JOC The Journal of Organic Chemistry

J. Org. Chem., 1998, 63(20), 6770-6771, DOI:10.1021/jo981181e

General Procedures

Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter at room temperature (21-22 °C). Concentrations (c) are reported in g/100 mL. Infrared spectra (**IR**) were obtained on a Perkin-Elmer Model 781 spectrometer or on a Mattson Polaris FT-IR equipped with a DTGS detector. Signals are reported in wavenumbers (cm^{-1}) with the designations (br), (s), and (w) referring to broad, strong, and weak signals respectively. Melting points (mp) were recorded with a Laboratory Devices Mel-Temp apparatus and are reported here uncorrected. Proton nuclear magnetic resonance (**^{1}H NMR**) spectra were recorded in deuterated solvents ($CDCl_3$, C_6D_6, CD_3OD) on a Bruker AC-300 (300 MHz), a Bruker WP-250 MHz (250 MHz), a Bruker AM-500 (500 MHz), or a Varian Unity-500 (500 MHz) spectrometer as indicated. Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS, δ 0.00). Proton NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sex), septet (sep), multiplet (m), apparent (ap), and broad (br) with the coupling constants reported in hertz (Hz). Signal expansions provided on individual spectra are drawn at a scale of 20 Hz/cm. Carbon nuclear magnetic resonance (**^{13}C NMR**) spectra were recorded in deuterated solvents ($CDCl_3$, C_6D_6, CD_3OD) on a Bruker AC-300 (75.4 MHz) or a Bruker AM-500 (125 MHz) spectrometer as indicated. Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS, δ 0.00). Carbon resonances were assigned using Distortionless Enhancement by Polarization Transfer (DEPT) spectra obtained with a phase angle of 135°: (C) not observed; (CH) positive; (CH_2) negative; (CH_3) positive. Due to magnetically and chemically equivalent carbons, the number of carbon resonances reported may not match the actual number of carbons in the molecule. Coincidental magnetically equivalent carbons were noted when relative signal intensity allowed. Signal expansions provided on individual ^{13}C NMR spectra are drawn at a scale of 200 Hz/cm. High resolution mass spectra (HRMS) using electron impact (EI, 70eV) were recorded on a Kratos MS-80RFA mass spectrometer (DS-55/DS-90 peak matching option). High and low resolution fast atom bombardment (FAB) mass spectra were obtained on a VG Analytical ZAB-2F (Ion Tech FAB gun, 8 kV, Xe carrier gas).

All moisture sensitive reactions were performed in flame-dried glassware under a stream of nitrogen unless otherwise noted. External bath temperatures were used to record all reaction temperatures. Concentrated *in vacuo* refers to the removal of volatile solvents via distillation using a Büchi rotary evaporator at water aspirator pressure, followed by residual solvent removal at high vacuum (approximately 5 μtorr). The acid free glassware utilized in the formation of vinyl ethers was obtained by immersing all items in a 0.5 M solution of HCl in EtOH for one hour, rinsing with de-ionized water, immersing the items in a 0.5 M solution of KOH in EtOH for at least one hour, rinsing again with de-ionized water, and oven drying.

Analytical thin layer chromatography (TLC) was carried out on E. Merck (Darmstadt) TLC plates pre-coated with silica gel 60 F_{254} (250 μ layer thickness). Visualization was accomplished using UV light, iodine vapors, a *p*-anisaldehyde (PAA) charring solution (18 mL *p*-anisaldehyde, 7.5 mL glacial acetic acid, 25 mL 12.0 M H_2SO_4, 675 mL absolute EtOH) and/or phosphomolybdic acid solution (10% PMA in EtOH). Flash column chromatography (FCC) was performed on EM Science silica gel 60 (230-400 mesh). Solvent mixtures for TLC and FCC are reported in either v_1/v_2 ratios or V_1/V_{total} x 100.

Immediately prior to use, tetrahydrofuran (THF), diethyl ether (Et_2O), and benzene (PhH) were distilled from sodium/benzophenone ketyl; toluene ($PhCH_3$) was distilled from sodium metal/anthracene; methanol (MeOH) was distilled from magnesium methoxide; and dichloromethane (CH_2Cl_2), hexanes (petroleum ether), diisopropylamine (*i*-Pr_2NH), and triethylamine (Et_3N) were distilled from calcium hydride. Acetonitrile (CH_3CN), ethylene glycol dimethylether (DME), collidine, pyridine (pyr), 1,1,1,3,3,3-hexamethyldisilazane (HMDS), and methylsulfoxide (DMSO) were distilled at reduced pressure from calcium hydride and stored over 4Å molecular sieves. *t*-Butanol utilized in the TPAP oxidation was distilled from sodium metal and stored over 4Å molecular sieves. Mesyl chloride (MsCl), titanium tetrachloride ($TiCl_4$), triethyl orthoacetate, boron trifluoride·diethyl etherate ($BF_3 \cdot OEt_2$), and propionic acid were distilled prior to use. 4-Dimethylaminopyridine (DMAP) was recrystallized from toluene. Lithium acetylide·ethylenediamine complex was purchased from Aldrich and used without further purification. Tebbe's reagent was prepared and recrystallized from toluene/hexanes in Schlenk glassware in a slight modification of Grubb's procedure.[127] The hydroborating agent, 9-BBN, was purchased as a 0.5 M solution in THF and used immediately. Disiamylborane (Sia_2BH) was prepared immediately prior to use from two equivalents of 2-methyl-2-butene and one equivalent of borane·THF complex in THF at -78 °C followed by stirring for one hour at 0 °C. The Dess-Martin reagent was prepared in bulk via Ireland's modified procedure,[97] and recrystallized from Ac_2O/TsOH as necessary. The trichloroacetimidate of *p*-methoxybenzyl alcohol was prepared according to literature precedent and Kugelrohr distilled immediately prior to use.[123] All other commercially obtained reagents and solvents were used as received without further purification unless otherwise indicated.

Preparation of *(3S)*-1-benzyloxy-hex-5-yn-3-ol

In a dry flask, 1.5 equivalents of lithium acetylide·ethylenediamine complex (6.42 g, 69.7 mmol) were suspended in DMSO (100 mL), and the heterogeneous mixture was chilled to a semi-frozen slurry with an ice bath. A solution of epoxide **2** (8.01 g, 44.9 mmol) was cannula transferred to the reaction flask with 40 ml of DMSO, and the reaction was allowed to warm to room temperature. After 12 hours, the reaction was diluted with 200 mL of Et_2O, cooled to 0 °C, quenched with 20 mL of water, and then acidified to pH 3 with 5% HCl(aq). The layers were separated, and the aqueous phase was extracted with three additional portions of Et_2O. The combined organics were dried over $NaSO_4$, filtered through a short plug of silica gel, and concentrated *in vacuo*. The crude terminal alkyne was used in the subsequent reaction without further purification. Data for *(3S)*-1-benzyloxy-hex-5-yn-3-ol: R_f 0.20 (50% Et_2O in hexanes, PAA); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.25-7.40 (m,5H), 4.52 (s, 2H), 3.94-4.04 (m, 1H), 3.60-3.78 (m, 2H), 3.13 (d, 1H, J = 3.8 Hz), 2.40 (m, 2H), 2.03 (t, 1H, J = 2.8 Hz), 1.77-1.97 (m, 2H).

Preparation of *(3S)*-1-benzyloxy-hex-4-yn-3-ol (3)

Crude terminal alkyne was dissolved in dry DMSO (150 mL) under a nitrogen atmosphere. The reaction mixture was cooled to 15 °C and solid potassium *t*-butoxide (21 g) added. After stirring for 40 minutes, the resulting dark brown solution was diluted with 200 mL of Et_2O and cooled to 0 °C. The reaction was carefully quenched by the dropwise addition of 3M aqueous HCl. The layers were transferred

to a separatory funnel, rinsing with Et_2O, and separated. The aqueous layer was extracted two additional times with 200 mL portions of Et_2O. The combined organics were washed with a 1:1 mixture of saturated $NaHCO_3$(aq) and brine, dried over $NaSO_4$, filtered through a plug of silica gel, and concentrated *in vacuo*. Silica gel chromatography with a 25 - 50% Et_2O/hexanes gradient elution yielded the internal alkyne **3** (7.91 g, 86% two step yield) as a pale yellow oil. Data for **3**: R_f 0.45 (1:1 Et_2O/hexanes, PAA); $[\alpha]^{22}_D$ -20.5 (c = 2.0, PhH); **IR** (thin film) 3402 (br), 3030, 2920, 2856, 2243 (w), 1101, 1076 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.25-7.40 (m, 5H), 4.60 (tdq, 1H, *J* = 6.1, 4.6, 2.2 Hz), 4.53 (s, 2H), 3.83 (ddd, 1H, *J* = 9.5, 7.2, 4.4 Hz), 3.66 (ddd, 1H, *J* = 9.5, 6.3, 4.8 Hz), 3.04 (d, 1H, *J* = 6.1 Hz), 2.04 (ddt, 1H, *J* = 14.3, 7.5, 4.6 Hz), 1.92 (dtd, 1H, *J* = 14.3, 6.2, 4.4 Hz), 1.82 (d, 3H, *J* = 2.2 Hz); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 137.8 (C), 128.4 (CH), 127.5 (CH), 127.5 (CH), 81.0 (C), 79.7 (C), 73.2 (CH_2), 67.7 (CH_2), 61.5 (CH), 37.0 (CH_2), 3.5 (CH_3); **HRMS** (EI) *m/e* (relative intensity, assignment) 204 (6, M^+), 203 (15, M^+-H), 186 (48, M^+-H_2O), 159 (34, M^+-H_2O-C_2H_3), 147 (54, M^+-H_2O-C_3H_3), 107 (67, $PhCH_2O^+$), 91 (100, $PhCH_2^+$); exact mass calcd for $C_{13}H_{16}O_2$ requires 204.1150, found 204.1145.

Preparation of *trans-(3S)*-1-benzyloxy-hex-4-en-3-ol (4)

Dry 95% lithium aluminum hydride (3.12 g, 82.2 mmol) was suspended in 200 mL of THF under an argon atmosphere, and the slurry was cooled to 0 °C. A solution of propargyl alcohol **3** (7.90 g, 38.7 mmol) in 100 mL of THF was added dropwise via cannula. After H_2(g) evolution had ceased, the ice bath was removed and the reaction was heated to reflux. After four hours at reflux, the reaction was cooled to 0 °C and quenched by a slow, dropwise addition of saturated aqueous potassium sodium tartrate while maintaining an argon atmosphere. After gas and heat evolution ceased, the reaction was transferred to a larger vessel and diluted with 800 mL of diethyl ether and 1000 mL of saturated aqueous potassium sodium tartrate. This slurry was vortexed with a magnetic stir plate for 12 hours, until a clean, biphasic solution was obtained. The phases were separated, and the aqueous layer extracted two additional times with 300 mL portions of diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered through a silica gel plug with additional diethyl ether, and concentrated *in vacuo*. Silica gel chromatography with 25% Et_2O/hexanes yielded the isomerically pure **4** (7.57 g, 96%) as a colorless oil. Data for **4**: R_f 0.35 (1:1 Et_2O/hexanes, PAA); $[\alpha]^{22}_D$ 1.15 (c = 6.0, PhH); **IR** (thin film) 3413, 3028, 2916, 2858, 1452, 1099 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.25-7.40 (m, 5H), 5.68 (dqd, 1H, *J* = 15.3, 6.4, 1.1 Hz), 5.49 (ddq, 1H, *J* = 15.3, 6.4, 1.3 Hz), 4.51 (s, 2H), 4.23-4.31 (m, 1H), 3.69 (ddd, 1H, *J* = 9.4, 5.8, 5.1 Hz), 3.61 (ddd, 1H, *J* = 9.4, 6.8, 5.5 Hz), 2.66 (d, 1H, *J* = 3.1 Hz), 1.75-1.90 (m, 2H), 1.69 (ddd, 3H, *J* = 6.4, 1.4, 0.9 Hz); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 138.0 (C), 133.6 (CH), 128.4 (CH), 127.7 (CH), 127.7 (CH), 126.4 (CH), 73.3 (CH_2), 71.7 (CH), 68.4 (CH_2), 36.7 (CH_2), 17.6 (CH_3); **HRMS** (EI) *m/e* (relative intensity, assignment) 206 (0.6, M^+), 188 (4, M^+-H_2O), 115 (61, M^+-CH_2Ph), 107 (100, $PhCH_2O^+$); exact mass calcd for $C_{13}H_{18}O_2$ requires 206.1307, found 206.1308.

Preparation of Ethyl *trans-(3S)*-7-benzyloxy-3-methylhept-4-enoate (5)

In a round bottom flask equiped with a reflux condensor, a solution of allylic alcohol **4** (11.1 g, 54.0 mmol) in 210 mL of triethyl orthoacetate with catalytic propionic acid (0.15 mL, 2.0 mmol) was

heated to 145 °C for 26 hours. After cooling to room temperature, the contents were diluted with 400 mL of EtOAc. The solution was cooled with an ice bath, and the excess triethyl orthoacetate quenched by the addition of 50 mL of 5% HCl(aq). After 10 minutes, the contents were transferred to a separatory funnel and the layers were separated. The aqueous phase was extracted with EtOAc, and the combined organics were washed with 1:1 saturated $NaHCO_3$(aq)/brine. The resulting solution was dried over $MgSO_4$, filtered through a small plug of silica gel with additional EtOAc and concentrated *in vacuo*. Silica gel chromatography with a gradient elution of 10-25% Et_2O/hexanes yielded the pure ethyl ester **5** (13.7g, 92%) as a pale yellow oil. Data for **5**: R_f 0.42 (1:3 Et_2O/hexanes, PAA); $[\alpha]^{22}_D$ 11.6 (c = 4.3, PhH); **IR** (thin film) 2850, 2769, 1734, 1172, 1101 cm^{-1}; **^{1}H NMR** (C_6D_6, 300 MHz) δ 7.05-7.35 (m, 5H), 5.29-5.51 (m, 2H), 4.31 (s, 2H), 3.95 (q, 2H *J* = 7.2 Hz), 3.30 (t, 2H, *J* = 7.2 Hz), 2.70 (hept, 1H, *J* = 6.7 Hz), 2.21-2.28 (m, 2H), 2.22 (dd, 1H, *J* = 14.7, 7.2 Hz), 2.10 (dd, 1H, *J* = 14.7, 7.4 Hz), 0.95 (t, 3H, *J* = 7.2 Hz), 0.95 (d, 3H, *J* = 6.8 Hz); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 172.5 (C), 138.5 (C), 136.1 (CH), 128.3 (CH), 128.3 (CH), 127.6 (CH), 127.5 (CH), 125.5 (CH), 72.8 (CH_2), 70.1 (CH_2), 60.1 (CH_2), 41.8 (CH_2), 33.6 (CH), 32.9 (CH_2), 20.2 (CH_3), 14.2 (CH_3); **HRMS** (EI) ***m/e*** (relative intensity, assignment) 276 (0.8, M^+), 258 (1, M^+-H_20), 230 (44, M^+-CH_3CH_2OH), 189 (40, M^+-CH_2CO_2Et), 155 (44, M^+-CH_2OBn), 91 (100, $PhCH_2^+$); exact mass calcd for $C_{17}H_{24}O_3$ requires 276.1725, found 276.1729.

Preparation of Ethyl 1-[*trans-(1S)*-5-benzyloxy-1-methyl-2-penten]-1-[*trans-(3S)*-7-benzyloxy-3-methylhept-4-en-1-one]acetate

Ethyl ester **5** (3.82 g, 13.8 mmol) was dissolved in 10 mL of THF and cooled to 0 °C. In a separate, flamed dried round bottom flask, LHMDS (7.3 mL, 34.6 mmol) and TMEDA (10.4 mL, 79.2 mmol) were combined in 10 mL of dry THF and cooled to 0 °C. *n*-Butyl lithium (2.68 M in hexane, 12.9 mL, 34.6 mmol) was added dropwise over 10 minutes, and the LHMDS solution was stirred for an additional 30 minutes. The freshly generated LHMDS/TMEDA solution was added dropwise to the solution of the ethyl ester over 4.5 hours. The reaction was diluted with 300 mL of Et_2O and quenched by the addition of 400 mL of 5% HCl(aq) immediately following the LHMDS addition. Shorter addition times led to lower yields of the β-ketoester with greater amounts of recovered starting material. Longer reaction times led to greater side product formation. The layers were separated, and the aqueous phase was extracted with two additional 200 mL portions of Et_2O. All three organic layers were washed with 1:1 saturated $NaHCO_3$(aq)/brine, and combined. The combined organics were dried over $MgSO_4$, filtered through a small plug of silica gel with additional diethyl ether, and concentrated *in vacuo*. Silica gel chromatography with 25% Et_2O/hexanes yielded the ethyl β-ketoester (2.95 g, 84%) as a mixture of diastereomers in the form of a colorless oil with a small amount of recovered starting material (0.60 g, 8%). Data for the β-ketoester: R_f 0.42 (1:3 Et_2O/hexanes, PAA); $[\alpha]^{22}_D$ 19.9 (c = 4.39, PhH); **IR** (thin film) 3026, 2956, 1741, 1714, 1454, 1101 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.24-7.40 (m, 20H), 5.28-58 (m, 8H), 4.50 (s, 4H), 4.49 (s, 2H), 4.48 (s, 2H), 4.15 (q, 2H, *J* = 7.2 Hz), 4.08 (q, 2H, *J* = 7.0 Hz), 3.40-3.50 (m, 8H), 3.33 (d, 1H, *J* = 6.8 Hz), 3.28 (d, 1H, *J* = 6.8 Hz), 2.85-3.05 (m, 2H), 2.60-2.77 (m, 2H), 2.22-2.55 (m, 12H), 1.24 (t, 3H, *J* = 7.2 Hz), 1.19 (t, 3H, *J* = 7.0 Hz), 1.02 (d, 3H, *J* = 6.6 Hz), 0.96

(d, 3H, J = 6.6 Hz), 0.95 (d, 3H, J = 6.6 Hz), 0.91 (d, 3H, J = 6.6 Hz); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 203.3 (C), 203.2 (C), 168.4 (C), 168.3 (C), 138.5 (C), 138.4 (C), 136.4 (CH), 136.2 (CH), 133.5 (CH), 133.4 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 125.4 (CH), 125.0 (CH), 72.8 (CH_2), 70.0 (CH_2), 69.8 (CH_2), 66.0 (CH), 65.6 (CH), 61.1 (CH_2), 61.0 (CH_2), 49.9 (CH_2), 49.7 (CH_2), 37.0 (CH), 36.8 (CH), 32.9 (CH_2), 31.9 (CH), 31.5 (CH), 20.0 (CH_3), 19.9 (CH_3), 18.6 (CH_3), 14.1 (CH_3); **MS** (FAB) *m/e* (relative intensity, assignment) 507 (50, $M+H^+$), 461 (26, M^+-OCH_3), 189 (60, $BnO(CH_2)_2(CH)_3CH_3^+$); mass calcd for $C_{32}H_{42}O_5+H^+$ is 507.3; found 507.3.

Preparation of *trans-trans*-(5S,9S)-1,13-Bisbenzyloxy-5,9-dimethyltridecane-4,10-dien-7-one (6)

The ethyl β-ketoester (12.4 g, 24.5 mmol) was dissolved in 100 mL of DMSO containing water (1.4 mL, 77.8 mmol) and lithium chloride (3.9 g, 92.0 mmol). The reaction pot was fitted with a reflux condenser, thoroughly flushed with nitrogen, and heated to 190 °C. After 40 minutes the reaction mixture was cooled to room temperature and transferred to a separatory funnel containing 50 mL of half saturated brine with 100 mL of EtOAc. The layers were separated, and the aqueous phase was extracted twice with 100 mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$ and filtered through a silica gel plug with Et_2O. The C_2-symmetric ketone **6** (10.2 g, 96%) was isolated after concentration *in vacuo* and silica gel chromatography with 3% EtOAc/PhH. Data for **6**: R_f 0.31 (1:3 Et_2O/hexanes, PAA); $[\alpha]^{22}_D$ 38.5 (c = 1.02, PhH); **IR** (thin film) 3028, 2958, 2925, 2848, 1709, 1097 cm^{-1}; **^{1}H NMR** (C_6D_6, 300 MHz) δ 7.05-7.35 (m, 10H), 5.31-5.49 (m, 4H), 4.35 (s, 4H), 3.33 (t, 4H J = 6.6 Hz), 2.75 (hept, 2H, J = 6.8 Hz), 2.28 (ap q, 4H), 2.06 (A of ABX, 2H, J_{AB} = 16.0 Hz, J_{AX} = 6.5 Hz), 2.03 (B of ABX, 2H, J_{AB} = 16.0 Hz, J_{BX} = 7.3 Hz), 0.94 (d, 6H, J = 6.8 Hz); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 209.3, (C), 138.5 (C) 128.3 (CH), 127.6 (CH), 127.5 (CH), 125.1 (CH), 72.8 (CH_2), 70.0 (CH_2), 50.5 (CH_2), 33.0 (CH_2), 32.4 (CH), 20.3 (CH_3); **MS** (FAB) *m/e* (relative intensity, assignment) 435 (48, $M+H^+$), 343 (31, M^+-C_7H_7), 221 (56, $M+H^+$-2x(C_7H_7O)), 147 (100, $BnOC_3H_4^+$); mass calcd for $C_{29}H_{38}O_3+H^+$ is 435.3; found 435.2.

Preparation of (2S,3S,4S,8S,9S,10S)-2,8-Di(2-benzyloxyethyl)-3,9-dihydroxy-4,10-dimethyl-1,7-dioxyspiro-[5,5]-undecane (7), and isomer 8

AD-mix-α (74 g, 2.3 eq.) was dissolved in 400 mL of water and 360 mL of *t*-butyl alcohol at room temperature. The homogeneous solution was cooled to 0 °C with an ice bath, initiating the precipitation of iron salts and the development of distinct organic and aqueous phases. The C_2-symmetric ketone **6** (10.1 g, 23.2 mmol) in 40 mL of *t*-butyl alcohol was added dropwise over 10 minutes. The reaction was vortexed with a magnetic stir bar at 0 °C for 24 hours. The reaction was diluted with 50 mL of water and excess oxidizing agent was then quenched by the addition of solid $Na_2S_2O_3$ (80 g, 500 mmol). After 10 minutes, the reaction was warmed to room temperature and stirred for an additional 30 minutes. The reaction contents were transferred to a separatory funnel with 300 mL of EtOAc and 100 mL of water. The phases were separated and the aqueous portion was further extracted with EtOAc (4x250 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude tetraol (R_f 0.20 (1:19

MeOH/CH_2Cl_2, PAA)) was used in the subsequent reaction without further purification. Reaction rates were appreciably slower at higher concentrations.

The crude tetraol was dissolved in 300 mL of benzene/methanol (2:1) in a round bottom flask equipped with a Dean/Stark trap. Catalytic CSA (158 mg, 0.68 mmol) was added to the reaction pot, and the system was heated to reflux. The reaction volume was then reduced by two thirds via the Dean/Stark trap. After cooling to room temperature, the resulting solution was transferred to a separatory funnel with 200 mL of EtOAc and washed with 150 mL of saturated $NaHCO_3$(aq)/brine (1:1). The aqueous layer was extracted twice with 150 mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Silica gel chromatography with gradient elution (10-30% EtOAc/CH_2Cl_2) yielded a 1.1:1 mixture (9.84 g, 88%) of the desired 1,7-dioxyspiro-[5,5]-undecane **7** and the undesired 1,6-dioxyspiro-[4,5]-decane **8** ketals respectively. Trace amounts of the 1,5-dioxyspiro-[4,4]-nonane were also observed. Data for 1,7-dioxyspiro-[5,5]-undecane **7**: R_f 0.65 (1:1 EtOAc/CH_2Cl_2, PAA); $[\alpha]^{22}_D$ -59.7 (c = 1.52, PhH); mp = 108-109 °C; **IR** (thin film) 3427 (br), 3032, 2954, 1454, 1205, 1103, 987, 743, 698 cm^{-1}; **^{1}H NMR** (C_6D_6, 300 MHz) δ 7.05-7.30 (m, 10H), 4.25 (s, 4H), 3.81 (ddd, 2H, *J* = 8.8, 4.9, 0.9 Hz), 3.49 (ap dd, 4H, *J* = 6.4, 5.5 Hz), 3.17 (br d, 2H, *J* = 5.6 Hz), 1.96-2.15 (m, 4H), 1.79-1.92 (m, 2H), 1.75 (br d, 2H *J* = 6.5 Hz), 1.28-1.42 (ap d, 4H), 0.99 (D, 6H, J = 5.0 Hz); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 138.1 (C), 128.2 (CH), 127.6 (CH), 127.5 (CH), 96.5 (C), 72.9 (CH_2), 70.3 (CH), 69.4 (CH), 66.7 (CH_2), 36.9 (CH_2), 31.6 (CH_2), 30.0 (CH), 17.4 (CH_3); **MS** (FAB) *m/e* (relative intensity, assignment) 485 (100, M+H$^+$); mass calcd for $C_{29}H_{40}O_6$+H$^+$ is 485.3, found 485.3. Data for 1,6-dioxyspiro-[4,5]-decane **8**: R_f 0.68 (1:1 EtOAc/CH_2Cl_2, PAA); **IR** (thin film) 3450 (br), 3030, 2954, 2925, 1454, 1097, 981 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.20-7.35 (m, 10H), 4.47 (AB_q, 2H, J_{AB} = 11.9 Hz, $\Delta\nu_{AB}$ = 19.8 Hz), 4.04 (br t, 1H, *J* = 6.2 Hz), 3.58-3.68 (m, 2H), 3.45-3.55 (m, 4H), 3.33 (br d, 1H, *J* = 5.3 Hz), 2.61 (d, 1H, *J* = 8.3 Hz), 2.49-2.62 (m, 1H), 2.17 (dd, 1H, *J* = 12.5, 7.0 Hz), 1.98-2.11 (m, 1H), 1.40-1.95 (m, 8H), 1.02 (d, 3H, *J* = 6.6 Hz), 0.97 (d, 3H, *J* = 6.8 Hz); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 138.5 (C), 138.1 (C), 128.3 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 105.7 (C), 90.7 (CH), 73.2 (CH_2), 72.7 (CH_2), 70.3 (CH), 69.9 (CH), 68.7 (CH), 67.3 (CH_2), 65.9 (CH_2), 47.2 (CH_2), 36.2 (CH_2), 35.0 (CH_2), 32.5 (CH), 31.8 (CH_2), 31.5 (CH), 17.7 (CH_3), 17.3 (CH_3); **MS** (FAB) *m/e* (relative intensity, assignment) 485 (100, M+H$^+$); mass calcd for $C_{29}H_{40}O_6$+H$^+$ is 485.3; found 485.2. Data for 1,5-dioxyspiro-[4,4]-nonane: R_f 0.68 (1:1 EtOAc/CH_2Cl_2, PAA); **IR** (thin film) 3450 (br), 3030, 2954, 2925, 1454, 1097, 981 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.20-7.35 (m, 10H), 4.48 (AB_q, 4H, J_{AB} = 12.0 Hz, $\Delta\nu_{AB}$ = 22.7 Hz), 3.57-3.75 (m, 6H), 3.45 (dd, 2H, *J* = 8.4, 2.8 Hz), 3.32 (br s, 1.5 H), 2.46-2.63 (m, 2H), 2.12 (dd, 2H, *J* = 12.3, 6.8 Hz), 1.67-1.92 (m, 4H), 1.66 (dd, 2H, *J* = 12.3, 12.1 Hz), 1.03 (d, 6H, *J* = 6.6 Hz); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 138.4 (C), 128.4 (CH), 127.6 (CH), 127.5 (CH), 113.7 (C), 89.4 (CH), 73.1 (CH_2), 68.8 (CH), 68.0 (CH_2), 44.0 (CH_2), 35.0 (CH_2), 33.5 (CH), 17.5 (CH_3).

Preparation of (2S,3S,4S,8S,9S,10S)-2,8-Di(2-hydroxyethyl)-3,9-dihydroxy-4,10-dimethyl-1,7-dioxyspiro-[5,5]-undecane (9)

The thermodynamic, regio-isomeric spiroketal mixture (8.5 g, 17.5 mmol) was dissolved in 200 mL of absolute ethanol. Catalytic palladium (II) hydroxide (20 w/w % on carbon, 369 mg, 0.529 mmol) was suspended in the ethanol solution, and the system was placed under one atmosphere of hydrogen. The reaction was vortexed with rapid stirring at room temperature for 12 hours, with periodic regeneration of the hydrogen atmosphere. The resulting mixture was diluted with 400 mL of CH_2Cl_2 and filtered through a plug of silica gel. The plug was flushed with 10% MeOH/CH_2Cl_2, and the solution was concentrated *in vacuo*. Residual hydroxylic solvents were removed azeotropically with benzene, and the residue was placed under vacuum overnight to afford a mixture of tetraol spiroketals (5.33 g, 100%). Silica gel chromatography with 3% MeOH/EtOAc cleanly separated 1,7-dioxyspiro-[5,5]-undecane ketal **9** from the undesired 1,6-dioxyspiro-[4,5]-decane ketal **10**. Data for 1,7-dioxyspiro-[5,5]-undecane **9**: R_f 0.23 (1:9 MeOH/EtOAc, PAA); $[\alpha]^{22}_D$ -110 (c = 0.200, MeOH); mp = 123-124 °C; **IR** (thin film) 3363 (br), 2922, 2872 cm^{-1}; **^{1}H NMR** (CD_3OD, 300 MHz) δ 3.72 (dd, 2H, *J* = 10.1, 2.9 Hz), 3.65-3.70 (m, 4H), 3.20 (br d, 2H, *J* = 1.5 Hz), 1.96-2.04 (m, 2H), 1.80 (ddt, 2H, *J* = 14.5, 10.1, 5.0 Hz), 1.55 (dddd, 2H, *J* = 14.5, 7.8, 6.6, 3.3 Hz), 1.35 (AB of ABX, 4H), 0.85 (d, 6H, *J* = 6.8 Hz); **^{13}C NMR** (CD_3OD, 75.4 MHz) δ 97.9 (C), 71.7 (CH), 70.2 (CH), 59.8 (CH_2), 38.0 (CH_2), 35.9 (CH_2), 31.6 (CH), 18.1 (CH_3); **MS** (FAB) *m/e* (relative intensity, assignment) 305 (100, M+H$^+$), 289 (65, M+H$^+$-H_2O); mass calcd for $C_{15}H_{28}O_6$+H$^+$ is 305.2; found 305.1. Data for 1,6-dioxyspiro-[4,5]-decane **10**: R_f 0.19 (1:9 MeOH/EtOAc, PAA); **^{1}H NMR** (CD_3OD, 300 MHz) δ 3.98 (ddd, 1H, *J* = 9.8, 3.6, 0.2 Hz), 3.44-65 (m, 6H), 3.35 (dd, 1H, *J* = 8.6, 4.6 Hz),3.15-3.22 (m, 2H), 2.29-2.46 (m, 1H), 1.90-2.12 (m, 2H), 1.44-1.78 (m, 6H), 1.13-1.42 (m, 3H), 0.94 (d, 3H, *J* = 6.6 Hz), 0.85 (d, 3H, *J* = 6.6 Hz); **^{13}C NMR** (CD_3OD, 75.4 MHz) δ 106.7 (C), 94.6 (CH), 71.4 (CH), 70.4 (CH), 70.1 (CH), 60.0 (CH_2), 59.1 (CH_2), 48.4 (CH_2), 37.6 (CH_2), 37.2 (CH_2), 35.6 (CH_2), 33.9 (CH), 32.9 (CH), 18.2 (CH_3), 17.6 (CH_3).

Equilibration to *(2S,3S,4S,8S,9S,10S)*-2,8-Di(2-hydroxyethyl)-3,9-dihydroxy-4,10-dimethyl-1,7-dioxyspiro-[5,5]-undecane (9)

The undesired 1,6-dioxyspiro-[4,5]-decane ketal **10** (2.1 g, 6.9 mmol) was dissolved with 50 mL of MeOH in a round bottom flask equipped with a reflux condenser. Catalytic triflic acid (0.06 mL, 0.78 mmol) was added, and the system was heated to reflux for 50 minutes. After cooling, the contents were diluted with 100 mL of PhH and concentrated *in vacuo*. The resulting mixture of ketals (2.06 g, 98%) was further azeotroped with two 100 mL portions of PhH, and then subjected to silica gel FCC with 3% MeOH/EtOAc. Any mixed fractions favoring the desired 1,7-dioxyspiro-[5,5]-undecane ketal **9** were recrystallized from EtOAc. All spectroscopic data for the recrystallized product was consistent with that of the previously synthesized spiroketal **9**. Data for 1,5-dioxyspiro-[4,4]-nonane **11**: R_f 0.16 (1:9 MeOH/EtOAc, PAA); **^{1}H NMR** (CD_3OD, 300 MHz) δ 4.57 (br s, 4H), 3.52-3.63 (m, 6H), 3.30 (dd, 2H, *J* = 8.4, 2.7 Hz), 2.32-2.51 (m, 2H), 2.02 (dd, 2H, *J* = 12.3, 6.7 Hz), 1.50-1.73 (m, 6H), 0.96 (d, 6H, *J* = 6.6 Hz); **^{13}C NMR** (CD_3OD, 75.4 MHz) δ 114.8 (C), 90.6 (CH), 68.7 (CH), 60.1 (CH_2), 45.1 (CH_2), 38.6 (CH_2), 34.8 (CH), 17.6 (CH_3).

Preparation of *(2S,3S,4S,8S,9S,10S)*-4,10-Dimethyl-3,9-dihydroxy-2,8-(2-ethanoic acid-γ-lactone)-1,7-dioxaspiro-[5,5]undecane (12)

The C_2-symmetric 1,7-dioxaspiro-[5,5]undecane **9** (1.85 g, 6.08 mmol) was combined with powdered 4Å molecular sieves and NMO (4.5 g, 38.4 mmol) in 100 mL of t-butyl alcohol/acetonitrile (1:1). After the heterogeneous solution was stirred at room temperature for 20 minutes, 5 mole % TPAP was added, and the reaction stirred for 60 minutes. An additional 5 mole % TPAP was added, and the reaction stirred for 12 hours, after which the starting tetraol was no longer present. The solution was diluted with 30 mL of CH_2Cl_2, and 1 mole % portions of TPAP were added every 20 minutes until partially oxidized intermediates were no longer observed by TLC. The reaction was diluted again with CH_2Cl_2 (500 mL) and filtered through a plug of silica gel, removing the 4 Å molecular sieves, TPAP, and excess NMO. The silica gel plug was rinsed with 25% Et_2O/CH_2Cl_2, the pale yellow solution was concentrated *in vacuo*. Complete removal of the oxidizing agents prior to concentration was necessary for optimum yields. The resulting bis(lactone) was immediately purified by silica gel chromatography (1:9 Et_2O/CH_2Cl_2). Any mixed fractions were further purified by dissolving the impure bis(lactone) in minimal amount of hot benzene, adding an equivalent volume of hot hexanes, and allowing overnight crystal growth at room temperature. Careful and rapid purification resulted in reproducibly high yields of the C_2-symmetric bis(lactone) **12** (1.35 g, 75%) as a white crystalline solid. Data for **12**: R_f 0.55 (1:3 Et_2O/CH_2Cl_2, PAA); R_f 0.1 (2% MeOH/Et_2O, PAA); $[\alpha]^{22}_D$ -188 (c = 0.365, CH_2Cl_2); dec. at 231 °C; **IR** (thin film) 2933, 1776, 1186, 1159, 1014 cm^{-1}; **^{1}H NMR** (C_6D_6, 300 MHz) δ 3.32 (t, 2H, J = 2.6 Hz), 3.21 (dd, 2H, J = 4.4, 2.2 Hz), 2.16 (A of ABX, 2H, J_{AB} = 16.9 Hz, J_{AX} = 0.1 Hz), 1.90 (B of ABX, 2H, J_{AB} = 16.9 Hz, J_{BX} = 4.3 Hz), 1.71-1.85 (m, 2H), 1.03 (A of ABX, 2H, J_{AB} = 13.6 Hz, J_{AX} = 14.7 Hz), 0.94 (B of ABX, 2H, J_{AB} = 13.6 Hz, J_{BX} = 6.1 Hz), 0.88 (d, 6H, J = 7.0 Hz); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 175.6 (C), 96.5 (C), 80.3 (CH), 69.2 (CH), 38.4 (CH_2), 35.7 (CH_2), 25.4 (CH), 17.1 (CH_3); **HRMS** (EI) *m/e* (relative intensity, assignment) 297 (0.9, $M+H^+$), 296 (3.6, M^+), 208 (23, M^+-2 x CO_2), 169 (22, $C_{10}H_{17}O_2^+$), 168 (100, $C_{10}H_{16}O_2^+$); exact mass calcd for $C_{15}H_{20}O_6$ requires 296.1260, found 296.1256.

Preparation of Primary alcohol (13)

The C_2-symmetric bis(lactone) **12** (67.8 mg, 0.229 mmol) was dissolved in 2.0 mL of THF and 2.0 mL of toluene with catalytic pyridine (0.015 mmol) under an argon atmosphere, and the solution was cooled to -78 °C. A 0.7 M solution Tebbe's reagent in toluene (0.24 ml, 0.168 mmol) was added dropwise, and after five minutes at -78 °C, the dry ice bath was removed and the reaction was warmed to room temperature. After 40 minutes, a 0.5 M solution of 9-borobicyclononane (9-BBN) in THF was added via syringe (0.46 mL, 0.23 mmol), and the reaction was stirred at room temperature for thirty minutes. The reaction was quenched with 2 mL of water, diluted with 10 mL of THF, and oxidized by adding excess sodium perborate·tetrahydrate (75 mg, 0.69 mmol) and stirring for 120 minutes. The reaction contents were poured onto 10 mL of saturated $NaHSO_3$(aq), and after 15 minutes, 30 mL of saturated Rochelle's salt(aq) was added. After 10 additional minutes, the biphasic system was transferred to a separatory funnel containing 10 mL of 1.25 M NaOH(aq). The layers were separated, and the aqueous phase was extracted

twice with 20 mL portions of EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting mixture of recovered starting material **12**, mono-functionalized alcohol **13**, and side products was loaded onto a silica gel column with CH_2Cl_2/hexanes (1:1). One column volume of hexanes followed by ten column volumes of Et_2O were used to elute higher R_f side products. Recovered starting material **12** and the desired primary alcohol **13** were then co-eluted with 1:1 Et_2O/CH_2Cl_2. The starting material (37 mg, 54%) and primary alcohol **13** (29 mg, 40%) were then separated by FCC using a 10-25% Et_2O/CH_2Cl_2 gradient. Data for mono-functionalized primary alcohol **13**: R_f 0.2 (2% MeOH/Et_2O, PAA); **IR** (thin film) 3462 (br), 2928, 2828, 1780, 1117 cm^{-1}; **^{1}H NMR** (C_6D_6, 300 MHz) δ 3.87-3.95 (m, 1H), 3.76 (ddd, 1H, J = 11.2, 3.7, 3.3 Hz), 3.48 (dt, 1H, J = 11.2 4.6 Hz), 3.40-3.42 (m, 1H), 3.38 (dd, 1H, J = 4.1, 2.4 Hz), 3.34 (dd, 1H, J = 3.2, 2.4 Hz), 3.16 (br t, 1H, J = 2.4 Hz), 2.24 (br t, 1H, J = 4.0 Hz), 2.22 (A of ABX, 1H, J_{AB} = 16.9 Hz, J_{AX} = 0.1 Hz), 1.91-2.10 (m, 2H), 1.92 (B of ABX, 1H, J_{AB} = 16.9 Hz, J_{BX} = 4.3 Hz), 1.60-1.74 (m, 2H), 1.31 (A of ABX, 1H, J_{AB} = 13.3 Hz, J_{AX} = 12.7 Hz), 1.17 (ap d, 1H), 1.09 (B of ABX, 1H, J_{AB} = 16.9 Hz, J_{BX} = 4.4 Hz), 1.02 (d, 3H, J = 7.2 Hz), 0.86 (d, 3H, J = 7.2 Hz); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 175.8 (C), 96.9 (C), 80.4 (CH), 79.6 (CH), 72.4 (CH), 68.9 (CH), 65.0 (CH), 38.4 (CH_2), 36.4 (CH_2), 36.2 (CH_2), 34.6 (CH_2), 29.6 (CH_2), 25.5 (CH), 25.5 (CH), 17.7 (CH_3), 17.2 (CH_3); **HRMS** (EI) *m/e* (relative intensity, assignment) 313 (0.3, $M+H^+$) 281 (17, M^+-CH_2OH) 144 (58, $C_7H_{12}O_3^+$); exact mass calcd for $C_{16}H_{24}O_6+H^+$ requires 313.1651, found 313.1645.

Preparation of C(51)-Aldehyde

The primary alcohol **13** (125 mg, 0.40 mmol) was combined with Dess-Martin's periodonate reagent (281 mg, 0.67 mmol) in 10 mL of dichloromethane. The reaction was stirred for 2.5 hours at room temperature, when only trace starting material remained. The resulting heterogeneous mixture was diluted with 10 mL of EtOAc and quenched with 20 mL of a saturated aqueous solution of sodium bicarbonate doped with sodium thiosulfate (25 g / 100 mL). After 10 minutes, the contents were transferred to a separatory funnel with an additional 30 mL of EtOAc, separated, and the organic layer was washed with brine. The aqueous layers were extracted one additional time with EtOAc, and the combined organics were dried over Na_2SO_4, filtered, and concentrated at 25 °C *in vacuo*. The crude aldehyde was used without further purification. Data for the aldehyde: R_f 0.32 (1:3 Et_2O/CH_2Cl_2, PAA); **^{1}H NMR** (C_6D_6, 300 MHz) δ 9.57 (br d, 1H, J = 0.7 Hz), 3.95 (br d, 1H, J = 9.9 Hz), 3.31-3.33 (m, 2H), 3.26-3.28 (m, 2H), 2.20 (A of ABX, 1H, J_{AB} = 16.7 Hz, J_{AX} = 0.1 Hz), 1.90 (m, 2H), 1.93 (B of ABX, 1H, J_{AB} = 16.7 Hz, J_{BX} = 0.1 Hz), 1.76-1.88 (m, 1H), 1.58-1.70 (m, 1H), 1.06-1.27 (m, 4H), 1.02 (d, 3H, J = 7.2 Hz), 0.85 (d, 3H, J = 7.0).

Preparation of C(51)-(*S*)-Homoallylic alcohol (14)

The crude C(51) aldehyde (0.40 mmol) was dissolved in 10 mL of dry CH_2Cl_2 under an argon atmosphere and cooled to - 78 °C. Freshly distilled $TiCl_4$ (60 μL, 0.547 mmol) was added dropwise, and the reaction mixture was aged for 10 minutes. Allyltri(*n*-butyl)stannane (0.19 mL, 0.612 mmol) was added dropwise via syringe, and the reaction was stirred for 20 minutes. One mL of water was added to quench

the reaction, and the dry ice/acetone bath was removed. After the slurry had reached room temperature, it was acidified with 3% HCl(aq) and transferred to a separatory funnel with 30 mL of EtOAc. The layers were separated, and the organic phase was washed once with a 1:1 mixture of saturated $NaHCO_3$(aq) and brine. The aqueous layers were extracted twice with 30 mL portions of EtOAc, and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Silica gel chromatography with EtOAc/CH_2Cl_2/hexanes (1:1:1) yielded the desired homoallylic alcohol **14** (109 mg, 77%) as a pale yellow oil. Stannane impurities often contaminated the homoallylic alcohol and necessitated repeated chromatography for high levels of purity. Data for **14**: R_f 0.26 (1:3 Et_2O/CH_2Cl_2, PAA), R_f 0.20 (1:1:1 EtOAc/CH_2Cl_2/hexanes, PAA); $[\alpha]^{22}_D$ -109 (c = 0.210, CH_2Cl_2); **IR** (thin film) 3465, 2927, 1786, 1200, 1016 cm^{-1}; **^{1}H NMR** (C_6D_6, 300 MHz) δ 5.82 (ddt, 1H, *J* = 17.1, 10.2, 7.0 Hz), 5.08 (dq, 1H, *J* = 17.1 1.5 Hz), 5.04 (dm, 1H, *J* = 10.2 Hz), 4.28 (dd, 1H, *J* = 3.9, 2.3 Hz), 4.22 (dd, 1H, *J* = 3.2, 2.3 Hz), 4.01-4.06 (m, 2H), 3.85-3.92 (m, 1H), 3.65-3.80 (m, 1H), 3.52 (dd, 1H, *J* = 3.0, 1.8 Hz), 2.84 (d, 1H *J* = 2.4 Hz), 2.67 (A of ABX, 1H, J_{AB} = 17.1 Hz, J_{AX} = 4.3 Hz), 2.50 (B of ABX, 1H, J_{AB} = 17.1 Hz, J_{BX} = 0.1 Hz), 1.97-2.41 (m, 5H), 1.37-1.52 (m, 4H), 1.06 (d, 3H, *J* = 7.0 Hz), 1.01 (d, 3H, *J* = 7.2 Hz); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 175.8 (C), 134.6 (CH), 117.2 (CH_2), 97.0 (C), 80.4 (CH), 80.0 (CH), 79.1 (CH), 72.2 (CH), 71.6 (CH), 68.9 (CH), 38.6 (CH_2), 38.4 (CH_2), 36.5 (CH_2), 36.1 (CH_2), 32.1 (CH_2), 25.4 (CH x 2), 17.7 (CH_3), 17.2 (CH_3).

Preparation of *(51S)*-BOC Carbonate

To homoallylic alcohol **14** (20.1 mg, 0.057 mmol) and DMAP (25 mg, 0.22 mmol) in pyridine (0.7 mL, 8.6 mmol), was added $(BOC)_2O$ (185 mg, 0.85 mmol) at room temperature. After 24 hours, the reaction was diluted with 2 mL of CH_2Cl_2 and monitored by TLC for starting material. Additional $(BOC)_2O$ (61 mg, 0.28 mmol) was added, and the reaction stirred for 3 more hours if the homoallylic alcohol persisted. The reaction was quenched with 5% aqueous HCl and extracted with EtOAc. The organic phase was washed with saturated $NaHCO_3$(aq)/brine (1:1). The aqueous layers were extracted with 20 mL of EtOAc. The combined organic layers were dried over $MgSO_4$ and filtered through a short plug of silica gel with additional EtOAc. After concentration *in vacuo*, silica gel chromatography with 50% Et_2O in hexanes yielded the BOC carbonate (23.3 mg, 91%) as an amorphous white solid. Data for the BOC carbonate: R_f 0.25 (3:1 Et_2O/hexanes, PAA); $[\alpha]^{22}_D$ -107 (c = 0.510, CH_2Cl_2); **IR** (thin film) 2962, 2929, 1785, 1741, 1277, 1250, 1163, 1016 cm^{-1}; **^{1}H NMR** (C_6D_6, 300 MHz) δ 5.82 (dddd, 1H, *J* = 17.3, 10.3, 7.7, 6.6 Hz), 5.12 (dq, 1H, *J* = 17.3, 1.3 Hz), 5.05 (ddt, 1H, *J* = 10.3, 1.9, 1.0 Hz), 4.76 (td, 1H, *J* = 7.7, 4.0 Hz), 4.28 (dd, 1H, *J* = 4.0, 2.3 Hz), 4.22 (dd, *J* = 2.8, 2.6 Hz), 3.95-4.02 (m, 2H), 3.59 (dd, 1H *J* = 2.9, 2.4 Hz), 2.68 (A of ABX, 1H, J_{AB} = 17.1 Hz, J_{AX} = 0.4 Hz), 2.52-2.62 (m, 1H), 2.50 (B of ABX, 1H, J_{AB} = 17.1 Hz, J_{BX} = 4.1 Hz), 2.20-2.47 (m, 3H), 2.18 (ddd, 1H, *J* = 14.1, 9.2, 5.0 Hz), 1.88 (dd, 1H *J* = 14.1, 3.8 Hz), 1.37-1.60 (m, 4H), 1.48 (s, 9H), 1.11 (d, 3H, *J* = 7.0 Hz),1.02 (d, 3H, *J* = 7.0 Hz); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 176.1 (C), 153.0 (C), 133.8 (CH), 117.5 (CH_2), 96.6 (C), 81.8 (C), 80.8 (CH), 79.9 (CH), 77.7 (CH), 77.6 (CH), 72.1 (CH), 68.8 (CH), 38.5 (CH_2), 36.6 (CH_2), 36.4 (CH_2), 35.7 (CH_2), 35.5 (CH_2), 27.8 (CH_3 x 3), 25.5 (CH), 17.7 (CH_3),

17.2 (CH_3); **MS** (FAB+NaI) *m/e* (relative intensity, assignment) 475 (92, $M+Na^+$), 375 (100, $M+Na^+$-BOC); mass calcd for $C_{24}H_{36}O_8+Na^+$ is 475.2; found 475.2.

Preparation of C(54)-Iodo-51(S),53(R)-carbonate (15)

Homoallylic carbonate (23.1 mg, 0.051 mmol) was dissolved in dry toluene under an argon atmosphere and cooled with a dry ice/Et_2O bath to -80 °C. A 1.0 M solution of IBr in CH_2Cl_2 (0.12 mL, 0.12 mmol) was added dropwise over 2 minutes, and the reaction was held at -80 °C for 3 hours. After warming to 0 °C and stirring for 15 minutes, the reaction was quenched with 10 mL saturated aqueous solution of sodium bicarbonate doped with sodium thiosulfate (25 g / 100 mL), diluted with 10 mL of EtOAc, and stirred until colorless. The layers were transferred to a separatory funnel, and the aqueous layer extracted twice with 20 mL portions of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered through a short silica gel plug with additional EtOAc, and concentrated *in vacuo*. Silica gel chromatography with a 0-50% EtOAc/Et_2O solvent gradient provided the iodocarbonate **15** in excellent yield (26.6 mg, 99%) as a single diastereomer within the detection limits of ^1H NMR. Data for **15**: R_f 0.58 (100% EtOAc, PAA); $[\alpha]^{22}_D$ -47.8 (c = 1.16, CH_2Cl_2); **IR** (thin film) 2926, 1754, 1187, 1116, 1018 cm^{-1}; **^1H NMR** (C_6D_6, 300 MHz) δ 3.83 (ddd, 1H, *J* = 10.9, 7.0, 2.8 Hz), 3.54 (ddd, 1H, *J* = 11.0, 9.0, 2.8 Hz), 3.41-3.45 (m, 2H), 3.29-3.38 (m, 1H), 3.37 (dd, 1H, *J* = 4.6, 1.8 Hz), 3.10 (dd, 1H, *J* = 2.6, 2.3 Hz), 2.53 (A of ABX, 1H, J_{AB} = 10.7 Hz, J_{AX} = 5.6 Hz), 2.44 (B of ABX, 1H, J_{AB} = 10.7 Hz, J_{BX} = 6.9 Hz), 2.26 (A of ABX, 1H, J_{AB} = 16.7 Hz, J_{AX} = 0.1 Hz), 2.01 (B of ABX, 1H, J_{AB} = 16.7 Hz, J_{BX} = 4.1 Hz), 1.90-2.08 (m, 3H), 1.84 (dd, 1H, *J* = 14.1, 3.4 Hz), 1.72 (ddd, 1H, *J* = 14.0, 9.8 4.8 Hz), 1.09-1.36 (m, 5H), 1.01 (d, 3H, *J* = 7.1 Hz), 0.95 (d, 3H, *J* = 6.9 Hz); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 174.6 (C), 147.1 (C), 96.6 (C), 80.0 (CH), 79.6 (CH), 79.5 (CH), 78.3 (CH), 76.5 (CH), 72.0 (CH), 69.1 (CH), 38.4 (CH_2), 36.8 (CH_2), 36.7 (CH_2), 35.5 (CH_2), 30.6 (CH_2), 25.8 (CH), 25.7 (CH), 17.9 (CH_3), 17.5 (CH_3), 5.9 (CH_2).

Preparation of C(51*S*,53*R*,54)-Triol lactone (16)

Iodocarbonate **15** (31.4 mg, 0.601 mmol) was combined with 1.0 M LiOH(aq) (0.9 mL, 0.9 mmol) in 3.5 mL of DME and 0.9 mL of water. The reaction was heated at 60 °C for 13 hours, after which, it was cooled to 0 °C and neutralized to pH 7.0 with HCl(aq). The reaction mixture was concentrated *in vacuo*, azeotroped with benzene (2x20 mL), and the resulting solids placed under vacuum for several hours. The flask was then fitted with a reflux condenser and charged with 10 mL of benzene and one equivalent of CSA (140 mg, 0.602 mmol). The system was refluxed for 1 hour, cooled to room temperature, and transferred to a separatory funnel with EtOAc. The solution was washed once each with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The aqueous phases were extracted with EtOAc several times, and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Silica gel chromatography (3% MeOH/CH_2Cl_2) cleanly provided the triol **16** (21.0 mg, 90%). The aqueous layers were saved until the mass recovery of the lactone triol **16** was confirmed. In cases of low

mass recovery, the saved aqueous phases were combined, brought to neutral pH with HCl(aq), and the extraction process repeated to recover additional **16**.

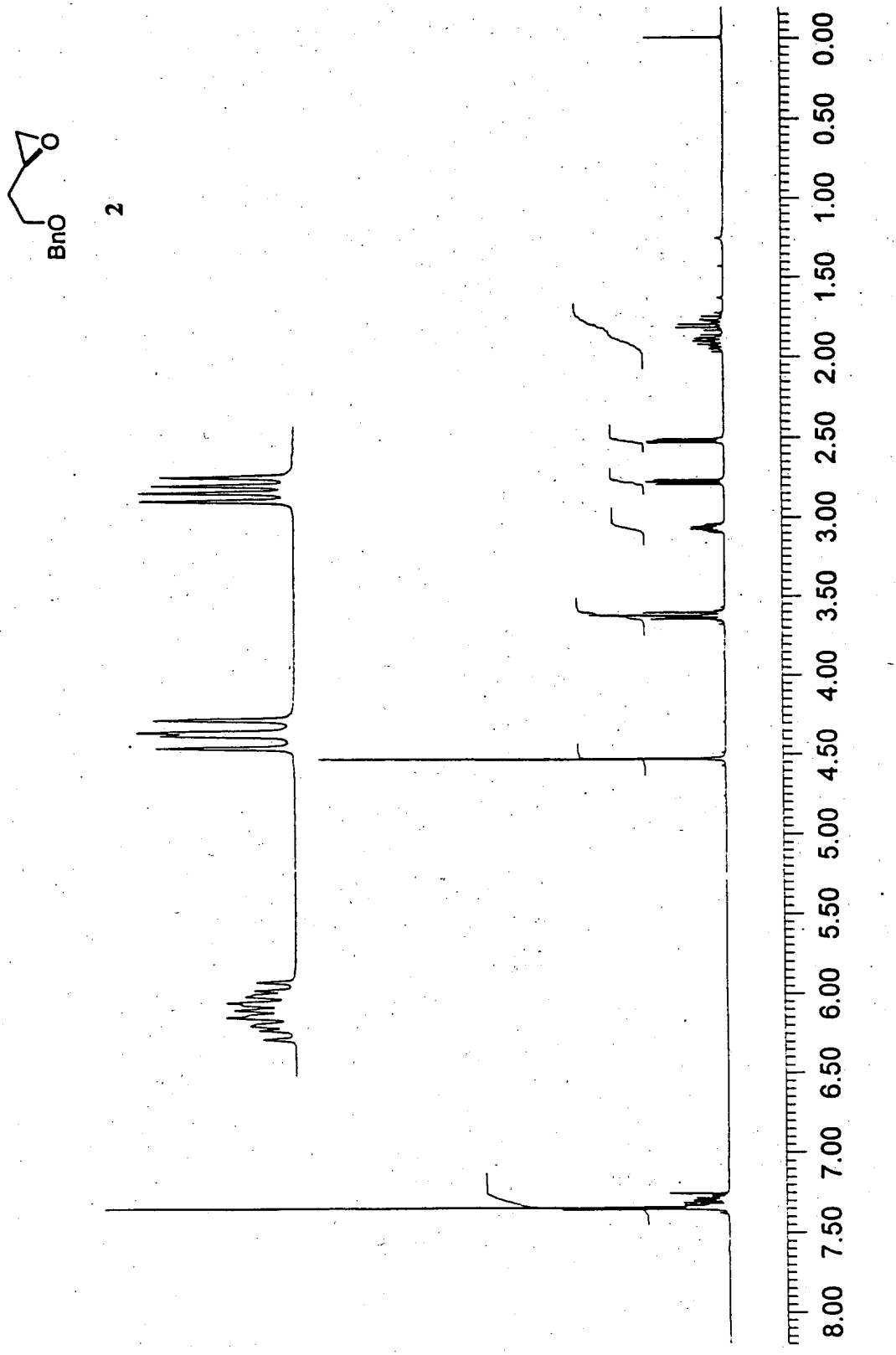
Preparation of C(54)-*t*-butyldiphenylsilyloxy-51(*S*),53(*R*)-diol

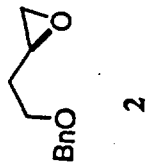
Triol **16** (10.9 mg, 0.028 mmol), DMAP (3 mg, 0.027 mmol), and excess pyridine (0.5 mL, 6.2 mmol) were combined in 1 mL of CH_2Cl_2. A slight excess of TBDPSCl (10 μL, 0.034 mmol) was added, and the reaction was stirred for 16 hours at room temperature. The excess TBDPSCl was consumed by the addition of 0.2 mL of MeOH. After 15 minutes, the reaction contents were transferred to a separatory funnel with 30 mL of EtOAc and washed with 20 mL of 5% aqueous HCl and then 20 mL of saturated $NaHCO_3$(aq). The aqueous layers were extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$. After concentration *in vacuo*, the selectively protected diol was purified by silica gel chromatography with a 50-100% Et_2O/hexanes gradient elution (15.9 mg, 90%). Data for diol: R_f 0.70 (100% EtOAc, PAA); $[\alpha]^{22}_D$ -62.7 (c = 0.415, PhH); **IR** (thin film) 3417 (br), 2954, 2929, 2856, 1786, 1427, 1113, 1016 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.59-7.70 (m, 4H), 7.30-7.45 (m, 6H), 4.30 (dd, 1H, J = 3.9, 2.3 Hz), 4.24 (br t, 1H, J = 2.7 Hz), 4.03 (dd, 1H, J = 4.4, 1.8 Hz), 3.90-4.00 (m, 3H), 3.62 (A of ABX, 1H, J_{AB} = 10.1 Hz, J_{AX} = 6.0 Hz), 3.60 (A of ABX, 1H, J_{AB} = 10.1 Hz, J_{BX} = 4.8 Hz), 3.55 (dd, 1H, J = 2.9, 2.0 Hz), 3.42 (br s, 1H), 3.36 (br s, 1H), 2.69 (A of ABX, 1H, J_{AB}= 17.1 Hz, J_{AX} = 4.1 Hz), 2.52 (B of ABX, 1H, J_{AB}= 17.1 Hz, J_{BX} = 0.1 Hz), 2.20-2.45 (m, 2H), 2.14 (ddd, 1H, J = 14.1, 9.2, 5.0 Hz), 2.03 (dd, 1H, J = 14.1, 3.4 Hz), 1.74 (dt, 1H, J = 15.0, 2.1 Hz), 1.22-1.52 (m, 5H), 1.09 (d, 3H, J = 7.0 Hz), 1.06 (s, 9H), 1.02 (d, 3H, J = 7.0 Hz); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 175.8 (C), 135.6 (CH x 4), 133.3 (C x 2), 129.8 (CH x 2), 127.8 (CH x 4), 97.0 (C), 80.6 (CH), 80.5 (CH), 79.3 (CH), 72.8 (CH), 72.3 (CH), 72.1 (CH), 69.0 (CH), 67.7 (CH_2), 38.5 (CH_2), 36.5 (CH_2 x 2), 36.3 (CH_2), 33.0 (CH_2), 26.5 (CH_3 x 3), 25.5 (CH x 2), 19.3 (C), 17.7 (CH_3), 17.2 (CH_3); **MS** (FAB+NaI) *m/e* (relative intensity, assignment) 647.4 (100, M+Na^+); mass calcd for $C_{35}H_{48}O_8Si$+Na^+ is 647.3; found 647.4.

Preparation of C(54)-*t*-Butyldiphenylsilyloxy-*(51S,53R)*-bis(triisopropyl silyloxy) lactone (1)

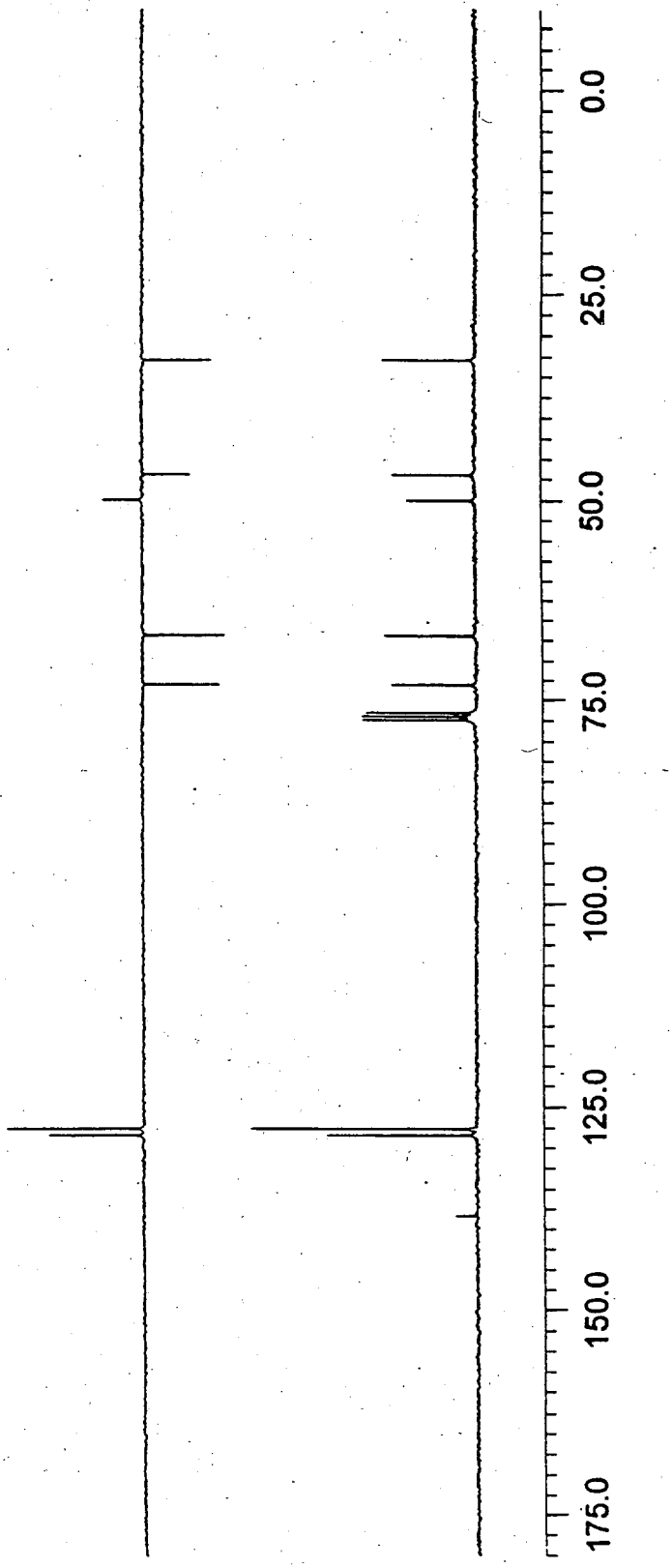
Diol **16** (125 mg, 0.200 mmol) was combined with DMAP (44 mg, 0.39 mmol) under a nitrogen atmosphere and then dissolved in 0.6 mL of dry pyridine. TIPSOTf (0.4 mL, 1.49 mmol) was added via syringe, and the reaction was stirred for 15 hours. Excess TIPSOTf was consumed by the addition of 1.5 mL of dry MeOH. After fifteen minutes, the reaction was transferred to a separatory funnel with Et_2O and washed first with 15 mL of 5% HCl and then with 20 mL of a 1:1 mixture of saturated $NaHCO_3$(aq) and brine. Aqueous layers were extracted with Et_2O (2x40 mL), and the combined organics were dried over $MgSO_4$. Filtration through a short silica gel plug with additional Et_2O and concentration *in vacuo* provided the crude, fully protected lactone **1**, which was purified by silica gel chromatography (25 % Et_2O in hexanes) to afford 187 mg (99%) of the lactone **1** as a pale yellow oil. Data for **1**: R_f 0.35 (1:1 Et_2O/hexanes, PAA); $[\alpha]^{22}_D$ +61.0 (c = 0.115, PhH); **IR** (thin film) cm^{-1}; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.63-7.70 (m, 4H), 7.32-7.44 (m, 6H), 4.28 (dd, 1H, J = 3.9, 2.4 Hz), 4.21 (br t, 1H, J = 2.5 Hz),

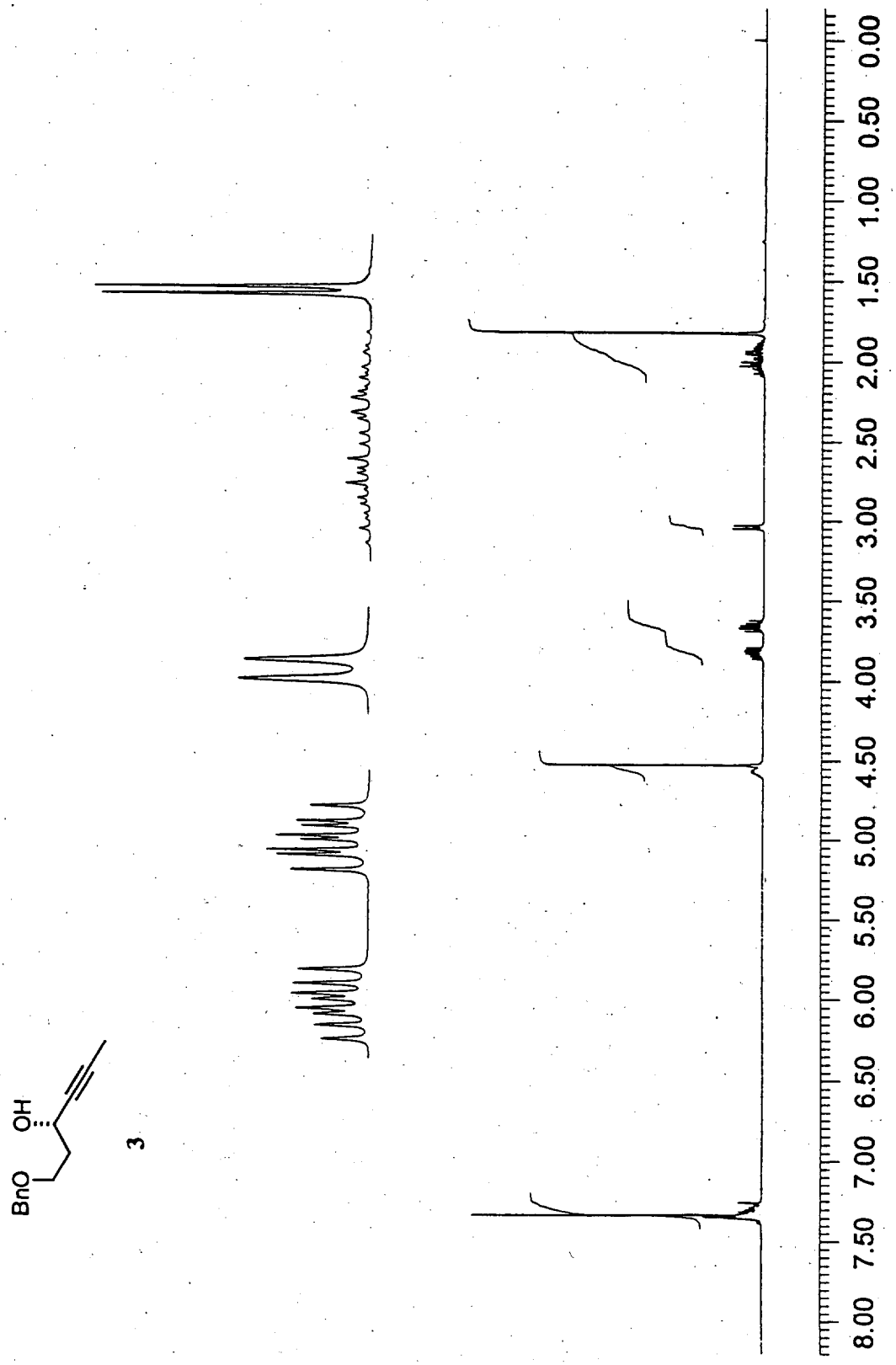
4.07-4.15 (m, 2H), 3.98 (dd, 1H, J = 6.0, 2.2 Hz), 3.83 (ddd, 1H, J = 9.5, 6.6, 3.4 Hz), 3.66 (A of ABX, 1H, J_{AB} = 10.3 Hz, J_{AX} = 4.7 Hz), 3.61 (B of ABX, 1H, J_{AB} = 10.3 Hz, J_{BX} = 5.5 Hz), 3.34 (br t, 1H, 2.6 Hz), 2.67 (A of ABX, 1H, J_{AB} = 17.3 Hz, J_{AX} = 4.5 Hz), 2.51 (B of ABX, 1H, J_{AB} = 17.3 Hz, J_{BX} = 0.1 Hz), 2.30-2.40 (m, 1H), 2.19-2.30 (m, 1H), 1.95-2.06 (m, 2H), 1.85-1.91 (m, 2H), 1.32-151 (m, 4H), 0.97-1.08 (m, 57H); **^{13}C NMR** ($CDCl_3$, 75.4 MHz) δ 174.6 (C), 136.1 (CH), 136.0 (CH), 134.1 (C), 133.7 (C), 130.0 (CH), 128.0 (CH), 96.8 (C), 81.2 (CH), 80.0 (CH), 79.8 (CH), 72.4 (CH), 71.8 (CH), 71.2 (CH), 69.0 (CH), 68.4 (CH_2), 38.7 (CH_2), 38.4 (CH_2), 37.0 (CH_2), 36.5 (CH_2), 34.9 (4xCH_3), 27.2 (CH_2), 25.8 (CH), 19.4 (C), 18.6 (2xCH_3), 18.0 (CH), 17.5 (CH), 13.5 (CH_3), 13.1 (CH_3); **MS** (FAB+NaI) *m/e* (relative intensity, assignment) 959.6 (100, M+Na^+); mass calcd for $C_{53}H_{88}O_8Si$+Na^+ is 959.6; found 959.6.

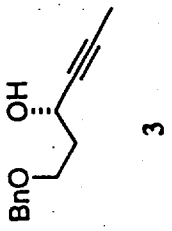




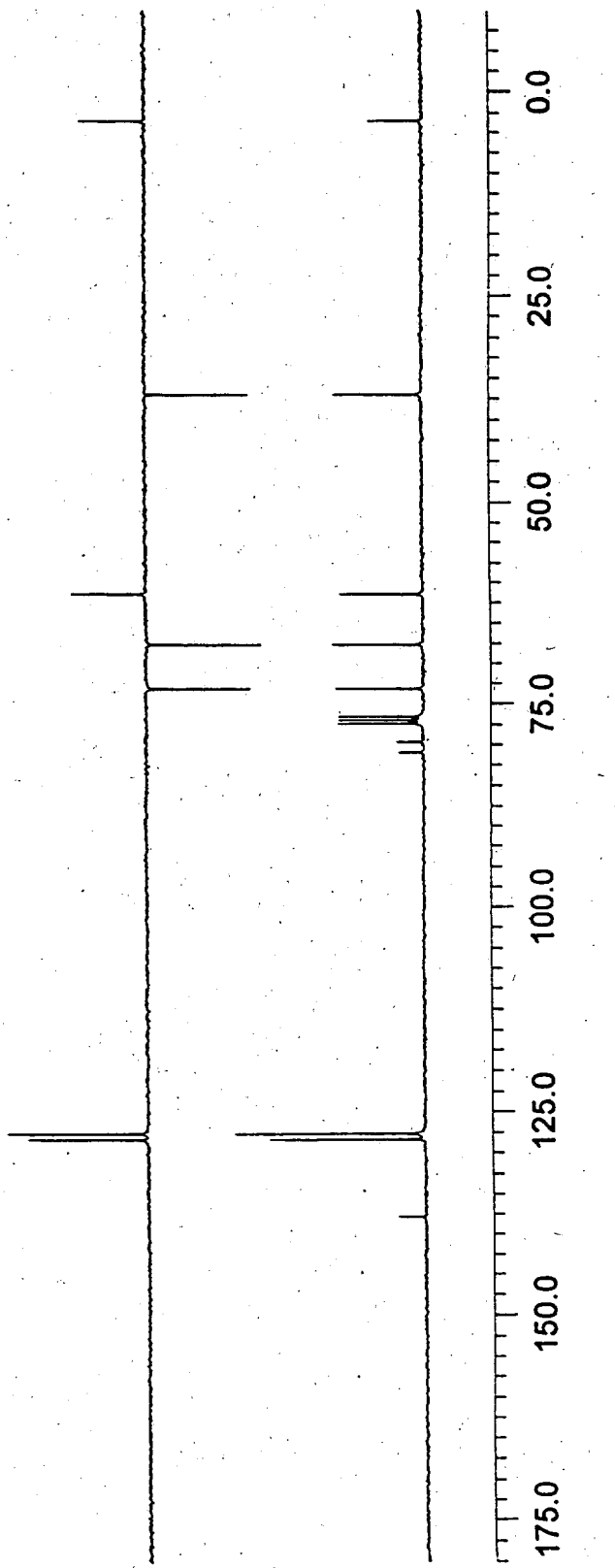
2

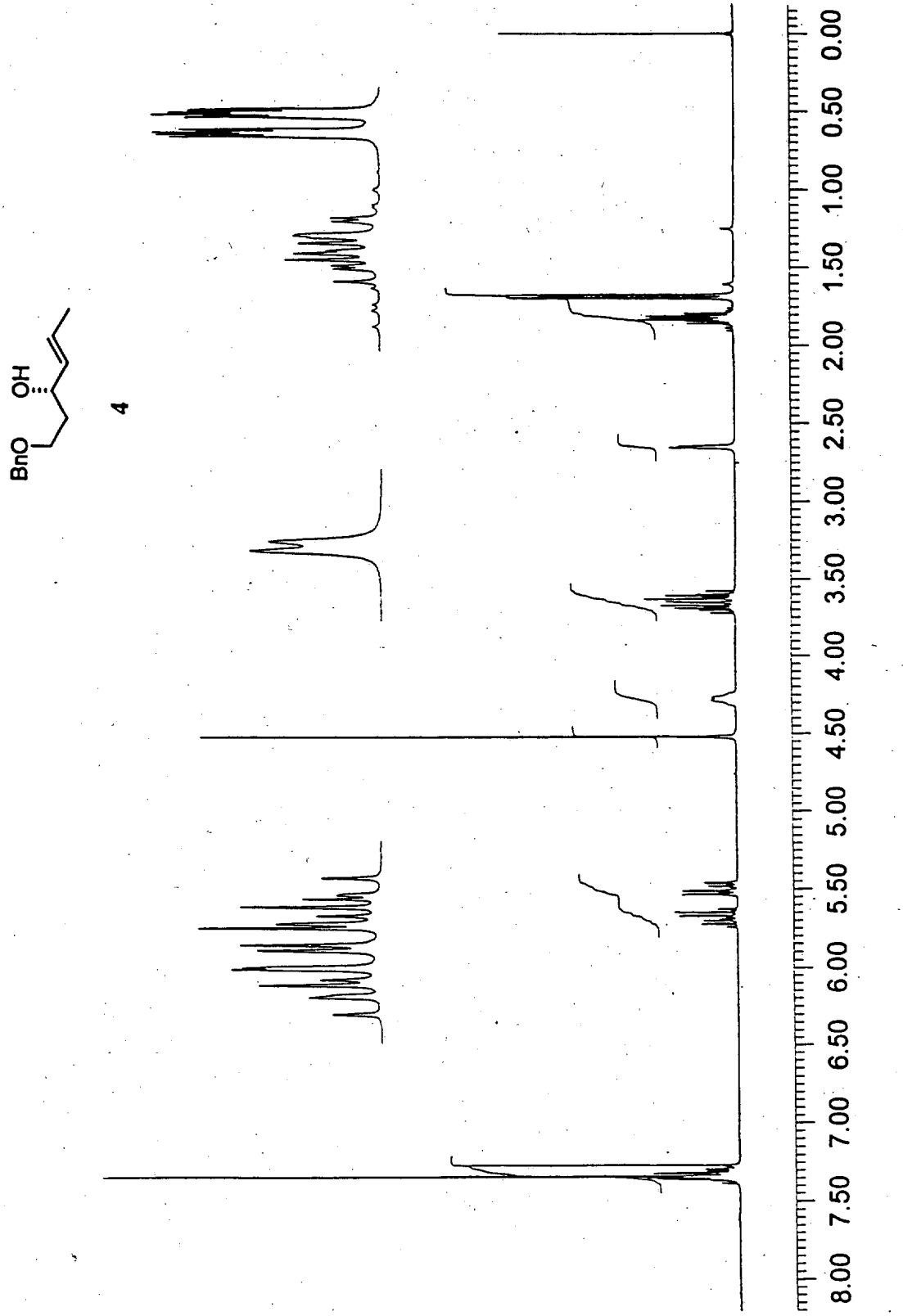


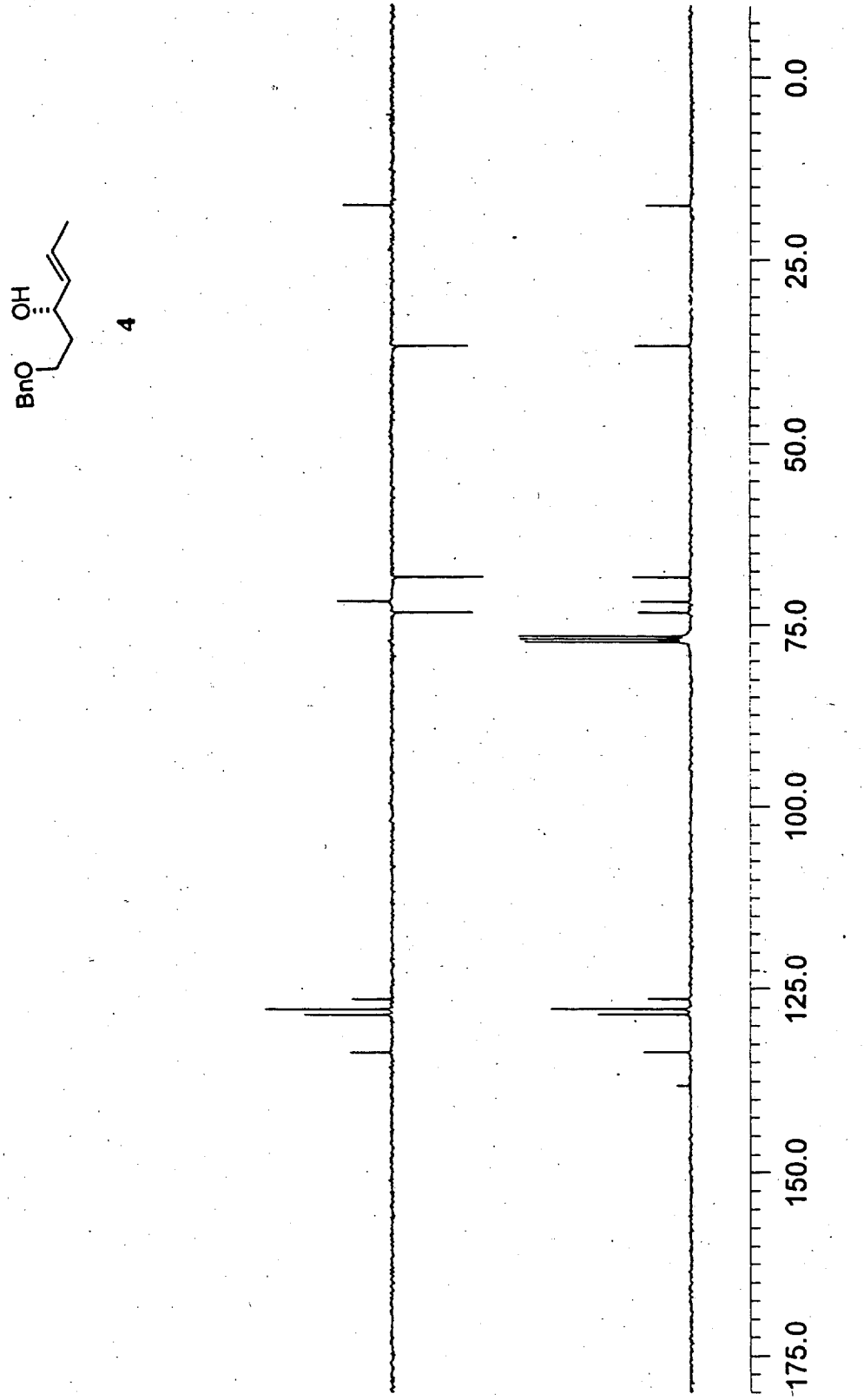


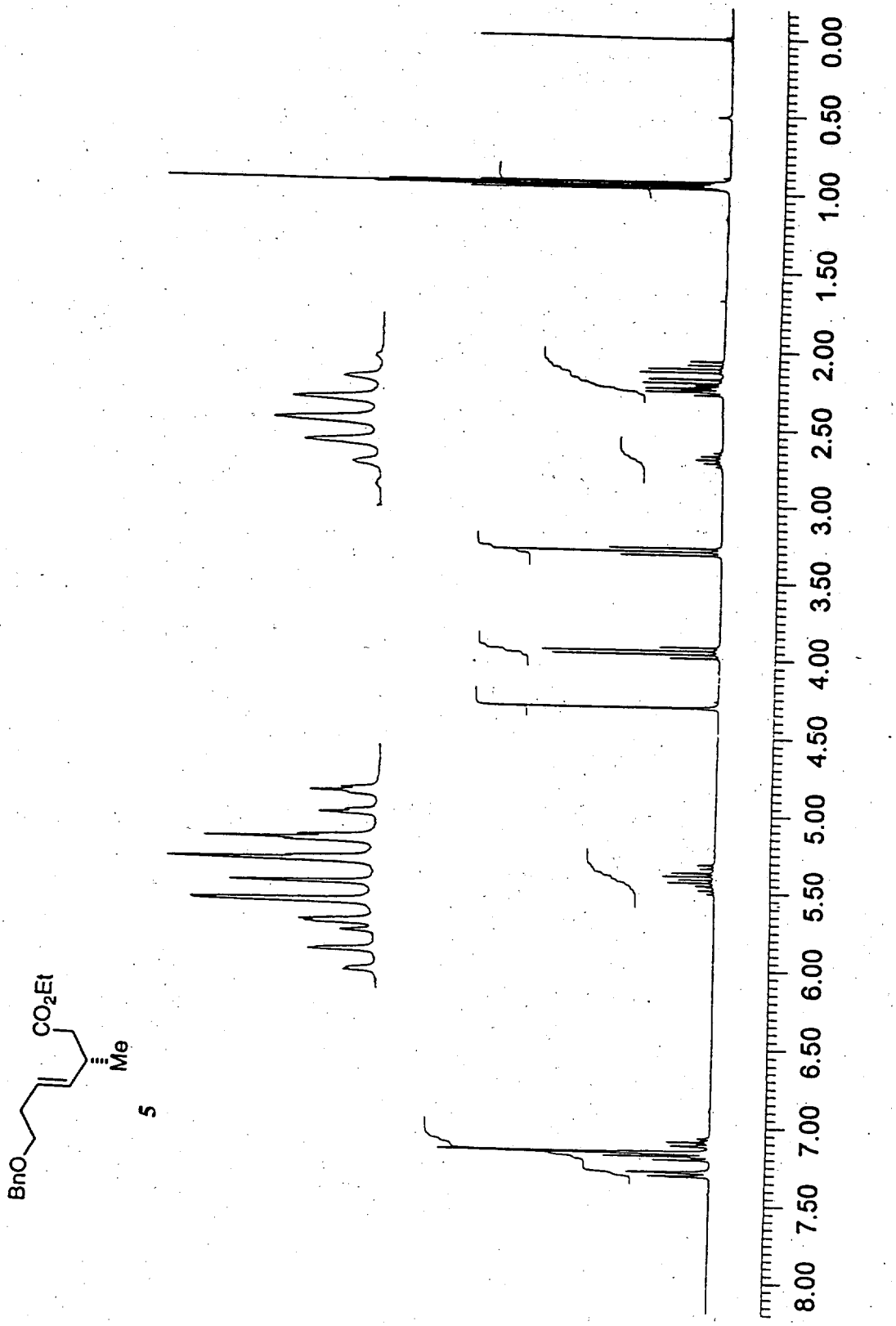


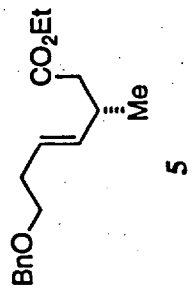
3



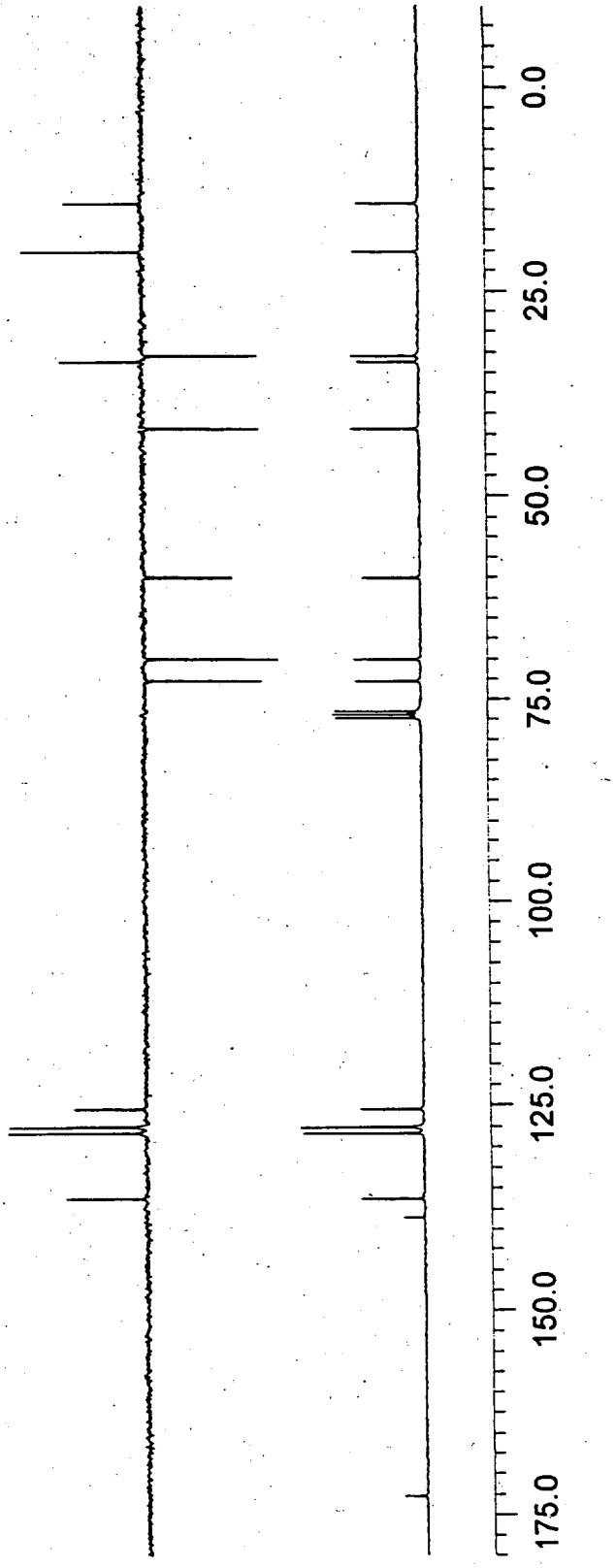


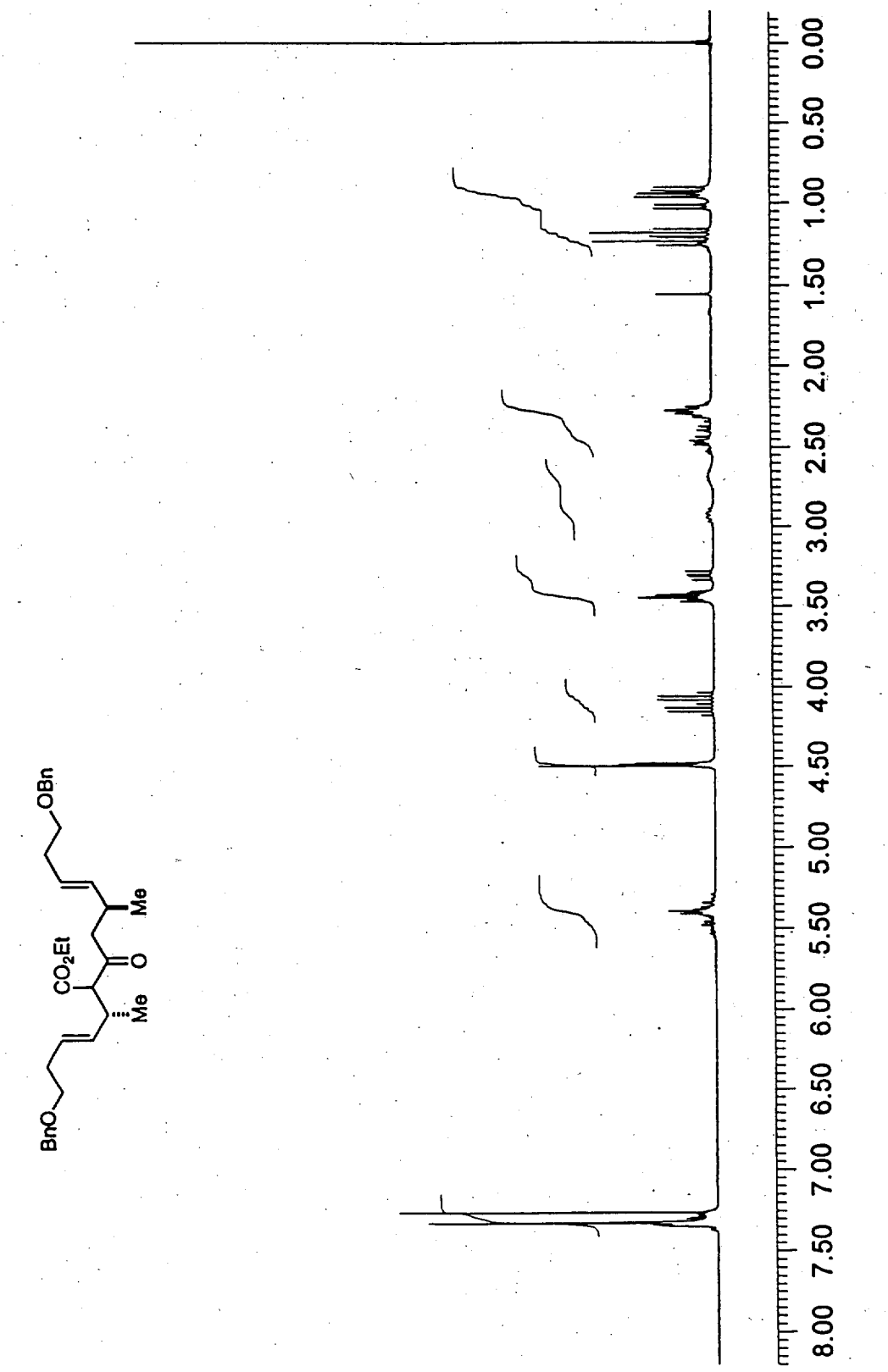


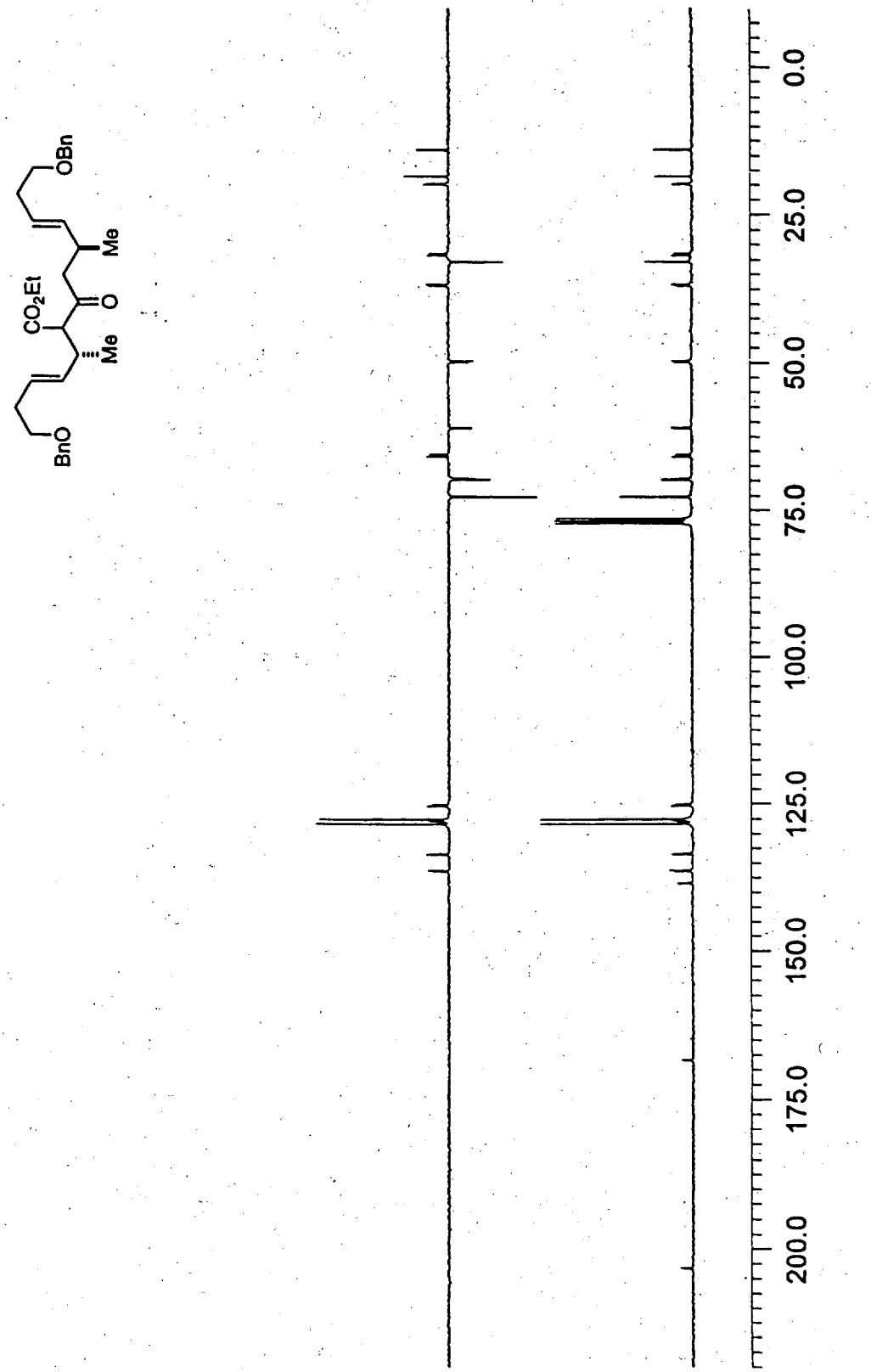


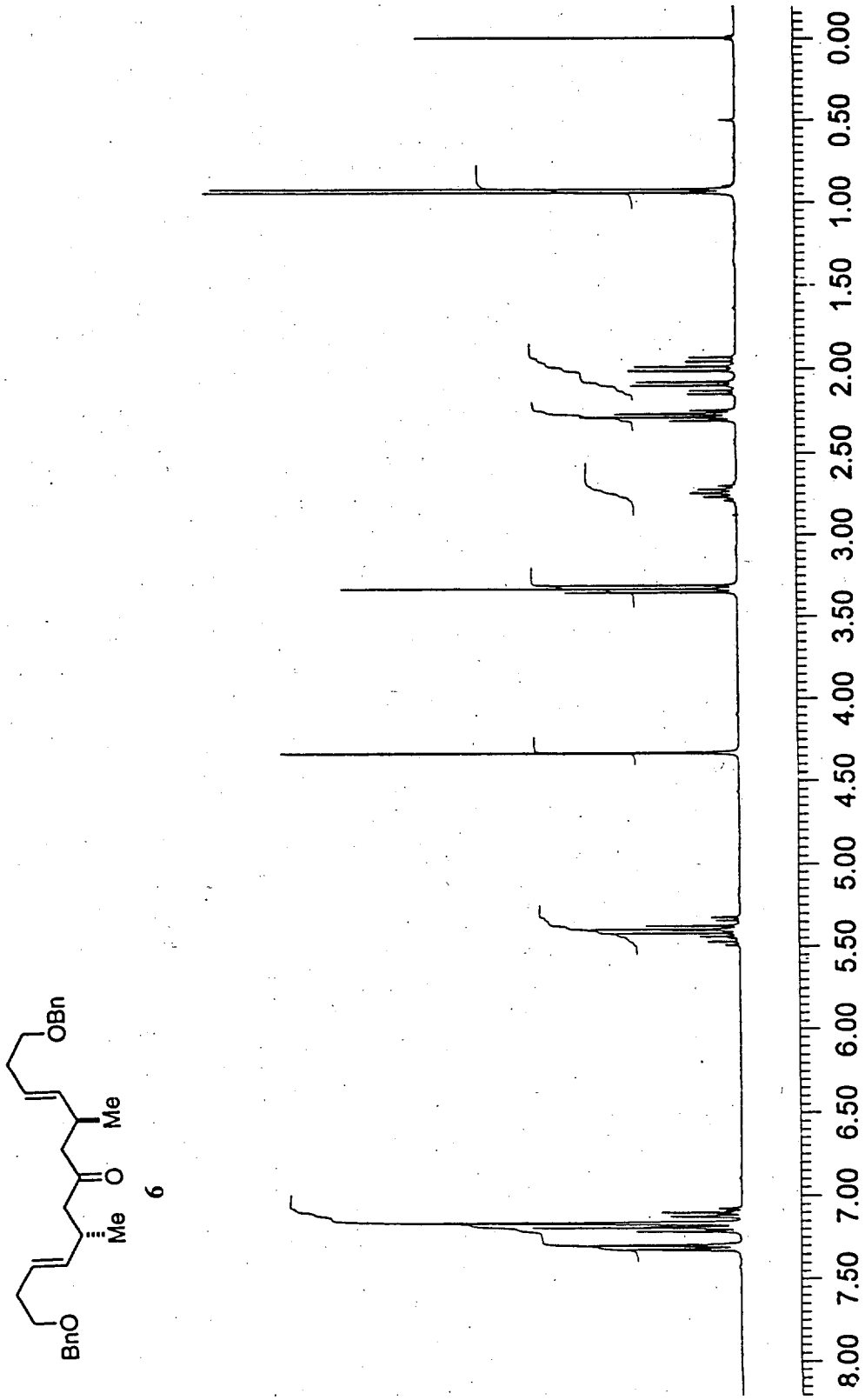


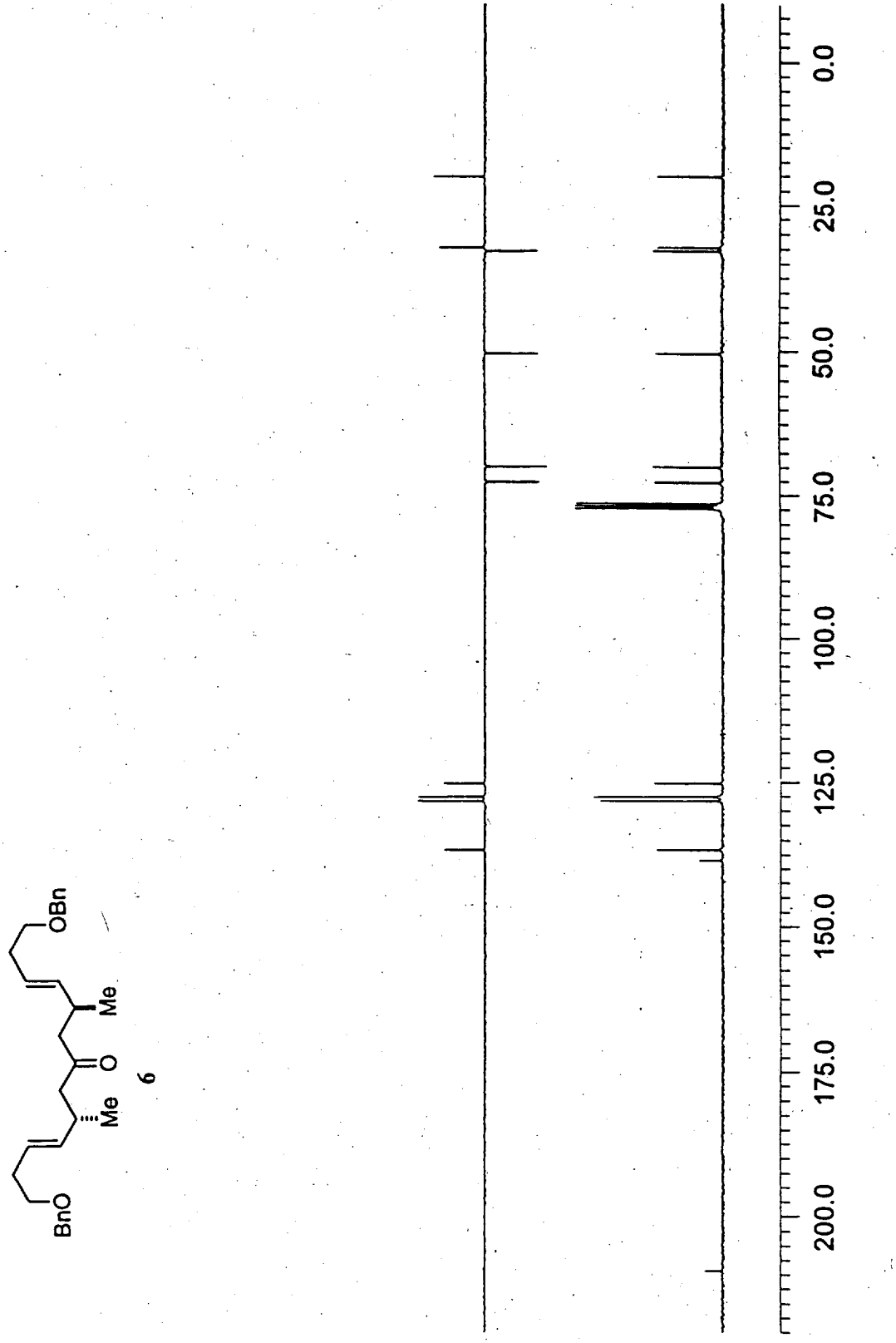
5

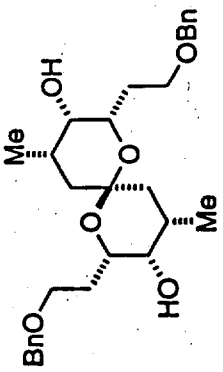




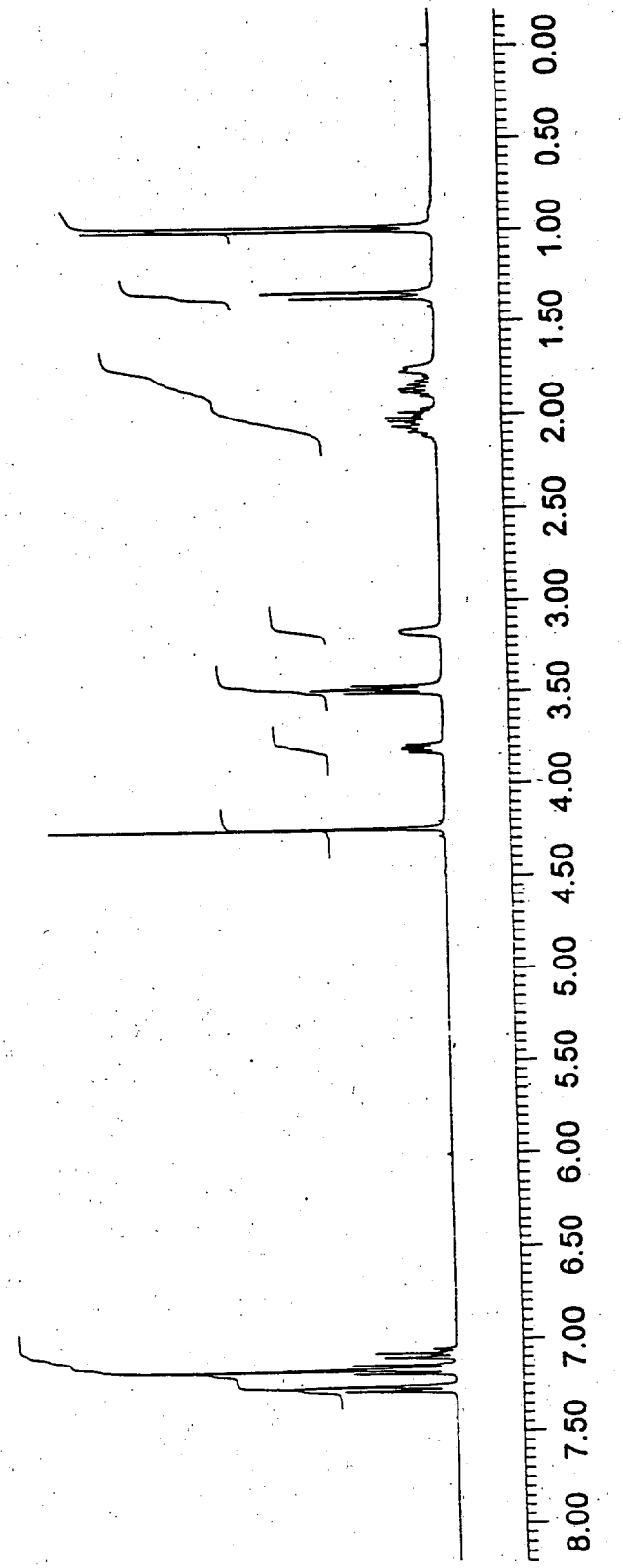


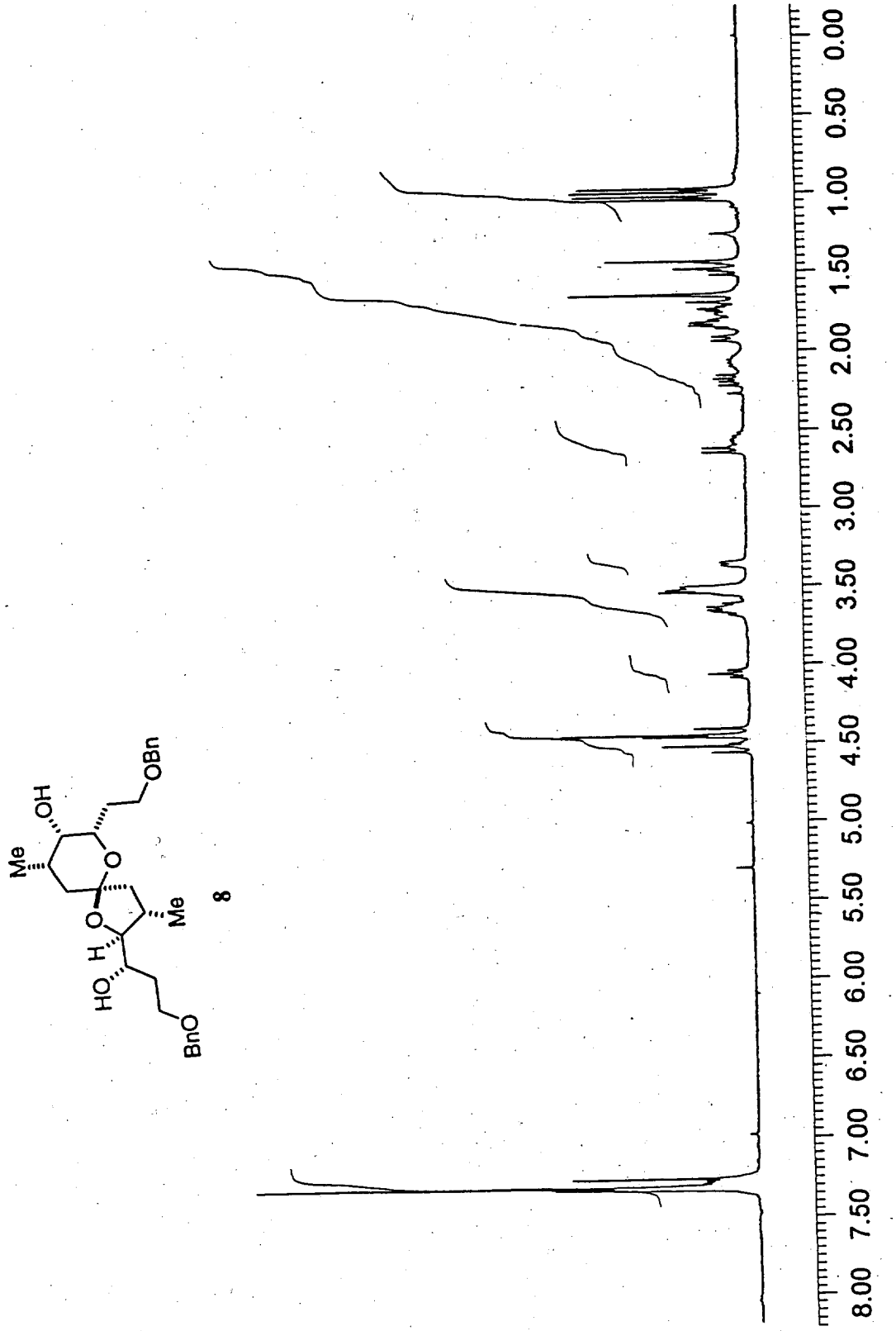


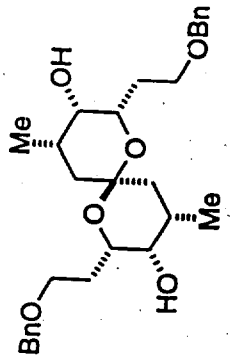




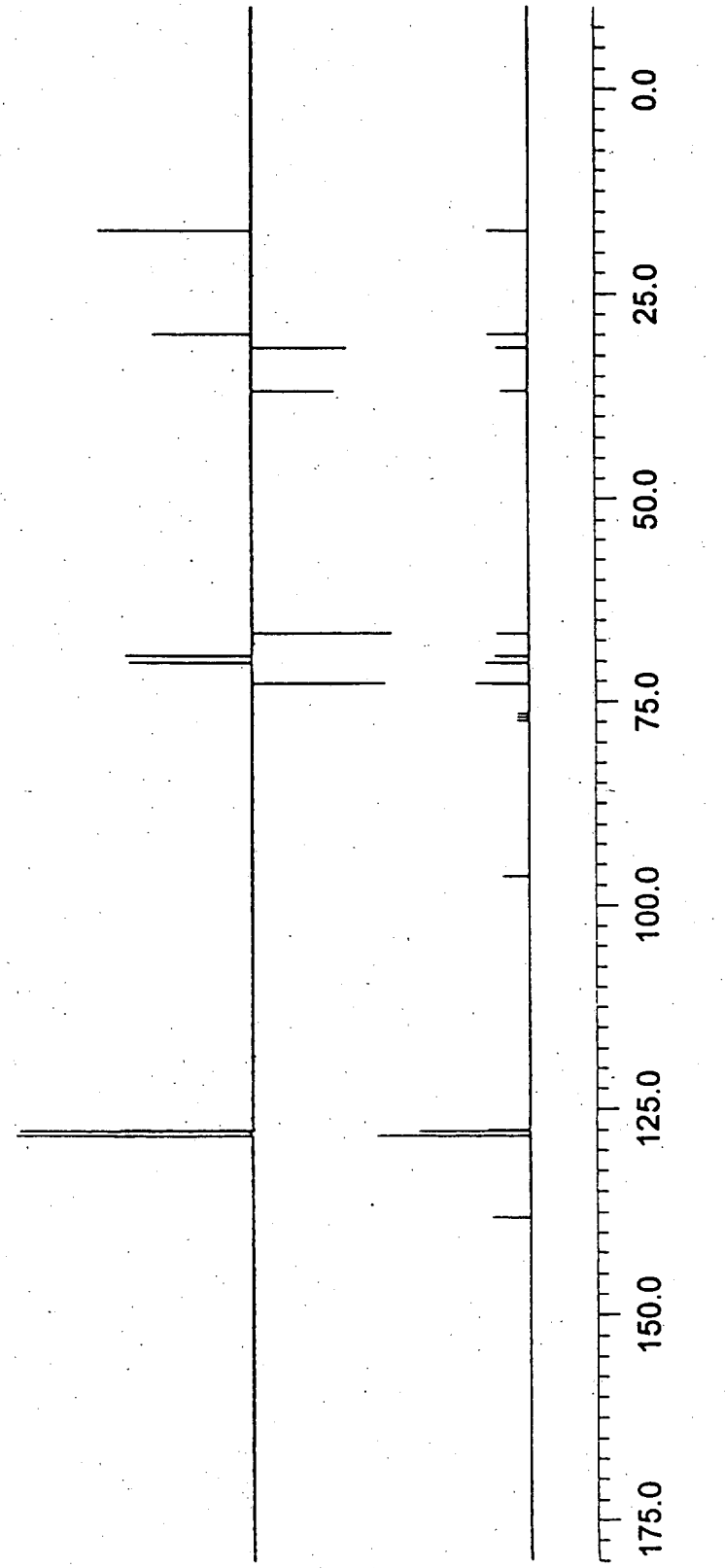
7

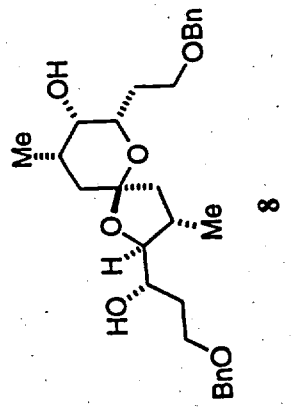




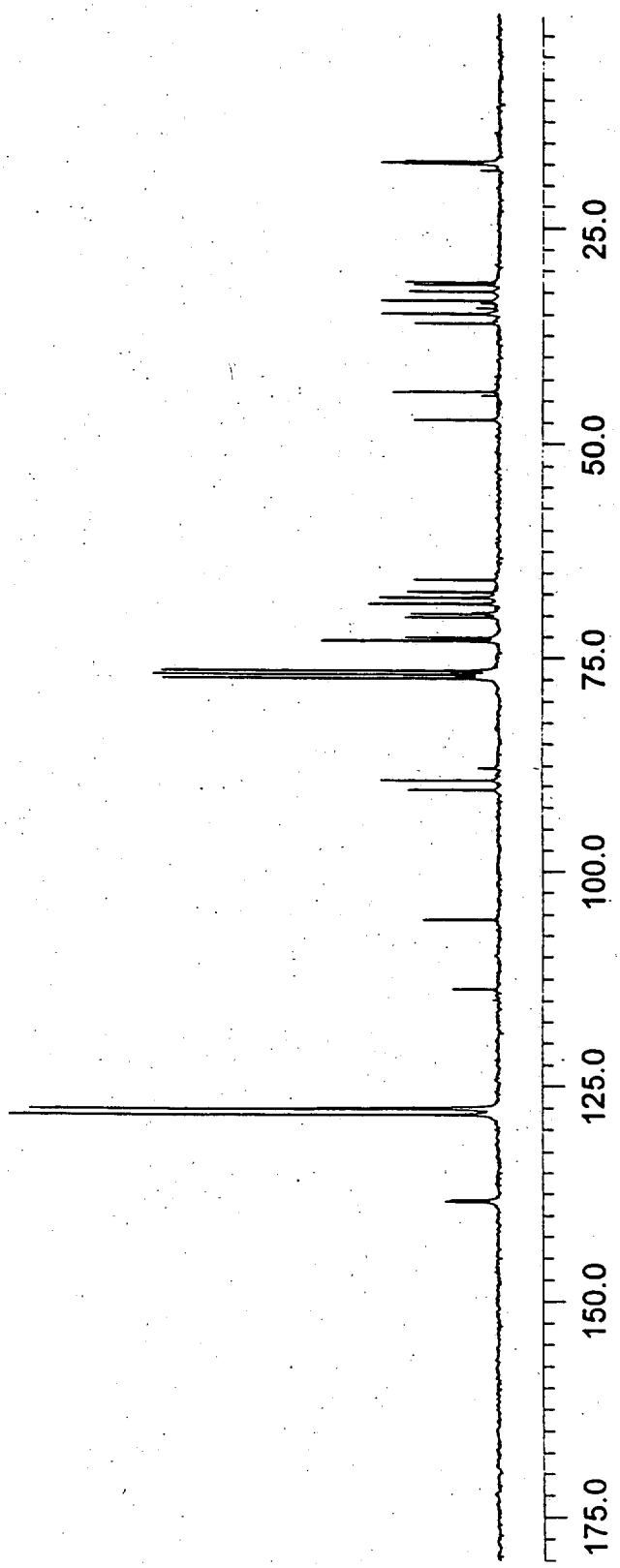


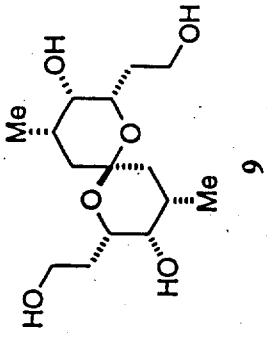
7





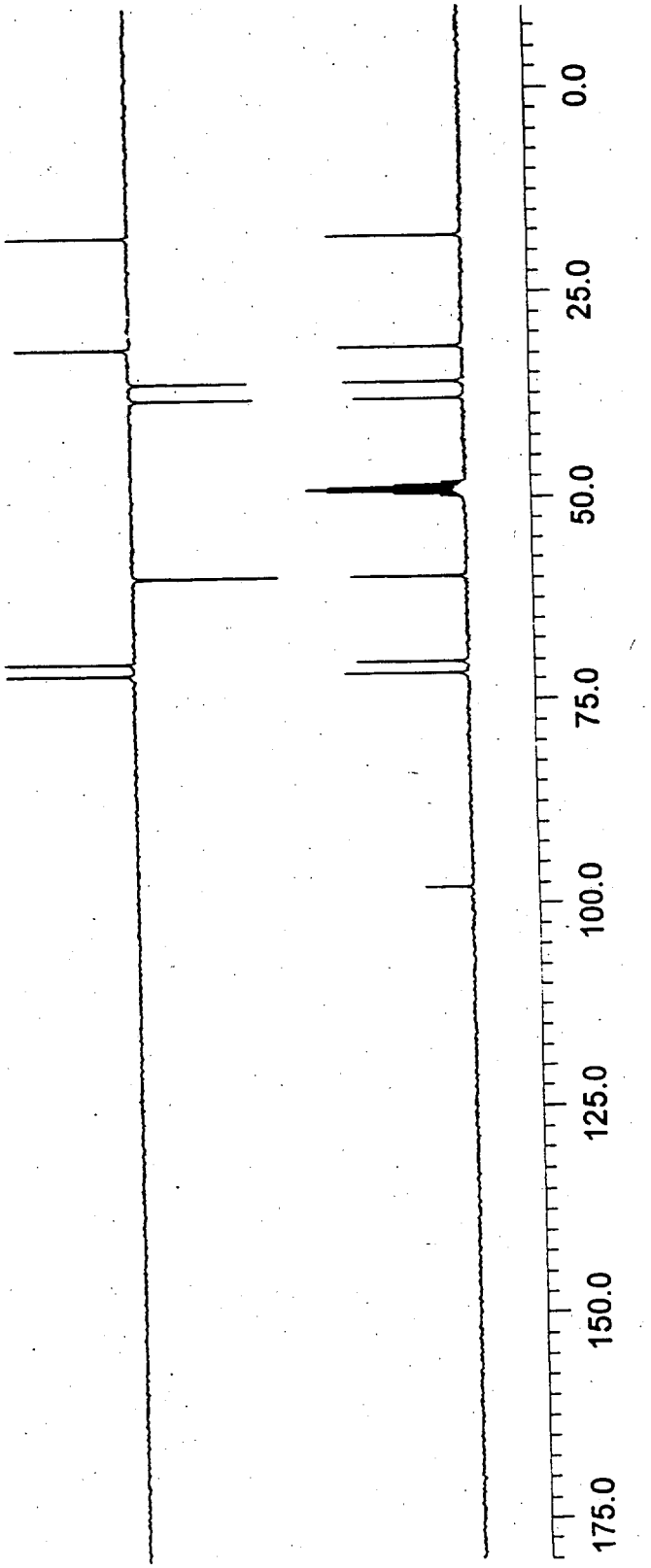
8

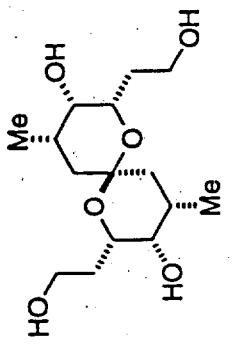




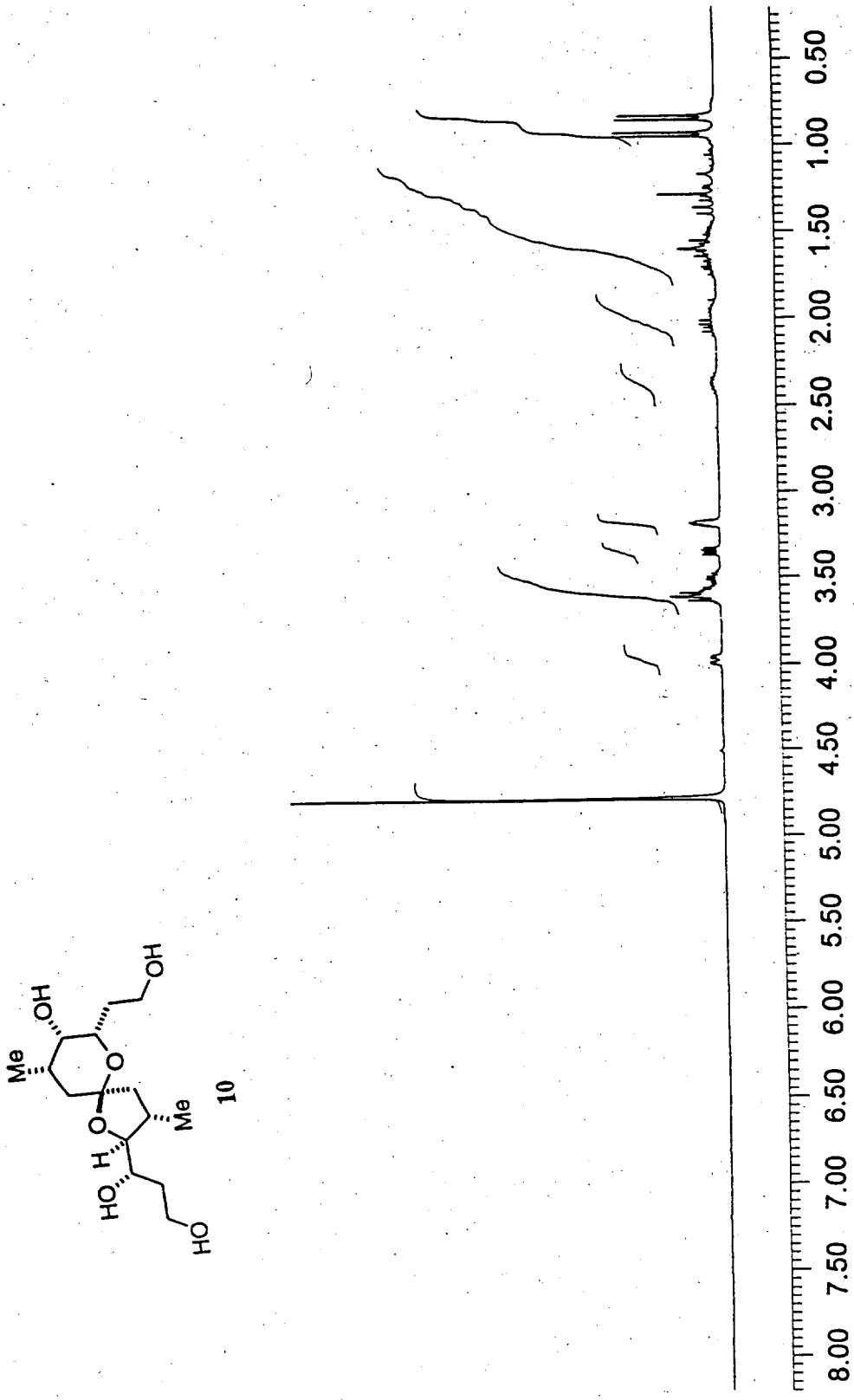
9

30

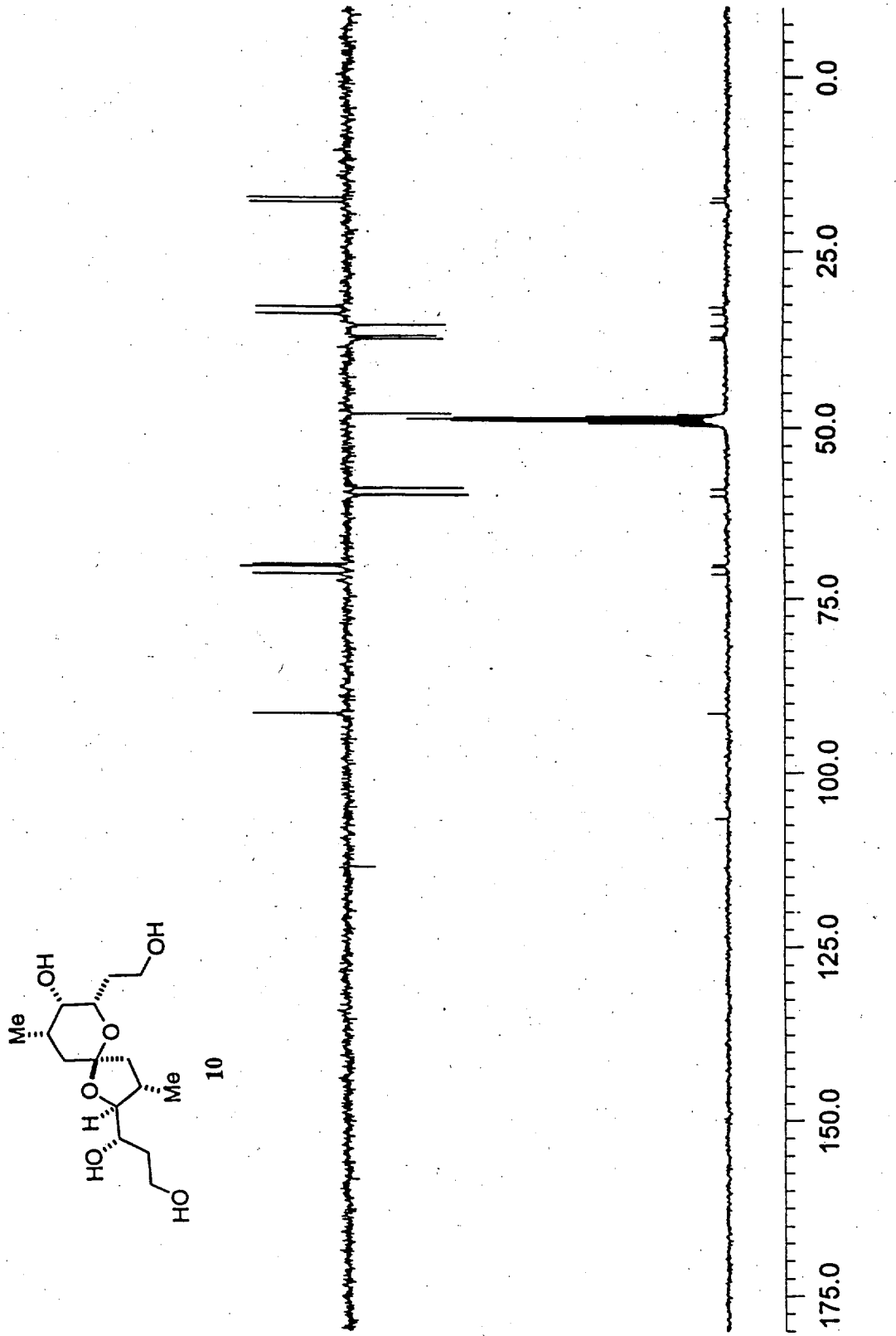


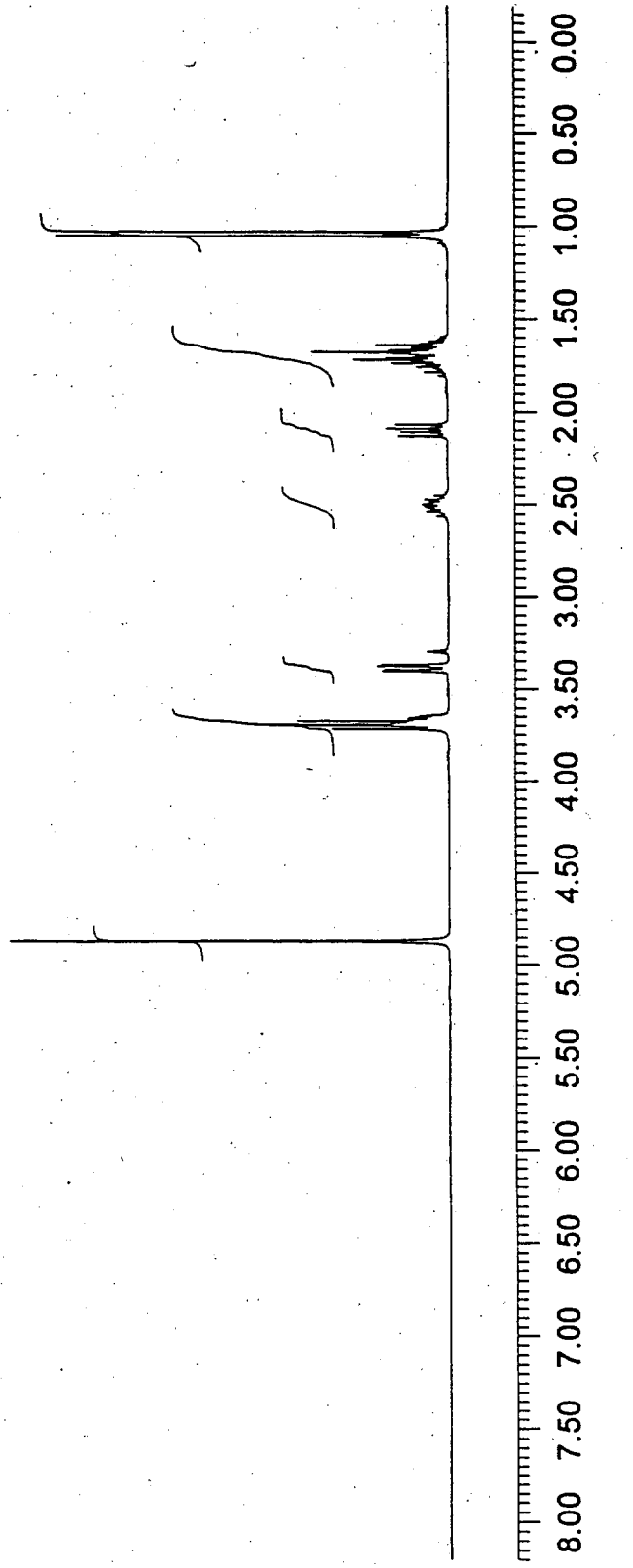


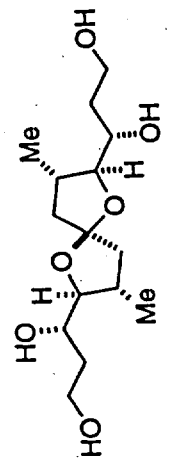
9



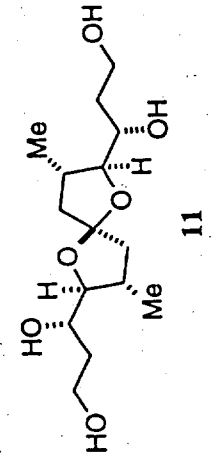
10



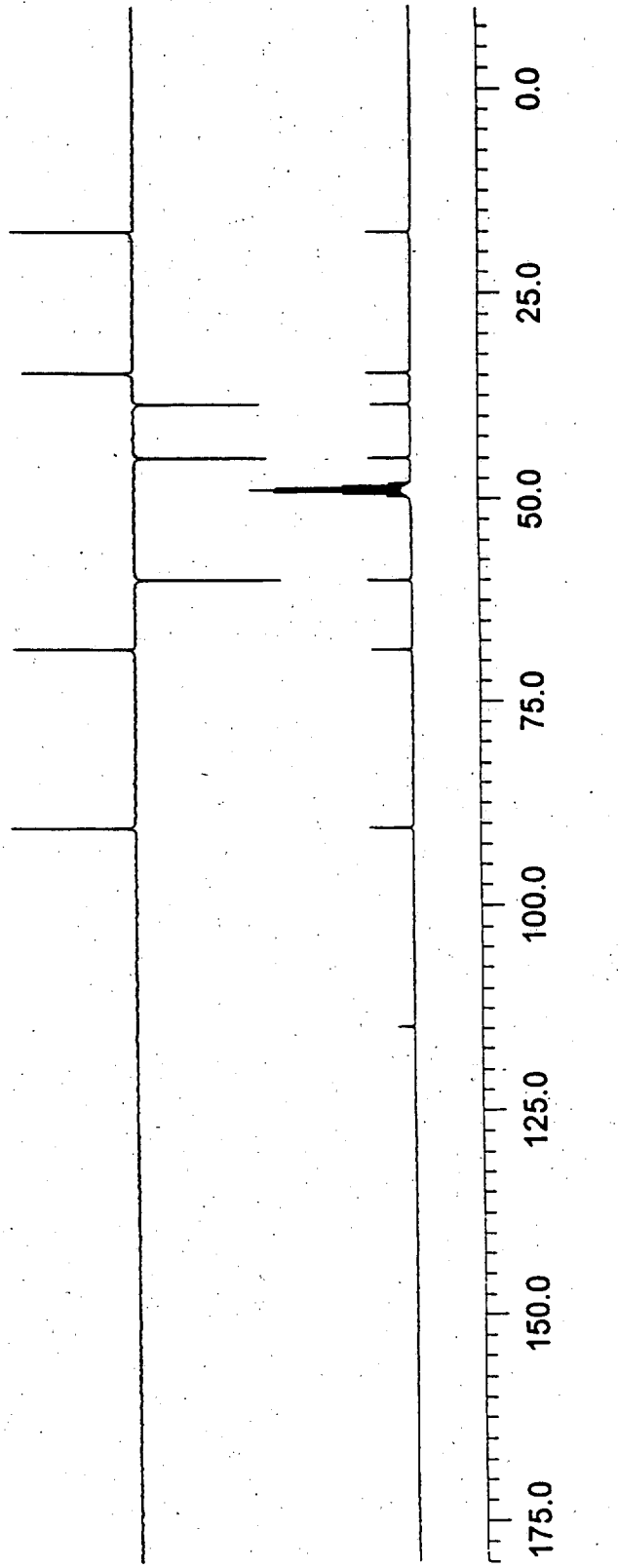


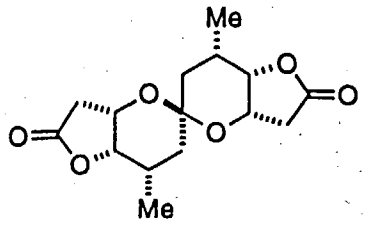


11

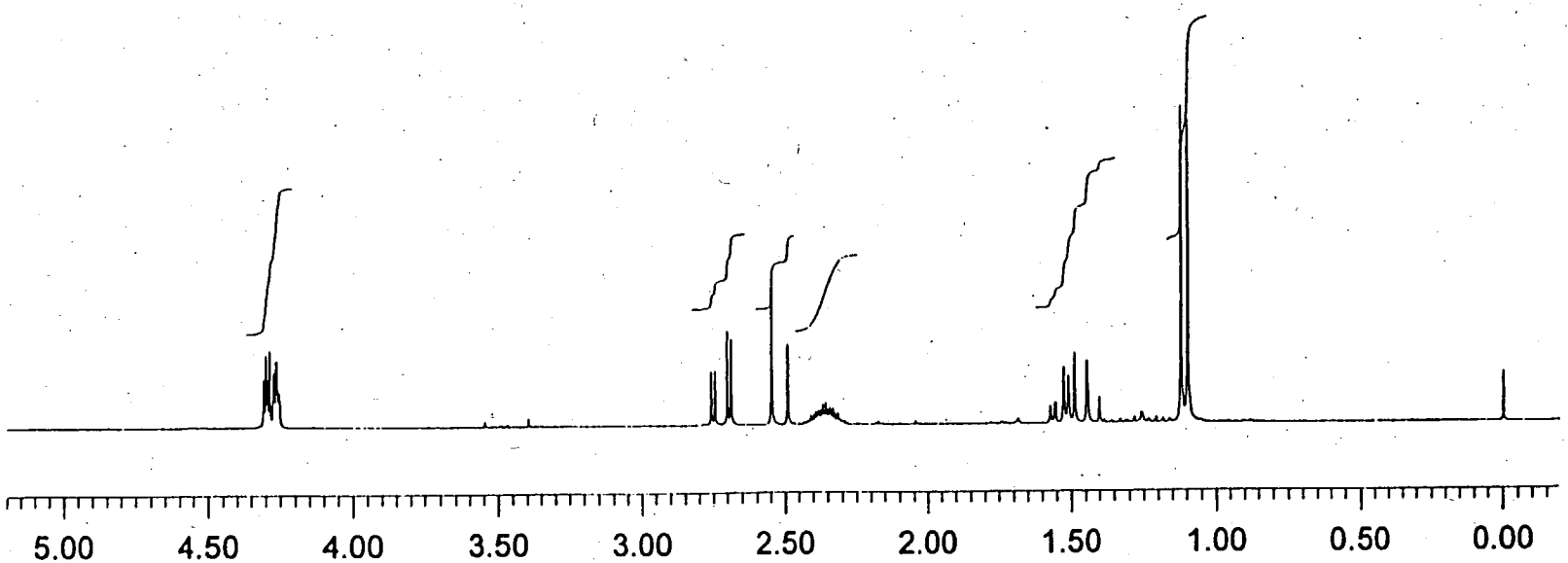


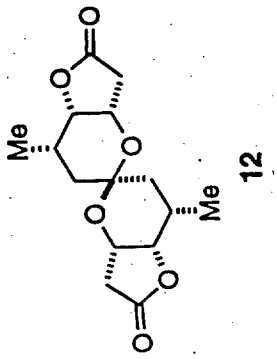
11



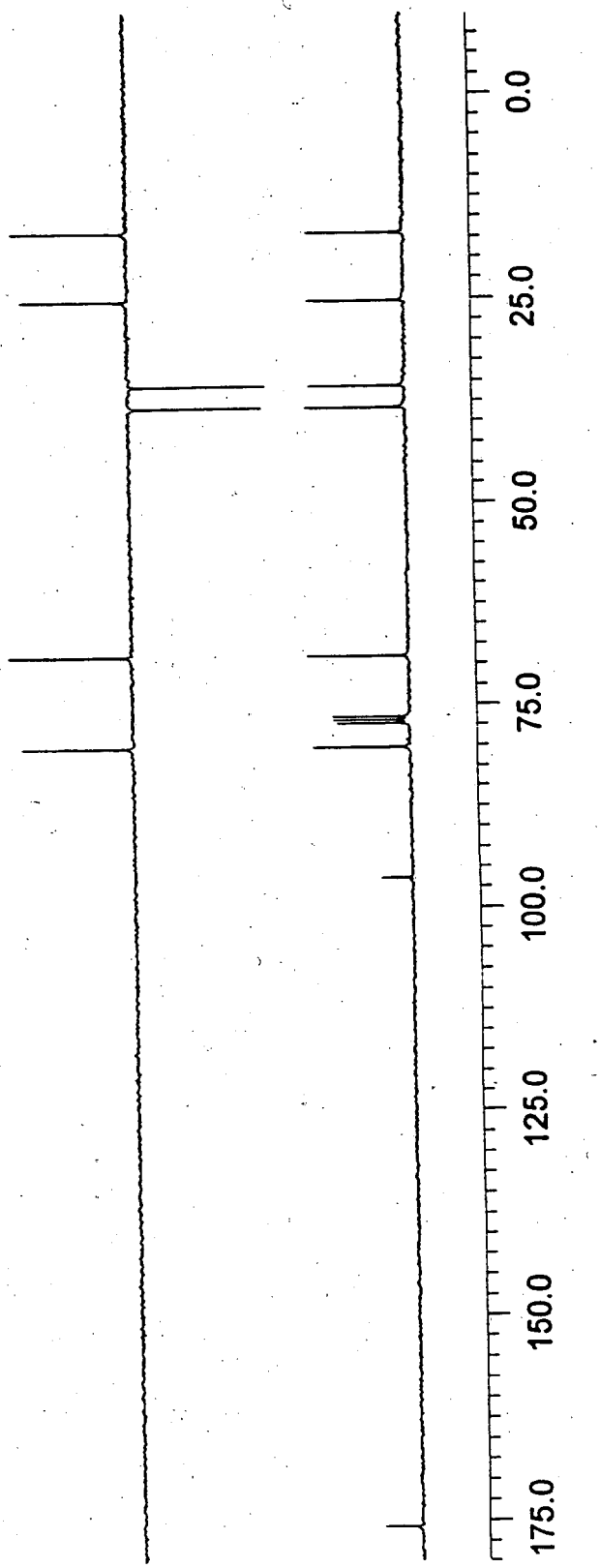


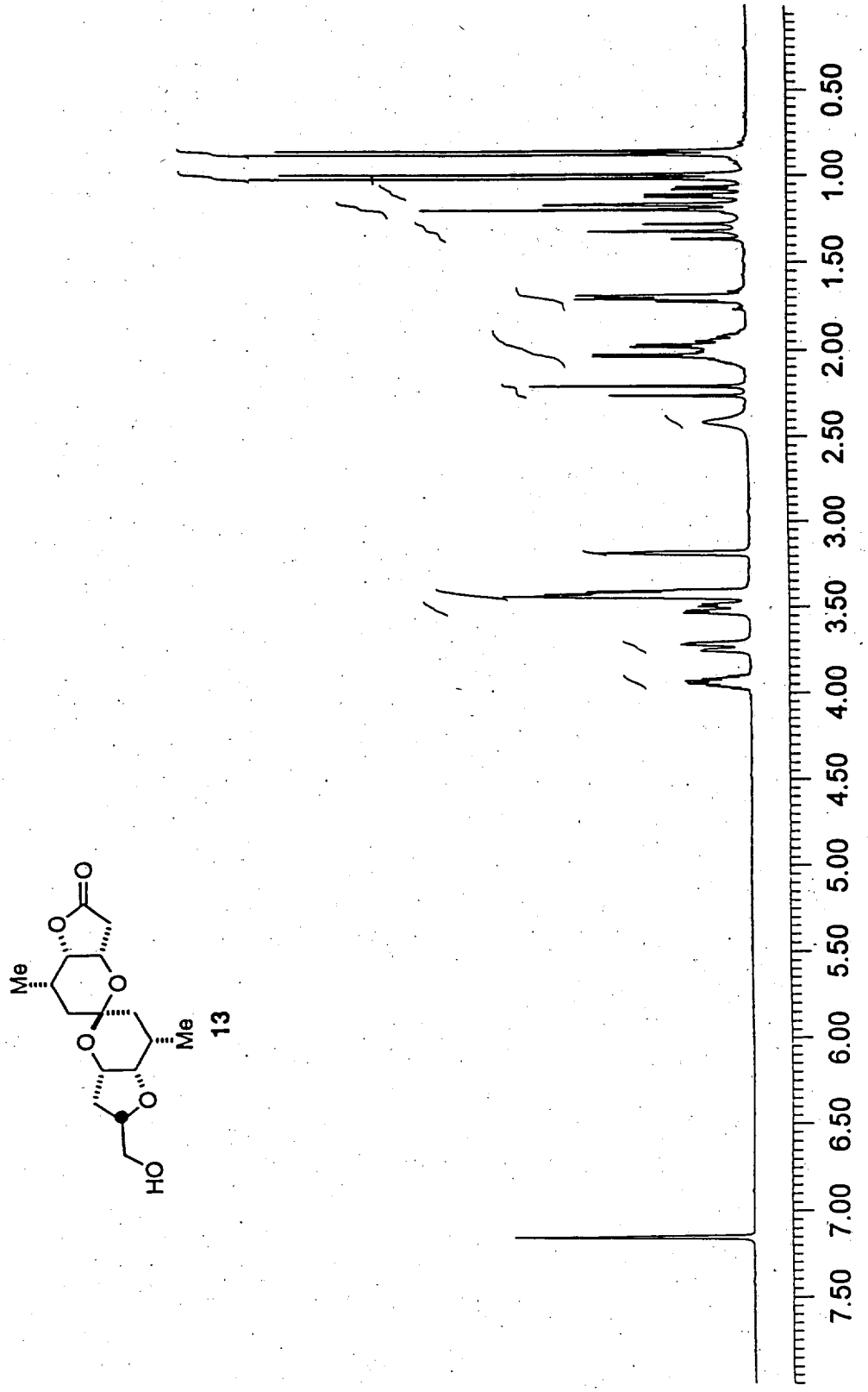
12



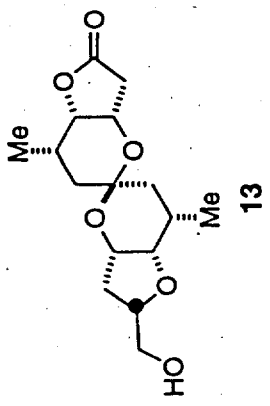


12





13



13