Supporting information
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A Unified Total Synthesis of the Actinoallolides, a Family of Potent Antitrypanosomal Macrolides

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Abstract: *Trypanosoma* protozoan parasites are the causative agents of Chagas disease and sleeping sickness, two neglected tropical diseases where there is an urgent need for improved treatments and the evaluation of promising drug leads like the actinoallolides. Enabled by the highly stereocontrolled aldol reactions of three chiral ketone building blocks, an efficient first total synthesis of the potent anti-trypanosomal macrolide (+)-actinoallolide A has been achieved in 17 steps and 8% overall yield. Our convergent route features an adventurous ring-closing metathesis to form the requisite trisubstituted (8*E*)-alkene in the 12-membered macrolactone, followed by the controlled installation of the labile transannular hemiacetal. Late-stage diversification then provides ready access to the congeneric (+)-actinoallolides B-E.

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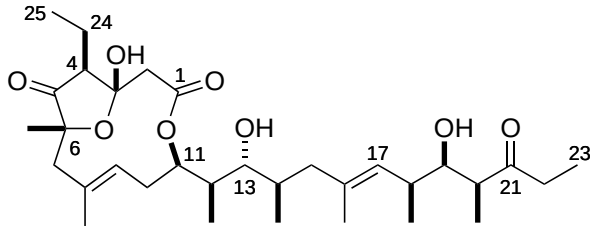
Contents

Nomenclature

The numbering system used for the actinoallolides follows that proposed by Omura and co-workers as shown below.[1] Methyl groups are denoted with reference to the skeletal carbon atom to which they are attached.



1 Experimental Procedures

1.1 General experimental procedures

Reagents were purified using standard laboratory procedures[2] and stored under an atmosphere of argon unless otherwise specified. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from potassium and sodium wire respectively with benzophenone as a radical indicator. Triethylamine (Et_3N) and diisopropylethylamine (DIPEA) were distilled from calcium hydride. Dicyclohexylboron chloride (Cy_2BCl) was distilled neat. All other chemicals were used as received from the supplier. All aqueous solutions were saturated unless otherwise stated.

Air or water sensitive reactions were carried out under positive pressure of argon in oven-dried glassware using standard air-free techniques. Purification by flash column chromatography was carried out using Merck Kieselgel 60 (230-400 mesh) silica gel and positive pressure of solvent.

1.2 Analytical procedures

TLC analysis was carried out using Merck Kieselgel 60 F254 plates and distilled solvents. The plates were visualised using UV (254 nm) light and stained using either a potassium permanganate or phosphomolybdic acid/cerium sulfate dip followed by heating.

NMR spectra were recorded using the following instruments: 400 MHz QNP Cryoprobe, 400 MHz AVIII HD BBO Smart Probe, 500 MHz DCH Cryoprobe, 500 MHz AVIII HD BBO Smart Probe, 500 MHz TCI Cryoprobe, 600 MHz Avance 600 BBI, 700 MHz TXO Cryoprobe. ^{1}H NMR spectra were recorded at 298 K in $CDCl_3$ using an internal deuterium solvent lock. These data are presented in the following format: chemical shift (δ/ppm, relative to trace undeuterated solvent (δ_H=7.26)), integration, multiplicity and coupling constants, assignment. Assignments have been made using the data shown as well as 2-D COSY, HSQC and HMBC spectra and comparison to assigned spectra of similar compounds. ^{13}C NMR spectra were recorded at 298 K in $CDCl_3$ using an internal deuterium solvent lock. Peaks are listed by chemical shift (δ/ppm) relative to solvent (δ_C=77.0).

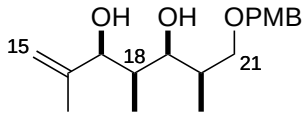
Fourier transform infrared (IR) spectroscopy was carried out using the thin-film technique on a Perkin-Elmer Spectrum One spectrometer. Maximal absorption wavelengths (ν_{max}) are reported in wavenumbers (cm^{-1}) and especially broad peaks are noted.

Optical rotation was measured at the sodium D line (589 nm) on a Perkin-Elmer 241 polarimeter using chloroform as the solvent and is reported as follows: $[\alpha]_D^{20}$, concentration (in g/100 mL).

High resolution mass spectrometry (HRMS) was carried out at the EPSRC UK National Mass Spectrometry Facility at Swansea University or the departmental mass spectrometry service (University Chemical Laboratories, Cambridge) using electrospray (ES) or nanospray (NS) ionisation techniques. The calculated and observed masses of the $[M+H]^+$, $[M+Na]^+$, $[M+K]^+$, $[M+NH_4]^+$ or $[M-H]^-$ ions are reported.

1.3 Experimental procedures and data

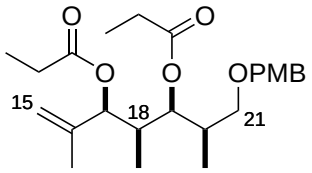
1,3-Diol 9



To a stirred solution of ketone **8** (5.00 g, 21.2 mmol) in CH_2Cl_2 (100 mL) at −78 °C was added a solution of $Ti(O^iPr)Cl_3$ (23.3 mmol) in CH_2Cl_2 (50 mL). DIPEA (4.05 mL, 23.3 mmol) was added dropwise followed by a solution of methacrolein (2.63 mL, 31.8 mmol) in CH_2Cl_2 (35 mL) over 1 h. Reaction progress was monitored by TLC and upon completion (30 min) was slowly added $LiBH_4$ at −78 °C (10.6 mL, 4 M in THF, 42.3 mmol). The reaction mixture was stirred for a further hour before quenching with AcOH (10 mL) and potassium sodium tartrate solution (100 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were stirred for 18 h with additional potassium sodium tartrate solution, dried with $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (P.E. 40-60:EtOAc, 10:1) to give diol **9** as a colourless oil (5.65 g, 19.1 mmol, 90%).

R_f: 0.16 (PE:EtOAc, 6:1). $[\alpha]_D^{20}$: −3.7 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23 (2H, d, J = 8.6 Hz, $H_{PMB\ Ar\text{-}H}$), 6.87 (2H, d, J = 8.6 Hz, $H_{PMB\ Ar\text{-}H}$), 5.02 (1H, m, H_{15A}), 4.92 (1H, m, H_{15B}), 4.42 (2H, s, $H_{PMB\ ArCH_2O}$), 4.20 (1H, m, H_{17}), 3.80 (3H, s, MeO_{PMB}), 3.80 (1H, m, H_{19}), 3.43 (2H, m, H_{21}), 2.90 (1H, d, J = 3.3 Hz, HO_{17}), 2.44 (1H, d, J = 3.0 Hz, HO_{19}), 1.98 (1H, m, H_{20}), 1.86 (1H, m, H_{18}), 1.66 (3H, s, Me_{16}), 1.06 (3H, d, J = 6.9 Hz, Me_{20}), 0.86 (3H, d, J = 7.0 Hz, Me_{18}). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.2, 145.9, 130.3, 129.2, 113.8, 110.2, 78.7, 78.2, 73.9, 73.0, 55.3, 36.9, 36.8, 29.7, 19.6, 13.2, 5.9. **IR** (thin film, ν_{max}/cm^{-1}): 3440 (br), 2922, 1610, 1514, 1247, 1035. **HRMS** (ES+): Calculated for $C_{18}H_{29}O_4$ $[M+H]^+$: 309.2060, found 309.2066.

Diester 10

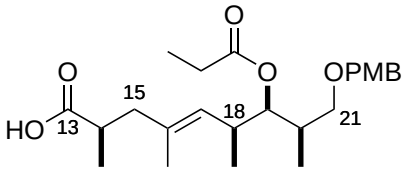


To a stirred solution of diol **9** (700 mg, 2.27 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added Et_3N (2.30 mL, 22.7 mmol), propionic anhydride (2.90 mL, 22.7 mmol) and DMAP (one crystal). The mixture was warmed to rt and stirred for 18 h before quenching with $NaHCO_3$ solution (10 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried with $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (P.E. 40-60:EtOAc, 20:1) to give diester **10** as a colourless oil (952 mg, 2.26 mmol, 99%).

R_f: 0.53 (PE:EtOAc, 6:1). $[\alpha]_D^{20}$: −13.7 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 (2H, d, J = 8.5 Hz, $H_{PMB\ Ar\text{-}H}$), 6.86 (2H, d, J = 8.5 Hz, $H_{PMB\ Ar\text{-}H}$), 5.14 (1H, d, J = 5.1

Hz, H_{17}), 5.05 (1H, dd, J = 6.6, 4.4 Hz, H_{19}), 4.92 (1H, m, H_{15A}), 4.83 (1H, m, H_{15B}), 4.36 (2H, s, $H_{PMB\ ArCH_2O}$), 3.80 (3H, s, MeO_{PMB}), 3.25 (2H, ABQ, H_{21}), 2.31 (4H, m, $H_{Propionate}$), 2.10 (1H, m, H_{20}), 2.10 (1H, m, H_{18}), 1.68 (3H, s, Me_{16}), 1.14 (3H, t, J = 7.6 Hz, $Me_{Propionate}$), 1.10 (3H, t, J = 7.6 Hz, $Me_{Propionate}$), 0.91 (3H, d, J = 7.2 Hz, Me_{20}), 0.89 (3H, d, J = 6.9 Hz, Me_{18}). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.8, 173.6, 159.0, 141.3, 130.6, 129.2, 113.6, 113.0, 76.8, 74.4, 72.7, 72.6, 55.3, 36.2, 35.1, 27.7, 27.7, 18.9, 11.6, 9.9, 9.4, 9.1. **IR** (thin film, ν_{max}/cm^{-1}): 2975, 2942, 1737, 1613, 1514, 1462, 1248, 1181, 1098. **HRMS** (ES+): Calculated for $C_{24}H_{37}O_6$ $[M+H]^+$: 421.2585, found 421.2584.

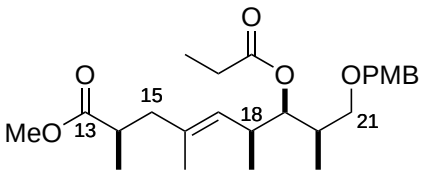
Carboxylic acid 11



To a stirred solution of diester **10** (50 mg, 0.119 mmol) in THF (15 mL) at −78 °C was added premixed and filtered Et_3N/TMSCl (0.30 mL, 1:1 v/v) and LDA (0.80 mL, 0.5 M in THF, 0.400 mmol). The mixture was stirred for 1.5 h then warmed to rt and stirred for a further 2 h before diluting with THF (15 mL) and heating to reflux for 4 h. The mixture was cooled to rt, diluted with ether (20 mL) and washed with 1 M HCl. The organic phase was dried with $MgSO_4$, concentrated *in vacuo* and the crude product submitted to the next reaction without purification.

R_f: 0.42 (PE:EtOAc, 1:1). **$[\alpha]_D^{20}$**: −1.0 (c 1.0, $CHCl_3$).**^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (2H, d, J = 8.5 Hz, $H_{PMB\ Ar\text{-}H}$), 6.87 (2H, d, J = 8.5 Hz, $H_{PMB\ Ar\text{-}H}$), 4.97 (1H, d, J = 10.0 Hz, H_{17}), 4.84 (1H, dd, J = 9.5, 2.2 Hz, H_{19}), 4.50 (1H, d, J = 11.4 Hz, $H_{PMB\ ArCH_2O}$), 4.38 (1H, d, J = 11.4 Hz, $H_{PMB\ ArCH_2O}$), 3.80 (3H, s, MeO_{PMB}), 3.24 (2H, m, H_{21}), 2.64 (1H, m, H_{14}), 2.64 (1H, m, H_{18}), 2.33 (2H, q, J = 7.6 Hz, $H_{Propionate}$), 2.25 (1H, dd, J = 13.2, 10.0 Hz, H_{15A}), 2.09 (1H, dd, J = 13.2, 6.3 Hz, H_{15B}), 2.06 (1H, m, H_{20}), 1.64 (3H, s, Me_{16}), 1.14 (3H, t, J = 7.6 Hz, $H_{Propionate}$), 1.13 (3H, d, J = 6.9 Hz, Me_{14}), 0.88 (3H, d, J = 6.6 Hz, Me_{20}), 0.85 (3H, d, J = 7.0 Hz, Me_{18}). **HRMS** (NSI-): Calculated for $C_{24}H_{35}O_6$ $[M-H]^-$: 419.2439, found 419.2444.

Methyl ester S1

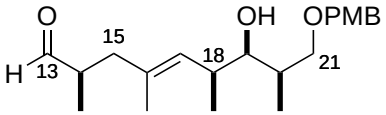


To a stirred solution of carboxylic acid **11** (50 mg, 0.119 mmol) in acetone (5 mL) was added K_2CO_3 (82 mg, 0.594 mmol) and MeI (0.074 mL, 1.19 mmol). The mixture was stirred for 24 h followed by addition of MeOH (2 mL) and stirring for an additional 2 h. The solvent was removed *in vacuo* and the residue dissolved in ether (5 mL) and H_2O (5 mL). The phases were separated and the aqueous phase extracted with ether (3 × 50 mL). The combined organic extracts were

dried with $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (P.E. 40-60:EtOAc, 20:1) to give methyl ester **S1** as a colourless oil (45 mg, 104 mmol, 87%).

R_f: 0.46 (PE:EtOAc, 6:1). $[\alpha]_D^{20}$: −5.5 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 (2H, d, J = 8.7 Hz, $H_{PMB\ Ar\text{-}H}$), 6.86 (2H, d, J = 8.7 Hz, $H_{PMB\ Ar\text{-}H}$), 4.95 (1H, m, H_{17}), 4.95 (1H, m, H_{19}), 4.39 (1H, d, J = 11.5 Hz, $H_{PMB\ ArCH_2O}$), 4.35 (1H, d, J = 11.5 Hz, $H_{PMB\ ArCH_2O}$), 3.80 (3H, s, MeO_{PMB}), 3.63 (3H, s, MeO), 3.24 (1H, dd, J = 9.1, 7.0 Hz, H_{21A}), 3.14 (1H, dd, J = 9.1, 6.8 Hz, H_{21B}), 2.63 (1H, m, H_{14}), 2.63 (1H, m, H_{18}), 2.36 (1H, dd, J = 13.7, 7.4 Hz, H_{15A}), 2.31 (2H, q, J = 7.6 Hz, $H_{Propionate}$), 2.02 (1H, dd, J = 13.7, 7.4 Hz, H_{15B}), 2.00 (1H, m, H_{20}), 1.62 (3H, d, J = 1.3 Hz, Me_{16}), 1.13 (3H, t, J = 7.6 Hz, $H_{Propionate}$), 1.09 (3H, d, J = 6.9 Hz, Me_{14}), 0.87 (3H, d, J = 6.8 Hz, Me_{20}), 0.87 (3H, d, J = 6.8 Hz, Me_{18}). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 176.9, 174.1, 159.1, 132.5, 130.7, 129.3, 129.1, 113.7, 76.9, 73.1, 72.8, 55.3, 51.6, 43.8, 37.8, 35.5, 34.8, 27.8, 17.6, 16.7, 16.0, 10.6, 9.5. **IR** (thin film, ν_{max}/cm^{-1}): 2973, 1737, 1613, 1514, 1461, 1360, 1248, 1186, 1086, 821. **HRMS** (ES+): Calculated for $C_{25}H_{39}O_6$ $[M+H]^+$: 435.2745, found 435.2741.

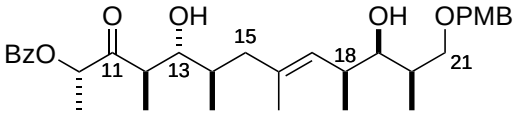
Aldehyde 12



To a stirred solution of diester **S1** (893 mg, 2.05 mmol) in toluene (40 mL) at −78 °C was added DIBAL-H (4.32 mL, 1 M in toluene, 4.32 mmol). The reaction mixture was stirred at −78 °C for 1 h before quenching with MeOH (1 mL) and potassium sodium tartrate solution (20 mL). The phases were separated and the aqueous phase extracted with ether (3 × 20 mL). The combined organic extracts were dried with $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (P.E. 40-60:EtOAc, 20:1) to give aldehyde **12** as a colourless oil (634 mg, 1.82 mmol, 89%).

R_f: 0.14 (PE:EtOAc, 6:1). $[\alpha]_D^{20}$: −11.9 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.59 (1H, d, J = 2.1 Hz, H_{13}), 7.24 (2H, d, J = 8.5 Hz, $H_{PMB\ Ar\text{-}H}$), 6.87 (2H, d, J = 8.5 Hz, $H_{PMB\ Ar\text{-}H}$), 4.93 (1H, d, J = 9.9 Hz, H_{17}), 4.45 (1H, d, J = 11.6 Hz, $H_{PMB\ ArCH_2O}$), 4.42 (1H, d, J = 11.6 Hz, $H_{PMB\ ArCH_2O}$), 3.81 (3H, s, MeO_{PMB}), 3.51 (1H, m, H_{19}), 3.48 (2H, m, H_{21}), 2.72 (1H, d, J = 2.8 Hz, HO_{19}), 2.48 (1H, m, H_{14}), 2.48 (1H, m, H_{18}), 2.39 (1H, dd, J = 13.7, 6.6 Hz, H_{15A}), 1.96 (1H, dd, J = 13.7, 7.9 Hz, H_{15B}), 1.80 (1H, m, H_{20}), 1.63 (3H, s, Me_{16}), 1.02 (3H, d, J = 6.7 Hz, Me_{14}), 1.02 (3H, d, J = 6.7 Hz, Me_{18}), 0.90 (3H, d, J = 7.0 Hz, Me_{20}). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 204.6, 158.9, 130.7, 130.4, 129.8, 128.8, 113.5, 77.7, 75.2, 72.8, 54.9, 44.0, 40.6, 36.3, 35.2, 17.6, 15.8, 12.7, 9.4. **IR** (thin film, ν_{max}/cm^{-1}): 3527 (br), 2931, 2353, 1724, 1513, 1247, 1089, 822. **HRMS** (ES+): Calculated for $C_{21}H_{33}O_4$ $[M+H]^+$: 349.2373, found 349.2368.

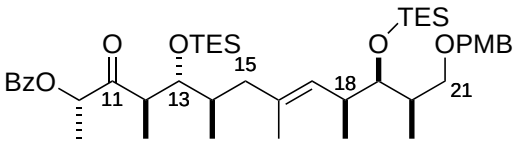
Aldol adduct 14



To a stirred solution of Cy_2BCl (3.90 mL, 17.8 mmol) in ether (18 mL) at 0 °C was added Et_3N (2.63 mL, 18.9 mmol) then a solution in ether (15 mL) of ketone **13** (3.54 g, 17.2 mmol). The mixture was stirred at 0 °C for 1.5 h before cooling to −78 °C. A solution of aldehyde **12** (1.73 mg, 4.91 mmol) in ether (15 mL) was added and the mixture stirred at −78 °C for 4 h then at -20 °C for 18 h and finally at 0 °C for 1.5 h. The reaction mixture was quenched with MeOH (12 mL), pH 7 buffer (12 mL) and H_2O_2 (30%, 11 mL) and stirred at rt for 1 h. The phases were separated and the aqueous phase extracted with ether (3 × 50 mL). The combined organic extracts were dried with $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (P.E. 40-60:EtOAc, 20:1) to give aldol adduct **14** as a colourless oil (2.43 g, 4.38 mmol, 89%).

R_f: 0.07 (PE:EtOAc, 6:1). $[\alpha]_D^{20}$: +13.0 (c 1.0 $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.08 (2H, d, J = 7.9 Hz, H_{Bz}), 7.59 (1H, t, J = 7.4 Hz, H_{Bz}), 7.46 (2H, t, J = 7.7 Hz, H_{Bz}), 7.23 (2H, d, J = 8.6 Hz, $H_{PMB\ Ar\text{-}H}$), 6.87 (2H, d, J = 8.6 Hz, $H_{PMB\ Ar\text{-}H}$), 5.46 (1H, q, J = 7.1 Hz, H_{10}), 4.87 (1H, d, J = 10.0 Hz, H_{17}), 4.43 (2H, ABQ, J = 11.6 Hz, $H_{PMB\ ArCH_2O}$), 3.80 (3H, s, MeO_{PMB}), 3.56 (1H, m, H_{13}), 3.50 (1H, m, H_{19}), 3.49 (2H, m, H_{21}), 3.07 (1H, q, J = 7.1 Hz, H_{12}), 2.68 (1H, d, J = 2.9 Hz, HO_{19}), 2.47 (1H, m, H_{18}), 2.41 (1H, d, J = 7.0 Hz, HO_{13}), 2.25 (1H, d, J = 12.6 Hz, H_{15A}), 1.85 (1H, m, H_{20}), 1.71 (1H, m, H_{14}), 1.70 (1H, dd, J = 12.6, 11.3 Hz, H_{15B}), 1.59 (3H, s, Me_{16}), 1.57 (3H, d, J = 7.1 Hz, Me_{10}), 1.28 (3H, d, J = 6.6 Hz, Me_{12}), 1.02 (3H, d, J = 6.5 Hz, Me_{18}), 0.91 (3H, d, J = 7.0 Hz, Me_{20}), 0.82 (3H, d, J = 6.5 Hz, Me_{14}). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 212.2, 165.9, 159.2, 133.4, 132.7, 130.2, 129.8, 129.8, 129.4, 129.2, 128.5, 113.8, 78.3, 78.0, 75.6, 74.6, 73.1, 55.3, 44.8, 40.4, 36.6, 35.6, 33.3, 18.0, 16.3, 16.1, 16.0, 14.7, 9.9. **IR** (thin film, ν_{max}/cm^{-1}): 2934, 1718, 1250, 1114, 713. **HRMS** (ES+): Calculated for $C_{33}H_{47}O_7$ $[M+H]^+$: 555.3322, found 555.3318.

Bis TES ether S2

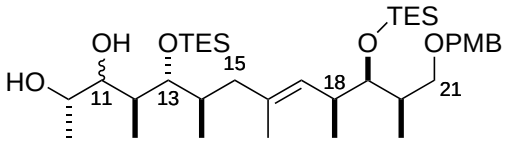


To a stirred solution of diol **14** (2.43 g, 4.37 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added 2,6-lutidine (2.00 mL, 17.3 mmol) then TESOTf (3.00 mL, 13.3 mmol). After 2 h, the reaction mixture was quenched by addition of MeOH (6 mL) then $NaHCO_3$ solution (20 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried with $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (P.E. 40-60:EtOAc, 20:1) to give bis TES ether **S2** as a colourless oil (3.40 mg, 4.34 mmol, 99%).

R_f: 0.71 (PE:EtOAc, 6:1). $[\alpha]_D^{20}$: +3.0 (c 1.0 $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.08 (2H, d, J = 8.0 Hz, H_{Bz}), 7.57 (1H, t, J = 7.4 Hz, H_{Bz}), 7.45 (2H, t, J = 7.7 Hz, H_{Bz}), 7.25 (2H, d, J = 8.6 Hz, $H_{PMB\ Ar\text{-}H}$), 6.87 (2H, d, J = 8.6 Hz, $H_{PMB\ Ar\text{-}H}$), 5.44 (1H, q, J = 7.0 Hz, H_{10}), 4.89 (1H, d, J = 9.7 Hz, H_{17}), 4.43 (1H, d, J = 11.6 Hz, $H_{PMB\ ArCH_2O}$), 4.38 (1H, d, J = 11.6 Hz, $H_{PMB\ ArCH_2O}$), 3.94 (1H, d, J = 9.0 Hz, H_{13}), 3.80 (3H, s, MeO_{PMB}), 3.56 (1H, dd, J = 8.4, 2.2, H_{19}), 3.35 (1H, dd, J = 8.8, 7.8 Hz, H_{21A}), 3.19 (1H, dd, J = 8.8, 6.7 Hz, H_{21B}), 3.11 (1H, m, H_{12}), 2.46 (1H, m, H_{18}), 2.08 (1H, m, H_{15A}), 1.93 (1H, m, H_{20}), 1.76 (1H, m, H_{14}), 1.75 (1H, m, H_{15B}), 1.55 (3H, s, Me_{16}), 1.51 (3H, d, J = 7.0 Hz, Me_{10}), 1.11

(3H, d, J = 7.0 Hz, Me_{12}), 0.94 (18H, m, $SiCH_2CH_3$), 0.92 (3H, m, Me_{18}), 0.84 (3H, d, J = 6.2 Hz, Me_{14}), 0.82 (3H, d, J = 6.8 Hz, Me_{20}), 0.58 (12H, m, $SiCH_2CH_3$). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 209.2, 165.7, 159.1, 133.2, 132.0, 130.8, 130.5, 129.8, 129.8, 129.3, 128.4, 113.7, 78.2, 77.2, 75.0, 73.5, 72.5, 55.2, 46.1, 41.0, 37.1, 37.0, 34.2, 18.3, 16.0, 16.0, 15.5, 14.3, 10.8, 7.1, 7.0, 5.5, 5.3. **IR** (thin film, ν_{max}/cm^{-1}): 2955, 1722, 1514, 1457, 1249. **HRMS** (ES+): Calculated for $C_{45}H_{78}O_7Si_2N$ $[M+NH_4]^+$: 800.5311, found 800.5306.

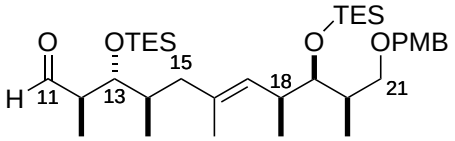
1,2-Diol S3



To a stirred solution of ketone **S2** (843 mg, 1.07 mmol) in THF (10 mL) at −78 °C was added $LiBH_4$ (1.63 mL, 4 M in hexanes, 6.5 mmol). The reaction mixture was warmed to rt and stirred for 24 h before quenching with NH_4Cl (10 mL). The phases were separated and the aqueous phase extracted with ether (3 × 10 mL). The combined organic extracts were dried with $MgSO_4$, concentrated *in vacuo* and the crude product submitted to the next reaction without purification.

R_f: 0.32 (PE:EtOAc, 6:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (2H, d, J = 8.4 Hz, $H_{PMB\ Ar\text{-}H}$), 6.87 (2H, d, J = 8.4 Hz, $H_{PMB\ Ar\text{-}H}$), 4.91 (1H, d, J = 9.8 Hz, H_{17}), 4.44 (1H, d, J = 11.5 Hz, $H_{PMB\ ArCH_2O}$), 4.38 (1H, d, J = 11.5 Hz, $H_{PMB\ ArCH_2O}$), 3.81 (3H, s, MeO_{PMB}), 3.77 (1H, m, H_{11}), 3.63 (1H, m, H_{10}), 3.57 (1H, dd, J = 8.4, 1.9, H_{19}), 3.51 (1H, t, J = 4.9 Hz, H_{13}), 3.48 (1H, s, HO_{11}), 3.35 (1H, dd, J = 8.7, 7.9 Hz, H_{21A}), 3.20 (1H, dd, J = 8.7, 6.8 Hz, H_{21B}), 2.83 (1H, d, J = 8.4 Hz, HO_{10}), 2.48 (1H, m, H_{18}), 2.19 (1H, d, J = 13.0 Hz, H_{15A}), 1.93 (1H, m, H_{20}), 1.81 (1H, m, H_{14}), 1.76 (1H, m, H_{12}), 1.61 (1H, m, H_{15B}), 1.56 (3H, s, Me_{16}), 1.17 (3H, d, J = 6.3 Hz, Me_{10}), 0.99 (9H, t, J = 7.9 Hz, $SiCH_2CH_3$), 0.95 (9H, t, J = 7.9 Hz, $SiCH_2CH_3$), 0.93 (3H, m, Me_{18}), 0.82 (3H, m, Me_{20}), 0.82 (3H, m, Me_{14}), 0.60 (6H, q, J = 7.9 Hz, $SiCH_2CH_3$), 0.57 (6H, q, J = 7.9 Hz, $SiCH_2CH_3$).

Aldehyde 15

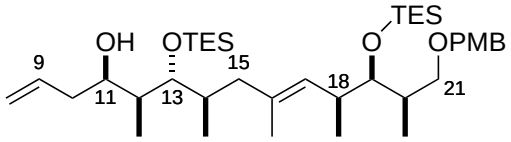


To a stirred solution of crude diol **S3** (730 mg, 1.07 mmol) in CH_2Cl_2 (15 mL) was added $NaIO_4$ on SiO_2 (8.80 g, 14% w/w, 5.87 mmol). The reaction mixture was stirred for 1 h before filtering through celite. The residue was concentrated *in vacuo* and purified by flash column chromatography (P.E. 40-60:EtOAc, 20:1) to give aldehyde **15** as a colourless oil (580 mg, 0.913 mmol, 85% over 2 steps).

R_f: 0.74 (PE:EtOAc, 6:1). **$[\alpha]_D^{20}$**: −12.0 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.78 (1H, d, J = 2.7 Hz, H_{11}), 7.24 (2H, d, J = 8.6 Hz, $H_{PMB\ Ar\text{-}H}$), 6.87 (2H, d, J = 8.6 Hz, $H_{PMB\ Ar\text{-}H}$), 4.90 (1H, d, J = 9.8 Hz, H_{17}), 4.43 (1H, d, J = 11.5 Hz, $H_{PMB\ ArCH_2O}$), 4.37 (1H,

d, J = 11.5 Hz, $H_{PMB\ ArCH_2O}$), 3.81 (3H, s, MeO_{PMB}), 3.72 (1H, t, J = 4.4 Hz, H_{13}), 3.57 (1H, dd, J = 8.4, 2.1, H_{19}), 3.34 (1H, dd, J = 8.8, 7.8 Hz, H_{21A}), 3.19 (1H, dd, J = 8.8, 6.6 Hz, H_{21B}), 2.52 (1H, m, H_{12}), 2.48 (1H, m, H_{18}), 2.14 (1H, dd, J = 12.9, 4.3 Hz, H_{15A}), 1.92 (1H, m, H_{20}), 1.83 (1H, m, H_{14}), 1.70 (1H, dd, J = 12.9, 10.0 Hz, H_{15B}), 1.55 (3H, s, Me_{16}), 1.09 (3H, d, J = 7.0 Hz, Me_{12}), 0.96 (9H, t, J = 7.9 Hz, $SiCH_2CH_3$), 0.95 (9H, t, J = 7.9 Hz, $SiCH_2CH_3$), 0.93 (3H, m, Me_{18}), 0.82 (3H, d, J = 6.8 Hz, Me_{20}), 0.79 (3H, d, J = 6.8 Hz, Me_{14}), 0.60 (12H, m, $SiCH_2CH_3$). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 205.4, 159.1, 131.7, 130.9, 130.7, 129.3, 113.7, 78.7, 76.9, 73.5, 72.6, 55.3, 49.2, 43.2, 37.1, 36.2, 29.7, 18.3, 16.0, 15.1, 12.3, 10.7, 7.2, 7.0, 5.6, 5.2. **IR** (thin film, ν_{max}/cm^{-1}): 2956, 2876, 1724, 1613, 1513, 1459, 1247, 1082, 1039, 1008, 820, 738. **HRMS** (ES+): Calculated for $C_{36}H_{67}O_5Si_2$ $[M+H]^+$: 635.4522, found 635.4519.

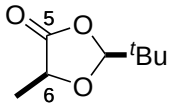
Side chain fragment 7



To a stirred solution of aldehyde **15** (5 mg, 7.89 μM) in CH_2Cl_2 (0.3 mL) over crushed CaH_2 at −78 °C was added allyltributyltin (5 μL, 15.8 μM) then $BF_3{\cdot}Et_2O$ (1.5 μL, 11.8 μM). The reaction mixture was stirred for 2 h, then quenched by addition of MeOH (50 μL) then NH_4Cl solution (1 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 2 mL). The combined organic extracts were dried with $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (P.E. 40-60:EtOAc, 10:1) to give alcohol **7** as a colourless oil (4.7 mg, 6.94 μM, 88%, dr = 15:1).

R_f: 0.52 (PE:EtOAc, 6:1). **$[\alpha]_D^{20}$**: +14.0 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (2H, d, J = 8.6 Hz, $H_{PMB\ Ar\text{-}H}$), 6.87 (2H, d, J = 8.6 Hz, $H_{PMB\ Ar\text{-}H}$), 5.80 (1H, dddd, J = 17.2, 10.2, 7.4, 6.9 Hz, H_9), 5.11 (1H, dd, J = 17.2, 1.7 Hz, H_{8A}), 5.06 (1H, d, J = 10.2 Hz, H_{8B}), 4.90 (1H, d, J = 9.5 Hz, H_{17}), 4.43 (1H, d, J = 11.5 Hz, $H_{PMB\ ArCH_2O}$), 4.39 (1H, d, J = 11.5 Hz, $H_{PMB\ ArCH_2O}$), 4.11 (1H, t, J = 7.1 Hz, H_{11}), 3.81 (3H, s, MeO_{PMB}), 3.57 (1H, m, H_{19}), 3.55 (1H, s, HO_{11}), 3.48 (1H, dd, J = 7.4, 2.3 Hz, H_{13}), 3.36 (1H, dd, J = 8.9, 7.5 Hz, H_{21A}), 3.20 (1H, dd, J = 8.9, 6.7 Hz, H_{21B}), 2.48 (1H, m, H_{18}), 2.31 (1H, m, H_{10A}), 2.27 (1H, m, H_{15A}), 2.09 (1H, m, H_{10B}), 1.93 (1H, m, H_{20}), 1.88 (1H, m, H_{14}), 1.73 (1H, m, H_{12}), 1.56 (3H, s, Me_{16}), 1.52 (1H, m, H_{15B}), 1.00 (3H, d, J = 7.3 Hz, Me_{12}), 0.98 (9H, t, J = 7.9 Hz, $SiCH_2CH_3$), 0.95 (9H, t, J = 7.9 Hz, $SiCH_2CH_3$), 0.94 (3H, m, Me_{18}), 0.83 (3H, d, J = 6.9 Hz, Me_{20}), 0.75 (3H, d, J = 6.8 Hz, Me_{14}), 0.67 (6H, q, J = 7.9 Hz, $SiCH_2CH_3$), 0.60 (6H, q, J = 7.9 Hz, $SiCH_2CH_3$). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.1, 135.5, 132.0, 131.0, 130.7, 129.3, 116.9, 113.7, 83.8, 76.9, 73.6, 72.6, 70.6, 55.3, 44.2, 39.4, 37.0, 37.0, 36.6, 35.5, 18.1, 15.9, 15.2, 11.7, 11.0, 7.2, 7.0, 5.6, 5.4. **IR** (thin film, ν_{max}/cm^{-1}): 2954, 1514, 1462, 1247, 1090, 1043, 1008, 823, 737. **HRMS** (ES+): Calculated for $C_{39}H_{73}O_5Si_2$ $[M+H]^+$: 677.4991, found 677.4985.

Dioxolanone 16

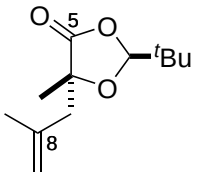


A solution of L-(+)-lactic acid (85% in H_2O, 14.6 g, 138 mmol) and $(MeO)_3CH$ (30.2 mL, 276 mmol) in cyclohexane (150 mL) was heated at 80 °C using Dean-Stark apparatus for 1 h with continual removal of a MeOH/cyclohexane mixture. The reaction was cooled to rt and concentrated *in vacuo*. Hexane (100 mL) as added and the solution cooled to 0 °C, followed by addition of *p*-TsOH·H_2O (0.600 g, 3.15 mmol). A solution of ^{t}BuCHO (10.0 mL, 92.1 mmol) in hexane (20 mL) was then added dropwise at 0 ℃. The reaction mixture was stirred at rt for 2 h, before being quenched with $NaHCO_3$ (200 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give crude dioxolanone **16**. This was purified by distillation under reduced pressure (62-64 ℃, 15 mmHg) to give pure dioxolanone **16** as a colourless oil (10.6 g, 101 mmol, 73%, >20:1 dr).

R_f: 0.48 (PE:EtOAc, 4:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.15 (1H, d, J = 1.2 Hz, H_{CH^tBu}), 4.36 (1H, qd, J = 6.7, 1.2 Hz, H_6), 1.48 (3H, d, J = 6.7 Hz, Me_6), 0.98 (9H, s, ^{t}Bu).

These data are consistent with those previously reported.[3]

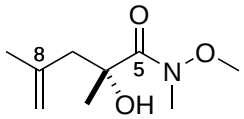
Alkylated dioxolanone 17



To a solution of LDA (12.4 mmol) in THF (50 mL) at −78 ℃ was added dropwise dioxolanone **16** (1.77 g, 11.2 mmol) in THF (10 mL) and the solution was stirred for 10 min. 3-Bromo-2-methylpropene (1.36 mL, 13.5 mmol) in THF (6 mL) was added dropwise and the solution was stirred for a further 30 min before warming to −10 ℃ over 3 h before being quenched with NH_4Cl (50 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (P.E. 40-60:EtOAc, 40:1) to yield dioxolanone **17** as a low melting point white solid (1.26 g, 5.94 mmol, 53%).

R_f: 0.21 (PE:EtOAc, 19:1). **$[\alpha]_D^{20}$**: +51.7 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.17 (1H, s, H_{CH^tBu}), 4.96 (1H, m, H_{9A}), 4.87 (1H, s, H_{9B}), 2.53 (1H, d, J = 13.8 Hz, H_{7A}, 2.32 (1H, d, J = 13.8 Hz, H_{7B}, 1.83 (3H, s, Me_8), 1.43 (3H, s, Me_6), 0.95 (9H, s, ^{t}Bu). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 175.8, 139.8, 116.4, 108.4, 80.5, 43.1, 34.4, 23.9, 23.2, 22.9. **IR** (thin film, ν_{max}/cm^{-1}): 2972, 2912, 2880, 1797, 1647, 1486, 1375, 1236, 1171, 1137, 1076, 979. **HRMS** (ES+): Calculated for $C_{12}H_{21}O_3$ $[M+H]^+$: 213.1491, found 213.1488.

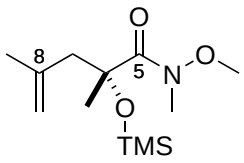
Weinreb amide 18



To a stirred solution of predried *N,O*-dimethylhydroxylamine hydrochloride (6.25 g, 164 mmol) in THF (160 mL) at −78 ℃ was added ^{n}BuLi (1.48 M in hexane, 86.5 mL, 128 mmol). The mixture was warmed to rt for 15 min then recooled to −78 ℃. Dioxolanone **17** (3.40 g, 16.0 mmol) in THF (10 mL) was then added and the reaction stirred for 1 h. The mixture was then warmed to −30 ℃ and stirred for a further 30 min before being quenched with NH_4Cl (100 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 70 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (P.E. 40-60:EtOAc, 10:1) to yield Weinreb amide **18** as a colourless oil (2.71 g, 149 mmol, 91%).

R_f: 0.15 (PE:EtOAc, 4:1). **$[\alpha]_D^{20}$**: +11.4 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.83 (1H, s, H_{9A}), 4.72 (1H, s, H_{9B}), 4.28 (1H, s, HO_6), 3.72 (3H, s, OMe), 3.25 (3H, s, NMe), 2.68 (1H, d, J = 13.8 Hz, H_{7A}), 2.38 (1H, d, J = 13.8 Hz, H_{7B}), 1.75 (3H, s, Me_8), 1.48 (3H, s, Me_6). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 176.8, 142.1, 114.1, 75.1, 60.8, 46.6, 33.8, 25.8, 24.2. **IR** (thin film, ν_{max}/cm^{-1}): 3416, 2971, 1638, 1460, 1353, 1175, 1100, 996, 894. **HRMS** (ES+): Calculated for $C_9H_{18}NO_3$ $[M+H]^+$: 188.1281, found 188.1280.

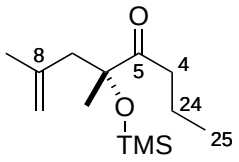
TMS ether S4



To a solution of alcohol **18** (2.70 g, 14.4 mmol) in CH_2Cl_2 (100 mL) was added Et_3N (5.00 mL, 36.1 mmol) and TMSCl (3.66 mL, 28.8 mmol). The reaction was stirred for 48 h before being quenched with $NaHCO_3$ (70 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (P.E. 40-60:EtOAc, 20:1) to yield TMS ether **S4** as a colourless oil (3.63 g, 14.0 mmol, 97%).

R_f: 0.38 (PE:EtOAc, 4:1). **$[\alpha]_D^{20}$**: +16.1 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.84 (1H, m, H_{9A}), 4.72 (1H, s, H_{9B}), 3.70 (3H, s, MeO), 3.31 (3H, br s, MeN), 2.55 (1H, d, J = 13.5 Hz, H_{7A}), 2.48 (1H, d, J = 13.5 Hz, H_{7B}), 1.75 (3H, s, Me_8), 1.52 (3H, s, Me_6), 0.16 (9H, s, TMS). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.2, 141.8, 114.6, 79.4, 60.4, 48.3, 35.6, 26.4, 23.9, 2.2. **IR** (thin film, ν_{max}/cm^{-1}): 2953, 1663, 1452, 1373, 1247, 1179, 1120, 1003, 842. **HRMS** (ES+): Calculated for $C_{12}H_{26}NO_3Si$ $[M+H]^+$: 260.1682, found 260.1652.

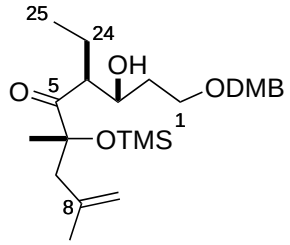
Propyl ketone 19



To a solution of Weinreb amide **S4** (3.60 g, 13.9 mmol) in THF (100 mL) at 0 ℃ was added ^{n}PrMgBr (63 mL, 1.1 M in THF, 69.4 mmol). The mixture was warmed to rt for 24 h before being quenched with NH_4Cl (70 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (P.E. 40-60:EtOAc, 30:1) to yield propyl ketone **19** as a colourless oil (2.95 g, 12.0 mmol, 86%).

R_f: 0.80 (PE:EtOAc, 4:1). $[\alpha]_D^{20}$: +1.7 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.79 (1H, s, H_{9A}), 4.63 (1H, s, H_{9B}), 2.56 (2H, t, J = 7.1 Hz, H_4), 2.50 (1H, d, J = 13.7 Hz, H_{7A}), 2.19 (1H, d, J = 13.7 Hz, H_{7B}), 1.72 (3H, s, Me_8), 1.54 (2H, app sex, J = 7.5 Hz, H_{24}), 1.35 (3H, s, Me_6), 0.90 (3H, t, J = 7.5 Hz, H_{25}), 0.16 (9H, s, TMS). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 215.3, 141.7, 114.5, 83.1, 48.6, 39.3, 26.0, 24.2, 16.8, 13.8, 2.3. **IR** (thin film, ν_{max}/cm^{-1}): 2958, 1716, 1645, 1453, 1369, 1250, 1120, 1036, 888, 836, 751. **HRMS** (ES+): Calculated for $C_{13}H_{27}NO_2Si$ $[M+H]^+$: 243.1780, found 243.1813.

Aldol adduct S5

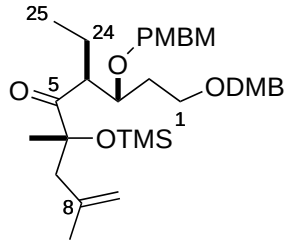


To a solution of LDA (0.86 mmol) in THF (12 mL) at −78 ℃ was added ketone **19** (700 mg, 2.89 mmol) in THF (6 mL). The reaction was stirred for 45 min before dropwise addition of aldehyde **20** (971 mg, 4.33 mmol) in THF (6 mL). The reaction was stirred for a further 3 h before being quenched with NH_4Cl (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (P.E. 40-60:EtOAc, 10:1) to yield aldol adduct **S5** as a colourless oil (952 mg, 2.04 mmol, 71%, 4:1 dr).

R_f: 0.21 (PE:EtOAc, 4:1). $[\alpha]_D^{20}$: +4.0 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.84 (3H, m, $H_{DMB\ Ar\text{-}H}$), 4.82 (1H, s, H_{9A}), 4.71 (1H, s, H_{9B}), 4.45 (2H, s, $H_{DMB\ ArCH_2O}$), 4.08 (1H, ddd, J = 9.8, 4.8, 2.4 Hz, H_3), 3.88 (3H, s, MeO_{DMB}), 3.87 (3H, s, MeO_{DMB}), 3.64 (2H, m, H_1), 3.23 (1H, ddd, J = 7.0, 4.8, 4.8 Hz, H_4), 3.07 (1H, d, J = 2.3 Hz, HO_3), 2.58 (1H, d, J = 14.0 Hz, H_{7A}, 2.21 (1H, d, J = 14.0 Hz, H_{7B}, 1.76 (2H, m, $H_{24A,2A}$), 1.75 (3H, s, Me_8), 1.67 (1H, m, H_{2B}), 1.60 (1H, m, H_{24B}), 1.37 (3H, s, Me_6), 0.87 (3H, t, J = 7.5 Hz, H_{25}), 0.19 (9H, s, TMS). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 217.4, 149.0, 148.6, 141.3, 130.6, 120.3, 115.3, 111.0, 110.9, 83.9, 73.2, 70.2, 68.7, 55.9, 55.8, 51.7, 47.5, 34.6, 26.8, 24.7, 19.0, 12.0, 2.5. **IR**

(thin film, ν_{max}/cm^{-1}): 3743, 3960, 1703, 1517, 1261, 1031, 843. **HRMS** (ES+): Calculated for $C_{25}H_{42}O_6SiNa$ $[M+Na]^+$: 489.2643, found 489.2643.

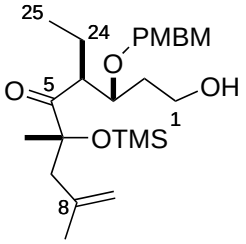
PMBM ether 21



To a solution of aldol adduct **S5** (820 mg, 1.76 mmol) in MeCN (36 mL) was added tetrabutylammonium iodide (30 mg, 0.09 mmol), DIPEA (1.53 mL, 8.79 mmol) and PMBMCl (1.28 mL, 70% by weight, 5.27 mmol). The reaction was heated under reflux for 12 h before being quenched with $NaHCO_3$ (20 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (P.E. 40-60:EtOAc, 10:1) to yield PMBM ether **21** as a colourless oil (1.01 g, 1.64 mmol, 93%).

$\mathbf{R_f}$: 0.27 (PE:EtOAc, 4:1). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$: +18.8 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23 (2H, d, J = 8.6 Hz, $H_{PMBM\ Ar\text{-}H}$), 6.85 (2H, d, J = 8.6 Hz, $H_{PMBM\ Ar\text{-}H}$), 6.83 (3H, m, $H_{DMB\ Ar\text{-}H}$), 4.79 (1H, s, H_{9A}), 4.71 (1H, s, H_{9B}), 4.68 (1H, d, J = 7.0 Hz, $H_{PMBM\ acetal\ A}$), 4.66 (1H, d, J = 7.0 Hz, $H_{PMBM\ acetal\ B}$), 4.50 (1H, d, J = 11.5 Hz, $H_{PMBM\ ArCH_2O}$), 4.46 (1H, d, J = 11.5 Hz, $H_{PMBM\ ArCH_2O}$), 4.40 (2H, s, $H_{DMB\ ArCH_2O}$), 4.15 (1H, dt, J = 8.4, 4.1 Hz, H_3), 3.88 (3H, s, MeO_{DMB}), 3.85 (3H, s, MeO_{DMB}), 3.79 (3H, s, MeO_{PMBM}), 3.55 (2H, m, H_1), 3.25 (1H, dt, J = 7.5, 4.4 Hz, H_4), 2.57 (1H, d, J = 14.0 Hz, H_{7A}), 2.21 (1H, d, J = 14.0 Hz, H_{7B}), 1.90 (2H, m, H_2), 1.83 (1H, dt, J = 14.2, 7.1 Hz, H_{24A}), 1.75 (3H, s, Me_8), 1.57 (1H, m, H_{24B}), 1.40 (3H, s, Me_6), 0.84 (3H, t, J = 7.5 Hz, H_{25}), 0.19 (9H, s, TMS). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 215.8, 159.2, 149.0, 148.5, 141.3, 131.1, 130.0, 129.5, 115.4, 113.7, 111.1, 110.8, 93.9, 84.1, 74.5, 72.8, 69.4, 66.9, 55.9, 55.8, 55.3, 51.3, 48.1, 34.3, 27.4, 24.8, 19.2, 12.3, 2.5. **IR** (thin film, ν_{max}/cm^{-1}): 2959, 1708, 1612, 1515, 1463, 1368, 1250, 1158, 1097, 1031, 843. **HRMS** (ES+): Calculated for $C_{34}H_{52}O_8SiNa$ $[M+Na]^+$: 639.3324, found 639.3337.

Primary alcohol 22

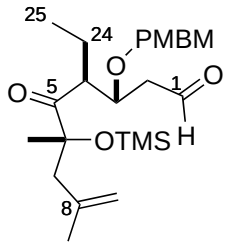


To a solution of DMB ether **21** (1.01 g, 1.64 mmol) in CH_2Cl_2/pH 7 buffer (30 mL, 9:1 v/v) at 0 ℃ was added DDQ (410 mg, 1.81 mmol). The reaction was carefully monitored *via* TLC analysis. Upon completion, the reaction mixture was quenched with $NaHCO_3$ (20 mL) and stirred vigorously for 1 h at rt. The layers were separated and the aqueous phase was extracted

with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (CH_2Cl_2 then P.E. 40-60:EtOAc, 3:1) to yield primary alcohol **22** as a colourless oil (650 mg, 1.39 mmol, 85%).

R_f: 0.08 (PE:EtOAc, 4:1). $[\alpha]_D^{20}$: +36.8 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (2H, d, J = 8.6 Hz, $H_{PMBM\ Ar\text{-}H}$), 6.87 (2H, d, J = 8.6 Hz, $H_{PMBM\ Ar\text{-}H}$), 4.80 (1H, s, H_{9A}), 4.73 (1H, d, J = 6.8 Hz, $H_{PMBM\ acetal\ A}$), 4.71 (1H, s, H_{9B}), 4.66 (1H, d, J = 6.8 Hz, $H_{PMBM\ acetal\ B}$), 4.62 (1H, d, J = 11.6 Hz, $H_{PMBM\ ArCH_2O}$), 4.47 (1H, d, J = 11.6 Hz, $H_{PMBM\ ArCH_2O}$), 4.16 (1H, dt, J = 8.0, 4.6 Hz, H_3), 3.80 (3H, s, MeO_{PMBM}), 3.80 (1H, m, H_{1A}), 3.73 (1H, m, H_{1B}), 3.27 (1H, dt, J = 7.3, 4.6 Hz, H_4), 2.56 (1H, d, J = 13.9 Hz, H_{7A}), 2.40 (1H, t, J = 5.7 Hz, HO_1), 2.21 (1H, d, J = 13.9 Hz, H_{7B}), 1.82 (2H, m, H_2), 1.78 (1H, m, H_{24A}), 1.75 (3H, s, Me_8), 1.50 (1H, m, H_{24B}), 1.41 (3H, s, Me_6), 0.84 (3H, t, J = 7.5 Hz, H_{25}), 0.21 (9H, s, TMS). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 216.2, 159.3, 141.2, 129.5, 129.4, 115.5, 113.9, 94.4, 84.2, 75.8, 69.8, 59.7, 55.3, 51.0, 48.0, 36.3, 27.3, 24.7, 19.4, 12.3, 2.6. **IR** (thin film, ν_{max}/cm^{-1}): 3490, 2959, 1708, 1514, 1251, 1033, 843. **HRMS** (ES+): Calculated for $C_{25}H_{42}O_6SiNa$ $[M+Na]^+$: 489.2643, found 489.2660.

Aldehyde S6

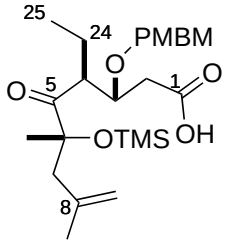


To a solution of $(COCl)_2$ (0.239 mL, 2.78 mmol) in CH_2Cl_2 (24 mL) at −78 ℃ was added DMSO (0.396 mL, 5.57 mmol) and the reaction was stirred for 30 min. A solution of primary alcohol **22** (650 mg, 1.39 mmol) in CH_2Cl_2 (6 mL) was added and the reaction stirred for 45 min. Et_3N (1.16 mL, 8.34 mmol) was then added and the reaction stirred for 45 min before being warmed to rt and stirred for a further 30 min. The reaction was then quenched with NH_4Cl (20 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (P.E. 40-60:EtOAc, 20:1) to yield aldehyde **S6** as a colourless oil (542 mg, 2.36 mmol, 85%).

R_f: 0.46 (PE:EtOAc, 4:1). $[\alpha]_D^{20}$: +19.0 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.79 (1H, dd, J = 2.9, 1.3 Hz, H_1), 7.25 (2H, d, J = 8.6 Hz, $H_{PMBM\ Ar\text{-}H}$), 6.87 (2H, d, J = 8.6 Hz, $H_{PMBM\ Ar\text{-}H}$), 4.81 (1H, s, H_{9A}), 4.74 (2H, s, $H_{PMBM\ acetal}$), 4.71 (1H, s, H_{9B}), 4.52 (1H, d, J = 11.5 Hz, $H_{PMBM\ ArCH_2O}$), 4.51 (1H, m, H_3), 4.42 (1H, d, J = 11.5 Hz, $H_{PMBM\ ArCH_2O}$), 3.80 (3H, s, MeO_{PMBM}), 3.42 (1H, dt, J = 5.8, 5.8 Hz, H_4), 2.74 (1H, ddd, J = 16.7, 7.6, 3.0 Hz, H_{2A}), 2.63 (1H, ddd, J = 16.7, 3.7, 1.3 Hz, H_{2B}), 2.61 (1H, d, J = 14.0 Hz, H_{7A}), 2.22 (1H, d, J = 14.0 Hz, H_{7B}), 1.81 (1H, ddq, J = 14.2, 7.1, 7.1 Hz, H_{24A}), 1.75 (3H, s, Me_8), 1.49 (1H, ddq, J = 14.2, 8.0, 7.5 Hz, H_{24B}), 1.38 (3H, s, Me_6), 0.87 (3H, t, J = 7.5 Hz, H_{25}), 0.22 (9H, s, TMS). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 215.7, 201.2, 159.3, 141.3, 129.5, 129.5, 115.4, 113.8, 94.0, 84.3, 72.7, 69.6, 55.3, 50.1, 47.6, 47.3, 27.1, 24.8, 20.1, 11.6, 2.5. **IR** (thin film, ν_{max}/cm^{-1}): 2960, 1721, 1613, 1514, 1250, 1034, 843. **HRMS** (ES+): Calculated for $C_{25}H_{41}O_6Si$ $[M+H]^+$:

465.2667, found 465.2658.

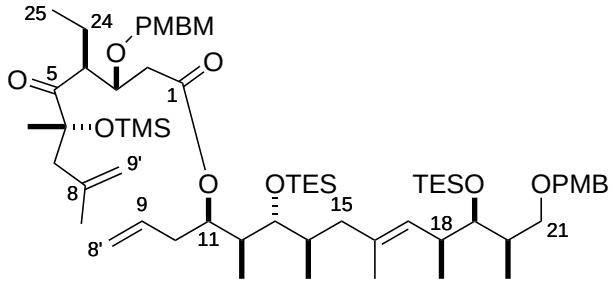
Carboxylic acid 6



To a solution of aldehyde **S6** (542 mg, 1.17 mmol) in ^{t}BuOH (20 mL) was added 2-methyl-2-butene (1.50 mL, 14.0 mmol). To this mixture was added a solution of $NaClO_2$ (80% by weight, 400 mg, 3.5 mmol) and $NaH_2PO_4{\cdot}2\,H_2O$ (1.10 g, 7.00 mmol) in H_2O (10 mL). The reaction was stirred for 2 h before being diluted with brine (10 mL) and CH_2Cl_2 (20 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to yield carboxylic acid **6** as a colourless oil (572 mg, 1.16 mmol, 99%).

R_f: 0.46 (PE:EtOAc, 4:1). $[\alpha]_D^{20}$: +13.6 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23 (2H, d, J = 8.4 Hz, $H_{PMBM\ Ar\text{-}H}$), 6.85 (2H, d, J = 8.4 Hz, $H_{PMBM\ Ar\text{-}H}$), 4.80 (1H, s, H_{9A}), 4.76 (1H, d, J = 7.0 Hz, $H_{PMBM\ acetal\ A}$), 4.72 (1H, d, J = 7.0 Hz, $H_{PMBM\ acetal\ B}$), 4.70 (1H, s, H_{9B}), 4.54 (1H, d, J = 11.8 Hz, $H_{PMBM\ ArCH_2O}$), 4.45 (1H, d, J = 11.8 Hz, $H_{PMBM\ ArCH_2O}$), 4.43 (1H, m, H_3), 3.79 (3H, s, MeO_{PMBM}), 3.44 (1H, dt, J = 5.7, 5.7 Hz, H_4), 2.69 (1H, dd, J = 15.9, 4.0 Hz, H_{2A}), 2.63 (1H, dd, J = 15.9, 7.1 Hz, H_{2B}), 2.81 (1H, d, J = 13.8 Hz, H_{7A}), 2.22 (1H, d, J = 13.8 Hz, H_{7B}), 1.82 (1H, ddq, J = 12.4, 6.2, 6.2 Hz, H_{24A}), 1.75 (3H, s, Me_8), 1.51 (1H, m, H_{24B}), 1.39 (3H, s, Me_6), 0.85 (3H, t, J = 7.4 Hz, H_{25}), 0.21 (9H, s, TMS). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 215.6, 175.9, 159.2, 141.4, 129.7, 129.6, 115.4, 113.8, 94.0, 84.4, 74.0, 69.6, 55.3, 50.1, 47.7, 38.5, 27.2, 24.8, 19.7, 11.7, 2.5. **IR** (thin film, ν_{max}/cm^{-1}): 2960, 1736, 1712, 1514, 1251, 1033, 843. **HRMS** (NSI−): Calculated for $C_{25}H_{39}O_7Si$ $[M-H]^-$: 479.2471, found 479.2457.

Ester S7

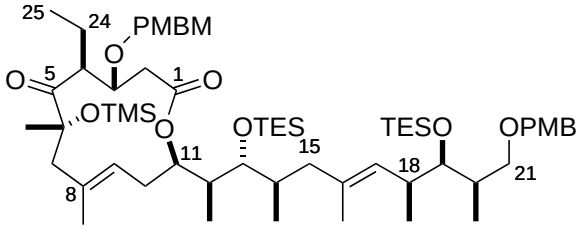


To a solution of carboxylic acid **6** (400 mg, 0.832 mmol) in toluene (10 mL) at 0 ℃ was added Et_3N (0.176 mL, 1.25 mmol) and 2,4,6-trichlorobenzoyl chloride (0.168 mL, 1.08 mmol). The reaction was stirred at rt for 6 h before addition of a solution of alcohol **7** (511 mg, 0.749 mmol) and DMAP (184 mg, 1.50 mmol) in toluene (6 mL). The reaction was stirred for 72 h then quenched with H_2O (10 mL). The layers were separated and the aqueous phase was extracted

with Et_2O (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (P.E. 40-60:EtOAc, 30:1) to yield ester **S7** as a colourless oil (883 mg, 99%).

R_f: 0.74 (PE:EtOAc, 4:1). $[\alpha]_D^{20}$: +5.0 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.26 (4H, m, $H_{PMBM\ and\ PMB\ Ar\text{-}H}$), 6.86 (4H, m, $H_{PMBM\ and\ PMB\ Ar\text{-}H}$), 5.68 (1H, dddd, J = 16.0, 9.4, 7.1, 7.1 Hz, H_9), 5.10 (1H, t, J = 6.6 Hz, H_{11}), 5.01 (1H, d, J = 16.0 Hz, $H_{8'A}$), 4.98 (1H, d, J = 9.4 Hz, $H_{8'B}$), 4.88 (1H, d, J = 9.9 Hz, H_{17}), 4.80 (1H, s, $H_{9'A}$), 4.72 (1H, s, $H_{9'B}$), 4.72 (2H, s, $H_{PMBM\ acetal}$), 4.51 (1H, d, J = 11.6 Hz, $H_{PMBM\ ArCH_2O}$), 4.50 (1H, m, H_3), 4.44 (1H, d, J = 11.6 Hz, $H_{PMBM\ ArCH_2O}$), 4.43 (1H, d, J = 11.5 Hz, $H_{PMB\ ArCH_2O}$), 4.38 (1H, d, J = 11.5 Hz, $H_{PMB\ ArCH_2O}$), 3.80 (3H, s, MeO_{PMB}), 3.79 (3H, s, MeO_{PMBM}), 3.55 (1H, dd, J = 8.2, 1.4 Hz, H_{19}), 3.44 (1H, m, H_4), 3.41 (1H, m, H_{13}), 3.35 (1H, dd, J = 8.6, 7.1 Hz, H_{21A}), 3.19 (1H, dd, J = 8.6, 7.1 Hz, H_{21B}), 2.61 (2H, m, H_2), 2.61 (1H, d, J = 13.8 Hz, H_{7A}), 2.47 (1H, m, H_{18}), 2.42 (1H, m, H_{10A}), 2.24 (1H, d, J = 13.8 Hz, H_{7B}), 2.19 (1H, m, H_{10B}), 2.06 (1H, d, J = 12.0 Hz, H_{15A}), 1.94 (1H, qd, J = 6.9, 1.2 Hz, H_{20}), 1.81 (1H, m, $_{24A}$), 1.75 (3H, s, Me_8), 1.75 (1H, m, H_{12}), 1.75 (1H, m, H_{14}), 1.69 (1H, m, H_{15B}), 1.55 (3H, s, Me_{16}), 1.43 (1H, m, $_{24B}$), 1.41 (3H, s, Me_6), 0.95 (18H, t, J = 8.0 Hz, $SiCH_2CH_3$), 0.93 (3H, d, J = 6.0 Hz, Me_{18}), 0.88 (3H, t, J = 7.4 Hz, H_{25}), 0.87 (3H, d, J = 7.0 Hz, Me_{12}), 0.82 (3H, d, J = 7.0 Hz, Me_{20}), 0.77 (3H, d, J = 6.2 Hz, Me_{14}), 0.62 (6H, q, J = 8.0 Hz, $SiCH_2CH_3$), 0.60 (6H, q, J = 8.0 Hz, $SiCH_2CH_3$), 0.22 (9H, s, TMS). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 215.7, 171.3, 159.1, 159.1, 141.5, 134.0, 132.3, 130.8, 130.3, 130.0, 129.6, 129.3, 117.4, 115.2, 113.7, 113.7, 93.9, 84.2, 78.5, 77.1, 73.9, 73.6, 73.5, 72.5, 69.4, 55.3, 55.3, 50.1, 47.7, 40.4, 39.2, 38.4, 37.1, 37.0, 36.9, 33.6, 27.1, 24.8, 20.1, 18.2, 16.8, 15.9, 12.1, 10.9, 10.5, 7.2, 7.1, 5.5, 5.5, 2.5. **IR** (thin film, ν_{max}/cm^{-1}): 2957, 2876, 1731, 1715, 1613, 1514, 1458, 1369, 1248, 1181, 1098, 1036, 842, 737. **HRMS** (ES+): Calculated for $C_{64}H_{114}O_{11}Si_3N$ $[M+NH_4]^+$: 1156.7694, found 1156.7685.

Macrocycle S8

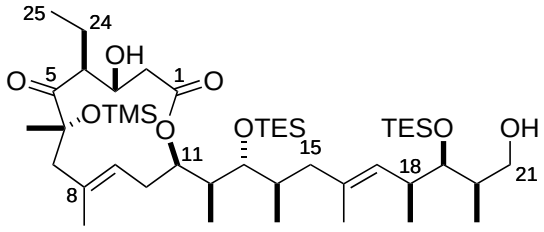


To a refluxing solution of ester **S7** (455 mg, 0.399 mmol) in thoroughly degassed (4 cycles of freeze-pump-thawing) toluene (500 mL) was added Hoveyda-Grubbs second generation catalyst (100 mg, 0.159 mmol) as a solution in degassed toluene (24 mL) in 3 portions over 3 days. After the first addition, the mixture was purged with argon to remove the ethene byproduct. The reaction was heated at reflux for a further 4 days before being filtered over a short plug of silica. The crude product was purified by flash column chromatography (P.E. 40-60:EtOAc, 20:1) to yield macrocycle **S8** as a colourless oil, inseparable from the byproduct formed by dimerisation of the terminal alkene. An analytically pure sample was not obtained at this stage as the C9 homodimer was inseparable from the macrocycle **S8**. Confirmation of **S8** was made in the subsequent step after PMB and PMBM deprotection.

The presence of the macrocycle in the crude mixture was confirmed by changes in the alkene

region of the ^{1}H NMR spectrum and by HRMS: Calculated for $C_{62}H_{106}O_{11}Si_3Na$ $[M+Na]^+$: 1133.6935, found 1133.6950.

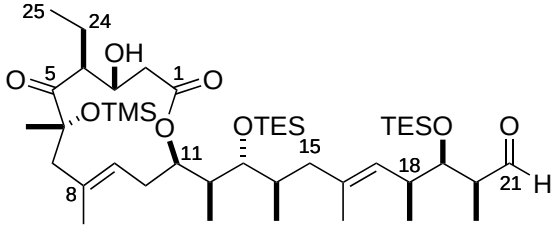
Diol 23



To a solution of crude macrocycle **S8** (58.0 mg, 0.050 mmol) in 9:1 CH_2Cl_2/pH 7 buffer (2 mL) at 0 ℃ was added DDQ (47.5 mg, 0.209 mmol). The reaction was warmed to rt and stirred for 1 h. When TLC analysis indicated that the reaction had gone to completion, it was quenched with $NaHCO_3$ (2 mL) and stirred vigorously for 1 h. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. THe filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (CH_2Cl_2 then P.E. 40-60:EtOAc, 15:1) to yield diol **23** as a colourless oil (35 mg, 0.0419 mmol, 70% over 2 steps).

$\mathbf{R_f}$: 0.56 (PE:EtOAc, 4:1). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$: −68.2 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.35 (1H, dt, J = 11.7, 3.2 Hz, H_{11}), 5.09 (1H, d, J = 10.8 Hz, H_9), 4.89 (1H, d, J = 9.5 Hz, H_{17}), 4.07 (1H, dddd, J = 8.7, 4.8, 3.6, 3.6 Hz, H_3), 3.65 (1H, d, J = 4.8 Hz, HO_3), 3.58 (1H, m, H_{19}), 3.58 (1H, m, H_{21A}), 3.47 (1H, m, H_{21B}), 3.38 (1H, dd, J = 4.5, 5.3 Hz, H_{13}), 2.83 (1H, dt, J = 5.5, 3.9 Hz, H_4), 2.61 (2H, m, H_7), 2.55 (1H, m, H_{18}), 2.50 (2H, m, H_2), 2.50 (1H, m, H_{10A}), 2.17 (1H, dd, J = 12.2, 2.4 Hz, H_{15A}), 1.95 (1H, m, H_{10B}), 1.88 (1H, m, H_{20}), 1.88 (1H, m, H_{24A}), 1.83 (1H, t, J = 5.4 Hz, HO_{21}), 1.82 (1H, m, H_{24B}), 1.79 (1H, m, H_{14}), 1.76 (1H, m, H_{12}), 1.63 (1H, dd, J = 12.2, 11.4 Hz, H_{15B}), 1.58 (3H, s, Me_{16}), 1.57 (3H, s, Me_8), 1.43 (3H, s, Me_6), 1.00 (3H, t, J = 7.6 Hz, H_{25}), 0.98 (9H, t, J = 7.9 Hz, $SiCH_2CH_3$), 0.96 (9H, t, J = 7.9 Hz, $SiCH_2CH_3$), 0.96 (3H, d, J = 6.3 Hz, Me_{18}), 0.95 (3H, d, J = 3.7 Hz, Me_{12}), 0.82 (3H, d, J = 7.1 Hz, Me_{20}), 0.78 (3H, d, J = 6.8 Hz, Me_{14}), 0.64 (6H, q, J = 8.0 Hz, $SiCH_2CH_3$), 0.64 (6H, q, J = 8.0 Hz, $SiCH_2CH_3$), 0.14 (9H, s, TMS). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 217.2, 171.5, 134.9, 132.4, 130.5, 125.5, 83.5, 79.3, 77.9, 73.3, 68.7, 66.3, 52.9, 49.5, 41.8, 41.0, 40.0, 39.2, 36.4, 34.5, 33.5, 28.5, 19.9, 18.3, 16.4, 16.0, 15.1, 12.6, 12.3, 11.3, 7.1, 7.1, 5.5, 5.4, 2.7. **IR** (thin film, ν_{max}/cm^{-1}): 2956, 2877, 1733, 1705, 1459, 1416, 1381, 1247, 1182, 1095, 1019, 974, 842, 736. **HRMS** (ES+): Calculated for $C_{45}H_{88}O_8Si_3K$ $[M+K]^+$: 879.5419, found 879.5452.

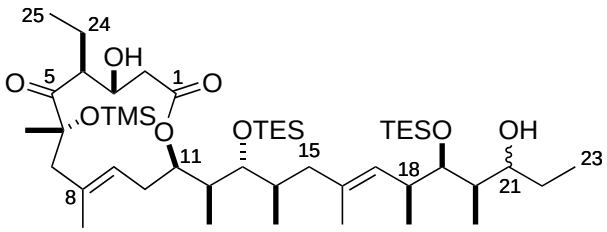
Aldehyde 24



To a solution of primary alcohol **S8** (24.2 mg, 0.0290 mmol) in CH_2Cl_2 (2 mL) was added bis(acetoxy)iodobenzene (13.9 mg, 0.0430 mmol) and TEMPO (1.8 mh, 0.0120 mmol). The reaction was stirred for 4 h before being quenched with $NaHCO_3/Na_2S_2O_3$ (2 mL, 1:1 v/v) and stirred vigorously for 1 h. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (P.E. 40-60:EtOAc, 20:1) to yield aldehyde **24** as a colourless oil (21.7 mg, 90%).

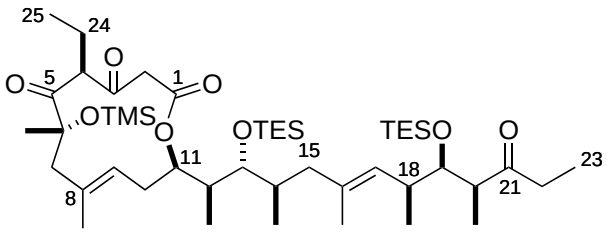
R_f: 0.78 (PE:EtOAc, 4:1). $[\alpha]_D^{20}$: −39.1 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.73 (1H, s, H_{21}), 5.35 (1H, dt, J = 11.6, 2.6 Hz, H_{11}), 5.09 (1H, d, J = 10.0 Hz, H_9), 4.90 (1H, d, J = 9.8 Hz, H_{17}), 4.07 (1H, dddd, J = 7.9, 4.3, 3.7, 3.7 Hz, H_3), 3.98 (1H, dd, J = 8.1, 2.2 Hz, H_{19}), 3.66 (1H, d, J = 5.0 Hz, HO_3), 3.38 (1H, dd, J = 4.7, 4.7 Hz, H_{13}), 2.83 (1H, dt, J = 4.0, 4.0 Hz, H_4), 2.61 (2H, m, H_7), 2.55 (1H, m, H_{18}), 2.50 (2H, m, H_2), 2.50 (1H, m, H_{10A}), 2.48 (1H, m, H_{20}), 2.18 (1H, d, J = 12.7 Hz, H_{15A}), 1.95 (1H, m, H_{10B}), 1.89 (1H, m, H_{24A}), 1.80 (1H, m, H_{24B}), 1.79 (1H, m, H_{14}), 1.76 (1H, m, H_{12}), 1.64 (1H, dd, J = 12.7, 11.9 Hz, H_{15B}), 1.58 (3H, s, Me_{16}), 1.57 (3H, s, Me_8), 1.43 (3H, s, Me_6), 1.09 (3H, d, J = 7.0 Hz, Me_{20}), 1.01 (3H, t, J = 7.5 Hz, H_{25}), 0.98 (3H, d, J = 6.6 Hz, Me_{18}), 0.97 (9H, t, J = 7.9 Hz, $SiCH_2CH_3$), 0.95 (9H, t, J = 7.9 Hz, $SiCH_2CH_3$), 0.95 (3H, m, Me_{12}), 0.78 (3H, d, J = 6.7 Hz, Me_{14}), 0.64 (6H, q, J = 8.0 Hz, $SiCH_2CH_3$), 0.59 (6H, q, J = 8.0 Hz, $SiCH_2CH_3$), 0.14 (9H, s, TMS). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 217.3, 205.5, 171.5, 134.9, 134.2, 129.5, 125.5, 83.6, 79.3, 75.7, 73.2, 68.7, 52.9, 51.2, 49.5, 41.8, 41.0, 39.2, 37.3, 34.3, 33.5, 28.6, 19.9, 17.8, 16.4, 16.1, 15.2, 12.6, 12.2, 7.5, 7.1, 7.0, 5.5, 5.3, 2.8. **IR** (thin film, ν_{max}/cm^{-1}): 2959, 1731, 1702, 1708, 1458, 1246, 1013, 843, 742. **HRMS** (ES+): Calculated for $C_{45}H_{87}O_8Si_3$ $[M+H]^+$: 839.5703, found 839.5743.

Diol S9



To a solution of aldehyde **24** (3.7 mg, 4.4 μmol) in Et_2O (0.5 mL) at −78 ℃ was added EtMgBr (22 μL, 0.8M in Et_2O, 18 μmol). The reaction was allowed to warm to −40 ℃ and maintained at that temperature for 30 min. The mixture was then recooled to −78 ℃ and quenched with MeOH (0.1 mL) then NH_4Cl (1 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 1 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The crude diol **S9** (3.8 mg) was carried forward to the next step without purification.

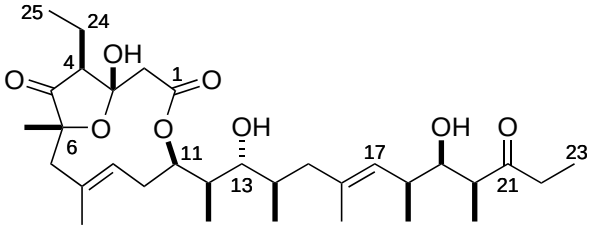
Triketone 25



To a solution of diol **S9** (20.0 mg, 23.8 μmol) in CH_2Cl_2 (5 mL) was added $NaHCO_3$ (23.8 mg, 283 μmol) then Dess-Martin periodinane (60.0 mg, 142 μmol) and the reaction was stirred for 18 h. The reaction was then quenched with $NaHCO_3$ (2 mL) and $Na_2S_2O_3$ (2 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography on florisil (P.E. 40-60:EtOAc, 40:1) to yield triketone **25** as a colourless oil (18.7 mg, 21.6 μmol, 91% over 2 steps).

R_f: 0.82 (PE:EtOAc, 4:1). $[\alpha]_D^{20}$: −64.9 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.23 (1H, dt, J = 11.1, 3.8 Hz, H_{11}), 5.18 (1H, dd, J = 9.3, 6.0 Hz, H_9), 4.89 (1H, d, J = 9.6 Hz, H_{17}), 4.05 (1H, t, J = 6.9 Hz, H_4), 3.88 (1H, dd, J = 6.5, 4.9 Hz, H_{19}), 3.51 (1H, d, J = 17.9 Hz, H_{2A}), 3.38 (1H, dd, J = 4.8, 4.8 Hz, H_{13}), 3.23 (1H, d, J = 17.9 Hz, H_{2B}), 2.68 (1H, d, J = 13.9 Hz, H_{7A}), 2.62 (1H, m, H_{20}), 2.46 (2H, qd, J = 7.0, 2.5 Hz, H_{22}), 2.38 (1H, m, H_{10A}), 2.37 (1H, m, H_{18}), 2.27 (1H, d, J = 13.9 Hz, H_{7B}), 2.20 (1H, d, J = 12.9 Hz, H_{15A}), 2.09 (1H, m, H_{24A}), 2.08 (1H, m, H_{10B}), 1.77 (1H, m, H_{24B}), 1.77 (1H, m, H_{14}), 1.77 (1H, m, H_{12}), 1.69 (3H, s, Me_8), 1.58 (1H, d, J = 12.9 Hz, H_{15B}), 1.54 (3H, s, Me_{16}), 1.45 (3H, s, Me_6), 1.08 (3H, d, J = 7.0 Hz, Me_{20}), 1.02 (3H, t, J = 7.3 Hz, H_{23}), 0.97 (3H, d, J = 7.4 Hz, Me_{12}), 0.96 (3H, d, J = 7.6 Hz, Me_{18}), 0.95 (18H, t, J = 7.6 Hz, $SiCH_2CH_3$), 0.91 (3H, t, J = 7.4 Hz, H_{25}), 0.75 (3H, d, J = 6.9 Hz, Me_{14}), 0.59 (12H, q, J = 7.6 Hz, $SiCH_2CH_3$), 0.19 (9H, s, TMS). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 214.0, 209.0, 198.0, 167.3, 134.8, 133.5, 130.5, 126.3, 85.5, 79.4, 77.1, 74.4, 64.8, 50.5, 49.5, 47.4, 42.3, 41.4, 37.6, 35.0, 34.1, 33.1, 28.8, 21.9, 18.3, 16.8, 16.3, 15.9, 12.3, 12.2, 12.0, 7.7, 7.1, 7.1, 5.4, 5.3, 2.3. **IR** (thin film, ν_{max}/cm^{-1}): 2956, 1878, 1737, 1726, 1713, 16941459, 1380, 1320, 1251, 1159, 1097, 1010, 976, 843, 737. **HRMS** (ES+): Calculated for $C_{47}H_{92}O_8Si_3N$ $[M+NH_4]^+$: 882.6125, found 882.6124.

Actinoallolide A (1)

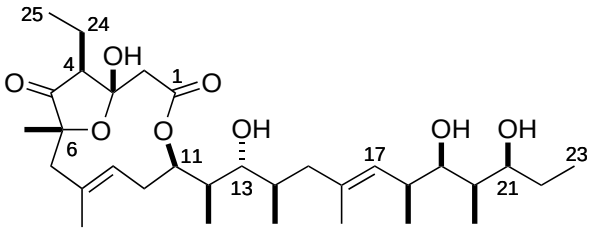


To a solution of triketone **25** (1.5 mg, 1.7 μmol) in THF (0.2 mL) at 0 ℃ was added pyridine:HF·pyridine (100 μL, 3:1 v/v, 960 μmol). The reaction was warmed to 40 ℃ and stirred for 2 h. The reaction was then quenched with $NaHCO_3$ (1 mL) followed by addition of solid $NaHCO_3$ until effervescence ceased. The layers were separated and the aqueous phase was extracted with Et_2O

(3 × 1 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (P.E. 40-60:EtOAc, 2:1) to yield actinoallolide A (**1**) as a colourless oil (1.0 mg, 1.7 μmol, 99%).

R_f: 0.46 (PE:EtOAc, 1:1). $[\alpha]_D^{20}$: +100.3 (c 0.1, MeOH), (lit. = +105.2 °)[1]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.40 (1H, ddd, J = 7.1, 7.1, 1.8 Hz, H_{11}), 5.13 (1H, dd, J = 7.8, 7.8 Hz, H_9), 4.88 (1H, d, J = 9.8 Hz, H_{17}), 3.64 (1H, ddd, J = 9.4, 2.3, 2.3 Hz, H_{19}), 3.26 (1H, ddd, J = 9.2, 4.9, 2.5 Hz, H_{13}), 2.91 (1H, d, J = 12.0 Hz, H_{2A}), 2.83 (1H, dd, J = 7.6, 5.5 Hz, H_4), 2.77 (1H, d, J = 12.0 Hz, H_{2B}), 2.67 (1H, qd, J = 7.3, 2.2 Hz, H_{20}), 2.52 (1H, m, H_{22A}), 2.50 (1H, m, H_{10A}), 2.46 (1H, m, H_{18}), 2.44 (1H, m, H_{22B}), 2.34 (1H, m, H_{10B}), 2.36 (1H, d, J = 13.4 Hz, H_{7A}), 2.30 (1H, d, J = 13.4 Hz, H_{7B}), 2.13 (1H, d, J = 11.0 Hz, H_{15A}), 1.84 (1H, m, H_{24A}), 1.83 (1H, m, H_{14}), 1.78 (1H, m, H_{12}), 1.78 (1H, m, H_{15B}), 1.63 (3H, s, Me_{16}), 1.61 (1H, m, H_{24B}), 1.47 (3H, s, Me_8), 1.34 (3H, s, Me_6), 1.14 (3H, t, J = 7.5 Hz, H_{25}), 1.07 (3H, d, J = 7.0 Hz, Me_{20}), 1.05 (3H, d, J = 6.4 Hz, Me_{18}), 1.05 (3H, t, J = 7.5 Hz, H_{23}), 1.01 (3H, d, J = 7.0 Hz, Me_{12}), 0.89 (3H, d, J = 6.6 Hz, Me_{14}). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 217.7, 217.3, 170.2, 133.7, 131.7, 128.8, 126.5, 102.3, 82.1, 76.6, 74.9, 73.6, 53.3, 48.9, 47.5, 46.7, 40.6, 38.8, 35.9, 34.8, 32.2, 29.9, 26.8, 18.7, 17.9, 17.2, 16.9, 16.1, 12.1, 10.2, 9.4, 7.7. **IR** (thin film, ν_{max}/cm^{-1}): 2926, 1704, 1455, 1314, 1147, 977. **HRMS** (ES+): Calculated for $C_{32}H_{52}O_8Na$ $[M+Na]^+$: 587.3554, found 587.3570.

Actinoallolide B (2)

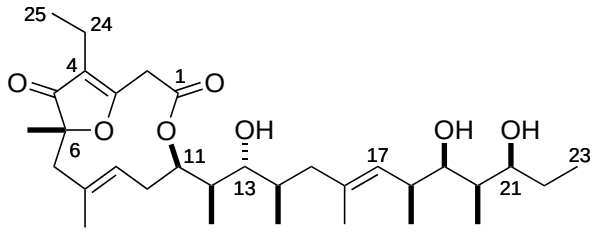


To a solution of actinoallolide A (**1**) (4.0 mg, 7.1 μmol) in THF (1 mL) was added triethylborane (31 μL, 1M solution in hexane, 31 μmol). After streaming of air (2 mL), the reaction was stirred for 2 h then cooled to −78 ℃ before addition of $NaBH_4$ (3.4 mg, 71 μmol), followed after 1 h by MeOH (0.25 mL). The reaction was stirred for a further 4 h before warming to rt. The reaction was then quenched with pH 7 buffer/30% H_2O_2/MeOH (1 mL, 1:1:1 v/v) and stirred for a further 30 min. After dilution with NH_4Cl (1 mL), the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography on florisil (P.E. 40-60:EtOAc, 3:1) to yield actinoallolide B (**2**) as a colourless oil (4.0 mg, 7.1 μmol, 99%).

R_f: 0.39 (PE:EtOAc, 1:1). $[\alpha]_D^{20}$: +82.0 (c 0.1, MeOH), (lit. = +102.7 °)[1]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.39 (1H, ddd, J = 7.9, 7.9, 1.8 Hz, H_{11}), 5.13 (1H, dd, J = 7.5, 7.5 Hz, H_9), 4.88 (1H, d, J = 9.9 Hz, H_{17}), 3.71 (1H, dd, J = 7.2, 6.2 Hz, H_{21}), 3.52 (1H, d, J = 9.5 Hz, H_{19}), 3.26 (1H, ddd, J = 9.6, 4.9, 2.6 Hz, H_{13}), 2.91 (1H, d, J = 12.1 Hz, H_{2A}), 2.84 (1H, dd, J = 7.9, 5.8 Hz, H_4), 2.77 (1H, m, J = 12.1 Hz, H_{2B}), 2.52 (1H, m, H_{18}), 2.51 (1H, m, H_{10A}), 2.35 (1H, m, H_{7A}), 2.33 (1H, m, H_{10B}), 2.29 (1H, m, H_{7B}), 2.12 (1H, d, J = 12.4 Hz, H_{15A}), 1.84 (1H, m, H_{24A}), 1.82 (1H, m, H_{14}), 1.78 (1H, m, H_{12}), 1.77 (1H, m, H_{15B}), 1.66 (1H, m,

H_{20}), 1.63 (3H, d, J = 0.7 Hz, Me_{16}), 1.61 (1H, m, H_{24B}), 1.53 (1H, m, H_{22A}), 1.47 (3H, d, J = 0.8 Hz, Me_8), 1.42 (1H, m, H_{22B}), 1.34 (3H, s, Me_6), 1.14 (3H, t, J = 7.5 Hz, H_{25}), 1.04 (3H, d, J = 6.6 Hz, Me_{18}), 1.00 (3H, d, J = 7.0 Hz, Me_{12}), 0.90 (3H, t, J = 7.4 Hz, H_{23}), 0.88 (3H, d, J = 6.4 Hz, Me_{14}), 0.84 (3H, d, J = 7.1 Hz, Me_{20}). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 217.7, 170.1, 133.2, 131.7, 129.1, 126.5, 102.3, 82.1, 82.0, 79.3, 76.6, 73.6, 53.3, 48.9, 46.7, 40.6, 38.7, 37.8, 36.8, 32.4, 29.9, 28.1, 26.8, 18.4, 17.9, 17.2, 17.0, 16.2, 12.0, 10.4, 10.3, 4.2. **IR** (thin film, ν_{max}/cm^{-1}): 3420, 2963, 1754, 1719, 1457, 1317, 1149, 1102, 972. **HRMS** (ES+): Calculated for $C_{32}H_{54}O_8K$ $[M+K]^+$: 605.3450, found 605.3431.

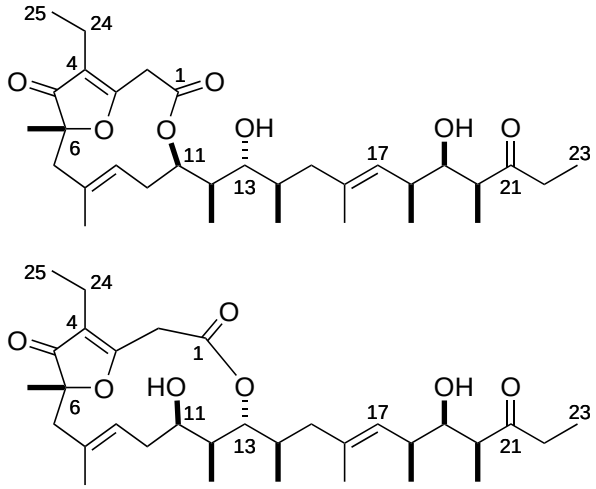
Actinoallolide D (4)



To a solution of actinoallolide B (**2**) (3.0 mg, 5.3 μmol) in CH_2Cl_2 (1 mL) at rt was added TFA (50 μL). The reaction was stirred for 3 min and concentrated *in vacuo*. The crude product was purified by flash column chromatography on florisil (P.E. 40-60:EtOAc, 3:1) to yield actinoallolide D (**4**) as a colourless oil (3.0 mg, 5.3 μmol, 99%).

R_f: 0.39 (PE:EtOAc, 1:1). $[\alpha]_D^{20}$: +108.0 (c 0.1, MeOH), (lit. = +167.7 °)[1]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.27 (1H, ddd, J = 7.0, 7.0, 1.3 Hz, H_{11}), 5.16 (1H, dd, J = 7.7, 7.7 Hz, H_9), 4.88 (1H, d, J = 9.8 Hz, H_{17}), 3.71 (1H, dd, J = 6.7, 6.7 Hz, H_{21}), 3.63 (1H, d, J = 11.4 Hz, H_{2A}), 3.52 (1H, d, J = 9.5 Hz, H_{19}), 3.31 (1H, d, J = 11.4 Hz, H_{2B}), 3.27 (1H, ddd, J = 9.0, 5.2, 2.7 Hz, H_{13}), 2.51 (1H, m, H_{18}), 2.49 (1H, m, H_{10A}), 2.47 (1H, d, J = 13.2 Hz, H_{7A}), 2.43 (1H, d, J = 13.2 Hz, H_{7B}), 2.29 (1H, m, H_{10B}), 2.27 (1H, m, H_{24A}), 2.19 (1H, m, H_{24B}), 2.12 (1H, d, J = 12.1 Hz, H_{15A}), 1.82 (1H, m, H_{14}), 1.79 (1H, m, H_{12}), 1.78 (1H, m, H_{15B}), 1.65 (1H, m, H_{20}), 1.63 (3H, s, Me_{16}), 1.53 (1H, m, H_{22A}), 1.43 (3H, s, Me_8), 1.41 (1H, m, H_{22B}), 1.41 (3H, s, Me_6), 1.04 (3H, t, J = 7.2 Hz, H_{25}), 1.04 (3H, d, J = 6.8 Hz, Me_{18}), 1.00 (3H, d, J = 7.0 Hz, Me_{12}), 0.90 (3H, t, J = 7.4 Hz, H_{23}), 0.89 (3H, d, J = 6.5 Hz, Me_{14}), 0.84 (3H, d, J = 7.1 Hz, Me_{20}). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 206.5, 177.4, 168.3, 133.2, 130.9, 129.1, 126.2, 119.0, 87.6, 82.0, 79.3, 76.6, 76.0, 47.9, 41.1, 38.7, 37.8, 37.5, 36.8, 32.3, 29.9, 28.1, 22.2, 17.9, 17.1, 17.0, 16.2, 14.9, 12.3, 10.4, 10.4, 4.2. **IR** (thin film, ν_{max}/cm^{-1}): 3458, 2934, 1734, 1716, 1693, 1683, 1614, 1458, 1398, 1272, 1210, 974, 958. **HRMS** (NSI−): Calculated for $C_{32}H_{51}O_7$ $[M-H]^-$: 547.3640, found 547.3641.

Actinoallolide C (3) and Actinoallolide E (5)



A solution of crude actinoallolide A (as prepared from triketone **25**) (2.6 mg, 4.6 μmol) in Et_2O (5 mL) was passed through a plug of alumina (Merck Aluminium oxide 90 standardised), which afforded a mixture of actinoallolides C and E. This mixture was purified by preparatory TLC ($CHCl_3$/MeOH, 15:1) to yield actinoallolide C (1.3 mg, 2.3 μmol, 50%) and actinoallolide E (1.2 mg, 2.2 μmol, 48%).

Actinoallolide C: $\mathbf{R_f}$: 0.71 (PE:EtOAc, 1:1). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$: +80.0 (c 0.1, MeOH), (lit. = +190.0 °)[1]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.28 (1H, ddd, J = 6.9, 6.9, 1.7 Hz, H_{11}), 5.17 (1H, dd, J = 7.9, 7.9 Hz, H_9), 4.89 (1H, d, J = 9.9 Hz, H_{17}), 3.64 (1H, m, H_{19}), 3.64 (1H, d, J = 11.4 Hz, H_{2A}), 3.31 (1H, d, J = 11.4 Hz, H_{2B}), 3.27 (1H, m, H_{13}), 2.67 (1H, qd, J = 7.2, 2.2 Hz, H_{20}), 2.49 (1H, m, H_{10A}), 2.48 (2H, m, H_{22}), 2.46 (1H, m, H_{18}), 2.46 (2H, m, H_7), 2.31 (1H, m, H_{10B}), 2.23 (2H, m, H_{24}), 2.13 (1H, d, J = 12.6 Hz, H_{15A}), 1.84 (1H, m, H_{14}), 1.80 (1H, m, H_{12}), 1.80 (1H, m, H_{15B}), 1.63 (3H, s, Me_{16}), 1.44 (3H, s, Me_8), 1.41 (3H, s, Me_6), 1.07 (3H, d, J = 7.2 Hz, Me_{20}), 1.05 (3H, d, J = 7.1 Hz, Me_{18}), 1.05 (3H, t, J = 7.0 Hz, H_{25}), 1.05 (3H, t, J = 7.0 Hz, H_{23}), 1.01 (3H, d, J = 7.0 Hz, Me_{12}), 0.89 (3H, d, J = 6.4 Hz, Me_{14}). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 217.3, 206.5, 177.4, 168.4, 133.7, 131.0, 128.8, 126.2, 119.0, 87.6, 76.6, 76.0, 74.9, 47.9, 47.5, 41.1, 38.9, 37.6, 36.0, 34.8, 32.2, 29.9, 22.3, 17.9, 17.0, 17.0, 16.1, 14.9, 12.3, 10.4, 9.4, 7.7. **IR** (thin film, ν_{max}/cm^{-1}): 2927, 1698, 1614, 1451, 1398, 1272, 979. **HRMS** (ES+): Calculated for $C_{32}H_{51}O_7$ $[M+H]^+$: 547.3629, found 547.3603.

Actinoallolide E: $\mathbf{R_f}$: 0.62 (PE:EtOAc, 1:1). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$: +73.0 (c 0.1, MeOH), (lit. = +120.1 °)[1]. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.23 (1H, dd, J = 8.2, 8.2 Hz, H_9), 4.97 (1H, dd, J = 9.4, 2.1 Hz, H_{13}), 4.82 (1H, d, J = 10.0 Hz, H_{17}), 3.82 (1H, d, J = 14.8 Hz, H_{2A}), 3.65 (1H, d, J = 9.2 Hz, H_{19}), 3.26 (1H, d, J = 14.8 Hz, H_{2B}), 3.26 (1H, d, J = 8.8 Hz, H_{13}), 2.65 (1H, qd, J = 7.2, 2.2 Hz, H_{20}), 2.62 (1H, d, J = 13.6 Hz, H_{7A}), 2.56 (1H, m, H_{22A}), 2.48 (1H, m, H_{22B}), 2.47 (1H, m, H_{18}), 2.47 (1H, d, J = 13.6 Hz, H_{7B}), 2.30 (1H, m, H_{24A}), 2.24 (1H, m, H_{10A}), 2.22 (1H, m, H_{24B}), 2.13 (1H, d, J = 13.2 Hz, H_{15A}), 1.97 (1H, m, H_{10B}), 1.93 (1H, m, H_{14}), 1.68 (1H, dd, J = 13.2, 11.7 Hz, H_{15B}), 1.63 (3H, s, Me_{16}), 1.54 (1H, m, H_{12}), 1.53 (3H, s, Me_8), 1.36 (3H, s, Me_6), 1.11 (3H, t, J = 7.5 Hz, H_{25}), 1.09 (3H, d, J = 7.2 Hz, Me_{20}), 1.06 (3H, t, J = 7.3 Hz, H_{23}), 1.05 (3H, d, J = 6.4 Hz, Me_{18}), 0.95 (3H, d, J = 7.2 Hz, Me_{12}), 0.81 (3H, d, J = 6.8 Hz, Me_{14}). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 217.3, 207.0, 177.7, 166.7, 132.9, 130.7, 129.4, 126.6,

117.6, 88.2, 81.4, 74.8, 72.7, 47.5, 46.4, 40.2, 39.5, 36.0, 35.8, 35.2, 34.8, 31.6, 24.9, 17.9, 17.7, 16.5, 15.9, 15.6, 13.1, 9.5, 8.1, 7.7. **IR** (thin film, ν_{max}/cm^{-1}): 2932, 1734, 1696, 1620, 1452, 1250, 979. **HRMS** (ES+): Calculated for $C_{32}H_{50}O_7Na$ $[M+Na]^+$: 547.3629, found 547.3620.

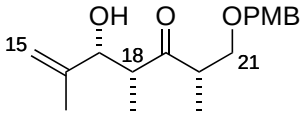
2 Confirmation of Configuration in Stereogenic Reactions

Due to availability of reagents, initial exploratory investigations towards the side chain fragment were performed in the opposite enantiomeric series. Thus, stereochemical proofs performed on the relevant compounds are enantiomeric to those presented in the final synthesis

2.1 C17 Stereocentre

The configuration of the alcohol at C17 formed in the titanium-mediated aldol reaction was determined by performing the reaction without the *in situ* reduction. Synthesis of the diastereomeric Mosher esters of the resulting alcohol then allowed for the unambiguous assignment of C17.[4]

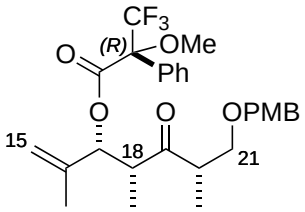
Aldol adduct S10



To a stirred solution of PMB-protected (*S*)-Roche ester ethyl ketone (200 mg, 0.846 mmol) in CH_2Cl_2 (6 mL) at −78 °C was added a solution of $Ti(O^iPr)Cl_3$ (0.931 mmol) in CH_2Cl_2 (4 mL). DIPEA (0.162 mL, 0.931 mmol) was added followed by a solution of methacrolein (0.20 mL, 1.27 mmol) in CH_2Cl_2 (4 mL) over 1.5 h. When TLC analysis indicated the reaction was complete, it was quenched by addition of MeOH (1 mL) upon completion (20 min). Potassium sodium tartrate solution (10 mL) was added and the mixture warmed to rt and stirred for 1 h. The phases were separated and the organic phase washed with H_2O, then $NaHCO_3$ solution and brine. The combined aqueous washings were back-extracted with CH_2Cl and the combined organic extracts dried with $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (P.E. 40-60:EtOAc, 10:1) to give aldol adduct **S10** as a colourless oil (190 mg, 0.646 mmol, 76%).

R_f: 0.27 (PE:EtOAc, 6:1). $[\alpha]_D^{20}$: +31.0 (c 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.20 (2H, d, J = 8.6 Hz, $H_{PMB\ Ar\text{-}H}$), 6.86 (2H, d, J = 8.6 Hz, $H_{PMB\ Ar\text{-}H}$), 5.09 (1H, m, H_{15A}), 4.93 (1H, m, H_{15B}), 4.50 (1H, m, H_{17}), 4.42 (1H, d, J = 11.7 Hz, $H_{PMB\ ArCH_2O}$), 4.38 (1H, d, J = 11.7 Hz, $H_{PMB\ ArCH_2O}$), 3.80 (3H, s, MeO_{PMB}), 3.58 (1H, dd, J = 8.8, 8.6 Hz, H_{21A}), 3.45 (1H, dd, J = 8.6, 5.0 Hz, H_{21B}), 3.18 (1H, d, J = 2.8 Hz, HO_{17}), 3.16 (1H, m, H_{20}), 2.86 (1H, qd, J = 7.2, 2.5 Hz, H_{18}), 1.63 (3H, s, Me_{16}), 1.03 (3H, d, J = 6.9 Hz, Me_{20}), 1.00 (3H, d, J = 7.2 Hz, Me_{18}). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 218.1, 159.3, 143.3, 129.6, 129.3, 113.8, 111.4, 73.1, 72.8, 72.5, 55.2, 48.5, 44.6, 19.6, 13.6, 8.2. **IR** (thin film, ν_{max}/cm^{-1}): 3494 (br), 2940, 1701, 1612, 1513, 1453, 1247, 1095, 1034, 818. **HRMS** (ES+): Calculated for $C_{18}H_{27}O_4$ $[M+H]^+$: 307.1904, found 307.1908.

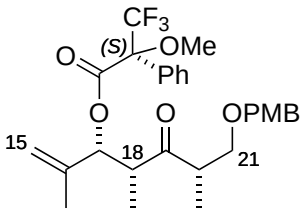
(*R*)-Mosher ester S11



To a stirred solution of aldol adduct **S10** (2.0 mg, 6.8 μmol) in CH_2Cl_2 (0.5 mL) was added (*R*)-MTPA (8.0 mg, 34 μmol), DCC (7.0 mg, 34 μmol) and DMAP (one crystal). The reaction mixture was stirred for 18 h then the solvent was removed *in vacuo*. The crude product was dissolved in ether (0.5 mL) and the resulting suspension filtered. The solvent was removed *in vacuo* and the residue analysed without further purification.

R_f: 0.46 (PE:EtOAc, 6:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.51 (2H, m, H_{Ph}), 7.40 (3H, m, H_{Ph}), 7.19 (2H, d, J = 8.5 Hz, $H_{PMB\ Ar\text{-}H}$), 6.85 (2H, d, J = 8.5 Hz, $H_{PMB\ Ar\text{-}H}$), 5.70 (1H, d, J = 6.7 Hz, H_{17}), 5.02 (1H, m, H_{15A}), 4.96 (1H, m, H_{15B}), 4.36 (2H, s, $H_{PMB\ ArCH_2O}$), 3.79 (3H, s, MeO_{PMB}), 3.53 (3H, s, MeO), 3.51 (2H, ABQ, J = 11.6 Hz, H_{21}), 3.04 (1H, m, H_{20}), 2.97 (1H, m, H_{18}), 1.68 (3H, s, Me_{16}), 1.04 (3H, d, J = 7.2 Hz, Me_{18}), 1.01 (3H, d, J = 7.0 Hz, Me_{20}).

(*S*)-Mosher ester S12



To a stirred solution of aldol adduct **S10** (2.0 mg, 6.8 μmol) in CH_2Cl_2 (0.5 mL) was added (*S*)-MTPA (8.0 mg, 34 μmol), DCC (7.0 mg, 34 μmol) and DMAP (one crystal). The reaction mixture was stirred for 18 h then the solvent was removed *in vacuo*. The crude product was dissolved in ether (0.5 mL) and the resulting suspension filtered. The solvent was removed *in vacuo* and the residue analysed without further purification.

R_f: 0.46 (PE:EtOAc, 6:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.52 (2H, m, H_{Ph}), 7.40 (3H, m, H_{Ph}), 7.19 (2H, d, J = 8.5 Hz, $H_{PMB\ Ar\text{-}H}$), 6.85 (2H, d, J = 8.5 Hz, $H_{PMB\ Ar\text{-}H}$), 5.67 (1H, d, J = 5.2 Hz, H_{17}), 4.87 (1H, m, H_{15A}), 4.79 (1H, m, H_{15B}), 4.35 (2H, s, $H_{PMB\ ArCH_2O}$), 3.79 (3H, s, MeO_{PMB}), 3.55 (3H, s, MeO), 3.52 (2H, ABQ, J = 11.6 Hz, H_{21}), 3.03 (1H, m, H_{20}), 3.00 (1H, m, H_{18}), 1.60 (3H, s, Me_{16}), 1.14 (3H, d, J = 7.2 Hz, Me_{18}), 1.03 (3H, d, J = 7.0 Hz, Me_{20}).

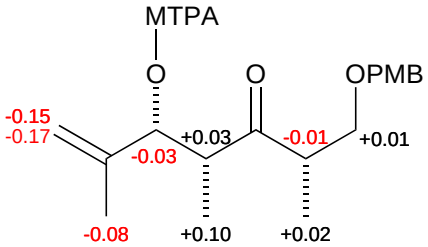
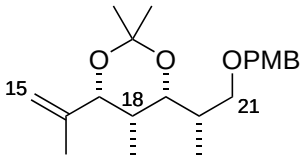


Figure 1: $\Delta\delta$ $(= \delta_S - \delta_R)$ values for MTPA esters **S11** and **S12**

2.2 C18 and C19 Stereocentres

The configuration of the methyl group at C18 and the alcohol at C19 formed in the titanium-mediated aldol/*in situ* reduction sequence were determined by forming the acetonide of the 1,3-diol and following Rychnovsky's method of analysis.[5,6]

Acetonide S13



To a solution of diol **S14** (10.0 mg, 0.0340 mmol) in CH_2Cl_2/2,2-dimethoxypropane (1 mL, 1:1 v/v) was added PPTS (one crystal) and the mixture stirred for 24 h. The reaction mixture was quenched with $NaHCO_3$ solution (1 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3 × 1 mL). The combined organic extracts were dried with $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (P.E. 40-60:EtOAc, 12:1) to give acetonide **S13** as a colourless oil (11.0 mg, 0.0320 mmol, 94%).

R_f: 0.66 (PE:EtOAc, 6:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 (2H, d, J = 8.6 Hz, $H_{PMB\ Ar\text{-}H}$), 6.88 (2H, d, J = 8.6 Hz, $H_{PMB\ Ar\text{-}H}$), 5.02 (1H, m, H_{15A}), 4.86 (1H, m, H_{15B}), 4.46 (1H, d, J = 11.8 Hz, $H_{PMB\ ArCH_2O}$), 4.37 (1H, d, J = 11.8 Hz, $H_{PMB\ ArCH_2O}$), 4.21 (1H, m, H_{17}), 3.81 (3H, s, MeO_{PMB}), 3.71 (1H, dd, J = 9.5, 2.0 Hz, H_{19}), 3.34 (2H, m, H_{21}), 1.84 (1H, m, H_{20}), 1.59 (1H, qt, J = 6.8, 2.0 Hz, H_{18}), 1.63 (3H, s, Me_{16}), 1.43 (3H, s, $Me_{acetonide}$), 1.42 (3H, s, $Me_{acetonide}$), 1.05 (3H, d, J = 6.6 Hz, Me_{20}), 0.71 (3H, d, J = 6.8 Hz, Me_{18}). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.1, 142.8, 130.6, 129.2, 113.8, 110.1, 98.9, 75.6, 75.4, 72.8, 71.2, 55.3, 35.3, 31.6, 30.0, 19.6, 19.4, 14.8, 5.3. **HRMS** (ES+): Calculated for $C_{21}H_{33}O_4$ $[M+H]^+$: 349.2373, found 349.2374.

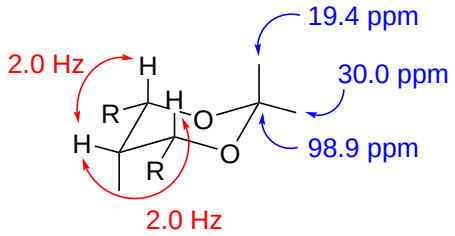
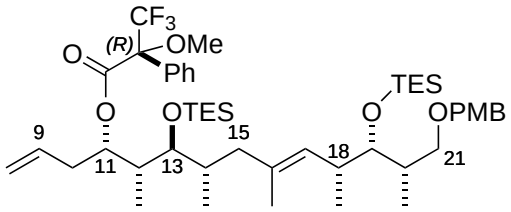


Figure 2: NMR analysis of acetonide **S13**

2.3 C11 Stereocentre

The configuration of the alcohol at C11 from the allylation reaction was determined by formation of the diastereomeric Mosher esters.

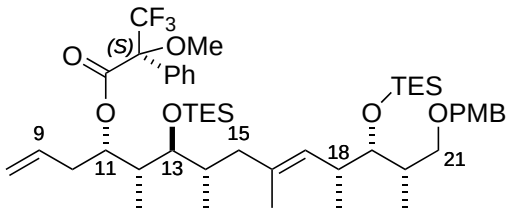
(*R*)-Mosher ester S14



To a stirred solution of alcohol **S15** (2.0 mg, 3.0 μmol) in CH_2Cl_2 (0.5 mL) was added (*R*)-MTPA (2.0 mg, 8.9 μmol), DCC (6.0 mg, 30 μmol) and DMAP (one crystal). The reaction mixture was stirred for 18 h then the solvent was removed *in vacuo*. The crude product was dissolved in ether (0.5 mL) and the resulting suspension filtered. The solvent was removed *in vacuo* and the residue analysed without further purification.

R_f: 0.59 (PE:EtOAc, 6:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.56 (2H, m, H_{Ph}), 7.42 (3H, m, H_{Ph}), 7.24 (2H, d, J = 8.2 Hz, $H_{PMB\ Ar\text{-}H}$), 6.87 (2H, d, J = 8.2 Hz, $H_{PMB\ Ar\text{-}H}$), 5.72 (1H, m, H_9), 5.38 (1H, t, J = 6.1 Hz, H_{11}), 5.10 (1H, d, J = 15.1, H_{8A}), 5.07 (1H, d, J = 8.3 Hz, H_{8B}), 4.86 (1H, d, J = 9.7 Hz, H_{17}), 4.40 (2H, ABQ, J = 11.5 Hz, $H_{PMB\ ArCH_2O}$), 3.80 (3H, s, MeO_{PMB}), 3.56 (3H, s, MeO), 3.54 (1H, m, H_{19}), 3.35 (1H, m, H_{21A}), 3.34 (1H, m, H_{13}), 3.19 (1H, m, H_{21B}), 2.54 (1H, m, H_{10A}), 2.46 (1H, m, H_{18}), 2.38 (1H, m, H_{10B}), 1.93 (1H, m, H_{20}), 1.91 (1H, m, H_{15A}), 1.79 (1H, m, H_{12}), 1.73 (1H, m, H_{15B}), 1.69 (1H, m, H_{14}), 1.54 (3H, s, Me_{16}), 0.95 (18H, m, $SiCH_2CH_3$), 0.92 (3H, m, Me_{18}), 0.81 (3H, d, J = 6.5 Hz, Me_{20}), 0.80 (3H, d, J = 6.7 Hz, Me_{12}), 0.76 (3H, d, J = 4.7 Hz, Me_{14}), 0.64 (6H, q, J = 7.9 Hz, $SiCH_2CH_3$), 0.59 (6H, t, J = 7.9 Hz, $SiCH_2CH_3$).

(*S*)-Mosher ester S16



To a stirred solution of alcohol **S15** (2.0 mg, 3.0 μmol) in CH_2Cl_2 (0.5 mL) was added (*S*)-MTPA (2.0 mg, 8.9 μmol), DCC (6.0 mg, 30 μmol) and DMAP (one crystal). The reaction mixture was stirred for 18 h then the solvent was removed *in vacuo*. The crude product was dissolved in ether (0.5 mL) and the resulting suspension filtered. The solvent was removed *in vacuo* and the residue analysed without further purification.

R_f: 0.59 (PE:EtOAc, 6:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.56 (2H, m, H_{Ph}), 7.42 (3H, m, H_{Ph}), 7.24 (2H, d, J = 8.3 Hz, $H_{PMB\ Ar\text{-}H}$), 6.86 (2H, d, J = 8.3 Hz, $H_{PMB\ Ar\text{-}H}$), 5.68 (1H, m, H_9), 5.39 (1H, t, J = 6.2 Hz, H_{11}), 5.06 (1H, d, J = 14.4, H_{8A}), 5.03 (1H, d, J = 7.2 Hz, H_{8B}), 4.88 (1H, d, J = 9.7 Hz, H_{17}), 4.40 (2H, ABQ, J = 11.5 Hz, $H_{PMB\ ArCH_2O}$), 3.79 (3H, s, MeO_{PMB}), 3.51 (3H, s, MeO), 3.54 (1H, m, H_{19}), 3.35 (1H, m, H_{21A}), 3.37 (1H, m, H_{13}), 3.19 (1H, m, H_{21B}), 2.46 (1H, m, H_{10A}), 2.46 (1H, m, H_{18}), 2.31 (1H, m, H_{10B}), 1.92 (1H, m, H_{20}), 1.91 (1H, m, H_{15A}), 1.80 (1H, m, H_{12}), 1.73 (1H, m, H_{15B}), 1.72 (1H, m, H_{14}), 1.55 (3H, s, Me_{16}), 0.94 (18H, m, $SiCH_2CH_3$), 0.92 (3H, m, Me_{18}), 0.86 (3H, d, J = 7.1 Hz, Me_{12}), 0.81 (3H, d, J = 6.7 Hz, Me_{20}), 0.79 (3H, d, J = 5.6 Hz, Me_{14}), 0.60 (12H, q, J = 7.9 Hz, $SiCH_2CH_3$).

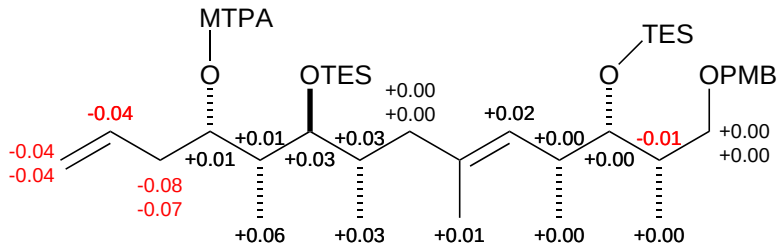


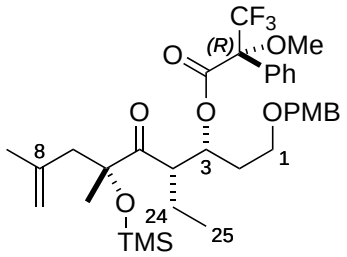
Figure 3: $\Delta\delta$ ($= \delta_S - \delta_R$) values for MTPA esters **S14** and **S16**

2.4 C3 and C4 Stereocentres

Initial investigations towards the macrocycle fragment were conducted with the PMB protecting group at C1. Thus, the relevant compounds in this section contain the PMB group instead of the DMB group used in the final synthesis

The configuration of the alcohol at C3 formed in the lithium aldol reaction was determined by forming the diastereomeric Mosher esters.

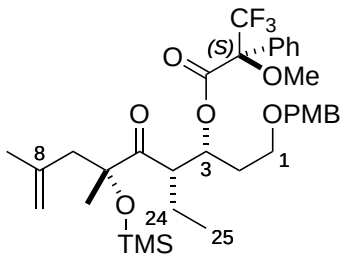
(*R*)-Mosher ester S17



To a stirred solution of alcohol **S18** (5.0 mg, 11 μmol) in CH_2Cl_2 (0.1 mL) was added (*R*)-MTPA (13.0 mg, 57.0 μmol), DCC (12.0 mg, 57.0 μmol) and DMAP (one crystal). The reaction mixture was stirred for 18 h then the solvent was removed *in vacuo*. The crude product was dissolved in ether (0.5 mL) and the resulting suspension filtered. The solvent was removed *in vacuo* and the residue analysed without further purification.

R$_f$: 0.52 (PE:EtOAc, 4:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55 (2H, m, Ph), 7.42 (2H, m, Ph), 7.38 (1H, m, Ph), 7.21 (2H, d, J = 8.6 Hz, $H_{PMB\ Ar\text{-}H}$), 6.85 (2H, d, J = 8.6 Hz, $H_{PMB\ Ar\text{-}H}$), 5.78 (1H, ddd, J = 9.3, 3.3, 3.3 Hz, H_3), 4.78 (1H, s, H_{9A}), 4.70 (1H, s, H_{9B}), 4.32 (2H, ABq, $H_{PMB\ ArCH_2O}$), 3.80 (3H, s, MeO_{PMB}), 3.54 (3H, s, OMe), 3.28 (1H, m, H_4), 3.20 (2H, m, H_1), 2.51 (1H, d, J = 14.0 Hz, H_{7A}, 2.21 (1H, d, J = 14.0 Hz, H_{7B}, 1.93 (2H, m, H_2), 1.76 (3H, s, Me_8), 1.79 (1H, m, H_{24A}), 1.50 (1H, m, H_{24B}), 1.43 (3H, s, Me_6), 0.78 (3H, t, J = 7.5 Hz, H_{25}), 0.21 (9H, s, TMS).

(*S*)-Mosher ester S19



To a stirred solution of alcohol **S18** (5.0 mg, 11 μmol) in CH_2Cl_2 (0.1 mL) was added (*S*)-MTPA (13.0 mg, 57.0 μmol), DCC (12.0 mg, 57.0 μmol) and DMAP (one crystal). The reaction mixture was stirred for 18 h then the solvent was removed *in vacuo*. The crude product was dissolved in ether (0.5 mL) and the resulting suspension filtered. The solvent was removed *in vacuo* and the residue analysed without further purification.

R$_f$: 0.52 (PE:EtOAc, 4:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55 (2H, m, Ph), 7.40 (3H, m, Ph), 7.21 (2H, d, J = 8.5 Hz, $H_{PMB\ Ar\text{-}H}$), 6.85 (2H, d, J = 8.5 Hz, $H_{PMB\ Ar\text{-}H}$), 5.75 (1H, ddd, J = 9.3, 3.6, 3.6 Hz, H_3), 4.78 (1H, s, H_{9A}), 4.68 (1H, s, H_{9B}), 4.37 (2H, ABq, $H_{PMB\ ArCH_2O}$), 3.79 (3H, s, MeO_{PMB}), 3.47 (3H, s, OMe), 3.39 (2H, m, H_1), 3.27 (1H, m, H_4), 2.50 (1H, d, J = 13.9 Hz, H_{7A}, 2.19 (1H, d, J = 13.9 Hz, H_{7B}, 1.98 (2H, m, H_2), 1.75 (3H, s, Me_8), 1.67 (1H, m, H_{24A}), 1.45 (1H, m, H_{24B}), 1.43 (3H, s, Me_6), 0.73 (3H, t, J = 7.5 Hz, H_{25}), 0.20 (9H, s, TMS).

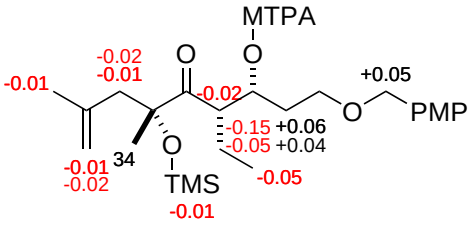


Figure 4: $\Delta\delta$ $(= \delta_S - \delta_R)$ values for MTPA esters **S17** and **S19**

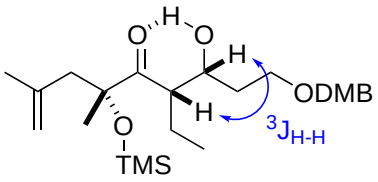


Figure 5: The diagnostic coupling constant in aldol adduct **S5**

The configuration of the adjacent ethyl group at C4 was determined by obtaining the $^3J_{\text{H-H}}$ coupling constant between H3 and H4 of aldol adduct **S5**. At 4.8 Hz, this was within the range observed for 1,2-*syn* aldol adducts and outside that observed for 1,2-*anti* adducts.[7]

2.5 C8-C9 Alkene geometry

As macrocycle **23** could not be separated from the RCM dimer byproduct, the geometry of the C8-C9 alkene was determined by analysis of diol **S8**. A NOESY spectrum was recorded and the relevant NOE releations are illustrated below. The strong positive NOE relations between H9 and H7 and between Me8 and H10 (shown in green below), along with the absence of an NOE between Me8 and H9 and between H7 and H10 (shown in red below) confirmed the desired *E* configuration of the macrocyclic alkene.

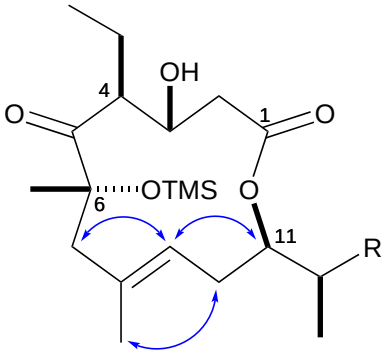
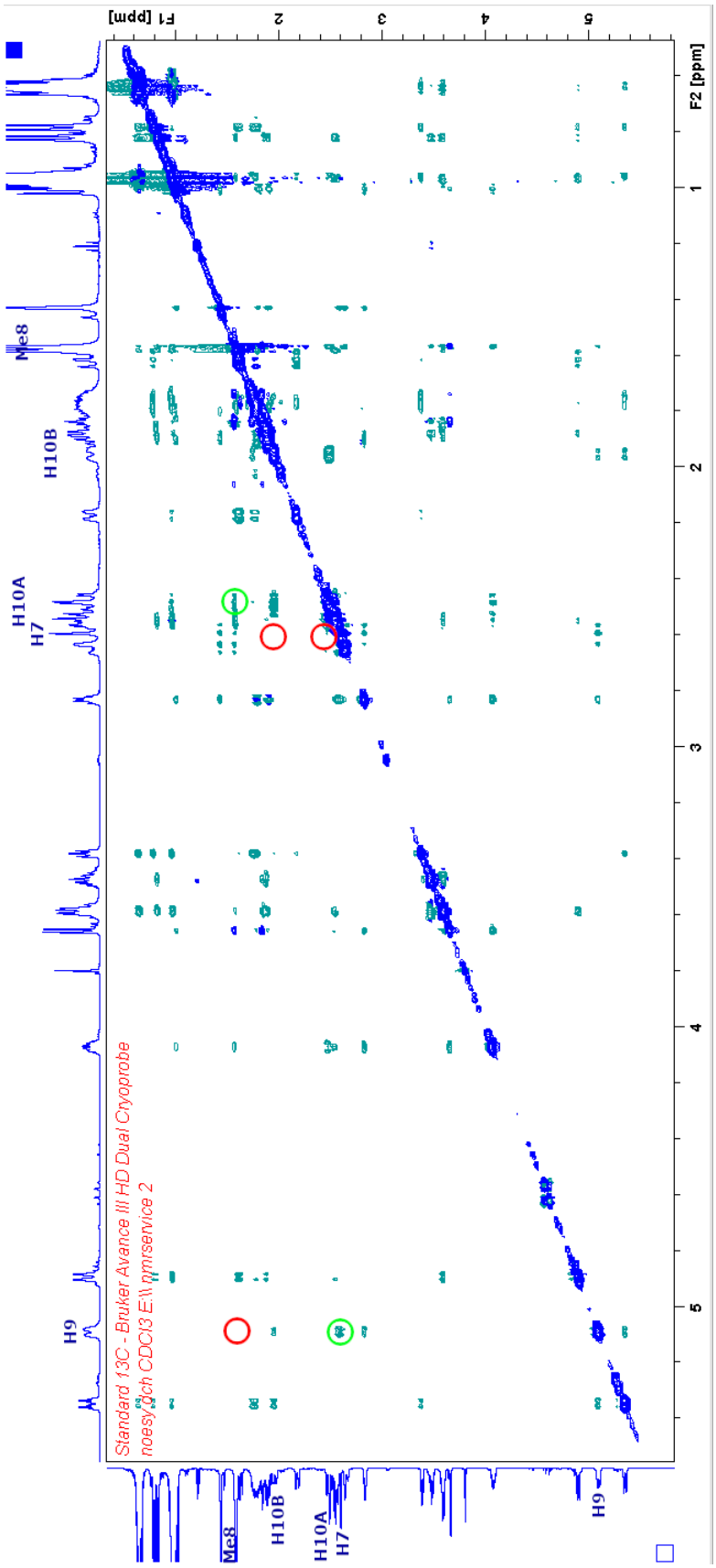


Figure 6: Selected NOE relations in diol **S8**


F1 [ppm]
F2 [ppm]
Me8
H10B
H10A
H7
H9
Standard 13C - Bruker Avance III HD Dual Cryoprobe
noesy dch CDCl3 E:\\ nmrservice 2

3 NMR Comparison Tables

Table 1: NMR comparison of natural and synthetic actinoallolide A in $CDCl_3$

	Natural		Synthetic	
Atom	**^{13}C**	**^{1}H**	**^{13}C**	**^{1}H**
1	170.2		170.2	
2	46.7	2.91 (1H, d, J = 12.0 Hz)	46.7	2.91 (1H, d, J = 12.0 Hz)
		2.77 (1H, d, J = 12.0 Hz)		2.77 (1H, d, J = 12.0 Hz)
3	102.3		102.3	
4	53.1	2.83 (1H, dd, J = 8.0, 5.6 Hz)	53.3	2.83 (1H, dd, J = 7.6, 5.5 Hz)
5	217.6		217.7	
6	82.2		82.1	
7	48.9	2.35 (1H, d, J = 13.4 Hz)	48.9	2.36 (1H, d, J = 13.4 Hz)
		2.30 (1H, d, J = 13.4 Hz)		2.30 (1H, d, J = 13.4 Hz)
8	131.7		131.7	
9	126.5	5.13 (1H, brdd, J = 7.8, 7.8 Hz)	126.5	5.13 (1H, dd, J = 7.8, 7.8 Hz)
10	29.9	2.49 (1H, m)	29.9	2.50 (1H, m)
		2.34 (1H, m)		2.34 (1H, m)
11	73.6	5.40 (1H, ddd, J = 7.2, 7.2, 2.0 Hz)	73.6	5.40 (1H, ddd, J = 7.1, 7.1, 1.8 Hz)
12	40.5	1.78 (1H, dqd, J = 9.4, 6.8, 2.0 Hz)	40.6	1.78 (1H, m)
13	76.5	3.26 (1H, dd, J = 9.4, 2.2 Hz)	76.6	3.26 (1H, ddd, J = 9.4, 2.3, 2.3 Hz)
14	32.2	1.81 (1H, m)	32.2	1.83 (1H, m)
15	38.8	2.13 (1H, brd, J = 11.6 Hz)	38.8	2.13 (1H, d, J = 11.0 Hz)
		1.79 (1H, m)		1.78 (1H, m)
16	133.7		133.7	
17	128.8	4.88 (1H, brd, J = 10.0 Hz)	128.8	4.88 (1H, d, J = 9.8 Hz)
18	36.0	2.45 (1H, ddq, J = 10.0, 9.7, 6.8 Hz)	35.9	2.46 (1H, m)
19	74.9	3.64 (1H, dd, J = 9.7, 2.1 Hz)	74.9	3.64 (1H, ddd, J = 9.4, 2.3, 2.3 Hz)
20	47.5	2.67 (1H, qd, J = 6.9, 2.1 Hz)	47.5	2.67 (1H, qd, J = 7.3, 2.2 Hz)
21	217.3		217.3	
22	34.8	2.50 (1H, m)	34.8	2.52 (1H, m)
		2.45 (1H, m)		2.44 (1H, m)
23	7.7	1.04 (3H, t, J = 6.2 Hz)	7.7	1.05 (3H, t, J = 7.5 Hz)
24	18.4	1.84 (1H, m)	18.7	1.84 (1H, m)
		1.61 (1H, m)		1.61 (1H, m)
25	12.1	1.14 (3H, t, J = 7.4 Hz)	12.1	1.14 (3H, t, J = 7.5 Hz)
26	26.8	1.34 (3H, s)	26.8	1.34 (3H, s)
27	17.2	1.47 (3H, brs)	17.2	1.47 (3H, s)
28	10.3	1.01 (3H, d, J = 6.8 Hz)	10.2	1.01 (3H, d, J = 7.0 Hz)
29	16.9	0.88 (3H, d, J = 6.4 Hz)	16.9	0.89 (3H, d, J = 6.6 Hz)
30	16.1	1.63 (3H, d, J = 1.2 Hz)	16.1	1.63 (3H, s)
31	17.9	1.05 (3H, d, J = 6.8 Hz)	17.9	1.05 (3H, d, J = 6.4 Hz)
32	9.4	1.07 (3H, d, J = 6.9 Hz)	9.4	1.07 (3H, d, J = 7.0 Hz)

Table 2: NMR comparison of natural and synthetic actinoallolide B in $CDCl_3$

	Natural		Synthetic	
Atom	**^{13}C**	**^{1}H**	**^{13}C**	**^{1}H**
1	170.1		170.1	
2	46.6	2.91 (1H, d, J = 12.2 Hz)	46.7	2.91 (1H, d, J = 12.1 Hz)
		2.75 (1H, d, J = 12.2 Hz)		2.77 (1H, d, J = 12.1 Hz)
3	102.3		102.3	
4	53.3	2.82 (1H, dd, J = 8.2, 5.8 Hz)	53.3	2.84 (1H, dd, J = 7.9, 5.8 Hz)
5	217.8		217.7	
6	82.1		82.1	
7	48.9	2.35 (1H, d, J = 13.6 Hz)	48.9	2.35 (1H, m)
		2.28 (1H, d, J = 13.6 Hz)		2.29 (1H, m)
8	131.7		131.7	
9	126.5	5.13 (1H, brdd, J = 7.4, 7.4 Hz)	126.5	5.13 (1H, dd, J = 7.5, 7.5 Hz)
10	29.8	2.52 (1H, m)	29.9	2.51 (1H, m)
		2.32 (1H, m)		2.33 (1H, m)
11	73.6	5.38 (1H, ddd, J = 7.2, 7.2, 1.6 Hz)	73.6	5.39 (1H, ddd, J = 7.9, 7.9, 1.8 Hz)
12	40.6	1.78 (1H, m)	40.6	1.78 (1H, m)
13	76.6	3.26 (1H, dd, J = 9.4, 2.2 Hz)	76.6	3.26 (1H, ddd, J = 9.6, 4.9, 2.6 Hz)
14	32.4	1.80 (1H, m)	32.4	1.82 (1H, m)
15	38.7	2.12 (1H, brd, J = 11.8 Hz)	38.7	2.12 (1H, d, J = 12.4 Hz)
		1.77 (1H, m)		1.77 (1H, m)
16	133.2		133.2	
17	129.1	4.88 (1H, brd, J = 10.0 Hz)	129.1	4.88 (1H, d, J = 9.9 Hz)
18	36.8	2.52 (1H, m)	36.8	2.52 (1H, m)
19	82.0	3.51 (1H, dd, J = 9.6, 1.6 Hz)	82.0	3.52 (1H, d, J = 9.5 Hz)
20	37.8	1.65 (1H, m)	37.8	1.66 (1H, m)
21	79.3	3.70 (1H, ddd, J = 7.8, 7.8, 2.0 Hz)	79.3	3.71 (1H, dd, J = 7.2, 6.2 Hz)
22	28.1	1.52 (1H, m)	28.1	1.53 (1H, m)
		1.42 (1H, m)		1.42 (1H, m)
23	10.4	0.90 (3H, t, J = 7.6 Hz)	10.4	0.90 (3H, t, J = 7.4 Hz)
24	18.4	1.82 (1H, m)	18.4	1.84 (1H, m)
		1.59 (1H, m)		1.61 (1H, m)
25	12.1	1.13 (3H, t, J = 7.4 Hz)	12.0	1.14 (3H, t, J = 7.5 Hz)
26	26.8	1.34 (3H, s)	26.8	1.34 (3H, s)
27	17.2	1.47 (3H, d, J = 0.8 Hz)	17.2	1.47 (3H, d, J = 0.8 Hz)
28	10.3	1.00 (3H, d, J = 6.8 Hz)	10.3	1.00 (3H, d, J = 7.0 Hz)
29	17.0	0.88 (3H, d, J = 6.4 Hz)	17.0	0.88 (3H, d, J = 6.4 Hz)
30	16.2	1.62 (3H, d, J = 1.2 Hz)	16.2	1.63 (3H, d, J = 0.7 Hz)
31	17.9	1.03 (3H, d, J = 6.8 Hz)	17.9	1.04 (3H, d, J = 6.6 Hz)
32	4.2	0.84 (3H, d, J = 7.2 Hz)	4.2	0.84 (3H, d, J = 7.1 Hz)

Table 3: NMR comparison of natural and synthetic actinoallolide C in $CDCl_3$

	Natural		Synthetic	
Atom	**^{13}C**	**^{1}H**	**^{13}C**	**^{1}H**
1	168.3		168.4	
2	37.5	3.63 (1H, d, J = 11.4 Hz)	37.6	3.64 (1H, d, J = 11.4 Hz)
		3.31 (1H, d, J = 11.4 Hz)		3.31 (1H, d, J = 11.4 Hz)
3	177.4		177.4	
4	119.0		119.0	
5	206.4		206.5	
6	87.6		87.6	
7	47.9	2.47 (1H, d, J = 13.0 Hz)	47.9	2.46 (2H, m)
		2.43 (1H, d, J = 13.0 Hz)		
8	131.0		131.0	
9	126.2	5.16 (1H, brdd, J = 7.8, 7.8 Hz)	126.2	5.17 (1H, dd, J = 7.9, 7.9 Hz)
10	29.9	2.48 (1H, m)	29.9	2.49 (1H, m)
		2.30 (1H, m)		2.31 (1H, m)
11	76.0	5.27 (1H, ddd, J = 6.8, 6.8, 1.6 Hz)	76.0	5.28 (1H, ddd, J = 6.9, 6.9, 1.7 Hz)
12	41.1	1.79 (1H, m)	41.1	1.80 (1H, m)
13	76.6	3.27 (1H, dd, J = 9.2, 2.4 Hz)	76.6	3.27 (1H, m)
14	32.2	1.82 (1H, m)	32.2	1.84 (1H, m)
15	38.9	2.13 (1H, brd, J = 12.4 Hz)	38.9	2.13 (1H, d, J = 12.6 Hz)
		1.80 (1H, m)		1.80 (1H, m)
16	133.7		133.7	
17	128.8	4.88 (1H, brd, J = 10.0 Hz)	128.8	4.88 (1H, d, J = 9.9 Hz)
18	35.9	2.44 (1H, m)	36.0	2.46 (1H, m)
19	74.9	3.64 (1H, dd, J = 8.8, 2.0 Hz)	74.9	3.64 (1H, m)
20	47.5	2.67 (1H, qd, J = 7.2, 2.0 Hz)	47.5	2.67 (1H, qd, J = 7.2, 2.2 Hz)
21	217.2		217.3	
22	34.7	2.46 (2H, m)	34.8	2.48 (2H, m)
23	7.7	1.04 (3H, t, J = 7.2 Hz)	7.7	1.05 (3H, t, J = 7.0 Hz)
24	14.9	2.19 (2H, m)	14.9	2.23 (2H, m)
25	12.3	1.04 (3H, t, J = 7.2 Hz)	12.3	1.05 (3H, t, J = 7.0 Hz)
26	22.2	1.41 (3H, s)	22.3	1.41 (3H, s)
27	17.0	1.43 (3H, brs)	17.0	1.44 (3H, s)
28	10.3	1.00 (3H, d, J = 6.8 Hz)	10.4	1.01 (3H, d, J = 7.0 Hz)
29	17.0	0.89 (3H, d, J = 6.4 Hz)	17.0	0.89 (3H, d, J = 6.4 Hz)
30	16.1	1.63 (3H, d, J = 0.8 Hz)	16.1	1.63 (3H, s)
31	17.9	1.05 (3H, d, J = 7.2 Hz)	17.9	1.05 (3H, d, J = 7.1 Hz)
32	9.4	1.07 (3H, d, J = 7.2 Hz)	9.4	1.07 (3H, d, J = 7.2 Hz)

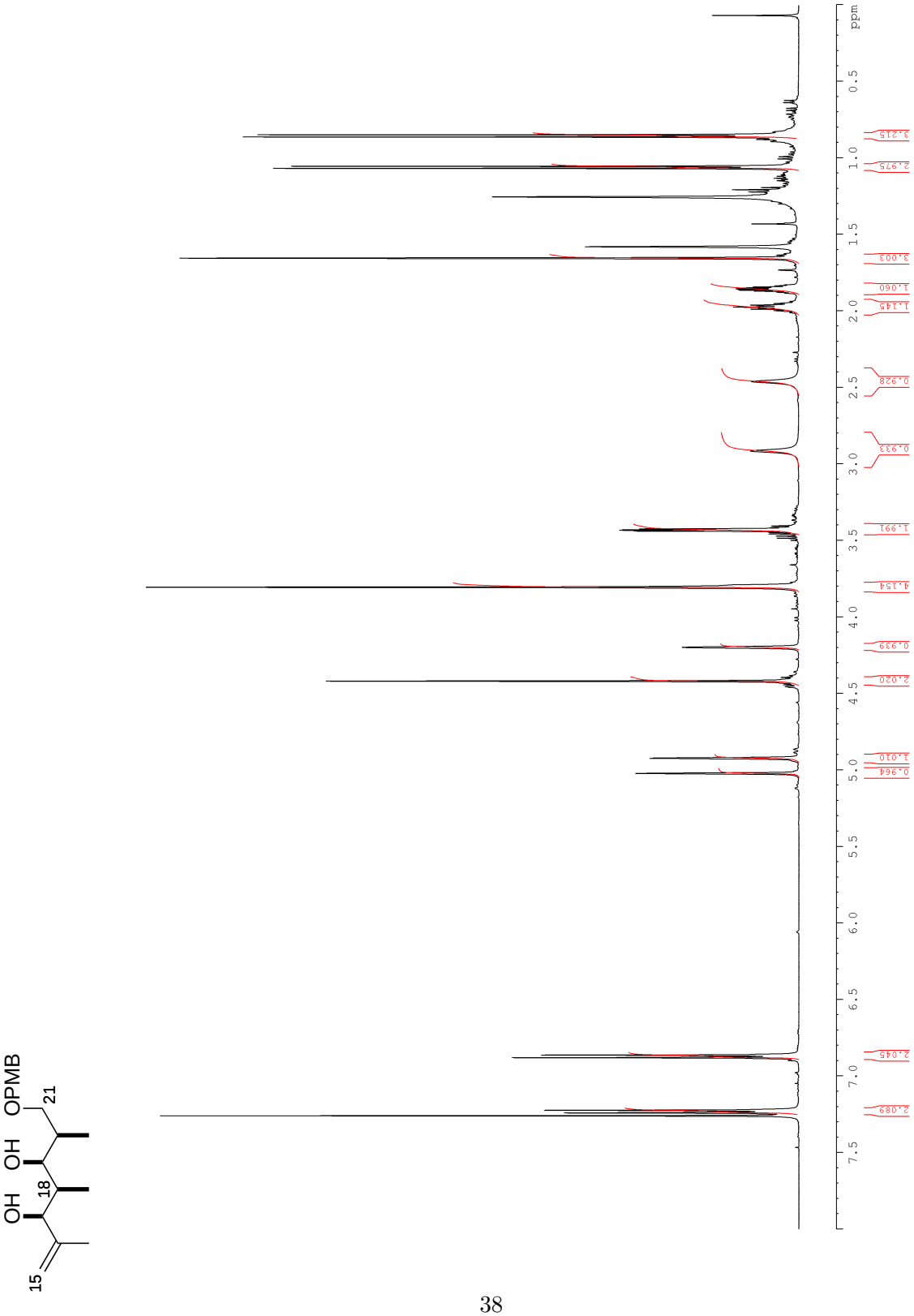
Table 4: NMR comparison of natural and synthetic actinoallolide D in $CDCl_3$

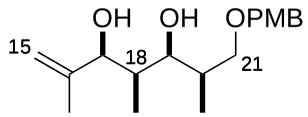
	Natural		Synthetic	
Atom	**^{13}C**	**^{1}H**	**^{13}C**	**^{1}H**
1	168.3		168.3	
2	37.5	3.63 (1H, d, J = 11.4 Hz)	37.5	3.63 (1H, d, J = 11.4 Hz)
		3.31 (1H, d, J = 11.4 Hz)		3.31 (1H, d, J = 11.4 Hz)
3	177.4		177.4	
4	119.0		119.0	
5	206.4		206.5	
6	87.6		87.6	
7	47.9	2.47 (1H, d, J = 13.2 Hz)	47.9	2.47 (1H, d, J = 13.2 Hz)
		2.43 (1H, d, J = 13.2 Hz)		2.43 (1H, d, J = 13.2 Hz)
8	130.9		130.9	
9	126.2	5.17 (1H, brdd, J = 8.0, 8.0 Hz)	126.2	5.16 (1H, dd, J = 7.7, 7.7 Hz)
10	29.9	2.48 (1H, m)	29.9	2.49 (1H, m)
		2.28 (1H, m)		2.29 (1H, m)
11	76.0	5.27 (1H, ddd, J = 6.8, 6.8, 1.6 Hz)	76.0	5.27 (1H, ddd, J = 7.0, 7.0, 1.3 Hz)
12	41.1	1.80 (1H, m)	41.1	1.79 (1H, m)
13	76.9	3.27 (1H, dd, J = 9.6, 2.4 Hz)	76.6	3.27 (1H, ddd, J = 9.0, 5.2, 2.7 Hz)
14	32.3	1.82 (1H, m)	32.3	1.82 (1H, m)
15	38.8	2.11 (1H, brd, J = 12.4 Hz)	38.7	2.12 (1H, d, J = 12.1 Hz)
		1.78 (1H, m)		1.78 (1H, d, J = 12.1 Hz)
16	133.2		133.2	
17	129.1	4.88 (1H, brd, J = 9.6 Hz)	129.1	4.88 (1H, d, J = 9.8 Hz)
18	36.8	2.50 (1H, m)	36.8	2.51 (1H, m)
19	82.0	3.52 (1H, dd, J = 9.2, 1.6 Hz)	82.0	3.52 (1H, d, J = 9.5 Hz)
20	37.8	1.66 (1H, m)	37.8	1.65 (1H, m)
21	79.3	3.70 (1H, ddd, J = 6.0, 6.0, 1.8 Hz)	79.3	3.71 (1H, dd, J = 6.7, 6.7 Hz)
22	28.1	1.50 (1H, m)	28.1	1.53 (1H, m)
		1.40 (1H, m)		1.41 (1H, m)
23	10.4	0.90 (3H, t, J = 7.4 Hz)	10.4	0.90 (3H, t, J = 7.4 Hz)
24	14.9	2.28 (1H, m)	14.9	2.27 (1H, m)
		2.19 (1H, m)		2.19 (1H, m)
25	12.3	1.05 (3H, t, J = 7.2 Hz)	12.3	1.04 (3H, t, J = 7.2 Hz)
26	22.2	1.41 (3H, s)	22.2	1.41 (3H, s)
27	17.0	1.43 (3H, brs)	17.0	1.43 (3H, s)
28	10.4	1.00 (3H, d, J = 7.2 Hz)	10.4	1.00 (3H, d, J = 7.0 Hz)
29	17.1	0.89 (3H, d, J = 6.0 Hz)	17.1	0.89 (3H, d, J = 6.5 Hz)
30	16.2	1.63 (3H, d, J = 0.8 Hz)	16.2	1.63 (3H, s)
31	17.9	1.04 (3H, d, J = 7.2 Hz)	17.9	1.04 (3H, d, J = 6.8 Hz)
32	4.2	0.84 (3H, d, J = 7.2 Hz)	4.2	0.84 (3H, d, J = 7.1 Hz)

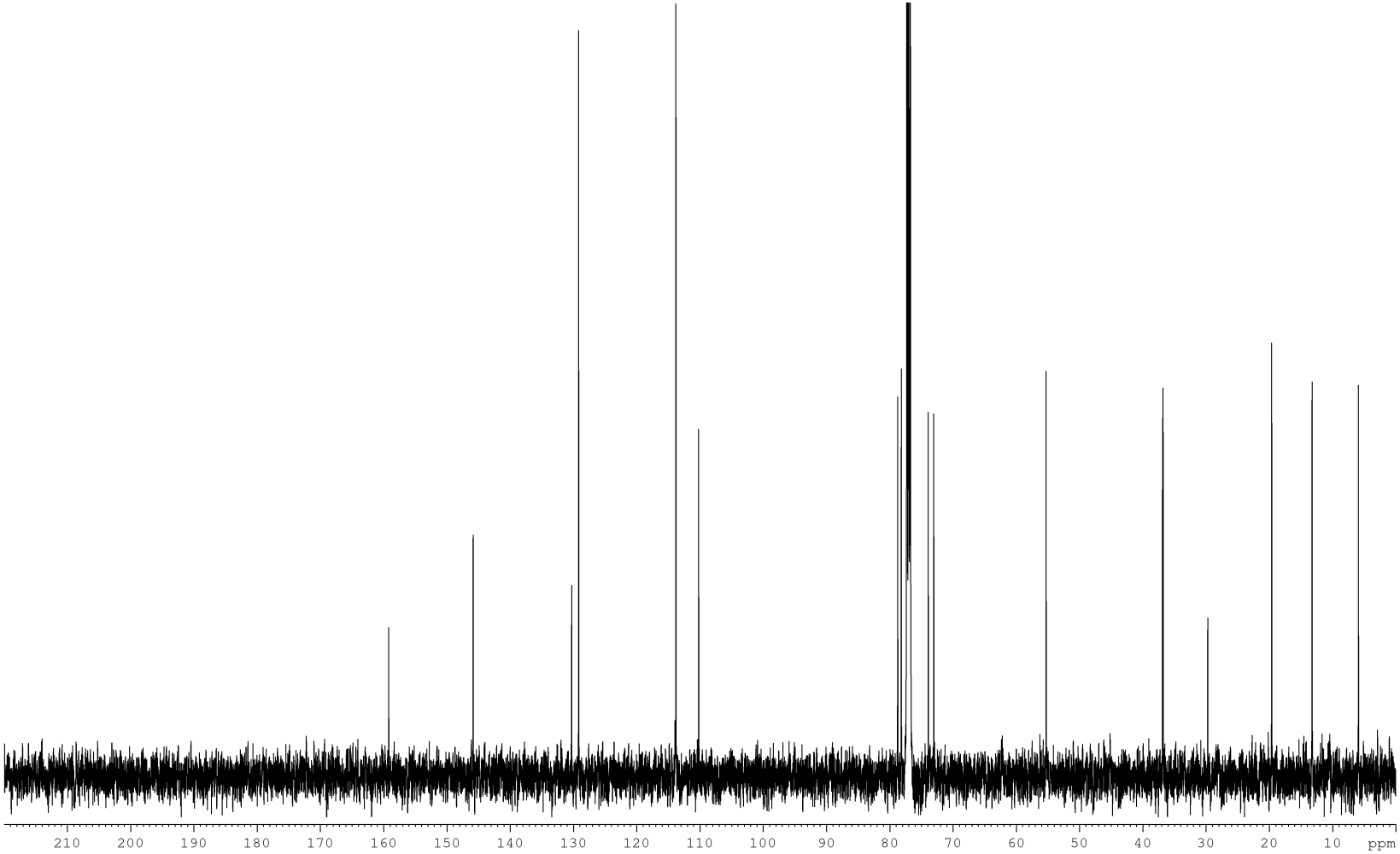
Table 5: NMR comparison of natural and synthetic actinoallolide E in $CDCl_3$

	Natural		Synthetic	
Atom	**^{13}C**	**^{1}H**	**^{13}C**	**^{1}H**
1	166.7		166.7	
2	35.9	3.82 (1H, d, J = 14.8 Hz)	36.0	3.82 (1H, d, J = 14.8 Hz)
		3.26 (1H, d, J = 14.8 Hz)		3.26 (1H, d, J = 14.8 Hz)
3	177.6		177.7	
4	117.6		117.6	
5	207.0		207.0	
6	88.2		88.2	
7	46.4	2.62 (1H, d, J = 13.8 Hz)	46.4	2.62 (1H, d, J = 13.6 Hz)
		2.47 (1H, d, J = 13.8 Hz)		2.47 (1H, d, J = 13.6 Hz)
8	130.7		130.7	
9	126.6	5.22 (1H, brdd, J = 8.0, 8.0 Hz)	126.6	5.23 (1H, dd, J = 8.2, 8.2 Hz)
10	35.2	2.23 (1H, m)	35.2	2.24 (1H, m)
		1.96 (1H, m)		1.97 (1H, m)
11	72.7	3.26 (1H, dd, J = 9.2, 1.2 Hz)	72.7	3.26 (1H, d, J = 8.8 Hz)
12	40.2	1.53 (1H, m)	40.2	1.54 (1H, m)
13	81.4	4.97 (1H, dd, J = 9.4, 2.2 Hz)	81.4	4.97 (1H, dd, J = 9.4, 2.1 Hz)
14	31.6	1.91 (1H, m)	31.6	1.93 (1H, m)
15	39.4	2.12 (1H, brd, J = 14.0 Hz)	39.5	2.13 (1H, d, J = 13.2 Hz)
		1.68 (1H, m)		1.68 (1H, dd, J = 13.2, 11.7 Hz)
16	132.9		132.9	
17	129.4	4.81 (1H, brd, J = 10.0 Hz)	129.4	4.82 (1H, d, J = 10.0 Hz)
18	35.8	2.46 (1H, m)	35.8	2.47 (1H, m)
19	74.8	3.64 (1H, dd, J = 9.2, 2.0 Hz)	74.8	3.65 (1H, d, J = 9.2 Hz)
20	47.5	2.66 (1H, qd, J = 7.2, 2.0 Hz)	47.5	2.65 (1H, qd, J = 7.2, 2.2 Hz)
21	217.3		217.3	
22	34.8	2.54 (1H, m)	34.8	2.56 (1H, m)
		2.49 (1H, m)		2.48 (1H, m)
23	7.7	1.06 (3H, t, J = 7.4 Hz)	7.7	1.06 (3H, t, J = 7.3 Hz)
24	15.6	2.30 (1H, m)	15.6	2.30 (1H, m)
		2.22 (1H, m)		2.22 (1H, m)
25	13.1	1.11 (3H, t, J = 7.6 Hz)	13.1	1.11 (3H, t, J = 7.5 Hz)
26	24.9	1.36 (3H, s)	24.9	1.36 (3H, s)
27	17.7	1.53 (3H, brs)	17.7	1.53 (3H, s)
28	8.1	0.94 (3H, d, J = 7.2 Hz)	8.1	0.95 (3H, d, J = 7.2 Hz)
29	16.5	0.81 (3H, d, J = 6.8 Hz)	16.5	0.81 (3H, d, J = 6.8 Hz)
30	15.9	1.62 (3H, d, J = 0.8 Hz)	15.9	1.63 (3H, s)
31	17.9	1.04 (3H, d, J = 6.8 Hz)	17.9	1.05 (3H, d, J = 6.4 Hz)
32	9.5	1.09 (3H, d, J = 7.2 Hz)	9.5	1.09 (3H, d, J = 7.2 Hz)

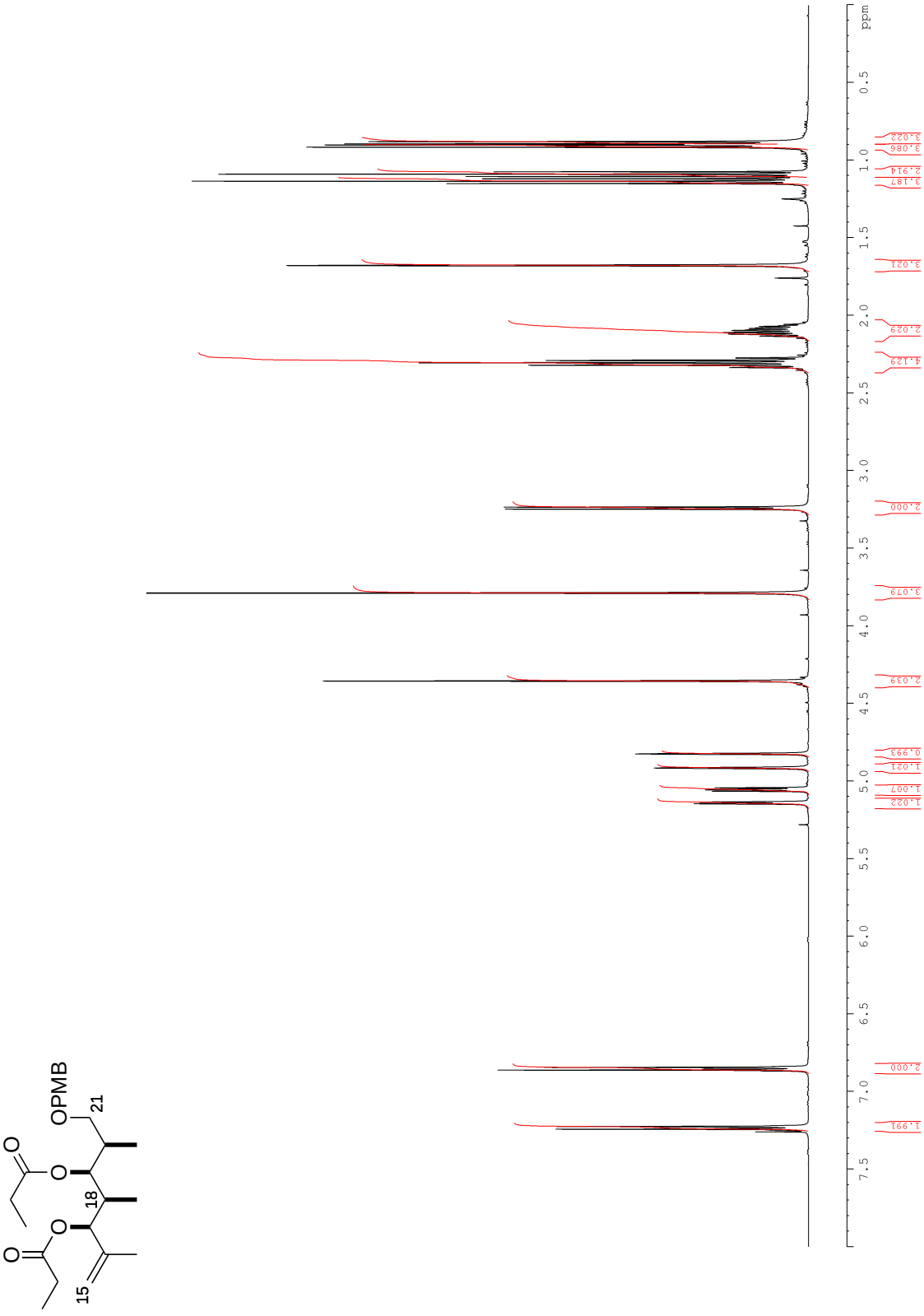
1,3-Diol 9


OPMB
21
OH
OH
18
15
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.215
2.975
3.003
1.060
1.145
0.928
0.933
1.991
4.154
0.939
2.020
1.010
0.964
2.045
2.089


OH
OH
OPMB
15
18
21


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

Diester 10


OPMB
21
18
15
O
O
O
O
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
3.022
3.086
2.914
3.187
3.021
2.029
4.129
2.000
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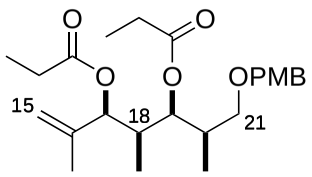
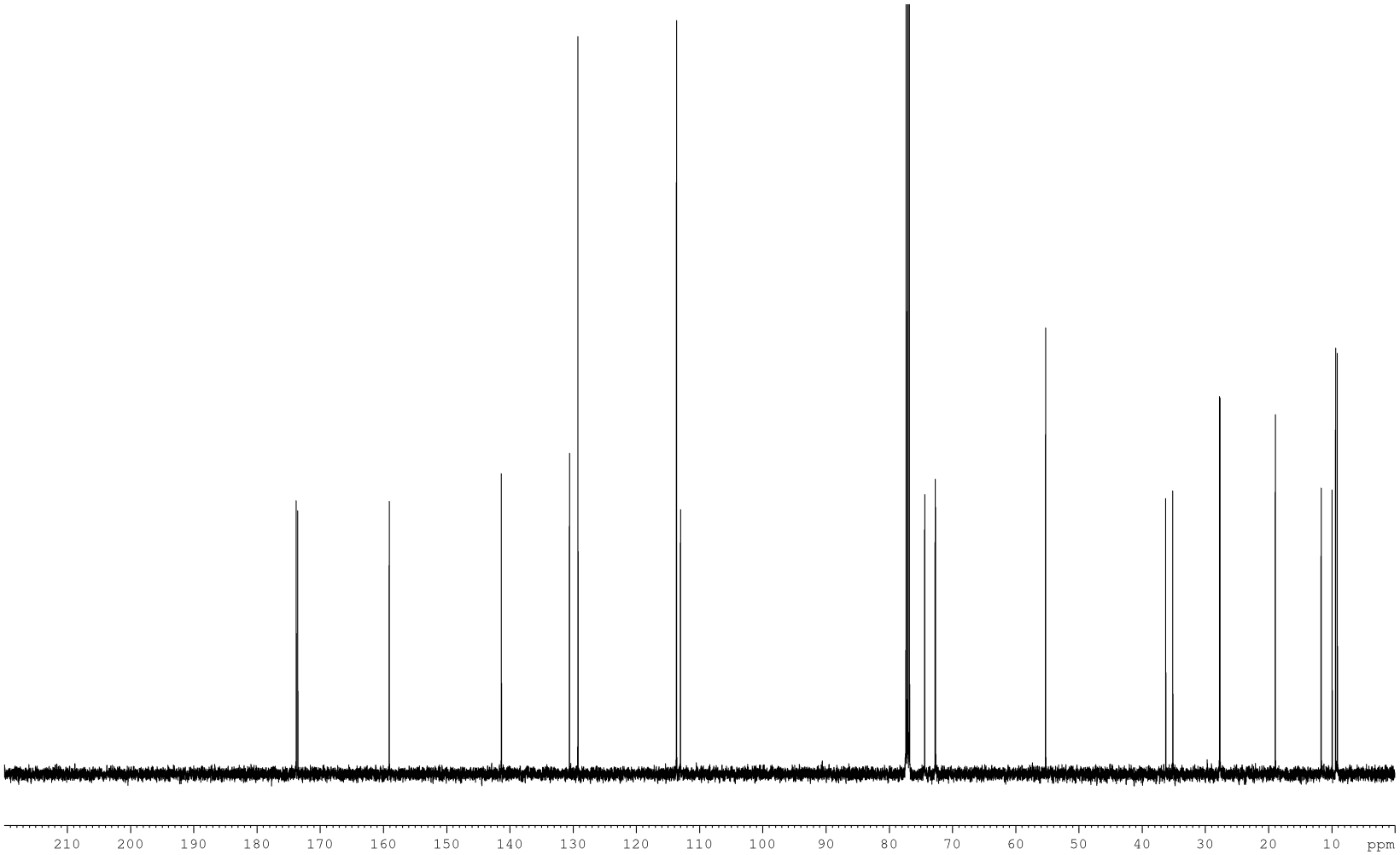
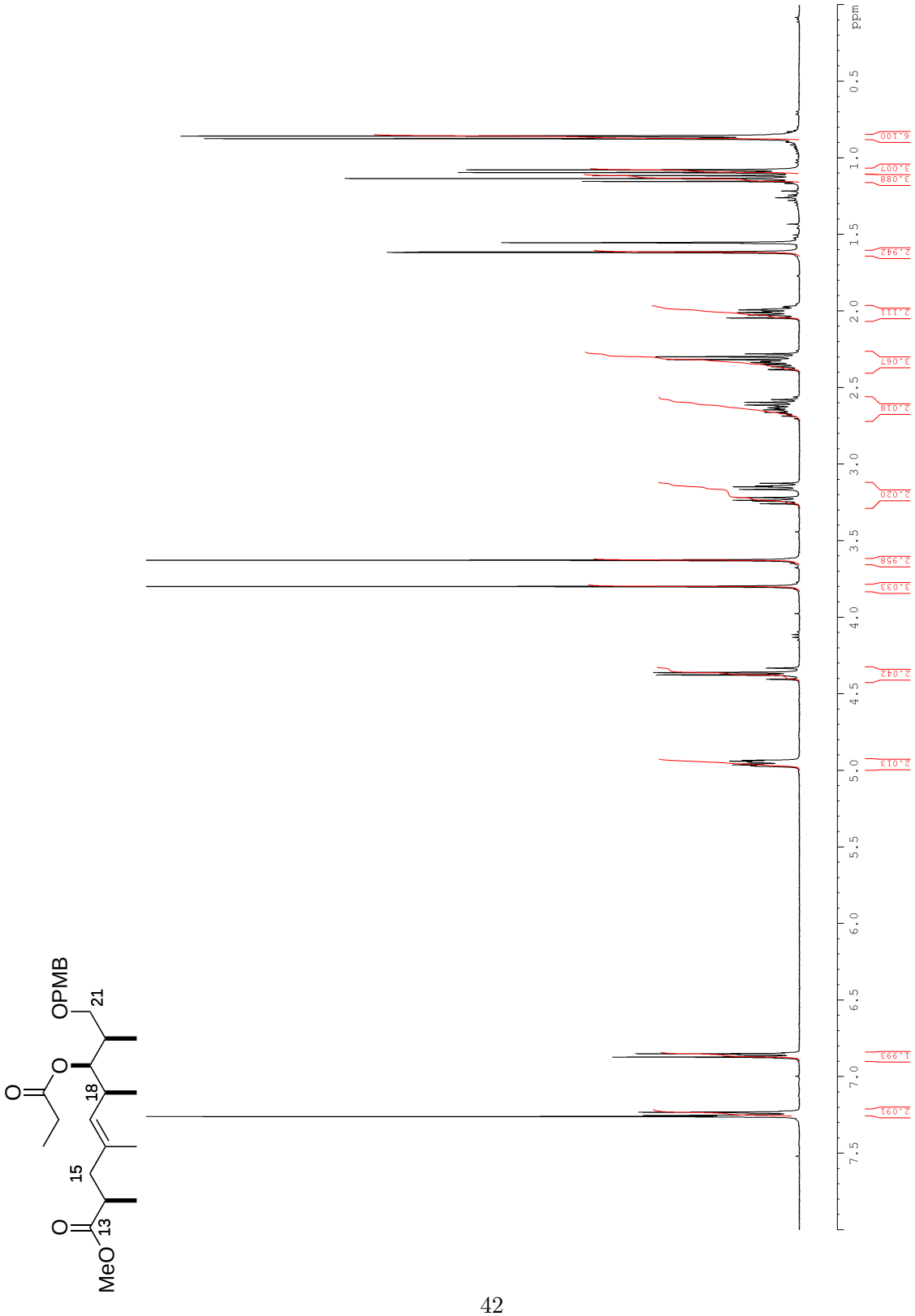
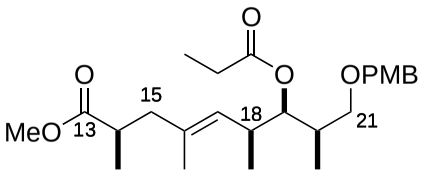
0.993
1.021
1.007
1.022
2.000
1.991

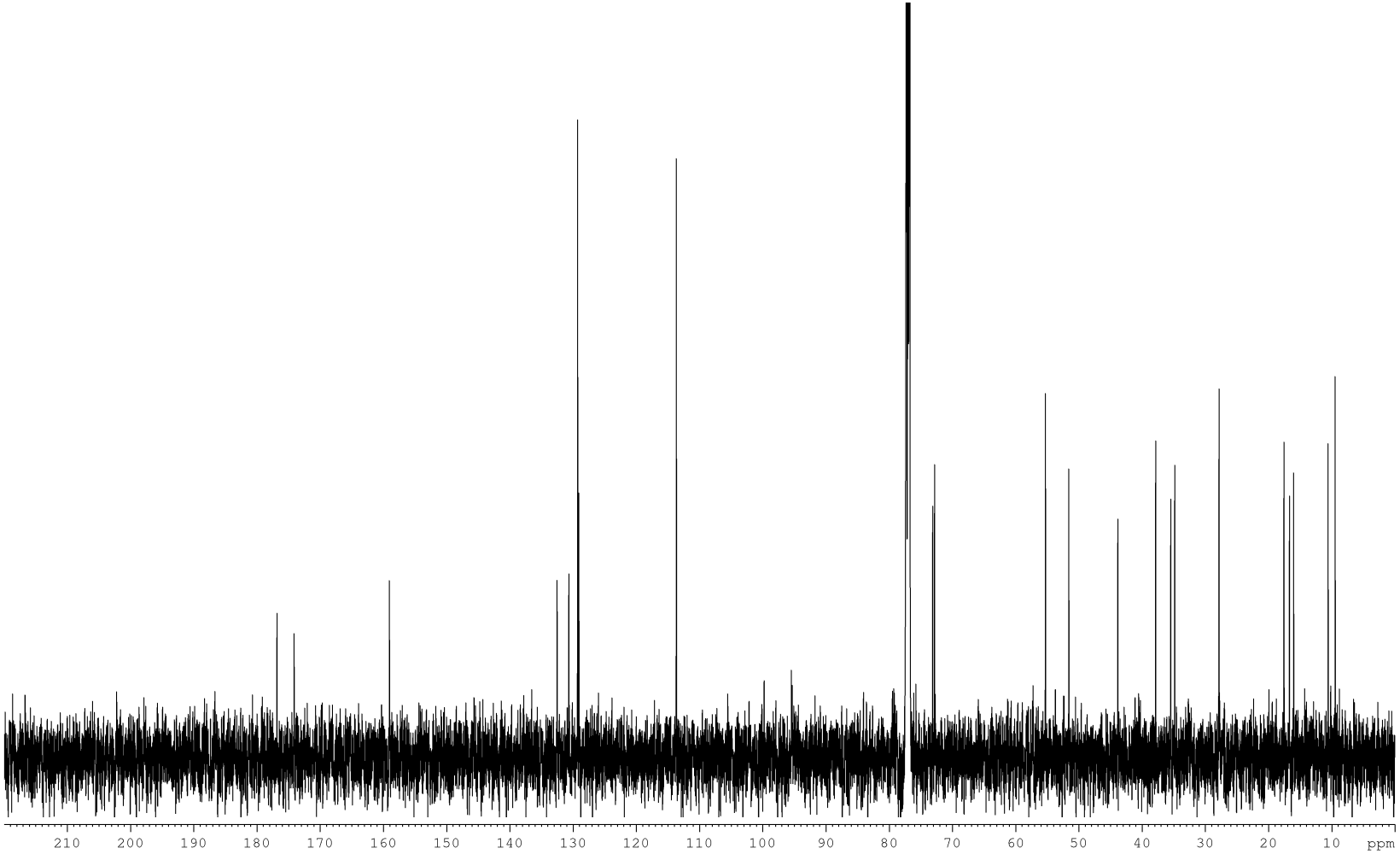

O
O
O
O
OPMB
15
18
21


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

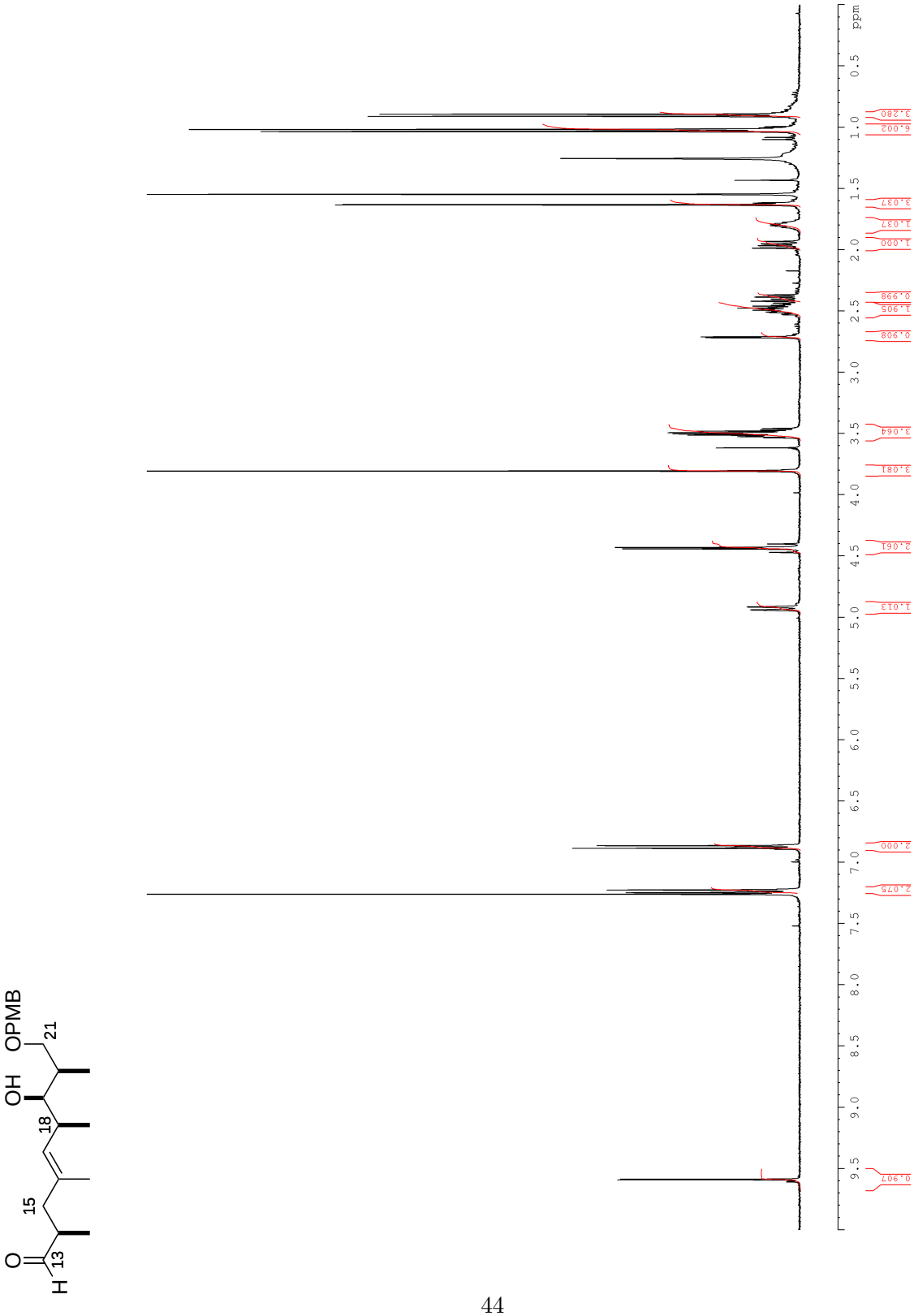
Methyl ester S1

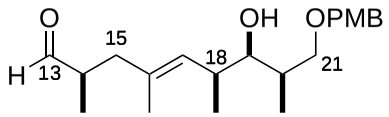


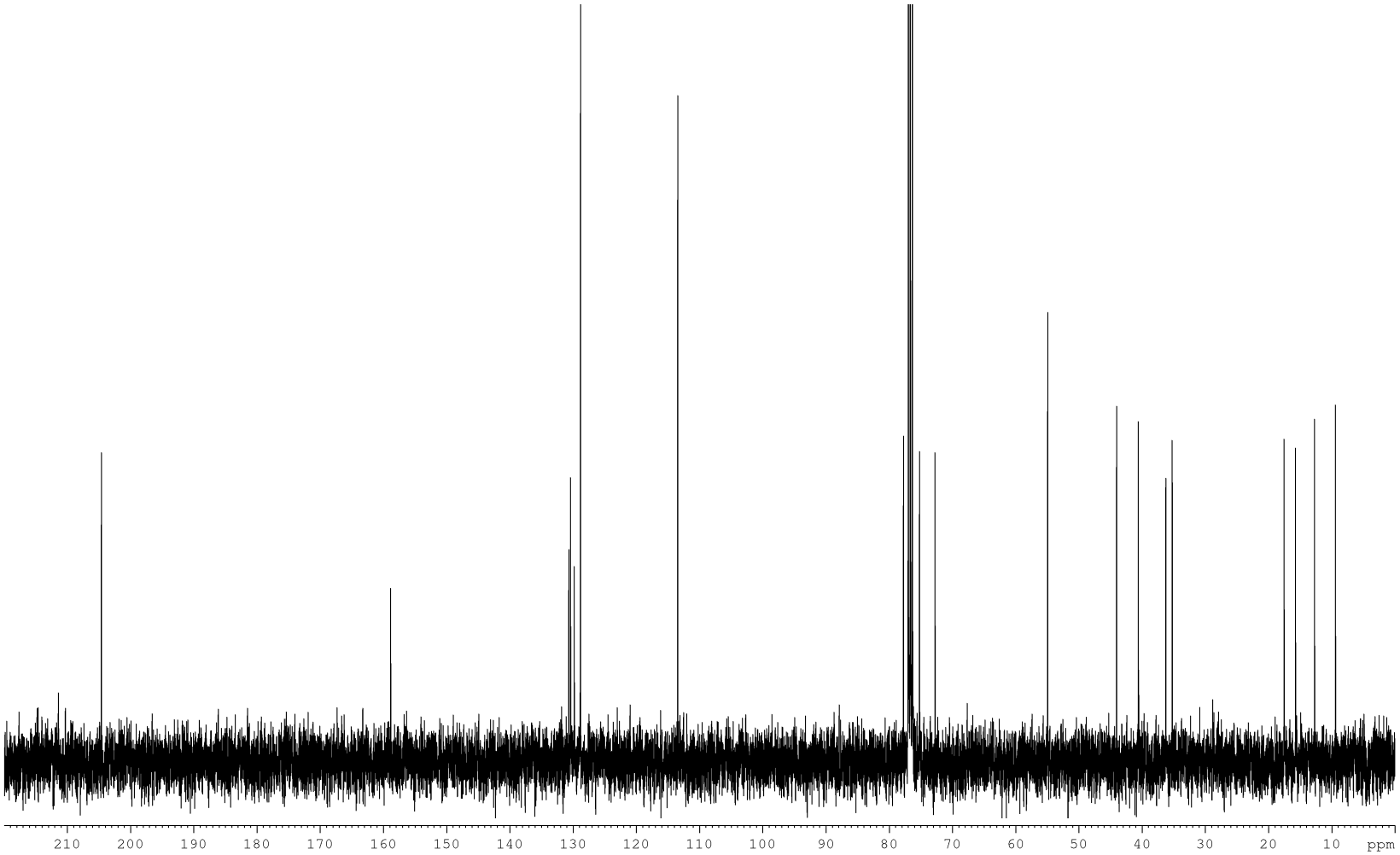

O
O
O
OPMB
15
18
MeO
13
21


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

Aldehyde 12


OPMB
OH
21
18
15
O
H
13
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
3.280
6.002
3.037
1.037
1.000
0.998
1.905
0.908
3.064
3.081
2.061
1.013
2.000
2.075
0.907


O
H
13
15
18
OH
OPMB
21


210
200
190
180
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160
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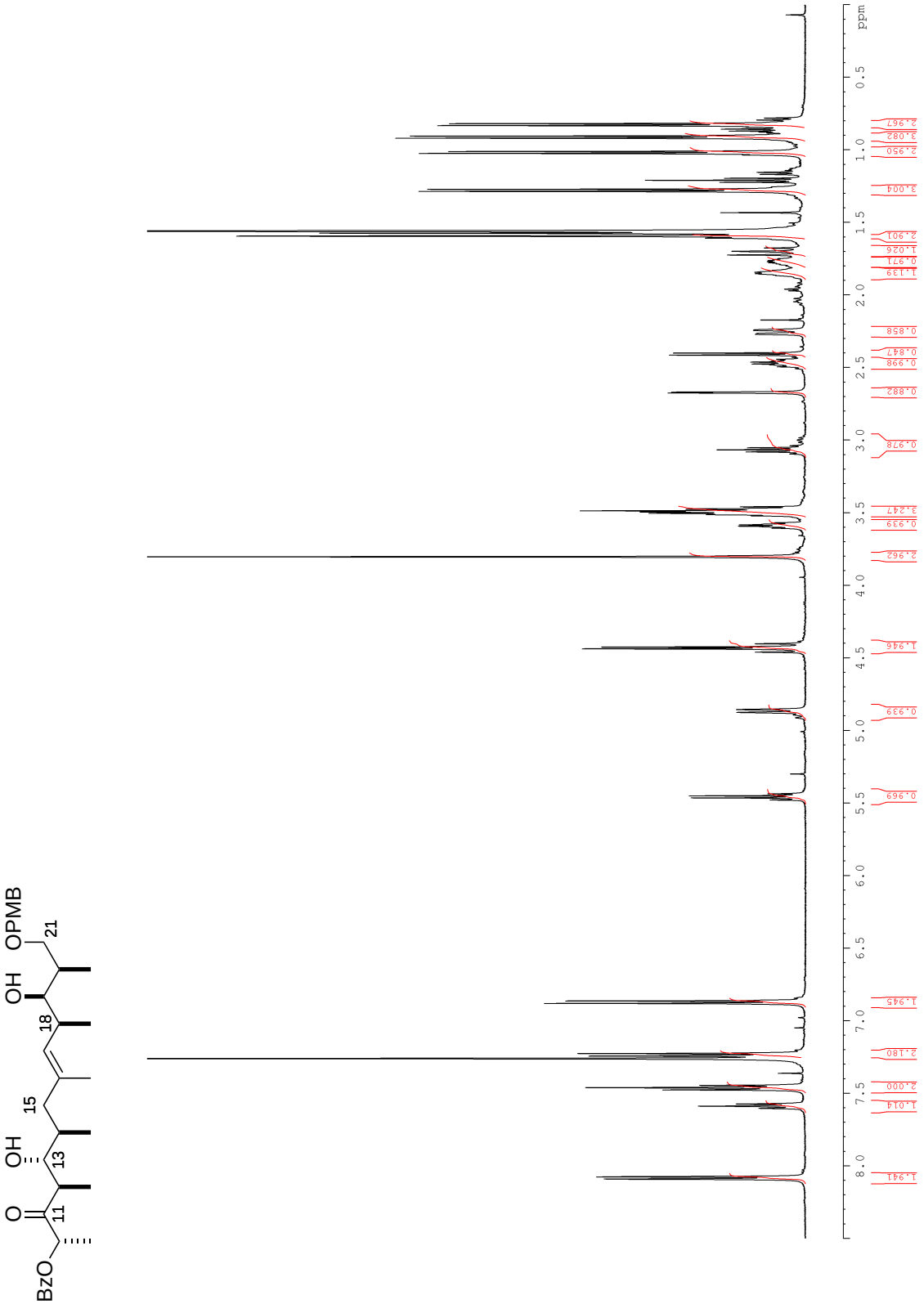
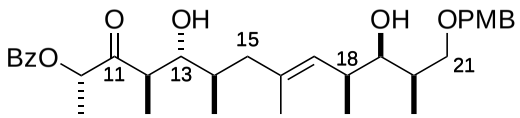
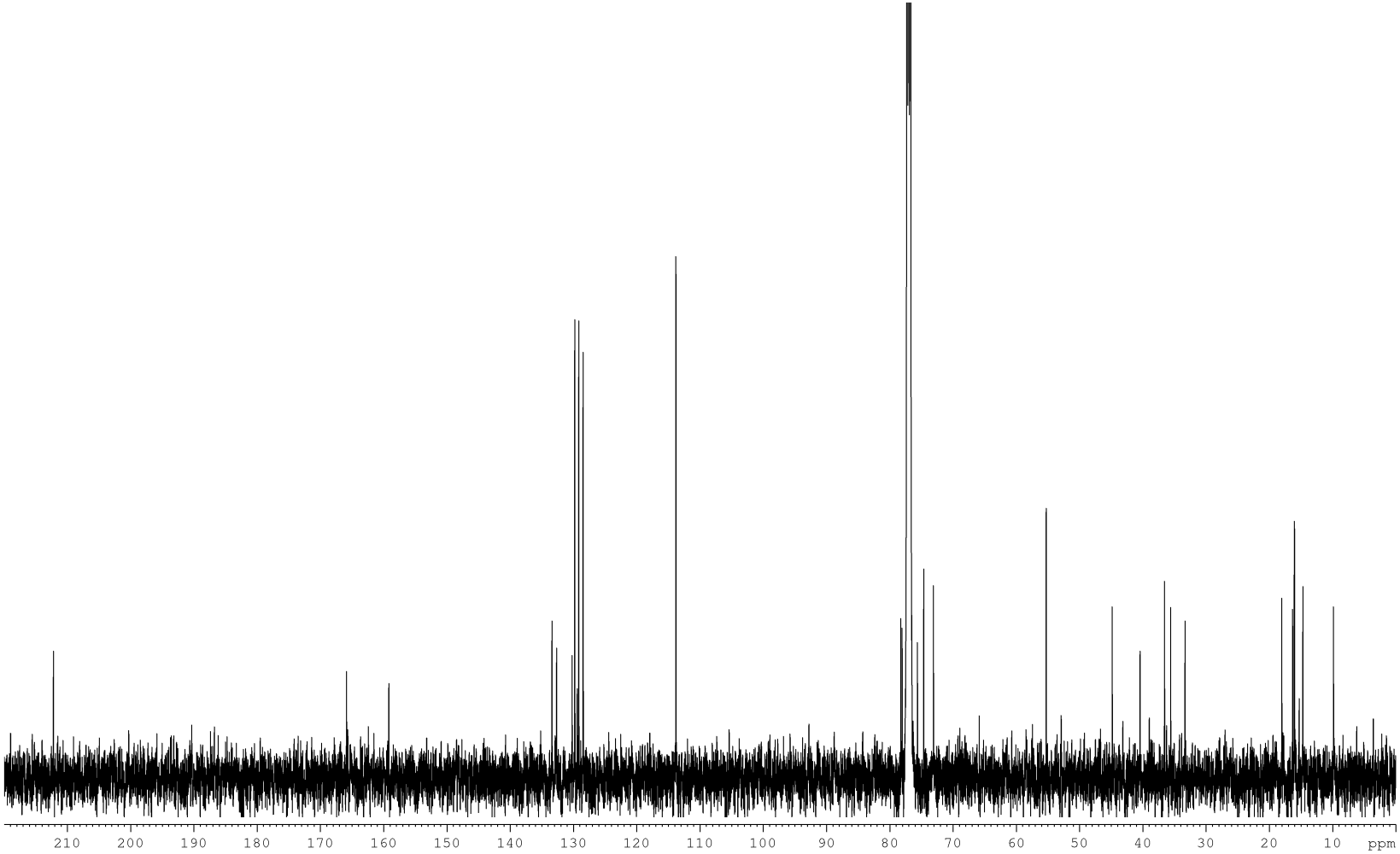
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

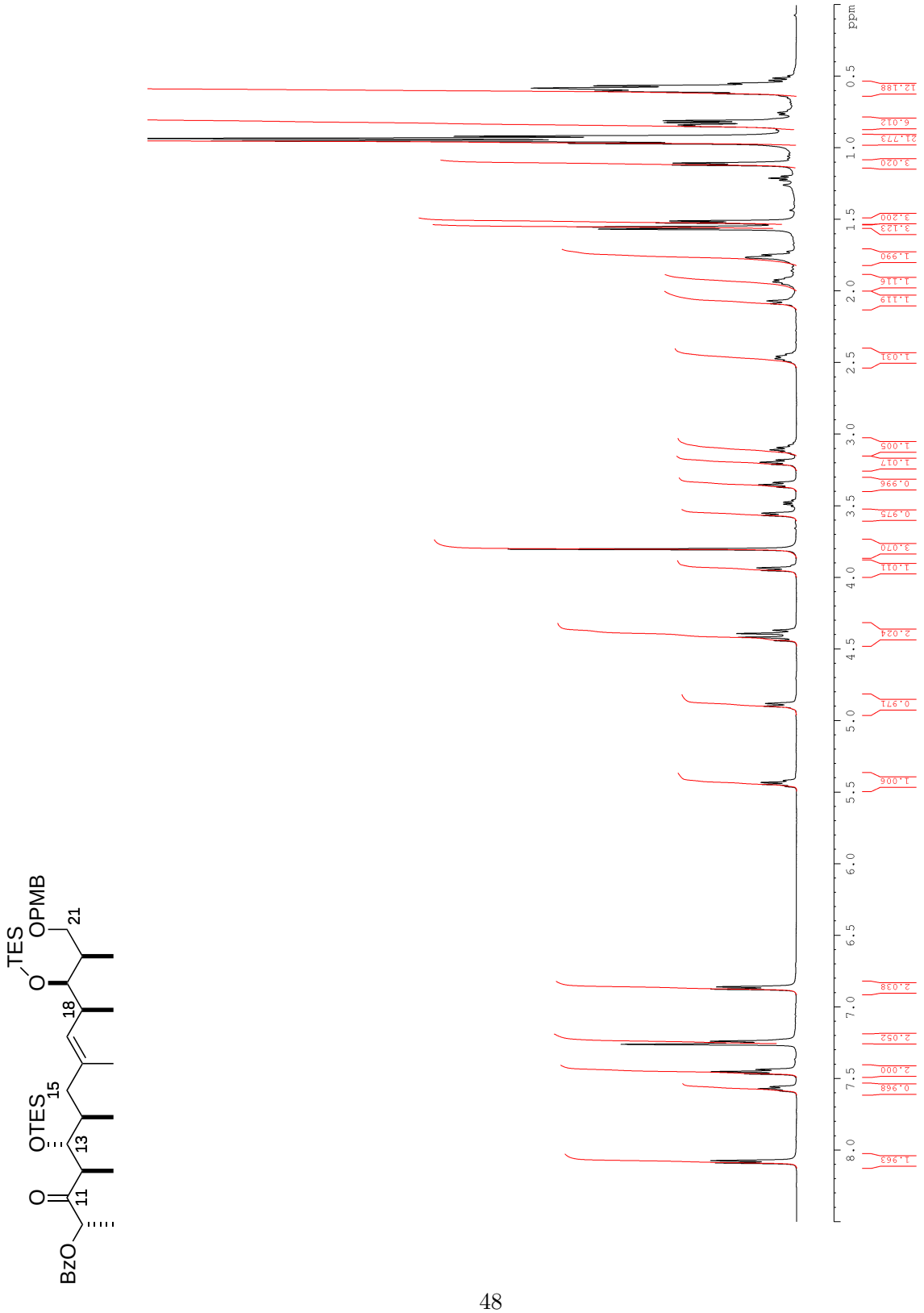
Aldol adduct 14

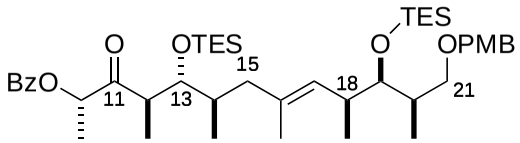


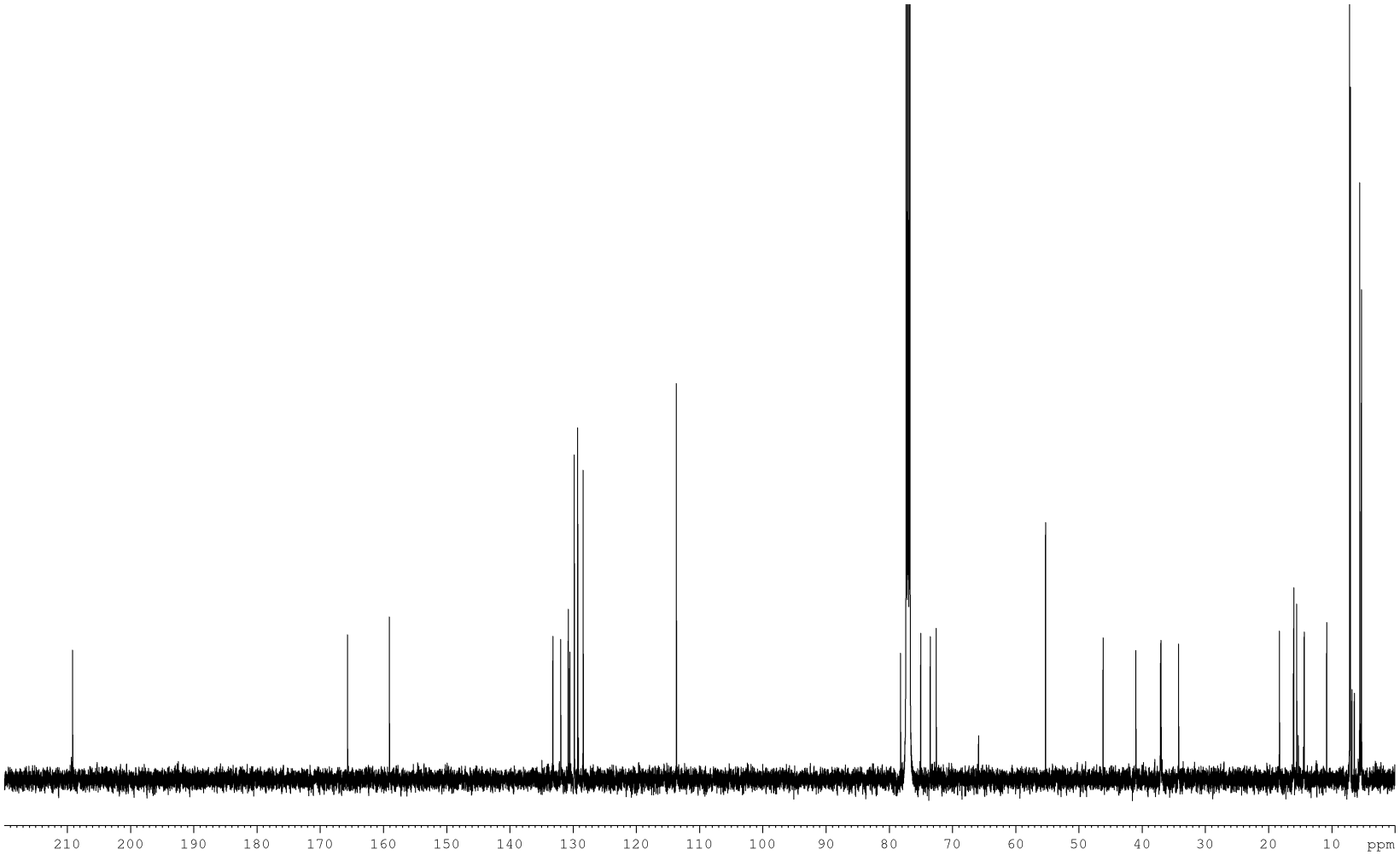

O
OH
OH
OPMB
BzO
11
13
15
18
21


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

Bis TES ether S2




BzO
O
OTES
TES
O
OPMB
11
13
15
18
21


210
200
190
180
170
160
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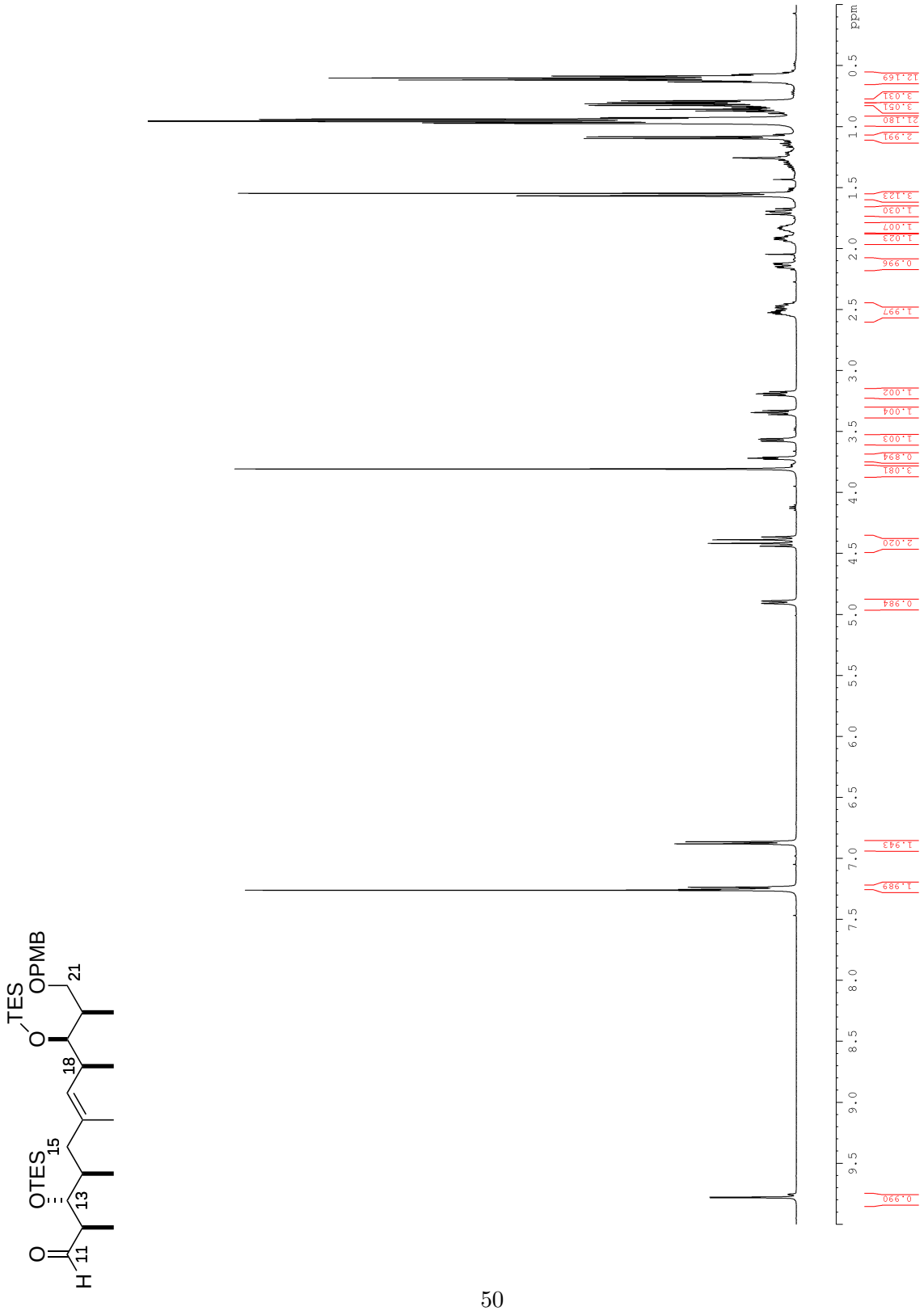
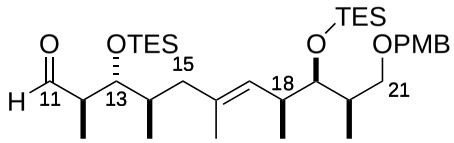
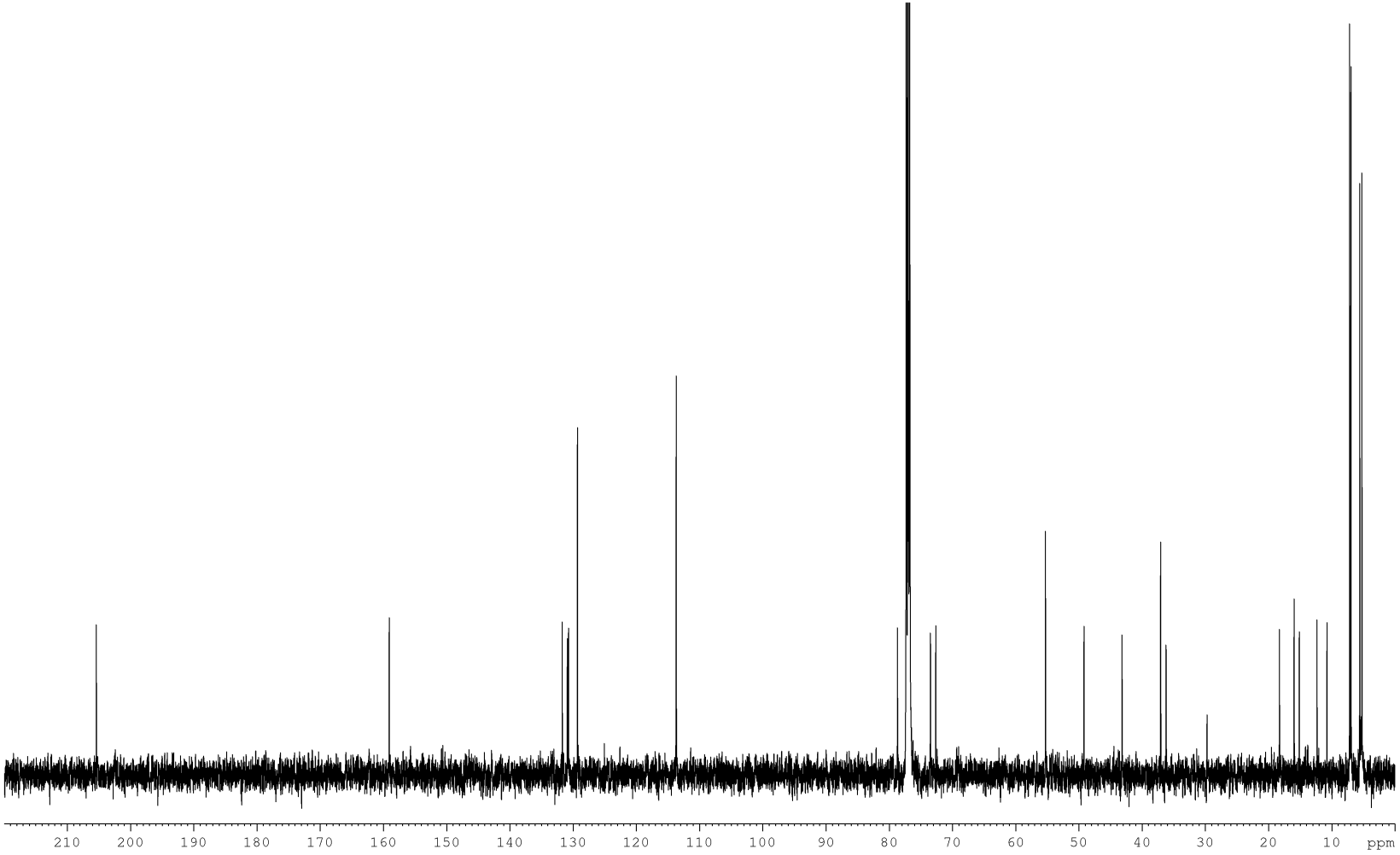
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

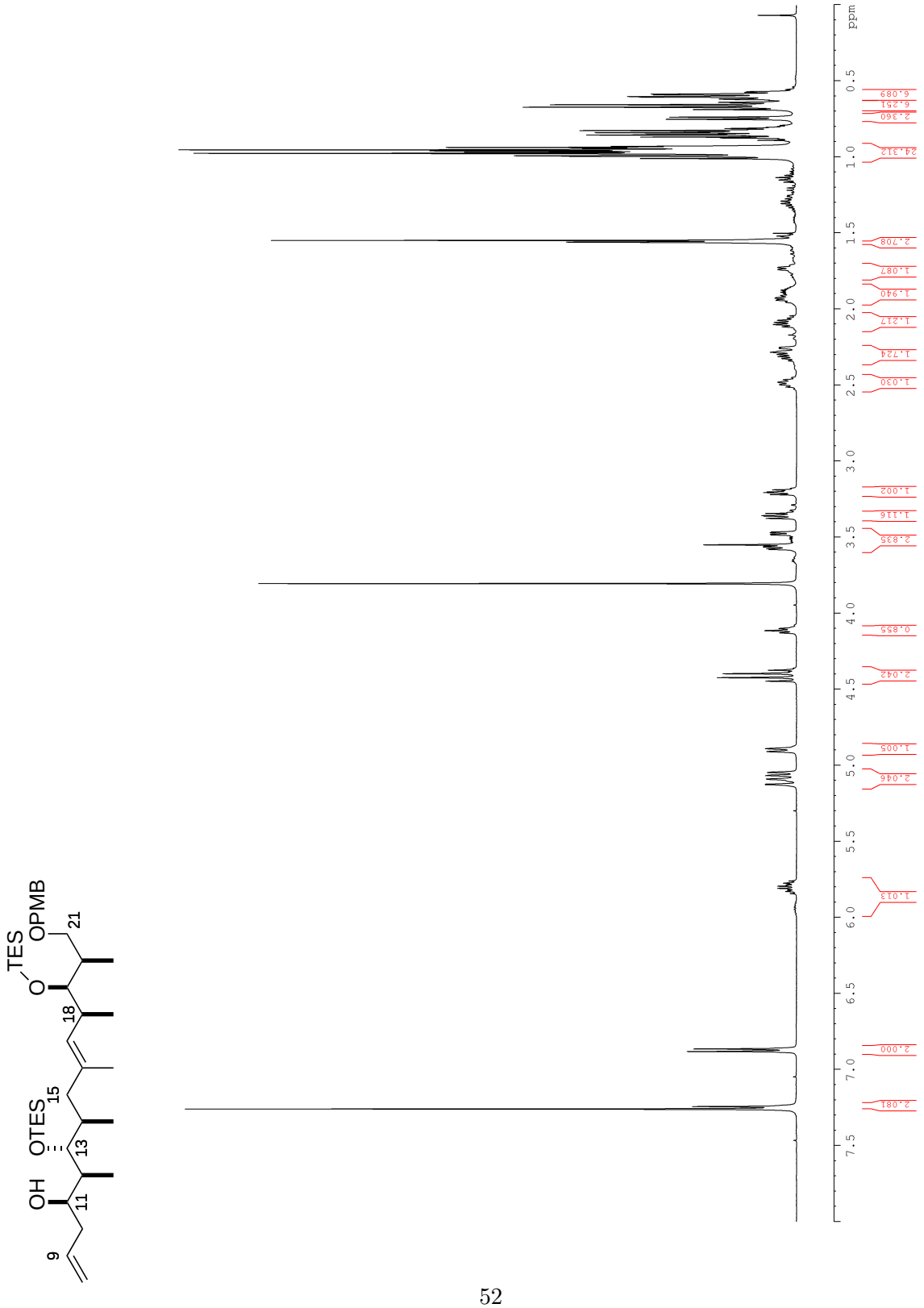
Aldehyde 15

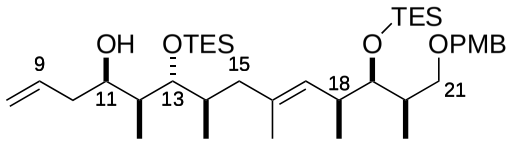

TES
OPMB
21
O
18
OTES
15
13
O
11
H
ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
12.169
3.051
3.031
21.180
2.991
3.123
1.030
1.007
1.023
0.996
1.997
1.002
1.004
1.003
0.894
3.081
2.020
0.984
1.943
1.989
0.990

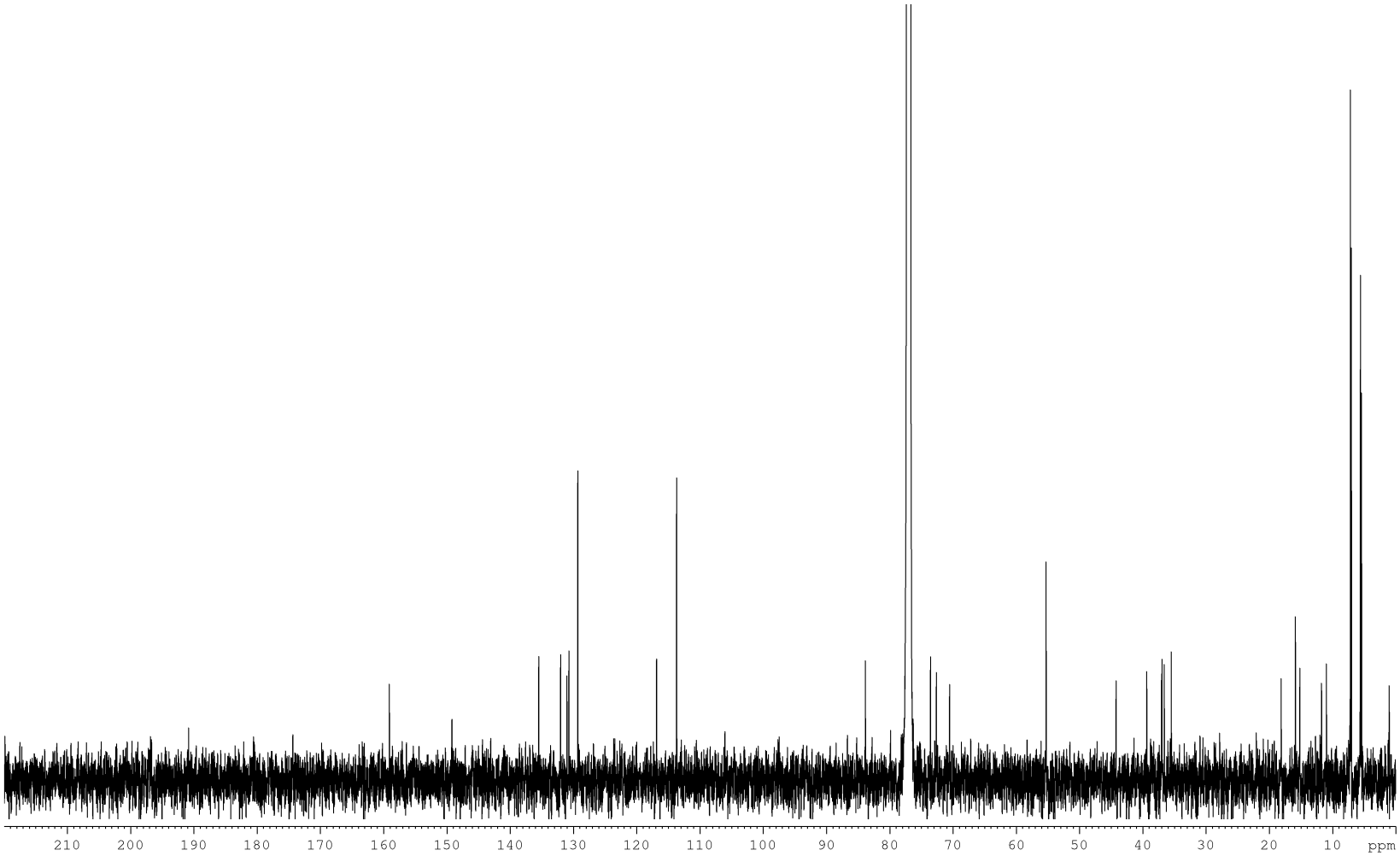

O
OTES
15
TES
O
OPMB
H
11
13
18
21


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

Side chain fragment 7




TES
OH
OTES
O
OPMB
9
15
18
11
13
21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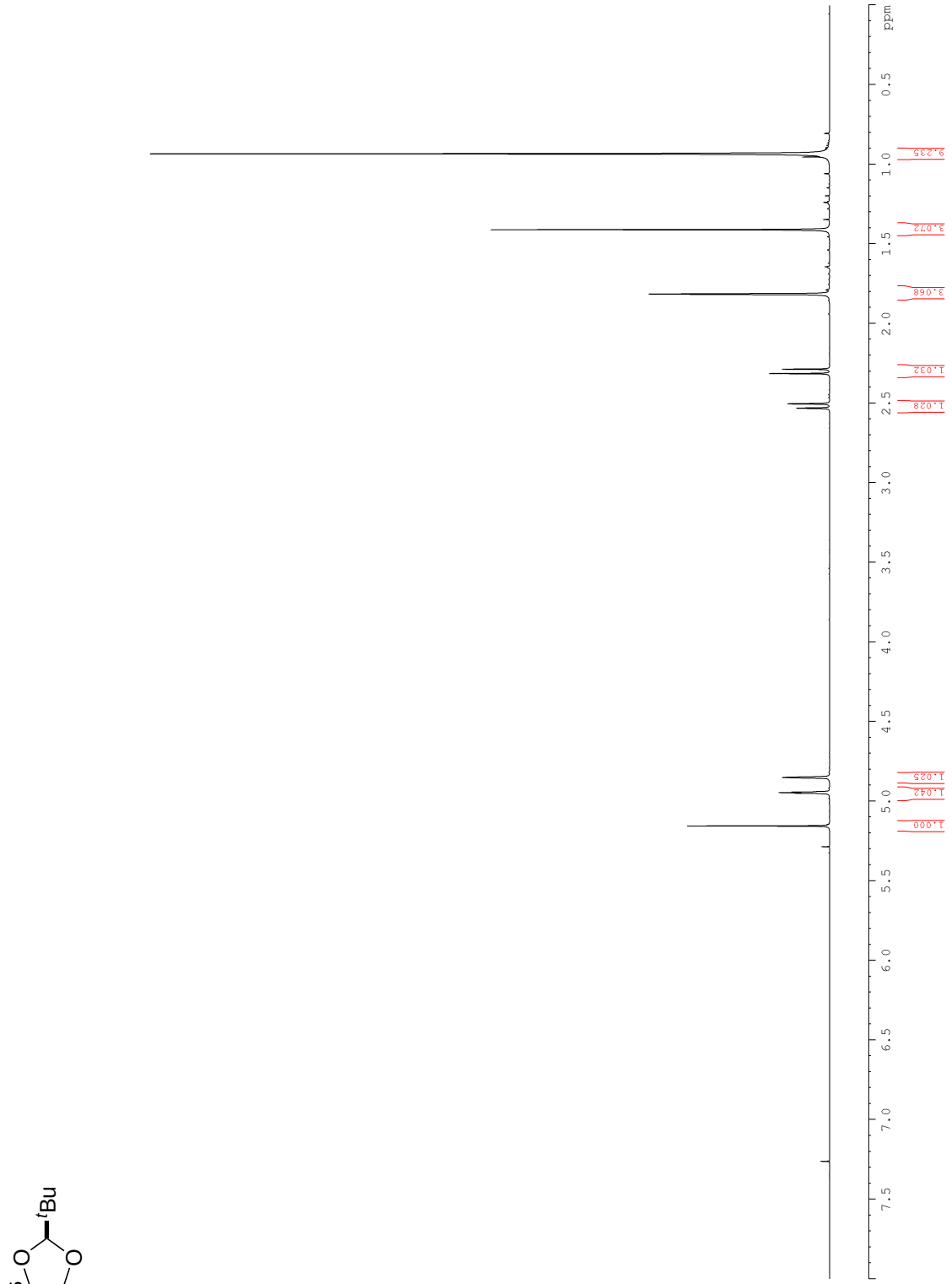
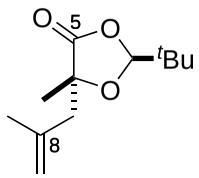
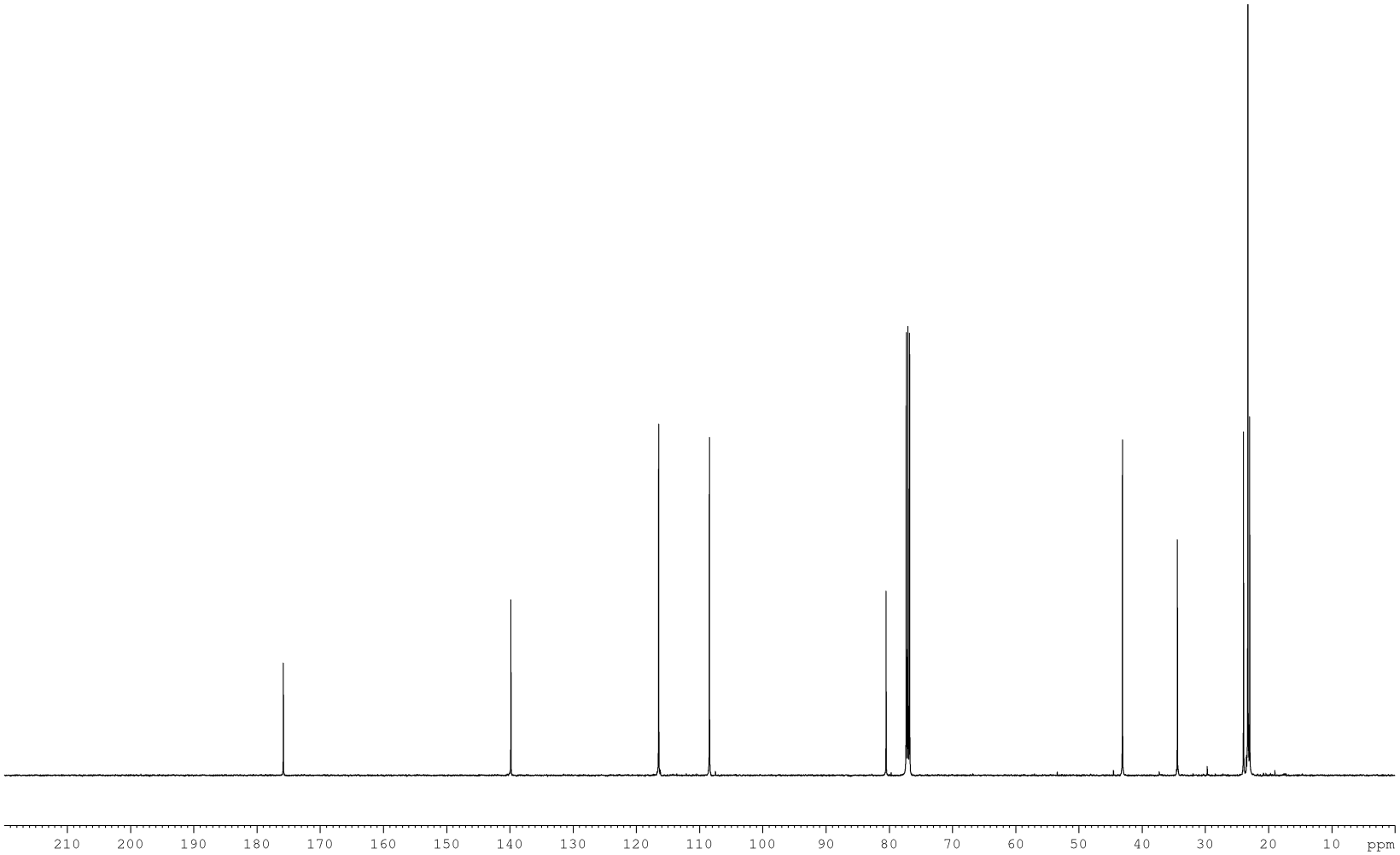
90
80
70
60
50
40
30
20
10
ppm

Alkylated dioxolanone 17




O
5
O
O
tBu
8

55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110
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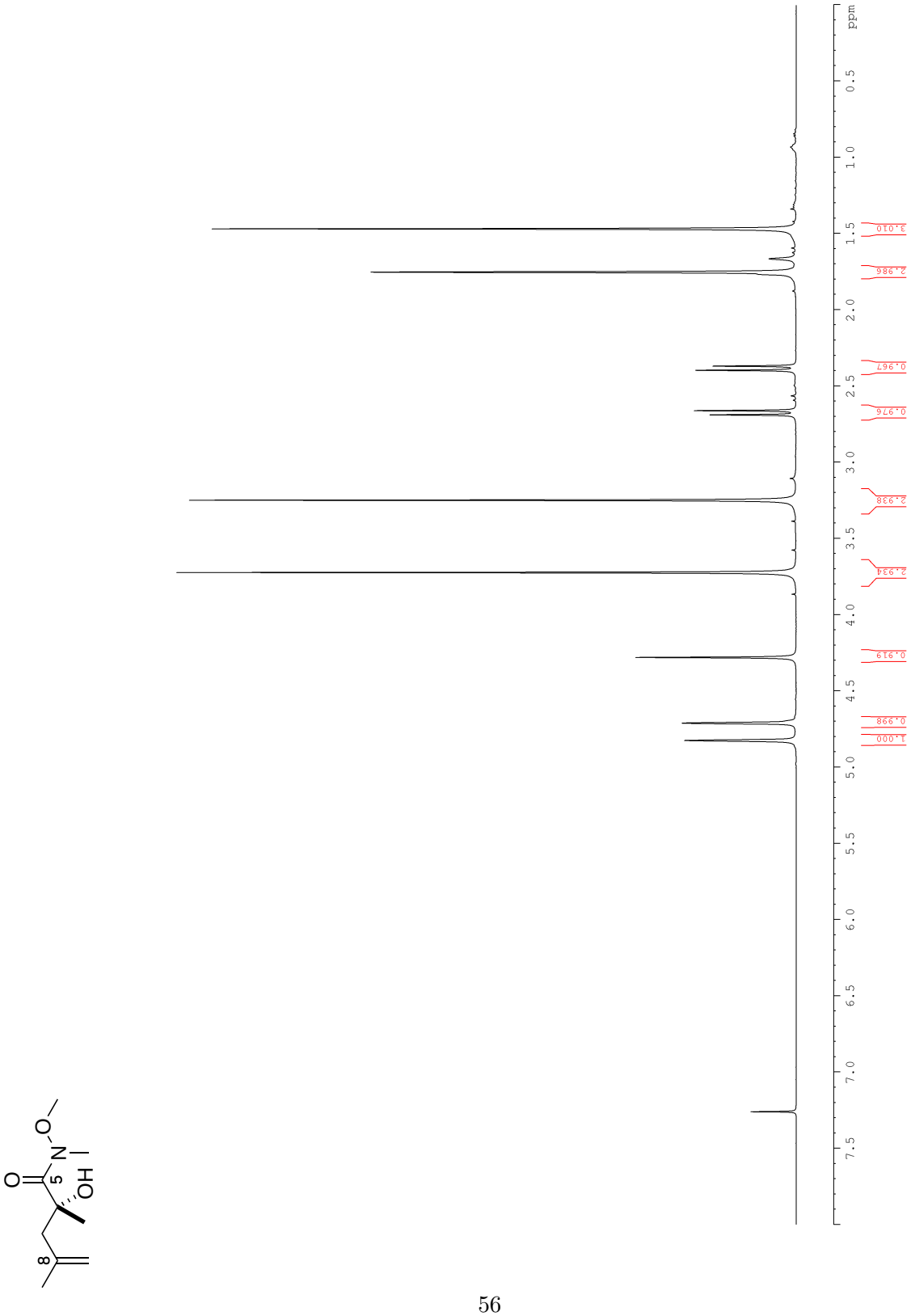
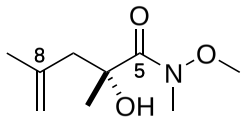
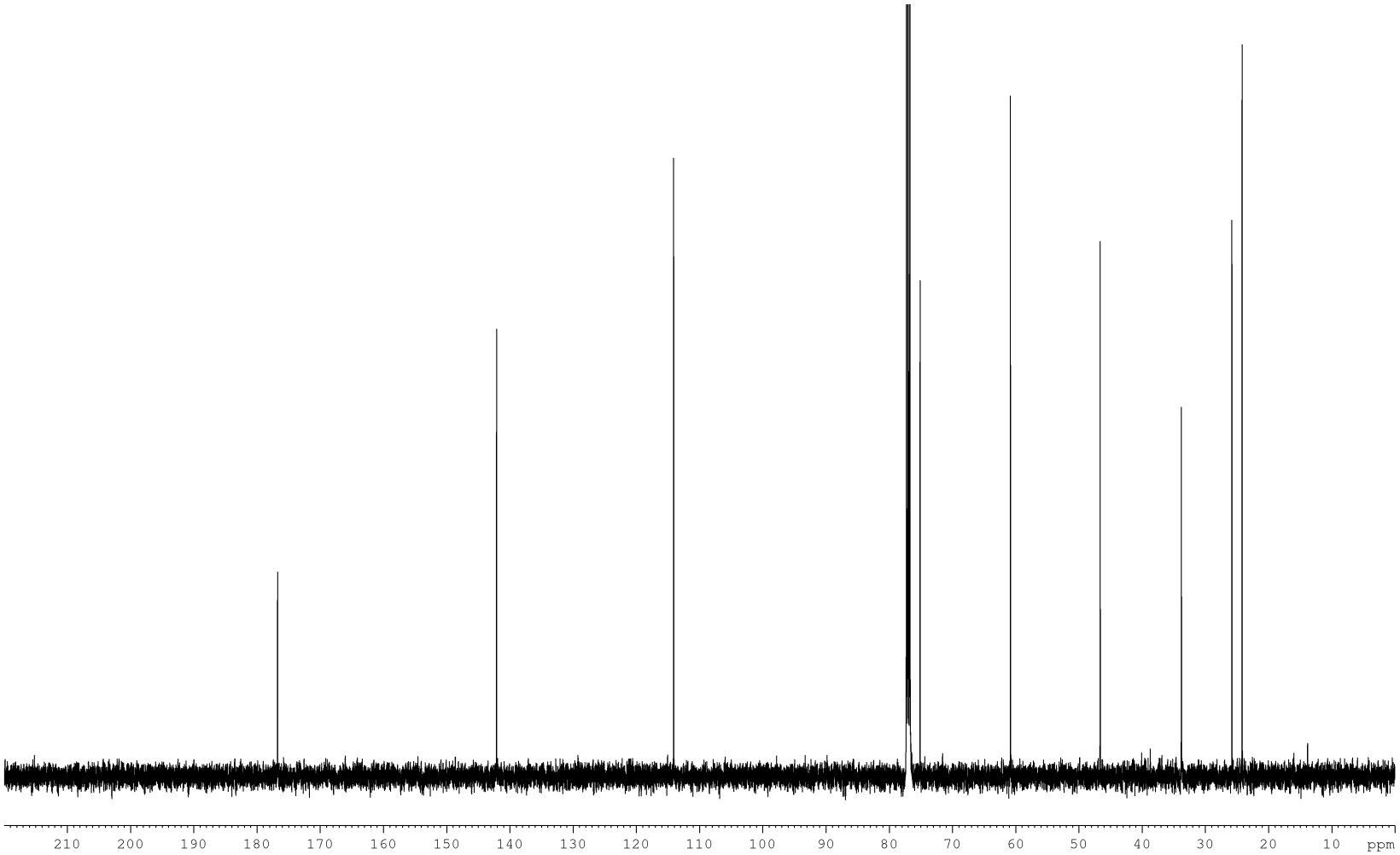
90
80
70
60
50
40
30
20
10
ppm

Weinreb amide 18




O
8
5
N
O
OH


210
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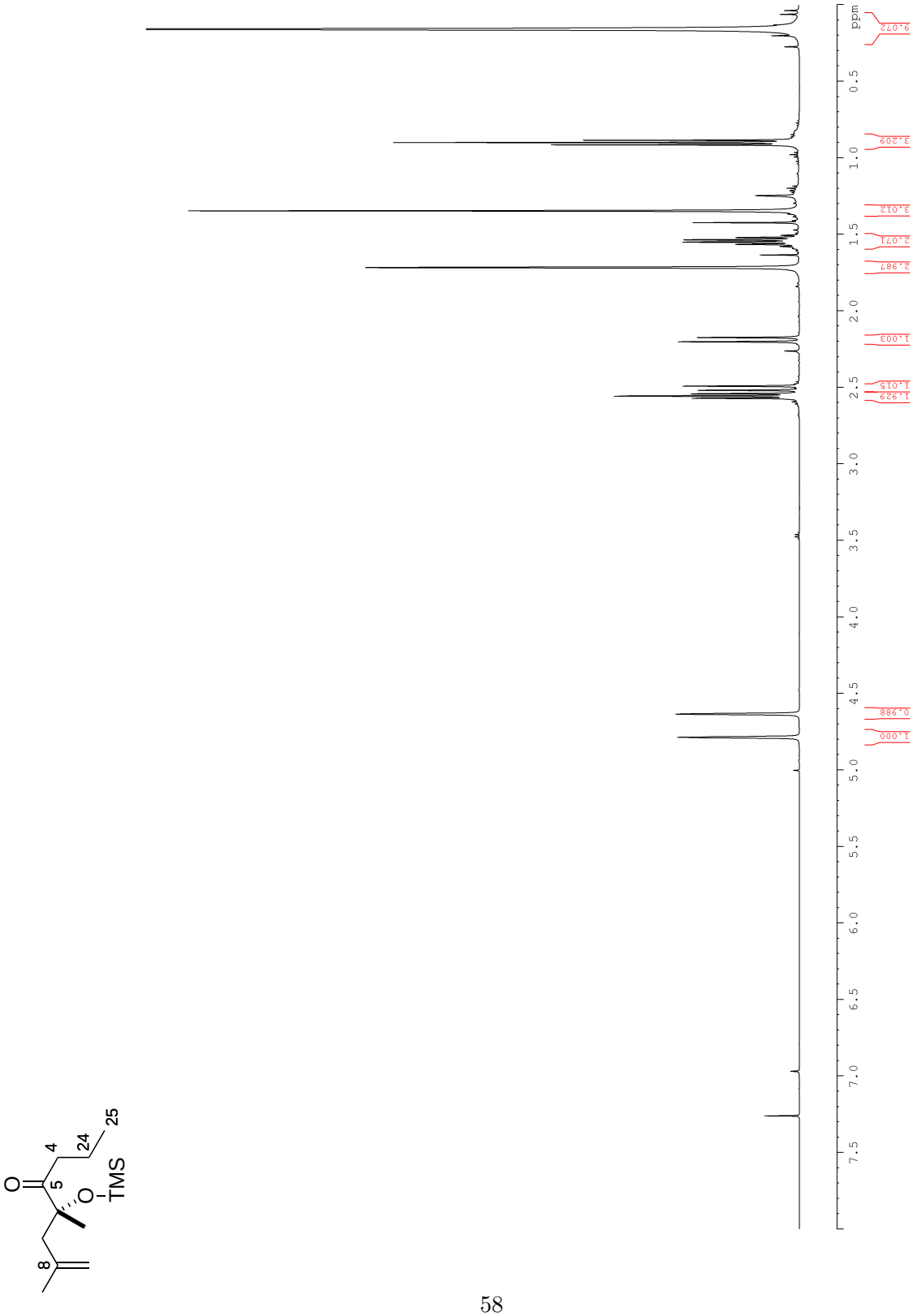
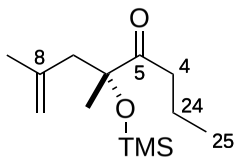
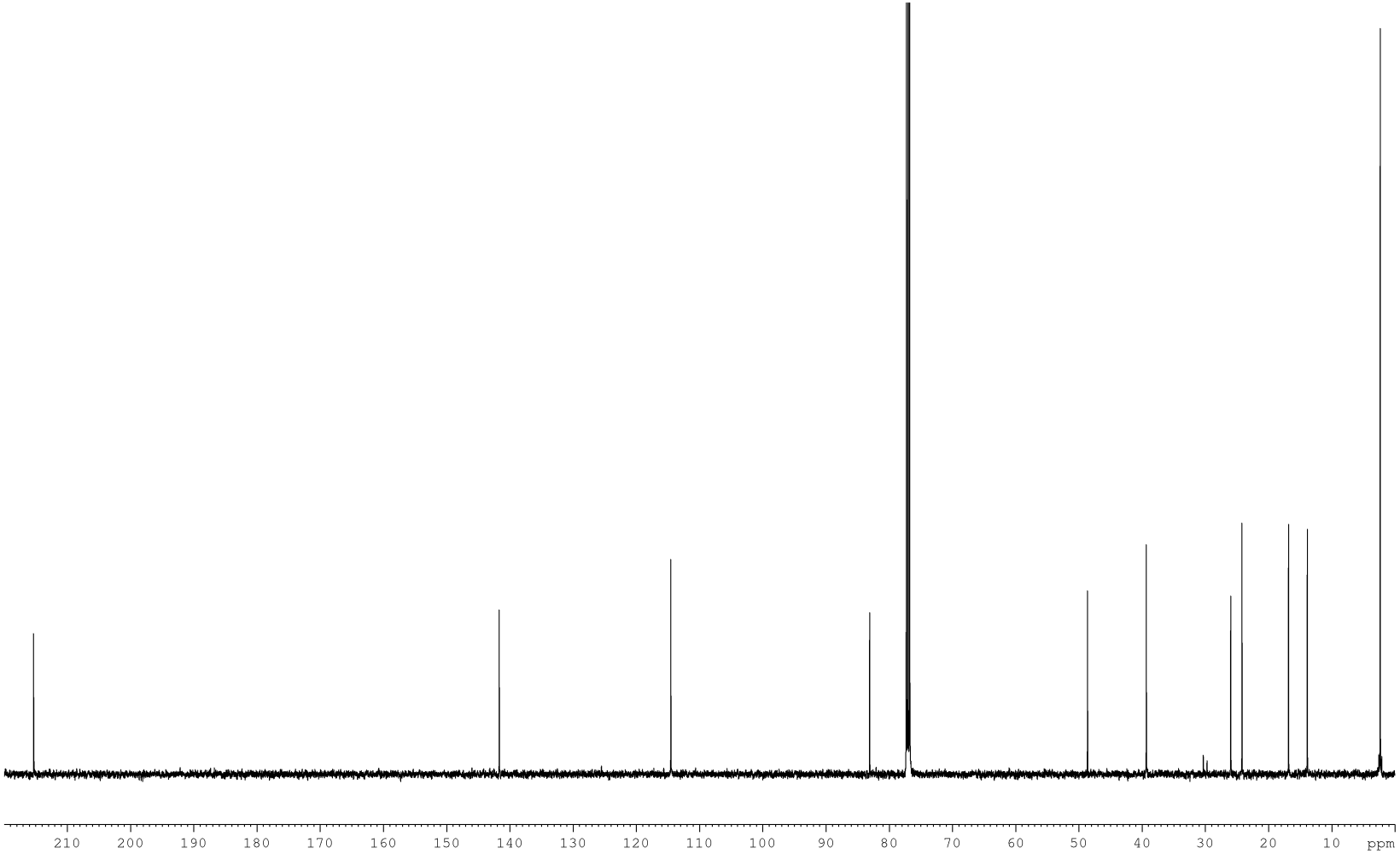
90
80
70
60
50
40
30
20
10
ppm

Propyl ketone 19




O
8
5
4
24
O
TMS
25


210
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180
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120
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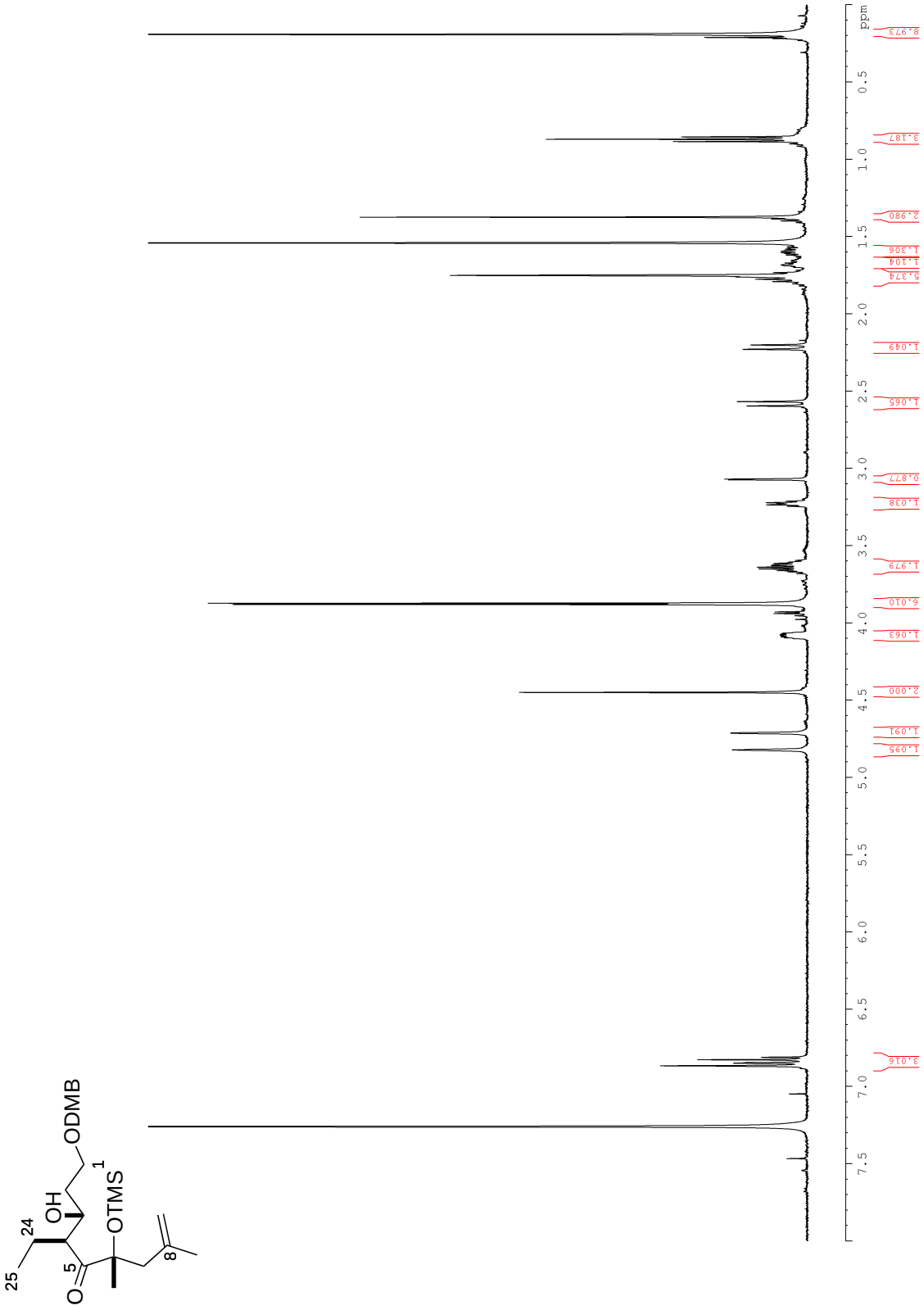
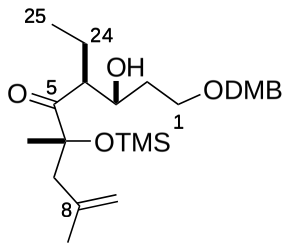
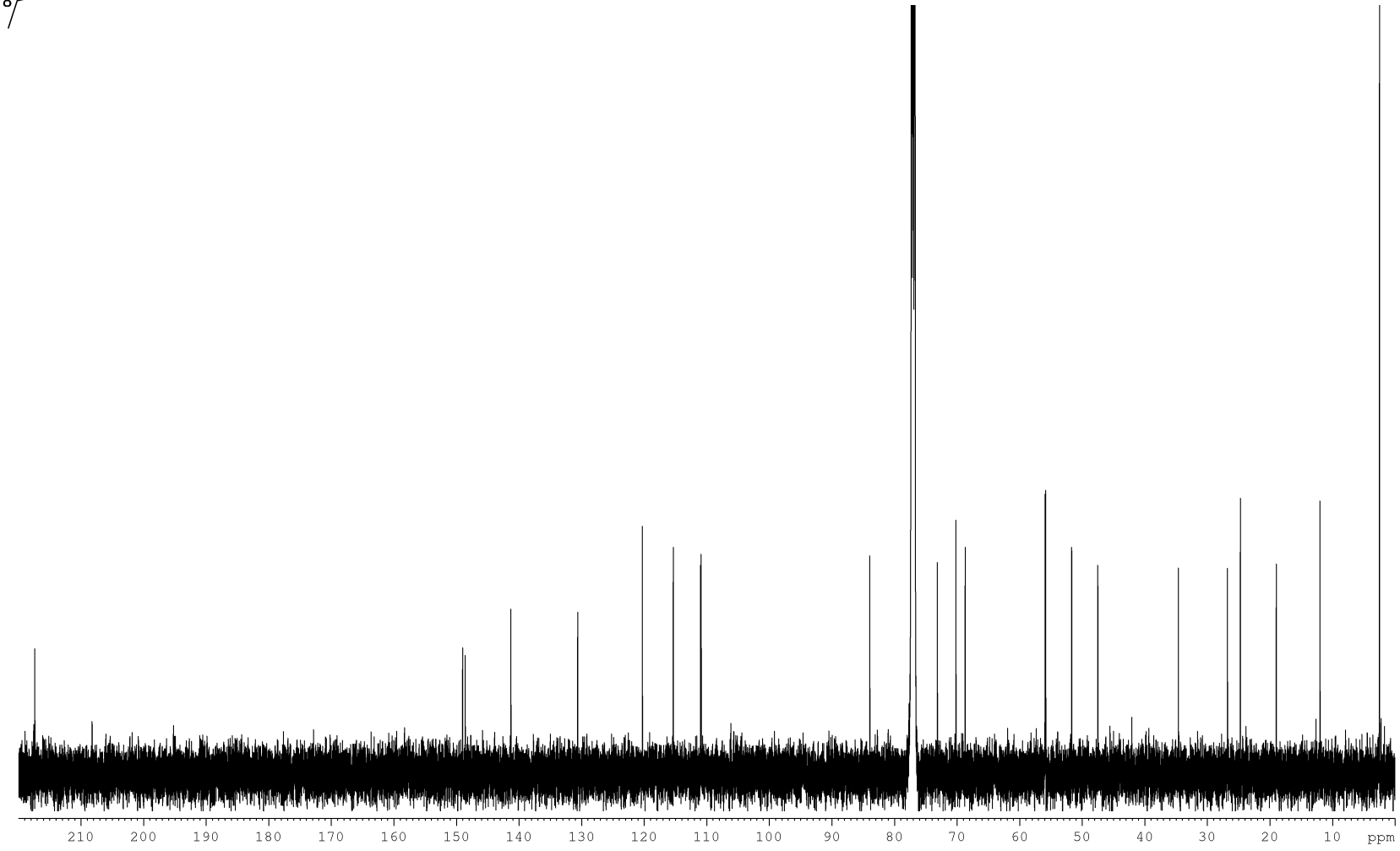
100
90
80
70
60
50
40
30
20
10
ppm

Aldol adduct S5




25
24
OH
O
5
ODMB
1
OTMS
8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180
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120
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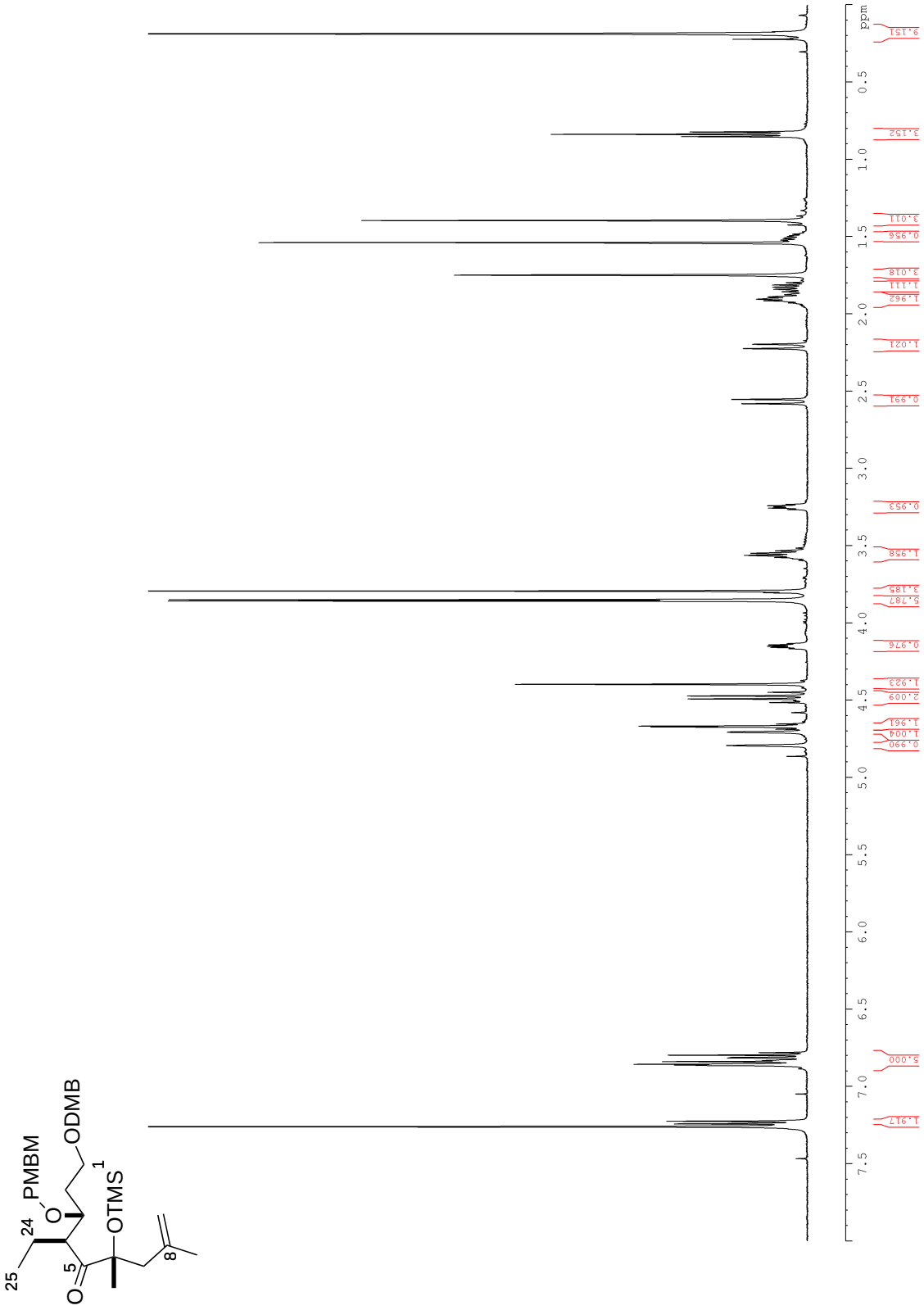
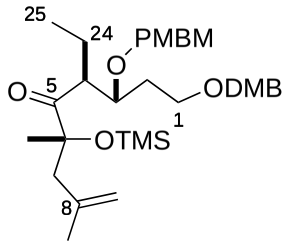
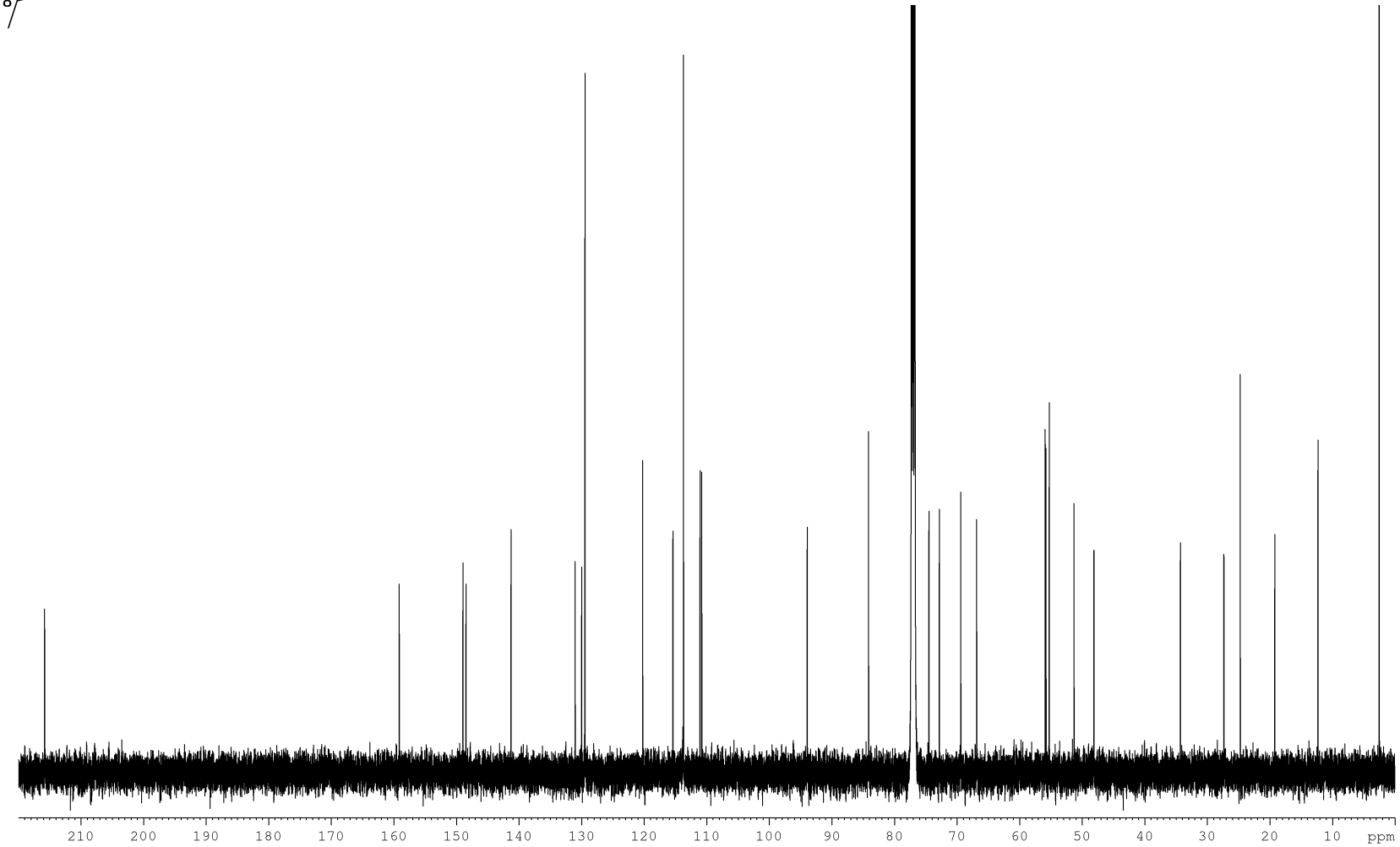
100
90
80
70
60
50
40
30
20
10
ppm

PMBM ether 21




25
24
PMBM
O
5
O
ODMB
1
OTMS
8

63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200
190
180
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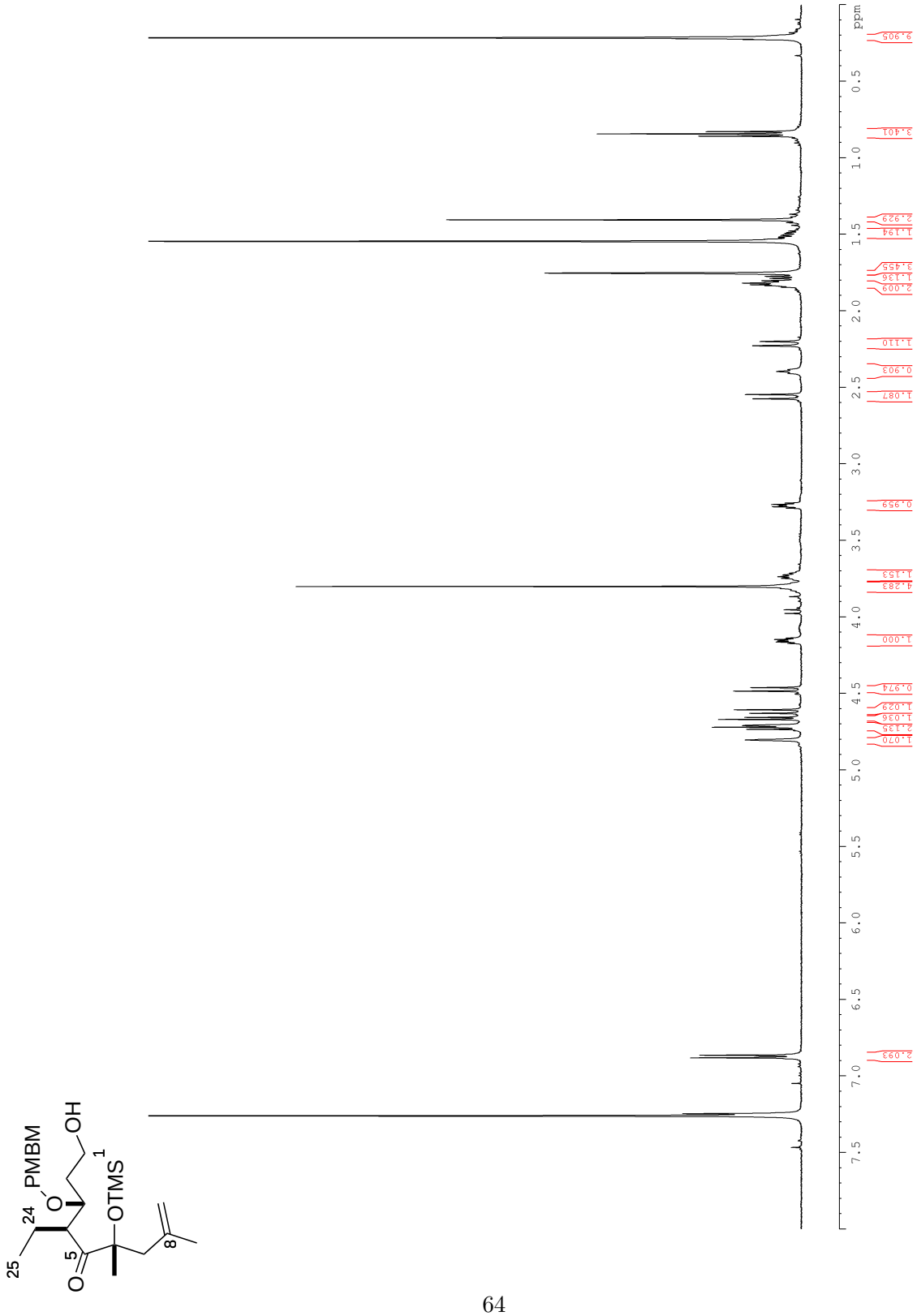
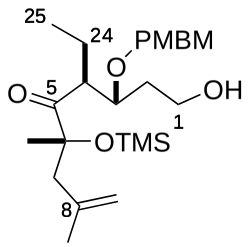
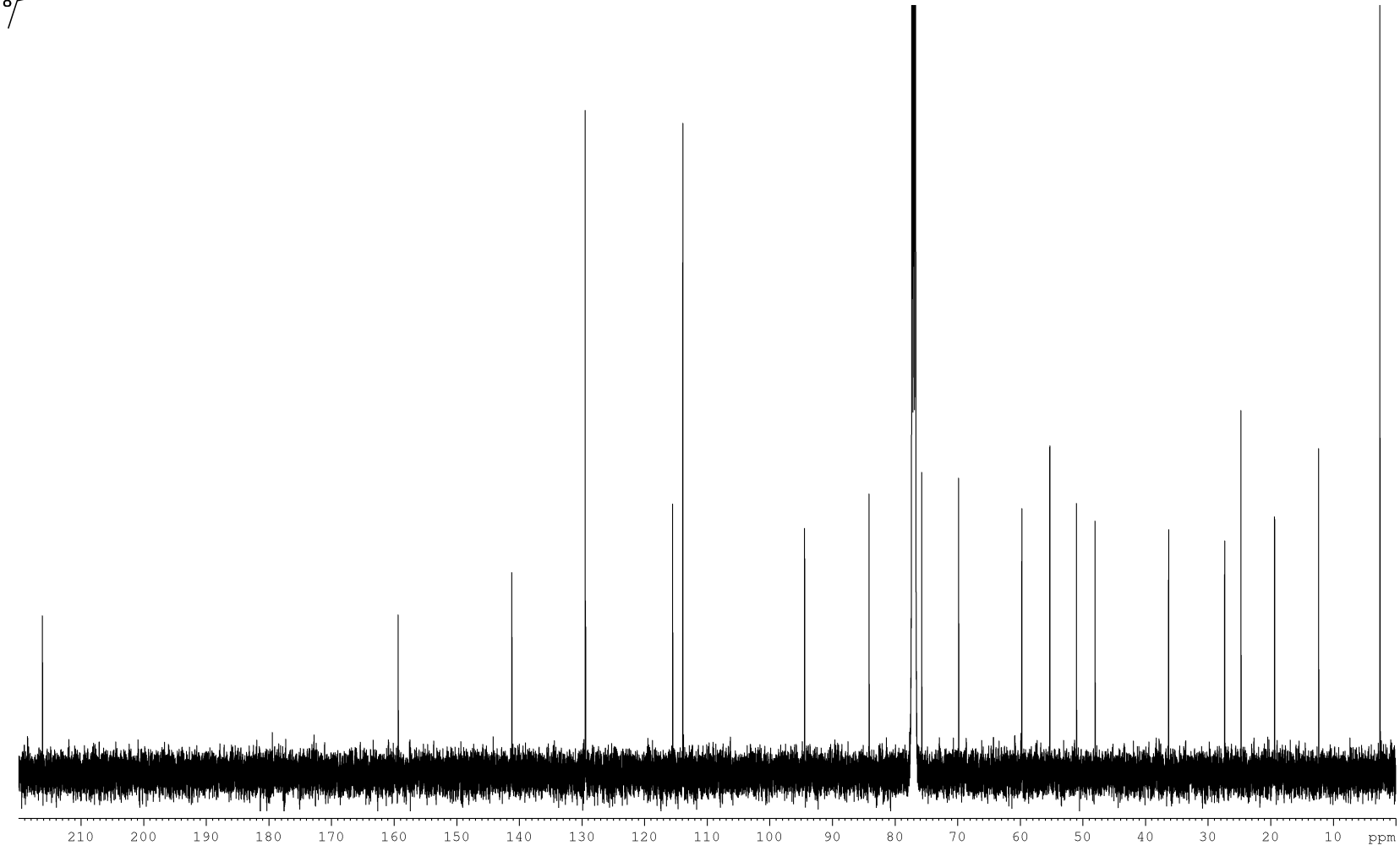
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

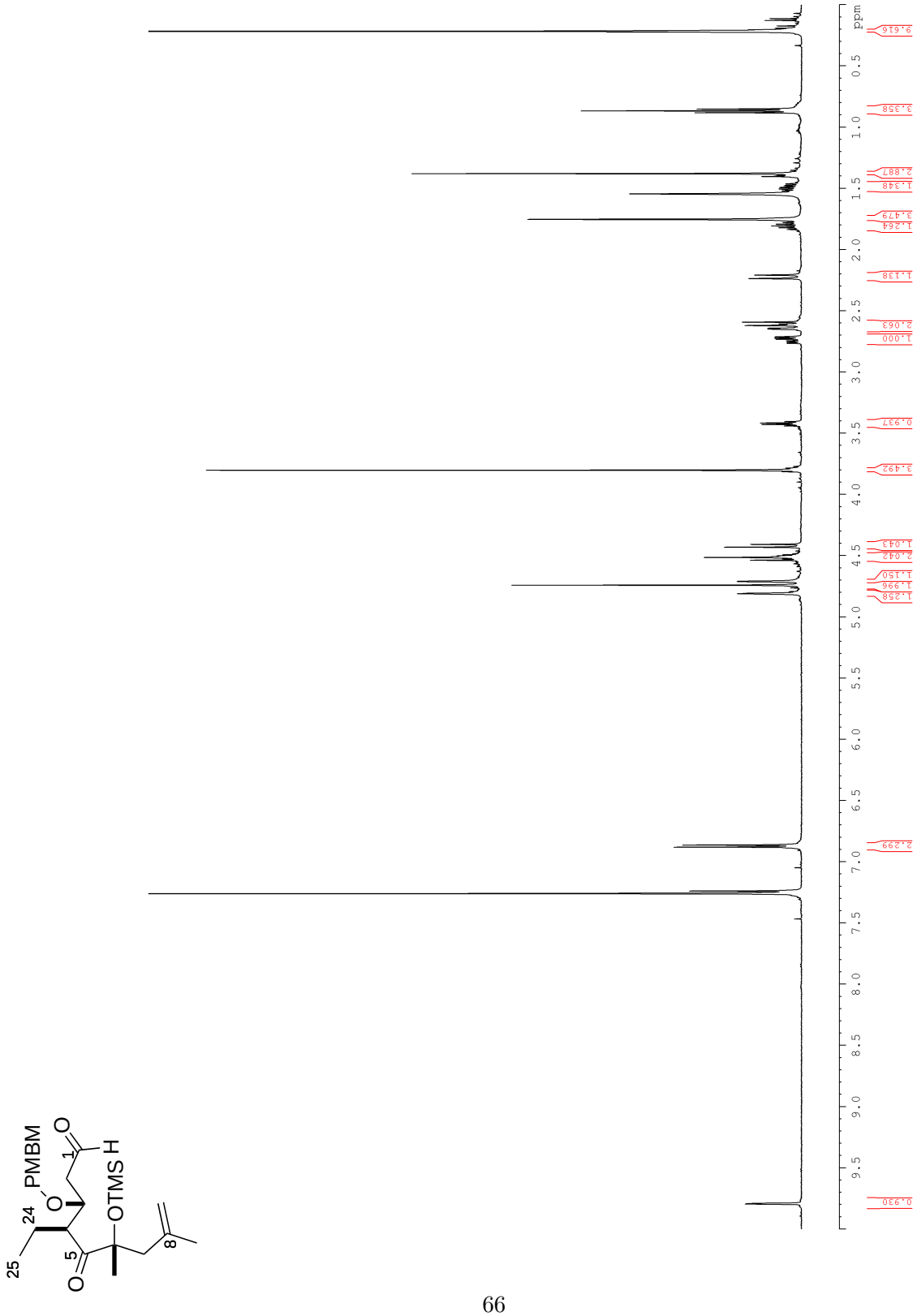
Primary alcohol 22

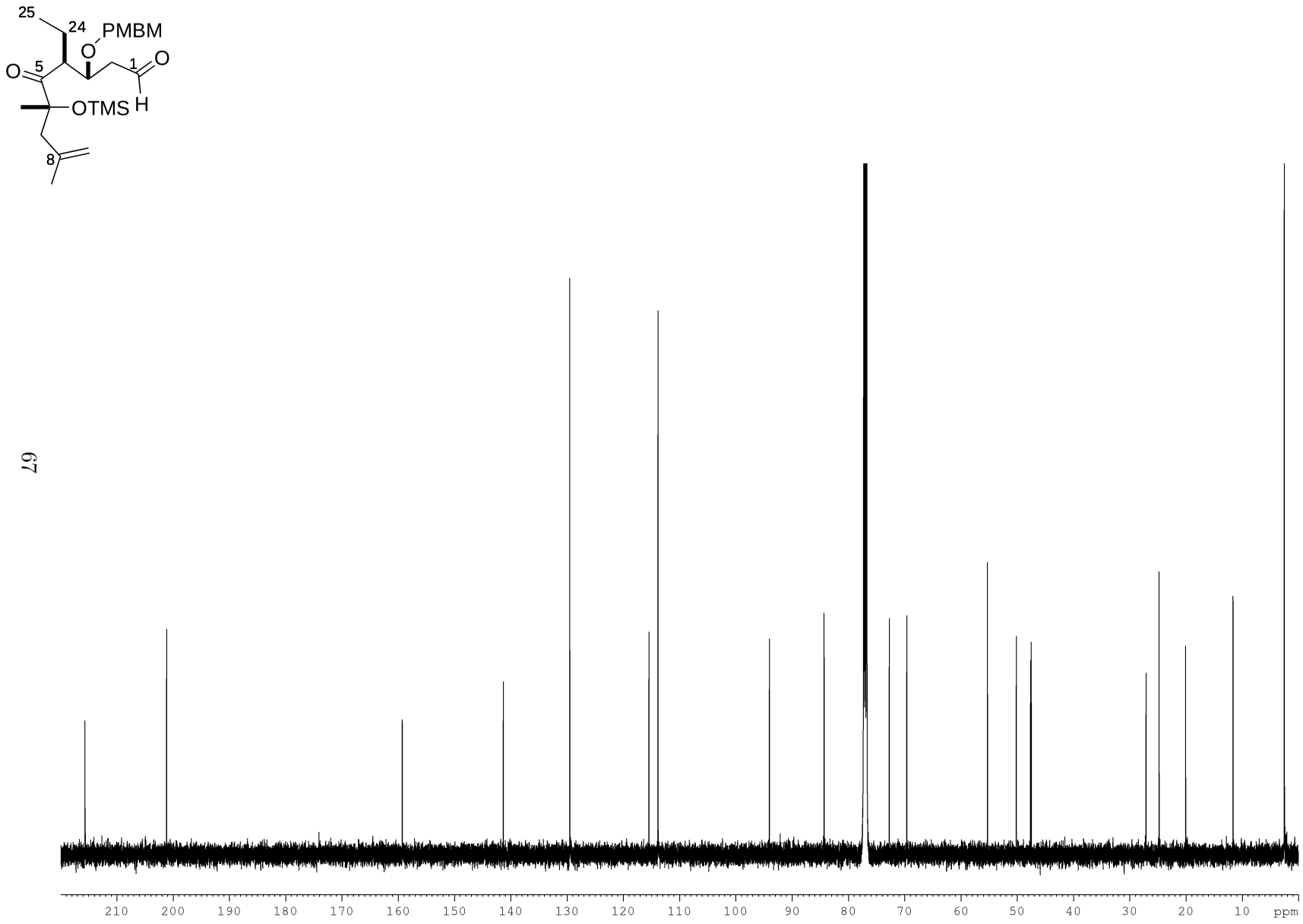



25
24
PMBM
O
O
5
OH
1
OTMS
8

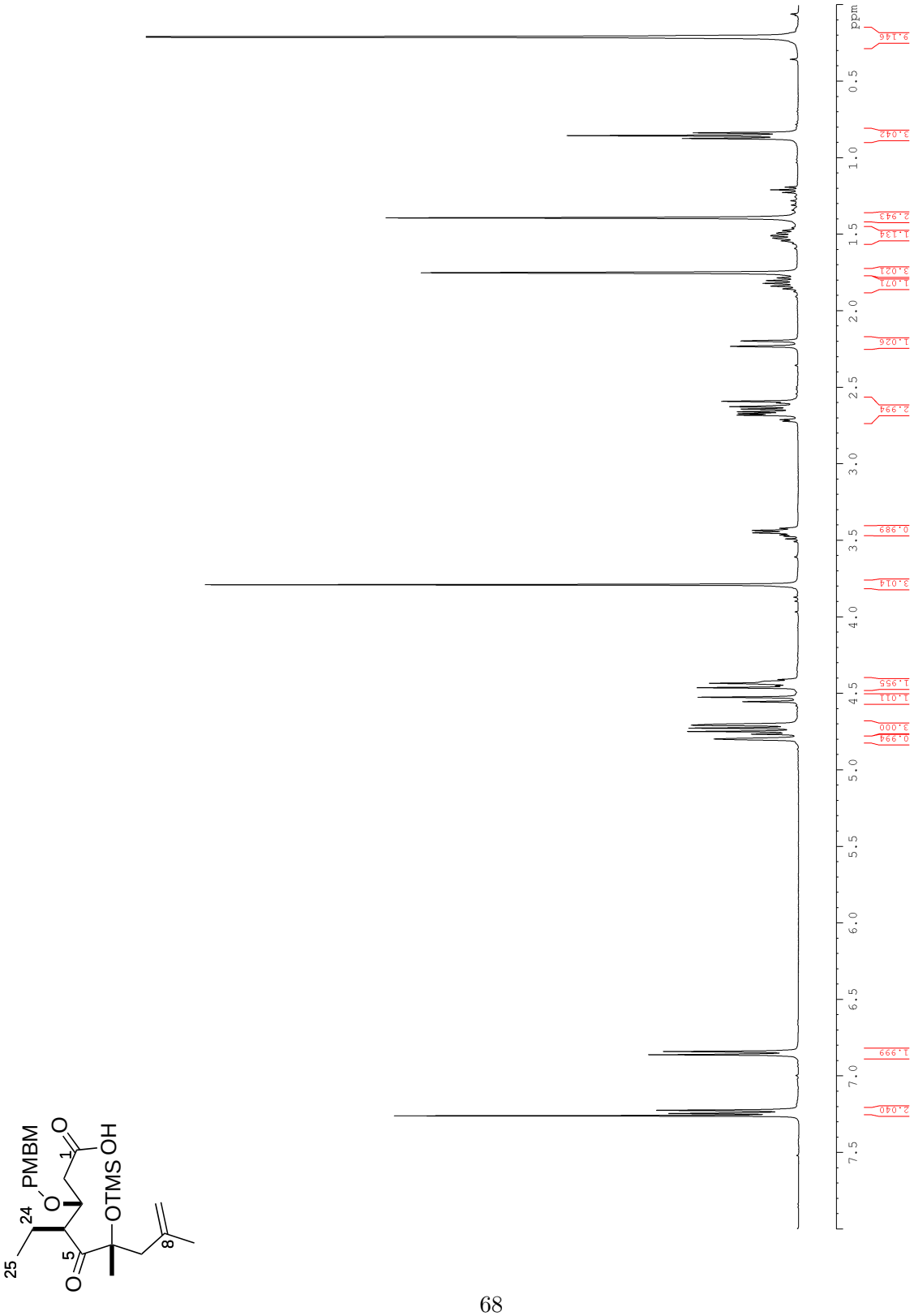

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

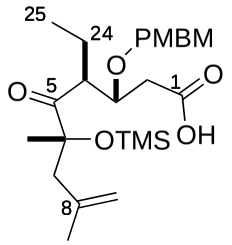
Aldehyde S6


PMBM
OTMS
H
O
1
5
8
24
25
ppm
9.616
3.358
2.887
1.348
3.479
1.264
1.138
2.063
1.000
0.937
3.492
1.043
2.042
1.150
1.996
1.258
2.299
0.930

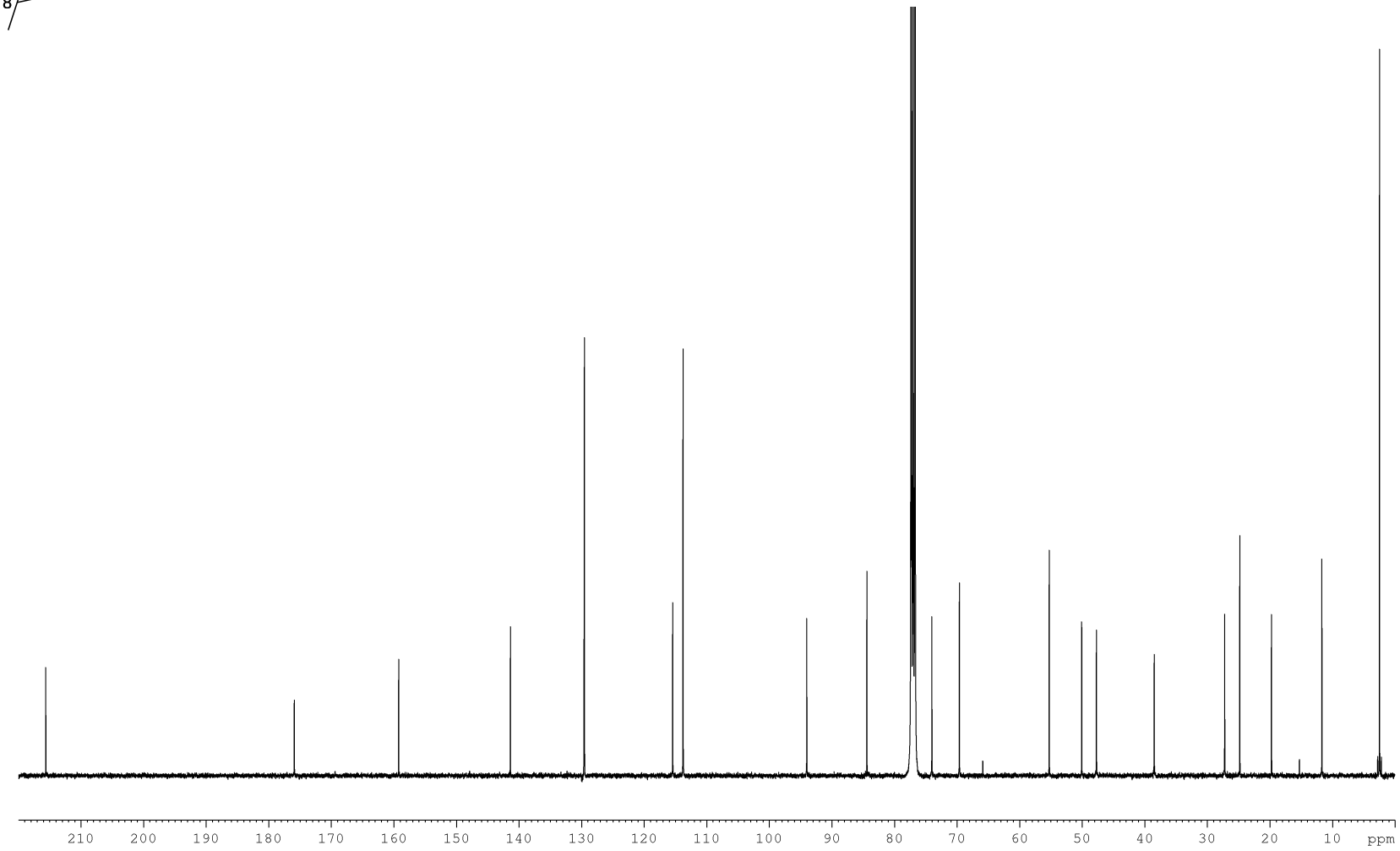

25
24
PMBM
O
O
5
1
O
OTMS
H
8
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

Macrocycle precursor fragment 6

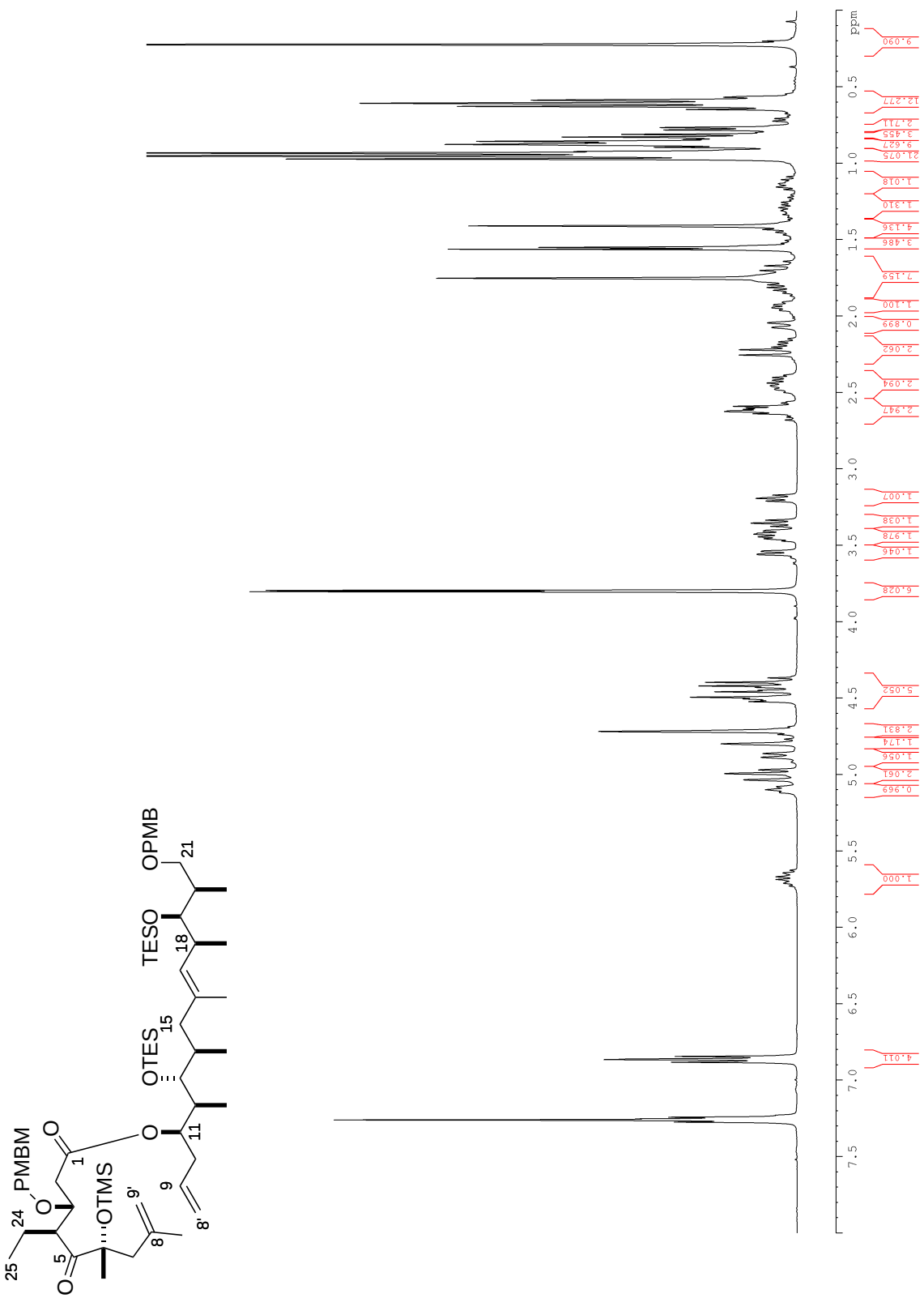


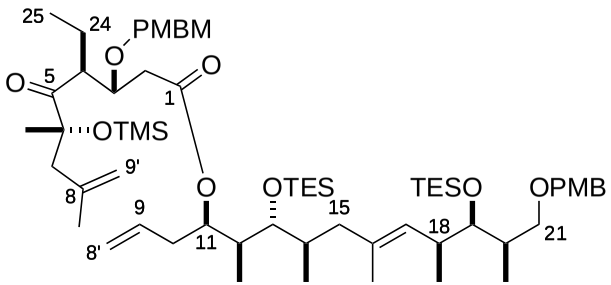

25
24
PMBM
O
O
5
1
O
OTMS
OH
8

69

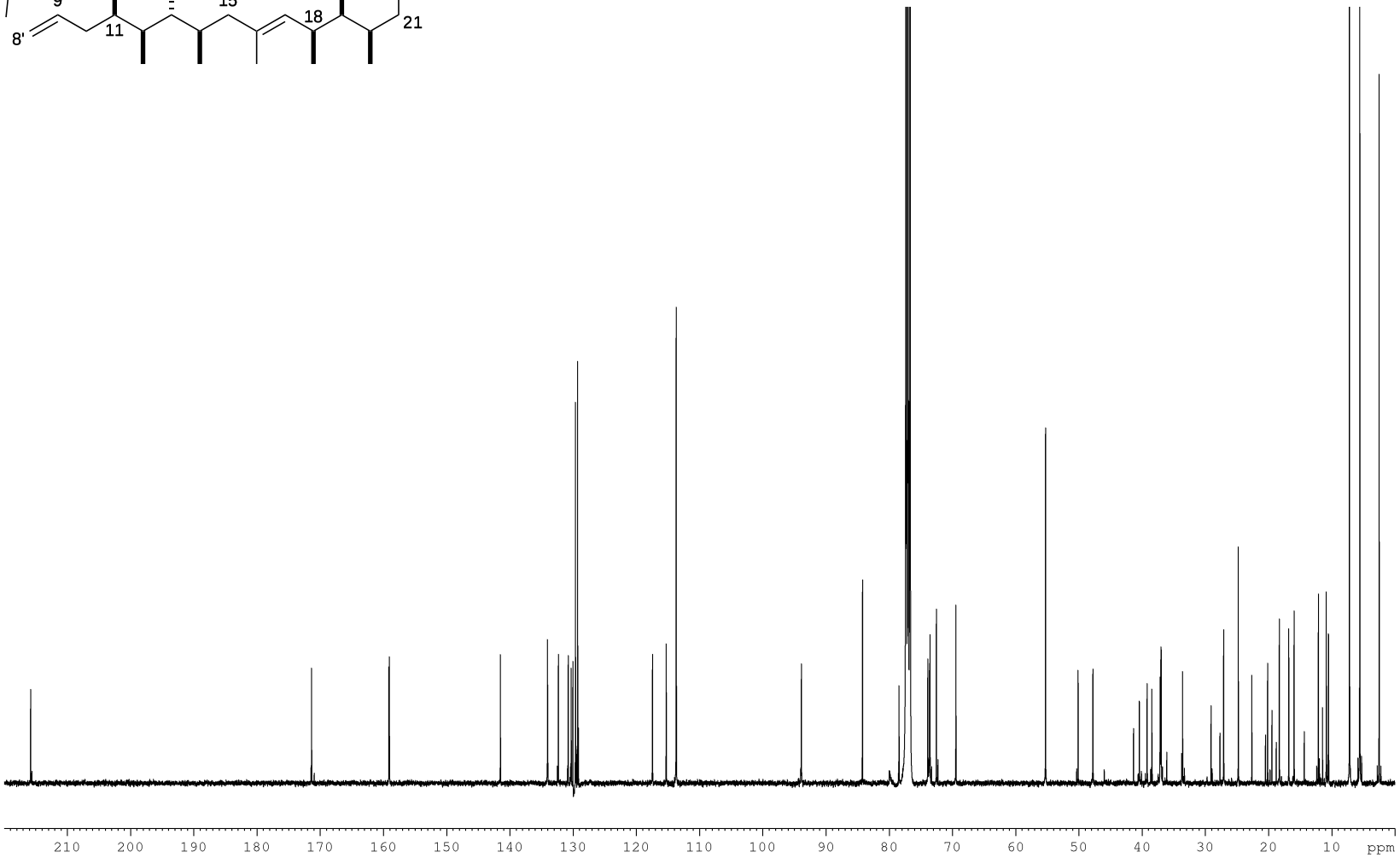

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

Ester S7

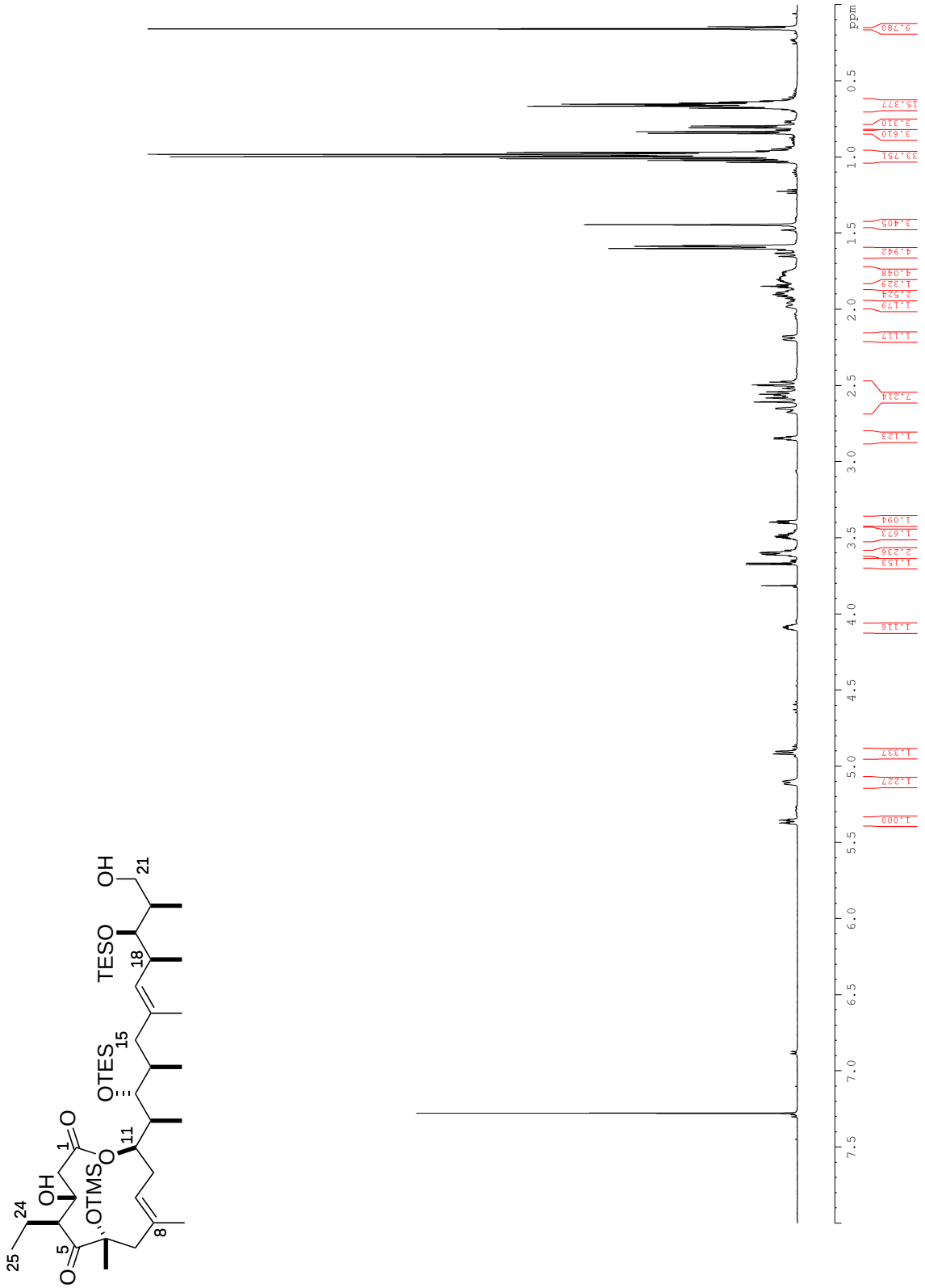


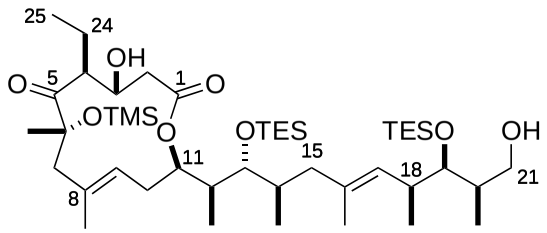

25
24
PMBM
O
O
5
O
1
OTMS
9'
8
O
OTES
15
TESO
OPMB
9
18
21
11
8'

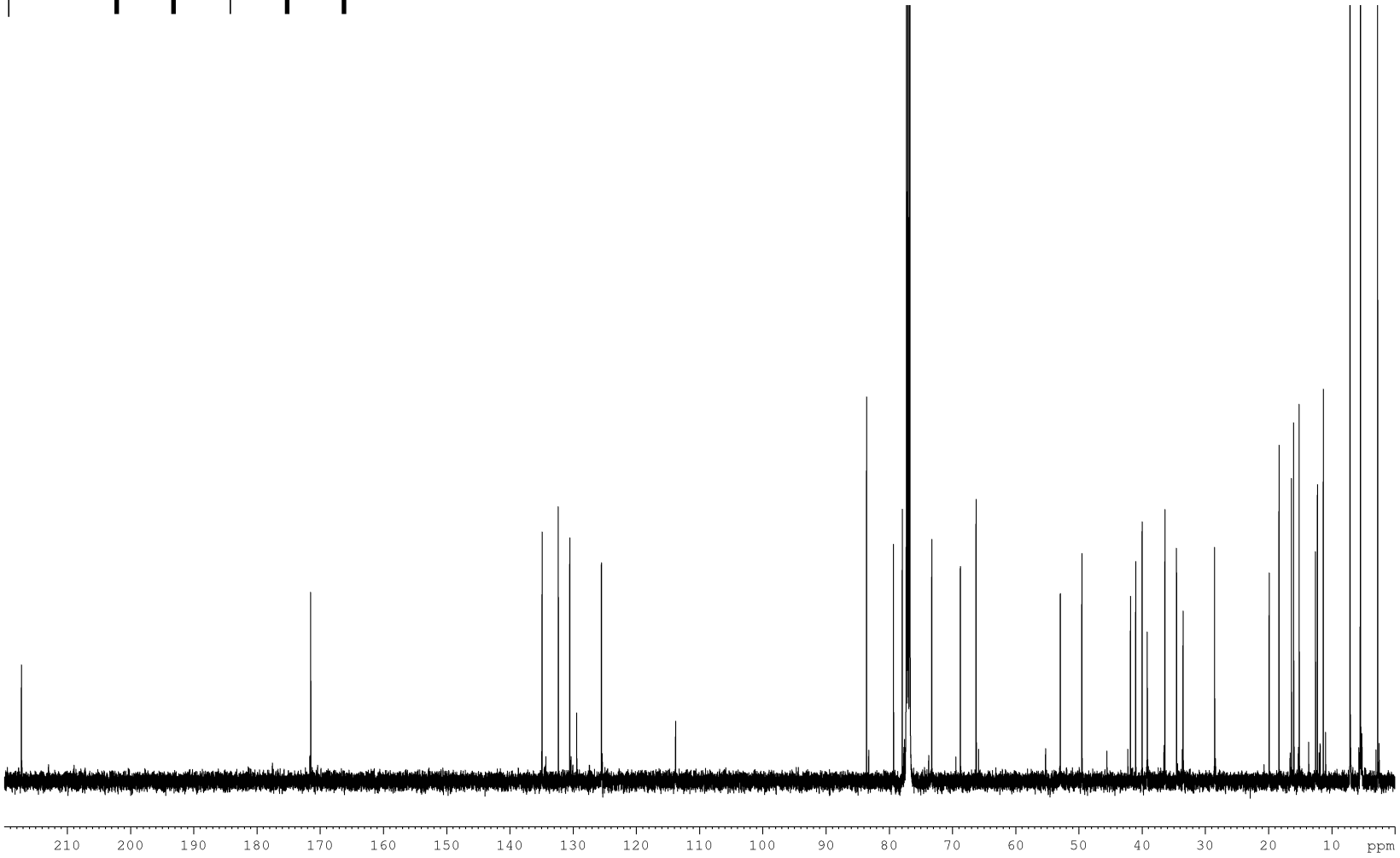
71


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

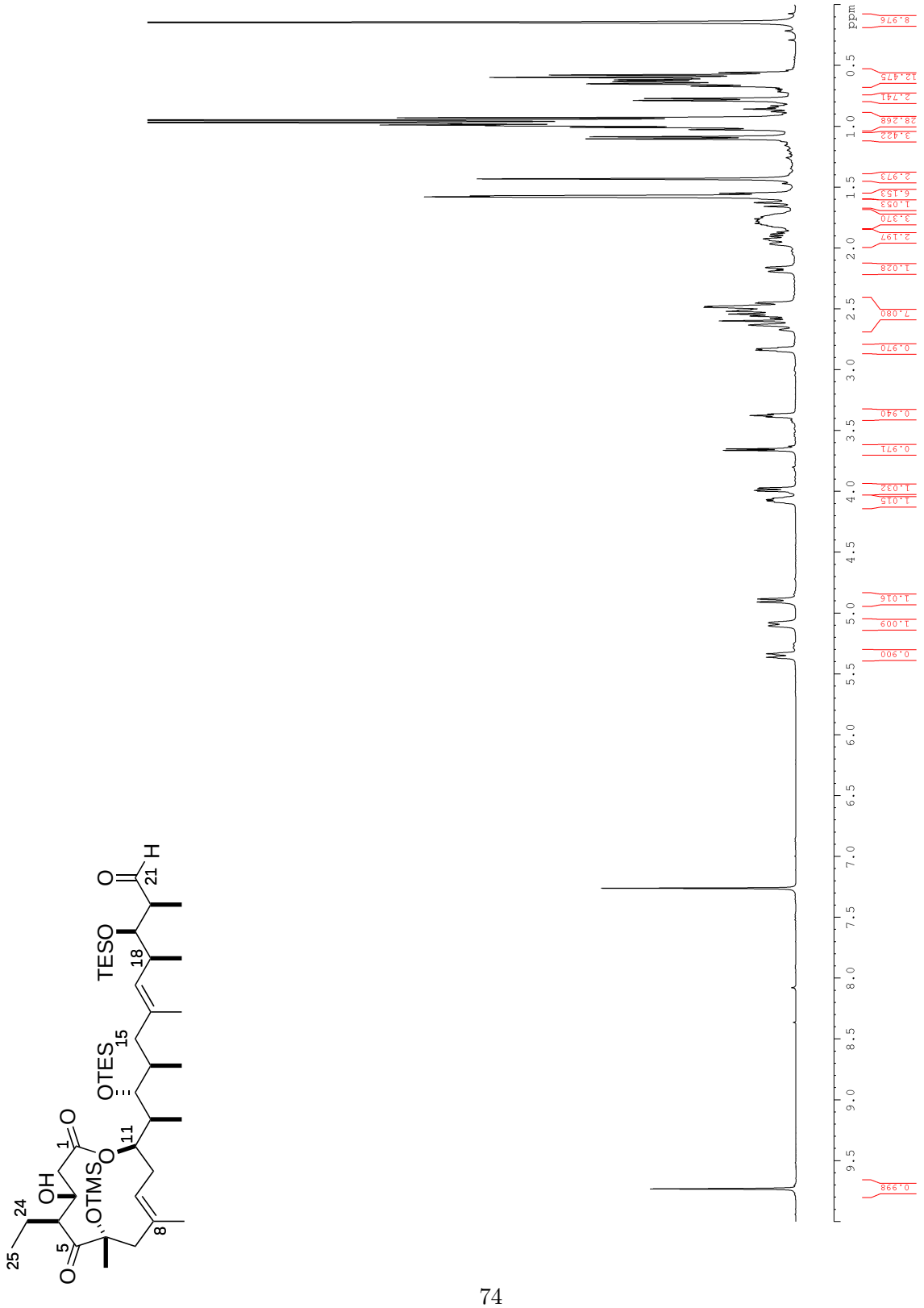
Diol 23

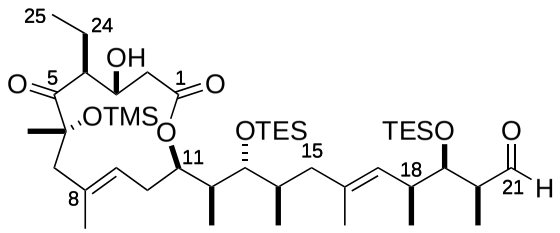

OH
TESO
OTES
OTMS
O
O
O
OH
1
5
8
11
15
18
21
24
25
ppm
9.780
15.377
3.610
3.310
33.751
3.405
4.942
4.048
1.329
2.524
1.179
1.117
7.214
1.123
1.094
1.673
2.236
1.153
1.116
1.337
1.227
1.000

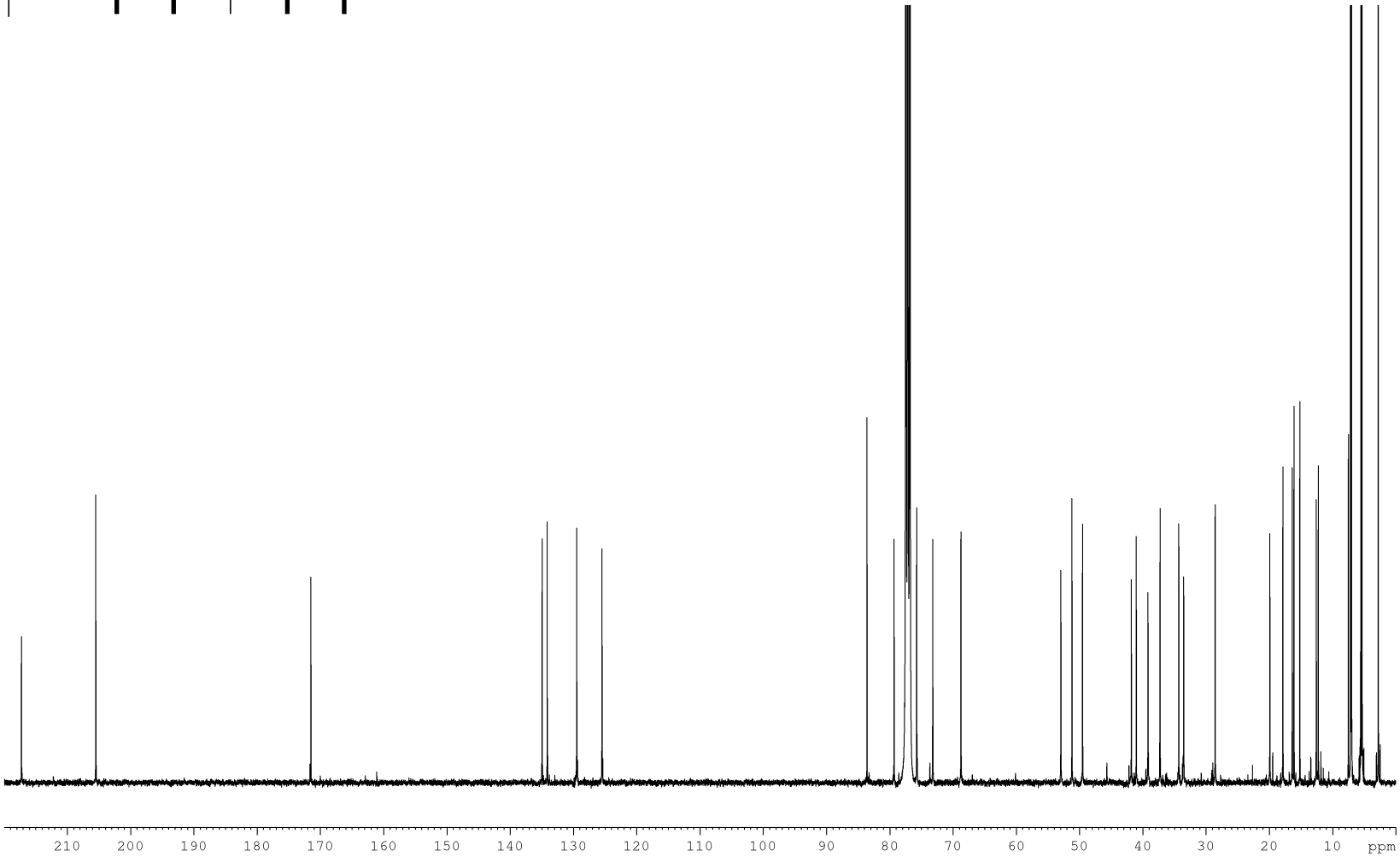

25
24
OH
O
5
1
O
OTMS
O
11
OTES
15
TESO
OH
18
21
8


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

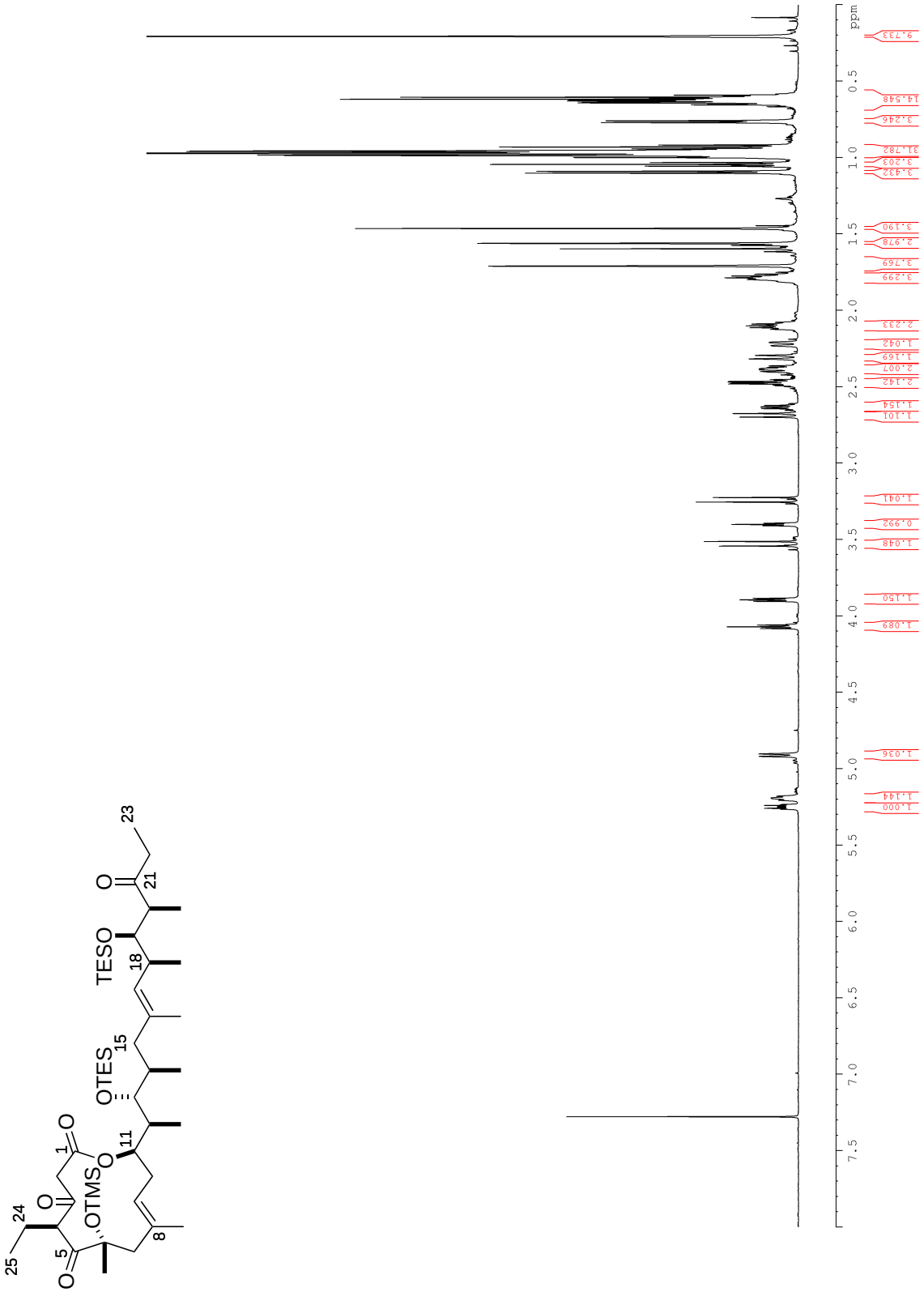
Aldehyde 24

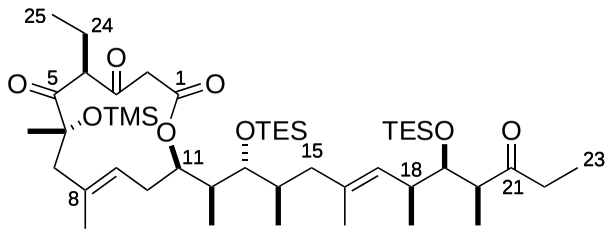

O
H
21
TESO
18
OTES
15
11
O
OTMS
OH
24
25
O
5
O
1
8
ppm
8.976
12.475
2.741
28.268
3.422
2.973
6.153
1.053
3.370
2.197
1.028
7.080
0.970
0.940
0.971
1.032
1.015
1.016
1.009
0.900
0.998


25
24
OH
O
5
1
O
OTMS
O
11
OTES
15
TESO
18
O
21
H
8

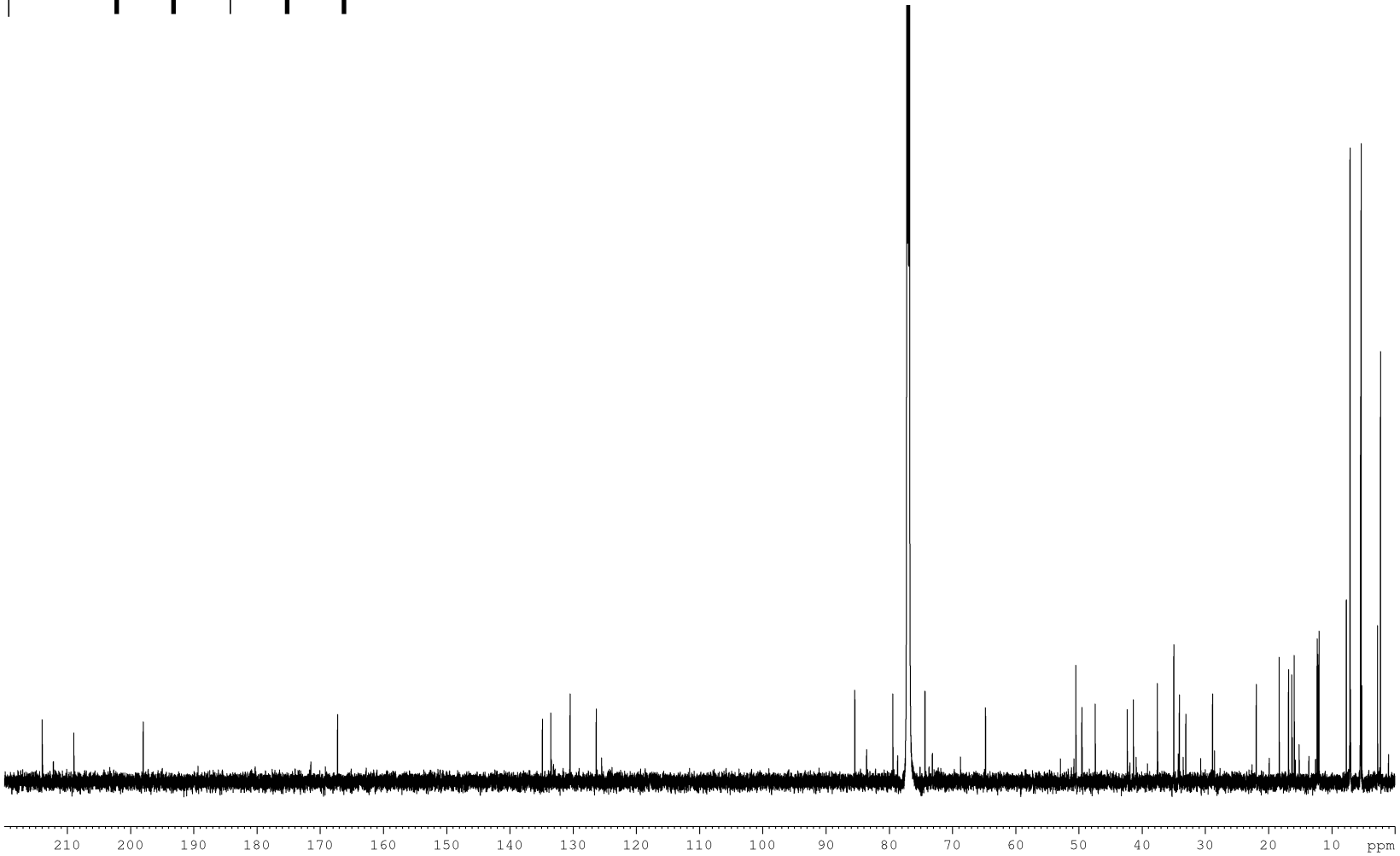

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

Triketone 25

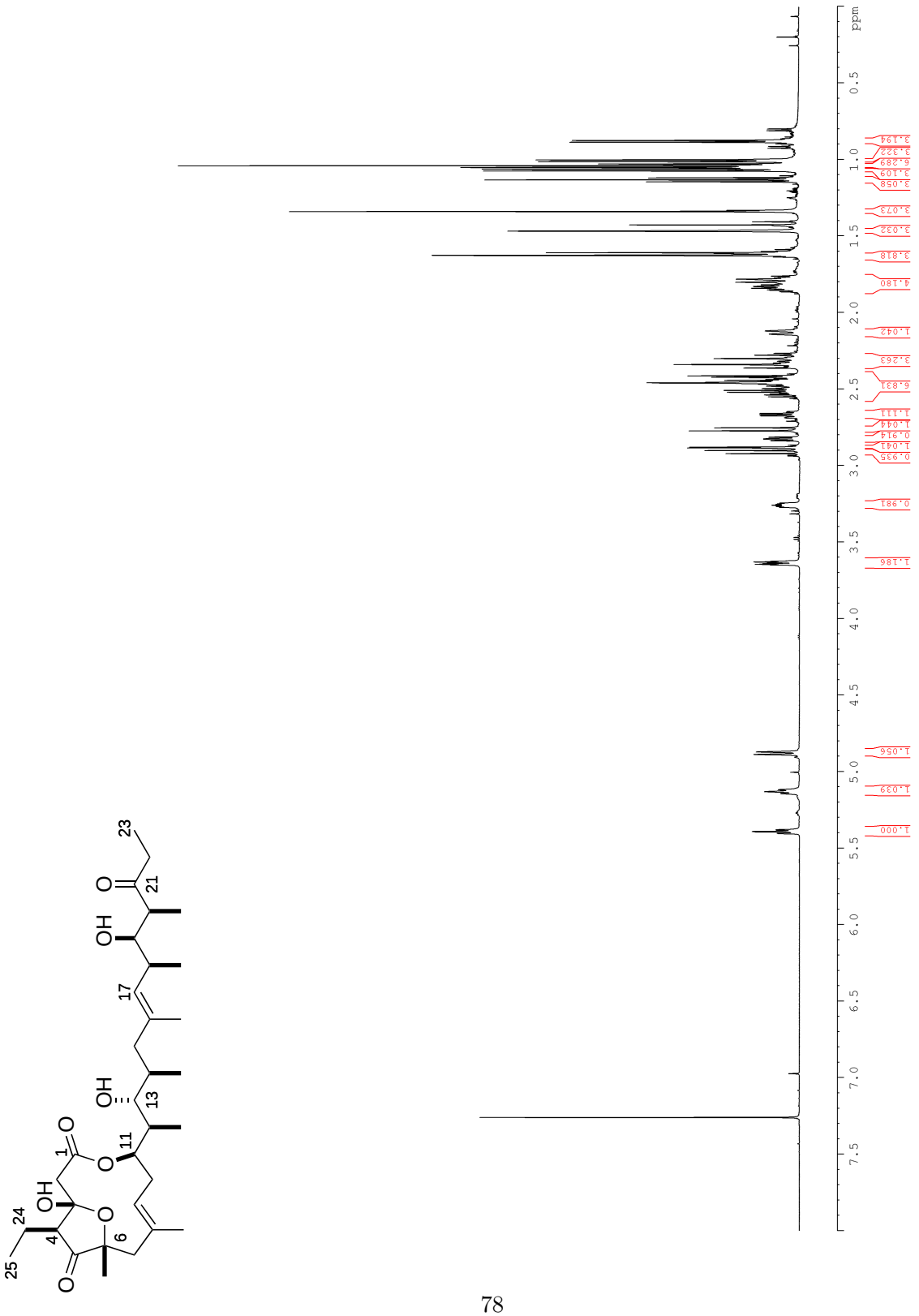


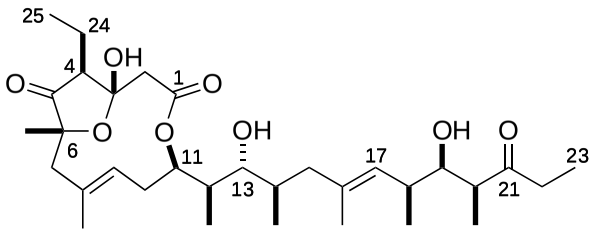

25
24
O
5
1
O
O
OTMS
O
11
OTES
15
TESO
18
O
21
23
8

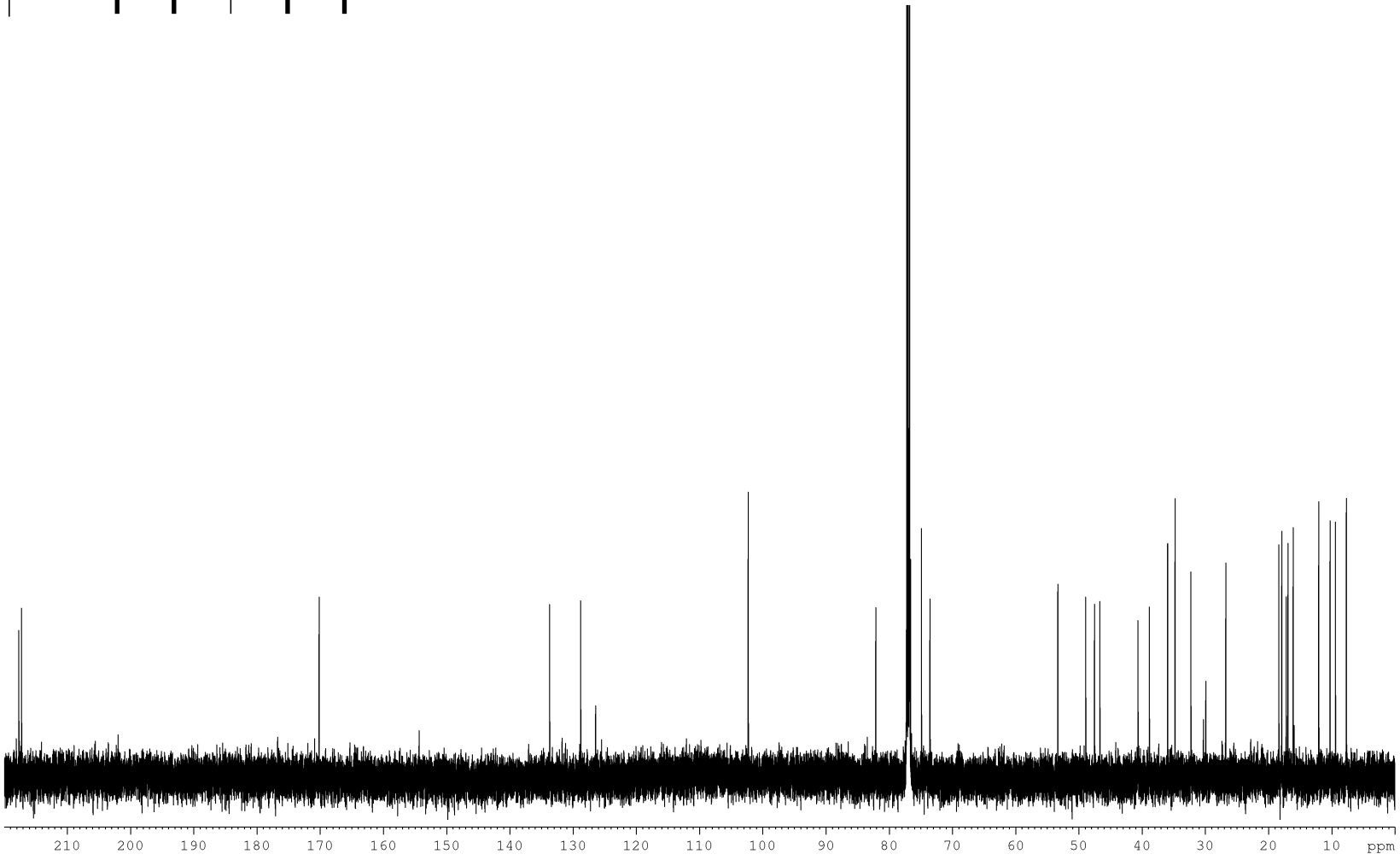
77


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

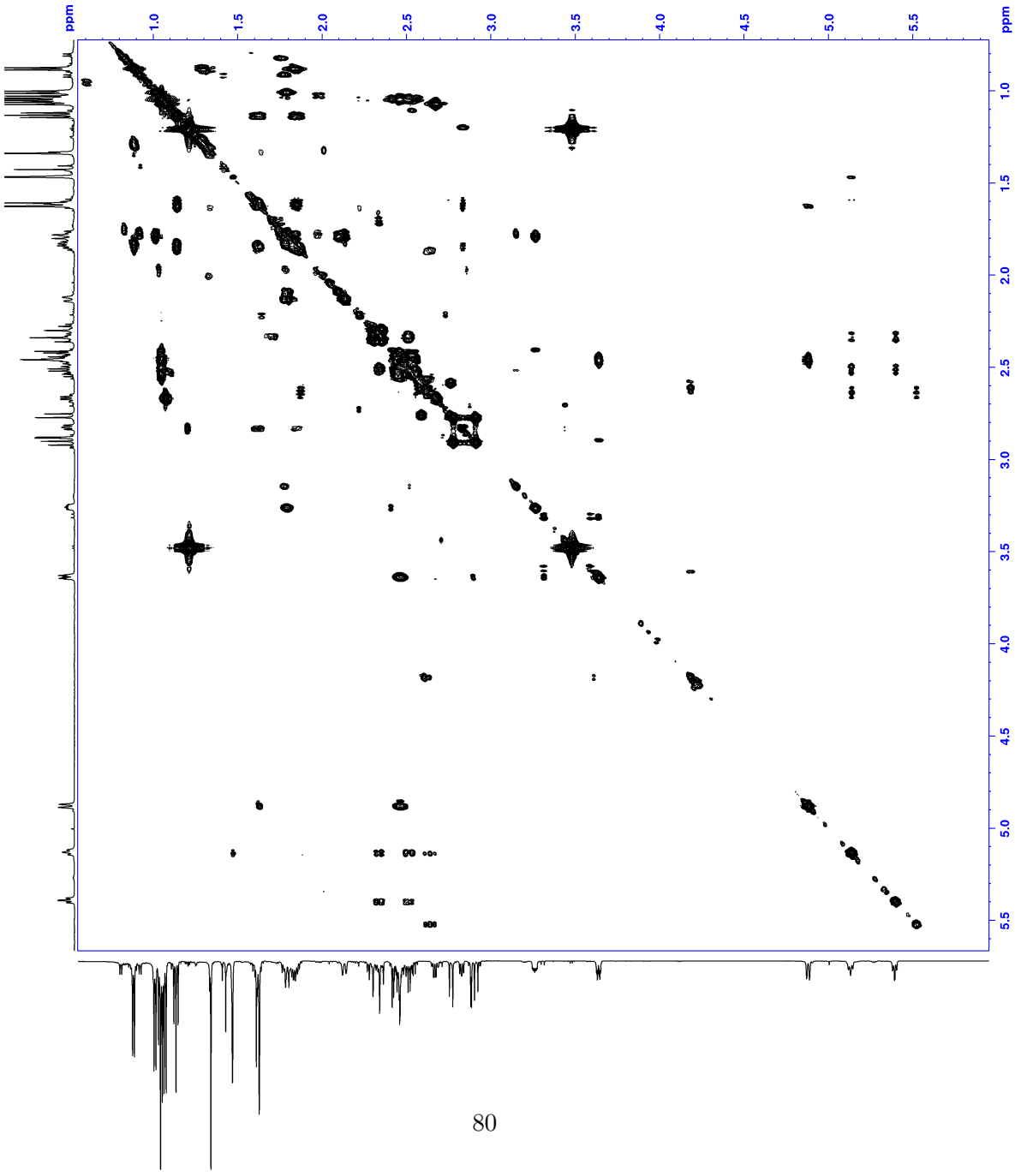
Actinoallolide A (1)



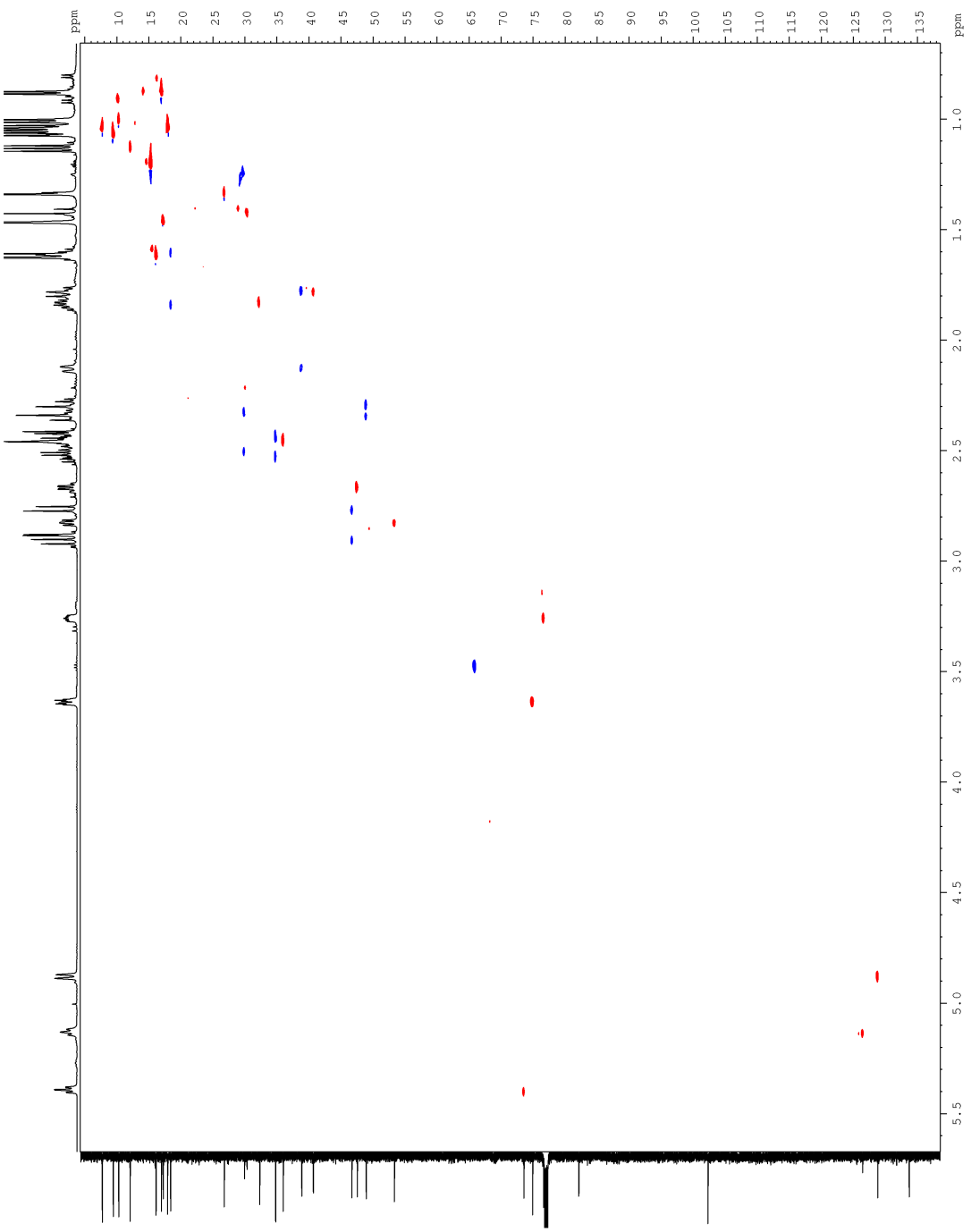

25
24
OH
4
1
O
O
O
O
6
O
11
OH
13
17
OH
O
21
23


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

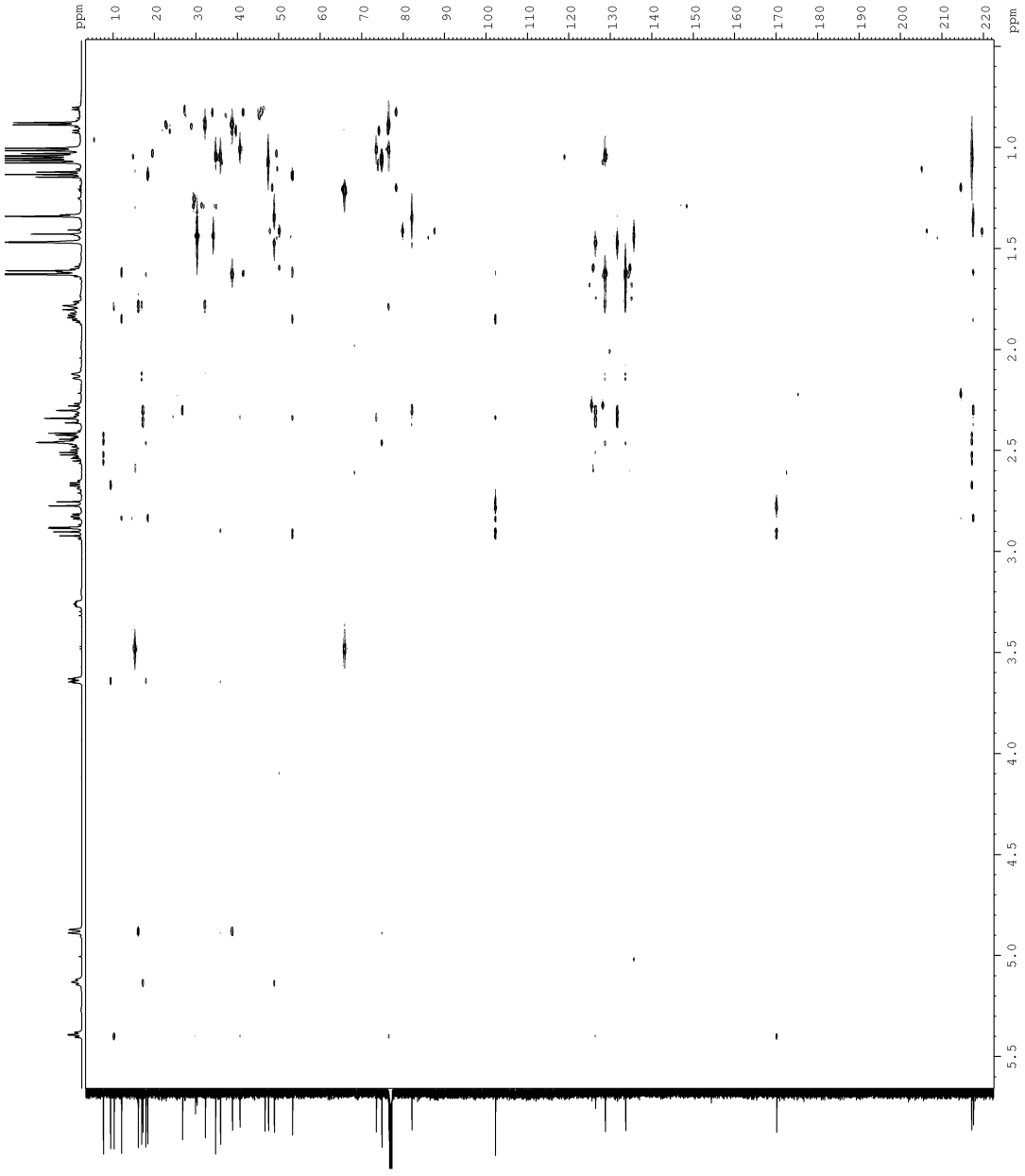
COSY



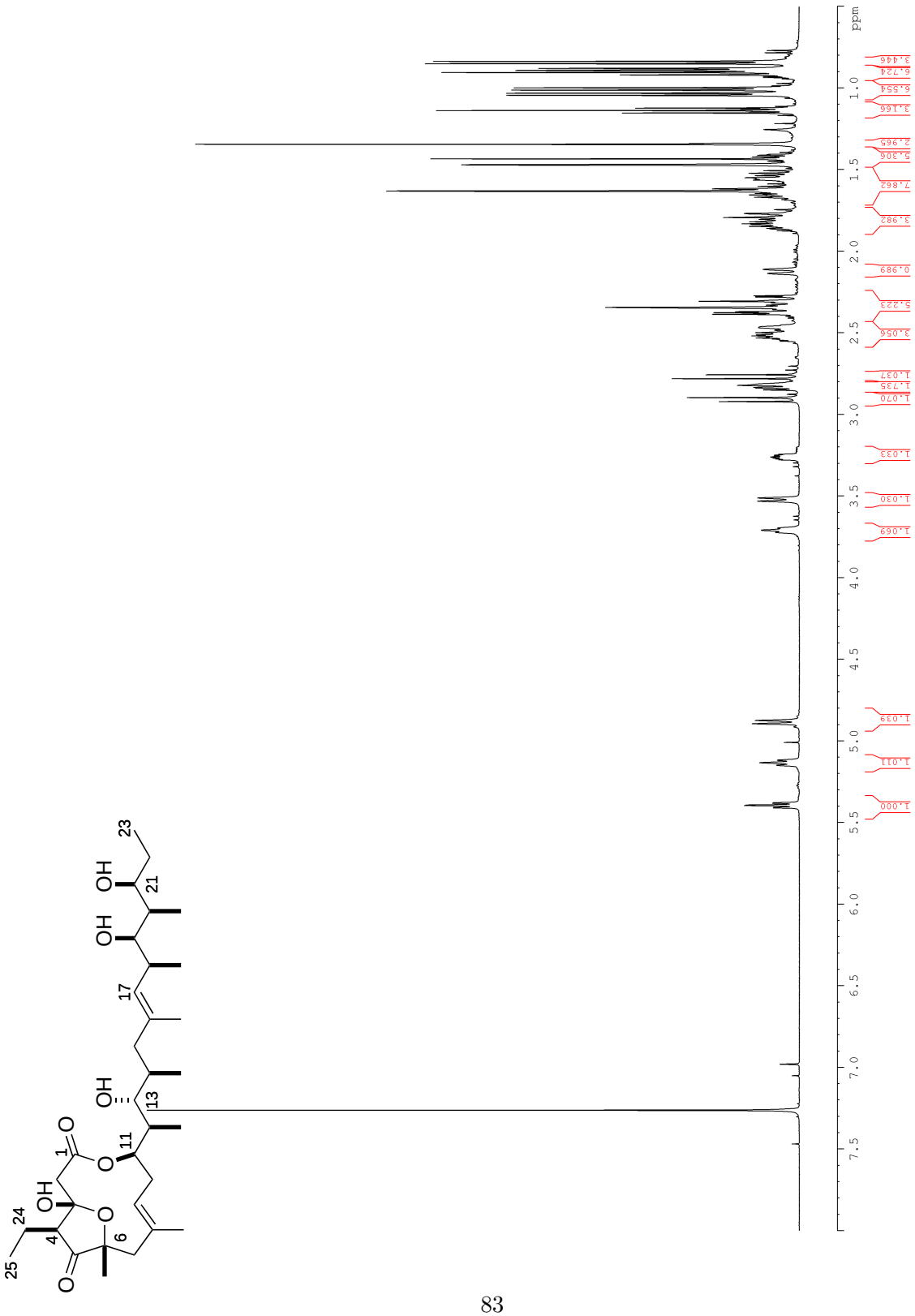
HSQC

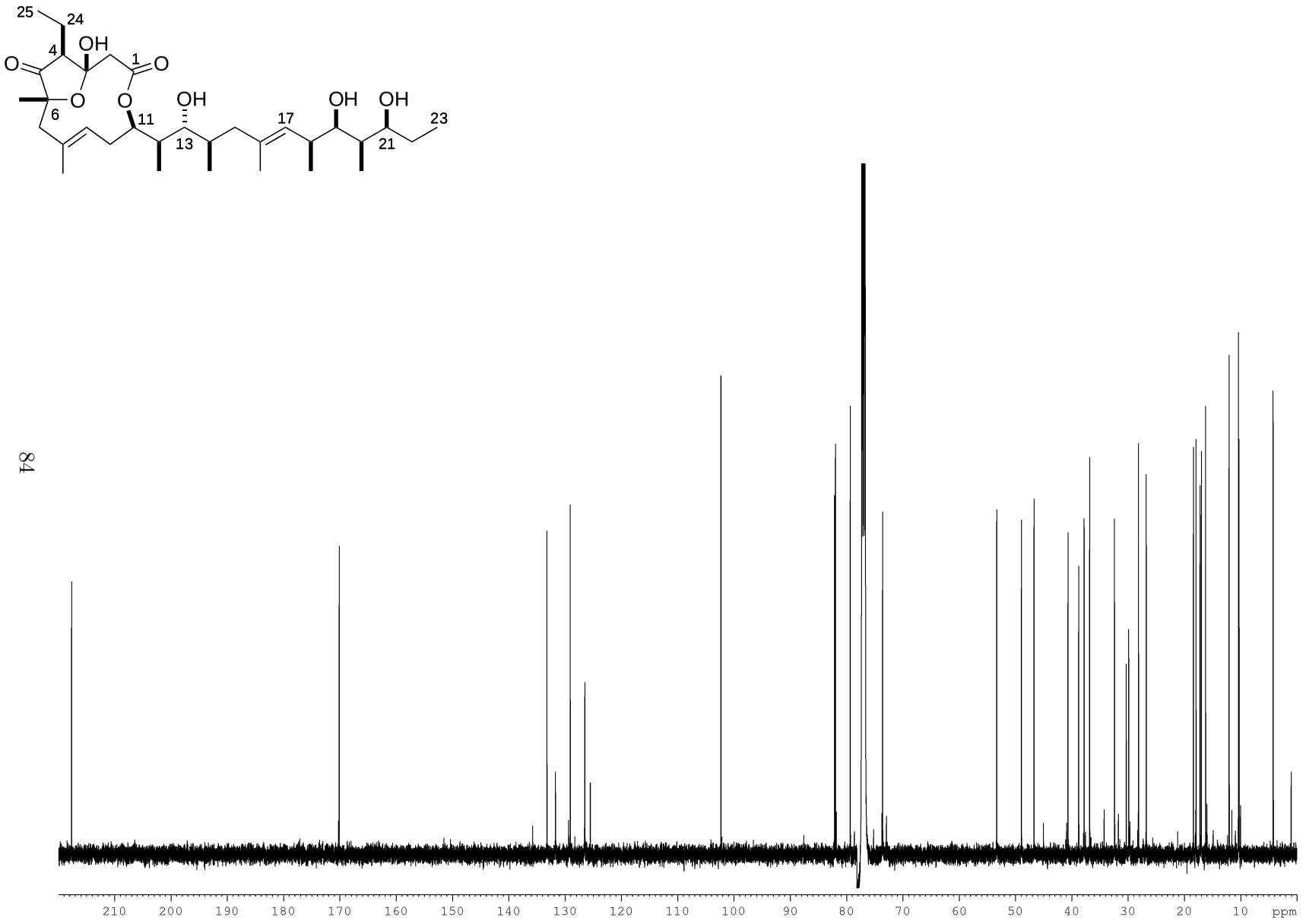

ppm
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5

HMBC

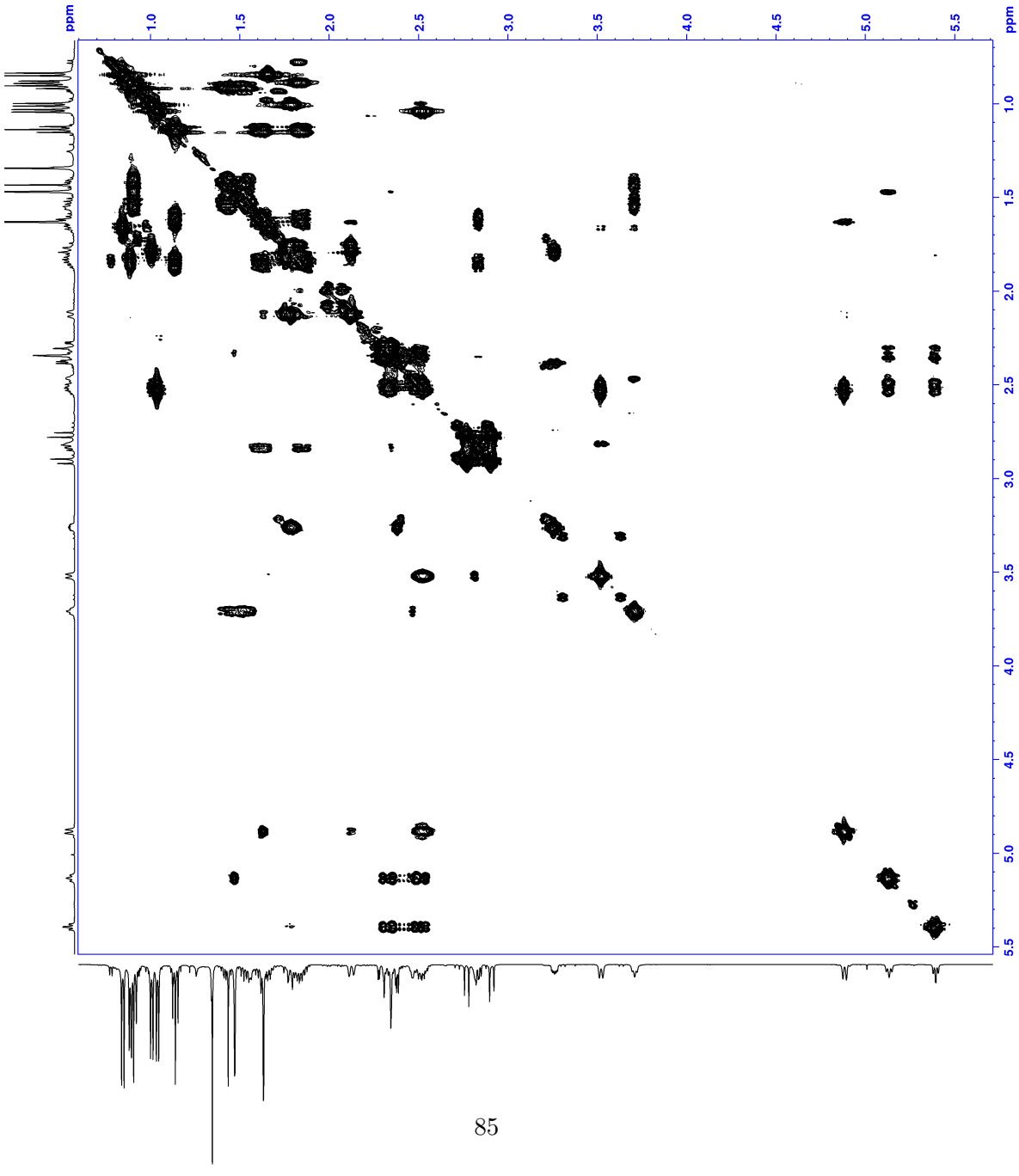

ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5

Actinoallolide B (2)

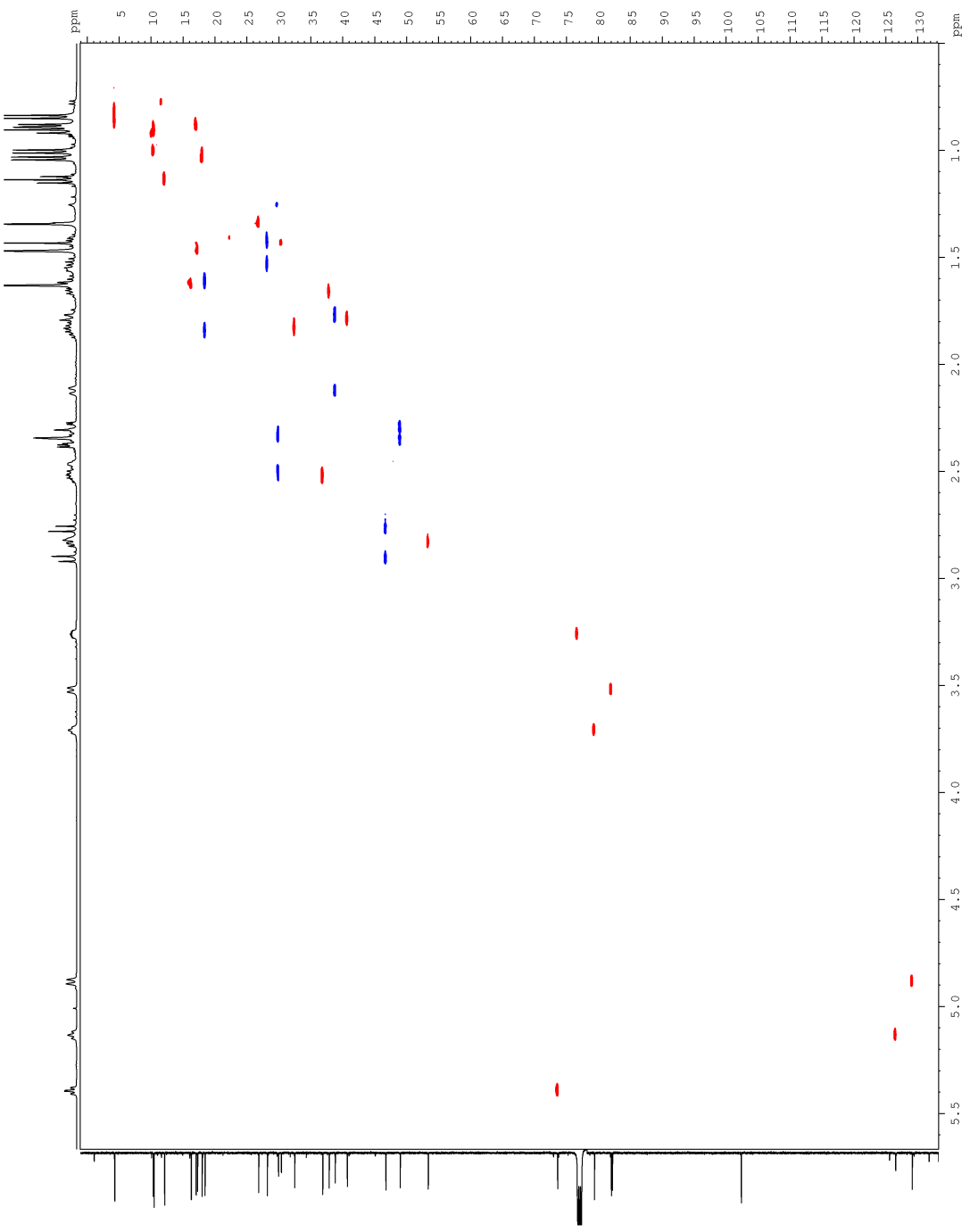



25
24
OH
4
1
O
O
O
O
6
11
OH
13
17
OH
OH
21
23
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

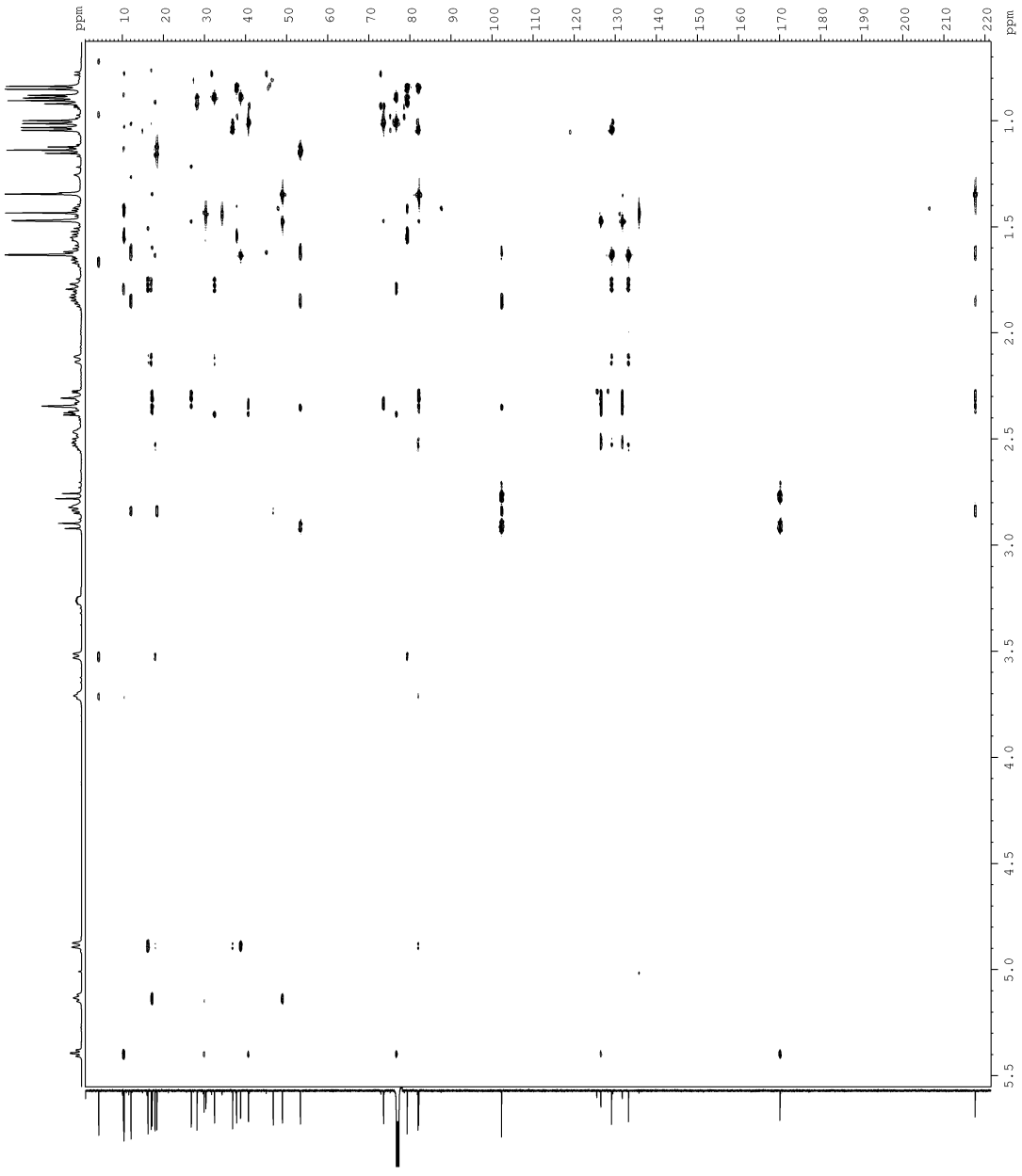
COSY



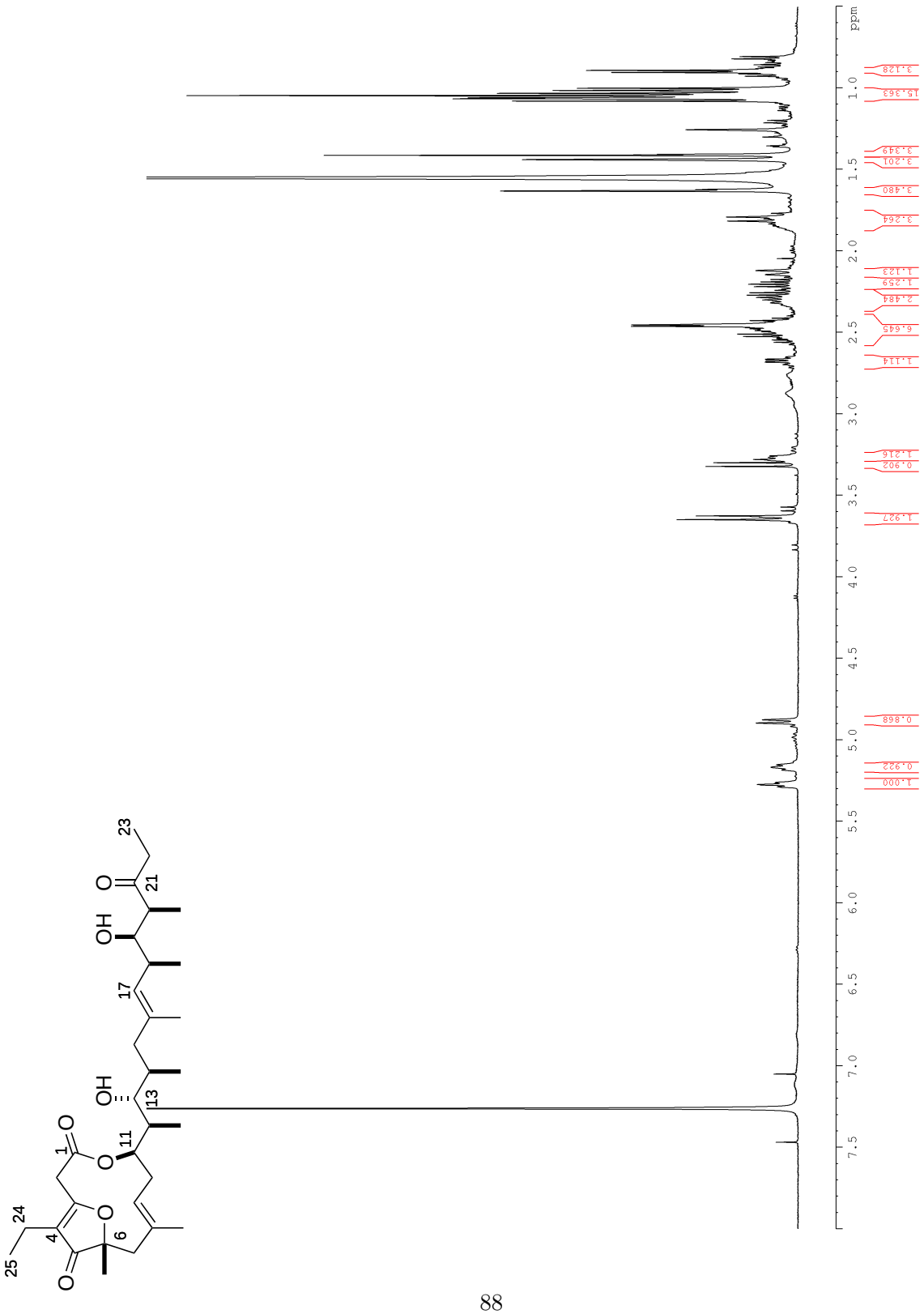
HSQC

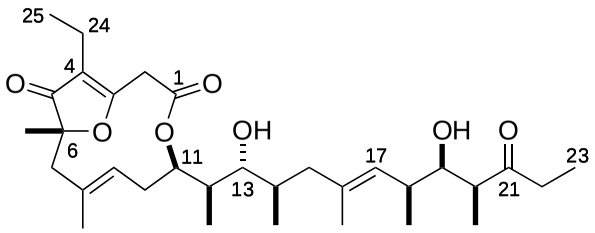

ppm
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5

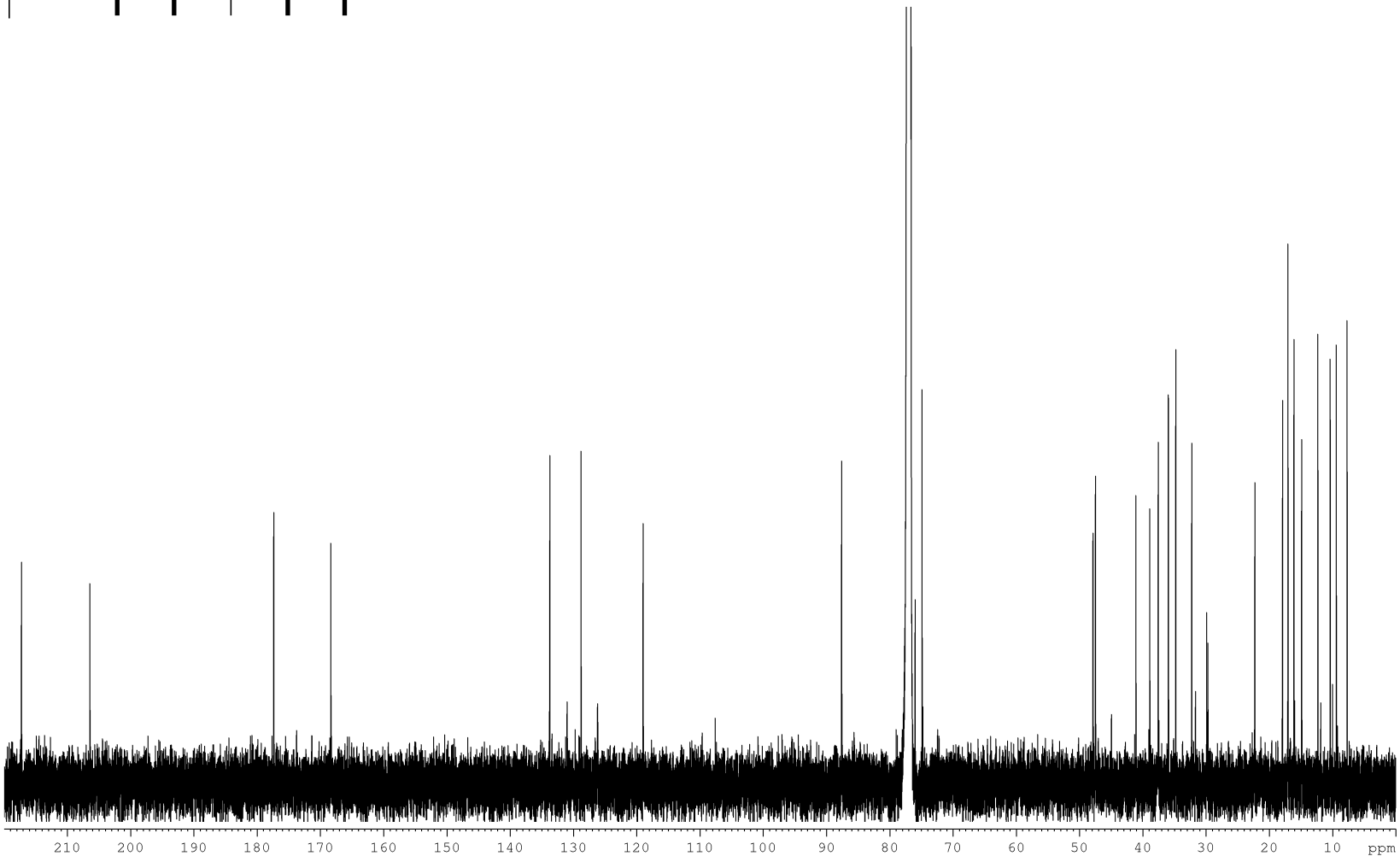
HMBC


ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5

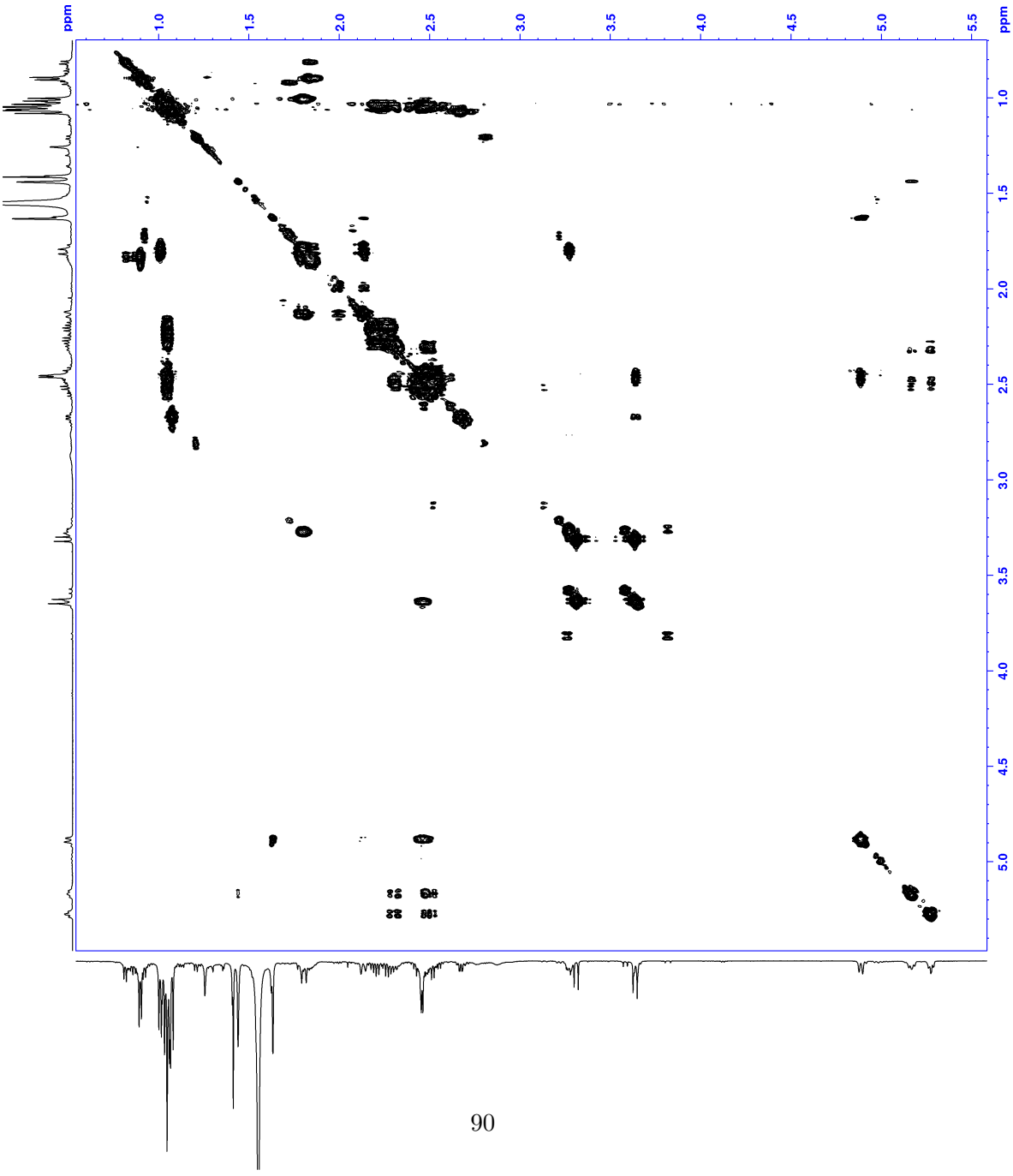
Actinoallolide C (3)



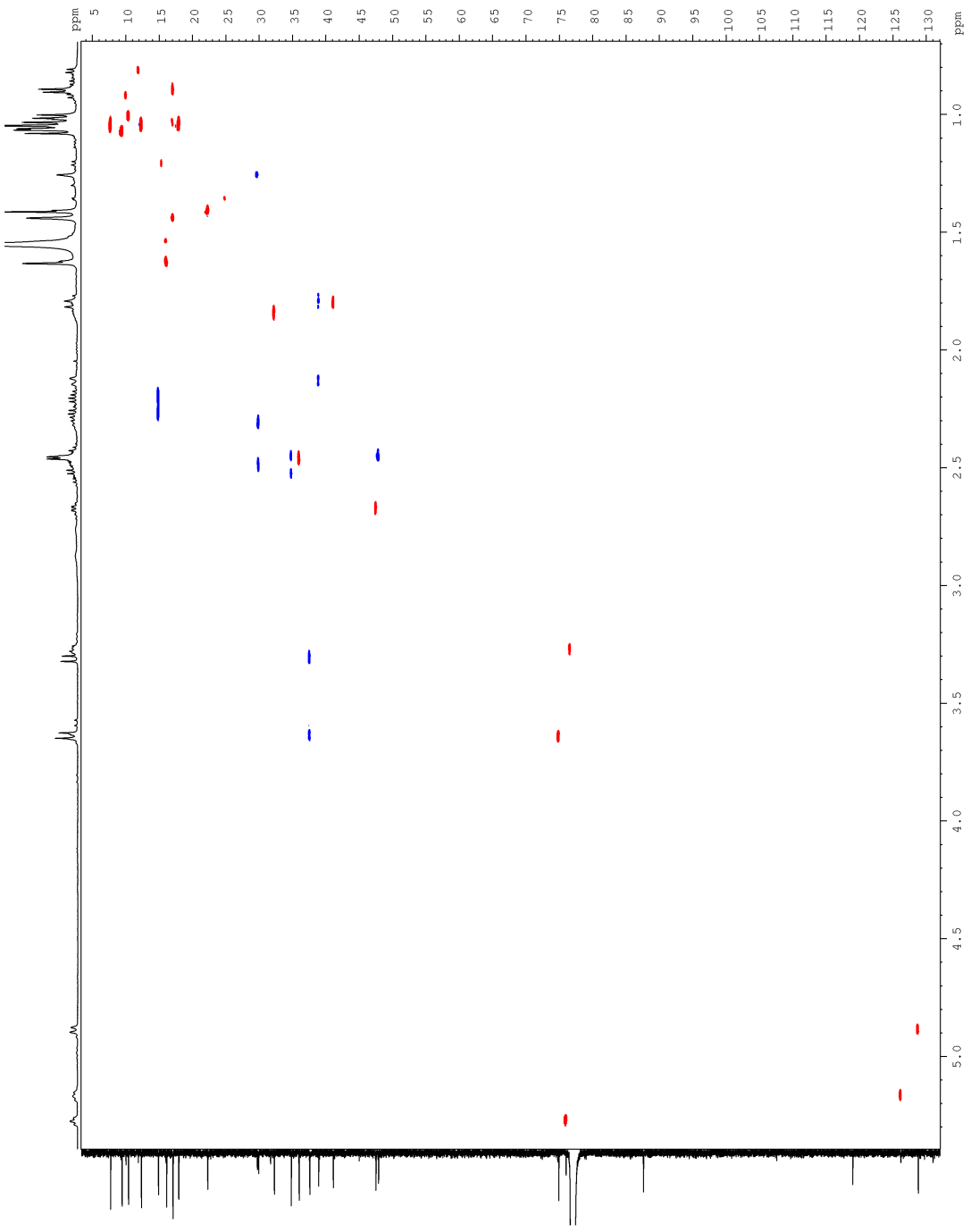

25
24
4
1
O
O
O
6
O
11
OH
13
17
OH
O
21
23


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

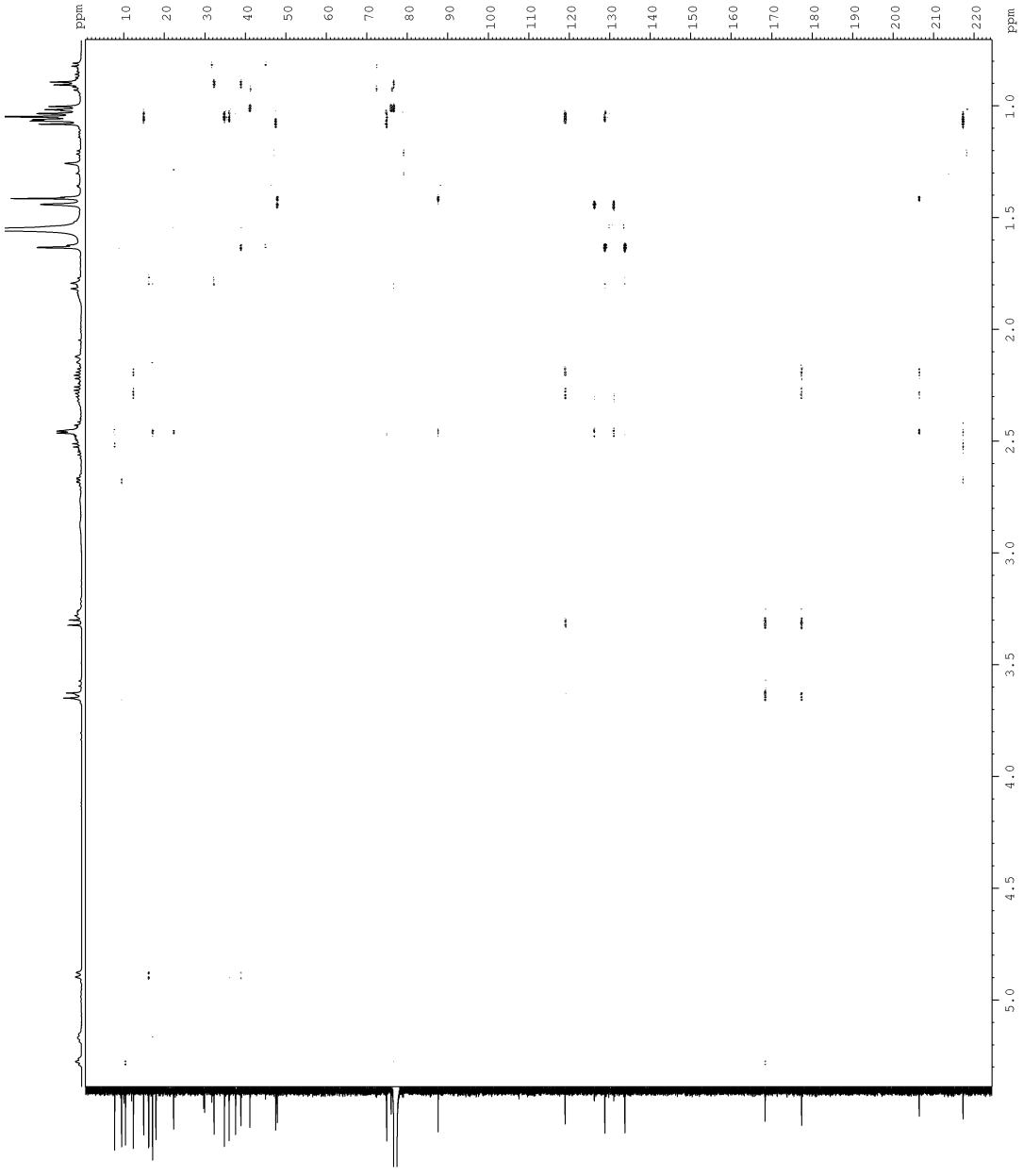
COSY



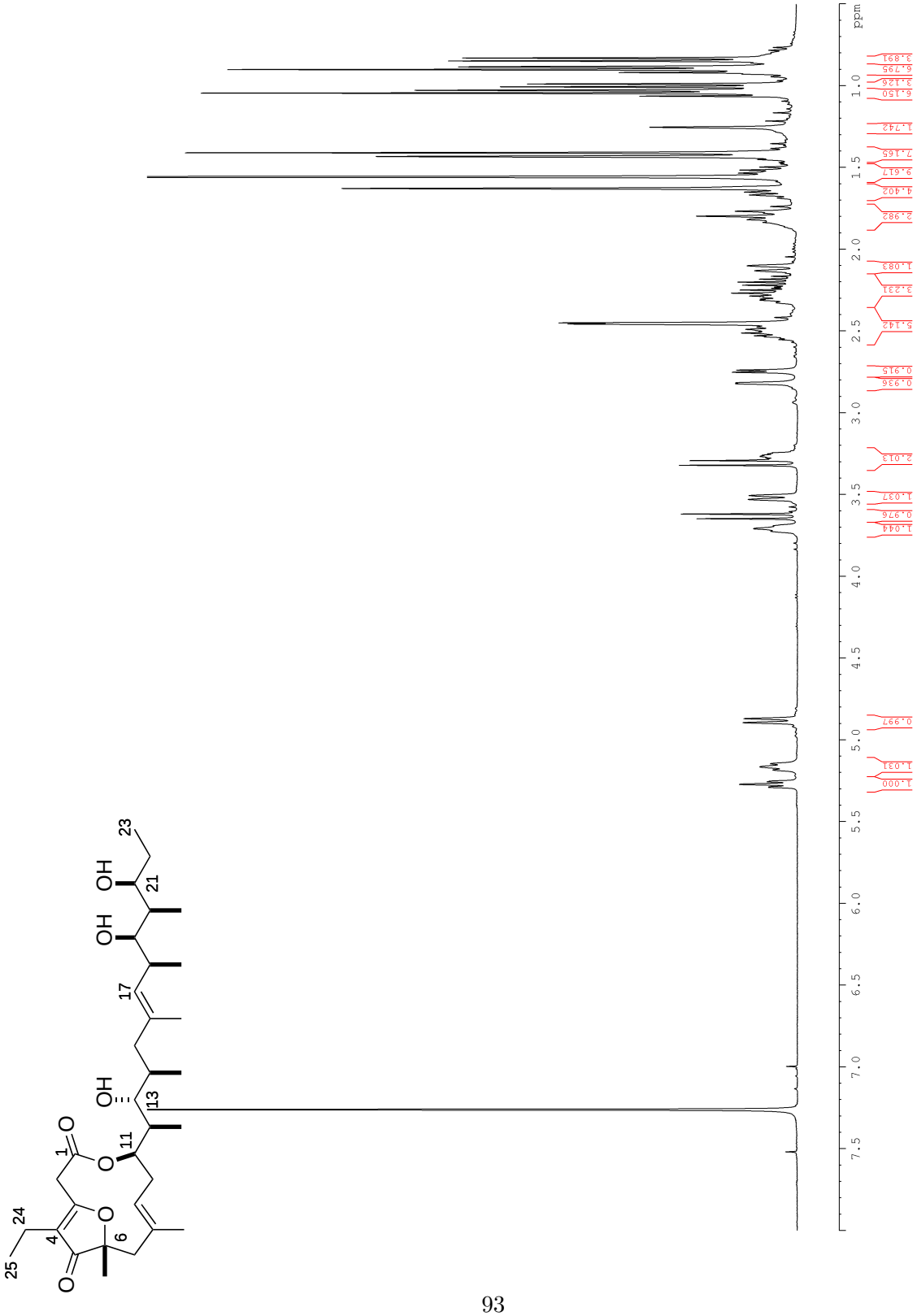
HSQC

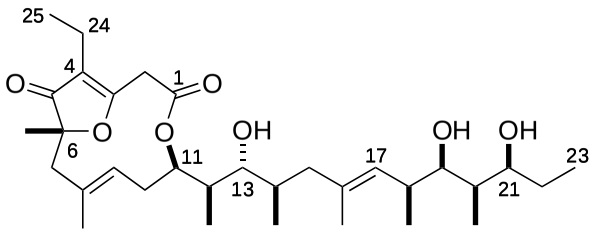

ppm
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0

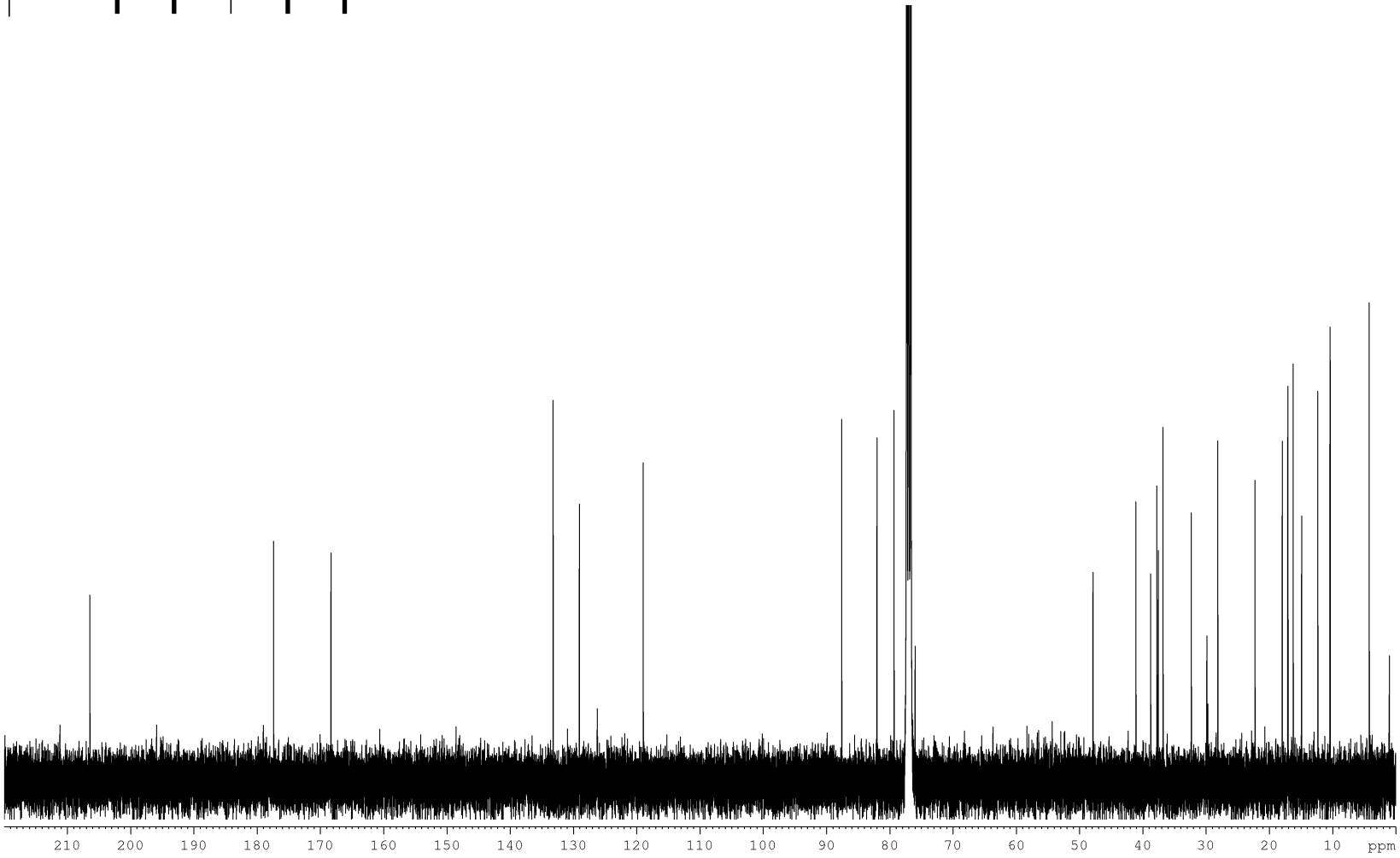
HMBC


ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0

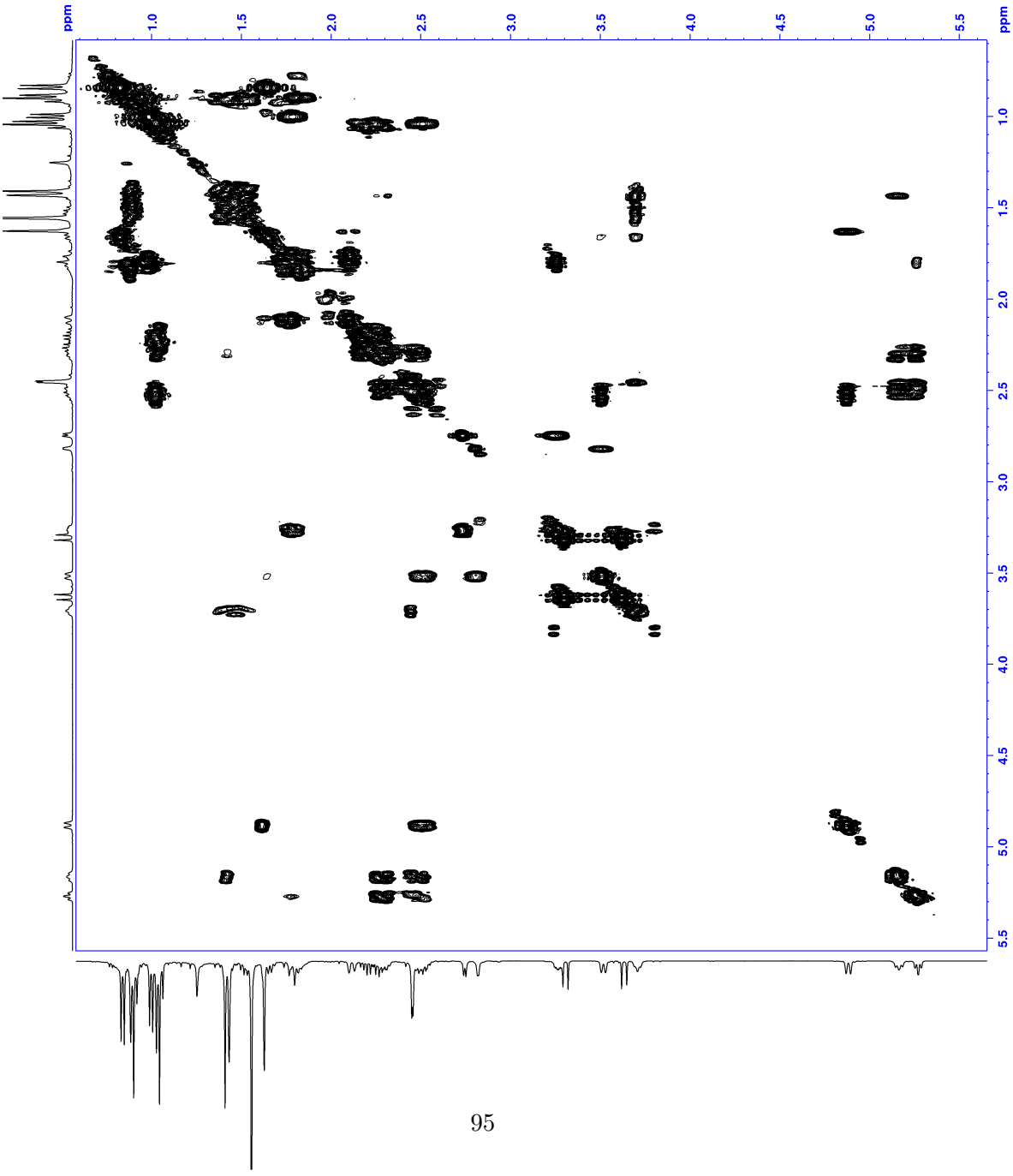
Actinoallolide D (4)



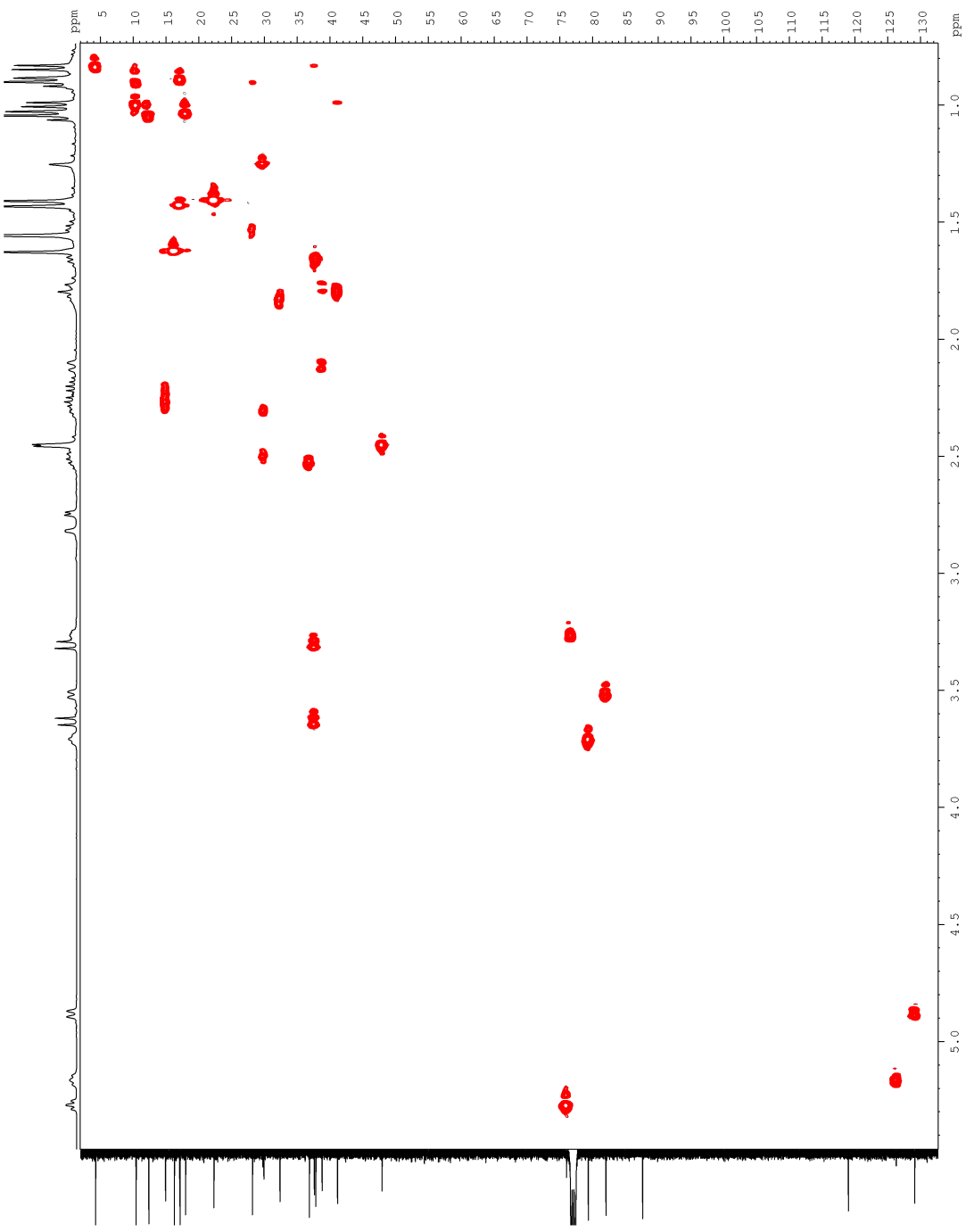

25
24
4
1
O
O
O
O
6
11
OH
13
17
OH
OH
21
23


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

COSY



HSQC


ppm
5
10
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35
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45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
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3.5
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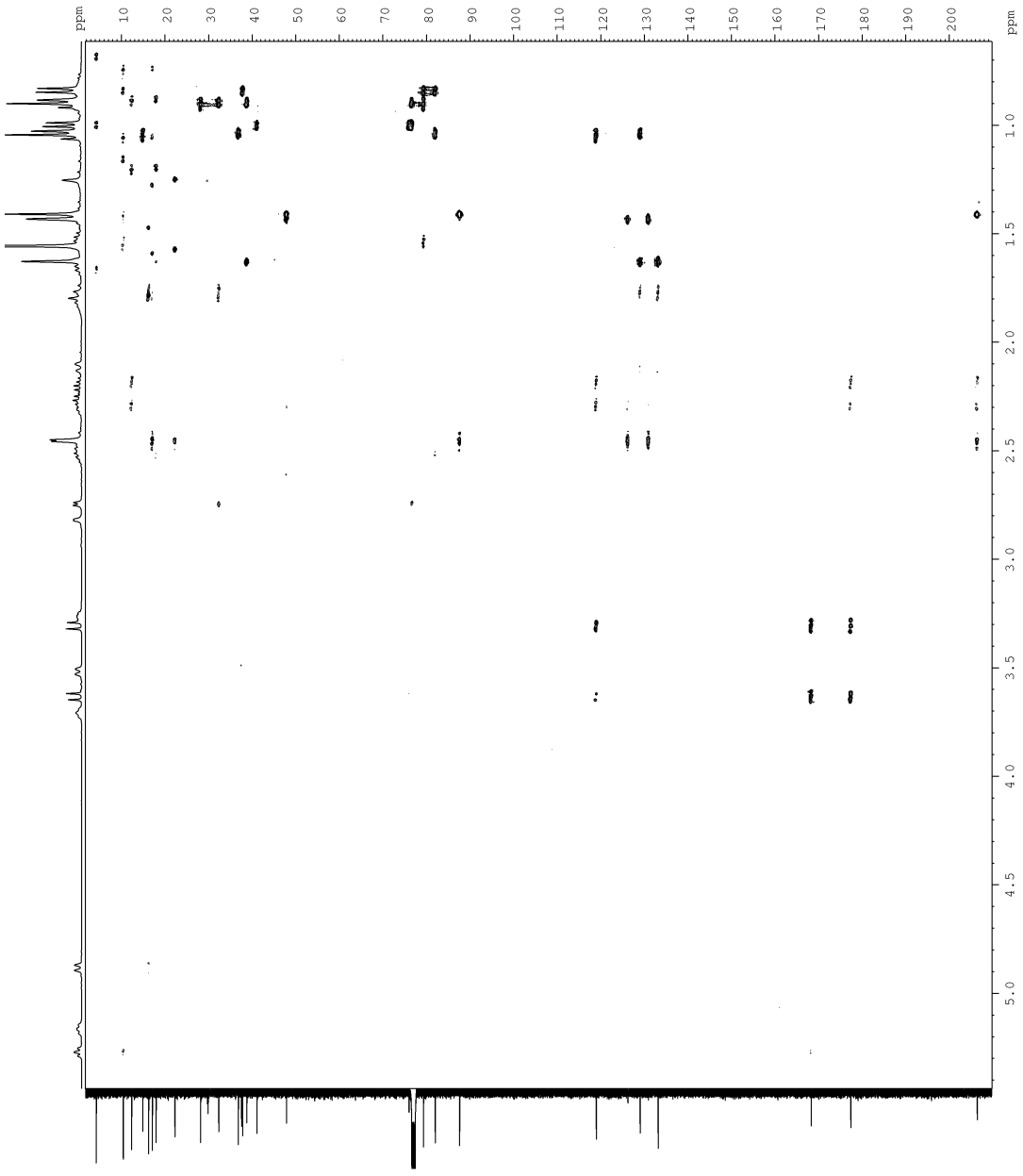
HMBC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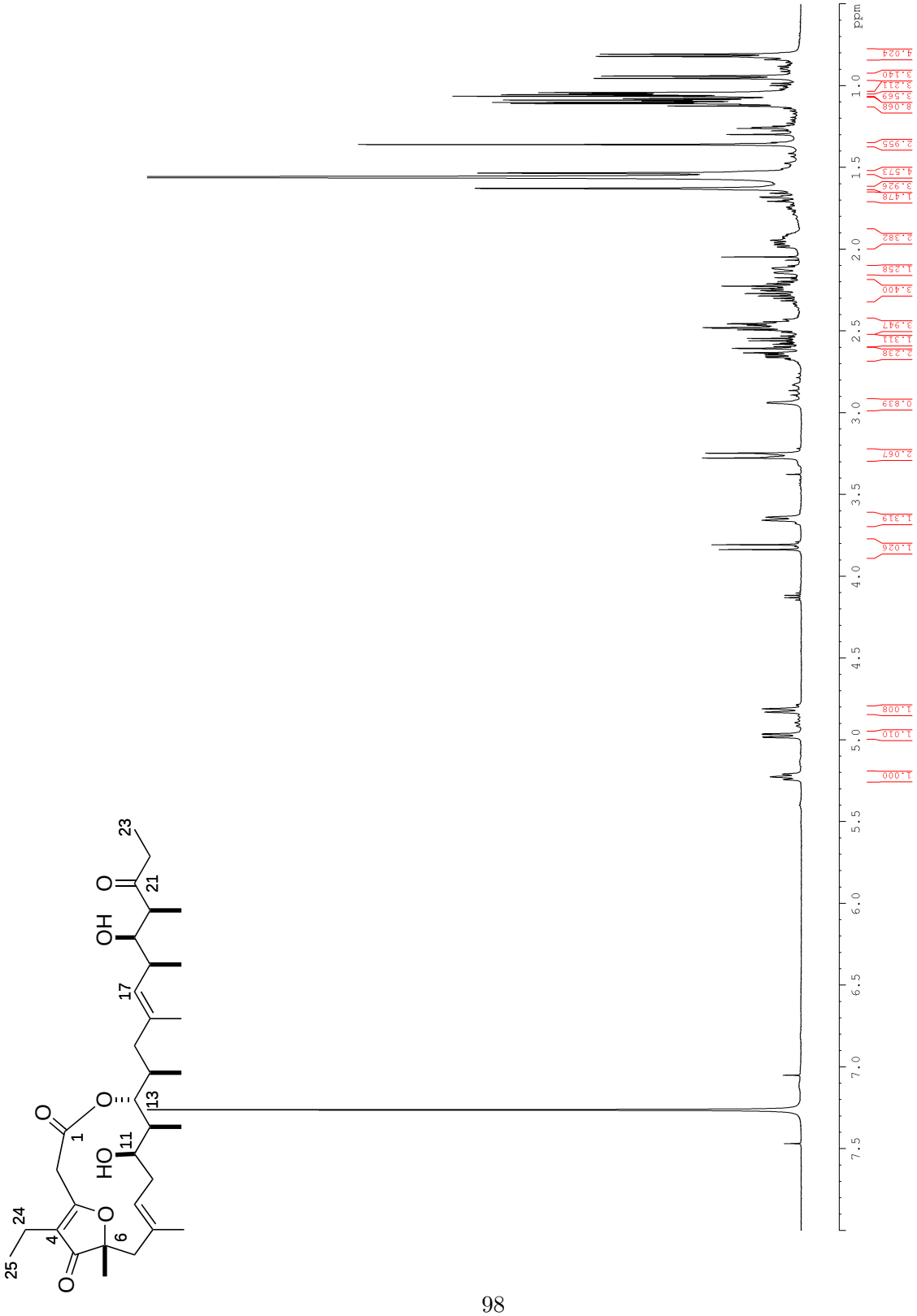
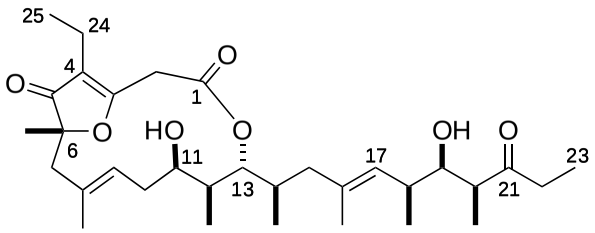
Actinoallolide E (5)

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O
1
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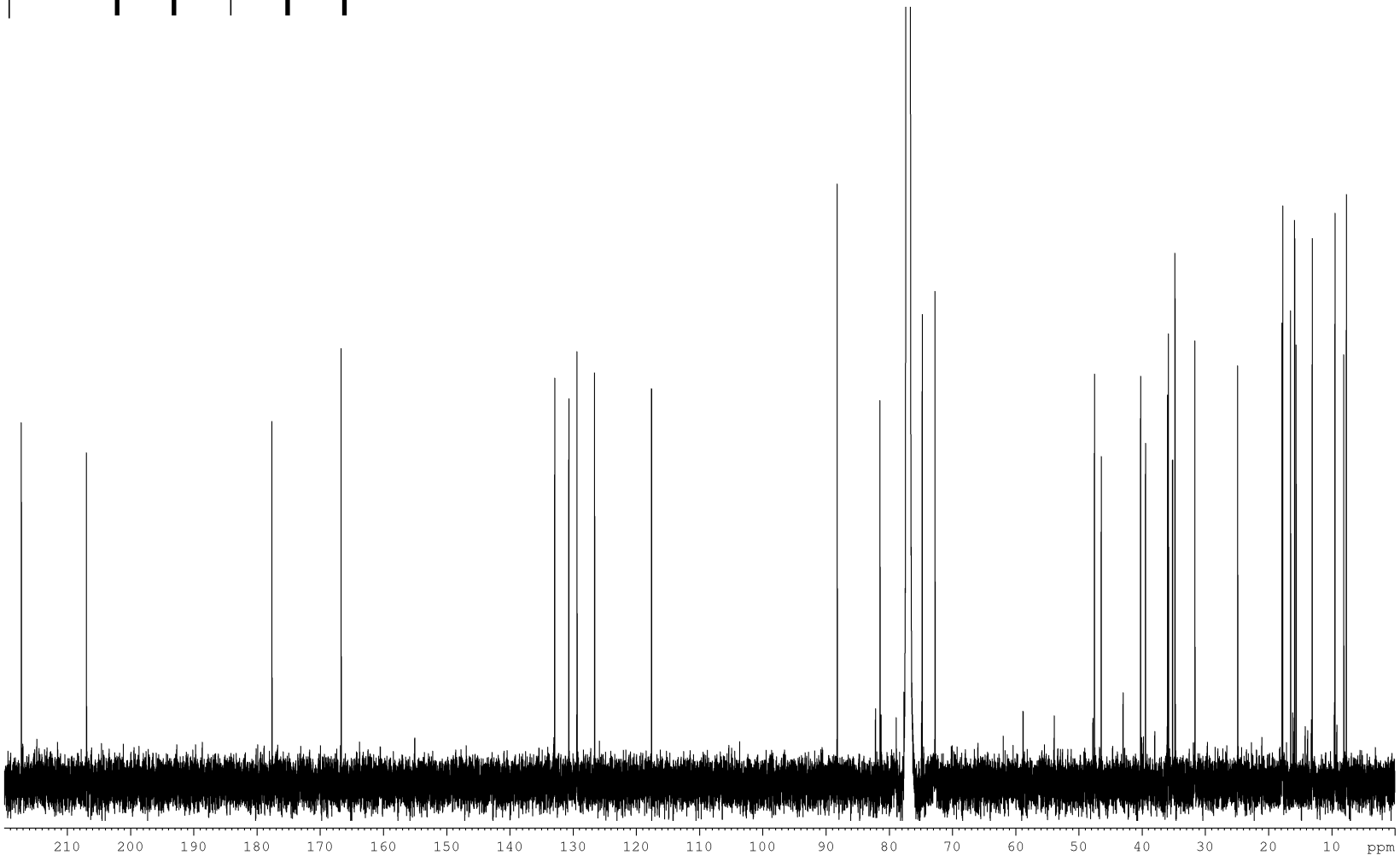
6
O
HO
11
13
17
OH
O
21
23

66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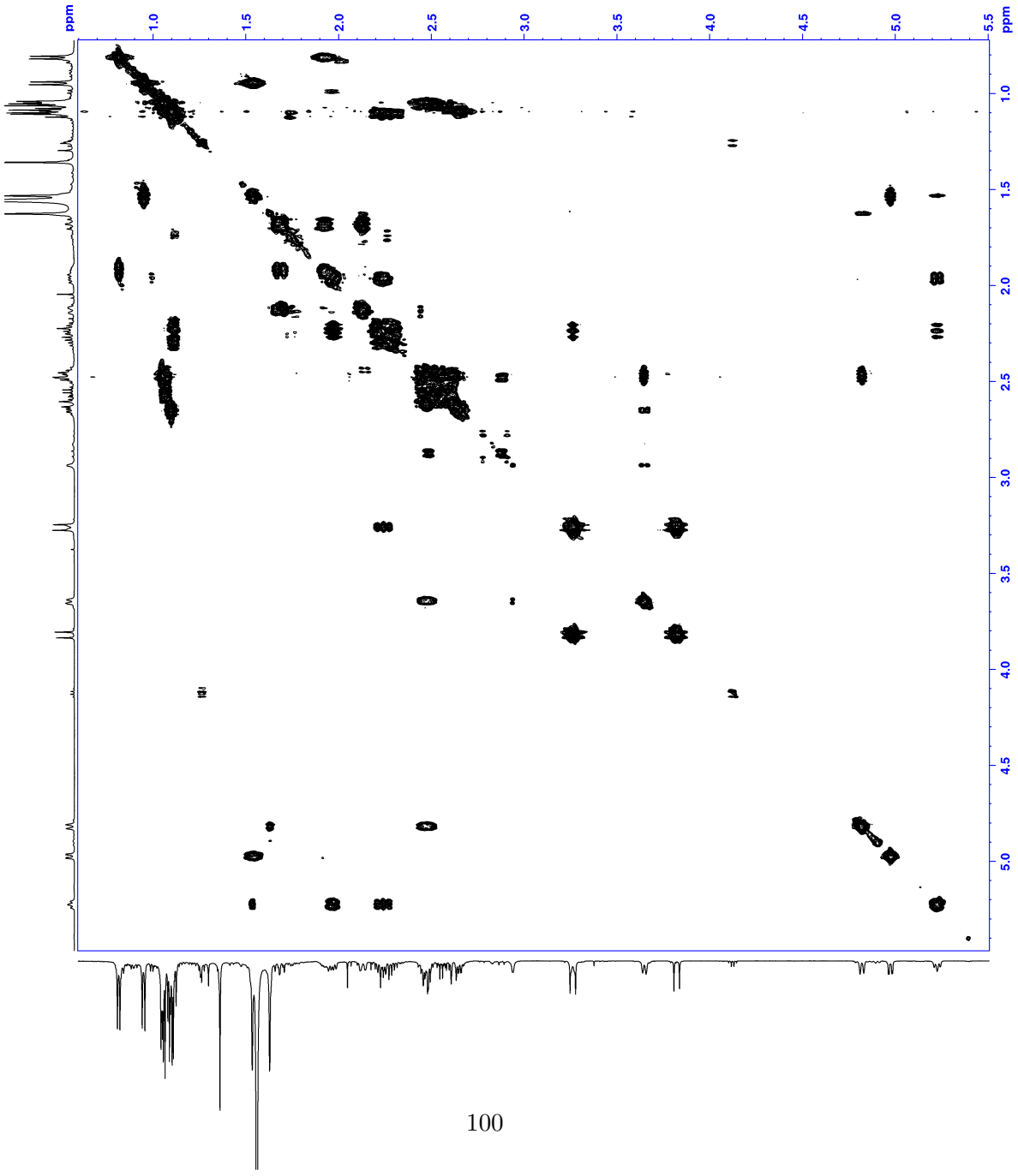
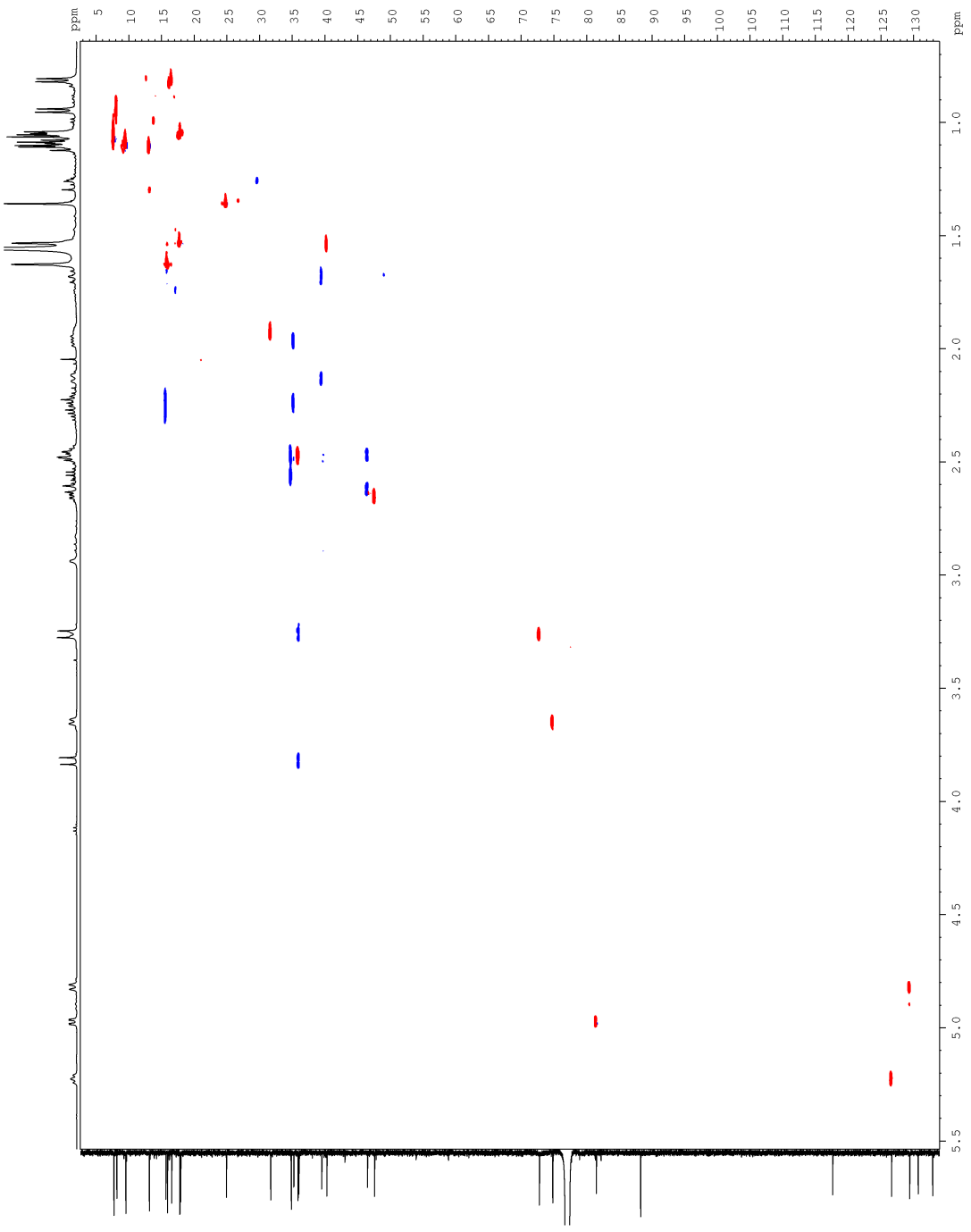
10
ppm

COSY



HSQC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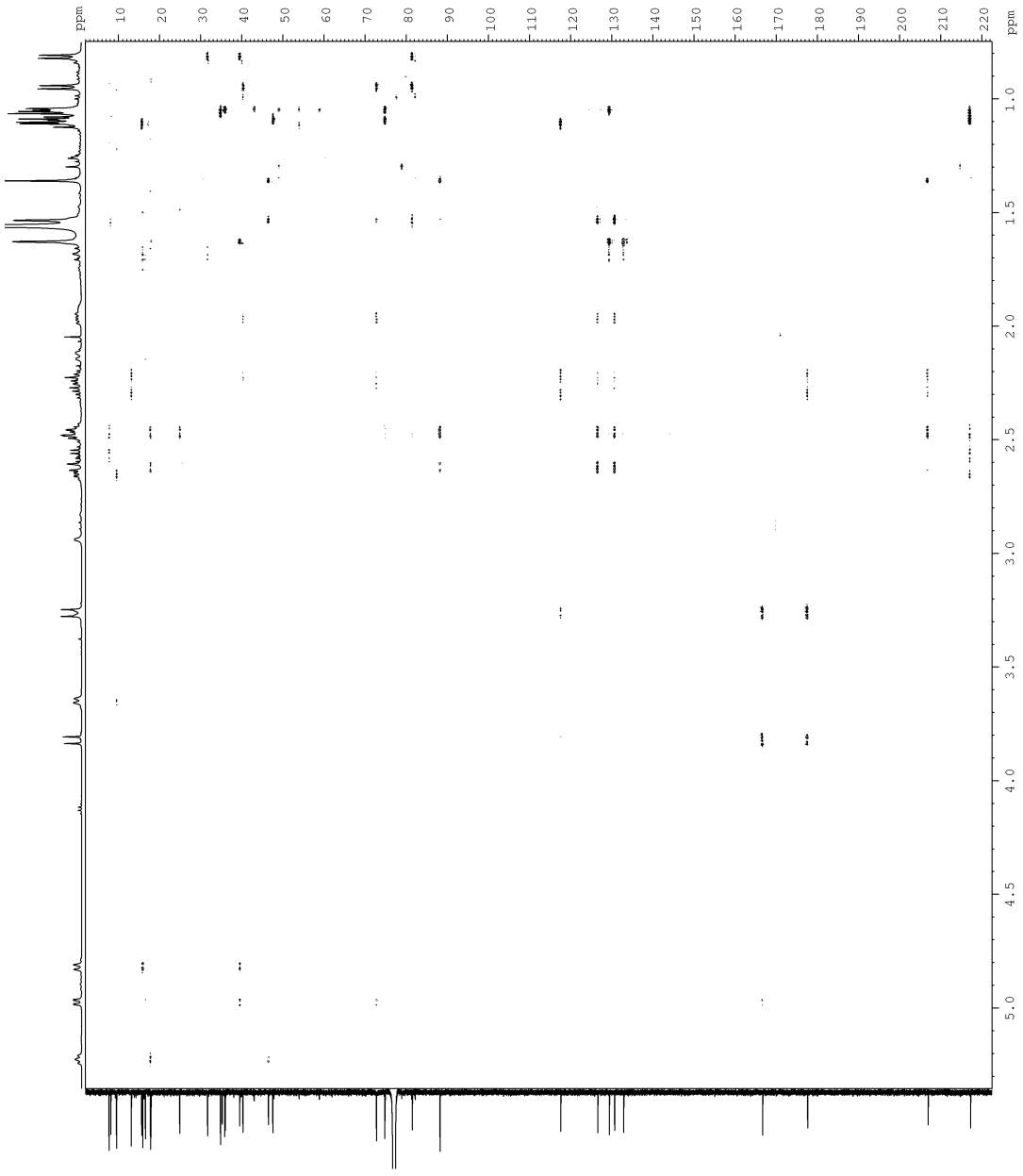
HMBC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2.5
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3.5
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4.5
5.0

References

[1] Y. Inahashi, M. Iwatsuki, A. Ishiyama, A. Matsumoto, T. Hirose, J. Oshita, T. Sunazuka, W. Panbangred, Y. Takahashi, M. Kaiser, K. Otoguro, S. Omura, *Org. Lett.* **2015**, *17*, 864–867.

[2] W. L. W. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, **1997**.

[3] R. Nagase, Y. Oguni, T. Misaki, Y. Tanabe, *Synthesis* **2006**, *22*, 3915–3917.

[4] T. R. Hoye, C. S. Jeffrey, F. Shao, *Nat. Protoc.* **2007**, *2*, 2451–2458.

[5] S. D. Rychnovsky, T. I. Richardson, B. N. Rogers, *J. Org. Chem.* **1997**, *62*, 2925–2934.

[6] D. A. Evans, D. L. Rieger, J. R. Gage, *Tetrahedron Lett.* **1990**, *31*, 7099–7100.

[7] M. Stiles, R. R. Winkler, L. Chang, Yu-Lanand Traynor, *JACS*, *86*, 3337–3342.