Supporting Information

Total Synthesis of Aplyronines A, C and D

Nika Anži ek, Simon Williams, Michael P. Housden and Ian Paterson

University Chemical Laboratory, University of Cambridge

Lensfield Road, Cambridge, CB2 1EW, UK

E-mail: ip100@cam.ac.uk

Table of contents

I.	General and Analytical Procedures	3
II.	Experimental Procedures for C_1–C_{14} Phosphonate **8**	6
III.	Experimental Procedures for C_{21}–C_{27} Aldehyde **14**	14
IV.	Experimental Procedures for C_{15}–C_{20} Phosphonate **19**	21
V.	Experimental Procedures for C_{15}–C_{27} Aldehyde **7**	25
VI.	Experimental Procedures for C_1–C_{27} Macrocyclic Aldehyde **28**	32
VII.	Experimental Procedures for Enantiopure *N*,*N*,*O*-Trimethylserine	41
VIII.	Experimental Procedures for Aplyronines A (**1**), C (**2**), D (**3**) and I (**30a**)	44
IX.	Experimental Procedures for a Linker-Modified Aplyronine D (**4**)	59
X.	^{1}H and ^{13}C NMR spectra	66

I. General and Analytical Procedures

Except where stated otherwise, all reactions were performed under anhydrous conditions under an atmosphere of argon at room temperature, using oven-dried glassware and standard techniques for handling air-sensitive materials.

Purification of reagents and solvents was carried out by standard means.[1] Acetonitrile (MeCN), benzene (PhH), toluene (PhMe), dichloromethane (CH_2Cl_2) and dimethyl sulfoxide (DMSO) were distilled from calcium hydride (CaH_2) and stored under an atmosphere of argon. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from benzophenone ketyl radical / potassium or sodium wire, respectively, and stored under an atmosphere of argon. *N*,*N*-dimethylformamide (DMF) was distilled from $MgSO_4$ and stored over 4Å molecular sieves. Solvents used for chromatography and extraction were distilled.

Triethylamine (Et_3N), pyridine (pyr) and 2,6-lutidine were distilled from and stored over CaH_2 under an argon atmosphere. *N*,*N*-Diisopropylethylamine ($^iPr_2NEt$) was first distilled from ninhydrin, then from potassium hydroxide (KOH) and stored over CaH_2 under an atmosphere of argon. 2,4,6-trichlorobenzoyl chloride (TCBC) and oxalyl chloride were distilled and stored under an argon atmosphere. Propionaldehyde was distilled from anhydrous calcium chloride ($CaCl_2$) and used immediately. Acetic acid (AcOH) was distilled from chromium trioxide and stored under an atmosphere of argon. 4 Å molecular sieves were activated by heating in a microwave oven and dried under vacuum. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was recrystallised from distilled chloroform. Proton sponge® was recrystallized from methanol (MeOH). Anhydrous barium hydroxide ($Ba(OH)_2$) was generated by drying barium hydroxide octahydrate ($Ba(OH)_2 \cdot 8H_2O$) at 130 ºC under vacuum overnight and stored in the glove box. Unless stated otherwise, all other chemicals were used as received.

Solutions of ammonium chloride (NH_4Cl), sodium hydrogencarbonate ($NaHCO_3$), sodium/potassium (Na^+/K^+) tartrate, brine (NaCl) and sodium thiosulfate ($Na_2S_2O_3$) were saturated and aqueous. Buffer solutions were prepared from stock tablets as directed.

[1] W.L.F. Armarego and D.D. Perrin, *Purification of Laboratory Chemicals*, 4th edition, Butterworth-Heinemann, 1996

Flash column chromatography was conducted on Merck Kieselgel 60 (230-400 mesh) silica gel under a positive pressure. Preparative thin layer chromatography was carried out using Merck Kieselgel 60 F254 plates. All solvent mixtures are reported as volume ratios.
Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F254 plates, coated with 0.25 mm of silica gel, using phosphomolybdic acid/cerium (IV) sulphate dip, potassium permanganate dip and/or ultraviolet light (254 nm) for visualisation.

Spectra were recorded on the following machines: Bruker Avance 500 BB, Bruker Avance TCI cryoprobe, Bruker Avance DCH cryoprobe (all 500 MHz) and Bruker Avance DRX 400 (400 MHz).

^{1}H nuclear magnetic resonance (NMR) spectra were recorded at ambient probe temperature (298 K) using an internal deuterium lock for $CDCl_3$ (δ_H = 7.26 ppm), MeOD (δ_H = 3.31 ppm) and acetone-d^6 (δ_H = 2.05 ppm). ^{1}H NMR data are presented as: chemical shift (in ppm, δ scale relative to tetramethylsilane, δ_{TMS} = 0 ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, obs = obscured), coupling constants (*J* in Hz). Signal assignment follows the numbering system for aplyronines as outlined by Yamada[2], except for methyl groups, which are labelled according to the skeletal carbon they are attached to (Figure 1). Assignments of protons were based on unambiguous chemical shifts and coupling patterns with the aid of 2D spectra, and by analogy to fully interpreted spectra for structurally related compounds. Proton-decoupled ^{13}C NMR spectra were recorded at at ambient probe temperature (298 K) and an internal deuterium lock for $CDCl_3$ (δ_C = 77.14 ppm), MeOD (δ_C = 49.0 ppm) and acetone-d^6 (δ_C = 29.8 ppm). Data are listed by chemical shift (in ppm, δ scale relative to tetramethylsilane, δ_{TMS} = 0 ppm).

Fourier transform IR (FT-IR) spectra were recorded as a thin film using a Perkin–Elmer Spectrum One spectrometer. Maximum absorbance frequencies (ν_{max}) are reported in wavenumbers (cm^{-1}).

Optical rotation measurements were performed on the Perkin-Elmer 343 polarimeter at the sodium D-line (589 nm) and reported in the following format: $[\alpha]_{2C}^{D}$, concentration of solution (*c* in g / 100 mL) and solvent.

[2] K. Yamada, M. Ojika, T. Ishigaki and Y. Yoshida *J. Am. Chem. Soc.* 1993, **115**, 11020

High resolution mass spectrometry (HRMS) spectra were recorded by the EPRSC National Mass Spectrometry facility (Swansea, UK) or the departmental Mass spectrometry service (University Chemical Laboratories, Cambridge) using the electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI) technique. The parent ion is quoted with the indicated cation: $[M+H]^+$, $[M+Na]^+$ or $[M+NH_4]^+$ or anion: $[M–H]^–$

Chiral HPLC was carried out on a Shimadzu XR-LC system using a Chiralpak® IA column and a solvent system of mixed hexanes and isopropanol.

Melting points are uncorrected.

Abbreviations:

Alloc = allyl carbonate, Bn = benzyl, CBz = carboxybenzyl, DBB = di-*tert*-butylbiphenyl, DCC = dicyclohexylcarbodi-imide, DIBAL = di-*iso*-butylaluminium hydride, DMAP = *N*,*N*-dimethylaminopyridine, DMP = Dess–Martin periodinane, Fmoc = Fluorenylmethyloxy-carbonyl, HWE = Horner–Wadsworth–Emmons, OTf = trifluoromethanesulphonate, PMB = para-methoxybenzyl, PMP = *para*-methoxyphenyl, TES = triethylsilyl, TBS = *tert*-butyl-dimethylsilyl, TMDS = tetramethyldisiloxane

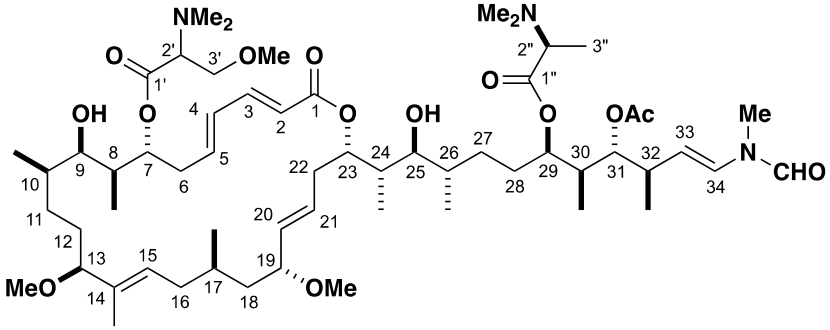
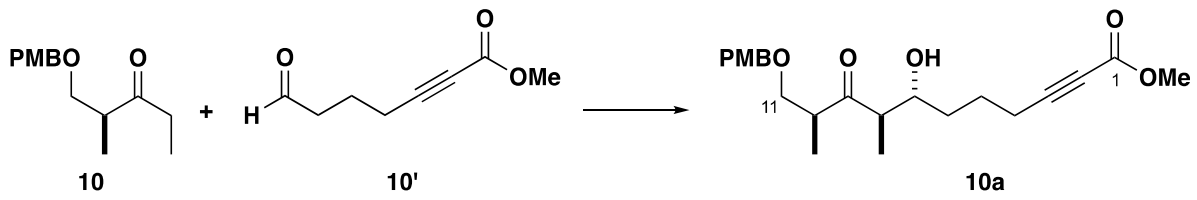


Figure 1: The numbering system for aplyronine A (**1**)

II. Experimental Procedures for C_1–C_{14} Phosphonate 8

Aldol adduct 10a



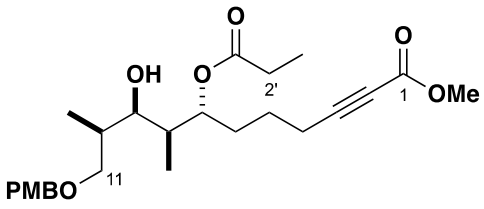
Et_3N (5.51 mL, 39.6 mmol) was added to a solution of dicyclohexylboron chloride (6.51 mL, 29.6 mmol) in Et_2O (40 mL) at –78 °C, followed by a solution of ketone **10**[3] (5.66 g, 23.7 mmol) in Et_2O (20 mL) *via* cannula. The reaction mixture was warmed to –20 °C and stirred for 1.5 h, before being cooled to –78 °C and a solution of aldehyde **10'**[4] (3.05 g, 19.8 mmol) in Et_2O (20 mL) was added *via* cannula. The mixture was stirred at –78 °C for 3 h then left to stand in the freezer at –20 °C for 16 h. After warming to 0 °C, the reaction was quenched with MeOH (80 mL) and pH 7 buffer solution (80 mL), followed by hydrogen peroxide solution (40 mL, 30% aq.). The mixture was stirred for 1 h at rt, before being poured into H_2O (80 mL) and extracted with CH_2Cl_2 (3 x 80 mL). The combined organics were washed with $NaHCO_3$ solution (80 mL) and brine (80 mL), then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:5 → 1:3) gave aldol adduct **10a** as a colourless oil (6.75 g, 17.3 mmol, 87%, >20:1 *dr*).

R_f 0.18 (EtOAc/40-60 PE, 3:10); **$[\alpha]_{2(}^{\nu}$** = +6.7 (*c* 3.3, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 3417, 2936, 2874, 2236, 1712, 1612, 1514; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.20 (2H, d, *J* = 8.8 Hz, ArH x 2), 6.87 (2H, d, *J* = 8.8 Hz, ArH x 2), 4.40 (2H, ABq, *J* = 11.6 Hz, $ArOCH_2$), 3.80 (3H, s, $ArOCH_3$), 3.75 (3H, s, CO_2CH_3), 3.72-3.68 (1H, m, H_7), 3.67 (1H, dd, *J* = 9.0, 9.0 Hz, H_{11a}), 3.39 (1H, dd, *J* = 8.8, 4.8 Hz, H_{11b}), 3.11-3.03 (1H, m, H_{10}), 3.00 (1H, br s, OH), 2.66 (1H, dq, *J* = 7.0, 7.0 Hz, H_8), 2.35 (2H, t, *J* = 7.0 Hz, H_4 x 2), 1.82-1.73 (1H, m, H_{6a}), 1.68-1.61 (2H, m, H_5 x 2), 1.49-1.39 (1H, m, H_{6b}), 1.14 (3H, d, *J* = 7.3 Hz, Me_8), 1.03 (3H, d, *J* = 7.0 Hz, Me_{10}); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 218.4, 159.3, 154.4, 129.9, 129.5, 113.8, 89.7, 73.1 x 2, 72.8, 72.0, 55.3, 52.7, 52.5, 44.7, 33.1, 23.6, 18.4, 13.9, 13.5; **HRMS** calculated for $C_{22}H_{34}NO_6$ $[M+NH_4]^+$ 408.2386, found 408.2386.

---

[3] I. Paterson, G.J. Florence, K. Gerlach, J.P. Scott and N. Sereinig *J. Am. Chem. Soc.* 2001, **123**, 9535
[4] I. Paterson, C. Cowden and M.D. Woodrow *Tetrahedron Lett.* 1998, **39**, 6037

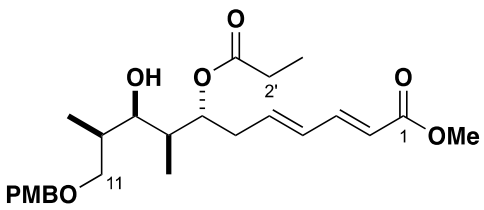
Propionate 10b



Freshly prepared SmI_2 (16.8 mL, 0.1 M in THF, 1.68 mmol) was added dropwise to a solution of propionaldehyde (7.25 mL, 100 mmol) in THF (30 mL) at 0 °C. The solution was stirred for 5 min until the deep blue colour had subsided and turned yellow. A solution of aldol adduct **10a** (6.54 g, 16.8 mmol) in THF (15 mL) was then added *via* cannula. The reaction mixture was stirred at 0 °C for 1 h, before being quenched with $NaHCO_3$ solution (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (EtOAc/40-60 PE, 1:4) to give propionate ester **10b** as a colourless oil (7.36 g, 16.4 mmol, 98%, >20:1 *dr*).

R_f 0.23 (EtOAc/40-60 PE, 3:10); **$[\alpha]_{20}^{D}$** = –6.0 (*c* 2.6, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 3490, 2939, 2236, 1714, 1613, 1586; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.22 (2H, d, *J* = 8.5 Hz, ArH x 2), 6.86 (2H, d, *J* = 8.6 Hz, ArH x 2), 4.94 (1H, ddd, *J* = 8.1, 8.1, 2.7 Hz, H_7), 4.43 (2H, ABq, *J* = 11.5 Hz, $ArOCH_2$), 3.79 (3H, s, $ArOCH_3$), 3.74 (3H, s, CO_2CH_3), 3.54 (1H, dd, *J* = 9.0, 4.8 Hz, H_{11a}), 3.49 (1H, dd, *J* = 8.9, 6.3 Hz, H_{11b}), 3.43 (1H, br d, *J* = 9.1 Hz, H_9), 3.27 (1H, d, *J* = 2.9 Hz, OH), 2.40-2.29 (4H, m, $H_{2'}$ x 2, H_4 x 2), 1.92-1.84 (1H, m, H_{10}), 1.84-1.77 (1H, m, H_{6a}), 1.77-1.72 (1H, m, H_8), 1.68-1.52 (3H, m, H_5 x 2, H_{6b}), 1.14 (3H, t, *J* = 7.6 Hz, $H_{3'}$ x 3), 0.88 (3H, d, *J* = 7.0 Hz, Me_{10}), 0.82 (3H, d, *J* = 6.9 Hz, Me_8); **^{13}C NMR** (62.5 MHz, $CDCl_3$): δ_C 174.7, 159.2, 154.1, 130.2, 129.2, 113.8, 89.1, 75.1, 74.8, 73.7, 73.2, 73.0, 55.2, 52.5, 38.7, 36.0, 32.9, 27.8, 23.5, 18.5, 13.7, 9.3, 8.4; **HRMS** calculated for $C_{25}H_{37}O_7$ $[M+H]^+$ 449.2539, found 449.25363.

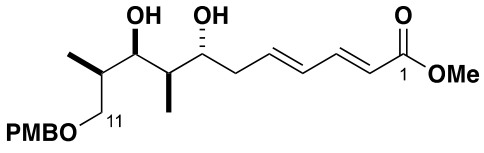
Dienoate 10c



PPh_3 (7.25 g, 27.6 mmol) and PhOH (2.73 g, 29.0 mmol) were added to a solution of alkyne ester **10b** (6.20 g, 13.8 mmol) in PhH (50 mL). The reaction mixture was stirred at rt for 48 h then quenched by pouring into a NaOH solution (50 mL, 10% aq.) and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude yellow oil which was purified by flash column chromatography (EtOAc/40-60 PE, 1:4) to yield dienoate **10c** as a colourless oil (5.83 g, 13.0 mmol, 94%).

R_f 0.17 (EtOAc/40-60 PE, 3:10); **$[\alpha]_{2\text{C}}^{\nu}$** = –69.6 (*c* 4.2, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 3496, 2974, 1716, 1645, 1614, 1586; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.24 (1H, dd, *J* = 15.8, 11.0 Hz, H_3), 7.23 (2H, d, *J* = 8.6 Hz, ArH x 2), 6.87 (2H, d, *J* = 8.6 Hz, ArH x 2), 6.20 (1H, dd, *J* = 15.1, 11.0 Hz, H_4), 6.06 (1H, dt, *J* = 14.9, 7.1 Hz, H_5), 5.80 (1H, d, *J* = 15.5 Hz, H_2), 5.02 (1H, ddd, *J* = 8.0, 8.0, 3.5 Hz, H_7), 4.44 (2H, ABq, *J* = 11.5 Hz, $ArOCH_2$), 3.80 (3H, s, $ArOCH_3$), 3.73 (3H, s, CO_2CH_3), 3.54 (1H, dd, *J* = 9.1, 4.6 Hz, H_{11a}), 3.50-3.46 (1H, obs, H_9), 3.49 (1H, dd, *J* = 9.1, 6.9 Hz, H_{11b}), 3.35 (1H, d, *J* = 2.8 Hz, OH), 2.64 (1H, ddd, *J* = 14.9, 4.6, 4.6 Hz, H_{6a}), 2.39 (1H, ddd, *J* = 15.2, 8.0, 8.0 Hz, H_{6b}), 2.31 (1H, q, *J* = 7.6 Hz, $H_{2a'}$), 2.31 (1H, q, *J* = 7.6 Hz, $H_{2b'}$), 1.92-1.84 (1H, m, H_{10}), 1.82-1.75 (1H, m, H_8), 1.12 (3H, t, *J* = 7.7 Hz, $H_{3'}$ x 3), 0.89 (3H, d, *J* = 6.9 Hz, Me_{10}), 0.80 (3H, d, *J* = 6.9 Hz, Me_8); **^{13}C NMR** (62.5 MHz, $CDCl_3$): δ_C 174.3, 167.5, 159.2, 144.6, 139.2, 130.9, 130.0, 129.2, 119.6, 113.8, 75.0, 74.6, 73.9, 73.0, 55.2, 51.4, 38.3, 36.0, 35.4, 27.8, 13.6, 9.3, 8.2; **HRMS** calculated for $C_{25}H_{37}O_7$ $[M+H]^+$ 449.2539, found 449.2539.

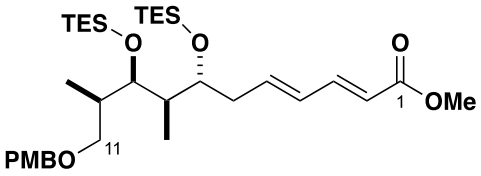
Diol 9



Potassium carbonate (3.08 g, 22.3 mmol) was added to a solution of ester **10c** (4.00 g, 8.92 mmol) in MeOH (150 mL) and the solution was stirred at rt for 2 h. Once complete, the reaction was poured into $NaHCO_3$ solution (100 mL) and extracted with EtOAc (4 x 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc/40-60 PE, 2:5) gave diol **9** as a waxy white solid (3.32 g, 8.46 mmol, 95%).

R$_f$ 0.33 (EtOAc/40-60 PE, 1:1); $[\alpha]_{2c}^{\nu}$ = –51.9 (*c* 2.8, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 3432, 2965, 1715, 1643, 1614, 1586; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.27 (1H, dd, *J* = 15.4, 10.4 Hz, H_3), 7.24 (2H, d, *J* = 8.5 Hz, Ar<u>H</u> x 2), 6.89 (2H, d, *J* = 8.7 Hz, Ar<u>H</u> x 2), 6.26 (1H, dd, *J* = 15.4, 10.4 Hz, H_4), 6.19 (1H, dt, *J* = 15.2, 7.1 Hz, H_5), 5.80 (1H, d, *J* = 15.4 Hz, H_2), 4.46 (2H, ABq, *J* = 11.5 Hz, ArOC<u>H</u>$_2$), 4.28 (1H, s, O<u>H</u>), 3.88 (1H, d, *J* = 9.4 Hz, H_9), 3.81 (3H, s, ArOC<u>H</u>$_3$), 3.74 (3H, s, CO_2C<u>H</u>$_3$), 3.71-3.66 (1H, m, H_7), 3.59 (1H, dd, *J* = 9.1, 3.7 Hz, H_{11a}), 3.45 (1H, dd, *J* = 9.3, 9.3 Hz, H_{11b}), 3.35 (1H, d, *J* = 7.3 Hz, O<u>H</u>), 2.50 (1H, ddd, *J* = 14.7, 7.1, 7.1 Hz, H_{6a}), 2.44 (1H, ddd, *J* = 14.4, 5.9, 5.9 Hz, H_{6b}), 2.05-1.95 (1H, m, H_{10}), 1.63-1.57 (1H, m, H_8), 1.01 (3H, d, *J* = 7.0 Hz, Me_8), 0.71 (3H, d, *J* = 6.9 Hz, Me_{10}); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 167.6, 159.3, 144.9, 141.3, 130.2, 129.4, 129.3, 119.2, 113.8, 76.7, 75.1, 73.2, 55.2, 51.4, 39.4, 37.8, 35.5, 30.9, 12.8, 10.2; **HRMS** calculated for $C_{22}H_{33}O_6$ $[M+H]^+$ 393.2277, found 393.2277.

***Bis*-TES PMB ether 9a**

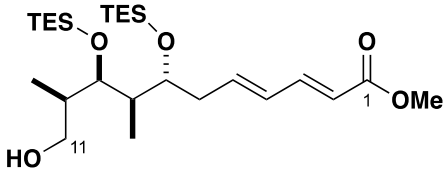


TESOTf (25.5 mL, 113 mmol) was added dropwise to a solution of diol **9** (20.1 g, 51.2 mmol) and 2,6-lutidine (14.9 mL, 128 mmol) in CH_2Cl_2 (300 mL) at –78 °C. The reaction mixture was stirred for 45 min, then quenched by addition of MeOH (20 mL) and warmed to rt. The mixture was diluted with $NaHCO_3$ solution (300 mL) and extracted with CH_2Cl_2 (2 x 300 mL). Combined organic phases were dried (Na_2SO_4), concentrated *in vacuo* and purified by flash column chromatography (gradient elution: EtOAc/40-60, PE 0:1 → 1:16) to give *bis*-TES ester **9a** (25.4 g, 40.9 mmol, 80%) as a colourless oil.

R$_f$ 0.50 (EtOAc/40-60 PE, 1:10); $[\alpha]_{2c}^{\nu}$ = +45.0 (*c* 1.6, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2953, 2911, 2876, 1721, 1644, 1615, 1513, 1459, 1302, 1246, 1172, 1138, 1082, 1037, 1001, 819, 723; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.28-7.23 (3H, m, Ar<u>H</u>, H_3), 6.87 (2H, d, *J* = 8.8 Hz, Ar<u>H</u>), 6.21-6.11 (2H, m, H_4, H_5), 5.79 (1H, d, *J* = 15.3 Hz, H_2), 4.41 (2H, s, ArC<u>H</u>$_2$O), 3.80 (3H, s, ArOC<u>H</u>$_3$), 3.74 (3H, s, CO_2C<u>H</u>$_3$), 3.74-3.69 (1H, m, H_7), 3.64 (1H, dd, *J* = 5.1, 3.7 Hz, H_{11a}), 3.49 (1H, dd, *J* = 9.2, 5.1 Hz, H_{11b}), 3.22 (1H, dd, *J* = 9.0, 7.9 Hz, H_9), 2.29-

2.20 (2H, m, H_6 x 2), 1.98-1.91 (1H, m, H_{10}), 1.78 (1H, ddq, J = 6.9, 6.7, 5.4 Hz, H_8), 0.96 (3H, d, J = 6.9 Hz, Me_{10}), 0.95 (9H, t, J = 7.9 Hz, $SiCH_2C\underline{H}_3$ x 3), 0.92 (9H, t, J = 7.9 Hz, $SiCH_2C\underline{H}_3$ x 3), 0.86 (3H, d, J = 6.9 Hz, Me_8), 0.60 (6H, t, J = 7.8 Hz, $SiC\underline{H}_2CH_3$ x 3), 0.55 (6H, t, J = 7.8 Hz, $SiC\underline{H}_2CH_3$ x 3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 167.7, 159.1, 145.1, 142.0, 130.8, 130.1, 129.1, 119.0, 113.7, 75.6, 73.8, 72.8, 72.2, 55.2, 51.5, 42.1, 38.8, 36.3, 14.8, 10.3, 7.1, 7.0, 5.6, 5.2; **HRMS** calculated for $C_{34}H_{61}O_6Si_2$ $[M+H]^+$ 621.4001, found 621.3993.

***Bis*-TES alcohol 9b**

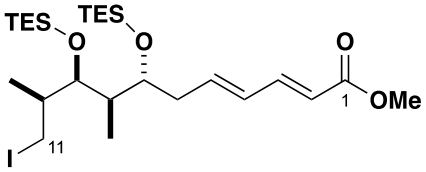


DDQ (5.48 g, 24.2 mmol) was added in one portion to a solution of PMB ether **9a** (10.0 g, 16.1 mmol) in CH_2Cl_2/pH 7 buffer (2:1, 300 ml) at 0 °C. The resulting dark green mixture was warmed to rt and stirred for 1 h until completion before quenching with $NaHCO_3$ (300 mL) and diluting with CH_2Cl_2 (200 mL). The emulsion was stirred for a further 1 h before being diluted with H_2O (600 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 500 mL). Combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and purified by flash column chromatography (PhMe, then gradient elution: EtOAc/40-60 PE, 1:7 → 1:5) to yield alcohol **9b** (7.27 g, 14.5 mmol, 90%) as a pale yellow oil.

R_f 0.31 (EtOAc/40-60 PE, 1:10); **$[\alpha]_{2c}^{\nu}$** = –11.1 (*c* 1.6, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 3456, 2953, 2912, 2877, 1722, 1703, 1644, 1617, 1458, 1436, 1415, 1303, 1240, 1174, 1139, 1063, 1003, 867, 804, 725; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.29 (1H, dd, J = 15.4, 10.0 Hz, H_3), 6.23 (1H, dd, J = 15.4, 10.0 Hz, H_4), 6.17 (1H, ddd, J = 15.4, 6.9, 6.0 Hz, H_5), 5.83 (1H, d, J = 15.3 Hz, H_2), 3.80-3.76 (2H, m, H_9, H_{11a}), 3.77 (3H, s, $CO_2C\underline{H}_3$), 3.74 (1H, ddd, J = 6.4, 3.7 Hz, H_7), 3.59-3.55 (1H, m, H_{11b}), 2.65 (1H, t, J = 5.1 Hz, O$\underline{H}$), 2.37-2.32 (1H, m, H_{6a}), 2.28 (1H, ddd, J = 14.7, 6.2, 3.9 Hz, H_{6b}), 1.88-1.81 (1H, m, H_8), 1.81-1.75 (1H, m, H_{10}), 1.03 (3H, d, J = 7.1 Hz, Me_{10}), 1.00 (9H, t, J = 7.9 Hz, $SiCH_2C\underline{H}_3$ x 3), 0.98 (9H, t, J = 7.9 Hz, $SiCH_2C\underline{H}_3$ x 3), 0.91 (3H, d, J = 6.9 Hz, Me_8), 0.68 (6H, t, J = 7.9 Hz, $SiC\underline{H}_2CH_3$ x

3), 0.62 (6H, t, J = 7.9 Hz, SiC<u>H</u>$_2$CH$_3$ x 3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 167.7, 144.8, 140.6, 130.5, 119.3, 77.6, 73.4, 65.3, 51.5, 42.5, 39.2, 36.7, 14.7, 11.0, 7.1, 7.0, 5.5, 5.3; **HRMS** calculated for $C_{26}H_{53}O_5Si_2$ $[M+H]^+$ 501.3426, found 501.3418.

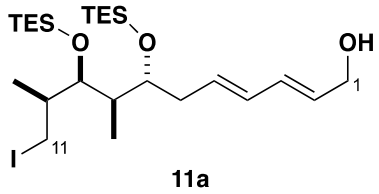
Iodide 11



PPh_3 (4.22 g, 16.1 mmol) and imidazole (1.34 g, 19.6 mmol) were added sequentially to a solution of alcohol **9b** (4.47 g, 8.93 mmol) in Et_2O/MeCN (1:1, 100 mL) at 0 °C, followed by portion-wise addition of I_2 (4.07 g, 16.1 mmol). The reaction mixture was warmed up to rt and stirred for 2 h before being quenched by addition of $NaHCO_3$ solution (100 mL). The mixture was extracted with Et_2O (3 x 100 mL), the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:50 → 1:10) yielded iodide **11** (4.18 g, 6.84 mmol, 77%, 92% BRSM) as a colourless oil.

R_f 0.58 (EtOAc/40-60 PE, 1:10); **$[\alpha]_{20}^{D}$** = –10.0 (*c* 2.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2955, 2911, 2877, 1722, 1645, 1617, 1458, 1434, 1415, 1300, 1264, 1241, 1140, 1102, 1064, 1003, 739, 723; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.27 (1H, dd, J = 15.4, 10.0 Hz, H_3), 6.21 (1H, dd, J = 15.0, 9.9 Hz, H_4), 6.15 (1H, ddd, J = 15.0, 6.9, 6.4 Hz, H_5), 5.81 (1H, d, J = 15.4 Hz, H_2), 3.74 (3H, s, $CO_2C\underline{H}_3$), 3.69 (1H, ddd, J = 6.7, 5.3, 4.1 Hz, H_7), 3.66 (1H, dd, J = 4.2, 3.8 Hz, H_9), 3.29 (1H, dd, J = 9.9, 4.2 Hz, H_{11a}), 2.99 (1H, dd, J = 9.9, 9.0 Hz, H_{11b}), 2.32-2.25 (2H, m, H_6 x 2), 1.86-1.79 (1H, m, H_{10}), 1.72-1.66 (1H, m, H_8), 1.05 (3H, d, J = 6.8 Hz, Me_{10}), 0.96 (9H, t, J = 7.8 Hz, $SiCH_2C\underline{H}_3$ x 3), 0.95 (9H, t, J = 7.8 Hz, $SiCH_2C\underline{H}_3$ x 3), 0.85 (3H, d, J = 6.8 Hz, Me_8), 0.68 (6H, t, J = 7.8 Hz, $SiC\underline{H}_2CH_3$ x 3), 0.59 (6H, t, J = 7.8 Hz, $SiC\underline{H}_2CH_3$ x 3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 167.6, 144.8, 141.0, 130.3, 119.2, 76.1, 73.7, 51.4, 42.1, 41.6, 36.7, 17.7, 11.5, 10.2, 7.0, 6.9, 5.5, 5.2; **HRMS** calculated for $C_{26}H_{52}O_4ISi_2$ $[M+H]^+$ 611.2443, found 611.2435.

Alcohol 11a

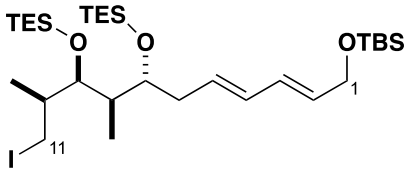


11a

DIBAL (38.7 mL, 1.0 M in hexanes, 38.7 mmol) was added dropwise to a solution of ester **11** (7.87 g, 12.9 mmol) in CH_2Cl_2 (250 mL) at –78 °C and the mixture stirred for 1.5 h. Upon completion, the mixture was quenched by addition of Na^+/K^+ tartrate solution (300 mL) and water (100 mL), then warmed to rt and stirred vigorously for 1.5 h. The phases were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 200 mL). The combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:20 → 1:15) to give alcohol **11a** (7.31 g, 12.5 mmol, 97%) as a colourless oil.

R_f 0.33 (EtOAc/40-60 PE, 1:5); **$[\alpha]_{2D}^{\nu}$** = –10.6 (*c* 0.8, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 3357, 2956, 2909, 2881, 1461, 1415, 1378, 1237, 1140, 1102, 1068, 1009, 993, 741, 727; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 6.23 (1H, dd, *J* = 15.3, 10.7 Hz, H_3), 6.08 (1H, dd, *J* = 15.3, 10.7 Hz, H_4), 5.77-5.69 (2H, m, H_2, H_5), 4.18 (2H, br d, *J* = 4.9 Hz, H_1 x 2), 3.67-3.64 (2H, m, H_7, H_9), 3.32 (1H, dd, *J* = 9.9, 3.7 Hz, H_{11a}), 2.98 (1H, dd, *J* = 9.9, 9.1 Hz, H_{11b}), 2.22-2.20 (2H, m, H_6 x 2), 1.87-1.79 (1H, m, H_{10}), 1.72-1.65 (1H, m, H_8), 1.33 (1H, t, *J* = 5.3 Hz, O<u>H</u>), 1.05 (3H, d, *J* = 6.9 Hz, Me_{10}), 0.96 (18H, t, *J* = 7.8 Hz, $SiCH_2C\underline{H}_3$ x 6), 0.84 (3H, d, *J* = 6.8 Hz, Me_8), 0.63 (6H, q, *J* = 7.8 Hz, $SiC\underline{H}_2CH_3$ x 3), 0.60 (6H, q, *J* = 7.8 Hz, $SiC\underline{H}_2CH_3$ x 3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 132.0, 131.6, 131.4, 129.8, 76.2, 73.9, 63.4, 42.0, 41.6, 36.3, 17.8, 11.8, 10.5, 7.0, 6.9, 5.5, 5.2; **HRMS** calculated for $C_{25}H_{52}O_3ISi_2$ $[M+H]^+$ 583.2494, found 583.2486.

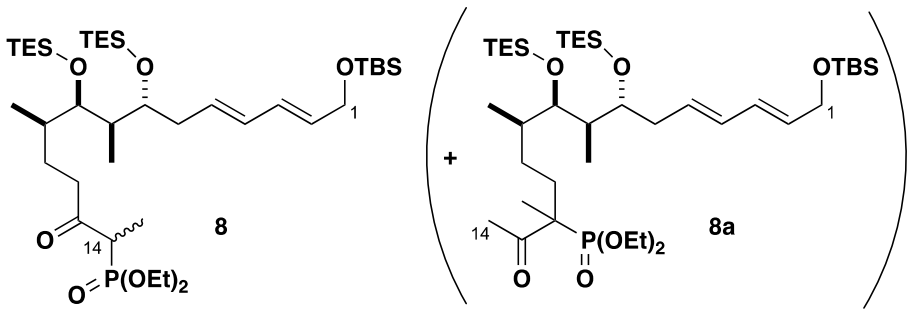
TBS ether 12



Imidazole (1.71 g, 25.1 mmol) and TBSCl (2.84 g, 18.8 mmol) were added sequentially to a solution of alcohol **11a** (7.31 g, 12.5 mmol) in CH_2Cl_2 (250 mL) and the resulting mixture stirred for 30 min until completion. The reaction was quenched with NH_4Cl solution (200 mL), the phases separated and the aqueous layer extracted with CH_2Cl_2 (2 x 200 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the residue purified by flash column chromatography (EtOAc/40-60 PE, 1:50). TBS ether **12** (8.63 g, 12.4 mmol, 99% yield) was obtained as a colourless oil.

R_f 0.72 (40-60 PE); **$[\alpha]_{2(}^{\nu}$** = –6.0 (*c* 1.2, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2952, 2873, 1459, 1413, 1378, 1260, 1255, 1241, 1104, 1062, 1007, 963, 836, 777, 737, 727; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 6.19 (1H, dd, *J* = 15.1, 10.4 Hz, H_3), 6.06 (1H, dd, *J* = 15.1, 10.9 Hz, H_4), 5.69-5.63 (2H, m, H_2, H_5), 4.21 (2H, d, *J* = 5.6 Hz, H_1 x 2), 3.66-3.64 (2H, m, H_7, H_9), 3.32 (1H, dd, *J* = 9.7, 3.7 Hz, H_{11a}), 2.98 (1H, dd, *J* = 9.7, 9.1 Hz, H_{11b}), 2.21-2.18 (2H, m, H_6 x 2), 1.88-1.81 (1H, m, H_{10}), 1.73-1.66 (1H, m, H_8), 1.05 (3H, d, *J* = 6.8 Hz, Me_{10}), 0.96 (18H, t, *J* = 7.8 Hz, $SiCH_2C\underline{H}_3$ x 6), 0.91 (9H, s, $SiC(C\underline{H}_3)_3$), 0.85 (3H, d, *J* = 6.9 Hz, Me_8), 0.62 (6H, q, *J* = 7.8 Hz, $SiC\underline{H}_2CH_3$ x 3), 0.61 (6H, q, *J* = 7.8 Hz, $SiC\underline{H}_2CH_3$ x 3), 0.07 ($SiC\underline{H}_3$ x 2); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 131.7, 131.5 x 2, 130.0, 76.3, 74.0, 63.5, 42.1, 41.5, 36.3, 25.9, 18.3, 17.9, 11.7, 10.5, 7.0, 6.9, 5.5, 5.2, –5.3; **HRMS** calculated for $C_{31}H_{66}O_3ISi_3$ $[M+H]^+$ 697.3359, found 697.3357.

Phosphonate 8



Phosphonate **13** (715 mg, 3.44 mmol) was added to a suspension of NaH (160 mg, 60% dispersion in mineral oil, 4.02 mmol) in THF (10 mL) at 0 °C and stirred at this temperature for 30 min, followed by dropwise addition of ^{n}BuLi (2.15 mL, 1.6 M in hexanes, 3.44 mmol). After stirring for a further 30 min, during which a clear pale yellow solution of the dianion was formed, the mixture was cooled to –10 °C and a solution of iodide **12** (400 mg, 0.574

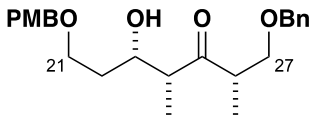
mmol) in THF (5 mL) was added *via* cannula over 10 min. The reaction mixture was stirred for 2 h, gradually developing a bright yellow colour, then quenched by addition of NH_4Cl solution (100 mL) and warmed to rt. The aqueous phase was extracted with EtOAc (3 x 20 mL), dried ($MgSO_4$) and the crude product purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:20 → 1:3). Phosphonate **8** was obtained as an inseparable mixture with the undesired regioisomer **8a** (336 mg, 0.432 mmol, 75%, 88% BRSM) in a 3 : 1 ratio.

R_f 0.23 (EtOAc/40-60 PE, 1:2); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 6.19 (1H, dd, *J* = 15.1, 10.6 Hz, H_3), 6.05 (1H, dd, *J* = 15.1, 10.6 Hz, H_4), 5.72-5.62 (2H, m, H_2, H_5), 4.21 (2H, d, *J* = 5.5 Hz, H_1 x 2), 4.17-4.08 (4H, m, P(OC$\underline{H}_2$CH$_3$) x 2), 3.67-3.57 (1H, m, H_7), 3.55-3.52 (1H, m, H_9), 3.23 (0.80H, dq, *J* = 25.1, 7.2 Hz, H_{14}), 2.88 (0.40H, ddd, *J* = 17.5, 9.9, 4.9 Hz, H_{12a}), 2.77-2.60 (0.80H, m, H_{12a}, H_{12b}), 2.47 (0.40H, ddd, *J* = 17.5, 9.5, 6.1 Hz, H_{12b}), [2.36] (0.75H, s, Me_{14}*), [1.89-1.81] (0.25H, m, H_{11b}*), 1.78-1.63 (2H, m, H_8, H_{11a}, H_{11b}), 1.55-1.48 (1H, m, H_{10}), 1.42-1.31 (10H, m, H_{11a}, H_{11b}, Me_{14}, P(OCH$_2$C$\underline{H}_3$) x 2), 1.00-0.85 (33H, m, Me_8, Me_{10}, Me_{14}*, SiCH$_2$C$\underline{H}_3$ x 6, C(C$\underline{H}_3$)$_3$), [0.72] (0.75H, d, *J* = 6.7 Hz, Me_8*), 0.64-0.55 (12H, m, SiC$\underline{H}_2$CH$_3$ x 6), 0.08 (6H, s, SiC$\underline{H}_3$ x 2); **HRMS** calculated for $C_{39}H_{85}NO_7PSi_3$ $[M+NH_4]^+$ 794.5366, found 794.5362.

Distinguishable resonances of the minor regioisomer are given in brackets and marked with an asterisk. Note that the diastereomeric ratio of **8** at C_{14} is approximately 1:1.

III. Experimental Procedures for C_{21}–C_{27} Aldehyde 14

Aldol adduct 17



Ti(O^{i}Pr)$_4$ (4.10 mL, 13.9 mmol) was added dropwise to a solution of $TiCl_4$ (4.55 mL, 41.4 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The mixture was stirred for 10 min, then warmed to rt and stirred for a further 20 min. The resulting colourless solution was added dropwise to a

solution of ketone **15**[5] (9.51 g, 46.1 mmol) in CH_2Cl_2 (210 mL) at −78 °C and a gradual colour change from colourless through yellow and finally bright orange was observed. The mixture was stirred for 10 min before $^{i}Pr_2NEt$ (8.83 mL, 50.7 mmol) was added dropwise and a colour change to dark red was observed. Aldehyde **16**[6] (12.1 g, 62.1 mmol) in CH_2Cl_2 (210 mL) was then added dropwise *via* syringe over 30 min. The mixture was stirred at −78 °C for a further 16 h before being quenched with MeOH (2 mL), warmed to rt and Na^+/K^+ tartrate solution (25 mL) added. The biphasic mixture was stirred at rt for a further 2 h before extracting with CH_2Cl_2 (3 x 250 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*.

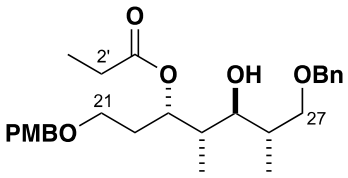
The crude product was dissolved in ^{t}BuOH/2-Me-but-2-ene (10:1, 88 mL) at 0 °C. A solution of $NaClO_2$ (4.65 g, 51.5 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (16.2 g, 103 mmol) in H_2O (80 mL) was added portion-wise and a colour change to bright yellow was observed. The mixture was warmed to rt and stirred for 64 h during which the colour had dissipated. The reaction was diluted with brine (100 mL), extracted with Et_2O (6 x 100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:8 → 1:4) to yield aldol adduct **17** (15.1 g, 37.7 mmol, 82%, 12:1 *dr*) as a colourless oil.

R_f 0.29 (EtOAc/40-60 PE, 1:3); $[\alpha]_{20}^{D}$ = −2.9 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 3495, 2935, 2861, 1709, 1613, 1513, 1455, 1363, 1302, 1247, 1174, 1094, 1032, 821, 739, 699; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.35-7.22 (7H, m, PhH, ArH), 6.87 (2H, d, *J* = 8.7 Hz, ArH), 4.48 (1H, d, *J* = 11.8 Hz, $ArCH_aH_bO$), 4.43 (1H, d, *J* = 11.8 Hz, $ArCH_aH_bO$), 4.42 (2H, s, $PhCH_2O$), 4.19-4.15 (1H, m, H_{23}) 3.80 (3H, s, $ArOCH_3$), 3.66 (1H, dd, *J* = 8.8 Hz, H_{21a}), 3.59-3.52 (2H, m, H_{27} × 2), 3.45 (1H, dd, *J* = 8.8, 5.0 Hz, H_{21b}), 3.21 (1H, d, *J* = 3.2 Hz, OH), 3.17 (1H, qdd, *J* = 7.0, 1.9, 1.7 Hz, H_{26}), 2.77 (1H, qd, *J* = 6.9, 4.0 Hz, H_{24}), 1.78-1.61 (2H, m, H_{22} × 2), 1.11 (3H, d, *J* = 7.0 Hz, Me_{26}), 1.03 (3H, d, *J* = 7.0 Hz, Me_{24}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 217.2, 159.2, 137.8, 130.3, 129.3, 128.5, 127.8, 127.7, 113.8, 73.4, 73.0, 72.8, 69.7, 68.0, 55.3, 51.3, 45.2, 33.8, 13.7, 10.2; **HRMS** calculated for $C_{24}H_{36}NO_5$ $[M+NH_4]^+$ 418.2588, found 418.2588.

[5] I. Paterson R.D. Norcross, R.A. Ward, P. Romea and M.A. Lister *J. Am. Chem. Soc.* 1994, **1169**, 11287

[6] F. Arikan, J. Li and D. Menche *Org. Lett.* 2008, **10**, 3521

Propionate 17a

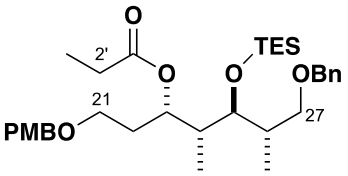


17a

Freshly prepared SmI_2 (25.6 mL, 0.1 M in THF, 2.56 mmol) was added dropwise to a solution of propionaldehyde (8.36 mL, 116 mmol) in THF (200 mL) at 0 °C. The mixture was stirred for 5 minutes until the dark blue colour turned yellow and cooled to −20 °C. A solution of aldol adduct **17** (10.2 g, 25.6 mmol) in THF (70 mL) was added *via* cannula and the green/yellow reaction mixture was stirred at −20 °C for 16 h. The reaction was then warmed up to −10 °C and stirred for a further 65 h before quenching with $NaHCO_3$ solution (200 mL) and warming to rt. The mixture was extracted with EtOAc (3 × 150 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:12 → 1:8) to afford propionate **17a** (11.0 g, 23.9 mmol, 93%, >20:1 *dr*) as a colourless oil.

R_f 0.66 (EtOAc/40-60 PE, 1:2); **$[\alpha]_{2C}^{\nu}$** = −13.2 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 3513, 2930, 2859, 1712, 1612, 1513, 1455, 1363, 1247, 1201, 1083, 1034, 1002, 820, 737, 698; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.36-7.26 (5H, m, PhH), 7.25 (2H, d, *J* = 8.7 Hz, ArH), 6.87 (2H, d, *J* = 8.7 Hz, ArH), 5.46 (1H, ddd, *J* = 9.3, 4.0, 1.7 Hz, H_{23}), 4.48 (2H, s, $PhCH_2O$), 4.40 (2H, ABq, *J* = 11.5 Hz, $ArCH_2O$), 3.80 (3H, s, $ArOCH_3$), 3.58 (1H, dd, *J* = 9.2, 5.2 Hz, H_{27a}), 3.49-3.42 (3H, m, H_{27b}, H_{21} × 2), 3.39 (1H, d, *J* = 5.7 Hz, OH), 3.12 (1H, ddd, *J* = 9.1, 5.7, 3.4 Hz, H_{25}), 2.30 (1H, dq, *J* = 15.9, 7.8 Hz, $H_{2a'}$), 2.29 (1H, dq, *J* = 15.9, 7.5 Hz, $H_{2b'}$), 2.10-1.96 (2H, m, H_{26}, H_{22a}), 1.85-1.72 (2H, m, H_{24}, H_{22b}), 1.12 (2H, t, *J* = 7.6 Hz, $H_{3'}$ × 3), 1.08 (3H, d, *J* = 7.1 Hz, Me_{26}), 0.90 (3H, d, *J* = 7.0 Hz, Me_{24}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 175.2, 159.2, 138.4, 130.4, 129.3, 128.4, 127.6, 127.5, 113.8, 76.3, 73.3, 72.8, 72.1, 71.2, 67.0, 55.3, 40.8, 34.8, 33.2, 27.8, 16.4, 10.3, 9.3; **HRMS** calculated for $C_{27}H_{39}O_6$ $[M+H]^+$ 459.2741, found 459.2738.

TES ether 17b

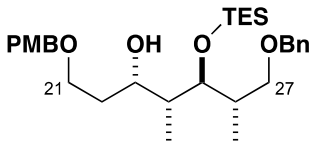


17b

TESOTf (6.48 mL, 28.7 mmol) was added dropwise to a solution of alcohol **17a** (11.0 g, 23.9 mmol) and 2,6-lutidine (5.53 mL, 47.8 mmol) in CH_2Cl_2 (500 mL) at −78 °C. The reaction mixture was stirred for 2 h, then quenched by the addition of $NaHCO_3$ solution (300 mL) and warmed to rt. The phases were separated and the organic layer was extracted with CH_2Cl_2 (2 x 300 mL). The combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:50 → 1:15) to afford TES ether **17b** (13.2 g, 22.9 mmol, 96%) as a colourless oil.

R_f 0.59 (EtOAc/40-60 PE, 1:5); **$[\alpha]_{2c}^{\nu}$** = −14.0 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2956, 2873, 1728, 1609, 1510, 1459, 1362, 1302, 1251, 1189, 1096, 1038, 1005, 820, 737, 700; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.38-7.34 (4H, m, PhH), 7.31-7.29 (1H, m, PhH), 7.28 (2H, d, *J* = 8.8 Hz, ArH), 6.89 (2H, d, *J* = 8.8 Hz, ArH), 5.22 (1H, ddd, *J* = 7.6, 5.5, 3.1, H_{23}), 4.50 (2H, s, PhCH_2O), 4.43 (1H, d, *J* = 11.3 Hz, ArCH_aH_bO), 4.40 (1H, d, *J* = 11.3 Hz, ArCH_aH_bO), 3.82 (3H, s, ArOCH_3), 3.59 (1H, dd, *J* = 9.3, 4.6 Hz, H_{27a}), 3.57 (1H, dd, *J* = 7.0, 3.9 Hz, H_{25}), 3.51-3.44 (2H, m, H_{21} × 2), 3.33 (1H, dd, *J* = 9.2, 7.9 Hz, H_{27b}), 2.30 (2H, q, *J* = 7.5 Hz, $H_{2'}$ x 2), 2.12-2.07 (1H, m, H_{26}), 2.00-1.93 (1H, m, H_{22a}), 1.90-1.83 (2H, m, H_{22b}, H_{24}), 1.14 (3H, t, *J* = 7.5 Hz, $H_{3'}$ x 3), 1.05 (3H, d, *J* = 7.1 Hz, Me_{26}), 0.96 (9H, t, *J* = 8.0 Hz, SiCH_2CH_3 x 3), 0.96 (3H, d, *J* = 7.0 Hz, Me_{24}), 0.63 (6H, q, *J* = 8.0 Hz, SiCH_2CH_3 x 3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 174.0, 159.1, 138.8, 130.5, 129.3, 128.3, 127.5, 127.4, 113.7, 76.9, 73.0, 72.7, 72.1, 71.9 67.2, 55.3, 41.1, 36.9, 33.5, 27.9, 15.9, 11.1, 9.2, 7.1, 5.4; **HRMS** calculated for $C_{33}H_{53}O_6Si$ $[M+H]^+$ 573.3606, found 573.3609.

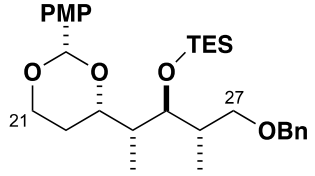
Alcohol 18



DIBAL (29.8 mL, 1.0 M in hexanes, 29.8 mmol) was added dropwise to a solution of TES ether **17b** (13.2 g, 22.9 mmol) in CH_2Cl_2 (350 mL) at –78 °C and the mixture was stirred at this temperature for 2 h. An additional portion of DIBAL (4.58 mL, 4.58 mmol) was added and the reaction stirred for a further 30 min. Upon completion, the mixture was quenched by the addition of Na^+/K^+ tartrate solution (500 mL), warmed to rt and stirred vigorously for 16 h. The layers were separated and the aqueous phase extracted with EtOAc (5 x 200 mL). Combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give alcohol **18** (11.8 g, 22.9 mmol, 99%) as a colourless oil which was used without further purification.

R_f 0.50 (EtOAc/40-60 PE, 1:4); **$[\alpha]_{2c}^{\nu}$** = −10.7 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2952, 2881, 1617, 1514, 1455, 1413, 1368, 1300, 1247, 1169, 1094, 1037, 1001, 819, 737, 696; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.39-7.34 (4H, m, PhH), 7.32-7.29 (1H, m, PhH), 7.27 (2H, d, *J* = 8.6 Hz, ArH), 6.89 (2H, d, *J* = 8.6 Hz, ArH), 4.54 (1H, d, *J* = 12.0 Hz, $ArCH_aH_bO$), 4.48 (1H, d, *J* = 12.0 Hz, $ArCH_aH_bO$), 4.46 (1H, d, *J* = 11.5 Hz, $PhCH_aH_bO$), 4.44 (1H, d, *J* = 11.5 Hz, $PhCH_aH_bO$), 4.22 (1H, dd, *J* = 8.9, 3.9, H_{23}), 3.82 (3H, s, $ArOCH_3$), 3.76 (1H, dd, *J* = 7.4, 3.2 Hz, H_{25}), 3.59 (2H, t, *J* = 6.4 Hz, H_{21} x 2), 3.52 (1H, dd, *J* = 9.0, 4.4 Hz, H_{27a}), 3.41 (1H, dd, *J* = 8.8, 6.4 Hz, H_{27b}), 2.12 (1H, ddd, *J* = 11.5, 6.8, 4.7 Hz, H_{26}), 1.91-1.84 (1H, m, H_{22a}), 1.70-1.64 (1H, m, H_{24}), 1.61-1.55 (1H, m, H_{22b}), 1.02 (3H, d, *J* = 7.0 Hz, Me_{24}), 1.00 (3H, d, *J* = 7.0 Hz, Me_{26}), 0.97 (9H, t, *J* = 8.0 Hz, $SiCH_2CH_3$ x 3), 0.66 (6H, q, *J* = 7.8 Hz, $SiCH_2CH_3$ x 3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.1, 138.6, 130.6, 129.3, 128.3, 127.6, 127.5, 113.8, 80.1, 73.1, 72.8, 72.6, 68.5, 68.0, 55.3, 38.1, 38.1, 35.1, 14.8, 11.6, 7.0, 5.3; **HRMS** calculated for $C_{30}H_{49}O_5Si$ $[M+H]^+$ 517.3344, found 517.3333.

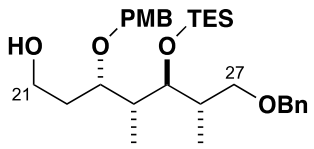
PMP acetal 18a



DDQ (7.80 g, 34.3 mmol) was added in one portion to a stirred slurry of alcohol **18** (11.8 g, 22.9 mmol) and activated 4 Å molecular sieves (~20 g) in CH_2Cl_2 (500 mL) at 0 °C. The resulting dark blue mixture was stirred at this temperature for 30 min before being warmed to rt and stirred for a further 1.5 h during which the colour had gradually changed to brown. The mixture was filtered through a plug of Celite® onto $NaHCO_3$ solution (300 mL) and rinsed with CH_2Cl_2 (200 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 300 mL), the combined organic extracts were dried ($MgSO_4$) and the crude product was purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:30 → 1:20) to afford PMP acetal **18a** (9.54 g, 18.5 mmol, 81%) as a colourless oil.

R_f 0.69 (EtOAc/40-60 PE, 1:4); **$[\alpha]_{2\text{D}}^{\nu}$** = +19.6 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2957, 2876, 1616, 1518, 1456, 1393, 1302, 1249, 1171, 1093, 1038, 1011, 827, 735, 698; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.40 (2H, d, *J* = 8.6 Hz, ArH), 7.35-7.27 (5H, m, PhH), 6.88 (2H, d, *J* = 8.6 Hz, ArH), 5.46 (1H, s, $ArCHO_2$), 4.51 (1H, d, *J* = 12.4 Hz, $PhCH_aH_bO$), 4.47 (1H, d, *J* = 12.4 Hz, $PhCH_aH_bO$), 4.27 (1H, dd, *J* = 11.2, 4.7, Hz, H_{21a}), 4.10-4.07 (1H, m, H_{23}), 3.94 (1H, br t, *J* = 11.2 Hz, H_{21b}), 3.80 (3H, s, $ArOCH_3$), 3.72 (1H, dd, *J* = 10.3, 8.3 Hz, H_{25}), 3.64 (1H, dd, *J* = 9.2, 4.9 Hz, H_{27a}), 3.29 (1H, dd, *J* = 9.2 Hz, H_{27b}), 2.13-1.98 (2H, m, H_{22a}, H_{26}), 1.73-1.66 (1H, m, H_{24}), 1.31-1.27 (1H, m, H_{22b}), 1.05 (3H, d, *J* = 7.0 Hz, Me_{26}), 0.99 (3H, d, *J* = 7.0 Hz, Me_{24}), 0.94 (9H, t, *J* = 7.8 Hz, $SiCH_2CH_3$ x 3), 0.63 (6H, q, *J* = 7.8 Hz, $SiCH_2CH_3$ x 3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.8, 138.9, 131.8, 128.3, 127.5, 127.4, 127.3, 113.5, 101.0, 76.6, 76.2, 73.0, 71.8, 67.3, 55.3, 42.7, 36.5, 29.2, 16.3, 11.0, 7.2, 5.6; **HRMS** calculated for $C_{30}H_{47}O_5Si$ $[M+H]^+$ 515.3187, found 515.3182.

Alcohol 18b

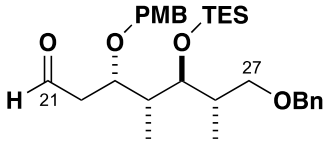


DIBAL (12.2 mL, 1.0 M in hexanes, 12.2 mmol) was added dropwise over 30 min to a solution of PMP acetal **18a** (2.11 g, 4.10 mmol) in CH_2Cl_2 (40 mL) at −78 °C and stirred at this temperature for 1 h. The reaction mixture was warmed to −30 °C for 1 h, during which a yellow colour gradually appeared. The solution was allowed to warm to 0 °C and stirred for a further 1 h before quenching with Na^+/K^+ tartrate solution (100 mL). The biphasic mixture

was stirred vigorously for 16 h, then extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (gradient elution: PhMe/CH_2Cl_2, 1:1 → 0:1, then EtOAc/40-60 PE, 1:4) to give alcohol **18b** (1.67 g, 3.23 mmol, 79%) as a colourless oil.

R_f 0.15 (EtOAc/40-60 PE, 1:5); **$[\alpha]_{2\text{C}}^{\nu}$** = −12.6 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 3428, 2955, 2876, 1613, 1514, 1455, 1413, 1301, 1247, 1173, 1039, 1011, 821, 735, 698; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.35-7.33 (4H, m, PhH), 7.31-7.28 (1H, m, PhH), 7.26 (2H, d, *J* = 8.7 Hz, ArH), 6.87 (2H, d, *J* = 8.7 Hz, ArH), 4.51 (2H, s, $PhCH_2O$), 4.49 (2H, s, $ArCH_2O$), 3.80 (3H, s, $ArOCH_3$), 3.79-3.69 (4H, m, H_{21} x 2, H_{23}, H_{25}), 3.62 (1H, dd, *J* = 9.2, 4.6 Hz, H_{27a}), 3.30 (1H, dd, *J* = 9.2, 8.0 Hz, H_{27b}), 2.11-2.01 (2H, m, H_{26}, OH), 1.90-1.76 (3H, m, H_{22} x 2, H_{24}), 1.03 (3H, d, *J* = 7.0 Hz, Me_{26}), 1.00 (3H, d, *J* = 7.2 Hz, Me_{24}), 0.95 (9H, t, *J* = 7.9 Hz, $SiCH_2CH_3$ x 3), 0.62 (6H, q, *J* = 7.9 Hz, $SiCH_2CH_3$ x 3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.0, 138.7, 130.8, 129.1, 128.2, 127.4, 127.3, 113.7, 78.2, 77.1, 73.0, 72.3, 71.8, 60.7, 55.2, 42.2, 37.1, 35.5, 15.9, 11.7, 7.0, 5.4; **HRMS** calculated for $C_{30}H_{49}O_5Si$ $[M+H]^+$ 517.3344, found 517.3335.

Aldehyde 14



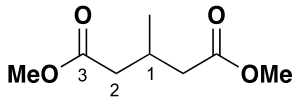
Dess–Martin periodinane (6.16 g, 14.5 mmol) was added portion-wise to a stirred slurry of alcohol **18b** (5.00 g, 9.68 mmol) and $NaHCO_3$ (2.44 g, 29.0 mmol) in CH_2Cl_2 (150 ml) at 0 °C. The reaction mixture was stirred at this temperature for 1 h, then warmed to rt and stirred for a further 75 min until complete. The suspension was quenched with $Na_2S_2O_3$ solution (300 mL) and stirred for 45 min before extracting with CH_2Cl_2 (2 x 200 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 0:1 → 1:5) to afford aldehyde **14** (4.57 g, 8.88 mmol, 92%) as a colourless oil.

R_f 0.49 (EtOAc/40-60 PE, 1:5); **$[\alpha]_{2\text{C}}^{\nu}$** = −5.2 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2956, 2876, 1725, 1613, 1514, 1455, 1302, 1248, 1173, 1087, 1039, 1011, 821, 736, 698; **^{1}H NMR**

(400 MHz, $CDCl_3$): δ_H 9.79 (1H, br t, *J* = 2.2 Hz, C<u>H</u>O), 7.35-7.32 (4H, m, Ph<u>H</u>), 7.30-7.27 (1H, m, Ph<u>H</u>), 7.23 (2H, d, *J* = 8.6 Hz, Ar<u>H</u>), 6.87 (2H, d, *J* = 8.6 Hz, Ar<u>H</u>), 4.49 (2H, s, ArC<u>H</u>$_2$O), 4.46 (2H, s, PhC<u>H</u>$_2$O), 4.23-4.19 (1H, m, H_{23}), 3.80 (3H, s, $ArOCH_3$), 3.75 (1H, dd, *J* = 6.7, 3.8 Hz, H_{25}), 3.59 (1H, dd, *J* = 9.2, 4.9 Hz, H_{27a}), 3.30 (1H, dd, *J* = 9.2, 7.8 Hz, H_{27b}), 2.78 (1H, ddd, *J* = 16.4, 6.9, 2.4 Hz, H_{22a}), 2.61 (1H, ddd, *J* = 16.4, 5.0, 1.9 Hz, H_{22b}), 2.12-2.06 (1H, m, H_{26}), 1.78 (1H, qdd, *J* = 7.0, 4.3, 3.7 Hz, H_{24}), 1.04 (3H, d, *J* = 6.9 Hz, Me_{26}), 0.99-0.94 (12H, m, Me_{24}, $SiCH_2C\underline{H}_3$ x 3), 0.64 (6H, q, *J* = 7.9 Hz, $SiC\underline{H}_2CH_3$ x 3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 201.1, 158.7, 138.4, 130.3, 128.6, 127.9, 127.1, 127.0, 113.4, 76.8, 74.0, 72.7, 71.7, 71.2, 54.9, 47.8, 42.3, 36.9, 15.4, 11.5, 6.8, 5.2; **HRMS** calculated for $C_{30}H_{47}O_5Si$ $[M+H]^+$ 515.3187, found 515.3180.

IV. Experimental Procedures for C_{15}–C_{20} Phosphonate 19

Dimethyl 3-methylglutarate 20



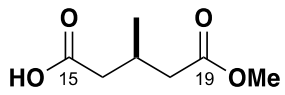
Acetyl chloride (29.3 mL, 411 mmol) was added dropwise to a solution of 3-methylglutaric acid (15.0 g, 103 mmol) in MeOH (200 mL) at 0 °C. The mixture was heated at reflux for 16 h, then cooled to rt. The solvent was removed under reduced pressure and the residue was neutralised by careful addition of $NaHCO_3$ solution (200 mL). Once gas evolution had ceased, the residue was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford diester **20** (15.9 g, 90.7 mmol, 89% yield) as a yellow oil, which was used without further purification.

R_f 0.61 (EtOAc/40-60 PE, 1:2); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 3.68 (6H, s, $OC\underline{H}_3$ x 2), 2.52-2.42 (1H, m, H_1), 2.40 (2H, dd, *J* = 15.0, 6.0 Hz, H_{2a} × 2), 2.25 (2H, dd, *J* = 15.0, 7.3 Hz, H_{2b} × 2), 1.03 (3H, d, *J* = 6.5 Hz, Me_{17}).

Data in agreement with B. Jones.[7]

[7] P. Lam, R.A.H.F. Hui and B. Jones *J. Org. Chem.* 1986, **51**, 2047

(*R*)-Methyl-3-methylglutarate 21



Dimethyl 3-methylglutarate **20** (17.8 g, 102 mmol) was dissolved in KH_2PO_4/Na_2PO_4 buffer solution (480 mL, 0.1 M, pH 7) and MeOH (120 mL). The solution was cooled to −10 °C and pig liver esterase (370 mg, 6660 U) was added. Aqueous NaOH (1.0 M, 102 mL, 102 mmol) was added dropwise at such a rate as to maintain the pH between 6.0 and 7.5. After 10 hours the addition was complete, the light brown suspension was filtered through a pad of Celite® and the residue was rinsed with H_2O (200 mL). The pH of the combined filtrates was adjusted to 3 with aqueous HCl (3 M) and the mixture extracted with Et_2O (8 × 400 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to give monoester **21** (15.9 g, 99.0 mmol, 97%) as a colourless liquid.

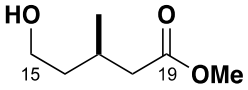
(–)-Cinchonidine (29.1 g, 99.0 mmol) was added to a solution of enantioenrichened monoester **21** in acetone (280 mL). The white suspension was heated to 40 °C. H_2O (35 mL) was added dropwise to the rapidly stirring mixture until a clear pale yellow solution formed. The solution was cooled to rt, then left to stand at −5 °C for 16 h to give off-white, needle-like crystals. The solid was collected by filtration, washed with ice-cold acetone (50 mL) and dried *in vacuo*. An additional crop of product was obtained from the mother liquor by leaving it to stand at −10 °C for 16 h, filtering and washing the solids with acetone (20 mL). The combined collected solids were dissolved in aqueous HCl (2 M, 200 mL), then extracted with Et_2O (5 × 200 mL). The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to yield monoester **21** as a colourless oil (9.90 g, 61.8 mmol, 62%, 96% *ee*).

GC analysis was performed using a 6890N Network GC system (Agilent Technologies Inc., Palo Alto, CA, USA), equipped with a Varian CP7502, CHIRASIL DEX CB (25.0 m x 250 μm x 0.25 μL nominal) capillary column. The GC analyses were carried out in split mode (ratio 50:1) using helium as a carrier gas at a flow rate of 134 mL min^{-1} 25.00 psi. The injection port temperature was 250 °C and the oven was maintained at 97 °C. The FID detector was at 250 °C, using H_2 flow at 40.00 mL min^{-1}, air at 450 mL min^{-1} and helium makeup flow at 45.0 mL min^{-1}. R_T (R) 165.6 min, R_T (*S*) 172.0 min, total run time 240 min.

R_f 0.24 (EtOAc/40-60 PE, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 3.70 (3H, s, OC$\underline{H}_3$), 2.53-2.42 (3H, m, H_{16a}, H_{17}, H_{18a}), 2.35-2.27 (2H, m, H_{16b}, H_{18b}), 1.08 (3H, d, J = 6.5 Hz, Me_{17}).

The data is in accordance with that reported by A. Fürstner.[8]

Alcohol 21a

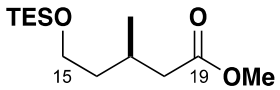


Borane–dimethylsulfide complex (3.41 mL, 35.9 mmol) was added dropwise to a solution of (*R*)-methyl-3-methylglutarate **21** (4.79 g, 29.9 mmol) in THF (200 mL) at 0 °C. The solution was stirred at 0 °C for 1 h, then warmed to rt and stirred for a further 2 h. Upon completion, the reaction mixture was cooled to 0 °C and quenched by the dropwise addition of $NaHCO_3$ solution (10 mL). The mixture was diluted with H_2O (50 mL) and extracted with Et_2O (6 x 200 mL). The combined organic phases were dried (Na_2SO_4), concentrated *in vacuo* and the residue was purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:4 → 1:1). Alcohol **21a** (4.28 g, 29.3 mmol, 98%) was obtained as a colourless oil.

R_f 0.31 (EtOAc/40-60 PE, 1:3); **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 3.70-3.65 (2H, obs m, H_{15} x 2), 3.68 (3H, s, OC$\underline{H}_3$), 2.35 (1H, dd, J = 14.9, 6.5 Hz, H_{18a}), 2.21 (1H, dd, J = 14.9, 7.1 Hz, H_{18b}), 2.20-2.11 (1H, m, H_{17}), 1.66 (1H, br s, O$\underline{H}$), 1.63-1.47 (2H, m, H_{16} x 2), 0.99 (3H, d, J = 6.6 Hz, Me_{17}).

The data is in accordance with that reported by C. Tamm.[9]

TES ether 21b



TESCl (2.45 mL, 14.6 mmol) was added dropwise to a solution of alcohol **21a** (1.78 g, 12.2 mmol) and imidazole (1.24 g, 18.2 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The reaction mixture

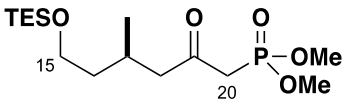
[8] K. Lehr, R. Mariz, L. Lesseure, B. Gabor and A. Fürstner *Angew. Chem. Int. Ed.* 2011, **50**, 11373
[9] P. Herold, P. Mohr and C. Tamm *Helv. Chim. Acta* 1983, **66**, 744

was warmed to rt and stirred for 1 h before being cooled to 0 °C, then quenched by addition of $NaHCO_3$ solution (100 mL). The mixture was warmed to rt and diluted with H_2O (50 mL). The phases were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:50 → 1:20) yielded ester **21b** (2.99 g, 11.5 mmol, 94%) as a colourless oil.

R_f 0.76 (EtOAc/40-60 PE, 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 3.70-3.64 (2H, m, H_{15} × 2), 3.69 (3H, s, $OC\underline{H}_3$), 2.38 (1H, dd, J = 14.1, 5.2 Hz, H_{18a}), 2.17-2.09 (1H, m, H_{17}), 2.16 (1H, dd, J = 14.1, 8.2 Hz, H_{18b}), 1.64-1.57 (1H, m, H_{16a}), 1.50-1.43 (1H, m, H_{16b}), 0.98 (9H, t, J = 8.0 Hz, $SiCH_2C\underline{H}_3$ x 3), 0.98 (3H, d, J = 6.5 Hz, Me_{17}), 0.62 (6H, q, J = 8.0 Hz, $SiC\underline{H}_2CH_3$ x 3).

The data is in accordance with that reported by C.-S. Lee.[10]

Phosphonate 19



^{n}BuLi (58.4 mL, 1.6 M in hexanes, 93.4 mmol) was added to a solution of dimethyl methylphosphonate (13.9 g, 112 mmol) in THF (350 mL) at −78 °C and the mixture was stirred for 45 min. A solution of ester **21b** (9.72 g, 37.3 mmol) in THF (50 mL) was added *via* cannula and the reaction mixture was stirred for 2.5 h. Upon completion, the mixture was quenched with NH_4Cl solution (200 mL), warmed to rt and diluted with water (200 mL). The aqueous phase was extracted with EtOAc (4 x 300 mL), the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:4 → 3:1) to yield phosphonate **19** (12.4 g, 35.1 mmol, 94%) as a colourless oil.

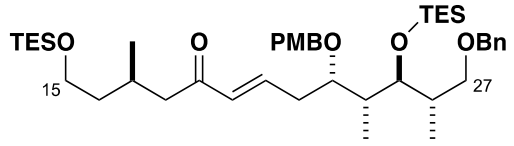
R_f 0.31 (EtOAc/40-60 PE, 1:1); **$[\alpha]_{2C}^{\nu}$** = +4.5 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2956, 2873, 1713, 1457, 1261, 1185, 1088, 1033, 807, 741; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 3.76

[10] X. Liu and C.-S. Lee *Org. Lett.* 2012, **14**, 2886

(6H, d, J = 11.2 Hz, P(OC<u>H</u>$_3$)$_2$), 3.64-3.56 (2H, m, H$_{15}$ x 2), 3.06 (1H, dd, J = 18.2, 13.6 Hz, H$_{20a}$), 3.02 (1H, dd, J = 18.2, 13.6 Hz, H$_{20b}$), 2.60 (1H, dd, J = 17.0, 5.4 Hz, H$_{18a}$), 2.44 (1H, dd, J = 17.0, 8.0 Hz, H$_{18b}$), 2.18-2.09 (1H, m, H$_{17}$), 1.54-1.47 (1H, m, H$_{16a}$), 1.41-1.34 (1H, m, H$_{16b}$), 0.93-0.89 (12H, Me$_{17}$, SiCH$_2$C<u>H</u>$_3$ x 3), 0.55 (6H, q, J = 8.1 Hz , SiC<u>H</u>$_2$CH$_3$ x 3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 201.4, 77.3, 60.6, 51.4, 41.0, 39.3, 25.9, 19.7, 6.7, 4.3; **HRMS** calculated for $C_{15}H_{34}O_5PSi_3$ $[M+H]^+$ 353.1908, found 353.1910.

V. Experimental Procedures for C_{15}–C_{27} Aldehyde 7

Enone 22

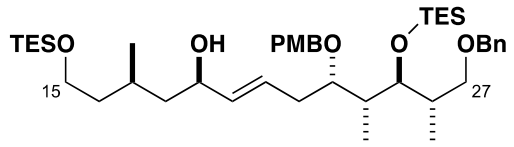


A solution of phosphonate **19** (7.26 g, 20.6 mmol) in THF (80 mL) was added to a suspension of anhydrous Ba(OH)$_2$ (see p. 3) (4.71 g, 27.4 mmol) in THF (60 mL) and the mixture stirred at rt for 1 h. A solution of aldehyde **14** (10.1 g, 19.6 mmol) in THF/H$_2$O (40:1, 120 mL) was added *via* cannula and the reaction stirred for 16 h. Upon completion, the mixture was quenched with NH$_4$Cl (200 mL) and diluted with H$_2$O (150 mL). The aqueous phase was extracted with EtOAc (3 x 300 mL), dried (MgSO$_4$) and concentrated *in vacuo*. The crude material was purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:30 → 1:20) to yield enone **22** (12.2 g, 16.5 mmol, 85%, > 20:1 *E*/*Z*) as a colourless oil.

R$_f$ 0.54 (EtOAc/40-60 PE, 1:10); $[\alpha]_{20}^{D}$ = −14.4 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2948, 2913, 2877, 1669, 1613, 1514, 1457, 1415, 1376, 1298, 1243, 1169, 1092, 1041, 1009, 973, 822, 737, 694; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.38-7.34 (4H, m, Ph<u>H</u>), 7.32-7.28 (1H, m, Ph<u>H</u>), 7.26 (2H, d, J = 8.5 Hz, Ar<u>H</u>), 6.88 (2H, d, J = 8.5 Hz, Ar<u>H</u>), 6.82 (1H, dt, J = 15.8, 7.3 Hz, H$_{21}$), 6.17 (1H, d, J = 15.8 Hz, H$_{20}$), 4.53 (1H, d, J = 11.1 Hz, ArC<u>H</u>$_a$H$_b$O), 4.50 (2H, ABq, J = 12.2 Hz, PhC<u>H</u>$_2$O), 4.44 (1H, d, J = 11.1 Hz, ArCH$_a$<u>H</u>$_b$O), 3.82 (3H, s, ArOC<u>H</u>$_3$), 3.78-3.71 (2H, m, H$_{23}$, H$_{25}$), 3.70-3.61 (3H, m, H$_{15}$ x 2, H$_{27a}$), 3.31 (1H, dd, J = 8.6 Hz, H$_{27b}$), 2.60-2.51 (2H, m, H$_{18a}$, H$_{22a}$), 2.49-2.44 (1H, m, H$_{22b}$), 2.36 (1H, dd, J = 15.4, 8.5 Hz, H$_{18b}$), 2.22-2.16 (1H, m, H$_{17}$), 2.11-2.05 (1H, m, H$_{26}$) 1.79-1.72 (1H, m, H$_{24}$), 1.62-1.56 (1H, m, H$_{16a}$), 1.49-1.42 (1H, m, H$_{16b}$), 1.05 (3H, d, J = 7.0 Hz, Me$_{26}$), 1.00-0.93 (24H, m, Me$_{17}$, Me$_{24}$,

SiCH$_2$C<u>H</u>$_3$ x 6), 0.66-0.60 (12H, m, SiC<u>H</u>$_2$CH$_3$ x 6); **^{13}C NMR** (125 MHz, CDCl$_3$): δ_C 199.9, 159.1, 143.7, 138.8, 132.5, 130.9, 128.9, 128.3, 127.5, 127.4, 113.8, 78.3, 77.1, 73.0, 72.2, 71.5, 60.9, 55.3, 47.6, 42.1, 39.9, 37.0, 36.0, 26.7, 20.0, 16.1, 11.1, 7.2, 6.8, 5.6, 4.4; **HRMS** calculated for $C_{43}H_{73}O_6Si_2$ $[M+H]^+$ 741.4940, found 741.4935.

Allylic alcohol 22a

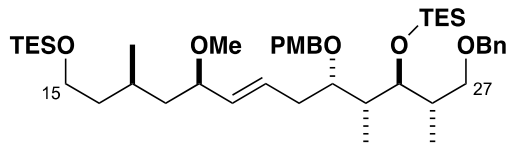


(*S*)-Me-CBS catalyst (673 μL, 1.0 M in PhMe, 0.673 mmol) was added to a solution of enone **22** (4.99 g, 6.73 mmol) in THF (100 mL) at –20 °C and stirred for 10 min. Borane–dimethylsulfide complex (761 μL, 15.4 mmol) was added dropwise, the reaction warmed to –10 °C and stirred for 1.5 h before being carefully quenched with MeOH (20 mL). The mixture was warmed to rt and stirred for a further 15 min before concentrating *in vacuo*. The residue was redissolved in MeOH (20 mL), then concentrated *in vacuo* and the procedure repeated three times. Purification by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:30 → 1:10) afforded allylic alcohol **22a** (4.97 g, 6.69 mmol, 99%, 13:1 *dr*) as a colourless oil.

R$_f$ 0.44 (EtOAc/40-60 PE, 1:5); **$[\alpha]_{20}^{D}$** = −5.2 (*c* 1.0, CHCl$_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2956, 2869, 1616, 1518, 1454, 1378, 1301, 1244, 1171, 1082, 1033, 996, 963, 820, 808, 729, 696; **^{1}H NMR** (500 MHz, CDCl$_3$): δ_H 7.34-7.35 (4H, m, Ph<u>H</u>), 7.32-7.28 (1H, m, Ph<u>H</u>), 7.27 (2H, d, *J* = 8.4 Hz, Ar<u>H</u>), 6.88 (2H, d, *J* = 8.4 Hz, Ar<u>H</u>), 5.64 (1H, ddd, *J* = 15.2, 8.0, 7.0 Hz, H$_{21}$), 5.54 (1H, dd, *J* = 15.2, 6.8 Hz, H$_{20}$), 4.57 (1H, d, *J* = 11.1 Hz, ArC<u>H</u>$_a$H$_b$O), 4.52 (1H, d, *J* = 12.2 Hz, PhC<u>H</u>$_a$H$_b$O), 4.49 (1H, d, *J* = 12.2 Hz, PhCH$_a$<u>H</u>$_b$O), 4.41 (1H, d, *J* = 11.1 Hz, ArCH$_a$<u>H</u>$_b$O), 4.21-4.14 (1H, m, H$_{19}$) 3.82 (3H, s, ArOC<u>H</u>$_3$), 3.74 (1H, dd, *J* = 7.0, 3.2 Hz, H$_{25}$), 3.72-3.63 (4H, m, H$_{15}$ x 2, H$_{23}$, H$_{27b}$), 3.32 (1H, dd, *J* = 8.8, 8.8 Hz, H$_{27b}$), 2.44 (1H, ddd, *J* = 14.2, 7.3, 6.0 Hz H$_{22a}$), 2.29 (1H, ddd, *J* = 14.2, 7.2, 7.2 Hz, H$_{22b}$), 2.13-2.05 (1H, m, H$_{26}$), 1.83-1.63 (4H, m, H$_{16a}$, H$_{17}$, H$_{24}$, O<u>H</u>) 1.50-1.37 (3H, m, H$_{16b}$, H$_{18}$ x 2), 1.06 (3H, d, *J* = 7.0 Hz, Me$_{26}$), 1.01-0.94 (24H, m, Me$_{17}$, Me$_{24}$, SiCH$_2$C<u>H</u>$_3$ x 6), 0.63 (12H, *J* = 7.9 Hz, SiC<u>H</u>$_2$CH$_3$ x 6); **^{13}C NMR** (125 MHz, CDCl$_3$): δ_C 158.8, 138.8, 135.4, 131.3, 128.7, 128.2, 128.0, 127.3, 127.2, 113.5, 78.6, 77.1, 72.9, 72.1, 70.9, 70.7, 60.9, 55.2, 44.4, 41.4, 39.4, 36.7,

35.1, 26.3, 20.3, 16.1, 10.6, 7.1, 6.7, 5.5, 4.3; **HRMS** calculated for $C_{43}H_{78}NO_6Si_2$ $[M+NH_4]^+$ 760.5362, found 760.5360.

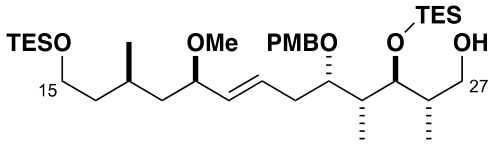
Methyl ether 23



Sodium hydride (3.99 g, 60% dispersion in mineral oil) was washed with hexane (2 x 20 mL) and dried *in vacuo* before adding THF (50 mL). The suspension was cooled to 0 °C and a solution of allylic alcohol **22a** (10.6 g, 14.2 mmol) in THF (70 mL) was added *via* cannula. The mixture was left to stir for 1 h before adding MeI (7.09 mL, 114 mmol) and warming to rt. The reaction mixture was stirred for 4 h until complete and carefully quenched with MeOH (50 mL) at 0 °C. The mixture was warmed to rt, poured into brine (200 mL), diluted with H_2O (100 mL) and extracted with EtOAc (2 x 250 mL). Combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 0:1 → 1:22) to give methyl ether **23** (9.57 g, 12.6 mmol, 89%) as a colourless oil.

R_f 0.79 (EtOAc/40-60 PE, 1:8); $[\alpha]_{20}^{D}$ = +3.6 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2956, 2875, 1613, 1514, 1455, 1248, 1091, 1041, 1011, 971, 818, 738; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.35-7.33 (4H, m, PhH), 7.31-7.27 (1H, m, PhH), 7.26 (2H, d, *J* = 8.3 Hz, ArH), 6.87 (2H, d, *J* = 8.3 Hz, ArH), 5.58 (1H, dt, *J* = 15.2, 7.4 Hz, H_{21}), 5.29 (1H, dd, *J* = 15.2, 8.6 Hz, H_{20}), 4.58 (1H, d, *J* = 11.1 Hz, $ArCH_aH_bO$), 4.48 (2H, ABq, *J* = 12.2 Hz, $PhCH_2O$), 4.40 (1H, d, *J* = 11.1 Hz, $ArCH_aH_bO$), 3.81 (3H, s, $ArOCH_3$), 3.74 (1H, dd, *J* = 7.8, 2.4 Hz, H_{25}), 3.72-3.59 (4H, m, H_{15} × 2, H_{23}, H_{27a}), 3.58-3.53 (1H, m, H_{19}), 3.29 (1H, dd, *J* = 8,8 8.8 Hz, H_{27b}), 3.22 (3H, s, OCH_3), 2.48 (1H, dt, *J* = 14.2, 5.4 Hz, H_{22a}), 2.29 (1H, dt, *J* = 14.2, 7.8 Hz, H_{22b}), 2.13-2.06 (1H, m, H_{26}), 1.83-1.75 (1H, m, H_{24}), 1.72-1.58 (2H, m, H_{16a}, H_{17}), 1.51-1.33 (3H, m, H_{16b}, H_{18} x 2), 1.05 (3H, d, *J* = 6.9 Hz, Me_{26}), 0.99-0.93 (21H, m, Me_{24}, $SiCH_2CH_3$ x 6), 0.89 (3H, d, *J* = 6.7 Hz, Me_{17}), 0.65-0.58 (12H, m, $SiCH_2CH_3$ x 6); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C 158.6, 138.5, 132.7, 131.0, 130.3, 128.3, 127.9, 127.1, 127.0, 113.3, 80.4, 78.1, 76.8, 72.7, 71.7, 70.6, 60.6, 55.4, 54.9, 42.7, 40.8, 39.7, 36.5, 34.8, 25.8, 19.6, 15.7, 10.0, 6.8, 6.5, 5.3, 4.1; **HRMS** calculated for $C_{44}H_{76}O_6NaSi_2$ $[M+Na]^+$ 779.5073, found 779.5057.

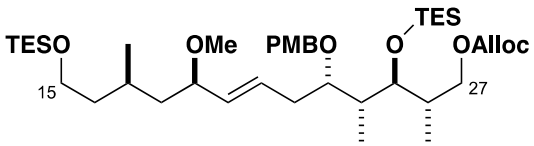
Alcohol 23a



A solution of LiDBB (20.0 mL, 1.0 M in THF, 20.0 mmol) was added to a solution of methyl ether **23** (3.03 g, 4.00 mmol) in degassed THF (145 mL) at –78 °C. The reaction mixture was stirred for 20 min before being quenched by addition of NH_4Cl and warming to rt. The phases were separated and the aqueous layer extracted with EtOAc (3 x 100 mL). Combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:50 → 1:8) to yield alcohol **23a** (2.04 g, 3.20 mmol, 77%, 96% BRSM) as a colourless oil.

R_f 0.51 (EtOAc/40-60 PE, 1:3); **$[\alpha]_{2\mathrm{C}}^{\nu}$** = +11.0 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 3452, 2960, 2877, 1615, 1514, 1459, 1417, 1378, 1302, 1251, 1169, 1088, 1038, 1011, 969, 820, 747; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.24 (2H, d, *J* = 8.6 Hz, Ar$\underline{H}$), 6.88 (2H, d, *J* = 8.6 Hz, Ar$\underline{H}$), 5.59 (1H, dt, *J* = 15.2, 6.6 Hz, H_{21}), 5.33 (1H, dd, *J* = 15.2, 8.2 Hz, H_{20}), 4.59 (1H, d, *J* = 11.1 Hz, ArC$\underline{H}_a$H$_b$O), 4.50, (1H, d, *J* = 11.1 Hz, ArCH$_a\underline{H}_b$O), 3.81 (3H, s, ArOC$\underline{H}_3$), 3.82-3.77 (2H, m, H_{25}, H_{27a}), 3.69-3.52 (5H, m, H_{15} × 2, H_{19}, H_{23}, H_{27b}), 3.24 (3H, s, OC$\underline{H}_3$), 2.66 (1H, dd, *J* = 7.3, 4.0 Hz, O$\underline{H}$), 2.51 (1H, dt, *J* = 14.1, 5.4 Hz, H_{22a}), 2.38 (1H, dt, *J* = 14.1, 7.9 Hz, H_{22b}), 1.91-1.85 (2H, m, H_{24}, H_{26}), 1.71-1.55 (2H, m, H_{16a}, H_{18a}), 1.52-1.33 (3H, m, H_{16b}, H_{17}, H_{18b}), 1.07 (3H, d, *J* = 6.9 Hz, Me_{26}), 0.99-0.94 (21H, m, Me_{24}, SiCH$_2$C$\underline{H}_3$ x 6), 0.89 (3H, d, *J* = 6.5 Hz, Me_{17}), 0.69-0.57 (12H, m, SiC$\underline{H}_2$CH$_3$ x 6); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.0, 133.5, 131.1, 130.0, 128.6, 113.7, 80.7, 79.8, 78.4, 70.7, 65.3, 61.0, 55.9, 55.3, 43.1, 42.0, 40.0, 36.2, 34.9, 26.2, 20.0, 16.6, 9.9, 7.0, 6.8, 5.4, 4.5; **HRMS** calculated for $C_{37}H_{74}NO_6Si_2$ $[M+NH_4]^+$ 684.5049, found 684.5048.

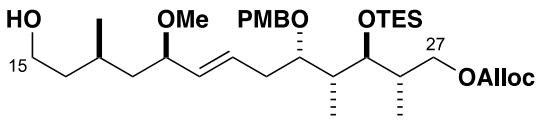
Allyl carbonate 24



Allyl chloroformate (5.00 mL, 47.2 mmol) was added dropwise to a solution of alcohol **23a** (3.16 g, 4.72 mmol) in CH_2Cl_2/pyr (1:1, 60 mL) at –60 °C and a white precipitate was observed. The resulting suspension was let to gradually warm to –20 °C and stirred at this temperature for 3 h before being quenched with $NaHCO_3$ (30 mL) and stirred until bubbling had ceased. The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic extracts dried (Na_2SO_4), concentrated *in vacuo* and purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:50 → 1:15). Allyl carbonate **24** (3.12 g, 4.15 mmol, 88%) was obtained as a colourless oil. The C_{15} TES-deprotected byproduct **24a** (203 mg, 0.319 mmol, 7%) was also isolated.

R_f 0.45 (EtOAc/40-60 PE, 1:10); $[\alpha]_{20}^{D}$ = +5.0 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2960, 2877, 1746, 1514, 1461, 1294, 1253, 1090, 1037, 1009, 969, 737, 727; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.26 (2H, d, *J* = 8.5 Hz, ArH), 6.89 (2H, d, *J* = 8.5 Hz, ArH), 6.00-5.92 (1H, m, CH=CH_2), 5.62-5.56 (1H, m, H_{21}), 5.38 (1H dd, *J* = 17.1, 1.2 Hz, CH=CH_aH_b), 5.34 (1H, dd, *J* = 15.5, 7.1 Hz, H_{20}), 5.29 (1H, dd, *J* = 10.3, 1.2 Hz, CH=CH_aH_b), 4.67-4.62 (2H, m, OCH_2), 4.60 (1H, d, *J* = 11.1 Hz, ArCH_aH_bO), 4.40 (1H, d, *J* = 11.1 Hz, ArCH_aH_bO), 4.32 (1H, dd, *J* = 10.6, 4.1 Hz, H_{27a}), 3.97 (1H, dd, *J* = 10.6, 9.3 Hz, H_{27b}), 3.82 (3H, s, ArOCH_3), 3.74 (1H, dd, *J* = 7.4, 2.6 Hz, H_{25}), 3.70-3.62 (3H, m, H_{15} × 2, H_{23}), 3.60-3.55 (1H, m, H_{19}), 3.25 (3H, s, OCH_3), 2.51 (1H, dt, *J* = 14.0, 5.5 Hz, H_{22a}), 2.31 (1H, dt, *J* = 14.0, 7.9 Hz, H_{22b}), 2.16-2.11 (1H, m, H_{26}), 1.84-1.77 (1H, m, H_{24}), 1.71-1.60 (2H, m, H_{17}, H_{18a}), 1.51-1.36 (2H, m, H_{16a} x 2, H_{18b}), 1.06 (3H, d, *J* = 6.9 Hz, Me_{26}), 1.00-0.96 (21H, m, Me_{24}, $SiCH_2CH_3$ x 6), 0.91 (3H, d, *J* = 6.9 Hz, Me_{17}), 0.67-0.59 (12H, m, $SiCH_2CH_3$ x 6); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 158.9, 155.2, 133.3, 131.8, 131.3, 130.3, 128.7, 118.8, 113.7, 80.8, 78.4, 77.0, 70.9, 69.9, 68.3, 61.0, 55.8, 55.3, 43.1, 41.3, 40.0, 35.7, 35.0, 26.2, 20.0, 16.0, 10.1, 7.1, 6.8, 5.6, 4.5; **HRMS** calculated for $C_{41}H_{78}NO_8Si_2$ $[M+NH_4]^+$ 768.5260, found 768.5253.

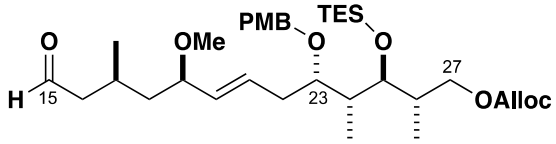
Alcohol 24a



Acetic acid (10 mL) was added dropwise to a solution of TES ether **24** (4.95 g, 6.58 mmol) in THF:H_2O (10 mL, 3:1) at 0 °C. The mixture was warmed to rt and stirred for 3.5 h. Upon completion, the reaction mixture was cannulated into $NaHCO_3$ (250 mL) at 0 °C and stirred until bubbling had ceased. The layers were separated and the aqueous phase extracted with EtOAc (3 x 300 ml). The combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:8 → 1:3) to afford alcohol **24a** (3.41 g, 5.35 mmol, 81%, 89% BRSM) as a colourless oil.

R_f 0.24 (EtOAc/40-60 PE, 1:2); **$[\alpha]_{2(}^{\nu}$** = +2.0 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 3464, 2956, 2877, 1742, 1512, 1457, 1395, 1376, 1292, 1253, 1167, 1092, 1041, 1009, 969, 822, 791, 735; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.26 (2H, d, *J* = 8.6 Hz, ArH), 6.89 (2H, d, *J* = 8.6 Hz, ArH), 6.00-5.92 (1H, m, CH=CH_2), 5.64-5.58 (1H, m, H_{21}), 5.38 (1H, dd, *J* = 17.1, 1.4 Hz, CH=CH_aH_b), 5.34 (1H, dd, *J* = 15.4, 8.3 Hz, H_{20}), 5.29 (1H, dd, *J* = 10.4, 1.4 Hz, CH=CH_aH_b), 4.67-4.62 (2H, m, OCH_2), 4.59 (1H, d, *J* = 11.1 Hz, ArCH_aH_bO), 4.40 (1H, *J* = 11.1 Hz, ArCH_aH_bO), 4.32 (1H, dd, *J* = 10.6, 4.1 Hz, H_{27a}), 3.96 (1H, dd, *J* = 10.5, 8.9 Hz, H_{27b}), 3.83 (3H, s, ArOCH_3), 3.74 (1H, dd, *J* = 7.5, 2.6 Hz, H_{25}), 3.72-3.64 (3H, m, H_{15} x 2, H_{23}), 3.62-3.58 (1H, m, H_{19}), 3.26 (3H, s, OCH_3), 2.52 (1H, dt, *J* = 14.1, 7.0 Hz, H_{22a}), 2.32 (1H, dt, *J* = 14.1, 7.8 Hz, H_{22b}), 2.17-2.10 (1H, m, H_{26}), 1.82-1.77 (1H, m, H_{24}), 1.75-1.69 (1H, m, H_{17}), 1.67-1.61 (1H, m, H_{18a}), 1.56-1.49 (1H, m, H_{16a}), 1.47-1.40 (2H, m, $H_{16b,}$ H_{18b}), 1.06 (3H, d, *J* = 6.8 Hz, Me_{26}), 0.97 (9H, t, *J* = 8.0 Hz, SiCH_2CH_3 x 3), 0.97 (3H, d, *J* = 7.0 Hz, Me_{24}), 0.94 (3H, d, *J* = 6.7 Hz, Me_{17}), 0.65 (6H, q, *J* = 8.0 Hz, SiC$H_2$$CH_3$ x 3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 158.9, 155.3, 133.1, 131.7, 131.2, 130.4, 128.6, 118.8, 113.7, 80.7, 78.3, 77.0, 70.8, 69.8, 68.3, 61.0, 55.8, 55.3, 42.8, 41.2, 39.8, 35.6, 34.9, 26.2, 20.2, 16.1, 10.2, 7.1, 5.6; **HRMS** calculated for $C_{35}H_{64}NO_8Si$ $[M+NH_4]^+$ 654.4396, found 654.4393.

Aldehyde 7

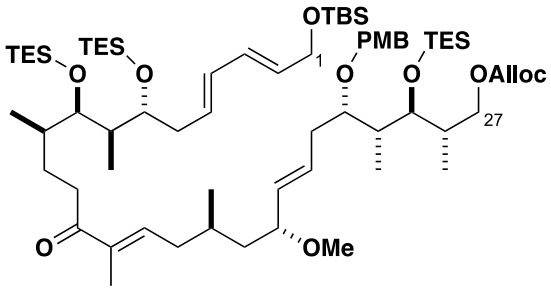


Dess–Martin periodinane (3.19 g, 7.52 mmol) was added portion-wise to a stirred mixture of alcohol **24a** (3.99 g, 6.27 mmol) and $NaHCO_3$ (2.11 g, 25.1 mmol) in CH_2Cl_2 (130 mL) at 0 °C. The reaction slurry was stirred at this temperature for 1 h until complete. The mixture was quenched with $Na_2S_2O_3$ (150 mL) and stirred for 45 min until the yellow colour had dissipated. After diluting with H_2O (100 mL) the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (5 x 100 mL). Combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:20 → 1:4) to yield aldehyde **7** (3.39 g, 5.34 mmol, 85%) as a colourless oil.

R_f 0.58 (EtOAc/40-60 PE, 1:2); **$[\alpha]_{20}^{D}$** = +1.1 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2956, 2873, 1750, 1726, 1609, 1510, 1463, 1399, 1378, 1294, 1247, 1175, 1098, 1037, 1013, 969, 822, 791, 739; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 9.74 (1H, t, *J* = 2.0 Hz, C<u>H</u>O), 7.26 (2H, d, *J* = 8.6 Hz, Ar<u>H</u>), 6.89 (2H, d, *J* = 8.6 Hz, Ar<u>H</u>), 6.00-5.92 (1H, m, C<u>H</u>=CH_2), 5.65-5.59 (1H, m, H_{21}), 5.38 (1H, dd, *J* = 17.2, 1.2, Hz, CH=C<u>H</u>$_a$H$_b$), 5.34 (1H, dd, *J* = 15.5, 7.1 Hz, H_{20}), 5.29 (1H, dd, *J* = 10.4, 1.2 Hz, CH=CH$_a$<u>H</u>$_b$), 4.67-4.62 (2H, m, OC<u>H</u>$_2$), 4.59 (1H, d, *J* = 10.9 Hz, ArC<u>H</u>$_a$H$_b$O), 4.41 (1H, d, *J* = 10.9 Hz, ArCH$_a$<u>H</u>$_b$O), 4.32 (1H, dd, *J* = 10.6, 4.2 Hz, H_{27a}), 3.96 (1H, dd, *J* = 10.6, 9.1 Hz, H_{27b}), 3.82 (3H, s, ArOC<u>H</u>$_3$), 3.74 (1H, dd, *J* = 7.6, 2.6 Hz, H_{25}), 3.70-3.67 (1H, m, H_{23}), 3.57-3.53 (1H, m, H_{19}), 3.24 (3H, s, OC<u>H</u>$_3$), 2.54-2.42 (2H, m, H_{16a}, H_{22a}), 2.35-2.22 (3H, m, H_{16b}, H_{17}, H_{22b}), 2.17-2.10 (1H, m, H_{26}), 1.83-1.76 (1H, m, H_{24}), 1.63-1.57 (1H, m, H_{18a}), 1.42 (1H, dt, *J* = 13.9, 6.1 Hz, H_{18b}), 1.06 (3H, d, *J* = 6.9 Hz, Me_{26}), 1.00-0.96 (15H, m, Me_{17}, Me_{24}, SiCH$_2$C<u>H</u>$_3$ x 3), 0.67-0.62 (6H, m, SiC<u>H</u>$_2$CH$_3$ x 3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 202.8, 159.0, 155.2, 132.8, 131.8, 131.2, 130.8, 128.6, 118.8, 113.7, 80.2, 78.3, 77.1, 70.8, 69.8, 68.3, 55.7, 55.3, 50.8, 42.7, 41.4, 35.6, 35.0, 24.8, 20.5, 16.0, 10.2, 7.1, 5.6; **HRMS** calculated for $C_{35}H_{58}O_8NaSi$ $[M+Na]^+$ 657.3793, found 657.3774.

VI. Experimental Procedures for C_1–C_{27} Macrocyclic Aldehyde 28

Enone 7a

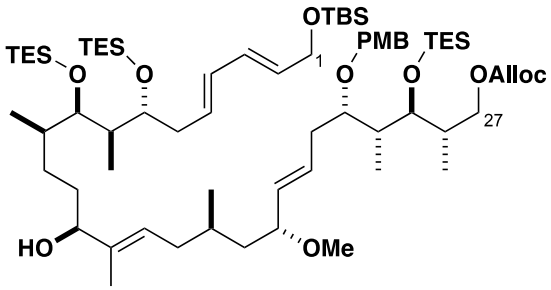


A suspension of anhydrous $Ba(OH)_2$ (see p.3) (47.0 mg, 0.275 mmol) in THF (2 mL) was sonicated for 5 min before a solution of **8** and **8a** (3:1, 336 mg, 0.324 mmol) in THF (2 mL) was added. The mixture was stirred at rt for 1.5 h before a solution of aldehyde **7** (166 mg, 0.262 mmol) in THF/H_2O (40:1, 2 mL) was added *via* cannula. The reaction mixture was stirred for 20 h before being quenched with NH_4Cl solution (5 mL) and diluted with H_2O (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). Combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the crude material purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:30 → 1:5). Enone **7a** (315 mg, 0.250 mmol, 96%) was obtained as a colourless oil.

R_f 0.53 (EtOAc/40-60 PE, 1:5); **$[\alpha]_{2C}^{\nu}$** = +1.1 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2953, 2876, 1746, 1670, 1514, 1459, 1377, 1292, 1247, 1169, 1092, 1038, 1006, 969, 835, 776, 736, 735, 723; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.26 (2H, d, *J* = 8.4 Hz, Ar<u>H</u>), 6.89 (2H, d, *J* = 8.4 Hz, Ar<u>H</u>), 6.64 (1H, t, *J* = 6.9 Hz, H_{15}), 6.21 (1H, dd, *J* = 15.0, 10.5 Hz, H_3), 6.07 (1H, dd, *J* = 15.0, 10.5 Hz, H_4), 6.00-5.92 (1H, m, C<u>H</u>=CH_2), 5.71 (1H, dt, *J* = 15.2, 7.5 Hz, H_2), 5.66 (1H, dt, *J* = 15.2, 5.5 Hz, H_5), 5.64-5.58 (1H, m, H_{21}), 5.38 (1H, dd, *J* = 17.2, 1.4 Hz, CH=C<u>H</u>$_a$H$_b$), 5.33 (1H, dd, *J* = 15.5, 8.5 Hz, H_{20}), 5.28 (1H, dd, *J* = 10.4, 1.3 Hz, CH=CH$_a$<u>H</u>$_b$), 4.67-4.62 (2H, m, OC<u>H</u>$_2$), 4.59 (1H, d, *J* = 11.1 Hz, ArC<u>H</u>$_a$H$_b$O), 4.40 (1H, d, *J* = 11.1 Hz, ArCH$_a$<u>H</u>$_b$O), 4.32 (1H, dd, *J* = 10.8, 4.3 Hz, H_{27a}), 4.22 (2H, d, *J* = 5.6 Hz, H_1 x 2), 3.96 (1H, dd, *J* = 10.5, 9.0 Hz, H_{27b}), 3.82 (3H, s, ArOC<u>H</u>$_3$), 3.74 (1H, dd, *J* = 7.5, 2.8 Hz, H_{25}), 3.71-3.63 (2H, m, H_7, H_{23}), 3.61-3.56 (2H, m, H_9, H_{19}), 3.26 (3H, s, OC<u>H</u>$_3$), 2.76 (1H, ddd, *J* = 15.3, 9.8, 5.3 Hz, H_{12a}), 2.62-2.50 (2H, m, H_{12b}, H_{22a}), 2.35-2.28 (2H, m, H_{16a}, H_{22b}), 2.20-2.05 (4H, m, H_6 x 2, H_{16b}, H_{26}), 1.84-1.73 (4H, m, H_8, H_{11a}, H_{17}, H_{24}), 1.79 (3H, s, Me_{14}), 1.60-1.53 (2H, m, H_{10},

H_{18a}), 1.46-1.39 (2H, m, H_{11b}, H_{18b}), 1.06 (3H, d, J = 6.9 Hz, Me_{26}), 1.00-0.92 (36H, m, Me_8, Me_{17}, Me_{24}, $SiCH_2C\underline{H}_3$ x 9), 0.93 (9H, s, $SiC(C\underline{H}_3)_3$), 0.88 (3H, d, J = 6.9 Hz, Me_{10}), 0.66-0.57 (18H, m, $SiC\underline{H}_2CH_3$ x 9), 0.09 (6H, s, $SiC\underline{H}_3$ x 2); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 201.9, 159.0, 155.2, 140.4, 138.1, 133.0, 131.7, 131.4, 131.2, 130.6, 130.4, 130.3, 128.6 x 2, 118.8, 113.7, 80.5, 78.3, 77.5, 74.5, 70.8, 69.8, 68.3, 63.7, 55.8, 55.3, 42.9, 41.8, 41.3, 38.1, 36.1 x 2, 35.6, 35.4, 34.9, 29.6, 26.8, 26.0 x 2, 20.0, 18.4, 16.2, 16.0, 11.6, 10.5, 10.2, 7.2, 7.1, 7.0, 5.6 x 2, 5.3, –5.2; **HRMS** calculated for $C_{70}H_{132}NO_{11}Si_4$ $[M+NH_4]^+$ 1274.8872, found 1274.8855.

Allylic alcohol 7b

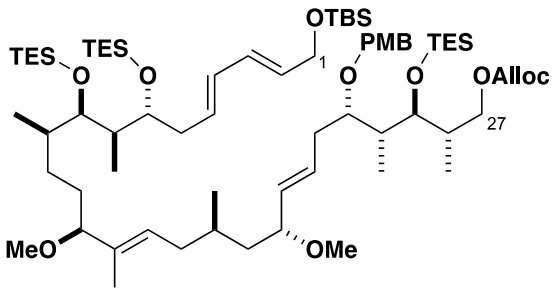


(*R*)-Me-CBS catalyst (1.62 mL, 1.0 M in PhMe, 1.61 mmol) was added to a solution of enone **7a** (1.56 g, 1.24 mmol) in THF (50 mL) at –20 °C, followed by dropwise addition of borane–dimethylsulfide complex (141 μL, 1.48 mmol). The mixture was warmed to –10 °C and stirred for 3 h before being slowly quenched with $NaHCO_3$ solution (10 mL), warmed to rt and stirred for a further 20 min until bubbling had ceased. The mixture was diluted with H_2O (20 mL), extracted with EtOAc (3 x 40 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:15 → 1:8) yielded allylic alcohol **7b** (1.45 g, 1.15 mmol, 93%, 20:1 *dr*) as a colourless oil.

R_f 0.44 (EtOAc/40-60 PE, 1:5); **$[\alpha]_{2C}^{D}$** = +6.3 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2952, 2873, 1748, 1516, 1460, 1415, 1379, 1299, 1248, 1100, 1042, 1006, 969, 834, 778, 741; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.26 (2H, d, J = 8.5 Hz, Ar$\underline{H}$), 6.89 (2H, d, J = 8.5 Hz, Ar$\underline{H}$), 6.21 (1H, dd, J = 15.0, 10.5, Hz, H_3), 6.06 (1H, dd, J = 15.0, 10.4 Hz, H_4), 5.96 (1H, ddt, J = 17.1, 10.4, 5.8 Hz, C$\underline{H}$=CH_2), 5.70 (1H, dt, J = 15.1, 7.5 Hz, H_2), 5.66 (1H, dt, J = 15.1, 5.3 Hz, H_5), 5.63-5.57 (1H, m, H_{21}), 5.40-5.36 (2H, m, H_{15}, CH=C$\underline{H}_a$$H_b$), 5.32-5.27 (2H, m, H_{20}, CH=C$H_a$$\underline{H}_b$), 4.65-4.63 (2H, m, OC$\underline{H}_2$), 4.60 (1H, d, J = 11.2 Hz, ArC$\underline{H}_a$$H_b$O), 4.40 (1H, d, J

= 11.2 Hz, $ArCH_a\underline{H}_bO$), 4.32 (1H, dd, *J* = 10.6, 4.2 Hz, H_{27a}), 4.23 (2H, d, *J* = 5.1 Hz, H_1 x 2), 3.98-3.94 (2H, m, H_{13}, H_{27b}), 3.82 (3H, s, $ArOC\underline{H}_3$), 3.74 (1H, dd, *J* = 7.7, 2.7 Hz, H_{25}), 3.69 (1H, ddd, *J* = 7.7, 5.3, 2.7 Hz, H_{23}), 3.64-3.61 (1H, m, H_7), 3.58-3.53 (1H, m, H_{19}), 3.52 (1H, dd, *J* = 5.0, 3.4 Hz, H_9), 3.25 (3H, s, $OC\underline{H}_3$), 2.52 (1H, dd, *J* = 14.1, 5.4 Hz, H_{22a}), 2.32 (1H, dd, *J* = 14.1, 7.9 Hz, H_{22b}), 2.22 (4H, m, H_6 x 2, H_{16a}, H_{26}), 1.87-1.74 (3H, m, H_8, H_{16b}, H_{24}), 1.68-1.60 (2H, m, H_{12a}, H_{18a}), 1.61 (3H, s, Me_{14}), 1.57-1.39 (6H, m, H_{10}, H_{11} x 2, H_{12b}, H_{17}, H_{18b}), 1.06 (3H, d, *J* = 6.9 Hz, Me_{26}), 0.99-0.95 (33H, m, Me_{10}, Me_{24}, $SiCH_2C\underline{H}_3$ x 9), 0.94 (9H, s, $SiC(C\underline{H}_3)_3$), 0.91 (3H, d, *J* = 6.8 Hz, Me_{17}), 0.88 (6H, d, *J* = 6.8 Hz, Me_8), 0.67-0.57 (18H, m, $SiC\underline{H}_2CH_3$ x 9), 0.10 (6H, s, $SiC\underline{H}_3$ x 2); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 158.9, 155.2, 138.0, 133.3, 131.7, 131.6, 131.4, 131.2, 130.3 x 2, 128.6, 125.8, 118.8, 113.7, 80.8, 79.0, 78.3, 77.7, 77.2, 74.6, 70.8, 69.8, 68.3, 63.7, 55.8, 55.2, 42.9, 41.9, 41.3, 38.5, 35.9, 35.6, 35.0, 34.9, 33.1, 29.9, 27.8, 26.0 x 2, 19.8, 18.5, 16.5, 16.1, 11.0, 10.4, 10.2, 7.2, 7.1, 7.0, 5.7, 5.6, 5.2, –5.1; **HRMS** calculated for $C_{70}H_{134}NO_{11}Si_4$ $[M+NH_4]^+$ 1276.9028, found 1276.9018.

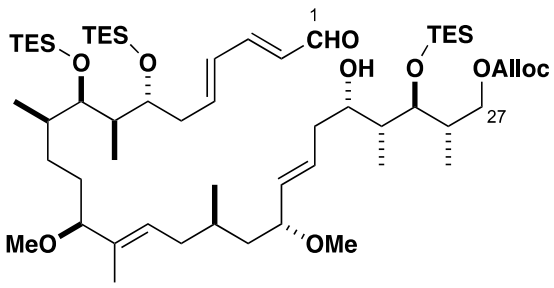
Methyl ether 25



A solution of allylic alcohol **7b** (1.66 g, 1.32 mmol) in CH_2Cl_2 (20 mL) was added *via* cannula to a flask containing trimethyloxonium tetrafluoroborate (1.36 g, 9.25 mmol) and proton sponge® (1.98 g, 9.25 mmol). The resulting mixture was stirred for 4 h during which a colour change from pale yellow to orange was observed, then quenched by addition of NH_4Cl solution (50 mL). Phases were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). Combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow solid. Crude product was purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:40 → 1:5) to give methyl ether **25** (1.28 g, 0.278 mmol, 76%) as a pale yellow oil.

R_f 0.64 (EtOAc/40-60 PE, 1:5); **$[\alpha]_{20}^{D}$** = +5.6 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2960, 2933, 2873, 1746, 1514, 1461, 1380, 1296, 1251, 1098, 1041, 1011, 989, 973, 843, 776, 739, 725; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.25 (2H, d, *J* = 8.5 Hz, ArH), 6.89 (2H, d, *J* = 8.5 Hz, ArH), 6.20 (1H, dd, *J* = 15.1, 10.5 Hz, H_3), 6.06 (1H, dd, *J* = 15.1, 10.5 Hz, H_4), 5.96 (1H, ddt, *J* = 17.1, 10.5, 5.8 Hz, CH=CH_2), 5.70 (1H, dt, *J* = 15.1, 7.5 Hz, H_2), 5.66 (1H, dt, *J* = 15.1, 5.4 Hz, H_5), 5.59 (1H, ddd, *J* = 14.8, 7.9, 6.3 Hz, H_{21}), 5.37-5.31 (1H, m, CH=CH_aH_b), 5.37-5.31 (2H, m, H_{15}, H_{20}), 5.30-5.27 (1H, m, CH=CH_aH_b), 4.67-4.62 (2H, m, OCH_2), 4.60 (1H, d, *J* = 11.0 Hz, ArCH_aH_bO), 4.40 (1H, d, *J* = 11.0 Hz, ArCH_aH_bO), 4.32 (1H, dd, *J* = 10.6, 4.3 Hz, H_{27a}), 4.23 (2H, d, *J* = 5.2 Hz, H_1 x 2), 3.96 (1H, dd, *J* = 10.6, 9.0 Hz, H_{27b}), 3.83 (3H, s, $ArOCH_3$), 3.75 (1H, dd, *J* = 7.5, 2.6 Hz, H_{25}), 3.71-3.67 (1H, m, H_{23}), 3.64-3.57 (2H, m, H_7, H_{19}), 3.51 (1H, dd, *J* = 4.3, 3.4 Hz, H_9), 3.38 (1H, dd, *J* = 7.0, 6.9 Hz, H_{13}), 3.26 (3H, s, OMe_{19}), 3.17 (3H, s, OMe_{13}), 2.52 (1H, ddd, *J* = 14.1, 5.5, 5.3 Hz, H_{22a}), 2.31 (1H, ddd, *J* = 14.1, 8.0, 7.3 Hz, H_{22b}), 2.20-2.12 (4H, m, H_6 x 2, H_{16a}, H_{26}), 1.89-1.74 (3H, m, H_8, H_{16b}, H_{24}), 1.68-1.63 (1H, m, H_{17}), 1.58-1.48 (4H, m, H_{10}, H_{11a}, H_{12} x 2), 1.52 (3H, s, Me_{14}), 1.46-1.40 (2H, m, H_{11b}, H_{18b}), 1.06 (3H, d, *J* = 6.9 Hz, Me_{26}), 0.99-0.96 (30H, m, Me_{24}, $SiCH_2CH_3$ x 9), 0.94 (9H, s, $SiC(CH_3)_3$), 0.91-0.87 (9H, m, Me_8, Me_{10}, Me_{17}), 0.67-0.58 (18H, m, $SiCH_2CH_3$ x 9), 0.10 (6H, s, $SiCH_3$ x 2); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.0, 155.2, 135.1, 133.4, 131.8 x 2, 131.4, 131.2, 130.3 x 2, 130.2, 128.7, 127.8, 118.8, 113.7, 88.5, 80.9, 78.4, 77.7, 77.1, 74.7, 70.8, 69.8, 68.2, 63.8, 55.9, 55.6, 55.3, 42.9, 41.7, 41.3, 38.6, 35.8, 35.6, 35.0, 34.8, 32.0, 29.9, 27.9, 26.0, 19.8, 18.4, 16.3, 15.9, 10.3, 10.2, 10.1, 7.2, 7.1, 7.0, 5.7, 5.6, 5.2, –5.2; **HRMS** calculated for $C_{71}H_{136}NO_{11}Si_4$ $[M+NH_4]^+$ 1290.9185, found 1290.9173.

Aldehyde 25a

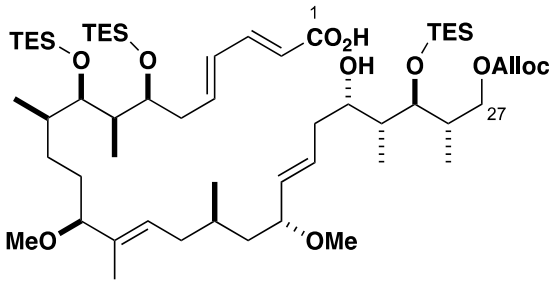


DDQ (107 mg, 0.471 mmol) was added to a stirred solution of TBS ether **25** (201 mg, 0.158 mmol) in CH_2Cl_2/pH 7 buffer solution (3:1, 10 mL) at 0 °C and a colour change to dark blue

was observed. The mixture was warmed to rt and stirred for 30 min during which a gradual colour change to red was seen. An additional portion of DDQ (18.0 mg, 79.0 μmol) was added and the mixture stirred for an additional 30 min until complete. The reaction was quenched with $NaHCO_3$ solution (10 mL), warmed to rt and stirred for 30 min. Phases were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). Combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:15 → 1:8). Aldehyde **25a** (133 mg, 0.128 mmol, 82%) was obtained as a pale yellow oil.

R_f 0.33 (EtOAc/40-60 PE, 1:5); **$[\alpha]_{2(}^{\mu}$** = +3.0 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2948, 2873, 1752, 1683, 1637, 1461, 1376, 1251, 1156, 1094, 1006, 967, 801, 795, 737, 723; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 9.57 (1H, d, *J* = 7.9 Hz, C<u>H</u>O), 7.10 (1H, dd, *J* = 15.3, 10.0 Hz, H_3), 6.38-6.30 (2H, m, H_4 H_5), 6.10 (1H, dd, *J* = 15.2, 7.9 Hz, H_2), 5.95 (1H, ddt, *J* = 17.1, 10.4, 5.8 Hz, C<u>H</u>=CH_2), 5.62 (1H, ddd, *J* = 15.1, 8.3, 5.9 Hz, H_{21}), 5.38 (1H, ddt, *J* = 17.1, 1.3, 1.3 Hz, CH=C<u>H</u>$_a$$H_b$), 5.36-5.31 (2H, m, H_{15}, H_{20}), 5.29 (1H, ddt, *J* = 10.4, 1.2, 1.2 Hz, CH=CH_a<u>H</u>$_b$), 4.67-4.62 (2H, m, OC<u>H</u>$_2$), 4.28 (1H, dd, *J* = 10.5, 3.9 Hz, H_{27a}), 4.09-4.05 (2H, m, H_{23}, H_{27b}), 3.74 (1H, dd, *J* = 7.7, 2.9 Hz, H_{25}), 3.70-3.67 (1H, m, H_7), 3.58-3.53 (1H, m, H_{19}), 3.51 (1H, dd, *J* = 4.0, 3.9 Hz, H_9), 3.37 (1H, dd, *J* = 6.9, 6.8 Hz, H_{13}), 3.24 (3H, s, OMe_{19}), 3.16 (3H, s, OMe_{13}), 2.37-2.27 (3H, m, H_6 x 2, H_{22a}), 2.19-2.12 (3H, m, H_{16a}, H_{22b}, H_{26}), 1.89-1.83 (1H, m, H_{16b}), 1.79-1.70 (2H, m, H_8, H_{24}), 1.66-1.60 (1H, m, H_{17}), 1.57-1.39 (7H, m, H_{10}, H_{11} x 2, H_{12} x 2, H_{18} x 2), 1.51 (3H, s, Me_{14}), 1.04 (3H, d, *J* = 7.1 Hz, Me_{24}), 1.01-0.95 (30H, m, Me_{26}, $SiCH_2C$<u>H</u>$_3$ x 9), 0.90-0.88 (9H, m, Me_8, Me_{10}, Me_{17}), 0.69 (6H, q, *J* = 7.9 Hz, SiC<u>H</u>$_2CH_3$ x3), 0.64-0.58 (12H, m, SiC<u>H</u>$_2CH_3$ x 6); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 194.0, 155.1, 152.4, 144.8, 135.1, 133.2, 131.6, 130.3 x 2, 130.2, 127.7, 119.0, 88.4, 80.8, 79.9, 77.4, 74.3, 70.3, 70.2, 68.4, 55.8, 55.7, 42.7, 41.6, 38.9, 37.9, 36.9 x 2, 36.4, 34.9, 32.0, 29.9, 29.7, 28.3, 19.9, 16.0, 14.4, 11.2, 10.4, 10.0, 7.1, 7.0, 5.6, 5.2 x 2; **HRMS** calculated for $C_{57}H_{112}NO_{10}Si_3$ $[M+NH_4]^+$ 1054.7589, found 1054.7586.

***Seco* acid 26**

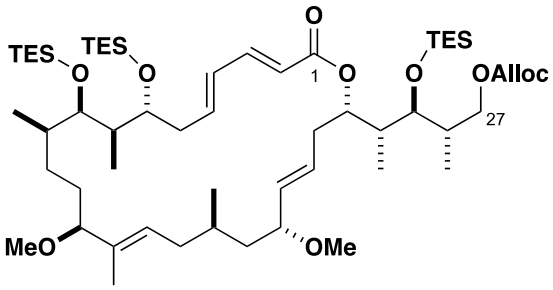


A solution of $NaClO_2$ (367 mg, 4.06 mmol) and $NaH_2PO_4 \cdot H_2O$ (845 mg, 5.42 mmol) in H_2O (8.3 mL) was added dropwise to a solution of aldehyde **25a** (281 mg, 0.271 mmol) in ^{t}BuOH/2-methyl-but-2-ene (10:1, 16.7 mL) at rt and stirred for 21 h. The mixture was diluted with H_2O (30 mL) and EtOAc (30 mL) and the phases were separated. The organic layer was washed with H_2O (3 x 20 mL) and back-extracted with EtOAc (2 x 10 mL). Combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. Crude *seco*-acid **26** (274 mg, 0.260 mmol, 96% yield) was used in the next step without additional purification.

R_f 0.37 (EtOAc/40-60 PE, 1:2); **$[\alpha]_{20}^{D}$** = –1.3 (*c* 1.0, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2952, 2916, 2880, 1746, 1722, 1692, 1639, 1460, 1417, 1395, 1377, 1252, 1092, 1034, 1004, 965, 743, 727; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.35-7.29 (1H, m, H_3), 6.27-6.16 (2H, m, H_4, H_5), 5.94 (1H, ddt, *J* = 17.1, 10.4, 5.8 Hz, C<u>H</u>=CH_2), 5.80 (1H, d, *J* = 15.3 Hz, H_2), 5.61 (1H, ddd, *J* = 14.9, 8.0, 6.4 Hz, H_{21}), 5.37 (1H, ddt, *J* = 17.2, 1.4, 1.4 Hz, CH=CH_a<u>H_b</u>), 5.36-5.29 (2H, m, H_{15}, H_{20}), 5.28 (1H, ddt, *J* = 10.4, 1.2, 1.2 Hz, CH=CH_a<u>H_b</u>), 4.69-4.59 (2H, m, O<u>CH_2</u>), 4.27 (1H, dd, *J* = 10.4, 3.7 Hz, H_{27a}), 4.12-4.04 (2H, m, H_{23}, H_{27b}), 3.74 (1H, dd, *J* = 7.8, 2.7 Hz, H_{25}), 3.67-3.63 (1H, m, H_7), 3.60-3.53 (2H, m, H_9, H_{19}), 3.36 (1H, dd, *J* = 6.9, 6.8 Hz, H_{13}), 3.23 (3H, s, OMe_{19}), 3.15 (3H, s, OMe_{13}), 2.38-2.27 (3H, m, H_6 x 2, H_{22a}), 2.19-2.09 (3H, m, H_{16a}, H_{22b}, H_{26}), 1.89-1.79 (1H, m, H_{16b}), 1.77-1.66 (2H, m, H_8, H_{24}), 1.65-1.58 (1H, m, H_{17}), 1.50 (3H, s, Me_{14}), 1.56-1.32 (7H, m, H_{10}, H_{11} x 2, H_{12} x 2, H_{18} x 2), 1.04 (3H, d, *J* = 7.2 Hz, Me_{24}), 1.00-0.93 (30H, m, Me_{26}, $SiCH_2C$<u>H_3</u> x 9), 0.89-0.84 (9H, m, Me_8, Me_{10}, Me_{17}), 0.68 (6H, q, *J* = 7.8 Hz, SiC<u>H_2</u>CH_3 x 3), 0.60 (6H, q, *J* = 7.8 Hz, SiC<u>H_2</u>CH_3 x 3), 0.58 (6H, q, *J* = 7.8 Hz, SiC<u>H_2</u>CH_3 x 3); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 171.6, 155.1, 146.8, 143.1, 135.0, 133.2, 131.6, 130.3, 130.0, 127.8, 118.9, 118.7, 88.4, 80.9, 79.8, 77.2, 74.3, 70.4, 70.1, 68.4, 55.8, 55.6, 42.6, 41.4, 39.0, 37.8, 36.9, 36.8, 36.4, 34.9, 31.9, 29.9, 28.3, 19.9, 15.8, 14.4, 11.2, 10.3, 10.2, 7.1, 7.0, 6.9, 5.6, 5.2 x 2; **HRMS** calculated for $C_{57}H_{112}NO_{11}Si_3$

$[M+NH_4]^+$ 1070.7538, found 1070.7544.

Macrolactone 27

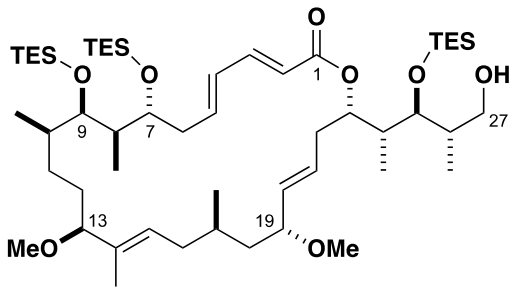


Et_3N (59 μL, 0.759 mmol) was added to a solution of *seco*-acid **26** (20.0 mg, 19.0 μmol) in THF (0.55 mL), followed by dropwise addition of TCBC (103 μL, 0.38 mmol). The mixture was stirred at rt for 1 h, then diluted with PhMe (2.2 mL) and the resulting cloudy orange solution added *via* syringe pump at a rate of 0.2 mL/h to a mixture of DMAP (139 mg, 1.14 mmol) and PhMe (3.4 mL). Upon completion, the reaction mixture was stirred for a further 3 h before being quenched with NH_4Cl solution (5 mL) and diluted with H_2O (3 mL). The organic layer was washed with NH_4Cl solution (3 x 5 mL), the combined organic phases dried (Na_2SO_4) and concentrated *in vacuo*. Crude residue was purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:15 → 1:8) to give macrolactone **27** (14.0 mg, 13.5 mmol, 70%) as a colourless oil.

R_f 0.50 (EtOAc/40-60 PE, 1:5); **$[\alpha]_{2C}^{\nu}$** = +46.8 (*c* 0.5, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 2948, 2885, 1748, 1713, 1641, 1459, 1300, 1259, 1235, 1084, 1054, 1039, 1003, 967, 791, 753; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.23 (1H, dd, *J* = 15.4, 10.8 Hz, H_3), 6.25 (1H, ddd, *J* = 14.5, 9.6, 4.4 Hz, H_5), 6.16 (1H, dd, *J* = 15.3, 10.8 Hz, H_4), 5.96 (1H, ddt, *J* = 16.5, 10.7, 5.8 Hz, C<u>H</u>=CH_2), 5.85 (1H, d, *J* = 15.3 Hz, H_2), 5.57 (1H, ddd, *J* = 14.9, 9.1, 6.1 Hz, H_{21}), 5.38 (1H, ddt, *J* = 17.2, 2.8, 1.6 Hz, CH=C<u>H</u>$_a$H$_b$), 5.31-5.27 (2H, m, CH=CH$_a$<u>H</u>$_b$, H_{23}), 5.06 (1H, dd, *J* = 15.5, 9.1 Hz, H_{20}), 5.05-5.02 (1H, m, H_{15}), 4.67-4.61 (2H, m, OC<u>H</u>$_2$), 4.30 (1H, dd, *J* = 10.6, 3.9 Hz, H_{27a}), 4.02 (1H, dd, *J* = 10.6, 7.5 Hz, H_{27b}), 3.65-3.62 (1H, m, H_7), 3.59 (1H, dd, *J* = 5.1, 5.1 Hz, H_{25}), 3.52 (1H, dt, *J* = 10.2, 4.2 Hz, H_{19}), 3.42-3.38 (2H, m, H_9, H_{13}), 3.22 (3H, s, OMe_{19}), 3.19 (3H, s, OMe_{13}), 2.40-2.33 (2H, m, H_{22} x 2), 2.31-2.25 (1H, m, H_{6a}), 2.19-2.12 (1H, m, H_{26}), 2.00-1.93 (2H, m, H_{6b}, H_{16a}), 1.86-1.80 (1H, m, H_{24}), 1.75-1.46 (6H, m, H_8, H_{10}, H_{12} x 2, H_{16b}, H_{18a}), 1.45 (3H, s, Me_{14}), 1.28-1.21 (2H, m, H_{17}, H_{18b}), 1.13-1.07

(2H, obs m, H_{11} x 2), 1.04 (3H, d, J = 7.1 Hz, Me_{24}), 1.03 (3H, d, J = 6.9 Hz, Me_{26}), 0.99-0.95 (30H, m, Me_{10}, $SiCH_2C\underline{H}_3$ x 9), 0.92 (3H, d, J = 7.0 Hz, Me_8), 0.82 (3H, d, J = 5.6 Hz, Me_{17}), 0.68-0.56 (18H, m, $SiC\underline{H}_2CH_3$ x 9); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 166.0, 155.1, 144.3, 142.1, 134.0, 132.9, 131.6, 131.2, 129.6, 129.4, 120.2, 118.7, 87.4, 81.5, 79.0, 77.1, 72.4, 71.4, 70.1, 68.2, 55.5, 55.5, 42.5, 42.2, 40.2, 39.0, 38.2, 36.7, 36.2, 35.9, 30.8, 29.5, 27.7, 19.9, 15.4, 14.2, 11.9, 11.4, 9.5, 6.9, 6.9, 6.9, 5.2, 5.2, 5.1; **HRMS** calculated for $C_{57}H_{110}NO_{10}Si_3$ $[M+NH_4]^+$ 1052.7432, found 1052.7430.

Macrolactone core 5

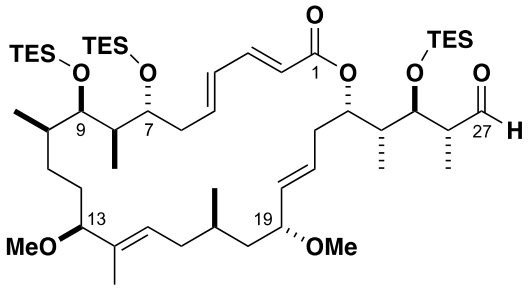


A solution of macrolactone **27** (18.0 mg, 17.4 μmol) in THF (2 mL) was added *via* cannula to a flask containing tetrakis(triphenylphosphine)palladium(0) (2.0 mg, 1.7 μmol) and dimedone (24.0 mg, 0.174 mmol) at rt. The mixture was stirred for 1 h until completion, then quenched with $NaHCO_3$ (10 mL) and extracted with EtOAc (2 x 20 mL). Combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and the yellow residue was purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:15 → 1:5). Macrolactone core **5** (16.4 mg, 0.124 mmol, 99%) was obtained as a pale yellow oil. Full characterisation of this compound is provided in the supporting information of our earlier paper.[13]

R_f 0.20 (EtOAc/40-60 PE, 1:5); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.25 (1H, dd, J = 15.2, 10.7 Hz, H_3), 6.27 (1H, ddd, J = 15.0, 10.2, 4.8 Hz, H_5), 6.17 (1H, dd, J = 14.9, 10.9 Hz, H_4), 5.85 (1H, d, J = 15.3 Hz, H_2), 5.58 (1H, ddd, J = 14.7, 10.2, 4.0 Hz, H_{21}), 5.26 (1H, ddd, J = 10.7, 4.9, 1.7 Hz, H_{23}), 5.08 (1H, dd, J = 15.2, 9.0 Hz, H_{20}), 5.04 (1H, dd, J = 10.5, 3.2 Hz, H_{15}), 3.72 (1H, ddd, J = 11.0, 5.5, 4.1 Hz, H_{27a}), 3.69 (1H, dd, J = 4.8, 4.8 Hz, H_{25}), 3.65-3.60 (2H, m, H_7, H_{27b}), 3.52 (1H, dt, J = 9.8, 4.1 Hz, H_{19}), 3.44-3.38 (2H, m, H_9, H_{13}), 3.22 (3H, s, OMe_{19}), 3.19 (3H, s, OMe_{13}), 2.53 (1H, t, J = 5.7 Hz, O$\underline{H}$), 2.45-2.41 (1H, m, H_{22a}), 2.35 (1H, t, J = 10.7 Hz, H_{22b}), 2.33-2.26 (1H, m, H_{6a}), 2.02-1.92 (3H, m, H_{6b}, H_{16a}, H_{26}), 1.91-1.87 (1H,

m, H_{24}), 1.76-1.46 (6H, m, H_8, H_{10}, H_{12} x 2, H_{16b}, H_{18a}), 1.45 (3H, s, Me_{14}), 1.26-1.21 (2H, m, H_{17}, H_{18b}), 1.14-1.07 (2H, obs m, H_{11} x 2), 1.05 (3H, d, J = 6.2 Hz, Me_{24}), 1.04 (3H, d, J = 6.2 Hz, Me_{26}), 0.99-0.95 (30H, m, Me_{10}, $SiCH_2C\underline{H}_3$ x 9), 0.92 (3H, d, J = 6.4 Hz, Me_8), 0.82 (3H, d, J = 5.8 Hz, Me_{17}), 0.73-0.67 (6H, m, $SiC\underline{H}_2CH_3$ x 3), 0.62 (6H, q, J = 7.8 Hz, $SiC\underline{H}_2CH_3$ x 3), 0.59 (6H, q, J = 7.8 Hz, $SiC\underline{H}_2CH_3$ x 3).

Aldehyde 28



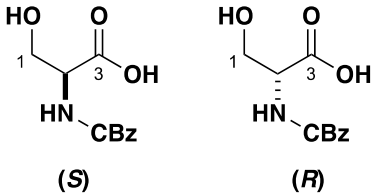
Oxalyl chloride (8 μL, 92 μmol) was added to a solution of DMSO (13 μL, 184 μmol) in CH_2Cl_2 (2.0 mL) at –78 °C. After stirring for 30 min, a solution of alcohol **5** (29.0 mg, 30.6 μmol) in CH_2Cl_2 (1.5 mL) was added. The mixture was stirred for 30 min, followed by addition of triethylamine (38 μL, 275 μmol). The reaction mixture was stirred at –78 °C for 30 min, then warmed to 0 °C for 30 min before being quenched with NH_4Cl solution (2 mL) and warmed to rt. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford aldehyde **28** (28.9 mg, 30.5 μmol, 99%) which was used immediately in the subsequent aldol reaction. Full characterisation of this compound is provided in the supporting information of our earlier paper.[13]

R_f 0.41 (EtOAc/40-60 PE, 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.78 (1H, d, J = 2.1 Hz, C$\underline{H}$O), 7.23 (1H, dd, J = 15.4, 10.6 Hz, H_3), 6.24 (1H, ddd, J = 15.3, 9.4, 4.6 Hz, H_5), 6.15 (1H, dd, J = 15.4, 10.5 Hz, H_4), 5.83 (1H, d, J = 15.2 Hz, H_2), 5.56 (1H, ddd, J = 14.8, 8.0, 6.0 Hz, H_{21}), 5.28 (1H, dt, J = 8.8, 3.9 Hz, H_{23}), 5.07 (1H, dd, J = 15.6, 9.2 Hz, H_{20}), 5.03 (1H, dd, J = 10.5, 4.6 Hz, H_{15}), 3.93 (1H, dd, J = 5.0, 3.9 Hz, H_{25}), 3.62 (1H, dd, J = 7.6, 4.4 Hz, H_7), 3.51 (1H, ddd, J = 9.7, 9.7, 4.5 Hz, H_{19}), 3.42 (1H, br d, J = 7.1 Hz, H_9), 3.37 (1H, dd, J = 10.8, 4.3 Hz, H_{13}), 3.19 (3H, s, OMe_{19}), 3.16 (3H, s, OMe_{13}), 2.63 (1H, qdd, J = 7.0, 3.9, 2.0 Hz, H_{26}), 2.38-2.32 (2H, m, H_{22} x 2), 2.27 (1H, m, H_{6a}), 2.04-1.92 (2H, m, H_{6b}, H_{16a}), 1.86 (1H, qdd, J = 7.1, 3.2, 1.7 Hz, H_{24}), 1.78-1.61 (3H, m, H_8, H_{12a}, H_{16b}), 1.61-1.47 (2H, m,

H_{10}, H_{12b}), 1.43 (1H, m, H_{18a}), 1.43 (3H, s, Me_{14}), 1.27-1.19 (2H, m, H_{17}, H_{18b}), 1.11 (3H, d, J = 7.1 Hz, Me_{26}), 1.08 (2H, m, H_{11} x 2), 0.99-0.92 (33H, m, Me_{10}, Me_{24}, $SiCH_2C\underline{H}_3$ x 9,), 0.90 (3H, d, J = 6.8 Hz, Me_8), 0.80 (3H, d, J = 6.0 Hz, Me_{17}), 0.66-0.54 (18H, m, $SiC\underline{H}_2CH_3$ x 9).

VII. Experimental Procedures for Enantiopure Trimethylserine

(*S*)- and (*R*)- *N*-carboxybenzyl serine (*S*)-32 and (*R*)-32



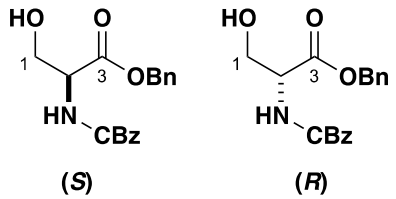
(L)-serine (2.50 g, 23.8 mmol) and $NaHCO_3$ (5.00 g, 59.5 mmol) were dissolved in water (20 mL) and THF (12 mL) at 0 °C. Benzyl chloroformate (3.75 mL, 26.3 mmol) was added and the reaction warmed to rt and stirred for 2 h. Water (10 mL) and Et_2O (10 mL) were added and the layers separated. The aqueous phase was acidified to approximately pH 2 with 3M HCl and extracted with EtOAc (3 × 20 mL). The organic extracts were washed with 3M HCl (10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the product **(*S*)-32** as a white solid (4.79 g, 20.0 mmol, 84%).

The opposite enantiomer **(*R*)-32** was prepared by an analogous procedure starting from (D)-serine (4.68 g, 19.6 mmol, 83%).

^{1}H NMR (500 MHz, MeOD) δ_H 7.41-7.27 (5H, m, Ph$\underline{H}$), 5.13 (2H, s, Ph$C\underline{H}_2$O), 4.29-4.26 (1H, m, H_2), 3.89 (1H, dd, J = 11.3, 5.0 Hz, H_{3a}), 3.84 (1H, dd, J = 11.2, 3.9 Hz, H_{3b}).

Data in agreement with that presented by J.W. Keillor.[11]

Benzyl esters (*S*)-32a and (*R*)-32a



[11] C. Gravel, D. Lapierre, J. Labelle and J.W. Keillor *Can. J. Chem.* 2007, **85**, 164

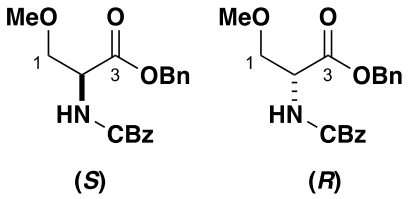
(*S*)-Cbz-serine (1.00 g, 4.18 mmol), was dissolved in MeOH (5 mL) and water (1 mL) at 0 °C and Cs_2CO_3 (844 mg, 2.09 mmol) was added. The reaction mixture was warmed to rt, stirred for 15 min and concentrated *in vacuo*. The resulting caesium salt was dissolved in DMF (5 mL) followed by addition of benzyl bromide (1.00 mL, 8.36 mmol). The reaction mixture was stirred at rt for 16 h before being quenched with water (10 mL) and the mixture extracted with Et_2O (3 × 7 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the crude product purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:2 → 2:3) to yield ester **(*S*)-32a** (1.07 g, 3.26 mmol, 78%, 99% *ee*) as a white solid.

The opposite enantiomer (**R)-32a** was prepared by an analogous procedure starting from (*R*)-Cbz-serine (1.12 g, 3.40 mmol, 82%, 99% *ee*).

R_f 0.52 (EtOAc/40-60 PE, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.38-7.20 (10H, m, PhH), 5.85 (1H, br d, *J* = 7.3 Hz, NH), 5.20 (2H, s, PhCH_2O), 5.11 (2H, s, PhCH_2O), 4.48 (1H, br m, H_2), 3.99 (1H, br d, *J* = 10.4 Hz, H_{3a}), 3.90 (1H, dd, *J* = 10.4 Hz, H_{3b}), 2.61 (1H, br s, OH); **Chiral HPLC** (Chiralpak® IA, ^{i}PrOH/hexane, 1:4) R_T (*R*) 9.01 min, R_T (*S*) 9.30 min.

Data in agreement with those presented by R. Marchelli.[12]

Methyl ethers (*S*)-32b and (*R*)-32b



(*S*)-32a (500 mg, 1.52 mmol), trimethyloxonium tetrafluoroborate (335 mg, 2.28 mmol) and proton sponge (650 mg, 3.04 mmol) were dissolved in CH_2Cl_2 (10 mL) at 0 °C and the mixture stirred for 6 h at rt. The reaction was quenched with $NaHCO_3$ (10 mL), the phases separated and the aqueous layer extracted with CH_2Cl_2 (3 × 7 mL). The combined organic extracts were washed with 3M HCl (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (gradient elution: EtOAc/40-60

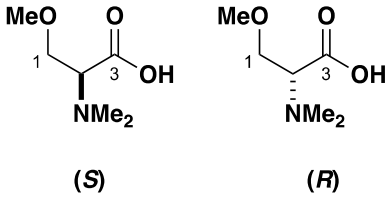
[12] V. Bocchi, G. Casnati, A. Dossena and R. Marchelli *Synthesis (Stuttg.)* 1979, 957

PE, 1:10 → 1:2) to yield methyl ether **(*S*)-32b** as a white solid (248 mg, 0.723 mmol, 48%, 97% *ee*, 86% BRSM).

(*R*)-Methyl ether **(*R*)-32b** was prepared by an analogous procedure (372 mg, 1.08 mmol, 73%, 88% BRSM, 99% *ee*).

R_f 0.76 (EtOAc/40-60 PE, 1:1); (*S*)-enantiomer $[\alpha]_{20}^{D}$ = −18.1 (*c* 0.97, MeOH), (*R*)-enantiomer $[\alpha]_{20}^{D}$ = +17.2 (*c* 2.78, MeOH); **IR** thin film, ν_{max} / cm^{-1}): 3328, 3035, 2933, 1717, 1499, 1455, 1388, 1337, 1294, 1193, 1116, 1044, 1028, 962, 912, 735, 696; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.40-7.28 (10H, m, PhH), 5.67 (1H, br d, *J* = 7.5 Hz, NH), 5.26 (1H, d, *J* = 12.2, $PhCH_aH_bO$), 5.17 (1H, d, *J* = 12.2, $PhCH_aH_bO$), 5.13 (2H, s, $PhCH_2O$), 4.45 (1H, br d, *J* = 8.8 Hz, H_2), 3.83 (1H, dd, *J* = 9.5, 3.1 Hz, H_{3a}), 3.64 (1H, dd, *J* = 9.4, 3.1 Hz, H_{3b}), 3.29 (3H, s, OCH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 170.3, 156.1, 136.3, 135.4, 128.6, 128.5, 128.4, 128.2, 128.1, 128.1, 72.4, 67.7, 67.1, 59.2, 54.5; **Chiral HPLC** (Chiralpak® IA, ^{i}PrOH / hexane, 1:4) R_T (*R*) 8.55 min, R_T (*S*) 13.52 min; **HRMS** Calculated for $C_{19}H_{22}NO_5$ $[M+H]^+$ 344.1492, found 344.1494.

(*S*)- and (*R*)-*N*,*N*,*O*-trimethylserine (*S*)-32c and (*R*)-32c



(*S*) (*R*)

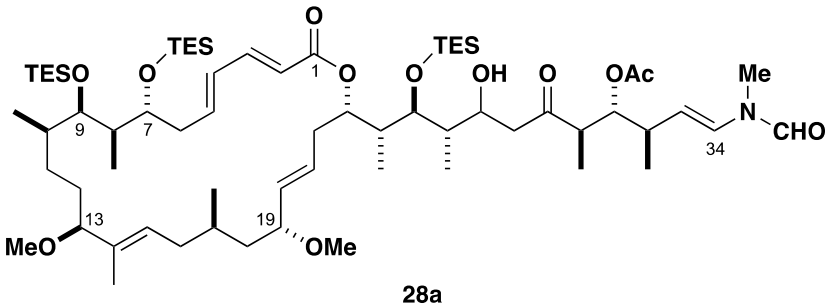
Palladium on charcoal (50.0 mg, 10 wt%, 47.1 μmol) and formaldehyde (0.500 mL, 37 wt% aqueous solution, 6.16 mmol) were added to a solution of **(*S*)-32b** (235 mg, 0.69 mmol) in ethanol (2.5 mL) and the mixture was placed under a hydrogen atmosphere (balloon pressure). The reaction mixture was stirred at rt for 48 h before being filtered through a plug of Celite® and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and loaded onto a column of DOWEX resin (WX8-100, H^+ form), which was then washed with CH_2Cl_2 and water followed by 1% aqueous ammonia solution to elute the product. The product-containing solution was concentrated *in vacuo* to yield (*S*)-*N*,*N*,*O*-trimethylserine **(*S*)-32c** as a white solid (82.1 mg, 0.558 mmol, 81%).

(*R*)-trimethylserine **(*R*)-32c** was prepared by an exactly analogous procedure starting from **(*R*)-32b** (339 mg, 0.988 mmol) in 62% yield (90.3 mg, 0.614 mmol).

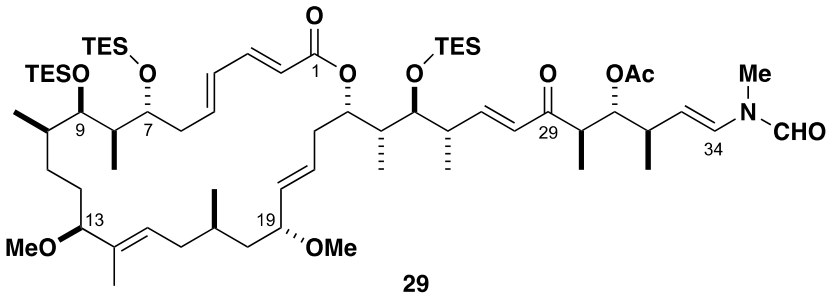
Melting point 148-152 °C; (*S*)-enantiomer $[\alpha]_{20}^{D}$ = +15.5 (*c* 0.20, MeOH), (*R*)-enantiomer $[\alpha]_{20}^{D}$ = −13.2 (*c* 0.31, MeOH); **IR** (thin film, ν_{max} / cm^{-1}): 3380, 1619, 1477, 1338, 1201, 1149, 1101, 1077, 1043, 1005, 976, 934, 870, 763; **^{1}H NMR** (500 MHz, MeOD) δ_H 3.93 (1H, dd, *J* = 11.7, 3.3 Hz, H_{3a}), 3.88 (1H, dd, *J* = 11.7, 6.3 Hz, H_{3b}), 3.75 (1H, dd, *J* = 6.1, 3.5 Hz, H_2), 3.39 (3H, s, $OC\underline{H}_3$); **^{13}C NMR** (125 MHz, MeOD) δ_C 168.8, 69.2, 68.5, 57.9, 41.1; **HRMS** calculated for $C_6H_{12}NO_3$ $[M–H]^-$ 146.0823, found 146.0825.

VIII. Experimental Procedures for Aplyronines A, C and D

Enone 29 *via* aldol adduct **28a**



28a



29

Ketone **6**[13] (37.7 mg, 0.148 mmol) and aldehyde **28** (28.9 mg, 30.5 μmol) were dried azeotropically with PhH and placed under vacuum for 18 h. Ketone **6** was dissolved in Et_2O (0.5 mL), followed by sequential addition of Et_3N (28 μL, 0.20 mmol) and Cy_2BCl (31 μL, 0.14 mmol) at 0 °C. The resulting cloudy yellow solution was stirred for 30 min at this temperature before being cooled to –78 °C and a solution of aldehyde **28** in Et_2O (1.5 mL) was added. The reaction mixture was stirred at –78 °C for 1 h, warmed to –10 °C over 2 h then quenched with pH 7 buffer (2 mL) and MeOH (2 mL). The mixture was stirred for 30

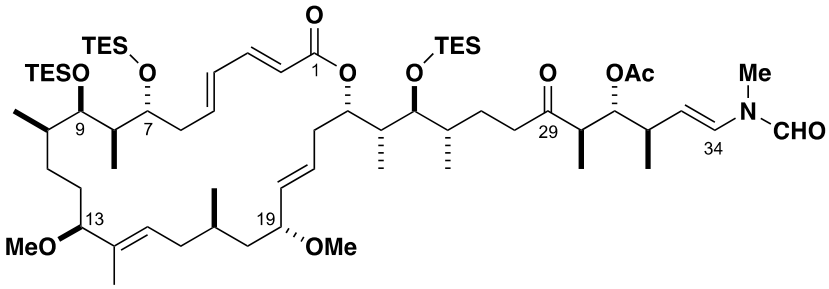
[13] I. Paterson, S.J. Fink, L.Y.W. Lee, S.J. Atkinson and S.B Blakey *Org. Lett.* 2013, **15**, 3118

min before being extracted with EtOAc (4 × 10 mL), dried over ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:4 → 3:2) and all fractions containing product along with recovered ketone **6** were collected and combined. The resulting mixture was used directly in the subsequent elimination.

Burgess reagent (15.0 mg, 53.2 μmol) was added to a flask containing the mixture of aldol adduct **28a** and ketone **6** followed by THF (0.5 mL). The reaction mixture was stirred at rt for 16 h before quenching with NH_4Cl solution (3 mL) and the mixture being extracted with EtOAc (4 × 5 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the crude product purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:4 → 3:2) to afford enone **29** (23.6 mg, 19.9 μmol, 65% over 2 steps) along with recovered ketone **6** (25.0 mg, 97.9 μmol).

R_f 0.90 and 0.85 (EtOAc/40-60 PE, 3:2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.29 (0.67H, s, C<u>H</u>O), [8.08] (0.33H, s, C<u>H</u>O*), 7.21 (1H, dd, *J* = 15.3, 10.7 Hz, H_3), [7.17] (0.33H, d, *J* = 14.7 Hz, H_{34}*), 6.99 (0.67H, dd, *J* = 15.8, 8.0 Hz, H_{27}), [6.97] (0.33H, dd, *J* = 15.7, 7.7 Hz, H_{27}*), 6.50 (0.67H, d, *J* = 14.1 Hz, H_{34}), 6.24 (1H, ddd, *J* = 15.2, 9.7, 4.3 Hz, H_5), 6.17 (0.67H, d, *J* = 15.8 Hz, H_{28}), [6.17] (0.33H, d, *J* = 15.9 Hz, H_{28}*), 6.15 (1H, dd, *J* = 15.2, 10.5 Hz, H_4), 5.82 (1H, d, *J* = 15.3 Hz, H_2), 5.56 (1H, m, H_{21}), 5.26 (1H, ddd, *J* = 13.4, 9.0, 4.4 Hz, H_{23}), 5.18 (0.67H, dd, *J* = 8.8, 3.7 Hz, H_{31}), [5.18] (0.33H, dd, *J* = 8.5, 3.5 Hz, H_{31}*), 5.08-4.98 (2H, m, H_{33}, H_{20}), 4.99 (1H, dd, *J* = 14.1, 9.3 Hz, H_{15}), 3.64-3.58 (2H, m, H_7, H_{25}), 3.50 (1H, ddd, *J* = 13.2, 9.8, 4.3 Hz, H_{19}), 3.40 (1H, obs, H_9), 3.37 (1H, dd, *J* = 10.9, 4.3 Hz, H_{13}), 3.19 (3H, s, OMe_{19}), 3.16 (3H, s, OMe_{13}), [3.07] (1H, s, NMe*), 3.03 (2H, s, NMe), 2.98 (0.67H, dq, *J* = 8.3, 7.2 Hz, H_{32}), [2.94] (0.33H, dq, *J* = 8.7, 7.0 Hz, H_{32}*), 2.65-2.47 (2H, m, H_{26}, H_{30}), 2.38-2.22 (3H, m, H_{6a}, H_{22} x 2), 1.98 (2H, s, COC<u>H</u>$_3$), [1.97] (1H, s, COC<u>H</u>$_3$*), 1.97-1.91 (2H, m, H_{6b}, H_{16a}), 1.78-1.60 (4H, m, H_8, H_{12a}, H_{16b}, H_{24}), 1.60-1.43 (3H, m, H_{10}, H_{12b}, H_{18a}), 1.42 (3H, s, Me_{14}), 1.24-1.17 (2H, m, H_{18b}, H_{17}), 1.11-1.05 (8H, m, H_{11} x 2, Me_{26}, Me_{32}), 1.04 (3H, d, *J* = 6.9 Hz, Me_{30}), 0.97-0.91 (30H, m, Me_{10}, $SiCH_2C$<u>H</u>$_3$ x 9), 0.92 (3H, d, *J* = 6.9 Hz, Me_{24}), 0.89 (3H, d, *J* = 6.7 Hz, Me_8), 0.79 (3H, d, *J* = 5.7 Hz, Me_{17}), 0.66-0.53 (18H, m, SiC<u>H</u>$_2CH_3$ x 9). Distinguishable resonances of the minor rotamer (2:1 ratio) are given in brackets and marked with an asterisk. Full characterisation of this compound is provided in the supporting information of our earlier paper.[12]

Ketone 29a



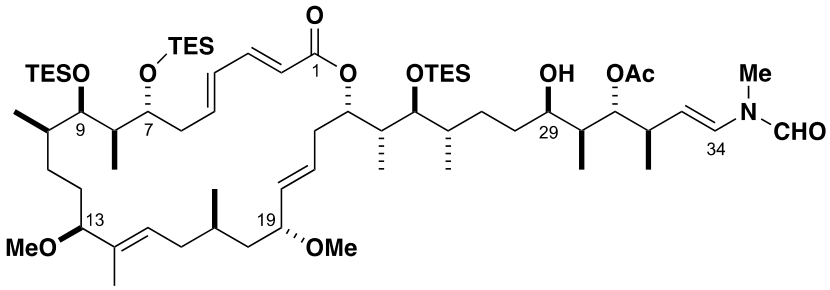
Preparation of Stryker's reagent: $Cu(OAc)_2 \cdot H_2O$ (25.0 mg, 0.125 mmol) and PPh_3 (65.0 mg, 0.25 mmol) were suspended in PhMe (4.66 mL) under an argon atmosphere. Tetramethyldisiloxane (0.330 mL, 2.43 mmol) was added and the bright blue mixture stirred for 16 h to produce a deep red solution (0.025 M in copper, 0.46 M in hydride) which was used directly in conjugate reduction reactions.

Stryker's reagent solution (0.160 mL, 4.00 μmol copper equivalent) was added to a stirred solution of enone **29** (23.6 mg, 19.9 μmol) in PhMe (0.24 mL). A further aliquot of Stryker's reagent solution (80 μL) was added after 1 h and the red solution stirred for a further 4 h at rt. The reaction mixture was applied directly to a column of silica gel and the product eluted (gradient elution: EtOAc/40-60 PE, 1:4 → 2:3) to afford ketone **29a** (19.8 mg, 17.2 μmol, 86%).

R_f 0.90 and 0.85 (EtOAc/40-60 PE, 3:2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.29 (0.67H, s, CHO), [8.08] (0.33H, s, CHO*), 7.20 (1H, dd, J = 15.2, 10.5 Hz, H_3), [7.16] (0.33H, d, J = 14.4 Hz, H_{34}*), 6.49 (0.67H, d, J = 14.1 Hz, H_{34}), 6.22 (1H, ddd, J = 15.3, 9.4, 4.3 Hz, H_5), 6.14 (1H, dd, J = 15.3, 10.7 Hz, H_4), 5.82 (1H, d, J = 15.4 Hz, H_2), 5.55 (1H, ddd, J = 15.6, 15.6, 7.4 Hz, H_{21}), 5.30 (1H, m, H_{23}), 5.13 (1H, dd, J = 9.0, 3.9 Hz, H_{31}), 5.06-4.94 (3H, m, H_{15}, H_{20}, H_{33}), 3.61 (1H, dd, J = 8.7, 4.0 Hz, H_7), 3.50 (1H, ddd, J = 10.5, 10.5, 4.0 Hz, H_{19}), 3.42-3.32 (3H, m, H_9, H_{13}, H_{25}), 3.19 (3H, s, OMe_{19}), 3.16 (3H, s, OMe_{13}), [3.07] (1H, s, NMe*), 3.03 (2H, s, NMe), 2.78 (0.67H, dq, J = 8.7, 7.2 Hz, H_{30}), [2.75] (0.33H, dq, J = 9.0, 7.1 Hz, H_{30}*), 2.58-2.36 (3H, m, H_{28} x 2, H_{32}), 2.33 (2H, m, H_{22} x 2), 2.26 (1H, m, H_{6a}), 2.01 (2H, s, $COCH_3$), [2.00] (1H, s, $COCH_3$*), 2.03-1.91 (2H, m, H_{6b}, H_{16a}), 1.80-1.45 (9H, m, H_8, H_{10} x 2, H_{12}, H_{16b}, H_{18a}, H_{24}, H_{26}, H_{27a}), 1.42 (3H, s, Me_{14}), 1.33-1.18 (3H, m, H_{17}, H_{18b}, H_{27b}), 1.10 (2H, obs, H_{11} x 2), 1.06 (3H, d, J = 7.0 Hz, Me_{32}), 1.05 (2H, d, J = 6.9 Hz, Me_{30}), [1.04]

(1H, d, J = 6.9 Hz, Me_{30}*), 0.99-0.94 (30H, m, Me_{26}, $SiCH_2C\underline{H}_3$ x 9), 0.93 (3H, obs, Me_{10}), 0.90 (3H, d, J = 6.5 Hz, Me_{24}), 0.89 (3H, d, J = 6.6 Hz, Me_8), 0.80 (3H, d, J = 5.8 Hz, Me_{17}), 0.67-0.54 (18H, m, $SiC\underline{H}_2CH_3$ x 9). Distinguishable resonances of the minor rotamer (2:1) are given in brackets and marked with an asterisk. Full characterisation of this compound is provided in the supporting information of our earlier paper.[12]

Alcohol 30

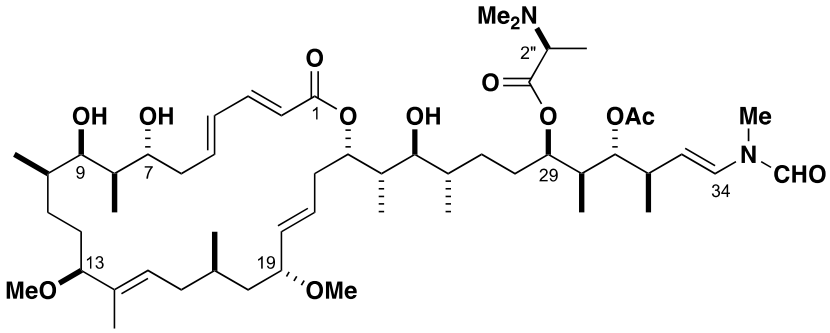


$Zn(BH_4)_2$ solution (0.50 mL, 0.175 M in Et_2O, 87.5 μmol) was added to a solution of ketone **29a** (19.8 mg, 16.7 μmol) in Et_2O (0.50 mL) at 0 °C and the reaction stirred at this temperature. Further aliquots of $Zn(BH_4)_2$ solution (0.25 mL) were added after 2 h, 3 h and 6 h and the reaction quenched with NH_4Cl (0.50 mL) and Na/K tartrate (1.0 mL) after a total of 7 h. The quenching mixture was stirred vigorously for 30 min, extracted with EtOAc (3 × 5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (gradient elution: CH_2Cl_2/EtOAc, 1:10 → 1:3) to yield alcohol **30** as a colourless oil (13.0 mg, 10.9 μmol, 65%).

R_f 0.60 (EtOAc/CH_2Cl_2, 1:3); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.29 (0.67H, s, C$\underline{H}$O), [8.08] (0.33H, s, C$\underline{H}$O*), 7.21 (1H, dd, J = 15.4, 10.4 Hz, H_3), [7.18] (0.33H, d, J = 14.8 Hz, H_{34}*), 6.51 (0.67H, d, J = 14.0 Hz, H_{34}), 6.22 (1H, ddd, J = 15.3, 9.0, 4.2 Hz, H_5), 6.14 (1H, dd, J = 15.6, 10.5 Hz, H_4), 5.82 (1H, d, J = 15.5 Hz, H_2), 5.57 (1H, ddd, J = 14.9, 9.8, 4.8 Hz, H_{21}), 5.30 (1H, m, H_{23}), 5.06-4.98 (3H, m, H_{15}, H_{33}, H_{20}), 4.82 (1H, m, H_{31}), 3.61 (1H, br dd, J = 8.6, 3.9 Hz, H_7), 3.50 (1H, ddd, J = 10.0, 10.0, 4.3 Hz, H_{19}), 3.46-3.35 (4H, m, H_9, H_{13}, H_{25}, H_{29}), 3.20 (3H, s, OMe_{19}), 3.17 (3H, s, OMe_{13}), [3.06] (1H, s, NMe*), 3.02 (2H, s, NMe), [2.62] (0.33H, m, H_{32}*), 2.57 (0.67H, m, H_{32}), 2.53 (1H, br s, O$\underline{H}$), 2.36 (2H, m, H_{22} x 2), 2.25 (1H, m, H_{6a}), 2.16 (2H, s, $COC\underline{H}_3$), [2.15] (1H, s, $COC\underline{H}_3$*), 1.99-1.91 (2H, m, H_{6b}, H_{16a}), 1.76 (1H, m, H_{24}), 1.74-1.45 (9H, m, H_8, H_{10} x 2, H_{12} x 2, H_{16b}, H_{26}, H_{27}, H_{30}), 1.45-1.36 (3H, m, H_{18a}, H_{28} x 2), 1.43 (3H, s, Me_{14}), 1.29-1.15 (2H, m, H_{17}, H_{18b}), 1.11 (2H, obs,

H_{11} x 2), 1.06 (2H, d, J = 6.9 Hz, Me_{32}), [1.05] (1H, d, J = 6.8 Hz, Me_{32}*), 0.98-0.92 (33H, m, Me_{10}, Me_{24}, $SiCH_2C\underline{H}_3$ x 9), 0.91 (3H, d, J = 6.5 Hz, Me_{26}), 0.90 (3H, d, J = 6.7 Hz, Me_{30}), 0.86 (3H, d, J = 6.9 Hz, Me_8), 0.80 (3H, d, J = 6.0 Hz, Me_{17}), 0.67-0.54 (18H, m, $SiC\underline{H}_2CH_3$ x 9). Distinguishable resonances of the minor rotamer (2:1 ratio) are given in brackets and marked with an asterisk. Full characterisation of this compound is provided in the supporting information of our earlier paper.[12]

Aplyronine C (**3**)



Alcohol **30**, (7.5 mg, 6.3 μmol), (*S*)-*N,N*-dimethylalanine (7.4 mg, 63 μmol), DMAP (7.6 mg, 63 μmol) and DMAP hydrochloride (10.0 mg, 63.0 μmol) were dissolved in CH_2Cl_2 (0.6 mL) and DCC solution (189 μL, 1 M in CH_2Cl_2, 189 μmol) was added. The reaction mixture was stirred at rt for 16 h, quenched with $NaHCO_3$ (2 mL), extracted with CH_2Cl_2 (4 × 2 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was triturated with Et_2O to remove dicyclohexylurea and transferred to a plastic reaction vessel.

A solution of HF·pyr was prepared by adding HF·pyr (100 μL) to a solution of pyr (200 μL) in THF (1.0 mL) at 0 °C and stirring at rt for 30 min. This solution was added to the crude dimethylalanine ester at 0 °C and the mixture stirred at rt overnight. The reaction was quenched at 0 °C with $NaHCO_3$ (5 mL), stirred vigorously at rt for 30 min and extracted with EtOAc (5 × 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and purified by preparative thin layer chromatography (CH_2Cl_2/EtOAc/MeOH, 4:4:1) to afford aplyronine C (**3**) as an amorphous white solid (4.8 mg, 5.1 μmol, 81%).

R_f 0.55 (CH_2Cl_2/EtOAc/MeOH, 4:4:1); **^{1}H NMR** (500 MHz, acetone-d^6) *See Table 1*; **^{13}C NMR** (125 MHz, acetone-d^6) *See Table 1*; **HRMS** calculated for $C_{53}H_{91}N_2O_{12}$ $[M+H]^+$ 947.6567, found 947.6597.

Data in agreement with K. Yamada.[14]

Atom	δ_C Synthetic (125 MHz)	δ_C Natural (150 MHz)	δ_H Synthetic (500 MHz)	Mult	*J* [Hz]	δ_H Natural (600 MHz)	Mult	*J* [Hz]
1	167.8	167.8						
2	120.7	120.7	5.92	d	15.3	5.93	d	15.0
3	145.8	145.8	7.26	dd	15.5, 9.7	7.26	dd	15.0, 9.6
4	130.8	130.7	6.37	dd	15.1, 9.6	6.37	dd	15.0, 9.6
5	143.6	143.5	6.42	ddd	14.9, 8.9, 4.9	6.42	ddd	15.0, 9.2, 5.0
6a	36.7	36.8	2.25	m		2.26	m	
6b			2.14	m		2.15	m	
7	73.4	73.4	3.67	br dd	8.6, 4.3	3.68	m	
7OH			3.79	br d	4.1	3.8	br s	
8	41.8	41.7	1.72	m		1.72	m	
8Me	11.9	11.9	1.00	d	6.9	1.00	d	7.0
9	77.2	77.2	3.41	m		3.43	m	
9OH			3.35	d	5.2	3.35	br s	
10	34.6	34.3	1.67	m		1.67	m	
10Me	16.4	16.4	0.97	d	6.7	0.98	d	6.5
11	24.4	24.5	1.20	m		1.20	m	
12	30.0	29.5	1.59	m		1.59	m	
13	87.1	87.1	3.48	m		3.50	m	
13OMe	55.6	55.6	3.12	s		3.13	s	
14	134.9	134.8						
14Me	10.1	10.1	1.43	s		1.45	s	
15	130.8	130.7	5.21	dd	10.7, 4.4	5.22	br dd	10.4, 4.6
16a	37.4	37.4	1.94	m		1.96	m	
16b			1.79	m		1.81	m	
17	30.4	30.5	1.25	m		1.26	m	
17Me	20.5	20.3	0.78	d	6.4	0.79	d	6.5
18a	41.3	41.3	1.54	m		1.55	m	
18b			1.16	m		1.17	m	
19	82.3	82.2	3.48	m		3.50	m	
19OMe	55.4	55.4	3.11	s		3.12	s	
20	133.4	133.4	5.00	dd	15.7, 9.4	5.01	dd	15.0, 9.2
21	132.9	132.8	5.62	ddd	15.0, 10.5, 4.1	5.63	ddd	15.0, 10.4, 4.0
22a	38.1	38.1	2.45	ddd	10.2, 10.2, 2.4	2.45	m	
22b			2.30	m		2.29	m	

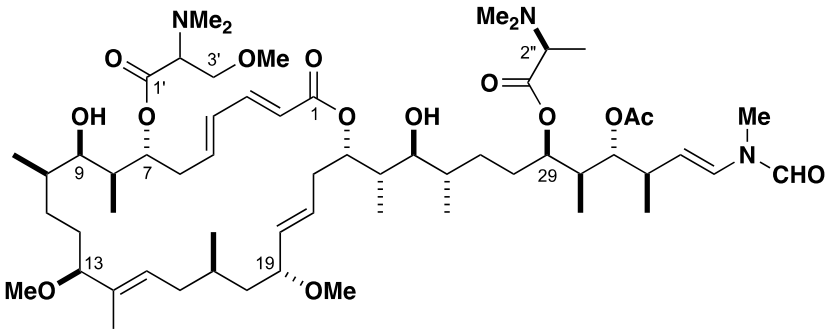
[14] M. Ojika, H. Kigoshi, Y. Yoshida, T. Ishigaki, M. Nisiwaki, I. Tsukada, M. Arakawa, H. Ekimoto and K. Yamada *Tetrahedron* **2007**, *63*, 3138

23	72.8	72.8	5.47	d	11.3	5.48	br d	10.8
24	42.0	42.0	1.72	m		1.74	m	
24Me	10.7	10.7	0.90	d	7.2	0.90	d	7.0
25	76.9	76.9	3.06	m		3.06	m	
25OH		34.8	3.58	d	5.2	3.58	br d	5.6
26	34.8		1.64	m		1.65	m	
26Me	17.9	17.9	0.98	d	6.6	0.99	m	
27a	25.3	25.2	1.37	m		1.38	m	
27b			1.16	m		1.16	m	
28a	31.1	30.7 [30.9]	1.64	m		1.65	m	
28b			1.52	m		1.53	m	
29	72.7	72.7	5.02	m		5.03	m	
30	38.1	38.1	1.97	m		1.98	m	
30Me	10.1	10.1 [10.0]	1.00	d	6.9	1.00	d	7.0
31	77.4	77.4	4.80 [4.80]	dd	10.0, 2.8 [9.9, 3.1]	4.80 [4.81]	dd	10.0, 2.8
32	37.6 [37.8]	37.6 [37.8]	2.65 [2.69]	m		2.65 [2.67]	m	
32Me	20.4	19.9	1.00	d	6.9	1.01	m	
33	110.0 [112.1]	110.0 [112.1]	5.05 [5.10]	dd	14.1, 9.4 [14.5, 9.5]	5.05 [5.11]	dd	14.4, 9.2
34	131.1 [126.3]	131.1 [126.3]	6.84 [7.16]	d	14.0 [14.5]	6.84 [7.16]	d	14.4
NMe34	27.3 [33.1]	27.3 [33.0]	2.97 [3.09]	s		2.97 [3.10]	s	
CHO	163.0 [161.8]	163.0 [161.7]	8.37 [8.11]	s		8.37 [8.11]	s	
OAc	170.8	170.7						
OAc	21.0	21.0	2.03	s		2.04 [2.03]	s	
1''	172.8	172.8						
2''	63.5	63.5 [62.9][a]	3.19 [3.19]	q	7.1 [6.9]	3.19 [3.22][a]	m	
NMe2'	41.7	41.6	2.33	br s		2.34	s	
3''	15.9	15.9 [15.2][a]	1.26 [1.26]	d	7.2 [7.2]	1.27 [1.22][a]	d	7.0

Table 1 NMR Data comparison of natural and synthetic aplyronine C. Minor counterparts of doubled signals due to vinyl formamide rotamers are given in brackets. [a]Minor signals in natural aplyronine C are due to diastereomers of the C_{29} dimethylalanine residue, this residue was synthesised in diastereomerically pure form in the synthetic sample.

Full characterisation of this compound is provided in the supporting information of our earlier paper.[12]

Aplyronine A (1)



A stock solution of (rac)-*N,N,O*-trimethylserine (3.8 mg, 21 μmol) and DMAP (2.6 mg, 21 μmol) in CH_2Cl_2 (0.50 mL, 0.042 M) was prepared. Another stock solution containing TCBC (5 μL, 32 μmol) and triethylamine (6 μL, 43 μmol) in PhH (0.5 mL, 0.064 M in TCBC) was also prepared. Aplyronine C (**3**) (4.8 mg, 5.1 μmol) was dissolved in CH_2Cl_2 and PhH (1:1, 0.8 mL) cooled to 0 °C and an aliquot of each stock solution was added (120 μL, 1 eq. trimethylserine, 1.5 eq TCBC). The reaction mixture was stirred at this temperature for 3 h with further additions of each stock solution (60 μL) every 30 minutes. The reaction was quenched with MeOH (0.1 mL), concentrated *in vacuo* and purified by preparative thin layer chromatography (CH_2Cl_2/EtOAc/MeOH, 4:4:1) to afford aplyronine A (**1**) (3.3 mg, 3.1 μmol, 61%, 82% BRSM) as an amorphous white solid, along with recovered aplyronine C (**3**) (1.2 mg, 1.3 μmol).

R_f 0.51 (CH_2Cl_2/EtOAc/MeOH, 4:4:1); **^{1}H NMR** (500 MHz, acetone-d^6) *See Table 2*; **^{13}C NMR** (125 MHz, acetone-d^6) *See Table 2*; **$[\alpha]_{2C}^{\mu}$** = +20.0 (*c* 0.075, MeOH); **IR** (thin film, ν_{max} / cm^{-1}): 3441, 2968, 2926, 1730, 1697, 1654, 1455, 1376, 1241, 1082, 968, 869; **HRMS** calculated for $C_{59}H_{102}N_3O_{14}$ $[M+H]^+$ 1076.7356, found 1076.7362.

Data in agreement with K. Yamada.[9]

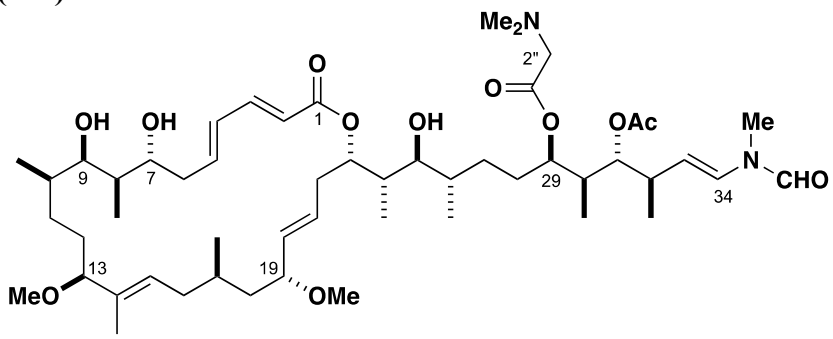
Atom	δ_C Synthetic (125 MHz)	δ_C Natural (150 MHz)	δ_H Synthetic (500 MHz)	Mult	*J* [Hz]	δ_H Natural (600 MHz)	Mult	*J* [Hz]
1	167.6	167.5						
2	121.8 [121.8]	121.7 [121.8]	5.98	d	15.4	5.98	d	15.3
3	145.1	145.0	7.22	dd	15.0, 11.0	7.23	dd	15.3, 10.8
4	131.7	131.7	6.45	dd	15.7, 10.8	6.43 [6.46]	dd	15.2, 10.8

	[131.8]	[131.8]	[6.46]		[15.5, 10.6]			
5	141.2	141.1	6.29	m		6.29	m	
6a	32.6 [32.5]	32.7 [32.6]	2.46	m		2.46	m	
6b			2.15	m		2.16	m	
7	76.6	76.6	4.75 [4.71]	br d	12.1 [12.1]	4.75 [4.72]	br d	10.0
8	39.4 [39.1]	39.3 [39.0]	2.01	m		2.01	m	
8Me		11.7 [11.5]	1.00	d	6.7	1.01 [0.99]	d	7.0
9	78.0	77.9	3.31	m		3.30	m	
10	33.1	33.3 [33.5]	1.67	m		1.67	m	
10Me	16.3	16.4	1.02	d	6.8	1.02	d	7.1
11a	22.5	22.6	1.54	m		1.55	m	
11b			1.30	m		1.28	m	
12	29.3	29.2	1.65	m		1.65	m	
13	86.8 [86.7]	86.8 [86.7]	3.52	m		3.52	m	
13OMe	55.5	55.5	3.12	s		3.13	s	
14	135.4 [135.5]	135.4 [135.5]						
14Me	10.3	10.3	1.51 [1.51]	s		1.51 [1.52]	s	
15	130.8 [130.7]	130.7 [130.6]	5.18	m		5.18	m	
16a	38.2 [38.6]	38.1 [38.5]	1.92	m		1.91 [1.93]	m	
16b			1.58 [1.61]	m		1.58 [1.60]	m	
17	30.7	30.5	1.19	m		1.19	m	
17Me	20.3	20.3	0.75 [0.74]	d	5.7 [5.6]	0.76 [0.74]	d	6.0
18a	41.1	41.1	1.55	m		1.56	m	
18b			1.13	m		1.14	m	
19	82.4	82.4	3.47	ddd	10.1, 9.4, 3.9	3.47	m	
19OMe	55.4	55.4	3.10	s		3.11	s	
20	133.3	133.4	4.96	dd	15.1, 9.5	4.95	dd	15.3, 9.3
21	132.9	132.8	5.61	ddd	15.1, 10.7, 4.4	5.61	ddd	15.3, 10.5, 4.0
22a	38.2	38.2	2.44	m		2.42	m	
22b			2.29	m		2.27	m	
23	72.8	72.7	5.47	br d	11.1	5.47	br d	11.0
24	41.9	41.9	1.75	m		1.74	m	
24Me	10.7	10.7	0.90	m		0.90	m	
25	76.9	77.0	3.05	br d	8.3	3.06	br d	8.7
26	34.8	34.8	1.65	m		1.63	m	
26Me	17.9	17.9	0.98	d	6.8	0.98	d	7.0
27a	25.3	25.3	1.38	m		1.38	m	
27b			1.16	m		1.16	m	
28a	30.8	30.7	1.66	m		1.65	m	
28b			1.51	m		1.51	m	

29	72.7	72.7	5.02	m		5.03	m	
30	38.1	38.0	1.97	m		1.97	m	
30Me	10.1	10.1 [10.0]	1.00	d	6.7	1.00	m	
31	77.4	77.4	4.80 [4.80]	dd	10.1, 2.9 [10.1, 3.2]	4.80 [4.81]	dd	10.1, 2.7
32	37.6 [37.8]	37.6 [37.8]	2.65	m		2.65 [2.67]	m	
32Me	19.9	19.9	1.02	d	6.9	1.01	d	6.7
33	110.0 [112.1]	110.0 [112.1]	5.05 [5.10]	dd	14.1, 9.4 [14.5, 9.5]	5.05 [5.11]	dd	14.0, 9.6
34	131.1 [126.3]	131.0 [126.3]	6.84 [7.15]	d	14.2 [14.7]	6.84 [7.16]	d	14.0
34NMe	27.3 [33.1]	27.3 [33.0]	2.97 [3.09]	s		2.97 [3.09]	s	
OAc	170.8	170.7						
OAc	21.0	21.0	2.03	s		2.03 [2.02]	s	
NCHO	163.0 [161.8]	162.9 [161.7]	8.36 [8.10]	s		8.36 [8.10]	s	
1’	170.5 [170.6]	170.4 [170.6]						
2’	68.0 [67.8]	68.0 [67.8]	3.37 [3.38]	dd	7.6, 5.6 [7.5, 5.5]	3.37 [3.38]	dd	7.4, 5.4
2’NMe_2	42.7	42.6	2.36 [2.38]	s		2.37 [2.38]	s	
3’a	72.5 [72.8]	72.4 [72.8]	3.69 [3.68]	dd	9.2, 7.7 [9.3, 7.7]	3.69 [3.68]	dd	9.4, 7.4
3’b			3.59	dd	9.4, 5.4	3.60	dd	9.4, 5.4
3'OMe	59.0 [59.0]	59.0 [58.9]	3.34 [3.31]	s		3.34 [3.31]	s	
1’’	172.8	172.8						
2’’	63.5	63.5 [62.9][c]	3.18 [3.19][b]	q	7.1	3.19 [3.22][c]	m	
2’’NMe_2	41.6	41.6	2.33 [2.33][b]	s		2.34 [2.32][c]	s	
3’’	15.9	15.9	1.25 [1.26]	d	7.2 [7.2]	1.26 [1.21][c]	d	7.3

Table 2 NMR Data comparison of natural and synthetic aplyronine A (**1**). Minor counterparts of doubled signals are given in brackets. [a]Minor signal due to diastereomers (1:1) of the C7 trimethylserine residue. [b]Minor signals due to rotamers of the formamide bond (2:1). [c]Minor signals due to diastereomers (10:1) of the C29 dimethylalanine residue, these are not observed in the synthetic sample as the 2’’ stereocentre was synthesised in diastereomerically pure fashion.

Aplyronine I (30a)



Alcohol **30** (6.0 mg, 5.1 µmol), *N,N*-dimethylglycine (2.6 mg, 25 µmol) and DMAP (3.1 mg, 25 µmol) were dissolved in THF and PhMe (1:1, 1.0 mL). Et_3N (7 µL, 50 µmol) and TCBC (6 µL, 35 µmol) were added and the reaction stirred at rt for 2 h. MeOH (0.5 mL) was added, the reaction mixture concentrated *in vacuo* and the crude product transferred to a plastic reaction vessel.

A solution of HF·pyr was prepared by adding HF·pyr (100 µL) to a solution of pyr (200 µL) in THF (1 mL) at 0 °C and stirring at rt for 30 min. This solution was added to the crude dimethylglycine ester at 0 °C and the reaction stirred at rt overnight. The reaction was quenched at 0 °C with $NaHCO_3$ solution (5 mL), stirred vigorously at rt for 30 min and extracted with EtOAc (5 × 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and purified by flash column chromatography (gradient elution: CH_2Cl_2/EtOAc/MeOH, 1:1:0 → 4:4:1) to afford aplyronine I **30a** as an amorphous white solid (3.7 mg, 4.0 µmol, 79%).

R_f 0.55 (CH_2Cl_2/EtOAc/MeOH, 4:4:1); **^{1}H NMR** (500 MHz, $CHCl_3$) *See Table 3*; **^{13}C NMR** (125 MHz, $CHCl_3$) *See Table 3*; $[\alpha]_{20}^{D}$ = +9.3 (*c* 0.40, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 3651, 2918, 1737, 1654, 1384, 1235, 1066, 869; **HRMS** calculated for $C_{52}H_{89}N_2O_{12}$ $[M+H]^+$ 933.6410, found 933.6427.

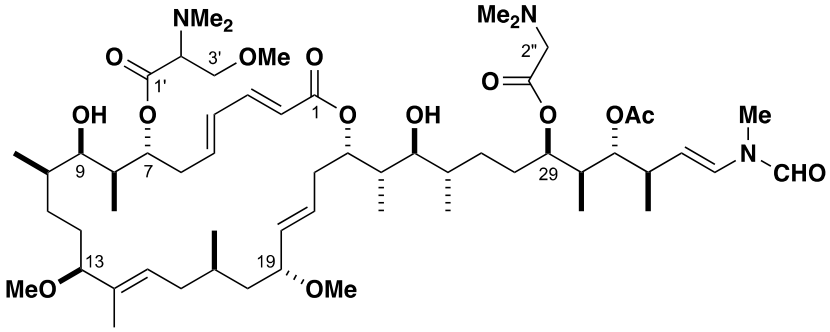
Proton	δ_C	δ_H	Mult	J [Hz]
1	162.2			
2	119.2	5.84	d	15.3
3	145.3	7.27	dd	15.4, 10.2
4	130.3	6.23	dd	15.3, 10.2
5	141.0	6.17	ddd	15.2, 8.4, 4.9

6a	38.1	2.51	m	
6b		2.24	m	
7	74.8	3.74	br ddd	6.8, 6.4, 3.2
8	38.1	1.68	m	
8Me	11.9	1.04	d	6.9
9	75.5	3.64	m	
10	35.6	1.64	m	
10Me	15.5	0.91	d	7.1
11a	26.2	1.22		
11b		1.09		
12	29.5	1.61	m	
13	87.2	3.43	dd	8.28, 6.78
13OMe	55.7	3.18	s	
14	134.7			
14Me	10.0	1.25	s	
15	128.9	5.11	dd	9.3, 4.9
16a	36.2	2.00	m	
16b		1.76	m	
17	29.7	1.30	m	
17Me	19.6	0.76	d	5.7
18a	40.9	1.48	m	
18b		1.29	m	
19	81.3	3.50	ddd	9.4, 9.4, 3.5
19OMe	55.7	3.20	s	
20	133.2	5.16	dd	15.4, 9.1
21	130.9	5.54	m	
22a	36.6	2.45	m	
22b		2.38	m	
23	73.0	5.37	d	10.3
24	41.2	1.74	m	
24Me	10.2	0.85	d	6.8
25	76.3	2.98	br d	9.45
26	34.2	1.59	m	
26Me	17.7 [17.8]	0.99	d	7.5
27a	24.2 [24.4]	1.3	m	
27b		1.12	m	
28a	30.0 [30.1]	1.61	m	
28b		1.50	m	
29	73.2	4.99	m	
30	36.8	1.84	m	
30Me	9.4 [9.3]	0.93 [0.92]	d	6.9 [7.0]
31	76.6	4.80 [4.80]	d	10.1 [10.0]
32	36.9 [37.0]	2.57	m	
32Me	19.5	1.01	d	7.2

33	110.1 [111.8]	4.96 [4.98]	m	
34	129.5 [125.5]	7.49 [7.16]	d	14.1 [14.6]
34NMe	27.6 [33.1]	3.03 [3.07]	s	
CHO	161.0	8.30 [8.08]	s	
OAc	170.8			
OAc	21.0	2.06	s	
1''	168.8			
2''	58.8	3.35	br s	
2''NMe	44.4	2.54	br s	

Table 3 NMR data for aplyronine D precursor **30a**. Minor counterparts of doubled signals due to formamide rotamers (2:1) shown in brackets.

Aplyronine D (2)



A stock solution of (rac)-*N,N,O*-trimethylserine (7.0 mg, 38 μmol), DMAP (5.0 mg, 41 μmol), TCBC (13 μL, 83 μmol) and triethylamine (17 μL, 120 μmol) was prepared in CH_2Cl_2 (5.0 mL). Triol **30a** (3.7 mg, 4.0 μmol) was dissolved in PhH (0.5 mL) cooled to 0 °C and an aliquot of the stock solution (0.5 mL) was added. The reaction mixture was stirred at this temperature for 1.5 h with further additions of each stock solution (0.2 mL) every 30 minutes. The reaction was quenched with water (0.1 mL), concentrated *in vacuo* and purified by preparative thin layer chromatography (CH_2Cl_2/EtOAc/MeOH, 4:4:1) to afford aplyronine D (**2**) (2.3 mg, 2.2 μmol, 55%, 100% BRSM) as an amorphous white solid, along with recovered starting material (1.7 mg, 1.8 μmol).

R_f 0.51 (CH_2Cl_2/EtOAc/MeOH, 4:4:1); **^{1}H NMR** (500 MHz, acetone-d^6) *See Table 4*; **^{13}C NMR** (125 MHz, acetone-d^6) *See Table 4*; $[\alpha]_{20}^{D}$ = +11.3 (*c* 0.12, MeOH); **IR** (thin film, ν_{max} / cm^{-1}): 3511, 2968, 2930, 1736, 1696, 1655, 1452, 1384, 1236, 1076, 967, 869; **HRMS** calculated for $C_{58}H_{100}N_3O_{14}$ $[M+H]^+$ 1062.7200 found 1062.7207.

Data in agreement with K. Yamada.[9]

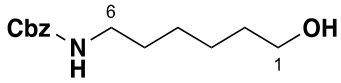
Atom	δ_C Synthetic (125 MHz)	δ_C Natural (150 MHz)	δ_H Synthetic (500MHz)	Mult	J [Hz]	δ_H Natural (600 MHz)	Mult	J [Hz]
1	167.6	167.5						
2	121.8 [121.8]	121.8	5.98	d	15.7	5.98	d	15.1
3	145.1	145.0	7.22	dd	15.2, 10.9	7.23	dd	15.3, 10.8
4	131.7 [131.8]	131.7 [131.8]	6.45 [6.46]	dd	15.4, 10.2 [15.5, 10.6]	6.43 [6.46]	dd	15.2, 10.8
5	141.2	141.1	6.30	m		6.29	m	
6a	32.6	32.6 [32.5]	2.47	m		2.46	m	
6b			2.14	m		2.16	m	
7	76.6	76.6	4.72 [4.74]	br d	11.1 [11.5]	4.76 [4.73]	br d	10.0
8	39.4	39.3 [39.1]	2.01	m		2.01	m	
8Me	11.7 [11.5]	11.7 [11.5]	1.01	d	6.8	1.01 [0.99]	d	7.0
9	78.0	78.0	3.32	m		3.33	m	
10	33.8	33.3	1.69	m		1.69	m	
10Me	16.4	16.4	1.02	d	6.8	1.02	d	6.7
11a	-[c]	22.5	-[c]			1.55	m	
11b			-[c]			1.30	m	
12	29.2	29.2	1.65	m		1.65	m	
13	86.8 [86.7]	86.8 [86.7]	3.52	m		3.52	m	
13OMe	55.5	55.5	3.12	s		3.13	s	
14	135.4	135.4						
14Me	10.3	10.3	1.51	s		1.51 [1.52]	s	
15	130.8 [130.7]	130.7 [130.6]	5.18	m		5.18	m	
16a	38.3	38.2 [38.5]	1.92	m		1.91 [1.93]	m	
16b			1.59	m		1.58 [1.60]	m	
17	30.6	30.6	1.17	m		1.19	m	
17Me	20.3	20.3	0.75 [0.74]	d	5.6 [5.7]	0.76 [0.75]	d	6.0
18a	41.1	41.0	1.55	m		1.56	m	
18b			1.13	m		1.14	m	
19	82.4	82.4	3.46	m		3.47	m	
19OMe	55.4	55.3	3.10	s		3.11	s	
20	133.3	133.3	4.96	dd	16.0, 9.8	4.97	dd	15.3, 9.1
21	133.0	132.9	5.61	ddd	14.9, 10.7, 4.2	5.62	ddd	15.3, 10.5, 4.0
22a	38.2	38.2	2.43	m		2.43	m	
22b			2.29	m		2.27	m	

23	72.8	72.8	5.46	d	11.1	5.47	d	11.0
24	41.9	41.9	1.73	m		1.74	m	
24Me	10.7	10.7	0.89 [0.89]	d	7.1 [6.7]	0.89 [0.90]	d	6.8
25	76.9	76.9	3.05	m		3.06	m	
25OH			3.53	br s				
26	34.9	34.9	1.64	m		1.63	m	
26Me	17.9	17.9	0.98	d	6.7	0.98	d	7.0
27a	25.2	25.2	1.36	m		1.37	m	
27b			1.14	m		1.16	m	
28a	30.6	30.6	1.63	m		1.65	m	
28b			1.51	m		1.51	m	
29	72.8	72.7	5.04	m		5.05	m	
30	37.9	37.9	1.97	m		1.99	m	
30Me	9.9	9.9	0.98	d	6.7	0.98	d	7.0
31	77.4	77.4	4.80 [4.81]	dd	9.9, 2.9 [9.9, 3.1]	4.80 [4.81]	dd	10.1, 2.7
32	37.6 [37.8]	37.5 [37.7]	2.65 [2.67]	m		2.65 [2.67]	m	
32Me	19.9	19.8 [19.8]	1.00	d	6.7	1.00	m	
33	110.0 [112.1]	110.0 [112.1]	5.04 [5.10]	dd	obs [14.7, 9.5]	5.05 [5.10]	dd	14.0, 9.6
34	131.1 [126.3]	131.1 [126.3]	6.84 [7.15]	d	14.1 [14.6]	6.83 [7.15]	d	14.0
34NMe	27.3 [33.0]	27.3 [33.0]	2.96 [3.08]	s		2.97 [3.09]	s	
CHO	163.0 [161.8]	163.0 [161.7]	8.36 [8.10]			8.36 [8.10]		
OAc	170.9	170.9						
OAc	21.0	21.0	2.02 [2.01]	s		2.02 [2.01]	s	
1'	170.6 [170.4]	170.4 [170.6]						
2'	68.0 [67.8]	68.0 [67.7]	3.37 [3.38]	dd	5.6, 7.8 [5.6, 7.5]	3.37 [3.38]	dd	7.4, 5.4
2'NMe	42.1	42.6 [42.7]	2.36 [2.38]	S		2.37 [2.39]	s	
3'a	72.6 [72.5]	72.4 [72.8]	3.69 [3.68]	dd	9.4, 7.8 [9.3, 7.8]	3.69 [3.68]	dd	9.4, 5.4
3'b			3.59	dd	9.3, 5.5	3.60	dd	9.4, 7.4
3'OMe	59.0 [59.0]	59.0	3.34 [3.31]	s		3.34 [3.31]	s	
1"	170.9	170.7						
2"	60.6	60.5	3.11	m		3.13	m	
2"NMe	45.0	44.9	2.31	s		2.34	s	

Table 4 NMR data comparison of natural and synthetic aplyronine D (**2**). Minor counterparts of doubled signals are given in brackets. [a]Minor signal due to diastereomers (1:1) of the C_7 trimethylserine residue. [b]Minor signals due to rotamers of the formamide bond (2:1). [c]C_{11}, H_{11a} and H_{11b} could not be identified.

IX. Experimental Procedures for a Linker-Modified Aplyronine D

Alcohol 31a

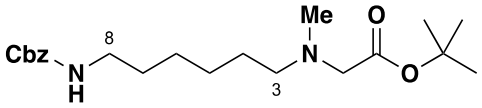


6-amino-hexan-1-ol (5.00 g, 42.7 mmol) was dissolved in THF (50 mL) and water (15 mL) and cooled to 0 °C. Benzyl chloroformate (7.30 mL, 51.1 mmol) was added and the pH of the solution adjusted to 9 with aqueous NaOH solution (10%). The reaction mixture was stirred at rt maintaining the pH at around 9 by addition of NaOH solution as required. Further benzyl chloroformate (3.00 mL, 21.0 mmol) was added after 1.5 h, and 2.5 h. After a total of 4 h the reaction mixture was extracted with Et_2O (2 × 100 mL), the combined organic extracts washed with 3M HCl (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (CH_2Cl_2) to yield a white solid which was washed with EtOAc/40-60 PE (1:10) to remove residual benzyl alcohol and afford alcohol **31a** (9.64 g, 38.3 mmol, 90%).

R_f 0.50 (CH_2Cl_2/MeOH, 20:1), **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.38-7.34 (4H, m, PhH), 7.32 (1H, m, PhH), 5.10 (2H, s, PhCH_2) 4.72 (1H, br s, NH), 3.51 (2H, t, J = 6.5 Hz, H_1), 3.20 (2H, dt, J = 6.9, 6.6 Hz, H_6), 1.56 (2H, tt, J = 6.8, 6.5 Hz, H_2), 1.51 (2H, tt, J = 7.0, 7.0 Hz, H_5), 1.44 (9H, s, C(CH_3)$_3$), 1.42-1.31 (4H, m, H_3 x 2, H_4 x 2).

Data in agreement with that presented by Y. Iwabuchi.[15]

Ester 31b



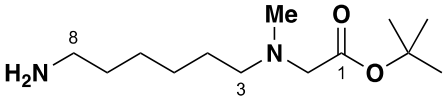
Alcohol **31a** (3.00 g, 11.9 mmol) was dissolved in THF (40 mL) and cooled to 0 °C. Triethylamine (2.5 mL, 17.9 mmol) and methanesulfonyl chloride (1.38 mL, 17.8 mmol) were added and the mixture stirred for 30 min at this temperature. The reaction was quenched with $NaHCO_3$ (30 mL), extracted with Et_2O (2 × 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was dissolved in EtOH (30 mL) and methylamine solution (28.0

[15] Y. Sasano, S. Nagasawa, M. Yamazaki, M. Shibuya, J. Park and Y. Iwabuchi *Angew. Chem. Int. Ed.* **2014**, *53*, 3236

mL, 33% in EtOH, 238 mmol) was added. The reaction mixture was stirred at rt for 16 h before the solvent was removed *in vacuo*. The residue was dissolved in DMF (20 mL), followed by addition of potassium carbonate (4.98 g, 36.0 mmol) and *tert*-butylbromoacetate (1.76 mL, 11.9 mmol). The reaction mixture was stirred for 8 h at rt before quenching with water (30 mL). The mixture was extracted with EtOAc (3 × 20 mL), the combined organic extracts washed with water (2 × 20 mL) and brine (2 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (gradient elution: CH_2Cl_2/MeOH, 1:0 → 20:1) afforded ester **31b** as a colourless oil (3.14 g, 8.29 mmol, 70%).

R_f 0.70 (CH_2Cl_2/MeOH, 20:1); **IR** (thin film, ν_{max} / cm^{-1}): 3315, 2974, 2935, 2861, 1718, 1532, 1456, 1368, 1253, 1150, 737, 697; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.38-7.34 (4H, m, PhH), 7.31 (1H, m, PhH), 5.10 (2H, s, PhCH_2) 4.77 (1H, br s, NH), 3.19 (2H, dt, *J* = 6.6, 6.6 Hz, H_8), 3.12 (2H, s, H_2 x 2), 2.45 (2H, t, *J* = 7.5 Hz, H_3), 2.34 (3H, s, NMe), 1.53-1.45 (4H, m, H_4 x 2, H_7 x 2), 1.46 (9H, s, C(CH_3)$_3$), 1.37-1.28 (4H, m, H_4 x 2, H_5 x 2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 170.3, 156.4, 136.7, 128.5, 128.1, 128.1, 80.8, 77.2, 66.6, 59.4, 56.9, 42.3, 29.9, 28.2, 27.4, 26.9, 26.6; **HRMS** calculated for $C_{21}H_{35}N_2O_4$ $[M+H]^+$ 379.2591, found 379.2591.

Amine 31c

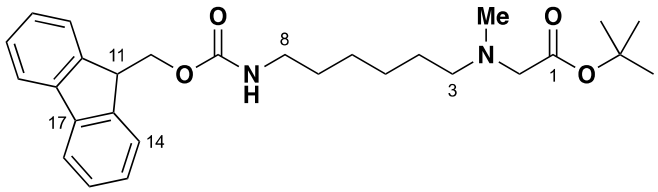


Palladium on carbon (70.0 mg, 10 wt%, 66.0 μmol) was added to a solution of benzyl carbamate **31b** (500 mg, 1.32 mmol) in EtOH (5.0 mL). The reaction was placed under a hydrogen atmosphere (balloon pressure) and stirred for 2 h at rt. The catalyst was removed by filtration through a plug of Celite® and the solvent removed *in vacuo* to afford amine **31c** as a colourless oil (316 mg, 1.29 mmol, 98%).

R_f 0.10 (CH_2Cl_2/MeOH, 20:1); **IR** (thin film, ν_{max} / cm^{-1}): 3371, 2931, 2860, 1732, 1456, 1368, 1251, 1221, 1152, 1064, 839; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 3.02 (2H, s, H_2 x 2), 2.58 (2H, t, *J* = 7.1 Hz, H_3), 2.35 (2H, t, *J* = 7.6, H_8), 2.24 (3H, s, NMe), 1.44-1.30 (4H, m, H_4 x 2, H_7 x 2), 1.36 (9H, s, C(CH_3)$_3$), 1.27-1.17 (4H, m, H_5, H_6); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C

170.2, 80.6, 59.3, 56.9, 42.2, 41.9, 33.2, 28.1, 27.4, 27.1, 26.7; **HRMS** calculated for $C_{13}H_{29}N_2O_2$ $[M+H]^+$ 245.2224, found 245.2221.

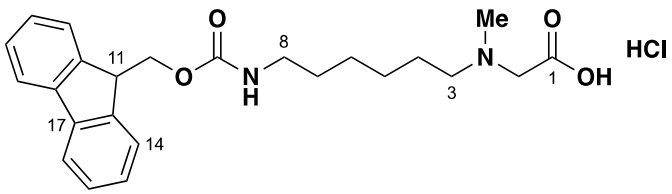
Ester 31d



Sodium carbonate (130 mg, 1.23 mmol) and 9-fluorenylmethyl chloroformate (159 mg, 0.610 mmol) were added to a solution of amine **31c** (100 mg, 0.41 mmol) in THF (1 mL) and water (1 mL) and the reaction mixture was stirred at rt for 2.5 h. Water (5 mL) was added and the reaction mixture extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the crude product purified by flash column chromatography (gradient elution: EtOAc/40-60 PE, 1:1 → 1:0) to yield ester **31d** (135 mg, 0.280 mmol, 70%) as a colourless oil.

R_f 0.45 (EtOAc); **IR** (thin film, ν_{max} / cm^{-1}): 2936, 1723, 1451, 1368, 1247, 1152, 741; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.75 (2H, d, J = 7.6 Hz, H_{16} x 2), 7.59 (2H, d, J = 7.5 Hz, H_{13} x 2), 7.39 (2H, t, J = 7.4 Hz, H_{14} x 2), 7.30 (2H, t, J = 7.4 Hz, H_{15} x 2), 4.84 (1H, br s, N<u>H</u>), 4.39 (2H, d, J = 7.0 Hz, H_{10}), 4.21 (1H, t, J = 6.8 Hz, H_{11}), 3.18 (2H, dt, J = 6.6, 6.6 Hz, H_8 x 2), 3.12 (2H, s, H_2 x 2), 2.45 (2H, t, J = 7.5 Hz, H_3), 2.34 (3H, s, N<u>Me</u>), 1.56-1.41 (4H, m, H_4 x 2, H_7 x 2), 1.46 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.37-1.27 (4H, m, H_5 x 2, H_6 x 2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 170.3, 156.4, 144.0, 141.3, 127.6, 127.0, 125.0, 120.0, 80.8, 66.5, 59.4, 58.1, 56.9, 47.3, 42.3, 29.9, 28.2, 27.4, 27.0, 26.6; **HRMS** calculated for $C_{28}H_{39}N_2O_4$ $[M+H]^+$ 467.2904, found 467.2899.

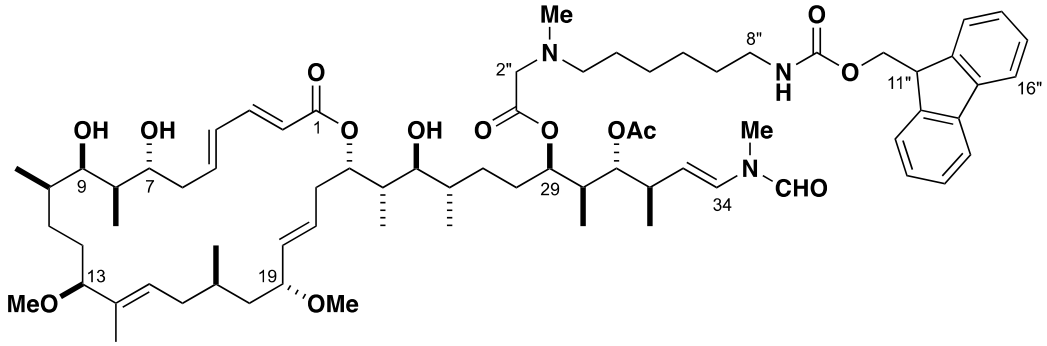
Carboxylic acid 31



Ester **31d** (37.0 mg, 79.0 μmol) was dissolved in CH_2Cl_2 (1 mL) and trifluoroacetic acid (1 mL) and stirred for 4 h at rt. The reaction mixture was concentrated *in vacuo*, 3M HCl solution (1 mL) was added and the mixture was concentrated again to afford hydrochloride salt **31** as a white foam (35.0 mg, 78.5 μmol, 99%).

IR (thin film, ν_{max} / cm^{-1}): 3323, 2941, 1696, 1532, 1450, 1248, 1140, 761, 741; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 10.33 (1H, br s, OH), 7.73 (2H, d, J = 7.5 Hz, H_{16} x 2), 7.59 (2H, d, J = 7.2 Hz, H_{13} x 2), 7.37 (2H, t, J = 7.4 Hz, H_{14} x 2), 7.29 (2H, d, J = 7.4 Hz, H_{15} x 2), 5.22 (1H, br s, NH), 4.33 (2H, d, J = 6.8 Hz, H_{10}), 4.18 (1H, t, J = 7.0 Hz, H_{11}), 4.09 (2H, br m, H_2 x 2), 3.31 (1H, br m, H_{3a}), 3.21-3.03 (3H, br m, H_{3b}, H_8 x 2), 2.95 (3H, br s, NMe), 1.80 (2H, br m, H_4 x 2), 1.46 (2H, br m, H_7 x 2), 1.41-1.19 (4H, br m, H_5 x 2, H_6 x 2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 167.0, 156.7, 144.0, 141.2, 127.7, 127.1, 125.2, 120.0, 66.6, 56.8, 55.6, 53.5, 47.2, 41.5, 40.7, 29.5, 26.0, 23.9; **HRMS** calculated for $C_{24}H_{31}N_2O_4$ $[M+H]^+$ 411.2278, found 411.2272.

Triol 30f



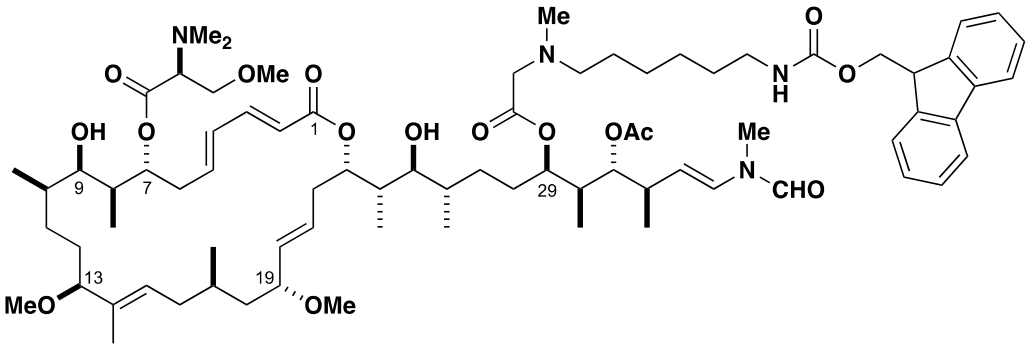
Alcohol **30** (13.7 mg, 11.6 μmol), acid **31** (10.4 mg, 23.2 μmol) and DMAP (2.8 mg, 23 μmol) were dissolved in THF and PhMe (1:1, 1.0 mL). Triethylamine (13 μL, 93 μmol) and TCBC (7 μL, 46 μmol) were added and the reaction stirred at rt for 1 h, then quenched with $NaHCO_3$ (1 mL) and extracted with EtOAc (4 × 3 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and the crude product transferred to a plastic reaction vessel.

A solution of HF·pyr was prepared by adding HF·pyr (100 μL) to a solution of pyr (200 μL) in THF (1 mL) at 0 °C and stirring at rt for 30 min. This solution was added to the crude *tris*-TES ether at 0 °C and the mixture stirred at rt for 16 h. The reaction was quenched at 0 °C

with $NaHCO_3$ (5 mL), stirred vigorously at rt for 30 min and extracted with EtOAc (5 × 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo* and purified by flash column chromatography (gradient elution: CH_2Cl_2/EtOAc/MeOH, 1:0:0 → 4:4:1) to afford triol **30f** as an amorphous white solid (13.4 mg, 10.6 μmol, 91%).

R_f 0.60 (CH_2Cl_2/EtOAc/MeOH, 4:4:1); $[\alpha]_{2\zeta}^{\nu}$ +26.8 (*c* 0.82, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 3438, 2927, 1717, 1654, 1582, 1404, 1245, 1076, 742; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.29 (0.67H, s, CHO), [8.07] (0.33H, s, CHO*), 7.76 (2H, d, *J* = 7.5 Hz, H_{16}'' x 2), 7.59 (2H, d, *J* = 7.4 Hz, H_{13}'' x 2), 7.40 (2H, t, *J* = 7.4 Hz, H_{14}'' x 2), 7.31 (2H, t, *J* = 7.5 Hz, H_{15}'' x 2), 7.27 (1H, obs, H_3), [7.15] (0.33H, d, *J* = 14.7 Hz, H_{34}*), 6.47 (0.67H, d, *J* = 14.0 Hz, H_{34}), 6.22 (1H, dd, *J* = 15.4, 10.2 Hz, H_4), 6.15 (1H, m, H_5), 5.83 (1H, d, *J* = 15.4 Hz, H_2), 5.53 (1H, ddd, *J* = 14.8, 9.8, 4.1 Hz, H_{21}), 5.36 (1H, d, *J* = 10.8 Hz, H_{23}), 5.16 (1H, dd, *J* = 8.9, 15.4 Hz, H_{20}), 5.10 (1H, dd, *J* = 7.7, 7.7 Hz, H_{15}), 5.02-4.92 (2H, m, H_{29}, H_{33}), 4.87 (1H, br s, NH), 4.80 (1H, d, *J* = 10.0 Hz, H_{31}), 4.38 (2H, d, *J* = 6.8 Hz, H_{10}'' x 2), 4.21 (1H, t, *J* = 6.6 Hz, H_{11}''), 3.72 (1H, br s, H_7), 3.64 (1H, br s, H_9), 3.49 (1H, ddd, *J* = 8.8, 8.8, 3.9 Hz, H_{19}), 3.45-3.37 (3H, m, H_{13}, H_2'' x 2), 3.20 (2H, obs, H_8'' x 2), 3.20 (3H, s, OMe_{19}), 3.18 (3H, s, OMe_{13}), [3.06] (1H, s, NMe_{34}*), 3.20 (2H, s, NMe_{34}), 2.98 (1H, m, H_{25}), 2.69 (2H, br s, H_3'' x 2), 2.51 (3H, s, NMe''), 2.60-2.32 (4H, m, H_{6a}, H_{6b}, H_{22a}, H_{32}), 2.22 (1H, br d, *J* = 14.5 Hz, H_{22b}), 2.06 (2H, s, $COCH_3$), [2.05] (1H, s, $COCH_3$*), 1.99 (1H, m, H_{16a}), 1.83 (1H, m, H_{30}), 1.79-1.69 (2H, m, H_{16b}, H_{24}), 1.69-1.54 (9H, m, H_8, H_{10}, H_{11} x 2, H_{12} x 2, H_{26}, H_4'' x 2), 1.54-1.43 (5H, m, H_{18a}, H_{28} x 2, H_7'' x 2), 1.46 (3H, s, Me_{14}), 1.39-1.17 (7H, m, H_{17}, H_{18b}, H_{27a}, H_5'' x 2, H_6'' x 2), 1.08 (1H, m, H_{27b}), 1.03 (3H, d, *J* = 6.8 Hz, Me_8), 1.02-0.96 (6H, m, Me_{26}, Me_{32}), 0.92 (3H, d, *J* = 6.9 Hz, Me_{30}), 0.90 (3H, d, *J* = 7.0 Hz, Me_{10}), 0.84 (3H, d, *J* = 6.8 Hz, Me_{24}), 0.76 (3H, d, *J* = 5.5 Hz, Me_{17}); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 170.8, 169.7, 168.0, 162.2, [161.0], 156.4, 145.3, 144.0, 141.3, 140.0, 134.8, 133.3, 130.9, 130.3, 129.5, 128.9, 127.7, 127.0, [125.5], 125.1, 120.0, 119.4, [111.9], 110.2, 87.2, 81.3, 76.4, 76.3, 75.4, 74.8, 73.0, 72.9, 66.5, 57.0, 56.3, 55.7, 55.7, 47.3, 41.6, 41.2, 40.9, 40.9, 38.2, 38.0, 37.0, 36.8, [36.8], [36.6], 36.6, 36.2, 35.8, [34.3], 34.2, [33.1], 30.0, 29.8, 29.7, 29.6, 29.5, 27.7, 26.8, 26.7, 26.5, 26.4, 21.0, 19.6, 19.5, [17.8], 17.7, 15.5, 12.0, 10.3, 10.1, 9.5, [9.4]; **HRMS** calculated for $C_{72}H_{110}N_3O_{14}$ $[M+H]^+$ 1240.7982 found 1240.7979. Distinguishable resonances of the minor rotamer (2:1 ratio) are given in brackets.

Trimethylserine ester 4



Triol **30f** (3.5 mg, 2.8 μmol), (*S*)-trimethylserine (1.0 mg, 5.5 μmol) and DMAP (1 crystal) were dissolved in THF and PhMe (1:1, 0.4 mL). Et_3N (1.5 μL, 11.0 μmol) and a solution of TCBC (40 μL, 0.13 M in THF, 5.1 μmol) were added and the reaction stirred at 0 °C for 20 min. Further TCBC (10 μL) was added and the reaction stirred for another 10 min before being quenched with water (50 μL) and concentrated *in vacuo*. Purification by flash column chromatography (gradient elution: CH_2Cl_2/MeOH, 1:0 → 20:1) afforded trimethylserine ester **4** (2.2 mg, 1.6 μmol, 58%).

R_f 0.55 (CH_2Cl_2/EtOAc/MeOH, 4:4:1); **$[\alpha]_{2C}^{\nu}$** = +11.8 (*c* 0.11, $CHCl_3$); **IR** (thin film, ν_{max} / cm^{-1}): 3367, 2935, 1716, 1578, 1546, 1459, 1370, 1245, 1130, 853, 822; **^{1}H NMR** (500 MHz, acetone-d^6) *See Table 5*; **^{13}C NMR** (125 MHz, acetone-d^6) *See Table 5*; **HRMS** calculated for $C_{78}H_{122}N_4O_{16}$ $[M+2H]^{2+}$ 685.4422 found 685.4413.

The (*R*)-trimethylserine ester **4a** was synthesised by an analogous procedure.

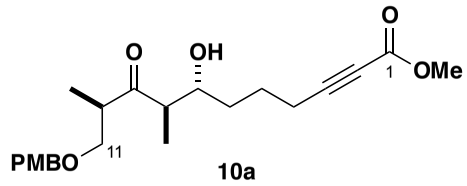
Atom	δ_C / ppm	δ_H / ppm	Mult	*J* (Hz)	δ_H / ppm	Mult	*J* (Hz)
1	167.6						
2	121.8	5.97	d	15.3	5.97	d	15.2
3	145.1	7.22	dd	15.2, 10.9	7.22	dd	15.5, 10.7
4	131.7	6.44	dd	15.2, 10.9	6.45	dd	15.2, 10.7
5	141.2	6.28	ddd	15.0, 10.1, 4.9	6.30	ddd	15.2, 10.1, 5.1
6a	32.6	2.46	m		2.45	m	
6b		2.16	m		2.16	m	
7	76.6	4.74	br d	10.8	4.71	br d	10.7
8	39.4	2.00	m		2.00	m	

8Me	11.7	1.00	d	6.9	1.00	d	6.8
9	78.0	3.32	m		3.31	m	
10	33.1	1.69	m		obs	m	
10Me	16.4	1.02	d	7.0	1.02	d	7.0
11	22.5	obs			obs		
12	29.2	1.64	m		obs	m	
13	86.8	3.52	dd	10.6, 5.9	3.52	dd	10.2, 5.1
13OMe	55.5	3.12	s		3.12	s	
14	135.4						
14Me	10.3	1.50	s		1.51	s	
15	130.8	5.17	dd	10.4, 4.5	5.18	br d	11.0
16a	38.2	1.91	m		1.92	m	
16b		1.57	m		1.58	m	
17	30.1	1.18	m		1.18	m	
17Me	20.4	0.75	d	5.6	0.74	d	5.9
18a	41.1	1.55	m		1.55	m	
18b		1.14	m		1.15	m	
19	82.4	3.46	br d	6.2	3.45	m	
19OMe	55.4	3.10	s		3.10	s	
20	133.4	4.96	dd	15.3, 9.0	4.96	dd	15.5, 9.6
21	132.9	5.61	ddd	15.1, 10.8, 4.2	5.61	ddd	15.3, 10.8, 4.3
22a	38.3	2.42	m		2.42	m	
22b		2.29	m		2.28	m	
23	72.8	5.47	d	11.1	5.46	d	10.9
24	41.9	1.73	m		1.73	m	
24Me	10.7	0.89	d	6.9	0.88	d	7.1
25	76.9	3.05	m		3.05	m	
26	34.9	1.63	m		1.63	m	
26Me	17.9	0.98	d	6.9	0.98	d	6.9
27a	25.2	1.36	m		1.36	m	
27b		1.15	m		1.15	m	
28a	30.6	1.62	m		1.62	m	
28b		1.50	m		1.50	m	
29	72.6	5.04	m		5.04	m	
30	37.9 (38.0)	1.97	m		1.97	m	
30Me	10.0	0.98	d	6.9	0.98	d	6.9
31	77.4	4.81 (4.81)	dd	10.0, 2.8 (9.8, 2.9)	4.81 (4.81)	dd	10.2, 2.8 (10.2, 2.9)
32	37.6 (37.8)	2.64 (2.68)	m		2.64 (2.68)	m	
32Me	19.9 [19.9]	1.00	d	6.9	1.00	d	6.9
33	110.0 (112.1)	5.04 (5.09)	dd	13.9, 9.5 (15.0, 9.4)	5.04 (5.09)	dd	14.5, 9.7 (14.9, 9.6)
34	131.1 (126.3)	6.83 (7.15)	d	14.0 (14.5)	6.83 (7.15)	d	14.0 (14.5)
34NMe	27.3 (33.1)	2.96 (3.08)	s		2.96 (3.08)	s	

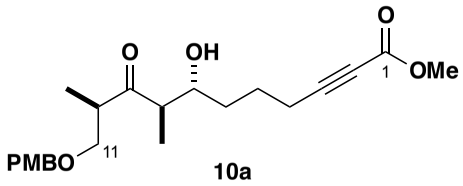
CHO	163.0 (161.8)	8.35 (8.10)	s		8.35 (8.10)	s	
OAc	170.9						
OAc	21.1	2.02 (2.01)	s		2.02 (2.01)	s	
1’	170.5						
2’	68.0	3.36	dd	7.5, 5.7	3.38	dd	7.5, 5.6
2’NMe	42.7	2.36	s		2.36	s	
3’a	72.5	3.69	dd	9.3 7.6	3.68	dd	9.5 7.7
3’b		3.59	dd	9.4, 5.6	3.59	dd	9.5, 5.8
3’OMe	59.1	3.34	s		3.30	s	
1’’	171.3						
2’’	58.8	3.19	m		3.20	m	
2’’NMe	42.4	2.34	s		2.34	s	
3’’	57.0	2.52	t	7.2	2.52	t	7.0
4’’	28.4	1.46	m		1.46	m	
5’’	27.7	1.32	m		1.32	m	
6’’	27.4	1.37	m		1.37	m	
7’’	30.5	1.52	m		1.52	m	
8’’	41.5	3.16	dt	6.5, 6.5	3.16	dt	6.5, 6.5
9’’	157.1						
10’’	66.7	4.32	d	7.0	4.32	d	7.1
11’’	48.2	4.22	t	7.2	4.22	t	7.2
12’’	145.3						
13’’	126.1	7.69	d	7.4	7.69	d	7.4
14’’	128.5	7.41	t	7.5	7.41	t	7.4
15’’	127.9	7.32	t	7.2	7.32	t	7.3
16’’	120.8	7.86	d	7.6	7.86	d	7.5
17’’	142.1						

Table 5 NMR data for compound **4**. Minor counterparts of doubled signals (2:1) due to formamide rotamers are shown in brackets.

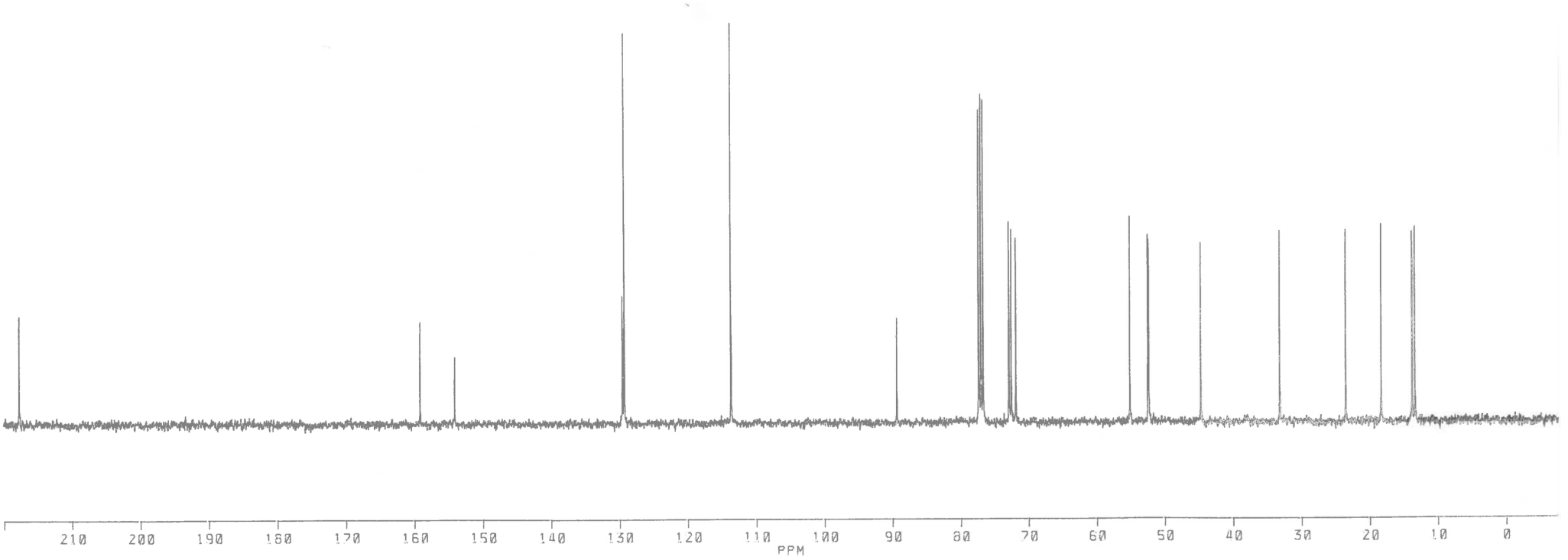
X. ^{1}H and ^{13}C NMR spectra

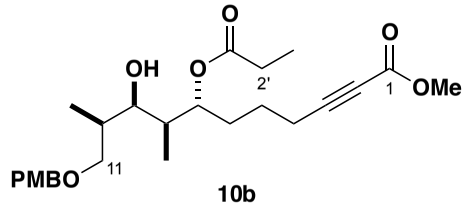


10a

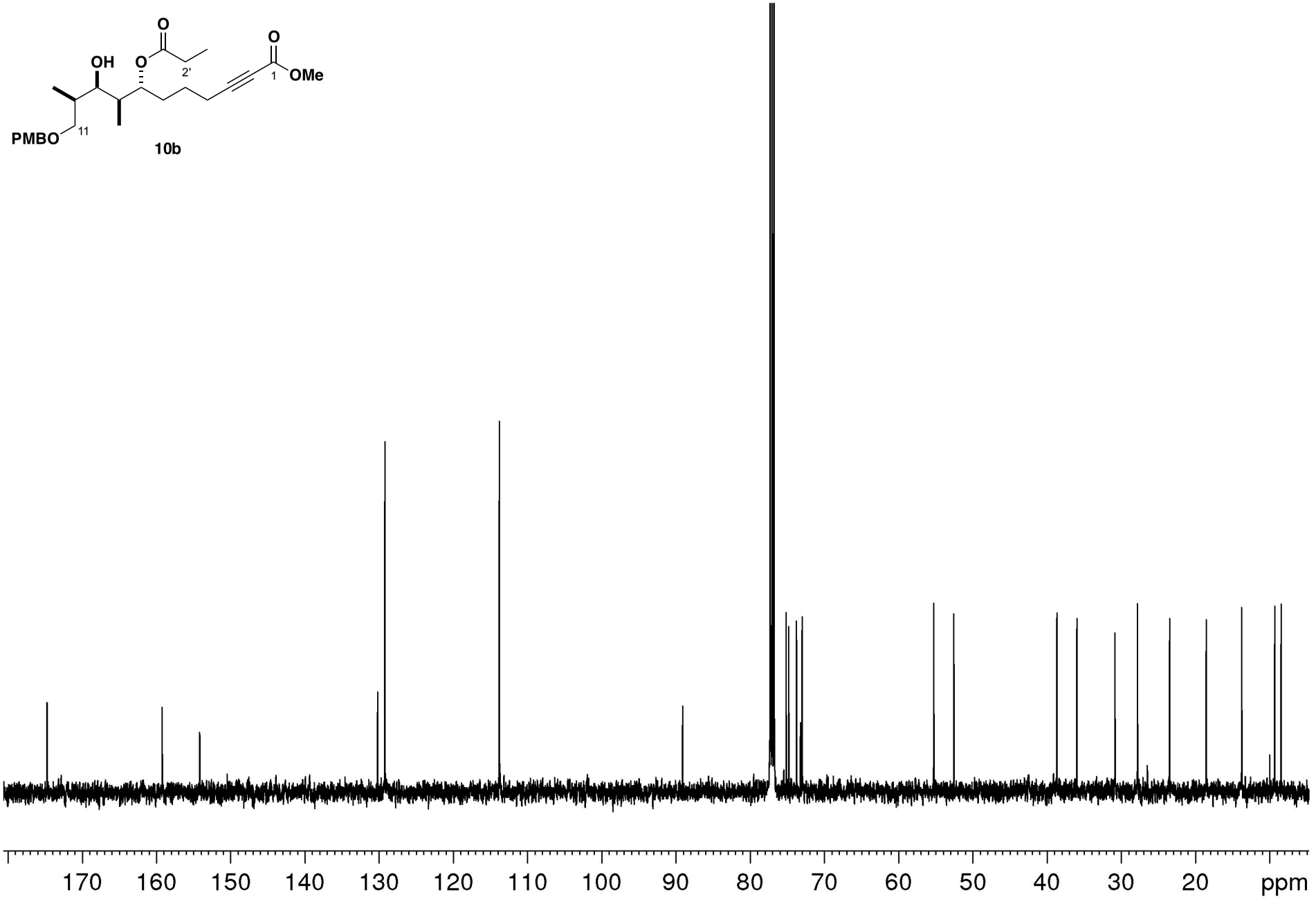

O
OH
O
1
OMe
PMBO
11

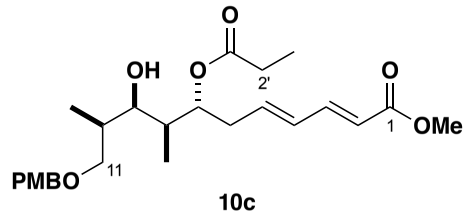
10a


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM

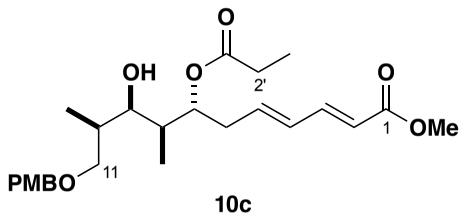


10b


O
OH
O
2'
O
1
OMe
PMBO
11
10b
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

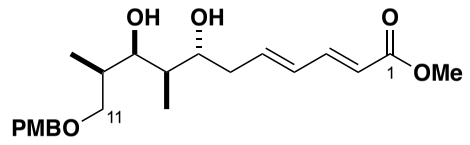


10c

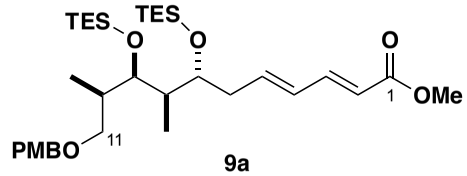

O
OH
O
2'
O
1
OMe
PMBO
11

10c

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM

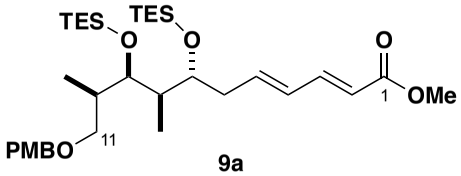


9


TES
TES
O
O
O
1
OMe
PMBO
11

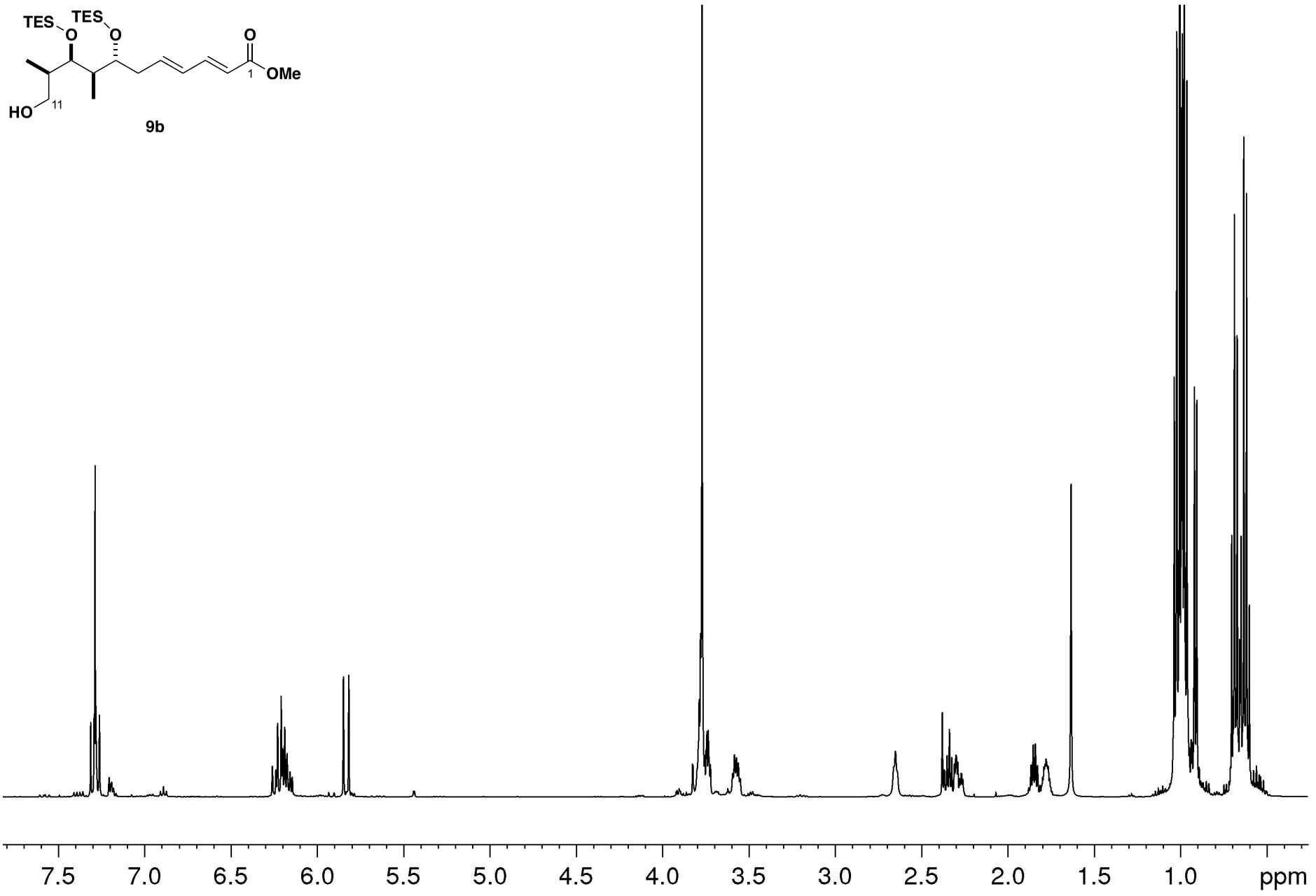
9a

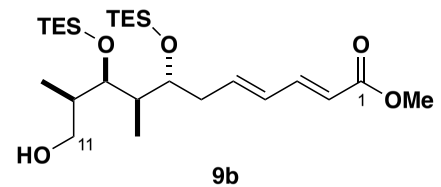
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


TES
TES
O
O
O
1
OMe
PMBO
11

9a

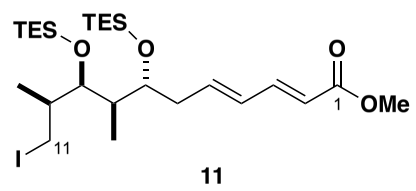
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


TES
TES
O
O
O
1
OMe
HO
11
9b
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

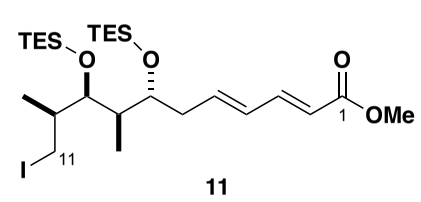

TES
TES
O
O
O
1
OMe
HO
11

9b

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

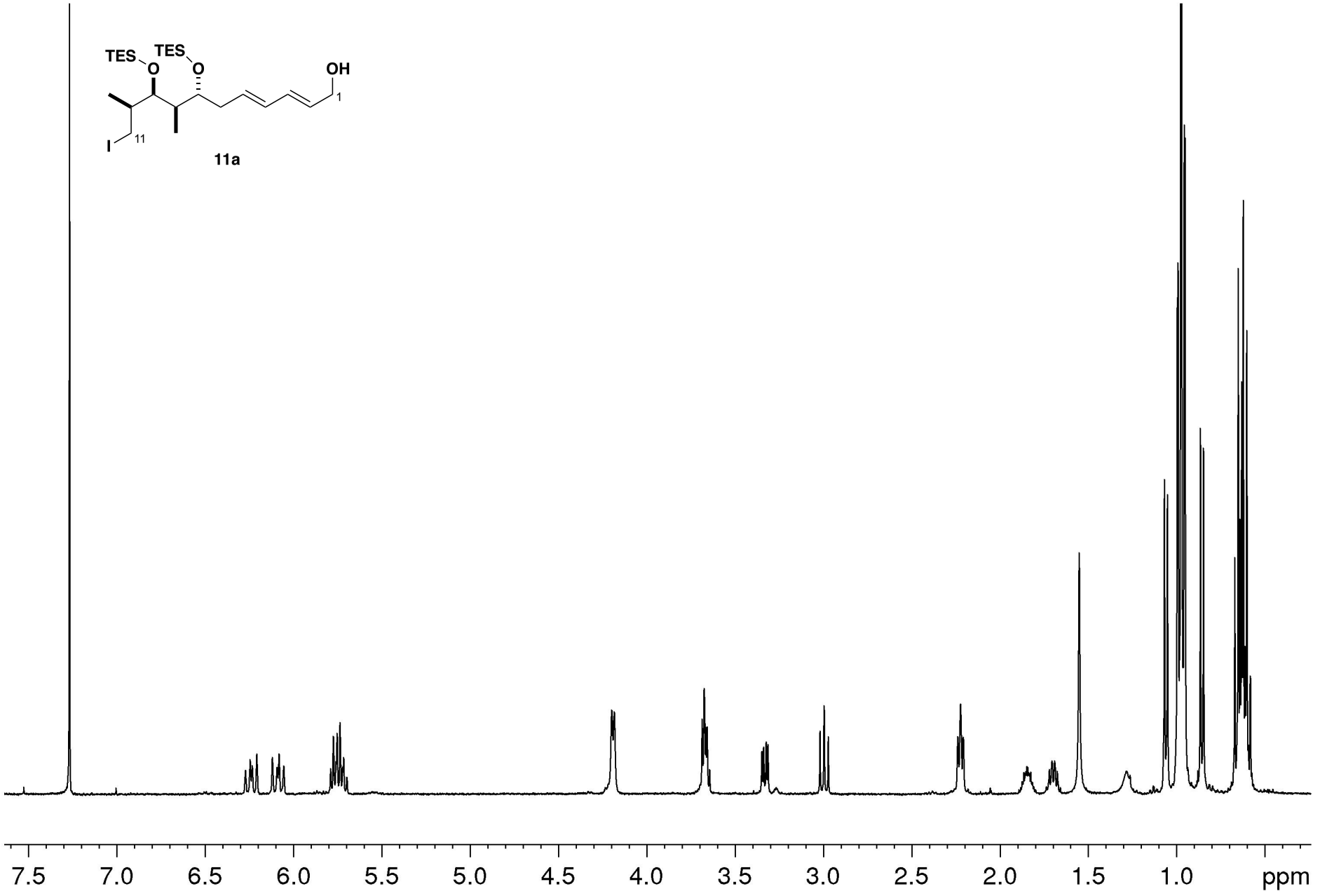


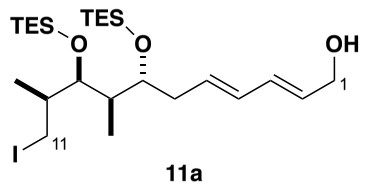
11


TES
TES
O
O
O
1
OMe
I
11

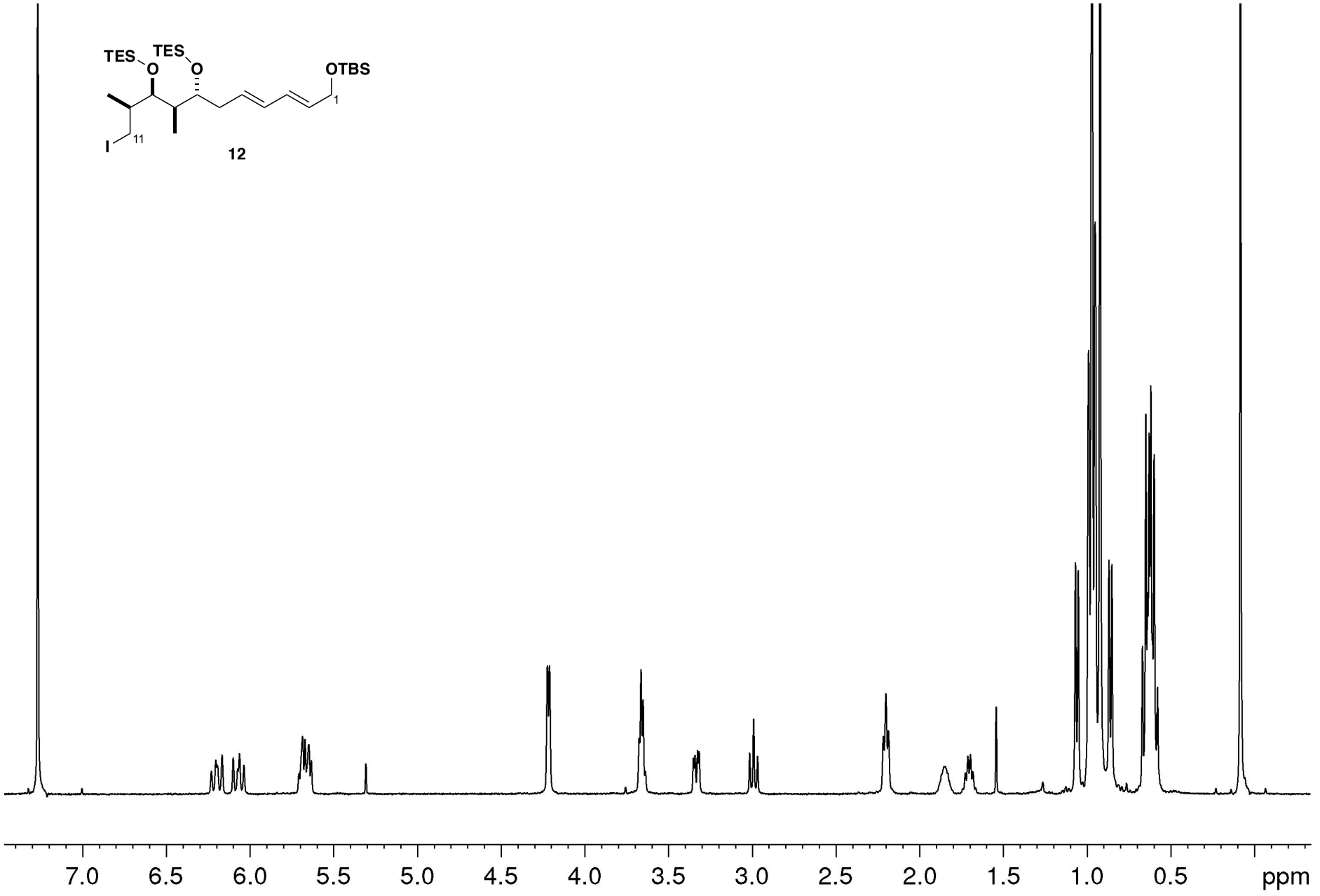
11

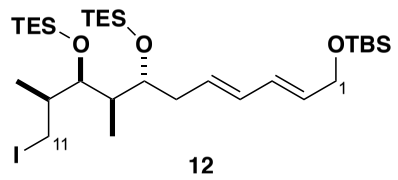
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


TES
TES
O
O
OH
1
I
11
11a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm



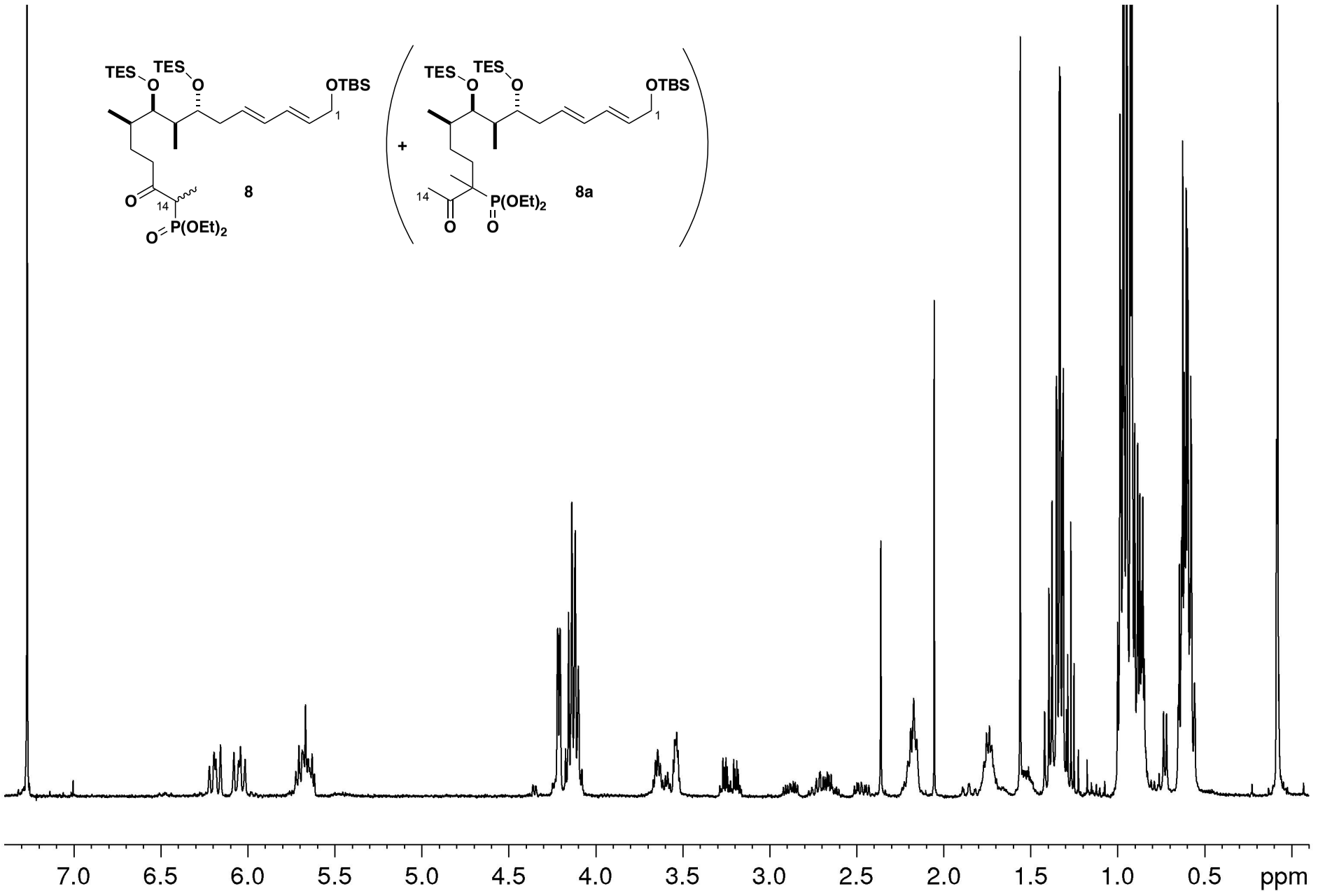
11a

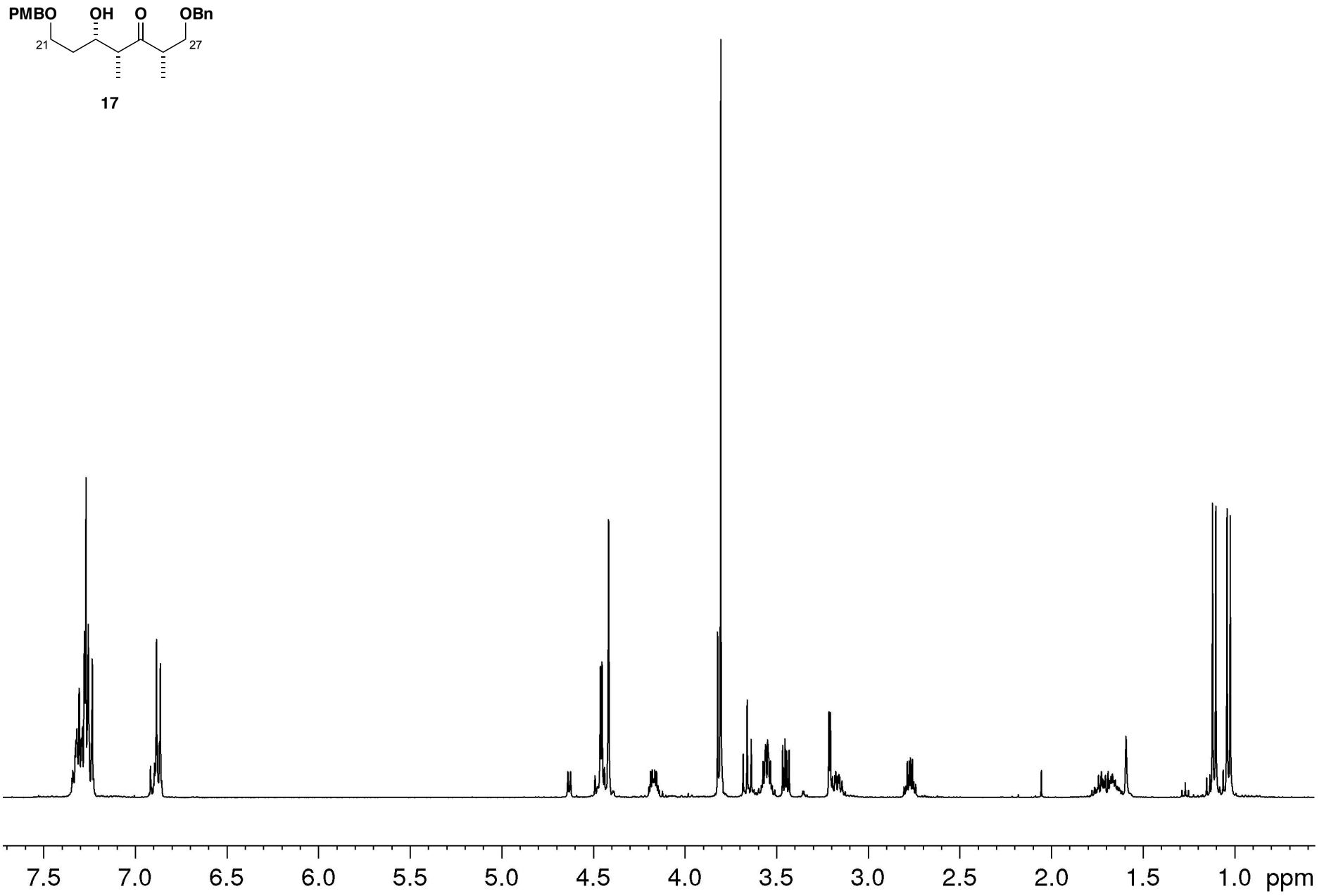

TES
TES
O
O
OTBS
1
I
11
12
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

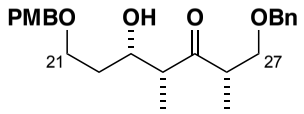

TES
TES
O
O
OTBS
1
I
11

12

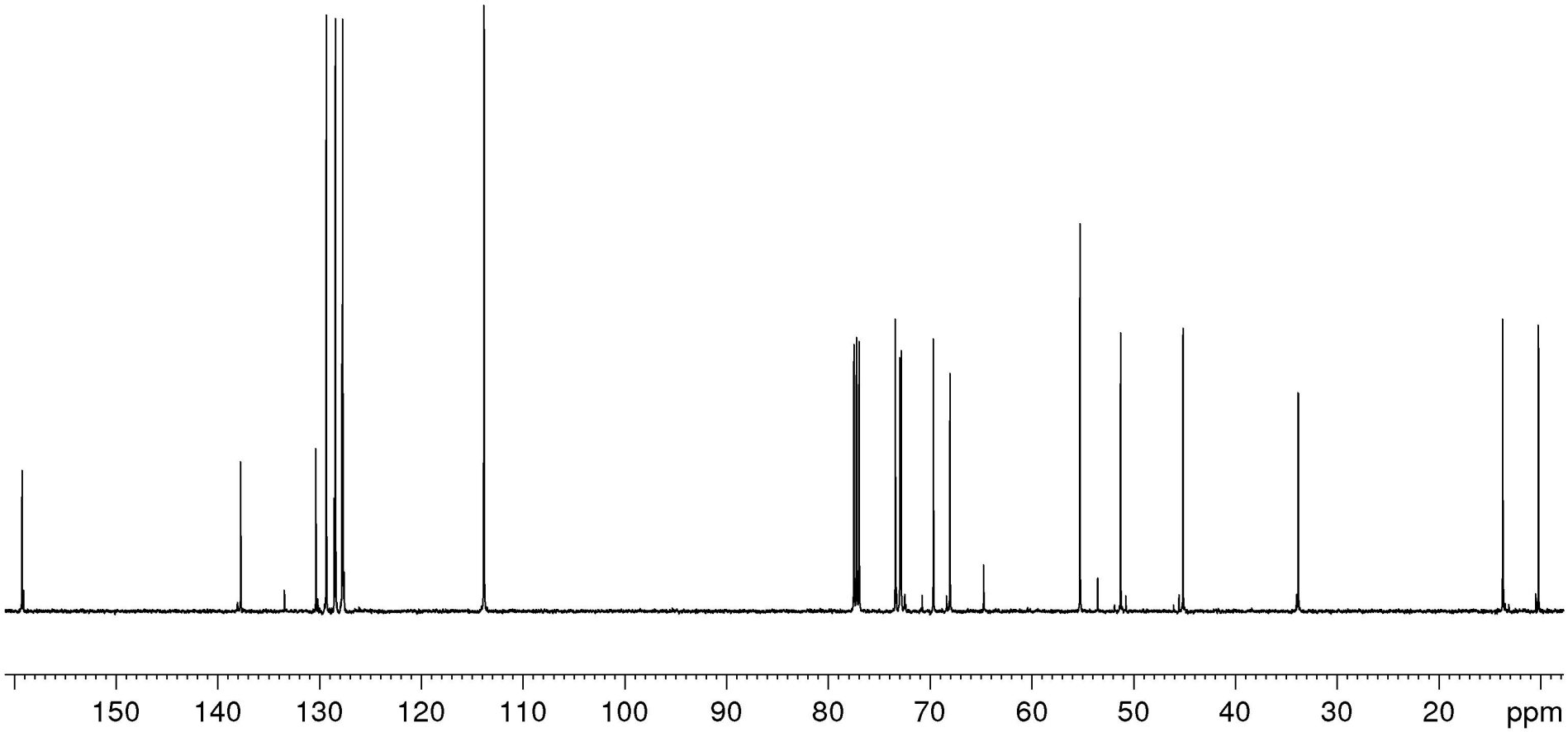
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

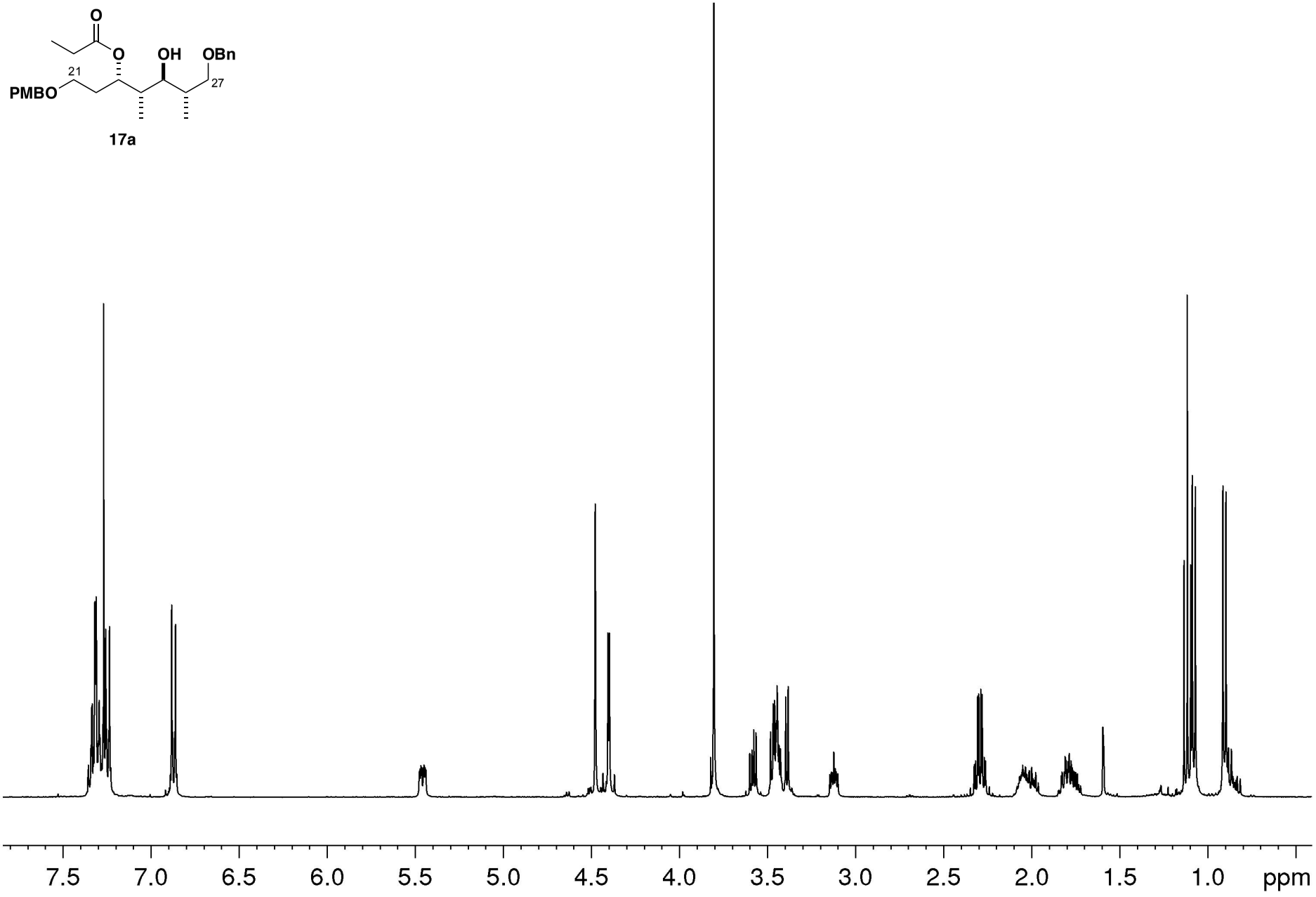

TES
TES
O
O
OTBS
1
O
14
O
P(OEt)2
8
+
8a
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

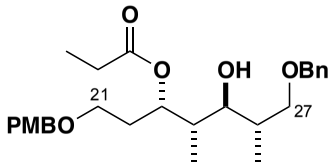

PMBO
OH
O
OBn
21
27
17
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


PMBO
OH
O
OBn
21
27

17

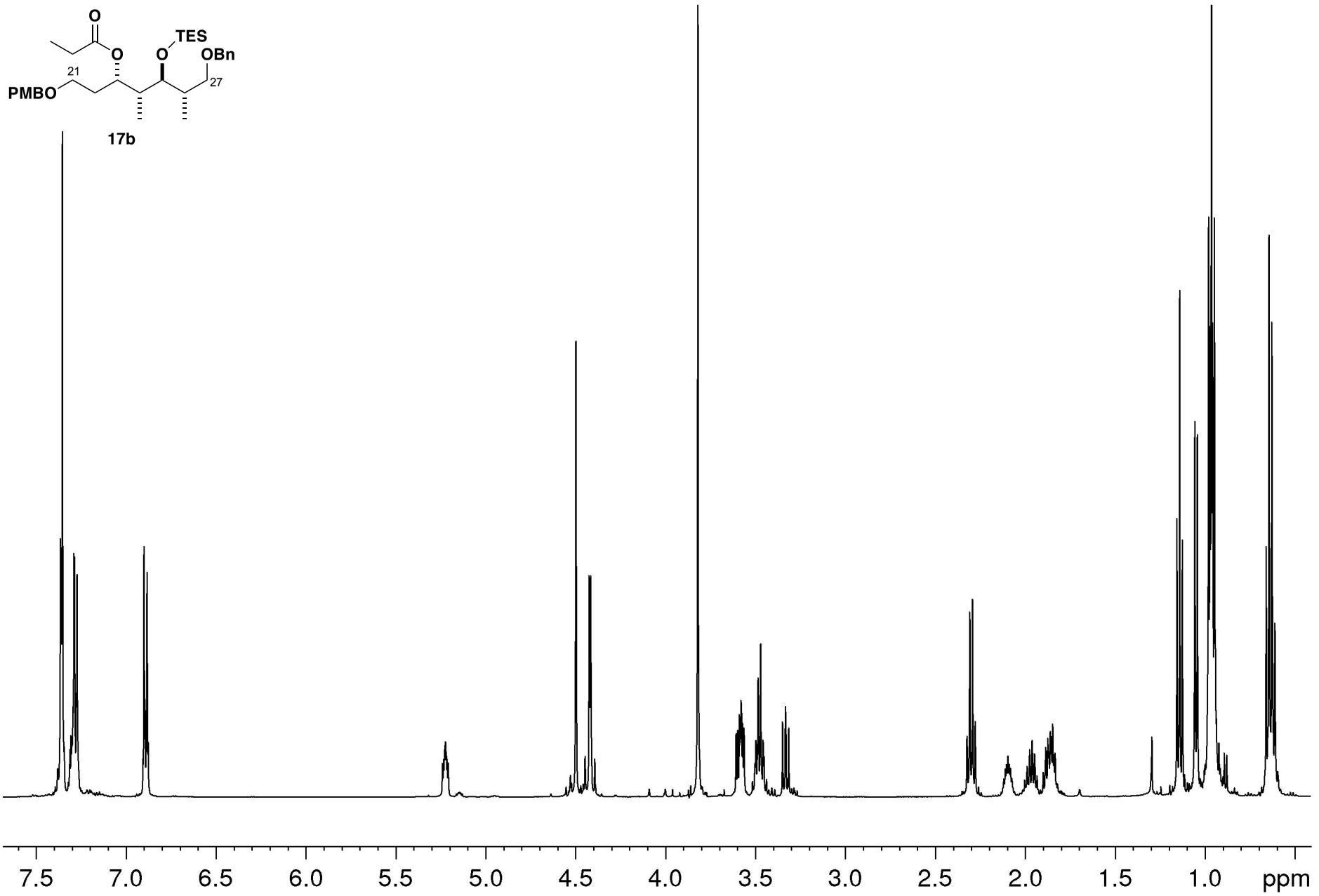

150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

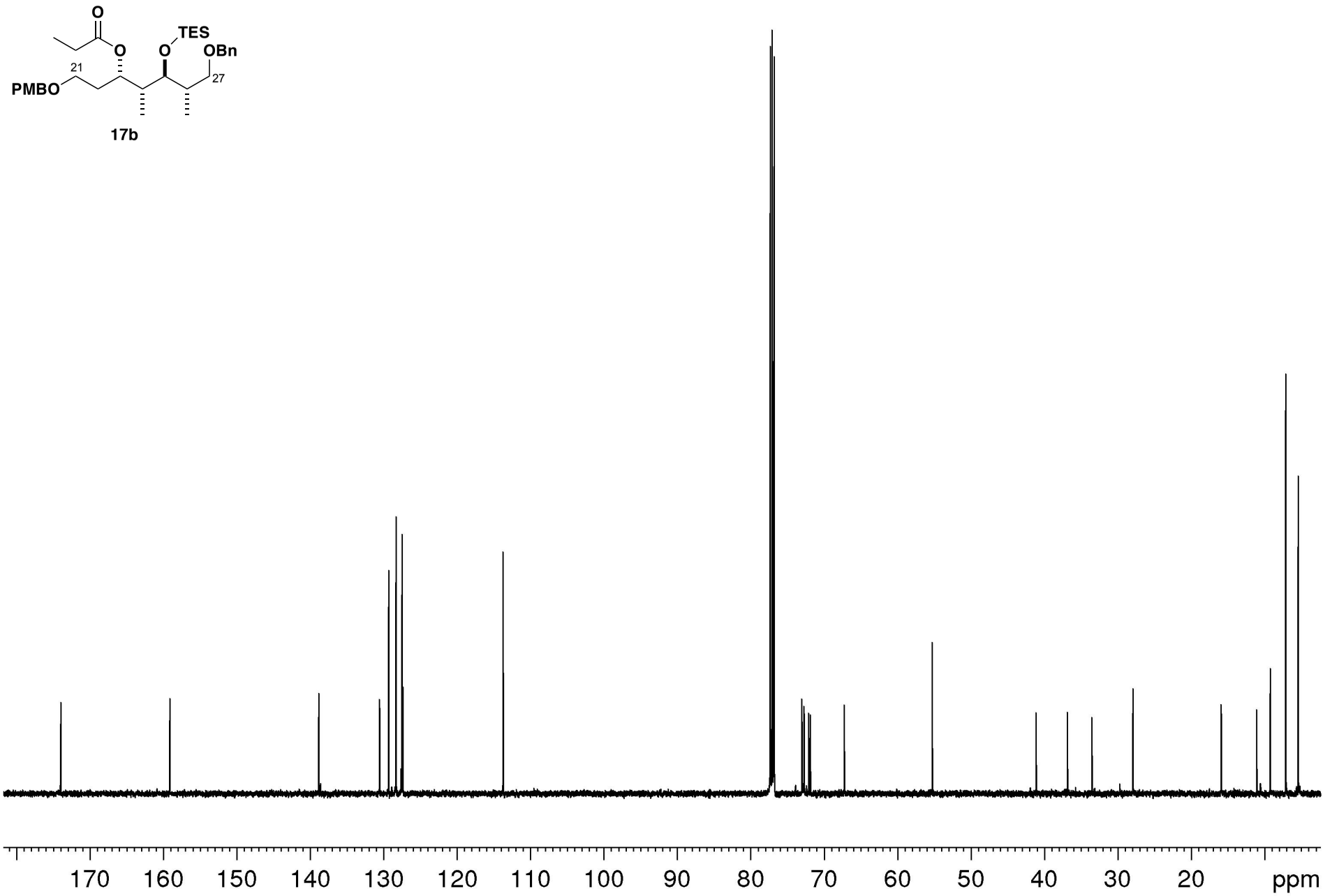

O
O
OH
OBn
21
27
PMBO
17a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

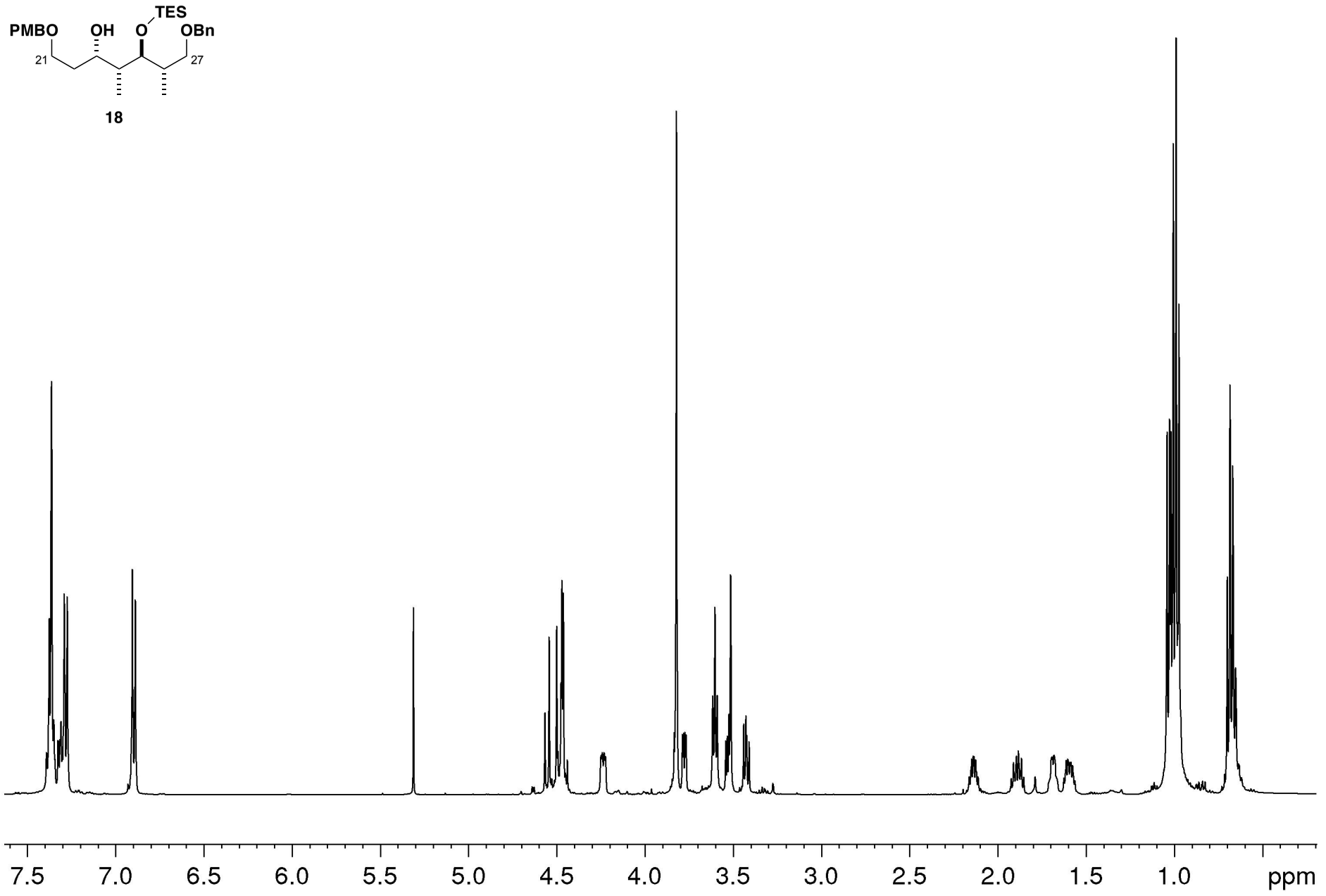

O
O
OH
OBn
21
27
PMBO

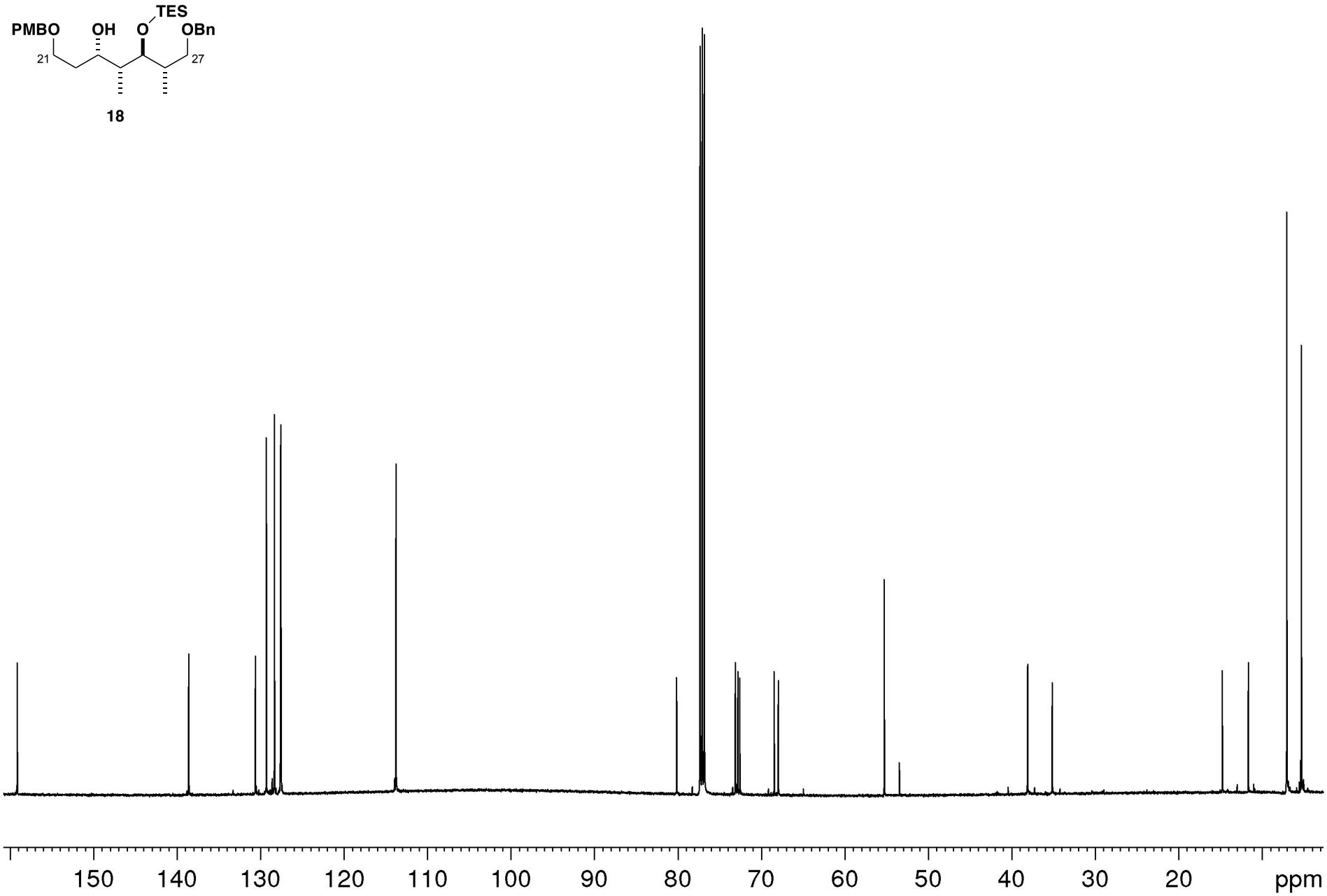
17a

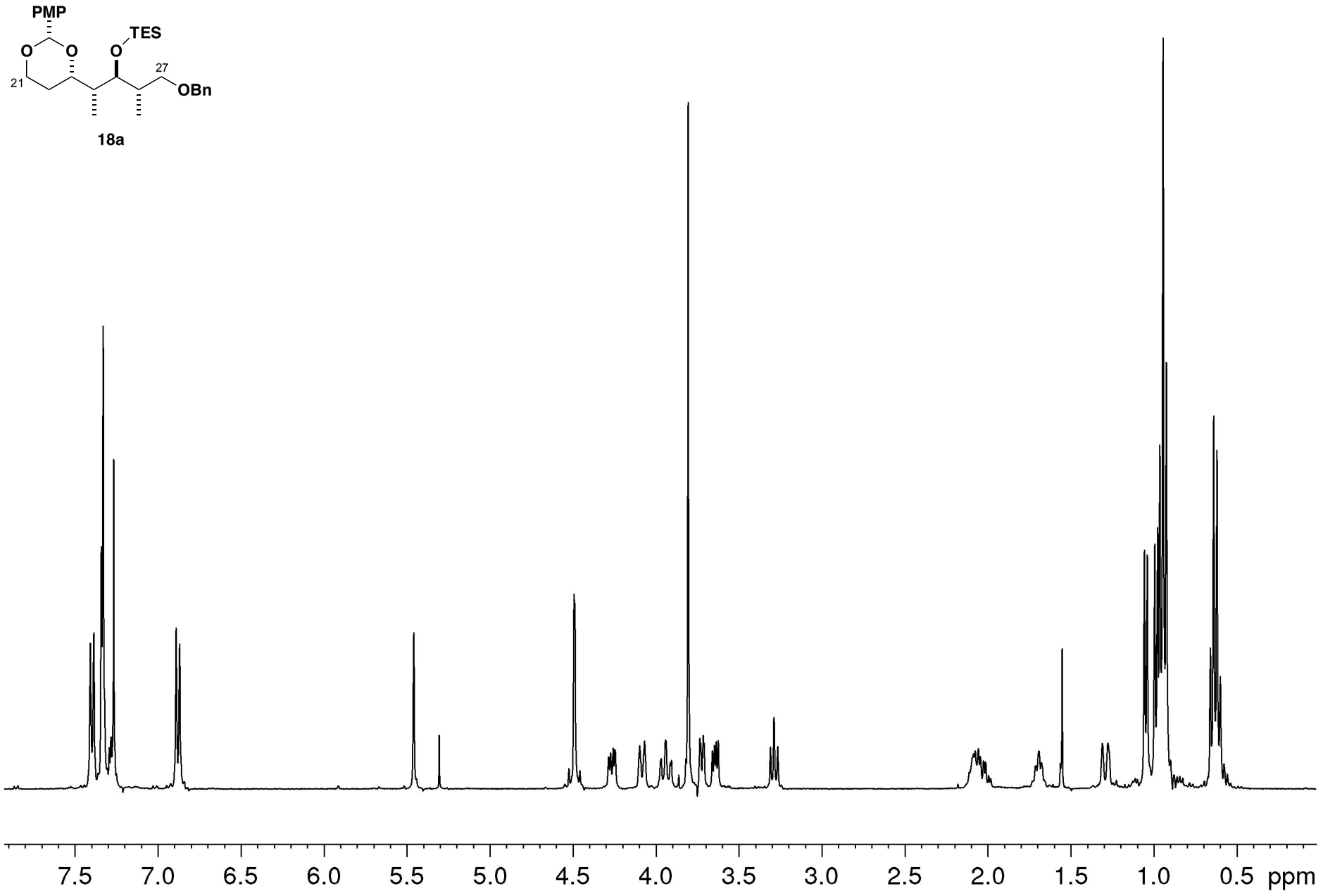
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

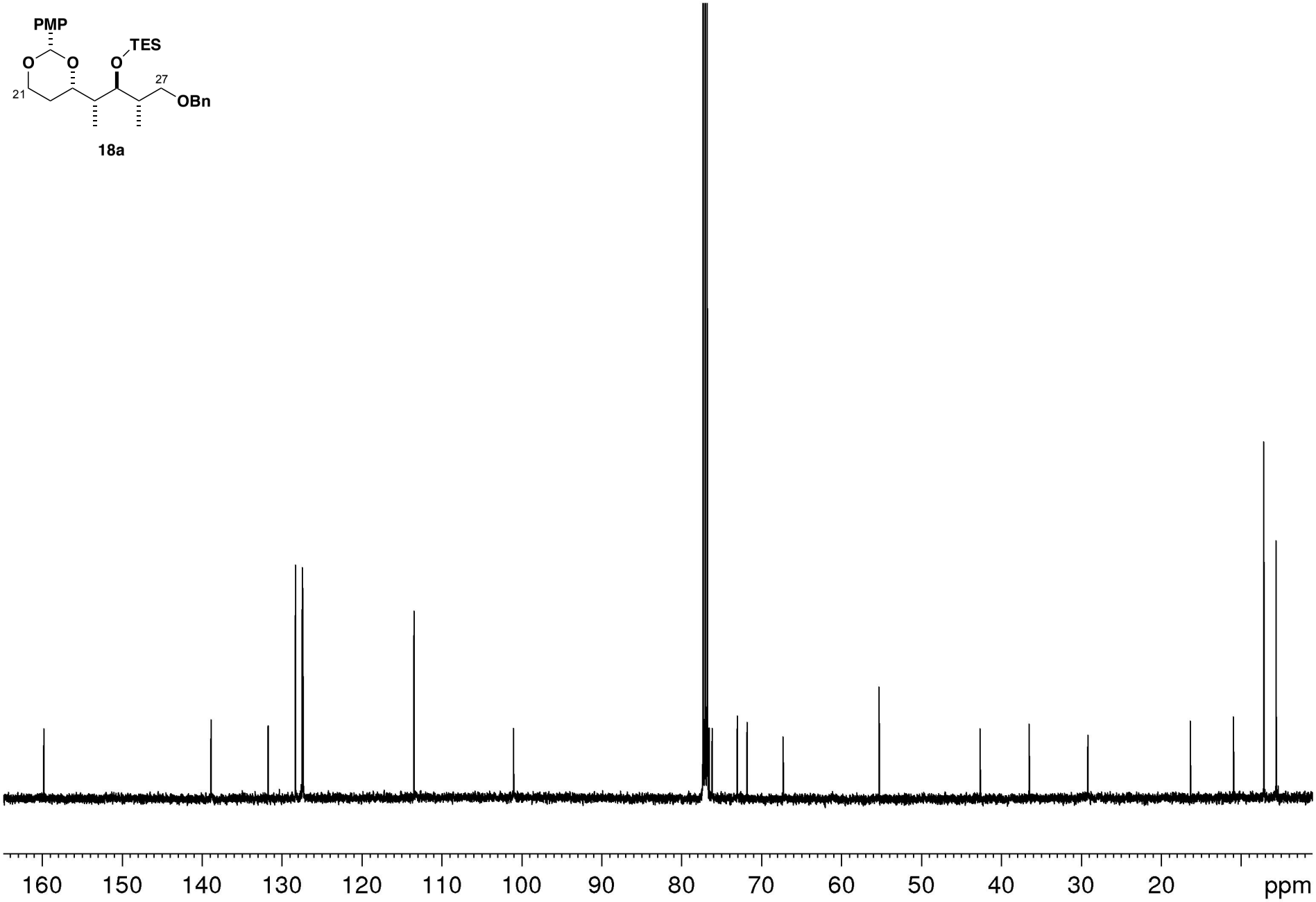

O
TES
O
O
OBn
21
27
PMBO
17b
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

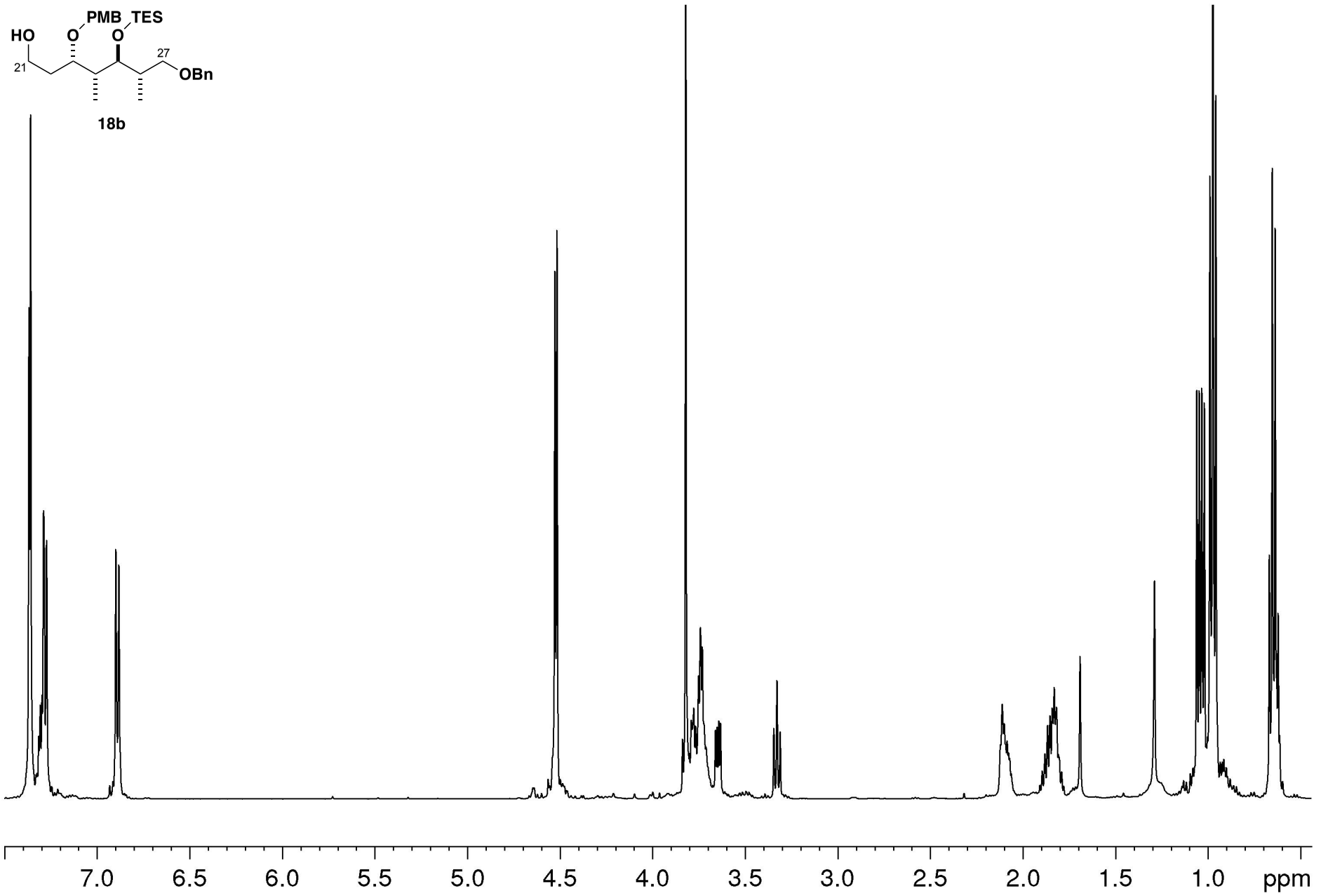

O
TES
O
O
OBn
21
27
PMBO
17b
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

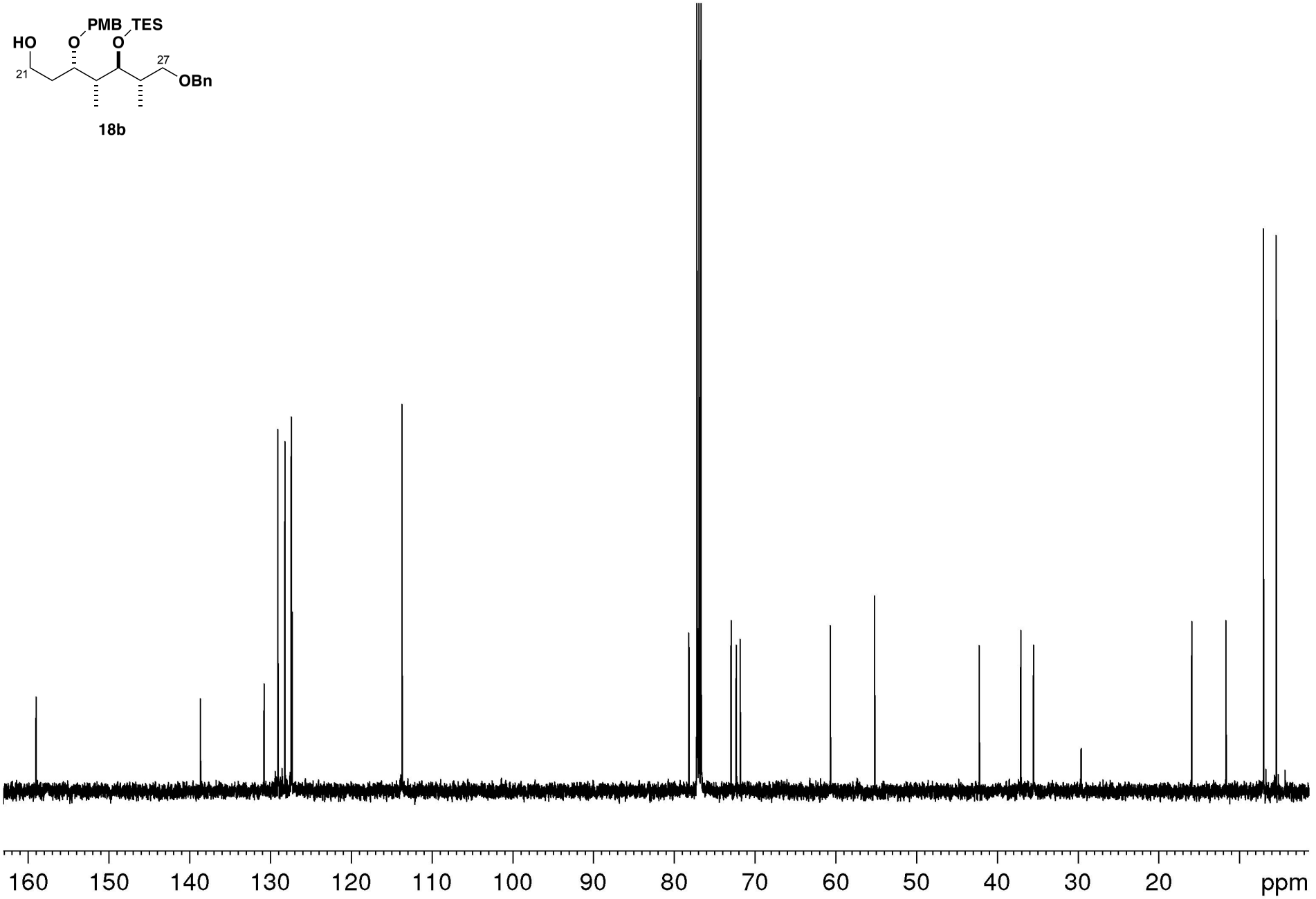

PMBO
OH
O
TES
OBn
21
27
18
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

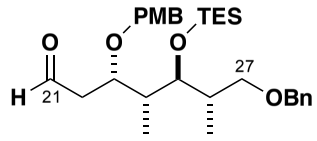

TES
PMBO
OH
O
OBn
21
27
18
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


PMP
TES
O
O
O
21
27
OBn
18a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

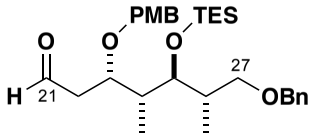

PMP
TES
O
O
O
21
27
OBn
18a
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


PMB
TES
HO
O
O
21
27
OBn
18b
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

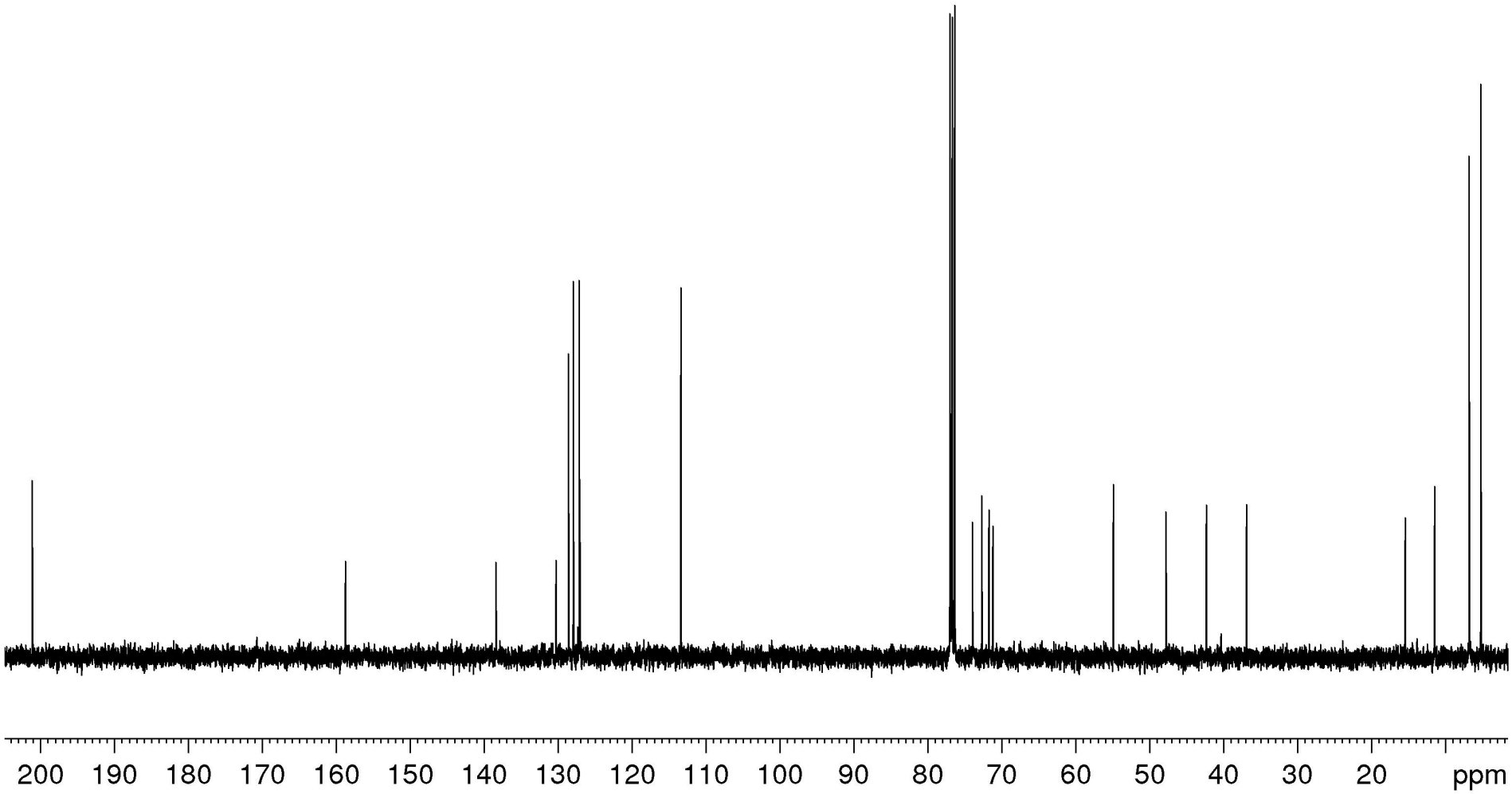

PMB
TES
HO
O
O
21
27
OBn
18b
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

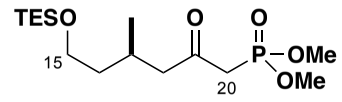


14

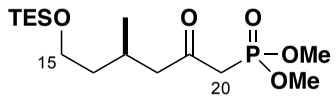

PMB
TES
O
O
O
H
21
27
OBn

14


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

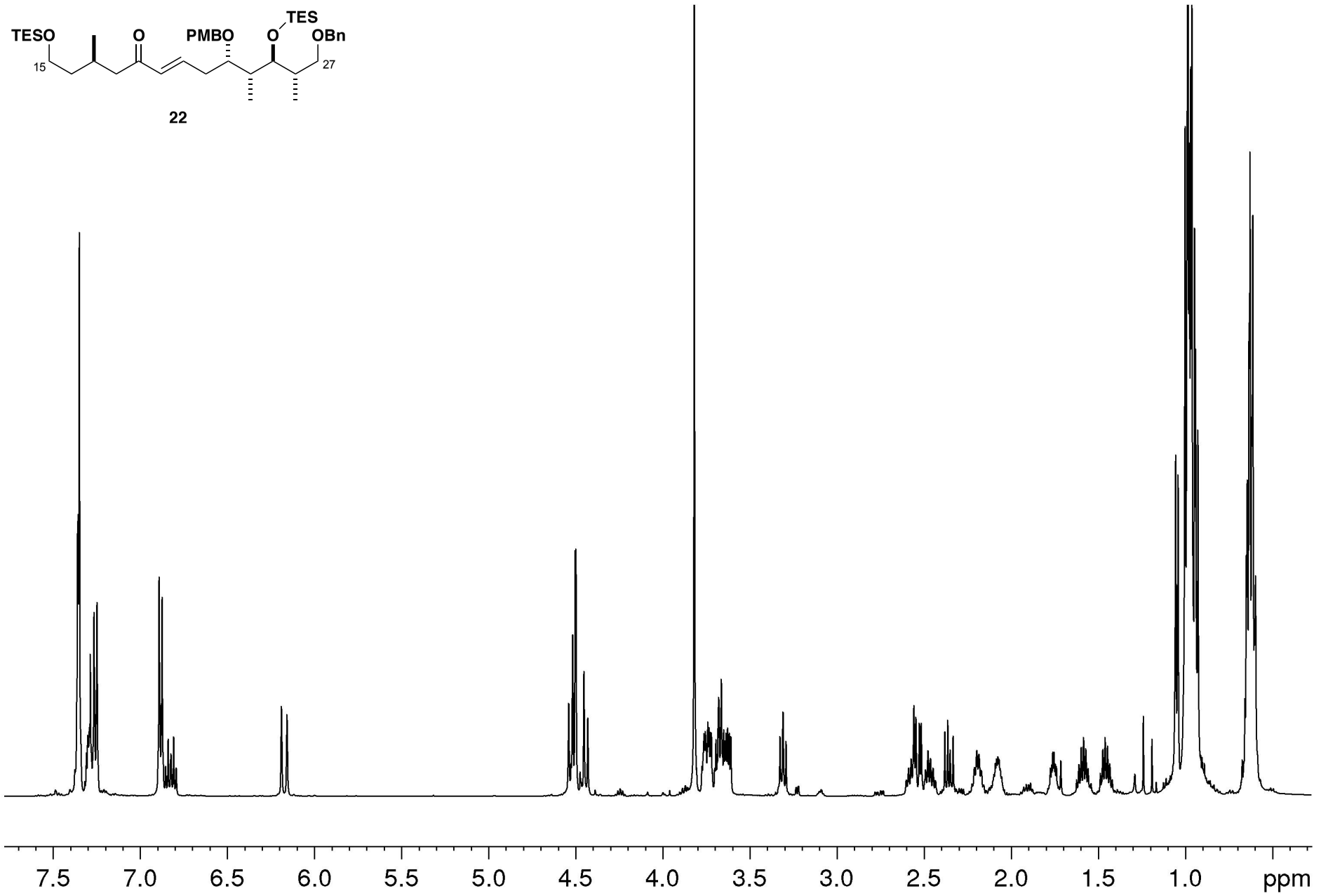


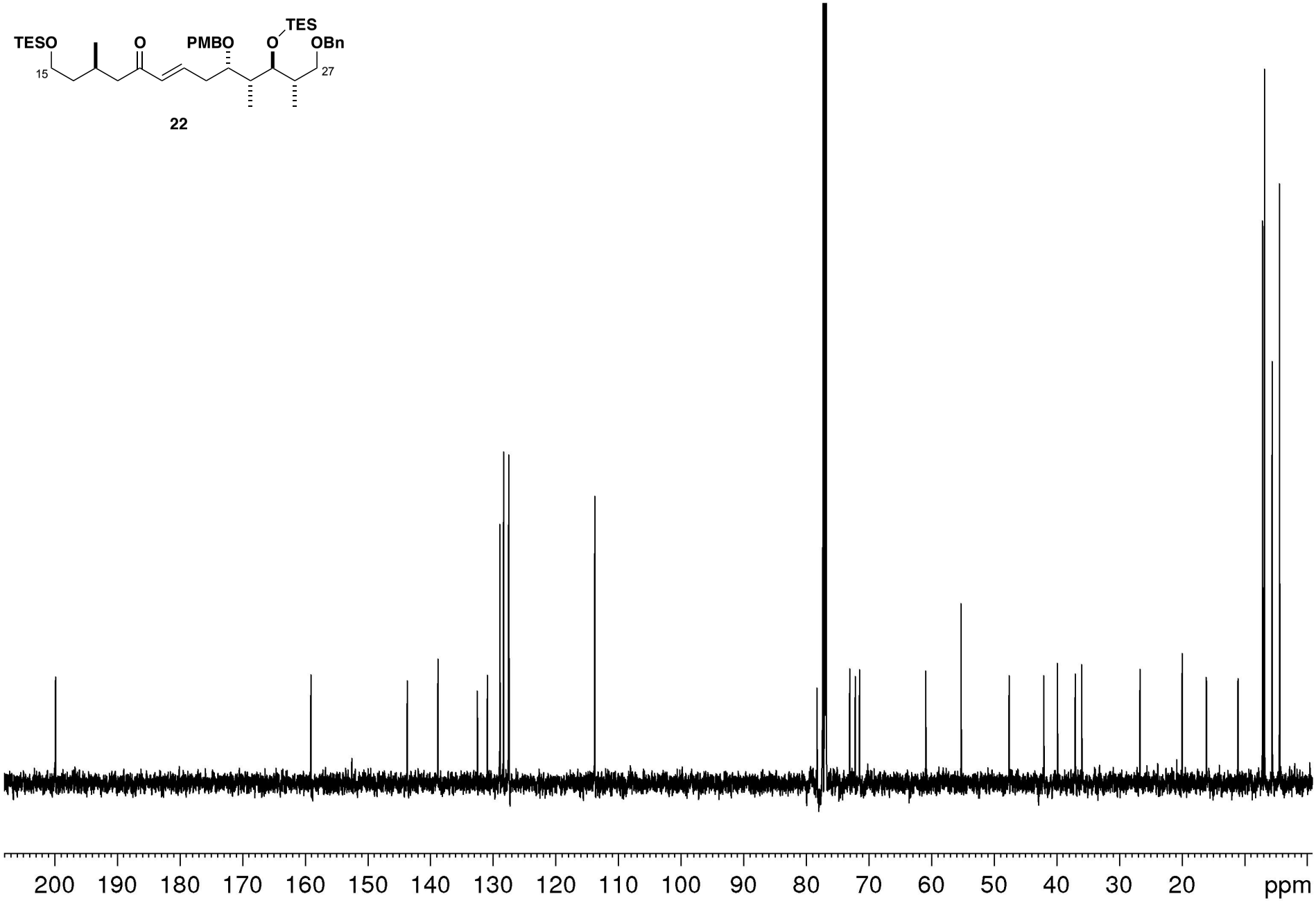
19

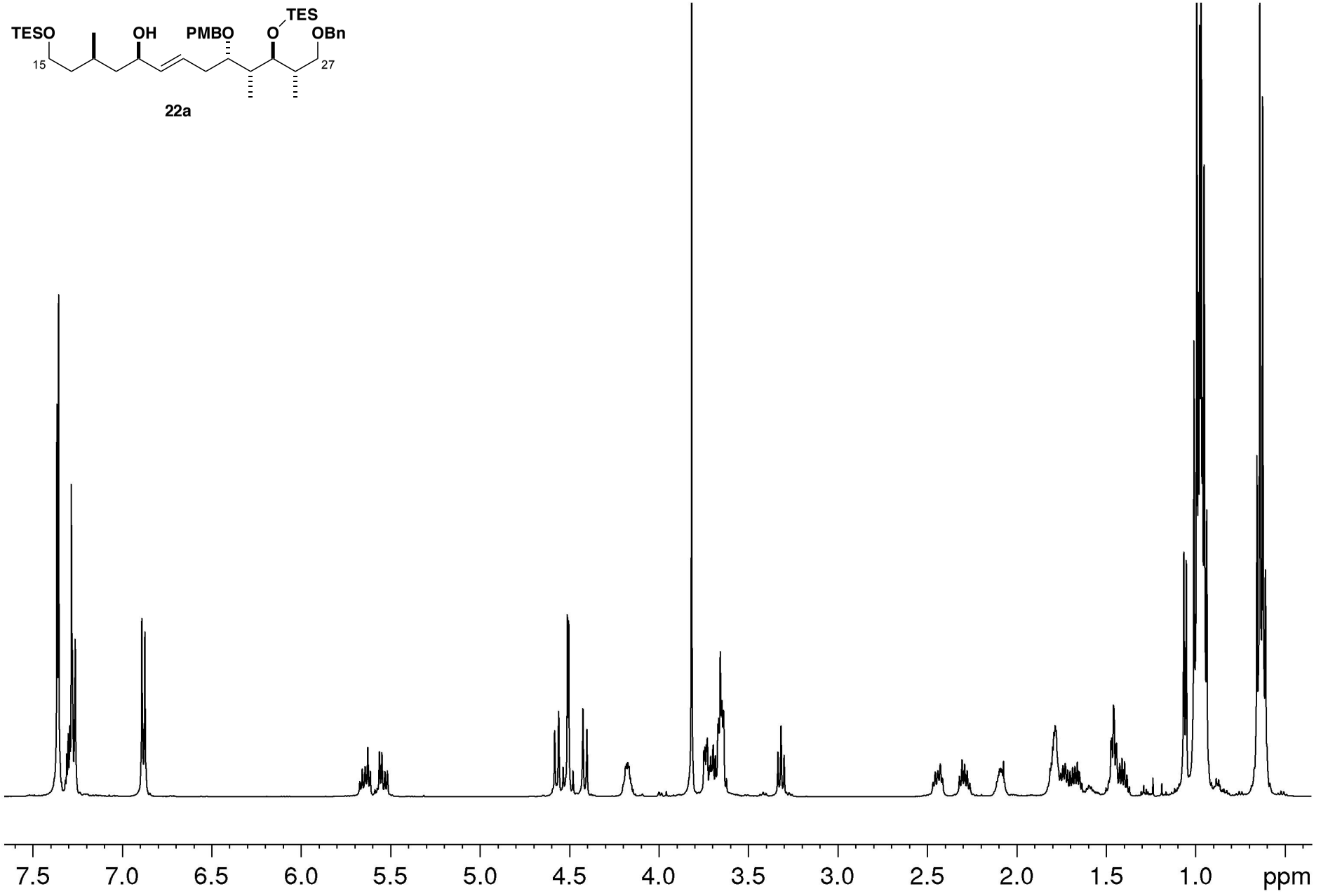

TESO
O
O
P
OMe
OMe
15
20

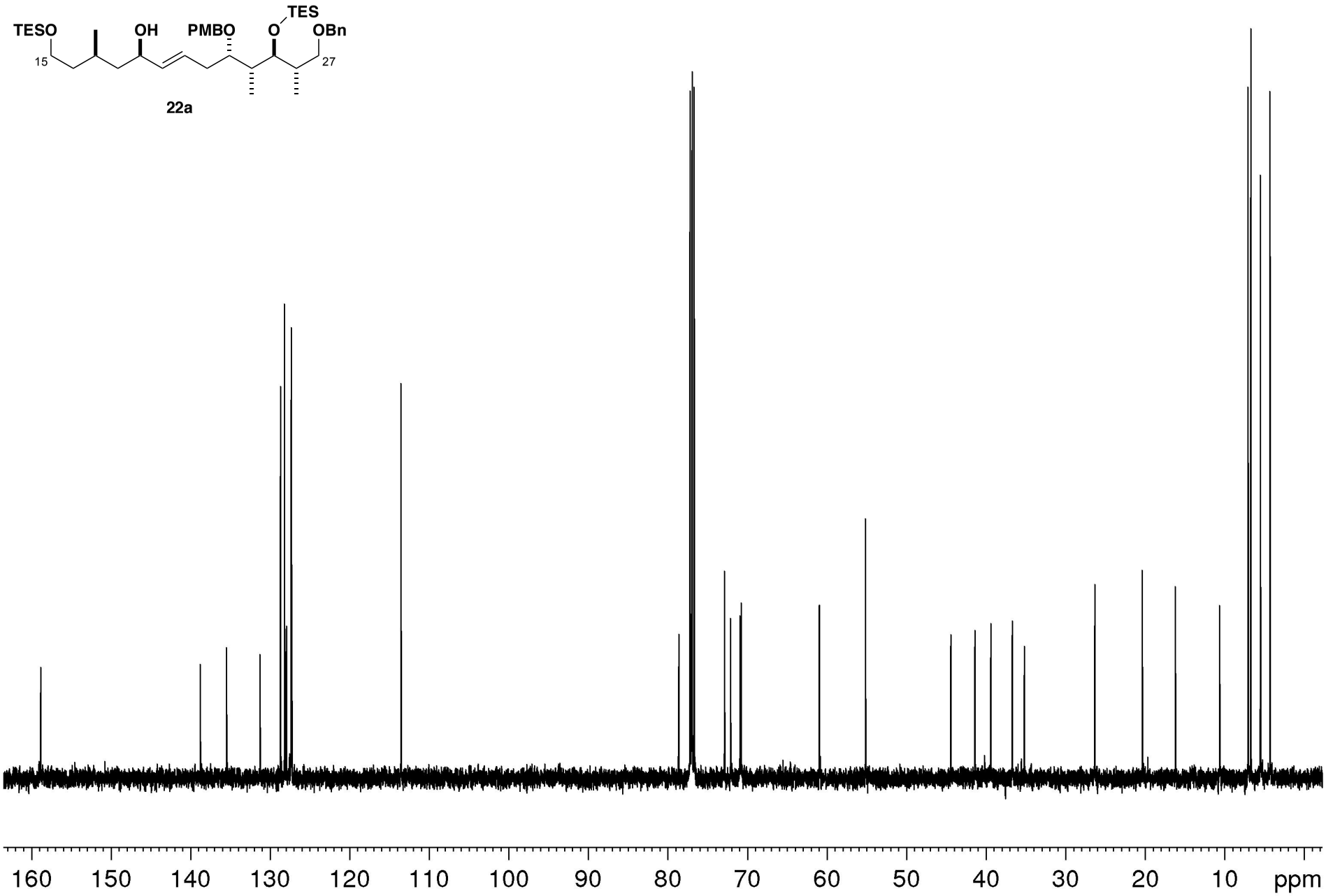
19

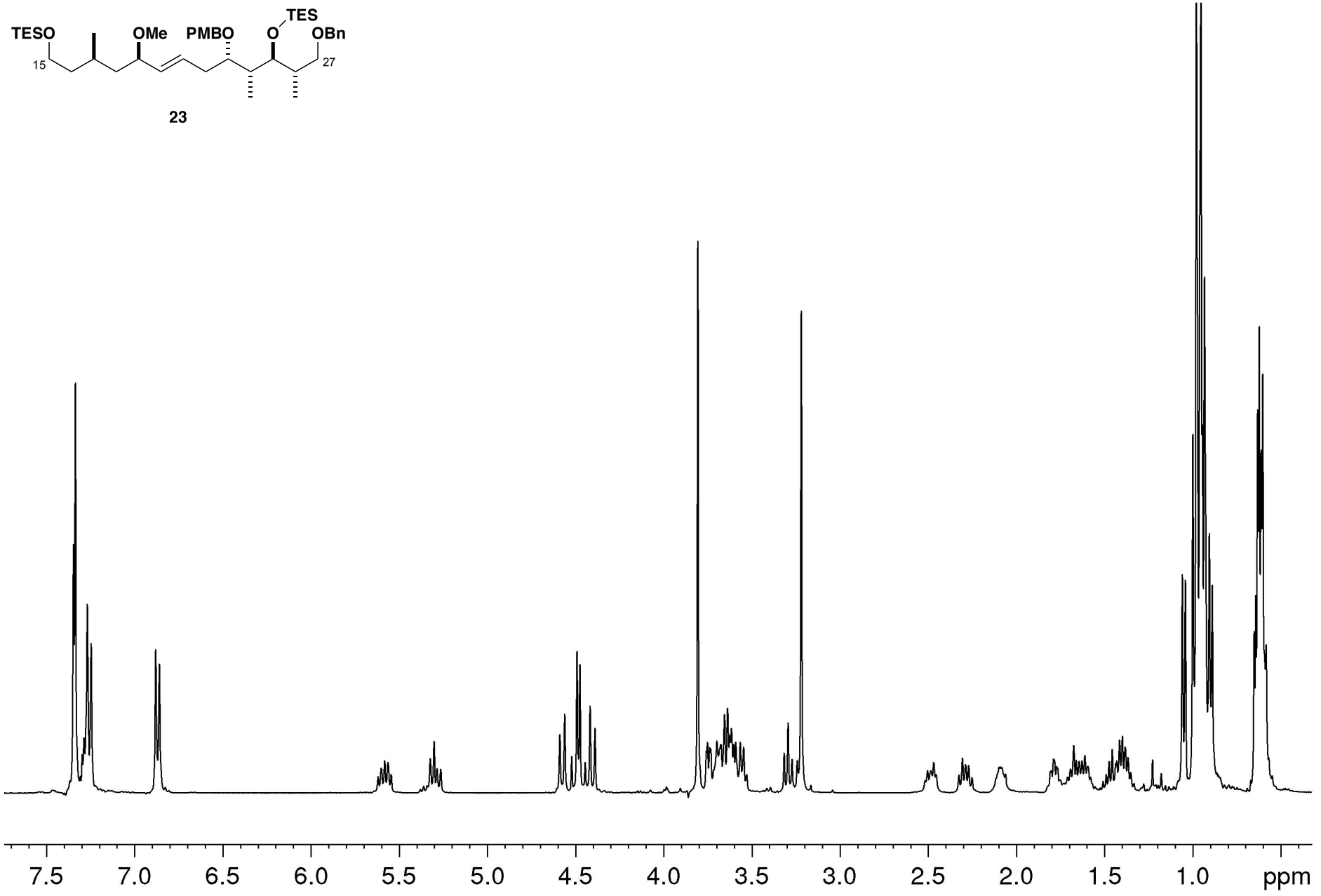
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

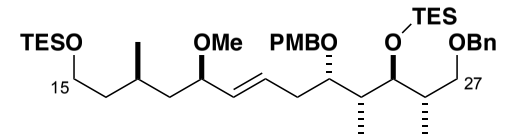

TESO
O
PMBO
O
TES
OBn
15
27
22
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


TESO
O
PMBO
O
TES
OBn
15
27
22
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


TESO
OH
PMBO
O
TES
OBn
15
27
22a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

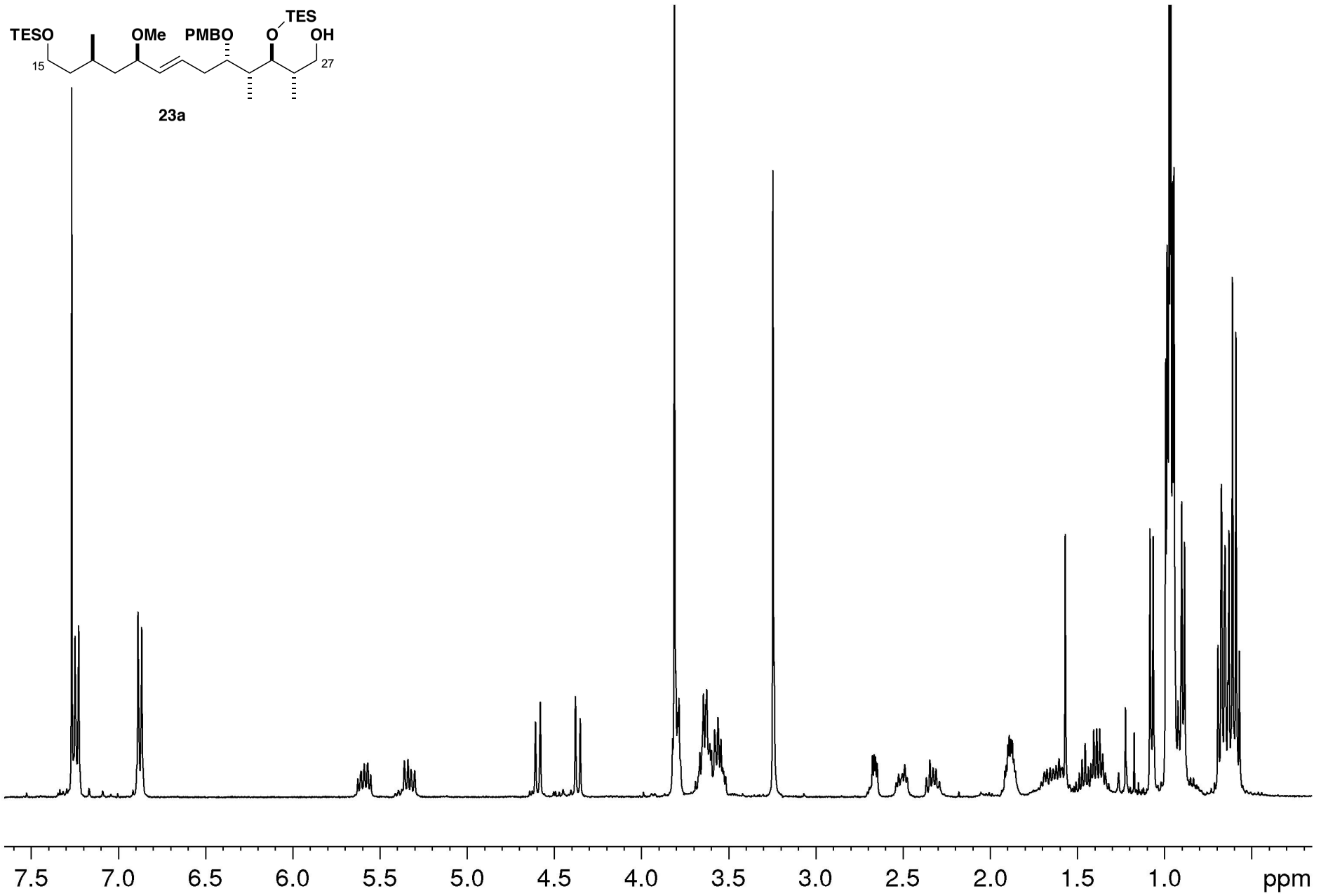

TESO
OH
PMBO
O
TES
OBn
15
27
22a
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

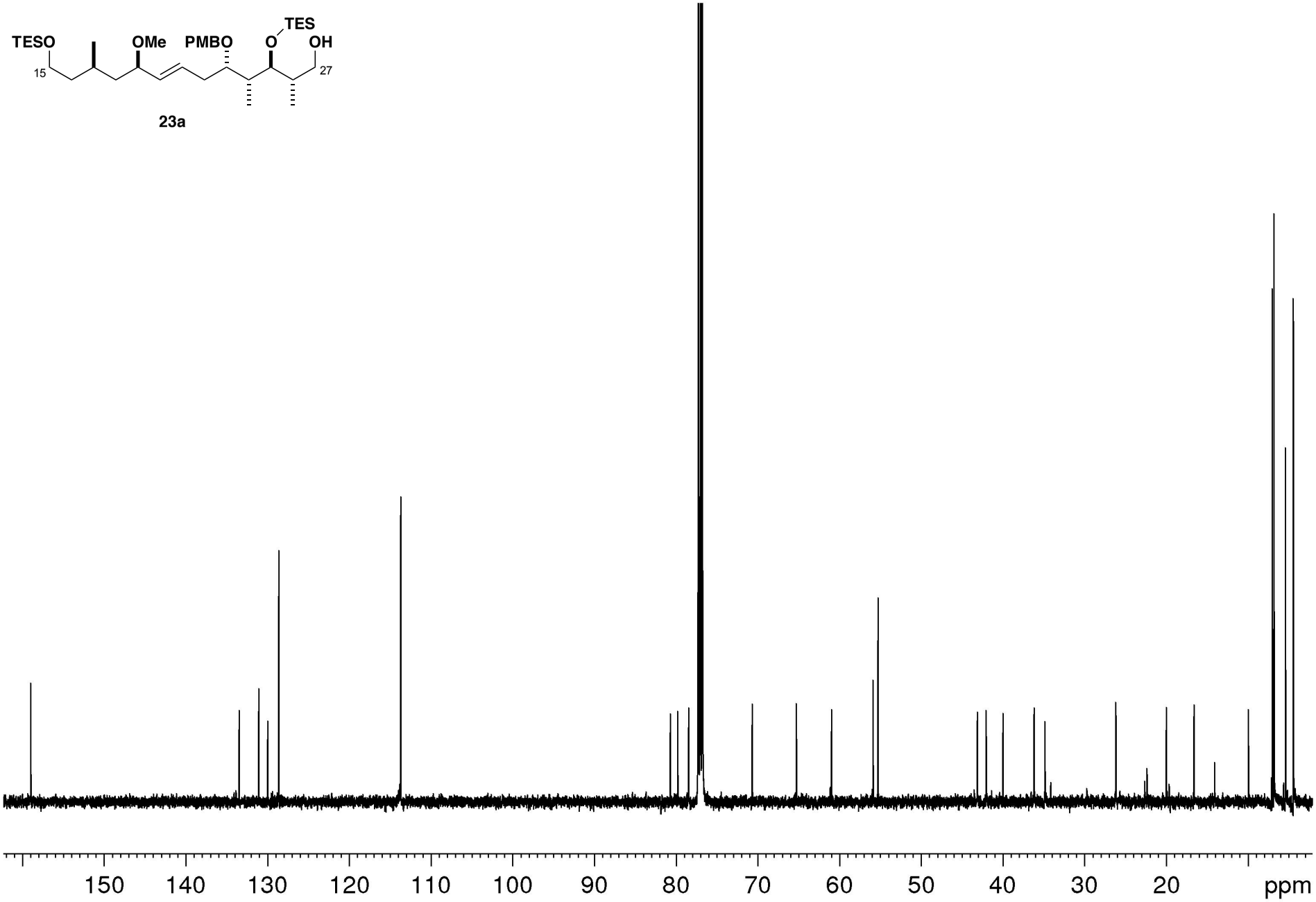

TESO
OMe
PMBO
O
TES
OBn
15
27
23
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

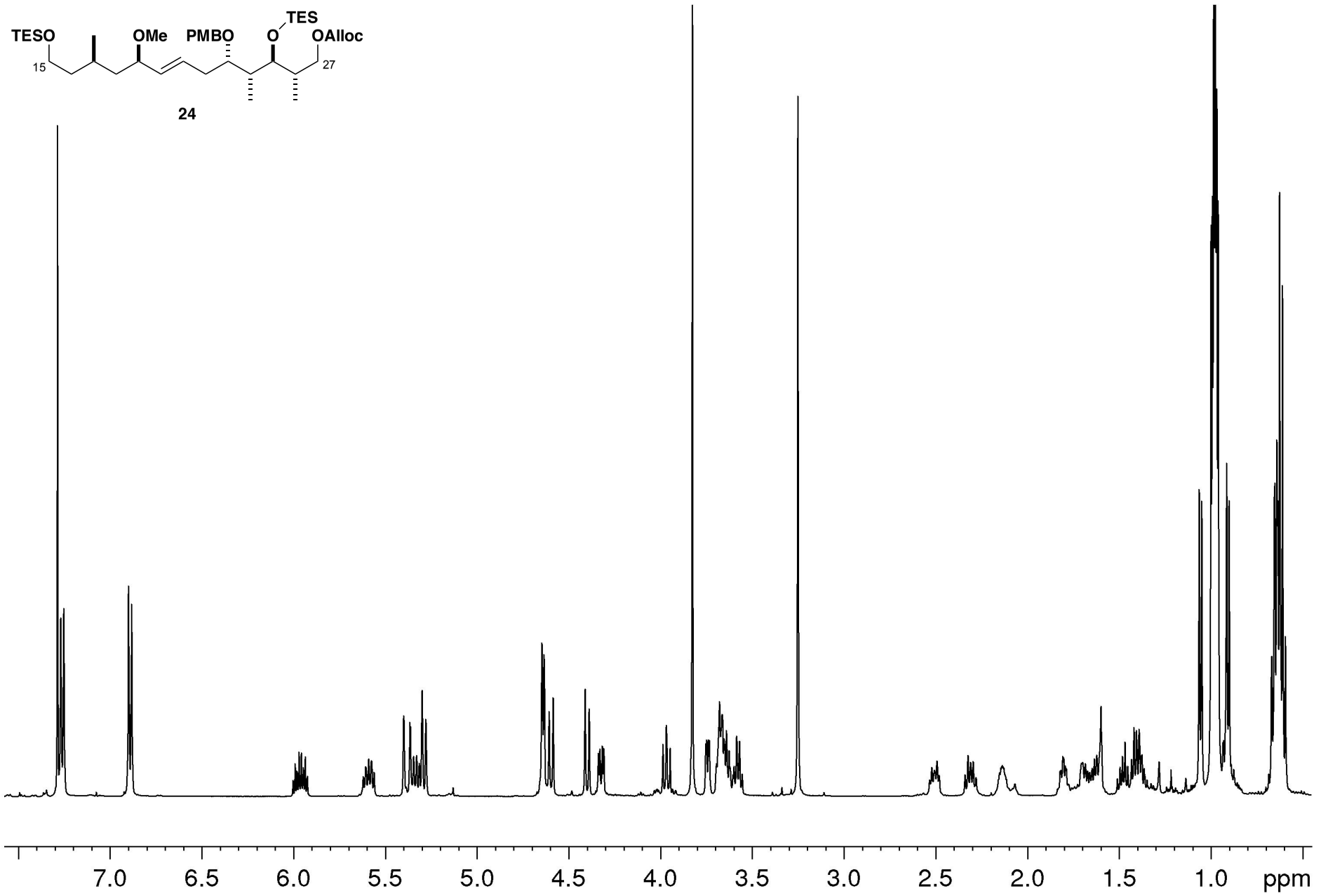

TESO
OMe
PMBO
O
TES
OBn
15
27

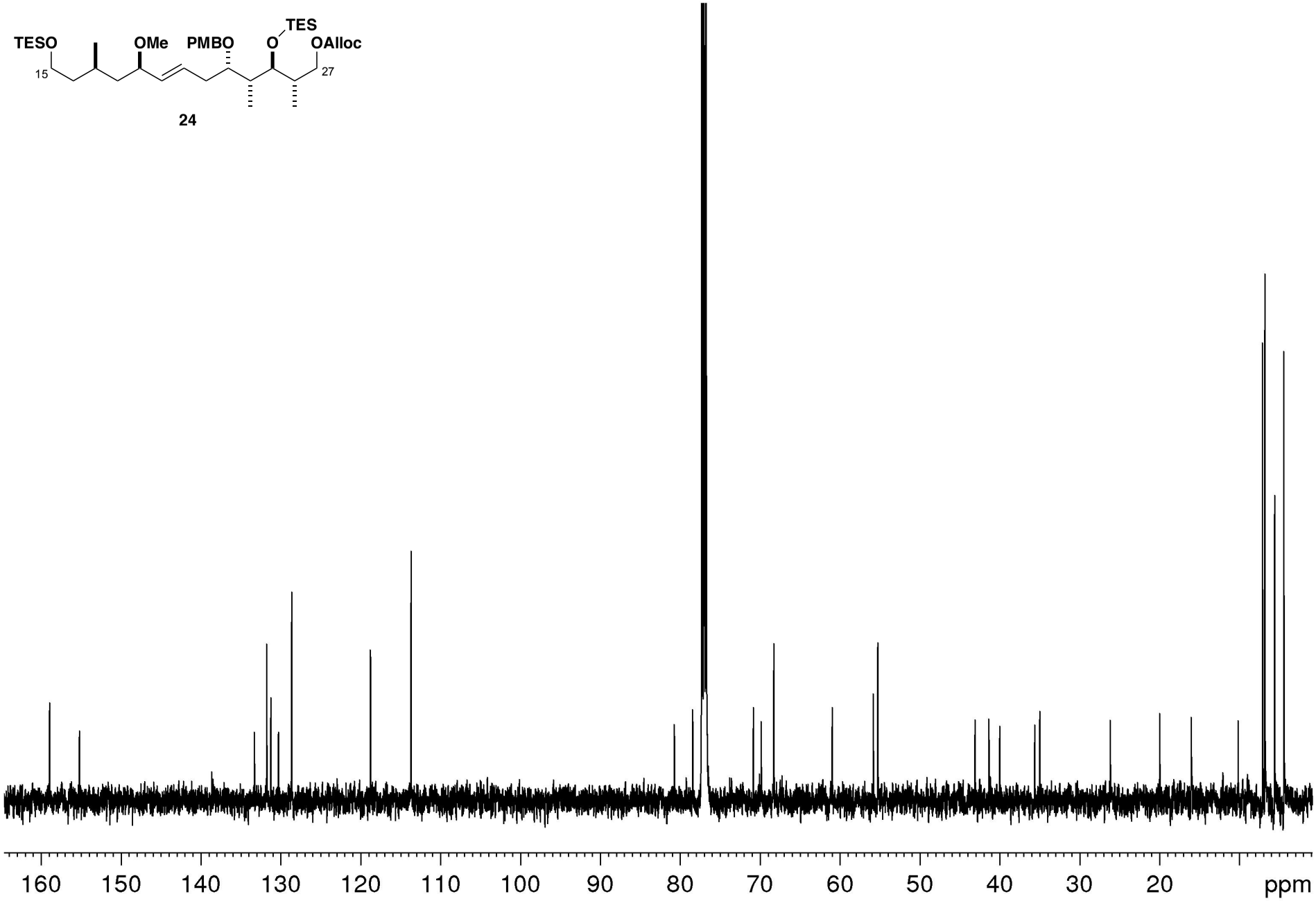
23

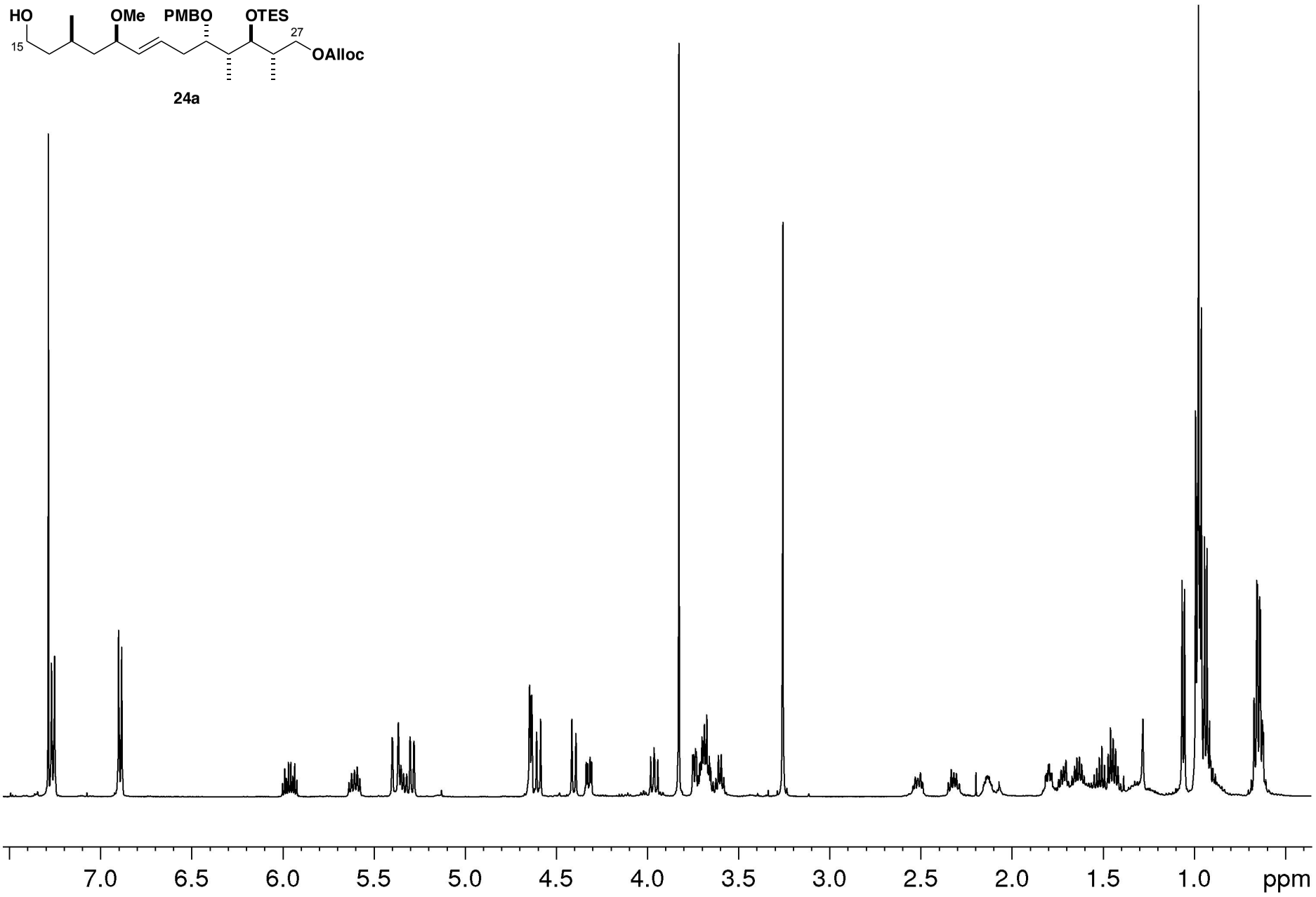
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

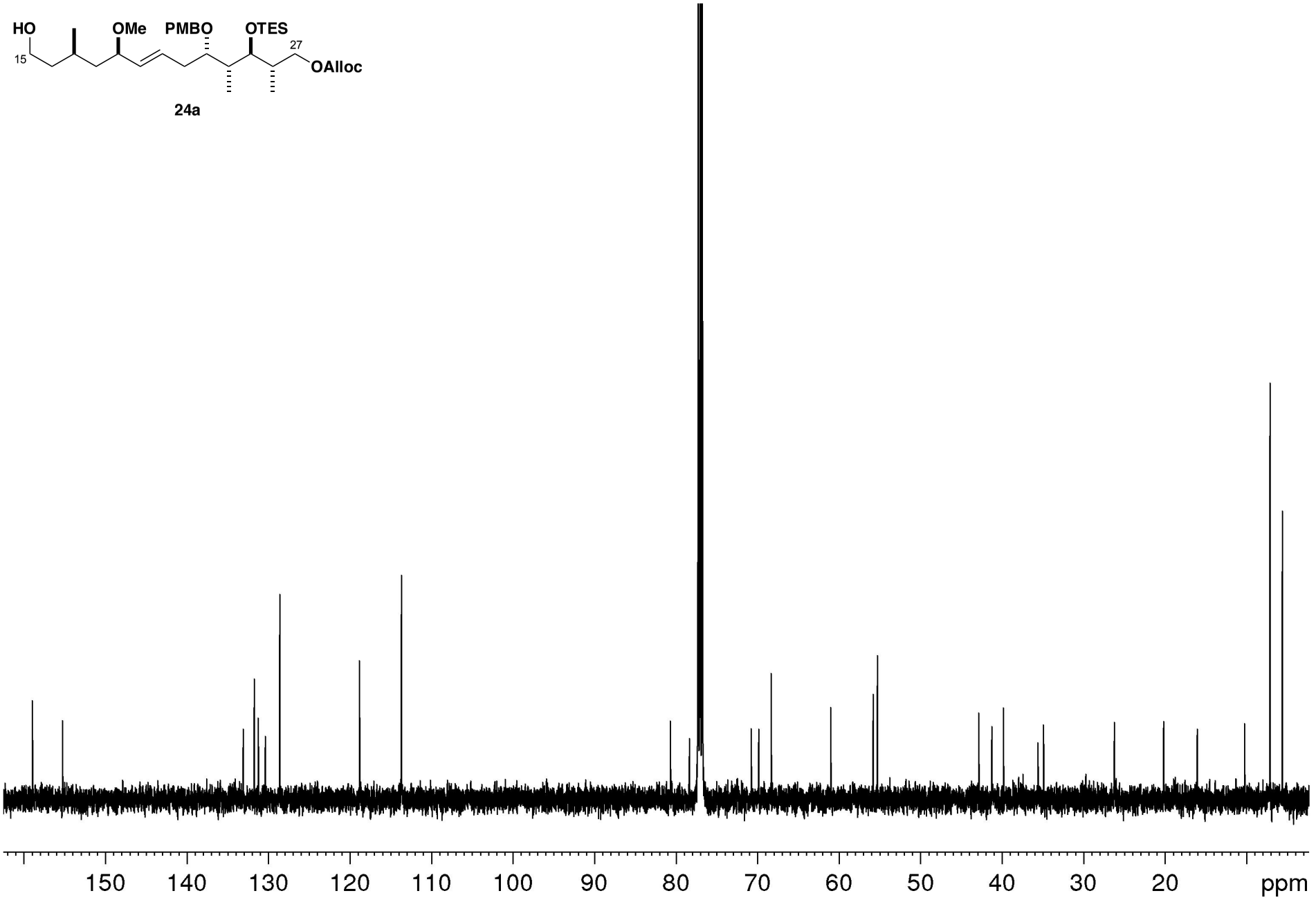

TESO
OMe
PMBO
O
TES
OH
15
27
23a
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

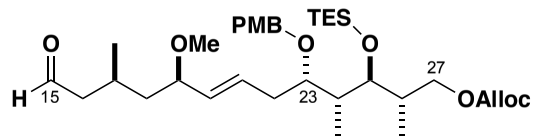

TESO
OMe
PMBO
O
TES
OH
15
27
23a
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


TESO
OMe
PMBO
O
TES
OAlloc
15
27
24
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

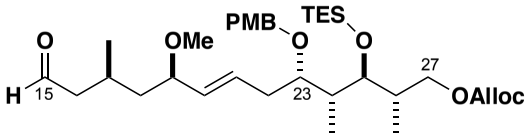

TESO
OMe
PMBO
O
TES
OAlloc
15
27
24
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


HO
OMe
PMBO
OTES
15
27
OAlloc
24a
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


HO
OMe
PMBO
OTES
15
27
OAlloc
24a
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

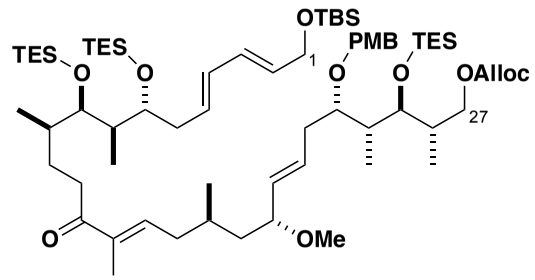


7


O
H
15
OMe
PMB
TES
O
O
23
27
OAlloc

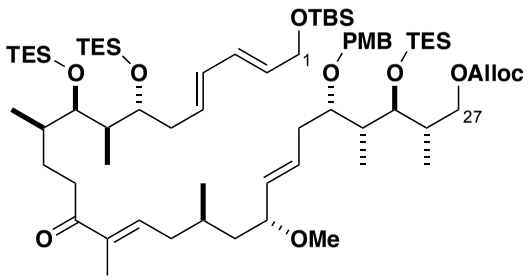
7

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


TES
TES
O
O
OTBS
1
PMB
TES
O
O
OAlloc
27
O
OMe

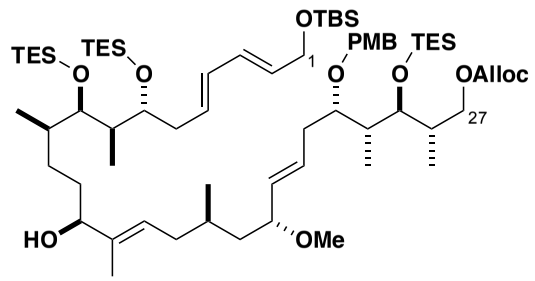
7a

7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


OTBS
PMB
TES
TES
TES
OAlloc
1
27
O
OMe

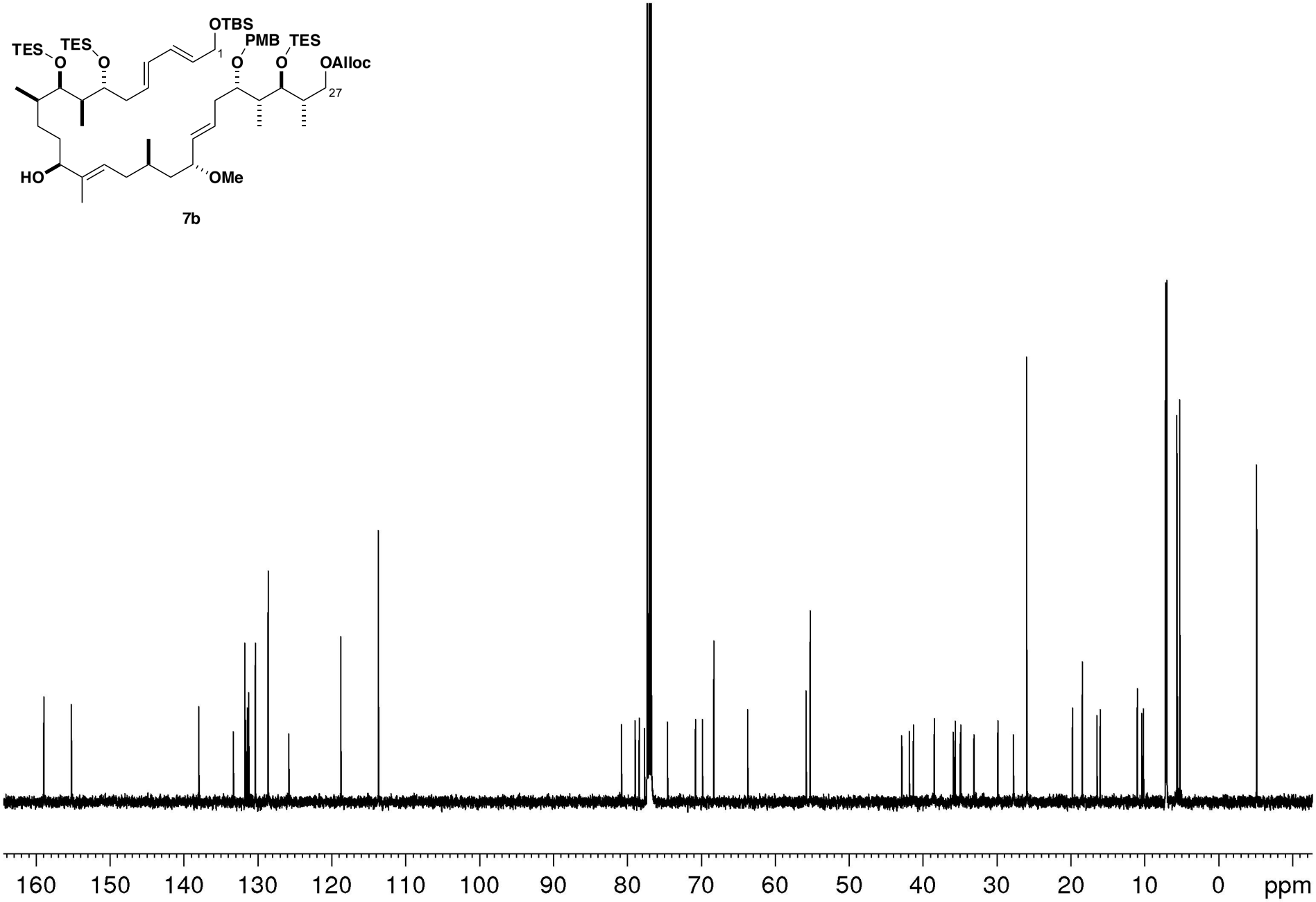
7a

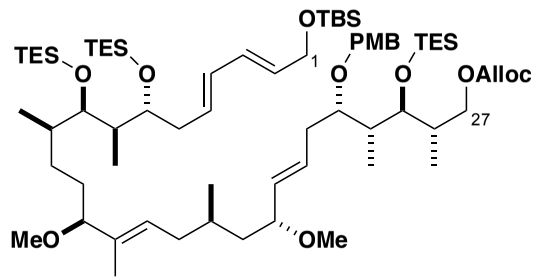
200
180
160
140
120
100
80
60
40
20
ppm


OTBS
TES
TES
PMB
TES
OAlloc
1
27
HO
OMe

7b

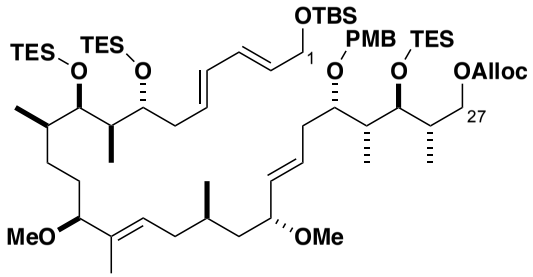
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


OTBS
PMB
TES
TES
TES
OAlloc
1
27
HO
OMe
7b
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


TES
TES
O
O
OTBS
1
PMB
TES
O
O
OAlloc
27
MeO
OMe

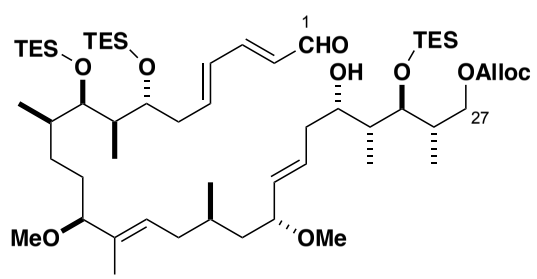
25

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


OTBS
PMB
TES
TES
TES
O
O
O
O
O
O
OAlloc
1
27
MeO
OMe

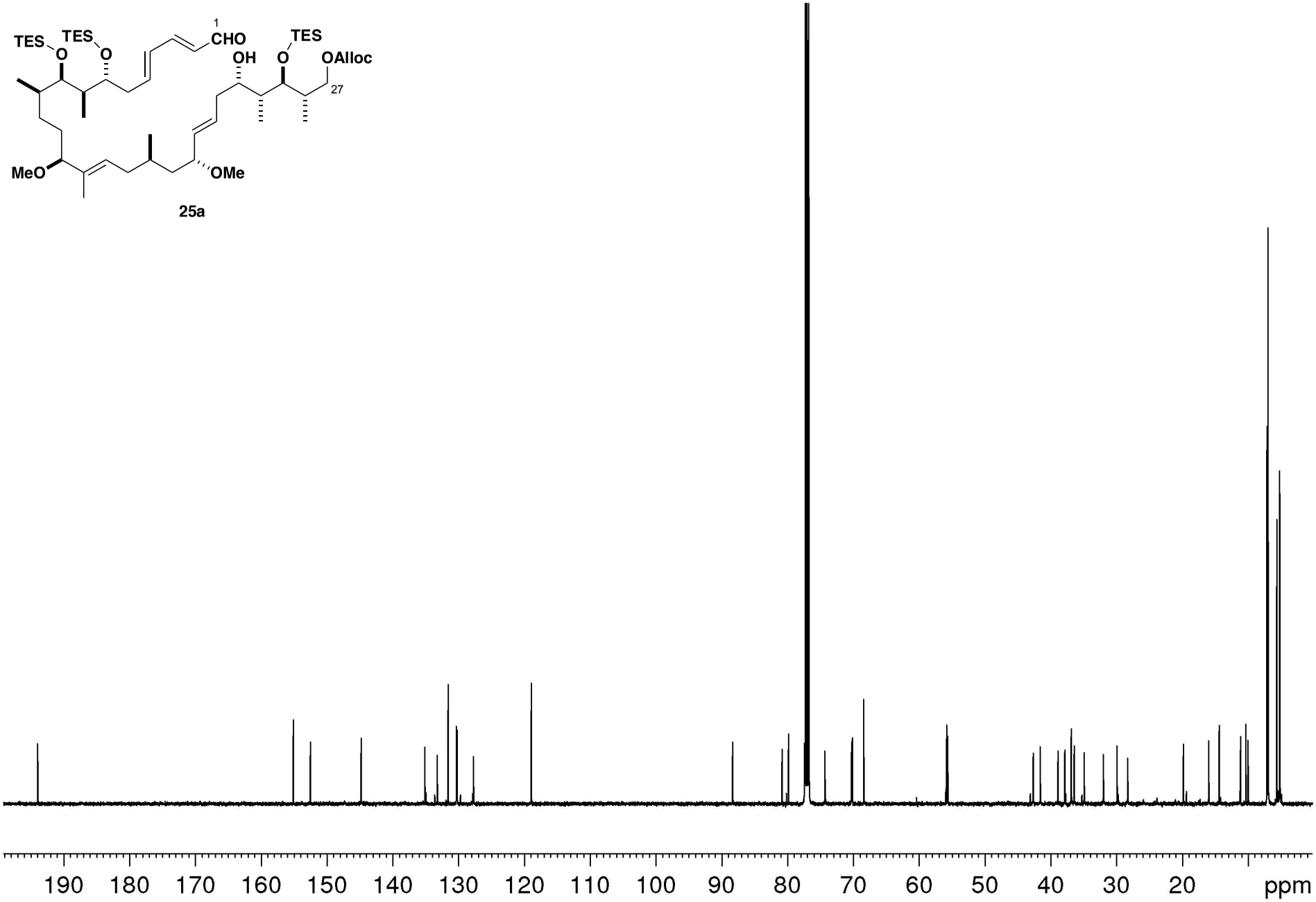
25

150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

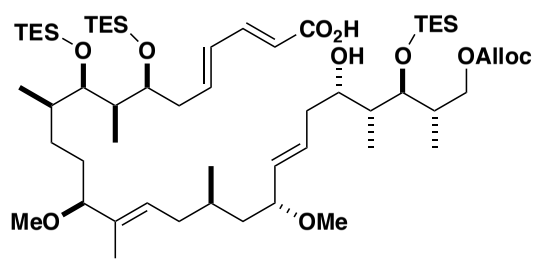

TES
TES
O
O
1
CHO
OH
TES
O
O
OAlloc
27
MeO
OMe

25a

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

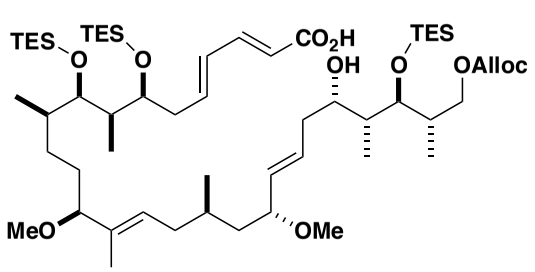

TES
TES
O
O
1
CHO
OH
TES
O
O
OAlloc
27
MeO
OMe
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

25a


TES
TES
O
O
CO2H
OH
TES
O
OAlloc
MeO
OMe

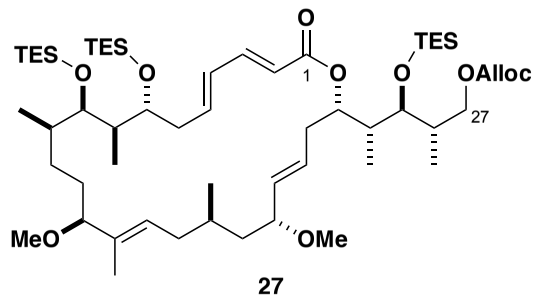
26

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


TES
TES
O
O
CO2H
OH
TES
O
OAlloc
MeO
OMe

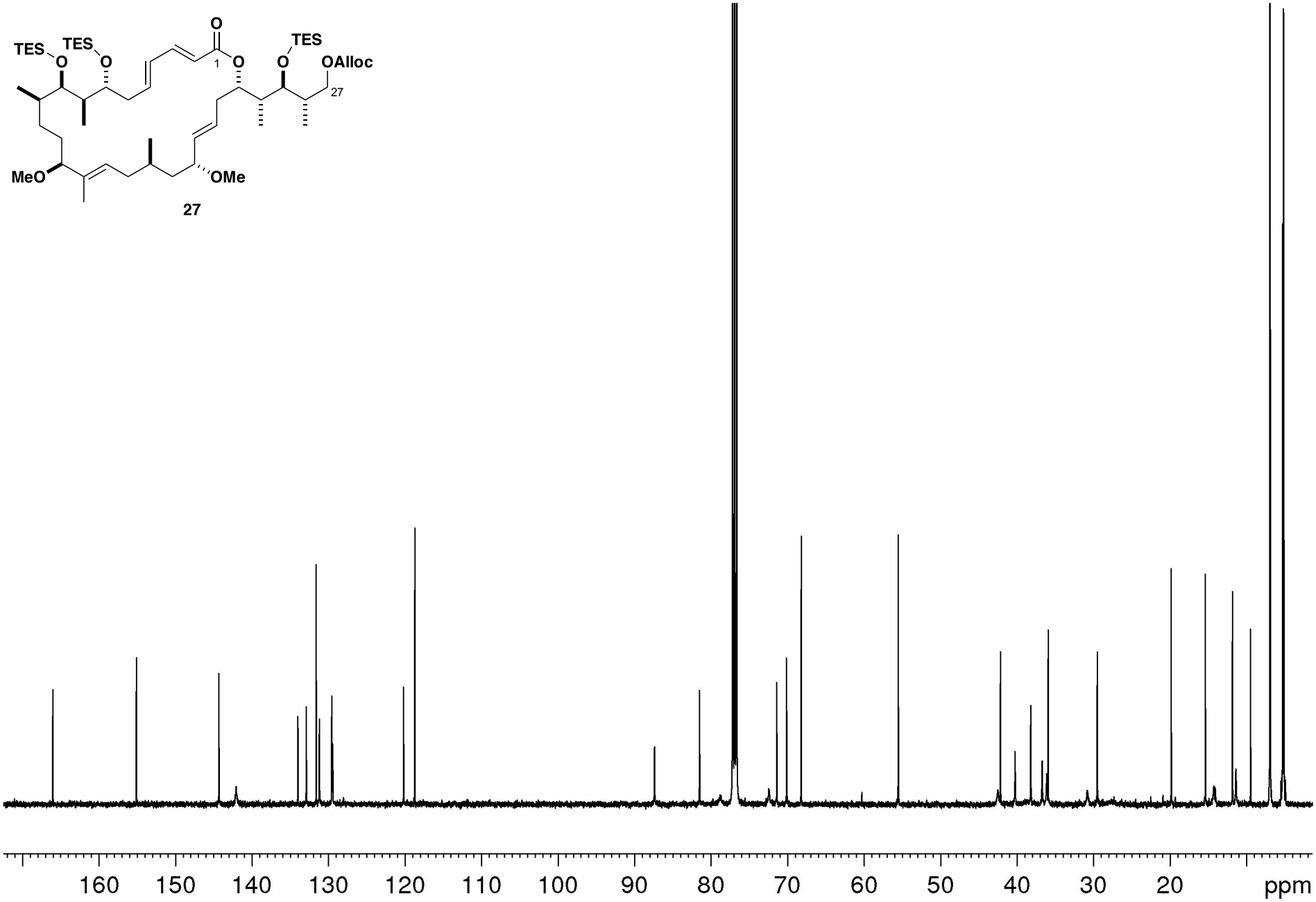
26

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

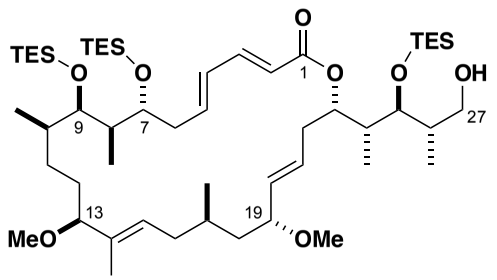

TES
TES
O
O
O
1
O
O
TES
OAlloc
27
MeO
OMe

27

7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

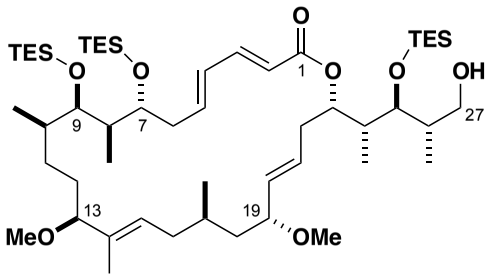

TES
TES
O
O
O
1
O
O
TES
OAlloc
27
MeO
OMe
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

27


TES
TES
O
O
O
1
O
TES
O
OH
9
7
27
13
19
MeO
OMe

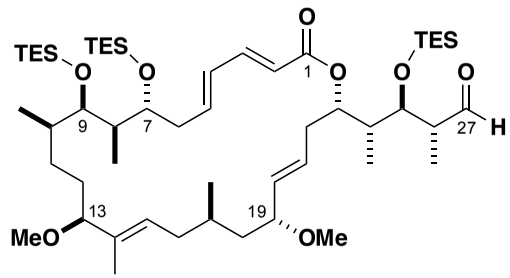
5

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

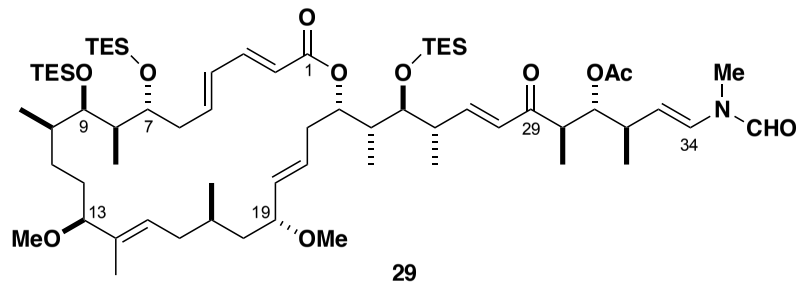

TES
TES
O
O
O
1
O
TES
O
OH
27
9
7
13
19
MeO
OMe

5

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

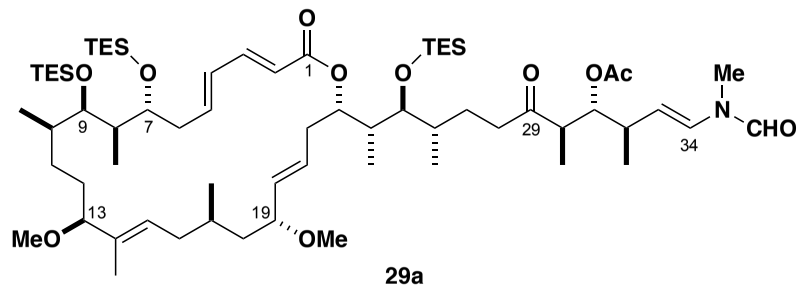


28


TES
TESO
O
1
O
O
TES
O
OAc
Me
N
CHO
9
7
29
34
13
19
MeO
OMe

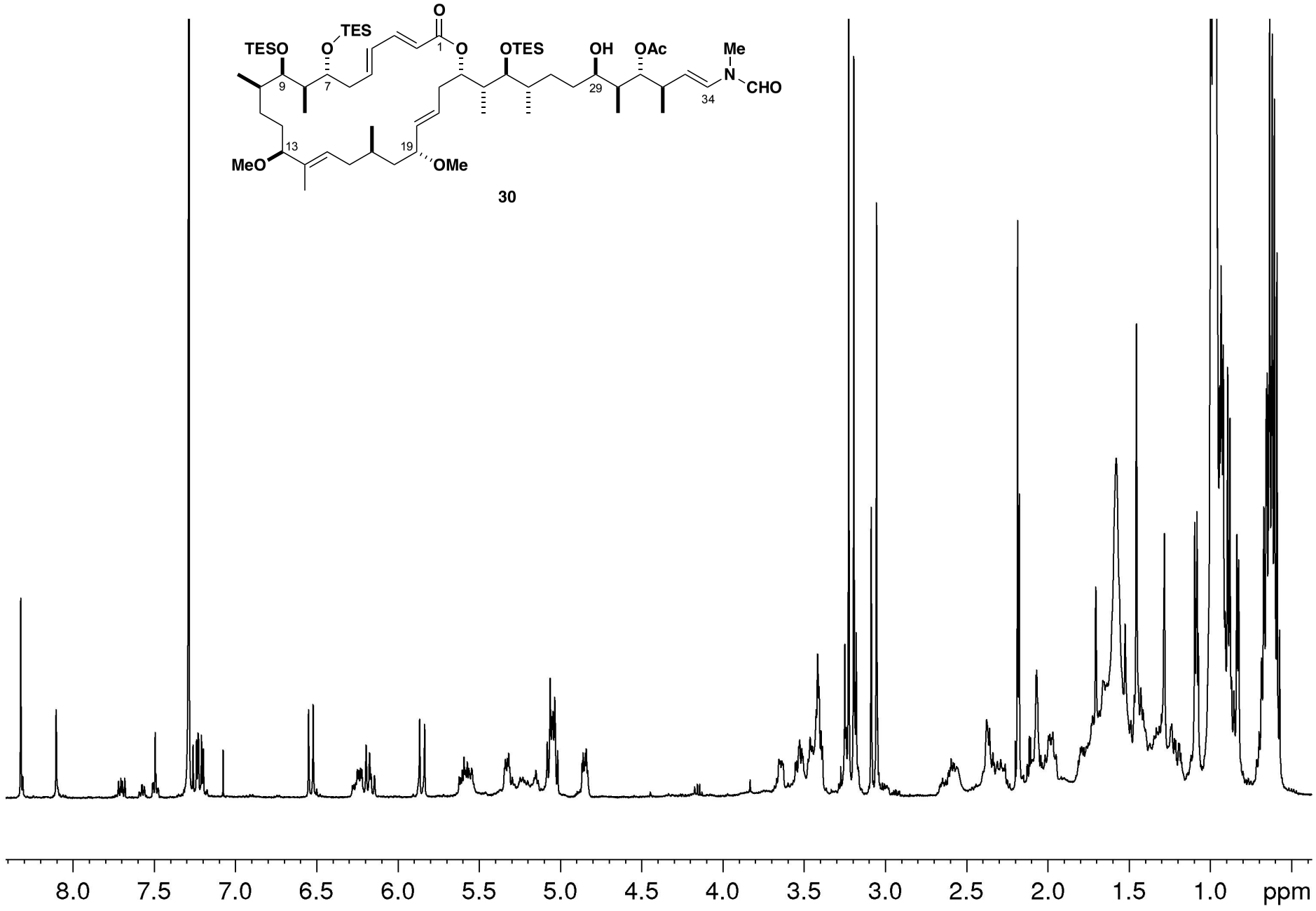
29

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

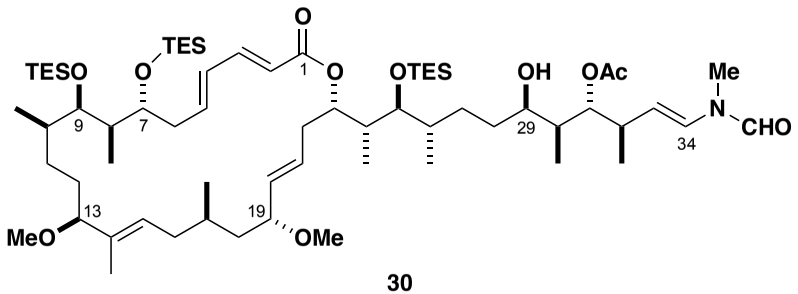

TES
TESO
O
1
O
O
TES
O
OAc
Me
N
CHO
9
7
29
34
13
19
MeO
OMe

29a

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

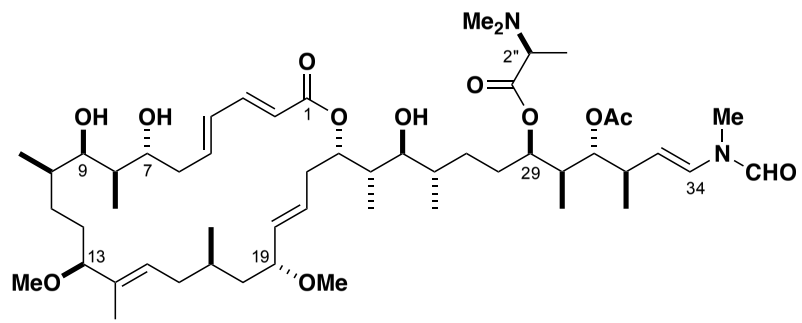

TESO
TES
O
1
O
OTES
OH
OAc
Me
N
CHO
9
7
29
34
13
19
MeO
OMe
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

30

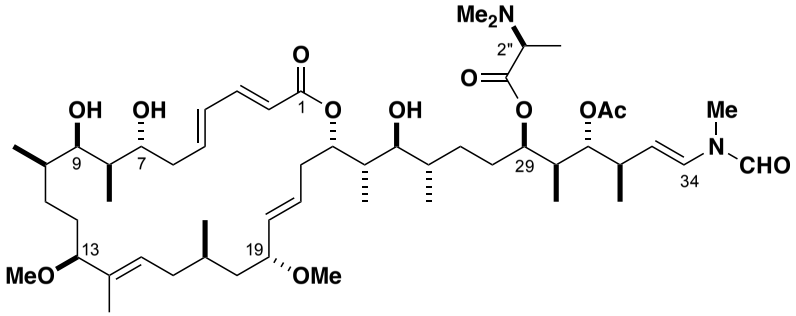

TESO
O
TES
O
1
O
OTES
OH
OAc
Me
N
CHO
9
7
29
34
13
19
MeO
OMe

30

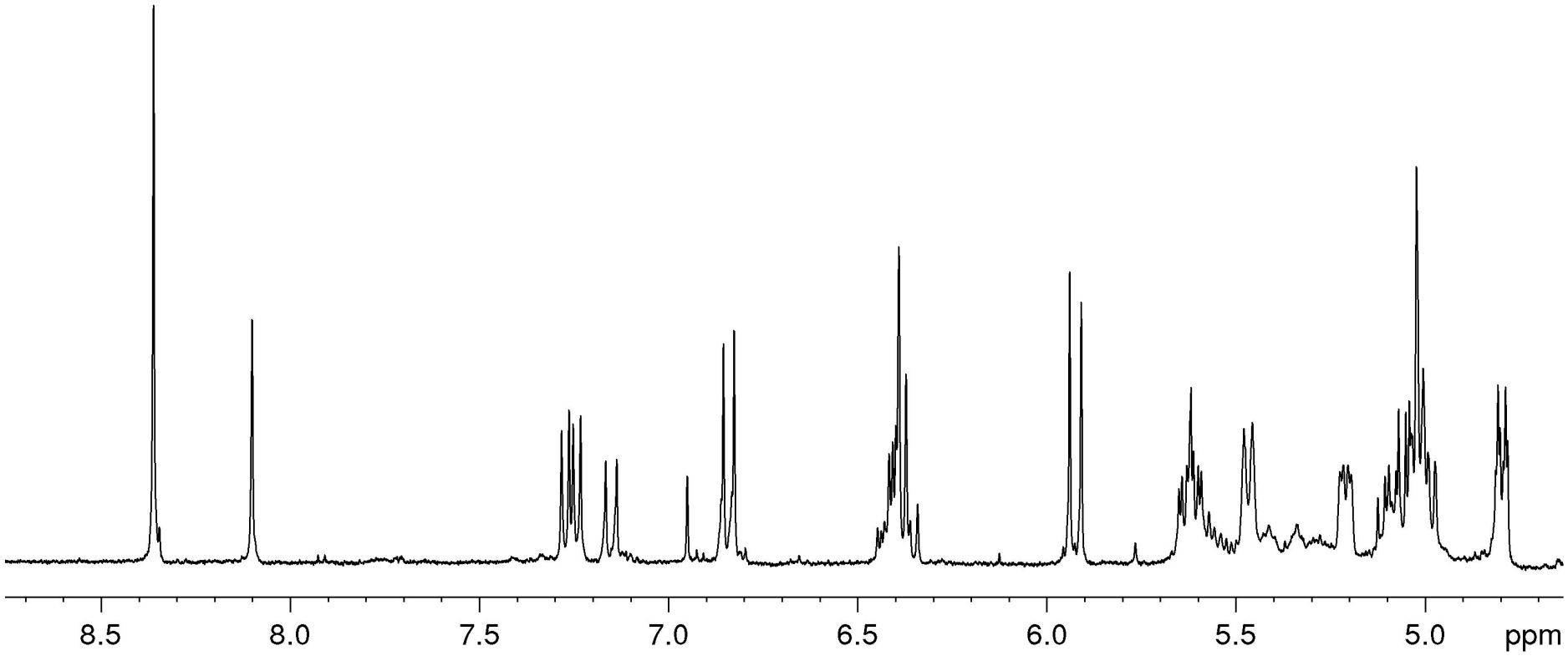
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

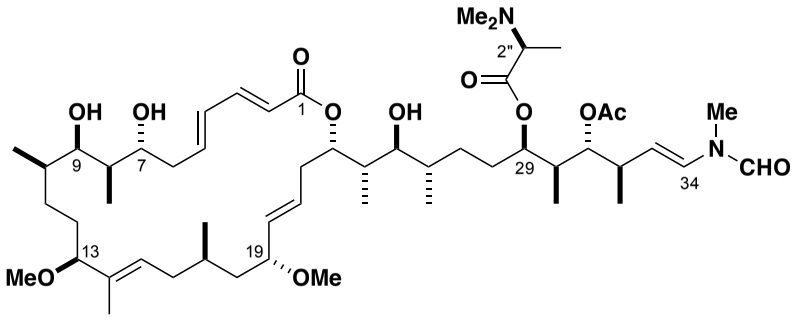


Aplyronine C 3

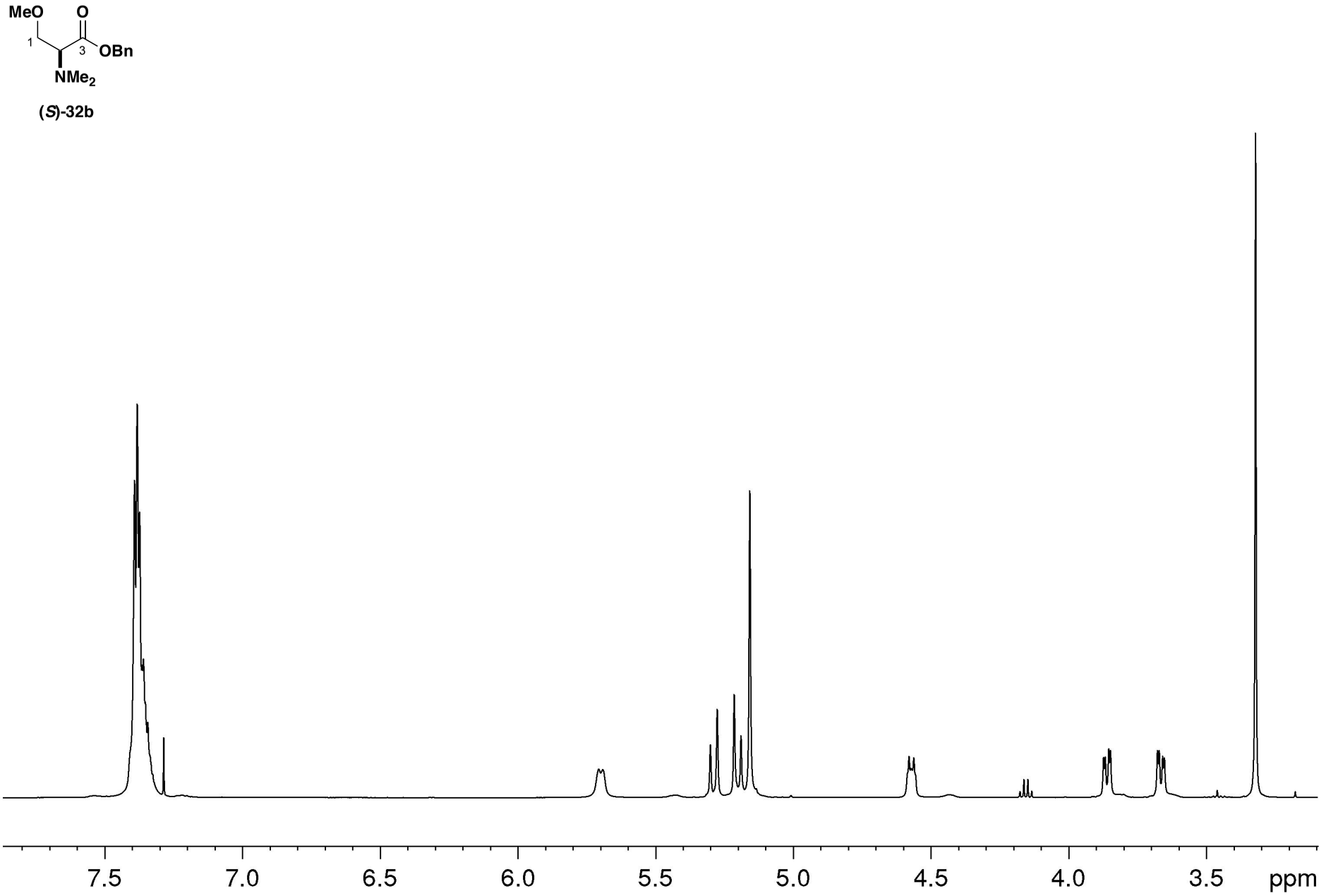


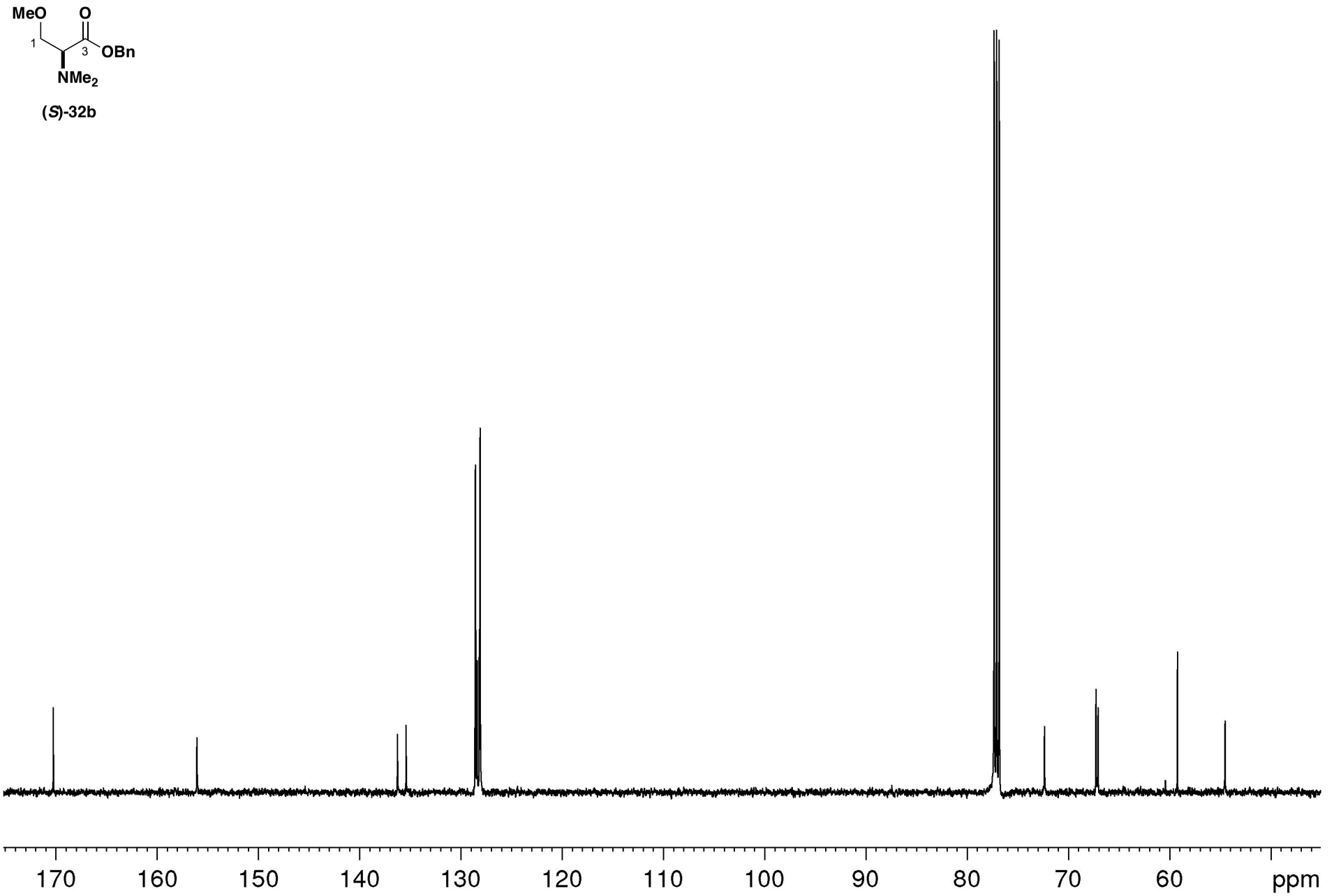
Aplyronine C 3

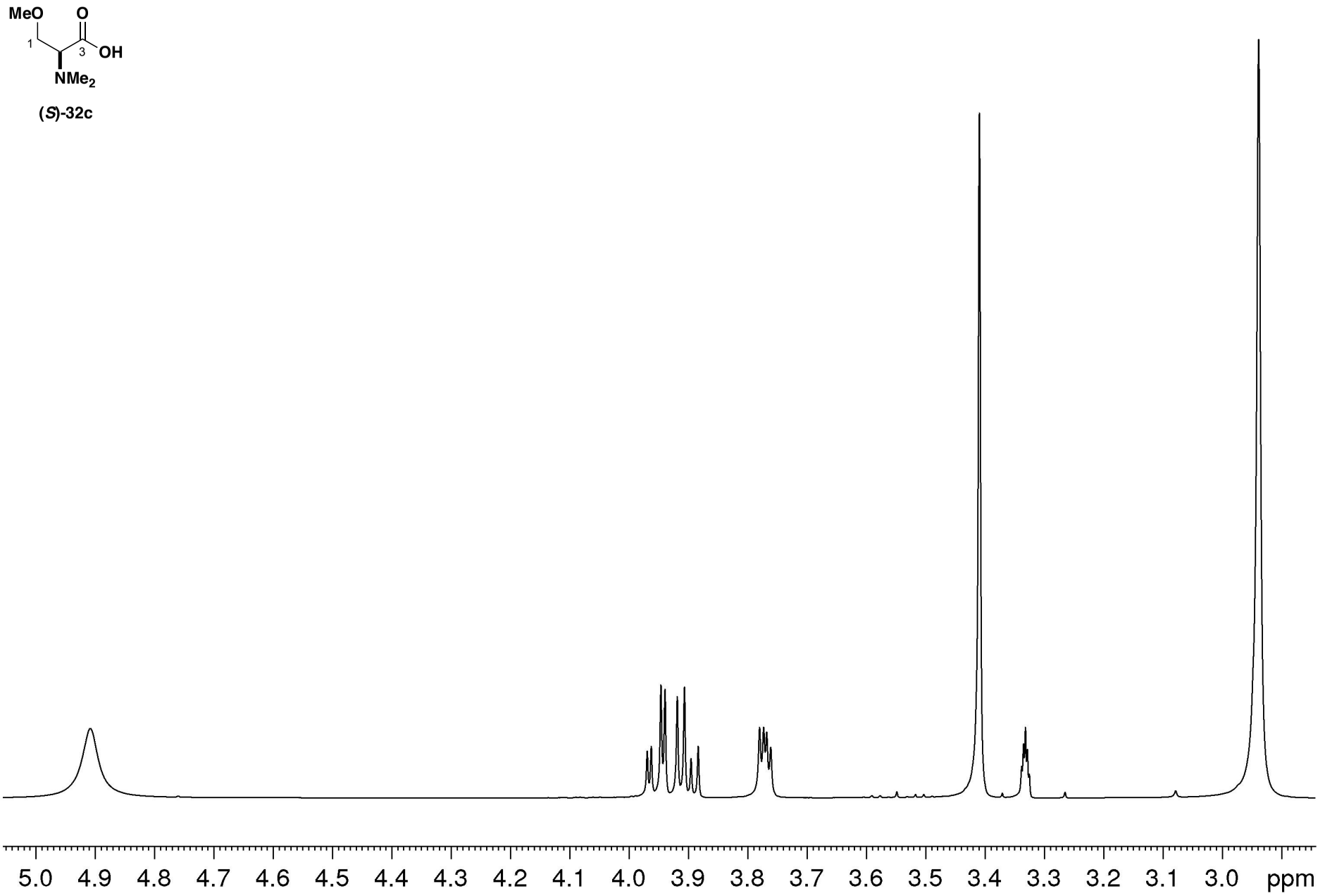


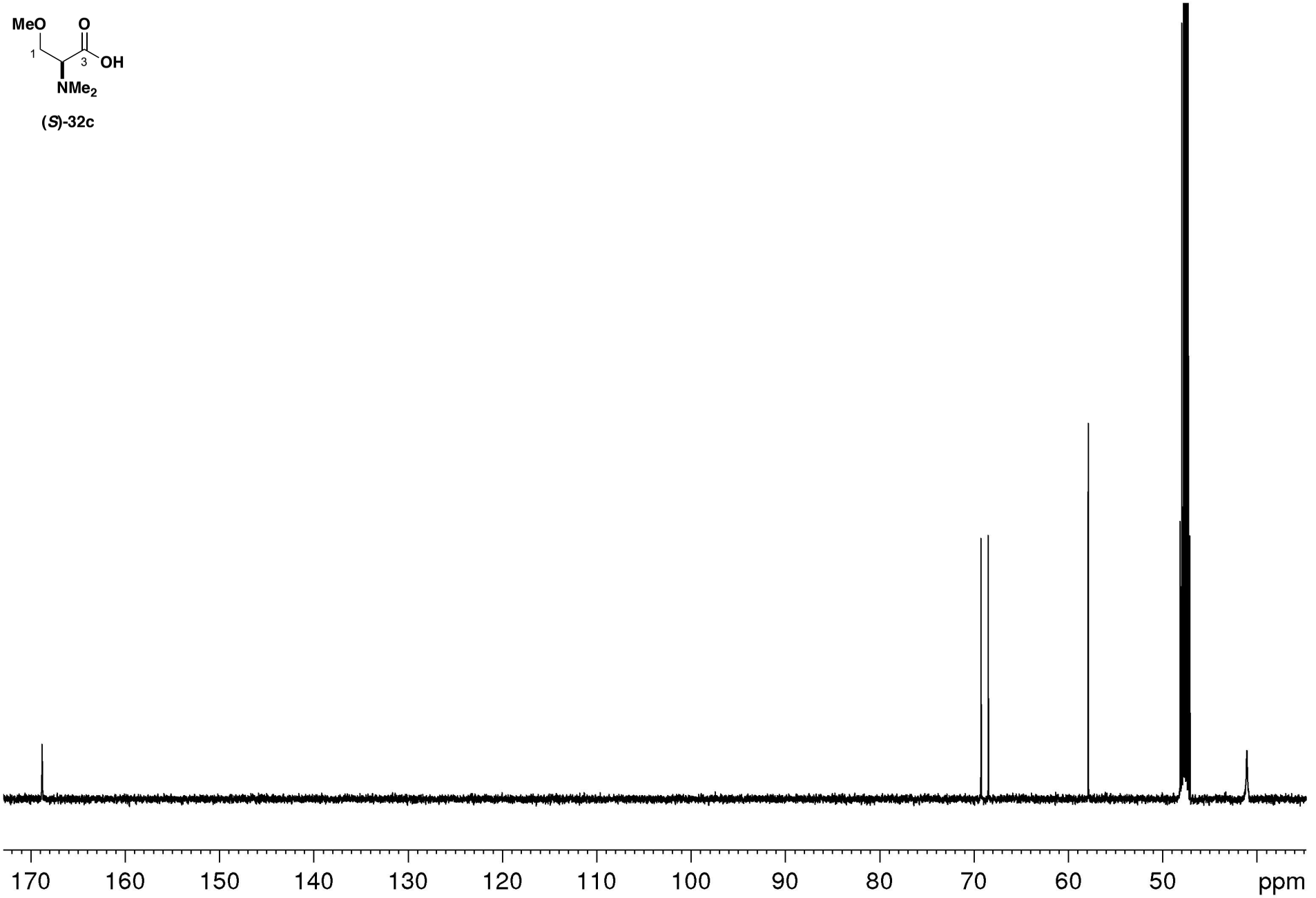


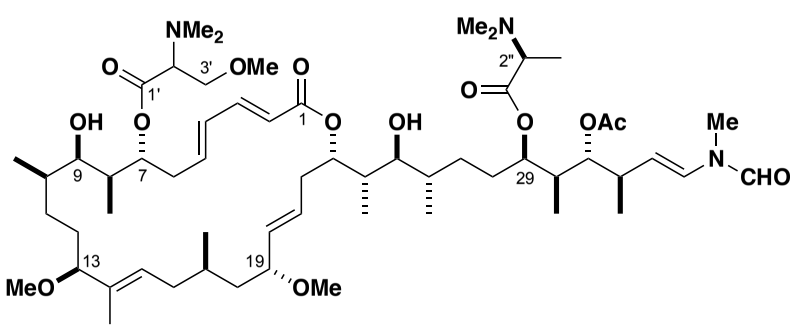
Aplyronine C 3


MeO
O
1
3
OBn
NMe2
(S)-32b
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm

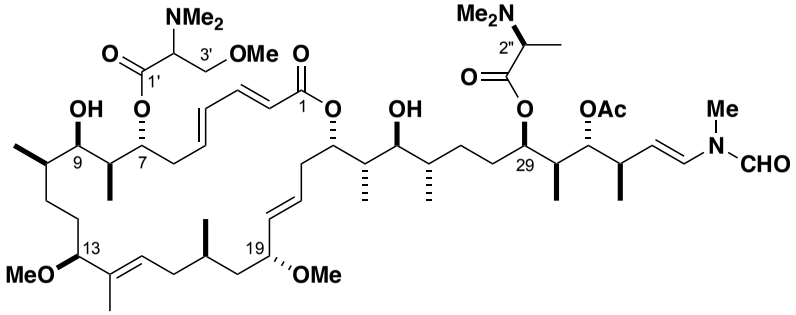

MeO
O
1
3
OBn
NMe2
(S)-32b
170
160
150
140
130
120
110
100
90
80
70
60
ppm


MeO
O
1
3
OH
NMe2
(S)-32c
5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 ppm

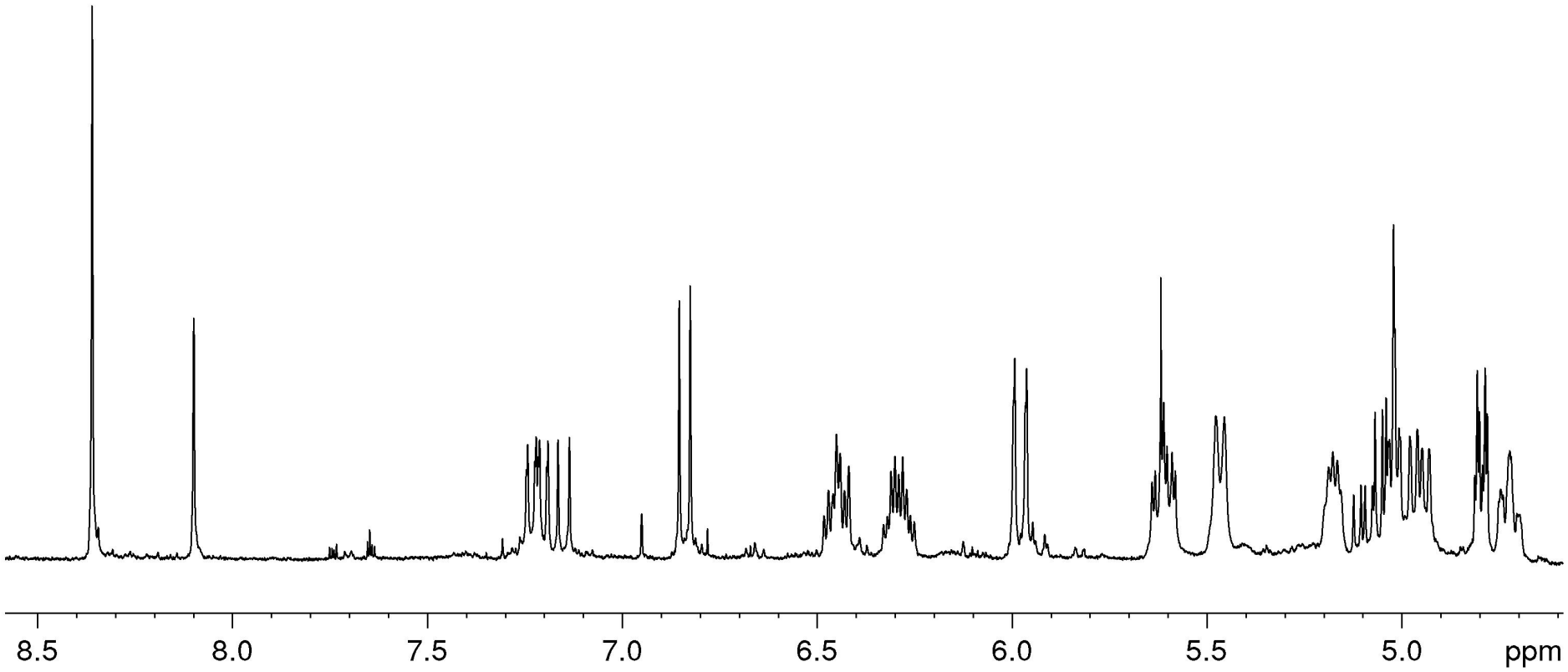

MeO
O
1
3
OH
NMe2
(S)-32c
170
160
150
140
130
120
110
100
90
80
70
60
50
ppm

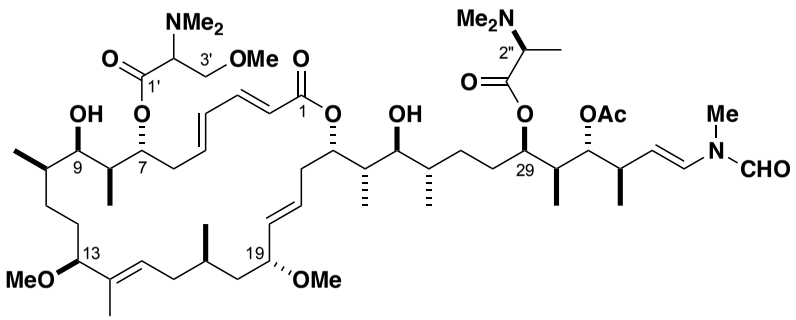


Aplyronine A 1

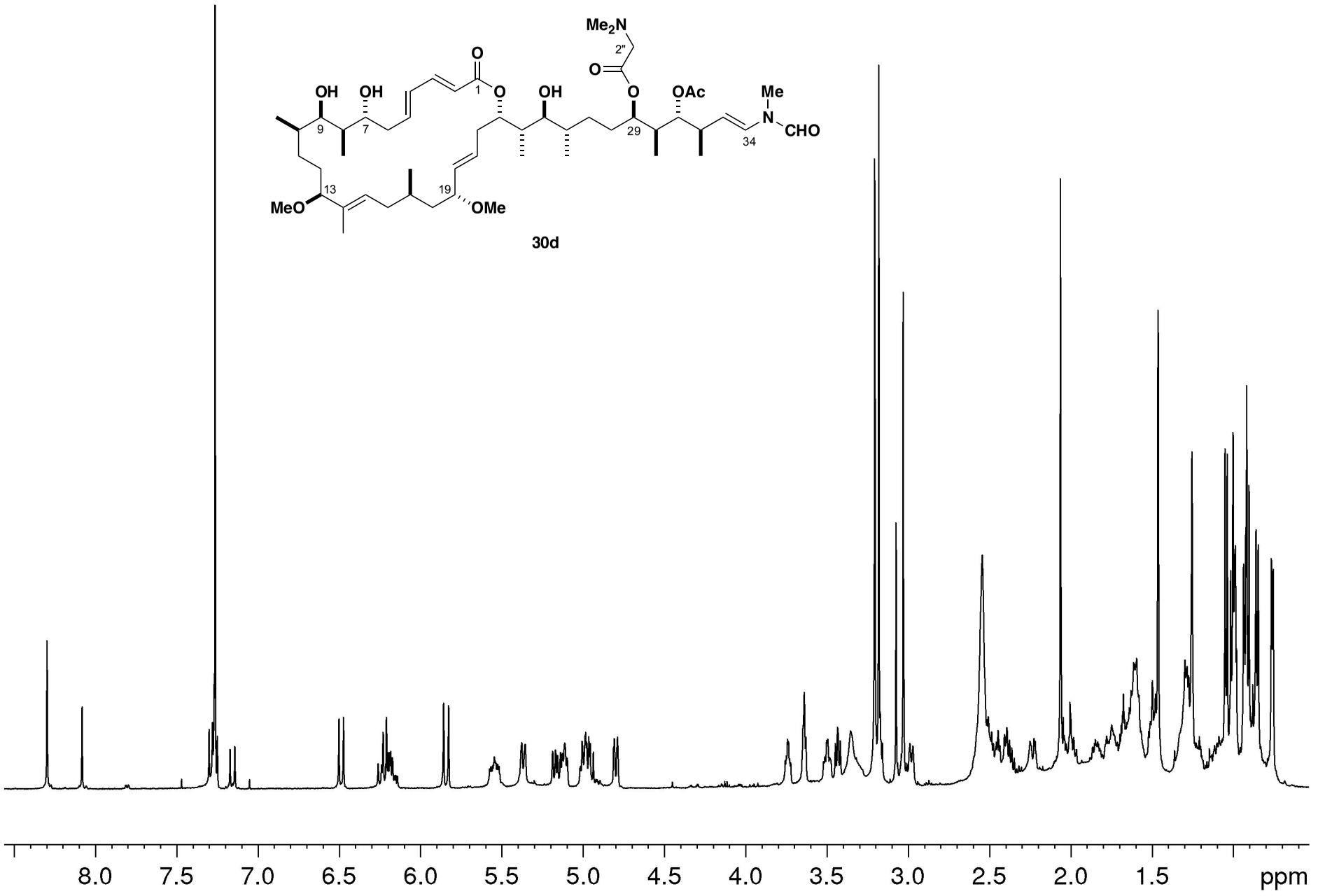


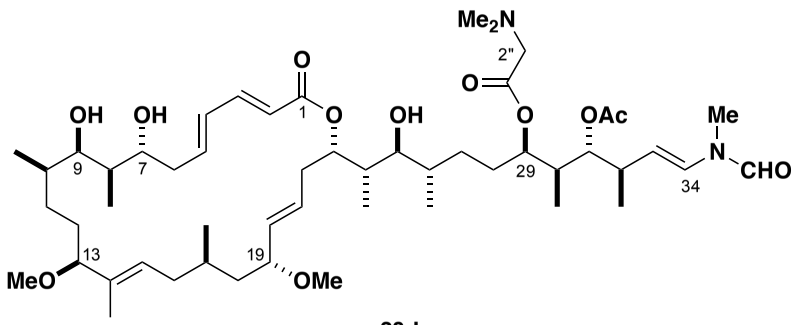
Aplyronine A 1





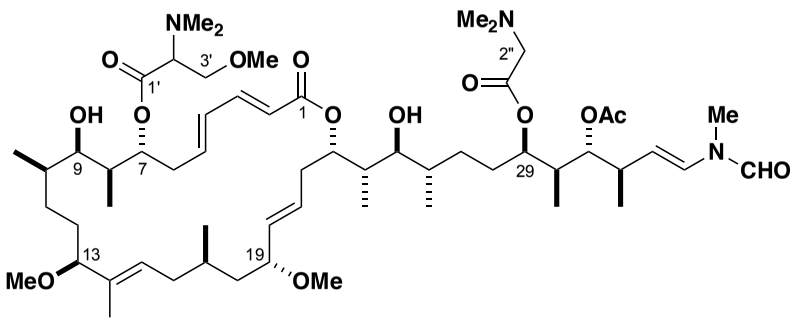
Aplyronine A 1


Me2N
2"
O
O
OH
OH
1
O
OH
O
OAc
Me
N
CHO
9
7
29
34
13
19
MeO
OMe
30d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

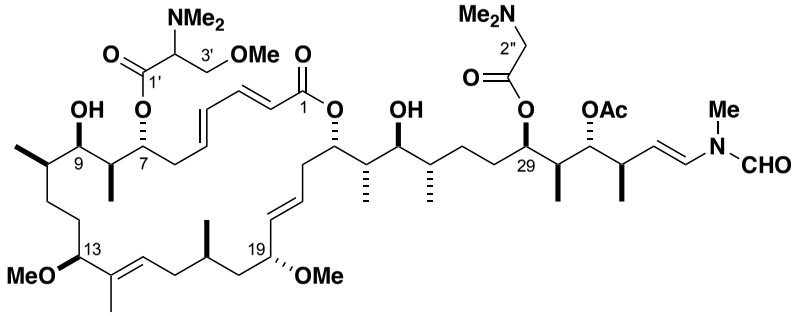

Me2N
2"
O
O
OH
OH
1
O
OH
O
OAc
Me
N
CHO
9
7
29
34
13
19
MeO
OMe

30d

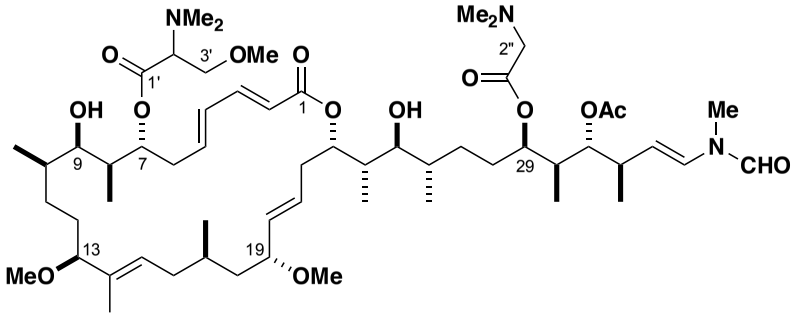
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm



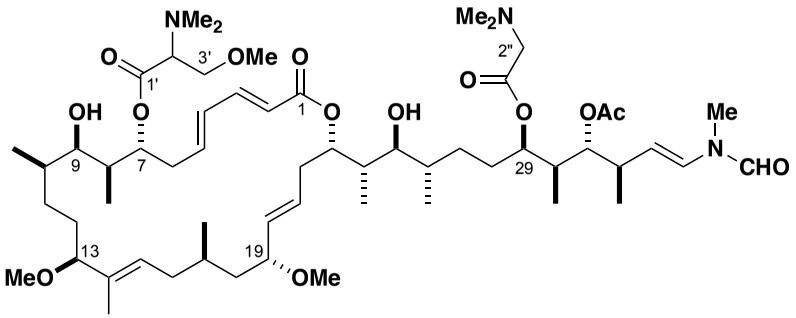
Aplyronine D 2



Aplyronine D 2

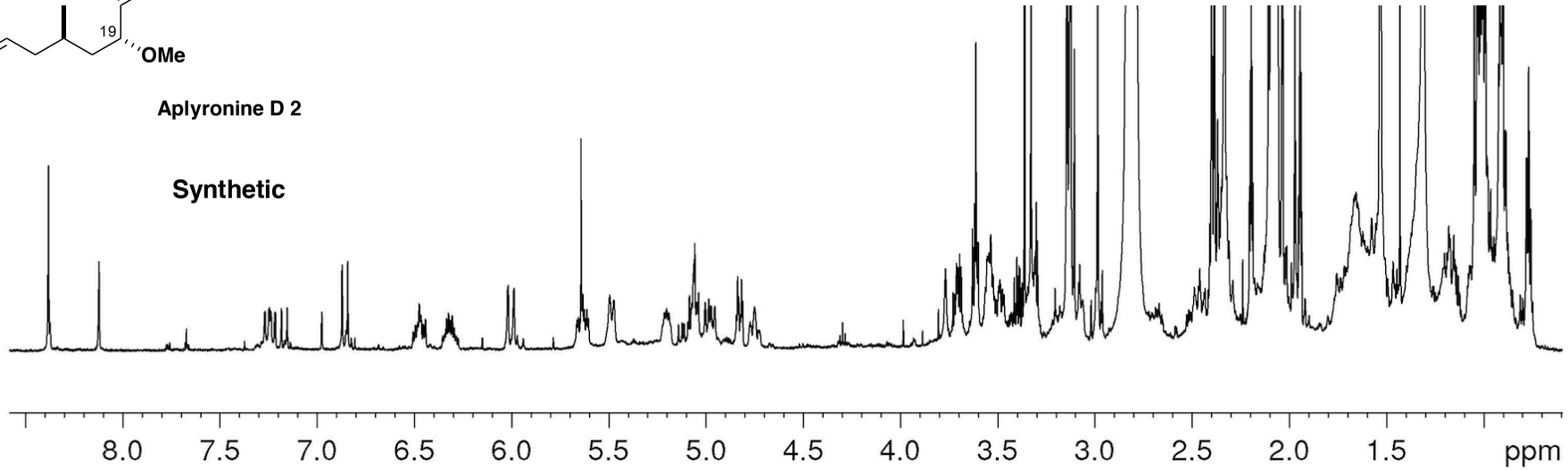


Aplyronine D 2

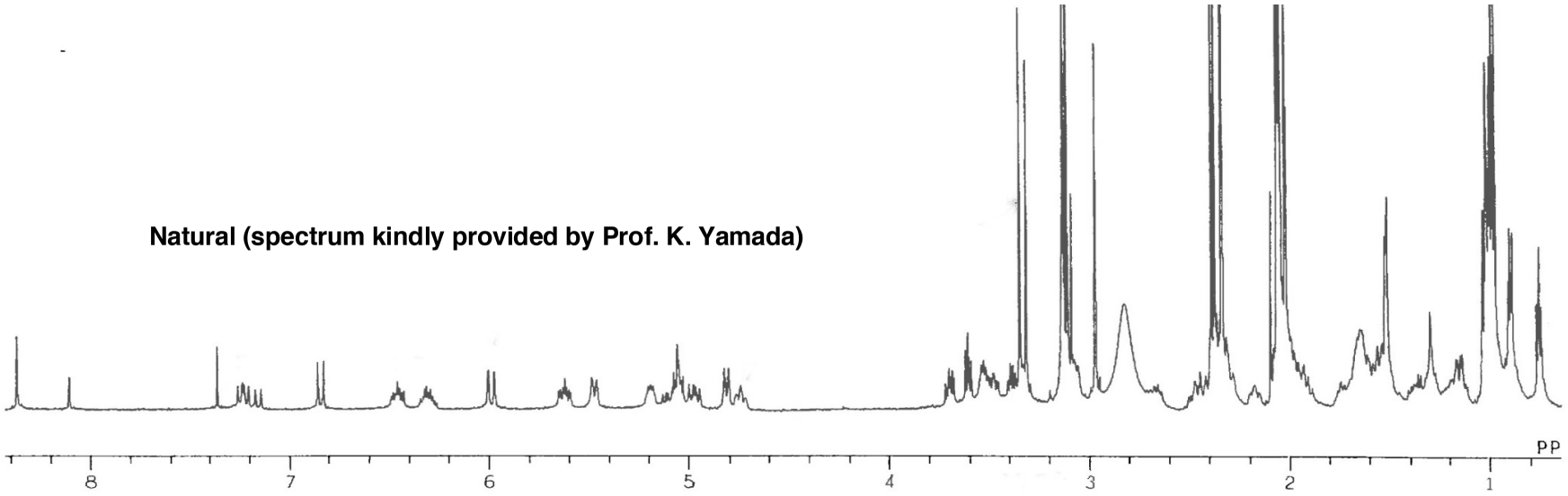


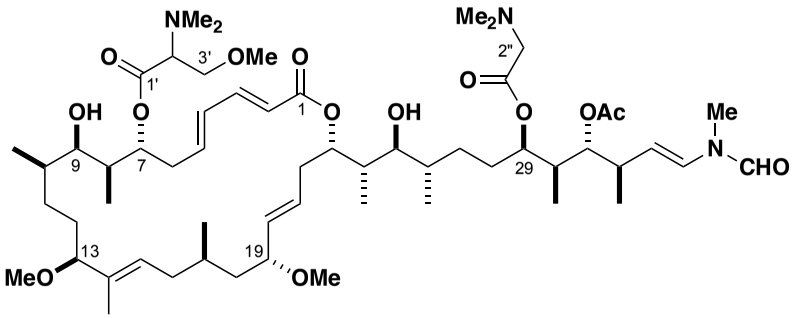
Aplyronine D 2

Synthetic



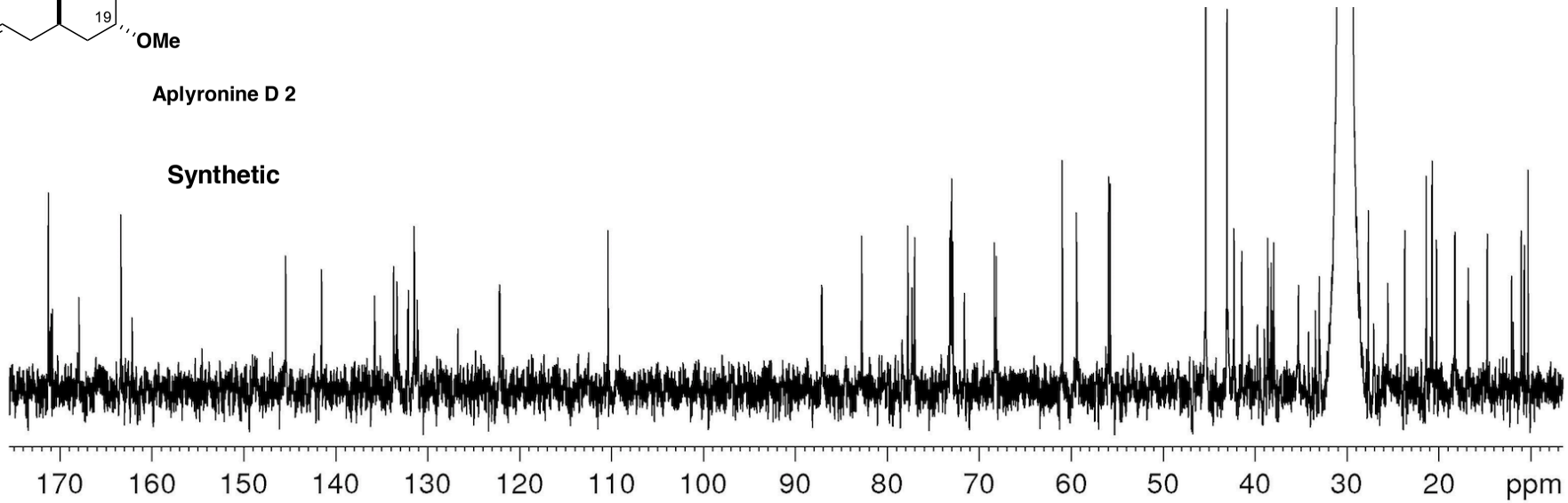
Natural (spectrum kindly provided by Prof. K. Yamada)



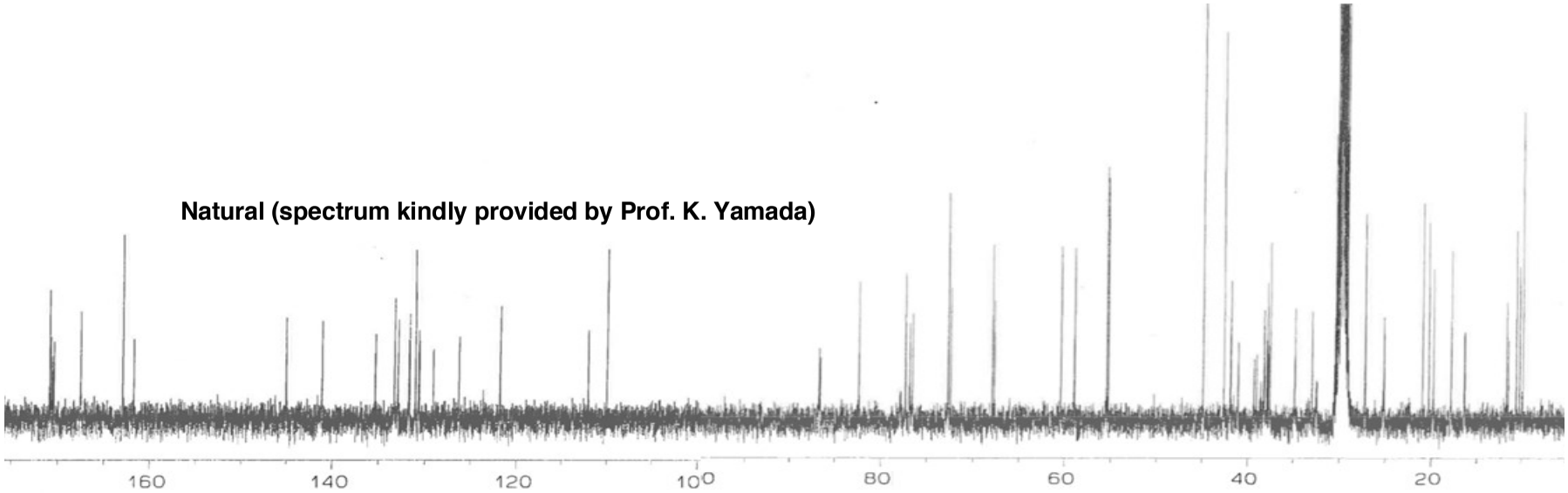


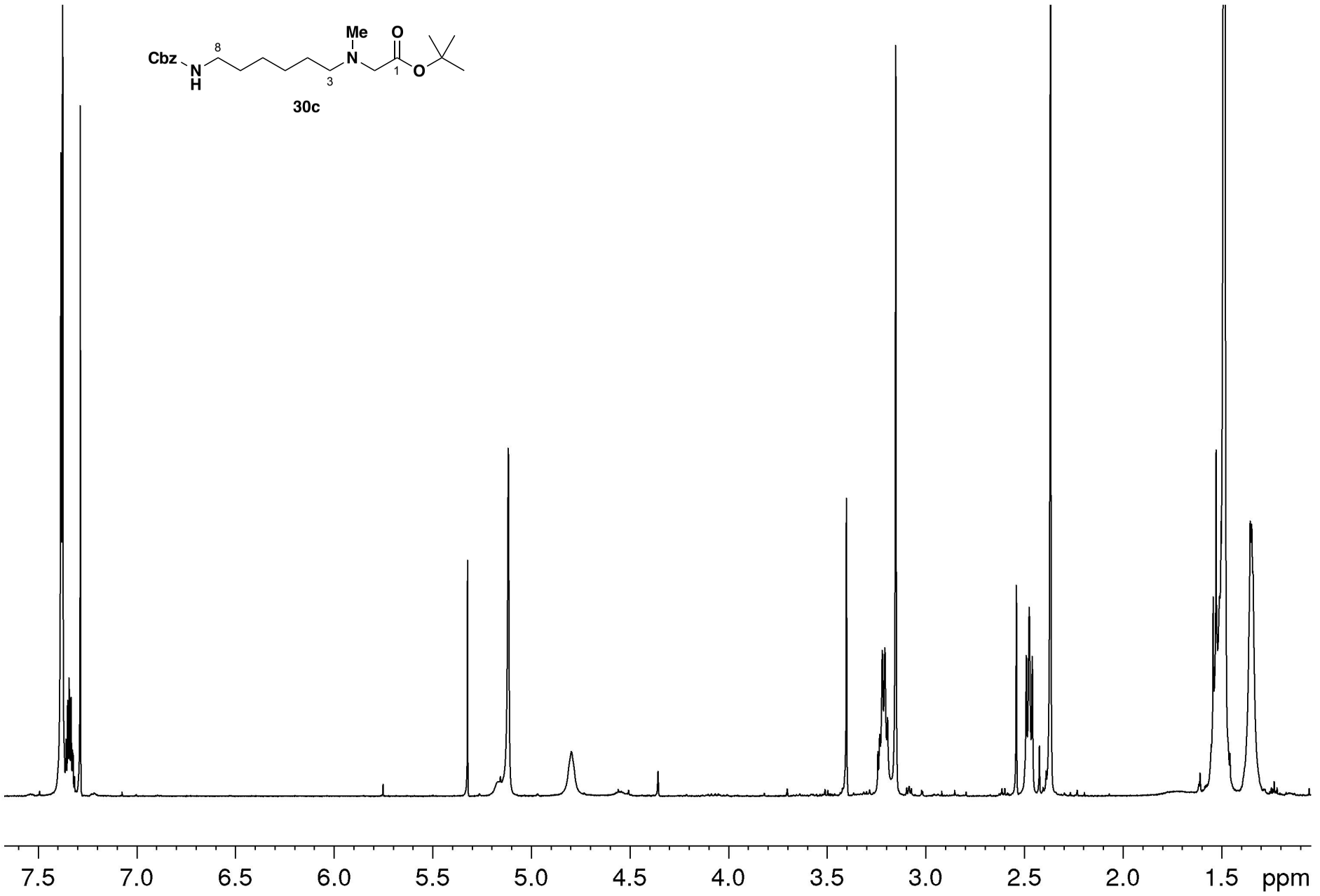
Aplyronine D 2

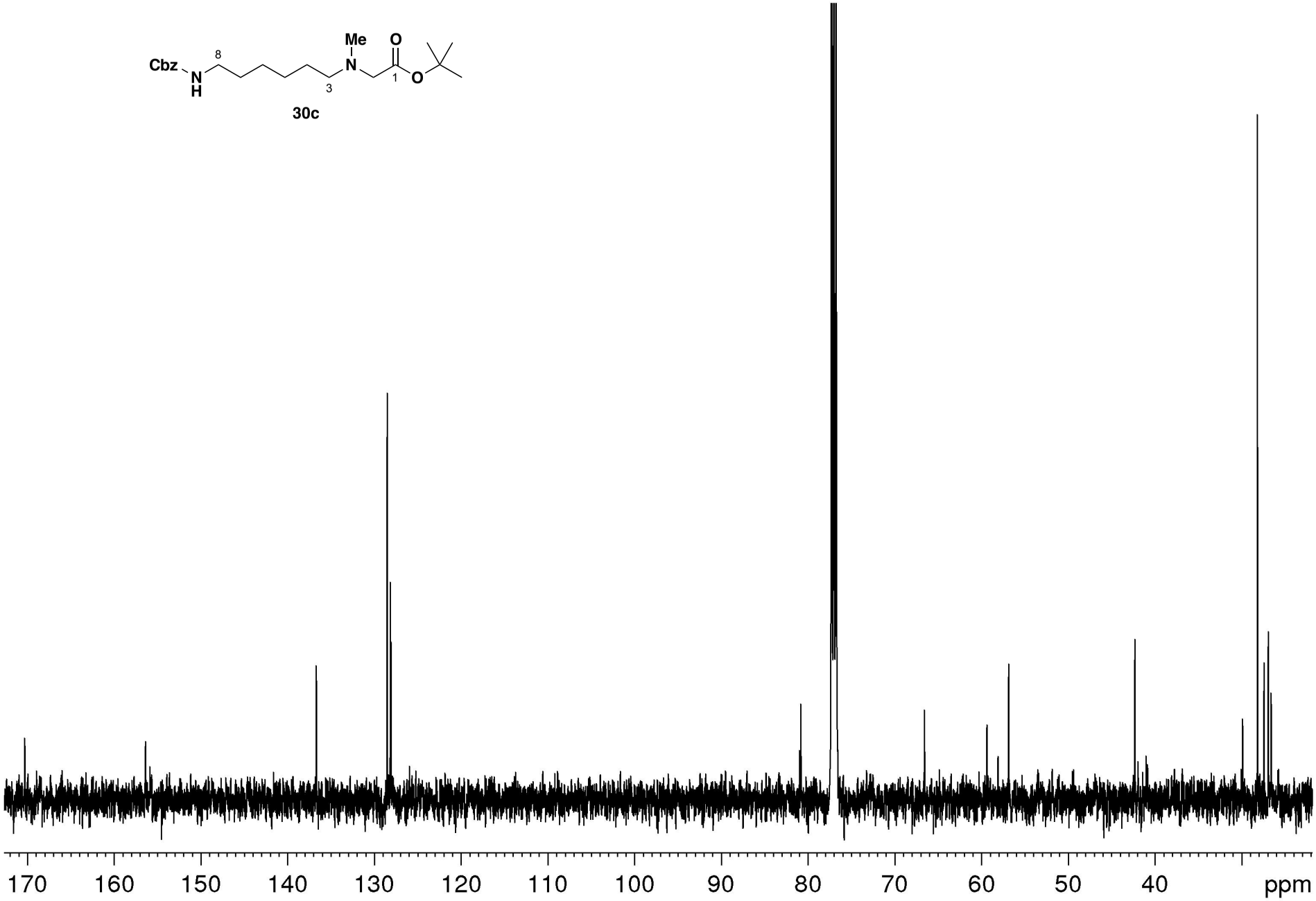
Synthetic

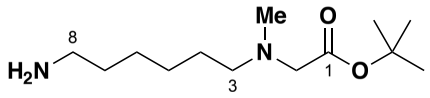


Natural (spectrum kindly provided by Prof. K. Yamada)

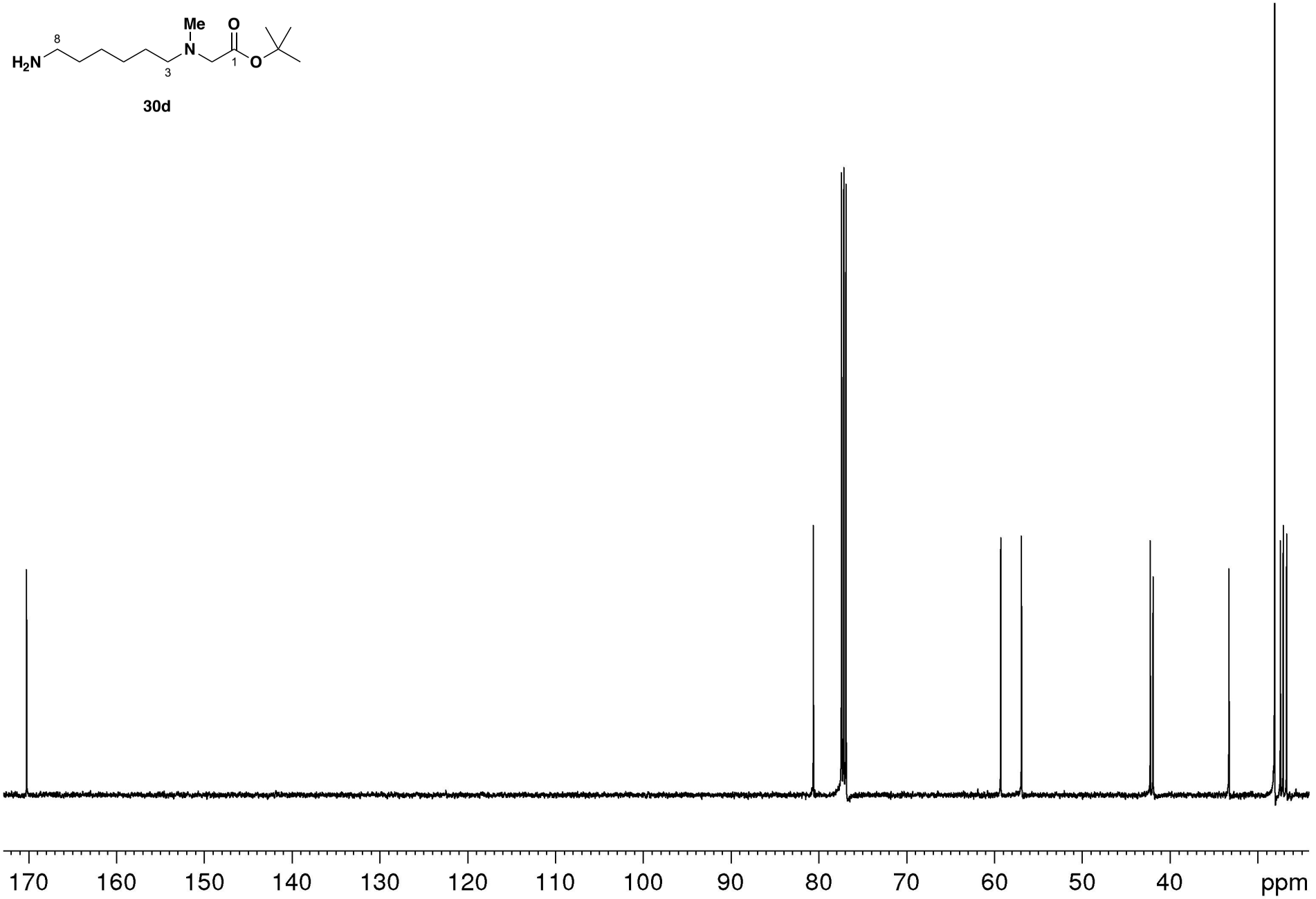


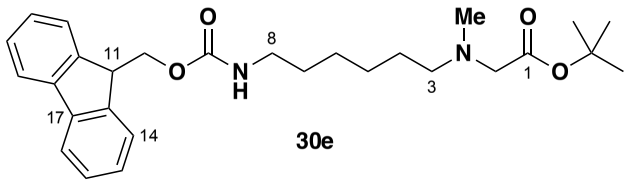

Cbz
N
H
8
3
N
Me
O
1
O
30c
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


Cbz
N
H
8
3
N
Me
1
O
O
30c
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

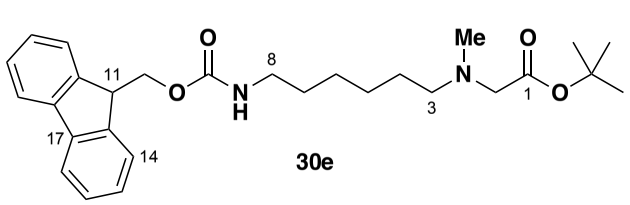


30d


Me
O
8
H_2N
N
1
O
3
30d
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

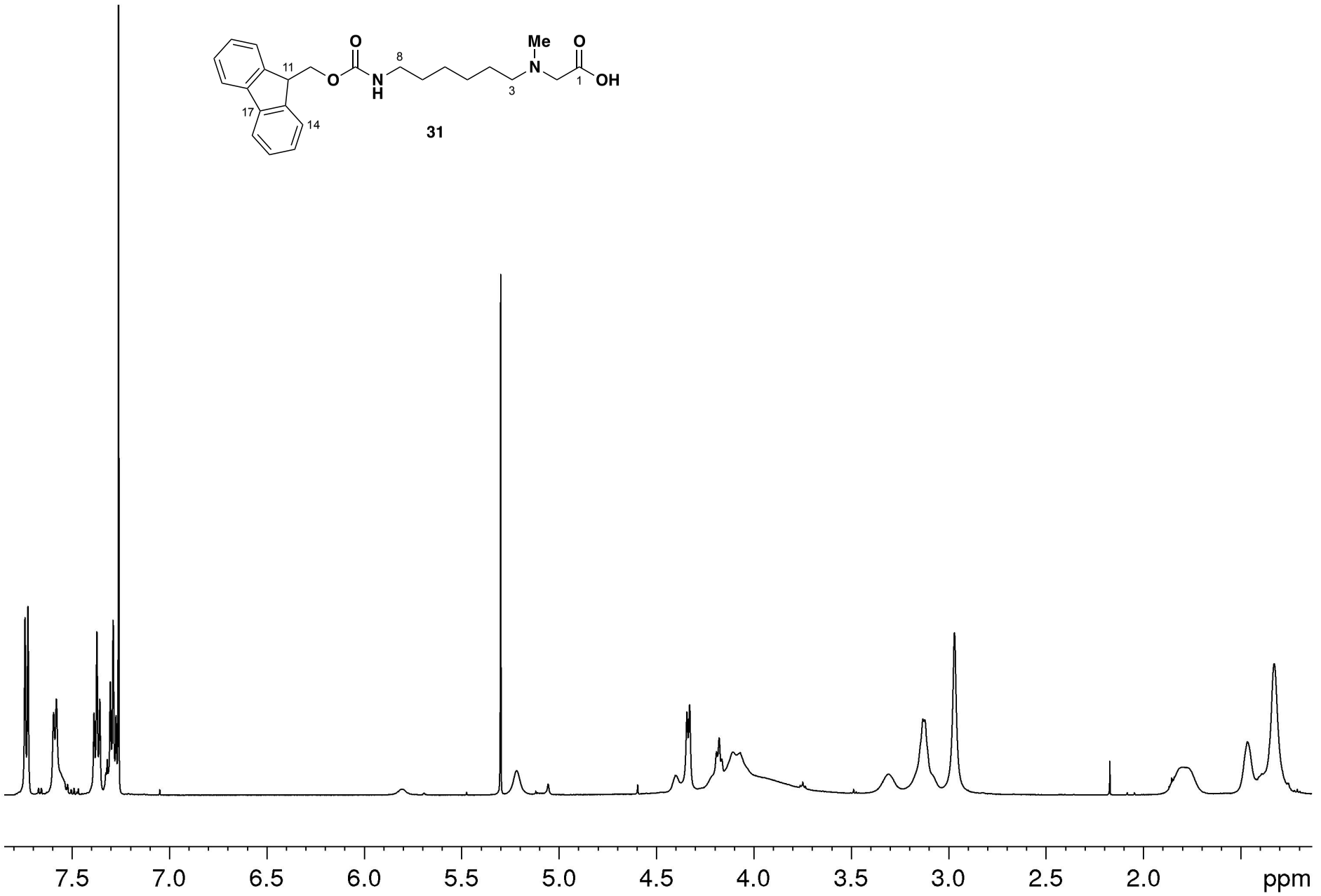


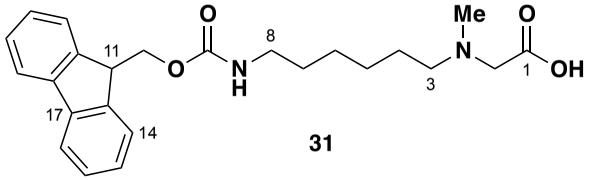
30e


O
Me
O
11
8
N
N
1
O
H
3
17
14

30e

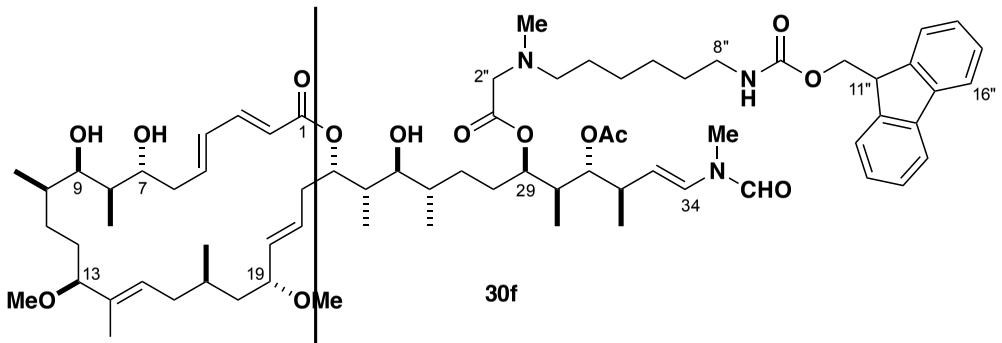
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm


O
Me
O
11
8
O
N
H
N
1
OH
3
17
14
31
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm

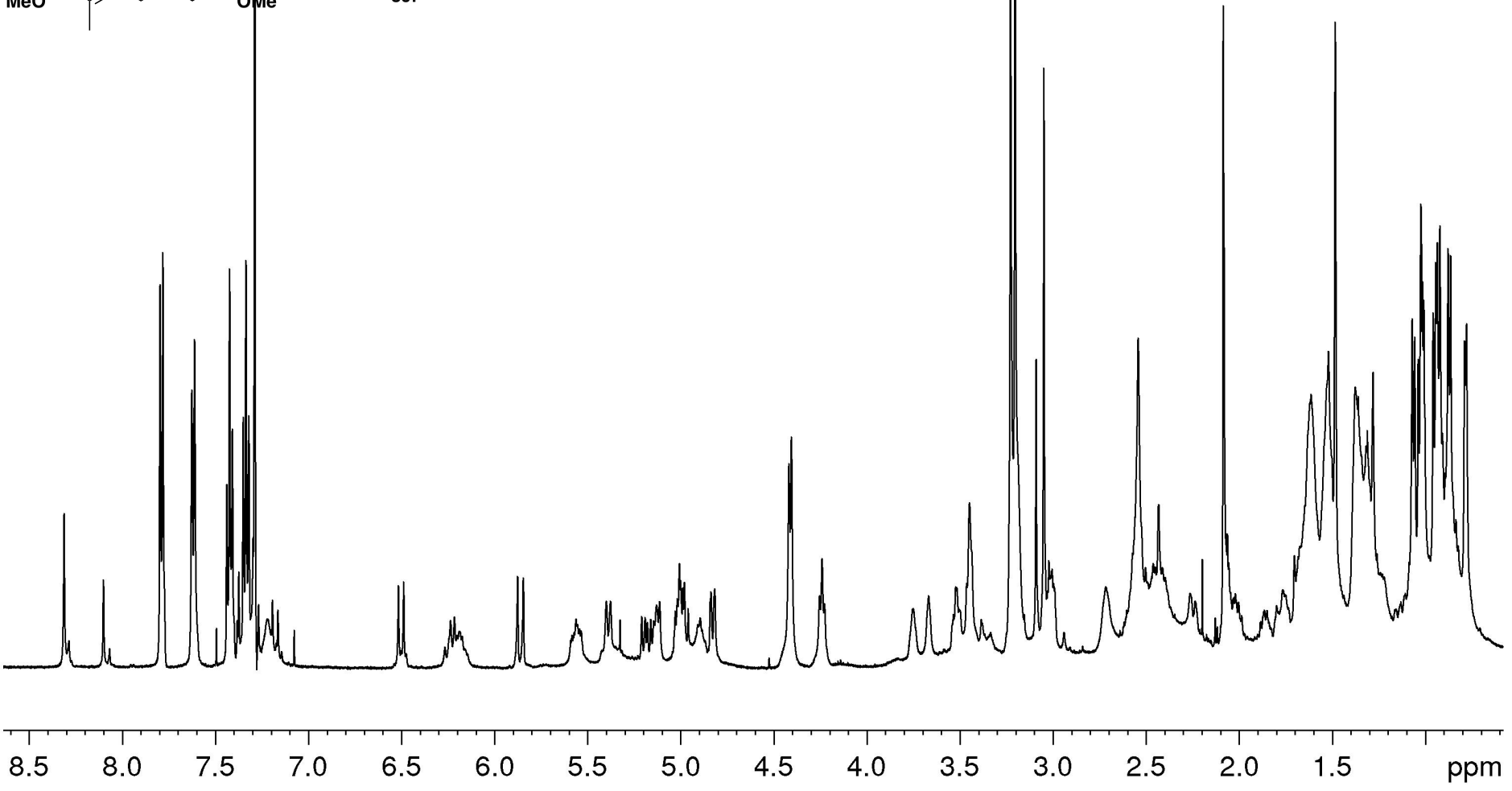

O
Me
O
11
8
O
N
H
N
1
OH
3
17
14

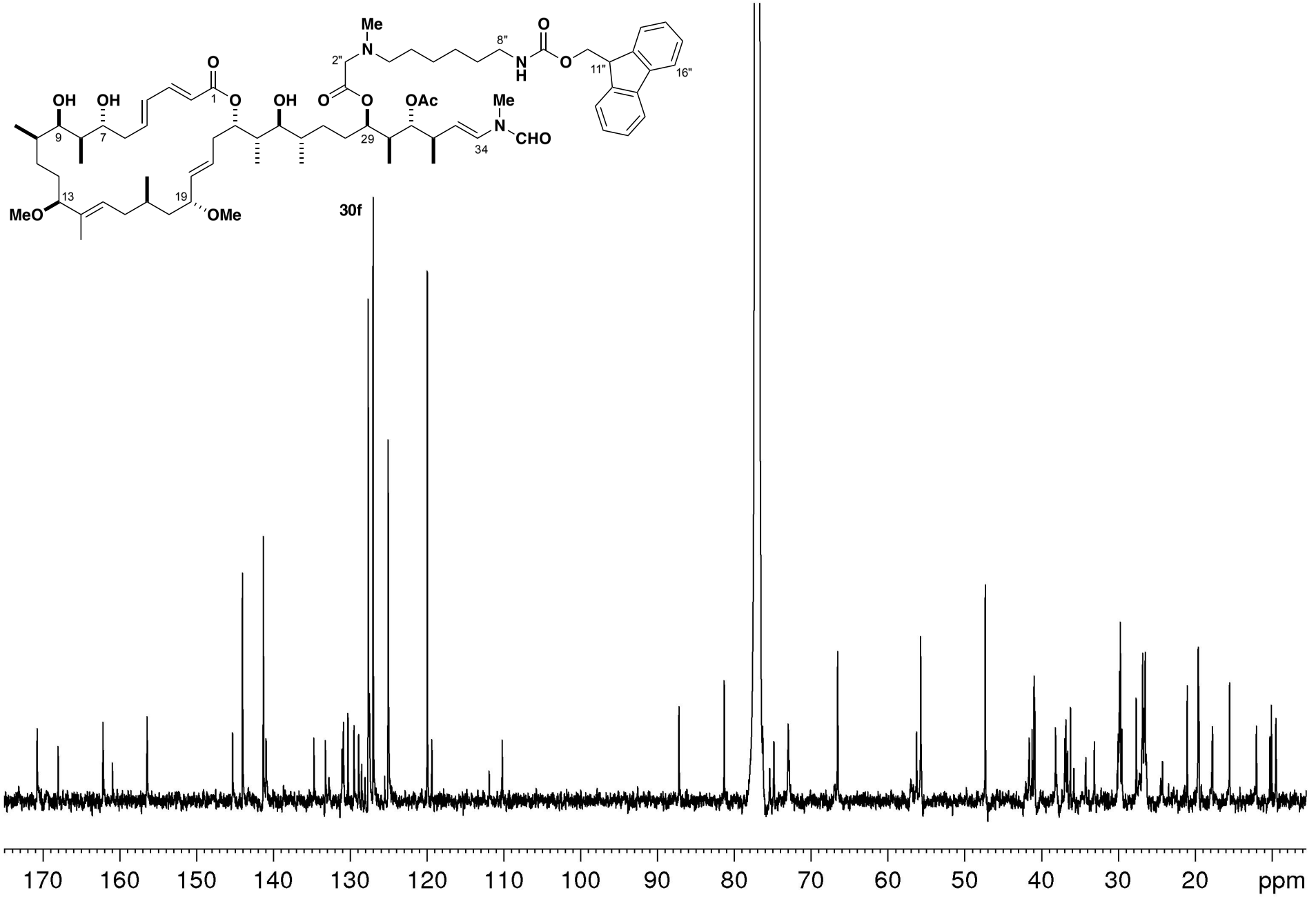
31

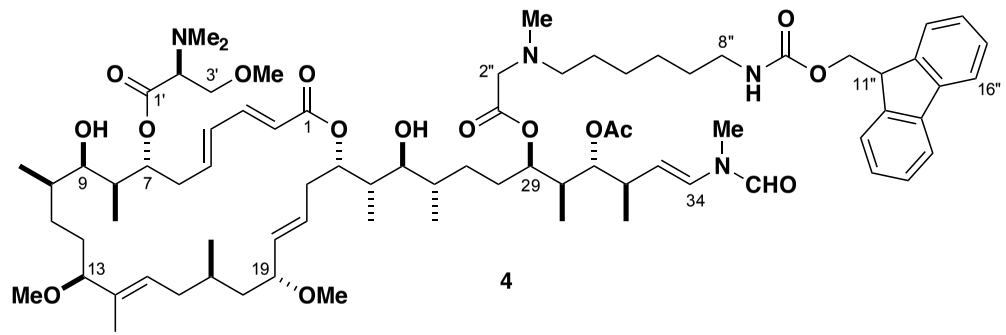
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


Me
N
2"
8"
N
H
O
O
11"
16"
OH
OH
O
1
O
OH
O
O
OAc
Me
N
CHO
9
7
29
34
13
19
MeO
OMe

30f

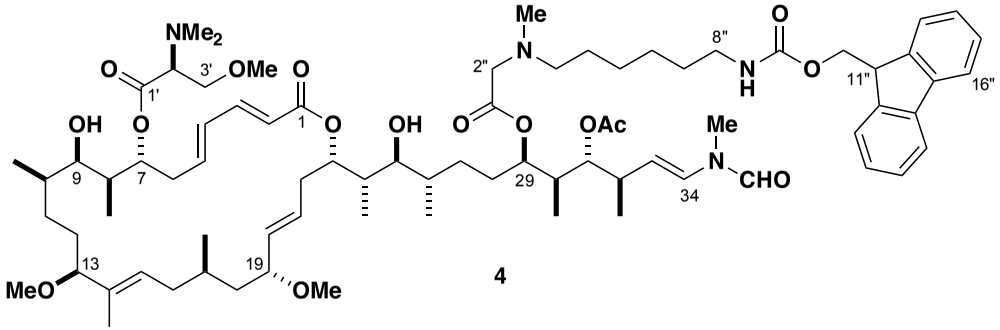

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


Me
N
2"
8"
N
H
O
O
11"
16"
OH
OH
O
1
O
OH
O
O
OAc
Me
N
CHO
9
7
29
34
13
19
MeO
OMe
30f
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


NMe2
O
1'
3'
OMe
O
1
O
OH
O
9
7
OH
O
O
OAc
29
Me
N
CHO
34
Me
N
2"
8"
N
H
O
O
11"
16"
13
19
MeO
OMe

4

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


NMe2
O
1'
3'
OMe
O
1
O
OH
O
9
7
OH
O
O
OAc
29
Me
N
CHO
34
Me
N
2"
8"
N
H
O
O
11"
16"
13
MeO
19
OMe

4

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm