The Stereocontrolled Total Synthesis of Altohyrtin A/Spongistatin 1. Part 2: The CD-Spiroacetal Segment

Ian Paterson, a* Mark J. Coster, b David Y.-K. Chen, Karl R. Gibson and Debra J. Wallace.

a University Chemical Laboratory, Lensfield Road, University of Cambridge, Cambridge CB2 1EW, UK. Fax: +44 1223 336 362; E-mail: ip100@cam.ac.uk
b Current address: School of Chemistry, University of Sydney, NSW 2006, Australia. Fax: +61 2 9351 3329; E-mail: m.coster@chem.usyd.edu.au

Contents (15 pages):
• General Experimental Details (p. S1)
• Experimental Procedures and Product Characterisation Data (p. S2–S15)

General Experimental Details

1H nuclear magnetic resonance (NMR) spectra were recorded at either 250, 400 500 or 800 MHz on Bruker DPX 250, DPX 400, DRX 500 or DRX 800 spectrometers at ambient temperature using an internal deuterium lock. The following internal references were used for the residual protons in the following solvents: CDCl3 (δH 7.26), C6D6 (δH 7.16) and CD3CN (δH 1.94). Data are presented as follows: chemical shift (in ppm on the δ scale relative to tetramethylsilane δTMS = 0), integration, multiplicity, coupling constant and interpretation XX-CH where XX refers to the carbon no. to which the proton in question is attached. Where reasonable, this numbering is based on the spongistatin skeleton. The following abbreviations for splitting patterns are used: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; m, multiplet; br, broad. When the multiplet is derived from couplings to non-equivalent protons with coincidentally the same coupling constants then the multiplet is referred to as app, apparent. Assignments were determined either on the basis of unambiguous chemical shift or coupling pattern, COSY experiments or by analogy to fully interpreted spectra for related compounds. 13C nuclear magnetic resonance (NMR) spectra were recorded at 100.6 MHz or 62.5 MHz on Bruker AM 400 or DPX 250 spectrometers respectively at ambient temperature using an internal deuterium lock, and all chemical shift values are reported in parts per million (δ) downfield relative to tetramethylsilane (TMS, δTMS = 0). An internal reference was used for CDCl3 (δC 77.16) and C6D6 (δC 128.06).

Infra-red spectra were recorded on Perkin-Elmer 1620 (FT-IR) spectrometers using 0.5 cm sodium chloride plates. Absorbance bands are reported in wavenumbers (cm⁻¹) relative to polystyrene as the calibrant, and the following abbreviations are used to describe their appearance: w, weak; s, strong; br, broad. Only the most significant bands are reported.

High and low resolution mass spectra were acquired using positive chemical ionisation using NH4⁺ (+CI, NH3) by the EPSRC National Mass Spectrometry Service Centre, Swansea, UK and the Departmental Mass Spectrometry Service, University Chemical Laboratory, Cambridge, using electron impact (EI), electrospray (+ESI), chemical ionisation (+CI) or fast atom bombardment (+FAB) ionisation techniques. The parent ion [M]⁺ or [MH]⁺ or [M + NH4]⁺ is quoted, followed by significant fragments with their relative intensities.

Optical rotations were recorded on a Perkin Elmer 241 polarimeter at the sodium D line (589 nm) and are reported as follows: [α]D, concentration (c in g/100 mL) and solvent (all the rotations were measured at a temperature of 20 °C). Melting points were recorded on a Kofler hot-stage and are uncorrected.

Analytical thin layer chromatography (TLC) was carried out using Merck Kieselgel 60 F254 plates with visualisation either by ultra violet light (254 nm), anisaldehyde or Goofy's dips. Flash column chromatography was carried out using Merck Kieselgel 60 (230-400 mesh) under a positive pressure using distilled solvents and in this thesis the term implies subsequent removal of the solvents in vacuo unless otherwise stated. High Performance Liquid Chromatography (HPLC) was
carried out using a Rainin Instrument Co. Inc. DYNAMAX Macro-HPLC column (internal diameter: 21.4 mm), prepacked with 8 micron irregular silica particles, and equipped with a Gilson refractive index detector (Model 131) or a Gilson UV detector (Model 111B) at a wavelength of 254 nm. A flow rate of 10 mL min\(^{-1}\) was used and all solvents were vacuum-filtered and degassed prior to use.

Reagents and solvents were prepared using standard means.\(^1\) Anhydrous CH\(_2\)Cl\(_2\), MeOH and hexane were distilled from CaH\(_2\) and stored under argon; ether was distilled from sodium metal/benzophenone ketyl and stored under an argon atmosphere; THF was distilled from either LiAlH\(_4\) or potassium metal/benzophenone ketyl and stored under an argon atmosphere. Triethylamine (Et\(_3\)N), \(i\)-Pr\(_2\)NEt, pyridine and 2,6-lutidine were distilled from and stored over CaH\(_2\). Acetic acid (AcOH) was distilled from CrO\(_3\) and Ac\(_2\)O and stored under an argon atmosphere. Simple aldehydes were distilled from calcium chloride immediately prior to use. All other reagents were used as received except where noted in the experimental procedure.

All experiments were performed under anhydrous conditions, utilising anhydrous solvents, under an atmosphere of argon, except where stated, using oven-dried glassware and employing standard techniques in handling air-sensitive materials. All reactants added via cannula were added using a positive pressure of argon. Where a reaction temperature is not specified the reaction was performed at RT. Where a compound has been published in the literature, all spectroscopic and physical properties matched those reported.

**Experimental Procedures and Product Characterisation Data**

**\((S\)-1\-\((\text{tert-Butyldimethylsiloxy})\)-oct-7-en-3-ol (16)\)**

To a cold (−78 °C), stirred solution of (−)-Ipc\(_2\)BOMe (2.95 g, 9.31 mmol, 1.8 equiv) in Et\(_2\)O (40 mL) was added allylmagnesium bromide (7.5 mL, 1 M in Et\(_2\)O, 7.5 mmol, 1.4 equiv.). The reaction was stirred for 15 mins and then allowed to warm to RT for 1 h. The reaction was re-cooled to −78 °C and a solution of aldehyde 15 (1.00 g, 5.31 mmol) in Et\(_2\)O (2 mL + 2 x 1 mL washings) was added via cannula. The reaction was stirred at -78 °C for 2 h and then allowed to warm to RT for 1 h. The reaction was quenched by the addition of NaOH solution (20 mL, 10% aqueous) and H\(_2\)O\(_2\) solution (20 mL, 30% aqueous) and then heated to reflux for 16 h after which time additional NaOH solution (5 mL, 10% aqueous) and additional H\(_2\)O\(_2\) solution (5 mL, 30% aqueous solution) were added and the reaction heated at reflux for a further 2 h. The reaction was cooled to RT and the layers were separated, the aqueous layer was extracted with Et\(_2\)O (3 x 40 mL). The combined organic extracts were washed with H\(_2\)O (25 mL) and brine (40 mL) and dried (MgSO\(_4\)). The solvent was removed \emph{in vacuo} and the crude reaction mixture was purified by flash chromatography (15:85 EtOAc/hexanes) to yield the title alcohol 16 (0.97 g, 79%, 84% ee as adjudged by MTPA ester analysis) as a colourless oil: \(R_f\) 0.21 (CH\(_2\)Cl\(_2\)); \(\lambda_{\text{max}}=\alpha_{\text{D}}\) \(-5.95\ (c\ 2.20,\ \text{CHCl}_3)\); IR (liquid film) 3416 (br), 1642, 1472 cm\(^{-1}\); \(^1\)H NMR \(\delta\) (400 MHz, CDCl\(_3\)) 5.82 (1H, ddt, \(J=17.1, 9.8, 7.1\) Hz, 19-CH\(_2\)), 5.07 (1H, dd, \(J=17.1, 1.3\) Hz, 19-C=CH\(_2\)A), 5.05 (1H, dd, \(J=10.0, 1.1\) Hz, 19-C=CH\(_2\)B), 3.91–3.75 (2H, m, 23-CH\(_2\)), 3.81–3.75 (1H, m, 21-CH), 3.39 (1H, d, \(J=1.8\) Hz, -OH), 2.22 (2H, m, 20-CH\(_2\)), 1.63 (1H, app q, \(J=5.2\) Hz, 22-CH\(_2\)), 0.87 (9H, s, -OSiMe\(_3\)\(tBu\)), 0.05 (6H, s, -OSiMe\(_3\)\(tBu\)); \(^{13}\)C NMR \(\delta\) (100.6 MHz, CDCl\(_3\)) 135.0, 117.2, 71.2, 62.3, 41.9, 37.7, 25.8, 18.1, \(-5.6\); HRMS [+Cl, NH\(_3\)] Calc. for C\(_{12}\)H\(_{27}\)O\(_2\)Si [MH\(^+\)] 231.1780; found 231.1780; \(m/z\) 231 ([MH\(^+\)]\(^1\)), 132 (10), 92 (20), 81 (15).

**\((3\text{S})\)-1\-\((\text{tert-Butyldimethylsilyloxy})\)-3\-methoxy-hex-5-ene (S1)\)**

NaH, 60% in oil dispersion (392 mg, 9.81 mmol), was washed in dry hexane (3 x 25 mL), rinsed in dry THF (25 mL), and suspended in dry THF (40 mL). A solution of alcohol 16 (376 mg, 1.63

mmol) in dry THF (5 mL + 2 x 1 mL washings) was added via cannula with stirring. After 25 mins MeI (203 µL, 3.26 mmol) was added and the reaction stirred at RT for 16 h. The reaction was quenched by the addition of NH4Cl solution (50 mL) and Et2O (50 mL) added. The layers were separated and the aqueous layer extracted with Et2O (3 x 40 mL). The combined organic extracts were washed with NaHCO3 solution (20 mL, sat. aqueous) and brine (20 mL) and dried (MgSO4). The solvent was removed in vacuo and the crude product was subjected to flash chromatography (CH2Cl2) to give the title methyl ether S1 (383 mg, 96%) as a colourless oil: Rf 0.40 (CH2Cl2); [α]D25 +8.80 (c 1.46, CHCl3). IR (liquid film) 1641, 1465 cm−1; 1H NMR δ (400 MHz, CDCl3) 5.06 (1H, ddt, J = 15.5 Hz, 19-C=CH2, 5.03 (1H, overlapping d, J = 9.4 Hz, 19-C=CH3), 3.68–3.64 (2H, m, 23-CH2A), 2.15 (2H, d, J = 6.9 Hz, 21-CH2), 3.32 (3H, s, -OMe), 2.61 (2H, dd, J = 6.9, 5.9 Hz, 20-CH2), 1.65 (2H, dt, J = 6.6, 6.4 Hz, 22-CH2), 0.91 (9H, s, -OSiMe3) as a colourless oil: Rf 0.45 (10:90 EtOAc/CH2Cl2); [α]D25 +5.18 (c 4.25, CHCl3). IR (liquid film) 2726, 1727, 1472 cm−1; 13C NMR δ (400 MHz, CDCl3) 201.5, 73.6, 59.1, 56.9, 48.2, 37.0, 25.9, 18.2, –5.4; HRMS [M+H]+ Calc. for C13H29O2Si [MH+] 245.1937; found: 245.19367; C13H29O2Si [MH+] 245.19367, found 245.1937;

(3R)-3-Methoxy-5-(tert-butyldimethylsilyloxy)-pentanal (14)

Ozone was bubbled through a cold (–78 °C), solution of alkene S1 (368 mg, 1.51 mmol) and NaHCO3 (solid approx. 100 mg) in dry CH2Cl2 (20 mL). When a blue colour persisted in the reaction indicating unreacted ozone, the flow of ozone was ceased and the apparatus flushed with argon. Triphenylphosphine (600 mg, 2.16 mmol) was added and the reaction was transferred to a –20 °C freezer for 16 h. The reaction was allowed to warm to RT and the solvent was removed in vacuo. Purification of the crude product containing triphenylphosphine was achieved by flash chromatography (CH2Cl2, then 10:90 EtOAc/CH2Cl2) to yield the title aldehyde 14 (331 mg, 90%) as a colourless oil: Rf 0.45 (10:90 EtOAc/CH2Cl2); [α]D25 +5.18 (c 4.25, CHCl3). IR (liquid film) 2726, 1727, 1472 cm−1; 1H NMR δ (500 MHz, CDCl3) 9.81 (1H, t, J = 2.2 Hz, 19-CH), 3.89 (1H, app quintet, J = 6.1 Hz, 21-CH), 3.75–3.67 (2H, m, 23-CH2), 3.36 (3H, s, -OMe), 2.61 (2H, dd, J = 6.0, 2.3 Hz, 20-CH2), 1.84 (1H, app dq, J = 14.1, 5.7 Hz, 22-CH2A), 1.71 (1H, app dq, J = 14.0, 5.7 Hz, 22-CH2B), 0.89 (9H, s, -OSiMe2Bu), 0.052 (3H, s, -OSiMe2Bu), 0.051 (3H, s, -OSiMe2Bu); 13C NMR δ (50 MHz, CDCl3) 201.5, 73.6, 59.1, 56.9, 48.2, 37.0, 25.9, 18.2, –5.4; HRMS [M+H]+ Calc. for C12H25O3Si [M+H+] 263; found: 245.1573, 245.1563; m/z (+CI, NH3) Calc. for C12H25O3Si [M+H+] 263 ([M + H + NH4]1+, 100), 245 ([M – H]1+, 20), 205 (90), 131 (40), 106 (40), 89 (40).

(3R,SR)-1-(tert-Butyldimethylsilyloxy)-3-methoxy-7-ethyl-oct-7-en-5-ol (17)

To a cold (–78 °C), stirred solution of aldehyde 14 (100 mg, 0.406 mmol) in dry CH2Cl2 (40 mL, 0.01 M in aldehyde) was added TiCl4 (49 µL, 0.45 mmol) and the reaction was subsequently cooled to –100°C over 5 mins. A mixture of allylsilane 13δ (1.41 g, 1:10 in pentane, 1.63 mmol) in dry CH2Cl2 (1 mL + 2 x 0.5 mL washings) was added dropwise via cannula. After 20 mins at –100 °C the reaction was quenched by the addition of NaHCO3 solution (20 mL, sat. aqueous). The reaction was allowed to warm to RT and the layers were separated. The aqueous layer was extracted with CH2Cl2 (4 x 10 mL). The combined organic extracts were washed with H2O (10 mL) and brine (20 mL) and dried (MgSO4). The solvent was removed in vacuo and the reaction mixture was purified by flash chromatography (25:75 EtOAc/hexanes) to yield the title alcohol 17 (102 mg, 79%), as a colourless oil, with 96:4 dr as adjudged by 1H NMR.

Major diastereomer 17: Rf 0.80 (Et2O), 0.37 (25:75 EtOAc/hexanes); Rf 17 mins (25% EtOAc/hexane); [α]D25 −5.2 (c 1.93, CHCl3); IR (liquid film) 3683, 1644 (w), 1522 cm−1; 1H NMR δ (500 MHz, CDCl3) 4.85 (1H, d, J = 1.6 Hz, 17-C=CH2), 4.80 (1H, s, 17-C=CH2B), 4.01–3.98 (1H, m, 19-CH), 3.70–3.64 (3H, m, 21-CH + 23-CH2), 3.38 (3H, s, -OMe), 2.79 (1H, d, J = 2.6 Hz, -OH), 2.23–2.16 (2H, m, 18-CH2), 2.09 (1H, strongly roofed dq, J = 16.0, 8.1 Hz, 16-CH2A), 2.03

(3R,5S)-1-(tert-Butyldimethylsilyloxy)-3-methoxy-5-(triisopropylsilyloxy)-7-ethyl-oct-7-ene (S2)

To a stirred solution of homoallylic alcohol 17 (46.7 mg, 0.148 mmol) in CH₂Cl₂ (7 mL) at –78 ºC was added 2,6-lutidine (23 µL, 0.195 mmol) followed by TIPSOTf (48 µL, 0.177 mmol). The reaction was stirred for 2 h and then quenched by the addition of NH₄Cl solution (5 mL, sat. aqueous) and allowed to warm to RT. The layers were separated and the aqueous layer extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were washed with brine (10 mL) and dried (MgSO₄). The solvent was removed in vacuo and the crude product was purified by flash chromatography (15:85 EtOAc/hexanes) to yield the title compound S2 (69.1 mg, 99%) as a colourless oil: Rf 0.65 (25:75 EtOAc/hexanes); [α]₂⁰/D –20.6 (c 1.53, CHCl₃); IR (liquid film) 2942, 2866, 1645 (w) cm⁻¹; ¹H NMR δ (250 MHz, CDCl₃) 4.78, 4.75 (2H, s, s, 17-C=CH₂), 4.16 (1H, app tt, J = 8.5, 4.2 Hz, 19-CH₂), 3.71–3.62 (2H, partially overlapping m, 23-CH₂), 3.63–3.52 (1H, partially overlapping m, 21-CH₂), 3.29 (3H, s, -OMe), 2.40 (1H, dd, J = 13.6, 4.3 Hz, 18-CH₂A), 2.13 (1H, dd, J = 13.6, 9.0 Hz, 18-CH₂B), 2.02 (2H, app q, J = 7.6 Hz, 16-CH₂), 1.80–1.59 (3H, m, 20-CH₂ + 22-CH₂A), 1.37 (1H, ddd, J = 15.0, 8.2, 3.7 Hz, 22-CH₂B), 1.10–1.06 (21H, m, -OSi(CH(CH₃)₂)₃), 1.02 (3H, app t, J = 7.5 Hz, 16-C-CH₃), 0.89 (9H, s, -OSiMe₂Bu), 0.04 (6H, s, -OSiMe₂Bu); ¹³C NMR δ (100.6 MHz, CDCl₃) 148.1, 110.5, 77.2, 68.3, 59.6, 55.8, 45.6, 42.1, 36.9, 29.0, 25.9, 18.3, 12.9, 12.2, –5.4; HRMS (+Cl, NH₃) Calc. for C₂₀H₄₃O₃Si [MH⁺]: 359.2981, found: 359.2981; m/z (+Cl, NH₃) 359 (MH⁺, 5), 371 (29), 299 (30), 267 (30), 135 (50), 132 (35), 106 (30), 58 (100).

(3R,5S)-3-Methoxy-5-(triisopropylsilyloxy)-7-ethyl-oct-7-en-1-ol (18)

To a cooled (0 ºC), stirred solution of silyl ether S2 (144 mg, 0.305 mmol) in MeOH (1 mL) and CH₂Cl₂ (9 mL) was added camphorsulfonic acid (7.0 mg, 0.030 mmol). The reaction was allowed to warm to RT and stirred until TLC analysis indicated all starting material had been consumed (4 h). The reaction was quenched by the addition of Et₃N (5 drops) and concentrated in vacuo. The crude mixture was purified by flash chromatography (25:75 EtOAc/hexanes) to yield the title alcohol 18 (92.1 mg, 84%) as a colourless oil: Rf 0.23 (25:75 EtOAc/hexanes); [α]₂⁰/D –13.8 (c 3.05, CHCl₃); IR (liquid film) 3395 (br), 2942, 1645 (w) cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 4.80, 4.76 (2H, s, s, 17-C=CH₂), 4.45 (1H, app tt, J = 8.5, 4.3 Hz, 19-CH₂), 3.83–3.77 (1H, m, 23-CH₂), 3.72 (1H, app qn, J = 5.6 Hz, 21-CH₂), 3.68–3.64 (1H, m, 23-CH₂B), 3.34 (3H, s, -OMe), 2.41 (1H, dd, J = 13.7, 4.1 Hz, 18-CH₂A), 2.31 (1H, t, J = 5.2 Hz, -OH), 2.14 (1H, dd, J = 13.6, 9.1 Hz, 18-CH₂B), 2.06–1.98 (2H, m, 16-CH₂), 1.92–1.85 (2H, m, 20-CH₂A + 22-CH₂A), 1.72–1.66 (1H, m, 22-CH₂B), 1.38 (1H, ddd, J = 12.7, 8.1, 4.3 Hz, 20-CH₂B), 1.10–1.06 (21H, m, -OSi(CH(CH₃)₂)₃), 1.03 (3H, app t, J = 7.4 Hz, 16-C-CH₃); ¹³C NMR δ (100.6 MHz, CDCl₃) 147.9, 110.7, 77.2, 66.5, 60.5, 56.0, 45.5, 41.2, 35.2, 29.0, 18.2, 12.7, 12.2; HRMS (+Cl, NH₃) Calc. for C₂₀H₄₃O₃Si [MH⁺]: 359.2981, found: 359.2981; m/z (+Cl, NH₃) 359 (MH⁺, 5), 371 (29), 299 (30), 267 (30), 135 (50), 132 (35), 106 (30), 58 (100).
(5E)-(4R)-Hepta-1,5-dien-4-ol [(R)-19]

To a stirred solution of racemic alcohol 19 (10.0 g, 89.2 mmol) and L-DIPT (2.82 mL, 13.4 mmol) in dry CH₂Cl₂ (300 mL) was added activated 4 Å molecular sieves (5 g, powdered, oven dried for 12 h). The reaction was cooled to −20 °C and Ti(Or-Pr)₄ solution (8.9 mL, 1 M in CH₂Cl₂, 8.9 mmol, distilled) was added dropwise. The reaction was stirred for 20 mins at −20 °C and tert-butyl hydroperoxide solution (16.4 mL, 3 M in isooctane, 49.2 mmol) added dropwise. The reaction was transferred to a −20 °C freezer for 20 h and then quenched by the addition of Me₂S (10 mL, 136 mmol) and stirred at RT for 14 h. The reaction mixture was filtered and the solvent removed carefully in vacuo (19 is volatile) and purified by flash chromatography (20:80 EtOAc/hexanes) to yield the title alcohol (R)-19 (4.04 g, 40%) as a colourless oil in greater than 95% ee as adjudged by MTPA ester analysis: Rᵣ 0.21 (20% EtOAc/hexane); 1H NMR δ (200 MHz, CDCl₃) 5.80–5.61 (2H, m, 25-CH₂), 5.49 (1H, ddq, J = 16.4, 7.0, 1.8 Hz, 28-CH₂), 5.19–5.03 (2H, m, 24-CH₂), 2.41–2.27 (2H, m, 26-CH₂), 1.67 (3H, d, J = 6.4 Hz, 30-CH₃), 1.63 (1H, br s, -OH).

(5E)-(4R)-4-p-Methoxybenzylxy-hepta-1,5-diene (20)

KH (1.51 g, 35% wt in mineral oil, 13.1 mmol) was washed with dry hexane (3 x 10 mL), rinsed with dry THF (10 mL) and then suspended in dry THF (50 mL). A solution of alcohol (R)-19 (0.969 g, 8.64 mmol) and tetrabutylammonium iodide (5 mg) in THF (10 mL + 2 x 1 mL washings) was added via cannula. The reaction was stirred for 40 mins and para-methoxybenzyl chloride (1.8 mL, 13.3 mmol) added. The reaction was stirred at RT for 14 h before being quenched by the CAREFUL addition of NH₄Cl solution (20 mL, sat. aqueous). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL), the combined organic extracts were washed with H₂O (20 mL) and brine (20 mL) and dried (MgSO₄). The solvent was removed in vacuo and the crude reaction mixture was purified by flash chromatography (15:85 EtOAc/hexanes) to yield the title compound 20 (1.39 g, 69%) as a colourless oil: Rᵣ 0.47 (20:80 EtOAc/hexanes); 1H NMR δ (250 MHz, CDCl₃) 7.25 (2H, d, J = 8.7 Hz, Ar), 6.87 (2H, d, J = 8.7 Hz, Ar), 5.80 (1H, app qt, J = 13.9, 7.0 Hz, 25-CH), 5.66 (1H, dq, J = 15.3, 6.4 Hz, 29-CH), 5.38 (1H, ddq, J = 15.3, 8.1, 1.5 Hz, 28-CH), 5.11–5.00 (2H, m, 24-CH₂), 4.51 (1H, d, J = 11.6 Hz, -OCH₂Ar), 4.39 (1H, d, J = 11.6 Hz, -OCH₂Ar), 3.80 (3H, s, -OMe), 3.76 (1H, app q, J = 7.8 Hz, 27-CH), 2.46–2.20 (2H, m, 26-CH₂), 1.75 (3H, dd, J = 6.4, 1.5 Hz, 30-CH₃); 13C NMR δ (50 MHz, CDCl₃) 158.9, 135.0, 131.5, 130.9, 129.2, 128.9, 116.5, 113.6, 79.2, 69.3, 55.2, 40.3, 17.7; HRMS (+Cl, NH₃) Calc. for C₁₅H₂₄NO₂ [M + NH₄]+: 250.1807, found: 250.1807; m/z (+Cl, NH₃) 250 ([M + NH₄]+, 5), 138 (30), 121 (100), 95 (10).

(E)-(4R)-4-p-Methoxybenzylxy-hept-5-en-2-one (11)

To a stirred solution of CuCl (2.00 g, 20.0 mmol) in DMF (70 mL) and H₂O (10 mL) was added PdCl₂ (120 mg, 0.677 mmol) and the reaction was stirred under an oxygen atmosphere (balloon) for 2 h during which time the reaction colour changed from green to black. A solution of ether (8.9 mL, 1 M in CH₂Cl₂, 8.9 mmol) in vacuo (+Cl, NH₃) 250 ([M + NH₄]+) was added. The reaction was stirred for 40 mins and para-methoxybenzyl chloride (1.8 mL, 13.3 mmol) added. The reaction was stirred at RT for 14 h before being quenched by the CAREFUL addition of NH₄Cl solution (20 mL, sat. aqueous). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL), the combined organic extracts were washed with H₂O (20 mL) and brine (20 mL) and dried (MgSO₄). The solvent was removed in vacuo and the crude reaction mixture was purified by flash chromatography (15:85 EtOAc/hexanes) to yield the title compound 11 (1.39 g, 69%) as a colourless oil: Rᵣ 0.47 (20:80 EtOAc/hexanes); 1H NMR δ (250 MHz, CDCl₃) 7.25 (2H, d, J = 8.7 Hz, Ar), 6.87 (2H, d, J = 8.7 Hz, Ar), 5.80 (1H, app qt, J = 13.9, 7.0 Hz, 25-CH), 5.66 (1H, dq, J = 15.3, 6.4 Hz, 29-CH), 5.38 (1H, ddq, J = 15.3, 8.1, 1.5 Hz, 28-CH), 5.11–5.00 (2H, m, 24-CH₂), 4.51 (1H, d, J = 11.6 Hz, -OCH₂Ar), 4.39 (1H, d, J = 11.6 Hz, -OCH₂Ar), 3.80 (3H, s, -OMe), 3.76 (1H, app q, J = 7.8 Hz, 27-CH), 2.46–2.20 (2H, m, 26-CH₂), 1.75 (3H, dd, J = 6.4, 1.5 Hz, 30-CH₃); 13C NMR δ (50 MHz, CDCl₃) 158.9, 135.0, 131.5, 130.9, 129.2, 128.9, 116.5, 113.6, 79.2, 69.3, 55.2, 40.3, 17.7; HRMS (+Cl, NH₃) Calc. for C₁₅H₂₄NO₂ [M + NH₄]+: 250.1807, found: 250.1807; m/z (+Cl, NH₃) 250 ([M + NH₄]+, 5), 138 (30), 121 (100), 95 (10).

---

removed in vacuo. The crude product was purified by flash chromatography (CH$_2$Cl$_2$) to yield the title ketone 11 as a colourless oil (1.01 g, 47%): R$_f$ 0.19 (CH$_2$Cl$_2$); 1H NMR $\delta$ 1.00 (3H, t, J = 7.4 Hz, Ar); 2.40–1.88 (2H, ABX m, $\delta_4$ = 2.62, $\delta_5$ = 2.57, J = 15.7, 5.7, 2.5 Hz, 18-(CH$_3$)$_2$), 2.45 (1H, dd, J = 13.7, 9.7 Hz, 26-(CH$_2$)$_2$); 2.02–1.98 (2H, m, 16-CH$_2$); 1.87 (1H, ddd, J = 14.2, 8.8, 3.5 Hz, 20-CH$_2$), 1.12 (3H, app t, J = 7.4 Hz, 16-C-CH$_3$); 1C NMR $\delta$ (75.5 MHz, CDCl$_3$) 130.4, 128.5, 129.4, 129.3, 113.6, 76.0, 69.7, 55.1, 49.7, 45.7, 42.2, 28.9, 16.2, 12.9, 12.2; HRMS (EI) Calc. for C$_{15}$H$_{20}$O$_3$ [M]$^+$: 248.1412, found: 248.1394; m/z (EI) 248 ([M]$^+$, 60), 164 (20), 154 (20), 137 (40), 121 (100).

(3S,5S)-3-Methoxy-5-(trisopropylsilyloxy)-7-ethyl-oct-7-enal (12)

To a stirred solution of alcohol 18 (19.9 mg, 0.055 mmol) in CH$_2$Cl$_2$ (2 mL) at RT was added solid Dess–Martin periodinane (52 mg, 0.122 mmol). The reaction was stirred open to the atmosphere for 12 h. The crude product was purified by flash chromatography (10:90 EtOAc/hexanes) to yield the title aldehyde 12 (18.9 mg, 96%) as a colourless oil: R$_f$ 0.48 (25:75 EtOAc/hexanes); 1H NMR $\delta$ 2.50 (6H, s, -OSi(CH$_3$)$_3$); 13C NMR $\delta$ (100.6 MHz, CDCl$_3$) 206.7, 157.0, 130.4, 130.3, 129.4, 129.3, 113.6, 76.0, 69.7, 55.1, 49.7, 31.0, 17.6; IR (solution cell, CHCl$_3$) 3520, 2962, 1710, 1645 (w), 1613, 1586, 1514 cm$^{-1}$; HRMS (EI) Calc. for C$_{19}$H$_{24}$O$_3$Si [M]$^+$: 357.2825, found: 357.2825; m/z (+Cl, NH$_3$) 357 ([MH]$^+$, 5), 257 (10), 183 (10), 174 (10), 151 (20), 137 (20), 136 (30), 94 (40), 74 (80), 44 (100).

(2E)-(4R,6S,8R,10S)-4-p-Methoxybenzylcyloxy-8-hydroxy-10-methoxy-12-(trisopropylsilyloxy)-14-ethyl-pentadeca-2,14-dien-6-one (23)

To a cooled (0 °C), stirred solution of dicyclohexylboron chloride (110 mg, 0.503 mmol) in dry ether (3 mL) was added dry Et$_3$N (79 µL, 0.568 mmol). A solution of ketone 11 (125 mg, 0.503 mmol) in Et$_2$O (1 mL + 2 x 0.5 mL washings) was added via cannula at which point a white precipitate appeared. The reaction was stirred at 0 °C for 30 mins and then cooled to −78 °C. A solution of alcohol 12 (107 mg, 0.299 mmol) in CH$_2$Cl$_2$ (1 mL + 2 x 0.5 mL washings) was added via cannula and the reaction stirred at −78 °C for 4 h before transferring to a −20 °C freezer for 12 h. The reaction was quenched by the addition of pH 7 buffer solution (3 mL), MeOH (3 mL), and H$_2$O$_2$ solution (3 mL, 30% aqueous). The reaction was stirred for 2 h and the layers separated. The aqueous layer was extracted with ether (3 x 10 mL) and the combined organic extracts were washed with H$_2$O (10 mL) and brine (10 mL) and dried (MgSO$_4$). The solvent was removed in vacuo and the crude product was purified by flash chromatography (10:90 EtOAc/hexanes).
To a stirred solution of diketone 10 (19.5 mg, 0.032 mmol) in CH₂Cl₂ (0.5 mL) and pH 7 buffer solution (60 μL), DDQ (11.0 mg, 0.048 mmol, recrystallised from CHCl₃) was added DDQ (11.0 mg, 0.048 mmol, recrystallised from CHCl₃). After stirring for 1 h, during which time the reaction became clear, the layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 2 mL). The combined organic extracts were washed with H₂O (1 mL) and brine (1 mL) and dried (MgSO₄). The solvent was removed in vacuo and the crude product was purified by flash chromatography (25:75 EtOAc/hexanes) to yield the title diketone 10 (10.3 mg, 85%) as a colourless oil: Rₖ 0.49 (25:75 EtOAc/hexanes); [α]D²⁻6.9 (c 0.91, CHCl₃), IR (solution cell, CHCl₃) 2944, 2866, 1731 (w), 1612 (br), 1570, 1370, 1210 (100%), 1170, 1055, 965, 764; 1H NMR (500 MHz, CDCl₃) 7.20 (2H, d, J = 7.4 Hz, Ar), 6.84 (2H, d, J = 8.6 Hz, Ar), 5.70 (1H, dq, J = 15.3, 6.5 Hz, 29-CH), 5.52 (1H, s, 24-CH), 5.38 (1H, ddq, J = 15.3, 8.2, 1.5 Hz, 28-CH), 4.77, 4.73 (2H, s, s, 17-C=CH₂), 4.48, 4.28 (2H, d, d, J = 11.4 Hz, -OCH₂Ar), 4.21–4.13 (2H, m, 19-CH + 27-CH), 3.89–3.86 (1H, m, 21-CH), 3.30 (3H, s, ArOMe), 3.31 (3H, s, -OMe), 2.62–2.56 (2H, m, 22-CH₂A + 26-CH₂B), 2.44–2.39 (2H, m, 18-CH₂A + 22-CH₂B or 26-CH₂B), 2.28 (1H, dd, J = 14.1, 6.5 Hz, 26-CH₂B or 22-CH₂B), 2.11 (1H, dd, J = 13.6, 9.6 Hz, 18-CH₂B), 2.04–1.96 (2H, m, 16-CH₂), 1.75–1.72 (1H, m, 20-CH₂A), 1.73 (3H, s, J = 6.5 Hz, 30-CH₃), 1.41–1.37 (1H, m, 20-CH₂B), 1.10–1.06 (2H, m, -OSi(CH₂)₃), 1.01 (3H, t, J = 7.4 Hz, 16-C=CH₂); 13C NMR δ (62.5 MHz, CDCl₃) 191.9, 190.9, 159.1, 148.0, 130.6, 130.2, 129.5, 129.3, 113.7, 110.6, 101.7, 76.3, 75.1, 69.7, 68.1, 56.4, 55.3, 45.7, 45.2, 43.1, 42.4, 29.7, 29.0, 18.3, 17.7, 14.0, 13.0, 12.2; HRMS (+FAB, NOBA) Calc. for C₃₅H₆₁O₆Si [MH]+: 605.4237, found: 605.4240; m/z (+CI, NH₃) 605.5 ([MH]+, 20), 495 (30), 468 (60), 451 (50), 413 (90), 386 (100), 382 (50).

(2E)-(4R,10S,12S)-4-Methoxybenzaldehyde-10-methoxy-12-(triisopropylsilyloxy)-14-ethyl-pentadeca-2,14-diene-6,8-dione (10)

To a stirred solution of the major diastereomer of aldol product 23 (12.2 mg, 0.0202 mmol) in dry CH₂Cl₂ (1 mL) at RT was added solid Dess–Martin periodinane (21.5 mg, 0.051 mmol). The reaction initially went green and this colour gradually changed to brown. After 30 mins an additional portion of DDQ (3.0 mg, 0.013 mmol) was added. After a further 15 mins the reaction was quenched by the addition of NaHCO₃ solution (4 mL, sat. aqueous) and CH₂Cl₂ (3 mL) and an additional portion of DDQ (3.0 mg, 0.013 mmol) was added. After a further 15 mins the reaction was monitored by NMR and after 7 days at RT was adjudged to be complete. The crude product solution was purified by flash chromatography (15:85 EtOAc/hexanes) to yield the title pyranone 24 (10.8 mg, 72%) as a colourless oil: Rₖ 0.24 (25:75 EtOAc/hexanes);
To a cold (−78 °C), stirred solution of pyranone 24 (7.2 mg, 0.016 mmol) in dry CH₂Cl₂ (3 mL) was added TMSOTf solution (70 µL, 1:19 in CH₂Cl₂, 0.019 mmol). The reaction was stirred for 20 mins and then quenched by the addition of pH 7 buffer solution (1 mL). The reaction was allowed to warm to RT and partitioned between CH₂Cl₂ (3 mL) and brine (2 mL). The layers were separated and the aqueous layer extracted with CH₂Cl₂ (3 x 2 mL). The combined organic extracts were washed with brine (3 mL) and dried (Na₂SO₄). The solvent was removed in vacuo and the residue containing 9 was filtered through a short plug of silica (50:50 EtOAc/hexanes) and used in subsequent reactions without further purification: ¹H NMR δ (500 MHz, CDCl₃) 5.86 (1H, dq, J = 15.3, 6.5 Hz, 29-CH), 5.65 (1H, dd, J = 15.4, 6.7 Hz, 28-CH), 5.39 (1H, s, 24-CH), 4.87 (1H, s, 17-C=CH₂A), 4.82–4.77 (1H, m, 27-CH), 4.81 (1H, s, 17-C=CH₂B), 4.00–3.93 (1H, m, 19-CH), 3.88–3.81 (1H, m, 21-CH), 3.40 (1H, s, -OMe), 2.58 (1H, dd, J = 13.9, 9.9 Hz, 22-CH₂A), 2.53 (1H, dd, J = 16.7, 11.8 Hz, 26-CH₂A), 2.44 (1H, dd, J = 16.8, 4.1 Hz, 22-CH₂B), 2.40 (1H, dd, J = 14.2, 6.2 Hz, 26-CH₂B), 2.33 (1H, br s, -OH), 2.18–2.16 (2H, m, 18-CH₂), 2.10–2.00 (2H, m, 16-CH₂), 1.77 (3H, d, J = 6.4 Hz, 30-CH₃), 1.68–1.61 (2H, m, 20-CH₂), 1.04 (3H, t, J = 7.4 Hz, 16-C-CH₃); ¹³C NMR δ (100.6 MHz, CDCl₃) 192.4, 174.1, 148.0, 131.0, 127.8, 111.2, 110.6, 79.7, 76.2, 65.7, 57.6, 45.1, 41.0, 40.9, 39.8, 28.6, 17.8, 12.2.

(4R,6S,8S,10S) and (4R,6S,8R,10S)-4-((E)-prop-2'-enyl)-8-(2'-ethyl-2'-propenyl)-10-methoxy-5,7-dioxaspiro[5.5]undecan-2-one (8 and 25)

To a cold (−78 °C), stirred solution of pyranone 9 (7.2 mg, 0.016 mmol) in dry CH₂Cl₂ (3 mL) was added TMSOTf solution (70 µL, 1:19 in CH₂Cl₂, 0.019 mmol). The reaction was stirred for 20 mins and then quenched by the addition of pH 7 buffer solution (1 mL). The reaction was allowed to warm to RT and partitioned between CH₂Cl₂ (3 mL) and brine (2 mL). The layers were separated and the aqueous layer extracted with CH₂Cl₂ (3 x 2 mL). The combined organic extracts were washed with brine (3 mL) and dried (Na₂SO₄). The solvent was removed in vacuo and the residue containing 9 was filtered through a short plug of silica (50:50 EtOAc/hexanes) and used in subsequent reactions without further purification: ¹H NMR δ (500 MHz, CDCl₃) 5.78 (1H, dq, J = 15.2, 6.5 Hz, 29-CH), 5.56 (1H, dd, J = 15.2, 7.1 Hz, 28-CH), 4.80–4.76 (1H, 

Electronic Supplementary Material for Organic & Biomolecular Chemistry

This journal is © The Royal Society of Chemistry 2005

465.3396; m/z (FIB, NOBA) 465 ([MH]+, 70), 421 (80), 295 (60), 243 (80), 157 (80), 137 (100).
overlapping m, 27-CH), 4.78 (1H, overlapping s, 17-C=CH$_2$A), 4.73 (1H, s, 17-C=CH$_2$B), 3.62–3.57 (1H, m, 19-CH), 3.41 (1H, app tt, $J = 11.4, 4.5$ Hz, 21-CH), 3.34 (3H, s, -OMe), 2.85 (1H, d, $J = 14.2$ Hz, 24-CH$_2$A), 2.39 (1H, overlapping d, $J = 14.1$ Hz, 24-CH$_2$B), 2.39–2.37 (2H, overlapping m, 26-CH$_2$), 2.33 (1H, dd, $J = 14.2, 7.7$ Hz, 18-CH$_2$A), 2.26 (1H, dd, $J = 12.4, 4.3$ Hz, 22-CH$_2$A), 2.18 (1H, dd, $J = 14.2, 5.2$ Hz, 18-CH$_2$B), 2.06–2.02 (1H, m, 20-CH$_2$A), 2.01 (2H, app q, $J = 8.2$ Hz, 16-CH$_2$), 1.72 (3H, d, $J = 6.5$ Hz, 30-CH$_3$), 1.58–1.53 (1H, m partly obscured by H$_2$O, 22-CH$_2$B), 1.17 (1H, app q, $J = 11.8$ Hz, 20-CH$_2$B), 1.01 (3H, t, $J = 7.4$ Hz, 16-C-CH$_3$); $^{13}$C NMR δ (100.6 MHz, CDC$_3$) 204.6, 147.1, 130.1, 129.1, 110.6, 100.8, 73.7, 71.3, 69.8, 55.6, 47.0, 46.6, 42.8, 41.8, 36.9, 28.7, 17.8, 12.2; HRMS (FIB, NOBA) Calc. for C$_{18}$H$_{29}$O$_4$ [MH$^+$]: 309.2066, found: 309.2079; m/z (FIB, NOBA) 309 ([MH$^+$]$^+$), 281 (40), 259 (25), 221 (40), 207 (60), 154 (90), 136 (100), 107 (60%).

Minor diasteromer 9: R$_f$ 0.31 (25:75 EtOAc/hexanes); R$_f$ 21.5 min (35:65 EtOAc/hexanes); $^{	ext{1}H}$ NMR δ (500 MHz, CDC$_3$) 5.72 (1H, dq, $J = 15.1, 6.6$ Hz, 29-CH), 5.48 (1H, dd, $J = 15.3, 7.2$ Hz, 28-CH), 4.81 (1H, s, 17-C=CH$_2$A), 4.76 (1H, s, 17-C=CH$_2$B), 4.53–4.48 (1H, m, 27-CH), 4.08–4.04 (1H, m, 19-CH), 3.69 (1H, app tt, $J = 11.2, 4.4$ Hz, 21-CH), 3.34 (3H, s, -OMe), 2.68 (1H, dd, $J = 16.5, 11.1$ Hz, 26-CH$_2$A), 2.58 (2H, ABq, $J = 16.2$ Hz, 24-CH$_2$), 2.36 (1H, dd, $J = 16.5, 3.6$ Hz, 26-CH$_2$B), 2.25–2.21 (2H, m, 18-CH$_2$A + 22-CH$_2$A), 2.13 (1H, dd, $J = 13.9, 5.7$ Hz, 18-CH$_2$B), 2.08–2.05 (1H, m, 20-CH$_2$A), 2.03 (2H, app q, $J = 7.4$ Hz, 16-CH$_2$), 1.72 (3H, d, $J = 6.4$ Hz, 30-CH$_3$), 1.24 (1H, app t, $J = 12.0$ Hz, 20-CH$_2$B), 1.06 (1H, app q, $J = 11.8$ Hz, 22-CH$_2$B), 1.02 (3H, t, $J = 7.4$ Hz, 16-C-CH$_3$); $^{13}$C NMR δ (100.6 MHz, CDC$_3$) 205.9, 147.6, 130.9, 128.3, 110.5, 100.0, 73.0, 72.7, 66.2, 55.5, 44.6, 42.4, 40.7, 36.7, 29.7, 29.2, 17.7, 12.1; HRMS (FIB, NOBA) Calc. for C$_{18}$H$_{29}$O$_4$ [MH$^+$]: 309.2066, found: 309.2074; m/z (FIB, NOBA) 309 ([MH$^+$]$^+$), 281 (40), 259 (25), 221 (40), 207 (60), 154 (90), 136 (100), 107 (60%).

(3R,5R)-5-Benzylxoy-3-methoxyhexanal (28)
Ozone was bubbled through a cooled (–78 °C) solution of alkene 27 (6.81 g, 29.1 mmol) in CH$_2$Cl$_2$ (300 mL) until a slight blue colour developed. The flask was purged with O$_2$ for 10 mins and then Ph$_3$P (9.92 g, 37.8 mmol, 1.3 equiv.) was added. The mixture was warmed to RT and stirred under an atmosphere of argon for 16 h. The solvent was removed in vacuo and the crude mixture was triturated with Et$_2$O (100 mL) and the solid washed with Et$_2$O (2 x 20 mL). The supernatant was concentrated in vacuo and the residue purified by flash chromatography (10:90 → 30:70 EtOAc/hexanes) to produce aldehyde 28 (6.32 g, 92%) as a colourless oil: R$_f$ 0.31 (30:70 EtOAc/hexanes); $^{	ext{1}H}$ NMR δ (500 MHz, CHCl$_3$) 3–30.8 (c 0.95, CHCl$_3$); $^{	ext{1}H}$ NMR δ (500 MHz, CDC$_3$) 9.73 (1H, br s, 19-CH), 7.25–7.36 (5H, m, Ph), 4.59 (1H, d, $J = 11.5$ Hz, OCH$_3$Ph), 4.39 (1H, d, $J = 11.5$ Hz, OCH$_3$Ph), 3.90 (1H, m, 21-CH), 3.63 (1H, m, 23-CH), 3.33 (3H, s, OCH$_3$), 2.46–2.55 (2H, m, 20-CH$_3$), 2.02 (1H, m, 22-CH$_3$H$_2$), 1.57 (1H, m, 22-CH$_3$H$_2$), 1.26 (3H, d, $J = 6.0$ Hz, 24-CH$_3$); $^{13}$C NMR δ (100.6 MHz, CDC$_3$) 201.4, 138.6, 128.4, 127.8, 127.6, 73.6, 71.3, 70.2, 56.6, 47.9, 40.6, 19.7; HRMS (+Cl, NH$_3$) Calc. for C$_{14}$H$_{24}$NO$_3$ [M + NH$_4$]$^+$: 254.1756, found: 254.1756; m/z (+Cl, NH$_3$) 254 ([M + NH$_4$]$^+$, 24), 222 (33), 162 (100), 114 (60), 97 (61).

(R)-5-(p-Methoxybenzyxoyloxy)-4-(triethyisiloxy)-1-pentene (S3)

![Structure](http://example.com/structure.png)

To a cold (–78 °C), stirred solution of the alcohol 31 (900 mg, 4.05 mmol, 1.0 equiv.) in dry CH$_2$Cl$_2$ (40 mL) was added 2,6-lutidine (1.4 mL, 12.15 mmol, 3.0 equiv.) followed by TESOTf (1.4 mL, 6.07 mmol, 1.5 equiv.). The reaction was stirred at –78 °C for 2 h and then EtOH (5 mL) was added to quench the excess TESOTf. Saturated aqueous NH$_4$Cl (25 mL) was added and the reaction was allowed to warm to rt. The layers were separated and the aqueous phase was extracted
with Et$_2$O (4 x 100 mL). The combined organic extracts were washed with pH 7 buffer (2 x 50 mL), dried (MgSO$_4$) and concentrated in vacuo. The crude oil was flash chromatographed (5:95 Et$_2$O/hexanes) to yield the TES ether S3 (1.35 g, 99%), as a colourless oil: $R_f$ 0.90 (30:70 EtOAc/hexanes); $[\alpha]_D^{20}$ +4.4 ($c$ 2.17, CHCl$_3$); IR (liquid film) 1642, 1614, 1514 cm$^{-1}$; $^1$H NMR $\delta$ (500 MHz, CDCl$_3$) 7.25 (2H, d, $J$ = 8.5 Hz, ArH), 6.87 (2H, d, $J$ = 8.5 Hz, ArH), 5.78–5.87 (1H, m, 25-CH$_2$), 5.02–5.08 (2H, m, C=CH$_2$), 4.45 (2H, s, OCH$_2$Ar), 3.86 (1H, quin., $J$ = 5.4 Hz, 27-CH$_2$), 3.36 (2H, d, $J$ = 5.4 Hz, 28-CH$_2$), 2.31–2.36 (1H, m, 26-CH$_2$), 2.22 (1H, br quin., $J$ = 6.9 Hz, 26-CH$_2$), 0.94 (9H, t, $J$ = 7.9 Hz, OSi(CH$_2$CH$_3$)$_3$), 0.59 (6H, q, $J$ = 7.9 Hz, OSi(CH$_2$CH$_3$)$_3$); $^{13}$C NMR $\delta$ (100.6 MHz, CDCl$_3$) 159.0, 134.8, 130.4, 129.1, 116.8, 113.5, 73.7, 72.8, 71.0, 55.0, 39.3, 6.7, 4.8; HRMS (+FAB) Calc. for C$_{19}$H$_{31}$O$_3$Si $[M–H]$: 335.2043, found: 335.2023.

(2RS,4R)-5-(p-Methoxybenzyloxy)-4-(triethylsiloxy)-pentane-1,2-diol (S4)

A solution of alkene S3 (9.42 g, 28.0 mmol) in 3:1 acetone (240 mL) and H$_2$O (80 mL) was treated with NMO (3.94 g, 33.6 mmol, 1.2 equiv.) and OsO$_4$ (0.02 M in t-BuOH, 2.8 mL, 0.056 mmol, 0.2 mol%) and the resultant mixture left for 3 days at RT. The remaining oxidant was quenched by the addition of 10% Na$_2$S$_2$O$_3$ (100 mL) and the mixture stirred for 40 minutes before the addition of Et$_2$O (50 mL) and separation of the layers. The aqueous phase was extracted with EtOAc (3 x 50 mL), the combined organic extracts were washed with brine (50 mL) and the brine was back-extracted with EtOAc (20 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography (60:40 EtOAc/hexanes) afforded a diastereomeric mixture of diols S4 (8.92 g, 86%), as a colourless oil: $R_f$ 0.10 (30:70 EtOAc/hexanes); IR (liquid film) 3406 (br, s), 1612, 1586, 1514 cm$^{-1}$; $^1$H NMR $\delta$ (500 MHz, CDCl$_3$) 7.24 (2H, d, $J$ = 8.5 Hz, ArH), 6.87 (2H, d, $J$ = 8.5 Hz, ArH), 4.43–4.49 (2H, m, OCH$_2$Ar), 4.06–4.15 (1H, t, $J$ = 6.2, 6.6 Hz, ratio of ~1:1, 1° OH), 1.64–1.78 (2H, m, 26-CH$_2$), 0.94 (9H, t, $J$ = 7.9 Hz, OSi(CH$_2$CH$_3$)$_3$), 0.59–0.64 (6H, m, OSi(CH$_2$CH$_3$)$_3$); $^{13}$C NMR $\delta$ (100.6 MHz, CDCl$_3$) 159.3, 130.0, 129.9, 129.4, 113.8, 74.4, 73.3, 73.1, 71.1, 70.4, 69.8, 69.0, 67.1, 66.9, 55.2, 37.8, 37.0, 6.7, 4.9, 4.8; HRMS (+CI, NH$_3$) Calc. for C$_{19}$H$_{35}$O$_5$Si $[MH]$+: 371.2253, found: 371.2254.

(R)-4-(p-Methoxybenzyloxy)-3-(triethylsiloxy)-butanal (7)

To a solution of S4 from the above procedure (5.00 g, 13.5 mmol) in 2.5:1 MeOH (100 mL) and pH 7 buffer (40 mL) was added H$_2$O (5 mL) until all the solid had dissolved. The resultant solution was cooled to 0 °C, NaIO$_4$ (3.47 g, 16.2 mmol, 1.2 equiv.) and the resultant mixture allowed to warm to RT overnight. The mixture was concentrated in vacuo and H$_2$O (150 mL) was added to dissolve the precipitate. The solution was extracted with EtOAc (3 x 50 mL), the combined organic extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography (15:85 EtOAc/hexanes) afforded aldehyde 7 (4.41 g, 97%) as a colourless oil: $R_f$ 0.85 (50:50 EtOAc/hexanes); IR (liquid film) 1726 (s), 1612, 1586 cm$^{-1}$; $^1$H NMR $\delta$ (250 MHz, CDCl$_3$) 9.79 (1H, t, $J$ = 2.4 Hz, 25-CHO), 7.23 (2H, br d, $J$ = 8.7 Hz, ArH), 6.88 (2H, br d, $J$ = 8.7 Hz, ArH), 4.45 (2H, s, OCH$_2$Ar), 4.34 (1H, br quin., $J$ = 5.8 Hz, 27-CH), 3.81 (3H, s, OCH$_3$), 3.47 (1H, dd, $J$ = 9.5, 4.9 Hz, 28-CH$_2$), 3.36 (1H, dd, $J$ = 9.5, 6.4 Hz, 28-CH$_2$), 0.92 (9H, t, $J$ = 8.0 Hz, OSi(CH$_2$CH$_3$)$_3$), 0.59 (6H, q, $J$ = 8.0 Hz, OSi(CH$_2$CH$_3$)$_3$); $^{13}$C NMR $\delta$ (100.6 MHz, CDCl$_3$) 201.5, 159.2, 129.9, 129.3, 113.7, 73.8, 73.0, 67.1, 55.2, 49.0, 6.7, 4.7.
To a cold (–78 °C) solution of alcohol 3 (1.01 g, 2.58 mmol) in CH₂Cl₂ (20 mL) was added 2,6-lutidine (0.9 mL, 7.73 mmol, 3.0 equiv.), followed by TBSOTf (1.18 mL, 5.15 mmol, 2.0 equiv.). The reaction mixture was stirred at –78 °C for 1 h then quenched by the addition of sat. aq. NaHCO₃ (30 mL) and allowed to warm to RT. The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 30 mL), combined organics were washed with brine (50 mL), dried (MgSO₄) and concentrated in vacuo. Flash chromatography (20:80 → 50:50 Et₂O/light petroleum) afforded the TBS ether 33 (1.30 g, 100%) as a colourless oil: Rf 0.25 (20:80 EtOAc/hexanes); [α]₂₀̅D –10.3 (c 1.00, CHCl₃); IR (liquid film) 1641, 1612, 1586, 1513 cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 7.26 (2H, dd, J = 6.8, 1.8 Hz, ArH), 6.87 (2H, dd, J = 6.8, 1.8 Hz, ArH), 5.81 (1H, m, 17-CH), 5.07 (1H, dd, J = 17.7, 1.5 Hz, trans-CH=CH₂aHb), 5.03 (1H, d, J = 10.2 Hz, cis-CH=CHaHb), 4.59 (1H, m, 27-CH), 4.51 (2H, AB q, J = 12.1 Hz, OCH₂Ar), 4.13 (1H, m, 25-CH), 3.80 (3H, s, ArOCH₃), 3.51–3.48 (3H, m, 19-CH₂+28-CH₂), 3.46 (1H, m, 21-CH), 3.32 (3H, s, OCH₃), 2.43 (1H, m, 18-CH₂aHb), 2.25 (1H, m, 18-CH₂aHb), 2.10 (1H, dd, J = 14.3, 2.1 Hz, 24-CH₃q), 2.08–2.01 (2H, m, 20-CH₃q+22-CH₃ax), 1.70 (1H, ddd, J = 13.7, 11.6, 3.5 Hz, 26-CH₃eq), 1.60 (1H, m, 26-CH₃ax), 1.49 (1H, d, J = 14.3, 3.8 Hz, 24-CH₃ax), 1.39 (1H, t, J = 11.9 Hz, 22-CH₃ax), 1.12 (1H, br q, J = 11.7 Hz, 20-CH₃ax), 0.89 (9H, s, Si(CH₃)₃), 0.05 (3H, s, Si(CH₃)a), 0.04 (3H, s, Si(CH₃)b); ¹³C NMR δ (100.6 MHz, CDCl₃) 159.0, 134.4, 130.6, 129.3, 117.2, 113.7, 113.6, 98.2, 74.2, 72.8, 72.6, 69.6, 64.7, 64.5, 55.4, 55.3, 43.3, 40.7, 36.6, 35.4, 35.1, 25.9, 18.3, –4.7, –4.9; HRMS (+FAB) Calc. for C₂₈H₄₆O₆SiNa [M + Na]+: 529.2961, found: 529.2980; m/z (+FAB) 529 ([M + Na]+, 100), 505 (20), 475 (20), 449 (20), 385 (30), 343 (45), 311 (30), 281 (40), 257 (35), 231 (40), 201 (65).

(R)-N-Methoxy-N-methyl-3-benzyloxybutanamide (S5)

MeONHMe•HCl (3.04 g, 31.2 mmol, 1.3 equiv.) was added dropwise over a 30 minute period to a cold (–20 °C), stirred mixture of methyl (R)-3-benzyloxybutanoate 4 (5.00 g, 24.0 mmol) and MeONHMe•HCl (3.04 g, 31.2 mmol, 1.3 equiv.) in THF (100 mL) whilst carefully maintaining the temperature ≤ –20 °C. The reaction was stirred at –20 °C for a further 45 mins then quenched by the addition of sat. NH₄Cl (30 mL) and the cooling bath removed. H₂O (20 mL) and Et₂O (20 mL) were added, the layers were separated and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (20 mL) and the crude material was purified by flash chromatography (60:40 EtOAc/hexanes) to produce amide S5 (4.10 g, 72%) as a pale yellow oil: Rf 0.32 (60:40 EtOAc/hexanes); ¹H NMR δ (500 MHz, CDCl₃) 159.0, 134.4, 130.6, 129.3, 117.2, 113.7, 113.6, 98.2, 74.2, 72.8, 72.6, 69.6, 64.7, 64.5, 55.4, 55.3, 43.3, 40.7, 36.6, 35.4, 35.1, 25.9, 18.3, –4.7, –4.9; HRMS (+FAB) Calc. for C₂₈H₄₆O₆SiNa [M + Na]+: 529.2961, found: 529.2980; m/z (+FAB) 529 ([M + Na]+, 100), 505 (20), 475 (20), 449 (20), 385 (30), 343 (45), 311 (30), 281 (40), 257 (35), 231 (40), 201 (65).

(R)-4-Benzylxoy-2-pentanone (37)

MeMgBr (3.0 M in Et₂O, 8.4 mL, 25.3 mmol, 1.5 equiv.) was added to a cooled (–78 °C) solution of amide S5 (4.00 g, 16.9 mmol) in THF (80 mL). The reaction was warmed to 0 °C and allowed to

---

stir at this temperature for 1 h before quenching with sat. NH₄Cl (40 mL). The biphasic mixture was warmed to RT. H₂O (20 mL) and Et₂O (20 mL) were added, the layers were separated and the aqueous phase was extracted with Et₂O (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na₂SO₄) and concentrated in vacuo. The crude material was purified by flash chromatography (30:70 EtOAc/hexanes) to provide ketone 37 (2.35 g, 73%) as a colourless oil: Rf 0.32 (30:70 EtOAc/hexanes); [α]₂₀°D –29.6 (c 1.05, EtOH); IR (liquid film) 1715 (s), 1606 cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 7.27–7.35 (5H, m, Ph), 4.57 (1H, d, J = 11.5 Hz, OCH₃Ph), 4.46 (1H, d, J = 11.5 Hz, OCH₂Ph), 4.04 (1H, m, 23-CH), 2.79 (1H, dd, J = 15.8, 7.3 Hz, 22-CHⱼPh), 2.48 (1H, dd, J = 15.8, 5.3 Hz, 22-CH₃Ph), 2.16 (3H, s, 20-CH₃), 1.24 (3H, d, J = 6.1 Hz, 24-CH₃); ¹³C NMR δ (100.6 MHz, CDCl₃) 207.3, 138.5, 128.3, 127.7, 127.6, 71.6, 70.8, 50.8, 31.0, 19.8.

(4R,6R,8R)-8-Benzyl oxide-2-ethyl-6-methoxy-4-propionoxy-1-nonene (S6)

To a cooled (0 °C) solution of alcohol 41 (320 mg, 0.918 mmol) in CH₂Cl₂ (3 mL) was added proton sponge (985 mg, 4.60 mmol, 5 equiv.) followed by Me₃OBF₄ (679 mg, 4.59 mmol, 5 equiv.), and the resultant mixture was left stirring at 0 °C for 3 h. The reaction was quenched by the addition of sat. NH₄Cl (10 mL) and the mixture diluted with Et₂O (10 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3 x 5 mL). The combined organic extracts were washed with saturated NH₄Cl (3 x 5 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification of the crude material by flash chromatography (30:70 EtOAc/hexanes) provided ether S6 (301 mg, 90%) as a colourless oil: Rf 0.37 (20:80 EtOAc/hexanes); [α]₂₀°D –34.7 (c 1.41, CHCl₃); IR (liquid film) 2968, 2934, 1734 (s) cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 7.26–7.34 (5H, m, Ph), 5.26 (1H, m, 19-CH), 4.77 (1H, d, J = 1.4 Hz, C=CHⱼPh), 4.73 (1H, br s, C=CHⱼPh), 4.58 (1H, d, J = 11.6 Hz, OCH₃Ph), 4.42 (1H, d, J = 11.6 Hz, OCH₂Ph), 3.60 (1H, m, 23-CH), 3.37 (1H, m, 21-CH), 3.28 (3H, s, OCH₃), 2.33 (1H, br dd, J = 13.8, 7.3 Hz, 18-CH₃Ph), 2.26 (2H, q, J = 7.5 Hz, COCH₂CH₃), 2.17 (1H, br dd, J = 13.8, 6.1 Hz, 18-CH₃Ph), 2.06 (2H, app q, 16-CH₂), 1.97 (1H, m, 22-CH₃Ph), 1.60–1.70 (2H, m, 20-CH₂), 1.46 (1H, dd, J = 14.1, 7.4, 4.7 Hz, 22-CH₃Ph), 1.23 (3H, d, J = 6.1 Hz, 24-CH₃), 1.10 (3H, t, J = 7.5 Hz, COCH₂CH₃), 1.01 (3H, t, J = 7.4 Hz, CH₂CH₃); ¹³C NMR δ (100.6 MHz, CDCl₃) 174.2, 147.6, 139.2, 128.7, 128.0, 127.8, 111.5, 75.2, 72.2, 70.7, 69.6, 57.2, 42.7, 41.5, 39.6, 28.9, 28.2, 20.4, 12.6, 9.7; HRMS (+CI, NH₃) Calc. for C₂₂H₃₅O₄ [MH]+: 363.2535, found: 363.2538; m/z (+CI, NH₃) 363 ([MH]+, 6), 331 (5), 291 (4), 289 (3), 257 (5), 181 (7), 108 (43), 106 (100), 91 (58), 74 (41), 52 (53), 44 (59).

(4R,6S,8R)-8-Benzyl oxide-2-ethyl-6-methoxy-non-1-en-4-ol (S7)

To a stirred solution of ester S6 (295 mg, 0.814 mmol) in MeOH (4 mL) was added K₂CO₃ (47.7 mg, 0.345 mmol, 5.0 equiv.). After 48 h at RT, the reaction was quenched by the addition of H₂O (10 mL) and Et₂O (5 mL), the layers were separated and the aqueous phase was extracted with Et₂O (3 x 5 mL). The combined organic extracts were washed with saturated NH₄Cl (3 x 5 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification of the crude material by flash chromatography (25:75 EtOAc/hexanes) gave alcohol S7 (220 mg, 88%) as a colourless oil: Rf 0.37 (20:80 EtOAc/hexanes); [α]₂₀°D –40.3 (c 1.58, CHCl₃); IR (liquid film) 3454 (br, s), 2966, 2934, 1644 (w) cm⁻¹; ¹H NMR δ (250 MHz, CDCl₃) 7.25–7.36 (5H, m, Ph), 4.84 (1H, br s, C=CHⱼPh), 4.79 (1H, br s, C=CHⱼPh), 4.59 (1H, d, J = 11.7 Hz, OCH₃Ph), 4.42 (1H, d, J = 11.7 Hz, OCH₂Ph), 3.97 (1H, m, 19-CH), 3.52–3.73 (2H, m, 21-CH + 23-CH), 3.36 (3H, s, OCH₃), 2.73 (1H, d, J = 3.0 Hz, OH), 1.98–2.17 (4H, m, 16-CH₂ + 18-CH₂), 1.48–1.71 (4H, m, 20-
A solution of alcohol S7 (220 mg, 0.718 mmol) in DMF (0.7 mL) was treated with imidazole (171 mg, 2.51 mmol, 3.5 equiv.) followed by TBSCI (271 mg, 1.80 mmol, 2.5 equiv.). After stirring at RT for 16 h the reaction was quenched at 0 °C by the addition of MeOH (0.25 mL). The mixture was partitioned between H2O (10 mL) and Et2O (10 mL). The layers were separated and the aqueous phase was extracted with Et2O (2 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na2SO4) and concentrated in vacuo. Purification by flash chromatography (2:98 → 10:90 EtOAc/hexanes) afforded silyl ether 42 (286 mg, 95%) as a colourless oil: Rf 0.40 (10:90 EtOAc/hexanes); δααα = 40.6 (c 1.91, CHCl3); IR (liquid film) 1643 (w) cm−1; 1H NMR δ (400 MHz, CDCl3) 7.25–7.36 (5H, m, Ph); 4.77 (1H, d, J = 1.2 Hz, C=CH2Hb); 4.73 (1H, br s, C≡CH2Hb); 4.57 (1H, d, J = 11.7 Hz, OCH2Ph); 4.46 (1H, d, J = 11.7 Hz, OCH2Ph); 4.04 (1H, m, 19-CH); 3.57–3.64 (2H, m, 23-CH + 21-CH); 3.30 (3H, s, OCH3); 2.33 (1H, dd, J = 13.6, 4.7 Hz, 18-CH2Hb); 2.12 (1H, dd, J = 13.6, 8.4 Hz, 18-CH2Hb); 1.99–2.06 (3H, m, 16-CH2-22-CH2Hb); 1.65 (1H, m, 20-CH2Hb); 1.40–1.47 (2H, m, 20-CH2Hb + 22-CH2Hb); 1.23 (3H, d, J = 6.0 Hz, 24-CH3); 1.03 (3H, t, J = 7.4 Hz, 16-CH2Hb); 0.90 (9H, s, Si(CH3)3); 0.09 (6H, s, Si(CH3)2); 13C NMR δ (100.6 MHz, CDCl3) 147.9, 110.9, 78.8, 68.7, 67.4, 55.5, 45.4, 43.3, 41.3, 29.1, 25.9, 23.7, 18.0, 12.2, –4.1, –4.6; HRMS (+ESI) Calc. for C25H45O3Si [MH]+: 331.2668, found: 331.2674; m/z (+Cl, NH3) 421 (100), 319 (8), 289 (10), 257 (12), 106 (12).

(2R,4R,6R)-6-(ter-Butyldimethylsiloxyl)-8-ethyl-4-methoxy-non-8-en-2-ol (S8)

To a solution of benzyl ether 42 (228 mg, 0.542 mmol) in degassed THF (3 mL) at –78 °C was added LiDBB (0.5 M, 3.8 mL, 1.9 mmol, 3.5 equiv.) via cannula. The reaction was monitored by TLC to ensure complete consumption of starting material. After 90 mins, the reaction was quenched by the addition of sat. NaHCO3 (5 mL) and warmed to RT. H2O (10 mL) and Et2O (10 mL) were added, the layers were separated and the aqueous phase was extracted with Et2O (2 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na2SO4) and concentrated in vacuo. The crude material was purified by flash chromatography (10:90 → 30:70 EtOAc/hexanes) to afford alcohol S8 (177 mg, 99%) as a colourless oil: Rf 0.41 (30:70 EtOAc/hexanes); δααα = –5.2 (c 1.26, CHCl3); IR (liquid film) 3442 (br), 1644 (w) cm−1; 1H NMR δ (400 MHz, CDCl3) 4.80 (1H, d, J = 1.3 Hz, C=CH2Hb); 4.74 (1H, br s, C≡CH2Hb); 3.87–3.98 (2H, m, 19-CH + 23-CH); 3.56 (1H, m, 21-CH); 3.32 (3H, s, OCH3); 3.14 (1H, br s, OH); 2.29 (1H, dd, J = 13.6, 5.1 Hz, 18-CH2Hb); 2.13 (1H, dd, J = 13.6, 8.0 Hz, 18-CH2Hb); 2.03 (2H, app q, 16-CH2); 1.82 (1H, ddd, J = 14.4, 4.1, 0.4 Hz, 20-CH2Hb); 1.66 (1H, app dt, J = 14.5, 8.8 Hz, 22-CH2Hb); 1.56 (1H, ddd, J = 14.5, 4.2, 3.0 Hz, 22-CH2Hb); 1.42 (1H, ddd, J = 14.4, 8.3, 5.6 Hz, 20-CH2Hb); 1.17 (3H, d, J = 6.3 Hz, 24-CH3); 1.03 (3H, t, J = 7.4 Hz, 16-CH2CH3); 0.89 (9H, s, Si(CH3)3); 0.08 (6H, s, Si(CH3)2); 13C NMR δ (100.6 MHz, CDCl3) 147.9, 110.9, 78.8, 68.7, 67.4, 55.5, 45.4, 43.3, 41.3, 29.1, 25.9, 23.7, 18.0, 12.2, –4.1, –4.5; HRMS (+ESI) Calc. for C18H39O3Si [MH]+: 331.2668, found: 331.2674; m/z (+Cl, NH3) 331 (14), 273 (13), 215 (33), 132 (100).

(4S,6R)-6-(ter-Butyldimethylsiloxyl)-8-ethyl-4-methoxy-8-nonen-2-one (43)
Electronic Supplementary Material for Organic & Biomolecular Chemistry

To a suspension of Dess–Martin periodinane (393 mg, 0.927 mmol, 2 equiv.) in CH₂Cl₂ (5 mL) was added pyridine (375 µL, 4.64 mmol, 10 equiv.). After 5 mins, alcohol 58 (153 mg, 0.463 mmol) in CH₂Cl₂ (2 mL + 2 x 1 mL washings) was added dropwise, via pipette. The resultant mixture was left stirring, open to the atmosphere, for 40 mins. The reaction was quenched by the addition of sat. NaHCO₃ (5 mL), followed by 20% aq. Na₂S₂O₃ (5 mL) and the biphasic mixture was stirred vigorously for 30 mins. The mixture was concentrated in vacuo, Et₂O (10 mL) was added, the layers were separated and the aqueous phase was extracted with Et₂O (2 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄) and concentrated in vacuo.

Purification by flash chromatography (20:80 EtOAc/hexanes) afforded ketone 43 (148 mg, 97%) as a colourless oil: Rf 0.58 (30:70 EtOAc/hexanes); [α]D²⁻ = -23.1 (c 2.63, CHCl₃); IR (liquid film) 1719 (s), 1644 cm⁻¹; ¹H NMR δ (400 MHz, CDCl₃) 4.76 (1H, d, J = 1.5 Hz, C=CH₂H₃b), 4.71 (1H, br s, C=CH₂H₃a), 3.96 (1H, m, 19-CH), 3.85 (1H, m, 21-CH), 3.28 (3H, s, OCH₃), 2.69 (1H, dd, J = 15.6, 6.4 Hz, 22-CH₂H₃b), 2.47 (1H, dd, J = 15.6, 5.9 Hz, 22-CH₂H₃b), 2.29 (1H, dd, J = 13.7, 4.8 Hz, 18-CH₃H₃b), 2.14 (3H, s, CH₃), 2.09 (1H, dd, J = 13.7, 8.4 Hz, 18-CH₂H₃b), 2.00 (2H, app q, 16-CH₂), 1.69 (1H, ddd, J = 14.2, 8.7, 3.0 Hz, 20-CH₃H₃b), 1.33 (1H, ddd, J = 14.2, 8.9, 3.7 Hz, 20-CH₂H₃b), 1.01 (3H, t, J = 7.4 Hz, 16-CH₂CH₃), 0.88 (9H, s, Si(CH₃)₃), 0.07 (3H, s, Si(CH₃)₂), 0.06 (3H, s, Si(CH₃)); ¹³C NMR δ (100.6 MHz, CDCl₃) 207.2, 147.9, 110.8, 73.9, 67.8, 56.2, 48.5, 45.4, 41.9, 30.7, 29.0, 25.9, 18.0, 12.2, -4.1, -4.7; HRMS (+ESI) Calc. for C₁₈H₃₇O₃Si [MH⁺]: 329.2512, found: 329.256; m/z (+Cl, NH₃) 329 ([MH⁺]⁺, 100), 301 (37), 227 (29), 197 (41), 165 (40), 132 (80).

(2R,4S,6R,8R,10S)- and (2R,4S,6S,8R,10S)-8-(2-Ethylallyl)-10-methoxy-2-(p-methoxybenzyl oxyxymethyl)-1,7-dioxaspiro[5.5]undecan-4-ol (46 and 47)

To a solution of ketone 45 (169 mg, 253 µmol) in MeCN (5 mL) at 0 °C was added HF (40% aq., 0.9 mL) in one portion. The reaction was quenched after 40 mins at 0 °C, by the cautious addition of sat. NaHCO₃ (10 mL) and diluted with Et₂O (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with sat. NaHCO₃ (5 mL) and brine (5 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification by flash chromatography (70:30 EtOAc/hexanes) provided spiroacetals 46 and 47 (94.1 mg, 88%) as a ca. 5:1 mixture, respectively.

Major spiroacetal (undesired) 46: Rf 0.15 (7:30:63 Et₂O/CH₂Cl₂/hexanes); [α]D²⁻ +45.8 (c 1.84, CHCl₃); IR (liquid film) 3440 (br), 2931, 1612, 1513 cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 7.25 (2H, d, J = 8.5 Hz, ArH), 6.88 (2H, d, J = 8.5 Hz, ArH), 4.80 (1H, s, C=CH₂H₃a), 4.75 (1H, s, C=CH₂H₃b), 4.49 (1H, d, J = 11.5 Hz, OCH₂H₃bAr), 4.45 (1H, d, J = 11.5 Hz, OCH₂H₃bAr), 4.17–4.22 (2H, m, 25-CH + 27-CH), 3.91 (1H, m, 19-CH), 3.81 (3H, s, ArOCH₃), 3.60 (1H, app tt, J = 11.2, 4.4 Hz, 21-CH), 3.56 (1H, s, 28-CH₂H₃b), 3.55 (1H, d, J = 2.0 Hz, 28-CH₂H₃b), 3.32 (3H, s, OCH₃), 2.33 (1H, dd, J = 12.6, 2.8 Hz, 22-CH₂eq), 2.25 (1H, dd, J = 13.6, 5.7 Hz, 18-CH₂H₃b), 2.09 (1H, dd, J = 13.6, 7.6 Hz, 18-CH₂H₃b), 1.96–2.08 (3H, m, 20-CH₂eq + 24-CH₂eq 26-CH₂eq), 1.50–1.60 (2H, m, 26-CH₃ + 24-CH₂ax), 1.41 (1H, br d, J = 2.8 Hz, OH), 1.20 (1H, br t, J = 12.0 Hz, 22-CH₂ax), 1.01 (3H, t, J = 7.3 Hz, 16-CH₂CH₃), 0.98 (1H, br q, J = 11.5 Hz, 20-CH₃ax); ¹³C NMR δ (100.6 MHz, CDCl₃) 159.2, 147.4, 130.3, 129.1, 113.8, 110.9, 99.8, 72.9, 72.8, 71.6, 71.1, 68.2, 61.7, 55.4, 55.3, 44.8, 42.8, 41.5, 36.7, 34.7, 29.3, 12.3; HRMS (+ESI) Calc. for C₂₄H₃₆O₆Na [M + Na]⁺: 443.2410, found: 443.2424.

Minor spiroacetal (desired) 47: Rf 0.26 (7:30:63 Et₂O/CH₂Cl₂/hexanes); [α]D²⁻ -32.9 (c 2.38, CHCl₃); IR (liquid film) 3519 (sharp), 2933, 1611, 1513 cm⁻¹; ¹H NMR δ (500 MHz, CDCl₃) 7.27 (2H, d, J = 8.5 Hz, ArH), 6.87 (2H, d, J = 8.5 Hz, ArH), 4.89 (2H, s, C=CH₂), 4.53 (2H, s, OCH₂Ar), 4.42 (1H, m, 27-CH), 4.04 (1H, app dt, J = 11.5, 2.9 Hz, 25-CH), 3.80 (3H, s, ArOCH₃), 3.70 (1H, m, 19-CH), 3.50 (2H, app d, J = 4.4 Hz, 28-CH₂), 3.48 (1H, d, J = 11.5 Hz, OH), 3.46 (1H, app tt, J = 11.3, 4.5 Hz, 21-CH), 3.34 (3H, s, OCH₃), 2.38 (1H, dd, J = 13.5, 8.9 Hz, 18-CH₂H₃b), 2.25 (1H, br d, J = 14.3 Hz, 24-CH₂eq), 2.20 (1H, dd, J = 13.5, 3.5 Hz, 18-CH₂H₃b), 2.01–2.15 (4H, m, 16-CH₂ + 22-CH₂eq + 20-CH₂eq), 1.75 (1H, br d, J = 13.6 Hz, 26-CH₂eq), 1.65 (1H, dt, J =
13.6, 2.8 Hz, 26-CH$_{\text{ax}}$), 1.41–1.47 (2H, m, 24-CH$_{\text{ax}}$ + 22-CH$_{\text{ax}}$), 1.27 (1H, br q, $J = 11.7$ Hz, 26-CH$_{\text{eq}}$), 1.04 (3H, t, $J = 7.4$ Hz, 16-CH$_2$CH$_3$); $^{13}$C NMR $\delta$ (100.6 MHz, CDCl$_3$) 159.1, 147.4, 130.4, 129.2, 113.7, 111.9, 99.7, 73.7, 72.9, 72.6, 69.8, 64.9, 64.6, 55.5, 55.2, 43.3, 42.6, 37.3, 34.4, 34.2, 28.9, 12.1; HRMS (+ESI) Calc. for C$_{24}$H$_{36}$O$_6$Na [M + Na]$^+$: 443.2410, found: 443.2401.

Equilibration of the CD spiroacetals

A mixture (ca. 5:1) of spiroacetals 46 and 47 (from above procedure, 55.3 mg, 131 $\mu$mol) in CH$_2$Cl$_2$ (2 mL) was treated with anhydrous HCl (2.0 M in Et$_2$O, 6.5 $\mu$L, 13 $\mu$mol, 0.1 equiv.) and the resultant solution allowed to stir at RT for 30 minutes. The mixture was cooled to 0 °C, Et$_3$N (30 $\mu$L, 215 $\mu$mol) was added dropwise and the solvent was removed in vacuo. The crude material was subjected to flash chromatography (40:40:20 EtOAc/CH$_2$Cl$_2$/hexanes) providing the desired 47 (23.8 mg, 43%) and undesired 46 (18.4 mg, 33%) spiroacetals.

(2R,4S,6R,8R,10S)-4-(t-Butyldimethylsiloxy)-8-(2-ethylallyl)-10-methoxy-2-(p-methoxybenzyloxymethyl)-1,7-dioxaspiro[5.5]undecane (S9)

To a solution of alcohol 47 (23.6 mg, 56.1 $\mu$mol) in CH$_2$Cl$_2$ (2 mL) at –78 °C was added 2,6-lutidine (26 $\mu$L, 223 $\mu$mol, 4 equiv.) followed by TBSOTf (26 $\mu$L, 113 $\mu$mol, 2 equiv.). After 1 h at this temperature, the reaction was quenched by the addition of MeOH (250 $\mu$L). Sat. NaHCO$_3$ (5 mL) was added and the resultant mixture allowed to warm to RT. The mixture was partitioned between H$_2$O (10 mL) and Et$_2$O (10 mL) and the layers were separated. The aqueous phase was extracted with Et$_2$O (2 x 10 mL), the combined organic extracts were washed with brine (5 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography (10:90 → 20:80 EtOAc/hexanes) afforded TBS ether S9 (23.0 mg, 77%) as a colourless oil: $R_f$ 0.47 (40:60 EtOAc/hexanes); $[\alpha]_{20}^D$ –12.3 ($c$ 2.30, CHCl$_3$); IR (liquid film) 2952, 2929, 1613, 1514 cm$^{-1}$; $^1$H NMR $\delta$ (400 MHz, CDCl$_3$) 7.25 (2H, dd, $J = 6.8$, 1.8 Hz, ArH), 6.85 (2H, dd, $J = 6.8$, 1.8 Hz, ArH), 4.78 (1H, d, $J = 1.4$ Hz, C=CH$_{\text{aHb}}$), 4.73 (1H, br s, C=CH$_{\text{aHb}}$), 4.55 (1H, m, 27-CH$_{\text{ax}}$), 4.51 (2H, d, $J = 4.7$ Hz, 28-CH$_2$), 4.34 (1H, dt, $J = 11.5$, 4.5 Hz, 19-CH), 3.48 (2H, d, $J = 13.8$ Hz, 22-CH$_2$), 2.47 (1H, dd, $J = 13.8$, 4.6 Hz, 18-CH$_2$), 2.18 (1H, dd, $J = 13.8$, 8.6 Hz, 18-CH$_2$), 2.02–2.10 (3H, m, 20-CH$_{\text{eq}}$ + 22-CH$_{\text{eq}}$ + 24-CH$_{\text{eq}}$), 2.01 (2H, q, $J = 7.4$ Hz, 16-CH$_2$), 1.72 (1H, ddd, $J = 13.5$, 11.3, 3.8 Hz, 26-CH$_{\text{eq}}$), 1.57 (1H, dt, $J = 13.5$, 2.8 Hz, 26-CH$_{\text{eq}}$), 1.53 (1H, dd, $J = 14.3$, 3.9 Hz, 24-CH$_{\text{ax}}$), 1.35 (1H, t, $J = 12.0$ Hz, 22-CH$_{\text{eq}}$), 1.08 (1H, app q, $J = 11.8$ Hz, 20-CH$_{\text{eq}}$), 1.01 (3H, t, $J = 7.4$ Hz, 16-CH$_2$), 0.88 (9H, s, Si(C(CH$_3$)$_3$)), 0.04 (6H, s, Si(CH$_3$)$_2$); $^{13}$C NMR $\delta$ (100.6 MHz, CDCl$_3$) 159.2, 147.7, 130.7, 129.4, 113.8, 110.5, 98.5, 74.5, 73.0, 72.7, 69.4, 65.1, 64.6, 55.5, 43.3, 42.9, 36.2, 35.4, 29.7, 26.2, 18.4, 12.5, –4.6, –4.7; HRMS (+ESI) Calc. for C$_{30}$H$_{50}$O$_6$SiNa [M + Na]$^+$: 557.3274, found: 557.3309.

Formation of the CD-spiroacetal ethyl ketone (2)

A solution of alkene S9 (22.6 mg, 42.3 $\mu$mol) in 2.5:1 acetone (1 mL) and H$_2$O (0.4 mL) was treated with NMO (15 mg, 128 $\mu$mol, 3 equiv.) and OsO$_4$ (0.1 M in $t$-BuOH, 21 $\mu$L, 2.1 $\mu$mol, 5 mol%), and the resultant mixture was stirred at RT for 6 h. The remaining oxidant was quenched by the addition of 20% aq.Na$_2$S$_2$O$_3$ (2 mL) and the mixture was stirred for 40 mins. Et$_2$O (2 mL) was added and the layers were separated. The aqueous phase was extracted with EtOAc (3 x 2 mL), the combined organic extracts were washed with brine (2 mL) and the brine back-extracted with EtOAc.
(1 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was dissolved in 2:1 MeOH (1 mL) and pH 7 buffer (0.5 mL). To the resultant solution was added NaIO$_4$ (18 mg, 84 µmol, 2 equiv.), and the mixture was allowed to stir at RT for 1 h. The mixture was diluted with H$_2$O (10 mL) and the resultant solution was extracted with Et$_2$O (3 x 3 mL). The combined organic extracts were washed with brine (2 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography (35:65 EtOAc/hexanes) afforded ketone 2 (18.6 mg, 82%) as a colourless oil, having identical physical and spectroscopic properties to material provided by the previous route.