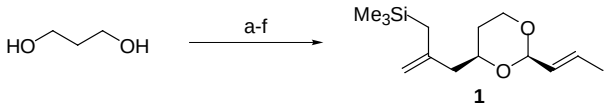
SUPPORTING INFORMATION

The "Aqueous" Prins Reaction

Danielle L. Aubele, Christopher A. Lee, and Paul E. Floreancig
Department of Chemistry
University of Pittsburgh
Pittsburgh, PA 15260

General Procedures. THF and Et_2O were dried by distillation over Na/benzophenone under N_2. Toluene, 1,2-dichloroethane, and CH_2Cl_2 were dried by distillation over CaH_2. Reagents were used as purchased without further purification unless noted. Chemical shifts (δ) are reported in ppm.

Scheme 1.



1

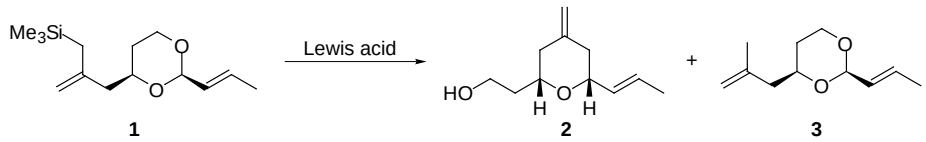
Reagents and Conditions
a) NaH, DMF, then TBDPSCl. b) Dess-Martin periodinane, CH_2Cl_2. c) 2,3-dibromopropene, Sn, HBr, Et_2O, H_2O. d) Bu_4NF, THF. e) Crotonaldehyde, *p*-TsOH, benzene, reflux. f) Me_3SiCH_2MgCl, $Pd(PPh_3)_4$, THF, reflux.

5-Bromo-hex-5-ene-1,3-diol

To 1,3-propanediol (1.00 g, 13.14 mmol) in THF (20 mL) under N_2 was added sodium hydride (60% dispersion in mineral oil, 0.54 g, 13.14 mmol). The reaction mix was stirred for 30 min. then *tert*-butylchlorodiphenylsilane (3.62 g, 13.14 mmol) was added. The reaction mixture was stirred for 1.5 h then quenched with ice chips, extracted into ether, dried ($MgSO_4$), and concentrated. The resulting residue was dissolved in CH_2Cl_2 (20 mL) under N_2 and the temperature was decreased to 0 °C. Dess-Martin periodinane (6.70 g, 15.77 mmol) was added, then the reaction mixture was stirred at 23 ºC for 30 min. and quenched with saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (5 mL). The mixture was stirred for an additional 20 min. before the two layers were separated. The organic layer was dried ($MgSO_4$), filtered, and concentrated. To a stirring suspension of tin powder (1.95 g, 16.42 mmol) in an ether-water mixture (25 mL:12.5 mL) were added a few drops of HBr, 2,3-dibromopropene (3.15 g, 15.76 mmol) and the crude aldehyde in 10 mL of ether. The reaction mixture was stirred for 18 h then was filtered through a pad of Celite. The filtrate was washed with brine. The organic layer was dried ($MgSO_4$), concentrated, and filtered through a plug of silica gel. The resulting residue was dissolved in THF (10 mL) under N_2 and tetrabutylammonium fluoride (1.72 g, 5.56 mmol) was added. The reaction mixture was stirred for 1 h, then concentrated and purified by flash chromatography (5% hexanes in EtOAc) to afford the desired product (0.84 g, 32%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (s, 1H), 5.51 (s, 1H), 4.16 (m, 1H), 3.85 (m, 3H), 2.62 (dd, *J* = 14.4, 7.8 Hz, 1H), 2.55 (dd. *J* = 14.3, 4.9 Hz, 1H), 1.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.5, 119.6, 69.2, 61.1, 49.6, 37.8; IR (neat) 3349, 2939, 1736, 1634, 1424, 1372, 1255, 1050, 886 cm^{-1}; HRMS (EI): *m/z* calcd for C_4H_5BrO (M – C_2H_7O) 147.9523, found 147.9523.

Trimethyl[2-(2-propenyl[1,3]dioxan-4-ylmethyl)allyl]silane (1)

Representative procedure for an acetal formation followed by palladium mediated coupling to afford an allylsilane: To 5-bromohex-5-ene-1,3-diol (200 mg, 1.02 mmol) in benzene (5 mL) under N_2 was added crotanaldehyde (80 mg, 0.82 mmol) and *p*-toluenesulfonic acid (cat.). The reaction mixture was refluxed for 2 h, then cooled to room temperature. Triethylamine (0.2 mL) was added and the mixture was stirred for 20 min. then extracted into ether. The resulting solution was washed with 10% aqueous NaOH and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (10% EtOAc in hexanes). The acetal was dissolved in THF (5 mL). $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) was added followed by trimethylsilylmethylmagnesium chloride (1.0 M in ether, 3.3 mL, 3.3 mmol). The reaction mixture was heated to reflux for 3 h, then cooled to room temperature and quenched with saturated aqueous NH_4Cl. The mixture was diluted with ethyl acetate, washed with H_2O, dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by flash chromatography (10% triethylamine, 5% EtOAc in hexanes) to afford the desired product (0.15 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (dq, *J* = 15.5, 6.5 Hz, 1H), 5.57 (m, 1H), 4.95 (d, *J* = 5.1 Hz, 1H), 4.66 (s, 1H), 4.61 (s, 1H), 4.15 (m, 1H), 3.80 (m, 2H), 2.38 (dd, *J* = 13.9, 5.7 Hz, 1H), 2.10 (dd, *J* = 13.9, 7.5 Hz, 1H), 1.75 (d, *J* = 1.5 Hz, 1H), 1.72 (d, *J* = 1.5 Hz, 1H), 1.64 (m, 2H), 1.55 (d, *J* = 2.9 Hz, 3H), 0.04 (s, 6H)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 129.8, 129.0, 110.0, 101.0, 75.9, 45.1, 31.5, 27.6, 19.6, -1.4; IR (neat) 3069, 2952, 1723, 1658, 1440, 1374, 1374, 1309, 1287, 1258, 1192, 1054, 974, 836 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{14}H_{26}O_2Si$ (M^+) 254.1702, found 254.1709.



1 **2** **3**

Cyclization of 1.

2-(4-Methylene-6-propenyl-tetrahydropyran-2-yl)-ethanol (2)

To a suspension of cerium chloride (190 mg, 0.79 mmol) in acetonitrile (5 mL) was added **1** (100 mg, 0.39 mmol). The reaction mixture was sonicated for 3 h, then quenched by the addition of saturated aqueous $NaHCO_3$. The reaction mixture was extracted with ether (2 x), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by flash chromatography (2% Et_2O in pentanes) to afford desilylated product **3** (20 mg, 22%) and the desired product **2** (40 mg, 57%). **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (dq, *J* = 15.4, 1.0 Hz, 1H), 5.49 (ddq, *J* = 16.9, 6.2, 1.5 Hz, 1H), 4.75 (d, *J* = 1.7 Hz, 1H), 4.74 (d, *J* = 1.7 Hz, 1H), 3.79 (m, 3H), 3.58 (m, 1H), 2.76 (bs, 1H), 2.22 (dd, *J* = 15.0, 11.2 Hz, 2H), 2.05 (dd, *J* = 12.5, 12.3 Hz, 2H), 1.85 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 131.9, 127.2, 109.0, 79.2, 78.7, 61.4, 41.1, 40.8, 38.4, 17.8; IR (neat) 3410, 3069, 2916, 2850, 1701, 1650, 1440, 1389, 1309, 1258, 1185, 1054 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{11}H_{18}O_2$ (M^+) 182.1306, found 182.1309. **3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (m, 1H), 5.54 (ddq, *J* = 15.5, 4.9, 1.3 Hz, 1H), 4.92 (d, *J* = 4.9 Hz, 1H), 4.79 (s, 1H), 4.73 (s, 1H), 4.13 (dd, 11.4, 4.8 Hz, 1H), 3.79 (m, 2H), 2.38 (dd, *J* = 13.9, 6.3 Hz, 1H), 2.16 (dd, 13.9, 6.7 Hz, 1H), 1.74 (s, 3H), 1.71 (d, *J* = 6.5 Hz, 3H), 1.61 (ddd, 23.8, 11.8, 4.9 Hz, 1H), 1.42 (d, *J* = 13.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 130.4, 128.5, 113.0, 100.8, 75.4, 66.7, 44.7, 31.1, 23.0,

17.8; IR (neat) 3076, 2960, 2916, 2850, 2727, 1687, 1636, 1440, 1367, 1316, 1243, 1134, 1076, 1010, 960, 887 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{11}H_{17}O_2$ (M^+) 181.1228, found 181.1228.

Representative procedure for aqueous Prins reactions

To **1** (0.10 g, 0.39 mmol) in H_2O (1 mL) was added sodium dodecylsulfate (30 mg, 0.12 mmol) followed by cerium nitrate hexahydrate (10 mg, 0.04 mmol). Micelles formed immediately upon the addition of the cerium nitrate and the reaction mixture was stirred vigorously for 18 h. The reaction mixture was extracted into ether, washed with 10% aqueous HCl, dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product **2** (60 mg, 76%).

Scheme 2.

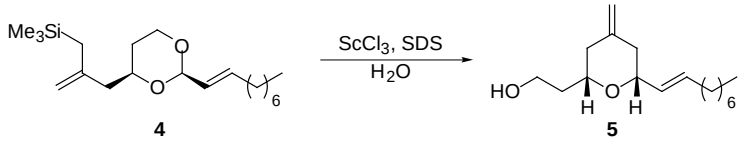
Trimethyl-[2-(2-non-1-enyl-[1,3]dioxan-4-ylmethyl)-allyl]-silane (4)

4

Reagents and Conditions

a) (*E*)-decenal, *p*-TsOH, benzene, reflux. b) Me_3SiCH_2MgCl, $Pd(PPh_3)_4$, THF, reflux.

This cyclization substrate was obtained using standard acid mediated acetal formation conditions with 5-bromohex-5-ene-1,3-diol (500 mg, 2.56 mmol) and *trans*-2-decenal (390 mg, 2.56 mmol). A portion (250 mg, 0.75 mmol) of the resulting residue was subjected to standard palladium mediated coupling conditions using $Pd(PPh_3)_4$ (90 mg, 0.08 mmol) and trimethylsilylmethylmagnesium chloride (1.0 M in ether, 3.77 mmol,



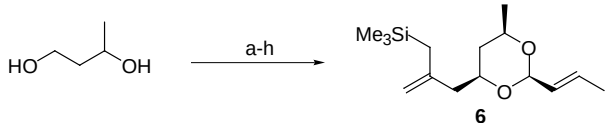
4 **5**

3.77 mL) to afford the desired cyclization substrate **(**0.18 g, 71%**)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (dt, *J* = 14.9, 6.6 Hz, 1H), 5.53 (ddt, *J* = 15.1, 5.0, 1.4 Hz, 1H), 4.95 (d, *J* = 5.0 Hz, 1H), 4.65 (s, 1H), 4.61 (s, 1H), 4.15 (ddd, *J* = 11.4, 4.8, 1.2 Hz, 1H), 3.82 (m, 3H), 2.38 (dd, *J* = 13.9, 5.5 Hz, 1H), 2.08 (m, 3H), 1.72 – 1.26 (m, 14H), 0.87 (t, *J* = 6.5 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 135.4, 127.4, 110.0, 101.1, 76.3, 66.8, 45.1, 32.2, 32.0, 31.4, 29.4, 29.3, 28.9, 27.5, 22.8, 14.4, -0.6; IR (neat) 2952, 2923, 2850, 1672, 1636, 1461, 1352, 1243, 1134, 1018, 967, 858 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{20}H_{38}O_2Si$ (M^+) 338.2641, found 338.2637.

Cyclization of 4.

2-(4-Methylene-6-non-1-enyl-tetrahydropyran-2-yl)-ethanol (5)

Allylsilane **4** (100 mg, 0.29 mmol) was subjected to standard aqueous Prins cyclization conditions using $ScCl_3$•nH_2O (4 mg, 0.03 mmol) and sodium dodecylsulfate (30 mg, 0.09 mmol) to afford the desired product (60 mg, 73%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (dtd, *J* = 15.4, 6.6, 0.9 Hz, 1H), 5.47 (ddt, *J* = 15.4, 6.2, 1.3 Hz, 1H), 4.73 (s, 1H), 3.79 (t, *J* = 5.0 Hz, 2H), 3.74 (m, 1H), 3.57 (m, 1H), 2.76 (s, 1H), 2.26 – 1.97 (m, 6H), 1.80 (m, 2H), 1.26 (m, 10H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 132.7, 130.5, 108.9, 79.3, 78.7, 61.3, 41.2, 40.8, 38.4, 32.4, 32.0, 29.8, 22.8, 14.1; IR (neat)



6

Reagents and Conditions

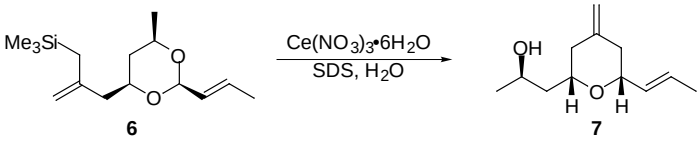
a) Me_3COCl, Et_3N, CH_2Cl_2. b) TBDPSCl, Et_3N, CH_2Cl_2. c)Na, MeOH. d) Dess-Martin periodinane, CH_2Cl_2. e) 2,3-dibromopropene, Sn, HBr, Et_2O, H_2O. f) Bu_4NF, THF. g) Crotonaldehyde, *p*-TsOH, benzene, reflux. h) Me_3SiCH_2MgCl,$Pd(PPh_3)_4$, THF, reflux.

3396, 2923, 2850, 1650, 1461, 1425, 1352, 1309, 1054, 960, 894 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{17}H_{30}O_2$ (M^+) 266.2245, found 266.2254.

Scheme 3.

2-Bromo-6-(*tert*-butyldiphenylsilanyloxy)hept-1-en-4-ol (6)

To 2,2-dimethyl-propionic acid 3-hydroxybutyl ester[1] (2.28 g, 13.08 mmol) in DMF (15 mL) under N_2 was added triethylamine (1.58 g, 15.70 mmol) followed by *tert*-butylchlorodiphenylsilane (3.95 g, 14.39 mmol). The reaction mixture was stirred for 48 h, and then quenched with H_2O. The two layers were separated and the organic layer was dried ($MgSO_4$), filtered, and concentrated. Sodium (0.299 g, 13.08 mmol) was dissolved in MeOH (20 mL) under N_2 at 0 °C. The silyl ether in MeOH (5 mL) was added dropwise. The reaction mixture was heated to 40 °C for 12 h, then cooled to room temperature, quenched with H_2O and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$), filtered, concentrated and purified by flash chromatography (20% EtOAc in hexanes) to afford the desired primary alcohol (2.05 g, 48%). The resulting alcohol was dissolved in CH_2Cl_2 (30 mL) under N_2 and was cooled to 0 °C. Dess-Martin periodinane (3.19 g, 7.50 mmol) was added and the reaction mixture was stirred for 1 h at room temperature. The temperature was then decreased to 0 °C and the reaction was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The mixture was warmed to room temperature and stirred for 30 min. before the two layers were separated. The organic layer was dried ($MgSO_4$), filtered, and concentrated. To a stirring suspension of tin powder (0.93 g, 7.82 mmol) in an ether-water mixture (15 mL:7 mL) were added a few drops of HBr, 2,3-dibromopropene (1.87 g, 7.50 mmol) and the resulting residue in ether (5 mL). The mixture was stirred for 18 h, then filtered through a pad of Celite. The filtrate was washed with brine, dried ($MgSO_4$), and concentrated. The cyclization substrate was obtained using standard acid mediated acetal formation conditions with 6-bromohept-6-ene-2,4-diol (500 mg, 2.39 mmol), crotonaldehyde (150 mg, 2.15 mmol) and *p*-toluenesulfonic acid. The resulting residue was purified by flash chromatography. The all *cis*-substituted product was isolated and subjected to standard palladium mediated coupling conditions using palladium tetrakistriphenylphosiphine (60 mg, 0.05 mmol) and trimethylsilylmethylmagnesium chloride (1.0 M in ether, 5.35 mmol, 5.35 mL) in THF (10 mL) to afford **6** (0.19 g, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (dq, *J* = 15.5, 6.5 Hz, 1H), 5.59 (m, 1H), 4.97 (d, *J* = 5.3 Hz, 1H), 4.65 (s, 1H), 4.61 (s, 1H), 3.80 (m, 1H), 2.36 (dd, *J* = 13.8, 5.7 Hz, 1H), 2.09 (dd, *J* = 13.8, 7.5 Hz, 1H), 1.74 (dd, *J* = 6.5, 1.4 Hz, 3H), 1.58 (m, 4H), 1.25 (m, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 130.3, 128.9, 109.8, 100.7, 74.1, 72.8, 44.9, 38.7, 27.5, 21.9, 14.2, -1.09; IR (neat) 2943, 2906, 2857, 1714, 1419, 1376, 1235, 1124, 1100, 1032, 842



6 **7**

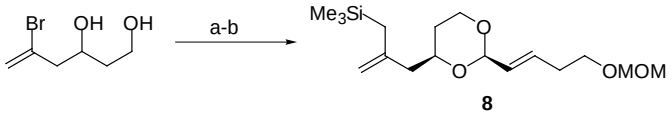
cm^{-1}; HRMS (EI): *m/z* calcd for $C_{15}H_{28}O_2Si$ (M^+) 268.1858, found 268.1858.

Cyclization of 6.

1-(4-Methylene-6-propenyltetrahydropyran-2-yl)propan-2-ol (7)

Allylsilane **6** (0.10 g, 0.37 mmol) was subjected to standard aqueous Prins cyclization conditions using $Ce(NO_3)_3$•$6H_2O$ (10 mg, 0.04 mmol) and sodium dodecylsulfate (50 mg, 0.19 mmol) to afford **7** (60 mg, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (dq, *J* = 15.4,

6.2 Hz , 1H), 5.51 (ddq, *J* = 15.4, 6.2, 1.3 Hz, 1H), 4.74 (s, 2H), 4.03 (m, 1H), 3.78 (m, 1H), 3.58 (m, 1H), 2.15 (m, 4H), 1.63 (m, 5H), 1.18 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 131.4, 127.7, 109.3, 79.7, 79.1, 68.3, 44.5, 41.0, 40.8, 23.6, 18.0;



8

Reagents and Conditions
a) 5-methoxymethoxypent-2-enal, *p*-TsOH, $MgSO_4$, CH_2Cl_2. b) Me_3SiCH_2MgCl, $Pd(PPh_3)_4$, THF, reflux.

IR (neat) 3418, 3069, 2923, 2850, 1643, 1440, 1374, 1309, 1061, 960, 887 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{12}H_{20}O_2$ (M^+) 196.1463, found 196.1466.

Scheme 4.

5-Methoxymethoxypent-2-enal

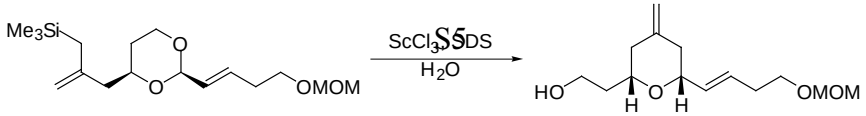
To 3-butenol (1.00 g, 13.9 mmol) in CH_2Cl_2 (10 mL) at 0 °C under N_2 were added *N*, *N'*-diisopropylethylamine (2.68 g, 20.8 mmol) and chloromethyl methyl ether (1.67 g, 20.80 mmol). The reaction was stirred for 1.5 h at room temperature, then poured into a separatory funnel containing Et_2O: 1N HCl and extracted. The organic layer was dried ($MgSO_4$) and concentrated. To a solution of the resulting residue in CH_2Cl_2 (10 mL) was added acrolein (0.49 g, 8.61 mmol) and Grubbs second generation metathesis catalyst (0.18 g, 0.22 mmol). The reaction mixture was heated to reflux for 18 h, cooled to room temperature and concentrated. The resulting residue was purified by flash chromatography (30% Et_2O in pentanes) to afford the desired product (0.17 g, 28%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (d, *J* = 7.8 Hz, 1H), 6.88 (dt, *J* = 15.7, 6.7 Hz, 1H), 6.22 (dd, *J* = 15.7, 7.8 Hz, 1H), 4.65 (s, 2H), 3.73 (t, *J* = 6.2, 2H), 3.37 (s, 3H), 2.64 (m, 2H).

4-(2-Bromoallyl)-2-(4-methoxymethoxybut-1-enyl)[1,3]-dioxane

To 5-bromohex-5-ene-1,3-diol (230 mg, 1.2 mmol) in CH_2Cl_2 (5 mL) at -20 °C under N_2 was added 5-methoxymethoxypent-2-enal (170 mg, 1.2 mmol), *p*-toluenesulfonic acid (20 mg, 0.1 mmol), and anhydrous $MgSO_4$ (170 mg, 1.4 mmol). The reaction mixture was stirred for 18 h, quenched with saturated aqueous $NaHCO_3$ (2 mL) and allowed to warm to room temperature. The two layers were separated, and the organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by flash chromatography (20% Et_2O in pentanes) to afford the desired acetal (290 mg, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (dt, *J* = 15.7, 6.7 Hz, 1H), 5.66 (s, 1H), 5.60 (ddt, *J* = 15.7, 4.6, 1.4 Hz, 1H), 5.48 (d, *J* = 1.5 Hz, 1H), 4.96 (d, *J* = 4.6 Hz, 1H), 4.60 (s, 2H), 4.11 (dd, *J* = 11.4, 4.9 Hz, 1, H), 3.99 (m, 1H), 3.80 (dt, *J* = 11.9, 2.6 Hz, 1H), 3.57 (t, *J* = 6.7 Hz, 2H), 3.33 (s, 3H), 2.75 (dd, *J* = 14.4, 6.7 Hz, 1H), 2.49 (dd, *J* = 14.4, 6.3 Hz, 1H), 2.36 (m, 2H), 1.64 (m, 1H), 1.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.6, 128.9, 119.6, 100.5, 96.4, 74.2, 66.7, 66.5, 55.3, 47.7, 32.6, 30.5; IR (neat) 2945, 2916, 2850, 1694, 1629, 1432, 1352, 1243, 1149, 1134, 1032, 974; HRMS (EI) *m/z* calcd for $C_{13}H_{20}O_4Br$ (M^+) 319.0544, found 319.0543.

{2-[2-(4-Methoxymethoxybut-1-enyl)-[1,3]dioxan-4-ylmethyl]allyl}trimethylsilane (8)

To 4-(2-bromoallyl)-2-(4-methoxymethoxy-but-1-enyl)-[1,3]dioxane (290 mg, 0.9 mmol) in THF (5 mL) under N_2 was added trimethylsilylmethylmagnesium chloride (1.0 M in Et_2O, 4.6 mmol, 4.6 mL) and $Pd(PPh_3)_4$ (50 mg, 0.05 mmol). The reaction mixture was heated to reflux for 3h, cooled to 0 °C, and quenched with saturated aqueous NH_4Cl. The reaction mixture was warmed to room temperature and extracted into Et_2O. The organic



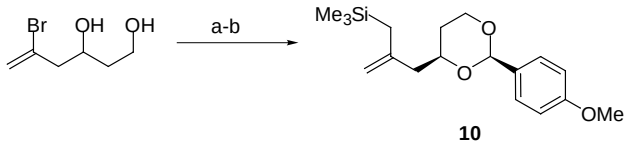
8 **9**

layer was dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by flash chromatography (10% triethylamine, 20% Et_2O in pentanes) to afford the desired product (0.24 g, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (dt, *J* = 15.7, 6.7 Hz, 1H), 5.63 (ddt, 15.7, 3.4, 1.3 Hz, 1H), 4.97 (d, *J* = 4.7 Hz, 1H), 4.65 (s, 2H), 4.63 (s, 2H), 4.15 (dd, *J* = 11.4, 4.9 Hz, 1H), 3.80 (m, 2H), 3.60 (t, *J* = 6.8 Hz, 2H), 3.35 (s, 3H), 2.37 (m, 3H), 2.10 (dd, *J* = 13.9, 7.3 Hz, 1H) 1.53 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 131.4, 129.2, 110.0, 100.6, 96.5, 75.7, 66.8, 55.3, 44.8, 32.6, 31.2, 27.3, 26.0, 14.2, -1.19; IR (neat) 3076, 2952, 2850, 1687, 1621, 1367, 1243, 1149, 1112, 1047, 967, 850; HRMS (EI): *m/z* calcd for $C_{17}H_{31}O_4Si$ (M^+) 327.1991 found, 327.1996.

Cyclization of 8.

2-[6-(4-Methoxymethoxybut-1-enyl)-4-methylenetetrahydropyran-2-yl]ethanol (9)

Allylsilane **8** (100 mg, 0.3 mmol) was subjected to standard aqueous Prins cyclization conditions using $ScCl_3$•nH_2O (4 mg, 0.03 mmol) and sodium dodecylsulfate (40 mg, 0.12 mmol) to afford the desired product (40 mg, 53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (m, 2H), 4.75 (d, *J* = 1.6 Hz, 1H), 4.74 (d, *J* = 1.6 Hz, 1H), 4.61 (s, 2H), 3.73 (t, *J* = 5.1 Hz, 3H), 3.57 (t, *J* = 6.8 Hz, 3H), 3.35 (s, 3H), 2.33 (m,2H), 2.17 (m, 4H), 1.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 132.4, 128.5, 109.2, 96.4, 78.9, 78.8, 67.1, 61.4, 55.2, 40.7, 40.5, 38.0, 32.8; IR (neat) 3440, 3069, 2930, 2880, 1658, 1425, 1352, 1316, 1149, 1105, 1047, 960, 901; HRMS (EI): *m/z* calcd for $C_{14}H_{24}O_4$ (M^+) 256.1674, found 256.1676.



10

Reagents and Conditions
a) *p*-Anisaldehyde, *p*-TsOH, benzene, reflux. b) Me_3SiCH_2MgCl, $Pd(PPh_3)_4$, THF, reflux.

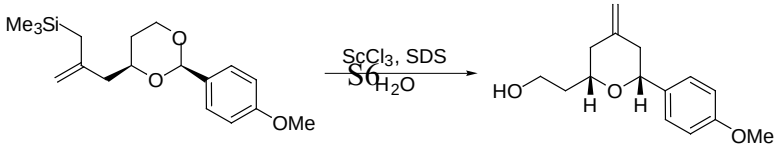
Scheme 5.

4-(2-Bromoallyl)-2-(4-methoxy-phenyl)-[1,3]dioxane

To 5-bromohex-5-ene-1,3-diol (500 mg, 2. 6 mmol) in benzene (50 mL) was added *p*-anisaldehyde (341 mg, 2.5 mmol) and PPTs (20 mg). A Dean Stark trap and reflux condenser was attached and the mixture was stirred at reflux under N_2 for 3 h. The reaction was cooled to 25 °C and concentrated. The brown oil was immediately purified by flash column chromatography (15% diethyl ether in hexanes) to provide the desired product as a clear oil (494 mg, 63%): ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.46 (d, 2H, *J* = 8.8 Hz), 6.93 (d, 2H, *J* = 8.8 Hz), 5.76 (s, 1H), 5.58 (s, 1H), 5.54 (s, 1H), 4.31 (dd, *J* = 11.4, 4.9 Hz), 4.23 (m, 1H), 4.01 (td, 1H, *J* = 11.9, 2.6 Hz), 3.84 (s, 3H), 2.91 (dd, 1H, *J* = 14.5, 6.9 Hz), 2.63 (dd, 1H, *J* = 14.5, 6.2 Hz), 1.82 (ddd, 1H, *J* = 12.9, 12.1, 5.0 Hz), 1.59 (d, 1H, *J* = 11.3 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 159.7, 130.9, 128.8, 127.2, 119.5, 113.4, 100.9, 74.4, 66.7, 55.5, 47.5, 30.3; IR (neat) 3073, 3037, 1388, 1362, 1116, 902 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{14}H_{17}BrO_3$ (M^+) 312.0361, found 312.0355.

{2-[2-(4-Methoxyphenyl)-[1,3]dioxan-4-ylmethyl]allyl}trimethylsilane (10)

To 4-(2-bromoallyl)-2-(4-methoxyphenyl)-[1,3]dioxane (313 mg, 1.0 mmol) in THF (8mL) was added $Pd(PPh_3)_4$ (56 mg, 0.05 mmol) and Me_3SiCH_2MgCl (1.0M in ether, 5.0 mL, 5.0 mmol). The yellow/green mixture heated to 70 °C for 3 hours. After cooling to 25 °C the reaction was poured into brine (10 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (4x10 mL). The combined organic layers



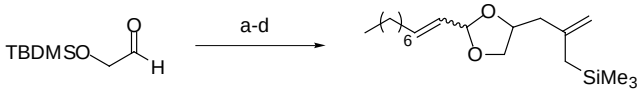
10 **11**

were dried ($MgSO_4$), filtered, and concentrated. The yellow oil was purified by flash column chromatography (7% Et_2O, 2% Et_3N in hexanes) to provide the desired product as a clear oil (206 mg, 64%): ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.38 (d, 2H, *J* = 8.4 Hz), 6.87 (d, 2H, *J* = 8.4 Hz), 5.45 (s, 1H), 4.73 (s, 1H), 4.61 (s, 1H**),** 4.21 (qd, 1H, *J* = 4.9, 1.4 Hz), 3.96 (m, 2H), 3.79 (s, 3H), 2.37 (dd, 1H, *J* = 14.2, 6.6 Hz), 2.15 (dd, 1H, *J* = 14.2, 6.6 Hz), 1.69 (m, 1H), 1.62 (s, 2H), 1.57 (m, 1H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 160.3, 144.1, 132.2, 127.8, 113.7, 109.9, 101.4, 76.3, 67.4, 55.6, 45.2, 31.7, 27.4, -1.2; IR (neat) 3068, 1634, 1608, 1116, 860 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{18}H_{28}SiO_3$ (M^+) 320.1807, found 320.1795.

Cyclization of 10.

2-[6-(4-Methoxy-phenyl)-4-methylene-tetrahydro-pyran-2]-ethanol (11)

Allylsilane **10** (75 mg, 0.23 mmol) was subjected to standard aqueous Prins cyclization conditions using $ScCl_3$•nH_2O (3 mg, 0.02 mmol) and sodium dodecylsulfate (75 mg, 0.23 mmol) to afford **11** (43 mg, 75%): ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.26 (d, 2H, *J* = 8.8 Hz), 6.86 (d, 2H, *J* = 8.8 Hz), 4.80 (s, 2H), 4.29 (dd, 1H, *J* = 11.3, 2.5 Hz), 3.77 (s, 3H),



12

Reagents and Conditions
a) 2-(Bromoallyl)trimethylsilane, $TiCl_4$, CH_2Cl_2, -78 °C. b) Bu_4NF, THF. c) (*E*)-2-decenal, *p*-TsOH, benzene, reflux. d) Me_3SiCH_2MgCl, $ZnBr_2$, $Pd(PPh_3)_4$, THF.

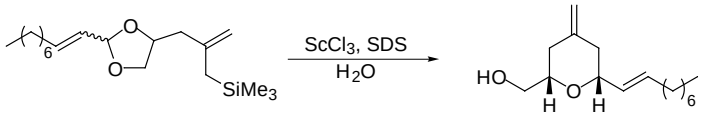
3.73 (t, 1H, *J* = 5.3 Hz), 3.67 (m, 1H), 2.37 (d, 2H, *J* = 13.3 Hz), 2.25 (d, 2H, *J* = 11.6 Hz), 2.14 (dd, 2H, *J* = 12.8, 6.9 Hz), 1.81 (m, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 159.5, 144.9, 135.0, 127.5, 114.1, 109.1, 80.6, 79.3, 61.3, 55.6, 43.0, 40.9, 38.7; IR (neat) 3452, 2978, 1516, 1117, 1056 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{15}H_{20}O_3$ (M^+) 248.1412, found 248.1418.

Scheme 6.

Trimethyl[2-(2-non-1-enyl[1,3]dioxolan-4-ylmethyl)allyl]silane (12)

To (2-bromoallyl)trimethylsilane (1.85 g, 9.6 mmol) in CH_2Cl_2 (15 mL) under N_2 at -78 °C was added *tert*-butyldimethylsilyloxyacetaldehyde[2] (1.11 g, 6.4 mmol) and $TiCl_4$ (1.5 g, 8.0 mmol). Then reaction mixture was stirred for 35 min., then cannulated into a stirring saturated aqueous $NaHCO_3$ (25 mL) at 0 °C. The mixture was stirred while warming to room temperature. The two layers were separated. The aqueous layer was washed with ethyl acetate (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford the desired product (1.10 g, 59%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (s, 1H), 5.53 (s, 1H), 4.01 (m, 1H), 3.69 (dd, *J* = 9.8, 3.5 Hz, 1H), 3.53 (dd, *J* = 9.9, 6.1 Hz, 1H), 2.58 (m, 2H), 2.41 (d, *J* = 4.3 Hz, 1H), 0.91 (s, 9H), 0.09 (s, 6H). To the resulting alcohol (1.10 g, 3.73 mmol) in THF (10 mL) under N_2 was added Bu_4NF (1.07 g, 4.11 mmol). The reaction mixture was stirred for 12 h then concentrated. The crude mixture was purified by flash chromatography (EtOAc). The resulting residue was subjected to standard acid mediated acetal formation conditions using *trans*-2-decenal (0.51 g, 3.28 mmol). A solution of zinc bromide (0.71 g, 3.15 mmol) in THF (3 mL) was added dropwise to a solution of Me_3SiCH_2MgCl (1.0 M in ether, 3.2 mL, 3.2 mmol) and was stirred for 18 h. A solution of the resulting residue from the acetal formation in THF (2 mL) was added, followed by $Pd(PPh_3)_4$ (40 mg, 0.03

mmol). The reaction mixture was stirred for 18 h then quenched with saturated aqueous NH_4Cl. The two layers were separated and the aqueous layer was washed with ether. The organic layers were combined, dried ($MgSO_4$), filtered, concentrated, and purified by



12 **13**

flash chromatography (10% triethylamine, 5% ether in pentanes) to afford **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (m, 1H), 5.48 (m, 1H), 5.32 (d, *J* = 6.6 Hz, 1H), 5.20 (d, *J* = 6.8 Hz, 1H), 4.64 (m, 1H), 4.60 (s, 1H), 4.26 (m, 1H), 4.14 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.96 (dd, *J* = 7.7, 6.5 Hz, 1H), 3.61 (dd, *J* = 7.7, 6.4 Hz, 1H), 3.52 (dd, *J* = 8.1, 6.9 Hz, 1H), 2.40 (m, 1H), 2.21 (m, 3H), 1.25 (m, 8H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 143.6, 138.0, 137.2, 126.9, 109.7, 104.7, 103.9, 75.6, 74.8, 70.5, 69.8, 42.6, 42.1, 32.2, 32.0, 29.0, 28.9, 27.6, 22.8, 14.2, -1.12; IR (neat) 3061, 2945, 2923, 1730, 1665, 1643, 1461, 1403, 1243, 1127, 1061, 967, 850; HRMS (EI): *m/z* calcd for $C_{19}H_{36}O_2Si$ (M^+) 324.2484, found 324.2479.

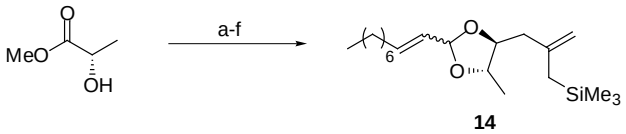
Cyclization of 12.

(4-Methylene-6-non-1-enyltetrahydropyran-2-yl)methanol (13)

Allylsilane **12** (50 mg, 0.15 mmol) was subjected to standard aqueous Prins cyclization conditions using $ScCl_3 \bullet nH_2O$ (2 mg, 0.02 mmol) and sodium dodecylsulfate (40 mg, 0.15 mmol) to afford the desired product (30 mg, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.49 (dd, *J* = 15.5, 6.4 Hz, 1H), 4.77 (s, 2H), 3.79 (m, 1H), 3.61 (m, 2H), 3.47 (m, 1H), 2.05 (m, 6H), 1.26 (m, 10H), 0.88 (t, *J* = 5.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 133.2, 130.3, 109.4, 79.2, 78.6, 66.1, 41.2, 36.3, 32.5, 32.0, 29.8, 29.3, 22.8, 14.3; IR (neat) 3418, 3069, 2930, 2850, 1650, 1461, 1345, 1098, 1054, 967, 894; HRMS (EI): *m/z* calcd for $C_{16}H_{28}O_2$ (M^+) 252.2089, found 252.2090.

Scheme 7.

2-Benzyloxypropionic acid methyl ester



14

Reagents and Conditions
a) BnBr, Ag_2O, Et_2O. b) DIBAL-H, CH_2Cl_2, -98 °C. c) 2-(Bromoallyl)trimethylsilane, $SnCl_4$, CH_2Cl_2, -78 °C. d) $TiCl_4$, THF, 0 °C. e) (*E*)-2-Decenal, *p*-TsOH, $MgSO_4$, CH_2Cl_2. f) Me_3SiCH_2MgCl, $ZnBr_2$, $Pd(PPh_3)_4$, THF.

To a suspension of silver oxide (4.45 g, 19.21 mmol) in ether (15 mL) under N_2 was added methyl-(*S*)-(-)-lactate (1.00 g, 9.60 mmol) and benzyl bromide (2.45 g, 14.40 mmol). The reaction mixture was stirred for 48 h then filtered through a pad of Celite and concentrated. The resulting residue was purified by flash chromatography (10% Et_2O in pentanes) to afford the desired product (1.09 g, 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.72 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.09 (q, *J* = 6.9 Hz, 1H), 3.76 (s, 3H), 1.44 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 137.6, 128.5, 128.1, 74.1, 72.1, 52.0, 18.8; $[\alpha]_D^{23}$ -92.3° ($CDCl_3$, *c* 0.37); lit:[3] $[\alpha]_D^{23}$ 78.5° ($CDCl_3$, *c* 0.37) for the (*R*)-(-) enantiomer.

2-Benzyloxy-5-bromohex-5-en-3-ol

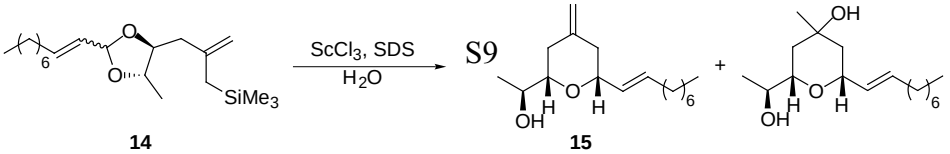
To 2-benzyloxypropionic acid methyl ester (500 mg, 2.77 mmol) in CH_2Cl_2 (10 mL) under N_2 at -98 °C was added diisobutylaluminum hydride (1.0 M in hexanes, 3.33 mL, 3.33 mmol,). The reaction mixture was stirred for 1 h, then quenched with ethyl acetate (2 mL) and stirred for 10 min. before a solution of saturated sodium, potassium tartrate (10mL) was added. The reaction mixture was warmed to room temperature and stirred for 2 h. The aqueous layer was washed with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was added to a solution of (2-bromoallyl)trimethylsilane (640 mg, 3.33 mmol) under N_2 at -78 °C in CH_2Cl_2 (10 mL). $SnCl_4$ (1.0 M in CH_2Cl_2, 5.55 mL, 5.55 mmol) was added and the reaction mixture was stirred for 45 min. The reaction was quenched with H_2O (10 mL), then warmed to room temperature. The aqueous layer was washed with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by flash chromatography (10% Et_2O in pentanes) to afford the desired product (460 mg, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.66 (d, *J* = 1.3 Hz, 1H), 5.15 (d, *J* = 1.5 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 3.85 (m, 1H), 3.52 (dq, *J* = 4.8, 6.2 Hz, 1H), 2.60 (d, *J* = 6.1 Hz, 2H), 1.28 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 130.8, 128.7, 128.0, 119.4, 76.5, 72.6, 71.1, 45.5, 15.8; IR (neat) 3447, 3083, 3061, 3025, 2952, 2923, 2872, 1621, 1505, 1447, 1374, 1207, 1069, 901, 734, 698 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{13}H_{17}O_2$ (M^+) 284.0411, found 284.0410; $[\alpha]_D^{23}$ 14.7° ($CHCl_3$, *c* 5.0). The enantiomeric excess was determined to be 80% by HPLC analysis using a Chiracel OD-H column. Conditions: Hex:*i*-PrOH 90:10, 0.80 mL/min.

4-(2-Bromoallyl)-5-methyl-2-non-1-enyl-[1,3]dioxolane

To 2-benzyloxy-5-bromohex-5-en-3-ol (310 mg, 1.08 mmol) in CH_2Cl_2 (10 mL) at 0 °C under N_2 was added $TiCl_4$ (250 mg, 1.36 mmol). The reaction mixture was stirred for 2h, and then quenched with saturated aqueous $NaHCO_3$ (5 mL) and allowed to warm to room temperature. The reaction mixture was extracted into ethyl acetate, and the aqueous layer was washed (5 x 20 mL) with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated, then the residue was filtered through a plug of silica gel using ethyl acetate. To a solution of the resulting residue in CH_2Cl_2 (5 mL) at -20 °C under N_2 was added *trans*-2-decenal (120 mg, 0.78 mmol), *p*-toluenesulfonic acid (10 mg, 0.08 mmol), and anhydrous $MgSO_4$ (110 mg, 0.89 mmol). The reaction mixture was stirred for 18 h, then was quenched with saturated aqueous $NaHCO_3$ (2 mL) and warmed to room temperature. The two layers were separated and the organic layer was dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by flash chromatography (5% Et_2O in pentanes) to afford the desired product (220 mg, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (dt, *J* = 15.3, 6.6 Hz, 1H), 5.75 (m, 1H), 5.53 (d, *J* = 1.7 Hz, 1H), 5.47 (m, 1H), 5.36 (d, *J* = 6.8 Hz, 1H), 5.30 (d, *J* = 6.9, Hz, 1H), 3.87 (m, 2H), 2.79 (m, 1H), 2.58 (dtd, *J* = 13.4, 4.3, 0.85 Hz, 1H), 2.05 (m, 2H), 1.37 (d, *J* = 5.9 Hz, 3H), 1.26 (m, 10H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 137.7, 129.3, 129.2, 127.1, 127.0, 119.4, 103.7, 103.5, 81.0, 79.9, 78.0, 76.6, 45.2, 44.7, 32.2, 32.0, 29.3, 28.8, 22.8, 18.3, 18.2, 15.4, 14.2; IR (neat) 3105, 2952, 2923, 2850, 1672, 1629, 1454, 1410, 1374, 1316, 1214, 1127, 1083, 1061, 974, 894; HRMS (EI): *m/z* calcd for $C_{16}H_{26}O_2Br$ (M^+) 329.1106, found 329.1105; $[\alpha]_D^{23}$ -10.9º (CH_2Cl_2 , *c* 5.7).

Trimethyl[2-(5-methyl-2-non-1-enyl-[1,3]dioxolan-4-ylmethyl)allyl]silane (14)

A solution of zinc bromide (0.57 g, 2.54 mmol) in THF (3 mL) was added dropwise to a solution of Me_3SiCH_2MgCl (1.0 M in ether, 2.5 mL, 2.54 mmol) and was stirred for 18 h.



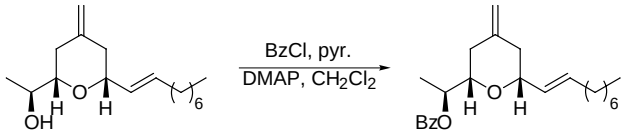
14 15

A solution of 4-(2-bromoallyl)-5-methyl-2-non-1-enyl-[1,3]dioxolane (170 mg, 0.51 mmol) in THF (2 mL) was added, followed by $Pd(PPh_3)_4$ (30 mg, 0.03 mmol). The reaction mixture was stirred for 18 h, and was then quenched with saturated aqueous NH_4Cl. The two layers were separated and the aqueous layer was washed with ether. The organic layers were combined, dried ($MgSO_4$), filtered, concentrated and purified by flash chromatography (5% Et_2O in pentanes, silica gel was neutralized with 10% triethylamine in pentanes) to afford **14** (150 mg, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (dt, *J* = 15.3, 6.6 Hz, 1H), 5.50 (m, 1H), 5.34 (d, *J* = 6.7 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 4.72 (s, 1H), 4.63 (s, 1H), 3.74 (m, 2H), 2.33 (m, 1H), 2.05 (m, 3H), 1.26 (m, 10H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 143.4, 138.2, 138.0, 127.0, 110.3, 103.4, 103.2, 82.1, 80.7, 78.5, 66.0, 41.5, 32.2, 31.9, 29.3, 28.8, 27.1, 22.8, 18.2, 14.3, -1.1; IR (neat) 3069, 2952, 2916, 2850, 1680, 1629, 1454, 1410, 1381, 1250, 1163, 1120, 1076, 1047, 960, 843; HRMS (EI): *m/z* calcd for $C_{20}H_{38}O_2Si$ (M^+) 338.2641, found 338.2636; $[\alpha]_D^{23}$ -12.8° (CH_2Cl_2, *c* 5.0).

Cyclization of 14.

1-(4-Methylene-6-non-1-enyltetrahydropyran-2-yl)ethanol (15)

Allylsilane **14** (50 mg, 0.15 mmol) was subjected to standard aqueous Prins cyclization conditions using $ScCl_3 \bullet nH_2O$ (2 mg, 0.01 mmol) and sodium dodecylsulfate (40 mg, 0.15 mmol) to afford **15** (20 mg, 51%) and the product of formal Markonikov hydration (6 mg, 12%). **15**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (dtd, *J* = 15.5, 5.8, 0.8 Hz, 1H), 5.47 (ddt, *J* = 15.5, 6.2, 1.2 Hz, 1H), 4.78 (s, 2H), 3.74 (m, 1H), 3.66 (m, 1H), 3.11 (m, 1H), 2.81 (s, 1H), 2.22 (m, 2H), 2.02 (m, 4H), 1.27 (m, 10H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.88 (t,



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J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 132.7, 130.5, 109.5, 82.9, 79.1, 70.7, 41.2, 36.7, 32.5, 32.0, 29.3, 22.8, 18.4, 14.2; IR (neat) 3440, 3076, 2916, 2850, 1650, 1469, 1367, 1250, 1061, 967, 887 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{17}H_{30}O_2$ (M^+) 266.2246, found 266.2247; $[\alpha]_D^{23}$ 0.2° (CH_2Cl_2, *c* 16.0). 2-(1-hydroxyethyl)-4-methyl-6-non-1-enyl-tetrahydropyran-4-ol: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (dt, *J* = 15.4, 6.8 Hz, 1H), 5.47 (dd, *J* = 15.6, 6.1 Hz, 1H), 4.17 (m, 1H), 3.85 (m, 1H), 3.64 (m, 2H), 3.16 (m, 1H), 2.04 (m, 2H), 1.62 (m, 6H), 1.36 (s, 3H), 1.27 (m, 10H), 1.17 (d, *J* = 6.3 Hz, 3H), 0.89 (t, *J* = 6.8, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.0, 132.6, 130.3, 130.0, 79.9, 75.7, 73.6, 70.7, 69.5, 46.4, 41.9, 32.5, 32.0, 29.9, 29.3, 26.3, 22.8, 18.3, 14.3; IR (neat) 3374, 2952, 2923, 2858, 1469, 1367, 1294, 1090, 1054, 967; HRMS (EI): *m/z* calcd for $C_{17}H_{32}O_3$ (M^+) 284.2351, found 284.2356.

Scheme 8.

Benzoic acid 1-(4-methylene-6-non-1-enyltetrahydropyran-2-yl)ethyl ester

To **15** (20 mg, 0.08 mmol) in CH_2Cl_2 (1 mL) under N_2 was added benzoyl chloride (10 mg, 0.11 mmol), anhydrous pyridine (1 mL), and a catalytic amount of DMAP. The reaction was stirred for 18 h, then concentrated and purified by flash chromatography (5% Et_2O in pentanes) to afford the desired product (0.02 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.0 Hz, 2H), 7.56 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.45 (dd, *J* = 7.2, 6.5 Hz, 2H), 5.66 (dt, *J* = 15.5, 6.4 Hz, 1H), 5.52 (dd, *J* = 15.5, 5.8 Hz, 1H), 5.27 (m, 2H),

4.78 (s, 2H), 3.76 (m, 1H), 3.52 (m, 1H), 2.15 (m, 6H), 1.40 (d, *J* = 6.5 Hz, 3H), 1.27 (m, 10H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 144.1, 133.0, 132.4, 130.8, 130.4, 129.8, 128.4, 109.5, 79.2, 72.3, 41.2, 35.7, 32.5, 32.0, 29.3, 22.8, 15.7, 14.3; IR (neat) 3061.8, 2923.6, 2850.9, 1716.3, 1650.9, 1592.7, 1447.2, 1352.7, 1309.1, 1280.0, 1170.9, 1112.7, 960.0, 887.2; HRMS (EI): *m/z* calcd $C_{24}H_{34}O_3$ (M^+) 370.2505 found, 370.2526; $[\alpha]_D^{23}$ 1.0º (CH_2Cl_2 , *c* 5.0). The enantiomeric excess was determined to be 86% by chiral HPLC analysis using a chirapak AD column. Conditions: Hex:*i*-PrOH 90:10, 0.40 mL/min, baseline resolution was not achieved.

Benzyloxyacetic acid methyl ester

To a suspension of silver (I) oxide (5.15 g, 22.20 mmol) in Et_2O (10 mL) under N_2 was added methyl glycolate (1.0 g, 11.10 mmol) and benzyl bromide (2.85 g, 16.65 mmol). The reaction mixture was heated to reflux and stirred for 18 h, then cooled to room temperature, filtered through a pad of Celite and concentrated. The resulting residue was purified by flash chromatography (10% Et_2O in pentanes) to afford the desired product (82%, 1.64 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.64 (s, 2H), 4.15 (s, 2H), 3.77 (s, 3H).

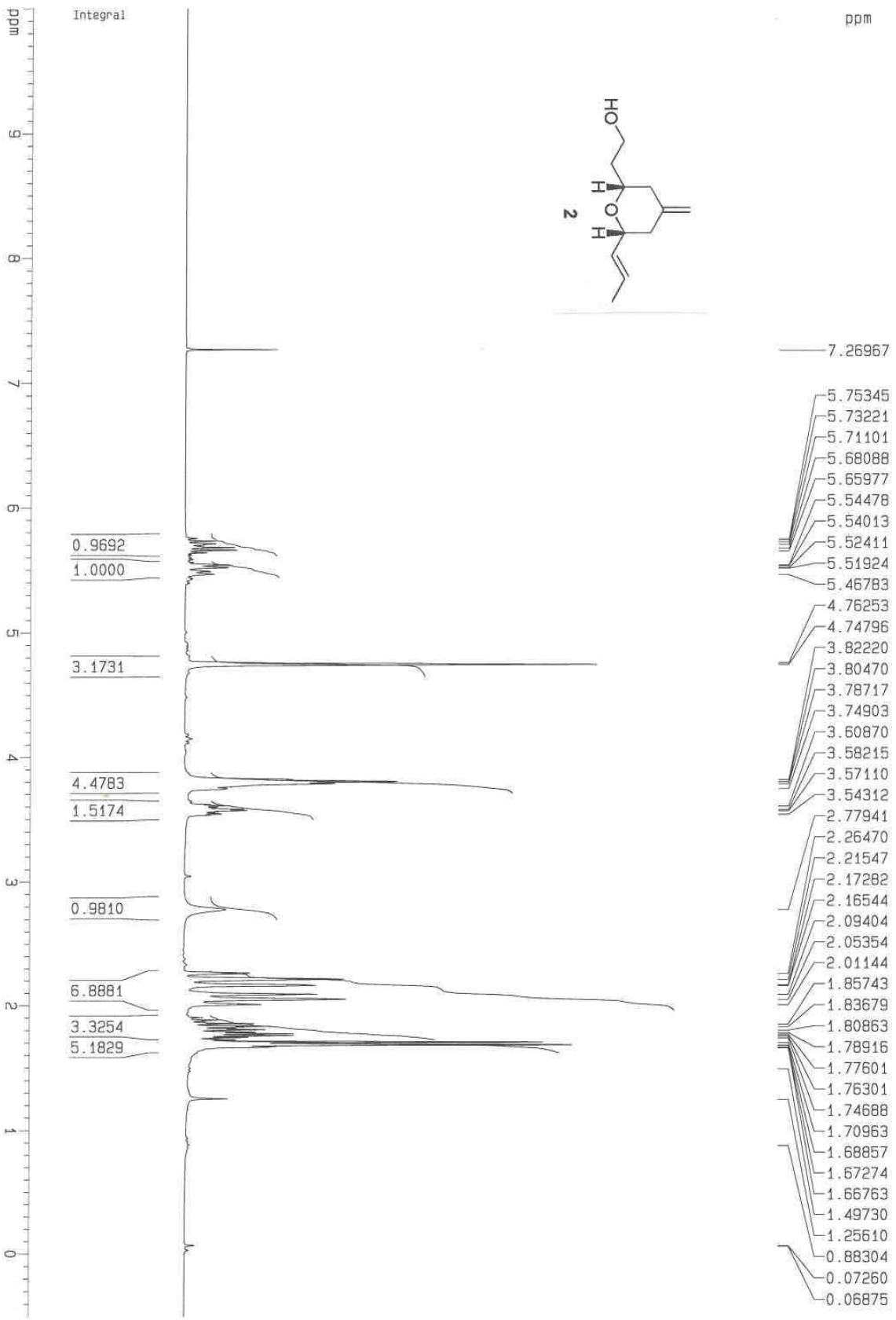
2-Benzyloxy-propionic acid methyl ester

To a stirring solution of LiHMDS (1.0 M in THF, 5.55 mL, 5.55 mmol) and HMPA (0.05 g, 0.28 mmol) at -78 °C under N_2 was added benzyloxyacetic acid methyl ester (500 mg, 2.77 mmol). The reaction mixture was stirred for 30 min, then iodomethane (1.96 g, 13.87 mmol) was added. The reaction mixture was stirred for 3 h, then quenched with saturated aqueous NH_4Cl and allowed to warm to room temperature. The reaction mixture was extracted into Et_2O and the aqueous layer was washed with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified by flash chromatography (10% Et_2O in pentanes) to afford the desired product (250 mg, 46%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.72 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.09 (q, *J* = 6.9 Hz, 1H), 3.76 (s, 3H), 1.44 (d, *J* = 6.8 Hz, 3H).

The racemic form of benzoic acid 1-(4-methylene-6-non-1-enyltetrahydropyran-2-yl)ethyl ester was synthesized in the same manner as the enantiopure form starting from 2-benzyloxypropionic acid methyl ester. The racemic form was used as a standard for HPLC analysis and enantiomeric excess determination.

References

1. Yamada, S. *J. Org. Chem.* **1992**, *57*, 1591.
2. Provencal, D. Q.; Gardelli, C.; Lafontaine, J. A.; Leahy, J. W. *Tetrahedron Lett.* **1995**, *36*, 6033.
3. Bauer, S.; Armstrong, R. *J. Am. Chem. Soc.* **1999**, *121*, 6355.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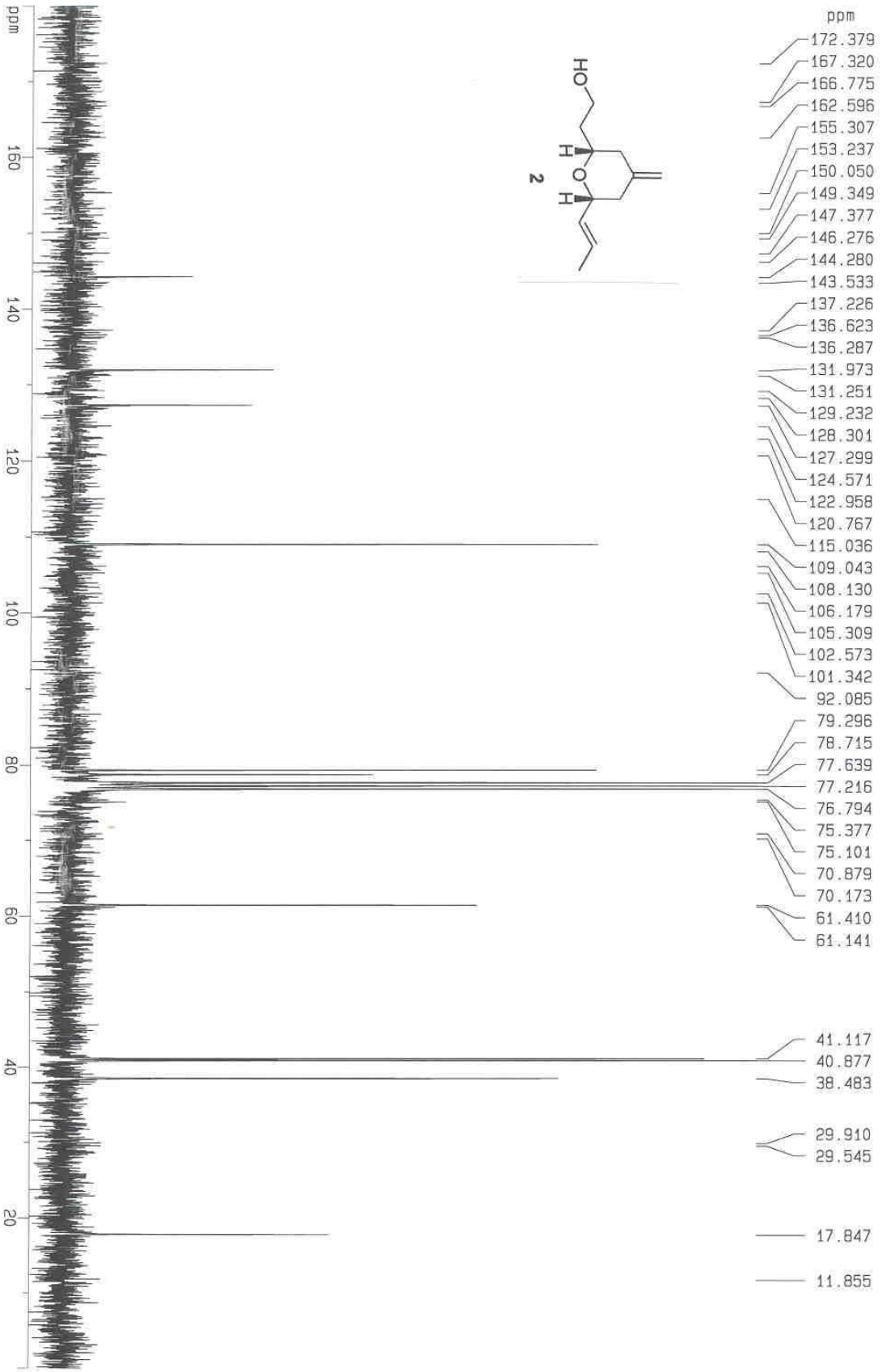
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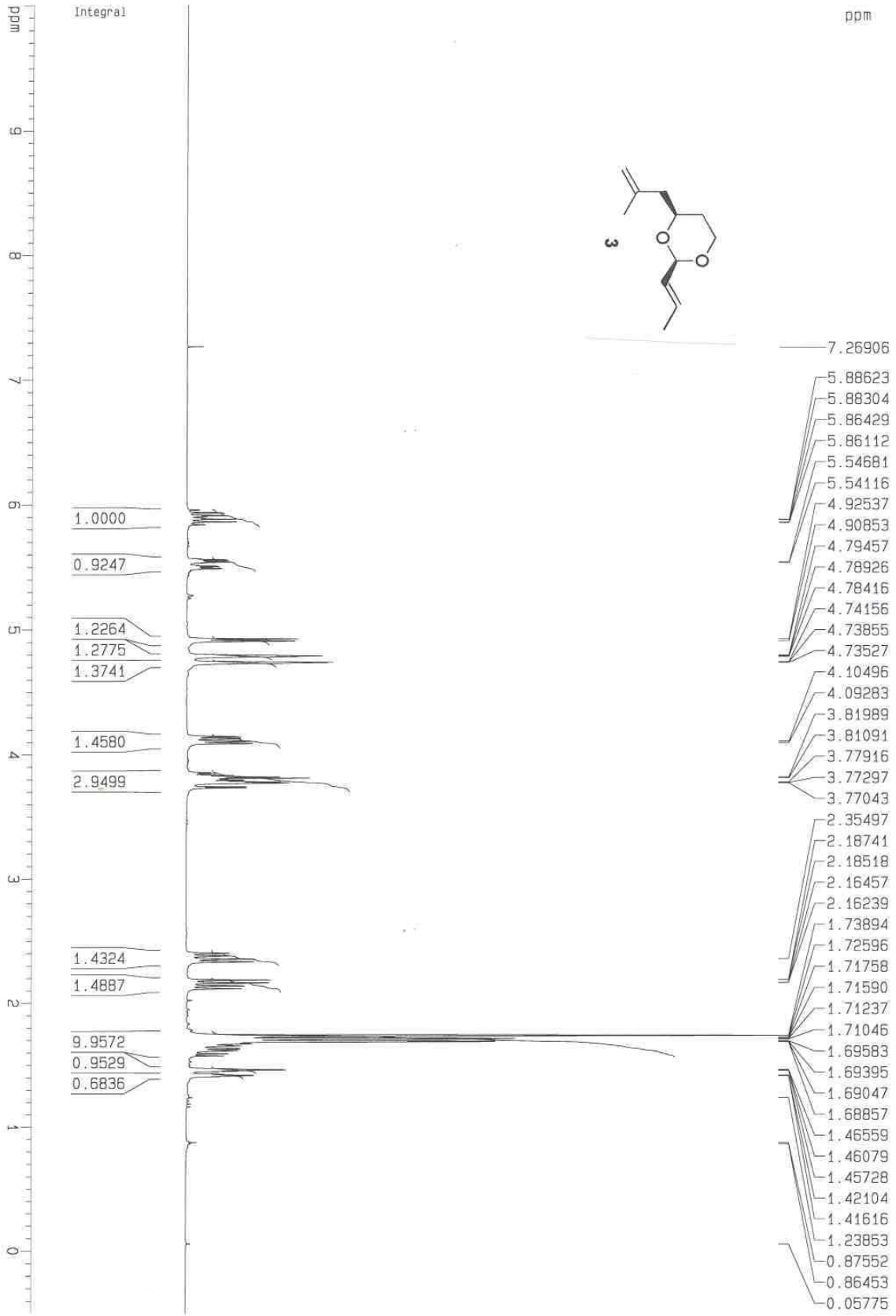
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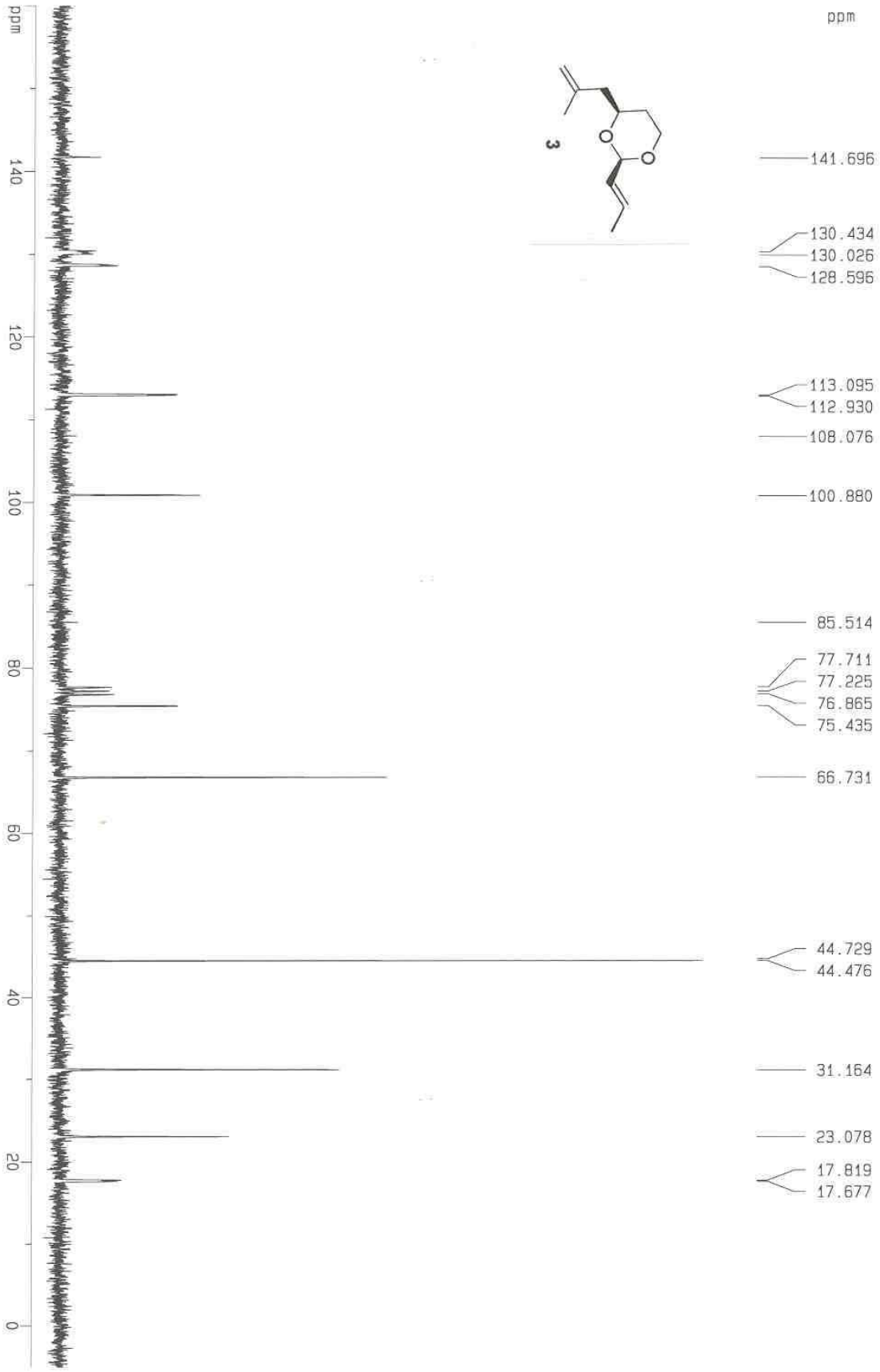
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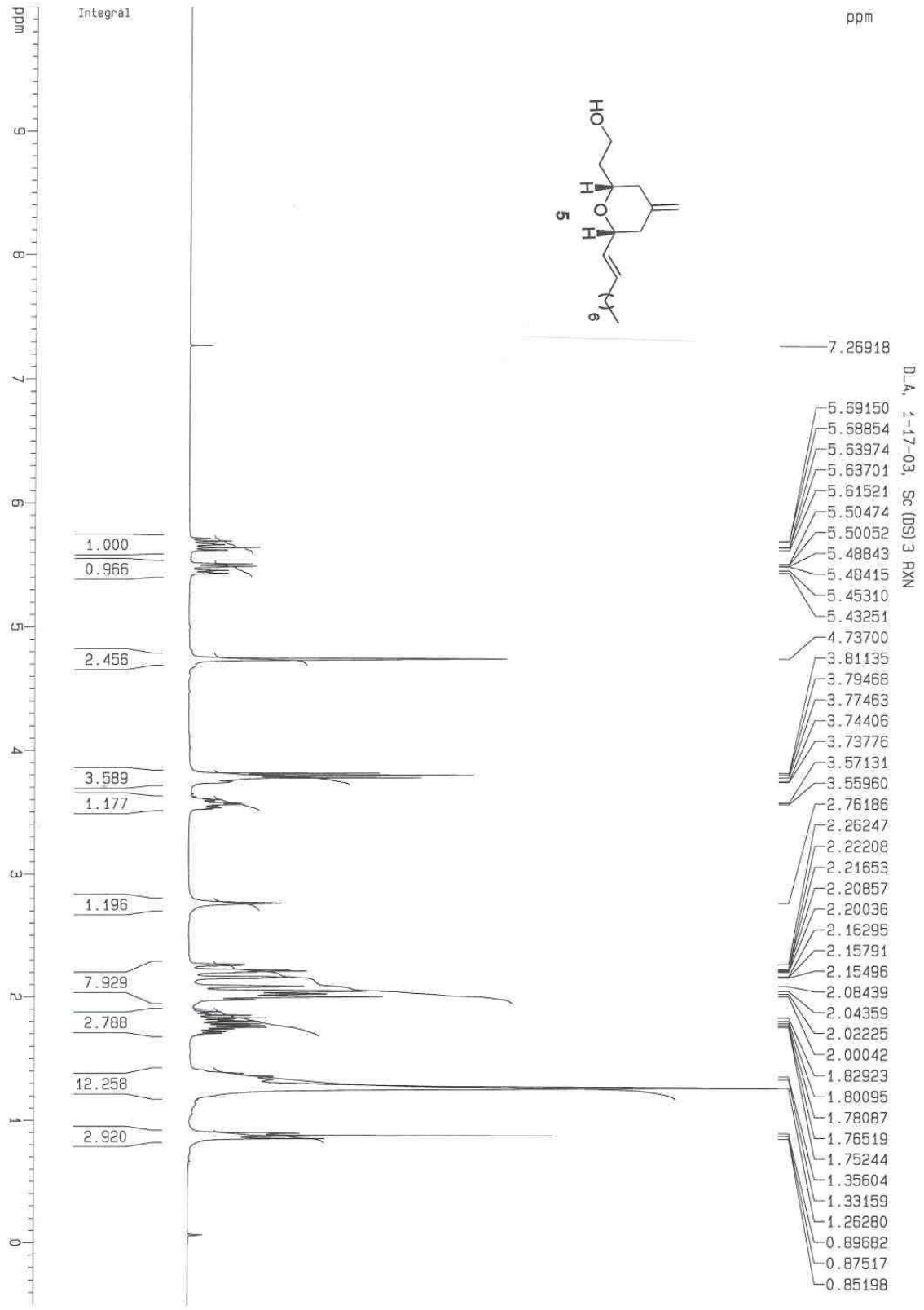
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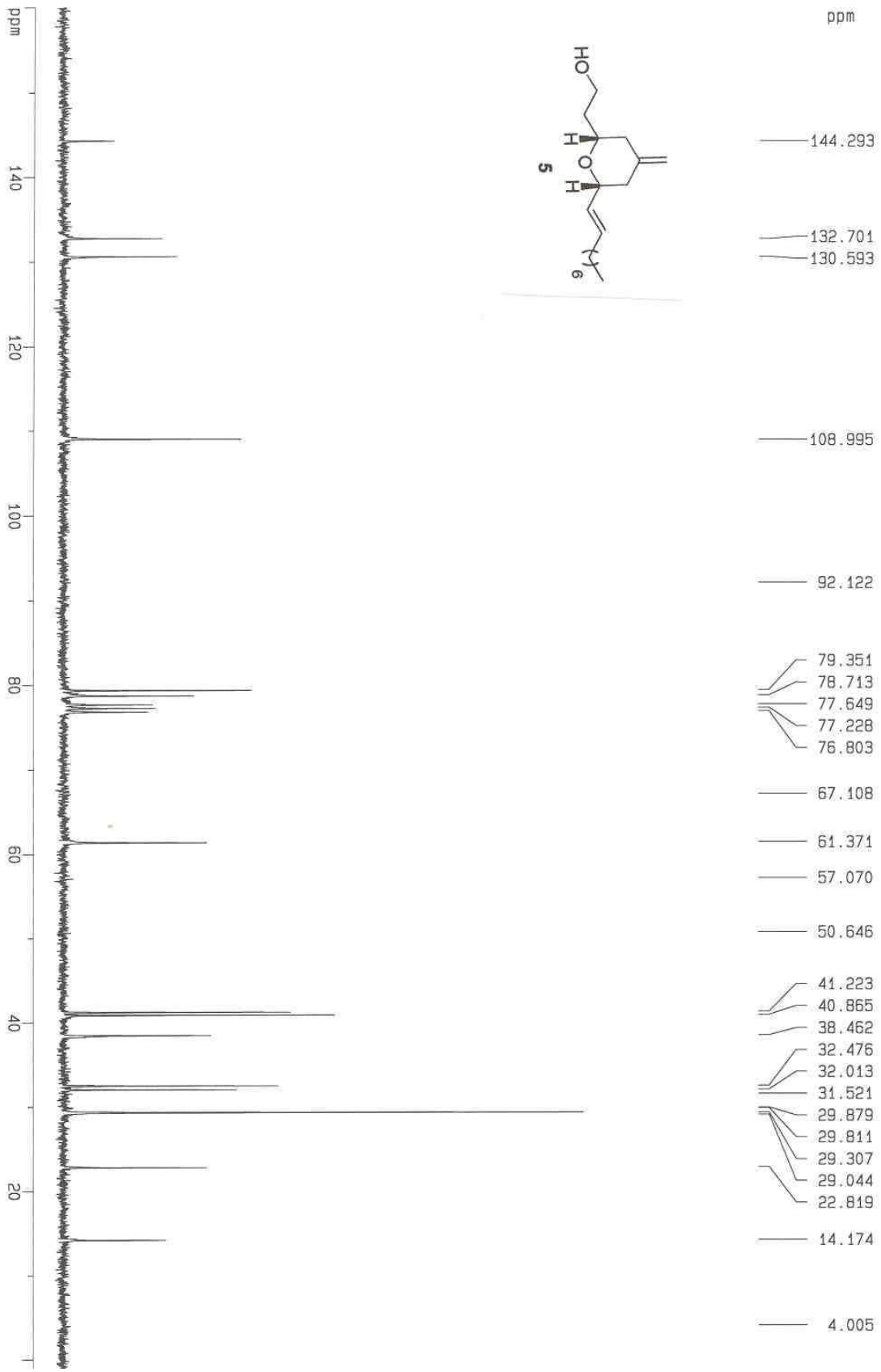
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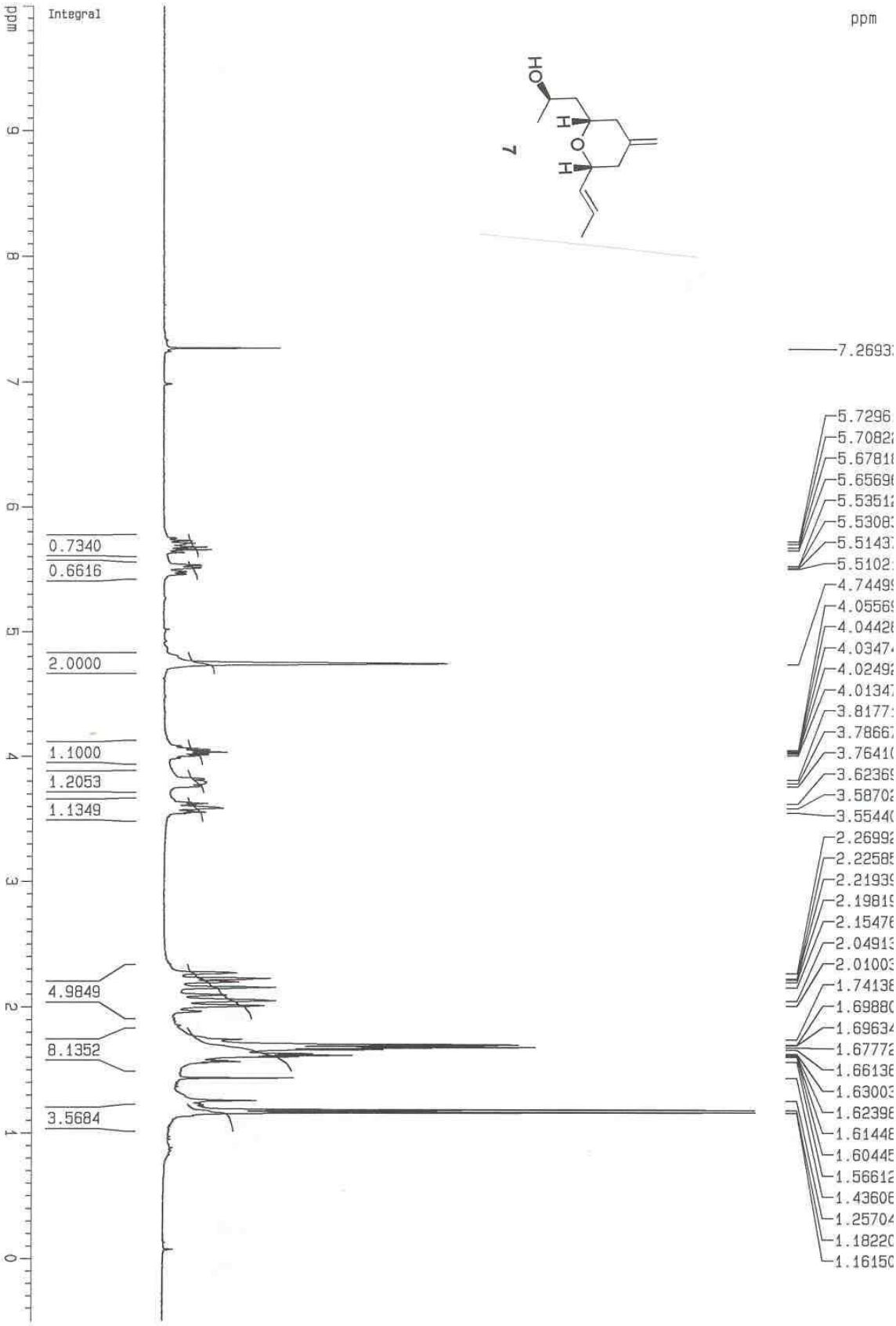
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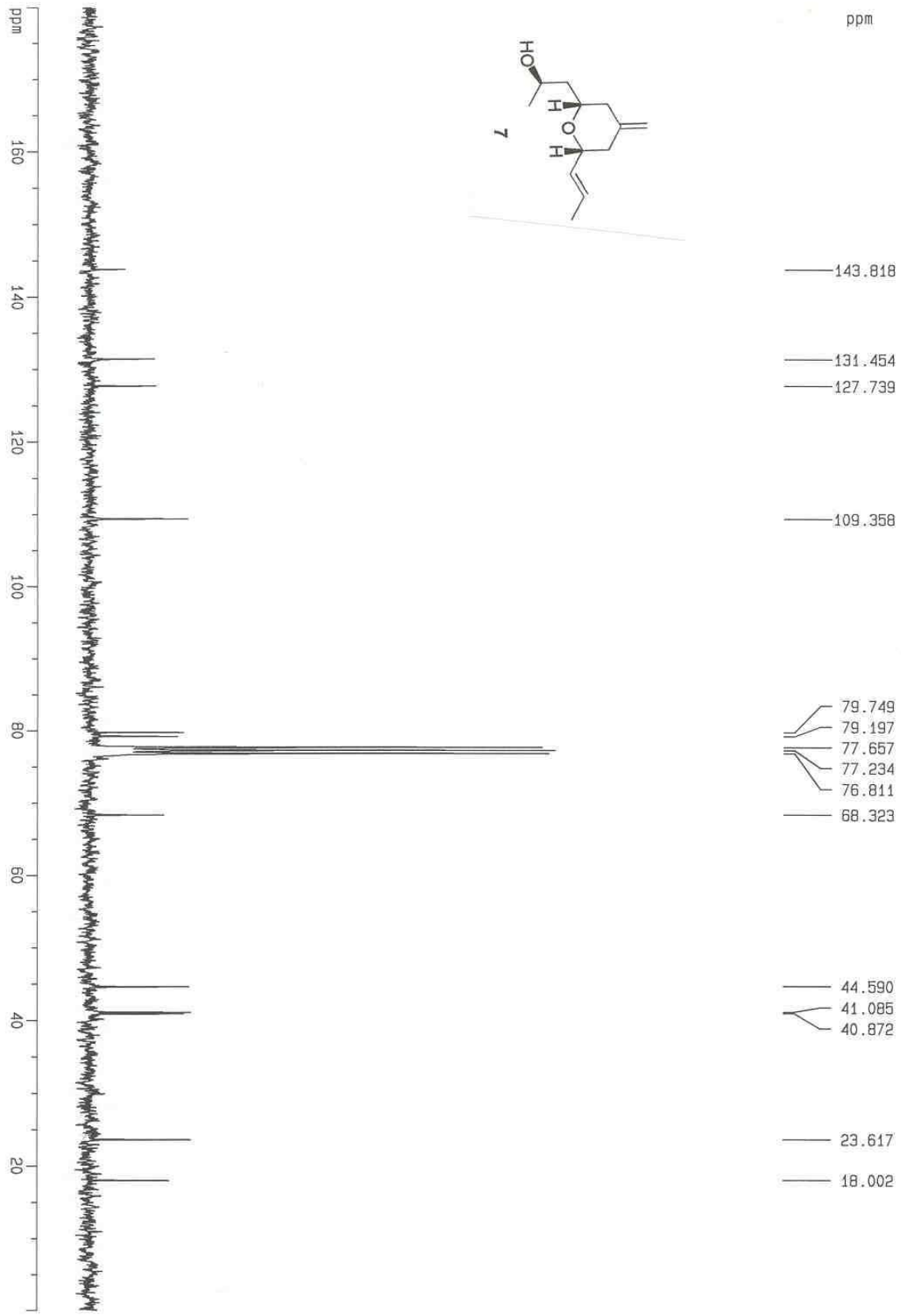
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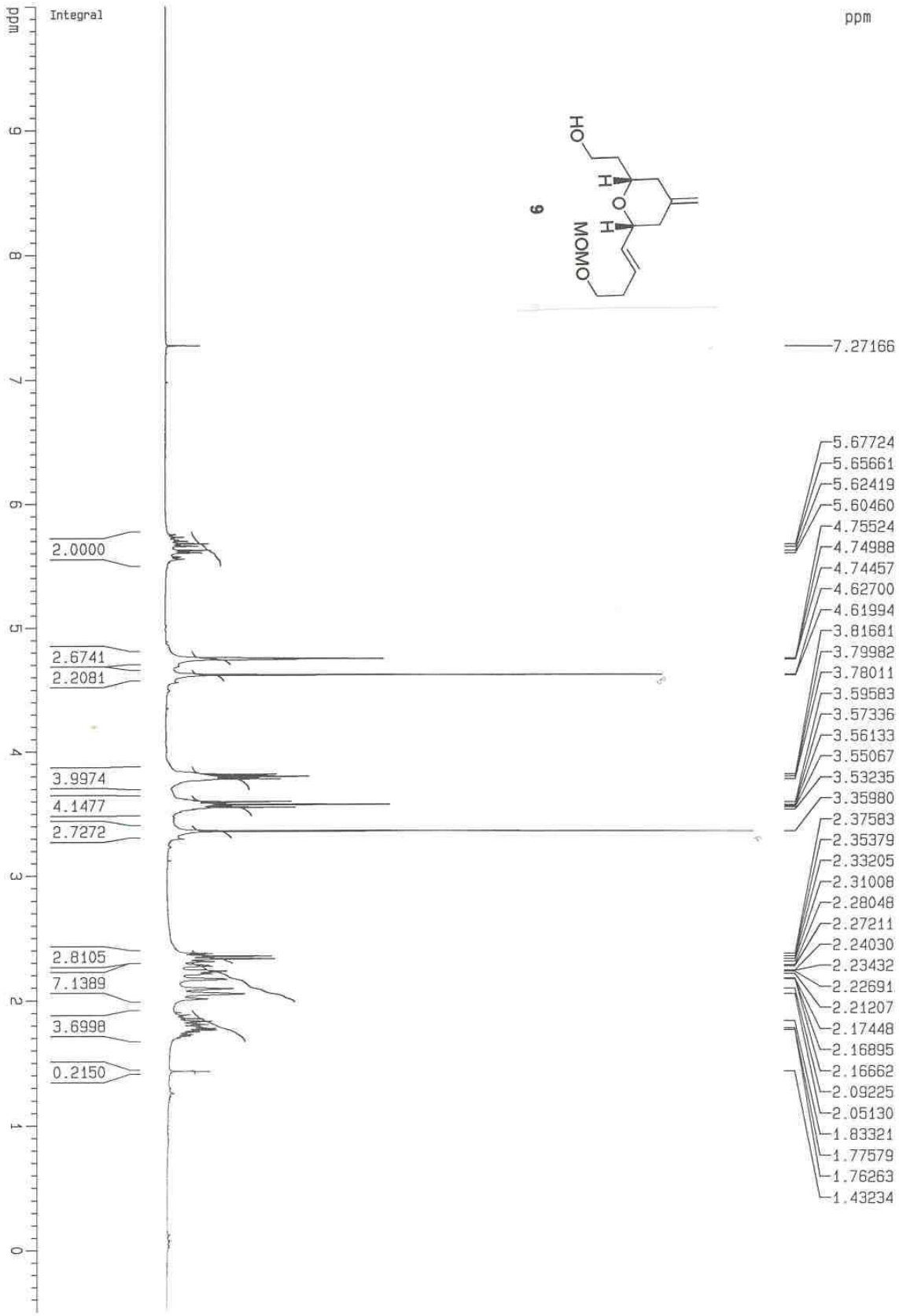
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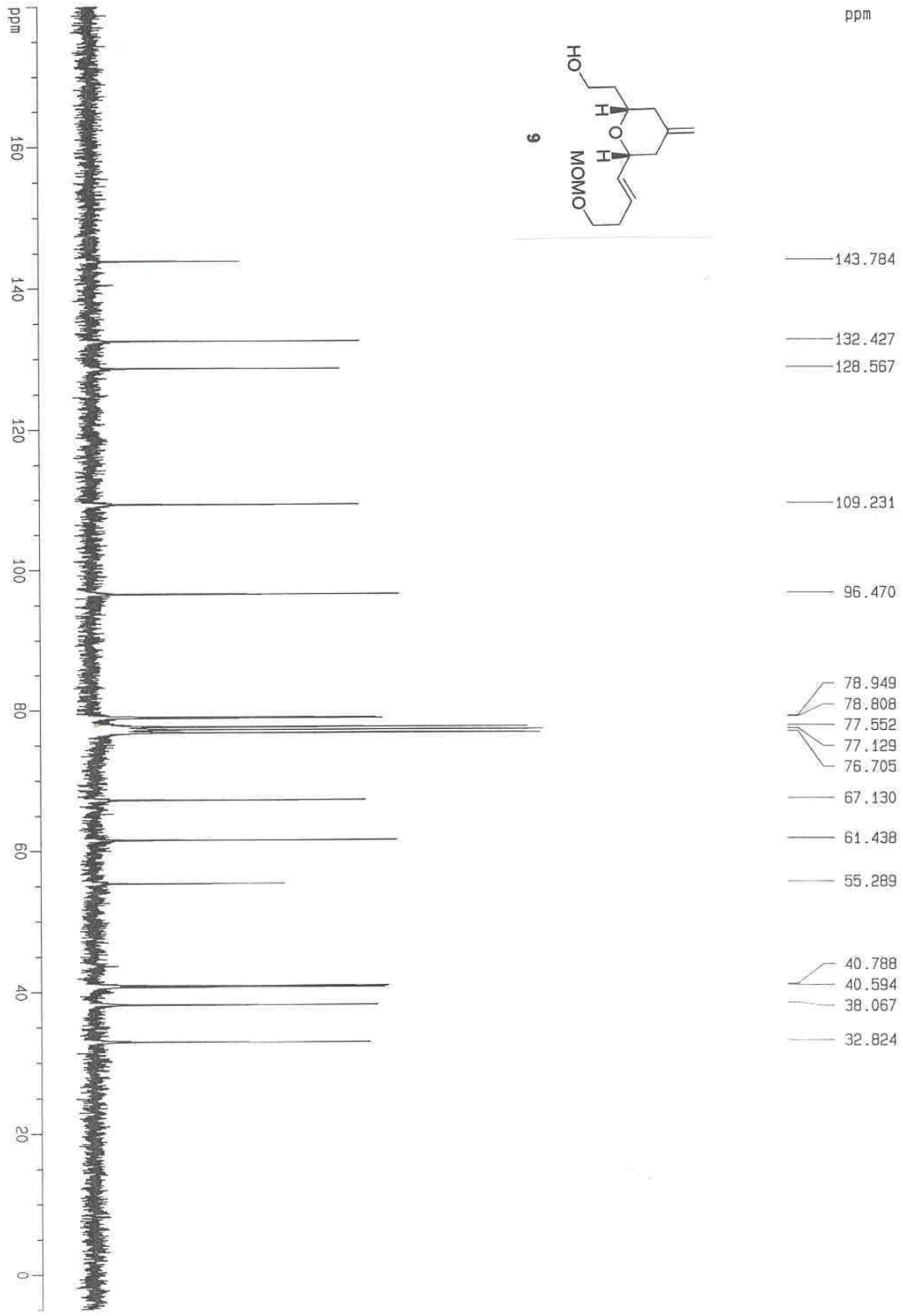
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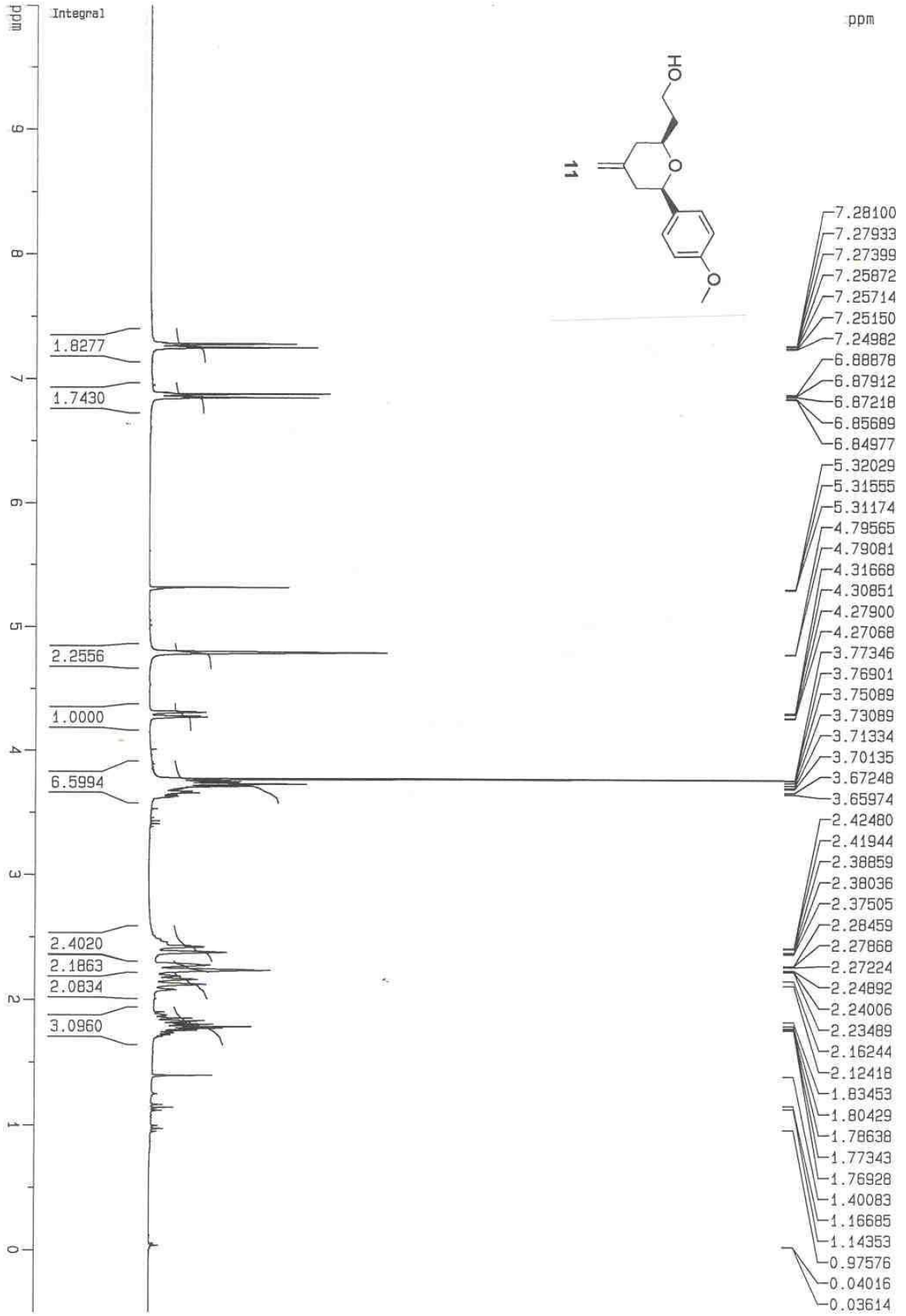
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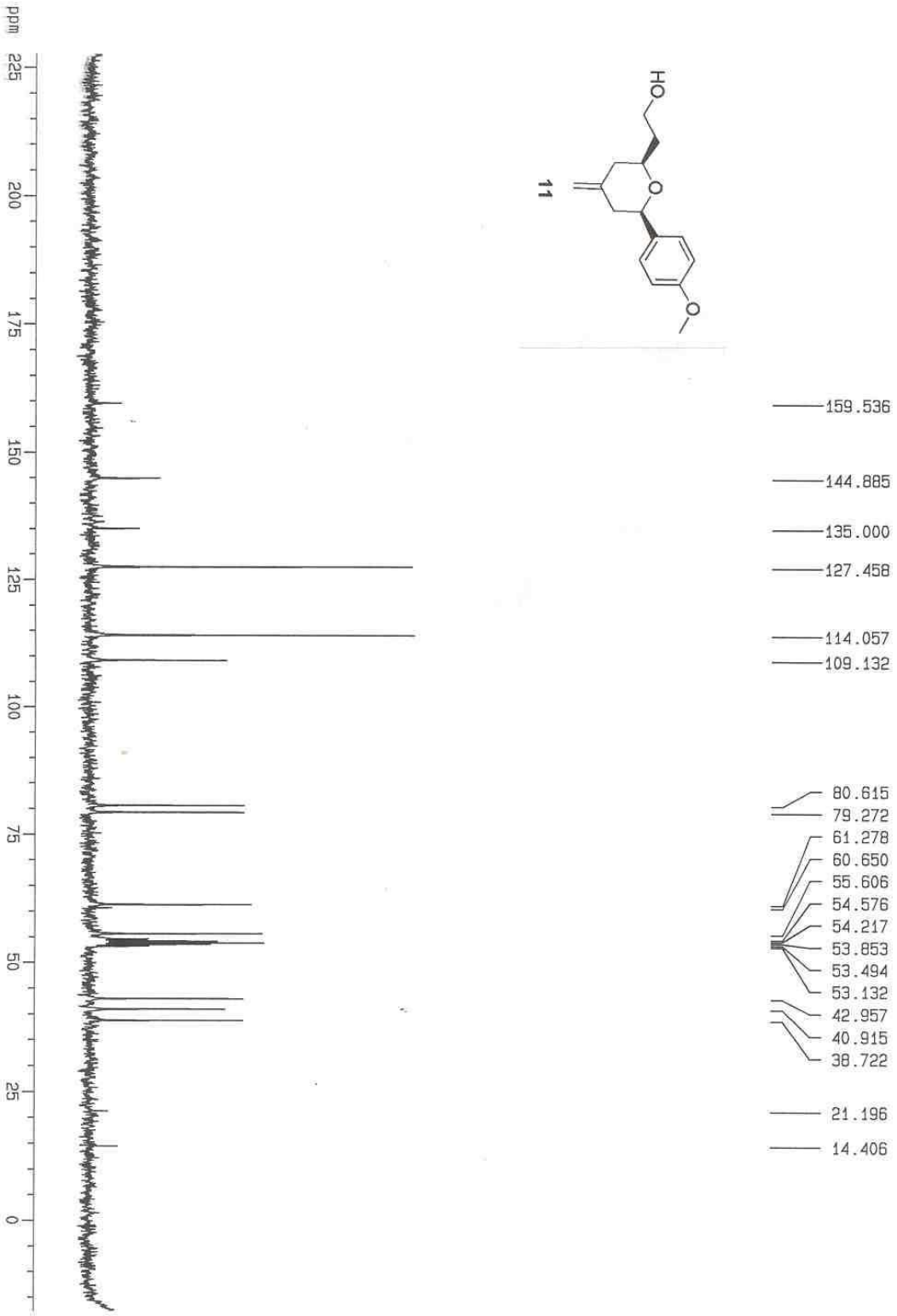
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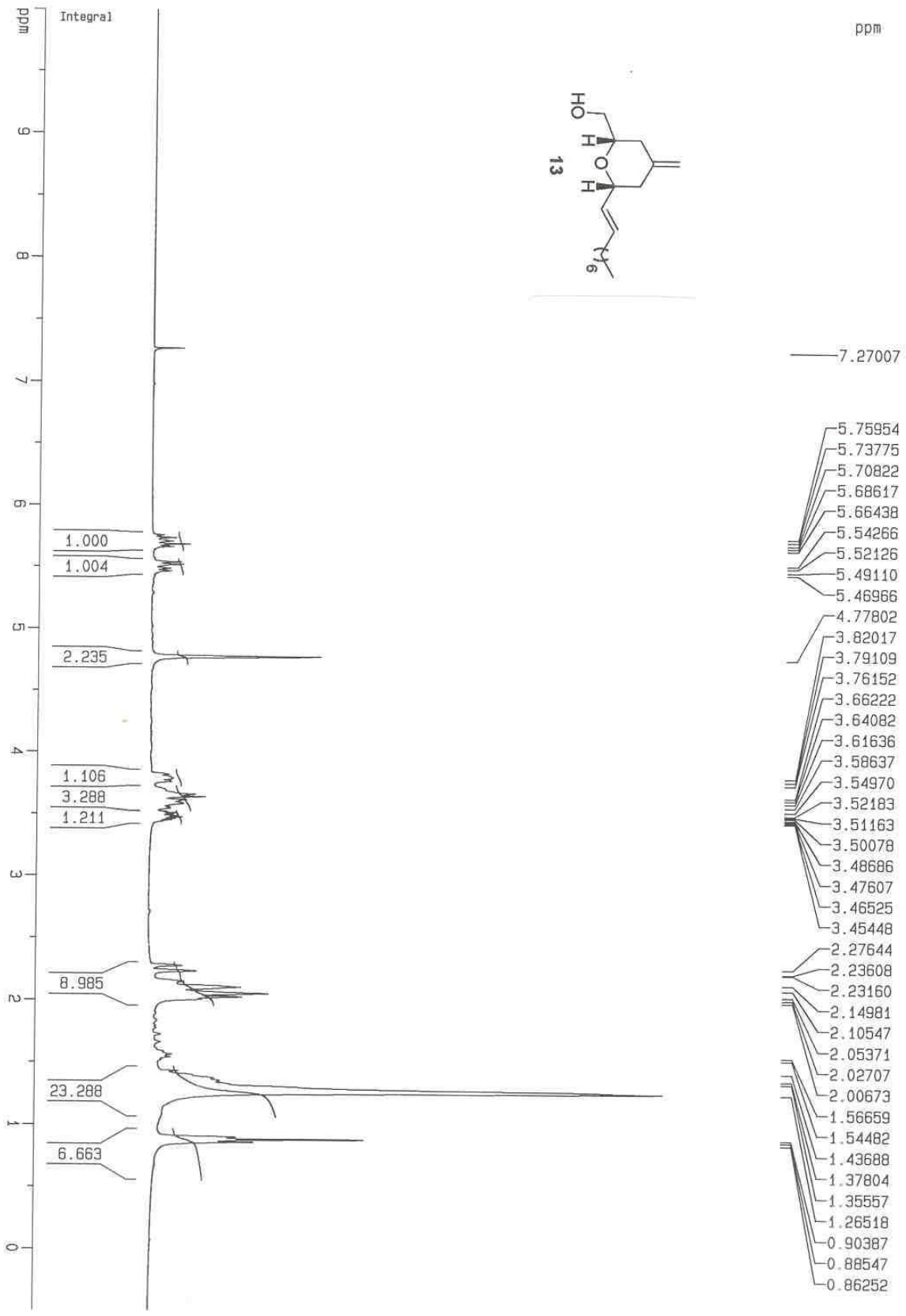
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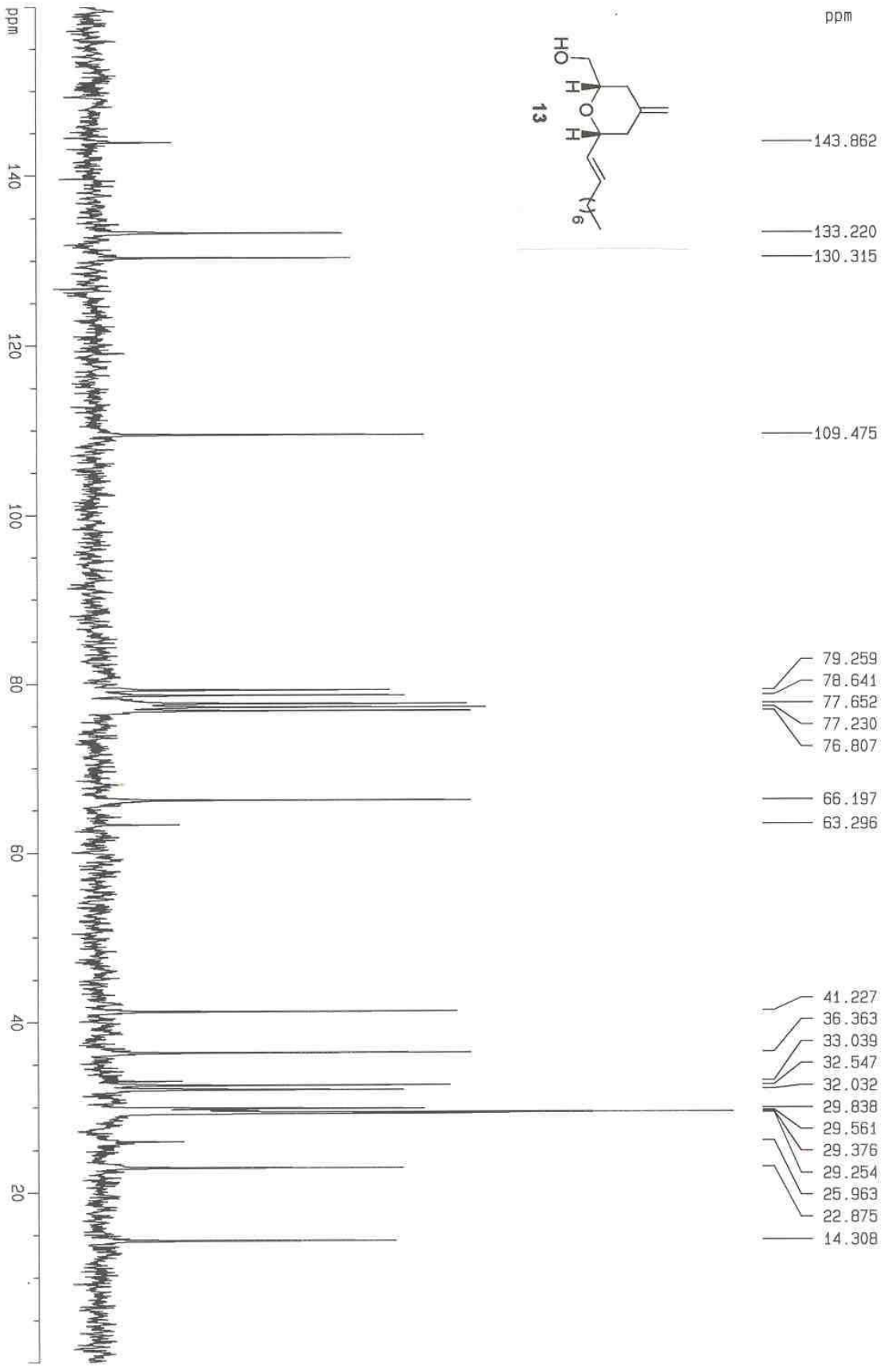
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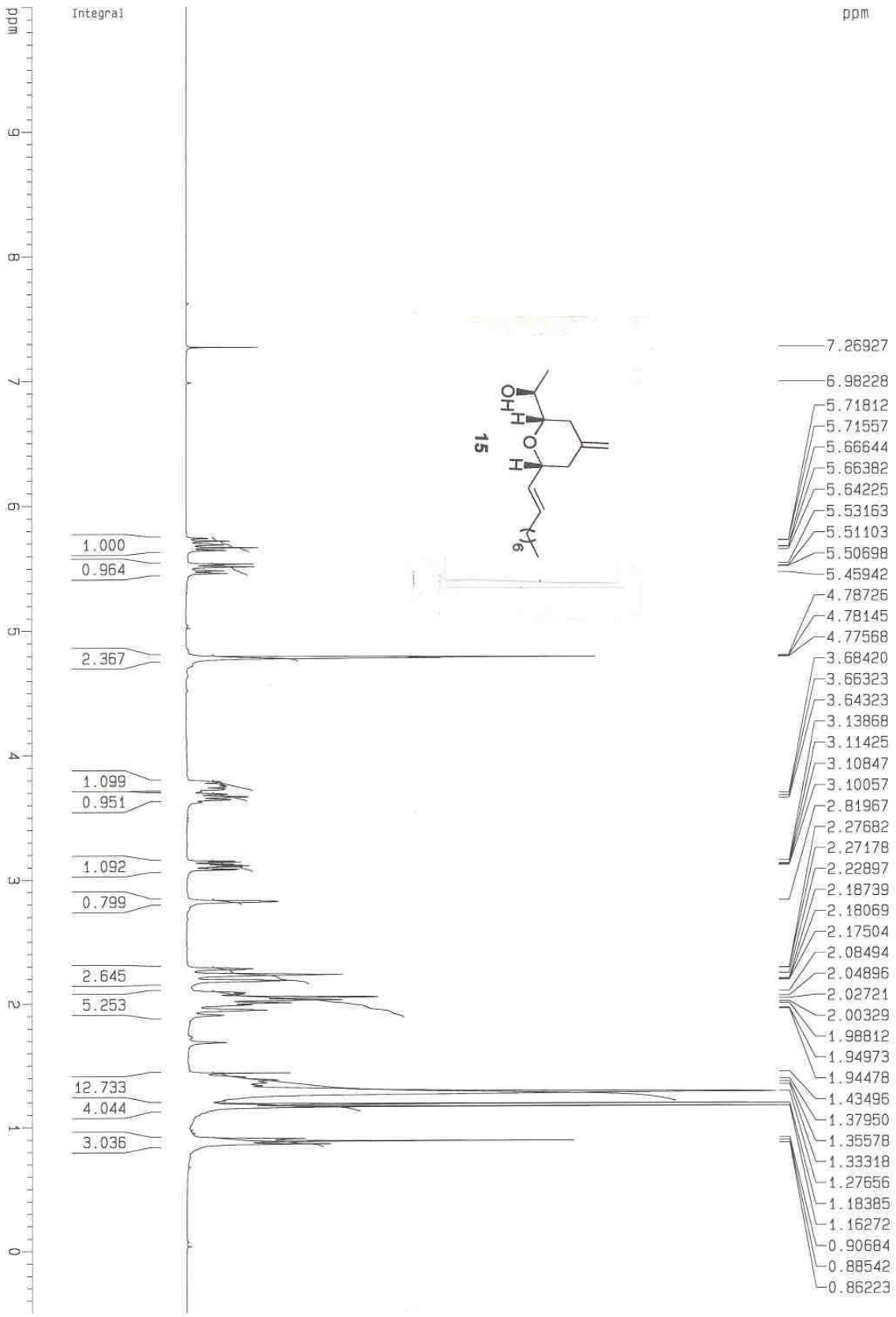
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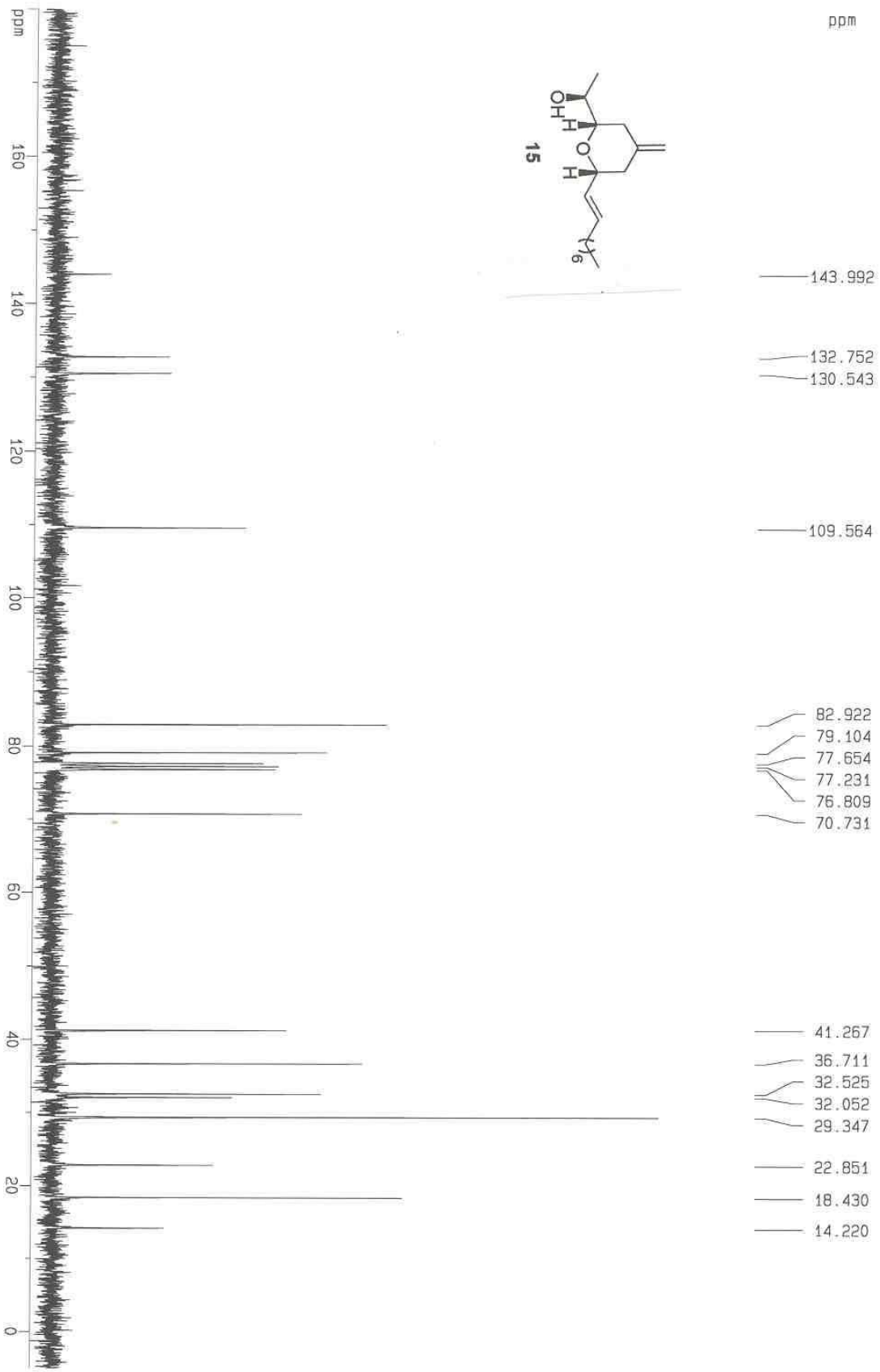
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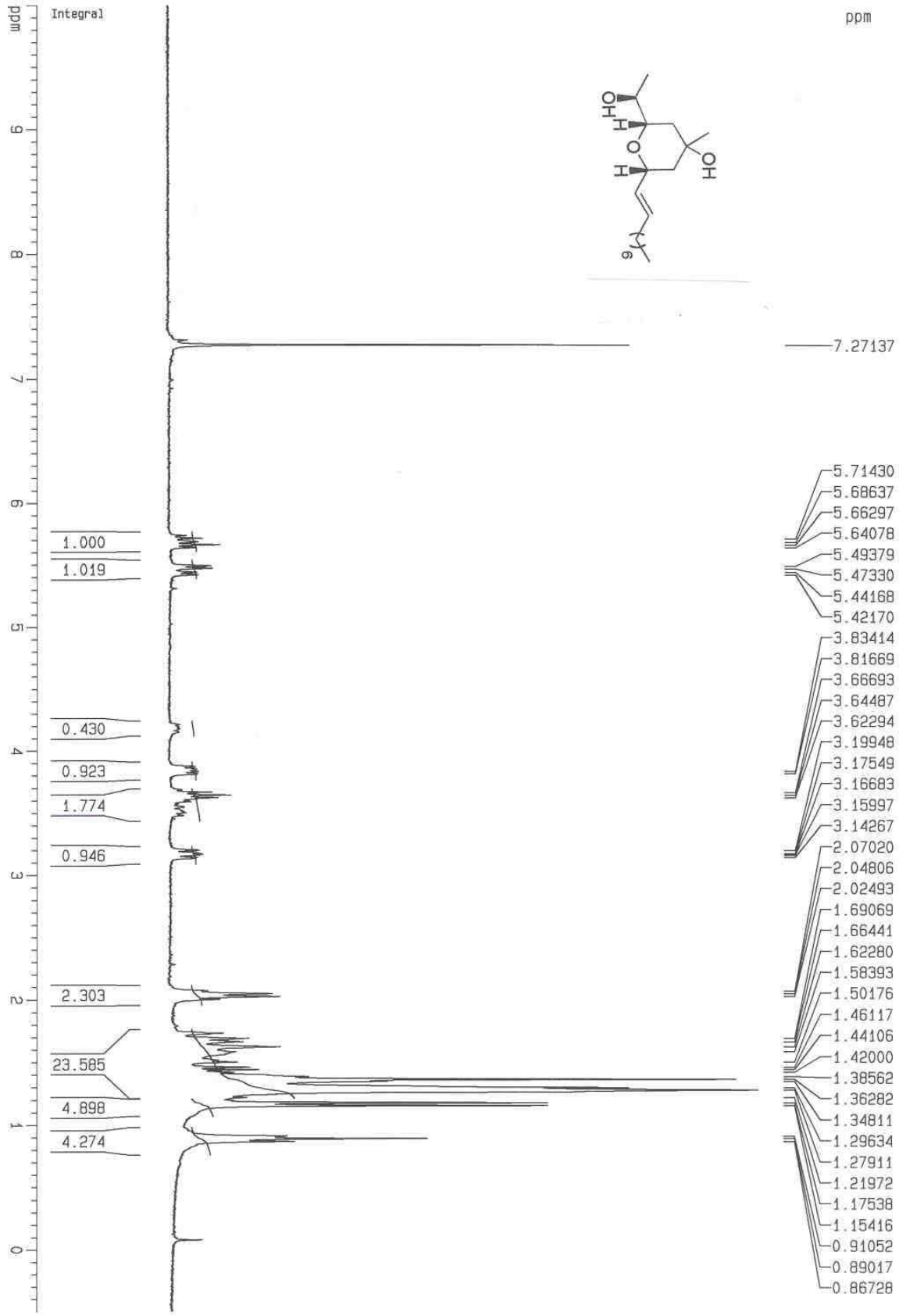
Integral
ppm
7.27137
5.71430
5.68637
5.66297
5.64078
5.49379
5.47330
5.44168
5.42170
3.83414
3.81669
3.66693
3.64487
3.62294
3.19948
3.17549
3.16683
3.15997
3.14267
2.07020
2.04806
2.02493
1.69069
1.66441
1.62280
1.58393
1.50176
1.46117
1.44106
1.42000
1.38562
1.36282
1.34811
1.29634
1.27911
1.21972
1.17538
1.15416
0.91052
0.89017
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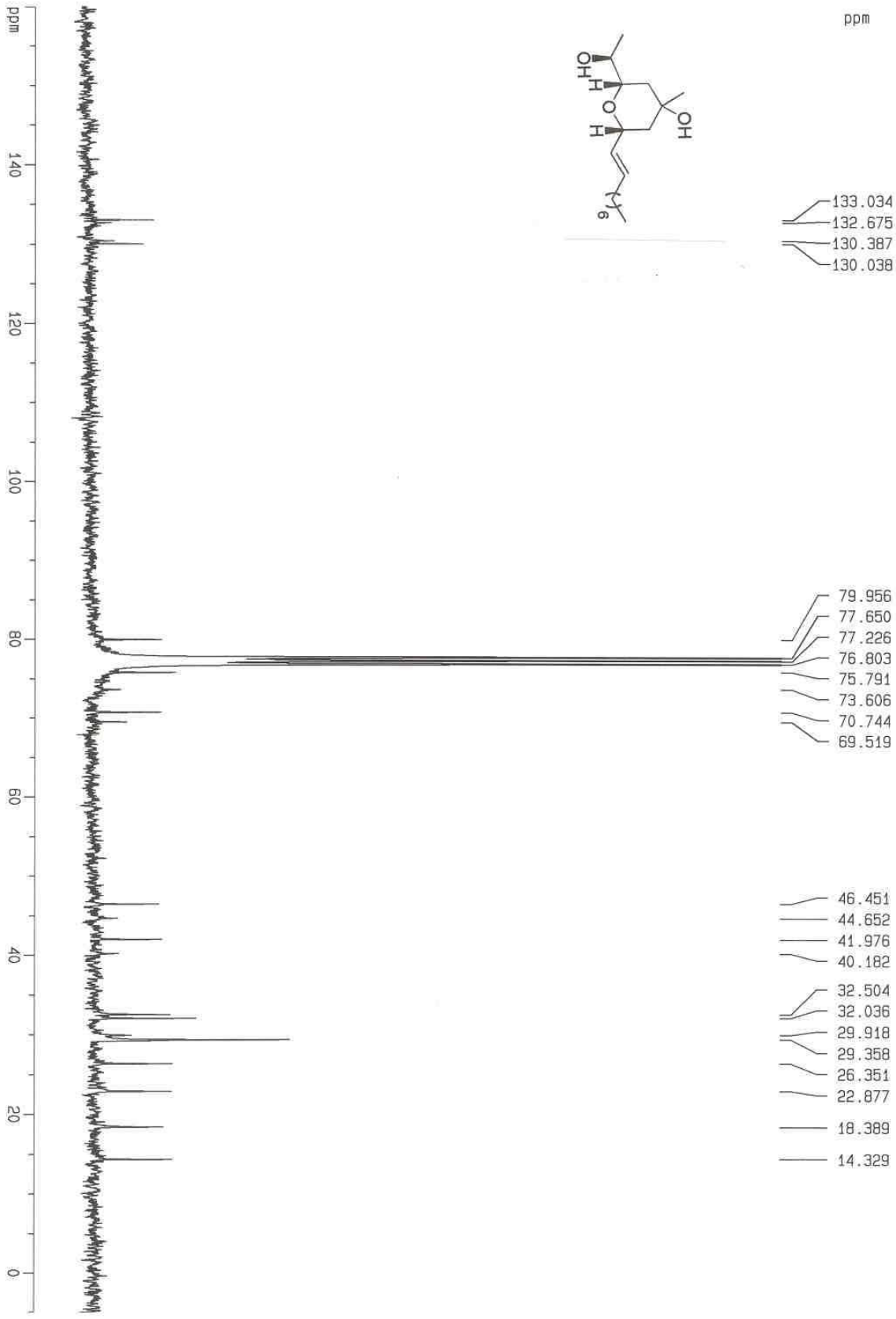
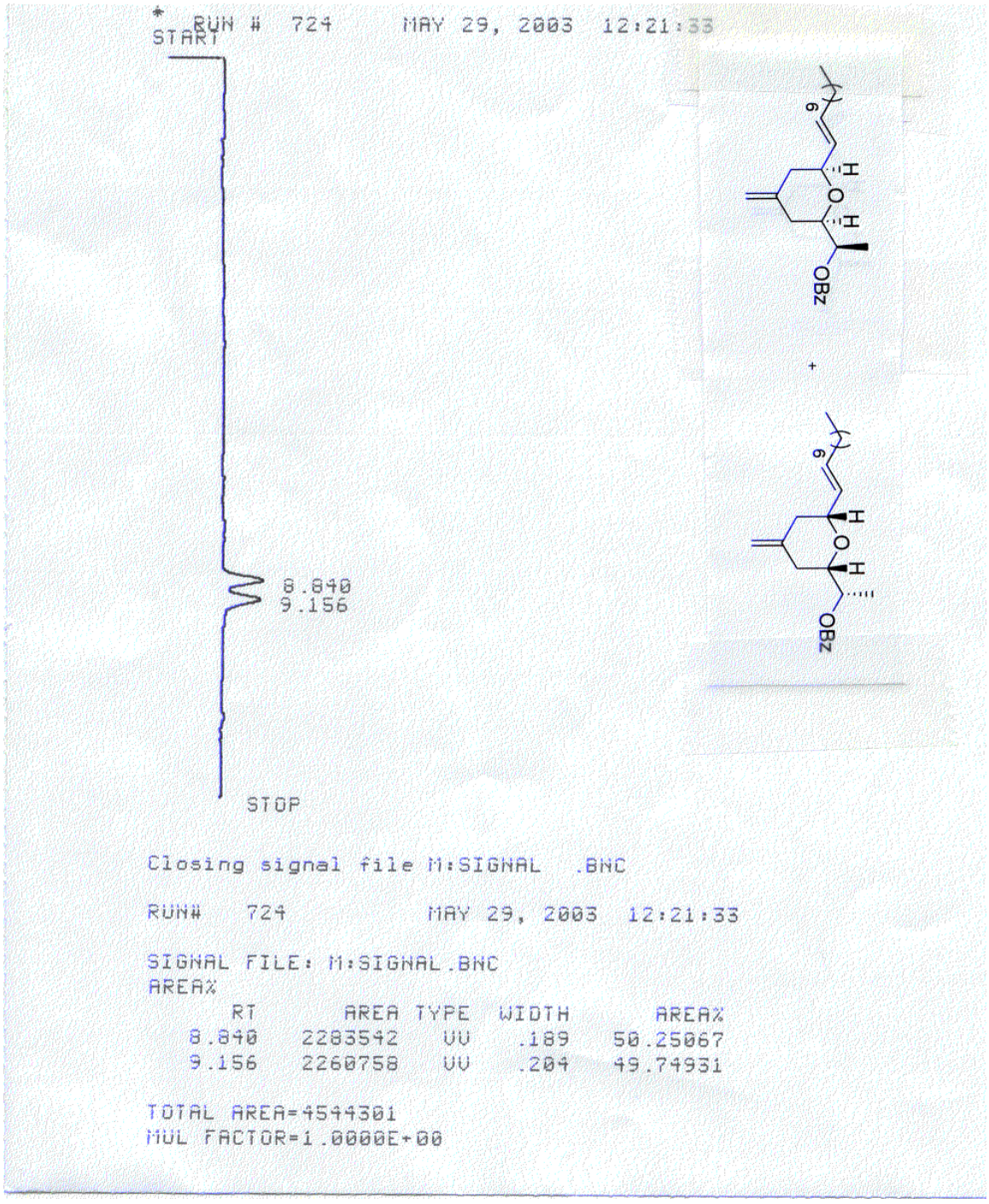
1.019
0.430
0.923
1.774
0.946
2.303
23.585
4.898
4.274


ppm
140
120
100
80
60
40
20
0
OH
H
O
H
OH
6
ppm
133.034
132.675
130.387
130.038
79.956
77.650
77.226
76.803
75.791
73.606
70.744
69.519
46.451
44.652
41.976
40.182
32.504
32.036
29.918
29.358
26.351
22.877
18.389
14.329



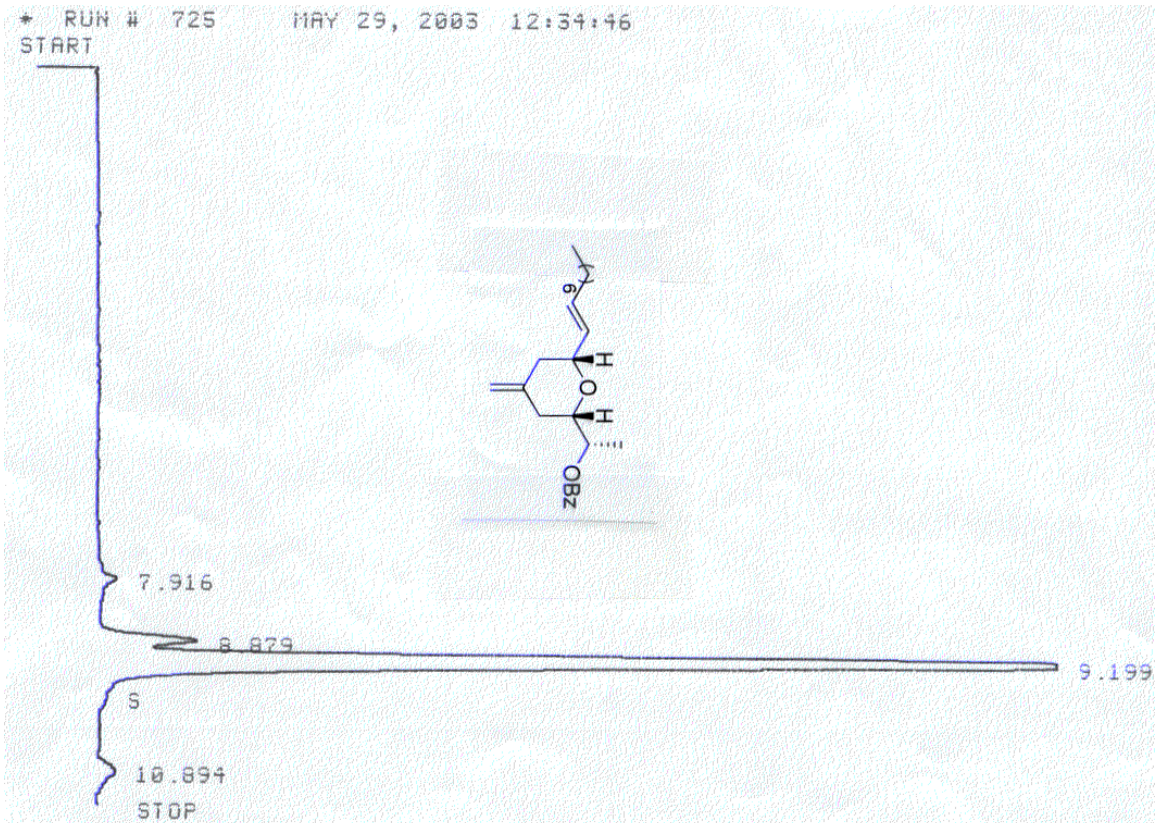
Closing signal file M:SIGNAL .BNC

RUN# 724 MAY 29, 2003 12:21:33

SIGNAL FILE: M:SIGNAL.BNC
AREA%

RT	AREA	TYPE	WIDTH	AREA%
8.840	2283542	VV	.189	50.25067
9.156	2260758	VV	.204	49.74931

TOTAL AREA=4544301
MUL FACTOR=1.0000E+00



Closing signal file M:SIGNAL .BNC

RUN# 725 MAY 29, 2003 12:34:46

SIGNAL FILE: M:SIGNAL.BNC
AREA%

RT	AREA	TYPE	WIDTH	AREA%
7.916	2058206	PU	.376	2.82187
8.879	4993952	UH	.192	6.84689
9.199	64278144	SHB	.194	88.12758
10.894	1607296	PP	.320	2.20366

TOTAL AREA=7.2938E+07
MUL FACTOR=1.0000E+00

*