Squalestatin synthetic studies: tethered control in a bicycloketalisation step

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A synthesis of an analogue of the dioxabicyclo[3.2.1]octane core structure of the squalestatins is reported in which control of the bicycloketalisation is achieved by a tethering strategy.

Introduction

The squalestatins (zaragozic acids), *e.g.* squalestatin 1 **1**, first reported in 1992,[1,2] have become molecules of much synthetic interest. To date this has resulted in a number of total syntheses[3–8] and a plethora of partial syntheses.[9] The common goal in much of this latter area has been the construction of the bicyclic ketal core. Whilst not the exclusive approach, the most common strategy has employed ketalisation as the crucial ring forming process. Although this has proved successful, in a number of cases problems have arisen through the competition between the various possible acetal structures.[10,11] For example, Armstrong and Barsanti have reported that, on mild acid treatment, ketone polyol **3** afforded a 1:1 mixture of ketals **4** and **5** (Fig. 1).[10] Recently, in an elegant series of papers, Myles and Hegde have demonstrated that high levels of control in the ketalisation of ketone polyols may be achieved through careful consideration of the substitution pattern and kinetics of the reaction.[12,13] In this paper, we describe an alternative approach, involving a synthesis of a model 2,8-dioxabicyclo[3.2.1]octane core structure (**2**) of these natural products, in which this problem is alleviated by means of a tethering strategy.

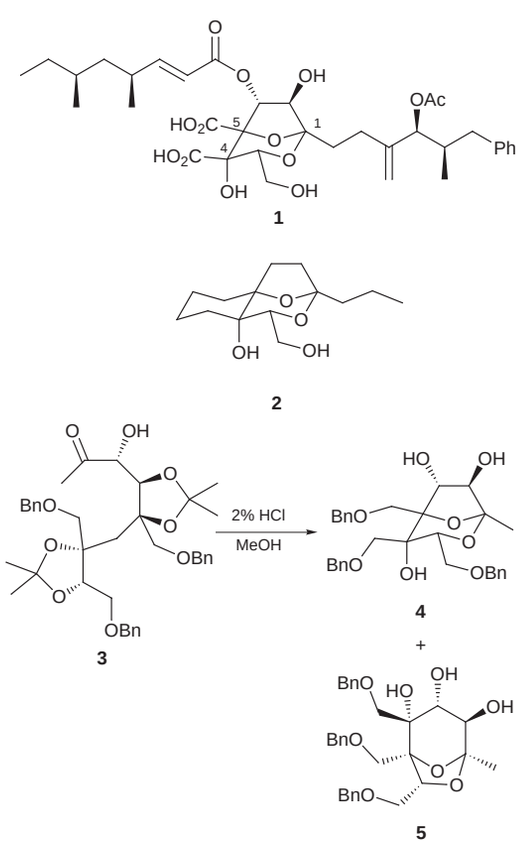
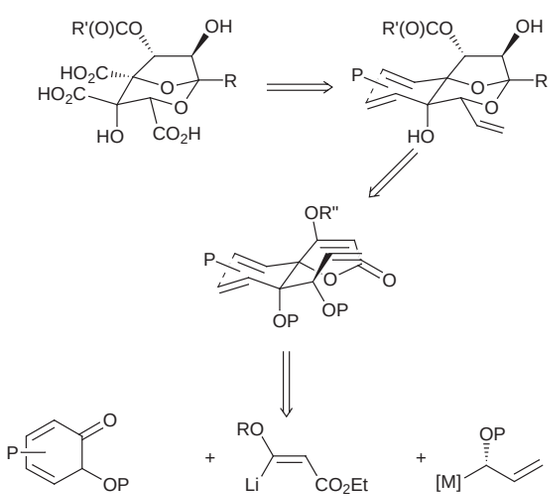


Fig. 1

Our synthetic design was based on the recognition that carboxylic acids can be prepared in masked form as alkenes, thus simplifying their handling. Furthermore, tethering of two of these alkenes may facilitate control in the bicycloketalisation step. This led to the synthetic plan shown in Scheme 1. To verify this latter hypothesis we have undertaken



Scheme 1

a model study using a simple cyclohexane ring as a model tether.

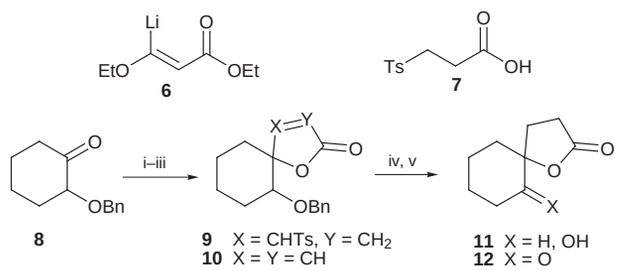
Results and discussion

As indicated above, in order to verify that a tether does not interfere with the bicycloketalisation, we have carried out this study using a simple model tether as represented by α-benzyloxycyclohexanone **8**.[14] This ketone was efficiently prepared *via* nucleophilic opening of cyclohexene oxide with the sodium salt of benzyl alcohol, followed by oxidation of the resultant alcohol using the Swern protocol.

The synthetic plan, outlined in Scheme 1, allows for flexibility in the order of the addition of the two side chains. Initially, we examined the formation of the butenolide moiety

prior to coupling with a C-4† chain unit. In this regard a variety of homoenolate equivalents have been reported in the literature and, in line with our retrosynthetic plan, the β-lithio-β-alkoxyacrylates **6**, developed by Schmidt,[15,16] were selected as the initial option. There is a limitation on the use of these reagents in that reaction of the anion must be rapid in order to prevent equilibration of the anion between the α and β positions of the acrylate. However, in our hands, at the temperatures required (< −90 °C) to maintain stereochemical integrity, these anions proved to be insufficiently nucleophilic to couple with ketone **8**. It is also possible that competing enolisation of the ketone inhibited the desired reaction, *vide infra*.

The dianion of 3-tolylsulfonylpropionic acid **7** as developed by Bonete and Najera, has been shown to be an effective homoenolate equivalent for the elaboration of ketones to butenolides.[17] With this reagent, whilst competing enolisation was again occurring, it proved possible to obtain routinely, following chromatography, a 48% yield of the desired lactone **9** together with 50% recovered starting material, Scheme 2.

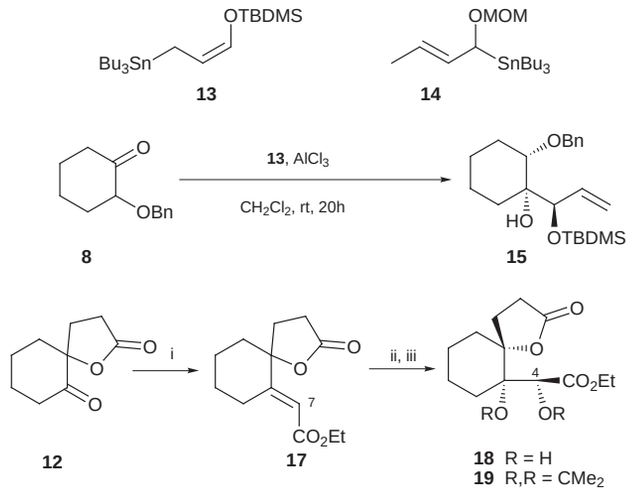


Scheme 2 *Reagents and conditions*: i, **7**, 2.2BuLi, THF −78 °C then warm to −40 °C; ii, TFAA, −30 °C; iii, LDA, THF (33% from **8** + 50% **8** recovered); iv, H_2, $Pd(OH)_2$, MeOH (87%); v, $(COCl)_2$, DMSO, Et_3N, −70 °C (85%)

Elimination of the sulfonyl group occurred smoothly on treatment with LDA to afford the required butenolide **10** as a 1.4:1 mixture of diastereoisomers. Attempts to attenuate the basicity of this dianion by transmetallation strategies, notably to the corresponding cerium reagent, proved unsuccessful. Likewise, a number of other homoenolate equivalents were assayed but none proved to be any more efficient.

Cleavage of the benzyl group and oxidation to the keto lactone **12** then alleviated the problem of diastereoisomers. Initial attempts to introduce the remaining side chain focused on the use of γ-alkoxyallylmetal chemistry.[18–20] Although very high selectivities with this class of reagents have been recorded, these are obtained almost exclusively with aldehydes and reactions with ketones are relatively rare. However, of relevance to the current problem, substrates with proximal alkoxy groups have shown evidence for enhanced reactivity and high selectivity compared with the parent carbonyl compound.[21] Following this example, we explored the reactivity of α-benzyloxy ketone **8** with siloxystannane **13**.[18] Although, with most Lewis acid promoters, the high temperatures required to obtain reaction with ketone **8**, resulted in decomposition of the stannane, the use of various aluminium based catalysts, ($AlCl_3$, $EtAlCl_2$), did afford the desired adduct **15** as a single diastereoisomer, albeit in low yield (≤ 22%). The illustrated stereochemistry was assigned by anology with the precedent quoted by Keck and by comparison with acetonide **19**. Although highly selective, the yield could not be further improved and attention turned to the more nucleophilic α-alkoxyallyllithium reagents. However, these reagents, prepared *in situ* by transmetallation of the corresponding α-alkoxystannane **14**[22] as reported by Chan and Chong,[23] proved to be no more successful.

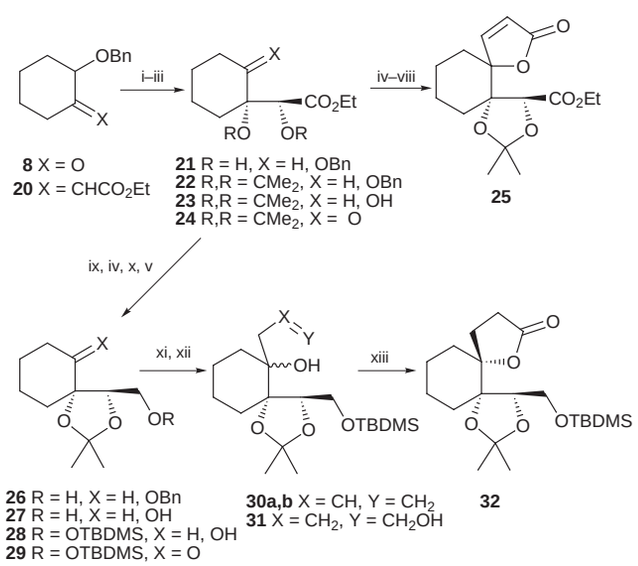
† Squalestatin numbering.



Scheme 3 *Reagents and conditions*: i, $Ph_3P{=}CHCO_2Et$ (**16**), PhH, 80 °C (67% + 30% **12**); ii, OsO_4, NMO, ^tBuOH (77%); iii, $(MeO)CMe_2$, TFA, $CHCl_3$, 70 °C (78%)

For expediency, a simpler stepwise elaboration of this side chain was then adopted, Scheme 3. This was achieved in good overall yield by reaction with the stabilised Wittig reagent **16**, dihydroxylation and diol protection to afford ester lactone **19**. Confirmation of the sterochemistry was attained through NOE experiments on enoate **17** and acetonide **19** which showed enhancements of the lactone protons at δ 2.49 and 2.2 on irradiation at C-7 δ 5.9 (**17**) and at δ 2.6 on irradiation at C-4 δ 4.64 (**19**) respectively.

In an attempt to enhance the overall efficiency of this sequence the synthesis of the cyclisation precursor was undertaken using the opposite mode of side chain attachment. In this pathway, the same Wittig–dihydroxylation sequence as before provided the C-4 chain from ketone **8**. After cleavage of the benzyl ether and oxidation, the butenolide unit was introduced using Najera chemistry, to produce ester–butenolide **25** in a respectable overall yield (51%), Scheme 4.

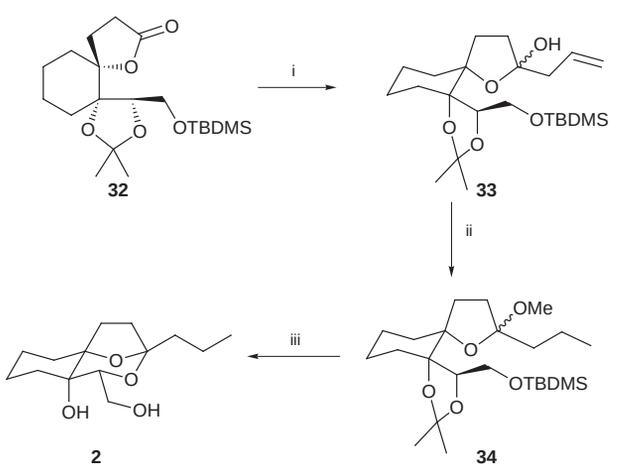


Scheme 4 *Reagents and conditions*: i, **16**, PhH, 80 °C (94%); ii, OsO_4, NMO, ^tBuOH (100%); iii, $(MeO)_2CMe_2$, TFA, $CHCl_3$, 70 °C (97%); iv, H_2, $Pd(OH)_2$, MeOH; v, $(COCl)_2$, DMSO, Et_3N, −70 °C; vi, **7**, 2.2BuLi, THF −78 °C then warm to −40 °C; vii, TFAA, −30 °C; viii, LDA, THF (51% from **22**); ix, DIBAL, THF, −70 °C; x, TBDMSCl, imidazole, DMF (66% from **22**); xi, allylMgBr, THF; xii, BH_3·THF then H_2O_2, NaOH; xiii, PCC (49% from **29**)

With the ester–lactone accessible, the introduction of a C-1 unit through the selective addition of organometallic units to the butenolide carbonyl group were explored. However, all

attempts to achieve this goal were thwarted by competitive reaction at the ester carbonyl. Accordingly, the synthetic strategy was then modified to allow prior reduction of the ester **22** and protection of the resultant alcohol as the corresponding TBDMS ether. Surprisingly, the silyl ether proved unstable to the hydrogenolysis conditions with the corresponding diol being produced. Fortunately selective protection of the primary alcohol proved straightforward and the desired ketone **29** could be efficiently accessed. However, addition of the tolylsulfonyl dianion to **29** failed, presumably due to increased steric hindrance of the TBDMS group. Consequently, for expediency, in order to rapidly generate the desired lactone **32**, we then resorted to a slightly less elegant approach involving addition of allylmagnesium bromide, hydroboration and oxidation. Whilst synthetically efficient the diastereoselectivity of this process was disappointing with a 1.3 : 1 separable mixture of diastereoisomers being generated in the initial Grignard reaction. The stereochemistry of the spirocentre was deduced by analogy with tricyclic lactone **19**. Unequivocal verification of this was demonstrated by the transformation of the major alcohol product **30a** into the squalestatin core structure **2**, *vide infra.* Similar chemistry commencing from the lactone derived from **30b** failed to yield any evidence of bicycloketalisation.

Reaction of this lactone with allylmagnesium bromide as a C-1 side chain surrogate now smoothly afforded the required lactol **33**, Scheme 5. Treatment of this compound with dilute



Scheme 5 *Reagent and conditions*: i, allylMgBr, Et_2O, −78 °C (95%); ii, $Pd(OH)_2$, MeOH, H_2 (94%); iii, 2% HCl, MeOH, 40 °C (37%)

acid produced not the desired lactone but rather an intractable mixture of compounds lacking any olefinic signals in the NMR spectra. Although related allyl systems have been successfully cyclised there have also been reports of similar problems during the ketalisation step.[24] Removal of the double bond by catalytic hydrogenation in methanol was accompanied by formation of the corresponding methyl glycoside **34**. Treatment of this compound with dilute methanolic HCl afforded a single component which was identified as the predicted bicyclic acetal **2** on the basis of its spectroscopic and analytical data. ^{13}C DEPT NMR showed the presence of one methyl, nine methylene and one methine carbons. The three quaternary carbons produced signals at δ 101(C1) and 78/69 (C5/C10) respectively which corresponds well with published data for other analogues of the squalestatins.[25]

In conclusion, the concept of tethering two of the side chains does not inhibit the bicycloketalisation but rather seems to direct this process to produce only one of the possible structural isomers. This may provide a useful synthetic strategy for the control of related bicycloketalisations of ketone polyols.

Experimental

All reactions were undertaken in an inert gas atmosphere of dry nitrogen or argon in pre-dried glassware. Unless otherwise stated nuclear magnetic resonance (NMR) spectra were obtained on a Varian VXR-400(s) (^1H at 399.952 MHz, ^{13}C at 100.577 MHz) spectrometer with $CDCl_3$ as solvent (δ 7.26) and are recorded in ppm (δ units) downfield of tetramethylsilane (δ 0) with coupling constants quoted in Hertz (Hz). Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR 1720X spectrometer. Low resolution mass spectra were recorded on a VG Analytical 7070E organic mass spectrometer, and gas chromatography-mass spectra (GC-MS) were recorded using a Hewlett Packard 5890 Series II gas chromatograph connected to a VG mass Lab trio 1000. Flash column chromatography was performed on silica (60–240 mesh). Melting points were determined using Gallenkamp melting point apparatus and are uncorrected. All solvents were distilled prior to use following standard protocols.[26] Petrol refers to the fraction boiling in the 40–60 °C range unless otherwise stated. Ether refers to diethyl ether.

6-Benzyloxy-2-oxo-1-oxaspiro[4.5]dec-3-ene 10

Butyllithium (33.43 ml, 53.51 mmol) was added slowly to a solution of 3-(*p*-tolylsulfonyl)propionic acid **7** (5.85 g, 26.7 mmol) in THF (300 ml) at −78 °C. The resulting yellow solution was stirred for 1 h when ketone **8** (4.37 g, 21.4 mmol) in THF (50 ml) was added. The mixture was then allowed to warm to −40 °C and stirred at this temperature for 16 h. Trifluoroacetic anhydride (7.18 ml, 53.4 mmol) was then added and the solution stirred for a further 4 h at −30 °C. The mixture was quenched with saturated aq. $NaHCO_3$, extracted with ether, dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (1 : 1, petrol–ether) gave lactone diastereoisomers **9** (4.26 g, 48%) and recovered 2-benzyloxycyclohexanone **8** (2.18 g, 50%). The mixture of lactones was then redissolved in THF (100 ml) and added to a 1 M solution of LDA (12.4 ml, 12.4 mmol) in THF at −78 °C and subsequently warmed to room temperature. After stirring for a further 12 h, the reaction was quenched with saturated aq. NH_4Cl, extracted with ether, washed with saturated aq. $NaHCO_3$, dried ($MgSO_4$) and concentrated to yield a yellow oil. Flash column chromatography (3 : 1, petrol–ether) yielded two separable diastereoisomers of the desired butenolide **10** (1.75 g, 66%) as a colourless oil. Major isomer: (Found $M + NH_4^+$, 276.1600. $C_{16}H_{22}NO_3$ requires *M*, 276.1600); $\nu_{max}(CDCl_3)/cm^{-1}$ 2937, 2859, 1756, 1496, 1453, 1262, 1207, 1160, 1097; δ_H 7.56 (1H, d, *J* 5.6, 4-H), 7.29–7.19 (5H, m, Ar-H), 6.02 (1H, d, *J* 5.6, 3-H), 4.45 (2H, ABq, *J* 12, $OCH_2C_6H_5$), 3.41 (1H, m, 6-H), 1.92–1.17 (8H, m, 7-H_2, 8-H_2, 9-H_2, 10-H_2); δ_C 171.3 (C=O), 157.4, 136.9, 127.3, 126.7, 126.6, 120.5, 89.3, 77.8, 70.9, 31.3, 26.7, 21.2, 19.9; *m*/*z* CI(NH_3) 276 ($M + NH_4^+$, 100%), 259 (MH^+, 51). Minor isomer: (Found $M + NH_4^+$, 276.1600. $C_{16}H_{22}NO_3$ requires *M*, 276.1600); $\nu_{max}(CDCl_3)/cm^{-1}$ 2933, 2867, 1767, 1494, 1450, 1350, 1267, 1206, 1133, 1100; δ_H 7.24–7.14 (6H, m, Ar-H, 4-H), 5.87 (1H, d, *J* 5.6, 3-H), 4.42 (2H, ABq, *J* 12, $OCH_2C_6H_5$), 3.34 (1H, dd, *J* 10.4, 4.4, 6-H), 1.91–1.12 (8H, m, 7-H_2, 8-H_2, 9-H_2, 10-H_2); δ_C 172.6 (C=O), 157.8, 138.0, 128.1, 127.4, 127.3, 121.3, 90.2, 77.2, 71.1, 33.8, 27.7, 23.2, 21.4; *m*/*z* CI(NH_3) 276 ($M + NH_4^+$, 100%), 259 (MH^+, 57).

2-Oxo-1-oxaspiro[4.5]decan-6-ol 11

A solution of butenolide **10** (0.69 g, 2.69 mmol) in methanol (20 ml) was added to a suspension of palladium hydroxide (0.29 g, 0.27 mmol) in methanol (5 ml). The mixture was degassed and stirred vigorously for 6 h under a hydrogen atmosphere. On completion of the reaction, the mixture was filtered through Celite, washed with methanol and concentrated. Flash column chromatography (ether) afforded

11 (0.4 g, 87%) as a colourless oil (Found MH^+, 171.1021. $C_9H_{15}O_3$ requires *M*, 171.1021); $\nu_{max}(CDCl_3)/cm^{-1}$ 3438, 2939, 2864, 2341, 1758, 1450, 1210; δ_H 3.4 (1H, dd, *J* 10.4, 4, 6-H), 2.72–2.32 (3H, m, 4-H, 3-H_2), 1.91–1.18 (9H, m, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 4-H); δ_C 177.7 (C=O lactone), 87.7, 74.4, 35.9, 30.9, 30.3, 29.1, 23.4, 21.5; *m*/*z* CI(NH_3) 188 ($M + NH_4^+$, 100%), 171 (MH^+, 38).

2-Oxo-1-oxaspiro[4.5]decan-6-one 12

DMSO (0.87 ml, 12.4 mmol) in DCM (120 ml) was added dropwise to a suspension of oxalyl chloride (0.54 ml, 6.2 mmol) in DCM (60 ml) at −78 °C. After stirring for a further 10 min, a solution of the alcohol **11** (0.88 g, 5.17 mmol) in DCM (50 ml) was added. The resulting solution was then stirred for 50 min before Et_3N (3.67 ml, 25.9 mmol) was added and the reaction warmed to room temperature. The mixture was then diluted with DCM and washed with 2 M HCl and saturated aq. $NaHCO_3$, then dried ($MgSO_4$) and concentrated to produce the desired ketone **12** (0.74 g, 88%) after purification by flash column chromatography (2:1, ether–petrol) (Found MH^+, 169.0865. $C_9H_{13}O_3$ requires *M*, 169.0865); $\nu_{max}(CDCl_3)/cm^{-1}$ 3544, 3422, 2944, 2867, 1772 (C=O lactone), 1722 (C=O ketone), 1420, 1319, 1250; δ_H 2.53 (2H, m, 3-H_2), 2.39 (3H, m, 4-H, 7-H_2), 2.04 (1H, m, 4-H), 1.8–1.6 (6H, m, 8-H_2, 9-H_2, 10-H_2); δ_C 205.7 (C=O ketone), 175.3 (C=O lactone), 88.0, 38.5, 38.4, 28.7, 27.6, 26.2, 21.2; *m*/*z* (EI) 169 (MH^+, 100%).

2-Benzyloxy-1-(1′-*tert*-Butyldimethylsilyloxyprop-2′-enyl)-cyclohexanol 15

Ketone **8** (0.10 g, 0.49 mmol) in DCM (1 ml) was added to a stirred solution of aluminium trichloride (0.01 g, 0.49 mmol) in DCM (2.5 ml) at −78 °C. After 10 min, a solution of allylstannane **13** (0.25 g, 0.54 mmol) in DCM (1 ml) was then added and the mixture was allowed to warm to room temperature. After a further 20 h at this temperature the solution was then quenched with saturated aq. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated to afford recovered starting material **8** (0.05 g, 51%) and the title alcohol **15** (0.04 g, 22%). $\nu_{max}(CDCl_3)/cm^{-1}$ 3497, 3065, 3031, 2949, 2933, 2857, 1720, 1253, 1089, 1073; δ_H 7.28 (5H, m, Ar-H), 5.88 (1H, m, 2′-H), 5.21 (2H, m, 3′-H_2), 4.53 (2H, ABq, *J* 11.2, OCH_2Ph), 4.31 (1H, d, *J* 6.8, 1′-H), 3.64 (1H, dd *J* 11.2, 4.8, 2-H), 2.26 (1H, br, O*H*); 2.01–0.92 (8H, m, 3-H_2, 4-H_2, 5-H_2, 6-H_2,), 0.89 (9H, s, OSi^t*Bu*), 0.00 (3H, s, CH_3SiCH$_3$), −0.08 (3H, s, CH_3SiCH$_3$); δ_C 138.9, 137.9 (*C*H=CH$_2$), 128.3, 127.4, 127.3, 117.3 (CH=*C*H$_2$), 77.4, 75.7, 75.3, 70.0, 28.5, 26.4, 26.0, 23.8, 20.5, 18.1, −3.5 [(*C*H$_3$)Si(CH$_3$)], −4.6 [(CH$_3$)Si(*C*H$_3$)].

6-(Ethoxycarbonylmethylidene)-2-oxo-1-oxaspiro[4.5]decane 17

The Wittig reagent **16** (0.46 g, 1.3 mmol) was added to a solution of ketone **12** (0.20 g, 1.2 mmol) in benzene (10 ml) and the mixture heated at 80 °C for 12 h. After cooling to room temperature, the mixture was filtered through Celite and concentrated. Flash column chromatography (1:1 petrol–ether) afforded the title ester **17** (0.19 g, 67%) as a 12:1 mixture of *E*:*Z* isomers and recovered starting material (0.06 g, 30%) (Found: C, 65.25; H, 7.68; $C_{13}H_{16}O_4$ requires C, 65.55; H, 7.56%) (Found $M + NH_4^+$, 256.1549. $C_{13}H_{22}NO_4$ requires *M*, 256.1549); $\nu_{max}(CDCl_3)/cm^{-1}$ 2984, 2943, 2865, 2256, 1774 (C=O lactone), 1710 (C=O ester), 1652, 1449, 1374, 1304, 1258, 1195, 1166; δ_H 5.9 (1H, s, =C*H*), 4.08 (2H, q, *J* 7.2, OCH_2CH$_3$), 3.84 (1H, br, 7-H_{ax}), 2.49 (2H, m, 3-H), 2.2 (2H, t, *J* 8, 4-H), 1.89 (2H, m, 7-H_{eq}, 9-H_{ax}), 1.80 (3H, m, 8-H_{eq}, 9-H_{eq}, 10-H_{eq}), 1.52 (1H, m, 10-H_{ax}), 1.33 (1H, m, 8-H_{ax}), 1.21 (3H, t, *J* 7.2, OCH$_2$CH_3); δ_C 174.7 (C=O ester), 165.4 (C=O lactone), 158.2, 110.9, 86.2, 59.0, 38.2, 30.3, 26.9, 25.9, 25.6, 22.2, 13.1; *m*/*z* CI(NH_3) 256 ($M + NH_4^+$, 92%), 239 (MH^+, 39), 195 ($MH^+ - OCH_2CH_3$, 100).

Ethyl 2-(6′-hydroxy-2′-oxo-1′-oxaspiro[4.5]decan-6′-yl)-2-hydroxyethanoate 18

NMO (0.06 g, 0.50 mmol) and a catalytic amount of OsO_4 (0.12 g, 0.49 mmol) in *tert*-butyl alcohol (5 ml) was added to a solution of alkene **17**. The reaction mixture was stirred at room temperature for 14 h when excess sodium metabisulfite was added. After stirring for a further 30 min the resulting mixture was filtered through Celite, and the residue washed with ethyl acetate. Concentration of the filtrate and purification by flash column chromatography (1:2, petrol–ether) afforded the title diol **18** (0.12 g, 77%). (Found $M + NH_4^+$, 290.1604. $C_{13}H_{24}NO_6$ requires *M*, 290.1604); $\nu_{max}(CDCl_3)/cm^{-1}$ 3444 (OH), 2944, 2867, 2356, 1739 (C=O lactone), 1639 (C=O ester), 1444, 1367, 1256, 1211, 1089, 1016; δ_H 4.32–4.09 [3H, m, OCH_2CH$_3$, C(OH)*H*], 3.45–3.05 (2H, br s, 2 × O*H*), 2.80–2.45 (3H, m, 7′-H_{ax}, 3′-H_2), 2.15–1.22 (12H, m, 4′-H_2, 7′-H, 8′-H_2, 9′-H_2, 10′-H_2, OCH$_2$CH_3); δ_C 177.4 (C=O lactone), 175.9 (C=O lactone), 173.2 (C=O ester), 172.0 (C=O ester), 90.1, 89.3, 76.2, 75.3, 74.1, 73.3, 62.4, 62.2, 36.4, 34.8, 31.7, 31.4, 28.9, 28.7, 28.4, 27.1, 22.2, 21.2, 20.3, 20.0, 14.3, 14.1; *m*/*z* CI(NH_3) 290 ($M + NH_4^+$, 100%), 272 (M^+, 39).

4-Ethoxycarbonyl-2,2,dimethyl-1,3,7-trioxadispiro[4.4.4.0]-tetradecan-8-one 19

Trifluoroacetic acid (0.02 g, 0.02 mmol) was added to a stirred solution of diol **18** (0.05 g, 0.21 mmol) and 2,2-dimethoxypropane (0.05 ml, 0.25 mmol) in chloroform (20 ml). The reaction mixture was then heated at reflux using a Soxhlet apparatus containing 4 Å molecular sieves. After 10 h the mixture was cooled to room temperature, quenched with saturated aq. $NaHCO_3$, dried ($MgSO_4$) and concentrated. Flash column chromotography (2:1 petrol–ether) yielded the desired ketal **19** (0.051 g, 78%) (Found $M + NH_4^+$, 330.1917. $C_{16}H_{28}NO_6$ requires *M*, 330.1916); $\nu_{max}(CDCl_3)/cm^{-1}$ 1783 (C=O lactone), 1756 (C=O ester), 1733, 1383, 1211; δ_H 4.64 (1H, s, 4-H), 4.32–4.14 (2H, m, OCH_2CH$_3$), 2.72–2.46 (3H, m, 9-H_2, 10-H), 2.00–1.28 (9H, m, 10-H, 11-H_2, 12-H_2, 13-H_2, 14-H_2), 1.53 (3H, s, 2-CH_3), 1.37 (3H, s, 2-CH_3), 1.30 (3H, t, *J* 7.2, OCH$_2$CH_3); δ_C 176.3 (C=O lactone), 170.0 (C=O ester), 111.0, 87.8, 86.8, 77.8, 61.5, 35.9, 30.9, 29.3, 29.0, 28.7, 27.0, 21.2, 21.0, 14.0; *m*/*z* CI(NH_3) 330 ($M + NH_4^+$, 100%), 313 (MH^+, 18).

Ethyl 2-(2′-benzyloxycyclohexylidene)ethanoate 20

In an analogous fashion to that employed for the synthesis of enoate **17**, ketone **8** (3.8 g, 18.8 mmol) was coupled with ylide **16** (19.3 g, 56.4 mmol) to afford, after flash column chromatography (5:1 petrol–ether), the title compound **20** (4.82 g, 94%) as an 8:1 mixture of *E*:*Z* isomers. Major isomer: mp 89 °C (Found MH^+, 275.1647. $C_{17}H_{23}O_3$ requires *M*, 275.1647); $\nu_{max}(CDCl_3)/cm^{-1}$ 2939, 2863, 1708, 1652, 1448, 1216; δ_H 7.38–7.34 (5H, m, Ar-H), 5.93 (1H, s, =C*H*), 4.54 (2H, ABq, *J* 12, OCH_2Ph), 4.20 (2H, q, *J* 6.8, OCH_2CH$_3$), 3.72 (1H, m, 2′-H), 3.06 (1H, m, 6′-H), 2.52 (1H, m, 6′-H), 1.90–1.16 (6H, m, 3′-H_2, 4′-H_2, 5′-H_2), 1.22 (3H, t, *J* 6.8, OCH$_2$CH_3); δ_C 166.7 (C=O ester), 161.1, 138.4 (Ar), 128.3 (Ar), 127.5 (Ar), 127.4 (Ar), 113.0, 80.1, 70.4, 59.7, 34.9, 27.8, 27.3, 22.8, 14.3; *m*/*z* CI(NH_3) 292 ($M + NH_4^+$, 32%), 275 (MH^+, 100).

Ethyl 2-(2′-benzyloxy-1′-hydroxycyclohexyl)-2-hydroxy-ethanoate 21

In an identical procedure as described for **18**, OsO_4 catalysed oxidation of enoate **20** afforded diol **21** (100%). (Found MH^+, 309.1727. $C_{17}H_{25}O_5$ requires *M*, 309.1702); $\nu_{max}(CDCl_3)/cm^{-1}$ 3497 (OH), 2941, 2856, 1722 (C=O ester), 1459, 1263, 1199; δ_H 7.36–7.18 (5H, m, Ar-H), 4.52 and 4.34 (2H, ABq, *J* 10.8, OCH_2Ph), 4.25 (1H, br d, *J* 8.4, C*H*CO$_2$Et), 4.17 (2H, q, *J* 7.2, OCH_2CH$_3$), 3.57 (1H, s, 2′-H), 3.55 (1H, br, OH), 2.77 (1H, br, OH), 1.87–1.29 (8H, m, 3′-H_2, 4′-H_2, 5′-H_2, 6′-H_2), 1.23 (3H, t, *J* 7.2, OCH$_2$CH_3); δ_C 173.7 (C=O ester), 138.2 (Ar),

128.3 (Ar), 127.7 (Ar), 127.6 (Ar), 77.8, 74.9, 73.7, 71.0, 61.4, 29.7, 24.3, 20.6, 19.5, 14.1; *m/z* CI(NH_3) 326 (M + NH_4^+, 18%), 309 (MH^+, 41), 108 ($OCH_2C_6H_5$, 100).

6-Benzyloxy-4-ethoxycarbonyl-2,2-dimethyl-1,3-dioxaspiro[4.5]-decane 22

Treatment of diol **21** in an identical fashion as that described for **19** afforded acetonide **22** (98%) (Found MH^+, 349.2015. $C_{20}H_{29}O_5$ requires *M*, 349.2015); $\nu_{max}(CDCl_3)/cm^{-1}$ 2939, 2865, 1744 (C=O ester), 1454, 1372, 1279, 1224, 1201; δ_H 7.33–7.18 (5H, m, Ar-H), 4.60 (1H, s, 4-H), 4.61 and 4.41 (2H, ABq, *J* 11.6, OCH_2Ph), 4.17–4.02 (2H, m, OCH_2CH_3), 3.41 (1H, m, 6-H), 1.86–1.34 (8H, m, 7-H_2, 8-H_2, 9-H_2, 10-H_2), 1.49 (3H, s, 2-CH_3), 1.31 (3H, s, 2-CH_3), 1.16 (3H, t, *J* 7.2, OCH_2CH_3); δ_C 170.2 (C=O ester), 138.7, 128.1, 127.3, 127.2, 110.8, 84.7, 81.0, 79.1, 70.7, 60.8, 29.7, 28.7, 25.0, 21.6, 19.5, 14.0; *m/z* CI(NH_3) 349 (MH^+, 13%), 291 [$MH^+ - (CH_3)_2CO$, 100].

4-Ethoxycarbonyl-2,2-dimethyl-1,3-dioxaspiro[4.5]decan-6-ol 23

Following an identical procedure as that described for the preparation of **11**, alcohol **23** (0.056 g, 99%) was isolated as a colourless oil (Found M^+, 258.1467. $C_{13}H_{22}O_5$ requires *M*, 258.1467); $\nu_{max}(CDCl_3)/cm^{-1}$ 3474 (OH), 2967, 2859, 1743 (C=O ester), 1710, 1216, 1188; δ_H 4.48 (1H, s, 4-H), 4.28–4.20 (2H, m, OCH_2CH_3), 3.70 (1H, m, 6-H), 1.71–1.25 (8H, m, 7-H_2, 8-H_2, 9-H_2, 10-H_2), 1.49 (3H, s, 2-CH_3), 1.32 (3H, s, 2-CH_3), 1.27 (3H, t, *J* 7.2, OCH_2CH_3); δ_C 170.3 (C=O ester), 109.9, 84.0, 81.0, 72.7, 62.0, 29.3, 28.5, 27.7, 27.3, 21.1, 19.4, 14.1; *m/z* (EI) 258 (M^+, 11%), 243 ($M^+ - CH_3$, 57), 59 [$(CH_3)_2COH^+$, 100].

4-Ethoxycarbonyl-2,2-dimethyl-1,3-dioxaspiro[4.5]decan-6-one 24

Alcohol **23** was oxidised following an identical procedure as that described for ketone **12** to afford after purification by flash column chromatography (5:1 petrol–ether) the title ketone **24** (100%) (Found MH^+, 257.1389. $C_{13}H_{21}O_5$ requires *MH*, 257.1389); $\nu_{max}(CDCl_3)/cm^{-1}$ 2953, 2869, 1757 (C=O ester), 1724 (C=O lactone), 1186, 1109; δ_H 5.30 (1H, s, 4-H), 4.25–4.11 (2H, m, OCH_2CH_3), 2.88–2.84 (1H, m, 7-H), 2.40–2.36 (1H, m, 7-H) 2.10–1.58 (6H, m, 8-H_2, 9-H_2, 10-H_2,), 1.56 (3H, s, 2-CH_3), 1.25 (3H, t, *J* 7.2, OCH_2CH_3), 1.20 (3H, s, 2-CH_3); δ_C 208.7 (C=O ketone), 169.9 (C=O ester), 111.6, 87.1, 77.2, 75.3, 60.96, 38.7, 35.4, 27.6, 26.3, 21.2, 14.1; *m/z* CI(NH_3) 257 (MH^+, 100%).

4-Ethoxycarbonyl-2,2-dimethyl-1,3,7-trioxadispiro[4.4.4.0]-tetradec-9-en-8-one 25

Following the same procedure as for **8** ketone **24** was treated with the dianion of **7** to afford, after flash column chromatography (1:1 petrol–ether), a 1.3:1 mixture of two separable isomers of the title butenolide **25** (0.18 g, 52%) as a white solid. Major isomer: mp 138 °C (Found M + NH_4^+, 328.1760. $C_{16}H_{26}NO_6$ requires *M*, 328.1760); $\nu_{max}(CDCl_3)/cm^{-1}$ 1740 (C=O lactone), 1220, 1102; δ_H 7.62 (1H, d, *J* 6, 10-H), 6.13 (1H, d, *J* 6, 9-H), 4.20–4.10 (2H, m, OCH_2CH_3), 4.11 (1H, s, 4-H), 2.42–2.35 (1H, m, 11-H), 1.80-1.32 (7H, m, 11-H, 12-H_2, 13-H_2, 14-H_2), 1.52 (3H, s, 2-CH_3), 1.47 (3H, s, 2-CH_3), 1.27 (3H, t, *J* 7.2, OCH_2CH_3); δ_C 171.9 (C=O lactone), 168.7 (C=O ester), 157.3, 121.6, 111.5, 89.9, 84.5, 76.3, 61.4, 34.1, 32.1, 28.8, 26.3, 25.1, 20.5, 14.1; *m/z* CI(NH_3) 328 (M + NH_4^+, 100%). Minor isomer: mp 138–139 °C (Found M + NH_4^+, 328.1760. $C_{16}H_{26}NO_6$ requires *M*, 328.1760); $\nu_{max}(CDCl_3)/cm^{-1}$ 1753 (C=O lactone), 1221, 1102; δ_H 7.54 (1H, d, *J* 6, 10-H), 6.21 (1H, d, *J* 6, 9-H), 4.22–4.12 (2H, m, OCH_2CH_3), 4.22 (1H, s, 4-H), 2.08–1.98 (1H, m, 11-H), 1.96–1.90 (1H, m, 11-H), 1.68–1.18 (6H, m, 12-H_2, 13-H_2, 14-H_2), 1.57 (3H, s, 2-CH_3), 1.38 (3H, s, 2-CH_3), 1.31 (3H, t, *J* 7.2, OCH_2CH_3); δ_C 174.4 (C=O lactone), 168.0 (C=O ester), 157.5, 122.7, 110.6, 89.2, 83.3, 77.8, 61.6, 32.9, 29.7, 28.4, 26.9, 21.0, 20.2, 13.9; *m/z* CI(NH_3) 328 (M + NH_4^+, 100%).

6-Benzyloxy-2,2-dimethyl-4-hydroxymethyl-1,3-dioxaspiro[4.5]-decane 26

DIBAL (1.58 ml, 1.58 mmol) was added to a stirred solution of ester **22** (0.25 g, 0.72 mmol) in THF (10 ml) at −78 °C. After 1 h at this temperature the mixture was allowed to warm to room temperature and stirring was continued for a further 1 h. The mixture was then recooled to −78 °C, methanol (0.16 g, 5.04 mmol) added and the mixture allowed to attain ambient temperature. Water (0.09 ml, 5.04 mmol) and Celite were added and the resultant mixture filtered. The residue was washed with ethyl acetate and the filtrate concentrated. Flash column chromatography (4:1 petrol–ether) afforded the desired alcohol **26** (0.22 g, 99%). (Found MH^+, 307.1909. $C_{18}H_{26}O_4$ requires *M*, 307.1909); $\nu_{max}(CDCl_3)/cm^{-1}$ 3455, 1249, 1217, 1061, 1085; δ_H 7.29–7.23 (5H, m, Ar-H), 4.58 and 4.31 (2H, ABq, *J* 11.2, OCH_2Ph), 3.83 (1H, t, *J* 6.4, 4-H), 3.63 (2H, br, CH_2OH), 3.33 (1H, m, 6-H), 2.83 (1H, br, O*H*), 1.91–1.36 (8H, m, 7-H_2, 8-H_2, 9-H_2, 10-H_2), 1.36 (3H, s, 2-CH_3), 1.24 (3H, s, 2-CH_3); δ_C 137.3, 128.5, 128.1, 128.0, 107.7, 83.4, 81.5, 79.6, 63.4, 60.8, 28.6, 27.2, 26.8, 24.6, 20.6, 19.3; *m/z* CI(NH_3) 306 (M^+, 22%), 141 [$M^+ - (CH_3)_2$-C(O)O − $CH_2C_6H_5$, 100].

2,2-Dimethyl-4-hydroxymethyl-1,3-dioxaspiro[4.5]decan-6-ol 27

Following an identical procedure as that described for the preparation of **11**, diol **27** (97%) was obtained as a white solid. Mp 86 °C (Found: C, 61.17; H, 9.32. $C_{11}H_{20}O_4$ requires C, 61.10; H, 9.25%) (Found M + NH_4^+, 234.1705. $C_{11}H_{24}NO_4$ requires *M*, 234.1705); $\nu_{max}(CDCl_3)/cm^{-1}$ 3367 (OH), 1245, 1219; δ_H 3.87 (1H, m, 4-H), 3.75–3.57 (5H, m, 6-H, CH_2OH, 2 × O*H*), 1.83–1.22 (8H, m, 7-H_2, 8-H_2, 9-H_2, 10-H_2), 1.36 (3H, s, 2-CH_3), 1.28 (3H, s, 2-CH_3); δ_C 107.8, 82.6, 82.2, 72.3, 59.9, 29.9, 28.5, 26.8, 26.1, 20.5, 19.2; *m/z* CI(NH_3) 216 (M^+, 8%), 141 [$MH^+ - (CH_3)_2C(O)O$, 100].

4-(*tert*-Butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxaspiro[4.5]decan-6-ol 28

Imidazole (0.18 g, 1.36 mmol) and *tert*-butyldimethylsilyl chloride (0.115 g, 0.75 mmol) were added to a stirred solution of the diol **27** (0.15 g, 0.68 mmol) in DMF (6 ml). After 20 h at room temperature, the reaction was quenched with saturated aq. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated. Flash column chromatography (10:1 petrol–ether) yielded the title ether **28** (0.22 g, 97.1%) (Found MH^+, 331.2304. $C_{17}H_{35}O_4Si$ requires *M*, 331.2304); $\nu_{max}(CDCl_3)/cm^{-1}$ 3408 (OH), 1470, 1374, 1254; δ_H 3.90–3.86 (2H, m, CH_2OSi), 3.84 (1H, br, O*H*), 3.66 (1H, t, *J* 10.8, 4-H), 3.57 (1H, m, 6-H), 1.76–1.32 (8H, m, 7-H_2, 8-H_2, 9-H_2, 10-H_2), 1.42 (3H, s, 2-CH_3), 1.35 (3H, s, 2-CH_3), 0.93 (9H, s, Si^tBu), 0.08 [6H, s, Si(CH_3)$_2$]; δ_C 107.8, 83.1, 82.3, 72.0, 60.6, 45.2, 29.1, 28.5, 26.7, 25.8, 20.7, 19.2, 18.3, −5.6, −5.7; *m/z* CI(NH_3) 331 (MH^+, 2%), 273 ($M^+ - {}^tBu$, 100).

4-(*tert*-Butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3-dioxaspiro[4.5]decan-6-one 29

As described for ketone **12** alcohol **28** was oxidised using the Swern protocol to afford the desired ketone **29** (69%) as a waxy solid. Mp 39–40 °C (ethyl acetate–hexane) (Found MH^+, 329.2148. $C_{17}H_{33}O_4Si$ requires *M*, 329.2148); $\nu_{max}(CDCl_3)/cm^{-1}$ 1719 (C=O ketone), 1372, 1255; δ_H 4.66 (1H, t, *J* 6, 4-H), 3.70 (2H, d, *J* 6, CH_2OSi), 2.87 (1H, dt, *J* 20, 6, 7-H) 2.39–2.34 (1H, m, 7-H), 2.19–1.90 (3H, m, 8-H, 10-H_2), 1.72–1.58 (3H, m, 8-H, 9-H_2), 1.43 (3H, s, 2-CH_3), 1.24 (3H, s, 2-CH_3), 0.87 (9H, s, Si^tBu), 0.07 (3H, s, SiCH_3), 0.07 (3H, s, SiCH_3); δ_C 210.3 (C=O ketone), 108.78, 85.5, 76.1, 61.7, 39.6, 34.2, 28.5, 27.7, 28.0, 25.8, 21.0, 18.2, −5.4, −5.45; *m/z* CI(NH_3) 329 (MH^+, 55%), 271 ($M^+ - {}^tBu$, 100). In addition starting material (13.4%) was recovered.

4-(*tert*-Butyldimethylsilyloxymethyl)-2,2-dimethyl-6-prop-2′-enyl-1,3-dioxaspiro[4.5]decan-6-ol 30

Allylmagnesium bromide (0.44 ml, 0.37 mmol) was added dropwise to a stirred solution of ketone **29** (0.100 g, 0.30 mmol) in ether (3 ml) at −78 °C. After 1 h at this temperature, the reaction was quenched with saturated aq. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated. Flash column chromatography (30:1 petrol–ether) afforded the title compound **30** (0.108 g, 97%) as a 1.3:1 mixture of separable isomers. Major isomer **30a**: mp 44 °C (Found: C, 64.81; H, 10.33. $C_{20}H_{38}O_4Si$ requires C, 64.87; H, 10.34%) (Found M^+, 370.2539. $C_{20}H_{38}O_4Si$ requires *M*, 370.2539); $\nu_{max}(CDCl_3)/cm^{-1}$ 3419, 1640, 1380, 1369, 1216, 1074; δ_H 5.95 (1H, m, 2′-H), 5.06 (2H, m, 3′-H_2), 4.24 (1H, m, 4-H), 3.82 (1H, m, 1′-H), 3.69–3.64 (2H, m, CH_2OSi), 2.42–2.40 (3H, m, 7-H, 1′-H, OH), 1.80-1.20 (7H, m, 7-H, 8-H_2, 9-H_2, 10-H_2), 1.41 (3H, s, 2-CH_3), 1.37 (3H, s, 2-CH_3), 0.88 (9H, s, Si^t*Bu*), 0.13 [6H, s, Si(CH_3)$_2$]; δ_C 135.0, 117.3, 107.3, 85.4, 76.6, 71.8, 60.7, 41.3, 33.2, 28.6, 27.1, 26.7, 25.8, 20.6, 20.3, 18.2, 1.0, −5.4; *m*/*z* CI(NH_3) 371 (MH^+, 18%), 277 [$MH^+ - (CH_3)_2{}^t$BuSiO, 100]. Minor isomer **30b**: mp 42 °C (Found M^+, 370.2539. $C_{20}H_{38}O_4Si$ requires *M*, 370.2539); $\nu_{max}(CDCl_3)/cm^{-1}$ 3480, 1640, 1378, 1369, 1258, 1086; δ_H 5.95 (1H, m, 2′-H), 5.06 (2H, m, 3′-CH_2), 4.35 (1H, m, 4-H), 3.76 (2H, m, CH_2OSi), 3.69–3.64 (2H, m, 1′-H, OH), 2.23 (2H, m, 1′-H, 7-H), 1.82–1.20 (7H, m, 7-H, 8-H_2, 9-H_2, 10-H_2), 1.43 (3H, s, 2-CH_3), 1.40 (3H, s, 2-CH_3), 0.89 (9H, s, Si^t*Bu*), 0.07 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$); δ_C 133.9, 117.5, 107.1, 86.5, 78.1, 74.5, 63.0, 37.3, 34.6, 29.1, 28.9, 26.9, 25.9, 22.5, 20.5, 1.0, −5.2, −5.35; *m*/*z* CI(NH_3) 371 (MH^+, 23%), 277 [$MH^+ - (CH_3)_2{}^t$BuSiO, 100].

4-(*tert*-Butyldimethylsilyloxymethyl)-2,2-dimethyl-6-(3′-hydroxypropyl)-1,3-dioxaspiro[4.5]decan-6-ol 31

Borane·THF complex (0.14 ml, 0.14 mmol) was added dropwise to a stirred, cooled (0 °C) solution of alkene **30a** (0.048 g, 0.13 mmol) in THF (1 ml). After stirring at room temperature for 2.5 h the mixture was cooled to 0 °C and 3 M NaOH (0.05 ml, 0.14 mmol) and hydrogen peroxide (0.06 ml, 0.48 mmol) were added dropwise such that the reaction temperature did not exceed 35 °C. On completion of the addition, the reaction was heated at reflux for 1 h, cooled to room temperature, quenched with saturated aq. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated. Flash column chromatography (4:1 petrol–ether) then afforded the title diol **31** (0.032 g, 63%) (Found M^+, 388.2645. $C_{20}H_{40}O_5Si$ requires *M*, 388.2645); $\nu_{max}(CDCl_3)/cm^{-1}$ 3392, 1255, 1216, 1077, 840; δ_H 4.28 (1H, dd, J_1 6.4, J_2 4, 4-H), 3.77–3.58 (4H, m, CH_2OSi, 3′-H_2), 2.80 (1H, br, O*H*), 2.45 (1H, br, O*H*), 1.90 (1H, m, 6′-H), 1.76–1.10 (11H, m, 1′-H_2, 2′-H_2, 7-H, 8-H_2, 9-H_2, 10-H_2), 1.43 (3H, s, 2-CH_3), 1.38 (3H, s, 2-CH_3), 0.88 (9H, s, Si^t*Bu*), 0.07 [6H, s, Si(CH_3)$_2$]; δ_C 107.1, 85.5, 78.3, 72.8, 63.4, 63.1, 33.9, 29.1, 29.0, 28.8, 26.9, 26.2, 26.0, 22.7, 20.5, 18.4, −5.1, −5.3; *m*/*z* CI(NH_3) 331 [$MH^+ - (CH_2)_3OH$, 26%], 313 (45), 199 (100).

4-(*tert*-Butyldimethylsilyloxymethyl)-2,2-dimethyl-1,3,7-trioxadispiro[4.4.4.0]tetradecan-8-one 32

A solution of diol **31** (0.035 g, 0.09 mmol) in DCM was added to a stirred suspension of PCC (0.03 g, 0.14 mmol) and alumina (0.15 g) in DCM. After 12 h an additional portion of PCC (0.03 g, 0.14 mmol) was added. After a further 4 h, the reaction mixture was filtered through a pad of Celite and the filtrate washed with water, dried ($MgSO_4$) and concentrated. Flash column chromatography (4:1 petrol–ether) yielded the desired lactone **32** (0.02 g, 79.9%) as a white solid. Mp 64 °C (Found: C, 62.13; H, 9.38. $C_{20}H_{36}O_5Si$ requires C, 62.46; H, 9.43%) (Found MH^+, 385.2410. $C_{20}H_{37}O_5Si$ requires *M*, 385.2410); $\nu_{max}(CDCl_3)/cm^{-1}$ 1768 (C=O lactone), 1463, 1251, 1158, 1018; δ_H 4.15 (1H, m, 4-H), 3.88 (2H, m, CH_2OSi), 2.58 (3H, m, 9-H_2, 10-H), 2.0–1.90 (1H, m, 10-H), 1.90–1.80 (1H, m, 14-H), 1.78–1.45 (7H, m, 11-H_2, 12-H_2, 13-H_2, 14-H), 1.42 (3H, s, 2-CH_3), 1.34 (3H, s, 2-CH_3), 0.89 (9H, s, Si^t*Bu*), 0.07 [6H, s, Si(CH_3)$_2$]; δ_C 176.6 (C=O lactone), 107.6, 87.3, 83.8, 79.8, 62.7, 36.1, 30.0, 29.2, 29.0, 28.8, 26.9, 25.9, 21.2, 20.7, 18.4, −5.3, −5.3; *m*/*z* CI(NH_3) 402 ($M + NH_4^+$, 82%), 253 [$M^+ - (CH_3)_2{}^t$BuSiO, 100].

6-Hydroxy-7-hydroxymethyl-9-propyl-8,12-dioxatricyclo-[7.2.1.0^{1,6}]dodecane 2

To a stirred solution of lactone **32** (0.034 g, 0.09 mmol) in ether (0.5 ml) at −78 °C was slowly added allylmagnesium bromide (0.11 ml, 0.086 mmol). After 0.5 h at this temperature the reaction was quenched with saturated aq. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated to afford a yellow oil which was subsequently purified by flash column chromatography (3:1 petrol–ether) to afford the desired lactol **33** (0.037 g, 95%) as a mixture of inseparable isomers.

This lactol **33** (0.058 g, 0.14 mmol) was reduced following an analogous procedure as that described for alcohol **11** to afford the methyl ketal **34** (0.057 g, 94%) as a colourless oil.

12 M HCl (0.06 ml, 0.72 mmol) in methanol (1 ml) was added to a stirred solution of **34** (0.052, 0.12 mmol) in methanol (1 ml) at 0 °C. The mixture was then heated at reflux for 12 h whereupon the reaction was quenched with saturated aq. NH_4Cl, extracted with ether, dried ($MgSO_4$) and concentrated. Flash column chromatography (2:1 petrol–ether) afforded the title ketal **2** (0.011 g, 37%) as a white solid. Mp 78–79 °C (Found MH^+, 257.1753. $C_{14}H_{25}O_4$ requires *M*, 257.1753) $\nu_{max}(CDCl_3)/cm^{-1}$ 1676, 1596, 1211, 1190, 1077; δ_H 4.29 (1H, dd, *J* 5.9, 3.0, 7-H), 3.50 (2H, m, CH_2OH), 2.07 (1H, m, 10-H), 1.93 (2H, m, 10-H, 11-H), 1.68 (6H, m, 2 × OH, 5-H, 11-H, 1′-H_2), 1.53–1.42 (9H, m, 2-H_2, 3-H_2, 4-H_2, 5-H, 2′-H_2), 0.93 (3H, t, *J* 5.9, 3′-H_3); δ_C 108, 83.5, 78.3, 69.1, 63.1, 39.5, 33.40, 33.37, 33.1, 24.8, 21.1, 20.3, 16.7, 14.2; *m*/*z* CI(NH_3) 257 (MH^+, 100%), 239 ($MH^+ - H_2O$, 100).

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