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A stereoselective cyclisation cascade mediated by SmI_2–H_2O: synthetic studies towards stolonidiol

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

ABSTRACT

A cascade reaction involving sequential conjugate reduction, stereoselective aldol cyclisation and chemoselective lactone reduction mediated by SmI_2–H_2O 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.

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 μg 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 SmI_2–H_2O-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 approach 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 (R = 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 spirolactones **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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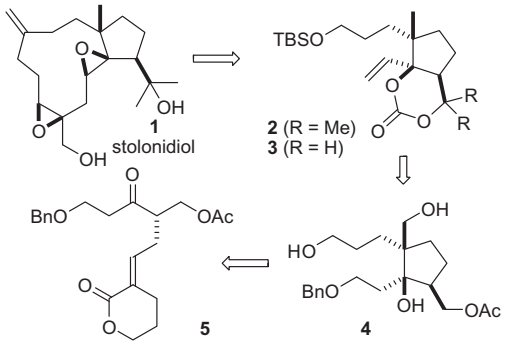
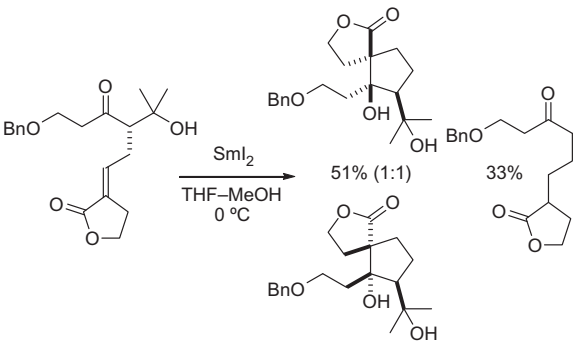
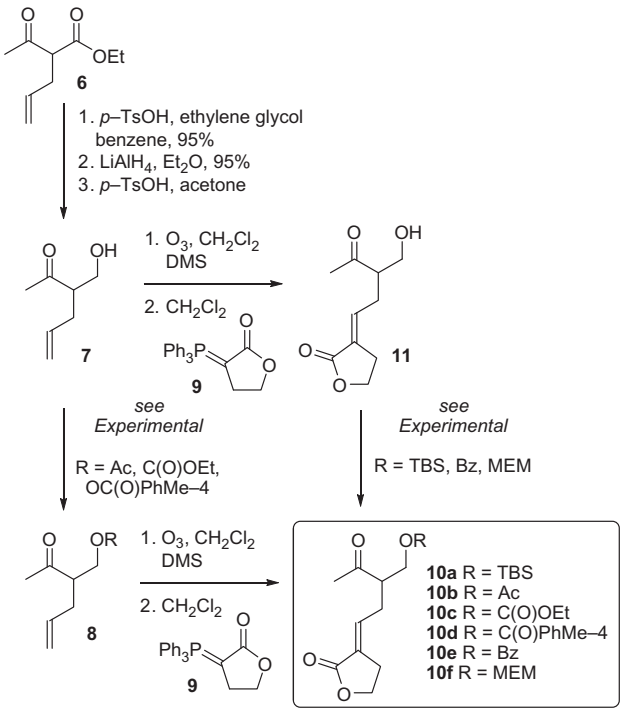


Scheme 1. Retrosynthetic analysis of stolonidiol **1**.

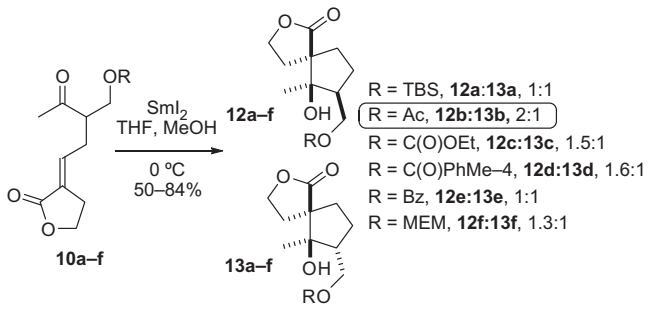


Scheme 2. A first generation Sm(II)-mediated approach to the cyclopentanol motif in stolonidiol.



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).



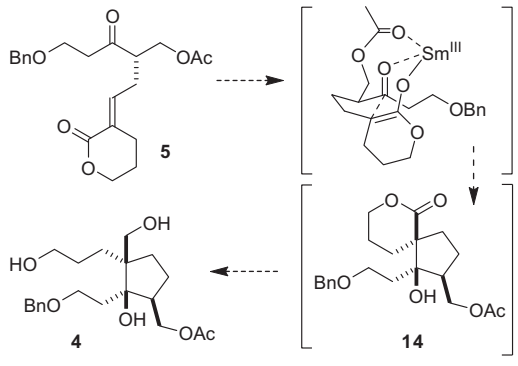
Scheme 4. Model cyclisation studies.

The synthesis of the cyclisation substrate **5** began with a boron–mediated asymmetric aldol reaction[10] 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 system[13] 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).

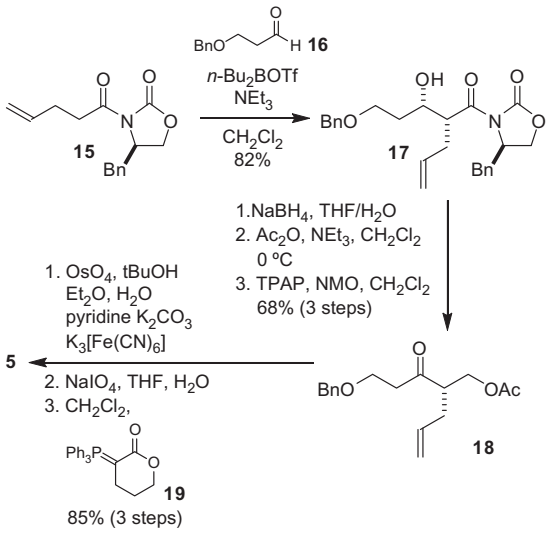
Upon treatment of substrate **5** with SmI_2 in THF and H_2O, we found that the sequential reaction proceeded as planned, giving the highly functionalised cyclopentanol **4** in 86% yield and as a 6:1 mixture of diastereoisomers in favour of the desired all-*syn*-isomer (Scheme 7).

The cascade begins with the conjugate reduction of the electron-deficient olefin, generating a Sm(III)-enolate[14] 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 % $Pd(OH)_2$/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).

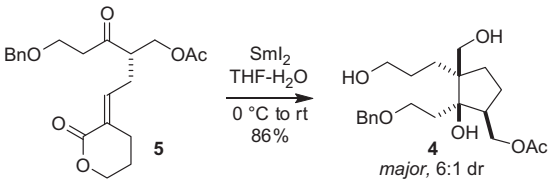
Having successfully secured a route to the functionalised cyclopentanol **4**, we focussed on its conversion to allylic carbonates **2** and **3**, strategically important intermediates in our proposed ap-



Scheme 5. Proposed stereoselective cyclisation cascade.



Scheme 6. Asymmetric synthesis of cyclisation substrate **5**.



Scheme 7. SmI_2–H_2O-mediated cyclization cascade.

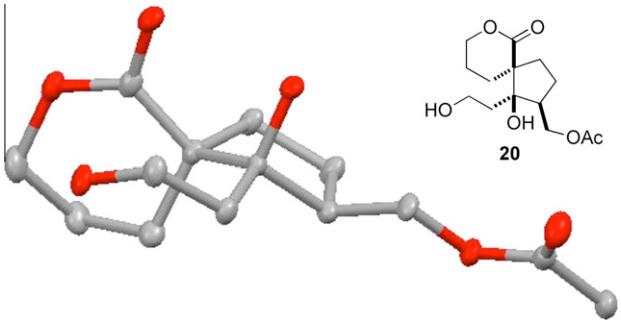
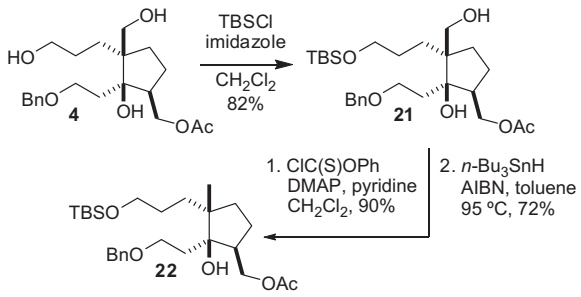


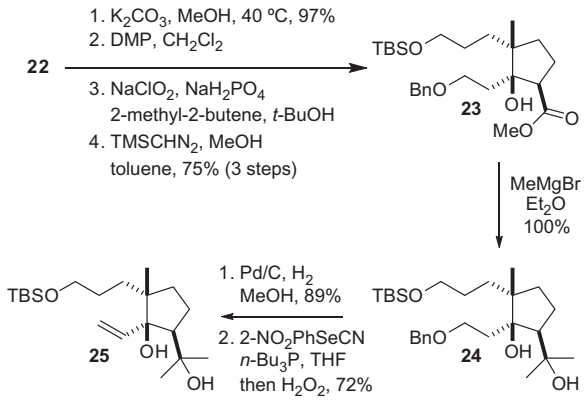
Figure 1. X-ray crystal structure of **20**.

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*-Bu_3SnH (Scheme 8).[16]



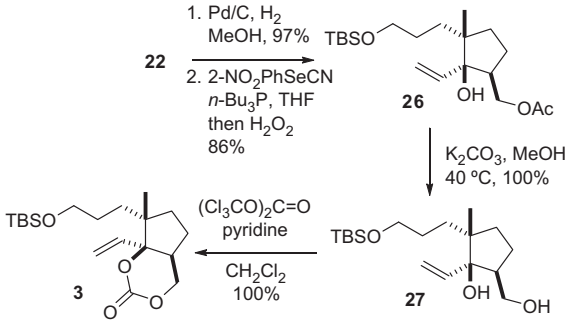
Scheme 8. Selective deoxygenation of triol **4**.

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** preceeded 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 conditions[17] 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).

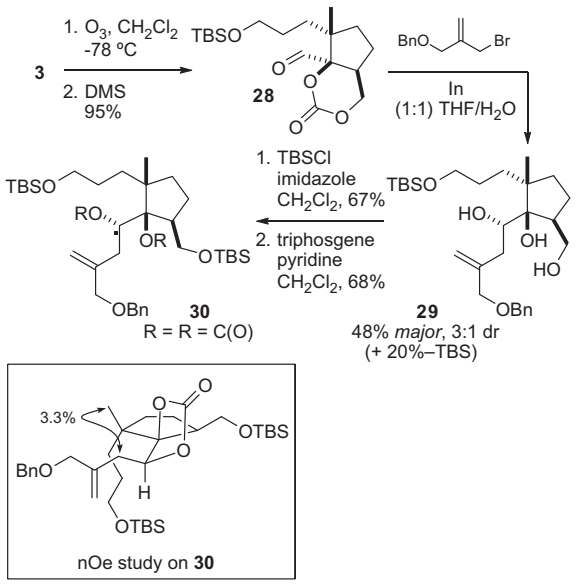


Scheme 10. Formation of allylic carbonate **3**.

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-benzyloxymethyl-3-bromopropene and indium powder[19] in 1:1 THF–H_2O 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 SmI_2–H_2O for the rapid, stereoselective synthesis of highly substituted cyclopentanols. 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 (δ_H = 7.27 or δ_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±) 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 Et_2O (4 × 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 °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, (CH_3CH_2O), 2.28 (3H, s, C(O)CH_3), 2.64 (2H, apparent t, J 7.4, $CH_2CH{=}CH_2$), 3.57 (1H, t, J 7.3, CH), 4.25 (2H, q, J 7.1, OCH_2CH_3), 5.07–5.18 (2H, m, CH=CH_2), 5.72–5.86 (1H, m, $CH{=}CH_2$); δ_C (100 MHz, $CDCl_3$) 14.4 (CH_3CH_2), 29.4 ($CH_3C(O)$), 32.4 ($CH_2CH{=}CH_2$), 59.5 (CH), 61.7 (OCH_2), 117.7 ($CH_2{=}CH$), 134.5 ($CH{=}CH_2$), 169.5 (ester $C(O)$), 202.8 (ketone $C(O)$); MS: m/z (CI^+) 188 (100%) [M^+NH_4], 171 (15%) [M^+H], HRMS Calcd for $C_9H_{18}O_3N$ ([M^+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 °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 $CH_2CH{=}CH_2$), 2.47–2.53 (1H, m, 1H from $CH_2CH{=}CH_2$), 2.75 (1H, dd, J = 11.4 Hz, 3.8, $CHCH_2CH{=}CH_2$), 3.94–4.06 (4H, m, OCH_2CH_2O), 4.17 (2H, q, J = 6 Hz, OCH_2CH_3), 5.0–5.11 (2H, m, $CH{=}CH_2$); ^{13}C NMR δ 14.3 (CH_3CH_2), 21.6 (CH_3), 32.4 ($CH_2CH{=}CH_2$), 60.5 ($CHCH_2CH{=}C$), 64.8 (OCH_2CH_2O), 64.9 (OCH_2CH_2O), 109.4 (C^q), 116.6 ($CH_2{=}CH$), 135.3 ($CH_2{=}CH$), 172.1 (C=O). MS: m/z (CI^+) 223 [M+NH_4]$^+$ (40%), 215 [M+H]$^+$ (100%), 87 (15%), HRMS Calcd for $C_{11}H_{18}O_4$: 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 Et_2O (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 Et_2O (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 °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; ^{1}H NMR δ 1.26 (3H, s, CH_3C^q), 1.80–1.89 (2H, m, 1H from CH_2CH=CH$_2$, CHCH$_2$OH), 2.23–2.28 (1H, m, 1H from CH_2CH=CH$_2$), 3.54–3.60 (2H, m, CH_2OH), 3.90–3.94 (4H, m, OCH_2CH_2O), 4.96–5.02 (2H, m, CH=CH_2), 5.70–5.77 (1H, m, CH=CH$_2$); ^{13}C NMR δ 20.8 (CH$_3$), 31.5 (CH$_2$CH=CH$_2$), 47.6 (CHCH$_2$CH=), 62.3 (CH$_2$OH), 64.4 (OCH$_2$CH$_2$O), 64.6 (OCH$_2$CH$_2$O), 112.5 (C^q), 116.4 (CH$_2$=CH), 136.8 (CH=CH$_2$); MS: m/z (CI)$^+$ 190 (40%), 173 (100%) [M+H]$^+$, 87 (35%), HRMS Calcd for $C_9H_{15}O_3$: 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 C(O)), 1642 m, 1424 m, 1037 m, 917 m; δ_H (500 MHz, CDCl$_3$) 2.15 (3H, s, CH_3C(O)), 2.19–2.24 (1H, m, 1H of CH_2CH=CH$_2$) 2.29–2.36 (1H, m, 1H of CH_2CH=CH$_2$), 2.69–2.74 (1H, m, CHCH$_2$CH=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, CH=CH_2), 5.67 (1H , ddt J 17.0, 10.1, 6.9, CH=CH$_2$); δ_C (100 MHz, CDCl$_3$) 30.0 (CH$_3$C(O)), 32.4 (CH$_2$CH=CH$_2$), 53.8 (CHCH$_2$OH), 62.4 (CH$_2$OH), 117.5 (CH$_2$=CH), 134.8 (CH=CH$_2$), 212.0 (ketone C(O)); MS: m/z (CI$^+$) 146 (100%) [M+NH$_4$]$^+$, 129 (63%) [M+H]$^+$, HRMS Calcd for $C_7H_{11}O_2$: 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$_2$Cl$_2$ (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$_2$Cl$_2$ (4 × 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 (C=O), 1718s (C=O), 1636w, 1560w, 1367m, 1236s, 1036m; ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.04 (3H, s, CH_3C(O)O), 2.18–2.27 (1H, m, 1H from CH_2CH=CH$_2$), 2.20 (3H, s, CH_3C=O), 2.35–2.44 (1H, m, 1H from CH_2CH=CH$_2$), 2.90 (1H, p, J = 7.0 Hz, CH$_3$C(O)CH), 4.21 (2H, d, J = 6.5 Hz, CH_2OC(O)CH$_3$), 5.07–5.18 (2H, m, CH=CH_2), 5.71 (1H, qt, J = 10.0, 7.0 Hz, CH=CH$_2$); ^{13}C NMR (125 MHz, CDCl$_3$) δ 20.7 (OC(O)CH$_3$), 29.9 (CH$_3$C=O), 32.5 (CH$_2$CH=CH$_2$), 51.0 (CHCH$_2$OC=O), 63.9 (CH$_2$OC=O), 117.9 (CH=CH$_2$), 134.1 (CH=CH$_2$), 170.7 (OC(O)CH$_3$), 208.7 (CH$_3$CO); MS: m/z (ES+ mode), 249 (12%), 193 (100%) [M+Na]$^+$; HRMS Calcd for $C_9H_{14}O_3Na$: 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$_2$Cl$_2$ (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$_2$Cl$_2$ (40 ml) and washed with saturated, aqueous citric acid solution (2 × 20 ml), H$_2$O (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 (C=O), 1718s (C=O), 1368w, 1261s, 1173w, 1010w, 922w, 791w; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.30 (3H, t, J = 7.0 Hz, OCH$_2$CH_3), 2.22 (3H, s, CH_3C=O), 2.23–2.27 (1H, m, 1H from CH_2CH=CH$_2$), 2.38–2.44 (1H, m, 1H from CH_2CH=CH$_2$), 2.93–2.98 (1H, m, CH$_3$C(O)CH), 4.19 (2H, q, J = 7.0 Hz, OCH_2CH$_3$), 4.21 (1H, dd, J = 11.0, 5.5 Hz, 1H from CH_2OC(O)O), 4.31 (1H, dd, J = 11.0, 8.0 Hz, 1H from CH_2OC(O)O), 5.08–5.12 (2H, m, CH=CH_2), 5.72 (1H, ddt, J = 17.0, 10.0, 7.0 Hz, CH=CH$_2$); ^{13}C NMR (125 MHz, CDCl$_3$) δ 14.1 (OCH$_2$CH$_3$), 30.1 (CH$_3$C=O), 32.4 (CH$_2$CH=CH$_2$), 50.9 (CHCH$_2$O), 64.2 (OCH$_2$CH$_3$), 66.9 (CH$_2$OC=O), 118. (CH=CH$_2$), 133.9 (CH=CH$_2$), 154.9 (OC(O)O), 208.4 (CH$_3$C=O); MS: m/z (ES+ mode) 223 (100%) [M+Na]$^+$, 218 (40%) [M+NH$_4$]$^+$, 201 (63%) [M+H]$^+$; HRMS Calcd for $C_{10}H_{16}O_4Na$: 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$_2$Cl$_2$ (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$_2$Cl$_2$ (4 × 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 (C=O), 1606s, (C=O), 1511m, 1419w, 1273m,1256s, 1167s, 1102m, 1028m, 848w, 770m; ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.25 (3H, s, CH_3C=O), 2.30–2.35 (1H, m, 1H from H$_2$C=CHCH_2), 2.45–2.51 (1H, m, 1H from H$_2$C=CHCH_2), 3.02–3.07 (1H, m, CH$_3$C(O)CH), 3.86 (3H, s, OCH_3), 4.43 (1H, dd, J = 11, 8 Hz, 1H from CH_2OC(O)), 4.47 (1H, dd, J = 11, 5 Hz, 1H from CH_2OC(O)), 5.08–5.14 (2H, m, H_2C=CH), 5.77 (1H, tdd, J = 14, 10.5, 7 Hz, CH$_2$=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 (CH$_3$C=O), 32.6 (CH$_2$CH=CH$_2$), 51.2 (C(O)CHCH$_2$), 55.5 (OCH$_3$), 64.1 (CH$_2$OC=O), 113.7 (2 × ArCH), 117.9 (CH=CH$_2$), 122.1 (ArC), 131.6 (2 × ArCH), 134.2 (CH=CH$_2$), 163.5 (ArC), 166.0 (OC=O), 208.9 (H$_3$CC=O); MS: m/z (ES+ mode) 285 (100%) [M+Na]$^+$, 263 (88%) [M+H]$^+$, HRMS Calcd for $C_{15}H_{19}O_4$: 263.1278. Found: 263.1267.

4.3. General procedure 1. Oxidative cleavage and Wittig olefination

A solution of keto-alkene in CH$_2$Cl$_2$ 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 discipated 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$_2$Cl$_2$. The combined organics were dried (MgSO$_4$), filtered and concentrated in vacuo to give the crude aldehyde. The crude aldehyde was dissolved in CH$_2$Cl$_2$ 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, CH_3C=O), 2.35–2.41 (1H, m, 1H from CH_2CH=C), 2.40–2.54 (1H, m, 1H from CH_2CH=CH_2), 2.80–2.85 (1H, m, 1H from CHCH_2CH=C), 2.86–2.90 (2H, m, CH_2CH_2O), 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, CH_2OC=O), 6.58–6,62 (1H, m, CH=C); ^{13}C NMR δ 25.1 (CH_2CH_2O), 28.3 (CH_2CH_2=C), 30.2 (CH_3C=O), 52.8 (CHCH_2CH=C), 62.3 (CH_2OH), 65.6 (OCH_2CH_2), 127.8 (C^q), 136.6 (CH=C), 171.0 (ester C=O), 210.5 (ketone C=O), MS: m/z $(CI)^+$ 216 $(M+NH_4)^+$ (100%), 199 $(M+H)^+$ (33%) 186 (100%), 169 (30%); HRMS Calcd for $C_{10}H_{13}O_4$: 197.0808. Found: 197.0806.

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

As described in general procedure 1. Ozonolysis performed on **8** (R = 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, OC(O)CH_3), 2.24 (3H, s, CH_3C=O), 2.31–2.37 (1H, m, 1H from CH_2CH=C), 2.55–2.61 (1H, m, 1H from CH_2CH=C), 2.85–2.96 (2H, m, CH_2CH_2OC=O), 3.01 (1H, p, J = 6.3 Hz, CHCH_2CH=C), 4.23 (1H, dd, J = 11.0, 6.3 Hz, 1H from CH_2OC(O)CH_3), 4.28 (1H, dd, J = 11.0, 5.4 Hz, 1H from CH_2O-C(O)CH_3), 4.39 (2H, apparent t, J = 7.6 Hz, CH_2CH_2OC=O), 6.59–6.64 (1H, m, CH=C); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.7 (CH_3C(O)O), 25.1 (CH=CCH_2CH_2), 28.7 (CH_2CH=C), 30.1 (CH_3C=O), 50.4 (CHCH_2O), 63.8 (CHCH_2O), 65.4 (CH_2CH_2OC=O), 128.0 (CH=C), 135.9 (CH=C), 170.5 (OC(O)CH_3), 207.4 (CH_3C=O); MS: m/z (ES+ mode) 263 (100%) $[M+Na]^+$; HRMS Calcd for $C_{12}H_{16}O_5Na$: 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** (R = C(O)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, CH_3C=O), 2.34–2.40 (1H, m, 1H from CH_2CH=CH_2), 2.57–2.62 (1H, m, 1H from CH_2CH=CH_2), 2.85–2.96 (2H, m, CH=CCH_2), 3.05 (1H, p, J = 6.5 Hz, CH_3C(O)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, CH=CCH_2CH_2), 6.58–6.62 (1H, m, CH=C); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2 (CH_3CH_2O), 25.1 (CH=CCH_2), 28.5 (CH_2CH=C), 30.2 (CH_3C=O), 50.3 (C(O)CH-CH_2O), 64.5 (CH_3CH_2O), 65.5 (CH_3CH_2OC=O), 66.8 (CH_2OC(O)O), 128.2 (C(O)C=CH), 135.6 (C(O)C=CH), 154.7 (OC(O)O), 170.7 (OC(O)C=CH), 207.2 (CH_3C=O); MS: m/z (ES+ mode) 562 (40%), 438 (37%), 293 (100%) $[M+Na]^+$; HRMS Calcd for $C_{13}H_{18}O_6Na$: 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** (R = C(O)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, H_3CC=O), 2.39–2.45 (1H, m, 1H from C=CHCH_2), 2.63–2.67 (1H, m, 1H from C=CHCH_2), 2.83–2.94 (2H, m, CH_2=CCH_2), 3.13 (1H, quint, J = 6 Hz, CH_3C(O)CH), 3.85 (3H, s, OCH_3), 4.33–4.36 (2H, m, CH_2=CCH_2CH_2), 4.46–4.49 (2H, m, CHCH_2OC(O)), 6.63–6.68 (1H, m, CH_2=C), 6.91 (2H, d, J = 8.5 Hz, H_3COCCH), 7.92 (2H, d, J = 7.5 Hz, H_3COCHCH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.1 (CH_2CH_2OC=O), 28.7 (CH_2CH=C), 30.0 (CH_3C=O), 50.6 (CHCH$_2$OC=O), 55.5 (OCH_3), 64.0 (CHCH_2OC=O), 65.5 (CH_2CH_2OC=O), 113.7 (2 × ArCH), 121.6 (ArC), 127.9 (C(O)C=CH), 131.7 (2 × ArCH), 136.2 (CH_2CH=C), 163.7 (ArC), 165.8 (PhC=O), 170.8 (CH_2CH_2OC=O), 207.5 (H_3CC=O); MS: m/z (ES+ mode) 355 (56%) $[M+Na]^+$, 350 (100%) $[M+NH_4]^+$, HRMS Calcd for $C_{18}H_{20}O_6Na$: 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, CH_3C=O), 2.44 (1H, p AB system, J = 7.9 Hz, 1H from CH_2CH=C), 2.68 (1H, p AB system, J = 7.9 Hz, 1H from CH_2CH=C), 2.84–2.98 (2H, m, CH_2CH_2OC=O), 3.12–3.19 (1H, m, CH_3C(O)CH), 4.36 (2H, t, J = 7.6 Hz, CH_2CH_2OC=O), 4.52 (2H, t, J = 5.4 Hz, CHCH_2OC=O), 4.65–4.69 (1H, m, CH_2CH=C), 7.45 (2H, t, J = 7.9 Hz, 2 × ArCH), 7.59 (1H, t, J = 7.6 Hz, ArCH), 7.98 (2H, d, J = 7.6 Hz, 2 × 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,

$CH_3C{=}O$), 2.23–2.30 (1H, m, 1H from C=CHCH_2), 2.47–2.54 (1H, m, 1H from C=CHCH_2), 2.77–2.91 (3H, m, C(O)CH, CH_2CH$_2$OC=O), 3.33 (3H, s, OCH_3), 3.47–3.49 (2H, m, OCH_2CH_2O), 3.55–3.62 (2H, m, OCH_2CH_2O), 3.63–3.69 (2H, m, C(O)CHCH_2), 4.31 (2H, t, J = 7.5 Hz, $CH_2OC{=}O$), 4.61 (2H, s, OCH_2O), 6.54–6.58 (1H, m, C=CHCH$_2$); ^{13}C NMR δ 25.10 (CH_2CH$_2$OC=O), 28.66 (C=CHCH_2), 30.29 (CH_3C=O), 51.38 (CH_3C(O)CH), 59.10 (OCH_3), 65.49 (C(O)CH-CH_2O), 67.13 (OCH_2CH$_2$O), 67.94 (CH_2OC=O), 71.66 (OCH_2CH$_2$O), 95.63 (OCH_2O), 136.80 (C=CHCH$_2$), (C=O) and (C(O)O) not observed; MS: m/z (ESI)$^+$ 332 (100%) [M+Na]$^+$; HRMS Calcd for $C_{14}H_{22}O_6Na$: 309.1309. Found: 309.1305.

4.4. Cyclisation of model substrates 10a–f

4.4.1. *rac*-(5*S*,6*S*,7*R*)-7-(*tert*-Butyl-dimethyl-silanyloxymethyl)-6-hydroxy-6-methyl-2-oxa-spiro[4.4]nonan-1-one 12a and *rac*-(5*S*,6*S*,7*S*)-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 $NaHCO_3$ solution (15 mL) and the aqueous phase extracted in CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with H_2O (3 × 20 mL), dried ($MgSO_4$), 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 SmI_2, (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 ($MgSO_4$) 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; ν_{max} (thin film)/cm^{-1} 2950m, 2362m, 1742s (C=O), 1150s; ^{1}H NMR δ 0.00 (6H, s, Si(CH_3)$_2$), 0.83 (9H, s, SiC(CH_3)$_3$), 1.27 (3H, s, C^{q}C(OH)CH_3), 1.61–1.70 (2H, m, 1H from C^{q}CH_2CH$_2$CH, 1H from CH_2CHCH$_2$OSi), 1.81–1.95 (3H, m, 1H from CH_2CH$_2$O, 1H from C^{q}CH_2CH$_2$CH, CH$_2$CHCH$_2$OSi), 2.16–2.26 (2H, m, 1H from CH_2CH$_2$O, 1H from CH_2CHCH$_2$OSi), 3.59 (1H, dd, J = 10, 6 Hz, 1H from CH_2OSi), 3.88 (1H, dd, J = 10, 6 Hz, 1H from CH_2OSi), 4.13–4.18 (1H, m, 1H from $CH_2OC{=}O$), 4.25 (1H, dt, J = 9, 4 Hz, 1H from $CH_2OC{=}O$); ^{13}C NMR δ −5.45 ($SiCH_3$), −5.27 ($SiCH_3$), 21.06 (CqC(OH)CH_3), 25.53 (C^q), 25.93 (SiC(CH_3)$_3$), 32.51 (CH_2CHCH$_2$OSi), 32.69 (CH_2CH$_2$OC=O), 50.28 (CHCH$_2$OSi), 55.80 (C^q), 62.74 (CH_2OSi), 65.33 (CH_2OC=O), 81.99 (C^q), 181.40 (C=O); MS: m/z (CI)$^+$ 315 (100%) [M+H]$^+$, 79 (35%); HRMS Calcd for $C_{16}H_{31}O_4Si$: 315.1986. Found: 315.1979. For the *syn, anti* spirocycle **13a**: mp 65.7–66.2 °C; ν_{max} (thin film)/cm^{-1} 2929 m, 1761s (C=O), 1375 m, 1254s, 1100s, 838s; ^{1}H NMR δ 0.00 (3H, s, Si(CH_3)$_2$), 0.01 (3H, s, Si(CH_3)$_2$), 0.82 (9H, s, SiC(CH_3)$_3$), 1.17 (3H, s, C^{q}C(OH)CH_3), 1.53 (1H, ddd, J = 14, 11, 4 Hz, 1H from C^{q}CH_2CH$_2$CH), 1.81–1.89 (1H, m, CH_2CHCH$_2$OSi), 1.98–2.11 (2H, m, 1H from CH_2CH$_2$O, 1H from C^{q}CH_2CH$_2$CH), 2.43 (1H, ddd, J = 13.5, 6.5, 4 Hz, 1H from CH_2CH$_2$O), 2.85–2.92 (1H, m, CH$_2$CHCH$_2$OSi), 3.59 (1H, t, J = 9.5 Hz, 1H, from CH_2OSi), 3.73 (1H, dd, J = 10, 5.5 Hz, 1H from CH_2OSi), 4.10–4.14 (1H, m, 1H from $CH_2OC{=}O$), 4.23–4.28 (1H, m, 1H from $CH_2OC{=}O$); ^{13}C NMR δ -5.71 ($SiCH_3$), -5.56 ($SiCH_3$), 18.79 (CqC(OH)CH_3), 22.58 (C^q), 25.78 (SiC(CH_3)), 25.88 (SiC(CH_3)), 25.93 (SiC(CH_3)), 30.90 (CH_2CHCH$_2$OSi), 31.01 (CH_2CH$_2$OC=O), 47.35 (CHCH$_2$OSi), 56.28 (C^q), 63.90 (CH_2OSi), 65.51 (CH_2OC=O), 81.80 (C^q), 180.98 (C=O); MS: m/z (CI)$^+$ 332 (10%) [M+NH$_4$]$^+$, 315 (45%) [M+H]$^+$, 182 (55%), 79 (100%); HRMS Calcd for $C_{16}H_{31}O_4Si$: 315.1986. Found: 315.2000.

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

To a stirred solution of SmI_2 (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 NH_4Cl solution (~20 ml). The aqueous phase was extracted with EtOAc (4 × 20 ml). The combined organic phases were dried over $MgSO_4$ 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 spirocylic 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**: ν_{max} (thin film)/cm^{-1} 3469w (OH), 2953w, 2918w, 2362w, 2342w, 1736s (C=O), 1464w, 1370 m, 1238s, 1147w, 1029 m; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (3H, s, CH_3COH), 1.72–1.80 (2H, m, 1H from CH_2CH_2CH, 1H from CH_2CH$_2$CH), 1.94–2.02 (2H, m, 1H from CH_2CH$_2$OC=O, 1H from CH_2CH_2CH), 2.05 (3H, s, CH_3C(O)O), 2.09 (1H, q, J = 7.5 Hz, CHCH$_2$OC(O)CH$_3$), 2.25–2.31 (2H, m, 1H from CH_2CH$_2$OC=O, 1H from CH_2CH$_2$CH), 4.16–4.26 (3H, m, 1H from CH_2CH_2OC=O, 1H from CH_2OC(O)CH$_3$, OH), 4.32–4.37 (2H, m, 1H from CH_2CH_2OC=O, 1H from CH_2OC(O)CH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0 (CH_3C=O), 21.8 (OHCCH_3), 25.6 (CH_2CH_2CH), 32.2 (CH_2CH$_2$CH), 32,5 (CH$_2$CH$_2$OC=O), 46.8 (CHCH$_2$OC=O), 55.4 (CH$_2$O-C(O)C), 63.9 (CHCH_2OC=O), 65.4 (CH$_2$CH_2OC=O), 81.7 (HOCCH$_3$), 171.1 (CH_3C=O), 181.6 (C=O); MS: m/z (ES+ mode) 507 (18%), 265 (100%) [M+Na]$^+$; HRMS Calcd for $C_{12}H_{18}O_5Na$: 265.1046. Found: 265.1049. For the *syn, anti* compound **13b**: ν_{max} (thin film)/cm^{-1} 3469w (OH), 2958w, 2918w, 2362w, 1736s (C=O), 1466w, 1370 m, 1244s, 1157w, 1029 m; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (3H, s, CH_3COH), 1.38–1.46 (1H, m, 1H from CH_2CH_2CH), 1.70 (1H, ddd, J = 15.0, 11.0, 4.0 Hz, 1H from CH_2CH$_2$CH), 1.99 (1H, ddd, J = 12.5, 6.5, 4.0 Hz, 1H from CH_2CH$_2$OC=O), 2.06 (3H, s, CH_3C=O), 2.06–2.13 (1H, m, 1H from CH_2CH_2CH), 2.20 (1H, ddd, J = 14.0, 10.0, 6.5 Hz, 1H from CH_2CH$_2$CH), 2.50 (1H, dt, J = 12.5, 8.0 Hz, 1H from CH_2CH$_2$OC=O), 2.78 (1H, s, OH), 2.98 (1H, tt, J = 10.0, 7.0 Hz, CHCH$_2$O-C(O)CH$_3$), 4.11 (1H, dd, J = 11.5, 7.5 Hz, 1H from CH_2OC(O)CH$_3$), 4.16–4.22 (2H, m, 1H from CH_2OC(O)CH$_3$, 1H from CH_2CH_2OC=O), 4.35 (1H, apparent dt, J = 8.5, 4.5 Hz, 1H from CH_2CH_2OC=O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.6 (OHCCH_3), 20.9 (CH_3C=O), 24.1 (CH_2CH_2CH), 31.1 (CH_2CH$_2$CH), 31.4 (CH_2CH$_2$OC=O), 46.2 (CHCH$_2$OC=O), 56.0 (CH$_2$OC(O)C), 64.7 (CHCH_2OC=O), 65.7 (CH$_2$CH_2OC=O), 80.9 (HOCCH$_3$), 171.0 (CH_3C=O), 180.6 (C=O); MS: m/z (ES+ mode) 507 (12%), 265 (100%) [M+Na]$^+$; HRMS Calcd for $C_{12}H_{18}O_5Na$: 265.1046. Found: 265.1047.

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

To a stirred solution of SmI_2 (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 NH_4Cl solution. The aqueous

layer was extracted with EtOAc (4 × 25 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by chromatography (silica gel, 40% EtOAc in petroleum ether (40–60 °C)) to give 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; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (3H, t, J = 7.0 Hz, CH_3CH$_2$O), 1.35 (3H, s, CH_3COH), 1.74–1.82 (2H, m, 1H from CH$_2$CH_2CH, 1H from CH_2CH$_2$CH), 1.96 (1H, ddd, J = 13.0, 7.0, 2.5 Hz, 1H from CH$_2$CH_2CH), 2.00–2.06 (1H, m, 1H from CH_2CH$_2$OC=O), 2.13 (1H, p, J = 9 Hz, CHCH$_2$OC(O)O), 2.25–2.33 (2H, m, 1H from CH_2CH$_2$OC=O, 1H from CH_2CH$_2$CH), 4.17–4.26 (4H, m, 2H from CH$_3$CH_2C=O, 1H from CH$_2$CH_2OC=O, 1H from CHCH_2O-C(O)O), 4.35 (1H, dt, J = 9.0, 2.5 Hz, 1H from CH$_2$CH_2OC=O), 4.55 (1H, dd, J = 10.5, 6.5 Hz, 1H from CHCH_2OC(O)O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3 (CH_3CH$_2$OC=O), 21.7 (CH_3COH), 25.7 (CH$_2$CH_2CH), 32.2 (CH_2CH$_2$CH), 32.5 (CH_2CH$_2$OC=O), 47.0 (CHCH$_2$OC=O), 55.3 (CH$_2$OC(O)C), 63.9 (CH$_3$CH_2OC=O), 65.4 (CH$_2$CH_2OC=O), 67.5 (CHCH_2OC=O), 81.7 (CH$_3$COH), 155.2 (OC(O)O), 181.5 (CH$_2$OC=O); MS: m/z (ES+ mode) 567 (22%), 295 (100%) [M+Na]$^+$; HRMS Calcd for $C_{13}H_{21}O_6$: 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; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (3H, s, CH_3COH), 1.31 (3H, t, J = 7.0 Hz, CH_3CH$_2$OC=O), 1.41–1.49 (1H, m, 1H from CH$_2$CH_2CH), 1.70 (1H, ddd, J = 14.5, 11.0, 4.0 Hz, 1H from CH_2CH$_2$CH), 1.99 (1H, ddd, J = 13.0, 6.5, 4.0 Hz, 1 H from CH_2CH$_2$OC=O), 2.08–2.22 (2H, m, 1H from CH_2CH$_2$CH, 1H from CH$_2$CH_2CH), 2.49 (1H, dt, J = 17.0, 8.5 Hz, 1H from CH_2CH$_2$OC=O), 2.84 (1H, s, OH), 3.01 (1H, tt, J = 19.0, 9.5, 7.0 Hz, CHCH$_2$OC(O)O), 4.14–4.23 (4H, m, 2H from CH$_3$CH_2OC=O, 1H from CH$_2$CH_2OC=O, 1H from CHCH_2OC(O)O), 4.27 (1H, dd, J = 10.5, 6.5 Hz, 1H from CHCH_2OC(O)O), 4.35 (1H, apparent dt, J = 8.5, 4.0 Hz, 1H from CH$_2$CH_2OC=O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3 (CH_3CH$_2$OC=O), 18.7 (CH_3COH), 23.9 (CH$_2$CH_2CH), 31.1 (CH_2CH$_2$CH), 31.3 (CH_2CH$_2$OC=O), 46.3 (CHCH$_2$OC=O), 56.0 (CH$_2$OC(O)C), 64.1 (CH$_3$CH_2OC=O), 65.7 (CH$_2$CH_2OC=O), 67.9 (CHCH_2OC=O), 80.9 (CH$_3$COH), 155.1 (OC(O)O), 180.6 (CH$_2$OC=O); MS: m/z (ES+ mode) 567 (18%), 295 (100%) [M+Na]$^+$; HRMS Calcd for $C_{13}H_{21}O_6$: 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 SmI_2 (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 NH_4Cl solution. The aqueous layer was extracted with EtOAc (4 × 25 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by chromatography (silica gel, 40% EtOAc in petroleum ether (40–60 °C)) to give 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; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (3H, s, HOCCH_3), 1.77–1.86 (2H, m, 1H from CH_2CH$_2$CH, 1H from CH$_2$CH_2CH), 1.98 (1H, ddd, J = 13, 7, 2.5 Hz, 1H from CH_2CH$_2$OC=O), 2.02–2.08 (1H, m, 1H from CH_2CH$_2$CH), 2.20–2.34 (3H, m, 1H from CH_2CH$_2$OC=O, 1H from CH$_2$CH_2CH, CH$_2$CH$_2$CH), 3.85 (3H, s, OCH_3), 4.21–4.26 (1H, m, 1H from CH$_2$CH_2OC=O), 4.35 (1H, dt, J = 9.5, 2.5 Hz, 1H from CH$_2$CH_2OC=O), 4.39–4.42 (1H, m, CHCH_2OC=O), 4.56 (1H, dd, J = 10.5, 8 Hz, CHCH_2OC=O), 6.91 (2H, d, J = 8.5 Hz, 2 × CHCHCOCH$_3$), 7.98 (2H, d, J = 9 Hz, 2 × CHCHC-OCH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.0 (HOCCH_3), 25.5 (CH_2CH$_2$CH), 32.2 (CH$_2$CH_2CH), 32.6 (CH_2CH$_2$OC=O), 47.1 (CHCH$_2$OC=O), 55.5 (CH$_2$CH$_2$OC(O)C), 55.5 (OCH_3), 63.8 (CHCH$_2$OC=O), 65.4 (CH$_2$CH_2OC=O), 81.7 (CH$_3$COH), 113.6 (2 × ArCH), 122.7 (ArC), 131.6 (2 × ArCH), 163.3 (ArC), 166.3 (CHCH$_2$OC=O), 181.7 (CH$_2$CH$_2$OC=O); MS: m/z (ES+ mode) 357 (88%) [M+Na]$^+$, 352 (45%) [M+NH$_4$]$^+$, 335 (94%) [M+H]$^+$, HRMS Calcd for $C_{18}H_{22}O_6Na$: 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; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (3H, s, HOCCH_3), 1.47–1.55 (1H, m, 1H from CH_2CH$_2$CH), 1.73 (1H, ddd, J = 13, 11, 4 Hz, 1H from CH$_2$CH_2CH), 2.01 (1H, ddd, J = 13, 5.4, 4 Hz, 1H from CH$_2$CH_2CH), 2.12–2.25 (2H, m, 1H from CH_2CH$_2$CH, 1H from CH_2CH$_2$OC=O), 2.52 (1H, dt, J = 13, 8.5 Hz, 1H from CH_2CH$_2$OC=O), 3.12 (1H, m, CH$_2$CH$_2$CH), 3.85 (3H, s, OCH_3), 4.20 (1H, dt, J = 8.5, 6.5 Hz, 1H from CH$_2$CH_2OC=O), 4.30–4.41 (3H, m, 1H from CH$_2$CH_2OC=O, CHCH_2OC=O), 6.91 (2H, d, J = 9 Hz, 2 × CHCHCOCH$_3$), 7.97 (2H, d, J = 9 Hz, 2 × CHCHCOCH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.7 (HOCCH_3), 24.2 (CH_2CH$_2$CH), 31.2 (CH$_2$CH_2CH), 31.4 (CH_2CH$_2$OC=O), 46.5 (CHCH$_2$OC=O), 55.5 (CH$_2$CH$_2$OC(O)C), 56.1 (OCH_3), 64.8 (CHCH_2OC=O), 65.7 (CH$_2$CH_2OC=O), 81.1 (CH$_3$COH), 113.7 (2 × ArCH), 122.4 (ArC), 131.6 (2 × ArCH), 163.4 (ArC), 166.3 (CHCH$_2$OC=O), 180.7 (CH$_2$CH$_2$OC=O); MS: m/z (ES+ mode) 357 (56%) [M+Na]$^+$, 352 (100%) [M+NH$_4$]$^+$, HRMS Calcd for $C_{18}H_{22}O_6Na$: 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 SmI_2 (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 NH_4Cl solution (10 ml). The aqueous phase was separated and extracted with EtOAc (5 × 10 ml). The combined organics were dried over $MgSO_4$, 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; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (3H, s, CH_3COH), 1.79–1.89 (2H, m, 1H from CH_2CH$_2$CH, 1H from CH$_2$CH_2CH), 1.99 (1H, ddd, J = 12.9, 6.9, 2.8 Hz, 1H from CH_2CH$_2$OC=O), 2.04–2.11 (1H m, 1H from CH_2CH$_2$CH), 2.23–2.37 (3H, m, 1H from CH_2CH$_2$OC=O, 1H from CH$_2$CH_2CH, 1H from CH$_2$CH$_2$CH), 4.26 (1H, apparent dt, J = 9.5, 6.7 Hz, 1H from CH$_2$CH_2OC=O), 4.34 (1H, d, J = 1.3 Hz, OH), 4.37 (1H, apparent dt, J = 9.2, 2.9 Hz, 1H from CH$_2$CH_2OC=O), 4.46 (1H, dd, J = 11.0, 6.6 Hz, 1H from CHCH_2OC=O), 4.62 (1H dd, J = 11.0, 7.6 Hz, 1H from CHCH_2CO=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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.0 (CH$_3$), 25.5 (CH$_2$CH$_2$CH), 32.2 (CH$_2$CH_2CH), 32.6 (CH_2CH$_2$OC=O), 47.1 (CHCH$_2$OC=O), 55.5 (CH$_2$CH$_2$OC(O)C), 64.2 (CHCH$_2$OC=O), 65.4 (CH$_2$CH_2OC=O), 81.7 (CH$_3$COH), 128.4 (ArC), 129.6 (ArC), 130.3 (ArC), 133.0 (ArC), 166.6 (CH$_2$CH$_2$OC=O), 181.7 (ArC=O), MS: m/z

(ES+ mode) 405 (23%), 327 (68%) $[M+Na]^+$, 179 (100%), 101 (84%); HRMS Calcd for $C_{17}H_{20}O_5Na$: 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, $CDCl_3$) δ 1.24 (3H, s, CH_3), 1.52–1.57 (1H, m, 1H from CH_2CH_2CH), 1.76 (1H, ddd, J = 14.5, 11.1, 4.1 Hz, 1H from CH_2CH_2CH), 2.02 (1H, ddd, J = 12.9, 6.6, 3.8 Hz, 1H from CH_2CH_2CH), 2.15–2.31 (2H, m, 1H from CH_2CH_2CH, 1H from CH_2CH_2OC=O), 2.54 (1H, dt, J = 12.6, 6.4 Hz, 1H from CH_2CH_2OC=O), 2.81 (1H, s, O*H*), 3.15 (1H, tt, J = 9.5, 7.3 Hz, CH_2CH_2CH), 4.22 (1H, apparent dt, J = 9.2, 6.7 Hz, 1H from CH_2CH_2OC=O), 4.35–4.39 (2H, m, 1H from CH_2CH_2OC=O, 1H from $CHCH_2OC$=O), 4.44 (1H, dd, J = 11.0, 6.9 Hz, 1H from $CHCH_2OC$=O), 7.45 (2H, t, J = 8.2 Hz, 2 × Ar*H*), 7.58 (1H, tt, J = 7.6, 1.3 Hz, Ar*H*), 8.03 (2H, dd, J = 8.2, 1.0 Hz, 2 × Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.7 (*C*H_3), 24.1 (CH_2CH_2CH), 31.2 (CH_2CH_2CH), 31.4 (CH_2CH_2OC=O), 46.5 ($CHCH_2OC$=O), 56.1 ($CH_2CH_2OC(O)C$), 65.1 ($CHCH_2OC$=O), 65.7 (CH_2CH_2OC=O), 81.0 (CH_3COH), 128.5 (Ar*C*), 129.6 (Ar*C*), 130.0 (Ar*C*), 133.1 (Ar*C*), 166.6 (CH_2CH_2OC=O), 181.7 (Ar*C*=O), MS: *m/z* (ES+ mode) 405 (18%), 327 (100%) $[M+Na]^+$, 322 (19%) $[M+NH_4]^+$, 179 (48%), 101 (48%); HRMS Calcd for $C_{17}H_{20}O_5Na$: 327.1203. Found: 327.1196.

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

To a solution of SmI_2 (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 ($MgSO_4$) 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, 1739*s* (lactone C=O), 1372*s*, 1201*s*; ^1H NMR δ 1.27 (3H, s, C(OH)CH_3), 1.65–1.72 (2H, m, 1H from $C^qCH_2CH_2CH$, 1H from CH_2CHCH_2O), 1.88–1.20 (3H, m, 1H from CH_2CH_2OC=O, CH_2CHCH_2O, 1H from $C^qCH_2CH_2CH$), 2.18–2.26 (2H, m, 1H from CH_2CH_2OC=O, 1H from CH_2CHCH_2O), 3.34 (3H, s, OCH_3), 3.50–3.16 (2H, m, OCH_2CH_2O), 3.54–3.55 (1H, m, 1H from CH_2CHCH_2O), 3.63–3.65 (2H, m, OCH_2CH_2O), 3.81 (1H dd, J = 10, 6.5 Hz, 1H from CH_2CHCH_2O), 4.17 (1H, dt, J = 9, 7 Hz, 1H from CH_2OC=O), 4.28 (1H, dt, J = 9, 3 Hz, 1H from CH_2OC=O), 4.66 (2H, dd, J = 7, 4.5 Hz, OCH_2O); ^{13}C NMR δ 22.11 ($C^q(OH)CH_3$), 26.00 (CH_2CHCH_2O), 32.39 ($C^qCH_2CH_2CH$), 32.58 (CH_2CH_2OC=O), 47.86 ($CHCH_2O$), 55.53 (C^q), 59.06 (OCH_3), 65.36 ($CHCH_2O$), 66.83, OCH_2CH_2O), 67.54 (CH_2OC=O), 71.80 (OCH_2CH_2O), 81.91 (C^q), 95.68 (OCH_2O), 181.62 (C=O); MS: *m/z* $(ESI)^+$ 311.1 (100%) $[M+Na]^+$; HRMS Calcd for $C_{14}H_{24}O_6Na$: 311.1465. Found: 311.1455. For the *syn*, *anti* spirocycle **13f**: ν_{max} (thin film)/cm^{-1} 3483 m, 2920 m, 1759*s* (lactone C=O), 1372 m, ^1H NMR δ 1.13 (3H, s, C(OH)CH_3), 1.22–1.27 (1H, m, 1H from CH_2CHCH_2O), 1.54–1.60 (1H, m, 1H from $C^qCH_2CH_2CH$), 1.93–2.00 (2H, m, 1H from CH_2CHCH_2O, 1H from $C^qCH_2CH_2CH$), 2.07–2.13 (1H, m, 1H from CH_2CH_2OC=O), 2.40–2.45 (1H, ddd, J = 14, 8, 7.5 Hz, 1H from CH_2CH_2OC=O), 2.91–2.98 (1H, m, CH_2CHCH_2O), 3.33 (3H, s, OCH_3), 3.49–3.51 (2H, m, OCH_2CH_2O), 3.57–3.59 (2H, m, CH_2CHCH_2O), 3.62–3.64 (2H, m, OCH_2CH_2O), 4.09–4.14 (1H, m, 1H from CH_2CH_2OC=O), 4.23–4.28 (1H, m, 1H from CH_2CH_2OC=O), 4.64 (2H, s, OCH_2O); ^{13}C NMR δ 18.79 ($C^q(OH)CH_3$), 23.49 ($C^qCH_2CH_2CH$), 31.17 (CH_2CH_2OC=O), 46.19 ($CHCH_2O$), 56.30 (C^q), 59.06 (OCH_3), 65.57 ($CHCH_2O$), 67.09 (OCH_2CH_2O), 68.56 (CH_2OC=O), 71.73 (OCH_2CH_2O), 81.43 (C^q), 95.72 (OCH_2O), 180.82 (C=O); MS: *m/z* $(ESI)^+$ 311.2 (100%) $[M+Na]^+$; HRMS Calcd for $C_{14}H_{24}O_6Na$: 311.1465. Found: 311.1454;

4.5. Asymmetric synthesis of 5

4.5.1. (2*S*,3*S*)-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 $NaBH_4$ (317 mg, 8.40 mmol, 4 equiv) in distilled H_2O (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 CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried ($MgSO_4$), 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 (2*S*,3*S*)-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; $[\alpha]_D$ = +14.0 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.58 (1H, dtd, J = 14.5, 2.8, 2.2 Hz, 1H from $CH_2CH(OH)$), 1.71–1.75 (1H, m, C*H*CH(OH)), 1.81–1.89 (1H, m, 1H from $CH_2CH(OH)$), 1.99–2.02 (2H, m, CH_2CH=CH_2), 3.56–3.69 (4H, m, CH_2OBn, CH_2OH), 4.00 (1H, dt, J = 10.0, 2.2 Hz, C*H*(OH)), 4.44 (2H, s, OCH_2Ph), 4.92–4.99 (2H, m, CH_2=CH), 5.72 (1H, ddt, J = 17.0, 10.1, 7.0 Hz, C*H*=CH_2), 7.21–7.28 (5H, m, 5 × ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.8 (CH_2CH=CH_2), 32.5 ($CH_2CH(OH)$), 44.3 ($CHCH_2CH$=CH_2), 64.1 (CH_2OH), 69.7 (CH_2OBn), 73.4 (OCH_2Ph), 74.4 (*C*H(OH)), 116.3 (CH_2=CH), 127.7 (2 × ArCH), 127.8 (ArCH), 128.5 (2 × ArCH), 137.0 (*C*H=CH_2), 137.7 (Ar*C*); MS: *m/z* (CI mode) 268 (20%) $[M+NH_4]^+$, 251 (100%) $[M+H]^+$, HRMS Calcd for $C_{15}H_{22}O_3$: 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 (2*S*,3*S*)-2-allyl-5-benzyloxy-pentane-1,3-diol (93 mg, 0.370 mmol, 1 equiv) in CH_2Cl_2 (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 $NaHCO_3$ solution (10 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic phases were 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)) 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, 1736*s* (C=O), 1451w, 1362 m, 1239*s*, 1090*s*, 1073*s*, 1036*s*, 915w, 769w, 737w; $[\alpha]_D$ = +9.7 (*c* 0.67, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.68–1.71 (1H, m, 1H from CH_2CH_2OBn), 1.82–1.91 (2H, m, 1H from CH_2CH_2OBn, $CHCH_2OAc$), 2.06 (3H, s, $CH_3C(O)$), 2.08–2.16 (1H, m, 1H from CH_2=$CHCH_2$), 2.26–2.33 (1H, m, 1H from CH_2=$CHCH_2$), 3.06 (1H, d, J = 2.8 Hz, O*H*), 3.63–3.69 (1H, m, 1H from CH_2CH_2OBn), 3.73–3.78 (1H, m, 1H from CH_2CH_2OBn), 3.91–3.94 (1H, m, C*H*OH), 4.09 (1H, dd, J = 11.4, 5.3 Hz, 1H from $CHCH_2OAc$), 4.16 (1H, dd, J = 11.4, 7.1 Hz, 1H from $CHCH_2OAc$), 4.52 (1H, d, J = 11.8 Hz, 1H from $PhCH_2OCH_2$), 4.55 (1H, d, J = 11.8 Hz, 1H from $PhCH_2OCH_2$), 5.02–5.09 (2H, m, CH_2=CH), 5.76–5.90 (1H, m, CH_2=C*H*), 7.30–7.38 (5H, m, 5 × ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 (CH_3C=O), 31.0 (CH_2CH=CH_2), 33.5 (CH_2CH_2OBn), 42.9 ($AcOCH_2CH$), 64.3 (CH_2OAc), 69.5 (CH_2CH_2OBn), 70.9 (*C*HOH), 73.4 ($PhCH_2OCH_2$),

116.6 ($CH_2CH{=}CH_2$), 127.7 (2 × Ar*C*H), 127.8 (Ar*C*H), 128.5 (2 × Ar*C*H), 136.6 ($CH_2CH{=}CH_2$), 137.8 (Ar*C*), 171.3 ($CH_3C{=}O$); MS: *m/z* (ES+ mode) 315 (100%) $[M+Na]^+$, 293 (44%) $[M+H]^+$, HRMS Calcd for $C_{17}H_{25}O_4$: 293.1747. Found: 293.1745.

4.5.3. (4*S*)-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 CH_2Cl_2 (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; $[\alpha]_D$ = +3.5 (*c* 0.34, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (3H, s, $CH_3C{=}O$), 2.19–2.27 (1H, m, 1H from $CH_2CH{=}CH_2$), 2.37–2.45 (1H, m, 1H from $CH_2CH{=}CH_2$), 2.79 (2H, dt, *J* = 6.3, 2.0 Hz, CH_2CH_2OBn), 2.91–2.98 (1H, m, $CHCH_2OAc$), 3.76 (2H, t, *J* = 6.6 Hz, CH_2CH_2OBn), 4.22 (2H, d, *J* = 6.8 Hz, $CHCH_2OAc$), 4.51 (2H, s, $PhCH_2OCH_2$), 5.05–5.11 (2H, m, $CH_2{=}CH$), 5.71 (1H, ddt, *J* = 17.2, 10.1, 7.1 Hz, $CH{=}CH_2$), 7.28–7.37 (5H, m, 5 × Ar*C*H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8 ($OC(O)CH_3$), 32.4 ($CH_2{=}CHCH_2$), 43.0 (CH_2CH_2OBn), 50.7 ($CHCH_2OAc$), 63.8 (CH_2OAc), 65.0 (CH_2OBn), 73.3 ($PhCH_2O$), 117.9 ($CH_2{=}CH$), 127.7 (3 × Ar*C*H), 128.4 (2 × Ar*C*H), 134.2 ($CH_2{=}CH$), 138.1 (Ar*C*), 170.7 ($CH_3C{=}O$), 209.1 ($CH_2C{=}O$); MS: *m/z* (ES+ mode) 213 (100%) $[M+Na]^+$, HRMS Calcd for $C_{17}H_{22}O_4Na$: 313.1410. Found: 313.1418.

4.5.4. 3-(Triphenylphosphoranylidene)tetrahydro-2*H*-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 CH_2Cl_2 (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 CH_2Cl_2 (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 NH_4Cl solution (2 × 30 mL). The organic phase was dried ($MgSO_4$), 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 H_2O (100 mL) and NaOH (170 mL, 20% concd in H_2O) was added dropwise. The aqueous phase was extracted with $CHCl_3$ (4 × 100 mL) and the combined organic phases dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by recrystallisation from $CHCl_3$, 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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82–1.94 (4H, m, $CH_2CH_2CH_2OC{=}O$, $CH_2CH_2CH_2OC{=}O$), 4.25–4.28 (2H, m, $CH_2CH_2CH_2OC{=}O$), 7.43–7.49 (6H, m, 6 × Ar*C*H), 7.52–7.58 (3H, m, 3 × Ar*C*H), 7.62–7.71 (6H, m, 6 × Ar*C*H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2 (d, *J* = 11.3 Hz, $CH_2CH_2CH_2OC{=}O$), 24.6 (d, *J* = 9.8 Hz, $CH_2CH_2CH_2OC{=}O$), 35.6 (d, *J* = 123.0 Hz, $C{=}PPh_3$), 67.4 ($CH_2CH_2CH_2OC{=}O$), 126.8 (d, *J* = 90 Hz, 3 × Ar*C*-P), 128.7 (d, *J* = 15 Hz, 6 × Ar*C*H), 131.9 (d, *J* = 3 Hz, 3 × Ar*C*H), 133.7 (d, *J* = 9.8 Hz, 6 × Ar*C*H), 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 $C_{23}H_{22}O_2P$: 361.1352. Found: 361.1362.

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

Pyridine (12 μL) was added to a stirred solution of K_2CO_3 (252 mg, 1.83 mmol, 3.0 equiv) and $K_3[Fe(CN)_6]$ (606 mg, 1.83 mmol, 3.0 equiv) in H_2O (7.7 mL) at room temperature. Next, *t*-BuOH (5.3 mL) and OsO_4 (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 Et_2O (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 ($MgSO_4$), filtered and concentrated in vacuo. The residue was re-dissolved in (1:1) THF/H_2O (15 mL) to which $KHCO_3$ (169 mg, 1.22 mmol, 2.0 equiv) and $NaIO_4$ (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 ($MgSO_4$), 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 CH_2Cl_2 (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; $[\alpha]_D$ = +25.1 (*c* 0.35, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86–1.92 (2H, m, $CH_2CH_2CH_2OC{=}O$), 2.02 (3H, s, $CH_3C{=}O$), 2.25–2.32 (1H, m, 1H from $CH_2CH{=}C$), 2.50–2.59 (3H, m, 1H from $CH_2CH{=}C$, $CH_2CH_2CH_2OC{=}O$), 2.73 (2H, t, *J* = 6.0 Hz, CH_2CH_2OBn), 3.05 (1H, quint, *J* = 6.6 Hz, $CHCH_2Oac$), 3.75 (2H, dt, *J* = 6.3, 1.5 Hz, CH_2CH_2Obn), 4.23 (2H, d, *J* = 5.8 Hz, $CHCH_2Oac$), 4.26–4.29 (2H, m, $CH_2CH_2CH_2OC{=}O$), 4.50 (2H, s, $PhCH_2O$), 6.92 (1H, tt, *J* = 7.6, 2.5 Hz, $CH{=}C$), 7.28–7.37 (5H, m, 5 × Ar*C*H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7 ($OC(O)CH_3$), 22.5 ($CH_2CH_2CH_2OC{=}O$), 23.6 ($CH_2CH_2CH_2OC{=}O$), 26.8 ($CH_2CH{=}C$), 43.0 ($BnOCH_2CH_2C{=}O$), 50.1 ($CHCH_2Oac$), 63.8 ($CHCH_2Oac$), 65.0 ($BnOCH_2CH_2$), 68.6 ($CH_2CH_2CH_2OC{=}O$), 73.3 ($ArCH_2O$), 127.7 (2 × Ar*C*H), 127.8 (2 × Ar*C*H), 128.4 (Ar*C*H, $CH_2CH{=}C$), 138.0 (Ar*C*), 141.4 ($CH_2CH{=}C$), 166.0 ($CH_2CH_2CH_2OC{=}O$), 170.6 ($CHCH_2OC{=}O$), 208.4 ($CH_2CH_2C{=}O$); MS: *m/z* (ES+ mode) 397 (100%) $[M+Na]^+$, HRMS Calcd for $C_{21}H_{30}O_6N$ $[M+NH_4]^+$: 392.2068. Found: 392.2061.

4.6. SmI_2-mediated cyclisations of 5

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

To a stirred solution of SmI_2 in THF (0.1 M, 2.94 mL, 0.294 mmol, 2.2 equiv) was added degassed, distilled H_2O (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 NH_4Cl solution (10 mL). Saturated aqueous $Na_2S_2O_3$ (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 ($MgSO_4$), 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, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44–1.49 (1H, m, 1H from C*H*$_2$CH$_2$CH$_2$OC=O), 1.16–1.72 (2H, m, 1H from CH$_2$C*H*$_2$CH$_2$OC=O, 1H from CH$_2$C*H*$_2$CH), 1.87–1.97 (4H, m, 1H from CH$_2$C*H*$_2$CH$_2$OC=O, 1H from C*H*$_2$CH$_2$CH, 1H from CH$_2$C*H*$_2$CH, 1H from C*H*$_2$CH$_2$OBn), 2.00–2.11 (2H, m, 1H from C*H*$_2$CH$_2$CH$_2$OC=O, 1H from C*H*$_2$CH$_2$OBn), 2.02 (3H, s, C*H*$_3$C=O), 2.13–2.26 (2H, m, 1H from C*H*$_2$CH$_2$CH, CH$_2$CH$_2$C*H*), 3.52–3.63 (2H, m, CH$_2$C*H*$_2$OBn), 3.75 (1H, ddd, *J* = 12.6, 10.8, 3.3 Hz, 1H from CH$_2$CH$_2$C*H*$_2$OC=O), 4.04–4.09 (1H, m, 1H from CH$_2$CH$_2$C*H*$_2$OC=O), 4.16 (1H, dd, *J* = 11.1, 7.0 Hz, 1H from C*H*$_2$OAc), 4.22 (1H, d, *J* = 11.8 Hz, 1H from PhC*H*$_2$OCH$_2$), 4.34 (1H, dd, *J* = 11.1, 6.8 Hz, 1H from C*H*$_2$OAc), 4.49 (1H, d, *J* = 11.8 Hz, 1H from PhC*H*$_2$OCH$_2$), 6.55 (1H, d, *J* = 1.2 Hz, O*H*), 7.27–7.36 (5H, m, 5 × ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (CH$_2$*C*H$_2$CH$_2$OC=O), 21.1 (*C*H$_3$C=O), 24.8 (CH$_2$CH$_2$CH), 26.6 (*C*H$_2$CH$_2$CH$_2$OC=O), 34.7 (*C*H$_2$CH$_2$OBn), 35.6 (*C*H$_2$CH$_2$CH), 46.2 (CH$_2$CH$_2$*C*H), 54.0 (CH$_2$CH$_2$OC(O)*C*), 64.8 (CHCH$_2$OAc), 65.6 (BnO*C*H$_2$), 69.3 (CH$_2$CH$_2$*C*H$_2$OC=O), 72.3 (Ar*C*H$_2$O), 83.7 (OCH$_2$CH$_2$*C*OH), 127.7 (Ar*C*H), 128.3 (2 × Ar*C*H), 128.5 (2 × Ar*C*H), 137.9 (Ar*C*), 171.1 (CHCH$_2$O*C*=O), 178.4 (CH$_2$CH$_2$CH$_2$O*C*=O); MS: *m/z* (ES+ mode) 394 (58%) [M+Na]$^+$, 377 (100%) [M+H]$^+$, HRMS Calcd for $C_{21}H_{32}O_6N$: 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, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44–1.55 (2H, m, C*H*$_2$CH$_2$CH$_2$OC=O), 1.65–1.71 (1H, m, 1H from CH$_2$C*H*$_2$CH$_2$OC=O), 1.79 (1H, ddd, *J* = 14.9, 3.8, 2.5 Hz, 1H from C*H*$_2$CH$_2$OBn), 1.84–2.11 (4H, m, 1H from CH$_2$C*H*$_2$CH$_2$OC=O, 1H from C*H*$_2$CH$_2$CH, 1H from C*H*$_2$CH$_2$OBn, 1H from CH$_2$C*H*$_2$CH), 2.04 (3H, s, C*H*$_3$C=O), 2.17–2.35 (2H, m, 1H from C*H*$_2$CH$_2$CH, 1H from CH$_2$C*H*$_2$CH), 2.42–2.50 (1H, m, CH$_2$CH$_2$C*H*), 3.56–3.60 (1H, m, 1H from C*H*$_2$OAc), 3.63–3.69 (1H, m, 1H from C*H*$_2$OAc), 3.76 (1H, dt, *J* = 11.8, 3.5 Hz, 1H from CH$_2$CH$_2$C*H*$_2$OC=O), 3.93 (1H, dd, *J* = 11.1, 8.0 Hz, 1H from C*H*$_2$OBn), 4.06–4.12 (2H, m, 1H from CH$_2$C*H*$_2$OBn, 1H from CH$_2$CH$_2$C*H*$_2$OC=O), 4.25 (1H, d, *J* = 11.9 Hz, 1H from PhC*H*$_2$O), 4.49 (1H, d, *J* = 11.9 Hz, 1H from PhC*H*$_2$O), 6.78 (1H, d, *J* = 1.0 Hz, O*H*), 7.28–7.36 (5H, m, 5 × ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (CH$_2$*C*H$_2$CH$_2$OC=O), 21.0 (*C*H$_3$C=O), 25.1 (CH$_2$*C*H$_2$CH), 25.2 (*C*H$_2$CH$_2$CH$_2$OC=O), 33.4 (*C*H$_2$CH$_2$OBn), 35.5 (*C*H$_2$CH$_2$CH), 50.1 (CH$_2$CH$_2$*C*H), 53.8 (CH$_2$CH$_2$OC(O)*C*), 65.3 (CHCH$_2$OAc), 66.5 (BnO*C*H$_2$), 68.1 (CH$_2$CH$_2$*C*H$_2$OC=O), 72.4 (Ar*C*H$_2$O), 84.9 (OCH$_2$CH$_2$*C*OH), 127.7 (Ar*C*H), 128.3 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 137.8 (Ar*C*), 171.1 (CHCH$_2$O*C*=O), 178.2 (CH$_2$CH$_2$CH$_2$O*C*=O); MS: *m/z* (ES+ mode) 399 (100%) [M+Na]$^+$, HRMS Calcd for $C_{21}H_{28}O_6Na$: 399.1778. Found: 399.1781.

4.6.2. (1*R*,2*S*,5*R*)-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 Et_2O (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 H_2. The reaction mixture was filtered through a plug of Celite, washing with MeOH. The filtrate was concentrated in vacuo giving crude diol that was recrystalized from hexane and EtOAc to give **20** as a white crystaline 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, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50–1.57 (1H, m, 1H from C*H*$_2$CH$_2$CH$_2$OC=O), 1.64–1.73 (2H, m, 1H from CH$_2$C*H*$_2$CH$_2$OC=O, 1H from CH$_2$C*H*$_2$CH), 1.80–1.86 (1H, m, 1H from C*H*$_2$CH$_2$CH), 1.88–2.08 (4H, m, 1H from CH$_2$C*H*$_2$CH, 1H from CH$_2$C*H*$_2$CH$_2$OC=O, C*H*$_2$CH$_2$OH), 2.05 (3H, s, C*H*$_3$C=O), 2.12 (1H, ddd, *J* = 12.6, 3.6, 2.0 Hz, 1H from C*H*$_2$CH$_2$CH$_2$OC=O), 2.17–2.30 (2H, m, 1H from C*H*$_2$CH$_2$CH, CH$_2$CH$_2$C*H*), 3.77 (1H, dt, *J* = 10.1, 4.0 Hz, 1H from CH$_2$CH$_2$C*H*$_2$OC=O), 3.94 (1H, dt, *J* = 10.1, 2.8 Hz, 1H from CH$_2$CH$_2$C*H*$_2$OC=O), 4.17 (1H, dd, *J* = 10.8, 7.0 Hz, 1H from C*H*$_2$OAc), 4.33–4.40 (3H, m, 1H from C*H*$_2$OAc, CH$_2$C*H*$_2$OH), 6.41 (1H, d, *J* = 1.0 Hz, O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7 (CH$_2$*C*H$_2$CH$_2$OC=O), 21.1 (*C*H$_3$C=O), 24.9 (CH$_2$*C*H$_2$CH), 26.9 (*C*H$_2$CH$_2$CH$_2$OC=O), 35.7 (*C*H$_2$CH$_2$OH), 36.0 (*C*H$_2$CH$_2$CH), 46.4 (CH$_2$CH$_2$*C*H), 54.3 (CH$_2$CH$_2$OC(O)*C*), 58.0 (CH$_2$CH$_2$*C*H$_2$OC=O), 64.8 (*C*H$_2$OAc), 69.9 (CH$_2$*C*H$_2$OH), 83.9 (HOCH$_2$CH$_2$*C*OH), 171.1 (CHCH$_2$O*C*=O), 179.2 (CH$_2$CH$_2$CH$_2$O*C*=O); MS: *m/z* (ES+ mode) 309 (100%) [M+Na]$^+$, 304 (39%) [M+NH$_4$]$^+$, 287 (62%) [M+H]$^+$, HRMS Calcd for $C_{14}H_{23}O_6$: 287.1489. Found: 287.1492.

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

To a stirred solution of SmI_2 in THF (0.1 M, 6.40 mL, 0.637 mmol, 12 equiv) at 0 °C was added degassed, distilled H_2O (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 NH_4Cl solution (1.5 mL). Saturated aqueous $Na_2S_2O_3$ (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 ($MgSO_4$), 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, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09–1.17 (1H, m, 1H from C*H*$_2$CH$_2$CH$_2$OH), 1.34–1.40 (1H, m, 1H from C*H*$_2$CH$_2$CH), 1.47–1.59 (4H, m, 1H from C*H*$_2$CH$_2$CH$_2$OH, 1H from CH$_2$C*H*$_2$CH, CH$_2$C*H*$_2$CH$_2$OH), 1.64 (1H, ddd, *J* = 14.9, 4.3, 2.8 Hz, 1H from C*H*$_2$CH$_2$OBn), 1.75–1.90 (2H, m, 1H from C*H*$_2$CH$_2$CH, 1H from CH$_2$C*H*$_2$CH), 2.05 (3H, s, C*H*$_3$C=O), 2.16 (1H, ddd, *J* = 14.9, 10.6, 4.3 Hz, 1H from C*H*$_2$CH$_2$OBn), 2.23–2.28 (1H, m, CH$_2$CH$_2$C*H*), 3.57 (1H, d, *J* = 11.8 Hz, 1H from CC*H*$_2$OH), 3.63 (2H, t, *J* = 5.8 Hz, CH$_2$CH$_2$C*H*$_2$OH), 3.71 (1H, d, *J* = 11.8 Hz, 1H from CC*H*$_2$OH), 3.86 (1H, dt, *J* = 9.6, 4.3 Hz, 1H from CH$_2$C*H*$_2$OBn),

3.95–4.02 (2H, m, 1H from CH_2OAc, 1H from CH_2CH_2OBn), 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), 7.30–7369 (5H, m, 5 × ArCH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH_3C=O), 26.6 (CH_2CH_2CH), 27.7 ($CH_2CH_2CH_2OH$), 28.0 ($CH_2CH_2CH_2OH$), 29.1 (CH_2CH_2CH), 34.9 (CH_2CH_2OBn), 45.7 ($CHCH_2OC$=O), 52.7 (CCH_2OH), 63.5 ($CH_2CH_2CH_2OH$), 64.6 (CCH_2OH), 66.8 (CH_2OAc), 68.2 ($BnOCH_2$), 73.7 ($PhCH_2O$), 87.2 ($BnCH_2CH_2COH$), 128.0 (2 × ArCH), 128.1 (ArCH), 128.6 (2 × ArCH), 137.0 (ArC), 171.3 (CH_3C=O); MS: m/z (ES+ mode) 403 (100%) $[M+Na]^+$, 381 (30%) $[M+H]^+$, HRMS Calcd for $C_{21}H_{33}O_6$: 381.2272. Found: 381.2268.

4.6.4. (1*S*,2*R*,3*S*)-1-Acetoxymethyl-2-(2-(benzyloxy)ethyl)-3-(3-((*tert*-butyldimethylsilyl)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 amterial)) as a colourless oil. ν_{max} (thin film)/cm^{-1} 3429 m (OH), 1953 m, 2923 m, 2854 m, 1738 m (C=O), 1461w, 1362w, 1246s, 1098s, 1034 m, 836s, 774w; $[\alpha]_D$ = −10.1 (c 1.45, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.045 (6H, s, Si(CH_3)$_2$), 0.89 (9H, s, SiC(CH_3)$_3$), 1.05–1.13 (1H, m, 1H from C$H_2$$CH_2CH_2$OTBS), 1.28–1.35 (1H, m, 1H from C$H_2$$CH_2CH_2$OTBS), 1.39 (1H, ddd, J = 13.4, 7.8, 5.8 Hz, 1H from C$H_2$$CH_2$CH), 1.45–1.58 (3H, m, 1H from CH_2CH_2CH, $CH_2CH_2CH_2$OTBS), 1.67 (1H, ddd, J = 14.9, 4.6, 3.0 Hz, 1H from C$H_2$$CH_2$OBn), 1.74–1.83 (1H, m, 1H from CH_2CH_2CH), 1.94 (1H, dt, J = 13.1, 8.3 Hz, 1H from C$H_2$$CH_2$CH), 2.05 (3H, s, CH_3C=O), 2.14 (1H, ddd, J = 14.9, 10.4, 4.3 Hz, 1H from C$H_2$$CH_2$OBn), 2.19–2.26 (1H, m, CH_2CH_2CH), 3.53–3.65 (4H, m, $CH_2CH_2CH_2$OTBS, CCH_2OH), 3.85–3.89 (1H, m, 1H from CH_2CH_2OBn), 3.94–4.01 (2H, m, 1H from CH_2CH_2OBn, 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 × ArCH); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.3 (SiCH_3), −5.2 (SiCH_3), 18.3 (SiC(CH_3)$_3$), 21.1 (CH_3C=O), 26.0 (SiC(CH_3)$_3$), 26.5 (CH_2CH_2CH), 27.8 ($CH_2CH_2CH_2$OTBS), 28.1 ($CH_2CH_2CH_2$OTBS), 28.5 (CH_2CH_2CH), 34.5 (CH_2CH_2OBn), 45.8 (CH_2CH_2CH), 52.8 (CCH_2OH), 63.6 ($CH_2CH_2CH_2$OTBS), 64.6 (CCH_2OH), 66.8 (CH_2OAc), 68.3 ($BnOCH_2$), 73.7 ($PhCH_2O$), 87.4 ($BnOCH_2CH_2COH$), 128.0 (2 × ArCH), 128.1 (ArCH), 128.6 (2 × ArCH), 137.0 (ArC), 171.3 (CH_3C=O); MS: m/z (ES+ mode) 517 (92%) $[M+Na]^+$, 495 (100%) $[M+H]^+$, HRMS Calcd for $C_{27}H_{47}O_6Si$: 495.3136. Found: 495.3124.

4.6.5. (1*S*,2*R*,3*S*)-1-Acetoxymethyl-2-(2-(benzyloxy)ethyl)-3-(3-((*tert*-butyldimethylsilyl)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-Bu_3SnH (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, 2854w, 2357s, 2328 m, 1733 m (C=O), 1649w, 1362w, 1254 m, 1098 m, 1029w, 833w, 774w; $[\alpha]_D$ = −8.0 (c 0.55, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s, Si(CH_3)$_2$), 0.90 (9H, s, SiC(CH_3)$_3$), 0.98 (3H, s, CCH_3), 1.17–1.23 (2H, m, $CH_2CH_2CH_2$OTBS), 1.40–1.62 (5H, m, 1H from CH_2CH_2CH, CH_2CH_2CH, $CH_2CH_2CH_2$OTBS), 1.70–1.80 (1H, m, 1H from CH_2CH_2CH), 1.85–1.99 (2H, m, CH_2CH_2OBn), 2.04 (3H, s, CH_3C=O), 2.21–2.28 (1H, m, CH_2CH_2CH), 3.59 (2H, t, J = 6.6 Hz, $CH_2CH_2CH_2$OTBS), 3.70 (1H, s, OH), 3.82–3.85 (2H, m, CH_2CH_2OBn), 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 × ArCH), ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (Si(CH_3)$_2$), 18.4 (SiC(CH_3)$_3$), 19.0 (CCH_3), 21.2 (CH_3C=O), 25.7 (CH_2CH_2CH), 26.0 (SiC(CH_3)$_3$), 28.2 ($CH_2CH_2CH_2$OTBS), 31.6 ($CH_2CH_2CH_2$OTBS), 33.4 (CH_2CH_2CH), 34.0 (CH_2CH_2OBn), 45.9 ($CHCH_2$OAc), 49.7 (CCH_3), 63.9 (CH_2OTBS), 66.9 (CH_2OAc), 68.2 ($BnOCH_2$), 73.6 ($PhCH_2O$), 84.2 ($BnOCH_2CH_2COH$), 127.9 (3 × ArCH), 128.5 (2 × ArCH), 137.4 (ArC), 171.3 (CH_3C=O); MS: m/z (ES+ mode) 501 (100%) $[M+Na]^+$, HRMS Calcd for $C_{27}H_{50}O_5NSi$: 496.3453. Found: 496.3446.

4.6.6. (1*R*,2*S*,5*S*)-1-(2-(Benzyloxy)ethyl)-2-(3-((*tert*-butyldimethylsilyl)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 (1*R*,2*S*,5*S*)-1-(2-(benzyloxy)ethyl)-2-(3-((*tert*-butyldimethylsilyl)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), 2948s, 2928s, 2854 m, 1619w, 1461w, 1385w, 1360w, 1254 m, 1095s, 1026w, 969w, 937w, 833s, 774 m, 732w; $[\alpha]_D$ = −4.9 (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s, Si(CH_3)$_2$), 0.90 (9H, s, SiC(CH_3)$_3$), 0.99 (3H, s, CCH_3), 1.18–1.26 (2H, m, $CH_2CH_2CH_2$OTBS), 1.47–1.67 (5H, m, $CH_2CH_2CH_2$OTBS, CH_2CH_2CH, 1H from CH_2CH_2CH), 1.75–1.87 (2H, m, 1H from CH_2CH_2CH, 1H from CH_2CH_2OBn), 1.95–2.10 (2H, m, 1H from CH_2CH_2OBn, CH_2CH_2CH), 3.43 (1H, dd, J = 9.1, 2.6 Hz, CH_2OH), 3.60 (2H, t, J = 6.6 Hz, $CH_2CH_2CH_2$OTBS), 3.61–3.68 (1H, m, 1H from CH_2OH), 3.76–3.81 (1H, m, 1H from CH_2CH_2OBn),3.87 (1H, dd, J = 9.2, 3.6 Hz, 1H from CH_2CH_2OBn), 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 × ArCH); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2 (Si(CH_3)$_2$), 18.3 (SiC(CH_3)$_3$), 19.0 (CCH_3), 23.2 (CH_2CH_2CH), 26.0 (SiC(CH_3)$_3$), 28.1 ($CH_2CH_2CH_2$OTBS), 31.6 ($CH_2CH_2CH_2$OTBS), 34.3 (CH_2CH_2OBn), 48.0 (CH_2CH_2CH), 49.6 (CCH_3), 63.3 (CH_2OH), 63.8 (CH_2OTBS), 68.2 ($BnOCH_2$), 73.7 ($PhCH_2O$), 86.9 ($BnOCH_2CH_2COH$), 128.0 (3 × ArCH), 128.6 (2 × ArCH), 137.2 (ArC); MS: m/z (ES+ mode) 459 (100%) $[M+Na]^+$, HRMS Calcd for $C_{25}H_{44}O_4Na$: 459.2901. Found: 459.2906.

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

To a stirred solution of (1*R*,2*S*,5*S*)-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 $Na_2S_2O_3$ (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 × 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; $[\alpha]_D = -15.1$ (*c* 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s, Si(C*H*$_3$)$_2$), 0.91 (9H, s, SiC(C*H*$_3$)$_3$), 0.99 (3H, s, CC*H*$_3$), 1.11–1.26 (2H, m, C*H*$_2$CH$_2$CH$_2$OTBS), 1.44–1.63 (3H, m, CH$_2$C*H*$_2$CH$_2$OTBS, 1H from C*H*$_2$CH$_2$CH), 1.71–1.78 (1H, m, 1H from C*H*$_2$CH$_2$CH), 1.83–1.99 (4H, m, CH$_2$C*H*$_2$CH, C*H*$_2$CH$_2$OBn), 2.94 (1H, dd, *J* = 10.3, 7.8 Hz, CH$_2$CH$_2$C*H*), 3.53 (3H, s, OC*H*$_3$), 3.60 (2H, dt, *J* = 6.6, 3.3 Hz, CH$_2$CH$_2$C*H*$_2$OTBS), 3.67–3.72 (2H, m, CH$_2$C*H*$_2$OBn), 4.45 (2H, s, PhC*H*$_2$O), 4.84 (1H, s, O*H*), 7.26–7.36 (5H, m, 5 × ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (Si(*C*H$_3$)$_2$), 18.0 (Si*C*(CH$_3$)$_3$), 18.4 (*C*CH$_3$), 25.7 (CH$_2$*C*H$_2$CH), 26.0 (SiC(*C*H$_3$)$_3$), 28.2 (CH$_2$CH$_2$*C*H$_2$OTBS), 31.4 (*C*H$_2$CH$_2$CH$_2$OTBS), 33.4 (*C*H$_2$CH$_2$CH), 34.7 (*C*H$_2$CH$_2$OBn), 49.0 (CH$_2$CH$_2$*C*H), 49.3 (*C*CH$_3$), 50.0 (O*C*H$_3$), 63.8 (*C*H$_2$OTBS), 66.9 (BnO*C*H$_2$), 73.0 (PhCH$_2$O), 83.8 (BnOCH$_2$CH$_2$*C*OH), 127.4 (2 × ArCH), 12.5 (ArCH), 127.6 (2 × ArCH), 138.1 (Ar*C*), 177.1 (*C*=O); MS: *m/z* (ES+ mode) 525 (100%), 487 (30%) [M+Na]$^+$, 482 (23%) [M+NH$_4$]$^+$, 465 (17%) [M+H]$^+$, HRMS Calcd for $C_{26}H_{44}O_5SiNa$: 487.2856. Found: 487.2862.

4.6.8. (1*R*,2*S*,5*S*)-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 × 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; $[\alpha]_D = -4.40$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s, Si(C*H*$_3$)$_2$), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 1.01 (CC*H*$_3$), 1.15 (3H, s, C(C*H*$_3$)$_2$OH), 1.22–1.26 (2H, m, C*H*$_2$CH$_2$CH$_2$OTBS), 1.45 (3H, s, C(C*H*$_3$)$_2$OH), 1.39–1.63 (5H, m, CH$_2$C*H*$_2$CH$_2$OTBS, C*H*$_2$CH$_2$CH, 1H from CH$_2$C*H*$_2$CH), 1.81–1.89 (3H, m, CH$_2$CH$_2$C*H*, 1H from CH$_2$C*H*$_2$CH, 1H from C*H*$_2$CH$_2$OBn), 2.43 (1H, ddd, *J* = 15.4, 10.6, 4.6 Hz, 1H from C*H*$_2$CH$_2$OBn), 3.60 (2H, dt, *J* = 6.6, 1.2 Hz, CH$_2$CH$_2$C*H*$_2$OTBS), 3.72 (1H, dt, *J* = 9.5, 4.6 Hz, 1H from CH$_2$C*H*$_2$OBn), 3.91 (1H, ddd, *J* = 10.6, 9.5, 3.0 Hz, 1H from CH$_2$C*H*$_2$OBn), 4.18 (1H, s, O*H*), 4.35 (1H, s, O*H*), 4.49 (2H, s, PhC*H*$_2$O), 7.30–7.39 (5H, m, 5 × ArC*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (Si(*C*H$_3$)$_2$), 18.3 (*C*CH$_3$), 19.4 (Si*C*(CH$_3$)$_3$), 24.3 (CH$_2$*C*H$_2$CH), 26.0 (SiC(*C*H$_3$)$_3$), 28.1 (CH$_2$*C*H$_2$CH$_2$OTBS), 29.7 (HOC(*C*H$_3$)$_2$), 31.2 (HOC(*C*H$_3$)$_2$), 31.4 (*C*H$_2$CH$_2$CH$_2$OTBS), 34.7 (*C*H$_2$CH$_2$CH), 35.7 (*C*H$_2$CH$_2$OBn), 49.8 (*C*CH$_3$), 54.8 (CH$_2$CH$_2$*C*H), 63.9 (*C*H$_2$OTBS), 68.7 (BnO*C*H$_2$), 73.1 ((CH$_3$)$_2$*C*OH), 73.6 (PhCH$_2$O), 87.7 (BnOCH$_2$CH$_2$*C*OH), 127.9 (2 × ArCH), 128.0 (ArCH), 128.6 (2 × ArCH), 137.2 (Ar*C*); MS: *m/z* (ES+ mode) 487 (67%) [M+Na]$^+$, 465 (100%) [M+H]$^+$, HRMS Calcd for $C_{27}H_{48}O_4NaSi$: 487.3220. Found: 487.3215.

4.6.9. (1*R*,2*S*,5*S*)-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 × 5 mL). The organics were concentrated in vacuo giving the primary alcohol (1*R*,2*S*,5*S*)-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; $[\alpha]_D = -9.0$ (*c* 0.62, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (6H, s, Si(C*H*$_3$)$_2$), 0.84 (9H, s, SiC(C*H*$_3$)$_3$), 1.00 (3H, s, CC*H*$_3$), 1.17 (3H, s, (C*H*$_3$)$_2$COH), 1.17–1.22 (2H, m, C*H*$_2$CH$_2$CH$_2$OTBS), 1.33–1.63 (5H, m, CH$_2$C*H*$_2$CH$_2$OTBS, C*H*$_2$CH$_2$CH, 1H from CH$_2$C*H*$_2$CH), 1.43 (3H, s, (C*H*$_3$)$_2$COH), 1.69–1.81 (2H, m, 1H from CH$_2$C*H*$_2$CH, 1H from C*H*$_2$CH$_2$OH), 1.85–1.91 (1H, m, CH$_2$CH$_2$C*H*), 2.09–2.19 (1H, m, 1H from C*H*$_2$CH$_2$OH), 2.89 (1H, t, *J* = 4.4 Hz, O*H*), 3.31 (1H, s, O*H*), 3.55 (2H, t, *J* = 6.4 Hz, CH$_2$CH$_2$C*H*$_2$OTBS), 3.80–3.88 (1H, m, 1H from CH$_2$C*H*$_2$OH), 3.96–4.01 (1H, m, 1H from CH$_2$C*H*$_2$OH), 4.37 (1H, s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2 (Si(*C*H$_3$)$_2$), 18.3 (*C*CH$_3$), 19.3 (Si*C*(CH$_3$)$_3$), 24.5 (CH$_2$*C*H$_2$CH), 26.0 (SiC(*C*H$_3$)$_3$), 28.2 (CH$_2$*C*H$_2$CH$_2$OTBS), 30.0 (HOC(*C*H$_3$)$_2$), 31.2 (HOC(*C*H$_3$)$_2$), 31.9 (*C*H$_2$CH$_2$CH$_2$OTBS), 34.7 (*C*H$_2$CH$_2$CH), 37.9 (*C*H$_2$CH$_2$OH), 49.8 (*C*CH$_3$), 54.5 (CH$_2$CH$_2$*C*H), 60.7 (CH$_2$*C*H$_2$OH), 63.9 (*C*H$_2$OTBS), 74.1 ((CH$_3$)$_2$*C*OH), 87.6 (HOCH$_2$CH$_2$*C*OH); MS: *m/z* (ES+ mode) 397 (100%) [M+Na]$^+$, 375 (64%) [M+H]$^+$, HRMS Calcd for $C_{20}H_{43}O_4Si$: 375.2925. Found: 375.2937.

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

To a stirred solution of (1*R*,2*S*,5*S*)-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_3P (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

H_2O_2 (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 $NaHCO_3$ solution (3.0 mL). The aqueous phase was extracted with EtOAc (4 × 5 mL) and the combined organics were dried ($MgSO_4$), 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, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (6H, s, (Si(CH_3)$_2$), 0.80 (CCH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 1.06–1.13 (1H, m, 1H from CH_2CH$_2$CH$_2$OTBS), 1.16 (3H, s, (CH_3)$_2$COH), 1.23–1.30 (1H, m, 1H from CH_2CH$_2$CH$_2$OTBS), 1.33 (3H, s, (CH_3)$_2$COH), 1.42–1.52 (2H, m, CH$_2$CH_2CH$_2$OTBS), 1.59–1.66 (2H, m, CH_2CH$_2$CH), 1.69–1.84 (1H, m, 1H from CH$_2$CH_2CH), 1.93–2.05 (1H, m, 1H from, CH$_2$CH_2CH), 2.19 (1H, dd, *J* = 10.4, 7.4 Hz, CH$_2$CH$_2$C*H*), 2.91 (1H, s, O*H*), 3.14 (1H, s, O*H*), 3.58 (2H, dt, *J* = 6.4, 2.5 Hz, CH$_2$CH$_2$CH_2OTBS), 5.18 (1H, dd, *J* = 10.9, 1.5 Hz, 1H from CH=CH_2), 5.27 (1H, dd, *J* = 17.3, 1.5 Hz, 1H from CH=CH_2), 5.99 (1H, dd, *J* = 17.3, 10.9 Hz, C*H*=CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2 (Si(CH_3)$_2$), 16.6 (CCH_3), 18.3 (SiC(CH_3)$_3$), 23.1 (CH$_2$CH$_2$CH), 26.0 (SiC(CH_3)$_3$), 28.2 (CH$_2$CH$_2$CH$_2$OTBS), 30.4 (HOC(CH_3)$_2$), 30.8 (HOC(CH_3)$_2$), 31.8 (CH$_2$CH$_2$CH$_2$OTBS), 32.8 (CH$_2$CH$_2$CH), 51.9 (CCH$_3$), 53.5 (CH$_2$CH$_2$CH), 63.8 (CH$_2$OTBS), 73.9 ((CH$_3$)$_2$COH), 87.2 (CH$_2$=CHCOH), 112.9 (CH=CH$_2$), 142.9 (CH=CH$_2$); MS: *m/z* (ES+ mode) 357 (100%) $[M+H]^+$, HRMS Calcd for $C_{20}H_{41}O_3Si$: 357.2819. Found: 357.2829.

4.6.11. ((1*S*,2*R*,3*S*)-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 H_2. The reaction mixture was stirred vigorously under H_2 for 4 h before being filtered through Celite, washing through with EtOH (2 × 5 mL). Concentration of the organic filtrate gave ((1*S*,2*R*,3*S*)-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, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (6H, s, Si(CH_3)$_2$), 0.89 (9H, s, SiC(CH_3)$_3$), 1.01 (3H, s, CCH_3), 1.16–1.27 (3H, m, CH_2CH$_2$CH$_2$OTBS, O*H*), 1.40–1.57 (5H, m, CH$_2$CH_2CH$_2$OTBS, CH_2CH$_2$CH, 1H from CH$_2$CH_2CH), 1.71–1.90 (3H, m, CH_2CH$_2$OH, 1H from CH$_2$CH_2CH), 2.06 (3H, s, CH_3C=O), 2.25–2.32 (1H, m, CH$_2$CH$_2$C*H*), 3.59 (2H, t, *J* = 6.5 Hz, CH$_2$CH$_2$CH_2OTBS), 3.99 (2H, t, *J* = 5.8 Hz, CH$_2$CH_2OH), 4.06 (1H, dd, *J* = 11.1, 7.3 Hz, 1H from CH_2OAc), 4.43 (1H, dd, *J* = 11.1, 5.8 Hz, 1H from CH_2OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (Si(CH_3)$_2$), 18.3 (SiC(CH_3)$_3$), 18.8 (CCH_3), 21.2 (CH$_3$C=O), 25.4 (CH$_2$CH$_2$CH), 26.0 (SiC(CH_3)$_3$), 28.1 (CH$_2$CH$_2$CH$_2$OTBS), 31.6 (CH$_2$CH$_2$CH$_2$OTBS), 33.3 (CH$_2$CH$_2$CH), 36.1 (CH$_2$CH$_2$OH), 45.8 (CH$_2$CH$_2$CH), 49.7 (CCH$_3$), 60.4 (CH$_2$CH$_2$OH), 63.8 (CH$_2$OTBS), 66.5 (CH$_2$OAc), 85.2 (HOCH$_2$CH$_2$COH), 171.4 (CH$_3$C=O); MS: *m/z* (ES+ mode) 411 (100%) $[M+Na]^+$, HRMS Calcd for $C_{20}H_{40}O_5NaSi$: 411.2537. Found: 411.2543.

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

To a stirred solution of ((1*S*,2*R*,3*S*)-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*-Bu_3P (52.3 μL, 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 H_2O_2 (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 $NaHCO_3$ solution (3.0 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 5 mL) and the combined organic phases dried ($MgSO_4$), 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, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (6H, s, Si(CH_3)$_2$), 0.87 (3H, s, CCH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 1.08–1.17 (1H, m, 1H from CH_2CH$_2$CH$_2$OTBS), 1.21–1.30 (1H, m, 1H from CH_2CH$_2$CH$_2$OTBS), 1.34–1.41 (1H, m, 1H from CH$_2$CH_2CH), 1.42–1.51 (2H, m, CH$_2$CH_2CH$_2$OTBS), 1.64–1.69 (2H, m, CH_2CH$_2$CH), 1.77–1.85 (1H, m, 1H from CH$_2$CH_2CH), 1.97 (3H, s, CH_3C=O), 2.31 (1H, s, O*H*), 2.54–2.62 (1H, m, CH$_2$CH$_2$C*H*), 3.52–3.62 (2H, m, CH_2OTBS), 3.93 (1H, dd, *J* = 11.4, 6.1 Hz, 1H from CH_2OAc), 4.43 (1H, dd, *J* = 11.4, 8.8 Hz, 1H from CH_2OAc), 5.14 (1H, dd, *J* = 10.8, 1.5 Hz, 1H from CH=CH_2), 5.21 (1H, dd, *J* = 17.4, 1.5 Hz, 1H from CH=CH_2), 5.87 (1H, dd, *J* = 17.4, 10.8 Hz, C*H*=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (Si(CH_3)$_2$), 17.1 (CCH_3), 18.3 (SiC(CH_3)$_3$), 21.0 (CH$_3$C=O), 24.3 (CH$_2$CH$_2$CH), 26.0 (SiC(CH_3)$_3$), 28.1 (CH$_2$CH$_2$CH$_2$OTBS), 32.1 (CH$_2$CH$_2$CH$_2$OTBS), 32.7 (CH$_2$CH$_2$CH), 45.7 (CH$_2$CH$_2$CH), 51.0 (CCH$_3$), 63.8 (CH$_2$OTBS), 64.4 (CH$_2$OAc), 84.4 (CH$_2$=CHCOH), 113.8 (CH$_2$=CH), 140.7 (CH$_2$=CH), 172.1 (CH$_3$C=O); MS: *m/z* (ES+ mode) 393 (100%) $[M+Na]^+$, HRMS Calcd for $C_{20}H_{39}O_4Si$: 371.2612. Found: 371.2615.

4.6.13. (1*R*,2*S*,5*S*)-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 K_2CO_3 (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 CH_2Cl_2 (5 × 5 mL). The combined organics were dried ($MgSO_4$), 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, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (6H, s, Si(CH_3)$_2$), 0.86 (3H, s, CCH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 1.12–1.20 (1H, m, 1H from CH_2CH$_2$CH$_2$OTBS), 1.26–1.34 (1H, m, 1H from CH_2CH$_2$CH$_2$OTBS), 1.46–1.53 (2H, m, CH$_2$CH_2CH$_2$OTBS), 1.61–1.70 (2H, m, CH_2CH$_2$CH), 1.72–1.80 (2H, m, CH$_2$CH_2CH), 2.25 (1H, s, O*H*), 2.27–2.34 (1H, m, CH$_2$CH$_2$C*H*), 3.54–3.64 (2H, m, CH_2OTBS), 3.70 (1H, dd, *J* = 11.3, 5.8 Hz, 1H from CHCH_2OH), 3.82 (1H, dd, *J* = 11.1, 3.5 Hz, 1H from CHCH_2OH), 5.24 (1H, dd, *J* = 10.8, 1.5 Hz, 1H from CH=CH_2), 5.35 (1H, dd, *J* = 17.2, 1.5 Hz, 1H from CH=CH_2), 5.97 (1H, dd, *J* = 17.2, 10.8 Hz, C*H*=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2 (Si(CH_3)$_2$), 17.3 (CCH_3), 18.3 (SiC(CH_3)$_3$), 22.9 (CH$_2$CH$_2$CH), 26.0 (SiC(CH_3)$_3$), 28.2 (CH$_2$CH$_2$CH$_2$OTBS), 32.1 (CH$_2$CH$_2$CH$_2$OTBS), 33.5 (CH$_2$CH$_2$CH), 46.8 (CH$_2$CH$_2$CH), 50.8 (CCH$_3$), 62.5 (CHCH$_2$OH), 63.8 (CH$_2$OTBS), 87.3 (CH$_2$=CHCOH), 114.3 (CH=CH$_2$), 140.7 (CH=CH$_2$); MS: *m/z* (ES+ mode) 351 (100%) $[M+Na]^+$, 329 (13%) $[M+H]^+$.

4.6.14. (4a*S*,7*S*,7a*R*)-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 (C=O), 1472w, 1394w, 1256 m, 1208w, 1132 m, 1100 m, 1045w, 1007w, 938w, 836 m, 813w, 776 m; $[\alpha]_D$ = −32.8 (*c* 0.72, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (6H, s, Si(CH_3)$_2$), 0.09 (9H, s, SiC(CH_3)$_3$), 1.02 (3H, s, CCH_3), 1.17–1.34 (2H, m, CH_2CH$_2$CH$_2$OTBS), 1.44–1.62 (3H, m, 1H from CH_2CH$_2$CH, CH$_2$CH_2CH$_2$OTBS), 1.77–1.86 (2H, m, 1H from CH_2CH$_2$CH, 1H from CH$_2$CH_2CH), 1.97–2.08 (1H, m, 1H from CH$_2$CH_2CH), 2.55 (1H, ddt, *J* = 11.2, 6.6, 2.8 Hz, CH$_2$CH$_2$C*H*), 3.54–3.66 (2H, m, CH_2OTBS), 4.18 (1H, dd, *J* = 11.2, 2.3 Hz, 1H from CH_2OC(O) O), 4.33 (1H, dd, *J* = 11.2, 2.8 Hz, 1H from CH_2OC(O)O), 5.41 (1H, dd, *J* = 11.1, 1.0 Hz, 1H from CH=CH_2), 5.44 (1H, m, 17.2, 1.0 Hz, 1H from CH=CH_2), 5.83 (1H, dd, *J* = 17.2, 11.1 Hz, C*H*=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ −6.3 (Si(CH_3)$_2$), 16.1 (CCH_3), 17.3 (SiC(CH_3)$_3$), 22.6 (CH$_2$CH$_2$CH), 24.9 (SiC(CH_3)$_3$), 26.6 (CH$_2$CH$_2$CH$_2$OTBS), 30.5 (CH$_2$CH$_2$CH$_2$OTBS), 32.4 (CH$_2$CH$_2$CH), 36.9 (CH$_2$CH$_2$CH), 50.6 (CCH$_3$), 62.3 (CH$_2$OTBS), 66.3 (CH$_2$OC(O)O), 96.5 (CH$_2$=CHCO-C(O)O), 117.6 (CH=CH$_2$), 133.0 (CH=CH$_2$), 148.1 (CH$_2$OC(O)O); MS: *m/z* (ES+ mode) 372 (100%) [M+NH$_4$]$^+$, HRMS Calcd for $C_{19}H_{34}O_4NaSi$: 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 persistant blue colour was observed. The reaction was subsequently degassed with O_2 then N_2 until the colour discipated. 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%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (6H, s, Si(CH_3)$_2$), 0.90 (9H, s, SiC(CH_3)$_3$), 1.05 (3H, s, CCH_3), 1.09–1.79 (7H, m, 7 × 1H 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 CH$_2$=CCH_2CHOH), 2.40–2.50 (1H, m, CH$_2$CH$_2$C*H*), 2.67 (1H, d, *J* = 13.8 Hz, 1H from CH$_2$=CCH_2CHOH), 2.83 (1H, s, O*H*), 3.55–3.68 (4H, m, CH_2OTBS, C*H*OH, 1H from CH$_2$=CCH_2OBn), 3.79 (1H, dd, *J* = 10.8, 2.3 Hz, 1H from CH$_2$=CCH_2OBn), 3.96–4.02 (2H, m, CHCH_2O), 4.56 (2H, s, PhCH_2OCH$_2$), 5.12 (1H, s, 1H from CH_2=C), 5.22 (1H, s, 1H from CH_2=C), 7.30–7.40 (5H, m, 5 × ArC*H*).

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%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (6H, s, Si(CH_3)$_2$), 0.09 (6H, s, Si(CH_3)$_2$), 0.90 (18H, s, 2 × SiC(CH_3)$_3$), 1.03 (3H, s, CCH_3), 1.27–1.34 (2H, m, 2 × 1H from CH_2), 1.36–1.42 (1H, m, 1H from CH_2), 1.47–1.53 (3H, m, 3 × 1H 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 CH$_2$=CCH_2CHOH), 2.30–2.35 (1H, m, CH$_2$CH$_2$C*H*), 2.58 (1H, d, *J* = 14.2 Hz, 1H from CH$_2$=CCH_2CHOH), 3.48–3.53 (1H, m, 1H from CH_2OTBS), 3.56–3.62 (1H, m, 1H from CH_2OTBS), 3.59 (1H, s, O*H*), 3.75–3.76 (2H, m, CHCH_2OTBS), 3.83 (1H, ddd, *J* = 11.3, 3.5, 2.6 Hz, C*H*OH), 3.99 (1H, d, *J* = 12.3 Hz, 1H from CH$_2$=CCH_2OBn), 4.10–4.12 (2H, m, 1H from CH$_2$=CCH_2OBn, O*H*), 4.49 (1H, d, *J* = 11.7 Hz, 1H from PhCH_2OCH$_2$), 4.54 (1H, d, *J* = 11.7 Hz, 1H from PhCH_2OCH$_2$), 5.06 (1H, s, 1H from CH_2=C), 5.15 (1H, s, 1H from CH_2=C), 7.28–7.35 (5H, m, 5 × ArC*H*); MS: *m/z* (ES+ mode) 629 (100%) [M+Na]$^+$, 607 (48%) [M+H]$^+$, HRMS Calcd for $C_{34}H_{63}O_5Si_2$: 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 (C=O), 1468w, 1461w, 1357w, 1256s, 1197 m, 1172 m, 1095s, 836s, 811 m, 720 m; $[\alpha]_D$ = −29.4 (*c* 0.34, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (6H, s, Si(CH_3)$_2$), 0.05 (3H, s, Si(CH_3)$_2$), 0.87 (9H, s, SiC(CH_3)$_3$), 0.89 (9H, s, SiC(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 × 1H from CH_2), 1.74–1.85 (1H, m, 1H from CH_2), 2.48–2.57

(2H, m, 1H from CH_2=CCH_2OC(O)O, CH_2CH_2CH), 2.70 (1H, d, J = 14.9 Hz, 1H from CH_2=CCH_2OC(O)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 CH_2=CCH_2OBn), 4.07 (1H, d, J = 12.1 Hz, 1H from CH_2=CCH_2OBn), 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 CH_2=C), 5.20 (1H, s, 1H from CH_2=C), 5.24 (1H, dd, J = 11.8, 2.0 Hz, CH_2CHOC(O)O), 7.28–7.38 (5H, m, 5 × ArCH); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.7 (Si(CH_3)$_2$), 5.3 (Si(CH_3)$_2$), 18.2 (SiC(CH_3)$_3$), 18.3 (SiC(CH_3)$_3$), 18.5 (CCH_3), 22.9 (CH_2CH_2CH), 25.9 (SiC(CH_3)$_3$), 25.9 (SiC(CH_3)$_3$), 27.7 ($CH_2CH_2CH_2$OTBS), 30.4 ($CH_2CH_2CH_2$OTBS), 33.8 (CH_2CH_2CH), 34.3 (CH_2=CCH_2CHO), 47.8 (CHCH$_2$OTBS), 49.5 (CCH_3), 62.6 (CH_2OTBS), 63.1 (CH_2OTBS), 72.0 (BnOCH_2), 72.8 (PhCH_2O), 81.5 (CHOC(O)O), 96.6 (COC(O)O), 115.6 (C=CH_2), 127.7 (2 × ArCH), 127.7 (ArCH), 128.4 (2 × ArCH), 138.1 (ArC), 141.2 (C=CH_2), 154.4 (OC(O)O); MS: m/z (ES+ mode) 655 (100%) $[M+Na]^+$, 652 (72%), 650 (36%) $[M+NH_4]^+$, HRMS Calcd for $C_{35}H_{60}O_6NaSi_2$: 655.3821. Found: 655.3833.

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