Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Toward the total synthesis of patellazole B: Synthesis of an advanced C1-C25 fragment corresponding to the macrocyclic skeleton

Andrew W. Phillips, Matthew J. Anketell, Tudor Balan, Nelson Y. S. Lam, Simon Williams and Ian Paterson*

University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, UK

*ip100@cam.ac.uk

Table of Contents

1. General experimental details

All reagents, obtained from Acros, Aldrich, Alfa Aesar, Fluka, Fluorochem and Lancaster fine chemicals suppliers, were used directly as supplied or purified by the methods described by Armarego and Chai[1] except where otherwise noted in the experimental text. All non-aqueous reactions were performed in oven-dried apparatus under argon or nitrogen atmospheres, using distilled anhydrous solvents, at room temperature (rt) unless otherwise indicated. CH_2Cl_2, acetonitrile and methanol were distilled from calcium hydride and stored under an argon atmosphere. Tetrahydrofuran (THF) was distilled from potassium wire/benzophenone ketyl radical under an argon atmosphere. Diethyl ether (Et_2O) was distilled from sodium wire/benzophenone ketyl radical under an argon atmosphere.

2,6-lutidine, trimethylamine (Et_3N), diisopropylamine (DIPA) and diisopropylethylamine (DIPEA) were distilled from calcium hydride or calcium chloride and stored under an argon atmosphere. Dimethyl sulfoxide (DMSO) and *N*,*N'*-dimethylformamide (DMF) were distilled from $MgSO_4$ and stored over 4Å molecular sieves (MS). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was recrystallised from chloroform and Proton Sponge® recrystallised from EtOH. Oxalyl chloride was distilled. All solvents used in extraction and chromatography were distilled. The use of ammonium chloride (NH_4Cl), sodium bicarbonate ($NaHCO_3$), sodium thiosulfate ($Na_2S_2O_3$), brine (NaCl) and sodium/potassium (Na/K) tartrate refers to saturated aqueous solutions unless otherwise stated. 4Å MS were activated by heating under high vacuum or in a microwave. $Ba(OH)_2$ was prepared by heating $Ba(OH)_2{\cdot}8H_2O$ at 150 °C overnight under high vacuum before being stored in a glove box.

Flash column chromatography was performed according to the method described by Still, Kahn and Mitra,[2] using a positive solvent pressure, with silica gel obtained from Merck Kieselgel 60 (230-400 mesh).

Reactions were monitored by TLC using pre-coated glass-backed plates (Merck Kieselgel 60 with fluorescent indicator UV254). Spots were visualised by quenching of UV fluorescence and staining with potassium permanganate or phosphomolybdic acid/$Ce_2(SO_4)_3$, ninhydrin, anisaldehyde or vanillin dips.

NMR spectra were recorded using an internal deuterium lock for the residual protons in $CDCl_3$ (δ_H 7.26 ppm) at ambient probe temperatures on the following instruments: Bruker AVANCE BB 500, AVANCE TCI cryoprobe (500 MHz) or AVANCE DRX 400 (400 MHz). Proton data are presented in the following way: chemical shift (in ppm on a δ-scale relative to δ_{TMS} = 0 ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, br = broad, app = apparent), coupling constants (J/Hz) and assignment. Assignments were determined either on the basis of unambiguous chemical shift or coupling patterns, 2D NMR experiments, or by analogy to fully interpreted spectra for structurally related compounds. Protons of OH groups are missing in some spectra due to proton exchange. ^{13}C spectra were recorded by broadband proton spin decoupling, at ambient probe temperatures on the following instruments: Bruker AVANCE BB 500 and AVANCE TCI 500 (125.7 MHz), using an internal deuterium lock for $CDCl_3$ (δ_C 77.0). Chemical shifts are given in ppm on a δ-scale relative to δ_{TMS} = 0.

Signals are assigned according to the numbering scheme for patellazole B (**Figure SI-1**), unless otherwise indicated. Signals for non-patellazole related compounds are denoted by a prime, e.g. H-1'. Optical rotations were recorded on a Perkin Elmer 241 polarimeter at the sodium D-line (589 nm) using a 10 cm path length cell and are reported as follows: $[a]_D^{20}$ concentration (*c* in g/100 mL) and solvent.

High and low resolution mass spectra were recorded by the EPSRC Mass Spectrometry facility (Swansea, UK), using chemical ionisation (CI), electron impact (EI) or electron spray ionisation (ESI) techniques. The parent ion $[M]^+$, $[M+H]^+$, $[M-H]^+$, $[M+NH_4]^+$ or $[M+Na]^+$ is quoted. HPLC analysis was carried out on an Agilent 1200 series running in normal phase under UV detection using a ZORBAX RX-SIL (150 mm x 4.6 mm ID) as the analytical column. Chiral analysis was carried out using a DAICEL CHIRALPAK-IA, IB, IC (250 mm x 4.6 mm ID). Fourier transform IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer with the sample being prepared as a thin film on a universal ATR sampling accessory. Wavelengths of maximum absorbance (ν_{max}) are quoted in cm^{-1}.

Gas chromatography (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) capilliary 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, 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}.

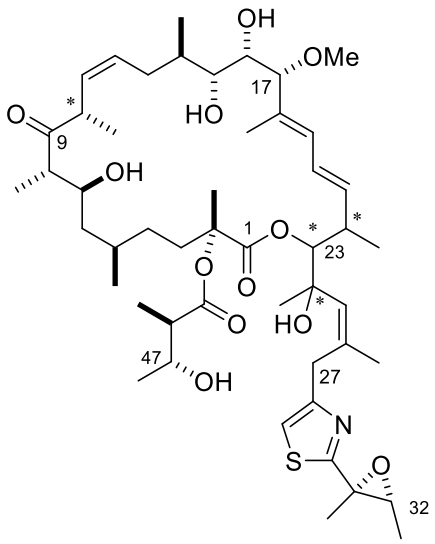
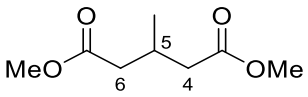


Figure SI-1. Numbering convention for patellazole B

2. Experimental Procedures

2.1. Preparation of the C1-C12 vinyl iodide

Diester 17

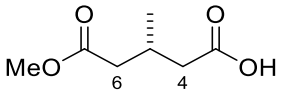


To a stirred solution of 3-methylglutaric acid (19.0 g, 13.0 mmol, 1.0 equiv.) in MeOH (250 mL) at 0 °C was added acetyl chloride (37.1 mL, 52.0 mmol, 4.0 equiv.) dropwise. The reaction mixture was heated to reflux for 3 h. The solvent was removed *in vacuo* and the residue redissolved in $NaHCO_3$ (100 mL) to neutralise. Once gas evolution had ceased, the product was extracted with CH_2Cl_2 (4 x 80 mL). Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give diester **17** as a yellow oil (20.2 g, 89%), which was used without further purification.

R_f 0.61 (2:1 PE/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 3.68 (6H, s, $CO_2\underline{Me}$), 2.52-2.42 (1H, m, H-5), 2.40 (2H, dd, *J* = 15.0, 6.0 Hz, H-4a, H-6a), 2.25 (2H, dd, *J* = 15.0, 7.3, Hz, H-4b, H-6b), 1.03 (3H, d, *J* =6.5 Hz, Me-5); **HRMS** (ES+): calc. for $C_8H_{15}O_4$ $[M+H]^+$ 175.0965, found 175.0962.

Data in agreement with literature values.[3]

Acid 17a



A solution of diester **17** (10.0 g, 57.1 mmol, 1.0 equiv.) in MeOH (44.5 mL) and pH 7 buffer (KH_2PO_4/Na_2HPO_4, 0.1 M, 220 mL) was cooled to –10 °C and pig liver esterase (550 mg, 9900 U) added. A solution of NaOH (1.0 M aq., 57.1 mL, 57.1 mmol, 1.0 equiv.) was added dropwise over 54 h, at such a rate as to maintain a pH between 6.5 and 8.0. After the addition was completed, the light brown suspension was filtered through Celite® and the residue rinsed with H_2O (150 mL). The pH of the combined filtrates was adjusted to 3 with HCl (3M aq.) and the mixture extracted with Et_2O (8 x 250 mL). Combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give the enantioenriched acid (8.92 g, 55.3 mmol, 97%) as a colourless liquid.

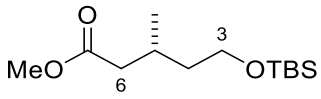
Enantioenriched acid was dissolved in acetone (180 mL) and cinchonidine (16.8 g 57.1 mmol, 1.0 equiv.) added. The white suspension was heated to 40 °C and stirred rapidly. H_2O (23 mL) was added dropwise until a pale-

yellow solution formed. The solution was cooled to rt and 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 (35 mL) and dried *in vacuo*. The mother liquor was recooled to –10 °C, left to stand for 16 h, filtered and the solids washed (acetone, 20 mL) and collected, to isolate a second crop of the crystals. Combined collected solids were dissolved in HCl (2M, 120 mL) and extracted with Et_2O (5 x 150 mL). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give acid **17a** as a colourless oil (5.53 g, 34.3 mmol, 62%, 96% ee).

R_f 0.24 (1:1 PE/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 3.70 (3H, s, OC<u>H</u>$_3$), 2.53-2.42 (3H, m, H-4a, H-5, H-6a), 2.35-2.27 (2H, m, H-4b, H-6b), 1.08 (3H, d, *J* = 6.5 Hz, Me-5); **HRMS** (ES+): calc. for $C_7H_{10}O$ $[M-H]^-$ 159.0663, found 159.0665. **R_T** (GC, CHIRASIL DEX CB, 134 mL min^{-1}, 25.00 psi, total run time 240 min) 165.6 min (major), 172.0 min (minor).

Data in agreement with literature values.[4]

TBS ether 18



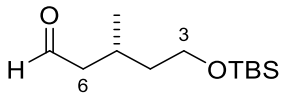
To a stirred solution of carboxylic acid **17a** (2.00 g, 12.5 mmol, 10.0 equiv.) In THF (200 mL) at 0 °C was added BH_3·DMS (6.8 mL, 13.75 mmol, 1.1 equiv.) dropwise. The reaction mixture stirred for 1 h. $NaHCO_3$ (150 mL) was then added and the layers separated. The aqueous layer was extracted with Et_2O (3 x 100 mL) and combined organic extracts dried over $MgSO_4$ before the solvent was carefully removed *in vacuo*. The crude material was used directly in the following reaction without further purification.

To a stirred solution of crude alcohol (1.82 g, 12.5 mmol, 1.0 equiv.) in CH_2Cl_2 (125 mL) was added imidazole (1.02 g, 15 mmol, 1.2 equiv.), then TBSCl (2.07 g, 13.75 mmol, 1.2 equiv.) The reaction mixture was stirred for 90 min before being quenched with NH_4Cl (80 mL). The layers were separated and the aqueous layer extracted with further CH_2Cl_2 (3 x 50 mL). Combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give TBS ether **18** as a colourless oil (2.98 g, 92% over two steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 3.69-3.61 (2H, m, H-3), 3.66 (3H, s, OMe), 2.36 (1H, dd, J = 12.9, 5.0 Hz, H-6), 2.17-2.04 (2H, m, H-6, H-5), 1.60-1.52 (1H, m,) 1.46-1.38 (1H, m), 0.96 (3H, d, *J* = 6.5 Hz, Me-5), 0.89 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.04 (9H, s, Si(C<u>H</u>$_3$)$_2$); **HRMS** (ES+): calc. for $C_{14}H_{31}O_3Si$ $[M+H]^+$ 275.2037, found 275.2038.

Data in agreement with literature values[5]

Aldehyde 13

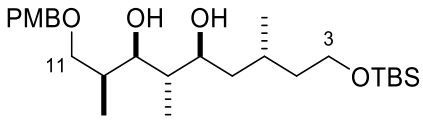


To a stirred solution of ester **18** (2.0 g, 7.69 mmol, 1.0 equiv.) in (80 mL) at –78 °C was added DIBAL (1 M in hexanes, 8.08 mL, 8.08 mmol, 1.05 equiv.) dropwise. The reaction mixture was maintained at this temperature for 1 h, before being quenched with Na/K tartrate (60 mL) and stirred for 1 h whilst warming to rt. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 40 mL). Combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (19:1 PE/EtOAc) to give aldehyde **13** as a colourless oil (1.63 g, 92%).

R_f 0.37 (9:1 PE/EtOAc); **IR** (thin film, ν_{max}/cm^{-1}): 1727, 1256, 1095, 913, 836, 774, 743; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 9.75 (1H, t, *J* = 2.3 Hz, H-7), 3.67 (1H, t, *J* = 6.4, 2.6 Hz, H-3), 2.46 (1H, ddd, *J* = 10.4, 8.6, 2.3 Hz, H-6a), 2.26 (1H, ddd, *J* = 10.4, 7.8, 2.3 Hz, H-6b), 1.61-1.43 (3H, m, H-5, H-4), 0.99 (3H, d, *J* = 6.5 Hz, Me-5), 0.90 (9H, s, $SiC(C\underline{H}_3)_3$), 0.05 (6H, s, $Si(C\underline{H}_3)_2$) ; **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 202.8, 60.7, 50.9, 39.5, 25.9, 25.1, 20.0, 18.3, –5.4; **HRMS** (ES+): calc. for $C_{12}H_{27}O_2Si$ $[M+H]^+$ 231.1775, found 231.1776.

Data in agreement with literature values.[6]

Diol 19

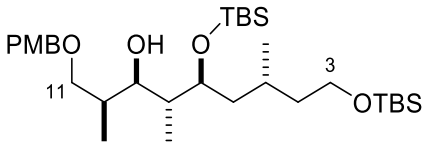


Cy_2BCl (6.86 mL, 31.7 mmol, 1.9 equiv.) and Et_3N (4.88 mL, 35.1 mmol, 2.1 equiv.) were sequentially added to Et_2O (60 mL) and cooled to 0 °C before stirring for 10 min. A solution of ketone **11**[7] (7.57 g, 33.5 mmol, 2.0 equiv.) in Et_2O (30 mL) was then added *via* cannula and the reaction mixture stirred for 90 min before cooling to –78 °C. A solution of aldehyde **13** (3.85 g, 16.7 mmol, 1.0 equiv.) in Et_2O (30 mL) was then added *via* cannula and the reaction mixture stirred at this temperature for a further 4 h before allowed to warm to –20 °C for 16 h. The reaction mixture was then re-cooled to –78 °C before the dropwise addition of $LiBH_4$ (4 M in THF, 16.7 mL, 66.8 mmol, 4.0 equiv.). After 2.5 h, the reaction was quenched with NH_4Cl (80 mL) and warmed to rt. The layers were separated and the aqueous layer extracted with Et_2O (3 x 50 mL). Combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude boronate was purified by flash column chromatography (9:1 → 4:1 PE/EtOAc) to remove excess reduced ketone before being redissolved in MeOH (75 mL). NaOH (10%

aq, 45 mL) and H_2O_2 (30% aq, 22.5 mL) were sequentially added and the solution stirred for 1 h before the product was extracted with Et_2O (3 x 50 mL) and EtOAc (50 mL). Combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude diol was then purified by flash column chromatography (9:1 → 4:1 PE/EtOAc) to give diol **19** as a colourless oil (6.73 g, 86%, >20:1 *dr*).

R_f 0.23 (4:1 PE/EtOAc); $[\alpha]_D^{20}$ –16.7 (*c* 1.55, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 3425, 1612, 1513, 1463, 1248, 1090, 1038, 980, 835, 775; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.27 (2H, d, *J* = 8.7 Hz, H-Ar), 6.88 (2H, d, *J* = 8.7 Hz, H-Ar), 4.48 (1H, d, *J* = 11.6 Hz, $OC\underline{H}_aH_bAr$), 4.45 (1H, d, *J* = 11.6 Hz, $OCH_a\underline{H}_bAr$), 3.81 (3H, s, $ArOC\underline{H}_3$), 3.78 (1H, dd, *J* = 10.3, 1.8 Hz, H-7), 3.67 (1H, dd, *J* = 6.5, 1.4 Hz, H-11a), 3.66 (1H, dd, *J* = 6.5, 1.9 Hz, H-11b), 3.61-3.58 (2H, m, H-2), 3.34 (1H, dd, *J* = 9.0, 6.2 Hz, H-9), 2.09-1.98 (2H, m, H-8, H-10), 1.52-1.30 (5H, m, H-4, H-5, H-6), 0.90 (3H, d, *J* = 6.8 Hz, Me-10), 0.89 (9H, s, $SiC(C\underline{H}_3)_3$), 0.80 (3H, d, *J* = 6.6 Hz, Me-8), 0.76 (3H, d, *J* = 6.9 Hz, Me-5), 0.05 (6H, s, $Si(C\underline{H}_3)_2$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.3, 130.0, 129.3, 113.9, 79.1 75.4, 74.0, 73.2, 61.6, 55.3, 42.1, 41.6, 40.9, 35.1, 26.2, 26.0, 19.4, 18.4, 12.9, 9.4, –5.3; **HRMS** (ES-): calc. for $C_{26}H_{47}O_5Si$ $[M-H]^-$ 467.3187, found 467.3183.

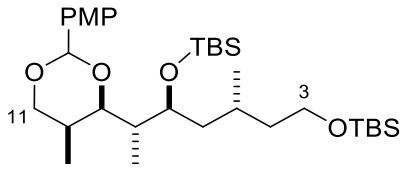
TBS ether 19a



To a solution of aldol adduct **19** (4.6 g, 10.0 mmol, 1.0 equiv.) in CH_2Cl_2 (100 mL) at –78 °C was added 2,6-lutidine (1.4 mL, 12.1 mmol, 1.2 equiv.) and TBSOTf (2.46 mL, 10.6 mmol, 1.05 equiv.) and stirred for 3 h before quenching with NH_4Cl (50 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 30 mL). Combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (9:1 PE/EtOAc) to give TBS ether **19a** as a colourless oil (4.93 g, 88%).

R_f 0.24 (9:1 PE/EtOAc); $[\alpha]_D^{20}$ –17.4 (*c* 1.25, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 3691, 1514, 1463, 1250, 1088, 835, 773; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H; 7.24 (2H, d, *J* = 8.6 Hz, H-Ar), 6.87 (2H, d, *J* = 8.6 Hz, H-Ar), 4.47 (1H, d, *J* = 11.7 Hz, $OC\underline{H}_aH_bAr$), 4.40 (1H, d, J = 11.7 Hz, $OCH_a\underline{H}_bAr$), 4.10 (1H, ddd, J = 9.7, 4.1, 2.4 Hz, H-7), 3.80 (3H, s, $ArOC\underline{H}_3$), 3.67-3.63 (2H, m, H-3a, H-3b), 3.55 (1H, dd, *J* = 10.5, 2.5 Hz, H-9), 3.53 (1H, dd, *J* = 9.0, 4.4 Hz, H-11a), 3.51 (1H, dd, *J* = 9.0, 5.1 Hz, H-11b), 2.71 (1H, d, *J* = 2.6 Hz, O-H), 1.87-1.81 (1H, m, H-10), 1.80-1.70 (2H, m, H-8, H-5), 1.56-1.49 (1H, m, H-4a), 1.43-1.34 (2H, m, H-6a, H-4b), 1.10 (1H, ddd, *J* = 12.9, 10.6, 2.2 Hz, H-6b), 0.93 (3H, d, *J* = 7.1 Hz, Me-10), 0.89 (9H, s, $SiC(C\underline{H}_3)_3$), 0.88 (9H, s, $SiC(C\underline{H}_3)_3$), 0.88 (3H, d, *J* = 7.0 Hz, Me-8), 0.75 (3H, d, *J* = 7.0 Hz, Me-5), 0.06 (3H, s, $Si(C\underline{H}a_3)(CHb_3)$, 0.05 (3H, s, $Si(CHa_3)(C\underline{H}b_3)$, 0.05 (6H, s, $Si(C\underline{H}_3)_2$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.2, 130.3, 129.2, 113.8, 75.3, 75.2, 73.1, 70.5, 61.5, 55.3, 41.8, 41.4, 39.1, 34.9, 26.0, 26.0, 25.7, 19.1, 18.4, 18.1, 10.3, 9.1,–4.2,–4.5,–5.3; **HRMS** (ES+): calc. for $C_{32}H_{62}O_5Si_2$ $[M+H]^+$ 583.4209, found 583.4195.

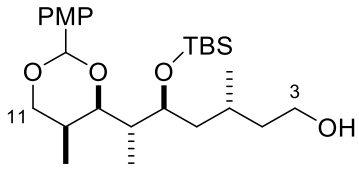
PMP acetal 20



To a slurry of DDQ (754 mg, 3.31 mmol, 1.1 equiv.) and 4Å MS (525 mg), in CH_2Cl_2 (20 mL) at 0 °C was added a solution of PMB ether **19a** (1.75 g, 3.01 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 1 h before being filtered through Celite® and washed with CH_2Cl_2 (15 mL). The filtrate was washed with $NaHCO_3$ (2 x 20 mL) and back extracted with CH_2Cl_2 (3 x 30 mL). Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (15:1 → 9:1 PE/EtOAc) to give PMP acetal **20** as a colourless oil (1.40 g, 80%, inconsequential mix of diastereomers).

R_f 0.38 (6:1 PE/EtOAc); $[\alpha]_D^{20}$ – 21.6 (*c* 0.31, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 1618, 1518, 1463, 1388, 1249, 1103, 833, 773; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.38 (2H, d, *J* = 8.7 Hz, H-Ar), 6.87 (2H, d, *J* = 8.7 Hz, H-Ar), 5.37 (1H, s, C<u>H</u>Ar), 4.19 (1H, ddd, *J* = 10.1 3.1, 1.7 Hz, H-7), 4.05 (1H, dd, *J* = 11.1, 2.2 Hz, H-11a), 4.01 (1H, dd, *J* = 11.1, 1.1 Hz, H-11b), 3.81 (3H, s, ArOC<u>H</u>$_3$), 3.65-3.61 (2H, m, H-3), 3.58 (1H, dd, *J* = 10.7, 2.1 Hz, H-9), 1.95 (1H, dqd, *J* = 10.7, 7.0, 3.1 Hz, H-8), 1.71 (1H, qddd, *J* = 6.8, 2.2, 2.1, 1.1 Hz, H-10), 1.6-1.26 (5H, m, H-4-6), 1.15 (3H, d, *J* = 6.8 Hz, Me-5), 0.89 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.88 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.79 (3H, d, *J* = 7.0 Hz, Me-8), 0.76 (3H, d, *J* = 6.6 Hz, Me-10), 0.04 (3H, s, Si(C<u>H</u>a$_3$)(CHb$_3$)), 0.04 (6H, s, Si(C<u>H</u>$_3$)$_2$), 0.02 (3H, s, Si(CHa$_3$)(C<u>H</u>b$_3$)); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.7, 131.7, 127.1, 113.4, 101.2, 81.2, 74.1, 68.6, 61.5, 55.3, 41.4, 40.4, 38.3, 29.9, 26.0, 26.0, 25.9, 19.0, 18.4, 18.1, 10.9, 7.9, –4.2, – 4.6, – 5.3, – 5.3; **HRMS** (ES+): calc. for $C_{32}H_{60}O_5Si_2$ $[M+H]^+$ 581.4052, found 581.4044.

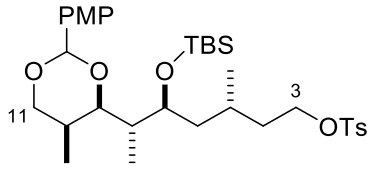
Alcohol 20a



To a solution of silyl ether **20** (3.70 g, 6.38 mmol, 1.0 equiv.) in THF (100 mL) at rt was added TBAF (1M in THF, 6.4 mL, 6.38 mmol, 1.0 equiv.) dropwise. The reaction mixture was stirred for 1 h before the addition of an extra 0.5 equiv. of TBAF. After a further h, the reaction was quenched with NH_4Cl (50 mL) and the layers separated. The aqueous layer was extracted with Et_2O (3 x 30 mL). Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (6:1 PE/EtOAc) to give alcohol **20a** as a colourless oil (2.52 g, 85%, inconsequential mix of diastereomers, 96% brsm).

R_f 0.16 (6:1 PE/EtOAc); $[\alpha]_D^{20}$ – 22.2 (*c* 0.6, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 3363, 1380, 1086, 1045, 880, 772; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.38 (2H, d, *J* = 8.6 Hz, H-Ar), 6.88 (2H, d, *J* = 8.6 Hz, H-Ar), 5.38 (1H, s, C<u>H</u>Ar), 4.19 (1H, ddd, *J* = 10.2, 3.6, 1.8 Hz, H-7), 4.06 (1H, dd, *J* = 11.0, 2.3 Hz, H-11a), 4.02 (1H, dd, *J* = 11.1, 1.3 Hz, H-11b), 3.81 (3H, s, OC<u>H</u>$_3$), 3.71-3.64 (2H, m, H-3), 3.58 (1H, dd, *J* = 10.6, 2.1 Hz, H-9), 1.97 (1H, dqd, *J* = 10.6, 7.0, 3.6 Hz, H-8), 1.70 (1H, qddd, *J* = 6.8, 2.3, 2.1, 1.3 Hz, H-10), 1.61-1.47 (2H, m, H-5, H-4a), 1.43 (1H, ddd, *J* = 12.8, 10.2, 2.6 Hz, H-6a), 1.28-1.24 (1H, m, H-4b), 1.15 (3H, d, *J* = 6.9 Hz, Me-5), 1.05 (1H, ddd, *J* = 12.8, 10.2, 1.8 Hz, H-6b), 0.89 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.80 (3H, d, *J* = 6.8 Hz, Me-10), 0.79 (3H, d, *J* = 7.0 Hz, Me-8), 0.05 (3H, s, Si(C<u>H</u>a$_3$)(CHb$_3$)), 0.03 (3H, s, Si(CHa$_3$)(C<u>H</u>b$_3$)); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.7, 131.6, 127.1, 113.4, 101.2, 81.2, 74.1, 68.9, 61.2, 55.3, 41.0, 40.4, 37.8, 29.9, 26.0, 25.9, 19.6, 18.1, 10.9, 7.9, –4.2, –4.6; **HRMS** (ES+): calc. for $C_{26}H_{47}O_4Si$ $[M+H]^+$ 467.3187, found 467.3184.

Tosylate 20b



To a solution of alcohol **20a** (420 mg, 0.91 mmol, 1.0 equiv.) in CH_2Cl_2/pyridine (1:1, 10 mL), was added tosyl chloride (516 mg, 2.72 mmol 3.0 equiv.) and stirred for 6 h. The reaction was then quenched with $NaHCO_3$ (12 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 8 mL), combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (15:1 PE/EtOAc) to give tosylate **20b** as a colourless oil (510 mg, 91%, inconsequential mix of diastereomers).

Major diastereomer:

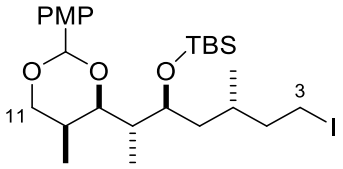
R_f 0.28 (6:1 PE/EtOAc); $[\alpha]_D^{20}$ – 7.0 (*c* 0.1, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 2927, 2339, 2012, 1613, 1360, 1249, 1177, 1073, 942, 828, 773; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.78 (2H, d, *J* = 8.3 Hz, H-Ar), 7.36 (2H, d, *J* = 8.8 Hz, H-Ar), 7.32 (2H, d, *J* = 8.3 Hz, H-Ar), 6.87 (2H, d, *J* = 8.8 Hz, H-Ar), 5.35 (1H, C<u>H</u>Ar), 4.14 (1H, ddd, *J* = 9.8, 3.4, 1.8 Hz, H-7), 4.09-4.02 (4H, m, H-11, H-3), 3.80 (3H, s, ArOC<u>H</u>$_3$), 3.53 (1H, dd, *J* = 10.7, 2.1 Hz, H-9), 2.44 (3H, s, ArC<u>H</u>$_3$), 1.98-1.91 (1H, m, H-10), 1.69-1.62 (1H, m, H-8), 1.60-1.24 (5H, m, H-4-6), 1.14 (3H, d, *J* = 6.8 Hz, Me-8), 0.86 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.76 (3H, d, *J* = 7.1 Hz, Me-10), 0.71 (3H, d, *J* = 6.4 Hz, Me-5), 0.03 (3H, s, Si(C<u>H</u>a$_3$)(CHb$_3$)), – 0.01 (3H, s, Si(CHa$_3$)(C<u>H</u>b$_3$)); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.7, 144.6, 133.3, 131.6, 129.8, 127.9, 127.0, 113.4, 101.2, 81.2, 74.1, 69.0, 68.4, 55.3, 40.3, 37.7, 36.9, 29.8, 25.9, 25.8, 21.6, 18.7, 18.1, 10.9, 7.9, –4.2, –4.7; **HRMS** (ES+): calc. for $C_{33}H_{53}O_7SSi$ $[M+H]^+$ 621.3281, found 621.3269.

Minor diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.79 (2H, d, 8.1 Hz, H-Ar), 7.36 (2H, d, *J* =8.8 Hz, H-Ar), 7.33 (2H, d, *J* = 8.1 Hz, H-Ar), 6.87 (2H, d, *J* = 8.8 Hz, H-Ar), 5.99 (1H, s, C<u>H</u>Ar), 4.27 (1H, dt, *J* = 11.4, 2.7 Hz, H-7), 4.09-4.02 (2H, m, H-3),

4.01 (1H, dd, *J* = 11.1, 1,2 Hz, H-11a, 3.82 (3H, s, ArOC$\underline{H}_3$), 3.62 (1H, dd, *J* = 11.1, 2.4 Hz, H-11b), 3.40 (1H, dd, *J* = 10.6, 2.2 Hz, H-9), 2.44 (3H, s, ArC$\underline{H}_3$), 1.98-1.91 (1H, m, H-10), 1.69-1.62 (1H, m, H-8), 1.60-1.24 (5H, m, H-4-6), 1.16 (3H, d, *J* = 7.1 Hz, Me-8), 0.88 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.95 (3H, d, *J* = 6.7 Hz, Me-5), 0.66 (3H, d, *J* = 7.1 Hz, Me-10), 0.10 (3H, s, Si(C$\underline{H}$a$_3$)(CHb$_3$)), 0.07 (3H, s, Si(CHa$_3$)(C$\underline{H}$b$_3$)); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.4, 144.6, 133.3, 131.6, 130.2, 128.2, 127.9, 113.8, 96.5, 81.1, 72.3, 68.1, 67.1, 55.3, 40.9, 37.1, 36.7, 30.7, 25.9, 25.7, 21.6, 18.5, 18.1, 10.9, 8.1, – 4.1, – 4.6.

Iodide 21



To a stirred solution of tosylate **20b** (500 mg, 0.808 mmol, 1.0 equiv.) in MeCN (20 mL) was added LiI (650 mg, 4.84 mmol, 6.0 equiv.) and heated to 60 °C for 4 h. Upon completion, the reaction mixture was cooled to rt and diluted with Et_2O (15 mL) and quenched with $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 20 mL). Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (10:1 PE/EtOAc) to give iodide **21** as a colourless oil (425 mg, 91%, inconsequential mix of diastereomers).

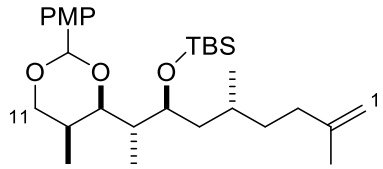
Major diastereomer:

R$_f$ 0.48 (6:1 PE/EtOAc); $[\alpha]_D^{20}$ – 22.8 (*c* 0.82, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 1616, 1518, 1463, 1380, 1249, 1164, 1036, 834, 774; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.38 (2H, d, *J* = 8.7 Hz, H-Ar), 6.88 (2H, d, *J* = 8.7 Hz, H-Ar), 5.37 (1H, s, C$\underline{H}$Ar), 4.18 (1H, ddd, *J* =10.1, 3.2, 1.6 Hz, H-7), 4.07-4.00 (2H, m, H-11), 3.81 (3H, s, ArOC$\underline{H}_3$), 3.56 (1H, dd, *J* = 10.7, 2.0 Hz, H-9), 3.27-3.14 (2H, m, H-3), 2.00-1.93 (1H, m, H-10), 1.89-1.80 (1H, m, H-8), 1.74-1.26 (5H, m, H-4, H-5, H-6), 1.15 (3H, d, *J* = 6.9 Hz, Me-5), 0.88 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.79 (3H, d, *J* = 7.1 Hz, Me-10), 0.76 (3H, d, *J* = 6.1 Hz, Me-8), 0.05 (3H, s, Si(C$\underline{H}$a$_3$)(CHb$_3$)), 0.05 (3H, s, Si(CHa$_3$)(C$\underline{H}$b$_3$)); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.7, 131.6, 127.1, 113.5, 101.2, 81.2, 74.1, 68.5, 55.3, 42.3, 40.4, 37.4, 30.4, 29.9, 26.0, 18.3, 18.1, 10.9, 7.9, 4.9, – 4.2, – 4.5; **HRMS** (ES+): calc. for $C_{26}H_{46}IO_4Si$ $[M+H]^+$ 577.2205, found 577.2196.

Minor diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.35 (2H, d, *J* = 8.7 Hz, H-Ar), 6.89 (2H, d, *J* = 8.7 Hz, H-Ar), 6.01 (1H, s, C$\underline{H}$Ar), 4.31 (1H, ddd, *J* = 11.5, 2.8, 2.0 Hz, H-7), 4.07-4.00 (2H, m, H-11a), 3.83 (3H, s, ArOC$\underline{H}_3$), 3.62 (1H, dd, *J* = 11.2, 2.3 Hz, H-9), 3.44 (1H, dd, *J* = 10.7, 2.4 Hz, H-11b), 3.27-3.14 (2H, m, H-3), 2.00-1.93 (1H, m, H-10), 1.89-1.80 (1H, m, H-8), 1.74-1.26 (5H, m, H-4, H-5, H-6), 1.17 (3H, d, *J* = 6.9 Hz, Me-5), 1.00 (3H, d, *J* = 6.6 Hz, Me-8), 0.88 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.71 (3H, d, *J* = 7.0 Hz, Me-10), 0.12 (6H, s, Si(CH$_3$)$_2$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.4, 130.3, 128.3, 113.8, 96.5, 72.3, 68.1, 67.1, 55.3, 42.5, 41.0, 36.3, 30.7, 30.3, 26.0, 22.6, 20.5, 18.2, 17.9, 11.5, –4.0

Alkene 22



A solution of iodide **21** (400 mg, 0.69 mmol, 1.0 equiv.) in Et_2O (7 mL) was cooled to –78 °C and *t*-BuLi (1.7 M in pentane, 1.6 mL, 2.78 mmol, 4.0 equiv.) added in a single portion. The reaction mixture was stirred for 3 min before the addition of B-Methoxy-9-BBN (1 M in hexanes, 4.27 mL, 4.27 mmol, 6.0 equiv.). After a further 5 min, the THF (7 mL) was added and the resulting solution slowly warmed to rt and stirred for a further h. K_3PO_4 (3M, 0.7 mL, 2.01 mmol, 3.0 equiv.), Pd(dppf)Cl_2 (51 mg, 0.069 mmol, 0.1 equiv.) and DMF (7 mL) were then added, followed by 2-bromopropene (0.18 mL, 2.07 mmol, 3.0 equiv.) The resulting solution was stirred for 16 h before being quenched with H_2O (20 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 15 mL). Combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (1:0 → 20:1 PE/EtOAc) to give alkene **22** as pale-yellow oil (231 mg, 67%, inconsequential mix of diastereomers) in an inseparable 3:1 mixture with the alkane arising from protonation of the lithiated intermediate.

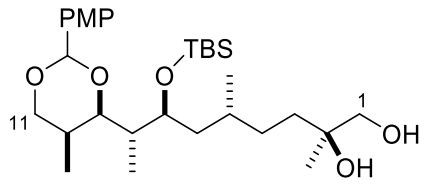
Major diastereomer:

R_f 0.58 (9:1 PE/EtOAc); $[\alpha]_D^{20}$ – 41.6 (*c* 0.37, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 2336, 1616, 1518, 1463, 1249, 1072, 833, 773; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.37 (2H, d, *J* = 8.6 Hz, H-Ar), 6.86 (2H, d, *J* =8.6 Hz, H-Ar), 5.36 (1H, s, C<u>H</u>Ar), 4.66-4.63 (2H, m, H-2), 4.17 (1H, ddd, *J* = 10.1, 3.2, 1.7 Hz, H-7), 4.04 (1H, dd, *J* = 11.2, 2.4 Hz, H-11a), 4.00 (1H, dd, *J* = 11.2, 1.2 Hz, H-11b), 3.79 (3H, s, ArOC<u>H</u>$_3$), 3.57 (1H, dd, *J* = 10.8, 2.0 Hz, H-9), 1.96-1.91 (1H, m, H-8), 1.84-1.78 (1H, m, H-10), 1.69 (3H, s, Me-2), 1.64-1.25 (7H, m, H-3, H-4, H-5, H-6), 1.13 (3H, d, *J* =6.9 Hz, Me-5), 0.87 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.78 (3H, d, *J* = 7.0 Hz, Me-8), 0.76 (3H, d, *J* = 6.6 Hz, Me-10), 0.03 (3H, s, Si(C<u>H</u>a$_3$)(CHb$_3$)), 0.00 (3H, s, Si(CHa$_3$)(C<u>H</u>b$_3$)); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.7, 146.5, 131.7, 127.1, 113.4, 109.5, 101.2, 81.2, 74.1, 68.7, 55.3, 40.5, 38.0, 36.4, 35.4, 29.9, 28.7, 25.9, 22.5, 19.1, 18.1, 10.9, 7.9, –4.2, –4.7; **HRMS** (ES+): calc. for $C_{29}H_{51}O_4Si$ $[M+H]^+$ 491.3551, found 491.3542.

Minor diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.35 (2H, d, *J*= 8.7 Hz, H-Ar), 6.88 (2H, d, *J* = 8.7 Hz, H-Ar), 6.00 (1H, s, C<u>H</u>Ar), 4.67-4.65 (2H, m, H-1), 4.30 (1H, ddd, *J* = 11.6, 2.7, 2.1 Hz, H-7), 4.00 (1H, dd, *J* = 11.2, 1.2 Hz, H-11a), 3.81 (3H, s, ArOC<u>H</u>$_3$), 3.61 (1H, dd, *J* = 11.2, 2.2 Hz, H-11b), 3.44 (1H, dd, *J* = 10.6, 2.5 Hz, H-9), 1.96-1.91 (1H, m, H-8), 1.84-1.78 (1H, m, H-10), 1.70 (3H, s, Me-2), 1.64-1.25 (7H, m, H3, H-4, H-5, H-6), 1.16 (3H, d, *J* = 6.9 Hz, Me-5), 1.00 (3H, d, *J* = 6.8 Hz, Me-10), 0.89 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.70 (3H, d, *J* = 7.1 Hz, Me-8), 0.10 (3H, s, Si(C<u>H</u>a$_3$)(CHb$_3$)), 0.08 (3H, s, Si(CHa$_3$)(C<u>H</u>b$_3$)).

Diol 22a



To a solution of alkene **22** (50 mg, 0.102 mmol, 1.0 equiv.) (as a 3:1 mixture with the alkane arising from the protonation of lithiated **21**), in *t*-BuOH/H_2O (1:1, 1 mL), were added $K_2OsO_2(OH)_4$ (0.74 mg, 2 µmol, 2.0 mol%), $(DHQ)_2AQN$ (2.3 mg, 3 µmol, 3.0 mol%), K_2CO_3 (42.5 mg, 0.306 mmol, 3.0 equiv.) and $K_3Fe(CN)_6$ (101 mg, 0.306 mg, 3.0 equiv.) and stirred for 16 h. The reaction was quenched with $Na_2S_2O_3$ (2 mL) and Et_2O (2 mL) before the layers were separated. The aqueous layer was extracted with Et_2O (3 x 3 mL) and EtOAc (2 x 3 mL). Combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash column chromatography (3:1 PE/EtOAc) to give diol **22a** as a viscous colourless oil (25 mg, 63%, >95:5 *dr*). The alkane arising from the protonation of the lithiated intermediate from **21** could be separated here (12 mg).

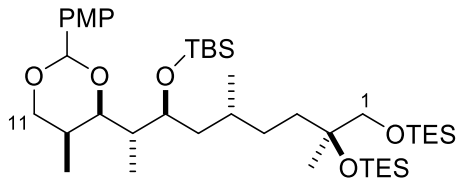
Major diastereomer:

R_f 0.18 (3:1 PE/EtOAc); $[\alpha]_D^{20}$ – 33.2 (*c* 1.80, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 3466, 3416, 1517, 1463, 1379, 1249, 1166, 1038, 834, 774; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.39 (2H, d, *J* = 8.8 Hz, H-Ar), 6.88 (2H, d, *J* = 8.8 Hz, H-Ar), 5.37 (1H, s, C<u>H</u>Ar), 4.20 (1H, ddd, *J* = 10.0, 3.1, 1.5 Hz, H-7), 4.04-4.01 (2H, m, H-11), 3.81 (3H, s, ArOC<u>H_3</u>), 3.58 (1H, dd, *J* = 10.3, 2.0 Hz, H-9), 3.45 (1H, d, *J* = 10.7 Hz, H-1a), 3.39 (1H, d, *J* = 10.7 Hz, H-1b), 2.04 (1H, br s, O-<u>H</u>), 2.00-1.93 (1H, m, H-10), 1.86 (1H, br s, O-<u>H</u>), 1.61-1.57 (1H, m, H-8), 1.55 -1.22 (7H, m, H-3-6), 1.16 (3H, d, *J* = 7.0 Hz, Me-8), 1.15 (3H, s, Me-2), 0.89 (9H, s, SiC(C<u>H_3</u>)$_3$), 0.79 (3H, d *J* = 6.4 Hz, Me-5), 0.80 (3H, d, *J* = 7.0 Hz, Me-10), 0.05 (3H, s, Si(C<u>H</u>a$_3$)(CHb$_3$)), 0.03 (3H, s, Si(CHa$_3$)(C<u>H</u>b$_3$)) ; **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.7, 131.6, 127.1, 113.5, 101.2, 81.3, 74.1, 73.0, 69.9, 68.7, 55.3, 40.5, 37.7, 36.2, 32.1, 29.9, 29.4, 25.9, 23.3, 19.2, 18.1, 10.9, 7.9, – 4.2, – 4.6; **HRMS** (ES+): calc. for $C_{29}H_{53}O_6Si$ $[M+H]^+$ 525.3611, found 525.3612.

Minor diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.39 (2H, d, *J* = 8.8 Hz, H-Ar), 6.90 (2H, d, *J* = 8.8 Hz, H-Ar), 6.02 (1H, s, C<u>H</u>Ar), 4.32 (1H, dt, *J* = 11.5, 2.1 Hz, H-7), 4.04-4.01 (2H, m, H-11), 3.83 (3H, s, ArOC<u>H_3</u>), 3.63 (1H, dd, *J* = 11.3, 2.1 Hz, H-9), 3.45 (1H, d, *J* = 10.7 Hz, H-1a), 3.39 (1H, d, *J* = 10.7 Hz, H-1b), 2.04 (1H, br s, O-<u>H</u>), 2.00-1.93 (1H, m, H-10), 1.88 (1H, br s, O-<u>H</u>), 1.18 (3H, d, *J* = 7.0 Hz, Me-8), 1.55-1.22 (7H, m, H-3-6), 1.15 (3H, s, Me-2), 0.91 (9H, s, SiC(C<u>H_3</u>)$_3$), 0.71 (3H, d, *J* = 7.1 Hz, Me-10), 0.13 (3H, s, Si(C<u>H</u>a$_3$)(CHb$_3$)), 0.11 (3H, s, Si(CHa$_3$)(C<u>H</u>b$_3$)); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.3, 130.3, 128.3, 113.9, 96.6, 81.2, 72.4, 68.2, 67.1, 65.9, 55.3, 41.1, 37.8, 36.1, 32.4, 30.7, 30.3, 23.3, 18.9, 18.2, 15.3, 10.9, 8.1, – 4.1, – 4.6.

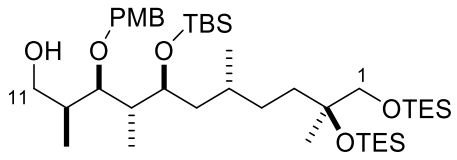
TES ether 22b



To a solution of diol **22a** (22 mg, 0.038 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL) at –78 °C were added 2,6-lutidine (49 µL, 0.478 mmol, 12.5 equiv.) and TESOTf (53 µL, 0.288 mmol, 7.5 equiv.) and stirred for 1 h before being warmed up to rt. After stirring for a further 30 min, the reaction was quenched with NH_4Cl (1 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 1 mL), combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (PE → 10:1 PE/EtOAc) to give TES ether **22b** as a colourless oil (31 mg, 99%, inconsequential mix of diastereomers).

R_f 0.61 (3:1 PE/EtOAc); $[\alpha]_D^{20}$ –12.7 (*c* 0.85, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 1517, 1461, 1249, 1166, 1106, 1014, 833, 740; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.39 (2H, d, *J* = 8.7 Hz, H-Ar), 6.88 (2H, d, *J* = 8.7 Hz, H-Ar), 5.38 (1H, s, C<u>H</u>Ar), 4.17 (1H, br d, *J* = 9.8 Hz, H-7), 4.06 (1H, dd, *J* = 11.3, 2.2, Hz, H-11a), 4.02 (1H, dd, *J* = 11.3, 1.1 Hz, H-11b), 3.81 (3H, s, ArOC<u>H</u>$_3$), 3.58 (1H, dd, *J* = 10.5, 2.0 Hz, H-9), 3.39 (1H, d, *J* = 9.4 Hz, H-1a), 3.30 (1H, dd, *J* = 9.4, 2.0 Hz, H-1b), 1.95 (1H, qddd, *J* = 7.0, 2.2, 2.0, 1.1 Hz, H-10), 1.61-1.56 (1H, m, H-8), 1.50-1.19 (7H, m, H-3-6), 1.15 (3H, d, *J* = 6.8 Hz, Me-8), 1.14 (3H, s, Me-2), 0.95 (9H, t, *J* = 8.0 Hz, Si(CH_2C<u>H</u>$_3$)$_3$), 0.93 (9H, t, *J* = 8.0 Hz, Si(CH_2C<u>H</u>$_3$)$_3$), 0.88 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.79 (3H, d, *J* = 7.0 Hz, Me-10), 0.75 (3H, d, *J* = 6.5 Hz, Me-5), 0.58 (6H, q, *J* = 7.9 Hz, Si(C<u>H</u>$_2$CH$_3$)$_3$), 0.56 (6H, q, *J* = 7.8 Hz, Si(C<u>H</u>$_2$CH$_3$)$_3$), 0.04 (3H, s, Si(C<u>H</u>a$_3$)(CHb$_3$)), 0.02 (3H, s, Si(CHa$_3$)(C<u>H</u>b$_3$)); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.7, 131.7, 127.1, 113.4, 101.2, 81.2, 75.9, 74.1, 69.9, 68.7, 55.3, 40.4, 38.1, 37.1, 31.9, 29.9, 29.5, 25.9, 25.3, 22.6, 19.3, 18.1, 10.9, 7.8, 7.2, 6.8, 4.4, – 4.2, – 4.7; **HRMS** (ES+): calc. for $C_{41}H_{81}O_6Si_3$ $[M+H]^+$ 753.5341, found 753.5349.

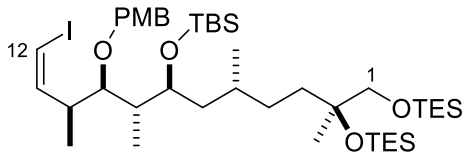
Alcohol 23



To a stirred solution of PMP acetal **22b** (87 mg, 0.116 mmol, 1.0 equiv.) in CH_2Cl_2 (1.2 mL) at –30 °C was added DIBAL (1 M in hexanes, 0.58 mL, 0.58 mmol, 5.0 equiv.) over 10 min. The reaction mixture was maintained at this temperature for 3 h before being quenched with Na/K tartrate (3 mL) and stirred for 1 h. The layers were then separated and the aqueous layer extracted with CH_2Cl_2 (3 x 3 mL). Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give alcohol **23** as a colourless oil, (48 mg 58%).

R_f 0.18 (9:1 PE/EtOAc); $[\alpha]_D^{20}$ –28.7 (*c* 1.30, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 3443, 1614, 1514, 1461, 1248, 1087, 1038, 822, 741; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.26 (2H, d, *J* = 8.8 Hz, H-Ar), 6.87 (2H, d, *J* = 8.8 Hz, H-Ar), 4.53 (1H, d, *J* = 11.0 Hz, C<u>H</u>aHbAr), 4.48 (1H, d, *J* = 11.0 Hz, CHa<u>H</u>bAr), 4.17 (1H, d, *J* = 10.7 Hz, H-7), 3.80 (3H, s, ArOC<u>H</u>$_3$), 3.66-3.58 (2H, m, H-11), 3.42 1H, dd, *J* = 10.1, 2.2 Hz, H-9), 3.40 (1H, d, *J* = 10.0 Hz, H-1a), 3.31 (1H, dd, *J* = 9.5, 2.6 Hz, H-1b), 2.04-1.97 (1H, m, H-8), 1.94-1.89 (1H, m, H-10), 1.60 (1H, t, *J* = 5.2 Hz, O-<u>H</u>), 1.53-1.19 (7H, m, H-3, H-4, H-5, H-6), 1.16 (3H, s, Me-2), 0.96 (9H, t, *J* = 8.0 Hz, Si(CH_2C<u>H</u>$_3$)$_3$), 0.94 (9H, t, *J* = 7.8 Hz, Si(CH_2C<u>H</u>$_3$)$_3$), 0.89 (3H, d, *J* = 7.0 Hz, Me-10), 0.88 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.85 (3H, d, *J* = 7.4 Hz, Me-5), 0.82 (3H, d, *J* = 7.0 Hz, Me-8), 0.59 (6H, q, *J* = 8.0 Hz, Si(C<u>H</u>$_2$CH$_3$)$_3$), 0.57 (6H, q, *J* = 7.8 Hz, Si(C<u>H</u>$_2$CH$_3$)$_3$), 0.05 (3H, s, Si(C<u>H</u>a$_3$)(CHb$_3$)), 0.02 (3H, s, Si(CHa$_3$)(C<u>H</u>b$_3$)); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 158.9, 131.2, 128.6, 113.7, 80.7, 75.9, 73.5, 69.9, 69.6, 66.2, 55.3, 42.6, 38.4, 37.8, 37.1, 31.9, 29.4, 25.9, 25.3, 19.4, 18.1, 15.3, 10.2, 9.9, 7.2, 6.8, 4.4, –4.2,–4.7; **HRMS** (ES+): calc. for $C_{41}H_{80}O_6Si_3Na$ $[M+Na]^+$ 777.5317, found 777.5315.

Vinyl iodide 5



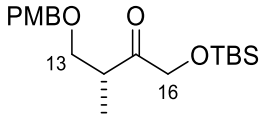
To a solution of alcohol **23** (32 mg, 0.042 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL) were added Dess-Martin Periodinane (36 mg, 0.085, 2.0 equiv.) and $NaHCO_3$ (10.6 mg, 0.126 mmol, 3.0 equiv.) and stirred for 20 min. Upon completion, $Na_2S_2O_3$ (0.5 mL) and $NaHCO_3$ (0.5 mL) were added and stirred for a further 10 min, before the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL). Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude aldehyde (31 mg, 97%) was used directly in the following reaction without further purification.

To a stirred suspension of (iodomethyl)triphenylphosphonium iodide (89 mg, 0.170 mmol, 4.0 equiv.) in THF (0.3 mL) at 0 °C was added NaHMDS (1 M in THF, 0.14 mL, 0.144 mmol, 3.5 equiv.) and stirred for 30 min. The reaction mixture was then cooled to –78 °C and a solution of the crude aldehyde (31 mg, 0.041 mmol, 1.0 equiv.) in THF (0.3 mL) added *via* cannula, before stirring for 1 h. The reaction was then quenched by addition of PE and filtered through a short plug of Celite®, before being concentrated *in vacuo*. The crude material was purified by flash column chromatography (19:1 PE/EtOAc) to give vinyl iodide **5** as a colourless oil (29 mg, 82%).

R_f 0.17 (19:1 PE/EtOAc); $[\alpha]_D^{20}$ +14.5° (*c* 1.00, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 1514, 1462, 1248, 1065, 836, 771; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.23 (2H, d, *J* = 8.5 Hz, H-Ar), 6.86 (2H, d, *J* 8.5 Hz, H-Ar), 6.23 (1H, dd, *J* =8.8, 7.2 Hz, H-11), 6.16 (1H, d, *J* = 7.3 Hz, H-12), 4.47 (1H, d, *J* = 11.0 Hz, C<u>H</u>aHbAr), 4.42 (1H, d, *J* = 11.0 Hz, CHa<u>H</u>bAr), 4.11 (1H, d, *J*= 10.1 Hz, H-7), 3.81 (3H, s, ArOC<u>H</u>$_3$), 3.40 (1H, d, *J* = 9.4 Hz, H-1a), 3.31 (1H, d, *J* = 9,4 Hz, H-1b), 3.26 (1H, dd, *J* = 9.6, 2.6 Hz, H-9), 2.76-2.70 (1H, m, H-10), 1.99-1.93 (1H, m, H-8), 1.55-1.26 (7H, m, H-3, H-4, H-5, H-6), 1.16 (3H, s, Me-2), 0.96 (9H, t, *J* = 8.0 Hz, Si(CH$_2$C<u>H</u>$_3$)$_3$), 0.94 (9H, t, *J* = 7.9 Hz, Si(CH$_2$C<u>H</u>$_3$)$_3$), 0.92 (3H, d, *J* 7.2 Hz, Me-8), 0.82 (3H, d, *J* = 6.5 Hz, Me-5), 0.59 (6H, q, *J* = 8.0 Hz, Si(C<u>H</u>$_2$CH$_3$)$_3$), 0.57 (6H, q, *J* = 8.0 Hz, Si(C<u>H</u>$_2$-CH$_3$)$_3$), 0.04 (6H, s, SiC(C<u>H</u>$_3$)$_3$), 0.02 (6H, s, SiC(C<u>H</u>$_3$)$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 158.9, 145.5, 131.2, 128.4, 113.6, 83.3, 80.8, 75.9, 74.0, 69.9, 69.5, 55.3, 42.8, 41.8, 38.6, 37.1, 32.0, 29.4, 25.9, 25.3, 22.6, 19.4, 18.1, 12.2, 10.3, 7.2, 6.8, 4.4, – 4.1, – 4.6 ; **HRMS** (ES+): calc. for $C_{42}H_{81}IO_5Si_3$ $[M+H]^+$ 899.4334, found 899.4336

2.2. Preparation of the C13-C19 vinyl iodide

TBS ether 12

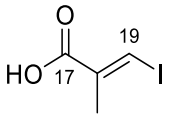


To a stirred solution of methyl ketone **24**[8] (1.00 g, 4.08 mmol, 1.0 equiv.) in THF (13 mL) at –78 °C was added LDA (1 M in THF, 5.70 mL, 5.70 mmol, 1.4 equiv.) *via* cannula. After 1 h at this temperature, TMSCl (0.9 mL, 6.53 mmol, 1.6 equiv.) was added and the solution stirred for another 1 h at this temperature before being allowed to warm to rt over the following h. The reaction mixture was then concentrated *in vacuo* and pentane (10 mL) added. The precipitate formed was filtered through Celite® and the filtrate concentrated *in vacuo.* The crude silyl enol ether was then redissolved in *t*-BuOH/H_2O/THF (1:1:1, 20 mL) and OsO_4 (4 wt% in H_2O, 1.4 mL, 0.22 mmol, 0.05 equiv.) and NMO (50 wt% in H_2O, 2.13 mL, 9.10 mmol, 2.2 equiv.) added. The reaction mixture was left to stir for 16 h before being quenched with $Na_2S_2O_3$ (15 mL) and Et_2O (20 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 20 mL) and EtOAc (20 mL). Combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was filtered over silica and the crude alcohol was used in the next step without further purification.

To a solution of crude alcohol (ca. 256 mg, ca. 0.59 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) were added imidazole (60.5 mg, 0.89 mmol, 1.5 equiv.) and TBSCl (107 mg, 0.71 mmol, 1.2 equiv.). The reaction mixture was stirred for 1 h before being quenched with NH_4Cl (5 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 4 mL) and combined organic layers dried over $MgSO_4$ before being concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 $\rightarrow$ 5:1 PE/EtOAc) to give TBS ether **12** as a colourless oil (321 mg, 72% over three steps).

R_f 0.49 (3:1 PE/EtOAc); $[\alpha]_D^{20}$ – 11.8 (*c* 1.00, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 2930, 1732, 1613, 1587, 1513, 1463, 1361, 1302, 1246, 1172, 1093, 1033, 939, 836, 779, 668; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.21 (2H, d, *J* = 8.3 Hz, H-Ar), 6.86 (2H, d, *J* = 8.3 Hz, H-Ar), 4.43 (1H, d, *J* = 11.5 Hz, C<u>H</u>aHbAr), 4.37 (1H, d, *J* = 11.5 Hz, CHa<u>H</u>bAr), 4.33 (1H, d, *J* = 19.2 Hz, H-16a), 4.26 (1H, d, *J* = 19.2 Hz, H-16b), 3.80 (3H, s, ArOC<u>H</u>$_3$), 3.58 (1H, t, *J* = 8.5 Hz, H-13a), 3.43 (1H, dd, *J* = 8.5, 5.4 Hz, H-13b), 3.07-2.99 (1H, m, H-14), 1.06 (3H, d, *J* = 7.1 Hz, Me-14), 0.91 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.07 (3H, s, Si(C<u>H</u>a$_3$)(CHb$_3$)), 0.06 (3H, s, Si(CHa$_3$)(C<u>H</u>b$_3$)); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 211.8, 159.2, 130.1, 129.2, 113.7, 72.9, 71.8, 69.5, 55.2, 41.9, 25.6, 18.3, 13.2, – 3.6, – 5.6; **HRMS** (ES+) calc. for $C_{19}H_{32}O_4SiNa$ $[M+Na]^+$ 375.1968, found 375.2008.

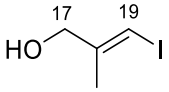
Acid 14a



To a suspension of NaH (60% in mineral oil, 2.23 g, 55.5 mmol, 1.2 equiv.) in Et_2O (70 mL) was added diethylmethylmalonate (8.0 mL, 46.4 mmol, 1.0 equiv.) slowly and then heated to reflux for 2 h. Iodoform (18.3 g, 46.4 mmol, 1.0 equiv.) was then added and the reaction mixture refluxed for a further 15 h, before cooling to 0 °C. Et_2O (50 mL) and HCl (3 M, 75 mL) were then added and the solution stirred for 10 min before the layers were separated and the aqueous layer extracted with Et_2O (3 x 40 mL). The product was concentrated *in vacuo* before being redissolved in EtOH (35mL) and KOH (4 M, 35 mL, 140 mmol, 3.0 equiv.). The solution was then heated to reflux for 16 h before being cooled to rt and concentrated *in vacuo*. The residue was redissolved in K_2CO_3 (10% *aq*, 100 mL) and the precipitate filtered, washing with CH_2Cl_2 (2 x 30 mL). The filtrate was acidified to pH 1 with conc. HCl and the product extracted with CH_2Cl_2 (8 x 40 mL). Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude acid **14a** was isolated as a yellow-brown solid (6.4 g, 65%) and used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 8.04 (1H, s, H-19), 2.05 (3H, Me-18). Data in agreement with literature values[9]

Alcohol 14b

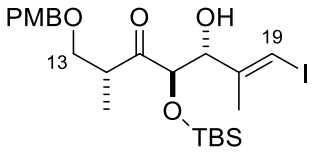


To a solution of carboxylic acid **14a** (300 mg, 1.42 mmol, 1.0 equiv.) in Et_2O (6 mL) at 0 °C was added $LiAlH_4$ (62 mg, 1.62 mmol, 1.15 equiv.) in 4 portions. The reaction mixture was slowly warmed to rt and stirred for 2 h before being quenched with Na_2SO_4 (4 mL) and then H_2SO_4 (1.5 M *aq*, 4 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 8 mL). Combined organic layers were washed with K_2CO_3 (10% *aq*, 10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (4:1 PE/EtOAc) to give alcohol **14b** as a colourless liquid (269 mg, 96%).

IR (thin film, ν_{max}/cm^{-1}): 3292, 1619, 1377, 1276, 1068, 1011, 774; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 6.29 (1H, sextet, *J* = 1.3 Hz, H-19), 4.13 (2H, br d, *J* = 3.7 Hz, H-17), 1.85 (3H, d, *J* = 1.3 Hz, Me-18), 1.6 (1H, t, *J* = 3.7 Hz, OH); **HRMS** (ES+) calc. for C_4H_6IO $[M-H]^-$ 196.9458, found 196.9458.

Data in agreement with literature values.[10]

Aldol adduct 25

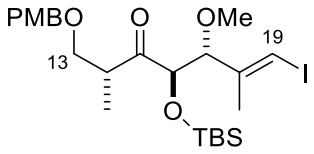


To a solution of allylic alcohol **14b** (1.7 g, 8.58 mmol, 1.0 equiv.) in Et_2O (40 mL) was added MnO_2 (7.47 g, 85.8 mmol, 10 equiv.) and stirred for 16 h. The reaction mixture was then filtered through Celite®, which was washed with Et_2O (20 mL). The filtrate was concentrated carefully *in vacuo* and the aldehyde (**14**) dried over 4Å MS before being used directly in the following reaction, without further purification.

To a solution of Cy_2BCl (1.01 mL, 5.48 mmol, 1.5 equiv.) in Et_2O (8 mL) at 0 °C was added Et_3N (0.86 mL, 6.21 mmol, 1.7 equiv.) and stirred for 10 min before the addition of a solution of ketone **12** (1.25 g, 3.65 mmol, 1.0 equiv.) in Et_2O (8 mL). The reaction mixture was stirred for a further 75 min before cooling to –78 °C. A solution of aldehyde **14** (2.5 g, 14.6 mmol, 3.5 equiv.) in Et_2O (8 mL) was then added *via* cannula and the reaction mixture allowed to stir at this temperature for 5 h before quenching with MeOH (4 mL), pH 7 buffer (4 mL) and H_2O_2 (30 wt% aq, 2.5 mL) and warming to rt, stirring for a further 30 min. The layers were then separated and the aqueous layer extracted with Et_2O (3 x 8 mL). Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give aldol adduct **25** as a pale-yellow oil (1.61 g, 82%, >20:1 *dr*).

R_f 0.26 (9:1 PE/EtOAc); $[\alpha]_D^{20}$ + 51.3 (*c* 2.49, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 3409, 1719, 1613, 1513, 1249, 1075, 838, 778; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.18 (2H, d, *J* = 8.7 Hz, H-Ar), 6.88 (2H, d, *J* = 8.7 Hz, H-Ar), 6.26 (1H, s, H-19), 4.43 (1H, d, *J* = 11.7 Hz, OCHaHbAr), 4.37 (1H, d, *J* = 11.7 Hz, OCHaHbAr), 4.29 (1H, dd, *J* = 7.8, 4.9 Hz, H-17), 3.89 (1H, d, *J* = 7.8 Hz, H-16), 3.81 (3H, s, ArOCH_3), 3.73 (1H, d, *J* = 4.9 Hz, O-H), 3.62 (1H, dd, *J* = 10.2, 8.1 Hz, H-13a), 4.49-4.41 (1H, m, H-14), 3.38 (1H, dd, *J* = 8.1, 4.2 Hz, H-13b), 1.82 (3H, s, Me-18), 1.00 (3H, d, *J* = 6.7 Hz, Me-14), 0.89 (9H, s, SiC(CH_3)$_3$), – 0.02 (3H, s, Si(CHa$_3$)(CHb$_3$)), – 0.03 (3H, s, Si(CHa$_3$)(CHb$_3$)); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 213.3, 159.6, 145.3, 129.7, 128.6, 114.0, 81.4, 79.9, 77.1, 73.3, 73.2, 55.3, 40.0, 30.1, 25.7, 23.7, 19.4, 17.9, 14.6, –4.8, – 5.1; **HRMS** (ES+) calc. for $C_{23}H_{37}IO_5SiNa$ $[M+Na]^+$ 571.1353, found 571.1365.

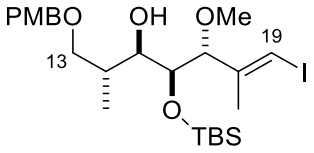
Methyl ether 25a



To a solution of aldol adduct **25** (1.60 g, 2.97 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) was added trimethyloxonium tetrafluoroborate (3.52 g, 23.8 mmol, 8.0 equiv.) and Proton Sponge® (6.36 g, 29.7 mmol, 10.0 equiv.) and stirred for 16 h before being quenched with $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 10 mL). Combined organic layers were then washed with citric acid (10% aq, 3 x 10 mL) to remove excess Proton Sponge®, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give methyl ether **25a** as a colourless oil (1.32 g, 82%).

R_f 0.37 (9:1 PE/EtOAc); $[\alpha]_D^{20}$ + 11.8 (*c* 0.51, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 2360, 1723, 1613, 1513, 1462, 1248, 1109, 839; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.24 (2H, d, *J* = 8.8 Hz, H-Ar), 6.87 (2H, d, *J* = 8.8 Hz, H-Ar), 6.28 (1H, br s, H-19), 4.43 (1H, d, *J* = 11.8 Hz, OC<u>H</u>aHbAr), 4.39 (1H, d, *J* = 11.8 Hz, OCHa<u>H</u>bAr), 4.11 (1H, d, *J* = 8.0 Hz, H-17), 3.80 (3H, s, ArOC<u>H</u>$_3$), 3.76 (1H, d, *J* = 8.0 Hz, H-16), 3.54 (1H, dd, *J* = 8.7, 6.8, Hz, H-13a), 3.37-3.29 (2H, m, H-13b, H-14), 3.07 (3H, s, OC<u>H</u>$_3$), 1.76 (3H, d, *J* = 1.1 Hz, Me-18), 1.06 (3H, d, *J* = 6.5 Hz, Me-14), 0.86 (9H, s, SiC(C<u>H</u>$_3$)$_3$), – 0.04 (3H, s, Si(C<u>H</u>a$_3$)(CHb$_3$)), – 0.06 (3H, s, Si(CHa$_3$)(C<u>H</u>b$_3$)); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 212.9, 159.2, 144.6, 130.1, 129.4, 113.8, 87.2, 82.6, 77.8, 72.9, 72.4, 56.4, 55.3, 42.6, 25.7, 18.9, 18.0, 14.1, – 4.8, – 5.1; **HRMS** (ES+) calc. for $C_{24}H_{43}I\,O_5NSi$ $[M+NH_4]^+$ 580.1950, found 580.1940.

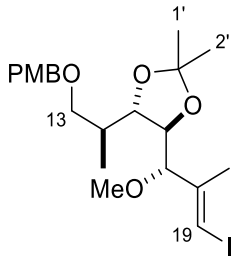
Alcohol 26



A solution of ketone **25a** (930 mg, 1.68 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) was cooled to –78 °C and DIBAL (1 M in hexanes, 8.40 mL, 8.42 mmol, 5.0 equiv.) added. The reaction mixture was stirred for 2 h before being quenched with NH_4Cl (10 mL) and Na/K tartrate (15 mL) and stirred for a further 2 h. The layers were then separated and the aqueous layer extracted with CH_2Cl_2 (4 x 20 mL). Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (8:1 PE/EtOAc) to give alcohol **26** as a colourless oil (838 mg, 90%, >20:1 *dr*).

R_f 0.29 (9:1 PE/EtOAc); $[\alpha]_D^{20}$ + 2.3 (*c* 0.40, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 3230, 1613, 1513, 1462, 1248, 1109, 839; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.26 (2H, d, *J* = 8.6 Hz, H-Ar), 6.87 (2H, d, *J* = 8.6 Hz, H-Ar), 6.27 (1H, s, H-19), 4.47 (1H, d, *J* = 12.0 Hz, OCHaHbAr), 4.43 (1H, d, *J* = 12.0 Hz, OCHaHbAr), 3.80 (3H, s, ArOCH_3), 3.81-3.75 (2H, m, H-17, H-13a), 3.68 (1H, dd, *J* = 9.0, 4.5 Hz, H-13b), 3.49 (1H, ddd, *J* = 9.2, 8.6, 1.8 Hz, H-15), 3.40 (1H, dd, *J* = 9.2, 6.6 Hz, H-16), 3.17 (3H, s, OCH_3), 2.76 (1H, d, *J* = 8.6 Hz, O-H), 1.94-1.86 (1H, m, H-14), 1.76 (3H, s, Me-18), 0.97 (3H, d, *J* = 6.8 Hz, Me-14), 0.87 (9H, s, SiC(CH_3)$_3$), 0.07 (3H, s, Si(CHa$_3$)(CHb$_3$)), 0.03 (3H, s, Si(CHa$_3$)(CHb$_3$)); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.0, 145.2, 130.8, 129.1, 113.7, 86.8, 82.3, 73.8, 73.1, 72.8, 72.1, 56.5, 55.3, 36.2, 26.1, 19.7, 18.3, 14.8, −3.7, −4.1; **HRMS** (ES+) calc. for $C_{24}H_{42}IO_5Si$ $[M+H]^+$ 565.1841, found 565.1832.

Confirmation of C15 stereochemistry: Acetonide Ac-26



To a solution of silyl ether ***ent*-26**[*] (10 mg, 0.018 mmol, 1.0 equiv.) in THF (0.5 mL) was added TBAF (1.0 M, 27 µL, 0.027 mmol, 1.5 equiv.) and stirred for 3 h. The reaction was then quenched with NH_4Cl (1 mL) and the layers separated. The aqueous layer was extracted with Et_2O (3 x 1 mL). Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was redissolved in PE/EtOAc (3:1) and filtered through a short plug of silica, before being used directly in the following reaction. To a solution of the crude diol (7 mg, 0.016 mmol, 1.0 equiv.) in CH_2Cl_2 (0.4 mL) were added 2,2-methoxypropane (0.3 mL, 2.44 mmol, 150 equiv.) and PPTS (1 crystal). The reaction mixture was stirred for 2 h before being concentrated *in vacuo*. The crude material was purified by flash column chromatography (4:1 PE/EtOAc) to give acetonide **Ac-26** as a colourless oil (6.5 mg, 75% over 2 steps).

R_f 0.57 (4:1 PE/EtOAc); **IR** (thin film, ν_{max}/cm^{-1}): 1613, 1513, 1463, 1368, 1247, 1095, 1038, 821; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.26 (2H, d, *J* = 8.7 Hz, H-Ar), 6.87 (2H, d, *J* = 8.7 Hz, H-Ar), 6.22 (1H, s, H-19), 4.44 (2H, s, OCH_2Ar), 4.01 (1H, dd, *J* = 6.8, 6.0 Hz, H-16), 3.88 (1H, app t, *J* = 6.0 Hz, H-17), 3.81 (3H, s, ArOCH_3), 3.63 (1H, d, *J* = 6.8 Hz, H-15), 3.61 (1H, dd, *J* = 9.3, 5.2 Hz, H-13a), 3.36 (1H, dd, *J* = 9.3, 6.7 Hz, H-13b), 3.19 (3H, s, OCH_3), 2.05 (1H, qdd, *J* = 7.0, 6.7, 5.2 Hz, H-14), 1.81 (3H, d, *J* = 1.0 Hz, Me-18), 1.35 (3H, s, Me-2'), 1.33 (3H, s, Me-1'), 1.00 (3H, d, *J* = 7.0 Hz, Me-14); **HRMS** (ES+) calc. for $C_{21}H_{35}INO_5$ $[M+NH_4]$+ 508.1554, found 508.1543.

[*] Exploratory studies on the C13-C19 fragment commenced with the enantiomeric series from (*S*)-Roche ester due to the greater availability of (*S*)-Roche ester in our laboratory.

Analysis of a series of 1D NOEs was carried out to determine the acetonide stereochemistry (**Figure SI-2**). We hypothesised that in the *anti*-acetonide case (desired diastereomer), H-15 and H-16 would exhibit asymmetric NOEs with respect to the two geminal methyl groups. A strong NOE was observed between H-15 and Me-1' (combined with a weak NOE to Me-2'), whereas the opposite was true for H-16. In the *syn*-acetonide case (undesired diastereomer), it was expected that both protons should observe similarly strong NOEs to one methyl group and correspondingly weak ones to the other. Thus, the observed asymmetric NOE correlations to the acetonide Me protons is diagnostic for our stereochemical assignment. To corroborate our observations, a conformational search and optimisation of the lowest energy conformers with density functional theory (DFT) (B3LYP/LACVP**) was conducted for **Ac-26**.[†] The optimised structure obtained **Figure SI-3** (coordinates shown in **Table SI-1**) confirmed the NOEs observed.

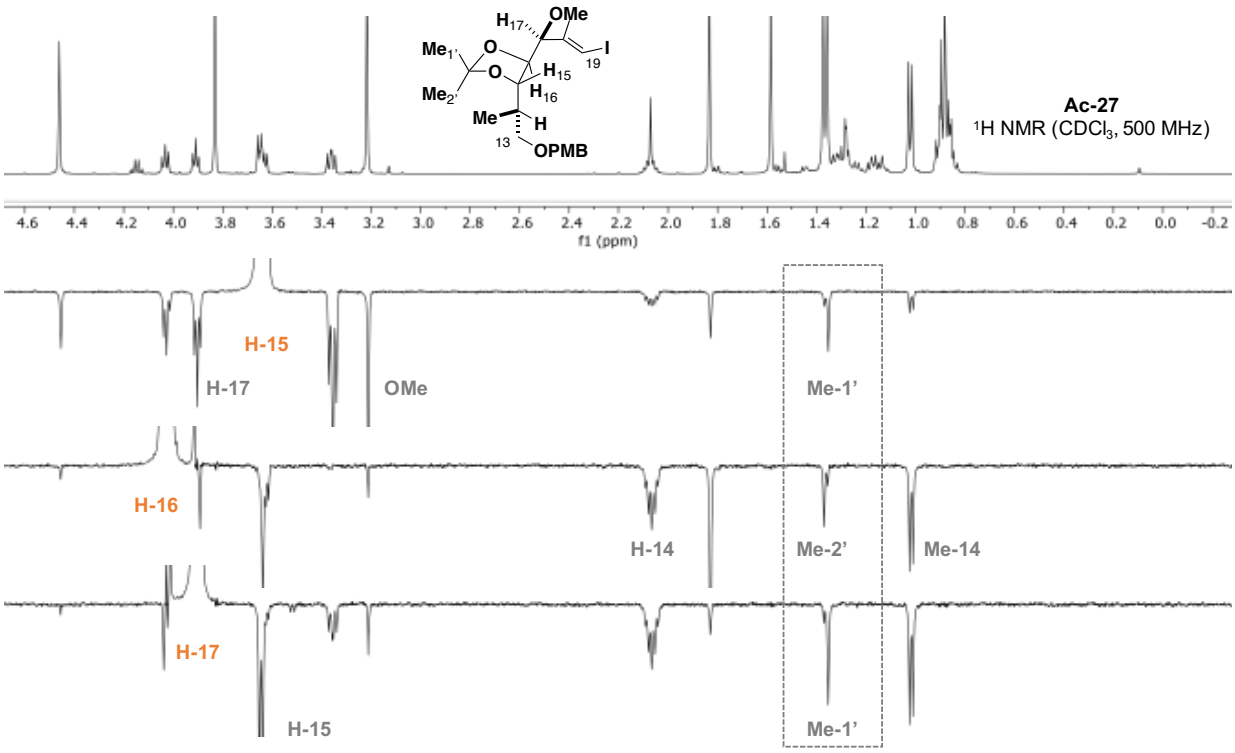


Figure SI-2. ^{1}H NMR spectra and 1D NOE correlations observed for acetonide **Ac-26**, with irradiated signals denoted in **orange** and diagnostic NOE correlations denoted in **grey**. The signals for Me-1' and Me-2' are marked by the box.

[†] Structure optimisation was conducted as follows: A conformational search was carried out in MacroModel[13] using a hybrid of Monte Carlo multiple−minimum (MCMM)[14]/ low−mode sampling[15] with the Merck Molecular Force Field (MMFF),[16] interfaced with Maestro 9.3.[17] The searches were carried out with a sufficient number of steps to find all conformers within 10 kJ mol^{-1}of the global minimum. Calculations were carried out in gas phase. All conformers within 10 kJ mol^{-1} of the global minimum were then further subjected to quantum mechanical calculations. Single point energies were evaluated at the B3LYP[18,19]/LACVP** level of theory, implemented with Jaguar 7.9

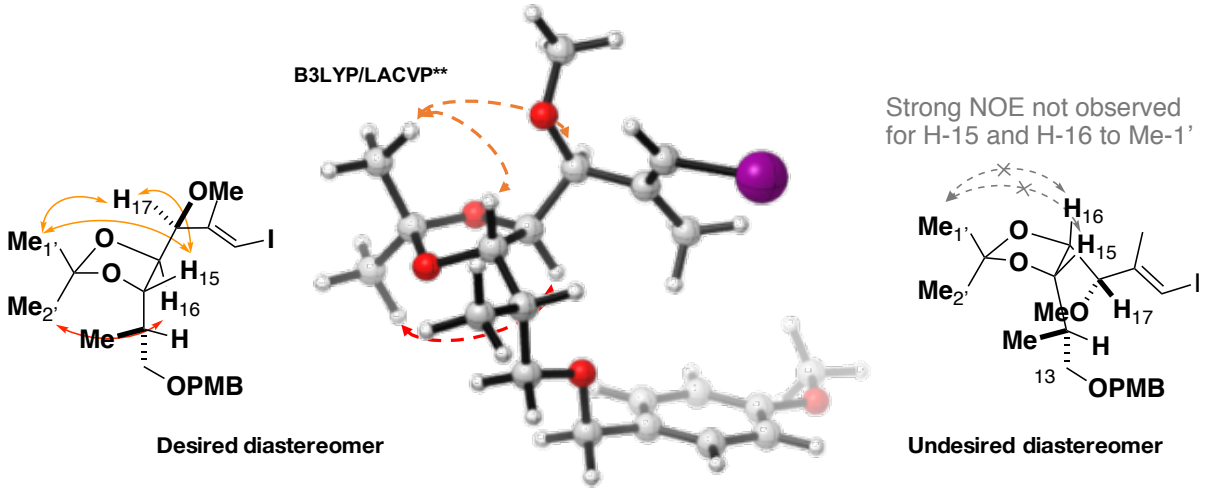


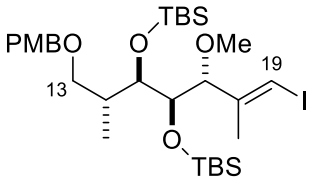
Figure SI-3. Key NOE interactions observed for acetonide **Ac-26** in support of the relative configuration

Table SI-1 Cartesian coordinates for the minimum energy conformer calculated for **Ac-26**

Atom	x	y	z
C1	-0.8357	2.2887	-2.0665
C2	-2.1881	1.5719	-1.8317
O3	-2.9191	2.4638	-0.9840
C4	-2.0865	3.5689	-0.6110
O5	-0.7600	3.1887	-0.9559
C6	-2.5197	4.8187	-1.3826
C7	-2.152	3.7513	0.9005
C8	-3.0201	1.3006	-3.1028
C9	-2.5457	0.0496	-3.8534
C10	-1.9836	0.2043	-5.0528
I11	-1.2582	-1.3675	-6.2921
C12	-2.7566	-1.2606	-3.1432
O13	-3.0265	2.4708	-3.9042
C14	-4.2206	2.6603	-4.6473
C15	0.4486	1.4414	-2.1125
C16	0.7149	0.6344	-0.8366
C17	1.6520	2.3521	-2.4163
O18	-0.1302	-0.5110	-0.8043
C19	0.0335	-1.2994	0.3735
C20	-0.8577	-2.5083	0.2677
C21	-2.1529	-2.5005	0.7871
C22	-3.0157	-3.5869	0.6177
C23	-2.5748	-4.7104	-0.0907
C24	-1.2716	-4.7379	-0.6102

C25	-0.4317	-3.6483	-0.4319
O26	-3.3265	-5.8233	-0.3297
C27	-4.6719	-5.8363	0.1191
H28	-0.8949	2.8610	-3.0016
H29	-2.0380	0.6293	-1.2999
H30	-2.4761	4.6278	-2.4570
H31	-3.5505	5.0801	-1.1244
H32	-1.8698	5.6640	-1.1363
H33	-1.8386	2.8279	1.3936
H34	-1.4923	4.5649	1.2158
H35	-3.1740	3.9885	1.2086
H36	-4.0431	1.0968	-2.7462
H37	-1.8405	1.1754	-5.5066
H38	-1.9204	-1.4727	-2.4671
H39	-2.8371	-2.0897	-3.8498
H40	-3.6667	-1.2354	-2.5336
H41	-4.0950	3.5823	-5.2205
H42	-4.4070	1.8313	-5.3431
H43	-5.0892	2.7696	-3.9824
H44	0.3330	0.7254	-2.9361
H45	0.5461	1.2670	0.0481
H46	1.7690	0.3112	-0.8184
H47	1.8159	3.0661	-1.6030
H48	2.5668	1.7660	-2.5510
H49	1.4839	2.9272	-3.3327
H50	-0.2196	-0.7030	1.2648
H51	1.0890	-1.6028	0.4704
H52	-2.5058	-1.6275	1.3313
H53	-4.0153	-3.5456	1.0343
H54	-0.9481	-5.6205	-1.1529
H55	0.5720	-3.6745	-0.8494
H56	-5.0869	-6.7938	-0.2007
H57	-4.7370	-5.7628	1.2125
H58	-5.2559	-5.0221	-0.3295

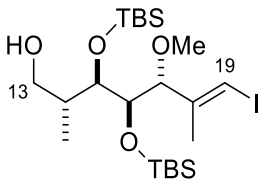
TBS ether 26a



To a solution of alcohol **26** (646 mg, 1.17 mmol, 1.0 equiv.) in CH_2Cl_2 (12 mL) at –78 °C were added TBSOTf (0.32 mL, 1.40 mmol, 1.2 equiv.) and 2,6-lutidine (0.20 mL, 1.75 mmol, 1.5 equiv.) and stirred for 1 h before the addition of NH_4Cl (10 mL). Upon warming to rt, the layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (19:1 PE/EtOAc) to give TBS ether **26a** as a pale-yellow oil (746 mg, 96%).

R_f 0.23 (19:1 PE/EtOAc); $[\alpha]_D^{20}$ – 9.8 (*c* 1.90, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 1611, 1512, 1462, 1248, 1107, 837, 775; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.26 (2H, d, *J* = 8.6 Hz, H-Ar), 6.87 (2H, d, *J* = 8.6 Hz, H-Ar), 6.19 (1H, s, H-19), 4.45 (1H, d, *J* = 11.9 Hz, OC<u>H</u>aHbAr), 4.39 (1H, d, *J* = 11.9 Hz, OCHa<u>H</u>bAr), 3.81 (3H, s, ArOC<u>H</u>$_3$), 3.74 (1H, app t, *J* = 7.7 Hz, H-17), 3.72 (1H, dd, *J* = 7.7, 2.3 Hz, H-16), 3.68 (1H, dd, *J* = 8.1, 2.3 Hz, H-15), 3.56 (1H, dd, *J* = 9.1, 3.4 Hz, H-13a), 3.24 (1H, dd, *J* = 9.1, 8.0 Hz, H-13b), 3.07 (3H, s, OC<u>H</u>$_3$), 2.06 (1H, dqdd, *J* = 8.0, 6.8, 3.4, 2.3 Hz, H-14), 1.74 (3H, s, Me-18), 1.02 (3H, d, *J* = 6.8 Hz, Me-14), 0.88 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.85 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.07 (3H, s, Si(C<u>H</u>a$_3$)(CHb$_3$)), 0.06 (3H, s, Si(C<u>H</u>a$_3$)(CHb$_3$)), 0.02 (3H, s, Si(CHa$_3$)(C<u>H</u>b$_3$)), 0.00 (3H, s, Si(CHa$_3$)(C<u>H</u>b$_3$)); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 159.0, 146.4, 131.0, 129.1, 113.7, 85.5, 82.0, 75.2, 73.9, 72.9, 72.6, 55.6, 55.3, 35.8, 26.1, 26.0, 19.4, 18.4, 18.3, 16.1, – 3.6, – 3.7, – 4.1, –4.4; **HRMS** (ES+) calc. for $C_{30}H_{56}IO_5Si_2$ $[M+H]^+$ 679.2705, found 679.2698

Alcohol 6



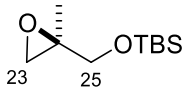
To a solution of PMB ether **26a** (720 mg, 1.08 mmol, 1.0 equiv.) in CH_2Cl_2/pH 7 buffer (9:1, 10 mL) at 0 °C was added DDQ (515 mg, 2.27 mmol, 2.1 equiv.) and stirred for 1 h. The reaction was then quenched with $NaHCO_3$ (10 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 8 mL) and combined organic layers dried over $MgSO_4$ before being concentrated *in vacuo*. The crude material was then subjected to Pinnick oxidation conditions to separate the product from the anisaldehyde by-product. The crude mixture was redissolved in *t*-BuOH (5 mL) and a solution of $NaClO_2$ (360 mg, 4.0 mmol, 3.7 equiv.) and $Na_2H_2PO_4$ (620 mg, 4.0

mmol, 3.7 equiv.) in H_2O (2 mL) added, followed by 2-methyl-but-2-ene (0.4 mL). The reaction mixture was stirred for 1 h, before being quenched with $NaHCO_3$ (5 mL) and Et_2O (5 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 5 mL). Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (9:1 $\rightarrow$ 4:1 PE/EtOAc) to give alcohol **6** as a colourless oil (542 mg, 90%).

R_f 0.34 (6:1 PE/EtOAc); $[\alpha]_D^{20}$ + 26.1 (*c* 0.15, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 3448, 1472, 1361, 1254, 1094, 834, 774; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 6.23 (1H, s, H-19), 3.84 (1H, d, *J* = 8.1 Hz, H-17), 3.73 (1H, dd, *J* = 6.2, 3.1 Hz, H-15), 3.69 (1H, dd, *J* = 8.1, 3.1 Hz, H-16), 3.61 (1H, ddd, *J* = 11.0, 7.1, 3.8 Hz, H-13a), 3.52 (1H, ddd, *J* = 11.0, 8.2, 4.2 Hz, H-13b), 3.10 (3H, s, $OC\underline{H}_3$), 2.76 (1H, br s, O-$\underline{H}$), 2.14 – 2.06 (1H, m, H-14), 1.74 (3H, s, Me-18), 0.96 (3H, d, *J* = 7.1 Hz, Me-14), 0.92 (9H, s, $SiC(C\underline{H}_3)_3$), 0.85 (9H, s, $SiC(C\underline{H}_3)_3$), 0.13 (3H, s, $Si(C\underline{H}a_3)(CHb_3)$), 0.11 (3H, s, $Si(C\underline{H}a_3)(CHb_3)$), 0.07 (3H, s, $Si(CHa_3)(C\underline{H}b_3)$), 0.00 (3H, s, $Si(CHa_3)(C\underline{H}b_3)$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 145.9, 86.2, 82.3, 73.6, 66.6, 60.4, 55.6, 36.0, 26.0, 25.9, 19.4, 18.2, 18.1, 16.7, – 3.5, – 3.9, – 4.5, – 4.6; **HRMS** (ES+) calc. for $C_{22}H_{48}IO_4Si_2$ $[M+H]^+$ 559.2130, found 559.2123.

2.3. Preparation of the C20-C25 alkene

TBS ether 28



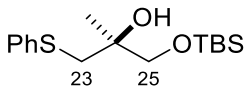
To activated powdered 3Å MS (1.50 g), were added CH_2Cl_2 (50 mL), L-(+)-diisopropyltartrate (0.13 mL, 0.60 mmol, 0.06 equiv.) and methallyl alcohol (0.84 mL, 10.0 mmol, 1.0 equiv.) at –20 °C. After stirring for 5 min, Ti(O*i*Pr)$_4$ (0.15 mL, 0.50 mmol, 0.05 equiv.) was added and the reaction mixture stirred for a further 30 min. Cumene hydroperoxide (80%, 3.60 mL, 20.0 mmol, 2.0 equiv.) was then added and the reaction flask placed in a freezer at –20 °C for 16 h. The excess peroxide was quenched with the dropwise addition of $P(OEt)_3$ (2.56 mL, 15.0 mmol, 1.5 equiv.) at –20 °C over 1 h, before Et_3N (2.14 mL, 15.0 mmol, 1.5 equiv.), DMAP (60.5 mg, 0.50 mmol, 0.05 equiv.) and TBSCl (2.26 g, 15.0 mmol, 1.5 equiv.) were added and the reaction stirred for a further h at 0 °C. Upon completion, the reaction mixture was filtered through Celite®. The filtrate was then washed with tartaric acid (10% aq, 20 mL). The layers were separated and the organic layer further washed with $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL), before being dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (20:1 $PE_{30\text{-}40}/Et_2O$) to give TBS ether **28** as a colourless oil (1.42 g, 70%).

The enantiomeric excess for the asymmetric epoxidation was determined *via* chiral HPLC by synthesising the analogous benzoate ester from methallyl alcohol (0.42 mL, 5.00 mmol, 1.0 equiv.) using the analogous procedure, substituting benzoyl chloride (0.87 mL, 7.50 mmol, 1.5 equiv.) for TBSCl to afford the benzoate ester (710 mg, 74% yield, 95% *ee*).

R_f 0.25 (9:1 PE/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 3.68 (1H, d, *J* = 11.2 Hz, H-25a), 3.62 (1H, d, *J* = 11.2 Hz, H-25b), 2.77 (1H, d, *J* = 5.0 Hz, H-23a), 2.62 (1H, d, *J* = 5.0 Hz, H-23b), 1.37 (3H, s, Me-24), 0.92 (9H, s, SiC($C\underline{H}_3$)$_3$, 0.09 (3H, s, Si($C\underline{H}a_3$)(CHb_3)), 0.08 (3H, s, Si(CHa_3)($C\underline{H}b_3$)); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 66.4, 57.0, 51.4, 25.7, 18.2, 17.9, –5.5. **R_T** (Benzoate ester, CHIRALPAK IA, 14 mL/min, 0.5% IPA/hexanes) 9.30 min (major), 10.06 min (minor).

Data in agreement with literature values.[11]

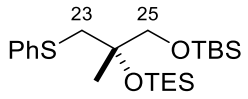
Thioether 28a



To a stirred solution of epoxide **28** (2.5 g, 12.38 mmol, 1.0 equiv.) in MeOH (70 mL) was added thiophenol (2.52 mL, 24.8 mmol, 2.0 equiv.) and Et_3N (5.17 mL, 37.1 mmol, 3.0 equiv.). The reaction mixture was stirred for 75 mins before being quenched with NH_4Cl (5 mL) and the product extracted with CH_2Cl_2 (3 x 40 mL). Combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to yield thioether **28a** as a colourless oil (3.48 g, 90%).

R_f 0.28 (9:1 PE/EtOAc); $[\alpha]_D^{20}$ – 3.9 (*c* 1.00, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 3506, 1472, 1253, 1090, 837, 777, 738, 690; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.37 – 7.09 (5H, m, H-Ar), 3.64 (1H, d, *J* = 9.4 Hz, H-25a), 3.41 (1H, d, *J* = 9.4 Hz, H-25b), 3.17 (1H, d, *J* = 12.7 Hz, H-23a), 3.11 (1H, d, *J* = 12.7 Hz, H-23b), 1.29 (3H, s, Me-24), 0.88 (9H, s, $SiC(C\underline{H}_3)_3$), 0.04 (3H, $Si(C\underline{H}a_3)(CHb_3)$), 0.03 (3H, $Si(CHa_3)(C\underline{H}b_3)$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 137.3, 129.3, 128.9, 126.0, 72.9, 68.6, 42.6, 25.9, 23.2, 18.3, –5.5; **HRMS** (ES+) calc. for $C_{16}H_{28}O_2SSiNa$ $[M+Na]^+$ 335.1471, found 335.1470.

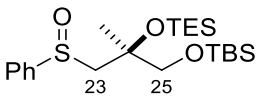
TES ether 29



A solution of alcohol **28a** (1.08 g, 3.46 mmol, 1.0 equiv.) in CH_2Cl_2 (33 mL) was cooled to –78 °C and 2,6-lutidine (0.60 mL, 5.19 mmol, 1.5 equiv.) and TESOTf (0.94 mL, 4.15 mmol, 1.2 equiv.) added. The reaction mixture was stirred for 15 min, before being stirred for a further h whilst gradually warming to rt. The reaction was then quenched with NH_4Cl (15 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash column chromatography (15:1 PE/EtOAc) to give TES ether **29** as a colourless oil (1.40 g, 96%).

R_f 0.44 (9:1 PE/EtOAc); $[\alpha]_D^{20}$ + 4.9 (*c* 1.00, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 1492, 1478, 1100, 1032, 838, 777, 735, 663; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H 7.37-7.35 (2H, m, H-Ar), 7.25-7.10 (3H, m, H-Ar), 3.64 (1H, d, *J* = 9.5 Hz, H-25a), 3.41 (1H, d, *J* = 9.5 Hz, H-25b), 3.17 (1H, d, *J* = 12.7 Hz, H-23a), 3.11 (1H, d, *J* = 12.7 Hz, H-23b), 1.29 (3H, s, Me-24), 0.94 (9H, t, *J* = 8.0 Hz, $Si(CH_2C\underline{H}_3)_3$, 0.88 (9H, s, $SiC(C\underline{H}_3)_3$), 0.58 (6H, q, *J* = 8.0 Hz, $Si(C\underline{H}_2CH_3)_3$), 0.43 (3H, s, $Si(C\underline{H}a_3)(CH_b)$), 0.42 (3H, s, $Si(CHa_3)(C\underline{H}b_3)$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 138.6, 128.7, 128.6, 125.2, 76.2, 69.1, 43.7, 25.9, 18.3, 7.1, 6.7, –5.4, –5.5; **HRMS** (ES+) calc. for $C_{22}H_{42}O_2SSi_2Na$ $[M+Na]^+$ 449.2336, found 449.2330.

Sulfoxide 29a

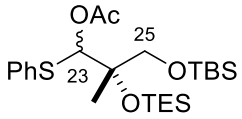


To a stirred solution of thioether **29** (500 mg, 1.17 mmol, 1.0 equiv.) in CH_2Cl_2 (12 mL) at – 5 °C was added *m*CPBA (technical grade < 77%, 263 mg, 1.17 mmol, 1.0 equiv.) in 5 portions. The reaction mixture was left to stir for 2 h before being quenched with $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 6 mL). Combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (3:1 PE/EtOAc) to give the diastereomeric sulfoxides **29a** as a colourless oil (451 mg, 88%, 95% brsm).

R_f 0.30 (2:1 PE/EtOAc); **IR** (thin film, ν_{max}/cm^{-1}): 1472, 1253, 1190, 1096, 1048, 837, 778, 745; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.64-7.45 (5H, m, H-Ar), 3.81 (0.45H, d, *J* = 9.90 Hz, H-25a), 3.69 (0.45H, d, *J* = 9.90 Hz, H-25b), 3.54 (0.55H, d, *J* = 9.7 Hz, H-25a*), 3.42 (0.55H, d, *J* = 9.7 Hz, H-25b*), 3.05-2.89 (2H, m, H-23), 1.50 (1.65H, s, Me-24*), 1.37 (1.35H, s, Me-24), 1.02-0.94 (9H, m, $Si(CH_2C\underline{H}_3)_3$), 0.91 (4H, s, $Si^*C(C\underline{H}_3)_3$), $SiC(C\underline{H}_3)_3$), 0.86 (5H, s, $SiC(C\underline{H}_3)_3$)), 0.71-0.59 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.11 (1.3H, m, $Si^*(C\underline{H}a_3)(CHb_3)$), 0.10 (1.3H, m, $Si^*(CHa_3)(C\underline{H}b_3)$), 0.03 (3.4H, $Si(C\underline{H}_3)_2$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 146.1, 146.0*, 130.5*, 130.3, 129.1, 129.1*, 123.9, 123.9*, 75.3*, 75.1, 71.0, 70.7*, 69.6*, 69.1, 25.9, 25.9*, 18.3, 18.3*, 7.1, 7.1*, 6.8, 6.7*, – 5.3*, – 5.4, – 5.4*, – 5.5; **HRMS** (ES+) calc. for $C_{22}H_{42}O_3SSi_2Na$ [M+Na]+ 465.291, found 465.2298.

* refers to the major diastereomer.

Hemithioacetal 30

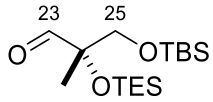


To a stirred solution of sulfoxide **29a** (2.67 g, 6.04 mmol, 1.0 equiv.) in acetic anhydride (30 mL) was added NaOAc (2.97 g, 36.2 mmol, 6.0 equiv.) and the reaction mixture heated to reflux for 16 h. After cooling to rt, the solution was diluted with CH_2Cl_2 (100 mL) and NaOH (1 M, aq, 100 mL) added slowly. After stirring for a further 30 min, the layers were separated and the aqueous layer extracted with further CH_2Cl_2 (3 x 50 mL). Combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (PE → 5:1 PE/EtOAc) to give the diastereomeric hemithioacetal **30** as a colourless oil (2.26 g, 79%, 1.6:1 *dr*).

R_f 0.41 (10:1 PE/EtOAc); **IR** (thin film, ν_{max}/cm^{-1}): 1753, 1369, 1222, 1104, 1018, 838, 776, 742 ; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.55-7.50 (2H, m, H-Ar), 7.31-7.22 (3H, m, H-Ar), 6.46 (0.5H, s, H23), 6.29 (0.5H, s, H23*), 3.92 (0.5H, d, *J* = 9.6 Hz, H-25a), 3.66 (0.5H, d, *J* = 9.7 Hz, H-25a*), 3.58 (0.5H, d, *J* = 9.7 Hz, H-25b*), 3.43 (0.5H, d, *J* = 9.6 Hz, H-25b), 2.05 (1.5H, s, $COCH_3$*), 2.03 (1.5H, s, $COCH_3$), 1.39 (1.5H, s, Me-24*), 1.32 (1.5H, s, Me-24), 1.01 (9H, q, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$), 0.91 (4.5H, s, $Si*C(CH_3)_3$), 0.90 (4.5H, s, $SiC(CH_3)_3$), 0.70-0.63 (6H, m, $Si(CH_2CH_3)_3$), 0.07 (1.5H, s, $Si*(CHa_3)_2$), 0.06 (1.5H, s, $Si*(CHb_3)_2$), 0.05 (3H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 169.7, 169.3*, 134.5, 133.9*, 132.5*, 132.0, 128.8*, 128.7, 127.5*, 127.2, 87.3, 86.3*, 78.6*, 78.4, 68.9, 68.0*, 25.9*, 25.8, 21.1*, 21.0 18.3*, 18.2, 7.1*, 7.0, 6.7, 6.7*, – 5.4, – 5.4*, – 5.5, – 5.5*; **HRMS** (ES+) calc. for $C_{24}H_{44}O_4SSi_2Na$ $[M+Na]^+$ 507.2397, found 507.2456.

* refers to the major diastereomer.

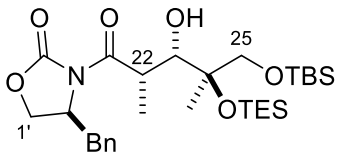
Aldehyde (*S*)-16



To a solution of thioacetal **30** (2.3 g, 4.85 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL) at –78 °C was added DIBAL (1 M in hexanes, 7.30 mL, 1.5 equiv.) dropwise and the reaction mixture stirred for 90 min at this temperature. Na_2CO_3 (30 mL) and Na/K tartrate (30 mL) were then added and the mixture left to stir for 30 min while warming to rt. The layers were then separated and the aqueous layer extracted with CH_2Cl_2 (3 x 30 mL). Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by flash column chromatography (19:1 PE/EtOAc) to give aldehyde **(*S*)-16** as a colourless oil (1.47 g, 92%).

R_f 0.21 (19:1 PE/EtOAc); $[\alpha]_D^{20}$ + 8.1 (*c* 1.00, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 1739, 1463, 1253, 1156, 1107, 1006; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 9.60 (1H, s, H-23), 3.65 (1H, d, *J* = 10.2 Hz, H-25a), 3.59 (1H, d, *J* = 10.2 Hz, H-25b), 1.26 (3H, s, Me-24), 0.96 (9H, t, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 0.62 (6H, q, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$), 0.04 (6H, s, $Si(CH_3)_2$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 204.3, 80.4, 68.5, 25.8, 20.0, 18.3, 6.9, 6.4, – 5.5, – 5.6; **HRMS** (ES+) calc. for $C_{16}H_{37}O_3Si_2$ $[M+H]+$ 333.2276, found 333.2283.

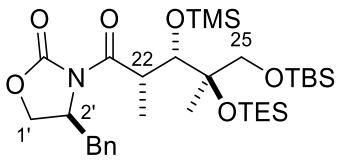
Aldol adduct 32



Oxazoline **31**[12] (211 mg, 0.90 mmol, 2.0 equiv.) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. $TiCl_4$ (105 µL, 0.95 mmol, 2.1 equiv.) was then added and the reaction mixture stirred for 65 mins with additions of DIPEA (173 µL, 1.00 mmol, 2.2 equiv.) and NMP (87 µL, 0.90 mmol, 2.0 equiv.) after 15 mins and 55 mins respectively. At this point, the reaction mixture was cooled to –78 °C and a solution of aldehyde (*S*)-**16** (150 mg, 0.45 mmol, 1.0 equiv.) in CH_2Cl_2 (1 mL) added *via* cannula. After stirring at this temperature for 2 h, the reaction mixture was quenched with NH_4Cl (3 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL) and combined organic layers dried over $MgSO_4$, with the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (6:1 PE/EtOAc) to give aldol adduct **32** as a colourless oil (198 mg, 78%, 92:8 *dr*).

R_f 0.33 (6:1 PE/EtOAc); $[\alpha]_D^{20}$ = + 15.5 (*c* 1.00, $CHCl_3$); **IR:** (thin film, ν_{max}/cm^{-1}): 3500(br), 1783, 1692, 1451, 1208, 1008, 838, 743; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.35-7.21 (5H, m, H-Ar), 4.66 (1H, qd, *J* = Hz, H-2'), 4.16-4.10 (3H, m, H-1', H-22), 3.95 (1H, dd, *J* = 10.0, 5.6 Hz, H-23), 3.79 (1H, d, *J* = 9.7 Hz, H-25a), 3.34 (1H, d, *J* = 9.7 Hz, H-25b), 3.30 (1H, dd, *J* = 13.3, 3.2 Hz, C$\underline{H}_a$H$_b$Ar), 3.02 (1H, d, *J* = 10.0 Hz, O-$\underline{H}$), 2.74 (1H, 13.3, 9.8 Hz, CH$_a$$\underline{H}_b$Ar), 1.38 (3H, s, Me-24), 1.29 (3H, d, *J* = 7.0 Hz, Me-22), 0.94 (9H, t, *J* = 8.0 Hz, Si(CH$_2$C$\underline{H}_3$)$_3$), 0.89 (9H, s, Si(C$\underline{H}_3$)$_3$), 0.59 (6H, q, *J* = 8.0 Hz, Si(C$\underline{H}_2$CH$_3$)$_3$), 0.08 (3H, s, Si(C$\underline{H}$a$_3$CHb$_3$)), 0.07 (3H, s, Si(CHa$_3$C$\underline{H}$b$_3$)); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 176.0, 153.1, 135.5 ,129.5, 128.9, 127.3, 75.0, 68.9, 65.9, 55.6, 39.2, 37.8, 25.8, 23.2, 18.2, 12.9, 7.0, 6.7, -5.6, -5.6 ; **HRMS** (ES+) calc. for $C_{29}H_{51}NO_6Si_2Na$ [M+Na]+ 588.3153, found 588.3158.

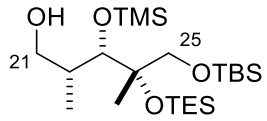
TMS ether 32a



A solution of aldol adduct **32** (217 mg, 0.38 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL) was cooled to 0 °C and imidazole (47.0 mg, 0.69 mmol, 1.8 equiv.) and TMSCl (65 µL, 0.5 mmol, 1.3 equiv.) added. The reaction mixture was left to stir for 1 h before being quenched with NH_4Cl (3 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL) and combined organic layers were dried over $MgSO_4$, before the solvent was removed *in vacuo*. The crude material was purified by flash column chromatography (9:1 PE/EtOAc) to give TMS ether **32a** as a colourless oil (217 mg, 89%).

R_f 0.35 (9:1 PE/EtOAc); $[\alpha]_D^{20}$ + 9.6 (*c* 0.97, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 1788, 1701, 1458, 1387, 1209, 1107, 1009, 838, 741; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.37-7.24 (5H, m, H-Ar), 4.71-4.67 (1H, m, H-2'), 4.24- 4.16 (4H, m, H-1', H-22, H-23), 3.69 (1H, d, *J* = 10.1 Hz, H-25a), 3.58 (1H, d, *J* = 10.1 Hz, H-25b), 3.28 (1H, dd, *J* = 13.4, 3.2 Hz, $C\underline{H}_aH_bAr$), 2.75 (1H, dd, *J* = 13.2, 9.6 Hz, $CH_a\underline{H}_bAr$), 1.22 (3H, s, Me-24), 1.20 (3H, d, *J* = 6.8 Hz, Me-22), 0.94 (9H, t, *J* = 8.0 Hz, $Si(CH_2C\underline{H}_3)_3$), 0.94 (9H, s, $Si(C\underline{H}_3)_3$), 0.63-0.55 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.21 (9H, s, $Si(C\underline{H}_3)_3$), 0.09 (3H, s, $Si(C\underline{H}a_3CHb_3)$, 0.08 (3H,s, $Si(CHa_3C\underline{H}b_3)_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 176.6, 152.9, 135.8, 129.4, 128.9, 127.2, 79.3, 74.7, 69.1, 65.8, 55.7, 38.4, 38.1, 26.0, 20.8, 18.4, 14.1, 7.1, 6.7, 0.59, –5.3, –5.5; **HRMS** (ES+) calc. for $C_{32}H_{60}NO_6Si_3$ $[M+H]^+$ 638.3723, found 638.3722.

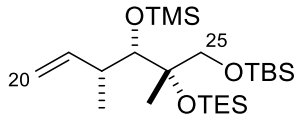
Alcohol 33



To a stirred solution of imide **32a** (210 mg, 0.33 mmol, 1.0 equiv.) in THF (3.5 mL) at 0 °C was added $LiBH_4$ (4 M in THF, 0.21 mL, 0.83 mmol, 2.5 equiv.) and MeOH (54 µL, 1.23 mmol, 4.0 equiv.) The reaction mixture was stirred for 100 min before being quenched with NH_4Cl (4 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 3 mL). The crude material was purified by column chromatography (9:1 PE/EtOAc) to give alcohol **33** as a colourless oil (129 mg, 85%).

R_f 0.33 (9:1 PE/EtOAc); $[\alpha]_D^{20}$ + 14.7 (*c* 1.00, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 3494, 1413, 1251, 1089, 1036, 884, 837, 775, 743, 668; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 3.65 (1H, d, *J* = 2.3 Hz, H-23), 3.61 (1H, d, *J* = 10.1 Hz, H-25a), 3.52-3.38 (2H, m, H-21), 3.34 (1H, d, *J* = 10.1 Hz, H-25b), 2.17-2.09 (1H, m, H-22), 1.81 (1H, t, *J* = 5.7 Hz, O-H), 1.19 (3H, s, Me-24), 0.94 (9H, t, *J* = 7.7 Hz, $Si(CH_2CH_3)_3$), 0.90 (9H, s, $Si(CH_3)_3$), 0.89 (3H, d, *J* = 7.1 Hz, Me-22), 0.62 (6H, q, *J* = 7.7 Hz, $Si(CH_2CH_3)_3$), 0.11 (9H, s, $Si(CH_3)_3$), 0.06 (3H, s, $Si(CHa_3)(CHb_3)$), 0.06 (3H, s, $Si(CHa_3)(CHb_3)$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 79.7, 77.9, 67.3, 36.8, 25.9, 23.6, 18.4, 12.9, 11.4, 7.0, 6.6, 6.5, 0.60, 0.56, – 5.5, – 5.6; **HRMS** (ES+) calc. for $C_{22}H_{52}O_4Si_3Na$ $[M+Na]^+$ 487.3066, found 487.3059.

Alkene 27



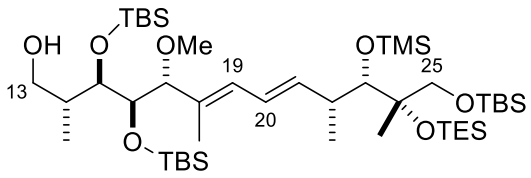
To a solution of alcohol **33** (125 mg, 0.27 mmol, 1.0 equiv.) in CH_2Cl_2 (3 mL) was added Dess-Martin Periodinane (232 mg, 0.54 mmol, 2.0 equiv.) and anhydrous $NaHCO_3$ (68.0 mg, 0.81 mmol, 3.0 equiv.) and stirred for 20 min before being quenched with $NaHCO_3$ (1 mL), and $Na_2S_2O_3$ (1 mL) and stirred for a further 10 min. The layers were then separated and the aqueous layer extracted with CH_2Cl_2 (3 x 2 mL). Combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo* to give the crude aldehyde as a colourless oil (120 mg, 96%), which was then used directly in the following reaction without further purification.

To a stirred solution of (bromomethyl)triphenylphosphonium bromide (326 mg, 0.91 mmol, 3.5 equiv.) in THF (1.5 mL) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 0.49 mL, 0.78 mmol, 3.0 equiv.) After 20 min, a solution of the crude aldehyde (115 mg, 0.26 mmol, 1.0 equiv.) in THF (1.5 mL) was added and the reaction mixture left to stir for a further hour before being quenched with PE. The precipitate was filtered through Celite® and the solvent removed *in vacuo*. The crude material was purified by flash column chromatography (PE $\rightarrow$ 20:1 PE/EtOAc) to give alkene **27** as a colourless oil (100 mg, 87%).

R_f 0.36 (20:1 PE/EtOAc); $[\alpha]_D^{20}$ + 19.7 (*c* 1.00, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 1461, 1364, 1250, 1216, 1091, 885, 836, 742; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 5.84 (1H, ddd, *J* = 17.3, 10.4, 7.0, H-21), 4.94 (1H, dt, *J* = 17.3, 1.6 Hz, H-20a), 4.92 (1H, ddd, *J* = 10.4, 1.6, 1.3 Hz, H-20b), 3.62 (1H, d, *J* = 9.7 Hz, H-25a), 3.49 (1H, d, *J* = 2.2 Hz, H-23), 3.46 (1H, d, *J* = 9.7 Hz, H-25b), 2.70-2.63 (1H, m, H-22), 1.17 (3H, s, Me-24), 0.96-0.92 (12H, m, Me-22, $Si(CH_2CH_3)_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 0.64-0.56 (6H, $Si(CH_2CH_3)_3$), 0.09 (9H, $Si(CH_3)_3$), 0.05 (3H, $Si(CHa_3)(CHb_3)$), 0.05 (3H, $Si(CHa_3)(CHb_3)$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 145.3, 112.3, 81.0, 79.7, 67.6, 37.5, 26.0, 23.7, 18.5, 14.4, 7.1, 6.8, 0.7, – 5.4, – 5.4; **HRMS** (ES+) calc. for $C_{23}H_{52}O_3Si_3Na$ $[M+Na]^+$ 483.3116, found 483.3113.

2.4. Fragment assembly

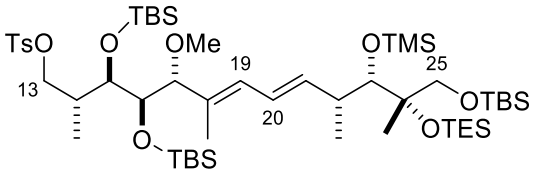
Diene 34



To a solution of alkene **27** (55 mg, 0.12 mmol, 1.0 equiv.) and vinyl iodide **6** (100.5 mg, 0.18 mmol, 1.5 equiv.) in DMF (1.0 mL) were added $Pd(OAc)_2$ (5.38 mg, 0.024 mmol, 0.2 equiv.) and Ag_2CO_3 (48.4 mg, 0.144 mmol, 1.2 equiv.). The reaction mixture was heated to 80 °C and stirred for 16 h. After cooling to rt, Et_2O (4 mL) was added and the suspension filtered through a plug of Celite®, washing with further Et_2O. The filtrate was then washed with brine (2 x 3 mL) and dried over $MgSO_4$, before being concentrated *in vacuo*. The crude material was purified by flash column chromatography (PE → 12:1 PE/EtOAc) to give diene **34** as a colourless oil (65.9 mg, 65%).

R_f 0.42 (9:1 PE/EtOAc); $[\alpha]_D^{20}$ + 16.3 (*c* 0.84, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 3471, 1470, 1463, 1361, 1251, 1091, 834, 774; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 6.18 (1H, dd, *J* = 15.0, 10.9 Hz, H-20), 5.97 (1H, d, *J* = 10.9 Hz, H-19), 5.68 (1H, dd, *J* = 15.0, 7.9 Hz, H-21), 3.76 (1H, dd, *J* = 6.2, 2.8 Hz, H-15), 3.70 (1H, dd, *J* = 8.1, 2.8 Hz, H-16), 3.65-3.59 (2H, m, H-13a, H-17), 3.63 (1H, d, *J* = 9.6 Hz, H-25a), 3.55 (1H, dd, *J* = 8.4, 4.0 Hz, H-13b), 3.49 (1H, d, *J* = 1.7 Hz, H-23), 3.43 (1H, d, *J* = 9.6 Hz, H-25b), 3.08 (3H, s, $OC\underline{H}_3$), 2.88 (1H, br s, O-$\underline{H}$), 2.77 (1H, dqd, *J* = 7.9, 6.8, 1.7 Hz, H-22), 2.17-2.10 (1H, m, H-14), 1.65 (3H, s, Me-18), 1.16 (3H, s, Me-24), 0.98 (3H, d, *J* =6.8 Hz, Me-22), 0.97-0.82 (39H, m, Me-14, 3 x $SiC(C\underline{H}_3)_3$, $Si(CH_2C\underline{H}_3)_3$), 0.62-0.57 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.14-–0.05 (27H, 3 x $Si(C\underline{H}_3)_2$, $Si(C\underline{H}_3)_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 141.4 (C-21), 132.2 (C-18), 131.4 (C-19), 123.9 (C-20), 87.3, 80.7, 79.6, 78.8, 73.4, 67.6, 66.6, 54.9, 36.8, 25.9, 25.8, 25.8, 25.7, 25.6, 23.7, 18.1, 18.0, 14.8, 11.7, 7.1, 6.7, 0.6, –3.7, –4.0, –4.7, –4.7, –5.4, –5.5; **HRMS** (ES+) calc. for $C_{48}H_{108}NO_7Si_5$ $[M+NH_4]^+$ 950.6966, found 950.6967.

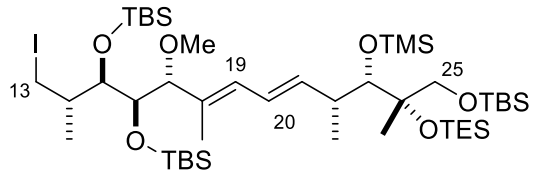
Tosylate 34a



To a stirred solution of alcohol **34** (25.0 mg, 0.029 mmol, 1.0 equiv.) in CH_2Cl_2/Py (1:1, 0.5 mL) was added tosyl chloride (16.9 mg, 0.089 mmol, 3.0 equiv.). After 4 h the reaction was quenched with $NaHCO_3$ (1 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL), combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (19:1 PE/EtOAc) to give tosylate **34a** as a colourless oil (22 mg, 75%).

R_f 0.36 (19:1 PE/EtOAc); $[\alpha]_D^{20}$ + 19.2 (*c* 0.54, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 2927, 2339, 2012, 1470, 1463, 1361, 1251, 1091, 834, 774; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.78 (2H, d, *J* = 8.2 Hz, H-Ar), 7.32 (2H, d, *J* = 8.2 Hz, H-Ar), 6.16 (1H, dd, *J* = 15.0, 10.3 Hz, H-20), 5.91 (1H, d, *J* = 10.3 Hz, H-19), 5.68 (1H, dd, *J* = 15.0, 7.8 Hz, H-21), 4.18 (1H, dd, *J* = 9.5, 3.3 Hz, H-13a), 3.85 (1H, t, *J* = 9.3 Hz, H-13b), 3.66-3.62 (3H, m, H-15, H-17, H-25a), 3.49 (1H, d, *J* = Hz, H-23), 3.47 (1H, d, *J* = 8.4 Hz, H-16), 3.42 (1H, d, *J* = 9.7 Hz, H-25b), 3.01 (3H, s, $OC\underline{H}_3$), 2.78-2.72 (1H, m, H-22), 2.44 (3H, s, $ArC\underline{H}_3$), 2.19-2.10 (1H, m, H-14), 1.61 (3H, s, Me-18), 1.54 (3H, s, Me-24), 0.99-0.78 (42H, m, Me-14, Me-22, 3 x $SiC(C\underline{H}_3)_3$), $Si(CH_2C\underline{H}_3)_3$), 0.62-0.57 (6H, m, $Si(C\underline{H}_2CH_3)_3$), 0.08- – 0.09 (27H, 3 x $Si(C\underline{H}_3)_2$, $Si(C\underline{H}_3)_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 144.5, 142.2, 141.6, 133.2, 132.4, 131.6, 129.7, 124.0, 86.6, 80.8, 79.6, 74.2, 74.1, 67.7, 62.4, 54.9, 37.0, 35.2, 29.7, 26.0, 25.9, 25.9, 23.7, 18.5, 18.3, 18.2, 14.9, 14.1, 11.7, 7.1, 6.8, 0.7, –3.7,–3.9, –4.2, –4.6, –5.3, –5.4; **HRMS** (ES+) calc. for $C_{52}H_{108}NO_9SSi_5$ $[M+NH_4]^+$ 1062.6586, found 1062.6587.

Iodide 35

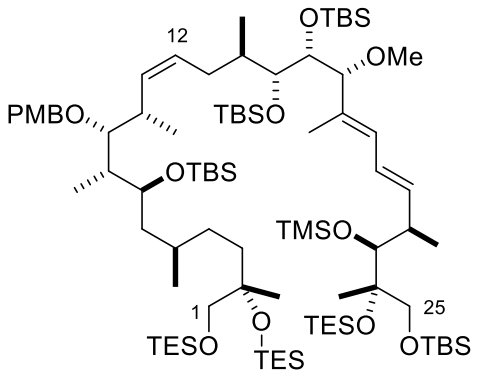


To a stirred solution of tosylate **34a** (6.0 mg, 5.7 µmol, 1.0 equiv.) in MeCN (0.15 mL) was added LiI (9.2 mg, 69 µmol, 12 equiv.) and heated to 60 °C. After 3 h a further 12 equivalents of LiI was added and the temperature raised to 70 °C before stirring for a further 2.5 h. Upon completion, the reaction mixture was cooled to rt and quenched with $NaHCO_3$ (1 mL) and diluted with Et_2O (1 mL). The layers were separated and the aqueous layer

extracted with Et_2O (5 x 1.5 mL) before combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (PE) to give iodide **35** as colourless oil (4.8 mg, 84%).

R_f 0.35 (19:1 PE/EtOAc); $[\alpha]_D^{20}$ + 8.9 (*c* 1.00, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 2956, 2369, 2162, 1420, 1251, 1102, 836, 774; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 6.18 (1H, dd, *J* = 15.1, 10.8 Hz, H-20), 5.95 (1H, d *J* = 10.8 Hz, H-19), 5.68 (1H, dd, *J* =15.1, 7.9 Hz, H-21), 3.77 (1H, dd, *J* = 7.5, 2.1 Hz, H-13a), 3.63 (1H, d, *J* = 9.6 Hz, H-25a), 3.61-3.57 (2H, m, H-13b, H-17), 3.49 (1H, d, *J* = 2.2 Hz, H-23), 3.47 (1H, dd, *J* = 9.2, 2.7 Hz, H-16), 3.42 (1H, d, *J* = 9.6 Hz, H-25b), 3.24 (1H, dd, *J* = 9.2, 6.6 Hz, H-15), 3.09 (3H, s, OC$\underline{H}_3$), 2.75 (1H, app quint, *J* = 7.9 Hz, H-22), 1.74-1.70 (1H, m, H-14), 1.66 (3H, s, Me-18), 1.54 (3H, s, Me-24), 1.03-0.83 (42H, m, Me-14, Me-22, 3 x SiC(C$\underline{H}_3$)$_3$), Si(CH$_2$C$\underline{H}_3$)$_3$), 0.62-0.57 (6H, m, Si(C$\underline{H}_2$CH$_3$)$_3$), 0.14- –0.03 (27H, 3 x Si(C$\underline{H}_3$)$_2$, Si(C$\underline{H}_3$)$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 141.5, 132.8, 131.6, 124.1, 86.8, 80.9, 79.7, 76.8, 74.8, 67.7, 55.2, 41.4, 37.0, 26.1, 26.0, 26.0, 23.8, 22.6, 18.5, 18.5, 18.3, 14.9, 14.3, 12.0, 7.2, 6.8, 0.7, –3.6, –3.8, –3.9, –4.3, –5.3, –5.4; **HRMS** (ES+) calc. for $C_{45}H_{97}IO_6Si_5Na$ $[M+Na]^+$ 1023.5068, found 1023.5069.

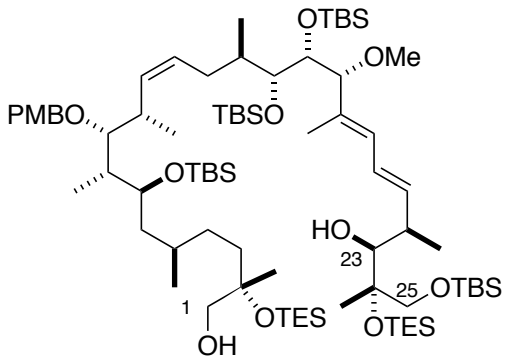
Protected C1-C25 fragment 36



A solution of iodide **35** (20.0 mg, 0.021 mmol, 1.25 equiv.) in Et_2O (0.3 mL) was stirred over crushed CaH_2 for 30 min. After cooling to –78 °C, *t*-BuLi (1.7 M in pentane, 74 µL, 0.127 mmol, 7.5 equiv.) was then added and the reaction mixture stirred for 3 min. B-Methoxy-9-BBN (1 M in hexanes, 0.21 mL, 0.212 mmol, 12.5 equiv.) was then added, followed by THF (0.3 mL). The reaction mixture was then stirred for 5 min at –78 °C before being warmed to rt and stirred for 1 h. $Pd(dppf)Cl_2$ (1.7 mg, 16.8 µmol, 0.1 equiv.), K_3PO_4 (3 M aq, 17 µL, 0.050 mmol, 3.0 equiv.), vinyl iodide **5** (14.7 mg, 0.017 mmol, 1.0 equiv.) and degassed DMF (0.3 mL) were then added. The reaction mixture was then stirred for 3 h and quenched with H_2O (1 mL). The layers were separated and the aqueous layer extracted with Et_2O (4 x 1 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (40:1 PE/Et_2O) to give the protected C1-C25 fragment **36** as a pale-yellow oil (15.1 mg, 54%).

R_f 0.69 (9:1 PE/EtOAc); $[\alpha]_D^{20}$ + 7.5 (*c* 0.72, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 3459, 2952, 2343, 1520, 1445, 1370, 1097, 834; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.25 (2H, d, *J* = 8.5 Hz, H-Ar), 6.86 (2H, d, *J* = 8.5 Hz, H-Ar), 6.19 (1H, dd, *J* = 15.0, 10.8 Hz, H-20), 5.95 (1H, d, *J* = 10.8 Hz, H-19), 5.68 (1H, dd, *J* = 15.0, 7.9 Hz, H-21), 5.55 (1H, t, *J* = 10.5 Hz, H-11), 5.30 (1H, dt, *J* = 10.5, 7.1 Hz, H-12), 4.56 (1H, d, *J* = 10.9 Hz, OCHaHbAr), 4.43 (1H, d, *J* = 10.9 Hz, OCHaHbAr), 4.13 (1H, br d, *J* = 9.8 Hz, H-7), 3.80 (3H, s ArOCH_3), 3.74 (1H, d, *J* = 8.3 Hz, H-17), 3.63 (1H, d, *J* = 9.8 Hz, H-25a), 3.61 (1H, d, *J* = 8.0 Hz, H-15), 3.57 (1H, d, *J* = 8.3 Hz, H-16), 3.50 (1H, d, *J* = 1.50 Hz, H-23), 3.42 (1H, d, *J* = 9.8 Hz, H-25b), 3.39 (1H, d, *J* = 9.5 Hz, H-1a), 3.31 (1H, d, *J* = 9.5 Hz, H-1b), 3.12-3.08 (4H, m, H-9, OCH_3), 2.76 (1H, dqd, *J* = 7.9, 7.1, 1.5 Hz, H-22), 2.71-2.65 (1H, m, H-10), 2.46 (1H, dd, *J* = 13.5, 7.1 Hz, H-13a), 1.96-1.90 (1H, m, H-8), 1.84-1.79 (1H, m, H-13b), 1.65 (3H, s, Me-18), 1.50-1.20 (8H, m, H-3, H-4, H-5, H-6, H-14), 1.16 (3H, s, Me-24), 1.15 (3H, s, Me-2), 1.04-0.80 (78H, Me-5, Me-8, Me-10, Me-14, Me-22, 4 x SiC(CH_3)$_3$), 3 x Si(CH_2CH_3)$_3$), 0.63-0.55 (18H, m, 3 x Si(CH_2CH_3)$_3$), 0.12-0.01 (33H, 4 x Si(CH_3)$_2$, Si(CH_3)$_3$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 158.7, 141.2, 135.2, 132.9, 131.6, 131.3, 128.4, 127.6, 124.2, 113.6, 86.6, 84.6, 80.9, 79.7, 76.8, 75.9, 74.0, 69.9, 69.5, 67.7, 65.9, 55.3, 55.2, 42.9, 41.4, 38.8, 37.3, 37.0, 36.4, 36.0, 33.9, 33.7, 32.0, 31.3, 29.0, 27.7, 26.2, 26.0, 25.9, 25.3, 23.8, 22.6, 20.4, 19.4, 18.8, 18.5, 18.1, 14.3, 11.9, 11.4, 10.3, 7.2, 6.8, 4.4, 0.7, –3.7, –3.8, –4.1, –4.1, –4.6, –4.6, –5.3, –5.4; **HRMS** (ES+) calc. for $C_{87}H_{178}O_{11}Si_8N$ $[M+NH_4]^+$ 1642.1884, found 1642.1881.

C1,C23 Diol 37



PPTS (one crystal) was added to a stirred solution of the protected C1-C25 fragment **36** (4 mg, 2.43 μmol) in CH_2Cl_2/MeOH (50 μL, 15 : 1) at 0 °C. MeOH was added (one drop per hour) to the stirred reaction mixture at 0 °C until the reaction was judged to be complete by TLC analysis (ca. 6 h). The reaction was diluted with EtOAc and quenched with $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 0.5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (40:1 PE/EtOAc) to give the C1,C23 diol **37** as a colourless oil (2.3 mg, 1.6 μmol, 66%).

R_f 0.34 (9:1 PE/EtOAc); $[\alpha]_D^{20}$ + 2.6 (*c* 0.04, $CHCl_3$); **IR** (thin film, ν_{max}/cm^{-1}): 3675, 2957, 2927, 2653, 1465, 1261, 1094, 1017, 801; **^{1}H NMR** (500 MHz, $CDCl_3$): δ_H 7.25 (2H, d, *J* = 8.6 Hz, H-Ar), 6.86 (2H, d, *J* = 8.6 Hz, H-Ar), 6.22 (1H, dd, *J* = 15.2, 11.0 Hz, H-20), 5.96 (1H, d, *J* = 11.0 Hz, H-19), 5.77 (1H, dd, *J* = 15.3, 8.6 Hz, H-21), 5.55 (1H, t, *J* = 10.4 Hz, H-11), 5.30 (1H, dt, *J* = 10.4, 6.8 Hz, H-12), 4.57 (1H, d, *J* = 10.7 Hz, OCHaHbAr), 4.41 (1H, d, *J* = 10.7 Hz, OCHaHbAr), 4.13 (1H, d, *J* = 8.7 Hz, H-7), 3.81 (3H, s ArOCH_3), 3.74-3.70 (2H, m, H-17, H-25a), 3.62 (1H, d, *J* = 8.4 Hz, H-15), 3.56 (1H, d, *J* = 8.4 Hz, H-16), 3.45 (1H, dd, *J* = 9.1, 4.2 Hz, H-23), 3.38 (1H, dd, *J* = 10.5, 6.7 Hz, H-1a), 3.33-3.28 (2H, m, H-1b, H-25b), 3.12-3.08 (4H, m, H-9, OCH_3), 2.69 (1H, m, H-10), 2.61 (1H, d, *J* = 9.0 Hz, OH-23), 2.52 (1H, m, H-22), 2.46 (1H, br d, *J* = 11.0 Hz, H-13a), 2.00 (1H, m, OH-1), 1.93 (1H, m, H-8), 1.82 (1H, m, H-14), 1.73 (1H, m, H-13b), 1.65 (3H, s, Me-18), 1.50-1.28 (7H, m, H-3, H-4, H-5, H-6), 1.27 (3H, s, Me-24), 1.25 (3H, s, Me-2), 1.10 (3H, d, *J* = 6.7 Hz, Me-22), 0.99-0.80 (66H, Me-5, Me-8, Me-10, Me-14, Me-22, 4 x SiC(CH_3)$_3$, 2 x Si(CH_2CH_3)$_3$), 0.63-0.55 (12H, m, 3 x Si(CH_2CH_3)$_3$), 0.12-0.01 (24H, 4 x Si(CH_3)$_2$); **^{13}C NMR** (125 MHz, $CDCl_3$): δ_C 158.8, 139.8, 135.2, 131.6, 131.5, 131.2, 128.3, 127.7, 124.3, 113.6, 86.5, 84.6, 78.2, 77.2, 77.1, 76.4, 74.0, 69.9, 69.4, 68.8, 68.2, 55.3, 55.3, 42.9, 42.8, 38.6, 38.3, 37.6, 36.0, 33.9, 33.4, 32.8, 31.3, 29.7, 26.3, 26.0, 25.9, 25.9, 24.3, 22.9, 19.3, 18.6, 18.5, 18.2, 18.1, 15.7, 13.6, 10.3, 10.2, 7.1, 6.8, 1.0, –3.6, –3.6, –4.1, –4.1, –4.6, –4.6, –5.4, –5.5; **HRMS** (ES+) calc. for $C_{78}H_{160}O_{11}Si_6N$ $[M+NH_4]^+$ 1455.0601, found 1455.0576.

3. References

(1) Armarego, W.; Chai, C. *Purification of Laboratory Chemicals*; 2012.

(2) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43* (14), 2923–2925.

(3) Lam, L. K. P.; Hui, R. A. H. F.; Jones, J. B. *J. Org. Chem.* **1986**, *51* (11), 2047–2050.

(4) Lehr, K.; Mariz, R.; Leseurre, L.; Gabor, B.; Fürstner, A. *Angew. Chem. Int. Ed.* **2011**, *50* (48), 11373–11377.

(5) Herold, P.; Mohr, P.; Tamm, C. *Helv. Chim. Acta* **1983**, *66* (3), 744–754.

(6) Lee, E.; Lee, Y. R.; Moon, B.; Kwon, O.; Shim, M. S.; Yun, J. S. *J. Org. Chem.* **1994**, *59* (6), 1444–1456.

(7) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123* (39), 9535–9544.

(8) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Lim, J. H.; Maltas, P.; Loiseleur, O.; Genovino, J.; Moessner, C. *Org. Biomol. Chem.* **2012**, *10* (30), 5861–5872.

(9) Baker, R.; Castro, J. L. *J. Chem. Soc. Perkin Trans. 1* **1990**, *0* (1), 47.

(10) Koukal, P.; Ulč, J.; Nečas, D.; Kotora, M. *Eur. J. Org. Chem.* **2016**, *2016* (12), 2110–2114.

(11) Savle, P. S.; Medhekar, R. A.; Kelley, E. L.; May, J. G.; Watkins, S. F.; Fronczek, F. R.; Quinn, D. M.; Gandour, R. D. *Chem. Res. Toxicol.* **1998**, *11* (1), 19–25.

(12) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103* (8), 2127–2129.

(13) *MacroModel, Version 9.9, Schrodinger LLC*; New York, 2012.

(14) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111* (12), 4379–4386.

(15) Kolossváry, I.; Guida, W. C. *J. Am. Chem. Soc.* **1996**, *118* (21), 5011–5019.

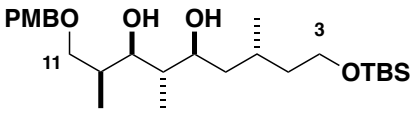
(16) Halgren, T. A. *J. Comput. Chem.* **1996**, *17* (5–6), 490–519.

(17) *Maestro, version 9.3, Schrodinger LLC,*; New York, 2012.

(18) Becke, A. D. *J. Chem. Phys.* **1993**, *98* (7), 5648–5652.

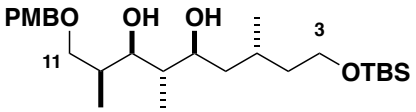
(19) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98* (45), 11623–11627.

4. ^{1}H and ^{13}C NMR spectra for new compounds



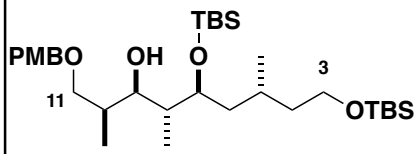
19

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



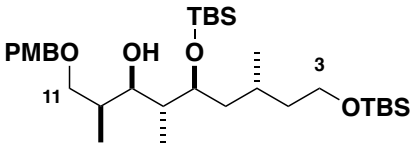
19

^{13}C NMR ($CDCl_3$, 125 MHz)



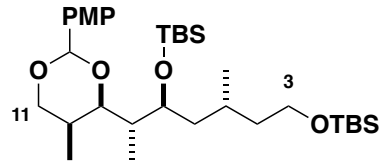
19a

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



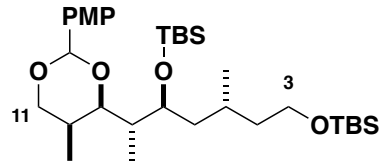
19a

^{13}C NMR ($CDCl_3$, 125 MHz)



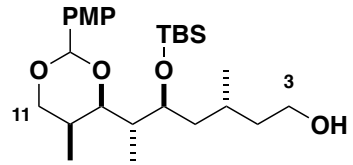
20

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



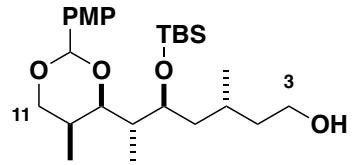
20

^{13}C NMR ($CDCl_3$, 125 MHz)



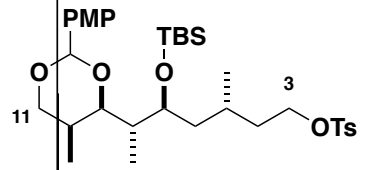
20a

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



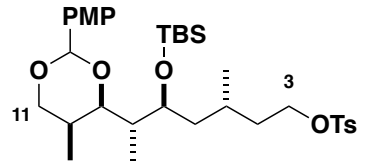
20a

^{13}C NMR ($CDCl_3$, 125 MHz)



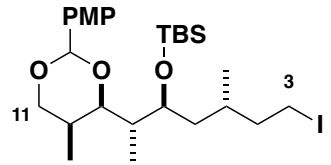
20b

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



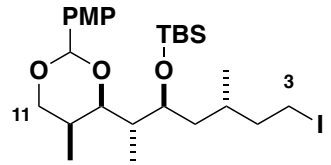
20b

^{13}C NMR ($CDCl_3$, 125 MHz)



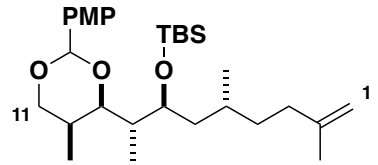
21

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



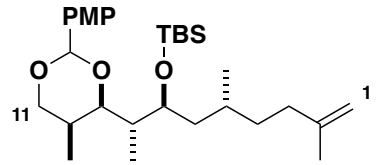
21

^{13}C NMR ($CDCl_3$, 125 MHz)



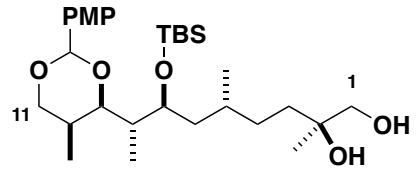
22

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



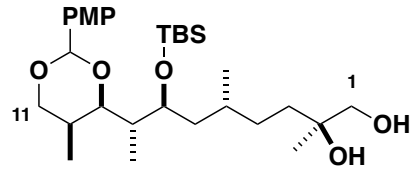
22

^{13}C NMR ($CDCl_3$, 125 MHz)



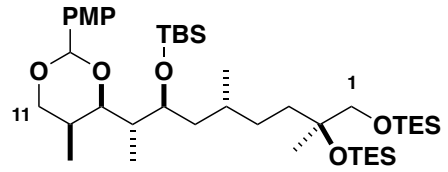
22a

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



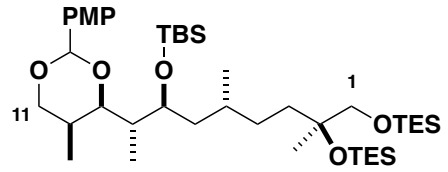
22a

^{13}C NMR ($CDCl_3$, 125 MHz)



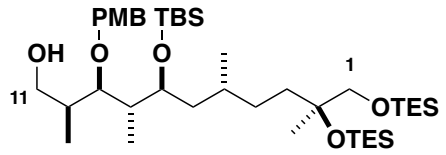
22b

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



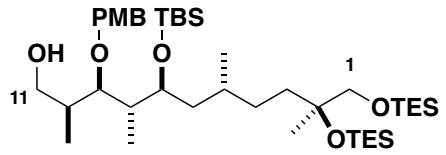
22b

^{13}C NMR ($CDCl_3$, 125 MHz)



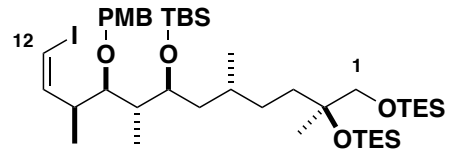
23

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



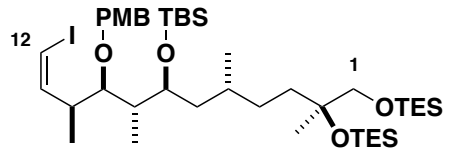
23

^{13}C NMR ($CDCl_3$, 125 MHz)



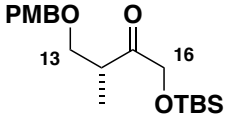
5

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



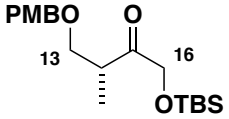
5

^{13}C NMR ($CDCl_3$, 125 MHz)



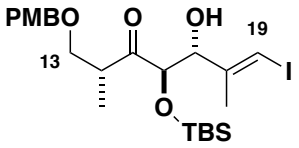
12

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



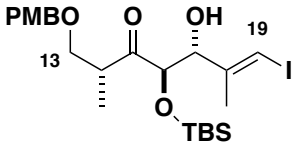
12

^{13}C NMR ($CDCl_3$, 125 MHz)



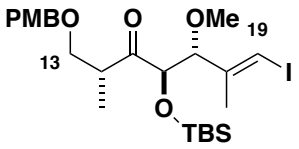
25

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



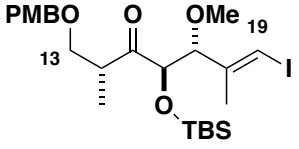
25

^{13}C NMR ($CDCl_3$, 125 MHz)



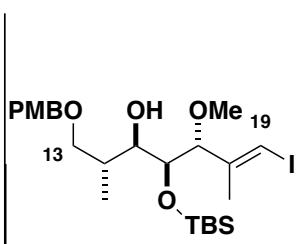
25a

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



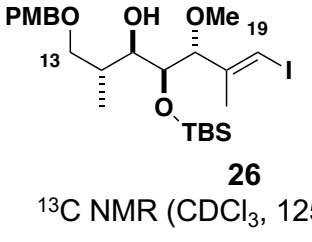
25a

^{13}C NMR ($CDCl_3$, 125 MHz)



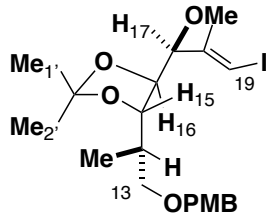
26

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



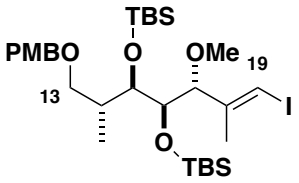
26

^{13}C NMR ($CDCl_3$, 125 MHz)



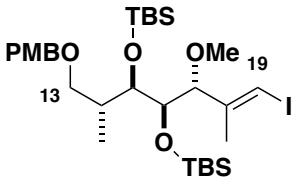
Ac-26

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



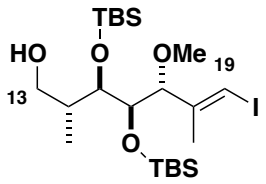
26a

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



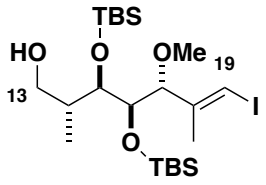
26a

^{13}C NMR ($CDCl_3$, 125 MHz)



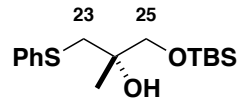
6

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



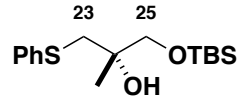
6

^{13}C NMR ($CDCl_3$, 125 MHz)



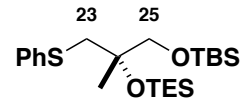
28a

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



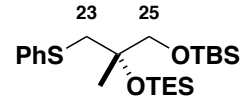
28a

^{13}C NMR ($CDCl_3$, 125 MHz)



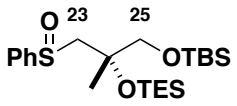
29

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



29

^{13}C NMR ($CDCl_3$, 125 MHz)

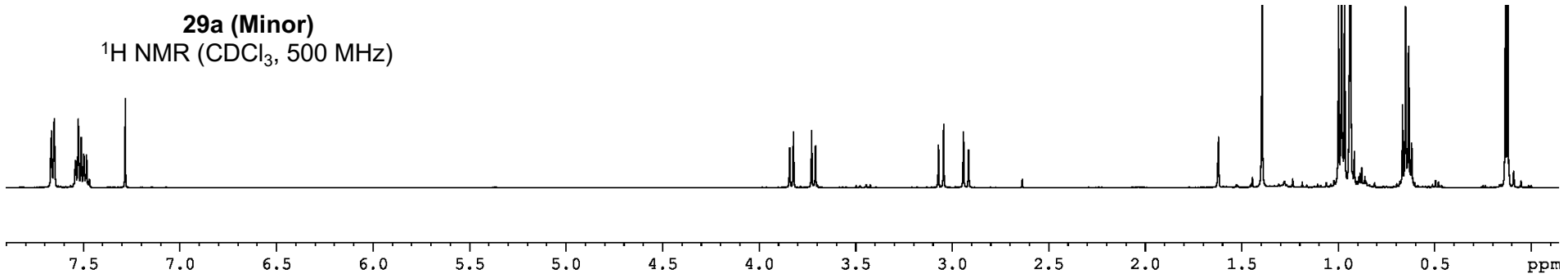


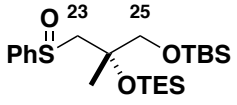
29a (Major)

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

29a (Minor)

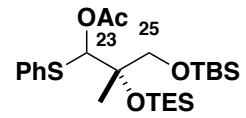
^{1}H NMR ($CDCl_3$, 500 MHz)





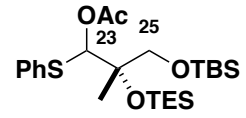
29a

^{13}C NMR ($CDCl_3$, 125 MHz)



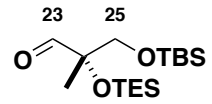
30

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



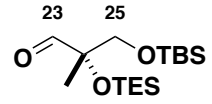
30

^{13}C NMR ($CDCl_3$, 125 MHz)



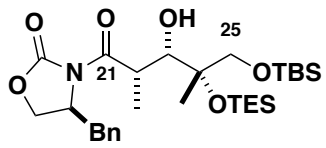
(*S*)-16

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



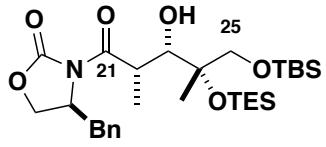
(*S*)-16

^{13}C NMR ($CDCl_3$, 125 MHz)



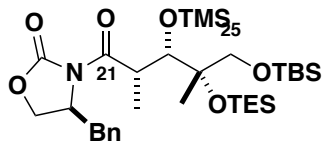
32

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



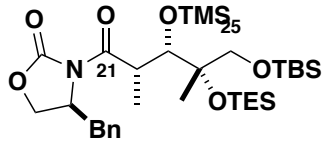
32

^{13}C NMR ($CDCl_3$, 125 MHz)



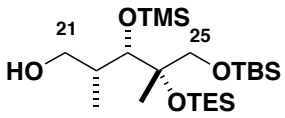
32a

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



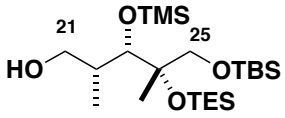
32a

^{13}C NMR ($CDCl_3$, 125 MHz)



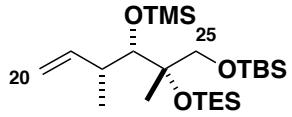
33

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



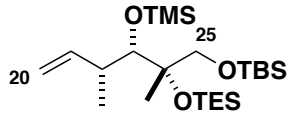
33

^{13}C NMR ($CDCl_3$, 125 MHz)



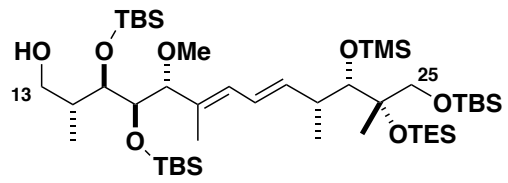
27

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



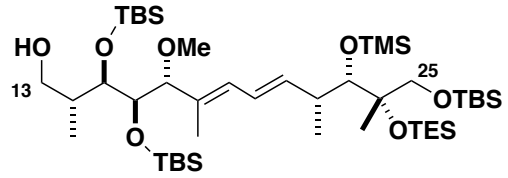
27

^{13}C NMR ($CDCl_3$, 125 MHz)



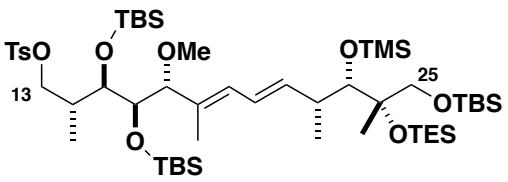
34

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



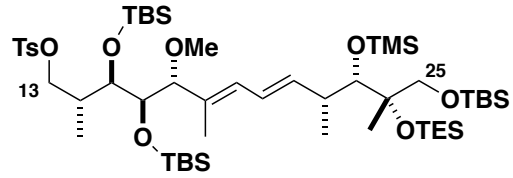
34

^{13}C NMR ($CDCl_3$, 125 MHz)



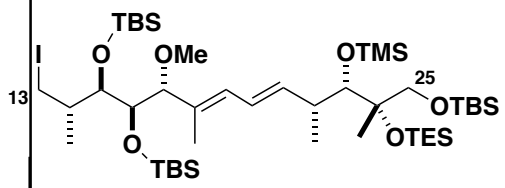
34a

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



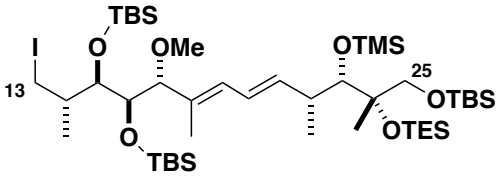
34a

^{13}C NMR ($CDCl_3$, 125 MHz)



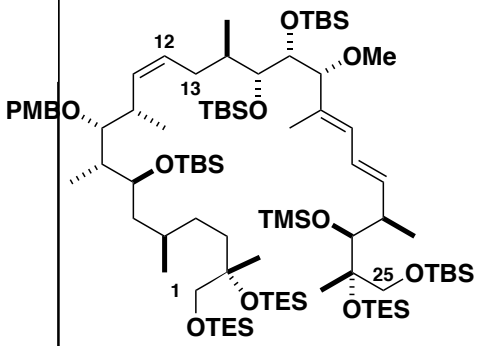
35

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



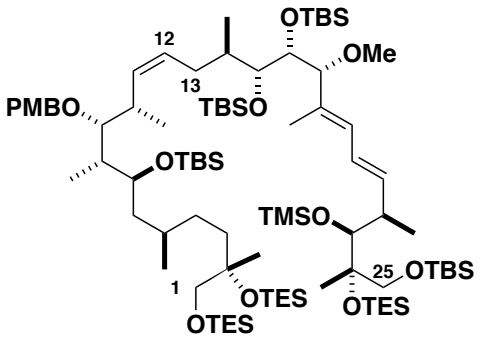
35

^{13}C NMR ($CDCl_3$, 125 MHz)



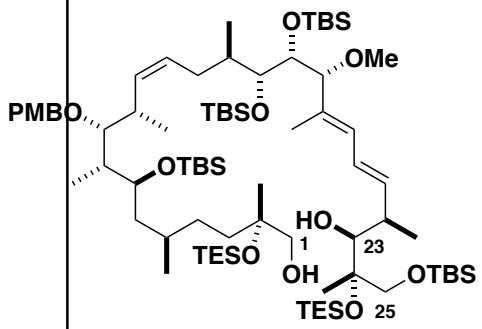
36

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



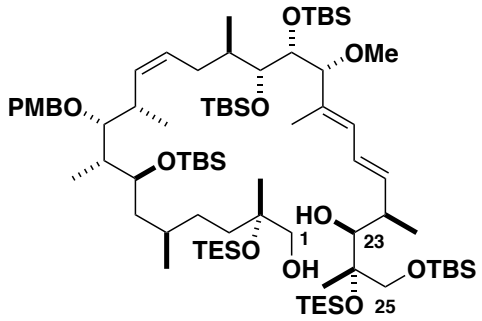
36

^{13}C NMR ($CDCl_3$, 125 MHz)



37

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



37

^{13}C NMR ($CDCl_3$, 125 MHz)