Total Synthesis of (±)-Specionin[1]

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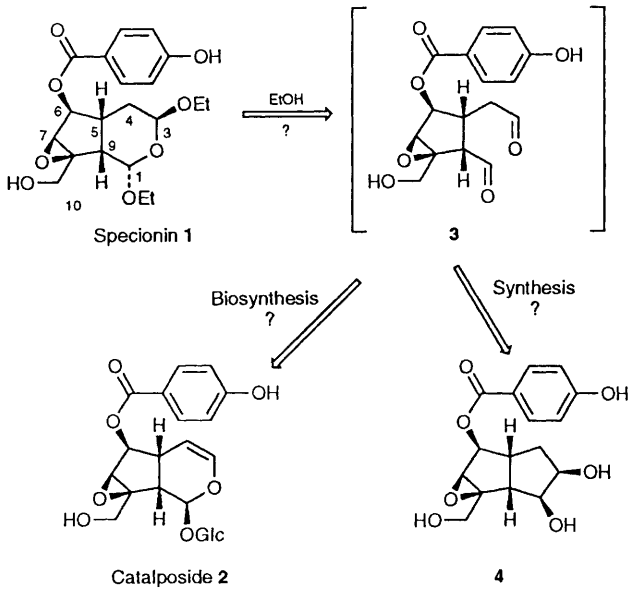
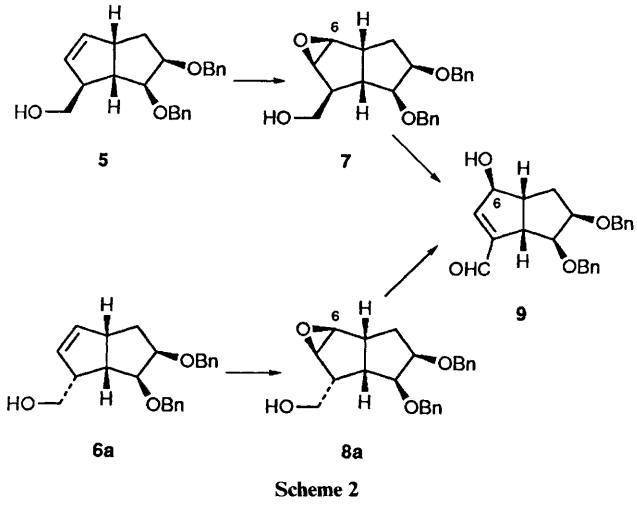
(±)-Specionin has been synthesized in a short, efficient sequence of reactions from (±)-*exo,exo*-6,7-bis(benzyloxy)-*exo*-4-(hydroxymethyl)-*cis*-bicyclo[3.3.0]oct-2-ene **5**. The key feature of the synthesis is a 'one-pot' hydrogenolysis–cyclopentanediol cleavage–bis-acetal cyclisation on intermediate **21a**, to provide specionin acetate stereoselectively. The 1β-H, 3α-H stereochemical arrangement of specionin is shown to be thermodynamically preferred and, with the functionality of the left-hand ring complete, the stereochemistry of the ethyl acetals is controlled by equilibration. A diastereoisomer of specionin acetate, **26a**, has also been prepared from (±)-*exo,exo*-6,7-bis-(benzyloxy)-*endo*-2-(hydroxymethyl)-*cis*-bicyclo[3.3.0]oct-2-ene **6a**, by an analogous series of reactions.

Once the structure of specionin had been clarified as **1**† its structural relationship to the iridoid glycoside catalposide **2** was striking and we thought it likely that specionin was either an artifact of catalposide, formed during isolation, or was indeed biosynthesized from it.[2]‡ In either case the involvement of a transient dialdehyde intermediate **3**, or cyclic acetal equivalent, was implied. We hypothesised that the stereochemistry at the acetal centres (C-1 and C-3) in specionin, created during cyclisation of diol **3**, might be controlled by the stereochemistry of the groups around the pre-formed cyclopentane ring. Thus, our synthetic strategy was focused on constructing dialdehyde **3**, in ethanolic solution, and our key synthetic target was diol **4** which should easily be cleaved to dialdehyde **3** by periodate in ethanol (Scheme 1). If our hypothesis was true, the overall synthetic strategy should be very effective and stereoselective with respect to the acetal stereocentres, and this could reinforce the idea that specionin is derived from catalposide.[3–5]§

In the preceding paper we described studies on the functionalisation of *cis*-bicyclo[3.3.0]oct-7-en-2-ol which eventually provided us with diastereoisomeric alcohols **5** and **6a** and these appeared to be appropriate synthons for an efficient conversion into specionin. The alcohols were readily separated from one another and we had distinguished them by a comprehensive range of nuclear Overhauser effect (NOE) studies. In the earlier work we had also devised a general method for introducing the C-6 hydroxy group *via* an epoxidation–alcohol oxidation–epoxide-opening sequence. With the stereoisomers **5** and **6a** available separately we thought that each of them could be transformed into a C-6β epoxide; compound **7** being formed by directed epoxidation from **5** and compound **8a** being formed by sterically controlled epoxidation of an alcohol derivative of compound **6a**. Thus our first objective was to prepare the alcohol **9** with the correct C-6β hydroxy-group stereochemistry which could then be used to direct epoxidation of the C-7, C-8 alkene (Scheme 2).



Scheme 1 Specionin synthetic plan *versus* biosynthetic hypothesis



Scheme 2

Results and Discussion

In the event, when we studied epoxidations of alkenes **5** and **6a–e**, some of the results obtained were curious. The convex face of each of the molecules is the β-face so we expected that attack

† The numbering system shown for specionin **1** will be used throughout the paper for all compounds, except for certain compounds in the Experimental section (q.v.).

‡ See preceding paper for background on the isolation and importance of specionin and a description of our background studies on functionalisation of *cis*-bicyclo[3.3.0]oct-7-en-2-ol.

§ Vandewalle[3] prepared specionin by forming the bis-acetal ring with incomplete functionality in the left-hand ring and obtained a mixture of acetal stereoisomers. These were, however, each converted into stereoisomers of specionin, allowing the structure of the natural product to be defined conclusively. The structure analysis work carried out by Vandewalle on specionin and its isomers has also been of great value to us and other workers interested in synthetic approaches to specionin.

from this face would be sterically preferred, and for epoxide **5** the directing effect of the homoallylic alcohol should reinforce this preference. Vanadium-catalysed *tert*-butyl hydroperoxide epoxidation can only proceed by a directed mechanism and, as expected, provided epoxide **7** exclusively from alkene **5** and epoxide **11a** exclusively from the epimer **6a**.[6] However, epoxidation of alkene **5** with *m*-chloroperbenzoic acid (MCPBA) was much less selective than expected, given that two controlling factors should favour β-face attack, and gave only a 3:1 ratio of epoxide **7** over its isomer **10**. We found the results of MCPBA epoxidation of alkenes **6a–e** even more surprising. The free alcohol **6a** gave a higher preference for directed attack than did compound **5**, with a 15:1 preference for α-face reaction, but we expected a reversal of this selectivity once a bulky group had been attached to the hydroxy group. In practice, when increasingly bulky hydroxy-protecting groups were installed, the proportion of the α-epoxide produced was lowered, but in all cases this isomer still predominated (Scheme 3).

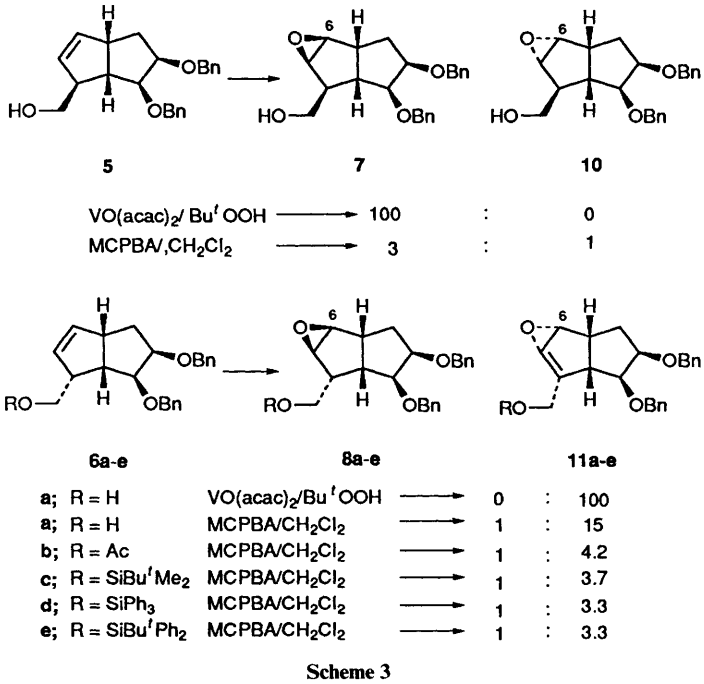
These results suggest that the basic bicyclic ring system, irrespective of the orientation of the C-8 side chain, has a pronounced steric preference for epoxidation from the concave α-face. To see whether this behaviour is general for this type of system, we epoxidised the acetate of the alcohol **12** and obtained a 1.7:1 mixture of diastereoisomeric epoxides **13** and **14**. These could not be distinguished directly, but their spectra were compared with those of benzoates **23a** and **22a**, the structures of which were assured by conversion into specionin and a diastereoisomer. The chemical shift and coupling-constant patterns were directly comparable and allowed us to assign the major isomer as *endo* epoxide **13**. Again the epoxidising agent reacts preferentially from the concave face and we find it difficult to rationalise this behaviour. It may be that the benzyl ether oxygens complex with the reagent, which does not react but causes steric crowding, making the convex face relatively less accessible.

Compounds **14** and **13** are analogues of our target specionin precursor and its diastereoisomer, simply lacking the C-6 hydroxy ester function. For this reason we thought that it would be useful to attempt a model 'one-pot deprotection–diol cleavage–bis-acetal cyclisation reaction sequence. Epoxide **13** was therefore hydrogenated in ethanol and, once hydrogenolysis was complete, sodium periodate was added to cleave the diol. A catalytic amount of toluene-*p*-sulfonic acid (PTSA) was then added to the mixture to complete bis-acetal cyclisation. The product from the reaction was quite clean by TLC, with only one major product detected, and the modest yield (34%) may have been because of the small scale (12 mg) of this single experiment. The ^{1}H NMR spectrum of the product **15** had only two methyl triplets, indicating that it might be a single diastereoisomer, and this was very encouraging for our planned specionin cyclisation. We think that the ethoxy groups in compound **15** are *trans* to one another but we did not confirm the stereochemistry. Simple analogues of specionin, such as compound **15**, are readily available by this route and a study of their biological properties might be useful (Scheme 4).

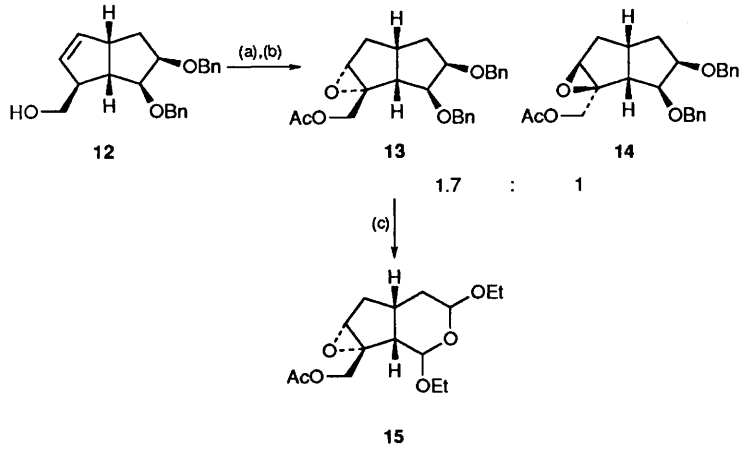
We were confident that we could complete the left-hand ring of specionin in a stereoselective manner from epoxy alcohol **7**. We thought it would also be interesting to carry out a parallel study with diastereoisomer **11a**, since we had already observed an unexpected pattern of stereoselectivity in some reactions on these bicyclic intermediates. In the first sequence of reactions the alcohols **7** and **11a** were converted into alcohols **17** and **18**, respectively, by Swern oxidation, followed by epoxide opening with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), then sodium borohydride–$CeCl_3$ enal reduction (Scheme 5).[7]

Before installing the required ester on the C-6 hydroxy group, the primary hydroxy group needed to be protected. The *tert*-butyldimethylsilyl (TBDMS) ethers and the acetates of epimers **17** and **18** were prepared, but none of the reactions were as clean as anticipated, small quantities of the diprotected products always being formed. These could, however, be recycled and the overall conversion into protected alcohols **19a**, **b** and **20a**, **b** was high. We expected tht MCPBA epoxidation of compound **19a** would be highly stereoselective because of directed attack from the C-6 hydroxy group and because the β-face of the molecule is the convex face. In the event the ratio of β- and α-epoxides from MCPBA epoxidation was only 7:2, but $VO(acac)_2$-catalysed* epoxidation gave only the directed epoxide for each of the alcohols **19a**, **b** and **20a**, **b**. The epoxidation products were each converted directly into the

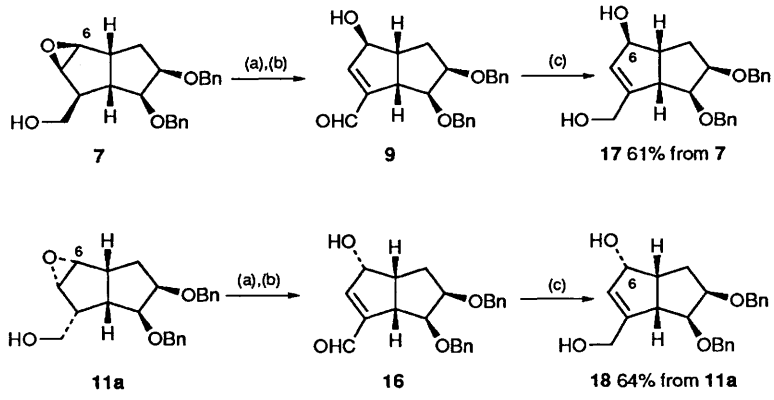
* acac = acetylacetonate.



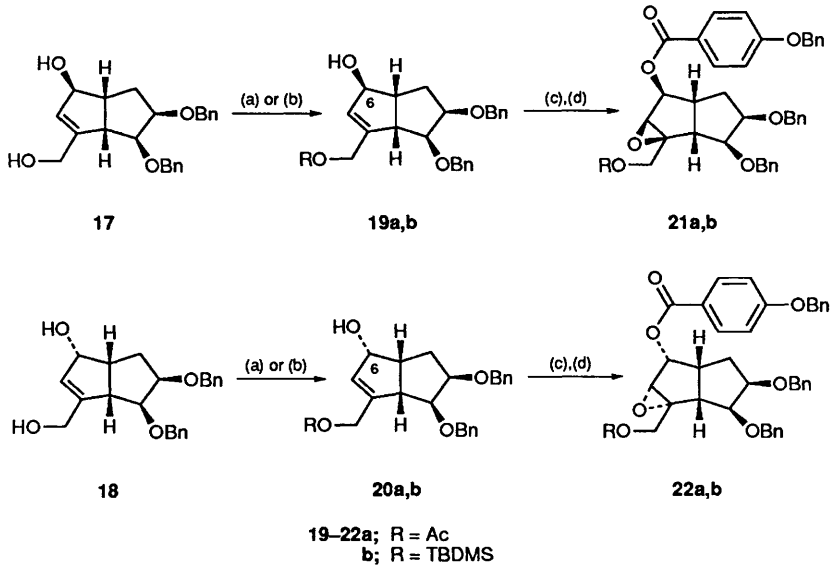
Scheme 3



Scheme 4 *Reagents:* (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (b) MCPBA, CH_2Cl_2; (c) i, H_2, PdC, EtOH; ii, $NaIO_4$; iii, TsOH



Scheme 5 *Reagents and conditions:* (a) Swern oxidation; (b) DBU, CH_2Cl_2; (c) $NaBH_4$, $CeCl_3$, MeOH



Scheme 6 *Reagents and conditions:* (a) Ac_2O, Et_3N, CH_2Cl_2; (b) TBDMSOTf, Et_3N; (c) Bu^tOOH, $VO(acac)_2$, CH_2Cl_2, reflux; (d) *p*-$BnOC_6H_4COCl$, DMAP, CH_2Cl_2

benzyl-protected esters **21a**, **b** and **22a**, **b**. The overall yields for the two steps were higher with the acetate protecting groups; 77% for **21a** and 70% for **22a** (Scheme 6).

With compounds **21a**, **b** on hand we had completed the construction of the left-hand ring of specionin and we were at the crucial stage of our synthetic plan. In model studies on a simple bicyclic system, described above and in the preceding paper, benzyl protecting groups were readily hydrogenolysed and the resulting cyclopentanediol was efficiently converted into a tetrahydropyran bis-ethyl acetal by treatment with $NaIO_4$ in ethanol. We were therefore fairly confident that the overall 'one-pot' transformation would be successful, and the crucial questions were: (i) Would the bis-ethyl acetal system be formed stereoselectively? (ii) Would the isomer with the same stereochemistry as specionin predominate? (iii) Could the stereochemistry of the process be kinetically or thermodynamically controlled?

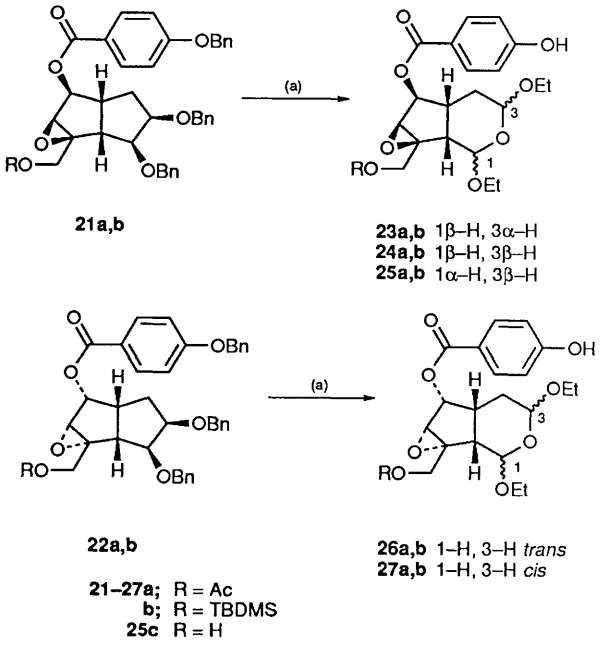
For our first attempt at the 'one-pot' deprotection–diol

Table 1 Comparison of NMR signals of isomers **23a**, **24a** and **25a** with those of specionin and its isomers

Proton[a]	Acetate isomer δ/ppm (J/Hz)		
	23a	**24a**	**25a**
6-H	5.34 (8.5 and 1.0) [5.37 (8.5 and 1.5)][b]	5.27 (6.5 and 1.5) [5.29 (6.5 and 1.5)]	5.55 (~9.0 and ~1.0) [5.59 (9.0 and 1.5)]
1-H	5.01 (4.0) [5.06 (4.0)]	4.98 (3.0) [5.04 (3.0)]	
3-H	4.85 (7.0 and 2.5) [4.89 (7.0 and 3.0)]	4.74 (9.5 and 4.0) [4.76 (9.5 and 3.5)]	4.97 (~4.0 and ~1.0) [5.02 (4.5 and 1.5)]
9-H	2.76 (8.0 and 4.0) [2.80 (8.0 and 4.0)]	2.69 (9.0 and 3.0) [2.69 (9.0 and 3.0)]	

[a] Specionin-numbering scheme. [b] Values in [ ] refer to the corresponding data for specionin and its anomers.

cleavage–acetal cyclisation sequence we used the silyl-protected alcohol **21a**. The hydrogenolysis and diol-cleavage steps appeared to proceed smoothly, as far as we could tell by TLC. To promote acetal cyclisation we chose to use pyridinium toluene-*p*-sulfonate (PPTS) as a catalyst instead of PTSA, as we thought this would be less likely to disturb the rest of the molecule, but this step did not proceed cleanly (as judged by TLC). We were, however, able to isolate a 1:1 mixture of two anomeric bis-ethyl acetals in 12% yield and these were assigned structures **23b** and **24b**, by comparison of their high-field NMR data with those of Vandewalle.[3] When the isomeric silyl ether **22b** was subjected to the same sequence of reactions the result was similar; a 10% yield of a 1:1 mixture of bis-ethyl acetals, assigned structures **26b** and **27b** (Scheme 7).



Scheme 7 *Reagents:* (a) i, Pd/C, H_2, EtOH; ii, $NaIO_4$; iii, PPTS or PTSA

We thought that problems at the acetal cyclisation step were responsible for the low overall yield of the reaction sequence. Some loss of the silyl protecting group was occurring and PPTS-catalysed cyclisation proceeded slowly, so we decided to switch to acetate protection of the hydroxy group and PTSA as the cyclisation catalyst. These small changes improved the efficiency of the 3-stage reaction sequence dramatically. Acetate **21a** was converted into a mixture of bis-ethyl acetals **23a–25a** in 73% yield and it was observed that the proportions of products were dependent on the length of time that the acid-catalysed cyclisation step was allowed to continue. When the cyclisation reaction was left for 10 h **23a**, **24a** and **25a** were obtained in proportions of ~10:10:1 respectively. Stereochemical assignments were made by comparison of the high-field NMR spectra with those of the corresponding free alcohols supplied to us by Professor Vandewalle (see Table 1).[3]

The mixture of anomers, obtained from the cyclisation described above, was redissolved in ethanol containing a catalytic quantity of PTSA and was left at room temperature for 24 h, after which a remarkable change had occurred in the NMR spectrum (Fig. 1). There was now only one major isomer present, corresponding to specionin 10-acetate **23a**, together with a small amount of the alternative *trans*-bis-acetal **25a** (ratio ~6:1) and *none* of the *cis*-isomer **24a**!

This result clearly shows that the stereochemical arrangement at the acetal centres in the right-hand ring can be controlled (as we had hypothesised) by the functionality of the left-hand ring. It may be that the *cis* product **24a** is initially formed selectively as the kinetic cyclisation product. It is, however, much less thermodynamically stable than either of the *trans* compounds, particularly **23a**, into which it is transformed on equilibration (Scheme 8). For stereoelectronic reasons at least one of the ethoxy groups prefers to adopt an axial arrangement to benefit from the anomeric effect with the ring oxygen. The *cis* isomers of the structure will have the ethoxy groups either di-equatorial or di-axial, but the di-equatorial arrangement would be highly disfavoured on steric grounds. So the *trans* isomers are thermodynamically preferred and specionin (1β-H, 3α-H) is clearly the more stable of the two *trans* isomers. It may be that this arrangement can adopt a reasonable boat conformation of the bis-acetal ring, with both ethoxy groups axial. Vandewalle and co-workers have also carried out equilibration studies on specionin itself using ethanolic BF_3·Et_2O and they also found a thermodynamic preference for the specionin diastereoisomer.[5]

The isomeric acetate **22a** was also subjected to the hydrogenolysis–diol cleavage–cyclisation procedure and this led to a 56% overall yield of two bis-ethyl acetal anomers **26a** and **27a** as a 1:1 mixture. No attempt was made to assign the stereochemistry of these isomers, which were equilibrated as before in acidic ethanol, this time giving a single stereoisomer which we assumed to be a *trans* isomer **26a**.

The final step in our synthesis was hydrolysis of the acetate protecting group from compound **23a**. This provided mainly specionin, which was identical in all respects to a natural sample, and a very small quantity of the alternative *trans* isomer.[3] This isomer was also identical with an authentic sample, but was always contaminated with specionin, probably due to equilibration on silica.

Experimental

For general experimental details see the preceding paper. Note that specionin, its isomers, and derivatives are numbered using

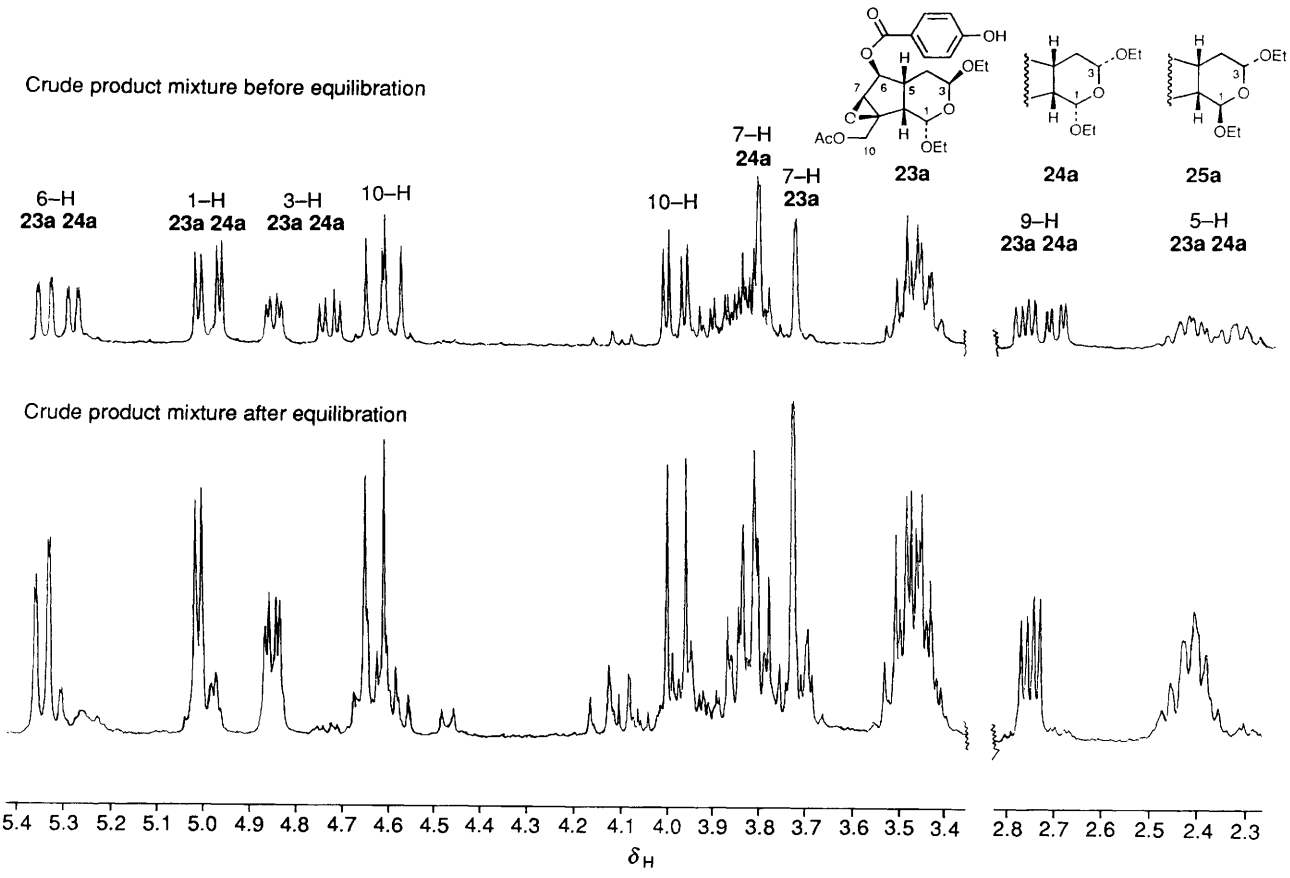


Fig. 1 ^{1}H NMR spectrum of bis-acetal cyclisation products **23a**–**25a** before and after equilibration

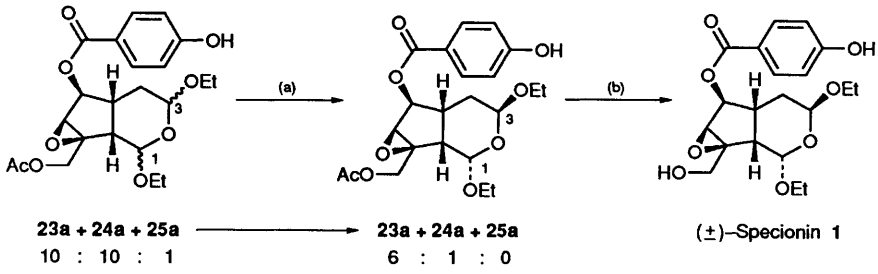
the specionin numbering system, as in the text, but all other compounds are named and numbered systematically.

(±)-exo,exo-6,7-*Bis*(*benzyloxy*)-exo-2,3-*epoxy*-exo-4-(*hydroxymethyl*)-cis-*bicyclo*[3.3.0]*octane* **7**.—A solution of the alcohol **5** (200 mg, 0.57 mmol), vanadyl acetylacetonate (10 mg) and *tert*-butyl hydroperoxide (5.36 mol dm^{-3} in dichloromethane; 0.2 cm^3, 1.07 mmol) in dry dichloromethane (15 cm^3) was heated at reflux for 2 h. The solution was then diluted with dichloromethane (30 cm^3), washed successively with saturated aq. $Na_2S_2O_5$ (30 cm^3) and saturated aq. $NaHCO_3$ (30 cm^3), dried, and evaporated. Purification by flash chromatography [(1:1) light petroleum–ethyl acetate] provided epoxide **7** (140 mg, 67%), ν_{max}/cm^{-1} 3300, 3075, 3050, 1460 and 700; δ_H(300 MHz) 1.65 (2 H, m, 8-H), 2.0–2.4 (3 H, m, 1-, 4-H, OH), 2.95 (1 H, m, 5-H), 3.30 (1 H, d, *J* 2.0, 2- or 3-H), 3.47 (1 H, t, *J* 1.5, 3- or 2-H), 3.59–3.70 (3 H, m, CH_2OH, 6-H), 3.86 (1 H, m, 7-H), 4.4–4.6 (4 H, m, 2 × CH_2Ph) and 7.31 (10 H, m, 2 × Ph); *m*/*z* (NH_3, CI) 384 ([M + NH_4]$^+$, 100%), 367 ([M + H]$^+$, 12), 275 (6), 259 (8), 108 (21) and 91 (15) (Found: [M + NH_4]$^+$, 384.2181. $C_{23}H_{30}NO_4$ requires *m*/*z*, 384.2175).

Epoxidation of the Alcohol **5** *using MCPBA*.—To a stirred suspension of the alcohol **5** (90 mg, 0.26 mmol) and anhydrous $NaHCO_3$ (110 mg, 1.31 mmol) in dichloromethane (8 cm^3) was added MCPBA (85%; 106 mg, 0.52 mmol). The suspension was stirred until no starting material remained as indicated by TLC (*ca.* 3 h) and, if necessary, more MCPBA was added. The mixture was then diluted with dichloromethane (25 cm^3), washed successively with saturated aq. $Na_2S_2O_5$ (20 cm^3) and saturated aq. $NaHCO_3$ (20 cm^3), dried, and evaporated. The crude product (76 mg, 81%) was found to be a mixture of epoxide **7** (as above) and its diastereoisomer, assigned as compound **10** in the ratio ~3:1 by high-field ^{1}H NMR spectroscopy.

(±)-exo,exo-6,7-*Bis*(*benzyloxyl*)-endo-2,3-*epoxy*-endo-4-(*hydroxymethyl*)-cis-*bicyclo*[3.3.0]*octane* **11a**.—The method was identical with that used for the preparation of the diastereoisomer **7** above. The alcohol **6a** (250 mg, 0.71 mmol) was treated with *tert*-butyl hydroperoxide (70% in water; 200 mm^3, 1.46 mmol) and VO(acac)$_2$ (15 mg) in benzene (25 cm^3) to provide, after flash chromatography [light petroleum–ethyl acetate (10:1, then 1:1)], epoxide **11a** (120 mg, 46%), ν_{max}/cm^{-1} 3400, 3100, 3075 and 700; δ_H(300 MHz) 1.68 (1 H, ddd, $J_{8\alpha,8\beta}$ 14.5, $J_{1,8\alpha}$ 6.5, $J_{8\alpha,7}$ 4.0, 8α-H), 2.11 (1 H, dd, $J_{8\alpha,8\beta}$ 14.5, $J_{1,8\beta}$ 9.0, 8β-H), 2.57 (1 H, m, 4-H), 2.73 (1 H, m, 1-H), 2.95 (1 H, ~q, *J* 10.5, 5-H), 3.31 (1 H, dd, *J* 2.5, 2.0, 2- or 3-H), 3.38 (1 H, br s, 3- or 2-H), 3.78 (1 H, dd, *J* 10.5, 6.0, CH_2OH), 3.84 (1 H, dd, *J* 10.5, 7.0, CH_2OH), 3.87 (1 H, dd, *J* 10.5, 3.5, 6-H), 4.06 (1 H, ~t, *J* 4.0, 3.5, 7-H), 4.33 (1 H, d, *J* 11.0, OCH_2Ph), 4.47 (1 H, d, *J* 12.0, OCH_2Ph), 4.50 (1 H, d, *J* 11.0, OCH_2Ph), 4.60 (1 H, d, *J* 12.0, OCH_2Ph) and 7.21–7.33 (10 H, m, 2 × Ph); *m*/*z* (NH_3, CI) 384 ([M + NH_4]$^+$, 100%), 367 ([M + H]$^+$, 20) and 91 (30) (Found: [M + NH_4]$^+$, 384.2180. $C_{23}H_{30}NO_4$ requires *m*/*z*, 284.2175).

Epoxidation of the Alcohol **6a** *using MCPBA*.—The procedure using compound **6a** (32 mg, 0.091 mmol) was the same as that described above for epoxidation of alcohol **5** with MCPBA. The crude product (26 mg, 81%) was found to be a mixture of epoxide **11a** (as above) and its diastereoisomer, assigned structure **8a**, in the ratio ~14:1 by ^{1}H NMR spectroscopy.



Scheme 8 *Reagents and conditions:* (a) EtOH, TsOH, room temp., 24 h; (b) K_2CO_3, MeOH

General Method for Preparation of Silyl Ethers of (±)-exo,exo-6,7-*Bis*(*benzyloxy*)-endo-4-*hydroxymethyl-cis-bicyclo*-[3.3.0]*oct*-2-*ene* **6c–e**.—A solution of the alcohol **6a** (110 mg, 0.31 mmol), imidazole (60 mg, 0.88 mmol) and the appropriate silyl chloride (0.59 mmol) in dry dimethylformamide (3 cm^3) was stirred at room temperature until no starting material remained, as indicated by TLC (*ca.* 24 h). The mixture was then diluted with water (10 cm^3), extracted with pentane (2 × 50 cm^3), and the extract was dried and evaporated. The crude product was purified by flash chromatography to provide the respective silyl ether: compound **6c** (92%), ν_{max}/cm^{-1} 3100, 3075, 1460 and 700; δ_H(60 MHz; standard Me_2SiBu^t) 0.0 (6 H, s), 0.85 (9 H, s), 1.5–2.2 (2 H, m), 2.75–4.0 (7 H, m), 4.5 (4 H, m, PhCH_2O × 2), 5.55 (2 H, m, 2- and 3-H) and 7.3 (10 H, m); compound **6d** (86%), ν_{max}/cm^{-1} 3100, 3050, 1600 and 700; δ_H(60 MHz) 1.5–2.4 (2 H, m), 2.8–3.5 (3 H, m), 3.5–4.2 (4 H, m), 4.45 (4 H, m, PhCH_2O × 2), 5.65 (2 H, s, 2- and 3-H) and 7.2–7.85 (25 H, m); compound **6e** (92%), ν_{max}/cm^{-1} 3075, 3050, 1430 and 710; δ_H(60 MHz) 1.05 (9 H, s), 1.5–2.4 (2 H, m), 2.8–3.4 (3 H, m), 3.45–4.15 (4 H, m), 4.2–4.65 (4 H, m, PhCH_2O × 2), 5.6 (2 H, m, 2- and 3-H) and 7.1–7.75 (20 H, m).

General Procedure for the Epoxidation of Alkenes **6b–e** *and Deprotection of Epoxides* **8b–e** *and* **11b–e**.—A suspension of the alkene (0.1 mmol) and sodium hydrogen carbonate (0.5 mmol) in dichloromethane (25 cm^3) was treated with MCPBA (85%; 0.2 mmol) and stirred for 4 h or until no starting material remained (TLC). If necessary, more reagent was added to ensure complete reaction. The mixture was then diluted with dichloromethane (45 cm^3), washed successively with saturated aq. $Na_2S_2O_5$ (50 cm^3) and saturated aq. $NaHCO_3$ (50 cm^3), dried, and evaporated. To unmask the alcohol group one of two methods was used, depending on the protecting group:

(i) *The acetate* was removed by addition of a small piece of sodium metal to the crude product in methanol (25 cm^3). After 30 min a small piece of solid CO_2 was added, and the mixture was then concentrated by evaporation and diluted with dichloromethane (50 cm^3). This mixture was washed with saturated aq. $NaHCO_3$ (40 cm^3), dried, evaporated, and purified by flash chromatography.

(ii) *Silyl groups* were removed by addition of tetrabutylammonium fluoride (1 mol dm^{-3} in THF; 0.2 cm^3, 0.2 mmol) to a stirred solution of the crude product in dry THF (25 cm^3). After 24 h the mixture was concentrated by evaporation, then was diluted with dichloromethane (50 cm^3), washed with saturated aq. $NaHCO_3$ (40 cm^3), dried, and evaporated before purification by flash chromatography.

(±)-exo-2-(*Acetoxymethyl*)-exo,exo-7,8-*bis*(*benzyloxy*)-endo-2,3-*epoxy*-cis-*bicyclo*[3.3.0]*octane* **13** *and* (±)-endo-2-(*Acetoxymethyl*)-exo,exo-7,8-*bis*(*benzyloxy*)-exo-2,3-*epoxy*-cis-*bicyclo*[3.3.0]*octane* **14**.—A solution of the alcohol **12** (105 mg, 0.3 mmol), acetic anhydride (100 mm^3, 1.06 mmol) and 4-(dimethylamino)pyridine (DMAP) (70 mg, 0.57 mmol) in dichloromethane (10 cm^3) was stirred overnight at room temperature. The mixture was then diluted with dichloromethane (25 cm^3), washed successively with 10% HCl (2 × 15 cm^3) and saturated aq. $NaHCO_3$, dried, and evaporated, to provide a crude acetate which was epoxidised directly.

A mixture of this acetate, MCPBA (85%; 120 mg, 0.59 mmol) and anhydrous $NaHCO_3$ (120 mg, 1.43 mmol) in dichloromethane (10 cm^3) was stirred at room temperature for 3 h. The mixture was then diluted with dichloromethane (25 cm^3), washed successively with saturated aq. $Na_2S_2O_5$ (20 cm^3) and saturated aq. $NaHCO_3$ (20 cm^3), dried, and evaporated. Purification by flash chromatography provided epoxides **13** and **14** (~1.7:1, 64%); epoxide **13**: ν_{max}/cm^{-1} 3050, 2950, 1740 and 740; δ_H(300 MHz) 1.32 (1 H, ddd, $J_{6\alpha,6\beta}$ 13, $J_{5,6\alpha}$ 9.5, $J_{6\alpha,7}$ 3.5, 6α-H), 1.73 (1 H, dd, *J* 15, 2.0, 4α-H), 1.93–2.06 (2 H, m, 4β- and 6β-H) 1.97 (3 H, s, Ac), 2.70 (1 H, dd, $J_{1,5}$ 10.5, $J_{1,8}$ 4.5, 1-H), 2.98 (1 H, m, 5-H), 3.49 (1 H, d, *J* 1.5, 3-H), 4.05 (2 H, m, 7- and 8-H), 4.19 (1 H, d, *J* 12.5, CH_2OAc), 4.34 (1 H, dd, *J* 12.5, CH_2OAc), 4.43–4.57 (4 H, 2 overlapping A/B patterns, 2 × CH_2Ph) and 7.20–7.33 (10 H, m, 2 × Ph); *m/z* (NH_3, CI) 426 ([M + NH_4]$^+$, 100%), 409 ([M + H]$^+$, 20) and 91 (85) (Found: [M + NH_4]$^+$, 426.2281. $C_{25}H_{32}NO_5$ requires *m/z*, 426.2280); epoxide **14**: ν_{max}/cm^{-1} 3050, 2950, 1740 and 740; δ_H(300 MHz) 1.28–1.36 (2 H, m, 6α- and 4α-H), 1.99 (3 H, s, Ac), 2.19–2.36 (2 H, m, 4β- and 6β-H), 2.48 (1 H, m, 5-H), 3.04 (1 H, t, *J* 9.0, 1-H), 3.43 (1 H, d, *J* 1.0, 3-H), 3.61 (1 H, dd, *J* 9, 3.0, 8-H), 3.98 (1 H, m, 7-H), 4.22 (1 H, d, *J* 12.5, CH_2OAc), 4.43–4.57 (5 H, m, 2 × CH_2Ph, CH_2OAc) and 7.20–7.34 (10 H, m, 2 × Ph); *m/z* (NH_3, CI) 426 ([M + NH_4]$^+$, 100%), 409 ([M + H]$^+$, 12) and 91 (70) (Found: [M + NH_4]$^+$, 426.2275. $C_{25}H_{32}NO_5$ requires *m/z*, 426.2280).

(±)-exo-9-(*Acetoxymethyl*)-endo-8,9-*epoxy*-2,4-*diethoxy*-3-*oxa*-cis-*bicyclo*[4.3.0]*nonane* **15**.—A stirred suspension of the ester **13** (12 mg, 0.04 mmol) and palladium (5%) on carbon (~3 mg) in absolute ethanol (3 cm^3) was hydrogenated at 1 atm for 6 h. The mixture was then filtered through Celite and to the filtrate was added sodium metaperiodate (20 mg, 0.094 mmol). The resulting suspension was stirred for 24 h at room temperature. PTSA (~3 mg) was then added and the mixture was stirred for 10 h. The bulk of the ethanol was then evaporated off, dichloromethane (30 cm^3) was added, and the mixture was washed with water (20 cm^3), dried and evaporated. Purification by flash chromatography [light petroleum–ethyl acetate (6:1)] provided compound **15** (3 mg, 34%), ν_{max}/cm^{-1} 2950 and 1740; δ_H(300 MHz) 1.06 (3 H, t, *J* 7.0, CH_2Me), 1.16 (3 H, t, *J* 7.0, CH_2Me), 1.47 (1 H, m), 1.78–2.07 (2 H, m), 2.07 (3 H, s, OAc), 2.28–2.36 (2 H, m), 2.64 (1 H, m, 6-H), 3.25–3.30 (1 H, 2 × overlapping q, CH_2Me), 3.40–3.50 (3 H, m, C$H_2$$CH_3$), 3.75–3.81 (2 H, m, 1- and 8-H), 4.17 (1 H, d, *J* 11.5, CH_2OAc), 4.41 (1 H, d, *J* 11.5, CH_2OAc), 4.98 (1 H, br d, *J* 3.5, 4-H) and 5.05 (1 H, d, *J* 3.5, 2-H); *m/z* (NH_3, CI) 318 ([M + NH_4]$^+$, 8%), 301 ([M + H]$^+$, 8), 272 (30) and 255 (100)

(Found: $[M + NH_4]^+$, 318.1912. $C_{15}H_{28}NO_6$ requires *m/z*, 318.1916).

(±)-exo,exo-7,8-*Bis*(*benzyloxy*)-4-exo-*hydroxy*-cis-*bicyclo*-[3.3.0]*oct*-2-*ene*-2-*carbaldehyde* **9**.—To a stirred solution of oxalyl dichloride (100 mm^3, 1.10 mmol) in dry dichloromethane (15 cm^3) at −78 °C was added dropwise a solution of dimethyl sulfoxide (200 mm^3, 2.58 mmol) in dichloromethane (1 cm^3). After 5 min, a solution of epoxide **7** (200 mg, 0.55 mmol) in dichloromethane (2 cm^3) was added dropwise and, after a further 20 min, triethylamine (1 cm^3, 7.61 mmol) was added. After 10 min at −78 °C the mixture was allowed to warm to room temperature, then was partitioned between 2 mol dm^{-3} HCl (30 cm^3) and dichloromethane (2 × 30 cm^3). The organic phase was washed with saturated aq. $NaHCO_3$ (40 cm^3), dried, and evaporated.

A solution of the crude product and 1,5-diazabicyclo-[5.4.0]undec-5-ene (167 mg, 1.1 mmol) in dichloromethane (15 cm^3) was stirred at room temperature for 2 h. The solution was then poured into 2 mol dm^{-3} HCl (20 cm^3) and extracted with dichloromethane (2 × 30 cm^3). The extract was washed with saturated aq. $NaHCO_3$ (40 cm^3), dried, and evaporated. Hydroxy enal **9** was pure enough to be used directly in the next step, but an analytical sample was obtained by flash chromatography [light petroleum–ethyl acetate (1:1)], ν_{max}/cm^{-1} 3400, 3075, 3050, 2750, 1690 and 700; δ_H(300 MHz) 1.84 (1 H, ddd, $J_{6\alpha,6\beta}$ 12.5, $J_{6\alpha,7}$ 6.5, $J_{6\alpha,5}$ 1.5, 6α-H), 2.37 (1 H, ddd, $J_{6\alpha,6\beta}$ 12.5, $J_{6\beta,7}$ 11.0, $J_{6\beta,5}$ 9.0, 6β-H), 2.68 (1 H, m, $J_{5,6\beta}$ 9.0, $J_{1,5}$ 8.0, $J_{5,6\alpha}$ 1.5, $J_{4,5}$ 1.5, 5-H), 3.47 (1 H, ddd, $J_{6\beta,7}$ 11.0, $J_{6\alpha,7}$ 6.5, $J_{7,8}$ 4.5, 7-H), 3.58 (1 H, ddd, $J_{1,5}$ 8.0, $J_{1,3}$ 1.0, $J_{1,8}$ 1.0, 1-H), 3.80 (1 H, dd, $J_{7,8}$ 4.5, $J_{1,8}$ 1.0, 8-H), 4.28 (1 H, d, *J* 11, CH_2Ph), 4.38 (1 H, d, *J* 12, CH_2Ph), 4.50 (1 H, dd, $J_{4,5}$ 1.5, $J_{3,4}$ 1.0, 4-H), 4.68 (1 H, d, *J* 12, CH_2Ph), 4.77 (1 H, d, *J* 11, CH_2Ph), 6.55 (1 H, ~t, $J_{1,3}$ 1.0, $J_{3,4}$ 1.0, 3-H), 7.15–7.50 (10 H, m, 2 × Ph) and 9.73 (1 H, s, CHO); *m/z* (FAB, thioglycerol) 365 ($[M + H]^+$, 10%), 364 (M^+, 7), 347 (9), 92 (47) and 57 (100).

(±)-exo,exo-7,8-*Bis*(*benzyloxy*)-2-(*hydroxymethyl*)-cis-*bicyclo*[3.3.0]*oct*-2-*en*-exo-4-*ol* **17**.—To a stirred solution of the crude hydroxy enal **9** and cerium(III) chloride (0.4 mol dm^{-3} in methanol; 1.5 cm^3, 0.6 mmol) in methanol (10 cm^3) at room temperature was added sodium borohydride (21 mg, 0.55 mmol). After 30 min the solvent was evaporated off and the residue was taken up in dichloromethane (60 cm^3). The resulting suspension was washed successively with 1 mol dm^{-3} HCl (40 cm^3) and saturated aq. $NaHCO_3$ (40 cm^3), dried, and evaporated. Purification by flash chromatography [light petroleum–ethyl acetate (1:2)] provided diol **17** (122 mg, 61% from the epoxide **7**), ν_{max}/cm^{-1} 3400, 3100, 3075, 1500 and 710; δ_H(300 MHz) 1.48 (1 H, m, 6α-H), 2.2–2.8 (2 H, m), 2.31 (1 H, ddd, *J* 14.0, 9.0, 5.4, 6β-H), 2.70 (1 H, ~dq, 5-H), 3.33 (1 H, m, 1-H), 3.51 (1 H, ~t, *J* 2.0, 8-H), 3.85 (1 H, ~q, *J* ~2.0, 7-H), 4.09 (2 H, br s, CH_2OH), 4.35–4.60 (5 H, m, 4-H and 2 × CH_2Ph), 5.51 (1 H, br s, 3-H) and 7.25–7.40 (10 H, m, 2 × Ph); *m/z* (CH_4, CI) 367 ($[M + H]^+$, 0.3%), 348 (0.4), 331 (0.5), 271 (0.5), 241 (4) and 91 (100).

(±)-exo,exo-7,8-*Bis*(*benzyloxy*)-endo-4-*hydroxy*-cis-*bicyclo*-[3.3.0]*oct*-2-*en*-2-*carbaldehyde* **16**.—The procedure was the same as that described for the preparation of enal **9**. Epoxide **11a** (120 mg, 0.33 mmol) was converted into hydroxy enal **16** which was used without further purification in the preparation of diol **20**. An analytical sample of compound **16** was obtained by flash chromatography [light petroleum–ethyl acetate (1:1)], ν_{max}/cm^{-1} 3400, 3075, 3050, 2750, 1690, 1620 and 705; δ_H(400 MHz) 2.05 (1 H, ddd, $J_{6\alpha,6\beta}$ 12.5, $J_{6\beta,7}$ 10.0, $J_{5,6\beta}$ 9.0, 6β-H), 2.17 (1 H, ddd, $J_{6\alpha,6\beta}$ 12.5, $J_{6\alpha,7}$ 6.0, $J_{5,6\beta}$ 2.5, 6α-H), 3.13 (1 H, dq, $J_{1,5}$ 9.0, $J_{4,5}$ 9.0, $J_{5,6\beta}$ 9.0, $J_{5,6\alpha}$ 2.5, 5-H), 3.45 (1 H, br d, $J_{1,5}$ 9.0, $J_{1,3}$ 2.0, $J_{1,8}$ 1.5, 1-H), 3.69 (1 H, ddd, $J_{6\beta,7}$ 10.0, $J_{6\alpha,7}$ 6.0, $J_{7,8}$ 4.0, 7-H), 3.96 (1 H, dd, $J_{7,8}$ 4.0, $J_{1,8}$ 1.5, 8-H), 4.37 (1 H, d, *J* 11, CH_2Ph), 4.43 (1 H, d, *J* 11, CH_2Ph), 4.71 (1 H, d, *J* 12, CH_2Ph), 4.77 (1 H, d, *J* 12, CH_2Ph), 5.04 (1 H, br d, $J_{4,5}$ 9.0, $J_{3,4}$ 2.0, 4-H), 6.65 (1 H, ~t, $J_{1,3}$ 2.0, $J_{3,4}$ 2.0, 3-H), 7.2–7.5 (10 H, m, 2 × Ph) and 9.81 (1 H, s, CHO); *m/z* (CH_4, CI) 365 ($[M + H]^+$, 7.4%), 347 (6), 273 (6), 181 (37), 167 (30) and 91 (100).

(±)-exo,exo-7,8-*Bis*(*benzyloxy*)-2-(*hydroxymethyl*)-cis-*bicyclo*[3.3.0]*oct*-2-*en*-endo-4-*ol* **18**.—The procedure, starting with the above crude enal **16**, was the same as that described for preparation of diol **17**. Purification by flash chromatography [light petroleum–ethyl acetate (1:2)] provided diol **18** (77 mg, 64% from the epoxide **11a**), ν_{max}/cm^{-1} 3400, 3075, 3050, 1500 and 700; δ_H(60 MHz) 1.6–2.25 (3 H, m), 2.9–3.45 (2 H, m), 3.5–3.8 (1 H, m), 3.85–4.3 (4 H, m), 4.35–4.9 (5 H, m), 5.5 (1 H, m, 3-H) and 7.3 (10 H, m); *m/z* (CH_4, CI) 367 ($[M + H]^+$, 2.0%), 349 (2), 331 (2), 181 (30) and 91 (100) (characterised further as its monoacetate **20a**—see below).

(±)-endo-2-(*Acetoxymethyl*)-exo,exo-7,8-*bis*(*benzyloxy*)-exo-4-(p-*benzyloxybenzoyloxy*)-exo-2,3-*epoxy*-cis-*bicyclo*-[3.3.0]*octane* **21a**.—A solution of the diol **17** (85 mg, 0.23 mmol), acetic anhydride (30 mm^3, 0.32 mmol) and triethylamine (150 mm^3, 1.07 mmol) in dichloromethane (8 cm^3) was stirred at room temperature for 30 h. The mixture was then diluted with dichloromethane (30 cm^3), and was washed successively with 1 mol dm^{-3} HCl (20 cm^3) and saturated aq. $NaHCO_3$ (20 cm^3), dried, and evaporated. Purification by flash chromatography [light petroleum–ethyl acetate (4:1, 2:1, then 1:2)], provided three compounds: monoacetate, (±)-2-(acetoxymethyl-*exo*,*exo*-7,8-bis(benzyloxy)-*cis*-bicyclo[3.3.0]-oct-2-en-*exo*-4-ol **19a** (40 mg, 42%), ν_{max}/cm^{-1} 3400, 3060, 3030, 1735 and 700; δ_H(300 MHz) 1.58 (1 H, m, 6α-H), 2.03 (3 H, s, AcO), 2.30 (1 H, ddd, *J* 13.0, 9.0, 7.0, 6β-H), 2.72 (1 H, m, 5-H), 3.34 (1 H, m, 1-H), 3.60 (1 H, t, *J* 3.7, 8-H), 3.78 (1 H, ddd, *J* 7.0, 4.0, 3.7. 7-H), 4.43 (1 H, m), 4.56 (1 H, m, 4-H), 4.45–4.62 (4 H, m, 2 × CH_2Ph), 4.58 (2 H, br s, CH_2OAc), 5.60 (1 H, m, 3-H) and 7.30 (10 H, m, 2 × Ph); diacetate, (±)-*exo*-4-acetoxy-2-(acetoxymethyl)-*exo*,*exo*-7,8-bis(benzylozy)-*cis*-bicyclo-[3.3.0]oct-2-ene (25 mg, 24%), ν_{max}/cm^{-1} 3075, 3050, 1730 and 1200; δ_H(90 MHz) 1.6–2.5 (2 H, m), 2.00 (3 H, s, AcO), 2.03 (3 H, s, AcO), 2.65–3.0 (1 H, m), 3.31 (1 H, m), 3.59 (1 H, m), 3.81 (1 H, m), 4.5 (6 H, m), 5.25 (1 H, m, 4-H), 5.50 (1 H, m, 3-H) and 7.3 (10 H, m, 2 × Ph); *m/z* (CH_4, CI) 451 ($[M + H]^+$, 0.3%), 391 (33), 301 (27), 241 (35) and 91 (100); and the starting diol **17** (18 mg, 21% recovery).

A solution of the above monoacetate **19a** (50 mg, 0.12 mmol), vanadyl acetylacetonate (10 mg) and *tert*-butyl hydroperoxide (5.36 mol dm^{-3} in dichloromethane; 46 mm^3, 0.25 mmol) in dry dichloromethane (8 cm^3) was heated at reflux for 2 h. The solution was then diluted with dichloromethane (25 cm^3), washed successively with saturated aq. $Na_2S_2O_5$ (25 cm^3) and saturated aq. $NaHCO_3$ (25 cm^3), dried, and evaporated. The crude product was taken up in dichloromethane (8 cm^3), then DMAP (45 mg, 0.37 mmol) and *p*-benzyloxybenzoyl chloride[8] (60 mg, 0.24 mmol) were added. After being stirred at room temperature for 2 h, the mixture was diluted with dichloromethane (25 cm^3), then was washed successively with 1 mol dm^{-3} HCl (25 cm^3) and saturated aq. $NaHCO_3$ (25 cm^3), dried, and evaporated. Purification by flash chromatography [light petroleum–ethyl acetate (10:1, then 4:1)] provided ester **21a** (60 mg, 77%), ν_{max}/cm^{-1} 3050, 3020, 1740, 1705, 1600 and 710; δ_H(300 MHz) 1.73 (1 H, dt, *J* 14.5, 5.0, 5.0, 6α-H), 1.98 (3 H, s, AcO), 2.38 (1 H, ddd, *J* 14.5, 10.0, 1.5, 6β-H), 2.51 (1 H, m, 5-H), 3.23 (1 H, ~t, $J_{1,8}$ 9.5, $J_{1,5}$ 9.5, 1-H), 3.63 (1 H, dd, $J_{1,8}$ 9.5, $J_{7,8}$ 3.5, 8-H), 3.7 (1 H, d, $J_{3,4}$ 1.0, 3-H), 4.04 (1 H, m, 7-H), 4.20–4.65 (6 H, m, 2 × CH_2Ph + CH_2OAc), 5.01 (1 H, dd, $J_{4,5}$ 5.5, $J_{3,4}$ 1.0, 4-H), 5.08 (2 H, ~s, PhCH_2OAr), 6.96 (2 H, d, *J* 9.0, ArH),

7.20–7.45 (15 H, m, 3 × Ph) and 7.98 (2 H, d, *J* 9.0, ArH); *m/z* (FAB, thioglycerol) 635 ($[M + H]^+$, 3%), 435 (2.5), 211 (30) and 91 (100).

(±)-exo-2-(*Acetoxymethyl*)-exo,exo-7,8-*bis*(*benzyloxy*)-endo-4-(p-*benzyloxybenzoyloxy*)-endo-2,3-*epoxy*-cis-*bicyclo*-[3.3.0]*octane* **22a**.—The procedure for acetylation of diol **18** (105 mg, 0.29 mmol) was the same as that described above, in the preparation of compound **21a**. Purification by flash chromatography [light petroleum–ethyl acetate (4:1, 2:1, then 1:2)] provided three compounds: monoacetate (±)-2-(acetoxymethyl-*exo*,*exo*-7,8-bis(benzyloxy)-*cis*-bicyclo[3.3.0]oct-2-en-*endo*-4-ol **20a** (79 mg, 67%), ν_{max}/cm^{-1} 3450, 3060, 3030, 1735, 1450 and 700; δ_H(300 MHz) 1.95 (1 H, m, 6β-H), 1.98–2.08 (1 H, m, 6α-H), 2.02 (3 H, s, AcO), 2.90–3.15 (2 H, m, 1- and 5-H), 3.68 (1 H, t, *J* 4.0, 7-H), 3.90 (1 H, ~q, *J* 4.0, 8-H), 4.50–4.62 (6 H, m, 2 × CH_2Ph and CH_2OAc), 4.79 (1 H, br d, *J* 8.0, 4-H), 5.57 (1 H, br s, 3-H) and 7.30 (10 H, m, 2 × Ph); *m/z* (CH_4, CI) 409 ($[M + H]^+$, 1%), 391 (4), 241 (13), 181 (21) and 91 (100); diacetate (±)-*endo*-4-acetoxy-2-(acetoxymethyl)-*exo*,*exo*-7,8-bis(benzyloxy)-*cis*-bicyclo[3.3.0]oct-2-ene (15 mg, 12%), ν_{max}/cm^{-1} 3075, 3050, 1730, 1370 and 700; δ_H(300 MHz) 1.57–1.67 (1 H, m, 6α-H), 1.91–2.06 (1 H, m, 6β-H), 1.98 (3 H, s, AcO) 2.03 (3 H, s, AcO), 3.17 (1 H, m, 1-H), 3.25 (1 H, m, 5-H), 3.66 (1 H, t, $J_{1,8}$ 4.0, $J_{7,8}$ 4.0, 8-H), 3.90 (1 H, ~q, *J* 4.0, 7-H), 4.42–4.65 (6 H, m, 2 × CH_2Ph and CH_2OAc), 5.53 (1 H, d, *J* 1.5, 3-H), 5.58 (1 H, br d, *J* 8.5, 4-H) and 7.22–7.36 (10 H, m, 2 × Ph); and the starting diol **18** (10 mg, 9% recovery).

The procedure for esterification of the monoacetate **20a** (75 mg, 0.18 mmol) was the same as that described for its epimer **19a**. Purification by flash chromatography [light petroleum–ethyl acetate (10:1, then 3:1)] provided ester **22a** (82 mg, 70%), ν_{max}/cm^{-1} 3075, 3050, 1740, 1710, 1610 and 710; δ_H(300 MHz) 1.70–1.90 (2 H, m, 6-H_2), 1.99 (3 H, s, AcO), 2.80 (1 H, dd, *J* 10.5, 5.0, 1-H), 3.22 (1 H, ~q, *J* ~10.0, 5-H), 3.78 (1 H, d, $J_{3,4}$ 1.5, 3-H), 4.18 (2 H, m, 7- and 8-H), 4.20–4.60 (6 H, m, 2 × CH_2Ph and CH_2OAc), 5.10 (2 H, ~s, PhCH_2OAr), 5.37 (1 H, dd, $J_{4,5}$ 9.5, $J_{3,4}$ 1.5, 4-H), 6.98 (2 H, d, *J* 9.0, ArH), 7.20–7.45 (15 H, m, 3 × Ph) and 7.99 (2 H, d, *J* 9.0, ArH); *m/z* (FAB, thioglycerol) 635 ($[M + H]^+$, 0.6%), 633 (0.5), 543 (0.5), 527 (0.5), 435 (0.5), 211 (33) and 91 (100).

(±)-exo,exo-7,8-*Bis*(*benzyloxy*)-exo-4-(p-*benzyloxybenzoyloxy*)-endo-2-(tert-*butyldimethylsiloxymethyl*)-exo-2,3-*epoxy*-cis-*bicyclo*[3.3.0]*octane* **21b**.—To a solution of the diol **17** (24 mg, 0.066 mmol) and triethylamine (20 mm^3, 0.144 mmol) in dry dichloromethane (3 cm^3) at 0 °C was added dropwise *tert*-butyldimethylsilyl triflate (TBDMSTf (16 mm^3, 0.07 mmol). After 40 min the mixture was diluted with dichloromethane (20 cm^3), washed with saturated aq. $NaHCO_3$ (15 cm^3), dried, and evaporated. Purification by flash chromatography [light petroleum–ethyl acetate (12:1, 4:1, 2:1, then 1:2)] provided four compounds: primary monosilyl ether (±)-*exo*,*exo*-7,8-bis-(benzyloxy)-2-(*tert*-butyldimethylsiloxymethyl)-*cis*-bicyclo-[3.3.0]oct-2-en-*exo*-4-ol, **19b** (6 mg, 19%), ν_{max}/cm^{-1} 3400, 3075, 3050, 1460 and 700; δ_H(300 MHz) 0.19 (3 H, s, SiMe), 0.31 (3 H, s, SiMe), 0.88 (9 H, s, SiBu^t), 1.58 (2 H, m), 2.29 (1 H, m), 2.70 (1 H, m), 3.25 (1 H, m), 3.58 (1 H, dd, *J* 3.5, 3.0, 7-H), 3.76 (1 H, m, 8-H), 4.11 (2 H, m, CH_2OSi), 4.41 (1 H, m, 4-H), 4.45–4.65 (4 H, m, OCH_2Ph × 2), 5.58 (1 H, ~t, *J* 2.0, 3-H) and 7.3 (10 H, m, 2 × Ph); bissilyl ether, (±)-*exo*,*exo*-7,8-bis(benzyloxy)-*exo*-4-(*tert*-butyldimethylsiloxy)-2-(*tert*-butyldimethylsiloxymethyl)-*cis*-bicyclo[3.3.0]oct-2-ene (12 mg, 31%), ν_{max}/cm^{-1} 3100, 3075, 1460 and 740; δ_H(90 MHz; standard Me_2SiBu^t) 0.00 (12 H, s), 0.85 (18 H, s), 1.65–2.8 (3 H, m), 3.28 (1 H, m), 3.5–3.9 (2 H, m, 7- and 8-H), 4.1 (2 H, br s, 2-CH_2), 4.40–4.65 (5 H, m), 5.45 (1 H, m, 3-H) and 7.3 (10 H, m, 2 × Ph); secondary monosilyl ether, (±)-*exo*,*exo*-7,8-bis(benzyloxy)-*exo*-4-(*tert*-butyldimethylsiloxy)-2-(hydroxymethyl)-*cis*-bicyclo[3.3.0]oct-2-ene (4 mg, 13%), ν_{max}/cm^{-1} 3400, 3100, 3075 and 1460; δ_H(300 MHz) 0.04 (6 H, s, $SiMe_2$), 0.85 (9 H, s), 1.58 (1 H, m), 2.10 (1 H, m), 2.31 (1 H, m), 2.72 (1 H, m), 3.36 (1 H, m), 3.52 (1 H, dd, *J* 5.0, 3.5, 8-H), 3.90 (1 H, ~q, 7-H), 4.14 (2 H, m, CH_2OSi), 4.4–4.6 (5 H, m, 2 × CH_2Ph and 4-H), 5.42 (1 H, ~t, *J* 1.5, 3-H) and 7.3 (10 H, m, 2 × Ph); and starting diol **17** (2 mg, 8% recovery).

The procedure for conversion of silyl ether **19b** (6 mg, 12.5 μmol) into epoxy ester **21b** was the same as that described above for conversion of acetate **19a** into **21a**. Purification by flash chromatography [light petroleum–ethyl acetate (19:1, then 9:1)] provided ester **21b** (4 mg, 45%), ν_{max}/cm^{-1} 3075, 3050, 1710, 1600 and 700; δ_H(300 MHz) 0.02 (3 H, s, SiMe), 0.03 (3 H, s, SiMe), 0.85 (9 H, s, SiBu^t), 1.82 (1 H, dt, $J_{6\alpha,6\beta}$ 14.5, $J_{5,6\alpha}$ 4.5, 6α-H), 2.34 (1 H, ddd, $J_{6\alpha,6\beta}$ 14.5, $J_{5,6\beta}$ 9.5, $J_{6\beta,7}$ 4.0, 6β-H), 2.51 (1 H, m, $J_{5,6\beta}$ 9.5, $J_{1,5}$ 8.5, $J_{4,5}$ 5.5, $J_{5,6\alpha}$ 4.5, 5-H), 3.12 (1 H, t, $J_{1,8}$ 8.5, $J_{1,5}$ 8.5, 1-H), 3.71 (1 H, dd, $J_{1,8}$ 8.5, $J_{7,8}$ 4.0, 8-H [overlapping 3-H]), 3.72 (1 H, d, $J_{3,4}$ 1.5, 3-H [overlapping 8-H]), 3.91 (1 H, d, *J* 11.5, CH_2OSi), 3.96 (1 H, m, 7-H), 4.35–4.65 (4 H, 2 × distorted A/B patterns, 2 × CH_2Ph), 3.98 (1 H, d, *J* 11.5, CH_2OSi), 5.01 (1 H, dd, $J_{4,5}$ 5.5, $J_{3,4}$ 1.5, 4-H), 5.09 (2 H, ~s, PhCH_2Ar), 6.96 (2 H, d, *J* 9.0, ArH), 7.35 (15 H, m, 3 × Ph) 8.01 (2 H, d, *J* 9.0, ArH); *m/z* (NH_3, CI) 724 ($[M + NH_4]^+$ 12%), 707 ($[M + H]^+$, 7), 615 (3.0), 542 (30), 496 (35), 228 (66), 106 (100) and 91 (57) (Found: $[M + NH_4]^+$, 724.3658. $C_{43}H_{54}NO_7Si$ requires *m/z*, 724.3667).

(±)-exo,exo-7,8-*Bis*(*benzyloxy*)-endo-4-(p-*benzyloxybenzoyloxy*)-exo-2-(tert-*butyldimethylsiloxymethyl*)-endo-2,3-*epoxy*-cis-*bicyclo*[3.3.0]*octane* **22b**.—The procedure for silylation of the diol **18** (24 mg, 0.066 mmol) was the same as that described for the preparation of compound **19b** from **17**. Purification by flash chromatography [light petroleum–ethyl acetate (19:1, 6:1, then 1:2)] provided: (±)-*exo*,*exo*-7,8-bis(benzyloxy)-2-*tert*-butyldimethylsiloxymethyl)-*cis*-bicyclo-[3.3.0]oct-2-en-*endo*-4-ol **20b** (10 mg, 32%), ν_{max}/cm^{-1} 3400, 3075, 3050, 1460 and 740; δ_H(90 MHz; standard Me_2SiBu^t) 0.00 (6 H, s, $SiMe_2$), 0.85 (9 H, s, SiBu^t), 1.65–2.00 (3 H, m), 3.00 (1 H, m), 3.7–4.2 (5 H, m), 4.45 (4 H, m, OCH_2Ph × 2), 4.7 (1 H, m, 4-H), 5.45 (1 H, m, 3-H) and 7.3 (10 H, m, 2 × Ph); and the starting diol **18** (3 mg, 12% recovery) as well as two other uncharacterised products (~10% of each), presumed to be the bissilylated ether and the secondary monosilylated ether.

The procedure for conversion of silyl ether **20b** (10 mg, 0.021 mmol) to epoxy ester **22b** was the same as that described above for conversion of acetate **19a** into **21a**. Purification by flash chromatography [light petroleum–ethyl acetate (19:1, then 9:1)] provided ester **22b** (7 mg, 48%), ν_{max}/cm^{-1} 3075, 3050, 1715, 1610 and 740; δ_H(300 MHz) 0.00 (3 H, s, SiMe), 0.01 (3 H, s, SiMe), 0.85 (9 H, s, SiBu^t), 1.76 (2 H, m, 6-H_2), 2.76 (1 H, dd, 1-H), 3.29 (1 H, m, 5-H), 3.75 (2 H, m, 3- and 7-H), 3.90 (1 H, d, *J* 11.0, 8-H), 4.11 (2 H, br s, CH_2OSi), 4.41 (2 H, d, CH_2Ph), 4.49 (2 H, d, CH_2Ph), 5.12 (2 H, s, CH_2Ph), 5.34 (1 H, br d, $J_{4,5}$ 9.0, 4-H), 6.97 (2 H, d, *J* 9.0, ArH), 7.20–7.45 (15 H, m, 3 × Ph) and 8.00 (2 H, d, *J* 9.0, ArH); *m/z* (FAB, thioglycerol) 707 ($[M + H]$, 6.5%), 615 (2), 599 (7), 371 (7), 221 (100) and 121 (28).

Specionin 10-*Acetate* **23a** *and its Anomers* **24a** *and* **25a**.—A stirred suspension of the ester **21a** (48 mg, 0.076 mmol) and palladium (5%) on carbon (~15 mg) in absolute ethanol (8 cm^3) was hydrogenated at 1 atm for 6 h. The mixture was then filtered through Celite and to the filtrate was added sodium metaperiodate (35 mg, 0.164 mmol). The resulting suspension was stirred for 24 h at room temperature, or until no starting material remained (TLC), and more sodium metaperiodate was added if necessary to ensure complete reaction. PTSA (~12 mg)

was then added and the mixture was stirred for 10–24 h. The bulk of the ethanol was then evaporated off, dichloromethane (30 cm^3) was added, and the mixture was washed with water (20 cm^3), dried, and evaporated. Purification by flash chromatography [light petroleum–ethyl acetate (5:1, then 2:1)] provided a mixture of the bis-acetals **23a**, **24a** and **25a** (~ 10:10:1) (24 mg, 73%), ν_{max}/cm^{-1} 3400, 3075, 1720, 1600 and 710; δ_H* (300 MHz) 1.15–1.25 (6 H, m, 2 × CH_2Me) 1.78–2.01 (2 H, m, 4-H_2), 2.08 (3 H/2, s, OAc), 2.09 (3 H/2, s, OAc), 2.30 (H/2, m, 5-H [**24a**]), 2.41 (H/2, m 5-H [**23a**]), 2.69 (H/2, dd, $J_{5,9}$ 9.0, $J_{1,9}$ 3.0, 9-H [**24a**]), 2.76 (H/2, dd, $J_{5,9}$ 8.0, $J_{1,9}$ 4.0, 9-H [**23a**]), 3.4–3.55 (2 H, m, CH_2Me), 3.74 (H/2, br s, 7-H [**23a**]), 3.80 (H/2 br s, 7-H [**24a**]), 3.75–3.85 (2 H, m, CH_2Me), 3.98 (H/2, d, J 12.0, 10-Ha [**24a**]), 4.00 (H/2, d, J 12.0, 10-Ha [**23a**]), 4.60 (H/2, d, J 12.0, 10-Hb [**24a**]), 4.63 (H/2, d, J 12.0, 10-Hb [**23a**]), 4.74 (H/2, dd, J 9.5, 4.0, 3-H [**24a**]), 4.85 (H/2, dd, J 7.0, 2.5, 3-H [**23d**]), 4.98 (H/2, J 3.0, 1-H [**24a**]), 5.01 (H/2, J 3.0, 1-H [**23a**]), 5.27 (H/2, dd, J 6.5, 1.5, 6-H [**24a**]), 5.34 (H/2, dd, J 8.5, 1.0, 6-H [**23a**]), 6.83 (2 H, ~d, J 8.5, ArH) and 7.92 (2 H, ~d, J 8.5, ArH) (see also Fig. 1 in Discussion section).

Equilibration of the Bis-acetals **23a**, **24a** *and* **25a**, *to give* (±)-*Specionin Acetate* **23a**.—A solution of the above bis-acetals **23a**, **24a** and **25a** (20 mg, 0.046 mmol) and PTSA (~ 5 mg) in ethanol (5 cm^3) was stirred at room temperature for 24 h. The bulk of the solvent was evaporated off, the residue was taken up in dichloromethane (20 cm^3), and the solution was washed with saturated aq. $NaHCO_3$ (15 cm^3), dried, and evaporated. No further purification of the product was carried out, and the ratio of the diastereoisomeric bis-acetals (**23a** and **27a**, ~6:1) was determined by high-field ^1H NMR analysis; ν_{max}/cm^{-1} 3400, 3075, 1720, 1600 and 710; δ_H*(300 MHz) 1.15–1.25 (6 H, m, 2 × CH_2Me), 1.8 (1 H, m, 4-Ha), 1.96 (1 H, m, 4-Hb), 2.09 (3 H, s, OAc), 2.41 (1 H, m, 5-H), 2.76 (1 H, dd, $J_{5,9}$ 8.0, $J_{1,9}$ 4.0, 9-H), 3.41–3.55 (2 H, m, CH_2Me), 3.74 (1 H, br s, 7-H), 3.75–3.85 (2 H, m, CH_2Me), 4.00 (1 H, d, J 12.0, 10-Ha), 4.63 (1 H, d, J 12.0, 10-Hb), 4.85 (1 H, dd, J 7.0, 2.5, 3-H), 5.01 (1 H, J 3.0, 1-H), 5.34 (1 H, dd, J 8.5, 1.0, 6-H), 6.83 (2 H, ~d, J 8.5, ArH) and 7.92 (2 H, ~d, J 8.5, ArH); m/z (NH_3, CI) 454 ([M + NH_3]$^+$, 34%), 437 ([M + H]$^+$, 29), 408 (45), 392 (23), 391 (100), 362 (14) and 121 (24) (Found: [M + NH_4]$^+$, 454.2075. $C_{22}H_{32}NO_9$ requires m/z, 454.2076).

10-O-(tert-*Butyldimethylsilyl*)*specionin* **23b** *and its Anomer* **24b**.—The procedure was essentially the same as that described for compound **23a**, the only exception being that PPTS was used instead of PTSA to promote cyclisation. The ester **21b** (6 mg, 8.5 μmol) gave a mixture of bisacetals **23b** and **24b** (0.5 mg, 12%) (ratio ~1:1), δ_H*(300 MHz) 0.04 (3 H, s, SiMe), 0.06 (3 H, s, SiMe), 0.09 (9 H, s, SiBu^t), 1.15–1.30 (6 H, m, CH_2Me), 2.00 (2 H, m, 4-H_2), 2.42 (1 H, m, 5-H), 2.67 (H/2, dd, J 9.0, 3.0, 9-H [**24b**]), 2.79 (H/2, dd, J 8.5, 4.0, 9-H [**23b**]), 3.4–3.55 (3 H, m, CH_2Me + 7-H), 3.78–3.90 (3 H, m), 4.15 (1 H, m, 10-H), 4.73 (H/2, dd, J 10.0, 4.0, 3-H [**24b**]), 4.84 (H/2, dd, J 7.0, 2.5, 3-H [**23b**]), 5.05 (1 H, 2 overlapping d, 1-H), 5.20–5.46 (1 H, m, 6-H), 6.80 (2 H, d, J 8.5, ArH) and 7.95 (2 H, d, J 8.5, ArH); m/z (FAB, thioglycercol) 491 ([M − 17], 0.6%), 463 ([M − 45], 8), 445 (4), 279 (9), 121 (100) and 73 (64).

(±)-exo-9-(tert-*Butyldimethylsiloxymethyl*)-2,4-*diethoxy*-endo-8,9-*epoxy*-endo-7-(p-*hydroxybenzoyloxy*)-3-*oxa*-cis-*bicyclo*[4.3.0]*nonane Anomers* **26b** *and* **27b**.—The procedure was the same as that described for the conversion of compound **21b** into bis-acetal **23b**. The ester **22b** (7 mg, 9.9 μmol) gave a mixture of bis-acetals **26b** and **27b** (0.5 mg, 10%) (ratio ~5:4), δ_H*(300 MHz) 0.04 (3 H, s, SiMe), 0.06 (3 H, s, SiMe), 0.08 (9 H, s, SiBu^t), 1.15–1.30 (6 H, m, CH_2Me), 1.80–2.00 (2 H, m), 2.30–2.50 (2 H, m), 3.4–3.60 (3 H, m), 3.70–4.10 (5 H, m), 4.73 (H/2, m), 4.95 (1 H, m), 5.10 (H/2, d, J 10, 1-H), 5.244 (1 H, m, 6-H), 6.82 (2 H, d, J 8.5, ArH) and 7.95 (2 H, m, ArH); m/z (FAB, thioglycerol) 509 ([M + H], 1.0%), 508 (M$^+$, 1.0), 463 (9), 417 (9), 331 (6) and 121 (100).

(±)-*Specionin* **1**.—A mixture of the above bis-acetals **23a** and **24a** and potassium carbonate (10 mg, 0.072 mmol) in methanol (2 cm^3) was stirred at room temperature for 15 min. The suspension was then partitioned between pH 7 phosphate buffer (10 cm^3) and dichloromethane (10 × 3 cm^3). The organic phase was dried and the solvent was evaporated off. Flash chromatography [light petroleum–ethyl acetate (2:1, then 1:1)] provided two compounds: (±)-specionin **1** (9 mg, 50%), which was identical with a natural sample, ν_{max}/cm^{-1} 3400, 1710, 1610, 1595 and 1270; δ_H*(300 MHz; C_6D_6) 0.93 (3 H, t, J 7.0, OCH_2Me), 1.09 (3 H, t, J 7.0, OCH_2Me), 2.00 (1 H, m, 4-Ha), 2.10 (1 H, m, 4-Hb), 2.67 (1 H, m, 5-H), 2.85 (1 H, dd, $J_{9,5}$ 8.5, $J_{1,9}$ 3.5, 9-H), 3.11 (1 H, m, CH_2Me), 3.22 (1 H, m, CH_2Me), 3.42 (1 H, br d, J 12.5, 10-Ha), 3.59 (1 H, m, CH_2Me), 3.65 (1 H, br s, J 1.0, 7-H), 3.75 (1 H, br d, J 12.5, 10-Hb), 3.77 (1 H, m, CH_2Me), 4.76 (1 H, dd, J 7.0, 3.0, 3-H), 4.92 (1 H, d, J 3.6, 1-H), 5.35 (1 H, m, OH), 5.61 (1 H, dd, $J_{5,6}$ 8.1, $J_{6,7}$ 1.0, 6-H), 6.51 (2 H, d, J 9.0, ArH) and 8.10 (2 H, d, J 9.0, ArH); m/z (NH_3, CI) 395 ([M + H]$^+$, 24%), 366 (12), 350 (19), 349 (100), 320 (26), 303 (12), 164 (12) and 121 (16) (Found: [M + H]$^+$, 395.1714. Calc. for $C_{20}H_{27}O_8$: m/z 395.1705), and (±)-2-epi,4-*specionin* **25c** (3 mg) (contaminated with specionin **1**), δ_H*(300 MHz; C_6D_6) 1.03 (6 H, m), 1.45 (1 H, m, OH), 1.49 (1 H, ddd, $J_{4\alpha,4\beta}$ 14.5, $J_{4\beta,5}$ 6.5, $J_{4\beta,3}$ 4.5, 4β-H), 1.70 (1 H, ddd, $J_{4\alpha,4\beta}$ 14.5, $J_{4\alpha,5}$ ~1.0, $J_{4\alpha,3}$ ~1.0, 4α-H), 2.45–2.53 (2 H, m, 5- and 9-H), 3.11–3.67 (4 H, m), 3.68 (1 H, d, J 1.0, 7-H), 3.74–3.94 (2 H, m), 4.59 (1 H, d, J 8.5, 1-H), 4.68 (1 H, dd, $J_{3,4\beta}$ 4.6, $J_{3,4\alpha}$ ~1.0, 3-H), 5.06 (1 H, m, OH), 5.91 (1 H, dd, $J_{6,5}$ 9.0, $J_{6,7}$ 1.0, 6-H), 6.51 (2 H, d, J 9.0, ArH) and 8.10 (2 H, d, J 9.0, ArH); m/z (NH_3, CI) 395 ([M + H]$^+$, 10%), 350 (20), 349 (100), 320 (22), 304 (16), 303 (15), 164 (16) and 121 (27) (Found: [M + H]$^+$, 395.1710. $C_{20}H_{27}O_8$ requires m/z, 395.1705).

(±)-exo-9-(*Acetoxymethyl*)-2,4-*diethoxy*-endo-8,9-*epoxy*-endo-7-(p-*hydroxybenzoyloxy*)-3-*oxa*-cis-*bicyclo*[4.3.0]*nonane* **26a**.—The procedure was the same as that described above for conversion of compound **23a** into bis-acetal **23a**. The ester **22a** (20 mg, 31.5 μmol) gave a mixture of bis-acetals **26a** and **27a** (8 mg, 56%), ν_{max}/cm^{-1} 3400, 3075, 1715, 1605 and 710; δ_H(300 MHz): signals for the presence of two isomeric products (ratio ~1:1). Equilibration, under the same conditions as described for compound **23a**, led to a single stereoisomer, assigned as *compound* **26a** (8 mg, quantitative), ν_{max}/cm^{-1} 3400, 3075, 1715, 1605 and 710; δ_H*(300 MHz) 1.18 (3 H, t, J 7.0, CH_2Me), 1.24 (3 H, t, J 7.0, CH_2Me), 1.72 (1 H, m), 1.88 (1 H, m), 2.04 (3 H, s, AcO), 2.40 (1 H, dd, $J_{5,9}$ 10.0, $J_{1,9}$ 7.0, 9-H), 2.70 (1 H, m, 5-H), 3.48 (1 H, m, CH_2Me), 3.58 (1 H, m, CH_2Me), 3.80 (1 H, d, J 1.0, 7-H), 3.82–3.72 (2 H, m, CH_2Me), 4.32 (1 H, d, J 12.5, 10-Ha), 4.41 (1 H, d, J 12.5, 10-Hb), 4.80 (1 H, dd, J 9.5, 6.0, 3-H), 5.11 (1 H, d, J 7.0, 1-H), 5.43 (1 H, dd, $J_{5,6}$ 8.5, $J_{6,7}$ 1.0, 6-H), 5.85 (1 H, m, OH), 6.82 (2 H, d, J 9.0, ArH) and 7.93 (2 H, d, J 9.0, ArH); m/z (NH_3, CI) 454 ([M + NH_4]$^+$, 40%), 437 ([M + H]$^+$, 7), 408 (17), 392 (23), 391 (100) and 227 (21) (Found: [M + NH_4]$^+$, 454.2075. $C_{22}H_{32}NO_9$ requires m/z, 454.2076).

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* Specionin numbering is used for specionin and all its stereoisomers and derivatives.

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