CH), 51.5 (CH), 43.0 (C), 42.7 (CH), 37.9 (CH_2), 34.3 (CH_2), 28.2 (CH_3), 25.7 (CH_3), 23.1 (CH_2), 17.9 (C), 17.4 (CH_2), 15.3 (CH_3), -4.8 (CH_3). -5.2 (CH_3). **IR (KBr, ν cm^{-1}):** 3312, 2931, 2857, 775. **EMBR (IQ):** 293 (3), 291 (4), 75 (6), 16 (100). **EMAR (IQ):** Calcd for $C_{18}H_{31}OSi$ 291.2144, found 291.2136.

(1S,4aS,5R,7aR)-1-(*tert*-Butyl-dimethylsilyl)oxi-5-1-iodoethynyl-4a-methyl-octahydro-indene (11). *n*-HexLi (5.6 mL, 14.0 mmol, 2.6 M in hexanes) was added to a solution of alkyne **10** (1.0g, 3.5 mmol) in dry THF (20 mL) at –78 °C. After the mixture was stirred for 1 h, a solution of iodine (4.46 g, 17.5 mmol) in dry THF (20 mL) was added dropwise. After the

mixture was stirred for 15 min, the mixture was extracted with Et_2O. The combined organic layers were dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (hexanes) to give 1.26 g of iodoalkyne **11**. [86 % , R_f 0.96, Hexanes, white solid]. **^{1}H RMN** δ (ppm): 4.02 (1H, s), 2.3-1.1 (12H, m), 1.00 (3H, s), 0.88 (9H, s), 0.01 (3H, s), 0,0 (3H, s). **^{13}C RMN** δ (ppm): 96.5 (C), 69.1 (CH), 51.7 (CH), 45.5 (CH), 44.1 (C), 38.5 (CH_2), 34.8 (CH_2), 28.6 (CH_2), 26.3 (CH_3), 23.6 (CH_2), 18.4 (C), 16.2 (CH_3), -3.7 (CH_3), -5.2 (CH_3). **IR (KBr, ν cm^{-1}):** 3436, 2932, 2860, 776. **EMBR (IQ):** 419 (15), 418 (6), 416 (27), 360 (52), 286 (65), 284 (22), 188 (11), 187 (12), 161 (30), 160 (100), 158 (85), 133 (24), 132 (13), 130 (14). **EMAR (IQ):** Calcd for $C_{18}H_{30}IOSi$ 417.1110, found 417.1112.

(1S,4aR,5S,7aR)-1-(*tert*-Butyl-dimethylsilyl)oxy-5-(5-methoxy-5-methyl-hexa-1,3diynyl)-4a-methyl-octahydro-indene (5). CuI (22 mg, 0.19 mmol) was added to a solution of iodoalkyne **11** (306 mg, 2.39 mmol) and propargyl ether **12** (500 mg, 1.1 mmol) in pyrrolydine (10 mL). This mixture was stirred during 1 h to room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl solution (80mL). The mixture was extracted with Et_2O. The combined organic layers were dried, filtrated and concentrated. The residue was purified by flash chromatography (5% EtOAc/Hexanes) to give 66 mg of diyne **5** [88%, R_f 0.5, 10% EtOAc/Hexanes, viscous oil]. **^{1}H RMN** δ (ppm): 4.88 (2H, s), 4.01 (1H, s), 3.37 (3H, s), 2.25-1,64 (8H, m), 1.51 (6H, s), 1.47-1.07 (4H, m), 1.03 (3H, s), 0.88 (9H, s), 0.01 (3H, s), 0.0 (3H, s). **^{13}C RMN** δ (ppm): 93.6 (CH_2), 77.9 (C), 71.7 (C), 70.2 (C), 69.1 (CH), 66.8 (C), 55.8 (CH_3), 51.9 (CH), 44.5 (C), 43.8 (CH), 38.4 (CH_2), 34.6 (CH_2), 30.3 (CH_3), 28.3 (CH_2), 26.3 (CH_3), 23.6 (CH_2), 18.3 (C), 17.8 (CH_2), 16.2 (CH_3), -4.4 (CH_3), -4.8 (CH_3). **IR (KBr, ν cm^{-1}):** 2931, 2821, 2249, 774. **EMBR (IQ):** 418 (4), 417 (12), 389 (19), 388 (12), 373 (22), 359 (10), 358 (36), 357 (100), 331 (13), 257 (26), 225 (16). **EMAR (IQ):** Calcd for $C_{25}H_{42}O_3Si$ 418.2903, found 418.2889.

General procedure for Sonogashira coupling. Dry Et_3N (1.6 mL, 11.4 mmol) and $PdCl_2(PPh_3)_2$ (197 mg, 0.28 mmol) were successively added to a solution of alkyne **7** (800 mg, 2.85 mmol) and methyl 3-trifluormethansulphonyloxibenzoate (1.1 g, 3.78 mmol) in dry DMF (20 mL). The mixture was heated to 80 °C overnight. The reaction was quenched with brine (80 mL) and extracted with Et_2O. The combined organic layers were dried, filtered and concentrated. The crude was purified by flash chromatography (5% Et_2O/Hexanes) to afford 805 mg of alkyne **6b** [67%, R_f 0.54, 5% Et_2O/Hexanes, viscous oil].

(1S,4aR,5S,7aR)-1-(*tert*-Butyl-dimethyl-silyloxy)-5-[3-(*tert*-butyl-dimethyl-silyloxy)-phenylethynyl]-4a-methyl-octahydro-indene (6a). Alkyne **6a** was obtained as the procedure above (53%, R_f 0.35, Hexanes, viscous oil). **^{1}H RMN** δ (ppm): 7.12 (1H, dd, *J*=7,6 y 8,0 Hz), 6.99 (1H, d, *J*=7,6 Hz), 6.87 (1H, s), 6.73 (1H, d, *J*=8,0 Hz), 4.05 (1H, s), 2.37-1.14 (12H, m), 1.10 (3H, s), 0.99 (9H, s), 0.91 (9H, s), 0.2 (6H, s), 0.04 (3H, s), 0.02 (3H, s). **^{13}C RMN** δ (ppm): 155.3 (C), 129.1 (CH), 125.3 (C), 124.8 (CH), 123.1 (CH), 119.5 (CH), 91.3 (C), 82.7 (C), 68.8 (CH), 51.6 (CH), 44.0 (C), 43.6 (CH), 38.2 (CH_2), 34.4 (CH_2), 28.4 (CH_2), 25.8 (CH_3), 25.6 (CH_3), 23.3 (CH_2), 18.1 (C), 18.0 (C), 17.5 (CH_2), 15.7 (CH_2), -4.4 (CH_3), -4.8 (CH_3). -5.2 (CH_3). **IR (KBr, ν cm^{-1}):** 3434, 2932, 2858, 780. **EMBR (IQ):** 499 (839), 498 (59), 497 (34), 484 (24), 483 (41), 443 (28), 442 (48), 441 (100), 425 (10), 423 (10), 395 (12), 383 (14), 367 880), 366 (32), 365 (30). **EMAR (IQ):** Calcd for $C_{30}H_{51}O_2Si_2$ 499.3427 found 499.3412.

(1S,4aR,5S,7aR)-1-(*tert*-Butyl-dimethyl-silyloxy)-4a-methyl-5-(3-methoxycarbonyl-phenylethynyl)-octahydro-indene (6b). Alkyne **6b** was obtained as the procedure above (67%, R_f 0.54, 5% Et_2O/Hexanes, viscous oil). **^{1}H RMN** δ (ppm): 8.04 (1H, s), 7.88 (2H, d, J=7.9 Hz), 7.53 (1H, d, J=7.72 Hz), 7.31 (2H, dd, J=7.9 y 7.7 Hz), 4.02 (1H, s), 3.87 (3H, s), 2.41-1.4 (12H, m), 1.09 (3H, s), 0.89 (9H, s), 0.01 (3H, s), 0.0 (3H, s). **^{13}C RMN** δ (ppm): 166.3 (C), 165.6 (CH), 132.5 (CH), 130.1 (C), 128.2 (CH), 128.0 (CH), 124.7 (C), 92.6 (C), 81.9 (C), 68.7 (CH), 51.9 (CH_3), 51.5 (CH), 43.5 (C), 43.4 (CH), 38.1 (CH_2), 34.3 (CH_2), 28.2 (CH_2), 25.6 (CH_3), 23.2 (CH_2), 17.8 (C), 17.4 (CH_2), 15.6 (CH_3), -4.9 (CH_3). -5.8 (CH_3). **IR (KBr, ν cm^{-1}):** 2950, 2880, 1728, 775. **EMBR (IQ):** 426 (3), 425 (9), 411 (13), 369 (23), 327 (20), 325 (11), 313 (10), 311 (58), 309 (27), 297 (24), 296 (22), 295 (92), 294 (15), 293 (41), 283 (13), 282 (10), 281 (20), 279 (41)267 (12), 265 (13), 263 (17), 253 (14), 241 (17). **EMAR (IQ):** Calcd for $C_{26}H_{39}O_3Si$ 427.2668, found 427.2656.

(1S,4aR,5S,7aR)-1-(*tert*-Butyl-dimethyl-silyloxy)-4a-methyl-5-(4-methoxycarbonyl-phenylethynyl)-octahydro-indene (6c). Alkyne **16** was obtained as the procedure above (69%, R_f 0.62, 5% Et_2O/Hexanes, viscous oil). **^{1}H RMN** δ (ppm): 7.93 (2H, d, *J*=8.2 Hz), 7.42 (2H, d, *J*=8.2 Hz), 4.02 (1H, s), 3.87 (3H, s), 2.36-1.16 (12H, m), 1.09 (3H, s), 0.89 (9H, s), 0.02 (3H, s), 0.0 (3H, s). **^{13}C RMN** δ (ppm): 166.5 (C), 131.1 (CH), 129.2 (CH), 129.1 (C), 128.4 (C), 95.1 (C), 82.4 (C), 68.6 (CH), 68.7 (CH), 51.9 (CH_3), 51.5 (CH), 43.7 (C), 43.5 (CH), 38.1 (CH_2), 34.3 (CH_2), 28.2 (CH_2), 25.7 (CH_3), 23.2 (CH_2), 17.9 (C), 17.4 (CH_2), 15.7 (CH_3), -4.8 (CH_3). -5.2 (CH_3). **IR (KBr, ν cm^{-1}):** 2929, 2856, 2219, 1721, 1604, 770. **EMBR**

(IQ): 427 (81), 426 (17), 425 (26), 411 (22), 396 (10), 395 (26), 371 (14), 370 (32), 369 (77), 323 (12), 296 (36), 295 (100), 294 (24), 293 (28), 264 (20), 263 (53), 235 (11), 177 (13), 74 (16). **EMAR (IQ):** Calcd for $C_{26}H_{39}O_3Si$ 427.2668, found 427.2647.

General procedures for Desilylation-Oxidation.

HF (45%, 1.5 mL) was added to a solution of compound **6c** (200 mg, 0.46 mmol). The mixture was stirred during 2 hours at room temperature. The reaction was quenched with a saturate aqueous solution of $NaHCO_3$ (200 mL) and extracted with Et_2O. The combined organic layers were dried, filtrated and concentrated. The residue was chromatographied to obtain 131 mg of the corresponding alcohol (90%, R_f 0.15, 20% EtOAc/Hexanes, white solid). Pyridinium dichromate (417 mg, 1.10 mmol) was added to a solution of alcohol (173 mg, 0.5 mmol) in CH_2Cl_2 (15 mL). The suspension was stirred during four hours at room temperature. The reaction was diluted with Et_2O and filtrated through celite. The organic layer was concentrated and the residue was chromatographied (20% EtOAc/hexanes) to afford 170 mg of ketone **16c** (99%, R_f 0.6, 30% EtOAC/hexanes, white solid).

(1S,4aR,5S,7aR)-4a-methyl-5-(5-Methoxymethoxy-5-methyl-hexa-1,3-diynyl)-octahydro-inden-1-one (14). Ketone **14** (170 mg) was prepared as above (99%, R_f 0.60, 20% EtOAc/Hexanes, white solid). **^{1}H RMN** δ (ppm): 4.79 (2H, s), 3.30 (3H, s), 2.56-1.47 (12H, m), 1.44 (6H, s), 0.69 (3H, s). **^{13}C RMN** δ (ppm): 210.3 (C), 93.5 (CH_2), 81.3 (C), 78.7 (C), 71.5 (C), 69.7 (C), 67.2 (C), 60.0 (CH), 55.7 (CH_3), 51.3 (C), 43.2 (CH), 40.8 (CH_2), 36.7 (CH_2), 30.2 (CH_3), 28.4 (CH_2), 23.8 (CH_2), 20.0 (CH_2), 14.4 (CH_3). **IR (KBr, ν cm^{-1}):** 2972, 2883, 2248, 1715. **EMBR (IQ):** 301 (8), 273 (27), 272 (37), 271 (12), 242 (129, 241 (100), 223 (13), 213 (19), 199 (10), 171 (10). **EMAR (IQ):** Calcd for $C_{19}H_{25}O_3$ 301.1803, found 301.1808.

(1S,4aR,5S,7aR)-5-(3-Hydroxy-phenyl-ethynyl)-4a-methyl-octahydro-inden-1-one (16a). Ketone **16a** (160 mg) was prepared as above (70%, R_f 0.35, 20% EtOAc/Hexanes, white solid). **^{1}H RMN** δ (ppm): 7.06 (1H, dd, *J*=7.8 y 7.8 Hz), 6.86 (1H, d, *J*=7.6 Hz), 6.8 (1H, s), 6.72 (1H, d, *J*=7.9 Hz), 6.7 (1H, broad s), 2.6-0.77 (9H, m), 1.74 (3H, s). **^{13}C RMN** δ (ppm): 213.0 (C), 156.2 (C), 129.8 (CH), 125.1 (C), 124.2 (CH), 118.7 (CH), 115.8 (CH), 89.9 (C), 83.5 (C), 60.4 (CH), 51,6 (C), 43.5 (CH), 41.1 (CH_2), 36.9 (CH_2), 28.9 (CH_2), 24.1 (CH_2), 20.0 (CH_2), 14.5 (CH_3). **IR (KBr, ν cm^{-1}):** 3361, 2963, 2879, 2224, 1697. **EMBR (IQ):** 269 (100), 268 (9), 251 (43). **EMAR (IQ):** Calcd for $C_{18}H_{21}O_2$ 269.1541, found 269.1538.

(1S,4aR,5S,7aR)-5-(3-Methoxycarbonyl-phenyl-ethynyl)-4a-methyl-octahydro-inden-1-one (16b). Ketone **16b** (176 mg) was prepared as above (60%, R_f 0.65, 20% EtOAc/Hexanes, white solid). **^{1}H RMN** δ (ppm): 7.95 (1H, s), 7.83 (1H, d, *J*=8.8 Hz), 7.46 (1H, d, *J*=8.8 Hz), 7.26 (1H, m), 4.03 (1H, s), 3.80 (3H, s), 2.64-0.74 (12H, m), 0.72 (3H, s). **^{13}C RMN** δ (ppm): 210 (C), 166.7 (C), 136.0 (CH), 132.9 (CH), 130.6 (C), 129.0 (CH), 128.7 (CH), 124.5 (C), 91.3 (C), 82.6 (C), 60.2 (CH), 52.5 (CH_3), 51.1 (C), 43.4 (CH), 40.9 (CH_2), 36.8 (CH_2), 28.8 (CH_2), 23.9 (CH_2), 20.0 (CH_2), 14.4 (CH_3). **IR (KBr, ν cm^{-1}):** 2953, 225, 1721. **EMBR (IQ)**: 312 (13), 311 (63), 293 (24), 279 (11), 55 (15), 41 (20), 29 (48), 27 (48), 16 (100), 15 (71). **EMAR (IQ):** Calcd for $C_{20}H_{23}O_3$, 311.1647, found 311.1644.

(1S,4aR,5S,7aR)-5-(4-Methoxycarbonyl-phenyl-ethynyl)-4a-methyl-octahydro-inden-1-one (16c). Ketone **16c** (170 mg) was prepared as above (99%, R_f 0.6, 30% EtOAC/hexanes, white solid).**^{1}H RMN** δ (ppm): 7.85 (2H, d, *J*=8.4 Hz), 7.34 (2H, d, *J*=8.4 Hz), 3.79 (3H, s), 2.66-1.40 (12H, m), 0.72 (3H, s). **^{13}C RMN**δ (ppm): 210.7 (C), 166.8 (C), 131.8 (CH), 129.7 (CH), 129.3 (C), 128.8 (C), 93.7 (C), 83.0 (C), 60.2 (CH), 52.5 (CH_3), 51.2 (CH), 43.5 (CH), 40.9 (C), 36.9 (CH_2), 28.7 (CH_2), 23.9 (CH_2), 20.0 (CH_2), 14.4 (CH_3). **IR (KBr, ν cm^{-1}):** 2970, 2877, 1715, 1275. **EMBR (IQ):** 312 (49, 311 (20), 68 (18), 67 (27), 59 (14), 55 (70), 42 (29), 41 (75), 27 (77), 16 (100). **EMAR (IQ):** Calcd for $C_{20}H_{23}O_3$ 311.1647, found 311.1642.

General procedure for Wittig-Horner Couplings. *n*-BuLi (0.51 mL, 1.28 mmol, 2.5 M in hexanes) was added to a solution of phosphine oxide **4** (1.2 g, 1.2 mmol, 2 equiv) in dry THF at –78 °C. The deep red solution was stirred for 1.5 h. A solution of ketone **14** (192 mg, 0.64 mmol, 1 equiv) in dry THF was added dropwise. The reaction mixture was stirred in the dark for 9 h at –78 °C and at –40 °C for 1 h. The reaction was quenched by the addition of H_2O (8 mL) and EtOAc (15 mL). The aqueous layer was extracted with Et_2O. The combined layers were washed with brine (5 mL), dried, filtered, and concentrated in vacuo. The residue was flash chromatographed (4% EtOAc/hexanes) to give 385 of protected analog **15** [80%, R_f = 0.9, 15 % EtOAc/hexanes, colourless oil].

(4aS,5S,7aS)-5-(5-Methoxymethoxy-5-methyl-hexa-1,3-diynyl)-4a-methyl-1-(*E*)-[2-(*Z*)-{(3S,5R)-2-methylene-3,5-*bis*-triisopropylsilanyloxy-cyclohexylidene}-ethylidene]-octahydro-indene (15). Protected vitamin D **15** (385 mg) was obtained as the procedure

above [80%, R_f = 0.9, 15 % EtOAc-hexanes, colourless oil]. **^{1}H RMN** δ (ppm): 6.20 (1H, d, *J*=11.1 Hz), 6.03 (1H, d, *J*=11.1 Hz), 5.23 (1H, s), 4.86 (2H, s), 4.50 (1H, m), 4.31 (1H, m), 3.36 (3H, s), 2.83 (1H, m), 2.52-1.56 (19H, m), 1.50 (6H, s), 1.04 (36H, s), 0.65 (6H, s); **^{13}C RMN** δ (ppm): 210.3 (C), 93.5 (CH_2), 81.3 (C), 78.7 (C), 71.5 (C), 69.7 (C), 67.2 (C), 60.0 (CH), 55.7 (CH_3), 51.3 (C), 43.2 (CH), 40.8 (CH_2), 36.7 (CH_2), 30.2 (CH_3), 28.4 (CH_2), 23.8 (CH_2), 20.0 (CH_2), 14.4 (CH_3). **IR (KBr, ν cm^{-1}):** 2972, 2883, 2248, 1715. **EMBR (IQ):** 301 (8), 273 (27), 272 (37), 271 (12), 242 (129, 241 (100), 223 (13), 213 (19), 199 (10), 171 (10). **EMAR (IQ):** Calcd for $C_{19}H_{25}O_3$ 301.1803, found 301.1808.

(4aS,5S,7aS)-5-(3-Hydroxy-phenylethynyl)-4a-methyl-1-(*E*)-[2-(*Z*)-{(3S,5R)-2-methylene-3,5-*bis*-triisopropylsilanyloxy-cyclohexylidene}-ethylidene]-octahydro-indene (17a). Protected vitamin D **22** (180 mg) was prepared as above [75%, R_f = 0.75, 30 % EtOAc/hexanes, colourless oil]. **^{1}H RMN**δ (ppm)**:** 6.20 (1H, d, *J*=11.1 Hz), 6.03 (1H, d, *J*=11.1 Hz), 5.23 (1H, s), 4.86 (2H, s), 4.50 (1H, m), 4.31 (1H, m), 3.36 (3H, s), 2.83 (1H, m), 2.52-1.56 (19H, m), 1.50 (6H, s), 1.04 (36H, s), 0.65 (6H, s). **^{13}C RMN**δ (ppm)**:** 148.7 (C), 139.5 (C), 136.1 (C), 122.6 (CH), 118.3 (CH), 111.1 (CH_2), 93.2 (CH_2), 82.8 (C), 77.7 (C), 72.0 (CH), 71.3 (C), 69.8 (C), 67.5 (CH), 66.1 (C), 55.4 (CH_3), 54.5 (CH), 47.5 (C), 46.3 (CH_2), 45.2 (CH_2), 42.8 (CH), 38.1 (CH_2), 29.9 (CH_3), 28.4 (CH_2), 28.1 (CH_2), 23.0 (CH_2), 22.4 (CH_2), 18.7 (CH_3), 13.7 (CH_3), 12.3 (CH_3). **IR (KBr, ν cm^{-1}):** 3388, 2942, 2866, 1463, 1035. **EMBR (IQ):** 751 (6), 707 (10), 690 (11), 689 (20), 629 (11), 615 (10), 613 (13), 578 (11), 577 (26), 576 (18), 547 (13), 545 (12), 543 (10), 533 (15), 531 (15), 529 (16), 527 (17), 517 (40), 515 (40), 513 (31), 499 (68), 485 (41), 483 (97), 471 (61), 455 (100), 443 (42). **EMAR (IQ):** Calcd for $C_{46}H_{79}O_4Si_2$ 751.5516, found 751.5540.

(4aS,5S,7aS)-5-(3-Methoxycarbonyl-phenylethynyl)-4a-methyl-1-(*E*)-[2-(*Z*)-{(3S,5R)-2-methylene-3,5-*bis*-triisopropylsilanyloxy-cyclohexylidene}-ethylidene]-octahydro-indene (17b). Protected vitamin D **17b** (260 mg) was prepared as above [65%, R_f = 0.8 20 % EtOAc/hexanes, colourless oil]. **^{1}H RMN** δ (ppm)**:** 8.03 (1H, s), 7.88 (1H, d, *J*=7.7 Hz), 7.52 (1H, d, *J*=7.6 Hz), 7.29 (1H, t, *J*=7.7 Hz), 6.23 (1H, d, *J*=11.2 Hz), 6.07 (1H, d, *J*=11.2 Hz), 5.24 (1H, s), 4.89 (1H, s), 4.51 (1H, s), 4.30 (1H, s), 3.86 (3H, s), 3.86-1.05 (19H, m), 1.04 (36H, s), 0.70 (6H, s). **^{13}C RMN**δ (ppm)**:** 166.3 (C), 148.7 (C), 139.8 (C), 135.5 (C), 135.6 (CH), 132.5 (CH), 130.1 (C), 128.3 (CH), 128.1 (CH), 124.6 (C), 122.7 (CH), 118.1 (CH), 111.1 (CH_2), 92.6 (C), 81.5 (C), 71.9 (CH), 67.5 (CH), 54.5 (CH), 51.9 (CH_3), 47.1 (C), 46.2 (CH_2), 45.2 (CH_2), 42.9 (CH), 38.2 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 23.1 (CH_2), 22.5 (CH_2),

18.0 (CH), 13.7 (CH_3), 12.4 (CH). **IR (KBr, ν cm^{-1}):** 2943, 2866, 1729. **EMBR (IQ):** 761 (26), 760 (54), 759 (89), 758 (21), 757 (17), 718 (14), 717 (36), 716 (59), 715 (100). **EMAR (IQ):** Calcd for $C_{47}H_{74}O_4Si_2$ 758.5125, found 758.5122

(4aS,5S,7aS)-5-(4-Methoxycarbonyl-phenylethynyl)-4a-methyl-1-(*E*)-[2-(*Z*)-{(3S,5R)-2-methylene-3,5-*bis*-triisopropylsilanyloxy-cyclohexylidene}-ethylidene]-octahydro-indene (17c). Protected vitamin D **17c** (282 mg) was prepared as above [75%, R_f = 0.8 20 % EtOAc/hexanes, colourless oil]. **^{1}H RMN** δ (ppm)**:** 7.91 (2H, d, *J*=8.3 Hz), 7.41 (2H, d, *J*=8.2 Hz), 6.23 (1H, d, *J*=11.1 Hz), 6.07 (1H, d, *J*=11.1 Hz), 5.25 (1H, s), 4.89 (1H, s), 4.50 (1H, m), 4.31 (1H, s), 3.85 (3H, s), 2.83 (1H, m), 2.56-1.17 (15H, m), 1.04 (39H, s), 0.70 (6H, s). **^{13}C RMN** δ (ppm)**:** 166.4 (C), 148.7 (C), 139.7 (C), 135.9 (C), 131.3 (CH), 129.2 (CH), 128.9 (C), 128.5 (C), 122.6 (CH), 118.1 (CH), 111.0 (CH_2), 95.1 (C), 81.9 (C), 71.9 (CH), 67.5 (CH), 54.5 (CH), 51.8 (CH_3), 47.2 (C), 46.2 (CH_2), 45.2 (CH), 43.0 (CH), 38.1 (CH_2), 28.5 (CH_2), 23.1 (CH_2), 22.5 (CH_2), 18.0 (CH_3), 13.6 (CH_3), 12.2 (CH_3). **EMBR (IQ):** 759 (2), 585 (11), 411 (26), 291 (11), 203 (19), 175 (27), 158 (21), 157 (89), 132 (26), 131 (100), 115 (18), 103 (38), 89 (14), 75 (17), 43 (35). **EMAR (IQ):** Calcd for $C_{47}H_{73}O_4Si_2$ 757.5047, found 757.5049.

(4aS,5S,7aS)-5-(5-Hydroxy-5-methyl-hexa-1,3-diynyl)-4a-methyl-1-(*E*)-[2-(*Z*)-{(3S,5R)-2-methylene-3,5-*bis*-triisopropylsilanyloxy-cyclohexylidene}-ethylidene]-octahydro-indene (2). ^{n}Bu_4NF (210 mg, 0.79 mmol) was added to a solution of compound **15** (200 mg, 0.27mmol) in THF (10 mL). The reaction mixture was stirred overnight. The reaction was quenched by addition of water and extracted with EtOAc. Concentration of organic layers gave a residue which was dissolved in MeOH (25 mL). AG50 WX4 resin (700 mg) was added. This suspension was stirred for 6 h to room temperature. The suspension was filtered and the combined organic layer was concentrated. The residue was purified by flash chromatography (80% EtOAc/hexanes) to afford 84 mg of vitamin D analog **3** [80%, R_f= 0.3 80 % EtOAC/hexanes, white solid]. **^{1}H RMN** δ (ppm): 6.46 (1H, d, J= 11.0 Hz), 6.24 (1H, d, J= 11.0 Hz), 5.45 (1H, s), 4.51 (1H, t, J= 5.4 Hz), 4.28 (1H, m), 3.46 (1H, m), 2.70- 1.00 , 1.79 (6H, s), 0.8 (3H, s). **^{13}C RMN** δ (ppm): 149.6 (C), 141.4 (C), 136.4 (C), 124.5 (CH), 119.3 (CH), 112.2 (CH_2), 82.9 (C), 81.9 (C), 71.3 (CH), 67.7 (C), 67.5 (CH), 67.2 (CH), 55.4 (CH), 46.0 (CH_2), 43.8 (CH_3), 43.6 (CH_2), 39.0 (CH_2), 31.5 (CH_3), 29.3 (CH_2), 24.2 (CH_2), 23.6 (CH_2), 14.5 (CH_2), 14.2 (CH_3).

(1R,3S)-5-[(2S, 4S, 7aS)-{2-[1-(3-Hydroxy-phenylethynyl)-7a-methyl-octahydro-inden-4-ylidene]-ethylidene}-4-methylene-cyclohexane-1,3-diol (3a). $^{n}Bu_4NF$ (138 mg, 0.53 mmol) was added to a solution of **17a** (125 mg, 0.17 mmol) in THF (10 mL). The reaction mixture was stirred overnight. The reaction was quenched by addition of water and extracted with EtOAc. The combined organic layers were dried, filtrated and concentrated. The residue was purified by flash chromatography (80% EtOAc/Hexanes) to afford 54 mg of **3a** [79 %, R_f= 0.24, 80 % EtOAc/hexanes, viscous oil]. **^{1}H RMN** δ (ppm): 7.26 (1H, t, *J*= 7.8 Hz), 6.73 (2H, m), 6.52 (1H, d, *J*= 11.1 Hz), 6.30 (1H, d, *J*= 11.1 Hz), 5.5 (1H, s), 4.55 (1H, t, *J*= 5.7 Hz) 4.30 (1H, m), 3.10 (1H, m), 2.82-0.85 (14H), 0.72 (3H, s); **^{13}C RMN** δ (ppm): 158.2 (C), 149.6 (C), 141.9 (C), 136.1 (C), 130.3 (CH), 126.4 (C), 124.7 (CH), 123.8 (CH), 119.1 (CH), 119.0 (CH), 115.9 (CH), 112.2 (CH_2), 91.5 (C), 83.8 (C), 71.4 (CH), 67.3 (CH), 55.5 (CH), 46.1 (CH_2), 44.1 (CH), 43.6 (CH_2), 39.2 (CH_2), 29.7 (CH_2), 24.3 (CH_2), 23.6 (CH_2), 14.2 (CH).

(1R,3S)-5-[(2S,4S,7aS)-2-{1-[3-(1-Hydroxy-1-methyl-ethyl)-phenylethynyl]-7a-methyl-octahydro-inden-4-ylidene}-ethylidene]-4-methylene-cyclohexane-1,3-diol (3b). MeLi (0.66 mL, 0.93 mmol, 1.4 M in Et_2O) was added dropwise to a solution of **17b** (229 mg, 0.31 mmol) in THF (10 mL) at –78 °C. The mixture was stirred for 2 h. The reaction was quenched by addition of water. The mixture was extracted with Et_2O. The combined organic layers were dried, filtrated and concentrated. The residue was purified by flash chromatography (80% EtOAc/hexanes) to afford 200mg of corresponding alcohol [87%, R_f 0.80, 30% EtOAC/hexanes, viscous oil]. $^{n}Bu_4NF$ (160 mg, 0.60 mmol) was added to a solution of alcohol (150 mg, 0.20 mmol) in THF (10 mL). The reaction was stirred overnight. The reaction was quenched with water and extracted with EtOAc. The combined organic layers were dried, filtrated and concentrated. The residue was purified by flash chromatography (80% EtOAc/Hexanes) to afford 200mg of **2c** [96 %, R_f= 0.26, 80% EtOAC/hexanes, viscous oil]. **^{1}H RMN** δ (ppm): 7.66 (1H,s), 7.56 (1H, d, J= 8.2 Hz), 7.38 (2H, m), 6.52 (1H, d, J= 11.0 Hz), 6.30 (1H, d, J= 10.9 Hz), 4.54 (1H, t, J= 5.7 Hz), 4.30 (1H, m), 2.74 (1H, m), 2.41 (2H, m), 2.26-1.05 (16H), 1.68 (6H, s), 0.91 (3H, s). **^{13}C RMN** δ (ppm): 148.8 (C), 148.2 (C), 140.1 (C), 135.8 (C), 131.4 (CH), 124.2 (CH), 122.7 (C), 122.5 (CH), 118.1 (CH), 111.1 (CH_2), 91.4 (C), 82.2 (C), 72.4 (C), 71.9 (CH), 67.5 (CH), 55.6 (CH), 47.2 (CH), 46.2 (CH_2), 44.2 (CH), 43.7 (CH_2), 39.3 (CH_2), 31.7 (CH_3), 29.7 (CH_2), 24.3 (CH_2), 23.6 (CH_2), 12.2 (CH).

(1R,3S)-5-[(2S, 4S, 7aS)-(2-{1-[4-(1-Hydroxy-1-methyl-ethyl)-phenylethynyl]-7a-methyl-octahydro-inden-4-ylidene}-ethylidene)-4-methylene-cyclohexane-1,3-diol (3c). Compound **3c** (35 mg) was prepared as above [81%, R_f 0.80, 30% EtOAC/hexanes, viscous oil]. **^{1}H RMN** δ (ppm): 7.30 (2H, d, *J*= 8.3 Hz), 7.18 (2H, d, *J*= 8.4 Hz), 6.23 (1H, d, *J*= 11.1 Hz), 6.95 (1H, d, *J*= 11.1, 5.19 (1H, s), 4.81 (1H, s), 4.25 (1H, t, *J*= 5.8 Hz), 4.02 (1H, m), 2.79 (1H, m), 2.42 (2H, m), 2.20-0.63 (16H), 1.39 (6H,s), 0.61 (3H, s). **^{13}C RMN** δ (ppm): 150.3 (C), 149.7 (C), 141.9 (C), 136.3 (C), 132.1 (CH), 125.6 (CH), 124.7 (CH), 123.5 (C), 119.2 (CH), 112.1 (CH2), 91.6 (C), 83.6 (C), 72.8 (CH), 71.5 (CH), 67.4 (C), 55.6 (CH), 47.9 (CH_2), 46.1 (CH), 44.3 (CH_2), 43.7 (CH_2), 39.3 (CH_2), 31.7 (CH_3), 29.7 (CH_2), 24.3 (CH_2), 23.6 (CH_2), 14.2 (CH_3).

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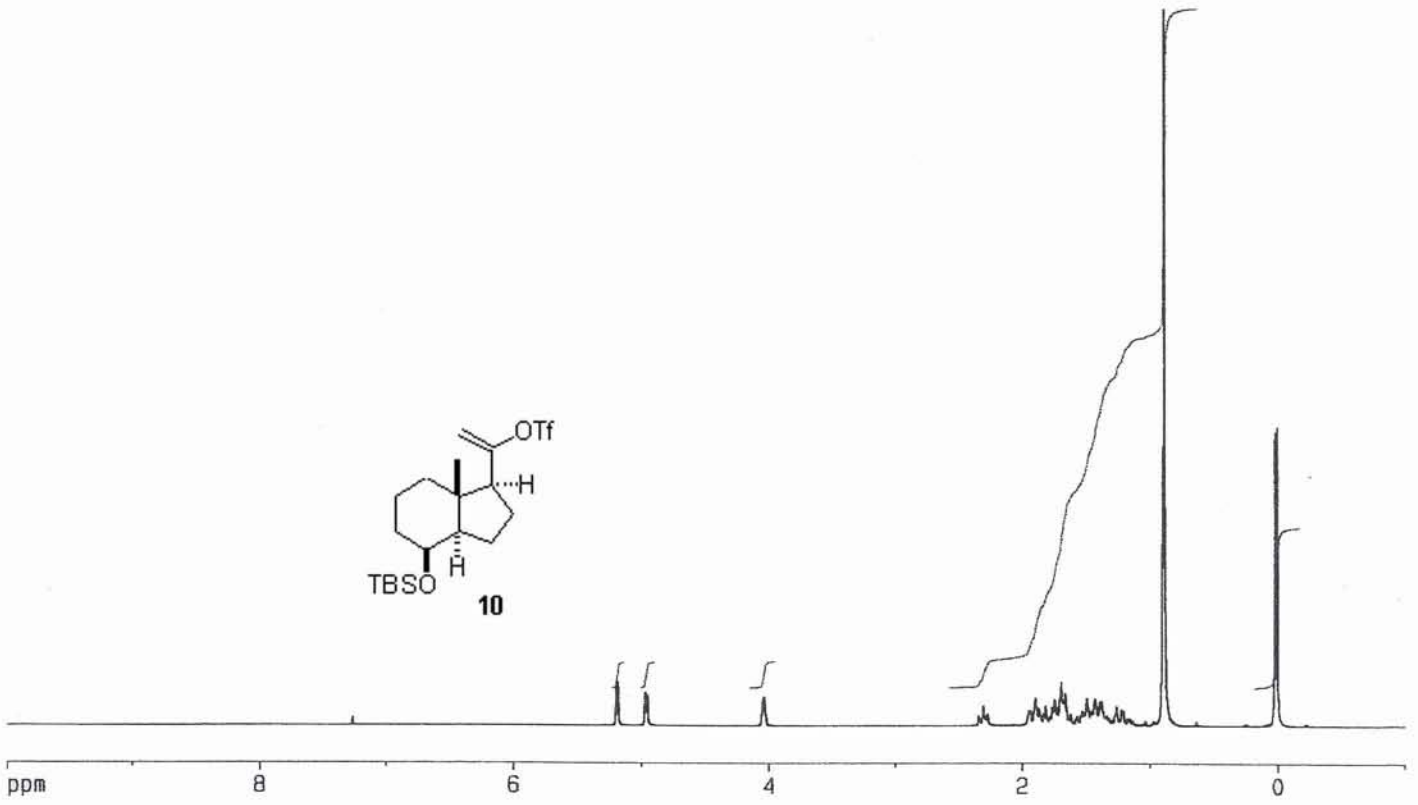
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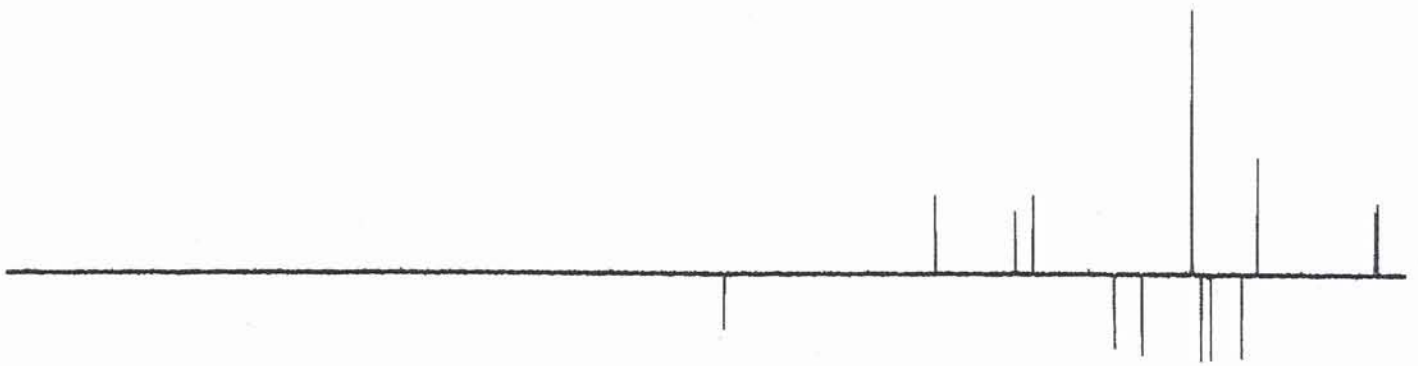

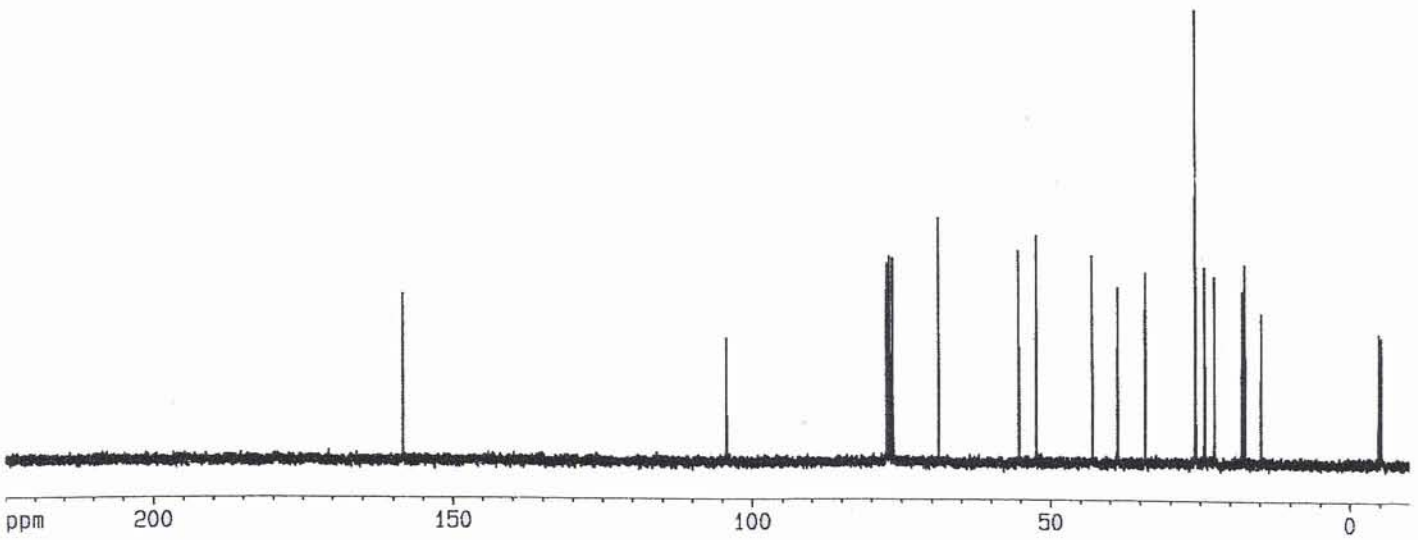
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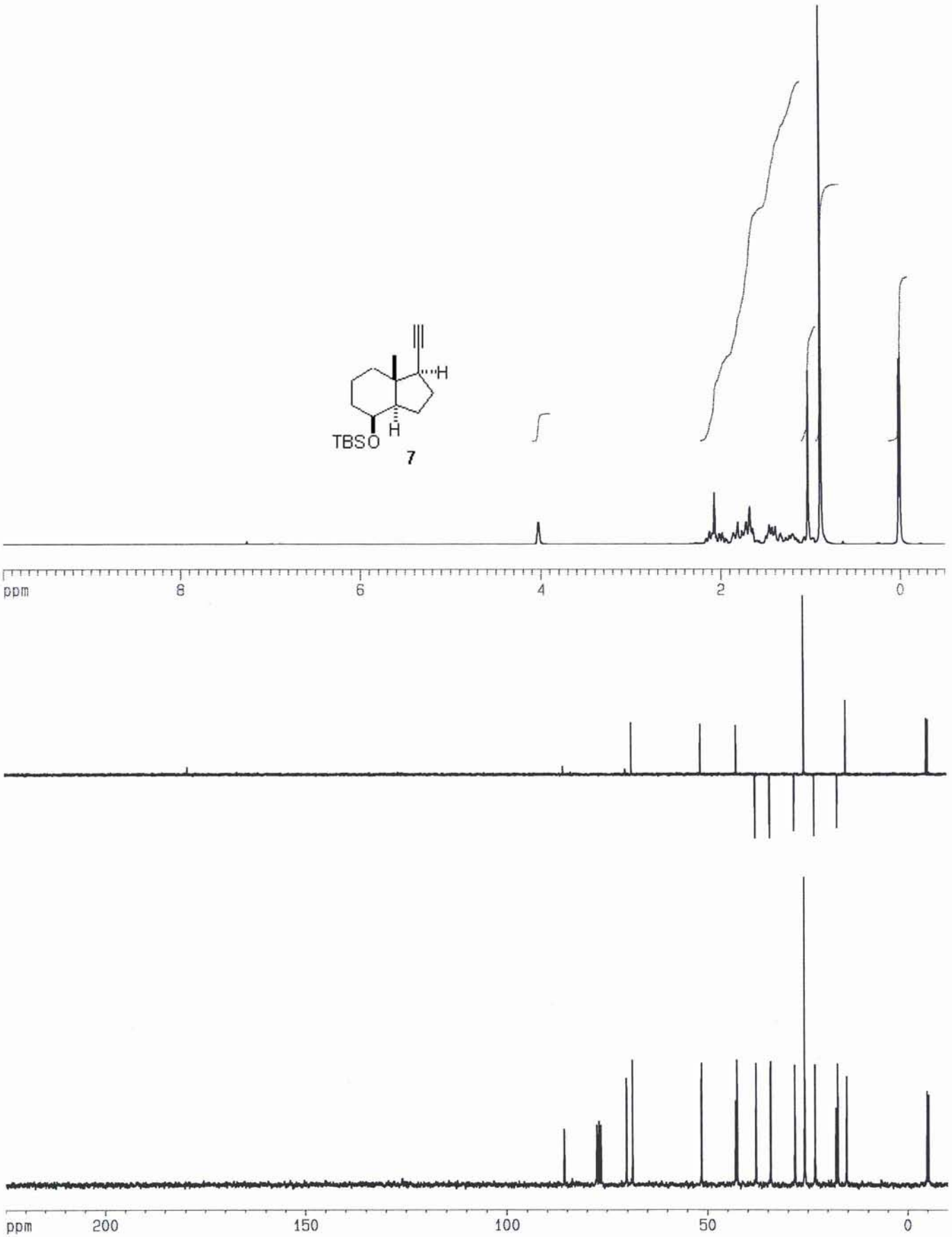
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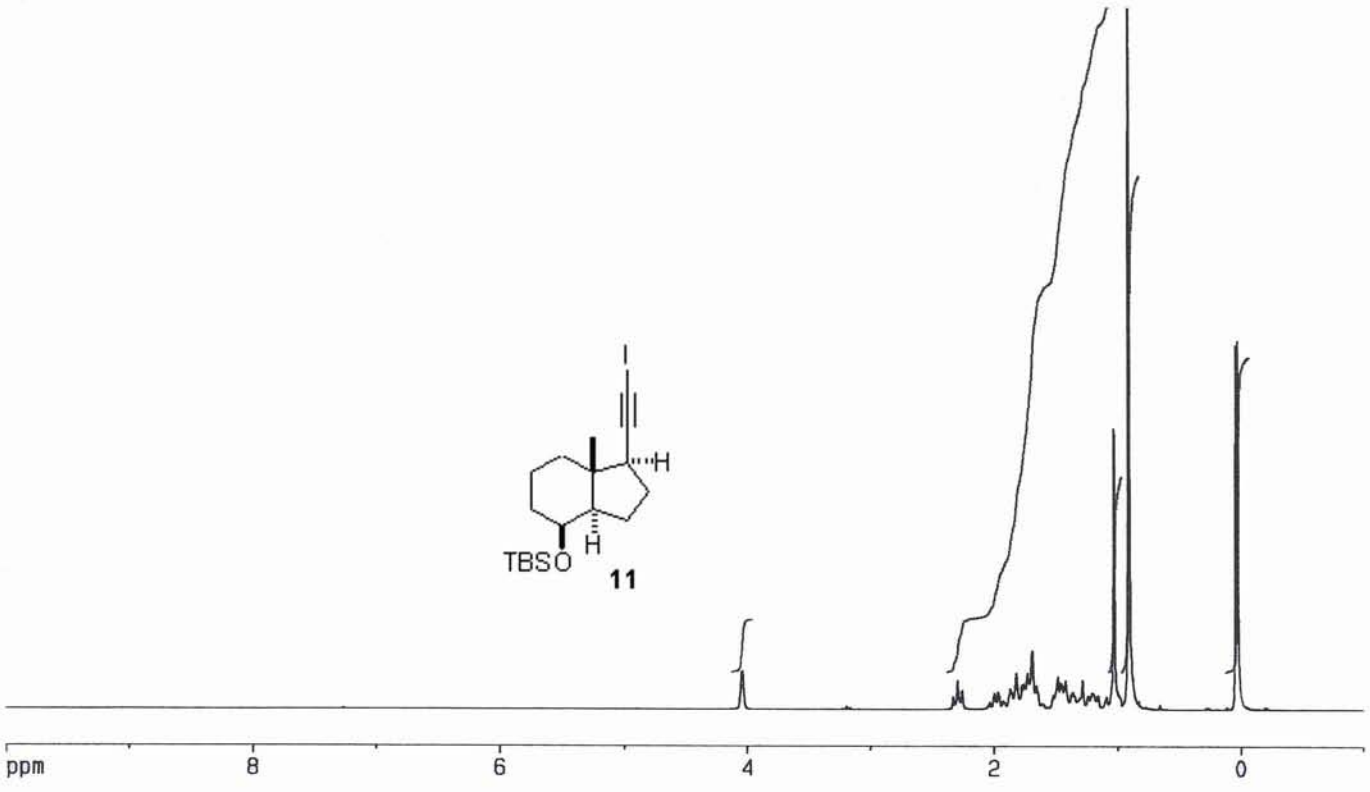
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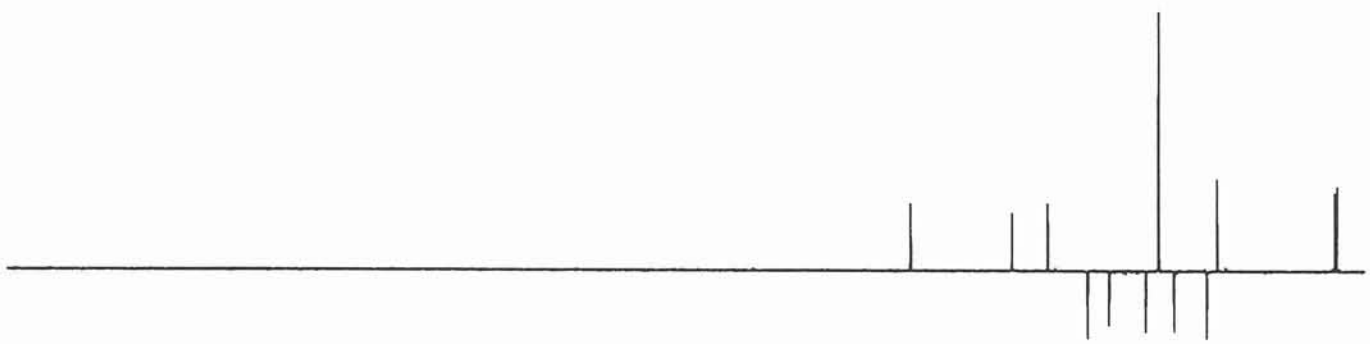

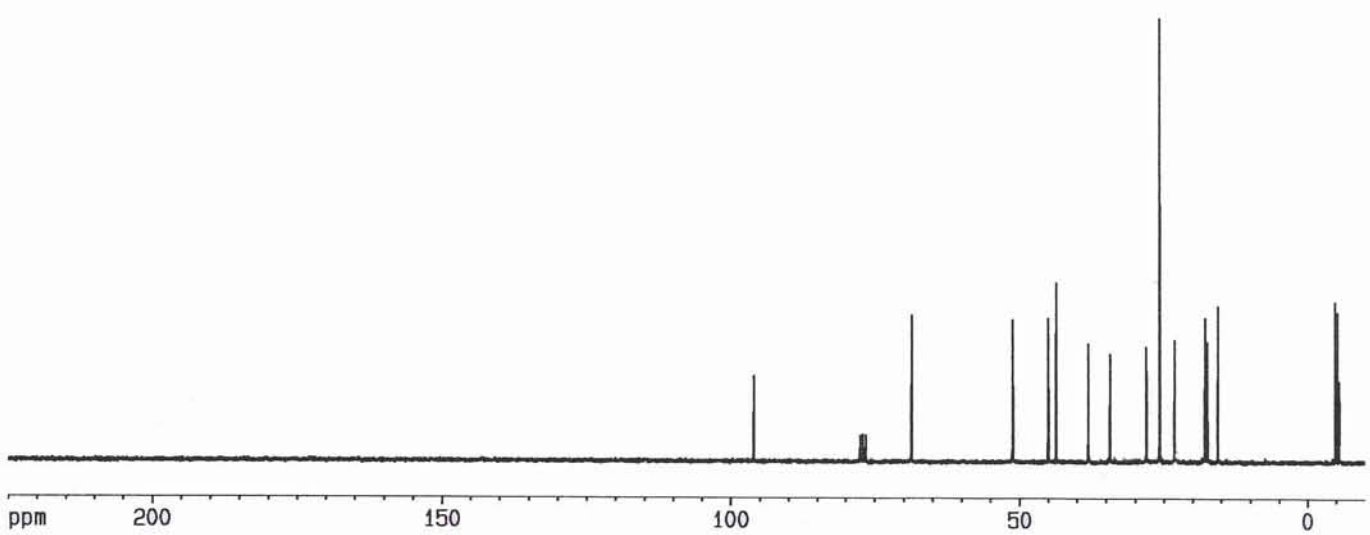
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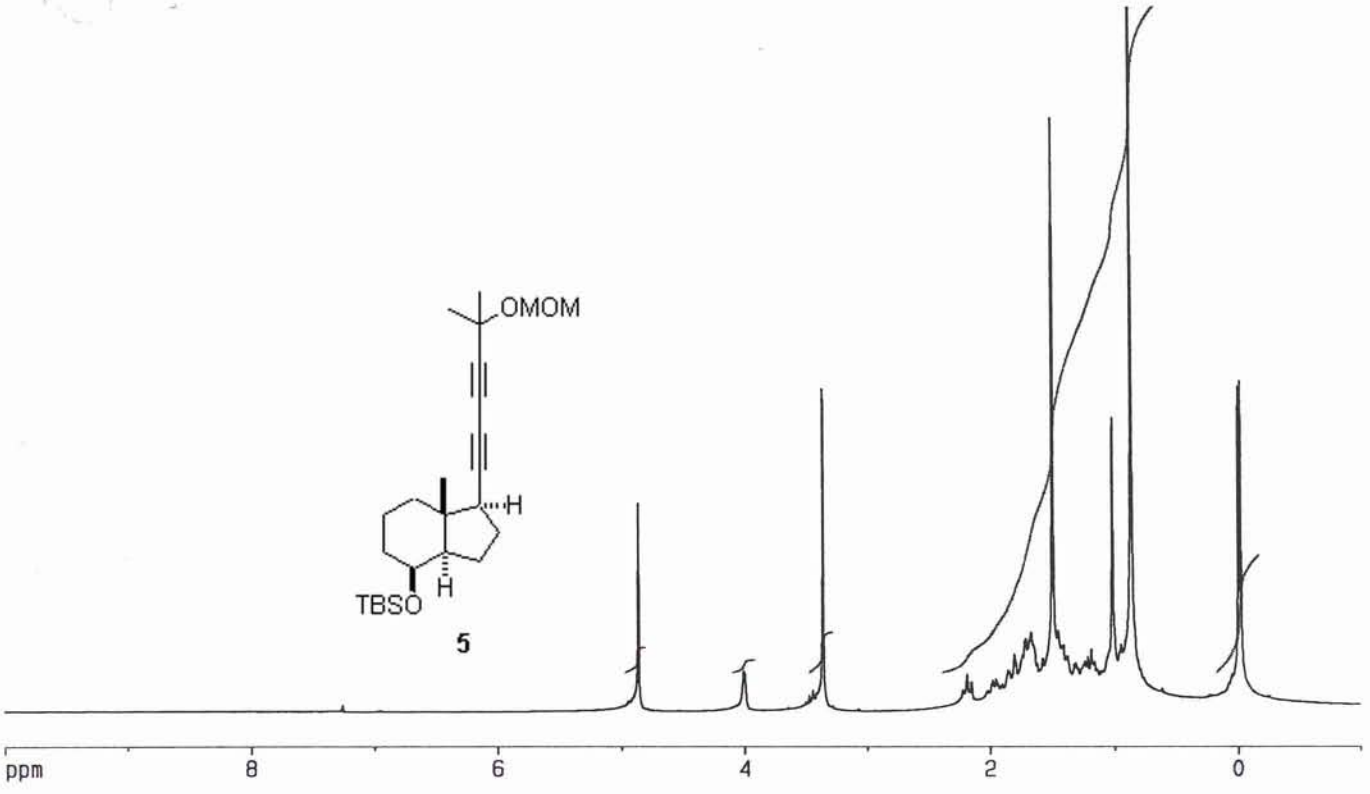

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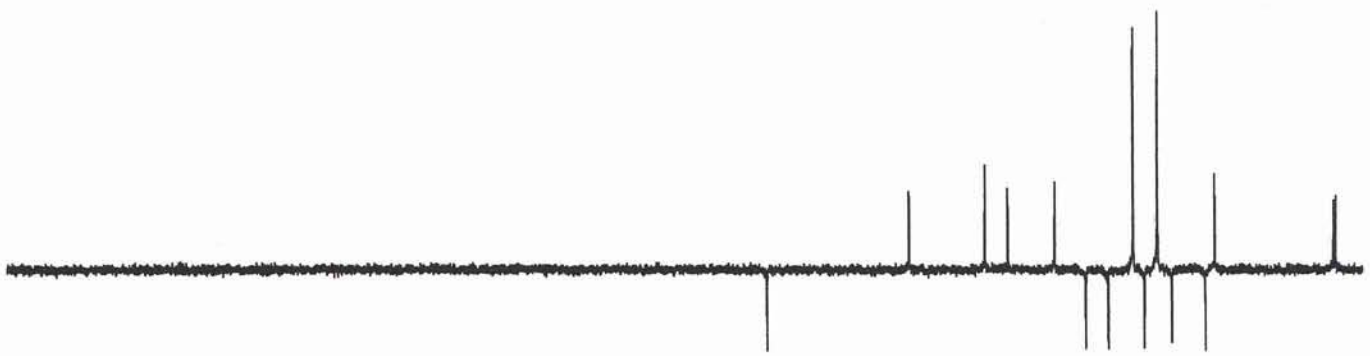

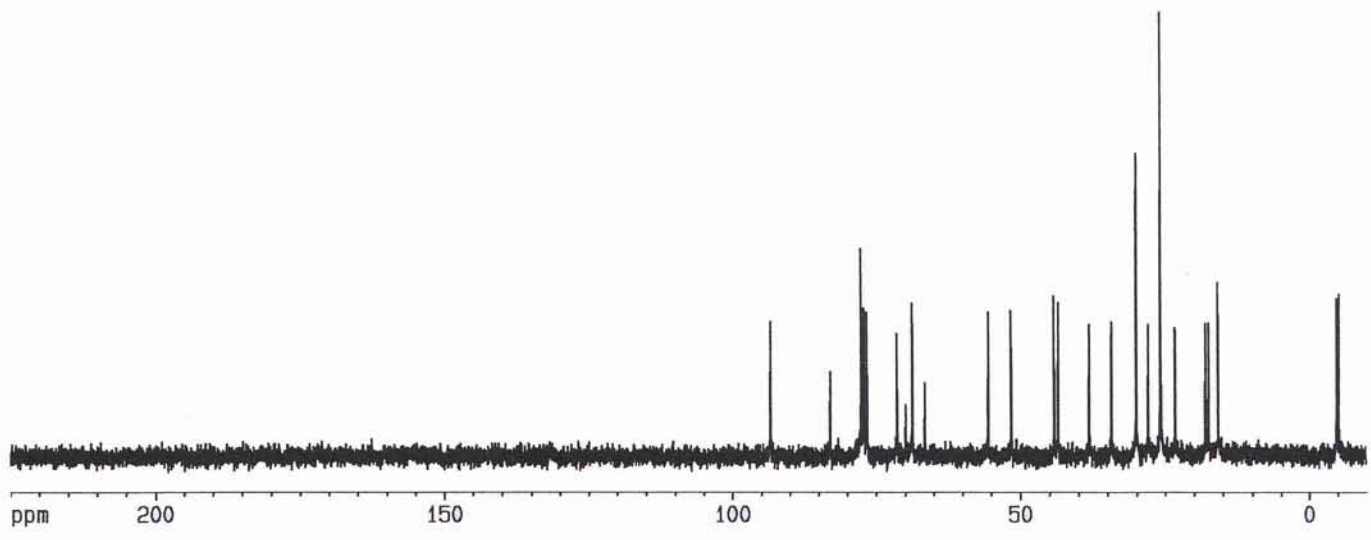

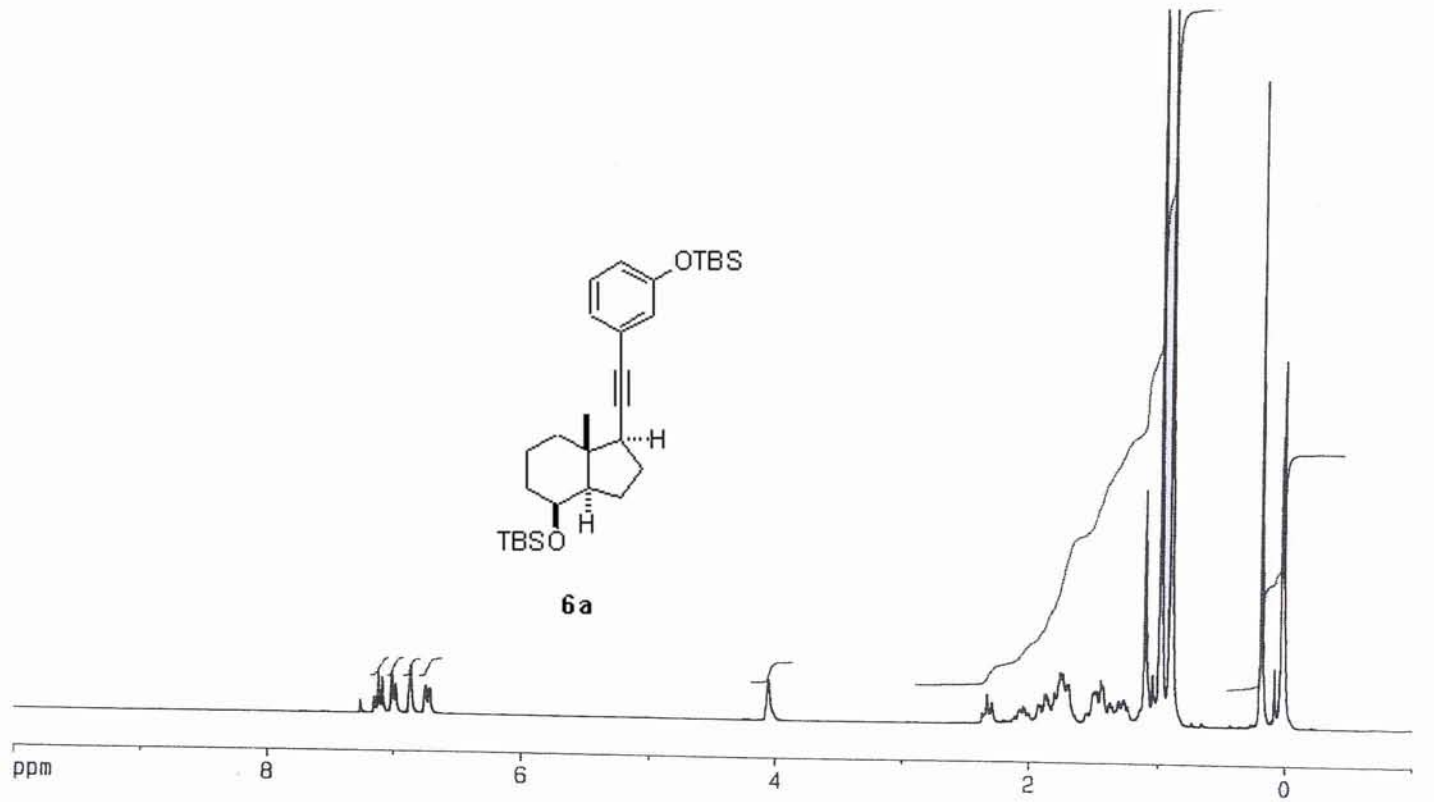

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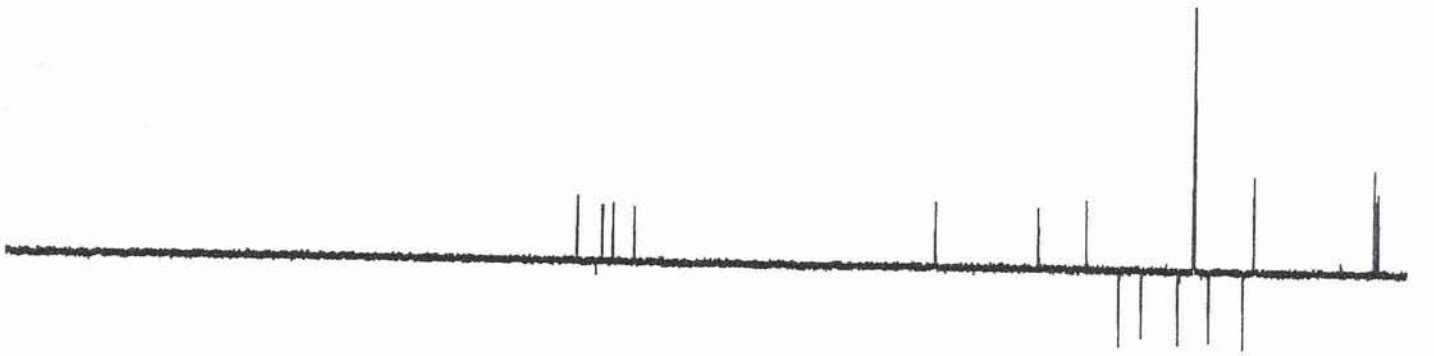

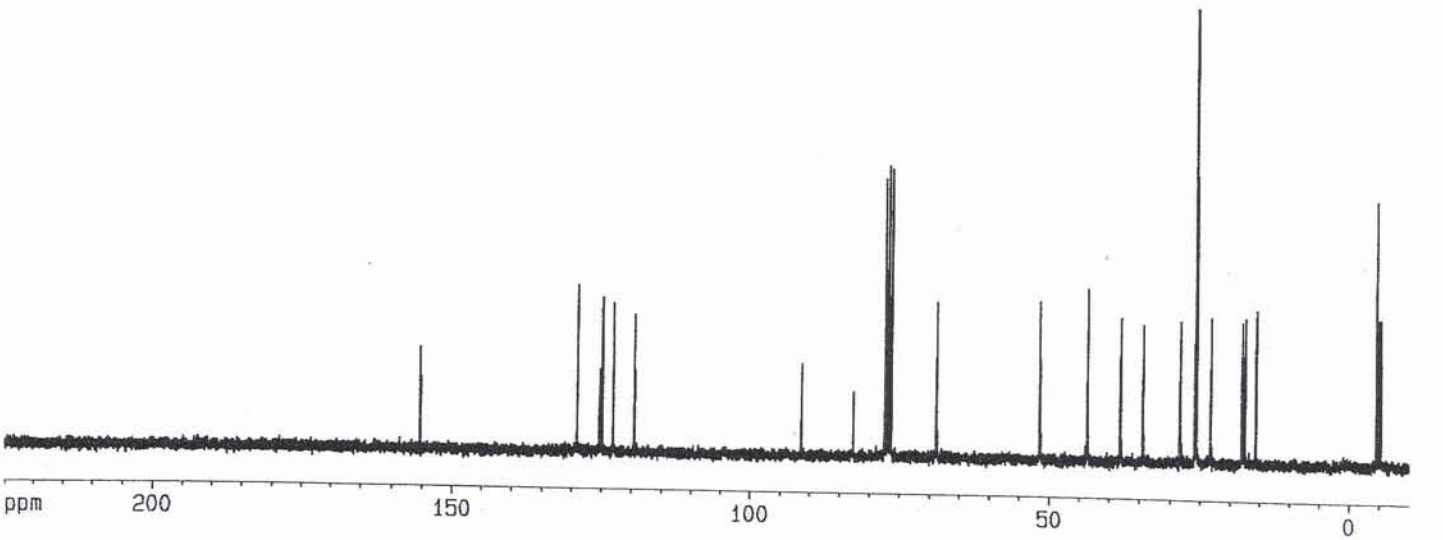

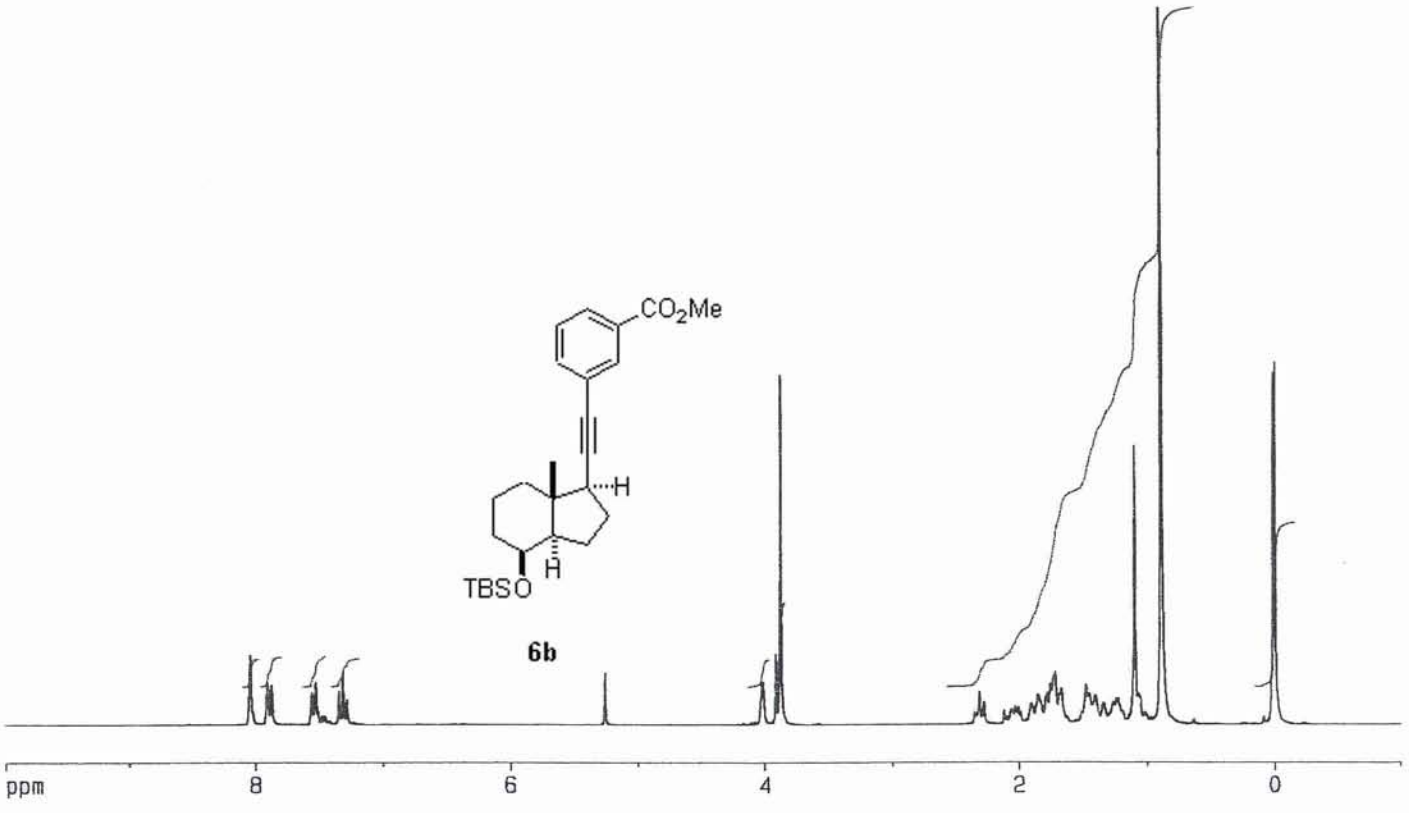

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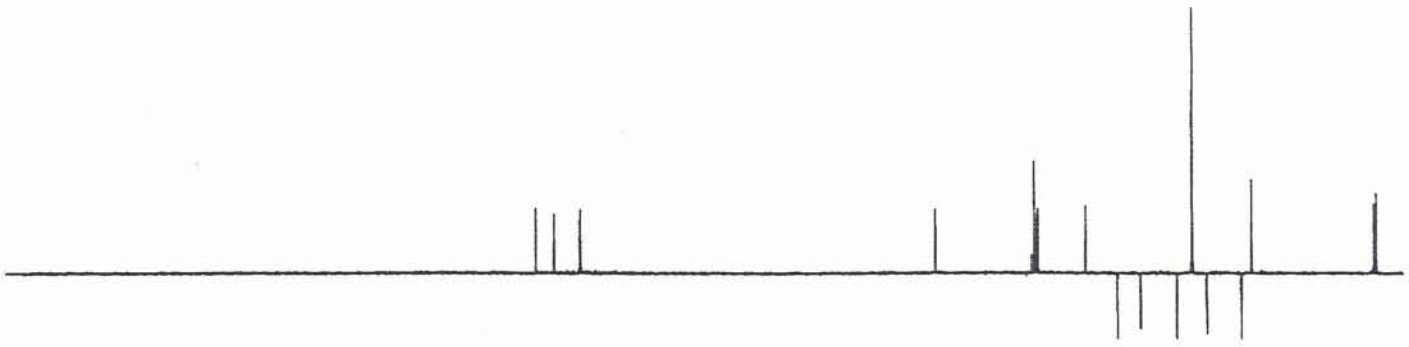

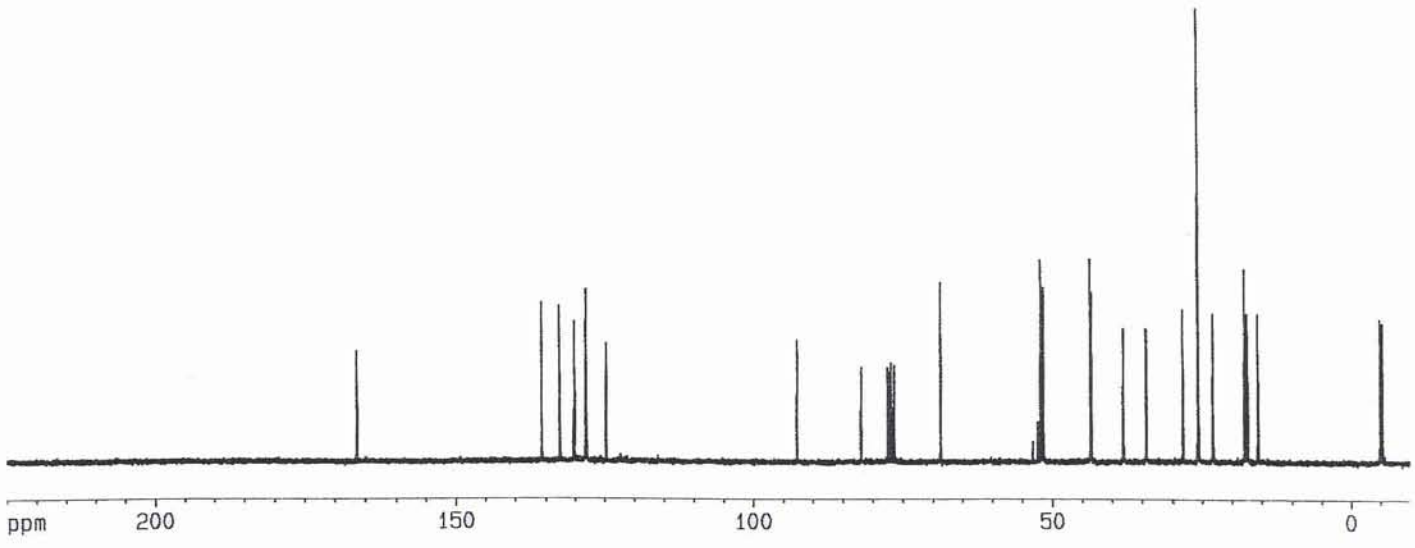

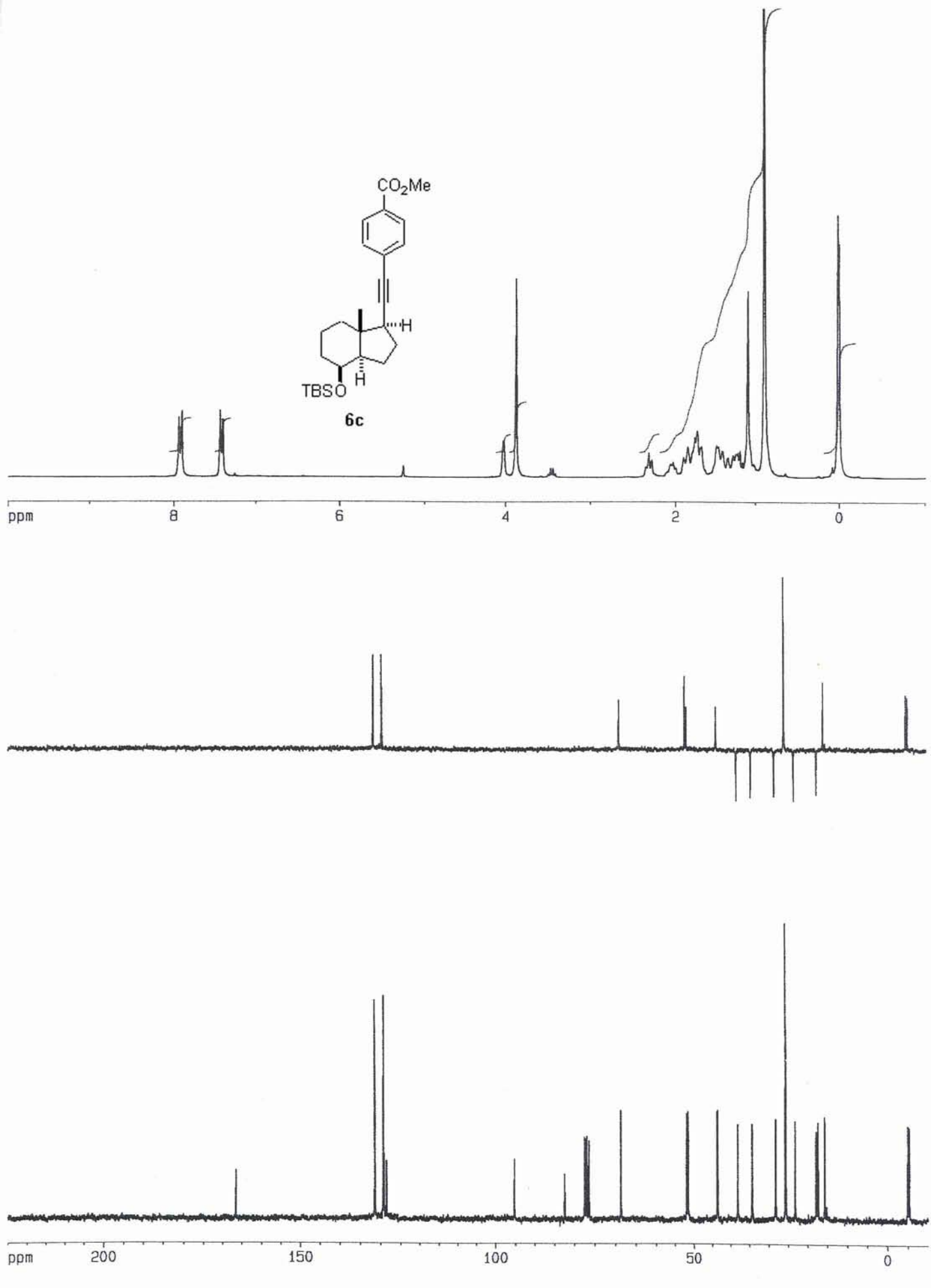
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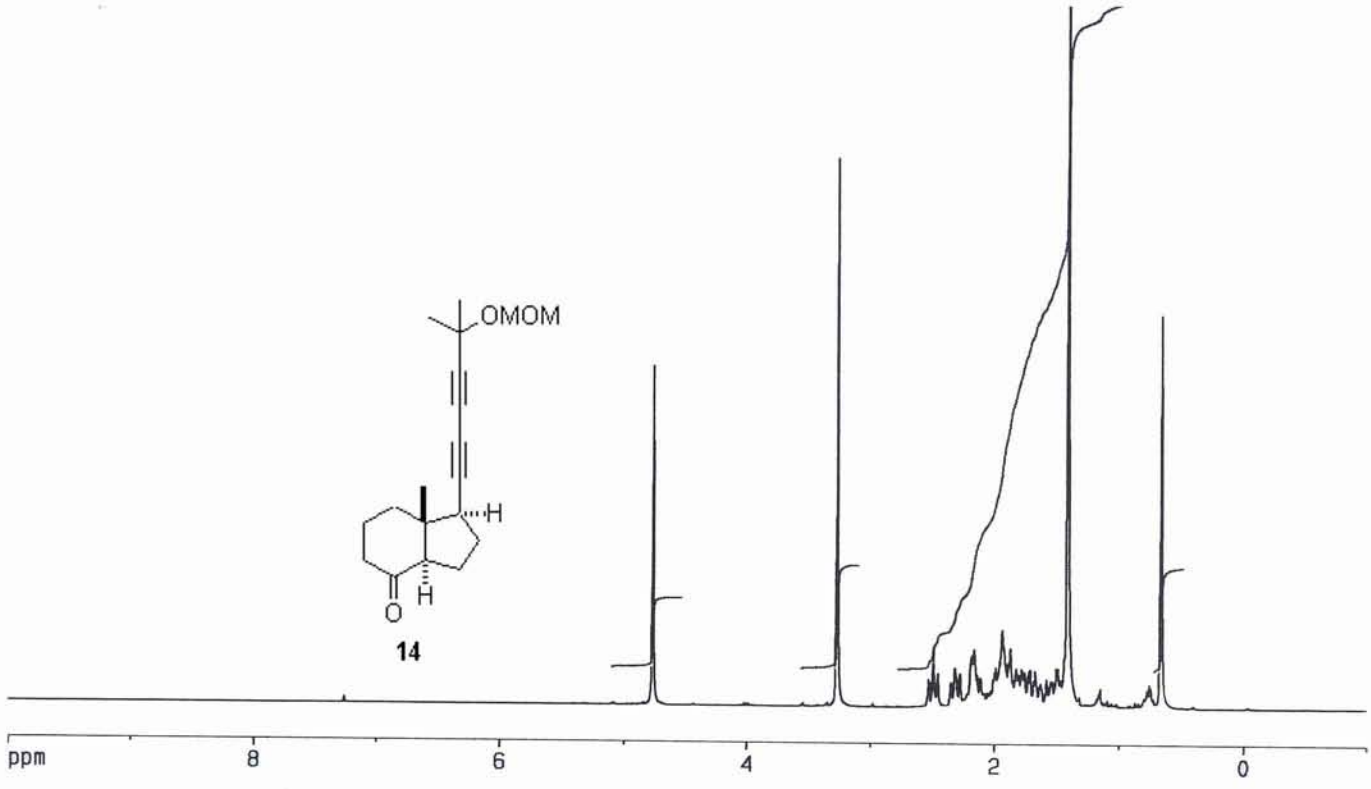

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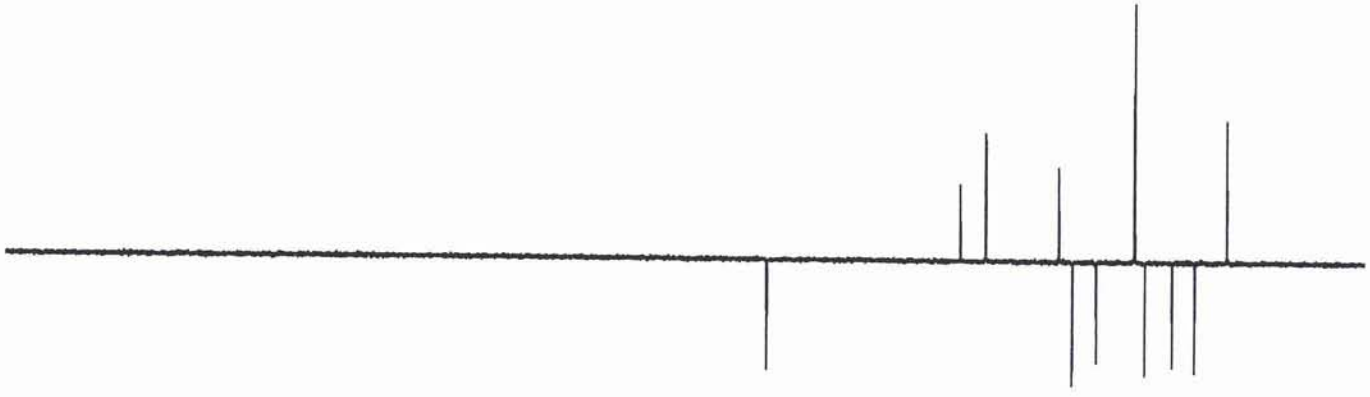

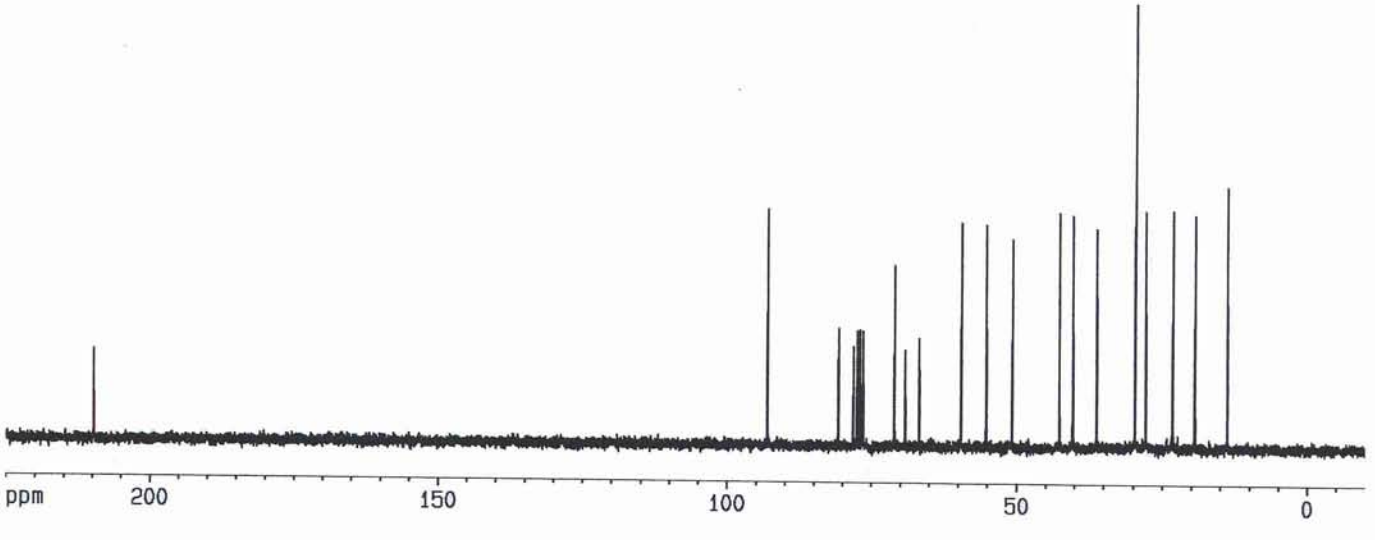

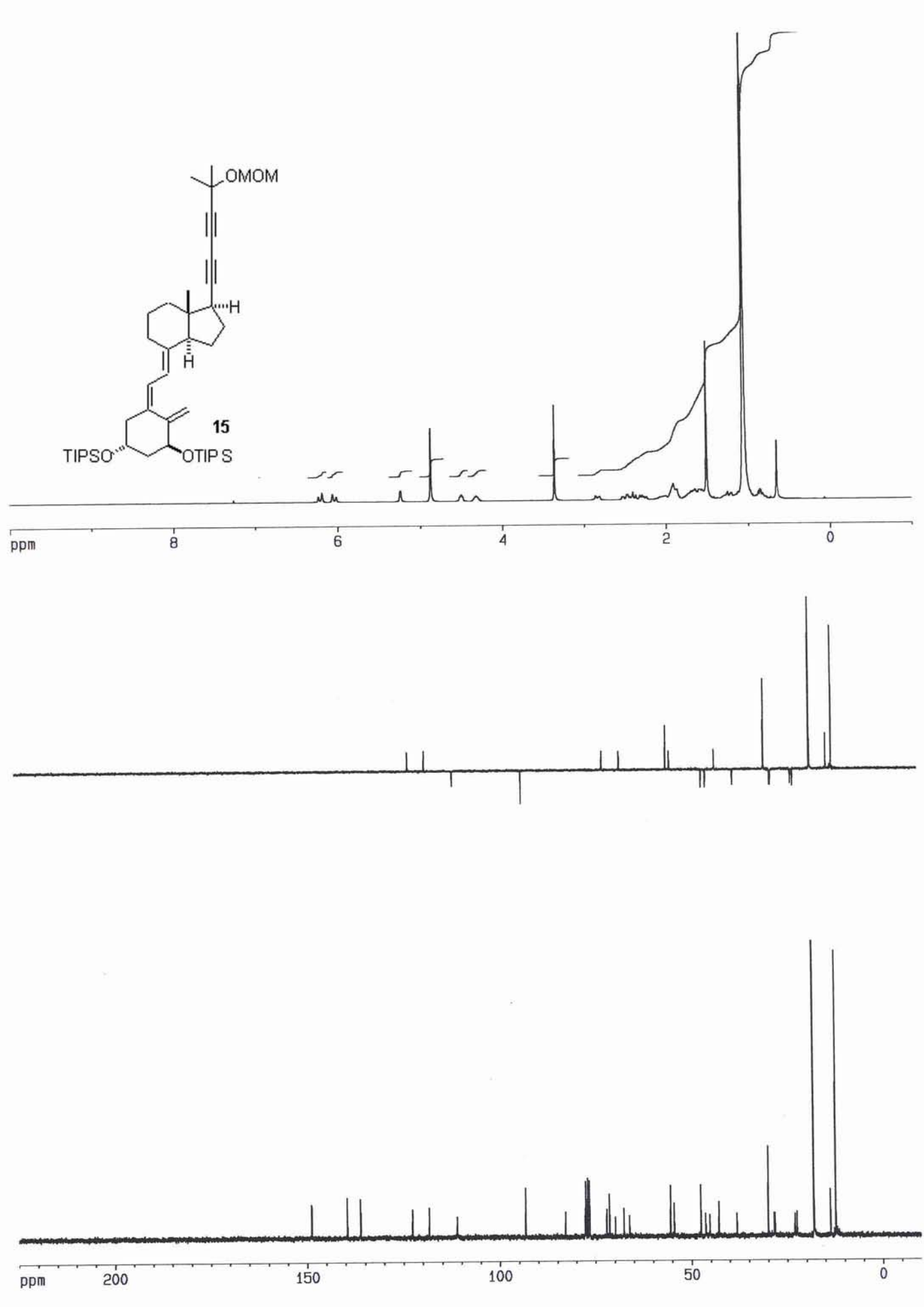
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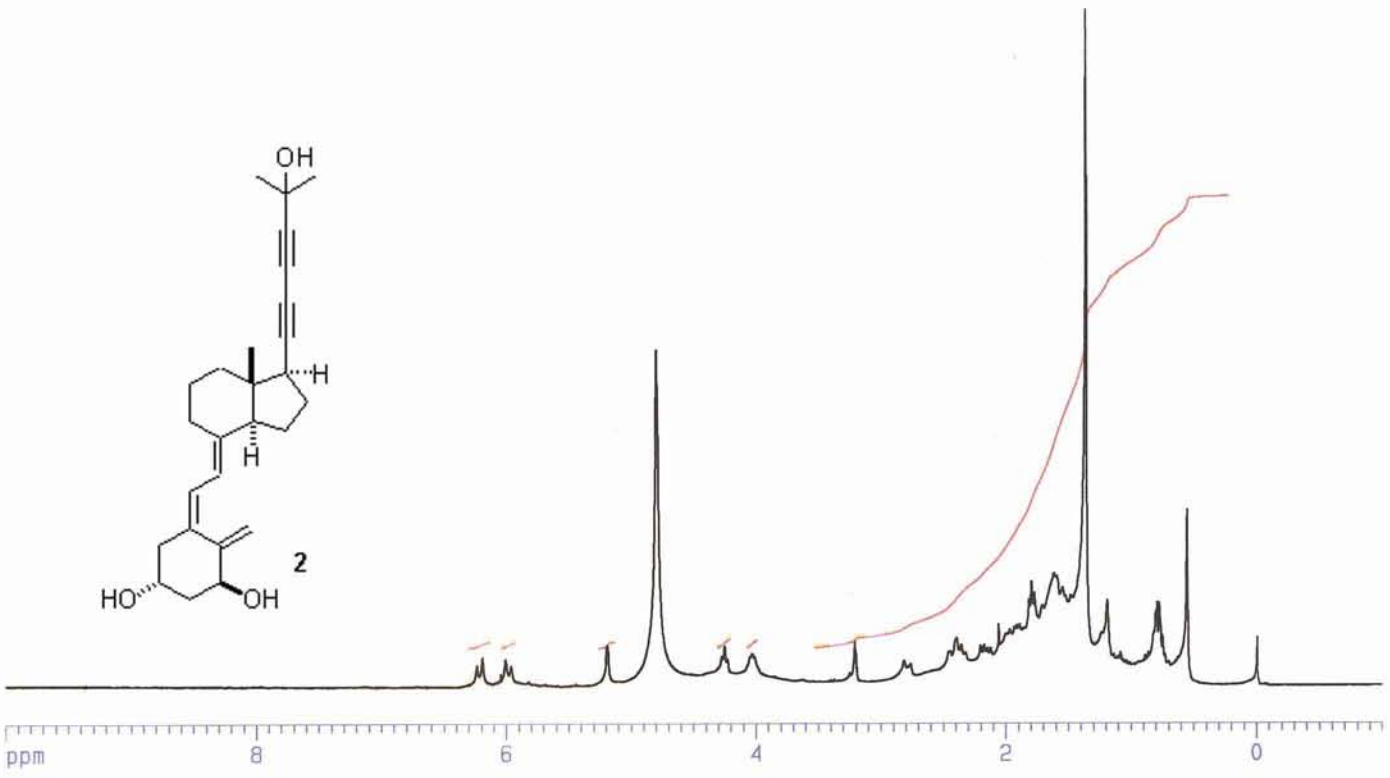
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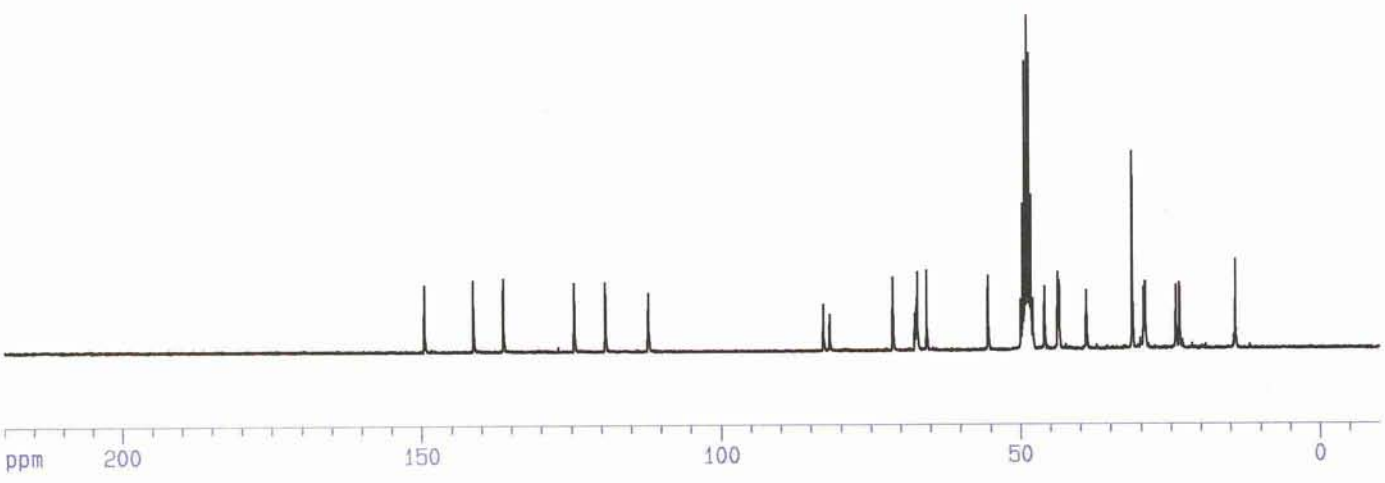
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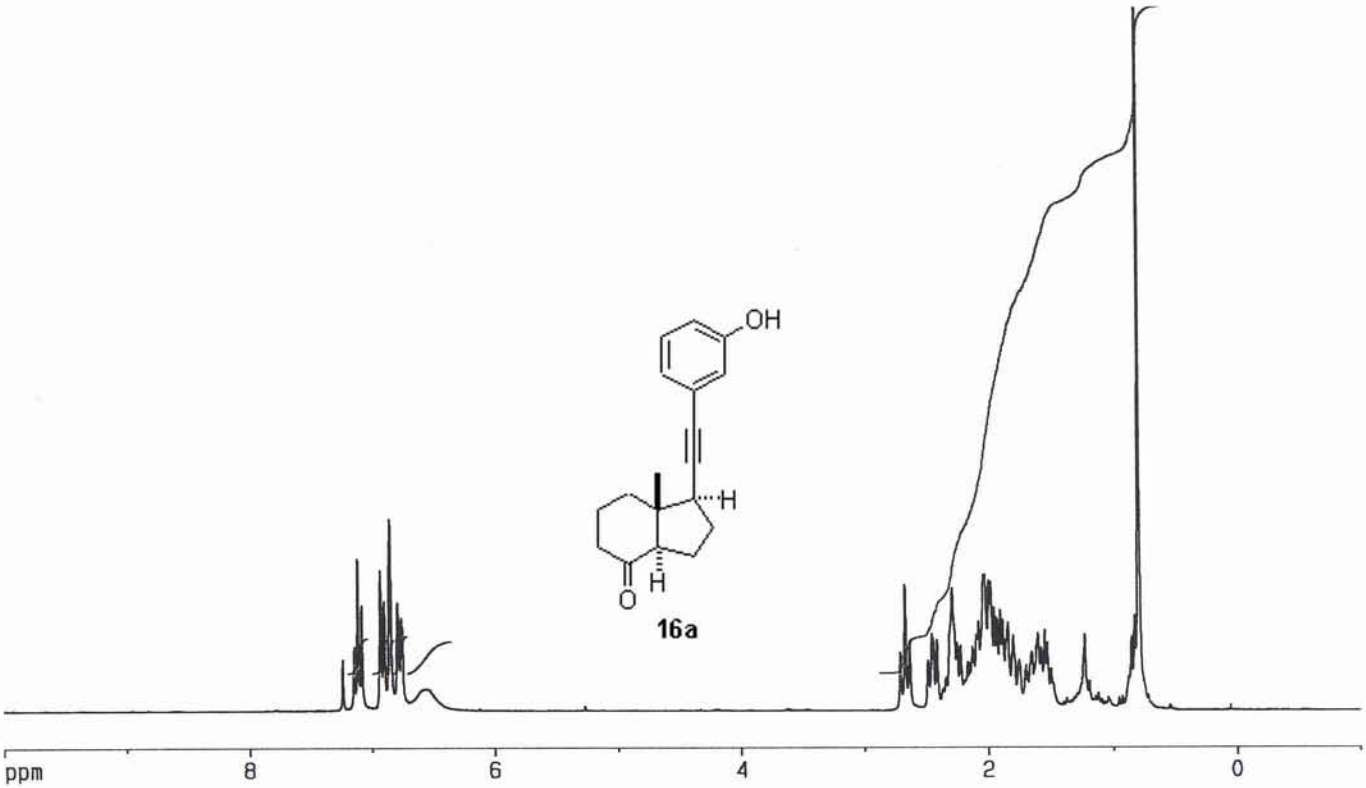
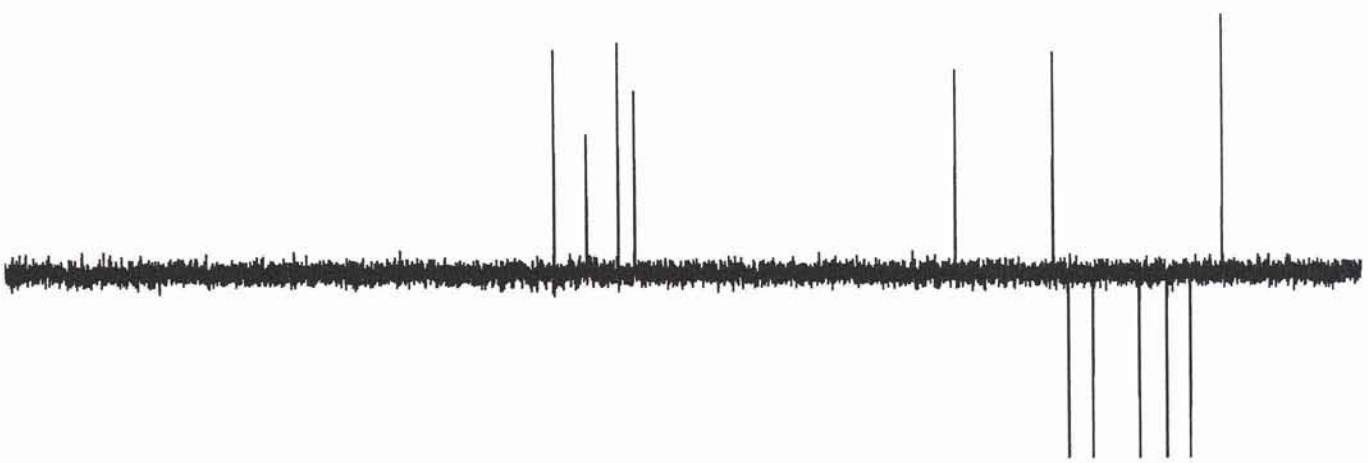
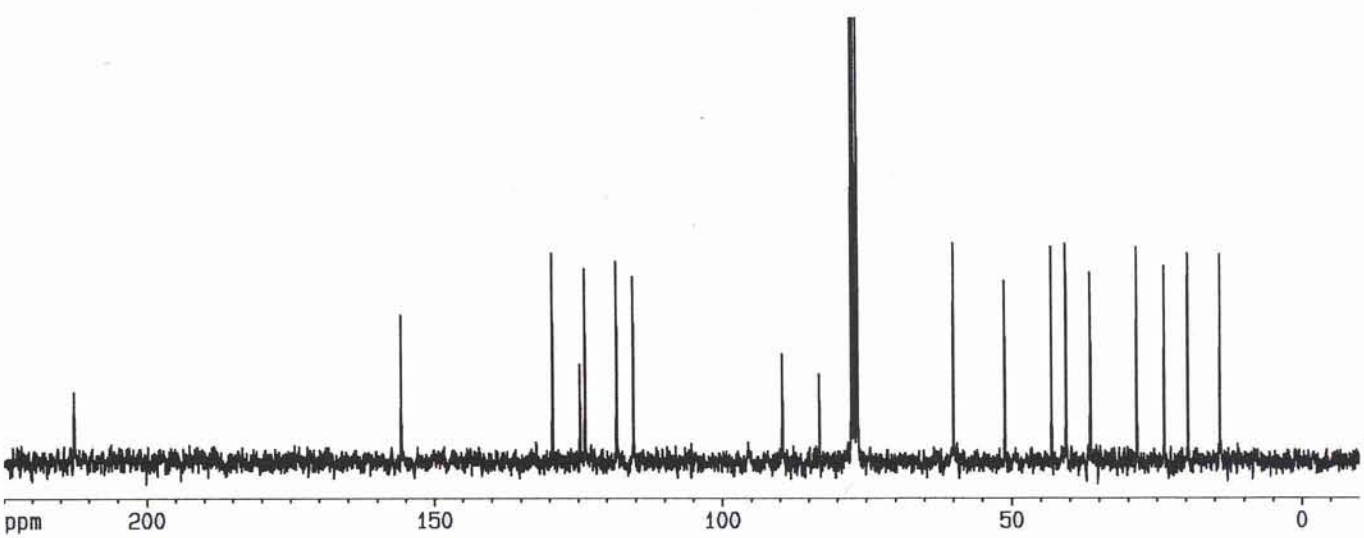
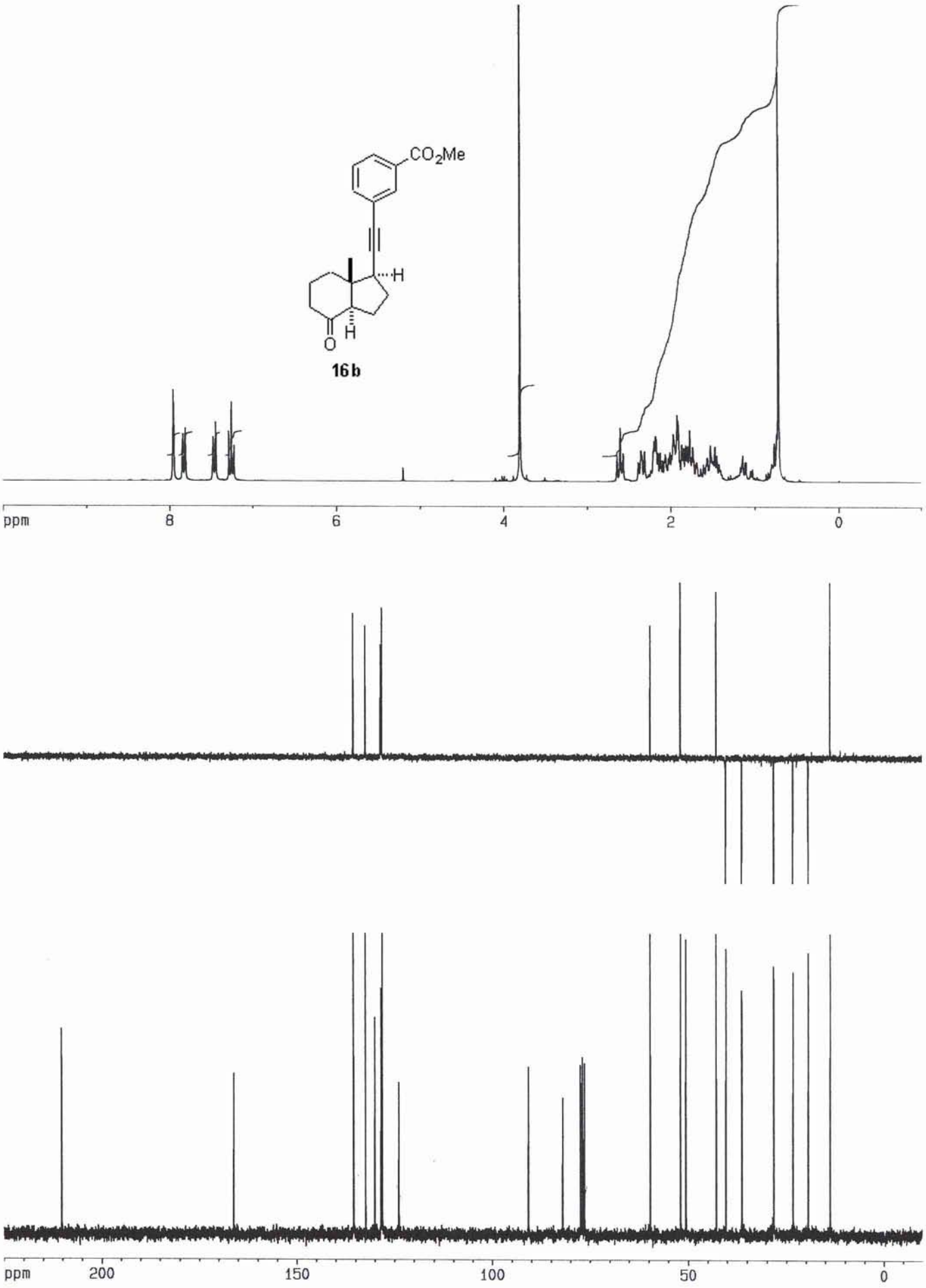


16a



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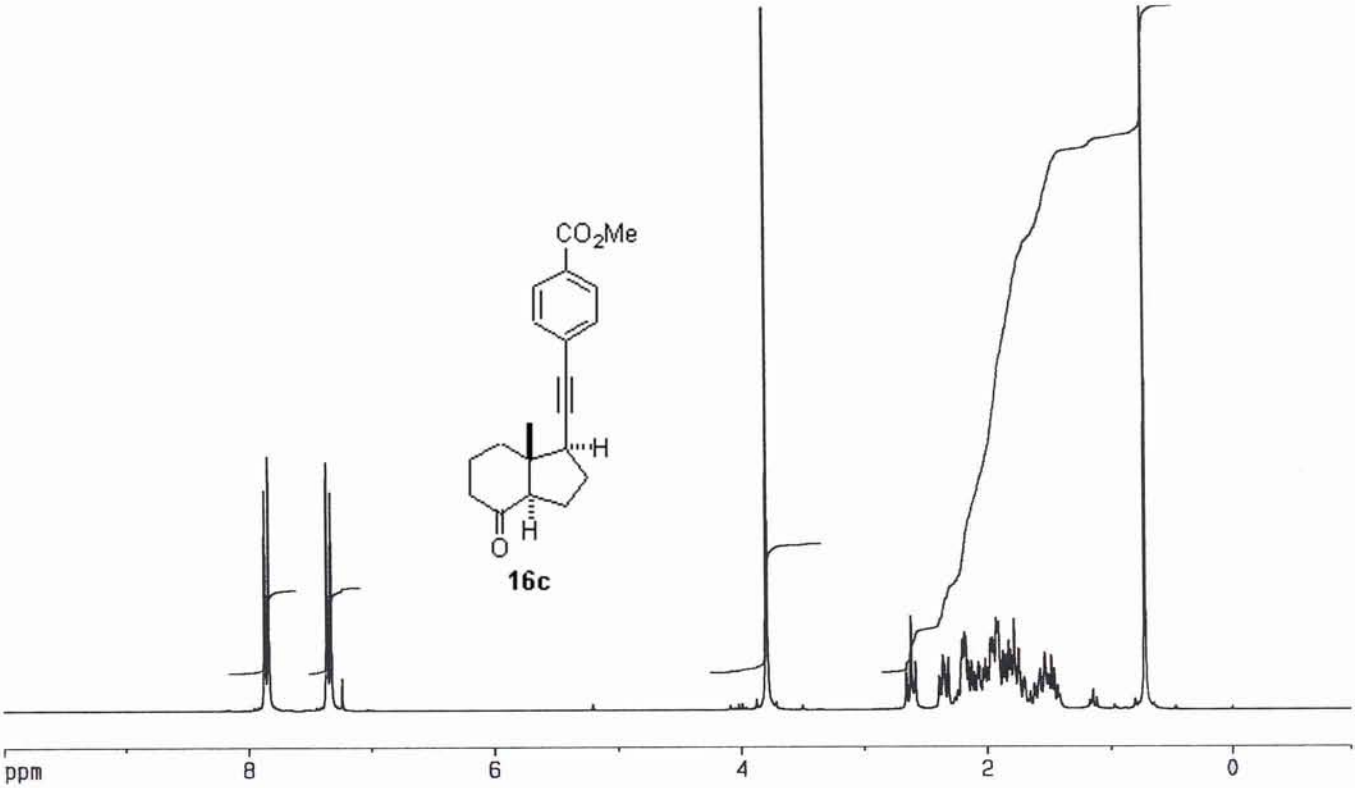
H
O
16b
ppm
8
6
4
2
0
ppm
200
150
100
50
0



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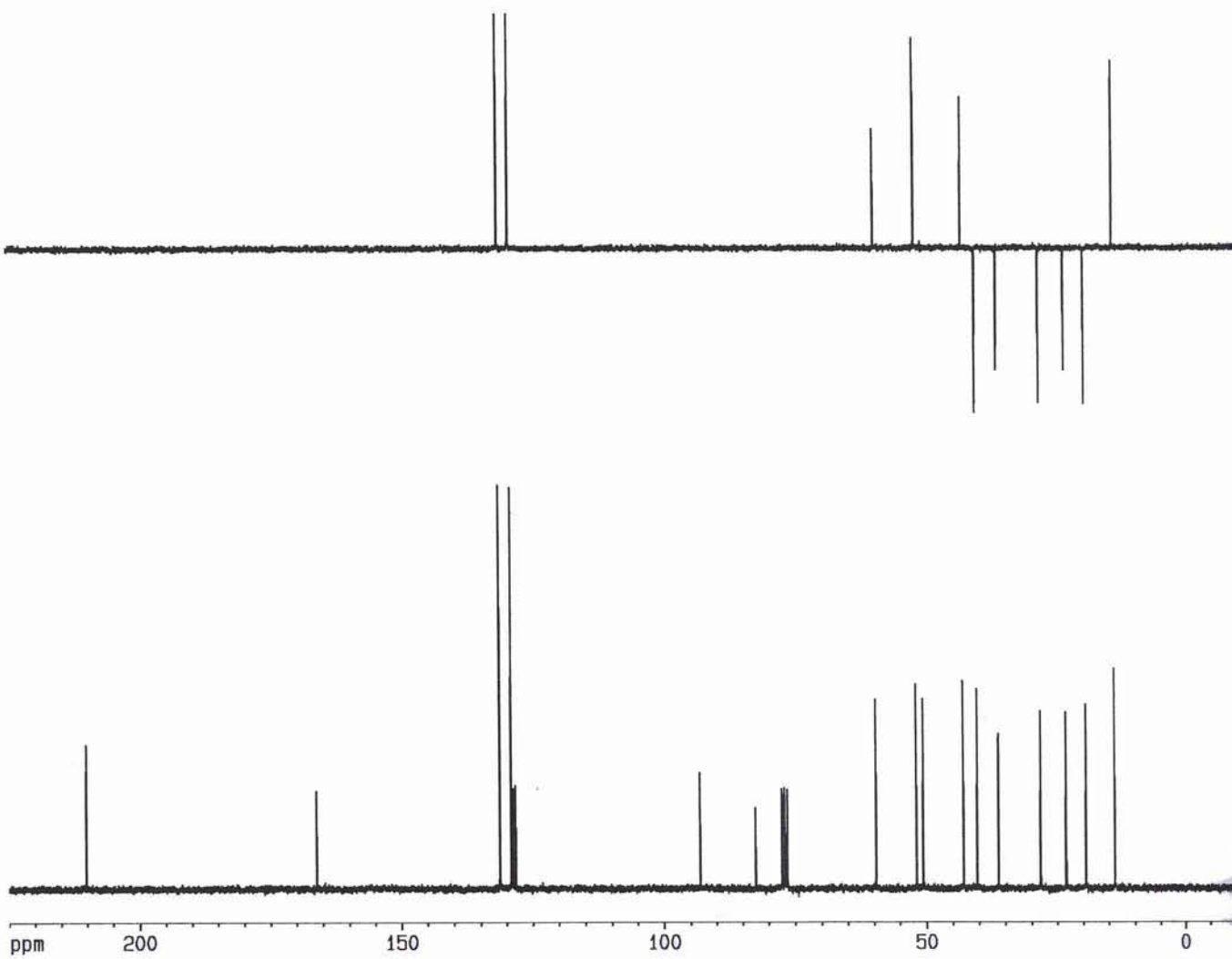
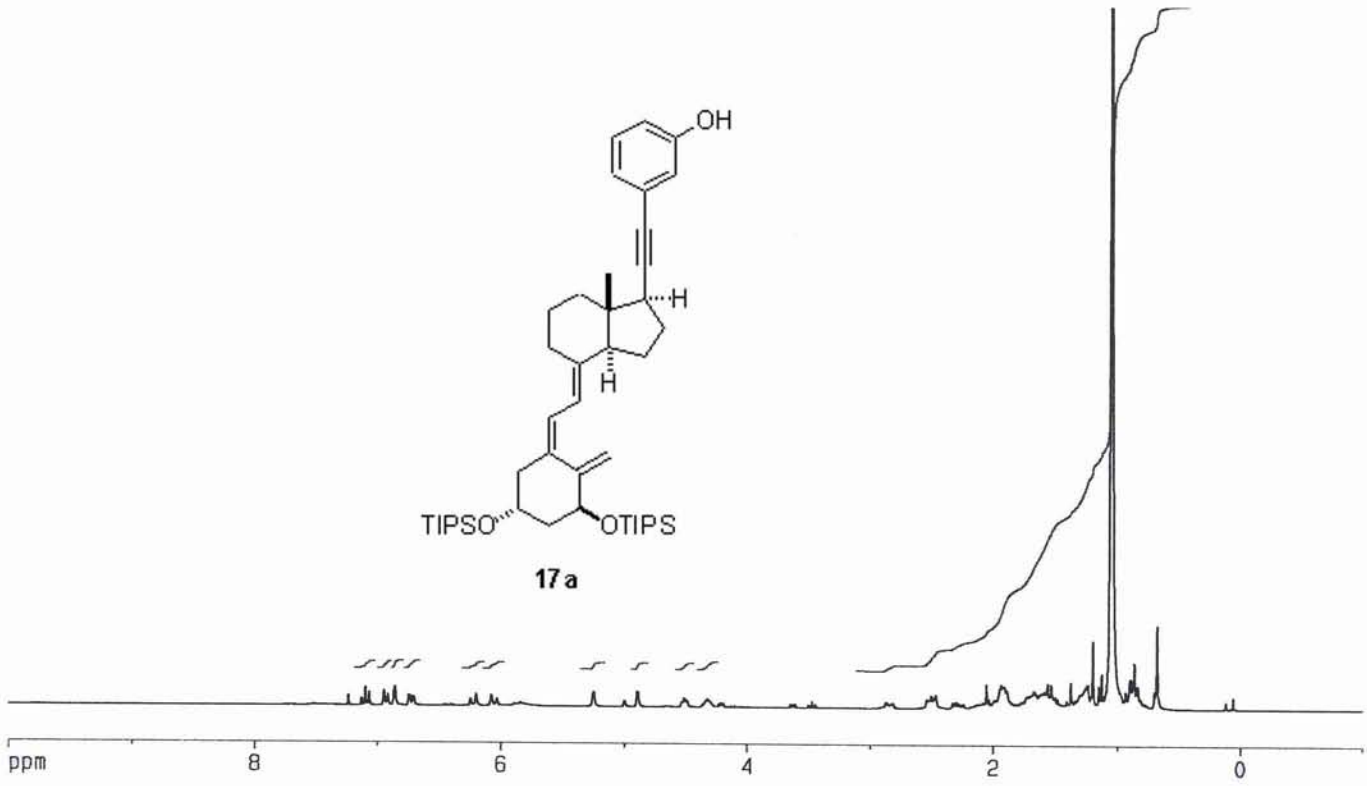
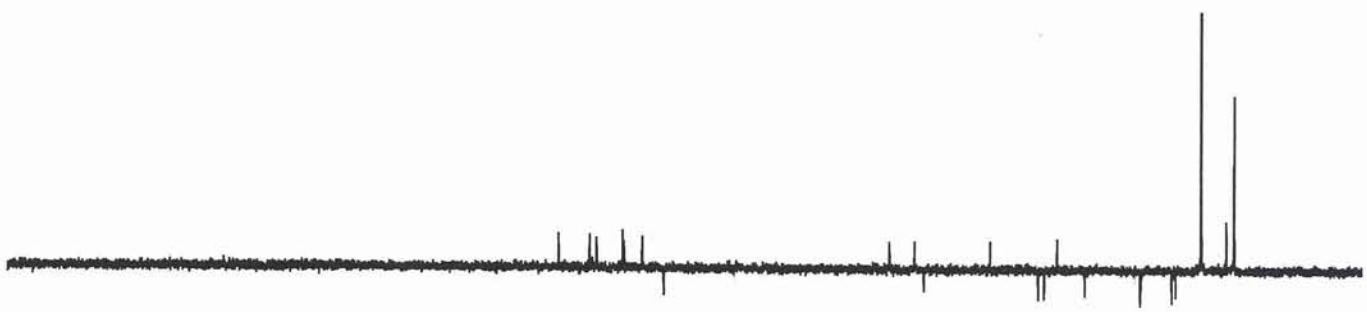
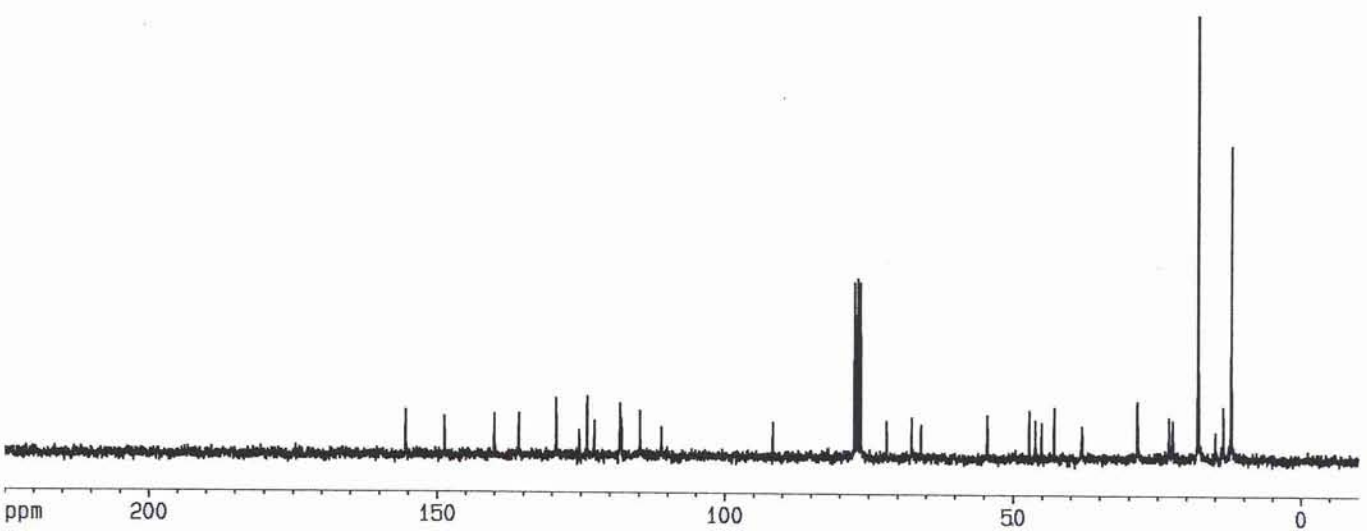
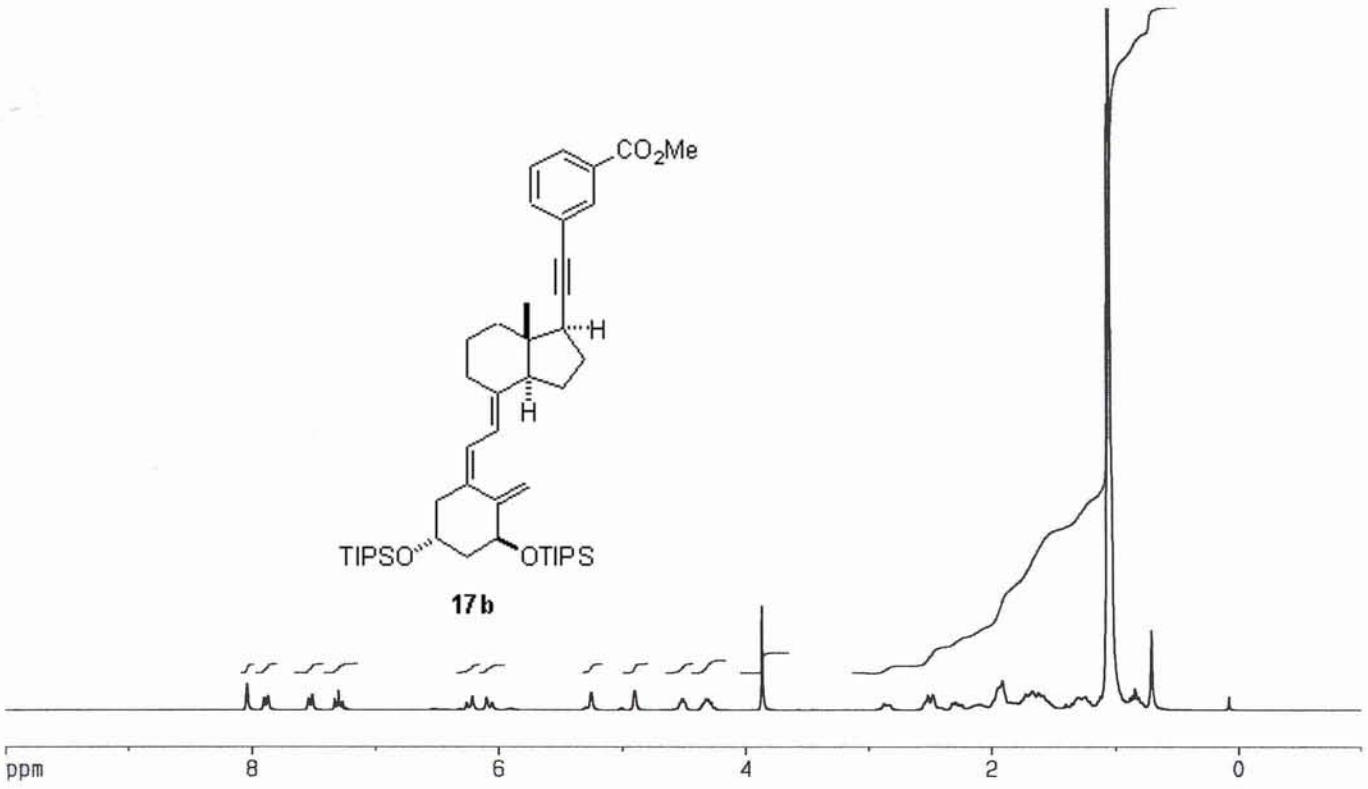




17a



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H
TIPSO
OTIPS
17b
ppm
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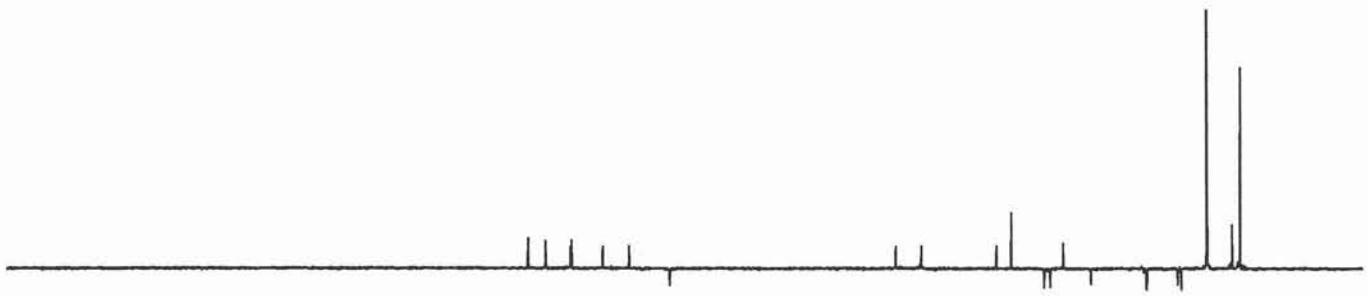
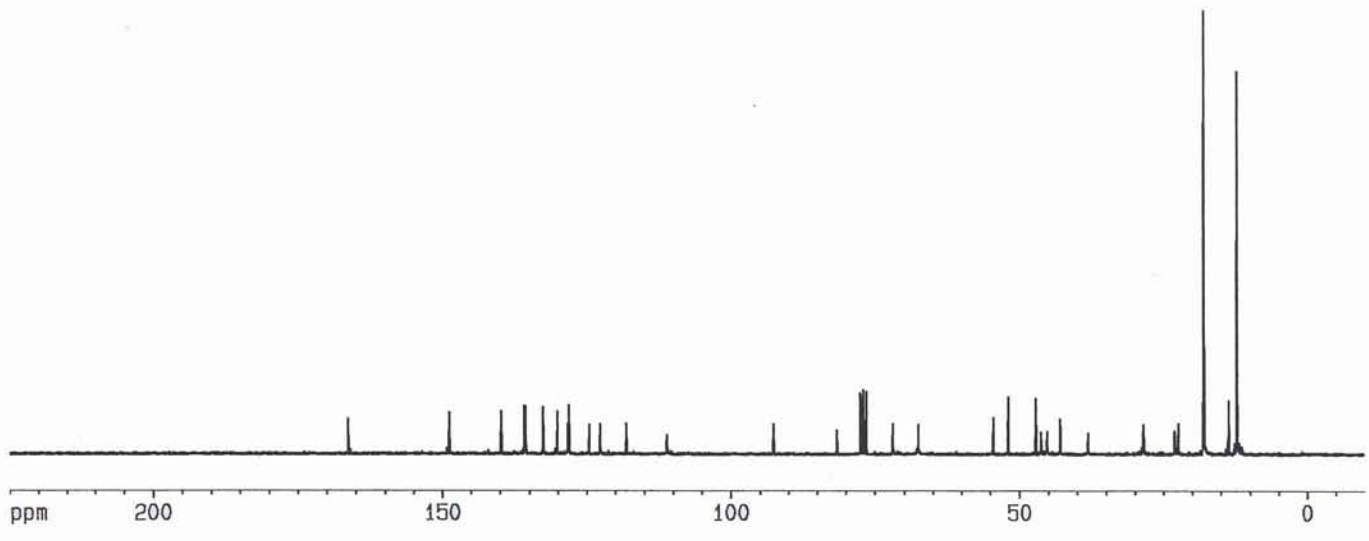
6
4
2
0

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150
100
50
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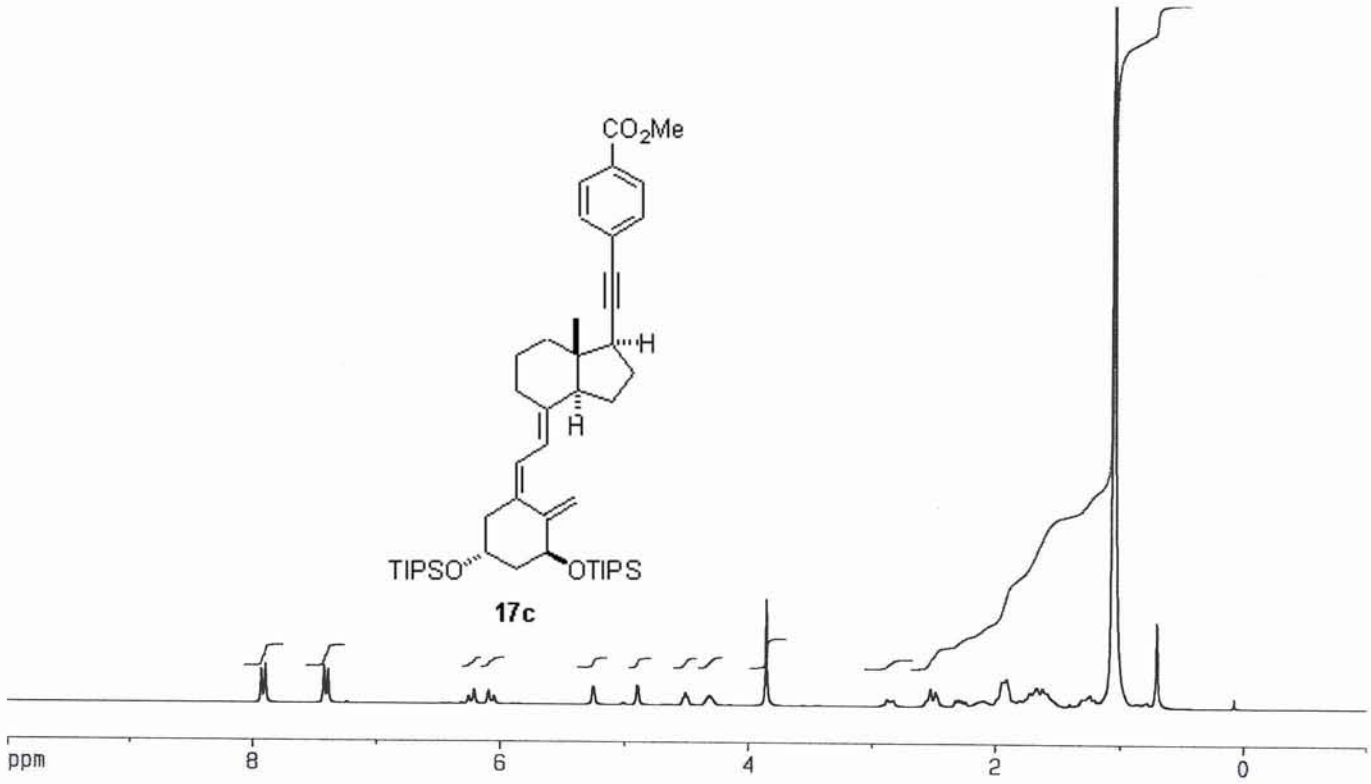
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H
TIPSO
OTIPS
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ppm
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6
4
2
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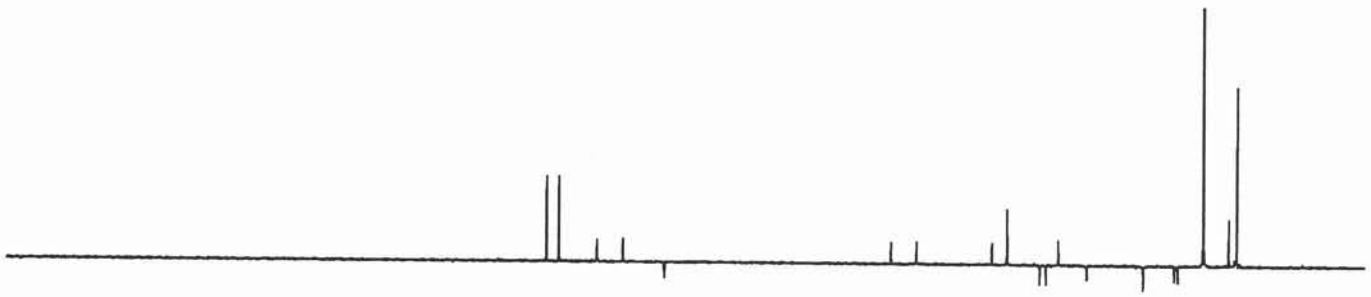

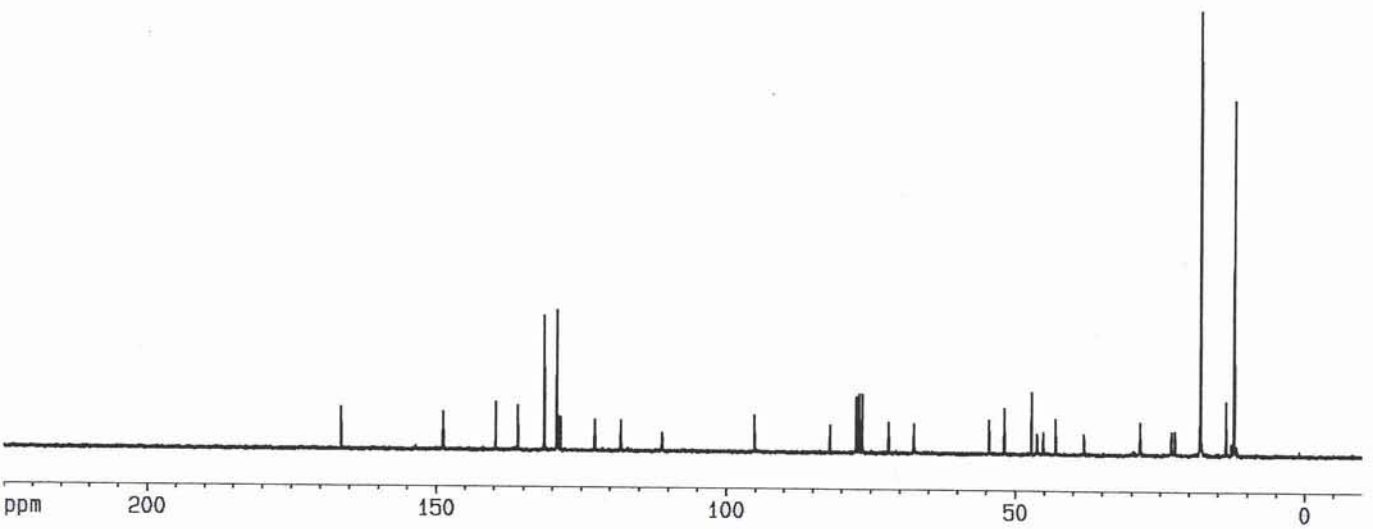
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150
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50
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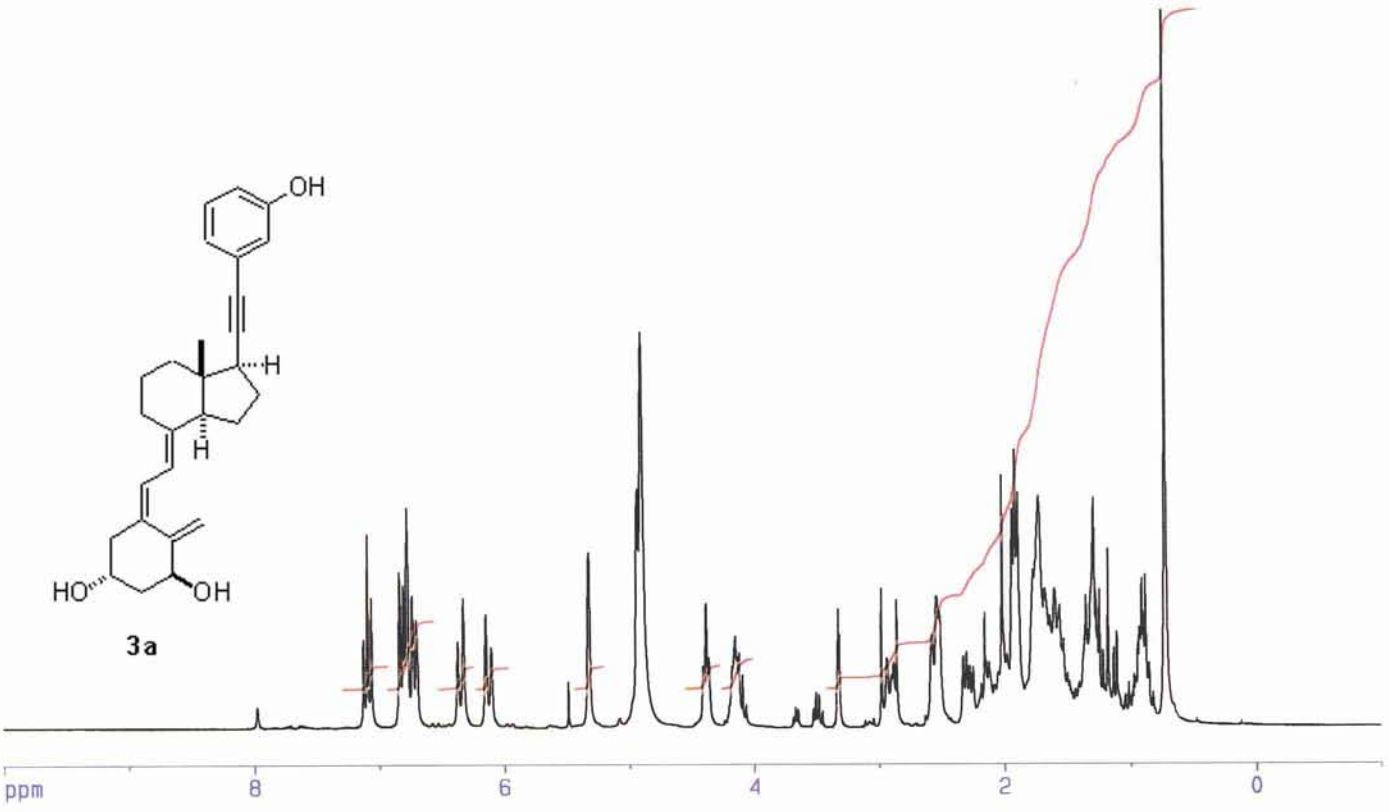
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H
HO
OH
3a
ppm
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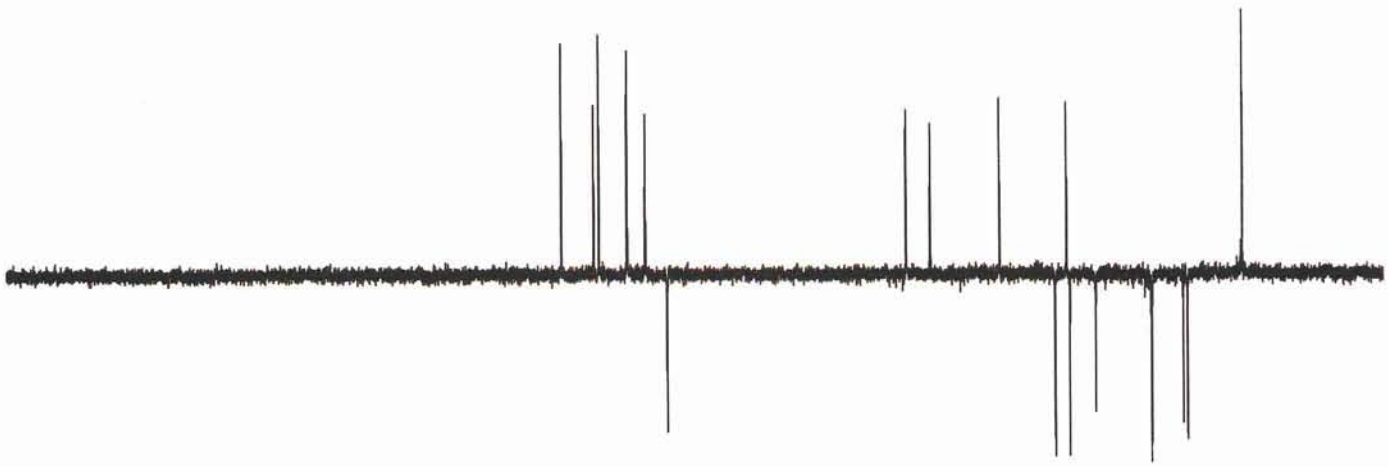
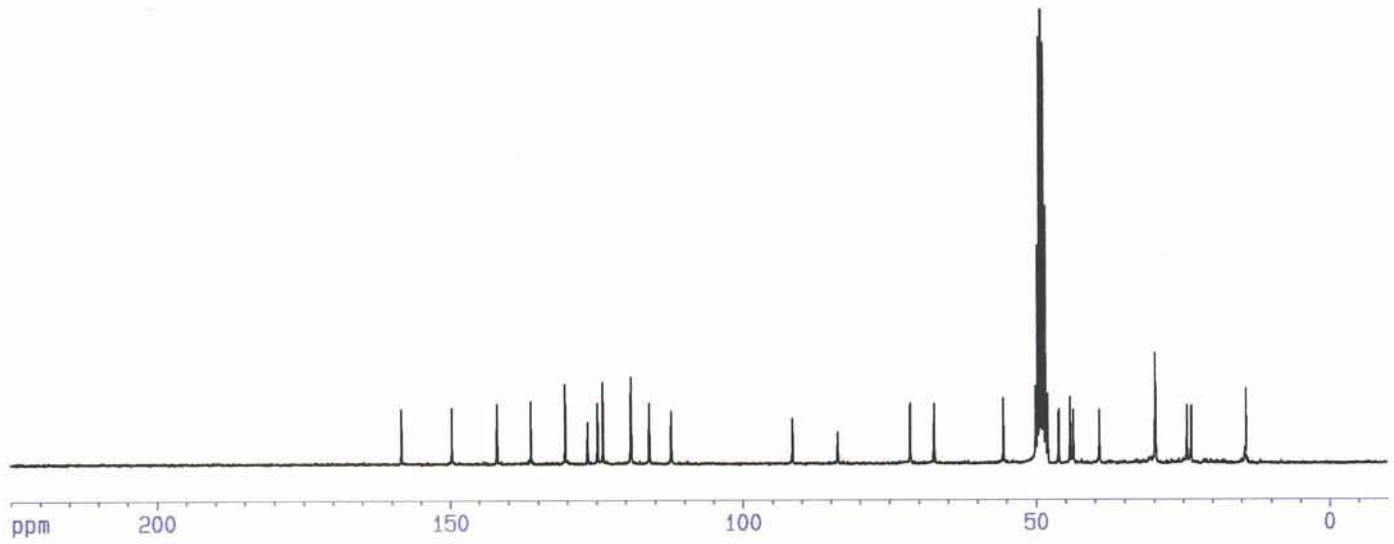
6
4
2
0

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150
100
50
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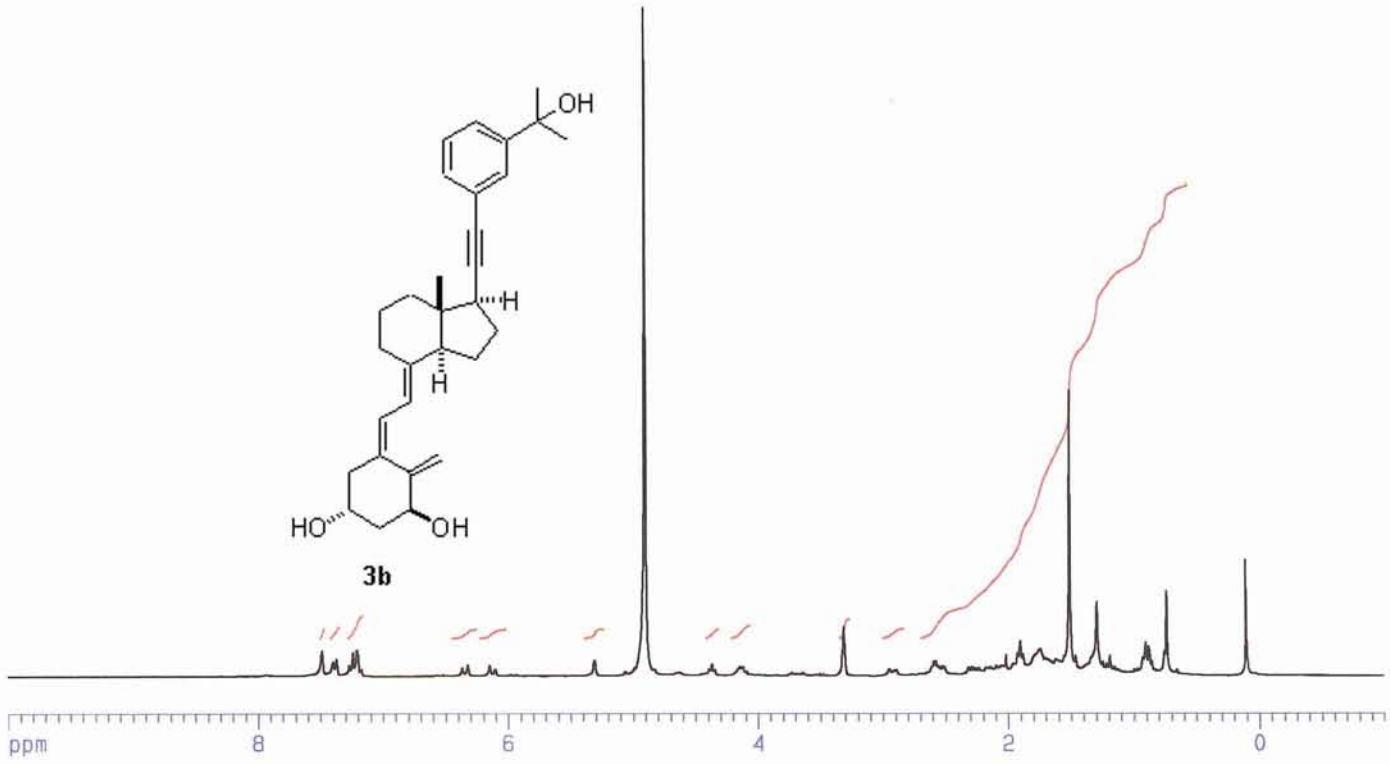
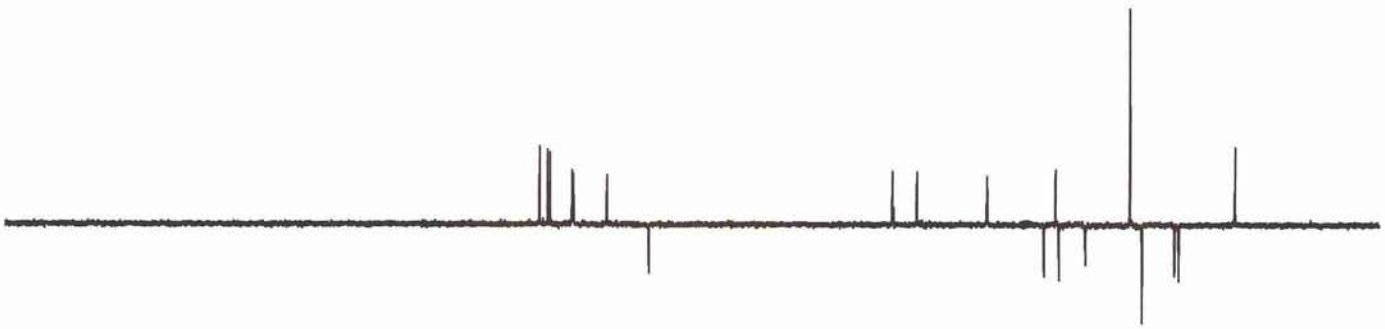
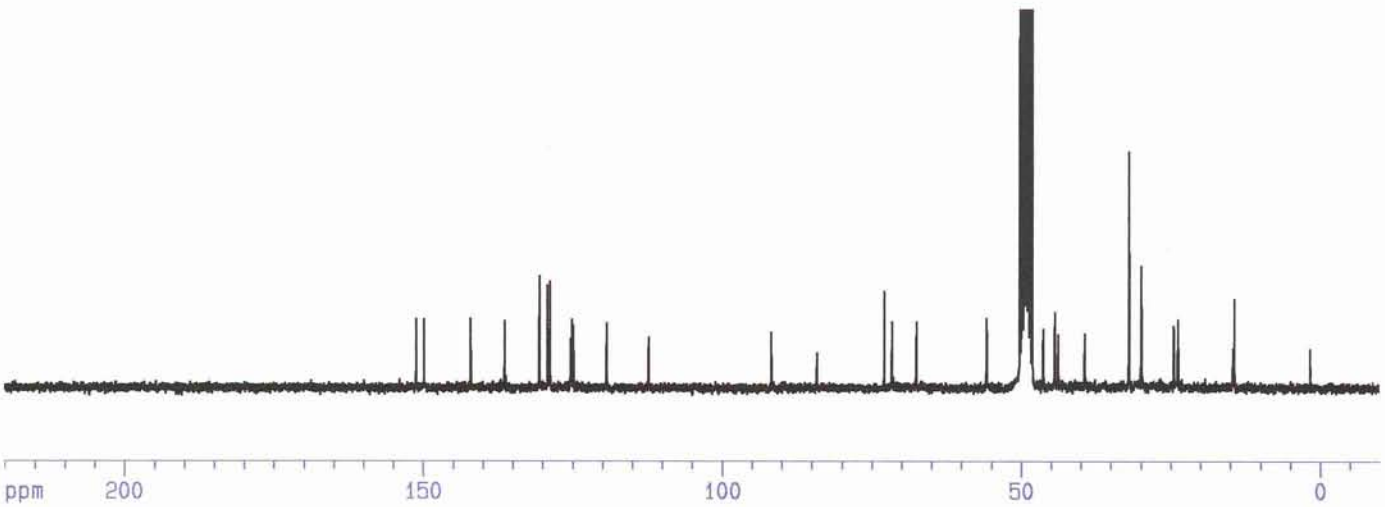
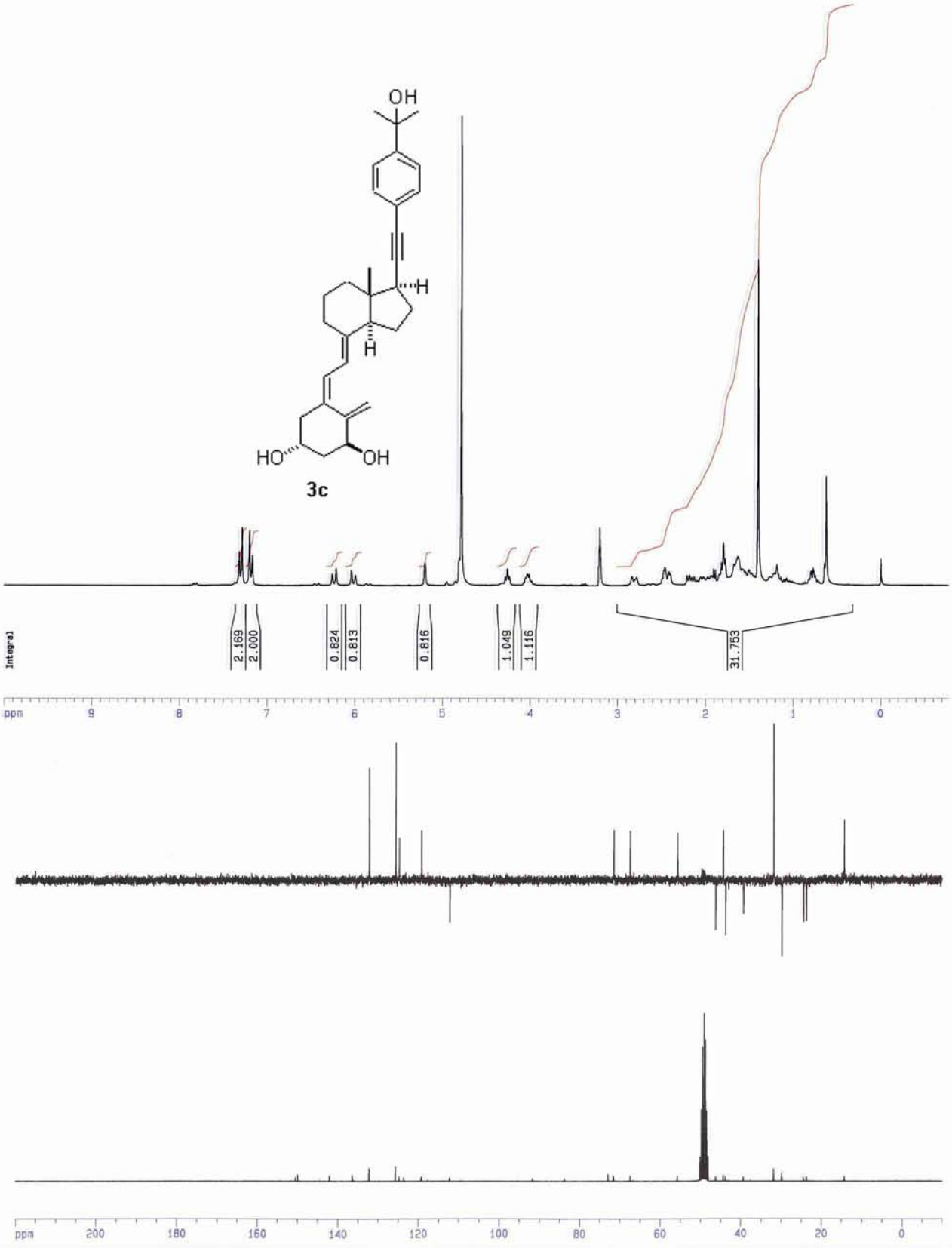


3b






OH
HO
OH
3c
Integral
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0.816
1.049
1.116
31.753
ppm
9
8
7
6
5
4
3
2
1
0
ppm
200
180
160
140
120
100
80
60
40
20
0