Supporting Information

IodoCyclization and Prins-Type Macrocyclization: An Efficient Formal Synthesis of Leucascandrolide A

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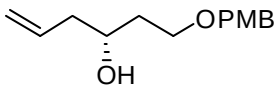
General methods: Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in an oven or flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, toluene and *t*-butyl methyl ether from Na and benzophenone; CH_2Cl_2, DMSO from CaH_2; MeOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using Spectrochem silica gel (60–120 mesh). Specific optical rotations $[\alpha]_D$ are given in 10^{-1} degcm^{2}g^{-1}. Infrared spectra were recorded in $CHCl_3$/neat (as mentioned) and reported in wave number (cm^{-1}). ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

(*R*)-1-(4-Methoxybenzyloxy)hex-5-en-3-ol (10):

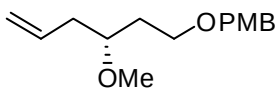


A freshly prepared vinyl magnesium bromide (76.9 mL, 76.92mmol) (1 M solution in THF) was added drop wise to a solution of CuI (0.73 g, 3.85 mmol) in THF (50 mL) at –20 ^{o}C. The mixture was stirred from 30 minutes and chiral epoxide **9** (8.0 g, 38.46 mmol) was added in THF (50 mL) dropwise to the above mixture. After 2 h, the reaction (monitored by TLC) was quenched with saturated solution of NH_4Cl (75 mL) and diluted with diethyl ether (50 mL). The two layers were separated and the aqueous layer extracted with diethyl ether (3 x 75 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced

pressure to get the crude mass. Purification by flash column chromatography over silica gel (ethyl acetate: hexane = 1:9) afforded the desired homoallyl alcohol **10** (7.7 g, 85%) as a colorless oil.

$[\alpha]_D^{25}$ +4.2 (*c* 0.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.83 (m, 1H), 5.14-5.06 (m, 2H), 4.45 (s, 2H), 3.85 (m, 1H), 3.80 (s, 3H), 3.76-3.57 (m, 2H), 2.94 (br s, 1H), 2.23 (t, *J* = 6.8 Hz, 2H), 1.81-1.71 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 134.8, 130.0, 129.3, 117.4, 113.8, 72.9, 70.4, 68.6, 55.2, 41.9, 35.8 ppm; IR (neat, KBr) 3434, 3074, 2933, 2862, 1613, 1513, 1464, 1302, 1249, 1174, 1019 cm^{-1}; ESI HRMS *m/z* calcd. $[M + Na]^+$: 259.1305, found 259.1306.

(*R*)-1-Methoxy-4-((3-methoxyhex-5-enyloxy)methyl)benzene (11):

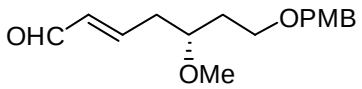


To a suspension of NaH (1.38 g, 34.74 mmol, 60% in mineral oil) in dry THF (50 mL), homoallyl alcohol **10** (4.1 g, 17.37 mmol) dissolved in dry THF (100 ml), was slowly added at 0 ^oC under N_2 atmosphere. The suspension was stirred for 1 h at room temperature. Then, methyl iodide (2.35 mL, 34.74 mmol) was added slowly at 0 ^oC to the above reaction mixture and then it was allowed to stir at room temperature for 4 h. After completion of the reaction (monitored by TLC), it was quenched with saturated solution of NH_4Cl (50 mL) at 0 ^oC and diluted with ethyl acetate (100 mL). The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (2 x 75 mL), dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure to obtain the crude mass which

on purification over silica gel column chromatography (ethyl acetate: hexane = 1:19) afforded methyl ether **11** (4.08 g, 94%) as a light yellow liquid.

$[\alpha]_D^{25}$ −15.5 (*c* 0.95, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 9.1 Hz, 2H), 5.77 (m, 1H), 5.09-5.00 (m, 2H), 4.40 (s, 2H), 3.78 (s, 3H), 3.56-3.44 (m, 2H), 3.38 (m, 1H), 3.32 (s, 3H), 2.25 (t, *J* = 6.3 Hz, 2H), 1.8-1.63 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 134.4, 130.5, 129.1, 116.9, 113.6, 77.3, 72.5, 66.4, 56.6, 55.1, 37.8, 33.8 ppm; IR (neat, KBr) 3074, 2932, 2854, 2837, 1613, 1513, 1464, 1248, 1094, 1036, 915, 821 cm^{-1}; ESI HRMS *m/z* calcd. for $C_{15}H_{22}NaO_3$ $[M + Na]^+$: 273.1461, found 273.1455.

(*R*,*E*)-5-Methoxy-7-(4-methoxybenzyloxy)hept-2-enal (12):

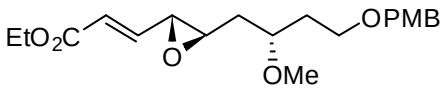


To a solution of methyl ether compound **11** (4.0 g, 16.0 mmol) in CH_2Cl_2 (10 mL) was added Hoveyda-Grubbs catalyst (0.98 mg, 1.6 mmol) followed by acrolein (9.0 g, 160.0 mmol) at room temperature under nitrogen atmosphere and the resulting mixture was stirred at the same temperature for 3 h. After completion of the reaction (monitored by TLC), it was concentrated to dryness under reduced pressure and the crude oil was directly purified by short flash column chromatography over silica gel (ethyl acetate: hexane = 1:7) furnished the desired *α*,*β* unsaturated aldehyde **12** (4.1 g, 92%) as a colorless liquid.

$[\alpha]_D^{25}$ −10.4 (*c* 0.55, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.48 (d, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.78 (m, 1H), 6.12 (dd, *J* = 7.9, 15.9 Hz, 1H), 4.40 (s, 2H), 3.79 (s, 3H), 3.57-3.42 (m, 3H), 3.33 (s, 3H), 2.63-2.40 (m, 2H),

1.85-1.63 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 159.1, 154.4, 134.8, 129.2, 113.7, 76.6, 72.6, 66.0, 56.9, 55.1, 36.7, 34.0 ppm; IR (neat, KBr) 2935, 2861, 2837, 2740, 1690, 1513, 1248, 1093, 1034, 821 cm^{-1}; ESI HRMS *m/z* calcd. for $C_{16}H_{22}NaO_4$ $[M+Na]^+$: 301.1410, found 301.1407.

(*E*)-Ethy 3-((2*R*,3*R*)-3-((*S*)-2-methoxy-4-(4-methoxybenzyloxy)butyl)oxiran-2-yl)acrylate (13):

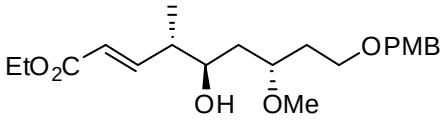


To a stirred solution of *α,β* unsaturated aldehyde **12** (3.9 g, 14.03 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added TMS-protected diphenyl prolinol catalyst (0.46 g, 1.40 mmol) followed by H_2O_2 (35 % aq., 1.23 mL, 18.23 mmol). The reaction mixture was stirred vigorously at room temperature until total consumption of the starting material (monitored by TLC). Then $Ph_3P{=}CHCO_2Et$ (5.8 g, 16.83 mmol) was added in one portion at 0 °C and stirred for another 1 h at room temperature. After removal of the solvents under reduced pressure, the residue was purified by column chromatography over silica gel (ethyl acetate: hexane = 1:8) to give the desired epoxy compound **13** (3.69 g, 80%) as a colorless oil.

$[\alpha]_D^{25}$ +5.4 (*c* 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 6.64 (dd, *J* = 6.8, 15.3 Hz, 1H), 6.07 (d, *J* = 15.9 Hz, 1H), 4.39 (s, 2H), 4.18 (q, *J* = 6.7 Hz, 2H), 3.79 (s, 3H), 3.55-3.41 (m, 3H), 3.34 (s, 3H), 3.17 (d, *J* = 7.6 Hz, 1H), 2.97 (dd, *J* = 6.8, 15.4 Hz, 1H), 1.86-1.64 (m, 4H), 1.29 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 159.2, 144.5, 130.4, 129.3, 123.8, 113.8, 75.9, 72.7, 66.1, 60.6, 58.6, 57.4, 56.7, 55.2, 37.0, 34.4, 14.2 ppm; IR (neat, KBr) 2979, 2935,

2861, 1720, 1657, 1613, 1513, 1303, 1249, 1182, 1092, 1035, 853, 821 cm^{-1}; ESI HRMS *m/z* calcd. $C_{20}H_{28}NaO_6$ for $[M + Na]^+$: 387.1778, found 387.1791.

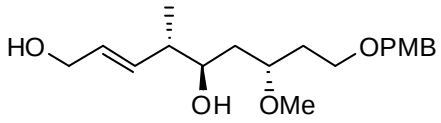
(4*S*,5*R*,7*S*,*E*)-Ethyl 5-hydroxy-7-methoxy-9-(4-methoxybenzyloxy)-4-methylnon-2-enoate (14):



The epoxy compound **13** (3.5 g, 9.3 mmol) was taken in a 250 mL RB and to it, CH_2Cl_2 (70 mL) was added under nitrogen atmosphere. The reaction mixture was cooled to −40 ^oC. Trimethyl aluminium (46.6 mL, 93.1 mmol, 2M in toluene) was slowly added under nitrogen atmosphere at the same temperature. After 10 min, H_2O (1.0 mL, 55.9 mmol) was added very carefully and slowly so that the internal temperature did not change. After effervescence ceased, it was allowed to stir for further 3 h at −40 ^oC and TLC showed the complete consumption of the starting material. It was quenched very slowly with saturated NH_4Cl (50 mL) and diluted with CH_2Cl_2 (100 mL). HCl (1.0 N, 50 mL) was added and vigorously stirred until a clear separation of the two layers took place. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, evaporated to dryness and then purified by silica gel column chromatography (ethyl acetate: hexane = 1:5) to get the desired product **14** (3.35 g, 92%) as a colorless oil. $[\alpha]_D^{25}$ −4.5 (*c* 1.45, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.3 Hz, 2H), 6.93 (dd, *J* = 7.5, 15.9 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 2H), 5.78 (d, *J* = 15.9 Hz, 1H), 4.38 (s, 2H), 4.17 (q, *J* = 6.8 Hz, 2H), 3.85 (m, 1H), 3.79 (s, 3H), 3.61 (m, 1H), 3.51-3.42 (m, 2H), 3.33 (s, 3H), 2.95 (br. s, 1H), 2.31 (m, 1H), 1.92 (m, 1H), 1.77-1.63 (m, 2H), 1.45

(m, 1H), 1.29 (t, J = 6.8 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 159.1, 150.6, 130.3, 129.3, 121.8, 113.7, 76.8, 72.7, 71.4, 66.3, 60.2, 57.1, 55.2, 42.8, 36.6, 33.1, 15.5, 14.2 ppm; IR (neat, KBr) 3472, 2936, 2874, 2836, 1713, 1651, 1613, 1513, 1301, 1250, 1180, 1092, 1036, 847, 821 cm^{-1}; ESI HRMS *m/z* calcd. for $C_{21}H_{32}NaO_6$ $[M + Na]^+$: 403.2096, found 403.2083.

(4*S*,5*R*,7*S*,*E*)-7-Methoxy-9-(4-methoxybenzyloxy)-4-methylnon-2-ene-1,5-diol:

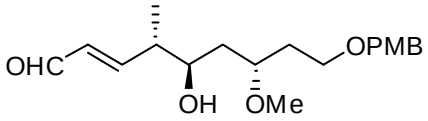


To astirred solution of *α*,*β*-unsaturated ester **14** (3.2 g, 8.2 mmol) was dissolved in CH_2Cl_2 (60 mL) and cooled to −78 °C under nitrogen atmosphere. DIBAL-*H* (14.5 mL, 20.4 mmol) was slowly added to it over a period of 5 min. After 30 min of stirring at the same temperature, TLC was checked which showed complete consumption of starting material. It was quenched by slow addition of saturated solution of sodium potassium tartrate (50 mL), diluted with CH_2Cl_2 (40 mL) and allowed to stir at room temperature for another 2 h to get a clear two separated layers. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed with brine (2 x 75 mL), dried over anhydrous Na_2SO_4, evaporated to dryness under vacuum which on silica gel column chromatography (ethyl acetate: hexane = 2:3) produced the desired *α*,*β*-unsaturated alcohol (2.43 g, 88%).

$[\alpha]_D^{25}$ +3.9 (*c* 0.73, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.3 Hz, 2H), 5.60 (d, J = 5.3 Hz, 2H), 4.39 (s, 2H), 4.02 (d, J = 3.8 Hz, 2H), 3.78 (s, 3H), 3.67-3.55 (m, 2H), 3.52-3.41(m, 2H), 3.34 (s, 3H), 2.13 (m, 1H), 1.94-1.63 (m,

2H), 1.61-1.46 (m, 2H), 0.98 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 134.3, 130.0, 129.3, 113.7, 76.6, 72.3, 71.9, 66.4, 63.4, 57.1, 55.2, 42.7, 37.1, 33.4, 16.3 ppm; IR (neat, KBr) 3408, 2933, 2871, 1612, 1513, 1302, 1248, 1087, 1035, 847, 821 cm^{-1}; ESI HRMS *m/z* calcd. for $C_{19}H_{30}NaO_5$ $[M + Na]^+$: 361.1985, found 361.1982.

(*4S*,5*R*,7*S*,*E*)-5-Hydroxy-7-methoxy-9-(4-methoxybenzyloxy)-4-methylnon-2-enal (2):

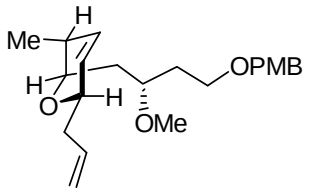


To a stirred solution of diol (2.35 g, 6.95 mmol) in CH_2Cl_2 (40 mL) at 0 °C, iodobenzenediacetate (2.46 g, 7.65 mmol) followed by TEMPO (0.217 g, 1.39 mmol) was added and allowed to stir at ambient temperature for 3 h. After conversion of the primary alcohol completely to aldehyde (monitored by TLC), the reaction mixture was quenched with saturated solution of $Na_2S_2O_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporation of solvent led to crude aldehyde which on purification by short flash chromatography over silica gel (ethyl acetate: hexane = 3:7) afforded aldehyde **2** (2.1 g, 90%) as a thick viscous liquid and used immediately for the next reaction.

$[\alpha]_D^{25}$ +2.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.49 (d, J = 8.3 Hz, 1H), 7.20 (d, J = 9.1 Hz, 2H), 7.09 (m, 1H), 6.84 (d, J = 9.1 Hz, 2H), 6.08 (m, 1H), 4.40 (s, 2H), 3.84 (m, 1H), 3.80 (s, 3H), 3.64 (m, 1H), 3.52-3.43 (m, 2H), 3.34 (s, 3H), 2.43 (m, 1H), 1.95 (m, 1H), 1.80-1.67 (m, 2H), 1.55-1.44 (m, 2H), 1.10 (d, J = 6.8 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 160.4, 159.2, 132.9, 130.2, 129.3, 113.7, 80.1, 72.7, 71.6, 66.2, 57.1, 55.2, 43.3, 36.7, 32.9, 15.6 ppm; IR (neat, KBr) 3459, 2936, 2874, 2837,

1689, 1613, 1513, 1302, 1248, 1089, 1034, 821 cm^{-1}; ESI HRMS *m/z* calcd. for $C_{19}H_{28}NaO_5$ $[M + Na]^+$: 359.1829, found 359.1830.

(2*R*,3*S*,6*R*)-6-Allyl-2-((*S*)-2-methoxy-4-(4-methoxybenzyloxy)butyl)-3-methyl-3,6-dihydro-2*H*-pyran (3):

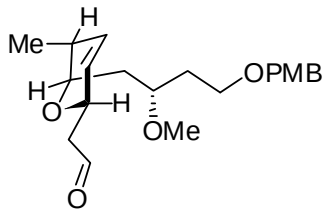


To a stirred solution of *δ*-hydroxy *α,β*-unsaturated aldehyde **2** (2.0 g, 5.95 mmol), and allyltrimethyl silane (1.45 mL, 8.93 mmol) in THF (30 mL) was added iodine (0.15 g, 0.59 mmol) at 0 ^oC and allowed to come to room temperature. After completion of the reaction (as indicated by TLC), it was quenched with saturated solution of $Na_2S_2O_3$ (10 mL) and diluted with *tert*-butyl methyl ether (20 mL). The organic layer was separated and the aqueous layer extracted with *tert*-butyl methyl ether (TBME) (2 x 40 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give pale yellow oil. This was finally purified by column chromatography over silica gel (ethyl acetate: hexane = 1:19) to obtain the cyclized product **3** (2.1 g, 96%).

$[\alpha]_D^{25}$ +14.2 (*c* 0.8 , $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$); δ 7.27 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.86 (m, 1H), 5.70-5.59 (m, 2H), 5.16-5.00 (m, 2H), 4.45-4.38 (m, 2H), 4.16 (m, 1H), 3.81-3.74 (m, 3H), 3.62 (m, 1H), 3.57-3.46 (m, 3H), 3.36-3.26 (m, 3H), 2.41 (m, 1H), 2.26 (m, 1H), 2.00-1.66 (m, 4H), 1.53 (m, 1H), 0.97 (d, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$); δ 159.0, 135.2, 131, 130.6, 129.2, 127.9, 116.7, 113.7, 74.8, 72.6, 71.5, 71.0, 66.5, 57.0, 55.2, 38.8, 38.8, 34.2, 34.0, 18.0 ppm; IR (neat,

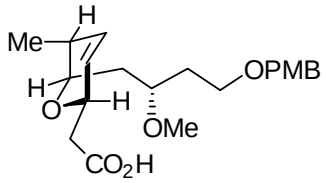
KBr) 3482, 2925, 2857, 1729, 1612, 1513, 1459, 1367, 1300, 1247, 1178, 1091, 1037, 914, 820, 723 cm^{-1}; ESI-HRMS *m/z* calcd. for $C_{22}H_{32}NaO_4$ $[M + Na]^+$: 383.2198, found 383.2195.

2-((2*R*,5*S*,6*R*)-6-((*S*)-2-methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-5,6-dihydro-2*H*-pyran-2-yl)acetaldehyde (15):



To a stirred solution of the compound **3** (1.8 g, 5.0 mmol) in 1,4-dioxane (25 mL) was added 2,6-lutidine (2.33 mL, 20.0 mmol) at room temperature. $NaIO_4$ (4.28 g, 20.0 mmol) was dissolved in distilled water (10 mL) and then added to the above reaction mixture. Finally, OsO_4 (0.5 mL, 0.5 mmol, 1 M solution in toluene) was added and stirring was continued for 3 h under dark at room temperature. After completion of the reaction (as indicated by TLC), the reaction mixture was quenched with saturated aq. $NaHSO_3$ (30 mL) solution. Organic solvent was removed under reduced pressure and the residual aqueous layer was extracted with *t*-butyl methyl ether (3 x 50 mL). The combined organic layer was washed with 1 N HCl (3 x 50 mL) to remove excess 2,6-lutidine. The organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude mass which was passed through a small pad of silica gel (ethyl acetate: hexane = 1:3) to afford aldehyde **15** as a colorless liquid which was immediately used for the next step.

2-((2*R*,5*S*,6*R*)-6-((*S*)-2-Methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-5,6-dihydro-2*H*-pyran-2-yl)acetic acid:

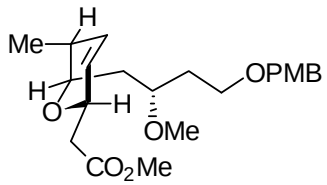


To a solution of aldehyde **15** (1.78 g, 4.92 mmol) in *tert*-butyl alcohol (25 mL), 2-methyl-2-butene (5.8 mL, 5.8 mmol, 1 M solution in THF) was added at room temperature. NaH_2PO_4 (1.8 g, 11.6 mmol) and sodium chlorite (0.59 g, 7.38 mmol) were dissolved in water (10 mL) to make a clear solution which subsequently added to the reaction mixture at 0 ^oC. It was then allowed to stir for further 3 h at room temperature. The reaction mixture was diluted with water (15 mL). The organic solvent was removed under reduced pressure and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate: hexane = 2:5) to afford the acid (1.53 g, 81% over two steps) as a colorless oil.

$[\alpha]_D^{25}$ +28.9 (*c* 1.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 5.66 (s, 2H), 4.60 (m, 1H), 4.42 (s, 2H), 3.79 (s, 3H), 3.36-3.41 (m, 4H), 3.31 (s, 3H), 2.64 (dd, *J* = 9.1, 15.1 Hz, 1H), 2.45 (dd, *J* = 4.5, 15.1 Hz, 1H), 1.98 (t, *J* = 6.8 Hz, 1H), 1.81 (q, *J* = 6.0 Hz, 1H), 1.72 (m, 1H), 1.52 (dt, *J* = 1.5, 9.0 Hz, 1H), 0.96 (d, *J* = *6.*8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 159.1, 132.1, 130.3, 129.3, 126.6, 113.7, 75.1, 72.7, 71.5, 68.7, 66.6, 56.6, 55.2, 39.0, 38.0, 34.1, 34.0, 17.7 ppm; IR (neat, KBr) 3029, 2931, 2876, 1732, 1713, 1612, 1513, 1301, 1248, 1094,

1035, 847, 821 cm^{-1}; ESI HRMS *m/z* calcd. for $C_{21}H_{30}NaO_6$ $[M + Na]^+$: 401.1935, found 401.1949.

Methyl 2-((2*R*,5*S*,6*R*)-6-((*S*)-2-methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-5,6-dihydro-2*H*-pyran-2-yl)acetate (16):

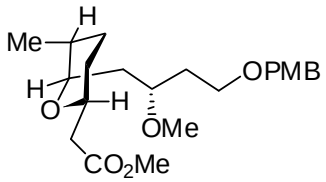


To a stirred solution of acid (1.3 g, 3.44 mmol) in ether at 0 ^oC, was added freshly prepared diazomethane solution in ether (25 mL). It was stirred for 10 min at the same temperature and then quenched with saturated solution of $Na_2S_2O_3$ (10 mL) at 0 ^oC. The reaction mixture was stirred at room temperature for 1 h to evaporate excess diazomethane. The organic layer was separated and the aqueous layer extracted with diethyl ether (2 x 40 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get the crude mass. The crude mass was purified by silica gel column chromatography (ethyl acetate: hexane = 1:8) to afford methyl ester **16** (1.29 g, 96%) as a light yellow liquid.

$[\alpha]_D^{25}$ +25.1 (*c* 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 2.64 (s, 2H), 4.58 (m, 1H), 4.39 (s, 2H), 3.78 (s, 3H), 3.64 (s, 3H), 3.55-3.36 (m, 4H), 3.32 (s, 3H), 2.61 (dd, *J* = 9.1, 15.1 Hz, 1H), 2.41 (dd, *J* = 4.5, 15.1 Hz, 1H), 1.98-1.42 (m, 5H), 0.97 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 159.1, 132.1, 131.9, 129.2, 127.0, 113.7, 74.8, 72.6, 71.3, 68.7, 66.6, 57.0, 55.2, 51.6, 39.1, 38.8, 36.7, 34.1, 17.8 ppm; IR (neat, KBr) 3027, 2951, 2875, 1737, 1612,

1513, 1458, 1301, 1248, 1197, 1095, 1036, 847, 821 cm^{-1}; ESI HRMS *m/z* calcd. for $C_{22}H_{32}NaO_6$ $[M + Na]^+$: 415.2096, found 415.2087.

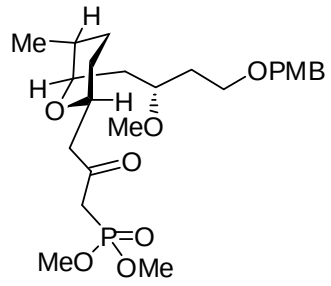
Methyl 2-((2*S*,5*S*,6*R*)-6-((*S*)-2-methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-tetrahydro-2*H*-pyran-2-yl)acetate (17):



Pd/C (10%) (50 mg) was added to a stirred solution of the compound **16** (1.2 g, 3.06 mmol) in toluene (20 mL) followed by catalytic amount of triethylamine at room temperature under hydrogen atmosphere. The mixture was stirred for 1 h at room temperature. After complete consumption of the starting material (monitored by TLC), the black reaction mass was filtered through a pad of Celite and then thoroughly washed with ethyl acetate (3 x 15 mL). The filtrate was concentrated under reduced pressure and purification of the crude product by silica gel column chromatography (ethyl acetate: hexane = 1:7) furnished the desired product **17** (1.12 g, 93%) as a colorless liquid.

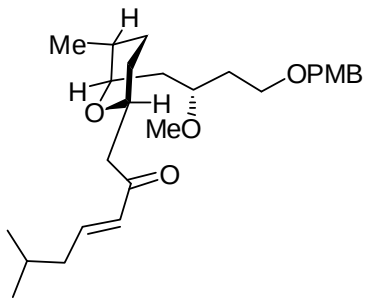
$[\alpha]_D^{25}$ +30.4 (*c* 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.47 (s, 2H), 4.26 (m, 1H), 3.86 (m, 3H), 3.60-3.42 (m, 4H), 3.37 (s, 3H), 2.70 (dd, *J* = 8.1, 14.9 Hz, 1H), 2.50 (dd, *J* = 5.8, 14.9 Hz, 1H), 1.89-1.32 (m, 7H), 1.03 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 159.1, 130.7, 129.2, 113.7, 74.9, 73.3, 72.6, 68.0 66.7, 57.2, 55.2, 51.5, 38.3, 38.2, 34.3, 33.6, 27.5, 26.3, 18.3 ppm; IR (neat, KBr) 2933, 2873, 1740, 1612, 1513, 1460, 1301, 1248, 1171, 1092, 1036, 846, 821 cm^{-1}; ESI HRMS *m/z* calcd. for $C_{22}H_{34}NaO_6$ $[M + Na]^+$: 417.2248, found 417.2240.

Dimethyl 3-((2*S*,5*S*,6*R*)-6-((*S*)-2-methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-tetrahydro-2*H*-pyran-2-yl)-2-oxopropylphosphonate (18):



To a stirred solution of the dimethyl methyl phosphonate (1.26 g, 10.15 mmol) in THF (30 mL), *n*-BuLi (4.1 mL, 10.15 mmol, 2.5 M in hexane) was slowly added at −78 ^{o}C under nitrogen atmosphere and allowed to slowly warm to 0 ^{o}C. After 1 h, the reaction mixture was again cooled to −78 ^{o}C and to it, ester **17** (1.0 g, 2.54 mmol) dissolved in THF (15 mL) was slowly added and stirred at the same temperature for 1 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl (30 mL), diluted with ethyl acetate (50 mL) and allowed to come to room temperature. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (100 mL) and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to obtain the crude mass which on purification by silica gel column chromatography (ethyl acetate: hexane = 5:1) afforded the desired keto phosphonate **18** (1.12 g, 92%) as a colorless liquid which was immediately used for next step without further characterization.

(*E*)-1-((2*S*,5*S*,6*R*)-6-((*S*)-2-Methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-tetra-hydro-2*H*-pyran-2-yl)-6-methylhept-3-en-2-one (19):

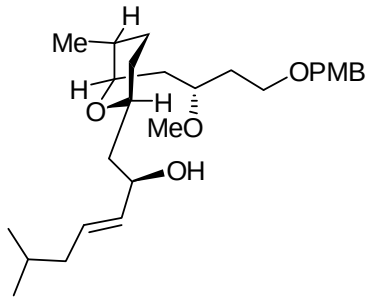


To a stirred solution of the keto phosphonate **18** (1.0 g, 2.06 mmol) in THF (20 mL) was added NaHMDS (2.67 mL, 2.67 mmol, 1M in THF) at −78 ^{o}C under nitrogen atmosphere and allowed to come to 0 ^{o}C. After 1 h, the reaction mixture was again cooled to −78 ^{o}C and isovaleraldehyde (0.354 g, 4.12 mmol) was slowly added to it and stirred at the same temperature for 1 h. After complete consumption of the starting material (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl (20 mL), diluted with ethyl acetate (50 mL) and allowed to come to room temperature. The two layers were separated and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with brine (2 x 50 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated to dryness under reduced pressure to get the crude product which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:6) furnished the desired keto **19** (0.74 g, 81%) as a colorless liquid.

$[\alpha]_D^{25}$ +19.1 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 6.81 (dd, *J* = 8.3, 15.9 Hz, 1H), 6.11 (d, *J* = 15.9 Hz, 1H), 4.43 (s, 2H), 4.30 (m, 1H), 3.80 (s, 3H), 3.56-3.46 (m, 4H), 3.30 (s, 3H), 2.90 (dd, *J* = *6.*8, 15.9 Hz, 1H), 2.70 (dd, *J* = 6.8, 15.9 Hz, 1H), 2.09 (t, *J* = 6.8 Hz, 2H), 1.85-1.24 (m, 10H), 0.96 (d, *J* = 6.0 Hz, 3H), 0.92 (dd, *J* = 6.8, 15.9 Hz, 6H) ppm; ^{13}C NMR (75 MHz,

$CDCl_3$) δ 198.4, 159.0, 146.6, 131.6, 130.6, 129.2, 113.6, 74.8, 73.2, 72.6, 67.6, 66.6, 57.1, 55.2, 43.5, 41.6, 38.2, 36.2, 34.0, 33.6, 27.8, 27.6, 26.4, 22.3, 18.3 ppm; IR (neat, KBr) 2956, 2927, 2854, 1717, 1606, 1513, 1463, 1256, 1169, 1091, 1034, 848, 821 cm^{-1}; ESI HRMS *m/z* calcd. for $C_{27}H_{42}NaO_5$ $[M + Na]^+$: 469.2924, found 469.2940.

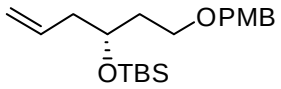
(*R*,*E*)-1-((2*S*,5*S*,6*R*)-6-((*S*)-2-Methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-tetrahydro-2*H*-pyran-2-yl)-6-methylhept-3-en-2-ol (7):



To a 50 mL round bottom flask charged with a magnetic stir bar was added *S*-CBS catalyst (0.087 g, 0.314 mmol) in THF (15 mL) under argon. The reaction was cooled to –20 °C and BH_3•Me_2S (1.57 mL, 3.14 mmol, 2M in THF) was added. To this reaction mixture, a solution of ketone **19** (0.71 g, 1.57 mmol) dissolved in THF (8 mL) was added dropwise. The reaction was stirred for 8 h at –20 °C and TLC checked which showed complete consumption of the starting material. MeOH (5 mL) was carefully added to quench excess BH_3. The reaction was diluted with saturated aqueous NH_4Cl (20 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude oil was purified by silica gel column chromatography (ethyl acetate: hexane = 1:5) giving the desired alcohol **7** (0.576 g, 82%) as a colorless liquid.

$[\alpha]_D^{25}$ +17.9 (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 5.62 (m, 1H), 5.46 (dd, *J* = 6.0, 15.3 Hz, 1H), 4.44 (s, 2H), 4.33 (m, 1H), 3.95 (m, 1H), 3.80 (s, 3H), 3.67-3.57 (m, 2H), 3.57-3.50 (t, *J* = 6.0 Hz, 2H), 3.35 (s, 3H), 1.94-1.32 (m, 14H), 1.01 (d, *J* = 6.2 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 134.2, 133.8, 130.3, 129.4, 113.7, 74.9, 73.6, 72.6, 68.7, 66.9, 66.5, 57.2, 55.2, 41.6, 40.8, 37.3, 34.0, 32.9, 28.2, 27.5, 26.0, 22.3, 22.2, 18.5 ppm; IR (neat, KBr) 3454, 2951, 2929, 2869, 1613, 1513, 1302, 1248, 1090, 1038, 820 cm^{-1}; ESI HRMS *m/z* calcd. for $C_{27}H_{44}NaO_5$ $[M + Na]^+$: 471.3081, found 471.3069.

(*R*)-*tert*-Butyl(1-(4-methoxybenzyloxy)hex-5-en-3-yloxy)dimethylsilane (20):

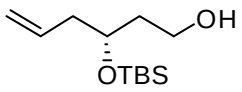


To a stirred solution of alcohol **10** (0.5 g, 2.12 mmol) in CH_2Cl_2 (30 mL) under nitrogen atmosphere, was added 2,6-lutidine (0.6 mL, 5.29 mmol) followed by TBSOTf (0.97 mL, 4.24 mmol) at 0 ^oC and allowed to stir for 30 min. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with water (20 mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and quickly washed with 1 N HCl (2 x 50 mL) to remove excess 2,6-lutidine. The organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, evaporated to dryness under vacuum to obtain the crude product which on purification by silica gel column chromatography purification (ethyl acetate: hexane produced = 1:19) furnished the desired TBS ether **20** (0.69 g, 93%).

$[\alpha]_D^{25}$ −8.1 (*c* 0.33, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J* = 9.1 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 5.77 (m, 1H), 5.04-4.96 (m, 2H), 4.36 (q, *J* = 7.5, 18.8 Hz, 2H), 3.87

(m, 1H), 3.78 (s, 3H), 3.45 (m, 2H), 2.19 (m, 2H), 1.68 (m, 2H), 0.87 (s, 9H), 0.03 (d, J = 3.7 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 134.9, 130.6, 129.2, 116.9, 113.6, 72.5, 68.9, 66.6, 55.1, 42.2, 36.6, 25.8, 18.0, −4.4, −4.8; IR (neat, KBr) 3075, 2999, 2953, 2930, 2857, 1613, 1513, 1463, 1249, 1093, 1040, 912, 836 cm^{-1}; ESI HRMS *m/z* calcd. for $C_{20}H_{34}NaO_3Si$ $[M + Na]^+$: 373.2169, found 373.2181.

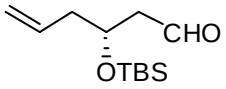
(*R*)-3-(*tert*-Butyldimethylsilyloxy)hex-5-en-1-ol (21):



To a solution of PMB protected compound **20** (0.55 g, 1.57 mmol) in CH_2Cl_2 (20 mL) and water (2 mL) was added DDQ (0.535 g, 2.36 mmol) at room temperature and allowed to stir for 2 h at the same temperature. After completion of the reaction, it was quenched with saturated $NaHCO_3$ (20 mL) solution. The two layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layer was washed with brine (2 x 40 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness to give red colored crude product which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:7) to afford the desired primary alcohol **21** (0.34 g, 94%) as a colorless liquid.

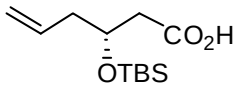
$[\alpha]_D^{25}$ −26.0 (*c* 0.46, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (m, 1H), 5.09-4.99 (m, 2H), 3.95 (m, 1H), 3.83-3.62 (m, 2H), 2.28 (t, J = 6.6 Hz, 2H), 2.16 (br s, 1H), 1.76 (m, 1H), 1.63 (m, 1H), 0.89 (s, 9H), 0.09 (d, J = 2.4 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5, 117.2, 71.0, 59.9, 41.6, 25.7, 35.7, 17.9, −4.5, −4.9 ppm; IR (neat, KBr) 3350, 3078, 2953, 2930, 2858, 1641, 1463, 1255, 1071 cm^{-1}; ESI HRMS *m/z* calcd. for $C_{12}H_{26}NaO_2Si$ $[M + H]^+$: 231.1780, found 231.1775.

(*R*)-3-(*tert*-Butyldimethylsilyloxy)hex-5-enal (22):



To a stirred solution of primary alcohol **21** (0.25 g, 1.09 mmol) and solid anhydrous $NaHCO_3$ (1.0 g) in CH_2Cl_2 (25 mL) at 0 ^oC, was added Dess-Martin periodinane (0.69 g, 1.63 mmol). The reaction mixture was stirred at 0 ^oC for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through a Celite bed and washed with CH_2Cl_2 (50 mL). The filtrate was washed with saturated $NaHCO_3$ (2 x 30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent removed under reduced pressure to get crude aldehyde **22** (0.24 g) as a pale yellow liquid which was directly used in the next step.

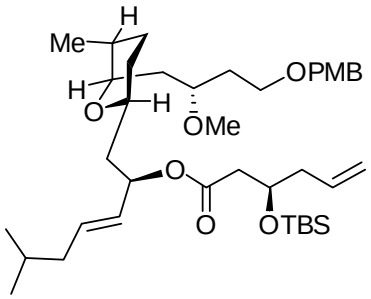
(*R*)-3-(*tert*-Butyldimethylsilyloxy)hex-5-enoic acid (8):



To a solution of aldehyde **22** (0.24 g, 1.05 mmol) in *tert*-butyl alcohol (15 mL), 2-methyl-2-butene (1.59 mL, 1.56 mmol, 1M solution in THF) was added at room temperature. Sodium dihydrogen phosphate (0.49 g, 3.15 mmol) and sodium chlorite (0.14 g, 1.56 mmol) were dissolved in water (5 mL) to make a clear solution which subsequently added to the reaction mixture at 0 ^oC. It was allowed to stir for further 3 h at room temperature. After completion of the reaction (monitored by TLC), it was diluted with ethyl acetate (30 mL). The two layers were separated and the aqueous layer extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (2 x

50 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography over silica gel (ethyl acetate: hexane = 1:9) to afford the desired acid **8** (0.22 g, 86% over two steps) as a colorless oil. $[\alpha]_D^{25}$ −18.9 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (m, 1H), 5.12-5.02 (m, 2H), 4.18 (m, 1H), 2.52-2.37 (m, 2H), 2.28 (t, *J* = 6.8 Hz, 2H), 0.86 (s, 9H), 0.06 (d, *J* = 6.6 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 133.7, 118.1, 68.8, 41.9, 41.7, 25.7, 17.9, −4.5, −5.0; IR (neat, KBr) 3079, 2956, 2930, 2858, 1713, 1642, 1463, 1256, 1089 ppm; ESI HRMS *m/z* calcd. for $C_{12}H_{24}NaO_3$ $[M + Na]^+$: 267.1387, found 267.1385.

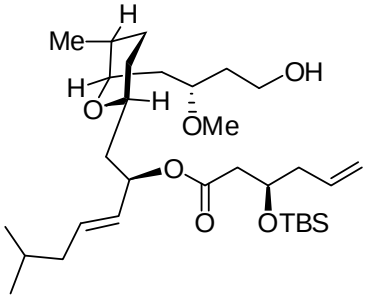
(*R*)-((*R*,*E*)-1-((2*S*,5*S*,6*R*)-6-((*S*)-2-Methoxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-tetrahydro-2*H*-pyran-2-yl)-6-methylhept-3-en-2-yl) 3-*(tert*-butyldimethylsilyloxy)-hex-5-enoate (23):



To a stirred solution of the acid **8** (0.49 g, 2.01 mmol) in dry toluene (10 mL) at 0 ^oC, Et_3N (0.31 mL, 4.02 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.63 mL, 4.02 mmol) was added and stirred for 30 min at room temperature. DMAP (1.22, 10.04 mmol) and alcohol **7** (0.45 g, 1.004 mmol) was dissolved in dry toluene (10 mL) and this was added to the above mentioned solution at 0 ^oC and allowed to stir at room temperature for 6 h. After completion of the reaction (monitored by TLC), it was diluted with ethyl acetate (50 mL) and water (25 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 40 mL). The combined organic layer was

washed with Na_2CO_3 (2 x 250 mL), brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and solvent evaporated under reduced pressure to give a colorless oil which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:12) furnished the desired coupled product **23** (0.63 g, 93%, based on the starting alcohol) as a colorless liquid. $[\alpha]_D^{25}$ +14.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 5.83-5.62 (m, 2H), 5.40-5.19 (m, 2H), 5.07-4.99 (m, 2H), 4.39 (s, 2H), 4.16 (m, 1H), 3.81 (m, 1H), 3.78 (s, 3H), 3.60-3.42 (m, 3H), 3.36 (s, 3H), 2.41-2.35 (m, 2H), 2.31-2.18 (m, 2H), 2.01-1.23 (m, 14H), 0.92-0.83 (m, 18H), 0.03 (d, *J* = 15.8 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 159.0, 134.3, 132.9, 129.7, 129.2, 128.2, 117.6, 113.7, 74.3, 72.6, 71.8, 68.7, 67.7, 66.5, 56.8, 55.2, 42.3, 41.9, 41.5, 38.8, 36.5, 34.7, 33.5, 28.2, 28.0, 26.9, 25.8, 22.3, 22.2, 18.2, 18.0, −4.6, −4.8 ppm; IR (neat, KBr) 3076, 2953, 2928, 2856, 1734, 1613, 1513, 1463, 1302, 1249, 1171, 1091, 1037, 836 cm^{-1}; ESI HRMS *m/z* calcd. for $C_{39}H_{70}NO_7Si$ $[M + NH_4]^+$: 692.4916, found 692.4883.

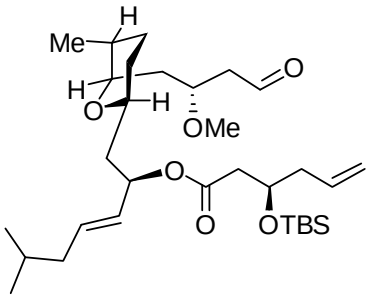
(*R*)-((*R*,*E*)-1-((2*S*,5*S*,6*R*)-6-((*S*)-4-Hydroxy-2-methoxybutyl)-5-methyl-tetrahydro-2*H*-pyran-2-yl)-6-methylhept-3-en-2-yl) 3-(*tert*-butyldimethylsilyloxy)hex-5-enoate (24):



To a solution of the compound **23** (0.31 g, 0.445 mmol) in CH_2Cl_2 (15 mL) and water (1 mL) at 0 ^oC, was added DDQ (0.152 g, 0.667 mmol) and allowed to stir for 2 h at room

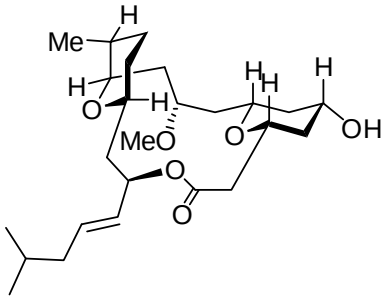
temperature. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL) and diluted with CH_2Cl_2 (15 mL). The two layers were separated and The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layer was washed with brine (2 x 40 mL), dried over anhydrous Na_2SO_4 and evaporated to give red colored crude product which on purification by silica gel column chromatography (ethyl acetate: hexane = 1:5) afforded the desired primary alcohol **24** (0.23 g, 95%) as a colorless liquid. $[\alpha]_D^{25}$ +23.0, (*c* = 0.52, $CHCl_3$); IR (neat, KBr) 3466, 3077, 2953, 2930, 1734, 1641, 1462, 1253, 1171, 1087, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.87-5.62 (m, 2H), 5.43-5.26 (m, 2H), 5.08-4.99 (m, 2H), 4.17 (m, 1H), 3.87-3.72 (m, 2H), 3.72-3.60 (m, 2H), 3.42 (s, 3H), 3.6 (m, 2H), 2.41 (d, *J* = 5.5 Hz, 2H), 2.34-2.15 (m, 2H), 2.06-1.24 (m, 14H), 0.94 (d, *J* = 5.7 Hz, 3H), 0.9-0.8 (m, 15H), 0.04 (d, *J* = 11.9 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 134.3, 133.0, 129.5, 117.6, 76.4, 72.9, 71.7, 68.7, 67.5, 59.8, 56.8, 42.2, 41.9, 41.5, 38.0, 36.6, 36.1, 35.1, 34.7, 28.4, 28.2, 28.0, 26.9, 25.8, 22.2, 18.3, −4.6, −4.8 ppm; ESI HRMS *m/z* calcd. for $C_{31}H_{58}NaO_6Si$ $[M + Na]^+$: 577.3895, found 577.3916.

(*R*)-((*R*,*E*)-1-((2*S*,5*S*,6*R*)-6-((*R*)-2-Methoxy-4-oxobutyl)-5-methyl-tetrahydro-2*H*-pyran-2-yl)-6-methylhept-3-en-2-yl) 3-(*tert*-butyldimethylsilyloxy)hex-5-enoate (6):



To a stirred solution of primary alcohol **24** (0.15 g, 0.271 mmol) and solid anhydrous $NaHCO_3$ (0.2 g) in CH_2Cl_2 (10 mL), Dess-Martin periodinane (0.173 g, 4.062 mmol) was added at 0 ^oC under nitrogen atmosphere. The reaction mixture was stirred at 0 ^oC for 4 h. After completion of reaction (monitored by TLC), the reaction mixture was filtered through a Celite bed and thoroughly washed with CH_2Cl_2 (50 mL). The filtrate was washed with saturated $NaHCO_3$ (30 mL) solution. The aqueous layer was again extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layer was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude aldehyde **6** (0.16 g) which was immediately used for next step without further purification and characterization.

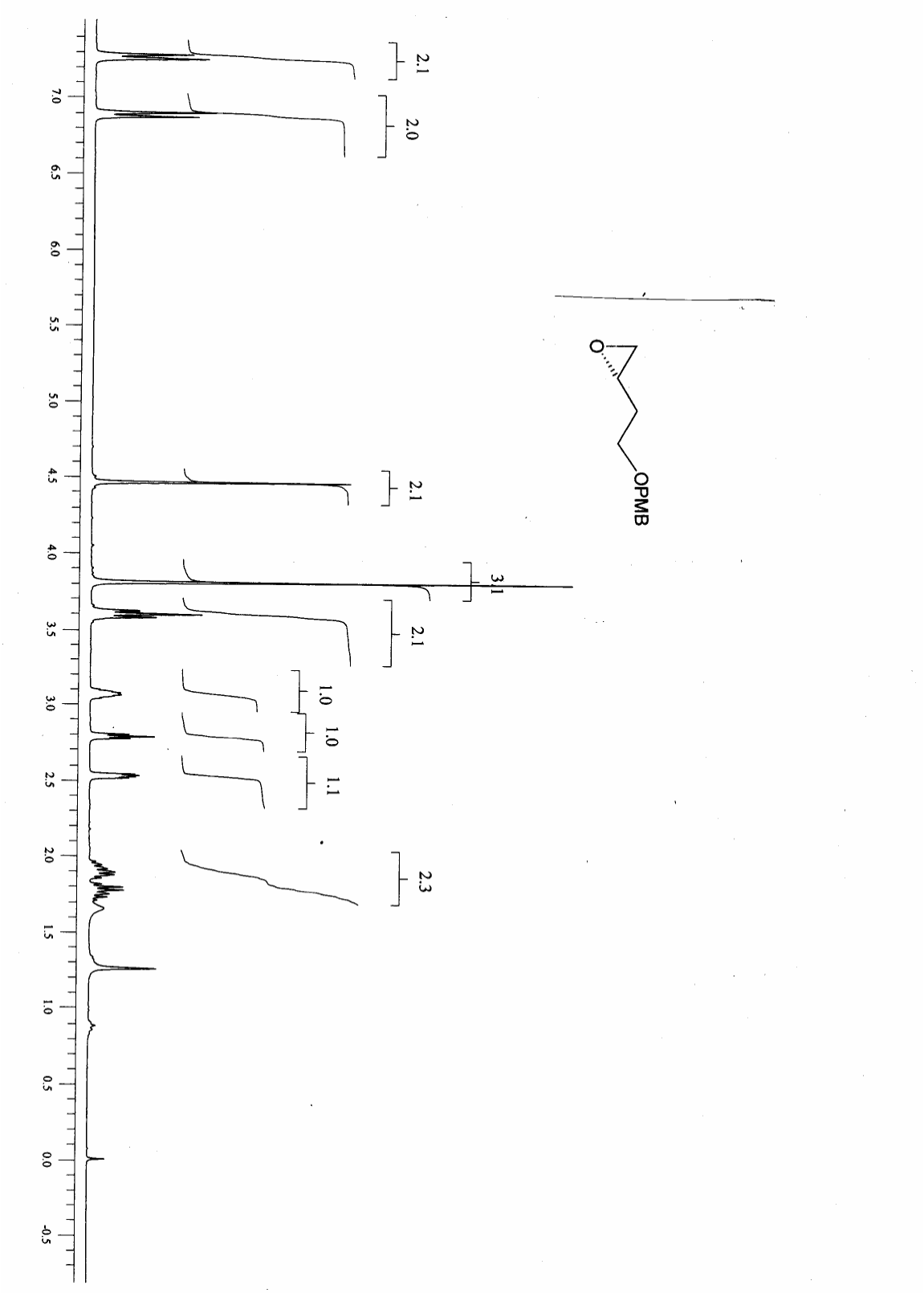
Macrolide (4):



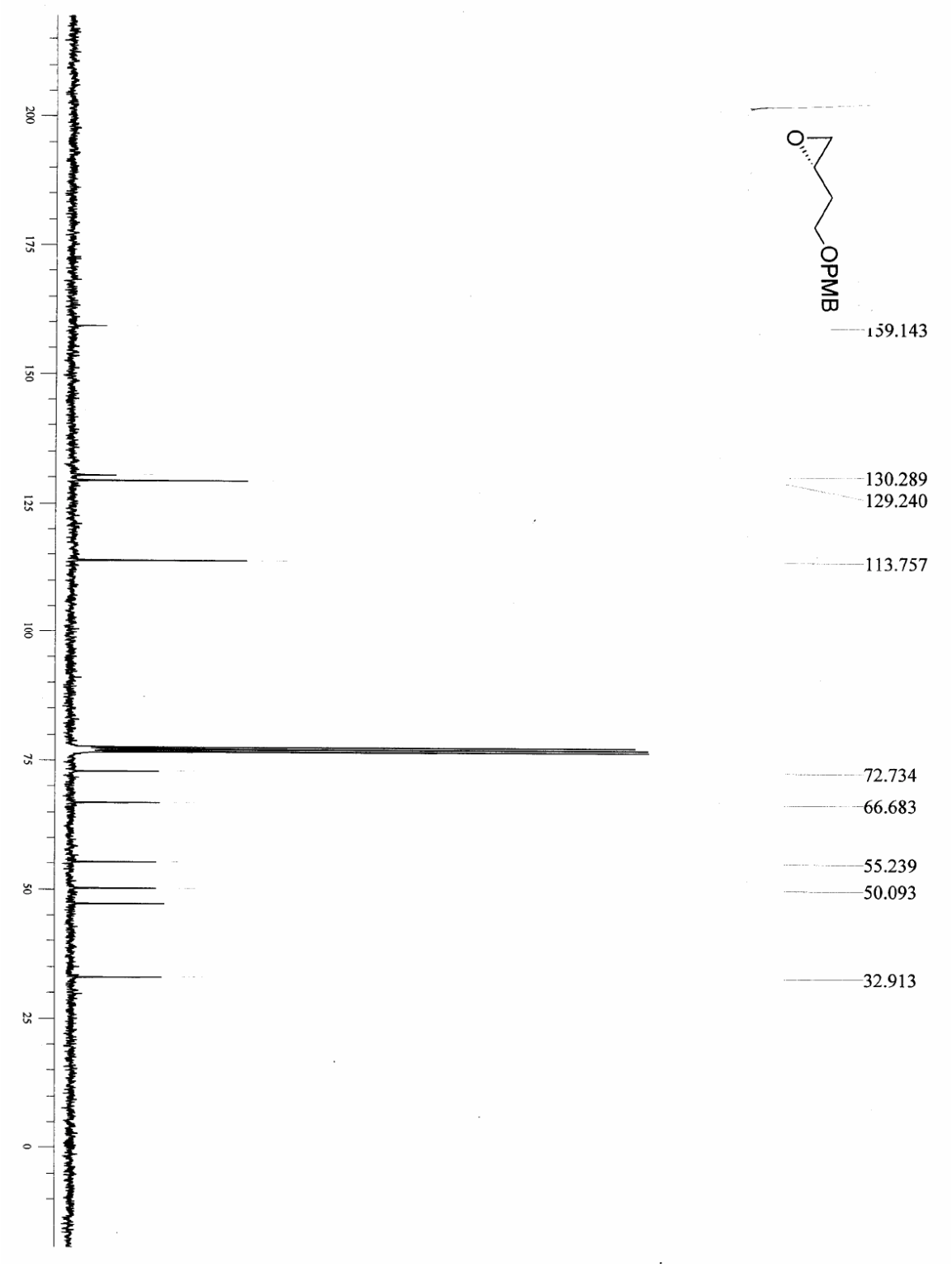
TMSOAc (1.71 mL, 11.21 mmol) was added to a solution of aldehyde **6** (0.16 mg, 0.28 mmol) in AcOH (15.0 mL) at room temperature. TESOTf (1.23 mL, 7.02 mmol) was added dropwise to the resulting solution at the same temperature. After 30 min, the reaction mixture was poured into diethyl ether (100 mL) and washed with $NaHCO_3$ (4 x 100 mL). The aqueous layer was again extracted with diethyl ether (3 x 50 mL). The combined organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain the crude product which was dissolved in MeOH (10 mL) and then treated with K_2CO_3 (0.37 g, 2.89 mmol) at room

temperature. The reaction mixture was stirred for 3 h at room temperature. After completion of the reaction (monitored by TLC), it was concentrated under reduced pressure. The residue was dissolved in water (10 mL) and diethyl ether (20 mL). The two layers were separated and the aqueous layer extracted with diethyl ether (3 x 20 mL). The combined organic layer was washed with brine (2 x 25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was finally purified by flash column chromatography over silica gel (ethyl acetate: hexane = 1:2) to afford the macrolide **4** (0.104 g, 72% over three steps).

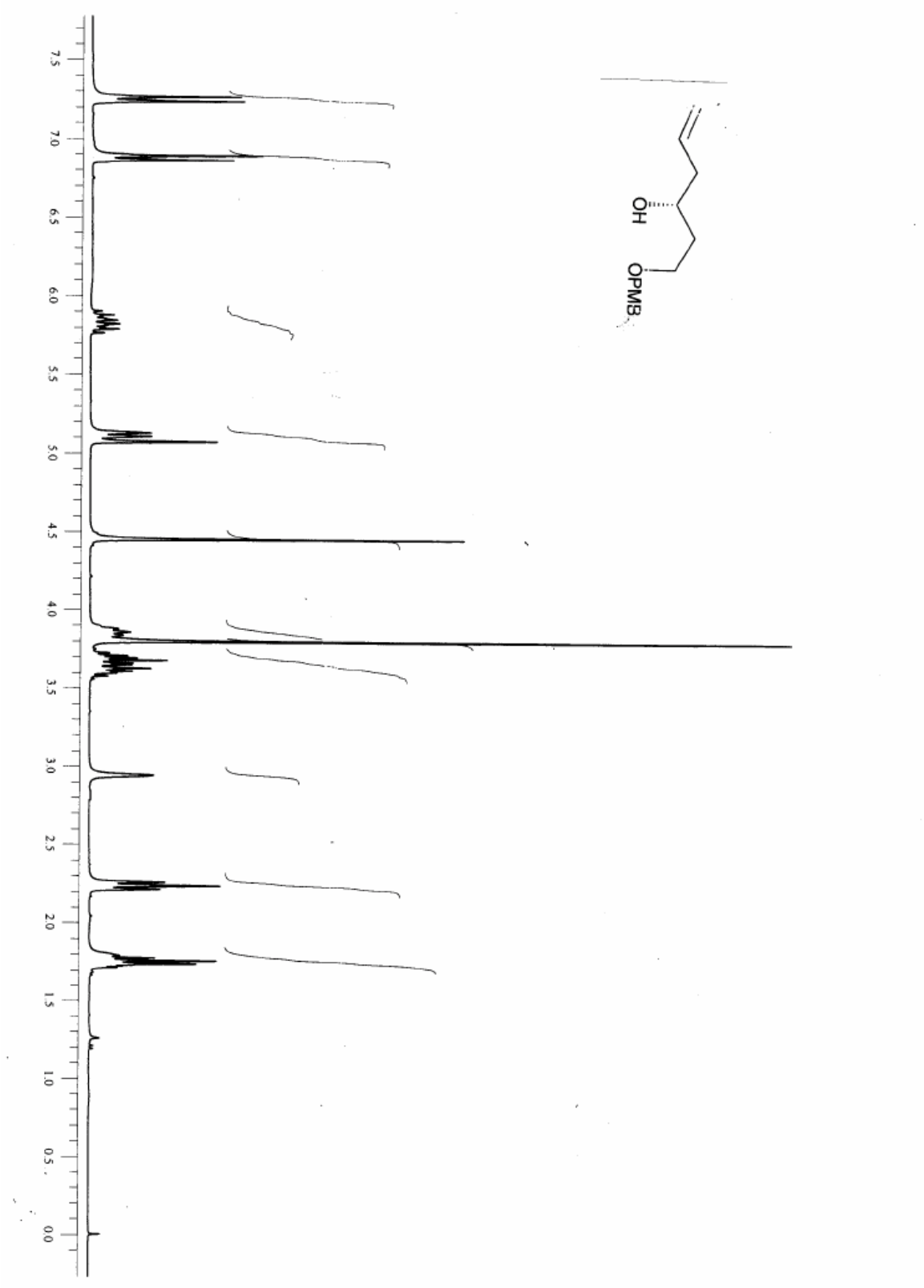
$[\alpha]_D^{25}$ +54.7 (*c* 1.18, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (m, 1H), 5.41-5.32 (m, 2H), 3.91 (m, 1H), 3.87 (m, 1H), 3.77-3.66 (m, 1H), 3.59-3.47 (m, 2H), 3.36 (s, 3H), 3.22 (m, 1H), 2.57 (dd, *J* = 4.5, 13.6 Hz, 1H), 2.44-2.30 (m, 3H), 2.09-1.96 (m, 3H), 1.95-1.83 (m, 4H), 1.36-1.23 (m, 8H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.03 (m, 1H), 0.85 (d, *J* = 6.8 Hz, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3, 132.4, 130.0, 73.6, 73.5, 73.0, 72.2, 70.8, 68.0, 63.0, 57.3, 43.0, 42.8, 41.6, 41.0, 40.8, 39.1, 35.4, 30.9, 28.1, 27.1, 24.1, 22.2, 18.2 ppm; IR (neat, KBr) 3452, 2954, 2925, 2854, 1736, 1643, 1261, 1083, 1034 cm^{-1}; ESI HRMS *m/z* calcd. for $C_{25}H_{42}NaO_6$ $[M + Na]^+$: 461.2874, found 461.2876.



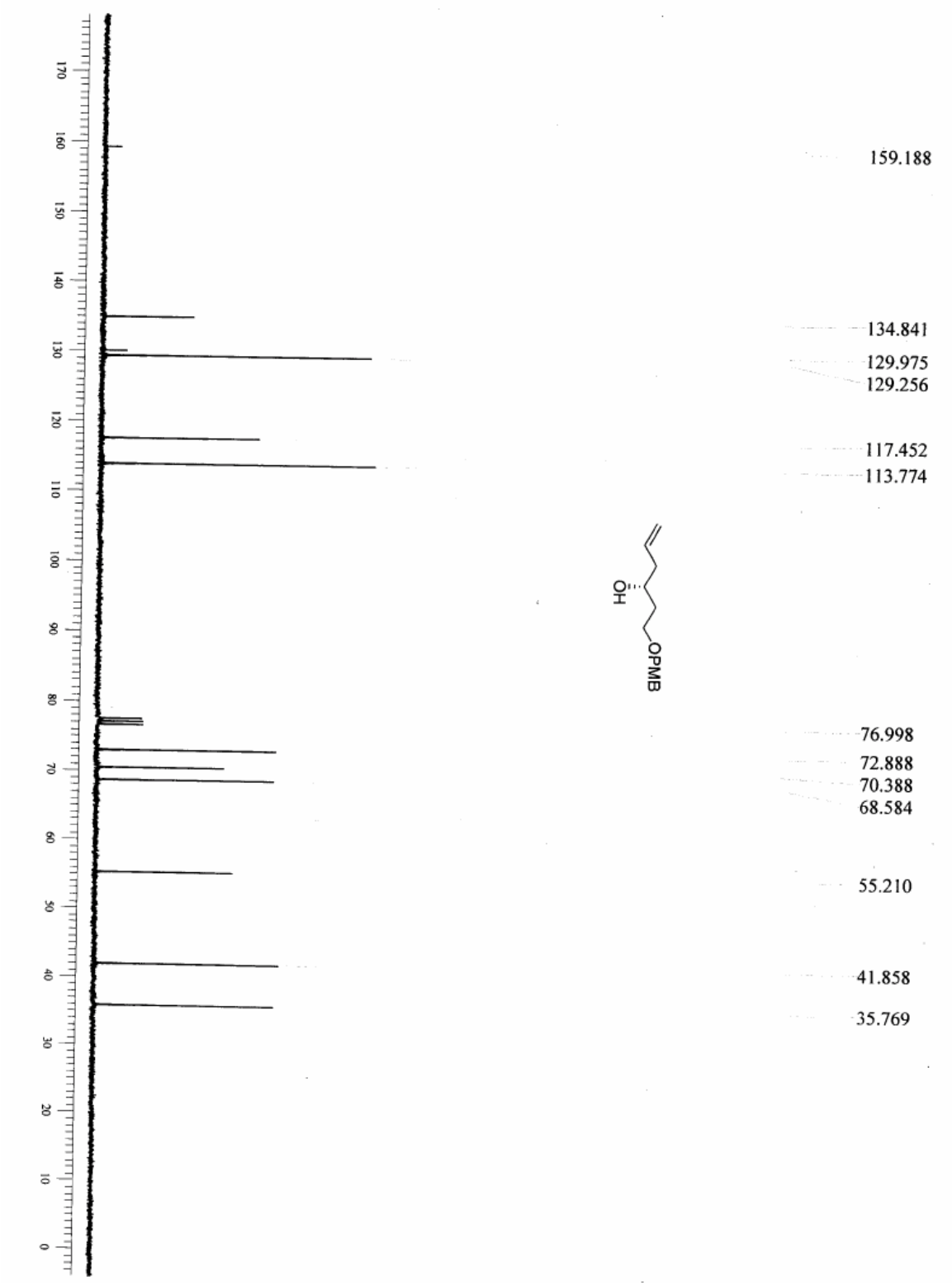
^{1}H NMR of 9 ($CDCl_3$, 300 MHz)



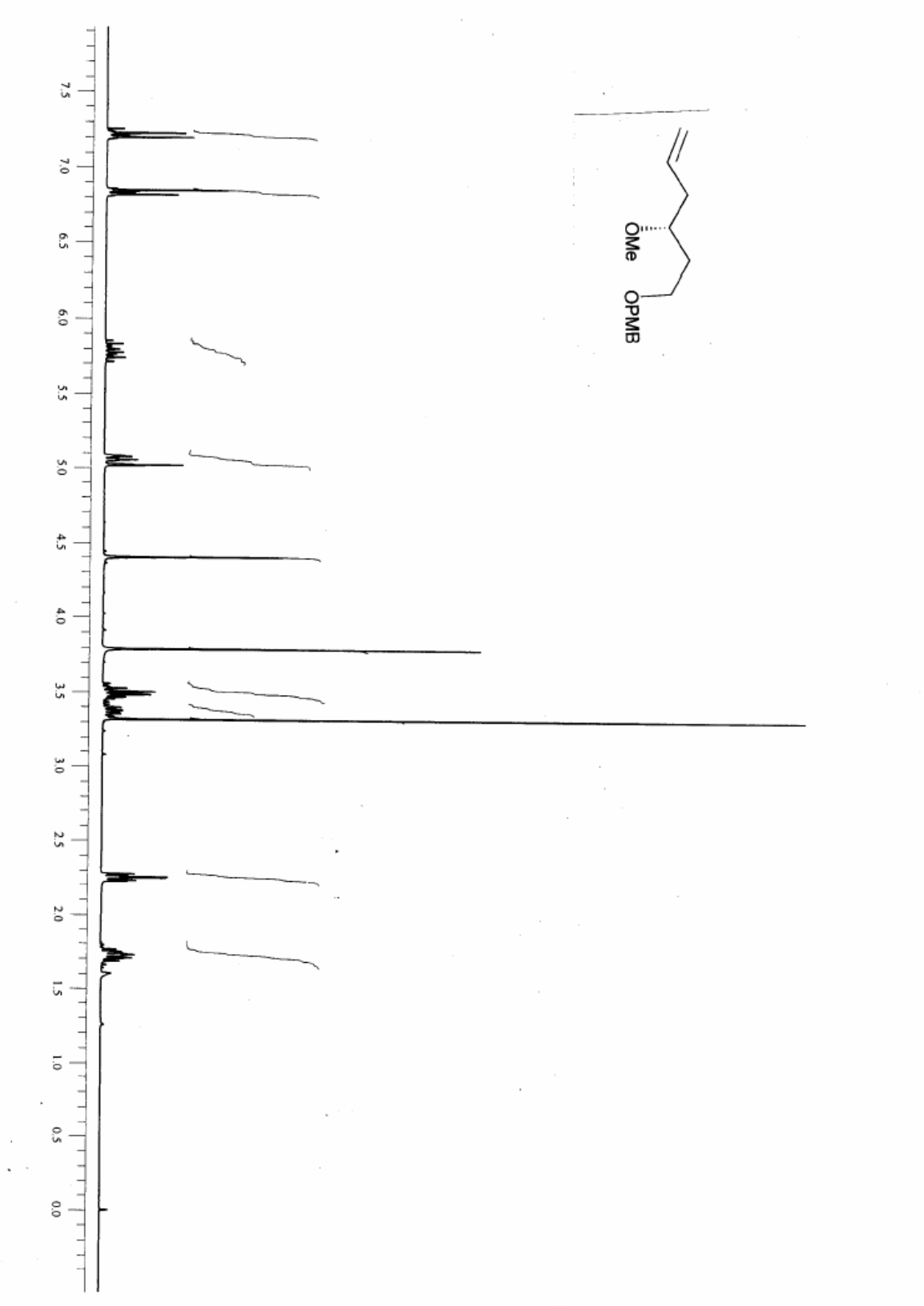
^{13}C NMR of 9 ($CDCl_3$, 75 MHz)



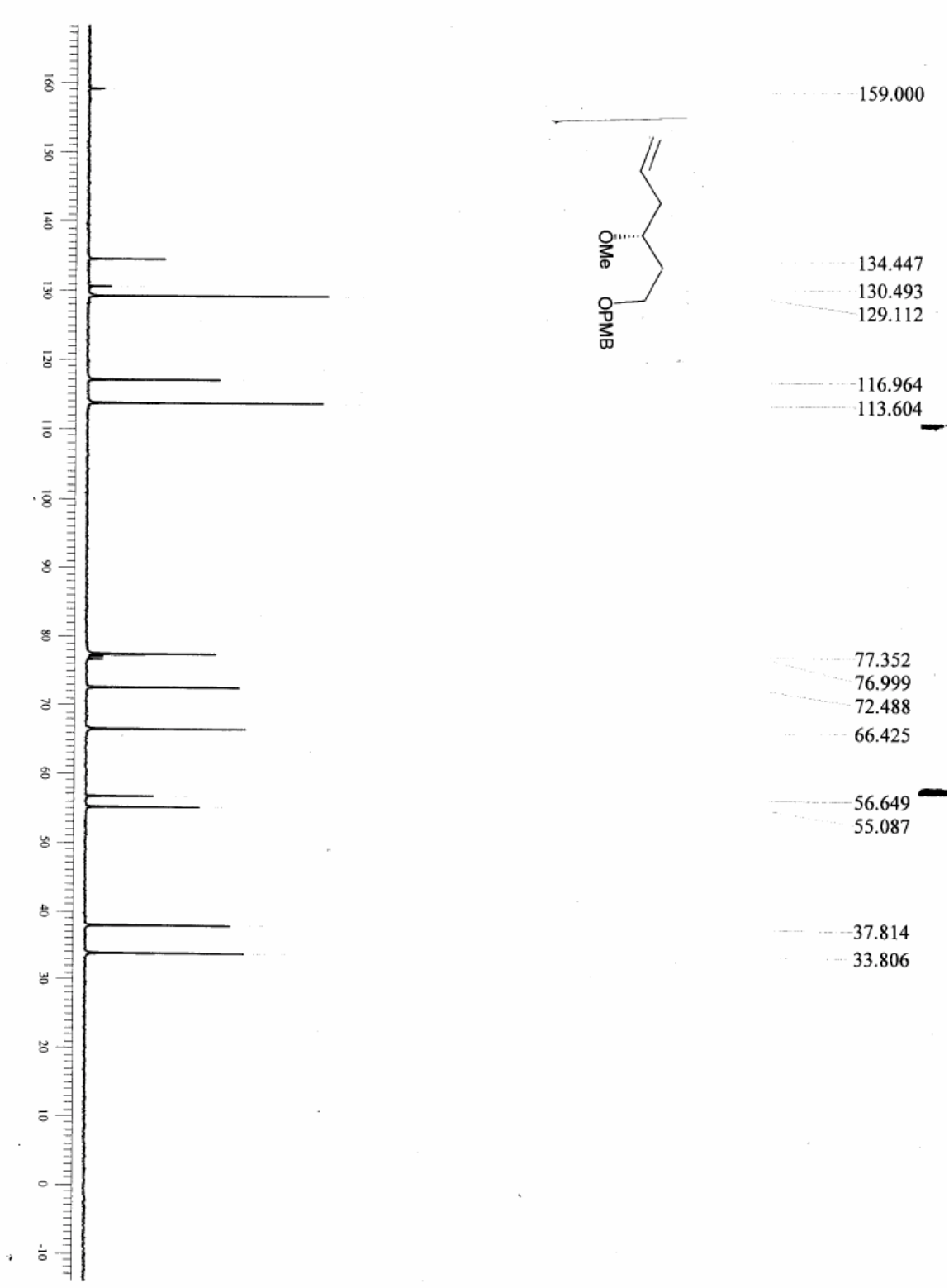
^{1}H NMR of 10 ($CDCl_3$, 300 MHz)



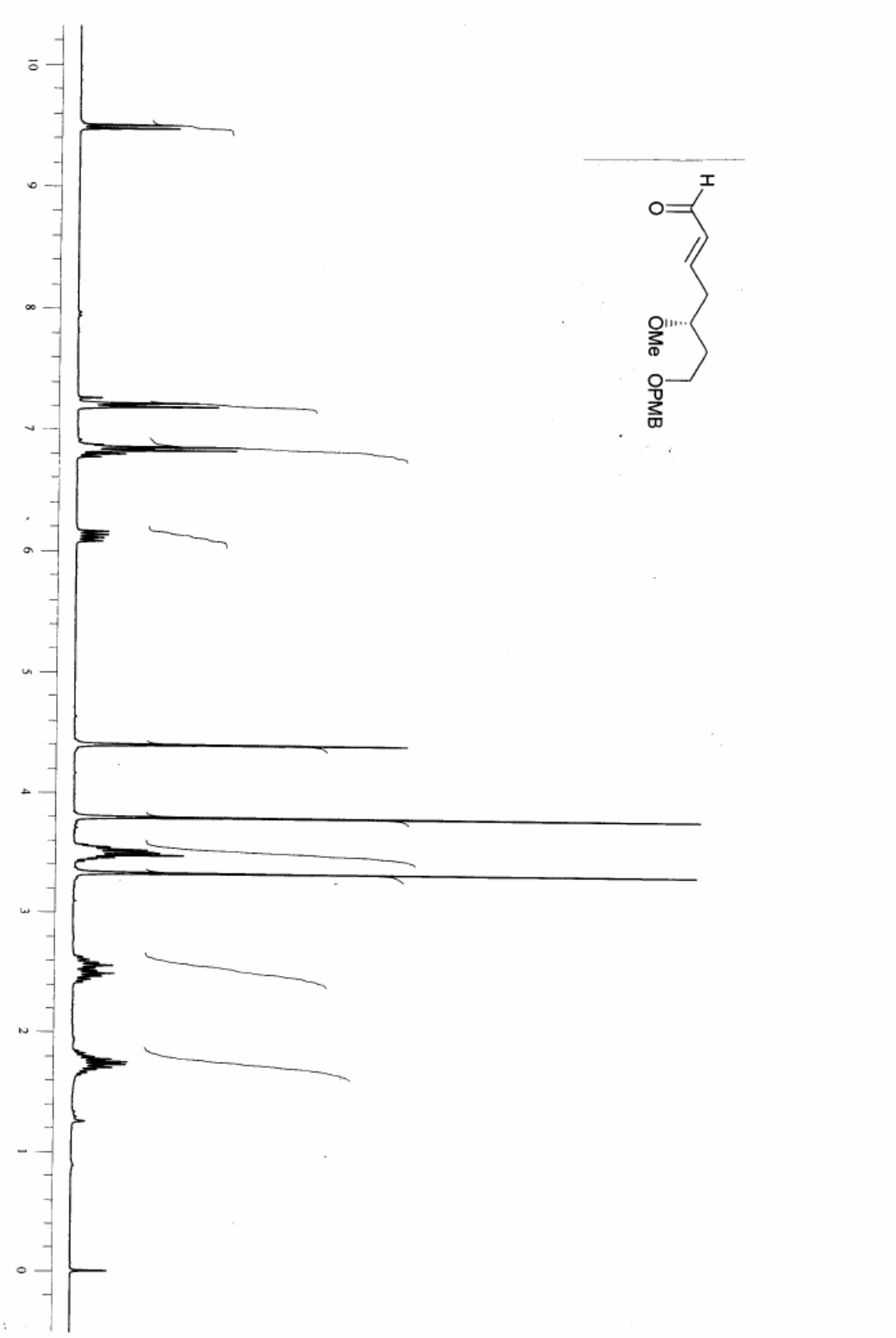
^{13}C NMR of 10 ($CDCl_3$, 75 MHz)



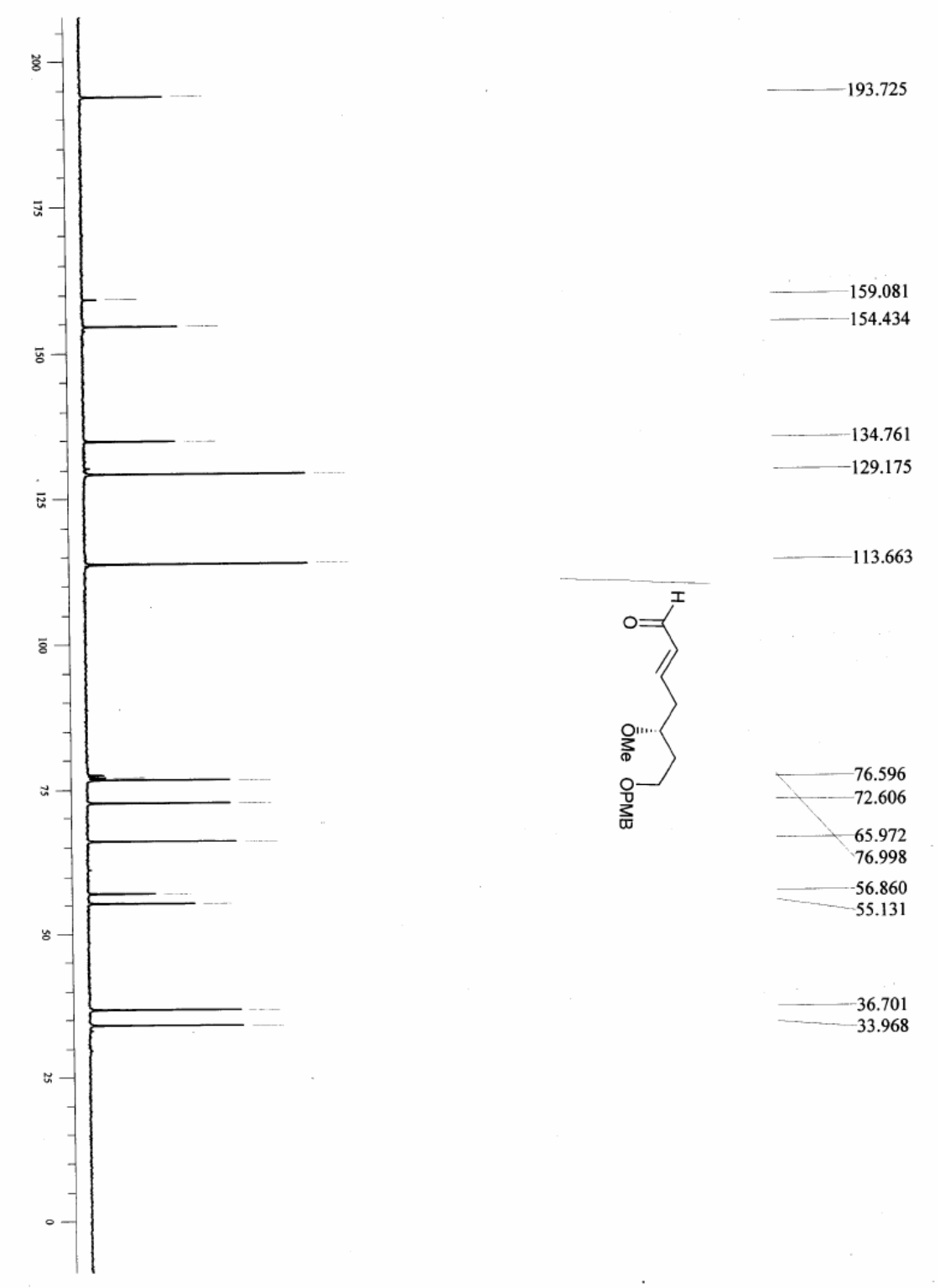
^{1}H NMR of 11 ($CDCl_3$, 300 MHz)



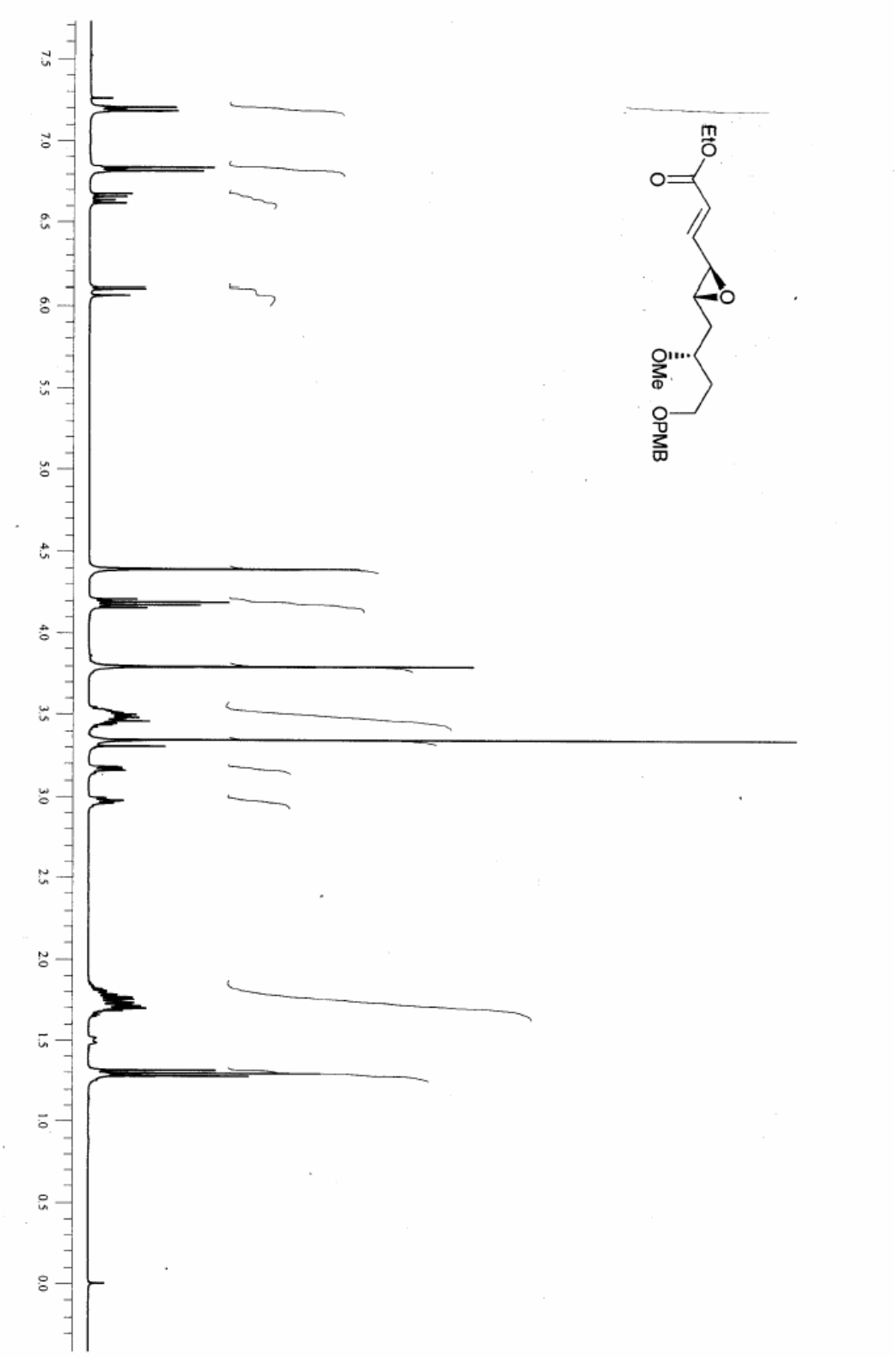
^{13}C NMR of 11 ($CDCl_3$, 75 MHz)



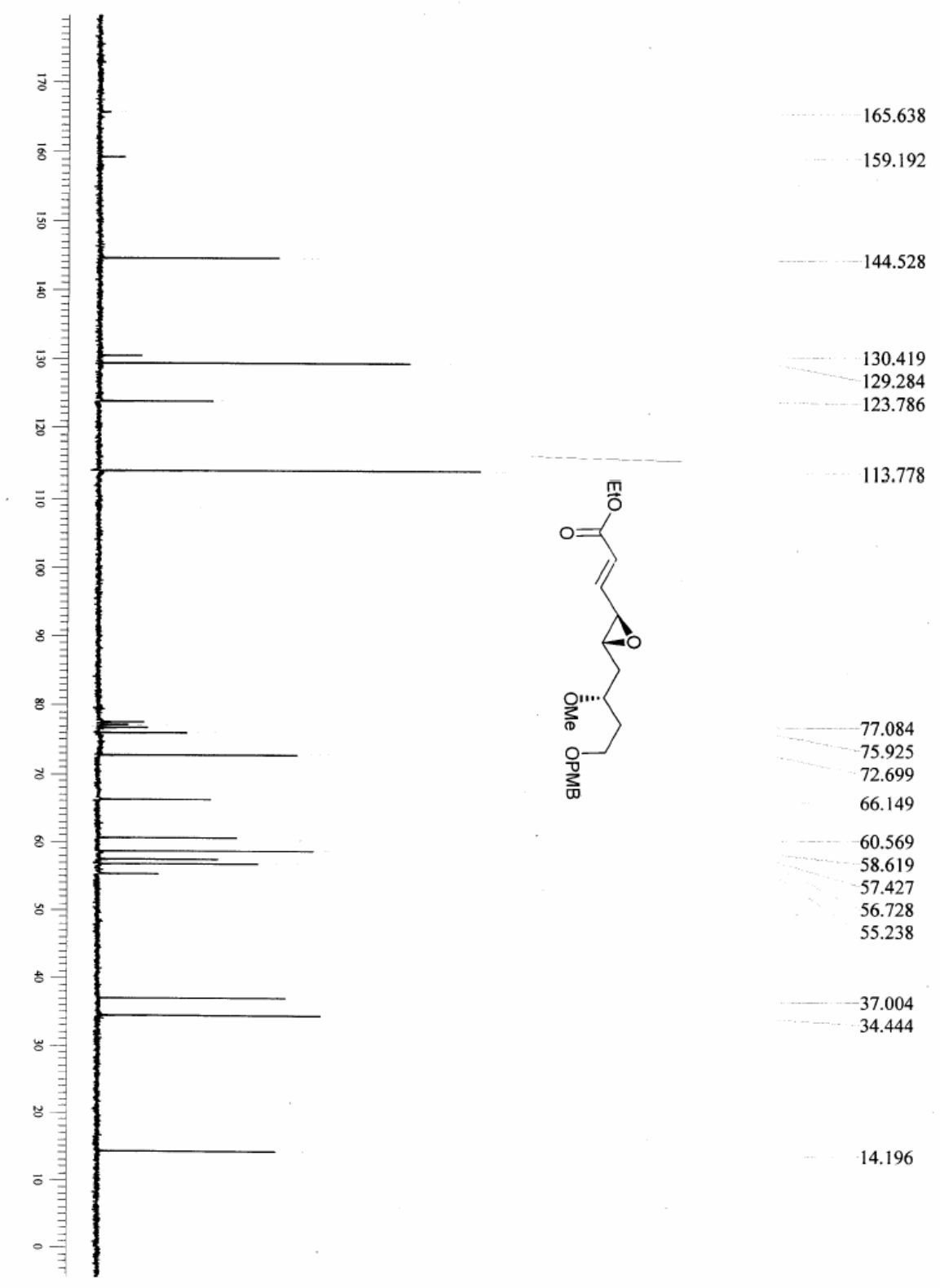
^{1}H NMR of 12 ($CDCl_3$, 300 MHz)



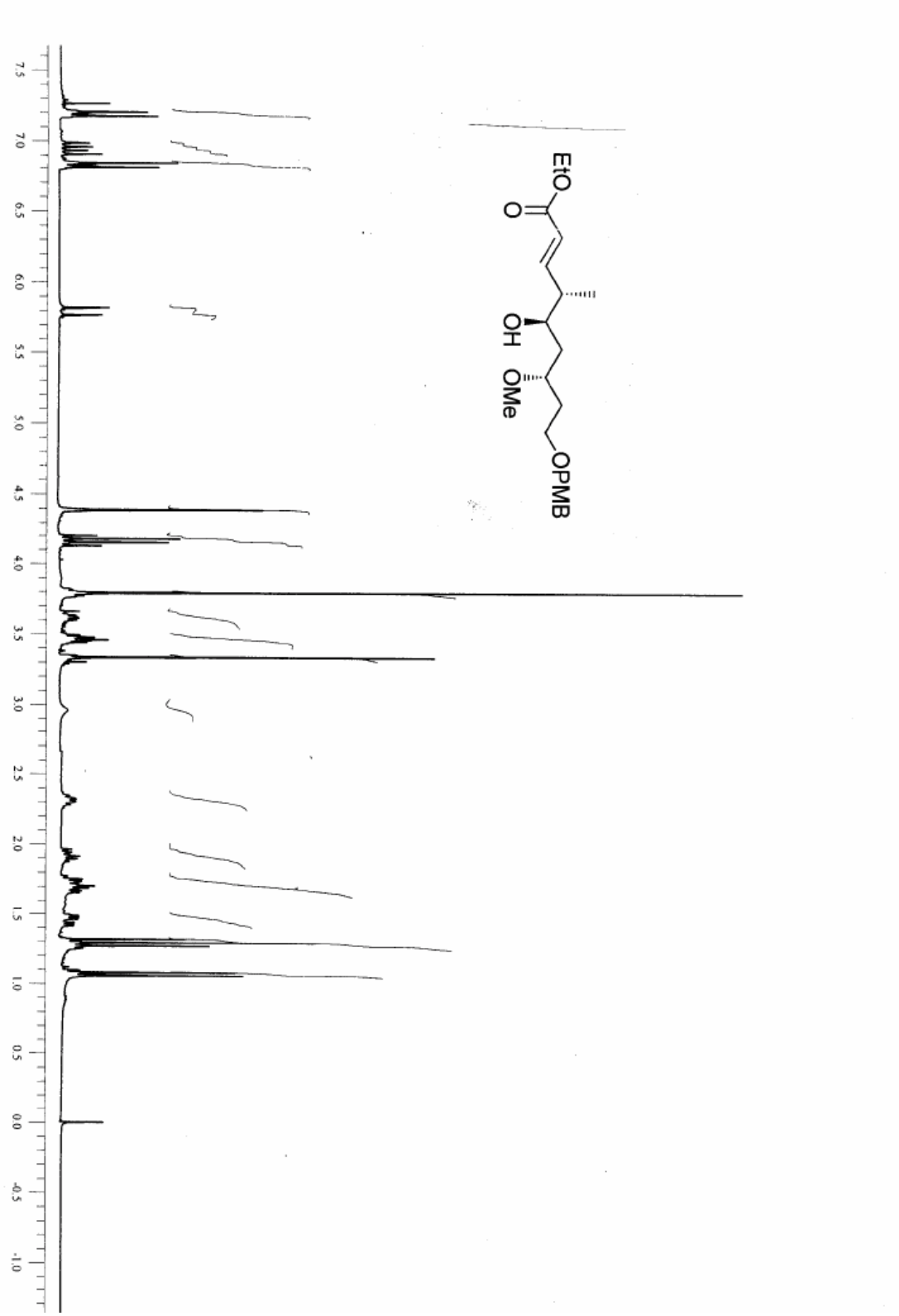
^{13}C NMR of 12 ($CDCl_3$, 75 MHz)



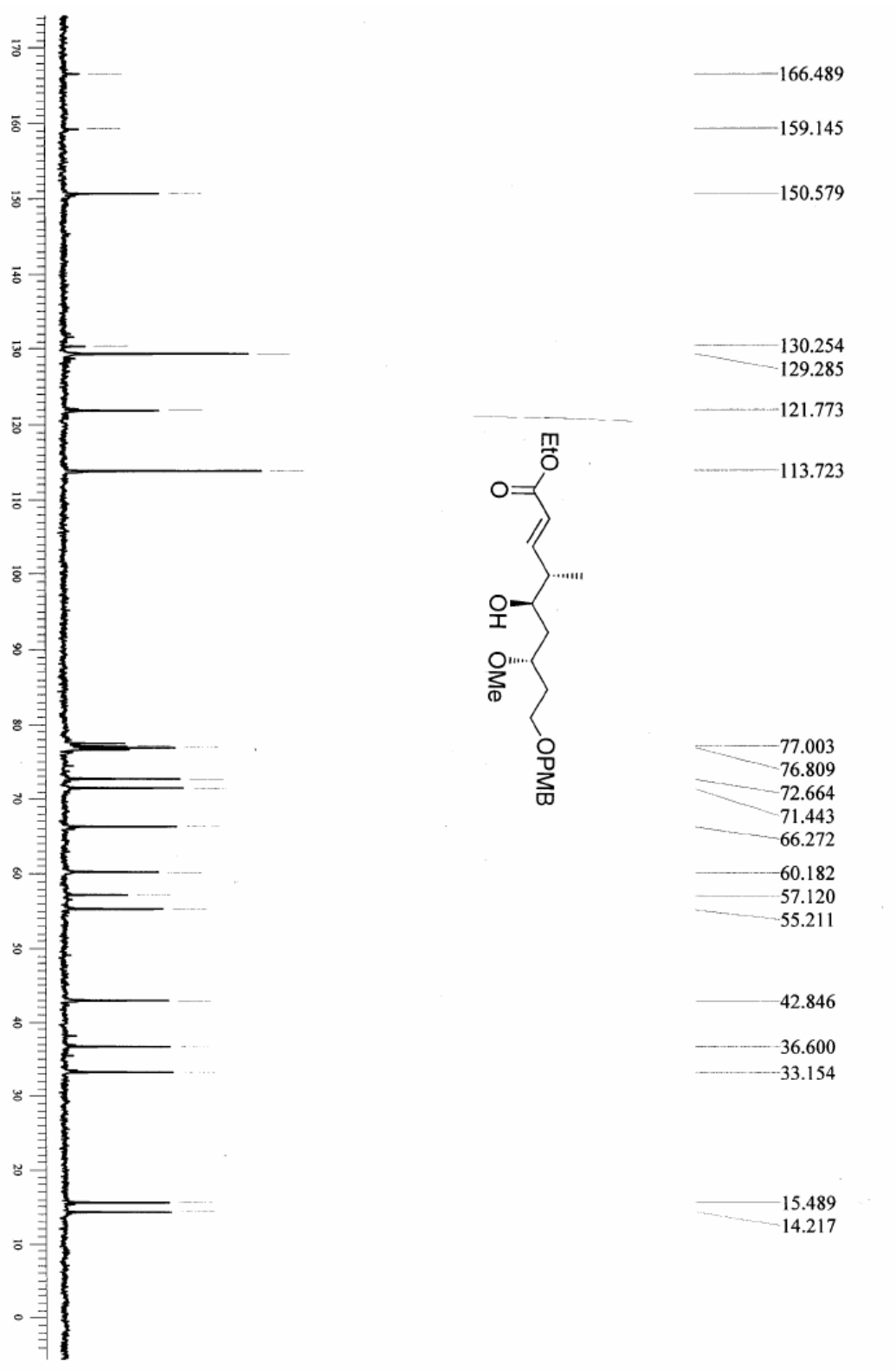
^{1}H NMR of 13 ($CDCl_3$, 400 MHz)



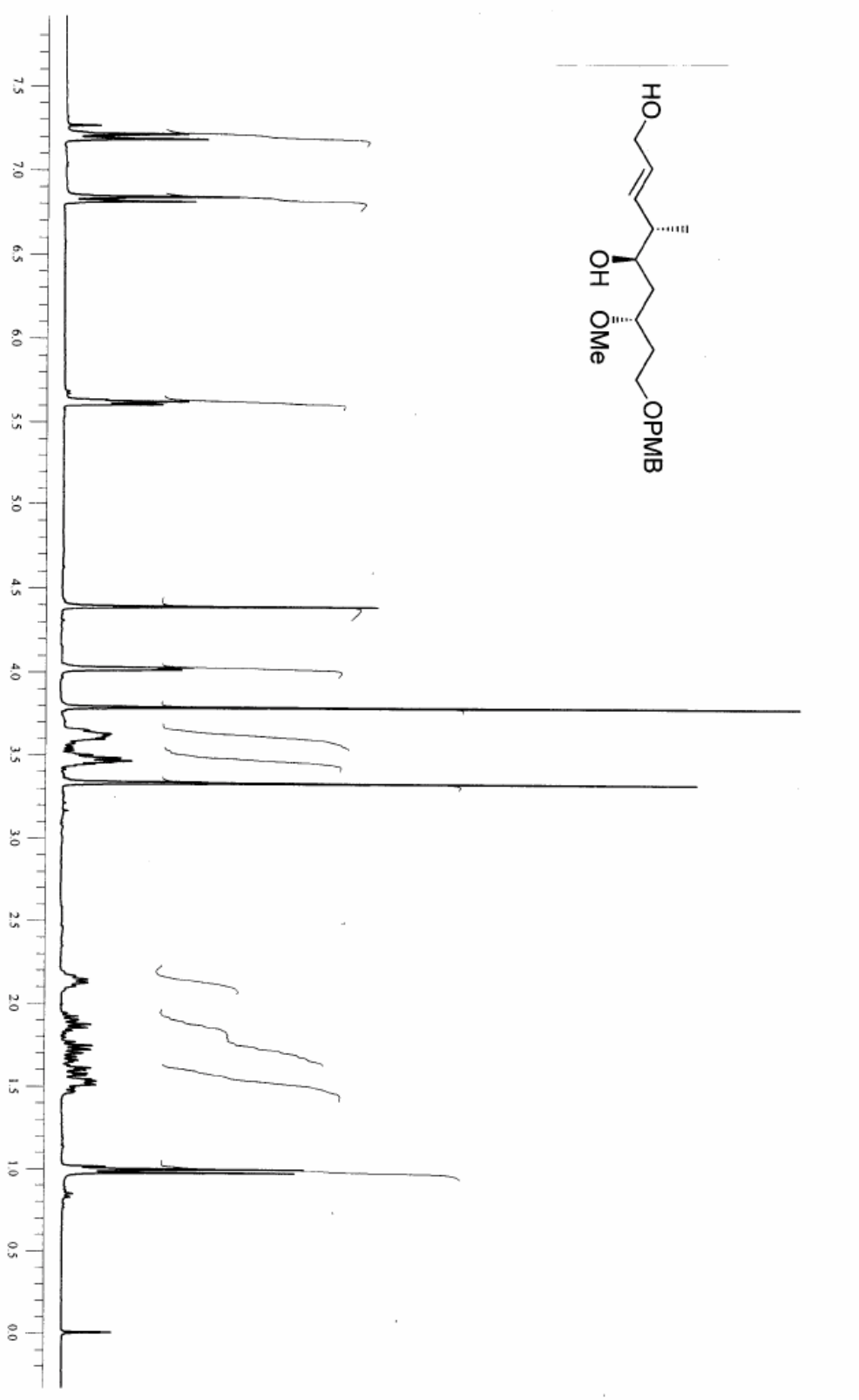
^{13}C NMR of 13 ($CDCl_3$, 75 MHz)



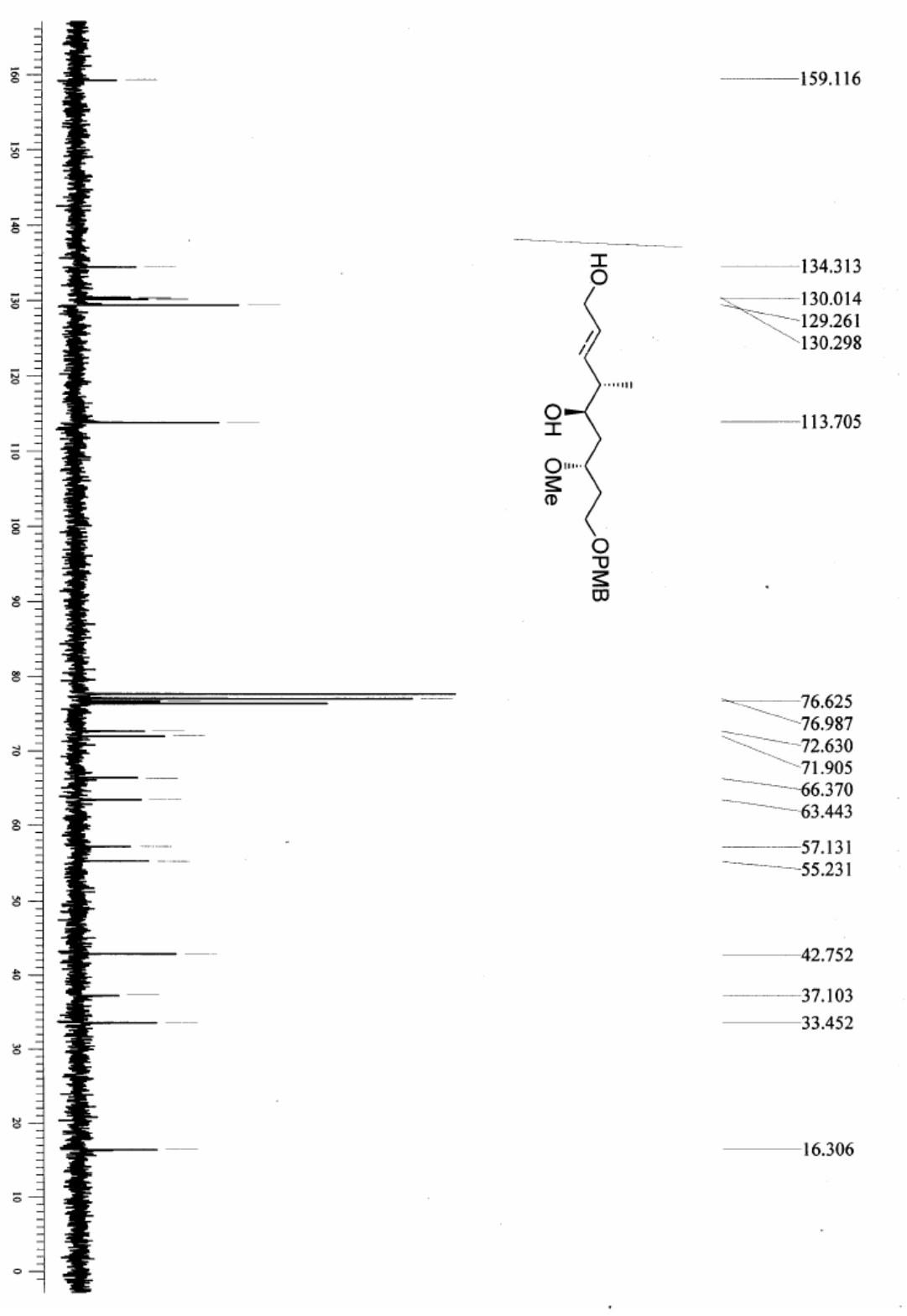
^{1}H NMR of 14 ($CDCl_3$, 300 MHz)



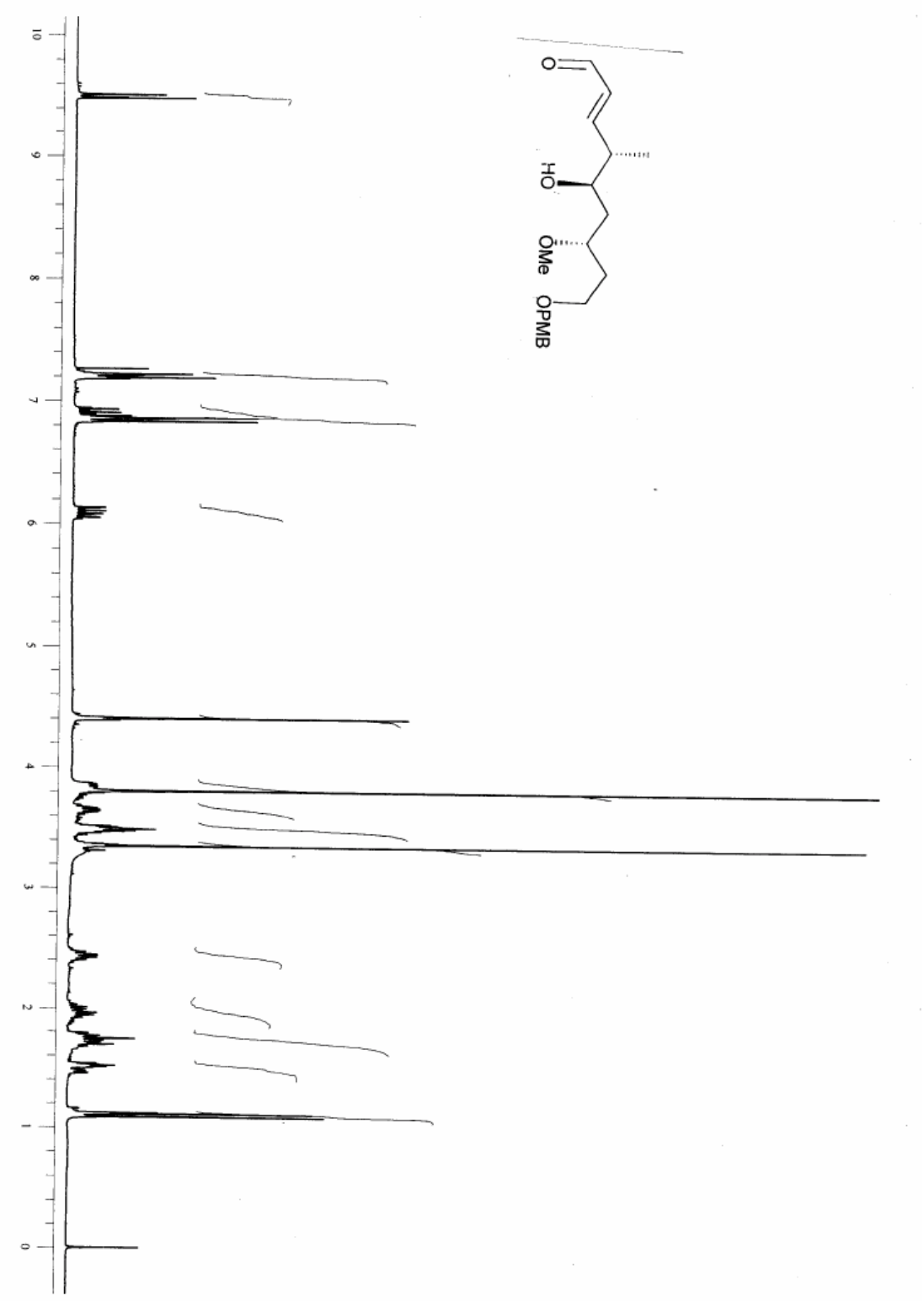
^{13}C NMR of 14 ($CDCl_3$, 75 MHz)



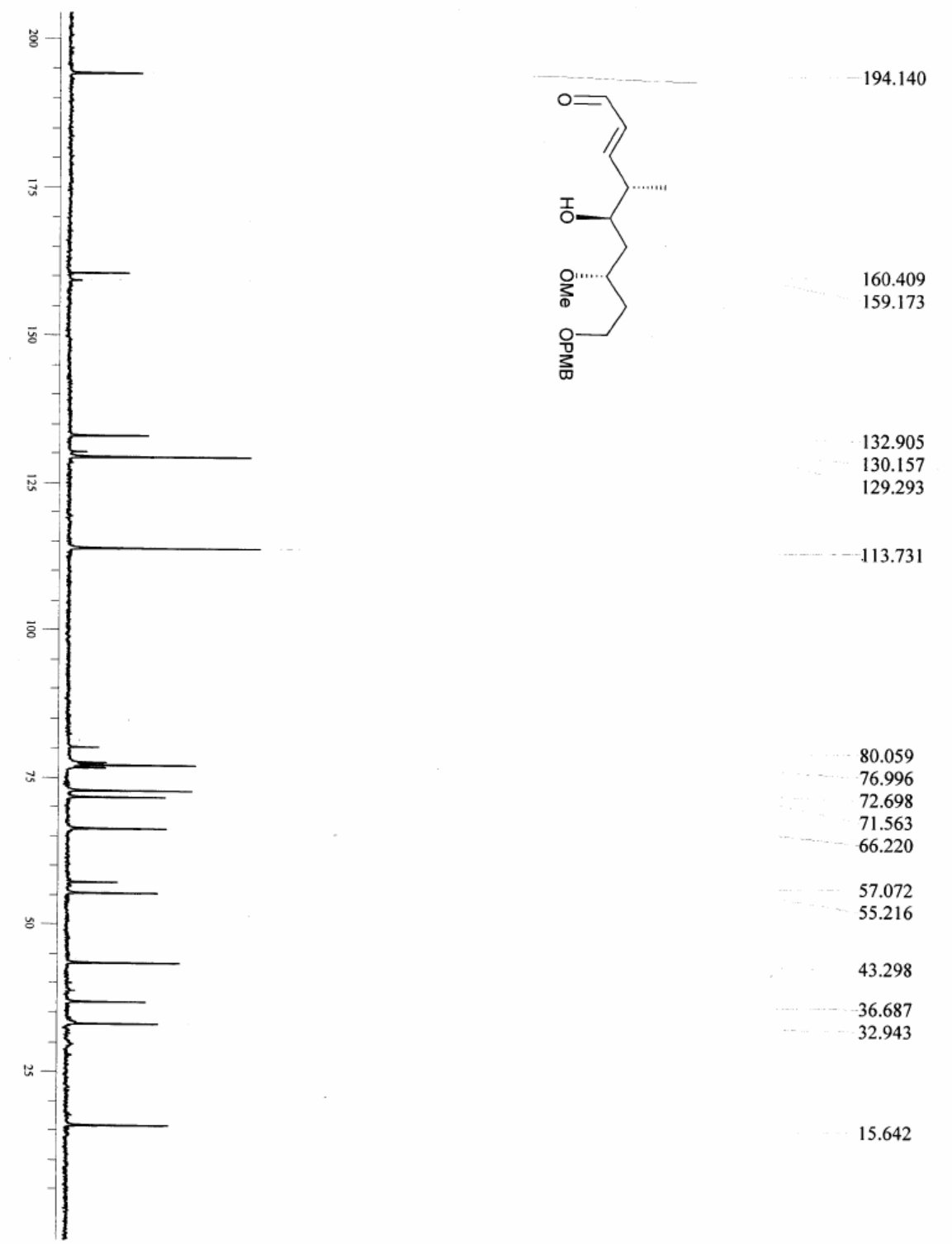
^{1}H NMR of allyl alcohol ($CDCl_3$, 300 MHz)



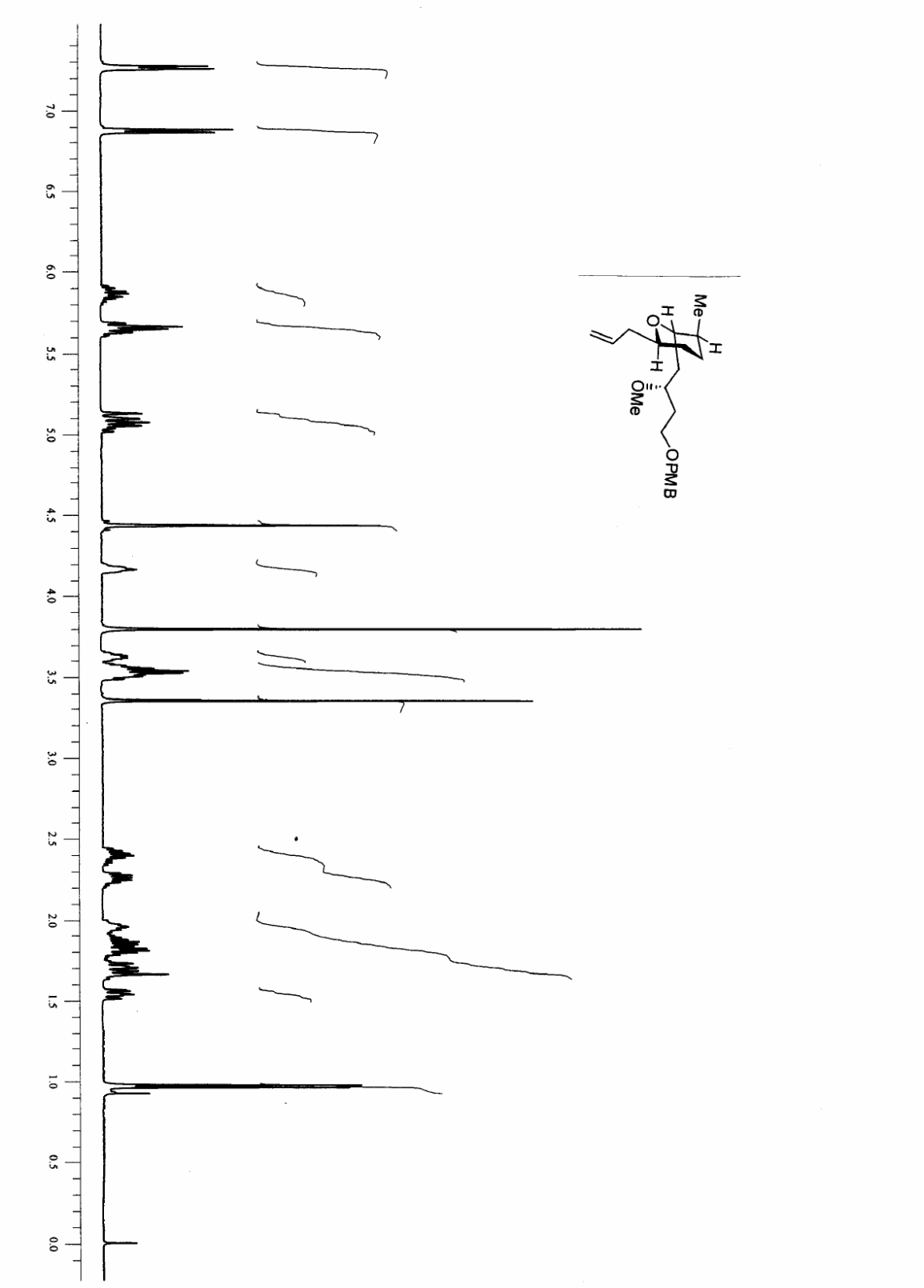
^{13}C NMR of allyl alcohol ($CDCl_3$, 75 MHz)



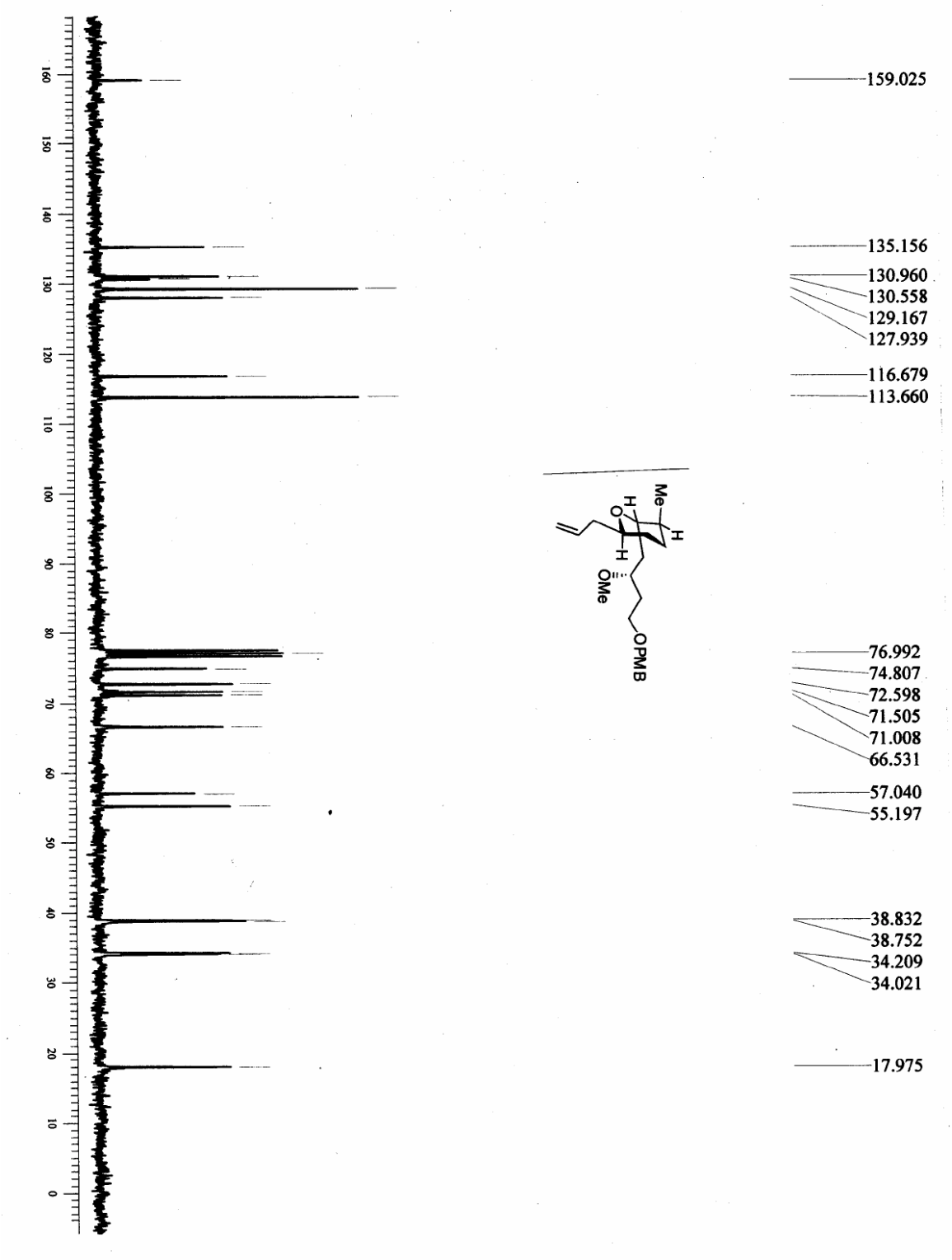
^{1}H NMR of 2 ($CDCl_3$, 300 MHz)



^{13}C NMR of 2 ($CDCl_3$, 75 MHz)



^{1}H NMR of 3 ($CDCl_3$, 500 MHz)



^{13}C NMR of 3 ($CDCl_3$, 75 MHz)

NPL-HPLC-REPORT

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Vail #	: 0
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Method File Name	: Hari Babu.lcm
Batch File Name	:
Report File Name	: NPL HPLC REPORT new.lcr
Data Acquired	: 2/22/2011 1:47:32 PM
Data Processed	: 2/22/2011 2:37:33 PM

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Flowrate:1.0ml/min
Detection:2205nm

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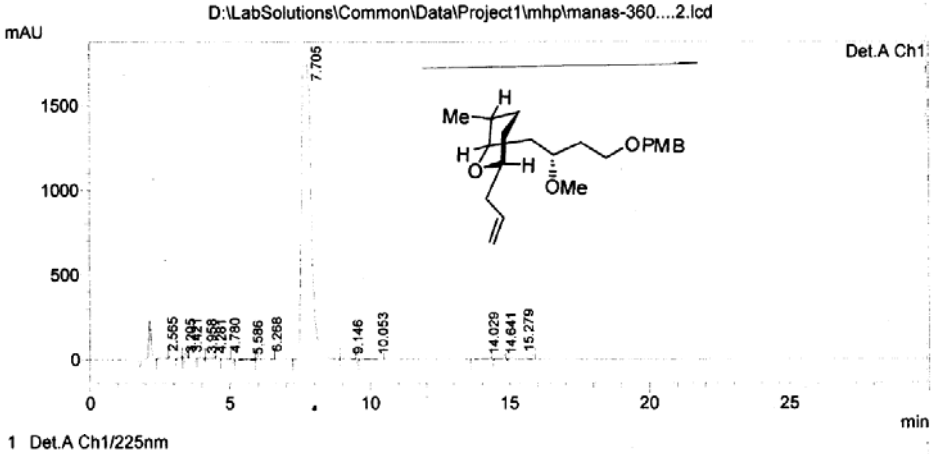

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Detector A Ch1 225nm

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4	3.958	52900	6602	0.122
5	4.281	63715	8137	0.147
6	4.780	108551	13108	0.250
7	5.586	56188	3699	0.129
8	6.268	298666	22378	0.688
9	7.705	41890265	1767928	96.453
10	9.146	70784	4426	0.163
11	10.053	49243	2378	0.113
12	14.029	62168	3210	0.143
13	14.641	41523	2436	0.096
14	15.279	440848	18614	1.015

D:\LabSolutions\Common\Data\Project1\mhp\manas-360...

HPLC Chromatogram of 3 (Filter Column)

Data File D:\DATA\MHP\19021133.D Sample Name: manas 360

Atantis; 70% ACN, 30% 0.1 TFA

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Acq. Operator   : raju
                                               Inj Volume : 10 µl
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Analysis Method : D:\METHODS\ONLYMASS.M
Last changed    : 2/23/2011 11:13:18 AM by sukumar
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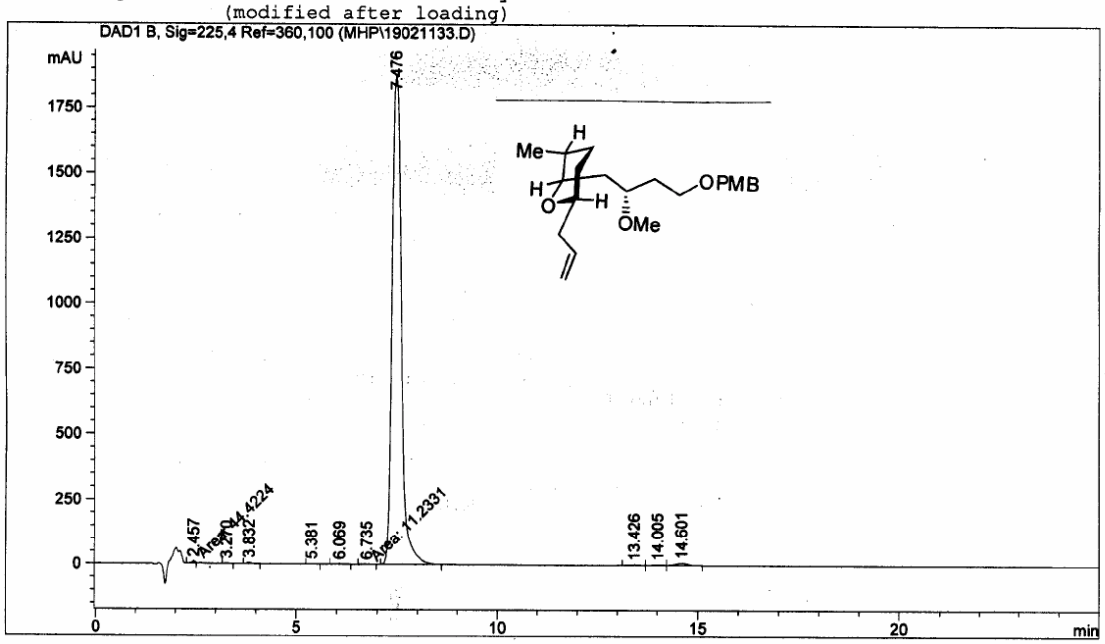


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                          Area Percent Report
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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 B, Sig=225,4 Ref=360,100

Peak RetTime  Type   Width     Area      Area     Name
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   2   3.270 VP      0.0942   12.61154   0.0413 ?
   3   3.832 VB      0.0927   33.19797   0.1086 ?
   4   5.381 BB      0.1305   10.56299   0.0346 ?
   5   6.069 BP      0.1649   20.93268   0.0685 ?
   6   6.735 MM      0.2431   11.23312   0.0367 ?
   7   7.476 BP      0.2519 3.01768e4  98.7189 ?
   8  13.426 BV      0.2480   34.37079   0.1124 ?
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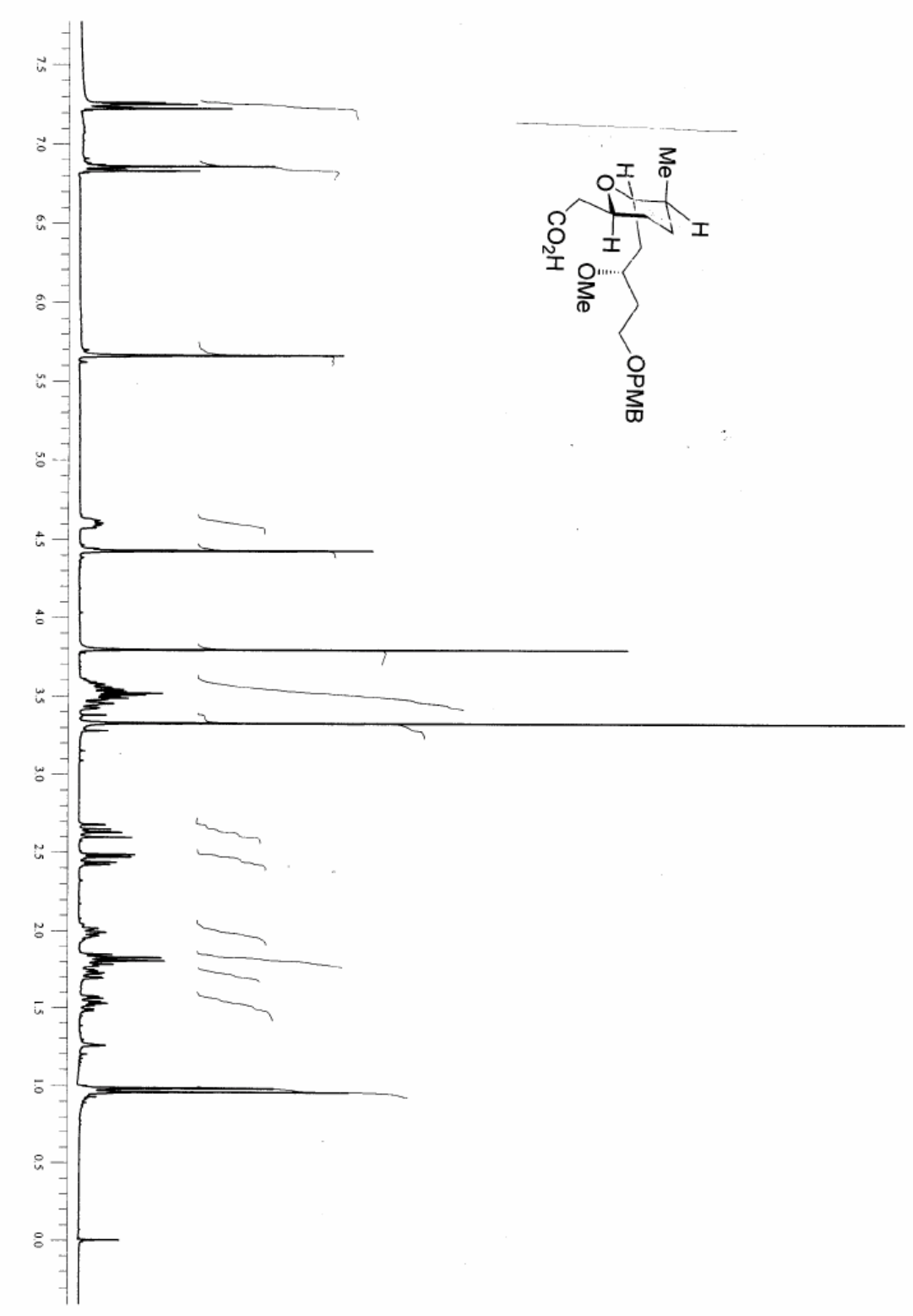
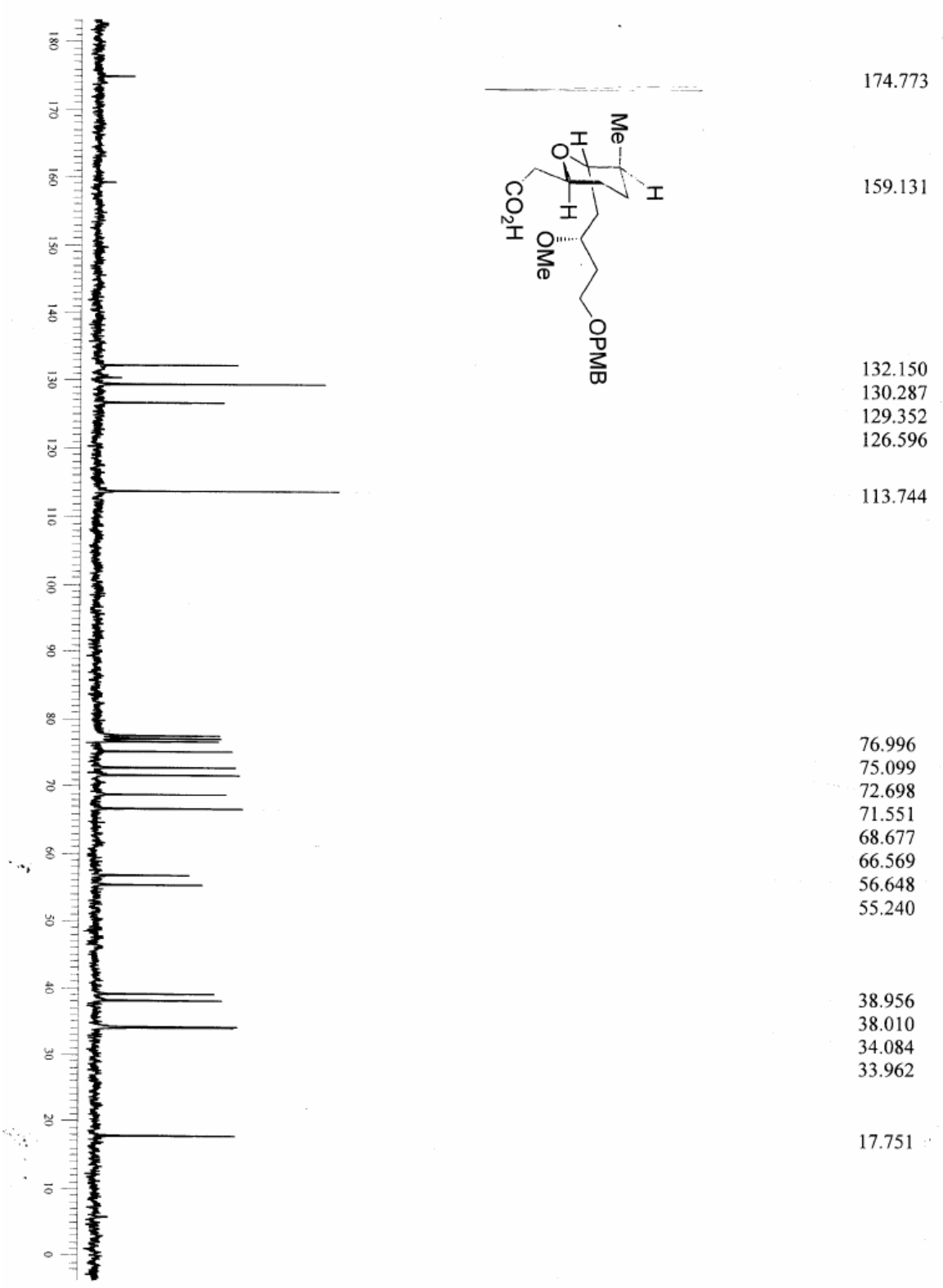
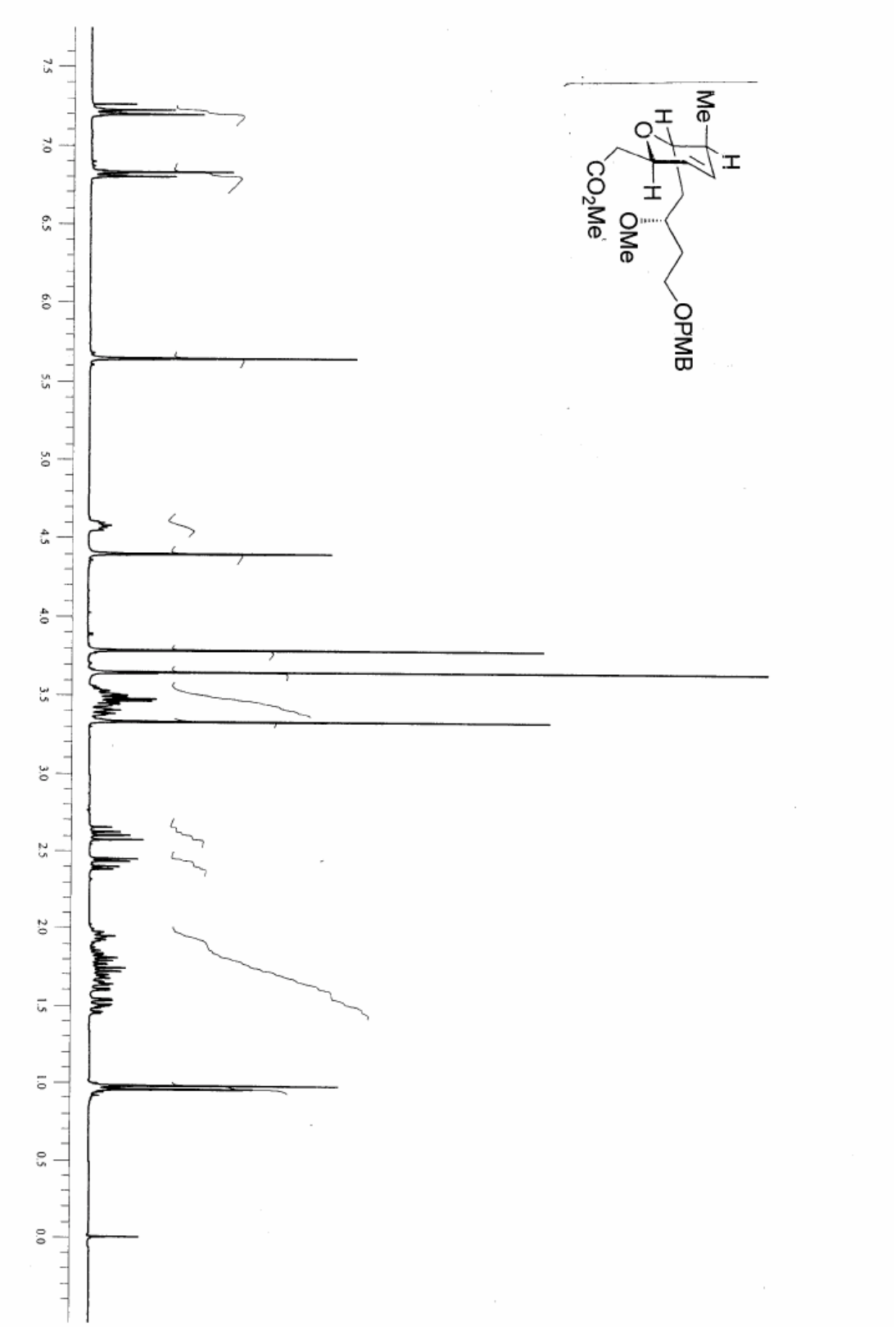
HPLC Chromatogram of 3 (Purification By Column Chromatography)



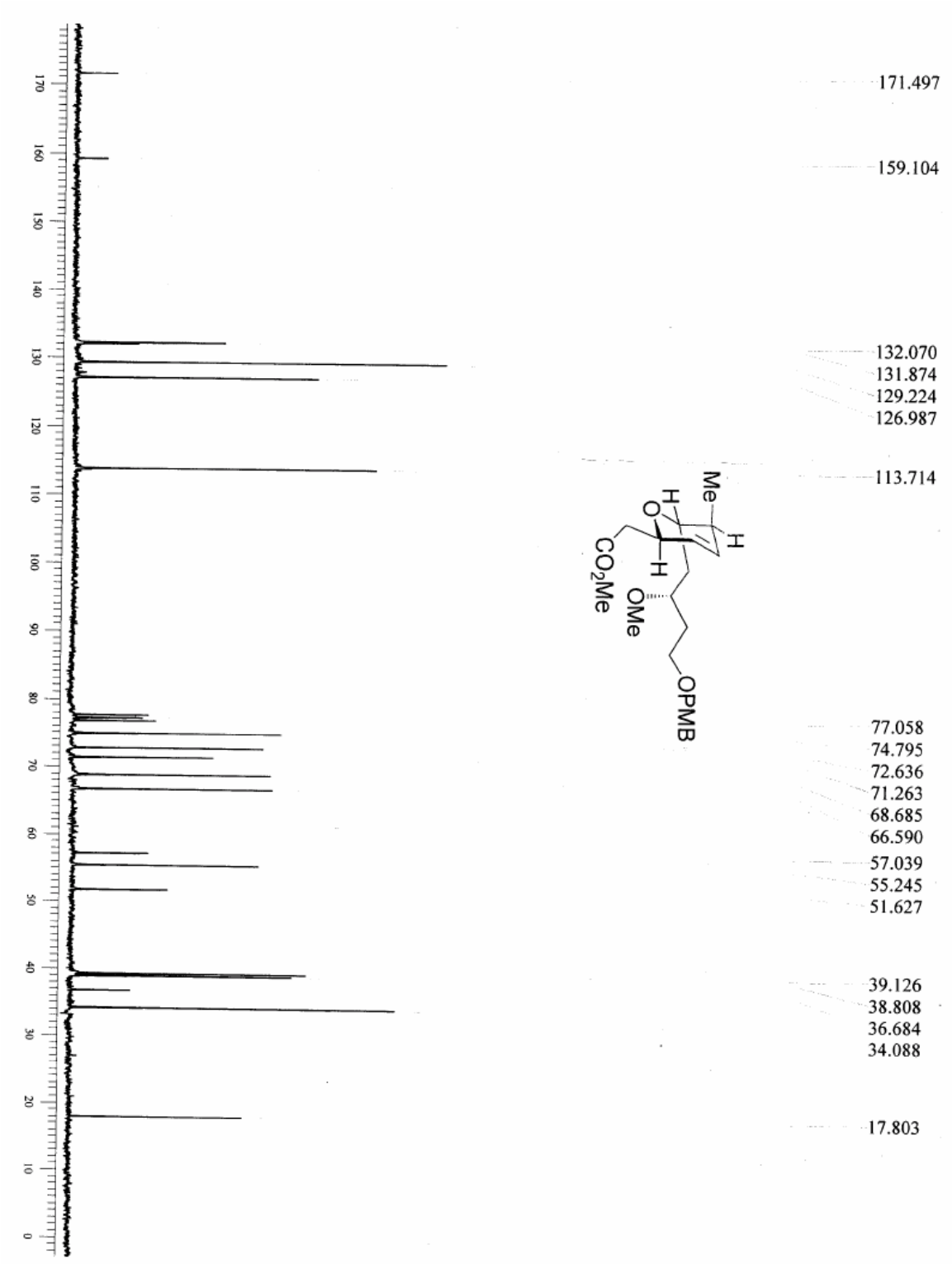
^{1}H NMR of the acid ($CDCl_3$, 300 MHz)



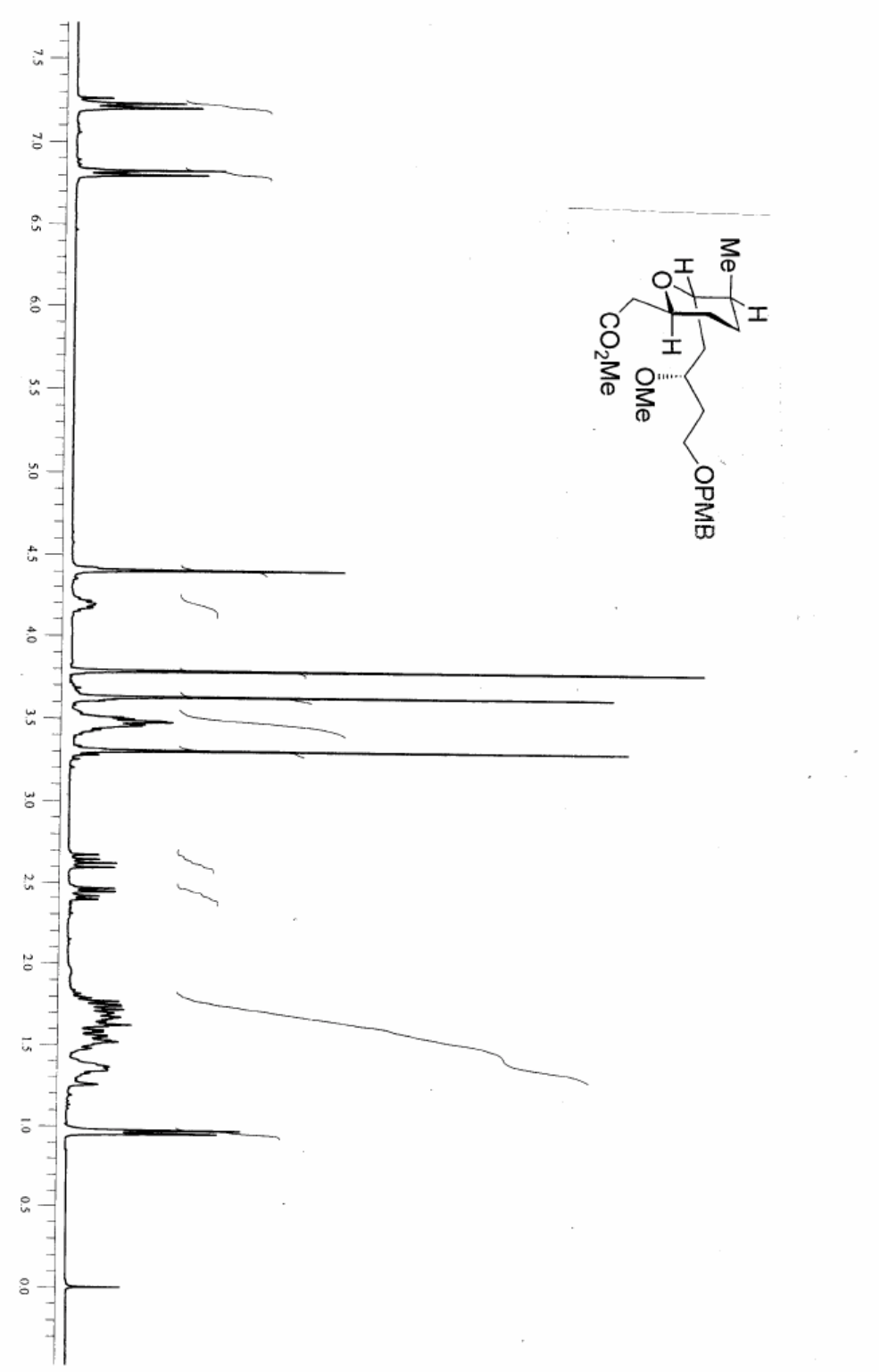
^{13}C NMR of the acid ($CDCl_3$, 75 MHz)



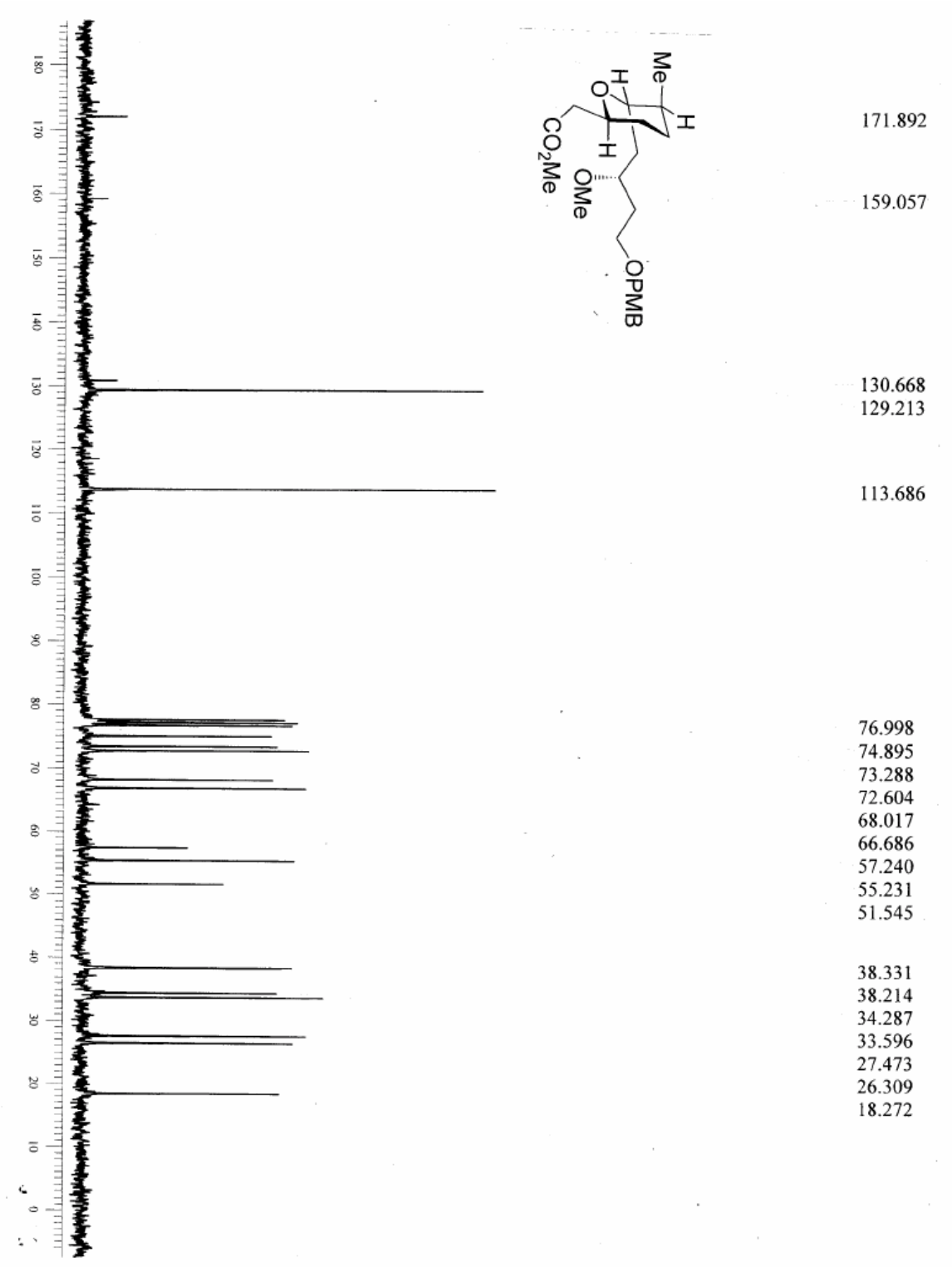
^{1}H NMR of 16 ($CDCl_3$, 300 MHz)



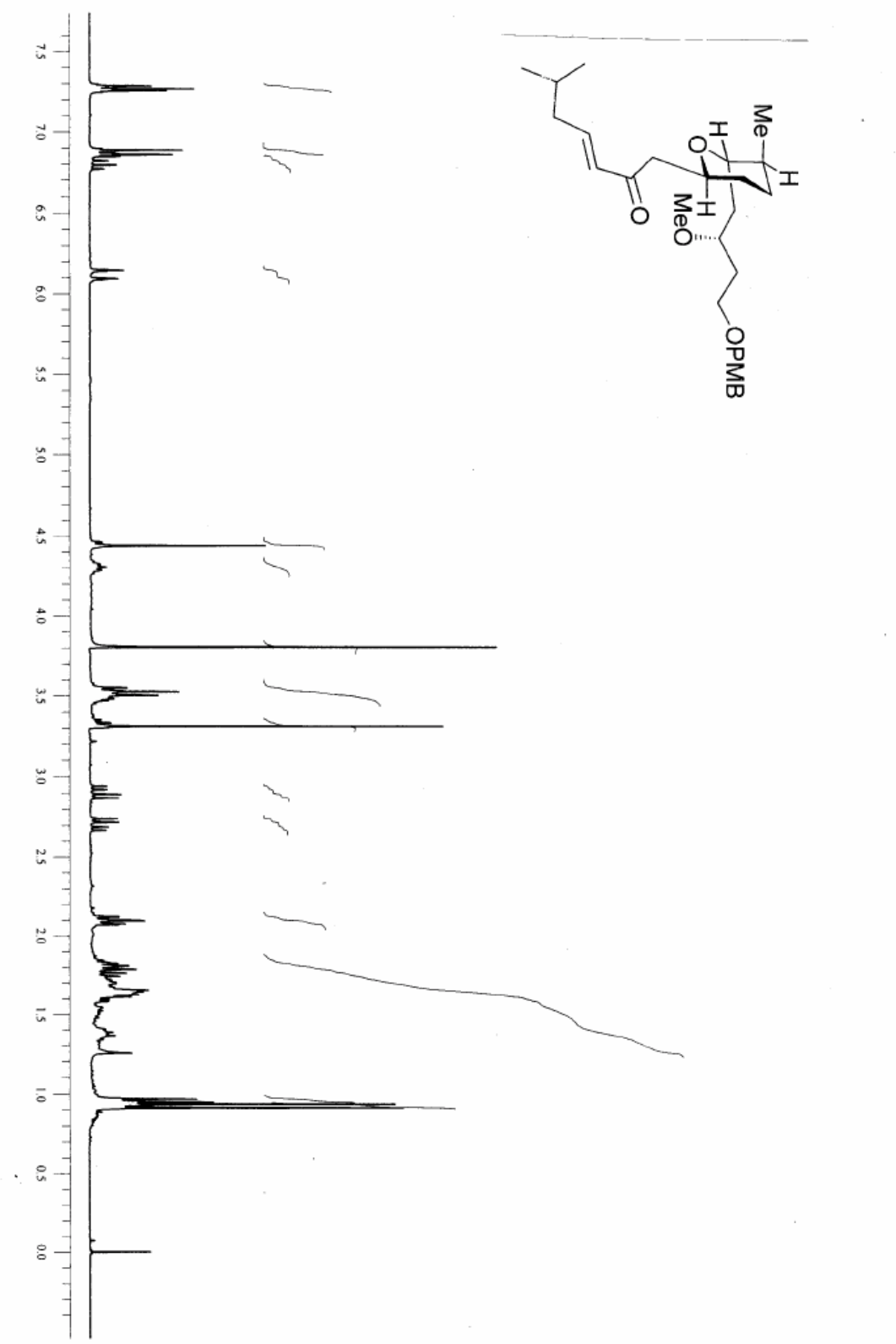
^{13}C NMR of 16 ($CDCl_3$, 75 MHz)



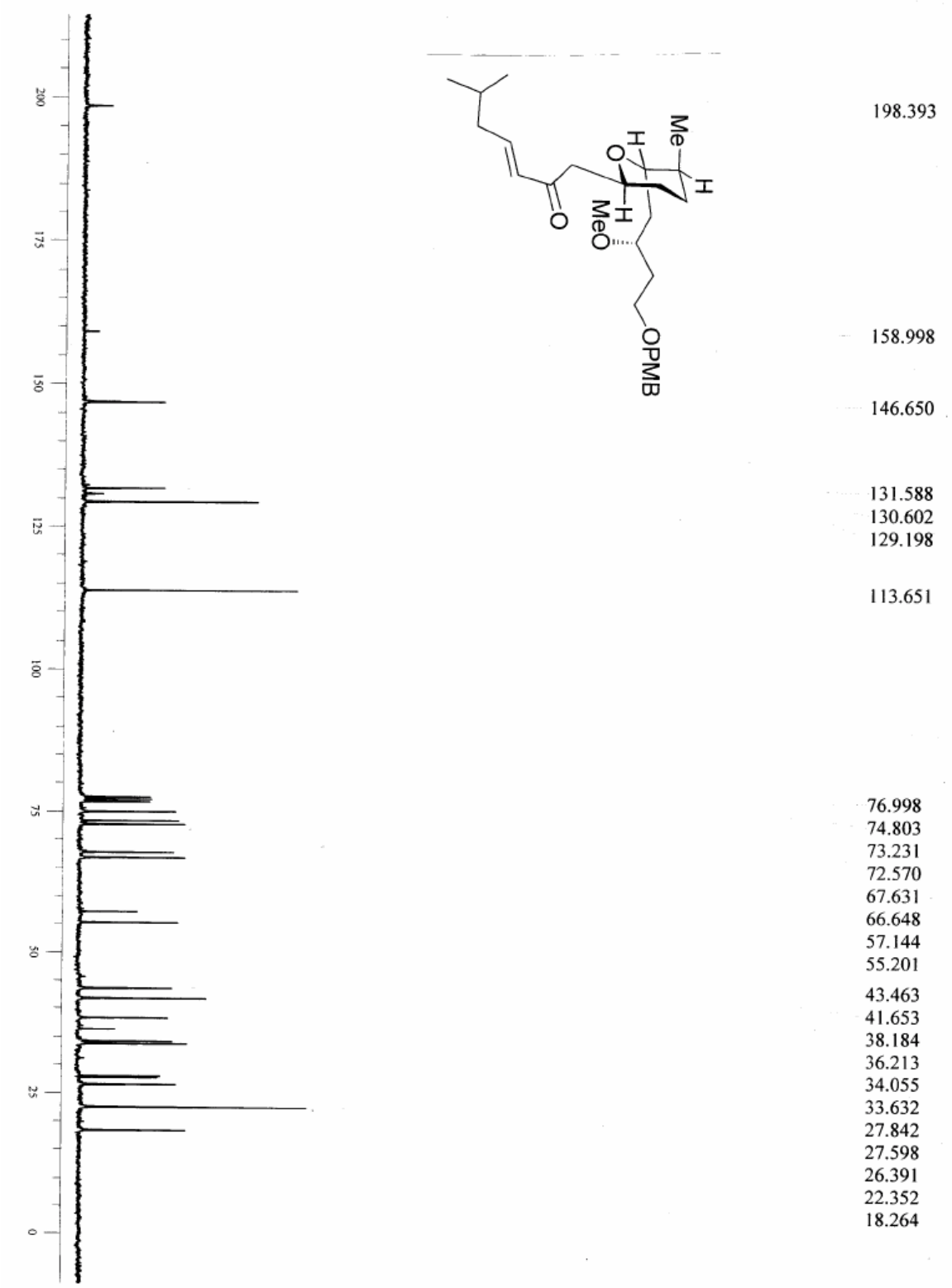
^{1}H NMR of 17 ($CDCl_3$, 300 MHz)



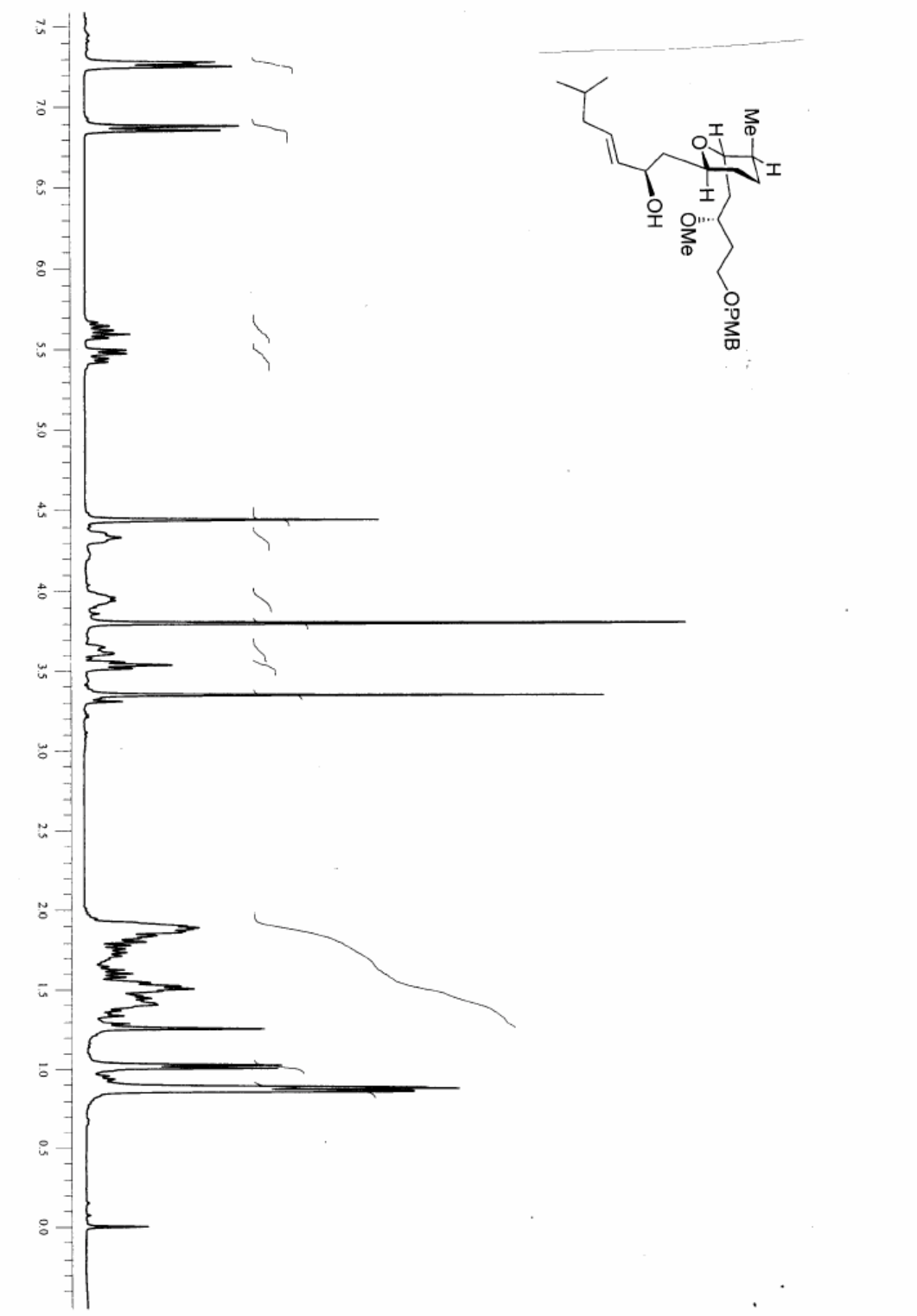
^{13}C NMR of 17 ($CDCl_3$, 75 MHz)



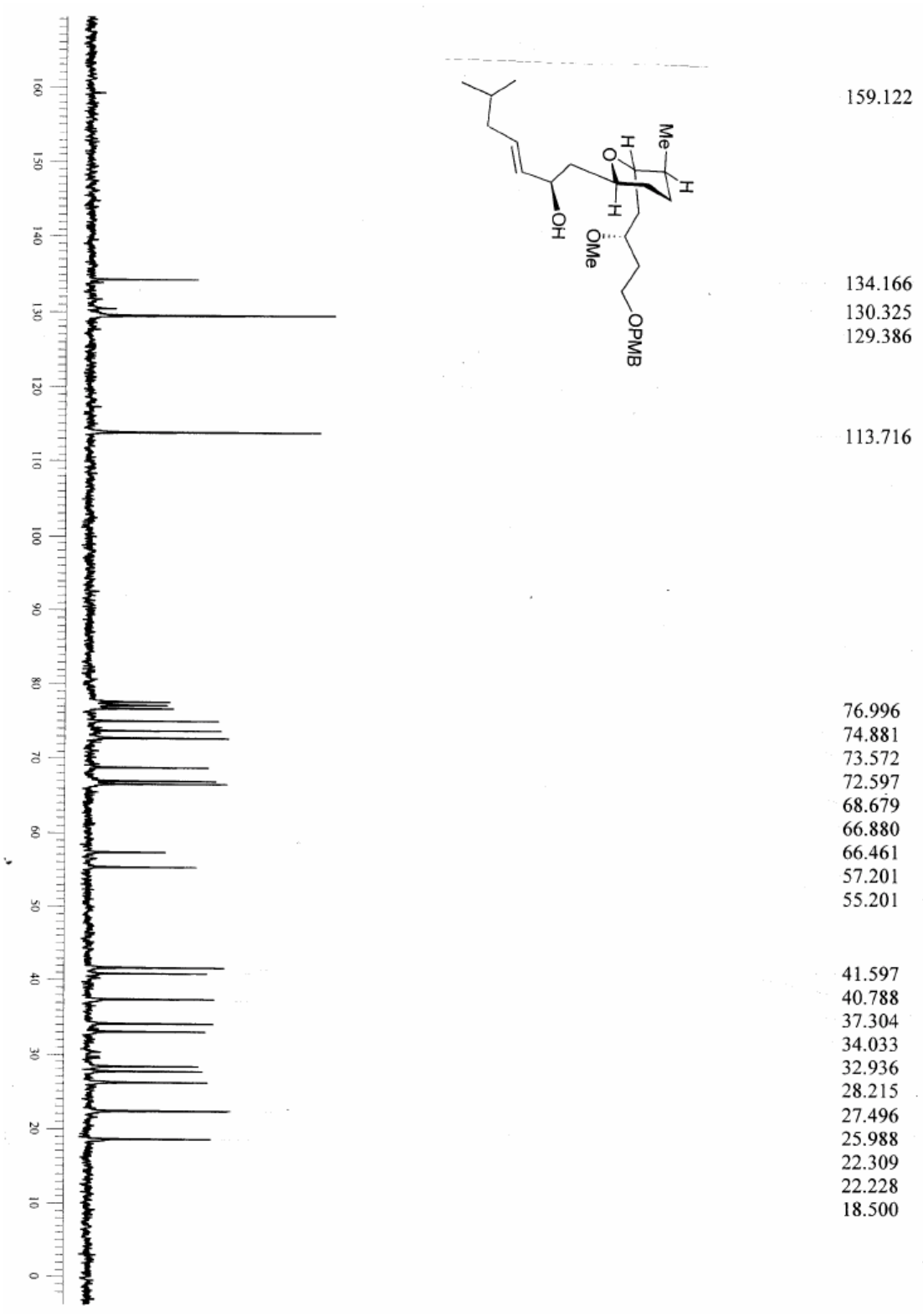
^{1}H NMR of 19 ($CDCl_3$, 300 MHz)



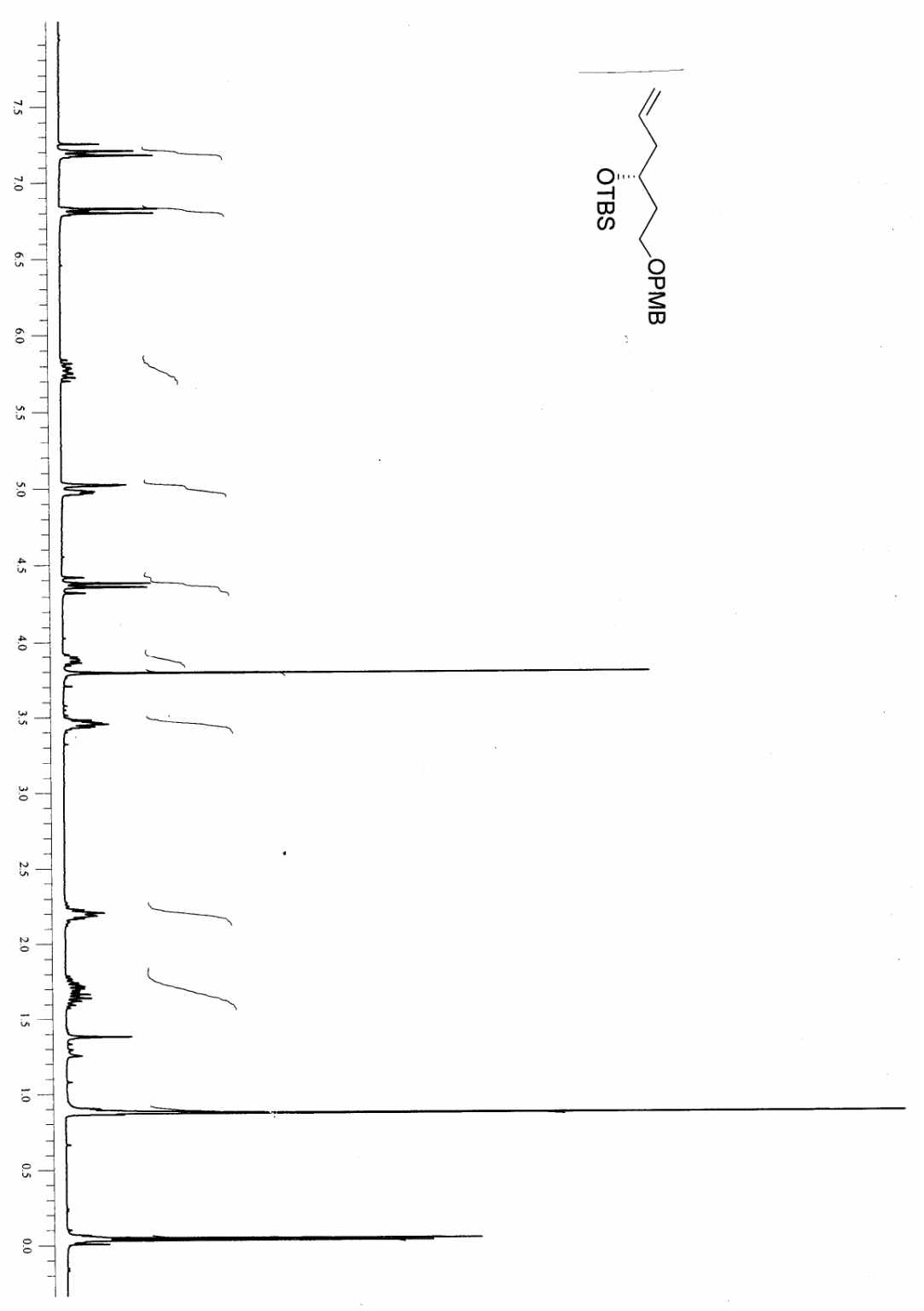
^{13}C NMR of 19 ($CDCl_3$, 75 MHz)



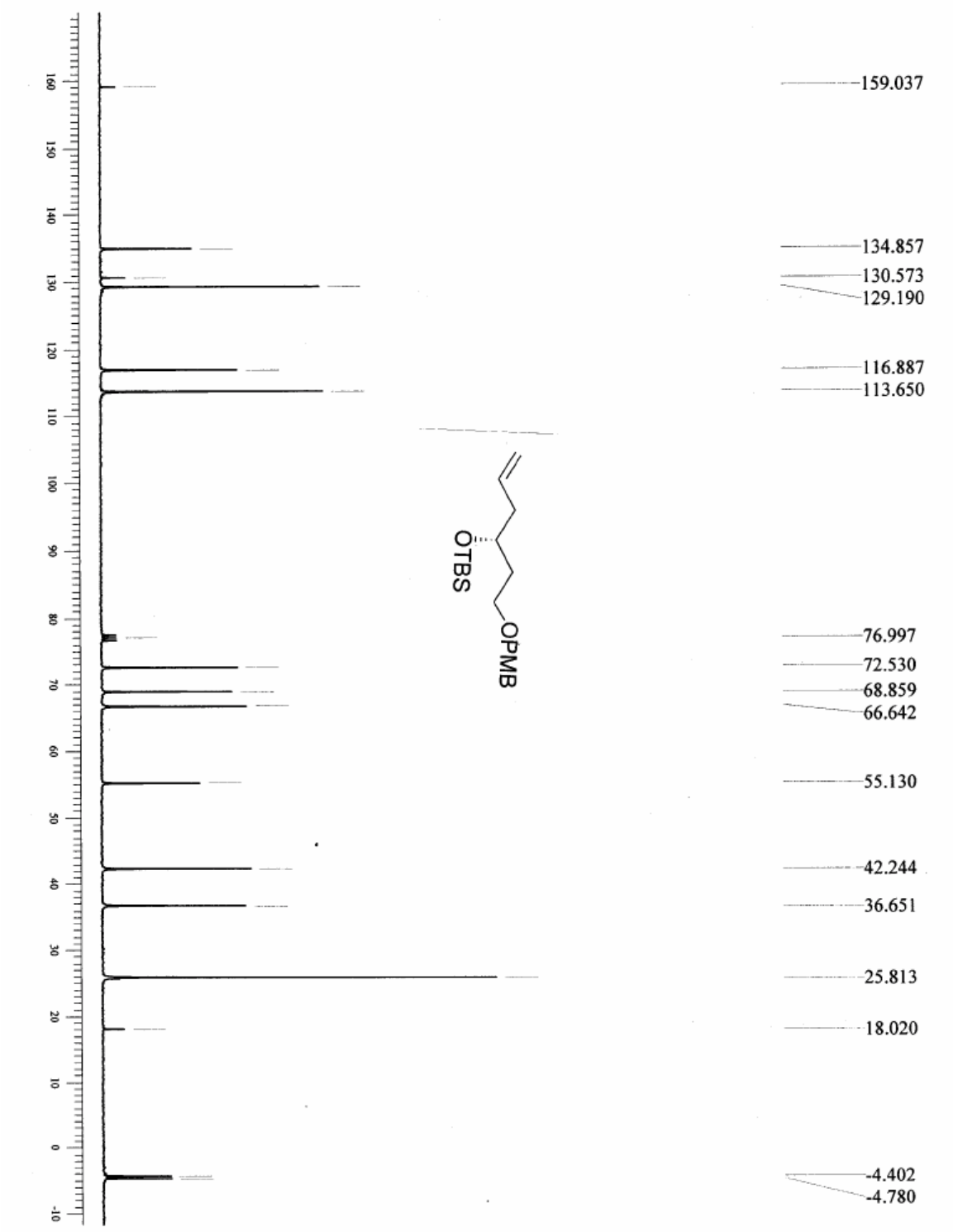
^{1}H NMR of 7 ($CDCl_3$, 300 MHz)



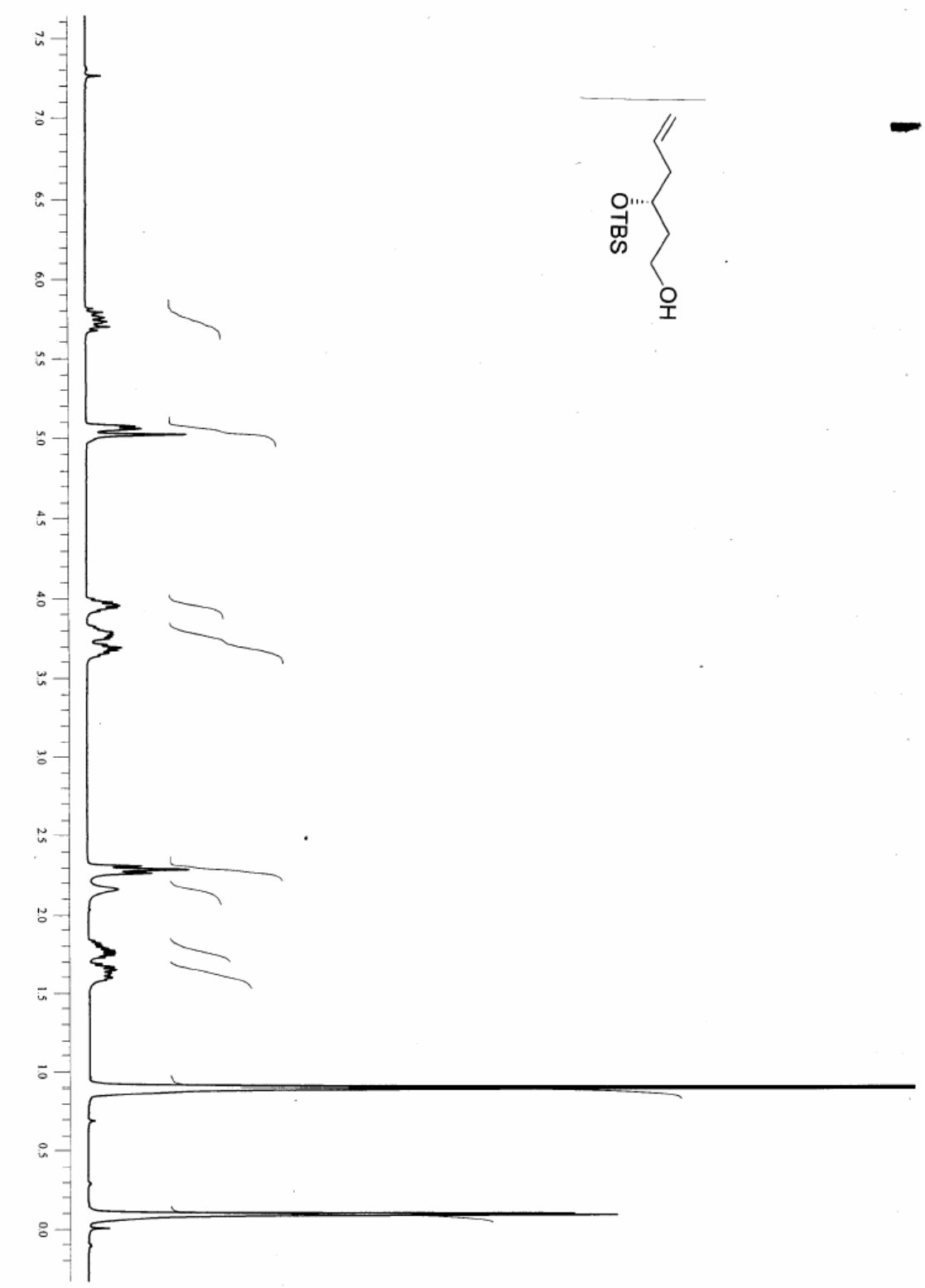
^{13}C NMR of 7 ($CDCl_3$, 75 MHz)



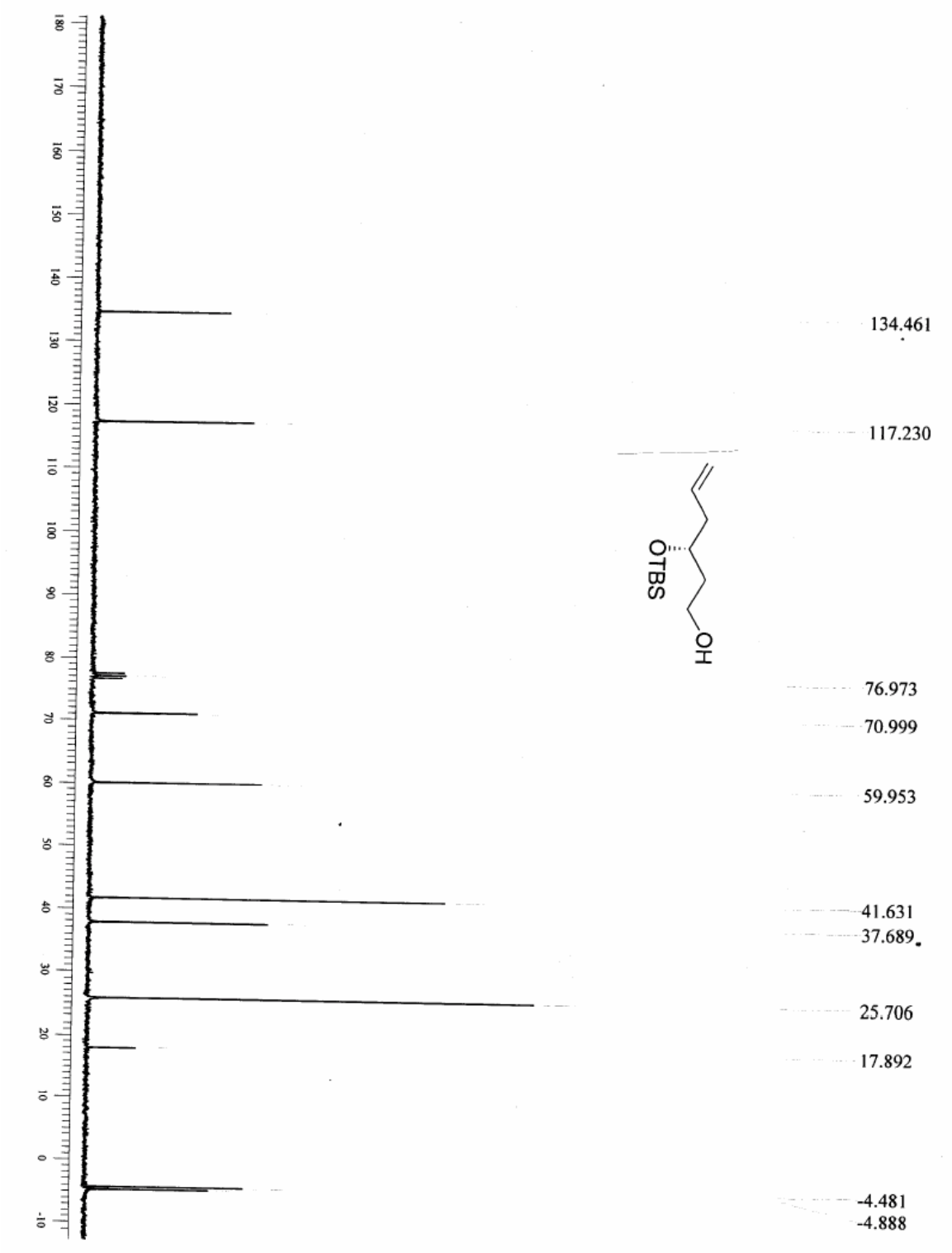
^{1}H NMR of 20 ($CDCl_3$, 300 MHz)



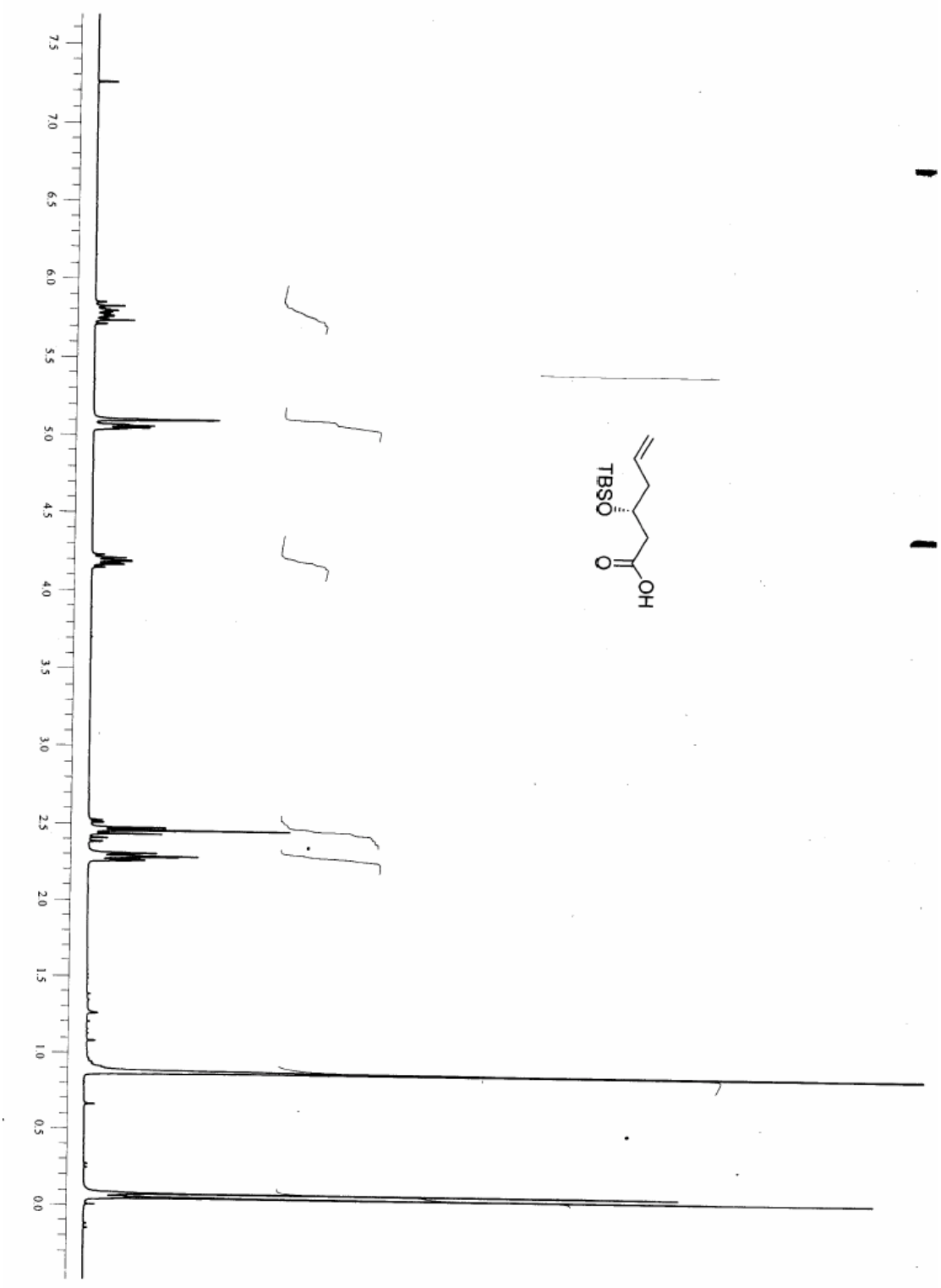
^{13}C NMR of 20 ($CDCl_3$, 75 MHz)



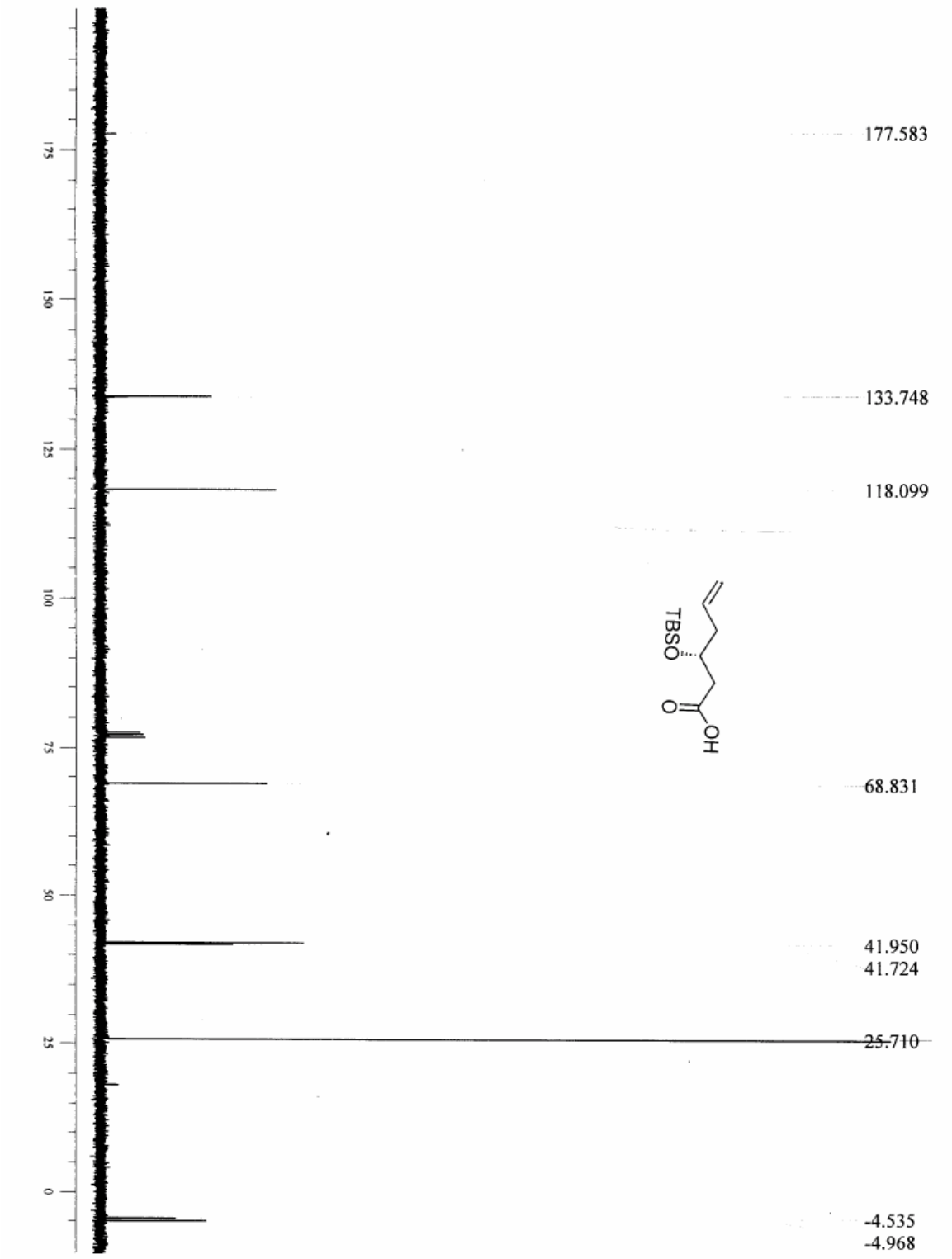
^{1}H NMR of 21 ($CDCl_3$, 300 MHz)



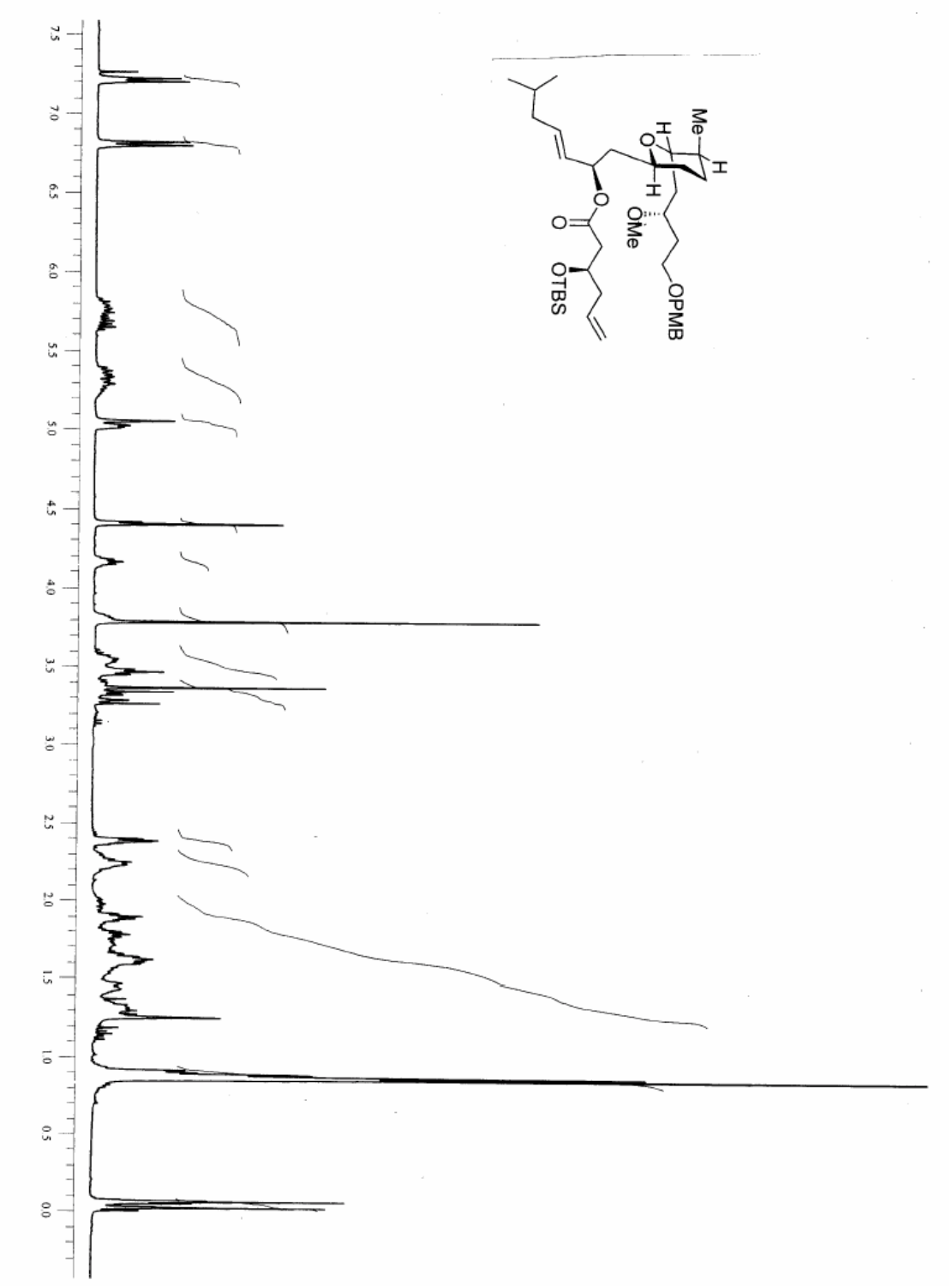
^{13}C NMR of 21 ($CDCl_3$, 75 MHz)



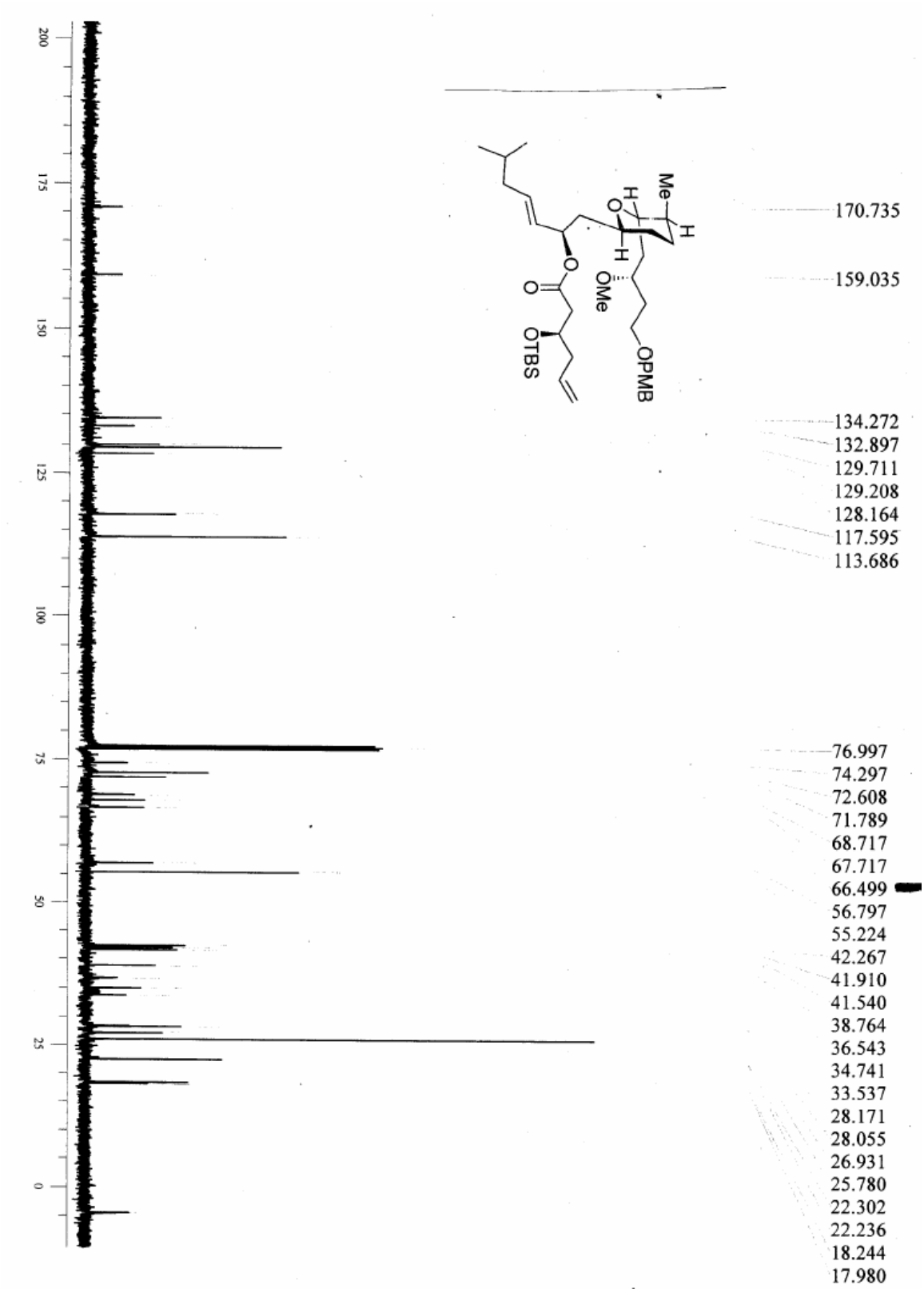
^{1}H NMR of 8 ($CDCl_3$, 300 MHz)



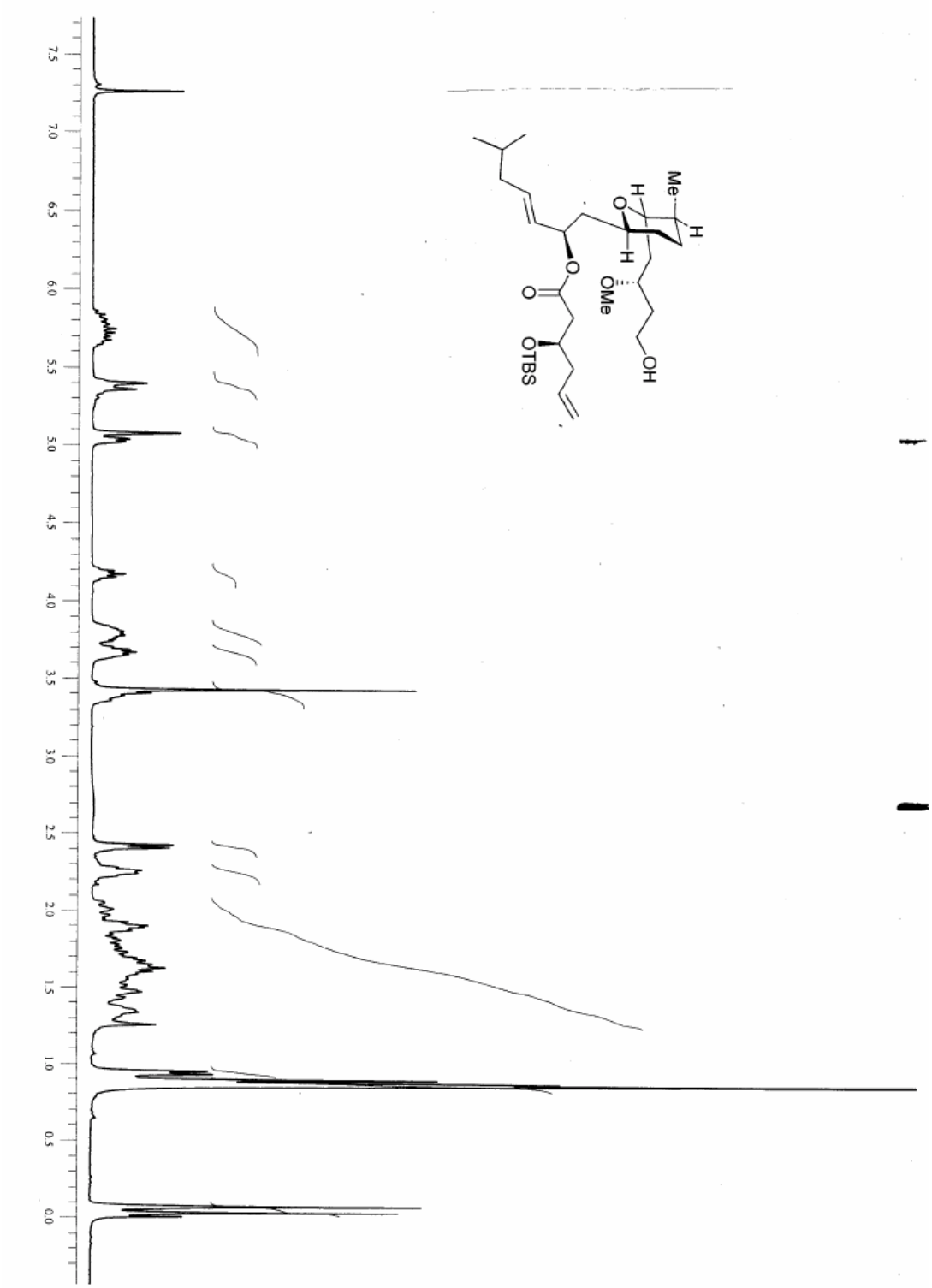
^{13}C NMR of 8 ($CDCl_3$, 75 MHz)



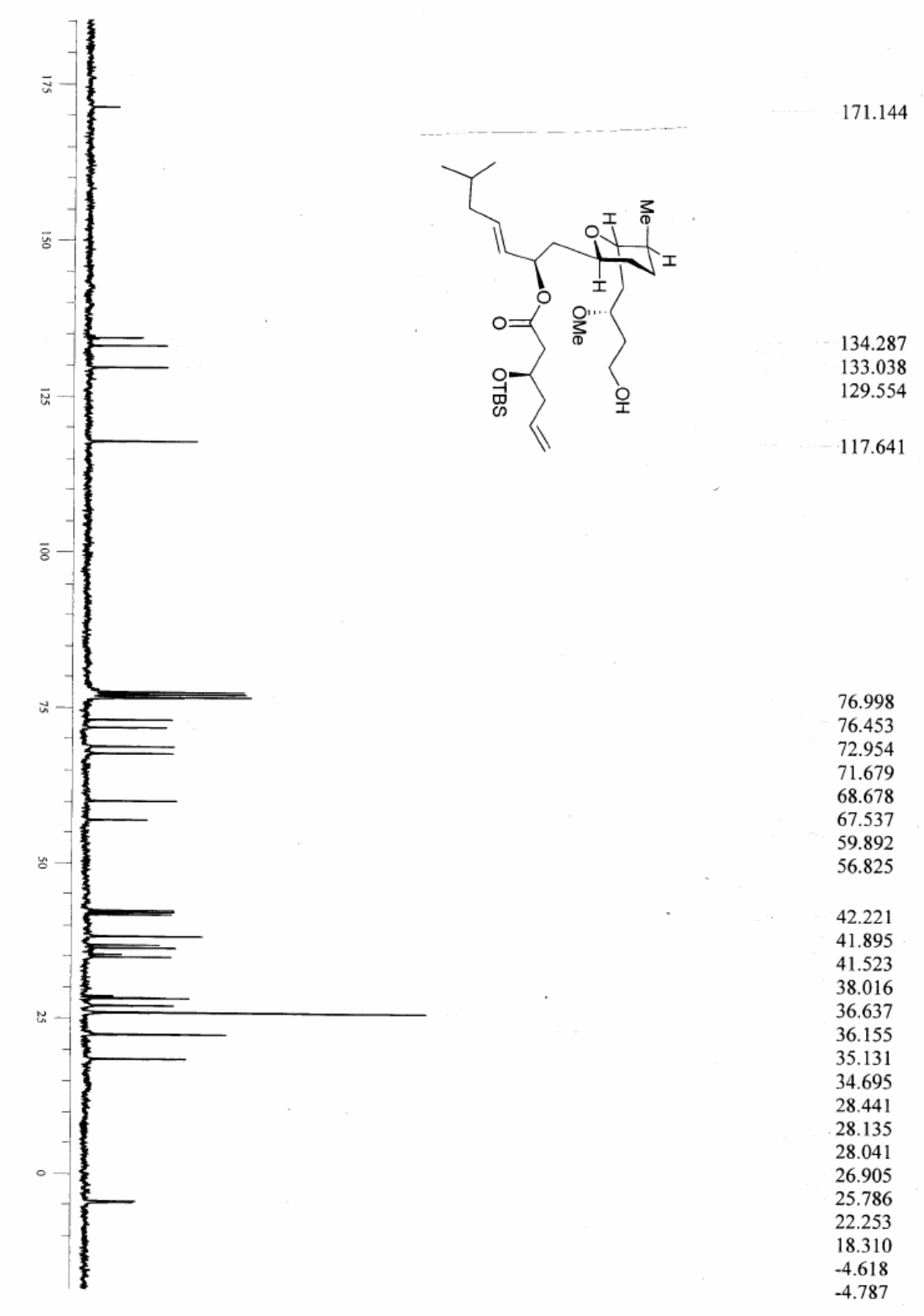
^{1}H NMR of 23 ($CDCl_3$, 400 MHz)



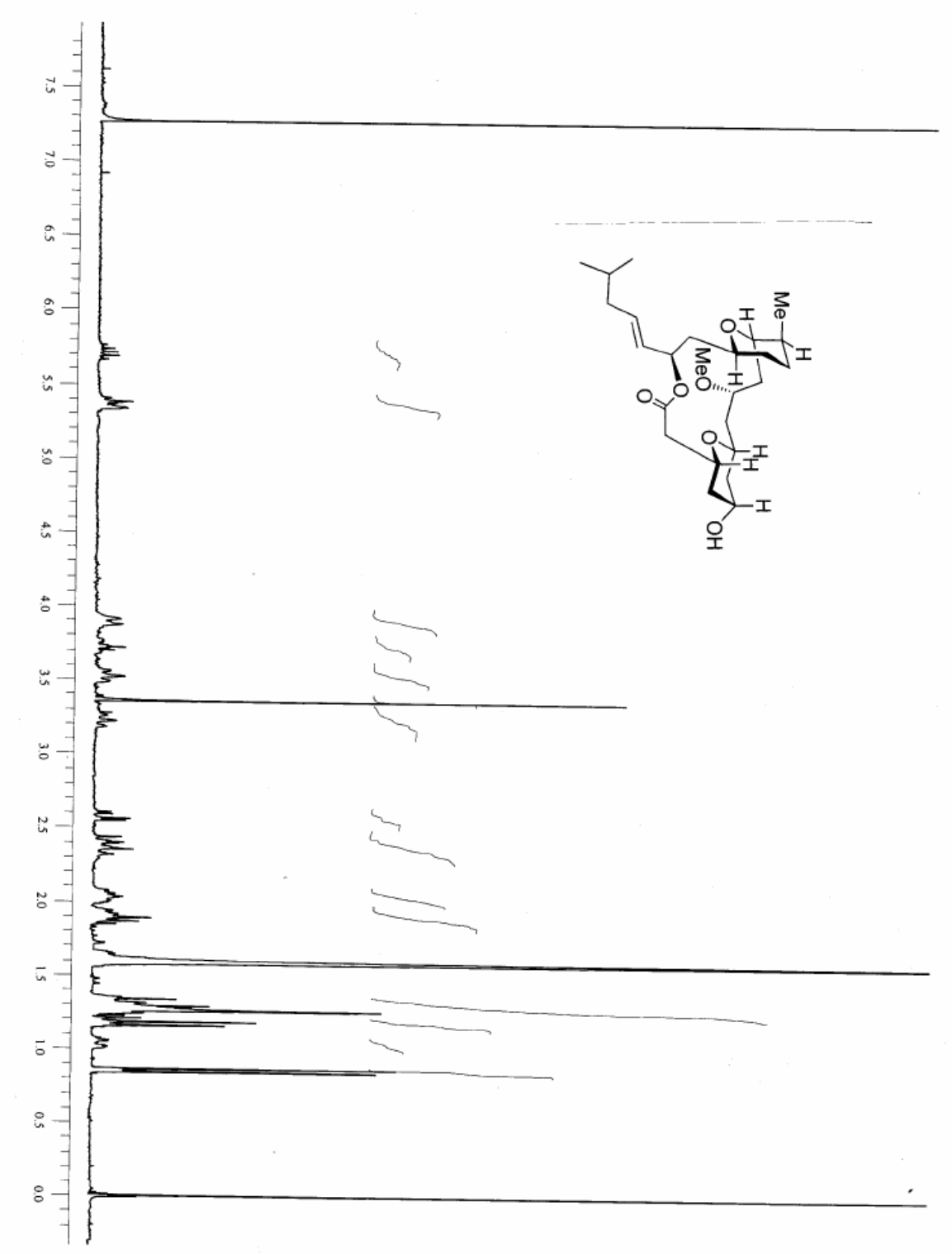
^{13}C NMR of 23 ($CDCl_3$, 100 MHz)



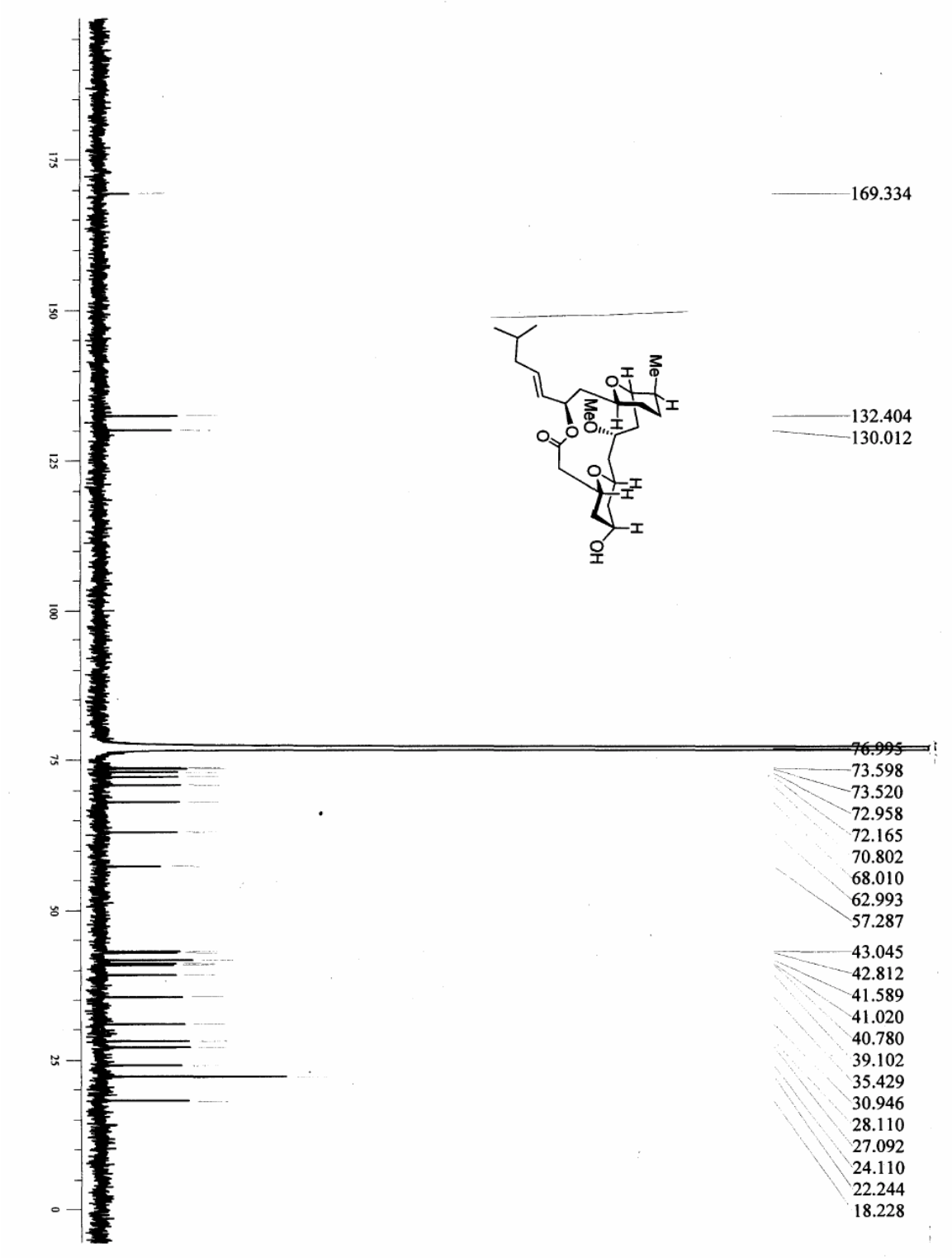
^{1}H NMR of 24 ($CDCl_3$, 300 MHz)



^{13}C NMR of 24 ($CDCl_3$, 75 MHz)



^{1}H NMR of 4 ($CDCl_3$, 300 MHz)



^{13}C NMR of 4 ($CDCl_3$, 75 MHz)