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A stereoselective cyclisation cascade mediated by $\text{SmI}_2\text{-H}_2\text{O}$: synthetic studies towards stolonidiol

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ARTICLE INFO

Article history:

Received 8 February 2010

Accepted 4 March 2010

Available online 11 May 2010

Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

A cascade reaction involving sequential conjugate reduction, stereoselective aldol cyclisation and chemo-selective lactone reduction mediated by $\text{SmI}_2\text{-H}_2\text{O}$ provides access to a cyclopentanol bearing two vicinal quaternary stereocentres with good stereocontrol. The functionalised cyclopentanol product has been converted to a key intermediate in ongoing asymmetric studies towards stolonidiol.

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1. Introduction

Since its introduction by Kagan,¹ the electron transfer reagent, samarium(II) iodide (SmI_2) has become one of the most important reducing agents in organic synthesis.² The versatile reagent has been used to mediate many processes, ranging from functional group interconversions to complex carbon–carbon bond-forming sequences.² Cyclisation reactions are arguably the most useful transformations mediated by SmI_2 , and these have been used extensively in natural product synthesis.^{2f,h}

The diterpenoid stolonidiol **1** was isolated in 1987 by Yamada from a Japanese soft coral.³ Preliminary assays showed it to possess strong cytotoxic activity against P388 leukaemia cells in vitro (IC_{50} $0.015 \mu\text{g mL}^{-1}$). More recently, stolonidiol has been shown to display potent choline acetyltransferase (ChAT) inducible activity, suggesting that it may act as a neurotrophic factor-like agent on the cholinergic nervous system.⁴ Agents with neurotrophic factor-like activity are potential therapeutics for dementia and disorders such as Alzheimer's disease. To date, Yamada has reported the only synthesis of stolonidiol.⁵ The cyclopentane ring in stolonidiol, bearing three contiguous stereocentres, including two vicinal, quaternary stereocentres, presents a major challenge in any approach to the natural product. We have chosen to address this problem by adapting and extending a reaction previously developed by our group.⁶ Our planned synthesis proceeds through the allylic carbonates **2** and **3**, obtained by manipulation of triol **4**, the anticipated product of a $\text{SmI}_2\text{-H}_2\text{O}$ -mediated cyclisation cascade of unsaturated keto-lactone **5** (Scheme 1).

We have previously reported the use of a Sm(II) -mediated spirocyclisation in a first generation approach to the functionalised cyclopentanol motif of stolonidiol (Scheme 2).⁷ Although this ap-

proach was successful in forming the challenging cyclopentanol motif, the lack of stereocontrol and unwanted retro-aldol pathways observed necessitated a revision of our synthetic strategy. Herein, we report a diastereoselective cascade approach to a cyclopentanol bearing two vicinal quaternary stereocentres. The functionalised cyclopentanol product has been converted to a key intermediate in our ongoing asymmetric studies on stolonidiol.

2. Results and discussion

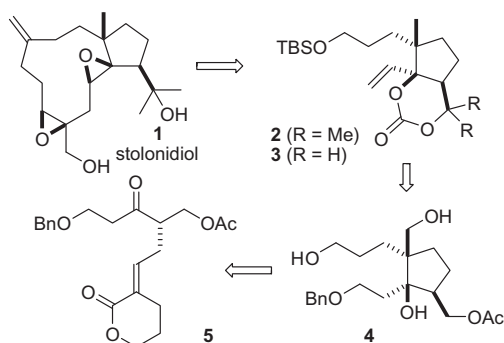
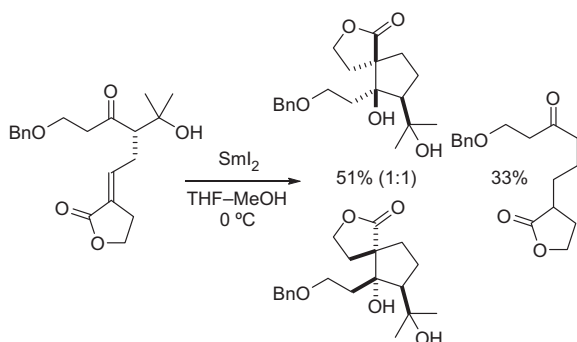
The second generation cyclisation substrate **5** was designed to address a number of problems encountered in our previous approach.⁷ Firstly, we proposed that replacement of the tertiary alcohol-bearing side chain with a protected methylene hydroxy group would disfavour retro-aldol fragmentation. In addition, we believed that judicious choice of the protecting group would result in improved diastereoselectivity in the spirocyclisation by coordination of the group to Sm(III) . We decided to use an acetate protecting group in **5** after carrying out cyclisation studies on model substrates. The model substrates were prepared from ketoester **6** that was first converted to β -hydroxyketone **7**. The introduction of a range of protecting groups then gave intermediates **8** which were converted to substrates **10** by ozonolysis and Wittig reaction with phosphorane **9**.⁸ For three substrates ($\text{R} = \text{TBS}$, Bz and MEM) it proved more efficient to proceed via intermediate **11** (Scheme 3).

Upon treatment with SmI_2 in THF and MeOH at 0°C , substrates **10a–f** underwent cyclisation to give spiro-lactones **12a–f** and **13a–f** in moderate to good yields. Only with the acetate **10b** was moderate selectivity for the desired all-*syn* isomer observed (Scheme 4).

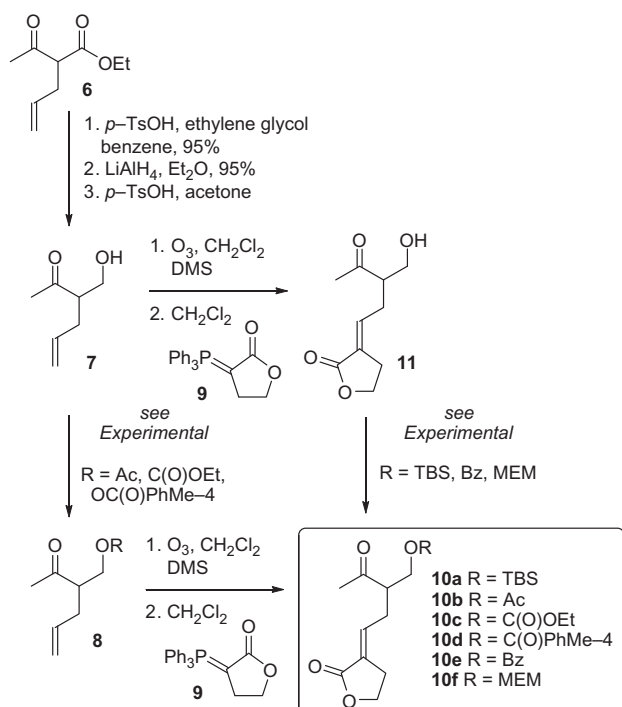
We proposed that the use of a six-membered lactone substrate, rather than the five-membered lactone system explored in our preliminary studies, would allow the initial product **14** to be reduced to triol **4** using the selective Sm(II) -mediated lactone reduction recently discovered in our group.⁹ In this way, the unprecedented

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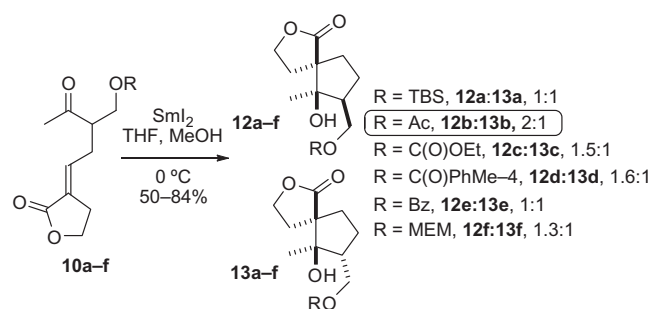
Scheme 1. Retrosynthetic analysis of stolonidiol **1**.

Scheme 2. A first generation Sm(II)-mediated approach to the cyclopentanol motif in stolonidiol.



Scheme 3. Preparation of model cyclisation studies.

three-stage reaction cascade, carried out in a one-pot reaction using one reagent, would allow rapid access to a key intermediate in our approach to the target (Scheme 5).



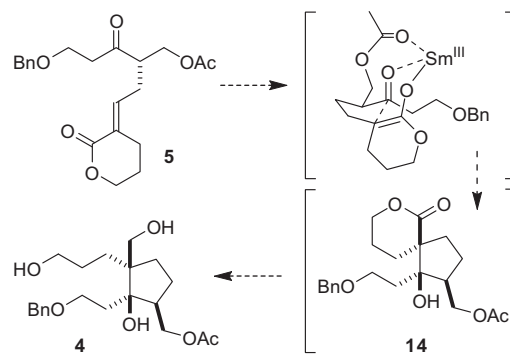
Scheme 4. Model cyclisation studies.

The synthesis of the cyclisation substrate **5** began with a boron-mediated asymmetric aldol reaction¹⁰ between known imide **15**¹¹ and aldehyde **16**¹² to give adduct **17** in 82% yield as a single diastereoisomer. The auxiliary was reductively removed with NaBH_4 followed by selective mono-acetylation of the resulting primary alcohol. The secondary hydroxyl group was subsequently oxidised to the corresponding ketone using the TPAP/NMO system¹³ to give ketone **18**. A two-step oxidative cleavage of the alkene moiety then gave the corresponding aldehyde. Subsequent Wittig reaction of the aldehyde with phosphorane **19** gave the cyclisation substrate **5** in good overall yield and as a single double bond isomer (Scheme 6).

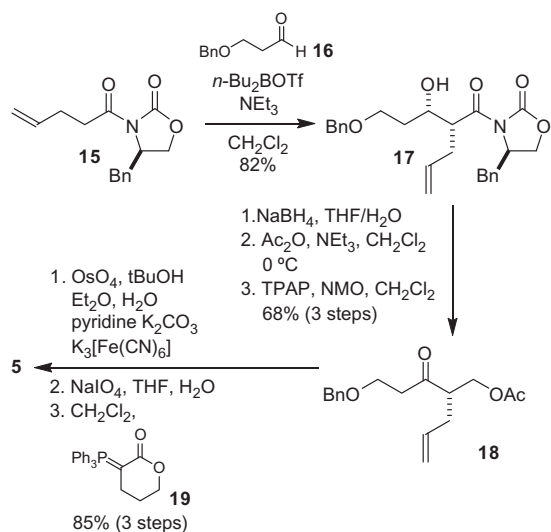
Upon treatment of substrate **5** with SmI_2 in THF and H_2O , we found that the sequential reaction proceeded as planned, giving the highly functionalised cyclopentanol **4** in 86% yield and as a 6:1 mixture of diastereoisomers in favour of the desired all-*syn*-isomer (Scheme 7).

The cascade begins with the conjugate reduction of the electron-deficient olefin, generating a Sm(III)-enolate¹⁴ which then undergoes a diastereoselective aldol cyclisation onto the pendant ketone, generating the spirocyclic cyclopentanol intermediate **14**.⁶ The spirocyclic lactone was then selectively reduced to triol **4**, in the presence of the primary acetate.⁹ The stereochemistry of the major isomer of **4** is consistent with the proposed transition structure in which both carbonyl groups complex to Sm(III) in the Sm(III)-enolate intermediate. The use of less SmI_2 prevents the final stage of the cascade taking place, allowing isolation of the major spirocyclic lactone intermediate **14**. Subsequent deprotection of the benzyl ether (20 mol % $\text{Pd}(\text{OH})_2/\text{C}$, H_2 , EtOH, 45%) provided crystalline diol **20** suitable for X-ray analysis,¹⁵ unambiguously confirming the stereochemistry of the spirocycle and the major triol product (Fig. 1).

Having successfully secured a route to the functionalised cyclopentanol **4**, we focussed on its conversion to allylic carbonates **2** and **3**, strategically important intermediates in our proposed ap-



Scheme 5. Proposed stereoselective cyclisation cascade.



Scheme 6. Asymmetric synthesis of cyclisation substrate 5.

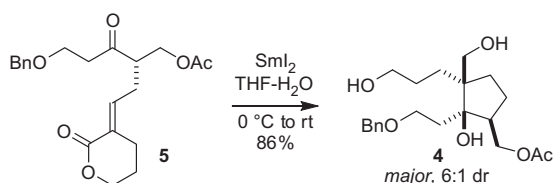
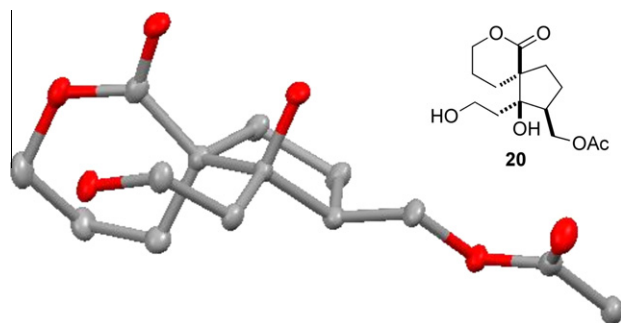
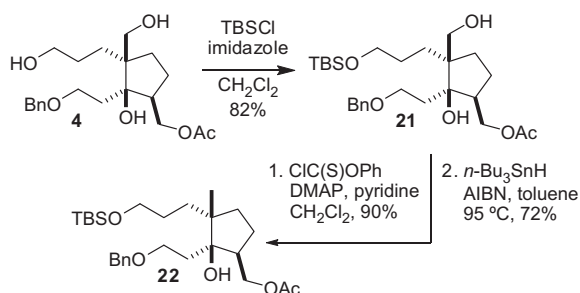
Scheme 7. SmI₂-H₂O-mediated cyclization cascade.

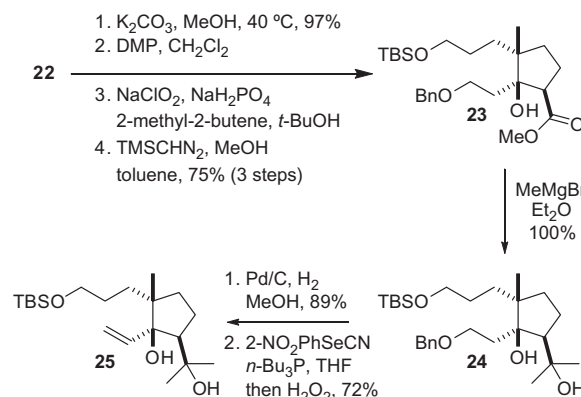
Figure 1. X-ray crystal structure of 20.

proach to stolonidiol. After protection of the distal primary hydroxyl group as the TBS ether, deoxygenation of the remaining free hydroxyl in **21** was achieved in two steps by conversion to the thiocarbonate and treatment with *n*-Bu₃SnH (Scheme 8).¹⁶



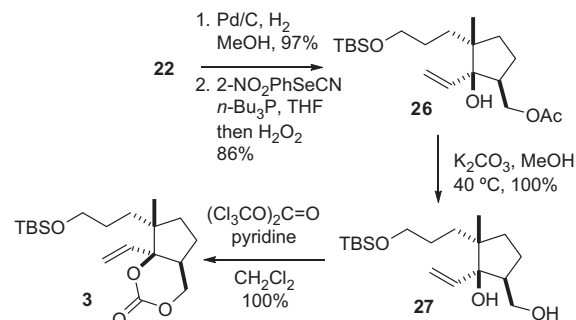
Scheme 8. Selective deoxygenation of triol 4.

We initially anticipated the introduction of the *gem*-dimethyl group, forming the tertiary alcohol side chain, at this stage in the synthesis. To this end, hydrolysis of the primary acetate in **22** preceded a two-step oxidation of the alcohol to the corresponding carboxylic acid, which was converted to the methyl ester **23**. Treatment with MeMgBr led to the desired tertiary alcohol **24** in a quantitative yield (Scheme 9). Unfortunately, attempts to form the corresponding cyclic carbonate from **24** proved unsuccessful using carbonyldiimidazole and triphosgene. Debenzylation of the primary benzyl-ether in **24** and elimination under Grieco's conditions¹⁷ afforded diol **25**. Unfortunately, conversion of **25** to the corresponding cyclic carbonate or the bis-acetate could not be achieved. As a result, it was concluded that a late stage installation of the two methyl groups would be more amenable to the continuation of the synthesis.



Scheme 9. An unsuccessful approach to allylic carbonate 2.

As such, compound **22** was debenzylated and subjected to elimination conditions, forming the allylic alcohol **26**. Upon removal of the primary acetate, treatment of the resulting diol **27** with triphosgene led to the isolation of the desired allylic carbonate **3** in an excellent yield (Scheme 10).

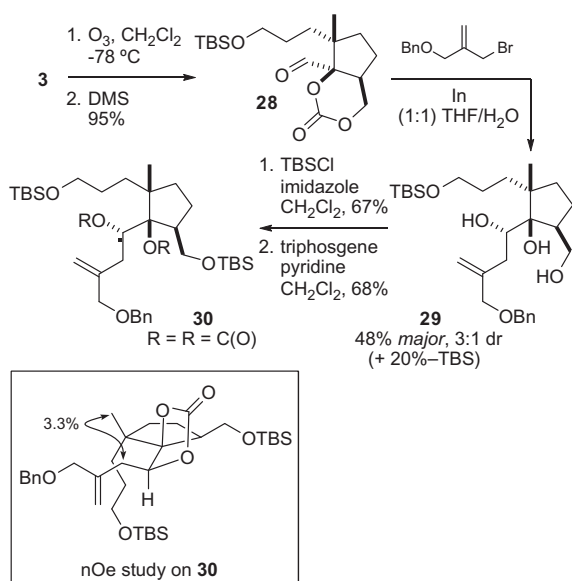


Scheme 10. Formation of allylic carbonate 3.

With this versatile intermediate, constituting the right-hand fragment of stolonidiol, completed, elaboration of the left-hand 11-membered ring can be approached in a number of ways, giving a degree of flexibility to the completion of the synthesis.

One strategy for extending the carbon framework involves the addition of a suitable organometallic to an aldehyde derived from **3**. A preliminary study has shown that ozonolysis of the allylic carbonate proceeds uneventfully to give the corresponding aldehyde **28** in an excellent yield.¹⁸ Treatment of this aldehyde with 2-benzoyloxymethyl-3-bromopropene and indium powder¹⁹ in 1:1 THF-H₂O gave the desired Barbier adduct **29** in 48% yield as a 3:1 mixture of diastereoisomers in addition to a diastereoisomeric mixture of adducts in which the primary TBS group had been lost.

Protection of the primary hydroxyl group in **29** as the TBS ether and subsequent cyclic carbonate formation gave the advanced intermediate **30** (Scheme 11).



Scheme 11. Preliminary studies on the elaboration of allylic carbonate **3**.

The stereochemistry of **30** and **29** was confirmed by NOE studies on **30** (Scheme 11). Thus, our preliminary studies show the value of the allylic carbonate **3** as an intermediate in an asymmetric approach to stolonidiol.

3. Conclusion

In conclusion, we have developed a cyclisation cascade mediated by $\text{SmI}_2\text{-H}_2\text{O}$ for the rapid, stereoselective synthesis of highly substituted cyclopentanol. The cascade features a reductive aldol-cyclisation followed by lactone reduction and allows two vicinal, fully substituted stereocentres to be constructed with good stereocontrol. The product of the cascade has been converted to a key intermediate in our ongoing studies towards the asymmetric synthesis of stolonidiol.

4. Experimental

4.1. General

All experiments were performed under an atmosphere of nitrogen, using anhydrous solvents, unless stated otherwise. THF was distilled from sodium/benzophenone, and when used in conjunction with SmI_2 , deoxygenated by bubbling with N_2 for 15 min. Dichloromethane was distilled from CaH_2 , and methanol was distilled from the corresponding magnesium alkoxide and stored under argon. Water was distilled before deoxygenation by the bubbling through of N_2 . ^1H NMR and ^{13}C NMR were recorded using 300, 400 and 500 MHz spectrometers, with chemical shift values being reported in ppm relative to residual chloroform ($\delta_{\text{H}} = 7.27$ or $\delta_{\text{C}} = 77.2$) as internal standards. All coupling constants (J) are reported in Hertz (Hz). Mass spectra were obtained using positive and negative electrospray (ES $^\pm$) or gas chromatography (GC) methodology. Infra-red spectra were recorded as evaporated films or neat using a FT/IR spectrometer. Column chromatography was carried out using 35–70 μ , 60A silica gel. Routine TLC analysis was carried out on aluminium sheets coated with Silica Gel 60 F254,

0.2 mm thickness. Plates were viewed using a 254 nm ultraviolet lamp and dipped in aqueous potassium permanganate or *p*-anisaldehyde.

4.2. Preparation of model substrates 10a–f

4.2.1. Ethyl 2-acetylpent-4-enoate **6**²⁰

A solution of sodium ethoxide was prepared by the slow, portion-wise addition of sodium metal (1.41 g, 61.3 mmol, 1.0 equiv) to a stirred solution of EtOH (40 ml) at room temperature and the resultant solution stirred for 0.5 h. Neat ethylacetoacetate (7.7 g, 61.3 mmol, 1.0 equiv) was then added dropwise and the solution stirred for 20 min before the addition of potassium iodide (1.01 g, 6.13 mmol, 0.1 equiv) and neat allylbromide (6.89 ml, 79.7 mmol, 1.3 equiv). The resultant solution was stirred at reflux for 17 h. The reaction mixture was cooled to room temperature and poured into a beaker of water (30 mL) and the aqueous layer was separated and extracted with Et₂O (4 \times 15 ml). The combined organic phases were dried (MgSO_4), filtered and concentrated in vacuo to give the crude product. Purification by column chromatography (eluting with 10% EtOAc in petroleum ether (40–60 $^\circ\text{C}$)) gave **6** (6.03 g, 32.02 mmol, 52%) as a clear oil. ν_{max} (ATR)/ cm^{-1} 2978 m, 2336 m, 1713br s (ketone and ester C(O)), 1438 m, 1331 m, 1183 m, 1024 m, 919 m; δ_{H} (500 MHz, CDCl_3) 1.32 (3H, t, J 7.1, ($\text{CH}_3\text{CH}_2\text{O}$), 2.28 (3H, s, $\text{C}(\text{O})\text{CH}_3$), 2.64 (2H, apparent t, J 7.4, $\text{CH}_2\text{CH}=\text{CH}_2$), 3.57 (1H, t, J 7.3, CH), 4.25 (2H, q, J 7.1, OCH_2CH_3), 5.07–5.18 (2H, m, $\text{CH}=\text{CH}_2$), 5.72–5.86 (1H, m, $\text{CH}=\text{CH}_2$); δ_{C} (100 MHz, CDCl_3) 14.4 (CH_3CH_2), 29.4 ($\text{CH}_3\text{C}(\text{O})$), 32.4 ($\text{CH}_2\text{CH}=\text{CH}_2$), 59.5 (CH), 61.7 (OCH_2), 117.7 ($\text{CH}_2=\text{CH}$), 134.5 ($\text{CH}=\text{CH}_2$), 169.5 (ester C(O)), 202.8 (ketone C(O)); MS: m/z (Cl^+) 188 (100%) [M^+NH_4], 171 (15%) [M^+H], HRMS Calcd for $\text{C}_9\text{H}_{18}\text{O}_3\text{N}$ ($[\text{M}^+\text{NH}_4]$): 188.1281. Found 188.1278.

4.2.2. Ethyl-2-(2-methyl-[1,3]dioxolan-2-yl)-pent-4-enoate

To a stirred solution of **6** (5.6 g, 32.9 mmol, 1 equiv) and *p*-toluenesulfonic acid (20 mg) in benzene (112 ml) at room temperature was added ethylene glycol (5.0 ml, 91.5 mmol, 2.7 equiv) and the resultant solution was stirred at reflux for 18 h under Dean Stark conditions. The reaction mixture was cooled to room temperature and concentrated in vacuo to give the crude product. The residue was purified by column chromatography (eluting with 10% EtOAc in petroleum ether (40–60 $^\circ\text{C}$)) giving ethyl-2-(2-methyl-[1,3]dioxolan-2-yl)-pent-4-enoate (7.18 g, 31.3 mmol, 95%) as a clear oil. ν_{max} (ATR)/ cm^{-1} 3075 m, 2980 m, 1714s (ester C=O), 1440 m, 1359 m, 1279 m, 12020, 1141 m, 1007 m; ^1H NMR δ 1.27 (3H, t, $J = 7$ Hz, OCH_2CH_3), 1.42 (3H, s, CH_3C^q), 2.35–2.41 (1H, m, 1H from $\text{CH}_2\text{CH}=\text{CH}_2$), 2.47–2.53 (1H, m, 1H from $\text{CH}_2\text{CH}=\text{CH}_2$), 2.75 (1H, dd, $J = 11.4$ Hz, 3.8, $\text{CHCH}_2\text{CH}=\text{CH}_2$), 3.94–4.06 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 4.17 (2H, q, $J = 6$ Hz, OCH_2CH_3), 5.0–5.11 (2H, m, $\text{CH}=\text{CH}_2$); ^{13}C NMR δ 14.3 (CH_3CH_2), 21.6 (CH_3), 32.4 ($\text{CH}_2\text{CH}=\text{CH}_2$), 60.5 ($\text{CHCH}_2\text{CH}=\text{C}$), 64.8 ($\text{OCH}_2\text{CH}_2\text{O}$), 64.9 ($\text{OCH}_2\text{CH}_2\text{O}$), 109.4 (C^q), 116.6 ($\text{CH}_2=\text{CH}$), 135.3 ($\text{CH}_2=\text{CH}$), 172.1 (C=O). MS: m/z (Cl^+) 223 [M^+NH_4] $^+$ (40%), 215 [M^+H] $^+$ (100%), 87 (15%), HRMS Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_4$: 214.1200. Found: 214.1199.

4.2.3. 2-(2-Methyl-[1,3]dioxolan-2-yl)-pent-4-en-1-ol

To a suspension of lithium aluminium hydride (3.0 g, 50.3 mmol, 1.5 equiv) in Et₂O (175 ml) was added a solution of ethyl-2-(2-methyl-[1,3]dioxolan-2-yl)-pent-4-enoate (7.18 g, 31.3 mmol 1 equiv) in Et₂O (51 ml) dropwise. The resultant solution was stirred at reflux for 4 h and allowed to cool to room temperature before being quenched by the addition of a water/NaOH solution (40 ml). The reaction was filtered and the filtrate dried (MgSO_4), filtered and concentrated in vacuo. The crude product was purified by column chromatography (eluting with 20% EtOAc in petroleum ether (40–60 $^\circ\text{C}$)) giving 2-(2-methyl-[1,3]dioxolan-2-yl)-pent-4-en-1-ol

(5.5 g, 31.9 mmol, 95%) as a clear oil. ν_{\max} (ATR)/ cm^{-1} 3413s, 2887 m, 1706 m, 1641 m, 1435 m, 1212 m, 1039 m, 864 m; ^1H NMR δ 1.26 (3H, s, $\text{CH}_3\text{C}^\text{O}$), 1.80–1.89 (2H, m, 1H from $\text{CH}_2\text{CH}=\text{CH}_2$, CHCH_2OH), 2.23–2.28 (1H, m, 1H from $\text{CH}_2\text{CH}=\text{CH}_2$), 3.54–3.60 (2H, m, CH_2OH), 3.90–3.94 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 4.96–5.02 (2H, m, $\text{CH}=\text{CH}_2$), 5.70–5.77 (1H, m, $\text{CH}=\text{CH}_2$); ^{13}C NMR δ 20.8 (CH_3), 31.5 ($\text{CH}_2\text{CH}=\text{CH}_2$), 47.6 ($\text{CHCH}_2\text{CH}=\text{CH}_2$), 62.3 (CH_2OH), 64.4 ($\text{OCH}_2\text{CH}_2\text{O}$), 64.6 ($\text{OCH}_2\text{CH}_2\text{O}$), 112.5 (C^q), 116.4 ($\text{CH}_2=\text{CH}$), 136.8 ($\text{CH}=\text{CH}_2$); MS: m/z ($\text{Cl}^\text{+}$) 190 (40%), 173 (100%) [$\text{M}+\text{H}^\text{+}$], 87 (35%), HRMS Calcd for $\text{C}_9\text{H}_{15}\text{O}_3$: 171.1016. Found: 171.1014.

4.2.4. 3-(Hydroxymethyl)hex-5-en-2-one 7

To a stirred solution 2-(2-methyl-1,3-dioxolan-2-yl)pent-4-en-1-ol (956 mg, 5.55 mmol, 1.0 equiv) in acetone (9.37 ml) at room temperature was added *p*-toluene sulfonic acid (20 mg, catalytic) and the resultant solution stirred at reflux for 2 h. The reaction mixture was cooled to room temperature and concentrated in vacuo to give the crude product. Purification by column chromatography (eluting with 30% EtOAc in petroleum ether (40–60 °C)) gave **7** (685 mg, 5.35 mmol, 96%) as a clear oil. ν_{\max} (ATR)/ cm^{-1} 3405s, 2928 m, 2888 m, 1704s (ketone $\text{C}(\text{O})$), 1642 m, 1424 m, 1037 m, 917 m; δ_H (500 MHz, CDCl_3) 2.15 (3H, s, $\text{CH}_3\text{C}(\text{O})$), 2.19–2.24 (1H, m, 1H of $\text{CH}_2\text{CH}=\text{CH}_2$), 2.29–2.36 (1H, m, 1H of $\text{CH}_2\text{CH}=\text{CH}_2$), 2.69–2.74 (1H, m, $\text{CHCH}_2\text{CH}=\text{CH}_2$), 3.67 (1H, dd J 11.4, 4.1, AB system 1H of CH_2OH), 3.73 (1H, dd J 11.6, 7.3, AB system 1H of CH_2OH), 5.00–5.06 (2H, m, $\text{CH}=\text{CH}_2$), 5.67 (1H, ddt J 17.0, 10.1, 6.9, $\text{CH}=\text{CH}_2$); δ_C (100 MHz, CDCl_3) 30.0 ($\text{CH}_3\text{C}(\text{O})$), 32.4 ($\text{CH}_2\text{CH}=\text{CH}_2$), 53.8 (CHCH_2OH), 62.4 (CH_2OH), 117.5 ($\text{CH}_2=\text{CH}$), 134.8 ($\text{CH}=\text{CH}_2$), 212.0 (ketone $\text{C}(\text{O})$); MS: m/z ($\text{Cl}^\text{+}$) 146 (100%) [$\text{M}+\text{NH}_4^\text{+}$], 129 (63%) [$\text{M}+\text{H}^\text{+}$], HRMS Calcd for $\text{C}_7\text{H}_{11}\text{O}_2$: 127.0754. Found: 127.0752.

4.2.5. 3-(Acetoxymethyl)hex-5-en-2-one 8 (R = Ac)

To a stirred solution of 3-(hydroxymethyl)hex-5-en-2-one **7** (100 mg, 0.78 mmol) in CH_2Cl_2 (15 ml) at room temperature was added pyridine (0.44 ml, 5.46 mmol, 7 equiv), acetic anhydride (0.37 ml, 3.90 mmol, 5 equiv) and DMAP (19.5 mg, 0.16 mmol, 0.2 equiv) sequentially, and the reaction stirred for 14 h. The reaction was quenched by the addition of saturated, aqueous NaHCO_3 solution (15 ml). The aqueous phase was extracted with CH_2Cl_2 (4 \times 20 ml) and the combined organics were dried (MgSO_4), filtered and concentrated in vacuo to give the desired acetate 3-(acetoxymethyl)hex-5-en-2-one **8** (R = Ac) (133 mg, 0.78 mmol, 100%) as a yellow oil. ν_{\max} (thin film)/ cm^{-1} 2913w, 2367w, 2333w, 1743s ($\text{C}=\text{O}$), 1718s ($\text{C}=\text{O}$), 1636w, 1560w, 1367m, 1236s, 1036m; ^1H NMR (500 MHz, CDCl_3) δ 2.04 (3H, s, $\text{CH}_3\text{C}(\text{O})\text{O}$), 2.18–2.27 (1H, m, 1H from $\text{CH}_2\text{CH}=\text{CH}_2$), 2.20 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.35–2.44 (1H, m, 1H from $\text{CH}_2\text{CH}=\text{CH}_2$), 2.90 (1H, p, J = 7.0 Hz, $\text{CH}_3\text{C}(\text{O})\text{CH}$), 4.21 (2H, d, J = 6.5 Hz, $\text{CH}_2\text{OC}(\text{O})\text{CH}_3$), 5.07–5.18 (2H, m, $\text{CH}=\text{CH}_2$), 5.71 (1H, qt, J = 10.0, 7.0 Hz, $\text{CH}=\text{CH}_2$); ^{13}C NMR (125 MHz, CDCl_3) δ 20.7 ($\text{OC}(\text{O})\text{CH}_3$), 29.9 ($\text{CH}_3\text{C}=\text{O}$), 32.5 ($\text{CH}_2\text{CH}=\text{CH}_2$), 51.0 ($\text{CHCH}_2\text{OC}=\text{O}$), 63.9 ($\text{CH}_2\text{OC}=\text{O}$), 117.9 ($\text{CH}=\text{CH}_2$), 134.1 ($\text{CH}=\text{CH}_2$), 170.7 ($\text{OC}(\text{O})\text{CH}_3$), 208.7 (CH_3CO); MS: m/z (ES+ mode), 249 (12%), 193 (100%) [$\text{M}+\text{Na}^\text{+}$]; HRMS Calcd for $\text{C}_9\text{H}_{14}\text{O}_3\text{Na}$: 193.0835. Found: 193.0826

4.2.6. Carbonic acid 2-acetyl-pent-4-enyl ethyl ester 8 (R = C(O)OEt)

To a stirred solution of 3-(hydroxymethyl)hex-5-en-2-one **7** (100 mg, 0.78 mmol) in CH_2Cl_2 (4 ml) at -50°C was added pyridine (0.16 ml, 1.95 mmol, 2.5 equiv) dropwise. After 5 min, ethyl chloroformate (0.082 ml, 0.86 mmol, 1.1 equiv) was added slowly over 30 min. The reaction was slowly warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 (40 ml) and washed with saturated, aqueous citric acid solution (2 \times 20 ml), H_2O (20 ml) and brine (20 ml). The organic phase was dried (MgSO_4), filtered and concentrated in vacuo giving carbonate

carbonic acid 2-acetyl-pent-4-enyl ester ethyl ester (115 mg, 0.57 mmol, 74%) as a pale yellow oil which was used directly without purification. ν_{\max} (thin film)/ cm^{-1} 2982w, 2933w, 2362w, 2337w, 1748s ($\text{C}=\text{O}$), 1718s ($\text{C}=\text{O}$), 1368w, 1261s, 1173w, 1010w, 922w, 791w; ^1H NMR (500 MHz, CDCl_3) δ 1.30 (3H, t, J = 7.0 Hz, OCH_2CH_3), 2.22 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.23–2.27 (1H, m, 1H from $\text{CH}_2\text{CH}=\text{CH}_2$), 2.38–2.44 (1H, m, 1H from $\text{CH}_2\text{CH}=\text{CH}_2$), 2.93–2.98 (1H, m, $\text{CH}_3\text{C}(\text{O})\text{CH}$), 4.19 (2H, q, J = 7.0 Hz, OCH_2CH_3), 4.21 (1H, dd, J = 11.0, 5.5 Hz, 1H from $\text{CH}_2\text{OC}(\text{O})\text{O}$), 4.31 (1H, dd, J = 11.0, 8.0 Hz, 1H from $\text{CH}_2\text{OC}(\text{O})\text{O}$), 5.08–5.12 (2H, m, $\text{CH}=\text{CH}_2$), 5.72 (1H, ddt, J = 17.0, 10.0, 7.0 Hz, $\text{CH}=\text{CH}_2$); ^{13}C NMR (125 MHz, CDCl_3) δ 14.1 (OCH_2CH_3), 30.1 ($\text{CH}_3\text{C}=\text{O}$), 32.4 ($\text{CH}_2\text{CH}=\text{CH}_2$), 50.9 (CHCH_2O), 64.2 (OCH_2CH_3), 66.9 ($\text{CH}_2\text{OC}=\text{O}$), 118. ($\text{CH}=\text{CH}_2$), 133.9 ($\text{CH}=\text{CH}_2$), 154.9 ($\text{OC}(\text{O})\text{O}$), 208.4 ($\text{CH}_3\text{C}=\text{O}$); MS: m/z (ES+ mode) 223 (100%) [$\text{M}+\text{Na}^\text{+}$], 218 (40%) [$\text{M}+\text{NH}_4^\text{+}$], 201 (63%) [$\text{M}+\text{H}^\text{+}$]; HRMS Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_4\text{Na}$: 223.0941. Found: 223.0937.

4.2.7. 4-Methoxy-benzoic acid 2-acetyl-pent-4-enyl ester 8 (R = C(O)PhMe-4)

To a stirred solution of 3-(hydroxymethyl)hex-5-en-2-one **7** (100 mg, 0.78 mmol, 1.0 equiv) in CH_2Cl_2 (3.1 mL) at 0°C was added pyridine (0.11 mL, 1.40 mmol, 1.8 equiv) dropwise. After 5 min, *p*-anisoyl chloride (0.16 mL, 1.17 mmol, 1.5 equiv) and DMAP (4.8 mg, 0.04 mmol, 5 mol %) were added in one portion. The reaction was stirred at 0°C for 10 min before being warmed to room temperature and stirred for an additional 2 h. The reaction was quenched by the addition of saturated aqueous NaHCO_3 solution (4 mL). The aqueous phase was extracted with CH_2Cl_2 (4 \times 5 mL) and the combined organic phases dried (MgSO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (eluting with 30% EtOAc in petroleum ether (40–60 °C)) to give 4-methoxy-benzoic acid 2-acetyl-pent-4-enyl ester **8** (R = C(O)PhMe-4) (199 mg, 0.76 mmol, 98%) as a colourless oil. ν_{\max} (thin film)/ cm^{-1} 3077w, 2953w, 2918w, 1839w, 2357w, 2337w, 1713s ($\text{C}=\text{O}$), 1606s ($\text{C}=\text{O}$), 1511m, 1419w, 1273m, 1256s, 1167s, 1102m, 1028m, 848w, 770m; ^1H NMR (500 MHz, CDCl_3) δ 2.25 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.30–2.35 (1H, m, 1H from $\text{H}_2\text{C}=\text{CHCH}_2$), 2.45–2.51 (1H, m, 1H from $\text{H}_2\text{C}=\text{CHCH}_2$), 3.02–3.07 (1H, m, $\text{CH}_3\text{C}(\text{O})\text{CH}$), 3.86 (3H, s, OCH_3), 4.43 (1H, dd, J = 11, 8 Hz, 1H from $\text{CH}_2\text{OC}(\text{O})$), 4.47 (1H, dd, J = 11, 5 Hz, 1H from $\text{CH}_2\text{OC}(\text{O})$), 5.08–5.14 (2H, m, $\text{H}_2\text{C}=\text{CH}$), 5.77 (1H, tdd, J = 14, 10.5, 7 Hz, $\text{CH}_2=\text{CH}$), 6.92 (2H, d, J = 9 Hz, CHCOCH_3), 7.95 (2H, d, J = 9 Hz, CHCHCOCH_3); ^{13}C NMR (125 MHz, CDCl_3) δ 30.0 ($\text{CH}_3\text{C}=\text{O}$), 32.6 ($\text{CH}_2\text{CH}=\text{CH}_2$), 51.2 ($\text{C}(\text{O})\text{CHCH}_2$), 55.5 (OCH_3), 64.1 ($\text{CH}_2\text{OC}=\text{O}$), 113.7 (2 \times ArCH), 117.9 ($\text{CH}=\text{CH}_2$), 122.1 (ArC), 131.6 (2 \times ArCH), 134.2 ($\text{CH}=\text{CH}_2$), 163.5 (ArC), 166.0 ($\text{OC}=\text{O}$), 208.9 ($\text{H}_3\text{CC}=\text{O}$); MS: m/z (ES+ mode) 285 (100%) [$\text{M}+\text{Na}^\text{+}$], 263 (88%) [$\text{M}+\text{H}^\text{+}$], HRMS Calcd for $\text{C}_{15}\text{H}_{19}\text{O}_4$: 263.1278. Found: 263.1267.

4.3. General procedure 1. Oxidative cleavage and Wittig olefination

A solution of keto-alkene in CH_2Cl_2 was degassed with N_2 then O_2 for 5 min at -78°C . Then O_3 was bubbled through the solution until a persistent blue colour was observed. The reaction was degassed with N_2 until the blue colour had dissipated and DMS added dropwise. The reaction was warmed to room temperature and stirred overnight. The reaction was quenched by the addition of saturated aqueous NaHCO_3 solution and the aqueous phase extracted with CH_2Cl_2 . The combined organics were dried (MgSO_4), filtered and concentrated in vacuo to give the crude aldehyde. The crude aldehyde was dissolved in CH_2Cl_2 at room temperature. Phosphorane **9** was added and the reaction stirred. The reaction mixture was concentrated in vacuo and purified by column chromatography to give the cyclisation substrate.

4.3.1. 3-(3-Hydroxymethyl-4-oxo-pentylidene)-dihydro-furan-2-one **11**

As described in general procedure 1. Ozonolysis performed on 3-hydroxymethyl-hex-5-en-2-one **7** (1.0 g, 7.81 mmol, 1.0 equiv) in CH_2Cl_2 (75 mL) and DMS (12 mL) gave the corresponding aldehyde (917 mg, 7.04 mmol, 90%). Subsequent Wittig olefination performed using phosphorane **9** (2.92 g, 8.46 mmol, 1.2 equiv) in CH_2Cl_2 (46 mL), stirring for 20 h, gave 3-(3-hydroxymethyl-4-oxo-pentylidene)-dihydro-furan-2-one **11** (334 mg, 1.87 mmol, 24%) after column chromatography (eluting with 60% EtOAc in petroleum ether (40–60 °C)). ν_{max} (ATR)/ cm^{-1} 3438s, 2923 m, 1740s (ketone C=O), 1706s (ester C=O), 1213 m, 1030 m; ^1H NMR δ 2.20 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.35–2.41 (1H, m, 1H from $\text{CH}_2\text{CH}=\text{C}$), 2.40–2.54 (1H, m, 1H from $\text{CH}_2\text{CH}=\text{CH}_2$), 2.80–2.85 (1H, m, 1H from $\text{CHCH}_2\text{CH}=\text{C}$), 2.86–2.90 (2H, m, $\text{CH}_2\text{CH}_2\text{O}$), 3.68–3.71 (1H, m, 1H from CH_2OH), 3.79–3.82 (1H, m, 1H from CH_2OH), 4.34 (2H, t, $J = 7.3$ Hz, $\text{CH}_2\text{OC}=\text{O}$), 6.58–6.62 (1H, m, $\text{CH}=\text{C}$); ^{13}C NMR δ 25.1 ($\text{CH}_2\text{CH}_2\text{O}$), 28.3 ($\text{CH}_2\text{CH}=\text{C}$), 30.2 ($\text{CH}_3\text{C}=\text{O}$), 52.8 ($\text{CHCH}_2\text{CH}=\text{C}$), 62.3 (CH_2OH), 65.6 (OCH_2CH_2), 127.8 (C^q), 136.6 ($\text{CH}=\text{C}$), 171.0 (ester C=O), 210.5 (ketone C=O); MS: m/z (Cl^-)⁺ 216 ($\text{M}+\text{NH}_4$)⁺ (100%), 199 ($\text{M}+\text{H}$)⁺ (33%), 186 (100%), 169 (30%); HRMS Calcd for $\text{C}_{10}\text{H}_{13}\text{O}_4$: 197.0808. Found: 197.0806.

4.3.2. 3-(3-Acetoxyethyl-4-oxo-pentylidene)-dihydro-furan-2-one **10b**

As described in general procedure 1. Ozonolysis performed on **8** ($\text{R} = \text{Ac}$) (140 mg, 0.823 mmol, 1.0 equiv) in CH_2Cl_2 (8.0 mL) and DMS (1.4 mL) gave the corresponding aldehyde (113 mg, 0.66 mmol, 80%). Wittig olefination performed using phosphorane **9** (440 mg, 1.30 mmol, 2 equiv) in CH_2Cl_2 (8.5 mL), stirring for 24 h, gave the cyclisation substrate **10b** (106 mg, 0.44 mmol, 68%) after column chromatography (eluting with 30% EtOAc in petroleum ether (40–60 °C)). ν_{max} (thin film)/ cm^{-1} 2928w, 1743s (C=O), 1716s (C=O), 1673m, 1431m, 1367m, 1224m, 1039m, 712w; ^1H NMR (500 MHz, CDCl_3) δ 2.06 (3H, s, $\text{OC}(\text{O})\text{CH}_3$), 2.24 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.31–2.37 (1H, m, 1H from $\text{CH}_2\text{CH}=\text{C}$), 2.55–2.61 (1H, m, 1H from $\text{CH}_2\text{CH}=\text{C}$), 2.85–2.96 (2H, m, $\text{CH}_2\text{CH}_2\text{OC}=\text{O}$), 3.01 (1H, p, $J = 6.3$ Hz, $\text{CHCH}_2\text{CH}=\text{C}$), 4.23 (1H, dd, $J = 11.0$, 6.3 Hz, 1H from $\text{CH}_2\text{OC}(\text{O})\text{CH}_3$), 4.28 (1H, dd, $J = 11.0$, 5.4 Hz, 1H from $\text{CH}_2\text{OC}(\text{O})\text{CH}_3$), 4.39 (2H, apparent t, $J = 7.6$ Hz, $\text{CH}_2\text{CH}_2\text{OC}=\text{O}$), 6.59–6.64 (1H, m, $\text{CH}=\text{C}$); ^{13}C NMR (125 MHz, CDCl_3) δ 20.7 ($\text{CH}_3\text{C}(\text{O})\text{O}$), 25.1 ($\text{CH}=\text{CCH}_2\text{CH}_2$), 28.7 ($\text{CH}_2\text{CH}=\text{C}$), 30.1 ($\text{CH}_3\text{C}=\text{O}$), 50.4 (CHCH_2O), 63.8 (CHCH_2O), 65.4 ($\text{CH}_2\text{CH}_2\text{OC}=\text{O}$), 128.0 ($\text{CH}=\text{C}$), 135.9 ($\text{CH}=\text{C}$), 170.5 ($\text{OC}(\text{O})\text{CH}_3$), 207.4 ($\text{CH}_3\text{C}=\text{O}$); MS: m/z (ES^+ mode) 263 (100%) [$\text{M}+\text{Na}$]⁺; HRMS Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_5\text{Na}$: 236.0890. Found: 236.0898.

4.3.3. Carbonic acid ethyl ester 3-oxo-2-[2-(2-oxo-dihydro-furan-3-ylidene)-ethyl]-butyl ester **10c**

As described in general procedure 1. Ozonolysis performed on **8** ($\text{R} = \text{C}(\text{O})\text{Et}$) (115 mg, 0.57 mmol, 1.0 equiv) in CH_2Cl_2 (5.6 mL) and DMS (1.0 mL) gave the corresponding aldehyde (118 mg, 0.58 mmol, 100%). Wittig olefination performed using phosphorane **9** (396 mg, 1.17 mmol, 2 equiv) in CH_2Cl_2 (7.6 mL), stirring for 24 h, gave the cyclisation substrate **10c** (125 mg, 0.46 mmol, 80%) after column chromatography (eluting with 30% EtOAc in petroleum ether (40–60 °C)). ν_{max} (thin film)/ cm^{-1} 2988w, 2913w, 1748s (C=O), 1718s (C=O), 1676 m, 1382w, 1367w, 1258s, 1194w, 1031w, 1011m, 962w, 7891w; ^1H NMR (500 MHz, CDCl_3) δ 1.30 (3H, t, $J = 7.0$ Hz, OCH_2CH_3), 2.25 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.34–2.40 (1H, m, 1H from $\text{CH}_2\text{CH}=\text{CH}_2$), 2.57–2.62 (1H, m, 1H from $\text{CH}_2\text{CH}=\text{CH}_2$), 2.85–2.96 (2H, m, $\text{CH}=\text{CCH}_2$), 3.05 (1H, p, $J = 6.5$ Hz, $\text{CH}_3\text{C}(\text{O})\text{CH}$), 4.19 (2H, q, $J = 7$ Hz, OCH_2CH_3), 4.29 (2H, t, $J = 5.5$ Hz, CHCH_2O), 4.38 (2H, t, $J = 7.5$ Hz, $\text{CH}=\text{CCH}_2\text{CH}_2$), 6.58–6.62 (1H, m, $\text{CH}=\text{C}$); ^{13}C NMR (125 MHz, CDCl_3) δ 14.2 ($\text{CH}_3\text{CH}_2\text{O}$), 25.1 ($\text{CH}=\text{CCH}_2$), 28.5 ($\text{CH}_2\text{CH}=\text{C}$), 30.2 ($\text{CH}_3\text{C}=\text{O}$), 50.3 ($\text{C}(\text{O})\text{CH}$),

CH_2O), 64.5 ($\text{CH}_3\text{CH}_2\text{O}$), 65.5 ($\text{CH}_3\text{CH}_2\text{OC}=\text{O}$), 66.8 ($\text{CH}_2\text{OC}(\text{O})\text{O}$), 128.2 ($\text{C}(\text{O})\text{C}=\text{CH}$), 135.6 ($\text{C}(\text{O})\text{C}=\text{CH}$), 154.7 ($\text{OC}(\text{O})\text{O}$), 170.7 ($\text{OC}(\text{O})\text{C}=\text{CH}$), 207.2 ($\text{CH}_3\text{C}=\text{O}$); MS: m/z (ES^+ mode) 562 (40%), 438 (37%), 293 (100%) [$\text{M}+\text{Na}$]⁺; HRMS Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_6\text{Na}$: 293.0996. Found: 293.1008.

4.3.4. 3-(3-(4-Methoxy)benzoyloxymethyl-4-oxo-pentylidene)-dihydro-furan-2-one **10d**

As described in general procedure 1. Ozonolysis performed on **8** ($\text{R} = \text{C}(\text{O})\text{PhMe-4}$) (186 mg, 0.71 mmol, 1.0 equiv) in CH_2Cl_2 (7.0 mL) and DMS (1.21 mL) gave the corresponding aldehyde (170 mg, 0.64 mmol, 91%). Wittig olefination performed using phosphorane **9** (436 mg, 1.29 mmol, 2 equiv) in CH_2Cl_2 (8.5 mL), stirring for 24 h, gave the cyclisation substrate **10d** (154 mg, 0.46 mmol, 75%) after column chromatography (eluting with 60% EtOAc in petroleum ether (40–60 °C)). ν_{max} (thin film)/ cm^{-1} 2958w, 2917w, 2839w, 2357w, 2337w, 1759s (C=O), 1711s (C=O), 1606s (C=O), 1580w, 1512m, 1420w, 1358w, 1317w, 1256s, 1192w, 1168m, 1102m, 1028m, 963w, 849w, 770m; ^1H NMR (500 MHz, CDCl_3) δ 2.28 (3H, s, $\text{H}_3\text{CC}=\text{O}$), 2.39–2.45 (1H, m, 1H from $\text{C}=\text{CHCH}_2$), 2.63–2.67 (1H, m, 1H from $\text{C}=\text{CHCH}_2$), 2.83–2.94 (2H, m, $\text{CH}_2=\text{CCH}_2$), 3.13 (1H, quint, $J = 6$ Hz, $\text{CH}_3\text{C}(\text{O})\text{CH}$), 3.85 (3H, s, OCH_3), 4.33–4.36 (2H, m, $\text{CH}_2=\text{CCH}_2\text{CH}_2$), 4.46–4.49 (2H, m, $\text{CHCH}_2\text{OC}(\text{O})$), 6.63–6.68 (1H, m, $\text{CH}_2=\text{C}$), 6.91 (2H, d, $J = 8.5$ Hz, H_3COCCH), 7.92 (2H, d, $J = 7.5$ Hz, H_3COCCH); ^{13}C NMR (125 MHz, CDCl_3) δ 25.1 ($\text{CH}_2\text{CH}_2\text{OC}=\text{O}$), 28.7 ($\text{CH}_2\text{CH}=\text{C}$), 30.0 ($\text{CH}_3\text{C}=\text{O}$), 50.6 ($\text{CHCH}_2\text{OC}=\text{O}$), 55.5 (OCH_3), 64.0 ($\text{CHCH}_2\text{OC}=\text{O}$), 65.5 ($\text{CH}_2\text{CH}_2\text{OC}=\text{O}$), 113.7 ($2 \times \text{ArCH}$), 121.6 (ArC), 127.9 ($\text{C}(\text{O})\text{C}=\text{CH}$), 131.7 ($2 \times \text{ArCH}$), 136.2 ($\text{CH}_2\text{CH}=\text{C}$), 163.7 (ArC), 165.8 ($\text{PhC}=\text{O}$), 170.8 ($\text{CH}_2\text{CH}_2\text{OC}=\text{O}$), 207.5 ($\text{H}_3\text{CC}=\text{O}$); MS: m/z (ES^+ mode) 355 (56%) [$\text{M}+\text{Na}$]⁺, 350 (100%) [$\text{M}+\text{NH}_4$]⁺; HRMS Calcd for $\text{C}_{18}\text{H}_{20}\text{O}_6\text{Na}$: 355.1152. Found: 355.1146.

4.3.5. 3-(3-Benzoyloxymethyl-4-oxo-pentylidene)-dihydro-furan-2-one **10e**

To a stirred solution of **11** (76 mg, 0.38 mmol) in CH_2Cl_2 (2.6 mL) at 0 °C was added triethylamine (0.06 mL, 0.42 mmol, 1.1 equiv), benzoyl chloride (0.05 mL, 0.42 mmol, 1.1 equiv) and DMAP (51.3 mg, 0.42 mmol, 1.1 equiv) dropwise. After 90 min, the solution was diluted with CH_2Cl_2 (20 mL), and washed with saturated aqueous NaCl solution (10 mL). The organic layer was dried (MgSO_4), filtered and concentrated in vacuo. The crude residue was purified by chromatography (silica gel, 40% EtOAc in petroleum ether (40–60 °C)) to give **10e** (21 mg, 0.07 mmol, 18%). **10e** was found to be unstable thus preventing full characterisation. ^1H NMR (500 MHz, CDCl_3) δ 2.30 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.44 (1H, p AB system, $J = 7.9$ Hz, 1H from $\text{CH}_2\text{CH}=\text{C}$), 2.68 (1H, p AB system, $J = 7.9$ Hz, 1H from $\text{CH}_2\text{CH}=\text{C}$), 2.84–2.98 (2H, m, $\text{CH}_2\text{CH}_2\text{OC}=\text{O}$), 3.12–3.19 (1H, m, $\text{CH}_3\text{C}(\text{O})\text{CH}$), 4.36 (2H, t, $J = 7.6$ Hz, $\text{CH}_2\text{CH}_2\text{OC}=\text{O}$), 4.52 (2H, t, $J = 5.4$ Hz, $\text{CHCH}_2\text{OC}=\text{O}$), 4.65–4.69 (1H, m, $\text{CH}_2\text{CH}=\text{C}$), 7.45 (2H, t, $J = 7.9$ Hz, $2 \times \text{ArCH}$), 7.59 (1H, t, $J = 7.6$ Hz, ArCH), 7.98 (2H, d, $J = 7.6$ Hz, $2 \times \text{ArCH}$).

4.3.6. 3-[3-(2-Methoxy-ethoxymethoxymethyl)-4-oxo-pentylidene]-dihydro-furan-2-one **10f**

To a stirred solution of **11** (100 mg, 0.5 mmol, 1 equiv) in CH_2Cl_2 (0.5 mL) was added diisopropylethylamine (1.05 mL, 6 mmol, 12 equiv) and the mixture stirred for 10 min at room temperature. MEMCl (0.34 mL, 3 mmol, 6 equiv) was added dropwise and the reaction stirred for 13 h. Et_2O (10 mL) and HCl (10 mL) were added and the aqueous phase extracted with Et_2O (3×10 mL). The combined organic phases were dried (MgSO_4), filtered and concentrated in vacuo to give the crude product which was purified by column chromatography (eluting with 50% EtOAc in petroleum ether (40–60 °C)) to give the desired MEM ether **10f** (76.4 mg, 54%) as a clear oil. ν_{max} (thin film)/ cm^{-1} 2899 m, 1754s (lactone C=O), 1714s (ketone C=O), 1032m; ^1H NMR δ 2.16 (3H, s,

CH₃C=O), 2.23–2.30 (1H, m, 1H from C=CHCH₂), 2.47–2.54 (1H, m, 1H from C=CHCH₂), 2.77–2.91 (3H, m, C(O)CH, CH₂CH₂OC=O), 3.33 (3H, s, OCH₃), 3.47–3.49 (2H, m, OCH₂CH₂O), 3.55–3.62 (2H, m, OCH₂CH₂O), 3.63–3.69 (2H, m, C(O)CHCH₂), 4.31 (2H, t, *J* = 7.5 Hz, CH₂OC=O), 4.61 (2H, s, OCH₂O), 6.54–6.58 (1H, m, C=CHCH₂); ¹³C NMR δ 25.10 (CH₂CH₂OC=O), 28.66 (C=CHCH₂), 30.29 (CH₃C=O), 51.38 (CH₃C(O)CH), 59.10 (OCH₃), 65.49 (C(O)CHCH₂O), 67.13 (OCH₂CH₂O), 67.94 (CH₂OC=O), 71.66 (OCH₂CH₂O), 95.63 (OCH₂O), 136.80 (C=CHCH₂), (C=O) and (C(O)O) not observed; MS: *m/z* (ESI)⁺ 332 (100%) [M+Na]⁺; HRMS Calcd for C₁₄H₂₂O₆Na: 309.1309. Found: 309.1305.

4.4. Cyclisation of model substrates 10a–f

4.4.1. *rac*-(5S,6S,7R)-7-(*tert*-Butyl-dimethyl-silanyloxymethyl)-6-hydroxy-6-methyl-2-oxa-spiro[4.4]nonan-1-one 12a and *rac*-(5S,6S,7S)-7-(*tert*-butyl-dimethyl-silanyloxymethyl)-6-hydroxy-6-methyl-2-oxa-spiro[4.4]nonan-1-one 13a

To a stirred solution of **11** (100 mg, 0.50 mmol, 1.0 equiv) in DMF (1.0 mL) at room temperature was added imidazole (171 mg, 2.5 mmol, 5.0 equiv) the TBSCl (226 mg, 1.5 equiv mmol, 3.0 equiv) and the reaction stirred overnight. The reaction was quenched by the addition of saturated aqueous NaHCO₃ solution (15 mL) and the aqueous phase extracted in CH₂Cl₂ (3 × 20 mL). The combined organic phases were washed with H₂O (3 × 20 mL), dried (MgSO₄), filtered and concentrated in vacuo to give the TBS protected cyclisation substrate **10a** (156 mg, 0.50 mmol, 100%) which was used without further purification. To a stirred solution of SmI₂ (20 mL, 0.1 M in THF, 2.0 mmol, 4.0 equiv) at 0 °C was added dry MeOH (4.68 mL) and the solution stirred for 10 min. TBDMS protected cyclisation substrate **10a** (156 mg, 0.5 mmol, 1 equiv) in THF (3.4 mL) was added and the reaction stirred for 30 min. The reaction was quenched by exposure to air followed by addition of saturated aqueous NaCl solution (10 mL). The aqueous phase was extracted with EtOAc and the combined organic extracts dried (MgSO₄) and concentrated to give the crude product. Purification by column chromatography (silica gel, 10% *i*-PrOH in petroleum ether (40–60 °C)) gave the all *syn* (46.2 mg, 29%) and *syn*, *anti* (43 mg, 27%) spirocycles **12a** and **13a**, respectively, as clear crystalline solids. For the all *syn* spirocycle **12a**: mp 70.7–71.2 °C; *v*_{max} (thin film)/cm^{−1} 2950m, 2362m, 1742s (C=O), 1150s; ¹H NMR δ 0.00 (6H, s, Si(CH₃)₂), 0.83 (9H, s, SiC(CH₃)₃), 1.27 (3H, s, C^q(OH)CH₃), 1.61–1.70 (2H, m, 1H from C^qCH₂CH₂CH, 1H from CH₂CHCH₂OSi), 1.81–1.95 (3H, m, 1H from CH₂CH₂O, 1H from C^qCH₂CH₂CH, CH₂CHCH₂OSi), 2.16–2.26 (2H, m, 1H from CH₂CH₂O, 1H from CH₂CHCH₂OSi), 3.59 (1H, dd, *J* = 10, 6 Hz, 1H from CH₂OSi), 3.88 (1H, dd, *J* = 10, 6 Hz, 1H from CH₂OSi), 4.13–4.18 (1H, m, 1H from CH₂OC=O), 4.25 (1H, dt, *J* = 9, 4 Hz, 1H from CH₂OC=O); ¹³C NMR δ −5.45 (SiCH₃), −5.27 (SiCH₃), 21.06 (C^q(OH)CH₃), 25.53 (C^q), 25.93 (SiC(CH₃)₃), 32.51 (CH₂CHCH₂OSi), 32.69 (CH₂CH₂OC=O), 50.28 (CHCH₂OSi), 55.80 (C^q), 62.74 (CH₂OSi), 65.33 (CH₂OC=O), 81.99 (C^q), 181.40 (C=O); MS: *m/z* (CI)⁺ 315 (100%) [M+H]⁺, 79 (35%); HRMS Calcd for C₁₆H₃₁O₄Si: 315.1986. Found: 315.1979. For the *syn*, *anti* spirocycle **13a**: mp 65.7–66.2 °C; *v*_{max} (thin film)/cm^{−1} 2929 m, 1761 s (C=O), 1375 m, 1254 s, 1100 s, 838 s; ¹H NMR δ 0.00 (3H, s, Si(CH₃)₂), 0.01 (3H, s, Si(CH₃)₂), 0.82 (9H, s, SiC(CH₃)₃), 1.17 (3H, s, C^q(OH)CH₃), 1.53 (1H, ddd, *J* = 14, 11, 4 Hz, 1H from C^qCH₂CH₂CH), 1.81–1.89 (1H, m, CH₂CHCH₂OSi), 1.98–2.11 (2H, m, 1H from CH₂CH₂O, 1H from C^qCH₂CH₂CH), 2.43 (1H, ddd, *J* = 13.5, 6.5, 4 Hz, 1H from CH₂CH₂O), 2.85–2.92 (1H, m, CH₂CHCH₂OSi), 3.59 (1H, t, *J* = 9.5 Hz, 1H, from CH₂OSi), 3.73 (1H, dd, *J* = 10, 5.5 Hz, 1H from CH₂OSi), 4.10–4.14 (1H, m, 1H from CH₂OC=O), 4.23–4.28 (1H, m, 1H from CH₂OC=O); ¹³C NMR δ −5.71 (SiCH₃), −5.56 (SiCH₃), 18.79 (C^q(OH)CH₃), 22.58 (C^q), 25.78 (SiC(CH₃)₃), 25.88 (SiC(CH₃)₃),

25.93 (SiC(CH₃)₃), 30.90 (CH₂CHCH₂OSi), 31.01 (CH₂CH₂OC=O), 47.35 (CHCH₂OSi), 56.28 (C^q), 63.90 (CH₂OSi), 65.51 (CH₂OC=O), 81.80 (C^q), 180.98 (C=O); MS: *m/z* (CI)⁺ 332 (10%) [M+NH₄]⁺, 315 (45%) [M+H]⁺, 182 (55%), 79 (100%); HRMS Calcd for C₁₆H₃₁O₄Si: 315.1986. Found: 315.2000.

4.4.2. *rac*-(5S,6S,7R)-7-(Acetoxymethyl)-6-hydroxy-6-methyl-2-oxa-spiro[4.4]nonan-1-one 12b and *rac*-(5S,6S,7S)-7-(acetoxymethyl)-6-hydroxy-6-methyl-2-oxa-spiro[4.4]nonan-1-one 13b

To a stirred solution of SmI₂ (0.1 M in THF, 6.24 mL, 0.624 mmol, 3 equiv) and MeOH (1.63 mL) at 0 °C was added a solution of lactone **10b** (50 mg, 0.208 mmol) in THF (0.35 mL) and the reaction stirred for 1 h. Air was introduced into the reaction vessel and the reaction quenched by the addition of saturated, aqueous NH₄Cl solution (~20 mL). The aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic phases were dried over MgSO₄ filtered and concentrated in vacuo. The crude residue was purified by chromatography (silica gel, 30% EtOAc in petroleum ether (40–60 °C)) to give the two spirocyclic compounds **12b** (17.0 mg, 0.071 mmol, 34%) and **13b** (8.9 mg, 0.037 mmol, 18%) as colourless oils. For the all *syn* compound **12b**: *v*_{max} (thin film)/cm^{−1} 3469w (OH), 2953w, 2918w, 2362w, 2342w, 1736s (C=O), 1464w, 1370 m, 1238s, 1147w, 1029 m; ¹H NMR (500 MHz, CDCl₃) δ 1.34 (3H, s, CH₃COH), 1.72–1.80 (2H, m, 1H from CH₂CH₂CH, 1H from CH₂CH₂CH), 1.94–2.02 (2H, m, 1H from CH₂CH₂OC=O, 1H from CH₂CH₂CH), 2.05 (3H, s, CH₃C(O)O), 2.09 (1H, q, *J* = 7.5 Hz, CHCH₂OC(O)CH₃), 2.25–2.31 (2H, m, 1H from CH₂CH₂OC=O, 1H from CH₂CH₂CH), 4.16–4.26 (3H, m, 1H from CH₂CH₂OC=O, 1H from CH₂OC(O)CH₃, OH), 4.32–4.37 (2H, m, 1H from CH₂CH₂OC=O, 1H from CH₂OC(O)CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 21.0 (CH₃C=O), 21.8 (OHCH₃), 25.6 (CH₂CH₂CH), 32.2 (CH₂CH₂CH), 32.5 (CH₂CH₂OC=O), 46.8 (CHCH₂OC=O), 55.4 (CH₂O-C(O)C), 63.9 (CHCH₂OC=O), 65.4 (CH₂CH₂OC=O), 81.7 (HOCCH₃), 171.1 (CH₃C=O), 181.6 (C=O); MS: *m/z* (ES⁺ mode) 507 (18%), 265 (100%) [M+Na]⁺; HRMS Calcd for C₁₂H₁₈O₅Na: 265.1046. Found: 265.1049. For the *syn*, *anti* compound **13b**: *v*_{max} (thin film)/cm^{−1} 3469w (OH), 2958w, 2918w, 2362w, 1736s (C=O), 1466w, 1370 m, 1244s, 1157w, 1029 m; ¹H NMR (500 MHz, CDCl₃) δ 1.16 (3H, s, CH₃COH), 1.38–1.46 (1H, m, 1H from CH₂CH₂CH), 1.70 (1H, ddd, *J* = 15.0, 11.0, 4.0 Hz, 1H from CH₂CH₂CH), 1.99 (1H, ddd, *J* = 12.5, 6.5, 4.0 Hz, 1H from CH₂CH₂OC=O), 2.06 (3H, s, CH₃C=O), 2.06–2.13 (1H, m, 1H from CH₂CH₂CH), 2.20 (1H, ddd, *J* = 14.0, 10.0, 6.5 Hz, 1H from CH₂CH₂CH), 2.50 (1H, dt, *J* = 12.5, 8.0 Hz, 1H from CH₂CH₂OC=O), 2.78 (1H, s, OH), 2.98 (1H, tt, *J* = 10.0, 7.0 Hz, CHCH₂O-C(O)CH₃), 4.11 (1H, dd, *J* = 11.5, 7.5 Hz, 1H from CH₂OC(O)CH₃), 4.16–4.22 (2H, m, 1H from CH₂OC(O)CH₃, 1H from CH₂CH₂OC=O), 4.35 (1H, apparent dt, *J* = 8.5, 4.5 Hz, 1H from CH₂CH₂OC=O); ¹³C NMR (125 MHz, CDCl₃) δ 18.6 (OHCH₃), 20.9 (CH₃C=O), 24.1 (CH₂CH₂CH), 31.1 (CH₂CH₂CH), 31.4 (CH₂CH₂OC=O), 46.2 (CHCH₂OC=O), 56.0 (CH₂OC(O)C), 64.7 (CHCH₂OC=O), 65.7 (CH₂CH₂OC=O), 80.9 (HOCCH₃), 171.0 (CH₃C=O), 180.6 (C=O); MS: *m/z* (ES⁺ mode) 507 (12%), 265 (100%) [M+Na]⁺; HRMS Calcd for C₁₂H₁₈O₅Na: 265.1046. Found: 265.1047.

4.4.3. *rac*-(5S,6S,7R)-7-(Methylenecarbonate-ethyl ester)-6-hydroxy-6-methyl-2-oxa-spiro[4.4]nonan-1-one 12c and *rac*-(5S,6S,7S)-7-(methylenecarbonate-ethyl ester)-6-hydroxy-6-methyl-2-oxa-spiro[4.4]nonan-1-one 13c

To a stirred solution of SmI₂ (0.1 M in THF, 5.6 mL, 0.560 mmol, 3 equiv) and MeOH (1.5 mL) at 0 °C was added a solution of lactone **10c** (50 mg, 0.185 mmol) in THF (0.322 mL) and the reaction stirred for 90 min. Air was introduced into the reaction vessel and the reaction quenched with saturated, aqueous NH₄Cl solution. The aqueous

layer was extracted with EtOAc (4 × 25 ml). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The crude residue was purified by chromatography (silica gel, 40% EtOAc in petroleum ether (40–60 °C)) to give the two spirocycles **12c** (19.4 mg, 0.071 mmol, 39%) and **13c** (14.1 mg, 0.052 mmol, 28%) as colourless oils. For the all-*syn* compound **12c**: ν_{\max} (thin film)/cm⁻¹ 3469w (OH), 2923w, 2853w, 2357w, 1738s (C=O), 1463w, 1370m, 1258s, 1026m, 789w; ¹H NMR (500 MHz, CDCl₃) δ 1.31 (3H, t, *J* = 7.0 Hz, CH₃CH₂O), 1.35 (3H, s, CH₃COH), 1.74–1.82 (2H, m, 1H from CH₂CH₂CH, 1H from CH₂CH₂CH), 1.96 (1H, ddd, *J* = 13.0, 7.0, 2.5 Hz, 1H from CH₂CH₂CH), 2.00–2.06 (1H, m, 1H from CH₂CH₂OC=O), 2.13 (1H, p, *J* = 9 Hz, CHCH₂OC(O)O), 2.25–2.33 (2H, m, 1H from CH₂CH₂OC=O, 1H from CH₂CH₂CH), 4.17–4.26 (4H, m, 2H from CH₃CH₂C=O, 1H from CH₂CH₂OC=O, 1H from CHCH₂OC(O)O), 4.35 (1H, dt, *J* = 9.0, 2.5 Hz, 1H from CH₂CH₂OC=O), 4.55 (1H, dd, *J* = 10.5, 6.5 Hz, 1H from CHCH₂OC(O)O); ¹³C NMR (125 MHz, CDCl₃) δ 14.3 (CH₃CH₂OC=O), 21.7 (CH₃COH), 25.7 (CH₂CH₂CH), 32.2 (CH₂CH₂CH), 32.5 (CH₂CH₂OC=O), 47.0 (CHCH₂OC=O), 55.3 (CH₂OC(O)C), 63.9 (CH₃CH₂OC=O), 65.4 (CH₂CH₂OC=O), 67.5 (CHCH₂OC=O), 81.7 (CH₃COH), 155.2 (OC(O)O), 181.5 (CH₂OC=O); MS: *m/z* (ES⁺ mode) 567 (22%), 295 (100%) [M+Na]⁺; HRMS Calcd for C₁₃H₂₁O₆: 273.1333. Found: 273.1335. For the *syn-anti* compound **13c**: ν_{\max} (thin film)/cm⁻¹ 3469w (OH), 2972w, 2923w, 1743s (C=O), 1466w, 1370 m, 1261s, 1029 m, 791w; ¹H NMR (500 MHz, CDCl₃) δ 1.17 (3H, s, CH₃COH), 1.31 (3H, t, *J* = 7.0 Hz, CH₃CH₂OC=O), 1.41–1.49 (1H, m, 1H from CH₂CH₂CH), 1.70 (1H, ddd, *J* = 14.5, 11.0, 4.0 Hz, 1H from CH₂CH₂CH), 1.99 (1H, ddd, *J* = 13.0, 6.5, 4.0 Hz, 1H from CH₂CH₂OC=O), 2.08–2.22 (2H, m, 1H from CH₂CH₂CH, 1H from CH₂CH₂CH), 2.49 (1H, dt, *J* = 17.0, 8.5 Hz, 1H from CH₂CH₂OC=O), 2.84 (1H, s, OH), 3.01 (1H, tt, *J* = 19.0, 9.5, 7.0 Hz, CHCH₂OC(O)O), 4.14–4.23 (4H, m, 2H from CH₃CH₂OC=O, 1H from CH₂CH₂OC=O, 1H from CHCH₂OC(O)O), 4.27 (1H, dd, *J* = 10.5, 6.5 Hz, 1H from CHCH₂OC(O)O), 4.35 (1H, apparent dt, *J* = 8.5, 4.0 Hz, 1H from CH₂CH₂OC=O); ¹³C NMR (125 MHz, CDCl₃) δ 14.3 (CH₃CH₂OC=O), 18.7 (CH₃COH), 23.9 (CH₂CH₂CH), 31.1 (CH₂CH₂CH), 31.3 (CH₂CH₂OC=O), 46.3 (CHCH₂OC=O), 56.0 (CH₂OC(O)C), 64.1 (CH₃CH₂OC=O), 65.7 (CH₂CH₂OC=O), 67.9 (CHCH₂OC=O), 80.9 (CH₃COH), 155.1 (OC(O)O), 180.6 (CH₂OC=O); MS: *m/z* (ES⁺ mode) 567 (18%), 295 (100%) [M+Na]⁺; HRMS Calcd for C₁₃H₂₁O₆: 273.1333. Found: 273.1341.

4.4.4. *rac*-((1*R*,2*S*,5*R*)-2-(4-Methoxy)benzyloxymethyl-1-methyl-1-hydroxy-6-oxo-7-oxaspiro[4.4]nonane) **12d** and *rac*-((1*R*,2*R*,5*R*)-2-(4-methoxy)benzyloxymethyl-1-methyl-1-hydroxy-6-oxo-7-oxaspiro[4.4]nonane) **13d**

To a stirred solution of Sml₂ (0.1 M in THF, 10.9 mL, 1.09 mmol, 3.0 equiv) and MeOH (2.82 mL) at 0 °C was added a solution of lactone **10d** (120 mg, 0.36 mmol, 1.0 equiv) in THF (0.61 mL) and the reaction stirred for 90 min. Air was introduced into the reaction vessel and the reaction quenched with saturated, aqueous NH₄Cl solution. The aqueous layer was extracted with EtOAc (4 × 25 ml). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The crude residue was purified by chromatography (silica gel, 40% EtOAc in petroleum ether (40–60 °C)) to give the two spirocycles **12d** (41 mg, 0.122 mmol, 34%) and **13d** (26 mg, 0.078 mmol, 21%) in a 1.6:1 ratio as colourless oils. For the all-*syn* isomer **12d**: ν_{\max} (thin film)/cm⁻¹ 3474w (OH), 2965 m, 1740s, 1707s, 1606s, 1512 m, 1465w, 1420w, 1371 m, 1317 m, 1277s, 1256s, 1204w, 1168s, 1148w, 1115 m, 1104 m, 1025s, 848 m, 771 m; ¹H NMR (500 MHz, CDCl₃) δ 1.39 (3H, s, HOCCH₃), 1.77–1.86 (2H, m, 1H from CH₂CH₂CH, 1H from CH₂CH₂CH), 1.98 (1H, ddd, *J* = 13, 7, 2.5 Hz, 1H from CH₂CH₂OC=O), 2.02–2.08 (1H, m, 1H from CH₂CH₂CH), 2.20–2.34 (3H, m, 1H from CH₂CH₂OC=O, 1H from CH₂CH₂CH, CH₂CH₂CH), 3.85 (3H, s, OCH₃), 4.21–4.26 (1H, m, 1H from CH₂CH₂OC=O), 4.35

(1H, dt, *J* = 9.5, 2.5 Hz, 1H from CH₂CH₂OC=O), 4.39–4.42 (1H, m, CHCH₂OC=O), 4.56 (1H, dd, *J* = 10.5, 8 Hz, CHCH₂OC=O), 6.91 (2H, d, *J* = 8.5 Hz, 2 × CHCHCOCH₃), 7.98 (2H, d, *J* = 9 Hz, 2 × CHCHCOCH₃); ¹³C NMR (125 MHz, CDCl₃) δ 22.0 (HOCCH₃), 25.5 (CH₂CH₂CH), 32.2 (CH₂CH₂CH), 32.6 (CH₂CH₂OC=O), 47.1 (CHCH₂OC=O), 55.5 (CH₂CH₂OC(O)C), 55.5 (OCH₃), 63.8 (CHCH₂OC=O), 65.4 (CH₂CH₂OC=O), 81.7 (CH₃COH), 113.6 (2 × ArCH), 122.7 (ArC), 131.6 (2 × ArCH), 163.3 (ArC), 166.3 (CHCH₂OC=O), 181.7 (CH₂CH₂OC=O); MS: *m/z* (ES⁺ mode) 357 (88%) [M+Na]⁺, 352 (45%) [M+NH₄]⁺, 335 (94%) [M+H]⁺, HRMS Calcd for C₁₈H₂₂O₆Na: 357.1309. Found: 357.1303. For the *syn-anti* isomer **13d**: ν_{\max} (thin film)/cm⁻¹ 3481w (OH), 2964w, 1757 m, 1707s, 1606s, 1512 m, 1465w, 1419w, 1375w, 1317w, 1277s, 1256s, 1168s, 1104 m, 1027 m, 962w, 849w, 771 m; ¹H NMR (500 MHz, CDCl₃) δ 1.22 (3H, s, HOCCH₃), 1.47–1.55 (1H, m, 1H from CH₂CH₂CH), 1.73 (1H, ddd, *J* = 13, 11, 4 Hz, 1H from CH₂CH₂CH), 2.01 (1H, ddd, *J* = 13, 5.4, 4 Hz, 1H from CH₂CH₂CH), 2.12–2.25 (2H, m, 1H from CH₂CH₂CH, 1H from CH₂CH₂OC=O), 2.52 (1H, dt, *J* = 13, 8.5 Hz, 1H from CH₂CH₂OC=O), 3.12 (1H, m, CH₂CH₂CH), 3.85 (3H, s, OCH₃), 4.20 (1H, dt, *J* = 8.5, 6.5 Hz, 1H from CH₂CH₂OC=O), 4.30–4.41 (3H, m, 1H from CH₂CH₂OC=O, CHCH₂OC=O), 6.91 (2H, d, *J* = 9 Hz, 2 × CHCHCOCH₃), 7.97 (2H, d, *J* = 9 Hz, 2 × CHCHCOCH₃); ¹³C NMR (125 MHz, CDCl₃) δ 18.7 (HOCCH₃), 24.2 (CH₂CH₂CH), 31.2 (CH₂CH₂CH), 31.4 (CH₂CH₂OC=O), 46.5 (CHCH₂OC=O), 55.5 (CH₂CH₂OC(O)C), 56.1 (OCH₃), 64.8 (CHCH₂OC=O), 65.7 (CH₂CH₂OC=O), 81.1 (CH₃COH), 113.7 (2 × ArCH), 122.4 (ArC), 131.6 (2 × ArCH), 163.4 (ArC), 166.3 (CHCH₂OC=O), 180.7 (CH₂CH₂OC=O); MS: *m/z* (ES⁺ mode) 357 (56%) [M+Na]⁺, 352 (100%) [M+NH₄]⁺, HRMS Calcd for C₁₈H₂₂O₆Na: 357.1309. Found: 357.1312.

4.4.5. *rac*-(5*S*,6*S*,7*R*)-7-(Methylenebenzoate)-6-hydroxy-6-methyl-2-oxa-spiro[4.4]nonan-1-one **12e** and *rac*-(5*S*,6*S*,7*S*)-7-(methylenebenzoate)-6-hydroxy-6-methyl-2-oxa-spiro[4.4]nonan-1-one **13e**

To a stirred solution of Sml₂ (0.1 M in THF, 1.98 mL, 0.198 mmol, 3 equiv) and MeOH (0.52 mL) at 0 °C was added a solution of benzoate ester **10e** (20 mg, 0.066 mmol) in THF (0.11 mL) and the reaction mixture stirred for 45 min. Air was introduced into the reaction vessel and the reaction quenched with saturated NH₄Cl solution (10 mL). The aqueous phase was separated and extracted with EtOAc (5 × 10 mL). The combined organics were dried over MgSO₄, filtered and concentrated in vacuo. The crude residue was purified by chromatography (silica gel, 50% EtOAc in petroleum ether (40–60 °C)) to give the two spirocycles **12e** (5.7 mg, 0.019 mmol, 28%) and **13e** (5.1 mg, 0.017 mmol, 25%) as clear oils. For the all-*syn* isomer **12e**: ν_{\max} (thin film)/cm⁻¹ 3478w, 2913w, 2849w, 2362w, 1740s (C=O), 1716 (C=O), 1370w, 1273w, 1204 m, 1115w, 1024 m, 709 m; ¹H NMR (500 MHz, CDCl₃) δ 1.41 (3H, s, CH₃COH), 1.79–1.89 (2H, m, 1H from CH₂CH₂CH, 1H from CH₂CH₂CH), 1.99 (1H, ddd, *J* = 12.9, 6.9, 2.8 Hz, 1H from CH₂CH₂OC=O), 2.04–2.11 (1H m, 1H from CH₂CH₂CH), 2.23–2.37 (3H, m, 1H from CH₂CH₂OC=O, 1H from CH₂CH₂CH, 1H from CH₂CH₂CH), 4.26 (1H, apparent dt, *J* = 9.5, 6.7 Hz, 1H from CH₂CH₂OC=O), 4.34 (1H, d, *J* = 1.3 Hz, OH), 4.37 (1H, apparent dt, *J* = 9.2, 2.9 Hz, 1H from CH₂CH₂OC=O), 4.46 (1H, dd, *J* = 11.0, 6.6 Hz, 1H from CHCH₂OC=O), 4.62 (1H dd, *J* = 11.0, 7.6 Hz, 1H from CHCH₂CO=O), 7.45 (2H, apparent t, *J* = 8.2 Hz, 2 × ArH), 7.57 (1H, tt, *J* = 7.6, 1.3 Hz, ArH), 8.05 (2H, dd, *J* = 8.2, 1.3 Hz, 2 × ArH); ¹³C NMR (125 MHz, CDCl₃) δ 22.0 (CH₃), 25.5 (CH₂CH₂CH), 32.2 (CH₂CH₂CH), 32.6 (CH₂CH₂OC=O), 47.1 (CHCH₂OC=O), 55.5 (CH₂CH₂OC(O)C), 64.2 (CHCH₂OC=O), 65.4 (CH₂CH₂OC=O), 81.7 (CH₃COH), 128.4 (ArC), 129.6 (ArC), 130.3 (ArC), 133.0 (ArC), 166.6 (CH₂CH₂OC=O), 181.7 (ArC=O), MS: *m/z*

(ES⁺ mode) 405 (23%), 327 (68%) [M+Na]⁺, 179 (100%), 101 (84%); HRMS Calcd for C₁₇H₂₀O₅Na: 327.1203. Found: 327.1196. For the *syn-anti* isomer **13e**: ν_{\max} (thin film)/cm⁻¹ 3578 m, 2913 m, 2849w, 2362w, 2333w, 1753s (C=O), 1713 (C=O), 1449w, 1372w, 1273s, 1174w, 1113 m, 1024 m, 712 m; ¹H NMR (500 MHz, CDCl₃) δ 1.24 (3H, s, CH₃), 1.52–1.57 (1H, m, 1H from CH₂CH₂CH), 1.76 (1H, ddd, *J* = 14.5, 11.1, 4.1 Hz, 1H from CH₂CH₂CH), 2.02 (1H, ddd, *J* = 12.9, 6.6, 3.8 Hz, 1H from CH₂CH₂CH), 2.15–2.31 (2H, m, 1H from CH₂CH₂CH, 1H from CH₂CH₂OC=O), 2.54 (1H, dt, *J* = 12.6, 6.4 Hz, 1H from CH₂CH₂OC=O), 2.81 (1H, s, OH), 3.15 (1H, tt, *J* = 9.5, 7.3 Hz, CH₂CH₂CH), 4.22 (1H, apparent dt, *J* = 9.2, 6.7 Hz, 1H from CH₂CH₂OC=O), 4.35–4.39 (2H, m, 1H from CH₂CH₂OC=O, 1H from CHCH₂OC=O), 4.44 (1H, dd, *J* = 11.0, 6.9 Hz, 1H from CHCH₂OC=O), 7.45 (2H, t, *J* = 8.2 Hz, 2 × ArH), 7.58 (1H, tt, *J* = 7.6, 1.3 Hz, ArH), 8.03 (2H, dd, *J* = 8.2, 1.0 Hz, 2 × ArH); ¹³C NMR (125 MHz, CDCl₃) δ 18.7 (CH₃), 24.1 (CH₂CH₂CH), 31.2 (CH₂CH₂CH), 31.4 (CH₂CH₂OC=O), 46.5 (CHCH₂OC=O), 56.1 (CH₂CH₂OC(O)C), 65.1 (CHCH₂OC=O), 65.7 (CH₂CH₂OC=O), 81.0 (CH₃COH), 128.5 (ArC), 129.6 (ArC), 130.0 (ArC), 133.1 (ArC), 166.6 (CH₂CH₂OC=O), 181.7 (ArC=O), MS: *m/z* (ES⁺ mode) 405 (18%), 327 (100%) [M+Na]⁺, 322 (19%) [M+NH₄]⁺, 179 (48%), 101 (48%); HRMS Calcd for C₁₇H₂₀O₅Na: 327.1203. Found: 327.1196.

4.4.6. *rac*-(5S,6S,7R)-6-Hydroxy-7-(2-methoxy-ethoxymethoxy methyl)-6-methyl-2-oxa-spiro[4.4]nonan-1-one **12f** and *rac*-(5S,6S,7S)-6-hydroxy-7-(2-methoxy-ethoxymethoxymethyl)-6-methyl-2-oxa-spiro[4.4]nonan-1-one **13f**

To a solution of Sml₂ (10.4 mL, 0.1 M in THF, 1.04 mmol, 4.0 equiv) at 0 °C was added dry MeOH (2.44 mL), and the solution stirred for 10 min. Next, the MEM protected cyclisation substrate **10f** (80 mg, 0.26 mmol, 1.0 equiv) was added and the reaction stirred at 0 °C for 40 min. The reaction was quenched by exposure to air followed by the addition of saturated aqueous NaCl solution (10 mL). The aqueous phase was extracted with EtOAc (4 × 15 mL) and the combined organic extracts dried (MgSO₄) and concentrated to give the crude product. Purification by column chromatography (eluting with 60% EtOAc in petroleum ether (40–60 °C)) gave the all *syn* (28 mg, 0.097 mmol, 37%) and *syn, anti* (35 mg, 0.122 mmol, 47%) spirocycles **12f** and **13f**, respectively, as clear oils. For the all *syn* spirocycle **12f**: ν_{\max} (thin film)/cm⁻¹ 3482 m, 2921 m, 1739s (lactone C=O), 1372s, 1201s; ¹H NMR δ 1.27 (3H, s, C(OH)CH₃), 1.65–1.72 (2H, m, 1H from C^qCH₂CH₂CH, 1H from CH₂CHCH₂O), 1.88–1.20 (3H, m, 1H from CH₂CH₂OC=O, CH₂CHCH₂O, 1H from C^qCH₂CH₂CH), 2.18–2.26 (2H, m, 1H from CH₂CH₂OC=O, 1H from CH₂CHCH₂O), 3.34 (3H, s, OCH₃), 3.50–3.16 (2H, m, OCH₂CH₂O), 3.54–3.55 (1H, m, 1H from CH₂CHCH₂O), 3.63–3.65 (2H, m, OCH₂CH₂O), 3.81 (1H dd, *J* = 10, 6.5 Hz, 1H from CH₂CHCH₂O), 4.17 (1H, dt, *J* = 9, 7 Hz, 1H from CH₂OC=O), 4.28 (1H, dt, *J* = 9, 3 Hz, 1H from CH₂OC=O), 4.66 (2H, dd, *J* = 7, 4.5 Hz, OCH₂O); ¹³C NMR δ 22.11 (C^q(OH)CH₃), 26.00 (CH₂CHCH₂O), 32.39 (C^qCH₂CH₂CH), 32.58 (CH₂CH₂OC=O), 47.86 (CHCH₂O), 55.53 (C^q), 59.06 (OCH₃), 65.36 (CHCH₂O), 66.83, OCH₂CH₂O), 67.54 (CH₂OC=O), 71.80 (OCH₂CH₂O), 81.91 (C^q), 95.68 (OCH₂O), 181.62 (C=O); MS: *m/z* (ESI)⁺ 311.1 (100%) [M+Na]⁺; HRMS Calcd for C₁₄H₂₄O₆Na: 311.1465. Found: 311.1455. For the *syn, anti* spirocycle **13f**: ν_{\max} (thin film)/cm⁻¹ 3483 m, 2920 m, 1759s (lactone C=O), 1372 m, ¹H NMR δ 1.13 (3H, s, C(OH)CH₃), 1.22–1.27 (1H, m, 1H from CH₂CHCH₂O), 1.54–1.60 (1H, m, 1H from C^qCH₂CH₂CH), 1.93–2.00 (2H, m, 1H from CH₂CHCH₂O, 1H from C^qCH₂CH₂CH), 2.07–2.13 (1H, m, 1H from CH₂CH₂OC=O), 2.40–2.45 (1H, ddd, *J* = 14, 8, 7.5 Hz, 1H from CH₂CH₂OC=O), 2.91–2.98 (1H, m, CH₂CHCH₂O), 3.33 (3H, s, OCH₃), 3.49–3.51 (2H, m, OCH₂CH₂O), 3.57–3.59 (2H, m, CH₂CHCH₂O), 3.62–3.64 (2H, m, OCH₂CH₂O), 4.09–4.14 (1H, m, 1H from CH₂CH₂OC=O), 4.23–4.28 (1H, m, 1H

from CH₂CH₂OC=O), 4.64 (2H, s, OCH₂O); ¹³C NMR δ 18.79 (C^q(OH)CH₃), 23.49 (C^qCH₂CH₂CH), 31.17 (CH₂CH₂OC=O), 46.19 (CHCH₂O), 56.30 (C^q), 59.06 (OCH₃), 65.57 (CHCH₂O), 67.09 (OCH₂CH₂O), 68.56 (CH₂OC=O), 71.73 (OCH₂CH₂O), 81.43 (C^q), 95.72 (OCH₂O), 180.82 (C=O); MS: *m/z* (ESI)⁺ 311.2 (100%) [M+Na]⁺; HRMS Calcd for C₁₄H₂₄O₆Na: 311.1465. Found: 311.1454;

4.5. Asymmetric synthesis of 5

4.5.1. (2S,3S)-2-Allyl-5-benzyloxy-pentane-1,3-diol

To a stirred solution of aldol adduct **17** (889 mg, 2.10 mmol, 1 equiv) in THF (21.3 mL) at 0 °C was added dropwise a solution of NaBH₄ (317 mg, 8.40 mmol, 4 equiv) in distilled H₂O (5.4 mL). The solution was warmed to room temperature and stirred for 2 h. The reaction was cooled to 0 °C and quenched with 1 M HCl (~40 mL). The aqueous phase was separated and extracted with CH₂Cl₂ (4 × 20 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by column chromatography (eluting with 40% EtOAc in petroleum ether (40–60 °C)) giving the product (2S,3S)-2-allyl-5-benzyloxy-pentane-1,3-diol (468 mg, 1.87 mmol, 89%) as a colourless oil. ν_{\max} (ATR)/cm⁻¹ 3376bs, 2922 m, 2866 m, 1641 m, 1448 m, 1094 m, 1029 m; $[\alpha]_D^{25} = +14.0$ (c 1.00, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.58 (1H, dtd, *J* = 14.5, 2.8, 2.2 Hz, 1H from CH₂CH(OH)), 1.71–1.75 (1H, m, CHCH(OH)), 1.81–1.89 (1H, m, 1H from CH₂CH(OH)), 1.99–2.02 (2H, m, CH₂CH=CH₂), 3.56–3.69 (4H, m, CH₂OBn, CH₂OH), 4.00 (1H, dt, *J* = 10.0, 2.2 Hz, CH(OH)), 4.44 (2H, s, OCH₂Ph), 4.92–4.99 (2H, m, CH₂=CH), 5.72 (1H, dtd, *J* = 17.0, 10.1, 7.0 Hz, CH=CH₂), 7.21–7.28 (5H, m, 5 × ArCH); ¹³C NMR (100 MHz, CDCl₃) δ 30.8 (CH₂CH=CH₂), 32.5 (CH₂CH(OH)), 44.3 (CHCH₂CH=CH₂), 64.1 (CH₂OH), 69.7 (CH₂OBn), 73.4 (OCH₂Ph), 74.4 (CH(OH)), 116.3 (CH₂=CH), 127.7 (2 × ArCH), 127.8 (ArCH), 128.5 (2 × ArCH), 137.0 (CH=CH₂), 137.7 (ArC); MS: *m/z* (CI mode) 268 (20%) [M+NH₄]⁺, 251 (100%) [M+H]⁺, HRMS Calcd for C₁₅H₂₂O₃: 250.1563. Found: 250.1568.

4.5.2. (S)-2-(3-Benzyloxy-1-(S)-hydroxy-propyl)-pent-4-en-1-yl acetate

To a stirred solution of (2S,3S)-2-allyl-5-benzyloxy-pentane-1,3-diol (93 mg, 0.370 mmol, 1 equiv) in CH₂Cl₂ (8.0 mL), at 0 °C was added triethylamine (0.23 mL, 2.22 mmol, 6 equiv) and acetic anhydride (0.097 mL, 1.11 mmol, 3 equiv). The reaction was warmed to room temperature and stirred for 36 h. The reaction was quenched by the addition of saturated aqueous NaHCO₃ solution (10 mL). The aqueous phase was separated and extracted with CH₂Cl₂ (4 × 10 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by column chromatography (eluting with 30% EtOAc in petroleum ether (40–60 °C)) giving the product (S)-2-(3-benzyloxy-1-(S)-hydroxy-propyl)-pent-4-en-1-yl acetate (82 mg, 0.28 mmol, 76%) as a colourless oil. ν_{\max} (thin film)/cm⁻¹ 2429 m (OH), 2913w, 2849w, 1736s (C=O), 1451w, 1362 m, 1239s, 1090s, 1073s, 1036s, 915w, 769w, 737w; $[\alpha]_D^{25} = +9.7$ (c 0.67, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 1.68–1.71 (1H, m, 1H from CH₂CH₂OBn), 1.82–1.91 (2H, m, 1H from CH₂CH₂OBn, CHCH₂OAc), 2.06 (3H, s, CH₃C(O)), 2.08–2.16 (1H, m, 1H from CH₂=CHCH₂), 2.26–2.33 (1H, m, 1H from CH₂=CHCH₂), 3.06 (1H, d, *J* = 2.8 Hz, OH), 3.63–3.69 (1H, m, 1H from CH₂CH₂OBn), 3.73–3.78 (1H, m, 1H from CH₂CH₂OBn), 3.91–3.94 (1H, m, CHOH), 4.09 (1H, dd, *J* = 11.4, 5.3 Hz, 1H from CHCH₂OAc), 4.16 (1H, dd, *J* = 11.4, 7.1 Hz, 1H from CHCH₂OAc), 4.52 (1H, d, *J* = 11.8 Hz, 1H from PhCH₂OCH₂), 4.55 (1H, d, *J* = 11.8 Hz, 1H from PhCH₂OCH₂), 5.02–5.09 (2H, m, CH₂=CH), 5.76–5.90 (1H, m, CH₂=CH), 7.30–7.38 (5H, m, 5 × ArCH); ¹³C NMR (100 MHz, CDCl₃) δ 21.0 (CH₃C=O), 31.0 (CH₂CH=CH₂), 33.5 (CH₂CH₂OBn), 42.9 (AcOCH₂CH), 64.3 (CH₂OAc), 69.5 (CH₂CH₂OBn), 70.9 (CHOH), 73.4 (PhCH₂OCH₂),

116.6 (CH₂CH=CH₂), 127.7 (2 × ArCH), 127.8 (ArCH), 128.5 (2 × ArCH), 136.6 (CH₂CH=CH₂), 137.8 (ArC), 171.3 (CH₃C=O); MS: *m/z* (ES+ mode) 315 (100%) [M+Na]⁺, 293 (44%) [M+H]⁺, HRMS Calcd for C₁₇H₂₅O₄: 293.1747. Found: 293.1745.

4.5.3. (4S)-1-Benzyloxy-4-(acetoxymethyl)-hept-6-en-3-one 18

To a stirred solution of (S)-2-(3-benzyloxy-1-(S)-hydroxy-propyl)-pent-4-en-1-yl acetate (57 mg, 0.195 mmol, 1 equiv) in CH₂Cl₂ (4 mL), was added crushed, oven dried 4 Å molecular sieves and the suspension stirred for 10 min. NMO (91.9 mg, 0.780 mmol, 4.0 equiv) was added followed by TPAP (2.5 mg, cat.) and the reaction stirred for 3 h. The crude reaction mixture was passed through a plug of silica gel (eluting with 30% EtOAc in petroleum ether (40–60 °C)), giving the product ketone **18** (57 mg, 0.195 mmol, 100%) as a colourless oil that was used without further purification. ν_{\max} (thin film)/cm⁻¹ 2923w, 2854w, 2357w, 1743s (C=O), 1713s (C=O), 1642w, 1451w, 1365 m, 1233s, 1097 m, 1039 m, 918w, 799w, 737w; [α]_D = +3.5 (c 0.34, CHCl₃) ¹H NMR (400 MHz, CDCl₃) δ 2.00 (3H, s, CH₃C=O), 2.19–2.27 (1H, m, 1H from CH₂CH=CH₂), 2.37–2.45 (1H, m, 1H from CH₂CH=CH₂), 2.79 (2H, dt, *J* = 6.3, 2.0 Hz, CH₂CH₂OBn), 2.91–2.98 (1H, m, CHCH₂OAc), 3.76 (2H, t, *J* = 6.6 Hz, CH₂CH₂OBn), 4.22 (2H, d, *J* = 6.8 Hz, CHCH₂OAc), 4.51 (2H, s, PhCH₂OCH₂), 5.05–5.11 (2H, m, CH₂=CH), 5.71 (1H, ddt, *J* = 17.2, 10.1, 7.1 Hz, CH=CH₂), 7.28–7.37 (5H, m, 5 × ArCH); ¹³C NMR (100 MHz, CDCl₃) δ 20.8 (OC(O)CH₃), 32.4 (CH₂=CHCH₂), 43.0 (CH₂CH₂OBn), 50.7 (CHCH₂OAc), 63.8 (CH₂OAc), 65.0 (CH₂OBn), 73.3 (PhCH₂O), 117.9 (CH₂=CH), 127.7 (3 × ArCH), 128.4 (2 × ArCH), 134.2 (CH₂=CH), 138.1 (ArC), 170.7 (CH₃C=O), 209.1 (CH₂C=O); MS: *m/z* (ES+ mode) 213 (100%) [M+Na]⁺, HRMS Calcd for C₁₇H₂₂O₄Na: 313.1410. Found: 313.1418.

4.5.4. 3-(Triphenylphosphoranylidene)tetrahydro-2H-pyran-2-one 19

To a stirred solution of diisopropylamine (15.7 mL, 110 mmol, 1.1 equiv) in THF (115 mL) at –78 °C was added *n*-BuLi (51.2 mL, 2.15 M in hexanes, 110 mmol, 1.1 equiv) dropwise and the resulting solution was stirred for 40 min. The reaction was warmed to room temperature and stirred for 10 min before being re-cooled to –78 °C and stirred for an additional 10 min. A solution of δ -valerolactone (9.30 mL, 100 mmol, 1.0 equiv) in THF (10 mL) was added dropwise and the reaction stirred for 10 min. Chlorotrimethylsilane (21.7 mL, 170 mmol, 1.7 equiv) was added in 1 portion and the reaction stirred for 1 h. The reaction was concentrated under vacuum at 35 °C and the remaining salts slurried in dry pentane, filtered under vacuum and concentrated. Purification was carried out by distillation under high vacuum at 60 °C giving the pure TMS ketene acetal (13.5 g, 78.5 mmol, 79%) as a colourless liquid. This was dissolved in CH₂Cl₂ (106 mL) and cooled to –15 °C. Triethylamine (13.2 mL, 94.2 mmol, 1.2 equiv) was added and after 5 min, a solution of bromine (4.10 mL, 78.5 mmol, 1.0 equiv) in CH₂Cl₂ (22 mL) was added dropwise over 10 min and the reaction stirred for a further 30 min. The reaction mixture was washed with saturated aqueous NH₄Cl solution (2 × 30 mL). The organic phase was dried (MgSO₄), filtered and concentrated in vacuo. The dark brown residue was eluted through a short plug of silica gel (eluting with 40% EtOAc in petroleum ether (40–60 °C)) giving α -bromo- δ -valerolactone as a brown oil (12.1 g, 67.9 mmol, 85%).²¹ This compound was dissolved in THF (29.6 mL). Triphenylphosphine (17.8 g, 67.9 mmol, 1.0 equiv) was added and the solution heated to reflux overnight. The reaction was concentrated in vacuo and the residue slurried in H₂O (100 mL) and NaOH (170 mL, 20% concd in H₂O) was added dropwise. The aqueous phase was extracted with CHCl₃ (4 × 100 mL) and the combined organic phases dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by recrystallisa-

tion from CHCl₃, giving phosphorane **19** (18.0 g, 50.1 mmol, 74%) as a cream coloured solid (decomposed at 194.6 °C).⁸ ν_{\max} (thin film)/cm⁻¹ 3061w, 2946w, 2913w, 2878w, 1724w, 1588s, 1565 m, 1480 m, 1461w, 1436 m, 1394 m, 1344 m, 1298 m, 1214w, 1142 m, 1093s, 1070s, 998w, 920w, 755 m, 716w; ¹H NMR (300 MHz, CDCl₃) δ 1.82–1.94 (4H, m, CH₂CH₂CH₂OC=O, CH₂CH₂CH₂OC=O), 4.25–4.28 (2H, m, CH₂CH₂CH₂OC=O), 7.43–7.49 (6H, m, 6 × ArCH), 7.52–7.58 (3H, m, 3 × ArCH), 7.62–7.71 (6H, m, 6 × ArCH); ¹³C NMR (75 MHz, CDCl₃) δ 24.2 (d, *J* = 11.3 Hz, CH₂CH₂CH₂OC=O), 24.6 (d, *J* = 9.8 Hz, CH₂CH₂CH₂OC=O), 35.6 (d, *J* = 123.0 Hz, C=PPh₃), 67.4 (CH₂CH₂CH₂OC=O), 126.8 (d, *J* = 90 Hz, 3 × ArC-P), 128.7 (d, *J* = 15 Hz, 6 × ArCH), 131.9 (d, *J* = 3 Hz, 3 × ArCH), 133.7 (d, *J* = 9.8 Hz, 6 × ArCH), 170.2 (d, *J* = 13.5 Hz, C=O); MS: *m/z* (ES+ mode) 383 (82%) [M+Na]⁺, 361 (100%) [M+H]⁺, HRMS Calcd for C₂₃H₂₂O₂P: 361.1352. Found: 361.1362.

4.5.5. (E)-3-((3S)-6-Benzyloxy-4-oxo-3-(acetoxymethyl)-hexylidene)-tetrahydro-pyran-2-one 5

Pyridine (12 μ L) was added to a stirred solution of K₂CO₃ (252 mg, 1.83 mmol, 3.0 equiv) and K₃[Fe(CN)₆] (606 mg, 1.83 mmol, 3.0 equiv) in H₂O (7.7 mL) at room temperature. Next, *t*-BuOH (5.3 mL) and OsO₄ (2.5% in *t*-BuOH, 0.61 mL, 0.061 mmol, 0.1 equiv) were added sequentially and the reaction cooled to 0 °C before the addition of alkene **18** in Et₂O (5.3 mL). The reaction was warmed to room temperature and stirred for 4 h. Sodium sulfite (906 mg, 3.65 mmol, 6 equiv) was added and the aqueous phase separated and extracted with EtOAc (3 × 15 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo. The residue was re-dissolved in (1:1) THF/H₂O (15 mL) to which KHCO₃ (169 mg, 1.22 mmol, 2.0 equiv) and NaIO₄ (314 mg, 1.46 mmol, 2.4 equiv) were added. The reaction was stirred for 13 h. The reaction was quenched with saturated aqueous NaCl solution (~15 mL) and the aqueous phase was extracted with EtOAc (4 × 15 mL). The combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo giving the corresponding aldehyde (171 mg, 0.585 mmol, 96%) as a colourless oil which was used without further purification.

The aldehyde (303 mg, 0.930 mmol, 1 equiv) was dissolved in CH₂Cl₂ (15.2 mL) at room temperature. Phosphorane **19** (666 mg, 1.86 mmol, 2 equiv) was added and the reaction stirred for seven days. The reaction mixture was concentrated in vacuo and eluted through a plug of silica gel (eluting with 50% EtOAc in petroleum ether (40–60 °C)). After concentration, the resulting oil was purified by column chromatography (eluting in 20% *i*-PrOH in petroleum ether (40–60 °C)) giving the lactone **5** (309 mg, 0.826 mmol, 89%) as a pale yellow oil. ν_{\max} (thin film)/cm⁻¹ 2948w, 2913w, 2859w, 1736s (C=O), 1708s (C=O), 1634 m, 1630 m, 1449w, 1362w, 1313w, 1231s, 1175 m, 1090 m, 1073 m, 1041 m, 967w, 735w; [α]_D = +25.1 (c 0.35, CHCl₃) ¹H NMR (400 MHz, CDCl₃) δ 1.86–1.92 (2H, m, CH₂CH₂CH₂OC=O), 2.02 (3H, s, CH₃C=O), 2.25–2.32 (1H, m, 1H from CH₂CH=CH₂), 2.50–2.59 (3H, m, 1H from CH₂CH=CH₂, CH₂CH₂CH₂OC=O), 2.73 (2H, t, *J* = 6.0 Hz, CH₂CH₂OBn), 3.05 (1H, quint, *J* = 6.6 Hz, CHCH₂OAc), 3.75 (2H, dt, *J* = 6.3, 1.5 Hz, CH₂CH₂OBn), 4.23 (2H, d, *J* = 5.8 Hz, CHCH₂OAc), 4.26–4.29 (2H, m, CH₂CH₂CH₂OC=O), 4.50 (2H, s, PhCH₂O), 6.92 (1H, tt, *J* = 7.6, 2.5 Hz, CH=CH₂), 7.28–7.37 (5H, m, 5 × ArCH); ¹³C NMR (100 MHz, CDCl₃) δ 20.7 (OC(O)CH₃), 22.5 (CH₂CH₂CH₂OC=O), 23.6 (CH₂CH₂CH₂OC=O), 26.8 (CH₂CH=CH₂), 43.0 (BnOCH₂CH₂C=O), 50.1 (CHCH₂OAc), 63.8 (CHCH₂OAc), 65.0 (BnOCH₂CH₂), 68.6 (CH₂CH₂CH₂OC=O), 73.3 (ArCH₂O), 127.7 (2 × ArCH), 127.8 (2 × ArCH), 128.4 (ArCH, CH₂CH=CH₂), 138.0 (ArC), 141.4 (CH₂CH=CH₂), 166.0 (CH₂CH₂CH₂OC=O), 170.6 (CHCH₂OC=O), 208.4 (CH₂CH₂C=O); MS: *m/z* (ES+ mode) 397 (100%) [M+Na]⁺, HRMS Calcd for C₂₁H₃₀O₆N [M+NH₄]⁺: 392.2068. Found: 392.2061.

4.6. Sml₂-mediated cyclisations of 5

4.6.1. (1R,2S,5R)-2-Acetoxymethyl-1-(2-(benzyloxy)ethyl)-1-hydroxy-6-oxo-7-oxaspiro[4.5]decane **14** and ((1S,2S,5S)-2-acetoxymethyl-1-(2-(benzyloxy)ethyl)-1-hydroxy-6-oxo-7-oxaspiro[4.5]decane

To a stirred solution of Sml₂ in THF (0.1 M, 2.94 mL, 0.294 mmol, 2.2 equiv) was added degassed, distilled H₂O (0.82 mL) resulting in the formation of a dark red solution. The solution was cooled to 0 °C and a solution of lactone **5** (50 mg, 0.134 mmol, 1.0 equiv) in THF (0.30 mL) added. The reaction was stirred for 3 min before being quenched by the addition of saturated aqueous NH₄Cl solution (10 mL). Saturated aqueous Na₂S₂O₃ (1.0 mL) and saturated aqueous K/Na tartrate (1.0 mL) solutions were added and the mixture vigorously stirred for 10 min. The aqueous phase was extracted with EtOAc (4 × 10 mL) and the combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by column chromatography (eluting with 40% EtOAc in petroleum ether (40–60 °C)) giving spirocyclic lactone **14** (28.3 mg, 0.075 mmol, 56%) as a colourless oil. Upon further elution, the *syn*, *anti*-spirocyclic lactone (3.3 mg, 0.0088 mmol, 7%) was also isolated as a colourless oil. For all-*syn* isomer **14**: ν_{\max} (thin film)/cm⁻¹ 3360w, 2923w, 2854w, 1736s (C=O), 1676s, 1449w, 1399 m, 1365 m, 1236s, 1174s, 1115 m, 1093w, 1031w, 977w, 749w, 737w; $[\alpha]_D = -28.3$ (c 0.58, CHCl₃), ¹H NMR (400 MHz, CDCl₃) δ 1.44–1.49 (1H, m, 1H from CH₂CH₂CH₂OC=O), 1.16–1.72 (2H, m, 1H from CH₂CH₂CH₂OC=O, 1H from CH₂CH₂CH), 1.87–1.97 (4H, m, 1H from CH₂CH₂CH₂OC=O, 1H from CH₂CH₂CH, 1H from CH₂CH₂CH, 1H from CH₂CH₂OBn), 2.00–2.11 (2H, m, 1H from CH₂CH₂CH₂OC=O, 1H from CH₂CH₂OBn), 2.02 (3H, s, CH₃C=O), 2.13–2.26 (2H, m, 1H from CH₂CH₂CH, CH₂CH₂CH), 3.52–3.63 (2H, m, CH₂CH₂OBn), 3.75 (1H, ddd, *J* = 12.6, 10.8, 3.3 Hz, 1H from CH₂CH₂CH₂OC=O), 4.04–4.09 (1H, m, 1H from CH₂CH₂CH₂OC=O), 4.16 (1H, dd, *J* = 11.1, 7.0 Hz, 1H from CH₂OAc), 4.22 (1H, d, *J* = 11.8 Hz, 1H from PhCH₂OCH₂), 4.34 (1H, dd, *J* = 11.1, 6.8 Hz, 1H from CH₂OAc), 4.49 (1H, d, *J* = 11.8 Hz, 1H from PhCH₂OCH₂), 6.55 (1H, d, *J* = 1.2 Hz, OH), 7.27–7.36 (5H, m, 5 × ArCH); ¹³C NMR (100 MHz, CDCl₃) δ 20.5 (CH₂CH₂CH₂OC=O), 21.1 (CH₃C=O), 24.8 (CH₂CH₂CH), 26.6 (CH₂CH₂CH₂OC=O), 34.7 (CH₂CH₂OBn), 35.6 (CH₂CH₂CH), 46.2 (CH₂CH₂CH), 54.0 (CH₂CH₂OC(O)C), 64.8 (CHCH₂OAc), 65.6 (BnOCH₂), 69.3 (CH₂CH₂CH₂OC=O), 72.3 (ArCH₂O), 83.7 (OCH₂CH₂COH), 127.7 (ArCH), 128.3 (2 × ArCH), 128.5 (2 × ArCH), 137.9 (ArC), 171.1 (CHCH₂OC=O), 178.4 (CH₂CH₂CH₂OC=O); MS: *m/z* (ES⁺ mode) 394 (58%) [M+Na]⁺, 377 (100%) [M+H]⁺, HRMS Calcd for C₂₁H₃₂O₆N: 394.2224. Found: 394.2223. For *syn*-*anti* isomer: ν_{\max} (thin film)/cm⁻¹ 3340w (OH), 2953 m, 2918 m, 2849 m, 1731s (C=O), 1674s, 1397w, 1362w, 1234s, 1167s, 1088 m, 1026 m, 957w, 745w; $[\alpha]_D = -27.7$ (c 0.40, CHCl₃), ¹H NMR (400 MHz, CDCl₃) δ 1.44–1.55 (2H, m, CH₂CH₂CH₂OC=O), 1.65–1.71 (1H, m, 1H from CH₂CH₂CH₂OC=O), 1.79 (1H, ddd, *J* = 14.9, 3.8, 2.5 Hz, 1H from CH₂CH₂OBn), 1.84–2.11 (4H, m, 1H from CH₂CH₂CH₂OC=O, 1H from CH₂CH₂CH, 1H from CH₂CH₂OBn, 1H from CH₂CH₂CH), 2.04 (3H, s, CH₃C=O), 2.17–2.35 (2H, m, 1H from CH₂CH₂CH, 1H from CH₂CH₂CH), 2.42–2.50 (1H, m, CH₂CH₂CH), 3.56–3.60 (1H, m, 1H from CH₂OAc), 3.63–3.69 (1H, m, 1H from CH₂OAc), 3.76 (1H, dt, *J* = 11.8, 3.5 Hz, 1H from CH₂CH₂CH₂OC=O), 3.93 (1H, dd, *J* = 11.1, 8.0 Hz, 1H from CH₂OBn), 4.06–4.12 (2H, m, 1H from CH₂CH₂OBn, 1H from CH₂CH₂CH₂OC=O), 4.25 (1H, d, *J* = 11.9 Hz, 1H from PhCH₂O), 4.49 (1H, d, *J* = 11.9 Hz, 1H from PhCH₂O), 6.78 (1H, d, *J* = 1.0 Hz, OH), 7.28–7.36 (5H, m, 5 × ArCH); ¹³C NMR (100 MHz, CDCl₃) δ 20.5 (CH₂CH₂CH₂OC=O), 21.0 (CH₃C=O), 25.1 (CH₂CH₂CH), 25.2 (CH₂CH₂CH₂OC=O), 33.4 (CH₂CH₂OBn), 35.5 (CH₂CH₂CH), 50.1 (CH₂CH₂CH), 53.8 (CH₂CH₂OC(O)C), 65.3 (CHCH₂OAc), 66.5 (BnOCH₂), 68.1 (CH₂CH₂CH₂OC=O), 72.4 (ArCH₂O), 84.9 (OCH₂CH₂

COH), 127.7 (ArCH), 128.3 (2 × ArCH), 128.6 (2 × ArCH), 137.8 (ArC), 171.1 (CHCH₂OC=O), 178.2 (CH₂CH₂CH₂OC=O); MS: *m/z* (ES⁺ mode) 399 (100%) [M+Na]⁺, HRMS Calcd for C₂₁H₂₈O₆Na: 399.1778. Found: 399.1781.

4.6.2. (1R,2S,5R)-2-Acetoxymethyl-1-hydroxy-1-(2-hydroxyethyl)-6-oxo-7-oxaspiro[4.5]decanane **20**

To a stirred solution of spirocyclic lactone **14** (26 mg, 0.069 mmol, 1 equiv) in Et₂O (0.05 mL) at room temperature was added Pd(OH)₂/C (5 mg, 0.0138 mmol, 20 mol %) and the suspension was vigorously stirred overnight under an atmosphere of H₂. The reaction mixture was filtered through a plug of Celite, washing with MeOH. The filtrate was concentrated in vacuo giving crude diol that was recrystallized from hexane and EtOAc to give **20** as a white crystalline solid (9.0 mg, 0.031 mmol, 45%). Mp 94.9–95.8 °C; ν_{\max} (thin film)/cm⁻¹ 3370 m (OH), 1953 m, 1736s (C=O), 1676s, 1451w, 1399 m, 1365 m, 1261s, 1239s, 1177 m, 1034 m, 979w, 898w, 843w, 725w; $[\alpha]_D = -5.1$ (c 0.86, CHCl₃), ¹H NMR (400 MHz, CDCl₃) δ 1.50–1.57 (1H, m, 1H from CH₂CH₂CH₂OC=O), 1.64–1.73 (2H, m, 1H from CH₂CH₂CH₂OC=O, 1H from CH₂CH₂CH), 1.80–1.86 (1H, m, 1H from CH₂CH₂CH), 1.88–2.08 (4H, m, 1H from CH₂CH₂CH, 1H from CH₂CH₂CH₂OC=O, CH₂CH₂OH), 2.05 (3H, s, CH₃C=O), 2.12 (1H, ddd, *J* = 12.6, 3.6, 2.0 Hz, 1H from CH₂CH₂CH₂OC=O), 2.17–2.30 (2H, m, 1H from CH₂CH₂CH, CH₂CH₂CH), 3.77 (1H, dt, *J* = 10.1, 4.0 Hz, 1H from CH₂CH₂CH₂OC=O), 3.94 (1H, dt, *J* = 10.1, 2.8 Hz, 1H from CH₂CH₂CH₂OC=O), 4.17 (1H, dd, *J* = 10.8, 7.0 Hz, 1H from CH₂OAc), 4.33–4.40 (3H, m, 1H from CH₂OAc, CH₂CH₂OH), 6.41 (1H, d, *J* = 1.0 Hz, OH); ¹³C NMR (100 MHz, CDCl₃) δ 20.7 (CH₂CH₂CH₂OC=O), 21.1 (CH₃C=O), 24.9 (CH₂CH₂CH), 26.9 (CH₂CH₂CH₂OC=O), 35.7 (CH₂CH₂OH), 36.0 (CH₂CH₂CH), 46.4 (CH₂CH₂CH), 54.3 (CH₂CH₂OC(O)C), 58.0 (CH₂CH₂CH₂OC=O), 64.8 (CH₂OAc), 69.9 (CH₂CH₂OH), 83.9 (HOCH₂CH₂COH), 171.1 (CHCH₂OC=O), 179.2 (CH₂CH₂CH₂OC=O); MS: *m/z* (ES⁺ mode) 309 (100%) [M+Na]⁺, 304 (39%) [M+NH₄]⁺, 287 (62%) [M+H]⁺, HRMS Calcd for C₁₄H₂₃O₆: 287.1489. Found: 287.1492.

4.6.3. (1S,2R,3S)-1-Acetoxymethyl-2-(2-(benzyloxy)ethyl)-2-hydroxy-3-(hydroxymethyl)-3-(3-hydroxypropyl)cyclopentane **4**

To a stirred solution of Sml₂ in THF (0.1 M, 6.40 mL, 0.637 mmol, 12 equiv) at 0 °C was added degassed, distilled H₂O (1.6 mL) resulting in the formation of a dark red solution. A solution of lactone **5** (20 mg, 0.0531 mmol, 1 equiv) in THF (0.5 mL) was added and the reaction stirred at 0 °C for 5 min. The reaction was warmed to room temperature and stirred for 16 h before quenching with saturated aqueous NH₄Cl solution (1.5 mL). Saturated aqueous Na₂S₂O₃ (1.0 mL) and K/Na tartrate (1.5 mL) solutions were added and the mixture stirred for 20 min. The aqueous phase was extracted with EtOAc (5 × 10 mL) and the combined organic phases were dried (MgSO₄), filtered and concentrated in vacuo. The crude product was filtered through a short plug of silica gel (eluting with 50% EtOAc in petroleum ether (40–60 °C)) giving triol **4** (17.3 mg, 0.0455 mmol, 86%) as a 6:1 mixture of diastereoisomers. For the major diastereoisomer **4**: ν_{\max} (thin film)/cm⁻¹ 3340s (OH), 2948 m, 2868 m, 1736s (C=O), 1654w, 1459w, 1362 m, 1241s, 1145w, 1098 m, 1071 m, 1031s, 739w; $[\alpha]_D = -12.5$ (c 2.50, CHCl₃), ¹H NMR (400 MHz, CDCl₃) δ 1.09–1.17 (1H, m, 1H from CH₂CH₂CH₂OH), 1.34–1.40 (1H, m, 1H from CH₂CH₂CH), 1.47–1.59 (4H, m, 1H from CH₂CH₂CH₂OH, 1H from CH₂CH₂CH, CH₂CH₂CH₂OH), 1.64 (1H, ddd, *J* = 14.9, 4.3, 2.8 Hz, 1H from CH₂CH₂OBn), 1.75–1.90 (2H, m, 1H from CH₂CH₂CH, 1H from CH₂CH₂CH), 2.05 (3H, s, CH₃C=O), 2.16 (1H, ddd, *J* = 14.9, 10.6, 4.3 Hz, 1H from CH₂CH₂OBn), 2.23–2.28 (1H, m, CH₂CH₂CH), 3.57 (1H, d, *J* = 11.8 Hz, 1H from CCH₂OH), 3.63 (2H, t, *J* = 5.8 Hz, CH₂CH₂CH₂OH), 3.71 (1H, d, *J* = 11.8 Hz, 1H from CCH₂OH), 3.86 (1H, dt, *J* = 9.6, 4.3 Hz, 1H from CH₂CH₂OBn),

3.95–4.02 (2H, m, 1H from CH_2OAc , 1H from $\text{CH}_2\text{CH}_2\text{OBn}$), 4.40 (1H, dd, $J = 11.1$, 5.0 Hz, 1H from CH_2OAc), 4.47 (1H, s, OH), 4.50 (1H, d, $J = 11.6$ Hz, 1H from PhCH_2O), 4.60 (1H, d, $J = 11.6$ Hz, 1H from PhCH_2O), 7.30–7.369 (5H, m, $5 \times \text{ArCH}$); ^{13}C NMR (100 MHz, CDCl_3) δ 21.1 ($\text{CH}_3\text{C}=\text{O}$), 26.6 ($\text{CH}_2\text{CH}_2\text{CH}$), 27.7 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$), 28.0 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$), 29.1 ($\text{CH}_2\text{CH}_2\text{CH}$), 34.9 ($\text{CH}_2\text{CH}_2\text{OBn}$), 45.7 ($\text{CHCH}_2\text{OC}=\text{O}$), 52.7 (CCH_2OH), 63.5 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$), 64.6 (CCH_2OH), 66.8 (CH_2OAc), 68.2 (BnOCH_2), 73.7 (PhCH_2O), 87.2 ($\text{BnCH}_2\text{CH}_2\text{COH}$), 128.0 ($2 \times \text{ArCH}$), 128.1 (ArCH), 128.6 ($2 \times \text{ArCH}$), 137.0 (ArC), 171.3 ($\text{CH}_3\text{C}=\text{O}$); MS: m/z (ES+ mode) 403 (100%) $[\text{M}+\text{Na}]^+$, 381 (30%) $[\text{M}+\text{H}]^+$, HRMS Calcd for $\text{C}_{21}\text{H}_{33}\text{O}_6$: 381.2272. Found: 381.2268.

4.6.4. (1S,2R,3S)-1-Acetoxymethyl-2-(2-(benzyloxy)ethyl)-3-(3-((tert-butyltrimethylsilyl)oxy)propyl)-2-hydroxy-3-(hydroxymethyl)cyclopentane **21**

To a stirred solution of triol **4** (440 mg, 1.156 mmol, 1.0 equiv) in CH_2Cl_2 (33.8 mL) at room temperature was added imidazole (236 mg, 3.47 mmol, 3.0 equiv) then TBSCl (174 mg, 1.16 mmol, 1.0 equiv) and the reaction stirred for 6.5 h. The reaction was quenched by the addition of saturated aqueous NaHCO_3 solution (20 mL), the aqueous phase was extracted with Et_2O (4×20 mL) and the combined organic phases dried (MgSO_4), filtered and concentrated in vacuo. The crude product was purified by column chromatography (eluting with 50% EtOAc in petroleum ether (40–60 °C)) giving the diol **21** (421 mg, 0.851 mmol, 74% (82% based on recovered starting material)) as a colourless oil. ν_{max} (thin film)/ cm^{-1} 3429 m (OH), 1953 m, 2923 m, 2854 m, 1738 m ($\text{C}=\text{O}$), 1461 w, 1362 w, 1246 s, 1098 s, 1034 m, 836 s, 774 w; $[\alpha]_{\text{D}} = -10.1$ (c 1.45, CHCl_3), ^1H NMR (400 MHz, CDCl_3) δ 0.045 (6H, s, $\text{Si}(\text{CH}_3)_2$), 0.89 (9H, s, $\text{Si}(\text{CH}_3)_3$), 1.05–1.13 (1H, m, 1H from $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 1.28–1.35 (1H, m, 1H from $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 1.39 (1H, ddd, $J = 13.4$, 7.8, 5.8 Hz, 1H from $\text{CH}_2\text{CH}_2\text{CH}$), 1.45–1.58 (3H, m, 1H from $\text{CH}_2\text{CH}_2\text{CH}$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 1.67 (1H, ddd, $J = 14.9$, 4.6, 3.0 Hz, 1H from $\text{CH}_2\text{CH}_2\text{OBn}$), 1.74–1.83 (1H, m, 1H from $\text{CH}_2\text{CH}_2\text{CH}$), 1.94 (1H, dt, $J = 13.1$, 8.3 Hz, 1H from $\text{CH}_2\text{CH}_2\text{CH}$), 2.05 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.14 (1H, ddd, $J = 14.9$, 10.4, 4.3 Hz, 1H from $\text{CH}_2\text{CH}_2\text{OBn}$), 2.19–2.26 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}$), 3.53–3.65 (4H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$, CCH_2OH), 3.85–3.89 (1H, m, 1H from $\text{CH}_2\text{CH}_2\text{OBn}$), 3.94–4.01 (2H, m, 1H from $\text{CH}_2\text{CH}_2\text{OBn}$, 1H from CH_2OAc), 4.41 (1H, dd, $J = 11.1$, 5.0 Hz, 1H from CH_2OAc), 4.47 (1H, s, OH), 4.51 (1H, d, $J = 11.4$ Hz, 1H from PhCH_2O), 4.60 (1H, d, $J = 11.4$ Hz, 1H from PhCH_2O), 7.30–7.39 (5H, m, $5 \times \text{ArCH}$); ^{13}C NMR (100 MHz, CDCl_3) δ -5.3 ($\text{Si}(\text{CH}_3)_2$), -5.2 ($\text{Si}(\text{CH}_3)_3$), 18.3 ($\text{Si}(\text{CH}_3)_3$), 21.1 ($\text{CH}_3\text{C}=\text{O}$), 26.0 ($\text{Si}(\text{CH}_3)_3$), 26.5 ($\text{CH}_2\text{CH}_2\text{CH}$), 27.8 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 28.1 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 28.5 ($\text{CH}_2\text{CH}_2\text{CH}$), 34.5 ($\text{CH}_2\text{CH}_2\text{OBn}$), 45.8 ($\text{CH}_2\text{CH}_2\text{CH}$), 52.8 (CCH_2OH), 63.6 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 64.6 (CCH_2OH), 66.8 (CH_2OAc), 68.3 (BnOCH_2), 73.7 (PhCH_2O), 87.4 ($\text{BnOCH}_2\text{CH}_2\text{COH}$), 128.0 ($2 \times \text{ArCH}$), 128.1 (ArCH), 128.6 ($2 \times \text{ArCH}$), 137.0 (ArC), 171.3 ($\text{CH}_3\text{C}=\text{O}$); MS: m/z (ES+ mode) 517 (92%) $[\text{M}+\text{Na}]^+$, 495 (100%) $[\text{M}+\text{H}]^+$, HRMS Calcd for $\text{C}_{27}\text{H}_{47}\text{O}_6\text{Si}$: 495.3136. Found: 495.3124.

4.6.5. (1S,2R,3S)-1-Acetoxymethyl-2-(2-(benzyloxy)ethyl)-3-(3-((tert-butyltrimethylsilyl)oxy)propyl)-2-hydroxy-3-methylcyclopentane **22**

To a stirred solution of diol **21** (50 mg, 0.101 mmol, 1.0 equiv) in CH_2Cl_2 (2.7 mL) at room temperature was added pyridine (22.3 μL) and DMAP (5 mg) and the mixture stirred for 2 min. *O*-Phenyl chlorothionoformate (40.3 μL , 0.303 mmol, 3.0 equiv) was added dropwise and the reaction stirred for 4 h. The reaction was diluted with EtOAc (~5 mL) forming a white suspension and the organic phase was washed with brine (3 mL), dried (MgSO_4), filtered and concentrated. The residue was purified immediately by column chromatography (eluting with 30% EtOAc in petroleum ether (40–60 °C))

giving the corresponding thiocarbonate (57 mg, 0.091 mmol, 90%) as a yellow oil.

The thiocarbonate (105 mg, 0.166 mmol, 1.0 equiv) was immediately dissolved in toluene (8.8 mL). Next, AIBN (5.5 mg, 0.033 mmol, 0.2 equiv) and *n*-Bu₃SnH (144.8 μL , 0.499 mmol, 3.0 equiv) were added and the reaction stirred at 95 °C for 2 h. The mixture was cooled to room temperature and concentrated in vacuo. The residue was purified by column chromatography (eluting with 10% EtOAc in petroleum ether (40–60 °C)), giving the deoxygenated product **22** (57.3 mg, 0.120 mmol, 72%) as a colourless oil. ν_{max} (thin film)/ cm^{-1} 2948 m, 2923 m, 2854 w, 2357 s, 2328 m, 1733 m ($\text{C}=\text{O}$), 1649 w, 1362 w, 1254 m, 1098 m, 1029 w, 833 w, 774 w; $[\alpha]_{\text{D}} = -8.0$ (c 0.55, CHCl_3), ^1H NMR (400 MHz, CDCl_3) δ 0.06 (6H, s, $\text{Si}(\text{CH}_3)_2$), 0.90 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.98 (3H, s, CCH_3), 1.17–1.23 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 1.40–1.62 (5H, m, 1H from $\text{CH}_2\text{CH}_2\text{CH}$, $\text{CH}_2\text{CH}_2\text{CH}$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 1.70–1.80 (1H, m, 1H from $\text{CH}_2\text{CH}_2\text{CH}$), 1.85–1.99 (2H, m, $\text{CH}_2\text{CH}_2\text{OBn}$), 2.04 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.21–2.28 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}$), 3.59 (2H, t, $J = 6.6$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 3.70 (1H, s, OH), 3.82–3.85 (2H, m, $\text{CH}_2\text{CH}_2\text{OBn}$), 4.02 (1H, dd, $J = 11.1$, 8.3 Hz, 1H from CH_2OAc), 4.40 (1H, dd, $J = 11.1$, 5.8 Hz, 1H from CH_2OAc), 4.49 (1H, d, $J = 11.3$ Hz, 1H from PhCH_2O), 4.53 (1H, d, $J = 11.3$ Hz, 1H from PhCH_2O), 7.28–7.37 (5H, m, $5 \times \text{ArCH}$), ^{13}C NMR (100 MHz, CDCl_3) δ -5.2 ($\text{Si}(\text{CH}_3)_2$), 18.4 ($\text{Si}(\text{CH}_3)_3$), 19.0 (CCH_3), 21.2 ($\text{CH}_3\text{C}=\text{O}$), 25.7 ($\text{CH}_2\text{CH}_2\text{CH}$), 26.0 ($\text{Si}(\text{CH}_3)_3$), 28.2 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 31.6 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 33.4 ($\text{CH}_2\text{CH}_2\text{CH}$), 34.0 ($\text{CH}_2\text{CH}_2\text{OBn}$), 45.9 (CHCH_2OAc), 49.7 (CCH_3), 63.9 (CH_2OTBS), 66.9 (CH_2OAc), 68.2 (BnOCH_2), 73.6 (PhCH_2O), 84.2 ($\text{BnOCH}_2\text{CH}_2\text{COH}$), 127.9 ($3 \times \text{ArCH}$), 128.5 ($2 \times \text{ArCH}$), 137.4 (ArC), 171.3 ($\text{CH}_3\text{C}=\text{O}$); MS: m/z (ES+ mode) 501 (100%) $[\text{M}+\text{Na}]^+$, HRMS Calcd for $\text{C}_{27}\text{H}_{50}\text{O}_5\text{NSi}$: 496.3453. Found: 496.3446.

4.6.6. (1R,2S,5S)-1-(2-(Benzyloxy)ethyl)-2-(3-((tert-butyltrimethylsilyl)oxy)propyl)-5-(hydroxymethyl)-2-methylcyclopentanol

To a stirred solution of acetate **22** (79 mg, 0.165 mmol, 1.0 equiv) in MeOH (7.9 mL) at room temperature was added K_2CO_3 (68.5 mg, 0.495 mmol, 3.0 equiv) and the reaction heated to 40 °C for 1 h. The reaction was cooled to room temperature, concentrated in vacuo and slurried in brine (10 mL). The aqueous phase was extracted with CH_2Cl_2 (4×10 mL) and the combined organics dried (MgSO_4), filtered and concentrate in vacuo giving (1R,2S,5S)-1-(2-(benzyloxy)ethyl)-2-(3-((tert-butyltrimethylsilyl)oxy)propyl)-5-(hydroxymethyl)-2-methylcyclopentanol (70 mg, 0.160 mmol, 97%) as a colourless oil that was used without purification. ν_{max} (thin film)/ cm^{-1} 3434 m (OH), 2948 s, 2928 s, 2854 m, 1619 w, 1461 w, 1385 w, 1360 w, 1254 m, 1095 s, 1026 w, 969 w, 937 w, 833 s, 774 m, 732 w; $[\alpha]_{\text{D}} = -4.9$ (c 0.6, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 0.05 (6H, s, $\text{Si}(\text{CH}_3)_2$), 0.90 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.99 (3H, s, CCH_3), 1.18–1.26 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 1.47–1.67 (5H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$, $\text{CH}_2\text{CH}_2\text{CH}$, 1H from $\text{CH}_2\text{CH}_2\text{CH}$), 1.75–1.87 (2H, m, 1H from $\text{CH}_2\text{CH}_2\text{CH}$, 1H from $\text{CH}_2\text{CH}_2\text{OBn}$), 1.95–2.10 (2H, m, 1H from $\text{CH}_2\text{CH}_2\text{OBn}$, $\text{CH}_2\text{CH}_2\text{CH}$), 3.43 (1H, dd, $J = 9.1$, 2.6 Hz, CH_2OH), 3.60 (2H, t, $J = 6.6$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 3.61–3.68 (1H, m, 1H from CH_2OH), 3.76–3.81 (1H, m, 1H from $\text{CH}_2\text{CH}_2\text{OBn}$), 3.87 (1H, dd, $J = 9.2$, 3.6 Hz, 1H from $\text{CH}_2\text{CH}_2\text{OBn}$), 3.95 (1H, dt, $J = 11.3$, 2.8 Hz, 1H from CH_2OH), 4.21 (1H, d, $J = 0.8$ Hz, OH), 4.51 (2H, s, PhCH_2O), 7.28–7.40 (5H, m, $5 \times \text{ArCH}$); ^{13}C NMR (75 MHz, CDCl_3) δ -5.2 ($\text{Si}(\text{CH}_3)_2$), 18.3 ($\text{Si}(\text{CH}_3)_3$), 19.0 (CCH_3), 23.2 ($\text{CH}_2\text{CH}_2\text{CH}$), 26.0 ($\text{Si}(\text{CH}_3)_3$), 28.1 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 31.6 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 34.3 ($\text{CH}_2\text{CH}_2\text{OBn}$), 48.0 ($\text{CH}_2\text{CH}_2\text{CH}$), 49.6 (CCH_3), 63.3 (CH_2OH), 63.8 (CH_2OTBS), 68.2 (BnOCH_2), 73.7 (PhCH_2O), 86.9 ($\text{BnOCH}_2\text{CH}_2\text{COH}$), 128.0 ($3 \times \text{ArCH}$), 128.6 ($2 \times \text{ArCH}$), 137.2 (ArC); MS: m/z (ES+ mode) 459 (100%) $[\text{M}+\text{Na}]^+$, HRMS Calcd for $\text{C}_{25}\text{H}_{44}\text{O}_4\text{Na}$: 459.2901. Found: 459.2906.

4.6.7. (1R,2R,3S)-Methyl-2-(2-(benzyloxy)ethyl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-hydroxy-3-methylcyclopentanecarboxylate **23**

To a stirred solution of (1R,2S,5S)-1-(2-(benzyloxy)ethyl)-2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-5-(hydroxymethyl)-2-methylcyclopentanol (28.8 mg, 0.066 mmol, 1.0 equiv) in CH_2Cl_2 (16.7 mL) at room temperature was added NaHCO_3 (11.5 mg, 0.132 mmol, 2.0 equiv). Dess–Martin periodinane (42 mg, 0.0989 mmol, 1.5 equiv) was added and the turbid reaction was stirred for 3 h. The reaction was diluted with EtOAc (35 mL) and a solution of saturated aqueous NaHCO_3 solution (35 mL) containing $\text{Na}_2\text{S}_2\text{O}_3$ (2.77 g) was added. After stirring vigorously for 30 min, EtOAc (35 mL) was added, the organic layer separated and washed with saturated aqueous NaHCO_3 solution (25 mL). The organic phase was dried (MgSO_4), filtered and concentrated. The crude aldehyde product was dissolved in *t*-BuOH (1.56 mL) and 2-methyl-2-butene (0.64 mL) was added. In a separate flask, a mixture of NaClO_2 (150 mg) and NaH_2PO_4 (150 mg) was dissolved in H_2O (1 mL). Upon complete dissolution, a portion of this solution (0.35 mL) was added to the aldehyde solution and the reaction stirred for 30 min. DMS (12 drops) was added and the reaction stirred for a further 30 min. The reaction mixture was diluted with brine (5 mL) and the aqueous phase extracted with CH_2Cl_2 (4 \times 5 mL). The combined organic phases were dried (MgSO_4), filtered and concentrated to give the crude carboxylic acid that was then dissolved in a 4:1 mixture of toluene/MeOH (1.8 mL). A solution of TMS-diazomethane (2.0 M in hexanes, 46.8 μL , 0.145 mmol, 2.2 equiv) was added dropwise and the reaction stirred for 2 h. The reaction mixture was concentrated in vacuo and purified directly by column chromatography (eluting with 30% EtOAc in petroleum ether (40–60 °C)) to give the methyl ester **23** (23.1 mg, 0.050 mmol, 75% over three steps) as a clear oil. ν_{max} (thin film)/ cm^{-1} 3459w (OH), 1945s, 1912s, 2854 m, 1705 m, 1454w, 1360w, 1254 m, 1199 m, 1177w, 1098s, 937w, 833s, 774 m, 734w; $[\alpha]_{\text{D}} = -15.1$ (c 1.15, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.06 (6H, s, $\text{Si}(\text{CH}_3)_2$), 0.91 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.99 (3H, s, $\text{C}(\text{CH}_3)_2$), 1.11–1.26 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 1.44–1.63 (3H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$, 1H from $\text{CH}_2\text{CH}_2\text{CH}$), 1.71–1.78 (1H, m, 1H from $\text{CH}_2\text{CH}_2\text{CH}$), 1.83–1.99 (4H, m, $\text{CH}_2\text{CH}_2\text{CH}$, $\text{CH}_2\text{CH}_2\text{OBn}$), 2.94 (1H, dd, $J = 10.3$, 7.8 Hz, $\text{CH}_2\text{CH}_2\text{CH}$), 3.53 (3H, s, OCH_3), 3.60 (2H, dt, $J = 6.6$, 3.3 Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 3.67–3.72 (2H, m, $\text{CH}_2\text{CH}_2\text{OBn}$), 4.45 (2H, s, PhCH_2O), 4.84 (1H, s, OH), 7.26–7.36 (5H, m, 5 \times ArCH); ^{13}C NMR (100 MHz, CDCl_3) δ -5.2 ($\text{Si}(\text{CH}_3)_2$), 18.0 ($\text{Si}(\text{CH}_3)_3$), 18.4 ($\text{C}(\text{CH}_3)_2$), 25.7 ($\text{CH}_2\text{CH}_2\text{CH}$), 26.0 ($\text{Si}(\text{CH}_3)_3$), 28.2 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 31.4 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 33.4 ($\text{CH}_2\text{CH}_2\text{CH}$), 34.7 ($\text{CH}_2\text{CH}_2\text{OBn}$), 49.0 ($\text{CH}_2\text{CH}_2\text{CH}$), 49.3 ($\text{C}(\text{CH}_3)_2$), 50.0 (OCH_3), 63.8 (CH_2OTBS), 66.9 (BnOCH_2), 73.0 (PhCH_2O), 83.8 ($\text{BnOCH}_2\text{CH}_2\text{COH}$), 127.4 (2 \times ArCH), 12.5 (ArCH), 127.6 (2 \times ArCH), 138.1 (ArC), 177.1 ($\text{C}=\text{O}$); MS: m/z (ES+ mode) 525 (100%), 487 (30%) [$\text{M}+\text{Na}$] $^+$, 482 (23%) [$\text{M}+\text{NH}_4$] $^+$, 465 (17%) [$\text{M}+\text{H}$] $^+$, HRMS Calcd for $\text{C}_{26}\text{H}_{44}\text{O}_5\text{SiNa}$: 487.2856. Found: 487.2862.

4.6.8. (1R,2S,5S)-1-(2-(Benzyloxy)ethyl)-2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-5-(2-hydroxypropan-2-yl)-2-methylcyclopentanol **24**

To a stirred solution of methyl ester **23** (3.6 mg, 7.75×10^{-3} mmol, 1.0 equiv), in Et_2O (0.01 mL) at -78 °C was added a solution of MeMgBr (3.0 M in Et_2O , 10.3 μL , 0.031 mmol, 4.0 equiv). The reaction was warmed to room temperature and stirred for 4 h. The reaction mixture was cooled to 0 °C and quenched by the dropwise addition of saturated aqueous NH_4Cl solution (1.0 mL). The aqueous phase was extracted in 80% EtOAc in petroleum ether (40–60 °C), (4 \times 2 mL) and the combined organic phases were dried (MgSO_4), filtered and concentrated in vacuo. The crude residue was purified by column chromatography (eluting with 30% EtOAc in petroleum ether (40–60 °C)) giving

the tertiary alcohol **24** (3.5 mg, 7.75×10^{-3} mmol, 100%) as a clear oil. ν_{max} (thin film)/ cm^{-1} 3459 m (OH), 1953s, 2923s, 2854 m, 1471 m, 1360 m, 1254 m, 1095s, 937w, 836s, 774 m, 732w; $[\alpha]_{\text{D}} = -4.40$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.06 (6H, s, $\text{Si}(\text{CH}_3)_2$), 0.90 (9H, s, $\text{Si}(\text{CH}_3)_3$), 1.01 ($\text{C}(\text{CH}_3)_2$), 1.15 (3H, s, $\text{C}(\text{CH}_3)_2\text{OH}$), 1.22–1.26 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 1.45 (3H, s, $\text{C}(\text{CH}_3)_2\text{OH}$), 1.39–1.63 (5H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$, $\text{CH}_2\text{CH}_2\text{CH}$, 1H from $\text{CH}_2\text{CH}_2\text{CH}$), 1.81–1.89 (3H, m, $\text{CH}_2\text{CH}_2\text{CH}$, 1H from $\text{CH}_2\text{CH}_2\text{CH}$, 1H from $\text{CH}_2\text{CH}_2\text{OBn}$), 2.43 (1H, ddd, $J = 15.4$, 10.6, 4.6 Hz, 1H from $\text{CH}_2\text{CH}_2\text{OBn}$), 3.60 (2H, dt, $J = 6.6$, 1.2 Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 3.72 (1H, dt, $J = 9.5$, 4.6 Hz, 1H from $\text{CH}_2\text{CH}_2\text{OBn}$), 3.91 (1H, ddd, $J = 10.6$, 9.5, 3.0 Hz, 1H from $\text{CH}_2\text{CH}_2\text{OBn}$), 4.18 (1H, s, OH), 4.35 (1H, s, OH), 4.49 (2H, s, PhCH_2O), 7.30–7.39 (5H, m, 5 \times ArCH); ^{13}C NMR (100 MHz, CDCl_3) δ -5.2 ($\text{Si}(\text{CH}_3)_2$), 18.3 ($\text{C}(\text{CH}_3)_2$), 19.4 ($\text{Si}(\text{CH}_3)_3$), 24.3 ($\text{CH}_2\text{CH}_2\text{CH}$), 26.0 ($\text{Si}(\text{CH}_3)_3$), 28.1 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 29.7 ($\text{HOC}(\text{CH}_3)_2$), 31.2 ($\text{HOC}(\text{CH}_3)_2$), 31.4 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 34.7 ($\text{CH}_2\text{CH}_2\text{CH}$), 35.7 ($\text{CH}_2\text{CH}_2\text{OBn}$), 49.8 ($\text{C}(\text{CH}_3)_2$), 54.8 ($\text{CH}_2\text{CH}_2\text{CH}$), 63.9 (CH_2OTBS), 68.7 (BnOCH_2), 73.1 ($(\text{CH}_3)_2\text{COH}$), 73.6 (PhCH_2O), 87.7 ($\text{BnOCH}_2\text{CH}_2\text{COH}$), 127.9 (2 \times ArCH), 128.0 (ArCH), 128.6 (2 \times ArCH), 137.2 (ArC); MS: m/z (ES+ mode) 487 (67%) [$\text{M}+\text{Na}$] $^+$, 465 (100%) [$\text{M}+\text{H}$] $^+$, HRMS Calcd for $\text{C}_{27}\text{H}_{48}\text{O}_4\text{NaSi}$: 487.3220. Found: 487.3215.

4.6.9. (1R,2S,5S)-2-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-1-(2-hydroxyethyl)-5-(2-hydroxypropan-2-yl)-2-methylcyclopentanol

A solution of benzyl ether **24** (16.7 mg, 0.036 mmol, 1.0 equiv) and Pd/C (10% activated charcoal) (37.9 mg, 0.036 mmol, 1.0 equiv) in MeOH (0.84 mL) at rt was degassed with H_2 . The reaction mixture was subsequently stirred under an H_2 atmosphere for 3 h. The suspension was filtered through a plug of Celite and washed through with MeOH (2 \times 5 mL). The organics were concentrated in vacuo giving the primary alcohol (1R,2S,5S)-2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-1-(2-hydroxyethyl)-5-(2-hydroxypropan-2-yl)-2-methylcyclopentanol (12.0 mg, 0.032 mmol, 89%) that was used without further purification. ν_{max} (thin film)/ cm^{-1} 3335 m (OH), 2953s, 2928s, 2854s, 1471 m, 1377 m, 1254 m, 1097s, 937w, 836s, 774 m; $[\alpha]_{\text{D}} = -9.0$ (c 0.62, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 0.00 (6H, s, $\text{Si}(\text{CH}_3)_2$), 0.84 (9H, s, $\text{Si}(\text{CH}_3)_3$), 1.00 (3H, s, $\text{C}(\text{CH}_3)_2$), 1.17 (3H, s, $(\text{CH}_3)_2\text{COH}$), 1.17–1.22 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 1.33–1.63 (5H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$, $\text{CH}_2\text{CH}_2\text{CH}$, 1H from $\text{CH}_2\text{CH}_2\text{CH}$), 1.43 (3H, s, $(\text{CH}_3)_2\text{COH}$), 1.69–1.81 (2H, m, 1H from $\text{CH}_2\text{CH}_2\text{CH}$, 1H from $\text{CH}_2\text{CH}_2\text{OH}$), 1.85–1.91 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}$), 2.09–2.19 (1H, m, 1H from $\text{CH}_2\text{CH}_2\text{OH}$), 2.89 (1H, t, $J = 4.4$ Hz, OH), 3.31 (1H, s, OH), 3.55 (2H, t, $J = 6.4$ Hz, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 3.80–3.88 (1H, m, 1H from $\text{CH}_2\text{CH}_2\text{OH}$), 3.96–4.01 (1H, m, 1H from $\text{CH}_2\text{CH}_2\text{OH}$), 4.37 (1H, s, OH); ^{13}C NMR (75 MHz, CDCl_3) δ -5.2 ($\text{Si}(\text{CH}_3)_2$), 18.3 ($\text{C}(\text{CH}_3)_2$), 19.3 ($\text{Si}(\text{CH}_3)_3$), 24.5 ($\text{CH}_2\text{CH}_2\text{CH}$), 26.0 ($\text{Si}(\text{CH}_3)_3$), 28.2 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 30.0 ($\text{HOC}(\text{CH}_3)_2$), 31.2 ($\text{HOC}(\text{CH}_3)_2$), 31.9 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 34.7 ($\text{CH}_2\text{CH}_2\text{CH}$), 37.9 ($\text{CH}_2\text{CH}_2\text{OH}$), 49.8 ($\text{C}(\text{CH}_3)_2$), 54.5 ($\text{CH}_2\text{CH}_2\text{CH}$), 60.7 ($\text{CH}_2\text{CH}_2\text{OH}$), 63.9 (CH_2OTBS), 74.1 ($(\text{CH}_3)_2\text{COH}$), 87.6 ($\text{HOCH}_2\text{CH}_2\text{COH}$); MS: m/z (ES+ mode) 397 (100%) [$\text{M}+\text{Na}$] $^+$, 375 (64%) [$\text{M}+\text{H}$] $^+$, HRMS Calcd for $\text{C}_{20}\text{H}_{43}\text{O}_4\text{Si}$: 375.2925. Found: 375.2937.

4.6.10. (1R,2S,5S)-2-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-5-(2-hydroxypropan-2-yl)-2-methyl-1-vinylcyclopentanol **25**

To a stirred solution of (1R,2S,5S)-2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-1-(2-hydroxyethyl)-5-(2-hydroxypropan-2-yl)-2-methylcyclopentanol (30 mg, 0.080 mmol, 1.0 equiv) in THF (0.3 mL) at room temperature was added 2-nitrophenyl selenocyanate (27.3 mg, 0.120 mmol, 1.5 equiv). *n*-Bu $_3$ P (29.7 μL , 0.120 mmol, 1.5 equiv) was added dropwise, forming a dark red solution, and the reaction stirred for 36 h. The reaction mixture was cooled to 0 °C and

H₂O₂ (30% w/w aq) was added. The reaction was warmed to room temperature and stirred for 4 h before being quenched by the addition of saturated aqueous NaHCO₃ solution (3.0 mL). The aqueous phase was extracted with EtOAc (4 × 5 mL) and the combined organics were dried (MgSO₄), filtered and concentrated in vacuo. The crude, yellow oil was purified by column chromatography (eluting with 20% EtOAc in petroleum ether (40–60 °C)) giving the allylic alcohol **25** (20.7 mg, 0.058 mmol, 72%) as a pale yellow oil. ν_{\max} (thin film)/cm⁻¹ 3390 m (OH), 2953s, 2923s, 2854 m, 2362w, 1528w, 1471 m, 1380w, 1256 m, 1162w, 1098s, 1004w, 937w, 917w, 833s, 774 m; $[\alpha]_D = -21.8$ (c 0.9, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 0.06 (6H, s, (Si(CH₃)₂), 0.80 (CCH₃), 0.90 (9H, s, SiC(CH₃)₃), 1.06–1.13 (1H, m, 1H from CH₂CH₂CH₂OTBS), 1.16 (3H, s, (CH₃)₂COH), 1.23–1.30 (1H, m, 1H from CH₂CH₂CH₂OTBS), 1.33 (3H, s, (CH₃)₂COH), 1.42–1.52 (2H, m, CH₂CH₂CH₂OTBS), 1.59–1.66 (2H, m, CH₂CH₂CH), 1.69–1.84 (1H, m, 1H from CH₂CH₂CH), 1.93–2.05 (1H, m, 1H from, CH₂CH₂CH), 2.19 (1H, dd, $J = 10.4$, 7.4 Hz, CH₂CH₂CH), 2.91 (1H, s, OH), 3.14 (1H, s, OH), 3.58 (2H, dt, $J = 6.4$, 2.5 Hz, CH₂CH₂CH₂OTBS), 5.18 (1H, dd, $J = 10.9$, 1.5 Hz, 1H from CH=CH₂), 5.27 (1H, dd, $J = 17.3$, 1.5 Hz, 1H from CH=CH₂), 5.99 (1H, dd, $J = 17.3$, 10.9 Hz, CH=CH₂); ¹³C NMR (75 MHz, CDCl₃) δ -5.2 (Si(CH₃)₂), 16.6 (CCH₃), 18.3 (SiC(CH₃)₃), 23.1 (CH₂CH₂CH), 26.0 (SiC(CH₃)₃), 28.2 (CH₂CH₂CH₂OTBS), 30.4 (HOC(CH₃)₂), 30.8 (HOC(CH₃)₂), 31.8 (CH₂CH₂CH₂OTBS), 32.8 (CH₂CH₂CH), 51.9 (CCH₃), 53.5 (CH₂CH₂CH), 63.8 (CH₂OTBS), 73.9 ((CH₃)₂COH), 87.2 (CH₂=CHCOH), 112.9 (CH=CH₂), 142.9 (CH=CH₂); MS: m/z (ES+ mode) 357 (100%) [M+H]⁺, HRMS Calcd for C₂₀H₄₁O₃Si: 357.2819. Found: 357.2829.

4.6.11. ((1S,2R,3S)-1-Acetoxymethyl-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-hydroxy-2-(2-hydroxyethyl)-3-methylcyclopentane)

To a stirred solution of benzyl ether **22** (21 mg, 0.0439 mmol, 1.0 equiv) in EtOH (0.9 mL) at room temperature was added Pd/C (10% activated charcoal) (46.2 mg, 0.044 mmol, 1.0 equiv) and the resulting suspension degassed with H₂. The reaction mixture was stirred vigorously under H₂ for 4 h before being filtered through Celite, washing through with EtOH (2 × 5 mL). Concentration of the organic filtrate gave ((1S,2R,3S)-1-acetoxymethyl-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-hydroxy-2-(2-hydroxyethyl)-3-methylcyclopentane) (16.6 mg, 0.043 mmol, 97%) that was used without further purification. ν_{\max} (thin film)/cm⁻¹ 3424 m (OH), 2953s, 2883w 2854 m, 1738s (C=O), 1716w, 1471 m, 1461 m, 1385 m, 1365 m, 1251s, 1098s, 1031 m, 940w, 833s, 774 m; $[\alpha]_D = -23.4$ (c 1.83, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.05 (6H, s, Si(CH₃)₂), 0.89 (9H, s, SiC(CH₃)₃), 1.01 (3H, s, CCH₃), 1.16–1.27 (3H, m, CH₂CH₂CH₂OTBS, OH), 1.40–1.57 (5H, m, CH₂CH₂CH₂OTBS, CH₂CH₂CH, 1H from CH₂CH₂CH), 1.71–1.90 (3H, m, CH₂CH₂OH, 1H from CH₂CH₂CH), 2.06 (3H, s, CH₃C=O), 2.25–2.32 (1H, m, CH₂CH₂CH), 3.59 (2H, t, $J = 6.5$ Hz, CH₂CH₂CH₂OTBS), 3.99 (2H, t, $J = 5.8$ Hz, CH₂CH₂OH), 4.06 (1H, dd, $J = 11.1$, 7.3 Hz, 1H from CH₂OAc), 4.43 (1H, dd, $J = 11.1$, 5.8 Hz, 1H from CH₂OAc); ¹³C NMR (100 MHz, CDCl₃) δ -5.2 (Si(CH₃)₂), 18.3 (SiC(CH₃)₃), 18.8 (CCH₃), 21.2 (CH₃C=O), 25.4 (CH₂CH₂CH), 26.0 (SiC(CH₃)₃), 28.1 (CH₂CH₂CH₂OTBS), 31.6 (CH₂CH₂CH₂OTBS), 33.3 (CH₂CH₂CH), 36.1 (CH₂CH₂OH), 45.8 (CH₂CH₂CH), 49.7 (CCH₃), 60.4 (CH₂CH₂OH), 63.8 (CH₂OTBS), 66.5 (CH₂OAc), 85.2 (HOCH₂CH₂COH), 171.4 (CH₃C=O); MS: m/z (ES+ mode) 411 (100%) [M+Na]⁺, HRMS Calcd for C₂₀H₄₀O₅NaSi: 411.2537. Found: 411.2543.

4.6.12. (1S,2R,3S)-1-Acetoxymethyl-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-hydroxy-3-methyl-2-vinylcyclopentane **26**

To a stirred solution of ((1S,2R,3S)-1-acetoxymethyl-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-hydroxy-2-(2-hydroxyethyl)-3-

methylcyclopentane) (55 mg, 0.142 mmol, 1.0 equiv) in THF (0.67 mL) at room temperature was added 2-nitrophenyl selenocyanate (48.3 mg, 0.212 mmol, 1.5 equiv). *n*-Bu₃P (52.3 μ L, 0.212 mmol, 1.5 equiv) was added dropwise forming a dark red solution that was stirred for 36 h. The reaction mixture was cooled to 0 °C and H₂O₂ (30% w/w aq 0.08 mL, 0.807 mmol, 5.7 equiv) added. The reaction was warmed to room temperature and stirred for 4 h before being quenched by the addition of saturated aqueous NaHCO₃ solution (3.0 mL). The aqueous phase was extracted with CH₂Cl₂ (4 × 5 mL) and the combined organic phases dried (MgSO₄), filtered and concentrated in vacuo. The dark yellow oil was purified by column chromatography (eluting with 30% EtOAc in petroleum ether (40–60 °C)) giving the allylic alcohol **26** (45.3 mg, 0.122 mmol, 86%) as a pale yellow oil. ν_{\max} (thin film)/cm⁻¹ 3479w (OH), 2953s, 2928s, 2854 m, 2357w, 1740 m, 1726 m, 1464 m, 1385 m, 1367 m, 1251s, 1091s, 1034 m, 1004w, 935w, 920w, 836s, 774 m; $[\alpha]_D = -58.7$ (c 1.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.05 (6H, s, Si(CH₃)₂), 0.87 (3H, s, CCH₃), 0.90 (9H, s, SiC(CH₃)₃), 1.08–1.17 (1H, m, 1H from CH₂CH₂CH₂OTBS), 1.21–1.30 (1H, m, 1H from CH₂CH₂CH₂OTBS), 1.34–1.41 (1H, m, 1H from CH₂CH₂CH), 1.42–1.51 (2H, m, CH₂CH₂CH₂OTBS), 1.64–1.69 (2H, m, CH₂CH₂CH), 1.77–1.85 (1H, m, 1H from CH₂CH₂CH), 1.97 (3H, s, CH₃C=O), 2.31 (1H, s, OH), 2.54–2.62 (1H, m, CH₂CH₂CH), 3.52–3.62 (2H, m, CH₂OTBS), 3.93 (1H, dd, $J = 11.4$, 6.1 Hz, 1H from CH₂OAc), 4.43 (1H, dd, $J = 11.4$, 8.8 Hz, 1H from CH₂OAc), 5.14 (1H, dd, $J = 10.8$, 1.5 Hz, 1H from CH=CH₂), 5.21 (1H, dd, $J = 17.4$, 1.5 Hz, 1H from CH=CH₂), 5.87 (1H, dd, $J = 17.4$, 10.8 Hz, CH=CH₂); ¹³C NMR (100 MHz, CDCl₃) δ -5.2 (Si(CH₃)₂), 17.1 (CCH₃), 18.3 (SiC(CH₃)₃), 21.0 (CH₃C=O), 24.3 (CH₂CH₂CH), 26.0 (SiC(CH₃)₃), 28.1 (CH₂CH₂CH₂OTBS), 32.1 (CH₂CH₂CH₂OTBS), 32.7 (CH₂CH₂CH), 45.7 (CH₂CH₂CH), 51.0 (CCH₃), 63.8 (CH₂OTBS), 64.4 (CH₂OAc), 84.4 (CH₂=CHCOH), 113.8 (CH₂=CH), 140.7 (CH₂=CH), 172.1 (CH₃C=O); MS: m/z (ES+ mode) 393 (100%) [M+Na]⁺, HRMS Calcd for C₂₀H₃₉O₄Si: 371.2612. Found: 371.2615.

4.6.13. (1R,2S,5S)-2-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-5-(hydroxymethyl)-2-methyl-1-vinylcyclopentanol **27**

To a stirred solution of acetate **26** (45 mg, 0.121 mmol, 1.0 equiv) in MeOH (5.8 mL) at room temperature was added K₂CO₃ (50 mg, 0.364 mmol, 3.0 equiv) and the mixture heated to 40 °C for 1 h. The reaction mixture was cooled to room temperature and concentrated in vacuo and the residue was slurried in brine (4.0 mL) and extracted with CH₂Cl₂ (5 × 5 mL). The combined organics were dried (MgSO₄), filtered and concentrated in vacuo giving the diol **27** (39.6 mg, 0.121 mmol, 100%) as a pale yellow oil which was used without further purification. ν_{\max} (thin film)/cm⁻¹ 3385 m (OH), 2953s, 2928s, 2854 m, 1471 m, 1461 m, 1406w, 1385w, 1254 m, 1098s, 1029w, 1002w, 972w, 937w, 922w, 833s, 774 m; $[\alpha]_D = -61.7$ (c 0.92, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.05 (6H, s, Si(CH₃)₂), 0.86 (3H, s, CCH₃), 0.90 (9H, s, SiC(CH₃)₃), 1.12–1.20 (1H, m, 1H from CH₂CH₂CH₂OTBS), 1.26–1.34 (1H, m, 1H from CH₂CH₂CH₂OTBS), 1.46–1.53 (2H, m, CH₂CH₂CH₂OTBS), 1.61–1.70 (2H, m, CH₂CH₂CH), 1.72–1.80 (2H, m, CH₂CH₂CH), 2.25 (1H, s, OH), 2.27–2.34 (1H, m, CH₂CH₂CH), 3.54–3.64 (2H, m, CH₂OTBS), 3.70 (1H, dd, $J = 11.3$, 5.8 Hz, 1H from CHCH₂OH), 3.82 (1H, dd, $J = 11.1$, 3.5 Hz, 1H from CHCH₂OH), 5.24 (1H, dd, $J = 10.8$, 1.5 Hz, 1H from CH=CH₂), 5.35 (1H, dd, $J = 17.2$, 1.5 Hz, 1H from CH=CH₂), 5.97 (1H, dd, $J = 17.2$, 10.8 Hz, CH=CH₂); ¹³C NMR (100 MHz, CDCl₃) δ -5.2 (Si(CH₃)₂), 17.3 (CCH₃), 18.3 (SiC(CH₃)₃), 22.9 (CH₂CH₂CH), 26.0 (SiC(CH₃)₃), 28.2 (CH₂CH₂CH₂OTBS), 32.1 (CH₂CH₂CH₂OTBS), 33.5 (CH₂CH₂CH), 46.8 (CH₂CH₂CH), 50.8 (CCH₃), 62.5 (CHCH₂OH), 63.8 (CH₂OTBS), 87.3 (CH₂=CHCOH), 114.3 (CH=CH₂), 140.7 (CH=CH₂); MS: m/z (ES+ mode) 351 (100%) [M+Na]⁺, 329 (13%) [M+H]⁺.

4.6.14. (4a,5*S*,7*aR*)-7-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-7-methyl-7a-vinylhexahydrocyclopenta[d][1,3]dioxin-2-one **3**

To a stirred solution of diol **27** (72 mg, 0.203 mmol, 1.0 equiv) in CH_2Cl_2 (12.8 mL) at room temperature was added pyridine (257 μL , 3.05 mmol, 15 equiv). The mixture was cooled to -78°C and a solution of triphosgene (54.4 mg, 0.203 mmol, 1.0 equiv) in CH_2Cl_2 (6.4 mL) was added dropwise. The reaction was warmed to room temperature and stirred overnight before being quenched by the addition of saturated aqueous NH_4Cl solution (6.0 mL). The aqueous phase was extracted in CH_2Cl_2 (5×10 mL) and the combined organic phases were dried (MgSO_4), filtered and concentrated in vacuo. The crude product was purified by column chromatography (eluting with 20% EtOAc in petroleum ether (40 – 60°C)) giving the allylic carbonate **3** (71.6 mg, 0.202 mmol, 100%) as a pale yellow oil. ν_{max} (thin film)/ cm^{-1} 2955 m, 2929 m, 2858 m, 1755s ($\text{C}=\text{O}$), 1472w, 1394w, 1256 m, 1208w, 1132 m, 1100 m, 1045w, 1007w, 938w, 836 m, 813w, 776 m; $[\alpha]_{\text{D}} = -32.8$ (c 0.72, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.05 (6H, s, $\text{Si}(\text{CH}_3)_2$), 0.09 (9H, s, $\text{Si}(\text{CH}_3)_3$), 1.02 (3H, s, CCH_3), 1.17–1.34 (2H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 1.44–1.62 (3H, m, 1H from $\text{CH}_2\text{CH}_2\text{CH}$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 1.77–1.86 (2H, m, 1H from $\text{CH}_2\text{CH}_2\text{CH}$, 1H from $\text{CH}_2\text{CH}_2\text{CH}$), 1.97–2.08 (1H, m, 1H from $\text{CH}_2\text{CH}_2\text{CH}$), 2.55 (1H, ddt, $J = 11.2, 6.6, 2.8$ Hz, $\text{CH}_2\text{CH}_2\text{CH}$), 3.54–3.66 (2H, m, CH_2OTBS), 4.18 (1H, dd, $J = 11.2, 2.3$ Hz, 1H from $\text{CH}_2\text{OC}(\text{O})\text{O}$), 4.33 (1H, dd, $J = 11.2, 2.8$ Hz, 1H from $\text{CH}_2\text{OC}(\text{O})\text{O}$), 5.41 (1H, dd, $J = 11.1, 1.0$ Hz, 1H from $\text{CH}=\text{CH}_2$), 5.44 (1H, m, 17.2, 1.0 Hz, 1H from $\text{CH}=\text{CH}_2$), 5.83 (1H, dd, $J = 17.2, 11.1$ Hz, $\text{CH}=\text{CH}_2$); ^{13}C NMR (100 MHz, CDCl_3) δ -6.3 ($\text{Si}(\text{CH}_3)_2$), 16.1 (CCH_3), 17.3 ($\text{Si}(\text{CH}_3)_3$), 22.6 ($\text{CH}_2\text{CH}_2\text{CH}$), 24.9 ($\text{Si}(\text{CH}_3)_3$), 26.6 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 30.5 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 32.4 ($\text{CH}_2\text{CH}_2\text{CH}$), 36.9 ($\text{CH}_2\text{CH}_2\text{CH}$), 50.6 (CCH_3), 62.3 (CH_2OTBS), 66.3 ($\text{CH}_2\text{OC}(\text{O})\text{O}$), 96.5 ($\text{CH}_2=\text{CHCO}(\text{O})\text{O}$), 117.6 ($\text{CH}=\text{CH}_2$), 133.0 ($\text{CH}=\text{CH}_2$), 148.1 ($\text{CH}_2\text{OC}(\text{O})\text{O}$); MS: m/z (ES^+ mode) 372 (100%) [$\text{M}+\text{NH}_4$] $^+$, HRMS Calcd for $\text{C}_{19}\text{H}_{34}\text{O}_4\text{NaSi}$: 377.2119. Found: 377.2120.

4.6.15. (1*R*,2*S*,5*S*)-1-(3-((Benzyloxy)methyl)-1-hydroxybut-3-en-1-yl)-2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-5-(hydroxymethyl)-2-methylcyclopentanol **29**

A stirred solution of alkene **3** (20 mg, 0.056 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) at -78°C was degassed with N_2 then O_2 for 5 min. Next, O_3 was bubbled through the reaction until a persistent blue colour was observed. The reaction was subsequently degassed with O_2 then N_2 until the colour dissipated. DMS (0.1 mL) was added dropwise and the reaction warmed to room temperature and stirred for 4 h. The reaction was quenched by the addition of saturated aqueous NaHCO_3 solution (2.0 mL) and the aqueous phase was extracted in Et_2O (3×4.0 mL). The combined organic phases were dried (MgSO_4), filtered and concentrated in vacuo giving the aldehyde **28** (19 mg, 0.053 mmol, 95%) that was used immediately without purification.

The aldehyde was re-dissolved in a 1:1 mixture of THF/ H_2O (2.0 mL) at room temperature and 2-benzyloxymethyl-3-bromopropene (21.8 mg, 0.091 mmol, 1.7 equiv) was added. Indium powder (6.7 mg, 0.059 mmol, 1.1 equiv) was then added and the reaction stirred vigorously overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution (2.0 mL) and the aqueous phase was extracted in EtOAc (4×5 mL) and the combined organic layers dried (MgSO_4), filtered and concentrated in vacuo. The crude mixture was purified by chromatography (eluting in 30% EtOAc in petroleum ether (40 – 60°C)) giving the major diastereoisomer of homoallylic alcohol **29** (6.1 mg, 0.0124 mmol, 23%) as a colourless oil together with a mixture of **29** and another stereoisomer (6.5 mg, 0.0132 mmol, 25%), and a mixture of both stereoisomers from which the TBS group had been lost (4.0 mg, 0.0106 mmol, 20%). ^1H NMR (400 MHz, CDCl_3) δ 0.05 (6H, s, $\text{Si}(\text{CH}_3)_2$), 0.90 (9H, s, $\text{Si}(\text{CH}_3)_3$), 1.05 (3H, s, CCH_3), 1.09–1.79

(7H, m, $7 \times 1\text{H}$ from CH_2), 1.97–2.10 (1H, m, 1H from CH_2), 2.32 (1H, dd, $J = 13.8, 11.1$ Hz, 1H from $\text{CH}_2=\text{CCH}_2\text{CHOH}$), 2.40–2.50 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}$), 2.67 (1H, d, $J = 13.8$ Hz, 1H from $\text{CH}_2=\text{CCH}_2\text{CHOH}$), 2.83 (1H, s, OH), 3.55–3.68 (4H, m, CH_2OTBS , CHOH , 1H from $\text{CH}_2=\text{CCH}_2\text{OBn}$), 3.79 (1H, dd, $J = 10.8, 2.3$ Hz, 1H from $\text{CH}_2=\text{CCH}_2\text{OBn}$), 3.96–4.02 (2H, m, CHCH_2O), 4.56 (2H, s, $\text{PhCH}_2\text{OCH}_2$), 5.12 (1H, s, 1H from $\text{CH}_2=\text{C}$), 5.22 (1H, s, 1H from $\text{CH}_2=\text{C}$), 7.30–7.40 (5H, m, $5 \times \text{ArCH}$).

4.6.16. (1*R*,2*S*,5*S*)-1-(3-((Benzyloxy)methyl)-1-hydroxybut-3-en-1-yl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-methylcyclopentanol

To a stirred solution of the major diastereoisomer of homoallylic alcohol **24** (6.1 mg, 0.0124 mmol, 1 equiv) in CH_2Cl_2 (0.5 mL) at room temperature was added imidazole (4.0 mg, 0.0588 mmol, 4.7 equiv), then TBSCl (5.3 mg, 0.0353 mmol, 2.8 equiv) and the reaction stirred for 3 h. The reaction was quenched by the addition of saturated aqueous NaHCO_3 solution (2.0 mL) and the aqueous phase extracted with Et_2O (4×3.0 mL). The combined organics were dried (MgSO_4), filtered and concentrated in vacuo and the crude residue was purified by column chromatography (eluting with 10% EtOAc in petroleum ether (40 – 60°C)) to give (1*R*,2*S*,5*S*)-1-(3-((Benzyloxy)methyl)-1-hydroxybut-3-en-1-yl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-methylcyclopentanol (4.8 mg, 7.9×10^{-3} mmol, 67%). ^1H NMR (500 MHz, CDCl_3) δ 0.04 (6H, s, $\text{Si}(\text{CH}_3)_2$), 0.09 (6H, s, $\text{Si}(\text{CH}_3)_2$), 0.90 (18H, s, $2 \times \text{Si}(\text{CH}_3)_3$), 1.03 (3H, s, CCH_3), 1.27–1.34 (2H, m, $2 \times 1\text{H}$ from CH_2), 1.36–1.42 (1H, m, 1H from CH_2), 1.47–1.53 (3H, m, $3 \times 1\text{H}$ from CH_2), 1.59–1.64 (1H, m, 1H from CH_2), 1.86–1.71 (1H, m, 1H from CH_2), 2.23 (1H, dd, $J = 14.2, 11.3$ Hz, 1H from $\text{CH}_2=\text{CCH}_2\text{CHOH}$), 2.30–2.35 (1H, m, $\text{CH}_2\text{CH}_2\text{CH}$), 2.58 (1H, d, $J = 14.2$ Hz, 1H from $\text{CH}_2=\text{CCH}_2\text{CHOH}$), 3.48–3.53 (1H, m, 1H from CH_2OTBS), 3.56–3.62 (1H, m, 1H from CH_2OTBS), 3.59 (1H, s, OH), 3.75–3.76 (2H, m, CHCH_2OTBS), 3.83 (1H, ddd, $J = 11.3, 3.5, 2.6$ Hz, CHOH), 3.99 (1H, d, $J = 12.3$ Hz, 1H from $\text{CH}_2=\text{CCH}_2\text{OBn}$), 4.10–4.12 (2H, m, 1H from $\text{CH}_2=\text{CCH}_2\text{OBn}$, OH), 4.49 (1H, d, $J = 11.7$ Hz, 1H from $\text{PhCH}_2\text{OCH}_2$), 4.54 (1H, d, $J = 11.7$ Hz, 1H from $\text{PhCH}_2\text{OCH}_2$), 5.06 (1H, s, 1H from $\text{CH}_2=\text{C}$), 5.15 (1H, s, 1H from $\text{CH}_2=\text{C}$), 7.28–7.35 (5H, m, $5 \times \text{ArCH}$); MS: m/z (ES^+ mode) 629 (100%) [$\text{M}+\text{Na}$] $^+$, 607 (48%) [$\text{M}+\text{H}$] $^+$, HRMS Calcd for $\text{C}_{34}\text{H}_{63}\text{O}_5\text{Si}_2$: 607.4209. Found: 607.4211.

4.6.17. (5*R*,6*S*,9*S*)-4-(2-((Benzyloxy)methyl)allyl)-9-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-6-methyl-1,3-dioxaspiro[4.4]nonan-2-one **30**

To a stirred solution of (1*R*,2*S*,5*S*)-1-(3-((benzyloxy)methyl)-1-hydroxybut-3-en-1-yl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-methylcyclopentanol (4.8 mg, 7.9×10^{-3} mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) at room temperature was added pyridine (10 μL , 0.119 mmol, 15 equiv). The reaction was cooled to -78°C and a solution of triphosgene (2 mg, 7.9×10^{-3} mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added dropwise. The reaction was warmed to room temperature and stirred overnight. The reaction was then quenched by the addition of saturated aqueous NH_4Cl solution (2.0 mL). The aqueous phase was extracted in CH_2Cl_2 (5×3 mL) and the combined organic phases dried (MgSO_4), filtered and concentrated in vacuo. The crude product was purified by column chromatography (eluting with 5% EtOAc in petroleum ether (40 – 60°C)) giving the spirocyclic carbonate **30** (3.4 mg, 5.4×10^{-3} mmol, 68%) as a colourless oil. ν_{max} (thin film)/ cm^{-1} 2953 m, 2928 m, 2854 m, 1800 m ($\text{C}=\text{O}$), 1468w, 1461w, 1357w, 1256s, 1197 m, 1172 m, 1095s, 836s, 811 m, 720 m; $[\alpha]_{\text{D}} = -29.4$ (c 0.34, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 0.05 (6H, s, $\text{Si}(\text{CH}_3)_2$), 0.05 (3H, s, $\text{Si}(\text{CH}_3)_2$), 0.87 (9H, s, $\text{Si}(\text{CH}_3)_3$), 0.89 (9H, s, $\text{Si}(\text{CH}_3)_3$), 1.14 (3H, s, CCH_3), 1.17–1.27 (1H, m, 1H from CH_2), 1.37–1.42 (1H, m, 1H from CH_2), 1.48–1.70 (5H, m, $5 \times 1\text{H}$ from CH_2), 1.74–1.85 (1H, m, 1H from CH_2), 2.48–2.57

(2H, m, 1H from $\text{CH}_2=\text{CCH}_2\text{OC}(\text{O})\text{O}$, $\text{CH}_2\text{CH}_2\text{CH}$), 2.70 (1H, d, $J=14.9$ Hz, 1H from $\text{CH}_2=\text{CCH}_2\text{OC}(\text{O})\text{O}$), 3.53–3.62 (2H, m, CH_2OTBS), 3.62 (1H, dd, $J=10.1$, 5.5 Hz, 1H from CHCH_2OTBS), 3.82 (1H, dd, $J=10.1$, 8.8 Hz, 1H from CHCH_2OTBS), 3.97 (1H, d, $J=12.1$ Hz, 1H from $\text{CH}_2=\text{CCH}_2\text{OBn}$), 4.07 (1H, d, $J=12.1$ Hz, 1H from $\text{CH}_2=\text{CCH}_2\text{OBn}$), 4.48 (H, d, $J=12.0$ Hz, 1H from PhCH_2O), 4.52 (1H, d, $J=12.0$ Hz, 1H from PhCH_2O) 5.09 (1H, s, 1H from $\text{CH}_2=\text{C}$), 5.20 (1H, s, 1H from $\text{CH}_2=\text{C}$), 5.24 (1H, dd, $J=11.8$, 2.0 Hz, $\text{CH}_2\text{CHOC}(\text{O})\text{O}$), 7.28–7.38 (5H, m, $5 \times \text{ArCH}$); ^{13}C NMR (100 MHz, CDCl_3) δ –5.7 ($\text{Si}(\text{CH}_3)_2$), 5.3 ($\text{Si}(\text{CH}_3)_2$), 18.2 ($\text{SiC}(\text{CH}_3)_3$), 18.3 ($\text{SiC}(\text{CH}_3)_3$), 18.5 (CCH_3), 22.9 ($\text{CH}_2\text{CH}_2\text{CH}$), 25.9 ($\text{SiC}(\text{CH}_3)_3$), 25.9 ($\text{SiC}(\text{CH}_3)_3$), 27.7 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 30.4 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{OTBS}$), 33.8 ($\text{CH}_2\text{CH}_2\text{CH}$), 34.3 ($\text{CH}_2=\text{CCH}_2\text{CHO}$), 47.8 (CHCH_2OTBS), 49.5 (CCH_3), 62.6 (CH_2OTBS), 63.1 (CH_2OTBS), 72.0 (BnOCH_2), 72.8 (PhCH_2O), 81.5 ($\text{CHOC}(\text{O})\text{O}$), 96.6 ($\text{COC}(\text{O})\text{O}$), 115.6 ($\text{C}=\text{CH}_2$), 127.7 ($2 \times \text{ArCH}$), 127.7 (ArCH), 128.4 ($2 \times \text{ArCH}$), 138.1 (ArC), 141.2 ($\text{C}=\text{CH}_2$), 154.4 ($\text{OC}(\text{O})\text{O}$); MS: m/z (ES+ mode) 655 (100%) $[\text{M}+\text{Na}]^+$, 652 (72%), 650 (36%) $[\text{M}+\text{NH}_4]^+$, HRMS Calcd for $\text{C}_{35}\text{H}_{60}\text{O}_6\text{NaSi}_2$: 655.3821. Found: 655.3833.

Acknowledgments

We thank the EPSRC (DTA project studentship, T.M.B.), EPSRC and GSK (Industrial CASE award, L.A.S.), Royal Society (India Fellowship, L.H.C.) and Japan Society for the Promotion of Science (Fellowship, M.M.) and the University of Manchester.

References

- (a) Namy, J. L.; Girard, P.; Kagan, H. B. *Nouv. J. Chim.* **1977**, *1*, 5; (b) Girard, P.; Namy, J.-L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.
- For recent reviews on the use of samarium(II) iodide: (a) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321; (b) Kagan, H.; Namy, J. L. In *Lanthanides: Chemistry and Use in Organic Synthesis*; Kobayashi, S., Ed.; Springer: Berlin, 1999; p 155; (c) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727; (d) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351; (e) Dahlén, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393; (f) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371; (g) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607; (h) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140; (i) Procter, D. J.; Flowers, R. A., II; Skrydstrup, T. *Organic Synthesis using Samarium Diodide: A Practical Guide*; RSC Publishing: Cambridge, 2010.
- Mori, K.; Iguchi, K.; Yamada, N.; Yamada, Y.; Inouye, Y. *Tetrahedron Lett.* **1987**, *28*, 5673.
- Yabe, T.; Yamada, H.; Shimomura, M.; Miyaoka, H.; Yamada, Y. *J. Nat. Prod.* **2000**, *63*, 433.
- Miyaoka, H.; Baba, T.; Mitome, H.; Yamada, Y. *Tetrahedron Lett.* **2001**, *42*, 9233.
- (a) Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett.* **2002**, *4*, 2345; (b) Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811; (c) Guazzelli, G.; Duffy, L. A.; Procter, D. J. *Org. Lett.* **2008**, *10*, 4291.
- Sloan, L. A.; Baker, T. M.; Macdonald, S. J. F.; Procter, D. J. *Synlett* **2007**, 3155.
- α -(Triphenylphosphoranylidene)- γ -butyrolactone was prepared by adapting the procedure of Baldwin: Baldwin, J. E.; Moloney, M. G.; Parsons, A. F. *Tetrahedron* **1992**, *48*, 9373.
- (a) Duffy, L. A.; Matsubara, H.; Procter, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 1136; (b) Parmar, D.; Duffy, L. A.; Sadasivam, D. V.; Matsubara, H.; Bradley, P. A.; Flowers, R. A., II; Procter, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 15467.
- Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
- Kamenecka, T. M.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2995.
- Oxidation of commercially available 3-benzyloxypropan-1-ol gave **16** ($\text{py}.\text{SO}_3$, DMSO, NEt_3 , CH_2Cl_2 , 78%).
- Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
- For a review of the chemistry of samarium enolates, see: Rudkin, I. M.; Miller, L. C.; Procter, D. J. *Organomet. Chem.* **2008**, *34*, 19.
- CCDC number 747958. The minor diastereoisomer formed in the cascade reaction is derived from the alternative *syn*-spirocycle.
- Evans, D. A.; Rajapakse, H. A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4569.
- (a) Grieco, P. A.; Gilman, S. J. *Org. Chem.* **1976**, *41*, 1485; (b) Crimmins, M. T.; Tabet, E. A. *J. Org. Chem.* **2001**, *66*, 4012.
- Ozonolysis of allylic alcohol **27** resulted in decomposition of the starting material. For examples, see: Jung, M. E.; Davidov, P. *Org. Lett.* **2001**, *3*, 627.
- Green, A. P.; Hardy, S.; Thomas, E. J. *Synlett* **2008**, 2103.
- Panizza, P.; Onetto, S.; Rodríguez, S. *Biocatal. Biotransform.* **2007**, *25*, 414.
- (a) Wolf, J.; Frenking, G.; Harms, K. *Chem. Ber.* **1991**, *124*, 551; (b) Gilleron, P.; Millet, R.; Domarkas, J.; Farce, A.; Houssin, R.; Hénichart, J. *J. Peptide Sci.* **2006**, *12*, 140.