Synthesis of 35-Deoxy Amphotericin B Methyl Ester: A Strategy for Molecular Editing

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Supporting Information

General Methods

All non-aqueous reactions were carried out using oven-dried or flame-dried glassware under a positive pressure of dry nitrogen or argon unless otherwise noted. Tetrahydrofuran, acetonitrile, toluene, Et₂O, and CH₂Cl₂ were purified by distillation and dried by passage over activated alumina under an argon atmosphere (H₂O content <30 ppm, Karl-Fischer titration).¹ Triethylamine and pyridine were distilled from KOH. n-Butyl lithium was titrated with s-BuOH/phenanthroline).² Except as indicated otherwise, reactions were magnetically stirred and monitored by thin layer chromatography (TLC) using Merck Silica Gel 60 F254 plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained using ceric ammonium molybdate or potassium permanganate stain. Chromatographic purification of products was performed on E. Merck Silica Gel 60 (230–400 mesh) using a forced flow of eluant at 0.3–0.5 bar pressure.³ Concentration under reduced pressure was performed by rotary evaporation at 40 °C (unless otherwise specified) at the appropriate pressure. Optical rotations were measured on a Jasco DIP-1000 polarimeter operating at the sodium D line with a 100 mm path length cell. NMR spectra were recorded on a Varian Mercury 300 spectrometer operating at 300 MHz and 75 MHz or Bruker instruments operating at 600 Mhz and 150 Hz for ¹H and ¹³C acquisitions, respectively. Chemical shifts are reported in ppm with the solvent resonance as the internal standard. Data are reported as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constants in Hz. IR spectra were recorded on a PerkinElmer Spectrum RXI FT-IR spectrophotometer. Absorptions are given in wavenumbers (cm⁻¹). Mass spectra were recorded by the MS service at ETH Zurich. EI-MS: VG-TRIBRID spectrometer; spectra were measured at 70 eV. MALDI-MS: IonSpec Ultima Fourier Transform Mass Spectrometer.

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Preparation of the C(1)-C(7) and C(8)-C(13) sub-units 7 and 8

S-Malic acid dimethyl ester (2)$^4$

![Chemical Structure](image)

100 g (745.9 mmol, 1 equiv.) of S-malic acid was dissolved in 1.5 L methanol and cooled to 0 °C. Thionyl chloride (119.8 mL, 1.64 mol, 2.2 equiv.) was added over 65 min using a dropping funnel. The reaction mixture was stirred for 1 hour at 0 °C and 1 hour at room temperature at which time the reaction was complete. Nitrogen was bubbled through the reaction mixture for 12 h, to ensure removal of HCl and sulfur dioxide. The solvent was removed under reduced pressure to afford 122 g of clear oil, which was taken to the next step without further purification.

$^1$H NMR (300 MHz, CDCl$_3$) δ 4.50 (dd, 1 H, J = 10.2, 5.7 Hz), 3.81 (s, 3 H), 3.71 (s, 3 H), 3.23 (d, OH, J = 5.4 Hz), 2.88 (dd, J = 4.4, 16.4, 1H), 2.79 (dd, J = 6.0, 16.5, 1H).

(S)-Methyl 4-[(tert-butyl)dimethylsilyloxy]-3-hydroxybutanoate (3)$^{5,6}$

![Chemical Structure](image)

S-malic acid dimethyl ester (50.3 g, 310 mmol) was dissolved in 500 mL THF and cooled to 0 °C. Borane dimethyl sulfide (30.9 mL, 325.8 mmol, 1.05 equiv.) was added over 20 min. The reaction mixture was then allowed to stir during 1 h. NaBH$_4$ (587 mg, 15.5 mmol, 0.05 equiv.) was added slowly using a solid addition funnel over 50 min at 0 °C (Caution fervent hydrogen evolution!). The reaction mixture was stirred for 45 min at 0 °C at which time gas evolution subsided. The ice bath was removed and the reaction stirred 1 h at room temperature. The organic volatiles were removed in vacuo and the product azeotroped 3 times with methanol and once with toluene to afford the product as an yellowish oil that was used directly in the next step.

Crude diol (2.5 g, 18.5 mmol) prepared as described above was dissolved in 30 mL dry dichloromethane. Imidazole (2.6 g, 38.85 mmol, 2.1 equiv.) was added followed by addition of a solution of TBSCl (2.9 g, 19.4 mmol, 1.05 equiv.) dissolved in 20 mL dichloromethane over 2 h using a dropping funnel. The mixture was stirred for 12 h at room temperature. Stirring was then stopped and the white salt was allowed to deposit. After filtration through a pad of celite dichloromethane was evaporated and the crude material dissolved into 2 L of ethyl acetate, washed twice with a 1 M HCl solution, followed by sat. NaHCO$_3$ solution and brine. The organic phase was dried over sodium sulfate and the volatiles evaporated. The product was used in the next step without further purification.

$^1$H NMR (300 MHz, CDCl$_3$) δ 4.11 (m, 1 H), 3.70 (s, 3 H), 3.65-3.54 (m, 2 H), 2.58-2.44 (m, 2 H), 0.89 (s, 9 H), 0.06 (s, 6 H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 172.4, 68.6, 66.2, 51.8, 37.9, 26.0, 18.4, -5.3.

Optical Rotation: [α]$^{19}$D (c 0.94, CHCl$_3$) -12.7°.

IR (thin film) ν 3469, 2955, 2930, 2858, 1740, 1472, 1438, 1362, 1256, 1170, 1121, 1074, 939, 837, 785, 669 cm$^{-1}$.

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(S)-tert-butyl 6-[(tert-butyl)dimethylsilyloxy]-5-hydroxy-3-oxohexanoate (4)\(^7\)

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{OH} & \quad \text{t-BuO}_2\text{C} & \quad \text{OH} \\
\text{TBS} & & \text{TBS}
\end{align*}
\]

225 mL (1.61 mol, 4.0 equiv.) of diisopropyl amine dissolved in 1400 mL of analytical THF (water content <200 ppm) were cooled to -78 °C and 644 mL (1.61 mol, 4.0 equiv.) of a 2.5 M BuLi solution in hexane were added dropwise over 45 min. After stirring at -78 °C for 30 minutes, 217.5 mL (1.61 mol, 4.0 equiv.) of tert-butyl acetate were added dropwise over 45 min. The reaction mixture was stirred for an additional 20 min and then 100 g (402.2 mmol, 1 equiv.) of crude methyl ester dissolved in 300 mL THF was added dropwise over 45 minutes. The temperature was allowed to rise until -55 °C during the addition. The cooling bath was removed and the reaction mixture was allowed to warm to -10 °C over 4 h. Then 500 mL of 10% HCl was added over 30 min from a dropping funnel. The temperature was allowed to reach 10 °C during the addition and the pH reached 2. The reaction mixture was transferred into a separation funnel and the phases were separated. The organic phase was washed with additional 2x200+2x50 mL 10% HCl until the pH of the water phase after separation reached 4.5. The combined water phases were extracted with 3x150 mL 50% THF/hexane. The combined organic phases were shaken with 50 mL sat. NaHCO\(_3\) for 5 min. and the water phase extracted with additional 4x150 mL diethyl ether. The combined organic phases were dried (Na\(_2\)SO\(_4\)) and the solvent removed under reduced pressure. Flash chromatography (gradient 10%-50% diethyl ether/ pentane) afforded 50 g (69 %, three steps, d.r. syn/anti ca. 15:1) of product.

Optical Rotation: \(\alpha\)-tert-butyl 6-[(tert-butyl)dimethylsilyloxy]-5-hydroxy-3-oxohexanoate (4) -17.4°.

\[^1\]H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.14-4.06 (m, 1 H), 3.62-3.50 (m, 2 H), 3.40 (s, 2 H), 2.70 (d, 2 H, \(J = 6.9\) Hz), 1.45 (s, 9 H), 0.88 (s, 9 H), 0.05 (s, 6 H).

\[^{13}\]C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 202.8, 166.1, 82.1, 68.1, 66.2, 51.3, 46.0, 28.1, 26.0, 18.4, -5.3.

IR (thin film) \(\nu\) 3474, 2955, 2931, 2858, 1735, 1715, 1647, 1472, 1464, 1409, 1393, 1369, 1323, 1255, 1149, 1118, 1074, 1006, 958, 838, 778, 671 cm\(^{-1}\).

tert-Butyl 2-((4R,6S)-6-[(tert-butyl)dimethylsilyloxy]-2,2-dimethyl-1,3-dioxan-4-yl)acetate (5)

\[
\begin{align*}
\text{t-BuO}_2\text{C} & \quad \text{OH} & \quad \text{t-BuO}_2\text{C} \\
\text{TBS} & & \text{TBS}
\end{align*}
\]

117 mL (481.6 mmol, 1.60 equiv.) of tributyl borane were dissolved in 750 mL dry THF and 195 mL (ca. 20.0 equiv.) of dry methanol under argon atmosphere. The resulting mixture was stirred for 10 h. Hydroxyester (100 g, 301 mmol, 1.0 equiv.) dissolved in 100 mL dry THF was added over about five minutes and the mixture stirred for 30 min. The reaction mixture was then cooled to -78 °C. Powdered NaBH\(_4\) (2.28 g, 60 mmol, 2.0 equiv.) was then added over 20 min. via a solid addition funnel (CAUTION! Gas evolution) and the mixture stirred for about 3 h. At -78 °C. Acetone (220 mL, 3 mol) was then added at rate that ensured that the internal temperature did not exceed -40 °C. The reaction mixture was poured into water (800 mL) and 500 mL diethyl ether added. The phases were separated and the water phase extracted with additional 4x150 mL diethyl ether. The combined organic phases were dried (Na\(_2\)SO\(_4\)) and the solvent removed under reduced pressure. The residue was dissolved in methanol (400 mL) and 100 mL 30% H\(_2\)O\(_2\) was added. The resulting solution was stirred for 13 h. and then concentrated. The residue was dissolved in diethyl ether (500 mL) and 500 mL sat. NaHCO\(_3\) was added. The phases were separated and the water phase extracted with additional 4x150 mL diethyl ether. The combined organic phases were dried (Na\(_2\)SO\(_4\)) and the solvent removed under reduced pressure. The crude material was treated with five times with 400 mL methanol to remove any residual borate. Toluol was finally used to remove any trace of water. Residual solvent was removed at high vacuum to afford 92 g of crude diol.

60 g of the crude diol from the batch described above was dissolved in 360 mL dichloromethane under an argon atmosphere and cooled to -35 °C. 20.27 mL (215.4 mmol, 1.20 equiv.) of methoxypropene was added, followed by PPTS (0.9 g, 3.6 mmol, 0.02 equiv.). The reaction mixture was allowed to warm to room temperature over 2.5 h. The reaction was quenched by the addition of triethyl amine (ca. 5 mL) and additional dichloromethane (500 mL) was added. The organic solution was washed with water (150 mL). The organic phase was dried over sodium sulfate and the solvent removed at reduced pressure. Flash chromatography (gradient 10%-50% diethyl ether/ pentane) afforded 50 g (69 %, three steps, d.r. syn/anti ca. 15:1) of product.

\[ R_f = 0.85 \text{ (30\% EtOAc/hexane; CAM).} \]

**Optical Rotation:** \([\alpha]_{D}^{25} \text{ (c 1.21, CHCl}_3 \text{) } -6.9^\circ.\]

**1H NMR** (300 MHz, CDCl\(_3\)) \(\delta 4.30-4.21\text{ (m, 1 H)}, 3.95-3.88\text{ (m, 1 H)}, 3.65\text{ (dd, 1 H, } J = 10.2, 5.4 \text{ Hz)}, 3.45\text{ (dd, 1 H, } J = 6.3, 3.6 \text{ Hz)}, 2.47-2.27\text{ (m, 2 H)}, 1.69-1.63\text{ (m, 1 H)}, 1.44\text{ (s, 3 H)}, 1.43\text{ (s, 9 H)}, 1.35\text{ (s, 3 H)}, 1.21-1.09\text{ (m, 1 H)}, 0.87\text{ (s, 9 H)}, 0.04\text{ (s, 6 H).}

**13C NMR** (75 MHz, CDCl\(_3\)) \(\delta 170.0, 98.5, 80.5, 69.7, 66.8, 66.1, 42.9, 33.4, 30.0, 28.2, 26.0, 19.8, 18.4, -5.1.

**IR** (thin film) \(\nu 2956, 2930, 2858, 1732, 1473, 1380, 1368, 1314, 1256, 1201, 1152, 1115, 1038, 992, 950, 836, 666 \text{ cm}^{-1}.

\((4S,6S)-6-(2-(Benzyloxy)ethyl)-4\text{-[(tert-butyl)dimethylsilyloxy]-2,2-dimethyl-1,3-dioxane (6)}\)

159 mL (158.7 mmol, 1 equiv.) of a 1 M solution of lithium aluminiumhydride in THF were added drop wise to 59.47 g (158.7 mmol, 1 equiv.) of \(t\)-butylester dissolved in 1 l of dry THF at –10 °C under argon atmosphere. The reaction mixture was stirred for the subsequent 2.5 h, quenched carefully with 100 mL of acetone and after 15 min with 75 g of sodium sulfate decahydrate. After about 4 h dry sodium sulfate was added and the mixture filtered over a pad of sodium sulfate. After evaporation of the solvents the crude material was dried further with toluene and finally taken to the next step.

The crude alcohol was dissolved in a minimal amount of dry THF and added drop wise to 4.57 g (190.4 mmol, 1.2 equiv.) of sodium hydride (95%), 37 mL (317.4 mmol, 2 equiv.) of benzylbromide and 58.6 g (158.7 mmol, 1 equiv.) tetrabutylammonium iodide dissolved in a 10:1 THF / DMF solution (800 mL, 0.25 M) at 0 °C under argon. After 24 h TLC showed almost complete conversion and 500 mL of sat. aq. NaHCO\(_3\) were poured into the reaction followed by 1000 mL of hexane and 200 mL of EtOAc. After 15 minutes stirring the two phases were separated and the aqueous phase was washed twice with 100 mL of 1:1 EtOAc/hexane. The organic phases were collected and dried over Na\(_2\)SO\(_4\). After evaporation of the volatiles and purification by column chromatography (3% then 25% EtOAc/hexane) 54.86 g (139.02 mmol, 88%) were isolated.

\( R_f \text{ (alcohol) } = 0.27 \text{ (30\% EtOAc/hexane; CAM).} \)

**Optical Rotation:** \([\alpha]_{D}^{25} \text{ (c 1.02, CHCl}_3 \text{) } -21.1^\circ.\]

**1H NMR** (300 MHz, CDCl\(_3\)) \(\delta 7.36-7.26\text{ (m, 5 H)}, 4.53\text{ (d, 1 H, } J = 12.3 \text{ Hz)}, 4.48\text{ (d, 1 H, } J = 12.0 \text{ Hz)}, 4.11-4.02\text{ (m, 1 H)}, 3.96-3.87\text{ (m, 1 H)}, 1.81-1.74\text{ (m, 2 H)}, 1.63-1.57\text{ (m, 1 H)}, 1.43\text{ (s, 3 H)}, 1.37\text{ (s, 3 H)}, 1.26-1.09\text{ (m, 1 H)}, 0.89\text{ (s, 9 H)}, 0.06\text{ (s, 6 H).}

**13C NMR** (75 MHz, CDCl\(_3\)) \(\delta 138.4, 128.2, 127.5, 127.4, 98.4, 73.0, 69.9, 67.0, 65.9, 36.7, 34.0, 30.1, 26.0, 20.0, 18.5, -5.3.

**IR** (thin film) \(\nu 2992, 2953, 2928, 2857, 1472, 1379, 1255, 1201, 1172, 1108, 1028, 1005, 938, 837, 781, 735, 697, 667 \text{ cm}^{-1}.

\((4S,6S)-6-(2-(Benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)methanol\)

70% HF-pyridine complex (148 mL) was added slowly to 148 mL pyridine at 0°C in a plastic vessel (CAUTION exothermic!). 65 g (164.9 mmol, 1 equiv.) of TBS-protected alcohol was dissolved in 600 mL of THF and cooled to 0 °C. The HF/pyridine mixture was added over 10 min using a cannula. The reaction mixture was stirred at 0 °C for 20 min. and room temperature for 3 h. Then it was cannulated carefully into a 1.5L suspension/solution of Na\(_2\)CO\(_3\) (500 g) over 10 min. The mixture was stirred an additional 10 min and then diethyl ether (1000 mL was added). The phases were separated and the water phase extracted with additional 2x250 mL diethyl ether. The combined organic phases were washed with brine (500 mL), dried (Na\(_2\)SO\(_4\)) and concentrated to afford 46 g of essentially pure alcohol which was used in the next step without further purification. \( R_f = 0.10 \text{ (30\% EtOAc/hexane; CAM).} \)

**References**


[9] Purification by column chromatography can be performed with 10→50% EtOAc/hexane (step 20%). Yield >90%.

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.36-7.28 (m, 5 H), 4.68-4.63 (m, 1 H), 4.52 (d, 1 H, J = 12.3 Hz), 4.48 (d, 1 H, J = 15.3 Hz), 4.10-4.01 (m, 1 H), 4.63-3.49 (m, 2 H), 2.46 (d, 1 H, J = 2.1 Hz), 1.85-1.57 (m, 3 H), 1.45 (s, 3 H), 1.43 (s, 3 H).

$^13$C NMR (75 MHz, CDCl$_3$) δ 138.3, 128.3, 127.6, 127.5, 99.3, 82.6, 73.1, 72.7, 65.9, 65.6, 60.3, 37.4, 36.3, 30.2, 19.6.

IR (thin film) ν 3401, 3088, 3064, 3031, 2993, 2941, 2924, 2864, 2125, 1955, 1876, 1813, 1721, 1604, 1586, 1496, 1454, 1380, 1363, 1329, 1260, 1201, 1165, 1099, 1056, 1029, 1008, 996, 959, 918, 874, 818, 775, 739, 699, 665 cm$^{-1}$.

118 mL (1.62 mol, 1 equiv.) of thionyl chloride were added drop wise to 300 g (1.46 mol, 1 equiv.) of L- (+)-diethyl tartrate over 15 min. After that 1.5 mL of DMF were carefully added and the result heated at 50 °C until the HCl gas evolution stopped (about 50 min). After cooling to 0 °C, 1.50 mL of acetone were added followed by 240 g (2.76 mmol, 1.9 equiv.) of anhydrous LiBr via solid addition funnel over 15 min. The solution was heated 4 h to 45 °C and turned from light green to yellow. After oil bath removal, 225 g (3.44 mol, 2.4 equiv.) of activated zinc was slowly added followed by 5 mL of water. The result was stirred at 45 °C for 1.5 h whereupon 50 mL of water were added and stirring at 45 °C was continued for the subsequent 6 h. Addition of 1000 mL of acetone was followed by filtration through a pad of celite. The remnant cake was washed with 250 mL of water and 250 mL of EtOAc. To this bi-phase 1750 mL of 2% aq. HCl were added (pH = 3) and acetone was evaporated. The aq. phase was washed three times with 1000 mL of EtOAc and the organic layers washed with brine and dried over Na$_2$SO$_4$. After evaporation of the volatiles and distillation of the crude material (80 °C, 0.4 mbar; bath temperature not higher than 120 °C) 195 g (1.03 mol, 71%) of D-malic acid diethyl ester were obtained as clear oil.

$R_D = 0.50$ (30% EtOAc/hexane; KBr).

Optical Rotation: $[\alpha]^{23}_D$ (c 2.15, EtOH) +11.2°.

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[12] Zinc was stirred with 10% HCl in water for 10 min, filtered off, and washed with water and Et$_2$O.
\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.47 (dd, 1 H, \(J = 6.0, 4.8\) Hz), 4.27 (q, 2 H, \(J = 14.4, 7.2\) Hz), 4.17 (q, 2 H, \(J = 14.1, 7.2\) Hz), 3.03 (s, OH), 2.89-2.74 (m, 2 H), 1.30 (t, 3 H, \(J = 7.2\) Hz), 1.26 (t, 3 H, \(J = 6.9\) Hz).

\((R)-Ethyl\ 4-[(tert-butyl)dimethylsilyloxy]-3-hydroxybutanoate\)

The compound was prepared as described for the \(S\)-enantiomer methyl ester.

\(R_f = 0.66\%\) EtOAc/hexane; CAM.

**Optical Rotation:** \([\alpha]^{23}\)\(_D\) (c 1.00, CHCl\(_3\)) +10.0\(^\circ\).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.15 (q, 2 H, \(J = 14.4, 7.2\) Hz), 4.10-4.03 (m, 1 H), 3.65-3.54 (m, 2 H), 2.77 (s, OH), 2.56-2.42 (m, 2 H), 1.26 (t, 3 H, \(J = 7.2\) Hz), 0.89 (s, 9 H), 0.06 (s, 6 H).

\(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 171.9, 68.5, 66.1, 60.6, 38.1, 25.9, 18.4, 14.3, -5.3.

IR (thin film) \(\nu\) 3476, 2956, 2930, 2858, 1737, 1472, 1464, 1374, 1255, 1178, 1120, 1073, 1030, 1007, 940, 837, 668 cm\(^{-1}\).

\((R)-\text{tert-butyl}\ 6-[(\text{tert-butyl})\text{dimethylsilyloxy}]-5-hydroxy-3-oxohexanoate\)

The compound was prepared as described for the \(S\)-enantiomer. Spectroscopic data were identical to those for the \(S\)-enantiomer.

**Optical Rotation:** \([\alpha]^{23}\)\(_D\) (c 1.00, CHCl\(_3\)) +16.0\(^\circ\).

\(\text{tert-Butyl}\ 2-((4S,6R)-6-[(\text{tert-butyl})\text{dimethylsilyloxy}]-2,2\text{-dimethyl-1,3-dioxan-4-yl})\text{acetate}\)

The compound was prepared as described for the \(S\)-enantiomer. Spectroscopic data were identical to those for the \(S\)-enantiomer.

**Optical Rotation:** \([\alpha]^{23}\)\(_D\) (c 1.00, CHCl\(_3\)) +6.6\(^\circ\).

\(\text{tert-Butyl}\ 2-((4S,6R)-6-(\text{hydroxymethyl})-2,2\text{-dimethyl-1,3-dioxan-4-yl})\text{acetate}\)

70% HF-pyridine complex (80 mL) was added to 80 mL pyridine at 0\(^\circ\)C in a plastic vessel (CAUTION exothermic!). The TBS ether (37.8 g, 100.91 mmol, 1 equiv.) was dissolved into 350 mL of THF in a second plastic vessel and cooled to 0 \(^\circ\)C. The HF/pyridine mixture was added slowly using a cannula. The reaction mixture was stirred for 4 h. and then cannulated carefully into a 1L suspension/solution of Na\(_2\)CO\(_3\) (360 g) over 10 min. The mixture was stirred an additional 10 min and then dichloromethane (600 mL was added). An emulsion formed, which was separated after filtration to a 5 cm plug of celite. The celite was washed with 4x100 mL of dichloromethane which was used to extract the water phase. The combined organic phases were washed with brine (500 mL), dried (Na\(_2\)SO\(_4\)) and concentrated. The resulting cloudy oil was redissolved in dichloromethane (100 mL) and filtered through a plug of Na\(_2\)SO\(_4\). The solution was then concentrated and used directly in the next step without further purification. \(R_f = 0.33\) (50% EtOAc/hexane; CAM).

**Optical Rotation:** \([\alpha]^{23}\)\(_D\) (c 1.46, CHCl\(_3\)) -7.7\(^\circ\).

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\[13\] The compound can be purified column chromatography (20% then 30% EtOAc/hexane) to obtain the pure product in yields exceeding 95%.
**H NMR**: (300 MHz, CDCl₃) δ 4.32-4.23 (m, 1 H), 4.03-3.95 (m, 1 H), 3.62-3.55 (m, 1 H), 3.52-3.44 (m, 1 H), 2.43 (dd, 1 H, J = 15.3, 6.9 Hz), 2.29 (dd, 1 H, J = 15.3, 6.0 Hz), 2.18-2.06 (m, 1 H), 1.45 (s, 3 H), 1.43 (s, 9 H), 1.37 (s, 3 H), 1.35-1.21 (m, 1 H).

**13C NMR**: (75 MHz, CDCl₃) δ 170.4, 99.1, 80.9, 69.7, 66.1, 66.0, 42.9, 32.0, 30.1, 28.3, 20.0.

**IR** (thin film) ν 3449, 2980, 2939, 1730, 1457, 1381, 1369, 1315, 1259, 1201, 1154, 1083, 1024, 989, 950, 896, 872, 842, 821 cm⁻¹.

**HRMS** (MALDI) m/z: calcld for C₁₉H₂₄O₅Na [M+Na]⁺, 283.1521; found 283.1510.

**tert-butyl 2-((4S,6R)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (8)**

![Chemical structure of tert-butyl 2-((4S,6R)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (8)](attachment)

Crude alcohol (7.9g, 30.34 mmol, 1.0 equiv.) obtained as described above was dissolved in 158 mL of CH₂Cl₂ under argon and cooled to 0 °C. KBr (361 mg, 3.0 mmol, 0.1 equiv.) and TEMPO (95 mg, 0.61 Mmol, 0.02 equiv.) and 158 ML carbonate buffer (pH=8.6) was added. A freshly titrated solution of cold 0.354 M bleach (94 mL, 33.34 mmol, 1.1 equiv.) was added over 7 min keeping the reaction temperature below 7 ºC. The color dissipated after 5 min. indicating completion of the reaction. 25 mL sat. Na₂S₂O₆ was added to reduce excess bleach and the mixture stirred 15 min. The phases were separated and the water phase was extracted with CH₂Cl₂ (3x50 mL). The combined organic phases were dried (Na₂SO₄) and concentrated under reduced pressur. The essentially pure aldehyde 6.3 g (81%) thus obtained was immediately used in the subsequent step.

**14Rf = 0.59 (50% EtOAc/hexane; CAM).**

**H NMR**: (300 MHz, CDCl₃) δ 9.55 (s, 1 H), 4.34-4.19 (m, 2 H), 2.43 (dd, 1 H, J = 15.3, 6.9 Hz), 2.31 (dd, 1 H, J = 15.6, 6.0 Hz), 1.80 (ddd, 1 H, J = 12.9, 2.4 Hz), 1.46 (s, 3 H), 1.42 (s, 9 H), 1.42-1.25 (m, 4 H).

**13C NMR**: (75 MHz, CDCl₃) δ 201.1, 170.0, 99.5, 81.1, 74.0, 65.8, 42.6, 30.8, 29.9, 28.3, 19.6.

**tert-butyl-2-((4S,6R)-6-((R)-3-((4S,6S)-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-1-hydroxyprop-2ynyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (9)**

![Chemical structure of tert-butyl-2-((4S,6R)-6-((R)-3-((4S,6S)-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)-1-hydroxyprop-2ynyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (9)](attachment)

A 100 mL flask was charged with 2.265 g (6.23 mmol, 1.1 equiv.) of zinc triflate and heated to 120 °C under high vacuum for 14 hours. After cooling to room temperature 18 mL of dry toluene followed by 1.218 g (6.79 mmol, 1.2 equiv.) of (-)-methylephedrine and 1.0 mL (7.36 mmol, 1.3 equiv.) of triethyl amine were added and the resultant inhomogeneous mixture was stirred for the 3 hours at room temperature under argon. 1.865 g (6.80 mmol, 1.2 equiv.) of alkyne dissolved into 9 mL of dry toluene were added over 5 minutes and the reaction was stirred for 30 minutes. After that 1.373 g (5.31 mmol, 1.0 equiv.) of aldehyde (dissolved in about 1 mL of dry toluene) were added over 3 minutes. After 2.5 hours TLC (30% ethyl acetate / hexane) showed no aldehyde left. The reaction was diluted with ether and quenched with a saturated aqueous ammonium chloride solution. The aqueous phase was washed 3 more times with ether. The organic phases washed with brine and dried over sodium sulfate. After evaporation of the volatiles column chromatography (20% followed by 50% ethyl acetate/hexane) yielded 2.773 g (5.21 mmol, 98%) of product.

**Rf = 0.18 (30% EtOAc/hexane; CAM).**

**Optical Rotation:** [α]D²⁵ +0.1°.

**H NMR**: (300 MHz, CDCl₃) δ 7.37-7.24 (m, 5 H), 4.68 (d, 1 H, J = 9.9 Hz), 4.51 (d, 1 H, J = 11.7 Hz), 4.45 (d, 1 H, J = 11.7 Hz), 4.32-4.21 (m, 2 H), 4.07-3.98 (m, 1 H), 3.93-3.86 (m, 1 H), 3.61-3.46 (m, 2 H), 2.69 (d, 1 OH, J = 3.3 Hz), 2.43 (dd, 1 H, J = 14.7, 7.2 Hz), 2.32 (dd, 1 H, J =15.0, 5.7 Hz), 1.78-1.16 (m, 6 H), 1.45 (s, 3 H), 1.44 (s, 9 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.38 (s, 3 H).

[14] The aldehyde could be purified by column chromatography (20% EtOAc/hexane) to afford the product in yield 75-80%.

SI-7
$^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.2, 138.6, 128.6, 127.9, 99.6, 99.5, 85.6, 81.6, 80.9, 73.3, 72.4, 66.3, 66.0, 65.8, 60.6, 42.9, 37.6, 36.4, 32.3, 30.3, 30.0, 28.3, 20.0, 19.6.

IR (thin film) ν 3448, 2990, 2922, 2868, 1729, 1454, 1380, 1368, 1315, 1259, 1200, 1163, 1123, 1017, 957, 875, 846, 741, 699, 523 cm$^{-1}$.

HRMS (MALDI) m/z: calcd for C$_{30}$H$_{44}$O$_8$Na [M+Na]$^+$, 555.2934; found 555.2935.

**Protected C(1)-C(13) fragment (10)**

A stirred heterogeneous mixture of alkyne (876 mg, 1.64 mmol), sodium hydrogen carbonate (200 mg) and 10% palladium on carbon (30 mg) in methanol (20 mL) under argon was evacuated and filled with hydrogen gas from a balloon three times. The mixture was stirred at room temperature for 16 h, purged with argon, diluted with 150 mL diethyl ether, filtered over a pad of Celite and concentrated to afford the corresponding alkane, which was used in the next step without further purification.

**Oxime (11):**

A solution of lithium aluminium hydride in tetrahydrofuran (1.0 M, 1.97 mL, 1.97 mmol, 1.2 equiv.) was added to a stirred solution of ester (1.07 g, 1.64 mmol, 1.0 equiv.) in anhydrous tetrahydrofuran (2 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 3.5 h and 0.5 mL of acetone was added. After stirring 10 minutes, sodium sulfate decahydrate (1.6 g) and diethyl ether (10 mL) were added. The resulting suspension was stirred 30 minutes at which point anhydrous sodium sulfate (2.0 g) and sodium sulfate decahydrate (1.0 g) were added. The mixture was stirred overnight, filtered and concentrated to afford alcohol (922 mg, 1.59 mmol, 97%), which was used in the next step without further purification.

An aqueous solution of sodium hypochlorite (0.607 M, 2.88 mL, 1.75 mmol, 1.1 equiv.) was added drop wise to a rapidly stirred mixture of alcohol (922 mg, 1.59 mmol, 1.0 equiv.), 2,2,6,6-tetramethylpiperidinyloxy radical (TEMPO) (2.5 mg, 15.9 µmol, 0.01 equiv.) and potassium bromide (19 mg, 159 µmol, 0.10 equiv.) in dichloromethane (4 mL) and aqueous carbonate buffer (pH 8.6, 6 mL) at 0 °C. After stirring for 30 minutes, the reaction was diluted with water (5 mL) and dichloromethane (30 mL) and several crystals of sodium thiosulfate were added. The resulting phases were separated and the aqueous phase was washed with dichloromethane (3x20 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated to afford aldehyde which was used without further purification.
Hydroxyamine hydrochloride (308 mg, 4.77 mmol, 3.0 equiv.) was added to a stirred solution of crude aldehyde prepared above in ethanol (15 mL) and pyridine (1 mL). The mixture was stirred at room temperature for 18 h and concentrated on a rotary evaporator. Purification by flash chromatography (20% 30% ethyl acetate in hexane) afforded the oxime as a 1:1 mixture of cis and trans isomers (797 mg, 1.34 mmol, 84% over two steps).

\[ \text{R} = 0.42 \text{ (33\% EtOAc/hexane; CAM).} \]

**Optical Rotation:** \([\alpha]_D^{24} = +2.9^\circ.\]

**1H NMR** (300 MHz, CDCl3) \(\delta 7.47 (t, J = 6.1, 0.5H, O\_H\text{-trans}), 7.38 - 7.23 (m, 5H), 6.85 (t, J = 5.1, 0.5H, O\_H\text{-cis}), 4.55 - 4.45 (ABm, 2H), 4.01 (m, 2H), 3.76 (m, 2H), 3.65 - 3.50 (m, 3H), 2.61 (dt, J = 4.8, 16.3, 0.5H), 2.48 (ddd, J = 5.0, 7.4, 16.3, 0.5H), 2.36 (t, J = 6.0, 1H), 1.85 - 1.64 (m, 2H), 1.59 - 1.30 (m, 13H), 1.42 (s, 3H), 1.29 - 1.06 (m, 2H), 0.88 (s, 9H), 0.07 (d, J = 7.1, 6H).

**13C NMR** (75 MHz, CDCl3) \(\delta 149.1, 138.4, 128.3, 127.6, 127.5, 98.7, 98.5, 74.6, 73.0, 72.2, 69.0, 67.1, 66.3, 66.1, 37.1, 36.7, 36.5, 32.0, 31.9, 31.7, 30.3, 30.1, 27.6, 26.1, 20.0, 19.7, 18.4, -3.9, -4.5.

**IR** (thin film) \(\nu 3359, 2992, 2959, 2928, 2857, 1472, 1462, 1380, 1255, 1200, 1167, 1104, 1029, 1005, 963, 939, 873, 835, 811, 776, 736, 698 \text{ cm}^{-1}.\]

**HRMS** (MALDI) \(m/z\): calcd for C32H55NO7SiNa [M+Na]+, 616.3645; found 616.3646.

**Preparation of the C(14)-C(19) homo allylic alcohol 13**

70% HF-pyridine complex (45.6 mL) was added slowly to 47 mL pyridine at 0ºC in a plastic vessel (CAUTION exothermic!). 80.5 g (185.7 mmol, 1 equiv.) of TBS-protected homoallylic alcohol 12 was dissolved in 2 L of THF. The solution was split into 3 equal portions and transferred to plastic vessels cooled to 0 ºC. To each of these a third of the HF/pyrididine mixture described above was added. The reactions were left for 14 h at 0 ºC. The three batches were all combined and split into two for the workup. Each batch was was cannulated carefully into the a suspension/solution of 2 L water and NaHCO3 (250 g) over 30 min (Caution avid CO2 formation!). The mixture was stirred an additional 30 min and then the resulting solution was extracted with 3x1.3 L ethyl acetate. The combined organic phases were washed with brine (1000 mL), dried (Na2SO4) and concentrated. The product thus obtained was used in the next step without further purification.

\[ \text{R} = 0.30 \text{ (80\% EtOAc/hexane; CAM).} \]

**Optical Rotation:** \([\alpha]_D^{25} = +67.4^\circ.\]

**1H NMR** (300 MHz, CDCl3) \(\delta 7.43-7.26 (m, 5 H), 6.06-5.93 (m, 1 H), 5.69 (d, 1 H, J = 7.2 Hz), 5.38-5.32 (m, 2 H), 4.84-4.75 (m, 1 H), 4.52 (dd, 1 H, J = 9.3, 4.2 Hz), 4.30-4.24 (m, 1 H), 3.82 (t, 2 H, J = 5.4 Hz), 1.89-1.77 (m, 1 H), 1.71-1.62 (m, 1 H), 0.86 (d, 3 H, J = 6.6 Hz).

**13C NMR** (75 MHz, CDCl3) \(\delta 173.4, 152.5, 132.9, 131.0, 128.7, 128.6, 128.4, 125.8, 125.5, 121.2, 78.9, 71.3, 60.9, 54.8, 52.7, 35.9, 14.4.

**IR** (thin film) \(\nu 3394, 2934, 1779, 1779, 1696, 1637, 1455, 1352, 1224, 1197, 1147, 1120, 1067, 1000, 930, 807, 767, 701 \text{ cm}^{-1}.\]

**HRMS** (MALDI) \(m/z\): calcd for C17H21NO5H [M+H]+, 320.1498; found 320.1488.

**Homo allylic alcohol 13**

Diol (36.5 g, 114.5 mmol, 1 equiv.) was dissolved in dichloromethane (286 mL) and cooled down to 0 ºC. 2,2,6,6-Tetramethylpiperidinyloxy radical (TEMPO, 2 68 mg, 1.72 mmol, 0.015 equiv.) and potassium bromide (1.36 g, 11.45 mmol, 0.10 equiv.) and aqueous carbonate buffer (pH 8.6, 458 mL) was added at 0 ºC. Then bleach (100 mL, 1.20 M, 120 mmol) was added over 11 min. After stirring for 10 minutes, 10 mL of methanol was added. Then brine (200 mL) was added and the mixture extracted with 3x1L ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated to afford aldehyde which was used without further purification.


SI-9
The crude aldehyde was dissolved in 1.4 L t-butanol and 477 mL 2-methyl-butene and cooled to 0 °C. 477 mL 2M NaH₂PO₄ (pH=4.6) was added followed by Sodium chlorite (103.6 g, 1.145 mol, 10 equiv.) was then added portionwise over 11 min. The reaction mixture was stirred for 45 min and then NaCl was added to saturate the solution (phases separate). The solution was then extracted with 3x800 mL ethyl acetate. The combined organic phases were dried over Na₂SO₄ and evaporated to yield the crude acid which was dissolved into 500 mL of 1:1 dioxane/methanol and cooled to 0 °C. TMSCHN₂ (68.7 mL, 137 mmol, 2 M in diethyl ether, 1.1 equiv.) was added and the reaction stirred for 3 min. Acetic acid was added until gas formation subsides. The solution was concentrated. Purification by column chromatography (30% EtOAc/hexane) afforded 25.1 g (63% over three steps) of the desired methyl ester.

**Optical Rotation:**
\[ [\alpha]_{D}^{23} +47.4° \]

**1H NMR** (300 MHz, CDCl₃) \( \delta \)
- 7.44-7.26 (m, 5 H),
- 6.06-5.93 (m, 1 H),
- 5.69 (d, 1 H, \( J = 7.2 \) Hz),
- 5.39 (s, 1 H),
- 5.35 (q, 1 H, \( J = 4.8, 1.2 \) Hz),
- 4.84-4.76 (m, 1 H),
- 4.59 (dd, 1 H, \( J = 8.7, 3.9 \) Hz),
- 4.51-4.44 (m, 1 H),
- 3.71 (s, 3 H),
- 2.62 (dd, 1 H, \( J = 15.9, 8.4 \) Hz),
- 2.53 (dd, 1 H, \( J = 15.9, 4.2 \) Hz),
- 0.87 (d, 3 H, \( J = 6.6 \) Hz).

**13C NMR** (75 MHz, CDCl₃) \( \delta \)
- 172.7, 172.2, 152.4, 133.0, 130.6, 128.8, 128.7, 125.6, 121.5, 79.0, 68.6, 54.9, 53.5, 52.0, 51.8, 38.6, 14.4.

**IR** (thin film) \( \nu \)
- 3505, 2952, 1781, 1735, 1697, 1456, 1438, 1352, 1294, 1223, 1197, 1121, 1067, 1033, 1000, 932, 844, 808, 767, 701 cm⁻¹.

**HRMS** (MALDI) \( m/z \) calcd for C₁₈H₂₁NO₆H \[M+H\]^+ 348.1447; found 348.1416.

**Completion of the C(1)-C(20) polyol 18**

**Isocyanate 15**

Lithium hydroxide monohydrate (271 mg, 6.45 mmol, 1.3 eq) was dissolved in a 1.95 % solution of hydrogenperoxide (31 mL, 17.6 mmol, 3 eq). The resulting solution of lithium peroxide was added to a solution of isoxazoline (4.6g, 4.87 mmol) in degassed dioxane (93 mL). The reaction mixture was stirred for 1 h, cooled to 0 °C and poured into a cold 2 M sodium dihydrogen phosphate (200 mL). A 0.5 M Na₂S₂O₃ solution (31 mL) was added slowly and the resulting mixture stirred for 5 min. Ethyl acetate (200 mL) was added. Sodium chloride was added until the water phase was...
saturated. The phases were separated and the water phase extracted with additional ethyl acetate (100 mL + 3×50 mL). The combined organic phases were dried (sodium sulphate) and the solution concentrated til approximately 150 mL. 50 mL methanol was added and 2M trimethylsilyldiazomethane in hexane was added drop wise until the solution was permanently yellow. The solvent was removed under reduced pressure. The resulting oil was purified by flash chromatography (43% ethyl acetate/hexane) to afford the desired dimethylester 2.58 g (67% yield over 2 steps) as a clear oil.

**Rf** = 0.35 (43% ethyl acetate/hexane, KMnO₄,CAM).

**Optical rotation** \( [\alpha] D^{23.5} \) (c 0.41, CHCl₃) = 35.52

**1H NMR** (300 MHz, CDCl₃) δ 7.32 (m, 5H), 4.94 (m, 1H), 4.50 (ABm, 2H), 4.36 (m, 1H), 4.04 (m, 2H), 3.75 (m, 2H), 3.71 (s, 6H), 3.54 (m, 3H), 3.46 (m, 1H), 3.16 (m, 2H), 2.74 (m, 1H), 2.56-2.46 (m, 4H), 1.74 (m, 2H), 1.55-1.42 (m, 6H), 1.41 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.16 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H).

**13C NMR** (75.5 MHz, CDCl₃) δ 172.6, 170.7, 157.2, 138.3, 128.2, 127.5, 127.4, 98.6, 98.3, 78.5, 74.5, 72.9, 72.1, 68.9, 67.0, 66.9, 66.2, 66.0, 55.1, 52.1, 52.0, 42.7, 38.8, 37.0, 36.6, 34.4, 31.7, 31.6, 30.3, 30.0, 27.5, 26.0, 20.0, 19.6, 18.3, -3.9, -4.5.

**IR** (thin film) ν 3469, 2992, 2951, 2856, 1737, 1438, 1380, 1263, 1200, 1168, 1102, 870, 835, 777.

**HRMS** (MALDI) m/z: calcd for C₄₁H₆₇NO₁₂SiNa [M+Na], 816.4330, found 816.4330.

**Hemiketal 16**

Isoxazoline 15 (75 mg, 95 µmol) was placed in a 25 mL flask fitted with a reflux condenser and a septum. Molybdenum hexacarbonyl (40 mg, 151 µmol, 1.6 eq.) was added. The flask was evacuated and nitrogen introduced. Acetonitrile (2 mL) and water (0.3 mL) was added and the reaction mixture heated to reflux for 5 h. The resulting black heterogeneous mixture was evaporated to dryness and azeotroped three times with benzene (10 mL). The black solid residue was suspended with silica in 1 mL 25% ethyl acetate/hexane and placed on a short silica gel column. Flash chromatography (gradient: 25% ethyl acetate/hexane then 50% ethyl acetate/hexane) afforded hemiketal (68 mg, 86% yield) as a yellow oil.

**Rf** = 0.33 (40% ethyl acetate/hexane, KMnO₄,CAM).

**1H NMR** (300 MHz, CDCl₃) δ 7.33 (s, 5H), 5.16 (d, J = 1.9, 1H), 4.55 (ddd, J = 4.8, 8.9, 10.3, 1H), 4.50 (ABm, 2H), 4.47 4.45 (m, 2H), 4.07 – 3.96 (m, 1H), 3.71 (m, 2H), 3.71 (s, 3H), 3.67 (s, 3H), 3.54 (m, 3H), 2.58 (dd, J = 3.9, 15.4, 1H), 2.50 (dd, J = 8.9, 15.4, 1H), 2.27 (t, J = 10.3, 1H), 2.15 (dd, J = 4.8, 12.2, 1H), 2.07 (d, J = 4.8, 1H), 1.85 (dd, J = 10.3, 14.8, 1H), 1.75 (m, 2H), 1.69 (dd, J = 1.55, 14.8, 1H), 1.46 (m, 6H), 1.43 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.26 (m, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H).

**13C NMR** (75.5 MHz, CD₂Cl₂) δ 172.4, 170.8, 139.1, 128.4, 127.7, 99.0, 97.4, 105.4, 98.5, 74.8, 73.1, 72.6, 69.2, 66.8, 66.6, 66.5, 66.2, 56.5, 52.2, 51.8, 45.8, 43.9, 39.4, 37.5, 37.0, 32.3, 32.1, 30.3, 30.1, 27.9, 26.1, 20.0, 19.9, 18.5, -3.9, -4.5.

**IR** (thin film) ν 3455, 2980, 2952, 2860, 1741, 1437, 1381, 1258, 1200, 1167, 1104, 833, 777.

**HRMS** (MALDI) m/z: calcd for C₄₁H₆₉O₁₃SiNa [M+Na], 819.4327, found 816.4332.

**Polyol 17**

Hemiketal 16 (1.75 g, 2.19 mmol) was dissolved in 2,2-dimethoxypropane (111 mL) and a solution of 2-chloro-pyridinium camphorsulfonate (151 mg, 0.44 mmol, 0.2 eq.) in methanol (4.4 mL) was added. The reaction mixture was stirred for 26 h. and then quenched by addition of triethylamine (1 mL). The solvents were removed at reduced pressure.
The resulting yellow oil was azeotroped with toluene (2×80 mL and 0.4 mL triethylamine) and remains of solvents were removed at 0.1 mmHg.

The crude material was dissolved in dry dichloromethane (100 mL) and the solution cooled to 0 °C. 2,6-Lutidine (2.55 mL, 21.9 mmol, 10 eq.) was added. t-Butyldimethylsilyltriflate (0.55 mL, 0.636 g, 2.41 mmol, 1.1 eq.) was added dropwise over 10 min. The reaction mixture was stirred for 30 min. poured into sat. sodium bicarbonate (100 mL) and the phases were separated. The water phase was extracted with 3×25 mL dichloromethane. The combined organic phases were dried and the solvent removed at reduced pressure. Flash chromatography (gradient: 1% triethylamine/15% ethyl acetate/hexane then 1% triethylamine/40% ethyl acetate/hexane) afforded desired fully protected C(1)-C(19) polyol (1.52 g, 75% yield over 2 steps) as a yellowish oil.

\[ R_f = 0.87 \text{ (40% ethyl acetate/hexane, KMnO}_4\text{, CAM).} \]

\[ ^1H \text{ NMR (300 MHz, CDCl}_3\text{, C}_5\text{H}_5\text{N}) \delta 7.30 \text{ (m, 5H)}, 4.56 – 4.45 \text{ (m, 2H)}, 4.30 \text{ (td, } J = 4.9, 10.9, 1H), 4.12 \text{ (m, 1H), 4.08 – 3.97 \text{ (m, 1H)}, 3.95 – 3.84 \text{ (m, 2H)}, 3.82 – 3.71 \text{ (m, 2H), 3.68 \text{ (s, 3H), 3.66 \text{ (s, 3H), 3.54 \text{ (m, 3H), 3.15 \text{ (m, 5H), 1.53 \text{ (m, 5H), 1.41 \text{ (s, 6H), 1.35 \text{ (s, 3H), 1.33 \text{ (s, 3H), 1.16 \text{ (m 2H), 0.87 (s, 9H), 0.83 (s, 9H), 0.04 (s, 9H), 0.01 (s, 3H).} \]

\[ ^13C \text{ NMR (75.5 MHz, CDCl}_3\text{, C}_5\text{H}_5\text{N}) \delta 172.6, 170.8, 127.7, 69.1, 68.0, 67.3, 66.5, 66.3, 65.1, 56.6, 51.7, 47.9, 43.3, 42.4, 39.2, 37.5, 37.0, 32.8, 32.3, 30.3, 30.2, 27.8, 26.1, 25.7, 20.0, 19.8, 18.5, 18.1, -3.8, -4.1, -4.4, -4.8.} \]

\[ \text{IR (thin film) ν 2991, 2951, 2855, 1746, 1745, 1471, 1462, 1435, 1379, 1313, 1255, 1201, 1139, 1101, 1035, 958, 866, 836, 777.} \]

\[ \text{HRMS (MALDI) m/z: calcd for C}_{48}\text{H}_{84}\text{O}_{13}\text{Si}_2\text{Na [M+Na], 947.5343, found 947.5332.} \]

Selective introduction of the dimethyl phosphonate functionality

Dimethyl ester 17 (2.8 g, 3.03 mmol) was dried azeotropically with toluene (3x70mL) and then dissolved in 75 mL THF. Dimethyl methanephosphonate (788 mg, 6.35 mmol, 2.1 eq.) was dissolved in dry THF (75 mL) and cooled to -78 °C. n-Butyl lithium (3.21 mL, 5.14 mmol, 1.8 equiv., 1.6 M) was added drop wise and the mixture stirred for 25 min. The solution of polyol was added via cannula and the cannula washed with 2x10 mL THF. The reaction mixture was heated to 0 °C and stirred at this temperature for 15 min. The reaction mixture was then cooled back to -78 °C and then cannulated into sat. NaHCO\textsubscript{3} (40 mL). The aqueous phase was extracted with diethyl ether (150+4x50 mL), dried (Na\textsubscript{2}SO\textsubscript{4}) and the solvent removed under reduced pressure. Flash Chromatography (Gradient: 1% pyridine/15-50% ethyl acetate/hexane) afforded recovered (750 mg, 27%) and desired phosphonate (1.6 g, 71% yield based on recovered starting material).

\[ R_f = 0.31 \text{ (50% ethyl acetate/hexane, KMnO}_4\text{, CAM).} \]

\[ ^1H \text{ NMR (300 MHz, CDCl}_3\text{, C}_5\text{H}_5\text{N}) \delta 7.30 – 7.23 \text{, (m, 5H), 4.49 (m, 2H), 4.28 (td, } J = 4.6, 10.7, 1H), 4.15 \text{ (td, } J = 2.7, 10.0, 1H), 4.07 – 3.94 \text{ (m, 1H), 3.94 – 3.82 \text{ (m, 1H), 3.78 (s, 3H), 3.74 \text{ (s, 3H), 3.82 – 3.69 \text{ (m, 2H), 3.67 \text{ (s, 3H), 3.55 \text{ (m, 3H), 3.15-3.08 \text{ (m, 2H), 3.12 \text{ (s, 3H), 2.84 (dd, } J = 9.3, 16.0, 1H), 2.52 \text{ (dd, } J = 2.7, 16.0, 1H), 2.23 \text{ (dt, } J = 7.6, 13.1, 2H), 1.89 – 1.66 \text{ (m, 3H), 1.48-1.00 \text{ (m, 7H), 1.405 \text{ (s, 3H), 1.395 \text{ (s, 3H), 1.34 \text{ (s, 3H), 1.32 \text{ (s, 3H), 1.27 – 1.04 \text{ (m, 3H), 0.86 (s, 9H), 0.82 (s, 9H), 0.04 (d, } J = 2.0, 6H), 0.02 (s, 3H), -0.01 (s, 3H).} \]

\[ ^13C \text{ NMR (75.5 MHz, CDCl}_3\text{, C}_5\text{H}_5\text{N}) \delta 199.38 (d), 172.71, 138.71, 129.19, 128.39, 127.71, 125.46, 100.63, 98.58, 98.46, 74.78, 73.15, 72.67, 69.07, 67.65, 66.82, 66.39, 66.21, 64.95, 56.57, 53.20 \text{ (d), 51.92, 48.06, 47.60, 43.57, 43.05, 42.18, 41.87, 37.18, 36.78, 32.60, 31.96, 30.43, 30.20, 27.50, 26.15, 25.75, 20.08, 19.85, 18.47, 17.99, -3.89, -4.14, -4.48, -4.91.} \]

\[ ^31P \text{ NMR (122 MHz, CDCl}_3\text{, C}_5\text{H}_5\text{N}) \delta 22.99. \]

\[ \text{IR (thin film) ν 2989, 2951, 2856, 1732, 1471, 1462, 1435, 1379, 1377, 1258, 1200, 1167, 1139, 1100, 1029, 967, 835, 764, 750.} \]

\[ \text{HRMS (MALDI) m/z: calcd for C}_{48}\text{H}_{82}\text{O}_{15}\text{PSi}_2\text{Na [M+Na], 1067.568, found 1067.567.} \]
Phosphonate (600 mg, 589 µmol) was placed in a round bottomed flask fitted with a valve and dissolved in ethyl acetate (60 mL) and placed under argon. Palladium hydroxide on carbon (64 mg) was added. The flask was evacuated and an atmosphere of hydrogen introduced using a balloon. This process was repeated three times. The reaction mixture was stirred for 5 h and then the hydrogen atmosphere was removed by a strong flow of argon. 2-methyl-butene (3 mL) was added to quench any residual hydrogen species absorbed on the palladium catalyst. 50 mL ethyl acetate was added the catalyst removed by filtration through a celite/Na₂SO₄ plug. The filtrate was washed with ethyl acetate (3x15mL) and the solvent removed under reduced pressure. The crude product was used directly without any further purification.

R_f=0.32 (100% ethyl acetate, KMnO₄, CAM).

**1H NMR** (300 MHz, CDCl₃, C₅H₅N) δ 4.27 (td, J=4.7, 10.6, 1H), 4.21 – 4.00 (m, 2H), 3.81-3.70 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H), 3.52 (m, 2H), 3.25 – 2.97 (m, 2H), 3.11 (s, 3H), 2.82 (dd, J=9.39, 16.0 1H), 2.71 – 2.56 (m, 1H), 2.54 (dd, J=2.6, 16.0, 1H), 2.30 – 2.15 (m, 2H), 1.81 (m, 1H), 1.63 – 1.03 (m, 12H), 1.43 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 0.86 (s, 9H), 0.82 (s, 9H), 0.03 (m, 9H), -0.01 (s, 3H).

**13C NMR** (75 MHz, CDCl₃, C₅H₅N) δ 198.91 (d), 172.30, 100.37, 98.48, 98.22, 74.54, 72.47, 69.34, 68.81, 67.46, 66.64, 64.77, 60.86, 56.40, 53.08 (d), 51.76, 47.91, 47.45, 43.42, 42.91, 42.06, 41.72, 38.17, 36.71, 32.43, 31.84, 30.31, 30.08, 27.48, 26.03, 25.49, 19.96, 19.75, 18.37, 17.90, -3.94, -4.20, -4.53, -4.96.

**31P NMR** (122 MHz, CDCl₃, C₅H₅N) δ 22.77.

The crude alcohol was dried azeotropically with toluene (2x10 mL) and dissolved in dichloromethane (60 mL). Pyridine (0.476 mL, 5.89 mmol, 10 equiv.) was added followed by Dess-Martin periodonane (375 mg, 885 µmol, 1.5 equiv.). The resulting heterogeneous mixture was stirred for 30 min. A 1:1 mixture of sat. NaHCO₃ and 0.5 M Na₂S₂O₃ (50 mL) was added and the mixture stirred for 10 min. The water phase was extracted with ethyl acetate (4x20 mL). The combined organic phases were dried (Na₂SO₄) and the solvent removed under reduced pressure.

The crude aldehyde was dissolved in a mixture of t-butanol (45 mL) and 2-methyl-2-butene (29 mL). Sodiumchlorite (106 mg, 1.18 mmol, 2 equiv.) were added followed by 2 M NaH₂PO₄ (29 mL). The reaction was stirred for 8 min. 25 mL NaH₂PO₄ and 50 mL ethyl acetate was added. Sodium chloride was added until the water phase was saturated. The phases were separated and the water phase extracted with ethyl acetate (6x 25 mL). The combined organic phases were dried (Na₂SO₄) and the solvent removed under reduced pressure. Flash chromatography through a short (7 cm) column afforded the carboxyclic acid 18 (600 mg, 99%) as its pyridine salt.

R_f=0.45 (10% methanol/dichloromethane, KMN₉₄, CAM).

**1H NMR** (300 MHz, CDCl₃, C₅H₅N) δ 4.28 (s, 2H), 4.20 – 4.08 (m, 1H), 3.94 – 3.72 (m, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H), 3.55 – 3.46 (m, 2H), 3.25 – 3.02 (m, 2H), 3.13 (s, 3H), 2.89 – 2.77 (m, 1H), 2.64 – 2.36 (m, 2H), 2.30 – 2.14 (m, 2H), 1.8 (m, 1H), 1.69 – 1.02 (m, 12H), 1.45 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.31 (s, 3H), 0.86 (s, 9H), 0.82 (s, 9H), 0.03 (d, J=2.1, 9H), -0.01 (s, 3H).

**13C NMR** (75 MHz, CDCl₃, C₅H₅N) δ 198.95(d), 172.44, 100.43, 98.74, 98.27, 74.64, 72.54, 68.78, 67.50, 66.68, 66.16, 64.81, 56.44, 53.12, 51.81, 47.96, 47.51, 43.41, 42.94, 42.10, 41.71, 36.58, 32.50, 31.91, 30.24, 30.13, 29.79, 27.41, 26.09, 25.69, 21.58, 19.94, 19.80, 18.42, 17.95, -3.90, -4.14, -4.47, -4.91.

**31P NMR** (122 MHz, CDCl₃) δ 22.77.

**HRMS** (MALDI) m/z: calcd for C₄₃H₸₁O₁₆PSi₂Na[M+Na], 963.4693, found 963.4677.
Synthesis of the C21-C37 Polyene Fragment

(2S,3S)-ethyl 3-hydroxy-2-methylbutanoate

\[ \text{Me} \quad \text{CO}_2\text{Et} \quad \text{OH} \quad \text{Me} \quad \text{CO}_2\text{Et} \]

294 mL (735 mmol, 2.1 equiv.) of a 2.5 M solution of butyllithium in hexane were added drop wise to 101 mL (770 mmol, 2.2 equiv.) of disopropylamine in 770 mL of dry THF under argon at -78 °C. The mixture was allowed to stir at the same temperature for about one hour, after that 45.8 mL (350 mmol, 1 equiv.) of ethyl (S)-(+-)-3-hydroxybutyrate (20) dissolved in 245 mL of dry THF and 105 mL of dry HMPA were added drop wise over about 35 min and the mixture allowed to stir from -78 °C to about -40 °C (flask removed from the cooling bath and reaction stirred at -40 °C over 20 min). After cooling back to -78 °C, 27.2 mL (438 mmol, 1.25 equiv.) of iodomethane were added and the reaction warmed to 0 °C over about 2 hours. The reaction was quenched with sat. aq. NH\(_4\)Cl. 1 M aq. HCl was carefully added until the aqueous phase was neutral. The aqueous phase was then washed 3 times with ether. The combined organic phases were washed with brine and dried over Na\(_2\)SO\(_4\). After evaporation of the volatiles, flash column chromatography (20% EtOAc/Hexane) of the crude material yielded 46.98 g (321 mmol, 92%, dr 95:5) of a pale yellow liquid.

\( R_f \) (product) = 0.36 (50% EtOAc/hexane; KMnO\(_4\)); \( R_f \) (starting material) = 0.30 (50% EtOAc/hexane; KMnO\(_4\)).

\( \text{b.p.} \) 80 °C, 10 Torr

\[^1\text{H} \text{NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 4.17 (q, 2 H, \( J = 6.9 \text{ Hz} \)), 3.92-3.83 (m, 1 H), 2.48-2.38 (m, 1 H), 1.27 (t, 3H, \( J = 7.2 \text{ Hz} \)), 1.22 (d, 3H, \( J = 6.3 \text{ Hz} \)), 1.18 (d, 3H, \( J = 4.5 \text{ Hz} \)).

\[^{13}\text{C} \text{NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) 176.2, 69.7, 60.8, 47.1, 31.7, 21.0, 14.4.

(2S,3S)-ethyl 2-methyl-3-[{trisopropylsilyl}oxy]-butanoate

\[ \text{Me} \quad \text{CO}_2\text{Et} \quad \text{TIPSO} \quad \text{Me} \quad \text{CO}_2\text{Et} \]

24.3 mL (90.44 mmol, 1.1 equiv.) of TIPSO\(_2\)Tf were added drop wise over about 5 min to a solution of 12.02 g (82.22 mmol, 1 equiv.) of the hydroxyster and 12.4 mL (0.106 mol, 1.3 equiv.) of 2,6-lutidine in 820 mL of dry CH\(_2\)Cl\(_2\) at 0 °C under argon. After 15 min TLC showed complete conversion and the reaction was quenched by adding a saturated solution of sodium bicarbonate. The aqueous phase was extracted two more times with CH\(_2\)Cl\(_2\). The combined organic phases were washed with brine, dried over Na\(_2\)SO\(_4\) and evaporated in vacuo to yield a colorless oil which was disuntiled to yield 35.13 g (116.24 mmol, 89%) of a colorless liquid.

\( R_f \) = 0.77 (5% EtOAc/hexane; KMnO\(_4\)).

\( \text{b.p.} \) 143°C, 5 Torr

\[^1\text{H} \text{NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 4.29-4.25 (m, 1 H), 2.62 (m, 1 H), 1.25 (t, 3H, \( J = 6.9 \text{ Hz} \)), 1.15-1.10 (2 d, 6H, \( J = 7.5, 7.2 \text{ Hz} \)), 1.05 (m, 21 H).

(2S,3S)-2-methyl-3-{[trisopropylsilyl]oxy}-1-butanol

44 mL (247 mmol, 2.50 equiv.) of DIBAL were dissolved into 250 mL of dry ether and added drop wise to a solution of 29.82 g (98.68 mmol, 1.00 equiv.) of the crude ester in dry ether at -78 °C. After the addition was complete the reaction was allowed to warm to 0 °C and then stirred at this temperature for the next 2 hours. TLC showed complete conversion and 10 mL of MeOH were added carefully at -78 °C, followed by addition of a saturated solution of Rochelle’s salt. The slurry was carefully allowed to warm to room temperature and after 4 h stirring the two phases were separated, the aqueous phase extracted twice with CH\(_2\)Cl\(_2\). The combined organic phases were washed with brine, dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure to yield a colorless oil which was disuntiled to yield 12.15 g (46.70 mmol, 92%).

\[ \text{Me} \quad \text{CO}_2\text{Et} \quad \text{OH} \quad \text{Me} \quad \text{CO}_2\text{Et} \]


[17] The diastereomeric ratio was determined after reduction to the diol by integrating the \( ^1\text{H} \text{NMR} \) spectrum at \( \delta = 0.90 \) and \( \delta = 0.84 \) (5:95).

[18] Alternative procedure with TIPSCI. 22.15 g (3 25.33 mmol, 2.50 equiv.) of imidazole followed by 33 mL (156.16 mmol, 1.20 equiv.) of TIPSCI were added to 19.02 g (130.13 mmol, 1.00 equiv.) of the alcohol dissolved in 65 mL of dry DMF at room temperature under argon. After 48 h the reaction was worked up by adding a saturated solution of ammonium chloride and extracting three times from ether. The organic phases were washed with brine, dried over Na\(_2\)SO\(_4\) and evaporated in vacuo to yield a colorless oil which was disuntiled to yield 35.13 g (116.24 mmol, 89%) of a colorless liquid.
47% over 2 steps) of a colorless liquid. The crude product was usually taken to the next step without further purification.

**Optical Rotation:** $[\alpha]^{24}_D$ (c 0.54, CHCl$_3$) $+15.3^\circ$.

**b.p.** 104 °C, 7 Torr

**$^1$H NMR** (300 MHz, CDCl$_3$) $\delta$ 4.05-3.98 (m, 1 H), 3.77-3.73 (m, 1 H), 3.58 (m, 1 H), 2.68 (s, OH), 1.72-1.63 (m, 1 H), 1.24 (d, 3H, $J = 6.0$ Hz), 1.08 (m, 21 H), 0.99 (d, 3H, $J = 6.6$ Hz).

**$^{13}$C NMR** (75 MHz, CDCl$_3$) $\delta$ 73.5, 66.0, 42.2, 21.7, 18.3, 14.1, 12.9.

**IR** (thin film) $\nu$ 3341, 2943, 2867, 1464, 1383, 1111, 1033, 953, 882, 791, 754, 678 cm$^{-1}$.  

**HRMS** (MALDI) $m/z$: calcd for C$_{14}$H$_{24}$O$_2$SiNa [M+Na]$^+$: 283.2069; found 283.2060.

((2S,3S)-4-iodo-3-methylbutan-2-yl)triisopropysilane (21)

4.43 g (16.88 mmol, 2.50 equiv.) of triphenylphosphine followed by 1.67 g (24.55 mmol, 3.70 equiv.) of imidazole and 4.88 g (19.21 mmol, 2.90 equiv.) of iodine were added to 1.74 g (6.67 mmol, 1.00 equiv.) of the alcohol dissolved into 80 mL of dry THF at room temperature under argon. After 4 h the reaction mixture was diluted with ethyl acetate and water was added. After separation of the phases the organic layer was washed with sat. aq. NaHCO$_3$, sat. aq. NaCl, and brine. After drying with Na$_2$SO$_4$ and evaporation of the solvents, purification by column chromatography (100% hexane) yielded 2.12 g (5.71 mmol, 86%) of a colorless liquid.

**Optical Rotation:** $[\alpha]^{25}_D$ (c 0.69, CHCl$_3$) $+6.3^\circ$.

**$^1$H NMR** (300 MHz, CDCl$_3$) $\delta$ 3.99-3.91 (m, 1 H), 3.25-3.15 (m, 2 H), 1.72-1.63 (m, 1 H), 1.12 (d, 3H, $J = 6.3$ Hz), 1.07 (m, 21 H), 1.00 (d, 3H, $J = 6.9$ Hz).

**HRMS** (MALDI) $m/z$: calcd for C$_{14}$H$_{32}$O$_2$SiNa [M+Na]$^+$: 393.1087; found 393.1080.

(2R,4R,5S)-5-[(Triisopropylsilyloxy)-N-(1S,2S)-1-hydroxy-1-phenylpropan-2-yl]-N,2,4-trimethylhexanamide 22

0.432 g (10.19 mmol, 13.2 equiv.) of anhydrous LiCl were flame dried in vacuo. After cooling to room temperature 2.5 mL of dry THF followed by 0.46 mL (3.24 mmol, 4.2 equiv.) of diisopropyamine were added and the suspension cooled down to -78 °C. 2 mL (3.09 mmol, 4 equiv.) of a 1.58 M butyllithium solution in hexane were added drop wise. After 1 h at the same temperature 0.359 g (1.62 mmol, 2.1 equiv.) of (+)-pseudoephedrine in 5.4 mL of dry THF were added drop wise. After 1 h at -78 °C, 30 min at 0 °C and 5 min at room temperature the reaction was cooled back to 0 °C and 0.286 g (0.772 mmol, 1 equiv.) of the iodide dissolved in 0.3 mL of dry THF were added. Stirring was allowed for the next 12 h and the temperature to increase to room temperature. The reaction was quenched with sat. aq. NH$_4$Cl, extracted three times with EtOAc, washed with brine and dried over MgSO$_4$. Purification by column chromatography (20% followed by 30% EtOAc/Hexane) yielded 0.048 g (0.129 mmol) of recovered iodide and 0.285 g (0.616 mmol, 80%; dr anti/syn 95:5)$^{[19]}$ of the alkylated product as a viscous oil which solidified to a white solid.

**Optical Rotation:** $[\alpha]^{26}_D$ (c 0.94, CHCl$_3$) $+55^\circ$.

**$^1$H NMR** (300 MHz, CDCl$_3$) $\delta$ 7.35-7.21 (m, 5 H), 4.62-4.58 (m, 1 H), 4.45-4.41 (m, 1 H), 3.88-3.79 (m, 1 H), 2.91 and 2.84 (s, 3 H), 2.67-2.58 (m, 1 H), 1.78 (s, OH), 1.68-1.60 (m, 1 H), 1.38-1.19 (m, 2 H), 1.12 (d, 3 H, $J = 6.9$ Hz), 1.07-1.04 (m, 24 H), 0.92 (d, 3 H, $J = 6.9$ Hz), 0.84 (d, 3 H, $J = 6.9$ Hz).

**$^{13}$C NMR** (75 MHz, CDCl$_3$) $\delta$ 179.2, 142.4, 128.2, 127.5, 126.2, 76.6, 72.0, 58.9, 37.8, 36.8, 34.4, 18.5, 18.3, 16.6, 14.6, 13.4, 12.9, 12.7.

$^{[19]}$ The diastereomeric ratio was determined after reduction to the primary alcohol by integrating the $^1$H NMR spectrum at $\delta = 0.90$ and $\delta = 0.84$ (5:95).
IR (thin film) v 3382, 2942, 2866, 1620, 1462, 1409, 1381, 1111, 1053, 960, 883, 754, 701, 679 cm\(^{-1}\).

HRMS (MALDI) m/z: calcd for C\(_{27}\)H\(_{49}\)NO\(_3\)SiNa [M+Na]\(^+\): 486.3379; found 486.3369.

(2R,4R,5S)-5-[(triisopropylsilyl)oxy]-2,4-dimethyl-1-hexanol

70 mL (0.113 mol, 3.9 equiv.) of a 1.6 M solution of butyllithium in hexane were added to 16 mL (0.113 mol, 3.9 equiv.) of disopropylamine in 115 mL of dry THF at -78 °C under argon. After 1 h at -78 °C the temperature was raised to 0 °C and 3.97 g (0.116 mol, 4 equiv.) of ammonia borane complex were carefully added in port ions. The ice bath was removed and the white slurry allowed to stir at room temperature over 1 h. After that 13.31 g (28.71 mmol, 1 equiv.) of amide dissolved in 75 mL of dry THF were added drop wise at 0 °C. The reaction was allowed to warm to room temperature and stirred for the subsequivuent 12 h. It was then cooled to 0 °C and 100 mL a 2M HCl aqueous solution were carefully added. The aqueous phase was extracted three times with 100 mL of ethyl acetate, washed with brine and dried over Na\(_2\)SO\(_4\). After evaporation of the volatiles the crude material was dissolved in 60 mL of THF and treated with 60 mL of a 1M KOH aqueous solution. After 1 h at room temperature, the mixture was neutralized by adding 60 mL of a 1M HCl aqueous solution. The aqueous phase was extracted three times with ethyl acetate, washed with brine and dried over Na\(_2\)SO\(_4\). After evaporation of the volatiles the crude material was purified by column chromatography with 10% EtOAc/hexane to get 6.29 g (20.79 mmol, 72%) of a clear liquid oil.

\[ R_f = 0.39 \] (20% EtOAc/hexane; KMnO\(_4\)).

Optical Rotation: \([\alpha]_{D}^{27} = +16.3^\circ\).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 3.86-3.78\ (1\ H), 3.52-3.39\ (2\ H), 2.22\ (s, OH), 1.76-1.62\ (2\ H), 1.33-1.09\ (2\ H), 1.08-1.04\ (m, 24\ H), 0.89\ (d, 3\ H, \ J = 6.6 Hz), 0.86\ (d, 3\ H, \ J = 6.9 Hz).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 74.4, 69.3, 37.5, 36.6, 33.4, 18.5, 18.3, 16.2, 13.3, 12.7.

(2R,4R,5S)-5-[(triisopropylsilyl)oxy]-2,4-dimethyl-1-hexanal

4.51 g (14.91 mmol, 1 equiv.) of alcohol were dissolved into 150 mL of CH\(_2\)Cl\(_2\) and cooled down to 0 °C. 47 mg (0.30 mmol, 0.1 equiv.) of TEMPO were added followed by 177 mg (1.49 mmol, 0.1 equiv.) of KBr and 16 mL (29.81 mmol, 2 equiv.) of 13% aqueous NaOCl in 60 mL of pH 8.6 carbonate buffer. After 15 min TLC showed partial conversion therefore some more NaOCl was carefully added (without any buffer) until the alcohol disapp eared, whereupon the reaction was quenched with 10 mL of MeOH. After addition of some water and separation of the two phases the aqueous one was washed two more times with CH\(_2\)Cl\(_2\). The organic phases were collected, washed with brine and dried over Na\(_2\)SO\(_4\). After evaporation of the volatiles 4.32 g (14.37 mmol, 96%) of aldehyde were obtained and used in the next step without further purification.

\[ R_f = 0.71 \] (20% EtOAc/hexane; CAM); 0.48 (10% EtOAc/he xane; CAM).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 9.62\ (d, 1\ H, \ J = 1.8 Hz), 3.92-3.81\ (m, 1\ H), 2.44\ (m, 1\ H), 1.74-1.59\ (m, 1\ H), 1.56-1.46\ (m, 1\ H), 1.34-1.25\ (m, 1\ H), 1.08\ (d, 3\ H, \ J = 6.3 Hz), 1.08-1.06\ (s, 24\ H), 0.89\ (d, 3\ H, \ J = 6.6 Hz).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 204.9, 71.9, 44.4, 37.7, 33.4, 18.8, 18.2, 16.2, 13.6, 13.2, 12.6.

[20] Alternative procedure: 2 g (6.61 mmol, 1 equiv.) of alcohol were dissolved into 13 mL of dry CH\(_2\)Cl\(_2\) and 3.31 g (0.5 g / mmol alcohol) of molecular sieves and 1.340 g (9.92 mmol, 1.5 equiv.) of NMO were added at room temperature under argon. After 30 min the reaction mixture was cooled down to 0 °C and 0.116 g (0.33 mmol, 0.05 equiv.) of TPAP were added. After 10 min the ice bath was removed and the black reaction mixture was allowed to stir for the next hour. The resultant was then poured on a silica gel column (ø 34 mm, 25 g SiO\(_2\)) and the solid removed by flashing with CH\(_2\)Cl\(_2\) until all the product came through. Concentration of the organic solution yielded 1.58 g (14.37 mmol, 96%) of aldehyde which was not further purified.
(2E,4E,6E,8R,10R,11S)-methyl 11-[(triisopropylsilyl)oxy]-8,10-dimethyldodeca-2,4,6-trienoate (23)

1 mL (1.64 mmol, 1.20 equiv.) of a 1.6 M solution of butyllithium in hexane was added to 0.24 mL (1.71 mmol, 1.25 equiv.) of diisopropylamine dissolved in 1.1 mL of dry THF at -78 °C under argon. After 1 hour 503 mg (1.92 mmol, 1.40 equiv.) of phosphonate dissolved in 10 mL of dry THF were added drop wise over 20 min to the LDA solution at -78 °C. The clear orange solution was stirred 5 more min whereupon 412 mg (1.37 mmol, 1.00 equiv.) of the aldehyde dissolved into 3 mL of dry THF were added drop wise over 10 min. The mixture was stirred 1 hour at -78 °C and then allowed to warm to 0 °C over 4 h. After 30 minutes at 0 °C the red-brown solution was quenched with a saturated aqueous ammonium chloride solution and extracted 4 times in ethyl acetate. Washing with brine, followed by drying over Na$_2$SO$_4$, evaporation of the solvents and purification by column chromatography (3% EtOAc/hexane) yielded 526 mg (1.29 mmol, 94%, dr (E)/(Z) 98:2$^{21}$ of the desired product as a colorless oil.

$R_f = 0.39$ (10% EtOAc/hexane; CAM and UV).

**Optical Rotation:** $[\alpha]^{25}_D (\text{c} 0.77, \text{CHCl}_3) -1.5^\circ$.

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.30 (dd, 1 H, $J = 15.0, 11.1$ Hz), 6.52 (dd, 1 H, $J = 14.7, 10.5$ Hz), 6.25-6.06 (m, 2 H), 5.87-5.77 (m, 2 H), 3.90-3.83 (s, 3 H), 2.34-2.22 (m, 1 H), 1.73-1.63 (m, 1 H), 1.29-1.07 (m, 2 H), 1.05-1.02 (s, 24 H), 0.98 (d, 3 H, $J = 6.6$ Hz), 0.85 (d, 3 H, $J = 6.6$ Hz).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 167.4, 140.9, 137.6, 128.9, 119.5, 71.2, 51.7, 40.8, 37.7, 35.0, 20.3, 18.4, 18.1, 13.8, 12.7.

IR (thin film) v 2960, 2944, 2866, 1720, 1618, 1456, 1435, 1373, 1264, 1191, 1135, 1040, 1005, 950, 921, 888, 854, 759, 678, 656 cm$^{-1}$.

HRMS (MALDI) $m/z$: calcd for C$_{32}$H$_{40}$O$_4$SiNa $[M+Na]^+$ 431.2957; found 431.2948.

(2E,4E,6E,8R,10R,11S)-Methyl 11-hydroxy-8,10-dimethyldodeca-2,4,6-trienoate

1.936 g (4.74 mmol) of the silyl ether were dissolved into 2.4 mL of CH$_2$Cl$_2$ and cooled down to 0 °C. 50 mL of an HF solution (95:5:1 acetonitrile/48% aq. HF/water) were added and the mixture allowed to warm to room temperature and stirred over 24 h. The reaction was quenched with careful addition of sat. aq. NaHCO$_3$. The aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. Purification by column chromatography (30% EtOAc/hexane) afforded 805 mg (3.19 mmol, 67%) of the desired product as a colorless oil.

$R_f = 0.53$ (50% EtOAc/hexane; CAM and UV).

**Optical Rotation:** $[\alpha]^{25}_D (\text{c} 0.33, \text{CHCl}_3) -4.9^\circ$.

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.28 (dd, 1 H, $J = 14.1, 9.9$ Hz), 6.50 (dd, 1 H, $J = 15.0, 10.8$ Hz), 6.25-6.06 (m, 2 H), 5.88-5.80 (m, 2 H), 3.72 (s, 3 H), 3.69-3.63 (m, 1 H), 2.37-2.23 (m, 1 H), 1.62-1.51 (m, 1 H), 1.43-1.34 (m, 1 H), 1.19-1.12 (m, 1 H), 1.10 (d, 3 H, $J = 6.3$ Hz), 0.98 (d, 3 H, $J = 6.6$ Hz), 0.85 (d, 3 H, $J = 6.6$ Hz).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 167.5, 146.6, 144.9, 141.3, 127.9, 127.6, 119.5, 71.6, 51.5, 39.7, 37.5, 34.7, 19.7, 19.3, 14.8.

IR (thin film) v 3426, 2965, 2927, 1717, 1701, 1616, 1456, 1435, 1373, 1346, 1312, 1264, 1191, 1135, 1040, 1005, 950, 921, 888, 854, 719 cm$^{-1}$.

(2E,4E,6E,8R,10R,11S)-methyl-11-[(trietylsilyl)oxy]-8,10-dimethyldodeca-2,4,6-trienoate

0.94 mL (4.15 mmol, 1.3 equiv.) of TESOTf were added drop wise to 0.805 g (3.19 mmol, 1 equiv.) of alcohol and 0.85 mL (7.34 mmol, 2.3 equiv.) of 2,6-lutidine dissolved in 30 mL of dry CH$_2$Cl$_2$ at 0 °C under argon. After 15 min at 0 °C the reaction was quenched with sat. aq. NaHCO$_3$, extracted three times with CH$_2$Cl$_2$, washed with brine and dried over

$^{[21]}$ The diastereomeric ratio was determined by integrating the 1H NMR spectrum at $\delta = 6.52$ and $\delta = 6.85$ (98:2).

$^{[22]}$ Higher yields (86-95%) were obtained when the TIPS protected alcohol was dissolved in THF. In all cases the un-reacted starting material could be recovered.
Na$_2$SO$_4$. Purification by column chromatography (5% EtOAc/hexane) afforded 944 mg (2.58 mmol, 81%) of the desired product as colorless oil.

**R**$_f$ = 0.39 (10% EtOAc/hexane; CAM and UV).

**Optical Rotation:** [$\alpha$]$^25_D$ (c 0.41, CHCl$_3$) -1.9°.

**1H NMR** (300 MHz, CDCl$_3$) δ 7.30 (dd, 1 H, $J$ = 15.3, 11.4 Hz), 6.53 (dd, 1 H, $J$ = 14.7, 10.8 Hz), 6.26-6.07 (m, 2 H), 5.90-5.80 (m, 2 H), 3.74 (s, 3 H, 5.1 Hz), 3.71-3.64 (m, 1 H), 2.33-2.23 (m, 1 H), 1.60-1.51 (m, 1 H), 1.38-1.29 (m, 1 H), 1.16-1.06 (m, 1 H), 1.04 (d, 3 H, $J$ = 6.3 Hz), 1.0-0.9 (3 H), 0.95 (q, 9 H, $J$ = 11.1, 6.6 Hz), 0.83 (d, 3 H, $J$ = 6.9 Hz), 0.59 (t, 6 H, $J$ = 3.3 Hz).

**13C NMR** (75 MHz, CDCl$_3$) δ 167.5, 146.8, 145.0, 141.4, 127.8, 127.7, 119.4, 71.4, 51.5, 40.2, 37.8, 34.9, 19.9, 19.1, 14.6, 7.1, 5.1.

**IR (thin film)** ν 2956, 2911, 2876, 1720, 1618, 1458, 1434, 1379, 1344, 1311, 1262, 1236, 1189, 1133, 1108, 1063, 1040, 1004, 963, 1917, 885, 799, 774, 742, 725, 668 cm$^{-1}$.

**HRMS** (MALDI) m/z: calcd for C$_{27}$H$_{33}$O$_5$SiNa [M+Na]$^+$, 389.2488; found 389.2477.

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(2E,4E,6E,8R,10R,11S)-11-[(trietylsilyl)oxy]-8,10-dimethyldodeca-2,4,6-triene-1-ol

![Chemical structure](image)

85 mL (0.47 mol, 5.00 equiv.) of a 1 M DIBAL solution in hexane were added drop wise to 36.01 g (94.60 mmol, 1 equiv.) of methyl ester dissolved in 380 mL of dry CH$_2$Cl$_2$ at -78 °C under argon. After about 20 min TLC showed complete conversion and the yellowish solution was quenched by carefully adding 20 mL of MeOH followed by a saturated aqueous Rochelle’s salt solution at -78 °C. The reaction mixture was allowed to warm up to room temperature and stir for an additional 4 hours. Separation of the phases followed by extraction of the aqueous phase two more times with CH$_2$Cl$_2$, washing with brine, drying over sodium sulfate, and evaporation of the solvent yielded a colorless oil which was taken further into the next step.$^{23}$

**R**$_f$ = 0.27 (20% EtOAc/hexane; CAM, UV).

**Optical Rotation:** [$\alpha$]$^25_D$ (c 0.89, CHCl$_3$) +8.5°.

**1H NMR** (300 MHz, CDCl$_3$) δ 6.30-6.00 (m, 4 H), 5.79 (dt, 1 H, $J$ = 15.0, 5.7 Hz), 5.63 (dd, 1 H, $J$ = 14.7, 7.8 Hz), 4.18 (d, 2 H, $J$ = 6.0 Hz), 3.72-3.63 (m, 1 H), 2.30-2.16 (m, 1 H), 1.61-1.51 (m, 2 H), 1.35-1.26 (m, 1 H), 1.15-1.07 (m, 1 H), 1.03 (d, 3 H, $J$ = 6.3 Hz), 0.97-0.92 (d hidden, 3 H), 0.94 (t, 9 H, $J$ = 8.1 Hz), 0.83 (d, 3 H, $J$ = 6.6 Hz), 0.57 (q, 6 H, $J$ = 15.9, 7.8 Hz).

**13C NMR** (75 MHz, CDCl$_3$) δ 142.2, 133.6, 131.7, 130.9, 129.5, 127.9, 71.4, 63.5, 40.4, 37.7, 34.6, 20.2, 18.9, 14.5, 7.0, 5.1

**IR (thin film)** ν 3344, 2956, 2875, 1455, 1379, 1238, 1073, 994, 724 cm$^{-1}$.

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(2E,4E,6E,8R,10R,11S)-11-[(trietylsilyl)oxy]-8,10-dimethyldodeca-2,4,6-triene-1-al

The crude alcohol of the previous experiment (<94.6 mmol, 1.00 equiv.) was dissolved into 1000 mL of dry CH$_2$Cl$_2$ and 82 g (0.95 mol, 10.0 equiv.) of active MnO$_2$ were added in one portion. After 12 h at room temperature under argon the solid was removed by filtration over a pad of Celite and the solution concentrated to a yellowish liquid which was taken to the next step without further purification.$^{24}$

**R**$_f$ = 0.64 (30% EtOAc/hexane; CAM, UV).

**Optical Rotation:** [$\alpha$]$^25_D$ (c 0.96, CHCl$_3$) +1.8°.

**1H NMR** (300 MHz, CDCl$_3$) δ 9.54 (d, 1 H, $J$ = 8.1 Hz), 7.11 (dd, 1 H, $J$ = 15.3, 11.1 Hz), 6.64 (dd, 1 H, $J$ = 14.1, 10.5 Hz), 6.35 (dd, 1 H, $J$ = 14.7, 10.8 Hz), 6.16 (dd, 1 H, $J$ = 15.0, 10.5 Hz), 6.12 (dd, 1 H, $J$ = 15.0, 7.8 Hz), 5.94 (dd, 1 H, $J$ = 15.3, 7.8 Hz), 3.71-3.60 (m, 1H), 2.38-2.24 (m, 1 H), 1.60-1.49 (m, 1 H), 1.40-1.31 (m, 1 H), 1.17-1.07 (m, 1 H), 1.04 (d, 3 H, $J$ = 6.3 Hz), 0.99 (d, 3 H, $J$ = 6.9 Hz), 0.94 (t, 9 H, $J$ = 8.1 Hz), 0.83 (d, 3 H, $J$ = 6.6 Hz), 0.56 (q, 6 H, $J$ = 15.9, 7.5 Hz).

**13C NMR** (75 MHz, CDCl$_3$) δ 193.4, 152.3, 148.6, 143.3, 130.5, 127.8, 127.6, 71.4, 40.0, 37.8, 35.0, 19.8, 19.2, 14.7, 7.0, 5.1.

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$^{[23]}$ Purification by column chromatography can be performed with 20% EtOAc/hexane. Yield 94%.

$^{[24]}$ TPAP oxidation afforded 79% of crude aldehyde.
(2E,4E,6E,8E,10E,12E,14R,16R,17S)-methyl 17-[(trietylsilyl)oxy]-14,16-dimethyloctadeca-2,4,6,8,10,12-hexaenoate

(113.52 mmol, 1.2 equiv.) of a 1.6 M solution of butyllithium in hexane were added to 17 mL (118.25 mmol, 1.25 equiv.) of diisopropylamine dissolved in 75 mL of dry THF cooled to -78 °C under argon. After 1 hour 36.59 g (132.44 mmol, 1.2 equiv.) of a 1.6 M solution of butyllithium in hexane were added to 17 mL (118.25 mmol, 1.2 equiv.) of phosphonate dissolved in 75 mL of dry THF at -78 °C under argon. The clear orange to deep red solution was stirred 5 more min whereupon the crude aldehyde of the previous experiment (<94.60 mmol, 1 equiv.) dissolved into 190 mL of dry THF cooled to -78 °C was drop wise transferred via cannula over 20 min. The mixture was stirred 1 hour at -78 °C and then allowed to warm to 0 °C over 4 h. After 30 min at 0 °C the red-brown solution was quenched with sat. aq. NH₄Cl and extracted 4 times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated. Purification by column chromatography (5% EtOAc/hexane) afforded 23.27 g (52.33 mmol, 55% over 3 steps) of the desired product as bright yellow solid.

Optical Rotation: [α]₀⁻²⁰.⁰.

H NMR (300 MHz, CDCl₃) δ 7.33 (dd, 1 H, J = 15.3, 11.7 Hz), 6.60 (dd, 1 H, J = 14.4, 11.4 Hz), 6.45 (dd, 1 H, J = 14.7, 11.1 Hz), 6.36-6.04 (m, 7 H), 5.86 (d, 1 H, J = 15.3 Hz), 5.69 (dd, 1 H, J = 14.7, 7.5 Hz), 3.74 (s, 3 H), 3.70-3.66 (m, 1 H), 2.28-2.21 (m, 1 H), 1.60-1.49 (m, 1 H), 1.36-1.27 (m, 1 H), 1.15-1.10 (m, 1 H), 1.04 (d, 3 H, J = 6.3 Hz), 0.97-0.92 (hidden d, 3 H, J = 6.9 Hz), 0.95 (t, 9 H, J = 8.1 Hz), 0.83 (d, 3 H, J = 6.6 Hz), 0.57 (q, 6 H, J = 15.9, 7.8 Hz).

C NMR (75 MHz, CDCl₃) δ 167.4, 144.6, 143.3, 140.9, 137.5, 135.9, 135.2, 131.5, 131.2, 130.5, 129.4, 128.3, 119.7, 71.4, 51.5, 40.4, 37.8, 34.8, 20.1, 19.0, 14.5, 7.1, 5.1.

IR (thin film) v 2957, 2876, 2342, 1712, 1618, 1561, 1458, 1241, 1139, 1010, 726, 668 cm⁻¹.
The crude alcohol of the previous experiment (<2.52 mmol, 1 equiv.) was dissolved into 52 mL of dry CH₂Cl₂ and cooled to -78 °C.²⁵ DIBAL (1 M in hexane, 16 mL, 16.0 mmol, 6.3 equiv.) was added drop wise. After 15 minutes at -78 °C TLC analysis showed complete conversion and the reaction was quenched with 1 mL of methanol. A sat. Rochelle’s salt solution was then poured into the reaction mixture and the temperature let to increase from -78 °C to room temperature. The two phases were separated and the aqueous phase was washed with EtOAc. The combined organic phases were dried over MgSO₄ and then filtered through a pad of Na₂SO₄ before concentration. The crude alcohol was dissolved into 30 mL of dry CH₂Cl₂ and 2.19 g (25.2 mmol, 10 equiv.) of MnO₂ were added. After 12 hours at room temperature under argon TLC analysis showed complete conversion, the solid was filtered off through a pad of Celite and washed extensively with CH₂Cl₂. After evaporation of the solvents 0.47 g (1.56 mmol, 62%) of an orange solid were obtained which were pure enough (1H NMR) and could be used in the subsequent step. 

Rᶠ = 0.45 (50% EtOAc/hexane; VIS yellow; CAM).

Optical Rotation: [α]²⁵ D (c 0.20, CHCl₃) -22.8°.

¹H NMR (300 MHz, CDCl₃) δ 9.55 (d, 1 H, J = 7.8 Hz), 7.14 (dd, 1 H, J = 15.0, 11.1 Hz), 6.71 (dd, 1 H, J = 14.7, 11.1 Hz), 6.56-6.06 (m, 9 H), 5.72 (dd, 1 H, J = 15.3, 8.1 Hz), 3.72-3.64 (m, 1 H), 2.34-2.25 (m, 1 H), 1.64-1.55 (m, 1 H), 1.43-1.34 (m, 1 H), 1.12 (d, 3 H, J = 6.3 Hz), 0.99 (d, 3 H, J = 6.6 Hz), 0.87 (d, 3 H, J = 6.9 Hz).

¹³C NMR (75 MHz, CDCl₃) δ 193.2, 151.8, 143.5, 142.7, 139.0, 136.8, 135.7, 131.4, 131.0, 130.6, 129.4, 128.3, 71.6, 39.8, 37.5, 34.7, 19.9, 19.2, 14.7.

IR (thin film) ν 3346, 2963, 2924, 1674, 1558, 1458, 1150, 1102, 1010 cm⁻¹.

HRMS (EI) m/z calcd for C₂₀H₂₈O₂ [M]+, 300.2089; found 300.2085

Macrocyclization and reduction

Coupling of alcohol 24 and carboxylic acid 18:

Alcohol (176 mg, 588 µmol, 3 equiv.), and pyridine (8 µL, 100 µmol, 0.5 equiv.) were dissolved in dichloromethane (20 mL) to form a red solution. 2,4,6-trichlorobenzoic acid chloride (77 µL, 490.5 µmol, 2.5 equiv.) was added. A mixture of carboxylic acid (200 mg, 196 µmol) and pyridine (73 µL mg, 900 µmol, 4.6 equiv.) in 5 mL dichloromethane was added over 10 h using a syringe pump. The reaction mixture was stirred for and additional 2 h and then poured into sat. NaHCO₃ (30 mL). The phases were separated and the water phase extracted with 3x 10 mL dichloromethane. The combined organic phases were dried (Na₂SO₄) and concentrated. Flash chromatography (gradient: 1% pyridine/10-30% ethyl acetate/89-69% hexane) to affords recovered alcohol 120 mg and desired ester (120 mg, 48%). Due to its instability the ester was used immediately.

Rᶠ =0.34 (33% ethyl acetate/hexane, KMnO₄, CAM).

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²⁵ More dichloromethane was required than usual because by addition of the DIBAL solution in hexane the starting material started to crash out.
Horner-Wadsworth-Emmons macrocyclization:

The ester described above (120 mg, 96 µmol) was split in two equal batches and dried azeotropically with toluene (3x4 mL) in a 100 mL pear shaped flask. To each batch was added 18-Crown-6 (158 mg, 588 µmol, 12 equiv.) and was added and the mixture dissolved in toluene (50 mL). Then freshly powdered K$_2$CO$_3$ (41 mg, 296 µmol, 6 equiv.) was added. The resulting heterogeneous mixture was placed on a preheated oil bath at 60 °C for 12 h with stirring (300 rpm). The resulting red solution was washed with 2x10 mL Brine and the two batches reunited. The combined batches were concentrated. Flash chromatography (1% pyridine/ 20% ethyl acetate/hexane) afforded desired macrolactone (55 mg, 53% yield) as an orange solid. $R_f$ = 0.25 (25% ethyl acetate/hexane, KMnO$_4$/CAM).

$^1$H NMR (600 MHz, CD$_3$Cl$_2$) δ 7.36 (dd, 1H, $J$ =11.2Hz, $J$ =15.6Hz), 6.70 (dd, 1H, $J$ =11.2Hz, $J$ =14.5Hz), 6.52 (dd, 1H, $J$ =11.1Hz, $J$ =14.6Hz), 6.44-6.18 (m, 3H), 6.07 (d, 1H, $J$ =15.6Hz), 5.40 (dd, 1H, $J$ =9.7Hz, $J$ =14.1Hz), 5.04 (dq, 1H, $J$ =4.3Hz, $J$ =6.5Hz), 4.24 (dd, 1H, $J$ =4.8Hz, $J$ =10.2Hz, $J$ =11.0Hz), 4.18 (m, 1H), 3.83 (m, 1H), 3.75 (dt, 1H, $J$ =2.0Hz, $J$ =10.5Hz), 3.72 (m, 1H), 3.69 (s, 3H), 3.62 (m, 1H), 3.47 (dd, 1H, $J$ =2.8Hz, $J$ =6.4Hz, $J$ =9.4Hz), 2.83 (s, 3H), 3.10 (dd, 1H, $J$ =10.6Hz, $J$ =12.2Hz), 2.38 (dd, 1H, $J$ =7.4Hz, $J$ =15.8Hz), 2.29 (t, 1H, $J$ =10.2Hz), 2.24-2.18 (m, 2H), 2.09 (dd, 1H, $J$ =1.8Hz, $J$ =12.3Hz), 1.72 (d, 1H, $J$ =14.9Hz), 1.51-0.88 (m, 17H), 1.38 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H), 1.06 (d, 3H, $J$ =6.5Hz) 0.99 (d, 3H, $J$ =6.5Hz), 0.86 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H).

$^{13}$C NMR (150 MHz, CD$_3$Cl$_2$) δ 6199.6, 172.8, 169.9, 147.7, 142.3, 140.6, 138.3, 136.4, 135.5, 134.5, 132.8, 132.5, 132.1, 132.0, 131.5, 130.7, 130.6, 100.8, 98.8, 98.7, 75.1, 73.7, 70.9, 69.6, 68.6, 68.3, 66.0, 65.3, 57.7, 52.0, 47.8, 43.6, 43.4, 42.5, 42.2, 41.7, 37.5, 35.6, 34.6, 33.5, 32.5, 32.3, 30.3, 30.2, 30.1, 30.0, 29.7, 27.5, 22.3, 23.1, 19.9, 19.7, 18.6, 18.1, 14.6, 12.9, 14.3, -3.7, -4.1, -4.4, -4.8.

IR (thin film) ν 3383, 3012, 2988, 2955, 2932, 2859, 1737, 1647, 1615, 1547, 1462, 1438, 1378, 1309, 1257, 1200, 1138, 1099, 836, 777.

HRMS (MALDI) m/z: calc'd for C$_{61}$H$_{100}$O$_{13}$Si$_4$Na [M+Na], 1119.660, found 1119.661.

Protected C(35)-Deoxyamphoteronolide B (19)

A solution of ketone (75 mg, 68.4 µmol) was dissolved in a 1% Solution of pyridine in methanol (15 mL). The solution was cooled to 0 °C and NaBH$_4$ (25.9 mg, 684 µmol, 10 equiv.) was added and the reaction stirred for 5 min. during which time the colour of the solution changed from a strong red to weakly yellow. Cold sat. NaHCO$_3$ (100 mL) was added and the mixture extracted with diethyl ether/toluene (1:1, 4x20 mL). The organic phases were dried (Na$_2$SO$_4$) and the solvent removed at reduced pressure. Due to the sensitive nature of the product it was generally used directly without any further purification. In one experiment, the reduction of 4.5 mg ketone was carried out as described above and the product purified by flash chromatography (1% pyridine/70% diethyl ether/pentane) to afford pure 35-deoxy amphoteronolide as a yellow solid (3.3 mg, 73% yield) $R_f$ = 0.15 (25% ethyl acetate/hexane, KMnO$_4$/CAM).

$^1$H NMR (600 MHz, CD$_3$Cl$_2$) δ 6.28 (s, 12H), 5.87 (dd, 1H, $J$ =6.9, 14.3, 1H), 5.40 (dd, 1H, $J$ =4.2Hz, $J$ =6.4Hz), 4.51 - 4.43 (m, 1H), 4.28 - 4.15 (m, 2H), 3.89 (dd, 1H, $J$ =2.6, 5.0, 6.7, 1H), 3.84 (d, 1H, $J$ =10.9, 1H), 3.67 (s, 3H), 3.58 - 3.49 (m, 1H), 3.49 - 3.41 (m, 1H), 3.05 (s, 3H), 2.40 (dd, 1H, $J$ =7.6Hz, $J$ =16.0Hz), 2.30 (t, 1H, $J$ =10.2Hz), 2.24 (dd, 1H, $J$ =4.4, 7.4, 1H), 2.21 (dd, 1H, $J$ =5.8, 9.7, 1H), 1.76 (m, 4H), 1.58-0.84 (m, 17H), 1.41 (s, 3H), 1.38 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H), 1.06 (d, 1H, $J$ =6.5, 3H), 0.99 (d, 1H, $J$ =6.6, 3H), 0.88 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), -0.01 (s, 3H).

$^{13}$C NMR (150 MHz, CD$_3$Cl$_2$) δ 6173.5, 170.0, 139.6, 137.9, 133.7, 133.6, 133.3, 133.3, 133.2, 133.0, 132.9, 132.7, 132.3, 132.2, 131.5, 129.2, 100.8, 98.8, 98.6, 75.3, 73.6, 71.2, 69.7, 68.9, 68.6, 66.9, 65.9, 65.5, 56.8, 51.9, 48.2, 43.5, 42.6, 42.0, 41.7, 40.7, 37.4, 35.2, 34.5, 33.4, 32.7, 32.3, 30.5, 30.3, 30.1, 27.8, 23.1, 22.0, 19.9, 19.9, 18.7, 18.1, 14.6, 14.3, 13.1, -3.7, -4.1, -4.3, -4.8.

SI-21
IR (thin film) ν 3424, 2992, 2932, 2855, 1733, 1462, 1436, 1379, 1320, 1256, 1198, 1135, 1102, 1036, 1008, 836, 777.

HRMS (MALDI) m/z: calcld for C_{61}H_{102}O_{13}Si_{2}Na [M+Na], 1121.6751, found 1121.6770

**^1H NMR Spectra**
Compound 3:

\[
\text{MeO} - \text{OH} - \text{OTBS}
\]
Compound 4:

\[
\text{t-BuO} \quad \text{O} \quad \text{OH} \quad \text{OTBS}
\]
Compound 5:

\[
\text{t-BuO} \quad \text{O} \quad \text{OTBS}
\]
Compound 6:

OTBS

OTBS
SI-28
Compound 7:
LOC ETH NMR Mercury vs 200MHz Nr.5 11/25/04 13:46:35 USER:memag GROUP:nom SAMPLE:DC-52-140

STANDARD 1H OBSERVE

Sample directory: DC-52-140
File: lowfieldmetabolism/conversioln/Non
Pulse Sequence: n2ov
Solvent: CDCl3
Ambient temperature
User: memag

Mercury-300B "gemSec"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.996 sec
Width 4000.5 Hz
10 repetitions
OBSERVE 195.59,7298165 MHz
DATA PROCESSING
fft size 32768
Total time 0 min, 49 sec

SI-30
Compound 8:

```
O
O
O
O
```

```
Ot-Bu
```

Pulse Sequence: 42pul
Solvent: CDOD
Ambient temperature
User: scorg
File: DC-92-141-mw
SEQTYPE: 000 "mmremf"
Relax. delay 1.090 sec
Pulse 45.5 degrees
Acq. time 1.998 sec
NMR run 4000.5 Hz
10 repetitions
OBSERVE 1H, 296.7729 MHz
DATA PROCESSING
256 average
Total time 5 min, 46 sec
Compound 9:
Compound 10:

\[ \text{OBn} \quad \text{OTBS} \quad \text{Ot-Bu} \]
Compound 11:

\[
\text{OBn} - \text{O} - \text{O} - \text{N}^{\text{OH}} - \text{OTBS}
\]
Compound 12:
Compound 14:

\[ \text{Structure of Compound 14} \]

NMR spectrum:

- df (ppm): 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5

SI-40
Compound 16:
Compound 17:
Compound 18:
Pulse Sequence: z2pul
Solvent: CDCl3
Ambient temperature
User naming
File: water-endback
UNETplus-500 "moso"

Pulse 90°-0°-degrees
Avg. line 3.156 sec
Width 5086.4 Hz
10 repetitions
OBSERVE H1, 299.9912510-MHz
DATA PROCESSING
FT size 20768
Total time 0 sec, 50 sec

14.74
6.73
11.82
6.73
TIPSO OEt

STANDARD H OBSERVE

Res: PROTON
Pulse Sequence: 62psw
Solvent: CDCl₃
Ambient temperature
User: scoring
GEMINI-2000030 "gem30x"

Pulse in a degrees
Avg. time 3.136 sec
Width GWR 4 Hz
16 repetitions
OBSERVE H, 300.000000 MHz
DATA PROCESSING
FT size 32768
Total time 5 min, 52 sec
OTIPS

OH

STANDARD: H-OBSERVE

Proton Resonance edited

Solvent: CDCl3
Ambient temperature
User: scoring
File: QI-50-12.txt
UNMRplus-99 "ominus"

Note: scalar moment
Avg. time 3.128 sec
Width: 2000.4 Hz
16 repetitions
OBSERVE: 91.259912510 MHz
DATA PROCESSING
FT size 50768
Total time 6 min, 20 sec

SI-50
Compound 21:

OTIPS

LOC ETHZ-NMR Mercury 300MHz N.4. 13/26/03 11:41:39 USER recceang GROUPname SAMPLE DC-S2-51

STANDARD 1H OBSERVE

Phase: transparent: tattep
Solvent: CDCl3
Ambient temperature: User: recceang
File: DC-S2-51-tattep UNETYslice-300 "wencp"

Phase 90° degrees
Avg. time 3.156 sec
Width 5095.4 Hz
10 repetitions
OBSERVE: H1, 299.61120/10 MHz
RESULTS: FILTERED
FT size 10768
Total time 6 min, 50 sec

SI-51
Compound 22:

OTIPS

\[ \text{Ph} \]

\[ \text{OH} \]
OTIPS OH

Pulse Sequence: 32pf
Solvent: CDCl3
Ambient temperature
User: OTIPS
File: DC-52-54-torr
UNITYplus-300 "temoc"

Pulse 90.0 degrees
Acq. time 3.136 sec
Width=5009.4 Hz
16 acquisitions
OBSEsive R, 296.301/2510 MHz
DATA PROCESSING
FT size 52768
Total time 0 min, 50 sec

SI-53
Compound 22:

\[ \text{OTIPS} \]

- **Si ETR2 NMR** Memory 300 MHz ft 4 12000 15-50 45 USER:scanning GROUP:same SAMPLE DC-52-55
- **STANDARD**: H N OBSERVE

- **Sequence**: csp
- **Solvent**: CDCl3
- **Temperature**: Ambient
- **Pulse**: 30.0 degrees
- **Acq. time**: 5.156 sec
- **Water**: 0.006 0.1 Hz
- **16 Repetitions**

**OBSEIVE** 1H, 293.0015 10 MHz

**DATA PROCESSING**
- FT size 30758
- Total time 6 min., 50 sec

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**NMR Spectrum**

- Peaks at 2.33, 2.52, 4.06, 1.69, 0.37, 1.66, 2.23, 6.12, 7.21 ppm
SI-56
SI-57
SI-58
OTES
SI-61
Compound 24:

LOC E212 NMR Mercury-res.300Hz-Nr-5 091704 11:57:27 USER: avinag GROUP:sample SAMPLE: DC-52-121

STANDARD 1H OBSERVE

Pulse Sequence: d2pul
Solvent: CDCl3
Ambient temperature
User: avinag
File: DC-52-121-base
UMEType: 300 "tesa"

Pulse 30.0 degrees
Avg. time 3.138 sec
Width 5036.4 Hz
16 repetitions
OBSERVE: 300.0223602 MHz
DATA PROCESSING
FT axis 979.58
Total time 0 min, 50 sec

2.69 3.08 2.00 2.92 2.59 13.204 8.511 8.62 12.04
Ethyl phosphonate ester:
Compound 19: