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Total Synthesis of Five Thapsigargins: Guaianolide Natural Products Exhibiting Sub-Nanomolar SERCA Inhibition

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Abstract: Herein we describe the total synthesis of five guaianolide natural products: thapsigargin, thapsivillosin C, thapsivillosin F, trilobolide and nortrilobolide. Prodrug derivatives of thapsigargin have shown selective in vivo cytotoxicity against prostate tumours and the need for further investigation of this phenomenon highlights the importance of these total syntheses. The first absolute stereochemical assignment of thapsivillosin C is also delineated.

Keywords: guaianolide · natural products · sesquiterpene · thapsigargin · total synthesis

Introduction

The Thapsigargins: Thapsigargin (**1**) is the most prominent and intensely studied member of the family of 17 structurally-related sesquiterpenones isolated from *Thapsia*, which are collectively termed the thapsigargins. All are densely oxygenated 6,12-guaianolides (Figure 1) differing only in the

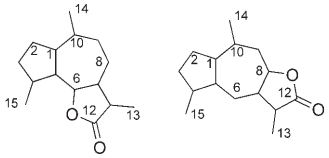
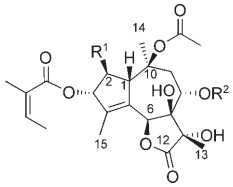


Figure 1. Structures of 6,12- and 8,12-guaianolides, respectively.

acyl groups appended to O-2 or O-8, with the exception of trilobolide (**2**), nortrilobolide (**3**) and thapsivillosin F (**4**) (the trilobolide series) which are not oxygenated at C-2 (Table 1).[1,2]

The first isolated thapsigargin was trilobolide (**2**), from *Laser trilobum* in 1968,[3] and it remains the only member of the family to have been discovered in a plant outside the *Thapsia* genus.[1a] Degradation of trilobolide and identification of the (*S*)-2-methylbutanoyl side chain allowed the first absolute stereochemical assignment of its crystal structure,[4] and these findings were used to aid the first correct stereo-

Table 1. The 17 known thapsigargins.



	Name	R^1	R^2
1	thapsigargin	O-Oct	But
2	trilobolide	H	(*S*)-2-MeBut
3	nortrilobolide	H	But
4	thapsivillosin F	H	Sen
5	thapsivillosin C	O-Oct	2-MeBut
6	thapsigargicin	O-Hex	But
7	thapsitranstagin	O-*i*Val	2-MeBut
8	thapsivillosin A	O-Ang	Sen
9	thapsivillosin B	O-Ang	2-MeBut
10	thapsivillosin D	O-6-MeOct	Sen
11	thapsivillosin E	O-6-MeOct	2-MeBut
12	thapsivillosin G	O-6-MeHep	2-MeBut
13	thapsivillosin H	O-Ang or -Sen	Ang or Sen
14	thapsivillosin I	O-Ang	But
15	thapsivillosin J	O-*i*Val	But
16	thapsivillosin L	O-But	But
17	thapsivillosin K	O-Sen	2-MeBut

Abbreviations: But = butanoyl, Sen = senecioyl, Ang = angeloyl, Hex = hexanoyl, Hep = heptanoyl, Oct = octanoyl, *i*Val = isovaleroyl.

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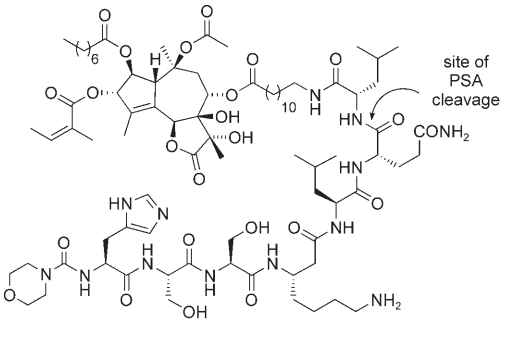
chemical assignment of thapsigargin,[5,6] isolated from *Thapsia garganica* L. in 1978.[7,8]

Owing to the extensive medicinal uses of *Thapsia* preparations, which have been recorded as far back as the time of Hippocrates (ca. 400 BC),[9] the isolation of thapsigargin prompted immediate investigation into the origins of its biological activity. Initially, thapsigargin was found to be a histamine liberator,[7,10] but the subsequent discovery of its potent inhibitory action on sarco/endoplasmic reticulum ATPases (SERCAs),[11,12] earned it widespread and increasing recognition as a powerful molecular tool for studying cell physiology.[13]

Thapsigargin is a sub-nanomolar inhibitor of molecular Ca^{2+} pumps, SERCA.[14] When applied to intact cells, thapsigargin can severely alter cellular Ca^{2+} levels,[15] leading to disrupted cell growth and function,[16] and in many cases to programmed cell death.[17,18] Recently, prodrug derivatives have shown potential as treatments for prostate cancer by exploiting this mechanism, and with the continual emergence of new analogues and a growing understanding of the SAR of the natural product, a viable drug candidate appears increasingly attainable.[19–23]

Coupling the peptide residue His-Ser-Ser-Lys-Leu-Gln to an amine linker attached to thapsigargin at O-8 generated **18** (Figure 2), which when used to treat mice with xenograft tumours, was cytotoxic specifically to prostate tumours, whilst having no observed effect on renal carcinomas.[24] Compound **18** is cell impermeant and stable in mouse and human blood plasma, but is cleaved extracellularly by prostate-specific antigen (PSA, found in the vicinity of prostate tumours). The enzyme recognises and cleaves the peptide sequence, delivering a cell permeable, cytotoxic thapsigargin derivative to the site of action.

Prostate cancer is the most frequently diagnosed cancer in men, accounting for more than 25% of new male cancer diagnoses in the UK (population ca. 61 million). The lifetime risk of being diagnosed with prostate cancer for men in the UK is 1 in 14, but currently, no method for the treatment of androgen-independent primary or metastatic prostate cancers exists.[19] In 2005, more than 30000 men were diagnosed with the disease and more than 10000 die as a direct result



18

Figure 2. Hexapeptide side chain of **18** is recognised and cleaved by a protease, releasing a cell-permeable, cytotoxic thapsigargin derivative.

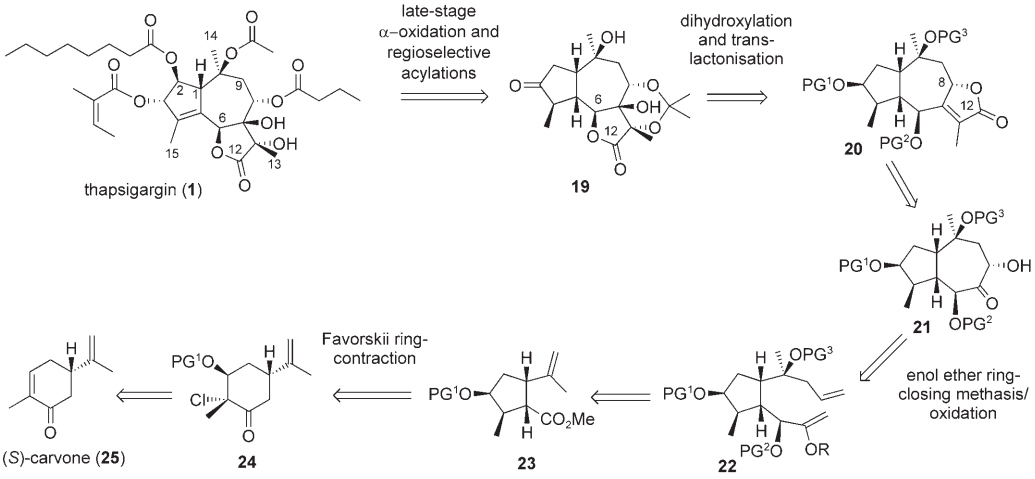
of it every year, elevating the need for an efficient route to the natural products and related analogues.[25]

Despite the wealth of biologically-related publications on the thapsigargins, the synthetic community has been slow to respond.[26] The intriguing structural complexity of the thapsigargins first attracted our attention some years ago, and we have previously published communications describing the total synthesis of the trilobolide series;[27] thapsigargin itself;[28] designed unnatural analogues,[23b] including those which exhibit sub-picomolar inhibition of SERCA;[23a] as well as a review in which we described our early synthetic strategies.[29] In this full paper, we detail how our current route may facilitate efficient access to all 17 of the known thapsigargins, as well as a range of unnatural analogues which have been used for SAR studies. We delineate five total syntheses, including the previously unpublished total synthesis and absolute stereochemical assignment of thapsivillosin C (**5**);[30] and demonstrate how degradation studies of a natural sample of thapsigargin helped resolve critical end-game stereochemical issues.

Synthetic plan: We have previously disclosed some of our early attempts to prepare the guaianolide skeleton of thapsigargin, and the iterations that led to our current route.[29] One of the major benefits of this route is the inherent substrate control that governs each newly established stereogenic centre, and this has allowed us to obtain thapsigargin as a single diastereomer in 42 synthetic steps from (*S*)-carvone (**25**) (average yield of 88.6% per step). Furthermore, these reactions can reliably be conducted on multi-gram scale and exhibit consistently high yields and selectivities without the need for extensive chromatographic purification between steps.

The polycyclic thapsigargins incorporate dense arrays of oxygenated stereocentres and up to four different ester functionalities. We anticipated that the late-stage C-2 oxidation of a suitable precursor, such as **19**, and sequential installation of the esters would impart a degree of flexibility to the route that would provide access to all 17 of the known thapsigargins, including trilobolide, nortrilobolide and thapsivillosin F, which do not carry oxygenation at C-2 (Scheme 1). Of further significance is the observation that we can tailor our approach to allow acylation at O-8 as the last step of the synthesis, allowing efficient access to prodrug conjugates for the treatment of prostate cancer.

Another key disconnection came from the recognition that the C-7/11 *anti* diol could be installed via the well-established *syn* osmylation reaction.[31] By performing a dihydroxylation/translactonisation protocol on a suitable precursor, such as 8,12-guaianolide **20**, the *syn* diol would be translated into the requisite *anti* C-7/11 diol with concomitant formation of the correct 6,12-guaianolide geometry. It was thought that the butenolide **20** could be derived from a bicyclic intermediate such as **21**, a molecule which later proved to be an important common intermediate for our analogue projects.[23] It was envisaged that ketone **21** would be available from enol ether **22** via ring-closing metathesis[32] and di-

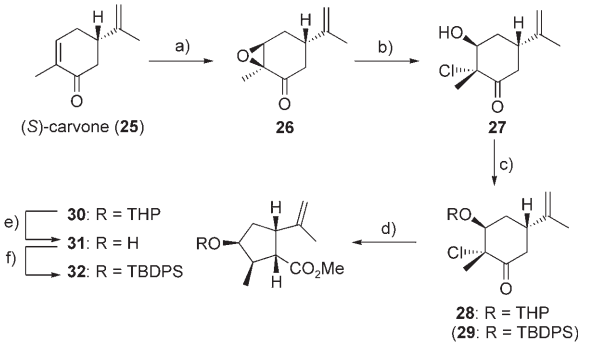


Scheme 1. Retrosynthesis of thapsigargin.

hydroxylation.[31] The enantiomer of cyclopentane **23** has previously been prepared in four steps from (*R*)-carvone,[33] and was used in the total synthesis of cladantholide and estafiatin.[34] Commercially-available (*S*)-carvone was therefore an ideal starting point for the generation of **23** via a Favorskii[35] ring-contraction of **24**.

Results and Discussion

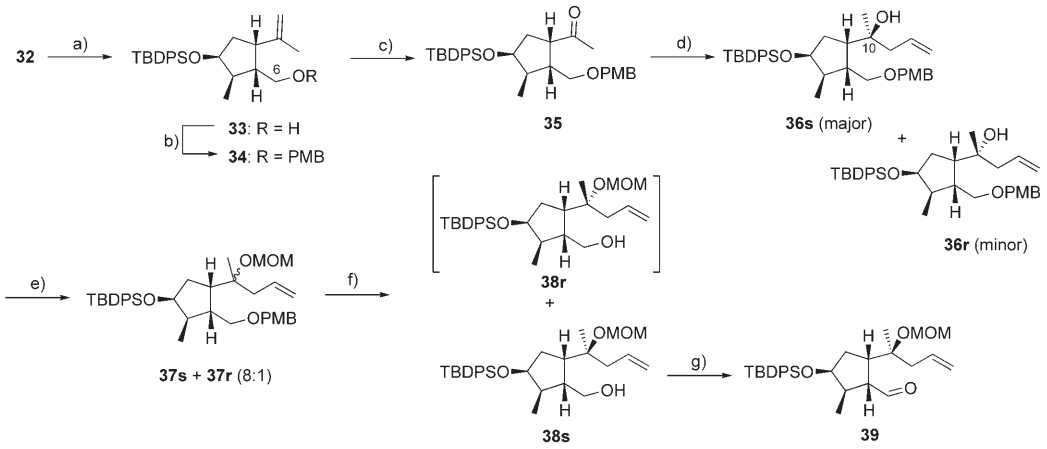
Synthesis and elaboration of cyclopentane fragment 32: The opening sequence of reactions leading to common intermediate **21** began with commercially-available (*S*)-carvone and used a Favorskii ring-contraction to deliver a functionalised cyclopentane unit **32** as a single diastereomer (dr >19:1).[33] Thus, stereoselective epoxidation[36] of enone **25** and acid-mediated opening of the resulting oxirane[37] afforded chlorohydrin **27** as a single diastereoisomer (dr >19:1, Scheme 2). Protection of the chlorohydrin as a tetrahydropyranyl acetal **28** was pivotal to the success of the Favorskii rearrangement: treatment of **28** with sodium methoxide at 0 °C effected a stereo- and regioselective rearrangement, affording one cyclopentane geometry (**30**) (but as a mixture of epimeric acetals), whereas, treatment of the analogous *tert*-butyldiphenylsilyl ether **29** with the same reaction conditions afforded 73% of the desired cyclopentane **32**.[38] With the functionalised cyclopentane motif **30** in hand, the more robust *tert*-butyldiphenylsilyl protecting group was introduced via a two-step process, affording **32** as a single diastereomer (dr >19:1). This opening sequence of reactions has been used effectively on scales in excess of 100 g of (*S*)-carvone to efficiently generate large quantities of synthetic intermediates.



Scheme 2. Generation of cyclopentane fragment **32**. a) H_2O_2, MeOH, NaOH, RT, 3 h; b) TFA, THF, LiCl, 0 °C, 90 min, 98% over two steps; c) 2,3-dihydropyran, PPTS, CH_2Cl_2, RT, 17 h, 84%; d) NaOMe, MeOH, Et_2O, 0 °C, 1 h; e) MeOH, PPTS, 50 °C, 15 h; f) TBDPSCl, imidazole, DMAP, DMF, RT, 16 h, 84% over three steps (TFA = trifluoroacetic acid, THF = tetrahydrofuran, PPTS = pyridinium *para*-toluenesulfonate, TBDPS = *tert*-butyldiphenylsilyl, THP = tetrahydropyran-2-yl).

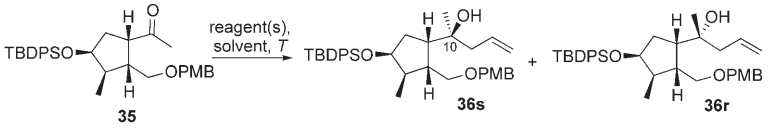
Based on previous work in our group, we were confident that the correct C-6 stereochemistry of the natural product could later be controlled by Felkin–Anh addition of a suitable nucleophile to a C-6 aldehyde,[39] so we now turned our attention to installing the C-10 stereocentre (Scheme 3). Reduction of methyl ester **32** and protection of the resultant primary hydroxyl as a *para*-methoxybenzyl ether[40] afforded **34** which was smoothly converted to ketone **35** by oxidative cleavage with osmium tetroxide and sodium periodate.[41] Dropwise addition of allylmagnesium bromide to the ketone at −78 °C afforded the desired C-10 (*S*)-configured homoallylic alcohol **36s** as the major product, but with a relatively low diastereomeric ratio of 3.5:1. Preliminary attempts to form **36s** via an enantioselective allylation reaction proved fruitless, but further optimisation of the Grignard reaction allowed the selectivity of the process to increase to 11:1 in favour of the desired product (Table 2).[42]

After further screening of reaction conditions, it was found that on a small scale (100 mg of ketone), pre-mixing ketone **35** with titanium(IV) isopropoxide in 1,2-dimethoxyethane, and then addition of allylmagnesium bromide, generated an 11:1 diastereomeric mixture of C-10 alcohols in preference for the desired Felkin–Anh product **36s**; however, on larger scales this ratio dropped to 6:1. By pre-mixing the ketone with $MgBr_2 \cdot Et_2O$ in 1,2-dimethoxyethane before addition of the Grignard reagent, it was found that a consis-



Scheme 3. Formation of aldehyde **39**. a) $LiAlH_4$, THF, 0 °C, 1 h, then RT, 1 h, 99 %; b) NaH, PMBCl, DMF, RT, 15 h, 82 %; c) OsO_4, NMO, Me_2CO, H_2O, RT, 4.5 h, then $NaIO_4$, 0 °C, 30 min, 92 %; d) $MgBr_2{\cdot}Et_2O$, DME, allylmagnesium bromide, −78 °C, 2 h, (dr 8:1); e) MOMCl, Hünig's base, DMAP, CH_2Cl_2, RT, 3 d, 84 % over two steps; f) DDQ, pH 7 buffer, RT, 30 min, then column chromatography, 75 % **38s** (dr >24:1); g) DMP, $NaHCO_3$, CH_2Cl_2, RT, 1 h (PMB = *para*-methoxylbenzyl, DMF = *N*,*N*-dimethylformamide, NMO = *N*-methylmorpholine-*N*-oxide, DME = 1,2-dimethoxyethane, MOM = methoxylmethyl, DMAP = 4-*N*,*N*-dimethylaminopyridine, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone).

Table 2. Allylation of **35**.



Reagent(s)	Solvent	*T* [°C]	Yield [%]	dr (**36s**/**36r**)
AllylMgBr	PhMe	−78	99	1.5:1
AllylMgBr	Et_2O	−78	98	1.8:1
AllylMgBr	THF	−78	99	3:1
AllylMgCl	THF	−78	82	3.5:1
AllylMgBr	THF	−100	89	3.5:1
AllylMgBr	DME	−78	99	7:1
AllylMgBr	DME	−100	93	7:1
AllylMgBr, $MgBr_2{\cdot}Et_2O$	THF	−78	99	5:1
AllylMgBr, $MgBr_2{\cdot}Et_2O$	DME	−78	99	8:1[a]
AllylMgBr, $Ti(OiPr)_4$	DME	−78	quantitative	11:1[b]
AllylMgBr, $Ti(OiPr)_4$	DME	−78	quantitative	6:1[c]

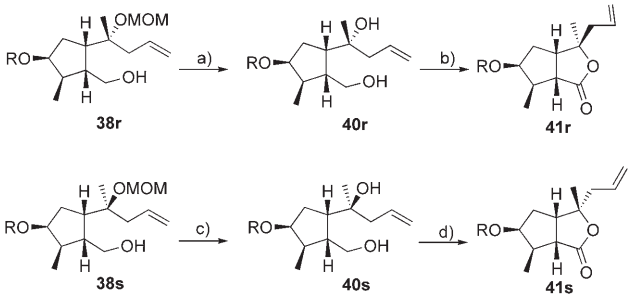
[a] Irrespective of scale. [b] 100 mg reaction scale w.r.t. ketone. [c] 1.9 g scale w.r.t. ketone.

tent ratio of C-10 alcohols could be achieved at 8:1 (*S*/*R*), regardless of scale.

When compared to the reaction with titanium(IV) isopropoxide, this procedure also had the added advantage that the metal salts generated on work-up were more easily removed at the end of the reaction, thus column chromatography could be avoided at this stage. Nonetheless, separation of the C-10 isomers was not trivial, and they were carried through the next two steps as a mixture. Protection of the alcohols as methoxymethyl acetals,[43] and oxidative cleavage of the benzylic ethers at pH 7[44] afforded a mixture of C-10 isomers (**38s** and **38r**). The C-10 diastereomers were separable by flash column chromatography at this stage, and oxidation[45] of the desired isomer **38s** to the requisite C-6 aldehyde was now possible.

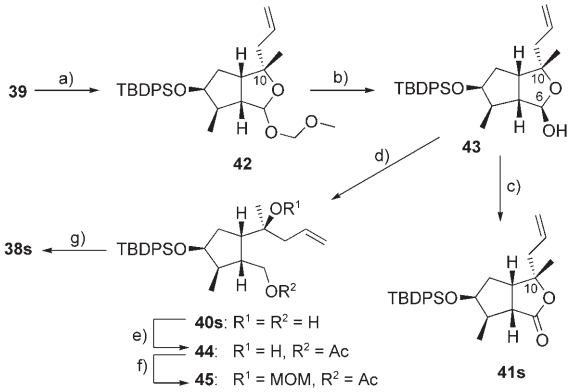
Following the successful separation of the two C-10 epimers, we were able to set about determining whether we had correctly assigned the stereochemistry of the major component. Removal of the methoxymethyl acetal from **38s** afforded diol **40s** which was oxidised[46] to lactone **41s** (Scheme 4; the corresponding lactone **41r** was also made in the same fashion). Comparison of the NOE data for the two lactones clearly demonstrated that the major product from the allylation of ketone **35** exhibited the desired C-10 stereochemistry.

With the successful formation of aldehyde **39**, we were now in a position to investigate the addition of nucleophiles to this substrate. Unfortunately, one relatively large batch of the aldehyde (ca. 20 g) was found to decompose on storage at 0 °C, affording **42** as the



Scheme 4. Synthesis of lactones **41s** and **41r** (R = TBDPS). a) PPTS, MeOH, RT, 34 %; b) cat. TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, RT, 76 %; c) PPTS, MeOH, RT, 32 %; d) cat. TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, RT, 92 % (TPAP = tetra-*n*-propylammonium perruthenate).

major decomposition product (Scheme 5). It was felt that we may be able to recover this material, but before attempting to regenerate the aldehyde from **42**, it was necessary to check the integrity of the C-10 stereocentre through the de-



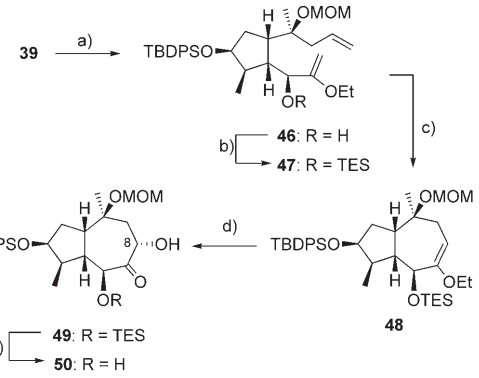
Scheme 5. Regeneration of alcohol **38s** from decomposition product **42**. a) decomposition of **42** at 0 °C; b) AcOH, THF, H_2O, 35 °C, 3 d, 62 %; c) cat. TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, 87 %; d) $NaBH_4$, MeOH, RT, 18 h, 75 %; e) Ac_2O, DMAP, pyridine, CH_2Cl_2, RT, 16 h; f) MOMCl, Hünig's base, DMAP, CH_2Cl_2, RT, 5 d; g) NaOMe, MeOH, 99 % over three steps.

composition. To this end, a sample of **42** was hydrolysed to **43**, and the lactol was oxidised to known lactone **41s**.[46] Thus, the integrity of the C-10 stereocentre had been retained through the decomposition of **42**, and we were able to set about salvaging this batch of material.

Lactol **43** was reduced with sodium borohydride affording diol **40s**; temporary protection of the primary hydroxyl as the corresponding acetate allowed selective formation of a methoxymethyl acetal at the more hindered tertiary alcohol. Transesterification of the acetate then afforded alcohol **38s**, the synthetic precursor of the aldehyde which had decomposed. This series of reactions ultimately regenerated over 10 g of the desired alcohol **38s**, and provided intermediates which were converted into simple analogues for SAR studies.

Synthesis of bicyclic intermediate 49: Addition of a solution of aldehyde **39** to the lithium anion of ethyl vinyl ether at −78 °C occurred as predicted, with Felkin–Anh control, to deliver the desired alcohol **46** as the major product (dr >19:1). Formation of the corresponding triethylsilyl ether provided the required metathesis precursor **47**, and continual dropwise addition of Grubbs' second generation catalyst[47] to the diene in refluxing dichloromethane generated enol ether **48** in a pleasing 88 % isolated yield (Scheme 6). Osmylation of **48** under Upjohn conditions[48] afforded a 12:1 mixture of α-hydroxy ketones, in favour of the desired C-8 (*S*)-diastereomer, and this ratio could be improved to 16:1 using Sharpless' biphasic conditions[49] with potassium ferricyanide and catalytic osmium tetroxide.

It is worthy of mention that although we could obtain the desired product **49** with a respectable diastereomeric ratio



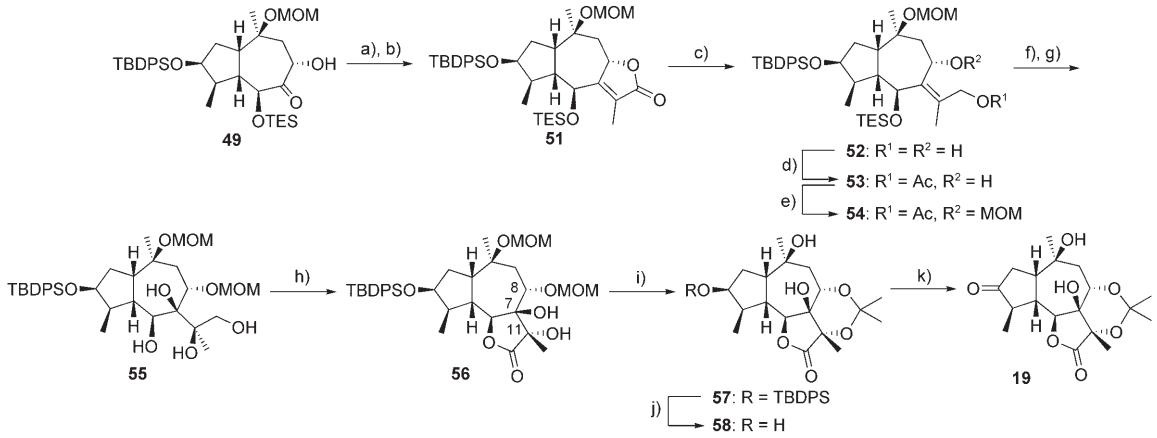
Scheme 6. Formation of bicyclic intermediate **49**. a) Ethyl vinyl ether, *t*BuLi, THF, −78 °C, 90 min; b) TESCl, imidazole, DMAP, DMF, RT, 19 h, 86 % over three steps from alcohol **38s**; c) Grubbs' second generation catalyst, CH_2Cl_2, reflux, 21 h, 88 %; d) AD-mix α, $NaHCO_3$, $MeSO_2NH_2$, *t*BuOH, H_2O, RT, 15 h, 96 %; e) TBAF, THF, 0 °C, 20 min (TES = triethylsilyl).

(16:1) without the use of chiral reagents, at this point we could opt to use Sharpless' asymmetric dihydroxylation conditions[50] to improve this ratio further. Treatment of enol ether **48** with AD mix-α led to the desired hydroxy ketone **49** as the only detectable isomer [dr >19:1; treatment of **48** with AD mix-β gave a product ratio of 1.3:1 (*S*/*R* at C-8)]. The relative stereochemistry of **49** was unambiguously determined by removal of the TES group, affording crystalline derivative **50**, which was subjected to X-ray analysis.[51]

Guaianolide formation: Butenolide **51** was prepared in two steps from α-hydroxy ketone **49** via a tethered Horner–Wadsworth–Emmons reaction (Scheme 7).[52] However, dihydroxylation of **51** proved difficult, presumably due to a combination of steric and electronic factors. To address this issue, the butenolide was reduced and differentially protected, affording **54**. The desired dihydroxylation reaction of the ring opened derivative **54** could be achieved; osmylation of **54** was slow, possibly due to steric hindrance from the neighbouring bulky silyl group, but the reaction proceeded with excellent facial selectivity and delivered the desired tetrol product **55** as the only detectable isomer (dr >19:1) after removal of the acetate and TES groups.

TPAP oxidation[46] of tetrol **55**, led exclusively to the desired 6,12-guaianolide system **56**, with the C-7/8/11 stereo triad bearing the correct stereochemistry of the natural products. In a one-pot reaction sequence, the methoxymethyl acetals were then hydrolysed under acidic conditions in wet acetone and after 48 h, molecular sieves were added to the reaction mixture to drive the formation of the isopropylidene ketal **57**.

The remaining key steps of the total synthesis of thapsigargin would involve the introduction of the C-4/5 alkene, stereoselective C-2 oxidation and regioselective installation of the four different esters. It was anticipated that the C-2 oxygen of thapsigargin could be installed using a Rubottom oxidation.[53] To that end, the O-3 hydroxyl was unmasked



Scheme 7. Generation of 6,12-guaianolide **19**. a) EDCI, $HO_2CCH(Me)P(O)(OEt)_2$, CH_2Cl_2, RT, 3 h, 81 %; b) NaH, reflux, 15 min; c) $LiBH_4$, THF, reflux, 40 h; d) Ac_2O, DMAP, 2,6-lutidine, CH_2Cl_2, RT, 3 h; e) MOMCl, Hünig's base, DMAP, CH_2Cl_2, RT, 18 h, 60 % over four steps; f) OsO_4, quinuclidine, K_2CO_3, $MeSO_2NH_2$, $K_3Fe(CN)_6$, *t*BuOH, H_2O, RT, 17 d; g) K_2CO_3, MeOH, RT, 85 % over two steps; h) 10 mol % TPAP, 40 equiv NMO, 4 Å molecular sieves, MeCN, RT, 74 %; i) Amberlyst 15, wet Me_2CO, 2,2-dimethoxypropane, RT, then 4 Å molecular sieves, 95 %; j) TBAF, THF, RT; k) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, RT, 91 % over two steps (EDCI = 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide, TBAF = tetrabutylammonium fluoride).

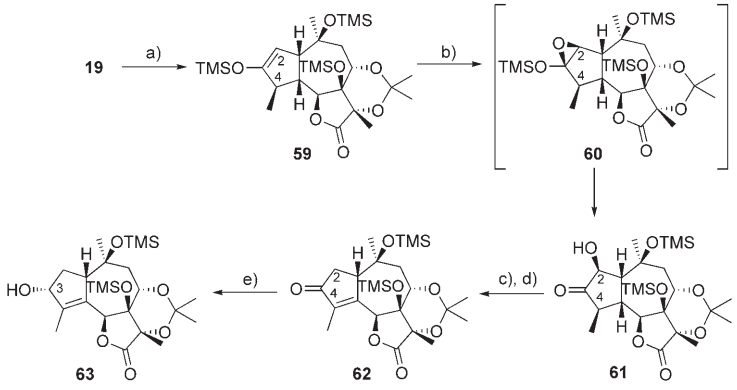
under standard conditions, and oxidised to the corresponding ketone **19** with Dess–Martin periodinane.[45]

Enone formation part I—Total synthesis of the trilobolide series: Enolisation of the ketone **19** was found to occur at the less hindered (C-2) position with trimethylsilyl chloride and triethylamine at 120 °C, affording silyl enol ether **59** (Scheme 8). Oxidation with dimethyldioxirane occurred exclusively from the *exo* face to give the desired C-2 alcohol **61** (dr > 19:1). It was found that treatment of **61** with trimethylsilyl chloride and triethylamine generated the corresponding silyl enol ether at C-4. Unexpectedly, treatment of this compound with phenylselenium bromide caused a catalytic reaction which resulted in loss of the newly installed C-2 oxygen, and formation of the desired enone functionality (**62**).[54] This "undesired" C-2 deoxygenation reaction had inadvertently provided a route to the trilobolide series, as trilobolide (**2**), nortrilobolide (**3**) and thapsivillosin F (**4**), do not harbour oxygenation at C-2. Reduction of **62** with sodium borohydride afforded the desired alcohol **63**, which is the fully oxygenated guaianolide skeleton required for the total synthesis of the trilobolide series.

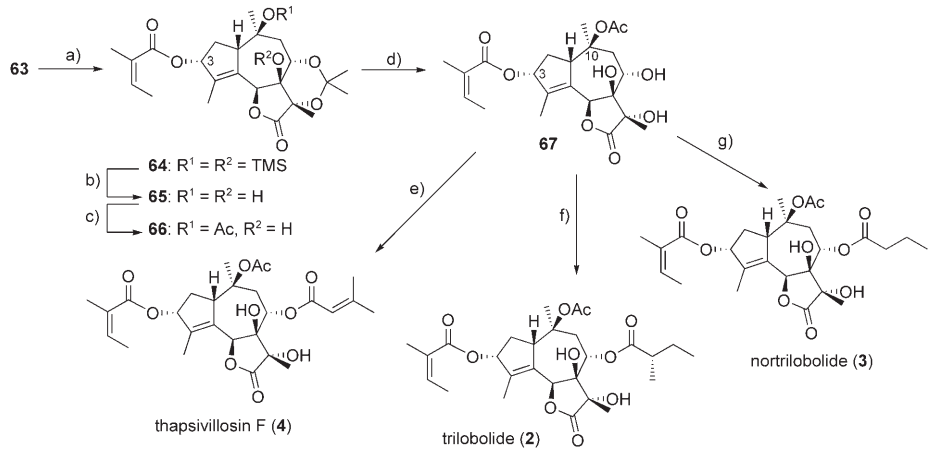
Esterification of **63** under Yamaguchi conditions,[55,56] and removal of the trimethylsilyl groups afforded **65** (Scheme 9). The diol was then selectively acetylated at O-10, and the acetonide removed to give the final precursor to the trilobolide series. Selective acylation at the more reactive (secondary) hydroxyl of **67** with (*S*)-2-methylbutyric anhydride, butyric anhydride or senecioic anhydride completed the first total syntheses of trilobolide (**2**), nortrilobolide (**3**) and thapsivillosin F (**4**), respectively.

Enone formation part II—O-2 MOM strategy: To address the issue of C-2 deoxygenation of **61**, the free alcohol was converted to the corresponding octanoate **68**, as required for the total synthesis of thapsigargin (Scheme 10), but unfortunately, installation of the C-4 selenide could not be achieved on this substrate.

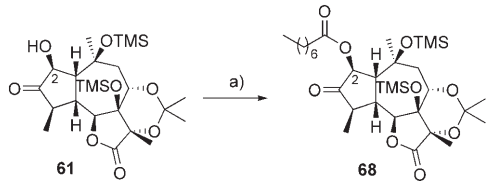
Alternatively, O-2 could be masked as a methoxymethyl acetal (**69**, Scheme 11).[43] Formation of the C-4 selenide of this substrate was possible via the silyl enol ether without loss of the C-2 oxygen, but an epimeric mixture of selenides **70** and **71** (87:13) was obtained. Once oxidised, the selenoxide derived from epimer **70** may undergo *syn* elimination with the desired C-5 proton to afford enone **73**, or it may eliminate with a proton from



Scheme 8. Enone formation, part I. a) TMSCl, Et_3N, DMF, 130 °C, 43 h; b) DMDO, Me_2CO, CH_2Cl_2, −78 °C for 30 min, then RT for 40 min, 87 % over two steps; c) TMSCl, Et_3N, DMF, 150 °C, 90 %; d) PhSeBr, CH_2Cl_2, 0 °C to RT, 94 %; e) $NaBH_4$, MeOH, 0 °C, 86 %, dr 4:1 (*R*/*S* at C-3) (TMS = trimethylsilyl, DMDO = dimethyldioxirane).



Scheme 9. Total synthesis of the trilobolides a) Angelic acid, Et_3N, 2,4,6-trichlorobenzoyl chloride, PhMe, 80 °C, 76 %; b) TBAF, THF, RT, 98 %; c) isopropenyl acetate, PS-*p*TsOH, CH_2Cl_2, RT, 68 %; d) HCl, MeOH, 40 °C; e) senecioic anhydride, DMAP, CH_2Cl_2, RT, 60 % over two steps; f) (*S*)-2-methylbutyric anhydride, DMAP, CH_2Cl_2, RT, 78 % over two steps; g) butyric anhydride, DMAP, CH_2Cl_2, RT, 72 % over two steps (PS = polymer supported, *p*TsOH = *para*-toluensulfonic acid).



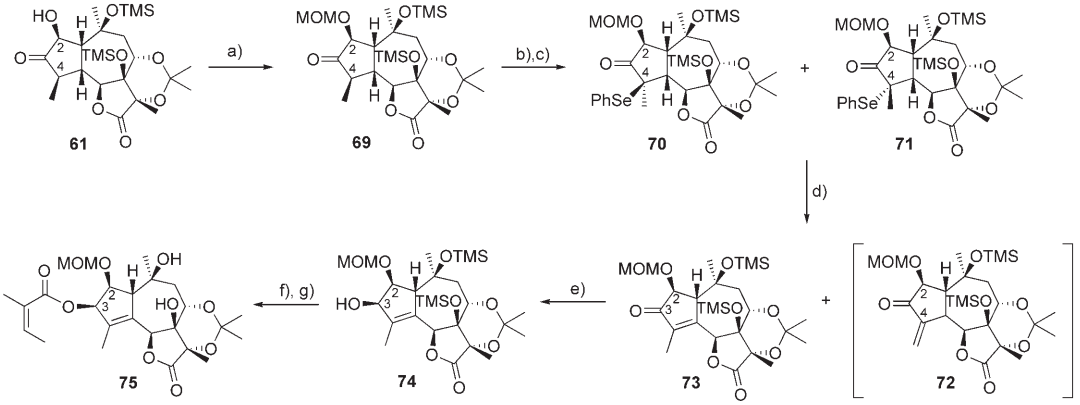
Scheme 10. C-2 octanoate installation. a) Octanoic anhydride, DMAP, CH_2Cl_2, 90 min, RT, 94 %.

the neighbouring methyl group, producing the exocyclic enone **72**. However, the same ratio of selenides (**70**/**71** 87:13) is expressed in the ratio of enones generated (**72**/**73**), suggesting that **70** leads solely to the desired endocyclic enone.

At the time of performing the reduction of **73** to afford the corresponding allylic alcohol, we were unable to convincingly assign the new stereogenic centre at C-3; however, the facial selectivity of the reduction with sodium borohydride appeared to be very high, as only one C-3 alcohol could be detected (dr >19:1). Having successfully generated the desired C-3 stereochemistry of **63** by a similar means en route to trilobolide (see enone formation part I, above), we postulated that once again the hydride had been delivered from the *exo* face of the ring system, and continued to the next step in the hope that we would be able to confirm the stereochemical course of this reduction at a later stage.

As such, removal of the silyl ethers formed during the selenation sequence, and angeloylation under Yamaguchi conditions[55,56] proceeded in moderate yield, but at this stage, we were still unable to confirm the C-3 stereochemistry. It was not until later that we showed by direct comparison with a derivative of a natural source of thapsigargin that we had formed the undesired epimer **74** in the reduction reaction, and that we had now formed the undesired C-3 angelate epimer **75** (see degradation and selective transformations of thapsigargin, below). Although unaware of the incorrect stereogenicity at the time of conducting this work, cleavage of the methoxymethyl acetal from **75** could not be satisfactorily achieved and we were, in any case, forced to re-evaluate the strategy.[57]

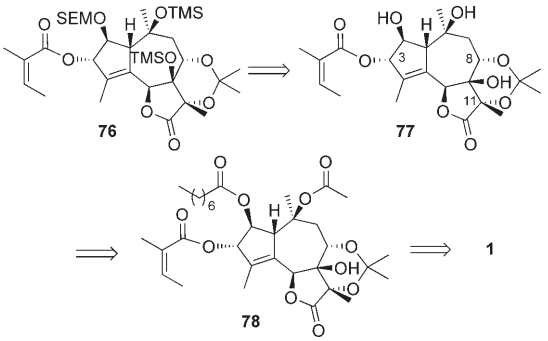
At this stage, we decided to use a 2-(trimethylsilyl)ethoxymethyl (SEM) acetal at O-2.[58] It was envisaged that this group should show similar behaviour to the methoxymethyl congener in terms of its installation and the local effects it exerts on the substrates bearing it, but should be more



Scheme 11. Enone formation, part II. a) MOMCl, Hünig's base, CH_2Cl_2, RT, 18 h, 88 %; b) NaHMDS, THF, −78 to −20 °C then TMSCl at −78 °C; c) PhSeCl, CH_2Cl_2, −78 °C, 2 h; d) O_3, −78 °C, 2 min then diisopropylamine, −78 °C to RT, 37 % **73** over three steps; e) $NaBH_4$, THF, RT, 19 h, 99 % (dr >19:1); f) TBAF, THF, 0 °C to RT, 35 min; g) 2,4,6-trichlorobenzoyl chloride, Et_3N, PhMe, angelic acid, 75 °C, 2 d, 48 % over two steps (HMDS = bis(trimethylsilyl)amide).

easily removed when required. At the same time as initiating the SEM route, we began a degradation study in which we used a natural sample of thapsigargin in an attempt to intercept the synthetic route and conclusively determine the C-3 stereochemistry of derivatives such as **75**.

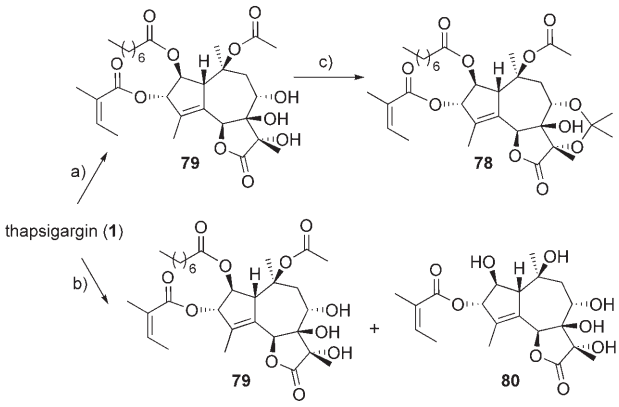
Degradation and selective transformations of thapsigargin: Some simple derivatives of thapsigargin have previously been obtained via degradation of the natural product.[1a] For example, the O-8/11 acetonide derivative (**78**) of thapsigargin has previously been reported, as has the selective removal of some of thapsigargin's esters. From the outset of this investigation, it was anticipated that further development of such transformations would allow access to **77**, and ultimately to compounds resembling our most advanced synthetic intermediates, such as **76** (Scheme 12). This would allow a conclusive assessment of the stereochemistry of our synthetic route by direct comparison with a natural product derivative, and may provide key advanced intermediates to test the viability of later steps on the new SEM route.



Scheme 12. Proposed degradation of thapsigargin.

Christensen showed that methanolysis of thapsigargin (**1**) in the presence of triethylamine could give O-8-debutanoyl thapsigargin (**79**),[8] and this was successfully converted to acetonide **78** (Scheme 13).[6] If the transesterification reaction was performed for prolonged reaction times at elevated temperature, the O-2 and O-10 esters were also removed, affording **80**.[59]

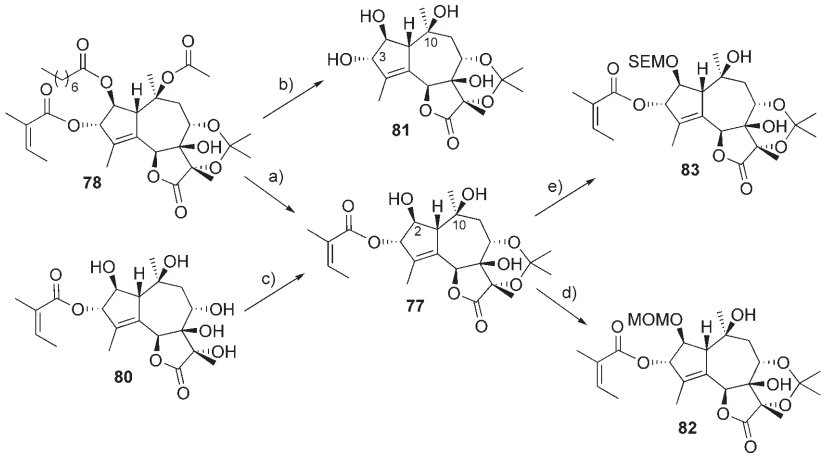
We used the latter conditions in an attempt to remove the O-2 and O-10 esters from **78**,[60] but when the acetonide was treated with triethylamine in methanol the reaction was sluggish at 75 °C; after 8 h, the temperature was increased to 95 °C but only 11 % of the desired triol **77** was isolated after a further 24 h at this temperature (Scheme 14). When **78** was treated with sodium methoxide it was found that the O-2 octanoyl and O-10 acetyl groups were cleaved, but unfortunately, the O-3 angelate ester was also transesterified under these conditions, affording the tetrol **81** in 81 % isolated yield.



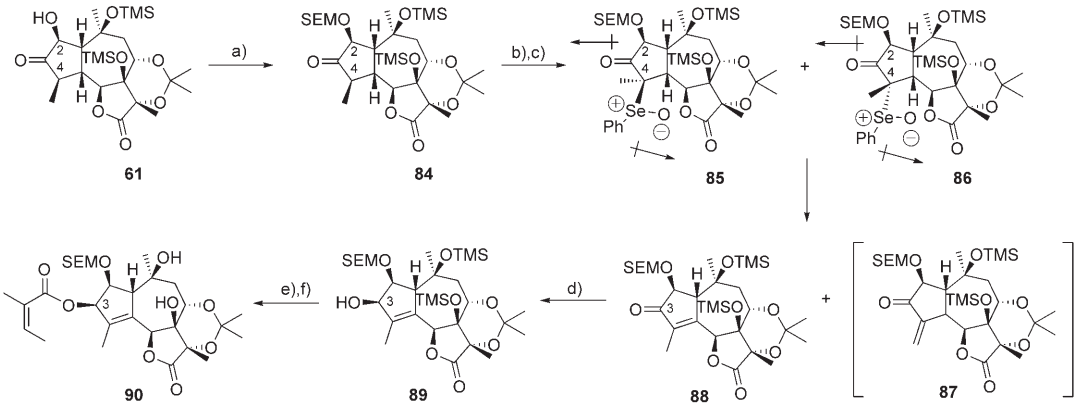
Scheme 13. Known transformations of thapsigargin. a) Et_3N, MeOH, RT, 7 h, 99 %;[8] b) Et_3N, MeOH, 75 °C 48 h, 47 % **79** + 48 % **80**;[59] c) 2,2-dimethoxypropane, Me_2CO, *p*TsOH, RT, 3 h (yield not reported).[6]

Pleasingly, it was found that the desired acetonide **77** could be formed from **80** by treatment of the pentol with 2,2-dimethoxypropane under acidic conditions, and that the acetonide could readily be selectively mono-alkylated with MOMCl[43] or SEMCl[58] affording **82** or **83**, respectively. At this stage, the direct comparison of **82** and **75** was possible, and this provided the first indication that we had not achieved the desired C-3 stereochemistry during the reduction of enone **73**.[61]

Enone formation part III—O-2 SEM Strategy: As anticipated, the SEM route proceeded similarly to the analogous O-2 MOM route, but an improved one-pot selenation procedure was developed, avoiding the need to isolate the unstable in-



Scheme 14. Selective transformation of thapsigargin derivatives. a) Et_3N, MeOH, 75 °C, 8 h, then 95 °C, 24 h, 11 %; b) NaOMe, MeOH, RT, 6 h, 81 %; c) *p*TsOH, Me_2CO, 2,2-dimethoxypropane, RT, 20 min, 67 %; d) MOMCl, Hünig's base, DMAP, CH_2Cl_2, RT, 90 min, 27 %; e) SEMCl, Hünig's base, DMAP, CH_2Cl_2, RT, 48 h, 71 % (SEM = 2-(trimethylsilyl)ethoxymethyl).

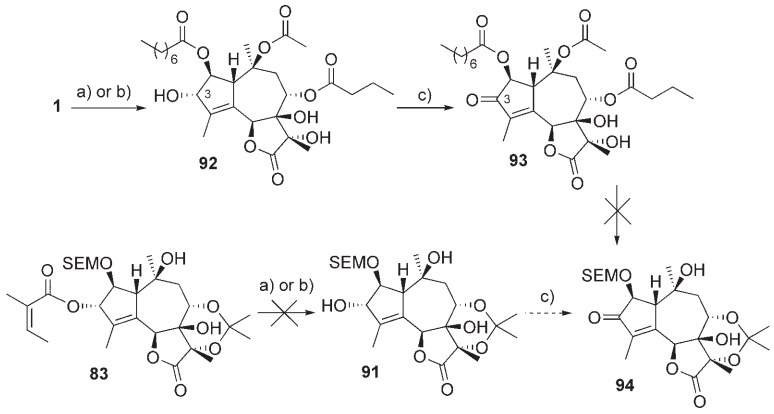


Scheme 15. Enone formation, part III. a) SEMCl, Hünig's base, CH_2Cl_2, RT, 18 h, 92%; b) LiHMDS, THF, −78 to −15°C, 2 h, then PhSeCl in THF, −90°C, 30 min; c) O_3 then diisopropylamine, −78°C, 60% over two steps; d) $NaBH_4$, MeOH, RT, 20 h, dr >95:5; e) TBAF, 0°C to RT, 2 h; f) 2,4,6-trichlorobenzoyl chloride, Et_3N, PhMe, angelic acid, 75°C, 2 d, 50% over three steps (Note: the angeloylation reaction was later found to work more efficiently by pre-forming and isolating the mixed anhydride, see below).

termediate silyl enol ether (Scheme 15). The new procedure still generated a mixture of C-4 selenides, and as before, the ratio of enone products (**88**/**87** 80:20) was the same as the ratio of these epimeric selenides.

Clearly, selenoxide **86** can only perform a *syn* elimination with a proton from the methyl group leading to the exocyclic enone **87**. One possible explanation for the observed reluctance of selenoxide **85** to eliminate with a proton from the C-4 methyl group may be derived from the predicted major conformation of this molecule. It may reasonably be assumed that the preferred conformation of the selenoxide is one in which the dipole of the Se–O bond opposes that of the neighbouring carbonyl group (i.e., **85** as drawn in Scheme 15).[62] This intrinsically places the proton at C-5 within close proximity to the selenoxide oxygen, favouring elimination from this site. Of course, this picture is somewhat simplified, as it does not take into account the configuration of the selenium atom, which can potentially exist as two stereoisomeric forms with different conformational preferences.

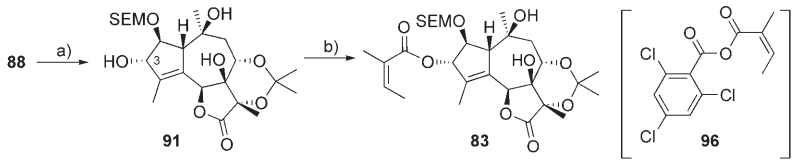
As with the analogous O-2 MOM derivative (**73**, Scheme 11), enone **88** was found to react with sodium borohydride with good facial selectivity, but the C-3 stereochemistry could not be determined at this stage. After removal of the trimethylsilyl groups and angeloylation under Yamaguchi conditions,[55,56] comparison of product **90** with degradation product **83** was possible. The NMR spectra of **90** from the synthetic route did not match those of **83** from the degradative route, and it was thought that the molecules differed only by their relative configuration at C-3. In order to show this was the difference and link the two routes together, we attempted to generate enone **94** from our natural source of thapsigargin (Scheme 16). If we could remove the angelate ester from **83** and oxidise the resulting secondary alcohol **91**, the product enone should match with the synthetic enone (**88** after removal of its TMS groups).



Scheme 16. Selective removal of angelate esters. a) 1) $KMnO_4$, $BnEt_3NCl$, PhMe, H_2O, 7 h, RT; 2) MeOH, pyridine, H_2O, reflux, 7 h, 46% for **1** to **92**; b) 1) O_3, CH_2Cl_2 −78°C for 2 min then PS-triphenylphosphine, RT, 18 h, 2) MeOH, pyridine, H_2O, reflux 2 h 15 min, 53% for **1** to **92**; c) Dess–Martin periodinane, pyridine, CH_2Cl_2, RT, 2 h, 77% for **92** to **93**.

Towards enone 94 from thapsigargin—Selective angelate cleavage: It has been shown that the angelate ester of thapsigargin can be selectively removed by first oxidising with potassium permanganate to the corresponding pyruvate, and then hydrolysing the crude product with aqueous pyridine,[59] but application of these conditions to degradation product **83** resulted in decomposition (Scheme 16). Whilst investigating milder procedures for the removal of angelate esters,

thapsigargin was treated for a limited time with ozone. It was found that selective ozonolysis of the angelate in the presence of the C-4 olefin was possible, as proved by hydrolysis of the product to afford known alcohol **92**. However, when this two-step ozonolysis procedure was performed on angelate **83**, decomposition was again observed and none of the desired C-3 alcohol **91** could be isolated.

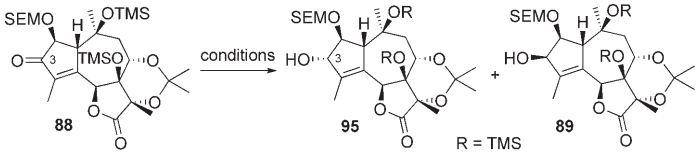


Scheme 17. Formation of angelate **83** via the synthetic route. a) $Zn(BH_4)_2$, THF, −30 °C to RT, then TBAF (EDTA work-up), 80 %; b) **96**, PhMe, $NaHCO_3$, 80 °C, 2 d, 52 %.

It was anticipated that an alternative route to **94** may be achieved from thapsigargin by changing the order of steps. First, oxidising **92** to the corresponding ketone **93**, then removing the remaining esters and introducing the O-8/11 acetonide and O-2 SEM groups. Oxidation of **92** to enone **93** was possible with Dess–Martin periodinane (Scheme 16).[45] However, attempts to remove the esters from **93** by treatment with sodium methoxide in methanol or triethylamine in methanol, caused decomposition and the formation of multiple products in each case.

Stereoselective enone reduction: Further studies on the synthetic route revealed that the observed facial selectivity of the reduction of **88** with sodium borohydride could be overturned by performing the reaction with freshly prepared zinc borohydride (Table 3).[63,64]

Table 3. Reduction of enone **88**.



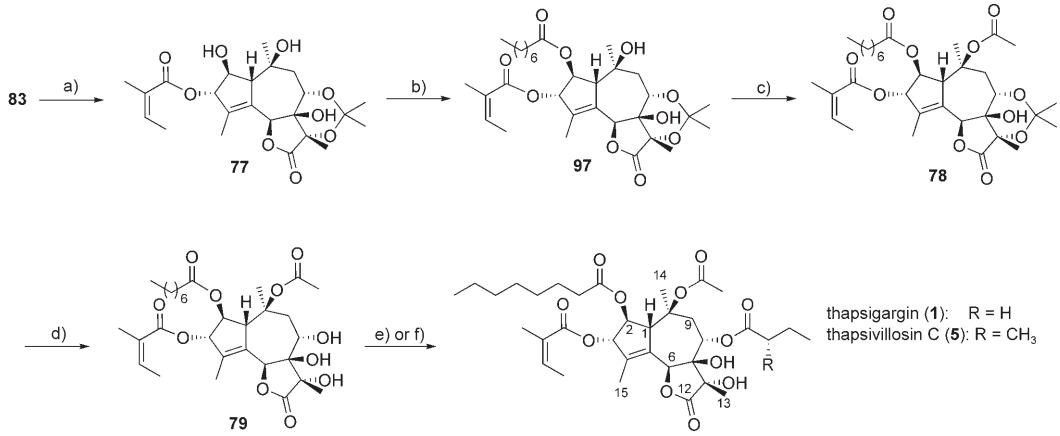
Reaction conditions	dr (**95**/**89**), comments
$NaBH_4$, THF, RT	<5:95
$NaBH_4$, MeOH, RT	<5:95
$CeCl_3{\cdot}7H_2O$, MeOH, RT then $NaBH_4$, −78 °C	<5:95
$LiBH_4$, THF, −30 °C	<5:95
L-Selectride, THF, Et_2O	<5:95
$Zn(BH_4)_2$, Et_2O, −20 °C (aq. NH_4Cl work-up)	62:38, decomposition on work-up
$Zn(BH_4)_2$, Et_2O, −20 °C (aq. $NaHCO_3$ work-up)	62:38, decomposition on work-up
PS-$Zn(BH_4)_2$, Et_2O, −20 °C → RT overnight	62:38, decomposition on work-up
$Zn(BH_4)_2$, THF, −30 °C → RT, then TBAF (EDTA work-up)	88:12, 90 % isolated yield (R = H)

Decomposition of **95** frequently occurred during the work-up of reactions with zinc borohydride, and its isolation proved troublesome. After extensive investigation it was found that the addition of TBAF at the end of a reaction, and the use of a tetrasodium EDTA work-up procedure, allowed **91** to be isolated cleanly in 80 % yield from **88** (Scheme 17). For previous substrates, our favoured angeloylation conditions had been to pre-mix angelic acid and 2,4,6-trichlorobenzoyl chloride with triethylamine in toluene to make the corresponding mixed anhydride **96** in situ and then treat the resulting mixture with a solution of the alcohol to be acylated.[56] However, when these conditions were applied to **91**, they resulted in the partial loss of SEM and bis-angeloylation at O-2/3.[65] By pre-forming and isolating anhydride **96**, and using a pure sample of this to treat the alcohol under mildly basic conditions, the desired angelate ester **83** could be isolated in 52 % yield.[66]

Compiling the results from all of the C-3 ketone reductions, we can make some generalisations. It appears that for the trilobolide precursor **62**, which bears no C-2 substituent, the most significant stereocontrolling factor during the ketone reduction, is the C-1 ring junction—sodium borohydride approaches the ketone predominantly from the least hindered (*exo*) face to afford the desired alcohol (**63**, Scheme 8) as the major product. However, for ketones **73** and **88**, sodium borohydride approaches predominantly from the *endo* face, as the bulky C-2 substituent now blocks the *exo* line of approach. However, by using a chelating metal in the source of the hydride, as with zinc borohydride, the oxygen rich C-2 protecting group can be used to deliver hydride from the desired (*exo*) face.[63]

Total synthesis of thapsigargin and thapsivillosin C: Fully aware of the facile isomerisation that angelate esters undergo to their tiglate counterparts,[67] we were gratified to find that treatment of **83** with *n*-butane thiol and $MgBr_2{\cdot}Et_2O$[68] effected clean removal of the O-2 SEM group with no observed substrate decomposition or angelate scrambling (Scheme 18). Selective acylation of the secondary C-2 alcohol **77** was possible with octanoic anhydride, affording **97**. However, it is important to note that esterification at this point should be possible with a range of acylating agents, allowing installation of any of the other C-2 ester moieties found in the thapsigargins (Table 1), or indeed a number of other functionalities that may be desirable for the generation of unnatural analogues.

It has been shown that acetylation at O-7 is relatively slow.[1a] Indeed, it was possible to acetylate **97** selectively at O-10 with neat isopropenyl acetate and a catalytic amount of *para*-toluenesulfonic acid, affording **78** in quantitative isolated yield. Solvolysis of **78** with acidic methanol at 45 °C generated the free C-8 hydroxyl derivative **79** in 83 % yield. Esterification of **79** with butyric anhydride or (*S*)-2-methylbutyric anhydride afforded thapsigargin (**1**) in 91 % isolated



Scheme 18. Total synthesis of thapsigargin and thapsivillosin C. a) *n*BuSH, $MgBr_2{\cdot}Et_2O$, K_2CO_3, Et_2O, 30 min, RT, 84%; b) octanoic anhydride, DMAP, CH_2Cl_2, RT, 1 h, 86%; c) isopropenyl acetate, *p*TsOH, RT, 2 h, quantitative; d) HCl, MeOH, 45°C, 45 min, 83%; e) butyric anhydride, DMAP, CH_2Cl_2, RT, 1 h, 91%; f) (*S*)-2-methylbutyric anhydride, DMAP, CH_2Cl_2, RT, 3 h 30 min, 92%.

yield or thapsivillosin C (**5**) in 92% isolated yield, respectively. By performing the esterification at O-8 as the last step, we have the ability to access the natural products bearing different acyl groups at this position, as well as unnatural analogues (including prodrug **18**), simply by using different acylating agents.

Until now, the stereochemistry of the methylbutanoyl side chain of thapsivillosin C was thought to be (*S*) (as was shown to be the case for trilobolide), but this had not been proven.[4] Comparison of our synthetic sample of thapsivillosin C with an authentic sample of the natural product has confirmed the (*S*)-configuration of the methylbutanoyl side chain.[69]

Conclusion

We have developed an efficient substrate-controlled synthetic route which may facilitate access to all 17 of the thapsigargins, as well as unnatural analogues. To illustrate this tenet, we have successfully completed the first total syntheses of five of the natural products: thapsigargin (**1**), trilobolide (**2**), nortrilobolide (**3**), thapsivillosin F (**4**) and thapsivillosin C (**5**). Thapsigargin, an important and prolific biological tool, and a promising lead in the development of a treatment for prostate cancer, was prepared in 42 synthetic steps in 0.61% overall yield (88.6% average yield per step). We have also delineated the first absolute stereochemical assignment of thapsivillosin C.

Experimental Section

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 diethyl ether over calcium hydride and lithium aluminium hydride; dichloromethane, toluene, methanol and acetonitrile over calcium hydride. Petroleum ether (PE) refers to the fraction of petroleum ether that was 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 operating at 400 MHz; Bruker Avance 500 with dual cryoprobe, operating at 500 MHz; Bruker DRX-600, operating at 600 MHz; or Bruker DRX-700, operating at 700 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 Bruker DPX-400 operating at 100 MHz; Bruker Avance 500 with dual cryoprobe operating at 125 MHz; Bruker DRX-600 operating at 150 MHz; or Bruker DRX-700, operating at 175 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 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} 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 and signals are quoted in cm^{-1}. Melting points are uncorrected and were measured with Reichert hot-stage apparatus using BDH microscopic slides.

Experimental procedures towards guaianolide 61

Epoxide 26: Hydrogen peroxide solution (97.0 mL, 1.00 mol, 35% v/v in H_2O) was steadily added to a solution of (*S*)-carvone (**25**) (50.0 g, 333 mmol) in methanol (400 mL) at 0°C over a period of 10 min. Aqueous sodium hydroxide solution (83.0 mL, 166 mmol, 2.0 M) was then added over a period of 30 min, such that the reaction temperature did not exceed 30°C. The mixture was cooled to 0°C, stirred for 30 min, then warmed to RT and stirred for 3 h. The reaction was diluted with water (400 mL) and quenched by the gradual addition of sodium sulfite (126 g, 1.00 mol) over 3 h, maintaining the internal temperature below 35°C.

The mixture was extracted with CH_2Cl_2 (3×300 mL) and the combined organics washed with brine (400 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude oil was used without further purification. $[\alpha]_D = -79.0$ ($c = 1.00$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.72 (s, 1H), 4.66 (s, 1H), 3.38 (d, J=2.0 Hz, 1H), 2.64 (m, 1H), 2.50 (m, 1H), 2.30 (m, 1H), 1.96 (ddd, J=13.4, 11.6, 2.6 Hz, 1H), 1.85 (ddd, J= 14.8, 12.1, 1.0 Hz, 1H), 1.63 (s, 3H), 1.34 (d, J=3.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.2, 146.2, 110.3, 61.2, 58.6, 41.6, 34.9, 28.5, 20.4, 15.1; IR (film): ν_{max} = 2977 (C-H), 2935 (C-H), 2851 (C-H), 1709 (C=O), 1649 cm^{-1} (w C=C); ESI+ MS: m/z: calcd for $C_{10}H_{15}O_2$: 167.1072; found: 167.1069 $[M+H]^+$.

Chlorohydrin 27: Epoxide **26** was split into two approximately equal batches and treated in parallel for ease of handling. TFA (34.4 mL, 447 mmol) was added dropwise to a mixture of epoxide **26** (24.8 g, 149 mmol) and LiCl (66.0 g, 1.55 mol) in THF (1.00 L) at 0°C over 15 min. The mixture was stirred at 0°C for 90 min and quenched by the gradual addition of aqueous $NaHCO_3$ solution (500 mL, 450 mmol) at 0°C over a period of 1 h. The mixture was stirred at RT overnight and extracted with Et_2O (3×200 mL). The combined extracts were washed with brine (2×150 mL), dried over $MgSO_4$ and concentrated in vacuo, leaving a cloudy oil. The two batches were combined, poured into water (600 mL) and extracted with Et_2O (3×300 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude yellow oil (66.1 g, 98% over two steps) was analytically pure and used without further purification. $[\alpha]_D = -47.3$ ($c = 1.00$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.79 (m, 2H), 4.24 (dd, J=3.2, 2.8 Hz, 1H), 3.02 (dd, J=13.7, 13.0 Hz, 1H), 2.82 (m, 1H), 2.42 (m, 2H), 2.06 (br s, 1H), 1.88 (m, 1H), 1.77 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.5, 146.5, 110.6, 77.0, 68.0, 41.1, 39.0, 32.9, 22.1, 20.3; IR (film): ν_{max} = 3447 (br OH), 2938 (C-H), 2688 (C-H), 1721 (C=O), 1646 cm^{-1} (w C=C); ESI+ MS: m/z: calcd for $C_{10}H_{15}O_2ClNa$: 225.0658; found: 225.0650 $[M+Na]^+$.

THP acetals 28: PPTS (532 mg, 211 mmol) was added at RT to a stirred solution of chlorohydrin **27** (42.8 g, 211 mmol) and dihydropyran (67.8 mL, 744 mmol) in CH_2Cl_2 (250 mL). After 17 h, the reaction was quenched by adding half saturated $NaHCO_3$ solution (600 mL). The reaction mixture was extracted with Et_2O (3×300 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (Et_2O/PE 5:95) to give THP ethers **28** (50.9 g, 84%; 1:1 mixture of epimers at the acetal carbon) as a colourless oil. $[\alpha]_D = -88.0$ ($c = 1.00$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.80 (m, 4H), 4.71 (m, 2H), 4.24 (m, 1H), 4.11 (m, 1H), 3.80 (m, 2H), 3.53 (m, 2H), 3.00 (m, 2H), 2.86 (m, 1H), 2.60 (m, 1H), 2.38 (m, 4H), 2.04 (m, 2H), 1.8–1.5 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.2, 146.9, 110.4, 101.7, 83.9, 67.8, 62.5, 41.1, 39.6, 32.1, 30.6, 27.6, 25.3, 22.7, 20.4, 19.1; IR (film): ν_{max} = 2941 (C-H), 2871 (C-H), 1726 (C=O), 1646 cm^{-1} (w C=C); ESI+ MS: m/z: calcd for $C_{15}H_{23}O_3ClNa$: 309.1233; found: 309.1229 $[M+Na]^+$.

Methyl esters 30: Freshly prepared sodium methoxide solution (250 mL, 250 mmol, 1.0 M in methanol) was added dropwise at 0°C via cannula to a solution of chloroketones **28** (48.1 g, 168 mmol) in Et_2O (700 mL). The mixture was stirred at 0°C for 1 h, quenched with saturated ammonium chloride solution (300 mL) and diluted with water (100 mL). The mixture was stirred at RT for 1 h and extracted with Et_2O (3×400 mL). The combined organics were washed with brine (300 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude oil was obtained as a 1:1 mixture of epimers at the acetal carbon, and was used without further purification. $[\alpha]_D = +14.0$ ($c = 1.00$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.80 (m, 2H), 4.7–4.6 (m, 4H), 4.24 (m, 1H), 4.13 (m, 1H), 3.88 (m, 2H), 3.60 (s, 6H), 3.30 (m, 2H), 3.20 (ddd, J=9.3, 9.3, 9.2 Hz, 1H), 3.04 (ddd, J= 10.2, 9.5, 7.1 Hz, 1H), 2.83 (m, 2H), 2.56 (m, 2H), 2.02 (dd, J=8.9, 3.0 Hz, 2H), 1.90 (m, 2H), 1.74 (s, 6H), 1.70–1.50 (m, 12H), 1.13 (d, J= 7.0 Hz, 3H), 1.01 (d, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1, 145.4, 111.3, 100.5, 81.8, 62.9, 53.6, 51.2, 46.8, 42.3, 38.2, 31.1, 25.6, 22.5, 19.9, 14.1; IR (film): ν_{max} = 2957 (C-H), 2929 (C-H), 2851 (C-H), 1727 (C=O), 1646 cm^{-1} (w C=C); ESI+ MS: m/z: calcd for $C_{16}H_{27}O_4$: 283.1909; found: 283.1901 $[M+H]^+$.

Alcohol 31: PPTS (1.00 g, 3.98 mmol) was added to a solution of acetals **30** (45.2 g, 160 mmol) in methanol (600 mL) and the resulting mixture stirred at 50°C for 15 h. The mixture was concentrated to ca. 50 mL under reduced pressure, quenched with saturated $NaHCO_3$ solution (200 mL) and further diluted with water (100 mL). The mixture was then extracted with Et_2O (3×400 mL) and the combined organic phases washed with brine (200 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude oil showed traces of pyridine in its ^1H NMR spectrum but was used without further purification. $[\alpha]_D = +4.20$ (c = 1.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.80 (apparent t, J= 1.5 Hz, 1H), 4.71 (s, 1H), 4.27 (dd, J=4.3, 4.3 Hz, 1H), 3.61 (s, 3H), 3.25 (ddd, J=10.2, 7.0, 6.5 Hz, 1H), 2.84 (dd, J=10.2, 8.8 Hz, 1H), 2.50 (m, 1H), 2.06 (ddd, J=13.5, 10.8, 4.3 Hz, 1H), 1.85 (ddd, J=13.5, 7.0, 1.0 Hz, 1H), 1.74 (s, 3H), 1.08 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9, 145.3, 111.5, 75.1, 53.2, 51.3, 46.7, 42.5, 39.4, 22.5, 13.6; IR (film): ν_{max} = 3490 (br OH), 2958 (C-H), 2924 (C-H), 2878 (C-H), 1731 (C=O), 1647 cm^{-1} (w C=C); ESI+ MS: m/z: calcd for $C_{11}H_{19}O_3$: 199.1334; found: 199.1328 $[M+H]^+$.

TBDPS-ether 32: Imidazole (11.1 g, 163 mmol), TBDPSCl (42.5 mL, 163 mmol) and DMAP (1.95 g, 16.0 mmol) were added to a solution of impure alcohol **31** (33.1 g) in DMF (110 mL) and stirred at RT overnight. The mixture was then poured into aqueous LiCl solution (450 mL, 10% w/w) and extracted with Et_2O (3×500 mL). The combined extracts were washed with brine (400 mL), dried ($MgSO_4$), concentrated in vacuo and purified by column chromatography (silica gel, neat PE gradually increasing to 5% Et_2O in PE) to afford the silyl ether as a colourless oil (61.2 g, 84% over three steps from chloroketone **28**). $[\alpha]_D = +29.6$ (c = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 4H), 7.42–7.38 (m, 6H), 4.72 (s, 1H), 4.61 (s, 1H), 4.32 (m, 1H), 3.59 (s, 3H), 3.27 (m, 1H), 2.95 (dd, J=10.1, 9.6 Hz, 1H), 2.36 (m, 1H), 1.68 (ddd, J=13.5, 10.4, 3.9 Hz, 1H), 1.67 (s, 3H), 1.64 (m, 1H), 1.09 (s, 9H), 1.02 (d, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9, 145.5, 136.0, 135.9, 134.7, 134.0, 129.6, 127.5, 111.5, 76.8, 53.7, 51.2, 46.4, 43.4, 39.6, 27.1, 22.3, 19.5, 14.5; IR (film): ν_{max} = 2929 (C-H), 2856 (C-H), 1730 (C=O), 1646 cm^{-1} (w C=C); ESI+ MS: m/z: calcd for $C_{27}H_{37}O_3Si$: 437.2512; found: 437.2506 $[M+H]^+$.

Alcohol 33: $LiAlH_4$ (121 mL, 121 mmol, 1.0 M in THF) was added over 20 min at 0°C to a stirred solution of methyl ester **32** (52.7 g, 121 mmol) in anhydrous THF (250 mL). The reaction was kept at 0°C for 1 h, then allowed to come to RT and stirred for another hour. After that time, the reaction was quenched by slowly adding a saturated solution of Rochelle's salt (70 mL), followed by water (200 mL). After stirring for 15 h, the reaction mixture was extracted with Et_2O (3×400 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was filtered through a short plug of silica gel, eluting with Et_2O to give alcohol **33** (48.8 g, 99%) as a clear, colourless oil. $[\alpha]_D = +15.5$ (c = 1.22, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 4H), 7.42–7.38 (m, 6H), 4.84 (s, 1H), 4.72 (s, 1H), 4.30 (m, 1H), 3.51 (m, 2H), 3.12 (m, 1H), 2.10 (m, 1H), 1.89 (m, 1H), 1.82 (m, 2H), 1.63 (s, 3H), 1.09 (s, 9H), 1.03 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.6, 136.0, 135.9, 134.7, 134.4, 129.9, 127.4, 110.8, 76.4, 53.7, 48.9, 44.8, 42.3, 39.0, 27.1, 22.8, 19.5, 14.9; IR (film): ν_{max} = 3402 (br OH), 2962 (C-H), 2931 (C-H), 1646 cm^{-1} (w C=C); ESI+ MS: m/z: calcd for $C_{26}H_{40}NO_2Si$: 426.2823; found: 426.2826 $[M+NH_4]^+$.

PMB-ether 34: NaH (2.2 g, 54.2 mmol, 60% dispersion in mineral oil) was added at 0°C in two portions over 2 min to a solution of alcohol **33** (17.7 g, 43.1 mmol) in DMF (100 mL). After stirring for 1 h at RT, a solution of *para*-methoxybenzyl chloride (6.8 mL, 50.0 mmol) in DMF (10 mL) was added. Stirring was continued for 15 h, the reaction mixture quenched with water (50 mL) and diluted with Et_2O. The aqueous layer was extracted with Et_2O (3×100 mL), the combined organic layers were dried with $MgSO_4$ and the solvent removed under reduced pressure. The product was purified by flash chromatography (PE/Et_2O 35:1) to yield **34** (18.8 g, 82%) as a colourless oil. $[\alpha]_D = +7.48$ (c = 1.08, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 4H), 7.42–7.38 (m, 6H), 7.21 (d, J=6.7 Hz, 2H), 6.84 (d, J=6.7 Hz, 2H), 4.74 (apparent t, J=1.4 Hz, 1H), 4.53 (s, 1H), 4.36 (d, J=11.4 Hz, 1H), 4.30 (d, J=11.4 Hz, 1H),

4.28 (m, 1H), 3.80 (s, 3H), 3.29 (dd, J=9.3, 6.5 Hz, 1H), 3.15 (dd, J=9.3, 7.0 Hz, 1H), 3.07 (dd, J=9.0, 8.9 Hz, 1H), 2.18 (dddd, J=9.0, 7.0, 6.8, 6.5 Hz, 1H), 1.84 (m, 1H), 1.73 (s, 3H), 1.62 (dd, J=8.9, 3.3 Hz, 2H), 1.08 (s, 9H), 1.07 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 146.1, 136.0, 136.0, 135.0, 134.5, 130.9, 129.5, 129.0, 127.5, 127.4, 113.7, 110.1, 76.2, 72.7, 71.6, 55.3, 46.3, 44.8, 43.5, 39.1, 27.1, 23.9, 19.5, 15.4; IR (film): ν_{max} = 2932 (C-H), 2857 (C-H), 1612 (w C=C), 1590 cm^{-1} (Ar); ESI+ MS: m/z: calcd for $C_{34}H_{48}NO_3Si$: 546.3404; found: 546.3400 $[M+NH_4]^+$.

Ketone 35: OsO_4 (2.5% solution in *t*BuOH, 25.8 mL, 2.54 mmol) was added to a stirred solution of PMB-ether **34** (67.1 g, 127 mmol) and *N*-methylmorpholine *N*-oxide (17.9 g, 152 mmol) in acetone/H_2O (420 mL, 3:1). After OsO_4 addition the reaction became immediately dark brown. The reaction mixture was stirred for 2 h at RT. After that time, the homogeneous orange mixture was cooled to 0°C and $NaIO_4$ (81.5 g, 380 mmol) was added in two portions. After stirring vigorously for 30 min, the reaction was allowed to warm up to RT. To maintain effective stirring, acetone (150 mL) and water (150 mL) were added. After stirring overnight, the reaction was quenched by adding a saturated NaS_2O_3 solution (100 mL) and water (100 mL). The suspension was filtered through a Buchner funnel and extracted with Et_2O (3×350 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by filitration through a pad of silica gel (PE/Et_2O 3:1) to give ketone **35** (61.7 g, 92%) as a pale yellow oil. $[\alpha]_D$ = +51.1 (c = 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 4H), 7.42–7.38 (m, 6H), 7.21 (d, J=6.7 Hz, 2H), 6.87 (d, J=6.7 Hz, 2H), 4.29 (m, 3H), 3.80 (s, 3H), 3.42 (m, 2H), 3.21 (dd, J=9.5, 9.4 Hz, 1H), 2.46 (dddd, J=9.7, 9.6, 9.4, 4.2 Hz, 1H), 2.12 (s, 3H), 1.75 (ddd, J=13.5, 9.3, 4.2 Hz, 1H), 1.67 (m, 1H), 1.61 (ddd, J=13.5, 7.8, 1.5 Hz, 1H), 1.07 (s, 9H), 0.98 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.1, 160.1, 135.9, 135.8, 134.8, 134.0, 130.2, 129.5, 129.5, 127.5, 113.7, 76.7, 72.9, 70.3, 55.2, 49.7, 47.5, 42.7, 37.9, 32.5, 27.1, 19.5, 14.1; IR (film): ν_{max} = 2932 (C-H), 2857 (C-H), 1705 (C=O), 1612 (Ar), 1513 cm^{-1} (Ar); ESI+ MS: m/z: calcd for $C_{33}H_{42}O_4SiNa$: 553.2750; found: 553.2758 $[M+Na]^+$.

Homoallylic alcohols 36s and 36r: A solution of ketone **35** (36.3 g, 68.4 mmol) in THF (150 mL) was treated with $MgBr_2{\cdot}Et_2O$ (35.3 g, 137 mmol) for 1 h at RT, then diluted with 1,2-dimethoxyethane (1.0 L) and cooled to −78°C. Allylmagnesiumbromide solution (103 mL, 103 mmol, 1.0 M in Et_2O) was added dropwise over 40 min and the reaction stirred for a further 2 h at −78°C. The reaction was then warmed to RT and quenched by stirring with saturated ammonium chloride solution (1.0 L) overnight. The crude mixture was further diluted with water (200 mL) to aid solubility, and extracted with Et_2O (3×500 mL). The combined extracts were washed with brine (500 mL), dried over $MgSO_4$ and evaporated under reduced pressure to afford the crude homoallylic alcohols as an 8:1 (*S*/*R*) mixture of C-10 epimers, used without further purification. *Major diastereomer* (**36s**): $[\alpha]_D$ = +25.7 (c = 1.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 4H), 7.42–7.38 (m, 6H), 7.16 (d, J=6.8 Hz, 2H), 6.83 (d, J=6.8 Hz, 2H), 5.79 (dddd, J=16.9, 10.2, 6.8, 6.7 Hz, 1H), 5.01 (d, J=10.2 Hz, 1H), 4.81 (d, J=16.9 Hz, 1H), 4.42 (d, J=11.3 Hz, 1H), 4.35 (d, J=11.3 Hz, 1H), 4.29 (ddd, J=5.2, 5.2, 1.6 Hz, 1H), 3.79 (s, 3H), 3.55 (dd, J=10.1, 3.7 Hz, 1H), 3.48 (dd, J=10.1, 6.8 Hz, 1H), 2.45 (ddd, J=8.6, 7.9, 3.8 Hz, 1H), 2.08 (m, 3H), 1.81 (m, 1H), 1.70 (ddd, J=11.9, 8.0, 7.9 Hz, 1H), 1.58 (ddd, J=13.1, 7.5, 1.6 Hz, 1H), 1.21 (s, 3H), 1.07 (s, 9H), 0.98 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 135.9, 135.0, 134.8, 134.4, 129.5, 129.5, 129.4, 129.2, 127.5, 117.2, 113.9, 74.9, 73.0, 72.6, 70.6, 55.2, 47.2, 46.3, 46.3, 42.9, 35.3, 27.1, 26.9, 19.4, 14.9; IR (film): ν_{max} = 3422 (br OH), 2930 (C-H), 2857 (C-H), 1621 (w Ar), 1514 cm^{-1} (w Ar); ESI+ MS: m/z: calcd for $C_{36}H_{52}O_4N$: 590.3666; found: 590.3663 $[M+NH_4]^+$.

MOM acetals 37s and 37r: A CH_2Cl_2 (300 mL) solution of the crude tertiary alcohols **36s** and **36r** (assume 71.4 mmol, crude from two batches) was treated with Hünig's base (124 mL, 714 mmol), MOMCl (36.3 mL, 478 mmol) and DMAP (867 mg, 7.14 mmol) at RT over a weekend. The resulting orange solution was quenched with half-saturated ammonium chloride solution (600 mL) and extracted with CH_2Cl_2 (3×500 mL). The combined organic extracts were washed with brine (500 mL), dried over $MgSO_4$ and concentrated in vacuo. The orange oil was purified by column chromatography (silica gel, PE/Et_2O 19:1) to afford as pale yellow oil, an 8:1 (*S*/*R*) mixture of the C-10 epimers (36.8 g, 84% over two steps). *Major diastereomer* (**37s**): $[\alpha]_D$ = −7.60 (c = 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 4H), 7.42–7.38 (m, 6H), 7.16 (d, J=6.7 Hz, 2H), 6.81 (d, J=6.7 Hz, 2H), 5.73 (dddd, J=17.6, 10.6, 7.6, 7.2 Hz, 1H), 5.12 (d, J=10.6 Hz, 1H), 4.99 (d, J=17.6 Hz, 1H), 4.63 (d, J=7.2 Hz, 1H), 4.54 (d, J=7.2 Hz, 1H), 4.37 (m, 1H, and d, J=11.8 Hz, 2H), 4.30 (d, J=11.8 Hz, 1H), 3.79 (s, 3H), 3.65 (dd, J=10.0, 4.8 Hz, 1H), 3.23 (s, 3H), 3.10 (dd, J=10.0, 10.0 Hz, 1H), 2.45 (ddd, J=11.2, 8.0, 7.9 Hz, 1H), 2.33 (dd, J=13.8, 7.2 Hz, 1H), 2.24 (m, 1H), 2.15 (dd, J=13.8, 7.6 Hz, 1H), 2.04 (m, 1H), 1.79 (ddd, J=13.1, 11.4, 7.2 Hz, 1H), 1.58 (m, 1H), 1.22 (s, 3H), 1.09 (s, 9H), 1.08 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 135.9, 134.9, 134.5, 131.0, 129.4, 128.9, 127.5, 127.4, 117.6, 113.7, 91.0, 78.8, 74.4, 72.5, 71.5, 55.5, 55.3, 47.0, 45.6, 44.4, 42.3, 33.9, 27.1, 21.6, 19.4, 15.6; IR (film): ν_{max} = 2931 (C-H), 2857 (C-H), 1621 (w C=C), 1513 cm^{-1} (w Ar); ESI+ MS: m/z: calcd for $C_{38}H_{56}O_5NSi$: 634.3928; found: 634.3923 $[M+NH_4]^+$.

Alcohols 38s and 38r:

Procedure A: A CH_2Cl_2 solution (300 mL) of the PMB-ethers **37s** and **37r** (36.5 g, 59.3 mmol) was treated with phosphate buffer solution (pH 7, 45 mL) and DDQ (27.5 g, 119 mmol). The solution immediately turned red and was stirred at RT for 30 min, then quenched by stirring with saturated $NaHCO_3$ solution (600 mL) for 30 min. The mixture was diluted with water (2.5 L) and extracted with CH_2Cl_2 (3×600 mL). The combined extracts were washed with brine (300 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was combined with a smaller batch and purified by repeated chromatography to separate C-10 epimers (silica gel, eluting with PE/EtOAc 8:1). The isomerically-pure primary alcohol (>24:1 *S*/*R* at C-10) was obtained as a colourless oil (23.6 g, 75%; based on theoretical maximum yield from the 8:1 mixture of isomeric PMB ethers).

Procedure B: A methanolic solution (10 mL) of the crude primary acetate **45** (combined from different batches, assume 12.0 mmol) was treated with sodium methoxide solution (50.0 mL, 25.0 mmol, 0.5 M in methanol) at RT for 16 h. The reaction was then quenched with saturated $NaHCO_3$ solution, diluted with water (100 mL) and extracted with Et_2O (3× 150 mL). The combined extracts were washed with brine (200 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude brown oil was purified by column chromatography (silica gel, Et_2O/PE 2:3) to afford **38s**, 6.22 g, 99% over three steps.

Compound 38s: $[\alpha]_D$ = +35.6 (c = 1.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 4H), 7.42–7.38 (m, 6H), 5.67 (dddd, J=16.9, 11.0, 7.5, 7.3 Hz, 1H), 5.01 (d, J=16.9 Hz, 1H), 4.99 (d, 1H, J=11.0 Hz, 1H), 4.79 (d, J=7.2 Hz, 1H), 4.70 (d, J=7.2 Hz, 1H), 4.41 (ddd, J=5.2, 5.2, 1.8 Hz, 1H), 3.81 (ddd, J=11.9, 4.5, 3.3 Hz, 1H), 3.62 (dd, J=4.5, 4.5 Hz, 1H), 3.45 (ddd, J=11.9, 5.0, 4.5 Hz, 1H), 3.34 (s, 3H), 2.52 (ddd, J=13.4, 7.5, 6.0 Hz, 1H), 2.41 (dd, J=13.5, 7.3 Hz, 1H), 2.20 (dd, J=13.5, 7.5 Hz, 1H), 2.06 (m, 1H), 1.85 (m, 1H), 1.66 (ddd, J=12.7, 12.7, 5.2 Hz, 1H), 1.53 (ddd, J=12.7, 7.1, 1.8 Hz, 1H), 1.38 (s, 3H), 1.09 (s, 9H), 1.02 (d, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.9, 134.9, 134.4, 133.8, 129.5, 127.4, 127.4, 117.4, 90.9, 80.3, 74.9, 63.1, 55.8, 48.6, 46.3, 44.1, 42.5, 36.0, 27.1, 22.5, 19.4, 15.1; IR (film): ν_{max} = 3465 (br OH), 2931 (C-H), 2889 (C-H), 1639 (w C=C), 1590 cm^{-1} (w Ar); ESI+ MS: m/z: calcd for $C_{30}H_{48}O_4NSi$: 514.3353; found: 514.3350 $[M+NH_4]^+$.

Compound 38r: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 4H), 7.42–7.38 (m, 6H), 5.80 (dddd, J=17.6, 10.1, 7.5, 7.3 Hz, 1H), 5.11 (d, J=17.6 Hz, 1H), 5.09 (d, J=10.1 Hz, 1H), 4.73 (s, 2H), 4.33 (m, 1H), 3.82 (m, 2H), 3.53 (m, 1H), 3.34 (s, 3H), 2.57 (m, 2H), 2.45 (dd, J=13.7, 7.3 Hz, 1H), 2.01 (m, 1H), 1.96 (m, 1H), 1.51 (m, 1H), 1.48 (m, 1H), 1.15 (s, 3H), 1.09 (s, 9H), 1.07 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.9, 135.8, 135.1, 134.3, 133.9, 129.5, 129.5, 127.4, 118.0, 91.2, 81.0, 75.1, 63.1, 55.9, 48.3, 45.9, 43.8, 42.6, 36.2, 27.1, 22.9, 19.5, 14.9; ESI+ MS: m/z: calcd for $C_{30}H_{48}O_4NSi$: 514.3353; found: 514.3351 $[M+NH_4]^+$.

Aldehyde 39: Pyridine (33.9 mL, 419 mmol) was added at RT before portionwise addition of Dess–Martin periodinane (28.4 g, 67.0 mmol) to a solution of alcohol **38s** (20.8 g, 41.9 mmol) in CH_2Cl_2 (200 mL). After stir-

ring for 1 h at RT, the reaction was quenched by the addition of saturated aqueous sodium thiosulfite solution (100 mL) and saturated aqueous $NaHCO_3$ solution (100 mL). The separated aqueous phase was extracted with ethyl acetate (3×80 mL), and the combined organics washed with saturated aqueous sodium thiosulfite solution (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound **39** which was used in the next step without further purification. $[\alpha]_D$ = +5.60 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.60 (d, J= 5.5 Hz, 1H), 7.67 (m, 4H), 7.42–7.38 (m, 6H), 5.62 (dddd, J=17.0, 10.0, 7.5, 7.2 Hz, 1H), 5.00 (m, 2H), 4.70 (d, J=7.3 Hz, 1H), 4.54 (d, J= 7.3 Hz, 1H), 4.43 (m, 1H), 3.28 (s, 3H), 2.78 (m, 1H), 2.53 (ddd, J=9.4, 6.0, 5.5 Hz, 1H), 2.38 (dd, J=13.5, 7.2 Hz, 1H), 2.26 (m, 1H), 2.13 (dd, J=13.5, 7.5 Hz, 1H), 1.83 (ddd, J=12.3, 12.3, 4.5 Hz, 1H), 1.70 (ddd, J= 12.3, 7.0, 1.4 Hz, 1H), 1.30 (s, 3H), 1.09 (s, 9H), 1.01 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.0, 135.9, 135.8, 134.4, 133.9, 133.7, 129.7, 129.6, 127.5, 127.4, 118.1, 90.8, 79.1, 76.1, 59.0, 55.6, 51.1, 44.0, 40.9, 35.9, 27.1, 22.4, 19.4, 14.3; IR (film): ν_{max} = 2932 (C-H), 2857 (C-H), 1710 (C=O), 1639 (w C=C), 1589 cm^{-1} (w Ar); ESI+ MS: m/z: calcd for $C_{30}H_{42}O_4SiNa$: 517.2750; found: 517.2753 $[M+Na]^+$.

Decomposition product 42: When aldehyde **39** was left at 0°C, it decomposed in less than one week. The crude oil was a complex mixture, from which the major component (the title compound) was separated by column chromatography of a small sample (silica gel, neat PE ramped gradually to 40% Et_2O/PE) to afford an analytically pure sample for characterisation purposes. $[\alpha]_D$ = −4.39 (c = 0.775, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 4H), 7.42 (m, 2H), 7.37 (m, 4H), 5.62 (dddd, J=17.3, 10.8, 7.2, 7.2 Hz, 1H), 5.01 (d, J=10.8 Hz, 1H), 4.97–4.94 (m, 2H), 4.86 (d, J=6.5 Hz, 1H), 4.54 (d, J=6.5 Hz, 1H), 4.25 (dd, J= 7.0, 3.7 Hz, 1H), 3.38 (s, 3H), 2.74 (m, 1H), 2.64 (dd, J=8.3, 7.6 Hz, 1H), 2.23 (dd, J=13.8, 7.2 Hz, 1H), 2.08 (dd, J=13.8, 7.2 Hz, 1H), 1.77 (m, 1H), 1.60–1.56 (ddd, J=13.3, 8.1, 2.9 Hz, 1H), 1.47–1.44 (ddd, J= 13.3, 9.1, 4.1 Hz, 1H), 1.31 (s, 3H), 1.09 (s, 9H), 1.06 (d, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.9, 135.8, 134.7, 134.3, 134.0, 129.58, 129.57, 127.53, 127.50, 117.5, 106.7, 93.1, 85.8, 78.2, 57.9, 55.5, 50.3, 44.9, 42.7, 35.3, 27.9, 27.0, 19.4, 14.6; IR (film): ν_{max} = 2930 (C-H), 2858 (C-H), 1641 (w C=C), 1589 cm^{-1} (w Ar); ESI+ MS: m/z: calcd for $C_{30}H_{42}O_4SiNa$: 517.2750; found: 517.2761 $[M+Na]^+$.

Hemiacetal 43: The crude acetal **42** (8.0 g, 16.2 mmol) was stirred in a mixture of acetic acid, THF and water (30:30:8, 68 mL) at 35°C for 4 d. The reaction was then cooled and added dropwise to $NaHCO_3$ solution (600 mL). The resulting mixture was extracted with Et_2O (3×200 mL), the combined extracts washed with brine (200 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography (silica gel, Et_2O/PE 1:4) afforded the diol as a colourless gum (4.56 g, 62%). $[\alpha]_D$ = +6.56 (c = 1.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 4H), 7.42 (m, 2H), 7.37 (m, 4H), 5.64 (dddd, J=17.1, 10.1, 7.3, 7.1 Hz, 1H), 5.12 (s, 1H), 5.02 (d, J=10.1 Hz, 1H), 4.99 (d, J=17.1 Hz, 1H), 4.21 (dd, J=7.2, 3.8 Hz, 1H), 2.75 (ddd, J=8.8, 8.7, 8.7 Hz, 1H), 2.58 (dd, J=7.7, 7.6 Hz, 1H), 2.46 (s, 1H), 2.18 (dd, J=13.8, 7.3 Hz, 1H), 2.03 (dd, J=13.8, 7.1 Hz, 1H), 1.75 (m, 1H), 1.58–1.54 (m, 4H), 1.45 (m, 1H), 1.09–1.08 (m, 12H) [no observed NOE interactions between H-1 and =C(H)CH_2 or C(OCO)CH_3 and H-6; NOE interactions were observed between H-1 and H-5 (3.5% enhancement), and H-1 and C(OCO)CH_3 (4% enhancement)]; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.9, 135.8, 134.2, 134.0, 129.6, 127.5, 127.5, 117.7, 104.8, 85.8, 78.0, 58.8, 50.9, 44.6, 42.8, 35.2, 28.8, 27.0, 19.4, 14.6; IR (film): ν_{max} = 3260–3505 (br OH), 2932 (C-H), 2858 (C-H), 1639 (w C=C), 1588 cm^{-1} (w Ar); ESI+ MS: calcd for $C_{28}H_{39}O_3Si$: 451.1002; found: 451.0999 $[M+H]^+$.

Lactone 41s: TPAP (3.2 mg, 9.2 μmol) was added to a mixture of NMO (32.3 mg, 276 μmol), lactol **43** (83 mg, 184 μmol) and 4 Å MS in CH_2Cl_2 (400 μL). The resulting black mixture was stirred at RT for 18 h then diluted with CH_2Cl_2 (20 mL) and washed with saturated Na_2SO_3 solution (20 mL). The separated aqueous phase was back-extracted with CH_2Cl_2 (20 mL) and the combined organic phases washed with brine (20 mL), $CuSO_4$ solution (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography (silica gel, Et_2O/PE 1:9) afforded the lactone (72 mg, 87%). $[\alpha]_D$ = +12.8 (c = 1.34, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (m, 4H), 7.44 (m, 2H), 7.38 (m, 4H), 5.56 (dddd, J=17.0, 10.2, 7.5, 7.0 Hz, 1H), 5.08 (d, J=10.2 Hz, 1H), 5.02 (d, J=17.0 Hz, 1H), 4.27 (dd, J=8.1, 4.1 Hz, 1H), 2.86 (m, 2H), 2.28 (m, 2H), 2.10 (dd, J=14.1, 7.5 Hz, 1H), 1.65 (ddd, J=13.4, 10.7, 0.8 Hz, 1H), 1.43 (ddd, J=13.4, 8.8, 4.3 Hz, 1H), 1.31 (s, 3H), 1.20 (d, J=7.0 Hz, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 135.8, 135.7, 134.3, 133.4, 132.2, 129.7, 127.6, 127.5, 119.1, 85.0, 76.6, 51.4, 47.2, 43.6, 41.2, 35.1, 27.0, 19.3, 15.1; IR (film): ν_{max} = 2963 (C-H), 2932 (C-H), 2858 (C-H), 1764 (C=O), 1642 (w C=C), 1588 cm^{-1} (w Ar); ESI+ MS: m/z: calcd for $C_{28}H_{37}O_3$: 449.2512; found: 449.2513 $[M+H]^+$.

Diol 40s: $NaBH_4$ (1.26 g, 33.0 mmol) was added portionwise to a stirring solution of lactol **43** (4.97 g, 11.0 mmol) in methanol (70 mL). After stirring at RT for 18 h, the mixture was added dropwise to ammonium chloride solution (200 mL) and extracted with Et_2O (3×200 mL). The combined organics were washed with brine (200 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography (silica gel, Et_2O/PE 3:7) afforded the diol as a colourless gum (3.70 g, 75%). $[\alpha]_D$ = +36.1 (c = 0.71, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (m, 4H), 7.42 (m, 2H), 7.37 (m, 4H), 5.79 (dddd, J=17.4, 10.1, 7.6, 7.5 Hz, 1H), 5.13 (d, J=10.1 Hz, 1H), 5.07 (d, J=17.4 Hz, 1H), 4.34 (m, 1H), 3.80 (dd, J=12.0, 2.6 Hz, 1H), 3.50 (dd, J=12.0, 5.8 Hz, 1H), 2.48 (ddd, 1H, J=12.3, 7.7, 7.7 Hz, 1H), 2.10 (m, 2H), 1.97–1.92 (m, 2H), 1.62 (ddd, J=12.9, 12.5 5.2 Hz, 1H), 1.56 (ddd, J=12.9, 7.7, 1.5 Hz, 1H), 1.45 (s, 3H), 1.09 (s, 9H), 1.05 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.9, 135.8, 134.9, 134.2, 133.7, 129.5, 127.4, 127.4, 119.1, 75.0, 73.5, 62.8, 48.5, 47.0, 46.6, 42.4, 35.7, 27.1, 26.6, 19.4, 14.9; IR (film): ν_{max} =3272 (br OH), 2931 (C-H), 1640 cm^{-1} (w C=C); ESI+ MS: m/z: calcd for $C_{28}H_{40}O_3SiNa$: 475.2639; found: 475.2659 $[M+Na]^+$.

Acetate 44: A stirring solution of diol **40s** (5.42 g, 12.0 mmol from several batches), DMAP (150 mg, 1.2 mmol) and pyridine (5.82 mL, 72.0 mmol) in CH_2Cl_2 (10 mL) was treated with acetic anhydride (5.42 mL, 47.9 mmol) and stirred at RT for 16 h. The reaction was quenched with ammonium chloride solution (400 mL) and extracted with Et_2O (3×150 mL). The combined extracts were washed with brine (400 mL), dried ($MgSO_4$) and concentrated in vacuo to afford the acetate which was used without further purification. $[\alpha]_D$ = +8.33 (c = 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (m, 4H), 7.41 (m, 2H), 7.37 (m, 4H), 5.78 (dddd, J=17.2, 10.2, 7.5, 7.2 Hz, 1H), 5.10 (d, J= 10.2 Hz, 1H), 5.04 (d, J=17.2 Hz, 1H), 4.38–4.35 (m, 2H), 3.85 (dd, J= 11.5, 9.2 Hz, 1H), 2.44 (ddd, J=12.1, 7.7, 7.7 Hz, 1H), 2.10–2.05 (m, 3H), 1.99 (s, 3H), 1.95 (m, 1H), 1.68 (m, 1H), 1.59 (m, 1H), 1.28 (s, 3H), 1.08 (s, 9H), 1.04 (d, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 135.8, 135.7, 134.6, 134.2, 133.8, 129.6, 129.5, 127.51, 127.48, 118.7, 74.2, 72.7, 66.0, 47.3, 46.7, 45.7, 42.8, 34.4, 27.0, 25.8, 21.0, 19.3, 15.6; IR (film): ν_{max} = 3478 (br OH), 2931 (C-H), 2859 (C-H), 1738 (C=O), 1639 (w C=C), 1590 cm^{-1} (w Ar); ESI+ MS: m/z: calcd for $C_{30}H_{42}O_4SiNa$: 517.2750; found: 517.2750 $[M+Na]^+$.

MOM acetal 45: MOMCl (6.02 mL, 79.2 mmol) was added to a stirring solution of alcohol **44** (assume 12.0 mmol), DMAP (150 mg, 1.2 mmol) and Hünig's base (21.0 mL, 120 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred at RT for 5 d then quenched with ammonium chloride solution (300 mL), diluted with water (100 mL) and extracted with CH_2Cl_2 (3×150 mL). The combined extracts were washed with brine (250 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography (silica gel, Et_2O/PE 1:4) afforded the MOM ether as a colourless oil. $[\alpha]_D$ = −5.67 (c = 0.635, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (m, 4H), 7.41 (m, 2H), 5.70 (dddd, J=17.3, 9.9, 7.6, 7.2 Hz, 1H), 5.01 (d, J=17.3 Hz, 1H), 5.00 (d, J=9.9 Hz, 1H), 4.71 (d, J= 7.3 Hz, 1H), 4.59 (d, J=7.3 Hz, 1H), 4.38 (m, 2H), 4.37 (m, 4H), 3.75 (dd, J=11.1, 10.8 Hz, 1H), 3.29 (s, 3H), 2.47 (ddd, J=11.6, 7.7, 7.6 Hz, 1H), 2.36 (dd, J=13.6, 7.2 Hz, 1H), 2.16 (dd, J=13.6, 7.6 Hz, 1H), 1.97 (s, 3H), 1.96 (m, 2H), 1.82 (ddd, J=12.9, 11.8, 6.5 Hz, 1H), 1.59 (ddd, J=12.9, 7.8, 2.8 Hz, 1H), 1.27 (s, 3H), 1.08 (s, 9H), 1.01 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 135.8, 134.6, 134.3, 134.2, 129.5, 129.4, 127.5, 127.4, 117.7, 90.6, 78.5, 74.2, 66.5, 55.6, 45.8, 45.6, 44.4, 42.7, 33.9, 27.0, 21.7, 21.0, 19.3, 15.7; IR (film): ν_{max} = 2963 (C-H), 2932 (C-H), 1737 (acetate C=O), 1639 (w C=C), 1588 cm^{-1} (w Ar); ESI+ MS: m/z: calcd for $C_{32}H_{46}O_5SiNa$: 561.3012; found: 561.3008 $[M+Na]^+$.

Allylic alcohol 46: A solution of *tert*-butyllithium (123 mL, 1.7 M in pentane, 209 mmol) was added at −78 °C via canula over 15 min to a solution of ethyl vinyl ether (40.1 mL, 418 mmol) in THF (300 mL). After a further 15 min, the resulting solution was warmed to 0 °C before stirring for 10 min. After cooling to −78 °C, a solution of the crude residue of aldehyde **39** in THF (75 mL) was added via canula over 20 min, before stirring for 1.5 h at −78 °C. After allowing to warm to RT over 40 min, the reaction mixture was allowed to warm to RT and stirred for a further 1.5 h. Half saturated aqueous $NaHCO_3$ solution (250 mL) was added and the aqueous phase extracted with ether (4×100 mL). The combined organics phases were dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude title compound **46** which was used in the next step without further purification. $[\alpha]_D = +19.7$ ($c = 1.10$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.67$ (m, 4H), 7.42–7.38 (m, 6H), 5.67 (dddd, J=17.2, 10.2, 7.6, 7.2 Hz, 1H), 5.01 (d, J=17.2 Hz, 1H), 4.92 (d, J=10.2 Hz, 1H), 4.81 (d, J=7.4 Hz, 1H), 4.68 (d, J=7.4 Hz, 1H), 4.47 (m, 2H), 4.18 (s, 1H), 3.98 (m, 2H), 3.72–3.67 (m, 2H), 3.31 (s, 3H), 2.57 (m, 1H), 2.41 (dd, J=13.5, 7.6 Hz, 1H), 2.21 (m, 2H), 2.08 (m, 1H), 1.71 (ddd, J=13.0, 9.1, 5.1 Hz, 1H), 1.55 (m, 1H), 1.43 (s, 3H), 1.26 (t, J=7.0 Hz, 3H), 1.08 (s, 9H), 0.85 (d, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.5$, 136.0, 136.0, 135.0, 134.5, 133.8, 129.4, 127.4, 118.1, 90.9, 80.4, 80.1, 75.2, 70.5, 62.3, 55.9, 48.3, 46.2, 44.9, 38.4, 36.3, 27.2, 21.8, 19.5, 15.3, 14.5; IR (film): $\nu_{max} = 3474$ (br OH), 2857 (C-H), 1662 cm^{-1} (w C=C); ESI+ MS: m/z: calcd for $C_{34}H_{50}O_5SiNa$: 589.3325; found: 589.3328 $[M+Na]^+$.

TES-ether 47: Imidazole (8.55 g, 126 mmol), TESCl (9.84 mL, 58.6 mmol) and catalytic DMAP were added to a solution of the crude residue of alcohol **46** in DMF (77 mL) and the reaction was stirred at RT for 19 h. Half-saturated aqueous $NaHCO_3$ solution and 10% w/v aqueous lithium chloride solution (150 mL) were then added and the separated aqueous phase was extracted with ether (4×80 mL). The combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography on basic alumina doped with triethylamine (Et_2O/PE 1:20 + 1% NEt_3) to afford the title compound as a colourless oil (24.4 g, 86% over three steps from alcohol **38s**). $[\alpha]_D = -7.50$ (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.67$ (m, 4H), 7.42–7.38 (m, 6H), 5.82 (dddd, J=17.1, 10.1, 7.8, 7.0 Hz, 1H), 5.07 (d, J=10.1 Hz, 1H), 5.05 (d, J=17.1 Hz, 1H), 4.82 (d, J=7.5 Hz, 1H), 4.64 (d, J=7.5 Hz, 1H), 4.55 (m, 2H), 3.98 (s, 1H), 3.83 (s, 1H), 3.65–3.62 (m, 2H), 3.31 (s, 3H), 2.56 (m, 1H), 2.49 (dd, J=13.6, 7.0 Hz, 1H), 2.40 (m, 1H), 2.25 (dd, J=13.6, 7.8 Hz, 1H), 2.00 (ddd, J=13.0, 12.9, 8.0 Hz, 1H), 1.82 (d, J=6.6 Hz, 1H), 1.44 (m, 1H), 1.29 (s, 3H), 1.23 (t, J=7.0 Hz, 3H), 1.09 (s, 9H), 0.95 (d, J=7.0 Hz, 3H), 0.79 (m, 9H), 0.43 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.2$, 135.9, 135.8, 135.4, 134.9, 129.2, 127.4, 127.3, 117.3, 90.6, 80.0, 79.1, 75.1, 71.8, 62.4, 55.1, 53.3, 45.7, 44.4, 37.8, 35.3, 27.1, 22.3, 19.4, 17.0, 14.4, 6.9, 5.1; IR (film): $\nu_{max} = 2954$ (C-H), 2987 (C-H), 1662 cm^{-1} (w C=C); ESI+ MS: calcd for $C_{40}H_{64}O_5Si_2Na$: 703.4190; found: 703.4183 $[M+Na]^+$.

Enol ether 48: A solution of diene **47** (17.0 g, 24.9 mmol) in CH_2Cl_2 (750 mL) was degassed with a stream of dry argon at RT for 1 h. Grubbs' second generation catalyst (529 mg, 0.62 mmol) was added before heating to reflux. Whilst stirring under reflux, a second portion of Grubbs' 2nd generation catalyst (529 mg, 0.62 mmol) as a solution in CH_2Cl_2 (20 mL) was added through a glass side arm (positioned between flask and condenser) via syringe pump over 14 h. After a total of 21 h at reflux, the reaction mixture was cooled to RT, concentrated under reduced pressure and purified by flash chromatography on basic alumina doped with triethylamine (Et_2O/PE 1:30 + 1% NEt_3 followed by 1:5, Et_2O/PE + 1% NEt_3) to afford the title compound as colourless oil (14.3 g, 88%). $[\alpha]_D = +14.0$ (c = 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.67$ (m, 4H; *o*-Ph), 7.42–7.38 (m, 6H; *m*-, *p*-Ph), 4.67 (d, J=7.5 Hz, 1H; OCH_2O), 4.63 (d, J=7.5 Hz, 1H; OCH_2O), 4.41 (dd, J=6.4, 6.3 Hz, 1H; H-8), 4.33 (ddd, J=7.2, 7.1, 4.7 Hz, 1H; H-3), 4.07 (dd, J=6.0, 1.0 Hz, 1H; H-6), 3.57 (q, J=7.0 Hz, 2H; OCH_2CH_3), 3.26 (s, 3H; OCH_3), 2.80 (dd, J=13.8, 6.3 Hz, 1H; H-9), 2.72 (m, 1H; H-1), 2.19 (ddd J=10.5, 6.4, 6.0 Hz, 1H; H-5), 1.93 (dd, J=13.8, 6.4 Hz, 1H; H-9), 1.82 (m, 2H; H-2, H-4), 1.55 (m, 1H; H-2), 1.24 (t, J=7.0 Hz, 3H; OCH_2CH_3), 1.08 (s, 9H; $C(CH_3)_3$), 1.01 (d, J=7.0 Hz, 3H; H-15), 0.92 (s, 3H; H-14), 0.88 (t, J=7.8 Hz, 9H; $Si(CH_2CH_3)_3$), 0.57 (q, J=7.8 Hz, 6H; $Si(CH_2)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 158.6$ (C-7), 136.0 (*o*-Ph), 135.9 (*o*-Ph), 135.0 (*ipso*-Ph), 134.4 (*ipso*-Ph), 129.4 (*p*-Ph), 127.4 (*m*-Ph), 127.4 (*m*-Ph), 92.2 (C-8), 90.3 (OCH_2O), 78.4 (C-10), 74.7 (C-3), 72.9 (C-6), 62.1 (OCH_2CH_3), 55.1 (OCH_3), 52.5 (C-5), 47.6 (C-1), 39.30 (C-4), 38.8 (C-2), 32.3 (C-9), 27.1 ($C(CH_3)_3$), 22.6 (C-14), 19.4 ($C(CH_3)_3$), 14.6 (OCH_2CH_3), 14.3 (C-15), 6.9 ($Si(CH_2CH_3)_3$), 4.7 ($Si(CH_2)_3$); IR (film): $\nu_{max} = 2958$ (C-H), 2932 (C-H), 2875 (C-H), 1668 cm^{-1} (w C=C); ESI+ MS: m/z: calcd for $C_{38}H_{60}O_5Si_2Na$: 675.3877; found: 675.3890 $[M+Na]^+$.

α-Hydroxy ketone 49: Solid $NaHCO_3$ (4.38 g, 52.1 mmol) was added at RT to a solution of AD mix-α (24.3 g) in *tert*-butanol and water 1:1 (210 mL). The resulting solution was added to the neat enol ether **48** (11.4 g, 17.4 mmol) before addition of methanesulfonamide (1.65 g, 17.4 mmol) and stirred at RT for 15 h. The reaction was quenched by the addition of sodium sulfite (7.50 g), with stirring for 1 h before addition of a half-saturated aqueous $NaHCO_3$ solution (200 mL) and ethyl acetate (200 mL). The separated aqueous phase was extracted with ethyl acetate (3×100 mL) and the combined organics dried ($MgSO_4$), concentrated under reduced pressure and purified by filtration through a short plug of silica gel (Et_2O/PE 1:5 → 1:1) to afford the title compound as a white amorphous solid (10.7 g, 96%). $[\alpha]_D = +42.9$ (c = 1.72, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.67$ (m, 4H; *o*-Ph), 7.42–7.38 (m, 6H; *m*- and *p*-Ph), 4.97 (ddd, 8.1, 6.1, 5.7 Hz, 1H; H-8), 4.89 (d, J=7.6 Hz, 1H; OCH_2O), 4.78 (d, J=7.6 Hz, 1H; OCH_2O), 4.25 (d, J=3.9 Hz, 1H; H-6), 4.14 (m, 1H; H-3), 3.33 (s, 3H; OCH_3), 3.10 (d, J=5.7 Hz, 1H; OH), 2.90 (m, 1H; H-1), 2.34 (dd, J=14.2, 6.1 Hz, 1H; H-9), 2.19 (ddd, J=10.7, 9.4, 3.9 Hz, 1H; H-5), 1.64 (m, 1H; H-4), 1.56 (dd, J=14.2, 8.1 Hz, 1H; H-9), 1.47 (ddd, J=13.6, 7.3, 1.8 Hz, 1H; H-2), 1.27 (m, 4H; H-2, H-14), 1.09 (d, J=7.0 Hz, 3H; H-15), 1.06 (s, 9H; $C(CH_3)_3$), 0.96 (t, J=7.8 Hz, 9H; $Si(CH_2CH_3)_3$), 0.61 (q, J=7.8 Hz, 6H; $Si(CH_2)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 213.5$ (C-7), 135.9 (*o*-Ph), 135.8 (*o*-Ph), 134.7 (*ipso*-Ph), 133.8 (*ipso*-Ph), 129.6 (*p*-Ph), 127.6 (*m*-Ph), 127.5 (*m*-Ph), 90.8 (OCH_2O), 78.4 (C-6), 78.2 (C-10), 74.8 (C-3), 69.9 (C-8), 55.4 (OCH_3), 51.0 (C-5), 46.4 (C-1), 42.1 (C-4), 41.4 (C-9), 38.3 (C-2), 31.2 (C-14), 27.1 ($C(CH_3)_3$), 19.4 ($C(CH_3)_3$), 14.2 (C-15), 6.7 ($Si(CH_2CH_3)_3$), 4.5 ($Si(CH_2)_3$); IR (film): $\nu_{max} = 3414$ (br OH), 2955 (C-H), 2878 (C-H), 1710 cm^{-1} (C=O); ESI+ MS: m/z: calcd for $C_{36}H_{56}O_6Si_2Na$: 663.3513; found: $[M+Na]^+$ 663.3513.

Butenolide 51: 2-(Diethoxyphosphoryl)propionic acid (5.27 g, 25.07 mmol) and EDCI (10.37 g, 54.09 mmol) were added at RT to a solution of ketoalcohol **49** (11.48 g, 17.91 mmol) in CH_2Cl_2 (210 mL). The reaction mixture was stirred for 3 h before addition of saturated aqueous $NaHCO_3$ solution (100 mL), separation of the phases, extraction of the aqueous with CH_2Cl_2 (2×60 mL) and drying the combined organics ($MgSO_4$). Purification by flash chromatography (ethyl acetate/PE 1:1 then 2:1) afforded the title compounds as a colourless oil (12.08 g, 81%; 1:1 mixture of diastereoisomers). To a solution of this ketophosphonate (12.08 g, 14.50 mmol) in THF (620 mL) was added NaH (617 mg of a 60 wt% dispersion in mineral oil, 15.43 mmol) at RT. After 5 min, the reaction mixture was heated to reflux (82 °C external temperature) for 15 min, after which time a colourless to yellow colour change was apparent. Cooling to RT, addition of saturated aqueous $NaHCO_3$/water 1:1 (400 mL), separation of the phases, extraction of the aqueous with CH_2Cl_2 (3×150 mL), drying the combined organics ($MgSO_4$) and concentration under reduced pressure afforded the crude residue of the title compound which was used without further purification. $[\alpha]_D = +50.5$ (c = 1.54, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.65$–7.64 (m, 4H; *o*-Ph), 7.43–7.42 (m, 2H; *p*-Ph), 7.41–7.33 (m, 4H; *m*-Ph), 5.40–5.38 (m, 1H; H-8), 4.98 (d, J=7.6 Hz, 1H; OCH_2O), 4.72 (d, J=2.4 Hz, 1H; H-6), 4.60 (d, J=7.6 Hz, 1H; OCH_2O), 4.11–4.08 (m, 1H; H-3), 3.39 (s, 3H; OCH_3), 3.07–3.06 (m, 1H; H-1), 2.37 (dd, J=13.8, 5.7 Hz, 1H; H-9), 2.34–2.30 (m, 1H; H-5), 1.75 (s, 3H; H-13), 1.45 (dd, J=13.0, 7.0 Hz, 1H; H-2), 1.33–1.26 (m, 1H; H-9), 1.25–1.24 (m, 1H; H-4), 1.13–1.12 (d, J=6.6 Hz, 3H; H-15), 1.08 (s, 9H; $C(CH_3)_3$), 1.05 (s, 3H; H-14), 0.95 (t, J=8.0 Hz, 9H; $SiCH_2CH_3$), 0.60–0.52 (m, 6H; $SiCH_2$); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 174.2$ (C-12), 163.4 (C-7), 135.9 (*o*-Ph), 135.8 (*o*-Ph), 134.6 (*ipso*-Ph), 133.7 (*ipso*-Ph), 129.7 (*p*-Ph), 129.7 (*p*-Ph), 127.6 (*m*-Ph), 127.6 (*m*-Ph), 123.2 (C-11), 91.6 (CH_2OCH_3), 78.6 (C-8), 75.2 (C-3), 67.9 (C-6), 55.3 (CH_2OCH_3), 51.5 (C-5), 44.5 (C-1), 44.2 (C-4), 40.8 (C-9), 39.0 (C-2), 29.3 (C-11), 27.1 (C-20), 19.5 (C-19), 14.5 (C-15), 9.0

(C-13), 6.7 ($SiCH_2CH_3$), 4.5 ($SiCH_2CH_3$); IR (film): ν_{max} = 2955, 2877, 1757, 1458, 1427, 1191, 1144, 1102, 1076, 1035, 1005, 918, 821, 741, 701 cm^{-1}; ESI+ MS: *m/z*: calcd for $C_{39}H_{58}O_6SiNa$: 701.3670; found: 701.3693 [*M*+Na].

Diol 52: A solution of lithium borohydride (140 mL of a 2.0 M solution in THF, 280 mmol) was added over 30 min via cannula at RT to the crude residue of butenolide **51** in THF (200 mL). The resulting solution was heated to reflux (84 °C external temperature) for 40 h, after which time TLC analysis of the reaction (ethyl acetate/PE 1:2) showed consumption of the starting lactone to product diol but also a quantity of the intermediate lactol. Addition of further lithium borohydride solution (40 mL of a 2.0 M solution in THF, 80 mmol) and heating under reflux for 24 h completed the reaction by TLC. The reaction mixture was carefully poured into a 1:1 mixture of saturated aqueous ammonium chloride solution and ice before stirring for 20 min. Separation of the phases, extraction of the aqueous with ether (3×150 mL), drying the combined organics ($MgSO_4$) and concentration under reduced pressure afforded the crude title compound as a white foam which was used without purification in the subsequent step. $[\alpha]_D$ = +26.6 (*c* = 1.22, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ = 7.66–7.65 (m, 4H; *o*-Ph), 7.41–7.40 (m, 2H; *p*-Ph), 7.39–7.33 (m, 4H; *m*-Ph), 4.81 (t, *J* = 8.3 Hz, 1H; H-8), 4.65 (d, *J* = 6.6 Hz, 1H; OCH_2O), 4.62 (d, *J* = 6.6 Hz, 1H; OCH_2O), 4.33 (d, *J* = 11.1 Hz, 1H; H-12), 4.26–4.24 (m, 1H; H-3), 4.04 (d, *J* = 11.2 Hz, 1H; H-6), 3.73 (d, *J* = 11.1 Hz, 1H; H-12), 3.33 (s, 3H; OCH_3), 2.80–2.77 (m, 1H; H-1), 2.41 (brs, 1H; OH), 2.27–2.25 (m, 1H; H-4), 2.04–2.00 (m, 6H; H-5, H-9, H-13), 1.59 (brs, 1H; OH), 1.57 (dd, *J* = 14.3, 5.2 Hz, 1H; H-9), 1.41–1.39 (m, 1H; H-2), 1.30–1.25 (m, 1H; H-2), 1.17 (d, *J* = 7.1 Hz, 3H; H-15), 1.07 (s, 9H; $C(CH_3)_3$), 1.02 (s, 3H; H-14), 0.86 (t, *J* = 8.0 Hz, 9H; $SiCH_2CH_3$), 0.51–0.48 (m, 6H; $SiCH_2$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 141.4 (C-11), 135.9 (*o*-Ph), 135.8 (*o*-Ph), 134.9 (*ipso*-Ph), 134.1 (*ipso*-Ph), 133.8 (C-7), 129.6 (*p*-Ph), 129.5 (*p*-Ph), 127.5 (*m*-Ph), 127.5 (*m*-Ph), 90.1 (CH_2OCH_3), 79.3 (C-10), 74.0 (C-3), 69.8 (C-6), 66.0 (C-8), 64.6 (C-12), 55.7 (CH_2OCH_3), 53.3 (C-5), 44.7 (C-1), 43.1 (C-4), 39.2 (C-9), 37.9 (C-2), 28.5 (C-14), 27.1 ($C(CH)_3$), 19.4 ($C(CH)_3$), 16.6 (C-15), 7.0 ($SiCH_2CH_3$), 4.8 ($SiCH_2CH_3$); IR (film): ν_{max} = 3366 (br), 2932, 2875, 1457, 1427, 1373, 1191, 1105, 1065, 1005, 928, 856, 820, 740, 701 cm^{-1}; ESI+ MS: *m/z*: calcd for $C_{39}H_{62}O_6SiNa$: 705.3983; found: 705.4001 $[M+Na]^+$.

Acetate 53: 2,6-Lutidine (4.90 mL, 41.97 mmol), acetic anhydride (1.58 mL, 16.75 mmol) and DMAP (60 mg) was added at RT to a solution of the crude diol **52** in CH_2Cl_2 (160 mL). After stirring for 3 h, a half-saturated aqueous ammonium chloride solution (200 mL) was added before separation of the phases and extraction of the aqueous with Et_2O (3×80 mL). The combined organics were dried ($MgSO_4$), then concentration under reduced pressure and filtration through a short plug of silica gel (Et_2O/PE 1:5) afforded the title compound, contaminated with ca. 15% 2,6-lutidine. The crude material was carried through the subsequent step without the need for further purification. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.68–7.63 (m, 4H; *o*-Ph), 7.43–7.32 (m, 6H; *m*-Ph, *p*-Ph), 5.37 (d, *J* = 11.0 Hz, 1H; H-12), 4.88–4.83 (m, 1H; H-8), 4.60 (d, *J* = 7.0 Hz, 1H; OCH_2O), 4.51 (d, *J* = 7.0 Hz, 1H; OCH_2O), 4.25–4.21 (m, 1H; H-3), 4.05 (d, *J* = 12.0 Hz, 1H; H-6), 3.97 (d, J = 11.0 Hz, 1H; H-12), 3.28 (s, 3H; OCH_3), 2.77 (s, 1H; 8-OH), 2.73 (dt, *J* = 13.0, 7.0 Hz, 1H; H-1), 2.31–2.24 (m, 1H; H-4), 2.02–1.96 (m, 2H; H-5, H-9), 2.02 (s, 3H; CH_3C=O), 1.94 (s, 3H; H-13), 1.58 (dd, *J* = 14.0, 9.0 Hz, 1H; H-9), 1.45–1.39 (m, 1H; H-2), 1.29 (dt, *J* = 13.0, 6.0 Hz, 1H; H-2), 1.15 (d, *J* = 7.0 Hz, 3H; H-15), 1.07 (s, 9H; $C(CH_3)_3$), 1.00 (s, 3H; H-14), 0.83 (t, *J* = 8.0 Hz, 9H; $SiCH_2CH_3$), 0.46 (dq, *J* = 8.0, 3.0 Hz, 6H; $SiCH_2CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.9 (C=O), 144.0 (C-7), 135.9 (*o*-Ph), 135.9 (*o*-Ph), 134.9 (C-11), 134.2 (*ipso*-Ph), 129.5 (*p*-Ph), 129.5 (*p*-Ph), 127.5 (*m*-Ph), 90.7 (CH_2OCH_3), 78.5 (C-10), 74.0 (C-3), 69.8 (C-6), 66.5 (C-12), 65.4 (C-8), 55.3 (CH_2OCH_3), 53.1 (C-5), 45.2 (C-1), 42.8 (C-4), 38.3 (C-9), 37.8 (C-2), 28.7 (C-14), 27.1 ($C(CH_3)_3$), 21.1 (C=OCH_3), 19.4 ($C(CH_3)_3$), 18.3 (C-13), 16.5 (C-15), 7.0 ($SiCH_2CH_3$), 4.6 ($SiCH_2CH_3$); IR (film): ν_{max} = 3410 (br OH), 2956 (C-H), 1725 cm^{-1} (C=O); ESI+ MS: *m/z*: calcd for $C_{41}H_{64}O_7Si_2Na$: 747.4088; found: 747.4094 $[M+Na]^+$.

MOM acetal 54: Diisopropylethylamine (19.10 mL, 109.91 mmol), MOMCl (8.30 mL, 109.91 mmol) and DMAP (60 mg) were added at RT to a solution of the crude alcohol **53** in CH_2Cl_2 (180 mL). After stirring for 18 h, a half-saturated aqueous ammonium chloride solution (300 mL) was added and stirring continued for 15 min. Separation of the phases, extraction of the aqueous with CH_2Cl_2 (3×80 mL), drying the combined organics ($MgSO_4$), concentration under reduced pressure and purification by flash chromatography (Et_2O/PE 1:10 → 1:1) afforded the title compound as a colourless oil (6.69 g, 60% yield over 4 steps from ketoalcohol **49**. $[\alpha]_D$ = −79.4 (*c* = 0.175, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ = 7.68–7.63 (m, 4H; *o*-Ph), 7.43–7.32 (m, 6H; *p*-Ph, *m*-Ph), 4.72 (d, *J* = 12.0 Hz, 1H; H-12), 4.67–4.55 (m, 5H; OCH_2O, H-8, H-12), 4.35 (d, *J* = 7.0 Hz, 1H; OCH_2O), 4.25–4.21 (m, 1H; H-3), 4.02 (d, *J* = 11.0 Hz, 1H; H-6), 3.32 (s, 3H; OCH_3), 3.31 (s, 3H; OCH_3), 2.80 (dt, *J* = 14.0, 8.0 Hz, 1H; H-1), 2.25–2.18 (m, 1H; H-4), 2.11–2.05 (m, 1H; H-5), 2.04 (s, 3H; CH_3C=O), 1.99–1.93 (m, 1H; H-9), 1.95 (s, 3H; H-13), 1.63 (dd, *J* = 14.0, 9.0 Hz, 1H; H-9), 1.44 (dd, *J* = 14.0, 6.0 Hz, 1H; H-2), 1.29 (dt, *J* = 12.0, 6.0 Hz, 1H; H-2), 1.17 (d, *J* = 7.0 Hz, 3H; H-15), 1.07 (s, 9H; $C(CH_3)_3$), 1.02 (s, 3H; H-14), 0.85 (t, *J* = 8.0 Hz, 9H; $SiCH_2CH_3$), 0.52–0.42 (m, 6H; $SiCH_2CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.1 (C=O), 138.7 (C-7), 135.9 (*o*-Ph), 135.9 (*o*-Ph), 135.0 (*ipso*-Ph), 134.2 (*ipso*-Ph), 131.0 (C-11), 129.5 (*p*-Ph), 129.5 (*p*-Ph), 127.5 (*m*-Ph), 127.5 (*m*-Ph), 92.4 (O-8-CH_2OCH_3), 90.9 (O-10-CH_2OCH_3), 78.6 (C-10), 74.1 (C-3), 70.5 (C-6), 68.1 (C-8), 65.4 (C-12), 55.4 (O-8-CH_2OCH_3), 55.1 (O-10-CH_2OCH_3), 53.3 (C-5), 44.8 (C-1), 43.2 (C-4), 38.6 (C-9), 38.0 (C-2), 28.9 (C-14), 27.1 ($C(CH_3)_3$), 20.9 (CH_3C=O), 19.4 ($C(CH_3)_3$), 17.6 (C-13), 16.6 (C-15), 6.9 ($SiCH_2CH_3$), 4.7 ($SiCH_2CH_3$); IR (film): ν_{max} = 2955 (C-H), 2933 (C-H), 1740 (C=O), 1725 cm^{-1} (C=O); ESI+ MS: *m/z*: calcd for $C_{43}H_{68}O_8Si_2Na$: 791.4350; found: 791.4385 $[M+Na]^+$.

Tetrol 55: To the commercially available solution of osmium tetroxide (4.70 mL of a 2.5% solution in *tert*-butanol) and water (13.7 mL) was added further solid osmium tetroxide (100 mg, 391 μmol), quinuclidine (968 mg, 8.70 mmol), potassium carbonate (3.65 g, 26.10 mmol), potassium hexacyanoferrate (8.57 g, 26.10 mmol) and methane sulfonamide (2.49 g, 26.10 mmol) with vigorous stirring at RT. Olefin **54** (6.70 g, 8.70 mmol) in *tert*-butanol (9.0 mL) was added before continuing vigorous stirring for 10 d (flask wrapped in foil to exclude light). After this time, sodium sulfite (6.10 g) was added and the reaction mixture stirred for 1 h. Addition of water (25 mL), separation of the phases, extraction of the aqueous with Et_2O (6×60 mL), drying the combined organics ($MgSO_4$) and concentration under reduced pressure afforded a crude residue in which the reaction was judged to be incomplete by TLC. Subjecting the crude mixture to exactly the same olefination conditions as described above for 7 d, followed by the same workup procedure, afforded the crude title compound as a dark amber oil which was used without further purification. To a solution of the crude residue of the diol in methanol (400 mL) was added solid potassium carbonate (10.90 g, 78.90 mmol). After vigorous stirring for 1 h, the reaction mixture was poured into a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and water. Separation of the phases, extraction of the aqueous with CH_2Cl_2 (4×80 mL), drying the combined organic layers ($MgSO_4$), concentrating under reduced pressure and purification by flash chromatography (ethyl acetate/PE 3:2) afforded the title compound as a pale yellow oil (4.78 g, 85% over two steps from olefin **54**). R_f = 0.56 (ethyl acetate); $[\alpha]_D$ = +1.7 (*c* = 1.18, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$): δ = 7.68–7.62 (m, 4H; *o*-Ph), 7.45–7.32 (m, 6H; *m*-Ph, *m*-Ph), 4.97 (s, 1H; 7-OH), 4.79 (d, *J* = 3 Hz, 1H; OCH_2O), 4.67–4.56 (m, 3H; OCH_2O), 4.36–4.31 (m, 1H; H-3), 4.19–4.06 (m, 4H; 6-OH, H-8, H-12), 3.77 (dd, *J* = 10, 3 Hz, 1H; H-6), 3.48–3.42 (m, 1H; H-12), 3.37 (s, 3H; OCH_3), 3.34 (s, 3H; OCH_3), 3.12–3.06 (m, 1H; 12-OH), 2.81–2.75 (m, 1H; H-1), 2.61–2.54 (m, 1H; H-4), 2.10–2.05 (m, 1H; H-5), 1.95 (dd, *J* = 16, 8 Hz, 1H; H-9), 1.82 (d, *J* = 16 Hz, 1H; H-9), 1.56–1.46 (m, 2H; H-2), 1.31 (s, 3H; H-13), 1.12 (d, *J* = 7 Hz, 3H; H-15), 1.07 (s, H-14 Hz, 12H; $C(CH_3)_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 135.8 (*o*-Ph), 135.8 (*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), 95.9 (O-8-CH_2OCH_3), 90.5 (O-10-CH_2OCH_3), 80.4 (C-7), 78.7 (C-8), 78.6 (C-10), 78.2 (C-11), 73.2 (C-3), 71.5 (C-6), 69.2 (C-12), 56.3 (OCH_3), 55.7 (OCH_3), 48.8 (C-5), 45.5 (C-1), 41.5 (C-4), 40.2 (C-9), 37.0 (C-2), 27.0 ($C(CH_3)_3$), 25.9 (C-14), 22.5 (C-13), 19.4 ($C(CH_3)_3$), 16.3 (C-15); IR (film): ν_{max} = 2955 (C-H), 2933 (C-H), 1740 (C=O), 1725 cm^{-1} (C=O); ESI+ MS: *m/z*: calcd for $C_{35}H_{54}O_9SiNa$: 669.3435; found: 669.3444 $[M+Na]^+$.

Lactone 56: NMO (14.41 g, 123 mmol) was suspended in acetonitrile (38 mL) before addition of 4 Å molecular sieves (14.11 g), TPAP (95 mg, 270 μmol) and stirring for 30 min. The starting tetraol **55** (1.59 g, 2.46 mmol) was dissolved in acetonitrile (38 mL) and added dropwise via cannula, to the original mixture. After stirring for a further 1.5 h, the reaction mixture was concentrated to dryness under reduced pressure before re-dissolving the crude mixture in ethyl acetate and filtering through a short plug of silica gel (ethyl acetate) to remove TPAP residues and afford the pure title compound as a white foam (1.17 g, 74%). R_f = 0.58 (ethyl acetate/PE 2:1); $[\alpha]_D$ = +8.0 (c = 2.25, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.68–7.61 (m, 4H; *o*-Ph), 7.45–7.33 (m, 6H; *m*-Ph, *p*-Ph), 5.21 (s, 1H; 11-OH), 4.87 (s, 1H; 7-OH), 4.85 (d, J = 7 Hz, 1H; OCH_2O), 4.74–4.68 (m, 3H; OCH_2O), 4.57 (d, J = 11 Hz, 1H; H-6), 4.45–4.40 (m, 1H; H-3), 4.20 (dd, J = 10, 6 Hz, 1H; H-8), 3.41 (s, 3H; OCH_3), 3.38 (s, 3H; OCH_3), 2.86–2.79 (m, 1H; H-1), 2.51–2.44 (m, 1H; H-4), 2.20–2.11 (m, 2H; H-5, H-9), 1.72 (dd, J = 14, 11 Hz, 1H; H-9), 1.55–1.48 (m, 1H; H-2), 1.46 (s, 3H; H-13), 1.38 (dd, J = 13, 6 Hz, 1H; H-2), 1.20 (d, J = 7 Hz, 3H; H-15), 1.17 (s, 3H; H-14), 1.08 (s, 9H; C-$(CH_3)_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.1 (C-12), 135.8 (*o*-Ph), 134.8 (*ipso*-Ph), 133.6 (*ipso*-Ph), 129.7 (*p*-Ph), 129.6 (*p*-Ph), 127.7 (*m*-Ph), 127.5 (*m*-Ph), 97.1 (O-8-CH_2OCH_3), 91.1 (O-10-CH_2OCH_3), 82.8 (C-6), 81.3 (C-8), 80.0, 79.8, 78.3 (C-7, C-10, C-11), 73.4 (C-3), 56.8 (O-8-CH_2OCH_3), 56.2 (O-10-CH_2OCH_3), 46.9 (C-1), 45.0 (C-5), 43.7 (C-4), 39.7 (C-9), 38.0 (C-2), 27.5 (C-14), 27.0 (C(CH_3)$_3$), 19.4 (C(CH_3)$_3$), 16.8 (C-13), 16.0 (C-15); IR (film): ν_{max} = 3419, 2924, 2853, 1789, 1459, 1110, 1014 cm^{-1}; ESI+ MS: m/z: calcd for $C_{47}H_{80}O_7SiNa$: 665.312; found: 665.3110 $[M+Na]^+$.

Acetonide 57: Amberlyst 15 (1.90 g) and 2,2-dimethoxypropane (3.50 mL) were added at RT to a rapidly stirred solution of bis-MOM diol **56** (2.23 g, 3.47 mmol) in acetone (53 mL). After stirring for 48 h, 4 Å molecular sieves (1.47 g) were added and vigorous stirring continued for a further 48 h. Filtration through celite with copious ethyl acetate washings, concentration under reduced pressure followed by filtration of the residue through a short plug of silica gel (Et_2O/PE 1:2 then 1:1) first afforded the title compound as a colourless oil (1.77 g). Switching to pure ethyl acetate afforded the crude residue of the intermediate tetraol (1.0 g of a cloudy gel). This was subjected without further purification, to the same 4 day transacetalisation as described above in acetone (15 mL), using Amberlyst 15 (0.48 g), 2,2-dimethoxypropane (1.00 mL) and after 48 h, 4 Å molecular sieves (0.50 g). This afforded an additional quantity of clean title compound after purification as above (0.19 g). (The total yield after one "recycle" was therefore 1.96 g, 95%.) R_f = 0.34 (ethyl acetate/PE 1:2); $[\alpha]_D$ = +4.0 (c = 0.250, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.61–7.59 (m, 4H; *o*-Ph), 7.39–7.28 (m, 6H; *m*-Ph, *p*-Ph), 4.32–4.30 (m, 2H; H-3, H-6), 4.05 (t, J = 5.2 Hz, 1H; H-8), 3.71 (s, 1H; OH), 2.55–2.50 (m, 2H; OH, H-1), 2.41–2.11 (m, 3H; H-4, H-5, H-9), 1.49–1.40 (m, 1H; H-9), 1.39–1.36 (m, 2H; H-2), 1.39 (s, 3H; H-13), 1.23, 1.19 (2×s, 6H; $(CH_3)_2C$), 1.17 (d, J = 7.1 Hz, 1H; H-15), 1.16 (s, 3H; H-14), 1.07 (s, 9H; C(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.8 (C-12), 135.9 (*o*-Ph), 135.8 (*o*-Ph), 134.7 (*ipso*-Ph), 133.6 (*ipso*-Ph), 129.7 (*p*-Ph), 129.6 (*p*-Ph), 127.6 (*m*-Ph), 127.5 (*m*-Ph), 98.3 (OCO), 82.2 (C-11), 78.9 (C-7), 74.8 (C-3), 73.8 (C-10), 69.7 (C-6), 67.0 (C-8), 53.7 (C-5), 49.6 (C-9), 44.5 (C-4), 43.7 (C-1), 38.5 (C-2), 30.4 (C(CH_3)(CH_3)), 29.2 (C-14), 27.1 (C(CH_3)$_3$), 23.6 (C-13), 19.4 (C(CH_3)(CH_3)), 18.9 (C(CH_3)$_3$), 16.1 (C-15); IR (film): ν_{max} = 3390 (br OH), 3200 (br OH), 2933 (C-H), 1764 cm^{-1} (C=O); ESI+ MS: m/z: calcd for; $C_{34}H_{46}O_7Si_1Na$: 617.2911; found: 617.2928 $[M+Na]^+$.

Ketone 19: A solution of TBAF (80 mL, 1.0 M in THF, 85 mmol) was added to neat TBDPS-ether **57** (1.49 g, 2.51 mmol) at RT. After stirring the resulting solution for 4 d, 4 Å molecular sieves (1.20 g) were added and vigorous stirring applied for a further 4 d. Filtration through Celite (washing with ethyl acetate), partitioning between water (80 mL) and ethyl acetate (80 mL), separation of the phases, extensive extraction of the aqueous with ethyl acetate (5×60 mL), drying the combined organics ($MgSO_4$), concentration under reduced pressure and filtration through a short plug of silica gel (ethyl acetate) afforded the title compound (883 mg) which was used immediately in the next step without further purification. R_f = 0.26 (ethyl acetate). To a solution of triol **58** in CH_2Cl_2 (52 mL) at RT was added solid $NaHCO_3$ (720 mg, 8.57 mmol) followed by Dess–Martin periodinane (1.81 g, 4.27 mmol). Stirring was continued for 90 min before addition of a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous sodium thiosulfate solution (80 mL) and CH_2Cl_2 (80 mL). The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3×50 mL), the combined organics washed with the afore-mentioned 1:1 solution (80 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (ethyl acetate/PE 1:1 → 2:1) to afford the title compound **19** as a white foam (810 mg, 91% over 2 steps from TBDPS-ether **57**). $[\alpha]_D$ = +0.41 (c = 1.75, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.61 (d, J = 11.7 Hz, 1H; H-6), 4.22 (m, 1H; H-8), 2.76 (m, 1H; H-4), 2.70 (m, 1H; H-1), 2.60 (m, 1H; H-5), 2.47 (dd, J = 15.8, 8.5 Hz, 1H; H-9), 2.34 (dd, J = 18.2, 7.7 Hz, 1H; H-2), 2.22 (m, 1H, H-2), 1.73 (dd, J = 15.8, 5.4 Hz, 1H; H-9), 1.51, 1.49 (2×s, 3H; H-13, C(CH_3)(CH_3)), 1.35 (s, 6H; H-14, C(CH_3)(CH_3)), 1.21 (d, J = 7.7 Hz, 3H; H-15); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 218.8 (C-3), 174.6 (C-12), 98.9 (C(CH_3)$_2$), 79.9 (C-6), 79.4 (C-11), 74.2 (C-10), 72.3 (C-7), 66.5 (C-8), 47.4 (C-4), 46.8 (C-1), 42.9 (C-5), 39.9 (C-2), 39.9 (C-9), 30.4 (C(CH_3)(CH_3)), 30.4 (C-14), 23.6 (C-13), 18.3 (C(CH_3)(CH_3)), 16.6 (C-15); IR (film): ν_{max} = 3408 (br OH), 3235 (br OH), 2973 (C-H), 2941 (C-H), 1767 (lactone C=O), 1734 cm^{-1} (ketone C=O); accurate mass analysis was performed, but the parent ion could not be found.

α-Hydroxy ketone 61: To a solution of ketone **19** (311 mg, 0.88 mmol) in DMF (9.8 mL) at RT was added triethylamine (60 mL) and TMSCl before heating to reflux (130 °C external temperature) for 43 h. The resulting mixture was carefully poured into a mixture of saturated aqueous $NaHCO_3$ solution and ice (200 mL, 1:1). Extraction with ethyl acetate (4×100 mL), drying ($MgSO_4$), concentration under reduced pressure and purification by brief filtration through a pad of silica gel (Et_2O/PE 1:10) afforded the silyl enol ether which was used immediately in the next step without further purification. To a solution of TMS enol ether (651 mg, derived from 1.26 mmol ketone **19**) in CH_2Cl_2 (9 mL) at −78 °C was added a freshly prepared solution of DMDO (60 mL, 1.50 mmol, 0.025 M) dropwise before continuing at −78 °C for 30 min. The resulting solution was warmed to RT before stirring for a further 40 min. Saturated aqueous ammonium chloride solution (7.5 mL) was added and the reaction vigorously stirred to complete hydrolysis of the intermediate silyl enol ether (15 h). Partitioning between further saturated aqueous ammonium chloride solution (100 mL) and CH_2Cl_2 (100 mL), separation of the phases, extraction of the aqueous with CH_2Cl_2 (3×40 mL), drying the combined organics ($MgSO_4$), concentration under reduced pressure and purification of the resulting residue by flash chromatography (ethyl acetate/PE 1:10 then 1:5, ethyl acetate/PE) afforded the title compound as a white foam (567 mg, 87% over two steps from ketone **19**). $[\alpha]_D$ = +7.5 (c = 1.08, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.19 (d, J = 10.3 Hz, 1H; H-6), 4.40 (s, 1H; H-2), 4.15 (m, 1H; H-8), 2.57 (m, 1H; H-4), 2.44 (m, 1H; H-1), 2.40 (d, J = 1.86, 1H; OH), 2.25 (m, 2H; H-5, H-9), 2.17 (dd, J = 3.2, 14.7; H-9), 1.57 (s, 3H; H-13), 1.54, 1.53 (2×s, 6H; C(CH_3)-(CH_3)), 1.34 (d, J = 6.6 Hz; H-15), 1.24 (s, 3H; H-14), 0.22, 0.17 (2×s, 18H; Si(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 216.7 (C-3), 173.2 (C-12), 112.0 (C(CH_3)(CH_3)), 99.9 (C-13), 82.6 (C-6), 79.1, 78.0 (C-7, C-10), 74.9 (C-2), 66.2 (C-8), 53.7 (C-1), 46.2 (C-4), 45.2 (C-9), 41.7 (C-5), 30.4 (C-15), 26.6 (C(CH_3)(CH_3)), 23.4 (C-13), 17.9 (C(CH_3)(CH_3)), 13.7 (C-14), 2.7 (Si(CH_3)$_3$); IR (film): ν_{max} = 2931, 2856, 1613, 1512, 1246, 1103, 1035, 821, 701 cm^{-1}; ESI+ MS: m/z: calcd for $C_{24}H_{42}O_8Si_2Na$: 537.2316; found: 537.2328 $[M+Na]^+$.

Experimental procedures towards the trilobolide series (2, 3 and 4) from 61

Enone 62: A solution of ketone **61** (150 mg, 0.256 mmol) in DMF (4 mL) in a three-neck round bottom flask fitted with reflux condenser, was treated with triethylamine (4 mL, 28.7 mmol) and TMSCl (3 mL, 23.6 mmol). The mixture was heated to reflux (125 °C) for 48 h, then cooled to RT and quenched into half-saturated aqueous $NaHCO_3$ solution (50 mL). The aqueous mixture was extracted with ethyl acetate (4×50 mL) and the combined organic extracts were dried with $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography (silica gel, PE/ethyl acetate 5:1) to obtain the TMS enol ether as an off-white foam (152 mg, 90%). R_f = 0.46 (PE/Et_2O 5:2). The TMS enol

ether (38 mg, 58 μmol) in CH_2Cl_2 at 0 °C was treated with a solution of PhSeBr (1.38 mg, 5.8 μmol) in CH_2Cl_2 (5 mL). The mixture was warmed to 10 °C over 2 h, after which the reaction was complete by TLC. The mixture was treated with saturated aqueous $NaHCO_3$ (3 mL), water (3 mL) and extracted into CH_2Cl_2 (3×10 mL). The combined extracts were dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography (silica gel, PE/Et_2O 5:1) to give the enone as a clear colourless oil (27 mg, 94%). R_f=0.26 (PE/Et_2O 5:2); $[\alpha]_D$ = −86.6 (c = 1.3, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$): δ = 5.98 (s, 1H; H-6), 4.21 (apparent t, J=3.5 Hz, 1H; H-8), 3.44 (brm, 1H; H-1), 2.46 (m, 2H; H-2), 2.33 (dd, J=14.5, 4.1 Hz, 1H; H-9), 2.14 (dd, J=14.5, 3.0 Hz, 1H; H-9), 1.98 (s, 3H; H-15), 1.60 (s, 3H; H-13), 1.58 (s, 3H; C(CH_3)(CH_3)), 1.51 (s, 3H; C(CH_3)(CH_3)), 1.40 (s, 3H; H-14), 0.13 (s, 9H; Si(CH_3)$_3$), 0.10 (s, 9H; Si(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 207.7 (C-3), 172.4 (C-12), 159.6 (C-4), 142.1 (C-5), 100.5 (C(CH_3)(CH_3)), 80.6 (C-7), 79.4 (C-11), 79.2 (C-6), 76.9 (C-10), 51.5 (C-1), 45.4 (C-9), 37.9 (C-2), 30.5 ((C(CH_3)(CH_3)), 23.5 (C(CH_3)(CH_3)), 23.1 (C-14), 17.0 (C-13), 9.5 (C-15), 2.7 (2×Si(CH_3)$_3$); IR (film): ν_{max} = 2957, 1798, 1709, 1385, 1254 cm^{-1}; ESI+ MS: m/z: calcd for $C_{24}H_{40}O_7Si_2Na$: 519.2210; found: 519.2224 $[M+Na]^+$.

Allylic alcohol 63: Enone **62** (27 mg, 54 μmol) in MeOH at 0 °C was treated with solid $NaBH_4$ (22 mg, 580 μmol) added in a single portion. The mixture was aged for 1 h at 0 °C then treated with saturated aqueous $NaHCO_3$ (5 mL), water (5 mL) and extracted into CH_2Cl_2 (4×15 mL). Combined extracts were dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography (silica gel, PE/Et_2O 2:1) to give the allylic alcohol as a clear oil (22 mg, 86%). R_f=0.22 (PE/Et_2O 1:1); $[\alpha]_D$=−64.0 (c = 0.630, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.81 (d, J=1.9 Hz, 1H; H-6), 4.45 (s, 1H; H-3), 4.11 (apparent t, J= 3.5 Hz; H-8), 2.99 (brm, 1H; H-1), 2.43 (m, 1H; H-2), 2.21 (dd, J=14.4, 3.9 Hz, 1H; H-9), 2.04 (dd, J=14.4, 3.2 Hz, 1H; H-9), 1.98 (s, 3H; H-15), 1.53 (s, 3H; H-13), 1.52 (s, 3H; C(CH_3)(CH_3)), 1.38 (s, 3H; C(CH_3)-(CH_3)), 1.20 (s, 3H; H-14), 0.12 (s, 9H; Si(CH_3)$_3$), 0.08 (s, 9H; Si(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.3 (C-12), 142.7 (C-4), 129.2 (C-5), 100.1 ((C(CH_3)(CH_3)), 80.0 (C-7), 79.5 (C-6), 79.2 (C-11), 77.7 (C-3), 76.9 (C-10), 67.2 (C-8), 55.0 (C-1), 45.2 (C-9), 36.7 (C-2), 30.5 ((C(CH_3)-(CH_3)), 23.5 ((C(CH_3)(CH_3)), 23.2 (C-14), 17.1 (C-13), 12.2 (C-15), 2.8, 2.7 (Si(CH_3)$_3$); IR (film): ν_{max} = 3431, 2953, 1792, 1372, 1251, 1191 cm^{-1}; ESI+ MS: m/z: calcd for $C_{24}H_{42}O_7Si_2Na$: 521.2367; found: 521.2372 $[M+Na]^+$.

Angelate ester 64: Angelic acid (50 mg, 50 μmol), 2,4,6-trichlorobenzoyl chloride (79 μL, 51 μmol) and triethylamine (70 μL, 51 μmol) were mixed in toluene (200 μL) at RT for 2 h. The mixture became cloudy and viscous and was then treated with allylic alcohol **63** (22 mg, 44 μmol) in toluene (200 μL) and was heated to 80 °C for 4 h. Saturated aqueous $NaHCO_3$ (3 mL) and water (3 mL) were added and the mixture was extracted into CH_2Cl_2 (3×10 mL). The combined extracts were dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography (silica gel, PE/Et_2O 1:1) to give the angelate as a clear oil (19 mg, 76%). R_f=0.14 (PE/Et_2O 1:1). The bis-TMS angelate (19 mg, 33 μmol) in THF (500 μL) was treated with TBAF (1 M in THF, 165 μL, 165 μmol) at RT and aged for 3 h. The mixture was partitioned between half-saturated aqueous $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organics were dried ($MgSO_4$), evaporated and purified by column chromatography (silica gel, PE/EtOAc 1:1) to give a clear oil (14 mg, 98%). R_f= 0.16 (PE/EtOAc 1:1); $[\alpha]_D$ = −0.825 (c = 1.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.12 (m, 1H; =CHCH_3), 5.86 (s, 1H; H-6), 5.45 (brm, 1H; H-3), 4.12 (brm, 1H; H-8), 3.42 (s, 1H; OH), 3.32 (brm, 1H; H-1), 2.67 (ddd, J=13.1, 7.4, 6.3 Hz, 1H; H-2), 2.29 (dd, J=14.5, 3.7 Hz, 1H; H-9), 2.07 (dd, J=14.5, 3.7 Hz, 1H; H-9), 1.99 (d, J=7.3 Hz, 3H; = CHCH_3), 1.92 (s, 3H; H-15), 1.90 (s, 3H; C(O)CCH_3), 1.59 (m, 1H; H-2), 1.56 (s, 3H; H-13), 1.54 (s, 3H; C(CH_3)(CH_3)), 1.42 (s, 3H; C(CH_3)-(CH_3)), 1.20 (s, 3H; H-14); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.0 (C-12), 168.3 (C=O angeloyl), 140.2 (=CHCH$_3$), 138.9 (C-5), 130.4 (C-4), 127.7 (C=CHCH$_3$), 100.7 ((C(CH_3)(CH_3)), 79.9 (C-3), 79.2 (C-11), 78.8 (C-6), 76.0 (C-7), 73.6 (C-10), 66.1 (C-8), 54.1 (C-1), 45.0 (C-9), 33.3 (C-2), 30.5 ((C(CH_3)(CH_3)), 23.6 ((C(CH_3)(CH_3)), 22.5 (C-14), 20.6 (C(O)CCH_3), 15.9 (C-13, =CHCH_3), 12.5 (C-15); IR (film): ν_{max} = 3420, 2925, 1775, 1687, 1455, 1383 cm^{-1}; ESI+ MS: m/z: calcd for $C_{23}H_{32}O_8SiNa$: 459.1995; found: 459.1996 $[M+Na]^+$.

Acetate 66: Isopropenyl acetate (100 μL, 909 μmol) in CH_2Cl_2 (300 μL) was treated with Amberlyst 15 resin (PS-pTsOH, 10 mg) and 4 Å molecular sieves (powdered, 10 mg) and aged for 1 h at RT. The angelate-diol **65** (14 mg, 32 μmol) in CH_2Cl_2 (300 μL) was then added to the resin suspension and the mixture was aged with gentle shaking for 16 h. The resin was removed by filtration and washed with CH_2Cl_2 (1 mL). The combined filtrates were evaporated to dryness and the residue was purified by column chromatography (silica gel, PE/EtOAc 2:1) to give a clear oil (10 mg, 68%). R_f=0.39 (PE/EtOAc 1:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.10 (apparent qd, J=7.2, 1.2 Hz, 1H; =CHCH$_3$), 5.85 (d, J=2.1 Hz, 1H; H-6), 5.57 (apparent t, J=6.8 Hz, 1H; H-3), 4.27 (m, 1H; H-8), 3.96 (m, 1H; H-1), 2.93 (dd, J=14.8, 4.6 Hz, 1H; H-9), 2.57 (ddd, J = 13.6, 7.6, 6.0 Hz, 1H; H-2), 2.43 (m, 2H; H-9, OH), 2.02 (apparent dd, J=7.2, 1.3 Hz; =CHCH_3), 1.95 (s, 3H; C(O)CH_3), 1.93 (s, 3H; H-15), 1.92 (d, J=1.3 Hz, 3H; C(O)CCH_3), 1.57 (s, 3H; H-13), 1.54 (s, 3H; C(CH_3)-(CH_3)), 1.42 (s, 3H; C(CH_3)(CH_3)), 1.38 (s, 3H; H-14); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.8 (C-12), 170.4 (C(O)CH$_3$), 167.7 (C=O angeloyl), 141.3 (=CHCH$_3$), 138.5 (C-5), 129.3 (C-4), 127.8 (C(O)CCH$_3$), 100.9 (C(CH_3)(CH_3)), 85.3 (C-10), 79.6 (C-3), 79.2 (C-11), 78.4 (C-6), 76.1 (C-7), 66.1 (C-8), 51.6 (C-1), 38.3 (C-9), 33.2 (C-2), 30.5 (C(CH_3)-(CH_3)), 23.6 (C(CH_3)(CH_3)), 22.4 (C(O)CH_3), 20.7 (C-14, C(O)CCH_3), 15.9, 15.8 (C-13, =CHCH_3), 12.6 (C-15); IR (film): ν_{max} = 3424, 2932, 1794, 1730, 1371, 1244 cm^{-1}; $[\alpha]_D$ = −43 (c = 0.18, $CHCl_3$); accurate mass analysis could not find the parent ion.

Trilobolide (2): A solution of the acetonide **66** (6 mg, 13 μmol) in MeOH (1 mL) was treated with 3 N HCl (75 μL) and heated at 40 °C until the reaction was complete by TLC (approximately 2 h). After cooling to RT, the reaction was quenched with half-saturated $NaHCO_3$ solution (1 mL) and extracted with CH_2Cl_2 (3×5 mL). The organics were dried ($MgSO_4$) and evaporated to dryness. The triol was dissolved in dry CH_2Cl_2 (0.5 mL) and treated with DMAP (2 mg) and (*S*)-2-methylbutyric anhydride (20 μL, 96 μmol, in 0.5 mL of CH_2Cl_2). The solution was stirred at RT until the triol was fully consumed (as observed by TLC, approximately 1 h) then 3 N HCl (0.5 mL) was added. The mixture was stirred for further 25 min, diluted with water (1 mL) and extracted with CH_2Cl_2 (3× 5 mL). The organics were dried ($MgSO_4$) and evaporated and the residue was purified by column chromatography (silica gel, PE/ethyl acetate 2:1) to obtain trilobolide as a clear oil (5 mg, 78% yield, 2 steps). R_f=0.23 (PE/ethyl acetate 2:1); $[\alpha]_D$ = −20 (c = 0.16, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$): δ = 6.14 (m, 1H; =CHCH$_3$), 5.73 (brs, 1H; H-6), 5.64 (m, 2H; H-3 H-8), 4.28 (brm, 1H; H-1), 3.07 (dd, J=14.8, 3.4 Hz, 1H; H-9), 2.62 (ddd, J=14.7, 8.5, 8.5 Hz, 1H; H-2), 2.38 (m, 1H; C-(CH_3)HCH$_2$).06 (m, 3H; =CHCH_3), 2.01 (s, 3H; C(O)CH$_3$), 1.96 (m, 6H; H-15, C(O)C(CH_3) =C), 1.54 (m, 2H; CH_2CH$_3$), 1.51 (s, 3H; H-13), 1.31 (s, 3H; H-14), 1.19 (m, 3H; C(CH_3)HCH$_2$), 0.94 (m, 3H; CH$_2$CH_3); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 175.2 (C-12), 174.8 (C=O 2-methylbutanoyl), 170.4 (C=O acetyl), 167.6 (C=O angeloyl), 144.4 (C-4), 138.6 (C(O)C=C), 130.5 (C-5), 127.7 (C(O)C=), 85.1 (C-10), 79.4 (C-3), 78.9, 78.6 (C-7, C-11), 77.4 (C-6), 66.5 (C-8), 51.3 (C-1), 41.4 (C(O)CHCH$_3$), 38.6 (C-9), 32.3 (C-2), 26.2 (CH$_2$CH$_3$), 22.4 (C=OCH$_3$), 22.0 (C-14), 20.7 (C(O)CCH_3), 16.4, 16.3 (C(O)CHCH$_3$, =CHCH_3), 15.9 (C-13), 13.2 (C-15), 11.6 (CH$_2$CH$_3$); IR (film): ν_{max} = 3442, 2923, 1790, 1734, 1713, 1459, 1381, 1239 cm^{-1}; ESI+ MS: m/z: calcd for $C_{27}H_{38}NaO_{10}$: 545.2363; found: 545.2361 $[M+Na]^+$.

Nortrilobolide (3): Prepared using the same procedure as described for trilobolide above, using butyric anhydride for the final acylation (3 mg, 72% over 2 steps). $[\alpha]_D$ = −43 (c = 0.18, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.12 (q, J=7.2 Hz, 1H; =CHCH$_3$), 5.71 (s, 1H; H-6), 5.61 (m, 2H; H-3, H-8), 4.21 (brm, 1H; H-1), 3.01 (dd, J=14.8, 3.2 Hz, 1H; H-9), 2.61 (m, 1H; H-2), 2.32 (dd, J=14.8, 4.0 Hz, 1H; H-9), 2.28 (m, 2H; C(O)CH_2CH$_2$), 2.02 (m, 3H; =CHCH_3), 1.97 (s, 3H; C(O)CH$_3$), 1.92 (s, 6H; H-15, C(O)CCH_3), 1.67 (m, 3H; H-2, C(O)CH$_2$CH_2), 1.51 (s, 3H; H-13), 1.26 (s, 3H; H-14), 0.86 (m, 3H; CH$_2$CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.0 (C-12), 172.3 (C=O 2-methylbutanoyl), 170.4 (C=OCH$_3$), 167.6 (C=O angeloyl), 144.2 (C-4), 138.4 (C(O)C=C), 130.6 (C-5), 127.8 (C(O)C=), 85.2 (C-10), 79.4 (C-3), 78.8, 78.6 (C-7, C-11), 77.4

(C-6), 66.4 (C-8), 51.3 (C-1), 38.6 (C-9), 36.5 (C(O)CH_2), 32.3 (C-2), 22.7 (C(O)CH_3), 22.4 (C(O)CH_2CH_2), 21.8 (C(O)CH_3), 20.6 (C(O)CCH_3), 18.0 (C-14), 16.4 (=$CHCH_3$), 15.8 (C-13), 13.7 (CH_2CH_3), 13.1 (C-15); IR (film): ν_{max} = 3447, 2923, 2853, 1789, 1712, 1458, 1370 cm^{-1}; ESI+ MS: *m/z*: calcd for $C_{26}H_{36}NaO_{10}$: 531.2206; found: 531.220 $[M+Na]^+$.

Thapsivillosin F (4): A solution of acetonide **66** (30 mg, 62.7 μmol) in MeOH (3.5 mL) was treated with 4 drops (200 μL) of 3 N HCl and heated at 40 °C for 2 h. After cooling down to RT, the reaction was quenched with 2 mL of half-saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (4×10 mL). The organics were dried (brine, $MgSO_4$), then evaporated. The obtained triol was dissolved, at RT in dry CH_2Cl_2 (2 mL), then catalytic DMAP and senecioic anhydride (11.4 mg, 62.7 μmol, in 0.5 mL of CH_2Cl_2) were added and the solution was stirred at RT for 2.5 h. 3 N HCl (0.2 mL) was added and the mixture was stirred for further 20 min before being diluted with water (3 mL)and extracted with CH_2Cl_2 (4×10 mL). The organics were dried (brine, $MgSO_4$) and evaporated the residue was purified by chromatography (PE/ethyl acetate 2:1 then 1:1) to obtain a white solid (18 mg, 60% over 2 steps). $[\alpha]_D$ = −35 (*c* = 0.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.10 (dq, *J* = 7, 2 Hz, 1H; =$CHCH_3$), 5.72 (d, *J* = 1, 1H; H-6), 5.62 (t, *J* = 1 Hz, 1H; =$CHCO_2$), 5.59 (m, 2H; H-3, H-8), 4.35 (br s, 1H; H-1), 3.10 (dd, *J* = 14.5, 3.5 Hz, 1H; H-9), 2.55 (m, 1H; H-2), 2.22 (dd, *J* = 14.5, 3.5 Hz, 1H; H-9), 2.17 (d, *J* = 1 Hz, 3H; =CH_3CH_3), 2.01 (dd, *J* = 7, 2 Hz, 3H; =$CHCH_3$), 1.96 (s, 3H; C(O)CCH_3), 1.90 (m, 9H; C-15, C(O)CH_3, =CH_3CH_3), 1.65 (m, 1H; H-2), 1.50 (s, 3H; H-13), 1.31 (s, 3H; H-14); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.2 (C-12), 170.8 (*C*(O)CH_3), 167.7 (C=O angeloyl), 165.15 (C=O senecioyl), 159.6 (=*C*CH_3CH_3), 144.0 (C-5), 138.3 (C-3), 78.9 (C-11), 78.8 (C-7), 77.5 (C-6), 66.4 (C-8), 50.9 (c-1), 38.4 (c-9), 32.1 (C-2), 27.5 (=CH_3CH_3), 22.3 (C(O)*C*H_3), 22.0 (C-14), 20.6 (C(O)CCH_3), 20.4 (=CH_3CH_3), 16.4 (C-13), 15.8 (=$CHCH_3$), 13.0 (C-15); IR (film): ν_{max} = 3429 (br OH), 2927 (C-H), 1770 (C=O), 1706 (C=O), 1648 cm^{-1} (C=C); ESI+ MS: *m/z*: calcd for $C_{27}H_{36}NaO_{10}$: 543.2206; found: 543.2145 $[M+Na]^+$.

Experimental procedures towards MOM derivative 75 from 61

Octanoate 68: DMAP (71.2 mL, 0.584 mmol) and octanoic anhydride (115.6 mg in 1.2 mL CH_2Cl_2) were added at RT to a solution of alcohol **61** (40 mg, 0.078 mmol) in CH_2Cl_2 (2.4 mL). The reaction mixture was stirred for 90 min and quenched by adding a saturated NH_4Cl solution (5 mL). The aqueous layer was extracted with Et_2O (4×10 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was submitted to flash chromatography (EtOAc/PE 1:20) to obtain **68** (47 mg, 94%) as a colourless oil. $[\alpha]_D$ = +8.7 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$): δ = 5.19 (d, *J* = 10.6 Hz, 1H; H-6), 5.07–5.06 (m, 1H; H-2), 4.13–4.12 (m, 1H; H-8), 2.66–2.56 (m, 1H; H-1), 2.51–2.47 (m, 2H; H-4 H-5), 2.35–2.30 (m, 2H; CH_2 octanoyl), 2.22 (dd, *J* = 14.6, 3.9 Hz, 1H; H-9), 2.13 (dd, *J* = 14.6, 3.9 Hz, 1H; H-9), 1.63–1.59 (m, 2H; CH_2 octanoyl), 1.56 (s, 3H; CH_3), 1.53 (s, 3H; CH_3), 1.41 (s, 3H; CH_3), 1.39 (s, 3H; CH_3), 1.33 (s, 3H; CH_3), 1.32–1.25 (m, 8H; CH_2 octanoyl), 0.88–0.86 (m, 3H; CH_3 octanoyl), 0.20, 0.14 (2×s, 18H; TMS); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 212.2 (C-3), 173.0 (C-12), 172.5 (CO octanoyl), 99.9 (*C*$(CH_3)(CH_3)$), 82.9 (C-6), 79.9, 79.1, 77.6 (C-7, C-10, C-11.), 77.0 (C-2), 66.1 (C-8), 52.3 (C-1), 47.7 (C-4), 45.1 (C-9), 42.0 (C-5), 33.7 (CH_2 octanoyl), 31.5 (CH_2 octanoyl), 30.3 (C(*C*H_3)(CH_3)), 28.9 (CH_2 octanoyl), 28.8 (CH_2 octanoyl), 26.0 (C-15), 24.8 (CH_2 octanoyl), 23.4 (C-17), 22.5 (CH_2 octanoyl), 17.9 (C(*C*H_3)(CH_3)), 14.0 (CH_3 octanoyl), 13.9 (C-11), 2.6 (TMS); IR (film): ν_{max} = 2955, 1793, 1761, 1734, 1372, 1284, 1253, 1193, 1155, 1127, 1111, 1033, 988, 868 cm^{-1}; accurate mass analysis could not find the parent ion.

MOM acetal 69: Alcohol **61** (88 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (1.8 mL) and treated with MOMCl (65 μL, 850 μmol), and Hünig's base (300 μL, 1.70 mmol) at RT for 12 h with stirring. The solution was the quenched by the addition of saturated $NaHCO_3$ solution, and the separated organic phase washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography (silica gel, PE/EtOAc 5:1) afforded the title compound (86 mg, 88%). $[\alpha]_D$ = +7.5 (*c* = 1.08, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.18 (d, *J* = 10.3 Hz, 1H, H-6), 4.68 (dd, *J* = 6.4, 6.4 Hz, 2H; OCH_2O), 4.31 (s, 1H; H-2), 4.14 (m, 1H; H-8), 3.40 (s, 3H; CH_3O), 2.56 (d, *J* = 9.8 Hz, 1H; H-1), 2.46 (dd, *J* = 9.9, 10.0 Hz; H-5), 2.38 (m, 1H; H-4), 2.37 (dd, *J* = 14.7, 3.9 Hz, 1H; H-9), 2.37 (dd, *J* = 14.7, 3.2 Hz, 1H; H-9), 1.57 (s, 3H; H-13), 1.54, 1.53 (2×s, 6H; C$(CH_3)(CH_3)$), 1.34 (d, *J* = 6.6 Hz, 3H; H-15), 1.24 (s, 3H; H-11), 0.22, 0.17 (2×s, 18H; Si$(CH_3)_3$); ^{13}C NMR (150 MHz, $CDCl_3$):δ = 216.7 (C-3), 173.2 (C-12), 127.8 (C-11), 100.3 (*C*$(CH_3)(CH_3)$), 94.1 (OCH_2O), 83.7 (C-6), 79.7 (C-2), 79.4, 77.3 (C-10, C-7), 66.2 (C-8), 55.5 (OCH_3), 53.7 (C-1), 48.1 (C-4), 46.0 (C-9), 42.8 (C-5), 30.4 (C-15), 23.4 (C-13), 17.7 (C(*C*H_3)(CH_3)), 16.2 (C(CH_3)(*C*H_3)), 2.8, 2.7 (2×Si$(CH_3)_3$); IR (film): ν_{max} = 2931, 2857, 1613, 1512, 1246, 1103, 1035, 821, 701 cm^{-1}; ESI+ MS: *m/z*: calcd for $C_{24}H_{42}O_8Si_2Na$: 581.2578; found: 581.2575 $[M+Na]^+$.

Alcohol 74: A solution of NaHMDS (0.38 mL of a 1.0 M solution in THF, 0.38 mmol) was added dropwise at −78 °C to a solution of ketone **69** (41 mg, 0.073 mmol) in THF (8 mL). The resulting solution was stirred at −78 °C for 30 min before warming to −20 °C and stirring for 1 h. After re-cooling to −78 °C, TMSCl (49 μL, 0.38 mmol) was added before stirring at −78 °C for 30 min, followed by warming to RT. The reaction mixture was then partitioned between saturated aqueous ammonium chloride solution (12 mL) and Et_2O (12 mL), the phases separated, the aqueous extracted with Et_2O (2×10 mL), the combined organics washed with saturated aqueous ammonium chloride solution (10 mL), dried ($MgSO_4$) and concentrated in vacuo to afford the intermediate TMS enol ether as a pale yellow oil which was immediately dissolved in CH_2Cl_2 (5.8 mL) and cooled to −78 °C. In a separate flask, phenylselenyl chloride (108 mg, 0.562 mmol) was dissolved in CH_2Cl_2 (4.0 mL) and cooled to −78 °C before being added to the TMS enol ether solution via cannula. After stirring at −78 °C for 2 h, saturated aqueous sodium thiosulfate solution was added and the reaction mixture was warmed to RT and partitioned between saturated aqueous $NaHCO_3$ solution (15 mL) and CH_2Cl_2 (10 mL). Separation of the phases, extraction of the aqueous with CH_2Cl_2 (3×10 mL), drying ($MgSO_4$), concentration in vacuo and filtration through a short plug of silica gel (ethyl acetate/PE 1:40 then 1:4) afforded the crude mixture of **70** and **71** (87:13 ratio by ^{1}H NMR) which were used directly without further purification. A stream of oxygen was bubbled through a solution of an 83:17 mixture of selenides **70** and **71** (derived from 0.073 mmol of ketone **69**) in CH_2Cl_2 (10 mL) 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 (0.6 mL) the reaction mixture was allowed to warm to RT and stirred for a further 30 min. Addition of saturated aqueous $NaHCO_3$ solution (15 mL), separation of the phases, extraction of the aqueous with Et_2O (3×10 mL), drying the combined organics ($MgSO_4$), concentration under reduced pressure and purification by flash chromatography (ethyl acetate/PE 1:20 then 1:13) afforded the title compound as a colourless foam (31 mg, 37% yield of **73** over 3 steps from ketone **69**). To a solution of enone **73** (7 mg, 0.013 mmol) in THF (1.5 mL) at RT was added sodium borohydride (2 mg, 0.083 mmol) before stirring at RT for 17 h. After this time, TLC analysis showed that the reaction was incomplete and so a second portion of sodium borohydride (2 mg, 0.083) was added before stirring for 2 h. Addition of saturated aqueous ammonium chloride solution (2 mL) and Et_2O (1 mL), stirring for 15 min, partitioning between further saturated aqueous ammonium chloride solution (10 mL) and Et_2O (10 mL), separation of the phases, extraction of the aqueous with Et_2O (3×5 mL), drying ($MgSO_4$) concentration in vacuo and purification by flash chromatography (1:30 then 2:3, ethyl acetate/petrol) afforded the title compound **74** as a colourless foam (7 mg, 99%). $[\alpha]_D$ = −66.1 (*c* = 0.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.68 (m, 1H; H-6), 4.83 (d, *J* = 6.0 Hz, 1H; OCH_2O), 4.63 (d, *J* = 6.0 Hz, 1H; OCH_2O), 4.36 (m, 1H; H-3), 4.23 (dd, *J* = 6.9, 3.9 Hz, 1H; H-2), 4.12 (m, 1H; H-8), 3.43 (s, 1H; OCH_3), 3.28 (m, 1H; H-1), 3.02 (d, *J* = 5.5 Hz, 1H; OH), 2.28 (dd, *J* = 14.5, 4.1 Hz, 1H; H-9), 2.07 (dd, *J* = 14.5, 3.1 Hz, 1H; H-9), 1.98 (s, 3H; H-15), 1.54 (s, 3H; C(*C*H_3)(CH_3)), 1.53 (s, 3H; H-13), 1.38 (s, 3H; C(CH_3)(*C*H_3)), 1.10 (s, 3H, 14-H), 0.22 (s, 9H; Si$(CH_3)_3$), 0.24 (s, 9H, Si$(CH_3)_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.4 (C-12), 142.3 (C-4), 127.1 (C-5), 100.4 (*C*$(CH_3)_2$), 96.6 (OCH_2O), 79.9 (C-11), 79.8 (C-6), 77.8 (C-3), 77.7 (C-2), 76.9 (C-10), 76.7 (C-7), 67.0 (C-8), 63.5 (C-1), 55.9 (OCH_3), 45.3 (C-9), 30.5 (C$(CH_3)(CH_3)$), 24.9 (C-14), 23.6 (C-13), 17.1 (C(CH_3)(*C*H_3)), 13.8 (C-15), 2.8 (Si$(CH_3)_3$), 2.7 (Si$(CH_3)_3$); IR (film):

ν_{max} = 3550 (br OH), 2952 (C-H), 1793 cm^{-1} (lactone C=O); ESI+ MS: *m/z*: calcd for $C_{26}H_{46}O_9NaSi_2$: 581.2578; found: 581.2603 $[M+Na]^+$.

Angelate ester 75: A solution of TBAF (0.2 mL of a 1.0 M solution in THF, 0.1 mmol) was added dropwise at 0 °C to a solution of alcohol **74** (9.5 mg, 0.017 mmol) in THF (0.7 mL). After warming the reaction mixture to RT, stirring was continued for 35 min before partitioning between saturated aqueous $NaHCO_3$ solution (10 mL) and ethyl acetate (10 mL). Separation of the phases, extraction of the aqueous with ethyl acetate (4×8 mL), drying ($MgSO_4$), concentration in vacuo and filtration through a short plug of silica gel (ethyl acetate/PE 4:1) afforded the intermediate triol which was used in the next step without further purification. In a separate flask, to a solution of angelic acid (90 mg, 0.896 mmol) in toluene (0.8 mL) at RT was added 2,4,6-trichlorobenzoyl chloride (140 μL, 0.896 mmol) and triethylamine (125 μL, 0.896 mmol). After stirring the resulting white suspension for 65 min, a solution of crude triols (derived from 0.017 mmol of alcohol **74**) was added via cannula before heating the reaction mixture to 75 °C for 48 h. Addition of saturated aqueous $NaHCO_3$ solution (15 mL) and ethyl acetate (15 mL), separation of the phases, extraction of the aqueous with ethyl acetate (2×5 mL), drying ($MgSO_4$), concentration in vacuo and purification by flash chromatography afforded the title compound **75** as a colourless oil (4 mg, 48% yield over 2 steps from alcohol **74**). $[\alpha]_D$ = −37.0 (*c* = 0.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.05 (m, 1H; =C*H*CH_3), 5.77 (m, 1H; H-6), 5.60 (d, *J* = 5.8 Hz, 1H; H-3), 4.75 (d, *J* = 6.6 Hz, 1H; OCH_2O), 4.55 (d, *J* = 6.6 Hz, 1H; OCH_2O), 4.32 (dd, *J* = 7.3, 5.9 Hz, 1H; H-2), 4.22 (dd, *J* = 4.3, 3.1 Hz, 1H; H-8), 3.38 (s, 3H; OCH_3), 2.00 (s, 3H; H-15), 1.96 (m, 3H; C*H*$_3$C=CH), 1.87 (m, 3H; =CHC*H*$_3$), 1.54 (s, 3H; (C(C*H*$_3$)(CH$_3$)), 1.53 (s, 3H; H-13), 1.42 (C(CH$_3$)(C*H*$_3$)), 1.25 (s, 3H; H-14); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.6 (C-12), 168.0 (C=O angeloyl), 137.7, 137.6 (C-4, =*C*HCH$_3$), 131.6 (C-5), 127.9 (*C*=CHCH$_3$), 100.7 (C(CH$_3$)(CH$_3$)), 97.1 (OCH_2O), 79.5 (C-11), 78.7 (C-6), 78.0 (C-3), 76.6 (C-7), 76.4 (C-2), 73.2 (C-10), 65.7 (C-8), 59.0 (C-1), 56.5 (OCH_3), 45.0 (C-9), 30.4 (C-(*C*H$_3$)(CH$_3$)), 23.7, 23.6 (C-14, (C(CH$_3$)(*C*H$_3$)), 20.6 (*C*H$_3$C=CH), 15.9 (=C*C*H$_3$), 15.8 (C-13), 14.7 (C-15); IR (film): ν_{max} = 3397 (br OH), 2926 (C-H), 1791 (C=O), 1711 cm^{-1} (C=O); ESI+ MS: *m/z*: calcd for $C_{25}H_{36}O_{10}Na$: 519.2206; found: 519.2216 $[M+Na]^+$.

Degradation and selective transformations of thapsigargin: **procedures** (also, see alternative procedures towards thapsigargin from **61**, see below)

Pentol 80: Triethylamine (950 μL, 6.82 mmol) was added to a solution of thapsigargin (**1**) (167 mg, 256 μmol) in methanol (17.0 mL) in a Smith vial. The vessel was flushed with Ar, sealed and heated (75 °C) for 48 h before being quenched by the addition of saturated ammonium chloride solution (60 mL). The crude mixture was diluted with water (10 mL), extracted with EtOAc (5×50 mL) and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and evaporated. Column chromatography (silica gel, EtOAc/PE 2:3 then EtOAc with 1% AcOH) afforded firstly the triol **79** (75.2 mg, 51%) then the pentol **80** (50.0 mg, 47%). NMR spectra in agreement with literature data: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.16 (br m, 1H; =C*H*CH$_3$), 5.76 (br s, 1H; H-6), 5.61 (br s, 1H; H-3), 4.29 (dd, *J* = 4.6, 4.5 Hz, 1H; H-2), 4.24 (dd, *J* = 3.4, 3.3 Hz, 1H; H-8), 3.35 (br s, 1H; H-1), 2.24 (dd, *J* = 14.5, 3.3 Hz, 1H; H-9), 2.00 (dd, *J* = 7.0, 1.3 Hz, 3H; =CHC*H*$_3$), 1.97 (m, 1H; H-9), 1.92 (br s, 3H; C*H*$_3$C=CHCH$_3$), 1.79 (s, 3H; H-15), 1.39 (s, 3H; H-13), 1.18 (s, 3H; H-14) (4 OH signals not observed); ^{13}C NMR (150 MHz, CD_3OD): δ = 176.0 (C-12), 167.9 (C-16), 137.7 (C-5), 137.1 (C-18), 131.7 (C-4), 127.6 (C-17), 86.3 (C-3), 78.9 (C-6), 78.8 (C-11), 77.7 (C-2), 77.5 (C-7), 72.9 (C-10), 68.6 (C-8), 61.4 (C-1), 48.1 (C-9), 23.3 (C-14), 19.3 (C-20), 14.9, 14.6 (C-13, C-19), 11.7 (C-15); ESI+ MS: *m/z*: calcd for $C_{20}H_{29}O_9Na$: 143.1812; found: 413.1799 $[M+H]^+$.

Tetrol 81: Acetonide **78** (14.0 mg, 22.6 μmol) was treated with sodium methoxide (1.0 mL, 500 μmol, 0.5 M in methanol) at RT for 6 h. The reaction was quenched with saturated ammonium chloride solution (20 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography (silica gel, EtOAc then EtOAc with 3% AcOH) afforded the tetrol (6.8 mg, 81%). $[\alpha]_D$ = −9.57 (*c* = 0.115, $CHCl_3$); ^{1}H NMR (600 MHz, CD_3OD): δ = 5.76 (br m, 1H; H-6), 4.26 (m, 2H; H-3, H-8), 4.03 (dd, *J* = 7.1, 6.3 Hz, 1H; H-2), 2.99 (m, 1H; H-1), 2.26 (dd, *J* = 14.8, 4.3 Hz, 1H; H-9), 1.95 (dd, *J* = 14.8, 5.1 Hz, 1H; H-9), 1.87 (s, 3H; H-15), 1.53 (s, 3H; C(C*H*$_3$)-(CH$_3$)), 1.46 (s, 3H; H-13), 1.37 (s, 3H; C(CH$_3$)(C*H*$_3$)), 1.23 (s, 3H; H-14); ^{13}C NMR (150 MHz, CD_3OD): δ = 173.8 (C-12), 138.3 (C-5), 125.8 (C-4), 100.3 (*C*(CH$_3$)(CH$_3$)), 82.7 (C-3), 80.8 (C-2), 79.3 (C-6), 79.2 (C-11), 75.4 (C-7), 73.2 (C-10), 65.9 (C-8), 58.3 (C-1), 44.6 (C-9), 29.4 (C-(*C*H$_3$)(CH$_3$)), 22.5 (C-14, C(CH$_3$)(*C*H$_3$)), 14.9 (C-13), 10.8 (C-15); IR (film): ν_{max} = 3357 (br OH), 2961 (C-H), 2923 (C-H), 2854 (C-H), 1774 cm^{-1} (C=O); ESI+ MS: *m/z*: calcd for $C_{18}H_{26}O_8Na$: 393.1525; found: 393.1520 $[M+Na]^+$.

Alcohol 92: Ozone was bubbled through a CH_2Cl_2 (10 mL) solution of thapsigargin (**1**) (20.0 mg, 30.8 μmol) at −78 °C for two minutes until the solution had turned pale blue. The solution was flushed with oxygen for a further 3 min and treated with pre-washed (methanol then CH_2Cl_2) polymer-supported triphenylphosphine (140 mg, 168 μmol, 1.2 mmol g^{-1}). The mixture was gradually warmed to RT, stirred for a further 18 h, then filtered and the resin washed thoroughly with CH_2Cl_2. Combined filtrates were evaporated under reduced pressure, dissolved in MeOH (5.0 mL) and treated with pyridine (400 μL) and water (250 μL). The resulting mixture was refluxed for 2 h 15 min, cooled, quenched with saturated ammonium chloride solution (30 mL) and extracted with EtOAc (3× 30 mL). Combined extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (silica gel, Et_2O/PE 1:1) afforded the C-3 alcohol as a colourless gum (9.3 mg, 53%). NMR spectra in agreement with literature data: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.62 (m, 2H; H-6, H-8), 4.87 (dd, *J* = 4.7, 3.3 Hz, 1H; H-2), 4.39 (m, 1H; H-3), 4.32 (m, 1H; H-1), 3.20 (dd, *J* = 14.8, 3.4 Hz, 1H; H-9), 2.30 (m, 2H; octanoyl CH_2), 2.24 (t, *J* = 7.5 Hz, 2H; butanoyl CH_2), 2.18 (dd, *J* = 14.8, 3.9 Hz, 1H; H-9), 1.92 (m, 3H; H-15), 1.88 (s, 3H; CH_3C=O), 1.63–1.57 (m, 4H; butanoyl CH_2, octanoyl CH_2), 1.45 (s, 3H; H-13), 1.35 (s, 3H; H-14), 1.32–1.25 (m, 8H; 4×octanoyl CH_2), 0.93 (t, *J* = 7.4 Hz, 3H; butanoyl CH_3), 0.85 (m, 3H; octanoyl CH_3) (3 OH signals not observed); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.8 (octanoyl C=O), 175.2 (C-12), 172.5 (butanoyl C=O), 170.3 (CH_3C=O), 144.3 (C-5), 126.5 (C-4), 84.6 (C-2), 84.6 (C-10), 83.7 (C-3), 78.63, 78.58 (C-7, C-11), 76.5 (C-6), 65.8 (C-8), 55.3 (C-1), 38.1 (C-9), 36.5 (butanoyl *C*H$_2$C=O), 34.1 (octanoyl *C*H$_2$C=O), 31.5 (octanoyl CH_2), 29.0 (octanoyl CH_2), 28.8 (octanoyl CH_2), 24.7 (octanoyl CH_2), 23.2 (C-14), 22.6 (octanoyl CH_2), 22.5 (*C*H$_3$C=O), 17.9 (C-18), 16.2 (C-13), 14.0 (octanoyl CH_3), 13.67 (butanoyl CH_3), 12.8 (C-15); ESI+ MS: *m/z*: calcd for $C_{29}H_{44}O_{11}Na$: 591.2781; found: 591.2801 $[M+Na]^+$.

Enone 93: Triol **92** (9.1 mg, 16 μmol) was dissolved in CH_2Cl_2 (1.0 mL) and treated with pyridine (1 drop) and Dess–Martin periodinane (6.8 mg, 16 μmol). The mixture was stirred at RT for 2 h and quenched with sodium thiosulfate solution (10 mL). The mixture was further diluted with $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (silica gel, Et_2O/PE 1:1 increasing to neat Et_2O) afforded the ketone as a colourless gum (7.0 mg, 77%). NMR spectra in agreement with literature data: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.84 (s, 1H; H-6), 5.69 (dd, *J* = 3.5, 3.8 Hz, 1H; H-8), 5.46 (d, *J* = 1.0 Hz, 1H; H-2), 4.52 (d, *J* = 1.0 Hz, 1H; H-1), 3.49 (dd, *J* = 14.8, 3.5 Hz, 1H; H-9), 2.36–2.29 (m, 5H; H-9, octanoyl CH_2C=O, butanoyl CH_2C=O), 2.02 (s, 3H; H-15), 1.96 (s, 3H; CH_3C=O), 1.62–1.57 (m, 4H; butanoyl CH_2, octanoyl CH_2), 1.53 (s, 3H; H-13), 1.40 (s, 3H; H-14), 1.30–1.27 (m, 8H; 4×octanoyl CH_2), 0.96 (t, *J* = 7.4 Hz, 3H; butanoyl CH_3), 0.88 (m, 3H; octanoyl CH_3.); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.2 (C-3), 174.0 (C-12), 172.7 (octanoyl C=O), 172.2 (butanoyl C=O), 170.4 (CH_3C=O), 155.7 (C-5), 142.3 (C-4), 83.5 (C-10), 79.0 (C-11), 78.4 (C-6), 77.7 (C-7), 73.0 (C-2), 65.8 (C-8), 51.8 (C-1), 38.7 (C-9), 36.4 (butanoyl CH_2), 33.8 (octanoyl CH_2), 31.6 (octanoyl CH_2), 29.6 (octanoyl CH_2), 28.9 (octanoyl CH_2), 24.6 (octanoyl CH_2), 22.9 (*C*H$_3$C=O), 22.6 (octanoyl CH_2), 22.5 (C-14), 17.9 (butanoyl CH_2), 16.5 (C-13), 14.0 (octanoyl CH_3), 13.6 (butanoyl CH_3), 10.2 (C-15); ESI+ MS: *m/z*: calcd for $C_{29}H_{42}O_{11}Na$: 589.2625; found: 589.2638 $[M+Na]^+$.

MOM acetal 82: A solution of triol **77** (5.4 mg, 11.9 μmol) and Hünig's base (40 μL, 230 μmol) in CH_2Cl_2 (800 μL) was treated sequentially with

MOMCl (15 μL, 197 μmol) and catalytic DMAP. The reaction was stirred at RT for 1.5 h, quenched with saturated ammonium chloride solution (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography (silica gel, EtOAc/PE 1:9 increasing to 1:1) afforded the title compound as a colourless gum (1.6 mg, 27%). $[\alpha]_D = -37.5$ ($c = 0.080$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 6.14$ (apparent q, $J = 7.2$, 1.3 Hz, 1H; =C*H*CH$_3$), 5.86 (brs, 1H; H-3), 5.82 (brs, 1H; H-6), 4.79 (d, $J = 6.8$ Hz, 1H; OCH$_2$O), 4.75 (d, $J = 6.8$ Hz, 1H; OCH$_2$O), 4.31 (dd, $J = 5.3$, 5.0 Hz, 1H; H-2), 4.24 (brs, 1H; H-8), 3.38 (s, H-22), 3.24 (brs, 1H, H-1), 2.22 (dd, $J = 14.5$, 4.2 Hz, 1H; H-9), 2.16 (dd, $J = 14.5$, 3.7 Hz, 1H; H-9), 2.03 (d, $J = 7.2$ Hz, 3H; =CHC*H*$_3$), 1.95 (brs, 3H; C(O)CCH$_3$), 1.85 (s, 3H; H-15), 1.56 (s, 6H; H-13, C(C*H*$_3$)(CH$_3$)), 1.43 (s, 3H, (C(CH$_3$)(C*H*$_3$)), 1.23 (s, 3H; H-14); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.6$ (C-12), 167.3 (*C*(O)C=C), 138.6 (=*C*HCH$_3$), 138.5 (C-5), 127.7 (C-4), 127.5 (C(O)*C*=), 100.8 (*C*(CH$_3$)$_2$), 96.9 (OCH$_2$O), 84.6 (C-2), 84.0 (C-3), 79.0 (C-11), 78.1 (C-6), 76.2 (C-7), 73.2 (C-10), 65.8 (C-8), 56.1 (C-1, OCH$_3$), 45.3 (C-9), 30.5 (C(*C*H$_3$)(CH$_3$)), 23.6 (C(CH$_3$)(*C*H$_3$)), 23.4 (C-14), 20.6 (C(O)CCH$_3$), 15.9 (C-13), 15.8 (=CH*C*H$_3$), 12.5 (C-15); IR (film): $\nu_{max} = 3394$ (br OH), 2924 (C-H), 2845 (C-H), 1793 (lactone C=O), 1713 cm^{-1} (angelate C=O); ESI+ MS: m/z: calcd for $C_{25}H_{36}O_{10}Na$: 519.2230; found: 519.2209 $[M+Na]^+$.

Experimental procedures towards thapsigargin (1) and thapsivillosin C (5) from 61

SEM acetal 84: To a solution of ketoalcohol **61** (460 mg, 0.89 mmol) in CH_2Cl_2 (4.1 mL) at 0°C was added diisopropylethyl amine (1.25 mL, 7.15 mmol), followed by SEMCl (0.47 mL, 2.68 mmol). The resulting solution was warmed to RT before addition of catalytic DMAP. After stirring for a further 24 h, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ solution (100 mL) and ethyl acetate (100 mL), the phases separated and the aqueous extracted with ethyl acetate (3× 50 mL). The combined organics were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography (Et_2O/PE 1:9) to afford the title compound **84** as a white foam (518 mg, 92%). $R_f = 0.67$ (ethyl acetate/PE 1:4); $[\alpha]_D = +8.2$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 5.17$ (d, $J = 10.2$ Hz, 1H; H-6), 4.68, 4.72 (2×d, $J = 6.5$ Hz, 1H; OCH$_2$O), 4.31 (s, 1H; H-2), 4.11 (m, 1H; H-8), 3.75 (m, 1H; SiCH$_2$C*H*HO), 3.58 (m, 1H; SiCH$_2$CH*H*O), 2.54 (d, $J = 9.1$ Hz, 1H; H-1), 2.44 (m, 1H; H-5), 2.34 (m, 1H; H-4), 2.23 (dd, $J = 14.7$, 3.9 Hz, 1H; H-9′), 2.09 (dd, $J = 14.7$, 3.1 Hz, 1H; H-9), 1.51, 1.56 (2×s, 3H; C-(CH$_3$)$_2$), 1.38 (s, 3H; H-13), 1.31 (d, $J = 6.9$ Hz, 3H; H-15), 1.22 (s, 3H; H-14), 0.94 (m, 2H; SiCH$_2$), 0.22 (s, 9H; Si(CH$_3$)$_3$), 0.16 (s, 9H; Si-(CH$_3$)$_3$), 0.00 (s, 9H; CH$_2$Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 216.4$ (C-3), 173.2 (C-12), 99.9 (*C*(CH$_3$)$_2$), 92.3 (OCH$_2$O), 83.7 (C-6), 79.7 (C-7), 79.4 (C-10), 77.5 (C-2), 76.6 (C-11), 66.2 (C-8), 65.3 (O*C*H$_2$CH$_2$Si), 53.6 (C-1), 48.0 (C-4), 46.1 (C-9), 42.8 (C-5), 30.4 (C-15), 26.5 (C-13), 17.9, 23.4 (2×C(*C*H$_3$)$_2$), 17.8 (SiCH$_2$), 16.3 (C-14), −1.5 (CH$_2$Si(*C*H$_3$)$_3$), 2.7 (2×Si(CH$_3$)$_3$); IR (film): $\nu_{max} = 2954$, 1794, 1747, 1385 1373, 1252, 1195, 1146, 1099, 1035, 1021, 1005, 988, 839 cm^{-1}; ESI+ MS: m/z: calcd for $C_{30}H_{56}O_9NaSi_3$: 667.3130; found: 667.3130 $[M+Na]^+$.

Enone 88: A solution of LiHMDS (2.0 mL of a 1.0 M solution in THF, 2.0 mmol) was added dropwise at −78°C to a solution of ketone **84** (256 mg, 0.40 mmol) in THF (10.0 mL). 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 (Et_2O/N_2) and a pre-cooled (−78°C) solution of phenylselenyl chloride (380 mg, 2.00 mmol) in THF (7.5 mL) 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 2.5 h before addition of pyridine (0.59 mL, 5.96 mmol) and transferring to an ice bath. After 10 min at 0°C, the reaction mixture was warmed to RT and saturated aqueous $NaHCO_3$ solution (20 mL) was added. Addition of CH_2Cl_2 (30 mL), separation of the phases, extraction of the aqueous with CH_2Cl_2 (3×15 mL), washing the combined organics with saturated aqueous $NaHCO_3$ solution (30 mL), drying ($MgSO_4$), concentration under reduced pressure and filtration through a short plug of silica gel (ethyl acetate/PE 1:50 then 1:10) afforded the title compounds (287 mg) as a pale amber foam in an 80:20 mixture of **85** to **86**, (containing 10% by mass of unreacted starting ketone **84**, as assessed by ^{1}H NMR). Note: The three component mixture had a common $R_f = 0.43$ (ethyl acetate/PE 1:7). This material was used without purification in the subsequent step. A stream of oxygen was bubbled through a solution of selenides **85**/**86** (287 mg, derived from 0.40 mmol of ketone **84**) in CH_2Cl_2 (35 mL) 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 mL) the reaction mixture was allowed to warm to RT and stirred for a further 2.5 h. Addition of saturated aqueous $NaHCO_3$ solution (30 mL), separation of the phases, extraction of the aqueous with CH_2Cl_2 (3×20 mL), drying ($MgSO_4$), concentration under reduced pressure and purification by flash chromatography (ethyl acetate/PE 1:20 then 1:13) afforded the title compound **88** as a colourless foam (153 mg, 60% over two steps), This followed the isolation of the clean *exo* double bonded compound **87** (26 mg, 10% over two steps) and in addition, a mixed *endo*/*exo* fraction (30 mg, approx. 1:1 ratio, 12% over two steps). $R_f = 0.33$ (ethyl acetate/PE 1:10); $[\alpha]_D = -17.9$ ($c = 0.35$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 5.96$ (s, 1H; H-6)), 5.00, 4.74 (2×d, $J = 6.0$ Hz, 1H; OCH$_2$O), 4.20 (dd, $J = 3.6$, 3.6 Hz, 1H; H-8), 4.17 (d, $J = 2.0$ Hz, 1H; H-2), 4.06 (m, 1H; SiCH$_2$C*H*HO), 3.58 (m, 1H; SiCH$_2$CH*H*O), 3.35 (d, $J = 2.0$ Hz, 1H; H-1), 2.36 (dd, $J = 14.6$, 3.6 Hz, 1H; H-9), 2.17 (dd, $J = 14.6$, 3.6 Hz, 1H; H-9), 1.97 (s, 3H; H-15), 1.58 (s, 3H; H-13), 1.54 (s, 3H; C(C*H*$_3$)CH$_3$), 1.41 (s, 3H; C(CH$_3$)C*H*$_3$), 1.18 (s, 3H; H-14), 0.99 (m, 2H; SiCH$_2$), 0.19 (s, 9H; Si(CH$_3$)$_3$), 0.15 (s, 9H; Si(CH$_3$)$_3$), 0.03 (s, 9H; CH$_2$Si(C*H*$_3$)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 205.5$ (C-3), 172.4 (C-12), 157.6 (C-4), 140.3 (C-5), 100.6 (*C*(CH$_3$)$_2$), 93.7 (OCH$_2$O), 80.4 (C-10), 79.4 (C-7), 78.6 (C-6), 76.4 (C-11), 75.3 (C-2), 66.8 (C-8), 65.5 (SiCH$_2$*C*H$_2$O), 59.3 (C-1), 45.3 (C-9), 30.5 (C(*C*H$_3$)CH$_3$), 24.5 (C-14), 23.5 (C(CH$_3$)*C*H$_3$), 18.0 (SiCH$_2$), 17.0 (C-13), 9.8 (C-15), 2.8 (Si(CH$_3$)$_3$), 2.7 (Si(CH$_3$)$_3$), −1.4 (CH$_2$Si(*C*H$_3$)$_3$); IR (film): $\nu_{max} = 2956$, 1800, 1721, 1383, 1254, 1191, 1144, 1123, 1066, 1028, 998, 840 cm^{-1}; ESI+ MS: m/z: calcd for $C_{30}H_{54}NaO_9Si_3$: 665.2973; found: 665.2989 $[M+Na]^+$.

Zinc borohydride (0.5 M in Et_2O): To a suspension of granular sodium borohydride (760 mg, 20.0 mmol) in dry Et_2O (10 mL) at 0°C (ice bath) was added a solution of zinc(II) chloride (10 mL of a 1.0 M solution in Et_2O, 10 mmol) dropwise. The suspension was then allowed to warm slowly to RT overnight. After a total of 3 d, 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 Et_2O), which was used directly by syringe-based removal of the supernatant, taking care to prevent inclusion of solid sodium chloride.

Allylic alcohol 91 and its C-3 epimer: To a solution of enone **88** (90 mg, 0.139 mmol) in dry Et_2O (5.7 mL) at −29°C was added a pre-cooled solution of zinc borohydride (10.0 mL of an 0.5 M solution in Et_2O, 5.70 mmol) at −29°C via cannula. After stirring the solution at −29°C for a further 2.5 h, a further quantity of zinc borohydride solution was added (1.4 mL of an 0.5 M solution in Et_2O, 0.80 mmol) and stirring continued for a further 30 min to ensure complete reaction. A solution of TBAF (12.8 mL of a 1.0 M solution in THF, 12.8 mmol) was then added and the resulting vigorously stirred solution was warmed to RT. After 30 min at RT, ethyl acetate (85 mL) and an aqueous solution of tetrasodium EDTA (85 mL, 30% w/w) were added and the biphasic system vigorously stirred at RT for 2 h. The phases were separated, the aqueous phase extracted with ethyl acetate (3×50 mL), the combined organics dried (Na_2SO_4) and concentrated to approximately 10 mL. After addition of petrol (10 mL), the resulting solution was loaded directly onto a silica column, eluting with petrol, followed by ethyl acetate/PE 1:2 to afford first the title compound **91** as a colourless oil (56 mg, 80%) [followed by a quantity of the C-3 epimeric compound (7 mg, 10%) on changing to ethyl acetate/PE 2:1].

compound: **91**: $R_f = 0.57$ (ethyl acetate/PE 5:1); $[\alpha]_D = -5.3$ ($c = 0.47$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 5.79$ (s, 1H; H-6)), 4.82, 4.86 (2×d, $J = 6.2$ Hz, 1H; OCH$_2$O), 4.40 (brm, 1H; H-3), 4.20 (m, 1H; H-8), 3.95 (brs, 1H; OH), 3.88 (m, 1H; SiCH$_2$C*H*HO), 3.83 (dd, $J = 15.7$, 14.2 Hz, 1H; H-2), 3.57 (m, 1H; SiCH$_2$CH*H*O), 3.21 (brs, 1H; OH), 3.10

(m, 1H; H-1), 2.18 (dd, J=15.1, 4.2 Hz, 1H; H-9′), 2.10 (dd, J=15.1, 2.9 Hz, 1H; H-9), 1.98 (s, 3H; H-15), 1.54 (s, 6H; C(CH_3)$_2$), 1.41 (s, 3H; H-13), 1.25 (s, 3H; H-14), 1.03 (ddd, J=11.5, 11.5, 5.9 Hz, 1H; SiC*H*H), 0.95 (ddd, J=11.5, 11.5, 5.4 Hz, 1H; SiCH*H*), 0.03 (s, 9H; SiC(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.7 (C-12), 140.7 (C-4), 123.8 (C-5), 100.7 (*C*(CH_3)$_2$), 95.6 (OCH_2O), 90.9 (C-2), 81.4 (C-3), 78.9 (C-11), 78.6 (C-6), 76.2 (C-10), 73.5 (C-7), 66.5 (O*C*H$_2$CH$_2$Si), 65.7 (C-8), 56.8 (C-1), 45.1 (C-9), 30.4 (C-13), 23.6 (C(*C*H$_3$)(CH$_3$)), 23.5 (C-14), 18.0 (OCH$_2$*C*H$_2$Si), 16.0 (C(CH$_3$)(*C*H$_3$)), 12.3 (C-15), −1.5 (Si(CH_3)$_3$); IR (film): ν_{max} = 3436, 3362, 2944, 1790, 1383, 1371, 1251, 1196, 1111, 1010, 857 cm^{-1}; ESI+ MS: m/z: calcd for $C_{24}H_{40}O_9SiNa$: 523.2339; found: 523.2349 [M+Na]$^+$.

C-3 epimer of 91: R_f=0.39 (ethyl acetate/PE 5:1); $[\alpha]_D^{25}$ = −74.5 (c = 0.35, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.73 (s, 1H; H-6)), 4.76, 4.83 (2×d, J=6.2 Hz, 1H; OCH_2O), 4.29 (d, J=5.4 Hz, 1H; H-2), 4.18 (m, 1H; H-8), 4.12 (m, 1H; H-3), 4.00 (s, 1H; OH), 3.68 (m, 2H; SiCH$_2$C*H*$_2$O), 3.40 (m, 1H; H-1), 3.35 (brs, 1H; OH), 3.18 (s, 1H; OH), 2.23 (dd, J=14.9, 4.1 Hz, 1H; H-9′), 2.06 (dd, J=14.9, 2.7 Hz, 1H; H-9), 2.02 (s, 3H; H-15), 1.52, 1.53 (2×s, 3H; C(CH_3)$_2$), 1.39 (s, 3H; H-13), 1.17 (s, 3H; H-14), 0.97 (m, 2H; SiCH_2), 0.04 (s, 9H; SiC(CH_3)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.9 (C-12), 140.7 (C-4), 128.7 (C-5), 100.6 (*C*(CH_3)$_2$), 95.3 (OCH_2O), 79.8 (C-2), 79.2 (C-3), 78.5 (C-11), 77.6 (C-6), 76.1 (C-10), 73.3 (C-7), 66.6 (O*C*H$_2$CH$_2$Si), 65.7 (C-8), 58.6 (C-1), 45.5 (C-9), 30.5 (C-13), 23.6 (C(*C*H$_3$)(CH$_3$)), 23.2 (C-14), 16.1 (OCH$_2$*C*H$_2$Si), 14.7 (C(CH$_3$)(*C*H$_3$)), 14.1 (C-15), −1.5 (Si(CH_3)$_3$); IR (film): ν_{max} = 3379, 3225, 2947, 1791, 1381, 1250, 1111, 1057, 1016, 860 cm^{-1}; ESI+ MS: m/z: calcd for $C_{24}H_{40}O_9SiNa$: 523.2339; found: 523.2354 [M+Na]$^+$.

Mixed anhydride 96: To a solution of 2,4,6-trichlorobenzoyl chloride (5.25 mL, 33.60 mmol) in toluene (6.7 mL) at RT was added a pre-mixed solution of angelic acid (336 mg, 3.36 mmol) and triethylamine (0.47 mL, 3.36 mmol) in toluene (16.0 mL), 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 Et_2O (200 mL) to cause precipitation of further triethylamine hydrochloride, filtered, and the resulting solution concentrated under reduced pressure until ca. 10 mL toluene remained. Purification of the reaction mixture by flash chromatography (ethyl acetate/PE 1:80) afforded the title compound as a white crystalline solid (480 mg, 48%). M.p. 66–68°C; R_f=0.42 (ethyl acetate/PE 1:20); ^{1}H NMR (600 MHz, $CDCl_3$):δ = 7.38 (s, 2H; 2×Ar-H)), 6.43 (m, 1H; =C(*H*)CH$_3$), 2.08 (m, 3H; =C(H)C*H*$_3$), 1.97 (brm, 3H; C(O)C(CH$_3$)); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 160.9 (*C*(O)CCH$_3$), 159.4 (PhC=O), 145.8 (=*C*(H)CH$_3$), 136.9 (C(O)*C*CH$_3$), 130.9 (Ar-C), 128.3×2 (2×Ar-C), 125.9 (Ar-C), 20.1 (C(O)C*C*H$_3$), 16.3 (=C(H)*C*H$_3$); IR (film): ν_{max} = 1798, 1738, 1637, 1577, 1549, 1436, 1370, 1212, 1071, 857, 820 cm^{-1} [extensive attempts were made, but mass spectral analysis was not successful for this compound].

Angelate ester 90: Solid $NaHCO_3$ (12.0 mg, 0.143 mmol) was added at RT to a solution of the C-3 epimer of **91** (7.0 mg, 0.014 mmol) in toluene (0.4 mL). A solution of mixed anhydride **96** (22.0 mg, 0.070 mmol) in toluene (0.5 mL) was added before heating to 80°C for 26 h. Further solid $NaHCO_3$ (12.0 mg, 0.143 mmol) and solid mixed anhydride **96** (22.0 mg, 0.070 mmol) were added before heating to 80°C for a further 28 h. Cooling to RT, addition of saturated aqueous $NaHCO_3$ solution (15 mL) and ethyl acetate (15 mL), separation of the phases, extraction of the aqueous with ethyl acetate (3×10 mL), drying the combined organics ($MgSO_4$), concentration under reduced pressure and flash chromatography (ethyl acetate/PE 1:50 then 1:2) afforded the title compound **90** as a colourless oil (7.9 mg, 98%). R_f=0.37 (ethyl acetate/PE 1:1); $[\alpha]_D$ = −125.0 (c = 0.24, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.05 (q, J=7.1 Hz, 1H; =C*H*CH$_3$)), 5.77 (brm, 1H; H-6), 5.60 (d, J=5.9 Hz, 1H; H-3), 4.63, 4.76 (d, J=6.6 Hz, each 1H; OCH_2O), 4.33 (dd, J=6.9, 5.9 Hz, 1H; H-2), 4.22 (m, 1H; H-8), 3.75–3.90 (brs, 1H; OH), 3.72 (m, 1H; SiCH$_2$C*H*HO), 3.53 (m, 1H; SiCH$_2$CH*H*O), 3.40 (brm, 1H; H-1), 2.26 (dd, J=15.2, 4.0 Hz, 1H; H-9′), 2.12 (dd, J=15.2, 2.7 Hz, 1H; H-9), 1.99 (s, 3H; H-15), 1.95 (d, J=7.1 Hz, 3H; =C(H)C*H*$_3$), 1.89 (s, 3H; C(O)C(CH$_3$)), 1.54 (s, 6H; H-13, C(C*H*$_3$)(CH$_3$)), 1.42 (s, 3H; C(CH$_3$)(C*H*$_3$)), 1.24 (s, 3H; H-14), 0.94 (m, 1H; SiC*H*H), 0.88 (m, 1H; SiCH*H*), 0.00 (s, 9H; SiC(CH$_3$)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.6 (C-12), 168.1 (OC(O)), 137.6 (C-4), 137.5 (=*C*(H)CH$_3$), 131.6 (C-5), 128.0 (*C*=C(H)CH$_3$), 100.7 (*C*(CH_3)$_2$), 95.2 (OCH_2O), 78.9 (C-11), 78.6 (C-6), 78.1 (C-3), 76.5 (C-2), 76.3 (C-7), 73.2 (C-10), 66.5 (O*C*H$_2$CH$_2$Si), 65.8 (C-8), 59.0 (C-1), 44.9 (C-9), 30.4 (C(*C*H$_3$)CH$_3$), 23.8 (C-14), 23.6 (C(CH$_3$)*C*H$_3$), 20.6 (C(O)C-(*C*H$_3$)), 18.1 (SiCH$_2$), 15.9 (=C(H)*C*H$_3$), 15.8 (C-13), 14.7 (C-15), −1.5 (Si(CH_3)$_3$); IR (film): ν_{max} = 3453, 2948, 2925, 1795, 1713, 1698, 1383, 1252, 1229, 1193, 1154, 1110, 1056, 997, 859, 837 cm^{-1}; ESI+ MS: m/z: calcd for $C_{29}H_{46}NaO_{10}Si$: 605.2758; found: 605.2759 [M+Na]$^+$.

Angelate ester 83: *Procedure A:* DMAP (1.0 mg, 8.2 μmol) was added to a solution of the triol **77** (8.5 mg, 18.8 μmol), SEMCl (4.0 μL, 22.5 μmol) and Hünig's base (10.0 μL, 56.0 μmol) in CH_2Cl_2 (1.25 mL). After stirring at RT for 48 h, the reaction was quenched by the addition of saturated ammonium chloride solution (20 mL) and extracted with EtOAc (3× 20 mL). The combined organic phases were washed with brine (30 mL), dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (silica gel, EtOAc/PE 2:3) afforded the SEM ether as a pale yellow gum (7.8 mg, 71%).

Procedure B: Solid $NaHCO_3$ (55 mg, 0.650 mmol) was added at RT to a solution of **91** (65 mg, 0.130 mmol) in toluene (0.4 mL). A solution of mixed anhydride **24** (120 mg, 0.390 mmol) in toluene (0.5 mL) was added before heating to 80°C for 42 h. Further solid $NaHCO_3$ (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 RT, addition of saturated aqueous $NaHCO_3$ solution (20 mL) and ethyl acetate (20 mL), separation of the phases, extraction of the aqueous with ethyl acetate (3×15 mL), drying the combined organics ($MgSO_4$), concentration under reduced pressure and flash chromatography (ethyl acetate/PE 1:50, 1:2 then 2:1) afforded the title compound **83** as a colourless oil (39 mg, 52%) [followed by a quantity of unreacted triol **91** (4 mg, 6%)]. R_f=0.29 (ethyl acetate/PE 1:1); $[\alpha]_D$ = −14.9 (c = 0.30, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.14 (m, 1H; =C*H*CH$_3$)), 5.83 (brm, 1H; H-3), 5.80 (brm, 1H; H-6), 4.77, 4.82 (2×d, J=6.9 Hz, 1H; OCH_2O), 4.30 (dd, J=5.1, 5.1 Hz, 1H; H-2), 4.23 (m, 1H; H-8), 3.70 (m, 1H; SiCH$_2$C*H*HO), 3.58 (m, 1H; SiCH$_2$CH*H*O), 3.44 (brs, 1H; OH), 3.27 (brm, 1H; H-1), 2.22 (dd, J=15.0, 4.4 Hz, 1H; H-9′), 2.12 (dd, J=15.0, 2.7 Hz, 1H; H-9), 2.02 (m, 3H; =C(H)C*H*$_3$), 1.87 (s, 3H; C(O)C(CH$_3$)), 1.83 (s, 3H; H-15), 1.55 (s, 3H; H-13), 1.42, 1.54 (2×s, 3H; C(CH_3)$_2$), 1.22 (s, 3H; H-14), 0.95 (m, 1H; SiC*H*H), 0.89 (m, 1H; SiCH*H*), 0.00 (s, 9H; SiC(CH$_3$)$_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.7 (C-12), 167.2 (OC(O)), 138.9 (=*C*(H)CH$_3$), 138.3 (C-5), 128.1 (C-4), 127.5 (*C*=C(H)CH$_3$), 100.8 (*C*(CH_3)$_2$), 95.2 (OCH_2O), 84.5 (C-2), 84.3 (C-3), 79.1 (C-11), 78.1 (C-6), 76.1 (C-7), 73.2 (C-10), 66.1 (O*C*H$_2$CH$_2$Si), 65.8 (C-8), 59.9 (C-1), 45.2 (C-9), 30.5 (C(*C*H$_3$)CH$_3$), 23.6 (C(CH$_3$)*C*H$_3$), 23.5 (C-14), 20.6 (C(O)C*C*H$_3$), 17.9 (SiCH$_2$), 15.9 (=C(H)*C*H$_3$), 15.8 (C-13), 12.5 (C-15), −1.5 (Si(CH_3)$_3$); IR (film): ν_{max} = 3441, 2950, 2922, 1794, 1717, 1383, 1251, 1229, 1156, 1130, 1109, 1058, 1018, 998, 838 cm^{-1}; ESI+ MS: m/z: calcd for $C_{29}H_{46}NaO_{10}Si$: 605.2758; found: 605.2760 [M+Na]$^+$.

Triol 77: *Procedure A: p*-Toluenesulfonic acid (15 mg, 87 μmol) was added to a solution of pentol **80** (25 mg, 606 μmol) in acetone (500 μL) and 2,2-dimethoxypropane (3.0 mL). After 20 min at RT, the reaction was quenched with saturated $NaHCO_3$ solution (30 mL), and extracted with EtOAc (3×30 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography (silica gel, EtOAc/PE 1:1 to 4:1) afforded the acetonide as a colourless gum (18.3 mg, 67%).

Procedure B: A methanolic solution (1.0 mL) of acetonide **78** (10.9 mg, 17.6 μmol) was treated with triethylamine (50 μL) and stirred at 75°C for 8 h. At this point TLC showed only a trace of product formation; the reaction was heated to 95°C and stirred for a further 24 h. There was little change by TLC: the reaction was cooled, quenched with saturated ammonium chloride solution (20 mL) and extracted with EtOAc (3× 20 mL). The combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$ and evaporated under reduced pressure. Column chromatography (silica gel, EtOAc/PE 1:1) afforded the triol (1.1 mg, 11%).

Procedure C: Solid K_2CO_3 (398 mg, 2.880 mmol), $MgBr_2{\cdot}Et_2O$ (390 mg, 1.509 mmol) and *n*-butane thiol (160 μL, 1.509 mmol) were added at RT to a solution of SEM-ether **83** (40 mg, 0.069 mmol) in dry Et_2O (7.5 mL).

The resulting heterogeneous mixture was vigorously stirred for 30 min. Partitioning between ethyl acetate (30 mL) and water (30 mL), separation of the phases, extraction of the aqueous with ethyl acetate (3× 20 mL), drying the combined organics ($MgSO_4$) and purification by flash chromatography (ethyl acetate/PE 1:1) afforded the title compound **77** as a white foam (26 mg, 84%). R_f=0.21 (ethyl acetate/PE 4:1); $[\alpha]_D$ = −106.0 (c = 0.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.05 (q, J= 7.2 Hz, 1H; =C*H*CH_3), 5.77 (brm, 1H; H-6), 5.37 (brm, 1H; H-3), 4.24 (m, 2H; H-2, H-8), 3.60–3.95 (brs, 1H; OH), 3.26 (brm, 1H; H-1), 2.28 (dd, J=14.9, 4.0 Hz, 1H; H-9), 2.07 (dd, J=14.9, 2.1 Hz, 1H; H-9), 2.03 (d, J=7.2 Hz, 3H; =C(H)C*H*$_3$), 1.92 (s, 6H; H-15, C(O)CC*H*$_3$), 1.54 (s, 3H; H-13), 1.53 (s, 3H; C(C*H*$_3$)(CH$_3$)), 1.40 (s, 3H; C(CH$_3$)(C*H*$_3$)), 1.22 (s, 3H; H-14); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.0 (C-12), 169.6 (OC(O)), 140.5 (=*C*(H)CH$_3$), 136.0 (C-5), 128.7 (C-4), 127.1 (*C*=C(H)CH$_3$), 100.7 (*C*(CH$_3$)$_2$), 87.9 (C-3), 79.3 (C-2), 79.1 (C-11), 78.4 (C-6), 76.1 (C-7), 73.6 (C-10), 65.8 (C-8), 59.6 (C-1), 44.9 (C-9), 30.5 (C-(*C*H$_3$)CH$_3$), 23.6 (C(CH$_3$)*C*H$_3$), 23.5 (C-14), 20.5 (C(O)C*C*H$_3$), 16.0 (=C(H)*C*H$_3$), 15.9 (C-13), 12.6 (C-15); IR (film): ν_{max} = 3439, 3423, 2994, 2929, 1777, 1697, 1384, 1258, 1231, 1198, 1158, 1134, 1108, 998, 733 cm^{-1}; ESI+ MS: m/z: calcd for $C_{23}H_{32}NaO_9$: 475.1944; found: 475.1938 $[M+Na]^+$.

Octanoate 97: A solution of octanoic anhydride (23.0 mg, 0.085 mmol) in CH_2Cl_2 (1.0 mL) and catalytic DMAP were added at RT to a solution of triol **77** (24.6 mg, 0.054 mmol) in CH_2Cl_2 (3.5 mL). 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 mL) and ethyl acetate (15 mL), separation of the phases, extraction of the aqueous with ethyl acetate (3× 10 mL), drying the combined organics ($MgSO_4$), concentration under reduced pressure and purification by flash chromatography (ethyl acetate/PE 1:4 then 1:1) afforded the title compound **97** as a colourless oil (27.0 mg, 86%). R_f=0.66 (ethyl acetate/PE 4:1); $[\alpha]_D$ = −16.0 (c = 0.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.12 (q, J=7.0 Hz, 1H; = C*H*CH_3), 5.78 (brm, 2H; H-3, H-6), 5.37 (dd, J=4.3, 4.3 Hz, 1H; H-2), 4.23 (brm, 1H; H-8), 3.38 (brm, 1H; H-1), 2.89 (brs, 1H; OH), 2.33 (m, 2H; C(O)CH$_2$ octanoyl), 2.24 (dd, J=15.1, 4.1 Hz, 1H; H-9), 2.02 (dd, J=15.1, 1.8 Hz, 1H; H-9), 1.97 (d, J=7.0 Hz, 3H; =C(H)C*H*$_3$), 1.90 (s, 3H; C(O)CCH$_3$), 1.87 (s, 3H; H-15), 1.60 (m, 2H; C(O)CH$_2$C*H*$_2$ octanoyl), 1.54 (s, 3H; C(C*H*$_3$)(CH$_3$)), 1.53 (s, 3H; H-13), 1.41 (s, 3H; C(CH$_3$)-(C*H*$_3$)), 1.24–1.28 (m, 8H; CH$_3$(C*H*$_2$)$_4$ octanoyl), 1.24 (s, 3H; H-14), 0.87 (t, J=6.8 Hz, 3H; CH$_3$ octanoyl); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.7 (C-12), 172.8 (C=O octanoyl), 167.4 (O*C*(O)C=), 139.1 (=*C*(H)CH$_3$), 137.6 (C-5), 129.4 (C-4), 127.3 (*C*=C(H)CH$_3$), 100.9 (*C*-(CH$_3$)$_2$), 83.4 (C-3), 79.1 (C-11), 78.7 (C-2), 77.9 (C-6), 76.0 (C-7), 72.9 (C-10), 65.8 (C-8), 59.9 (C-1), 44.3 (C-9), 34.4 (OC(O)*C*H$_2$ octanoyl), 31.6 (CH$_2$ octanoyl), 30.5 (C(*C*H$_3$)(CH$_3$)), 29.0 (CH$_2$ octanoyl), 28.9 (C-14), 24.7 (OC(O)CH$_2$*C*H$_2$ octanoyl), 24.0 (CH$_2$ octanoyl), 23.6 (C(CH$_3$)-(*C*H$_3$)), 22.6 (CH$_2$ octanoyl), 20.5 (C(O)C*C*H$_3$), 15.9 (=C(H)*C*H$_3$), 15.8 (C-13), 14.0 (CH$_3$ octanoyl), 12.5 (C-15); IR (film): ν_{max} = 3428, 2928, 2858, 1796, 1778, 1713, 1457, 1381, 1256, 1227, 1151, 1133, 1100, 1043, 996, 845 cm^{-1}; ESI+ MS: m/z: calcd for $C_{31}H_{46}NaO_{10}$: 601.2989; found: 601.2991 $[M+Na]^+$.

Acetonide 78: *Procedure A:* *p*-Toluenesulfonic acid (12 mg, 70 μmol) was added to a stirring solution of triol **79** (28 mg, 482 μmol) in acetone (400 μL) and 2,2-dimethoxypropane (2.5 mL). After 1 h at RT the reaction was quenched by the addition of $NaHCO_3$ solution (30 mL) and extracted with EtOAc (3×30 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography (silica gel, Et_2O/PE 3:7 increasing to 1:1) afforded the acetonide as a white solid (27.1 mg, 91%).

Procedure B: *p*-Toluenesulfonic acid monohydrate (22.0 mg, 0.130 mmol) was added at RT to a solution of diol **97** (23.5 mg, 0.041 mmol) in isopropenyl acetate (2.0 mL). After stirring for 1 h 45 min, saturated aqueous $NaHCO_3$ solution (15 mL) and ethyl acetate (15 mL) were added. The phases were separated and the aqueous extracted with ethyl acetate (3× 10 mL), the combined organics dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography (ethyl acetate/PE 1:10, 1:5 then 3:1) to afford the title compound **78** as a colourless oil (25.0 mg, quant.). R_f=0.65 (ethyl acetate/PE 1:1); $[\alpha]_D$ = −33.7 (c 0.41, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.09 (m, 1H; =C*H*CH_3), 5.77 (brm, 1H; H-6), 5.73 (brm, 1H; H-3), 5.48 (dd, J=4.6, 4.6 Hz, 1H; H-2), 4.27 (m, 1H; H-8), 3.95 (brm, 1H; H-1), 3.30 (brs, 1H; OH), 2.64 (dd, J=14.7, 2.7 Hz, 1H; H-9), 2.30 (m, 2H; C(O)CH$_2$ octanoyl), 2.24 (dd, J=14.7, 4.5 Hz, 1H; H-9), 1.97 (m, 3H; =C(H)C*H*$_3$), 1.91 (brm, 3H; C(O)CCH$_3$), 1.87 (s, 6H; H-15, C(O)CH$_3$), 1.59 (m, 2H; C(O)CH$_2$C*H*$_2$ octanoyl), 1.54 (s, 3H; H-13), 1.53 (s, 3H; C(C*H*$_3$)(CH$_3$)), 1.47 (s, 3H; H-14), 1.42 (s, 3H; C(CH$_3$)(C*H*$_3$)), 1.22–1.34 (m, 8H; CH$_3$(C*H*$_2$)$_4$ octanoyl), 0.87 (t, J=6.8 Hz, 3H; CH$_3$ octanoyl); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.9 (C-12), 172.6 (C=O octanoyl), 170.4 (*C*(O)CH$_3$), 167.4 (O*C*(O)C=), 138.7 (=*C*(H)CH$_3$), 138.6 (C-5), 128.5 (C-4), 127.5 (*C*=C(H)CH$_3$), 101.1 (*C*(CH$_3$)$_2$), 84.7 (C-10), 84.0 (C-3), 79.4 (C-11), 78.0 (C-2), 77.7 (C-6), 76.0 (C-7), 65.8 (C-8), 57.3 (C-1), 38.0 (C-9), 34.3 (OC(O)*C*H$_2$ octanoyl), 31.6 (CH$_2$ octanoyl), 30.4 (C(*C*H$_3$)(CH$_3$)), 29.1 (CH$_2$ octanoyl), 28.9 (CH$_2$ octanoyl), 24.7 (OC(O)CH$_2$*C*H$_2$ octanoyl), 23.6 (C(CH$_3$)(*C*H$_3$)), 22.6 (CH$_2$ octanoyl), 21.2 (C-14), 20.5 (C(O)C*C*H$_3$), 15.8 (=C(H)*C*H$_3$), 15.7 (C-13), 14.0 (CH$_3$ octanoyl), 12.6 (C-15); IR (film): ν_{max} = 3438, 2930, 2857, 1797, 1775, 1738, 1457, 1441, 1372, 1237, 1188, 1160, 1137, 1101, 1001 cm^{-1}; ESI+ MS: m/z: calcd for $C_{33}H_{48}NaO_{11}$: 643.3094; found: 643.3096 $[M+Na]^+$.

O-8 Debutanoyl thapsigargin 79: *Procedure A:* See the formation of **80** via the degradation of **1** (see above).

Procedure B: Triethylamine (50 μL, 359 μmol) was added to a solution of thapsigargin (**1**) (11.5 mg, 17.7 μmol) in methanol (1.0 mL). The resulting mixture was stirred at RT for 6 h 30 min before quenching by the addition of saturated ammonium chloride solution (20 mL). The crude mixture was extracted with EtOAc (5×15 mL) and the combined organic layers washed with brine (50 mL), dried ($MgSO_4$) and evaporated. Column chromatography (silica gel, EtOAc/PE 2:3) afforded the triol as a white solid (10.2 mg, 99%).

Procedure C: An aqueous solution of HCl (50 μL of a 3 N solution) was added dropwise at RT to a solution of acetonide **79** (24.0 mg, 0.039 mmol) in dry methanol (1.5 mL). The reaction mixture was heated to 45 °C for 45 min before cooling to RT, followed by careful addition of saturated aqueous $NaHCO_3$ solution (10 mL) and ethyl acetate (10 mL). Separation of the phases, extraction of the aqueous with ethyl acetate (3×10 mL), drying the combined organics ($MgSO_4$), concentration under reduced pressure and purification by flash chromatography (ethyl acetate/PE 1:2 then 1:1) afforded the title compound **79** as a colourless oil (18.6 mg, 83%). R_f=0.57 (ethyl acetate/PE 2:1); $[\alpha]_D$ = −27.3 (c = 0.31, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.11 (m, 1H; = C*H*CH_3)), 5.81 (brm, 1H; H-6), 5.70 (brm, 1H; H-3), 5.45 (dd, J=3.5, 3.1 Hz, 1H; H-2), 4.70 (brm, 1H; OH), 4.35 (m, 1H; H-8), 4.20 (brm, 1H; H-1), 4.00 (brm, 1H; OH), 3.25 (brs, 1H; OH), 2.64 (dd, J=14.3, 3.1 Hz, 1H; H-9), 2.58 (m, 2H; C(O)CH$_2$ octanoyl), 2.24 (dd, J=14.3, 2.5 Hz, 1H; H-9), 1.98 (m, 3H; =C(H)C*H*$_3$), 1.90 (brm, 6H; H-15, C(O)CH$_3$), 1.84 (s, 3H; C(O)CCH$_3$), 1.59 (m, 2H; C(O)CH$_2$C*H*$_2$ octanoyl), 1.50 (s, 3H; H-13), 1.44 (s, 3H; H-14), 1.23–1.33 (m, 8H; CH$_3$(C*H*$_2$)$_4$ octanoyl), 0.87 (t, J=6.8 Hz, 3H; CH$_3$ octanoyl); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.4 (C-12), 172.6 (C=O octanoyl), 171.2 (*C*(O)CH$_3$), 167.2 (O*C*(O)C=), 141.1 (=*C*(H)CH$_3$), 138.8 (C-5), 130.0 (C-4), 127.4 (*C*=C(H)CH$_3$), 85.3 (C-10), 84.1 (C-3), 79.6 (C-11), 79.4 (C-7), 77.9 (C-2), 77.2 (C-6), 68.6 (C-8), 57.5 (C-1), 39.1 (C-9), 34.3 (OC(O)*C*H$_2$ octanoyl), 31.6 (CH$_2$ octanoyl), 29.1 (CH$_2$ octanoyl), 28.9 (CH$_2$ octanoyl), 24.8 (OC(O)CH$_2$*C*H$_2$ octanoyl), 22.8 (C-14), 22.7 (C(O)CH$_3$), 22.6 (CH$_2$ octanoyl), 20.5 (C(O)C*C*H$_3$), 16.3 (C-13), 15.8 (=C(H)*C*H$_3$), 14.0 (CH$_3$ octanoyl), 12.8 (C-15); IR (film): ν_{max} = 3401, 2928, 2858, 1790, 1771, 1737, 1710, 1457, 1368, 1238, 1153, 1132, 1114, 1083, 989 cm^{-1}; ESI+ MS: m/z: calcd for $C_{30}H_{44}NaO_{11}$: 603.2781; found: 603.2779 $[M+Na]^+$.

Thapsigargin (1): To a solution of triol **79** (16.2 mg, 0.028 mmol) in CH_2Cl_2 (0.1 mL) at RT was added a stock solution of butyric anhydride (9.1 μL, 0.056 mmol, added as 0.3 mL of a stock solution consisting of 150 μL in 5.0 mL CH_2Cl_2). After stirring for 75 min, the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (15 mL) and ethyl acetate (15 mL). Separation of the phases, extraction of the aqueous with ethyl acetate (3×10 mL), drying the combined organics ($MgSO_4$), concentration under reduced pressure and pu-

rification by flash chromatography (ethyl acetate/PE 1:2) 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 (ethyl acetate/PE 1:2); $[\alpha]_D = -42.4$ (c = 0.17, $CHCl_3$); an optical rotation on a sample of the natural product was also measured in our laboratory: $[\alpha]_D = -36.0$ (c = 0.15, $CHCl_3$); ^{1}H NMR (600 MHz, 3.4 mg sample in 0.65 mL $CDCl_3$): δ = 6.09 (m, 1H; =C*H*CH$_3$), 5.72 (br m, 1H; H-3), 5.67 (br m, 1H; H-6), 5.62 (m, 1H; H-8), 5.50 (dd, J= 3.3, 3.2 Hz, 1H; H-2), 4.18 (br m, 1H; H-1), 2.96 (dd, J=14.8, 3.2 Hz, 1H; H-9′), 2.53 (br s, 1H; OH), 2.38 (dd, J=14.8, 4.0 Hz, 1H; H-9), 2.25–2.40 (m, 4H; C(O)CH$_2$ octanoyl, C(O)CH$_2$ butanoyl), 2.00 (m, 3H; = C(H)C*H*$_3$), 1.92 (m, 3H; C(O)CCH$_3$), 1.88 (s, 3H; C(O)CH$_3$), 1.87 (s, 3H; H-15), 1.62 (m, 4H; C(O)CH$_2$C*H*$_2$ octanoyl, C(O)CH$_2$C*H*$_2$ butanoyl), 1.51 (s, 3H; H-13), 1.42 (s, 3H; H-14), 1.25–1.35 (m, 8H; CH$_3$(C*H*$_2$)$_4$ octanoyl), 0.95 (t, J=7.4 Hz, 3H; CH$_3$ butanoyl), 0.87 (t, J=6.8 Hz; CH$_3$ octanoyl); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.3 (C-12), 172.6×2 (C=O octanoyl, C=O butanoyl), 170.8 (*C*(O)CH$_3$), 167.1 (O*C*(O)C=), 141.8 (C-5), 138.7 (=*C*(H)CH$_3$), 130.1 (C-4), 127.4 (*C*=C(H)CH$_3$), 84.6 (C-10), 84.1 (C-3), 78.6×2 (C-7, C-11), 77.7 (C-2), 76.8 (C-6), 66.2 (C-8), 57.5 (C-1), 38.2 (C-9), 36.5 (OC(O)*C*H$_2$ butanoyl), 34.2. (OC(O)*C*H$_2$ octanoyl), 31.6 (CH$_2$ octanoyl), 29.0 (CH$_2$ octanoyl), 28.9 (CH$_2$ octanoyl), 24.8 (OC(O)CH$_2$*C*H$_2$ octanoyl), 22.9 (C-14), 22.6 (CH$_2$ octanoyl), 22.5 (C(O)CH$_3$), 20.5 (C(O)*C*CH$_3$), 18.0 (OC(O)CH$_2$*C*H$_2$ butanoyl), 16.2 (C-13), 15.8 (=C(H)*C*H$_3$), 14.0 (CH$_3$ octanoyl), 13.7 (CH$_3$ butanoyl), 12.9 (C-15); IR (film): ν_{max} = 3435, 2959, 2927, 2858, 1790, 1775, 1741, 1721, 1459, 1369, 1256, 1237, 1161, 1128, 1102, 1043, 1019, 987, 802 cm^{-1}; ESI+ MS: m/z: calcd for $C_{34}H_{50}NaO_{12}$: 673.3200; found: 673.3188 $[M+Na]^+$.

Thapsivillosin C (5): (*S*)-2-Methyl butyric anhydride (20 μL, 102 μmol) was added to a solution of O-8-debutanoyl thapsigargin (**79**) (29 mg, 50.0 μmol) followed by a catalytic amount of DMAP (ca. 1 mg). The resulting mixture was stirred at RT for 3.5 h and then quenched by the addition of saturated aqueous ammonium chloride solution (20 mL). The mixture was then extracted with EtOAc (3×20 mL), and the combined organics washed with brine (50 mL) and dried ($MgSO_4$). The crude residue was purified by flash chromatography (silica gel, Et_2O/PE 1:1 then 7:3) to afford thapsivillosin C (**5**) as a white solid (30.5 mg, 92%). $[\alpha]_D = -21.9$ (c = 1.53, $CHCl_3$); ^{1}H NMR (600 MHz, 1.6 mg in 650 μL $CDCl_3$): δ = 6.11 (apparent qd, J=7.2, 1.0 Hz, 1H; =C*H*(CH$_3$)), 5.72 (br s, 1H; H-3), 5.65 (br s, 1H; H-6), 5.63 (dd, J=3.7, 3.6 Hz, 1H; H-8), 5.50 (apparent t, J=3.2 Hz, 1H; H-2), 4.23 (br s, 1H; H-1), 2.99 (dd, J=14.8, 3.3 Hz, 1H; H-9), 2.37–2.25 (m, 4H; H-9′, C(O)C*H*$_2$CH$_2$, C(O)C*H*(CH$_3$)), 2.01 (apparent dd, J=7.2, 1.2 Hz, 3H; =CH(C*H*$_3$)), 1.93 (s, 3H; C(O)CH$_3$), 1.91 (s, 3H; C(O)CCH$_3$), 1.89 (s, 3H; H-15), 1.72 (m, 1H; C(O)CH(CH$_3$)C*H*H), 1.62 (m, 2H; C(O)CH$_2$C*H*$_2$), 1.52 (s, 3H; H-13), 1.44 (m, 1H; C(O)CH(CH$_3$)CH*H*), 1.42 (s, 3H; H-14), 1.35–1.25 (m, 8H; 4×octanoyl C*H*$_2$), 1.85 (d, J=7.4 Hz, 3H; C(O)CH(C*H*$_3$)), 0.92 (m, 3H; C(O)CH(CH$_3$)CH$_2$C*H*$_3$), 0.88 (m, 3H; octanoyl CH$_3$); ^{13}C NMR (150 MHz, 30 mg in 650 μL $CDCl_3$): δ = 175.7 (C-12), 175.5 (*C*(O)CHCH$_3$), 172.6 (*C*(O)CH$_2$), 171.0 (*C*(O)CH$_3$), 167.1 (*C*(O)CCH$_3$), 141.6 (C-4), 138.6 (=*C*HCH$_3$), 130.4 (C-5), 127.5 (*C*=CHCH$_3$), 84.8 (C-10), 84.2 (C-3), 78.6, 78.5 (C-7, C-11), 77.7 (C-2), 76.9 (C-6), 66.2 (C-8), 57.2 (C-1), 41.4 (C(O)*C*HCH$_3$), 38.3 (C-9), 34.2 (CH$_2$ octanoyl), 31.6 (CH$_2$ octanoyl), 29.0 (CH$_2$ octanoyl), 29.0 (CH$_2$ octanoyl), 26.1 (C(O)C(H)*C*H$_2$), 24.8 (CH$_2$ octanoyl), 23.2 (C-14), 22.6, 22.5 (CH$_2$ octanoyl, C(O)*C*H$_3$), 20.5 (C(O)*C*CH$_3$), 16.2 (C-13), 16.1 (C(O)C(H)*C*H$_3$), 15.8 (=CH*C*H$_3$), 14.0 (CH$_3$ octanoyl), 12.9 (C-15), 11.6 (C(O)CHCH$_2$*C*H$_3$); IR (film; $CHCl_3$): ν_{max} = 3448 (br OH), 2926 (C-H), 1793 (C=O), 1775 (C=O), 1740 (C=O), 1718 (C=O), 1460, 1369, 1235; ESI+ MS: m/z: calcd for $C_{35}H_{52}NaO_{12}$: 687.3357; found: 687.3359 $[M+Na]^+$.

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