Supporting Information

An Expedient Total Synthesis of Chivosazole F: an Actin-Binding Antimitotic Macrolide from the Myxobacterium Sorangium Cellulosum

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Supporting Information

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1. General and analytical procedures

Reactions were carried out under an atmosphere of argon using oven dried glassware and standard techniques for handling air sensitive chemicals, unless the reaction contained aqueous reagents or unless otherwise stated.

Reagents were purified using standard laboratory procedures, benzene, toluene, CH$_2$Cl$_2$, and acetonitrile were distilled from CaH$_2$ and stored under an atmosphere of argon. THF and Et$_2$O were distilled from potassium or sodium wire / benzophenone ketyl radical and stored under argon. Solvents used for extraction and chromatography were distilled. 2,6-lutidine, di-isopropyl ethylamine, triethylamine and HMPA were distilled from CaH$_2$ and stored over CaH$_2$ under an atmosphere of argon. DMF was distilled from MgSO$_4$ and stored over 4Å molecular sieves, DMSO was distilled from and stored over 4Å molecular sieves. Oxalyl chloride was distilled. DDQ was recrystallised from CHCl$_3$, proton sponge was recrystallised from ethanol. All other chemicals were used as received from the manufacturer unless otherwise stated.

Aqueous solutions of ammonium chloride (NH$_4$Cl), sodium bicarbonate (NaHCO$_3$), sodium thiosulfate (Na$_2$S$_2$O$_3$), brine (NaCl) and sodium / potassium (Na/K) tartrate were saturated. Buffer solutions were prepared as directed from stock tablets.

Petroleum ether, boiling point 40 – 60°C is abbreviated to PE

Purification by flash column chromatography was carried out using Kieselgel 60 (230-400 mesh) and a positive solvent pressure. Preparative thin layer chromatography used Merck Kieselgel 60 F254 plates.

Analytical procedures:

TLC was carried out using Merck Kieselgel 60 F254 plates which were visualised using UV light (254 nm) and stained using potassium permanganate, anisaldehyde or phosphomolybdic acid / Ce$_2$(SO$_4$)$_3$ dips.
NMR spectra were recorded using the following machines: Bruker Avance TXO cryoprobe (700 MHz), Avance DCH cryoprobe (500 MHz), Avance 500 BB (500 MHz), Avance TCI cryoprobe (500 MHz), Avance 400 DRX (400 MHz). 1H NMR spectra were recorded at 298 K using an internal deuterium lock for CDCl₃ (δ_H = 7.26) or MeOD (δ_H = 3.31 ppm). 1H NMR data are presented as: chemical shift δ (in ppm, relative to TMS (δ_TMS = 0)), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad,) and coupling constants (J in Hz). Signals are assigned according to the numbering scheme for chivosazole F figure 1 unless otherwise indicated. Substituents are denoted by the backbone carbon they are attached to. Assignments have been made based on the 1D data presented along with a range of 2D spectra, and comparison with fully assigned spectra for similar compounds.

13C NMR spectra were recorded at 298 K with proton decoupling and an internal deuterium lock for CDCl₃ (δ_C = 77.0 ppm) or MeOD (δ_C = 49.0 ppm). Data are listed by chemical shift (δ / ppm) relative to TMS (δ_TMS = 0). Multiplicity and coupling constants are listed where coupling to a heteroatom is observed.

Fourier transform IR spectroscopy (FT-IR) was carried out using a Perkin-Elmer Spectrum-One spectrometer, and spectra were recorded as a thin film. Wavelengths of maximum absorption (υ_max) are reported in wavenumbers (cm⁻¹).

Optical rotations were measured using a Perkin-Elmer 241 polarimeter at the sodium D line (589 nm) and are reported as [α]D20, concentration (c in g / 100 mL) and solvent.

High resolution mass spectroscopy (HRMS) was carried out by the EPSRC National Mass Spectrometry facility (Swansea, UK) or the departmental Mass spectrometry service (University Chemical Laboratories, Cambridge) using electrospray ionisation (ESI) or atmospheric pressure chemical ionisation (APCI). The parent ion [M+NH₄]⁺, [M+Na]⁺ or [M+H]⁺ is quoted.

Figure 1 Atom numbering for chivosazole F
2. Detailed experimental procedures

a. North-western fragment 3

Aldol adduct 10

To a solution of (−)-Ipc-BCl (1.86 g, 5.80 mmol) and Et3N (0.93 mL, 6.67 mmol) in Et2O (9.0 mL) at 0 °C was added a solution of ketone 8 1 (1.30 g, 5.80 mmol) in Et2O (6.0 mL). The reaction mixture was stirred for 30 min then cooled to −78 °C and a solution of aldehyde 7 1 (0.65 g, 4.06 mmol) in Et2O/CH2Cl2 (1:1, 6.0 mL) was added. The reaction mixture was stirred for 30 min at −78 °C then warmed to −20 °C for 16 h, before being quenched with pH 7 buffer (12 mL) at 0 °C and stirred for 30 min. The reaction mixture was extracted with Et2O (3 x 15 mL), and the combined organic extracts were washed with brine (20 mL) and stirred over silica gel (15 g) for 30 min. The resulting slurry was filtered, the filtrate was concentrated in vacuo and purified by flash column chromatography (EtOAc/PE 1:10 → 1:5) to afford aldol adduct 10 (1.23 g, 3.41 mmol, 84%, >95:5 dr) as a yellow oil.

Rf 0.2 (EtOAc/hexane 1:2); [α]D 28 = +25.0 (c 2.0, CHCl3); IR νmax = 3452, 2937, 1709, 1516; 1H NMR (500 MHz, CDCl3) δ 6.79 – 7.63 (3H, m, ArH), 6.58 (1H, dd, J = 13.4, 10.9 Hz, H25), 6.22 (1H, d, J = 13.4 Hz, H26), 6.09 (1H, dd, J = 15.4, 10.9 Hz, H24), 5.62 (1H, dd, J = 15.4, 5.5 Hz, H23), 4.56 – 4.49 (1H, m, H22), 4.34 (2H, s, OCH2Ar), 3.80 (3H, s, ArOME), 3.79 (3H, s, ArOME), 3.52 (1H, dd, J = 9.0, 9.0 Hz, H18a), 3.41 (1H, dd, J = 9.0, 5.2 Hz, H18b), 3.33 (1H, d, J = 3.8 Hz, OH), 2.86 – 2.76 (1H, m, H19), 2.67 – 2.56 (2H, m, H21), 0.99 (3H, d, J = 7.6 Hz, Me19); 13C NMR (125 MHz, CDCl3) δ 213.4, 149.4, 149.1, 137.1, 135.7, 130.7, 127.7, 120.7, 111.4, 111.3, 109.5 73.6, 72.2, 67.8, 56.3, 56.2, 48.8, 47.2, 13.5; HRMS (ES+) calc for C20H20NBrO5 [M+NH4]+ 430.1224, found 430.1228.

Alcohol S1

To a solution of propionaldehyde (0.120 mL, 1.61 mmol) in THF (1.5 mL) at −20 °C was added samarium diiodide (1.35 mL, 0.10 M solution in THF, 0.135 mmol) followed by a solution of aldol adduct 10 (120 mg, 0.315 mmol) in THF (5 mL). The reaction mixture was stirred for 45 min, before being quenched with NaHCO3 (5 mL), extracted with Et2O (3 x 5 mL), and the combined organic extracts were dried (Na2SO4) and concentrated in vacuo. Purification by flash chromatography (EtOAc/PE 1:7) afforded alcohol S1 (132 mg, 0.302 mmol, 96%, >95:5 dr) as a colourless oil.

Rf 0.2 (EtOAc/hexane 1:2); [α]D 28 = +15.4 (c 1.0, CHCl3); IR νmax = 3499, 2941, 1733, 1595, 1516; 1H NMR (500 MHz, CDCl3) δ 6.85 – 6.78 (3H, m, ArH), 6.63 (1H, dd, J = 13.9, 11.1 Hz, H25), 6.31 (1H, d, J = 13.9 Hz, H26), 6.14 (1H, dd, J = 15.6, 10.5 Hz, H24), 5.67 (1H, dd, J = 15.6, 6.6 Hz, H23), 5.56 – 5.49 (1H, m, H22), 4.45 – 4.37 (2H, m, OCH2Ar), 3.85 (3H, s, ArOME), 3.84 (3H, s, ArOME), 3.51 (1H, dd, J = 9.1, 4.6 Hz, H18a), 3.51 – 3.46 (1H, m, H20), 3.42 (1H, dd, J = 9.1, 6.9 Hz, H18b), 3.38 (1H, d, J = 4.0 Hz, OH), 2.31 (2H, q, J = 7.6 Hz, CO2CH2CH3), 1.84 – 1.78 (1H, m, H21a), 1.79 – 1.73 (1H, m, H19), 1.59 (1H,
d, J = 13.8, 10.5, 3.0 Hz, H21b), 1.11 (3H, t, J = 7.8 Hz, CO2CH2CH3), 0.89 (3H, d, J = 7.1 Hz, Me19); 13C NMR (125 MHz, CDCl3) δ 174.5, 149.4, 149.1, 136.9, 133.3, 130.8, 129.4, 120.7, 111.4, 111.3, 110.3, 74.2, 73.7, 71.4, 71.2, 56.3, 56.2, 40.4, 39.1, 28.1, 14.3, 9.5; HRMS (ES+) calcd for C23H28BrO6 [M+Na]+ 488.1640, found 488.1642.

**Methyl ether S2**

To a solution of alcohol S1 (150 mg, 0.341 mmol) in CH2Cl2 (4.0 mL) at 0 °C was added Proton Sponge™ (0.589 g, 2.75 mmol) followed by trimethylxonium tetrafluoroborate (0.407 g, 2.75 mmol). The reaction mixture was stirred for 1 h, before being quenched with NaHCO3 (5 mL), filtered through Celite®, and extracted with CH2Cl2 (2 x 5 mL). The combined organic extracts were washed with aqueous citric acid (10 mL, 1.0 M), dried (MgSO4) and concentrated in vacuo. Purification by flash chromatography (EtOAc/PE 1:7 → 1:4) afforded methyl ether S2 (142 mg, 0.314 mmol, 92%) as a colourless oil.

Rf 0.4 (EtOAc/hexane 1:2) |α|D = +15.3 (c 2.0, CHCl3); IR νmax = 2941, 1736, 1516; 1H NMR (500 MHz, CDCl3) δ 6.89 – 6.81 (3H, m, ArH), 6.65 (1H, dd, J = 13.8, 11.0 Hz, H25), 6.32 (1H, d, J = 13.8 Hz, H26), 6.15 (1H, dd, J = 15.6, 10.3 Hz, H24), 5.66 (1H, dd, J = 15.6, 6.6 Hz, H23), 5.49 – 5.44 (1H, m, H22), 4.43 (2H, m, OCH2Ar), 3.88 (3H, s, ArOMe), 3.87 (3H, s, ArOMe), 3.34 (2H, d, J = 6.4 Hz, H18a, H18b), 3.29 (3H, s, OMe20), 3.29 – 3.27 (1H, m, H20), 2.31 (2H, q, J = 7.6 Hz, CO2CH2CH3), 2.19 – 2.12 (1H, m, H19), 1.70 (1H, ddd, J = 14.7, 9.9, 2.3 Hz, H21a), 1.59 (1H, ddd, J = 14.7, 9.9, 3.3 Hz, H21b), 1.13 (3H, t, J = 7.5 Hz, CO2CH2CH3), 0.89 (3H, d, J = 6.9 Hz, Me19); 13C NMR (125 MHz, CDCl3) δ 173.6, 149.0, 148.6, 136.5, 133.0, 131.0, 129.1, 120.1, 111.0, 110.9, 109.8, 78.2, 73.0, 72.2, 70.9, 57.8, 55.9, 55.8, 35.7, 35.6, 27.8, 12.0, 9.2; HRMS (ES+) calcd for C23H28BrO6Na [M+Na]+ 502.1797, found 502.1799.

**Alcohol 11**

To a solution of ester S2 (400 mg, 0.882 mmol) in MeOH (7.7 mL) was added K2CO3 (173 mg, 1.25 mmol). The reaction mixture was stirred for 16 h, before being quenched with water (8 mL), extracted with CH2Cl2 (3 x 10 mL), and the combined organic extracts dried (Na2SO4) and concentrated in vacuo. Purification by flash chromatography (EtOAc/PE 1:5) yielded alcohol 11 (344 mg, 0.865 mmol, 91%) as a colourless oil.

Rf 0.3 (EtOAc/hexane 1:2); |α|D = +18.6 (c 1.5, CHCl3); IR νmax = 3473, 2937, 1590, 1516; 1H NMR (400 MHz, CDCl3) δ 6.87 – 6.81 (3H, m, ArH), 6.69 (1H, dd, J = 13.2, 11.0 Hz, H25), 6.28 (1H, d, J = 13.2 Hz, H26), 6.19 (1H, dd, J = 15.3, 11.0 Hz, H24), 5.73 (1H, dd, J = 15.3, 5.2 Hz, H23), 4.41 (2H, s, OCH2Ar), 4.40 – 4.33 (1H, m, H22), 3.87 (3H, s, ArOMe), 3.86 (3H, s, ArOMe), 3.57 – 3.51 (1H, m, H20), 3.36 – 3.33 (2H, m, H18a, H18b), 3.32 (3H, s, OMe20), 3.16 (1H, d, J = 4.2 Hz, OH), 2.24 – 2.16 (1H, m, H19), 1.69 (1H, ddd, J = 14.6, 8.6, 3.1 Hz, H21a), 1.56 (1H, ddd, J = 14.6, 8.1, 3.1 Hz, H21b), 0.88 (3H, d, J = 6.9 Hz, Me19); 13C NMR (100 MHz, CDCl3) δ 149.4, 149.0, 138.0, 137.3, 131.3, 127.1, 120.6, 111.5, 111.3, 108.8, 80.2, 73.5, 72.6, 69.7, 57.5, 56.3, 56.2, 35.9, 35.4, 12.4; HRMS (ES+) calcd for C20H15NO4 [M+NH4]+ 446.1534, found 446.1537.

**TBS ether S3**
To a solution of alcohol 11 (200 mg, 0.503 mmol) in CH₂Cl₂ (10 mL) was added imidazole (36.0 mg, 0.554 mmol). After stirring for 15 min, TBSCI (82.0 mg, 0.554 mmol) was added. The reaction mixture was stirred for 2 h, before being quenched with NaHCO₃ solution (2 mL), extracted with CH₂Cl₂ (3 x 5 mL), and the combined organic extracts dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (EtOAc/PE 1:10 → 1:3) afforded TBS ether S3 (247 mg, 0.483 mmol, 96%) as a colourless oil.

R₇ 0.7 (EtOAc/hexane 1:2); [α]₂⁰ₒ = +20.5 (c 1.5, CHCl₃); IR νmax = 2956, 2850, 1514; ¹H NMR (400 MHz, CDCl₃) δ 6.89 – 6.79 (3H, m, ArH), 6.65 (1H, dd, J = 13.9, 10.6 Hz, H25), 6.24 (1H, d, J = 13.9 Hz, H26), 6.05 (1H, dd, J = 15.5, 10.6 Hz, H24), 5.68 (1H, dd, J = 15.5, 6.5 Hz, H23), 4.43 (1H, d, J = 11.6 Hz, OCH₂H₂Ar), 4.39 (1H, d, J = 11.6 Hz, OCH₂H₂Ar), 4.33 – 4.27 (1H, m, H22), 3.86 (3H, s, Ar(OMe)), 3.85 (3H, s, Ar(OMe)), 3.52 – 3.46 (1H, m, H20), 3.30 (1H, dd, J = 9.1, 6.7 Hz, H18a), 3.30 (3H, s, OMe20), 3.23 (1H, dd, J = 9.0, 6.7 Hz, H18b), 2.27 – 2.19 (1H, m, H19), 1.44 – 1.38 (2H, m, H21a, H21b), 0.88 (3H, d, J = 6.8 Hz, Me19), 0.87 (9H, s, SitBuMe₁), 0.04 (3H, s, SitBuMe₂), 0.01 (3H, s, SitBuMe₃); ¹³C NMR (125 MHz, CDCl₃) δ 149.4, 148.9, 139.4, 137.4, 131.5, 126.7, 120.5, 111.3, 111.1, 108.8, 78.2, 73.5, 73.0, 70.0, 57.0, 56.3, 56.2, 39.5, 34.9, 26.3, 18.5, 11.8, –3.5, –4.5; HRMS (ES⁺) calc for C₂₉H₄₉BrNO₅Si [M+Na]+ 560.2400, found 560.2401.

Alcohol S4

To a solution of DMB ether S5 (1.00 g, 1.95 mmol) in CH₂Cl₂ (85 mL) at 0 °C was added pH 7 buffer (20 mL) followed by DDQ (0.460 g, 2.03 mmol). The reaction mixture was warmed to rt over 15 min and stirred for a further 1 h, before being quenched with NaHCO₃ solution (70 mL). The mixture was extracted with CH₂Cl₂ (3 x 30 mL), the combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (EtOAc/PE 1:10) yielded alcohol S4 (607 mg, 1.54 mmol, 79%) as a yellow oil.

R₇ 0.5 (EtOAc/hexane 1:2); [α]₂⁰ₒ = +22.5 (c 1.5, CHCl₃); IR νmax = 3400, 2931, 2865, 1469; ¹H NMR (500 MHz, CDCl₃) δ 6.70 (1H, dd, J = 12.0, 12.0 Hz, H25), 6.30 (1H, d, J = 12.0 Hz, H26), 6.09 (1H, dd, J = 15.3, 10.9 Hz, H24), 5.71 (1H, dd, J = 15.3, 6.6 Hz, H23), 4.32 (1H, ddd, J = 6.6, 6.3, 6.3 Hz, H22), 3.67 – 3.60 (1H, m, H18a), 3.59 – 3.52 (1H, m, H18b), 3.48 – 3.43 (1H, m, H20), 3.39 (3H, s, OMe20), 2.28 – 2.24 (1H, m, OH), 2.00 – 1.96 (1H, m, H19), 1.60 – 1.57 (2H, m, H21a, H21b), 0.92 (3H, d, J = 7.0 Hz, Me19), 0.91 (9H, s, SitBuMe₁), 0.09 (3H, s, SitBuMe₂), 0.03 (3H, s, SitBuMe₃); ¹³C NMR (125 MHz, CDCl₃) δ 138.4, 136.8, 126.7, 108.5, 80.6, 70.1, 65.8, 57.4, 40.2, 37.5, 25.9, 18.1, 12.5, –3.9, –4.8; HRMS (ES⁺) calc for C₁₇H₂₉BrO₅Si [M+Na]+ 415.1275, found 415.1275.

Carboxylic acid 9

To a solution of alcohol S4 (100 mg, 0.254 mmol) in MeCN/H₂O (1:1, 5 mL) was added TEMPO (51.3 mg, 0.330 mmol) and Phil(OAc)₃ (413 mg, 1.28 mmol). The reaction mixture was stirred for 2 h, before being diluted with EtOAc/H₂O (1:1, 10 mL), extracted with EtOAc (3 x 5 mL) and the combined organic extracts dried (Na₂SO₄) and concentrated in vacuo.
Purification by flash chromatography (PE then CH₂Cl₂/MeOH 9:1) yielded acid 9 (98.0 mg, 0.241 mmol, 95%) as a yellow oil.

\[ R = 0.3 \text{ (EtOAc/hexane 1:2); } [\alpha]_D^{29} = +16.0 \text{ (c 1.5, CHCl}_3\text{); IR } \nu_{\text{max}} = 2941, 1726, 1380; \text{ H NMR (500 MHz, CDCl}_3\text{) } \delta = 6.67 \text{ (1H, dd, } J = 13.8, 10.8 \text{ Hz, H25)}, 6.27 \text{ (1H, d, } J = 13.8 \text{ Hz, H26)}, 6.08 \text{ (1H, dd, } J = 15.3, 10.8 \text{ Hz, H24)}, 5.69 \text{ (1H, dd, } J = 15.3, 6.9 \text{ Hz, H23)}, 4.35 - 4.28 \text{ (1H, m, H22)}, 3.80 - 3.74 \text{ (1H, m, H20)}, 3.38 \text{ (3H, s, OMe20)}, 2.95 - 2.86 \text{ (1H, m, H19)}, 1.63 - 1.48 \text{ (2H, m, H21a, H21b)}, 1.10 \text{ (3H, d, } J = 7.0 \text{ Hz, Me19)}, 0.89 \text{ (9H, s, SitBuMe3)}, 0.07 \text{ (3H, s, SitBuMe3)}, 0.01 \text{ (3H, s, SitBuMe3)}; \text{ C NMR (125 MHz, CDCl}_3\text{) } \delta = 180.2, 138.7, 137.2, 127.1, 108.9, 78.3, 69.9, 57.5, 41.9, 40.3, 26.3, 18.5, 10.7, -3.5, -4.5; \text{ HRMS (ES\textsuperscript{+}) } C_{21}H_{31}BrO_SiNa [M+Na]% 405.1100, found 405.1102.

**Vinyl iodide S5**

\[
\begin{align*}
\text{O} & \quad \text{Boc} \\
\text{I} & \\
\end{align*}
\]

To a solution of DMSO (426 μL, 6.00 mmol) in CH₂Cl₂ (12 mL) at −78 °C was added oxalyl chloride (515 μL, 6.00 mmol). After stirring for 15 min, a solution of Garner’s alcohol \(^3\) (925 mg, 4.00 mmol) in CH₂Cl₂ (5.0 mL) was added via cannula and the reaction mixture was stirred for a further 1 h. Et₂N (1.67 mL, 12.0 mmol) was added and the reaction mixture was stirred at 0 °C for 30 min, before being quenched with H₂O and extracted with CH₂Cl₂. The organic extracts were dried (MgSO₄), concentrated in vacuo and the crude aldehyde was used immediately in the subsequent reaction.

To a vigorously stirred solution of CrCl₂ (6.65 g, 54.1 mmol) in THF (60 mL) at 0 °C was added the crude aldehyde in THF (30 mL) and the mixture was stirred for 5 min. Iodoform (6.66 g, 16.9 mmol) was added and the reaction mixture was warmed to rt and stirred in the dark for 18 h, before being diluted with H₂O (50 mL) and extracted with Et₂O (3 × 40 mL). The organic extracts were washed with brine, dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (EtOAc/PE/Et₂N 0:1:0.02 → 1:10:0.02) gave vinyl iodide S5 (791 mg, 2.24 mmol, 56%) as a bright yellow oil.

\[ R = 0.39 \text{ (EtOAc/PE 1:10); } [\alpha]_D^{29} = +76.8 \text{ (c 0.75, CHCl}_3\text{); IR } \nu_{\text{max}} = 2978, 2936, 2873, 1693, 1608; \text{ H NMR (500 MHz, CDCl}_3\text{) } \delta = 6.51 \text{ (1H, dd, } J = 14.6, 7.6 \text{ Hz, H15)}, 6.31 \text{ (1H, brd, } J = 14.6 \text{ Hz, H14)}, 4.30 \text{ (1H, brs, H16)}, 4.00 \text{ (1H, dd, } J = 9.0, 6.3 \text{ Hz, H17a)}, 3.77 \text{ (1H, dd, } J = 9.0, 2.2 \text{ Hz, H17b)}, 1.60 \text{ (3H, s, CMe2)}, 1.50 \text{ (3H, s, CMe2)}, 1.46 \text{ (9H, s, O-t-Bu)}; \text{ C NMR (125 MHz, CDCl}_3\text{, 25 °C) } \delta = 151.9*, 151.6, 144.3, 143.9*, 94.2, 93.7*, 80.6*, 80.1, 79.0*, 78.2, 67.1, 61.3, 61.1*, 28.4, 27.6*, 26.6, 24.6*, 23.6; \text{ HRMS (ES\textsuperscript{+}) calc for C}_{19}H_{20}O NOI\textsubscript{3} [M+H]% 354.0561, found 354.0564.

*Two rotamers are observed for this compound. At 25 °C two sets of carbon signals are resolved but the proton spectrum suffers from significant broadening of peaks. The proton spectrum is thus recorded at elevated temperature to observe a single set of well resolved peaks. Signals for both rotamers are reported for the carbon spectrum with the minor components (approx. 3:2 ratio) denoted *.

**Amino alcohol 12**

\[
\begin{align*}
\text{OH} & \\
\text{NH}_2\text{HCl} & \\
\end{align*}
\]
Acetyl chloride (15.0 mL, 212 mmol) was added dropwise to MeOH (150 mL) at 0 °C to prepare a methanolic solution of HCl. A solution of protected amino alcohol S6 (1.00 g, 2.83 mmol) in MeOH (50 mL) was added dropwise and the reaction stirred at rt for 2 h. Concentration of the reaction mixture in vacuo gave the amino alcohol 12 (694 mg, 2.78 mmol, 98%) as a yellow hydrochloride salt.

\[ \alpha \]_D = +4.4 (c 1.43, CHCl_3), IR \nu_{max} = 3354, 2921, 1678, 1598; \textsuperscript{1}H NMR (500 MHz, MeOD) \delta = 6.96 (1H, d, J = 15.1 Hz, H14), 6.67 (1H, dd, J = 15.1, 8.1 Hz, H15), 4.89 (3H, brs, OH, NH_2), 3.79 (1H, dd, J = 12.1, 4.1 Hz, H17a), 3.65 (1H, dd, J = 12.1, 7.1 Hz, H17b); \textsuperscript{13}C NMR (125 MHz, MeOD) \delta = 140.3, 85.7, 63.1, 58.9; HRMS (ESI) calc for C_4H_8INO [M+H]^+ 213.9729, found 213.9726.

Amide S6

To a solution of acid 9 (200 mg, 0.491 mmol) and hydroxybenzotriazole (72.1 mg, 0.541 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added iPr_2NEt (90 \mu L, 0.541 mmol) and EDC (108 \mu L, 0.541 mmol) and the resulting mixture was stirred for 10 min. Amino alcohol 12 (126 mg, 0.590 mmol) was added and the reaction mixture was allowed to warm to rt and stirred for 1 h before being quenched with water (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with NaHCO_3 (20 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (EtOAc/PE 1:1) yielded amide S6 (290 mg, 0.481 mmol, 98%) as a white solid.

\[ \alpha \]_D = −17.6 (c 1.5, CHCl_3), IR \nu_{max} = 3307, 2956, 2926, 2870, 1648, 1534; \textsuperscript{1}H NMR (400 MHz, CDCl_3) \delta = 6.65 (1H, dd, J = 13.1, 11.0 Hz, H11), 6.54 (1H, dd, J = 14.5, 6.0 Hz, H15), 6.49 (1H, d, J = 8.2 Hz, NH), 6.37 (1H, d, J = 14.5 Hz, H14), 6.28 (1H, d, J = 13.1 Hz, H26), 6.06 (1H, dd, J = 15.7, 11.0 Hz, H24), 5.65 (1H, dd, J = 15.7, 6.0 Hz, H23), 4.54 – 4.49 (1H, m, H16), 4.31 – 4.23 (1H, m, H22), 3.67 – 3.59 (2H, m, H17a, H17b), 3.49 – 3.41 (1H, m, H14), 3.38 (3H, s, OMe20), 2.45 (1H, dt, J = 6.9, 6.6 Hz, H19), 1.69 – 1.51 (2H, m, H21a, H21b), 1.13 (3H, d, J = 6.9 Hz, Me19), 0.87 (9H, s, SitBuMe_2), 0.04 (3H, s, SitBuMe_2), 0.02 (3H, s, SitBuMe_2); \textsuperscript{13}C NMR (100 MHz, CDCl_3) \delta = 174.9, 143.0, 138.2, 137.1, 127.5, 109.3, 79.9, 79.5, 70.5, 64.6, 59.1, 55.8, 46.0, 41.6, 26.3, 18.6, 14.4, −3.4, −4.3; HRMS (ESI) calc for C_{21}H_{37}BrNO_4Si [M+H]^+ 602.0793, found 602.0779.

\textbf{Bis-halide 3}

DAST (443 \mu L, 3.35 mmol) was added dropwise to a solution of amide S6 (200 mg, 0.332 mmol) in CH_2Cl_2 (4.6 mL) at −78 °C. After stirring for 30 min, the reaction mixture was quenched with K_2CO_3 (695 mg, 5.03 mmol) and allowed to warm to rt, before NaHCO_3 was added and the phases separated. The aqueous phase was extracted with CH_2Cl_2 and the combined
organic extracts were washed with brine, dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography (EtOAc/PE 1:7) afforded oxazoline 3 (146 mg, 0.249 mmol, 75%) as a pale yellow oil.

**R**$_t$ 0.7 (1:4 EtOAc/hexane); [α]$_D^{28}$ = +48.4 (c 2.0, CHCl$_3$); IR: ν$_{max}$ = 2928, 2892, 1655, 1469; $^1$H NMR (500 MHz, CDCl$_3$) δ 6.64 (1H, dd, J = 13.4, 11.0 Hz, H$25$), 6.47 (1H, dd, J = 14.5, 6.5 Hz, H$15$), 6.36 (1H, d, J = 14.5 Hz, H$14$), 6.24 (1H, d, J = 13.4 Hz, H$26$), 6.04 (1H, dd, J = 15.6, 11.0 Hz, H$24$), 5.66 (1H, dd, J = 15.6, 6.4 Hz, H$23$), 4.56 (1H, ddd, J = 8.3, 6.5, 6.5 Hz, H$16$), 4.29 – 4.21 (2H, m, H$7$1a, H$7$22), 3.92 (1H, dd, J = 8.3, 8.3 Hz, H$7$1b), 3.70 – 3.65 (1H, m, H$20$), 3.32 (3H, s, OMe$20$), 2.95 – 2.88 (1H, m, H$19$), 1.54 – 1.37 (2H, m, H$21$a, H$21$b), 1.09 (3H, d, J = 7.0 Hz, Me$19$), 0.87 (9H, s, SitBuMe$3$), 0.04 (3H, s, SitBuMe$3$), −0.02 (3H, s, SitBuMe$3$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 170.1, 145.1, 138.5, 136.9, 126.5, 108.3, 79.1, 77.8, 71.2, 69.7, 69.4, 56.9, 39.5, 34.9, 25.9, 18.1, 10.4, −3.9, −4.9; HRMS (ES$^+$) calc for C$_2$H$_{13}$IBrNO$_3$Si [M+H]+ 584.0687, found 584.0681.

**b. Southern Fragment 4**

Vinyl stannane 19

Vinyl stannane 19

$t$BuLi (1.7 M in hexanes, 16.8 mL, 26.8 mmol) was added dropwise to a solution of vinyl bromide 13 (2.34 g, 6.70 mmol) in Et$_2$O (120 mL) at −78 °C. After stirring for 5 min, Bu$_3$SnCl (10.9 mL, 40.2 mmol) was added and the reaction mixture was warmed to rt, quenched with H$_2$O (100 mL) and extracted with EtOAc (3 × 100 mL). The organic extracts were washed with H$_2$O (100 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography (1:5:0.02 Et$_2$O/PE/Et$_3$N) afforded stannane 19 (2.62 g, 4.55 mmol, 68%) as a colourless oil.

**R**$_t$ 0.50 (EtOAc/PE 1:5); [α]$_D^{28}$ = +13.4 (c 0.98, CHCl$_3$); IR: ν$_{max}$ = 3380, 2957, 2923, 2875, 1458; $^1$H NMR (500 MHz, CDCl$_3$) δ, 6.42 (1H, dd, J = 13.2, 8.4 Hz, H$12$), 5.84 (1H, d, J = 13.2 Hz, H$13$), 5.40 (1H, d, J = 9.8 Hz, H$9$), 4.00 (2H, br s, H$7$), 3.77 (1H, dd, J = 8.5, 4.2 Hz, H$11$), 2.46 (1H, dqd, J = 9.8, 6.9, 4.2 Hz, H$10$), 1.64 (3H, s, Me$8$), 1.52 – 1.46 (6H, m, Sn(CH$_3$CH$_2$CH$_2$CH$_3$)$_3$), 1.36 – 1.29 (6H, m, Sn(CH$_3$CH$_2$CH$_2$CH$_3$)$_3$), 0.97 (3H, d, J = 6.9 Hz, Me$10$), 0.97 – 0.88 (24H, m, Sn(CH$_3$CH$_2$CH$_2$CH$_3$)$_3$), Sn(CH$_3$CH$_2$CH$_2$CH$_3$)$_3$, 0.56 (6H, q, J = 7.8 Hz, Si(CH$_3$)$_2$CH$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ, 215.6, 153.4, 128.2, 127.6, 79.8, 69.2, 39.9, 29.2, 27.4, 17.5, 14.1, 13.7, 10.2, 6.9, 5.0; HRMS (ES$^+$) calc for C$_2$H$_{13}$IBrNO$_3$Si$^{113}$Sn [M+H]+ 553.3171, found 553.3171.

Vinyl iodide 4

To a solution of alcohol 19 (300 mg, 0.522 mmol) in CH$_2$Cl$_2$ (6.0 mL) was added MnO$_2$ (1.13 g, 13.1 mmol). After stirring for 15 min, the reaction mixture was filtered through a short pad of Celite®. The filtrate was concentrated in vacuo to afford the corresponding aldehyde, which was used without further purification.

To a suspension of (Ph$_3$P)$_3$I$^+$ (712 mg, 1.34 mmol) in THF (18 mL) was added NaHMD5 (1M in THF, 1.34 mL, 1.34 mmol). The solution was stirred until a deep orange solution was obtained. The reaction mixture was then cooled to −78 °C, HMPA (383 µL) was added, followed by the crude aldehyde in THF (18 mL). The reaction mixture was allowed to warm to rt over 1
h, before being diluted with hexane, filtered through a short pad of Celite® and concentrated in vacuo. The residue was taken up in hexane, washed with water and brine, dried (MgSO₄), filtered through Celite® and concentrated in vacuo to afford vinyl iodide 4 (356 mg, 0.522 mmol, 99%, single geometrical isomer) as a yellow oil.

Rf 0.35 (PE); [α]D²⁰ = +42.1 (c 0.42, CHCl₃); IR νmax (500 MHz, CDCl₃) δ, 6.76 (1H, d, J = 8.4 Hz, H6), 6.49 (1H, dd, J = 12.9, 8.5 Hz, H12), 6.09 (1H, d, J = 8.4 Hz, H7), 5.86 (1H, d, J = 12.9 Hz, H13), 5.71 (1H, d, J = 9.8 Hz, H9), 3.82 (1H, dd, J = 9.8, 8.5 Hz, H11), 2.55 (1H, dqq, J = 9.8, 6.9 Hz, H10), 1.53 – 1.46 (6H, m, Sn(CH₂CH₂CH₂CH₂CH₃)₃), 1.36 – 1.29 (6H, m, Sn(CH₂CH₂CH₂CH₂CH₃)₃), 0.57 (6H, q, J = 7.8 Hz, Si(CH₂CH₂CH₃)₃); ¹³C NMR (125 MHz, CDCl₃) δ, C 152.0, 142.6, 136.8, 132.1, 128.0, 79.9, 74.2, 40.7, 29.2, 27.4, 15.9, 13.8, 10.4, 7.1, 5.2; HRMS (ES⁺) calcd for C₂₈H₅₄IO₅Sn [M-H]⁺ 673.2019, found 673.2019.

### c. North-eastern fragment S

Vinyl stannane S7

![Vinyl stannane S7](image)

To a solution of vinyl iodide 14¹ (230 mg, 625 µmol) in THF (10 mL) was added PdCl₂(PPh₃)₂ (21.9 mg, 31.3 µmol), Li₂CO₃ (231 mg, 3.12 mmol) and Me₆Sn₂ (1.02 mL, 3.12 mmol). The reaction mixture was stirred at 40 °C for 5 h before it was cooled to rt and concentrated in vacuo. Purification by flash chromatography on Florisil® (EtOAc/PE 0:1 → 1:20) provided stannane S7 (165 mg, 407 µmol, 65%) as a colourless oil.

Rf 0.50 (EtOAc/hexane 1:9); [α]D²⁰ = +14.3 (c 1.03, CHCl₃); IR νmax 3537, 2974, 2937, 1595, 1459, 1379; ¹H NMR (500 MHz, CDCl₃) δ, 6.36 (1H, dd, J = 12.4, 9.5 Hz, H28), 5.94 (1H, d, J = 12.3 Hz, H27), 3.99 – 3.92 (1H, m, H34), 3.89 (1H, dt, J = 9.8, 6.4 Hz, H32), 3.72 (1H, ddd, J = 9.2, 1.7, 1.7 Hz, H30), 2.31 (1H, d, J = 1.9 Hz, OH30), 2.19 – 2.08 (1H, m, H29), 1.78 (1H, ddd, J = 15.8, 9.8, 6.0 Hz, H33a), 1.69 – 1.61 (1H, m, H31), 1.55 (1H, ddd, J = 15.7, 9.5, 6.2 Hz, H33b), 1.34 (3H, s, CMe₃), 1.34 (3H, s, CMe₃), 1.20 (3H, d, J = 6.3 Hz, H35), 0.92 (3H, d, J = 6.7 Hz, Me29), 0.88 (3H, d, J = 7.0 Hz, Me31), 0.18 (9H, s, SnMe₃); ¹³C NMR (125 MHz, CDCl₃) δ, C 152.4, 130.7, 100.5, 72.4, 69.4, 63.1, 44.6, 38.6, 38.5, 24.9, 24.5, 21.7, 17.1, 8.8, −8.3; HRMS (ES⁺) calcd for C₁₂H₁₄NaO₃¹⁰⁵Sn [M+Na]⁺ 429.1428, found 429.1424.

Phosphonate 5

![Phosphonate 5](image)
To a solution of alcohol 57 (100 mg, 247 µmol) and acid 155 (144 mg, 494 µmol) in PhMe (5.0 mL) was added DCC (102 mg, 494 µmol) and the mixture was stirred for 5 min before being concentrated in vacuo. Purification by flash chromatography (EtOAc/PE/Et3N 1:10:0.02) afforded phosphate 5 (130 mg, 191 µmol, 77%) as a yellow oil.

Rf 0.45 (EtOAc/PE 1:5); [α]d28 +5.8 (c 0.98, CHCl3); IR νmax = 2972, 2934, 1737, 1703, 1593; 1H NMR (500 MHz, CDCl3) δ, 7.35 – 7.29 (4H, m, ArH), 7.24 – 7.21 (4H, m, ArH), 7.21 – 7.16 (2H, m, ArH), 6.34 (1H, dd, J = 12.4, 9.9 Hz, H28), 5.75 (1H, d, J = 12.4 Hz, H27), 5.36 (1H, dd, J = 9.4, 1.8 Hz, H30), 3.88 (1H, ddq, J = 9.2, 6.1, 6.1 Hz, H34), 3.60 (1H, dt, J = 9.6, 6.1 Hz, H32), 3.24 – 3.11 (2H, m, H2), 2.33 (1H, ddq, J = 9.8, 9.4, 6.9 Hz, H29), 1.79 (1H, ddq, J = 9.5, 6.9, 1.8 Hz, H31), 1.58 (1H, ddd, J = 12.6, 9.6, 6.1 Hz, H33a), 1.41 (1H, ddd, J = 12.6, 9.2, 6.1 Hz, H33b), 1.32 (3H, s, CMe2), 1.30 (3H, s, CMe2), 1.10 (3H, d, J = 6.1 Hz, Me35), 1.00 (3H, d, J = 6.9 Hz, Me29), 0.90 (3H, d, J = 6.9 Hz, Me31), 0.18 (9H, s, SnMe3); 13C NMR (125 MHz, CDCl3) δ: 163.9 (d, J = 6.5 Hz), 150.9, 149.9 (d, J = 2.6 Hz), 149.8 (d, J = 2.6 Hz), 129.8, 129.8, 129.7, 125.5, 120.8 (d, J = 3.2 Hz), 120.8, d (J = 3.7 Hz), 100.6, 77.2, 66.8, 62.5, 44.2, 39.6, 39.1, 34.7, 33.6, 24.7 (d, J = 20.8 Hz), 21.7, 17.7, 8.3, –8.4; HRMS (ES+) calc for C31H48O3P112Sn [M+H]+ 681.2004, found 681.1992.

d. Revised North-eastern Fragment 20

Acetonide 58

To a solution of diol 22 (6.20 g, 14.1 mmol) in CH2Cl2 (200 mL) was added 2,2-dimethoxypropane (85.4 mL, 697 mmol) and pyridinium p-toluenesulfonate (360 mg, 1.43 mmol). After stirring for 16 h, the reaction mixture was quenched with NaHCO3 solution (100 mL) extracted with CH2Cl2 (2 x 200 mL) and the combined organic extracts were dried (MgSO4) and concentrated in vacuo. Purification by flash chromatography (EtOAc/PE 1:9) afforded acetonide 58 (6.29 g, 13.1 mmol, 93%) as a yellow oil.

Rf 0.81 (EtOAc/hexanes 3:7); [α]d30 +13.8 (c 0.80, CHCl3); IR (thin film) νmax = 2932, 1614, 1514; 1H NMR (500 MHz, CDCl3) δ: 7.24 (2H, d, J = 8.6 Hz, ArH), 6.87 (2H, d, J = 8.6 Hz, ArH), 4.40 (2H, s, OCH2Ar), 3.95 – 3.88 (1H, m, H34), 3.80 (3H, s, ArOCH3), 3.64 (1H, dd, J = 10.8, 4.6 Hz, H30), 3.54 (1H, dd, J = 9.0, 4.2 Hz, H28a), 3.41 – 3.38 (1H, m, H32), 3.38 (1H, dd, J = 9.0, 6.2 Hz, H28b), 1.88 – 1.79 (1H, m, H29), 1.59 – 1.56 (1H, m, H31), 1.56-1.52 (2H, m, H33b, H33b), 1.33 (3H, s, CMe2), 1.27 (3H, d, J = 5.9 Hz, H35), 0.93 (3H, d, J = 6.7 Hz, Me29), 0.88 (9H, s, SitBuMe2), 0.84 (3H, d, J = 7.0 Hz, Me30), 0.06 (3H, s, SitBuMe2), 0.04 (3H, s, SitBuMe2); 13C NMR (125 MHz, CDCl3) δ: 159.2, 131.1, 129.1, 113.7, 100.6, 72.8, 72.3, 72.3, 69.9, 65.7, 55.3, 46.2, 38.5, 33.8, 29.7, 25.9, 24.9, 24.0, 18.0, 13.5, 11.1, –3.5, –4.7; HRMS (ES+) calc for C23H48O3Si [M+H]+ 481.3349, found 481.3352.
To a solution of PMB ether S8 (6.20 g, 12.9 mmol) in CH₂Cl₂ (200 mL) and pH 7 buffer solution (40 mL) at 0 °C was added DDQ (3.22 g, 14.2 mmol) in three portions. After stirring for 1 h at 0 °C, the reaction mixture was quenched with pH 7 buffer solution (250 mL, aq.) and the phases separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 100 mL) and the combined organic layers dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (EtOAc/PE 1:9) yielded alcohol 23 (4.20 g, 11.7 mmol, 91%) as a colourless oil.

Rᵣ 0.30 (EtOAc/hexane 1:4); [α]ᵣD²⁰ = −22.9 (c 0.96, PhH); IR νmax = 3496, 2958, 2933, 2858, 1462, 1378; ¹H NMR (500 MHz, CDC₁₇) δ 3.96 – 3.87 (1H, m, H34), 3.67 (1H, dd, J = 10.5, 4.5 Hz, H30), 3.57 (1H, ddd, J = 10.7, 8.1, 1.6 Hz, H32), 3.55 – 3.48 (1H, m, J, H28a), 3.46 – 3.40 (1H, m, H28b), 3.19 (1H, dd, J = 9.6, 1.7 Hz, OH), 1.96 – 1.85 (1H, m, H29), 1.62 – 1.57 (1H, m, H31), 1.57 – 1.52 (2H, m, H33), 1.38 (3H, s, CMe₂), 1.34 (3H, s, CMe₂), 1.14 (3H, d, J = 6.2 Hz, H35), 0.89 (9H, s, SibBuMe₂), 0.87 (3H, d, J = 6.9 Hz, Me29), 0.76 (3H, d, J = 6.8 Hz, Me31), 0.06 (3H, s, SibBuMe₂), 0.04 (3H, s, SibBuMe₂); ¹³C NMR (125 MHz, CDCl₃) δ 100.7, 75.7, 72.0, 69.1, 65.6, 46.1, 38.8, 35.0, 25.9, 25.1, 24.7, 24.3, 18.0, 12.7, 11.1, –3.5, –4.7; HRMS (ES+) calc for C₁₉H₂₃NaO₅Si [M+Na]⁺ 383.2594, found 383.2583.

Vinyl iodide S9

To a stirred solution of alcohol 23 (3.92 g, 10.9 mmol) in DCM (70 mL) was added NaHCO₃ (5.4 g, 64 mmol) and Dess–Martin periodinane (13.6 g, 32.2 mmol). The reaction mixture was stirred for 30 min, before being quenched with NaHCO₃, extracted with CH₂Cl₂, and the organic extracts were dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography on silica gel (EtOAc/PE 1:9) gave the ensuing aldehyde (3.36 g, 9.37 mmol, 86%) as a yellow oil, which was immediately used in the subsequent step.

To a suspension of (Ph₃PCH₂)⁺TI⁻ (12.2 g, 23.0 mmol) in THF (150 mL) was added NaHMDS (1M in THF, 23.0 mL, 23.0 mmol). The solution was stirred until a deep orange solution was obtained. The reaction mixture was then cooled to −78 °C, and the freshly prepared aldehyde (3.33 g, 9.37 mmol) in THF (100 mL) was added. The reaction mixture was warmed to rt over 2 h, before being diluted with hexane, filtered through a short pad of Celite® and concentrated in vacuo. Purification by flash chromatography (EtOAc/PE 1:20) afforded vinyl iodide S9 (4.20 g, 8.71 mmol, 93%, Z-isomer only) as a yellow oil.

Rᵣ 0.89 (EtOAc/hexane 1:4); [α]ᵣD²⁰ = +18.2 (c 0.88, CHCl₃); IR νmax = 2960, 2932, 2353, 1461, 1378, 1256; ¹H NMR (500 MHz, CDCl₃) δ 6.14 (1H, d, J = 7.5 Hz, H27), 6.12 (1H, t, J = 7.4 Hz, H28), 3.96 – 3.88 (1H, m, H34), 3.70 (1H, dd, J = 9.1, 4.7 Hz, H30), 3.43 – 3.36 (1H, m H32), 2.64 – 2.54 (1H, m, H29), 1.65 – 1.57 (1H, m, H31), 1.57 – 1.52 (2H, m, H33), 1.31 (3H, s, CMe₂), 1.29 (3H, s, CMe₂), 1.45 (3H, d, J = 6.2 Hz, H35), 1.14 (3H, d, J = 6.1 Hz, Me29), 0.89 (9H, s, SibBuMe₂), 0.87 (3H, d, J = 6.3 Hz, Me31), 0.06 (3H, s, SibBuMe₂), 0.04 (3H, s, SibBuMe₂); ¹³C NMR (125 MHz, CDCl₃) δ 144.5, 100.6, 81.3, 72.1, 71.9, 65.6, 46.0, 39.5, 39.0, 25.9, 24.8, 24.7, 24.2, 18.0, 15.6, 11.3, –3.5, –4.7; HRMS (ES+) calculated for C₂₉H₂₃NaO₅Si [M+Na]⁺ 505.1611, found 505.1613.

Triol 24

![Triol](image_url)
To a solution of TBS ether 59 (3.55 g, 7.36 mmol) in MeOH (50 mL) was added PPTS (555 mg, 2.21 mmol). The mixture was stirred for 16 h, the volatiles were removed in vacuo and the crude product purified by flash column chromatography (EtOAc / PE 1:4) to yield triol 24 (2.17 g, 6.62 mmol, 90%) as an off-white solid.

**Rf** 0.29 (EtOAc/PE 1:4); [α]_D^28 +30.0 (c 0.20, CHCl₃); IR ν max = 3347, 2966, 2930, 2348, 2326, 1456, 1376, 1260, 1066, 972, 804, 699; ¹H NMR (500 MHz, CDCl₃) δₙ, 6.33 (1H, d, J = 7.4 Hz, H27), 6.18 (1H, dd, J = 8.8, 7.4 Hz, H28), 4.35–4.15 (1H, m, H32), 3.92–3.87 (1H, m, H33), 3.12 (3H, d, J = 5.2 Hz, OH), 2.78–2.69 (1H, m, H29), 1.82 (1H, ddd, J = 14.5, 9.6, 3.1 Hz, H33a), 1.77–1.70 (1H, m, H31), 1.56 (1H, ddd, J = 14.5, 7.4, 2.4 Hz, H33b), 1.28 (3H, d, J = 6.3 Hz, H35), 1.03 (3H, d, J = 7.1 Hz, Me31), 0.96 (3H, d, J = 6.8 Hz, Me29); ¹³C NMR (125 MHz, CDCl₃) δₖ 144.0, 83.3, 75.0, 72.6, 65.9, 43.1, 42.2, 39.3, 23.4, 16.0, 10.7; HRMS (ES⁺) calc for C₁₁H₂₂O₄Si [M+H]⁺ 329.0608, found 329.0611.

**Alcohol 25**

To a solution of triol 24 (500 mg, 1.52 mmol) in CH₂Cl₂ (20 mL) at −78 °C was added 2,6-lutidine (0.88 mL, 7.60 mmol) and Di-t-butylsilyl bis(trifluoromethanesulfonate) (0.59 mL, 1.82 mmol) dropwise. The reaction mixture was stirred at −78 °C for 1 h, before being quenched with MeOH (5 mL) followed by NaHCO₃ solution (20 mL). The residue was extracted with CH₂Cl₂ (3 × 20 mL), and the combined organic extracts were dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography (EtOAc/PE 1:20) afforded alcohol 25 (684 mg, 1.46 mmol, 96%) as a colourless oil.

**Rf** 0.25 (Et₂O/PE 9:1); [α]_D^18 +59.5 (c 1.0, CHCl₃); IR ν max = 3481, 2964, 2932, 2892, 2858, 1474, 1385, 1259, 1134, 978, 896, 865, 825, 797, 730, 648; ¹H NMR (500 MHz, CDCl₃) δₙ, 6.29–6.23 (2H, m, H27, H28), 4.47–4.40 (1H, m, H32), 4.24 (1H, ddd, J = 10.1, 5.4, 1.9 Hz, H32), 3.96 (1H, dd, J = 8.0, 1.7 Hz, H33), 3.00 (1H, d, J = 14.3, 10.1, 5.9 Hz, H33a), 1.72 –1.65 (1H, m, H31), 1.52 –1.47 (1H, m, H33b), 1.30 (3H, d, J = 6.6 Hz, H35), 1.03 (3H, d, J = 7.0 Hz, Me31), 1.00 (18H, s, Si(tBu)₃), 0.95 (3H, d, J = 7.1 Hz, Me29); ¹³C NMR (125 MHz, CDCl₃) δₖ 144.8, 82.2, 74.6, 73.2, 67.8, 43.0, 40.7, 38.8, 27.5, 27.4, 23.8, 21.5, 20.8, 16.5, 10.9; HRMS (ES⁺) calc for C₁₀H₁₀O₃Si [M+H]⁺ 469.1629, found 469.1619.

**Vinyl stannane S10**

To a stirred solution of vinyl iodide 25 (916 mg, 1.96 mmol) in THF (20 mL) was added PdCl₂(PPh₃)₂ (138 mg, 0.20 mmol), Li₂CO₃ (723 mg, 9.78 mmol) and (Me₃Sn)₂ (2.03 mL, 9.78 mmol). The reaction mixture was stirred at 40 °C for 3h, cooled to rt and concentrated in vacuo. Purification by flash chromatography (EtOAc/PE 1:20) afforded stannane S10 (644 mg, 1.27 mmol, 65%) as a colourless oil.

**Rf** 0.58 (Et₂O/PE 1:9); [α]_D^18 +65.0 (c 0.1, CHCl₃); IR ν max = 2962, 2930, 2857, 2360, 1726, 1598, 1474, 1376, 1258, 1133, 1101, 981, 899, 864, 825, 799, 769, 730; ¹H NMR (500 MHz, CDCl₃) δₙ, 6.38 (1H, dd, J = 12.3, 9.5 Hz, H28), 5.94 (1H, d, J = 12.4 Hz, H28), 4.39 (1H, dq, J = 6.1, 2.6 Hz, H34), 4.24 (1H, ddd, J = 9.4, 6.4, 2.4 Hz, H32), 3.96 (1H, brd, J = 8.0 Hz, H30), 3.71 (1H, dq, J = 5.4, 2.4 Hz, H29).
2.51 (1H, d, J = 1.8 Hz, OH), 2.15 (1H, dqd, J = 9.5, 6.5, 3.1 Hz, H29), 2.11 (1H, ddd, J = 14.3, 9.8, 5.7 Hz, H33a), 1.64 (1H, dqd, J = 7.1, 7.1, 1.5 Hz, H31), 1.56 (1H, ddd, J = 14.2, 2.4, 2.4 Hz, H33b), 1.29 (3H, d, J = 6.7 Hz, H35), 1.01 (9H, s, SiBu3), 0.99 (9H, s, SiBu3), 0.92 (3H, d, J = 7.1 Hz, Me31), 0.91 (3H, d, J = 6.7 Hz, Me29) 0.18 (9H, s, SnMe3).

**Phosphonate 20**

![Phosphonate 20](image)

To a solution of alcohol S10 (410 mg, 811 µmol) and acid 26 (370 mg, 1.22 mmol) in CH2Cl2 (20 mL) was added DCC (1 M, 0.89 mL, 890 µmol) and the reaction mixture was stirred for 10 min before being concentrated in vacuo. Purification by flash chromatography (EtOAc/PE 1:20) afforded phosphonate 20 (488 mg, 616 µmol, 76%) as a yellow oil.

**RF 0.21 (Et2O/PE 1:9):** \[\delta_{\text{ppm}}^{13}C = +62.4 (c 1.0, CHCl3); \delta_{\text{ppm}}^{1}H \nu_{\text{max}} = 2971, 2860, 1736, 1474, 1386, 1298, 1267, 1174, 1143, 1097, 1071, 963, 900, 826, 769, 648; \]

**1H NMR** (500 MHz, CDCl3) δH 6.30 (1H, dd, J = 12.3, 9.8 Hz, H28), 5.81 (1H, d, J = 12.2 Hz, H27), 5.54 (1H, dd, J = 9.6, 1.3 Hz, H30), 4.51 – 4.38 (4H, m, OCH2CF3), 4.39 – 4.32 (1H, m, H34), 3.82 (1H, ddd, J = 9.8, 8.9, 3.1 Hz, H32), 3.13 – 2.96 (2H, m, H2), 2.36 – 2.26 (1H, m, H29), 1.87 – 1.76 (2H, m, H31, H33a), 1.67 (1H, ddd, J = 14.4, 4.2, 3.6 Hz, H33b), 1.28 (3H, d, J = 6.4 Hz, Me35), 1.00 (9H, s, SiBu3), 0.99 (3H, d, J = 6.5 Hz, Me29), 0.98 (9H, s, SiBu3) 0.84 (3H, d, J = 7.0 Hz, Me31), 0.18 (9H, s, SnMe3).

**13C NMR** (125 MHz, CDCl3) δC 164.1 (d, J = 2.8 Hz), 151.0, 129.9, 128.5, 122.3 (qd, J = 278, 6.0 Hz), 76.9, 69.9, 67.3, 63.0 – 62.2 (2C, m), 44.3, 40.9, 38.2, 34.1, 27.5, 27.2, 23.8, 20.6 (d 33.5 Hz), 17.7, 9.5, –8.3; **HRMS (ES+)** calc for C23H35F6O7PSi112Sn [M+H]+ 802.2434, found 802.2439.

e. **Fragment coupling strategy 1 – Approach I**

**Trienolate 16**

![Trienolate 16](image)

To Pd2dba3 (23.5 mg, 25.7 µmol) and tBu3P (20.8 mg, 103 µmol) was added DMF (2 mL) and the catalyst solution was stirred for 5 min before it was cooled to 0 °C and placed in the dark. A solution of stannane 6 (241 mg, 642 µmol) in DMF (2 mL) was added, followed by a solution of CuTC (73.7 mg, 386 µmol) and Ph3POxSnBu4 (593 mg, 1.29 mmol) in DMF (2 mL) and a solution of iodide 4 (175 mg, 257 µmol) in DMF (10 mL). After stirring for 1 h, complete consumption of iodide 4 was observed by TLC. An additional portion of CuTC (3.1 mg, 16.2 µmol) was added and the reaction mixture was stirred for 15 min, before being diluted with PE and quenched with NaHCO3 solution (10 mL). The aqueous phase was extracted with EtO/PE (1:1) (2 × 5 mL) and the combined organic extracts were dried (MgSO4) and concentrated in vacuo. Purification by flash chromatography on Florisil® (EtO/PE 1:1) gave triene 16 (118 mg, 185 µmol, 72%) as a colourless oil.
**Heptaene 17**

To Pd$_2$dba$_3$ (2.2 mg, 2.4 μmol) and tBu$_3$P (2.0 mg, 9.4 μmol) was added DMF (0.4 mL) and the catalyst solution was stirred for 5 min before it was cooled to 0 °C and kept in the dark. A solution of stannane 16 (15.0 mg, 23.5 μmol) and bis-halide 3 (20.6 mg, 35.3 μmol) in DMF (0.8 mL) was added, followed by a solution of CuTC (9.0 mg, 47.0 μmol) and Ph$_3$PO$_2$NBu$_4$ (52.4 mg, 118 μmol) in DMF (0.8 mL). After stirring for 2 h, the reaction mixture was diluted with PE and quenched with NaHCO$_3$ solution (5 mL). The aqueous phase was extracted with Et$_2$O/PE (1:1) (2 × 5 mL) and the combined organic extracts were dried (MgSO$_4$) and concentrated in vacuo. Purification by flash chromatography on Florisil$^\odot$ (EtOAc/PE 1:7 → 1:4) and preparative TLC (EtOAc/PE 5:1) gave heptaene 17 (13.5 mg, 16.7 μmol, 71%) as a colourless oil.

**Octaene 18**

To Pd$_2$dba$_3$ (0.9 mg, 0.99 μmol) and tBu$_3$P (0.8 mg, 4.0 μmol) was added DMF (0.1 mL) and the catalyst solution was stirred for 5 min before it was cooled to 0 °C. A solution of bromide 17 (8.0 mg, 9.9 μmol) and stannane 5 (10.1 mg, 14.9 μmol) in DMF (0.2 mL) was added, followed by a solution of CuTC (3.8 mg, 19.8 μmol) and Ph$_3$PO$_2$NBu$_4$ (22 mg, 49.5 μmol) in DMF (0.3 mL). After stirring for 30 min in the dark, the reaction mixture was diluted with PE and quenched with NaHCO$_3$ solution.
f. Octaene dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography on Florisil® (EtOAc/PE 1:3 → 1:2) gave octaene 18 (10.1 mg, 8.2 μmol, 83%) as a pale yellow oil.

\[ R_f 0.26 \text{ (EtOAc/PE 1:3); } [\alpha]_D^{28} = +5.9 \text{ (c 1.30, CHCl}_3); \text{ IR } \nu_{\text{max}} = 2956, 2878, 2160, 1738, 1655, 1613, 1593; ^1H NMR (500 MHz, CDCl₃) δ 7.84 (1H, dd, J = 15.2, 12.3 Hz, H5), 7.33 – 7.29 (4H, m, Ph), 7.22 – 7.15 (6H, m, Ph), 6.41 (1H, dd, J = 15.2, 11.2 Hz, H14), 6.40 (1H, dd, J = 14.3, 11.1 Hz, H26), 6.21 (1H, d, J = 11.5 Hz, H7), 6.14 (1H, dd, J = 11.1, 10.5 Hz, H27), 6.12 (1H, dd, J = 14.4, 10.9 Hz, H24), 6.01 (1H, dd, J = 11.5, 11.5 Hz, H6), 5.97 (1H, dd, J = 11.2, 11.2 Hz, H13), 5.97 (1H, dd, J = 14.3, 10.9 Hz, H25), 5.85 (1H, d, J = 15.5 Hz, H4), 5.65 (1H, dd, J = 14.4, 7.1 Hz, H23), 5.58 (1H, dd, J = 15.2, 8.1 Hz, H15), 5.52 (1H, d, J = 9.7 Hz, H9), 5.41 (1H, dd, J = 11.2, 9.4 Hz, H12), 5.34 (1H, dd, J = 10.7, 10.7 Hz, H28), 5.27 (1H, dd, J = 8.2, 2.4 Hz, H30), 4.62 (1H, ddd, J = 8.8, 8.8, 8.8 Hz, H16), 4.39 (1H, dd, J = 9.2, 5.3 Hz, H11), 4.40 – 4.31 (2H, m, H22, H17a) 3.91 – 3.85, m, H34, H17b), 3.74 (3H, s, CO₂Me), 3.73 – 3.69 (1H, m, H20), 3.62 (1H, ddd, J = 9.4, 5.6, 5.6 Hz, H32), 3.37 (3H, s, OMe20), 3.23 – 3.09 (2H, m, H2), 3.01 – 2.96 (1H, m, H29), 2.96 – 2.91 (1H, m, H19), 2.60 – 2.54 (1H, m, H10), 1.89 (3H, s, Me8), 1.86 – 1.80 (1H, m, H31), 1.64 – 1.58 (1H, m, H33a), 1.56 – 1.50 (2H, m, H21a, H21b), 1.45 – 1.40 (1H, m, H33b), 1.32 (3H, s, CMe₃), 1.29 (3H, s, CMe₃), 1.13 (3H, d, J = 7.2 Hz, Me19), 1.12 (3H, d, J = 6.1 Hz, H35), 1.00 (3H, d, J = 6.9 Hz, Me10), 0.98 (3H, d, J = 7.1 Hz, Me29), 0.92 – 0.89 (21H, m, Me31, SitBuMe₂ and Si(CH₃CH₂)₃), 0.53 (6H, q, J = 8.3 Hz, Si(CH₂CH₃)₃), 0.06 (3H, s, SitBuMe₂), 0.01 (3H, s, SitBuMe₂). ^13C NMR (125 MHz, CDCl₃) δ 169.7, 167.7, 164.1 (d, J = 6.4, 150.0 (d, J = 3.6 Hz), 149.9 (d, J = 3.6 Hz), 142.5, 141.6, 139.5, 138.1, 134.6, 134.5, 134.1, 133.6, 133.1, 129.8, 129.7, 129.3, 129.1, 127.7, 127.4, 127.0, 125.5, 124.4, 121.0, 120.8, 120.7, 100.5, 78.2, 77.6, 72.3, 72.1, 70.2, 68.0, 66.9, 62.6, 57.1, 51.4, 40.3, 40.0, 39.8, 38.8, 35.2, 35.1, 29.7, 25.9, 24.7 (d, J = 30.0 Hz), 21.6, 18.1, 17.6, 16.9, 16.7, 10.8, 8.6, 8.6, 5.0, –3.7, –4.9; HRMS [ES⁺] calc for C₆₀H₇₀O₄Si₁₅P₂[N=H]⁺ 1242.6857, found 1242.6858.

One-Pot procedure

To Pd₂dba₃ (2.7 mg, 3.0 μmol) and tBu₃P (2.4 mg, 11.8 μmol) was added DMF (0.5 mL) and the catalyst solution was stirred for 5 min before it was cooled to 0 °C and kept in the dark. A solution of iodide 4 (20 mg, 29.4 μmol) in DMF (0.5 mL) was added, followed by a solution of stannane 6 (14.3 mg, 38.2 μmol), CuTC (7.3 mg, 38.2 μmol) and Ph₃PO₂NBu₄ (167 mg, 147 mmol) in DMF (1.0 mL). After stirring for 30 min, complete consumption of iodide 4 was observed by TLC and a solution of bis-halide 3 (17.2 mg, 29.4 μmol) in DMF (1.0 mL) was added, followed by a solution of CuTC (7.3 mg, 38.2 μmol) in DMF (1.0 mL). The reaction mixture was stirred until complete consumption of bis-halide 3 was observed by TLC (30 min), after which a solution of stannane 5 (20.0 mg, 29.4 μmol) and CuTC (7.3 mg, 38.2 μmol) in DMF (1.0 mL) was added. The reaction mixture was warmed to rt and stirred for a further 30 min, before it was diluted with PE and quenched with NaHCO₃ solution (5 mL). The aqueous phase was extracted with Et₂O/PE (1:1) and the combined organic extracts were dried (MgSO₄) and concentrated in vacuo. Purification by flash chromatography on Florisil® (EtOAc/PE 1:3 → 1:2) gave octaene 18 (20.5 mg, 16.5 μmol, 56%) as a pale yellow oil, as characterised above.

f. Fragment coupling strategy 2 – Approach II
To a solution of Pd(PPh₃)₄ (2.5 mg, 2.2 µmol), CuTC (3.5 mg, 11.0 µmol) and [Ph₆PO₂][NBu₄] (20.0 mg, 11.0 µmol) in DMF (0.4 mL) at 0 °C, was added a solution of bis-halide 3 (6.0 mg, 10.2 µmol) and stannane 19 (5.0 mg, 8.94 µmol) in DMF (0.4 mL). After stirring at 0 °C in the dark for 2 h, the reaction mixture was quenched with water (1 mL) and extracted with Et₂O (2 × 1 mL) and EtOAc (2 × 1 mL). The organic extracts were dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (EtOAc/PE 1:4) gave pentene 27 (5.4 mg, 7.43 µmol, 83%) as a pale yellow oil.

Rf 0.25 (EtOAc/PE 1:4); ¹H NMR (500 MHz, CDCl₃) δ₆ 6.66 (1H, dd, J = 13.4, 10.9 Hz, H25), 6.37 (1H, dd, J = 15.0, 11.4 Hz, H14), 6.26 (1H, d, J = 13.4 Hz, H26), 6.06 (1H, dd, J = 15.3, 10.9 Hz, H24), 5.97 (1H, t, J = 11.2 Hz, H13), 5.69 (1H, dd, J = 15.3, 6.9 Hz, H23), 5.63 (1H, dd, J = 15.0, 5.7 Hz, H15), 5.39 (1H, dd, J = 11.2, 8.6 Hz, H12), 5.07 (1H, d, J = 9.8 Hz, H9), 4.64 – 4.70 (1H, m, H16), 4.45 (1H, dd, J = 8.4, 4.2 Hz, H11), 4.33 (1H, dd, J = 9.8, 8.4 Hz, H17a), 4.26 – 4.30 (1H, m, H22), 3.94 – 3.97 (2H, m, H7), 3.92 (1H, t, J = 8.4 Hz, H17b), 3.69 (1H, ddd, J = 8.8, 5.1, 2.6 Hz, H20), 3.35 (3H, s, OMe), 2.90 – 2.97 (1H, m, H19), 2.58 – 2.66 (1H, m, H10), 1.72 (3H, d, J = 1.1 Hz, Me8), 1.45 – 1.56 (2H, m, H21), 1.15 (3H, d, J = 7.1 Hz, Me19), 0.94 (9H, t, J = 8.0 Hz, Si(CH₃)₂CH₂), 0.93 (9H, d, J = 6.7 Hz, Me10), 0.89 (9H, s, Si(Bu₃)₂), 0.56 (6H, q, J = 8.0 Hz, Si(CH₃)₂CH₂), 0.06 (3H, s, Si(Bu₃)₂), 0.00 (3H, s, Si(Bu₃)₂). ¹³C NMR (125 MHz, CDCl₃) δ 170.4, 138.5, 136.9, 135.7, 133.8, 132.8, 128.9, 127.2, 126.9, 126.5, 108.3, 78.0, 72.7, 71.7, 69.6, 69.1, 66.0, 57.0, 40.0, 39.8, 35.5, 25.9, 18.1, 14.3, 13.9, 11.1, 6.8, 4.9, –3.8, –4.9; HRMS (ES⁺) calcd for C₉₁H₆₄²⁷⁸BrNO₃Si₄[M+H]⁺ 726.3585, found 726.3579.

To a solution of Pd(PPh₃)₄ (10.5 mg, 9.05 µmol), CuTC (17.2 mg, 90.5 µmol) and [Ph₆PO₂][NBu₄] (100 mg, 218 µmol) in DMF (3.0 mL) at 0 °C was added a solution of vinyl bromide 27 (31.0 mg, 42.5 µmol) and stannane 20 (71.6 mg, 90.5 µmol) in DMF (3.0 mL). After stirring for 2 h in the dark, the reaction mixture was quenched with water (5 mL) and extracted with Et₂O (2 × 5 mL) and EtOAc (2 × 5 mL). The extracts were dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (EtOAc/PE 1:4) gave hexaene 28 (47.5 mg, 37.3 µmol, 88%) as a yellow oil.

**One-Pot Procedure**

To a solution of Pd(PPh₃)₄ (9.9 mg, 8.57 µmol), CuTC (13.7 mg, 71.8 µmol) and [Ph₆PO₂][NBu₄] (33.0 mg, 71.8 µmol) in DMF (1.0 mL) at 0 °C as added a solution of bis-halide 3 (20.0 mg, 34.2 µmol) and stannane 19 (19.1 mg, 34.2 µmol) in DMF (1.0 mL). After stirring at 0 °C for 2 h in the dark, a solution of stannane 20 (43.4 mg, 54.8 µmol) in DMF (1.0 mL) was added. The reaction mixture was stirred for another 2 h before being quenched with water (3 mL) and extracted with Et₂O (2 × 2 mL) and EtOAc (2 × 2 mL). The extracts were dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (EtOAc/PE 1:2) gave hexaene 28 (35.0 mg, 27.5 µmol, 80%) as a yellow oil.
4.32 (1H, dd, J = 10.2, 8.4 Hz, H17a), 4.00
4.66 (1H, m, H16), dd, J = 10.5 Hz, H28), 5.39 (1H, dd, J = 11.1, 8.5 Hz, H12), 5.29 H2*),
6.33 (2H, m, H3, H14, H26), 6.20 Hz, H3*), 6.79 (0.1007, 837, 806, 776; R
Vinyl stannane S11

To a solution of phosphonate 28 (20.0 mg, 15.7 µmol) in THF (4.0 mL) at 0 °C was added sodium hydride (6.0 mg, 250 µmol). After 30 min, the reaction mixture was cooled to −78 °C and aldehyde 21 (20.0 mg, 58.8 µmol) in THF (1 mL) was added. After stirring for 48 h, the reaction mixture was quenched with water (5 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were dried (Na2SO4) and concentrated in vacuo. Purification by flash chromatography (Et2O/PE 1:9) gave vinyl stannane S11 (17.1 mg, 12.6 µmol, 80%) as a colourless oil as a 2.5:1 mixture of Z/Z isomers.

Rf 0.8 (PE / EtOAc 6:4); [α]D20 +9.97 (c 1.1, CHC13); IR νmax 2929, 1716, 1663, 1619, 1461, 1376, 1250, 1191, 1143, 1088, 1007, 837, 776; 1H NMR (500 MHz, CDCl3) 6δ 7.79 (0.66H, ddd, J =18.8, 10.6, 1.0 Hz, H4), 7.14 (0.33H, dd, J = 15.3, 10.3 Hz, H3*), 6.79 (0.33H, d, J = 18.7 Hz, H5*), 6.69 (0.66H, d, J = 18.7 Hz, H5), 6.63 (0.33H, dd, J = 18.5, 10.3 Hz, H4*), 6.45 – 6.33 (2.66H, m, H3, H14, H26), 6.20 – 6.08 (2H, m, H24, H25), 6.05 – 5.94 (2H, m, H13, H27), 5.79 (0.33H, d, J = 15.4 Hz, H2*), 5.67 – 5.59 (2H, m, H15, H23), 5.51 (0.66H, d, J = 11.4 Hz, H2), 5.46 (0.33H, dd, J = 10.5, 10.5 Hz, H28*), 5.42 (0.66H, dd, J = 10.5 Hz, H28), 5.39 (1H, dd, J = 11.1, 8.5 Hz, H12), 5.29 – 5.24 (1H, m, H30, H30*), 5.06 (1H, dd, J = 10.0, 1.1 Hz, H9), 4.66 (1H, m, H16), 4.45 (1H, ddd, J = 8.3, 4.4, 1.1 Hz, H11), 4.39 (1H, dqd, J = 6.4, 6.4, 2.3 Hz, H34), 4.35 – 4.29 (1H, m, H22), 4.32 (1H, dd, J = 10.2, 8.4 Hz, H17a), 4.00 – 3.90 (1H, m, H32), 3.95 (2H, s, H7), 3.91 (1H, dd, J = 7.8, 7.8 Hz, H17b), 3.79 –
3.67 (2H, m, H20, OH7), 3.36 (3H, s, OMe20), 2.98 – 2.90 (1H, m, H29), 2.90 (1H, dqd, J = 6.9, 5.5 Hz, H19), 2.63 (1H, dqd, J = 9.6, 6.8, 3.8 Hz, H10), 1.96 – 1.83 (2H, m, H31, H33a), 1.72 (3H, d, J = 1.1 Hz, Me8), 1.56 – 1.46 (9H, m, H21a, H21b, H33b, Sn(CH2CH2CH2CH2O)2), 1.36 – 1.23 (9H, m, H35, Sn(CH2CH2CH2CH2O)2), 1.15 (3H, d, J = 7.1 Hz, Me19), 1.02 – 0.86 (60H, Me10, Me29, Me31, Sn(CH2CH2CH2CH2O)2, Si(tBu)2, Si(tBu)2Me, Si(CH2)2O)2, 0.56 (6H, q, J = 7.9 Hz, Si(CH2)2O), 0.07 (3H, s, Si(tBu)2Me), 0.01 (3H, s, Si(tBu)2Me). 11C NMR (125 MHz, CDCl3) 178.6, 167.0*, 165.5, 147.3, 146.8*, 146.4, 146.2*, 144.4*, 142.8, 137.2*, 137.4, 135.7, 134.0, 133. 132.8, 132.7, 129.8, 129.0, 128.9, 127.8, 127.6*, 127.2, 126.9, 120.2*, 116.2, 78.2, 76.0, 75.4, 72.7, 71.7, 70.2, 69.6*, 69.4, 69.1, 67.6, 66.0, 57.2, 41.6*, 41.4, 40.1, 40.1, 37.3, 35.8, 35.5*, 35.2, 29.1, 29.0*, 27.4, 27.3, 27.1, 25.9, 23.6, 21.3, 20.7, 18.1, 18.0*, 17.8, 14.3, 14.1, 13.9, 13.7, 11.4, 9.7, 9.6*, 6.9, 4.9, −3.6, −4.8; HRMS ESI calc. for C72H120NO8Si112Sn [M+H]+ 1350.8253, found 1350.8276.

*Identifiable resonances for the minor Δ2-ε isomer.

Aldehyde 29

Oxazoline S11 (8.0 mg, 5.9 µmol) was dissolved in benzene (1.0 mL) and 4Å molecular sieves (50 mg) were added. Activated manganese dioxide (5 x 30 mg portions) was added every 30 min until the reaction was judged complete by TLC analysis (2.5 h total). The reaction mixture was filtered through Celite and concentrated in vacuo. Purification by preparative thin layer chromatography (PE / EtOAc, 10:1) afforded the pure Z-isomer 29 (1.6 mg, 1.2 µmol, 20%) along with a 1:1 mixture of E and Z isomers (1.0 mg, 0.75 µmol, 13%).

RF 0.7 (PE / EtOAc 4:1); [α]_D^28 5.90 (c 0.16, CHCl3); IR νmax 2927, 1716, 1691, 1457, 1377, 1246, 1093, 1038, 1006, 826, 742;

1H NMR (500 MHz, CDCl3) δ 9.42 (1H, s, H7), 7.81 (1H, dd, J = 18.8, 10.6 Hz, H4), 7.52 (1H, s, H17), 7.12 (1H, dd, J = 15.0, 11.8 Hz, H14), 6.71 (1H, d, J = 19.0 Hz, H5), 6.51 (1H, d, J = 10.0 Hz, H9), 6.47 – 6.38 (2H, m, H3, H26), 6.38 (1H, d, J = 15.2 Hz, H15), 6.21 – 6.09 (3H, m, H13, H24, H25), 6.01 (1H, dd, J = 11.1, 11.1 Hz, H27), 5.61 (1H, dd, J = 14.3, 7.4 Hz, H23), 5.52 (1H, d, J = 11.5 Hz, H2), 5.48 – 5.38 (2H, m, H12, H28), 5.29 (1H, dd, J = 7.1, 4.1 Hz, H30), 4.66 (1H, dd, J = 8.9, 4.5 Hz, H11), 4.41 (1H, dqd, J = 6.6, 6.6, 1.5 Hz, H34), 4.33 (1H, ddd, J = 9.5, 9.5, 2.5 Hz, H22), 3.97 (1H, ddd, J = 8.2, 8.2, 1.5 Hz, H32), 3.86 – 3.76 (1H, m, H20), 3.42 – 3.35 (1H, m, H19), 3.40 (3H, s, OMe20), 2.94 (1H, ddd, J = 9.8, 6.8, 6.8 Hz, H29), 2.89 – 2.80 (1H, m, H10), 1.97 – 1.84 (2H, m, H31, H33a), 1.76 (3H, s, Me8), 1.57 – 1.48 (9H, m, H21a, H21b, H33b, Sn(CH2CH2CH2CH2O)2), 1.376 – 1.28 (12H, m, H35, Me10, Sn(CH2CH2CH2CH2O)2), 1.10 (3H, d, J = 7.1 Hz, Me19), 1.04 – 0.86 (57H, Me29, Me31, Sn(CH2CH2CH2CH2O)2, Si(tBu)2, Si(tBu)2Me, Si(CH2)2O)2, 0.59 (6H, q, J = 8.0 Hz, Si(CH2)2O), 0.08 (3H, s, Si(tBu)2Me), 0.02 (3H, s, Si(tBu)2Me); 13C NMR (125 MHz, CDCl3) 195.6, 166.0, 165.5, 156.8, 147.4, 146.4, 142.8, 139.3, 138.7, 137.3, 135.4, 134.1, 133.8, 132.6, 129.8, 129.1, 128.9, 127.9, 124.9, 122.5, 116.2, 79.1, 75.3, 71.8, 70.3, 69.4, 67.6, 57.4, 41.4, 41.1, 40.2, 37.3, 36.0, 35.2, 29.1, 27.4, 27.3, 27.1, 25.9, 23.5, 21.3, 20.7, 18.1, 17.8, 16.1, 13.7, 11.5, 9.8, 9.7, 9.5, 6.8, 5.0, −3.7, −4.8; HRMS ESI calc. for C72H120NO8Si112Sn [M+H]+ 1346.7940 found 1346.7935.
Chivosazole F (1)

To a suspension of \([\text{PPh}_3\text{CH}_2\text{I}][\text{I}]\) (10.0 mg, 18.9 µmol) in THF (300 µL) was added sodium hexamethyldisilazide solution (0.63 M in THF, 30.0 µL, 18.9 µmol) to form a clear, orange solution. The solution was cooled to −78 °C and a solution of aldehyde 29 (1.6 mg, 1.2 µmol) in THF (300 + 100 µL) was added via cannula. The reaction mixture was stirred at −78 °C for 1 h before being diluted with hexane (1 mL) and warmed to rt. The reaction mixture was filtered through a short plug of silica gel and concentrated in vacuo to yield the vinyl iodide which was used directly without further purification.

A stock solution of Pd(\text{PPh}_3)_4 (3.2 mg, 2.7 µmol), CuTC (5.0 mg, 26.2 µmol) and \([\text{Ph}_2\text{PO}_2][\text{NBu}_4]\) (12.5 mg, 27.2 µmol) was prepared in DMF (1.0 mL). A portion of this solution (100 µL) was transferred to a flask, diluted with DMF (2.0 mL), cooled to 0 °C and placed in the dark. A solution of the crude vinyl iodide in DMF (2.0 mL) was added to the catalyst solution over 2.5 h via syringe pump and the reaction mixture stirred for 30 min following completion of the addition. The reaction mixture was filtered through a plug of silica (eluting with EtOAc), concentrated in vacuo and filtered again through a plug of silica (eluting with PE / EtOAc, 4:1). The solution of crude macrocycle was concentrated in vacuo, transferred to a plastic reaction vessel and submitted directly to the subsequent deprotection.

A stock solution of HF-pyridine was prepared from HF-pyridine (100 µL), pyridine (150 µL) and THF (150 µL) and stirred for 30 min at rt. A portion of this solution (100 µL) was added to the crude macrocycle and the reaction stirred overnight at rt. The reaction mixture was carefully quenched with NaHCO₃ solution (100 µL) and filtered through a plug of Celite (washing with EtOAc). The resulting mixture was concentrated in vacuo and purified by preparative thin layer chromatography (EtOAc / PE / MeOH, 6:3:1) to afford chivosazole F as a white amorphous solid (340 µg, 0.49 µmol, 41%).

\[ [\alpha]_D^{20} = -3.3 (c 0.03, \text{MeOH}), cf \text{ lit}^5 [\alpha]_D^{20} = -5.0 (c 0.2, \text{MeOH}); ^{1}H \text{ NMR} (700 MHz, CD₃OD) \text{See Table S1; } ^{13}C \text{ NMR} (175 MHz, CD₃OD) \text{See Table S1; } \text{HRMS ESI calc. for } C_{41}H_{57}NO₈Na [M+Na]^+ 714.3982, \text{found 714.3969.} \]
3. Comparison of NMR Data for natural and synthetic chivosazole F

Table S1: Comparison of NMR data for natural⁶ and synthetic chivosazole F (CD₃OD)

| Carbon | δₓ Natural / ppm 100 MHz | δₓ Synthetic / ppm 175 MHz | δₓ Natural / ppm 400 MHz | J/Hz | δₓ Synthetic / ppm 700 MHz | J/Hz |
|--------|--------------------------|---------------------------|--------------------------|------|---------------------------|------|
| 1      | 168.9                    | 168.9                     |                          |      |                           |      |
| 2      | 117.9                    | 117.9                     | 5.43                     | d    | 11.5                      | 5.43 | d | 11.4 |
| 3      | 145.4                    | 145.3                     | 6.51                     | dd   | 11.5, 11.5                | 6.51 | dd | 11.7, 11.7 |
| 4      | 130.6                    | 130.6                     | 7.07                     | dd   | 14.9, 11.8                | 7.07 | dd | 14.9, 11.7 |
| 5      | 139.8                    | 139.8                     | 6.88                     | dd   | 14.9, 11.0                | 6.88 | dd | 14.9, 11.2 |
| 6      | 129.0                    | 129.0                     | 5.99 – 5.92 m            |      |                           | 5.91 | dd | 11.3, 11.3 |
| 7      | 139.9                    | 139.9                     | 5.85                     | d    | 11.3                      | 5.85 | d | 11.3 |
| 8      | 134.3                    | 134.3                     |                          |      |                           |      |
| 9      | 136.3                    | 136.3                     | 5.07                     | d    | 9.0                       | 5.08 | d | 8.9 |
| 10     | 40.4                     | 40.4                      | 2.88 – 2.79 m            |      |                           | 2.83 | ddq | 9.0, 6.8, 6.8 |
| 11     | 70.5                     | 70.5                      | 4.73                     | dd   | 9.0, 5.8                  | 4.73 | dd | 9.0, 5.8 |
| 12     | 132.4                    | 132.4                     | 5.49                     | dd   | 10.1, 10.1                | 5.50 | dd | 10.2, 10.2 |
| 13     | 131.3                    | 131.3                     | 6.22                     | dd   | 11.2, 11.2                | 6.22 | dd | 11.3, 11.3 |
| 14     | 127.3                    | 127.3                     | 7.17                     | dd   | 15.2, 11.8                | 7.17 | dd | 15.2, 11.7 |
| 15     | 122.0                    | 122.0                     | 6.37                     | d    | 15.2                      | 6.37 | d | 15.2 |
| 16     | 140.1                    | 140.1                     |                          |      |                           |      |
| 17     | 137.7                    | 137.6                     | 7.73                     | s    |                           | 7.73 | s  |
| 18     | 167.4                    | 167.4                     |                          |      |                           |      |
| 19     | 36.4                     | 36.4                      | 3.54 – 3.48 m            |      |                           | 3.50 | ddq | 6.9, 3.7 |
| 20     | 80.0                     | 80.0                      | 3.94                     | ddd  | 10.4, 3.5, 1.4            | 3.94 | ddd | 10.7, 3.8, 1.8 |
| 21     | 39.6                     | 39.6                      | 1.71 – 1.65 m            |      |                           | 1.66 | m  |
| 22     | 68.0                     | 68.1                      | 4.35                     | brd  | 9.3                       | 4.35 | brd | 10.5 |
| 23     | 138.7                    | 138.7                     | 5.78                     | dd   | 15.2, 3.6                 | 5.77 | dd | 15.2, 3.6 |
| 24     | 129.2                    | 129.2                     | 6.43 – 6.34 m            |      |                           | 6.39 | ddd | 15.0, 11.0, 1.8 |
| 25     | 134.4                    | 134.4                     | 6.18                     | dd   | 14.7, 10.8                | 6.18 | dd | 14.6, 10.8 |
| 26     | 128.6                    | 128.6                     | 6.56                     | dd   | 14.7, 11.4                | 6.55 | dd | 14.6, 11.4 |
| 27     | 130.2                    | 130.2                     | 5.92 – 5.88 m            |      |                           | 5.96 | dd | 11.0, 11.0 |
| 28     | 135.5                    | 135.5                     | 5.18                     | dd   | 10.6, 10.6                | 5.17 | dd | 10.4, 10.4 |
| 29     | 35.7                     | 35.7                      | 3.20 – 3.12 m            |      |                           | 3.16 | ddq | 10.1, 10.1, 6.3 |
| 30     | 78.1                     | 78.1                      | 5.26                     | dd   | 10.3, 1.0                 | 5.26 | dd | 10.3, 1.0 |
| 31     | 41.8                     | 41.8                      | 1.83 – 1.75 m            |      |                           | 1.80 | m  |
| 32     | 70.3                     | 70.3                      | 3.47 – 3.43 m            |      |                           | 3.4  | ddd | 14.2, 6.7, 4.7 |
| 33     | 44.7                     | 44.7                      | 1.65 – 1.60 m            |      |                           | 1.6  | m  |
| 34     | 65.2                     | 65.2                      | 4.02                     | dqq  | 12.2⁶, 6.2, 2.3           | 4.02 | dqq | 9.2⁶, 6.4, 2.3 |
| 35     | 24.5                     | 24.4                      | 1.18                     | d    | 6.2                       | 1.18 | d  | 6.3 |
| Me 10  | 14.3                     | 14.3                      | 1.05                     | d    | 6.8                       | 1.05 | d  | 6.8 |
| Me 19  | 10.8                     | 10.9                      | 1.36                     | d    | 7.1                       | 1.36 | d  | 7.1 |
| Me 29  | 17.8                     | 17.8                      | 1.02                     | d    | 6.7                       | 1.02 | d  | 6.7 |
| Me 31  | 10.4                     | 10.4                      | 0.99                     | d    | 6.9                       | 0.99 | d  | 6.9 |
| Me 8   | 17.2                     | 17.2                      | 1.91                     | s    |                           | 1.89 | s  |
| OMe 20 | 58.2                     | 58.2                      | 3.50                     | s    |                           | 3.49 | s  |

Full data and NMR spectra for an authentic sample of natural chivosazole F was disclosed by Kalesse when reporting his synthesis of chivosazole F and this data has been used for comparison.⁶ Upon inspection, the multiplets appear identical, however, we believe that the coupling constants may have been determined erroneously. Applying Hoye’s protocol⁶ gives coupling constants of c. 9, 6 and 2 Hz as recorded.
4 References

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5. $^1$H and $^{13}$C NMR spectra

$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl₃)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)

50 °C

25 °C
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CD$_3$OH)
$^{13}$C NMR (125 MHz, CD$_3$OH)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^{1}$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
^1H NMR (500 MHz, CDCl₃)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^1\text{H NMR (500 MHz, CDCl}_3\text{)}$
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (125 MHz, CDCl$_3$)
$^1$H NMR (700 MHz, CD$_3$OD)
$^1$H NMR (700 MHz, CD$_3$OD)
$^{13}$C NMR (175 MHz, CD$_3$OD)
