Total Synthesis of Dolabelide D

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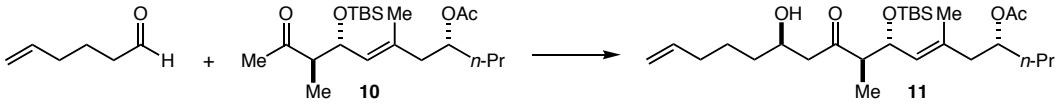
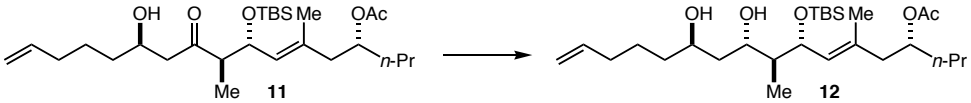
Supporting Information

General Information. All non-aqueous reactions were carried out under an atmosphere of nitrogen in flame- or oven-dried glassware with magnetic stirring unless otherwise indicated. High pressure reactions were carried out in a Parr stainless steel pressure vessel equipped with a pressure gauge, gas inlet, and pressure release valve. Degassed solvents were purified by passage through an activated alumina column. Triethylamine and diisopropylethylamine were distilled from calcium hydride. All other commercially obtained reagents were used as received, except where specified otherwise. Flash chromatography was performed on Silicycle SiliaFlash P60 silica gel (230-400 mesh). ^{1}H NMR spectra were recorded on a Bruker DPX300 (300 MHz), DRX400 (400 MHz), or DMX500 (500 MHz) spectrometer and are reported in ppm from $CDCl_3$, C_6D_6, or pyridine-d_5 internal standard (7.26, 7.15, and 8.71 ppm, respectively). Data are reported as follows: (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, br = broad; coupling constant(s) in Hz; integration; assignment). Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker DRX300WB (75 MHz) or DRX400 (100 MHz) spectrometer and are reported in ppm from $CDCl_3$ or pyridine-d_5 internal standard (77.0 and 149.8 ppm, respectively). Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer. Optical rotations were recorded on a JASCO DIP-1000 digital polarimeter. Low resolution atmospheric pressure chemical ionization (APCI) mass spectra were obtained on a JEOL JMS-LCmate LC/MS system. Low and high resolution fast atom bombardment (FAB) mass spectra were obtained on a JEOL JMS-HX110 mass spectrometer in the Columbia University Mass Spectrometry Laboratory.



(4*R*,8*R*,9*R*,12*R*,*E*)-8-(*tert*-butyldimethylsilyloxy)-12-hydroxy-6,9-dimethyl-10-oxoheptadeca-6,16-dien-4-yl acetate (11). To a solution of 5-hexen-1-ol (0.9 mL, 7.49 mmol) in CH_2Cl_2 (12 mL) was added pyridinium chlorochromate (2.45 g, 11.4 mmol). The resulting dark red solution was stirred for 14 h at room temperature, diluted with pentane (12 mL), filtered through a plug of silica, and rinsed through with 1:1 CH_2Cl_2/pentane (7 × 25 mL). The filtrate was concentrated to give 5-hexen-1-al as a clear, colorless oil. The unpurified aldehyde was carried immediately into the next step without further purification.

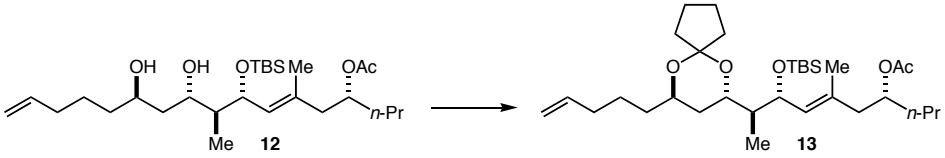
To a cooled (0 °C) solution of (+)-*B*-chlorodiisopinocampheylborane (532 mg, 1.66 mmol) in Et_2O (3 mL) was added triethylamine (0.37 mL, 2.66 mmol), resulting in a white precipitate. A solution of ketone **10**[1] (245 mg, 0.638 mmol; azeotroped twice with benzene) in Et_2O (3 mL) was then added via cannula (rinsed 1 × 3 mL). The white, heterogeneous mixture was stirred for 95 min at 0 °C. The mixture was then cooled to -78 °C, and a solution of 5-hexen-1-al in Et_2O (3 mL) was added via cannula (rinsed 1 × 3 mL). The reaction mixture was maintained at -78 °C for 3.5 h; the dry ice/acetone bath was subsequently allowed to warm to room temperature while stirring for an additional 15.5 h. The reaction was quenched by the addition of MeOH (4.4 mL) and pH 7 buffer (0.88 mL), yielding a homogeneous, clear, colorless solution. This was followed by ***dropwise addition*** of H_2O_2 (30 wt % in H_2O, 1.3 mL) (**CAUTION: Exothermic!**). The resulting cloudy, white mixture was stirred for 1.5 h at room temperature, diluted with CH_2Cl_2 (50 mL), and poured into H_2O (50 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine (60 mL), dried (Na_2SO_4), filtered, and concentrated to give a cloudy, pale yellow oil. Purification by flash chromatography (column 1: 85-100% CH_2Cl_2/hexanes then 0-10% EtOAc/CH_2Cl_2; column 2: 10% EtOAc/hexanes) afforded β-hydroxy ketone **11** as a clear, yellow oil in 85% yield (261 mg, 0.541 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (m, 1H, C**H**=CH_2), 5.08-4.91 (m, 4H, CH=C**H**$_2$, C**H**OAc, (CH_3)C=C**H**), 4.44 (apparent t, *J* = 9.2 Hz, 1H, C**H**OTBS), 4.02 (m, 1H, C**H**OH), 3.17 (d, *J* = 2.1 Hz, 1H, O**H**), 2.74-2.50 (m, 3H, C**H**$_2$C(O)C**H**(CH_3)), 2.27 (dd, *J* = 13.9, 6.9 Hz, 1H, one of C**H**$_2(CH_3)$C=CH), 2.19 (dd, *J* = 14.0, 6.3 Hz, 1H, one of C**H**$_2(CH_3)$C=CH), 2.06-2.02 (m, 2H, C**H**$_2$CH=CH_2), 1.99 (s, 3H, OC(O)C**H**$_3$), 1.68 (s, 3H, (C**H**$_3$)C=CH), 1.52-1.23 (m, 8H, C**H**$_2$C**H**$_2$$CH_2$CH=$CH_2$, C**H**$_2$C**H**$_2$$CH_3$), 0.90-0.83 (m, 6H, CH_2CH_2C**H**$_3$, CH(C**H**$_3$)), 0.79 (s, 9H, Si(C(C**H**$_3$)$_3$)), -0.06 (s, 6H, Si(C**H**$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.9, 170.6, 138.5, 134.1, 129.5, 114.5, 72.3, 66.8, 52.9, 51.3, 44.1, 36.0, 35.5, 33.5, 25.7, 24.6, 21.3, 18.4, 17.9, 17.4, 13.9, 12.9, -4.3, -5.2; IR (thin film) 3512 (br), 3077, 2958, 2931, 2858, 1739, 1712, 1641, 1472, 1461, 1409, 1373, 1247, 1125, 1058, 1024, 1006, 938, 910, 837, 814, 777 cm^{-1}; $[\alpha]^{22}_D$ (*c* 1.40, CH_2Cl_2) -29.7°; LRMS (FAB+) *m/z* calc'd for $[M+Na]^+$ ($C_{27}H_{50}O_5SiNa$) requires 505.33, found 505.38.



(4*R*,8*R*,9*S*,10*S*,12*R*,*E*)-8-(*tert*-butyldimethylsilyloxy)-10,12-dihydroxy-6,9-dimethylheptadeca-6,16-dien-4-yl acetate (12). To a solution of acetic acid (4 mL) in acetonitrile (4 mL) was added tetramethylammonium triacetoxyborohydride (668 mg, 2.54 mmol). After stirring for 15 min at room

(1) Schmidt, D. R.; Park, P. K.; Leighton, J. L. *Org. Lett.* **2003**, *5*, 3535-3537.

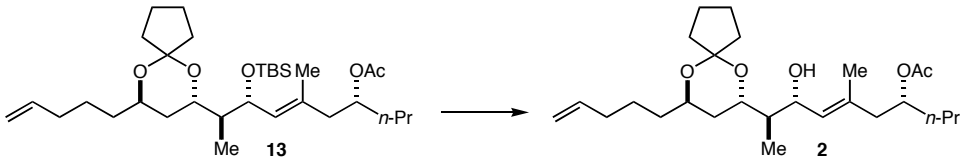
temperature, the mixture was cooled to -40 °C, and a solution of β-hydroxy ketone **11** (259 mg, 0.536 mmol) in 5:2 acetonitrile/THF (2.8 mL) was added via cannula (rinsed 1 × 2.8 mL). The mixture was then placed in a -20 °C freezer for 37 h (without stirring). The reaction was quenched at low temperature with a saturated aqueous solution of Rochelle salt and was stirred for 10 min while warming to room temperature. The mixture was diluted with CH_2Cl_2 (25 mL), and the layers were separated. The organic phase was washed with saturated aqueous $NaHCO_3$ (20 mL), and the combined aqueous phases were back-extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with brine (20 mL), and the brine wash was back-extracted with CH_2Cl_2 (2 × 10 mL). All the organic layers were then combined, dried (Na_2SO_4), filtered, and concentrated to give a cloudy, yellow-green oil. Purification by flash chromatography (5-15% EtOAc/hexanes) afforded diol **12** as a clear, colorless oil in 91% yield (236 mg, 0.487 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (m, 1H, C**H**=CH_2), 5.16 (d, *J* = 9.1 Hz, 1H, (CH_3)C=C**H**), 5.02-4.90 (m, 3H, CH=C**H$_2$**, C**H**OAc), 4.64 (apparent s, 1H, O**H**), 4.30 (apparent t, *J* = 8.7 Hz, 1H, C**H**OTBS), 3.90 (m, 2H, 2 × C**H**OH), 3.57 (d, *J* = 3.3 Hz, 1H, O**H**), 2.27 (dd, *J* = 13.8, 7.0 Hz, 1H, one of C**H$_2$**(CH_3)C=CH), 2.20 (dd, *J* = 13.9, 6.3 Hz, 1H, one of C**H$_2$**(CH_3)C=CH), 2.06-2.04 (m, 2H, C**H$_2$**CH=CH_2), 2.00 (s, 3H, OC(O)C**H$_3$**), 1.72-1.61 (m, 3H, C**H**(CH_3), HOCHC**H$_2$**CHOH), 1.67 (s, 3H, (C**H$_3$**)C=CH), 1.57-1.26 (m, 8H, C**H$_2$**C**H$_2$**CH_2CH=CH_2, C**H$_2$**C**H$_2$**CH_3), 0.89-0.84 (m, 12H, CH_2CH_2C**H$_3$**, Si(C(C**H$_3$**)$_3$)), 0.67 (d, *J* = 6.9 Hz, 3H, CH(C**H$_3$**)), 0.04 (s, 3H, SiC**H$_3$**), 0.00 (s, 3H, SiC**H$_3$**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 138.8, 133.3, 130.5, 114.4, 75.8, 73.6, 72.4, 68.6, 44.2, 39.3, 36.9, 36.0, 33.8, 25.7, 25.0, 21.3, 18.4, 17.9, 17.3, 13.9, 12.5, -3.8, -5.1; IR (thin film) 3432 (br), 2958, 2933, 2858, 1740, 1472, 1464, 1375, 1249, 1051, 1024, 1005, 910, 836, 775, 666 cm^{-1}; $[\alpha]^{19}_D$ (*c* 1.30, CH_2Cl_2) -6.8°; LRMS (FAB+) *m/z* calc'd for $[M+K]^+$ ($C_{27}H_{52}O_5SiK$) requires 523.32, found 523.4.



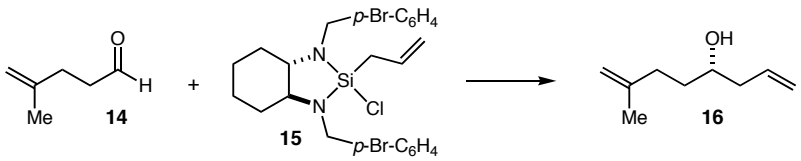
(4*R*,8*R*,9*S*,*E*)-8-(*tert*-butyldimethylsilyloxy)-6-methyl-9-((7*S*,9*R*)-9-(pent-4-enyl)-6,10-dioxaspiro[4.5]decan-7-yl)dec-6-en-4-yl acetate (13). To a solution of diol **12** (93.5 mg, 0.193 mmol) in CH_2Cl_2 (0.5 mL) and 1,1-dimethoxycyclopentane[2] (1.5 mL) was added pyridinium *p*-toluenesulfonate (5.6 mg, 21.8 μmol). After stirring for 24 h at room temperature, the volatiles were removed on a rotary evaporator. Purification by flash chromatography (2% EtOAc/hexanes) afforded ketal **13** as a clear, colorless oil in 80% yield (85.1 mg, 0.154 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (m, 1H, C**H**=CH_2), 5.23 (d, *J* =

(2) Hamada, N.; Kazahaya, K.; Shimizu, H.; Sato, T. *Synlett* **2004**, *6*, 1074-1076.

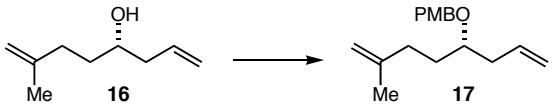
9.2 Hz, 1H, $(CH_3)C=C\mathbf{H}$), 5.03-4.93 (m, 3H, $CH=C\mathbf{H}_2$, $C\mathbf{H}OAc$), 4.41 (dd, *J* = 9.2, 5.0 Hz, 1H, $C\mathbf{H}OTBS$), 3.70-3.67 (m, 2H, $C\mathbf{H}CH_2C\mathbf{H}$), 2.27 (dd, *J* = 13.7, 6.9 Hz, 1H, one of $C\mathbf{H}_2(CH_3)C=CH$), 2.17 (dd, *J* = 13.8, 6.2 Hz, 1H, one of $C\mathbf{H}_2(CH_3)C=CH$), 2.06-2.05 (m, 2H, $C\mathbf{H}_2CH=CH_2$), 2.01 (s, 3H, $OC(O)C\mathbf{H}_3$), 1.79-1.75 (m, 3H, $C\mathbf{H}(CH_3)$, $CHC\mathbf{H}_2CH$), 1.72-1.25 (m, 16H, $(C\mathbf{H}_2)_4$, $C\mathbf{H}_2C\mathbf{H}_2CH_2CH=CH_2$, $C\mathbf{H}_2C\mathbf{H}_2CH_3$), 1.67 (s, 3H, $(C\mathbf{H}_3)C=CH$), 0.89 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2C\mathbf{H}_3$), 0.86 (s, 9H, $Si(C(C\mathbf{H}_3)_3)$), 0.81 (d, *J* = 7.0 Hz, 3H, $CH(C\mathbf{H}_3)$), 0.01 (s, 3H, $SiC\mathbf{H}_3$), -0.03 (s, 3H, $SiC\mathbf{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 138.8, 132.2, 129.5, 114.5, 111.4, 72.2, 69.6, 68.3, 68.2, 44.9, 44.6, 36.8, 36.0, 35.4, 35.3, 33.7, 25.9, 25.0, 23.5, 23.4, 21.4, 18.5, 18.1, 17.1, 14.0, 10.0, -4.0, -5.0; IR (thin film) 2958, 2934, 2859, 1740, 1460, 1374, 1331, 1239, 1121, 1052, 1024, 909, 836, 775 cm^{-1}; $[\alpha]^{21}_D$ (*c* 0.905, CH_2Cl_2) +10.0°; LRMS (FAB+) *m/z* calc'd for $[M+K]^+$ ($C_{32}H_{58}O_5SiK$) requires 589.37, found 589.45.



(4*R*,8*R*,9*R*,*E*)-8-hydroxy-6-methyl-9-((7*S*,9*R*)-9-(pent-4-enyl)-6,10-dioxaspiro[4.5]decan-7-yl)dec-6-en-4-yl acetate (2). To a solution of ketal **13** (263 mg, 0.477 mmol) in THF (4.8 mL) was added tetrabutylammonium fluoride (1 M in THF, 4.8 mL, 4.8 mmol). The resulting clear, yellow solution was stirred for 40 h at room temperature, diluted with Et_2O (100 mL), and washed with saturated aqueous NH_4Cl (50 mL) and brine (50 mL). The combined aqueous phases were back-extracted with EtOAc (2 × 100 mL). The organic layers were then combined, dried ($MgSO_4$), filtered, and concentrated to give a cloudy, yellow oil. Purification by flash chromatography (column 1: 15% EtOAc/hexanes; columns 2 & 3: 2-10% Et_2O/CH_2Cl_2) afforded alcohol **2** as a clear colorless oil in 62% yield (130 mg, 0.298 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (m, 1H, $C\mathbf{H}=CH_2$), 5.15 (d, *J* = 9.0 Hz, 1H, $(CH_3)C=C\mathbf{H}$), 5.05-4.92 (m, 3H, $CH=C\mathbf{H}_2$, $C\mathbf{H}OAc$), 4.26 (apparent t, *J* = 8.7 Hz, 1H, $C\mathbf{H}OH$), 3.91 (apparent s, 1H, $O\mathbf{H}$), 3.73-3.67 (m, 2H, $C\mathbf{H}CH_2C\mathbf{H}$), 2.27-2.16 (m, 2H, $C\mathbf{H}_2(CH_3)C=CH$), 2.07-2.04 (m, 2H, $C\mathbf{H}_2CH=CH_2$), 2.01 (s, 3H, $OC(O)C\mathbf{H}_3$), 1.92-1.24 (m, 19H, $C\mathbf{H}(CH_3)$, $CHC\mathbf{H}_2CH$, $(C\mathbf{H}_2)_4$, $C\mathbf{H}_2C\mathbf{H}_2CH_2CH=CH_2$, $C\mathbf{H}_2C\mathbf{H}_2CH_3$), 1.70 (s, 3H, $(C\mathbf{H}_3)C=CH$), 0.88 (t, *J* = 7.3 Hz, 3H, $CH_2CH_2C\mathbf{H}_3$), 0.68 (d, *J* = 6.9 Hz, 3H, $CH(C\mathbf{H}_3)$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 138.6, 134.9, 129.2, 114.6, 112.1, 73.5, 72.6, 72.0, 68.2, 44.7, 43.9, 38.0, 36.3, 36.1, 35.8, 35.1, 33.5, 24.8, 23.2, 21.2, 18.5, 17.1, 13.9, 11.3; IR (thin film) 3476 (br), 3076, 2960, 2937, 2874, 1737, 1641, 1434, 1375, 1332, 1239, 1197, 1121, 1021, 983, 910 cm^{-1}; $[\alpha]^{19}_D$ (*c* 1.25, CH_2Cl_2) +20.5°; LRMS (FAB+) *m/z* calc'd for M^+ ($C_{26}H_{44}O_5$) requires 436.32, found 436.37.



(*S*)-7-methylocta-1,7-dien-4-ol (16). To a cooled (-20 °C) solution of allylsilane **15**[3] (436 mg, 785 μmol) in CH_2Cl_2 (7 mL) was added aldehyde **14**[4] (82 μL, 714 μmol) dropwise via syringe. The mixture was then placed in a -20 °C freezer for 29 h (without stirring). The reaction was quenched while cold with HCl (1 M in H_2O, 3 mL) and then stirred vigorously for 15 min while warming to room temperature. The layers were separated, and the aqueous phase was extracted with EtOAc (5 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a clear, yellow oil. Purification by flash chromatography (0-10% Et_2O/pentane) afforded alcohol **16** as a clear, colorless oil in 80% yield (80.3 mg, 573 μmol, 98% *ee*[5]). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (m, 1H, C**H**=CH_2), 5.17-5.12 (m, 2H, CH=C**H$_2$**), 4.72 (s, 2H, (CH_3)C=C**H$_2$**), 3.67 (m, 1H, C**H**OH), 2.37-2.02 (m, 4H, C**H$_2$**CH=CH_2, C**H$_2$**(CH_3)C=CH_2), 1.75 (s, 3H, (C**H$_3$**)C=CH_2), 1.71-1.54 (m, 3H, CH_2C**H$_2$**CHO**H**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 134.7, 117.9, 110.0, 70.4, 41.9, 34.5, 33.9, 22.4; IR (thin film) 3366 (br), 3076, 2972, 2936, 1644, 1444, 1375, 1074, 995, 915, 887 cm^{-1}; $[\alpha]^{21}_D$ (*c* 0.33, CH_2Cl_2) -11.8°; LRMS (APCI+) *m/z* calc'd for $[M+H]^+$ ($C_9H_{17}O$) requires 141.13, found 141.14.



(*S*)-1-methoxy-4-((7-methylocta-1,7-dien-4-yloxy)methyl)benzene (17). A round-bottom flask was charged with a 60% dispersion of sodium hydride in mineral oil (1.95 g, 48.8 mmol); the oil was removed by washing with hexanes (20 mL). THF (30 mL) was then added, and the resulting cloudy white suspension was cooled to 0 °C. A solution of alcohol **16** (5.70 g, 40.7 mmol) in THF (10 mL) was added via syringe, followed by *p*-methoxybenzyl bromide[6] (9.81 g, 48.8 mmol). The reaction mixture was stirred at reflux for 2 h. Upon cooling, the reaction was carefully quenched with saturated aqueous NH_4Cl (100 mL). The layers

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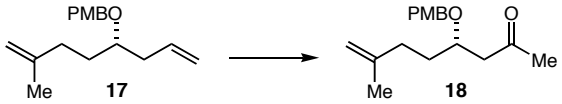
(3) Kubota, K.; Leighton, J. L. *Angew. Chem. Int. Ed.* **2003**, *42*, 946-948.

(4) Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C.; Blake, A. J. *Tetrahedron* **2005**, *61*, 353-363.

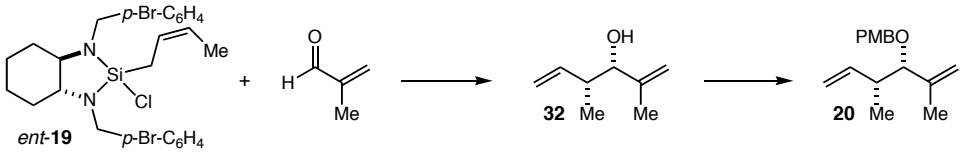
(5) The enantiomeric excess of the homoallylic alcohol was determined by analyzing the corresponding Mosher ester derivative (Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549) by ^{1}H and ^{19}F NMR spectroscopy.

(6) Freshly prepared by combining one part 4-methoxybenzyl alcohol to two parts HBr (48 wt % in H_2O) and two parts Et_2O (by volume). The brown, biphasic mixture was stirred for 2 h at room temperature and then diluted with 2 parts Et_2O. The layers were separated, and the organic phase was washed with 2 parts saturated aqueous NaBr, dried (K_2CO_3), filtered through Celite, and concentrated. For an example, see: Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11054-11080.

were separated, and the aqueous layer was extracted with Et_2O (50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (EtOAc/hexanes) afforded PMB ether **17** in 95% yield (8.75 g, 35.5 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, buried under residual $CHCl_3$, 2H, Ar**H**), 6.88 (d, J = 8.6 Hz, 2H, Ar**H**), 5.85 (m, 1H, C**H**=CH_2), 5.13-5.06 (m, 2H, CH=C**H$_2$**), 4.71 (s, 1H, one of (CH_3)C=C**H$_2$**), 4.68 (s, 1H, one of (CH_3)C=C**H$_2$**), 4.47 (AB quartet, ν_B = 4.52, ν_A = 4.42, J_{AB} = 11.1 Hz, 2H, C**H$_2$**Ar), 3.81 (s, 3H, ArOC**H$_3$**), 3.45 (apparent quint, J = 5.9 Hz, 1H, C**H**OPMB), 2.42-2.27 (m, 2H, C**H$_2$**CH=CH_2), 2.21-2.01 (m, 2H, C**H$_2$**(CH_3)C=CH_2), 1.73 (s, 3H, (C**H$_3$**)C=CH_2), 1.71-1.64 (m, 2H, C**H$_2$**$CH_2(CH_3)$C=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 145.6, 134.8, 131.0, 129.2, 116.8, 113.6, 109.8, 77.7, 70.5, 55.1, 38.2, 33.4, 31.8, 22.4; IR (thin film) 3074, 2935, 2860, 1642, 1613, 1586, 1514, 1442, 1347, 1302, 1248, 1173, 1080, 1037, 914, 887, 821 cm^{-1}; $[\alpha]^{20}_D$ (*c* 1.33, CH_2Cl_2) -20.7°; LRMS (FAB+) *m/z* calc'd for $[M-H]^+$ ($C_{17}H_{23}O_2$) requires 259.17, found 259.24.

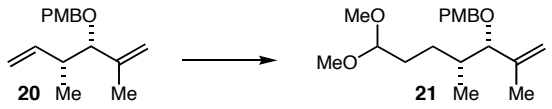


(*S*)-4-(4-methoxybenzyloxy)-7-methyloct-7-en-2-one (18). A round-bottom flask was charged with copper(I) chloride (5.17 g, 52.2 mmol), and a solution of PMB ether **17** (9.06 g, 34.9 mmol) in DMF (230 mL) was added, followed by H_2O (35 mL) and palladium(II) chloride (1.54 g, 8.69 mmol). The reaction mixture was stirred under a balloon of oxygen for 48 h at room temperature and filtered through a pad of Celite over filter paper. The filtrate was diluted with hexanes (500 mL) and brine (100 mL). The layers were separated, and the aqueous layer was extracted with hexanes (5 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (EtOAc/hexanes) afforded ketone **18** in 81% yield (7.81 g, 28.3 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8.6 Hz, 2H, Ar**H**), 6.86 (d, J = 8.6 Hz, 2H, Ar**H**), 4.72 (s, 1H, one of (CH_3)C=C**H$_2$**), 4.69 (s, 1H, one of (CH_3)C=C**H$_2$**), 4.45 (AB quartet, ν_B = 4.47, ν_A = 4.43, J_{AB} = 11.0 Hz, 2H, C**H$_2$**Ar), 3.93 (apparent quint, J = 6.0 Hz, 1H, C**H**OPMB), 3.80 (s, 3H, ArOC**H$_3$**), 2.77 (dd, J = 15.9, 7.2 Hz, 1H, one of C**H$_2$**$C(O)CH_3$), 2.53 (dd, J = 15.9, 5.1 Hz, 1H, one of C**H$_2$**$C(O)CH_3$), 2.17 (s, 3H, C(O)C**H$_3$**), 2.15-2.02 (m, 2H, C**H$_2$**(CH_3)C=CH_2), 1.74 (s, 3H, (C**H$_3$**)C=CH_2), 1.74-1.60 (m, 2H, C**H$_2$**$CH_2(CH_3)$C=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 159.1, 145.3, 130.5, 129.3, 113.7, 110.1, 74.8, 71.2, 55.2, 48.5, 33.2, 32.3, 31.1, 22.4; IR (thin film) 3072, 2935, 2837, 1716, 1648, 1613, 1586, 1514, 1443, 1357, 1302, 1248, 1173, 1088, 1035, 888, 822 cm^{-1}; $[\alpha]^{21}_D$ (*c* 3.66, CH_2Cl_2) +2.6°; LRMS (FAB+) *m/z* calc'd for $[M+H]^+$ ($C_{17}H_{25}O_3$) requires 277.18, found 277.22.

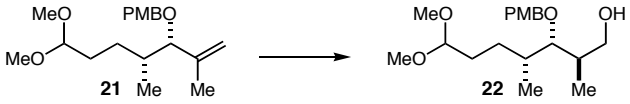


(3*S*,4*R*)-2,4-dimethylhexa-1,5-dien-3-ol (32). To a solution of crotylsilane *ent*-**19**[7] (1.36 g, 9.7 mmol) in CH_2Cl_2 (80 mL) was added methacrolein (1.61 mL, 19.4 mmol) slowly via syringe. After 48 h, the reaction mixture was poured slowly into a flask containing HCl (1 M in H_2O, 100 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (EtOAc/hexanes) afforded alcohol **32** in 61% yield (745 mg, 5.90 mmol, >20:1 *dr*, 88% *ee*[5]). **1-(((3*S*,4*R*)-2,4-dimethylhexa-1,5-dien-3-yloxy)methyl)-4-methoxybenzene (20).** A round-bottom flask was charged with a 60% dispersion of sodium hydride in mineral oil (2.40 g, 60.0 mmol); the oil was removed by washing three times with hexanes. THF (10 mL) was then added, and the resulting cloudy white suspension was cooled to 0 °C. Alcohol **32** (6.31 g, 50.0 mmol) was then cannulated into the reaction as a solution in 10 mL of THF (rinsed 1 × 10 mL), followed by a solution of freshly prepared *p*-methoxybenzyl bromide[6] (12.1 g, 60.0 mmol) in 10 mL of THF (rinsed 1 × 10 mL). The mixture was stirred at reflux for 5.5 h, cooled to 0 °C, and carefully quenched with saturated aqueous NH_4Cl (100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with brine (100 mL), and the brine wash was back-extracted with EtOAc (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a cloudy, yellow oil. Purification by flash chromatography (1% EtOAc/hexanes) afforded PMB ether **20** as a clear, pale yellow oil in 87% yield (10.76 g, 43.7 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.5 Hz, 2H, Ar**H**), 6.87 (d, *J* = 8.7 Hz, 2H, Ar**H**), 5.63 (ddd, *J* = 17.3, 10.3, 7.8 Hz, 1H, C**H**=CH_2), 5.01-4.96 (m, 2H, one of CH=C**H**$_2$, one of (CH_3)C=C**H**$_2$), 4.92 (ddd, *J* = 10.3, 1.7, 0.7 Hz, 1H, one of CH=C**H**$_2$), 4.87 (s, 1H, one of (CH_3)C=C**H**$_2$), 4.45 (d, *J* = 11.4 Hz, 1H, one of C**H**$_2$Ar), 4.17 (d, *J* = 11.5 Hz, 1H, one of C**H**$_2$Ar), 3.81 (s, 3H, OC**H**$_3$), 3.40 (d, *J* = 8.7 Hz, 1H, C**H**OPMB), 2.38 (m, 1H, C**H**(CH_3)), 1.68 (s, 3H, (C**H**$_3$)C=CH_2), 1.09 (d, *J* = 6.6 Hz, 3H, CH(C**H**$_3$)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 143.4, 140.7, 130.8, 129.4, 114.9, 113.7, 113.6, 87.0, 69.6, 55.2, 40.6, 16.9, 16.8; IR (thin film) 2961, 1613, 1514, 1458, 1372, 1302, 1248, 1172, 1069, 1038, 908, 822 cm^{-1}; $[\alpha]^{20}_D$ (*c* 1.00, CH_2Cl_2) -45.2°; LRMS (FAB+) *m/z* calc'd for M^+ ($C_{16}H_{22}O_2$) requires 246.16, found 246.23.

(7) Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375-4377.

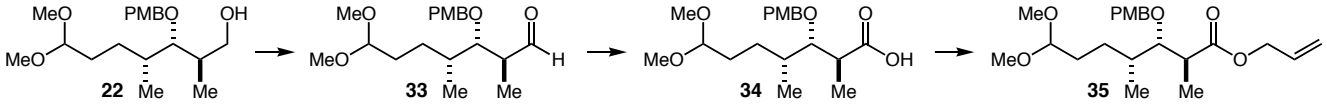


1-(((3*S*,4*R*)-7,7-dimethoxy-2,4-dimethylhept-1-en-3-yloxy)methyl)-4-ethoxybenzene (21). A glass liner for a 600 mL Parr stainless steel high pressure vessel was charged with PMB ether **20** (4.53 g, 18.4 mmol) and 2,2-dimethoxypropane (100 mL). $Rh(acac)(CO)_2$ (95.9 mg, 0.372 mmol), triphenylphosphine (483 mg, 1.84 mmol), and pyridinium *p*-toluenesulfonate (236 mg, 0.939 mmol) were then added. The glass liner was placed in the pressure vessel and the gas inlet/pressure gauge assembly was attached. The pressure vessel was charged and vented three times with a 1:1 mixture of H_2/CO and was then charged to 725 psi H_2/CO. The reaction mixture was then heated in an oil bath set at 60 °C with magnetic stirring. After 56 h, the apparatus was cooled in a dry ice/acetone bath and then vented. Upon warming to room temperature, the reaction mixture was concentrated to give a cloudy, yellow oil. Purification by flash chromatography (5-15% EtOAc/hexanes) afforded dimethyl acetal **21** as a clear, pale yellow oil in 72% yield (4.30 g, 13.3 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H, Ar**H**), 6.86 (d, *J* = 8.7 Hz, 2H, Ar**H**), 5.03 (m, 1H, one of $(CH_3)C{=}C\mathbf{H}_2$), 4.90 (m, 1H, one of $(CH_3)C{=}C\mathbf{H}_2$), 4.45 (d, *J* = 11.4 Hz, 1H, one of $C\mathbf{H}_2Ar$), 4.29 (t, *J* = 5.8 Hz, 1H, $C\mathbf{H}(OCH_3)_2$), 4.15 (d, *J* = 11.4 Hz, 1H, one of $C\mathbf{H}_2Ar$), 3.80 (s, 3H, $ArOC\mathbf{H_3}$), 3.35 (d, *J* = 8.2 Hz, 1H, C**H**OPMB), 3.29 (s, 3H, one of $CH(OC\mathbf{H_3})_2$), 3.28 (s, 3H, one of $CH(OC\mathbf{H_3})_2$), 1.69-1.60 (m, 2H, $C\mathbf{H}(CH_3)$, one of $C\mathbf{H}_2CH(OCH_3)_2$), 1.67 (s, 3H, $(C\mathbf{H_3})C{=}CH_2$), 1.48 (m, 1H, one of $C\mathbf{H}_2CH(OCH_3)_2$), 1.35 (m, 1H, one of $C\mathbf{H}_2CH(CH_3)$), 1.02 (m, 1H, one of $C\mathbf{H}_2CH(CH_3)$), 0.97 (d, *J* = 6.6 Hz, 3H, $CH(C\mathbf{H_3})$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 143.3, 130.9, 129.3, 114.8, 113.6, 104.6, 87.2, 69.7, 55.2, 52.6, 52.3, 34.8, 29.6, 27.7, 17.1, 15.7; IR (thin film) 2954, 2834, 1613, 1586, 1515, 1464, 1375, 1302, 1248, 1173, 1127, 1071, 1038, 902, 822 cm^{-1}; $[\alpha]^{21}_D$ (*c* 1.09, CH_2Cl_2) -29.6°; LRMS (FAB+) *m/z* calc'd for $[M+K]^+$ ($C_{19}H_{30}O_4K$) requires 361.18, found 361.3.



(2*R*,3*S*,4*R*)-7,7-dimethoxy-3-(4-methoxybenzyloxy)-2,4-dimethylheptan-1-ol (22). To a cooled (-78 °C) solution of dimethyl acetal **21** (819 mg, 2.54 mmol; azeotroped twice with benzene) in THF (2.4 mL) was added 9-BBN (0.5 M in THF, 10.2 mL, 5.1 mmol) slowly via syringe. The resulting solution was stirred for 9 h as the dry ice/acetone bath gradually warmed to room temperature. NaOH (3 M in H_2O, 7 mL) was then added slowly followed by ***dropwise addition*** of H_2O_2 (30 wt % in H_2O, 5 mL) (**CAUTION: Exothermic!**). The mixture was allowed to cool to room temperature while stirring under a reflux condenser. After 1 h, the reaction mixture was diluted with Et_2O (40 mL) and brine (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic layers were dried

($MgSO_4$), filtered, and concentrated to give a cloudy pale yellow oil. Purification by flash chromatography (10% Et_2O/CH_2Cl_2) afforded alcohol **22** as a cloudy, pale yellow oil in 87% yield (750 mg, 2.20 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.6 Hz, 2H, Ar**H**), 6.87 (d, J = 8.6 Hz, 2H, Ar**H**), 4.54 (AB quartet, ν_B = 4.59, ν_A = 4.50, J_{AB} = 10.6 Hz, 2H, C**H**$_2$Ar), 4.34 (t, J = 5.5 Hz, 1H, C**H**$(OCH_3)_2$), 3.79 (s, 3H, ArOC**H**$_3$), 3.63-3.59 (m, 2H, C**H**$_2$OH), 3.33 (s, 3H, one of CH(OC**H**$_3)_2$), 3.32 (s, 3H, one of CH(OC**H**$_3)_2$), 3.26 (dd, J = 7.4, 3.5 Hz, 1H, C**H**OPMB), 2.78 (br s, 1H, O**H**), 1.91 (m, 1H, C**H**$(CH_3)CH_2OH$), 1.75-1.66 (m, 2H, CH_2CH_2C**H**(CH_3), one of C**H**$_2CH_2CH(CH_3)$), 1.64-1.50 (m, 2H, one of C**H**$_2CH_2CH(CH_3)$, one of CH_2C**H**$_2CH(CH_3)$), 1.36 (m, 1H, one of CH_2C**H**$_2CH(CH_3)$), 0.97 (d, J = 6.8 Hz, 3H, CH_2CH_2CH(C**H**$_3$)), 0.94 (d, J = 7.0 Hz, 3H, CH(C**H**$_3)CH_2OH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 130.3, 129.1, 113.7, 104.6, 87.8, 74.8, 66.4, 55.2, 52.9, 52.7, 37.7, 36.1, 30.8, 29.4, 15.6, 14.5; IR (thin film) 3448 (br), 2958, 2834, 1613, 1586, 1515, 1464, 1384, 1302, 1249, 1174, 1124, 1036, 984, 953, 823 cm^{-1}; $[\alpha]^{20}_D$ (*c* 1.17, CH_2Cl_2) +12.5°; LRMS (FAB+) *m/z* calc'd for $[M+Na]^+$ ($C_{19}H_{32}O_5Na$) requires 363.21, found 363.3.

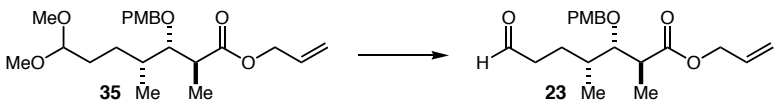


(2*S*,3*S*,4*R*)-allyl 7,7-dimethoxy-3-(4-methoxybenzyloxy)-2,4-dimethylheptanoate (35). To a cooled (-78 °C) solution of oxalyl chloride (0.49 mL, 5.62 mmol) in CH_2Cl_2 (10 mL) was added dimethyl sulfoxide (0.94 mL, 13.2 mmol) slowly via syringe, with concomitant gas evolution. After stirring for 10 min at -78 °C, a solution of alcohol **22** (748 mg, 2.20 mmol) in CH_2Cl_2 (10 mL) was added via cannula (rinsed 2 × 5 mL). The resulting cloudy, white reaction mixture was stirred for 15 min at -78 °C. Triethylamine (2.2 mL, 15.8 mmol) was then added, and the mixture was stirred for another 3 h at -78 °C. The reaction was quenched while cold with saturated aqueous $NaHCO_3$ (20 mL) and was allowed to warm to room temperature with vigorous stirring. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered through a silica plug, and rinsed through with 1:1 EtOAc/CH_2Cl_2 (3 × 20 mL). The filtrate was concentrated to give aldehyde **33** as a cloudy, yellow oil. The crude aldehyde (prone to epimerization) was carried immediately into the next step without further purification.

To a solution of crude aldehyde **33** in *t*-butanol (44 mL) was added 2-methyl-2-butene (15 mL, 142 mmol). A clear, yellow solution of sodium chlorite (technical grade, 80%; 2.49 g, 22.0 mmol) and sodium dihydrogen phosphate (1.87 g, 15.5 mmol) in H_2O (22 mL) was added. The yellow, biphasic mixture was stirred at room temperature for 1 h, diluted with Et_2O (60 mL), and poured into H_2O (60 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 60 mL). The combined organic layers

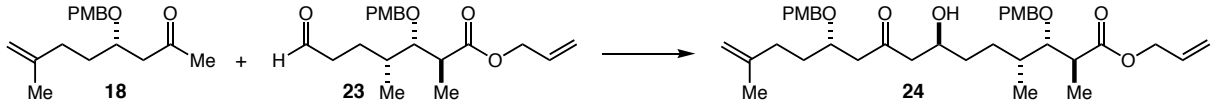
were dried ($MgSO_4$), filtered, and concentrated to give carboxylic acid **34** as a cloudy, yellow oil. The crude carboxylic acid was taken directly into the next step without further purification.

To a solution of crude carboxylic acid **34** in dry acetone (21 mL) was added potassium carbonate (608 mg, 4.40 mmol) and allyl bromide (0.85 mL, 10.0 mmol). The reaction mixture was stirred at reflux for 2 h. Upon cooling, the volatiles were removed on a rotary evaporator. The residue was resuspended in EtOAc (120 mL), washed with $KHSO_4$ (0.1 M in H_2O, 60 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated to give a cloudy, yellow oil. Purification by flash chromatography (15% EtOAc/hexanes) afforded allyl ester **35** as a clear, pale yellow oil in 86% overall yield over three steps (745 mg, 1.79 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.6 Hz, 2H, Ar**H**), 6.84 (d, J = 8.6 Hz, 2H, Ar**H**), 5.89 (m, 1H, C**H**=CH_2), 5.30 (dd, J = 17.2, 1.5 Hz, 1H, CH_2CH=C$\mathbf{H}_{trans}$), 5.20 (dd, J = 10.4, 1.3 Hz, 1H, CH_2CH=C$\mathbf{H}_{cis}$), 4.60-4.51 (m, 2H, C$\mathbf{H}_2$CH=CH_2), 4.48 (s, 2H, C$\mathbf{H}_2$Ar), 4.32 (t, J = 5.6 Hz, 1H, C**H**$(OCH_3)_2$), 3.79 (s, 3H, ArOC$\mathbf{H}_3$), 3.63 (dd, J = 9.0, 2.6 Hz, 1H, C**H**OPMB), 3.32 (s, 3H, one of CH(OC$\mathbf{H}_3)_2$), 3.32 (s, 3H, one of CH(OC$\mathbf{H}_3)_2$), 2.78 (m, 1H, C**H**$(CH_3)CO_2CH_2$), 1.71-1.46 (m, 4H, CH_2C**H**(CH_3), C$\mathbf{H}_2$CH$(OCH_3)_2$, one of C$\mathbf{H}_2$CH(CH_3)), 1.36 (m, 1H, one of C$\mathbf{H}_2$CH(CH_3)), 1.11 (d, J = 7.1 Hz, 3H, CH(C$\mathbf{H}_3)CO_2CH_2$), 0.91 (d, J = 6.8 Hz, 3H, CH_2CH(C$\mathbf{H}_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 158.9, 132.1, 131.0, 129.0, 118.3, 113.5, 104.6, 84.1, 74.2, 65.1, 55.2, 52.8, 52.6, 43.3, 34.8, 30.7, 29.3, 14.3, 13.3; IR (thin film) 2952, 2834, 1733, 1613, 1515, 1460, 1380, 1302, 1249, 1175, 1127, 1056, 1036, 983, 822 cm^{-1}; $[\alpha]^{24}_D$ (*c* 1.11, CH_2Cl_2) +3.1°; LRMS (FAB+) *m/z* calc'd for $[M+K]^+$ ($C_{22}H_{34}O_6K$) requires 433.2, found 433.3.



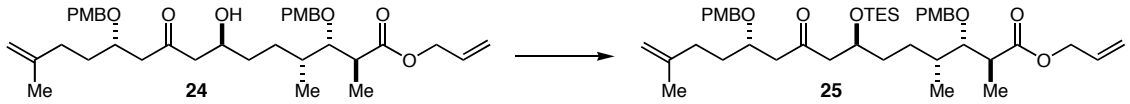
(2*S*,3*S*,4*R*)-allyl 3-(4-methoxybenzyloxy)-2,4-dimethyl-7-oxoheptanoate (23). To a solution of allyl ester **35** (530 mg, 1.34 mmol) in acetone (10 mL) and H_2O (2 mL) was added pyridinium *p*-toluenesulfonate (86.2 mg, 343 mmol). The reaction mixture was stirred at reflux for 1 h. Upon cooling, the mixture was diluted with EtOAc (30 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL). The aqueous wash was back-extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a cloudy, yellow oil. Purification by flash chromatography (15% EtOAc/hexanes) afforded aldehyde **23** as a clear, pale yellow oil in 92% yield (433 mg, 1.24 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (t, J = 1.6 Hz, 1H, C**H**O), 7.20 (d, J = 8.6 Hz, 2H, Ar**H**), 6.84 (d, J = 8.7 Hz, 2H, Ar**H**), 5.89 (m, 1H, C**H**=CH_2), 5.31 (dd, J = 17.2, 1.5 Hz, 1H, CH_2CH=C$\mathbf{H}_{trans}$), 5.21 (dd, J = 10.4, 1.2 Hz, 1H, CH_2CH=C$\mathbf{H}_{cis}$), 4.61-4.54 (m, 2H, C$\mathbf{H}_2$CH=CH_2), 4.48 (AB quartet, ν_B = 4.51, ν_A = 4.44, J_{AB} = 10.7 Hz, 2H, C$\mathbf{H}_2$Ar), 3.79 (s, 3H, ArOC$\mathbf{H}_3$), 3.63 (dd, J = 9.0, 2.5 Hz, 1H, C**H**OPMB), 2.79 (m, 1H, C**H**$(CH_3)CO_2CH_2$), 2.54-2.37 (m, 2H, C$\mathbf{H}_2$CHO), 1.77 (m, 1H, one of C$\mathbf{H}_2CH_2$CHO), 1.70-1.58 (m, 2H, CH_2C**H**(CH_3), one of

C**H**$_2$CH$_2$CHO), 1.11 (d, J = 7.1 Hz, 3H, CH(C**H$_3$**)CO$_2$CH$_2$), 0.92 (d, J = 6.6 Hz, 3H, CH$_2$CH(C**H$_3$**)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 175.3, 159.0, 132.1, 130.8, 129.1, 118.3, 113.6, 83.7, 74.1, 65.1, 55.2, 43.2, 41.9, 34.3, 26.5, 14.2, 13.1; IR (thin film) 2939, 2837, 2723, 1728, 1613, 1515, 1460, 1380, 1302, 1248, 1176, 1061, 1035, 936, 822 cm^{-1}; $[\alpha]^{20}_{D}$ (*c* 1.07, CH_2Cl_2) +4.1°; LRMS (FAB+) *m/z* calc'd for $[M-H]^+$ ($C_{20}H_{27}O_5$) requires 347.19, found 347.26.

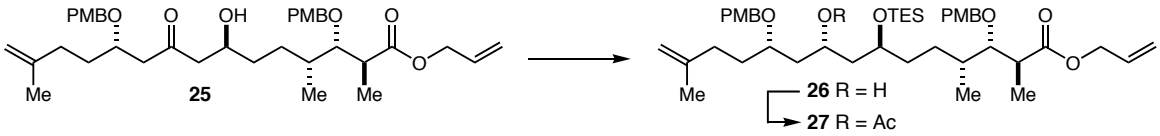


(2*S*,3*S*,4*R*,7*S*,11*S*)-allyl 7-hydroxy-3,11-bis(4-methoxybenzyloxy)-2,4,14-trimethyl-9-oxopentadec-14-enoate (24). To a cooled (-78 °C) solution of ketone **18** (304 mg, 1.10 mmol; azeotroped three times with benzene) and diisopropylethylamine (0.22 mL, 1.26 mmol) in Et_2O (7 mL) was added freshly distilled dibutylboron triflate (0.3 mL, 1.19 mmol) dropwise via syringe. The resulting cloudy, pale yellow mixture was stirred at -78 °C for 30 min. The mixture was then cooled to -110 °C (Et_2O/liquid N_2), and a solution of aldehyde **23** (425 mg, 1.22 mmol) in Et_2O (2 mL) (pre-cooled to -110 °C) was added dropwise via cannula (rinsed 2 × 1 mL). After stirring for 1 h at -110 °C, the reaction was quenched by the addition of a pH 7 buffer/MeOH (1:6 v/v, 7 mL) solution. The reaction flask was then transferred to a 0 °C bath, and a 30 wt % H_2O_2/MeOH (1:2 v/v, 3 mL) solution was added. The mixture was stirred for 1 h while warming to room temperature and was then poured into Et_2O (50 mL) and H_2O (50 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (50 mL), and the aqueous $NaHCO_3$ wash was back-extracted with EtOAc (3 × 25 mL). All the organic layers were then combined, washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated to give a cloudy, yellow oil. Purification by flash chromatography (5% Et_2O/CH_2Cl_2) afforded β-hydroxy ketone **24** as a clear, yellow oil in 79% yield (543 mg, 0.869 mmol, 10:1 mixture of diastereomers). ^{1}H NMR (500 MHz, C_6D_6) δ 7.31 (d, J = 8.5 Hz, 2H, Ar**H**), 7.23 (d, J = 8.6 Hz, 2H, Ar**H**), 6.82-6.78 (m, 4H, Ar**H**), 5.74 (m, 1H, C**H**=CH$_2$), 5.12 (dd, J = 17.2, 1.5 Hz, 1H, CH$_2$CH=C**H$_{trans}$**), 4.94 (dd, J = 10.4, 1.2 Hz, 1H, CH$_2$CH=C**H$_{cis}$**), 4.81 (s, 2H (CH$_3$)C=C**H$_2$**), 4.63 (AB quartet, ν_B = 4.69, ν_A = 4.56, J_{AB} = 10.9 Hz, 2H, C**H$_2$**Ar), 4.54-4.44 (m, 2H, C**H$_2$**CH=CH$_2$), 4.35 (AB quartet, ν_B = 4.38, ν_A = 4.33, J_{AB} = 11.1 Hz, 2H, C**H$_2$**Ar), 3.99-3.90 (m, 2H, C**H**OH, C$^{(11)}$**H**OPMB), 3.74 (dd, J = 8.9, 2.6 Hz, 1H, C$^{(3)}$**H**OPMB), 3.30 (s, 6H, 2 × ArOC**H$_3$**), 2.94 (d, J = 3.4 Hz, 1H, O**H**), 2.89 (m, 1H, C**H**(CH$_3$)CO$_2$CH$_2$), 2.49 (dd, J = 15.6, 7.7 Hz, 1H, one of O=CC**H$_2$**CHOPMB), 2.27-2.17 (m, 2H, O=CC**H$_2$**CHOH), 2.12 (dd, J = 15.6, 4.6 Hz, 1H, one of O=CC**H$_2$**CHOPMB), 2.04 (t, J = 7.9 Hz, 2H, C**H$_2$**(CH$_3$)C=CH$_2$), 1.77-1.55 (m, 4H, CH$_2$C**H**(CH$_3$), C**H$_2$**CH$_2$(CH$_3$)C=CH$_2$, one of C**H$_2$**CH(CH$_3$)), 1.65 (s, 3H, (C**H$_3$**)C=CH$_2$), 1.41 (m, 1H, one of

C**H**$_2$CH$_2$CH(CH$_3$)), 1.33-1.26 (m, 2H, one of C**H**$_2$CH(CH$_3$), one of C**H**$_2$CH$_2$CH(CH$_3$)), 1.04 (d, *J* = 7.1 Hz, 3H, CH(C**H**$_3$)CO$_2$CH$_2$), 0.94 (d, *J* = 6.8 Hz, 3H, CH$_2$CH(C**H**$_3$)); ^{13}C NMR (100 MHz, CDCl$_3$) δ 210.9, 175.6, 159.2, 158.9, 145.1, 132.1, 131.1, 130.3, 129.4, 129.0, 118.3, 113.7, 113.5, 110.2, 84.2, 74.9, 74.3, 71.3, 67.7, 65.1, 55.2, 50.5, 48.2, 43.3, 34.9, 34.5, 33.1, 32.1, 30.3, 22.4, 14.4, 13.3; IR (thin film) 3504 (br), 2937, 1731, 1613, 1515, 1459, 1376, 1302, 1248, 1174, 1035, 822 cm^{-1}; $[\alpha]^{19}_{D}$ (*c* 1.15, CH$_2$Cl$_2$) +15.8°; LRMS (FAB+) *m/z* calc'd for [M-H]$^+$ (C$_{37}$H$_{51}$O$_8$) requires 623.36, found 623.3.



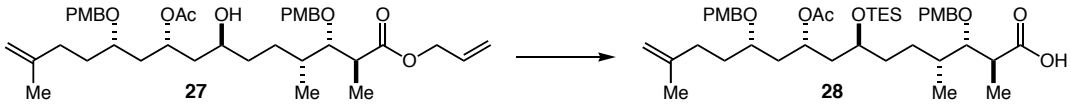
(2*S*,3*S*,4*R*,7*S*,11*S*)-allyl 3,11-bis(4-methoxybenzyloxy)-2,4,14-trimethyl-9-oxo-7-(triethylsilyloxy)pentadec-14-enoate (25). To a solution of β-hydroxy ketone **24** (530 mg, 0.848 mmol, 10:1 mixture of diastereomers) and imidazole (233 mg, 3.43 mmol) in CH$_2$Cl$_2$ (17 mL) was added chlorotriethylsilane (0.5 mL, 2.98 mmol). Immediate formation of a white precipitate was observed, and the heterogeneous mixture was stirred at room temperature. Additional portions of imidazole (233 mg, 3.43 mmol) and chlorotriethylsilane (0.5 mL, 2.98 mmol) were added at 4 h and 8 h. After a total reaction time of 19 h, saturated aqueous NH$_4$Cl (20 mL) was added, and the layers were separated. The aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 20 mL), and the combined organic layers were dried (MgSO$_4$), filtered, and concentrated to give a clear, pale yellow oil. Purification by flash chromatography (10% EtOAc/hexanes) afforded ketone **25** as a clear, pale yellow oil in 94% yield (590 mg, 0.798 mmol, 10:1 mixture of diastereomers). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.23 (d, *J* = 8.6 Hz, 2H, Ar**H**), 7.19 (d, *J* = 8.6 Hz, 2H, Ar**H**), 6.84 (apparent t, *J* = 8.4 Hz, 4H, Ar**H**), 5.88 (m, 1H, C**H**=CH$_2$), 5.29 (dd, *J* = 17.2, 1.5 Hz, 1H, CH$_2$CH=C**H**$_{\mathbf{trans}}$), 5.19 (dd, *J* = 10.4, 1.2 Hz, 1H, CH$_2$CH=C**H**$_{\mathbf{cis}}$), 4.71 (s, 1H one of (CH$_3$)C=C**H**$_2$), 4.68 (s, 1H one of (CH$_3$)C=C**H**$_2$), 4.60-4.50 (m, 2H, C**H**$_2$CH=CH$_2$), 4.47 (s, 2H, C**H**$_2$Ar), 4.43 (s, 2H, C**H**$_2$Ar), 4.17 (apparent br quint, *J* = 5.3 Hz, 1H, C**H**OTES), 3.93 (apparent quint, *J* = 6.0 Hz, 1H, C$^{(11)}$**H**OPMB), 3.78 (s, 6H, 2 × ArOC**H**$_3$), 3.60 (dd, *J* = 9.2, 2.1 Hz, 1H, C$^{(3)}$**H**OPMB), 2.81-2.45 (m, 5H, C**H**(CH$_3$)CO$_2$CH$_2$, C**H**$_2$C(O)C**H**$_2$), 2.11-2.03 (m, 2H, C**H**$_2$(CH$_3$)C=CH$_2$), 1.72 (s, 3H, (C**H**$_3$)C=CH$_2$), 1.70-1.26 (m, 7H, C**H**$_2$C**H**$_2$C**H**(CH$_3$), C**H**$_2$CH$_2$(CH$_3$)C=CH$_2$), 1.10 (d, *J* = 7.1 Hz, 3H, CH(C**H**$_3$)CO$_2$CH$_2$), 0.93 (t, *J* = 7.9 Hz, 9H, Si(CH$_2$C**H**$_3$)$_3$), 0.90 (d, *J* = 6.7 Hz, 3H, CH$_2$CH(C**H**$_3$)), 0.58 (q, *J* = 7.9 Hz, 6H, Si(C**H**$_2$CH$_3$)$_3$)); ^{13}C NMR (100 MHz, CDCl$_3$) δ 208.2, 175.6, 159.1, 158.9, 145.3, 132.2, 131.1, 130.6, 129.3, 128.9, 118.2, 113.7, 113.5, 110.0, 84.5, 74.6, 74.4, 71.3, 68.7, 65.1, 55.2, 51.4, 49.2, 43.4, 36.0, 35.1, 33.2, 32.4, 30.2, 22.5, 14.4, 13.2, 6.9, 4.9; IR (thin film) 2953, 2877, 1736, 1613, 1515, 1459, 1376, 1302, 1248, 1174, 1086, 1037, 822, 744 cm^{-1}; $[\alpha]^{22}_{D}$ (*c* 1.30, CH$_2$Cl$_2$) +7.8°; LRMS (FAB+) *m/z* calc'd for [M-H]$^+$ (C$_{43}$H$_{65}$O$_8$Si) requires 737.44, found 737.50.



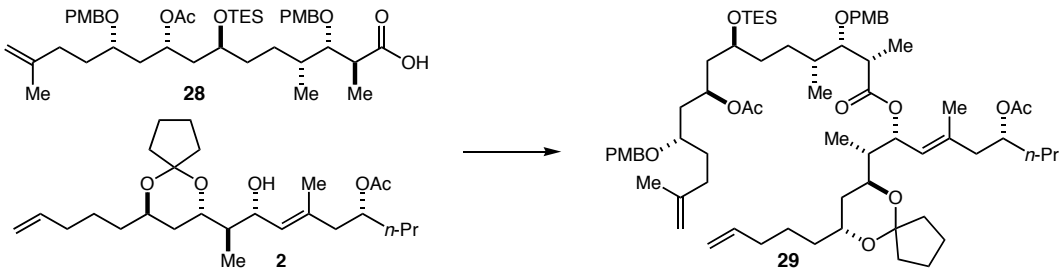
(2*S*,3*S*,4*R*,7*S*,9*S*,11*S*)-allyl 9-acetoxy-3,11-bis(4-methoxybenzyloxy)-2,4,14-trimethyl-7-(triethylsilyloxy)pentadec-14-enoate (27). To a cooled (-78 °C) solution of ketone **25** (584 mg, 0.791 mmol, 10:1 mixture of diastereomers) in CH_2Cl_2 (14 mL) was added L-Selectride (1 M in THF, 1.6 mL, 1.6 mmol) along the side of the flask slowly via syringe. After stirring for 40 min at -78 °C, the reaction was quenched by successive addition of MeOH (1 mL), NaOH (1 M in H_2O, 7 mL), and H_2O_2 (30 wt % in H_2O). The mixture was allowed to warm to room temperature while stirring vigorously and was then diluted with EtOAc (50 mL) and brine (25 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (4 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a cloudy pale yellow oil. Purification by flash chromatography (2% Et_2O/CH_2Cl_2) afforded alcohol **26** as an inseparable mixture of multiple diastereomers, which was taken directly into the next step.

To a solution of alcohol **26** and pyridine (1.9 mL, 23.5 mmol) in CH_2Cl_2 (12 mL) was added acetic anhydride (1.1 mL, 11.7 mmol) and 4-dimethylaminopyridine (9.5 mg, 77.8 μmol). After stirring for 18 h at room temperature, saturated aqueous NH_4Cl (15 mL) was added, and the layers were separated. The aqueous phase was extracted with EtOAc (4 × 15 mL), and the combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated to give a clear, pale yellow oil. Purification by flash chromatography (0-3% EtOAc/CH_2Cl_2) afforded allyl ester **27** as a clear, golden yellow oil in 51% overall yield over two steps (317 mg, 0.405 mmol, single diastereomer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, buried under residual $CHCl_3$, 2H, Ar**H**), 7.19 (d, *J* = 8.6 Hz, 2H, Ar**H**), 6.86 (d, *J* = 8.7 Hz, 2H, Ar**H**), 6.83 (d, *J* = 8.7 Hz, 2H, Ar**H**), 5.88 (m, 1H, C**H**=CH_2), 5.29 (dd, *J* = 17.2, 1.5 Hz, 1H, CH_2CH=C$\mathbf{H}_{\mathbf{trans}}$), 5.19 (dd, *J* = 10.4, 1.2 Hz, 1H, CH_2CH=C$\mathbf{H}_{\mathbf{cis}}$), 5.11 (m, 1H, C**H**OAc), 4.69 (s, 1H one of (CH_3)C=C$\mathbf{H}_2$), 4.66 (s, 1H one of (CH_3)C=C$\mathbf{H}_2$), 4.60-4.50 (m, 2H, C$\mathbf{H}_2$CH=CH_2), 4.48 (s, 2H, C$\mathbf{H}_2$Ar), 4.41 (s, 2H, C$\mathbf{H}_2$Ar), 3.79 (s, 3H, ArOC$\mathbf{H}_3$), 3.78 (s, 3H, ArOC$\mathbf{H}_3$), 3.72 (m, 1H, C**H**OTES), 3.61 (dd, *J* = 9.1, 2.4 Hz, 1H, C$^{(3)}$**H**OPMB), 3.45 (apparent quint, *J* = 5.8 Hz, 1H, C$^{(11)}$**H**OPMB), 2.77 (m, 1H, C**H**$(CH_3)CO_2CH_2$), 2.14-1.95 (m, 3H, C$\mathbf{H}_2(CH_3)$C=CH_2, one of CH(OAc)C$\mathbf{H}_2$CH(OPMB)), 1.98 (s, 3H, OC(O)C$\mathbf{H}_3$), 1.76-1.26 (m, 10H, one of CH(OAc)C$\mathbf{H}_2$CH(OPMB), CH(OAc)C$\mathbf{H}_2$CH(OTES), C$\mathbf{H}_2$C$\mathbf{H}_2$C**H**(CH_3), C$\mathbf{H}_2CH_2(CH_3)$C=CH_2), 1.71 (s, 3H, (C$\mathbf{H}_3$)C=CH_2), 1.11 (d, *J* = 7.1 Hz, 3H, CH(C$\mathbf{H}_3$)CO_2CH_2), 0.94 (t, *J* = 7.9 Hz, 9H, Si$(CH_2C\mathbf{H}_3)_3$), 0.91 (d, *J* = 6.8 Hz, 3H, CH_2CH(C$\mathbf{H}_3$)), 0.58 (q, *J* = 7.9 Hz, 6H, Si$(C\mathbf{H}_2CH_3)_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 170.4, 159.0, 158.9, 145.6, 132.1, 131.0, 130.8, 129.3, 128.9, 118.3, 113.7, 113.6, 109.8, 84.6, 75.2, 74.4, 70.0, 69.8, 69.1, 65.1, 55.2, 43.4, 42.1, 39.2, 36.2, 35.2, 33.2, 31.8, 29.7, 22.5, 21.3, 14.4, 13.3, 7.0, 5.1; IR

(thin film) 2953, 2877, 1736, 1613, 1514, 1458, 1374, 1302, 1247, 1174, 1037, 821, 744 cm^{-1}; $[\alpha]^{22}_D$ (*c* 1.98, CH_2Cl_2) +11.9°; LRMS (FAB+) *m/z* calc'd for $[M-H]^+$ ($C_{45}H_{69}O_9Si$) requires 781.47, found 781.34.

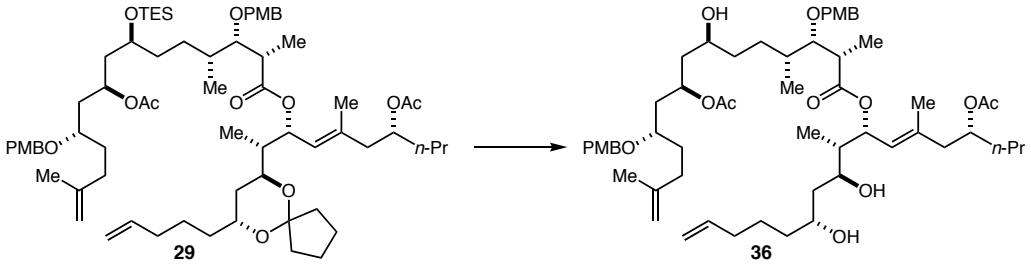


(2*S*,3*S*,4*R*,7*S*,9*S*,11*S*)-9-acetoxy-3,11-bis(4-methoxybenzyloxy)-2,4,14-trimethyl-7-(triethylsilyloxy)pentadec-14-enoic acid (28). To a solution of allyl ester **27** (308 mg, 0.393 mmol) in THF (5.4 mL) was added a solution of $Pd(PPh_3)_4$ (45.4 mg, 39.3 μmol) in THF (2 mL) via cannula (rinsed 2 × 0.5 mL) followed by freshly distilled morpholine (0.4 mL, 4.59 mmol). After stirring for 2 h at room temperature, the volatiles were removed on a rotary evaporator. The resulting cloudy, yellow oil was dissolved in CH_2Cl_2 (80 mL) and washed with $KHSO_4$ (0.1 M in H_2O, 40 mL) and brine (40 mL). The brine wash was back-extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a clear, yellow oil. Purification by flash chromatography (5-20% acetone/hexanes) afforded carboxylic acid **28** as a clear, yellow oil in 92% yield (270 mg, 0.364 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, buried under residual $CHCl_3$, 2H, Ar**H**), 7.25 (d, *J* = 8.6 Hz, 2H, Ar**H**), 6.90-6.86 (m, 4H, Ar**H**), 5.13 (m, 1H, C**H**OAc), 4.72 (s, 1H one of $(CH_3)C=C\mathbf{H}_2$), 4.69 (s, 1H one of $(CH_3)C=C\mathbf{H}_2$), 4.58 (AB quartet, ν_B = 4.60, ν_A = 4.56, J_{AB} = 10.6 Hz, 2H, C$\mathbf{H}_2$Ar), 4.45 (s, 2H, C$\mathbf{H}_2$Ar), 3.82 (s, 3H, ArOC$\mathbf{H}_3$), 3.81 (s, 3H, ArOC$\mathbf{H}_3$), 3.74 (m, 1H, C**H**OTES), 3.53 (dd, *J* = 6.4, 3.9 Hz, 1H, C$^{(3)}$**H**OPMB), 3.47 (apparent quint, *J* = 5.8 Hz, 1H, C$^{(11)}$**H**OPMB), 2.79 (apparent quint, *J* = 7.0 Hz, 1H, C**H**$(CH_3)CO_2CH_2$), 2.17-1.97 (m, 3H, C$\mathbf{H}_2(CH_3)C=CH_2$, one of CH(OAc)C$\mathbf{H}_2$CH(OPMB)), 2.01 (s, 3H, OC(O)C$\mathbf{H}_3$), 1.79-1.27 (m, 10H, one of CH(OAc)C$\mathbf{H}_2$CH(OPMB), CH(OAc)C$\mathbf{H}_2$CH(OTES), C$\mathbf{H}_2$C$\mathbf{H}_2$C**H**(CH_3), C$\mathbf{H}_2CH_2(CH_3)C=CH_2$), 1.74 (s, 3H, (C$\mathbf{H}_3$)$C=CH_2$), 1.24 (d, *J* = 7.2 Hz, 3H, CH(C$\mathbf{H}_3$)CO_2CH_2), 0.99-0.95 (m, 12H, $Si(CH_2C\mathbf{H}_3)_3$, $CH_2CH(C\mathbf{H}_3)$), 0.61 (q, *J* = 7.9 Hz, 6H, $Si(C\mathbf{H}_2CH_3)_3$)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 170.5, 159.1, 159.0, 145.6, 130.8, 130.3, 129.3, 129.2, 113.7, 109.9, 84.5, 75.2, 74.5, 69.9, 69.8, 69.0, 55.22, 55.16, 43.0, 42.0, 39.1, 36.0, 35.6, 33.1, 31.7, 29.3, 22.5, 21.3, 14.7, 13.7, 7.0, 5.1; IR (thin film) 2953, 2877, 1736, 1708, 1613, 1514, 1459, 1374, 1302, 1248, 1174, 1037, 821, 744 cm^{-1}; $[\alpha]^{21}_D$ (*c* 1.80, CH_2Cl_2) +12.5°; LRMS (FAB+) *m/z* calc'd for $[M-H]^+$ ($C_{42}H_{65}O_9Si$) requires 741.44, found 741.56.

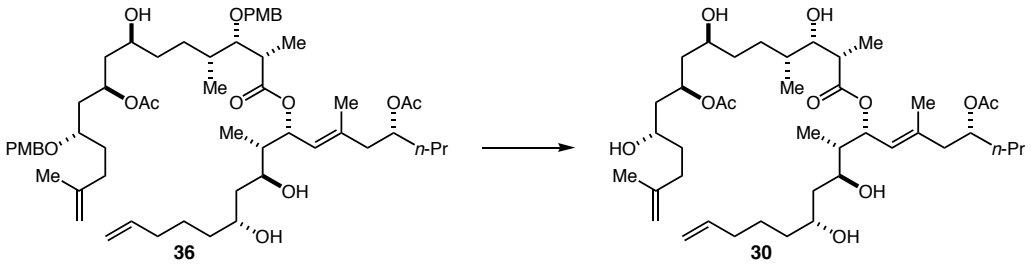


(2*S*,3*S*,4*R*,7*S*,9*S*,11*S*)-((2*S*,3*R*,7*R*,*E*)-7-acetoxy-5-methyl-2-((7*S*,9*R*)-9-(pent-4-enyl)-6,10-dioxaspiro[4.5]decan-7-yl)dec-4-en-3-yl) 9-acetoxy-3,11-bis(4-methoxybenzyloxy)-2,4,14-trimethyl-7-(triethylsilyloxy)pentadec-14-enoate (29). To a cooled (-78 °C) solution of alcohol **2** (12.5 mg, 28.6 μmol), carboxylic acid **28** (23.4 mg, 31.5 μmol), and 4-dimethylaminopyridine (177 mg, 1.45 mmol) in toluene (5.6 mL, distilled from calcium hydride) was added triethylamine (90 μL, 0.646 mmol), followed by 2,4,6-trichlorobenzoyl chloride (0.1 mL, 0.640 mmol). The resulting thick, heterogeneous, white slurry was stirred for 21 h as the dry ice/acetone bath warmed to approximately -65 °C. The reaction flask was then placed at -42 °C and stirred for 3.5 h as the dry ice/acetonitrile bath warmed to 0 °C. After stirring for another 2 h at 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ (6 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 6 mL). The combined organic layers were washed with brine (6 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (3% EtOAc/CH_2Cl_2) afforded ester **29** as a clear, colorless oil in 74% yield (24.7 mg, 21.3 μmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.5 Hz, 2H, Ar**H**), 7.17 (d, J = 8.5 Hz, 2H, Ar**H**), 6.85 (d, J = 8.6 Hz, 2H, Ar**H**), 6.81 (d, J = 8.6 Hz, 2H, Ar**H**), 5.79 (m, 1H, C**H**=CH_2), 5.69 (dd, J = 9.7, 5.3 Hz, 1H, $CH(CH_3)CO_2CH$), 5.17 (d, J = 9.8 Hz, 1H, $(CH_3)C$=C**H**), 5.11 (m, 1H, $C^{(9)}$**H**OAc), 5.01-4.93 (m, 3H, CH=C$\mathbf{H_2}$, $C^{(27)}$**H**OAc), 4.69 (s, 1H, one of $(CH_3)C$=C$\mathbf{H_2}$), 4.65 (s, 1H, one of $(CH_3)C$=C$\mathbf{H_2}$), 4.44 (AB quartet, ν_B = 4.50, ν_A = 4.38, J_{AB} = 10.9 Hz, 2H, C$\mathbf{H_2}$Ar), 4.40 (s, 2H, C$\mathbf{H_2}$Ar), 3.78 (s, 3H, ArOC$\mathbf{H_3}$), 3.77 (s, 3H, ArOC$\mathbf{H_3}$), 3.70-3.65 (m, 2H, C**H**OTES, $C^{(19)}$**H**), 3.59 (dd, J = 9.1, 2.0 Hz, 1H, $C^{(3)}$**H**OPMB), 3.53 (m, 1H, $C^{(21)}$**H**), 3.43 (apparent quint, J = 5.8 Hz, 1H, $C^{(11)}$**H**OPMB), 2.69 (m, 1H, $C^{(2)}$**H**(CH_3)), 2.15-1.94 (m, 8H, C$\mathbf{H_2}(CH_3)$C=CH, C$\mathbf{H_2}(CH_3)$C=CH2, C$\mathbf{H_2}$CH=CH_2, $C^{(22)}$**H**(CH_3), one of $C^{(10)}\mathbf{H_2}$), 2.00 (s, 3H, OC(O)C$\mathbf{H_3}$), 1.97 (s, 3H, OC(O)C$\mathbf{H_3}$), 1.82-1.20 (m, 28H, $C^{(4)}$**H**(CH_3), $C^{(5)}\mathbf{H_2}$, $C^{(6)}\mathbf{H_2}$, $C^{(8)}\mathbf{H_2}$, one of $C^{(10)}\mathbf{H_2}$, $C^{(12)}\mathbf{H_2}$, $C^{(17)}\mathbf{H_2}$, $C^{(18)}\mathbf{H_2}$, $C^{(20)}\mathbf{H_2}$, $C^{(28)}\mathbf{H_2}$, $C^{(29)}\mathbf{H_2}$, $(C\mathbf{H_2})_4$), 1.74 (s, 3H, (C$\mathbf{H_3}$)C=CH), 1.71 (s, 3H, (C$\mathbf{H_3}$)C=CH_2), 1.07 (d, J = 7.1 Hz, 3H, $C^{(2)}$H(C$\mathbf{H_3}$)), 0.93 (t, J = 7.9 Hz, 9H, $Si(CH_2C\mathbf{H_3})_3$), 0.89-86 (m, 9H, $C^{(4)}$H(C$\mathbf{H_3}$), $C^{(22)}$H(C$\mathbf{H_3}$), $CH_2CH_2C\mathbf{H_3}$), 0.56 (q, J = 7.9 Hz, 6H, $Si(C\mathbf{H_2}CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 170.5, 170.4, 159.0, 158.8, 145.6, 138.7, 138.6, 131.3, 130.8, 129.2, 128.6, 122.6, 114.5, 113.7, 113.5, 111.5, 109.8, 83.9, 75.2, 73.9, 72.1, 71.1, 70.0, 69.8, 69.1, 68.5, 67.9, 55.2, 55.1, 44.3, 43.6, 42.1, 41.8, 39.3, 36.5, 36.3, 36.2, 35.9, 35.24, 35.16, 33.6, 33.2, 31.8, 29.8, 24.9, 23.5, 23.4, 22.5, 21.3, 21.2, 18.4, 17.6, 14.7, 13.9, 13.2, 9.8, 7.0, 5.1; IR (thin film) 2956, 2875,

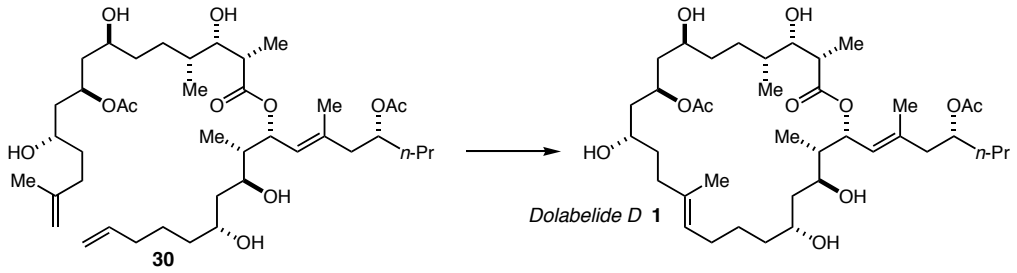
1736, 1613, 1514, 1458, 1374, 1331, 1302, 1247, 1174, 1037, 821, 745 cm^{-1}; $[\alpha]^{20}_D$ (*c* 1.16, CH_2Cl_2) +17.0°; LRMS (FAB+) *m/z* calc'd for $[M+Na]^+$ ($C_{68}H_{108}O_{13}SiNa$) requires 1183.75, found 1183.92.



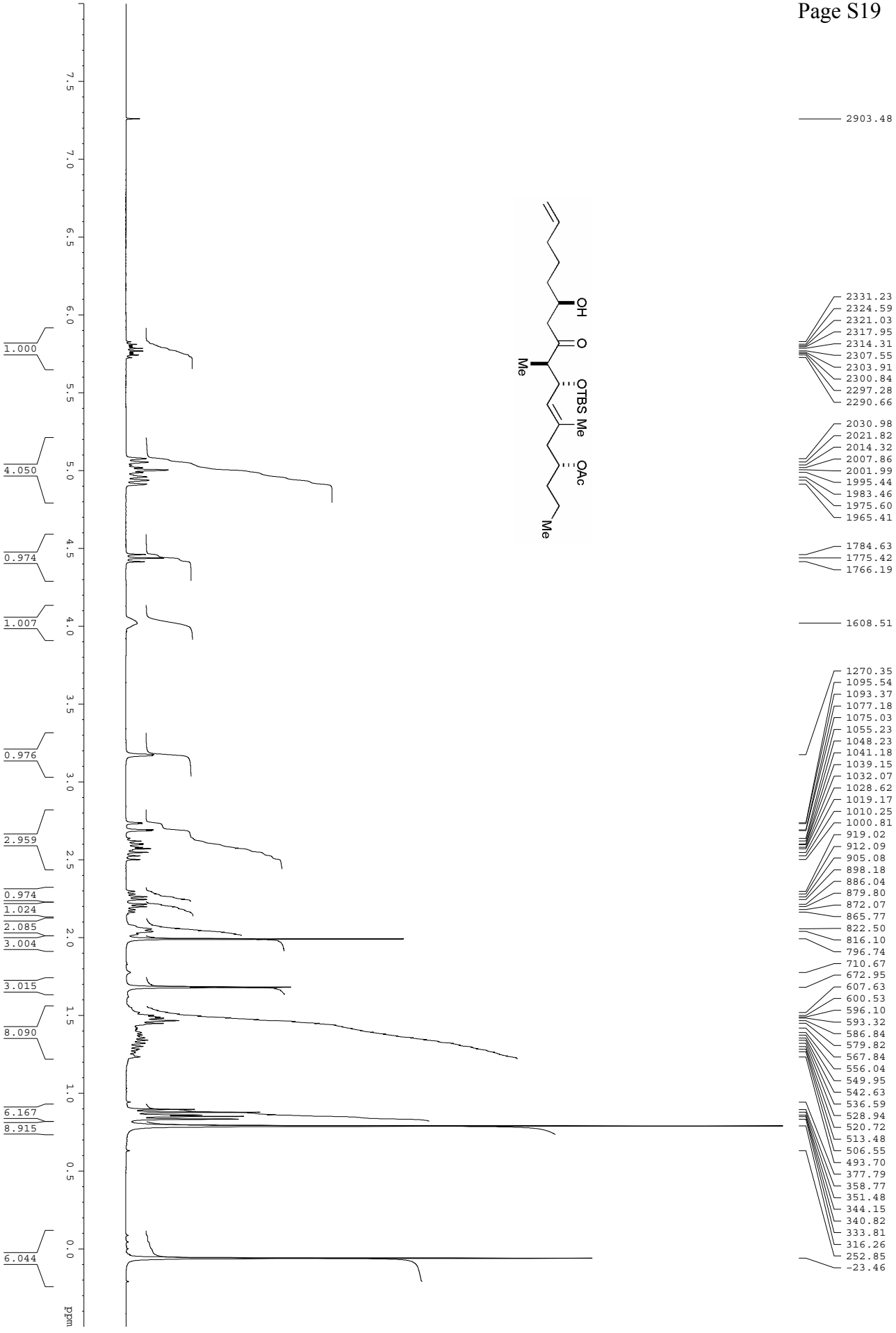
(2*S*,3*S*,4*R*,7*S*,9*R*,11*S*)-((4*R*,8*R*,9*S*,10*S*,12*R*,*E*)-4-acetoxy-10,12-dihydroxy-6,9-dimethylheptadeca-6,16-dien-8-yl) 9-acetoxy-7-hydroxy-3,11-bis(4-methoxybenzyloxy)- 2,4,14-trimethylpentadec-14-enoate (36). To a solution of ester **29** (73.1 mg, 62.9 μmol) in MeOH (2 mL) was added pyridinium *p*-toluenesulfonate (1.6 mg, 6.37 μmol). After stirring for 11 h at room temperature, the reaction mixture was diluted with EtOAc (10 mL) and H_2O (5 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated to give a cloudy, yellow oil. Purification by flash chromatography (20% acetone/hexanes) afforded trihydroxy ester **36** as a clear, colorless oil in 90% yield (55.6 mg, 56.7 μmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H, Ar**H**), 7.20 (d, *J* = 8.6 Hz, 2H, Ar**H**), 6.87 (d, *J* = 8.6 Hz, 2H, Ar**H**), 6.83 (d, *J* = 8.6 Hz, 2H, Ar**H**), 5.80 (m, 1H, C**H**=CH_2), 5.67 (dd, *J* = 9.6, 6.1 Hz, 1H, $CH(CH_3)CO_2C$**H**), 5.22 (m, 1H, $C^{(9)}$**H**OAc), 5.15 (d, *J* = 9.6 Hz, 1H, $(CH_3)C$=C**H**), 5.03-4.93 (m, 3H, CH=C$\mathbf{H_2}$, $C^{(27)}$**H**OAc), 4.70 (s, 1H, one of $(CH_3)C$=C$\mathbf{H_2}$), 4.65 (s, 1H, one of $(CH_3)C$=C$\mathbf{H_2}$), 4.50-4.41 (m, 4H, 2 × C$\mathbf{H_2}$Ar), 3.86 (m, 1H, C**H**OH), 3.79 (s, 3H, ArOC$\mathbf{H_3}$), 3.78 (s, 3H, ArOC$\mathbf{H_3}$), 3.68 (m, 1H, C**H**OH), 3.59 (dd, *J* = 7.9, 2.8 Hz, 1H, $C^{(3)}$**H**OPMB), 3.46-3.35 (m, 2H, $C^{(11)}$**H**OPMB, C**H**OH), 3.09 (d, *J* = 3.6 Hz, 1H, O**H**), 2.73 (apparent quint, *J* = 7.3 Hz, 1H, $C^{(2)}$**H**(CH_3)), 2.59 (d, *J* = 5.2 Hz, 1H, O**H**), 2.50 (br s, 1H, O**H**), 2.15-1.90 (m, 8H, C$\mathbf{H_2}(CH_3)$C=CH, C$\mathbf{H_2}(CH_3)$C=CH_2, C$\mathbf{H_2}$CH=CH_2, $C^{(22)}$**H**(CH_3), one of $C^{(10)}\mathbf{H_2}$), 2.02 (s, 3H, OC(O)C$\mathbf{H_3}$), 2.01 (s, 3H, OC(O)C$\mathbf{H_3}$), 1.77 (s, 3H, (C$\mathbf{H_3}$)C=CH), 1.71 (s, 3H, (C$\mathbf{H_3}$)C=CH_2), 1.71-1.14 (m, 20H, $C^{(4)}$**H**(CH_3), $C^{(5)}\mathbf{H_2}$, $C^{(6)}\mathbf{H_2}$, $C^{(8)}\mathbf{H_2}$, one of $C^{(10)}\mathbf{H_2}$, $C^{(12)}\mathbf{H_2}$, $C^{(17)}\mathbf{H_2}$, $C^{(18)}\mathbf{H_2}$, $C^{(20)}\mathbf{H_2}$, $C^{(28)}\mathbf{H_2}$, $C^{(29)}\mathbf{H_2}$), 1.09 (d, *J* = 7.1 Hz, 3H, $C^{(2)}$H(C$\mathbf{H_3}$)), 0.90-84 (m, 9H, $C^{(4)}$H(C$\mathbf{H_3}$), $C^{(22)}$H(C$\mathbf{H_3}$), $CH_2CH_2C\mathbf{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 172.1, 170.9, 159.2, 158.9, 145.4, 138.6, 138.3, 131.2, 130.5, 129.4, 128.8, 123.4, 114.6, 113.8, 113.5, 110.0, 83.9, 75.1, 73.5, 73.2, 72.4, 70.3, 69.9, 69.5, 68.8, 67.3, 55.23, 55.18, 44.2, 43.3, 43.2, 43.0, 39.4, 39.0, 37.0, 36.2, 35.3, 35.1, 33.6, 33.1, 31.6, 30.4, 25.1, 22.5, 21.2, 21.1, 18.4, 17.7, 14.1, 13.9, 13.8, 10.8; IR (thin film) 3454 (br), 2936, 1731, 1613, 1513, 1458, 1374, 1301, 1247, 1178, 1034, 940, 913, 821, 754, 708, 610 cm^{-1}; $[\alpha]^{22}_D$ (*c* 0.885, CH_2Cl_2) +15.9°; LRMS (FAB+) *m/z* calc'd for $[M+Na]^+$ ($C_{57}H_{88}O_{13}Na$) requires 1003.61, found 1003.54.



(2*S*,3*S*,4*R*,7*S*,9*R*,11*S*)-((4*R*,8*R*,9*S*,10*S*,12*R*,*E*)-4-acetoxy-10,12-dihydroxy-6,9-dimethylheptadeca-6,16-dien-8-yl) 9-acetoxy-3,7,11-trihydroxy-2,4,14-trimethylpentadec-14-enoate (30). To a rapidly stirred, biphasic mixture of trihydroxy ester **36** (66.0 mg, 67.3 μmol) in CH_2Cl_2 (3 mL) and pH 7 phosphate buffer (3 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (77.9 mg, 0.343 mmol), resulting in a green color that slowly changed to a dark reddish brown. After 1.5 h, the reaction mixture was diluted with CH_2Cl_2 (12 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL). The aqueous phase was back-extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give a cloudy, reddish brown oil. Purification by flash chromatography (25% acetone/hexanes) afforded pentahydroxy ester **30** as a clear, colorless oil in 78% yield (39.1 mg, 52.8 μmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (m, 1H, C**H**=CH_2), 5.29-5.19 (m, 2H, CH(CH_3)CO_2C**H**, C**H**OAc), 5.08-4.92 (m, 4H, (CH_3)C=C**H**, CH=C**H**$_2$, C**H**OAc), 4.72 (s, 1H, one of (CH_3)C=C**H**$_2$), 4.70 (s, 1H, one of (CH_3)C=C**H**$_2$), 4.09 (m, 1H, C**H**OH), 4.01 (br d, *J* = 5.8 Hz, 1H O**H**), 3.86 (m, 1H, C**H**OH), 3.70 (m, 4H, 2 × C**H**OH, 2 × O**H**), 3.49 (m, 1H C**H**OH), 2.71 (br s, 2H, 2 × O**H**), 2.55 (m, 1H, C$^{(2)}$**H**(CH_3)), 2.28-1.19 (m, 28H, C**H**$_2$(CH_3)C=CH, C**H**$_2$(CH_3)C=CH_2, C**H**$_2$CH=CH_2, C$^{(22)}$**H**(CH_3), C$^{(4)}$**H**(CH_3), C$^{(5)}$**H**$_2$, C$^{(6)}$**H**$_2$, C$^{(8)}$**H**$_2$, C$^{(10)}$**H**$_2$, C$^{(12)}$**H**$_2$, C$^{(17)}$**H**$_2$, C$^{(18)}$**H**$_2$, C$^{(20)}$**H**$_2$, C$^{(28)}$**H**$_2$, C$^{(29)}$**H**$_2$), 2.07 (s, 3H, OC(O)C**H**$_3$), 2.01 (s, 3H, OC(O)C**H**$_3$), 1.79 (s, 3H, (C**H**$_3$)C=CH), 1.72 (s, 3H, (C**H**$_3$)C=CH_2), 1.04 (d, *J* = 7.0 Hz, 3H, C$^{(2)}$H(C**H**$_3$)), 0.88 (t, *J* = 7.3 Hz, 3H, CH_2CH_2C**H**$_3$), 0.82 (d, *J* = 6.5 Hz, 6H, C$^{(4)}$H(C**H**$_3$), C$^{(22)}$H(C**H**$_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 172.2, 170.8, 145.5, 138.7, 138.0, 125.0, 114.6, 110.3, 73.6, 72.9, 72.5, 70.2, 68.8, 68.1, 44.9, 44.3, 42.944, 42.867, 42.1, 37.7, 37.5, 36.1, 35.4, 34.6, 34.2, 33.8, 33.6, 30.1, 25.0, 22.4, 21.3, 21.2, 18.5, 17.8, 13.9, 13.7, 12.8, 9.9; IR (thin film) 3400 (br), 2937, 1735, 1457, 1376, 1245, 1024, 610 cm^{-1}; $[\alpha]^{24}_D$ (*c* 0.455, CH_2Cl_2) +4.8°; LRMS (FAB+) *m/z* calc'd for $[M+Na]^+$ ($C_{41}H_{72}O_{11}Na$) requires 763.50, found 762.90.



Dolabelide D (1). To a refluxing solution of pentahydroxy ester **30** (5.1 mg, 6.89 μmol) in CH_2Cl_2 (12.8 mL) was added a clear, pink solution of 2nd generation Grubbs catalyst (**31**) (0.6 mg/mL in CH_2Cl_2, 1.0 mL, 0.707 μmol) via syringe. The resulting clear, pale pink solution was heated at reflux; it changed to a clear yellow color after several min. Additional 0.5 mL portions of catalyst **31** solution (0.6 mg/mL in CH_2Cl_2) were added after 2, 4, and 6 h. After 6 h 10 min total, the reaction mixture was reduced in volume to <0.5 mL on a rotary evaporator and purified directly by flash chromatography (1:10:39 MeOH/acetone/CH_2Cl_2) to yield a mixture of products containing the ring-closed (*E*)- and (*Z*)-isomers in a 1.3:1 ratio (by ^{1}H NMR). Careful repeated chromatography (1:10:39 MeOH/acetone/CH_2Cl_2, Silicycle UltraPure Flash Silica Gel, 230-400 mesh, 40 Å pore size) afforded synthetic dolabelide D (**1**) as a clear, colorless oil in 31% yield (1.5 mg, 2.10 μmol). ^{1}H NMR (500 MHz, pyridine-d_5) δ 6.39-5.82 (m, 5H, 5 × O**H**), 6.05 (m, 1H, C$^{(9)}$**H**OAc), 5.72 (t, *J* = 9.3 Hz, 1H, CH(CH$_3$)CO$_2$C**H**), 5.41 (d, *J* = 9.1 Hz, 1H, (CH$_3$)C=C$^{(24)}$**H**), 5.33 (br t, *J* = 6.5 Hz, 1H, (CH$_3$)C=C$^{(15)}$**H**), 5.27 (m, 1H, C$^{(27)}$**H**OAc), 4.80 (m, 1H, C$^{(21)}$**H**OH), 4.38 (m, 1H, C$^{(19)}$**H**OH), 4.15 (br d, *J* = 9.1 Hz, 1H, C$^{(3)}$**H**OH), 4.07-4.05 (m, 2H, C$^{(7)}$**H**OH, C$^{(11)}$**H**OH), 2.93 (m, 1H, C$^{(2)}$**H**(CH$_3$)), 2.50 (m, 1H, C$^{(22)}$**H**(CH$_3$)), 2.38 (m, 1H, one of C$^{(13)}$**H**$_2$(CH$_3$)C=CH), 2.32 (dd, *J* = 14.0, 7.9 Hz, 1H, one of C$^{(26)}$**H**$_2$(CH$_3$)C=CH), 2.28 (dd, *J* = 13.8, 5.4 Hz, 1H, one of C$^{(26)}$**H**$_2$(CH$_3$)C=CH), 2.21-2.17 (m, 3H, one of C$^{(8)}$**H**$_2$, one of C$^{(10)}$**H**$_2$, one of C$^{(13)}$**H**$_2$(CH$_3$)C=CH), 2.11-1.90 (m, 7H, one of C$^{(5)}$**H**$_2$, one of C$^{(6)}$**H**$_2$, one of C$^{(8)}$**H**$_2$, one of C$^{(10)}$**H**$_2$, one of C$^{(12)}$**H**$_2$, (CH$_3$)C=CHC**H**$_2$), 2.07 (s, 3H, OC(O)C**H**$_3$), 2.03 (s, 3H, OC(O)C**H**$_3$), 1.99 (s, 3H, OC(O)C**H**$_3$), 1.87-1.83 (m, 2H, C$^{(20)}$**H**$_2$), 1.79-1.62 (m, 5H, C$^{(4)}$**H**(CH$_3$), one of C$^{(6)}$**H**$_2$, one of C$^{(12)}$**H**$_2$, one of C$^{(17)}$**H**$_2$, one of C$^{(18)}$**H**$_2$), 1.62-1.55 (m, 3H, one of C$^{(5)}$**H**$_2$, one of C$^{(17)}$**H**$_2$, one of C$^{(18)}$**H**$_2$), 1.58 (s, 3H, (C**H**$_3$)C$^{(14)}$=CH), 1.54-1.45 (m, 2H, C$^{(28)}$**H**$_2$), 1.38-1.25 (m, 2H, C$^{(29)}$**H**$_2$), 1.193 (d, *J* = 6.7 Hz, 3H, C$^{(2)}$H(C**H**$_3$)), 1.185 (d, *J* = 6.7 Hz, 3H, C$^{(22)}$H(C**H**$_3$)), 0.97 (d, *J* = 6.7 Hz, 3H, C$^{(4)}$H(C**H**$_3$)), 0.84 (t, *J* = 7.3 Hz, 3H, CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (100 MHz, pyridine-d_5) δ 174.0, 170.7, 170.4, 136.6, 133.8, 127.1, 126.4, 74.0, 73.4, 71.8, 71.1, 67.8, 67.7, 67.5, 66.1, 46.4, 44.5, 43.8, 42.9, 42.0, 38.6, 37.9, 36.3, 35.8, 35.61, 35.55, 34.3, 30.3, 27.7, 26.6, 21.3, 21.0, 18.8, 17.6, 15.6, 14.0, 13.7, 13.2, 11.1; IR (thin film) 3396 (br), 2935, 1736, 1463, 1378, 1261, 1024 cm^{-1}; $[\alpha]^{22}_D$ (*c* 0.27, CH_2Cl_2) +2.8°; HRMS (FAB+) *m/z* calc'd for $[M+H]^+$ ($C_{39}H_{69}O_{11}$) requires 713.4840, found 713.4844.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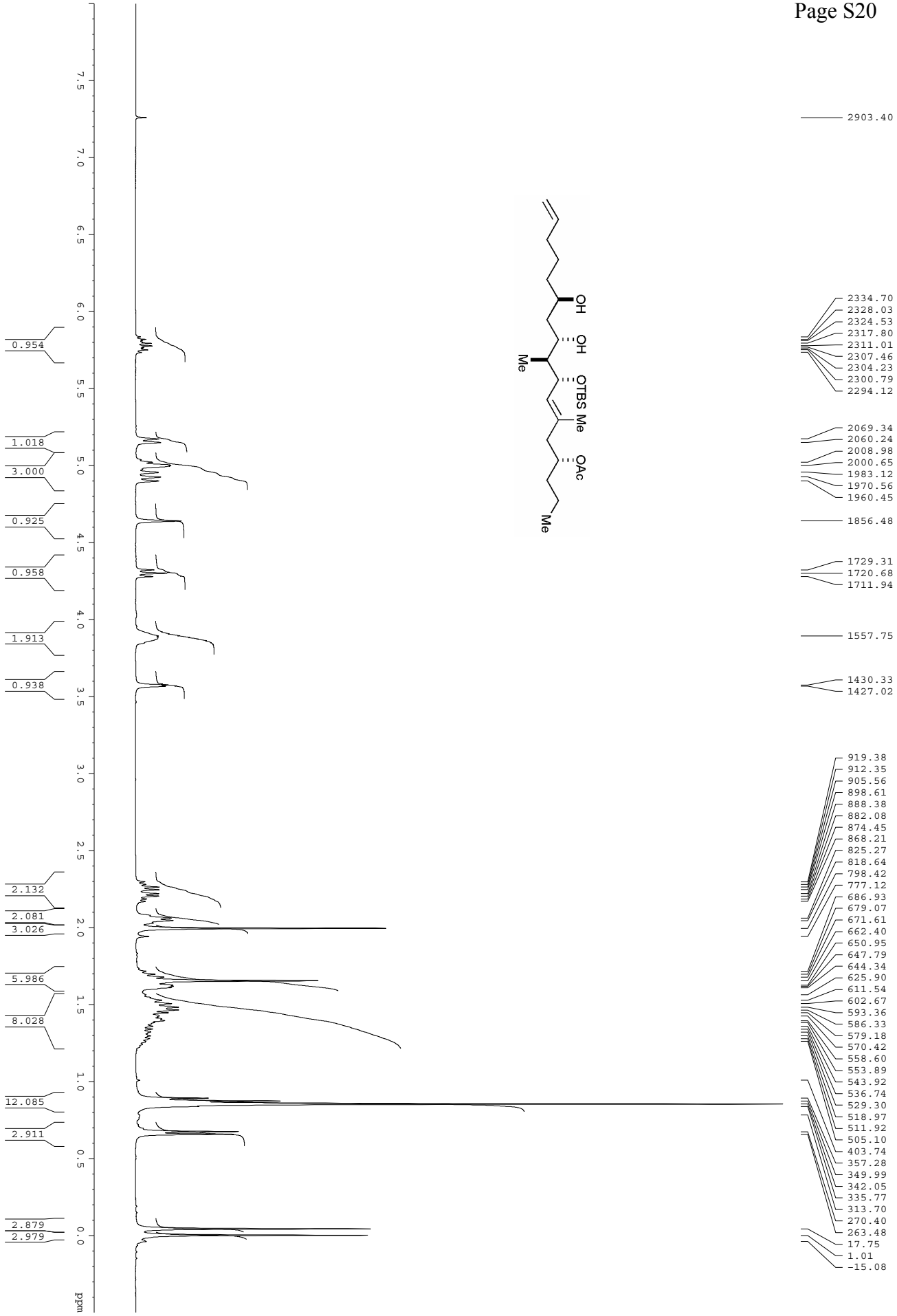
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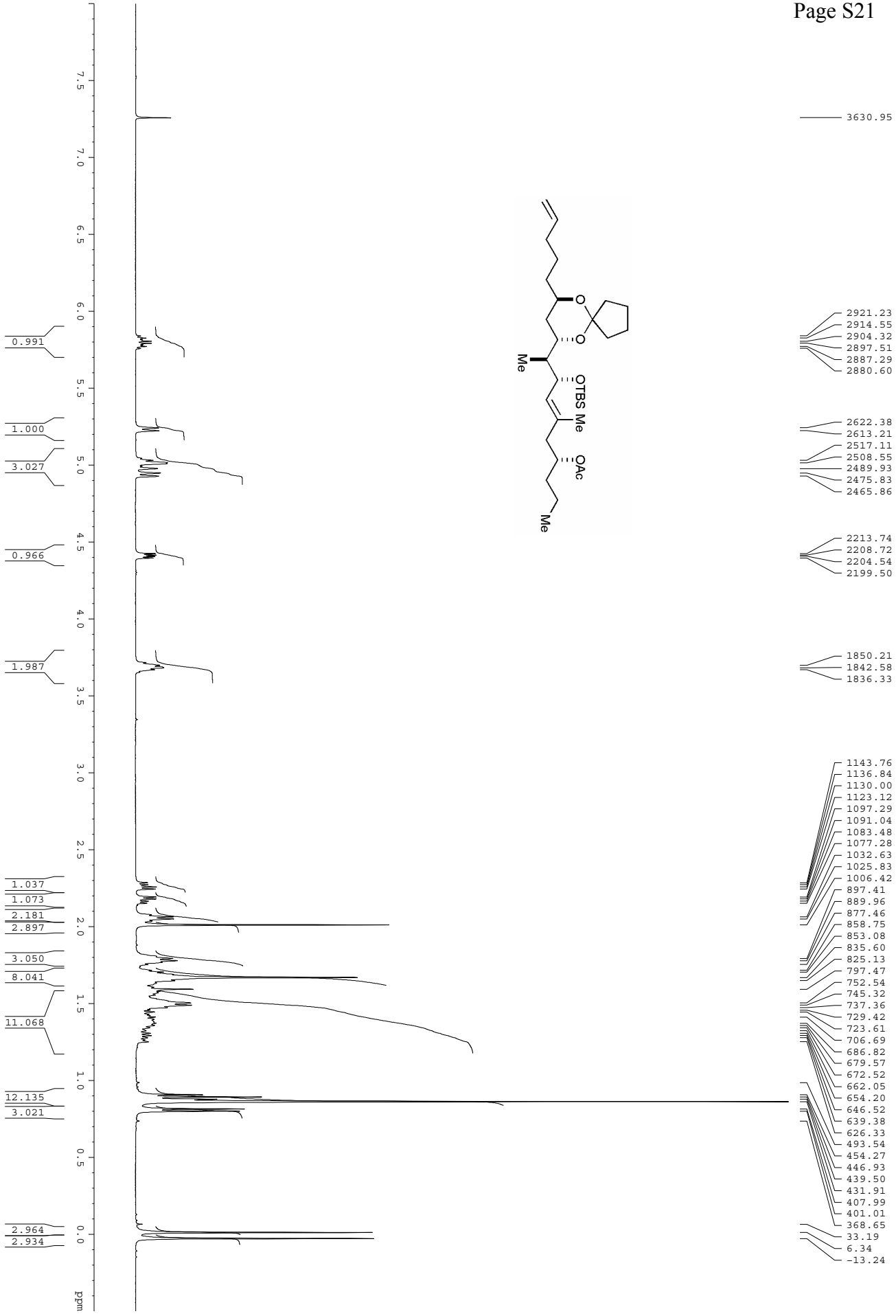
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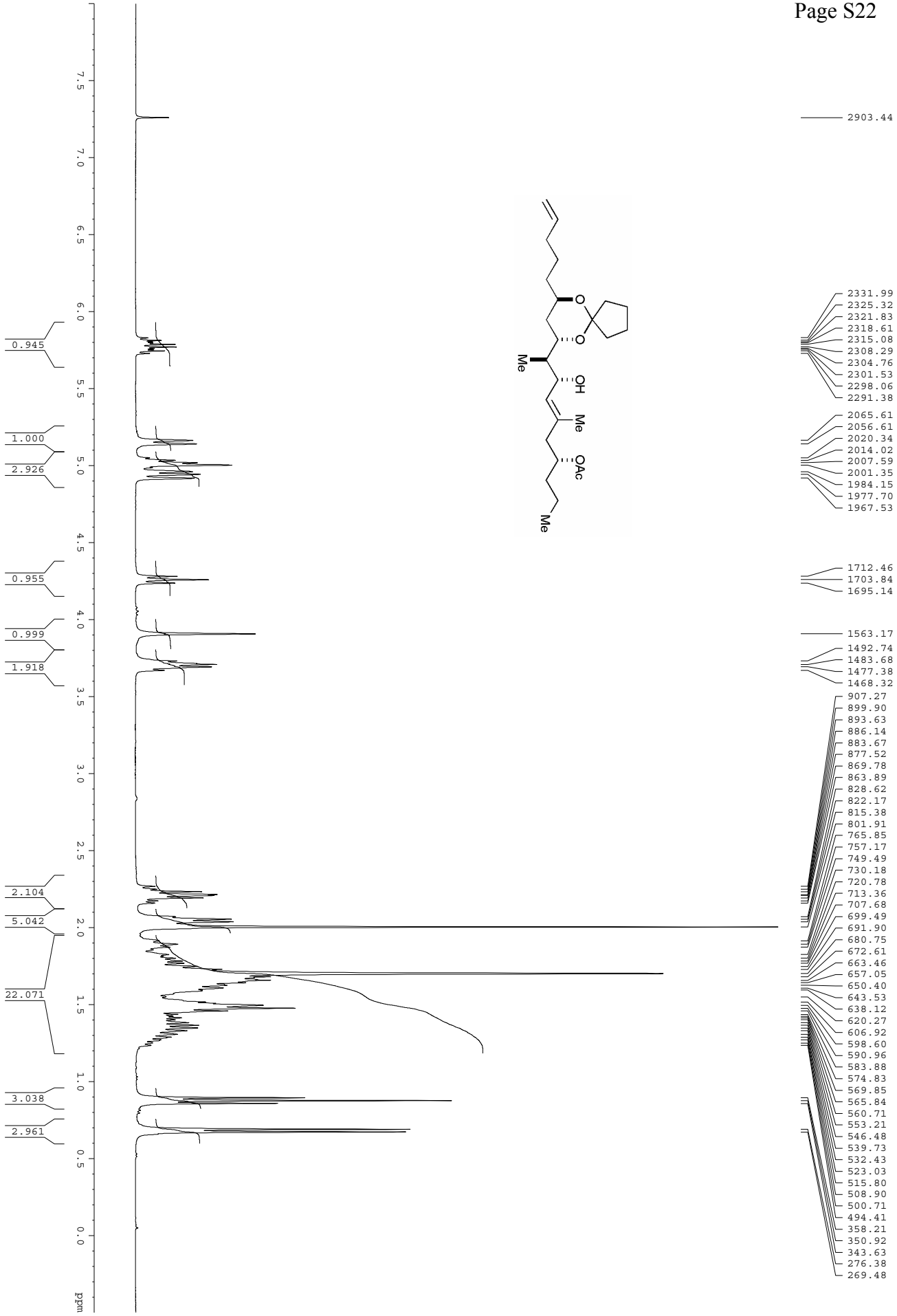
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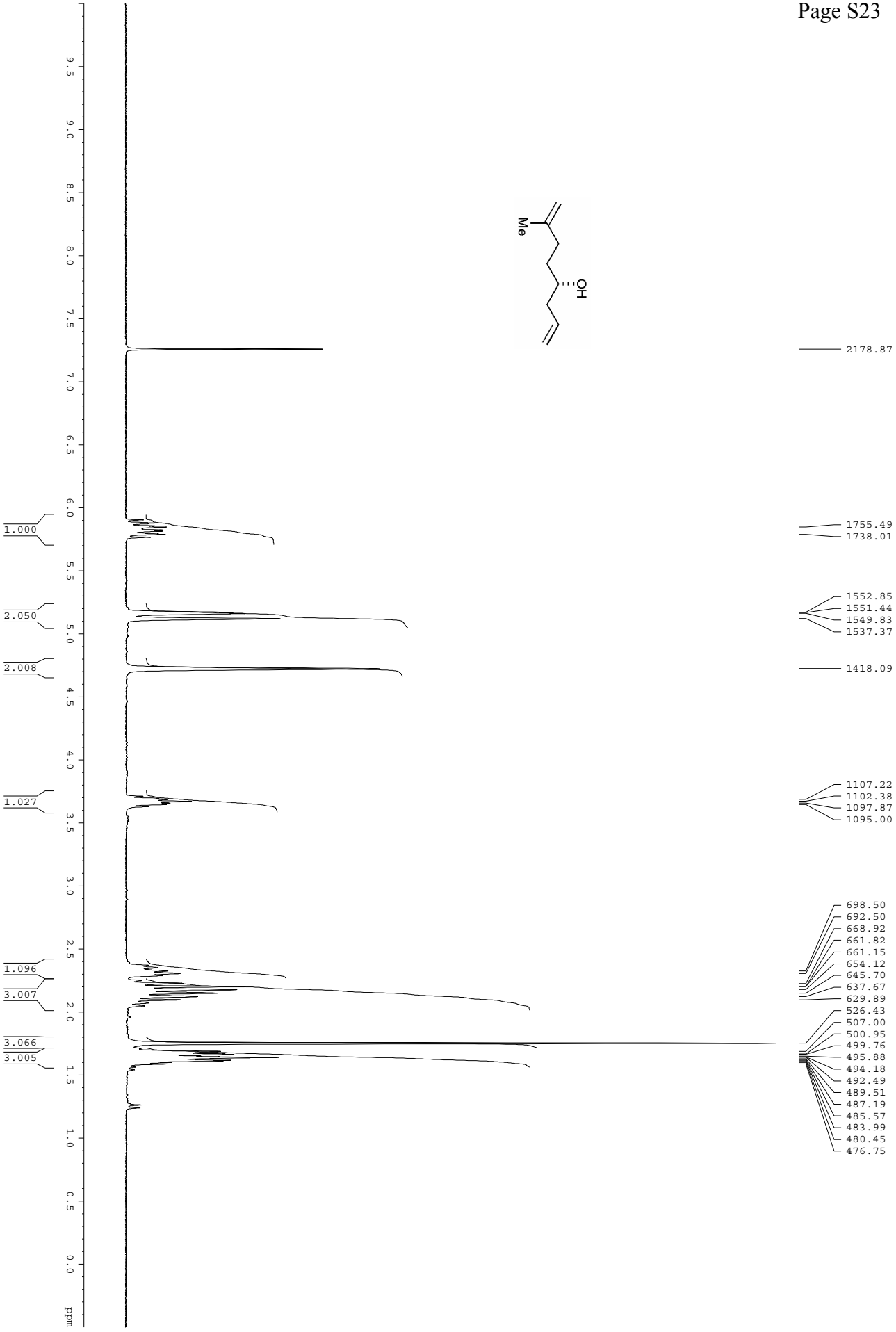
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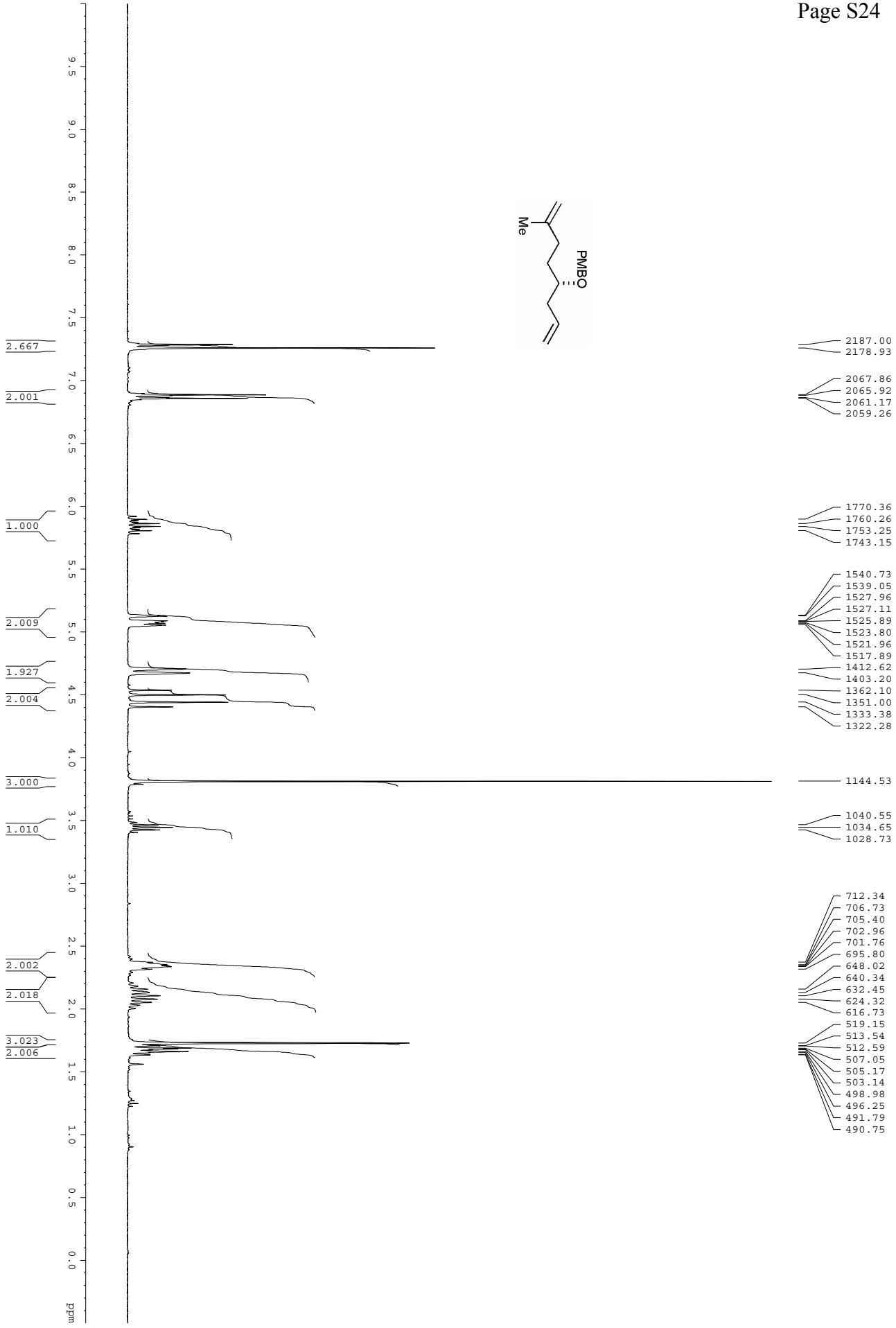
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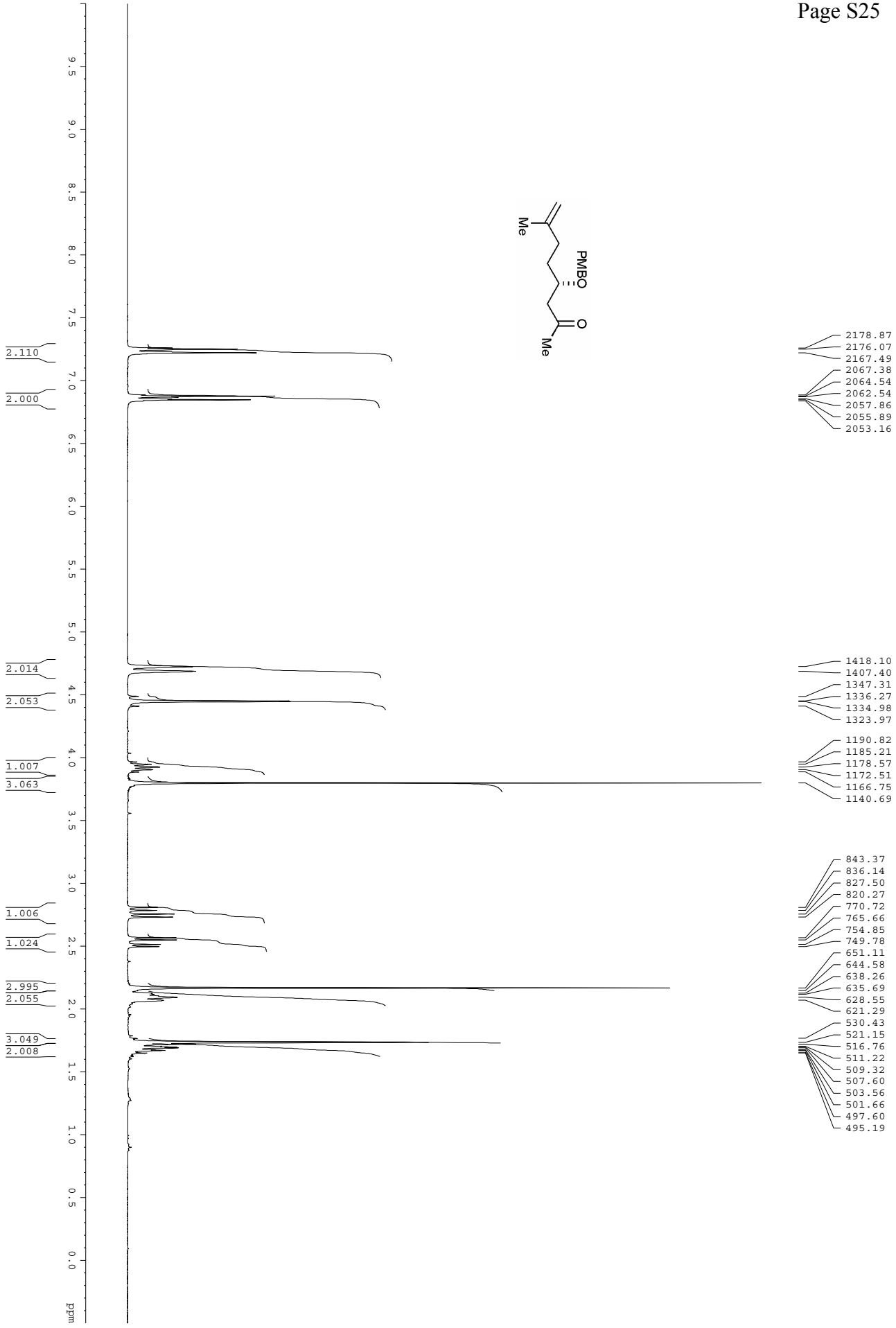
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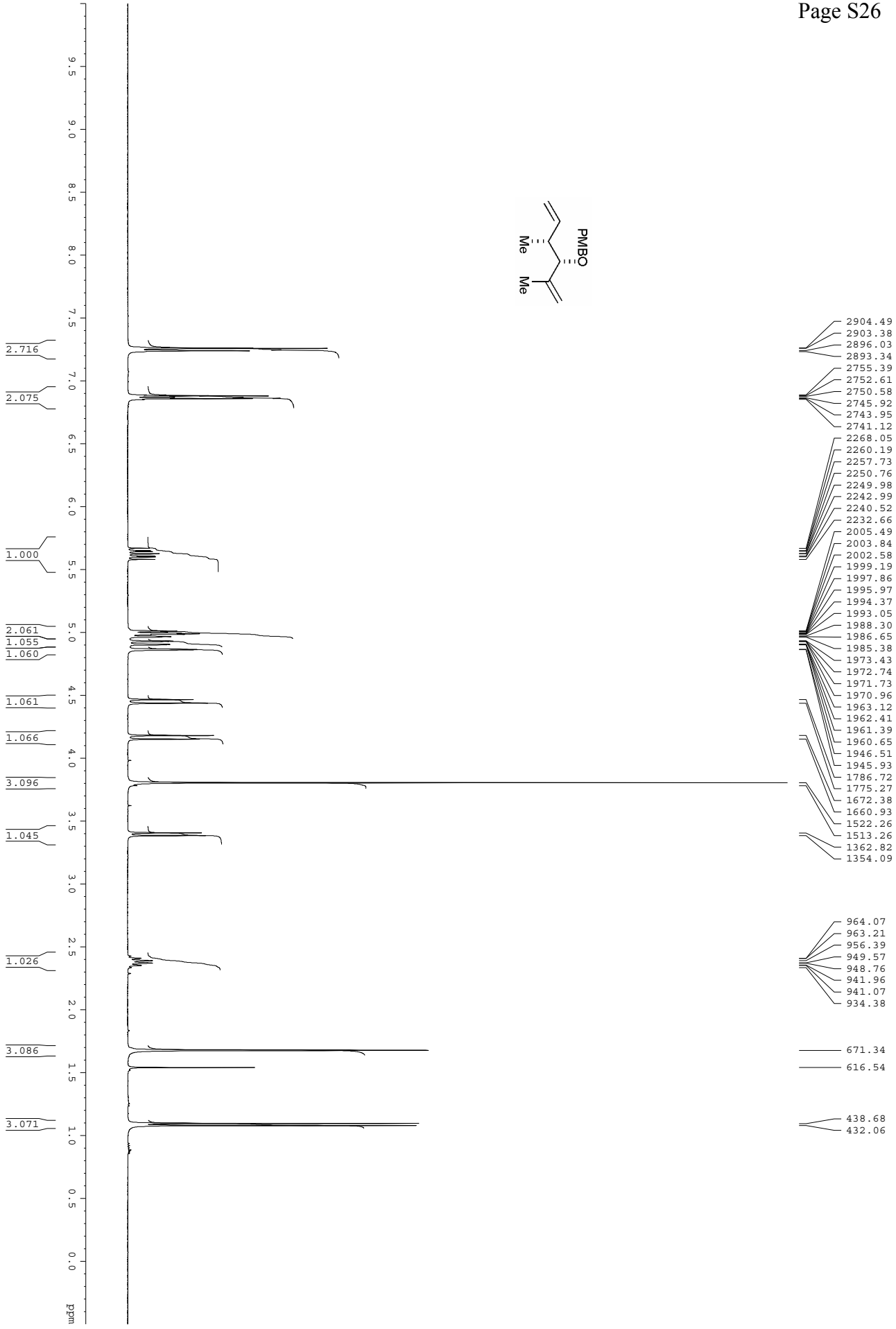
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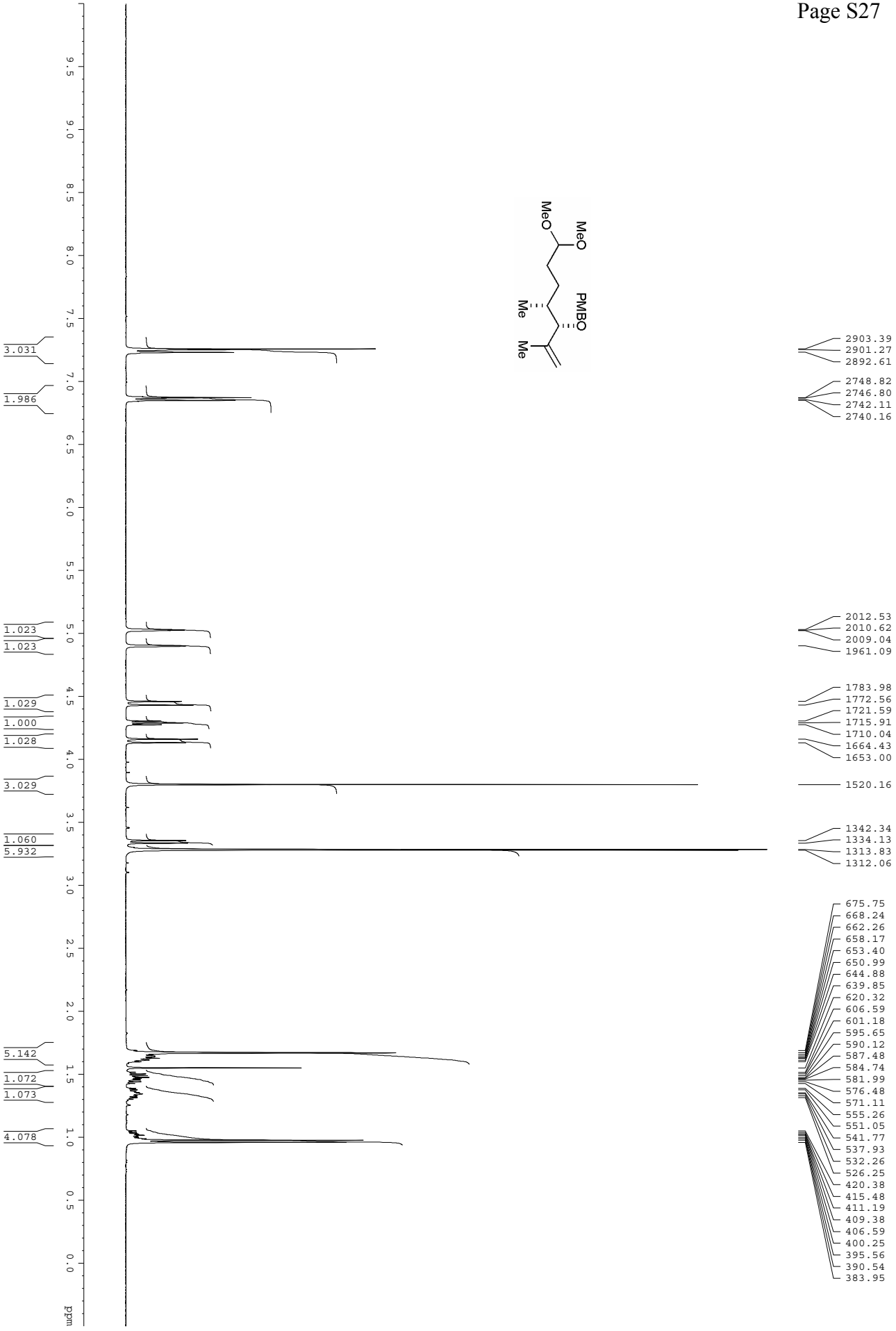
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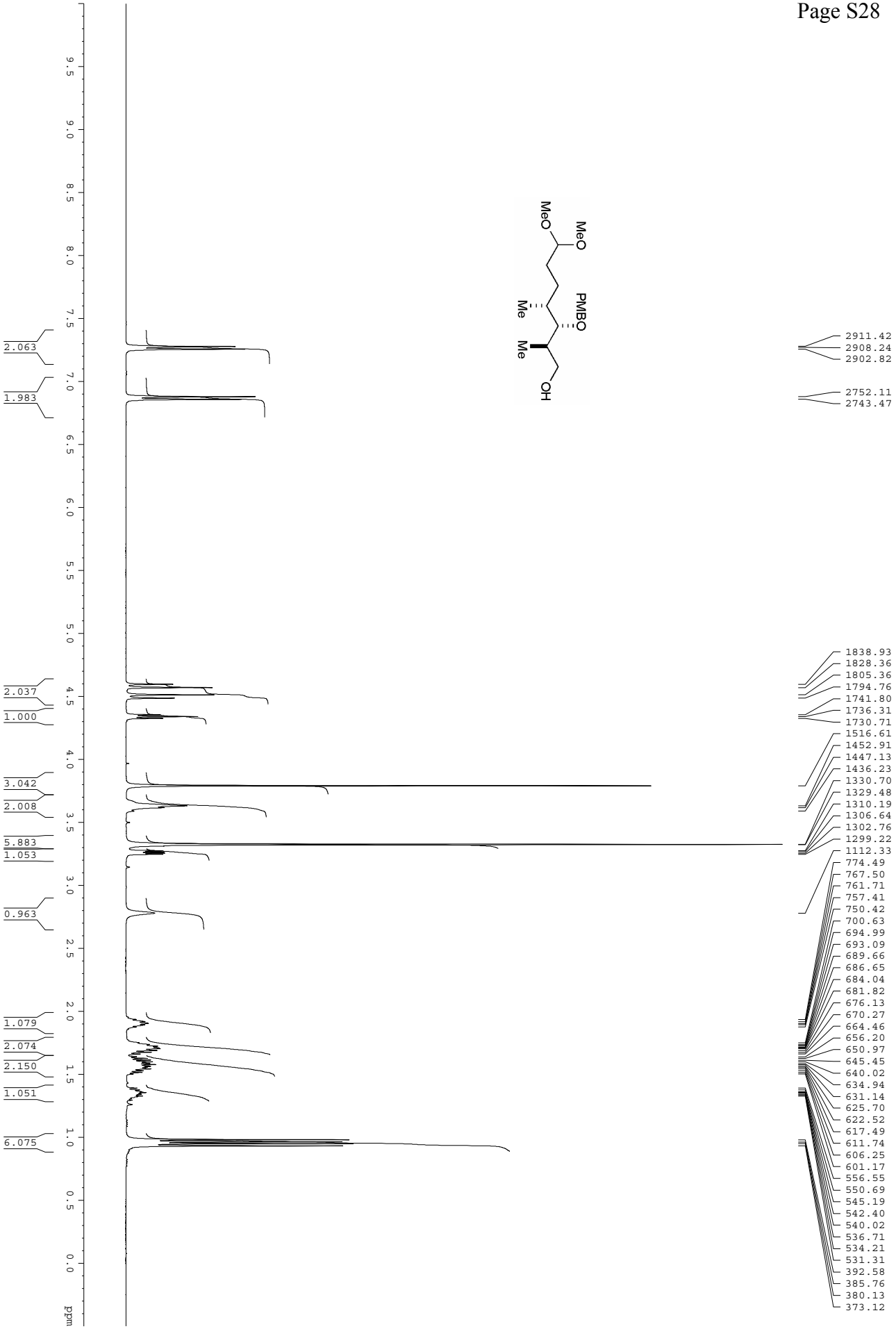
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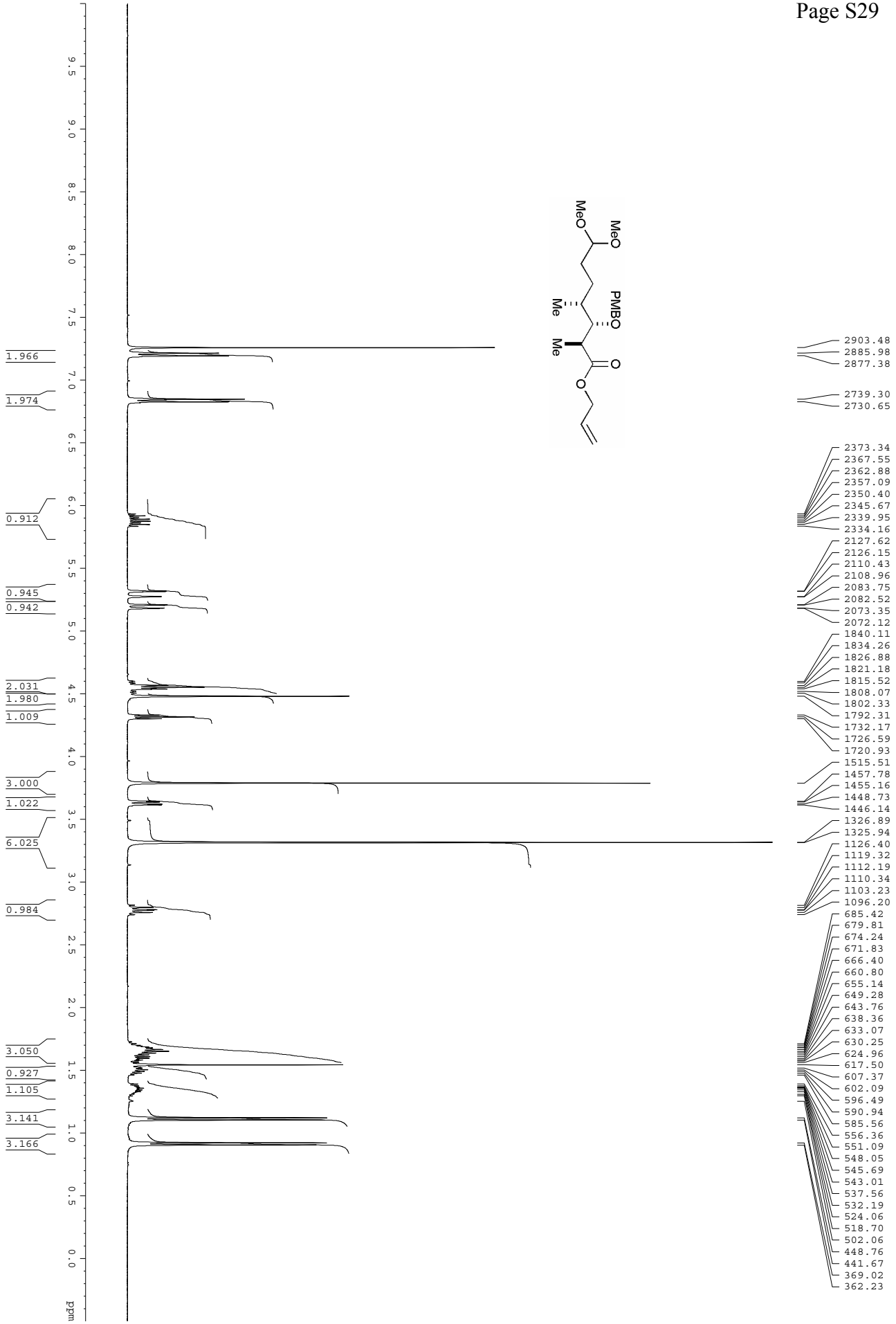
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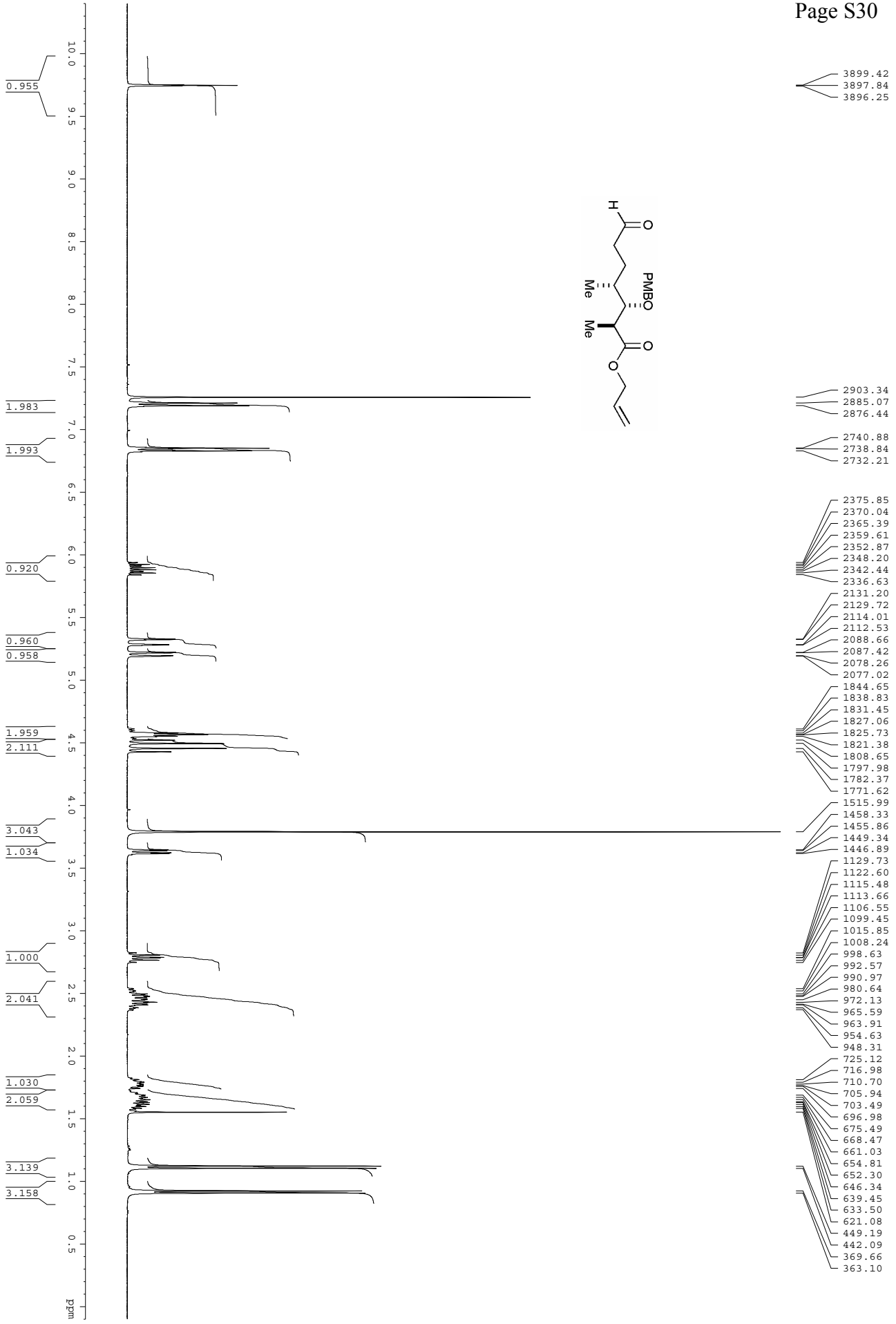
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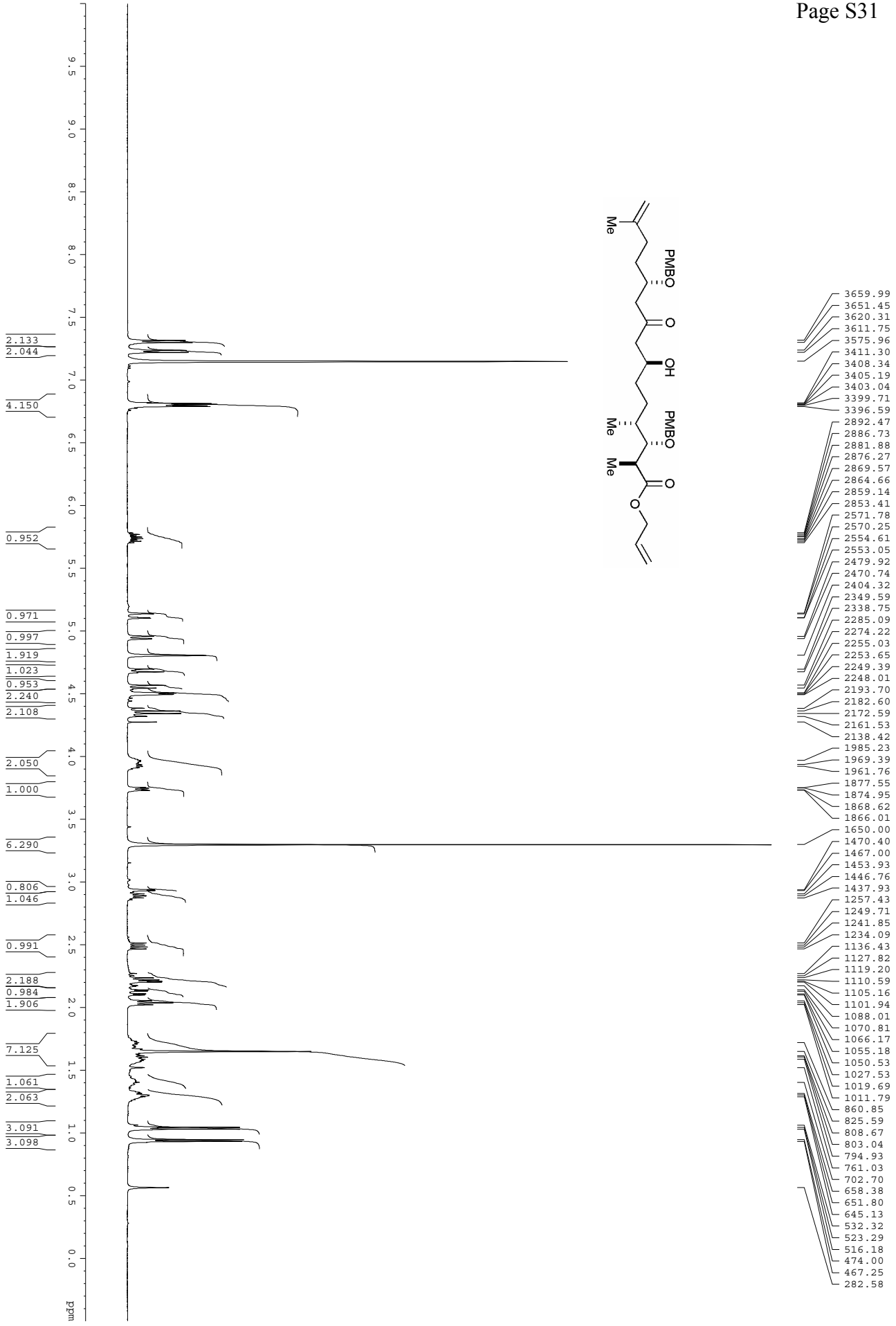
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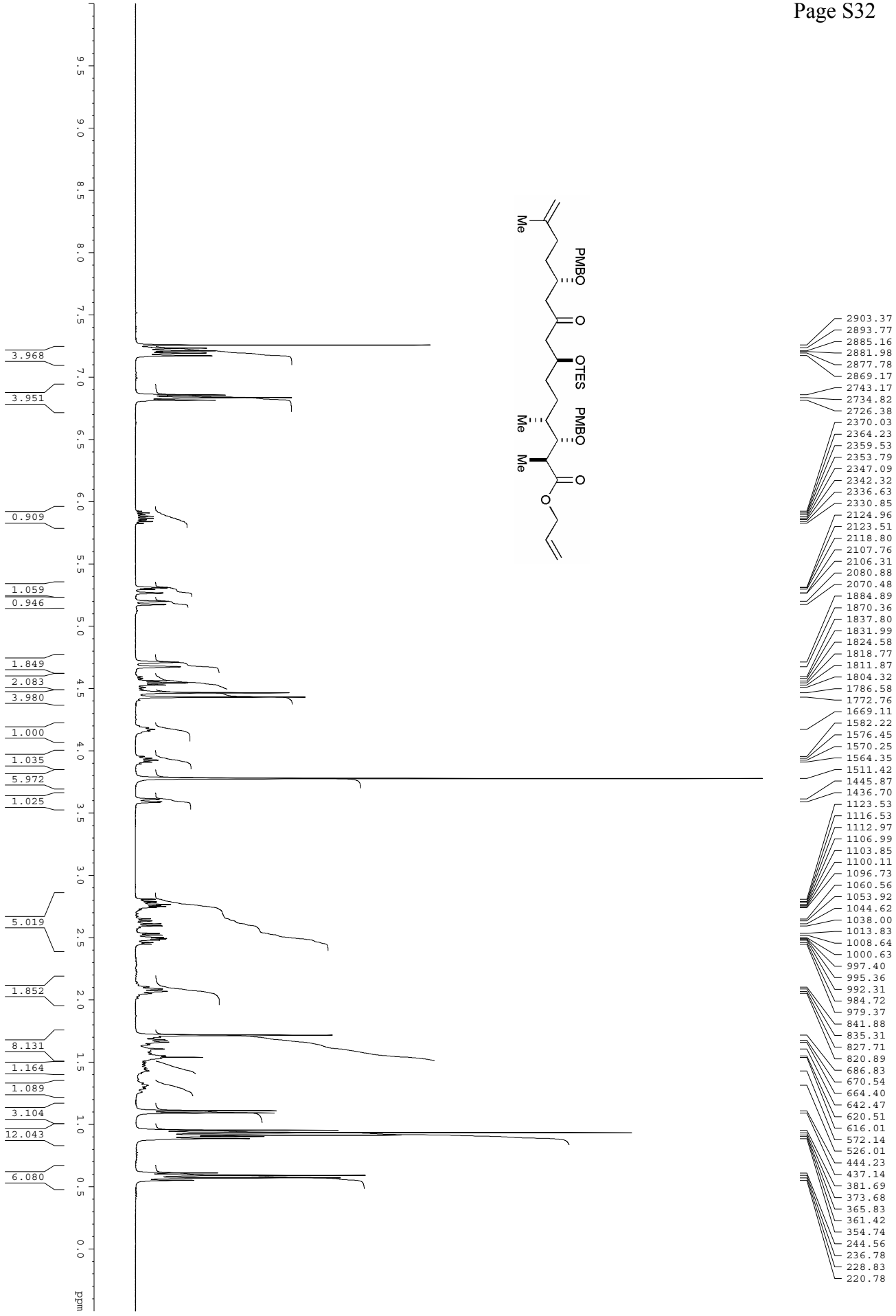
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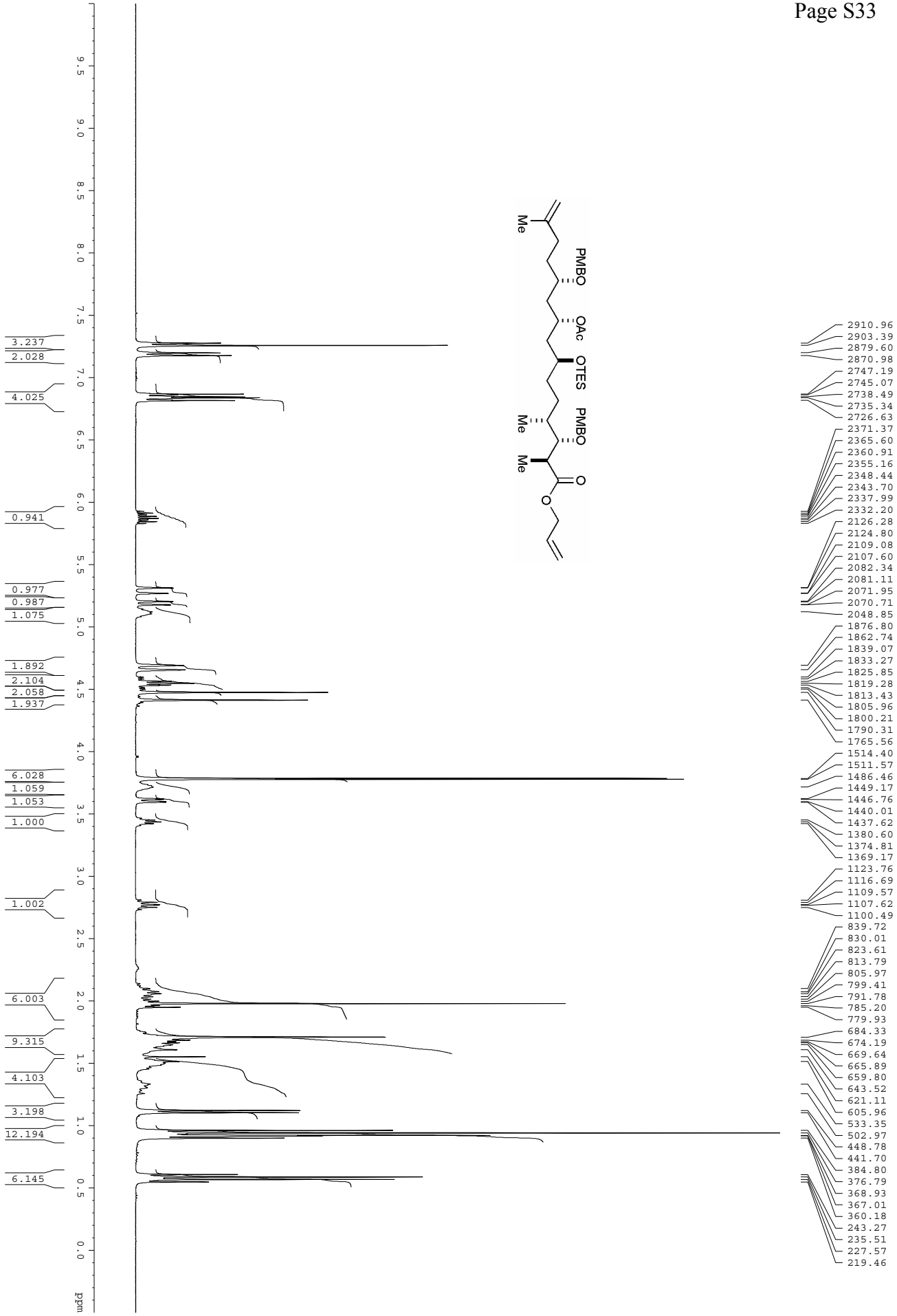
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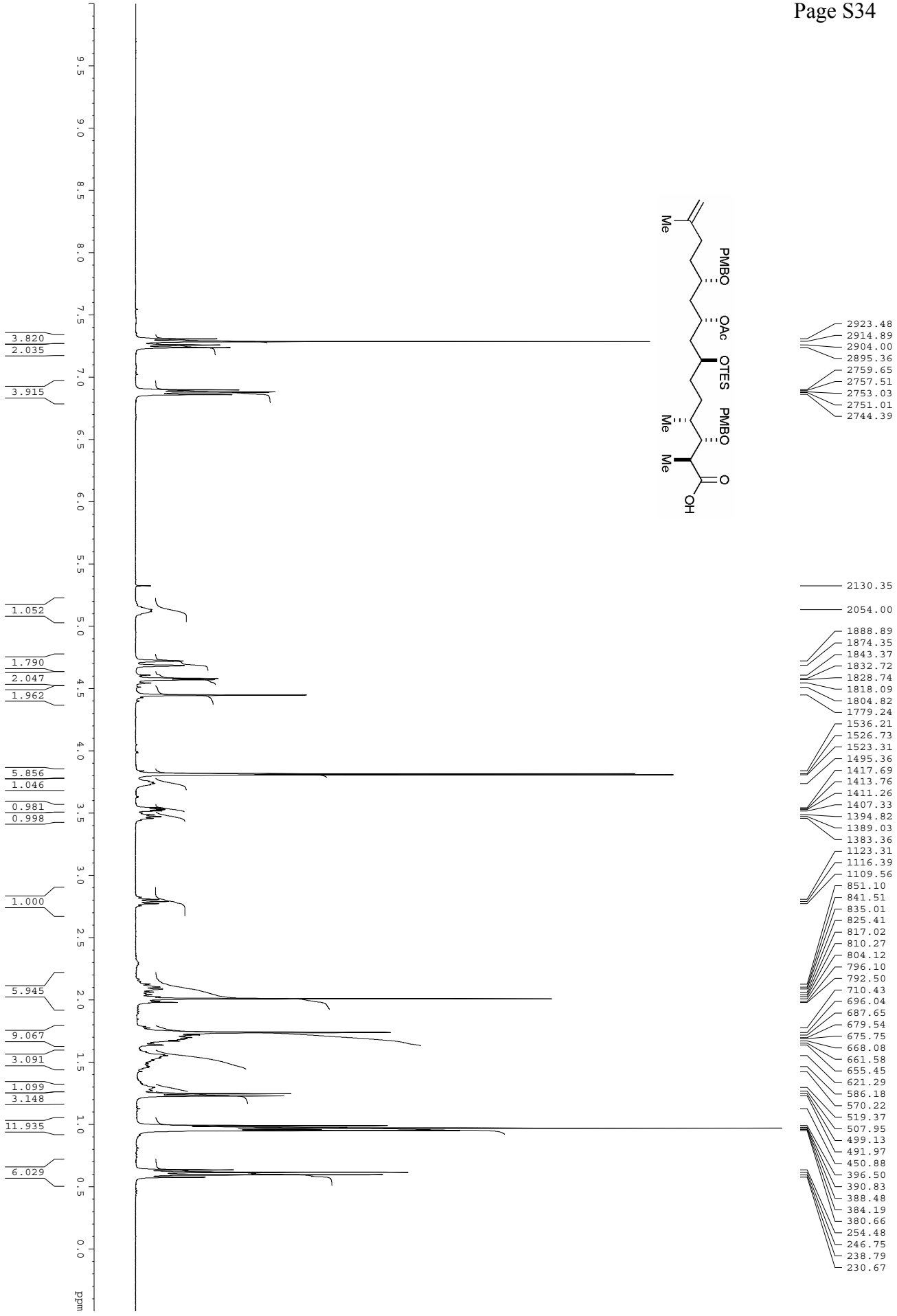
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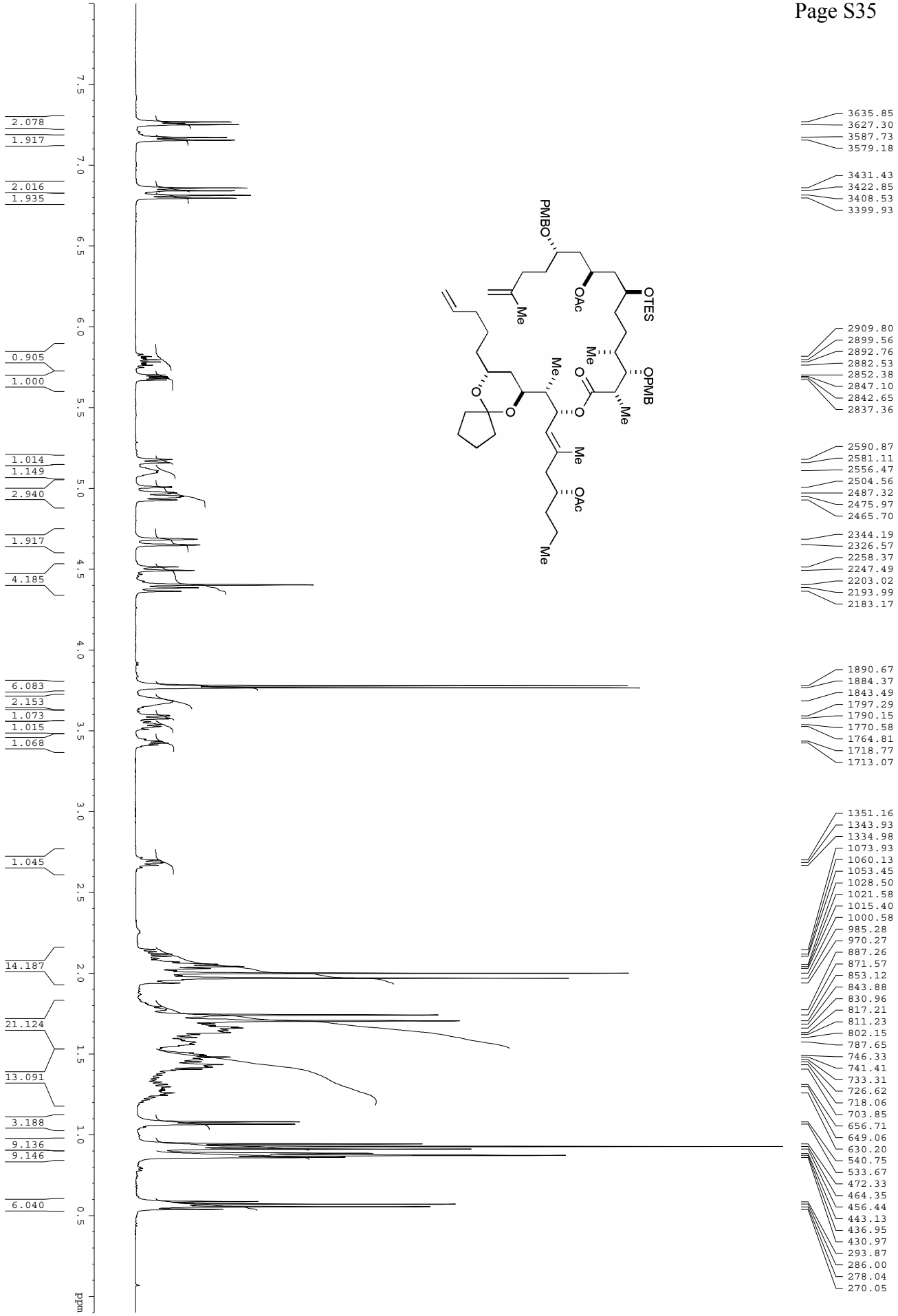
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1.073
1.015
1.068
1.045
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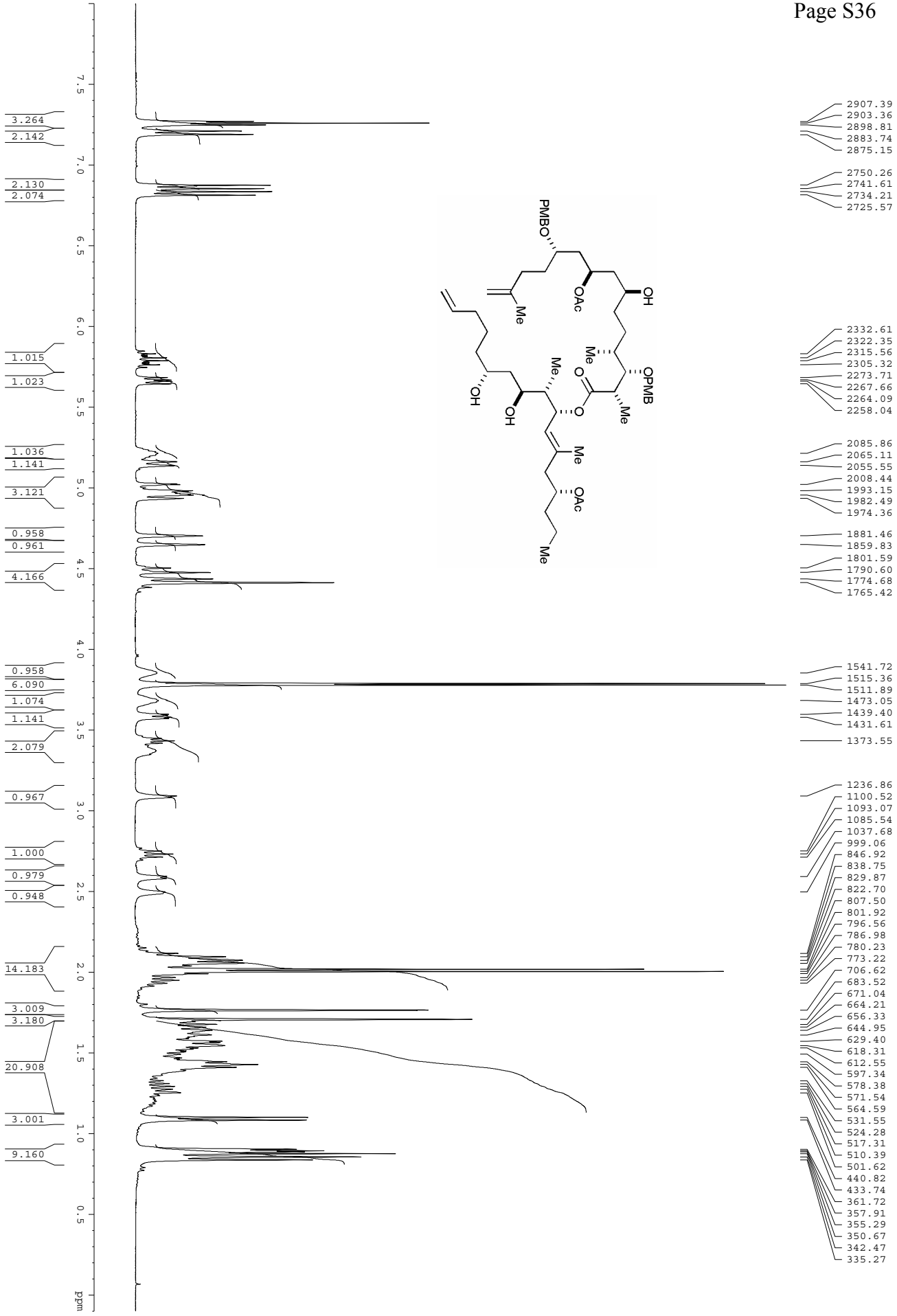
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OPMB
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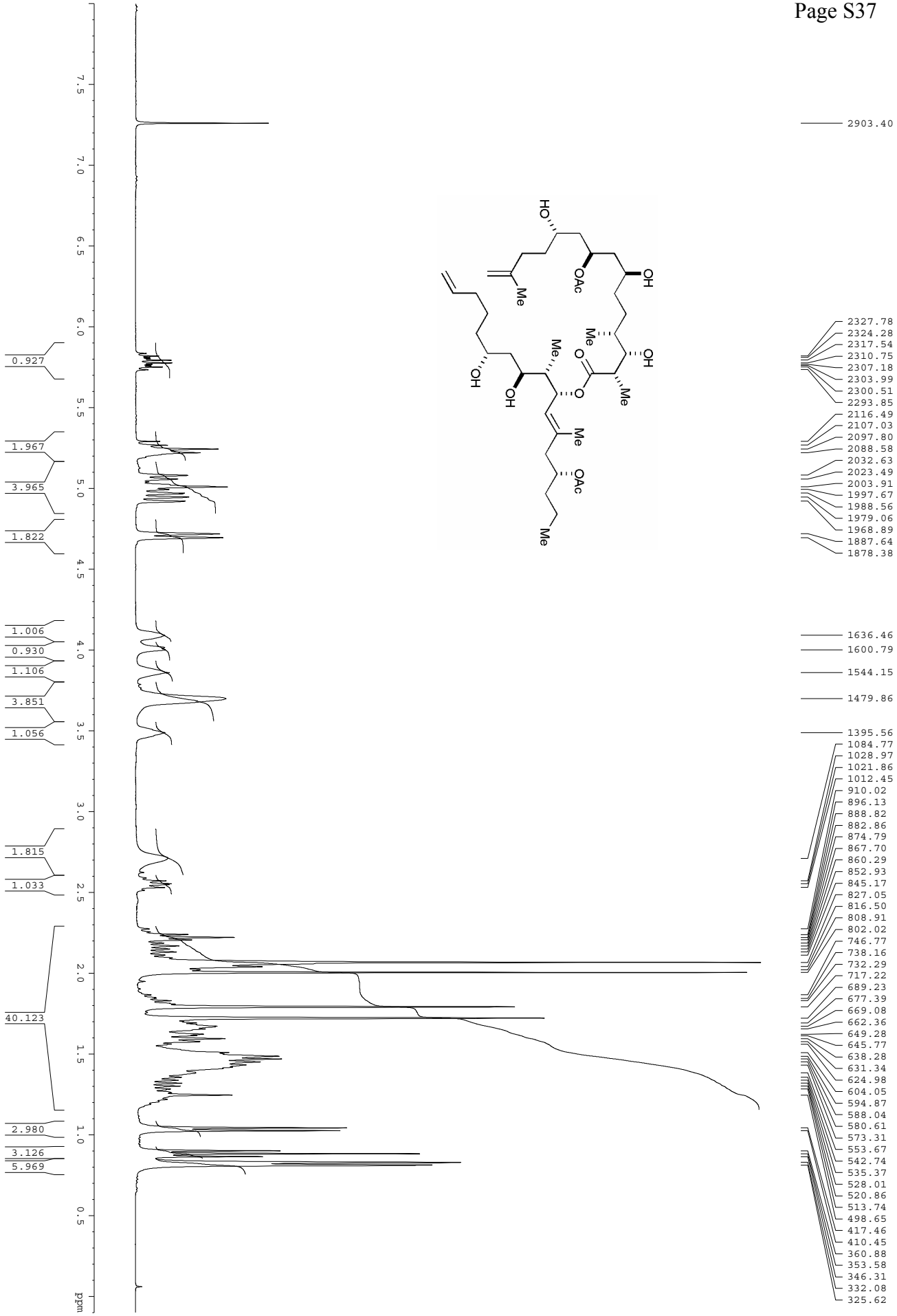
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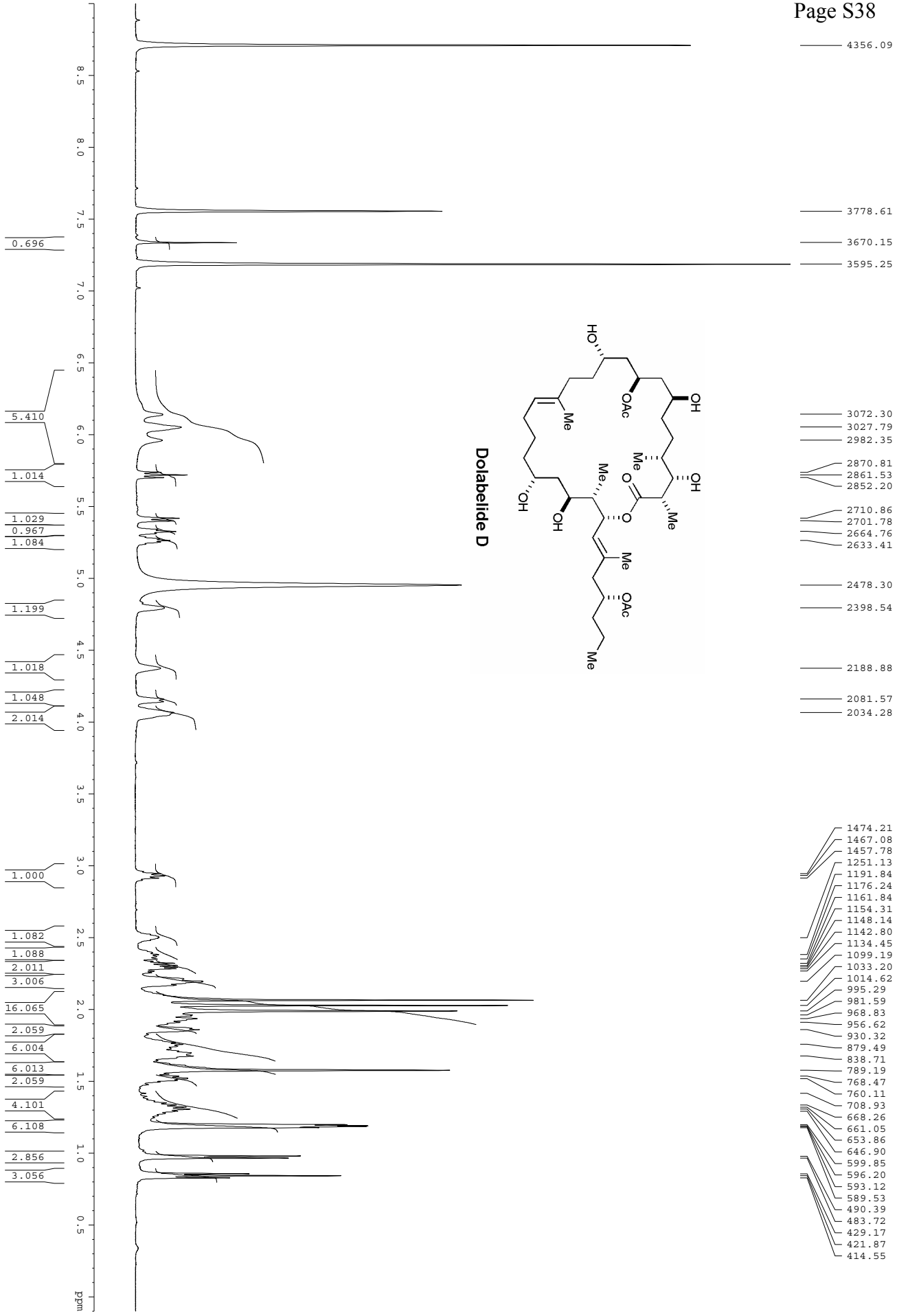
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6.004
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3.056
ppm
Dolabelide D
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OH
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Me
Me
O
O
OH
OH
Me
Me
OAc
Me