Electronic Supplementary Material for Organic & Biomolecular Chemistry

The Stereocontrolled Total Synthesis of Altohyrtin A/Spongistatin 1. Part 3: The Southern Hemisphere EF 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 δ_{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, δ_{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 room temperature. Where a compound has been published in the literature, all spectroscopic and physical properties matched those reported.

Experimental Procedures and Product Characterisation Data

5-Chloropentanal (12)

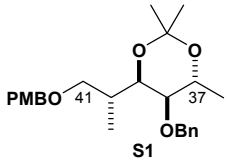
To a cold (–78 °C) solution of methyl 5-chlorovalerate (1.75 mL, 12.2 mmol) in PhMe (65 mL) was added DIBAL-H (1M in hexanes, 15.2 mL, 15.2 mmol, 1.25 equiv.) dropwise. The reaction was stirred at –78 °C for 3.5 h before being quenched by careful addition of aq. HCl (5%, 40 mL). The mixture was allowed to warm to RT and stirred vigorously for further 1 h. The layers were separated and the organic phase was washed with water (2 x 30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to approximately 5 g. The crude aldehyde **12** in PhMe was used without further purification: $\mathbf{R_f}$ 0.18 (15:85 EtOAc/hexanes); **^{1}H NMR** δ (500 MHz, $CDCl_3$) 9.79 (1H, s, 33-C<u>H</u>O), 3.42 (2H, t, *J* = 6.4 Hz, 29-C<u>H</u>$_2$), 2.49 (2H, t, *J* = 7.1 Hz, 32-C<u>H</u>$_2$), 1.88–1.94 (2H, m, 30-C<u>H</u>$_2$), 1.77–1.83 (2H, m, 31-C<u>H</u>$_2$).

(2*R*,4*S*,5*R*)-9-Chloro-5-triethylsiloxy-2-hydroxy-4-methyl-nonan-3-one (15)

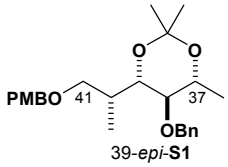
To a cold (0 °C) solution of *p*-methoxybenzyl ether **14** (2.97 g, 6.49 mmol) in CH_2Cl_2/pH7 buffer (10:1, 110 mL) was added DDQ (17.7 g, 77.9 mmol, 12 equiv.) over a period of 2 h (1 equiv. every 10 min). The reaction was quenched by pouring into sat. aq. $NaHCO_3$ (250 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL), combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (2.5:97.5 → 30:70 EtOAc/light petroleum) afforded alcohol **15** (1.88 g, 86%) as a colourless oil: $\mathbf{R_f}$ 0.50 (30:70 EtOAc/hexanes); $[\alpha]_D^{20}$ +2.7 (*c* 2.60, $CHCl_3$); **IR** (film) 3464 (br, OH), 2954, 2876, 1708 (C=O) cm^{-1}; **^{1}H NMR** δ (400 MHz, $CDCl_3$) 4.29–4.33 (1H, m, 36-C<u>H</u>), 3.97–4.00 (1H, m, 33-C<u>H</u>), 3.67 (1H, d, *J* = 4.8 Hz, O<u>H</u>), 3.51 (2H, t, *J* = 6.5 Hz, 29-C<u>H</u>$_2$), 2.95 (1H, qn, *J* = 7.1 Hz, 34-C<u>H</u>), 1.68–1.80 (2H, m, 30-C<u>H</u>$_2$), 1.40–1.57 (4H, m, 31-C<u>H</u>$_2$ + 32-C<u>H</u>$_2$), 1.35 (3H, d, *J* = 7.0 Hz, 36-CHC<u>H</u>$_3$), 1.13 (3H, d, *J* = 7.1 Hz, 34-CHC<u>H</u>$_3$), 0.96 (9H, t, *J* = 8.0 Hz, Si(CH_2C<u>H</u>$_3$)$_3$), 0.63 (6H, q, *J* = 8.0 Hz, Si(C<u>H</u>$_2$$CH_3$)$_3$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 215.4, 73.1, 71.8, 47.2, 44.8, 34.6, 32.6, 22.6, 19.7, 14.3, 6.9, 5.1.

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

(2*R*,3*R*,4*R*,5*R*)- and (2*R*,3*R*,4*S*,5*R*)-5-Benzyloxy-4-[1-(*p*-methoxybenzyloxy)-prop-2-(*R*)-yl]-2,2,6-trimethyl-1,3-dioxane (S1 and 39-*epi*-S1)



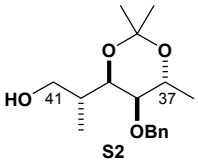
S1



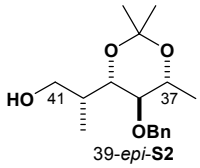
39-*epi*-**S1**

To a solution of diols **19** and 39-*epi*-**19** (*ca*. 4:1 mixture, 23.0 g, 61.5 mmol) in CH_2Cl_2/2,2-DMP (1:1, 500 mL) was added PPTS (cat.). The reaction was then stirred at RT for 16 h before being quenched by pouring into a solution of sat. aq. $NaHCO_3$ (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 200 mL). Combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (5:95 Et_2O/light petroleum → 75:25 EtOAc/light petroleum) afforded an inseparable mixture of the *syn* and *anti* acetonides, **S1** and 39-*epi*-**S1**, and recovered diols **19** and 39-*epi*-**19**. The recovered diols were re-subjected to the above conditions and after 5 cycles a *ca*. 4:1 mixture of acetonides **S1** and 39-*epi*-**S1**, respectively, (20.4 g, 80%) was obtained as a colourless oil. Characterisation of pure *anti* acetonide **S1**: $\mathbf{R_f}$ 0.52 (30:70 EtOAc/hexanes); $[\alpha]_D^{20}$ –11.8 (*c* 1.02, $CHCl_3$); **IR** (liquid film) 1612 (m), 1586 (w), 1513 (s), 1455 cm^{-1} (m); **^{1}H NMR** δ (500 MHz, $CDCl_3$) 7.30–7.38 (5H, m, ArH), 7.25 (2H, d, *J* = 8.6 Hz, ArH), 6.87 (2H, d, *J* = 8.6 Hz, ArH), 4.65 (1H, d, *J* = 11.5 Hz, OCH_aH_bAr), 4.47 (1H, d, *J* = 11.5 Hz, OCH_aH_bAr), 4.41 (2H, s, OCH_2Ar), 3.86–3.94 (1H, m, 37-CH), 3.80 (3H, s, $ArOCH_3$), 3.72 (1H, dd, *J* = 10.2, 3.1 Hz, 39-CH), 3.47–3.56 (2H, m, 41-CH_2), 3.37 (1H, dd, *J* = 5.4, 3.1 Hz, 38-CH), 2.19–2.29 (1H, m, 40-CH), 1.39 (3H, s, CMe_aMe_b), 1.31 (3H, d, *J* = 6.4 Hz, 36-CH_3), 1.28 (3H, s, CMe_aMe_b), 0.97 (3H, d, *J* = 6.8 Hz, 40-$CHCH_3$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 158.9, 138.3, 131.1, 129.1, 128.3, 127.9, 127.5, 113.6, 100.6, 82.5, 72.7, 72.7, 71.9, 71.4, 69.9, 55.2, 32.7, 24.9, 23.9, 21.3, 13.6; **HRMS** (+CI, NH_3) Calc. for $C_{25}H_{35}O_5$ $[M + H]^+$: 415.2484 found: 415.2484; **m/z** (+CI, NH_3) 415 ($[M + H]^+$, 17), 121 (100).

(4*R*,5*R*,6*R*)- and (4*R*,5*R*,6*S*)-5-Benzyloxy-4-[(1-hydroxy-prop-2-(*R*)-yl]-2,2,6-trimethyl-1,3-dioxane (S2 and 39-*epi*-S2)



S2



39-*epi*-**S2**

To a cold (0 °C) solution of acetonides **S1** and 39-*epi*-**S1** (*ca*. 4:1 mixture, 11.8 g, 28.5 mmol) in CH_2Cl_2/pH7 buffer (5:1, 144 mL) was added DDQ (7.76 g, 34.2 mmol, 1.2 equiv.). The reaction mixture was stirred at 0 °C for further 1.5 h before being quenched by addition of sat. aq. $NaHCO_3$ (200 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 150 mL). The combined organics were washed with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (10:90 → 50:50 EtOAc/light petroleum) afforded the 1,3-*syn* 1° alcohol and **S2** (1.61 g, 19%) and the 1,3-*anti* diastereomer 39-*epi*-**S2** (6.38 g, 76%) as colourless oils:

S2: $\mathbf{R_f}$ 0.44 (50:50 EtOAc/hexanes); $[\alpha]_D^{20}$ +20.1 (*c* 1.03, $CHCl_3$); **IR** (liquid film) 3456 (s, br), 1497 (w), 1454 (m), 1380 cm^{-1} (s); **^{1}H NMR** δ (400 MHz, $CDCl_3$) 7.25–7.40 (5H, m, Ph), 4.66 (1H, d, *J* = 11.5 Hz, OCH_aH_bPh), 4.49 (1H, d, *J* = 11.5 Hz, OCH_aH_bPh), 3.87–3.95 (1H, m, 37-CH), 3.69 (1H, dd, *J* = 9.8, 3.2 Hz, 39-CH), 3.58–3.63 (2H, m, 41-CH_2), 3.36 (1H, dd, *J* = 5.6, 3.2 Hz, 38-CH), 2.88 (1H, br s, OH), 2.24–2.35 (1H, m, 40-CH), 1.41 (3H, s, CMe_aMe_b), 1.36 (3H, s, CMe_aMe_b), 1.31 (3H, d, *J* = 6.4 Hz, 36-CH_3), 0.80 (3H, d, *J* = 6.8 Hz, 40-$CHCH_3$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 138.1, 128.4, 127.8, 127.6, 100.8, 82.1, 76.3, 73.0, 69.7, 68.0, 33.9, 25.2, 23.9, 21.1, 13.2; **HRMS** (+CI, NH_3) Calc. for $C_{17}H_{27}O_4$ $[MH]^+$: 295.1909, found: 295.1909; **m/z** (+CI, NH_3) 295 ($[MH]^+$, 25), 254 (82), 237 (100).

39-*epi*-**S2:** $\mathbf{R_f}$ 0.47 (50:50 EtOAc/hexanes); **^{1}H NMR** δ (400 MHz, $CDCl_3$) 7.27–7.41 (5H, m, Ph), 4.63 (1H, d, *J* = 10.7 Hz, OCH_aH_bPh), 4.58 (1H, d, *J* = 10.8 Hz, OCH_aH_bPh), 3.95 (1H, dd, *J* = 9.8 Hz, 2.1 Hz, 39-CH), 3.80–3.89 (1H, m, 37-CH), 3.73 (1H, dd, *J* = 10.7, 4.0 Hz, 41-CH_aH_b), 3.63 (1H, dd, *J* = 10.7, 5.6 Hz, 41-CH_aH_b), 3.06 (1H, app t, *J* = 9.4 Hz, 38-CH), 2.02–2.10 (1H, m, 40-CH), 1.46 (3H, s, CMe_aMe_b), 1.37 (3H, s, CMe_aMe_b), 1.31 (3H, d, *J* = 6.1 Hz, 36-CH_3), 1.02 (3H, d, *J* = 7.1 Hz, 40-CHCH_3).

(*S*)-2-[5-(*R*)-Benzyloxy-2,2,6-(6*R*)-trimethyl-1,3-dioxan-4-(*R*)-yl]-propionaldehyde (20)

To a solution of alcohol **S2** (6.57 g, 22.3 mmol) in CH_2Cl_2 (100 mL) was added Dess–Martin periodinane (18.9 g, 44.6 mmol, 2 equiv.). The reaction mixture was stirred at RT for 1 h and quenched by pouring into a sat. aq. $Na_2S_2O_3$/$NaHCO_3$ solution (1:1, 200 mL). The biphasic mixture was stirred for further 15 min and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 60 mL), combined organics were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (10:90 → 50:50 Et_2O/light petroleum) afforded aldehyde **20** (5.24 g, 80%), as a colourless oil: $\mathbf{R_f}$ 0.56 (50:50 Et_2O/hexanes); $[\alpha]_D^{20}$ +18.2 (*c* 0.93, $CHCl_3$); **IR** (liquid film) 1721 (s), 1455 (m), 1380 (s), 1224 cm^{-1} (s); **^{1}H NMR** δ (400 MHz, $CDCl_3$) 9.79 (1H, d, *J* = 2.8 Hz, 41-CHO), 7.23–7.38 (5H, m, ArH), 4.56 (1H, d, *J* = 11.5 Hz, OCH_aH_bAr), 4.47 (1H, d, *J* = 11.5 Hz, OCH_aH_bAr), 3.95 (1H, dd, *J* = 7.1, 3.6 Hz, 39-CH), 3.88 (1H, m, 37-CH), 3.36 (1H, dd, *J* = 6.0, 3.6 Hz, 38-CH), 2.70–2.78 (1H, m, 40-CH), 1.39 (3H, s, CMe_aMe_b), 1.30 (3H, s, CMe_aMe_b), 1.27 (3H, d, *J* = 6.4 Hz, 36-CH_3), 1.03 (3H, d, *J* = 7.1 Hz, 40-CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 204.4, 137.6, 128.4, 127.9, 127.9, 100.9, 82.5, 73.3, 72.3, 69.4, 45.1, 24.6, 23.8, 20.7, 11.3; **HRMS** (+CI, NH_3) Calc. for $C_{17}H_{25}O_4$ $[M + H]^+$: 293.1753, found: 293.1753; **m/z** (+CI, NH_3) 293 ($[M + H]^+$, 7), 217 (100).

(2*S*,3*R*)-7-Chloro-2-methyl-3-(triethylsiloxy)-heptanal (7)

To a cold (–78 °C) solution of ketone **15** (3.78 g, 11.2 mmol) in THF (200 mL) was added $LiAlH_4$ (1M in THF, 28.0 mL, 28.0 mmol, 2.5 equiv.) dropwisely. The reaction mixture was stirred at –78 °C for further 30 min then quenched by careful addition of MeOH (20 mL). The reaction was allowed to warm to RT and aq. sodium potassium tartrate (10%, 300 mL) was added. The mixture was vigorously stirred for 1 h and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 200 mL), combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (10:90 → 50:50 EtOAc/light petroleum) afforded a diastereomeric mixture of diols (3.65 g, 96%).

To a cold (0 °C) solution of the diols from the above procedure (1.66 g, 4.88 mmol) in CH_2Cl_2 (20 mL) was added Na_2CO_3 (1.04 g, 9.77 mmol, 2 equiv.) and $Pb(OAc)_4$ (2.60 g, 5.86 mmol, 1.2 equiv.). The reaction mixture was stirred at 0 °C for 40 min then filtered through a short pad of celite eluting with EtOAc/hexanes (1:1, 50 mL). The filtrate was concentrated to approximately one third volume, added heptane (30 mL) and concentrated *in vacuo*. Flash chromatography (2.5:97.5 → 25:75 Et_2O/light petroleum) afforded aldehyde **7** (1.30 g, 91%) as a colourless oil: $\mathbf{R_f}$ 0.45 (30:70 EtOAc/hexanes); $[\alpha]_D^{20}$ +39.3 (*c* 1.40, $CHCl_3$); **IR** (liquid film) 2954, 2876, 1726 (C=O) cm^{-1}; **^{1}H NMR** δ (500 MHz, $CDCl_3$) 9.78 (1H, s, 35-CHO), 4.08–4.12 (1H, m, 33-CH), 3.54 (2H, t, *J* = 6.5 Hz, 29-CH_2), 2.42–2.50 (1H, m, 34-CH), 1.78 (2H, quin., *J* = 6.6 Hz, 30-CH_2), 1.38–1.56 (4H, m, 31-CH_2 + 32-CH_2), 1.07 (3H, d, *J* = 7.0 Hz, 34-CHCH_3), 0.95 (9H, t, *J* = 7.9 Hz, Si(CH_2CH_3)$_3$), 0.59 (6H, q, *J* = 7.9 Hz, Si(CH_2CH_3)$_3$); **^{13}C NMR** δ (62.5 MHz, $CDCl_3$) 205.4, 71.9, 51.3, 44.8, 33.8, 32.4, 23.0, 7.8, 6.8, 4.9; **HRMS** (+ESI) Calc. for $C_{14}H_{29}O_2ClSiNa$ $[M + Na]^+$: 315.1523, found: 315.1541.

(2*R*,4*S*,5*S*,6*R*)-4-(*t*-butyldimethylsiloxy)-6-(4-chlorobutyl)-2-methoxy-2-[[4,5-(*R*,*R*)-*bis*-(*p*-methoxybenzyloxy)-3-(*R*)-methyl-6-(*R*)-(2-methylallyl)-tetrahydropyran-2-(*R*)-yl]-((*S*)-*p*-methoxybenzyloxy)-methyl]-5-methyl-tetrahydropyran (28)

To a solution of alcohol **27** (703 mg, 0.866 mmol) in DMF (3.6 mL) was added imidazole (708 mg, 10.4 mmol, 12 equiv.), TBSCl (1.31 g, 8.66 mmol, 10 equiv.) and Et_3N (242 μL, 1.74 mmol, 2.0 equiv.). The reaction mixture was stirred at RT for 48 h then quenched at 0 °C by the addition of MeOH (2.0 mL). The mixture was allowed to warm to RT and stirred for further 10 min. H_2O (20 mL) and Et_2O (20 mL) were added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 50 mL), combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (2.5:97.5 → 50:50 EtOAc/light petroleum) afforded TBS ether **28** (782 mg, 98%) as a colourless oil: $\mathbf{R_f}$ 0.45 (30:70 EtOAc/hexanes); $[\alpha]_D^{20}$ +9.2 (*c* 0.80, $CHCl_3$); **IR** (liquid film) 2933 cm^{-1}; **^{1}H NMR** δ (500 MHz, $CDCl_3$) 7.32 (2H, d, *J* = 8.4 Hz, ArH), 7.24 (4H, d, *J* = 8.4 Hz, ArH), 6.87 (2H, d, *J* = 8.1 Hz, ArH), 6.87 (2H, d, *J* = 8.5 Hz, ArH), 6.86 (2H, d, *J* = 8.1 Hz, ArH), 4.82 (1H, d, *J* = 11.5 Hz, OCH_aH_bAr), 4.76–4.80 (4H, m, $C{=}CH_2$ + OCH_2Ar), 4.73 (1H, d, *J* = 11.5 Hz, OCH_aH_bAr), 4.57 (1H, d, *J* = 10.6 Hz, OCH_aH_bAr), 4.50 (1H, d, *J* = 10.6 Hz, OCH_aH_bAr), 4.12–4.15 (1H, m, 33-CH), 3.81 (3H, s, $ArOCH_3$), 3.80 (3H, s, $ArOCH_3$), 3.80 (3H, s, $ArOCH_3$), 3.73–3.76 (1H, m, 35-CH), 3.60 (2H, t, *J* = 6.1 Hz, 29-CH_2), 3.46 (1H, s, 38-CH), 3.33 (1H, dd, *J* = 9.2, 1.8 Hz, 43-CH), 3.18 (1H, t, *J* = 9.0 Hz, 42-CH), 3.12 (3H, s, 37-$COCH_3$), 3.07–3.14 (2H, m, 39-CH + 41-CH), 2.49 (1H, d, *J* = 14.1 Hz, 44-CH_aH_b), 2.27 (1H, dd, *J* = 14.3, 9.3 Hz, 44-CH_aH_b), 2.15 (1H, dd, *J* = 15.6, 3.6 Hz, 36-CH_aH_b), 1.87 (2H, qn, *J* = 7.0 Hz, 30-CH_2), 1.73 (3H, s, 46-CH_3), 1.60–1.80 (4H, m, 31-CH_aH_b + 32-CH_aH_b + 36-CH_aH_b + 40-CH), 1.50–1.58 (1H, m, 31-CH_aH_b), 1.38–1.50 (2H, m, 32-CH_aH_b + 34-CH), 0.89 (9H, s, $SiC(CH_3)_3$), 0.88 (3H, d, *J* = 7.0 Hz, 34-$CHCH_3$), 0.40 (3H, d, *J* = 6.4 Hz, 40-$CHCH_3$), 0.05 (3H, s, $Si(CH_3)_a$), 0.01 (3H, s, $Si(CH_3)_b$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 159.3, 159.1, 159.1, 142.8, 131.2, 130.8, 130.6, 129.8, 129.5, 129.4, 113.8, 113.8, 113.6, 112.6, 102.6, 86.8, 82.8, 79.6, 77.7, 74.6, 74.4, 73.7, 72.8, 70.2, 66.7, 55.3, 55.3, 55.3, 47.1, 45.1, 39.3, 38.5, 38.0, 32.7, 32.3, 30.6, 25.7, 23.5, 22.6, 17.9, 12.5, 10.2, –4.7, –4.7; **HRMS** (+ESI) Calc. for $C_{52}H_{77}O_{10}ClSiNa$ $[M + Na]^+$: 947.4872, found: 947.4906.

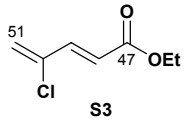
(2*R*,4*S*,5*S*,6*R*)-4-(*t*-butyldimethylsiloxy)-6-(4-chlorobutyl)-2-methoxy-2-[[4,5-(*R*,*R*)-*bis*-(*p*-methoxybenzyloxy)-3-(*R*)-methyl-6-(*R*)-(propanone)-tetrahydropyran-2-(*R*)-yl]-((*S*)-*p*-methoxybenzyloxy)-methyl]-5-methyl-tetrahydropyran (3)

To a solution of alkene **28** (1.96 g, 2.12 mmol) in acetone/H_2O (8:1, 45 mL) at RT was added Me_3NO (968 mg, 8.48 mmol, 4 equiv.) and OsO_4 (2.5 wt% in ^{t}BuOH, 558 μL, 0.042 mmol, 2 mol%). The reaction mixture was stirred at RT for 16 h then quenched by addition of sat. aq. $Na_2S_2O_3$ (50 mL) and Et_2O (50 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (30:70 → 100:0 EtOAc/light petroleum) afforded a diastereomeric mixture of diols (1.96 g, 97%).

To a cold (0 °C) solution of the diols from the above procedure (1.96 g, 2.04 mmol) in CH_2Cl_2 (150 mL) was added Na_2CO_3 (2.16 g, 20.4 mmol, 10 equiv.) and $Pb(OAc)_4$ (2.47 g, 6.12 mmol, 3.0 equiv.). The reaction mixture was stirred at 0 °C for 40 min then filtered through a short pad of celite eluting with EtOAc/hexanes (1:4, 100 mL). The filtrate was concentrated to approximately one third volume, added heptane (100 mL) and concentrated *in vacuo*. Flash chromatography (2.5:97.5 → 50:50 EtOAc/light petroleum) afforded ketone **3** (1.76 g, 93%) as a colourless oil: $\mathbf{R_f}$ 0.33 (30:70 EtOAc/hexanes); $[\alpha]_D^{20}$ +23.7 (*c* 0.50, $CHCl_3$); **IR** (liquid film) 2933, 1719 (C=O) cm^{-1}; **^{1}H NMR** δ (400 MHz, $CDCl_3$) 7.30 (2H, d, *J* = 8.6 Hz, ArH), 7.23 (2H, d, *J* = 8.3 Hz, ArH), 7.21 (2H, d, *J* = 8.2 Hz, ArH), 6.87 (4H, d, *J* = 8.6 Hz, ArH), 6.85 (2H, d, *J* = 8.6 Hz, ArH), 4.80 (1H, d, *J* = 11.4 Hz, OCH_aH_bAr), 4.80 (1H, d, *J* = 10.9 Hz, OCH_aH_bAr), 4.76 (1H, d, *J* = 10.7 Hz, OCH_aH_bAr), 4.70 (1H, d, *J* = 11.4 Hz, OCH_aH_bAr), 4.51 (1H, d, *J* = 10.7 Hz, OCH_aH_bAr), 4.51 (1H, d, *J* = 10.4 Hz, OCH_aH_bAr), 4.14 (1H, ddd, *J* = 8.3, 5.0, 1.7 Hz, 33-CH), 3.80 (6H, s, 2 x $ArOCH_3$), 3.80 (3H, s, $ArOCH_3$), 3.67–3.76 (2H, m, 35-CH + 43-CH), 3.60 (2H, t, *J* = 6.7 Hz, 29-

C$\underline{H}_2$), 3.46 (1H, s, 38-C$\underline{H}$), 3.22 (1H, d, J = 10.3 Hz, 39-C$\underline{H}$), 3.18 (1H, t, J = 9.1 Hz, 42-C$\underline{H}$), 3.13 (3H, s, 37-COC$\underline{H}_3$), 3.12 (1H, t, J = 9.3 Hz, 41-C$\underline{H}$), 2.63 (1H, dd, J = 15.7, 4.3 Hz, 44-C$\underline{H}_a$H$_b$), 2.56 (1H, dd, J = 15.8, 7.7 Hz, 44-CH$_a\underline{H}_b$), 2.07–2.11 (1H, m, 36-C$\underline{H}_a$H$_b$), 2.07 (3H, s, 46-C$\underline{H}_3$), 1.87 (2H, quin., J = 7.0 Hz, 30-C$\underline{H}_2$), 1.60–1.78 (3H, m, 31-C$\underline{H}_a$H$_b$ + 32-C$\underline{H}_a$H$_b$ + 40C$\underline{H}$), 1.52–1.60 (2H, m, 31-CH$_a\underline{H}_b$ + 36-CH$_a\underline{H}_b$), 1.35–1.50 (2H, m, 32-CH$_a\underline{H}_b$ + 34-C$\underline{H}$), 0.89 (9H, s, SiC(C$\underline{H}_3$)$_3$), 0.87 (3H, d, J = 7.4 Hz, 34-CHC$\underline{H}_3$), 0.44 (3H, d, J = 6.5 Hz, 40-CHC$\underline{H}_3$), 0.08 (3H, s, Si(C$\underline{H}_3$)$_a$), 0.01 (3H, s, Si(C$\underline{H}_3$)$_b$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 205.0, 159.4, 159.2, 159.2, 131.0, 130.6, 130.5, 129.4, 113.8, 113.8, 113.7, 102.4, 86.6, 82.0, 79.8, 75.5, 74.7, 74.2, 74.1, 73.3, 70.2, 66.8, 55.3, 55.3, 55.3, 47.3, 46.3, 45.0, 38.5, 38.0, 32.7, 32.2, 30.6, 30.4, 25.8, 23.5, 18.0, 12.5, 10.2, –4.7, –5.1; **HRMS** (+ESI) Calc. for $C_{51}H_{75}O_{11}ClSiNa$ $[M + Na]^+$: 949.4665, found: 949.4653.

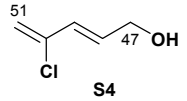
Ethyl (E)-4-chloro-2,4-pentadienoate (S3)



S3

NaHMDS (30.8 mL of a 1M solution in THF, 30.8 mmol) was added dropwise to a stirred solution of $(EtO)_2P(O)CH_2CO_2Et$ (6.28 g, 28 mmol) in THF (130 mL) at –78 °C. When the addition of the base was completed, two spatulas of catechol were added and the resulting mixture was stirred for 5 min. Freshly distilled 2-chloroacrolein[2] (3.8 g, 42 mmol) was then added and the resulting mixture was stirred for 2 h at –78 °C and then transferred to a freezer at –20 °C for 17 h. The reaction was quenched by addition of water (150 mL) at 0 °C. The reaction mixture was then diluted with Et_2O (150 mL) and the organic layer separated. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (15:85 EtOAc/hexanes) provided the desired ester **S3** as a colourless oil (3.95 g, 88%): **R_f** (15:85 EtOAc/hexanes) 0.42; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (1H, d, J = 15.0 Hz, C$\underline{H}$=CHCOOEt), 6.29 (1H, d, J = 15.0 Hz, C$\underline{H}$COOEt), 5.72 (1H, s, C$\underline{H}_2$=C(Cl)), 5.70 (1H, s, C$\underline{H}_2$=C(Cl)), 4.24 (2H, q, J = 7.1 Hz, OC$\underline{H}_2$), 1.31 (3H, t, J = 7.1 Hz, Me); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 166.0, 140.5, 136.8, 123.2, 122.6, 60.7, 14.1.

(*E*)-4-Chloro-2,4-pentadien-1-ol (S4)



S4

DIBAL (72.6 mL of a 1M solution in hexanes, 72.6 mmol) was slowly added to a stirred solution of ester **S3** (2.91 g, 18.14 mmol) in CH_2Cl_2 (200 mL) at –78 °C. After 1.5 h, TLC analysis of the reaction showed consumption of starting material. The reaction was quenched by addition of a solution of sodium potassium tartrate (54 g, 10 equiv.) in water (300 mL) at –78 °C. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) provided the desired alcohol (1.93 g, 90%) as a highly unstable oil that was dissolved in 40 mL of CH_2Cl_2 in order to form a 0.4M solution, for storage. This solution was been kept (covered from light in a freezer) for months without observing any loss of purity. **R_f** 0.10 (15:85 EtOAc/hexanes); **^{1}H NMR** δ (400 MHz, $CDCl_3$) 6.38 (1H, d, J = 15.0 Hz, 49-C$\underline{H}$), 6.25 (1H, dt, J = 15.0, 4.6 Hz, 48-C$\underline{H}$), 5.36 (2H, s, 51-C$\underline{H}_2$), 4.29 (2H, d, J = 4.6 Hz, 47-C$\underline{H}_2$), 1.81 (1H, br s, O$\underline{H}$); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 138.0, 133.7, 127.2, 115.5, 62.3.

(*E*)-4-Chloro-2,4-pentadienal (4)

[2] K. Griesbaum, A. R. Bandyopadhyay and M. Meister, *Can. J. Chem.*, 1986, **64**, 1553-1559.

To a cold (–78 °C) solution of $(COCl)_2$ (1M in CH_2Cl_2, 3.20 mL, 3.20 mmol, 2 equiv.) was added a solution of DMSO (1M in CH_2Cl_2, 6.39 mL, 6.39 mmol, 4 equiv.) dropwise. The reaction mixture was stirred at –78 °C for 5 min and a solution of the precursor 1° alcohol **S4** (1.69M in CH_2Cl_2, 0.944 mL, 1.60 mmol) was added and the resultant mixture was allowed to stir at –78 °C for further 15 min. Et_3N (1.34 mL, 9.61 mmol, 6 equiv.) was added and the reaction mixture was stirred at –78 °C for 1 h. The reaction was quenched by addition of water (20 mL) and allowed to warm to RT. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were washed with water (3 x 50 mL), dried (Na_2SO_4) and concentrated *in vacuo* (250 mmHg). Flash chromatography (100% CH_2Cl_2) through alumina column and concentration *in vacuo* (250 mmHg) afforded aldehyde **4** as a yellow oil which was used immediately in the subsequent reaction without further purification: $\mathbf{R_f}$ 0.38 (CH_2Cl_2); **^{1}H NMR** δ (400 MHz, $CDCl_3$) 9.70 (1H, d, J = 7.6 Hz, 47-C<u>H</u>O), 7.13 (1H, d, J = 15.0 Hz, 49-C<u>H</u>), 6.53 (1H, dd, J = 15.0, 7.6 Hz, 48-C<u>H</u>), 5.85 (1H, s, 51-C<u>H$_a$</u>H$_b$), 5.82 (1H, s, 51-CH$_a$<u>H$_b$</u>).

(4*S*)-1-[6-[[4-(*S*)-(*t*-Butyldimethylsiloxy)-6-(*R*)-(4-chlorobutyl)-2-(*R*)-methoxy-5-(*S*)-methyl-tetrahydropyran-2-yl]-(*S*)-(*p*-methoxybenzyloxy)-methyl]-(6*R*)-3,4-(*R*,*R*)-*bis*-(*p*-methoxybenzyloxy)-5-(*R*)-methyl-tetrahydropyran-2-(*R*)-yl]-4-(*t*-butyldimethylsiloxy)-7-chloro-octa-5,7-dien-2-one (34)

To a solution of aldol product **33** (377 mg, 0.36 mmol) in DMF (3.5 mL) was added imidazole (1.46 g, 21.4 mmol, 60 equiv.) and TBSCl (708 mg, 4.70 mmol, 13 equiv.). The reaction mixture was stirred at RT for 2 h then quenched at 0 °C by the addition of MeOH (3.0 mL). The mixture was allowed to warm to RT and stirred for further 10 min. Then sat. aq. $NaHCO_3$ (10 mL) and Et_2O (10 mL) were added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 20 mL), combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (5:95 → 40:60 EtOAc/light petroleum) afforded TBS ether **34** (390 mg, 93%) as a colourless oil: $\mathbf{R_f}$ 0.55 (30:70 EtOAc/hexanes); $[\alpha]_D^{20}$ +19.1 (*c* 0.64, $CHCl_3$); **IR** (liquid film) 2926, 1721, 1612, 1513 cm^{-1}; **^{1}H NMR** δ (500 MHz, $CDCl_3$) 7.28 (2H, d, J = 8.5 Hz, Ar<u>H</u>), 7.22 (2H, d, J = 8.4 Hz, Ar<u>H</u>), 7.21 (2H, d, J = 8.3 Hz, Ar<u>H</u>), 6.83–6.87 (6H, m, Ar<u>H</u>), 6.22 (1H, d, J = 14.9 Hz, 49-C<u>H</u>), 6.03 (1H, dd, J = 14.9, 5.5 Hz, 48-C<u>H</u>), 5.31 (1H, s, 51-C<u>H$_a$</u>H$_b$), 5.27 (1H, s, 51-CH$_a$<u>H$_b$</u>), 4.80 (1H, d, J = 10.9 Hz, OC<u>H$_a$</u>H$_b$Ar), 4.79 (1H, d, J = 11.5 Hz, OC<u>H$_a$</u>H$_b$Ar), 4.75 (1H, d, J = 10.6 Hz, OC<u>H$_a$</u>H$_b$Ar), 4.67 (1H, d, J = 11.5 Hz, OCH$_a$<u>H$_b$</u>Ar), 4.65–4.69 (1H, m, 47-C<u>H</u>), 4.56 (1H, d, J = 10.9 Hz, OCH$_a$<u>H$_b$</u>Ar), 4.49 (1H, d, J = 10.6 Hz, OCH$_a$<u>H$_b$</u>Ar), 4.13 (1H, t, J = 5.8 Hz, 33-C<u>H</u>), 3.80 (6H, s, 2 x ArOC<u>H$_3$</u>), 3.79 (3H, s, ArOC<u>H$_3$</u>), 3.71–3.76 (1H, m, 35-C<u>H</u>), 3.65–3.70 (1H, m, 43-C<u>H</u>), 3.60 (2H, t, J = 6.5 Hz, 29-C<u>H$_2$</u>), 3.45 (1H, s, 38-C<u>H</u>), 3.20 (1H, t, J = 10.7 Hz, 39-C<u>H</u>), 3.18 (1H, t, J = 9.3 Hz, 42-C<u>H</u>), 3.12 (3H, s, 37-COC<u>H$_3$</u>), 3.09–3.13 (1H, m, 41-C<u>H</u>), 2.62–2.68 (2H, m, 44-C<u>H$_a$</u>H$_b$ + 46-C<u>H$_a$</u>H$_b$), 2.53 (1H, dd, J = 15.5, 6.5 Hz, 44-CH$_a$<u>H$_b$</u>), 2.44 (1H, dd, J = 16.0, 6.0 Hz, 46-CH$_a$<u>H$_b$</u>), 2.07 (1H, dd, J = 15.3, 3.8 Hz, 36-C<u>H$_a$</u>H$_b$), 1.86 (2H, quin., J = 7.0 Hz, 30-C<u>H$_2$</u>), 1.66–1.78 (3H, m, 31-C<u>H$_a$</u>H$_b$ + 32-CH$_a$<u>H$_b$</u> + 40-C<u>H</u>), 1.50–1.62 (2H, m, 31-CH$_a$<u>H$_b$</u> + 36-CH$_a$<u>H$_b$</u>), 1.45–1.50 (1H, m, 34-C<u>H</u>), 1.36–1.42 (1H, m, 32-CH$_a$<u>H$_b$</u>), 0.89 (9H, s, SiC(C<u>H$_3$</u>)$_3$), 0.86 (9H, s, SiC(C<u>H$_3$</u>)$_3$), 0.86 (3H, d, J = 7.4 Hz, 34-CHC<u>H$_3$</u>), 0.46 (3H, d, J = 6.4 Hz, 40-CHC<u>H$_3$</u>), 0.08 (3H, s, SiC<u>H$_3$</u>), 0.01 (9H, s, 3 x SiC<u>H$_3$</u>); **^{13}C NMR** δ (100.6 MHz, $CDCl_3$) 205.4, 159.3, 159.2, 159.2, 138.1, 137.3, 130.9, 130.6, 130.6, 130.6, 129.5, 129.3, 126.4, 115.3, 113.8, 113.7, 102.4, 86.6, 81.9, 79.7, 75.1, 74.6, 74.2, 74.1, 73.4, 70.3, 68.6, 66.8, 55.3, 55.2, 51.6, 47.1, 46.7, 45.0, 38.5, 38.0, 32.7, 32.2, 29.7, 25.8, 25.8, 23.5, 18.1, 18.0, 12.5, 10.2, –4.4, –4.5, –4.9, –5.1; **HRMS** (+ESI) Calc. for $C_{62}H_{94}O_{12}Cl_2Si_2Na$ $[M + Na]^+$: 1179.5553, found: 1179.5499.