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Spiro epoxide fused *cis* bicyclo[3.3.0]octanes: enantioselective rearrangement and utilisation of the products in synthetic adventures

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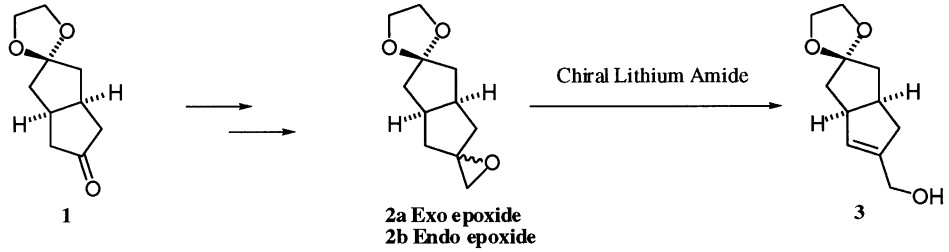
Abstract—The monoketal derived from *cis*-bicyclo[3.3.0]octane-3,7-dione was converted into the corresponding *exo* and *endo* epoxides. The meso *exo* epoxide was rearranged via enantioselective deprotonation using chiral lithium amide bases to provide a synthetically useful alcohol with up to 80% ee. In contrast it was discovered that, under the same conditions, a related epoxide was less reactive and provided the corresponding alcohol with only 23% ee. The use of these alcohol products in synthesis is also discussed.

1. Introduction

Several groups have utilised the mono ketal of *cis*-bicyclo[3.3.0]octane-3,7-dione **1** as a starting material for the stereoselective synthesis and as a substrate for asymmetric desymmetrisation. Asymmetric deprotonation of **1** has been investigated by ourselves and by Koga et al. and leads directly to the formation of chiral enolates or silyl enol ethers, with a high degree of enantioselectivity.[1,2] Such chiral enolate derivatives have been used in asymmetric synthetic routes to a range of natural products and other biologically important compounds.[2,3] Chiral tertiary amines have also been used in enantioselective elimination reactions involving trifluoromethyl sulfonates derived from *cis*-bicyclo[3.3.0]octane-3,7-dione.[4]

There has been a sustained interest in chiral base mediated enantioselective rearrangement of epoxides for many years and this remains a topical area of research with good potential the development of practically viable methodology.[5,6] It seemed to us that *meso*-epoxides **2a** and **2b**, should be readily derived from **1** and might also be suitable substrates for asymmetric desymmetrisation, using chiral lithium amide bases (Scheme 1).[7]

In this paper we describe studies carried out to test the viability of converting *meso*-epoxides **2a** and **2b** into chiral allylic alcohol **3**. We also describe some synthetic studies carried out to develop **3** as a potential synthon for stereoselective synthesis of carbacyclin derivatives and yohimbine alkaloid derivatives.



Scheme 1.

Keywords: asymmetric induction; bicyclic aliphatic compounds; deprotonation; synthons; allylic alcohol; epoxides.

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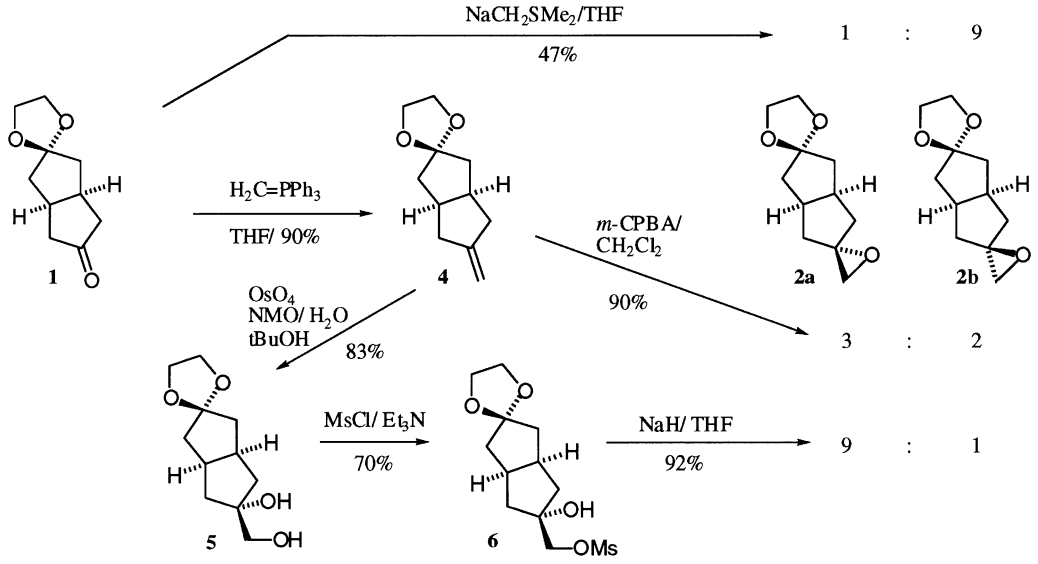


Scheme 2.

2. Results and discussion

2.1. Epoxide synthesis

We have developed several different routes to epoxides **2** (Scheme 2). In the first instance, ketone **1** was converted into alkene **4** (90%) by a Wittig reaction with methylene triphenylphosphorane. For generation of the Wittig reagent it was important to avoid lithium bases in order to achieve a high yield (NaHMDS worked well). Epoxidation of the alkene with *m*-CPBA/$NaHCO_3$ provided a mixture of **2a/2b** (85%). The epoxides formed in this way appeared to be homogeneous by TLC, but ^{13}C NMR spectroscopy was particularly useful in revealing that it was in fact a mixture of *exo* and *endo* epoxides in a ratio of 3:2. Dihydroxylation of alkenes, via osmylation, is normally more stereoselective than epoxidation, and in this case dihydroxylation of **4** gave diol **5** with a selectivity of 9:1 over the *endo* form. This was readily transformed into a 9:1 mixture of epoxides **2a** and **2b** by mesylation of the primary hydroxyl, followed by epoxide cyclisation under basic conditions. Alternatively, a 9:1 mixture of *endo*/*exo* epoxides (47%) was formed directly from ketone **1** by reaction with methylene dimethylsulfonium ylide. The behaviour of these different diastereoisomer mixtures, under epoxide rearrangement conditions, was informative (vide infra).

2.2. Enantioselective epoxide rearrangement studies

For initial studies a 3:2 mixture of epoxides **2a** and **2b** was used, as derived from **4** by reaction with *m*-CPBA. Reaction with LDA in THF at 0°C for 24 h provided a racemic mixture of **3** in 58% yield, together with recovered epoxide. By ^{13}C NMR spectroscopy, it was discovered that the epoxide recovered from the reaction comprised the *endo* compound **2b** only. It was no surprise then to find that when the epoxide prepared from the sulfur ylide (9:1 *endo*/*exo*) was reacted, under the same conditions, only 15% of alyllic alcohol **3** was obtained, after three days at 0°C. Lithium amide mediated epoxide rearrangements are generally considered to proceed via a cyclic transition state, with the removal of a proton *syn* to the epoxide oxygen.[8] If this is the case, it is not surprising to find that the *endo* epoxide is much less reactive, as removal of a proton from the concave face of the molecule would be required. From the results above, we concluded that hindered lithium amide bases differentiate quite cleanly between the *exo* and *endo* diastereoisomers of epoxide **2** (Fig. 1).

Chiral lithium amide bases **7**,[5d] **8**[9] and 9[10] were chosen for an initial enantioselective epoxide rearrangement study, with benzene, THF and diethyl ether as solvents. The results of this study are presented in Table 1.

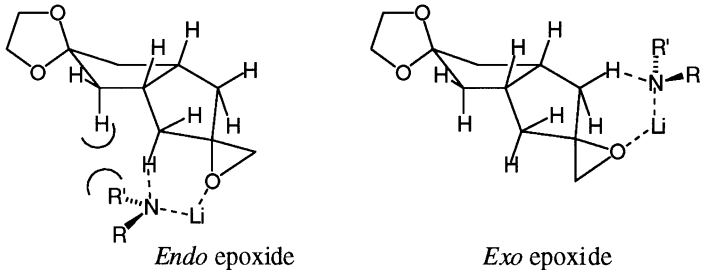
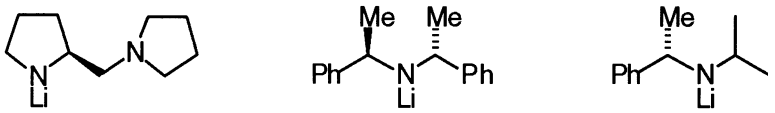


Figure 1.

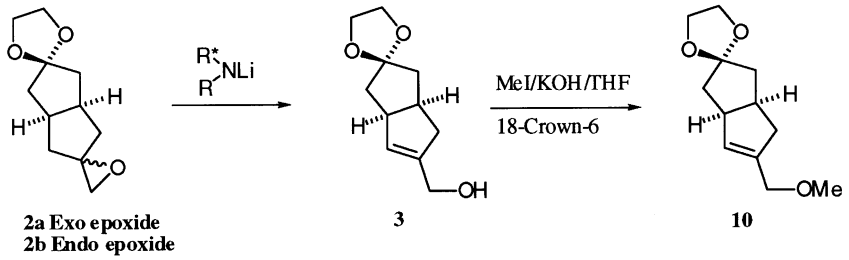
Table 1. Reaction of chiral bases with epoxide **2a/2b** (3:2 *exo/endo*)



7 **8** **9**

Base	Solvent	Yield (%)[a]	Major enant.[12]	ee (%)[b]
LDA	THF	58	–	0[c]
7	THF	58	D-(+)	21
7	Benzene	35	L-(−)	58
7	Et_2O	50	D-(+)	23[c]
8	THF	50	D-(+)	76 (80)
8	Benzene	40	D-(+)	21[c]
8	Et_2O	56	D-(+)	23[c]
9	THF	55	L-(−)	42[c]
9	Benzene	0	–	–
9	Et_2O	53	L-(−)	20

[a] Isolated yield, chromatographically pure (not optimised).
[b] Determined by chiral shift reagent on methyl ether **10**.
[c] Reactions carried out at 0°C.[13]



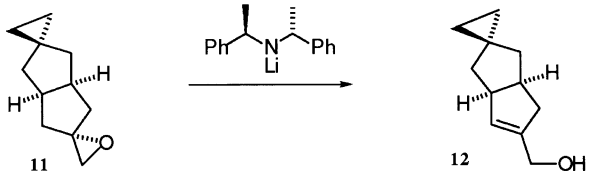
Scheme 3.

The C_2 symmetric base **8** in THF gave the best results and this was used in later preparative work, where the *exo*-epoxide **2a** was prepared more selectively, via the dihydroxylation route. Enantioselectivities of up to 80% ee were obtained for this reaction.

We could not find a suitable, reliable method for determining the ee of alyllic alcohol **3** directly, but it was converted cleanly into methyl ether **10** and this proved to be a suitable substrate for analysis, using the chiral solvating agent (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl) ethanol (TFAE), which caused complete resolution of the methoxyl singlets. This method was used for all the results described here, but it was found later that when enantiomers of **3** were converted into their benzoate esters, these could be resolved by chiral HPLC using a Chiracel OD-H column (Scheme 3).

Sometime later we thought that this type of methodology might be applicable in a synthetic route to triquinanes such as hirsutene (Scheme 4).[14] In this case we chose to examine epoxide **11** (single diastereoisomer) as a substrate for the chiral base reaction. To our surprise, compared with **2a**, epoxide **11** was quite unreactive towards a range of lithium amide bases, and elevated reaction temperatures (~25°C) were required to bring about the reaction. Under such conditions base **8** provided allylic alcohol **12** in moderate yield, but with only 23% ee. A range of other base types were evaluated, but none gave the product with high ee.[14] The enantiomeric purity of allylic alcohol **12** was determined by chiral HPLC (Chiracel OD-H column) on the benzoate derivative.

It is interesting to consider this result together with those for the opening of epoxide **2a**. For each of the substrates a co-ordinating solvent (THF or ether) is required for high enantioselectivity when a monodentate base is employed. However, for substrate **2** the bidentate base **7** gave higher enantioselectivity in benzene than in THF or diethyl ether, and there was also an intriguing reversal in the direction of enantioselectivity between the two solvents. The reason for the lack of reactivity and enantioselectivity of substrate **11**, in either type of solvent might be related to the observations above. The most obvious difference between substrates **2** and **11** is that the cyclopropane lacks remote co-ordinating oxygen atoms. It appears that co-ordination of the base in



Scheme 4.

the transition state is important in facilitating epoxide fragmentation and in controlling both the degree and direction of enantioselectivity. Thus, different mechanisms may be involved, depending on the co-ordinating properties of the base, the solvent and the substrate.

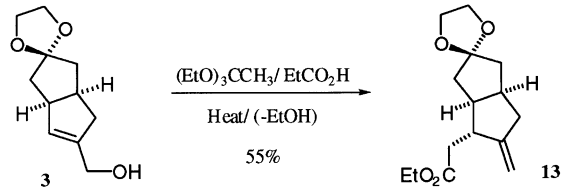
The tertiary amine in base **7** provides strong co-ordination of the lithium atom and in a previous study we noticed that benzene was a particularly good solvent with a substrate in which a further *internal* co-ordination site was available.[5d] It is known that bases of type **7** exist as dimers in non-co-ordinating solvents, such as benzene, but monomers in THF. The observed reversal of enantioselectivity for substrate **2** in co-ordinating solvents could be because, in benzene it is the substrate, rather than THF, that solvates the base, thus providing a very different reagent with a different stereochemical bias in the reaction transition state. The oxygen atoms of the ketal appear to be too far away to offer direct internal co-ordination, if the generally accepted cyclic transition state for epoxide opening operates in this case. However, it could be that an oligermeric base complex is involved, or that in some cases the reaction proceeds via a non-cyclic transition state.

It is difficult to understand why substrate **11** is so unreactive relative to **2**, even in LDA/THF or with base **8** in THF. This might suggest that even with a monodentate base in a co-ordinating solvent, substrate solvation has an influence on the mode of reaction. We are presently trying to build substrates of different types, in order to evaluate the influence of ether oxygen atoms with different arrangements relative to the epoxide.

An interesting general observation is that methyl benzylamine derived bases of type **8** are normally ineffective for enantioselective epoxide opening reactions,[5a] but do give products with high ee when used for enolisations. However, the transition state for cleavage of spiro-epoxides is probably quite different from that of other epoxides, and comparison of models indicates that it may actually be quite closely related to the transition state of enolisation reactions.[12]

2.3. Synthetic transformations using allylic alcohol 3[†]

2.3.1. Sigmatropic rearrangements. We wanted to extend the utility of the epoxide opening products with the general aim of creating synthons with potential use in enantioselective approaches to natural products and other important compounds. First of all we investigated derivatising allylic alcohol **3** via sigmatropic rearrangements, in order to create a new stereogenic centre with complete diastereoisomeric control. When allylic alcohol **3** was heated with triethylorthoacetate and a catalytic amount of propionic acid, with removal of ethanol by distillation, a smooth Claisen orthoester rearrangement[15] occurred to provide ester **13** as the only isolated product (Scheme 5). We have explored the potential of this compound for the synthesis of triquinanes and related natural products.



3 13

Scheme 5.

[2,3]-Sigmatropic Wittig–Still rearrangements are also useful for chirality transfer.[16] In a two step procedure alcohol **3** was converted into alcohol **15** via stannane **14** (Scheme 6). The yields for the sequence were modest, but reactions were carried out on a small scale and are unoptimised. The product has clear potential as an intermediate for the enantioselective synthesis of biologically important compounds, such as carbacyclin derivatives.

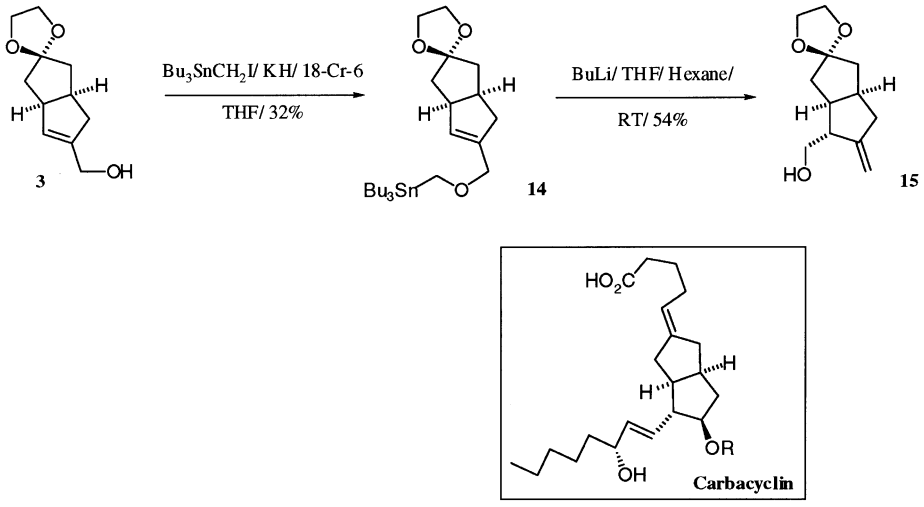
2.3.2. Ring expansion—preparation of a potential reserpine precursor. Previously, we have prepared heteroyohimbine synthons from *cis*-bicyclo[3.3.0]-octane systems in a sequence that involved selective cleavage of each 5-membered ring.[4] With the extra carbon atom present in allylic alcohol **3** we thought that it might be possible to build a system that could become the carbocyclic D/E rings of highly functionalised yohimbine alkaloids, such as reserpine.

With the ultimate aim of synthesising either Stork's reserpine precursor **19**[17] or Woodward's precursor **20**,[18] we first wanted to cleave the alkene bond in methyl ether **10**, then re-cyclise with an aldol condensation to provide enone **17**. This appears to have stereochemistry and functionality appropriate for conversion into the synthetic objective (Scheme 7).

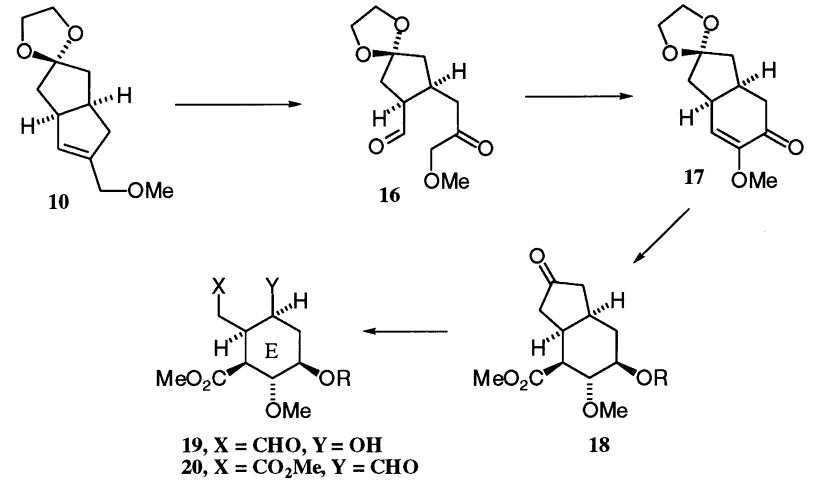
In the first instance we attempted to cleave the alkene in a single step with ozone, using either dichloromethane or methanol as solvent, with dimethyl sulfide for reductive work-up. To our surprise, the only compounds to be isolated were cyclic ozonides, and we therefore adopted a two-step dihydroxylation-diol cleavage process. Dihydroxylation of **10**, using catalytic osmium tetroxide and NMO, was clean and provided diol **21** as a single diastereoisomer. When the diol was cleaved using lead tetraacetate, in benzene at room temperature,[19] the *cis*-aldehyde **22** was formed in 48% yield. However, when this was treated with sodium hydrogen carbonate it was converted into another isomeric aldehyde, presumed to be the more thermodynamically stable *trans*-aldehyde **23**. This transformation was accompanied by a shift in the position of the aldehyde signal, in the proton NMR spectrum, from δ 9.70 to 9.56 (Scheme 8).

Contrary to our predictions the aldehydes **22** and **23** were stable and unaffected by flash chromatography. The next challenge was to bring about aldol cyclisation and for this we tried a wide variety of reagents. These fell into one of two categories: base catalysts, the best of which was sodium hydride in refluxing THF, which gave *cis*/*trans* ring junction isomers **17** and **24** in a ratio of 1:1, with a moderate 36% yield; amine salts proved to be more effective cyclisation catalysts and the best of these was *N*-methyl anilinium

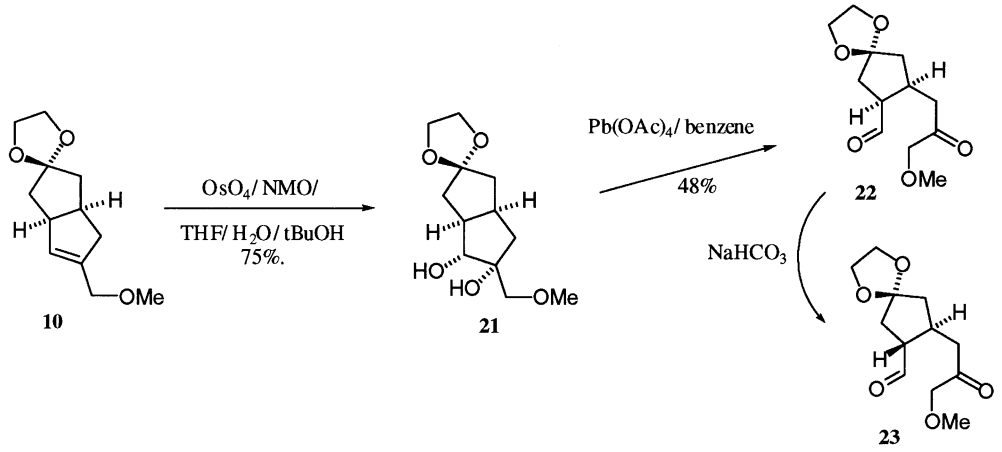
[†] All synthetic transformations have been carried out on enantiomerically enriched material, prepared using base **8**.



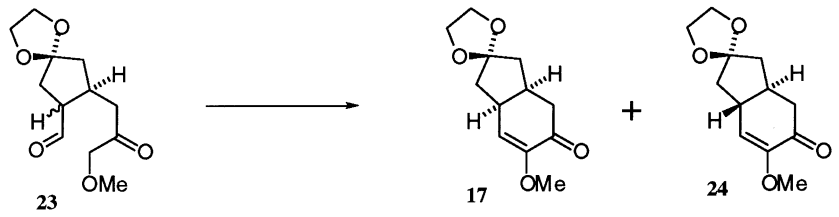
Scheme 6.



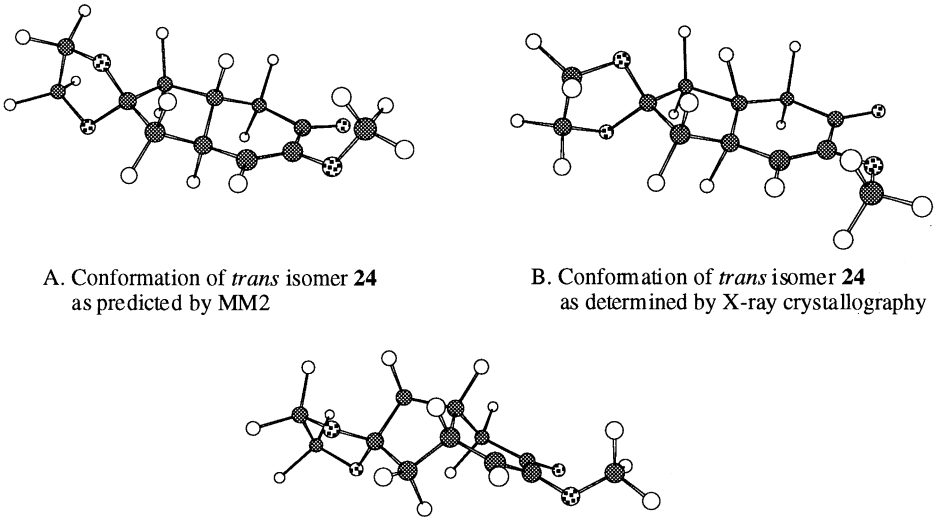
Scheme 7.



Scheme 8.



Scheme 9.



A. Conformation of *trans* isomer **24** as predicted by MM2

B. Conformation of *trans* isomer **24** as determined by X-ray crystallography

C. Conformation of *cis* isomer **17** as predicted by MM2

Figure 2.

trifluoroacetate in benzene at 60°C, which gave *cis*/*trans* ring junction isomers **17** and **24** in a ratio of 1:10 and a yield of 42% (Scheme 9).

We had anticipated that the cyclised *cis* isomer **17** would be more thermodynamically stable than the *trans* isomer **24**, but in no case was the *cis* isomer initially formed in excess from a cyclisation reaction. It was also interesting to discover that the ratio of isomeric products appeared to be independent of the stereoisomer ratio of the aldehydes **22** and **23**. However, upon heating isomer mixtures of **17** and **24** in a mixture of triethylamine and dichloromethane, equilibration did occur to provide *cis* isomer **17** as the major compound in a ratio of 5:1. One explanation for the observed behaviour is that, under cyclisation conditions, aldehyde stereoisomers are in equilibrium and the *trans* isomer cyclises more rapidly than the *cis* isomer, leading to **24** as the major product formed initially. However, this is less thermodynamically stable than *cis* isomer **17**, into which it can be inter-converted, via a conjugated enol form.

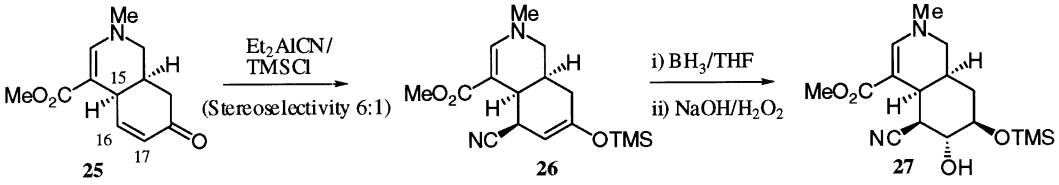
Although we had tentatively assigned the more thermodynamically stable cyclic isomer as the *cis* enone **17**, it was not easy to be certain of our assignment from NMR spectroscopic data. Fortunately, we were able to grow a crystal of one isomer that was suitable for X-ray crystallography.[‡] To our surprise the stereochemistry of the compound was not immediately apparent from the X-ray structure. The bicyclic ring system was quite flat, and the position of the ring junction protons was difficult to determine. Molecular mechanics calculations (Macromodel 3, MM2)[20] proved to be very helpful, as the predicted shapes of the two compounds were quite different. Significantly, the *trans* ring junction isomer was predicted to be an almost flat compound whereas the *cis* isomer was predicted to be have a folded shape (Fig. 2). The X-ray structure was almost identical to the structure predicted for the *trans* isomer. This isomer was also predicted to be less thermodynamically stable than the *cis* isomer and this was also in accord with our empirical results.

For progress towards a reserpine precursor, conjugate addition of a carbon nucleophile onto the enone of **17** was envisaged. Some time ago Mariano found that cyanide adds stereoselectively to enone **25**, leading to the preparation of **27**, with functionality and stereochemistry equivalent to that found in the reserpine E-ring (Scheme 10).[21]

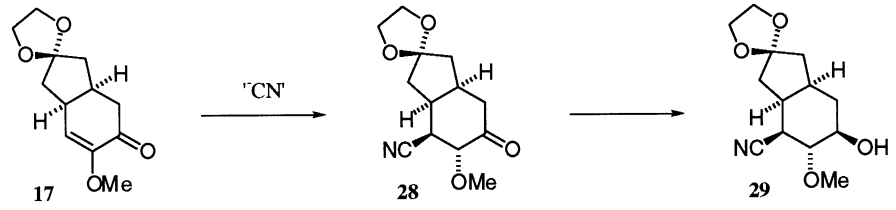
Encouraged by this result, we thought that axial addition of cyanide to enone **17** might also deliver the nucleophile *trans* to the ring junction hydrogens, as required for reserpine. This would provide ketone **28** from which it should be possible to obtain **29**, a credible reserpine precursor (Scheme 11).

Unfortunately, further progress towards a reserpine precursor was curtailed when we were unable to effect cyanide

[‡] X-Ray crystallographic data submitted to Cambridge Crystallographic Data Centre, deposition number CCDC 180482.



Scheme 10.



Scheme 11.

addition to **17**. A range of conditions were tried: first involving diethylaluminium cyanide and trimethyl silyl chloride; then involving the use of cyanotrimethylsilane catalysed by the addition of Lewis acids, such as diethylaluminium chloride (Et_2AlCl)[22] or triethylaluminium (Et_3Al).[23] It is likely that the enone is deactivated towards conjugate addition by the α-methoxy group, but we had hoped that addition of Lewis acids might counteract this affect.

3. Conclusion

In conclusion, we have shown that chiral lithium amide bases cleave *meso* spiro epoxide **2a** with a high degree of enantioselectivity providing the useful chiral allylic alcohol **3**, with an ee of up to 80%. It is significant that phenylethylamine derived base **8** was found to be effective. This base is also cheap and easy to prepare in either enantiomeric form. It was surprising to discover that the closely related spiro-epoxide **11** was much less reactive towards the epoxide fragmentation reaction than **2a** and that it reacted to give a product with much lower ee. In this study we have also shown several ways in which chiral alyllic alcohol **3** can be converted into other chiral synthons, with potential utility in synthesis.

4. Experimental

Melting points were determined on an electrothermal apparatus and are uncorrected. Infra-red absorption spectra were recorded on a Perkin–Elmer FT-1710 instrument, as liquid films or solutions in chloroform. ^{1}H NMR spectra were recorded on a Bruker AC 300 instrument, and were referenced to a deuteriochloroform lock. Samples were run as solutions in deuteriochloroform unless otherwise stated. The following abbreviations have been used to describe the signal multiplicity; br (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). The ~ symbol before the multiplicity indicates that the signal multiplicity is apparent (or approximate). Mass spectra were measured at low resolution on a Finnigan 4500 instrument. High resolution spectra were measured on a Kratos Concept 1-S instrument. Percentile figures refer to relative intensity as a proportion of the base peak. Thin layer chromatography was carried out on Merck Kieselgel 60 F_{254} glass backed plates and visualised sequentially with UV lamp, iodine and ethanolic vanillin dip, followed by heating. During work-up procedures: the term 'dried' refers to dying the solution over magnesium sulphate, unless otherwise stated; the term 'evaporated' refers to removal of solvents on a rotary evaporator. Flash chromatography was carried out over Merck silica gel-60 (particle sizes 40–63 μ). Petroleum ether refers to the petroleum fraction boiling in the range 40–60°C, unless stated otherwise. Where necessary, solvents and reagents were dried and purified according to the recommended methods.[24]

4.1. Methods for ee determination of allylic alcohols 3 and 12

Samples of alyllic alcohol **3**, were converted into methyl ether **10**, as described below, for the purpose of ee determination. NMR samples of ethers **10** (5 mg) in $CDCl_3$ were then prepared. NMR spectra were run on the samples, prior to addition of 3 equiv. of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl) ethanol (TFAE) in $CDCl_3$. The spectra were then re-acquired and complete resolution of the methoxyl singlets was normally observed. In a few cases resolution was incomplete and the addition of another equivalent of the chiral solvating agent was required.

Samples of allylic alcohol **12** were converted into their benzoate ester derivative, as described below, for the purposes of ee determination. This provided a chromophore for HPLC detection. HPLC analysis of benzoate esters was carried out using a CHIRALCEL OH-D column (4.6 mm×25 cm). A solvent mixture of hexane/isopropanol (99:1) provided complete separation of the two enantiomers.

Each of the procedures above was validated by analysis of racemic samples, prepared by using LDA instead of chiral base for the epoxide rearrangement step. In each case the ratio of enantiomers observed was exactly 1:1.

4.1.1. 7,7-Ethylenedioxy-3-methylidene-*cis*-bicyclo[3.3.0]-octane 4. To a stirred suspension of methyltriphenylphosphonium bromide (439 mg, 1.23 mmol) in THF

(30 mL) under argon, at 0°C, was added sodium bis(trimethylsilyl)amide in THF (1 M, 1.17 mL, 1.17 mmol). A solution of ketone **1**[4] (150 mg, 0.82 mmol) in THF (5 mL) was added dropwise and the mixture was maintained at 0°C for 30 min. It was then allowed to warm to ambient temperature and after 1.5 h it was diluted with dichloromethane (40 mL). The mixture was then washed with water (2×25 mL), dried and evaporated. Purification by flash chromatography (light petroleum/ethyl acetate, 4:1) provided the alkene **4** as a pale yellow oil (134 mg, 90%): ν_{max} (cm^{-1}) 2918, 1660, 1113; δ_H (300 MHz, $CDCl_3$) 4.82–4.77 (2H, m, C=CH_2), 3.86 (4H, s, OCH_2CH_2O), 2.62–2.39 (4H, m, 2α-H, 4α-H, 1-H, 5-H), 2.07 (2H, d, J=14 Hz, 2β-H, 4β-H), 1.96 (2H, dd, J=8, 14 Hz, 8α-H, 6α-H), 1.54 (2H, dd, J=7, 14 Hz, 8β-H, 6β-H); δ_C (75 MHz, $CDCl_3$) 151.9 (C-3), 118.3 (C-7), 105.9 (=CH_2), 64.3 and 63.6 (OCH_2CH_2O), 41.7 (C-8, C-6), 39.7 (C-1, C-5), 39.4 (C-2, C-4); *m/z* (NH_3, Cl) 198 ($[M+NH_4]^+$, 12%), 181 ($[M+H]^+$, 100%); Found: 181.1221. Calcd for $C_{11}H_{17}O_2$, 181.1228.

4.1.2. *exo*/*endo*-7,7-Ethylenedioxy-3-methylidene-*cis*-bicyclo[3.3.0]octane-3,1′-oxides 2a/2b (3:2 mixture). To a stirred mixture of the alkene **4** (1.61 g, 8.93 mmol) and sodium hydrogen carbonate (3.08 g, 36.66 mmol) in dichloromethane (50 mL), was added *m*-CPBA (1.57 g, 9.07 mmol), in portions, at 0°C. After 2 h sodium thiosulphate solution (10% w/v, 25 mL) was added and after a further 15 min the mixture was washed with saturated aqueous sodium hydrogen carbonate (3×15 mL), dried and evaporated. Purification by flash chromatography (light petroleum/ethyl acetate, 6:1) gave epoxides **2a** and **2b** (*exo*/*endo*, 3:2) as a yellow oil (1.58 g, 90% yield): see data below.

4.1.3. 7,7-Ethylenedioxy-3-hydroxy-3-hydroxymethyl-*cis*-bicyclo[3.3.0]octane 5. To a rapidly stirred mixture of alkene **3** (500 mg, 2.77 mmol), *N*-methylmorpholine-*N*-oxide (NMO) (336 mg, 2.87 mmol) in water (0.7 mL), ^{t}butanol (2.5 mL) and THF (1.0 mL) was added a 3% solution of osmium tetroxide in ^{t}butanol (seven drops). After 48 h the mixture was concentrated and purification by flash chromatography (light petroleum/ethyl acetate, 4:1, ethyl acetate) to give the diol **5** (490 mg, 83%) as a white solid: mp 92–93°C; ν_{max} (cm^{-1}) 3291, 2955, 1435; δ_H (300 MHz, $CDCl_3$) 3.96–3.81 (4H, m, OCH_2CH_2O), 3.60 (2H, s, CH_2OH), 2.87–2.76 (2H, m, 1-H, 5-H), 2.59 (2H, br s, OH×2), 2.10–1.90 (4H, m), 1.65–1.46 (4H, m); *m/z* (NH_3, Cl) 232 ($[M+NH_4]^+$ 100%), 215 ($[M+H]^+$ 20%); Found: $[M+NH_4]^+$ 232.1557. $C_{11}H_{22}O_4N$ requires 232.1549; Found: (C, 72.53; H, 9.86. $C_{11}H_{18}O$ requires C, 72.49; H, 9.96%).

4.1.4. 7,7-Ethylenedioxy-3-hydroxy-*cis*-bicyclo[3.3.0]-octane-3-methanol methanesulfonate 6. To a stirred solution of diol **5** (130.8 mg, 0.61 mmol) and triethylamine (5 drops) in dichloromethane (20 mL) at 0°C, was added methanesulfonyl chloride (48 μΛ, 0.62 mmol). After 5 min TLC indicated that no starting material remained. The mixture was washed with saturated aqueous sodium hydrogen carbonate solution (3×5 mL), dried and evaporated. Purification by flash chromatography (light petroleum/ethyl acetate, 4:1) provided mesylate **6** as a white crystalline solid (125.0 mg, 70% yield); mp 81–82°C (solidified); ν_{max} (cm^{-1}) 3507, 2933, 1649, 1462, 1376, 1286; δ_H (300 MHz, $CDCl_3$) 4.19 (2H, s, CH_2OSO_2Me), 3.85 (4H, m, OCH_2CH_2O), 3.02 (3H, s, OSO_2Me), 2.85–2.77 (2H, m, H-1, H-5), 2.40–2.30 (1H, br., OH), 1.99–1.91 (4H, m), 1.65–1.50 (4H, m); δ_C NMR (75 MHz) 220.0 (C-7), 81.5 (C-3), 75.5 (CH_2OSO_2Me), 63.6 (OCH_2CH_2O), 44.0 (C-2, C-4 or C-6, C-8), 43.9 (C-2, C-4 or C-6, C-8), 37.8 (C-1, C-5), 37.4 (*Me*); *m/z* (NH_3, CI) 310 ($[M+NH_4]^+$, 100%), 293 ($[M+H]^+$, 40); Found $[M+NH_4]^+$ 310.1332. $C_{12}H_{24}O_6SN$ requires 310.1324.

4.1.5. *exo*-7,7-Ethylenedioxy-3-methylidene-*cis*-bicyclo-[3.3.0]octane-3,1′-oxide 2a. A mixture of the mesylate **6** (438.1 mg, 1.50 mmol) and sodium hydride (115.2 mg, 4.80 mmol) in anhydrous THF (20 mL) was heated to reflux under an atmosphere of argon for 16 h. After cooling, solid carbon dioxide was added and the mixture was then diluted with dichloromethane. The organic phase was washed with saturated aqueous sodium hydrogen carbonate (3×10 mL), dried and evaporated. Purification by flash chromatography (light petroleum/ethyl acetate, 6:1) provided epoxides **2a** and **2b** (*exo*/*endo*, 9:1) as a yellow oil (270.8 mg, 92% yield): ν_{max} (cm^{-1}) 2930, 1225; δ_H (300 MHz, $CDCl_3$) 3.87 (4H, ~s, OCH_2CH_2O), 2.80 (2H, s, H-1′×2), 2.76–2.70 (2H, m, H-5, H-2), 2.10–1.97 (3H, m), 1.8–1.75 (3H, m), 1.61 (2H, dd, J=14, 3.5 Hz, H-2a/4a, or H-6a/8a); δ_C (75 MHz, $CDCl_3$) 118.6 (C-7), 65.9 (C-3), 64.4 and 63.9 (OCH_2CH_2O), 51.4 (C-1′), 41.9 (C-6, C-8), 39.0 (C-2, C-4), 38.8 (C-1, C-5); *m/z* (NH_3, CI) 179 (100%), 197 ($[M+H]^+$, 65%), 214 (50); Found $[M+H]^+$ 197.1182. $C_{11}H_{17}O_3$ requires 197.1178.

4.1.6. *endo*-7,7-Ethylenedioxy-3-methylidene-*cis*-bicyclo[3.3.0]octane-3,1′-oxide 2b. To a stirred suspension of trimethylsulfonium iodide (245 mg, 1.2 mmol), in anhydrous (THF 25 mL), at 0°C, under nitrogen, *n*-BuLi (0.78 mL, 1.1 mmol, 1.4 M) was added. After 5 min a solution of the monoketone **1**[4] (182 mg, 1 mmol) in dry THF (5 mL) was added and after a further 30 min the mixture was allowed to stir at room temperature. After 1 h the mixture was evaporated to remove most of the THF and hexane, water (15 mL) was added and the mixture was extracted with pentane (3×15 mL). The extracts were further washed with water, then dried and evaporated. Purification by flash chromatography (light petroleum/ethyl acetate, 4:1) provided epoxides **2a** and **2b** (*exo*/*endo*, 1:9) (100 mg, 47%), as a colourless oil: ν_{max} (cm^{-1}) 3054, 2987, 1263; δ_H (300 MHz, $CDCl_3$) 3.88 (4H, ~s, OCH_2CH_2O), 2.69 (2H, s, H-1′×2), 2.68–2.55 (2H, m, H-5, H-2), 2.15–1.95 (4H, m, H-2β, H-4β, H-6β, H-8β), 1.74 (2H, dd, J=18.5, 6 Hz, H-2α/4α, or H-6α/8α), 1.56 (2H, dd, J=14, 3.5 Hz, H-2α/4α, or H-6α/8α); δ_C (75 MHz, $CDCl_3$) 118.2 (C-7), 65.6 (C-3), 64.6 and 63.8 (OCH_2CH_2O), 49.5 (C-1′), 41.9 (C-6, C-8), 38.9 (C-2, C-4), 38.5 (C-1 and C-5); *m/z* (NH_3, CI) 179 (100%), 197 ($[M+H]^+$, 65%), 214 (50); Found $[M+H]^+$ 197.1180. $C_{11}H_{17}O_3$ requires 197.1178.

4.1.7. Screening of chiral lithium amide bases for the preparation 7,7-ethylenedioxy-3-hydroxymethyl-*cis*-bicyclo[3.3.0]oct-2-ene from 7,7-ethylenedioxy-3-methylidene-*cis*-bicyclo[3.3.0]octane-3,1′-oxide. To a solution diisopropylamine or the selected chiral amine (1.22 mmol)

in anhydrous THF (6 mL), at 0°C, under nitrogen, was added *n*-BuLi in hexane (1.42 M, 0.82 mL, 1.17 mmol). After 30 min a solution of epoxide **2a/2b** (3:2, *exo*/*endo*) (0.10 g, 0.51 mmol) in anhydrous THF (2 mL) was added. The temperature of the solution was maintained at 0°C and the progress of the reaction was monitored by TLC. After ca. 18 h the mixture was diluted with diethyl ether (20 mL), washed with saturated ammonium chloride solution (15 mL), then the organic extract was dried and evaporated. Purification by flash chromatography (light petroleum/ethyl acetate, 4:1) afforded the alcohol **3** (57 mg, 57%) as a pale yellow liquid: δ_H (300 MHz): 5.48 (1H, d, J=1.5 Hz, H-2), 4.74 (1H, br.s, O*H*), 4.12 (2H, br.s, CH_2OH), 3.92–3.81 (4H, m, OCH_2CH_2O), 3.24–3.14 (1H, m, H-1), 2.80 (1H, ~d quintet, J=4×9, 2 Hz, H-5), 2.61 (1H, ~dd, J=16, 9 Hz, H-4α), 2.10 (1H, d J=9 Hz, H-4β), 2.05–1.90 (2H, m, H-8α, H-6α), 1.66–1.50 (2H, m, H-8β, H-6β); δ_C (75 MHz) 142.5 (C-3), 128.8 (C-2), 118.1 (C-7), 64.6 and 63.8 (O*C*H_2*C*H_2O), 61.8 (*C*H_2OH), 47.1 (C-1), 42.4 (C-4), 40.1 (C-8), 39.3 (C-6), 38.2 (C-5); *m*/*z* (NH_3, CI) 179 (100%), 214 ([M+NH_4]$^+$, 62), 197 ([M+H]$^+$, 52); Found [M+H]$^+$ 197.1171. $C_{11}H_{17}O_3$ requires 197.1178.

4.1.8. (1*R,5*R**)-7,7-Ethylenedioxy-3-hydroxymethyl-*cis*-bicyclo[3.3.0]oct-2-ene 3.** To a stirred solution of (+)-bis-[(*R*)-1-phenylethyl]amine (1.36 g, 6.04 mmol), in anhydrous THF (30 mL) at 0°C, under argon, was added *n*-BuLi in hexane (1.55 M, 3.80 mL, 5.89 mmol). After 10 min epoxide **2a** (1.05 g, 5.35 mmol) in anhydrous THF (5 mL) was added and the mixture was maintained at 0°C for 16 h. The mixture was then allowed to warm to room temperature, diluted with diethyl ether, washed with saturated aqueous ammonium chloride solution (4×10 mL), dried and evaporated. Purification by flash chromatography (light petroleum/ethyl acetate, 4/1) provided allylic alcohol **3** as a pale yellow oil (598 mg, 57% yield): Data as above.

4.1.9. (1*R,5*S**)-3-Hydroxymethyl-*cis*-(bicyclo[3.3.0]oct-7-ene)-7-spirocyclopropane 12.** To a stirred solution of (+)-bis-[(*R*)-1-phenylethyl]amine (795 mg, 3.53 mmol), in anhydrous THF (15 mL) at 0°C, under argon, was added *n*-BuLi in hexane (1.55 M, 2.36 mL, 3.36 mmol). After ca. 15 min a slution of epoxide **11** (300 mg, 1.83 mmol) in THF (5 mL) was added and the mixture was allowed to warm to ambient temperature over 18 h. It was diluted with diethyl ether (15 mL), washed with saturated aqueous ammonium chloride (2×20 mL), dried and evaporated. Purification by flash chromatography (light petroleum/ethyl acetate, 4:1) provided alcohol **12** (195 mg, 65%): ν_{max} (cm^{-1}) 3338, 3066, 2931, 1443, 1009: δ_H (300 MHz) 5.45 (1H, d, J=1.5 Hz, H-2), 4.13 (2H, br.s, CH_2OH), 3.26–3.23 (1H, m, H-1), 2.89–2.81 (1H, m, H-5), 2.58 (1H, dd, J=9, 16 Hz, H-4α), 2.12 (1H, d, J=16 Hz, H-4β), 1.67–1.75 (2H, m, H-6α, H-8α), 1.60 (1H, br.s, OH), 1.34–1.25 (2H, m, H-6β-H, H-8β), 0.43–0.25 (4H, m, cyclopropane CH_2×2); *m*/*z* (NH_3, Cl) 182 ([M+NH_4]$^+$, 50%), 164 ([M]$^+$, 100%), 147 ([M−OH]$^+$, 35%); Found: [M+NH_4]$^+$ 182.1538. $C_{11}H_{20}ON$ requires 182.1546.

4.1.10. (1*R,5*S**)-3-(Benzoyloxymethyl)-*cis*-bicyclo[3.3.0]-oct-3-ene-7-spirocyclopropane.** To a solution of **12** (78 mg, 0.46 mmol) in dichloromethane (5 mL) was added benzoic anhydride (215 mg, 0.95 mmol) and 4-dimethylaminopyridine (5.8 mg, 0.04 mmol), the mixture was stirred for 2 h. The reaction was quenched with water (ca. 5 mL) and evaporated. The aqueous layer was extracted with diethyl ether (4×10 mL), washed with 2 M HCl (10 mL), water (10 mL), saturated aqueous sodium hydrogen carbonate (20 mL), saturated aqueous sodium chloride (20 mL), dried and evaporated. Purification by flash chromatography (light petroleum/ethyl acetate, 4:1) provided the title compound (100 mg, 79%) as a pale yellow oil: ν_{max} (cm^{-1}) 3067, 2931, 1722, 712; δ_H (300 MHz) 8.03 (2H, dd, J=1.5, 7 Hz, H-2′, H-6′), 7.58–7.50 (1H, m, H-4′), 7.47–7.38, (2H, m, H-3, H-5′), 5.60 (1H, s, H-2), 4.83 (2H, s, CH_2O), 3.35–3.24 (1H, m, H-1), 2.97–2.81 (1H, m, H-5), 2.74–2.60 (1H, dd, J=8.5, 16.5 Hz, H-4α), 2.20 (1H, d, J=16.5 Hz, H-4β), 1.80–1.61 (2H, m, H-8α, H-6α), 1.38–1.1 (2H, m, H-8β, H-6β), 0.44–0.23 (4H, m, cyclopropane CH_2×2); *m*/*z* (NH_3, Cl) 286 ([M+NH_4]$^+$, 50%), 269 ([M+H]$^+$, 5%), 196 (100); Found: [M+H]$^+$ 269.1538 $C_{18}H_{21}O_2$ requires 269.1541.

4.1.11. (7,7-Ethylenedioxy-3-methylidene-*cis*-bicyclo-[3.3.0]octane)-2-acetic acid ethyl ester 13. A solution of the allylic alcohol **3** (60 mg, 0.3 mmol), ethyl orthoacetate (2 mL), and propionic acid (two drops) was heated at 110°C, under conditions for distillative removal of ethanol, and the reaction was closely monitored by TLC. After 70 min the mixture was allowed to cool to room temperature, diluted with dichloromethane (10 mL), and washed with saturated aqueous sodium hydrogen carbonate (2×3 mL). The extracted organic phase was dried, filtered and evaporated. Purification of the residue by flash chromatography (light petroleum/ethyl acetate, 4:1) afforded the title ester (44 mg, 55%) as a colourless oil: ν_{max} (cm^{-1}) (neat) 2926, 2854, 1741, 1660, 1377; δ_H (300 MHz, $CDCl_3$) 4.82 (1H, ~s, =CH_2), 4.74 (1H, ~s, =CH_2), 4.10 (2H, ~q, J=7 Hz, OCH_2), 3.86 (4H, br. s., OCH_2CH_2O), 2.80–2.55 (2H, m), 2.46 (1H, dd, J=6.5, 15 Hz, CH_2CO), 2.28 (1H, dd, J=7, 15 Hz, CH_2CO), 2.20–1.90 (3H, m), 1.75–1.45 (4H, m), 1.23 (3H, ~t, J=7 Hz, OCH_2CH_3); *m*/*z* (NH_3, CI) 284 ([M+NH_4]$^+$, 100%), 267 ([M+H]$^+$, 256). Found: 284.1885. Calculated for $C_{16}H_{22}O_4$+NH_4=284.1861.

4.1.12. (1*R,5*R**)-7-Ethylenedioxy-3-(tributylstannylmethoxy)methyl-*cis*-bicyclo[3.3.0]oct-2-ene 14.** To a stirred solution of the allylic alcohol **3** (347.9 mg, 1.77 mmol) in anhydrous THF (10 mL), under an atmosphere of argon, were added potassium hydride (127.5 mg, 3.18 mmol) and 18-crown-6 (35.5 mg, 0.134 mmol). After 10 min tributyltin methyl iodide[25] (2.59 g, 6.00 mmol) was added and the mixture was heated at reflux for 18 h. It was then cooled, diluted with diethyl ether (10 mL) and washed with water (2×15 mL). The organic phase was then dried and evaporated. Purification by flash chromatography (light petroleum/ethyl acetate, 4:1) provided stannylmethyl ether **14** as a colourless oil (282.8 mg, 32%): ν_{max} (cm^{-1}) 2956; δ_H (300 MHz, $CDCl_3$) 5.49 (1H, br.s, H-2), 4.14 (2H, br.s, CH_2O), 3.87 (4H, br.s, OCH_2CH_2O), 3.25–3.15 (1H, m, H-1), 2.80 (1H, ~d quin., J=3×9, 2.5 Hz, H-5), 2.58 (1H, dd, J=16, 9 Hz, H-4α), 2.11 (1H br. d., J=16 Hz, H-4β), 2.05–1.95 (2H, m, H-8α, H-6α), 1.92 (2H, s, OCH_2Sn), 1.65–1.45 (8H, m), 1.34–1.23 (10H, m), 0.98–0.86 (11H, m); *m*/*e* (NH_3, CI) 518, 516 ([M+NH_4]$^+$, 304), 306, 179, 181.

4.1.13. (1*R,2*R**,5*R**)-7-Ethylenedioxy-3-methylidene-2-hydroxymethyl-*cis*-bicyclo[3.3.0]octane 15.** To a solution of stannyl ether **14** (63 mg, 0.13 mmol) in THF (3 mL), at −78°C, under Ar, was added *n*-BuLi in hexane (1.35 M, 0.3 mL, 0.41 mmol). After 40 min the mixture was allowed to warm to room temperature, diluted with ether (5 mL) and washed with saturated aqueous sodium chloride solution (3×6 mL). The organic phase was then dried and evaporated. Purification by flash chromatography (light petroleum/ethyl acetate, 2:1) provided alcohol **15** as a yellow oil (14.7 mg, 54% yield): ν_{max} (cm^{-1}) 3400, 2929; δ_H (300 MHz, $CDCl_3$) 4.97 (1H, br.s, =C*H*$_2$), 4.90 (1H, br.s, =C*H*$_2$), 3.87 (4H, br.s, OC*H*$_2$C*H*$_2$O), 3.65–3.55 (1H, m, C*H*$_2$OH), 3.50–3.37 (2H, m, C*H*$_2$OH, OH), 2.60–2.50 (1H, m, H-1, H-2 or H-5), 2.45–2.25 (2H, m, H-1, H-2 or H-5), 2.20–1.95 (4H, m), 1.70–1.50 (2H, m); *m/z* (NH_3, CI) 228 ([M+NH_4]$^+$, 100%), 211 ([M+H]$^+$, 40); Found [M+H]$^+$ 211.1342. $C_{12}H_{19}O_3$ requires 211.1334.

4.1.14. (1*R,5*R**)-7-Ethylenedioxy-3-methoxymethyl-*cis*-bicyclo[3.3.0]oct-2-ene 10.** To a stirred solution of the allylic alcohol **3** (113.7 mg, 0.58 mmol) in anhydrous THF (5 mL), were added freshly ground potassium hydroxide (38.6 mg, 0.69 mmol) and 18-crown-6 (10.7 mg, 0.04 mmol). After 10 min methyl iodide (0.08 mL, 1.29 mmol) was added and the mixture was maintained at room temperature for 18 h. It was then diluted with dichloromethane, washed with water, dried and evaporated. Purification by flash chromatography (light petroleum/ethyl acetate, 4:1) provided methyl ether **10** as a brown oil (107.4 mg, 88% yield); ν_{max} (cm^{-1}) 2910, 2850, 1649, 1460, 1108; δ_H (300 MHz, $CDCl_3$) 5.49 (1H, br.s, H-2), 3.90 (2H, br.s, C*H*$_2$OMe), 3.86 (4H, br.s, OC*H*$_2$C*H*$_2$O), 3.28 (3H, s, O*Me*), 3.26–3.17 (1H, m, H-1), 2.85–2.75 (1H, ~d quin., *J*=4×9, 2.5 Hz, H-5), 2.60–2.51 (1H, dd, *J*=16.5, 9 Hz, H-4a), 2.08, (1H, d, *J*=16.5 Hz, H-4b), 2.04–1.93 (2H, m, H-8a, H-6a), 1.66–1.52 (2H, m, H-8b, H-6b); δ_C NMR (75 MHz, $CDCl_3$) 139.5 (C-3), 132.0 (C-2), 118.1 (C-7), 71.2 (C*H*$_2$OMe), 64.6 and 63.8 (OC*H*$_2$C*H*$_2$O), 58.7 (O*Me*), 48.1 (C-1), 42.4, 40.2 and 39.5 (C-4, C-6 and C-8), 38.5 (C-5); *m/z* (NH_3, CI) 228 ([M+NH_4]$^+$, 100%), 211 ([M+H]$^+$, 50); Found [M+H]$^+$ 211.1323. $C_{12}H_{19}O_3$ requires 211.1334.

4.1.15. (1*S,2*R**,3*R**,5*R**)-2,3-Dihydroxy-7-ethylenedioxy-3-methoxymethyl-*cis*-bicyclo[3.3.0]octane 21.** To a rapidly stirred mixture of ether **10** (785.1 mg, 3.73 mmol) and *N*-methyl morpholine-*N*-oxide (451.0 mg, 3.85 mmol) in *t*-butanol (5.50 mL), water (2.90 mL) and THF (1.80 mL), were added several drops of osmium tetroxide. After 16 h the solvents were evaporated and the residue was purified by flash chromatography (light petroleum/ethyl acetate, 4:1) to give the diol **21** as a pale yellow oil (683.4 mg, 75% yield): ν_{max} (cm^{-1}) 2888, 1430, 1325, 1105; δ_H (300 MHz, $CDCl_3$) 3.95 (1H, d, *J*=7 Hz, H-2), 3.92–3.82 (4H, m, OC*H*$_2$C*H*$_2$O), 3.47 (2H, distorted d, *J*=9 Hz, C*H*$_2$OMe), 3.42 (2H, distorted d, *J*=9 Hz, C*H*$_2$OMe), 3.34 (3H, s, O*Me*), 2.90 (1H, br.s, O*H*), 2.80 (1H, ~d pentet, *J*=4×~9, 4 Hz, H-5), 2.52 (1H, br.s, O*H*), 2.48 (1H, ~dq, 3×~9, 3, H-1), 2.03–1.90 (3H, m, H-6α, H-8α, H-4α), 1.82 (1H, ~dt, *J*=14, 2, 2 Hz, H-8β), 1.50 (1H, br.dd, *J*=10, 4, 2 Hz, H-6β), 1.40 (1H, dd, *J*=14, 9 Hz, H-4β); δ_C (75 MHz, $CDCl_3$) 119.0 (C-7), 83.1 (C-2), 80.4 (*C*H$_2$OMe), 79.4 (C-3), 64.3 and 64.1 (O*C*H$_2$*C*H$_2$O), 59.5 (O*Me*), 46.2 (C-1), 41.1 (C-4), 39.8 (C-8), 39.0 (C-6), 35.9 (C-5); *m/z* (NH_3, CI) 262 ([M+NH_4]$^+$, 100%), 245 ([M+H]$^+$, 20); Found [M+H]$^+$ 245.1389. $C_{12}H_{21}O_5$ requires 245.1389.

4.1.16. (1*S,2*R**)-4,4-Ethylenedioxy-2-(3-methoxy-2-oxo-propyl) cyclopentane carbaldehyde 22.** To a stirred solution of the diol **21** (458.0 mg, 1.87 mmol) in benzene (5 mL), at room temperature, was added lead tetraacetate (1.18 g, 2.66 mmol). After 15 min the mixture was diluted with diethyl ether and filtered through celite. The filtrate was evaporated and purified by flash chromatography (light petroleum/ethyl acetate, 1:1) to give aldehyde **22** as a pale yellow oil (272.0 mg, 60% yield): ν_{max} (cm^{-1}) 2938, 2890, 1719, 1329, 1107; δ_H (300 MHz, $CDCl_3$) 9.70 (1H, d, *J*=2.5 Hz, C*H*O), 3.94 (2H, s, C*H*$_2$OMe), 3.89–3.82 (4H, m, OC*H*$_2$C*H*$_2$O), 3.38 (3H, s, O*Me*), 3.07 (1H, ~q, *J*=3×7.5–9 Hz, H-1), 2.89 (1H, ~h, *J*=5×~7.5 Hz, H-2), 2.73 (1H, dd, *J*=18, 7 Hz, H-1′), 2.56 (1H, dd, *J*=18, 7 Hz, H-1′), 2.29 (1H, dd, *J*=14, 6 Hz, H-3b), 2.14–1.96 (2H, m, H-3a, H-5b), 1.62 (1H, dd, *J*=13.5, 9 Hz, H-5a); δ_C (75 MHz, $CDCl_3$) 207.3 (*C*=O), 203.6 (*C*HO), 116.0 (C-4), 77.6 (*C*H$_2$OMe), 64.6 and 64.2 (O*C*H$_2$*C*H$_2$O), 59.3 (O*Me*), 51.1 (C-1), 42.1 (C-1′), 39.5 (C-5), 36.1 (C-3), 34.2 (C-2); *m/z* (NH_3, CI) 260 ([M+NH_4]$^+$, 100%), 243 ([M+H]$^+$, 84), 225 (65); Found [M+H]$^+$ 243.1230. $C_{12}H_{19}O_5$ requires 243.1232.

4.1.17. (1*R,2*R**)-4,4-Ethylenedioxy-2-(3-methoxy-2-oxo-propyl) cyclopentane carbaldehyde 23.** The procedure for the preparation of (1*S**,2*R**)-4,4-ethylenedioxy-2-(3-methoxy-2-oxo-propyl) cyclopentane carbaldehyde **22** (see above) was followed with one modification. To the diol **21** (66.0 mg, 0.27 mmol) in benzene, sodium hydrogen carbonate was added prior to the addition of lead tetraacetate to afford the *trans* aldehyde **23** (61.7 mg, 94%): δ_H (300 MHz, $CDCl_3$) 9.56 (1H, d, *J*=3 Hz, C*H*O), 3.95–3.80 (6H, m, COC*H*$_2$OMe, OC*H*$_2$C*H*$_2$O), 3.34 (3H, s, O*Me*), 2.80–2.39 (4H, m, H-1, H-2, H-1′a, H-1′b), 2.25–1.98 (3H, m), 1.49–1.44 (1H, m, H-5 or H-3).

4.1.18. (1*S,6*S**)-8,8-Ethylenedioxy-3-methoxy-bicyclo-[4.3.0]non-2-en-4-one 24.** To a solution of the aldehydes **22** (310 mg, 1.24 mmol) in anhydrous benzene (6.00 mL), at room temperature, was added *N*-methyl anilinium trifluoroacetate (497 mg, 1.59 mmol). After heating at 60°C for 18 h the mixture was cooled, then washed with 0.1 M hydrochloric acid (2×10 mL), saturated aqueous sodium hydrogen carbonate solution (2×10 mL) and saturated aqueous sodium chloride solution (2×10 mL). The organic phase was then dried and evaporated. Purification by flash chromatography (light petroleum/ethyl acetate, 4:1) provided the enone as a white crystalline solid (117 mg, 42% yield). The crude product was a mixture of *cis* and *trans* isomers in a ratio of 1:10. Pure *trans* isomer was obtained by recrystallisation from petroleum ether/ethyl acetate, to provide crystals suitable for X-ray analysis: mp 136–137°C (from light petroleum ether 60–80°C/ethyl acetate): ν_{max} (cm^{-1}) 2923, 1737, 1687, 1162, 1015; δ_H (300 MHz, $CDCl_3$) 5.87 (1H, d, *J*=2 Hz, H-2), 3.96–3.80 (4H, m, OC*H*$_2$C*H*$_2$O), 3.58 (1H, s, O*Me*), 2.80 (1H, dd, *J*=17, 4 Hz, H-5α), 2.54–2.44 (1H, m, H-1), 2.30–2.18

(2H, m, H-5β, H-6), 2.11–1.96 (2H, m, H-7α, H-9α), 1.71–1.64 (2H, m, H-7β, H-9β); δ_C (75 MHz, $CDCl_3$) 193.7 (*C*=O), 152.1 (C-2), 116.7 (C-3), 116.3 (C-8), 64.2 (OCH_2CH_2O), 54.9 (O*Me*), 43.7 (C-5), 42.9 (C-9, C-7), 42.5 (C-6 or C-1), 41.1 (C-6 or C-1); *m/z* (NH_3, CI) 242 ($[M+NH_4]^+$, 100%), 225 ($[M+H]^+$, 38); Found $[M+NH_4]^+$ 242.1403. $C_{12}H_{20}O_4N$ requires 242.1392.

4.1.19. (1*R,6*S**)-8-Ethylenedioxy-3-methoxy-bicyclo-[4.3.0]non-2-en-4-one 17.** To a solution of the aldehyde **22** (22.5 mg, 0.09 mmol) in THF (10 mL), sodium hydride (26 mg, 1.10 mmol) was added and the reaction heated under reflux for ca. 18 h. After cooling, solid carbon dioxide was added and the mixture was evaporated. The residue was diluted with dichloromethane and the solution was washed with saturated aqueous sodium hydrogen carbonate solution (4×10 mL), dried and evaporated. Purification by flash chromatography (light petroleum/ethyl acetate, 4:1) provided enones **17** and **24** as a 1:1 mixture of *cis* and *trans* isomers, (7.3 mg, 36% yield). The proportion of the *cis* isomer **17** could be increased by equilibration of the mixture in refluxing dichloromethane, in the presence of triethylamine, to give *cis*/*trans* isomers in a ratio of 5:1: mp 131–132°C (from light petroleum 60–80°C/ethyl acetate); δ_H (300 MHz, $CDCl_3$) 5.57 (1H, d, *J*=4 Hz, H-2), 3.92–3.78 (4H, m, OCH_2CH_2O), 3.56 (3H, s, O*Me*), 3.04–2.95 (1H, m, H-1), 2.69–2.56 (1H, m, H-5b), 2.20–2.30 (2H, m, H-5a, H-6), 2.08–1.91 (2H, m, H-7b, H-9b), 1.74–1.65 (2H, m, H-7a, H-9a).

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