A Formal Synthesis of Ionomycin Featuring a Permanganate-Mediated Oxidative Cyclisation

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General Information and Materials

All reagents and solvents were obtained from commercial suppliers and used as supplied unless otherwise stated. Reactions requiring anhydrous conditions were conducted in flame-dried glassware under a nitrogen atmosphere. The concentration of alkyllithium reagents was determined by titration using BHT and fluorene. Tetrahydrofuran and diethyl ether were freshly distilled from sodium benzophenone ketyl under nitrogen prior to use. Dichloromethane, acetonitrile, pyridine, dimethylsulfoxide, pentane, toluene and 1,2-dimethoxyethane were freshly distilled from calcium hydride under nitrogen; methanol was distilled from magnesium methoxide under nitrogen. Amines were distilled over calcium hydride prior to storage over sodium hydroxide. Solvents were removed by rotary evaporator at or below 40 °C. Thin layer chromatography was conducted on Merck Kieselgel 60 F 254 aluminium backed plates, visualised by UV and/or staining with basic KMnO 4 or phosphomolybdic acid (PMA). Column chromatography was carried out using Merck Flash Silica Gel 60 (230–400 mesh). The term petrol refers to the fraction of petroleum ether boiling between 40 and 60 °C. 1H and 13C NMR spectra were recorded in CDCl 3 solutions on a Bruker DPX 300 spectrometers at 300 MHz for 1H NMR and 75 MHz for 13C NMR and referenced to the residual chloroform signal (δH = 7.27 ppm, δC = 77.2 ppm, middle peak of triplet). Chemical shifts are quoted in parts per million (ppm) and the coupling constants (J) in Hertz (Hz). Multiplicities in 1H NMR spectra are quoted as: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, app. = apparent, obs. = obstructed. High resolution mass spectra were collected on a Micromass LCT Spectrometer and low resolution mass spectra collected on a Waters ZMD spectrometer using ES ionisation unless stated otherwise. Infra-red spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer, using a diamond transmission accessory for solids or neat on sodium chloride plates. Elemental Analysis was carried out by the Microanalysis Laboratory, Department of Chemistry, University of Leeds, using a Carlo Erba Elemental Analyser 1108. Melting points were measured using a Reichert Hot Stage apparatus. Optical rotations were recorded at ambient temperature (20±4 °C) as solutions in CHCl 3, using a 2.5 or 10 cm cell on an AA 1000 polarimeter and reported in 10−1deg cm2 g−1.

Experimental Procedures

Compound 11

TBS protection: A solution of hydroxyster 5 (10.0 g, 85 mmol, 1.0 equiv) in DCM (150 mL) was treated with imidazole (6.9 g, 102 mmol, 1.2 equiv), DMAP (1.03 g, 8.5 mmol, 10 mol%) and TBSCl (14.0 g, 93 mmol, 1.1 equiv) at 0 ºC and the reaction mixture allowed to stir at rt for 3 d. Water (100 mL) was added and the aqueous layer was extracted with DCM (5×50 mL). The combined extracts were dried (MgSO 4), filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel (petroleum ether–diethyl ether 10:1) to afford silyl ether 6 (18.5 g, 79.7 mmol, 94%) as a colourless oil; [α]D24 = −18.8 (c 1.04 in CHCl 3); lit.[1] [α]D = −21.2 (c 3.21 in DCM). The 1H and 13C NMR spectroscopic data agrees with those reported the literature.[1]
Reduction: Diisobutylaluminium hydride (1.5 M solution in toluene, 65.0 mL, 98 mmol, 2.5 equiv) was added dropwise to a solution of ester 6 (9.1 g, 39.2 mmol, 1 equiv) in DCM (200 mL) at –78 ºC and stirred for 1.5 h, before being allowed to warm gradually to –30 ºC for a further 1 h. Sat. aq. sodium potassium tartrate (Rochelle’s salt) solution (150 mL) was added and the mixture stirred at rt for 1 h, until the suspension cleared. The aqueous layer was extracted with ether (3×100 mL) and the combined extracts, washed with brine (100 mL), dried (MgSO4), filtered and concentrated in vacuo to afford crude alcohol 7 (7.4 g, 36.2 mmol, 92%) as a pale yellow oil, which was used directly without further purification.

Swern oxidation: A solution of DMSO (2.4 mL, 34.1 mmol, d 1.102, 2.6 equiv) in DCM (60 mL) was cooled to –78 ºC and oxalyl chloride (1.5 mL, 17.0 mmol, d 1.455, 1.3 equiv) added dropwise, maintaining the internal temperature below –60 ºC. After 30 min at –78 ºC, a solution of crude alcohol 7 (2.68 g, 13.1 mmol, 1 equiv) in DCM (10 mL) was added via cannula over 30 min, maintaining the temperature below –70 ºC. Stirring was continued for a further 2 h and the mixture warmed gradually to –55 ºC whereupon freshly distilled triethylamine (11.9 mL, 85.2 mmol, d 0.726, 6.5 equiv) was added over 15 min. The reaction was allowed to warm to rt and a solution of 2 N HCl-sat. aq. brine (50 mL) added. The organic layer was separated and washed with brine (50 mL), dried (MgSO4), filtered and concentrated in vacuo to afford the aldehyde 8 (2.65 g, 13.1 mmol, ca. 100%) as a pale yellow oil, which was used directly without any further purification.

Brown crotylboration. 2, 3 trans-2-Butene (7.9 mL, 79.3 mmol, 2 equiv) was added via cannula to a solution of potassium tert-butoxide (4.46 g, 39.7 mmol, 1 equiv), which had been rigorously dried (80 ºC, 18 h, under high vacuum) in THF (75 mL). n–BuLi (1.6 M solution in hexanes, 24.8 mL, 39.7 mmol, 1 equiv) was added dropwise at –78 ºC and the mixture was warmed to –50 ºC for 30 min before being re−cooled to –78 ºC. B−Methoxydiisopinocampheyl borane (1.0 M solution in THF, 15.2 g, 47.5 mmol, 1.2 equiv) was added and the reaction stirred for 30 min after which time the viscous yellow mixture dissolved to a clear solution. BF3·OEt2 (6.5 mL, 51.6 mmol, 1.3 equiv) was added dropwise to the “ate” complex to form the requisite (Ipc)2B−crotyl species in situ, which was stirred at –78 ºC for 30 min (white suspension). Aldehyde 8 (1.0 M solution in THF, 9.9 g, 47.6 mmol, 1.2 equiv) was added dropwise and the reaction stirred at –78 ºC for 12 h. A 3 M NaOH solution (150 mL) was added followed by H2O2 solution (30 % v/v, 50 mL) and the mixture allowed to warm to rt over 18 h. The organic layer was separated and the aqueous layer extracted with ethyl acetate (5×150 mL). The organic phase was washed with sat. aq. Na2S2O3 (200 mL) and brine (200 mL), dried (MgSO4), filtered and concentrated in vacuo. The residual oil was purified by chromatography on silica gel (petroleum ether–ethyl acetate 10:1) to give compound 11 (6.57 g, 25.4 mmol, 52%) as a pale-yellow oil: [α]D20 = −21.3 (c 1.05 in CHCl3). IR (film): νmax = 3493, 2955, 2924, 2854, 1462, 1256, 1088 cm−1. 1H NMR (300 MHz, CDCl3): δ = 5.95 (1H, ddd, J15.5, 12, 8.5, C21H), 5.11–5.03 (2H, m, C22H2), 3.94–3.80 (1H, m, C19OH), 3.75 (1H, dd, J10.0, 4.1, C17H2), 3.62 (1H, dd, J 9.7, 8.2, C17H2), 3.39 (1H, dd, J 8, 3.6, C19H), 2.43–2.90 (1H, m, C20H), 1.86–1.70 (1H, m, C18H), 1.12 (3H, d, J 6.9, C20Me), 0.91 (9H, s, t-Bu), 0.82 (3H, d, J 6.9, C18Me), 0.08 (6H, s, SiMe2). 13C NMR (75 MHz, CDCl3): δ = 140.0 (C21H), 114.9 (C22H2), 80.3 (C19H), 68.8 (C17H2), 41.3 (C18H), 37.5 (C20H), 25.8 (CMe3), 18.1 (CMe3), Si t-Bu, 17.7 (C20Me), 13.4 (C18Me), −5.4 (SiMe2). 13C NMR (75 MHz, CDCl3): δ = 140.0 (C21H), 114.9 (C22H2), 80.3 (C19H), 68.8 (C17H2), 41.3 (C18H), 37.5 (C20H), 25.8 (CMe3), 18.1 (CMe3), Si t-Bu, 17.7 (C20Me), 13.4 (C18Me), −5.4 (SiMe2). LRMS: m/z = 259.2 [(M + H)+, 100%], 241.2 (50), 203.1 (25). HRMS (CI): Found: 259.2096 [M+H]+. C14H30O2Si requires: 259.2093. Compound 12

Triflic acid (26 μL, 294 μmol, d 1.696, 0.3 mol%) was added to a solution of homoallylic alcohol 11 (2.54 g, 9.8 mmol, 1 equiv) and p-methoxybenzyl trichloroacetimidate (3.61 g, 12.8 mmol, 1.3 equiv) in DCM–cyclohexane (45 mL, 1:2) at 0 ºC. The mixture was allowed to warm to rt and then stirred for 18 h
whereupon a white precipitate formed. The reaction was quenched with water (50 mL) and the solid filtered (washed with petroleum ether). The combined filtrate was washed with sat. aq. NaHCO₃ (2 × 50 mL) and brine (50 mL) dried (MgSO₄), filtered and concentrated in vacuo. The residual oil was purified by chromatography on silica gel (petroleum ether–diethyl ether 10:1) to afford compound 12 (2.75 mg, 7.3 mmol, 75%) as a colourless oil: [α]D²³ = +22.6 (c 1.03 in CHCl₃). IR (film): νmax = 2951, 2926, 2861, 1613, 1513, 1462, 1246, 1084, 1040 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.27 (2ArH, d, J 8.7), 6.88 (2ArH, d, J 8.7), 5.91 (1H, d, J 11.8, OCH₂H₂Ar), 4.51 (1H, d, J 11.8, OCH₂H₂Ar), 3.81 (3H, s, OMe), 3.73 (1H, dd, J 9.7, 5.1, C₁₇H₄H₂Ar), 3.61 (1H, dd, J 9.5, 3.4, C₁₇H₂H₂Ar), 3.25 (1H, dd, J 8.5, 3.4, C₁₉H₂H₂Ar), 2.53–2.39 (1H, m, C₂₀H), 1.85–1.70 (1H, m, C₁₈H), 1.10 (3H, d, J 6.8, C₂₀Me), 0.90 (3H, d, J 6.8, C₁₈Me), 0.89 (9H, s, t-Bu), 0.029 and 0.026 (3H each, s, SiMe₂). ¹³C NMR (75 MHz, CDCl₃): δ = 159.2 (C₂₁H), 141.0 (C₂₁H), 131.6 (C₂₁H), 129.4 (2C₂₁H), 114.6 (C₂₂H₂), 113.9 (2C₂₁H), 84.5 (C₁₉H), 74.7 (OCH₂H₂Ar), 65.0 (C₁₇H₂), 55.5 (OMe), 40.9 (C₂₀H), 39.1 (C₂₁H), 26.2 (C₆Me₃), 18.6 (C₂₀Me), 18.5 (C₂₂H₂), 14.6 (C₁₈Me), −4.9 and −5.1 (SiMe₂). LRMS (EI): m/z = 401.1 [(M + Na)+, 100%], 379.2 (23). HRMS: Found: 401.2473 [M+Na]+. C₂₂H₃₈O₃Na₂₈Si requires: 401.2488.

Compound 13

Compound 13 was prepared using a Wacker oxidation as modified by Smith.⁴ A suspension of the alkene 12 (1.04 g, 2.75 mmol, 1 equiv), Pd(II)Cl₂ (97 mg, 0.55 mmol, 20 mol%), Cu(OAc)₂·H₂O (1.1 g, 5.5 mmol, 2 equiv) in N,N-dimethylacetamide (4 mL) and water (0.6 mL) was placed under O₂ (1 atm.) and stirred at rt for 3 d. The mixture was diluted with ether (20 mL) and filtered through Celite washing with further aliquots of ether (3 × 30 mL). The combined extracts were washed with brine (3 × 30 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The residual oil was purified by chromatography on silica gel (petroleum ether–ether 19:1 → 9:1) to give compound 13 (910 mg, 2.31 mmol, 89% based on the consumed starting material) as a colourless oil and starting alkene 12 (20.6 mg, 54 μmol, 2%). [α]D¹⁹ = −17.9 (c 0.47 in CHCl₃). IR (film): νmax = 2955, 2930, 2854, 2879, 1712, 1512, 1462, 1246, 1170, 1079, 1037 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.22 (2ArH, d, J 8.7, Ar), 6.87 (2ArH, d, J 8.7, Ar), 4.49 (1H, d, J 10.2, OCH₂H₂Ar), 4.42 (1H, d, J 10.7, OCH₂H₂Ar), 3.81 (3H, s, OMe), 3.74–3.63 (2H, m, C₁₇H₂H₂ and C₁₉H), 3.57 (1H, dd, J 9.7, 6.2, C₁₇H₂H₂), 2.97 (1H, dq, J 7.2, 7.1, C₂₀H), 2.17 (3H, s, C₂₂H₂), 1.99–1.85 (1H, m, C₁₈H), 1.09 (3H, d, J 6.7, C₂₀Me), 0.98 (3H, d, J 7.2, C₁₈Me), 0.91 (9H, s, t-Bu), 0.088 (6H, s, SiMe₂). ¹³C NMR (75 MHz, CDCl₃): δ = 212.6 (C₂₁), 159.3 (C₂₁), 131.0 (C₂₁), 129.5 (C₂₂H₂), 113.9 (C₂₁H), 83.6 (C₁₉H), 74.3 (OCH₂H₂Ar), 64.5 (C₁₇H), 55.4 (OMe), 49.6 (C₂₀H), 38.5 (C₁₈H), 30.7 (C₂₂H₂), 26.1 (C₂₂H₂), 18.4 (C₂₂H₂), 15.0 (C₂₀Me), 13.6 (C₁₈Me), −5.2 and −5.3 (SiMe₂). LRMS: m/z = 417.3 [(M + Na)⁺, 100%], 241.2 (37). HRMS (EI): Found: 401.2473 [M+Na]+. C₂₂H₃₈O₄Si requires: 401.2488.

Compound 3

A solution of lithium diisopropylamide [2.83 mmol, 2.6 equiv, prepared from diisopropylamine (1.75 mL, 1.25 mmol, d 0.722, 4.4 equiv) and n-BuLi (1.5 M solution in hexanes, 1.9 mL, 2.83 mmol, 1 equiv) at -30 °C in THF (6 mL)] at -78 °C was treated dropwise with TMSCl (0.91 mL, 7.19 mmol, d 0.856, 6.6 equiv).
and the pre-cooled (−78 °C) ketone 13 (430 mg, 1.1 mmol, 1 equiv) as a solution in THF (4 mL). The reaction mixture was stirred at −78 °C for 30 min after which time the cooling bath was removed and the solution was allowed to warm to rt, whereupon it was poured into a mixture of hexanes and sat. aq. NaHCO₃ (1:1, 10 mL). The organic layer was washed with sat. aq. NaHCO₃ (10 ml) and dried over K₂CO₃ for 2 h and concentrated in vacuo to give the crude enol silyl ether 3 which was pure by NMR and used directly in the next reaction without purification. ¹H NMR (300 MHz, CDCl₃): δ = 7.27 (2ArH, d, J=8.2), 6.86 (2ArH, d, J=8.7), 4.56 (1H, d, J=10.7, OCH₃H₂Ar), 4.41 (1H, d, J=10.7, OCH₃H₂Ar), 4.14 (1H, s, CH₂H₂H₂b), 4.05 (1H, s, CH₂H₂H₂b), 3.80 (3H, s, OMe), 3.69 (1H, dd, J=9.7, 4.6, C17H₂H₂b), 3.46 (1H, dd, J=6.7, 5.6, C19H), 2.50 (1H, dq, J=6.7, 6.7, C20H), 1.97–1.82 (1H, m, C18H), 1.06 (3H, d, J=6.7, C20Me), 0.98 (3H, d, J=6.7 C18Me), 0.90 (9H, s, t-Bu), 0.24 (9H, s, SiMe₂), 0.04 (6H, s, SiMe₂). ¹³C NMR (75 MHz, CDCl₃): δ = 161.4 (C21), 159.1 (C₆Ar), 131.8 (C₁Ar), 129.6 (2C ArH), 113.7 (2C₆ArH), 89.6 (C22H₂), 73.9 (OCH₃Ar), 64.7 (C17H₂), 55.4 (OMe), 43.1 (C20H), 38.1 (C18H), 26.2 (CMe₃), 15.6 (C20Me), 15.3 (C18Me), 0.3 (SiMe₂), −5.2 (SiMe₂).

**Compound 15**

The alkyne 15 was synthesised in 6 steps (35% overall yield) from neryl acetate (14) as shown in the following Scheme:

\[
\begin{align*}
\text{14} & \quad \text{OAc} \\
\text{n-BuLi (1.6 M in hexanes, 15.6 mL, 24.9 mmol, 1 equiv)} & \quad \text{DCM, 0 °C, 1 h} \\
\text{96% (172 mmol scale)} & \quad \text{OAc} \\
\text{HIO₄ (1.1 equiv)} & \quad \text{THF-H₂O, 0 °C, 45 min} \\
\text{85% (151 mmol scale)} & \quad \text{OAc} \\
\text{ethylene glycol (2.0 equiv)} & \quad \text{p-TSA (1 mol%), PhH, Δ (−H₂O)} \\
\text{94%} & \quad \text{213 mmol scale} \\
15 & \quad \text{Cl} \\
\text{C₇H₁₀O₂} & \quad \text{MW: 194.27} \\
\end{align*}
\]

**Compound 16**

\[
\begin{align*}
\text{15} & \quad \text{C₇H₁₀O₂} \\
\text{MW: 194.27} & \quad \text{OAc} \\
\text{n-BuLi (1.1 equiv)} & \quad \text{THF, −78 to 0 °C} \\
\text{94% (22.6 mmol scale)} & \quad \text{OAc} \\
\text{ClCO₂Me (2.0 equiv)} & \quad \text{THF, −50 °C} \\
\text{94% (22.6 mmol scale)} & \quad \text{OAc} \\
\text{C₇H₁₀O₂} & \quad \text{CO₂Me} \\
\text{MW: 252.31} & \quad \text{CO₂Me} \\
\end{align*}
\]

n-BuLi (1.6 M in hexanes, 15.6 mL, 24.9 mmol, 1.1 equiv) was added to a stirred solution of alkyne 15 (4.4 g, 22.6 mmol, 1 equiv) in THF (125 mL) at −78 °C. The temperature was allowed to rise to −5 °C. The reaction mixture was re-cooled to −90 °C and freshly distilled methyl chloroformate (3.5 mL, d 1.223, 45.3 mmol, 2 equiv) added in one portion. The solution was allowed to warm to −10 °C over 2 h whereupon sat. aq. NH₄Cl (100 mL) was added and the organic layer separated. The aqueous layer was extracted with ether (5×150 mL) and the combined organic extracts dried over MgSO₄, filtered and concentrated in vacuo. The residual brown oil was purified by chromatography on silica gel (petroleum ether–diethyl ether 5:1) to afford compound 16 (5.35 g, 21.2 mmol, 94%) as a colourless oil. ¹H and ¹³C NMR spectroscopic data agree with those previously reported.⁵
Compound 17

A solution of MeLi·LiBr (1.5 M solution in hexanes, 16.9 mL, 25.4 mmol, 2.2 equiv) was added dropwise to a stirred suspension of CuI (2.40 g, 12.7 mmol, 1.1 equiv) in THF (100 mL) at –78 °C. The flask was transferred to a cooling bath at –25 °C and stirred for 35 min, in which time the internal temperature rose to –25 °C. The mixture was cooled to –85 °C and the alkynyl ester 16 (2.91 mg, 11.5 mmol, 1 equiv) in THF (50 mL) was added dropwise over 45 min and the resulting mixture stirred for 3 h at –85 °C. Pre-cooled methanol (15 mL) was added to quench the reaction and after a further 15 min at –85 °C, the mixture was poured into rapidly stirring saturated aqueous NH4Cl (150 mL). The organic layer was separated and the aqueous layer was extracted with ether (5 × 50 mL). The combined extracts were washed with brine (2 × 30 mL), dried (MgSO4) and concentrated in vacuo. The residual pale-yellow oil was purified by chromatography on silica gel (petroleum ether–ether 2:1) to afford compound 17 (2.81 g, 10.5 mmol, 96%) as a colourless oil. IR (film): νmax = 2952, 2860, 1717, 1648, 1436, 1378, 1271, 1157 cm−1. 1H NMR (300 MHz, CDCl3): δ = 5.67 (1H, s, C31H), 5.19 (1H, t, J7, C27H), 4.86 (1H, t, J4.7, C23H), 4.02–3.81 (4H, m, OCH2CH2O), 3.69 (3H, s, OMe), 2.66 (2H, t, J 7.7, C25H2), 2.24–2.14 (4H, m, C28H2 and C29H2), 1.90 (3H, d, J 1.3, C30Me), 1.78–1.66 (2H, m, C24H2), 1.70 (3H, s, C26Me). 13C NMR (75 MHz, CDCl3): δ = 166.9 (C32), 160.8 (C30), 135.2 (C26), 125.0 (C27H), 116.0 (C31H), 104.5 (C23H), 65.0 (OCH2CH2O), 51.0 (OMe), 33.8 (C29H2), 32.4 (C24H2), 26.6 (C28H2 or C25H2), 26.3 (C28H2 or C25H2), 25.6 (C30Me), 23.4 (C26Me). LRMS: m/z = 291.3 [(M+Na)+, 100%], 269.3 (38). Elemental Analysis: Found: C 67.2, H 9.3%. C15H24O3 requires C 67.14, H 9.01%.

Compound 18

A magnetically-stirred, heterogeneous mixture of ester 17 (2.44 g, 9.2 mmol, 1.0 equiv), NaOH (2.00 g, 50.0 mmol, 5.5 equiv), NaHCO3 (382 mg, 4.6 mmol, 0.5 equiv) in methanol (30 mL) and water (120 mL) was refluxed for 2 h, by which time the mixture became homogeneous. After cooling to 0 °C, ether (200 mL) was added and the mixture acidified with 2 M HCl. The organic layer was separated and the aqueous layer extracted with ether (4 × 200 mL). The combined extracts were dried (MgSO4), filtered, and concentrated in vacuo to give the crude acid as a yellow oil. A solution of the crude acid in ether (20 mL) was cooled to 0 °C and treated with 1-chloro-N,N-trimethyl-1-propen-1-amine (Aldrich, 1.56 mL, 11.8 mmol, 1.25 equiv) and the reaction mixture was stirred for 30 min before being concentrated in vacuo. In a separate flask, a solution of (1R,2S)-camphor-10,2-sultam (Aldrich, 1.94 g, 9.0 mmol, 1.0 equiv) in toluene (10 mL) was added dropwise to a solution of sodium hydride (55% dispersion in mineral oil, 540 mg, 13.6 mmol, 1.5 equiv) in toluene (10 mL), which had been pre-washed with anhydrous pentane (3 × 5 mL). The grey suspension was stirred at rt for 1 h and the crude activated carboxylic acid (prepared as described above) in toluene (20 mL) added dropwise via cannula at rt and stirred for a further 3.5 h. The orange solution was treated with sat. aq. NaHCO3 (4 × 20 mL) and then extracted with ether (5 × 50 mL). Purification by chromatography on silica gel (petroleum ether–ether 2:1 → 1:1) gave compound 18 (3.75 g, 8.3 mmol, 90% overall yield) as a viscous yellow oil: [α]D22 = +45.8 (c 1.53 in CHCl3). IR (film): νmax = 2956, 2881, 1674, 1628, 1451, 1327, 1268, 1116, 1055, 1039 cm−1. 1H NMR (300 MHz, CDCl3): δ = 6.27 (1H, s, C31H), 5.15 (1H, t, J 6.9, C27H), 4.81 (1H, t, J 4.6, C23H), 4.00–3.75 (5H, m, OCH2CH2O,
Compound 21

To a rapidly stirred mixture of N-enoyl sultam 18 (90 mg, 0.2 mmol, 1 equiv), pH 6 acetate buffer solution (0.75 mL) and acetone (5 mL) cooled to –35 ºC was added a solution of KMnO₄ (63 mg, 0.4 mmol, 2 equiv) and acetic acid (26 μL, 0.44 mmol d 1.049, 2.2 equiv) in water (1.2 mL) and acetone (2 mL) over 2 h. After a further 3 h, the brown mixture was treated with a solution of sodium thiosulfate (5 g) in water (10 mL) and ether (10 mL). After 15 min, the remaining solid was filtered off and the organic layer was separated, re-extracting the aqueous layer with ether (5×10 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ (10 mL), dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel (pre-washed with a 1% solution of triethylamine) (petroleum ether–ether 2:1) to afford the intermediate tetrahydrofuran diol 19 (54 mg, 0.11 mmol, 54%) as an inseparable mixture of diastereoisomers (ca. 7:1 according to 1H NMR analysis), which was used directly in the next reaction.

A solution of the diol 19 (54 mg, 0.108 mmol, 1 equiv) in ethyl acetate (1.5 mL) was ozonolysed (5 psi, 90 V) at –80 ºC for 1–2 min. After discharge of excess ozone in a stream of nitrogen, the solvent was evaporated and the residue containing the ester 20 treated with p-TSA (1 mg) in DCM (1 mL) for 8 h at rt. The reaction mixture was diluted with DCM (5 mL), washed with sat. aq. NaHCO₃ (2×2 mL), dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel (petroleum ether–diethyl ether 1:3) to give compound 21 (34 mg, 75 μmol, 69%) as a white solid: mp 172–174 ºC (EtOH). [α]D₁⁹ = +63.7 (c 0.86 in CHCl₃). IR (film): νmax = 3518, 2955, 2879, 1762, 1696, 1452, 1329, 1212, 1132, 1060 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 4.59 (1H, s, C₃₁H), 4.02 (1H, dd, J 8.8, 6.3, C₁′H), 3.91 (1H, dd, J 7.1, 3.5, C₂₇H), 3.56 (1H, d, J 13.8, C₈’H₃H₃), 3.47 (1H, d, J 13.8, C₈’H₃H₃), 2.63–1.68 (13H, m), 1.44–1.32 (2H, m), 1.36 (3H, s, C₃₀Me), 1.27–1.25 (1H, m), 1.27 (3H, s, C₂₆Me), 1.16 and 0.98 (3H each, s, C₇’Me₂). ¹³C NMR (75 MHz, CDCl₃): δ = 177.3 (C₂₃), 169.1 (C₃₂), 87.7 (C₃₀), 84.5 (C₂₆), 82.0 (CH), 75.3 (CH), 65.2 (C₈’H₂), 53.1 (C₈’H₂), 49.1 (C), 48.0 (C), 44.7 (CH), 38.1 (CH₂), 33.0 (CH₂), 32.9 (CH₂), 29.8 (CH₂), 28.8 (CH₂), 28.0 (CH₂), 26.6 (CH₂), 23.8 (C₃₅Me and C₂₆Me), 21.0 and 20.0 (C₇’Me₂). LRMS: m/z = 455.4 [(M+H)⁺, 100%], 472.4 (87), 427.4 (75), 253.7 (47), 212.7 (50). HRMS: Found: 456.2056 [M+H⁺]. C₂₂H₃₄NO₃S₂ requires: 456.2056.
The levorotatory enantiomer of lactone 21 (see above) was similarly prepared by KMnO₄ oxidation of the diene (−)-18 and its absolute and relative configuration determined by X-ray crystallography. Crystallographic data for lactone (−)-21 have been deposited at the Cambridge Crystallographic Data Centre as Supplementary Publication no. CCDC 774938. Copies of these data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk/conts/retrieving.html.

Best results in the forgoing sequence were obtained when the ozonolysis was terminated as soon as a faint blue colour is detected. In the presence of excess ozone, the ester 20 is further degraded to the lactone 29.

IR (film): \(\nu_{\text{max}} = 3481, 3367, 2955, 2879, 1768, 1693, 1458, 1414, 1376, 1325, 1268, 1234, 1218, 1164, 1132, 1088, 1063 \text{ cm}^{-1}\). ¹H NMR (300 MHz, CDCl₃): \(\delta = 4.74 (1H, s, C31H), 3.90 (1H, dd, J 7.6, 5, C1′H), 3.60 (1H, d, J 13.8, C8′H2H6), 3.48 (1H, d, J 14.1, C8′H4H6), 2.82–2.45 (3H, m), 2.20–1.80 (6H, m), 1.50–1.15 (3H, m), 1.47 (3H, s, C30Me), 1.14 and 0.97 (3H each, s, C7′Me2). ¹³C NMR (75 MHz, CDCl₃): \(\delta = 177.7 (C27), 168.6 (C32), 86.8 (C30), 74.5 (CH), 65.1 (C1′H), 53.0 (C8′H2), 49.1 (C), 48.0 (C), 44.6 (CH), 38.0 (CH2), 32.8 (CH2), 29.8 (CH2), 29.0 (CH3), 26.5 (CH2), 24.1 (C30Me), 20.9 and 19.9 (C7′Me2). LRMS: \(m/z = 371.9 [(M+H)^+ , 90\%], 353.9 (87), 215.9 (100). \)

Elemental Analysis: Found: C 54.7, H 6.9, N 3.5, S 8.55%. C₁₇H₂₅O₆NS requires: C 54.97, H 6.78, N 3.77, S, 8.63%.

Compound 22

To a magnetically stirred solution of lactone 21 (30 mg, 65 µmol, 1 equiv) in THF (1 mL) at −10 ºC, was added BH₃·SMe₂ (2.0 M solution in toluene, 50 µL, 1.5 equiv) followed by NaBH₄ (2.2 mg, 58 µmol, 1.5 equiv). The effervescing mixture was stirred at −10 ºC for 2 h, whereupon 10% MeOH in DCM (1 mL) was added. The solvent was removed in vacuo and the residue was purified by chromatography on silica gel (petroleum ether–ethyl acetate 1:1 → DCM–methanol 9:1) to give compound 22 (12.3 mg, 50 µmol, 76%) as a white solid: mp 110–111 ºC (ethyl acetate–petroleum ether); \([\alpha]D_{19}^- = +11.6 (c 0.45 \text{ in } \text{CHCl}_3)\); IR (film): \(\nu_{\text{max}} = 3405, 3208, 2974, 2955, 2879, 1731, 1316, 1268, 1082, 1053, 1018 \text{ cm}^{-1}\). ¹H NMR (300 MHz, CDCl₃): \(\delta = 4.02 (1H, t, J 7.4, C27H), 3.75 (1H, dd, J 10.5, 3.1, C32H_2H_6), 3.70 (1H, dd, J 7.4, 3.1, C31H), 3.55 (1H, dd, J 10.5, 7.2, C32H_4H_6), 2.63 (2H, app. t, J 8.3, C24H_2), 2.27–1.87 and 18.2–1.56 (8H, m, C25H_2, C28H_2, C29H_2, C31O_H and C32O_H), 1.43 (3H, s, C30Me), 1.18 (3H, s, C26Me). ¹³C NMR (75 MHz, CDCl₃): \(\delta = 176.7 (C23), 87.2 (C30), 85.4 (C26), 82.1 (C27H), 76.8 (C31H), 63.3 (C32H_2), 32.8, 29.5, 29.1 and 27.1 (C24H_2, C25H_2, C28H_2 and C29H_2), 23.9 and 22.5 (C26Me and C30Me). LRMS: \(m/z = 245.3 [(M+H)^+ , 100\%], 262.3 (89), 227.3 (23). \)

Elemental Analysis: Found: C 58.75, H 8.35%. C₁₂H₂₀O₅S requires: C 59.00, H 8.25%.
Dibutyltin oxide (787 mg, 3.16 mmol, 1.2 equiv) was added to a solution of diol 22 (385 mg, 1.58 mmol, 1 equiv) in benzene (30 mL) at rt. The reaction mixture was heated at reflux for 3 h and then cooled to room temperature. p-Toluenesulfonyl chloride (332 mg, 1.74 mmol, 1.1 equiv) was added, followed by tetrabutylammonium bromide (255 mg, 0.79 mmol, 50 mol%) and the reaction mixture was stirred at rt for 30 min and then concentrated in vacuo. The residue was purified by chromatography on silica gel (diethyl ether) to give compound 23 (565 mg, 1.42 mmol, 90%) as a colourless oil which solidified on storage: mp 85–86 ºC (diethyl ether). $\alpha$D $^22 = +27.9$ (c 0.66 in CHCl$_3$). IR (film): $\nu$max = 3391, 2977, 2886, 2867, 1745, 1361, 1168, 1094, 1075 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.79 (2H, d, J = 8.2, ArH), 7.36 (2H, d, J = 8, ArH), 4.21 (1H, dd, J = 10.4, 2.3, C$_{32}$H$_A$H$_B$), 4.02–3.93 (2H, m, C$_{32}$H$_A$H$_B$ and C$_{27}$H), 3.76 (1H, dd, J = 8, 2, C$_{31}$H), 3.11 (1H, br s, C$_{31}$OH), 2.53 (2H, app. t, J = 8.5, C$_{24}$H$_2$), 2.44 (3H, s, ArMe), 2.22–2.07, 1.97–1.79 and 1.60–1.70 (6H, m, C$_{25}$H$_2$, C$_{28}$H$_2$ and C$_{29}$H$_2$), 1.31 (3H, s, C$_{30}$Me), 1.10 (3H, s, C$_{26}$Me). 13C NMR (75 MHz, CDCl$_3$): $\delta$ = 177.3 (C$_{23}$), 145.5 (C Ar), 132.9 (C$_{Ar}$), 130.4 (2C$_{Ar}$H$_2$), 128.3 (2C$_{Ar}$H), 87.6, 84.7 (C$_2$ and C$_3$), 34.9, 29.6, 29.1 and 27.1 (C$_{24}$H$_2$, C$_{25}$H$_2$, C$_{28}$H$_2$ and C$_{29}$H$_2$), 24.0 (C$_{26}$Me or C$_{30}$Me), 21.7 (C$_{26}$Me or C$_{30}$Me). LRMS: m/z = 399.0 [(M + H)$^+$, 98%], 421.0 [(M + Na)$^+$, 62%], 209.1 (100). HRMS: Found 399.1493 [M+H]$^+$. C$_{19}$H$_{27}$O$_7$S requires: 399.1478. Elemental Analysis: Found: C 57.0, H 6.58, S 7.95%. C$_{19}$H$_{26}$O$_7$S requires C 57.27, H 6.65, S 7.95%.

**Compound 24**

Tosylate 23 (3.0 g, 7.53 mmol, 1 equiv) was dissolved in dry, degassed DME (50 mL). Freshly distilled tributyltin hydride (5.06 mL, 18.8 mmol, d 1.082, 2.5 equiv), sodium iodide (2.82 g, 18.8 mmol, 2.5 equiv) and VAZO [1,1′-azobis(cyclohexanecarbonitrile), 183 mg, 0.75 mmol, 10 mol%)] were added and the mixture heated at 80 ºC for 18 h. Upon cooling, the solvent was removed in vacuo. The residue was purified by chromatography on silica gel (petroleum ether–diethyl ether 1:3 → neat diethyl ether) to give compound 24 (1.65 g, 7.23 mmol, 96%) as a colourless oil which solidified on storage: mp 60–62 ºC (DCM–petroleum ether). $\alpha$D $^22 = +3.2$ (c 0.62 in CHCl$_3$). IR (film): $\nu$max = 3496, 2975, 2937, 2863, 2155, 2018, 1972, 1749, 1730, 1451, 1371, 1275, 1247, 1172, 1079 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 3.96 (1H, dd, J = 8.4, 6.9, C$_{27}$H), 3.68 (1H, q, J = 6.4, C$_{31}$H), 2.54 (2H, app. t, J = 8.4, C$_{24}$H$_2$), 2.21–1.80 (5H, m, C$_{25}$H$_2$, C$_{28}$H$_2$H$_B$, C$_{29}$H$_2$H$_B$ and C$_{31}$OH), 1.69–1.56 (1H, m, C$_{28}$H$_2$H$_B$), 1.53–1.44 (1H, m, C$_{29}$H$_2$H$_B$), 1.34 (3H, s, C$_{30}$Me), 1.07 (3H, s, C$_{26}$Me), 1.06 (3H, d, J = 6.4, C$_{32}$H$_3$). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 177.0 (C$_{23}$), 87.5, 87.4 (C$_2$ and C$_3$), 82.3 (C$_{27}$H$_2$), 72.7 (C$_{31}$H), 30.9, 29.7, 29.4 and 27.4 (C$_{24}$H$_2$, C$_{25}$H$_2$, C$_{28}$H$_2$ and C$_{29}$H$_2$), 24.0, 22.9 (C$_{26}$Me and C$_{30}$Me), 18.1 (C$_{32}$H$_3$). LRMS: m/z = 229.1 [(M + H)$^+$, 85%], 251.1 [(M + Na)$^+$, 68%], 211.1 (100), 193.1 (75). HRMS: Found 229.1434 [M+H]$^+$. C$_{12}$H$_{21}$O$_4$S requires: 229.1440. Elemental Analysis: Found: C 63.14, H 8.83%. C$_{12}$H$_{20}$O$_4$S requires C 63.05 H 8.75%.

**Compound 25**
A solution of tert–butyldimethylsilyl chloride (261 mg, 1.73 mmol, 1.2 equiv), triethylamine (0.24 mL, 1.73 mmol, 1.2 equiv), DMAP (17.7 mg, 0.145 mmol, 0.1 equiv) and alcohol 24 (330 mg, 1.45 mmol, 1 equiv) in DCM (2 mL) was heated at reflux for 3 d. The mixture was quenched by adding DCM (1 mL) and then sat. aq. NaHCO₃ solution (1.5 mL). The phases were separated and the aqueous phase extracted with DCM (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried over MgSO₄, and concentrated in vacuo. The residue was purified by chromatography on silica gel (petroleum ether–diethyl ether 7:3) to give compound 25 (462 mg, 1.35 mmol, 93%) as a colourless oil which solidified on storage: mp 63–65 ºC (DCM–petroleum ether). \([\alpha]_D^{22} = −12.1 \ (c \ 1.00 \text{ in CHCl}_3)\). IR (film): \(\nu_{\text{max}} = 2950, 2925, 2881, 2857, 1773, 1460, 1371, 1250, 1154, 1095 \text{ cm}^{-1}\). \(^1\)H NMR (300 MHz, CDCl₃): δ = 3.97 (1H, dd, \(J = 8.2, 6.3, \text{C}_{27}\)), 3.61 (1H, q, \(J = 6.2, \text{C}_{31}\)), 2.65 (1H, ddd, \(J = 17.9, 10.3, 7.6, \text{C}_{24}\)), 2.55 (1H, ddd, \(J = 17.9, 10.1, 5.8, \text{C}_{24}\)), 2.26 (1H, ddd, \(J = 12.9, 10.4, 5.8, \text{C}_{25}\)), 1.97–1.91 (2H, m, \(\text{C}_{28}\)), 1.90–1.82 (1H, m, \(\text{C}_{25}\)), 1.71–1.55 (2H, m, \(\text{C}_{28}\)), 1.50 (3H, s, \(\text{C}_{30}\)), 1.04 (3H, s, \(\text{C}_{26}\)), 1.00 (3H, d, \(J = 6.2, \text{C}_{32}\)), 0.82 (9H, s, t-Bu), −0.009 and −0.017 (SiMe₂). \(^{13}\)C NMR (75 MHz, CDCl₃): δ = 177.6 (C₂₃), 88.1, 86.8 (C₂₆ and C₃₀), 84.8 (C₂₇), 73.9 (C₃₁), 33.5, 30.3, 29. and 27.9 (C₂₄, C₂₅, C₂₈ and C₂₉), 26.2 (C₃₅), 23.8, 23.0 (C₂₆ and C₃₀), 19.7 (C₂₃), 18.3 (C₃₂), −4.0, −4.4 (SiMe₂). LRMS: \(m/z = 343.1 \ [(M + H) +, 80\%]\), 211.0 (100), 193.0 (32). Elemental Analysis: Found: C 62.95, H 10.00%. \(\text{C}_{18}\text{H}_{34}\text{O}_{4}\text{Si}\) requires C 63.11 H 10.00%.

Di–isobutylaluminium hydride (1.5 M solution in toluene, 1.80 mL, 2.66 mmol, 1.2 equiv) was added dropwise to a solution of lactone 25 (760 mg, 2.2 mmol, 1 equiv) in toluene (30 mL) at −78 ºC. The mixture was stirred at −78 ºC for 2 h, sat. aq. sodium potassium tartrate solution (50 mL) was added, and the mixture stirred for a further 1 h at rt. The phases were separated and the aqueous phase extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ solution (50 mL), dried over MgSO₄ and NaHCO₃ for 18 h, and concentrated in vacuo to give the crude lactol intermediate which was used directly in the next step without further purification.

Dry CaCl₂ (730 mg, 6.6 mmol, 3 equiv) and freshly prepared benzenesulfinic acid (571 mg, 4.0 mmol, 1.8 equiv) was added to a solution of the crude lactol in DCM (20 mL) at rt. The reaction was stirred at rt for 18 h. The mixture was quenched by adding DCM (30 mL) and sat. aq. NaHCO₃ solution (50 mL). The phases were separated and the aqueous phase extracted with ether (4×50 mL). The combined organic extracts were washed with brine (50 mL), dried over MgSO₄ and NaHCO₃, and concentrated in vacuo to give the crude lactol intermediate which was used directly in the next step without further purification.

Dry CaCl₂ (730 mg, 6.6 mmol, 3 equiv) and freshly prepared benzenesulfinic acid (571 mg, 4.0 mmol, 1.8 equiv) was added dropwise to a solution of lactone 25 (760 mg, 2.2 mmol, 1 equiv) in toluene (30 mL) at −78 ºC. The mixture was stirred at −78 ºC for 2 h, sat. aq. sodium potassium tartrate solution (50 mL) was added, and the mixture stirred for a further 1 h at rt. The phases were separated and the aqueous phase extracted with ethyl acetate (3×50 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ solution (50 mL), dried over MgSO₄ and NaHCO₃, and concentrated in vacuo to give the crude lactol intermediate which was used directly in the next step without further purification.
**Linkage of Fragments 3 and 4**

To a solution of sulfone 4 (267 mg, 0.570 mmol, 1.0 equiv) in DCM (4 mL) at −78 °C was added a solution of trimethylsilyl enol ether 3 (320 mg, 0.685 mmol 1.2 equiv) in DCM (4 mL). The reaction mixture was stirred at −78 °C for 10 min before slow dropwise addition of a solution of Et₃AlCl₂ [1.4 mL, 0.683 mmol, 1.2 equiv, 0.5 M solution, freshly prepared by mixing equimolar amounts of EtAlCl₃ (1.0 M in hexanes, 0.7 mL) and Et₂AlCl (1.0 M solution in hexanes, 0.7 mL) at rt for 10 min stirring]. The resulting yellow-green mixture was stirred at −78 °C for a further 30 min and then allowed to warm to −30 °C. The reaction was quenched at −30 °C by pouring the solution into a stirred mixture of ether (60 mL) and sat. aq. NH₄Cl (40 mL). The layers were separated, the aqueous layer extracted with ether (3×60 mL), the combined organic washed with sat. aq. NaHCO₃ and brine (2×10 mL each) dried (Na₂SO₄), filtered and concentrated in vacuo. The residue was purified by repeated column chromatography on silica gel (diethyl ether–hexanes 1:10) to give the diastereoisomeric coupling products 30 and 31 (402 mg, 0.557 mmol, 98%) as an inseparable mixture of diastereoisomers (dr = 1:2) and recovered ketone 13 (40 mg, 0.101 mmol).

**Compound 30** (major diastereoisomer)

\[ \delta_{10}^{19} = -16.4 \ (c \ 0.90 \ \text{in CHCl}_3) \]. IR (film): νmax = 2955, 2930, 2854, 1712, 1613, 1512, 1462, 1370, 1250, 1094, 1037 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.19 (2H, d, J 8.2, ArH), 6.85 (2H, d, J 8.7, ArH), 4.45 (1H, d, J 10.7, OCH₂H₂Ar), 4.38 (1H, d, J 10.7, OCH₂H₂Ar), 4.37–4.27 (1H, m, C23H), 3.85–3.79 (1H, m, C27H), 3.79 (3H, s, OMe), 3.71 (1H, dd, J 9.7, 5.6, C17H₃Ar), 3.70–3.65 (1H, m, C19H), 3.56 (1H, q, J 6.1, C31H), 3.53 (1H, dd, J 9.7, 6.7, C17H₃Ar), 3.04–2.95 (1H, m, C20H), 2.94 (1H, dd, J 16.6, 5.6, C22H₂Ar), 2.51 (1H, dd, J 16.9, 7.2, C22H₂Ar), 2.15–2.04, 2.07–1.77, 1.67–1.37 (9H, m, C18H, C24H₂, C25H₂, C28H₂ and C29H₂), 1.12 (3H, d, J 6.2, C32H), 1.11 and 1.09 (3H each, s, C26Me and C30Me), 1.05 (3H, d, J 7.1, C20Me), 0.98 (3H, d, J 7.1, C22Me), 0.91 (9H, s, t-Bu), 0.88 (9H, s, t-Bu), 0.054 (9H, s, 3xSiMe), 0.048 (9H, s, SiMe). ¹³C NMR (75 MHz, CDCl₃): δ = 212.8 (C21), 159.2 (C19), 131.1 (C40), 129.3 (2C₃₇H), 113.8 (2C₃₄H), 85.6, 84.4 (C26 and C30), 84.0, 83.8 (C19H and C27H), 74.6 (C23H), 74.2 (OCH₂Ar), 73.4 (C31H), 64.5 (C17H₃), 55.4 (OMe), 50.1 (C22H₂), 49.3 (C20H), 38.3 (C18H), 39.7, 34.2, 32.3, 27.1 (C24H₂, C25H₂, C28H₂ and C29H₂), 26.1 (CMe₃), 26.0 (CMe₂), 23.0, 19.4, 18.5 (CMe₃ and C32H₃), 18.4 (CMe₂), 18.1 (CMe₃), 15.1 (C18Me), 13.4 (C20Me), −3.3, −3.7, −4.7, −5.2 (2xSiMe₂). LRMS: m/z = 743.1 [(M+Na)+, 100%], 629.1 (95). HRMS: Found: 743.4693 [M+Na–H]⁺. C₄₀H₇₁O₇Na₂S₂ requires: 743.4714.

**Compound 31** (minor diastereoisomer)

\[ \delta_{10}^{19} = -18.5 \ (c \ 0.95 \ \text{in CHCl}_3) \]. IR (film): νmax = 2955, 2924, 2854, 1712, 1613, 1512, 1468, 1462, 1370, 1250, 1094, 1041 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 7.20 (2H, d, J 8.7, ArH), 6.85 (2H, d, J 8.7, ArH), 4.43 (1H, d, J 10.7, OCH₂H₂Ar), 4.41 (1H, d, J 10.7, OCH₂H₂Ar), 4.35–4.27 (1H, m, C23H), 3.90 (1H, t, J 7.2, C27H), 3.80 (3H, s, OMe), 3.70 (1H, dd, J 10.0, 5.4, C17H₃Ar), 3.65 (1H, dd, J 7.2, 4.6, C19H), 3.59 (1H, q, J 6.1, C31H), 3.54 (1H, dd, J 9.5, 6.4, C17H₃Ar), 2.98 (1H, dq, J 7.0, 7.0, C20H), 2.87 (1H, dd, J 16.4, 5.6, C22H₂Ar), 2.61 (1H, dd, J 16.4, 7.7, C22H₂Ar), 2.15–2.04, 2.02–1.80 and 1.67–1.42 (9H, m, C18H, C24H₂, C25H₂, C28H₂ and C29H₂), 1.12 (3H, d, J 7.2, C32H), 1.10 (6H, s, C26Me and C30Me), 1.07 (3H, d, J 7.1, C20Me), 0.97 (3H, d, J 7.1, C18Me), 0.90 (9H, s, t-Bu), 0.88 (9H, s, t-Bu), 0.058 (3H, s, SiMe), 0.050 (6H, s, SiMe₂), 0.044 (3H, s, SiMe). ¹³C NMR (75 MHz, CDCl₃): δ = 212.8 (C21), 159.2 (C30), 131.1 (C40), 129.4 (2C₃₄H), 87.5, 84.3 (C26 and C30), 84.2, 83.6 (C19H and C27H), 75.9 (C23H), 74.2 (OCH₂Ar), 73.4 (C31H), 64.5 (C17H₃), 55.4 (OMe), 50.1 (C22H₂), 49.0 (C20H), 26.1 (CMe₃), 26.0 (CMe₂), 23.0, 19.4, 18.5 (CMe₃ and C32H₃), 18.4 (CMe₂), 18.1 (CMe₃), 15.1 (C18Me), 13.4 (C20Me), −3.3, −3.7, −4.7, −5.2 (2xSiMe₂). LRMS: m/z = 743.1 [(M+Na)+, 100%], 629.1 (95). HRMS: Found: 743.4693 [M+Na–H]⁺. C₄₀H₇₁O₇Na₂S₂ requires: 743.4714.

**Compound 32**

![Chemical Structure of Compound 32](image)

The method of Evans was used.6 MeAlCl2 (1.0 M solution in hexanes, 486 μL, 486 μmol, 5 equiv) was added dropwise to a 0.1 M solution of ketone 31 (70 mg, 97 μmol, 1 equiv) in DCM (1 mL) at −78 °C. After 2 minutes, n-Bu3SnH (130 μL, 486 μmol, 5 equiv) was added and the reaction stirred for 1 h. The reaction was quenched at −78 °C by addition of excess sat. aq. NaHCO3 (2 mL) and allowed to warm to rt. Water (10 mL) was added and the aqueous layer was extracted with DCM (3×20 mL), combined, dried (Na2SO4), filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel (petroleum ether–diethyl ether 5:1) to afford compound 32 (36 mg, 60 μmol, 62%, 80% brsm) as a colourless oil and unreacted starting material (11.5 mg, 16 μmol). [α]D21 = −13.8 (c 0.61 in CHCl3). IR (film): νmax = 3449, 2955, 2935, 2854, 1468, 1462, 1370, 1253, 1091 cm−1. 1H NMR (300 MHz, CDCl3): δ = 4.40–4.12 (3H, m, C23 and 2×O2H), 4.07 (1H, dd, J9.6, 5.4, C27H), 3.96 (1H, dd, J7.2, 6.9, C19H), 3.91–3.55 (3H, m, C17H2 and C31H), 3.44 (1H, dd, J8, 3.4, C21H), 2.15–1.28 (12H, m, C18H, C20H, C22H2, C24H2, C25H2, C28H2 and C29H2), 1.15 (3H, s, C26Me or C30Me), 1.13 (3H, s, C26Me or C30Me), 1.11 (3H, s, C26Me or C30Me), 1.09 (3H, s, C7, C20Me) 0.93 (9H, s, t-Bu), 0.91 (9H, s, t-Bu), 0.89 (3H, obstructed, C18Me), 0.105 and 0.08 (12H, m, 4SiMe). 13C NMR (75 MHz, CDCl3): δ = 85.8 (CH), 85.4 (C), 84.5 (C), 81.4 (CH), 80.1 (CH), 74.6 (CH), 73.1 (CH), 66.1 (CH2), 41.9 (CH), 39.9 (CH2), 36.5 (CH), 36.1 (CH), 33.9 (CH2), 32.9 (CH2), 30.0 (CH2), 26.1 (CMe3), 26.0 (CMe3) 24.6 (CH3), 19.6 (CH3), 18.3 (CH3), 18.1 (2CMe3), 15.5 (CH3), 12.8 (CH3), −3.7, −4.7, −5.3, −5.4 (2SiMe2). LRMS: m/z = 604 [(M+H)+, 100%], 489.8 (68), 453.8 (67), 321.5 (71). HRMS: Found: 603.4485 [M+H]+. C32H67O6Si28Si2 requires: 603.4476.

**Compounds 33 and 2**

![Chemical Structure of Compounds 33 and 2](image)

To a solution of the diol 32 (73 mg, 121 μmol) in dry acetone (1.6 mL) was added 2,2-dimethoxypropane (0.49 g, 0.58 mL, 4.7 mmol) and d,l-camphorsulfonic acid (50 μmol). The resulting solution was stirred at rt for 4 h. Triethylamine (0.5 mL) was added and the solvent was removed in vacuo. Brine (2 mL) was added to the residue and then the mixture was extracted with EtOAc (4×6 mL). The combined extracts were dried over MgSO4, concentrated and the residue was purified by column chromatography on SiO2 (5% and then 30% Et2O in petroleum ether) to afford acetonide 33 (41 mg, 64 μmol, 53%) together with the target alcohol 2 (22 mg, 42 μmol, 35%), both of which are clear oils.

Spectroscopic data for acetonide 33: 1H NMR (300 MHz, CDCl3): δ = 4.20–4.08 (1H, m, C23H), 3.94 (1H, dd, J7.2, 6.9, C27H), 3.79 (1H, dd, J 10, 6.4, C17H2H8), 3.62 (1H, q, J 6.2, C31H), 3.48–3.31 (3H, m,
overlapped C21H, C19H, C17H, Hb), 2.04–1.80 and 1.73–1.50 (12H, m, C18H, C20H, C22H, C24H, C25H, C28H, C29H), 1.35 and 1.31 (3H each, s, acetonide-Me), 0.93 (3H, d, J 7.2, C18Me) 0.89 (9H, s, t-Bu), 0.88 (9H, t-Bu), 0.79 (3H, d, J 6.2, C20Me), 0.06 (3H, s, SiMe), 0.04 (9H, s, 3SiMe). 13C NMR (75 MHz, CDCl3): δ = 97.7 (C), 85.6 (C), 84.6 (CH), 83.7 (C), 77.4 (CH), 77.3 (CH), 73.4 (CH), 72.7 (CH), 63.8 (CH2), 39.3 (CH2), 36.6 (CH), 36.2 (CH), 36.0 (CH2), 34.3 (CH2), 31.5 (CH2), 30.3 (CH3, acetonide-Me), 27.3 (CH2), 26.2 (CMes), 26.0 (CMes), 24.2 (CH3), 19.7 (CH3), 19.4 (CH3, acetonide-Me), 18.5 (CH3), 18.4 (CH3), 18.1 (2CMes), 15.7 (CH3), 12.4 (CH3), −3.7 (SiCH3), −4.7 (SiCH3), −5.2 (2SiCH3). LRMS: m/z = 644.1 (M+H)+, 45%, 667.1 (M+Na)+, 43%, 585.9 (100), 453.7 (95). HRMS: Found: 643.4790 [M+H]+. C35H71O6Si2 requires: 643.4789.

To a solution of the bis-TBS ether 33 (40 mg, 62 μmol) in THF (1.5 mL) in a polypropylene vial was added freshly prepared HF·py solution (3.16 M, 0.10 mL, 0.316 mmol in THF and pyridine (v/v = 3:1)) at rt. The reaction was closely followed by TLC and additional HF·py solution (3.16 M, 0.1 mL, 0.316 mmol) was added after 18 h and the reaction was stirred at rt for a further 12 h. Saturated aq. NaHCO3 solution (4 mL) was added. The resulting mixture was extracted with EtOAc (4 × 6 mL) and the combined organic extracts were dried over Na2SO4. The solvent was evaporated and the residue was purified by column chromatography (SiO2, 30% Et2O in petrol) to provide compound 2 (23 mg, 44 μmol, 72%) as a colourless oil. The combined overall yield of compound 2 for the two steps (46 mg, 86 μmol) was 71%. [α]D = −20.2 (c 1.04 in CHCl3); lit.7 [α]D = −20.9 (c 0.604 in CHCl3). HRMS: Found: 529.3926 [(M+H)+]. C29H57O6Si requires 529.3924. The 1H and 13C NMR spectroscopic data recorded for 2 were consistent with the data previously reported by us8 and Hanessian7.

References
SUPPLEMENTARY INFORMATION

A Formal Synthesis of Ionomycin Featuring a Permanganate-Mediated Oxidative Cyclisation

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$^1$H and $^{13}$C NMR Spectra

- Compound 2
- Compound 3
- Compound 4
- Compound 11
- Compound 12
- Compound 13
- Compound 17
- Compound 18
- Compound 21
- Compound 22
- Compound 23
- Compound 24
- Compound 25
- Compound 29
- Compound 30
- Compound 31
- Compound 32
- Compound 33
Compound 2
500 MHz, CDCl₃

Compound 2
125 MHz, CDCl₃
Compound 3
300 MHz, CDCl₃

Compound 3
75 MHz, CDCl₃
**Compound 4**  
300 MHz, CDCl₃

**Compound 4**  
75 MHz, CDCl₃
Compound 11
300 MHz, CDCl₃

Compound 11
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Compound 17
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Compound 18
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Compound 18
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Compound 22
300 MHz, CDCl$_3$

Compound 22
75 MHz, CDCl$_3$
Compound 23
300 MHz, CDCl₃

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Compound 33
75 MHz, CDCl₃