Studies on the stereoselectivity of osmylation of *cis*-bicyclo[3.3.0]-oct-6-enes

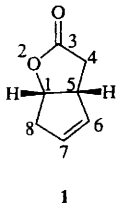
Nigel Broom,[b] Peter J. O'Hanlon,[b] Thomas J. Simpson,[a] Rosamund Stephen[a] and Christine L. Willis*,[a]

[a] *School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, UK*
[b] *SmithKline Beecham Pharmaceuticals, Brockham Park, Betchworth, Surrey RH3 7AJ, UK*

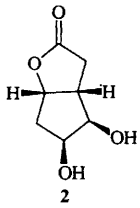
Treatment of *cis*-2-oxabicyclo[3.3.0]oct-6-en-3-one 1 with osmium tetraoxide under a variety of conditions led predominantly to attack from the more hindered face of the alkene to give, after protection of the diol, the *endo*-acetonide 8 as the major product. It is apparent that the stereochemical outcome of this reaction is due to a directing effect from the lactone carbonyl at C-3 since osmylation of the analogous lactols 3, acetals 4 and cyclic ethers 5 gave attack mainly from the less hindered *exo*-face. The *exo*-acetonide 7 was prepared in a 3-stage procedure from *cis*-bicyclo[3.2.0]heptenone 6 in 54% yield. In this case the stereoselectivity of the osmylation reaction was governed, as expected, by the conformation of the bicyclic skeleton, no directing effect from the ketone carbonyl was apparent.

Introduction

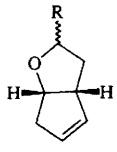
In studies towards the stereoselective functionalisation of *cis*-2-oxabicyclo[3.3.0]oct-6-enes such as **1** to give intermediates for the preparation of polyketide-derived natural products, we required the *exo*-diol **2**. Osmium tetraoxide has been used extensively to prepare *syn* diols from alkenes.[1] It is well established that the stereochemical outcome of the reaction may be affected by the presence of allylic substituents such as



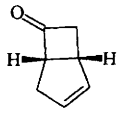
1



2



3 R = OH
4 R = OMe
5 R = CH_2CO_2Me

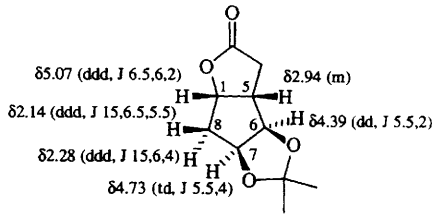


6

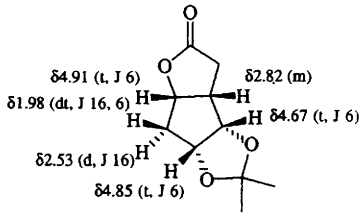
alcohols.[2] However, in the case of **1** with no allylic functional groups, it was anticipated, by analogy for example with the Prins reaction on **1** with formaldehyde,[3] that attack would occur predominantly from the open, convex face of the alkene to give the *exo*-diol **2**. Surprisingly, we have found that variations in the functionality at C-3 have a significant effect on the stereochemistry of the *syn* 6,7-diol formed. The results of osmylation studies on a series of *cis*-2-oxabicyclo[3.3.0]oct-6-enes **1**, **3**, **4** and **5** as well as on the ketone **6** are now described.

Results and discussion

Treatment of the alkene **1** with a catalytic amount of osmium tetraoxide in the presence of *N*-methylmorpholine *N*-oxide (NMMNO)[4] in acetone followed by protection of the resultant *syn* diols, using dimethoxypropane and camphorsulfonic acid, gave a mixture of two products **7** and **8** which were separated by flash chromatography (Scheme 1). The more polar product was



7



8

Fig. 1 Assignment of selected ^{1}H NMR resonances in **7** and **8**

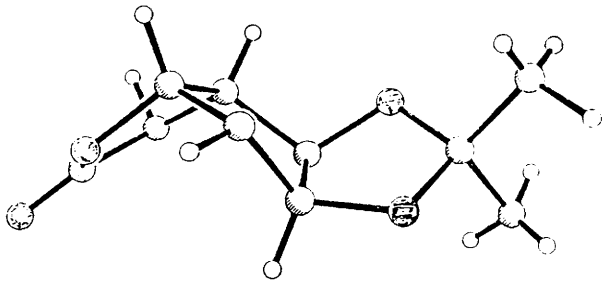
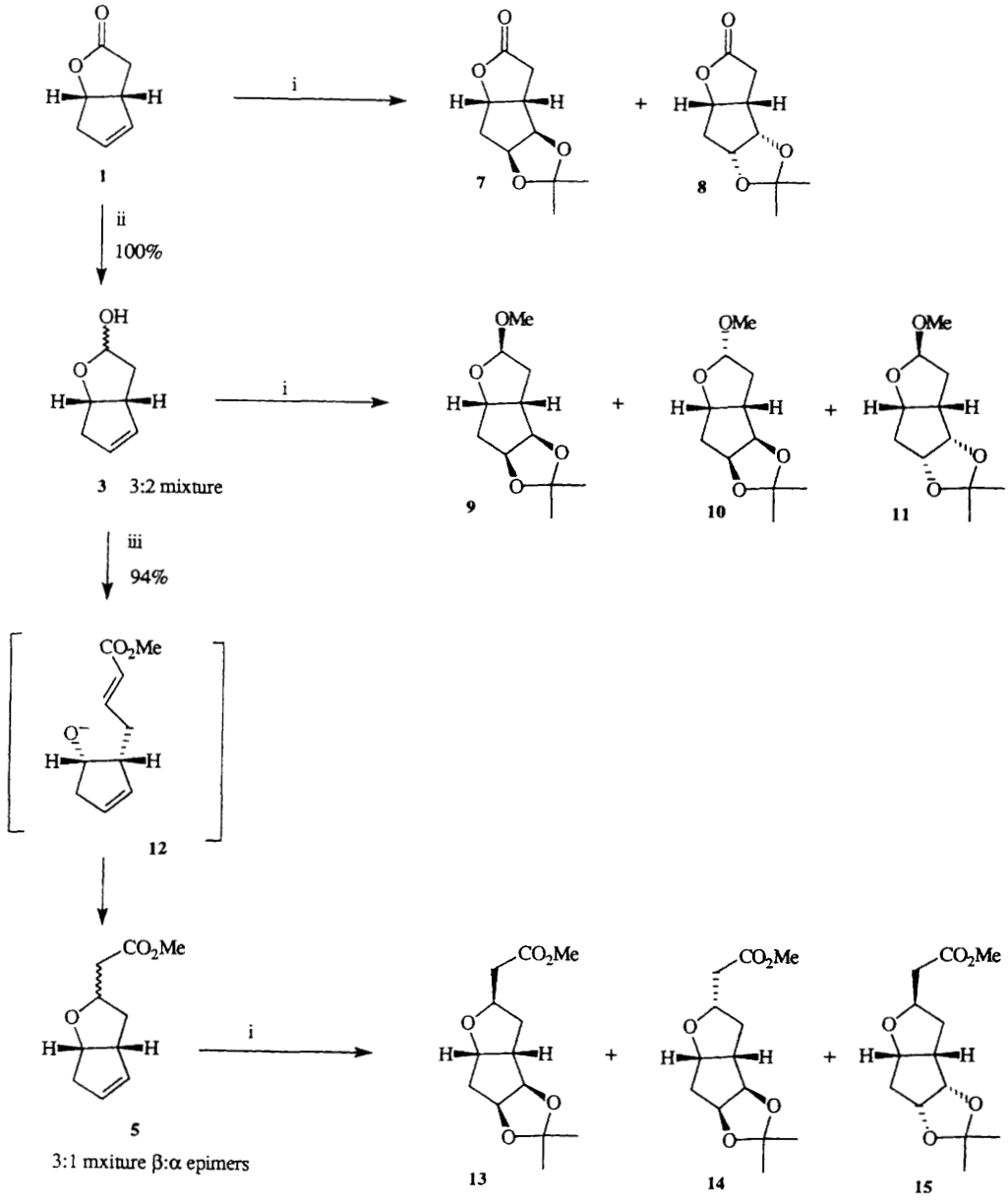


Fig. 2 X-Ray crystal structure of *exo*-acetonide **7**

crystalline and was isolated in 30% yield, while the less polar compound was a gum obtained in 68% yield. The assignments of the signals in the ^{1}H NMR spectra of the two acetonides **7** and **8** are given in Fig. 1. From an examination of molecular models it was apparent that in the case of the *endo*-acetonide, all the hydrogens on the β-face are essentially eclipsed and therefore have dihedral angles of 0° giving rise to mutual vicinal couplings, all of 6 Hz. In addition, 8α-H couples solely to 8β-H since it has a dihedral angle of close to 90° to both 7-H and 1-H and so the major product was assigned as the *endo*-isomer **8**. The more complex coupling pattern of the minor product is



Scheme 1 *Reagents:* i, OsO_4, NMMNO, Me_2CO then H^+, $Me_2C(OMe)_2$; ii, DIBALH; iii, $Ph_3P{=}CHCO_2Me$

in accord with the *exo*-acetonide **7**. This assignment was confirmed by X-ray crystallography (Fig. 2).[5]

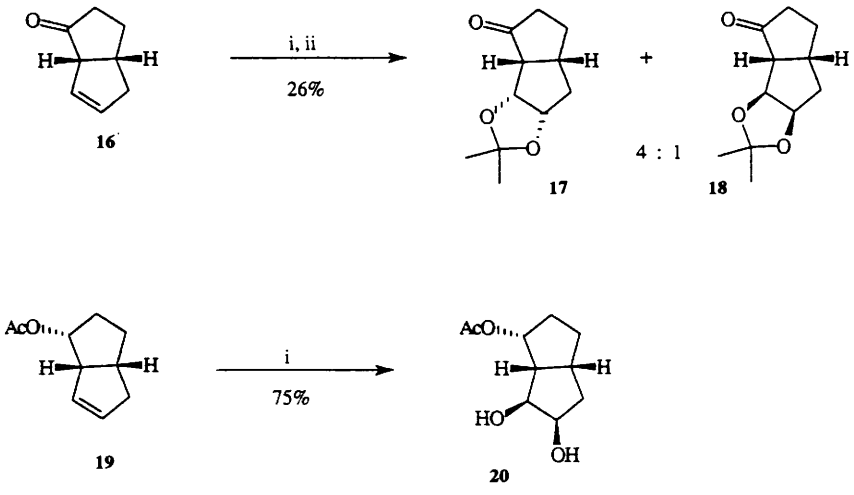
Thus it is apparent that *cis*-hydroxylation of the unsaturated lactone **1** and subsequent protection of the resultant *syn*-diol proceeded in good yield (98% overall) to give the *endo*-acetonide **8** as the major product. Similar stereoselectivity was observed when the osmylation of **1** was repeated using a stoichiometric amount of osmium tetraoxide in a 1:1 mixture of chloroform and pyridine.

Table 1 Stereochemical outcome of osmylation of alkene under catalytic conditions followed by protection of the resultant *syn* diol with 2,2-dimethoxypropane

Alkene	Solvent	Products	Product ratio (*exo*:*endo*)
1	acetone	**7** and **8**	1:2
1	propanol	**7** and **8**	1:2.5
1	water	**7** and **8**	1:7
3	acetone	**9**, **10** and **11**	4.5:1
4	acetone	**9**, **10** and **11**	4:1
5	acetone	**13**, **14** and **15**	>6:1
6	acetone	**7** and **8** (after Baeyer–Villiger oxidation)	9:1

It has been reported recently that the stereochemistry of the osmium-catalysed dihydroxylation of a series of homochiral allylic amides and carbamates is dependent upon the polarity of the solvent.[6] To investigate whether the stereochemistry of the osmium-catalysed dihydroxylation of **1** was also affected by the solvent, the reaction was repeated in propan-2-ol, and water. In propanol a 2.5:1 mixture of *endo*-:*exo*-acetonides **8**:**7** was obtained in 55% yield from **1** (a similar ratio to that obtained when acetone was used as the solvent), whereas in water a 7:1 mixture of *endo*-:*exo*-acetonides was formed in 73% yield (see Table 1). Therefore, it is apparent that greater stereoselectivity can be achieved using water as the solvent for the osmium-catalysed dihydroxylation of **1**; however, in each case the *endo*-acetonide **8** was the major product.

A possible reason for the preferred attack of osmium tetraoxide to the sterically more hindered face of the alkene in the unsaturated lactone **1** may be a directing effect from the carbonyl group at C-3. Interestingly, it has been reported recently[7] that osmylation of the *cis*-bicyclo[3.3.0]oct-7-en-2-one **16** also occurs predominantly from the more hindered *endo*-face to give **17** as the major product, whereas the acetate **19**



Scheme 2 *Reagents:* i, OsO_4, NMMNO, THF, Bu^{t}OH, H_2O; ii, $Me_2C(OMe)_2$, CH_2Cl_2, TsOH

gives the *exo*-diol **20** (Scheme 2). To examine whether the carbonyl was indeed directing osmylation of **1** to the *endo*-face, we repeated the reaction on a mixture of the epimeric lactols **3**.

Reduction of **1** with DIBALH (diisobutylaluminium hydride) gave the lactol **3** as a 3:2 mixture of epimers in quantitative yield (Scheme 1).[8] Osmium-catalysed dihydroxylation of the mixture of lactols in acetone followed by protection of the resultant diols using dimethoxypropane under acidic conditions gave a mixture of products in 98% yield. From the ^{1}H NMR spectrum of the crude mixture it was apparent that three products had been formed in a 5:4:2 ratio and that in each case the conditions used for the protection of the diols had also led to conversion of the lactol into a methyl acetal. The products ran very closely together by TLC but were successfully separated by multiple elution PLC. However, it was difficult to assign their ^{1}H NMR spectra unambiguously and hence deduce the stereochemistry of the three acetonides. Therefore, the structures were confirmed *via* chemical correlation as follows.

The *endo*-acetonide **8**, prepared from the lactone **1** as described above, was reduced with DIBALH and the resultant lactol then treated with dimethoxypropane under acidic conditions to give the 3β-methyl acetal **11** as the sole product. In the ^{1}H NMR spectrum of **11** the methoxy group resonated as a singlet at δ 3.34 and 3-H gave a doublet of doublets (J 5.7 and 2.3 Hz) at δ 5.07. Steric hinderance from the *endo*-acetonide prevents the formation of the 3-epimer, *i.e.* the *endo*-acetonide 3α-methyl acetal. The *exo*-acetonide **7** was reduced and protected in an analogous way to give the two expected C-3 epimers in a ratio of 1.2:1 by ^{1}H NMR. These epimeric acetals, **9** and **10**, were separated by multiple elution PLC. In the ^{1}H NMR spectrum of the less polar product, the methoxy group gave a singlet at δ 3.31 and 3-H a broad doublet (J 5.5 Hz) at δ 5.02 and was tentatively assigned the structure **9**. In the more polar product **10** the methoxy group gave a singlet at δ 2.89 and 3-H appeared as a doublet (J 5 Hz) at δ 4.94. Due to the similar coupling constants (J 5 or 5.5) for 3-H in both **9** and **10** the stereochemistry at C-3 could not be assigned conclusively. NOE studies gave no further useful distinction. However, by comparison of the spectral data (further details of which are given in the Experimental section) of the three acetonides **9**, **10** and **11** with those isolated from the osmylation/protection reaction on the lactols **3**, it may be concluded that osmylation of **3** occurs predominantly on the *exo*-face of the alkene to give a 9:2 mixture of **9** and **10**:**11** (Scheme 1).

During the osmylation of **3**, it is possible that the lactol may have opened to the hydroxy aldehyde thus affecting the conformation of the molecule. In order to eliminate this possibility, the lactols **3** were converted into the methyl acetal derivatives **4** by treatment with Dowex in methanol. From the ^{1}H NMR spectrum it was apparent that a 2:7 mixture of α:β epimers were formed which were inseparable by flash chromatography. In the major isomer, the signal for the methoxy group appears at δ 3.35 and the 3-H was coupled to both protons on C-4, whereas in the minor isomer, this signal appears at δ 3.28 and the 3-H coupled to only the 4β-H since there is a dihedral angle of 90° between 3-H and 4α-H. Osmylation of the mixture of acetals **4** followed by protection of the resultant *syn* diols as before, gave a mixture of the three acetonides **9**, **10** and **11** in essentially quantitative yield and in the ratio 3:1:1. Hence it is apparent that osmylation of a *cis*-2-oxabicyclo[3.3.0]oct-6-ene which does not contain a carbonyl group at C-3 indeed occurs mainly from the less hindered *exo*-face (*i.e.* approximately 4:1 *exo*:*endo* attack in the case of both the lactols **3** and the acetals **4**), whereas in the presence of the 3-carbonyl group attack is predominantly on the more hindered face of the double bond (1:2 *exo*:*endo* attack, see Table 1). A final experiment which further verified these conclusions was the osmylation of the unsaturated bicyclic ether **5**. The ether **5** was synthesised from the lactol **3** *via* a Wittig chain extension using methyl (triphenylphosphoranylidene)acetate (Scheme 1). The intermediate unsaturated ester **12** was not isolated but immediately cyclised *via* a conjugate addition to give a 3:1 mixture of isomers of **5** in 94% yield. Osmium-catalysed dihydroxylation of the cyclic ethers **5** in acetone followed by acetonide formation gave a mixture of three compounds **13**, **14** and **15** in which it was apparent that >6:1 *exo*:*endo* stereoselection had occurred during the osmylation reaction. The structures of the acetonides **13**, **14** and **15** were confirmed by chemical correlation *via* DIBALH reduction followed by the Wittig chain extension on both the *exo*-acetonide **7** and *endo*-acetonide **8**.

Therefore, returning to the original problem of the synthesis of the *exo*-diol **2**, it was found that the corresponding acetonide **7** could be prepared efficiently as follows. It has previously been shown[9] that the lactone **1** may be prepared in good yield *via* a Baeyer–Villiger oxidation of the *cis*-bicyclo[3.2.0]heptenone **6**. Although **6** has a ketone moiety which may direct *syn*-hydroxylation of the double bond to the *endo*-face, examination of molecular models reveals that the *endo*-face of the double bond is more hindered than in the case of the lactone **1**. This has been demonstrated previously, for example, by the reaction of **6** with bromine in acetic acid which proceeds exclusively *via* the *exo*-bromonium ion,[10] whereas reaction of the lactone **1** under the same conditions gives a mixture of *exo*- and *endo*-bromonium ions. Hence, the ketone **6** in acetone was treated with osmium tetraoxide under catalytic conditions. The resultant *syn* diols were protected as the acetonides and the

crude mixture of products subjected to a Baeyer–Villiger oxidation with *m*-chloroperoxybenzoic acid (MCPBA). The required *exo*-acetonide **7** was isolated as the major product in 54% overall yield from **6**. The minor product **8** was formed in only 6% yield.

In conclusion, we have shown that treatment of *cis*-2-oxabicyclo[3.3.0]oct-6-en-3-one **1** with osmium tetraoxide under a range of conditions unexpectedly gave the *endo*-diol as the major product.[11] The stereochemical outcome of this reaction appears to be due to a directing effect from the lactone carbonyl at C-3 and indeed treatment of lactols **3**, acetals **4** or the cyclic ethers **5** with osmium tetraoxide gave attack predominantly from the less hindered *exo* face (Table 1). In contrast, osmylation of bicyclo[3.2.0]heptenone **6** gives mainly *exo* attack on the alkene leading, after Baeyer–Villiger oxidation, to a 9:1 mixture of *exo*- and *endo*-acetonides **7** and **8**. In this case the carbonyl group does not effect the stereochemical outcome of the reaction and predominant attack of osmium tetraoxide from the less hindered *exo*-face is observed.

Experimental

General experimental details are described in a previous paper.[12] ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM GX-400 MHz spectrometer with deuteriochloroform as the solvent unless otherwise stated, using tetramethylsilane as the internal standard.

General procedure for the osmylation reactions and subsequent formation of the isopropylidene derivative

A solution of *N*-methylmorpholine *N*-oxide (1.1 equiv.), unsaturated substrate (1 equiv.) and a small crystal of osmium tetraoxide (catalytic) in solvent (*ca.* 10 cm^3/100 mg) was stirred at room temperature until TLC showed complete reaction. The solvent was removed under reduced pressure to yield the crude diol and the product was purified by dry flash chromatography. The purified diol was then dissolved in acetone (*ca.* 5 cm^3, 100 mg) and 2,2-dimethoxypropane (*ca.* 5 cm^3, 100 mg) and camphorsulfonic acid (catalytic) were added to it. The reaction mixture was stirred at room temperature until TLC showed that the reaction was complete. The reaction mixture was then washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride and the aqueous layers were extracted with ethyl acetate. The combined organic phases were dried and the solvent removed under reduced pressure to yield the crude product. The ratio of isomeric products was obtained from the ^{1}H NMR spectrum of the crude product of the reaction. Further purification may then be carried out.

Osmylation of the unsaturated lactone 1 in acetone

The osmylation reaction was carried out according to the general procedure using lactone **1** (500 mg, 4.0 mmol) as the substrate and acetone as the solvent. After 4 h no starting material was observed by TLC. Protection of the resultant diol as the isopropylidene derivative was then carried out, again according to the general procedure. After 24 h two components were observed by TLC which were separated by flash column chromatography [light petroleum–ethyl acetate (1:1)]. The less polar product was the *endo*-acetonide **8** which was obtained as a yellow oil (0.542 g, 67.8%) and the more polar component was the *exo*-acetonide **7** obtained as a white crystalline solid (0.242 g, 30.3%).

***endo*-Acetonide 8.** ν_{max}/cm^{-1} 2983, 2938, 1770 and 1071; δ_H 1.30 and 1.44 (6 H, 2 × s, 2 × CH_3), 1.98 (1 H, dt, *J* 16, 6, 8β-H), 2.53 (1 H, d, *J* 16, 8α-H), 2.56 (1 H, dd, *J* 17 and 9, 4α-H), 2.81 (1 H, d, *J* 17, 4β-H), 2.82 (1 H, m, 5-H), 4.67 (1 H, t, *J* 6, 6-H), 4.85 (1 H, t, *J* 6, 7-H) and 4.91 (1 H, t, *J* 6, 1-H); *m*/*z* (NH_3; CI) 199 ([MH]$^+$, 15%), 183 (70), 141 (45) and 123 (100) (Found: [MH]$^+$, 199.0965. $C_{10}H_{15}O_4$ requires MH, 199.0970).

***exo*-acetonide 7.** Mp 69–71 °C (from light petroleum–ethyl acetate); ν_{max}/cm^{-1} 2985, 2936 and 1770; δ_H 1.23 and 1.40 (6 H, 2 × s, 2 × CH_3), 2.14 (1 H, ddd, *J* 15, 6.5 and 5.5, 8α-H), 2.80 (1 H, ddd, *J* 15, 6 and 4, 8β-H), 2.94 (1 H, m, 5-H), 2.52 (2 H, dd, *J* 18 and 6, 4β-H), 2.75 (1 H, dd, *J* 18 and 11, 4α-H), 2.95 (1 H, m, 5-H), 4.39 (1 H, dd, *J* 5.5 and 2, 6-H), 4.73 (1 H, td, *J* 5.5 and 4, 7-H) and 5.07 (1 H, ddd, *J* 6.5, 6 and 2, 1-H); *m*/*z* (NH_3; CI) 199 ([MH]$^+$, 14%), 183 (82), 141 (65) and 123 (100) (Found: C, 60.96; H, 7.30. $C_{10}H_{14}O_4$ requires C, 60.59; H, 7.12%) (Found [MH]$^+$, 199.0965. $C_{10}H_{15}O_4$ requires MH, 199.0970).

Osmylation of the unsaturated lactone 1 in propan-2-ol

The osmylation reaction was carried out according to the general procedure using lactone **1** (100 mg, 0.81 mmol) as the substrate and propan-2-ol as the solvent. After 24 h no starting material was observed by TLC. Protection of the resultant diol as the isopropylidene derivative was then carried out, again according to the general procedure. After 24 h TLC showed the reaction to be complete and the crude product was obtained as a light brown oil (86.2 mg, 55%). ^{1}H NMR of the crude product showed that a 2.5:1 mixture of *endo*:*exo* acetonides **8**:**7** had been formed (based on the integrals of the signals assigned to 1-H in each isomer).

Osmylation of the unsaturated lactone 1 in water

The osmylation reaction was carried out according to the general procedure using lactone **1** (100 mg, 0.81 mmol) as the substrate and water as the solvent. After 48 h no starting material was observed by TLC. Protection of the resultant diol as the isopropylidene derivative was then carried out according to the general procedure. After 24 h TLC showed the reaction to be complete and the crude product was obtained as a light brown oil (116 mg, 73%). ^{1}H NMR of the crude product showed that a 7:1 mixture of *endo*:*exo* acetonides **8**:**7** had been formed (based on the integrals of the signals assigned to 1-H in each isomer).

(±)-*cis*-2-Oxabicyclo[3.3.0]oct-6-en-3ξ-ol 3

To a stirred solution of the lactone **1** (500 mg, 4.0 mmol) in THF (30 cm^3) at −78 °C was added DIBALH (1 mol dm^{-3} solution in pentane, 12.1 cm^3, 12.1 mmol). The reaction mixture was stirred for 4 h at −78 °C by which time no starting material was observed by TLC. A saturated aqueous solution of Rochelle salt (potassium sodium tartrate) (20 cm^3) was added and the reaction mixture stirred for at room temperature for 0.5 h. The aqueous layer was extracted with ethyl acetate (4 × 30 cm^3) and the combined organic layers washed with saturated aqueous sodium chloride (20 cm^3). The solvent was removed under reduced pressure to yield the crude product as a yellow oil (0.522 g), which was purified using dry flash column chromatography to give the purified lactol **3** as a viscous, light yellow oil (0.498 g, 98%). This was shown to be a 3:2 mixture of isomers by ^{1}H NMR spectroscopy; ν_{max}/cm^{-1} (liquid film) 3403, 2931 and 1035; δ_H 2.0 (4 H, m, 8-H_2 and 8-H_2′), 2.5 (4 H, m, 4-H_2 and 4-H_2′), 3.4 (2 H, m, 5-H and 5-H′), 4.79 (1 H, t, *J* 4, 1-H), 4.89 (1 H, t, *J* 4, 1-H′), 5.4 (1 H, d, *J* 5, 3-H), 5.5 (1 H, dd, *J* 5 and 2, 3-H′) and 5.7 (4 H, m, 6-H, 6-H′, 7-H and 7-H′); *m*/*z* (NH_3; CI) 12 ([MH]$^+$, 1.5%), 109 (100), 81 (40), 79 (25) and 57 (29).

Osmylation of unsaturated lactol 3 in acetone

The osmylation reaction was carried out according to the general procedure using lactol **3** (50 mg, 0.40 mmol) as the substrate and acetone as the solvent. After 3 h no starting material was observed by TLC. Protection of the resultant diol as the isopropylidene derivative was then carried out again according to the general procedure. After 4 h TLC indicated the reaction had reached completion. The crude product was obtained as a light brown oil (81.5 mg, 96%). TLC of the crude product indicated the presence of three components of similar

polarity. From the integrals assigned to the 3-H in each isomer in the ^{1}H NMR spectrum, it was apparent that a 5:4:2 mixture of **9**:**10**:**11** had been formed. A portion of the mixture (15 mg) was purified by TLC using light petroleum–ethyl acetate (20:1) as the solvent system and eluting the plates 10 times, giving in each case the purified product as a gum.

***exo*-Acetonide 9.** ν_{max}/cm^{-1} 2934, 1075 and 1033; δ_H(270 MHz) 1.28 (3 H, s, CH_3), 1.48 (3 H, s, CH_3'), 1.81 (1 H, ddd, *J* 13, 7 and 5, 4α-H), 2.12 (1 H, br t, *J* 5, 8α-H), 2.12 (1 H, br t, *J* 5, 8β-H), 2.20 (1 H, br dd, *J* 13 and 9, 4β-H), 2.88 (1 H, m, 5-H), 3.31 (3 H, s, 3-OMe), 4.32 (1 H, dd, *J* 5 and 1.5, 6-H), 4.73 (1 H, br q, *J* 5.0, 1-H), 4.77 (1 H, br q, *J* 5.0, 7-H) and 5.02 (1 H, br d, *J* 5.5, 3-H); *m*/*z* (NH_3; CI) 215 ([MH]$^+$, 3%), 183 (100), 125 (39), 97 (15), 85 (34), 83 (100) and 59 (49) (Found: [MH]$^+$, 215.1130. $C_{11}H_{19}O_4$ requires MH, 215.1127).

***exo*-Acetonide 10.** ν_{max}/cm^{-1} 2983, 1068 and 1025; δ_H(270 MHz) 1.29 (3 H, s, CH_3), 1.47 (3 H, s, CH_3), 1.92–2.30 (4 H, overlapping signals, 4-H_2 and 8-H_2), 2.81 (1 H, m, 5-H), 3.89 (3 H, s, 3-OMe), 4.78 (1 H, td, *J* 6.5 and 2.5, 1-H), 4.55 (1 H, dd, *J* 5.5 and 1.5, 6-H), 4.73 (1 H, br q, *J* 5.5, 7-H) and 4.94 (1 H, d, *J* 5, 3-H); *m*/*z* (NH_3; CI) 199 (5%), 183 (3), 157 (2), 139 (3), 125 (12) and 83 (100).

***endo*-Acetonide 11.** δ_H(270 MHz) 1.3 (3 H, s, CH_3), 1.47 (3 H, s, CH_3) 1.86 (1 H, ddd, *J* 14, 6 and 2.3, 4α-H), 1.90 (1 H, ddd, *J* 16, 6 and 5, 8β-H), 2.28 (1 H, d, *J* 16, 8α-H), 2.60 (1 H, m, 4β-H), 2.66 (1 H, m, 5-H), 3.34 (3 H, s, 3-OMe), 4.52 (1 H, br t, *J* 6.0, 6-H), 4.56 (1 H, t, *J* 5.0, 1-H), 4.78 (1 H, t, *J* 6.0, 7-H) and 5.07 (1 H, dd, *J* 5.7 and 2.3, 3-H); *m*/*z* (NH_3; CI) 215 ([MH]$^+$, 2%), 199 (8), 183 (35), 125 (26), 109 (18) and 83 (100) (Found: [M − 31]$^+$, 183.1020. $C_{10}H_{15}O_3$ requires M − 31, 183.1021).

DIBALH reduction of *exo*-acetonide 7 followed by derivatisation

To a stirred solution of *exo*-acetonide **7** (180 mg, 0.9 mmol) in THF (20 cm^3) at −78 °C was added DIBALH (1 mol dm^{-3} solution in pentane; 2.3 cm^3, 2.3 mmol). The reaction mixture was stirred for 4 h at −78 °C by which time no starting material was observed by TLC. The reaction mixture was quenched with a saturated aqueous solution of Rochelle salt (20 cm^3) and the resulting gelatinous mixture stirred at room temperature for 0.5 h. The aqueous layer was extracted with ethyl acetate (5 × 20 cm^3) and the combined organic layers washed with saturated aqueous sodium chloride (20 cm^3). The solvent was removed under reduced pressure to yield the crude product as a yellow oil (238 mg, 129%). A portion of the crude product (50 mg) was dissolved in methanol (2 cm^3) and 2,2-dimethoxypropane (1 cm^3) and a catalytic amount of DOWEX were added. The reaction mixture was stirred at room temperature for 12 h after which time no starting material was observed by TLC. The reaction mixture was washed with saturated aqueous sodium hydrogen carbonate (5 cm^3) and the aqueous layers extracted with ethyl acetate (3 × 10 cm^3). The combined organic phases were dried and the solvent removed under reduced pressure to yield the crude product as a yellow oil (55 mg, 102%). ^{1}H NMR of the crude product showed that a 1.2:1 mixture of acetonides **9**:**10** had been formed. The epimeric acetals were separated by multiple elution PTLC; spectroscopic data as before.

DIBALH reduction of *endo*-acetonide 8 followed by derivatisation

To a stirred solution of *endo*-acetonide **8** (140 mg, 0.7 mmol) in THF (20 cm^3) at −78 °C was added DIBALH (1 mol dm^{-3} solution in pentane; 2.1 cm^3, 2.1 mmol). The reaction mixture was stirred for 4 h at −78 °C by which time TLC showed that no starting material was present. The reaction mixture was quenched with a saturated aqueous solution of Rochelle salt (20 cm^3) and the resulting gelatinous mixture stirred at room temperature for 0.5 h. The aqueous layer was extracted with ethyl acetate (5 × 20 cm^3) and the combined organic layers washed with saturated aqueous sodium chloride (20 cm^3). The solvent was removed under reduced pressure to yield the crude product as a yellow oil (140 mg, 98%). A portion of the crude product (120 mg, 0.6 mmol) was dissolved in methanol (2 cm^3) and dimethoxypropane (1 cm^3) and a catalytic amount of camphorsulfonic acid were added. The reaction mixture was stirred at room temperature for 12 h after which time no starting material was observed by TLC. The reaction mixture was washed with saturated aqueous sodium hydrogen carbonate (5 cm^3) and the aqueous layers extracted with ethyl acetate (3 × 10 cm^3). The combined organic phases were dried and the solvent removed under reduced pressure to yield the crude product as a yellow oil (139 mg, 92%). ^{1}H NMR of the crude product showed that the single isomer of the *endo*-acetonide **11** had been formed. The product was purified by flash chromatography; spectroscopic data as before.

(±)-*cis*-2-Oxa-3ξ-methoxybicyclo[3.3.0]oct-6-ene 4

A catalytic amount of DOWEX was added to a solution of the lactol **3** (115 mg, 0.9 mmol) in methanol (10 cm^3) and the mixture stirred at room temperature for 2 h. After this time TLC showed that no starting material was present. Saturated aqueous sodium hydrogen carbonate (10 cm^3) was added to it and the aqueous phase extracted with ethyl acetate (3 × 20 cm^3). The combined organic layers were washed with saturated aqueous sodium chloride (20 cm^3), dried and the solvent removed under reduced pressure to yield the methoxy acetal **4** (83 mg, 75%) as a 1:3.6 mixture of α:β isomers at C-3, as shown by ^{1}H NMR spectroscopy, which were inseparable by flash chromatography, ν_{max}/cm^{-1} (liquid film) 3420, 2930, 1057 and 851; δ_H for major isomer 1.81 (1 H, dt, *J* 13.0 and 5.0, 4β-H), 2.13 (1 H, ddd, *J* 13.0, 9.5 and 1.3, 4α-H'), 2.47 (1 H, br d, 8α-H), 2.61 (1 H, m, 8β-H), 3.35 (3 H, s, OCH_3), 3.40 (1 H, m, 5-H), 4.73 (1 H, t, *J* 6.5, 1-H), 5.01 (1 H, overlapping m, 3-H) and 5.60 (2 H, m, 6-H and 7-H); δ_H(500 MHz) for minor isomer 1.95 (1 H, d, 13.5, 4α-H), 2.12 (1 H, overlapping signal, 4β-H) 2.53 (1 H, m, 8α-H), 2.68 (1 H, m, 8β-H), 3.28 (3 H, s, OCH_3), 3.39 (1 H, m, 5-H), 4.87 (1 H, br t, 7.0, 1-H), 5.0 (1 H, overlapping m, 3-H) and 5.67 (2 H, m, 6-H and 7-H); *m*/*z* (NH_3; CI) 141 ([MH]$^+$, 9.7%), 123 (34), 109 (74), 85 (58), 71 (54) and 57 (100) (Found: [MH]$^+$, 141.0918. $C_8H_{13}O_2$ requires MH, 141.0916).

Osmylation of the unsaturated acetal 4 in acetone

The osmylation was carried out according to the general procedure, using acetal **4** (63 mg, 0.45 mmol) as the substrate and acetone as the solvent. Protection of the resultant diol as the isopropylidene derivative was then carried out, again according to the general procedure, and the crude product was obtained as a yellow oil (93 mg, 97%). From the integrals of the signals assigned to 3-H in each isomer in the ^{1}H NMR spectrum of the crude product, it was apparent that a 3:1:1 mixture of **9**:**10**:**11** had been formed.

Treatment of lactol 3 with methyl (triphenylphosphoranylidene)-acetate

A solution of the lactol **3** (250 mg, 1.98 mmol) in acetonitrile (10 cm^3) was added dropwise over 15 min to a stirred solution of methyl (triphenylphosphoranylidene)acetate (1.0 g, 2.98 mmol) and sodium hydrogen carbonate (250 mg, 3.6 mmol) in acetonitrile (10 cm^3) at 35 °C. After 2 h, no starting material was observed by TLC and the reaction mixture was cooled, filtered through a bed of Celite and the filtrate absorbed onto silica. The crude product was purified by flash column chromatography [light petroleum–ethyl acetate (200 cm^3 9:1, 200 cm^3 4:1 then 7:3)] to give the bicyclic ether **5** (321 mg, 89%) as an inseparable 3:1 mixture of the β:α isomers at C-3, as shown by ^{1}H NMR spectroscopy, ν_{max}/cm^{-1} (liquid film) 2927, 1735 and 1436; δ_H

for major isomer 1.69 (1 H, ddd, *J* 17.5, 12.5 and 5.5, 8β-H), 1.96 (1 H, br dd, *J* 12.0 and 5.0, 8α-H), 2.55 (4 H, m, 9-H_2, 4-H_2), 3.39 (1 H, m, 5-H), 3.69 (3 H, s, CO_2CH_3), 4.19 (1 H, m, 3-H), 4.76 (1 H, t, *J* 6.5, 1-H), 5.53 (1 H, ddd, *J* 6.0, 4.5 and 2.0, 7-H), 5.75 (1 H, ddd, *J* 6.0, 4.5 and 2.0, 6-H); *m/z* (NH_3; CI) 169 ($[MH]^+$, 0.7%), 149 (100), 113 (92), 109 (78), 71 (67) and 57 (71).

Osmylation of the unsaturated bicyclic ether 5 in acetone

The osmylation was carried out according to the general procedure using the [3.3.0] bicyclic ether **5** (50 mg, 0.27 mmol) as the substrate and acetone as the solvent. After 1 h no starting material was observed by TLC and the crude diol was obtained as a yellow oil (65.2 mg, 112%). Protection of the diol as the isopropylidene derivative was then carried out, again according to the general procedure. After 0.5 h TLC indicated the reaction had reached completion and the crude product was obtained as a yellow oil (74.3 mg, 105%). TLC indicated the presence of three close running components, which were shown by ^1H NMR of the crude product to be in the ratio 1:2.5:11. Separation of these components by MPLC was attempted but was unsuccessful, giving the purified mixture of products as a colourless oil (49.1 mg, 70%). A small scale separation of the products was carried out by multiple elution TLC using light petroleum–ethyl acetate (20:1) as the solvent system, which led to successful purification of the major product **13**, but the minor components, **14** and **15**, were again obtained as a mixture.

***endo*-Acetonide 13.** δ_H 1.26 (3 H, s, CH_3), 1.43 (3 H, s, CH_3), 1.82 (1 H, ddd, *J* 13.0, 9.0 and 7.5, 4-H), 1.97 (1 H, ddd, *J* 13.0, 6.5 and 4.0, 4-H), 2.05 (2 H, t, *J* 5.0, 3′-H_2), 2.38 (1 H, dd, *J* 15.0 and 6.0, 8-H), 2.56 (1 H, dd, *J* 15.0 and 7.0, 8-H), 2.77 (1 H, m, 5-H), 3.66 (3 H, s, CO_2CH_3), 4.27 (1 H, t, *J* 7.0, 1-H), 4.34 (1 H, dd, *J* 5.5 and 2.0, 6-H) and 4.72 (2 H, m, 3-H and 7-H); *m/z* (NH_3; CI) 257 ($[MH]^+$, 33%), 241 (27), 237 (17), 199 (23), 183 (41), 83 (100) and 57 (15).

Osmylation of the unsaturated ketone 6 in acetone followed by protection and Baeyer–Villiger oxidation

The osmylation was carried out according to the general procedure using the ketone **6** (500 mg, 4.63 mmol) as the substrate and acetone as the solvent. After 4 h no starting material was observed by TLC. Protection of the resultant diol as the isopropylidene derivative was then carried out, again according to the general procedure. After 24 h TLC indicated the reaction had reached completion. The crude product was obtained as a brown oil (601 mg).

To a stirred solution of the crude product (601 mg) in chloroform (10 cm^3) was added sodium hydrogen carbonate (1 g). A solution of MCPBA (5.7 g, 33 mmol) in chloroform (20 cm^3) was washed with saturated aqueous sodium hydrogen carbonate and added dropwise to the reaction mixture. After 48 h the reaction mixture was washed with saturated aqueous sodium sulfite (3 × 20 cm^3) and saturated aqueous sodium hydrogen carbonate (3 × 20 cm^3). The combined organic layers were dried and the solvent removed under reduced pressure. TLC examination of the crude product indicated the presence of two components which were separated by flash column chromatography [light petroleum–ethyl acetate (3:1), then (1:1)]. The major product was the *exo*-acetonide **7** (497 mg, 54% from the ketone **6**) and the minor product was the isomeric *endo*-acetonide **8** (56.2 mg, 6% from the ketone **6**). Spectroscopic data as before.

Acknowledgements

We are grateful to EPSRC for a studentship to R. S. and SmithKline Beecham for financial support. In addition, we would like to thank Dr Torren Peakmann for assistance with NMR studies and Mr Cole Clissold for the X-ray analysis.

References

1 M. Schroder, *Chem. Rev.*, 1980, 187.
2 J. K. Cha, W. J. Christ and Y. Kishi, *Tetrahedron Lett.*, 1983, **24**, 3943 and 3947; C. L. Willis, *Tetrahedron Lett.*, 1990, **31**, 6437.
3 I. Tomoskoi, L. Gruber, G. Kovacs, I. Szekly and V. Simonidesz, *Tetrahedron Lett.*, 1979, **20**, 4639.
4 V. Van Rheenan, R. C. Kelly and D. Y. Cha, *Tetrahedron Lett.*, 1976, 1973.
5 C. Clissold, A. G. Orpen and C. L. Willis, unpublished results.
6 D. J. Krysan, T. W. Rockway and A. R. Haight, *Tetrahedron Asymmetry*, 1994, **5**, 625.
7 J. Leonard and N. Hussain, *J. Chem. Soc., Perkin Trans. 1*, 1994, 49.
8 J. Schmilden and A. Wettstein, *Helv. Chim. Acta*, 1963, **46**, 2799.
9 P. A. Grieco, *J. Org. Chem.*, 1972, **37**, 2363.
10 T. V. Lee, S. M. Roberts, M. J. Dimsdale, R. F. Newton, D. K. Rainey and C. F. Webb, *J. Chem. Soc., Perkin Trans. 1*, 1978, 122.
11 Interestingly it has been shown that epoxidation of **1** occurs predominantly from the *endo* face, see: J. J. Partridge, N. K. Chadha and M. R. Uskokovic, *J. Am. Chem. Soc.*, 1993, **95**, 7171.
12 K. Hanson, J. A. O'Neill, T. J. Simpson and C. L. Willis, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2493.

Paper 5/04451K
Received 7*th July* 1995
Accepted 31*st July* 1995