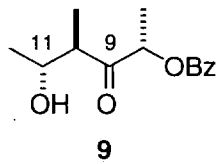
Total Synthesis of Elaiolide Using a Copper(I)-Promoted, Stille Cyclodimerisation Reaction.

Ian Paterson,* Henry-Georges Lombart and Charlotte M. N. Allerton
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

SUPPLEMENTARY MATERIAL

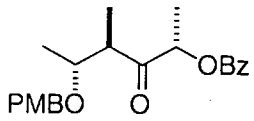
General. Melting points were taken on an Electrothermal melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer 241 polarimeter at the sodium D line (589 nm) and are reported as follows: $[\alpha]_D^{t^\circ C}$ (*c* in g/100 ml, solvent). Infra-red spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrophotometer. ^{1}H nuclear magnetic resonance spectra were recorded on a Bruker ARX500 (500 MHz) or on a Bruker DRX400 (400 MHz) spectrometer at ambient temperature using an internal deuterium lock. Chemical shifts are reported in parts per million (δ) downfield relative to tetramethylsilane (TMS, $\delta_{TMS} = 0$) and data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Elaiophylin numbering[1] is used for proton assignments of all intermediates. ^{13}C nuclear magnetic resonance spectra were recorded on a Bruker DRX400 (100 MHz) or on a Bruker DPX250 (63 MHz) spectrometer at ambient temperature using an internal deuterium lock with complete proton decoupling. Chemical shifts are reported in parts per million (δ) downfield relative to tetramethylsilane (TMS, $\delta_{TMS} = 0$). High and low resolution mass spectra were carried out by the EPSRC Mass Spectrometry Service Centre, Swansea, UK and by the Departmental Mass Spectrometry Service at the University Chemical Laboratories, Cambridge. Analytical thin-layer chromatography was carried out using Merck Kieselgel 60 F_{254} plates. Flash chromatography[2] was carried out on Merck Kieselgel 60 (230-400 mesh). All experiments were carried out under an argon atmosphere with anhydrous solvents. The following solvents and reagents were purified and dried according to recommended procedures: THF, Et_2O, CH_2Cl_2, MeOH, DMF, AcOH, Me_2NEt, Et_3N, imidazole and DDQ.[3] All other commercially obtained reagents were used as received.



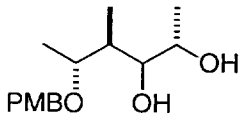
9

(2*S*, 4*R*, 5*R*)-2-benzoyloxy-5-hydroxy-4-methylhexan-3-one (9). To a stirring solution of dimethylethylamine (6.72 ml, 62.06 mmol) and dicyclohexylboron chloride[4] (12.40 ml, 58.18 mmol) in dry Et_2O (160 ml) at -10 °C was added a solution of (*S*)-2-benzoyloxypenta-3-one[5] ((*S*)-**8**) (8.00 g, 38.79 mmol) in dry Et_2O (60 ml) *via* cannula. The reaction mixture was stirred at -10 °C for 1 h and warmed to 0 °C for 1 h, before being cooled to -78 °C. Freshly distilled acetaldehyde (10.52 ml, 194.00 mmol) was then added *via* syringe, and the reaction mixture was stirred for 30 min and for a further 3 h while the temperature warmed to -20 °C. The reaction was quenched at 0 °C by addition of pH 7 buffer (400 ml) and extracted with Et_2O (3 x 500 ml). The combined organic layers were concentrated *in vacuo*. The crude oil was suspended in methanol (240 ml) and pH 7 buffer (240 ml), followed by addition of hydrogen peroxide (120 ml, 30% aq.) dropwise under cooling at 0 °C. The reaction mixture was stirred for 2 h, then poured into water (600 ml) and extracted with CH_2Cl_2 (3 x 700 ml). The combined organic layers were washed with $NaHCO_3$ solution (600 ml, sat. aq.) and brine (600 ml), dried

($MgSO_4$) and concentrated *in vacuo* to give a solid. The crude product was purified by flash column chromatography (5% Et_2O in hexane) to yield the aldol adduct **9** as a white solid (8.97 g, 95%). **TLC** R_f = 0.20 (25% EtOAc/hexane); **m.p.** 83-84 °C; $[\alpha]_D^{20}$ = +38.3 ° (*c* = 1.4, $CHCl_3$); **IR** ν_{max} (liquid film) 3530, 3007, 2984, 2938, 1716, 1602, 1585, 1452 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (2H, dd, *J* = 8.3, 1.3 Hz, ArH), 7.60 (1H, tt, *J* = 6.8, 1.5 Hz, ArH), 7.43 (2H, dd, *J* = 7.6, 7.6 Hz, ArH), 5.43 (1H, q, *J* = 7.1 Hz, C_8-H), 3.97 (1H, dq, *J* = 6.6, 6.3 Hz, C_{11}-H), 2.80 (1H, dq, *J* = 7.3, 7.3 Hz, C_{10}-H), 2.64 (1H, d, *J* = 5.5 Hz, C_{11}-OH), 1.55 (3H, d, *J* = 7.1 Hz, C_8-CH_3), 1.22 (3H, d, *J* = 7.3 Hz, C_{10}-CH_3), 1.20 (3H, d, *J* = 6.5 Hz, C_{11}-CH_3); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 211.6, 165.8, 133.3, 129.7, 129.3, 128.4, 74.5, 69.4, 49.9, 20.8, 15.7, 14.3; **HRMS** Exact mass calcd. for $C_{14}H_{19}O_4$ [$(M+H)^+$]: 251.1283; found 251.1283 (CI^+, NH_3).

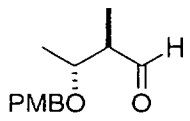


(2*S*, 4*R*, 5*R*)-2-benzoyloxy-5-(4-methoxybenzyloxy)-4-methylhexan-3-one. To a stirring solution of the aldol adduct **9** (8.67 g, 34.64 mmol) in Et_2O (500 ml) at 0 °C was added 4-methoxybenzyltrichloroacetimidate[6] (19.78 g, 69.28 mmol) in Et_2O (100 ml). Triflic acid (6 µl, 0.069 mmol, 0.2 mol%) was added cautiously to the reaction mixture and then stirring was continued at ambient temperature for 4 h. The reaction mixture was then carefully poured into $NaHCO_3$ solution (300 ml, aq. sat.). The aqueous layer was extracted with Et_2O (3 x 400 ml) and the combined organic extracts washed with brine (500 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow solid. The crude solid was triturated with cold hexane (50 ml), filtered and the filtrate concentrated *in vacuo*. The crude product was purified by flash column chromatography (5% EtOAc/hexane) to yield the PMB ether as a pale yellow oil (11.78 g, 92%). **TLC** R_f = 0.44 (25% EtOAc/hexane); $[\alpha]_D^{20}$ = -25.4 ° (*c* = 2.0, $CHCl_3$); **IR** ν_{max} (liquid film) 3014, 2976, 1716, 1613, 1586, 1513, 1450 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (2H, dd, *J* = 8.4, 1.2 Hz, ArH), 7.56 (1H, tt, *J* = 7.2, 1.2 Hz, ArH), 7.35 (2H, dd, *J* = 7.4, 7.4 Hz, ArH), 7.16 (2H, d, *J* = 8.5 Hz, PMB-H), 6.84 (2H, d, *J* = 8.6 Hz, PMB-H), 5.39 (1H, q, *J* = 7.1 Hz, C_8-H), 4.44 (1H, d, *J* = 10.8 Hz, PMB-CH_2), 4.27 (1H, d, *J* = 10.8 Hz, one of PMB-CH_2), 3.85-3.74 (1H, m, C_{11}-H), 3.78 (3H, s, PMB-OCH_3), 2.96 (1H, dq, *J* = 8.9, 7.1 Hz, C_{10}-H), 1.48 (3H, d, *J* = 7.0 Hz, C_8-CH_3), 1.20 (3H, d, *J* = 6.2 Hz, C_{11}-CH_3), 1.16 (3H, d, *J* = 7.1 Hz, C_{10}-CH_3); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 210.0, 165.8, 159.0, 133.1, 130.5, 129.7, 129.6, 129.3, 128.4, 113.5, 76.7, 75.0, 71.1, 55.2, 49.0, 17.0, 15.2, 13.7; **HRMS** Exact mass calcd. for $C_{22}H_{30}NO_5$ [$(M+NH_4)^+$]: 388.2124; found 388.2124 (CI^+, NH_3).



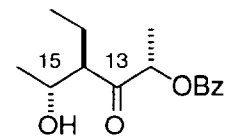
(2*S*, 3S, 4*S*, 5*R*)- and (2*S*, 3R, 4*S*, 5*R*)-5-(4-methoxybenzyloxy)-4-methylhexan-2,3-diol. To a stirring solution of sodium borohydride (1.97 g, 51.96 mmol) in methanol (200 ml) at 0 °C, was added (2*S*, 4*R*, 5*R*)-2-benzoyloxy-5-(4-methoxybenzylyloxy)-4-methylhexan-3-one (11.78 g, 31.8 mmol) in methanol (20 ml). The reaction was allowed to warm to room temperature and stirred for 30 min. The reaction was quenched at 0 °C by the addition of pH 7 buffer (200 ml), the methanol removed under reduced pressure and the resulting white oily suspension was extracted with Et_2O (3 x 300 ml). The combined organic layers were washed with brine (200 ml), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude keto-reduced product as a colourless oil

(11.61 g). The resulting oil was then taken up in dry methanol (220 ml) and stirred over anhydrous K_2CO_3 (19.20 g, 138.56 mmol) at ambient temperature for 4 h. The reaction was quenched with brine (200 ml) and extracted with Et_2O (3 x 200 ml). The combined organic extracts were washed with brine (200 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10→40% EtOAc/hexane) to afford the diol as a 9:1 mixture of diastereoismers (determined by 400 MHz ^1H NMR integration) (8.02 g, 95%). **Major diastereomer**: **TLC** R_f = 0.12 (25% EtOAc/hexane); **IR** ν_{max} (liquid film) 3442, 3018, 2976, 1616, 1586, 1514, 1450 cm^{-1}; **^1H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, d, J = 8.5 Hz, PMB-H), 6.87 (2H, d, J = 8.6 Hz, PMB-H), 4.57 (1H, d, J = 10.9 Hz, one of PMB-CH_2), 4.37 (1H, d, J = 10.9 Hz, one of PMB-CH_2), 3.80-3.77 (1H, m, C_{11}-H), 3.79 (4H, s, C_9-OH and PMB-OCH_3), 3.67 (1H, dq, J = 9.2, 6.3 Hz, C_8-H), 3.55 (1H, dd, J = 8.2, 2.6 Hz, C_9-H), 2.97 (1H, d, J = 5.8 Hz, C_8-OH), 1.75-1.70 (1H, m, C_{10}-H), 1.22 (3H, d, J = 6.1 Hz, C_{11}-CH_3), 1.14 (3H, d, J = 6.4 Hz, C_8-CH_3), 0.82 (3H, d, J = 7.0 Hz, C_{10}-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.2, 129.7, 129.4, 113.6, 78.5, 77.8, 70.3, 68.2, 55.2, 40.6, 16.4, 16.1, 12.1; **HRMS** Exact mass calcd. for $C_{15}H_{28}NO_4$ [$(M+NH_4)^+$]: 286.2018; found 286.2018 (CI^+, NH_3).



7

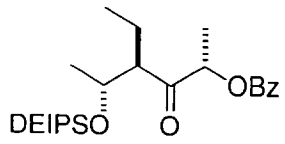
(2*R*, 3*R*)-3-(4-methoxybenzyloxy)-2-methyl-1-butanal (7). To a stirring solution of the diols (2*S*, 3S, 4*S*, 5*R*)- and (2*S*, 3R, 4*S*, 5*R*)-5-(4-methoxybenzyloxy)-4-methylhexan-2,3-diol (8.02 g, 29.89 mmol) in methanol - water (2:1, 266 ml, c = 0.1 M) was added sodium periodate (38.70 g, 179.31 mmol) and the reaction was stirred for 1 h at ambient temperature. The mixture was diluted with water (130 ml) and extracted with CH_2Cl_2 (3 x 150 ml). The combined organic layers were washed with brine (200 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10% Et_2O/hexane) to yield the aldehyde **7** as a colourless oil (6.39 g, 96%, 84% over four steps from **9**). **TLC** R_f = 0.41 (25% EtOAc/hexane); $[\alpha]_D^{20}$ = -49.1 ° (c = 2.0, $CHCl_3$); **IR** ν_{max} (liquid film) 3020, 2977, 2937, 2874, 2838, 1723, 1613, 1586, 1514, 1465 cm^{-1}; **^1H NMR** (500 MHz, $CDCl_3$) δ 9.70 (1H, d, J = 2.4 Hz, C_9-H), 7.25 (2H, d, J = 8.5 Hz, PMB-H), 6.87 (2H, d, J = 8.5 Hz, PMB-H), 4.56 (1H, d, J = 11.3 Hz, one of PMB-CH_2), 4.38 (1H, d, J = 11.3 Hz, one of PMB-CH_2), 3.81 (3H, s, PMB-OCH_3), 3.80-3.75 (1H, m, C_{11}-H), 2.54 (1H, dq, J = 7.1, 2.3, C_{10}-H), 1.24 (3H, d, J = 6.2 Hz, C_{11}-CH_3), 1.08 (3H, d, J = 7.1 Hz, C_{10}-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.5, 159.1, 130.1, 129.2, 113.7, 74.8, 70.2, 55.2, 51.6, 16.8, 10.0; **HRMS** Exact mass calcd. for $C_{13}H_{22}NO_4$ [$(M+NH_4)^+$]: 240.1600; found 240.1600 (CI^+, NH_3).



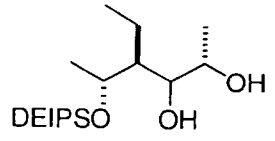
11

(2*S*, 4*R*, 5*R*)-2-benzoyloxy-4-ethyl-5-hydroxy-hexan-3-one (11). To a stirring solution of dimethylethylamine (3.15 ml, 29.12 mmol) and dicyclohexylboron chloride[4] (5.80 ml, 27.30 mmol) in dry Et_2O (75 ml) at -10 °C, was added a solution of ketone (*S*)-2-benzoyloxyhexa-3-one[5] ((*S*)-**10**) (4.00 g, 18.20 mmol) in dry Et_2O (28 ml) *via* cannula. The reaction mixture was stirred at -10 °C for 1 h and warmed to 0 °C for 1 h, before being cooled to -78 °C. Freshly distilled acetaldehyde (4.95 ml, 91.00 mmol) was then added *via* syringe and the reaction mixture was stirred for 30 min and for a further 3 h while the temperature warmed to -20 °C. The

reaction was quenched at 0 °C by addition of pH 7 buffer (240 ml) and extracted with Et_2O (3 x 300 ml). The combined organic layers were concentrated *in vacuo*. The crude oil was suspended in methanol (140 ml) and pH 7 buffer (140 ml), followed by addition of hydrogen peroxide (70 ml, 30% aq.) dropwise under cooling at 0 °C. The reaction mixture was stirred for 2 h, then poured into water (350 ml) and extracted with CH_2Cl_2 (4 x 400 ml). The combined organic layers were washed with $NaHCO_3$ solution (400 ml, sat. aq.) and brine (400 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a solid. The crude product was purified by recrystallisation (Et_2O - hexane) to yield the aldol adduct **11** as a white solid (4.56 g, 95%). **TLC** R_f = 0.27 (25% EtOAc/hexane); **m.p.** 70-71 °C; $[\alpha]_D^{20}$ = +60.8 ° (*c* = 2.0, $CHCl_3$); **IR** ν_{max} (liquid film) 3527, 3024, 2971, 1715, 1603, 1452 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.09 (2H, dd, *J* = 7.8, 1.1 Hz, ArH), 7.60 (1H, tt, *J* = 7.4, 1.0 Hz, ArH), 7.48 (2H, dd, *J* = 7.7, 7.7 Hz, ArH), 5.48 (1H, q, *J* = 7.1 Hz, C_{12}-H), 4.04 (1H, dq, *J* = 6.6, 6.5 Hz, C_{15}-H), 2.74 (1H, dt, *J* = 6.4, 6.4 Hz, C_{14}-H), 2.42 (1H, d, *J* = 7.0 Hz, C_{15}-OH), 1.86-1.71 (2H, m, C_{14}-CH_2CH_3), 1.58 (3H, d, *J* = 7.1 Hz, C_{12}-CH_3), 1.24 (3H, d, *J* = 6.4 Hz, C_{15}-CH_3), 1.02 (3H, t, *J* = 7.5 Hz, C_{14}-CH_2CH_3); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 211.4, 165.6, 133.2, 129.6, 129.4, 128.3, 75.3, 67.8, 55.8, 22.2, 21.4, 15.6, 11.4; **HRMS** Exact mass calcd. for $C_{15}H_{20}O_4$ [M^+]: 264.1362; found 264.1365 (EI).

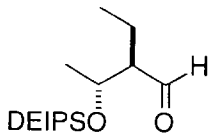


(2*S*, 4*R*, 5*R*)-2-benzoyloxy-5-(diethyl-*iso*-propylsilyloxy)-4-ethylhexan-3-one. To a mixture of the aldol adduct **11** (4.56 g, 17.26 mmol) and imidazole (2.82 g, 69.02 mmol) in DMF (16 ml) at ambient temperature was added diethyl-*iso*-propylsilyl chloride[7] (6.34 ml, 34.51 mmol) and the resulting mixture stirred for 24 h. The mixture was diluted with Et_2O (30 ml) and washed with $NaHCO_3$ solution (50 ml, sat. aq.). The aqueous layer was re-extracted with Et_2O (3 x 50 ml) and the combined organic extracts washed with brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (5% Et_2O/hexane) to yield the DEIPS protected compound as a colourless oil (6.64 g, 98%). **TLC** R_f = 0.71 (20% EtOAc/hexane); $[\alpha]_D^{20}$ = -10.1 ° (*c* = 3.0, $CHCl_3$); **IR** ν_{max} (liquid film) 2957, 2877, 1722, 1603, 1452 cm^{-1}; **^{1}H NMR** (500MHz, $CDCl_3$) δ 8.09 (2H, dd, *J* = 7.8, 1.1 Hz, ArH), 7.59 (1H, tt, *J* = 7.4, 1.0 Hz, ArH), 7.47 (2H, dd, *J* = 7.7, 7.7 Hz, ArH), 5.48 (1H, q, *J* = 6.9 Hz, C_{12}-H), 4.07 (1H, dq, *J* = 9.2, 6.1 Hz, C_{15}-H), 2.86 (1H, ddd, *J* = 8.7, 8.7, 3.7 Hz, C_{14}-H), 1.72-1.63 (1H, m, one of C_{14}-CH_2CH_3), 1.61-1.56 (1H, m, one of C_{14}-CH_2CH_3), 1.52 (3H, d, *J* = 6.9 Hz, C_{12}-CH_3), 1.19 (3H, d, *J* = 6.1 Hz, C_{15}-CH_3), 0.97-0.93 (15H, m, C_{14}-CH_2CH_3, $SiCH_2CH_3$ and $SiCH(CH_3)_2$), 0.89-0.83 (1H, m, $SiCH(CH_3)_2$), 0.64-0.54 (4H, m, $SiCH_2CH_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 209.3, 165.5, 133.0, 129.8, 129.7, 128.3, 75.8, 69.8, 57.1, 21.6, 21.5, 17.2, 17.2, 15.2, 12.9, 11.6, 6.9, 6.9, 3.8, 3.7; **HRMS** Exact mass calcd. for $C_{22}H_{37}O_4Si$ [$(M+H)^+$]: 393.2461; found 393.2461 (CI^+, NH_3).



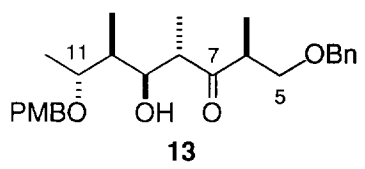
(2*S*, 3*S*, 4*S*, 5*R*)- and (2*S*, 3R, 4*S*, 5*R*)-5-(diethyl-*iso*-propylsilyloxy)-4-ethylhexan-2,3-diol. To a stirring solution of sodium borohydride (987 mg, 25.89 mmol) in methanol (100 ml) at 0 °C, was added (2*S*, 4*R*, 5*R*)-2-benzoyloxy-5-(diethyl-*iso*-propylsilyloxy)-4-ethylhexan-3-one (6.77 g, 17.26 mmol) in methanol

(10 ml). The reaction was allowed to warm to room temperature and stirred for 30 min. The reaction was quenched at 0 °C by the addition of pH 7 buffer (100 ml), the methanol removed under reduced pressure and the resulting white oily suspension was extracted with Et_2O (3 x 150 ml). The combined organic layers were washed with brine (100 ml), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude keto-reduced product as a colourless oil (6.71 g). The resulting oil was then taken up in dry methanol (110 ml) and stirred over anhydrous K_2CO_3 (9.60 g, 69.04 mmol) at ambient temperature for 4 h. The reaction was quenched with brine (100 ml) and extracted with Et_2O (3 x 150 ml). The combined organic extracts were washed with brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20% EtOAc/hexane) to afford the diol as a 7.6:1 mixture of diastereoisomers (determined by 500 MHz ^1H NMR integration) (4.50 g, 90%). **Major diastereomer**: **TLC** R_f = 0.22 (20% EtOAc/hexane); **IR** ν_{max} (liquid film) 3417, 2958, 2877, 1462, 1386 cm^{-1}; **^1H NMR** (500MHz, $CDCl_3$) δ 4.14 (1H, dq, J = 6.3, 4.2 Hz, C_{15}-H), 3.82 (1H, dq, J = 9.1, 6.1 Hz, C_{12}-H), 3.68 (1H, dd, J = 5.3, 3.7 Hz, C_{13}-H), 3.31 (1H, d, J = 3.5 Hz, C_{13}-OH), 2.97 (1H, d, J = 6.1 Hz, C_{12}-OH), 1.49-1.40 (3H, m, C_{14}-H and C_{14}-CH_2CH_3), 1.32 (3H, d, J = 6.4 Hz, C_{12}-CH_3), 1.21 (3H, d, J = 6.2 Hz, C_{15}-CH_3), 1.03-0.99 (12H, m, $SiCH_2CH_3$ and $SiCH(CH_3)_2$), 0.97-0.95 (1H, m, $SiCH(CH_3)_2$), 0.92 (3H, t, J = 7.2 Hz, C_{14}-CH_2CH_3), 0.71-0.66 (4H, m, $SiCH_2CH_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 76.2, 69.4, 67.8, 48.8, 22.0, 20.2, 17.7, 17.0, 17.0, 12.8, 12.0, 6.8, 6.8, 3.8, 3.6; **HRMS** Exact mass calcd. for $C_{15}H_{35}O_3Si$ [(M+H)$^+$]: 291.2355; found 291.2355 (CI^+, NH_3).



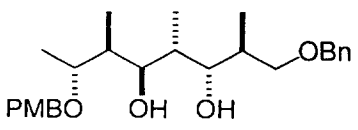
5

(2*R*, 3*R*)-3-(diethyl-*iso*-propylsilyloxy)-2-ethyl-1-butanal (5). To a stirring solution of the diols (2*S*, 3S, 4*S*, 5*R*)- and (2*S*, 3R, 4*S*, 5*R*)-5-(diethyl-*iso*-propylsilyloxy)-4-ethylhexan-2,3-diol (1.14 g, 3.92 mmol) in methanol - water (2:1, 196 ml, c = 0.02 M) was added sodium periodate (1.70 g, 7.84 mmol) and the reaction was stirred for 2 h at ambient temperature. The mixture was diluted with water (50 ml) and extracted with CH_2Cl_2 (3 x 60 ml). The combined organic layers were washed with brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10% Et_2O/hexane) to yield the aldehyde **5** as a colourless oil (0.93 g, 97%, 86% over four steps from **11**). **TLC** R_f = 0.75 (20% EtOAc/hexane); $[\alpha]_D^{20}$ = -18.6 ° (c = 1.0, $CHCl_3$); **IR** ν_{max} (liquid film) 2961, 2877, 1719, 1604, 1462, 1381 cm^{-1}; **^1H NMR** (500MHz, $CDCl_3$) δ 9.71 (1H, d, J = 3.7 Hz, C_{13}-H), 4.14 (1H, dq, J = 6.2, 5.2 Hz, C_{15}-H), 2.13 (1H, dt, J = 13.2, 4.7 Hz, C_{14}-H), 1.74 (1H, ddq, J = 13.1, 7.4, 5.0 Hz, one of C_{14}-CH_2CH_3), 1.57 (1H, ddq, J = 13.1, 7.4, 5.0 Hz, one of C_{14}-CH_2CH_3), 1.22 (3H, d, J = 6.3 Hz, C_{15}-CH_3), 0.99-0.96 (12H, m, $SiCH_2CH_3$ and $SiCH(CH_3)_2$), 0.94-0.93 (1H, m, Si-$CH(CH_3)_2$), 0.92 (3H, t, J = 7.5 Hz, C_{14}-CH_2CH_3), 0.65-0.59 (4H, m, $SiCH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 205.4, 68.8, 61.2, 22.2, 19.2, 17.2, 17.2, 13.0, 11.9, 7.0, 7.0, 4.0, 3.8; **HRMS** Exact mass calcd. for $C_{13}H_{29}O_2Si$ [(M+H)$^+$]: 245.1937; found 245.1937 (CI^+, NH_3).



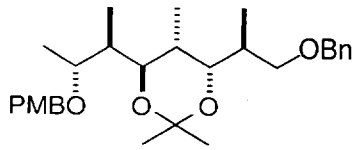
13

(2*S*, 4*S*, 5*S*, 6*S*, 7*R*)-1-benzyloxy-5-hydroxy-7-(4-methoxybenzyloxy)-2,4,6-trimethyloctan-3-one (13). To a stirring solution of triethylamine (4.81 ml, 35.50 mmol) and dicyclohexylboron chloride[4] (6.91 ml, 31.62 mmol) in dry Et_2O (36 ml) at -10 °C was added a solution of (*S*)-1-benzyloxy-2-methylpenta-3-one[8] ((*S*)-**8**) (6.52 g, 31.62 mmol, 1.1 eq. with respect to aldehyde) in dry Et_2O (34 ml) *via* cannula. The reaction mixture was stirred at -10 °C for 1 h and warmed to 0 °C for 1 h, before being cooled to -78 °C. Freshly synthesised aldehyde **7** (6.39 g, 28.75 mmol) in dry Et_2O (43 ml) was then added *via* cannula and the reaction mixture was stirred for 1 h and for a further 4 h while the temperature warmed to -20 °C, before being left to stand at - 20 °C in the freezer for 14 h. The reaction was quenched at 0 °C by addition of pH 7 buffer (40 ml) and extracted with Et_2O (3 x 100 ml). The combined organic layers were concentrated *in vacuo*. The crude oil was suspended in methanol (40 ml) and pH 7 buffer (40 ml), followed by addition of hydrogen peroxide (20 ml, 30% aq.) dropwise under cooling at 0 °C. The reaction mixture was stirred for 2 h, then poured into water (400 ml) and extracted with CH_2Cl_2 (4 x 400 ml). The combined organic layers were washed with $NaHCO_3$ solution (300 ml, sat. aq.) and brine (300 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10→15% EtOAc/hexane) to yield the aldol adduct **13** as a colourless oil (11.77 g, 96%). **TLC** R_f = 0.22 (20% EtOAc/hexane); $[\alpha]_D^{20}$ = +6.6 ° (*c* = 2.0, $CHCl_3$); **IR** ν_{max} (liquid film) 3477, 3415, 2976, 2877, 1708, 1612, 1513, 1455, 1249 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 -7.26 (5H, m, ArH), 7.23 (2H, d, *J* = 8.6 Hz, PMB-H), 6.87 (2H, d, *J* = 8.6 Hz, PMB-H), 4.56 (1H, d, *J* = 11.2 Hz, one of PMB-CH_2), 4.49 and 4.47 (2H, ABq, *J* = 12 Hz, Bn-CH_2), 4.28 (1H, d, *J* = 11.2 Hz, one of PMB-CH_2), 4.22 (1H, d, *J* = 9.8 Hz, C_9-CH), 3.78 (3H, s, PMB-OCH_3), 3.66 (1H, dd, *J* = 8.5, 8.5 Hz, one of C_5-CH_2), 3.63 (1H, dq, *J* = 6.2, 5.0 Hz, C_{11}-H), 3.48 (1H, dd, *J* = 9.0, 5.2, one of C_5-CH_2), 3.10-3.04 (1H, m, C_6-H), 3.08 (1H, d, *J* = 2.4 Hz, C_9-OH), 2.85 (1H, dq, *J* = 9.7, 7.0 Hz, C_8-H), 1.60-1.55 (1H, dq, *J* = 6.8, 5.3, C_{10}-H), 1.27 (3H, d, *J* = 6.3 Hz, C_{11}-CH_3), 1.06 (3H, d, *J* = 6.9 Hz, C_6-CH_3), 0.95 (3H, d, *J* = 7.0 Hz, C_{10}-CH_3), 0.92 (3H, d, *J* = 7.0 Hz, C_8-CH_3); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 217.3, 159.2, 138.0, 130.4, 129.3, 128.8, 128.3, 127.5, 113.8, 78.5, 73.2, 72.6, 72.3, 70.9, 55.2, 49.1, 46.7, 39.5, 17.5, 13.2, 12.8, 10.2; **HRMS** Exact mass calcd. for $C_{26}H_{40}NO_5$ [$(M+NH_4)^+$]: 446.2906; found 446.2906 (CI^+, NH_3).



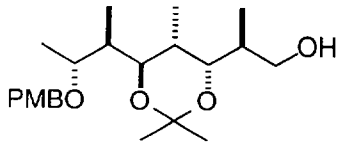
(2*S*, 3*S*, 4*R*, 5*R*, 6*S*, 7*R*)-1-benzyloxy-7-(4-methoxybenzyloxy)-2,4,6-trimethyl-3,5-octandiol. To a stirring solution of tetramethylammoniumtriacetoxyborohydride[9] (70.00 g, 220.24 mmol) in dry MeCN (120 ml) at ambient temperature was added glacial acetic acid (140 ml) and stirring was continued for 1 hr being cooled to -30 °C. A solution of the β-hydroxyketone **13** (11.77 g, 27.53 mmol) in dry MeCN (50 ml) was then added dropwise *via* cannula and the mixture stirred at -30 °C for 2.5 h, before being left to stand at - 20 °C in the freezer for 14 h. The reaction was then quenched at 0 °C by careful addition of potassium tartrate solution (500 ml, 0.5 N aq.) and vigorous stirring maintained for 3 h at ambient temperature. The reaction mixture was then diluted with CH_2Cl_2 (500 ml) and washed with $NaHCO_3$ solution (500 ml, sat. aq.). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 500 ml). The combined organic layers were then washed with more $NaHCO_3$ solution (2 x 300 ml, sat. aq.) and brine (500 ml), dried

($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10→50% EtOAc/hexane) to yield the desired *anti*-1,3-diol as a colourless oil (11.74 g, 99%). **TLC** R_f = 0.11 (20% EtOAc/hexane); $[\alpha]_D^{20}$ = +13.3 ° (*c* = 2.0, $CHCl_3$); **IR** ν_{max} (liquid film) 3500, 2969, 1612, 1513 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 -7.28 (5H, m, ArH), 7.24 (2H, d, *J* = 8.4 Hz, PMB-H), 6.87 (2H, d, *J* = 8.4 Hz, PMB-H), 4.56 and 4.53 (2H, ABq, *J* = 11.4 Hz, Bn-CH_2), 4.50 (1H, d, *J* = 11.2 Hz, one of PMB-CH_2), 4.33 (1H, d, *J* = 11.2 Hz, one of PMB-CH_2), 3.98 (1H, d, *J* = 8.6 Hz, C_9-H), 3.91 (1H, d, *J* = 9.4 Hz, C_7-H), 3.80 (3H, s, PMB-OCH_3), 3.70 (1H, br. s, C_7-OH), 3.64 (1H, dq, *J* = 6.2, 6.2 Hz, C_{11}-H), 3.58 (1H, dd, *J* = 8.5, 3.8 Hz, one of C_5-CH_2), 3.55 (1H, dd, *J* = 8.5, 8.5 Hz, one of C_5-CH_2), 3.48 (1H, br. s, C_9-OH), 2.02-1.98 (1H, m, C_6-H), 1.69-1.67 (2H, m, C_8-H and C_{10}-H), 1.27 (3H, d, *J* = 6.3 Hz, C_{11}-CH_3), 1.01 (3H, d, *J* = 7.0 Hz, C_{10}-CH_3), 0.82 (3H, d, *J* = 6.9 Hz, C_8-CH_3), 0.77 (3H, d, *J* = 6.9 Hz, C_6-CH_3); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 159.1, 137.8, 130.5, 129.2, 128.4, 128.4, 127.7, 113.8, 79.0, 76.8, 75.1, 73.5, 71.5, 70.8, 55.2, 39.8, 37.1, 36.0, 17.1, 13.2, 10.7, 9.2; **HRMS** Exact mass calcd. for $C_{26}H_{39}O_5$ [(M+H)$^+$]: 431.2797; found 431.2797 (CI$^+$, NH_3).



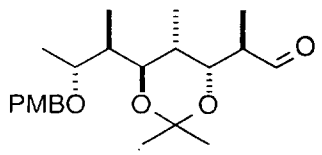
12

(2*S*, 3*S*, 4*R*, 5*S*, 6*R*, 7*R*)-1-benzyloxy-7-(4-methoxybenzyloxy)-3,5-isopropylidenedioxy-2,4,6-trimethyloctane (12). To a stirring solution of (2*S*, 3*S*, 4*R*, 5*R*, 6*S*, 7*R*)-1-benzyloxy-7-(4-methoxybenzyloxy)-2,4,6-trimethyl-3,5-octandiol (11.74 g, 27.27 mmol) in CH_2Cl_2 (70 ml) and 2,2-dimethoxypropane (70 ml) at ambient temperature was added a few crystals of PPTS (catalytic). After 24 h stirring, removal of the solvent *in vacuo* and subsequent flash column chromatography (10→50% EtOAc/hexane) provided the desired acetonide **12** as a colourless oil (11.96 g, 93%, 92% over two steps from **8**). **TLC** R_f = 0.54 (20% EtOAc/hexane); $[\alpha]_D^{20}$ = -37.7 ° (*c* = 0.7, $CHCl_3$); **IR** ν_{max} (liquid film) 3500, 2969, 1612, 1513 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 (4H, app. d, *J* = 4.3 Hz, ArH), 7.28 (3H, app. d, *J* = 8.4 Hz, PMB-H and ArH), 6.87 (2H, d, *J* = 8.4 Hz, PMB-H), 4.53 (1H, d, *J* = 11.0 Hz, one of PMB-CH_2), 4.50 (2H, app. s, Bn-CH_2), 4.38 (1H, d, *J* = 11.0 Hz, one of PMB-CH_2), 3.80 (3H, s, PMB-OCH_3), 3.65 (1H, dd, *J* = 7.5, 1.4 Hz, C_9-H), 3.58 (1H, d, *J* = 4.2 Hz, C_7-H), 3.56 (1H, dd, *J* = 10.0, 3.3 Hz, one of C_5-CH_2), 3.48-3.42 (2H, m, C_{11}-H, and one of C_5-CH_2), 1.90-1.84 (1H, m, C_6-H), 1.84-1.78 (1H, m, C_8-H), 1.64-1.57 (1H, m, C_{10}-H), 1.28 (3H, s, one of $C(CH_3)_2$), 1.26 (3H, s, one of $C(CH_3)_2$), 1.18 (3H, d, *J* = 6.2 Hz, C_{11}-CH_3), 0.98 (3H, d, *J* = 6.7 Hz, C_6-CH_3), 0.90 (3H, d, *J* = 7.0 Hz, C_{10}-CH_3), 0.87 (3H, *J* = 6.6 Hz, C_8-CH_3); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 159.0, 138.9, 131.2, 128.9, 128.2, 127.5, 127.3, 113.7, 100.4, 76.5, 73.7, 73.2, 72.6, 70.5, 70.4, 55.2, 42.2, 35.3, 33.8, 24.9, 23.7, 17.1, 13.4, 11.6, 9.4; **HRMS** Exact mass calcd. for $C_{29}H_{43}O_5$ [(M+H)$^+$]: 471.3110; found 471.3110 (CI$^+$, NH_3).

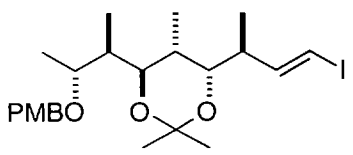


(2*S*, 3*S*, 4*R*, 5*S*, 6*R*, 7*R*)-7-(4-methoxybenzyloxy)-3,5-isopropylidenedioxy-2,4,6-trimethyloctan-1-ol. To a slurry of W-2 Raney nickel (previously washed with EtOH, 30 ml, 50% suspension in water) in ethanol (30 ml), was added *via* cannula a solution of the acetonide

12 (4.60 g, 9.77 mmol) in EtOH (72 ml). The flask was then flushed with hydrogen three times and the reaction mixture was stirred at ambient temperature for 16 h before removal of the Raney nickel by elution through a short column of celite with ethanol and the solvent removed *in vacuo* to give the primary alcohol as a colorless oil (3.56 g, 96%), which was taken on to the next reaction without further purification. **TLC** R_f = 0.21 (20% EtOAc/hexane); $[\alpha]_D^{20}$ = -13.9 ° (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (liquid film) 3476, 2973, 2935, 1614, 1514, 1462, 1379 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 (2H, d, *J* = 8.4 Hz, PMB-H), 6.90 (2H, d, *J* = 8.4 Hz, PMB-H), 4.52 (1H, d, *J* = 11.0 Hz, one of PMB-CH_2), 4.35 (1H, d, *J* = 11.0 Hz, one of PMB-CH_2), 3.80 (3H, s, PMB-OCH_3), 3.68 (1H, dd, *J* = 7.6, 1.6 Hz, C_9-H), 3.60 (1H, dd, *J* = 10.5, 4.4 Hz, one of C_5-CH_2), 3.58 (1H, d, *J* = 9.4 Hz, C_7-H), 3.53 (1H, dd, *J* = 10.6, 2.9 Hz, one of C_5-CH_2), 3.44 (1H, dq, *J* = 7.9, 6.3 Hz, C_{11}-H), 3.25 (1H, d, *J* = 9.6 Hz, C_5-OH), 1.94-1.86 (1H, m, C_6-H), 1.84-1.78 (1H, dq, *J* = 11.5, 6.8 Hz, C_8-H), 1.60-1.57 (1H, m, C_{10}-H), 1.35 (3H, s, one of $C(CH_3)_2$), 1.27 (3H, s, one of $C(CH_3)_2$), 1.17 (3H, d, *J* = 6.1 Hz, C_{11}-CH_3), 0.89 (3H, d, *J* = 6.7 Hz, C_{10}-CH_3), 0.87 (3H, *J* = 6.3 Hz, C_8-CH_3), 0.78 (3H, d, *J* = 6.7 Hz, C_6-CH_3); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 159.0, 131.1, 128.9, 113.8, 100.5, 76.5, 76.3, 73.4, 70.5, 69.1, 55.2, 42.2, 35.5, 35.0, 25.2, 23.6, 17.1, 12.7, 11.7, 9.4; **HRMS** Exact mass calcd. for $C_{22}H_{37}O_5$ [(M+H)$^+$]: 381.2641; found 381.2641 (CI$^+$, NH_3).

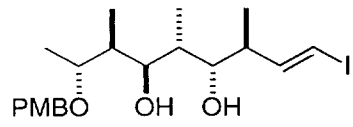


(2*R*, 3*R*, 4*S*, 5*S*, 6*R*, 7*R*)-7-(4-methoxybenzyloxy)-3,5-isopropylidenedioxy-2,4,6-trimethyloctan-1-al. To a -78 °C stirred solution of oxalyl chloride (24.50 ml, 2.0 M in CH_2Cl_2, 48.85 mmol) was added dropwise dimethylsulfoxide (6.94 ml, 97.70 mmol) and the mixture was stirred for 30 mins. A solution of (2*S*, 3*S*, 4*R*, 5*S*, 6*R*, 7*R*)-7-(4-methoxybenzyloxy)-3,5-isopropylidenedioxy-2,4,6-trimethyloctan-1-ol (3.71 g, 9.77 mmol) in CH_2Cl_2 (68 ml) was then added *via* cannula and the reaction mixture was stirred at -78 °C for a further 1 h. Triethylamine (233.70 ml, 244.25 mmol) was added at -78 °C and the reaction mixture allowed to warm to -20 °C for a further 30 mins. The reaction was quenched by the addition of NH_4Cl solution (160 ml, sat. aq.), the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 x 120 ml). The combined organic layers were washed with brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* . The crude aldehyde was eluted through a short column of celite with CH_2Cl_2, and the pale yellow oil (3.54 g, 96%) remaining after evaporation *in vacuo* was taken on to the next reaction without further purification. **TLC** R_f = 0.29 (20% EtOAc/hexane); $[\alpha]_D^{20}$ = -55.3 ° (*c* = 0.9, $CHCl_3$); **IR** ν_{max} (liquid film) 2976, 2936, 1729, 1613, 1514, 1460, 1380 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.69 (1H, d, *J* = 2.9 Hz, C_5-H), 7.26 (2H, d, *J* = 8.5 Hz, PMB-H), 6.87 (2H, d, *J* = 8.5 Hz, PMB-H), 4.52 (1H, d, *J* = 11.0 Hz, one of PMB-CH_2), 4.35 (1H, d, *J* = 11.0 Hz, one of PMB-CH_2), 3.89 (1H, dd, *J* = 10.8, 4.4Hz, C_9-H), 3.79 (3H, s, PMB-OCH_3), 3.72 (1H, dd, *J* = 7.7, 1.3 Hz, C_7-H), 3.44 (1H, dq, *J* = 8.1, 6.2 Hz, C_{11}-H), 2.49 (1H, dqd, *J* = 10.5, 7.0, 3.0 Hz, C_6-H), 1.84 (1H, dq, *J* = 11.6, 6.9 Hz, C_8-H), 1.58 (1H, dq, *J* = 7.4, 7.4 Hz, C_{10}-H), 1.27 (3H, s, one of $C(CH_3)_2$), 1.26 (3H, s, one of $C(CH_3)_2$), 1.18 (3H, d, *J* = 6.2 Hz, C_{11}-CH_3), 0.98 (3H, d, *J* = 6.9 Hz, C_6-CH_3), 0.89 (3H, *J* = 7.1 Hz, C_{10}-CH_3), 0.87 (3H, d, *J* = 6.7 Hz, C_8-CH_3); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 204.8, 159.0, 131.1, 129.0, 113.8, 100.7, 76.5, 76.3, 73.4, 70.5, 55.3, 46.0, 42.3, 35.0, 25.0, 23.4, 17.1, 11.7, 10.1, 9.4; **HRMS** Exact mass calcd. for $C_{22}H_{35}O_5$ [(M+H)$^+$]: 379.2484; found 379.2484 (CI$^+$, NH_3).



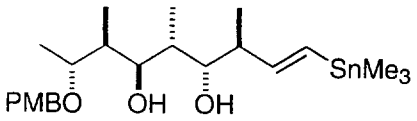
14

(1*E*, 3*S*, 4*S*, 5*R*, 6*S*, 7*R*, 8*R*)-1-iodo-8-(4-methoxybenzyloxy)-4,6-isopropylidenedioxy-3,5,7-trimethylnon-1-ene (14). To a stirring solution of anhydrous chromium (II) chloride (15.50 g, 117.24 mmol) in dry THF (40 ml) at ambient temperature was added dropwise *via* cannula a solution of (2*R*, 3*R*, 4*S*, 5*S*, 6*R*, 7*R*)-7-(4-methoxybenzyloxy)-3,5-isopropylidenedioxy-2,4,6-trimethyloctan-1-al (3.54 g, 7.05 mmol) and iodoform (15.3 g, 39.08 mmol) in THF:dioxane (40.0 ml : 80.0 ml). The reaction mixture was stirred in the dark at ambient temperature for 3.5 h, during which time it turned brown. The reaction was quenched by the addition of water (200 ml) and the phases were separated. The aqueous layer was extracted with Et_2O (4 x 200 ml) and the combined organic layers were washed with $Na_2S_2O_3$ solution (330 ml, 0.5 N aq.) and brine (300 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow solid. The crude product was purified by flash column chromatography (0→5% EtOAc/hexane) to afford the vinyl iodide **14** as a 20:1 *E*:*Z* mixture of diastereomers (determined by 500 MHz ^{1}H NMR integration) as a pale yellow oil (3.92 g, 87%, 80% over three steps from **12**). **TLC** R_f = 0.49 (20% EtOAc/hexane); $[\alpha]_D^{20}$ = -51.8 ° (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (liquid film) 2974, 2936, 1614, 1586, 1514, 1454, 1378 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.6 Hz, PMB-H), 6.86 (2H, d, *J* = 8.6 Hz, PMB-H), 6.54 (1H, dd, *J* = 14.5, 7.4 Hz, C_5-H), 6.03 (1H, d, *J* = 14.5 Hz, C_4-H), 4.52 (1H, d, *J* = 11.0 Hz, one of PMB-CH_2), 4.35 (1H, d, *J* = 11.0 Hz, one of PMB-CH_2), 3.80 (3H, s, PMB-OCH_3), 3.65 (1H, d, *J* = 7.6 Hz, C_7-H), 3.43 (1H, dq, *J* = 8.0, 6.3 Hz, C_{11}-H), 3.39 (1H, dd, *J* = 10.4, 4.2 Hz, C_9-H), 2.31 (1H, dqd, *J* = 10.2, 7.0, 7.0 Hz, C_6-H), 1.79 (1H, dq, *J* = 11.4, 6.9 Hz, C_8-H), 1.56 (1H, dq, *J* = 7.0, 7.0 Hz, C_{10}-H), 1.27 (3H, s, one of $C(CH_3)_2$), 1.26 (3H, s, one of $C(CH_3)_2$), 1.17 (3H, d, *J* = 6.2 Hz, C_{11}-CH_3), 0.95 (3H, d, *J* = 6.8 Hz, C_6-CH_3), 0.87 (3H, *J* = 7.0 Hz, C_{10}-CH_3), 0.84 (3H, d, *J* = 6.6 Hz, C_8-CH_3); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 159.0, 149.7, 131.2, 129.0, 113.8, 100.6, 76.5, 74.3, 73.6, 72.8, 70.6, 55.3, 42.2, 40.2, 35.5, 24.9, 23.6, 17.2, 15.3, 11.6, 9.4; **HRMS** Exact mass calcd. for $C_{23}H_{36}O_4I$ [$(M+H)^+$]: 503.1660; found 503.1658 (CI^+, NH_3).



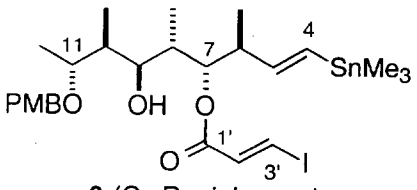
(1*E*, 3*S*, 4*S*, 5*R*, 6*R*, 7*S*, 8*R*)-1-iodo-8-(4-methoxybenzyloxy)-3,5,7-trimethylnon-1-en-4,6-diol. To a stirring solution of the vinyl iodide **14** (3.60 g, 7.17 mmol) in CH_2Cl_2 - methanol (1:1, 30 ml) at ambient temperature was added a few crystals of CSA (catalytic). After 24 h stirring, removal of the solvent *in vacuo* and subsequent flash column chromatography (15→30% EtOAc/hexane) provided the desired diol as a colourless oil, as well as some recovered starting material. This starting material was resubmitted to the above conditions for 24 h, concentrated *in vacuo* and purified by flash column chromatography (15→30% EtOAc/hexane) to yield the diol as a colourless oil, which was combined with the previous material (3.14 g, 95%). **TLC** R_f = 0.25 (20% EtOAc/hexane); $[\alpha]_D^{20}$ = -12.1 ° (*c* = 0.5, $CHCl_3$); **IR** ν_{max} (liquid film) 3464, 2969, 2936, 1613, 1587, 1514, 1455, 1377 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.6 Hz, PMB-H), 6.87 (2H, d, *J* = 8.6 Hz, PMB-H), 6.58 (1H, dd, *J* = 14.4, 8.8 Hz, C_5-H), 6.10 (1H, d, *J* = 14.5 Hz, C_4-H), 4.59 (1H, d, *J* = 11.0 Hz, one of PMB-CH_2), 4.30 (1H, d, *J* = 11.0 Hz, one of PMB-CH_2), 4.01 (1H, d, *J* = 9.1 Hz, C_9-H), 3.80 (3H, s, PMB-OCH_3), 3.68 (1H, ddd, *J* = 8.2, 4.6, 2.4 Hz, C_7-H), 3.62 (1H, q, *J* = 3.4 Hz, C_{11}-H), 3.39 (1H, d, *J* = 1.7 Hz, C_9-OH), 2.41 (1H, d, *J* = 4.6 Hz, C_7-OH), 2.31 (1H,

ddq, J = 7.7, 7.7, 7.0 Hz, C_6-H), 1.76 (1H, dqd, J = 9.1, 7.0, 2.2 Hz, C_8-H), 1.63-1.59 (1H, m, C_{10}-H), 1.28 (3H, d, J = 6.3 Hz, C_{11}-CH_3), 0.99 (3H, d, J = 7.1 Hz, C_{10}-CH_3), 0.96 (3H, J = 6.8 Hz, C_6-CH_3), 0.77 (3H, d, J = 6.9 Hz, C_8-CH_3); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 159.1, 149.9, 130.1, 129.1, 113.7, 78.8, 74.8, 73.6, 71.7, 70.7, 55.3, 44.0, 39.6, 36.8, 17.1, 16.3, 10.7, 9.7; **HRMS** Exact mass calcd. for $C_{20}H_{32}O_4I$ [(M+H)$^+$]: 463.1345; found 463.1345 (CI$^+$, NH_3).

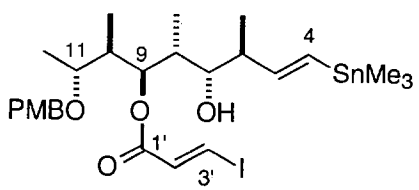


15

(1*E*, 3*S*, 4*S*, 5*R*, 6*R*, 7*S*, 8*R*)-1-trimethylstannyl-8-(4-methoxybenzyloxy)-3,5,7-trimethylnon-1-en-4,6-diol (15). To a stirring solution of lithium carbonate (638 mg, 8.64 mmol) and dichlorobis(triphenylphosphine)palladium(II) (311 mg, 0.43 mmol) in THF (160 ml) was added hexamethylditin (2.30 ml, 10.82 mmol) followed by (1*E*, 3*S*, 4*S*, 5*R*, 6*R*, 7*S*, 8*R*)-1-iodo-8-(4-methoxybenzyloxy)-3,5,7-trimethylnon-1-en-4,6-diol (1.00 g, 2.16 mmol) in THF (45 ml) dropwise *via* cannula over 1 hr. The reaction mixture was then stirred at 40 °C for a further 2 h. The reaction was quenched by the addition of pH 7 buffer (100 ml) and the phases were separated. The aqueous layer was extracted with EtOAc (4 x 100 ml) and the combined organic layers were washed with brine (200 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography on basic alumina (BDH active alumina oxide Brookman grade II-III, 0→50% EtOAc/hexane) to yield the vinyl stannane **15** as a colourless oil (875 mg, 81%, 77% over two steps from **14**). **TLC** R_f = 0.32 (20% EtOAc/hexane); $[\alpha]_D^{20}$ = -6.6 ° (c = 0.3, $CHCl_3$); **IR** ν_{max} (liquid film) 3477, 2970, 2936, 1613, 1514, 1462, 1378 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 8.6 Hz, PMB-H), 6.86 (2H, d, J = 8.6 Hz, PMB-H), 6.10 (1H, d, J = 18.9 Hz, C_4-H), 5.90 (1H, dd, J = 18.9, 8.0 Hz, C_5-H), 4.59 (1H, d, J = 11.2 Hz, one of PMB-CH_2), 4.32 (1H, d, J = 11.2 Hz, one of PMB-CH_2), 4.03 (1H, ddd, J = 9.2, 2.4, 2.4 Hz, C_9-H), 3.80 (3H, s, PMB-OCH_3), 3.69 (1H, ddd, J = 9.0, 2.0, 2.0 Hz, C_7-H), 3.64 (1H, q, J = 3.5 Hz, C_{11}-H), 3.41 (1H, d, J = 2.0 Hz, C_9-OH), 2.27 (1H, ddq, J = 8.0, 8.0, 7.0 Hz, C_6-H), 2.09 (1H, d, J = 2.6 Hz, C_7-OH), 1.74 (1H, dqd, J = 9.1, 7.0, 2.2 Hz, C_8-H), 1.68-1.66 (1H, m, C_{10}-H), 1.28 (3H, d, J = 6.3 Hz, C_{11}-CH_3), 1.00 (3H, d, J = 7.1 Hz, C_{10}-CH_3), 0.95 (3H, J = 6.7 Hz, C_6-CH_3), 0.79 (3H, d, J = 6.9 Hz, C_8-CH_3), 0.11 (9H, s, $Sn(CH_3)_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 159.9, 152.2, 130.4, 130.3, 129.1, 113.7, 79.1, 72.6, 71.5, 70.8, 55.2, 45.9, 39.6, 36.3, 17.2, 16.4, 10.7, 9.3, -9.7; **HRMS** Exact mass calcd. for $C_{23}H_{41}O_4Sn$ [(M+H)$^+$]: 501.2027; found 501.2030 (CI$^+$, NH_3).



3 (C_7-Regioisomer)



(C_9-Regioisomer)

(1*E*, 3*S*, 4*S*, 5*S*, 6*S*, 7*S*, 8*R*)-1-trimethylstannyl-6-hydroxy-8-(4-methoxybenzyloxy)-3,5,7-trimethylnon-1-en-4-yl-(*E*)-3-iodopropenoate (3) and (1*E*, 3*S*, 4*S*, 5*R*, 6*R*, 7*R*, 8*R*)-1-trimethylstannyl-4-hydroxy-8-(4-methoxybenzyloxy)-3,5,7-trimethylnon-1-en-6-yl-(*E*)-3-iodopropenoate. To a stirring solution of diol **15** (556 mg, 1.11 mmol), DMAP (196 mg, 1.67 mmol) and (*E*)-3-iodoacrylic acid[10] (1.32 g, 6.68 mmol) in CH_2Cl_2 (22 ml) at -25 °C

was added DCC (1.60 mg, 7.77 mmol) and stirring was continued at -25 °C for 5 h. More (*E*)-3-iodoacrylic acid (440 mg, 2.23 mmol), DMAP (65 mg, 0.56 mmol) and DCC (533 mg, 2.59 mmol) were then added and the mixture stirred at -20 °C for a further 2 h, before being left to stand at - 20 °C in the freezer for 14 h. The reaction mixture was then directly purified by flash column chromatography on basic alumina (BDH active alumina oxide Brookman grade II-III, 0→40% Et_2O/hexane) to afford the macrocycle precursor as an inseparable 1.2:1 C_7:C_9 mixture of regioisomers (determined by 500 MHz ^1H NMR integration) as a colourless oil (586 mg, 78%).

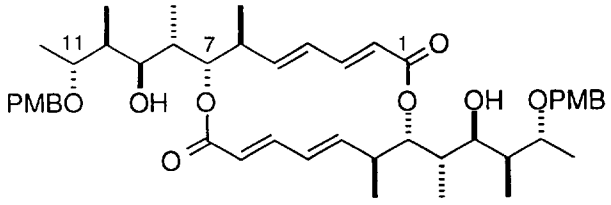
Isomeristion C_9- to C_7-regioisomer. *Method A*. The resulting ester product (586 mg, 0.86 mmol) was stirred at ambient temperature over basic alumina (BDH active alumina oxide Brookman grade II-III, 4 g) in Et_2O:hexane (1:1, 30 ml) for 3 h before removal of alumina by elution through a short column of celite with Et_2O and the solvent removed *in vacuo* to afford the macrocycle precursor as an inseparable 6.5:1 C_7:C_9 mixture of regioisomers (determined by 500 MHz ^1H NMR integration) as a colourless oil (586 mg, 78% from **15**), which was taken on to the next reaction without further purification.

Method B. To a stirring solution of the resulting ester product (892 mg, 1.31 mmol) in Et_2O:hexane (1:1, 30 ml) at ambient temperature was added titanium(IV) isoppropoxide (14.9 ml, 65.67 mmol) and stirring was continued for 15 h. The reaction was quenched at 0 °C by careful addition of NH_4Cl solution (20 ml, sat. aq.) and water (20 ml), the layers were separated, and the aqueous phase was extracted with Et_2O (3 x 60 ml). The combined organic layers were washed with brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* . The crude esters were purified by flash column chromatography on basic alumina (BDH active alumina oxide Brookman grade II-III, 0→10% EtOAc/hexane) to afford the macrocycle precursor as an inseparable 9.6:1 C_7:C_9 mixture of regioisomers (determined by 500 MHz ^1H NMR integration) as a colourless oil (810 mg, 87%, 68% from **15**).

C_7-regioisomer macrocycle precursor (3): **TLC** R_f = 0.52 (25% EtOAc/hexane); **IR** ν_{max} (liquid film) 3456, 2976, 2936, 1699, 1638, 1613, 1513, 1464, 1302 cm^{-1}; **^1H NMR** (500 MHz, $CDCl_3$) δ 7.81 (1H, d, *J* = 14.8 Hz, $C_{3'}$-H), 7.19 (2H, d, *J* = 8.6 Hz, PMB-H), 6.86 (2H, d, *J* = 8.6 Hz, PMB-H), 6.84 (1H, d, *J* = 14.7 Hz, $C_{2'}$-H), 5.95 (1H, d, *J* = 18.7 Hz, C_4-H), 5.74 (1H, dd, *J* = 18.7, 8.0 Hz, C_5-H), 5.19 (1H, dd, *J* = 9.8, 1.1 Hz, C_7-H), 4.53 (1H, d, *J* = 11.0 Hz, one of PMB-CH_2), 4.28 (1H, d, *J* = 11.0 Hz, one of PMB-CH_2), 3.82 (3H, s, PMB-OCH_3), 3.64 (1H, dd, *J* = 10.0, 1.9 Hz, C_9-H), 3.56 (1H, dq, *J* = 6.6, 6.6 Hz, C_{11}-H), 3.05 (1H, d, *J* = 3.7 Hz, C_9-OH), 2.27 (1H, ddq, *J* = 8.4, 8.4, 7.4 Hz, C_6-H), 1.83-1.81 (1H, m, C_8-H), 1.62-1.56 (1H, m, C_{10}-H), 1.22 (3H, d, *J* = 6.2 Hz, C_{11}-CH_3), 1.00 (3H, d, *J* = 6.8 Hz, C_6-CH_3), 0.86 (3H, *J* = 7.0 Hz, C_{10}-CH_3), 0.79 (3H, d, *J* = 7.0 Hz, C_8-CH_3), 0.07 (9H, s, $Sn(CH_3)_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.6, 159.2, 150.6, 136.6, 130.7, 129.7, 129.4, 113.9, 99.3, 77.4, 77.2, 71.0, 69.4, 55.3, 44.4, 40.3, 36.9, 17.6, 16.6, 9.3, 9.0, -9.6; **HRMS** Exact mass calcd. for $C_{26}H_{42}O_5ISn$ [(M+H)$^+$]: 681.1101; found 681.1103 (CI^+, NH_3).

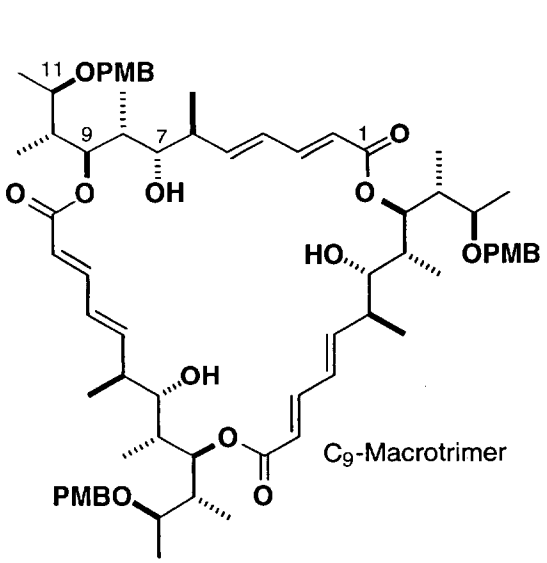
C_9-regioisomer macrocycle precursor: **TLC** R_f = 0.52 (25% EtOAc/hexane); **^1H NMR** (500 MHz, $CDCl_3$) δ 7.88 (1H, d, *J* = 14.8 Hz, $C_{3'}$-H), 7.29 (2H, d, *J* = 8.6 Hz, PMB-H), 6.89 (1H, d, *J* = 14.8 Hz, $C_{2'}$-H), 6.86 (2H, d, *J* = 8.6 Hz, PMB-H), 6.04 (1H, d, *J* = 18.9 Hz, C_4-H), 5.95 (1H, dd, *J* = 19.0, 6.8 Hz, C_5-H), 5.51 (1H, dd, *J* = 9.9, 1.5 Hz, C_9-H), 4.43 (1H, d, *J* = 10.4 Hz, one of PMB-CH_2), 4.23 (1H, d, *J* = 10.4 Hz, one of PMB-CH_2), 3.80 (3H, s, PMB-OCH_3), 3.23 (1H, dq, *J* = 8.1, 6.1 Hz, C_{11}-H), 3.13 (1H, dd, *J* = 9.5, 1.8 Hz, C_7-H), 2.55 (1H, d, *J* = 3.4 Hz, C_7-OH), 2.34 - 2.28 (1H, m, C_6-H), 1.91 - 1.84 (2H, m, C_8-H, C_{10}-H), 1.20 (3H, d, *J* = 6.1 Hz, C_{11}-CH_3), 0.93 (3H, d, *J* = 7.1 Hz, C_{10}-CH_3), 0.91 (3H, *J*

= 6.9 Hz, C_6-C<u>H</u>$_3$), 0.85 (3H, d, J = 6.9 Hz, C_8-C<u>H</u>$_3$), 0.11 (9H, s, Sn(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 164.8, 159.1, 152.1, 136.5, 130.6, 129.6, 129.0, 113.8, 100.0, 76.2, 75.5, 72.6, 70.7, 55.4, 44.5, 40.2, 36.4, 17.1, 16.4, 9.7, 8.6, -9.6.

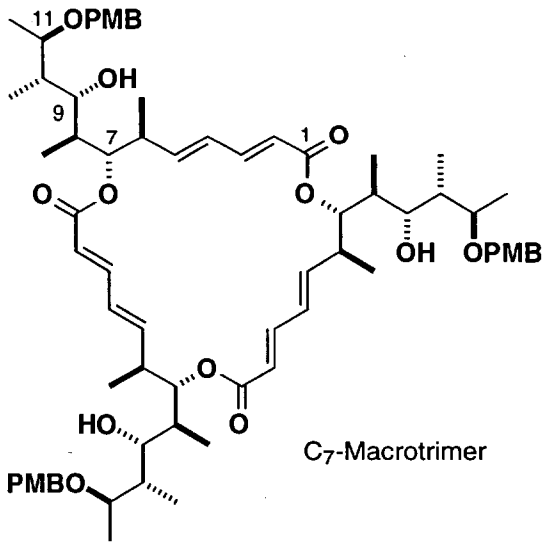


16

(3*E*, 5*E*, 7*S*, 8*S*, 11*E*, 13*E*, 15*S*, 16*S*)-8,16-bis[(1*S*,2*S*,3*S*,4*R*)-2-hydroxy-4-(4-methoxybenzyloxy)-1,3-dimethylpentyl]-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione (16, C_7-macrodimer). To a stirring solution of the macrocycle precursor **3** (780 mg, 1.15 mmol, 9.6:1 C_7:C_9 regioisomers) in dry *N*-methyl pyrrolidinone (120 ml, c = 0.01 M) at ambient temperature, was added copper (I) thiophene-2-carboxylate[11] (CuTC, 2.21 g, 11.48 mmol) and stirring was continued for 15 mins. After concentrating *in vacuo*, the reaction mixture was then directly purified by flash column chromatography (20→50% EtOAc/hexane) to yield the macrocycles (92%). The resulting products were dried on the high vacuum line for 24 hours to yield the C_7-macrodimer macrocycle **16** as a white crystalline solid (356 mg, 80%, 88% based on C_7 regioisomer) and the C_9-trimer macrocycle as a white crystalline solid (32 mg, 7%, 76% based on C_9 regioisomer). **TLC** Rf = 0.66 (33% hexane/EtOAc); **m.p.** 206-208 °C; $[\alpha]_D^{20}$ = +34.9 ° (c = 1.1, $CHCl_3$); **IR** ν_{max} (liquid film) 3486, 2974, 2936, 1695, 1642, 1615, 1513, 1464, 1376, 1249, 1150, 1001 cm^{-1}; **^{1}H NMR** (500MHz, $CDCl_3$) δ 7.18 (4H, d, J = 8.5 Hz, PMB-<u>H</u>), 7.04 (2H, dd, J = 15.3, 11.2 Hz, C_3-<u>H</u>), 6.82 (4H, d, J = 8.5 Hz, PMB-<u>H</u>), 6.10 (2H, dd, J = 15.0, 11.2 Hz, C_4-<u>H</u>), 5.68 (2H, dd, J = 15.1, 11.6 Hz, C_5-<u>H</u>), 5.66 (2H, d, J = 15.4 Hz, C_2-<u>H</u>), 5.05 (2H, d, J = 10.2 Hz, C_7-<u>H</u>), 4.54 (2H, d, J = 11.1 Hz, one of each PMB-C<u>H</u>$_2$), 4.29 (2H, d, J = 11.1 Hz, one of each PMB-C<u>H</u>$_2$), 3.79-3.77 (2H, m, C_9-<u>H</u>), 3.77 (6H, s, PMB-OC<u>H</u>$_3$), 3.57 (2H, dq, J = 6.6, 6.2 Hz, C_{11}-<u>H</u>), 3.11 (2H, d, J = 2.6 Hz, C_9-O<u>H</u>), 2.52 (2H, ddq, J = 10.2, 9.8, 6.7 Hz, C_6-<u>H</u>), 1.90 (2H, dq, 7.8, 7.2 Hz, C_8-<u>H</u>), 1.62 (2H, dq, J = 7.0, 6.5 Hz, C_{10}-<u>H</u>), 1.23 (6H, d, J = 6.1 Hz, C_{11}-C<u>H</u>$_3$), 1.05 (6H, d, J = 6.7 Hz, C_6-C<u>H</u>$_3$), 0.88 (6H, d, J = 7.0 Hz, C_{10}-C<u>H</u>$_3$), 0.83 (6H, d, J = 6.9 Hz, C_8-C<u>H</u>$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.8, 159.1, 144.9, 144.6, 131.4, 130.7, 129.5, 121.3, 113.8, 77.3, 77.2, 70.9, 69.5, 55.2, 41.3, 40.3, 36.1, 17.6, 15.3, 9.2, 8.9; **HRMS** Exact mass calcd. for $C_{46}H_{64}O_{10}Na$ [(M+Na)$^+$]: 799.4397; found 799.4408 (FAB$^+$).



C_9-Macrotrimer

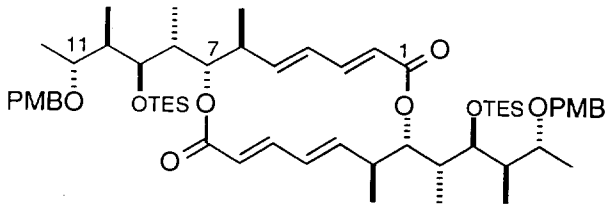


C_7-Macrotrimer

(3*E*, 5*E*, 7*S*, 8*S*, 9*R*, 10*R*, 13*E*, 15*E*, 17*S*, 18*S*, 19*R*, 20*R*, 23*E*, 25*E*, 27*S*, 28*S*, 29*R*, 30*R*)-10,20,30-tris[(1*R*,2*R*)-2-(4-methoxybenzyloxy)-1-methylpropyl]-7,9,17,19,27,29-hexamethyl-8,18,28-trihydroxy-1,11,21-trioxacyclotriaconta-3,5,13,15,23,25-hexaene-2,12,22-trione (C_9-macrotrimer), (3*E*, 5*E*, 7*S*, 8*S*, 11*E*, 13*E*, 15*S*, 16*S*, 19*E*, 21*E*, 23*S*, 24*S*)-8,16,24-tris[(1*S*,2*S*,3*S*,4*R*)-2-hydroxy-(4-methoxybenzyloxy)-1,3-dimethylpentyl]-7,15,23-trimethyl-1,9,17-trioxacyclotetracosa-3,5,11,13,19,21-hexaene-2,10,18-trione (C_7-macrotrimer) and 13 (C_7-macrodimer). To a stirring solution of the macrocycle precursor **3** (556 mg, 0.82 mmol, 6.5:1 C_7:C_9 regiosomers) in dry *N*-methyl pyrrolidinone (4.2 ml, *c* = 0.2 M) at ambient temperature, was added copper (I) thiophene-2-carboxylate[11] (CuTC, 1.57 g, 8.19 mmol) and stirring was continued for 15 mins. After concentrating *in vacuo*, the reaction mixture was then directly purified by flash column chromatography (20→50% EtOAc/hexane) to first elute the C_9-trimer macrocycle as a white crystalline solid (40 mg, 13%, 94% based on C_9 regioisomer) followed by the the C_7-dimer macrocycle **13** as a white crystalline solid (134 mg, 42%, 49% based on C_7 regioisomer) and finally the C_7-trimer macrocycle as a white crystalline solid (109 mg, 34%, 26% based on C_7 regioisomer). **C_9-macrotrimer: TLC** R_f = 0.71 (33% hexane/EtOAc); $[\alpha]_D^{20}$ = +15.3 ° (*c* = 0.9, $CHCl_3$); **IR** ν_{max} (liquid film) 3475, 2979, 2936, 1692, 1638, 1614, 1514, 1464, 1384, 1246, 1147, 1006 cm^{-1}; **^{1}H NMR** (500MHz, $CDCl_3$) δ 7.43 (3H, dd, *J* = 15.0, 11.2 Hz, C_3-H), 7.28 (6H, d, *J* = 8.1 Hz, PMB-H), 6.86 (6H, d, *J* = 8.1 Hz, PMB-H), 6.86-6.83 (3H, m, C_5-H), 6.15 (3H, dd, *J* = 15.4, 11.4 Hz, C_4-H), 5.82 (3H, d, *J* = 15.3 Hz, C_2-H), 5.41 (3H, d, *J* = 10.7 Hz, C_9-H), 4.38 (3H, d, *J* = 10.2 Hz, one of each PMB-CH_2), 4.17 (3H, d, *J* = 10.2 Hz, one of each PMB-CH_2), 3.80 (9H, s, PMB-OCH_3), 3.68 (3H, d, *J* = 1.8 Hz, C_7-OH), 3.19 (2H, dq, *J* = 7.1, 6.8 Hz, C_{11}-H), 2.97 (3H, dd, *J* = 10.5, 2.6 Hz, C_7-H), 2.44 (3H, s br, C_6-H), 1.88-1.80 (6H, m, C_8-H, C_{10}-H), 1.19 (9H, d, *J* = 5.9 Hz, C_{11}-CH_3), 0.96 (9H, d, *J* = 6.6 Hz, C_6-CH_3), 0.92 (9H, d, *J* = 6.9 Hz, C_{10}-CH_3), 0.86 (9H, d, *J* = 6.6 Hz, C_8-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.1, 159.1, 150.4, 148.2, 130.4, 129.8, 125.2, 117.9, 113.8, 75.9, 74.0, 73.0, 70.9, 55.2, 40.2, 37.4, 36.5, 17.3, 12.8, 9.4, 8.0; **HRMS** Exact mass calcd. for $C_{69}H_{96}O_{15}Na$ [(M+Na)$^+$]: 1187.6647; found 1187.6624 (ESI$^+$).

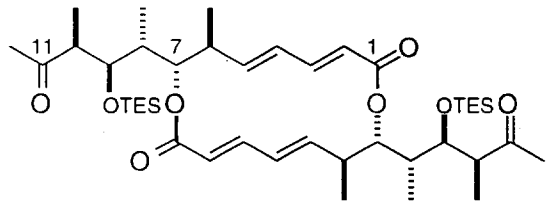
C_7-macrotrimer: TLC R_f = 0.62 (33% hexane/EtOAc); $[\alpha]_D^{20}$ = +32.8 ° (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (liquid film) 3486, 2975, 2936, 1699, 1638, 1613, 1513, 1464, 1379, 1302, 1150, 1001 cm^{-1}; **^{1}H NMR** (500MHz, $CDCl_3$) δ 7.25 (3H, dd, *J* = 15.4, 11.1 Hz, C_3-H), 7.15 (6H, d, *J* = 8.5 Hz, PMB-H), 6.80 (6H,

PMB-H), 6.80 (6H, d, J = 8.5 Hz, PMB-H), 6.13 (3H, dd, J = 15.0, 11.0 Hz, C_5-H), 5.91 (3H, dd, J = 15.0, 9.6 Hz, C_4-H), 5.73 (3H, d, J = 15.3 Hz, C_2-H), 5.23 (3H, d, J = 10.0 Hz, C_7-H), 4.49 (3H, d, J = 10.8 Hz, one of each PMB-CH_2), 4.28 (3H, d, J = 10.8 Hz, one of each PMB-CH_2), 3.78 (9H, s, PMB-OCH_3), 3.63 (3H, dd, J = 10.4, 10.4 Hz, C_9-H), 3.54 (2H, dq, J = 6.7, 6.3 Hz, C_{11}-H), 3.11 (3H, d, J = 3.2, C_9-OH), 2.56 (3H, ddq, J = 8.3, 8.3, 6.8 Hz, C_6-H), 1.87 (3H, dq, J = 8.1, 8.1 Hz, C_8-H), 1.60 (3H, dq, J = 7.0, 6.5 Hz, C_{10}-H), 1.20 (9H, d, J = 6.0 Hz, C_{11}-CH_3), 1.04 (9H, d, J = 6.7 Hz, C_6-CH_3), 0.85 (9H, d, J = 6.9 Hz, C_{10}-CH_3), 0.80 (9H, d, J = 6.8 Hz, C_8-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.5, 159.1, 147.0, 146.0, 130.7, 129.5, 128.5, 119.0, 113.8, 76.8, 75.2, 71.0, 69.0, 55.2, 40.4, 40.4, 36.7, 17.6, 16.4, 9.1, 8.6; **HRMS** Exact mass calcd. for $C_{69}H_{96}O_{15}Na$ [(M+Na)$^+$]: 1187.6647; found 1187.6641 (ESI$^+$).



(3*E*, 5*E*, 7*S*, 8*S*, 11*E*, 13*E*, 15*S*, 16*S*)-8,16-bis[(1*R*,2*S*,3*R*,4*R*)-(4-methoxybenzyloxy)-2-triethylsilyloxy-1,3-dimethylpentyl]-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione. To a mixture of the hydroxymacrocycle **16** (250 mg, 0.32 mmol) and imidazole (4.46 g, 64.40 mmol) in DMF (9.6 ml) at ambient temperature was added TESCl (8.75 ml, 32.20 mmol) and the resulting mixture stirred at 50 °C for 30 h. After cooling to ambient temperature, the mixture was diluted with Et_2O (30 ml) and washed with $NaHCO_3$ solution (15 ml, sat. aq.). The aqueous layer was re-extracted with Et_2O (2 x 40 ml) and the combined organic extracts washed successively with H_2O (20 ml) and brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10% Et_2O/hexane) to yield the TES protected macrocycle as a white solid (300 mg, 93%). **TLC** R_f = 0.68 (25% EtOAc/hexane); **m.p.** 184-185 °C; $[\alpha]_D^{20}$ = +34.2 ° (c = 1.0, $CHCl_3$); **IR** ν_{max} (liquid film) 3053, 3020, 2986, 1707, 1638, 1610, 1513, 1422 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 (4H, d, J = 8.5 Hz, PMB-H), 6.98 (2H, dd, J = 15.4, 11.2 Hz, C_3-H), 6.83 (4H, d, J = 8.5 Hz, PMB-H), 6.00 (2H, dd, J = 15.0, 11.2 Hz, C_4-H), 5.66 (2H, dd, J = 15.1, 10.0 Hz, C_5-H), 5.61 (2H, d, J = 15.4 Hz, C_2-H), 4.97 (2H, d, J = 10.1 Hz, C_7-H), 4.50 (2H, d, J = 11.3 Hz, one of each PMB-CH_2), 4.35 (2H, d, J = 11.3 Hz, one of each PMB-CH_2), 3.89 (2H, dd, J = 6.4, 2.2 Hz, C_9-H), 3.78 (6H, s, PMB-OCH_3), 3.43 (2H, dq, J = 6.9, 6.2 Hz, C_{11}-H), 2.45-2.40 (2H, m, C_6-H), 1.89-1.82 (4H, m, C_8-H and C_{10}-H), 1.15 (6H, d, J = 6.1 Hz, C_{11}-CH_3), 0.99 (6H, d, J = 6.6 Hz, C_6-CH_3), 0.96 (6H, d, J = 7.1 Hz, C_{10}-CH_3), 0.95 (18H, t, J = 8.0 Hz, $SiCH_2CH_3$), 0.84 (6H, d, J = 6.9 Hz, C_8-CH_3), 0.70-0.57 (12H, m, $SiCH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.5, 158.8, 145.2, 144.6, 131.3, 130.6, 128.7, 121.3, 113.7, 76.4, 76.0, 74.6, 69.0, 55.2, 42.4, 40.7, 38.4, 16.4, 16.1, 10.4, 9.7, 7.1, 5.6; **HRMS** Exact mass calcd. for $C_{58}H_{92}O_{10}Si_2Na$ [(M+Na)$^+$]: 1027.6126; found 1027.6121 (ESI$^+$).

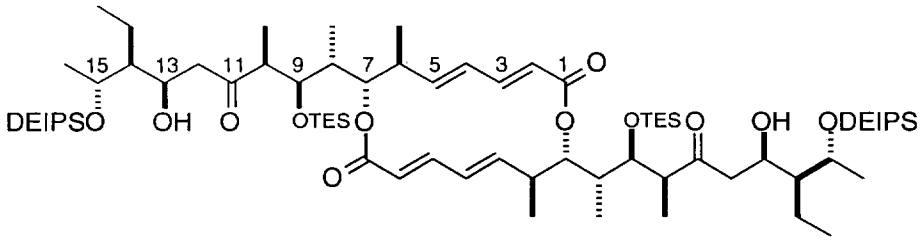
dione. To a 0 °C stirred solution of (3*E*, 5*E*, 7*S*, 8*S*, 11*E*, 13*E*, 15*S*, 16*S*)-8,16-bis[(1*R*,2*S*,3*R*,4*R*)-4-(4-methoxybenzyloxy)-2-triethylsilyloxy-1,3-dimethylpentyl]-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione (175 mg, 0.17 mmol) in CH_2Cl_2 - pH 7 buffer (10:1, 22 ml) was added DDQ (159 mg, 0.70 mmol). The resultant orange/brown suspension was stirred at 0 °C for 30 min. $NaHCO_3$ solution (10 ml, sat. aq.) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 ml) and the combined organic extracts washed successively with H_2O (20 ml) and brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20% EtOAc/hexane) to yield the hydroxy macrocycle as a white solid (95 mg, 71%). **TLC** R_f = 0.39 (25% EtOAc/hexane); **m.p.** 198-199 °C; $[\alpha]_D^{20}$ = +59.7 ° (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (liquid film) 3474, 2963, 2912, 2877, 1705, 1639, 1458, 1386 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.95 (2H, dd, *J* = 15.4, 11.2 Hz, C_3-H), 6.00 (2H, dd, *J* = 15.0, 11.2 Hz, C_4-H), 5.65 (2H, dd, *J* = 15.1, 10.0 Hz, C_5-H), 5.60 (2H, d, *J* = 15.4 Hz, C_2-H), 4.96 (2H, d, *J* = 10.1 Hz, C_7-H), 3.96 (2H, d, *J* = 7.1 Hz, C_9-H), 3.64-3.62 (2H, m, C_{11}-H), 2.47-2.41 (2H, m, C_6-H), 2.33 (2H, s br, C_9-OH), 2.03-1.99 (2H, m, C_8-H), 1.55-1.50 (2H, m, C_{10}-H), 1.16 (6H, d, *J* = 6.1 Hz, C_{11}-CH_3), 1.06 (6H, d, *J* = 6.6 Hz, C_6-CH_3), 0.98 (6H, d, *J* = 7.1 Hz, C_{10}-CH_3), 0.97 (18H, t, *J* = 8.0 Hz, $SiCH_2CH_3$), 0.81 (6H, d, *J* = 7.0 Hz, C_8-CH_3), 0.70-0.62 (12H, m, $SiCH_2CH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.8, 145.4, 144.7, 130.7, 121.3, 77.1, 74.9, 69.4, 44.2, 42.3, 38.3, 22.4, 16.3, 11.8, 10.0, 7.0, 5.3; **HRMS** Exact mass calcd. for $C_{42}H_{76}O_8Si_2Na$ [(M+Na)$^+$]: 787.4976; found 787.4971 (ESI$^+$).



17

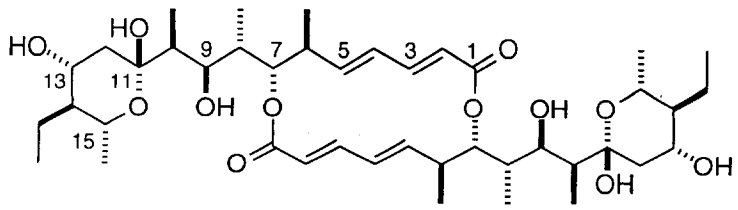
(3*E*, 5*E*, 7*S*, 8*S*, 11*E*, 13*E*, 15*S*, 16*S*)-8,16-bis[(1*R*,2*R*,3*S*)-4-oxo-2-triethylsilyloxy-1,3-dimethylpentyl]-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione (17). To a stirring solution of Dess-Martin periodinane[12] (191 mg, 4.65 mmol) in CH_2Cl_2 (5 ml) was added dropwise at ambient temperature a solution of (3*E*, 5*E*, 7*S*, 8*S*, 11*E*, 13*E*, 15*S*, 16*S*)-8,16-bis[(1*R*,2*S*,3*R*,4*R*)-4-hydroxy-2-triethylsilyloxy-1,3-dimethylpentyl]-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione (89 mg, 0.12 mmol) in CH_2Cl_2 (2 ml) and the resulting mixture stirred for 3h. The mixture was then diluted with Et_2O (10 ml) and the resulting white suspension treated with $NaHCO_3$/$Na_2S_2O_3$ mixture (1:7, 8 ml, sat. aq.). Stirring was continued at ambient temperature until the mixture became clear (*ca.* 10 min). The organic solution was separated, washed with $NaHCO_3$ solution (6 ml, sat. aq.) and brine (6 ml) and then dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the crude product purified by flash chromatography (15% EtOAc/hexane) to give **17** as a white crystalline solid (75 mg, 85%, 56% over three steps from **16**). **TLC** R_f = 0.46 (25% EtOAc/hexane); **m.p.** 165-166 °C; $[\alpha]_D^{20}$ = +98.0 ° (*c* = 1.0, $CHCl_3$); **IR** ν_{max} (liquid film) 2957, 2912, 2877, 1707, 1639, 1614, 1458, 1356 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.95 (2H, dd, *J* = 15.3, 11.2 Hz, C_3-H), 5.99 (2H, dd, *J* = 15.0, 11.2 Hz, C_4-H), 5.64 (2H, dd, *J* = 15.1, 10.0 Hz, C_5-H), 5.58 (2H, d, *J* = 15.5 Hz, C_2-H), 4.94 (2H, d, *J* = 10.1 Hz, C_7-H), 4.01 (2H, dd, *J* = 5.8, 4.5 Hz, C_9-H), 2.76-2.71 (2H, m, C_{10}-H), 2.44-2.39 (2H, m, C_6-H), 2.19 (6H, s, C_{11}-CH_3), 1.89 (2H, dq, *J* = 6.8, 6.8 Hz, C_8-H), 1.12 (6H, d, *J* = 7.0 Hz, C_{10}-CH_3), 1.02 (6H, d, *J* = 6.5 Hz, C_6-CH_3), 0.99 (6H, d, *J* = 7.1 Hz, C_8-CH_3), 0.94 (18H, t, *J* = 8.0 Hz, $SiCH_2CH_3$), 0.64-0.59 (12H, m,

SiC<u>H</u>$_2$CH$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 211.2, 167.4, 145.3, 144.4, 130.8, 121.3, 75.7, 74.7, 50.5, 42.3, 37.9, 29.3, 16.2, 11.4, 10.6, 7.0, 5.2; **HRMS** Exact mass calcd. for $C_{42}H_{72}O_8Si_2Na$ [(M+Na)$^+$]: 783.4663; found 783.4656 (ESI$^+$).



18

(3*E*, 5*E*, 7*S*, 8*S*, 11*E*, 13*E*, 15*S*, 16*S*)-8,16-bis[(1*R*,2*R*,3*S*,6*R*,7*S*,8*R*)-8-(diethyl-*iso*-propylsilyloxy)-7-ethyl-6-hydroxy-4-oxo-2-triethylsilyloxy-1,3-dimethylnonyl]-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione (18). To a stirring solution of the macrocyclic ketone **17** (71 mg, 93 μmol) in THF (5.5 ml) at -78 °C was added dropwise LiHMDS (0.56 ml, 0.56 mmol). The reaction mixture was stirred at -78 °C for 1 h and the aldehyde **5** (381 mg, 1.40 mmol) was added as a solution in THF (5 ml) dropwise *via* cannula. After stirring for 1.5 h at -78 °C, the reaction was diluted with Et_2O (5 ml) and quenched by the addition of $NaHCO_3$ solution (10 ml, sat. aq.), warmed to 0 °C and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 ml) and the combined organic extracts washed with brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10→20% EtOAc/hexane) to yield the macrocycle aldol adduct **17** as a white solid (87 mg, 75%). **TLC** R_f = 0.62 (25% EtOAc:hexane); **m.p.** 155-156 °C; $[\alpha]_D^{20}$ = +46.8 ° (*c* = 0.8, $CHCl_3$); **IR** ν_{max} (liquid film) 3491, 3020, 2959, 2880, 1707, 1639, 1614, 1475, 1302 cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.93 (2H, dd, *J* = 15.3, 11.2 Hz, C_3-<u>H</u>), 5.99 (2H, dd, *J* = 14.9, 11.2 Hz, C_4-<u>H</u>), 5.62 (2H, dd, *J* = 15.0, 9.8 Hz, C_5-<u>H</u>), 5.58 (2H, d, *J* = 15.5 Hz, C_2-<u>H</u>), 4.95 (2H, d, *J* = 10.1 Hz, C_7-<u>H</u>), 4.60 (2H, app. t, *J* = 6.1 Hz, C_{13}-<u>H</u>), 4.17 (2H, dq, *J* = 7.5, 6.3 Hz, C_{15}-<u>H</u>), 3.97 (2H, dd, *J* = 5.1, 5.1 Hz, C_9-<u>H</u>), 3.61 (2H, s, C_{13}-O<u>H</u>), 2.81 (2H, dd, *J* = 16.4, 7.7 Hz, one of each C_{12}-<u>H</u>), 2.81-2.79 (2H, m, C_{10}-<u>H</u>), 2.44 (2H, dd, *J* = 16.5, 4.7 Hz, one of each C_{12}-<u>H</u>), 2.37 (2H, ddq, *J* = 13.1, 6.8, 6.8 Hz, C_6-<u>H</u>), 1.88 (2H, ddq, *J* = 13.3, 6.7, 6.7 Hz, C_8-<u>H</u>), 1.54-1.44 (4H, m, C_{14}-C<u>H</u>$_2$CH$_3$), 1.32 (6H, d, *J* = 6.4 Hz, C_{15}-C<u>H</u>$_3$), 1.23-1.17 (2H, m, C_{14}-<u>H</u>), 1.10 (6H, d, *J* = 7.0 Hz, C_{10}-C<u>H</u>$_3$), 1.00-0.95 (56H, m, C_6-C<u>H</u>$_3$, C_8-C<u>H</u>$_3$, SiCH$_2$C<u>H</u>$_3$, Si<u>C</u>H(CH$_3$)$_2$ and SiCH(C<u>H</u>$_3$)$_2$), 0.93 (6H, t, *J* = 7.9 Hz, C_{14}-CH$_2$C<u>H</u>$_3$), 0.68-0.57 (20H, m, SiC<u>H</u>$_2$CH$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 212.0, 167.3, 145.2, 144.4, 130.8, 121.4, 75.7, 75.1, 70.2, 67.0, 50.9, 50.2, 46.7, 42.4, 37.8, 22.3, 17.7, 17.4, 17.3, 17.3, 16.2, 12.9, 12.7, 11.5, 10.9, 7.0, 6.9, 5.3, 4.0, 3.7; **HRMS** Exact mass calcd. for $C_{68}H_{128}O_{12}Si_4Na$ [(M+Na)$^+$]: 1271.8380; found 1271.8375 (ESI$^+$).



***Elaiolide* (2)**

(3*E*, 5*E*, 7*S*, 8*S*, 11*E*, 13*E*, 15*S*, 16*S*)-8,16-bis[(1*S*,2*R*,3*S*)-3-[(2*R*,4*R*,6*R*)-5-ethyl-3,4,5,6-tetrahydro-2,4-dihydroxy-6-methyl-2H-pyran-2-yl]-2-hydroxy-1-methylbutyl]-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione, Elaiolide (2). To a solution of **18** (16.2 mg, 13 μmol) in THF (0.8 ml) at ambient temperature was added a buffered solution of pyridinium hydrofluoride (0.1 ml, stock solution prepared from 1 g of Aldrich pyridinium hydrofluoride, 5 ml of pyridine, and 6.5 ml of THF) and 1 drop of water. After stirring for 3 h, more buffered solution of pyridinium hydrofluoride (0.1 ml) and 1 drop of water were added and the mixture was stirred at ambient temperature for 10 h. The reaction was diluted with CH_2Cl_2 (15 ml), quenched by the addition of $NaHCO_3$ solution (20 ml, sat. aq.) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 ml) and the combined organic extracts washed with brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by preparative thin-layer chromatography (0.25 x 200 x 200 mm plate, 20% hexane/EtOAc) to afford Elaiolide **2** as a white, crystalline solid (7.9 mg, 80%). **TLC** R_f = 0.32 (80% EtOAc/hexane); $[\alpha]_D^{20}$ = +28.2° (*c* = 0.3, $CHCl_3$) (lit.: +28 °, *c* = 0.3, $CHCl_3$);[12] **IR** ν_{max} (liquid film) 3425, 2970, 2932, 1694, 1638, 1614, 1463, 1384, 1305, 1259, 1227, 1184, 1150, 1000 cm^{-1}; **^{1}H NMR** (500MHz, $CDCl_3$) δ 6.98 (2H, dd, *J* = 15.3, 11.2 Hz, C_3-H), 6.12 (2H, dd, *J* = 15.0, 11.2 Hz, C_4-H), 5.69 (2H, d, *J* = 15.4 Hz, C_2-H), 5.63 (2H, dd, *J* = 15.0, 9.6 Hz, C_5-H), 5.28 (2H, d, *J* = 1.8 Hz, C_{11}-OH), 4.72 (2H, dd, *J* = 10.2, 1.4 Hz, C_7-H), 4.10 (2H, s, C_9-OH), 4.09 (2H, m, C_9-H), 3.95 (2H, ddd, *J* = 10.5, 10.5, 4.6 Hz, C_{13}-H), 3.87 (2H, dq, *J* = 10.2, 6.2 Hz, C_{15}-H), 2.54 (2H, ddq, *J* = 10.2, 9.6, 6.8 Hz, C_6-H), 2.28 (2H, dd, *J* = 11.9, 4.7 Hz, C_{12}-H_{eq}), 1.95 (2H, m, C_8-H), 1.72 (2H, q, *J* = 7.0 Hz, C_{10}-H), 1.65-1.60 (2H, m, one of each C_{14}-CH_2CH_3), 1.54-1.48 (2H, m, one of each C_{14}-CH_2CH_3), 1.28-1.23 (2H, m, C_{14}-H), 1.25 (2H, s, C_{13}-OH), 1.17 (2H, ddd, *J* = 11.3, 11.3, 1.8 Hz, C_{12}-H_{ax}), 1.10 (6H, d, *J* = 6.2 Hz, C_{15}-CH_3), 1.03 (6H, d, *J* = 6.6 Hz, C_6-CH_3), 1.00 (6H, d, *J* = 7.1 Hz, C_{10}-CH_3), 0.90 (6H, t, *J* = 7.6 Hz, C_{14}-CH_2CH_3), 0.81 (6H, d, *J* = 6.9 Hz, C_8-CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.0, 145.0, 144.3, 132.0, 121.0, 99.1, 77.9, 70.6, 67.1, 66.9, 51.0, 43.5, 41.5, 40.8, 35.9, 19.4, 19.2, 14.9, 9.9, 8.7, 7.0; **HRMS** Exact mass calcd. for $C_{42}H_{68}O_{12}Na$ [(M+Na)$^+$]: 787.4608; found: 787.4567 (ESI$^+$).

The synthetic sample of elaiolide (**2**) was confirmed by comparison with a sample (5 mg) obtained from the degradation of elaiophylin according to the procedure described by Zeeck[13] (elaiophylin was kindly provided by Professor S. V. Ley, Cambridge). Tabulated ^{1}H and ^{13}C NMR data for elaiolide are presented alongside comparative data previously reported for **2** by Zeek,[13] and Evans.[14]

Table I: ^{1}H NMR Data Comparison in $CDCl_3$ for Elaiolide.

Atom	δ H ppm, mult., *J* Hz[a]	δ H ppm, mult., *J* Hz (Lit[13,a])	δ H ppm, mult., *J* Hz (Lit[14,b])
2	5.69, d, 15.4Hz	5.70, d, 16Hz	5.68, d, 15.4Hz
3	6.98, dd, 15.3/11.2Hz	6.97, dd, 16/12Hz	6.97, dd, 15.4/11.1Hz
4	6.12, dd, 15.0/11.2Hz	6.13, dd, 15/12Hz	6.12, dd, 15.0/11.1Hz
5	5.63, dd, 15.0/9.6Hz	5.64, dd, 15/9Hz	5.62, dd, 15.0/9.5Hz
6	2.54, ddq, 10.2/9.6/6.8Hz	2.54, m	2.54, ddq, 10.1/9.5/6.8Hz
6-C<u>H</u>$_3$	1.03, d, 6.6Hz	1.04, d, 7Hz	1.03, d, 6.8Hz
7	4.72, dd, 10.2/1.4Hz	4.73, d br, 10Hz	4.72, dd, 10.1/1.4Hz
8	1.95, m	1.96, t br	1.95, ddq, 10.0/6.9/1.4Hz
8-C<u>H</u>$_3$	0.81, d, 6.9Hz	0.80, d, 7Hz	0.80, d, 6.9Hz
9	4.09, m	4.11, d br, 10Hz	4.10, ddd, 10/3.6/1.5Hz
9-O<u>H</u>	4.10, s	4.13, s	4.16, d, 3.6Hz
10	1.72, q br, 7.0Hz	1.74, q br, 7Hz	1.71, q, 7.1Hz
10-C<u>H</u>$_3$	1.00, d, 7.1Hz	1.00, d, 7Hz	0.99, d, 7.1Hz
11-O<u>H</u>	5.28, d, 1.8Hz	5.23, d, 2Hz	5.32, d, 1.8Hz
12_{eq}	2.28, dd, 11.9/4.7Hz	2.30, dd, 12/5Hz	2.28, dd, 11.9/4.7Hz
12_{ax}	1.17, ddd, 11.3/11.3/1.8Hz	1.17, ddd, 11/11/2Hz	1.16, dt, 11.7/2.0Hz
13	3.95, ddd, 10.5/10.5/4.6Hz	3.95, ddd, 10/10/5Hz	3.94, m
13-O<u>H</u>	1.25, s		1.66, s
14	1.25, m	~1.4, m	1.07, m
14-C<u>H</u>$_2$-CH$_3$	1.62 and 1.51, m	1.5-1.7, m	1.62 and 1.49, m
14-CH$_2$-C<u>H</u>$_3$	0.90, t, 7.6Hz	0.89, t, 7Hz	0.89, t, 7.6Hz
15	3.87, dq, 10.2/6.2Hz	3.85, dq, 10/7Hz	3.86, dq, 10.2/6.2Hz
15-C<u>H</u>$_3$	1.10, d, 6.2Hz	1.10, d, 6Hz	1.10, d, 6.2Hz

[a]Measured at 500 MHz. [b]Measured at 400 MHz.

Table II: ^{13}C NMR Data Comparison in $CDCl_3$ for Elaiolide.

Atom	δ C ppm	δ C ppm (Lit[13])	δ C ppm (Lit[14])
1	170.0	170.6	170.1
2	121.0	121.0	121.0
3	145.0	145.1	145.1
4	132.0	132.0	132.1
5	144.3	144.3	144.4
6	40.8	40.8	40.8
6-<u>C</u>H$_3$	14.9	14.9	15.0
7	77.9	77.9	77.9
8	35.9	35.9	35.9
8-<u>C</u>H$_3$	9.9	9.9	9.8
9	70.6	70.6	70.6
10	41.5	41.6	41.5
10-<u>C</u>H$_3$	7.0	7.0	7.0
11	99.1	99.1	99.2
12	43.5	43.5	43.5
13	67.1	67.1	67.0
14	51.0	51.0	50.9
14-<u>C</u>H$_2$-CH$_3$	19.4	19.4	19.4
14-CH$_2$-<u>C</u>H$_3$	8.7	8.7	8.8
15	66.9	66.8	66.9
15-<u>C</u>H$_3$	19.2	19.2	19.3

Footnotes and References:

1) Neupert-Laves, K.; Dobler, M. *Helv. Chim. Acta* **1982**, *65*, 262.

2) Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

3) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd Ed., Pergamon Press: Oxford, 1988.

4) $(Chx)_2BCl$ (31 ml, 130.3 mmol, 78%) was prepared as described in: Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1992**, *57*, 2417.

5) (*S*)-2-benzoyloxypentan-3-one ((*S*)-**8**, 15.85 g, 76.85 mmol, 70%, 3 steps) and (*S*)-2-benzoyloxyhexan-3-one ((*S*)-**10**, 8.20 g, 37.23 mmol, 63%, 3 steps) were prepared as described in: Paterson, I.; Wallace, D.; Cowden, C. *Synthesis* **1998**, 639.

6) PMB-OTCA (56.4 g, 199.60 mmol, 92%) was prepared as described in: Paril, V. J. *Tetrahedron Lett.* **1996**, *37*, 499, 1481.

7) DEIPSCl (20.15 g, 122.31 mmol, 85%) was prepared as described in: Toshima, K.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2369.

8) (*S*)-1-benzyloxy-2-methylpentan-3-one ((*S*)-**6**, 15.25 g, 73.93 mmol, 87%, 3 steps) was prepared as described in: Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287 and Williams, M. J.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461 for the formation of the Weinreb amide.

9) Tetramethylammonium triacetoxyborohydride was prepared as described in: Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

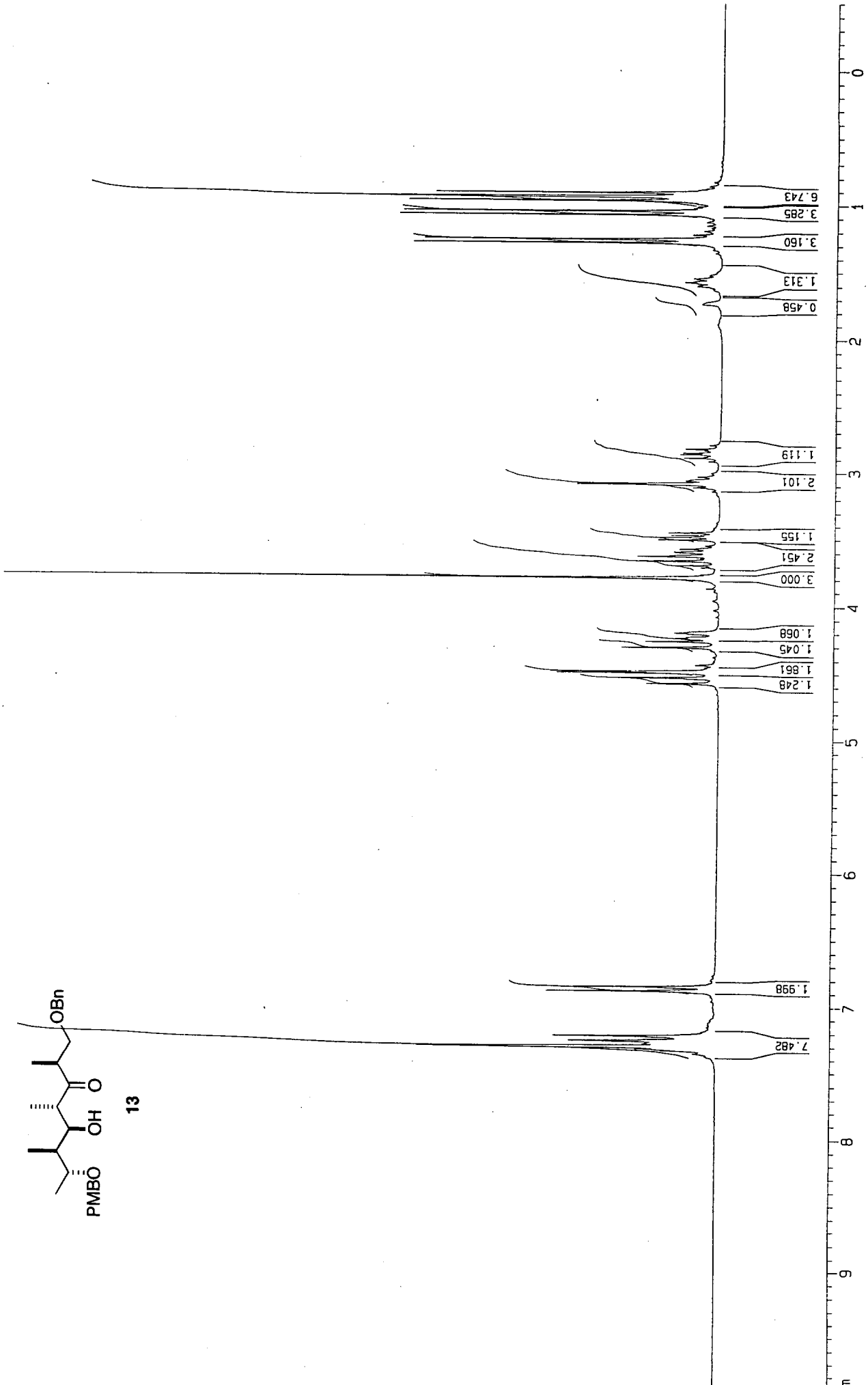
10) (*E*)-3-iodoacrylic acid prepared according to a modified procedure from Zoller, T.; Ugen, D. *Tetrahedron Lett.* **1998**, *39*, 6719, as following: The crude *Z*-*E*-3-iodoacrylic acid (5.6 g, 28.29 mmol, 5:1 *Z*:*E* mixture determined by 500 MHz ^1H NMR integration) was taken up in 55% HI (10 ml) and the resulting solution was stirred at 90 °C for less than 5 min to provide, after workup and recrystallization from CH_2Cl_2/hexane, the pure (*E*)-3-iodoacrylic acid as a white solid (4.75 g, 85%, m.p. 140-141 °C).

11) CuTC was prepared as described in: Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

12) Dess-Martin periodinane was prepared as described in: Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277 and Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

13) Bindseil, K. U.; Zeeck, A. *J. Org. Chem.* **1993**, *58*, 5487.

14) Evans, D.A.; Fitch, D. M. *J. Org. Chem.* **1997**, *62*, 454.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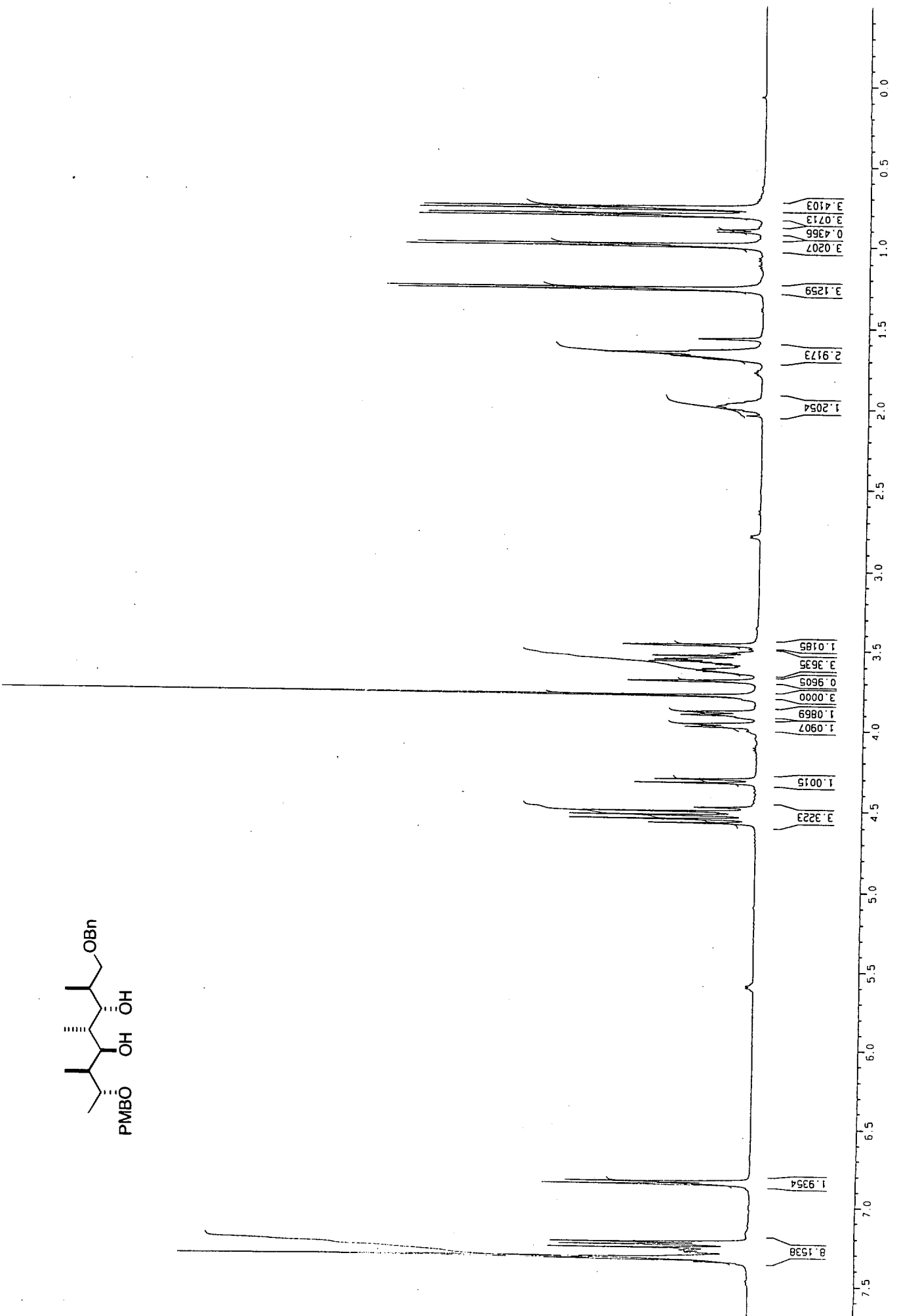

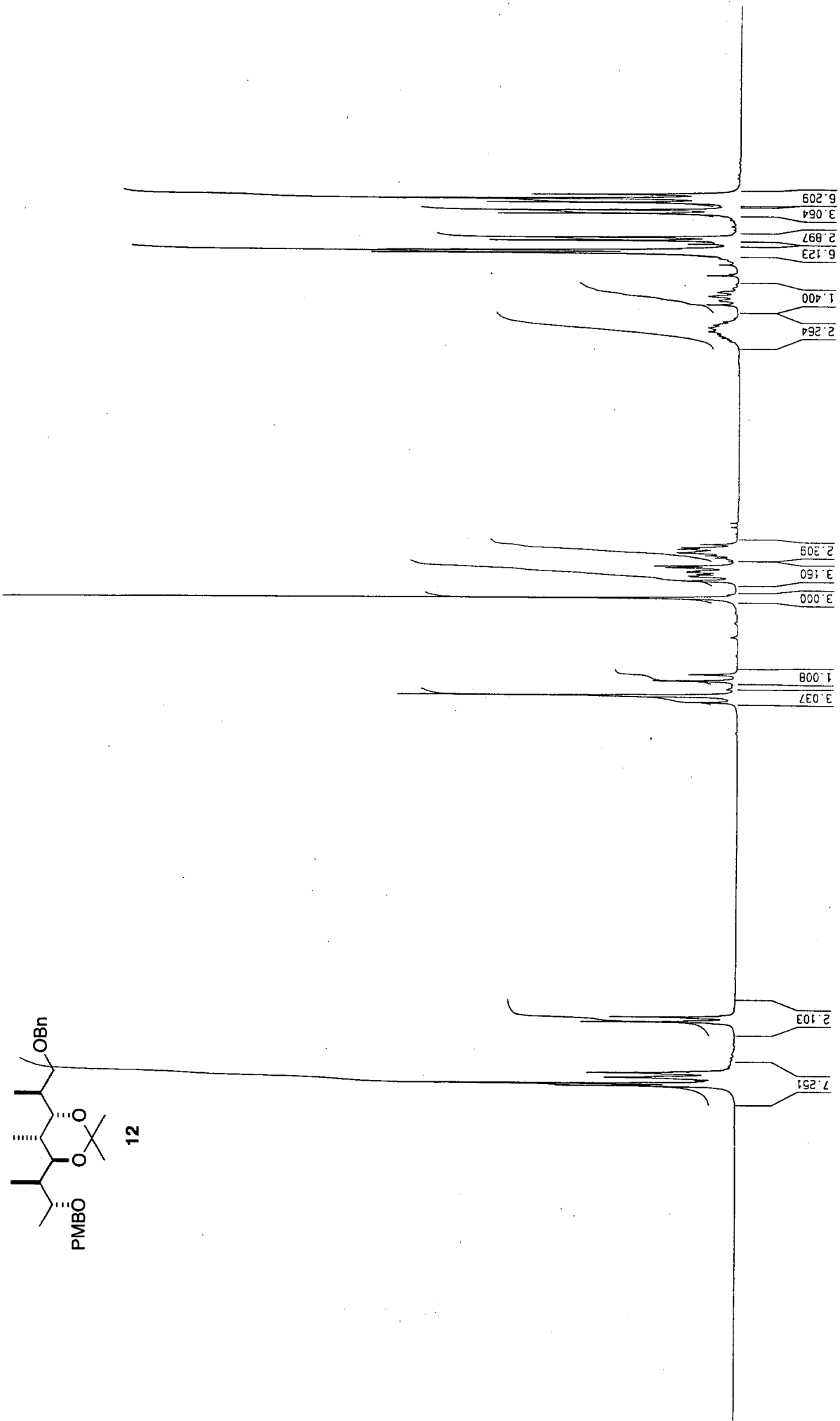

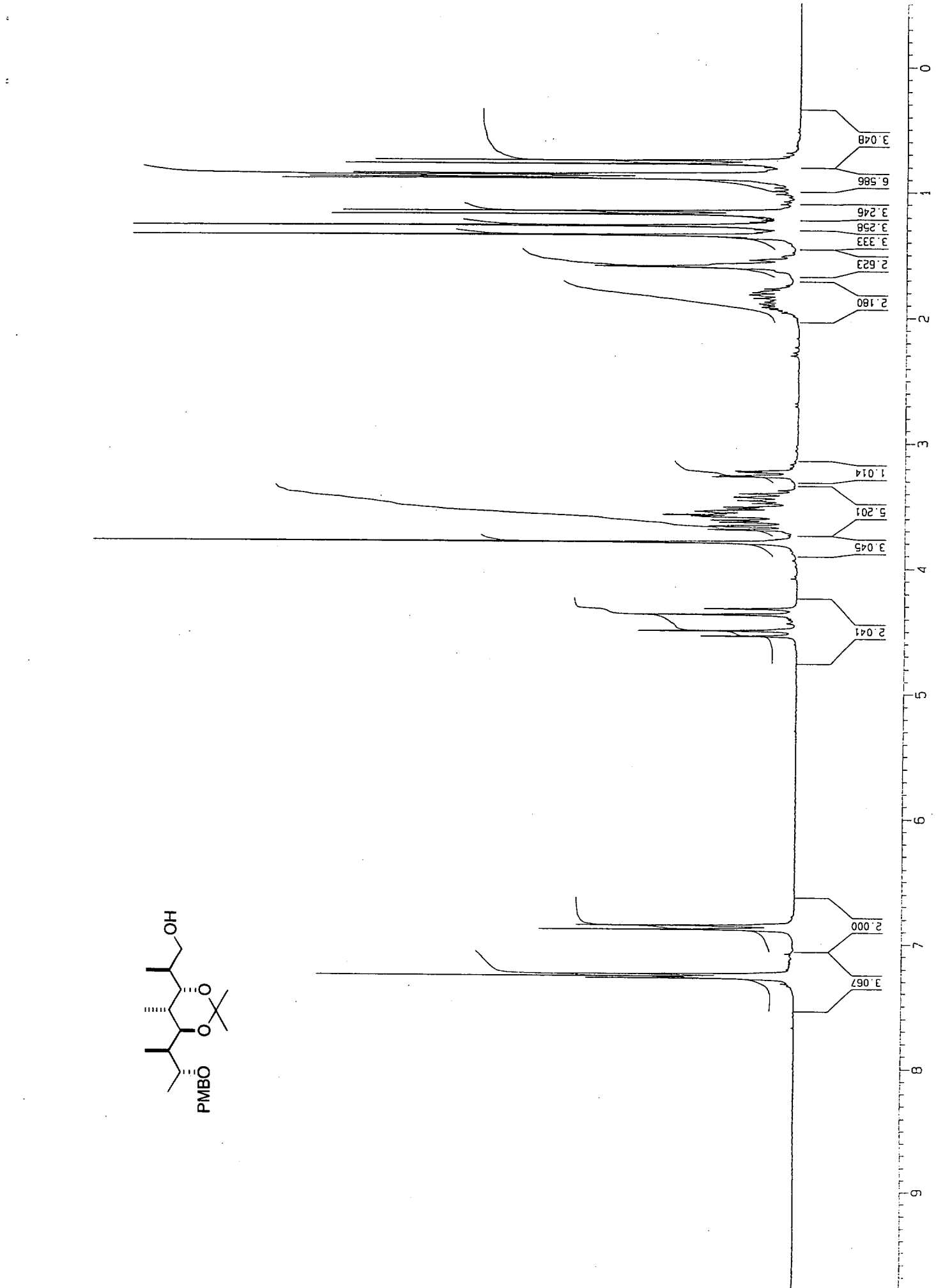

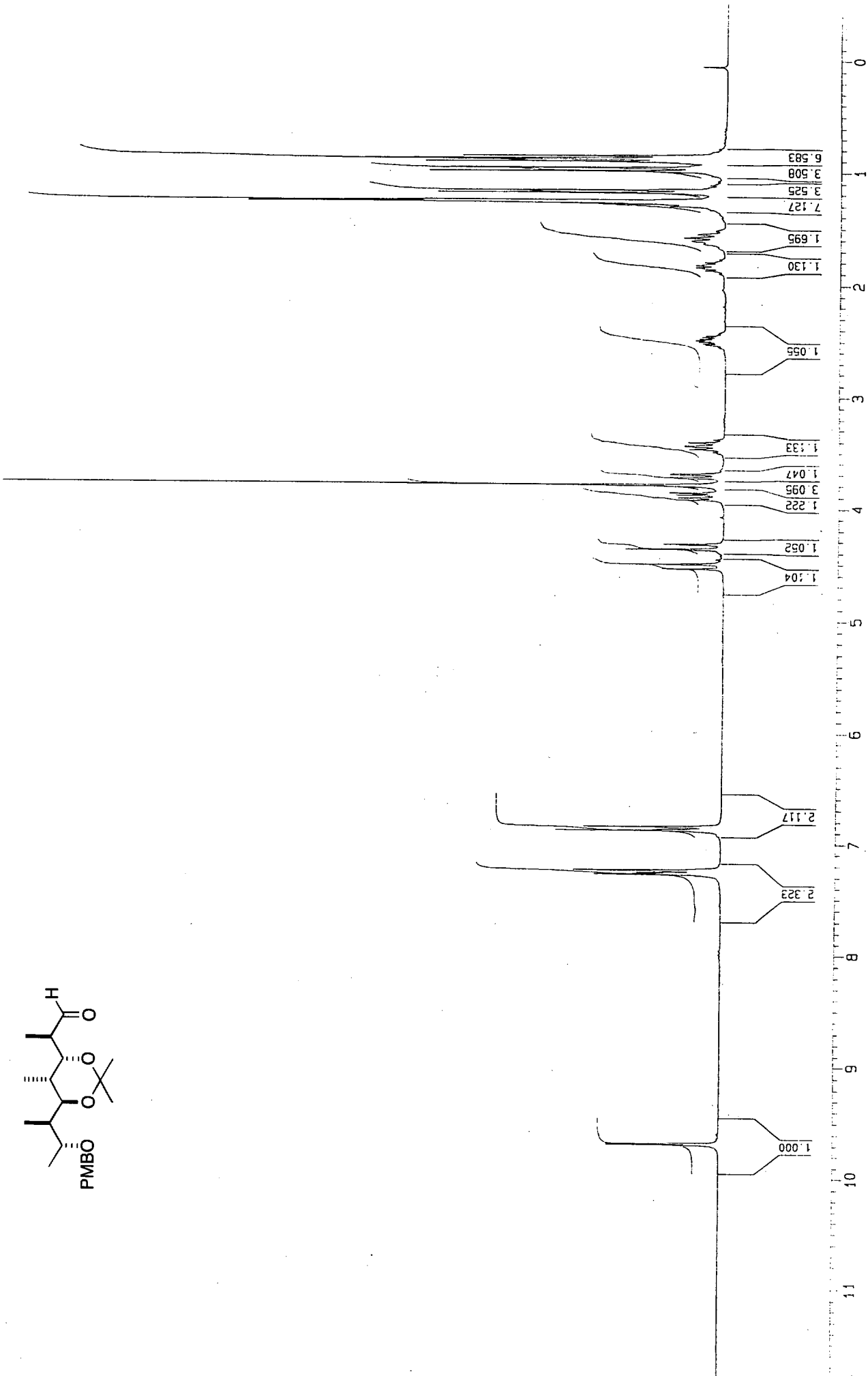

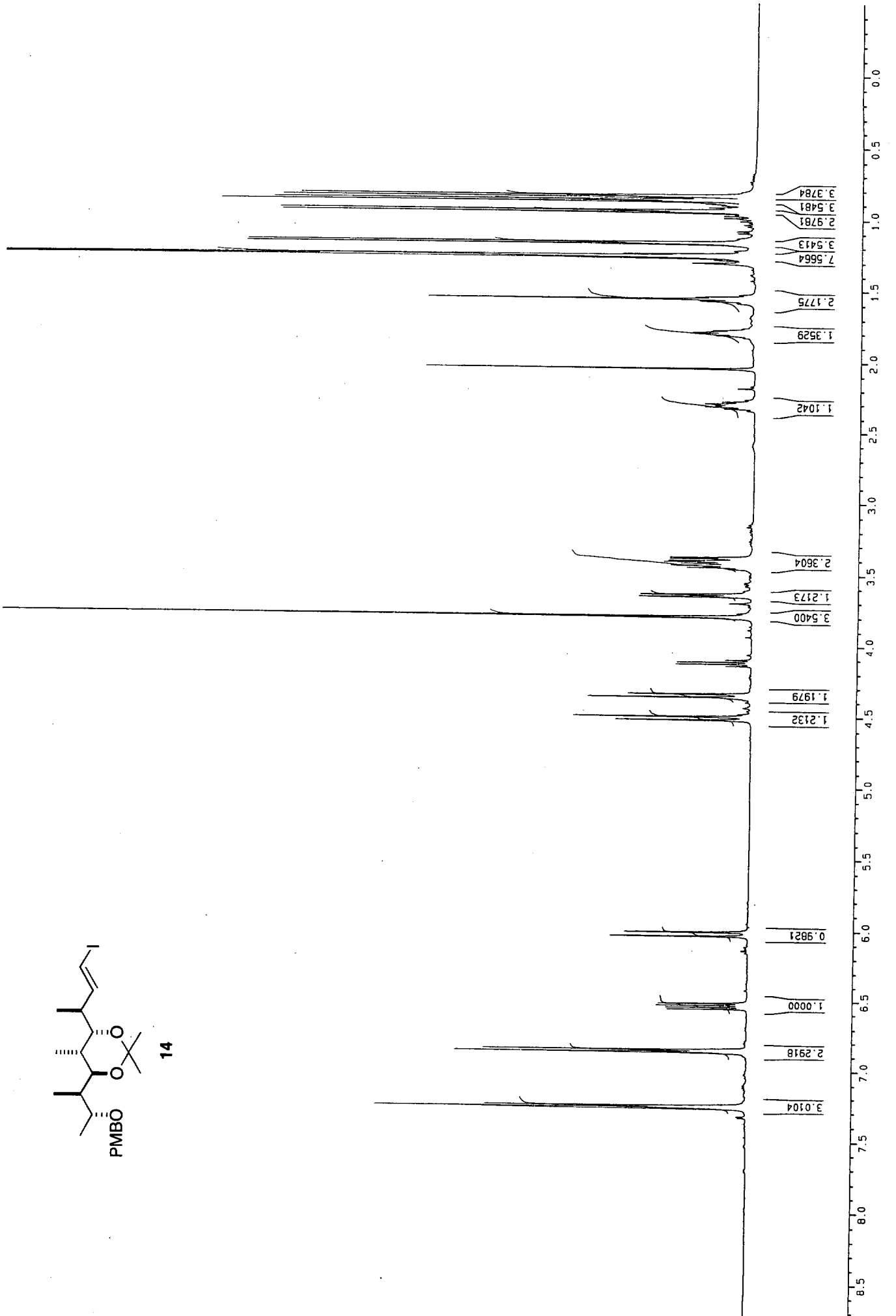

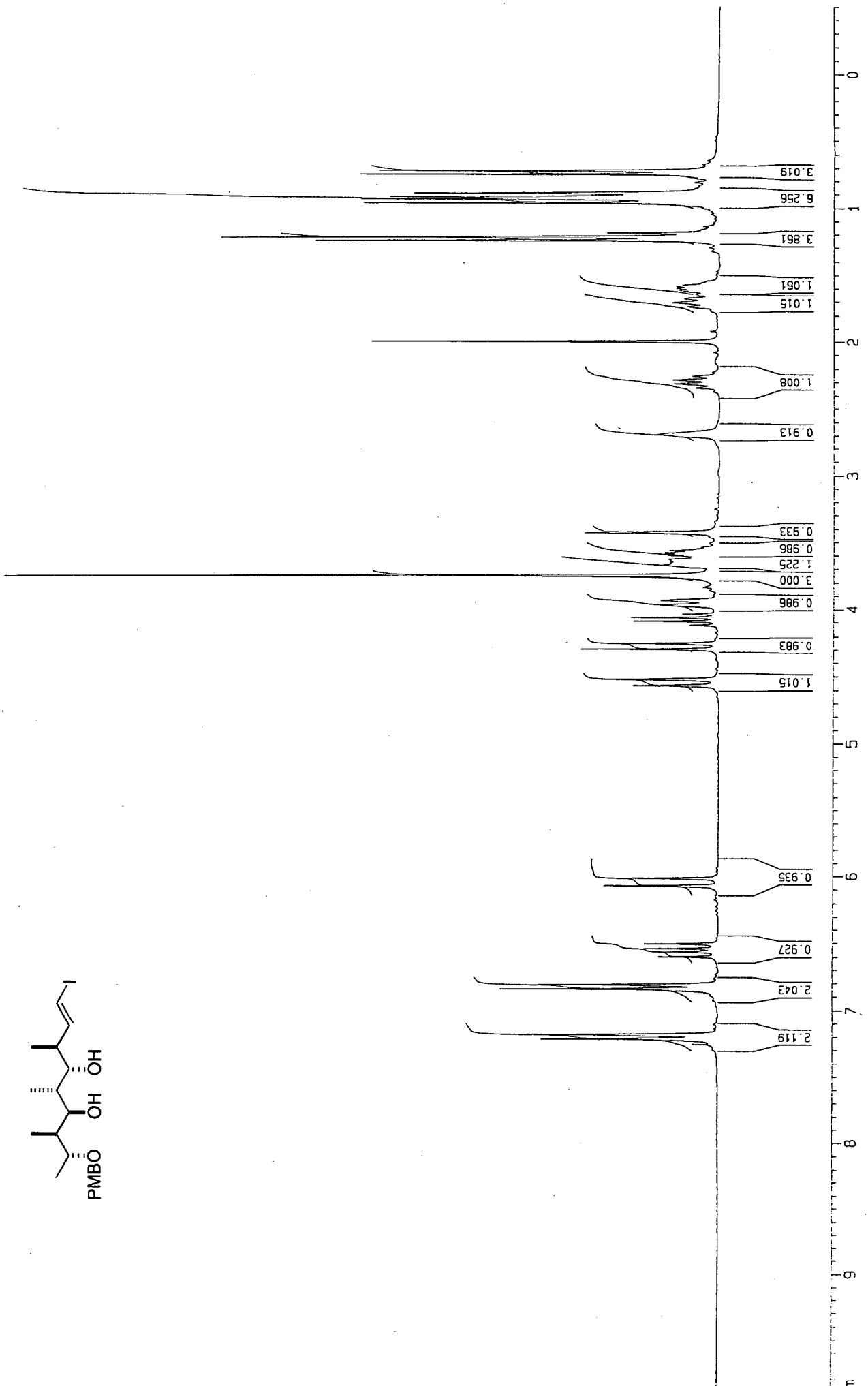

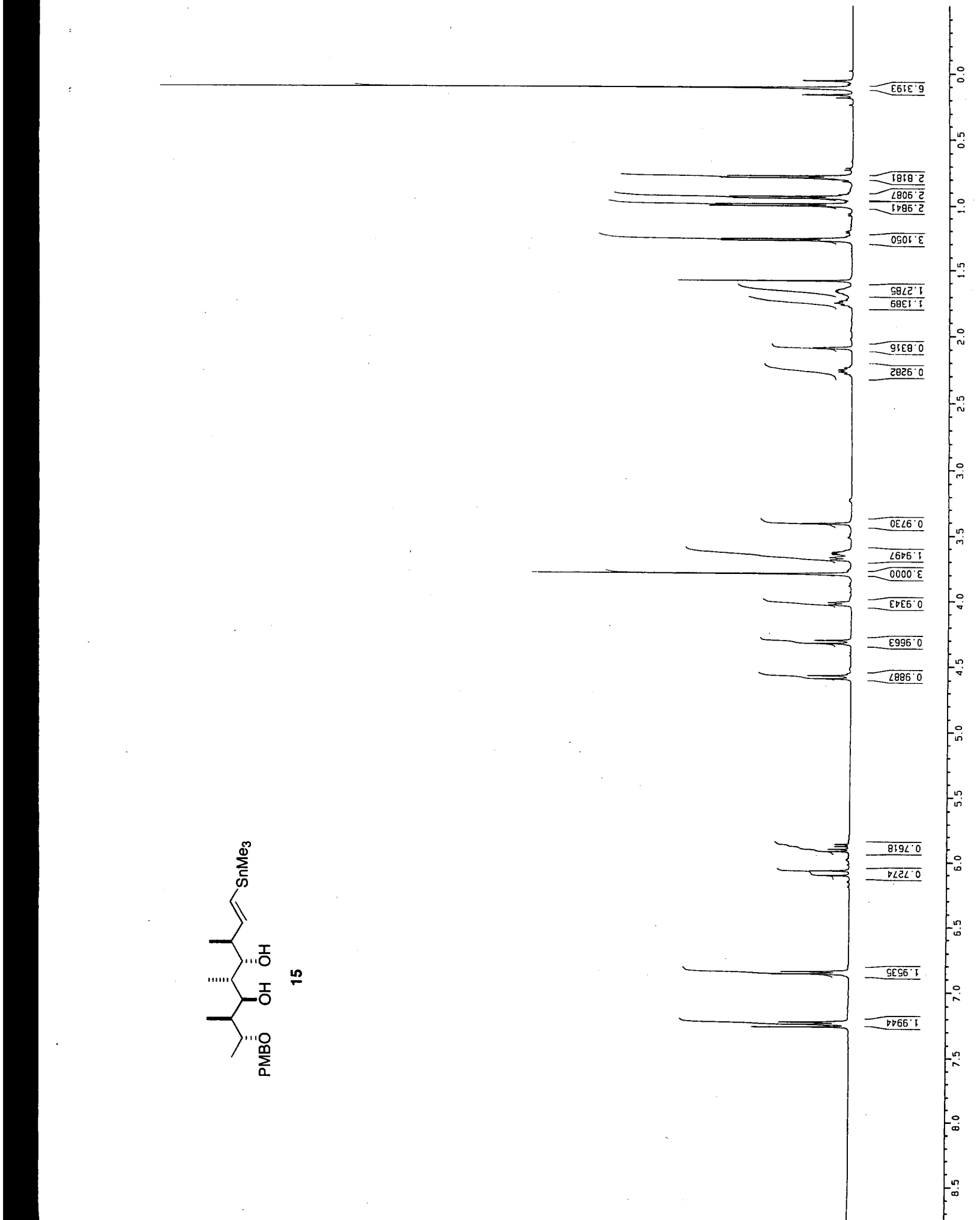

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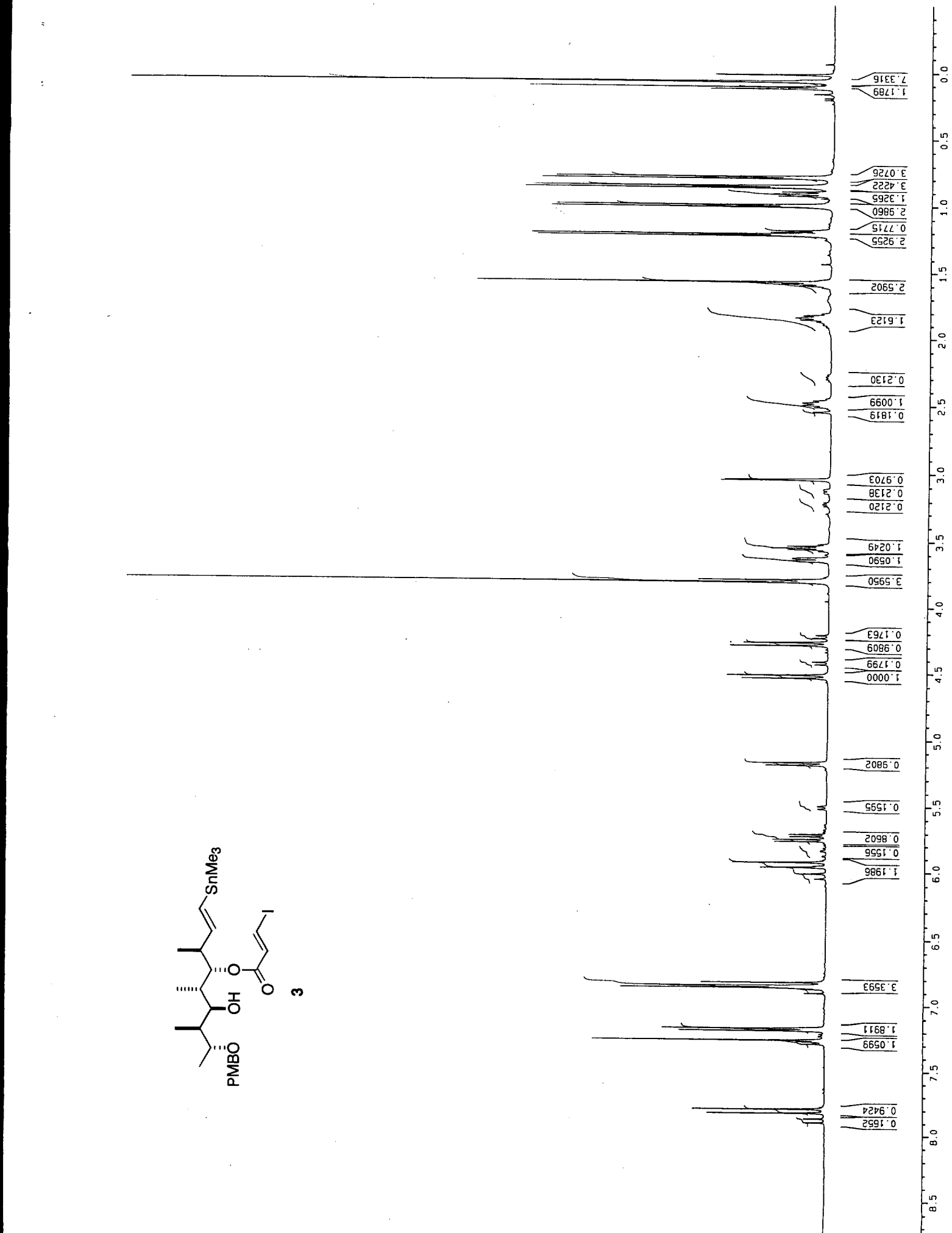

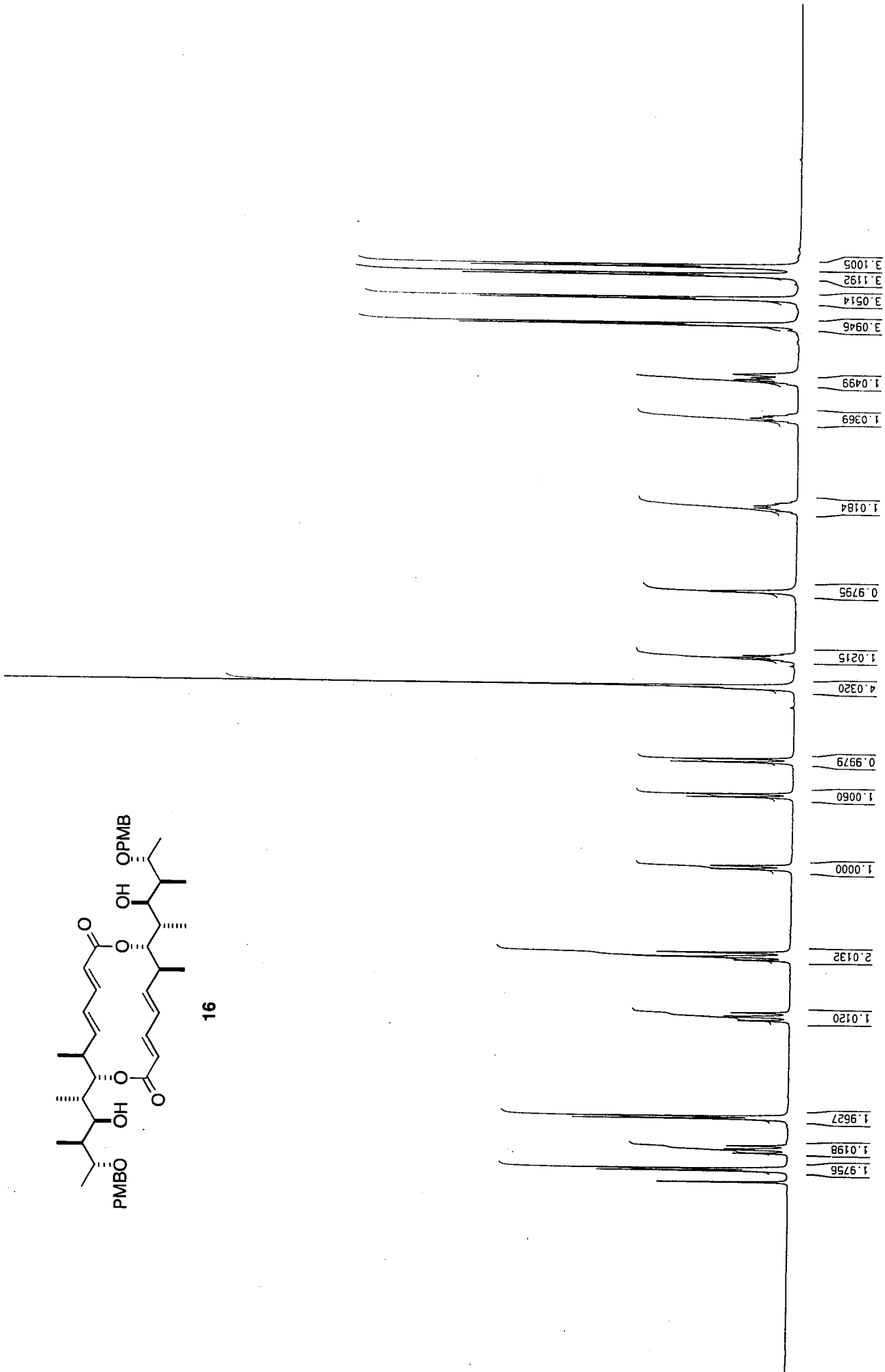
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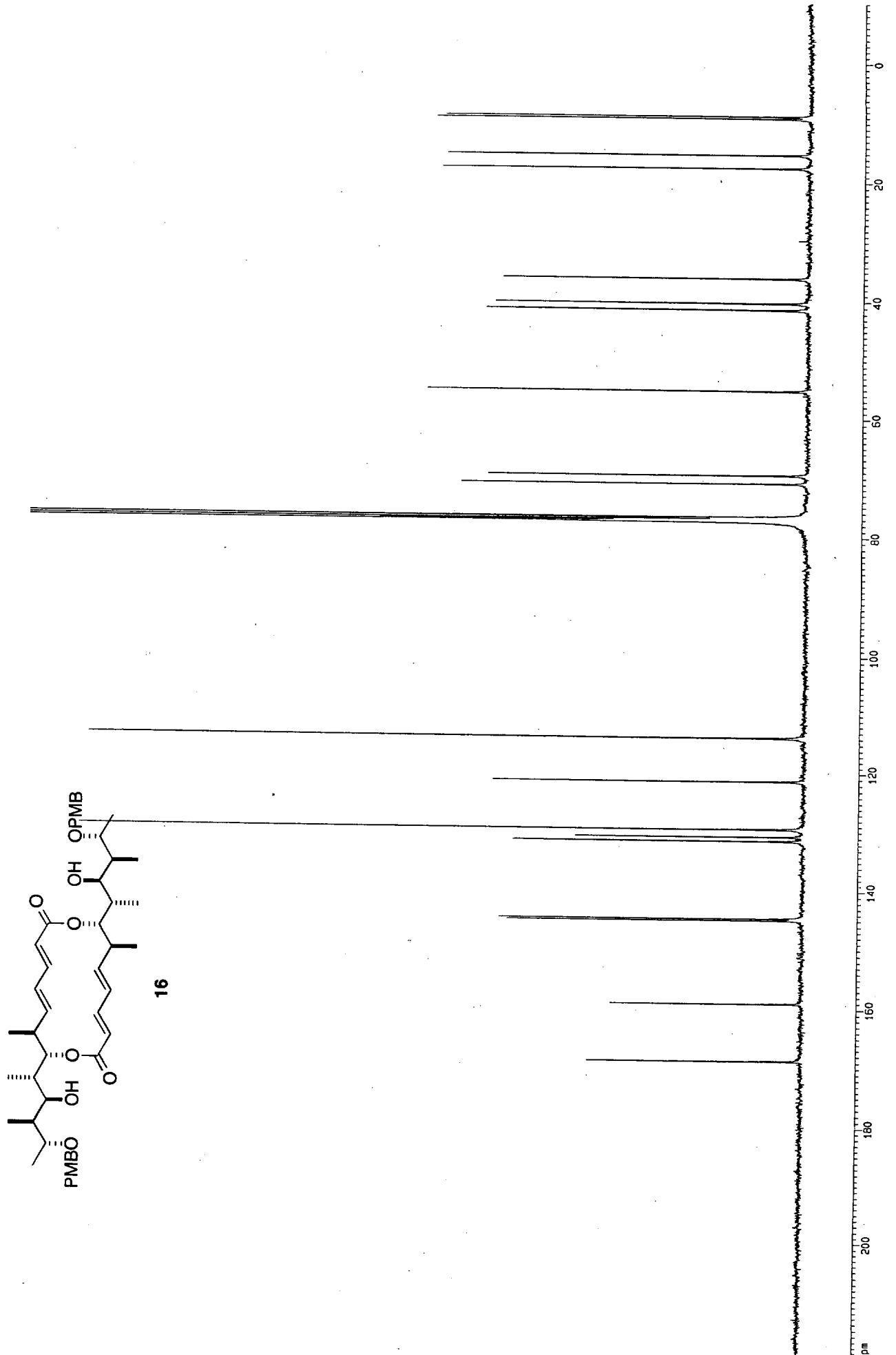

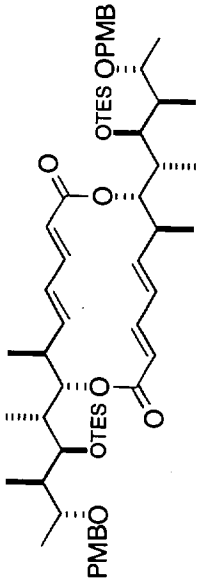
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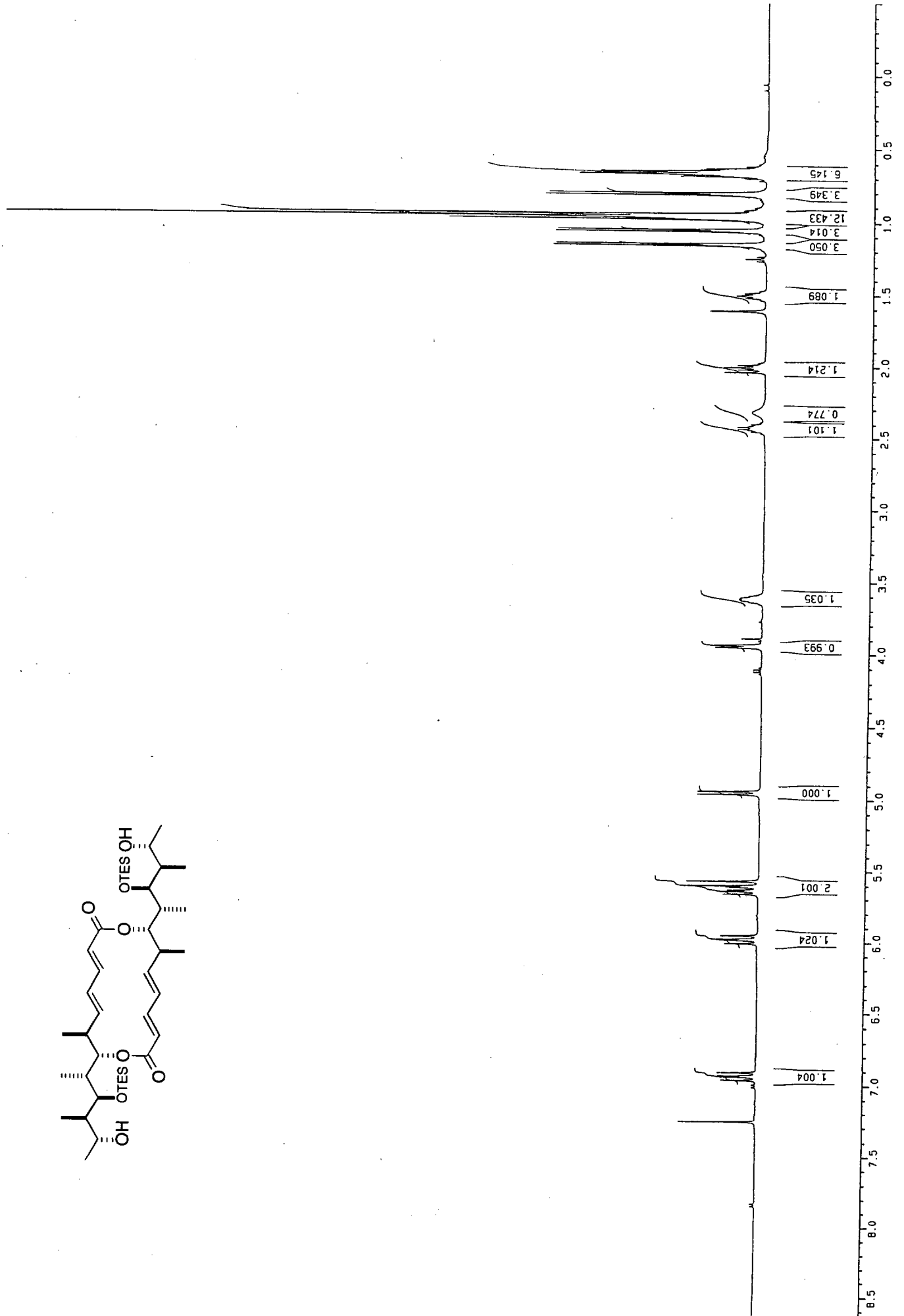
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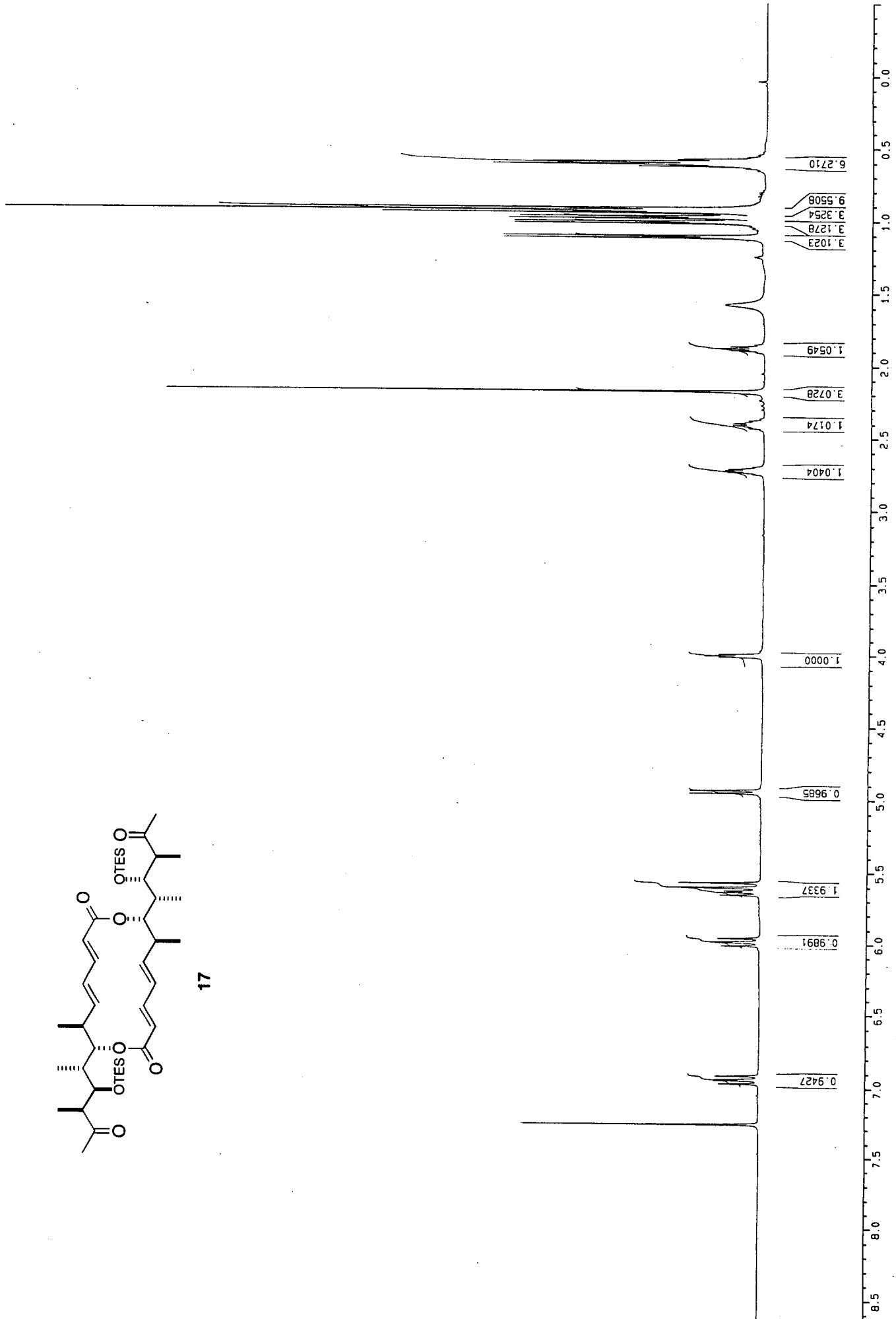

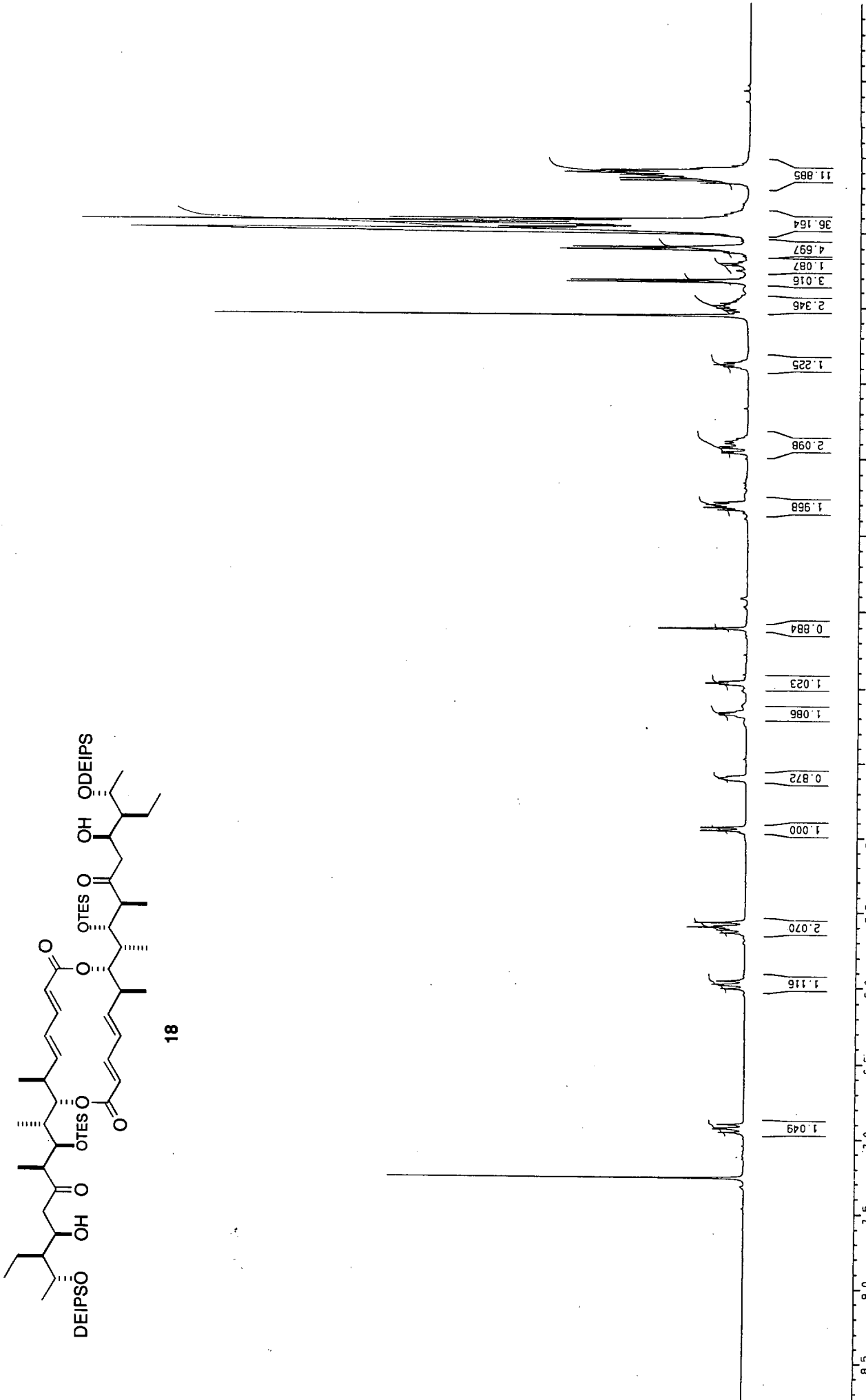

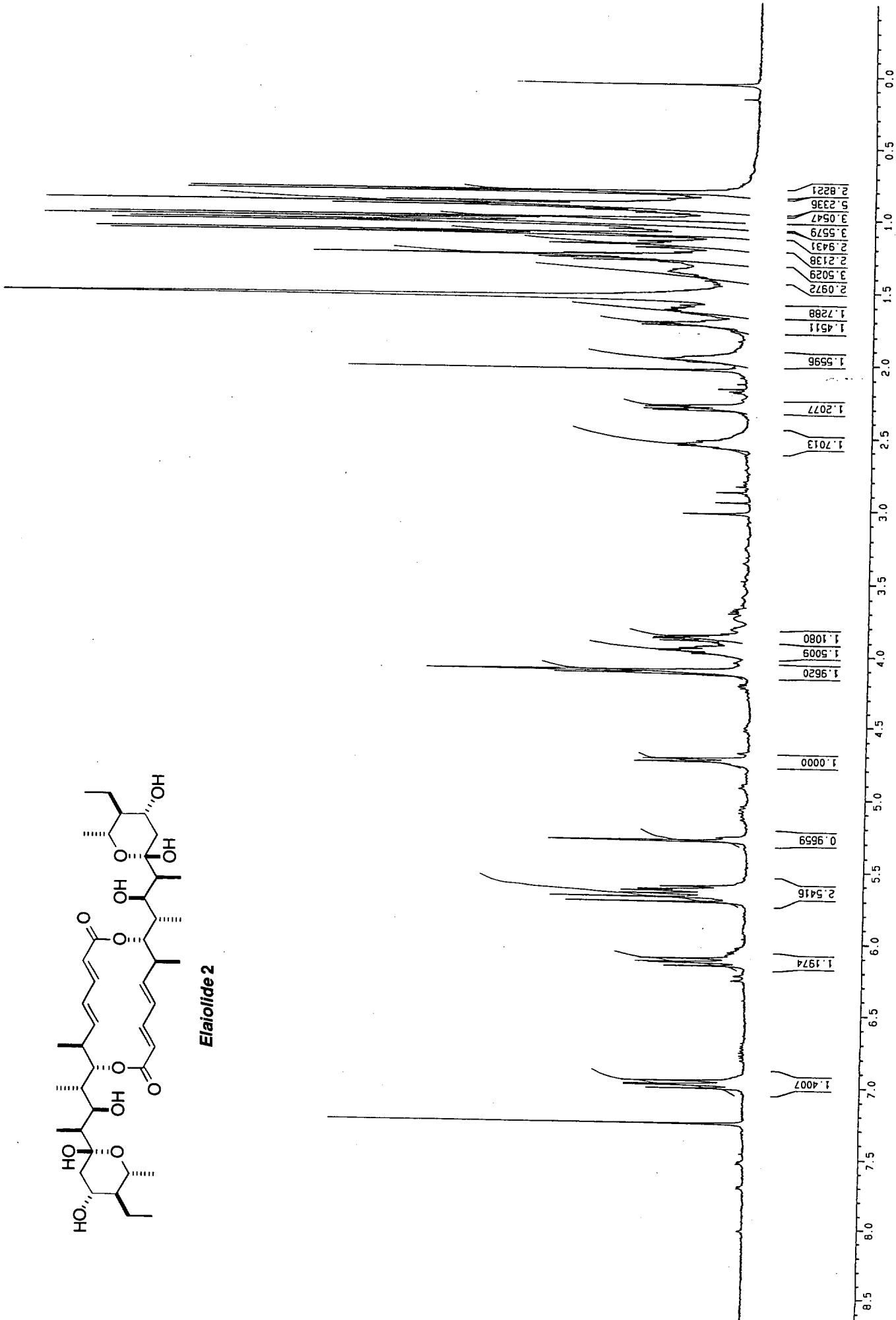

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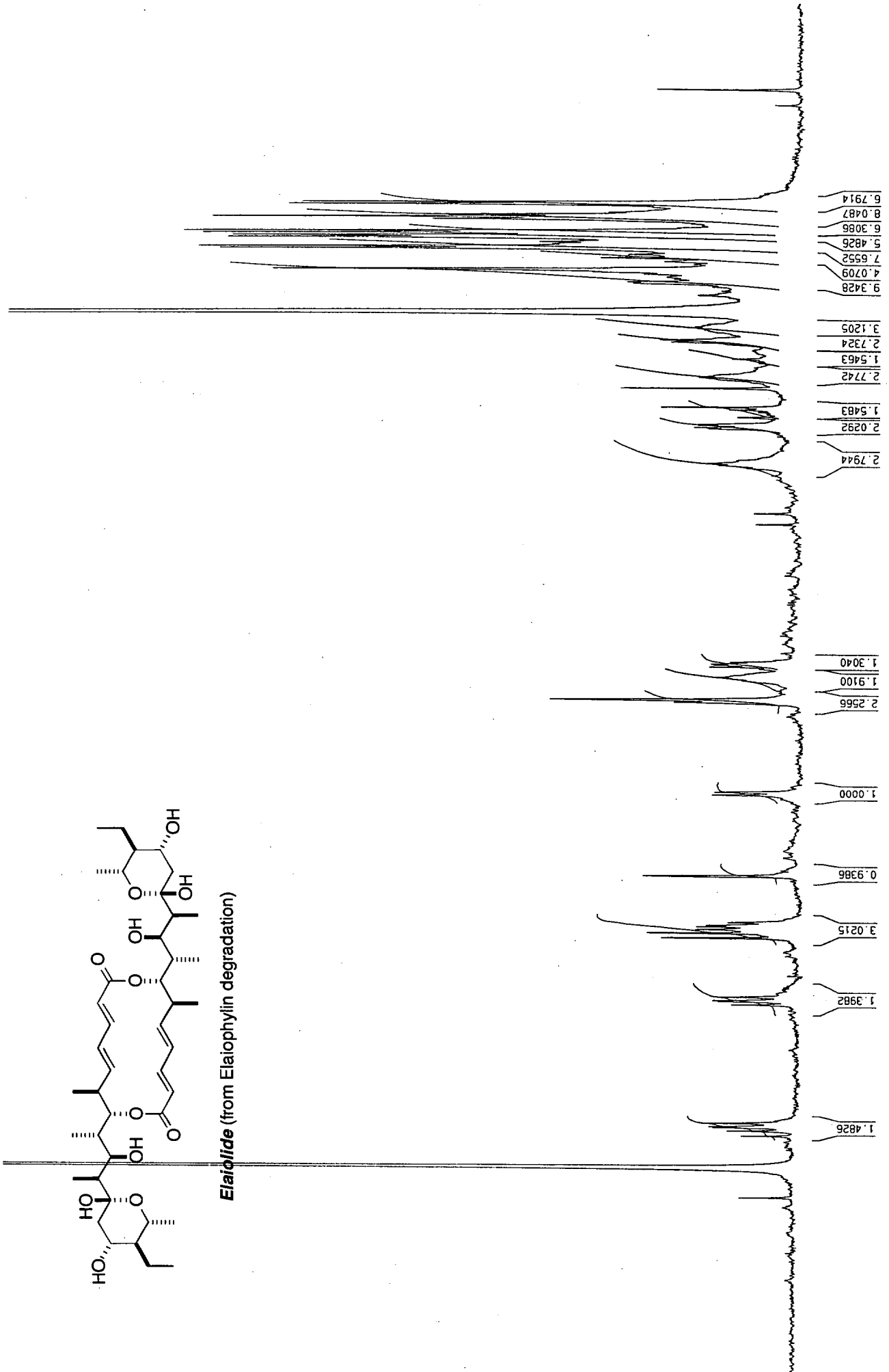
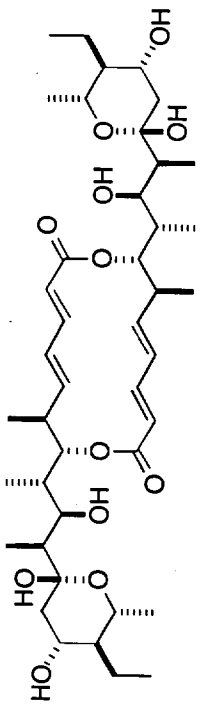


Elaiolide (from Elaiophylin degradation)



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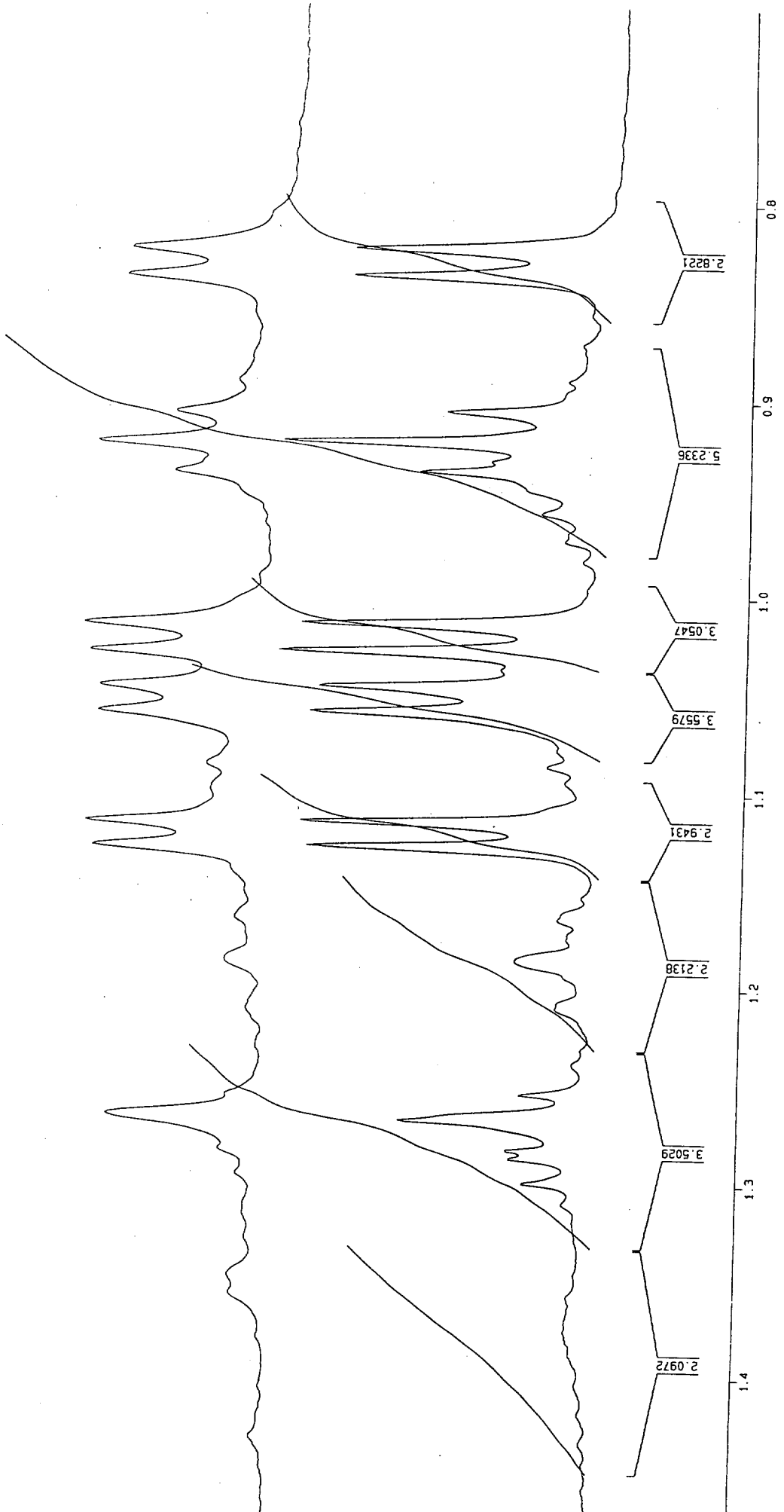

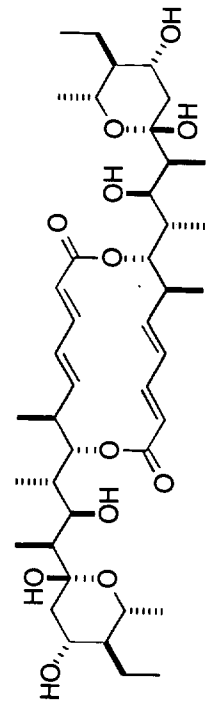

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