Total Synthesis of Thapsigargin, a Potent SERCA pump inhibitor.

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General Experimental

All non-aqueous reactions were performed in oven-dried (200 °C) glassware under an argon atmosphere; synthetic intermediates were dried *in vacuo* before use. All reagents were obtained from commercial sources and used as supplied unless otherwise stated. Molecular sieves were dried at 200 °C before use and amberlyst-15 resin washed thoroughly with methanol and dichloromethane then dried *in vacuo* before use. Solvents used were of reagent grade and were distilled before use: tetrahydrofuran and diethylether over calcium hydride and lithium aluminium hydride; dichloromethane, toluene, methanol and acetonitrile over calcium hydride. Petrol ether refers to the fraction of petroleum ether that was distilled between 40 and 60 °C; *iso*-propanol and anhydrous *N,N*-dimethylformamide and acetone were sourced commercially and used as supplied.

Flash column chromatography was performed with Merck 60 Kieselgel (230-400 mesh). Thin layer chromatography (TLC) was performed with Merck 60 F254 silica gel plates and viewed under UV radiation (254 nm) or by staining with acidic ammonium molybdate (IV) and heating as necessary. All ¹H NMR spectra were recorded on a Bruker DRX-600 machine, operating at 600 MHz. Samples were either dissolved in CDCl₃ and the residual protic solvent calibrated to 7.27 ppm. Signals are

quoted in ppm to the nearest 0.01 ppm and multiplicities (*J*) are recorded to the nearest 0.1 Hz. ^{13}C NMR spectra were recorded on a Bruker DRX-600 machine, operating at 150 MHz. Samples were dissolved in CDCl_3 and the residual solvent calibrated to 77.0 ppm. Signals are quoted in ppm to the nearest 0.1 ppm unless two signals are within 0.1 ppm, in which case they are reported within 0.01 ppm. COSY, HMQC, HMBC and DEPT experiments were used to aid the assignment of NMR signals.

High-resolution mass spectrometry was conducted using a Kratos Concept spectrometer or Waters Micromass LCT Premier spectrometer using EI or ESI ionisation techniques. Optical rotations were recorded on a Perkin-Elmer 343 digital polarimeter at 25 °C, path length 10 cm using a sodium lamp (589 nm) as the light source, reported in $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$ (concentration, *c.* in g per 100 mL). Infrared spectra of sample films were recorded by a Perkin-Elmer Spectrum One spectrometer equipped with an attenuated total reflectance sampler. Melting points are uncorrected and were measured with Reichert hot-stage apparatus using BDH microscopic slides.

Experimental Procedures

(see final entry for synthesis of Thapsigargin (1))

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To a solution of ketoalcohol **8** (460 mg, 0.89 mmol) in DCM (4.1 cm^3) at 0°C was added diisopropylethyl amine (1.25 cm^3 , 7.15 mmol), followed by SEM-Cl (0.47 cm^3 , 2.68 mmol). The resulting solution was warmed to room temperature before addition of DMAP (cat.) After stirring for a further 24 h, the reaction mixture was partitioned between saturated aqueous sodium hydrogen carbonate solution (100 cm^3) and ethyl acetate (100 cm^3), the phases separated and the aqueous extracted with ethyl acetate ($3 \times 50 \text{ cm}^3$). The combined organics were dried (MgSO_4), concentrated under

reduced pressure and purified by flash chromatography (1 : 9, ether : petrol) to afford the title compound **9** as a white foam (518 mg, 92%). $R_f = 0.67$ (1 : 4, ethyl acetate petrol). $[\alpha]_D^{25} +8.2$ (c 1.0, CHCl_3); (Found $[\text{M}+\text{Na}]^+$, 667.3130. $\text{C}_{30}\text{H}_{56}\text{O}_9\text{NaSi}_3$ requires $\text{M}+\text{Na}$, 667.3130); $\nu_{\text{max}} / \text{cm}^{-1}$ 2954, 1794, 1747, 1385 1373, 1252, 1195, 1146, 1099, 1035, 1021, 1005, 988 and 839; δ_{H} 0.00 (9 H, s, $\text{CH}_2\text{Si}(\text{CH}_3)_3$), 0.16 (9 H, s, $\text{Si}(\text{CH}_3)_3$), 0.22 (9 H, s, $\text{Si}(\text{CH}_3)_3$), 0.94 (2 H, m, SiCH_2), 1.22 (3 H, s, 14- H_3), 1.31 (3 H, d, J 6.9, 15- H_3), 1.38 (3 H, s, 13- H_3), 1.51 and 1.56 (each 3 H, s, $\text{C}(\text{CH}_3)_2$), 2.09 (1 H, dd, $J_{9,9'} 14.7$, $J_{9,8} 3.1$, 9- H), 2.23 (1 H, dd, $J_{9',9} 14.7$, $J_{9',8} 3.9$, 9- H'), 2.34 (1 H, m, 4- H), 2.44 (1 H, m, 5- H), 2.54 (1 H, d, $J_{1,5} 9.1$, 1- H), 3.58 (1 H, m, OCHHSi), 3.75 (1 H, m, OCHHSi), 4.11 (1 H, m, 8- H), 4.31 (1 H, s, 2- H), 4.68 and 4.72 (each 1 H, d, J 6.5, OCH_2O), and 5.17 (1 H, d, $J_{6,5} 10.2$, 6- H); δ_{C} -1.5 ($\text{CH}_2\text{Si}(\text{CH}_3)_3$), 2 x 2.7 (each $\text{Si}(\text{CH}_3)_3$), 16.3 (C-14), 17.8 (SiCH_2), 17.9 and 23.4 ($\text{C}(\text{CH}_3)_2$), 26.5 (C-13), 30.4 (C-15), 42.8 (C-5), 46.1 (C-9), 48.0 (C-4), 53.6 (C-1), 65.3 ($\text{OCH}_2\text{CH}_2\text{Si}$), 66.2 (C-8), 76.6 (C-11), 77.5 (C-2), 79.4 (C-10), 79.7 (C-7), 83.7 (C-6), 92.3 (OCH_2O), 99.9 ($\text{C}(\text{CH}_3)_2$), 173.2 (C-12) and 216.4 (C-3).

11/12

To a solution of ketone **9** (256 mg, 0.40 mmol) in tetrahydrofuran (10.0 cm^3) at -78°C was added a solution of LiHMDS (2.0 cm^3 of a 1.0M solution in tetrahydrofuran, 2.0 mmol) dropwise. After a further 5 min at -78°C , the reaction flask was transferred to a -12°C cooling bath and the resulting solution maintained at -12 to -13°C (cryocool apparatus) for 2 h. The reaction flask was then transferred to a -95°C cooling bath (ether / N_2) and a pre-cooled (-78°C) solution of phenylselenenyl chloride (380 mg, 2.00 mmol) in tetrahydrofuran (7.5 cm^3) was added *via* cannula. The external reaction temperature was maintained between -90 and -95°C for 30 min before allowing to warm to -78°C over 10 min. After transferring to a -78°C bath (acetone / CO_2) the resulting orange solution was stirred for 2 h 30 min before addition of pyridine (0.59 cm^3 , 5.96 mmol) and transferring to an ice bath. After 10 min at 0°C , the reaction

mixture was warmed to room temperature and saturated aqueous sodium hydrogen carbonate solution (20 cm³) was added. Addition of DCM (30 cm³), separation of the phases, extraction of the aqueous with DCM (3 x 15 cm³), washing the combined organics with saturated aqueous sodium hydrogen carbonate solution (30 cm³), drying (MgSO₄), concentration under reduced pressure and filtration through a short plug of silica (eluting with 1 : 50 then 1 : 10, ethyl acetate : petrol) afforded the title compounds (287 mg) as a pale amber foam in an 80 : 20 mixture of **11** to **12**, (containing 10% by mass of unreacted starting ketone **9**, as assessed by ¹H NMR). Note: The three component mixture common had a common R_f = 0.43 (1 : 7, ethyl acetate : petrol). This material was used without purification in the subsequent step.

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A stream of oxygen was bubbled through a solution of selenides **11/12** (287 mg, derived from 0.40 mmol of ketone **9**) in DCM (35 cm³) at -78°C before a stream of ozone was bubbled through until a deep blue colour was observed (2 min). Oxygen was again applied until no blue colour remained (2 min). After addition of diisopropylamine (1.40 cm³) the reaction mixture was allowed to warm to room temperature and stirred for a further 2 h 30 min. Addition of saturated aqueous sodium hydrogen carbonate solution (30 cm³), separation of the phases, extraction of the aqueous with DCM (3 x 20 cm³), drying (MgSO₄), concentration under reduced pressure and purification by flash chromatography (1 : 20 then 1 : 13, ethyl acetate :

petrol) afforded the title compound **13** as a colourless foam (153 mg, 60% over two steps), $R_f = 0.33$ (1 : 10, ethyl acetate : petrol). $[\alpha]_D^{25} -17.9$ (c 0.35, CHCl_3); (Found $[\text{M}+\text{Na}]^+$, 665.2989, $\text{C}_{30}\text{H}_{54}\text{NaO}_9\text{Si}_3$ requires $M+\text{Na}$, 665.2973); $\nu_{\text{max}} / \text{cm}^{-1}$ 2956, 1800, 1721, 1383, 1254, 1191, 1144, 1123, 1066, 1028, 998 and 840; δ_{H} 0.03 (9 H, s, $\text{CH}_2\text{Si}(\text{CH}_3)_3$), 0.15 (9 H, s, $\text{Si}(\text{CH}_3)_3$), 0.19 (9 H, s, $\text{Si}(\text{CH}_3)_3$), 0.99 (2 H, m, SiCH_2), 1.18 (3 H, s, 14- H_3), 1.41 (3 H, s, $\text{C}(\text{CH}_3)\text{CH}_3$), 1.54 (3 H, s, $\text{C}(\text{CH}_3)\text{CH}_3$), 1.58 (3 H, s, 13- H_3), 1.97 (3 H, s, 15- H_3), 2.17 (1 H, dd, $J_{9,9'}$ 14.6, $J_{9',8}$ 3.6, 9- H), 2.36 (1 H, dd, $J_{9',9}$ 14.6, $J_{9',8}$ 3.6, 9- H'), 3.35 (1 H, d, $J_{1,2}$ 2.0, 1- H), 3.58 (1 H, m, SiCH_2CHHO), 4.06 (1 H, m, SiCH_2CHHO), 4.17 (1 H, d, $J_{2,1}$ 2.0, 2- H), 4.20 (1 H, dd, $J_{8,9}$ 3.6 $J_{8,9'}$ 3.6, 8- H), 4.74 and 5.00 (each 1 H, d, J 6.0, OCH_2O) and 5.96 (1 H, s, 6- H); δ_{C} -1.4 ($\text{CH}_2\text{Si}(\text{CH}_3)_3$), 2.7 ($\text{Si}(\text{CH}_3)_3$), 2.8 ($\text{Si}(\text{CH}_3)_3$), 9.8 (C-15), 17.0 (C-13), 18.0 (SiCH_2), 23.5 ($\text{C}(\text{CH}_3)\text{CH}_3$), 24.5 (C-14), 30.5 ($\text{C}(\text{CH}_3)\text{CH}_3$), 45.3 (C-9), 59.3 (C-1), 65.5 ($\text{SiCH}_2\text{CH}_2\text{O}$), 66.8 (C-8), 75.3 (C-2), 76.4 (C-11), 78.6 (C-6), 79.4 (C-7), 80.4 (C-10), 93.7 (OCH_2O), 100.6 ($\text{C}(\text{CH}_3)_2$), 140.3 (C-5), 157.6 (C-4), 172.4 (C-12) and 205.5 (C-3).

This followed the isolation of the clean *exo* double bonded compound **14** (26 mg, 10% yield over two steps; data below) and in addition, a mixed *endo-exo* fraction (30 mg, approx. 1 : 1 ratio, 12% over two steps).

14

$R_f = 0.35$ (1 : 10, ethyl acetate : petrol). $[\alpha]_D^{25} -22.4$ (c 0.60, CHCl_3); (Found $[\text{M}+\text{Na}]^+$, 665.2999, $\text{C}_{30}\text{H}_{54}\text{NaO}_9\text{Si}_3$ requires $M+\text{Na}$, 665.2973); $\nu_{\text{max}} / \text{cm}^{-1}$ 2955, 1797, 1733, 1253, 1195, 1148, 1102, 1026, 989 and 840; δ_{H} 0.02 (9 H, s, $\text{CH}_2\text{Si}(\text{CH}_3)_3$), 0.18 (9 H, s, $\text{Si}(\text{CH}_3)_3$), 0.26 (9 H, s, $\text{Si}(\text{CH}_3)_3$), 0.86 (1 H, m, SiCHH), 0.96 (1 H, m, SiCHH), 1.05 (3 H, s, 14- H_3), 1.37 (3 H, s, 13- H_3), 1.53 and 1.59 (each 3 H, s, $\text{C}(\text{CH}_3)_2$), 2.06 (1 H, dd, $J_{9,9'}$ 14.7, $J_{9,8}$ 2.9, 9- H), 2.26 (1 H, dd, $J_{9',9}$ 14.7, $J_{9',8}$

3.7, 9-*H'*), 2.62 (1 H, d, $J_{1,5}$ 9.1, 1-*H*), 3.41 (1 H, m, 5-*H*), 3.63 (2 H, m, OCH_2Si), 4.13 (1 H, m, 8-*H*), 4.39 (1 H, s, 2-*H*), 4.68 and 4.77 (each 1 H, d, J 6.7, OCH_2O), 5.22 (1 H, d, $J_{6,5}$ 10.0, 6-*H*), 5.91 and 6.26 (each 1 H, d, J 3.0, 15-*H*₂); δ_{C} -1.5 ($\text{CH}_2\text{Si}(\text{CH}_3)_3$), 2 x 2.7 (each $\text{Si}(\text{CH}_3)_3$), 17.7 ($\text{C}(\text{CH}_3)\text{CH}_3$), 17.9 (SiCH_2), 23.4 (*C*-13), 25.8 (*C*-14), 30.4 ($\text{C}(\text{CH}_3)\text{CH}_3$), 40.2 (*C*-5), 46.1 (*C*-9), 52.7 (*C*-1), 65.3 ($\text{OCH}_2\text{CH}_2\text{Si}$), 66.2 (*C*-8), 76.5 (*C*-2), 79.4 (*C*-10), 79.8 (*C*-11), 82.8 (*C*-6), 92.5 (OCH_2O), 100.0 ($\text{C}(\text{CH}_3)\text{CH}_3$), 121.4 (*C*-15), 145.6 (*C*-4), 153.3 (*C*-12) and 202.0 (*C*-3).

Zinc borohydride (0.5 M in ether)

To a suspension of granular sodium borohydride (760 mg, 20.0 mmol) in dry ether (10 cm³) at 0°C (ice bath) was added a solution of zinc (II) chloride (10 cm³ of a 1.0 M solution in ether, 10 mmol) dropwise. The suspension was then allowed to warm slowly to room temperature overnight. After a total of 3 days, stirring was discontinued to allow the solid sodium chloride to settle. This resulted in a solution of zinc borohydride over sodium chloride (theoretically 0.5 M in ether) which was used directly by syringe-based removal of the supernatant, taking care to prevent inclusion of solid sodium chloride.

20

To a solution of enone **13** (90 mg, 0.139 mmol) in dry ether (5.7 cm³) at -29°C was added a precooled solution of zinc borohydride (10.0 cm³ of an 0.5 M solution in ether, 5.70 mmol) at -29°C *via* cannula. After stirring the solution at -29°C for a further 2 h 30 min, a further quantity of zinc borohydride solution was added (1.4 cm³ of an 0.5 M solution in ether, 0.80 mmol) and stirring continued for a further 30 min to ensure complete reaction. A solution of TBAF (12.8 cm³ of a 1.0 M solution in

tetrahydrofuran, 12.8 mmol) was then added and the resulting vigorously stirred solution was warmed to room temperature. After 30 min at room temperature, ethyl acetate (85 cm³) and a 30% w/w aqueous solution of tetrasodium EDTA (85 cm³) were added and the biphasic system vigorously stirred at room temperature for 2 h. The phases were separated, the aqueous phase extracted with ethyl acetate (3 x 50 cm³), the combined organics dried (sodium sulfate) and concentrated to approximately 10 cm³. After addition of petrol (10 cm³), the resulting solution was loaded directly onto a silica column, eluting with petrol, followed by 1 : 2 ethyl acetate : petrol to afford first the title compound **20** as a colourless oil (56 mg, 80% over two steps). $R_f = 0.57$ (5 : 1, ethyl acetate : petrol). $[\alpha]_D^{25} -5.3$ (c 0.47, CHCl₃); (Found $[M+Na]^+$, 523.2349, C₂₄H₄₀O₉SiNa requires $M+Na$, 523.2339); ν_{max} / cm⁻¹ 3436, 3362, 2944, 1790, 1383, 1371, 1251, 1196, 1111, 1010 and 857; δ_H 0.03 (9 H, s, SiC(CH₃)₃), 0.95 (1 H, ddd, J 11.5, 11.5, 5.4, SiCHH), 1.03 (1 H, ddd, J 11.5, 11.5, 5.9, SiCHH), 1.25 (3 H, s, 14-H₃), 1.41 (3 H, s, 13-H₃), 1.54 (6 H, s, C(CH₃)₂), 1.98 (3 H, s, 15-H₃), 2.10 (1 H, dd, $J_{9,9'}$ 15.1, $J_{9,8}$ 2.9, 9-H), 2.18 (1 H, dd, $J_{9',9}$ 15.1, $J_{9',8}$ 4.2, 9'-H), 3.10 (1 H, m, 1-H), 3.21 (1 H, br. s, OH), 3.57 (1 H, m, SiCH₂CHHO), 3.83 (1 H, dd, J 15.7, 14.2, 2-H), 3.88 (1 H, m, SiCH₂CHHO), 3.95 (1 H, br. s, OH), 4.20 (1 H, m, 8-H), 4.40 (1 H, br. m, 3-H), 4.82 and 4.86 (each 1 H, d, J 6.2, OCH₂O) and 5.79 (1 H, s, 6-H); δ_C -1.5 (Si(CH₃)₃), 12.3 (C-15), 16.0 (C(CH₃)(CH₃)), 18.0 (OCH₂CH₂Si), 23.5 (C-14), 23.6 (C(CH₃)(CH₃)), 30.4 (C-13), 45.1 (C-9), 56.8 (C-1), 65.7 (C-8), 66.5 (OCH₂CH₂Si), 73.5 (C-7), 76.2 (C-10), 78.6 (C-6), 78.9 (C-11), 81.4 (C-3), 90.9 (C-2), 95.6 (OCH₂O), 100.7 (C(CH₃)₂), 123.8 (C-5), 140.7 (C-4) and 172.7 (C-12).

followed by a quantity of the epimeric compound (**20a**) (7 mg, 10% over two steps) on changing to 2 : 1, ethyl acetate : petrol.

20a

$R_f = 0.39$ (5 : 1, ethyl acetate : petrol). $[\alpha]_D^{25} -74.5$ (c 0.35, CHCl_3); (Found $[\text{M}+\text{Na}]^+$, 523.2354, $\text{C}_{24}\text{H}_{40}\text{O}_9\text{SiNa}$ requires $M+\text{Na}$, 523.2339); $\nu_{\text{max}} / \text{cm}^{-1}$ 3379, 3225, 2947, 1791, 1381, 1250, 1111, 1057, 1016 and 860; δ_{H} 0.04 (9 H, s, $\text{SiC}(\text{CH}_3)_3$), 0.97 (2 H, m, SiCH_2), 1.17 (3 H, s, 14- H_3), 1.39 (3 H, s, 13- H_3), 1.52 and 1.53 (each 3 H, s, $\text{C}(\text{CH}_3)_2$), 2.02 (3 H, s, 15- H_3), 2.06 (1 H, dd, $J_{9,9'} 14.9$, $J_{9,8} 2.7$, 9- H), 2.23 (1 H, dd, $J_{9',9} 14.9$, $J_{9',8} 4.1$, 9- H'), 3.18 (1 H, s, OH), 3.35 (1 H, br. s, OH), 3.40 (1 H, m, 1- H), 3.68 (2 H, m, $\text{SiCH}_2\text{CH}_2\text{O}$), 4.00 (1 H, s, OH), 4.12 (1 H, m, 3- H), 4.18 (1 H, m, 8- H), 4.29 (1 H, d, J 5.4, 2- H), 4.76 and 4.83 (each 1 H, d, J 6.2, OCH_2O) and 5.73 (1 H, s, 6- H); δ_{C} -1.5 ($\text{Si}(\text{CH}_3)_3$), 14.1 (C-15), 14.7 ($\text{C}(\text{CH}_3)(\text{CH}_3)$), 16.1 ($\text{OCH}_2\text{CH}_2\text{Si}$), 23.2 (C-14), 23.6 ($\text{C}(\text{CH}_3)(\text{CH}_3)$), 30.5 (C-13), 45.5 (C-9), 58.6 (C-1), 65.7 (C-8), 66.6 ($\text{OCH}_2\text{CH}_2\text{Si}$), 73.3 (C-7), 76.1 (C-10), 77.6 (C-6), 78.5 (C-11), 79.2 (C-3), 79.8 (C-2), 95.3 (OCH_2O), 100.6 ($\text{C}(\text{CH}_3)_2$), 128.7 (C-5), 140.7 (C-4) and 172.9 (C-12).

24

To a solution of 2,4,6-trichlorobenzoyl chloride (5.25 cm^3 , 33.60 mmol) in toluene (6.7 cm^3) at room temperature was added a pre-mixed solution of angelic acid (336 mg, 3.36 mmol) and triethylamine (0.47 cm^3 , 3.36 mmol) in toluene (16.0 cm^3), dropwise over 12 min. The resulting solution was stirred for 3 h 40 min, after which time a fine dispersion of triethylamine hydrochloride had formed. The mixture was triturated with dry ether (200 cm^3) to cause precipitation of further triethylamine hydrochloride, filtered, and the resulting solution concentrated under reduced pressure until *ca.* 10 cm^3 toluene remained. Purification of the reaction mixture by flash chromatography (1 : 80, ethyl acetate : petrol) afforded the title compound as a white crystalline solid (480 mg, 48%). $R_f = 0.42$ (1 : 20, ethyl acetate : petrol). mp = 66 – 68°C. $\nu_{\text{max}} / \text{cm}^{-1}$ 1798, 1738, 1637, 1577, 1549, 1436, 1370, 1212, 1071, 857 and

820; δ_{H} 1.97 (3 H, br. m, $\text{C}(\text{O})\text{C}(\text{CH}_3)$), 2.08 (3 H, m, $=\text{C}(\text{H})\text{CH}_3$), 6.43 (1 H, m, $=\text{C}(\text{H})\text{CH}_3$) and 7.38 (2 H, s, 2 x Ar- H); δ_{C} 16.3 ($=\text{C}(\text{H})\text{CH}_3$), 20.1 ($\text{C}(\text{O})\text{CCH}_3$), 125.9 (Ar-C), 2 x 128.3 (Ar-C), 130.9 (Ar-C), 136.9 ($\text{C}(\text{O})\text{CCH}_3$), 145.8 ($=\text{C}(\text{H})\text{CH}_3$), 159.4 ($\text{PhC}=\text{O}$) and 160.9 ($\text{C}(\text{O})\text{CCH}_3$). [Extensive attempts were made, but mass spectral analysis was not successful for this compound].

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To a solution of **20** (65 mg, 0.130 mmol) in toluene (0.4 cm³) was added solid sodium hydrogen carbonate (55 mg, 0.650 mmol) at room temperature. A solution of mixed anhydride **24** (120 mg, 0.390 mmol) in toluene (0.5 cm³) was added before heating to 80°C for 42 h. Further solid sodium hydrogen carbonate (33 mg, 0.393 mmol) and solid mixed anhydride **24** (80 mg, 0.260 mmol) were added before heating to 80°C for a further 23 h. Cooling to room temperature, addition of saturated aqueous sodium hydrogen carbonate solution (20 cm³) and ethyl acetate (20 cm³), separation of the phases, extraction of the aqueous with ethyl acetate (3 x 15 cm³), drying the combined organics (MgSO_4), concentration under reduced pressure and flash chromatography (1 : 50, 1 : 2 then 2 : 1, ethyl acetate : petrol) afforded the title compound **25** as a colourless oil (39 mg, 52%), [followed by a quantity of unreacted triol **20** (4 mg, 6%)]. R_f = 0.29 (1 : 1, ethyl acetate : petrol). $[\alpha]_{\text{D}}^{25}$ -14.9 (c 0.30, CHCl_3); (Found $[\text{M}+\text{Na}]^+$, 605.2760, $\text{C}_{29}\text{H}_{46}\text{NaO}_{10}\text{Si}$ requires $M+\text{Na}$, 605.2758); ν_{max} / cm⁻¹ 3441, 2950, 2922, 1794, 1717, 1383, 1251, 1229, 1156, 1130, 1109, 1058, 1018, 998 and 838; δ_{H} 0.00 (9 H, s, $\text{SiC}(\text{CH}_3)_3$), 0.89 (1 H, m, SiCHH), 0.95 (1 H, m, SiCHH), 1.22 (3 H, s, 14- H_3), 1.42 and 1.54 (each 3 H, $\text{C}(\text{CH}_3)_2$), 1.55 (3 H, s, 13- H_3), 1.83 (3 H, s, 15- H_3), 1.87 (3 H, s, $\text{C}(\text{O})\text{C}(\text{CH}_3)$), 2.02 (3 H, m, $=\text{C}(\text{H})\text{CH}_3$), 2.12 (1 H, dd, $J_{9,9}$ 15.0, $J_{9,8}$ 2.7, 9- H), 2.22 (1 H, dd, $J_{9,9}$ 15.0, $J_{9,8}$ 4.4, 9- H'), 3.27 (1 H, br. m, 1- H), 3.44 (1 H, br. s, OH), 3.58 (1 H, m, SiCH_2CHHO), 3.70 (1 H, m, SiCH_2CHHO), 4.23

(1 H, m, 8-*H*), 4.30 (1 H, dd, *J* 5.1, *J* 5.1, 2-*H*), 4.77 and 4.82 (each 1 H, d, *J* 6.9, OCH₂O), 5.80 (1 H, br. m, 6-*H*), 5.83 (1 H, br. m, 3-*H*) and 6.14 (1 H, m, =CHCH₃); δ_C -1.5 (Si(CH₃)₃), 12.5 (C-15), 15.8 (C-13), 15.9 (=C(H)CH₃), 17.9 (SiCH₂), 20.6 (C(O)CCH₃), 23.5 (C-14), 23.6 (C(CH₃)CH₃), 30.5 (C(CH₃)CH₃), 45.2 (C-9), 59.9 (C-1), 65.8 (C-8), 66.1 (OCH₂CH₂Si), 73.2 (C-10), 76.1 (C-7), 78.1 (C-6), 79.1 (C-11), 84.3 (C-3), 84.5 (C-2), 95.2 (OCH₂O), 100.8 (C(CH₃)₂), 127.5 (C=C(H)CH₃), 128.1 (C-4), 138.3 (C-5), 138.9 (=C(H)CH₃), 167.2 (OC(O)) and 172.7 (C-12).

25a

To a solution of triol **20a** (7.0 mg, 0.014 mmol) in toluene (0.4 cm³) was added solid sodium hydrogen carbonate (12.0 mg, 0.143 mmol) at room temperature. A solution of mixed anhydride **24** (22.0 mg, 0.070 mmol) in toluene (0.5 cm³) was added before heating to 80°C for 26 h. Further solid sodium hydrogen carbonate (12.0 mg, 0.143 mmol) and solid mixed anhydride **24** (22.0 mg, 0.070 mmol) were added before heating to 80°C for a further 28 h. Cooling to room temperature, addition of saturated aqueous sodium hydrogen carbonate solution (15 cm³) and ethyl acetate (15 cm³), separation of the phases, extraction of the aqueous with ethyl acetate (3 x 10 cm³), drying the combined organics (MgSO₄), concentration under reduced pressure and flash chromatography (1 : 50 then 1 : 2, ethyl acetate : petrol) afforded the title compound **25a** as a colourless oil (7.9 mg, 98%). *R_f* = 0.37 (1 : 1, ethyl acetate : petrol). $[\alpha]_D^{25}$ -125.0 (*c* 0.24, CHCl₃); (Found $[M+Na]^+$, 605.2759. C₂₉H₄₆NaO₁₀Si requires *M+Na*, 605.2758); ν_{max} / cm⁻¹ 3453, 2948, 2925, 1795, 1713, 1698, 1383, 1252, 1229, 1193, 1154, 1110, 1056, 997, 859 and 837; δ_H 0.00 (9 H, s, SiC(CH₃)₃), 0.88 (1 H, m, SiCHH), 0.94 (1 H, m, SiCHH), 1.24 (3 H, s, 14-*H*₃), 1.42 (3 H, s, C(CH₃)(CH₃)), 1.54 (6 H, s, 13-*H*₃ + C(CH₃)(CH₃)), 1.89 (3 H, s, C(O)C(CH₃)), 1.95

(3 H, d, J 7.1, =C(H)CH₃), 1.99 (3 H, s, 15-H₃), 2.12 (1 H, dd, $J_{9,9'}$ 15.2, $J_{9,8}$ 2.7, 9-H), 2.26 (1 H, dd, $J_{9',9}$ 15.2, $J_{9',8}$ 4.0, 9-H'), 3.40 (1 H, br. m, 1-H), 3.53 (1 H, m, SiCH₂CHHO), 3.72 (1 H, m, SiCH₂CHHO), 3.75 - 3.90 (1 H, br. s, OH), 4.22 (1 H, m, 8-H), 4.33 (1 H, dd, $J_{2,1}$ 6.9, $J_{2,3}$ 5.9, 2-H), 4.63 and 4.76 (each 1 H, d, J 6.6, OCH₂O), 5.60 (1 H, d, $J_{2,3}$ 5.9, 3-H), 5.77 (1 H, br. m, 6-H) and 6.05 (1 H, q, J 7.1, =CHCH₃); δ_c -1.5 (Si(CH₃)₃), 14.7 (C-15), 15.8 (C-13), 15.9 (=C(H)CH₃), 18.1 (SiCH₂), 20.6 (C(O)C(CH₃)), 23.6 (C(CH₃)CH₃), 23.8 (C-14), 30.4 (C(CH₃)CH₃), 44.9 (C-9), 59.0 (C-1), 65.8 (C-8), 66.5 (OCH₂CH₂Si), 73.2 (C-10), 76.3 (C-7), 76.5 (C-2), 78.1 (C-3), 78.6 (C-6), 78.9 (C-11), 95.2 (OCH₂O), 100.7 (C(CH₃)₂), 128.0 (C=C(H)CH₃), 131.6 (C-5), 137.5 (=C(H)CH₃), 137.6 (C-4), 168.1 (OC(O)) and 172.6 (C-12).

27

To a solution of SEM ether **25** (40 mg, 0.069 mmol) in dry ether (7.5 cm³) at room temperature was added solid potassium carbonate (398 mg, 2.880 mmol), magnesium bromide diethyl etherate (390 mg, 1.509 mmol) and *n*-butane thiol (160 μ l, 1.509 mmol). The resulting heterogeneous mixture was vigorously stirred for 30 min. Partitioning between ethyl acetate (30 cm³) and water (30 cm³), separation of the phases, extraction of the aqueous with ethyl acetate (3 x 20 cm³), drying the combined organics (MgSO₄) and purification by flash chromatography (1 : 1, ethyl acetate : petrol) afforded the title compound **27** as a white foam (26 mg, 84%). R_f = 0.21 (4 : 1, ethyl acetate : petrol). $[\alpha]_D^{25}$ -106.0 (*c* 0.3, CHCl₃); (Found $[M+Na]^+$, 475.1938,

$C_{23}H_{32}NaO_9$ requires $M+Na$, 475.1944); ν_{max} / cm^{-1} 3439, 3423, 2994, 2929, 1777, 1697, 1384, 1258, 1231, 1198, 1158, 1134, 1108, 998 and 733; δ_H 1.22 (3 H, s, 14- H_3), 1.40 (3 H, s, $C(CH_3)(CH_3)$), 1.53 (3 H, s, $C(CH_3)(CH_3)$), 1.54 (3 H, s, 13- H_3), 1.92 (6 H, s, 15- H_3 + $C(O)CCH_3$), 2.03 (3 H, d, J 7.2, $=C(H)CH_3$), 2.07 (1 H, dd, $J_{9,9'}$ 14.9, $J_{9,8}$ 2.1, 9- H), 2.28 (1 H, dd, $J_{9',9}$ 14.9, $J_{9',8}$ 4.0, 9- H'), 3.26 (1 H, br. m, 1- H), 3.60 - 3.95 (1 H, br. s, OH), 4.24 (2 H, m, 2- H + 8- H), 5.37 (1 H, br. m, 3- H), 5.77 (1 H, br. m, 6- H) and 6.05 (1 H, q, J 7.2, $=CHCH_3$); δ_C 12.6 (C -15), 15.9 (C -13), 16.0 ($=C(H)CH_3$), 20.5 ($C(O)CCH_3$), 23.5 (C -14), 23.6 ($C(CH_3)CH_3$), 30.5 ($C(CH_3)CH_3$), 44.9 (C -9), 59.6 (C -1), 65.8 (C -8), 73.6 (C -10), 76.1 (C -7), 78.4 (C -6), 79.1 (C -11), 79.3 (C -2), 87.9 (C -3), 100.7 ($C(CH_3)_2$), 127.1 ($C=C(H)CH_3$), 128.7 (C -4), 136.0 (C -5), 140.5 ($=C(H)CH_3$), 169.6 ($OC(O)$) and 173.0 (C -12).

28

To a solution of triol **27** (24.6 mg, 0.054 mmol) in DCM (3.5 cm³) at room temperature was added a solution of octanoic anhydride (23.0 mg, 0.085 mmol) in DCM (1.0 cm³) and catalytic DMAP. After stirring for 1 h, further octanoic anhydride (23.0 mg, 0.085 mmol) and catalytic DMAP were added before stirring for a further 1 h. Addition of saturated aqueous ammonium chloride solution (15 cm³) and ethyl acetate (15 cm³), separation of the phases, extraction of the aqueous with ethyl acetate (3 x 10 cm³), drying the combined organics (MgSO₄), concentration under reduced pressure and purification by flash chromatography (1 : 4 then 1 : 1, ethyl acetate : petrol) afforded the title compound **28** as a colourless oil (27.0 mg, 86%). R_f = 0.66 (4

: 1, ethyl acetate : petrol). $[\alpha]_D^{25}$ -16.0 (c 0.3, CHCl_3); (Found $[\text{M}+\text{Na}]^+$, 601.2991, $\text{C}_{31}\text{H}_{46}\text{NaO}_{10}$ requires $M+\text{Na}$, 601.2989); ν_{max} / cm^{-1} 3428, 2928, 2858, 1796, 1778, 1713, 1457, 1381, 1256, 1227, 1151, 1133, 1100, 1043, 996 and 845; δ_{H} 0.87 (3 H, t, J 6.8, CH_3^{oct}), 1.24 (3 H, s, 14- H_3), 1.24 - 1.28 (8 H, m, $\text{CH}_3(\text{CH}_2)_4^{\text{oct}}$), 1.41 (3 H, s, $\text{C}(\text{CH}_3)(\text{CH}_3)$), 1.53 (3 H, s, 13- H_3), 1.54 (3 H, s, $\text{C}(\text{CH}_3)(\text{CH}_3)$), 1.60 (2 H, m, $\text{C}(\text{O})\text{CH}_2\text{CH}_2^{\text{oct}}$), 1.87 (3 H, s, 15- H_3), 1.90 (3 H, s, $\text{C}(\text{O})\text{CCH}_3$), 1.97 (3 H, d, J 7.0, $=\text{C}(\text{H})\text{CH}_3$), 2.02 (1 H, dd, $J_{9,9'} 15.1$, $J_{9,8} 1.8$, 9- H), 2.24 (1 H, dd, $J_{9',9} 15.1$, $J_{9',8} 4.1$, 9- H'), 2.33 (2 H, m, $\text{C}(\text{O})\text{CH}_2^{\text{oct}}$), 2.89 (1 H, br. s, OH), 3.38 (1 H, br. m, 1- H), 4.23 (1 H, br. m, 8- H), 5.37 (1 H, dd, J 4.3, 4.3, 2- H), 5.78 (2 H, br. m, 3- H + 6- H) and 6.12 (1 H, q, J 7.0, $=\text{CHCH}_3$); δ_{C} 12.5 (C-15), 14.0 (CH_3^{oct}), 15.8 (C-13), 15.9 ($=\text{C}(\text{H})\text{CH}_3$), 20.5 ($\text{C}(\text{O})\text{CCH}_3$), 22.6 (CH_2^{oct}), 23.6 ($\text{C}(\text{CH}_3)(\text{CH}_3)$), 24.0 (CH_2^{oct}), 24.7 ($\text{OC}(\text{O})\text{CH}_2\text{CH}_2^{\text{oct}}$), 28.9 (C-14), 29.0 (CH_2^{oct}), 30.5 ($\text{C}(\text{CH}_3)(\text{CH}_3)$), 31.6 (CH_2^{oct}), 34.4 ($\text{OC}(\text{O})\text{CH}_2^{\text{oct}}$), 44.3 (C-9), 59.9 (C-1), 65.8 (C-8), 72.9 (C-10), 76.0 (C-7), 77.9 (C-6), 78.7 (C-2), 79.1 (C-11), 83.4 (C-3), 100.9 ($\text{C}(\text{CH}_3)_2$), 127.3 ($\text{C}=\text{C}(\text{H})\text{CH}_3$), 129.4 (C-4), 137.6 (C-5), 139.1 ($=\text{C}(\text{H})\text{CH}_3$), 167.4 ($\text{OC}(\text{O})\text{C}=\text{O}$), 172.8 ($\text{C}=\text{O}^{\text{oct}}$) and 174.7 (C-12).

29

To a solution of diol **28** (23.5 mg, 0.041 mmol) in isopropenyl acetate (2.0 cm^3) at room temperature was added *p*-toluenesulfonic acid monohydrate (22.0 mg, 0.130 mmol). After stirring for 1 h 45 min, saturated aqueous sodium hydrogen carbonate solution (15 cm^3) and ethyl acetate (15 cm^3) were added. The phases were separated and the aqueous extracted with ethyl acetate (3 x 10 cm^3), the combined organics dried (MgSO_4), concentrated under reduced pressure and purified by flash chromatography (1 : 10, 1 : 5 then 3 : 1, ethyl acetate : petrol) to afford the title compound **29** as a colourless oil (25.0 mg, quant.). R_f = 0.65 (1 : 1, ethyl acetate : petrol). $[\alpha]_D^{25}$ -33.7 (c 0.41, CHCl_3); (Found $[\text{M}+\text{Na}]^+$, 643.3096, $\text{C}_{33}\text{H}_{48}\text{NaO}_{11}$

requires $M+Na$, 643.3094); $\nu_{\max}$ / cm^{-1} 3438, 2930, 2857, 1797, 1775, 1738, 1457, 1441, 1372, 1237, 1188, 1160, 1137, 1101 and 1001; δ_{H} 0.87 (3 H, t, J 6.8, CH_3^{oct}), 1.22 - 1.34 (8 H, m, $\text{CH}_3(\text{CH}_2)_4^{\text{oct}}$), 1.42 (3 H, s, $\text{C}(\text{CH}_3)(\text{CH}_3)$), 1.47 (3 H, s, 14- H_3), 1.53 (3 H, s, $\text{C}(\text{CH}_3)(\text{CH}_3)$), 1.54 (3 H, s, 13- H_3), 1.59 (2 H, m, $\text{C}(\text{O})\text{CH}_2\text{CH}_2^{\text{oct}}$), 1.87 (6 H, s, 15- H_3 + $\text{C}(\text{O})\text{CH}_3$), 1.91 (3 H, br. m, $\text{C}(\text{O})\text{CCH}_3$), 1.97 (3 H, m, $=\text{C}(\text{H})\text{CH}_3$), 2.30 (2 H, m, $\text{C}(\text{O})\text{CH}_2^{\text{oct}}$), 2.64 (1 H, dd, $J_{9,9'} 14.7$, $J_{9,8} 2.7$, 9- H), 2.24 (1 H, dd, $J_{9',9} 14.7$, $J_{9',8} 4.5$, 9- H'), 3.30 (1 H, br. s, OH), 3.95 (1 H, br. m, 1- H), 4.27 (1 H, m, 8- H), 5.48 (1 H, dd, J 4.6, 4.6, 2- H), 5.73 (1 H, br. m, 3- H), 5.77 (1 H, br. m, 6- H) and 6.09 (1 H, m, $=\text{CHCH}_3$); δ_{C} 12.6 (C-15), 14.0 (CH_3^{oct}), 15.7 (C-13), 15.8 ($=\text{C}(\text{H})\text{CH}_3$), 20.5 ($\text{C}(\text{O})\text{CCH}_3$), 21.2 (C-14), 22.6 (CH_2^{oct}), 23.6 ($\text{C}(\text{CH}_3)(\text{CH}_3)$), 24.7 ($\text{OC}(\text{O})\text{CH}_2\text{CH}_2^{\text{oct}}$), 28.9 (CH_2^{oct}), 29.1 (CH_2^{oct}), 30.4 ($\text{C}(\text{CH}_3)(\text{CH}_3)$), 31.6 (CH_2^{oct}), 34.3 ($\text{OC}(\text{O})\text{CH}_2^{\text{oct}}$), 38.0 (C-9), 57.3 (C-1), 65.8 (C-8), 76.0 (C-7), 77.7 (C-6), 78.0 (C-2), 79.4 (C-11), 84.0 (C-3), 84.7 (C-10), 101.1 ($\text{C}(\text{CH}_3)_2$), 127.5 ($\text{C}=\text{C}(\text{H})\text{CH}_3$), 128.5 (C-4), 138.6 (C-5), 138.7 ($=\text{C}(\text{H})\text{CH}_3$), 167.4 ($\text{OC}(\text{O})\text{C}=\text{O}$), 170.4 ($\text{C}(\text{O})\text{CH}_3$), 172.6 ($\text{C}=\text{O}^{\text{oct}}$) and 172.9 (C-12).

30

To a solution of acetone **29** (24.0 mg, 0.039 mmol) in dry methanol (1.5 cm^3) at room temperature was added an aqueous solution of HCl (50 μl of a 3N solution) dropwise. The reaction mixture was heated to 45°C for 45 min before cooling to room temperature, followed by careful addition of saturated aqueous sodium hydrogen carbonate solution (10 cm^3) and ethyl acetate (10 cm^3). Separation of the phases, extraction of the aqueous with ethyl acetate (3 x 10 cm^3), drying the combined organics (MgSO_4), concentration under reduced pressure and purification by flash chromatography (1 : 2 then 1 : 1, ethyl acetate : petrol) afforded the title compound **30** as a colourless oil (18.6 mg, 83%). R_f = 0.57 (2 : 1, ethyl acetate : petrol). $[\alpha]_{\text{D}}^{25}$ -27.3

(c 0.31, CHCl_3); (Found $[\text{M}+\text{Na}]^+$, 603.2779, $\text{C}_{30}\text{H}_{44}\text{NaO}_{11}$ requires $M+\text{Na}$, 603.2781); $\nu_{\text{max}} / \text{cm}^{-1}$ 3401, 2928, 2858, 1790, 1771, 1737, 1710, 1457, 1368, 1238, 1153, 1132, 1114, 1083 and 989; δ_{H} 0.87 (3 H, t, J 6.8, CH_3^{oct}), 1.23 - 1.33 (8 H, m, $\text{CH}_3(\text{CH}_2)_4^{\text{oct}}$), 1.44 (3 H, s, 14- H_3), 1.50 (3 H, s, 13- H_3), 1.59 (2 H, m, $\text{C}(\text{O})\text{CH}_2\text{CH}_2^{\text{oct}}$), 1.84 (3 H, s, $\text{C}(\text{O})\text{CCH}_3$), 1.90 (6 H, br. m, 15- H_3 + $\text{C}(\text{O})\text{CH}_3$), 1.98 (3 H, m, $=\text{C}(\text{H})\text{CH}_3$), 2.58 (2 H, m, $\text{C}(\text{O})\text{CH}_2^{\text{oct}}$), 2.64 (1 H, dd, $J_{9,9'} 14.3$ $J_{9,8} 3.1$, 9- H), 2.24 (1 H, dd, $J_{9',9} 14.3$, $J_{9',8} 2.5$, 9- H'), 3.25 (1 H, br. s, OH), 4.00 (1 H, br. m, OH), 4.20 (1 H, br. m, 1- H), 4.35 (1 H, m, 8- H), 4.70 (1 H, br. m, OH), 5.45 (1 H, dd, J 3.5, 3.1, 2- H), 5.70 (1 H, br. m, 3- H), 5.81 (1 H, br. m, 6- H) and 6.11 (1 H, m, $=\text{CHCH}_3$); δ_{C} 12.8 (C-15), 14.0 (CH_3^{oct}), 15.8 ($=\text{C}(\text{H})\text{CH}_3$), 16.3 (C-13), 20.5 ($\text{C}(\text{O})\text{CCH}_3$), 22.6 (CH_2^{oct}), 22.7 ($\text{C}(\text{O})\text{CH}_3$), 22.8 (C-14), 24.8 ($\text{OC}(\text{O})\text{CH}_2\text{CH}_2^{\text{oct}}$), 28.9 (CH_2^{oct}), 29.1 (CH_2^{oct}), 31.6 (CH_2^{oct}), 34.3 ($\text{OC}(\text{O})\text{CH}_2^{\text{oct}}$), 39.1 (C-9), 57.5 (C-1), 68.6 (C-8), 77.2 (C-6), 77.9 (C-2), 79.4 (C-7), 79.6 (C-11), 84.1 (C-3), 85.3 (C-10), 127.4 ($\text{C}=\text{C}(\text{H})\text{CH}_3$), 130.0 (C-4), 138.8 (C-5), 141.1 ($=\text{C}(\text{H})\text{CH}_3$), 167.2 ($\text{OC}(\text{O})\text{C}=\text{O}$), 171.2 ($\text{C}(\text{O})\text{CH}_3$), 172.6 ($\text{C}=\text{O}^{\text{oct}}$) and 175.4 (C-12).

Thapsigargin, Tg (1)

To a solution of triol **30** (16.2 mg, 0.028 mmol) in DCM (0.1 cm^3) at room temperature was added a stock solution of butyric anhydride (9.1 μl , 0.056 mmol, added as 0.3 cm^3 of a stock solution consisting of 150 μl in 5.0 cm^3 DCM). After stirring for 1 h 15 min, addition of saturated aqueous ammonium chloride solution (15 cm^3) and ethyl acetate (15 cm^3), separation of the phases, extraction of the aqueous with ethyl acetate (3 x 10 cm^3), drying the combined organics (MgSO_4), concentration under reduced pressure and purification by flash chromatography (1 : 2, ethyl acetate : petrol) afforded the title compound as a colourless oil (16.6 mg, 91%) which was

identical to an authentic sample of the natural product by normal spectroscopic analysis. $R_f = 0.19$ (1 : 2, ethyl acetate : petrol). $[\alpha]_D^{25} -42.4$ (c 0.17, CHCl_3)*; (Found $[\text{M}+\text{Na}]^+$, 673.3188. $\text{C}_{34}\text{H}_{50}\text{NaO}_{12}$ requires $M+\text{Na}$, 673.3200); $\nu_{\text{max}} / \text{cm}^{-1}$ 3435, 2959, 2927, 2858, 1790, 1775, 1741, 1721, 1459, 1369, 1256, 1237, 1161, 1128, 1102, 1043, 1019, 987 and 802; δ_{H} (3.4 mg sample in 0.65 cm^3 CDCl_3 , 600 MHz) 0.87 (3 H, t, J 6.8, CH_3^{oct}), 0.95 (3 H, t, J 7.4, CH_3^{but}), 1.25 – 1.35 (8 H, m, $\text{CH}_3(\text{CH}_2)_4^{\text{oct}}$), 1.42 (3 H, s, 14- H_3), 1.51 (3 H, s, 13- H_3), 1.62 (4 H, m, $\text{C}(\text{O})\text{CH}_2\text{CH}_2^{\text{oct}}$ + $\text{C}(\text{O})\text{CH}_2\text{CH}_2^{\text{but}}$), 1.87 (3 H, s, 15- H_3), 1.88 (3 H, s, $\text{C}(\text{O})\text{CH}_3$), 1.92 (3 H, m, $\text{C}(\text{O})\text{CCH}_3$), 2.00 (3 H, m, $=\text{C}(\text{H})\text{CH}_3$), 2.25 – 2.40 (4 H, m, $\text{C}(\text{O})\text{CH}_2^{\text{oct}}$ + $\text{C}(\text{O})\text{CH}_2^{\text{but}}$), 2.38 (1 H, dd, $J_{9,9'}$ 14.8 $J_{9,8}$ 4.0, 9- H), 2.53 (1 H, br. s, OH), 2.96 (1 H, dd, $J_{9',9}$ 14.8, $J_{9',8}$ 3.2, 9- H'), 4.18 (1 H, br. m, 1- H), 5.50 (1 H, dd, J 3.3, 3.2, 2- H), 5.62 (1 H, m, 8- H), 5.67 (1 H, br. m, 6- H), 5.72 (1 H, br. m, 3- H) and 6.09 (1 H, m, $=\text{CHCH}_3$); δ_{C} 12.9 (C-15), 13.7 (CH_3^{but}), 14.0 (CH_3^{oct}), 15.8 ($=\text{C}(\text{H})\text{CH}_3$), 16.2 (C-13), 18.0 ($\text{OC}(\text{O})\text{CH}_2\text{CH}_2^{\text{but}}$), 20.5 ($\text{C}(\text{O})\text{CCH}_3$), 22.5 ($\text{C}(\text{O})\text{CH}_3$), 22.6 (CH_2^{oct}), 22.9 (C-14), 24.8 ($\text{OC}(\text{O})\text{CH}_2\text{CH}_2^{\text{oct}}$), 28.9 (CH_2^{oct}), 29.0 (CH_2^{oct}), 31.6 (CH_2^{oct}), 34.2 ($\text{OC}(\text{O})\text{CH}_2^{\text{oct}}$), 36.5 ($\text{OC}(\text{O})\text{CH}_2^{\text{but}}$), 38.2 (C-9), 57.5 (C-1), 66.2 (C-8), 76.8 (C-6), 77.7 (C-2), 2 x 78.6 (C-7 + C-11), 84.1 (C-3), 84.6 (C-10), 127.4 ($\text{C}=\text{C}(\text{H})\text{CH}_3$), 130.1 (C-4), 138.7 ($=\text{C}(\text{H})\text{CH}_3$), 141.8 (C-5), 167.1 ($\text{OC}(\text{O})\text{C}=\text{O}$), 170.8 ($\text{C}(\text{O})\text{CH}_3$), 2 x 172.6 ($\text{C}=\text{O}^{\text{oct}}$ + $\text{C}=\text{O}^{\text{but}}$) and 175.3 (C-12).

* An optical rotation on a sample of the natural product, kindly donated by Prof. S. B. Christensen, was measured in our laboratory to be $[\alpha]_D^{25} -36.0$ (c 0.15, CHCl_3); this is in reasonable accord with our synthetic material.

mb1355/2 3.4 mg
in 0.65 mL CDCl₃
Standard 1H NMR-600

S18

Current Data Parameters
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EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060801
Time 10:2

mg 1.33427 g/L
Standard 13C NMR 600

ppm
172.55
170.89
167.07

Thapsigargin 1
(synthetic 3.4 mg in 0.65 mL)

138.55
130.11
127.43
84.56
84.12
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78.55
77.72
77.19
76.98
76.84
76.77
66.16
57.51

38.24
36.52
34.16
31.64
29.03
28.94
24.79
22.85
22.56
22.33
20.53
17.95
16.19
15.77
14.02
13.66
12.92

100% authentic Tg
 in 0.65 mL CHCl₃
 Standard 1H NMR-600

Thapsigargin 1
 (natural, 3.4 mg in 0.65 mL)

F2 - Acquisition Parameters
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 Time 12:02

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1.7 mg mL⁻¹ 355/2 + 1.7 mg
 authentic lg
 in v 65 cm³ CDCl₃
 Standard 1H NMR-600

Current Data Parameters
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2 - Acquisition Parameters
 Date_ 20060815
 Time_ 19.42

Current Data Parameters
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 PROCNO 1

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 30.37
 30.29
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 23.41
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 17.66
 17.67
 14.00
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 2.70
 2.53
 1.47

Integral

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4.269

1.982

10.861

4.101

55.429

19.892

mb1_348/11 Column 2
 Elmer (mb1_348)
 Standard 1H DEX-600

20a

S30

Avance 500 13C Cryo
 MBL 340/2
 M. Ball - SVL

Current Data Parameters
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 PROCNO 1

F2 - Acquisition Parameters

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 TD 65536
 SOLVENT CDCl3
 NS 3200
 DS 8
 SWH 34013.605 Hz
 FIDRES 0.519006 Hz
 AQ 0.9634439 sec
 RG 4096
 DW 14.700 usec
 DE 6.00 usec
 TE 300.0 K
 D1 3.00000000 sec
 D11 0.03000000 sec
 D12 0.00001000 sec

===== CHANNEL f1 =====
 NUC1 13C
 P1 9.15 usec
 PL1 -6.00 dB
 SFO1 125.7520828 MHz

===== CHANNEL f2 =====
 CPDPRG2 waltz16
 NUC2 1H
 PCPD2 100.00 usec
 PL2 -6.00 dB
 PL12 12.00 dB
 PL13 16.00 dB
 SFO2 500.0517480 MHz

F2 - Processing parameters
 SI 65536
 SF 125.7376767 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.00

172.951
 140.723
 128.706
 100.617
 95.359
 79.849
 79.206
 78.482
 77.662
 77.257
 77.210
 77.002
 76.748
 76.153
 73.357
 66.650
 65.731
 58.623
 45.478
 30.488
 29.696
 23.606
 23.238
 18.326
 16.071
 14.732
 14.194
 14.123
 1.013
 -1.452

20a

Current Data Parameters
 NAME MB360/6
 EXPNO 1
 PROCNO 1
 F2 - Acquisition Parameters
 Date_ 20061201
 Time 9:15

Standard 1H DRX-500
 MB360/6 angeloyl/yanaguchol
 mixed anhydride

20.10
16.23

77.20
76.99
76.78

136.91
132.81
128.34
128.29
125.94

150.91
149.41

Standard 13C DFX-600
ppm

24

S34

mb1 349/15 product
Standard 13C DRX-600

```

-2 - Acquisition Parameters
Date_ 20060829
Time 19.01

```

S40

Current Data Parameters
NAME mb1352_2 pure
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060826
Time 15:13

44.28
34.43
33.68
31.60
30.45
29.99
28.36
28.29
26.85
24.71
24.69
24.00
23.62
22.56
20.53
15.63
15.81
14.92
12.54

83.40
79.14
78.74
77.87
77.50
77.19
76.98
76.77
76.04
72.91
72.90
65.77
59.86

139.08
137.62
137.58
129.36
129.32
127.33

157.44
172.98
174.61
159

Current Data Parameters
NAME mb1353_2.cel
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060826
Time 18:20

mb1_353/2 column:4
Standard 1H NMR 1340

38.02
 34.26
 31.64
 30.44
 29.07
 29.93
 24.70
 23.98
 22.56
 22.51
 21.19
 20.50
 15.76
 15.74
 14.02
 12.99

57.27

65.81
 75.96
 76.77
 76.98
 77.20
 77.71
 78.00
 79.36
 83.98
 84.73

101.11

127.46
 128.47

138.62
 138.71

167.37
 170.42
 172.93
 172.94

Current Data Parameters
NAME mb1354.2.cel
EXPNO 20
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060828
Time 14:20

12.82
14.02
15.79
16.28
20.52
22.56
22.66
22.79
24.77
28.92
29.05
31.63
34.25
39.14

57.49

68.63
76.77
76.98
77.19
77.94
79.38
79.59
84.08
85.31

127.41
130.00
139.76
141.05

155.43
156.58
171.82
167.23