Design and total synthesis of unnatural analogues of the sub-nanomolar SERCA inhibitor thapsigargin†

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Thapsigargin is a densely oxygenated guaianolide which displays potent sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA) binding affinities. The total syntheses of designed unnatural analogues of this important natural product are described. This article constitutes the chemical synthesis behind an ongoing project. Rational modifications have been made to the lactone region of thapsigargin in order to obtain derivatives for future structure–activity relationship studies.

Introduction

Thapsigargin (**1**) is a potent and selective inhibitor of sarco/endoplasmic reticulum Ca^{2+} ATPases (SERCAs).[1,2] As such, thapsigargin is capable of severely unbalancing cellular Ca^{2+} concentrations,[3] often leading to disrupted cell function and growth,[4] and apoptosis of the affected cell.[5] Significantly, this has led to the development of a thapsigargin-derived prodrug for the treatment of prostate cancer. When tested *in vivo*, the prodrug was selectively cytotoxic to prostate tumours, whilst displaying minimal host toxicity.[6]

Following the recent publication of the first total synthesis of thapsigargin,[7,8] and with a growing understanding of its structure–activity relationship (SAR), highly active analogues of the natural product with simplified structures are increasingly within reach of the synthetic chemist.[9] Furthermore, owing to the difficulties in cultivating *Thapsia* (from which thapsigargin is harvested in relatively small quantities), total synthesis appears attractive as a means of obtaining thapsigargin and related analogues.[10]

Existing SAR

Chemical transformations of natural samples of thapsigargin have previously provided analogues with modified peripheral functionality.[10] Stereocentres of the natural product have also been epimerised, and together, these studies have provided valuable SAR data. However, there are very few literature examples of analogues in which the core structure of the molecule has been significantly modified, or which have been prepared by total synthesis.[9e,11,12] Upon analysing literature SAR data it also becomes apparent that very few analogues have been prepared in which the lactone region of thapsigargin has been modified, but of those that have been tested, many exhibit exceptional levels of SERCA inhibition.

For example, modification of the C-7/11 diol functionality of thapsigargin afforded acetates **2** and **3**, which exhibit SERCA binding affinities of the same order of magnitude as thapsigargin (Table 1). Ether **4** and lactol **5** display even higher potencies, which are almost as great as that of the natural product.[10,13] Another important discovery was that other members of the thapsigargin family are highly active, including nortrilobolide (**6**), which is equipotent with thapsigargin, despite lacking the large octanoate group at C-2.[9a] Of further significance is the observation that another C-2 deoxygenated compound (**7**, also obtained by total synthesis), which lacks the internal C-4/5 olefin moiety of the thapsigargins, is ten times more potent than thapsigargin.[9e] Conversely, analogues of thapsigargin with epimerised C-3 or C-8 stereogenic centres have been shown to possess lower SERCA inhibition properties by factors of 438 and 3124, respectively.[10]

We have previously reported the synthesis of some unnatural analogues of thapsigargin.[9e,12] In this article, we describe the chemical synthesis of our most recent generation of targets.

Results and discussion

Target analogues

To address the issue of obtaining simplified analogues of thapsigargin by total synthesis, we sought to prepare a complimentary set of compounds from known common intermediate **12** (Scheme 1). It was anticipated that this group of analogues (**8**, **9**, **10** and **11**) would reveal key SAR data concerning the importance of the rigidity of the lactone ring, as well as the necessity for hydrogen bond donors/acceptors at this site of the pharmacophore. These particular molecules were chosen, in part, for their availability from common intermediate **12**. However, we aimed to retain high activity in these analogues, so all targets would incorporate the key features discussed above: they would retain the C-3 and C-8 stereochemistry of the natural product, but would lack oxygen at C-2 and be saturated at C-4/5.[14]

Synthesis of butenolide analogue 8

During our work on the total synthesis of thapsigargin, we developed a route capable of generating large quantities of **12** as a single diastereomer.[8,15] By modifying our existing method for generating the lactone of thapsigargin from this intermediate, we

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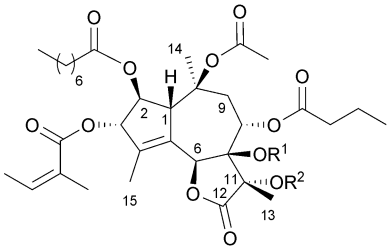
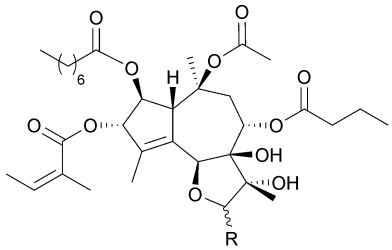
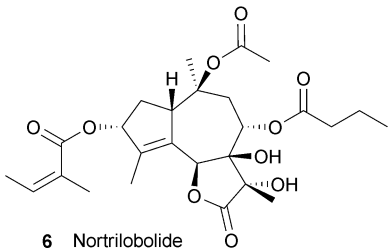
Table 1 Relative potencies of thapsigargin (**1**) and related analogues



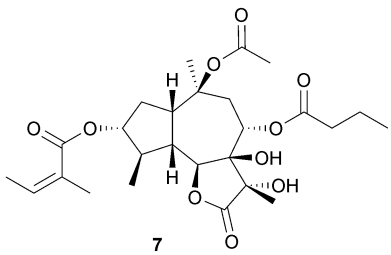
1 $R^1 = R^2 = H$ Thapsigargin
2 $R^1 = Ac$, $R^2 = H$
3 $R^1 = H$, $R^2 = Ac$



4 R = H
5 R = OH



6 Nortrilobolide



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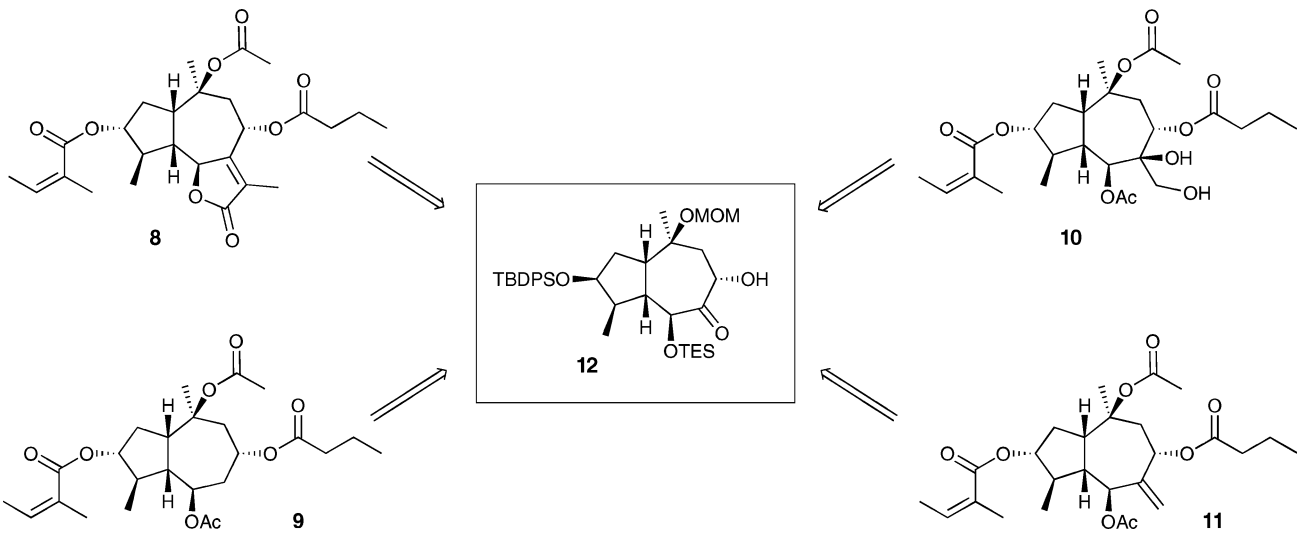
Compound	IC_{50}(analogue)/IC_{50}(**1**) [a]
1	1.0
2	2.8
3	2.6
4	1.1
5	1.6
6	1
7	0.1
C-8-*epi*-**1**	3124

[a] IC_{50} = concentration of inhibitor required to elicit 50% inhibition of SERCA.



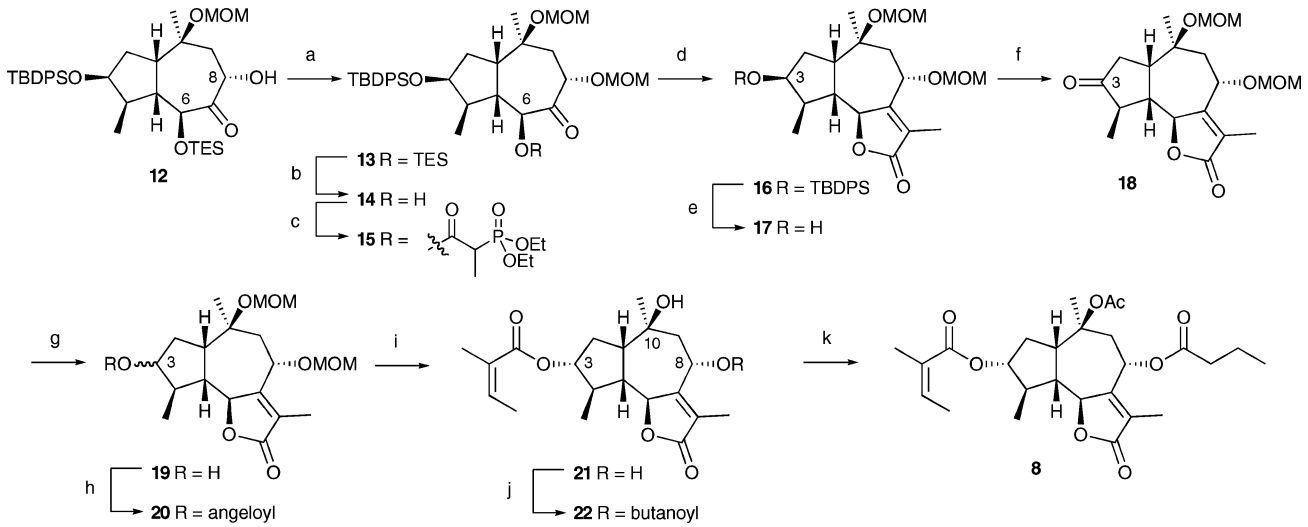
Scheme 1 Possible generation of target analogues **8**, **9**, **10** and **11** from common intermediate **12**.

anticipated that butenolide **16** would be available from **12** in four steps *via* a tethered Horner–Wadsworth–Emmons reaction, and that subsequent installation of the peripheral ester moieties would proceed in an analogous fashion to those in our natural product synthesis.

To this end, protection of the free C-8 hydroxyl of **12** as a methoxymethyl acetal,[16] and selective cleavage of the TES group with HF·pyridine at room temperature, generated alcohol **14** (Scheme 2). Construction of the butenolide proceeded by first tethering the requisite phosphonate to O-6, and then performing the intramolecular olefination.[17] The hydroxyl at C-3 was unmasked by treatment of silyl ether **16** with HF·pyridine, and then inverted with a two-step protocol involving oxidation with catalytic amounts of TPAP,[18] and stereoselective reduction of the resulting ketone (**18**) with sodium borohydride (d.r. = 3 : 1).[19] Separation of the epimeric alcohols was not possible at this stage, so they were carried through the next two steps as a mixture. Methanolysis of the methoxymethyl acetals under acidic conditions, and then selective acylation[20] afforded **22** as a single diastereomer (64% after separation of the C-3 epimeric angelates by flash chromatography, theoretical maximum yield = 75%). Finally, installation of the acetate group at O-10 furnished the desired analogue **8**, in a total of 11 steps from common intermediate **12**.

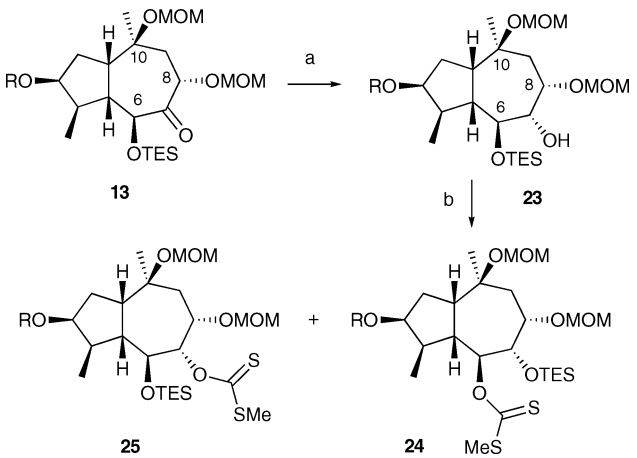
Synthesis of analogue 9

We aimed to remove the C-7 oxygenation of **13** by forming a xanthate at this position, and then performing a Barton–McCombie deoxygenation reaction.[21] Reduction of ketone **13** proceeded with excellent facial selectivity, affording alcohol **23** as



Scheme 2 Synthesis of analogue **8**. *Reagents and conditions*: a) MOM-Cl, Hünig's base, DMAP, CH_2Cl_2, rt, 16 h; b) HF·pyridine, pyridine, THF, rt, 25 min, 96% over two steps; c) EDCI, $HO_2CCH(Me)P(O)(OEt)_2$, CH_2Cl_2, rt, 13 h, 90%; d) NaH, THF, reflux, 20 min; e) HF·pyridine, THF, pyridine, rt, 7 days, 77%; f) TPAP, NMO, 4 Å MS, rt, 30 min, 91%; g) $NaBH_4$, MeOH, −30 °C, 1 h (d.r. = 3 : 1, *R*:*S*); h) angelic acid, 2,4,6-tricholorobenzoyl chloride, Et_3N, PhMe, 75 °C, 2 days, 85% over two steps (d.r. = 3 : 1, *R*:*S*); i) HCl, MeOH, 40 °C, 3 h 45 min, quantitative (d.r. = 3 : 1, *R*:*S*); j) butyric anhydride, DMAP, CH_2Cl_2, rt, 1 h, separation of C-3 isomers, 64%; k) isopropenyl acetate, *p*-TsOH, CH_2Cl_2, rt, 16 h, 99%.

a single diastereomer (d.r. >19 : 1), but it was necessary to perform and quench the reaction at 0 °C in order to suppress migration of the neighbouring TES group (Scheme 3). However, when **23** was treated with carbon disulfide and NaHMDS, migration of the TES group was again observed, and a mixture of the two regioisomeric xanthates **24** and **25** was isolated.[22]



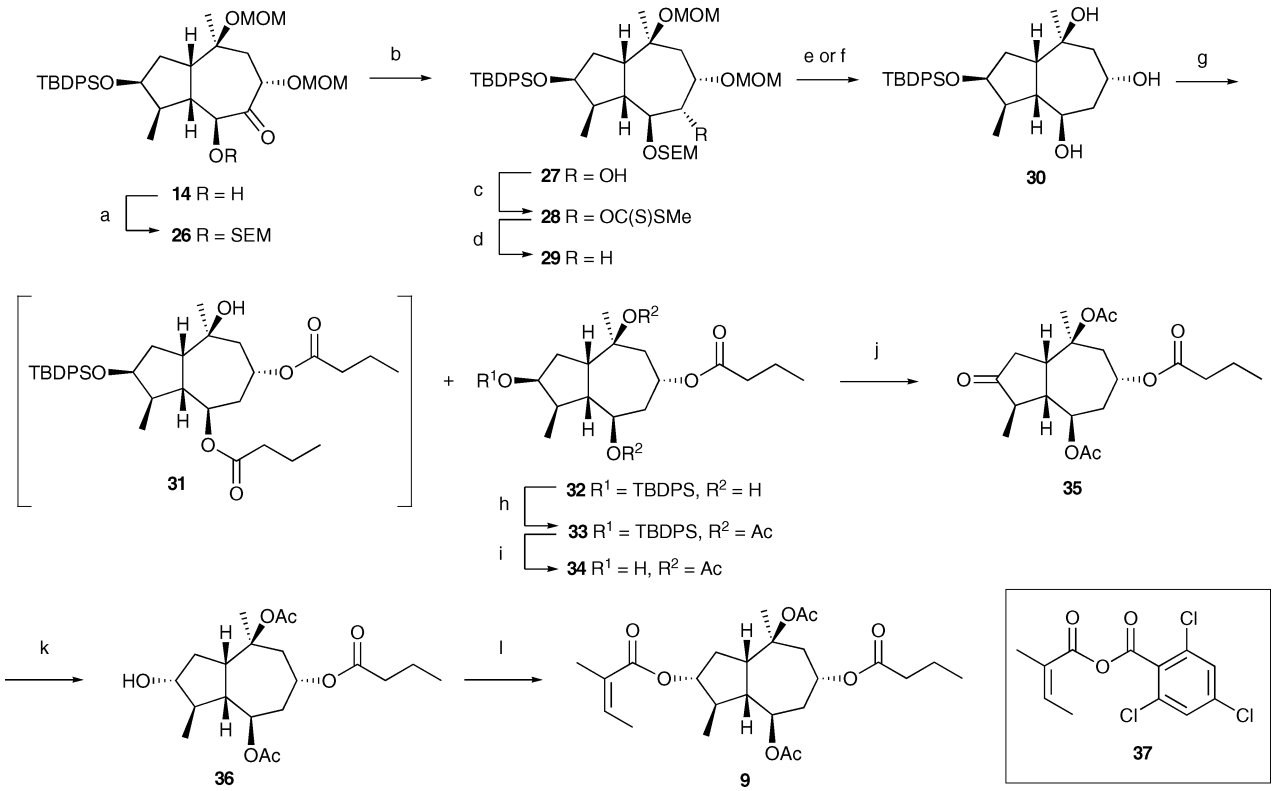
Scheme 3 TES migrations under xanthate-forming conditions (R = TBDPS). *Reagents and conditions*: a) $NaBH_4$, THF, 0 °C, 5.5 h, 91%, (d.r. >19 : 1); b) CS_2, THF, −78 °C, 30 min, then NaHMDS, 1 h, then MeI, 1.5 h to rt, 13 h.

To overcome the problem of migration of the triethylsilyl group, it was necessary to replace it with a more robust protecting group at O-6, and the 2-(trimethylsilyl)ethoxymethyl (SEM) group was chosen for this purpose (Scheme 4).[23,24] Treatment of **14** with SEMCl and Hünig's base afforded **26**, which could be successfully reduced and converted to the corresponding xanthate (**28**). Treatment of the xanthate with tributyltin hydride and AIBN effected the deoxygenation, affording a 71% isolated yield of **29** over the three steps, with no observed migration of the SEM group.[21] Cleavage of the MOM and SEM acetals from **29** was possible with magnesium bromide diethyl etherate and butane thiol, or with HCl/methanol.[25] Treatment of the resulting triol (**30**) with butyric anhydride afforded a 2 : 1 mixture of desired butanoate **32** and the bis-acylated compound **31**. Double acetylation of diol **32** afforded silyl ether **33** which was deprotected and inverted at C-3 (similarly to **16** in Scheme 2, but now with a significantly higher facial selectivity (d.r. >19 : 1) for the ketone reduction). Finally, esterification of the free alcohol under conditions developed for the total synthesis of thapsigargin[7] afforded the desired bicyclic analogue **9** in 92% yield.

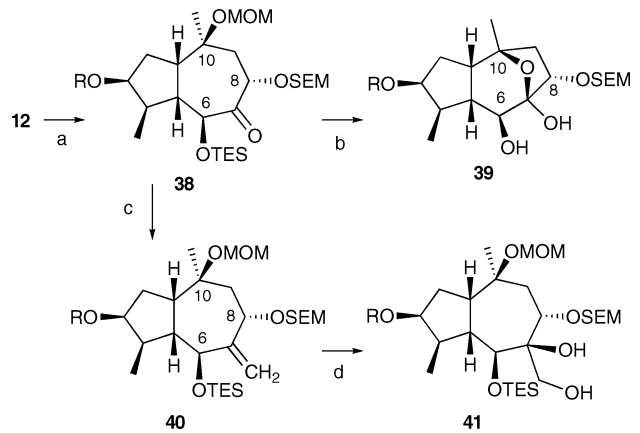
Towards the synthesis of analogue 10

Intermediate **12** was protected at O-8 as the corresponding SEM acetal (**38**, Scheme 5).[23] Owing to the high levels of oxygenation in target molecule **10**, we intended to install the requisite acetyl functionalities at O-6 and O-10 early, in order to circumvent the further need for protecting groups at these positions. However, deprotection of **38** at O-6 and O-10 caused the formation of unwanted lactol derivatives such as **39**.[26]

In order to prevent the formation of such lactols, it was ultimately necessary to mask the C-7 ketone. Thus, formation of the *exo*-methylene functionality (**40**),[27] required for later dihydroxylation, served to achieve this goal. However, by performing the olefination reaction on this particular substrate, in which bulky protecting groups flanked the ketone, the yield was somewhat compromised.[28] Dihydroxylation of **40** was performed with Sharpless' biphasic conditions,[29] and it was found that the reaction proceeded in good yield and with excellent facial selectivity to afford the desired diol **41**. However, it was felt that the extra oxygenation at C-7/11 should be installed later in the synthesis to simplify protecting group strategies, so we focused our attention on installing the C-6 and C-10 acetates on **40**.



Scheme 4 Synthesis of analogue **9**. *Reagents and conditions*: a) SEM-Cl, Hünig's base, DMAP, CH_2Cl_2, rt, 15 h, 80%; b) $NaBH_4$, THF, 0 °C, 2 h then rt, 20 h, 92%, (d.r. >19 : 1); c) CS_2, THF, −78 °C, 30 min then NaHMDS, 1.5 h, then MeI, 1.5 h, 98%; d) Bu_3SnH, catalytic AIBN, PhMe, 110 °C, 3 h, 79%; e) K_2CO_3, *n*-BuSH, $MgBr_2{\cdot}Et_2O$, Et_2O, rt, 45 min, 85%; f) HCl, MeOH, 40 °C, 2 h, 92%; g) butyric anhydride, DMAP, CH_2Cl_2, rt, 3 h, 57% **32**, 30% **31**; h) *p*-TsOH, isopropenyl acetate, rt, 16 h, 87%; i) TBAF, THF, rt, 15.5 h, 75%; j) catalytic TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 30 min, 93%; k) $NaBH_4$, MeOH, −30 °C, 1 h, 88%, (d.r. >19 : 1); l) **37**, $NaHCO_3$, PhMe, 80 °C, 18.5 h, 92%.



Scheme 5 Formation of lactol derivative **39**, and dihydroxylation of **40** (R = TBDPS). *Reagents and conditions*: a) SEMCl, Hünig's base, DMAP, CH_2Cl_2, rt, 18 h, quantitative; b) Amberlyst-15, MeOH, 4 Å MS, rt, 4 h, 57%; c) 2.0 eq. $PPh_3{}^+CH_3\,Br^-$, 1.9 eq. KHMDS, THF, −78 °C to rt over 45 min, 34%; d) OsO_4, $K_3Fe(CN)_6$, $MeSO_2NH_2$, quinuclidine, K_2CO_3, *t*-BuOH, H_2O, rt, 3 days, 81% (d.r. >19 : 1).

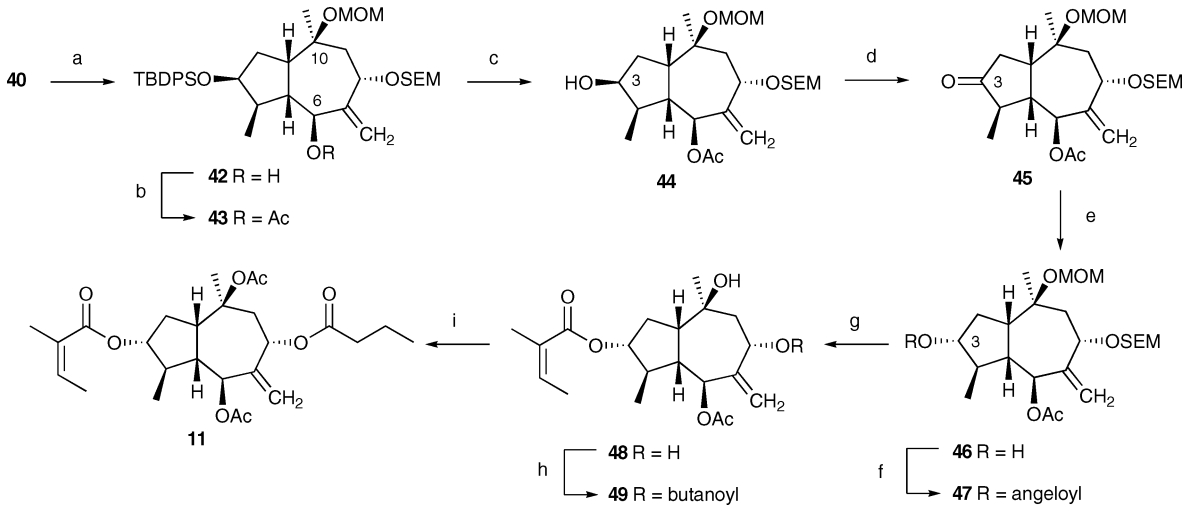
Synthesis of analogue 11

Application of the Amberlyst-15 deprotection conditions to **40** cleanly removed the TES group, but did not cleave the MOM acetal on this substrate (Scheme 6). Nonetheless, acetylation of **42** with acetic anhydride generated **43**, and silyl deprotection and C-3 inversion of **44** proceeded smoothly, providing alcohol **46** as a single diastereomer (d.r. >19 : 1). Angeloylation of **46** under the conditions used for lactone **19** resulted in decomposition,[20] and the formation of a complex mixture of products.[30] However, application of our milder angeloylation conditions to the remaining portion of alcohol **46**[7] effected clean conversion to the desired angelate **47** in 96% isolated yield.

Double acetal deprotection of **47**, followed by selective acylation of the secondary hydroxyl with butyric anhydride, and then acetylation of the remaining alcohol (**49**), afforded olefin **11**. However, dihydroxylation of a sample of **11** using the same conditions that had successfully generated **41** resulted in decomposition of the molecule.

Conclusions

Thapsigargin is a valuable compound which is routinely used for studying cell physiology. Prodrug derivatives of the natural product have shown potential in the development of a treatment for prostate cancer. However, thapsigargin is in relatively short supply as its natural source (*Thapsia*) cannot be cultivated—the demand for material must therefore be met by the synthetic chemist. In the continuing search for a greater understanding of this intriguing pharmacophore, numerous analogues have been prepared by derivatising the natural product, and they have been used for comparative binding studies. However, there have



Scheme 6 Synthesis of analogue **11**. *Reagents and conditions*: a) Amberlyst-15, 4 Å MS, MeOH, rt, 16 h, 76%; b) Ac_2O, DMAP, pyridine, CH_2Cl_2, rt, 18 h, 91%; c) TBAF, THF, rt 12 h, 88%; d) TPAP, NMO, 4 Å MS, CH_2Cl_2, 1 h, rt, 67%; or DMP, $NaHCO_3$, CH_2Cl_2, rt, 30 min, 80%; e) $NaBH_4$, MeOH, 0 °C, 2 h, 74%; f) PhMe, $NaHCO_3$, 37, 80 °C, 22 h, 96%; g) HCl, MeOH, 40 °C, 30 min; h) butyric anhydride, DMAP, CH_2Cl_2; i) isopropenyl acetate, *p*-TsOH, CH_2Cl_2, rt, 18 h, 42% over three steps.

been few attempts to greatly simplify the parent structure for this purpose. In this article, we have demonstrated the utility of total synthesis in the generation of analogues with modified carbon skeletons by preparing analogues **8**, **9** and **11**. This work constitutes the chemical synthesis behind an ongoing project; our efforts to generate further synthetic analogues of this important natural product are continuing in order to improve the current understanding of its SAR. The results of other analogue syntheses, and the biological evaluation of all of these compounds, will be reported in due course.

Experimental

Representative experimental procedures are supplied here. All other procedures for reactions featured in this article (including compounds referenced in the footnotes) can be found in the ESI†, along with ^{1}H and ^{13}C spectra for each compound.

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 was washed thoroughly with methanol and dichloromethane and 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 or petroleum ether (PE) refers to the fraction distilled between 40 and 60 °C; 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 aqueous ammonium molybdate(IV) and heating as necessary. All ^{1}H NMR spectra were recorded on a Bruker DPX-400 spectrometer operating at 400 MHz, a Bruker Avance 500 spectrometer with dual cryoprobe operating at 500 MHz, or a Bruker DRX-600 spectrometer operating at 600 MHz, as stated with each experiment. Samples were either dissolved in $CDCl_3$ and the residual protic solvent calibrated to 7.27 ppm, or in CD_3OD and the residual solvent calibrated to 3.31 ppm (as stated). Signals are quoted in ppm to the nearest 0.01 ppm and multiplicities (*J*) are recorded in Hertz (Hz). ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer operating at 100 MHz, a Bruker Avance 500 spectrometer with dual cryoprobe operating at 125 MHz, or a Bruker DRX-600 spectrometer operating at 150 MHz (as stated). Samples were either dissolved in $CDCl_3$ and the solvent calibrated to 77.0 ppm, or in CD_3OD and the residual solvent calibrated to 49.0 ppm (as stated). Signals are quoted in ppm to the nearest 0.1 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 spetrometer using EI or ESI ionisation techniques. Optical rotations were recorded on a Perkin–Elmer 343 digital polarimeter at 25 °C with a path length of 10 cm, using a sodium lamp (589 nm) as the light source, and are reported in 10^{-1} deg cm^2 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.

Phosphonate 15

EDCI (450 mg, 2.35 mmol) was added to a solution of hydroxy ketone **14** (446 mg, 782 µmol) and 2-(diethoxy-phosphoryl)propionic acid (247 mg, 1.17 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred at room temperature for 13 h, then quenched with saturated sodium bicarbonate solution (70 mL) and extracted with EtOAc (3 × 70 mL). The combined organic phases were washed with brine

(100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was filtered through a pad of silica, eluting with EtOAc–PE 4 : 1, to furnish the phosphonate as a colourless oil and as a 1 : 1 mixture C-11 epimers (539 mg, 90%); (*Note*: assignments A and B do not refer to the two epimers specifically); δ_H (600 MHz; $CDCl_3$) 7.65 (8H, m, *o*-Ph_A and *o*-Ph_B), 7.43 (4H, m, *p*-Ph_A and *p*-Ph_B), 7.39 (8H, m, *m*-Ph_A and *m*-Ph_B), 5.05 (2H, m, H-6_A and H-6_B), 4.71 (2H, m, O-10_A-CH_2O and O-10_B-CH_2O), 4.62 (2H, m, O-$10_{A'}$-CH_2O and O-$10_{B'}$-CH_2O), 4.55 (2H, m, O-8_A-CH_2O and O-8_B-CH_2O), 4.51 (1H, m, O-$8_{A'}$-CH_2O and O-$8_{B'}$-CH_2O), 4.31 (2H, m, H-3_A and H-3_B), 4.19 (2H, m, H-8_A and H-8_B), 4.14 (4H, m, Et_A and Et_B CH_2), 3.33 and 3.32 (2 × 6H, s, O-10_A-CH_2OCH_3, O-10_B-CH_2OCH_3, O-8_A-CH_2OCH_3 and O-8_B-CH_2OCH_3), 3.17 (1H, m, PCH_A), 3.11 (1H, m, PCH_B), 2.85 (2H, m, H-1_A and H-1_B), 2.17–2.07 (6H, m, H-4_A, H-5_A, H-9_A H-4_B, H-5_B and H-9_B), 1.80 (2H, m, H-$9_{A'}$ and H-$9_{B'}$), 1.51–1.43 (10H, m, H-2_A, H-2_B, H-$2_{A'}$, H-$2_{B'}$, $PC(CH_3)_A$ and $PC(CH_3)_B$), 1.31 (6H, m, Et_A and Et_B CH_2CH_3), 1.26 (6H, m, H-15_A and H-15_B), 1.20 (6H, s, H-14_A and H-14_B), 1.08 (18H, s, $(C(CH_3)_3)_A$ and $(C(CH_3)_3)_B$); δ_C (150 MHz; $CDCl_3$) 201.9 (C-7_A and C-7_B), 169.1 (C-12 C-12_B), 135.9 (*o*-Ph_A and *o*-Ph_B), 135.8 (*o*-$Ph_A$and *o*-Ph_B), 134.6 (*ipso*-Ph_A and *ipso*-Ph_B), 133.6 (*ipso*-Ph_A and *ipso*-Ph_B), 129.68 (*p*-Ph_A and *p*-Ph_B), 129.68 (*p*-Ph_A and *p*-Ph_B), 127.61 (*m*-Ph_A and *m*-Ph_B), 127.56 (*m*-Ph_A and *m*-Ph_B), 94.73 and 94.68 (O-8_A-CH_2O and O-8_B-CH_2O), 90.63 and 90.60 (O-10_A-CH_2O and O-10_B-CH_2O), 78.2 and 77.8 (C-10_A and C-10_B), 77.7 and 77.2 (C-6_A and C-6_B), 74.2, 73.96, 73.93 and 73.8 (C-3_A, C-3_B, C-8_A and C-8_B), 62.69 and 62.65 (Et_A and Et_B OCH_2), 55.93, 55.88, 55.70 and 55.62 (O-8_A-CH_2O, O-8_B-CH_2O, O-10_A-CH_2O and O-10_B-CH_2O), 48.0 and 47.9 (C-5_A and C-5_B), 46.54 and 46.49 (C-1_A and C-1_B), 44.24 and 44.24 (C-$4_A$and C-4_B), 39.4 and 38.5 (PCH_A and PCH_B), 37.6 and 37.4 (C-2_A and C-2_B), 36.6 and 34.2 (C-9_A and C-9_B), 30.2 and 29.7 ($PC(CH_3)_A$ and $PC(CH_3)_B$), 27.8 and 27.7 (C-14_A and C-14_B), 27.0 ($(C(CH_3)_3)_A$ and $(C(CH_3)_3)_B$), 19.4 ($(C(CH)_3)_A$ and $(C(CH)_3)_B$), 16.40 and 16.37 (Et_A and Et_B OCH_2CH_3), 15.94 and 15.85 (C-15_A and C-15_B); ν_{max} (film; cm^{-1}) 2932 (C–H), 2857 (C–H), 1756 (C=O), 1733 (ketone C=O), 1257 (P=O), 1022 (P–O–C); found (ESI+) $[MNa]^+$ 785.3447; $C_{39}H_{59}O_{11}PSiNa$ requires *M*, 785.3462.

Butenolide 16

A solution of the phosphonate ester **15** (610 mg, 801 µmol) in THF (30 mL) was treated with NaH (60% dispersion in oil, 33.7 mg, 841 µmol) at rt for 5 min and then refluxed for 20 min. The reaction was cooled, quenched with ammonium chloride solution (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was used without further purification; δ_H (600 MHz; $CDCl_3$) 7.65 (4H, m, *o*-Ph), 7.43 (2H, m, *p*-Ph), 7.40 (4H, m, *m*-Ph), 4.84 (1H, dd, *J* 10.2, 5.9, H-8), 4.72 (1H, d, *J* 7.2, O-10-CH_2O), 4.62 (1H, d, *J* 10.7, H-6), 4.60–4.55 (3H, m, 2 × O-8-CH_2O and 1 × O-10-CH_2O), 4.45 (1H, m, H-3), 3.33 (3H, s, O-8-CH_2OCH_3), 3.28 (3H, s, O-10-CH_2OCH_3), 2.77 (1H, ddd, *J* 12.4, 7.4, 6.5, H-1), 2.51 (1H, m, H-4), 2.12 (1H, dd, *J* 14.5, 5.9, H-9), 1.88 (3H, s, H-13), 1.82 (1H, dd, *J* 14.5, 10.2, H-9), 1.60 (2H, m, H-2 and H-5), 1.49 (1H, ddd, *J* 13.0, 12.9, 6.7, H-2), 1.20 (3H, s, H-14), 1.15 (3H, d, *J* 7.3, H-15), 1.10 (9H, s, $C(CH_3)_3$); δ_C (150 MHz; $CDCl_3$) 174.2 (C=O), 161.2 (C-11), 135.8 (*o*-Ph), 135.7 (*o*-Ph), 134.6 (*ipso*-Ph), 133.7 (*ipso*-Ph), 129.7 (*p*-Ph), 129.6 (*p*-Ph), 127.6 (*m*-Ph), 127.5 (*m*-Ph), 126.2 (C-7), 94.7 (O-8-CH_2O), 90.6 (O-10-CH_2O), 82.5 (C-6), 77.3 (C-10), 73.3 (C-3), 66.9 (C-8), 55.8 and 55.6 (O-8-CH_2OCH_3 and O-10-CH_2OCH_3), 54.1 (C-5), 46.1 (C-1), 43.7 (C-4), 37.6 (C-9), 37.1 (C-2), 27.7 (C-14), 27.0 ($C(CH_3)_3$), 19.3 ($C(CH_3)_3$), 15.5 (C-15), 9.0 (C-13); ν_{max} (film; cm^{-1}) 2932 (C–H), 2857 (C–H), 1756 (C=O), 1590w (Ar); $[\alpha]_D$ +10.1 (*c.* 0.495, $CHCl_3$); found (ESI+) $[MNa]^+$ 631.3085; $C_{35}H_{48}O_7SiNa$ requires *M*, 631.3067.

Alcohol 17

Two batches of TBDPS ether **16** were treated separately and combined for workup: a stock solution of HF·pyridine (1.4 mL) and pyridine (1.2 mL) in THF (3.0 mL) was added to a stirring solution of crude *tert*-butyldiphenylsilylether **16** (278 µmol transferred by mass) in pyridine (4.0 mL) and THF (6.0 mL). The resulting mixture was stirred at room temperature for 7 days, then quenched by drop-wise addition of saturated sodium bicarbonate solution (100 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude oil was combined with that from a second batch (a reaction of 154 µmol) and chromatographed (SiO_2, Et_2O–PE 1 : 4, increasing gradually to 3 : 2 to recover starting material (33 mg, 13%), then EtOAc–PE 4 : 1) to afford the alcohol as a colourless oil (117 mg, 77%); δ_H (600 MHz; $CDCl_3$) 4.88 (1H, dd, *J* 10.0, 5.8, H-8), 4.81 (1H, d, *J* 10.5, H-6), 4.74 (1H, d, *J* 7.3, O-10-CH_2O), 4.62 (3H, m, 2 × O-8-CH_2O and 1 × O-10-CH_2O), 4.39 (1H, m, H-3), 3.37 (3H, s, O-8-CH_2OCH_3), 3.28 (3H, s, O-10-CH_2OCH_3), 2.71 (1H, ddd, *J* 12.9, 7.1, 6.4, H-1), 2.55 (1H, m, H-4), 2.22 (1H, dd, *J* 14.5, 5.8, H-9), 2.01 (1H, dd, *J* 14.5, 10.0, H-9′), 1.91 (3H, s, H-13), 1.82 (1H, ddd, *J* 13.2, 13.0, 6.0, H-2), 1.77 (1H, dd, *J* 13.2, 6.9, H-2), 1.61 (1H, m, H-5), 1.33 (3H, s, H-14), 1.10 (3H, d, *J* 7.4, H-15) (OH signal not observed); δ_C (150 MHz; $CDCl_3$) 174.2 (C-12), 161.0 (C-11), 126.4 (C-7), 94.7 (O-8-CH_2O), 90.5 (O-10-CH_2O), 82.9 (C-6), 77.3 (C-10), 72.0 (C-3), 66.8 (C-8), 55.8 (O-8-CH_2OCH_3), 55.6 (O-10-CH_2OCH_3), 53.9 (C-5), 46.6 (C-1), 43.6 (C-4), 38.0 (C-9), 37.3 (C-2), 27.7 (C-14), 14.5 (C-15), 9.0 (C-13); ν_{max} (film; cm^{-1}) 3474 (br, O–H), 2935 (C–H), 1749 (C=O), 1672w (C=C); $[\alpha]_D$ +4.00 (*c* 0.75, $CHCl_3$); found (ESI+) $[MNa]^+$ 393.1870; $C_{19}H_{30}O_7Na$ requires *M*, 393.1889.

Ketone 18

A stirring mixture of alcohol **17** (115 mg, 311 µmol), NMO (55.0 mg, 467 µmol), 4 Å MS (200 mg) and CH_2Cl_2 (1.0 mL) was treated with TPAP (11 mg, 31 µmol). The mixture was stirred at room temperature for 30 min then filtered, concentrated *in vacuo* and purified by column chromatography (SiO_2, EtOAc–PE 1 : 1) to afford the ketone as a colourless oil, 104 mg, 91%; δ_H (600 MHz; $CDCl_3$) 4.93 (1H, dd, *J* 10.6, 6.0, H-8), 4.84 (2H, m, H-6 and 1 × O-10-CH_2O), 4.67 (1H, d, *J* 7.1, O-8-CH_2O), 4.65 (1H, d, *J* 7.1, O-8-CH_2O), 4.63 (1H, d, *J* 7.4, O-10-CH_2O), 3.39 (3H, s, O-10-CH_2OCH_3), 3.12 (3H, s, O-8-CH_2OCH_3), 2.84 (1H, q, *J* 7.5, H-4), 2.78 (1H, ddd, *J* 14.2, 7.1, 7.0, H-1), 2.34 (2H, m, H-2 and H-9), 2.25 (1H, m, H-2′), 2.04 (1H, dd, *J* 14.7, 10.6, H-9′), 1.98 (1H, dd, *J* 10.6, 6.3, H-5), 1.95 (3H, s, H-13), 1.34 (3H, s, H-14), 1.19 (3H, d, *J* 7.5, H-15); δ_C (150 MHz; $CDCl_3$) 217.8 (C-3), 173.7 (C-12), 160.5 (C-11), 127.2 (C-7), 95.1 (O-8-CH_2O), 90.9

(O-10-CH_2O), 80.5 (C-6), 76.7 (C-10), 67.1 (C-8), 56.0 and 55.9 (O-8-CH_2OCH_3 and O-10-CH_2OCH_3), 51.6 (C-5), 48.4 (C-4), 45.1 (C-1), 39.4 (C-2), 37.1 (C-9), 27.8 (C-14), 16.4 (C-15), 9.1 (C-13); ν_{max} (film; cm^{-1}) 2932 (C–H), 1755 (lactone C=O), 1742 (acetate C=O), 1675w (C=C); $[\alpha]_D$ +48.3 (*c* 0.555, $CHCl_3$); found (ESI+) $[MH]^+$ 369.1929; $C_{19}H_{29}O_7$ requires *M*, 369.1913.

Alcohols 19

Sodium borohydride (92.3 mg, 2.43 mmol) was added to a solution of ketone **18** (89.4 mg, 243 μmol) in methanol (1.0 mL) at −30 °C. The resulting mixture was stirred at −30 °C for 1 h then warmed to room temperature, quenched with saturated ammonium chloride solution (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The product was determined to be a 3 : 1 (*R*:*S*) mixture of C-3 epimers by ^1H NMR and used without further purification. Major diastereomer (C-3-(*R*)): δ_H (600 MHz; $CDCl_3$) 5.26 (1H, d, *J* 10.6, H-6), 4.89 (1H, dd, *J* 10.4, 5.8, H-8), 4.76 (1H, d, *J* 7.3, O-10-CH_2O), 4.67 (1H, d, *J* 7.0, O-8-CH_2O), 4.65 (1H, d, *J* 7.0, O-8-CH_2O), 4.59 (1H, d, *J* 7.3, O-10-CH_2O), 3.98 (1H, m, H-3), 3.39 (3H, s, CH_3O), 3.28 (3H, s C′H_3O) 2.42 (2H, m, H-1 and H-2), 2.23 (2H, m, H-4 and H-9), 2.12 (1H, dd, *J* 14.4, 10.6, H-9′), 1.98 (3H, s, H-13), 1.58 (1H, m, H-2′), 1.57 (1H, m, H-5), 1.31 (3H, s, H-14), 1.08 (3H, d, *J* 7.4, H-15); δ_C (150 MHz; $CDCl_3$) 174.4 (C-12), 161.6 (C-11), 126.2 (C-7), 95.0 (O-8-CH_2O), 90.7 (O-10-CH_2O), 82.4 (C-6), 78.7 (C-3), 77.3 (C-10), 67.2 (C-8), 55.9 (O-8-CH_2OCH_3), 55.8 (O-10-CH_2OCH_3), 53.7 (C-5), 47.4 (C-1), 37.6 (C-9), 37.1 (C-4), 31.9 (C-2), 28.0 (C-14), 19.4 (C-15), 9.1 (C-13); ν_{max} (film; cm^{-1}) 3430 (br, O–H), 2918 (C–H), 2850 (C–H), 1750 (C=O), 1675w (C=C); found (ESI+) $[MH]^+$ 371.2077; $C_{19}H_{31}O_7$ requires *M*, 371.2070.

Angelates 20

2,4,6-Trichlorobenzoyl chloride (380 μL, 2.43 mmol) was added to a solution of angelic acid (243 mg, 2.43 mmol) in toluene (2.0 mL) followed by Et_3N (338 μL, 2.43 mmol). The mixture was stirred at room temperature for 2 h then treated with a solution of the crude alcohols **19** (assume 243 μmol) in toluene (3 mL). The resulting mixture was stirred at 75 °C for 2 days then cooled, quenched with saturated ammonium chloride solution (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2, EtOAc–PE 15 : 85 to 30 : 70) afforded a 3 : 1 (*R*:*S*) mixture of epimeric C-3 alcohols (93.0 mg, 85%) over two steps. Major diastereomer (C-3-(*R*)): δ_H (600 MHz; $CDCl_3$) 6.08 (1H, m, C=C(*H*)CH_3), 5.15 (1H, m, H-6), 5.10 (1H, m, H-3), 4.88 (1H, m, H-8), 4.76 (1H, m, O-10-CH_2O), 4.68 (1H, m, O-8-CH_2O), 4.66 (1H, m, O-8-CH_2O), 4.58 (1H, m, O-10-CH_2O), 3.49 and 3.27 (3H, s, O-8-CH_2OCH_3 and 3H, s, O-10-CH_2OCH_3), 2.68 (1H, m, H-4), 2.50 (1H, m, H-1), 2.37 (1H, m, H-2), 2.24 (1H, m, H-9), 2.04 (1H, m, H-9′), 1.95 (3H, d, *J* 7.2, C=C(H)CH_3), 1.90 (3H, s, H-13), 1.88 (3H, s, C(O)CCH_3), 1.82 (1H, m, H-2), 1.67 (1H, m, H-5), 1.26 (3H, s, H-14), 1.13 (3H, d, *J* 7.5, H-15); δ_C (150 MHz; $CDCl_3$) 174.2 (C-12), 169.6 (*C*(O)CCH_3), 161.4 (C-11), 138.3 (C=*C*(H)CH_3), 127.6 (*C*=C(H)CH_3), 126.5 (C-7), 95.2, (O-8-CH_2O), 90.7 (O-10-CH_2O), 81.4 (C-6), 80.1 (C-10), 74.2 (C-3), 67.3 (C-8), 55.9 and 55.8 (O-8-CH_2OCH_3 and O-10-CH_2OCH_3), 53.4 (C-5), 47.4 (C-1), 43.8 (C-4), 37.4 (C-9), 35.0 (C-2), 27.9 (C-14), 20.6 (C(O)C*C*H_3), 19.3 (C-15), 16.5 (C=C(H)*C*H_3), 9.1 (C-13); ν_{max} (film; $CHCl_3$) 2931 (C–H), 1754 (lactone C=O), 1713 (angelate C=O); found (ESI+) $[MH]^+$ 453.2510; $C_{24}H_{37}O_8$ requires *M*, 453.2488.

Diols 21

Concentrated HCl (3 drops) was added to a solution of the MOM ethers **20** (91.0 mg, 201 μmol) in MeOH (2.0 mL). The mixture was stirred at 40 °C for 3 h 45 min, cooled, quenched with sodium bicarbonate solution (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography (SiO_2, EtOAc–PE 1 : 1 then 7 : 3) afforded the diol as a 3 : 1 (*R*:*S*) mixture of C-3 epimers (74.6 mg, quantitative). Major diastereomer (C-3-(*R*)): δ_H (600 MHz; $CDCl_3$) 6.08 (1H, m, C=C(*H*)CH_3), 5.43 (2H, m, H-3 and H-6), 4.87 (1H, m, H-8), 2.75 (1H, m, H-4), 2.51 (1H, m, H-1), 2.23 (1H, m, H-5), 2.05 (2H, m, H-2 and H-9), 2.00 (3H, m, C=C(H)CH_3), 1.97 (3H, s, C(O)CCH_3), 1.88 (3H, s, H-13), 1.88 (1H, m, H-9′), 1.64 (1H, m, H-2′), 1.35 (3H, s, H-14), 1.13 (3H, d, *J* 7.5, H-15) (2 OH signals not observed); δ_C (150 MHz; $CDCl_3$) 174.0 (C-12), 167.7 (*C*(O)CCH_3), 163.3 (C-7), 138.4 (C=*C*(H)CH_3), 127.8 and 127.1 (C-11 and *C*=C(H)CH_3), 81.2 (C-6), 80.5 (C-10), 71.8 (C-3), 62.5 (C-8), 53.2 (C-5), 50.8 (C-1), 43.7 (C-4), 40.3 (C-9), 34.9 (C-2), 33.4 (C-14), 15.8 (C(O)C*C*H_3), 15.7 (C=C(H)*C*H_3), 9.1 (C-13); ν_{max} (film; $CHCl_3$) 3429 (OH), 2929 (C-H), 1734 (br, 2 × C=O); found (ESI+) $[MNa]^+$ 387.1800; $C_{20}H_{28}O_6Na$ requires *M*, 387.1784.

Butyrate 22

Butyric anhydride (36 μL, 220 μmol) was added to a solution of alcohols **21** (73 mg, 201 μmol) in CH_2Cl_2 (1.0 mL) followed by catalytic DMAP. The mixture was stirred for 1 h at room temperature, then quenched with saturated ammonium chloride solution (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. At this stage, the C-3 epimers were separable: column chromatography (SiO_2, EtOAc–PE 1 : 4) afforded the *R*-configured C-3 epimer **22** (46.6 mg, 64%; theoretical maximum yield = 75%); δ_H (600 MHz; $CDCl_3$) 6.10 (2H, m, H-8 and C=C(*H*)CH_3), 5.14 (1H, d, *J* 11.3, H-6), 4.87 (1H, m, H-3), 2.74 (1H, m, H-4), 2.50 (1H, ddd, *J* 13.7, 7.6, 7.0, H-2), 2.29 (3H, m, H-1 and C$H_2CH_2CH_3$), 2.14 (1H, dd, *J* 14.0, 10.8, H-9), 2.05 (3H, s, C(O)CCH_3), 2.04 (1H, m, H-9′), 2.00 (3H, dd, *J* 7.2, 1.0, C=C(H)CH_3), 1.89 (3H, s, H-13), 1.66 (4H, m, H-2′, H-5 and $CH_2CH_2CH_3$), 1.35 (3H, s, H-14), 1.14 (3H, d, *J* 7.5, H-15), 0.96 (3H, t, *J* 7.4, $CH_2CH_2CH_3$) (OH signal not observed); δ_C (150 MHz; $CDCl_3$) 173.6 (C-12), 172.4 (*C*(O)CH_2), 167.6 (*C*(O)CCH_3), 159.9 (C-7), 138.3 (C=*C*(H)CH_3), 127.67 and 127.64 (C-11 and *C*=C(H)CH_3), 81.1 (C-6), 80.0 (C-3), 71.7 (C-10), 64.7 (C-8), 55.0 (C-5), 50.2 (C-1), 43.6 (C-4), 36.8 (C-9), 36.0 (*C*$H_2CH_2CH_3$), 34.7 (C-2), 33.1 (C-14), 20.6 (C=C(H)*C*H_3), 19.3 (C-15), 18.4 ($CH_2CH_2CH_3$), 15.8 (C(O)C*C*H_3), 13.6 ($CH_2CH_2CH_3$), 9.0 (C-13); ν_{max} (film; cm^{-1}) 3478 (br, O–H), 2967 (C–H), 2927 (C–H), 2876 (C–H), 1757 (lactone C=O), 1733 (acetate C=O), 1718 (angelate C=O),

1645w (C=C); $[\alpha]_D$ −56.5 (*c* 1.08, $CHCl_3$); found (ESI+) $[MNa]^+$ 457.2207; $C_{24}H_{34}O_7Na$ requires *M*, 457.2202.

Analogue 8

A solution of the alcohol **22** (8.3 mg, 19.1 μmol) in CH_2Cl_2 (500 μL) was treated with isopropenyl acetate (200 μL, 1.82 mmol) and catalytic *p*-TsOH for 16 h at room temperature. The mixture was then quenched with saturated sodium bicarbonate solution (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (40 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography (SiO_2, Et_2O–PE 3 : 7 increasing to 1 : 1) afforded the title compound as a colourless oil (9.0 mg, 99%); δ_H (600 MHz; $CDCl_3$) 6.08 (1H, qd, *J* 7.1, 1.0, C=C(*H*)CH_3), 5.93 (1H, dd, *J* 11.0, 5.6, H-8), 5.18 (1H, d, *J* 9.0, H-6), 4.89 (1H, m, H-3), 3.01 (1H, ddd, *J* 13.7, 6.9, 6.8, H-1), 2.71 (1H, m, H-4), 2.53 (2H, m, H-2 and H-9), 2.27 (2H, t, *J* 7.3, C$H_2$$CH_2CH_3$), 2.19 (1H, dd, *J* 14.1, 11.0, H-9), 2.01 (3H, dd, *J* 7.1, 1.0, C=C(H)CH_3), 1.98 (3H, s, C(O)CH_3), 1.90, (3H, s, C(O)CCH_3), 1.84 (3H, s, H-13), 1.64 (3H, s, H-14), 1.63 (3H, m, H-2′ and $CH_2CH_2CH_3$), 1.51 (1H, dd, *J* 10.8, 6.1, H-5), 1.14 (3H, d, *J* 7.6, H-15), 0.94 (3H, t, *J* 7.3, $CH_2CH_2CH_3$); δ_C (150 MHz; $CDCl_3$) 173.4 (C-12), 172.0 (*C*(O)CH_2), 169.8 (*C*(O)CH_3), 167.5 (*C*(O)CCH_3), 159.2 (C-7), 138.6 (C=*C*(H)CH_3), 128.1 (C-11), 127.5 (*C*=C(H)CH_3), 82.6 (C-10), 81.2 (C-6), 79.7 (C-3), 63.8 (C-8), 52.6 (C-5), 46.1 (C-1), 43.7 (C-4), 35.9 (*C*$H_2CH_2CH_3$), 35.3 (C-9), 34.1 (C-2), 27.4 (C-14), 21.9 (C(O)*C*H_3), 20.6 (C(O)C*C*H_3), 19.2 (C-15), 18.4 (CH_2*C*H_2CH_3), 15.8 (C=C(H)*C*H_3), 13.5 (CH_2CH_2*C*H_3), 8.9 (C-13); ν_{max} (film; cm^{-1}) 2966 (C–H), 1761 (lactone C=O), 1736 (acetate C=O), 1715 (angelate C=O), 1649w (C=C); $[\alpha]_D$ −69.0 (*c* 0.455, $CHCl_3$); found (ESI+) $[MNa]^+$ 499.2311; $C_{26}H_{36}O_8Na$ requires *M*, 499.2308.

Alcohol 27

A solution of ketone **26** (764 mg, 1.09 mmol) in THF (24 mL) at 0 °C was treated portionwise with sodium borohydride (214 mg, 5.66 mmol). The suspension was stirred at this temperature for 2 h then warmed to room temperature over 1.5 h. A further portion of sodium borohydride (86 mg, 2.27 mmol) was added and the mixture stirred at room temperature for a further 18.5 h, at which point it was cooled to 0 °C and quenched with aqueous ammonium chloride (20 mL). After warming to room temperature over 30 min, the solution was extracted with EtOAc (4 × 30 mL), then the combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to a clear oil. This was purified by flash chromatography (SiO_2, Et_2O–PE, 1 : 4) to yield the title compound as a clear oil (704 mg, 92%, *S*:*R* ratio > 20 : 1); δ_H (400 MHz; $CDCl_3$) 7.68–7.65 (4 H, m, *o*-Ph), 7.44–7.33 (6 H, m, *m*-Ph, *p*-Ph), 4.74 (1 H, d, *J* 7.1, O-10-CH_2O), 4.70 (1 H, d, *J* 7.2, O-10-CH_2O), 4.69 (1 H, d, *J* 6.8, O-6-CH_2O), 4.68 (1 H, d, *J* 6.7, O-8-CH_2O), 4.63 (1 H, d, *J* 6.6, O-8-CH_2O), 4.56 (1 H, d, *J* 6.9, O-6-CH_2O), 4.21–4.18 (1 H, m, H-3), 4.13 (1 H, ddd, *J* 2.9, 6.0, 11.6, H-8), 4.06 (1 H, ddd, *J* 3.6, 3.6, 7.4, H-7), 3.69–3.56 (2 H, m, $SiCH_2CH_2$), 3.56 (1 H, dd, *J* 7.1, 7.1, H-6), 3.38 (3 H, s, O-10-CH_2OCH_3), 3.34 (3 H, s, O-8-CH_2OCH_3), 2.86–2.78 (1 H, m, H-1), 2.82 (1 H, d, *J* 4.1, OH) 2.20–2.12 (1 H, m, H-4), 1.99 (1 H, ddd, *J* 6.6, 6.6, 9.0, H-5), 1.90–1.80 (2 H, m, H-9), 1.57–1.43 (2H, m, H-2), 1.12–1.08 (15H, m, H-11, H-12, $C(CH_3)_3$), 0.94–0.90 (2H, m, $SiCH_2CH_2$), 0.01 (9H, s, $Si(CH_3)_3$) [selected NOE contacts: H-5 to H-1, 13.3%; H-5 to H-7, 5.8% enhancement]; δ_C (100 MHz; $CDCl_3$) 135.9 (*o*-Ph), 135.9 (*o*-Ph), 134.9 (*ipso*-Ph), 134.2 (*ipso*-Ph), 129.5 (*p*-Ph), 127.5 (*m*-Ph), 127.5 (*m*-Ph), 96.2 (O-8-CH_2O), 95.8 (O-6-CH_2O), 90.8 (O-10-CH_2O), 79.6 (C-6), 78.0 (C-10), 74.6 (C-3), 74.5 (C-7), 74.4 (C-8), 65.7 ($SiCH_2CH_2$), 55.6 (O-10-CH_2OCH_3), 55.5 (O-8-CH_2OCH_3), 50.0 (C-5), 46.1 (C-1), 44.1 (C-4), 38.0 (C−2), 37.5 (C-9), 28.0 (C-11), 27.1 ($C(CH_3)_3$), 19.5 (*C*$(CH_3)_3$), 18.1 ($SiCH_2CH_2$), 15.5 (C-12), −1.4 ($Si(CH_3)_3$); ν_{max} (film; cm^{-1}) 3453w, 2953m, 2893m, 1719w, 1568w, 1463w, 1428m, 1372w, 1249m, 1193m, 1148m, 1103s, 1037s, 917m, 860m, 835m, 741m, 702s; $[\alpha]_D$ 22.0 (*c* 0.30, $CHCl_3$); found (ESI+) $[MNa]^+$ 725.3875; $C_{38}H_{62}O_8NaSi_2$ requires *M*, 725.3881.

Xanthate 28

Carbon disulfide (361 μL, 6.01 mmol) was added to a solution of alcohol **27** (704 mg, 1.00 mmol) in THF (29 mL) at −78 °C. After stirring at this temperature for 30 min the mixture was treated dropwise with NaHMDS (1.3 mL of a 1 M solution in THF, 1.30 mmol). The resulting yellow solution was stirred for 1.5 h then treated with MeI (623 μL, 10.01 mmol) and stirred for a further 1.5 h. After this time the reaction mixture was quenched at −78 °C with aqueous ammonium chloride (15 mL) then allowed to warm to room temperature over 40 min. After partitioning between water (10 mL) and EtOAc (30 mL) the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. This was purified by flash chromatography (SiO_2, Et_2O–PE, 30:70) to yield the title compound as a yellow oil, 781 mg, 98%; δ_H (400 MHz; $CDCl_3$) 7.68–7.65 (4 H, m, *o*-Ph), 7.44–7.33 (6 H, m, *m*-Ph, *p*-Ph), 6.24 (1 H, dd, *J* 2.2, 7.2, H-7), 4.83 (1 H, d, *J* 7.1, O-10-CH_2O), 4.74 (1H, d, *J* 7.1, O-10-CH_2O), 4.71 (1H, d, *J* 7.1, O-8-CH_2O), 4.69 (1H, d, *J* 7.1, O-8-CH_2O), 4.59 (1H, d, *J* 6.9, O-6-CH_2O), 4.57 (1H, d, *J* 6.9, O-6-CH_2O), 4.40–4.36 (1H, m, H-8), 4.23–4.22 (1H, m (br), H-3), 3.94 (1H, dd, *J* 4.4, 7.2, H-6), 3.71–3.58 (2H, m, $SiCH_2CH_2$), 3.43 (3H, s, O-10-CH_2OCH_3), 3.31 (3H, s, O-8-CH_2OCH_3), 2.94 (1H, ddd, *J* 6.4, 9.8, 13.3, H-1), 2.53 (3H, s, C(S)SCH_3), 2.11–2.05 (1H, m, H-5), 1.98–1.90 (2H, m, H−9), 1.87–1.79 (1H, m, H-4), 1.53 (1H, ddd, *J* 3.8, 12.7, 12.7, H-2), 1.44 (1H, dd, *J* 6.4, 11.8, H-2′), 1.11–1.09 (6H, m, H-11, H-12), 1.08 (9H, s, $C(CH_3)_3$), 1.01–0.92 (2H, m, $SiCH_2CH_2$), 0.02 (9H, s, $Si(CH_3)_3$); δ_C (100 MHz; $CDCl_3$) 215.9 (OC(S)), 136.0 (*o*-Ph), 135.9 (*o*-Ph), 135.0 (*ipso*-Ph), 134.1 (*ipso*-Ph), 129.6 (*p*-Ph), 129.5 (*p*−Ph), 127.5 (*m*-Ph), 127.5 (*m*-Ph), 95.6 (O-8-CH_2O), 94.5 (O-6-CH_2O), 90.9 (O-10-CH_2O), 84.3 (C-7), 77.6 (C-10), 74.6 (C-3), 74.1 (C-6), 71.1 (C-8), 65.5 ($SiCH_2CH_2$), 55.7 (O-10-CH_2OCH_3), 55.5 (O-8-CH_2OCH_3), 49.4 (C−5), 46.3 (C-1), 45.4 (C-4), 38.5 (C-2), 38.1 (C-9), 28.6 (C-11), 27.1 ($C(CH_3)_3$), 19.5 (*C*$(CH_3)_3$), 19.3 (C(S)*S*CH_3), 18.2 ($SiCH_2CH_2$), 15.5 (C-12), −1.4 ($Si(CH_3)_3$); υ_{max} (film; cm^{-1}) 3075w, 2948m, 2929m, 2889m, 2857w, 1461w, 1428m, 1373w, 1249m, 1218m, 1187m, 1149m, 1103m, 1040s, 967m, 919m, 860m, 835m, 741m, 703m; $[\alpha]_D$ +248.5 (*c* 1.01, $CHCl_3$); found (ESI+) $[MNa]^+$ 815.3488; $C_{40}H_{64}O_8NaSi_2S_2$ requires *M*, 815.3479.

Tris-acetal 29

Bu_3SnH (795 μL, 2.95 mmol) and AIBN (10 granules) were added to a solution of xanthate **28** (781 mg, 0.99 mmol) in degassed

toluene (43 mL) and the mixture was heated at reflux for 3 h. After cooling to room temperature the mixture was concentrated *in vacuo*, then the residue was partitioned between water (20 mL) and EtOAc (30 mL). The aqueous layer was extracted with EtOAc (3 × 30 mL), then the combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to a clear oil. This was purified by flash chromatography (SiO_2, Et_2O–PE, neat PE then 1 : 10 to 1 : 1) to yield the title compound as a clear oil (535 mg, 79%); δ_H (600 MHz; $CDCl_3$) 7.67 (4H, d (br), *J* 7.6, *o*-Ph), 7.43–7.34 (6H, m, *m*-Ph, *p*-Ph), 4.74 (1H, d, *J* 7.6, O-10-CH_2O), 4.73 (1H, d, *J* 7.6, O-10-CH_2O), 4.65 (1H, d, *J* 7.0, O-8-CH_2O), 4.62 (1H, d, *J* 6.8, O-6-CH_2O), 4.57 (1H, d, *J* 6.7, O-6-CH_2O), 4.56 (1H, d, *J* 7.0, O-8-CH_2O), 4.23–4.22 (1H, m, H-3), 4.01–3.97 (1H, m, H-8), 3.66–3.55 (2H, m, $SiCH_2CH_2$), 3.52 (1H, dd, *J* 8.3, 8.3, H-6), 3.40 (3H, s, O-10-CH_2OCH_3), 3.32 (3H, s, O-8-CH_2OCH_3), 2.87–2.83 (1H, m, H-1), 2.17 (1H, ddd, *J* 3.7, 9.3, 18.1, H-7), 1.98 (1H, dd, *J* 5.9, 14.4, H-9), 1.95–1.86 (2H, m, H-4, H-5), 1.80 (1H, dd, *J* 5.5, 14.3, H−7′), 1.56 (1H, dd, *J* 9.9, 14.4, H-9′), 1.49 (1H, dd, *J* 6.5, 12.6, H-2), 1.35 (1H, ddd, *J* 4.6, 12.9, 12.9, H-2′), 1.13 (3H, d, *J* 6.9, H-12), 1.08 (9H, s, $C(CH_3)_3$), 1.07 (3H, s, H-11), 0.92–0.87 (2H, m, $SiCH_2CH_2$), 0.01 (9H, s, $Si(CH_3)_3$); δ_C (150 MHz; $CDCl_3$) 135.9 (*o*-Ph), 135.9 (*o*-Ph), 134.9 (*ipso*-Ph), 134.1 (*ipso*-Ph), 129.5 (*p*-Ph), 129.5 (*p*-Ph), 127.5 (*m*-Ph), 127.5 (*m*-Ph), 94.7 (O-8-CH_2O), 93.2 (O-6-CH_2O), 90.9 (O-10-CH_2O), 78.1 (C-10), 74.8 (C-6), 74.5 (C-3), 70.6 (C-8), 65.2 ($SiCH_2CH_2$), 55.6 (O-10-CH_2OCH_3), 55.2 (O-8-CH_2OCH_3), 52.1 (C-5), 46.1 (C-1), 44.5 (C-4), 40.5 (C-9), 38.4 (C-2), 37.6 (C-7), 28.7 (C-11), 27.1 ($C(CH_3)_3$), 19.5 ($C(CH_3)_3$), 18.1 ($SiCH_2CH_2$), 15.8 (C-12), −1.4 ($Si(CH_3)_3$); ν_{max} (film; cm^{-1}) 2953m, 2931m, 2893m, 2304w, 1456m, 1428m, 1373m, 1249m, 1191m, 1145m, 1096m, 1036s, 940m, 918m, 860m, 836m, 741m, 702m, 613m; $[\alpha]_D$ +2.2 (*c* 2.6, $CHCl_3$); found (ESI+) $[MNa]^+$ 709.3940; $C_{38}H_{62}O_7NaSi_2$ requires *M*, 709.3932.

Analogue 9

To a solution of alcohol **36** (6.7 mg, 0.0174 mmol) in toluene (0.5 mL) was added sodium bicarbonate (15 mg, 0.174 mmol) followed by (2*Z*)-2-methyl-2-butenoic 2,4,6-trichlorobenzoic anhydride (2.7 mg, 0.087 mmol) as a solution in toluene (0.66 mL). The mixture was heated at 80 °C for 18.5 h then cooled and quenched with aqueous sodium bicarbonate (5 mL). After extracting with EtOAc (4 × 7 mL), the combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to a clear oil. This was purified twice by flash chromatography (SiO_2, EtOAc–PE, 1 : 19 to 1 : 4; then a second column: SiO_2, EtOAc–PE 1 : 10 then 1 : 4) to yield the title compound as a clear oil (7.5 mg, 92%); δ_H (600 MHz; $CDCl_3$) 6.07 (1 H, qd, *J* 1.3, 7.1, C=C(*H*)CH_3), 5.14–5.10 (1H, m, H-8), 5.04 (1H, dd (br), *J* 9.1, 9.1, H-6), 4.71 (1H, dd, *J* 7.0, 13.1, H-3), 3.00 (1H, ddd, *J* 7.5, 7.5, 13.3, H-1), 2.53 (1H, dd, *J* 6.6, 14.5, H-9), 2.35 (1H, ddd, *J* 6.9, 6.9, 12.7, H-2), 2.32–2.24 (2H, m, $CH_2CH_2CH_3$), 2.12–1.87 (5H, m, H-4, H-5, H-7, H-9′), 2.04, 2.03 (6H, 2 × s, O-6-C(O)CH_3/O-10-C(O)CH_3), 1.98 (3H, d (fine splitting), *J* 7.2, C=C(H)CH_3), 1.88 (3H, s, C(O)CCH_3), 1.66–1.63 (2H, m, $CH_2CH_2CH_3$), 1.61–1.52 (1H, m, H-2′), 1.54 (3H, s, H-13), 1.12 (3H, d, *J* 7.1, H-14), 0.94 (3H, t, *J* 7.5, $CH_2CH_2CH_3$); δ_C (150 MHz; $CDCl_3$) δ 172.9 (O-8-*C*(O)CH_2), 170.1, 170.0 (O-6-*C*(O)CH_3/O-10-*C*(O)CH_3), 168.0 (O-3-*C*(O)C), 138.1 (C=*C*(H)CH_3), 127.8 (*C*=C(H)CH_3), 83.6 (C-10), 79.1 (C-3), 71.4 (C-6), 67.4 (C-8), 50.9 (C-5), 45.2 (C-1), 43.6 (C-4), 38.0 (C-9), 37.9 (C-7), 36.5 ($CH_2CH_2CH_3$), 34.3 (C-2), 27.5 (C-13), 22.4, 21.3 (O-6-C(O)CH_3/O-10-C(O)CH_3), 20.6 (O-3-C(O)CCH_3), 18.9 (C-14), 18.3 ($CH_2CH_2CH_3$), 15.8 (C=C(H)CH_3), 13.7 ($CH_2CH_2CH_3$); ν_{max} (film; cm^{-1}) 3676m, 2972s, 2902m, 1733s, 1647w, 1455m, 1406m, 1394m, 1374m, 1235s, 1177m, 1159m, 1076s, 1067s, 1046s, 946w, 880s; $[\alpha]_D$ −46.1 (*c* 0.38, $CHCl_3$); found (ESI+) $[MNa]^+$ 489.2442; $C_{25}H_{38}O_8Na$ requires *M*, 489.2464.

Olefin 40

KHMDS (1.43 mL, 716 µmol, 0.5 M in PhMe) was added dropwise to a stirring suspension of methyltriphenylphosphonium bromide (269 mg, 754 µmol) in THF (3.0 mL). The resulting yellow mixture was stirred at rt for 1 h then cooled to −78 °C. The ketone **38** (291 mg, 377 µmol) was added dropwise as a solution in THF (3.0 mL), and the mixture warmed to room temperature with stirring for 45 min. The reaction was filtered through a pad of silica, concentrated under reduced pressure, and purified by column chromatography (SiO_2, Et_2O–PE 1 : 19) to afford the title compound as a colourless oil (98.6 mg, 34%); δ_H (600 MHz; $CDCl_3$) 7.67 (4 H, m, *o*-Ph), 7.44 (2 H, *p*-Ph), 7.38 (4 H, *m*-Ph), 5.15 (1H, s, =CH), 5.12 (1H, s, C=H′), 4.70 (1H, d, *J* 7.2, O-10-CH_2O), 4.68 (1H, d, *J* 7.2, O-10-CH_2O), 4.67 (1H, d, *J* 6.9, O-8-CH_2O), 4.51 (1H, d, *J* 6.9, O-8-CH_2O), 4.43 (1H, dd, *J* 9.5, 6.5, H-8), 4.23 (1H, m, H-3), 3.95 (1H, d, *J* 7.6, H-6), 3.72 (1H, ddd, *J* 16.3, 7.3, 6.9, $SiCH_2CH_2$), 3.49 (1H, ddd, *J* 16.3, 6.9, 6.2, $SiCH_2CH_2$), 3.36 (3H, s, OCH_3), 2.81 (1H, ddd, *J* 12.6, 7.6, 7.1, H-1), 2.08 (1H, m, H-4), 2.00 (1H, dd, *J* 14.2, 6.5, H-9), 1.85 (1H, dd, *J* 12.6, 7.6, H-5), 1.63 (1H, dd, *J* 14.2, 9.5, H-9′), 1.47–1.44 (1H, m, H-2), 1.34 (1H, m, H-2′) 1.25 (3H, s, H-14), 1.13 (3H, d, *J* 7.1, H-15), 1.08 (9H, s, $(C(CH_3)_3)$, 0.98–0.89 (11H, m, $SiCH_2CH_2$ and $SiCH_2CH_3$), 0.51 (6H, q, *J* 8.1, $SiCH_2CH_3$), 0.02 (9H, s, $Si(CH_3)_3$); δ_C (150 MHz; $CDCl_3$) 150.1 (C-7), 135.90 (*o*-Ph), 135.86 (*o*-Ph), 134.9 (*ipso*-Ph), 134.2 (*ipso*-Ph), 129.50 (*p*-Ph), 129.47 (*p*-Ph), 127.4 (*m*-Ph), 112.3 (=CH_2), 91.3 (O-8-CH_2O), 90.8 (O-10-CH_2O), 78.0 (C-10), 74.2 (C-3), 72. 9 (C-6), 72.7 (C-8), 65.0 ($SiCH_2CH_2$), 56.1 (OCH_3), 55.5 (C-5), 45.5 (C-1), 43.6 (C-4), 39.9 (C-9), 38.1 (C-2), 29.3 (C-14), 27.0 ($C(CH_3)_3$), 19.4 ($C(CH_3)_3$), 18.1 ($SiCH_2CH_2$), 15.7 (C-15), 6.9 ($Si(CH_2CH_3)_3$), 4.7 ($Si(CH_2)_3$, −1.4 ($Si(CH_3)_3$); ν_{max} (film; cm^{-1}) 2954 (C–H), 2926 (C–H), 1461 (Ar), 1428 (Ar), 835 ($Si(CH_3)_3$); $[\alpha]_D$ −24.4 (*c* 0.93, $CHCl_3$); found (ESI+) $[MNa]^+$ 791.4543; $C_{43}H_{72}O_6Si_3Na$ requires *M*, 791.4534.

Diol 41

A solution of olefin **40** (22.7 mg, 29.5 µmol) in ^{t}BuOH (400 µL) was treated with a biphasic solution of OsO_4 (75 µL, 6.0 µmol, 2.5% by weight in ^{t}BuOH), K_2CO_3 (12.0 mg, 88.5 µmol), $K_3Fe(CN)_6$ (29.0 mg, 88.5 µmol), $MeSO_2NH_2$ (8.4 mg, 88.5 µmol) and quinuclidine (3.3 mg, 29.5 µmol) in ^{t}BuOH–H_2O (600 µL, 2 : 1). The resulting mixture was stirred in the dark for 3 days and quenched by stirring with saturated sodium sulfite solution (5.0 mL) for 1 h. The mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography (SiO_2, Et_2O–PE 1 : 9) afforded the diol as a colourless oil (19.2 mg, 81%); C-7 stereochemistry tentatively assigned as (*R*): weak NOE (<1%)

observed between H-6 and H-11, NOESY coupling between H-6 and H-11 observed. No NOESY or NOE interaction observed between H-11 and H-8; δ_H (600 MHz; $CDCl_3$) 7.67 (4H, m, *o*-Ph), 7.44 (2H, *p*-Ph), 7.38 (4H, *m*-Ph), 4.84 (1H, d, *J* 7.3, O-10-CH_2O), 4.80 (1H, d, *J* 6.7, O-8-CH_2O), 4.71 (1H, d, *J* 7.3, O-10-CH_2O), 4.69 (1H, d, *J* 6.7, O-8-CH_2O), 4.22 (1H, m, H-3), 4.00 (1H, br d, *J* 8.6, OH), 3.92 (1H, dd, *J* 11.0, 2.5, H-8), 3.79 (1H, d, *J* 10.7, H-11), 3.74 (1H, dd, *J* 9.3, 5.7, H-6), 3.63 (3H, m, $SiCH_2CH_2$ and H-11′), 3.47 (3H, s, OCH_3), 3.31 (1H, br s, OH), 2.83 (1H, m, H-1), 2.36 (1H, m, H-5), 2.29 (1H, m, H-4), 1.82 (1H, dd, *J* 14.7, 11.0, H-9), 1.76 (1H, dd, *J* 14.7, 2.5, H-9′), 1.48 (1H, m, H-2), 1.43 (3H, s, H-14), 1.32 (1H, m, H-2′), 1.11 (3H, d, *J* 7.0, H-15), 1.08 (9H, s, $C(CH_3)_3$), 0.91 (11H, m, $SiCH_2CH_2$ and $SiCH_2CH_3$), 0.57 (6H, q, *J* 8.0, $SiCH_2CH_3$), −0.10 (9H, s, $Si(CH_3)_3$); δ_C (150 MHz; $CDCl_3$) 135.9 (*o*-Ph), 135.8 (*o*-Ph), 135.0 (*ipso*-Ph), 134.1 (*ipso*-Ph), 129.5 (*p*-Ph), 127.52 (*m*-Ph), 127.46 (*m*-Ph), 95.9 (O-8-CH_2O), 90.6 (O-10-CH_2O), 79.6 (C-10), 78.7 (C-7), 77.4 (C-8), 74.9 (C-3), 72.5 (C-6), 65.3 ($SiCH_2CH_2$), 64.0 (C-11), 55.6 (OCH_3), 48.5 (C-5), 46.7 (C-1), 42.0 (C-4), 38.2 (C-9), 38.0 (C-2), 29.6 (C-14), 27.1 ($C(CH_3)_3$), 19.4 ($C(CH_3)_3$), 18.0 ($SiCH_2CH_2$), 15.4 (C-15), 6.7 ($Si(CH_2CH_3)_3$), 4.3 ($Si(CH_2CH_3)_3$), −1.5 ($Si(CH_3)_3$); ν_{max} (film; cm^{-1}) 3413 (br, O–H), 2929 (C–H), 1460 (Ar), 1428 (Ar), 822 ($Si(CH_3)_3$); $[\alpha]_D$ +61.4 (*c* 0.28, $CHCl_3$); found (ESI+) $[MNa]^+$ 825.4572; $C_{43}H_{74}O_8Si_3Na$ requires *M*, 825.4589.

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