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The first synthetic studies on pestalotiopsin A. A stereocontrolled approach to the functionalised bicyclic core †

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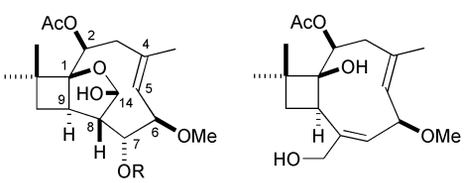
Received 17th September 2002, Accepted 11th November 2002
First published as an Advance Article on the web 13th December 2002

Pestalotiopsin A is a structurally unique, caryophyllene-type sesquiterpene which has shown immunosuppressive activity and cytotoxicity in preliminary assays. A stereocontrolled approach to the functionalised 2-oxabicyclo[3.2.0]-heptane core of pestalotiopsin A is described. This constitutes the first synthetic studies on pestalotiopsin A. Our approach includes a samarium(II)-mediated 4-*exo-trig* cyclisation and a trans-lactonisation process triggered by the addition of alkylytterbium reagents to a cyclobutanone intermediate. Further manipulation provides access to advanced intermediates which are excellent precursors for the future construction of the final ring of the target.

Introduction

The pestalotiopsins are caryophyllene-type, sesquiterpenes isolated from *Pestalotiopsis* sp., an endophytic fungus of *Taxus brevifolia*, the Pacific yew.[1,2] The discovery of taxol triggered a thorough examination of the secondary metabolites of the Pacific Yew. This search has now widened to include micro-organisms associated with the tree and has led to the isolation of the pestalotiopsins. Pestalotiopsin A **1** is of particular interest as it possesses an oxatricyclic structure unique amongst natural products,[3] and has shown immunosuppressive activity and cytotoxicity in preliminary assays.[1] It would appear possible that the activity of this compound originates from the 2-oxabicyclo[3.2.0]heptan-3-ol core, as pestalotiopsin B, which lacks this structural feature, has no reported activity (Fig. 1).



1 R= H, pestalotiopsin A
R= Me, pestalotiopsin C

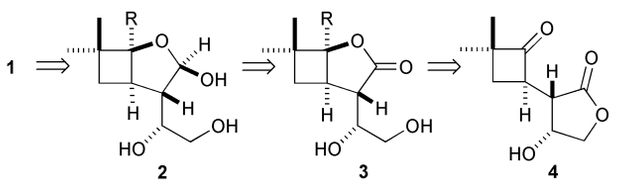
pestalotiopsin B

Fig. 1 The pestalotiopsin natural products.

We have recently developed a stereoselective approach to functionalised cyclobutanols using a samarium(II)-mediated[4] 4-*exo-trig* cyclisation of unsaturated aldehydes.[5,6] We now report in full, the application of this chemistry to the successful synthesis of the functionalised 2-oxabicyclo[3.2.0]heptane system found in pestalotiopsin A. The second part of our approach involves an efficient trans-lactonisation process triggered by the addition of an alkylytterbium reagent to a cyclobutanone intermediate.[7] Our work represents the first synthetic studies on the pestalotiopsin natural products.

Results and discussion

Our retrosynthetic analysis of pestalotiopsin A (Scheme 1) reveals possible disconnections of the nine-membered ring at several points between C1 and C6 (pestalotiopsin A numbering scheme – Fig. 1). We felt a disconnection between C3 and C4



Scheme 1 Retrosynthetic analysis of pestalotiopsin A.

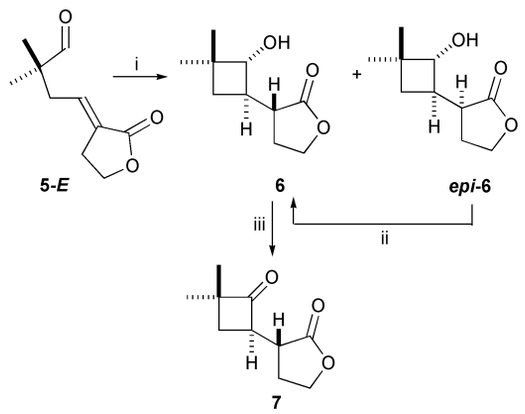
was particularly attractive although several alternative approaches are also possible. Bicyclic lactones **3**, therefore, are important intermediates in our approach to pestalotiopsin A. Importantly, flexibility in the nature of the 'R' group is crucial for the examination of future approaches to the final, nine-membered carbocyclic ring. The addition of alkylmetal reagents to cyclobutanone **4** should proceed selectively from the opposite face to the lactone substituent,[8] thus triggering trans-lactonisation and releasing the hydroxyethyl side chain necessary for the construction of the final ring. We felt that cyclobutanones such as **4**, could be prepared using our previously reported samarium(II) cyclisation chemistry. A feature of our strategy is that stereocentres at C8 and C9 are established directly in the samarium(II)-cyclisation step and carried intact through the addition/trans-lactonisation sequence.

We have previously described the cyclisation of unsaturated aldehyde **5-*E*** to give *anti*-cyclobutanol **6** in good yield and as a 4 : 1 mixture at the centre α- to the lactone carbonyl.[5b] In this reaction three contiguous stereocentres are established in a single step with significant control. In addition, ***epi*-6** can be readily epimerised to give a 1 : 1 mixture of **6** and ***epi*-6** in 69% yield, thus providing even more efficient access to the desired diastereoisomer **6**. We felt cyclobutanol **6** would be an excellent model compound to assess the feasibility of our approach to pestalotiopsin A. Oxidation of **6** with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) gave cyclobutanone **7** in quantitative yield (Scheme 2).

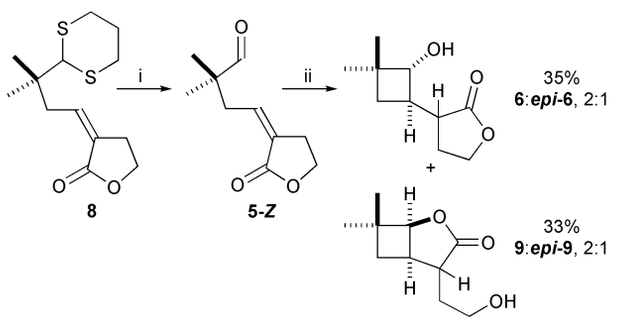
In order to assess the effect of the initial double bond geometry on the stereoselectivity of the reaction, we next examined the cyclisation of **5-*Z*** (Scheme 3). Cyclisation substrate **5-*Z*** was conveniently prepared by deprotection of thioacetal **8**.[5b] Interestingly, cyclisation of **5-*Z*** gave a complex mixture of products. In stark contrast to the complete *anti*-selectivity observed in the cyclisation of **5-*E***, a 1 : 1 mixture of *syn* and *anti*-cyclisation products was obtained, the *syn* products undergoing spontaneous lactonisation to give lactones **9**. In addition, 2 : 1 mixtures at the centre α- to the lactone carbonyl group were also

† Electronic supplementary information (ESI) available: crystal structure analysis of **18a**. See http://www.rsc.org/suppdata/ob/b2/b209066j/

DOI: 10.1039/b209066j



Scheme 2 *Reagents and conditions:* i, SmI_2, THF–MeOH (4 : 1), 0 °C, 79%, 4 : 1 mixture of **6** : ***epi*-6**; ii, DBU, toluene, 80 °C, 69%, 1 : 1 mixture of **6** : ***epi*-6**; iii, TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 100%.



Scheme 3 *Reagents and conditions:* i, $CaCO_3$, MeI, MeCN, H_2O, 60 °C, 90%; ii, SmI_2, THF–MeOH (4 : 1), 0 °C.

obtained. It is therefore clear that the initial double bond stereochemistry has a profound effect on the relative stereochemistry across the newly-formed ring junction but has a less dramatic effect on the stereochemistry α- to the lactone carbonyl group. Enholm has observed a marked dependence of diastereoselectivity on the olefin-geometry in samarium(II)-mediated reductive cyclisations to form five-membered carbocycles.[9] Lactones **9** and ***epi*-9** were prepared independently to help elucidate the outcome of the cyclisation (*vide infra*).

In the cyclisation of **5-*Z***, we believe the loss of stereoselectivity can be explained by examination of the *syn* and *anti*-transition states for both **5-*E*** and **5-*Z*** (Fig. 2). It has been noted

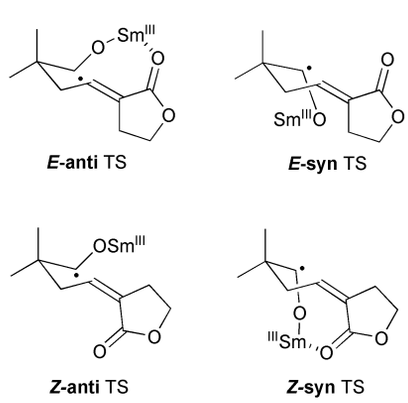
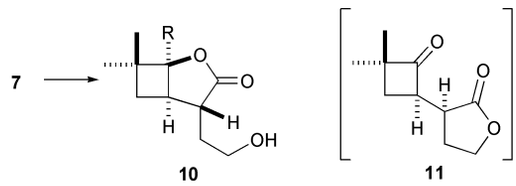
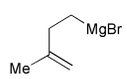
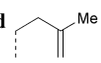
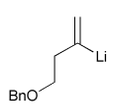
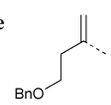


Fig. 2 Transition state structures for the cyclisation of **5-*E*** and **5-*Z***.

previously that ketyl-olefin cyclisations display a marked *anti*-selectivity.[4d] This has been ascribed to electronic factors.[4d,10] Coordination of the Lewis acidic samarium(III) ion of the ketyl-radical anion to the ester carbonyl is also likely to be important as it leads to activation of the radical acceptor. Thus the E-anti transition structure is favoured over the *E-syn* transition structure, thus giving complete *anti*-selectivity in the

Table 1 Alkylytterbium additions to cyclobutanone **7**



Alkylmetal	Product	Yield[a]
MeLi	**10a** R = Me	68%
	**10b** R = vinyl	67%
	**10c** 	78%
	**10d** 	85%
	**10e** 	50%

[a] *General procedure:* To a solution of $Yb(OTf)_3$ in THF at −78 °C was added the alkylmetal reagent. The resulting alkylytterbium reagent was added to a solution of **7** in THF at −78 °C.

cyclisation. Upon examination of the possible transition structures for the cyclisation of **5-*Z***, the situation is less clear-cut. It might be expected that the *Z-anti* transition structure would be electronically favoured, however, only in the *Z-syn* transition structure can chelation occur between the samarium(III) centre of the ketyl-radical anion and the ester carbonyl group. Thus little stereoselectivity is observed in the cyclisation as neither transition structure is significantly favoured over the other.

Having an efficient approach to **7**, we turned our attention to the sequential nucleophilic addition–trans-lactonisation step. We began by examining the addition of simple alkylmetal reagents to cyclobutanone **7**.

Initial attempts to add MeMgBr and MeLi to **7** led to substantial epimerisation of the starting material, giving cyclobutanone **11**, however, the desired bicyclic lactone **10a** was also obtained in low yield (29% and 15%, respectively). Cyclobutanone **11** was prepared independently, by oxidation of the minor diastereoisomer ***epi*-6**, formed in the samarium(II) mediated 4-*exo-trig* cyclisation (TPAP, NMO, CH_2Cl_2, rt, 97%). We next investigated the use of less basic organocerium reagents. Although less epimerisation was observed using these reagents, the yields obtained from the addition were still unsatisfactory and difficulties in transferring the heterogeneous THF solutions of the organocerium reagents led us to seek an alternative approach. Molander has reported that organoytterbium reagents, prepared by the addition of alkyllithium or Grignard reagents to ytterbium(III) triflate‡,[11] exist as brightly coloured, homogeneous solutions in THF and are attractive alternatives to organocerium reagents.[12] Such reagents have also been shown to give enhanced diastereoselectivities, when compared to the parent organolithium and magnesium reagents, in additions to simple carbonyl compounds.[12] Using Molander's approach, alkylytterbium reagents derived from MeLi and vinylmagnesium bromide added smoothly to cyclobutanone **7** to give **10a** and **10b**, respectively, in good yield and with no trace of epimerised by-products (Table 1).[12b] Results from the additions of other alkylmetal reagents are also shown in Table 1. Clearly, by varying the alkylmetal reagent employed

‡ The IUPAC name for triflate is trifluoromethanesulfonate.

in the addition, a variety of approaches to the final nine-membered ring can be accommodated, thus giving our approach substantial flexibility.

Interestingly, attempts to add the vinylytterbium reagent derived from 2-bromo-4-*tert*-butyldiphenylsilyloxybutene **12** to **7** lead only to recovered cyclobutanone and vinylsilane **13** (97% yield), formed *via* a facile retro-Brook rearrangement[13] at −78 °C (Fig. 3). Treating vinylbromide **12** with *tert*-butyl-

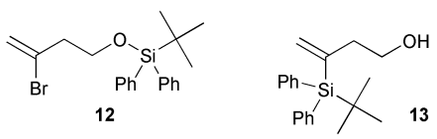
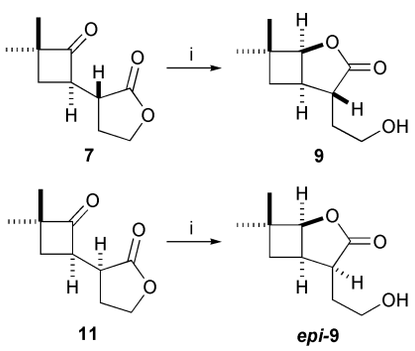


Fig. 3

lithium at −78 °C also leads to a quantitative yield of the rearrangement product **13**, thus clearly showing that the rearrangement is not dependent upon trans-metallation to ytterbium. The use of non-silicon based protecting groups circumvents this problem (Table 1, formation of **10e**).

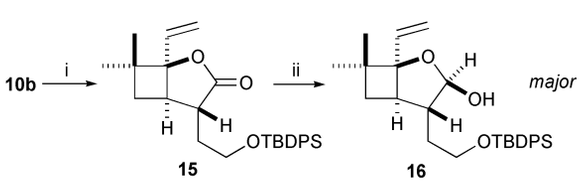
To confirm the stereochemistry of the bicyclic lactone products, **10a** was converted to the corresponding *p*-nitrobenzoate **14** (p-$O_2NC_6H_4COCl$, pyridine, rt, 88%) and its structure determined by X-ray crystallography.[7]

In a related addition–trans-lactonisation process, the reduction of cyclobutanones **7** and **11** with L-Selectride at −78 °C was found to give lactones **9** and ***epi*-9** respectively in 59% and 88% yield (Scheme 4). This confirmed our assignment of the products from the cyclisation of **5-*Z***.



Scheme 4 *Reagents and conditions:* i, L-Selectride, THF, −78 °C, 59% for **9**, and 88% for ***epi*-9**.

To complete our approach to the bicyclic core of pestalotiopsin A, the primary hydroxy group of **10b** was protected, and the lactone **15** reduced to the lactol **16**. Treatment of the lactone with DIBAL-H gave a 2 : 1 mixture of lactols (Scheme 5).



Scheme 5 *Reagents and conditions:* i, TBDPSCl, imidazole, DMF, rt, 73%; ii, DIBALH, CH_2Cl_2, −78 °C, 86% [2 : 1 mixture of diastereoisomers].

We expected that the major product would arise from reduction from the 'outside' of the bicyclic system. NOE studies on the lactols did indeed reveal that **16** was the major product from the reduction (Fig. 4). (The stereochemistry at C3 in the major lactol isomer was determined by comparison of NOE values for both isomers. For example, in the minor isomer an NOE of 5.6% between H3 and H4 was observed, whilst a 2.3% NOE was observed between the two protons in the major isomer). The retention of the desired stereochemistry at C4 was clear

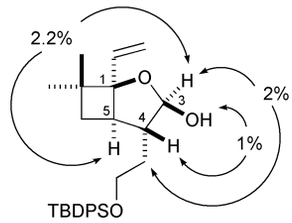
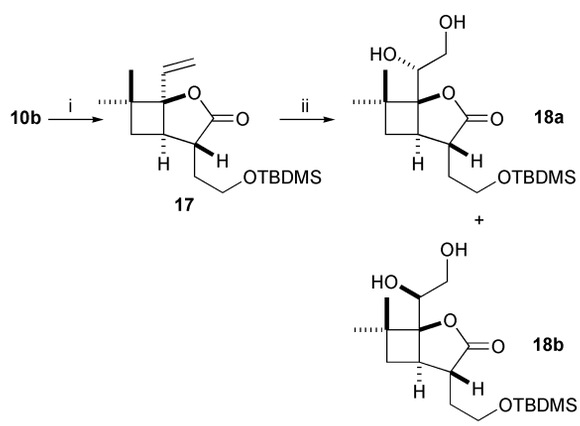


Fig. 4 NOE study on lactol **16**.

from the lack of coupling between H4 and H5, the dihedral angle between the two protons being virtually 90° in the correct C4 epimer (see Fig. 4 for numbering).

We next investigated the functionalisation of the 2,3-double bond in the vinyl addition products. Thus, the primary hydroxy group of **10b** was protected, and the alkene **17** dihydroxylated to give a mixture of diastereoisomeric diols, **18a** and **18b** in a 2.2 : 1 ratio, respectively (Scheme 6).



Scheme 6 *Reagents and conditions:* i, TBDMSCl, imidazole, DMF, rt, 60%; ii, OsO_4 (10 mol%), $K_3Fe(CN)_6$, K_2CO_3, pyridine (cat.), ^tBuOH–H_2O–Et_2O (1.5 : 1.5 : 1), 0 °C, 85% [2.2 : 1 mixture of diastereoisomers].

The stereochemistry of the major diastereoisomer **18a** was confirmed by X-ray crystallographic analysis (Fig. 5).

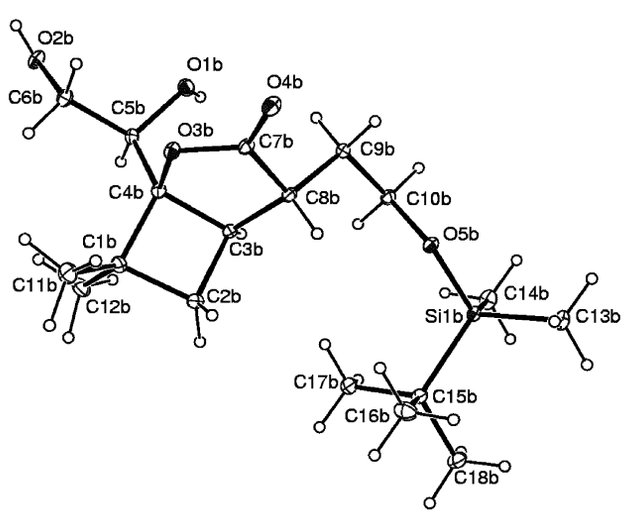
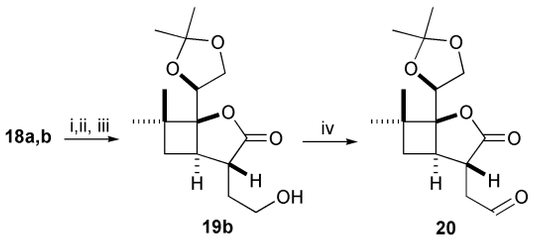


Fig. 5 Molecular drawing of **18a** showing the atom numbering and 20% probability ellipsoids.

Protection of the mixture of diols **18a**–**b** as the corresponding acetonides and removal of the TBDMS protecting group gave a mixture **19a**–**b** from which both diastereoisomers could be easily isolated by chromatography. Oxidation of the primary hydroxy in **19a** and **19b** was best achieved with pyridinium chlorochromate (PCC) in CH_2Cl_2. In the case of **19b**, oxidation gave aldehyde **20**, a versatile precursor for the construction of the final nine-membered ring and a key intermediate in our approach to pestalotiopsin A (Scheme 7).



Scheme 7 *Reagents and conditions:* i, 2,2-dimethoxypropane, dry acetone, camphor sulfonic acid (cat.), rt, quantitative; ii, HF–pyridine complex, THF–pyridine, 78%; iii, chromatography; iv, PCC, CH_2Cl_2, 4 Å MS, 70%.

Conclusions

The functionalised 2-oxabicyclo[3.2.0]heptane core of pestalotiopsin A has been prepared with stereocontrol at four contiguous stereocentres using an approach based on a samarium(II)-mediated 4-*exo*-*trig* cyclisation and a trans-lactonisation process triggered by the addition of alkylytterbium reagents. Importantly, our approach is sufficiently versatile to allow for disconnections at a number of positions around the final nine-membered ring. We are currently preparing the fully functionalised core of pestalotiopsin A using this approach and are developing strategies for the closure of the final 9-membered carbocyclic ring.

Experimental section

General considerations

All reactions were performed under argon or nitrogen atmospheres with anhydrous solvents unless otherwise stated. THF was distilled from sodium benzophenone ketyl radical. CH_2Cl_2 was distilled from CaH_2. Toluene was distilled from sodium wire. MeOH, EtOH and ^{t}BuOH were distilled from the corresponding magnesium alkoxide and stored under argon. Samarium(II) iodide was prepared by the method of Imamoto [14] with the modification that the samarium–iodine THF solution was heated at 60 °C rather than at reflux.

Melting points were measured on a Kofler hot stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker DPX 400 spectrometer with chemical shift values being reported in ppm relative to residual chloroform (δ_H = 7.27) and $CDCl_3$ (δ_C = 77.2) respectively, as internal standards unless otherwise stated. All coupling constants (*J*) are reported in Hertz (Hz). Infrared spectra were recorded using JASCO FT/IR 410 and Impact 400 spectrometers and mass spectra were obtained using a JEOL JMS-700 spectrometer. Microanalyses were carried out at the University of Glasgow using an Elemental Analyser MOD 1106. Column chromatography was carried out using Fisher Matrex silica 60. Macherey-Nagel aluminium backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by UV or staining with iodine or alkali $KMnO_4$.

(*Z*)-2,2-Dimethyl-4-(2-oxodihydrofuran-3-ylidene)butanal 5-*Z*

To a stirred solution of **8** (246 mg, 0.90 mmol) in acetonitrile (5.6 mL) and distilled water (1.4 mL) was added $CaCO_3$ (271 mg, 2.71 mmol, 3 eq.) and iodomethane (1.13 mL, 18.1 mmol, 20 eq.). The mixture was then heated at reflux for 19 h before a further quantity of iodomethane (0.28 mL, 4.52 mmol, 5 eq.) was added. The mixture was then passed through a short column of silica gel (eluting with 50% EtOAc in hexane). Concentration *in vacuo* gave the aldehyde **5-*Z*** (147 mg, 0.81 mmol, 90%) as a clear, pale yellow oil which was used without further purification: ν_{max} (neat)/cm^{-1} 2969s (C–H), 2930s (C–H), 2873s, 2816m (CHO), 2712m (CHO), 1752s (lactone C=O), 1725s (aldehyde C=O), 1681s (C=C), 1366m ($C(CH_3)_2$), 1354m ($C(CH_3)_2$), 1214s, 1034s; δ_H (400 MHz, $CDCl_3$) 9.48 (1H, s, C*H*O), 6.17 (1H, t, *J* 7.9, CH_2CH=), 4.33 (2H, t, *J* 7.3, CH_2O), 2.97–2.92 (4H, m, 2H from CH_2CH_2O and 2H from CH_2CH=) and 1.13 (6H, s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 205.5 (*C*HO), 170.1 (*C*=O), 138.4 (*C*H=C), 126.5 (CH=*C*), 65.5 (CH_2O), 46.8 ($C(CH_3)_2$), 34.1 (CH_2CH=), 29.3 (CH_2CH_2O) and 21.5 ($C(CH_3)_2$); *m*/*z* (CI$^+$ mode, isobutane) 183 (100%), 165 (6), 153 (7), 101 (3), 81 (6) and 69 (12) (Found (M + H)$^+$ 183.1021. $C_{10}H_{15}O_3$ requires 183.1017).

rel-(3*R*)-3-[*rel*-(1*R*,2*R*)-2-Hydroxy-3,3-dimethylcyclobutyl]-4,5-dihydrofuran-2(3*H*)-one 6 and *rel*-(3*S*)-3-[*rel*-(1*R*,2*R*)-2-Hydroxy-3,3-dimethylcyclobutyl]-4,5-dihydrofuran-2(3*H*)-one *epi*-6

To a stirred solution of SmI_2 (11.8 mL, 0.1 M in THF, 1.18 mmol, 2 eq.) in MeOH (2.94 mL) at 0 °C was added dropwise a solution of aldehyde **5-*E*** (108 mg, 0.59 mmol) in THF (1.5 mL). After 0.5 h, another quantity of SmI_2 (3.0 mL, 0.1 M in THF, 0.30 mmol, 0.5 eq.) was added and the reaction stirred for a further 1 h before quenching by the addition of aqueous saturated NaCl (5 mL) and citric acid (310 mg, 1.48 mmol, 2.5 eq.). The aqueous layer was separated and extracted with 80% EtOAc in hexane (4 × 30 mL) and the combined organic layers dried ($MgSO_4$). Concentration *in vacuo* followed by purification of the residue by column chromatography (eluting with 50% EtOAc in hexane) gave cyclobutanols **6** and ***epi*-6** (86 mg, 0.47 mmol, 79%) as a 4 : 1 mixture, respectively; ν_{max} (soln. in $CHCl_3$)/cm^{-1} 3548m, 3025s, 2961s, 2925s, 2867s, 1762s (C=O), 1375s, 1216s, 1105s, and 1028s; *m*/*z* (CI$^+$ mode, isobutane) 185 (41%), 167 (100), 149 (1), 128 (3), and 113 (2) (Found (M + H)$^+$ 185.1178. $C_{10}H_{17}O_3$ requires 185.1173). The epimers were separated by further chromatography (eluting with 50% EtOAc in hexane): major cyclobutanol **6**; δ_H (400 MHz, $CDCl_3$) 4.40 (1H, td, *J* 8.8, 2.6, 1H from CH_2CH_2O), 4.27–4.20 (1H, m, 1H from CH_2CH_2O), 3.76 (1H, d, *J* 7.7, C*H*OH), 2.81 (1H, br s, CHO*H*), 2.60 (1H, q, *J* 9.6, C*H*C(O)O), 2.38–2.30 (1H, m, 1H from CH_2CH_2O), 2.23–2.14 (1H, m, C*H*), 1.99–1.88 (1H, m, 1H from CH_2CH_2O), 1.71 (1H, apparent t, *J* 9.9, 1H from CH_2), 1.16 (1H, obscured, 1H from CH_2), 1.13 (3H, s, CH_3), and 1.12 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 180.0 (*C*=O), 78.1 (*C*HOH), 67.6 (CH_2CH_2O), 44.0 ($CHCO_2$), 41.6 (CH), 38.8 (C), 32.4 (CH_2), 28.8 (CH_3), 27.7 (CH_2CH_2O), 21.0 (CH_3); minor cyclobutanol ***epi*-6**; δ_H (400 MHz, $CDCl_3$) 4.33 (1H, dt, *J* 8.7, 4.2, 1H from CH_2CH_2O), 4.26–4.19 (1H, m, 1H from CH_2CH_2O), 3.78 (1H, d, *J* 8.0, C*H*OH), 2.66 (1H, apparent q, *J* 8.5, C*H*C(O)O), 2.43–2.28 (2H, m, 1H from CH_2CH_2O and 1H from CCH_2CH), 2.17–2.05 (1H, m, 1H from CH_2CH_2O), 1.82 (1H, apparent t, *J* 10.3, 1H from CCH_2CH), 1.20 (1H, apparent t, *J* 10.3, 1H from CCH_2CH) and 1.09 (6H, s, $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 178.7 (*C*=O), 77.0 (CHOH), 66.9 (CH_2CH_2O), 42.2 (*C*HC(O)O), 41.5 (CCH_2CH), 39.2 ($C(CH_3)_2$), 32.1 (CCH_2CH), 28.3 (CH_3), 27.2 (CH_2CH_2O) and 20.7 (CH_3).

Epimerisation of *epi*-6 to 6

To a stirred solution of cyclobutanol ***epi*-6** (23 mg, 0.13 mmol) in toluene (2 mL) was added DBU (38 mg, 0.25 mmol, 2 eq.) and the solution heated at 80 °C for 19 h. The solvent was then evaporated and the residue purified by column chromatography (eluting with 50% EtOAc in petroleum ether (40–60 °C)) to give **6** and ***epi*-6** as a 1 : 1 mixture (15.9 mg, 0.09 mmol, 69%).

rel-(3*R*)-3-[*rel*-(1*R*)-3,3-Dimethyl-2-oxocyclobutyl]-4,5-dihydrofuran-2(3*H*)-one 7

To a stirred solution of **6** (101 mg, 0.55 mmol) in CH_2Cl_2 (5.5 mL) at room temperature was added 4 Å molecular sieves (10 mg), *N*-methylmorpholine *N*-oxide (256 mg, 2.19 mmol,

4 eq.), and tetrapropylammonium perruthenate (8 mg, 0.02 mmol). After 3 h, the reaction mixture was poured onto a short column of silica gel and eluted with 50% EtOAc in petroleum ether (40–60 °C). Concentration *in vacuo* gave the cyclobutanone **7** (100 mg, 0.55 mmol, 100%) as a clear colourless oil: ν_{max} (soln. in $CHCl_3$)/cm^{-1} 3028s (C–H), 2949s, 1756s (C=O), 1709s (C=O), 1656m, 1530m, 1467m, and 1367m; δ_H (400 MHz, $CDCl_3$) 4.41 (1H, td, *J* 8.9, 1.9, 1H from CH_2O), 4.24–4.18 (1H, m, 1H from CH_2O), 3.98–3.92 (1H, m, $(Me)_2CCH_2CH$), 3.00–2.94 (1H, m, CHCH$_2$), 2.39–2.32 (1H, m, 1H from CH_2CH$_2$O), 2.19–2.08 (1H, m, 1H from CH_2CH$_2$O), 2.05 (1H, apparent t, *J* 11.0, 1H from $(Me)_2CCH_2$), 1.91–1.86 (1H, m, 1H from $(Me)_2CCH_2$), 1.30 (3H, s, 3H from C(CH_3)$_2$) and 1.16 (3H, s, 3H from C(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 214.8 (C=O), 177.5 (*C*=O), 66.8 (*C*H$_2$O), 58.1 (*C*(CH$_3$)$_2$), 53.7 ($(Me)_2CCH_2CH$), 37.7 (*C*HCH$_2$), 28.7 ($(Me)_2CCH_2$), 26.1 (*C*H$_2$CH$_2$O), 24.0 (C(*C*H$_3$)$_2$) and 21.2 (C(*C*H$_3$)$_2$); *m*/*z* (EI$^+$ mode) 182 (26%), 154 (11), 126 (35), 111(12), 82 (35), 70 (100) and 41 (27) (Found M$^+$ 182.0943. $C_{10}H_{14}O_3$ requires 182.0943).

rel-(1*S*,4*R*,5*R*)-4-(2-Hydroxyethyl)-7,7-dimethyl-2-oxa-bicyclo[3.2.0]heptan-3-one 9

To a stirred solution of cyclobutanone **7** (22 mg, 0.12 mmol) in THF (0.5 mL) at −78 °C was added L-Selectride (0.14 mL, 1.0 M in THF, 0.14 mmol, 1.1 eq.) dropwise. After 1 h, aqueous saturated $NaHCO_3$ (0.5 mL) was added and the aqueous layer separated and extracted with EtOAc (4 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless cloudy oil. Purification by column chromatography (eluting with 60% EtOAc in petroleum ether (40–60 °C)) gave bicyclic lactone **9** (13 mg, 0.07 mmol, 59%) as a clear, colourless oil: ν_{max} ($CHCl_3$ soln.)/cm^{-1} 3619s (O–H), 3149s, 2959s (C–H), 2931s (C–H), 2863s (C–H), 1755s (C=O), 1637m, 1559m, 1464s, 1380s, 1167s and 1094s; δ_H (400 MHz, $CDCl_3$) 4.50–4.48 (1H, dd, *J* 5.8, 2.6, *H*COC(O)), 3.84–3.71 (2H, m, CH_2OH), 2.85–2.79 (1H, m, CCH$_2$C*H*), 2.65 (1H, dt, *J* 7.4, 1.4, C*H*C(O)O), 2.10–2.04 (1H, m, 1H from CCH_2CH), 1.92–1.74 (2H, m, CH_2CH$_2$OH), 1.63–1.58 (1H, dd, *J* 12.2, 6.8, 1H from CCH_2CH), 1.20 (3H, s, CH_3) and 1.15 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 181.8 (C=O), 85.6 (*C*HOC(O)), 60.5 (CH$_2$OH), 44.9 (*C*HCO), 39.0 (*C*(CH$_3$)$_2$), 38.7 (C*C*H$_2$CH), 34.6 (CCH$_2$*C*H), 34.5 (*C*H$_2$CH$_2$OH), 27.0 (*C*H$_3$) and 22.6 (*C*H$_3$); *m*/*z* (CI$^+$ mode, isobutane) 185 (100%), 167 (21), 149 (2), 139 (1), 128 (4), 110 (2), 95 (1) and 83 (1) (Found (M + H)$^+$ 185.1178. $C_{10}H_{17}O_3$ requires 185.1173).

rel-(1*S*,4*S*,5*R*)-4-(2-Hydroxyethyl)-7,7-dimethyl-2-oxa-bicyclo[3.2.0]heptan-3-one *epi*-9

To a stirred solution of cyclobutanone **11** (22 mg, 0.12 mmol) in THF (0.5 mL) at −78 °C was added L-Selectride (1.0 M in THF, 0.13 mL, 0.13 mmol, 1.1 eq) dropwise. After 1 h, aqueous saturated $NaHCO_3$ (1 mL) was added and the aqueous layer separated and extracted with EtOAc (4 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude as a clear colourless oil. Purification by column chromatography (eluting with 60% EtOAc in petroleum ether (40–60 °C)) gave bicyclic lactone ***epi*-9** (20 mg, 0.11 mmol, 88%) as a clear colourless oil: ν_{max} ($CHCl_3$ soln.)/cm^{-1} 3681s (O–H), 3020s (C–H), 2959s (C–H), 2869s (C–H), 1761s (C=O), 1520s, 1425s, 1021s and 932s; δ_H (400 MHz, $CDCl_3$) 4.44 (1H, dd, *J* 5.2, 3.0, *H*COC(O)), 3.83–3.77 (1H, m, 1H from CH_2OH), 3.70–3.64 (1H, m, 1H from CH_2OH), 3.24–3.17 (1H, m, CCH$_2$C*H*), 2.85–2.79 (1H, apparent q, *J* 8.0, C*H*C(O)O), 2.11–2.01 (1H, m, 1H from CH_2CH$_2$OH), 1.87–1.76 (1H, m, 1H from CCH_2CH), 1.73–1.65 (2H, m, 1H from CH_2CH$_2$OH and 1H from CCH_2CH), 1.23 (3H, s, CH_3) and 1.13 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 199.1 (*C*=O), 85.1 (*C*HOC(O)), 61.4 (*C*H$_2$OH), 41.1 (*C*HCO), 38.3 (*C*(CH$_3$)$_2$), 33.3 (CCH$_2$*C*H), 33.2 (C*C*H$_2$CH), 29.0 (*C*H$_2$CH$_2$OH), 26.4 (*C*H$_3$) and 22.4 (*C*H$_3$); *m*/*z* (CI$^+$ mode, isobutane) 185 (100%), 167 (8), 128 (2) and 111 (2) (Found (M + H)$^+$ 185.1176. $C_{10}H_{17}O_3$ requires 185.1173).

Cyclisation of 5-*Z*: compounds 6 and *epi*-6 and 9 and *epi*-9

To a stirred solution of SmI_2 (0.1 M in THF, 4.70 mL, 0.47 mmol, 2 eq.) in MeOH (1.17 mL) at 0 °C was added dropwise a solution of aldehyde **5-*Z*** (43 mg, 0.23 mmol) in THF (0.6 mL). After 10 minutes, another quantity of SmI_2 (0.1 M in THF, 2.30 mL, 0.23 mmol, 1 eq.) was added and the reaction stirred for a further 1 h before quenching by the addition of aqueous saturated NaCl (2 mL) and citric acid (148 mg, 0.70 mmol, 3 eq.). The aqueous layer was separated and extracted with 80% EtOAc in hexane (4 × 15 mL) and the combined organic layers dried ($MgSO_4$). Concentration *in vacuo* gave the crude product mixture as a red oil. Purification of the residue by column chromatography (eluting with 50% EtOAc in hexane) gave an approximately 2 : 1 : 2 : 1 mixture of compounds **6** : ***epi*-6** : **9** : ***epi*-9** (29 mg, 0.16 mmol, 68% (combined yield)). Elucidation of the product mixture was achieved by the preparation of bicyclic lactones **9** and ***epi*-9** by an independent method (*vide infra*).

rel-(1*S*,4*R*,5*R*)-4-(2-Hydroxyethyl)-1,7,7-trimethyl-2-oxa-bicyclo[3.2.0]heptan-3-one 10a

To a stirred solution of Yb(OTf)$_3$ (185 mg, 0.30 mmol, 2 eq.) in THF (7.2 mL) at −78 °C was added MeLi·LiBr (0.24 mL, 1.26 M in THF, 0.30 mmol, 2 eq.) and the mixture left for 40 minutes. A solution of the cyclobutanone **7** (27 mg, 0.15 mmol) in THF (0.35 mL) at −78 °C was then added dropwise *via* cannula to the purple solution of the organoytterbium reagent also at −78 °C. After 35 minutes, aqueous saturated $NaHCO_3$ (1 mL) was added and the aqueous layer separated and extracted with $CHCl_3$ (4 × 15 mL), the organic layers dried ($MgSO_4$). Concentrated *in vacuo* followed by column chromatography (eluting with 50% EtOAc in petroleum ether (bp 40–60 °C)) gave lactone **10a** as a clear oil (20 mg, 0.10 mmol, 68%): ν_{max} (soln. in $CHCl_3$)/cm^{-1} 3480br m (O–H), 3028s, (C–H), 2959s (C–H), 1750s (C=O), 1519s, 1477s and 1425s; δ_H (400 MHz, $CDCl_3$) 3.86–3.74 (2H, m, CH_2OH), 2.66 (1H, t, *J* 7.7, COC*H*), 2.55 (1H, td, *J* 8.0, 1.0, $(Me)_2CCH_2CH$), 2.02 (1H, dd, *J* 12.2, 8.8, 1H from $(Me)_2CCH_2$), 1.93–1.85 (1H, m, 1H from CH_2CH$_2$OH), 1.83–1.74 (1H, m, 1H from CH_2CH$_2$OH), 1.54 (1H, dd, *J* 12.2, 7.1, 1H from $(Me)_2CCH_2$), 1.36 (3H, s, CH_3), 1.15 (3H, s, 3H from C(CH_3)$_2$), and 1.04 (3H, s, 3H from C(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 181.0 (*C*=O), 92.3 (*C*OC(O)), 60.8 (*C*H$_2$OH), 46.3 (*C*HC(O)), 40.7 (*C*(CH$_3$)$_2$), 40.9 ($(Me)_2CCH_2CH$), 38.1 ($(Me)_2CCH_2$), 35.4 (*C*H$_2$CH$_2$OH), 25.8 (C(*C*H$_3$)$_2$), 22.4 (C(*C*H$_3$)$_2$), and 19.7 (*C*H$_3$); *m*/*z* (CI$^+$ mode, isobutane) 199 (100%), 181 (18), 155 (4), 142 (5), 115 (15), and 69 (3) (Found (M + H)$^+$ 199.1334. $C_{11}H_{19}O_3$ requires 199.1334).

rel-(1*S*,4*R*,5*R*)-4-(2-Hydroxyethyl)-7,7-dimethyl-1-vinyl-2-oxa-bicyclo[3.2.0]heptan-3-one 10b

To a stirred solution of Yb(OTf)$_3$ (359 mg, 0.58 mmol, 3.2 eq.) in THF (14 mL) at −78 °C was added vinylmagnesium bromide (0.58 mL, 1.0 M in THF, 0.58 mmol, 3.2 eq.) and the mixture left for 15 min. Half of the orange coloured solution (7 mL, 0.29 mmol, 1.6 eq.) was then added dropwise *via* cannula to a stirred solution of cyclobutanone **7** (33 mg, 0.18 mmol) in THF (0.4 mL) also at −78 °C. After 20 minutes, the remaining vinylytterbium solution (7 mL, 0.29 mmol, 1.6 eq.) was added to the reaction mixture and the solution stirred for another 20 minutes. Aqueous saturated $NaHCO_3$ (2 mL) was then added followed by citric acid (122 mg, 0.58 mmol, 3.2 eq.). The aqueous layer was separated and extracted with EtOAc (4 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The

residue was then purified by column chromatography (eluting with 20% EtOAc in CH_2Cl_2) to give lactone **10b** (26 mg, 0.12 mmol, 67%) as a clear colourless oil: ν_{max} (soln. in $CHCl_3$)/cm^{-1} 3627br s (OH), 3023s, 1756s (C=O), 1519s, 1425s, 1230s and 1204s; δ_H (400 MHz, $CDCl_3$) 6.02 (1H, dd, *J* 17.3, 11.0, C*H*=CH_2), 5.34 (1H, d, *J* 17.3, *trans* 1H from CH=CH_2), 5.23 (1H, d, *J* 11.0, *cis* 1H from CH=CH_2), 3.80–3.72 (2H, m, CH_2OH), 2.83 (1H, t, *J* 8.2, $(Me)_2CCH_2CH$), 2.67 (1H, t, *J* 7.8, C*H*C(O)), 2.01 (1H, dd, *J* 12.1, 8.8, 1H from $(Me)_2CCH_2$), 1.86–1.68 (2H, m, CH_2CH_2OH), 1.57 (1H, dd, *J* 12.0, 7.6, 1H from $(Me)_2CCH_2$), 1.15 (3H, s, CH_3) and 1.06 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 180.6 (*C*=O), 134.4 (*C*H=CH_2), 116.5 (CH=*C*H_2), 93.2 (*C*OC(O)), 60.7 (*C*H_2OH), 45.5 (*C*HC(O)), 42.3 (*C*$(CH_3)_2$), 39.3 ($(Me)_2CCH_2CH$), 37.4 (CCH_2CH), 34.5 (CH_2CH_2OH), 26.1 (CH_3) and 22.3 (CH_3); *m*/*z* (CI^+ mode, isobutane) 211 (100%), 193 (17), 167 (5), 154 (7), 136 (3), 115 (9), 107 (2) and 79 (2) (Found $(M + H)^+$ 211.1334. $C_{12}H_{19}O_3$ requires 211.1334).

rel-(1*R*,4*R*,5*R*)-4-(2-Hydroxyethyl)-7,7-dimethyl-1-isopropenyl-2-oxabicyclo[3.2.0]heptan-3-one 10c

To a stirred solution of $Yb(OTf)_3$ (184 mg, 0.30 mmol, 2.4 eq.) in dry THF (6.5 mL) at −78 °C was added isopropenylmagnesium bromide (0.67 mL, 0.5 M in THF, 0.33 mmol, 2.7 eq.). After 40 minutes, cyclobutanone **7** (22.5 mg, 0.12 mmol) in THF solution (2.3 mL), was added dropwise, *via* cannula. After a further 2 h, aqueous saturated $NaHCO_3$ (1 mL) and citric acid (62.3 mg, 0.30 mmol, 2.4 eq.) were added, and the mixture stirred for a further 5 minutes before separating and extracting the aqueous layer with Et_2O (4 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Column chromatography of the residue (eluting with 40% EtOAc in petroleum ether (40–60 °C)) gave lactone **10c** (21.7 mg, 0.097 mmol, 78%) as a colourless oil: ν_{max} (soln. in $CHCl_3$)/cm^{-1} 3485w (OH), 3012s, 1756s (C=O), 1519s, 1424s, 1230s, 1010m and 926s; δ_H (400 MHz, $CDCl_3$) 5.04 (1H, s, 1H from CH_2=), 4.88 (1H, s, 1H from CH_2=), 3.85–3.73 (2H, m, CH_2OH), 3.01 (1H, t, *J* 8.2, C*H*$CH_2C(Me)_2$), 2.67 (1H, t, *J* 8.0, C*H*C(O)O), 1.94 (1H, dd, *J* 12.0, 8.9, 1H from C$H_2C(Me)_2$), 1.88–1.70 (2H, m, CH_2CH_2OH), 1.77 (3H, s, CH_3C=), 1.51 (1H, dd, *J* 12.0, 7.5, 1H from C$H_2C(Me)_2$), 1.15 (3H, s, CH_3) and 1.04 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 180.2 (*C*=O), 142.2 (*C*=CH_2), 113.4 (C=*C*H_2), 96.5 (*C*OC(O)), 60.6 (*C*H_2OH), 45.7 (*C*HC(O)), 41.0 (*C*$(Me)_2$), 36.9 (*C*$H_2C(Me)_2$), 36.5 (*C*H$CH_2C(Me)_2$), 34.3 (*C*H_2CH_2OH), 25.1 (*C*H_3), 22.9 (*C*H_3) and 19.0 (*C*H_3C=); *m*/*z* (CI^+ mode, isobutane) 225 (100%), 207 (27), 168 (55), 150 (54), 138 (20), and 115 (30) (Found: $(M + H)^+$ 225.1492. $C_{13}H_{21}O_3$ requires 225.1491).

rel-(1*S*,4*R*,5*R*)-4-(2-Hydroxyethyl)-1-(3-methylbut-3-enyl)-7,7-dimethyl-2-oxabicyclo[3.2.0]heptan-3-one 10d

To a stirred solution of $Yb(OTf)_3$ (170 mg, 0.27 mmol, 2 eq.) in THF (6 mL) at −78 °C was added 3-methylbut-3-enylmagnesium bromide (0.41 mL, 1.0 M in THF, 0.41 mmol, 3 eq.) dropwise and the mixture left for 15 minutes. After that time a solution of cyclobutanone **7** (25 mg, 0.14 mmol) in THF (2.5 mL) also at −78 °C was added to the lilac coloured mixture. The reaction mixture was left at that temperature for 3 h before aqueous saturated $NaHCO_3$ (1 mL) was added followed by citric acid (58 mg, 0.27 mmol, 3.2 eq.). The aqueous layer was then separated and extracted with Et_2O (4 × 15 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo* to give a cloudy, colourless oil. Purification by column chromatography (eluting with 40% EtOAc in petroleum ether (40–60 °C)) gave lactone **10d** (23 mg, 0.09 mmol, 66%) as a clear colourless oil: ν_{max} (soln. in $CHCl_3$)/cm^{-1} 3496m (OH), 2965s, 1751s (C=O), 1467s, 1383s and 1183m; δ_H (400 MHz, $CDCl_3$) 4.73 (1H, s, 1H from CH_2=), 4.68 (1H, s, 1H from CH_2=), 3.87–3.74 (2H, m, CH_2OH), 2.66 (1H, t, *J* 7.8, C*H*CO), 2.53 (1H, t, *J* 7.6, C*H*$CH_2C(Me)_2$), 2.19–2.12 (1H, m, 1H from CH_2CH_2), 2.06–1.88 (4H, m, 1H from C$H_2C(Me)_2$, 1H from CH_2CH_2OH, 1H from CH_2CH_2 and 1H from CH_2CH_2), 1.81–1.64 (2H, m, 1H from CH_2CH_2OH and 1H from CH_2CH_2), 1.74 (3H, s, CH_3C=), 1.50 (1H, dd, *J* 12.2, 6.9, 1H from C$H_2C(Me)_2$), 1.22 (3H, s, CH_3) and 1.11 (3H s, CH_3); δ_C (100 MHz, $CDCl_3$) 181.3 (I=O), 145.3 (*C*=CH_2), 110.1 (C=*C*H_2), 93.9 (*C*OC(O)), 61.0 (*C*H_2OH), 46.4 (*C*HC(O)O), 41.3 (*C*$(Me)_2$), 39.8 (*C*H$CH_2C(Me)_2$), 38.3 (*C*$H_2C(Me)_2$), 35.2 (*C*H_2CH_2OH), 33.2 (CH_2CH_2), 31.7 (*C*H_2CH_2), 25.5 (*C*H_3), 23.7 (*C*H_3) and 22.8 (*C*H_3C=); *m*/*z* (CI^+ mode, isobutane) 253 (100%), 235 (20), 196 (30), 179 (20) and 115 (15) (Found: $(M + H)^+$ 253.1800. $C_{15}H_{25}O_3$ requires 253.1804).

rel-(1*R*,4*R*,5*R*)-4-(2-Hydroxyethyl)-1-[1-(2-benzyloxyethyl)-vinyl]-7,7-dimethyl-2-oxabicyclo[3.2.0]heptan-3-one 10e

To a stirred solution of 1-benzyloxy-3-bromobut-3-ene (102 mg, 0.42 mmol, 2.8 eq.) in THF (1.4 mL) at −78 °C was added *tert*-butyllithium (0.57 mL, 1.48 M in pentane, 0.84 mmol, 5.5 eq.) slowly over 2 min. After 30 min the orange–brown solution was added dropwise to a stirred solution of $Yb(OTf)_3$ (285 mg, 0.46 mmol, 3 eq.) in THF (10 mL) also at −78 °C. After a further 10 min, a solution of cyclobutanone **7** (28 mg, 0.15 mmol) in THF (3.3 mL) at −78 °C was added. After 1 h at −78 °C, aqueous saturated $NaHCO_3$ (1 mL) was added followed by citric acid (97 mg, 0.46 mmol, 3 eq.). The aqueous layer was separated and extracted with Et_2O (4 × 15 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (eluting with 50% EtOAc in petroleum ether (40–60 °C)) gave lactone **10e** (28 mg, 0.08 mmol, 53%) as a clear colourless oil: ν_{max} ($CDCl_3$ soln.)/cm^{-1} 3691m (OH), 3617m, 3154s, 2981s, 2963s, 1758s (C=O), 1641m (C=C), 1604m, 1561m, 1468s and 1382s; δ_H (400 MHz, $CDCl_3$) 7.39–7.28 (5H, m, 5 × Ar*H*), 5.15 (1H, s, 1H from C=CH_2), 5.02 (1H, s, 1H from C=CH_2), 4.55 (AB system, 1H, d, *J* 11.9, 1H from PhCH_2), 4.51 (AB system, 1H, d, *J* 11.9, 1H from PhCH_2), 3.83–3.71 (2H, m, CH_2OH), 3.70–3.59 (2H, m, CH_2OBn), 3.02 (1H, apparent t, *J* 8.2, CMe_2CH_2CH), 2.67 (1H, apparent t, *J* 7.9, C*H*C(O)), 2.51–2.44 (1H, m, 1H from CH_2CH_2OBn), 2.36–2.28 (1H, m, 1H from CH_2CH_2OBn), 1.94 (1H, dd, *J* 12.0, 9.0, 1H from CMe_2CH_2), 1.87–1.66 (2H, m, CH_2CH_2OH), 1.51 (1H, dd, *J* 12.0, 7.5, 1H from CMe_2CH_2), 1.15 (3H, s, CH_3) and 1.02 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 180.2 (*C*=O), 143.4 (*C*=), 138.5 (Ar*C*), 128.6 (2 × Ar*C*H), 127.9 (2 × Ar*C*H), 127.8 (Ar*C*H), 113.8 (=*C*H_2), 96.8 (*C*OC(O)), 73.1 (Ph*C*H_2), 69.0 (*C*H_2O), 60.7 (*C*H_2O), 45.8 (*C*HC(O)), 41.5 (*C*$(CH_3)_2$), 37.1 (CMe_2CH_2), 36.8 (CMe_2CH_2CH), 34.3 (*C*H_2CH_2OH), 31.8 (*C*H_2CH_2OBn), 25.5 (*C*H_3) and 23.1 (*C*H_3); *m*/*z* (CI^+ mode, isobutane) 345 (13%), 327 (13), 270 (11), 253 (20), 235 (49), 223 (19), 197 (22), 167 (11), 149 (11), 138 (16), 109 (11), 91 (100) (Found M^+ 344.1989. $C_{21}H_{28}O_4$ requires 344.1980).

rel-(3*S*)-3-[*rel*-(1*R*)-3,3-Dimethyl-2-oxocyclobutyl]-4,5-dihydrofuran-2(3*H*)-one 11

To a stirred solution of cyclobutanol ***epi*-6** (70 mg, 0.38 mmol) in CH_2Cl_2 (3.8 mL) at room temperature was added 4 Å molecular sieves, *N*-methylmorpholine *N*-oxide (177 mg, 1.51 mmol, 4 eq.), and tetrapropylammonium perruthenate (7 mg, 0.02 mmol, 0.05 eq.). After 5 h, the reaction mixture was poured onto a short column of silica gel and eluted with 50% EtOAc in petroleum ether (40–60 °C). Concentration *in vacuo* gave the cyclobutanone **11** (67 mg, 0.37 mmol, 97%) as a clear colourless oil: ν_{max} ($CHCl_3$ soln.)/cm^{-1} 3028s (C–H), 2949s (C–H), 2875s (C–H), 1756s (lactone C=O), 1709s (ketone C=O), 1656m, 1530m, 1467m, and 1367m; δ_H (400 MHz, $CDCl_3$) 4.37 (1H, td, *J* 8.8, 2.9, 1H from CH_2O), 4.21 (1H, dt, *J* 9.3, 6.7, 1H

from CH_2O), 3.66–3.60 (1H, m, CCH_2CH), 2.89–2.82 (1H, m, $CHC(O)O$), 2.49–2.41 (1H, m, 1H from CH_2CH_2O), 2.18 (1H, apparent t, *J* 11.2, 1H from CCH_2CH), 2.15–2.04 (1H, m, 1H from CH_2CH_2O), 1.78 (1H, dd, *J* 11.2, 8.4, 1H from CCH_2CH), 1.27 (3H, s, CH_3) and 1.19 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 214.4 (*C*=O, ketone), 177.2 (*C*=O, ester), 67.0 (CH_2O), 58.5 ($C(CH_3)_2$), 54.2 (CCH_2CH), 39.6 ($CHC(O)O$), 31.5 (CCH_2CH), 27.3 (CH_2CH_2O), 24.1 (CH_3) and 21.9 (CH_3); *m*/*z* (CI^+ mode, isobutane) 182 (22%), 154 (9), 126 (27), 111 (12), 83 (36), 70 (100) and 41 (21) (Found M^+, 182.0943. $C_{10}H_{14}O_3$ requires 182.0939).

3-(*tert*-Butyldiphenylsilyl)but-3-en-1-ol 13

To a stirred solution of bromide **12**[15] (117 mg, 0.30 mmol) in THF (9.4 mL) at −78 °C was added *tert*-butyllithium (0.46 mL, 1.32 M in pentane, 0.60 mmol, 2 eq.). After 1.5 h aqueous saturated $NaHCO_3$ (1 mL) was added at −78 °C and the aqueous layer separated and extracted with Et_2O (4 × 10 mL). The combined organic layers were then dried ($MgSO_4$) and concentrated *in vacuo* to give the crude vinylsilane **13** (93 mg, 0.30 mmol, 100%) as a cloudy colourless oil (Found: C, 77.26; H 8.43. $C_{20}H_{26}OSi$ requires C, 77.36; H, 8.44%); ν_{max} ($CHCl_3$ soln.)/cm^{-1} 3616m (O–H), 3022s (C–H), 2965s (C–H), 2949s (C–H), 2933s (C–H), 1604m (C=C), 1525s, 1472s, 1367m ($C(CH_3)_2$) and 1335m ($C(CH_3)_2$); δ_H (400 MHz, $CDCl_3$) 7.63–7.61 (4H, m, 4 × *o*Ar*H*), 7.44–7.35 (6H, m, 4 × *m*Ar*H* and 2 × *p*Ar*H*), 6.06 (1H, d, *J* 2.6, 1H from C=CH_2), 5.78 (1H, d, *J* 2.6, 1H from C=CH_2), 3.55 (2H, t, *J* 6.7, CH_2OH), 2.47 (2H, t, *J* 6.7, CH_2CH_2OH), 1.32 (1H, br s, O*H*) and 1.17 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 143.4 (*C*=CH_2), 136.4 (4 × *o*Ar*C*H), 134.5 (2 × Ar*C*), 131.9 (C=*C*H_2), 129.4 (2 × *p*Ar*C*H), 127.9 (4 × *m*Ar*C*H), 61.6 (CH_2OH), 40.4 (CH_2CH_2O), 28.8 ($C(CH_3)_3$) and 18.7 ($C(CH_3)_3$); *m*/*z* (FAB^+ mode, sodium) 333 (28%), 253 (73), 199 (100), 175 (33), 135 (52) and 105 (15) (Found $(M + Na)^+$, 333.1647. $C_{20}H_{26}OSiNa$ requires *M*, 333.1644).

p-Nitrobenzoic acid-2-[*rel*-(1*S*,4*R*,5*R*)-1,7,7-trimethyl-2-oxa-3-oxobicyclo[3.2.0]hept-4-yl]ethyl ester 14

To a stirred solution of **10a** (15 mg, 0.08 mmol) in pyridine (0.5 mL) at room temperature was added *p*-nitrobenzoyl chloride (21 mg, 0.12 mmol, 1.5 eq.) and the reaction mixture stirred at that temperature for 3.5 days. Aqueous saturated $NaHCO_3$ (1 mL) was then added and the aqueous layer separated and extracted with $CHCl_3$ (4 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give crude **14** as a yellow solid (23 mg, 0.07 mmol, 88%). Recrystallisation from EtOH gave white crystals suitable for crystallographic analysis (mp 146–147 °C) (Found: C, 62.29; H, 6.10; N, 3.91. $C_{18}H_{21}O_6N$ requires, C, 62.24; H, 6.09; N, 4.03%); ν_{max} ($CDCl_3$ soln.)/cm^{-1} 3154s, 2980s (C–H), 2933s (C–H), 2902s (C–H), 2870m (C–H), 1756s (C=O, lactone), 1724s (C=O, ester), 1646m, 1614m, 1567m (NO_2), 1530s (NO_2) and 1383s (NO_2); δ_H (400 MHz, $CDCl_3$) 8.31–8.29 (2H, apparent d, *J* 8.8, 2 × Ar*H*), 8.22–8.20 (2H, apparent d, *J* 8.8, 2 × Ar*H*), 4.56–4.46 (2H, m, CH_2O), 2.66–2.58 (2H, m, 1H from COC*H* and 1H from CCH_2CH), 2.24–2.16 (1H, m, 1H from CH_2CH_2OH), 2.08–1.96 (2H, m, 1H from CCH_2CH and 1H from CH_2CH_2OH), 1.55 (1H, dd, *J* 12.2, 7.0, 1H from CCH_2CH), 1.37 (3H, s, $CH_3COC(O)$), 1.16 (3H, s, 3H from $C(CH_3)_2$), and 1.06 (3H, s, 3H from $C(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 179.5 (*C*=O, lactone), 164.5 (*C*=O, ester), 150.6 (Ar*C*), 135.4 (Ar*C*), 131.0 (2 × Ar*C*H), 123.8 (2 × Ar*C*H), 91.8 (CCH_3), 63.4 (CH_2CH_2O), 46.0 ($CHCO$), 41.0 ($C(CH_3)_2$), 40.2 (CCH_2CH), 38.1 (CCH_2CH), 31.4 (CH_2CH_2O), 25.8 (CCH_3), 22.5 ($C(CH_3)_2$) and 19.8 ($C(CH_3)_2$); *m*/*z* (CI^+ mode, isobutane) 348 (100%), 318 (6), 291 (2), 181 (5), 163 (2) and 150 (2) (Found $(M + H)^+$, 348.1450. $C_{18}H_{22}O_6N$ requires 348.1441).

rel-(1*S*,4*R*,5*R*)-4-(2-*tert*-Butyldiphenylsilyloxyethyl)-7,7-dimethyl-1-vinyl-2-oxabicyclo[3.2.0]heptan-3-one 15

To a stirred solution of **10b** (9 mg, 0.04 mmol) in DMF (0.2 mL) at room temperature was added imidazole (9 mg, 0.13 mmol, 3.3 eq.) and TBDPSCl (17 µl, 0.07 mmol, 1.8 eq.). After 43 h a further quantity of imidazole (4 mg, 0.06 mmol, 1.5 eq.) and TBDPSCl (8 µl, 0.03 mmol, 0.75 eq.) was added. After a further 12 h, aqueous saturated $NaHCO_3$ (0.5 mL) was added and the aqueous layer extracted with 50% EtOAc in petroleum ether (40–60 °C). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a cloudy oil. Purification by column chromatography (eluting with 5% EtOAc in petroleum ether (40–60 °C)) gave **15** as a clear, colourless oil (14 mg, 0.03 mmol, 73%): ν_{max} (soln. in $CHCl_3$)/cm^{-1} 2990m, 1762m (C=O), 1475s, 1387s and 1099s; δ_H (400 MHz, $CDCl_3$) 7.67–7.63 (4H, m, 4 × Ar*H*), 7.47–7.37 (6H, m, 6 × Ar*H*), 5.95 (1H, dd, *J* 17.3, 11.0, C*H*=CH_2), 5.27 (1H, dd, *J* 17.3, 1.3, *trans* 1H from CH=CH_2), 5.16 (1H, dd, *J* 11.0, 1.3, *cis* 1H from CH=CH_2), 3.80–3.74 (1H, m, 1H from CH_2OH), 3.71–3.66 (1H, m, 1H from CH_2OH), 2.84 (1H, t, *J* 8.2, $(Me)_2CCH_2CH$), 2.68 (1H, dd, *J* 10.3, 4.9, C*H*C(O)), 2.00–1.91 (2H, m, 1H from CH_2CH_2OH and 1H from $(Me)_2CCH_2$), 1.60–1.52 (2H, m, 1H from CH_2CH_2OH and 1H from $(Me)_2CCH_2$), 1.11 (3H, s, CH_3), 1.06 (9H, s, $C(CH_3)_3$) and 1.05 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 180.5 (*C*=O), 135.7 (4 × Ar*C*H), 134.5 (*C*H=), 133.6 (2 × Ar*C*), 129.9 (2 × Ar*C*H), 127.9 (4 × Ar*C*H), 116.3 (=CH_2), 92.7 (*C*OC(O)), 61.9 (CH_2OH), 45.4 (*C*HC(O)), 42.1 ($C(CH_3)_2$), 38.3 ($(Me)_2CCH_2CH$), 37.4 ($(Me)_2CCH_2$), 34.2 (CH_2CH_2OH), 27.0 (3 × $C(CH_3)_3$), 26.1 (CH_3), 22.3 (CH_3) and 20.0 (*C*Si); *m*/*z* (CI^+ mode, isobutane) 449 (27%), 391 (30), 371 (100), 335 (7), 293 (4), 199 (6) and 107 (3) (Found $(M + H)^+$, 449.2513. $C_{28}H_{37}O_3Si$ requires 449.2512).

rel-(1*S*,3*R*,4*R*,5*R*)-4-(2-*tert*-Butyldiphenylsilyloxyethyl)-7,7-dimethyl-1-vinyl-2-oxabicyclo[3.2.0]heptan-3-ol 16

To a stirred solution of **15** (39 mg, 0.09 mmol) in CH_2Cl_2 (0.45 mL) at −78 °C was added DIBAL-H (76 µl, 1.5 M in toluene, 0.11 mmol, 1.2 eq.) dropwise. After 3.5 h, aqueous saturated $NaHCO_3$ (1 mL) was added and the aqueous layer separated and extracted with CH_2Cl_2 (3 × 10 mL) and dried ($MgSO_4$). Concentration *in vacuo* gave a 2 : 1 mixture of lactols as a clear, colourless oil [diastereoisomers were inseparable by chromatography] (34 mg, 0.08 mmol, 86%): ν_{max} (soln. in $CHCl_3$)/cm^{-1} 3603m (OH), 1643m, 1464s, 1380s and 1094s; δ_H (400 MHz, $CDCl_3$) 7.69–7.65 (8H, m, 4 × Ar*H* of major and 4 × Ar*H* of minor), 7.46–7.38 (12H, m, 6 × Ar*H* of major and 6 × Ar*H* of minor), 6.10 (1H, dd, *J* 17.3, 10.8, C*H*=CH_2 of minor), 5.97 (1H, dd, *J* 17.2, 10.8, C*H*=CH_2 of major), 5.69 (1H, dd, *J* 6.6, 5.0, C*H*OH of minor), 5.50 (1H, dd, *J* 3.7, 1.2, C*H*OH of major), 5.26 (1H, dd, *J* 17.3, 1.9, *trans* 1H from CH=CH_2 of minor), 5.18 (1H, dd, *J* 17.2, 2.0, *trans* 1H from CH=CH_2 of major), 5.10 (1H, dd, *J* 10.8, 1.9, *cis* 1H from CH=CH_2 of minor), 5.03 (1H, dd, *J* 10.8, 2.0, *cis* 1H from CH=CH_2 of major), 3.74–3.65 (4H, m, 2H from CH_2O of major, 2H from CH_2O of minor), 3.08 (1H, d, *J* 6.6, O*H* of minor), 2.93 (1H, d, *J* 3.7, O*H* of major), 2.58–2.51 (2H, m, $(Me)_2CCH_2CH$ of major and $(Me)_2CCH_2CH$ of minor), 2.37–2.25 (1H, m, C*H*CHOH of minor), 2.20 (1H, t, *J* 7.7, C*H*CHOH of major), 2.03 (1H, dd, *J* 11.4, 7.6, 1H from $(Me)_2CCH_2$ of major), 1.87–1.79 (2H, m, 1H from CH_2CH_2OH, 1H from $(Me)_2CCH_2$ both minor), 1.72 (1H, dd, *J* 11.4, 9.0, 1H from $(Me)_2CCH_2$ of major), 1.68–1.59 (1H, m, 1H from CH_2CH_2OH of major), 1.52–1.41 (3H, m, 1H from CH_2CH_2OH of major, 1H from CH_2CH_2OH of minor and 1H from $(Me)_2CCH_2$ of minor), 1.06 (18H, s, 9H from $C(CH_3)_3$ of major, 9H from $C(CH_3)_3$ of minor), 1.07–1.05 (9H, obscured singlets, 6H from $C(CH_3)_2$ of major, 3H from $C(CH_3)_2$ from minor) and 1.01 (3H, s, 3H from $C(CH_3)_2$ of minor); δ_C (100 MHz, $CDCl_3$) 138.8 (H*C*=, minor), 137.8 (H*C*=, major), 135.6 (8 × Ar*C*H, major and minor), 133.8

(2 × Ar*C*, major), 133.5 (2 × Ar*C*, minor), 129.7 (2 × Ar*C*H, minor), 129.6 (2 × Ar*C*H, major), 127.7 (4 × Ar*C*H, major), 127.6 (4 × Ar*C*H, minor), 113.4 (=*C*H_2, major), 113.3 (=*C*H_2, minor), 107.7 (*C*HOH, major), 102.1 (*C*HOH, minor), 94.7 (*C*(O)CH(OH), major), 90.3 (*C*(O)CH(OH), minor), 62.9 (*C*H_2O, minor), 62.5 (*C*H_2O, major), 49.5 (*C*HCHOH, major), 48.6 (*C*HCHOH, minor), 42.3 ((Me)$_2$CCH$_2$*C*H, major), 41.5 ((Me)$_2$CCH$_2$*C*H, minor), 40.4 ((Me)$_2$*C*, minor), 39.3 ((Me)$_2$*C*, major), 37.1 ((Me)$_2$C*C*H$_2$, minor), 36.4 ((Me)$_2$C*C*H$_2$, major), 35.2 (*C*H$_2$CH$_2$O, major), 31.6 (*C*H$_2$CH$_2$O, minor), 27.3 (*C*H$_3$, major), 26.8 (6 × SiC(*C*H$_3$)$_3$, major and minor, *C*H$_3$ minor), 23.4 (*C*H$_3$, minor), 22.5 (*C*H$_3$, major) and 19.2 (2 × *C*Si, major and minor); *m/z* (FAB$^+$ mode, sodium) 473 (40%), 433 (60), 319 (35), 199 (95), 177 (72), 135 (100) and 107 (48) (Found: (M + Na)$^+$ 473.2490. $C_{28}H_{38}O_3SiNa$ requires 473.2488).

rel-(1*S*,4*R*,5*R*)-4-(2-*tert*-Butyldimethylsilyloxyethyl)-7,7-dimethyl-1-vinyl-2-oxabicyclo[3.2.0]heptan-3-one 17

To a solution of alcohol **10b** (54 mg, 0.26 mmol) in DMF (0.3 mL) at room temperature was added imidazole (105 mg, 1.54 mmol, 6 eq.) and TBDMSCl (116 mg, 0.77 mmol, 3 eq.) and the mixture stirred for 90 minutes before quenching with water (2 mL). The layers were separated and the aqueous layer extracted with Et$_2$O (3 × 10 mL) and the combined organic layers dried (MgSO$_4$) and concentrated. Column chromatography (25% EtOAc in petroleum ether (40–60 °C)) gave **17** (50 mg, 0.15 mmol, 60%) as a colourless oil: ν_{max}(film)/cm^{-1} 3070m (C–H), 3049m (C–H), 2957s (C–H), 2931s (C–H), 2858s (C–H), 1771s (C=O), 1472m, 1449w, 1428s, 1389w, 1111m; δ_H (400 MHz, CDCl$_3$): 6.01 (1H, dd, *J* 17.2, 11.2, C*H*=CH$_2$), 5.33 (1H, dd, *J* 17.2, 1.2, *trans* 1H from CH=C*H*$_2$), 5.21 (1H, dd, *J* 11.2, 1.2, *cis* 1H from CH=C*H*$_2$), 3.76–3.65 (1H, m, 2H from C*H*$_2$OTBDMS), 2.91 (1H, t, *J* 8.4, CH$_2$C*H*CHC(O)), 2.61 (1H, dd, *J* 9.2, 5.6, C*H*C(O)), 1.98 (1H, dd, *J* 12.0, 8.8, 1H from CMe$_2$C*H*$_2$), 1.92–1.84 (1H, m, 1H from C*H*$_2$CH$_2$OTBDMS), 1.61–1.53 (2H, m, 1H from C*H*$_2$CH$_2$OTBMS and 1H from CMe$_2$C*H*$_2$), 1.14 (3H, s, C*H*$_3$), 1.06 (3H, s, C*H*$_3$), 0.90 (9H, s, C(C*H*$_3$)$_3$), 0.06 (3H, s, C*H*$_3$Si) and 0.05 (3H, s, C*H*$_3$Si); δ_C (100 MHz, CDCl$_3$) 180.3 (*C*=O), 134.4 (*C*H=), 116.1 (=*C*H$_2$), 92.5 (*C*OC(O)), 60.8 (*C*H$_2$OTBDMS), 45.2 (*C*HC(O)), 41.9 (*C*(CH$_3$)$_2$), 38.4 (CMe$_2$CH$_2$*C*H), 37.2 (CMe$_2$*C*H$_2$), 34.3 (*C*H$_2$CH$_2$OTBDMS), 25.9 (C(*C*H$_3$)$_3$), 25.7 (*C*H$_3$), 22.2 (*C*H$_3$), 18.2 (*C*(CH$_3$)$_3$), −5.4 (*C*H$_3$Si) and −5.4 (*C*H$_3$Si); *m/z* (CI mode, isobutane) 326 (26%), 325 (100), 307 (10), 267 (30), 211 (11) (Found (M + H)$^+$, 325.2197. $C_{18}H_{33}O_3Si$ requires 325.2199).

rel-(1*S*,4*R*,5*R*)-4-(2-*tert*-Butyldimethylsilyloxyethyl)-7,7-dimethyl-1-[*rel*-(1*R*)-1,2-dihydroxyethyl]-2-oxabicyclo[3.2.0]-heptan-3-one 18a and *rel*-(1*S*,4*R*,5*R*)-4-(2-*tert*-butyldimethylsilyloxyethyl)-7,7-dimethyl-1-[*rel*-(1*S*)-1,2-dihydroxyethyl]-2-oxabicyclo[3.2.0]heptan-3-one 18b

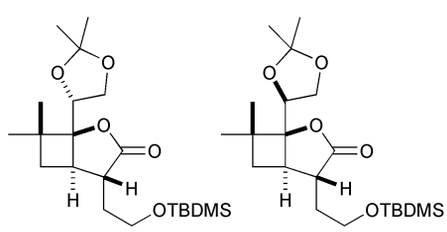
To a stirred solution of K_2CO_3 (49 mg, 0.35 mmol, 3 eq.), $K_3Fe(CN)_6$ (118 mg, 0.36 mmol, 3 eq.) and pyridine (2 μL, 0.013 mmol) in water (1.5 mL) was added ^{t}BuOH (1.0 mL) and OsO_4 (76 μL, 5% in ^{t}BuOH, 0.012 mmol, 0.1 eq.). The mixture was cooled to 0 °C before the addition of alkene **17** (39 mg, 0.12 mmol) in ^{t}BuOH–Et$_2$O (2 : 1, 1.5 mL) *via* syringe. The mixture was stirred overnight at 0 °C before the addition of Na_2SO_3 (245 mg, 1.94 mmol, 16 eq.), after which the mixture was stirred for a further 45 minutes. The aqueous mixture was then extracted with EtOAc (3 × 5 mL) and the combined organics dried (MgSO$_4$) and concentrated. Column chromatography (25% EtOAc in petroleum ether (40–60 °C)) of the residue gave diols **18a** and **18b** (36 mg, 0.10 mmol, 84%, 2 : 1 mixture of diastereoisomers): ν_{max}(KBr)/cm^{-1} 3407m (O–H), 2928m (C–H), 2955m (C–H), 1775s (C=O), 1731s (C=O), 1472s, 1191s, 1075s; *m/z* (CI mode, isobutane) 360 (26%), 359 (100), 301 (20) (Found (M + H)$^+$, 359.2253. $C_{18}H_{35}O_5Si$ requires 359.2254).

The diastereomers were separated by fractional crystallisation (EtOAc and petroleum ether (40–60 °C)) to give **18a** as white needles suitable for X-ray crystallography (mp 132 °C), and **18b** as a colourless oil.

18a: δ_H (400 MHz, CDCl$_3$): 3.95 (1H, dt, *J* 6.4, 3.6, 1H from C*H*OH), 3.82–3.68 (4H, m, 2H from C*H*$_2$OH and 2H from C*H*$_2$OTBDMS), 2.88 (1H, t, *J* 7.6, 1H from CH$_2$C*H*CHC(O)), 2.70 (1H, d, *J* 6.4, 1H from OH), 2.63 (1H, dd, *J* 8.8, 4.8, C*H*C(O)), 2.06 (1H, dd, *J* 12.0, 9.2, 1H from CMe$_2$C*H*$_2$), 2.01–1.95 (2H, m, 2H from C*H*$_2$CH$_2$OTBDMS), 1.51 (1H, dd, *J* 12.4, 7.2, 1H from CMe$_2$C*H*$_2$), 1.23 (3H, s, C*H*$_3$), 1.08 (3H, s, C*H*$_3$), 0.91 (9H, s, C(C*H*$_3$)$_3$), 0.08 (3H, s, C*H*$_3$Si) and 0.07 (3H, s, C*H*$_3$Si); δ_C (100 MHz, CDCl$_3$) 181.1 (*C*=O), 93.1 (*C*OC(O)), 71.1 (*C*HOH), 62.7 (*C*H$_2$OH), 60.9 (*C*H$_2$OTBDMS), 45.3 (*C*HC(O)), 39.9 (*C*(CH$_3$)$_2$), 38.7 (CMe$_2$*C*H$_2$), 36.6 (CMe$_2$-CH$_2$*C*H), 33.6 (*C*H$_2$CH$_2$OTBDMS), 25.9 (C(*C*H$_3$)$_3$), 25.6 (*C*H$_3$), 23.1 (*C*H$_3$), 18.3 (*C*(CH$_3$)$_3$), −5.4 (*C*H$_3$Si) and −5.5 (*C*H$_3$Si). **18b**: δ_H (400 MHz, CDCl$_3$): 3.98 (1H, m, 1H from C*H*OH), 3.82–3.68 (3H, m, 1H from C*H*$_2$OH and 2H from C*H*$_2$OTBDMS), 3.60 (1H, m, 1H from C*H*$_2$OH), 2.80 (1H, m, 1H from CH$_2$C*H*CHC(O)), 2.70 (1H, m, C*H*C(O)), 2.10–1.95 (3H, m, 1H from CMe$_2$C*H*$_2$ and 2H from C*H*$_2$CH$_2$OTBMS), 1.50 (1H, m, 1H from CMe$_2$C*H*$_2$), 1.35 (3H, s, C*H*$_3$), 1.14 (3H, s, C*H*$_3$), 0.91 (9H, s, C(C*H*$_3$)$_3$), 0.07 (3H, s, C*H*$_3$Si) and 0.06 (3H, s, C*H*$_3$Si); δ_C (100 MHz, CDCl$_3$) 180.5 (*C*=O), 91.8 (*C*OC(O)), 73.0 (*C*HOH), 62.6 (*C*H$_2$OH), 60.9 (*C*H$_2$OTBDMS), 46.0 (*C*HC(O)), 41.3 (*C*(CH$_3$)$_2$), 39.1 (CMe$_2$*C*H$_2$), 35.5 (CMe$_2$-CH$_2$*C*H), 34.4 (*C*H$_2$CH$_2$OTBDMS), 25.9 (C(*C*H$_3$)$_3$), 25.9 (*C*H$_3$), 24.0 (*C*H$_3$), 18.2 (*C*(CH$_3$)$_3$), −5.39 (*C*H$_3$Si) and −5.41 (*C*H$_3$Si).

Crystal data for 18a§. $C_{18}H_{34}O_5Si$, *M* = 358.54, triclinic, *a* = 12.6770(2), *b* = 12.7397(2), *c* = 13.0974(2) Å, *α* = 102.147(1), *β* = 95.218(1), *γ* = 91.166(1)°, *U* = 2057.62(6) Å^3, *T* = 100(2) K, space group *P*-1 (no. 2), *Z* = 4, *μ*(Mo–K$_α$) = 0.14 mm^{-1}, θ_{max} = 27.5°, 31303 intensity measurements, all 9393 unique reflections (R_{int} = 0.028) gave *R*(*F*) = 0.049, *wR*(*F*^{2}) = 0.094, |Δ*ρ*| < 0.53 e Å^{-3}.

rel-(1*S*,4*R*,5*R*)-4-(*tert*-Butyldimethylsilyloxyethyl)-1-[*rel*-(4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl]-7,7-dimethyl-2-oxabicyclo-[3.2.0]heptan-3-one and *rel*-(1*S*,4*R*,5*R*)-4-(*tert*-butyldimethylsilyloxyethyl)-1-[*rel*-(4*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl]-7,7-dimethyl-2-oxabicyclo[3.2.0]heptan-3-one



To a stirred solution of **18a/18b** (52 mg, 0.15 mmol, 2 : 1 mixture of diastereoisomers) in acetone (2.5 mL) at room temperature, was added 2,2-dimethoxypropane (178 μL, 1.45 mmol, 10 eq.) followed by camphor sulfonic acid (1.1 ml, 3 mg mL^{-1} in acetone, 0.014 mmol, 0.1 eq.). The solution was stirred for 40 minutes before removal of the solvent *in vacuo*. The residue was purified by column chromatography (25% to 50% EtOAc in petroleum ether (40–60 °C)) to give *rel*-(1*S*,4*R*,5*R*)-4-(*tert*-butyldimethylsilyloxyethyl)-1-(*rel*-(4*R*/*S*)-2,2-dimethyl-[1,3]-dioxolan-4-yl)-7,7-dimethyl-2-oxabicyclo[3.2.0]heptan-3-one (55 mg, 0.138 mmol, 95%, 2 : 1 mixture of diastereomers) as a white solid: ν_{max} (KBr)/cm^{-1} 2958s (C–H), 2929s (C–H), 2856m

§ CCDC reference number 194435. See http://www.rsc.org/suppdata/ob/b2/b209066j/ for crystallographic files in .cif or other electronic format.

(C–H), 1762s (C=O)s, 1471m, 1369m, 1280m, 1259s, 1103s, 1085s; *m*/*z* (CI mode, isobutane) 400 (30%), 399 (100), 341 (78) (Found (M + H)$^+$, 399.2565. $C_{21}H_{39}O_5Si$ requires 399.2567). **Major**: δ_H (400 MHz, $CDCl_3$): 4.34 (1H, t, *J* 7.1, 1H from C*H*($OCMe_2$)), 4.02 (1H, dd, *J* 8.1, 6.8, 1H from CH_2($OCMe_2$)), 3.88 (1H, t, *J* 7.8, 1H from CH_2($OCMe_2$)), 3.78 (1H, m, 1H from CH_2OTBDMS), 3.67 (1H, m, 1H from CH_2OTBDMS), 2.80 (1H, t, *J* 8.7, 1H from $CH_2CHCHC(O)$), 2.63 (1H, dd, *J* 10.0, 4.8, C*H*C(O)), 2.06 (1H, dd, *J* 12.1, 9.1, 1H from CMe_2CH_2), 2.02–1.97 (1H, m, 1H from CH_2CH_2OTBMS), 1.90–1.82 (1H, m, 1H from CH_2CH_2OTBMS), 1.56 (1H, m, 1H from CMe_2CH_2), 1.36 (6H, s, 6H from C(CH_3)$_2$), 1.19 (3H, s, CH_3), 1.06 (3H, s, CH_3), 0.91 (9H, s, C(CH_3)$_3$), 0.07 (3H, s, CH_3Si) and 0.06 (3H, s, CH_3Si); δ_C (100 MHz, $CDCl_3$) 181.1 (*C*=O), 109.4 (CMe_2O_2), 89.9 (*C*OC(O)), 75.7 (*C*H($OCMe_2$)), 64.4 (*C*H_2($OCMe_2$)), 61.1 (*C*H_2OTBDMS), 45.4 (*C*HC(O)), 39.6 (*C*(CH_3)$_2$), 38.6 (CMe_2CH_2), 36.9 (CMe_2CH_2CH), 33.7 (*C*H_2CH_2OTBDMS), 25.9 (C(*C*H_3)$_3$), 25.8 (*C*H_3), 25.7 (*C*H_3), 25.6 (*C*H_3), 23.2 (*C*H_3), 18.3 (*C*(CH_3)$_3$), −5.3 (*C*H_3Si) and −5.4 (*C*H_3Si). **Minor**: δ_H (400 MHz, $CDCl_3$): 4.35 (1H, m, 1H from C*H*($OCMe_2$)), 4.01 (1H, m, 1H from CH_2($OCMe_2$)), 3.79 (2H, m, 1H from CH_2($OCMe_2$) and 1H from CH_2OTBDMS), 3.67 (1H, m, 1H from CH_2OTBDMS), 2.70 (1H, dt, *J* 8.8, 6.8, 1H from $CH_2CHCHC(O)$), 2.63 (1H, m, C*H*C(O)), 2.03 (2H, m, 1H from CMe_2CH_2 and 1H from CH_2CH_2OTBMS), 1.86 (1H, m, 1H from CH_2CH_2OTBMS), 1.55 (1H, m, 1H from CMe_2CH_2), 1.42 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.12 (3H, s, CH_3), 0.91 (9H, s, C(CH_3)$_3$), 0.07 (3H, s, CH_3Si) and 0.06 (3H, s, CH_3Si); δ_C (100 MHz, $CDCl_3$) 180.6 (*C*=O), 109.2 (CMe_2O_2), 90.1 (*C*OC(O)), 76.3 (*C*H($OCMe_2$)), 64.8 (*C*H_2($OCMe_2$)), 60.9 (*C*H_2OTBDMS), 45.7 (*C*HC(O)), 41.1 (*C*(CH_3)$_2$), 38.8 (CMe_2CH_2), 35.9 (CMe_2CH_2CH), 34.4 (*C*H_2CH_2OTBDMS), 26.0 (*C*H_3), 25.9 (C(*C*H_3)$_3$), 25.3 (*C*H_3), 25.2 (*C*H_3), 24.0 (*C*H_3), 18.2 (*C*(CH_3)$_3$), −5.3 (*C*H_3Si) and −5.4 (*C*H_3Si).

rel-(1*S*,4*R*,5*R*)-4-(2-Hydroxyethyl)-1-[*rel*-(4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl]-7,7-dimethyl-2-oxabicyclo[3.2.0]heptan-3-one 19a and *rel*-(1*S*,4*R*,5*R*)-4-(2-hydroxyethyl)-1-[*rel*-(4*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl]-7,7-dimethyl-2-oxabicyclo[3.2.0]-heptan-3-one 19b

To a stirred solution of *rel*-(1*S*,4*R*,5*R*)-4-(*tert*-butyldimethylsilyloxyethyl)-1-(*rel*-(4*R*/*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-7,7-dimethyl-2-oxabicyclo[3.2.0]heptan-3-one (55 mg, 0.14 mmol, 3 : 1 mixture of diastereomers) in THF (1.0 mL) at room temperature, was added pyridine (0.10 mL) followed by HF–pyridine complex (50 μL, approx. 1.35 mmol). The reaction mixture was stirred for 2 h, after which silica gel (200 mg) was added and the solvent removed *in vacuo*. Direct purification by column chromatography (50% to 80% EtOAc in petroleum ether (40–60 °C)) gave the alcohols **19a** (26 mg, 0.091 mmol, 66%) and **19b** (4.6 mg, 0.016 mmol, 12%) as colourless oils: *m*/*z* (CI mode, isobutane) 286 (17%), 285 (100), 227 (47), 209 (50) (Found (M + H)$^+$, 285.1701. $C_{15}H_{24}O_5$ requires 285.1702).

19a: ν_{max} (KBr)/cm^{-1} 3487s (O–H), 2985m (C–H), 2974m (C–H), 2952m (C–H), 2865w (C–H), 1762s (C=O), 1465m, 1261s, 1207s, 1193s, 1094s, 1064s; δ_H (400 MHz, $CDCl_3$): 4.36 (1H, t, *J* 7.2, 1H from C*H*($OCMe_2$)), 4.04 (1H, dd, *J* 8.0, 7.2, 1H from CH_2($OCMe_2$)), 3.88 (1H, t, *J* 8.0, 1H from CH_2($OCMe_2$)), 3.82 (1H, m, 1H from CH_2OH), 3.72 (1H, m, 1H from CH_2OH), 2.78 (1H, ddd, *J* 8.8, 7.2, 1.2, CH_2-C*H*CHC(O)), 2.68 (1H, t, *J* 7.2, C*H*C(O)), 2.28 (1H, br s, O*H*), 2.09 (1H, dd, *J* 12.4, 9.2, 1H from CMe_2CH_2), 2.07–2.01 (1H, m, 1H from CH_2CH_2OH), 1.96–1.88 (1H, m, 1H from CH_2CH_2OH), 1.57 (1H, dd, *J* 12.4, 7.6, 1H from CMe_2CH_2), 1.37 (6H, s, CH_3), 1.19 (3H, s, CH_3) and 1.06 (6H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 181.1 (*C*=O), 109.5 (CMe_2O_2), 90.3 (*C*OC(O)), 75.7 (*C*H($OCMe_2$)), 64.6 (*C*H_2O($OCMe_2$)), 60.9 (*C*H_2OH), 46.0 (*C*HC(O)), 39.7 (*C*(CH_3)$_2$), 38.6 (CMe_2CH_2), 37.6 (CMe_2CH_2CH), 33.7 (*C*H_2CH_2OH), 25.9 (*C*H_3), 25.7 (*C*H_3), 25.6 (*C*H_3) and 23.25 (*C*H_3). **19b**: ν_{max} (KBr)/cm^{-1} 3503m (O–H), 2964m (C–H), 2936m (C–H), 2887m (C–H), 1742s (C=O), 1452m, 1382s, 1371s, 1261s, 1225s, 1059s; δ_H (400 MHz, $CDCl_3$): 4.36 (1H, dd, *J* 7.6, 6.4, 1H from C*H*($OCMe_2$)), 4.04 (1H, dd, *J* 8.0, 6.8, 1H from CH_2($OCMe_2$)), 3.85 (1H, m, 1H from CH_2OH), 3.77 (1H, m, 1H from CH_2OH), 3.73 (1H, t, 1H from CH_2($OCMe_2$)), 2.72–2.64 (2H, m, 1H from CH_2CH-CHC(O) and 1H from C*H*C(O)), 2.08 (1H, dd, *J* 12.0, 9.2, 1H from CMe_2CH_2), 2.07 (1H, t, *J* 2.4, O*H*), 1.91 (1H, m, 1H from CH_2CH_2OH), 1.75 (1H, m, 1H from CH_2CH_2OH), 1.56 (1H, dd, *J* 12.4, 6.8, 1H from CMe_2CH_2), 1.44 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.27 (3H, s, CH_3) and 1.14 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 180.7 (*C*=O), 109.2 (CMe_2O_2), 90.8 (*C*OC(O)), 76.1 (*C*H($OCMe_2$)), 64.9 (*C*H_2($OCMe_2$)), 60.6 (*C*H_2OH), 45.9 (*C*HC(O)), 41.2 (*C*(CH_3)$_2$), 38.7 (CMe_2CH_2), 36.5 (CMe_2-CH_2CH), 34.5 (*C*H_2CH_2OH), 26.0 (*C*H_3), 25.2 (*C*H_3), 25.2 (*C*H_3) and 24.1 (*C*H_3).

2-[*rel*-(1*S*,4*R*,5*R*)-1-(*rel*-(4*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-7,7-dimethyl-3-oxo-2-oxabicyclo[3.2.0]heptan-4-yl]ethanal 20

To a stirred solution of alcohol **19b** (4.7 mg, 0.017 mmol) in CH_2Cl_2 (1.0 mL) was added 4 Å MS (5 mg). The mixture was cooled to 0 °C, PCC (30 mg, 0.14 mmol, 8 eq.) was added and the mixture stirred for 4.5 h. The crude mixture was then passed through a short silica plug (eluting with 50% EtOAc in petroleum ether (40–60 °C)) to give **20** (3.2 mg, 0.011 mmol, 69%) as a white solid (mp 131–132 °C, EtOAc–petroleum ether 1 : 1): ν_{max} (KBr)/cm^{-1} 2961m (C–H), 2927m (C–H), 2854m (C–H), 1759s (C=O lactone), 1718s (C=O aldehyde), 1261s, 1076s, 1028s, 800s; δ_H (400 MHz, $CDCl_3$): 9.80 (1H, s, C*H*O), 4.35 (1H, dd, *J* 8.0, 6.4, C*H*($OCMe_2$)), 4.06 (1H, dd, *J* 8.0, 6.4 1H from CH_2($OCMe_2$)), 3.71 (1H, t, *J* 8.0, 1H from CH_2O($OCMe_2$)), 3.09–2.92 (2H, m, 1H from CH_2CHO and C*H*C(O)O), 2.71 (1H, dd, *J* 19.2, 11.6, 1H from CH_2CHO), 2.54 (1H, ddd, *J* 8.8, 6.0, 2.0, $CH_2CHCHC(O)O$), 2.13 (1H, dd, *J* 12.4, 9.2, 1H from CMe_2CH_2), 1.65 (1H, dd, *J* 12.4, 6.0, 1H from CMe_2CH_2), 1.44 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.21 (3H, s, CH_3) and 1.15 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 198.6 (*C*HO), 179.3 (*C*=O), 109.0 (CMe_2O_2), 91.1 (*C*OC(O)), 75.7 (*C*H($OCMe_2$)), 65.1 (*C*H_2($OCMe_2$)), 45.4 (*C*H_2CHO), 42.7 (*C*HC(O)O), 40.9 (*C*Me_2CH_2), 38.7 (CMe_2CH_2CH), 36.2 (CMe_2CH_2CH), 26.2 (*C*H_3), 25.1 (*C*H_3), 25.1 (*C*H_3) and 24.2 (*C*H_3); *m*/*z* (FAB$^+$ mode) 283.2 (100%), 267 (12), 225 (20), 209 (18), 179 (22), 147 (25), 101 (24), 85 (30), 74 (74) (Found (M + H)$^+$, 283.1544. $C_{15}H_{23}O_5$ requires 283.1545).

Acknowledgements

We thank the EPSRC (D.J., grant no. GR/M13572), the Carnegie Trust (Summer studentship to D.J.E.) and the Leverhulme Trust (E.C., PDRA grant F/00179/G) for financial support. We also thank Mr J. Gall from the NMR Spectroscopy Laboratory at the University of Glasgow for technical assistance.

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