

A Concise Synthesis of the Octalactins

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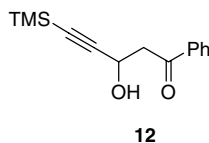
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Supporting Information

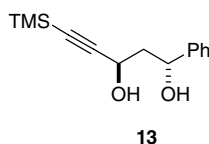
¹H NMR spectra were recorded on Bruker AC-200 (200 MHz), DPX-250 (250 MHz), WM-400 (400 MHz), AM-400 (400 MHz), DRX-400 and DRX-500 (500 MHz) spectrometers. Chemical shifts are quoted in ppm relative to tetramethylsilane ($\delta = 0$ ppm) and referenced to the solvent residual. For convenience, the following abbreviations are used; s - singlet, d - doublet, t - triplet, q - quartet, qn - quintet, m - multiplet, dd - doublet of doublets etc. Coupling constants (J) are given in Hz. Where useful, the FID was zero-filled (128 K) and sine-bell shifted (SSB = 30) prior to Fourier Transformation in order to provide baseline resolved multiplets and, as a result, easily identifiable and measurable coupling constants. Two dimensional (2D) spectra were recorded on a DRX-400 and a Bruker DRX-500 spectrometer fitted with gradient coils. Double Quantum Filtered (DQF) and magnitude COSY spectra were typically acquired with 256 slices in F_1 and 2048 points in F_2 (acquisition time approximately 20 min). 1D gradient NOE spectra were acquired using standard

Gauss selective pulses and mixing times (τ_m) of the order of 1.2 s.¹ ^{13}C NMR spectra were recorded on Bruker AC-200 (50 MHz), DPX-250 (62.5 MHz), AM-400 (100 MHz), WM-400 (100 MHz), DRX-400 (400 MHz), and WM-200 (50 MHz) spectrometers in the solvent indicated and with proton decoupling. Chemical shifts are quoted relative to tetramethylsilane ($\delta = 0$ ppm). The attached proton tests (APT) was used to assign signals in particular cases. Infrared spectra were recorded on a Perkin-Elmer 1600 FT IR spectrophotometer. The sample was prepared as a thin liquid film, a KBr disc or as a solution in the solvent indicated. Calibration was relative to polystyrene at 1603 cm^{-1} . Mass Spectra were carried out at the EPSRC Mass Spectrometry Service Centre, University of Swansea or at the Cambridge University Chemical Laboratory. In Swansea, Electron Impact (EI) and Chemical Ionization (CI) low resolution spectra were carried out on a VG model 12-253 (under ACE conditions) and a Quattro II low resolution triple quadrupole MS. Accurate mass measurements for EI and CI were performed on +VG ZAB-E and Finnigan MAT 900 XLT instruments. In Cambridge FAB, EI and CI, low resolution and accurate mass, spectra were performed on a KRATOS MS-890 and on a Micromass Q-TOF instrument. Electrospray spectra were determined with an ES Bruker FTICR. All CI measurements were performed with NH_3 as the carrier gas. Optical rotations were measured using a Perkin-Elmer 241 polarimeter, in a cell of 1 dm path length. The concentration (c) is expressed in g/100 mL (equivalent to g/0.1 dm³). Specific rotations denoted as $[\alpha]_D^T$, imply units of $^\circ\text{dm}^2\text{g}^{-1}$ ($T = \text{temp } ^\circ\text{C}$). Microanalyses were carried out by the staff of the Cambridge University Chemical Laboratory Microanalytical Department. Melting points (mp) were determined using a Kofler block or a Büchi 510 melting point apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was carried out on Merck pre-coated 0.25 mm thick plates of Kieselgel 60 F₂₅₄. Preparative layer chromatography was carried out on 1 mm thick plates (18 cm \times 20 cm) of Merck Kieselgel PF₂₅₄. Flash chromatography² was carried out using Merck Kieselgel 60 (230-400 mesh). Non-aqueous reactions were carried out under an atmosphere of dry argon unless indicated to the contrary. Dry THF was distilled from potassium in a recycling still using benzophenone ketyl as indicator. Other dry solvents were purified by standard techniques.³ Ether refers to diethyl ether. Light petroleum refers to

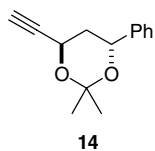
the fraction boiling between 40 °C and 60 °C. Brine refers to a saturated solution of sodium chloride in water.



3-Hydroxy-1-phenyl-5-trimethylsilyl-pent-4-yn-1-one 12. A solution of acetophenone (150 μ L, 1.29 mmol) and Et_3N (240 μ L, 1.72 mmol) in dry CH_2Cl_2 (12 mL) at -65 °C was treated with Bu_2BOTf (1.60 mL, 1 M in CH_2Cl_2 , 1.6 mmol), added *via* syringe at such a rate as to maintain the temperature below -60 °C. The mixture was stirred for 40 min, warmed to 0 °C over 10 min, stirred for 70 min and finally re-cooled to -60 °C. TMS-propynal **11b**⁴ (168 mg, 1.33 mmol) was added *via* cannula as a solution in CH_2Cl_2 (0.5 mL, 0.5 mL rinse) and the mixture was allowed to warm to 0 °C over 1 h. After an additional 1.5 h at 0 °C the reaction was quenched with a solution of methanol (8 mL), pH 7 buffer (4 mL) and H_2O_2 (100 v/v, 2 mL), allowed to warm to 20 °C and stirred for 1.5 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 \times 50 mL). The combined organic layers were washed with water (50 mL), dried (MgSO_4) and concentrated. The product was purified by flash chromatography (ethyl acetate:hexane, 1:9) to give the title compound **12** as a yellow oil (235 mg, 0.95 mmol, 74%); R_f (ethyl acetate:hexane, 3:7) 0.38; ^1H NMR (250 MHz, CDCl_3) δ 7.98-7.95 (m, 2H), 7.64-7.57 (m, 1H), 7.50-7.44 (m, 2H), 5.00 (dd, J = 8.2, 3.6 Hz, 1H), 3.47 (dd, J = 17.7, 8.2 Hz, 1H), 3.34 (dd, J = 17.7, 3.6 Hz, 1H), 3.00-2.50 (s, 1H), 0.16 (s, 9H); ^{13}C NMR (62.5 MHz, CDCl_3) 198.9, 136.4, 133.8, 128.8, 128.2, 104.8, 90.1, 59.1, 45.5, -0.2; IR (film) 3540-3160, 1670 cm^{-1} ; MS (CI, NH_3) m/z (rel intensity) 247 [100, ($\text{M} + \text{H}$)⁺]; HRMS (CI, NH_3) m/z 247.1154 (247.1155 calcd for $\text{C}_{14}\text{H}_{19}\text{O}_2\text{Si}$, MH). Anal. Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_2\text{Si}$: C, 68.3; H, 7.4. Found: C, 68.2; H, 7.4.



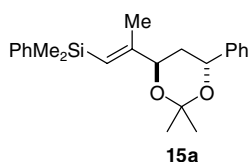
1(*R*^{*}),3(*R*^{*})-1-Phenyl-5-trimethylsilyl-pent-4-yne-1,3-diol 13. To a cooled (-35 °C) solution of tetramethylammonium triacetoxy borohydride (1.72 g, 6.54 mmol) in acetonitrile (6 mL) and dry AcOH (3 mL), **12** (340 mg, 1.38 mmol) was added *via* cannula as a solution in acetonitrile (1 mL, 1 mL rinse). The mixture was stirred for 30 min then warmed to -20 °C and stirred for 18 h. The reaction was quenched with 0.5 M aqueous Rochelle's salt (15 mL) and allowed to warm to 20 °C over 2 h. The mixture was poured onto ice, neutralized with saturated NaHCO₃ solution and extracted with CH₂Cl₂ (3 × 50 mL). The aqueous layer was saturated with solid NaCl and extracted with EtOAc (50 mL) and the combined organic layers were washed with saturated NaHCO₃ (50 mL), dried (MgSO₄) and concentrated *in vacuo* to yield the title compound **13** as a white solid (309 mg, 1.24 mmol, 90%); *R_f* (ethyl acetate:hexane, 3:7) 0.25; m.p. 92-94 °C (EtOAc/hexane); ¹H NMR (200 MHz, CDCl₃) δ 7.38-7.28 (m, 5H), 4.63 (m, 1H), 4.22 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.00 (s, 1H), 2.66 (s, 1H), 2.22-2.12 (ddd, *J* = 14.5, 9.2, 4.0 Hz, 1H), 2.09-1.97 (ddd, *J* = 14.5, 6.4, 3.2 Hz, 1H), 1.19 (s, 9H); ¹³C NMR (62.5 MHz, CDCl₃) δ 143.9, 128.7, 127.8, 125.8, 106.0, 90.5, 72.1, 61.4, 45.0, 0.0; IR (film) 3540-3140 cm⁻¹; MS (CI, NH₃) *m/z* (rel intensity) 266 [60, (M + NH₄)⁺], 248 [100, (M + H)⁺]; HRMS (CI, NH₃) *m/z* 266.1576 (266.1577 calcd for C₁₄H₂₄NO₂Si, MNH₄). Anal. Calcd for C₁₄H₂₀O₂Si: C, 67.7; H, 8.1. Found: C, 67.5; H, 8.1.



4(*R*^{*}),6(*R*^{*})-4-Ethynyl-2,2-dimethyl-6-phenyl-[1,3]dioxane, 14. A solution of **13** (285 mg, 1.15 mmol) in MeOH (5 mL) at 0 °C was treated with a solution of 2 N aqueous NaOH (5 mL) in MeOH (15 mL). After 10 min, the mixture was diluted with water (50 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. The product was purified by flash chromatography (ethyl acetate:hexane, 1:5) to give 1(*R*^{*}),3(*R*^{*})-1-phenyl-pent-4-yne-1,3-diol (181 mg, 1.03 mmol, 89%) as a light straw-colored oil; *R_f* (ethyl acetate:hexane, 3:7) 0.13; ¹H

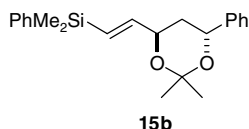
NMR (200 MHz, CDCl₃) δ 7.46-7.24 (m, 5H), 5.26 (dd, J = 9.6, 3.0 Hz, 1H), 4.67-4.62 (m, 1H), 2.78 (s, 2H), 2.55 (d, J = 2.2 Hz, 1H), 2.27-2.16 (ddd, J = 14.6, 9.6, 3.0 Hz, 1H), 2.07-1.98 (ddd, J 14.6, 6.2, 3.0 Hz, 1H); ¹³C NMR (62.5 MHz, CDCl₃) δ 143.8, 128.8, 128.0, 125.8, 84.3, 73.7, 72.2, 60.9, 44.6; IR (film) 3520-3100, 3270 cm⁻¹; MS (CI, NH₃) m/z (rel intensity) 194 [35, (M + NH₄)⁺], 176 [100, (M + H)⁺]; HRMS (CI, NH₃) m/z 194.1181 (194.1182 calcd for C₁₄H₂₄NO₂Si, MNH₄). Anal. Calcd for C₁₁H₁₂O₂: C, 75.0; H, 6.9. Found: C, 74.7; H, 6.9.

A solution of 1(*R*^{*}),3(*R*^{*})-1-phenyl-pent-4-yne-1,3-diol (556 mg, 3.16 mmol) and PPTS (136 mg, 0.541 mmol) in acetone (6 mL) at 0 °C was treated with 2-methoxypropene (0.60 mL, 6.26 mmol). After 3 h additional 2-methoxypropene (0.40 mL, 4.18 mmol) was added. The mixture was stirred for 30 min and then poured into water (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate:hexane, 1:19) afforded the acetonide **14** (613 mg, 2.83 mmol, 90%) as a clear colorless oil; R_f (ethyl acetate:hexane, 3:7) 0.63; ¹H NMR (400 MHz, C₆D₆) δ 7.35-7.32 (m, 2H), 7.26-7.10 (m, 3H), 5.25 (dd, J = 10.9, 3.5 Hz, 1H), 4.73 (m, 1H), 2.07 (d, J = 2.3 Hz, 1H), 2.02-1.91 (m, 1H), 1.86-1.75 (m, 1H), 1.79 (s, 3H), 1.55 (s, 3H); ¹³C NMR (62.5 MHz, CDCl₃) δ 142.6, 128.7, 127.7, 126.3, 100.9, 85.1, 74.3, 68.1, 60.4, 38.8, 23.7; IR (film) 3270 cm⁻¹.

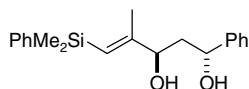


(*E*),4(*R*^{*}),6(*R*^{*})-4-[2-(1-Phenyldimethylsilyl)propenyl]-6-phenyl-2,2-dimethyl-1,3-dioxane 15a. A cooled (-20 °C) solution of phenyldimethylsilyllithium (1.4 mmol) in THF (10 mL) was added to a dry flask containing CuCN (62.8 mg, 0.70 mmol), and the dark red solution was stirred at 0 °C for 45 min. The mixture was cooled to -60 °C and treated with a solution of the alkyne **14** (111 mg, 0.513 mmol) in THF (3 mL). After 10 min the mixture was allowed to warm to 0 °C, was stirred for 45 min and

was then treated with MeI (150 μ L, 2.41 mmol). The mixture was allowed to warm to 20 °C and stirred for 14 h after which the red color had faded. The reaction was quenched by the addition of saturated aqueous NH_4Cl (15 mL), diluted with water (50 mL) and extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (100 mL), dried (MgSO_4) and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate:hexane, 1:49) provided the title compound **15a** (106 mg, 0.289 mmol, 56%) as well as some recovered **14** (54.7 mg, 0.253 mmol, 49%; including minor impurities). *Data for 15a*; R_f (ethyl acetate:hexane, 1:19) 0.13; ^1H NMR (250 MHz, C_6D_6) δ 7.63-7.50 (m, 2H), 7.37-7.10 (m, 8H), 5.99 (s, 1H), 4.90 (dd, $J = 9.2, 6.8$ Hz, 1H), 4.36 (t, $J = 7.9$ Hz, 1H), 2.06-1.88 (m, 2H), 1.72 (s, 3H), 1.46 (s, 3H), 1.45 (s, 3H), 0.42 (s, 6H); ^{13}C NMR (250 MHz, C_6D_6) δ 156.2, 143.4, 139.8, 134.1, 129.2, 128.5, 127.4, 126.1, 119.8, 101.1, 72.1, 68.8, 40.1, 25.1, 25.0, 18.3, -0.8; IR (film) 1625, 1175 cm^{-1} ; MS (CI, NH_3) m/z (rel intensity) 367 [2, ($\text{M} + \text{H}$) $^+$].

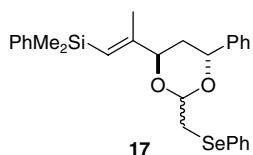


(*E*),4(*R* *),6(*R* *)-4-[2-(1-Phenyldimethylsilyl)vinyl]-6-phenyl-2,2-dimethyl-1,3-dioxane 15b. R_f (ethyl acetate:hexane, 1:9) 0.40; ^1H NMR (250 MHz, CDCl_3) δ 7.55-7.49 (m, 2H), 7.33-7.09 (m, 8H), 6.31 (dd, $J = 18.9, 4.2$ Hz, 1H), 6.09 (dd, $J = 18.9, 1.2$ Hz, 1H), 4.87 (dd, $J = 9.0, 6.7$ Hz, 1H), 4.50-4.40 (m, 1H), 1.93-1.83 (m, 2H), 1.44 (s, 3H), 1.43 (s, 3H), 0.32 (s, 6H); IR (film) 1620 cm^{-1} .



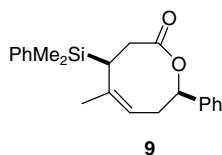
(*E*),1(*R* *),5(*R* *)-4-Methyl-1-phenyl-5-(phenyldimethylsilyl)-1,3-dihydroxy-pent-4-ene. A solution of the acetonide **15a** (100 mg, 0.27 mmol) in THF (2 mL) was stirred vigorously with 1 N HCl (2 mL) at 20 °C for 1.5 h. The mixture was dissolved in water (20 mL) and extracted with EtOAc (2×50

mL). The combined organic extracts were washed with water (20 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate:hexane, 1:49→1:9) yielded the title compound (45.6 mg, 0.14 mmol, 52%); *R_f* (ethyl acetate:hexane, 3:7) 0.23; ¹H NMR (400 MHz, CDCl₃) δ 7.54-7.49 (m, 2H), 7.40-7.25 (m, 8H), 5.78 (s, 1H), 4.98 (dd, *J* = 8.9, 2.8 Hz, 1H), 4.29 (dd, *J* = 7.6, 2.9 Hz, 1H), 2.05 (ddd, *J* = 14.6, 8.8, 3.3 Hz, 1H), 1.89 (ddd, *J* = 14.7, 7.6, 2.9 Hz, 1H), 1.67 (s, 3H), 0.42 (s, 6H); IR (film) 3520-3200, 1605 cm⁻¹.



(*E*),4(*R*^{*}),6(*R*^{*})-6-Phenyl-[4-(1-Phenyldimethylsilyl)propenyl]-2-phenylselanyl methyl-

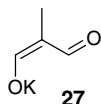
[1,3]dioxane, 17. A solution of the diol (*E*),1(*R*^{*}),5(*R*^{*})-4-methyl-1-phenyl-5-(phenyldimethylsilyl)-1,3-dihydroxy-pent-4-ene (48.3 mg, 0.148 mmol), phenylselenoacetaldehyde diethylacetal **16** (52.1 mg, 0.191 mmol) and PPTS (*ca.* 5 mg) in toluene (2 mL) was heated at reflux for 1 h. The mixture was then poured into water (50 mL) and extracted with Et₂O (3 × 50 mL). The combined organic layers were washed with water (20 mL), dried (MgSO₄) and evaporated *in vacuo*. Purification by flash chromatography (diethyl ether:hexane, 3:97) gave the title compound (47.6 mg, 0.094 mmol, 63%) as a clear colorless oil; *R_f* (ethyl acetate:hexane, 1:9) 0.53; ¹H NMR (200 MHz, CDCl₃) δ (mixture of diastereomers) 7.57-7.14 (m, 15H), 5.82 and 5.69 (2 × s, 1H), 5.34-5.32 (m, 0.5H), 5.15-4.98 (m, 1H), 4.60-4.59 (m, 0.5H), 4.14-4.05 (m, 1H), 3.12-3.07 (m, 2H), 2.33-2.16 (m, 2H), 1.82 and 1.72 (2 × s, 3H), 0.42 and 0.39 (2 × s, 6H).



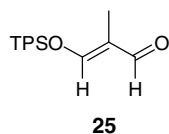
4(S*),8(R*)-5-Methyl-8-phenyl-4-(phenyldimethylsilyl)-3,4,7,8-tetrahydro-oxocin-2-one 9. To a solution of the selenides **17** (28 mg, 55 μ mol) in a mixture of methanol (6 mL, water (1 mL) and ethyl acetate (2 mL) was added sodium hydrogencarbonate (24 mg, 0.8 mmol) and sodium periodate (58 mg, 0.7 mmol). The resulting suspension was stirred for 1.5 h and was then poured into water. Ethyl acetate and hexane were added and the organic phase was separated, dried (MgSO₄) and concentrated *in vacuo*. Residual solvent was removed under reduced pressure for 18 h to give the corresponding selenoxides which were used in the next reaction without further purification. The selenoxides were dissolved in xylene (4 mL), 1-*tert*-butyldimethylsiloxy-1-methoxy-ethene **18** (806 mg, 4.28 mmol) and DBU (40 μ L, 0.27 mmol) were added. The resulting solution was heated in a NaOH-washed sealed tube at 185 °C for 5 h. The xylene was removed under high vacuum and the residue subjected to flash chromatography (ethyl acetate:hexane, 1:19 to 1:9) to provide the title lactone **9** (6 mg, 0.017 mmol, 31%); *R_f* (ethyl acetate:hexane, 1:9) 0.28; ¹H NMR (400 MHz, C₆D₆) δ 7.24-7.03 (m, 10H), 5.18 (t, *J* = 8.7 Hz, 1H), 5.12 (t, *J* = 8.5 Hz, 1H), 2.39 (t, *J* = 12.5 Hz, 1H), 2.34 (dd, *J* = 12.5, 6.4 Hz, 1H), 2.22-2.17 (m, 2H), 2.13-2.08 (m, 1H), 1.51 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H); ¹³C NMR (400 MHz, C₆D₆) δ 174.0, 142.3, 141.5, 137.0, 134.2, 129.6, 128.7, 125.8, 118.5, 75.6, 37.6, 33.6, 33.4, 26.7, -3.6, -3.9; IR (film) 1720 cm⁻¹; MS (CI, NH₃) *m/z* (rel intensity) 351 [16, (M + H)⁺]; HRMS (CI, NH₃) *m/z* 351.1780 (351.1781 calcd for C₂₇H₂₇O₂Si, MH).

1,1,3,3-Tetraethoxy-2-methyl-propane.⁵ To degassed triethyl orthoformate (100.5 mL, 600 mmol) was added boron trifluoride etherate (0.42 mL, 3.0 mmol) followed by the dropwise addition of ethyl 1-propenyl ether (33.0 mL, 300 mmol) maintaining the temperature below 45 °C. After the addition was complete (10 min), the mixture was heated at 45 °C for 1 h. Solid sodium carbonate (3.0 g) was added and stirring was continued for a further 3 h after which the mixture was allowed to cool. Purification *via* reduced pressure distillation provided the title compound as a clear and colorless

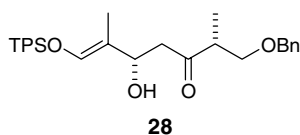
liquid (62.0 g, 260 mmol, 88%); bp 60-65 °C / 0.3 mm Hg; ^1H NMR (250 MHz, CDCl_3) δ 4.43 (d, J = 5.7 Hz, 2H), 3.73-3.45 (m, 8H), 2.09-1.95 (m, 1H), 1.20 (td, J = 7.0, 3.1 Hz, 12H), 0.95 (d, J = 6.9 Hz, 3H).



Potassium 2-methyl-3-oxo-propen-1-olate 27. From 1,1,3,3-tetraethoxy-2-methyl-propane.⁶ Hydrochloric acid (6 M, 17.0 mL) was added to a stirring solution of 1,1,3,3-tetraethoxy-2-methyl-propane and the mixture was stirred at 80 °C for 1 h resulting in the reaction mixture becoming a dark amber color developed. The mixture was then cooled in an ice bath and adjusted to pH 13 with 5 M aqueous potassium hydroxide solution (45 mL). The crude residue was washed with ether (20 mL) and the aqueous layer was concentrated under vacuum (15 mm Hg) for 1 hour. The resultant solid was re-dissolved in hot absolute ethanol, as filtered and re-concentrated to a yield a light brown solid. The product was dried at 90-100 °C under high vacuum to provide the title compound **27** (13.3 g, 0.107 mmol, 87%). The salt was used in the next step without further purification; ^1H NMR (250 MHz, DMSO-d_6) δ 8.45 (s, 2H), 1.32 (s, 3H). From 3-ethoxymethacrolein. 3-Ethoxymethacrolein (4.0 mL, 34 mmol) was added to aqueous hydrochloric acid (5 M, 5.5 mL) and the solution was heated at 80 °C for 1 h. The reaction mixture was cooled in an ice bath and was adjusted to pH 13 with aqueous potassium hydroxide solution (3 M). The solution was washed with ether (2×50 mL) and the water was removed under high vacuum. The resultant solid was azeotroped twice with toluene and then dissolved in ethanol (50 mL). The resultant mixture was heated and then filtered to remove solid impurities. The filtrate was concentrated to provide the title compound **27** as a yellow-orange solid (2.64 g, 21 mmol, 63%).

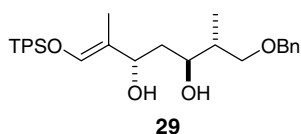


(E)-3-(tert-Butyldiphenylsilyloxy)-2-methyl-propenal 25. To a solution of the potassium salt **27** (2.38 g, 19.2 mmol) and triethylamine (3.20 mL, 23 mmol) in Et₂O (18 mL) at -10 °C was added *tert*-butyldiphenylsilyl chloride (10 mL, 38.5 mmol) as a solution in Et₂O (10 mL) at such a rate so as to maintain the temperature below -5 °C. The reaction was allowed to warm slowly to room temperature with stirring for 16 h during which time a white precipitate formed. The mixture was filtered and the solvent removed *in vacuo*. Purification by Kugelrohr distillation (0.75 mm Hg, 180-195 °C) provided the aldehyde **25** as a clear gum (2.68 g, 8.25 mmol, 43%); *R_f* (ethyl acetate:hexane, 1:4) 0.5; ¹H NMR (250 MHz, CDCl₃) δ 9.16 (s, 1H), 7.65-7.63 (m, 4H) 7.52-7.25 (m, 6H), 7.06 (q, *J* = 1.1 Hz, 1H), 1.85 (d, *J* = 1.1 Hz, 3H), 1.13 (s, 9H); IR (CHCl₃) 1743 (CO) cm⁻¹; ¹³C NMR (62.5 MHz, CDCl₃) 192.9, 162.8, 135.3, 130.9, 130.7, 128.2, 124.3, 26.5, 19.3, 6.5; IR (film) 1678 cm⁻¹; MS (CI, NH₃) *m/z* (rel intensity) 235 [100, (M + H)⁺]; HRMS (CI, NH₃) *m/z* 325.1624 (325.1625 calcd for C₁₄H₁₉O₂Si, MH).



(E,3S,5R)-7-Benzyloxy-1-(tert-butyldiphenyl)silyloxy-3-hydroxy-2,6-dimethyl-hept-1-ene-5-one 28. To a cooled (0 °C) solution of (+)-Ipc₂BCl (1.82 g, 5.67 mmol) in Et₂O (30 mL) was added triethylamine (0.8 mL, 5.74 mmol) followed by a solution of the ketone **26**⁷ (890 mg, 4.63 mmol) as a solution in Et₂O (15 mL) and the resultant white suspension was stirred for 2.5 h. The mixture was cooled to -78 °C and a solution of the aldehyde **25** (1.50 g, 4.6 mmol) in Et₂O (10 mL) was added dropwise. The reaction mixture was maintained at -78 °C for 2 h and then at -40 °C for 1 h. The reaction was quenched by the addition of a mixture of methanol (60 mL), pH 7 buffer (16 mL) and H₂O₂ (100 v/v, 4 mL) and the biphasic system was stirred vigorously at 0 °C for 10 min and then at

room temperature for 1 h. The mixture was extracted with CH₂Cl₂ (3 × 50 mL) then Et₂O (50 mL). The combined organic extracts were dried (MgSO₄) and then concentrated *in vacuo*. Purification by flash chromatography (hexane:EtOAc, 20:1 → 10:1) provided **28** (1.31 g, 2.53 mmol, 55%) as a clear and colorless oil; *R_f* 0.20 (hexane:ethyl acetate, 4:1); $[\alpha]_D^{22}$ -13.8 (*c* 0.92, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.65-7.62 (m, 4H), 7.64-7.23 (m, 11H), 6.34 (br s, 1H), 4.44 (m, 2H), 4.38 (m, 1H), 3.57 (dd, *J* 9.0, 8.0 Hz, 2H), 3.44 (dd, *J* 9.0, 5.2 Hz, 1H), 2.90-2.75 (m, 3H), 2.54 (dd, *J* 17.2, 2.6, 1H), 1.75 (br s, 3H), 1.07 (s, 9H), 0.89 (d, *J* 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 213.8, 137.9, 137.4, 135.4, 132.9, 132.7, 130.0, 128.4, 127.8, 127.7, 127.6, 118.0, 73.3, 72.1, 69.3, 47.7, 46.9, 26.6, 19.3, 13.2, 8.7; IR (film) 3460, 1709, 1670 cm⁻¹; MS (FAB) *m/z* (rel intensity) 515 [7, (M-H)]; HRMS (FAB) *m/z* 515.2645 (515.2619 calcd for C₃₂H₃₉O₄Si, M-H).

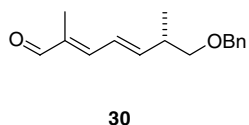
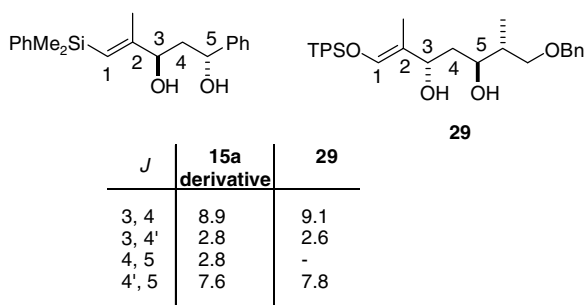


(*E*),3(*S*),5(*S*),6(*R*)-7-Benzyloxy-1-(*tert*-butyldiphenyl)silyloxy-2,6-dimethyl-hept-1-ene-3,5-diol

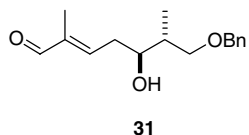
29. To a solution of tetramethylammonium triacetoxymethylborohydride (3.76 g, 14.3 mmol) in acetonitrile (8 mL) and acetic acid (2 mL) at -50 °C was added a cooled solution of **28** (305 mg, 0.59 mmol) as a solution in acetonitrile (8 mL). The reaction mixture was allowed to warm to -30 °C over 30 min and was maintained at that temperature for 20 h. A saturated solution of sodium potassium tartrate (6 mL) was added. The mixture was allowed to come to room temperature and was stirred for 50 min. The mixture was poured onto ice and was neutralized with saturated aqueous sodium hydrogencarbonate. The mixture was extracted with CH₂Cl₂ (3 × 100 mL). The aqueous phase was saturated with sodium chloride and was then extracted with EtOAc (100 mL). The combined organic phases were washed with saturated aqueous sodium hydrogencarbonate and then dried (MgSO₄). After filtration the product **29** was stored in solution at -20 °C and was used without purification (266 mg, 0.51 mmol, 89%); *R_f* 0.38 (ethyl acetate:hexane, 2:3); ¹H NMR (400 MHz, CDCl₃) δ 7.67-7.64 (m, 4H), 7.43-7.22

(m, 1H), 6.38 (br s, 1H), 4.97 (s, 2H), 4.25 (br d, J 9.1 Hz, 1H), 3.83 (d, J 2.6 Hz) 3.75 (tt, J 7.8, 2.6, 1H), 3.64-3.54 (m, 1H), 3.50-3.43 (m, 1H), 2.61 (d, J 2.6 Hz, 1H), 1.96-1.84 (m, 2H), 1.75 (br s, 3H), 1.50 (ddd, J 14.3, 7.8, 2.6 Hz 1H), 1.08 (s, 9H), 0.81 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 136.7, 135.4, 133.0, 129.9, 128.5, 128.4, 127.8, 127.7, 127.6, 119.8, 75.6, 74.3, 73.5, 70.5, 38.9, 37.9, 26.6, 19.3, 13.7, 8.9; IR (film) 3242, 1669 cm^{-1} .

Assignment of the relative stereochemistry of 29 by J value comparison with the diol derived from 15a.

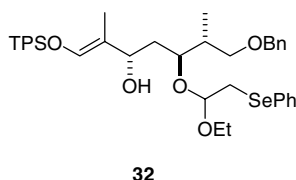
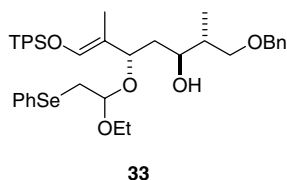


(*E*),(*E*),(*S*)-7-Benzyloxy-2,6-dimethyl-hepta-2,4-dienal 30. ^1H NMR (200 MHz, CDCl_3) δ 9.43 (s, 1H), 7.41-7.23 (m, 5H), 6.83 (dd, J 11.0, 1.0 Hz, 1H), 6.46 (ddd, J 15.0, 11.0, 1.0 Hz, 1H), 6.22 (dd, J 15.0, 7.3 Hz, 1H), 4.53 (s, 2H), 3.42 (d, J 6.5 Hz, 2H), 2.74-2.67 (m, 1H), 1.84 (d, J 1.0 Hz, 3H), 1.12 (d, J 7.5 Hz, 3H); IR (film) 1679, 1633 cm^{-1} .



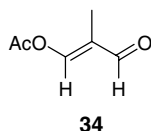
(*E*),5(*S*),6(*R*)-7-Benzyloxy-5-hydroxy-2,6-dimethyl-hept-2-enal 31. ^1H NMR (250 MHz, CDCl_3) δ 9.44 (s, 1H), 7.40-7.31 (m, 5H), 6.72 (br t, J 7.5 Hz, H) 4.54 (s, 2H), 3.83 (br s, 1H), 3.80-3.72 (m,

1H), 3.67 (dd, *J* 10.0, 5.0 Hz, 1H), 3.49 (dd, t, *J* 10 Hz, 1H), 2.60-2.44 (m, 2H), 2.01-1.88 (m, 1H), 1.76 (br s, 3H), 0.91 (d, *J* 7.5 Hz, 3H).

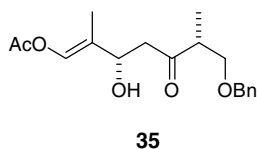


(*E*),2(*R*),3(*S*),4(*S*)-1-Benzyloxy-7-(*t*-butyldiphenylsilyl)oxy-5-(1-ethoxy-2-phenylselanyl-ethoxy)-2,6-dimethyl-hept-6-en-3-ol **33 and (*E*),2(*R*),3(*S*),4(*S*)-7-benzyloxy-1-(*t*-butyldiphenylsilyl)oxy-5-(1-ethoxy-2-phenylselanyl-ethoxy)-2,6-dimethyl-hept-1-en-3-ol **32**.** To a solution of PhSeCl (63 mg, 0.33 mmol) in THF (2 mL) at room temperature was added ethyl vinyl ether (32 μ L, 0.33 mmol) which caused the color of the solution to change from orange to yellow. The solution was stirred for 30 min. In a separate flask, a solution of the diol **29** (85 mg, 0.16 mmol) in THF (5 mL) was stirred for 30 min over 4 Å molecular sieves. The diol was treated with diisopropylamine (46 μ L, 0.33 mmol) followed by the PhSeCl/ethyl vinyl ether solution and the mixture was stirred for 3 days at room temperature. The reaction mixture was filtered and diluted (1:1 mixture, EtOAc:hexanes, 20 mL). The organic phase was washed with water, brine and then dried (MgSO₄). Purification by flash chromatography (hexanes:EtOAc, 50:1→100:7) provided the acetals **33** (44 mg, 57 μ mol) and **32** (25 mg, 32 μ mol) in a combined yield of 55%; *Data for 33*: *R_f* (EtOAc:hexane, 1:9) 0.17; ¹H NMR (400 MHz, CDCl₃) δ 7.64-7.60 (m, 4H), 7.45-7.24 (m, 14H), 7.05-7.00 (m, 2H), 6.17 (q, *J* 1.0 Hz, 1H), 4.48 (s, 2H), 4.39 (dd, *J* 6.6, 3.5 Hz, 1H), 3.84 (dd, *J* 10.4, 2.5 Hz, 1H) 3.76-3.72 (m, 1H), 3.66-3.38 (m, 3H), 3.34 (d, *J* 3.7 Hz, 1H), 3.30-3.20 (m, 1H), 3.10 (dd, *J* 12.7, 3.5 Hz, 1H), 3.01 (dd, *J* 12.7, 6.6 Hz, 1H), 1.96-1.89 (m, 1H), 1.82-1.70 (m, 1H), 1.73 (d, *J* 1.0 Hz, 3H), 1.34-1.28 (m, 1H), 1.10 (t, *J* 7.1 Hz,

3H), 1.06 (s, 9H), 0.88 (d, J 7.0 Hz, 3H). *Data for 32:* R_f (EtOAc:hexane, 1:9) 0.09; ^1H NMR (200 MHz, CDCl_3) δ 7.65-7.62 (m, 4H), 7.53-7.17 (m, 16H), 6.25 (q, J 1.0 Hz, 1H), 4.50 (s, 2H), 4.47 (t, J 5.6 Hz, 1H), 4.09-4.02 (m, 1H), 3.76-3.68 (m, 1H), 3.57-3.41 (m, 2H), 3.40-3.24 (m, 2H), 3.18 (d, J 4.2 Hz, 1H), 3.05-3.01 (m, 2H), 1.97-1.70 (m, 2H), 1.73 (d, J 1.1 Hz, 3H), 1.45-1.31 (m, 1H), 1.09 (s, 9H), 1.00 (t, J 7.1 Hz, 3H), 0.94 (d, J 6.9 Hz, 3H).



3-Acetoxy-2-methylpropenal 34. To a suspension of **27** (4.0 g, 32.3 mmol) in Et_2O (30 mL) and triethylamine (6.5 mL, 47.1 mmol) at $-10\text{ }^\circ\text{C}$ was added a solution of acetyl chloride (3.36 mL, 47.1 mmol) in Et_2O (10 mL) dropwise *via* syringe at such a rate as to maintain the temperature below $-5\text{ }^\circ\text{C}$. The reaction mixture was warmed to ambient temperature over 1.5 h and was stirred for an additional 6 h during which time a brown precipitate formed. The reaction was quenched with water (50 mL) and was extracted with Et_2O ($3 \times 30\text{ mL}$). The combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate:hexane, 9:1) provided the title compound as a clear colorless oil (3.2 g, 25 mmol, 79%). R_f (ethyl acetate:hexane, 2:3) 0.5; ^1H NMR (250 MHz, CDCl_3) δ 9.46 (s, 1H), 8.01 (q, J = 1.3 Hz, 1H), 2.29 (s, 3H), 1.77 (d, J = 1.3 Hz, 3H); IR (CHCl_3) 1743 cm^{-1} .



(*E*),3(*S*),6(*R*)-1-Acetoxy-7-benzyloxy-3-hydroxy-2,6-dimethyl-6-hept-1-ene-3-one 35. To a cooled ($0\text{ }^\circ\text{C}$) solution of (+)- Ipc_2BCl (1.94 g, 6.04 mmol) in Et_2O was added Et_3N (0.88 mL, 6.31 mmol) followed by a solution of ketone **26** (0.74 g, 4.15 mmol) dissolved in Et_2O (5.0 mL). The resultant white suspension was stirred at this temperature for 2.5 h. The mixture was then cooled to -

78 °C and a solution of the aldehyde **34** (1.09 g, 8.50 mmol, 2.05) was added slowly *via* cannula as a solution in Et₂O (4.0 mL, 3.0 mL rinse) upon which the suspension turned light yellow. After stirring for 20 min the solution was transferred to a freezer where it was stored for 17 h at -20 °C. The mixture was then stirred at 0 °C for 40 min. The reaction was quenched with a solution of MeOH (90 mL), pH 7 buffer (35 mL) and H₂O₂ (100 v/v, 9.0 mL), and the biphasic system was stirred vigorously at 0 °C for 10 min then at ambient temperature for 1 h. The mixture was poured into water (80 mL) and was extracted with 1:1 EtOAc:hexane (1 L). The aqueous layer was re-extracted with the same solvent mixture (2 × 100 mL). The combined organic layers were washed with water (100 mL), dried (MgSO₄) and evaporated *in vacuo*. Purification by flash chromatography (ethyl acetate:hexane, 1;9 to 3:7) furnished the product **35** (0.85 g, 2.78 mmol, 69%) as a colorless oil; *R_f* (EtOAc:hexane, 6:4) 0.48; $[\alpha]_D^{21}$ -38.1 (*c* 0.8, CHCl₃); ¹H NMR (250 MHz, CDCl₃) δ 7.37-7.24 (m, 5H), 7.21 (br s, 1H) 4.55 (br d, *J* = 8.8 Hz, 1H), 4.48 (s, 2H), 3.61 (m, 1H), 3.50 (m, 1H), 3.19 (br s, 1H), 2.93-2.86 (m, 1H), 2.78 (dd, *J* = 17.3, 9.2 Hz, 1H), 2.70 (dd, *J* = 17.3, 3.0 Hz, 1H), 2.15 (1H, s), 1.65 (s, 3H), 1.08 (d, *J* = 6.9 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 213.5, 168.0, 137.8, 132.3, 128.4, 127.8, 127.7, 122.1, 73.3, 72.1, 68.8, 47.4, 46.9, 20.7, 13.1, 9.9; IR (CHCl₃) 3604, 1748, 1706, 1601 cm⁻¹; MS (CI) *m/z* (rel intensity) 303 [53, (M+H-H₂O)], 83 (100); HRMS (CI) *m/z* 303.1596 (303.1597 calcd for C₁₈H₂₃O₄, M+H-H₂O).

Proof of Stereochemistry at C3 of **35**

The corresponding (*R*) and (*S*) Mosher esters of **35** were prepared. Relevant ¹H NMR data is shown in Figure 1.

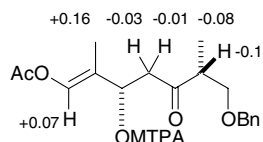
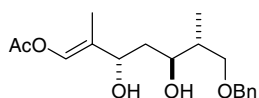
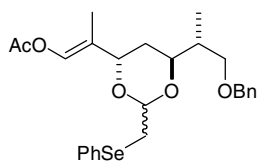


Figure 1. $\Delta\delta$ ($\delta_s - \delta_r$) values (in ppm) for the (*R*) and (*S*) Mosher esters prepared from **35**. According to the Kakisawa model⁸ the absolute stereochemistry of C3 in **35** is therefore (*S*).



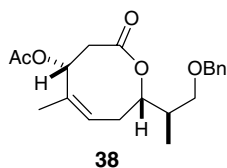
36

(*E*),3(*S*),5(*S*),6(*R*)-1-Acetoxy-7-benzyloxy-2,6-dimethyl-1-heptene-3,5-diol **36.** To a cooled (-45 °C) solution of $\text{Me}_4\text{NBH}(\text{OAc})_3$ (6.7 g, 25.5 mmol) in dry acetonitrile (100 mL) and dry acetic acid (16.3 mL) was added a cooled solution of the β -hydroxy ketone **35** (2.3 g, 7.18 mmol) *via* cannula as a solution in acetonitrile (20.0 mL, 5.0 mL rinse). The mixture was stirred at -30 °C for 36 h and the reaction was then quenched with saturated aqueous sodium potassium tartrate (80 mL), and allowed to warm to ambient temperature at which it was stirred for 30 min. The mixture was poured over ice and adjusted to pH 9 with saturated aqueous NaHCO_3 , and was extracted with EtOAc (400 mL). The aqueous layer was saturated with NaCl and was extracted with EtOAc (3 \times 200 mL). The combined organic layers were washed with NaHCO_3 (3 \times 100 mL), dried (MgSO_4) and evaporated *in vacuo* affording the title compound **36** (2.27 g, 7.04 mmol, 98%). The unstable diol was stored in solution in toluene at -20 °C and was used without purification; R_f (EtOAc in hexane, 3:10) 0.28; $[\alpha]_D^{21}$ -15.8 (c 1.9, CHCl_3); ^1H NMR (250 MHz, CDCl_3) δ 7.38-7.23 (m, 6H), 4.52 (s, 2H), 4.41 (dd, J = 8.7, 2.3 Hz, 1H), 4.10-3.92 (br s, 1H), 3.82 (td, J = 7.9, 3.0 Hz, 1H), 3.63 (dd, J = 9.2, 4.1 Hz, 1H), 3.48 (dd, J = 9.2, 8.2 Hz, 1H), 3.34 (br s, 1H), 2.15 (s, 3H), 2.02-1.93 (m, 1H), 1.85 (ddd, J = 14.3, 8.7, 3.0 Hz, 1H), 1.70-1.62 (ddd, J = 14.3, 7.9, 2.3 Hz, 1H), 1.68 (d, J = 1.2 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl_3) δ 168.1, 137.5, 131.8, 128.5, 127.9, 127.7, 123.9, 75.6, 74.5, 73.6, 70.3, 38.4, 37.8, 20.8, 13.7, 10.1; IR (CHCl_3) 3466, 1747, 1601 cm^{-1} ; MS (CI, NH_3) m/z (rel intensity) 340 [25, ($\text{M} + \text{NH}_4$) $^+$], 245 (100); HRMS (CI, NH_3) m/z 340.2124 (340.2125 calcd for $\text{C}_{18}\text{H}_{30}\text{NO}_5$, MNH_4).



37

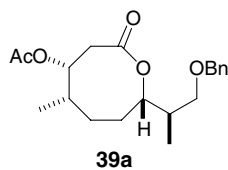
(E),4(S),6(S)-6-[1(R)-2-Benzoyloxy-1-methyl-ethyl]-2-phenylselanylmethyl-4-(2-acetoxy-1-methylvinyl)-[1,3]dioxane 37. A solution of **36** (396 mg, 1.23 mmol), phenylselenoacetaldehyde diethylacetal **16** (553 mg, 2.02 mmol) and PPTS (43 mg, 0.171 mmol) in toluene (15 mL) with freshly dried crushed 4 Å molecular sieves was heated at reflux for 48 h. Additional phenylselenoacetaldehyde diethylacetal **16** (100 mg, 0.366 mmol) was added and the reaction mixture was heated at reflux for a further 14 h. The cooled mixture was filtered and diluted with EtOAc (100 mL). The solution was washed sequentially with water (50 mL) then with saturated aqueous NaHCO₃ (50 mL). The organic layer was dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate:hexane, 4:96 then 5:95) to give the title compound **37** as a mixture of 2 diastereomers (345 mg, 0.686 mmol, 56%) as a light yellow oil; *R_f* (ethyl acetate:hexane, 1:4) 0.44; $[\alpha]_D^{22} +17.4$ (*c* 1.17, CHCl₃); ¹H NMR (250 MHz, CDCl₃) δ (mixture of 2 diastereomers) 7.52-7.47 (m, 2H), 7.36-7.21 (m, 8H), 7.10 (s, 1H), 5.06 (t, *J* = 5.0 Hz, 0.5H), 4.89 (t, *J* = 5.0 Hz, 1H), 4.60-4.42 (m, 2H), 4.23-4.18 (m, 1H), 3.94-3.79 (m, 1H), 3.71-3.66 (m, 0.5H), 3.49-3.33 (m, 1.5H), 3.11-3.01 (m, 2H), 2.52-2.38 (m, 1H), 2.17 (s, 1.5H), 2.15 (s, 1.5H), 2.11-1.83 (m, 2H), 1.73, (s, 1.5H), 1.71 (s, 1.5H), 0.90-0.82 (m, 3H); IR (CHCl₃) 1749 cm⁻¹; ¹³C NMR (100 MHz, CDCl₃) δ 168.0, 138.7, 133.7, 132.6, 132.1, 132.0, 130.7, 129.0, 128.3, 127.6, 127.5, 127.4, 126.7, 126.6, 121.1, 121.0, 95.4, 94.9, 74.2, 73.9, 73.3, 73.1, 73.0, 72.0, 71.4, 38.5, 32.2, 31.7, 31.6, 29.3, 27.8, 20.8, 14.7, 12.6, 12.1, 10.1; MS (CI, NH₃) *m/z* (rel intensity) 522 [22, (M + NH₄)⁺]; HRMS (CI, NH₃) *m/z* 522.1760 (522.1760 calcd for C₂₆H₃₆O₅Se, MNH₄).



(Z),4(R),8(S)-4-Acetoxy-8-[1(R)-2-benzyloxy-1-methyl-ethyl]-5-methyl-3,4,7,8-tetrahydro-2H-oxocin-2-one 38. A mixture of acetals **37** (250 mg, 0.496 mmol), NaIO₄ (414 mg, 1.93 mmol) and NaHCO₃ (204 mg, 2.43 mmol) in EtOAc (4 mL), methanol (8 mL) and water (1.5 mL) was stirred

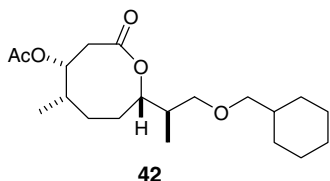
vigorously at 22 °C for 1.5 h. The reaction mixture was poured into water (50 mL) and was extracted with EtOAc (100 mL). The aqueous layer was saturated with NaCl and extracted again with EtOAc (2 × 100 mL). The combined organic layers were dried (MgSO₄) and concentrated *in vacuo* to give a quantitative yield of the selenoxide (262 mg) which was used in the next step without purification.

A solution of the above selenoxide (262 mg, 0.496 mmol) and 1-*tert*-butyldimethylsiloxy-1-methoxy ethene **18** (1.17 g, 6.19 mmol) in dry xylene (30 mL) with K₂CO₃ (362 mg, 2.62 mmol) was heated in a sealed tube at 180 °C for 2.5 h. The mixture was cooled then washed with saturated aqueous NH₄Cl (100 mL). The xylene was removed under high vacuum, and the residue was purified by flash chromatography (ethyl acetate:hexane, 1:9) to give the title compound **38** (68 mg, 0.196 mmol, 40%) as a clear oil. Also recovered was the selenide **37** (60.5 mg, 0.120 mmol, 24%). *Data for 38*; *R_f* (ethyl acetate:hexane, 1:4) 0.25; $[\alpha]_D^{21}$ -12.8 (*c*, 2.18, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.27 (m, 5H), 5.65 (t, *J* = 7.2 Hz, 1H), 5.42 (t, *J* = 6.7 Hz, 1H), 4.66 (q, *J* = 7.5 Hz, 1H), 4.47 (s, 2H), 3.48 (dd, *J* 5.5, 9.1 Hz, 1H) 3.44 (dd, *J* = 4.4, 9.1 Hz, 1H), 3.10 (dd, *J* = 14.3, 7.2 Hz, 1H), 2.87 (dd, *J* = 14.3, 7.2 Hz, 1H), 2.39 (dd, *J* = 6.8, 7.2 Hz, 2H), 2.03 (s, 3H), 2.02-1.97 (m, 1H), 1.72 (s, 3H), 1.02 (d, *J* = 8.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.4, 170.0, 138.4, 137.7, 128.4, 127.6, 121.8, 79.5, 73.2, 71.6, 70.1, 42.3, 38.5, 31.1, 20.9, 20.0, 13.7; IR (CHCl₃) 1734 cm⁻¹; MS (CI, NH₃) *m/z* (rel intensity) 347 [36, (M + H)⁺].

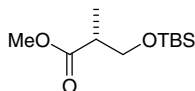


4(R),5(S),8(S)-4-Acetoxy-8-[1(R)-benzyloxy-1-methyl-ethyl]-5-methyl-oxocan-2-one 39a. To a solution of the lactone **38** (35 mg, 100 μmmol) in EtOAc (2 mL) was added PtO₂ and the mixture was stirred vigorously under an atmosphere of H₂ for 10 h. The mixture was filtered through Celite™ followed by concentration *in vacuo* provided the title compound **39a**; *R_f* (hexane:ethyl acetate, 4:1)

0.14; ^1H NMR (500 MHz, CDCl_3 , major diastereomer) δ 7.37-7.27 (m, 5H), 5.00 (br d, $J = 6.2$ Hz, 1H), 4.47-4.40 (m, 3H), 3.61 (dd, $J = 9.0, 4.4$ Hz, 1H), 3.37 (dd, $J = 9.0, 4.4$ Hz, 1H), 2.89 (dd, $J = 13.5, 6.2$ Hz, 1H), 2.73 (dd, $J = 13.5, 1.8$ Hz, 1H), 2.10 (s, 3H), 2.09-1.90 (m, 1H), 1.88-1.91 (m, 2H), 1.77-1.71 (m, 1H), 1.70-1.65 (m, 3H), 1.02 (d, $J = 7.1$ Hz, 6H).

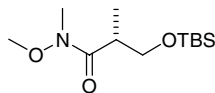


4(R),5(S),8(S)-4-Acetoxy-8-[1(R)-2-cyclohexylmethoxy-1-methyl-ethyl]-5-methyl-3,4,7,8-tetrahydro-oxocin-2-one 42. R_f (EtOAc in hexane, 1:4) 0.28; ^1H NMR (200 MHz, CDCl_3) δ 5.03 (d, $J = 5.8$ Hz, 1H), 4.43 (m, 1H), 3.54-3.21 (m, 2H), 3.15 (d, $J = 6.4$ Hz, 2H), 2.10 (s, 3H), 1.99-1.51 (m, 11H), 1.48-1.15 (m, 4H), 1.09-0.85 (m, 8H).

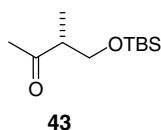


Methyl-(R)-3-(tert-butyldimethylsiloxy)-2-methyl-propionate.⁹ To a solution of methyl-(R)-3-hydroxy-2-methyl-propionate (10.3 g, 87.2 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added imidazole (9.9 g, 145 mmol) and DMAP (106 mg, 0.87 mmol). A solution of TBSCl (16.6 g, 110 mmol) in CH_2Cl_2 (25 mL) was added dropwise *via* syringe. After the addition the cooling bath was removed and the mixture was stirred at ambient temperature for 40 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (120 mL), followed by water (50 mL). The aqueous layer was extracted with Et_2O (4×60 mL). The combined organic extracts were dried (MgSO_4) and evaporated *in vacuo*. Purification by flash column chromatography (hexane:ether, 40:1, 20:1 and finally 10:1) afforded the title compound (19.9 g, 87 mmol, 98%) as a clear colorless oil; R_f (hexane:ether, 9:1) 0.31; $[\alpha]_D^{20}$ -18.2 (c 0.89, CHCl_3), {lit.⁹ $[\alpha]_D^{24}$ -18.4 (c 2.02, CHCl_3)}; ^1H NMR (400 MHz, CDCl_3) δ 3.79 (dd, $J = 9.7, 6.8$ Hz, 1H), 3.65 (s, 3H), 3.65-3.61 (dd, $J = 9.7, 6.8$ Hz, 1H), 2.67-2.59 (m, 1H),

1.12 (d, $J = 7.1$ Hz, 3H), 0.86 (s, 9H), 0.12 (d, $J = 1.4$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.4, 65.2, 51.4, 42.5, 25.7 18.2 13.4, -5.6; IR (CDCl_3) 1733 cm^{-1} ; MS (CI, NH_3) m/z (rel intensity) 233 [45, ($\text{M} + \text{H}$) $^+$]. HRMS (Q-TOF) m/z 255.1392 (255.1392 calcd for $\text{C}_{11}\text{H}_{24}\text{O}_3\text{SiNa}$, MNa).

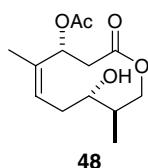


(*R*)-3-(*tert*-Butyldimethylsiloxy)-*N*-methoxy-2,*N*-dimethylpropanamide. A solution of methyl-*(R)*-3-(*tert*-butyldimethylsiloxy)-2-methyl-propionate (19.7 g, 84.7 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (10.5 g, 107.5 mmol) in THF (220 mL) was cooled to $-10\text{ }^\circ\text{C}$ using an ice-salt bath. Isopropylmagnesium bromide (107 mL, 2.0 M in Et_2O) was added dropwise, maintaining the temperature below $-5\text{ }^\circ\text{C}$ (addition time 40 min). The mixture was stirred at $-10\text{ }^\circ\text{C}$ for 30 min and was quenched by the addition of saturated NH_4Cl solution (150 mL). After the addition of H_2O (150 mL), the mixture was extracted with Et_2O ($4 \times 100\text{ mL}$). The combined organic extracts were dried (MgSO_4) and evaporated *in vacuo*. Purification by flash chromatography (EtOAc) through a short plug of silica yielded the title compound as a colorless oil (21.5 g, 82.2 mmol, 97%). R_f (hexane:ether, 9:1) 0.06; $[\alpha]_{\text{D}}^{20} -17.1$ (c 0.795, CHCl_3), {lit. enantiomer¹⁰ $[\alpha]_{\text{D}}^{24} +24.4$ (c 1.0, CHCl_3)}; ^1H NMR (250 MHz, CDCl_3) δ 3.80 (dd, $J = 9.7, 6.8$ Hz, 1 H), 3.68 (s, 3H), 3.50 (dd, $J = 9.7, 6.8$ Hz, 1H), 3.15 (s, 3H), 1.05 (d, $J = 6.8$ Hz, 3H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (62.5 MHz, CDCl_3) δ 175.9, 65.7, 61.4, 38.1, 32.1, 25.8, 18.2, 13.7, -5.5; IR (CDCl_3) 1650 cm^{-1} ; HRMS (Q-TOF) m/z 284.1686 (284.1658 calcd for $\text{C}_{12}\text{H}_{27}\text{O}_3\text{SiNa}$, MNa).



(*R*)-4-(*tert*-Butyldimethylsiloxy)-3-methyl-butan-2-one 43. To a solution of the *(R)*-3-(*tert*-butyldimethylsiloxy)-*N*-methoxy-2,*N*-dimethylpropanamide (12.7 g, 48.7 mmol) in THF (150 mL)

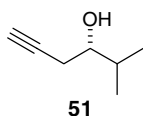
cooled to 0 °C was added methylmagnesium bromide (27.6 ml, 2.0 M in ether, 82.7 mmol) dropwise *via* syringe. After 40 min the reaction was quenched with aqueous NH₄Cl (150 mL) and the mixture was allowed to warm to ambient temperature. The resultant suspension was extracted with Et₂O (3 × 150 mL). The combined organic extracts were washed with brine (150 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by flash chromatography (ethyl acetate:hexane, 3:1) yielded the title compound (10.3 g, 48.0 mmol, 98%) as a clear colorless oil. *R_f* (hexane:ether, 3 :1) 0.56; $[\alpha]_{\text{D}}^{20}$ -29.1 (*c* 0.87, CHCl₃), {lit. enantiomer¹⁰ $[\alpha]_{\text{D}}^{20}$ +33.5 (*c* 1.0, CHCl₃)}; ¹H NMR (250 MHz, CDCl₃) δ 3.65 (m, 2H), 2.68 (m, 1H), 2.15 (s, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.84 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ¹³C NMR (62.5 MHz, CDCl₃) δ 211.6, 65.4, 49.3, 29.4, 25.8, 18.1, 12.8, -5.6; IR (CHCl₃) 1711 cm⁻¹; Anal. Calcd for C₁₁H₂₄O₂Si: C, 61.1; H, 11.2. Found: C, 61.1; H, 11.1. HRMS (Q-TOF) *m/z* 239.1459 (239.1443 calcd for C₁₁H₂₄O₂SiNa, MNa).



5(Z),4(R),8(S),9(S)-4-Acetoxy-5,9-dimethyl-8-hydroxy-3,4,7,8,9,10-hexahydro-oxecin-2-one 48.

To a solution of the lactone **47** (11.0 mg, 0.031 mmol) in THF (550 μL) and pyridine (250 μL) at 0 °C was added 70% HF/pyridine (100 μL). The cooling bath was removed and the reaction was stirred at ambient temperature for 24 h. Filtration of the reaction mixture through silica gave the title compound **48** (7.4 mg, 0.029 mmol, 94%) as colorless needles; mp 117 °C (ether); $[\alpha]_{\text{D}}^{22}$ +30.6 (*c* 0.81, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 6.08 (dd, *J* = 11.4, 5.8 Hz, 1H), 5.22 (d, *J* = 12.4 Hz, 1H), 4.36 (dd, *J* = 11.1, 2.4 Hz, 1H), 3.90 (t, *J* = 11.1 Hz, 1H), 3.77 (m, 1H), 2.98-2.88 (m, 2H), 2.52 (dd, *J* = 13.6, 11.5 Hz, 1H), 2.35-2.30 (m, 1H), 2.05 (s, 3H), 2.00-1.96 (m, 1H), 1.70 (s, 3H), 1.58 (s, 1H), 0.92 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.0, 168.6, 132.7, 125.4, 73.7, 68.6, 37.7, 36.0, 33.9, 21.0,

17.4, 14.7; IR (CHCl₃) 3515, 1738; MS (CI, NH₃) *m/z* (rel intensity) 256 [2, (M + H)⁺], 274 [100, (M + NH₄)⁺]; HRMS (CI, NH₃) *m/z*. 274.1654 (274.1654 calcd for C₁₃H₂₄NO₅ MNH₄).



(S)-4-Hydroxy-5-methyl-1-hexyne, 51. Allenylboronic acid **24** (3.4 g, 40.5 mmol) and freshly dried crushed 5 Å molecular sieves (15 g) were suspended in dry toluene (80 mL). (+)-Diethyltartrate was added and the mixture was stirred for 24 h at ambient temperature under a stream of Ar. The solution was decanted *via* cannula into a dry flask under Ar, and the residue was washed through with toluene (20 mL). The solution was cooled to -78 °C and isobutyraldehyde (6.0 mL, 66.0 mmol) was added dropwise *via* syringe. The mixture was stirred at -70 °C for 21 h. The reaction was quenched by the addition of ice cold 1 M HCl (120 mL), diluted with Et₂O (250 mL) and transferred to a separating funnel. The aqueous layer was washed with Et₂O (3 × 150 mL) (Difficult phase separation was aided by the addition of solid NaCl). The combined organic extracts were dried (MgSO₄), filtered, and evaporated *in vacuo* at -10 °C. The volatile title compound was stored as a solution in toluene; *R_f* (hexane:ethyl acetate 1:5) 0.13; [α]_D²⁰ +7.1 (*c* 1.6, CHCl₃); ¹H NMR (250 MHz, CDCl₃) δ 3.55-3.44 (m, 1H), 2.51-2.26 (m, 2H), 2.04 (t, *J* = 2.6 Hz, 1H), 1.95 (d, *J* = 4.8 Hz, 1H), 1.88-1.71 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); ¹³C (100 MHz, CDCl₃) δ 81.2, 74.7, 70.5, 32.6, 24.6, 18.6, 17.6. IR (CDCl₃) 3532, 3307 cm⁻¹

Proof of Stereochemistry at C3 of 51

The corresponding (*R*) and (*S*) Mosher esters of **51** were prepared. Relevant ¹H NMR data is shown in Figure 2.

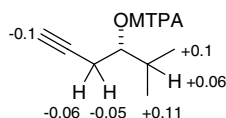
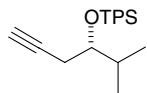
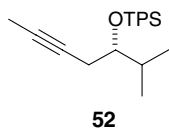


Figure 2. $\Delta\delta$ ($\delta_S - \delta_R$) values for the (*R*) and (*S*) Mosher esters prepared from **51**. According to the Kakisawa model the absolute stereochemistry of C3 in **51** is therefore (*S*).

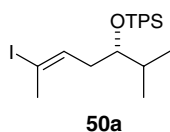


(*S*)-4-(*tert*-Butyldiphenylsiloxy)-5-methyl-1-hexyne. A solution of the alcohol **51** (approximately 4.0 g, 35 mmol), *t*-butyldimethylsilylchloride (15.7 g, 105 mmol, 3 eq) and imidazole (14.3 g, 210 mmol, 6 eq) in 1:1 toluene/DMF (120 mL) was stirred at ambient temperature for 4 days. The mixture was diluted with water (250 mL) and was extracted with a mixture of EtOAc:hexane 1:1 (3 × 100 mL). The combined organic layers were washed with brine and dried (MgSO₄). Evaporation *in vacuo* provided the crude product as a viscous oil. Flash chromatography (hexane) afforded the title compound (3.3 g, 14.6 mmol, 35%, 2 steps); *R_f* (hexane) 0.23; $[\alpha]_D^{20} +18.1$ (*c* 14.0, CHCl₃; ¹H NMR (250 MHz, CDCl₃) δ 7.75-7.70 (m, 4H), 7.48-7.35 (m, 6H), 3.72 (m, 1H), 2.31-2.26 (m, 2H), 2.18-1.95 (m, 1H), 1.87 (m, 1H), 1.10 (s, 9H), 0.94 (d, *J* = 2.1 Hz), 0.92 (d, *J* = 2.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 136.1, 136.0, 134.6, 133.8, 129.6, 129.6, 129.0, 128.2, 127.5, 127.4, 81.7, 76.1, 69.9, 32.2, 27.1, 24.2, 19.6, 18.9, 16.6; IR (CDCl₃) 3308, 1261, 1101 cm⁻¹; MS (CI, NH₃) *m/z* (rel intensity) 351 [18, (M + H)⁺]; HRMS (EI) *m/z* 351.2144 (351.2145 calcd for C₂₃H₃₁OSi, MH).



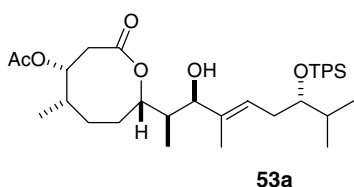
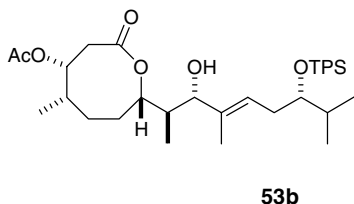
(*S*)-5-(*tert*-Butyldiphenylsiloxy)-6-methyl-2-heptyne **52.** To a solution of the (*S*)-4-(*tert*-butyldiphenylsiloxy)-5-methyl-1-hexyne (5.0 g, 14.26 mmol) in dry THF (80 mL) at -78 °C was added *n*BuLi (14.0 mL, 1.6 M solution in hexane, 22.5 mmol) and the mixture was stirred for 25 min. MeI (1.9 mL, 30.1 mmol) was added and the mixture was allowed to warm to 0 °C over 1.5 h. It was then warmed to ambient temperature and stirred for 1 h. Water (200 mL) was added to the reaction mixture

followed by Et₂O (150 mL). The layers were separated and the aqueous layer was washed with Et₂O (2 × 150 mL). The combined organic layers were dried (MgSO₄) and concentrated. The crude product was passed through a short plug of silica eluting with hexane to give the title compound (6.2 g, 14.2 mmol, 95%) as a clear oil; *R_f* (hexane) 0.23; $[\alpha]_{\text{D}}^{20}$ +20.6 (*c* 3.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.79-7.74 (m, 4H), 7.50-7.40 (m, 6H), 3.78-3.74 (td, *J* = 6.3, 3.6 Hz, 1H), 2.33-2.27 (m, 2H), 2.06-1.98 (m, 1H), 1.70 (t, *J* = 2.5 Hz, 3H), 1.15 (s, 9H), 0.98 (d, *J* = 2.0 Hz, 3H), 0.96 (d, *J* = 2.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 136.1, 136.0, 134.7, 129.5, 129.4, 127.5, 127.3, 77.1, 76.5, 32.2, 27.1, 24.4, 19.6, 18.8, 16.5, 3.4; IR (CDCl₃) 1472, 1428, 1111, 1064 cm⁻¹; MS (CI, NH₃) *m/z* (rel intensity) 365 [(M + H)⁺]; HRMS (CI, NH₃) *m/z* 365.2295 (365.2301 calcd for C₂₄H₃₃OSi, MH).



(S)-5-(tert-Butyldiphenylsiloxy)-6-methyl-2-iodo-2-heptene 50a. A dry 3-necked flask was attached to a vacuum manifold and evacuated with heating for 1 h prior to use. Bis(cyclopentadienyl) zirconium chloride hydride (4.0 g, 15.5 mmol) was weighed into a vial in a glove box and was transferred to the flask under a dry Ar stream. To the flask was added THF (80 mL). The heptyne **52** (1.4 g, 3.84 mmol) was then added *via* cannula as a solution in THF (5.0 mL, 2.0 mL rinse). The flask was excluded from light and the mixture was stirred for 4 h. A solution of I₂ (3.9 g, 15.4 mmol) in THF (20 mL) was added over 5 min. The mixture was stirred for a further 40 min at ambient temperature. Hexane (70 mL) was added to the mixture, and the resultant suspension was passed through a plug of silica eluting with hexane. The eluent was concentrated and the crude product was purified by flash chromatography (hexane) to afford the title compound (1.13 g, 2.3 mmol, 60%) as a 9:1 inseparable mixture of **50a:50b**; *R_f* (hexane) 0.34; $[\alpha]_{\text{D}}^{20}$ +12.8 (*c* 2.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃, major diastereomer) δ 7.74-7.68 (m, 4H), 7.45-7.36 (m, 6H), 5.98 (td, *J* = 7.5, 1.3 Hz, 1H), 3.58 (td, *J* = 6.2, 3.5 Hz, 1H), 2.13 (s, 3H), 2.10-2.06 (m, 2H), 1.75-1.67 (m, 1H), 1.07 (s, 9H), 0.92 (d,

$J = 6.9$ Hz 3H), 0.84 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.1, 136.1, 136.1, 136.0, 136.0, 134.1, 129.6, 129.5, 127.5, 127.5, 127.4, 94.8, 34.5, 32.4, 27.5, 27.0, 18.4, 17.0, 14.1; MS (EI) m/z (rel intensity) 435 (100); HRMS (EI) m/z (molecular ion peak could not be detected) 435.0645 [435.0643 calcd for $\text{C}_{20}\text{H}_{24}\text{OSiI}$, (M- C_3H_7)].



4(S),5(S),8(S)-4-Acetoxy-8-[(E),1(R),2(R),6(S)-6-(tert-butyl diphenylsilyloxy)-2-hydroxy-1,3,7-trimethyl-oct-3-enyl]-5-methyl-oxocan-2-one 53a and **4(S),5(S),8(S)-4-acetoxy-8-[(E),1(R),2(S),6(S)-6-(tert-butyl diphenylsilyloxy)-2-hydroxy-1,3,7-trimethyl-oct-3-enyl]-5-methyl-oxocan-2-one 53b**. The aldehyde **41** (6.0 mg, 23.2 μmol) was azeotropically evaporated twice with toluene (2×2 mL) and freeze dried under high vacuum in a Schlenk flask prior to use. DMSO (1 mL) was added *via* syringe followed by the vinyl iodine **50** (90.3 mg, 0.183 μmol) as a solution in DMSO *via* cannula (0.5 mL, 0.5 mL rinse). A mixture of 1% NiCl_2 in CrCl_2 (30 mg, 244 μmol) was pre-weighed in a glove box and added to the reaction mixture under a stream of Ar. The resultant dark green solution was stirred at ambient temperature with the exclusion of light for 22 h after which time it was quenched with saturated aqueous NH_4Cl (8 mL) and extracted with EtOAc (5×10 mL). The combined organic extracts were washed with brine (10 mL) and dried (Na_2SO_4). Concentration *in vacuo* was followed by flash chromatography (ethyl acetate:hexane, 1:4) to provide **53a** (6.5 mg, 10.4 μmol , 44%) and **53b** (3.5 mg, 5.6 μmol , 25%) as clear colorless oils. Data for **53a**: R_f (hexane:ethyl acetate, 3:1) 0.24; $[\alpha]_{\text{D}}^{24}$ -23 (c , 0.5, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 7.71-7.66 (m, 4H), 7.45-7.35

(m, 6H), 5.07 (t, $J = 6.6$ Hz, 1H), 5.02 (t, $J = 5.8$ Hz, 1H), 4.71 (dt, $J = 12.9, 4.3$ Hz, 1H), 3.63 (m, 1H), 3.47 (d, $J = 9.4$ Hz, 1H), 2.95 (dd, $J = 13.9, 5.8$ Hz), 2.79 (d, $J = 13.9$ Hz, 1H), 2.17-2.01 (m, 6H, CH_3O), 1.86-1.69 (m, 5H), 1.39 (s, 3H), 1.05 (s, 9H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.88 (d, $J = 6.8$ Hz, 6H), 0.66 (d, $J = 6.8$ Hz, 3H); MS (CI, NH_3) m/z (rel intensity) 640 [30, $(\text{M} + \text{NH}_4)^+$] 151 (100); HRMS (CI, NH_3) m/z 640.4030 (640.4033 calcd for $\text{C}_{37}\text{H}_{58}\text{O}_6\text{NSi}$, MNH_4). *Data for 53b*: R_f (hexane:ethyl acetate, 3:1) 0.36; $[\alpha]_D^{24}$ -54 (c , 0.15, CHCl_3); ^1H NMR (400 MHz, CDCl_3) 7.72-7.65 (m, 4H), 7.44-7.33 (m, 6H), 5.15 (t, $J = 6.8$ Hz, 1H), 5.04 (d, $J = 5.9$ Hz, 1H), 4.39-4.32 (m, 1H), 3.99 (s, 1H), 3.63 (dd, $J = 9.5, 6.2$ Hz, 1H), 2.94 (dd, $J = 13.6, 5.9$ Hz, 1H), 2.82 (dd, $J = 13.5, 1.9$ Hz, 1H), 2.20-2.04 (m, 6H), 1.80-1.60 (m, 5H), 1.31 (s, 3H), 1.05 (s, 9H), 0.94 (d, $J = 6.9$ Hz, 3H), 0.62 (d, $J = 7.0$ Hz, 3H).

Proof of Stereochemistry at C2' of 53a

The corresponding (*R*) and (*S*) Mosher esters of **53a** were prepared. Relevant ^1H NMR data is shown in Figure 3.

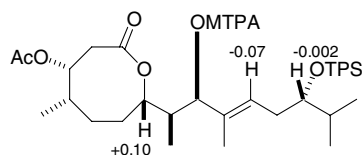
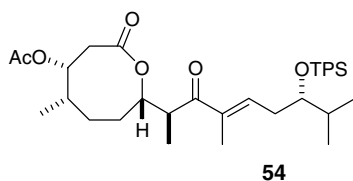
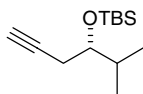


Figure 3. $\Delta\delta$ ($\delta_s - \delta_R$) values (in ppm) for the (*R*) and (*S*) Mosher esters prepared from **53a**. According to the Kakisawa model⁸ the absolute stereochemistry of C2' in **53a** is therefore (*R*).

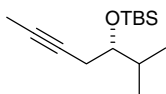


4(R),5(S),8(S)-4-Acetoxy-8-[(*E*),1(*S*),6(*R*)-6-(*tert*-butyldiphenylsiloxy)-1,3,7-trimethyl-2-oxo-oct-3-enyl]-5-methyl-oxocan-2-one 54. To a solution of **53** (7 mg, 11.2 μmol) in CH_2Cl_2 (2 mL) was added the Dess Martin periodinane (34 mg, 80 μmol). The mixture was stirred at ambient temperature

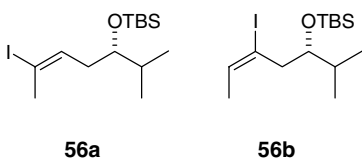
for 2 h. The solvent was exchanged with EtOAc and the reagent was removed by passing the mixture through a short plug of Florisil™, eluting with EtOAc. The crude product was purified by flash chromatography (hexane:ethyl acetate, 6:1 to 5:1) to furnish the title compound **54** (5.0 mg, 8.05 μ mol, 72%) as a colorless oil; R_f (hexane:ethyl acetate, 1:1) 0.63; $[\alpha]_D^{22}$ -25 (c 0.4, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ •7.71-7.66 (m, 5 H), 7.46-7.34 (m, 5 H), 6.55 (t, J 6.6 Hz, 1H), 5.04 (s, 1H), 4.78-4.63 (td, J 11, 3 Hz, 1H), 3.71 (m, 1H), 3.25-3.05 (m, 1H), 3.02-2.84 (m, 2H), 2.37-2.28 (m, 2H), 2.08 (s, 3H), 1.55 (s, 1H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ •202.7, 170.7, 170.6, 141.3, 136.8, 136.0, 135.9, 134.4, 133.4, 133.4, 129.8, 129.6, 127.7, 127.5, 76.5, 73.1, 44.1, 36.4, 35.5, 33.5, 33.1, 29.0, 27.0, 26.7, 24.0, 22.6, 21.7, 20.1, 19.5, 17.7, 17.6, 15.2, 14.1, 11.6, 11.4; IR (CDCl_3) 1740, 1663, 1240, 913 cm^{-1} ; MS (CI, NH_3) m/z (rel intensity) 641 (10), 311 (11), 169 (15), 77 (100); HRMS (CI, NH_3) m/z 638.3880 (638.3877 calcd for $\text{C}_{37}\text{H}_{56}\text{O}_6\text{NSi}$, MNH_4).



(S)-4-(tert-Butyldimethylsiloxy)-5-methyl-1-hexyne. A solution of **51** (4.0 g, 35 mmol), *tert*-butyldimethylsilylchloride (15.7 g, 105 mmol) and imidazole (14.3 g, 210 mmol) in 1:1 toluene:DMF (120 mL) was stirred at ambient temperature for 72 h. The mixture was diluted with water (250 mL) and was extracted with EtOAc:hexane, 1:1 (3×100 mL). The combined organic extracts were washed with brine and dried (MgSO_4). Evaporation *in vacuo* provided the crude product, purified by flash chromatography (hexane) to give the title compound (3.3 g, 0.0146 mmol, 35% over 2 steps) as a clear colorless liquid; R_f (10% EtOAc/hexane) 0.71; $[\alpha]_D$ +9.3 (c 2.1, CDCl_3); ^1H NMR (400 MHz, CDCl_3) δ 3.60 (m, 1H), 2.30 (d, J = 5.0 Hz, 2H), 1.93 (d, J = 2.3 Hz, 1H), 1.97-1.85 (m, 1H), 0.96-0.85 (m, 15H), 0.09-0.04 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 82.1, 75.2, 69.6, 32.3, 25.8, 24.6, 19.0, 18.1, 16.3, -4.3, -4.7; IR (CDCl_3) 3308, 2118 cm^{-1} .



(S)-5-(tert-Butyldimethylsiloxy)-6-methyl-2-heptyne. To a solution of (S)-4-(tert-butyldimethylsiloxy)-5-methyl-1-hexyne (291 mg, 1.25 mmol) in dry THF (8 mL) at -78 °C was added *n*-BuLi (1.1 mL, 1.6 M in hexane, 1.76 mmol) dropwise *via* syringe and the mixture was stirred for 20 min. Methyl iodide (135 μ L, 2.17 mmol) was added *via* syringe and the mixture was allowed to warm to 0 °C over 1.5 h. It was then warmed to ambient temperature and stirred for 30 min after which the reaction was quenched with water (20 mL). The mixture was extracted with Et₂O (3 \times 20 mL). The combined organic layers were dried (MgSO₄), filtered, and evaporated *in vacuo* at -5 °C. The residue was passed through a short plug of silica (hexane) to give the title compound as a clear colorless oil (263 mg, 1.09 mol, 88%); *R_f*(hexane) 0.58; $[\alpha]_D^{20}$ +5.7 (*c* 5.0, CDCl₃); ¹H (400 MHz, CDCl₃) δ 3.58 (dt, *J* = 6.4, 3.7 Hz, 1H), 2.23-2.21 (m, 2H), 1.92-1.80 (m, 1H), 1.75 (t, *J* = 2.5 Hz, 3H), 0.78-0.97 (m, 15H), 0.06 (s, 3H), 0.03 (s, 3H); ¹³C(100 MHz, CDCl₃) δ 76.7, 75.7, 75.2, 32.2, 25.9, 24.8, 19.1, 16.1, 18.1, 3.5, -4.3, -4.8; IR (CDCl₃) 1918, 1253 cm⁻¹.



(E),(S)-5-(tert-Butyldimethylsiloxy)-6-methyl-2-iodo-2-heptene, 56a and (E),(S)-5-(tert-butyldimethylsiloxy)-6-methyl-3-iodo-2-heptene 56b. Cyclopentadienyl zirconium hydride chloride (330 mg, 1.28 mmol) was pre-weighed in a glove box and transferred to an oven dried Schlenk tube under a stream of Ar. The flask was then flushed with argon and degassed benzene (2.0 mL) was added *via* syringe. (S)-5-(tert-Butyldimethylsiloxy)-6-methyl-2-heptyne (95 mg, 0.395 mmol) was then added *via* cannula as a solution in benzene (1.0 mL + 0.5 mL wash). The mixture was stirred under Ar with the exclusion of light at 40 °C for a period of 4 h. It was then allowed to cool to ambient temperature (15 min) and was cooled to 5 °C. I₂ (210 mg, 0.83 mmol) was added *via* syringe

as a solution in THF (0.4 M), titrating it until the color change persisted. The mixture was allowed to warm to ambient temperature and stirred for 30 min. 5 % w/v Na₂S₂O₃ (2.5 mL) was added to quench the reaction (a white precipitate resulted) and the flask was stirred vigorously for 10 min. The mixture was filtered through a short plug of Celite™ eluting with EtOAc (30 mL). Water (20 mL) was added to the eluent and the aqueous layer was washed with EtOAc (3 × 20 mL). The combined organic extracts were dried (MgSO₄) and evaporated. Purification by flash chromatography (hexane) gave the regioisomeric products **56a** (105 mg, 0.285 mmol, 70%) and **56b** (10 mg, 0.027 mmol, 7%). *Data for 56a:* *R_f* (hexane) 0.5; [α]_D²⁰ -6.5 (*c* 0.65, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 6.17 (m, 1H), 3.48 (dt, *J* = 6.6, 5.0 Hz, 1H), 2.37 (s, 3H), 2.20-2.06 (m, 2H), 1.74-1.66 (m, 1H), 0.89 (s, 9H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.05 (s, 3H), 0.03 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 138.6, 94.5, 75.9, 34.8, 33.1, 27.7, 25.9, 18.2, 17.5, -4.6, -4.2; IR (film) 2958, 2929, 1472, cm⁻¹; MS (EI) *m/z* (rel intensity) 367 [10]; HRMS (EI) *m/z* 368.1050 (368.1034 calcd for C₁₄H₂₉OSiI, MH).

Data for 56b. *R_f* (hexane) 0.55; [α]_D²⁰ -8.5 (*c* 0.8, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 6.28 (q, *J* = 7.1 Hz, 1H), 3.82 (ddd, *J* = 7.6, 4.8, 3.0 Hz, 1H), 2.56 (dd, *J* = 14.3, 7.4 Hz, 1H), 2.34 (dd, *J* = 14.4, 4.9 Hz, 1H), 1.74 (m, 1H), 1.66 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 137.4, 101.0, 75.4, 41.6, 32.6, 25.9, 18.1, 18.0, 16.9, -3.9, -4.7.

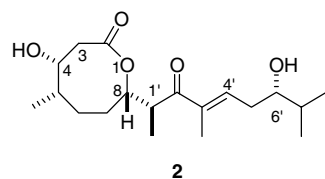


Table 1. Comparison of the ¹³C NMR data of synthetic and natural¹¹ octalactin B (**2**).

Carbon	δ_C Synthetic ^a	δ_C Natural ^b	$ \delta_{\text{Nat}} - \delta_{\text{Syn}} $
C2'	203.3	203.3	0
C2	172.5	172.6	0.1

C4'	141.4	141.4	0
C3'	137.5	137.5	0
C8	79.4	79.4	0
C6'	75.9	75.8	0.1
C4	71.4	71.4	0
C1'	44.2	44.3	0.1
C3	39.2	39.2	0
C7'	38.0	38.0	0.1
C5'	34.1	34.1	0
C5	33.9	33.9	0
C7	32.2	32.2	0
C6	22.6	22.7	0.1
CH ₃ -7'	22.0	22.0	0
CH ₃ -5	18.7	18.7	0
CH ₃ -7'	17.4	17.4	0
CH ₃ -3'	15.0	14.9	1
CH ₃ -1'	11.7	11.7	0

^aSpectrum run at 100 MHz in CDCl₃. ^bSpectrum run at 50 MHz in CDCl₃.

Table 2. Comparison of the ¹H NMR data of synthetic and natural¹¹ octalactin B (**2**).

Proton	δ_{H} Synthetic ^a	δ_{H} Natural ^{b,c}	$ \delta_{\text{Nat}} - \delta_{\text{Syn}} $
H4'	6.86, t, $J = 7.0$ Hz	6.87, t, $J = 6.8$ Hz	0.01
H8	4.75, t, $J = 10.7$ Hz	4.76, br t, $J = 9.7$ Hz	0.01
H4	4.03, br s	4.04, br s	0.01
H1', H6'	3.56-3.51, m	3.55, qu, $J = 7.2$ Hz, 3.52, br s	-

H3 _a	3.05, dd, $J = 13.3, 1.5$ Hz	3.05, dd, $J = 13.3, 1.8$	0
H3 _b	2.72, dd, $J = 13.3, 6.5$	2.70, dd, $J = 13.3, 6.1$	0.02
H5' _a	2.45, m	2.45 ddd, $J = 15.1, 6.8, 3.6$	0
H5' _b	2.35, m	Not listed	-
OH	1.96, d, $J = 4.8$ Hz	Not listed	-
H7 _a , H7 _b , H6 _a , H5, H7'	1.81-1.74, 1.73-1.68, m	1.80, 1.70, 1.65, 1.60, m	-
CH ₃ -1'	1.78, s	1.78, s	0
H6 _b	1.24-1.18, m	1.23, m	0
CH ₃ -7'	1.14, d, $J = 7.1$ Hz	1.14, d, $J = 7.2$ Hz	0
CH ₃ -1'	1.05, d, $J = 7.2$ Hz	1.05, d, $J = 7.2$ Hz	0
CH ₃ -5	0.98, d, $J = 6.6$ Hz	0.97, d, $J = 6.8$ Hz	0.01
CH ₃ -7'	0.96, d, $J = 6.8$ Hz	0.96, d, $J = 6.8$ Hz	0

^aSpectrum run at 500 MHz in CDCl₃. ^bSpectrum run at 360 MHz in CDCl₃. ^cProtons which form part of an unresolved multiplet were not listed in the original isolation paper.¹¹

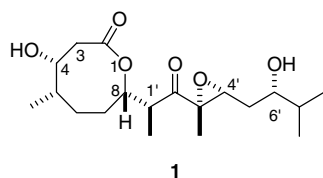


Table 3. Comparison of the ¹³C NMR data of synthetic and natural¹¹ octalactin A (**1**).

Carbon	δ_C Synthetic ^a	δ_C Natural ^b	$ \delta_{\text{Nat}} - \delta_{\text{Syn}} $
C2'	212.5	212.4	0.1
C2	172.5	172.4	0.1
C8	79.3	79.3	0
C6'	74.5	74.5	0

C4	71.3	71.3	0
C3'	62.4	62.4	0.0
C4'	58.9	58.8	0.1
C1'	42.4	42.5	0.1
C3	39.2	39.3	0.1
C7'	38.0	38.0	0.1
C5	34.0	34.0	0
C5'	32.2	32.3	0.1
C7	32.0	32.0	0
C6	22.4	22.5	0.1
CH ₃ -7'	22.1	22.0	0.1
CH ₃ -5	18.5	18.4	0.1
CH ₃ -7'	17.6	17.6	0
CH ₃ -3'	13.5	13.4	0.1
CH ₃ -1'	12.6	12.6	0

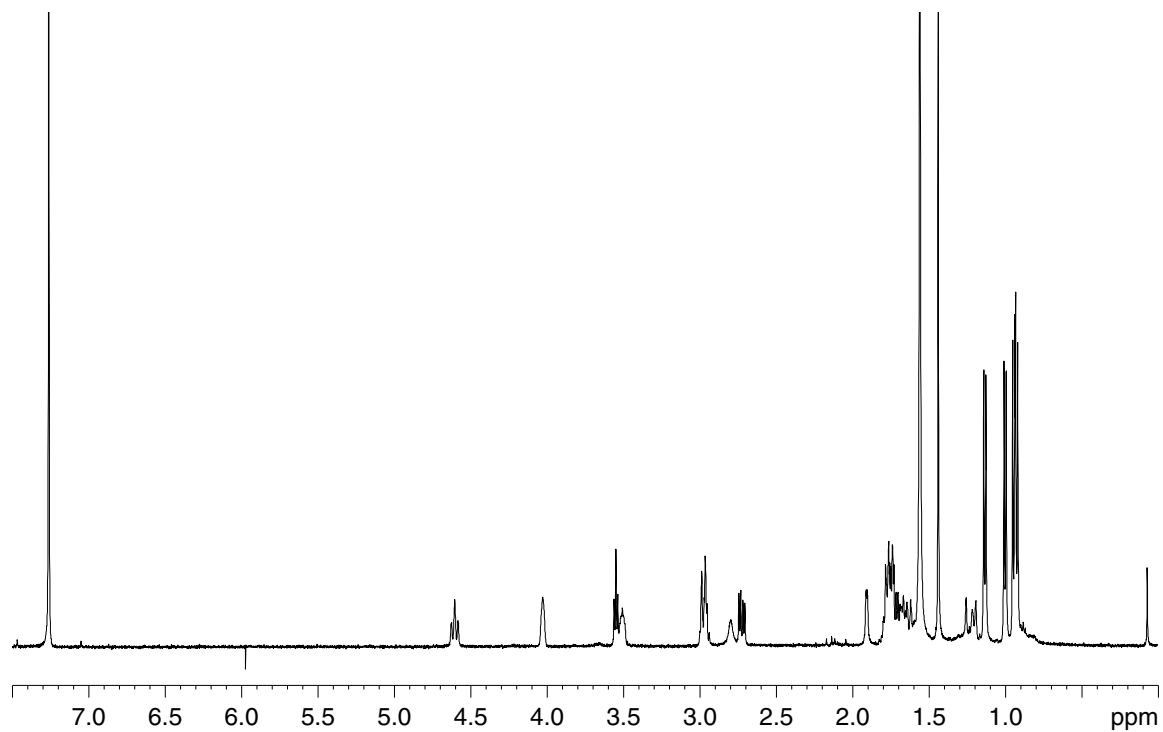
^aSpectrum run at 100 MHz in CDCl₃. ^bSpectrum run at 50 MHz in CDCl₃.

Table 4. Comparison of the ¹H NMR data of synthetic and natural¹¹ octalactin A (**2**).

Proton	δ_{H} Synthetic ^a	δ_{H} Natural ^{b, c}	$ \delta_{\text{Nat}} - \delta_{\text{Syn}} $
H8	4.60, t, $J = 10.3$ Hz	4.60, t, $J = 9.7$ Hz	0
H4	4.03, br s	4.03, br s	0
H4'	3.55, t, $J = 6.2$ Hz	3.55, t, $J = 6.2$ Hz	0
H6'	3.58-3.48, m	3.50, m	-
H1'	3.00-2.93, m	2.96, m	-
OH	2.79, br d, $J = 3.1$ Hz	Not listed	-

H3 _a	2.72, dd, $J = 13.4, 6.3$ Hz	2.72, dd, $J = 13.3, 6.1$	0
OH	1.89, br d, $J = 3.1$ Hz	Not listed	-
H5, H6 _a , H7 _a , H7 _b , H5' _a , H5' _b , H7'	1.79-1.57, m	Not listed	-
CH ₃ -1'	1.44, s	1.44, s	0
H6 _b	1.23-1.18, m	Not listed	-
CH ₃ -7'	1.13, d, $J = 7.1$ Hz	1.14, d, $J = 6.8$ Hz	0
CH ₃ -3'	1.00, d, $J = 7.0$ Hz	1.00, d, $J = 6.8$ Hz	0
CH ₃ -7'	0.94, d, $J = 6.8$ Hz	0.94, d, $J = 6.8$ Hz	0
CH ₃ -5	0.92, d, $J = 6.8$ Hz	0.92, d, $J = 6.8$ Hz	0

^aSpectrum run at 500 MHz in CDCl₃. ^bSpectrum run at 360 MHz in CDCl₃. ^cProtons which form part of an unresolved multiplet were not listed in the original isolation paper.¹¹



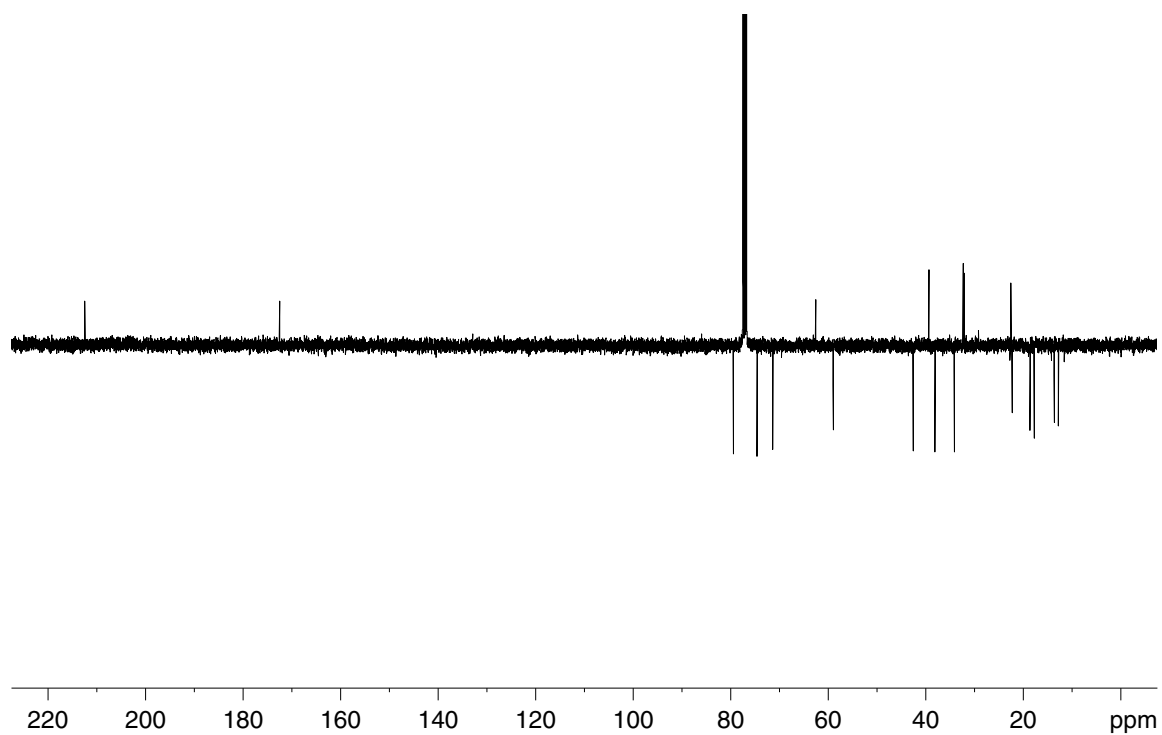
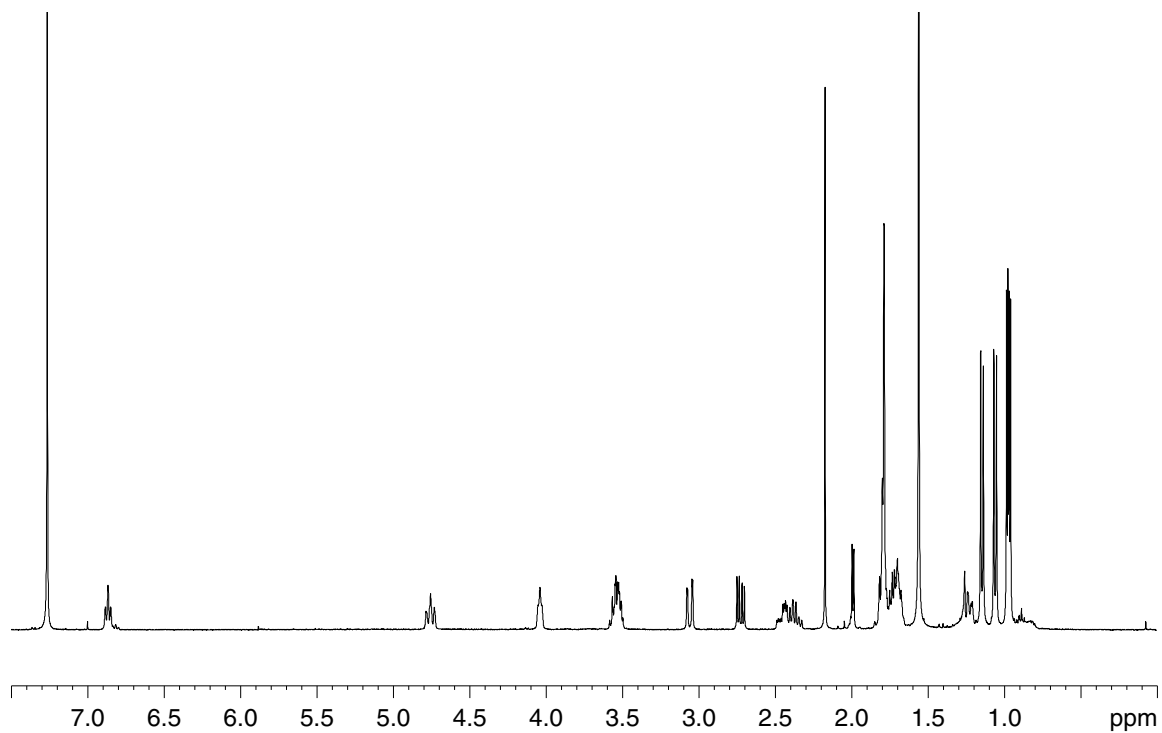


Figure 4. ^1H NMR (500 MHz, CDCl₃) and ^{13}C NMR (100 MHz, CDCl₃ APT) of synthetic (-)-octalactin A **1**.



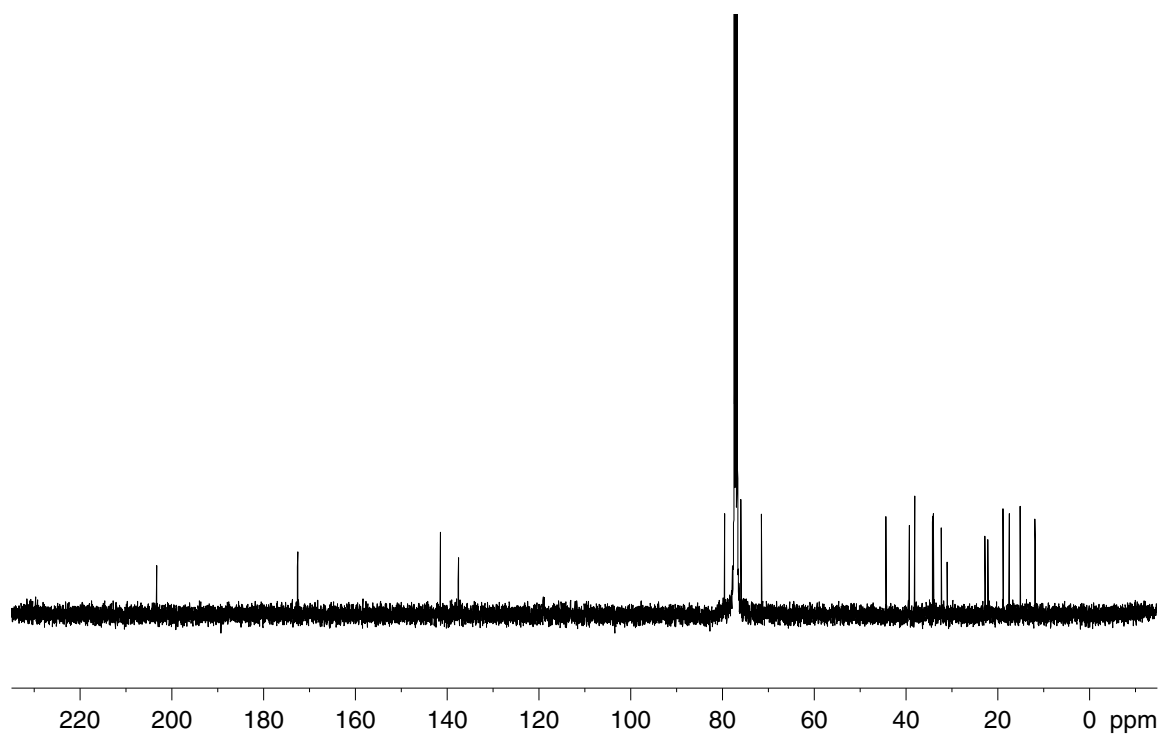


Figure 5. ^1H NMR (400 MHz, CDCl_3) and ^{13}C NMR (100 MHz, CDCl_3) of synthetic (-)-octalactin B

2.

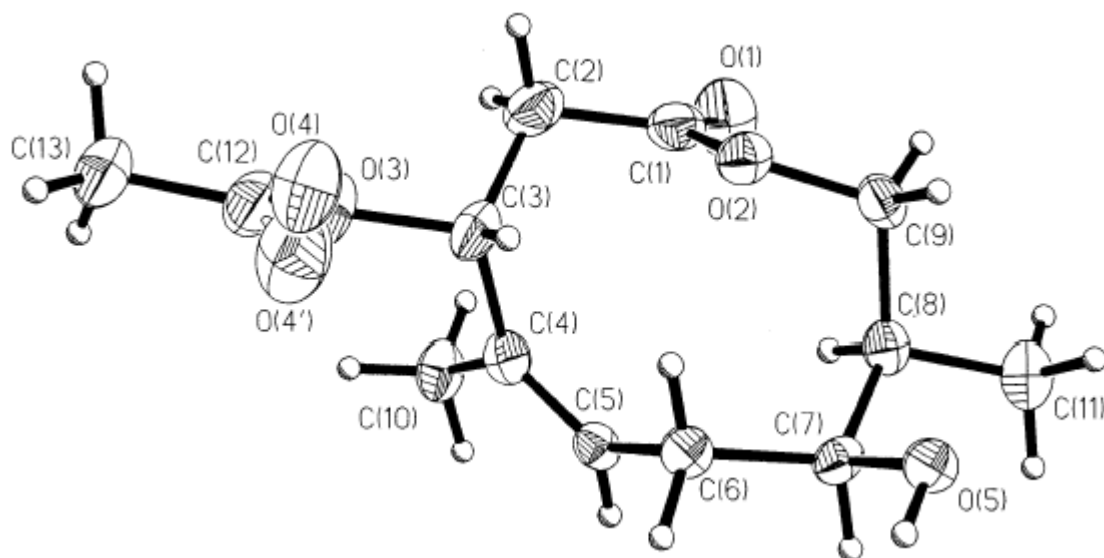
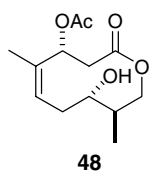


Figure 6. The X-ray crystal structure of the lactone **48**. The acetate carbonyl oxygen atom is disordered.

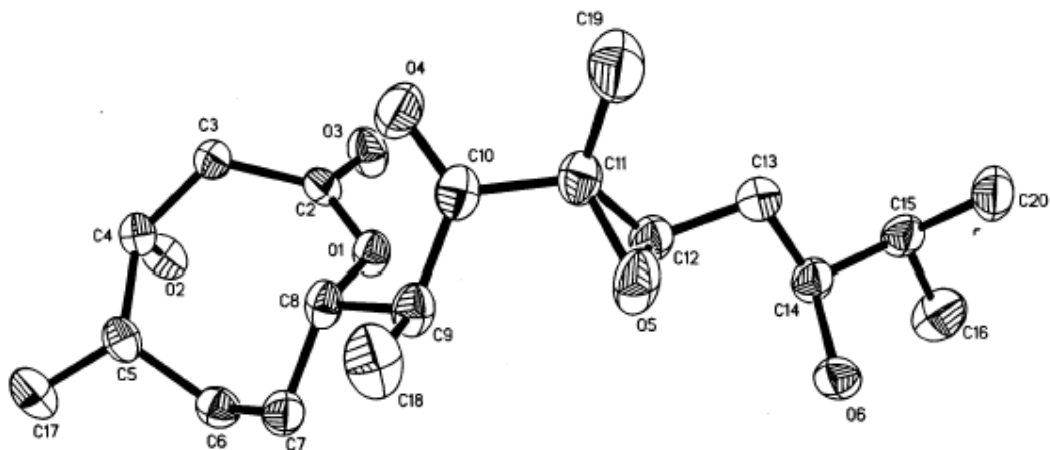
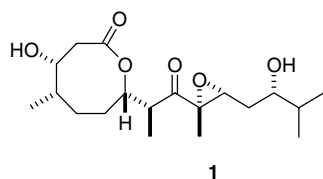


Figure 7. The X-ray crystal structure of synthetic octalactin A (**1**).

References

- (1) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T. L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199-4200.
- (2) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.
- (3) Perrin, D. D.; Amarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; 2nd ed.; Pergamon: Oxford, 1980.
- (4) Kruithof, K. J. H.; Schmitz, R. F.; Klumpp, G. W. *Tetrahedron* **1983**, *39*, 3073-3081.
- (5) Ficini, J.; Normant, H. *Bull. Soc. Chim. Fr.* **1964**, 1294-1298.
- (6) Ullrich, F.-W.; Rotscheldt, K.; Breitmaier, E. *Chem. Ber.* **1986**, *119*, 1737-1744.

- (7) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, 30, 7121-7124.
- (8) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, 113, 4092-4096.
- (9) Mori, K.; Koseki, K. *Tetrahedron* **1988**, 44, 6013-6020.
- (10) Denmark, S. E.; Fujimori, S. *Synlett* **2001**, 1024-1029.
- (11) Tapiolas, D. M.; Roman, M.; Fenical, W.; Stout, T. J.; Clardy, J. *J. Am. Chem. Soc.* **1991**, 113, 4682-4683.