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

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General Experimental Details

^{1}H 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: $CDCl_3$ (δ_H 7.26), C_6D_6 (δ_H 7.16) and CD_3CN (δ_H 1.94). Data are presented as follows: chemical shift (in ppm on the δ scale relative to tetramethylsilane $\delta_{TMS} = 0$), integration, multiplicity, coupling constant and interpretation XX-C<u>H</u> 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. ^{13}C 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, $\delta_{TMS} = 0$). An internal reference was used for $CDCl_3$ (δ_C 77.16) and C_6D_6 (δ_C 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 NH_4^+ (+CI, NH_3) 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 $[M + NH_4]^+$ 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: $[\alpha]_D^{20}$, 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 F_{254} 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_2Cl_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_3N), *i*-Pr_2NEt, pyridine and 2,6-lutidine were distilled from and stored over CaH_2. Acetic acid (AcOH) was distilled from CrO_3 and Ac_2O 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.

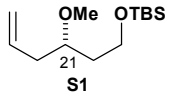
All experiments were performed under anhydrous conditions, utilising anhydrous solvents, under an atmosphere of argon, except where stated, using oven-dried glassware and employing standard techniques in handling air-sensitive materials. All reactants added *via* cannula were added using a positive pressure 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-(*tert*-Butyldimethylsiloxy)-oct-7-en-3-ol (16)

To a cold (–78 °C), stirred solution of (–)-Ipc_2BOMe (2.95 g, 9.31 mmol, 1.8 equiv) in Et_2O (40 mL) was added allylmagnesium bromide (7.5 mL, 1 M in Et_2O, 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_2O (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_2O_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_2O_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_2O (3 x 40 mL). The combined organic extracts were washed with H_2O (25 mL) and brine (40 mL) and dried ($MgSO_4$). The solvent was removed *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: $\mathbf{R_f}$ 0.21 (CH_2Cl_2); $[\alpha]_D^{20}$ –5.95 (*c* 2.20, $CHCl_3$); **IR** (liquid film) 3416 (br), 1642, 1472 cm^{-1}; **^{1}H NMR** δ (400 MHz, $CDCl_3$) 5.82 (1H, ddt, *J* = 17.1, 9.8, 7.1 Hz, 19-C<u>H</u>), 5.07 (1H, dd, *J* =17.1, 1.3 Hz, 19-C=C<u>H</u>$_{2A}$), 5.05 (1H, dd, *J* = 10.0, 1.1 Hz, 19-C=C<u>H</u>$_{2B}$), 3.91–3.82 (2H, m, 23-C<u>H</u>$_2$), 3.81–3.75 (1H, m, 21-C<u>H</u>), 3.39 (1H, d, *J* = 1.8 Hz, -O<u>H</u>), 2.22 (2H, m, 20-C<u>H</u>$_2$), 1.63 (1H, app q, *J* = 5.2 Hz, 22-C<u>H</u>$_2$), 0.87 (9H, s, -OSiMe$_2$^{t}<u>Bu</u>), 0.05 (6H, s, -OSi<u>Me</u>$_2$^{t}Bu); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 135.0, 117.2, 71.2, 62.3, 41.9, 37.7, 25.8, 18.1, –5.6; **HRMS** [+CI, NH_3] Calc. for $C_{12}H_{27}O_2Si$ $[MH]^+$ 231.1780; found 231.1780; **m/z** 231 ($[MH]^+$, 100), 132 (10), 92 (20), 81 (15).

(3*S*)-1-(*tert*-Butyldimethylsilyloxy)-3-methoxy-hex-5-ene (S1)



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

[1] D. A. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemical*s, Pergamon Press, Oxford, 1988.

mmol) in dry THF (5 mL + 2 x 1 mL washings) was added *via* cannula with stirring. After 25 mins MeI (203μL, 3.26 mmol) was added and the reaction stirred at RT for 16 h. The reaction was quenched by the addition of NH_4Cl solution (50 mL) and Et_2O (50 mL) added. The layers were separated and the aqueous layer extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with $NaHCO_3$ solution (20 mL, sat. aqueous) and brine (20 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude product was subjected to flash chromatography (CH_2Cl_2) to give the title methyl ether **S1** (383 mg, 96%) as a colourless oil: $\mathbf{R_f}$ 0.40 (CH_2Cl_2); $[\alpha]_D^{20}$ +8.80 (*c* 1.46, $CHCl_3$); **IR** (liquid film) 1641, 1465 cm^{-1}; **^{1}H NMR** δ (400 MHz, $CDCl_3$) 5.80 (1H, ddt, *J* = 16.6, 10.3, 6.8 Hz, 19-C<u>H</u>), 5.06 (1H, overlapping d, *J* = 15.5 Hz, 19-C=C<u>H</u>$_{2A}$), 5.03 (1H, overlapping d, *J* = 9.4 Hz, 19-C=C<u>H</u>$_{2B}$), 3.68–3.64 (2H, m, 23-C<u>H</u>$_2$), 3.38 (1H, app quintet, *J* = 6.9 Hz, 21-C<u>H</u>), 3.32 (3H, s, -O<u>Me</u>), 2.26 (2H, dd, *J* = 6.9, 5.9 Hz, 20-C<u>H</u>$_2$), 1.65 (2H, dt, *J* = 6.6, 6.4 Hz, 22-C<u>H</u>$_2$), 0.87 (9H, s, -OSiMe$_2$<u>^{t}Bu</u>), 0.03 (6H, s, -OSi<u>Me</u>$_2$^{t}Bu); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 134.7, 116.9, 77.1, 59.5, 56.6, 37.8, 36.6, 25.9, 18.3, –5.4; **HRMS** [+CI, NH_3] Calc. for $C_{13}H_{29}O_2Si$ [MH^+] 245.19367, found 245.1937; **m/z** 247 (10), 246 (20), 247 (100), 136 (20), 123 (25), 121 (15), 106 (15), 58 (15), 52 (17), 44 (15).

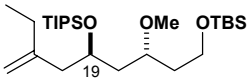
(3*R*)-3-Methoxy-5-(*tert*-butyldimethylsilyloxy)-pentanal (14)
Ozone was bubbled through a cold (–78 °C), solution of alkene **S1** (368 mg, 1.51 mmol) and $NaHCO_3$ (solid approx. 100 mg) in dry CH_2Cl_2 (20 mL). When a blue colour persisted in the reaction indicating unreacted ozone, the flow of ozone 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 (CH_2Cl_2, then 10:90 EtOAc/CH_2Cl_2) to yield the title aldehyde **14** (331 mg, 90%) as a colourless oil: $\mathbf{R_f}$ 0.45 (10:90 EtOAc/CH_2Cl_2); $[\alpha]_D^{20}$ +5.18 (*c* 4.25, $CHCl_3$); **IR** (liquid film) 2726, 1727, 1472 cm^{-1}; **^{1}H NMR** δ (500 MHz, $CDCl_3$) 9.81 (1H, t, *J* = 2.2 Hz, 19-C<u>H</u>), 3.89 (1H, app quintet, *J* = 6.1 Hz, 21-C<u>H</u>), 3.75–3.67 (2H, m, 23-C<u>H</u>$_2$), 3.36 (3H, s, -O<u>Me</u>), 2.61 (2H, dd, *J* = 6.0, 2.3 Hz, 20-C<u>H</u>$_2$), 1.84 (1H, app dq, *J* = 14.1, 5.7 Hz, 22-C<u>H</u>$_{2A}$), 1.71 (1H, app dq, *J* = 14.0, 5.7 Hz, 22-C<u>H</u>$_{2B}$), 0.89 (9H, s, -OSiMe$_2$<u>^{t}Bu</u>), 0.052 (3H, s, -OSi<u>Me</u>$_{2A}$^{t}Bu), 0.051 (3H, s, -OSi<u>Me</u>$_{2B}$^{t}Bu); **^{13}C NMR** δ (50 MHz, $CDCl_3$) 201.5, 73.6, 59.1, 56.9, 48.2, 37.0, 25.9, 18.2, –5.4; **HRMS** (+CI, NH_3) Calc. for $C_{12}H_{25}O_3Si$ [M - H]$^+$: 245.1573, found: 245.1563; **m/z** (+CI, NH_3) 263 ([M – H + NH_4]$^+$, 100), 245 ([M – H]$^+$, 20), 205 (90), 131 (40), 106 (40), 89 (40).

(3*R*,5*R*)-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 CH_2Cl_2 (40 mL, 0.01 M in aldehyde) was added $TiCl_4$ (49 μL, 0.45 mmol) and the reaction was subsequently cooled to –100°C over 5 mins. A mixture of allylsilane **13**[2] (1.41 g, 1:10 in pentane, 1.63 mmol) in dry CH_2Cl_2 (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 $NaHCO_3$ solution (20 mL, sat. aqueous). The reaction was allowed to warm to RT and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (20 mL) and dried ($MgSO_4$). 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 ^{1}H NMR.
Major diastereomer **17**: $\mathbf{R_f}$ 0.80 (Et_2O), 0.37 (25:75 EtOAc/hexanes); $\mathbf{R_t}$ 17 mins (25% EtOAc/hexane); $[\alpha]_D^{20}$ –5.2 (*c* 1.93, $CHCl_3$); **IR** (liquid film) 3683, 1644 (w), 1522 cm^{-1}; **^{1}H NMR** δ (500 MHz, $CDCl_3$) 4.85 (1H, d, *J* = 1.6 Hz, 17-C=C<u>H</u>$_{2A}$), 4.80 (1H, s, 17-C=C<u>H</u>$_{2B}$), 4.01–3.98 (1H, m, 19-C<u>H</u>), 3.70–3.64 (3H, m, 21-C<u>H</u> + 23-C<u>H</u>$_2$), 3.38 (3H, s, -O<u>Me</u>), 2.79 (1H, d, *J* = 2.6 Hz, -O<u>H</u>), 2.23–2.16 (2H, m, 18-C<u>H</u>$_2$), 2.09 (1H, strongly roofed dq, *J* = 16.0, 8.1 Hz, 16-C<u>H</u>$_{2A}$), 2.03

[2] M. B. Anderson and P. L. Fuchs, *Synth. Commun.*, 1987, **17**, 621-635.

(1H, strongly roofed dq, J = 15.9, 8.3 Hz, 16-C$\underline{H}_{2B}$), 1.84 (1H, app dq, J = 12.4, 6.3 Hz, 22-C$\underline{H}_{2A}$), 1.69–1.65 (2H, m, 20-C$\underline{H}_{2A}$ + 22-C$\underline{H}_{2B}$), 1.60 (1H, ddd, J = 13.1, 7.1, 2.8 Hz, 20-C$\underline{H}_{2A}$), 1.04 (3H, t, J = 7.4 Hz, 16-C-C$\underline{H}_3$), 0.89 (9H, s, -OSiMe$_2^{t}\underline{Bu}$), 0.05 (3H, s, -OSi$\underline{Me}_{2A}$^{t}Bu), 0.04 (3H, s, -OSi$\underline{Me}_{2B}$^{t}Bu); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 148.3, 110.1, 76.3, 66.4, 59.5, 57.1, 44.9, 39.8, 36.6, 28.7, 25.9, 18.2, 12.2, –5.4; **HRMS** (+CI, NH_3) Calc. for $C_{17}H_{37}O_3Si$ $[MH]^+$: 317.2512, found: 317.2512; **m/z** (+CI, NH_3) 317 (MH^+) (100%), 247 (90), 232 (50), 215 (30), 203 (30), 135 (25), 106 (25), 58 (25).

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



S2

To a stirred solution of homoallylic alcohol **17** (46.7 mg, 0.148 mmol) in CH_2Cl_2 (7 mL) at –78 °C 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 NH_4Cl solution (5 mL, sat. aqueous) and allowed to warm to RT. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). 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: **R_f** 0.65 (25:75 EtOAc/hexanes); $[\alpha]_D^{20}$ –20.6 (*c* 1.53, $CHCl_3$); **IR** (liquid film) 2942, 2866, 1645 (w) cm^{-1}; **^{1}H NMR** δ (250 MHz, $CDCl_3$) 4.78, 4.75 (2H, s, s, 17-C=C$\underline{H}_2$), 4.16 (1H, app tt, J = 8.5, 4.2 Hz, 19-C$\underline{H}$), 3.71–3.62 (2H, partially overlapping m, 23-C$\underline{H}$), 3.63–3.52 (1H, partially overlapping m, 21-C$\underline{H}$), 3.29 (3H, s, -O$\underline{Me}$), 2.40 (1H, dd, J = 13.6, 4.3 Hz, 18-C$\underline{H}_{2A}$), 2.13 (1H, dd, J = 13.6, 9.0 Hz, 18-C$\underline{H}_{2B}$), 2.02 (2H, app q, J = 7.6 Hz, 16-C$\underline{H}_2$), 1.80–1.59 (3H, m, 20-C$\underline{H}_2$ + 22-C$\underline{H}_{2A}$), 1.37 (1H, ddd, J = 15.0, 8.2, 3.7 Hz, 22-C$\underline{H}_{2B}$), 1.10–1.06 (21H, m, -OSi(C$\underline{H}$(C$\underline{H}_3$)$_2$)$_3$), 1.02 (3H, app t, J = 7.5 Hz, 16-C-C$\underline{H}_3$), 0.89 (9H, s, -OSiMe$_2^{t}\underline{Bu}$), 0.04 (6H, s, -OSi$\underline{Me}_2$^{t}Bu); **^{13}C NMR** δ (50 MHz, $CDCl_3$) 148.1, 110.5, 74.6, 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** (+CI, NH_3) Calc. for $C_{26}H_{57}O_3Si_2$ $[MH]^+$: 473.3846, found: 473.3846; **m/z** (+CI, NH_3) 473 (MH^+, 30), 371 (25), 299 (30), 267 (30), 135 (50), 132 (35), 106 (30), 58 (100).

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

To a cooled (0 °C), stirred solution of silyl ether **S2** (144 mg, 0.305 mmol) in MeOH (1 mL) and CH_2Cl_2 (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 Et_3N (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: **R_f** 0.23 (25:75 EtOAc/hexanes); $[\alpha]_D^{20}$ –13.8 (*c* 3.05, $CHCl_3$); **IR** (liquid film) 3395 (br), 2942, 1645 (w) cm^{-1}; **^{1}H NMR** δ (500 MHz, $CDCl_3$) 4.80, 4.76 (2H, s, s, 17-C=C$\underline{H}_2$), 4.45 (1H, app tt, J = 8.5, 4.3 Hz, 19-C$\underline{H}$), 3.83–3.77 (1H, m, 23-C$\underline{H}_{2A}$), 3.72 (1H, app qn, J = 5.6 Hz, 21-C$\underline{H}$), 3.68–3.64 (1H, m, 23-C$\underline{H}_{2B}$), 3.34 (3H, s, -O$\underline{Me}$), 2.41 (1H, dd, J = 13.7, 4.1 Hz, 18-C$\underline{H}_{2A}$), 2.31 (1H, t, J = 5.2 Hz, -O$\underline{H}$), 2.14 (1H, dd, J = 13.6, 9.1 Hz, 18-C$\underline{H}_{2B}$), 2.06–1.98 (2H, m, 16-C$\underline{H}_2$), 1.92–1.85 (2H, m, 20-C$\underline{H}_{2A}$ + 22-C$\underline{H}_{2A}$), 1.72–1.66 (1H, m, 22-C$\underline{H}_{2B}$), 1.38 (1H, ddd, J = 12.7, 8.1, 4.3 Hz, 20-C$\underline{H}_{2B}$), 1.10–1.06 (21H, m, -OSi(C$\underline{H}$(C$\underline{H}_3$)$_2$)$_3$), 1.03 (3H, app t, J = 7.4 Hz, 16-C-C$\underline{H}_3$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 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** (+CI, NH_3) Calc. for $C_{20}H_{43}O_3Si$ $[MH]^+$: 359.2981, found: 359.2981; **m/z** (+CI, NH_3) 359 (MH^+, 5), 257 (30), 155 (25), 100 (20), 58 (100), 44 (60).

(5*E*)-(4*R*)-Hepta-1,5-dien-4-ol [(*R*)-19][3]

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 CH_2Cl_2 (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(O*i*-Pr)$_4$ solution (8.9 mL, 1 M in CH_2Cl_2, 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 Me_2S (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 oilin greater than 95% *ee* as adjudged by MTPA ester analysis: $\mathbf{R_f}$ 0.21 (20% EtOAc/hexane); $[\alpha]_D^{20}$ +15.4 (*c* 2.735, $CHCl_3$); **^{1}H NMR** δ (200 MHz, $CDCl_3$) 5.80–5.61 (2H, m, 25-C<u>H</u> + 29-C<u>H</u>), 5.49 (1H, ddq, *J* = 16.4, 7.0, 1.8 Hz, 28-C<u>H</u>), 5.19–5.03 (2H, m, 24-C<u>H$_2$</u>), 4.18–4.04 (1H, m, 27-C<u>H</u>), 2.41–2.27 (2H, m, 26-C<u>H$_2$</u>), 1.67 (3H, d, *J* = 6.4 Hz, 30-C<u>H$_3$</u>), 1.63 (1H, br s, -O<u>H</u>).

(5*E*)-(4*R*)-4-*p*-Methoxybenzyloxy-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 NH_4Cl solution (20 mL, sat. aqueous). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL), the combined organic extracts were washed with H_2O (20 mL) and brine (20 mL) and dried ($MgSO_4$). 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: $\mathbf{R_f}$ 0.47 (20:80 EtOAc/hexanes); $[\alpha]_D^{20}$ +37.7 (*c* 4.40, $CHCl_3$); **IR** (liquid film) 3000, 1671, 1641, 1613 (s), 1586, 1513 cm^{-1}; **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.25 (2H, d, *J* = 8.7 Hz, <u>Ar</u>), 6.87 (2H, d, *J* = 8.7 Hz, <u>Ar</u>), 5.80 (1H, app qt, *J* = 13.9, 7.0 Hz, 25-C<u>H</u>), 5.66 (1H, dq, *J* = 15.3, 6.4 Hz, 29-C<u>H</u>), 5.38 (1H, ddq, *J* = 15.3, 8.1, 1.5 Hz, 28-C<u>H</u>), 5.11–5.00 (2H, m, 24-C<u>H$_2$</u>), 4.51 (1H, d, *J* = 11.6 Hz, -OC<u>H$_{2A}$</u>Ar), 4.39 (1H, d, *J* = 11.6 Hz, -OC<u>H$_{2B}$</u>Ar), 3.80 (3H, s, -O<u>Me</u>), 3.76 (1H, app q, *J* = 7.8 Hz, 27-C<u>H</u>), 2.46–2.20 (2H, m, 26-C<u>H$_2$</u>), 1.75 (3H, dd, *J* = 6.4, 1.5 Hz, 30-C<u>H$_3$</u>); **^{13}C NMR** δ (50 MHz, $CDCl_3$) 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** (+CI, NH_3) Calc. for $C_{15}H_{24}NO_2$ [M + NH_4]$^+$: 250.1807, found: 250.1807; **m/z** (+CI, NH_3) 250 ([M + NH_4]$^+$, 5), 138 (30), 121 (100), 95 (10).

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

To a stirred solution of CuCl (2.00 g, 20.0 mmol) in DMF (70 mL) and H_2O (10 mL) was added $PdCl_2$ (120 mg, 0.677 mmol) and the reaction stirred under an oxygen atmosphere (balloon) for 2 h during which time the reaction colour changed from green to black. A solution of ether **20** (2.00 g, 8.61 mmol) in DMF (5 mL + 2 x 1 mL washings) was added *via* cannula and the reaction stirred under an oxygen atmosphere at RT for 14 h. The reaction was quenched by the addition of NH_4Cl solution (50 mL, sat. aqueous) and the reaction mixture was extracted with Et_2O (4 x 50 mL). The combined organic extracts were washed with H_2O (50 mL) and brine (50 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo*. The crude product was dissolved in ^{t}BuOH (100 mL) and 2-methyl-2-butene (1.2 mL, 11.3 mmol) added. A solution of $NaClO_2$ (2.52 g, 23.7 mmol) and $NaH_2PO_4.H_2O$ (3.50 g, 25.4 mmol) in H_2O (100 mL) was added over 5 mins. The reaction was stirred at RT for 2 h and poured into brine (100 mL). The reaction mixture was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic extracts were dried ($MgSO_4$) and the solvent

[3] W. R. Roush and R. J. Brown, *J. Org. Chem.*, 1983, **48**, 5093-5101; I. Paterson and S. P. Wren, *J. Chem. Soc., Chem. Commun.*, 1993, 1790-1792.

removed *in vacuo*. The crude product was purified by flash chromatography (CH_2Cl_2) to yield the title ketone **11** as a colourless oil (1.01 g, 47%): $\mathbf{R_f}$ 0.19 (CH_2Cl_2); $[\alpha]_D^{20}$ +19.8 (*c* 1.67, $CHCl_3$); **IR** (liquid film) 3000, 1717 (s), 1641 (w), 1613, 1586, 1513 (s) cm^{-1}; ^{1}**H NMR** δ (400 MHz, $CDCl_3$) 7.20 (2H, d, *J* = 8.5 Hz, Ar), 6.84 (2H, d, *J* = 8.5 Hz, Ar), 5.70 (1H, dq, *J* = 15.3, 6.6 Hz, 29-CH), 5.35 (1H, ddq, *J* = 15.2, 8.2, 1.5 Hz, 28-CH), 4.45 (1H, d, *J* = 11.8 Hz, -OCH_{2A}Ar), 4.25 (1H, d, *J* = 11.8 Hz, -OCH_{2B}Ar), 4.20 (1H, app td, *J* = 8.3, 4.9 Hz, 27-CH), 3.78 (3H, s, -OMe), 2.77 (1H, dd, *J* = 15.4, 8.4 Hz, 26-CH_{2A}), 2.48 (1H, dd, *J* = 15.4, 9.4 Hz, 26-CH_{2B}), 2.12 (3H, s, 24-CH_3), 1.72 (3H, dd, *J* = 6.5, 1.4 Hz, 30-CH_3); ^{13}**C NMR** δ (100.6 MHz, $CDCl_3$) 206.7, 157.0, 130.44, 130.38, 129.4, 129.3, 113.6, 76.0, 69.7, 55.1, 49.7, 31.0, 17.6; **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).

(3*S*,5*S*)-3-Methoxy-5-(triisopropylsilyloxy)-7-ethyl-oct-7-enal (12)
To a stirred solution of alcohol **18** (19.9 mg, 0.055 mmol) in CH_2Cl_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 30 mins and then quenched by addition of $NaHCO_3$ solution (2 mL, sat. aqueous) followed by $Na_2S_2O_3$ (2 mL, 10 % aqueous). After stirring for 30 mins, during which time the reaction became clear, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were washed with H_2O (3 mL) and brine (5 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 yield the title aldehyde **12** (18.9 mg, 96%) as a colourless oil: $\mathbf{R_f}$ 0.48 (25:75 EtOAc/hexanes); $[\alpha]_D^{20}$ –25.6 (*c* 2.42, $CHCl_3$); **IR** 2943, 2849, 2720 (w), 1727 (s), 1643 (w) cm^{-1}; ^{1}**H NMR** δ (500 MHz, $CDCl_3$) 9.79 (1H, t, *J* = 2.5 Hz, 23-CH), 4.79, 4.74 (2H, s, s, 17-C=CH_2), 4.23–4.17 (1H, m, 19-CH or 21-CH), 4.01–3.97 (1H, m, 21-CH or 19-CH), 3.31 (3H, s, -OMe), 2.65–2.54 (2H, ABX m, δ_A = 2.62, δ_B = 2.57, *J* = 15.9, 5.7, 2.5 Hz, 22-CH_2), 2.45 (1H, dd, *J* = 13.7, 3.9, 18-CH_{2A}), 2.11 (1H, dd, *J* = 13.7, 9.7 Hz, 18-CH_{2B}), 2.02–1.98 (2H, m, 16-CH_2), 1.87 (1H, ddd, *J* = 14.2, 9.2, 2.2 Hz, 20-CH_{2A}), 1.39 (1H, ddd, *J* = 14.2, 8.8, 3.5 Hz, 20-CH_{2B}), 1.10–1.07 (21H, m, -OSi(CH(CH_3)$_2$)$_3$), 1.02 (3H, app t, *J* = 7.4 Hz, 16-C-CH_3); ^{13}**C NMR** δ (100.6 MHz, $CDCl_3$) 201.5, 147.8, 110.8, 73.0, 68.0, 56.2, 47.9, 45.7, 42.2, 28.9, 16.2, 12.9, 12.2; **HRMS** (+CI, NH_3) Calc. for $C_{20}H_{41}O_3Si$ $[MH]^+$: 357.2825, found: 357.2825; **m/z** (+CI, NH_3) 357 ($[MH]^+$, 5), 257 (10), 183 (10), 174 (10), 151 (20), 137 (20), 136 (30), 94 (40), 74 (80), 44 (100).

(2*E*)-(4*R*,6*S*,8*R*,10*S*)-4-*p*-Methoxybenzyloxy-8-hydroxy-10-methoxy-12-(triisopropylsilyloxy)-14-ethyl-pentadeca-2,14-dien-6-one (23)
To a cooled (0 °C), stirred solution of dicyclohexylboron chloride (110 μL, 0.508 mmol) in dry ether (3 mL) was added dry Et_3N (79 μL, 0.568 mmol). A solution of ketone **11** (125 mg, 0.503 mmol) in Et_2O (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 aldehyde **12** (107 mg, 0.299 mmol) in Et_2O (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_2O_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_2O (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 yield the aldol product **23** with 84:16 *dr* by ^{1}H NMR. The major diastereomer **23** could be separated by HPLC (20:80 EtOAc/hexanes). The total yield of aldol adducts after HPLC purification was 129 mg, 72 %. Major diastereomer **23**: $\mathbf{R_f}$ 0.35 (25:75 EtOAc/hexanes); $\mathbf{R_t}$ 39 min (20:80 EtOAc/hexanes), $[\alpha]_D^{20}$ +3.7 (*c* 1.00, $CHCl_3$), **IR** (solution cell, $CHCl_3$) 3520, 2962, 1710, 1645 (w), 1613, 1514 cm^{-1}; ^{1}**H NMR** δ (500 MHz, $CDCl_3$) 7.19 (2H, d, *J* = 8.5 Hz, Ar), 6.85 (2H, d, *J* = 8.6 Hz, Ar), 5.72 (1H, dq, *J* = 15.3, 6.3 Hz, 29-CH), 5.36 (1H, ddq, *J* = 15.3, 8.2, 1.5 Hz, 28-CH), 4.79, 4.75 (2H, s, s, 17-C=CH_2), 4.46, 4.25 (2H, d, d, *J* = 11.3 Hz, -OCH_2Ar), 4.23–4.18 (1H, partially overlapping m, 27-

C<u>H</u>), 4.18–4.11 (2H, overlapping m, 19-C<u>H</u> + 23-C<u>H</u>), 3.79 (3H, s, ArO<u>Me</u>), 3.67–3.65 (1H, m, 21-C<u>H</u>), 3.38 (1H, d, *J* = 2.5 Hz, -O<u>H</u>), 3.28 (3H, s, -O<u>Me</u>), 2.79 (1H, dd, *J* = 15.4, 8.5 Hz, 26-C<u>H</u>$_{2A}$), 2.57–2.55 (2H, m, 24-C<u>H</u>$_2$), 2.47 (1H, dd, *J* = 15.4, 4.7, 26-C<u>H</u>$_{2B}$), 2.40 (1H, dd, *J* = 13.6, 4.0 Hz, 18-C<u>H</u>$_{2A}$), 2.14 (1H, dd, *J* = 13.7, 9.2 Hz, 18-C<u>H</u>$_{2B}$), 2.04–1.98 (2H, m, 16-C<u>H</u>$_2$), 1.80–1.70 (2H, m, 20-C<u>H</u>$_{2A}$ + 22-C<u>H</u>$_{2A}$), 1.73 (3H, dd, *J* = 6.4, 1.4 Hz, 30-C<u>H</u>$_3$), 1.47–1.38 (2H, m, 20-C<u>H</u>$_{2B}$ + 22-C<u>H</u>$_{2B}$), 1.10–1.06 (21H, m, -OSi(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$), 1.02 (3H, app t, *J* = 7.3 Hz, 16-C-C<u>H</u>$_3$); **^{13}C NMR** δ (62.5 MHz, $CDCl_3$) 209.0, 159.1, 148.0, 130.43, 130.36, 129.6, 129.4, 113.8, 110.7, 76.2, 76.0, 69.8, 68.4, 65.8, 55.4, 55.2, 51.1, 49.6, 45.6, 41.6, 40.1, 29.1, 18.3, 17.7, 12.9, 12.3; **HRMS** (+CI, NH_3) Calc. for $C_{35}H_{61}O_6Si$ $[MH]^+$: 605.4237, found: 605.4240; **m/z** (+CI, NH_3) 605.5 ($[MH]^+$, 20), 495 (30), 468 (60), 451 (50), 413 (90), 386 (100), 382 (50).

(2*E*)-(4*R*,10*S*,12*S*)-4-*p*-Methoxybenzyloxy-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 CH_2Cl_2 (1 mL) at RT was added solid Dess–Martin periodinane (21.5 mg, 0.051 mmol). The reaction was stirred for 20 mins and then quenched by addition of $NaHCO_3$ solution (1 mL, sat. aqueous) followed by $Na_2S_2O_3$ (1 mL, 10 % aqueous). After stirring for 1 h, during which time the reaction became clear, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were washed with H_2O (1 mL) and brine (1 mL) and dried ($MgSO_4$). 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: $\mathbf{R_f}$ 0.49 (25:75 EtOAc/hexanes); $[\alpha]_D^{20}$ –6.9 (*c* 0.91, $CHCl_3$), **IR** (solution cell, $CHCl_3$) 2944, 2866, 1731 (w), 1612 (br), 1514; **^{1}H NMR** δ (500 MHz, $CDCl_3$) 7.20 (2H, d, *J* = 8.6 Hz, <u>Ar</u>), 6.84 (2H, d, *J* = 8.6 Hz, <u>Ar</u>), 5.70 (1H, dq, *J* = 15.3, 6.5 Hz, 29-C<u>H</u>), 5.52 (1H, s, 24-C<u>H</u>), 5.38 (1H, ddq, *J* = 15.3, 8.2, 1.5 Hz, 28-C<u>H</u>), 4.77, 4.73 (2H, s, s, 17-C=C<u>H</u>$_2$), 4.48, 4.28 (2H, d, d, *J* = 11.4 Hz, -OC<u>H</u>$_2$Ar), 4.21–4.13 (2H, m, 19-C<u>H</u> + 27-C<u>H</u>), 3.89–3.86 (1H, m, 21-C<u>H</u>), 3.79 (3H, s, ArO<u>Me</u>), 3.31 (3H, s, -O<u>Me</u>), 2.62–2.56 (2H, m, 22-C<u>H</u>$_{2A}$ + 26-C<u>H</u>$_{2A}$), 2.44–2.39 (2H, m, 18-C<u>H</u>$_{2A}$ + 22-C<u>H</u>$_{2B}$ or 26-C<u>H</u>$_{2B}$), 2.28 (1H, dd, *J* = 14.1, 6.5 Hz, 26-C<u>H</u>$_{2B}$ or 22-C<u>H</u>$_{2B}$), 2.11 (1H, dd, *J* = 13.6, 9.6 Hz, 18-C<u>H</u>$_{2B}$), 2.04–1.96 (2H, m, 16-C<u>H</u>$_2$), 1.75–1.72 (1H, m, 20-C<u>H</u>$_{2A}$), 1.73 (3H, d, *J* = 6.5 Hz, 30-C<u>H</u>$_3$), 1.41–1.37 (1H, m, 20-C<u>H</u>$_{2B}$), 1.10–1.06 (21H, m, -OSi(C<u>H</u>(C<u>H</u>$_3$)$_2$)$_3$), 1.01 (3H, t, *J* = 7.4 Hz, 16-C-C<u>H</u>$_3$); **^{13}C NMR** δ (62.5 MHz, $CDCl_3$) 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 $C_{35}H_{59}O_6Si$ $[MH]^+$: 603.4081, found: 603.4059; **m/z** (+FAB, NOBA) 603 ($[MH]^+$, 18), 559 (20), 379 (20), 353 (50), 295 (25), 243 (30), 157 (30), 137 (80), 121 (100%).

(6*R*)-2-((2'*S*,4'*S*)-2'-Methoxy-4'-(triisopropylsilyloxy)-6'-ethyl-hept-6'-ene)-6-(*E*-prop-2'-enyl)-5,6-dihydropyran-3-one (24)

To a cooled (0 °C), stirred solution of diketone **10** (19.5 mg, 0.032 mmol) in CH_2Cl_2 (0.5 mL) and pH 7 buffer solution (60 μL) was added DDQ (11.0 mg, 0.048 mmol, recrystallised from $CHCl_3$). 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 $NaHCO_3$ solution (4 mL, sat. aqueous) and CH_2Cl_2 (3 mL) and stirred for 5 mins. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were washed with $NaHCO_3$ solution (2 mL, sat. aqueous) and brine (3 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude product was filtered through a short plug of silica, initially eluting with CH_2Cl_2 to elute *p*-methoxybenzaldehyde, followed by elution with 50:50 EtOAc/hexanes to elute deprotection products. After removal of the solvent *in vacuo* the products were then dissolved in CD_2Cl_2 (2 mL) and PPTS (0.5 mg, 0.002 mmol) was added. 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: $\mathbf{R_f}$ 0.24 (25:75 EtOAc/hexanes);

$[\alpha]_D^{20}$ –53.5 (*c* 0.71, $CHCl_3$); **IR** (solution cell, $CHCl_3$) 2942, 1655 (s), 1602 (s) cm^{-1}; **^{1}H NMR** δ (500 MHz, $CDCl_3$) 5.83 (1H, dq, *J* = 15.3, 6.4 Hz, 29-C<u>H</u>), 5.62 (1H, ddq, *J* = 15.4, 6.7, 1.5 Hz, 28-C<u>H</u>), 5.36 (1H, s, 24-C<u>H</u>), 4.80–4.76 (1H, m, 27-C<u>H</u>), 4.78, 4.73 (2H, s, s, 17-C=C<u>H$_2$</u>), 4.20–4.17 (1H, m, 19-C<u>H</u>), 3.84–3.79 (1H, m, 21-C<u>H</u>), 3.32 (3H, s, -O<u>Me</u>), 2.55 (1H, partly overlapping dd, *J* = 14.0, 5.8 Hz, 22-C<u>H$_{2A}$</u>), 2.54–2.40 (3H, partly overlapping m, 26-C<u>H$_2$</u> + 18-C<u>H$_{2A}$</u>), 2.30 (1H, dd, *J* = 14.0, 7.5 Hz, 22-C<u>H$_{2B}$</u>), 2.09 (1H, dd, *J* = 13.5, 10.0 Hz, 18-C<u>H$_{2B}$</u>), 2.04–1.96 (2H, m, 16-C<u>H$_2$</u>), 1.76 (3H, partly overlapping d, *J* = 6.3 Hz, 30-C<u>H$_3$</u>), 1.73 (1H, partly overlapping ddd, *J* = 14.1, 9.8, 2.2 Hz, 20-C<u>H$_{2A}$</u>), 1.36 (1H, ddd, *J* = 14.2, 9.2, 2.6 Hz, 20-C<u>H$_{2B}$</u>), 1.12–1.05 (21H, m, -OSi(C<u>H</u>(C<u>H$_3$</u>)$_2$)$_3$), 1.02 (3H, app t, *J* = 7.4 Hz, 16-C-C<u>H$_3$</u>); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 192.6, 174.7, 147.9, 130.7, 127.9, 110.6, 105.9, 79.6, 75.0, 67.7, 56.3, 45.8, 42.0, 41.0, 39.6, 28.9, 16.31, 16.27, 17.8, 12.9, 12.2; **HRMS** (FIB, NOBA) Calc. for $C_{27}H_{49}O_4Si$ $[MH]^+$: 465.3400, found: 465.3396; **m/z** (FIB, NOBA) 465 ($[MH]^+$, 70), 421 (80), 295 (60), 243 (80), 157 (80), 137 (100).

(6*R*)-2-((2'*S*,4'*S*)-2'-Methoxy-6'-ethyl-hept-6'-en-4'-ol)-6-(*E*-prop-2'-enyl)-5,6-dihydropyran-3-one (9)

To a cold (–78 °C), stirred solution of pyranone **24** (7.2 mg, 0.016 mmol) in dry CH_2Cl_2 (3 mL) was added TMSOTf solution (70 μL, 1:19 in CH_2Cl_2, 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 CH_2Cl_2 (3 mL) and brine (2 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were washed with brine (3 mL) and dried (Na_2SO_4). 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: **R_f** 0.11 (20:80 EtOAc/hexanes); **^{1}H NMR** δ (500 MHz, $CDCl_3$) 5.86 (1H, dq, *J* = 15.3, 6.5 Hz, 29-C<u>H</u>), 5.65 (1H, dd, *J* = 15.4, 6.7 Hz, 28-C<u>H</u>), 5.39 (1H, s, 24-C<u>H</u>), 4.87 (1H, s, 17-C=C<u>H$_{2A}$</u>), 4.82–4.77 (1H, m, 27-C<u>H</u>), 4.81 (1H, s, 17-C=C<u>H$_{2B}$</u>), 4.00–3.93 (1H, m, 19-C<u>H</u>), 3.88–3.81 (1H, m, 21-C<u>H</u>), 3.40 (3H, s, -O<u>Me</u>), 2.58 (1H, dd, *J* = 13.9, 9.9 Hz, 22-C<u>H$_{2A}$</u>), 2.53 (1H, dd, *J* = 16.7, 11.8 Hz, 26-C<u>H$_{2A}$</u>), 2.44 (1H, dd, *J* = 16.8, 4.1 Hz, 22-C<u>H$_{2B}$</u>), 2.40 (1H, dd, *J* = 14.2, 6.2 Hz, 26-C<u>H$_{2B}$</u>), 2.33 (1H, br s, -O<u>H</u>), 2.18–2.16 (2H, m, 18-C<u>H$_2$</u>), 2.10–2.00 (2H, m, 16-C<u>H$_2$</u>), 1.77 (3H, d, *J* = 6.4 Hz, 30-C<u>H$_3$</u>), 1.68–1.61 (2H, m, 20-C<u>H$_2$</u>), 1.04 (3H, t, *J* = 7.4 Hz, 16-C-C<u>H$_3$</u>); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 192.4, 174.1, 148.0, 131.0, 127.8, 111.2, 106.0, 79.7, 76.2, 65.7, 57.6, 45.1, 41.0, 40.9, 39.8, 28.6, 17.8, 12.2.

(4*R*,6*S*,8*S*,10*S*) and (4*R*,6*S*,8*R*,10*S*)-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 CH_2Cl_2 (3 mL) was added TMSOTf solution (70 μL, 1:19 in CH_2Cl_2, 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 CH_2Cl_2 (3 mL) and brine (2 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were washed with brine (3 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue filtered through a short plug of silica (50:50 EtOAc/hexanes) and the solvent removed *in vacuo*. The residue was dissolved in dry CH_2Cl_2 (2 mL) and DBU solution added (180 μL, 1:9 in CH_2Cl_2, mmol). The reaction was stirred for 16 h at RT and quenched by the addition of NH_4Cl solution (1 mL, sat. aqueous). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (4 x 1 mL). The combined organic extracts were washed with brine (2 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the crude reaction mixture purified by flash chromatography (25:75 EtOAc/hexanes) to yield an *ca*. 60:40 mixture of spiroacetals **8** and **25**, respectively (3.1 mg, 67%). The spiroacetals could be separated by HPLC.

Major diastereomer **8**: R_f 0.25 (25:75 EtOAc/hexanes); **R_t** 23 min (35:65 EtOAc/hexanes); $[\alpha]_D^{20}$ +12.9 (*c* 0.24, $CHCl_3$); **IR** (solution cell) 1722 (s), 1601 cm^{-1}; **^{1}H NMR** δ (500 MHz, $CDCl_3$) 5.78 (1H, dq, *J* = 15.2, 6.5 Hz, 29-C<u>H</u>), 5.56 (1H, dd, *J* = 15.2, 7.1 Hz, 28-C<u>H</u>), 4.80–4.76 (1H,

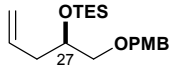
overlapping m, 27-C<u>H</u>), 4.78 (1H, overlapping s, 17-C=C<u>H</u>$_{2A}$), 4.73 (1H, s, 17-C=C<u>H</u>$_{2B}$), 3.62–3.57 (1H, m, 19-C<u>H</u>), 3.41 (1H, app tt, *J* = 11.4, 4.5 Hz, 21-C<u>H</u>), 3.34 (3H, s, -O<u>Me</u>), 2.85 (1H, d, *J* = 14.2 Hz, 24-C<u>H</u>$_{2A}$), 2.39 (1H, overlapping d, *J* = 14.1 Hz, 24-C<u>H</u>$_{2B}$), 2.39–2.37 (2H, overlapping m, 26-C<u>H</u>$_2$), 2.33 (1H, dd, *J* = 14.2, 7.7 Hz, 18-C<u>H</u>$_{2A}$), 2.26 (1H, dd, *J* = 12.4, 4.3 Hz, 22-C<u>H</u>$_{2A}$), 2.18 (1H, dd, *J* = 14.2, 5.2 Hz, 18-C<u>H</u>$_{2B}$), 2.06–2.02 (1H, m, 20-C<u>H</u>$_{2A}$), 2.01 (2H, app q, *J* = 8.2 Hz, 16-C<u>H</u>$_2$), 1.72 (3H, d, *J* = 6.5 Hz, 30-C<u>H</u>$_3$), 1.58–1.53 (1H, m partly obscured by H_2O, 22-C<u>H</u>$_{2B}$), 1.17 (1H, app q, *J* = 11.8 Hz, 20-C<u>H</u>$_{2B}$), 1.01 (3H, t, *J* = 7.4 Hz, 16-C-C<u>H</u>$_3$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 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 ($[MH]^+$, 30), 281 (40), 259 (25), 221 (40), 207 (60), 154 (90), 136 (100), 107 (60%).

Minor diastereomer **9**: **R_f** 0.31 (25:75 EtOAc/hexanes); **R_t** 21.5 min (35:65 EtOAc/hexanes); $[\alpha]_D^{20}$ +14.4 (*c* 0.34, $CHCl_3$); **IR** (solution cell) 1725, 1602 cm^{-1}; **^{1}H NMR** δ (500 MHz, $CDCl_3$) 5.72 (1H, dq, *J* = 15.1, 6.6 Hz, 29-C<u>H</u>), 5.48 (1H, dd, *J* = 15.3, 7.2 Hz, 28-C<u>H</u>), 4.81 (1H, s, 17-C=C<u>H</u>$_{2A}$), 4.76 (1H, s, 17-C=C<u>H</u>$_{2B}$), 4.53–4.48 (1H, m, 27-C<u>H</u>), 4.08–4.04 (1H, m, 19-C<u>H</u>), 3.69 (1H, app tt, *J* = 11.2, 4.4 Hz, 21-C<u>H</u>), 3.34 (3H, s, -O<u>Me</u>), 2.68 (1H, dd, *J* = 16.5, 11.1 Hz, 26-C<u>H</u>$_{2A}$), 2.58 (2H, ABq, *J* = 16.2 Hz, 24-C<u>H</u>$_2$), 2.36 (1H, dd, *J* = 16.5, 3.6 Hz, 26-C<u>H</u>$_{2B}$), 2.25–2.21 (2H, m, 18-C<u>H</u>$_{2A}$ + 22-C<u>H</u>$_{2A}$), 2.13 (1H, dd, *J* = 13.9, 5.7 Hz, 18-C<u>H</u>$_{2B}$), 2.08–2.05 (1H, m, 20-C<u>H</u>$_{2A}$), 2.03 (2H, app q, *J* = 7.4 Hz, 16-C<u>H</u>$_2$), 1.72 (3H, d, *J* = 6.4 Hz, 30-C<u>H</u>$_3$), 1.24 (1H, app t, *J* = 12.0 Hz, 20-C<u>H</u>$_{2B}$), 1.06 (1H, app q, *J* = 11.8 Hz, 22-C<u>H</u>$_{2B}$), 1.02 (3H, t, *J* = 7.4 Hz, 16-C-C<u>H</u>$_3$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 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 ($[MH]^+$, 65), 281 (40), 259 (50), 223 (80), 191 (70), 154 (70), 136 (80), 107 (100).

(3*R*,5*R*)-5-Benzyloxy-3-methoxyhexanal (28)

Ozone was bubbled through a cooled (–78 °C) solution of alkene **27** (6.81 g, 29.1 mmol) in CH_2Cl_2 (300 mL) until a slight blue colour developed. The flask was purged with O_2 for 10 mins and then PPh_3 (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_2O (100 mL) and the solid washed with Et_2O (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); $[\alpha]_D^{20}$ –30.8 (*c* 0.95, $CHCl_3$); **IR** (liquid film) 2827, 2727, 1724 (s), 1604 cm^{-1}; **^{1}H NMR** δ (500 MHz, $CDCl_3$) 9.73 (1H, br s, 19-C<u>H</u>), 7.25–7.36 (5H, m, <u>Ph</u>), 4.59 (1H, d, *J* = 11.5 Hz, OC<u>H</u>$_a$H$_b$Ph), 4.39 (1H, d, *J* = 11.5 Hz, OCH$_a$<u>H</u>$_b$Ph), 3.90 (1H, m, 21-C<u>H</u>), 3.63 (1H, m, 23-C<u>H</u>), 3.33 (3H, s, OC<u>H</u>$_3$), 2.46–2.55 (2H, m, 20-C<u>H</u>$_2$), 2.02 (1H, m, 22-C<u>H</u>$_a$H$_b$), 1.57 (1H, m, 22-CH$_a$<u>H</u>$_b$), 1.26 (3H, d, *J* = 6.0 Hz, 24-C<u>H</u>$_3$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 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** (+CI, NH_3) Calc. for $C_{14}H_{24}NO_3$ $[M + NH_4]^+$: 254.1756, found: 254.1756; **m/z** (+CI, NH_3) 254 ($[M + NH_4]^+$, 24), 222 (33), 162 (100), 114 (60), 97 (61).

(*R*)-5-(*p*-Methoxybenzyloxy)-4-(triethylsiloxy)-1-pentene (S3)

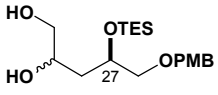


S3

To a cold (–78 °C), stirred solution of the alcohol **31** (900 mg, 4.05 mmol, 1.0 equiv.) in dry CH_2Cl_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 resultant solution was stirred at –78 °C for 2 h and then EtOH (5 mL) was added to quench the excess TESOTf. Saturated aqueous NH_4Cl (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_2O (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_2O/hexanes) to yield the TES ether **S3** (1.35 g, 99%), as a colourless oil: $\mathbf{R_f}$ 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** δ (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), 5.02–5.08 (2H, m, C=CH_2), 4.45 (2H, s, OCH_2Ar), 3.86 (1H, quin., *J* = 5.4 Hz, 27-CH), 3.81 (3H, s, OCH_3), 3.36 (2H, d, *J* = 5.4 Hz, 28-CH_2), 2.31–2.36 (1H, m, 26-CH_aH_b), 2.22 (1H, br quin., *J* = 6.9 Hz, 26-CH_aH_b), 0.94 (9H, t, *J* = 7.9 Hz, OSi(CH_2CH_3)$_3$), 0.59 (6H, q, *J* = 7.9 Hz, OSi(CH_2CH_3)$_3$); **^{13}C NMR** δ (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 $C_{19}H_{31}O_3Si$ $[M–H]^+$: 335.2043, found: 335.2023.

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



S4

A solution of alkene **S3** (9.42 g, 28.0 mmol) in 3:1 acetone (240 mL) and H_2O (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% $Na_2S_2O_3$ (100 mL) and the mixture stirred for 40 minutes before the addition of Et_2O (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_2SO_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: $\mathbf{R_f}$ 0.10 (30:70 EtOAc/hexanes); **IR** (liquid film) 3406 (br, s), 1612, 1586, 1514 cm^{-1}; **^{1}H NMR** δ (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_2Ar), 4.06–4.15 (1H, m, 25- or 27-CH), 3.92–3.94 (1H, m, 25- or 27-CH), 3.81 (3H, s, OCH_3), 3.35–3.61 (5H, m, 28-CH_2, CH_2OH, and 2° OH), 2.03, 2.09 (1H, t, 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_2CH_3)$_3$), 0.59–0.64 (6H, m, OSi(CH_2CH_3)$_3$); **^{13}C NMR** δ (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 $C_{19}H_{35}O_5Si$ $[MH]^+$: 371.2253, found: 371.2254.

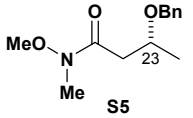
(*R*)-4-(*p*-Methoxybenzyloxy)-3-(triethylsiloxy)-butanal (7)

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_2O (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.) added and the resultant mixture allowed to warm to RT overnight. The mixture was concentrated *in vacuo* and H_2O (150 mL) was added to dissolve the precipitate. The solution was extracted with Et_2O (3 x 50 mL), the combined organic extracts were washed with brine (40 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (15:85 EtOAc/hexanes) afforded aldehyde **7** (4.41 g, 97%) as a colourless oil: $\mathbf{R_f}$ 0.85 (50:50 EtOAc/hexanes); **IR** (liquid film) 1726 (s), 1612, 1586 cm^{-1}; **^{1}H NMR** δ (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_2Ar), 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_aH_b), 3.36 (1H, dd, *J* = 9.5, 6.4 Hz, 28-CH_aH_b), 2.51–2.70 (2H, m, 26-CH_2), 0.92 (9H, t, *J* = 8.0 Hz, OSi(CH_2CH_3)$_3$), 0.59 (6H, q, *J* = 8.0 Hz, OSi(CH_2CH_3)$_3$); **^{13}C NMR** δ (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.

(2*R*,4*S*,6*R*,8*R*,10*S*)-8-(2-Allyl)-4-(*t*-butyldimethylsiloxy)-10-methoxy-2-(*p*-methoxybenzyloxymethyl)-1,7-dioxaspiro[5.5]undecane (33)

To a cold (–78 °C) solution of alcohol **3** (1.01 g, 2.58 mmol) in CH_2Cl_2 (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. $NaHCO_3$ (30 mL) and allowed to warm to RT. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL), combined organics were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (20:80 → 50:50 Et_2O/light petroleum) afforded the TBS ether **33** (1.30 g, 100%) as a colourless oil: $\mathbf{R_f}$ 0.25 (20:80 EtOAc/hexanes); $[\alpha]_D^{20}$ –10.3 (*c* 1.00, $CHCl_3$); **IR** (liquid film) 1641, 1612, 1586, 1513 cm^{-1}; **^{1}H NMR** δ (500 MHz, $CDCl_3$) 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*- *C*H=CH$_a$H$_b$), 5.03 (1H, d, *J* = 10.2 Hz, *cis*- *C*H=CH$_a$H$_b$), 4.59 (1H, m, 27-CH), 4.51 (2H, AB$_q$, *J* = 12.1 Hz, OCH$_2$Ar), 4.13 (1H, m, 25-CH), 3.80 (3H, s, ArOCH$_3$), 3.51–3.48 (3H, m, 19-CH + 28-CH$_2$), 3.46 (1H, m, 21-CH), 3.32 (3H, s, OCH$_3$), 2.43 (1H, m, 18-CH$_a$H$_b$), 2.25 (1H, m, 18-CH$_a$H$_b$), 2.10 (1H, dd, *J* = 14.3, 2.1 Hz, 24-CH$_{eq}$), 2.08–2.01 (2H, m, 20-CH$_{eq}$ + 22-CH$_{ax}$), 1.70 (1H, ddd, *J* = 13.7, 11.6, 3.5 Hz, 26-CH$_{eq}$), 1.60 (1H, m, 26-CH$_{ax}$), 1.49 (1H, dd, *J* = 14.3, 3.8 Hz, 24-CH$_{ax}$), 1.39 (1H, t, *J* = 11.9 Hz, 22-CH$_{ax}$), 1.12 (1H, br q, *J* = 11.7 Hz, 20-CH$_{ax}$), 0.89 (9H, s, SiC(CH$_3$)$_3$), 0.05 (3H, s, Si(CH$_3$)$_a$), 0.04 (3H, s, Si(CH$_3$)$_b$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 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 $C_{28}H_{46}O_6SiNa$ $[M + Na]^+$: 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)



S5

i-PrMgCl (2.0 M in THF, 30.0 mL, 60.0 mmol, 2.5 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. NH_4Cl (30 mL) and the cooling bath removed. H_2O (20 mL) and Et_2O (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), dried (Na_2SO_4) and concentrated *in vacuo*. 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: $\mathbf{R_f}$ 0.32 (60:40 EtOAc/hexanes); **^{1}H NMR** δ (500 MHz, $CDCl_3$) 7.29–7.38 (5H, m, Ph), 4.59 (1H, d, *J* = 11.6 Hz, OCH$_a$H$_b$Ph), 4.51 (1H, d, *J* = 11.6 Hz, OCH$_a$H$_b$Ph), 4.10 (1H, m, 23-CH), 3.66 (3H, s, OCH$_3$), 3.19 (3H, s, NCH$_3$), 2.90 (1H, m, 22-CH$_a$H$_b$), 2.46 (1H, dd, *J* = 15.1, 5.8, 22-CH$_a$H$_b$), 1.28 (3H, d, *J* = 6.1 Hz, 24-CH$_3$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 172.3, 138.8, 128.3, 127.7, 127.4, 72.3, 71.0, 61.3, 39.4, 32.1, 20.2.

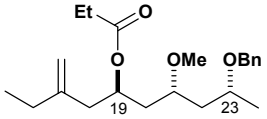
(*R*)-4-Benzyloxy-2-pentanone (37)

MeMgBr (3.0 M in Et_2O, 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

[4] D. Seebach, U. Braendli, P. Schnurrenberger, and M. Przybylski, *Helv. Chim. Acta*, 1988, **71**, 155-167; D. Seebach, A. K. Beck, R. Breitschuh, and K. Job, *Org. Synth.*, 1992, **71**, 39-47; M. Sasaki, N. Matsumori, T. Maruyama, T. Nonomura, M. Murata, K. Tachibana, and T. Yasumoto, *Angew. Chem. Int. Ed.*, 1996, **35**, 1672-1675.

stir at this temperature for 1 h before quenching with sat. NH_4Cl (40 mL). The biphasic mixture was warmed to RT. H_2O (20 mL) and Et_2O (20 mL) were added, the layers were separated and the aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) 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: $\mathbf{R_f}$ 0.32 (30:70 EtOAc/hexanes); $[\alpha]_D^{20}$ –29.6 (*c* 1.05, EtOH); **IR** (liquid film) 1715 (s), 1606 cm^{-1}; **^{1}H NMR** δ (500 MHz, $CDCl_3$) 7.27–7.35 (5H, m, Ph), 4.57 (1H, d, *J* = 11.5 Hz, OCH_aH_bPh), 4.46 (1H, d, *J* = 11.5 Hz, OCH_aH_bPh), 4.04 (1H, m, 23-CH), 2.79 (1H, dd, *J* = 15.8, 7.3 Hz, 22-CH_aH_b), 2.48 (1H, dd, *J* = 15.8, 5.3 Hz, 22-CH_aH_b), 2.16 (3H, s, 20-CH_3), 1.24 (3H, d, *J* = 6.1 Hz, 24-CH_3); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 207.3, 138.5, 128.3, 127.7, 127.6, 71.6, 70.8, 50.8, 31.0, 19.8.

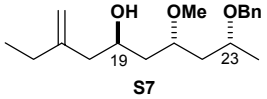
(4*R*,6*R*,8*R*)-8-Benzyloxy-2-ethyl-6-methoxy-4-propionoxy-1-nonene (S6)



S6

To a cooled (0 °C) solution of alcohol **41** (320 mg, 0.918 mmol) in CH_2Cl_2 (3 mL) was added proton sponge (985 mg, 4.60 mmol, 5 equiv.) followed by Me_3OBF_4 (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. NH_4Cl (10 mL) and the mixture diluted with Et_2O (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with saturated NH_4Cl (3 x 5 mL), dried (Na_2SO_4) 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: $\mathbf{R_f}$ 0.37 (20:80 EtOAc/hexanes); $[\alpha]_D^{20}$ –34.7 (*c* 1.41, $CHCl_3$); **IR** (liquid film) 2968, 2934, 1734 (s) cm^{-1}; **^{1}H NMR** δ (500 MHz, $CDCl_3$) 7.26–7.34 (5H, m, Ph), 5.26 (1H, m, 19-CH), 4.77 (1H, d, *J* = 1.4 Hz, C=CH_aH_b), 4.73 (1H, br s, C=CH_aH_b), 4.58 (1H, d, *J* = 11.6 Hz, OCH_aH_bPh), 4.42 (1H, d, *J* = 11.6 Hz, OCH_aH_bPh), 3.60 (1H, m, 23-CH), 3.37 (1H, m, 21-CH), 3.28 (3H, s, OCH_3), 2.33 (1H, br dd, *J* = 13.8, 7.3 Hz, 18-CH_aH_b), 2.26 (2H, q, *J* = 7.5 Hz, $COCH_2CH_3$), 2.17 (1H, br dd, *J* = 13.8, 6.1 Hz, 18-CH_aH_b), 2.06 (2H, app q, 16-CH_2), 1.97 (1H, m, 22-CH_aH_b), 1.60–1.70 (2H, m, 20-CH_2), 1.46 (1H, ddd, *J* = 14.1, 7.4, 4.7 Hz, 22-CH_aH_b), 1.23 (3H, d, *J* = 6.1 Hz, 24-CH_3), 1.10 (3H, t, *J* = 7.5 Hz, $COCH_2CH_3$), 1.01 (3H, t, *J* = 7.4 Hz, CH_2CH_3); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 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, NH_3) Calc. for $C_{22}H_{35}O_4$ $[MH]^+$: 363.2535, found: 363.2538; **m/z** (+CI, NH_3) 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).

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



S7

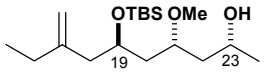
To a stirred solution of ester **S6** (295 mg, 0.814 mmol) in MeOH (4 mL) was added K_2CO_3 (47.7 mg , 0.345 mmol, 5.0 equiv.). After 48 h at RT, the reaction was quenched by the addition of H_2O (10 mL) and Et_2O (5 mL), the layers were separated and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (25:75 EtOAc/hexanes) gave alcohol **S7** (220 mg, 88%) as a colourless oil: $\mathbf{R_f}$ 0.19 (20:80 EtOAc/hexanes); $[\alpha]_D^{20}$ –40.3 (*c* 1.58, $CHCl_3$); **IR** (liquid film) 3454 (br, s), 2966, 2934, 1644 (w) cm^{-1}; **^{1}H NMR** δ (250 MHz, $CDCl_3$) 7.25–7.36 (5H, m, Ph), 4.84 (1H, br s, C=CH_aH_b), 4.79 (1H, br s, C=CH_aH_b), 4.59 (1H, d, *J* = 11.7 Hz, OCH_aH_bPh), 4.42 (1H, d, *J* = 11.7 Hz, OCH_aH_bPh), 3.97 (1H, m, 19-CH), 3.52–3.73 (2H, m, 21-CH + 23-CH), 3.36 (3H, s, OCH_3), 2.73 (1H, d, *J* = 3.0 Hz, OH), 1.98–2.17 (4H, m, 16-CH_2 + 18-CH_2), 1.48–1.71 (4H, m, 20-

C$\underline{H}_2$ + 22-C$\underline{H}_2$), 1.24 (3H, d, *J* = 6.1 Hz, 24-C$\underline{H}_3$), 1.04 (3H, t, *J* = 7.4 Hz, CH$_2$C$\underline{H}_3$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 150.2, 140.6, 130.2, 129.6, 112.5, 78.2, 73.7, 72.2, 68.2, 58.5, 46.8, 42.4, 41.7, 30.6, 21.8, 14.1; **HRMS** (+CI, NH_3) Calc. for $C_{19}H_{31}O_3$ $[MH]^+$: 307.2273, found: 307.2276; **m/z** (+CI, NH_3) 307 ($[MH]^+$, 6), 281 (4), 237 (7), 199 (8), 167 (22), 165 (13), 129 (15), 114 (38), 108 (67), 106 (72), 97 (64), 91 (92), 86 (42), 58 (67), 52 (42), 46 (63), 44 (100), 36 (91).

(4*R*,6*R*,8*R*)-8-Benzyloxy-4-(*t*-butyldimethylsiloxy)-2-ethyl-6-methoxy-1-nonene (42)

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 TBSCl (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 H_2O (10 mL) and Et_2O (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) 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: **R_f** 0.40 (10:90 EtOAc/hexanes); $[\alpha]_D^{20}$ –40.6 (*c* 1.91, $CHCl_3$); **IR** (liquid film) 1643 (w) cm^{-1}; **^{1}H NMR** δ (400 MHz, $CDCl_3$) 7.25–7.36 (5H, m, Ph), 4.77 (1H, d, *J* = 1.2 Hz, C=C$\underline{H}_a$H$_b$), 4.73 (1H, br s, C=CH$_a\underline{H}_b$), 4.57 (1H, d, *J* = 11.7 Hz, OC$\underline{H}_a$H$_b$Ph), 4.46 (1H, d, *J* = 11.7 Hz, OCH$_a\underline{H}_b$Ph), 4.04 (1H, m, 19-C$\underline{H}$), 3.57–3.64 (2H, m, 23-C$\underline{H}$ + 21-C$\underline{H}$), 3.30 (3H, s, OC$\underline{H}_3$), 2.33 (1H, dd, *J* = 13.6, 4.7 Hz, 18-C$\underline{H}_a$H$_b$), 2.12 (1H, dd, *J* = 13.6, 8.4 Hz, 18-CH$_a\underline{H}_b$), 1.99–2.06 (3H, m, 16-C$\underline{H}_2$ + 22-C$\underline{H}_a$H$_b$), 1.65 (1H, m, 20-C$\underline{H}_a$H$_b$), 1.40–1.47 (2H, m, 20-CH$_a\underline{H}_b$ + 22-CH$_a\underline{H}_b$), 1.23 (3H, d, *J* = 6.0 Hz, 24-C$\underline{H}_3$), 1.03 (3H, t, *J* = 7.4 Hz, 16-CH$_2$C$\underline{H}_3$), 0.90 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.09 (6H, s, Si(C$\underline{H}_3$)$_2$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 148.1, 138.9, 128.3, 127.6, 127.3, 110.6, 74.4, 72.0, 70.3, 67.7, 55.4, 45.7, 41.9, 29.0, 26.0, 20.0, 18.1, 12.3, –4.1, –4.6; **HRMS** (+ESI) Calc. for $C_{25}H_{45}O_3Si$ $[MH]^+$: 421.3138, found: 421.3136; **m/z** (+CI, NH_3) 421 ($[MH]^+$, 100), 319 (8), 289 (10), 257 (12), 106 (12).

(2*R*,4*R*,6*R*)-6-(*t*-Butyldimethylsiloxy)-8-ethyl-4-methoxy-non-8-en-2-ol (S8)



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. $NaHCO_3$ (5 mL) and warmed to RT. H_2O (10 mL) and Et_2O (10 mL) were added, the layers were separated and the aqueous phase was extracted with Et_2O (2 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) 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: **R_f** 0.41 (30:70 EtOAc/hexanes); $[\alpha]_D^{20}$ –5.2 (*c* 1.26, $CHCl_3$); **IR** (liquid film) 3442 (br), 1644 (w) cm^{-1}; **^{1}H NMR** δ (400 MHz, $CDCl_3$) 4.80 (1H, d, *J* = 1.3 Hz, C=C$\underline{H}_a$H$_b$), 4.74 (1H, br s, C=CH$_a\underline{H}_b$), 3.87–3.98 (2H, m, 19-C$\underline{H}$ + 23-C$\underline{H}$), 3.56 (1H, m, 21-C$\underline{H}$), 3.32 (3H, s, OC$\underline{H}_3$), 3.14 (1H, br s, O$\underline{H}$), 2.29 (1H, dd, *J* = 13.6, 5.1 Hz, 18-C$\underline{H}_a$H$_b$), 2.13 (1H, dd, *J* = 13.6, 8.0 Hz, 18-CH$_a\underline{H}_b$), 2.03 (2H, app q, 16-C$\underline{H}_2$), 1.82 (1H, ddd, *J* = 14.4, 6.1, 4.0 Hz, 20-C$\underline{H}_a$H$_b$), 1.66 (1H, app dt, *J* = 14.5, 8.8 Hz, 22-C$\underline{H}_a$H$_b$), 1.56 (1H, ddd, *J* = 14.5, 4.2, 3.0 Hz, 22-CH$_a\underline{H}_b$), 1.42 (1H, ddd, *J* = 14.4, 8.3, 5.6 Hz, 20-CH$_a\underline{H}_b$), 1.17 (3H, d, *J* = 6.3 Hz, 24-C$\underline{H}_3$), 1.03 (3H, t, *J* = 7.4 Hz, 16-CH$_2$C$\underline{H}_3$), 0.89 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.08 (6H, s, Si(C$\underline{H}_3$)$_2$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 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 $C_{18}H_{39}O_3Si$ $[MH]^+$: 331.2668, found: 331.2674; **m/z** (+CI, NH_3) 331 ($[MH]^+$, 14), 273 (13), 215 (33), 132 (100).

(4*S*,6*R*)-6-(*t*-Butyldimethylsiloxy)-8-ethyl-4-methoxy-8-nonen-2-one (43)

To a suspension of Dess–Martin periodinane (393 mg, 0.927 mmol, 2 equiv.) in CH_2Cl_2 (5 mL) was added pyridine (375 μL, 4.64 mmol, 10 equiv.). After 5 mins, alcohol **S8** (153 mg, 0.463 mmol) in CH_2Cl_2 (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. $NaHCO_3$ (5 mL), followed by 20% aq. $Na_2S_2O_3$ (5 mL) and the biphasic mixture was stirred vigorously for 30 mins. The mixture was concentrated *in vacuo*, Et_2O (10 mL) was added, the layers were separated and the aqueous phase was extracted with Et_2O (2 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (20:80 EtOAc/hexanes) afforded ketone **43** (148 mg, 97%) as a colourless oil: $\mathbf{R_f}$ 0.58 (30:70 EtOAc/hexanes); $[\alpha]_D^{20}$ –23.1 (*c* 2.63, $CHCl_3$); **IR** (liquid film) 1719 (s), 1644 cm^{-1}; **^{1}H NMR** δ (400 MHz, $CDCl_3$) 4.76 (1H, d, *J* = 1.5 Hz, C=C$\underline{H}_a$H$_b$), 4.71 (1H, br s, C=CH$_a\underline{H}_b$), 3.96 (1H, m, 19-C$\underline{H}$), 3.85 (1H, m, 21-C$\underline{H}$), 3.28 (3H, s, OC$\underline{H}_3$), 2.69 (1H, dd, *J* = 15.6, 6.4 Hz, 22-C$\underline{H}_a$H$_b$), 2.47 (1H, dd, *J* = 15.6, 5.9 Hz, 22-CH$_a\underline{H}_b$), 2.29 (1H, dd, *J* = 13.7 , 4.8 Hz, 18-C$\underline{H}_a$H$_b$), 2.14 (3H, s, 24-C$\underline{H}_3$), 2.09 (1H, dd, *J* = 13.7, 8.4 Hz, 18-CH$_a\underline{H}_b$), 2.00 (2H, app q, 16-C$\underline{H}_2$), 1.69 (1H, ddd, *J* = 14.2, 8.7, 3.0 Hz, 20-C$\underline{H}_a$H$_b$), 1.33 (1H, ddd, *J* = 14.2, 8.9, 3.7 Hz, 20-CH$_a\underline{H}_b$), 1.01 (3H, t, *J* = 7.4 Hz, 16-CH$_2$C$\underline{H}_3$), 0.88 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.07 (3H, s, Si(C$\underline{H}_3$)$_a$), 0.06 (3H, s, Si(C$\underline{H}_3$)$_a$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 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 $C_{18}H_{37}O_3Si$ $[MH]^+$: 329.2512, found: 329.2516; **m/z** (+CI, NH_3) 329 ($[MH]^+$, 100), 301 (37), 227 (29), 197 (41), 165 (40), 132 (80).

(2*R*,4*S*,6*R*,8*R*,10*S*)- and (2*R*,4*S*,6*S*,8*R*,10*S*)-8-(2-Ethylallyl)-10-methoxy-2-(*p*-methoxybenzyloxymethyl)-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. $NaHCO_3$ (10 mL) and diluted with Et_2O (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. $NaHCO_3$ (5 mL) and brine (5 mL), dried (Na_2SO_4) 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**: $\mathbf{R_f}$ 0.15 (7:30:63 Et_2O/CH_2Cl_2/hexanes); $[\alpha]_D^{20}$ +45.8 (*c* 1.84, $CHCl_3$); **IR** (liquid film) 3440 (br), 2931, 1612, 1513 cm^{-1}; **^{1}H NMR** δ (500 MHz, $CDCl_3$) 7.25 (2H, d, *J* = 8.5 Hz, Ar$\underline{H}$), 6.88 (2H, d, *J* = 8.5 Hz, Ar$\underline{H}$), 4.80 (1H, s, C=C$\underline{H}_a$H$_b$), 4.75 (1H, s, C=CH$_a\underline{H}_b$), 4.49 (1H, d, *J* = 11.5 Hz, OC$\underline{H}_a$H$_b$Ar), 4.45 (1H, d, *J* = 11.5 Hz, OCH$_a\underline{H}_b$Ar), 4.17–4.22 (2H, m, 25-C$\underline{H}$ + 27-C$\underline{H}$), 3.91 (1H, m, 19-C$\underline{H}$), 3.81 (3H, s, ArOC$\underline{H}_3$), 3.60 (1H, app tt, *J* = 11.2, 4.4 Hz, 21-C$\underline{H}$), 3.56 (1H, s, 28-C$\underline{H}_a$H$_b$), 3.55 (1H, d, *J* = 2.0 Hz, 28-CH$_a\underline{H}_b$), 3.32 (3H, s, OC$\underline{H}_3$), 2.33 (1H, dd, *J* = 12.6, 2.8 Hz, 22-C$\underline{H}_{eq}$), 2.25 (1H, dd, *J* = 13.6, 5.7 Hz, 18-C$\underline{H}_a$H$_b$), 2.09 (1H, dd, *J* = 13.6, 7.6 Hz, 18-CH$_a\underline{H}_b$), 1.96–2.08 (3H, m, 20-C$\underline{H}_{eq}$ + 24-C$\underline{H}_{eq}$ 26-C$\underline{H}_{eq}$), 1.50–1.60 (2H, m, 26-C$\underline{H}_{ax}$ + 24-C$\underline{H}_{ax}$), 1.41 (1H, br d, *J* = 2.8Hz, O$\underline{H}$), 1.20 (1H, br t, *J* = 12.0 Hz, 22-C$\underline{H}_{ax}$), 1.01 (3H, t, *J* = 7.3 Hz, 16-CH$_2$C$\underline{H}_3$), 0.98 (1H, br q, *J* = 11.5 Hz, 20-C$\underline{H}_{ax}$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 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 $C_{24}H_{36}O_6Na$ $[M + Na]^+$: 443.2410, found: 443.2424.

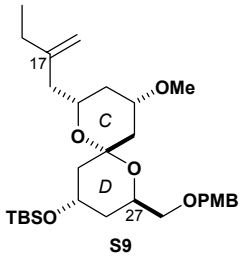
Minor spiroacetal (desired) **47**: $\mathbf{R_f}$ 0.26 (7:30:63 Et_2O/CH_2Cl_2/hexanes); $[\alpha]_D^{20}$ –32.9 (*c* 2.38, $CHCl_3$); **IR** (liquid film) 3519 (sharp), 2933, 1611, 1513 cm^{-1}; **^{1}H NMR** δ (500 MHz, $CDCl_3$) 7.27 (2H, d, *J* = 8.5 Hz, Ar$\underline{H}$), 6.87 (2H, d, *J* = 8.5 Hz, Ar$\underline{H}$), 4.89 (2H, s, C=C$\underline{H}_2$), 4.53 (2H, s, OC$\underline{H}_2$Ar), 4.42 (1H, m, 27-C$\underline{H}$), 4.04 (1H, app dt, *J* = 11.5, 2.9 Hz, 25-C$\underline{H}$), 3.80 (3H, s, ArOC$\underline{H}_3$), 3.70 (1H, m, 19-C$\underline{H}$), 3.50 (2H, app d, *J* = 4.4 Hz, 28-C$\underline{H}_2$), 3.48 (1H, d, *J* = 11.5 Hz, O$\underline{H}$), 3.46 (1H, app tt, *J* = 11.3, 4.5 Hz, 21-C$\underline{H}$), 3.34 (3H, s, OC$\underline{H}_3$), 2.38 (1H, dd, *J* = 13.5, 8.9 Hz, 18-C$\underline{H}_a$H$_b$), 2.25 (1H, br d, *J* = 14.3 Hz, 24-C$\underline{H}_{eq}$), 2.20 (1H, dd, *J* = 13.5, 3.5 Hz, 18-CH$_a\underline{H}_b$), 2.01–2.15 (4H, m, 16-C$\underline{H}_2$ + 22-C$\underline{H}_{eq}$ + 20-C$\underline{H}_{eq}$), 1.75 (1H, br d, *J* = 13.6 Hz, 26-C$\underline{H}_{eq}$), 1.65 (1H, dt, *J* =

13.6, 2.8 Hz, 26-C$\underline{H}_{ax}$), 1.41–1.47 (2H, m, 24-C$\underline{H}_{ax}$ + 22-C$\underline{H}_{ax}$), 1.27 (1H, br q, J = 11.7 Hz, 26-C$\underline{H}_{ax}$), 1.04 (3H, t, J = 7.4 Hz, 16-$CH_2C\underline{H}_3$); **^{13}C NMR** δ (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 $C_{24}H_{36}O_6Na$ $[M + Na]^+$: 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 μmol) in CH_2Cl_2 (2 mL) was treated with anhydrous HCl (2.0 M in Et_2O, 6.5 μL, 13 μmol, 0.1 equiv.) and the resultant solution allowed to stir at RT for 30 minutes. The mixture was cooled to 0 °C, Et_3N (30 μL, 215 μmol) was added dropwise and the solvent was removed *in vacuo*. The crude material was subjected to flash chromatography (40:40:20 EtOAc/CH_2Cl_2/hexanes) providing the desired **47** (23.8 mg, 43%) and undesired **46** (18.4 mg, 33%) spiroacetals.

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



S9

To a solution of alcohol **47** (23.6 mg, 56.1 μmol) in CH_2Cl_2 (2 mL) at –78 °C was added 2,6-lutidine (26 μL, 223 μmol, 4 equiv.) followed by TBSOTf (26 μL, 113 μmol, 2 equiv.). After 1 h at this temperature, the reaction was quenched by the addition of MeOH (250 μL). Sat. $NaHCO_3$ (5 mL) was added and the resultant mixture allowed to warm to RT. The mixture was partitioned between H_2O (10 mL) and Et_2O (10 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (2 x 10 mL), the combined organic extracts were washed with brine (5 mL), dried (Na_2SO_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); $[\alpha]_D^{20}$ –12.3 (*c* 2.30, $CHCl_3$); **IR** (liquid film) 2952, 2929, 1613, 1514 cm^{-1}; **^{1}H NMR** δ (400 MHz, $CDCl_3$) 7.25 (2H, dd, J = 6.8, 1.8 Hz, Ar$\underline{H}$), 6.85 (2H, dd, J = 6.8, 1.8 Hz, Ar$\underline{H}$), 4.78 (1H, d, J = 1.4 Hz, C=C$\underline{H}_a\underline{H}_b$), 4.73 (1H, br s, C=C$H_a\underline{H}_b$), 4.55 (1H, m, 27-C$\underline{H}$), 4.51 (2H, s, OC$\underline{H}_2$Ar), 4.12 (1H, quin., J = 3.9 Hz, 25-C$\underline{H}$), 3.79 (3H, s, ArOC$\underline{H}_3$), 3.64 (1H, m, 19-C$\underline{H}$), 3.48 (2H, d, J = 4.7 Hz, 28-C$\underline{H}_2$), 3.43 (1H, tt, J = 11.5, 4.5 Hz, 21-C$\underline{H}$), 3.31 (3H, s, OC$\underline{H}_3$), 2.47 (1H, dd, J = 13.8, 4.6 Hz, 18-C$\underline{H}_a$H$_b$), 2.18 (1H, dd, J = 13.8, 8.6 Hz, 18-CH$_a\underline{H}_b$), 2.02–2.10 (3H, m, 20-C$\underline{H}_{eq}$ + 22-C$\underline{H}_{eq}$ + 24-C$\underline{H}_{eq}$), 2.01 (2H, q, J = 7.4 Hz, 16-C$\underline{H}_2$), 1.72 (1H, ddd, J = 13.5, 11.3, 3.8 Hz, 26-C$\underline{H}_{eq}$), 1.57 (1H, dt, J = 13.5, 2.8 Hz, 26-C$\underline{H}_{ax}$), 1.53 (1H, dd, J = 14.3, 3.9 Hz, 24-C$\underline{H}_{ax}$), 1.35 (1H, t, J = 12.0 Hz, 22-C$\underline{H}_{ax}$), 1.08 (1H, app q, J = 11.8 Hz, 20-C$\underline{H}_{ax}$), 1.01 (3H, t, J = 7.4 Hz, 16-$CH_2C\underline{H}_3$), 0.88 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.04 (6H, s, Si(C$\underline{H}_3$)$_2$); **^{13}C NMR** δ (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 $C_{30}H_{50}O_6SiNa$ $[M + Na]^+$: 557.3274, found: 557.3309.

Formation of the CD-spiroacetal ethyl ketone (2)

A solution of alkene **S9** (22.6 mg, 42.3 μmol) in 2.5:1 acetone (1 mL) and H_2O (0.4 mL) was treated with NMO (15 mg, 128 μmol, 3 equiv.) and OsO_4 (0.1 M in *t*-BuOH, 21 μL, 2.1 μmol, 5 mol%), and the resultant mixture was stirred at RT for 6 h. The remaining oxidant was quenched by the addition of 20% aq.$Na_2S_2O_3$ (2 mL) and the mixture was stirred for 40 mins. Et_2O (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_2SO_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_2O (10 mL) and the resultant solution was extracted with Et_2O (3 x 3 mL). The combined organic extracts were washed with brine (2 mL), dried (Na_2SO_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.