Supporting Information

Synthetic studies toward marine metabolite prorocentin-4: Synthesis of the C1–C23 fragment

Praveen AnkiReddy, Sandeep AnkiReddy and Gowravaram Sabitha*

Natural Product Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad-500 007, India

Corresponding Author: E-mail: gowravaramsr@yahoo.com; sabitha@iict.res.in;
Fax: +91-40-27160512

H and 13C spectra for all compounds 14-44
Experimental section

General methods

All the air and moisture sensitive reactions were carried out under inert atmosphere (nitrogen or argon). Oven-dried glass apparatus were used to perform all the reactions. Freshly distilled anhydrous solvents were used for air and moisture sensitive reactions. Commercially available reagents were used as such. Purification of compounds was carried out via column chromatography by using silica gel (60-120 or 100-200 mesh) packed in glass columns. $^1$H NMR and $^{13}$C NMR were recorded in CDCl$_3$ solvent on 300 MHz, 400 MHz, 500 MHz, 700 MHz and 75 MHz, 100 MHz, 125 MHz spectrometer, respectively, using TMS as an internal standard. Chemical shifts are measured as ppm values relative to internal CDCl$_3$ δ 7.26 or TMS δ 0.0 for $^1$H NMR and CDCl$_3$ δ 77 for $^{13}$C NMR. In $^1$H NMR multiplicity defined as: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublet; ddd = doublet of doublet of doublet; dt = doublet of triplet; m = multiplet; brs = broad singlet. Optical rotation values were recorded on Horiba sepa 300 polarimeter using a 2 mL cell with a 10 mm path length. FTIR spectra were recorded on Alpha (Bruker) infrared Spectrophotometer. High resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer. The diastereomeric excess of the products was measured by HPLC using Shimadzu LC-20AT series with XDB C18, 150 × 4.6, 5U column. Mass spectra were recorded on Micro Mass VG-7070H mass spectrometer for ESI and EI are given in mass units (m/z). High-resolution mass spectra (HRMS) [ESI] were obtained using either a TOF or a double focusing spectrometer.

Spectral data for all compounds

($4\text{S},5\text{S},E$)-ethyl 7-(benzyloxy)-5-((tert-butyldimethylsilyl)oxy)-4-methylhept-2-enoate (13): To an ice-cooled solution of 2-(iodooxy)benzoic acid (2.3 g, 8.27 mmol) in anhydrous CH$_3$CN (10 mL) was added a solution of alcohol 7 (2.0 g, 5.91 mmol). The mixture was refluxed for 1 h, and then allowed to cool to RT. The solvent was removed under reduced pressure and the unstable crude aldehyde product was used directly for the next step without further purification by column chromatography.

The crude product was immediately dissolved in C$_6$H$_6$ (20 mL), and stable two-carbon Wittig yilide (2.5 g, 7.09 mmol) was added. The reaction mixture was refluxed for 3 h and then allowed to cool to RT. The solvent was removed under reduced pressure and the unstable crude aldehyde product was used directly for the next step without further purification by column chromatography.

($4\text{S},5\text{S},E$)-7-(benzyloxy)-5-((tert-butyldimethylsilyl)oxy)-4-methylhept-2-en-1-ol (13a): To a solution of 13 (1.7 g, 4.19 mmol) in CH$_2$Cl$_2$ (20 mL) was added 8.4 mL of DIBAL-H (1.6 M in hexane, 13.4 mmol) at 0 °C. The solution was warmed to room temperature and stirred for 3 h until two clear layers were observed. The layers were separated, and the aqueous layer was further extracted with CH$_2$Cl$_2$ (2 × 20 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, and solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (10% EtOAc/ hexane) to provide 13a (1.4 g, 95%) as colorless oil. $[\alpha]_{D}^{25}$: $-5.4$ (c = 1.2, CHCl$_3$); IR (neat): 2930, 2856, 1721, 1459, 1047 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.31-7.18 (m, 5H), 5.58-5.51 (m, 2H), 4.42 (ABq, $J = 17.3, 11.3$ Hz, 2H), 4.06-3.96 (m, 2H), 3.73-3.63 (m, 1H), 3.48-3.40 (m, 2H), 2.28-2.17 (m, 1H), 1.77-1.45 (m, 2H), 0.81 (s, 9H), 0.76 (d, $J = 6.8$Hz, 3H), 0.04 (s, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 138.4, 132.1, 130.1, 128.2, 127.5, 127.4, 72.8, 72.5, 67.4, 63.5, 38.6, 34.6, 25.8, 18.0, 14.4, $-4.4$, $-4.5$. HRMS (ESI) m/z calcld for C$_{22}$H$_{40}$O$_3$NaSi [M+Na]$^+$ = 443.2588, found = 443.2591.

[$\alpha$]$_D^{25}$: $-5.4$ (c = 1.2, CHCl$_3$); IR (neat): 2930, 2856, 1721, 1459, 1047 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.31-7.18 (m, 5H), 5.58-5.51 (m, 2H), 4.42 (ABq, $J = 17.3, 11.3$ Hz, 2H), 4.06-3.96 (m, 2H), 3.73-3.63 (m, 1H), 3.48-3.40 (m, 2H), 2.28-2.17 (m, 1H), 1.77-1.45 (m, 2H), 0.81 (s, 9H), 0.76 (d, $J = 6.8$Hz, 3H), 0.04 (s, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 138.4, 132.1, 130.1, 128.2, 127.5, 127.4, 72.8, 72.5, 67.4, 63.5, 38.6, 34.6, 25.8, 18.0, 14.4, $-4.4$, $-4.5$. HRMS (ESI) m/z calcld for C$_{22}$H$_{40}$O$_3$NaSi [M+Na]$^+$ = 443.2588, found = 443.2591.
chromatography (10% EtOAc/hexane) to afford the epoxide extracted with EtOAc (3 × 10 mL). The combined organic fraction was dried over anhydrous Na$_2$SO$_4$. To a freshly flame-dried, double-necked roundbottom flask that was equipped with activated molecular sieves (4 Å, ca. 3 g) and dry CH$_2$Cl$_2$ (20 mL) at –20 °C were added Ti(OiPr)$_4$ (0.20 mL, 0.71 mmol) and l-(-)-di Ethyl tartrate (0.18 g, 0.71 mmol), and the mixture was stirred for 30 min. To the reaction was added allyl alcohol 13a (1.3 g, 3.57 mmol) followed by tosyl-imidazole (0.92 g, 4.18 mmol), and the resulting mixture was stirred vigorously for 1 h. The mixture was warmed to 0 °C and then filtered through Celite. The filtrate was quenched with water (10 mL) and a 15% aqueous NaOH solution (1mL), and the resulting mixture was stirred vigorously for 1 h. The biphasic solution was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 10 mL). The combined organic extracts were dried with anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The crude residue was purified by column chromatography (30% EtOAc/hexane) to afford the pure epoxide 14 (1.26 g, 93%) as a colorless oil; $[\alpha]_D^{25}$: −30.7 ($c = 1.2$, CHCl$_3$); IR (neat): 3422, 2930, 1461, 1074, 771 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38-7.27 (m, 3H), 4.53-4.44 (m, 3H), 4.02-3.97 (m, 1H), 3.92 (dd, $J = 12.5$, 2.4 Hz, 1H), 3.64-3.51 (m, 2H), 3.48 (t, $J = 6.7$ Hz, 1H), 3.0-2.87 (m, 2H), 1.98-1.84 (m, 1H), 1.81 (q, $J = 6.7$ Hz, 1H), 1.31 (d, $J = 6.2$ Hz, 3H), 0.89 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 138.4, 134.8, 128.8, 128.3, 127.5, 127.4, 72.9, 72.0, 66.9, 61.8, 57.6, 57.5, 40.4, 34.6, 25.8, 18.1, 9.8, −4.4, −4.6. HRMS (ESI) m/z calced for C$_{22}$H$_{30}$O$_2$Si [M+H]$^+$ = 381.2455, found = 381.2455.

((2R,3R)-3-(2S,3S)-5-(benzylxoy)-3-((tert-butyl(dimethyl)silyloxy)pentan-2-yl)oxiran-2-yl)methanol (14): To a freshly flame-dried, double-necked roundbottom flask that was equipped with activated molecular sieves (4 Å, ca. 3 g) and dry CH$_2$Cl$_2$ (20 mL) at –20 °C were added Ti(OiPr)$_4$ (0.20 mL, 0.71 mmol) and l-(-)-di Ethyl tartrate (0.18 g, 0.71 mmol), and the mixture was stirred for 30 min. After completion of reaction, water was added and the mixture was stirred for 30 min at 0 °C. After completion of reaction, water was added and the mixture was stirred for 30 min at 0 °C. After completion of reaction, water was added and the mixture was stirred for 30 min at 0 °C. After completion of reaction, water was added and the mixture was stirred for 30 min at 0 °C. After completion of reaction, water was added and the mixture was stirred for 30 min at 0 °C. After completion of reaction, water was added and the mixture was stirred for 30 min at 0 °C. After completion of reaction, water was added and the mixture was stirred for 30 min at 0 °C. After completion of reaction, water was added and the mixture was stirred for 30 min at 0 °C. After completion of reaction, water was added and the mixture was stirred for 30 min at 0 °C. After completion of reaction, water was added and the mixture was stirred for 30 min at 0 °C. After completion of reaction, water was added and the mixture was stirred for 30 min at 0 °C. After completion of reaction, water was added and the mixture was stirred for 30 min at 0 °C.

$[\alpha]_D^{25}$: +5.0 ($c = 1.1$, CHCl$_3$); IR (neat): 3408, 2930, 1461, 1074, 771 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.39-7.27 (m, 5H), 4.51 (d, $J = 12.0$ Hz, 1H), 4.46 (d, $J = 11.7$ Hz, 1H), 4.07-3.99 (m, 1H), 3.85-3.36 (m, 5H), 1.95-1.53 (m, 5H), 0.94-0.83 (m, 12H), 0.10 (s, 3H), 0.06 (s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 138.2, 128.2, 127.6, 72.7, 72.8, 70.9, 67.2, 67.0, 35.9, 34.6, 31.9, 25.8, 17.9, 14.1, −4.3, −4.9. HRMS (ESI) m/z calced for C$_{22}$H$_{30}$O$_2$Si [M+H]$^+$ = 383.2619, found = 383.2612.
The solvent was removed under reduced pressure and the unstable crude product was purified by column chromatography (60% EtOAc/hexane) to afford compound 15 (0.3 g, 95%) as a colorless oil; [α]_D^{25}: +3.6 (c = 0.12, CHCl₃); IR (neat): 3417, 2929, 1453, 1092 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.36-7.28 (m, 5H), 4.54-4.50 (m, 2H), 4.15-3.98 (m, 1H), 3.90-3.77 (m, 1H), 3.70-3.46 (m, 4H), 2.44-2.27 (m, 1H), 2.03-1.89 (m, 1H), 1.75-1.65 (m, 3H), 0.96 (d, J = 7.0 Hz, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 138.4, 128.2, 127.5, 127.4, 127.3, 78.5, 77.2, 72.9, 67.8, 65.4, 36.1, 35.3, 30.6, 14.1. HRMS (ESI) m/z calcd for C₁₃H₂₀O₃Si [M+H]^+ = 251.1643, found = 251.1641.

(E)-ethyl 3-((2R,4S,5S)-5-(2-benzyloxy)ethyl)-4-methyltetrahydrofuran-2-yl)acrylate (16): To an ice-cold solution of 2-(iodooxy)benzoic acid (0.47 g, 1.68 mmol) in anhydrous MeCN (5 mL) was added a solution of triethyl phosphonoacetate (0.28 g, 1.44 mmol) in THF (5 mL) was added slowly to a stirred solution of NaH (0.05 g, 2.4 mmol) in THF (5 mL) at 0 °C under N₂. The mixture was stirred for 30 min, after which a solution of the crude aldehyde in THF (10 mL) was added dropwise over 10 min at 0 °C. The resulting mixture was stirred at 0 °C for a further 30 min. The mixture was quenched with saturated NH₄Cl solution (5 mL), and the product extracted with EtOAc (3 × 5 mL). The combined extracts were dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude residue was purified by column chromatography (10% EtOAc–hexane) to afford the (E)-alkene ester 16 (0.3 g, 85% over 2 steps) as a colorless liquid. [α]_D^{25}: +7.2 (c = 1.0, CHCl₃); IR (neat): 2964, 1716, 1370, 1299, 786 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.36-7.28 (m, 5H), 4.68-4.62 (m, 1H), 4.53 (s, 2H), 4.19 (q, J = 7.2 Hz, 2H), 1.89-1.61 (m, 3H), 1.34-1.17 (m, 2H), 0.92 (t, J = 6.8 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 138.4, 128.2, 127.5, 127.4, 127.3, 78.5, 77.2, 72.9, 67.8, 65.4, 36.1, 35.3, 30.6, 14.1. HRMS (ESI) m/z calcd for C₂₁H₃₂O₃Si [M+H]^+ = 317.1750, found = 317.1747.

A solution of triethyl phosphonoacetate (0.28 g, 1.44 mmol) in THF (5 mL) was added slowly to a stirred solution of NaN₃ (0.05 g, 2.4 mmol) in THF (5 mL) at 0 °C under N₂. The mixture was stirred at 0 °C for 30 min, after which a solution of the crude aldehyde in THF (10 mL) was added dropwise over 10 min at 0 °C. The resulting mixture was stirred at 0 °C for a further 30 min. The mixture was quenched with sat. NH₄Cl solution (5 mL), and the product extracted with EtOAc (3 × 5 mL). The combined extracts were dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude residue was purified by column chromatography (10% EtOAc–hexane) to afford the (E)-alkene ester 16 (0.3 g, 85% over 2 steps) as a colorless liquid. [α]_D^{25}: +7.2 (c = 1.0, CHCl₃); IR (neat): 2964, 1716, 1370, 1299, 786 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.36-7.28 (m, 5H), 4.68-4.62 (m, 1H), 4.53 (s, 2H), 4.19 (q, J = 7.2 Hz, 2H), 1.89-1.61 (m, 3H), 1.34-1.17 (m, 2H), 0.92 (t, J = 6.8 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 138.4, 128.2, 127.5, 127.4, 127.3, 78.5, 77.2, 72.9, 67.8, 65.4, 36.1, 35.3, 30.6, 14.1. HRMS (ESI) m/z calcd for C₂₁H₃₂O₃Si [M+H]^+ = 317.1750, found = 317.1747.
and then filtered through Celite. The filtrate was quenched with water (2 mL) and a 15% aqueous NaOH solution (2 mL), and the resulting mixture was stirred vigorously for 1 h. The biphasic solution was separated, and the aqueous layer was extracted with CH₂Cl₂ (2 x 5 mL). The combined organic extracts were dried with anhydrous Na₂SO₄ and concentrated under vacuum. The crude residue was purified by column chromatography (30% EtOAc/hexane) to afford the pure epoxide 17 (0.12 g, 80%) as a yellow oil.

To a stirred suspension of CuI (0.29 g, 1.53 mmol) in dry Et₂O (5 mL) was slowly added methyl lithium (1.9 mL, 1.6 M) in ether at 0 °C under nitrogen atmosphere, and the resulting solution was stirred for 15 min at 0 °C. Epoxy alcohol 17 (0.15 g, 0.51 mmol) in dry Et₂O (3 mL) was then added dropwise at -40 °C. Once the addition was completed, the reaction mixture was stirred at 0 °C for 3 h. The reaction was quenched by the addition of saturated aqueous NH₄Cl. The mixture was filtered through a Celite pad, and the salts were washed several times with Et₂O. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure to provide a 3:1 mixture of the regioisomeric diols. The crude mixture was dissolved in 10% aqueous THF (5 mL), and NaIO₄ was added at 0 °C to cleave the 1,2-diol. The reaction was completed in 1 h. After the layers were separated, the aqueous layer was extracted with Et₂O. The organic layer was dried over anhydrous Na₂SO₄, and solvent was removed under reduced pressure. The crude residue was purified on silica gel column chromatography (70% EtOAc/hexane) to provide the desired diol 9 (0.12 g, 80%) as a yellow oil. [α]D²⁵: +18.1 (c = 1.2, CHCl₃); IR (neat): 3448, 1634, 771 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.28 (m, 5H), 4.51 (s, 2H), 4.17-4.01 (m, 2H), 3.72 (dd, J = 12.6, 2.3 Hz, 1H), 2.34-2.27 (m, 1H), 1.79-1.70 (m, 3H), 0.93 (d, J = 7.0 Hz, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 138.4, 128.3, 127.6, 127.5, 79.2, 75.3, 73.0, 67.9, 61.2, 57.2, 56.5, 36.0, 35.7, 30.8, 13.9. HRMS (ESI) m/z calced for C₁₉H₂₆O₄ [M+H]⁺ = 293.1748, found = 293.1747.
mixture was stirred for 1 h at room temperature and quenched by addition of water. The aqueous layer was extracted with CH$_2$Cl$_2$ dried over Na$_2$SO$_4$ and concentrated. The crude reaction mixture was purified by silica gel column chromatography (5% EtOAc/hexane) to provide the desired product 18 (0.13 g, 93%) as a colorless oil. [a]$_D^{25}$: +10.5 (c = 1.2, CHCl$_3$); IR (neat): 2956, 1465, 1253, 772 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.36-7.28 (m, 5H), 4.50 (ABq, $J$ = 14.0, 11.7 Hz, 2H), 4.10-4.02 (m, 2H), 3.66-3.51 (m, 5H), 2.29-2.21 (m, 1H), 2.0-1.94 (m, 1H), 1.92-1.85 (m, 1H), 1.76-1.69 (m, 3H), 0.98 (d, $J$ = 7.0 Hz, 3H), 0.92 (d, $J$ = 6.1 Hz, 3H), 0.89 (s, 9H), 0.80 (s, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 138.4, 128.3 (2C), 127.6, 127.5, 78.9, 78.1, 77.7, 73.0, 67.8, 65.1, 40.1, 37.0, 36.3, 30.7, 25.9, 25.6, 18.1, 17.9, 14.2, 11.8, −3.6 (2C), −4.2, −4.4. HRMS (ESI) $m/z$ calced for C$_{30}$H$_{56}$NaO$_6$Si$_2$[M+Na]$^+$ = 559.3615, found = 559.3614.

(2S,3S)-3-((2R,4S,5S)-5-(2-(benzylxylo)ethyl)-4-methyltetrahydrofuran-2-yl)-3-((tert-butylidemethylsilyloxy)-2-methylpropan-1-ol (19): To a stirred solution of 18 (0.08 g, 0.15 mmol) in MeOH (2 mL) was added PPTS, and the mixture was stirred for 1 h at 0 °C. After completion of reaction, it was quenched with solid NaHCO$_3$, and methanol was removed under reduced pressure. Water was added and extracted with EtOAc (3 × 5 mL). The combined organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified on silica gel column chromatography (20% EtOAc/hexane) to provide 19 (0.058 g, 93%) as colorless oil. [a]$_D^{25}$: +5.0 (c = 0.8, CHCl$_3$); IR (neat): 3447, 2955, 1461, 1088, 773 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.36-7.28 (m, 5H), 4.50 (ABq, $J$ = 14.0, 11.7 Hz, 2H), 4.10-4.02 (m, 2H), 3.66-3.51 (m, 5H), 2.29-2.21 (m, 1H), 2.0-1.94 (m, 1H), 1.92-1.85 (m, 1H), 1.76-1.69 (m, 3H), 0.98 (d, $J$ = 7.0 Hz, 3H), 0.92 (d, $J$ = 6.1 Hz, 3H), 0.89 (s, 9H), 0.80 (s, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 138.4, 128.3, 127.6, 127.5, 78.9, 78.1, 77.7, 73.1, 67.9, 65.2, 40.2, 37.3, 35.8, 30.1, 25.9, 18.0, 14.1, 11.8, −4.2, −4.4. HRMS (ESI) $m/z$ calced for C$_{24}$H$_{43}$O$_6$Si [M+Na]$^+$ = 423.2931, found = 423.2928.

diethyl (3R,4S)-4-((2R,4S,5S)-5-(2-(benzylxylo)ethyl)-4-methyltetrahydrofuran-2-yl)-4-((tert-butyldemethylsilyloxy)-3-methyl-2-oxobutylolyphosphonate (3): Dess–Martin periodinane (0.04 g, 0.11 mmol) and NaHCO$_3$ (7 mg, 0.18 mmol) were added to a solution of alcohol 19 (0.04 g, 0.094 mmol) in CH$_2$Cl$_2$ (5 mL) at 0 °C. After stirring for 30 min, the reaction was warmed to 25 °C for 1 h. The reaction mixture was poured into a solution of Na$_2$S$_2$O$_3$ (3 mL), NaHCO$_3$ (5 mL) and Et$_2$O (5 mL), and then stirred for 30 min. The organic layer was separated and the aq layer was extracted with Et$_2$O (2 × 5 mL). The combined organic layers were washed with Na$_2$S$_2$O$_3$ (5 mL), NaHCO$_3$ (5 mL) and brine (5 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure to provide the corresponding aldehyde as an oil. This aldehyde was used immediately in the next reaction without purification.

To a dry round-bottomed flask equipped with an addition funnel, under Ar, was added dimethyl methylphosphonate (0.04 mL, 0.28 mmol) in THF (5 mL). The solution was cooled to −78 °C and n-BuLi (0.15 mL, 1.6 M, 0.23 mmol) was added dropwise. The resulting white suspension was stirred for 1 h at −78 °C, after which the crude aldehyde in THF (8 mL) was added. The mixture was stirred for 1 h at −78 °C and then quenched with sat. NH$_4$Cl solution and warmed to r.t. The layers were separated and the aq layer was extracted with Et$_2$O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product (0.05 g, 90%) was used immediately in the next reaction.

To a solution of the above crude material (0.05 g, 0.05 mmol) in CH$_2$Cl$_2$ (5 mL) were added Dess–Martin periodinane (0.03 g, 0.06 mmol) and NaHCO$_3$ (8 mg, 0.1mmol) at 0 °C. The mixture was stirred for 30 min at r.t., quenched with sat. Na$_2$S$_2$O$_3$-NaHCO$_3$ (5:1) solution, and stirred for 30 min at r.t. The layers were separated and the aq layer was extracted with CH$_2$Cl$_2$ (2 × 5 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and then concentrated under reduced pressure. The
crude product was purified via column chromatography (Rf = 0.4; hexane–EtOAc, 10:90) to afford ketone 3 (0.043 g, 81% over 3 steps) as a colorless liquid. [α]D25: +2.4 (c = 0.5, CHCl3); IR (neat): 2930, 1710, 1640, 1253, 1023, 772 cm−1; 1H NMR (400 MHz, CDCl3): δ 7.36-7.27 (m, 5H), 4.49 (ABq, J = 23.3, 15.7 Hz, 2H), 4.19-4.08 (m, 4H), 4.04 (dd, J = 6.2, 5.2 Hz, 1H), 3.97-3.89 (m, 1H), 3.56-3.47 (m, 2H), 3.27 (dd, J = 22.5, 14.0 Hz, 1H), 3.09 (dd, J = 21.8, 13.9 Hz, 1H), 2.88-2.82 (m, 1H), 2.36-2.21 (m, 2H), 2.07-1.94 (m, 1H), 1.70-1.60 (m, 3H), 1.32 (t, J = 6.8 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H). 13C NMR (CDCl3, 75 MHz): δ 202.4, 138.4, 128.3, 127.6, 127.4, 78.4, 77.2, 76.3, 72.9, 67.9, 62.4, 51.6, 36.4, 35.9, 30.9, 29.6, 25.8, 17.9, 16.2, 14.1, 10.2, −4.5, −4.6 HRMS (ESI) m/z calced for C20H23O3PSi [M+H]⁺ = 571.3218, found = 571.3218.

(R)-tert-butyl(1-((4-methoxybenzyl)oxy)but-3-yn-2-yl)oxy)dimethylsilane (10a): The compound 10 (2.5 g, 12.13 mmol) was dissolved in CH2Cl2 (10 mL), and then imidazole (1.65 g, 24.26 mmol) was added followed by TBDMSCl (2.24 g, 14.55 mmol). After 16 h the reaction was washed with water (1 × 10 mL), and the aqueous layer was extracted with CH2Cl2 (2 × 10 mL), dried over Na2SO4, and concentrated. Purification by silica gel chromatography (5% EtOAc/hexane) provided the silyl ether 10a (3.5 g, 90%) as a yellow oil. [α]D25: +15.4 (c = 1.2, CHCl3); IR (neat): 2931, 1513, 1249, 836 cm−1; 1H NMR (400 MHz, CDCl3): δ 7.27-7.23 (m, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.53 (s, 2H), 3.81-3.76 (m, 4H), 3.57-3.49 (m, 2H), 2.39 (d, J = 2.1 Hz, 1H), 0.89 (s, 9H), 0.11 (d, J = 9.4 Hz, 3H), 0.08 (d, J = 6.1 Hz, 3H). 13C NMR (CDCl3, 75 MHz): δ 159.1, 129.2, 127.5, 113.7, 83.2, 74.0, 73.1, 72.9, 62.7, 55.2, 25.7, 18.2, −4.7, −4.9. HRMS (ESI) m/z calced for C16H25O3NSi [M+NH4]⁺ = 338.2146, found = 338.2146.

(R)-4-((tert-butyldimethylsilyloxy)-5-((4-methoxybenzyl)oxy)pent-2-yn-1-ol (11): A solution alkylene 10a (2.0 g, 6.25 mmol) in dry THF (10 mL) was added dropwise to stirred solution of freshly prepared EtMgBr (prepared in situ from 0.3 g (12.5 mmol of Mg) and 0.92 mL (12.5 mmol) of ethyl bromide in 5 mL of dry THF) at 0 °C. After 1 h at rt para-formaldehyde (0.6 g) was added. The resulting mixture was further stirred for 3 h at rt and then quenched with saturated aque. NH4Cl solution. The organic layer was separated and aqueous layer was extracted with EtOAc (2 X 100 mL). The combined organic layers were washed with brine solution and dried over anhydrous Na2SO4, Concentrated and purified by silica-gel column chromatography (10% EtOAc/Hexane) provided alcohol 11 (1.96 g, 90%) as a liquid. [α]D25: +15.0 (c = 1.1, CHCl3); IR (neat): 3421, 2930, 1513, 1250, 835 cm−1; 1H NMR (400 MHz, CDCl3): δ 7.26 (d, J = 8.6 Hz, 12H), 6.89 (d, J = 8.5 Hz, 12H), 4.59-4.50 (m, 3H), 4.33 (dd, J = 3.0, 1.7 Hz, 1H), 4.28-4.25 (m, 1H), 3.81 (s, 3H), 3.63-3.50 (m, 2H), 0.91 (s, 9H), 0.13-0.09 (m, 6H). 13C NMR (CDCl3, 75 MHz): δ 159.4, 129.5, 129.2, 113.9, 83.4, 74.2, 73.1, 73.0, 63.0, 61.6, 55.2, 25.7, 18.2, −3.6, −5.1. HRMS (ESI) m/z calced for C18H30O3Si [M+H]⁺ = 351.1992, found = 351.1992.

(R,E)-ethyl 6-((tert-butyldimethylsilyloxy)-7-((4-methoxybenzyl)oxy)hept-2-enoate (20): A 50 mL two-neck, round-bottomed flask was charged with Pd(OH)2/C (7 mol%). Benzene (5 mL) was added and a H2 filled balloon was placed over the mixture for 30 min (to activate the catalyst). The balloon was removed and stirring was continued for 10 min, after which a solution of alcohol 11 (1.5 g, 4.28 mmol) in benzene (3 mL) was added. The reaction mixture was stirred for a further 60 min. After complete conversion of the alcohol into the corresponding aldehyde 5 (indicated by TLC), stable Wittig ylide (5.13 mmol) was added and the mixture was stirred at room temperature for 3 h. The reaction mixture was cooled r.t. and Concentrated and purified by silica-gel column chromatography (10% EtOAc/Hexane) provided alcohol 20 (1.60 g, 90%) as a liquid. [α]D25: +16.6 (c = 1.0, CHCl3); IR (neat): 2938, 2857, 1720, 1515, 1251 cm−1; 1H NMR (400 MHz, CDCl3): δ 7.24 (d, J = 8.6 Hz, 2H), 6.97 (dt, J = 15.5, 6.8 Hz, 1H), 6.87 (d, J = 8.6 Hz, 2H), 5.80 (dt, J = 15.7, 1.5 Hz,
(R,E)-ethyl 6-hydroxy-7-((4-methoxybenzyl)oxy)hept-2-enoate (21): To a stirred solution of 20 (1.0 g, 2.37 mmol) in MeOH (5 mL) was added PPTS, and the mixture was stirred for 1 h at 0 °C. After completion of reaction, it was quenched with solid NaHCO₃ (1.0 g, 2.37 mmol) in MeOH (5 mL) was added PPTS, and the mixture was stirred for 1 h at 0 °C. The solution was warmed to room temperature and stirred for 3 h until two clear layers were separated. The layers were separated, and the aqueous layer was further extracted with CH₂Cl₂ (3 × 10 mL). The combined extracts were dried (Na₂SO₄) and concentrated. The unstable crude aldehyde product was used directly for the next step without further purification by column chromatography.

Ethyl 2-((R,S,5R)-5-(((4-methoxybenzyl)oxy)methyl)tetrahydrofuran-2-yl)acetate (22): To a stirred solution of α,β-unsaturated ester 21 (0.5 g, 1.62 mmol) described above in MeOH (15 mL), a 40 wt% MeOH solution of Triton B (0.35 mL, 1.94 mmol) was added at r.t., and the mixture was stirred at r.t. for 15 min. After cooling to 0 °C, the mixture was diluted with sat. aq NH₄Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined extracts were dried (Na₂SO₄) and concentrated. The residual oil was purified by column chromatography on silica gel (30 g; hexane–EtOAc, 9:1) to give 2,5-trans-tetrahydrofuran 22 (0.43 g, 92%). [α]₀⁺: −16.7 (c = 1.0, CHCl₃); IR (neat): 2951, 2873, 1716, 1513, 1248 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.26 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.54-4.46 (m, 2H), 4.41-4.35 (m, 1H), 4.23-4.17 (m, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 3.46-3.39 (m, 2H), 2.70-2.64 (m, 1H), 2.50-2.43 (m, 1H), 2.17-2.06 (m, 1H), 2.04-1.92 (m, 1H), 1.75-1.57 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz): δ 171.6, 159.1, 130.4, 129.3, 113.7, 77.8, 75.4, 72.9, 72.3, 55.2, 51.6, 40.4, 31.5, 28.4. HRMS (ESI) m/z calced for C₁7H₂₅O₃ [M+H⁺]⁺ = 309.1702, found = 309.1712.

(2R,5R)-2-(((4-methoxybenzyl)oxy)methyl)-5-((E)-pent-2,4-dien-1-yl)tetrahydrofuran (23): To a solution of 22 (0.1 g, 0.32 mmol) in CH₂Cl₂ (5 mL) was added 0.27 mL of DIBAL-H (1.6 M in hexane, 0.41 mmol) at −78 °C. The solution was stirred for 1 h and quenched by addition of saturated Na/K tartrate at 0 °C. The solution was warmed to room temperature and stirred for 3 h until two clear layers were observed. The layers were separated, and the aqueous layer was further extracted with CH₂Cl₂ (2 × 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, and solvent was evaporated under reduced pressure. The unstable crude aldehyde product was used directly for the next step without further purification by column chromatography.
of 1° C and stirred vigorously for 30 min. The solid was filtered off and washed thoroughly with EtOAc. The organic phase was separated, and the aq phase was extracted with EtOAc. The combined organic phase was washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography (SiO₂, hexane/EtOAc = 50/1 - 30/1) to provide the desired olefinic product 23 as a nearly colorless oil (0.07 g, 85% yield based on BuLi). [$\alpha$]D²⁵: +4.9 (c = 1.2, CHCl₃); IR (neat): 2923, 1512, 1247, 1082 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.28-7.25 (m, 2H), 6.87 (d, J = 8.5 Hz, 2H), 6.35-6.26 (m, 1H), 6.13-6.05 (m, 1H), 5.70 (dt, J = 15.0, 7.3 Hz, 1H), 5.10 (dd, J = 16.9 Hz, 1H), 4.98 (dd, J = 10.0 Hz, 1H), 4.53 (d, J = 11.7 Hz, 1H), 4.48 (dd, J = 11.9 Hz, 1H), 4.22-4.16 (m, 1H), 4.09-4.0 (m, 1H), 3.80 (3H, 3H), 3.49-3.41 (m, 2H), 2.45-2.35 (m, 1H), 2.30-2.23 (m, 1H), 2.03-1.89 (m, 2H), 1.70-1.62 (m, 1H), 1.58-1.49 (m, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ 159.1, 137.1, 133.0, 130.9, 130.4, 129.3, 115.3, 113.7, 78.8, 77.8, 77.2, 72.9, 55.2, 38.7, 31.1, 28.5. HRMS (ESI) m/z calced for C₁₈H₂₅O₃ [M+H]+ = 289.1801, found = 289.1798.

((2R,5R)-5-((E)-penta-2,4-dien-1-yl)tetrahydrofuran-2-yl)methanol (4a): To a solution of the compound 23 (0.05 g, 0.17 mmol) in CH₂Cl₂ (10 mL) and water (1 mL), DDQ (0.05 g, 0.20 mmol) was added at 0 °C and allowed to stir for 2 h at room temperature. The reaction mixture was quenched with saturated NaHCO₃ solution (5 mL) and diluted with CH₂Cl₂ (10 mL). The two layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layer was washed with brine (2 x 5 mL), dried over anhydrous Na₂SO₄ and evaporated to give the crude product which was purified by column chromatography (5% EtOAc/Hexane) to provide the desired alcohol 4a (0.024 g, 85%) as a colourless oil. [$\alpha$]D²⁵: +10.9 (c = 1.2, CHCl₃); IR (neat): 3423, 2825, 1517, 1238, 1072 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.35-6.26 (m, 1H), 6.13-6.05 (m, 1H), 5.70 (dt, J = 15.0, 7.3 Hz, 1H), 5.10 (dd, J = 16.9 Hz, 1H), 4.98 (dd, J = 10.0 Hz, 1H), 4.53 (d, J = 11.7 Hz, 1H), 4.48 (dd, J = 11.9 Hz, 1H), 4.22-4.16 (m, 1H), 4.09-4.0 (m, 1H), 3.49-3.39 (m, 2H), 2.45-2.35 (m, 1H), 2.30-2.23 (m, 1H), 2.03-1.89 (m, 2H), 1.70-1.62 (m, 1H), 1.58-1.49 (m, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ 159.1, 137.1, 133.0, 130.9, 130.4, 129.3, 115.3, 113.7, 78.8, 77.8, 77.2, 72.9, 38.7, 31.1, 28.5. HRMS (ESI) m/z calced for C₁₈H₂₅O₃ [M+H]+ = 289.1801, found = 289.1798.

2-((2R,5R)-5-(((4-methoxybenzyl)oxy)methyl)tetrahydrofuran-2-yl)ethanol (24): To a solution of 22 (0.2 g, 0.68 mmol) in CH₂Cl₂ (10 mL) was added 1.3 mL of DIBAL-H (1.6 M in hexane, 2.04 mmol) at 0 °C. The solution was stirred for 1 h and quenched by addition of saturated Na/K tartrate at 0 °C. The solution was warmed to room temperature and stirred for 3 h until two clear layers were observed. The layers were separated, and the aqueous layer was further extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (10% EtOAc/ hexane) to provide 24 (0.17 g, 95%) as colorless oil. [$\alpha$]D²⁵: +20.0 (c = 0.8, CHCl₃); IR (neat): 3381, 2938, 1444, 1051 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.26 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.2 Hz, 2H), 4.52-4.47 (m, 2H), 4.24-4.06 (m, 2H), 3.80 (3H, 3H), 3.80-377 (m, 2H), 3.47-3.41 (m, 2H), 2.08-1.61 (m, 6H). ¹³C NMR (CDCl₃, 75 MHz): δ 159.1, 130.3, 129.2, 113.7, 79.1, 77.8, 72.9, 72.3, 61.4, 55.2, 37.3, 32.0, 28.2. HRMS (ESI) m/z calced for C₁₇H₃₂NaO₄ [M+Na]+ = 289.1416, found = 289.1426.

tert-butyl(2-((2R,5R)-5-(((4-methoxybenzyl)oxy)methyl)tetrahydrofuran-2-yl)ethoxy)dimethylsilane (25): The compound 24 (0.07 g, 0.24 mmol) was dissolved in CH₂Cl₂ (10 mL), and then imidazole (0.03 g, 0.28 mmol) was added followed by TBDMSCl (0.05 g, 0.48 mmol). After 2 h the reaction was washed with water (1 x 5 mL), and the aqueous layer was extracted with CH₂Cl₂ (2 x 5 mL), dried over Na₂SO₄, and concentrated. Purification by silica gel chromatography (5% EtOAc/hexane) provided the silyl ether 25 (0.081 g, 90%) as a yellow oil. [$\alpha$]D²⁵: +37.5 (c = 1.1,
CHCl₃); **IR (neat):** 2930, 2858, 1513, 1250, 1065 cm⁻¹; **¹H NMR (400 MHz, CDCl₃):** δ 7.26 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.50 (ABq, J = 25.7, 11.9 Hz, 2H), 4.19-4.14 (m, 1H), 4.09-4.01 (m, 1H), 3.80 (s, 3H), 3.74-3.68 (m, 2H), 3.47-3.38 (m, 2H), 2.03-1.80 (m, 2H), 1.70-1.51 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H); **¹³C NMR (CDCl₃, 75 MHz):** δ 159.1, 130.5, 129.2, 113.6, 77.8, 76.5, 72.9, 72.7, 60.5, 55.2, 38.8, 31.8, 28.6, 25.9, 18.3, −5.3, −5.4. HRMS (ESI) m/z calcd for C₂₁H₂₅O₃Si [M+H]+= 381.2461, found = 381.2450.

((2R,5R)-5-(2-((tert-butyldimethylsilyloxy)ethyl)tetrahydrofuran-2-yl)methanol (4): To a solution of the compound 25 (0.07 g, 0.18 mmol) in CH₂Cl₂ (5 mL) and water (0.1 mL), DDQ (0.05 g, 0.21 mmol) was added at 0°C and allowed to stir for 2 h at room temperature. The reaction mixture was quenched with saturated NaHCO₃ solution (5 mL) and diluted with CH₂Cl₂ (5 mL). The two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layer was washed with brine (2 x 5 mL), dried over anhydrous Na₂SO₄ and evaporated to give the crude product which was purified by column chromatography (5% EtOAc/Hexane) to provide the desired alcohol 4 (0.043 g, 90%) as a colourless oil. [α]D²⁵ +14.9 (c = 1.2, CHCl₃); **IR (neat):** 3423, 2936, 1710, 1631, 1253, 1093, 773 cm⁻¹; **¹H NMR (400 MHz, CDCl₃):** δ 4.14-3.97 (m, 2H), 3.74-3.69 (m, 2H), 3.62 (dd, J = 11.4, 3.3 Hz, 1H), 3.51-3.45 (m, 1H), 2.08-1.56 (m, 6H), 0.89 (s, 9H), 0.06 (s, 6H); **¹³C NMR (CDCl₃, 75 MHz):** δ 78.7, 76.3, 65.0, 60.4, 38.7, 32.2, 27.4, 25.9, 18.3, −5.3 (2C). HRMS (ESI) m/z calcd for C₁₉H₂₆O₃Si [M+H]+= 261.1886, found = 261.1890.

((4R,5S,E)-5-((2R,4S,5S)-5-(2-(benzoxyl)ethyl)-4-methyltetrahydrofuran-2-yl)-5-((tert-butyldimethylsilyloxy)-1-(2R,5R)-5-(2-((tert-butyldimethylsilyloxy)ethyl)tetrahydrofuran-2-yl)-4-methylpent-1-en-3-one (26): Dess–Martin periodinane (0.06 g, 0.14 mmol) and NaHCO₃ (0.07 g, 0.18 mmol) in CH₂Cl₂ (5 mL) and water (5 mL), NaHCO₃ (5 mL) and Et₂O (5 mL), and then stirred for 30 min. The organic layer was separated and the aq layer was extracted with Et₂O (2 x 5 mL). The combined organic layers were washed with Na₂S₂O₃ (5 mL), NaHCO₃ (5 mL) and brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to provide the corresponding aldehyde 4c as an oil. This aldehyde 4c was used immediately in the next reaction without purification.

To a solution of phosphonate 3 (0.03 g, 0.052 mmol) in THF (10 mL) was added Ba(OH)₂·8H₂O (0.02 g, 0.10 mmol, predried at 120°C for 2 h). The resulting solution was allowed to stir at r.t. for 30 min. Next, a solution of the aldehyde 4c (0.026 g, 0.052 mmol) in THF-H₂O (40:1, 2 mL) was added to the phosphonate solution, followed by another portion of the THF-H₂O mixture (2 mL). After stirring for 30 min, the mixture was diluted with EtOAc and filtered through a small pad of Celite. The filtrate was washed with aq NaHCO₃, and the organic layer was separated and the aq layer extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by column chromatography (Rf = 0.1, hexane–EtOAc, 9:1) to provide the product 26 (0.03 g, 85%) as a colorless oil. [α]D²⁵ +27.0 (c = 1.0, CHCl₃); **IR (neat):** 2931, 2924, 2858, 1513, 1253, 1093, 773 cm⁻¹; **¹H NMR (400 MHz, CDCl₃):** δ 7.37-7.27 (m, 5H), 6.73 (dd, J = 15.6, 7.1, 5.2 Hz, 1H), 6.39 (dd, J = 15.4, 5.5 Hz, 1H), 4.58-4.41 (m, 4H), 4.14 (t, J = 5.5 Hz, 1H), 4.10-3.96 (m, 2H), 3.95-3.79 (m, 1H), 3.77-3.69 (m, 2H), 3.60-3.46 (m, 1H), 2.81 (t, J = 6.8 Hz, 1H), 2.29-1.96 (m, 4H), 1.84-1.56 (m, 7H), 1.07 (d, J = 6.6 Hz, 3H), 0.93-0.82 (m, 21H), 0.10-0.01 (m, 12H); **¹³C NMR (CDCl₃, 75 MHz):** δ 201.1, 145.8, 138.6, 128.2, 127.7, 127.6, 127.5, 127.4, 78.4, 77.8, 77.4, 78.9, 75.2, 73.0, 68.3, 60.4, 49.3, 38.9, 36.2, 34.7, 31.9, 31.5, 31.0, 26.0, 25.9, 18.3, 18.0, 14.3, 11.8, −4.5, −4.6, −5.3 (2C). HRMS (ESI) m/z calcd for C₅₈H₇₀O₂₆NSi₂ [M+Na]+= 692.4743, found = 692.4736.
(1S,2R)-1-((tert-butyldimethylsilyl)oxy)-5-((2R,5R)-5-((tert-butyldimethylsilyl)oxy)ethyl)tetrahydrofuran-2-yl)-1-((2R,4S,5S)-5-(2-hydroxyethyl)-4-methyltetrahydrofuran-2-yl)-2-methylpentan-3-one (5): 10% Palladium on activated charcoal (100 mg) was added to a solution of 26 (0.02 g, 0.029 mmol) in hexane (5 mL) and was stirred for 3 h under a hydrogen (ballon) atmosphere. It was then filtered through a short pad of Celite and the Celite pad was washed with ether (10 mL). Evaporation of the solvent furnished 5 (0.015 g, 90%) as colorless oil. \([\alpha]_D^{25} = +4.9\) (c 1.2, CHCl$_3$); \(\text{IR (neat)}:\) 3448, 2930, 2857, 1710, 1253, 1099 cm$^{-1}$; \(^1\H NMR (400 MHz, CDCl$_3$):\) δ 4.14-4.08 (m, 1H), 4.03-3.95 (m, 2H), 3.93-3.85 (m, 1H), 3.84-3.74 (m, 1H), 3.73-3.65 (m, 4H), 2.68-2.51 (m, 3H), 2.29-2.22 (m, 1H), 2.06-1.93 (m, 3H), 1.83-1.47 (m, 11H), 1.12 (d, \(J = 7.0\) Hz, 3H), 0.92-0.86 (m, 21H), 0.10 (s, 3H), 0.07 (s, 3H), 0.04 (s, 6H). \(^{13}\C NMR (CDCl$_3$, 75 MHz):\) δ 210.9, 80.5, 78.2, 77.6, 75.3, 61.0, 60.5, 39.1, 38.6, 36.2 (2C), 32.6, 32.1, 31.1, 29.6, 25.9, 25.8, 18.3, 18.0, 14.3, 10.2, -4.4, -4.5, -5.3 (2C). HRMS (ESI) m/z calced for C$_{31}$H$_{60}$O$_4$NSi$_2$ [M+NH$_4$]$^+$ = 604.4429, found = 604.4423.

(1S,2R)-1-((tert-butyldimethylsilyl)oxy)-5-((2R,5R)-5-((tert-butyldimethylsilyl)oxy)ethyl)tetrahydrofuran-2-yl)-2-methyl-1-((2R,4S,5S)-4-methyl-5-(2-oxopropyl)tetrahydrofuran-2-yl)pentan-3-one (27): To a solution of alcohol 5 (0.011 g, 0.016 mmol) in dry CH$_2$Cl$_2$ (5 mL) were added Dess–Martin periodinane (9 mg, 0.019 mmol) and NaHCO$_3$ (3 mg, 0.032 mmol) at 0 °C under nitrogen atmosphere. The turbid solution was allowed to warm to room temperature and was stirred for 2 h. The reaction was diluted with CH$_2$Cl$_2$ (5 mL) and quenched with saturated aqueous NaHCO$_3$ (5 mL) and saturated aqueous Na$_2$S$_2$O$_3$ (5 mL). The mixture was vigorously stirred until a clear solution was formed. The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 5 mL). The combined organic extracts were washed with brine (1 × 5 mL), dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated to give a crude aldehyde, which was used for the next step without further purification.

MeMgBr (0.03 mL, 1M, 0.024 mmol) was added dropwise to a stirred solution of the aldehyde in dry THF (5 mL) at 0 °C. After addition was completed, the reaction mixture was allowed to stir at room temperature for 1 h and then quenched with saturated aqueous NH$_4$Cl solution. The organic layer was separated, and the compound from the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with water and brine solution, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude mass was purified by silica gel column chromatography (20% EtOAc/hexane) to afford a racemic mixture as a viscous liquid.

To a solution of the above racemic alcohol (0.010 g, 0.016 mmol) in dry CH$_2$Cl$_2$ (5 mL) were added Dess–Martin periodinane (8 mg, 0.019 mmol) and NaHCO$_3$ (2 mg, 0.032 mmol) at 0 °C under nitrogen atmosphere. The turbid solution was allowed to warm to room temperature and was stirred for 2 h. The reaction was diluted with CH$_2$Cl$_2$ (2 mL) and quenched with saturated aqueous NaHCO$_3$ (4 mL) and saturated aqueous Na$_2$S$_2$O$_3$ (4 mL). The mixture was vigorously stirred until a clear solution was formed. The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 5 mL). The combined organic extracts were washed with brine (1 × 5 mL), dried over anhydrous Na$_2$SO$_4$, filtered, concentrated, and purified by silica gel column chromatography (20% EtOAc/hexane) to afford methyl ketone 27 (0.008 g, 75% for 3 steps) as a viscous liquid. \([\alpha]_D^{25} = +42.6\) (c = 0.6, CHCl$_3$); \(\text{IR (neat)}:\) 3448, 2930, 2857, 1710, 1253, 773 cm$^{-1}$; \(^1\H NMR (400 MHz, CDCl$_3$):\) δ 4.23-4.17 (m, 1H), 4.09 (t, \(J = 5.5\) Hz, 1H), 4.01-3.93 (m, 1H), 3.92-3.83 (m, 1H), 3.79-3.65 (m, 3H), 2.58-2.51 (m, 4H), 2.35 (dd, \(J = 15.8, 5.4\) Hz, 2H), 2.15 (s, 3H), 2.06-1.99 (m, 2H), 1.96-1.92 (m, 1H), 1.81-1.57 (m, 6H), 1.53-1.45 (m, 2H), 1.07 (d, \(J = 4.0\) Hz, 3H), 0.90-0.83 (m, 21H), 0.08-0.02 (m, 12H). \(^{13}\C NMR (CDCl$_3$, 75 MHz):\) δ 211.0, 207.7, 78.1, 77.7, 76.4, 75.6, 75.2,
60.6, 51.2, 44.9, 39.3, 39.0, 35.7, 35.3, 32.1, 31.9, 30.7, 29.6, 25.9, 25.8, 18.3, 18.0, 14.3, 10.6, −4.4, −4.6, −5.3 (2C). HRMS (ESI) m/z calced for C_{32}H_{60}NaO_{3}Si_{2} [M+Na]^+ = 621.3983, found = 621.3983.

**(E)-**tert-butyl((6-((4-methoxybenzyl)oxy)-3-methylhex-3-en-1-yl)oxy)diphenylsilane (30): To a solution of 29 (0.5 g, 1.71 mmol) in CH_{2}Cl_{2} (20 mL) was added 5.1 mL of DIBAL-H (1.6 M in hexane, 5.13 mmol) at 0 °C. The solution was stirred for 1 h then adds TBDPSCl at 0 °C. The solution was stirred for 1 h and quenched by addition of saturated Na/K tartrate at 0 °C. The solution was warmed to room temperature and stirred for 3 h until two clear layers were observed. The layers were separated, and the aqueous layer was further extracted with CH_{2}Cl_{2} (2 × 10 mL). The combined organic layers were dried over anhydrous Na_{2}SO_{4}, and solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (10% EtOAc/ hexane) to provide 30 (0.75 g, 90%) as colorless oil. IR (neat): 2930, 2857, 1619, 1257, 1084, 773 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.73-7.65 (m, 4H), 7.43-7.35 (m, 6H), 7.25-7.22 (m, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.17 (dt, J = 22.4, 7.0 Hz, 1H), 4.41 (d, J = 19.0 Hz, 2H), 3.80 (s, 3H), 3.69 (dt, J = 21.0, 6.9 Hz, 2H), 3.37 (dt, J = 24.0, 14.5 Hz, 2H), 2.30 (t, J = 7.2 Hz, 2H), 2.26-2.19 (m, 2H), 1.55 (s, 3H), 1.07 (s, 9H).

\(^13\)C NMR (CDCl\(_3\), 75 MHz): δ 159.0, 135.5, 134.7, 129.5, 129.4, 129.2, 127.6, 127.5, 122.8, 113.7, 72.4, 69.9, 62.4, 55.2, 35.3, 28.5, 26.8, 19.1. HRMS (ESI) m/z calced for C_{33}H_{41}O_{3}Si [M+H]^+ = 489.2825, found = 489.2820.

**(E)-**6-((tert-butyldiphenylsilyl)oxy)-4-methylhex-3-en-1-ol (31): To a solution of the compound 30 (0.5 g, 1.02 mmol) in CH_{2}Cl_{2} (10 mL) and water (1 mL), DDQ (0.27 g, 1.22 mmol) was added at 0 °C and allowed to stir for 2 h at room temperature. The reaction mixture was quenched with saturated NaHCO\(_3\) solution (5 mL) and diluted with CH_{2}Cl_{2} (10 mL). The two layers were separated and the aqueous layer was extracted with CH_{2}Cl_{2} (3 × 5 mL). The combined organic layer was washed with brine (2 × 5 mL), dried over anhydrous Na_{2}SO_{4} and evaporated to give the crude product which was a purified by column chromatography (5% EtOAc/Hexane) to provide the desired alcohol 31 (0.32 g, 85%) as a colourless oil. IR (neat): 3447, 2935, 1560, 1253, 1099 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.70-7.64 (m, 4H), 7.43-7.35 (m, 6H), 7.25-7.22 (m, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.17 (dt, J = 22.4, 7.0 Hz, 1H), 4.41 (d, J = 19.0 Hz, 2H), 3.80 (s, 3H), 3.69 (dt, J = 21.0, 6.9 Hz, 2H), 3.37 (dt, J = 24.0, 14.5 Hz, 2H), 2.30 (t, J = 7.2 Hz, 2H), 2.26-2.19 (m, 2H), 1.55 (s, 3H), 1.07 (s, 9H). \(^13\)C NMR (CDCl\(_3\), 75 MHz): δ 135.8, 135.6, 135.5, 133.7, 129.2, 129.6, 129.5, 127.6, 127.5, 114.3, 62.3, 55.5, 35.1, 31.4, 26.8, 19.1. HRMS (ESI) m/z calced for C_{33}H_{41}O_{3}Si [M+Na]^+ = 369.2250, found = 369.2247.

**Salt 6:** To a stirred solution of 31 (0.2 g, 0.54 mmol) in 10 mL of anhydrous THF, TPP (0.18 g, 0.70 mmol), imidazole (0.074 g, 1.08 mmol) and iodine (0.20 g, 0.81 mmol) were added successively at 0 °C. The resulting mixture was stirred at room temperature for 1 h. After completion of reaction, monitored by TLC, the reaction mixture was quenched with 10% aqueous Na_{2}SO_{4} solution, extracted with ether and dried over anhydrous Na_{2}SO_{4}. The combined organic layer was concentrated under reduced pressure and purified by silica gel column chromatography (pet.ether:ethyl acetate, 9:1) to afford 30 as a liquid, the unstable iodo compound 31a was immediately used for the next reaction.

A stirred suspension of 31a (0.2 g, 0.40 mmol) and TPP (0.52 g, 2.0 mmol) in anhydrous CH\(_2\)CN (10 mL) was stirred at reflux temperature for 20 h. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (pet.ether:ethyl acetate, 8:2) to furnish 6 (0.23 g, 95%) as a clear colourless oil. IR (neat): 2920, 2857, 1619, 1257, 1084, 773 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.86-7.61 (m, 10H), 7.37-7.28 (m, 15H), 5.45 (t, J = 13.7 Hz, 1H), 3.66-3.55 (m, 5H), 2.47-2.32 (m, 2H), 2.11 (dt, J = 24.5, 7.4 Hz, 1H), 1.59 (s, 3H), 0.96 (s, 9H). \(^13\)C NMR (CDCl\(_3\), 75 MHz): δ 137.0, 135.3, 135.1,
(1S,2R)-1-((tert-butyldimethylsilyl)oxy)-5-((2R,5R)-5-((tert-butyldimethylsilyl)oxy)ethyl)tetrahydrofuran-2-yl)-1-((2R,4S,5S)-5-((2Z,5E)-8-((tert-butyldiphenylsilyl)oxy)-2,6-dimethylocta-2,5-dien-1-yl)-4-methyltetrahydrofuran-2-yl)-2-methylpentan-3-one (2): Salt 6 (9 mg, 0.015 mmol) was added to a 10-mL flask and dried under high vacuum for 1 h. After freshly dried THF (5 mL) was added under Ar, n-BuLi (6 µL of a 2.5 M solution in THF and 0.015 mmol) was added dropwise. After being stirred for 1 h at 23 °C, the deep-red suspension was cooled to −78 °C, and a precooled (−78 °C) solution of keto compound 27 (0.003 g, 0.005 mmol) in THF (5 mL) was added through a cannula. After being stirred for 8 h at 78 °C, the mixture was warmed to 23 °C and stirred for 8 h. During that time, a large amount of pale-white solid separated. The reaction was quenched with satd aq NH₄Cl at 0 °C and stirred vigorously for 30 min. The solid was filtered off through Celite and washed thoroughly with Et₂O. The organic phase was separated, and the aq phase was extracted with Et₂O. The combined organic phase was washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography (SiO₂, hexane/EtOAc = 50/1 - 30/1) to provide the desired olefinic product 2 as a nearly colorless oil (0.003 g, E/Z = 1/12.5, 80% yield based on BuLi). [α]D25: +12.9 (c = 0.1, CHCl₃); IR (neat): 2930, 2857, 1710, 1253, 1099 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.72-7.62 (m, 4H), 7.47-7.32 (m, 6H), 5.35 (t, J = 13.7 Hz, 1H), 5.15 (t, J = 7.3 Hz, 1H), 4.23-4.07 (m, 2H), 4.02-3.95 (m, 1H), 3.91- 3.79 (m, 2H), 3.76-3.60 (m, 4H), 2.64-2.44 (m, 4H), 2.09-1.92 (m, 4H), 1.79-1.59 (m, 8H), 1.53-1.40 (m, 4H), 1.25 (s, 3H), 1.15 (s, 3H), 1.08 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 0.87 (m, 27H), 0.08 (s, 6H), 0.04 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz): δ 207.5, 140.6, 138.6, 135.5, 133.9, 129.5, 127.6, 81.8, 78.4, 77.5, 76.5, 74.7, 75.2, 60.6, 51.2, 47.6, 41.5, 39.0, 38.5, 32.1, 31.2, 30.6, 29.7, 26.8, 26.1, 25.9, 25.8, 23.3, 18.3, 18.1, 16.9, 14.1, 11.2, −4.1, −4.6, −5.3 (2C); HRMS (ESI) m/z calced for C₅₅H₉₂NaO₆Si₃ [M+Na]⁺ = 956.5616, found = 956.5617.
$^{1}$HNMR (CDCl$_3$, 300MHz)

$^{13}$CNMR (CDCl$_3$, 75MHz)
$\text{HNMR (CDCl}_3, 500\text{MHz)}$

$\text{CNMR (CDCl}_3, 125\text{MHz)}$
\[ \text{BnO} \xrightarrow{\text{OTBS}} \text{OH} \xrightarrow{\text{14a}} \]\n
\[ \text{1H NMR (CDCl}_3, 500\text{MHz)} \]

\[ \text{BnO} \xrightarrow{\text{OTBS}} \text{OH} \xrightarrow{\text{14a}} \]\n
\[ \text{13C NMR (CDCl}_3, 75\text{MHz)} \]
$^1$HNMR (CDCl$_3$, 400MHz)

$^{13}$CNMR (CDCl$_3$, 75MHz)
\[ \text{BnO-} \]

\[ \begin{array}{c}
\text{15} \\
\text{BnO-} \end{array} \]

\[ \text{HNMR (CDCl}_3, 400\text{MHz)} \]

\[ \text{BnO-} \]

\[ \begin{array}{c}
\text{15} \\
\text{BnO-} \end{array} \]

\[ \text{13CNMR (CDCl}_3, 75\text{MHz)} \]
$^1$HNMR (CDCl$_3$, 400MHz)

$^{13}$CNMR (CDCl$_3$, 75MHz)
$^1$HNMR (CDCl$_3$, 400MHz)

$^{13}$CNMR (CDCl$_3$, 125MHz)
$^1$HNMR (CDCl$_3$, 400MHz)

$^{13}$CNMR (CDCl$_3$, 125MHz)
$^1$HNMR (CDCl$_3$, 300MHz)

$^{13}$CNMR (CDCl$_3$, 125MHz)
$^{1}$HNMR (CDCl$_3$, 300MHz)

$^{13}$CNMR (CDCl$_3$, 75MHz)
$^{1}\text{H}NMR$ (CDCl$_3$, 400MHz)

$^{13}\text{C}NMR$ (CDCl$_3$, 125MHz)
$^{13}$CNMR (CDCl$_3$, 125MHz)
$^1$HNMR (CDCl$_3$, 500MHz)

$^{13}$CNMR (CDCl$_3$, 125MHz)
$^{1} \text{HNMR (CDCl}_3, 500 \text{MHz} \right)$

$^{13} \text{CNMR (CDCl}_3, 125 \text{MHz} \right)$
$\mathrm{^1HNMR\ (CDCl_3,\ 500MHz)}$

$\mathrm{^{13}CNMR\ (CDCl_3,\ 125MHz)}$
$^1$HNMR (CDCl$_3$, 400MHz)

$^{13}$CNMR (CDCl$_3$, 100MHz)
PMBO\_\text{O} \quad 23

$\text{^{1}HNMR (CDCl}_3\text{, 500MHz)}$

PMBO\_\text{O} \quad 23

$\text{^{13}CNMR (CDCl}_3\text{, 75MHz)}$

32
$^{1}\text{HNMR (CDCl}_3, 500\text{MHz)}$

$^{13}\text{CNMR (CDCl}_3, 75\text{MHz)}$
\[ \text{HNMR} (\text{CDCl}_3, 500\text{MHz}) \]

\[ \text{CNMR} (\text{CDCl}_3, 100\text{MHz}) \]
$^1$HNMR (CDCl$_3$, 500MHz)

$^{13}$CNMR (CDCl$_3$, 125MHz)
$^{1}$HNMR (CDCl$_3$, 500MHz)

$^{13}$CNMR (CDCl$_3$, 125MHz)
$\textbf{1H NMR (CDCl}_3, 400\text{MHz)}$

$\textbf{13C NMR (CDCl}_3, 75\text{MHz)}$
$^1$HNMR (CDCl$_3$, 400MHz)

$^{13}$CNMR (CDCl$_3$, 75MHz)
$^{13}$CNMR (CDCl$_3$, 75MHz)
HNMR (CDCl₃, 400MHz)

C1-C23 fragment (2)

¹H NMR (CDCl₃, 400MHz)
CNMR (CDCl₃, 100 MHz)

C1-C23 fragment (2)