Functionalised bicyclic alcohols by enantioselective α-deprotonation–rearrangement of *meso*-epoxides †

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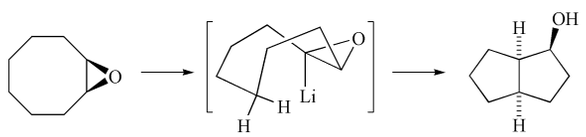
Enantioselective α-deprotonation–rearrangement of achiral substituted cyclooctene oxides **7**, **27** and **28** and *N*-Boc hexahydroazonine oxide **45** using organolithiums in the presence of (−)-sparteine **3** or (−)-α-isosparteine **4** gives the functionalised bicyclo[3.3.0]octan-2-ols **9**, **29**, and **32** and indolizinol **47** in 50–72% yields and 83–89% ees.

Introduction

Enantioselective desymmetrisation of achiral materials is an attractive and powerful concept in asymmetric synthesis.[1] *meso*-Epoxides represent an important class of substrates for new desymmetrisation methodologies,[1,2] and base-induced enantioselective rearrangements of such epoxides are a focus of current interest.[3] The α-deprotonation transannular C–H insertion chemistry of cyclooctene oxide **1** was originally investigated by Cope and subsequently studied further by Whitesell and by Boeckman.[4] We recently reported an asymmetric variant of this process for the synthesis of fused ring systems by enantioselective α-deprotonation of achiral medium-sized cycloalkene oxides.[5] This method uses a secondary organolithium in combination with a chiral ligand such as (−)-sparteine **3**[6] or (−)-α-isosparteine **4** (Fig. 1) to give bicyclic alcohols such as **2** in good yields and ees (77–84% ee, Scheme 1).



1 **1-Li** (−)-**2**

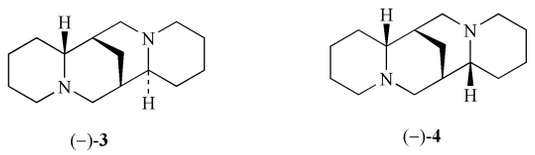
Scheme 1

In our original work, unsubstituted cycloalkene oxides were examined which only generate a single functional group in the bicyclic products.[5] Two strategies to enhance the utility of this transformation would be to examine substituted cycloalkene and heterocycloalkene-derived achiral epoxides. Here we detail our studies concerning the synthesis of such epoxides, by elaboration of readily available cycloocta-1,5-diene **5**, and their rearrangement chemistry.[7]

Results and discussion

In the first strategy, the rearrangement of substituted cycloalkene oxides was anticipated to lead to bicyclo[3.3.0]octanes with functionality in each ring suitable for the stereocontrolled assembly of more complex structures, and thus would provide versatile intermediates, particularly for polycyclopentanoid synthesis.[8]

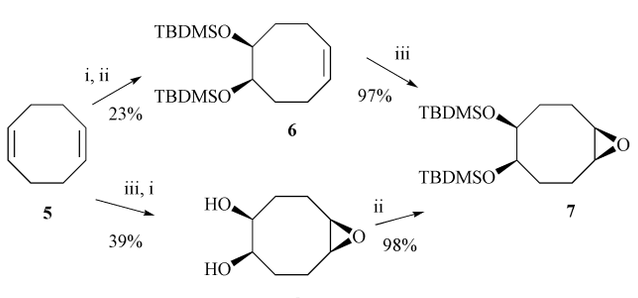
† Electronic supplementary information (ESI) available: the preparation and characterisation of derivatives for ee determinations. Epoxides **36**–**38**, **44**, **44-D** and **44a**. See http://www.rsc.org/suppdata/p1/b1/b105369h/



(−)-**3** (−)-**4**

Fig. 1 (−)-Sparteine **3** and (−)-α-isosparteine **4**

Epoxidation of the known alkene **6**,[9] available from cycloocta-1,5-diene **5** by dihydroxylation[10] and subsequent protection, resulted in exclusive formation of epoxide **7** (97%), assigned as the all *cis* compound (*vide infra*, Scheme 2). We now



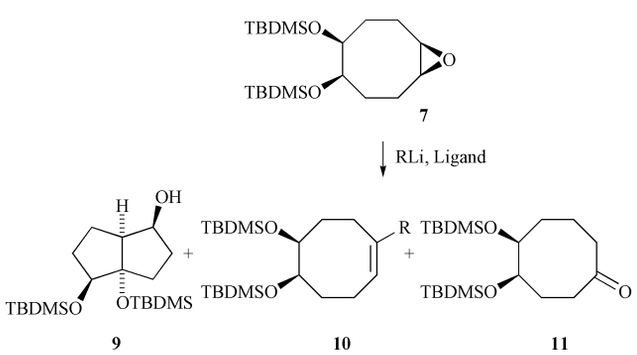
Scheme 2 *Reagent and conditions:* i, cat. OsO_4, NMO, THF : acetone : H_2O (1 : 1 : 1), 0 °C to 25 °C, 16 h; ii, TBDMSCl, imidazole, DMF, 2 °C, 18 h; iii, MCPBA, Na_2CO_3, CH_2Cl_2, 0 °C to 25 °C, 30 min.

prefer an alternative route to epoxide **7** *via* epoxydiol **8**. Monoepoxidation[11] of cycloocta-1,5-diene **5** proceeds to give a 1 : 1 mixture of **5** and the monoepoxide (54%, 100% based on recovered **5**) which is easily separated by distillation. No diepoxide was observed despite treatment with a slight excess of MCPBA. Dihydroxylation with OsO_4–NMO gives, after isolation by continuous extraction, epoxydiol **8**[12] (73%). Protection of epoxydiol **8** with TBDMSCl gives epoxide **7** in near quantitative yield. This latter route is more efficient than the approach *via* alkene **6** and uses less OsO_4.

That the desired transannular rearrangement of epoxide **7** would occur by analogy to cyclooctene oxide **1** (*cf.*, Scheme 1) was not a forgone conclusion. The relatively bulky TBDMSO substituents in epoxide **7** could impede epoxide lithiation, or once lithiation had taken place their steric demands might prevent the transannular chemistry from occurring. The epoxide **7** also has a potential complication with regard to restricted rotation of the bond between the carbon atoms that are attached to the OTBDMS groups. To interconvert between low energy (enantiomeric) conformations the TBDMSO groups are

required to suffer an unfavourable eclipsing interaction. The interconversion of enantiomeric conformations was observed to be slow, at least on a 500 MHz ^{1}H NMR time-scale. In a spectrum acquired at 25 °C the C(*H*)OTBDMS protons were observed as two broad singlets (δ 3.75 and 4.05 ppm in d_8-toluene). Further spectra were acquired at 40 °C, then 50 °C, at which temperature the peaks coalesced to give a broad singlet at 3.90 ppm. The observation that the peaks coalesce at a chemical shift halfway between them is consistent with a 1 : 1 mixture of conformers (which must be the case for enantiomeric conformers). The standard conformations of eight-membered rings are not normally equally populated.[13] Further heating to 90 °C sharpened the peak (3.95 ppm, t, J = 8 Hz). Applying the relevant formulae[14] indicates the barrier to exchange [$\Delta G^{\ddagger}$ (50 °C)] = 64 kJ mol^{-1} and the rate of exchange [k_{int} (50 °C)] = 293 Hz. For cyclooctene oxide **1** the barrier to interconversion between the (enantiomeric) boat–chair conformations [$\Delta G^{\ddagger}$ (−120 °C)] = 33 kJ mol^{-1} and the rate of exchange [k_{int} (−120 °C)] = 13 Hz.[15] At the low reaction temperatures required for a good level of enantioselectivity in the α-deprotonation of epoxides,[5] the presence of chiral conformations which interconvert slowly (or not at all) on the time-scale of the deprotonation (and/or the lifetime of the intermediate lithiated epoxide, *cf.* **1-Li**, Scheme 1) could result in an erosion of ee, or a channelling to products other than the desired bicyclic alcohol.

The first conditions examined for the rearrangement of epoxide **7** used Bu^{s}Li (2.4 equiv.) and (−)-sparteine **3** (2.5 equiv.) in Et_2O at −78 °C. The organolithium·sparteine complex was preformed at −78 °C and then the epoxide **7** was added slowly as a solution in Et_2O, without allowing any warming to occur. After 5 h at −78 °C the solution was allowed to warm slowly to room temperature. From this reaction three compounds were isolated (Scheme 3).



Scheme 3

Encouragingly, the major product of this initial reaction was the desired bicyclic alcohol **9** {[α]$_D^{23}$ +26.4 (*c* 1.0, $CHCl_3$)}, isolated in 51% yield. The two by-products were subsequently identified as the alkene **10** {R = Bu^s, 23% yield, [α]$_D^{23}$ −34.3 (*c* 1.0, $CHCl_3$)}, arising from reductive alkylation,[16] and the ketone **11** {8% yield, [α]$_D^{23}$ +5.2 (*c* 1.0, $CHCl_3$)} resulting from α-ring opening of the carbenoid intermediate followed by insertion into the LiOC–H bond.[17] The asymmetric induction in the desired bicyclic alcohol **9** in this initial rearrangement was determined by chiral HPLC on the 2,6-dibenzoylated derivative of the corresponding triol **12** and was found to be in 73% ee. The rearrangement of unfunctionalised cyclooctene oxide **1** under similar conditions gave bicyclic alcohol **2** in 70% ee.[5] The similarity between these two values indicates that lack of conformational mobility in epoxide **7**, as observed by ^{1}H NMR, did not affect the enantioselectivity. Importantly, this result suggests that whilst epoxide **7** may exist in at least two (enantiomeric) conformations at the temperature at which the reaction is conducted, and even though these might not interconvert within the timescale of the deprotonation, it is not crucial that the organolithium·sparteine complex sees a truly *meso*-species

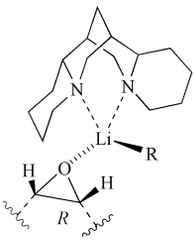


Fig. 2

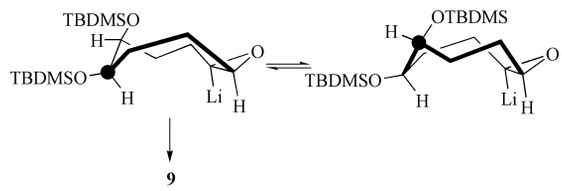
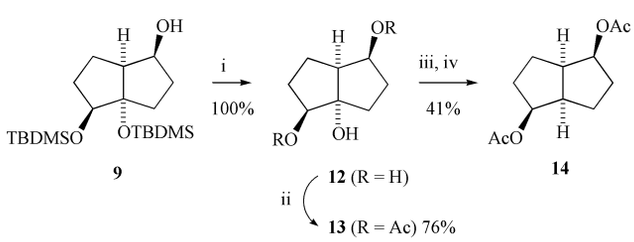


Fig. 3

for the deprotonation. This may be due to the approach of the organolithium·sparteine complex to the unsubstituted face of the rigid epoxide (Fig. 2) where the conformation of the eight membered ring has little impact. Certainly, the levels of asymmetric induction with the range of achiral 1,2-disubstituted epoxides that we have studied to date are broadly similar.

An intriguing question relates to whether conformational interconversion can occur within the lifetime of the lithiated epoxide. If the conformation of the ring does not dictate the regioselectivity of deprotonation, then conformational interconversion is required if all the lithiated epoxide is to have the possibility to undergo a transannular C–H insertion (Fig. 3, carbon whose CH bond is undergoing insertion highlighted by $^{\bullet}$). The potential for a ligand to prolong the lifetime of a lithiated epoxide has been recently reported,[18] and in the present case this could be an important factor in promoting the desired transannular reaction over other decomposition pathways potentially available to the lithiated epoxide (*vide infra*).[4,16]

Proof that the stereochemical course of events from cycloocta-1,5-diene **5** to alcohol (+)-**9**, is as discussed above, was provided by the following transformations; desilylation of alcohol (+)-**9** (of 80% ee) using HF[19] gave triol **12**, which was selectively diacetylated at the secondary hydroxy groups and the resulting tertiary alcohol **13** was deoxygenated[20] to give the diacetate **14** (Scheme 4), which has been used in prostaglandin syntheses.[21]



Scheme 4 *Reagents and conditions:* i, HF (40% aq.), MeCN, 25 °C, 1 h; ii, Ac_2O, pyridine, 25 °C, 16 h; iii, $ClCOCO_2Me$, DMAP, THF, 25 °C, 30 min; iv, Bu_3SnH, AIBN, toluene, Δ, 1 h.

The ^{13}C spectral data of diacetate **14** indicated a symmetric compound (6 signals) and were in agreement with the data previously reported for the *endo*,*endo*,*cis*-fused system,[22] and differed significantly from the ^{13}C data of the *exo*,*exo*,*cis*-fused diacetate.[21] The absolute configuration of the major enantiomer of the alcohol (+)-**9**, obtained with (−)-sparteine **3**, is as shown in Scheme 3 and was established by polarimetric comparison for diacetate **14** {[α]$_D^{22}$ −78.7 (*c* 1.0 in $CHCl_3$), lit.,[21] [α]$_D^{20}$ +104.3 (*c* 1.0 in $CHCl_3$) for 1*S*,2*R*,5*S*,6*R* isomer}. The sense of asymmetric induction observed in bicyclic alcohol **9** using RLi–**3**

Table 1 Effect of experimental conditions on the rearrangement of epoxide **7**

Entry[a]	RLi	Ligand	*T*/°C	**9** : **10** : **11**[b]	Yield **9** (%)[c]	ee **9** (%)[d]	**10** Yield (%)[c]	**11** Yield (%)[c]
1	Bu^{s}Li	**3**	−78	57 : 32 : 11	51	+73	23	8
2	Pr^{i}Li	**3**	−78	55 : 25 : 20	52	+76	19	15
3	Bu^{n}Li	**3**	−78	51 : 37 : 12	47	+39	22	6
4	PhLi	**3**	−78	—[e]	12[f]	+32	—	—
5	Bu^{s}Li	**3**	−90	69 : 21 : 10	59	+73	18	9
6	Pr^{i}Li	**3**	−90	62 : 28 : 10	57	+80	25	7
7[g]	Bu^{s}Li	**3**	−78	—[e]	12[h]	+70	1	0
8[i]	Bu^{s}Li	**3**	−78	57 : 33 : 10	51	+75	20	8
9[j]	Bu^{s}Li	**3**	−78	49 : 41 : 10	35	+66	29	7
10	Bu^{s}Li	–	−78	—[e]	18[k]	—	16	1
11	Bu^{s}Li	**15**	−78	46 : 40 : 14	43	—	38	13
12	Bu^{s}Li	**16**	−78	90 : 0 : 10	70	—	0	10
13	Bu^{s}Li	**17**	−78	—[e]	25[l]	—	8	2
14	Bu^{s}Li	**3**[m]	−78	58 : 32 : 10	46	+71	25	9
15	Bu^{s}Li	**3**[n]	−78	54 : 38 : 8	50	+70	29	12
16	Bu^{s}Li	**4**	−78	73 : 17 : 10	65	+77	9	5
17	Pr^{i}Li	**4**	−78	78 : 15 : 7	62	+77	12	6
18	Bu^{s}Li	**4**	−90	70 : 23 : 7	71	+84	18	6
19	Pr^{i}Li	**4**	−90	83 : 10 : 7	72	+89	8	7
20	Bu^{s}Li	**19**	−78	100 : 0 : 0	15[o]	−52	0	0
21	Bu^{t}Li	**19**	−78	100 : 0 : 0	49[p]	−52	0	0

[a] Reactions carried out in Et_2O (~0.03 mol dm^{-3} in epoxide **7**) unless indicated otherwise. [b] Ratios determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yields. [d] Determined by chiral HPLC, negative values correspond to enrichment in (−)-alcohol **9**. [e] Unreacted starting epoxide **7** prevented ratio determination. [f] 20% based on recovered starting material (brsm). [g] 0.01 mol dm^{-3} in epoxide **7**. [h] 26% brsm. [i] Bu^{t}OMe as solvent. [j] Pentane as solvent. [k] 27% brsm. [l] 34% brsm. [m] 1.4 equiv. used. [n] 5 equiv. used. [o] 48% brsm. [p] 66% brsm.

with epoxide **7** parallels all our previous observations on enantioselective α-deprotonation rearrangement of epoxides using the sparteines, where proton removal at the *R*-epoxide stereocentre is consistently seen (Fig. 2).[5,23] The predominant sense of asymmetric induction in the by-products arising from α-deprotonation (alkene **10** and ketone **11**) is therefore tentatively assigned as that shown in Scheme 3. Products from rearrangements of related epoxides discussed later in this paper are also assigned by analogy as being derived from proton removal at the *R*-epoxide stereocentre when using the sparteines.

Several other reaction conditions (variation of RLi, ligand and temperature) were then examined using epoxide **7** (Table 1), with the aim of optimising the product yield/profile and asymmetric induction with respect to alcohol **9**.

Of the organolithiums examined with (−)-sparteine **3**, it was found that as in our earlier studies,[5] secondary alkyllithiums were most effective (Table 1, entries 1–4). With the secondary alkyllithiums it was found that reducing the reaction temperature from −78 °C to −90 °C improves the proportion of alcohol **9** in the crude product, leading to better isolated yields of alcohol **9** (Table 1, entries 5 and 6), and with Pr^{i}Li the ee also improved to 80%.

Having confirmed that secondary organolithiums give the best results, a brief study into the effect of solvent was carried out. For the rearrangement of cyclooctene oxide **1**, Et_2O has been shown to give the best results.[5] However, highly enantioselective Bu^{s}Li–(−)-sparteine **3** reactions have been carried out in hydrocarbon solvents or Bu^{t}OMe.[6] Firstly, a dilution experiment was carried out to see if formation of alkene **10**, which requires attack by a second equivalent of RLi, would be less favoured. However, when the reaction was run at 0.01 mol dm^{-3} in epoxide **7**, the reaction was retarded significantly and 54% of starting material was recovered (Table 1, entry 7), which prevented a conclusion on the effect of concentration on product profile. The use of Bu^{t}OMe rather than Et_2O made no difference (Table 1, entries 1 and 8), but the use of pentane resulted in lower ee and a higher proportion of alkene (Table 1, entry 9). Thus all further reactions in the current study used Et_2O as solvent.

When no ligand was present (Table 1, entry 10) the reaction did not go to completion and the isolated yield of the two

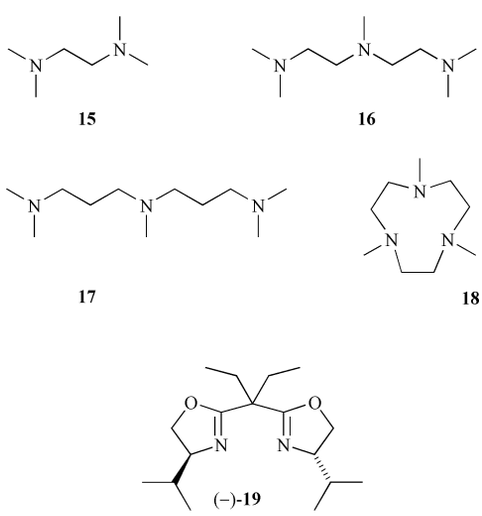


Fig. 4 Ligands **15**–**19**.

principal products, alcohol **9** and alkene **10**, remained close to 1 : 1. The addition of TMEDA **15** resulted in an increase in reactivity, with the reaction now proceeding to completion (Table 1, entry 11). However, the ratio of **9** and **10** was close to 1 : 1. These early results without a ligand, or with sparteine **3** or TMEDA **15**, indicate that the product profile derived from the intermediate lithiated epoxide (*cf.* **1-Li**, Scheme 1) is influenced by the choice of ligand; that is the lithiated epoxide should not be considered in isolation, but rather as a ligand associated complex. The use of PMDETA **16** (Fig. 4) was then examined, since the tridentate nature of this ligand might influence aggregation in the intermediate complex,[24] and result in a change of selectivity. This was indeed the case with a dramatic alteration in the product profile: no alkene **10** was detected in the crude ^{1}H NMR, and a 9 : 1 ratio of alcohol **9** to ketone **11** was observed (Table 1, entry 12). In order to test whether this effect was general for tridentate ligands or specific to PMDETA **16**, two other commercially available tridentate ligands were also studied. In the presence of PMDPTA **17** (Fig. 4) the reaction did not proceed to completion, with 27% of starting epoxide **7** recovered (Table 1, entry 13). The ratio of alcohol **9** to alkene **10**

was 3 : 1 which, while not as impressive as the result with PMDETA **16** did show a tendency for formation of the desired alcohol **9** when compared to TMEDA **15**. Another tridentate ligand, the cyclic triamine **18**, appeared to form an insoluble complex with Bu^{s}Li and, possibly as a result of this, only unreacted starting epoxide **7** was recovered (79%).

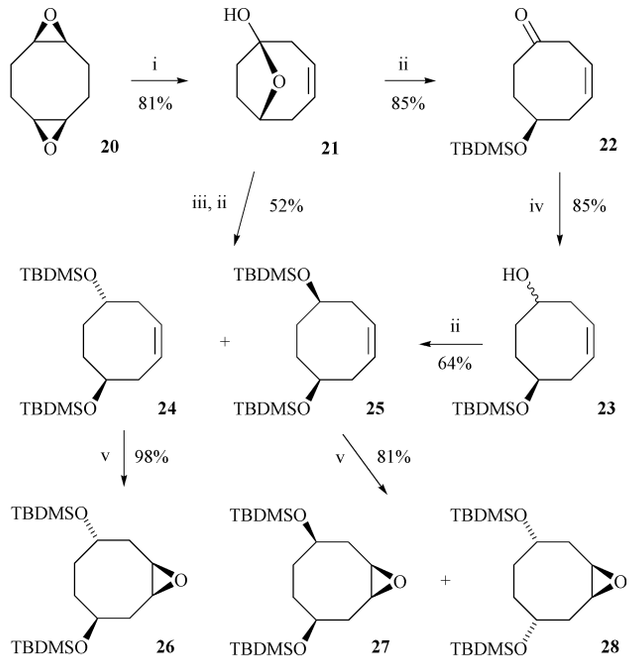
Tridentate ligand PMDETA **16** changed the selectivity of the reaction in favour of the desired alcohol **9**. With the aim of altering the nature of the aggregation in the presence of (−)-sparteine **3**, two reactions were carried out where the ratio of Bu^{s}Li to (−)-sparteine **3** was varied. However, these changes in the equivalents of (−)-sparteine **3** made very little difference to the crude ratios, isolated yield, or ee of the alcohol **9** (Table 1, compare entries 1, 14 and 15). Reactions were carried out with (−)-α-isosparteine **4** (prepared from the monohydrate *in situ*) using both Bu^{s}Li and Pr^{i}Li at −78 °C and −90 °C (Table 1, entries 16–19), so as to provide a full comparison with (−)-sparteine **3** (Table 1, entries 1, 2, 5 and 6).

The use of (−)-α-isosparteine **4** generally gave a higher ee and isolated yield of the alcohol **9**, with the crude ratios reflecting this improved selectivity. The trends match those observed with (−)-sparteine **3** with a drop in temperature resulting in slightly better yields and ees for the desired product; a switch from Bu^{s}Li to Pr^{i}Li gave the highest levels of ee. In the present study, the best conditions for this transformation were therefore Pr^{i}Li with (−)-α-isosparteine **4** at −90 °C, which gave alcohol (+)-**9** in 72% yield and 89% ee (Table 1, entry 19).

We previously introduced C_2-symmetric bisoxazolines [such as (−)-**19**] as ligands for alkyllithiums in enantioselective deprotonation (of cyclooctene oxide **1**).[5] The use of PhLi[23] with bisoxazoline (−)-**19** resulted only in recovery of **7** (73%), whereas using Bu^{s}Li gave only a 15% yield of alcohol (−)-**9** in 52% ee (Table 1, entry 20). Bu^{t}Li has been shown to form an effective complex with bisoxazolines,[25] and the use of Bu^{t}Li with bisoxazoline (−)-**19** resulted in an improved yield of alcohol (−)-**9** but with unchanged ee (Table 1, entry 21). This short study shows the potential for the use of bisoxazolines to obtain the (2*R*)-(−)-enantiomer of alcohol **9**. Interestingly, only the desired alcohol **9** and recovered starting epoxide **7** were isolated from these reactions, with no alkene **10** being observed. We had previously observed no alkene side-product when bisoxazolines were used in the asymmetric deprotonation of *N*-Boc 7-azanorbornene ‡ oxide.[23]

The effect of varying the position and relative configuration of substituents on the desymmetrisation process was next examined. The known hemiacetal **21** was first prepared by base-induced rearrangement[26] of readily available *cis*,*cis*-cycloocta-1,5-diene dioxide **20**[27] (Scheme 5).

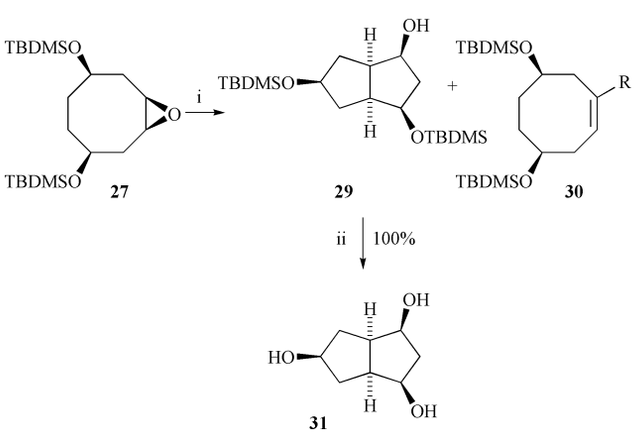
Reduction of hemiacetal **21** with either $LiAlH_4$ or L-Selectride (4 equiv.) in THF at −78 °C was unselective, generating a chromatographically inseparable 1 : 1 mixture of *cis*- and (undesired) *trans*-cyclooct-6-ene-1,4-diol (83% and 63% yields, respectively). The ratios were determined following bis-silylation (80%) to the bis ethers **24** and **25**, which are easily separable. An attempt to effect a hydroxy-directed reduction of **21** using $NaBH(OAc)_3$ resulted in no reaction,[28] suggesting that the hydroxy group was not suitably positioned to facilitate the reduction. As no selectivity had been induced with either a small or a bulky hydride source, the free hydroxy group was first silylated to give enone **22**. The reduction of enone **22** with $LiAlH_4$ at −78 °C in THF proceeded efficiently (72%) but without selectivity, however L-Selectride gave modest selectivity (1.7 : 1) in favour of the alcohol *cis*-**23**. The relative configuration was determined by silylation to the bis ethers **24** and **25** followed by epoxidation with MCPBA of the individual isomers. The *trans*-bis ether **24** gave a single epoxide **26**, which was not symmetrical (4 methine and 4 methylene signals in the ^{13}C



Scheme 5 *Reagents and conditions:* i, LDA, BuLi, THF, 0 °C (4 h) to 25 °C (16 h); ii, TBDMSCl, imidazole, DMF, 18 h, iii, $LiAlH_4$, THF, −78 °C (4 h) to 25 °C (16 h); iv, L-Selectride, THF, −78 °C, 1 h; v, MCPBA, Na_2CO_3, CH_2Cl_2, 0 °C, 2 h.

NMR spectrum), whereas the *cis*-bis ether **25** gave two epoxides **27** and **28** (1 : 2), which when separated (27% and 54% yields, respectively) were both symmetrical (2 methine and 2 methylene signals in each ^{13}C NMR spectrum). In an attempt to alter the selectivity of the epoxidation reaction the temperature was raised from 0 °C to room temperature, but this did not alter the ratio of products or the yield. By lowering the temperature to −40 °C the reaction was simply closed down, with only starting material recovered. Changing the reaction solvent from CH_2Cl_2 to toluene at room temperature lowered the selectivity to 5 : 6, **27**–**28** (71% yield). Selectivity for the formation of **27** or **28** was not probed further, as the rearrangement chemistry of both *meso*-epoxides **27** and **28** was of interest.

The rearrangement of epoxide **27** was first examined using Bu^{s}Li and (−)-sparteine **3** at −78 °C to ascertain whether the rearrangement would give the expected products (Scheme 6 and



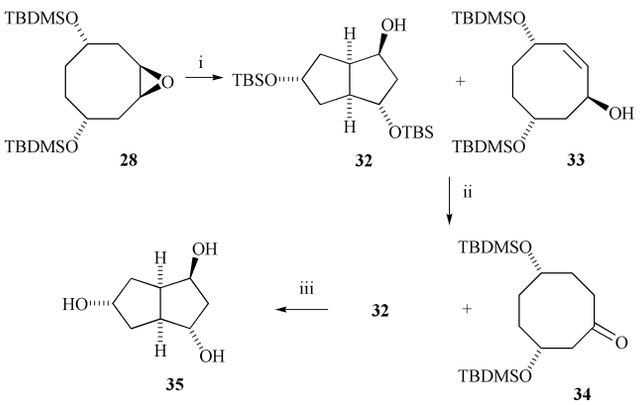
Scheme 6 *Reagents and conditions:* i, RLi (2.4 equiv.), ligand (2.45 equiv.), Et_2O, −78 or −98 °C (5 h) to 25 °C (15 h); ii, HF, H_2O, MeCN, 25 °C, 1 h.

Table 2). Indeed, the alcohol **29** was produced in 47% yield and 72% ee {$[\alpha]_D^{23}$ +1.1 (*c* 1.0, $CHCl_3$)}, with the only by-product being subsequently identified as alkene **30** {R = Bu^s, 18% yield, $[\alpha]_D^{23}$ −24.1 (*c* 1.0, $CHCl_3$)}. For epoxide **27** the best conditions found were using Pr^{i}Li and (−)-sparteine **3**, resulting in 70%

‡ The IUPAC name for norbornane is bicyclo[2.2.1]heptane.

yield and 84% ee of the desired alcohol **29** (Table 2, entry 5). This yield and level of enantioselectivity compares well with the best results for the rearrangement of epoxide **7** (Table 1, entry 19, 72% yield, 89% ee). With epoxide **27** there is little difference in the level of enantioselection using (−)-sparteine **3** or (−)-α-isosparteine **4**, but the yields are higher in the presence of (−)-sparteine **3**. The alkene by-product **30** was typically present in 10–20% yield. Desilylation of bicyclic alcohol **29** afforded the *meso* triol **31** quantitatively, which establishes the relative configuration of the precursor epoxide **27**.

Interestingly, the rearrangement of epoxide **28** resulted in 2 principal products, the ratio between them being strongly influenced by the ligand present (Scheme 7, Table 3). In the absence



Scheme 7 *Reagents and conditions:* i, RLi (2.4 equiv.), ligand, Et_2O, −78 or −98 °C (5 h) to 25 °C (15 h); ii, Pd/C, H_2 (1 atm), EtOAc, 25 °C, 1 h; iii, HF, MeCN, 25 °C, 1 h.

of a ligand, bicyclic alcohol **32** was observed as the minor product, with allylic alcohol **33** as the major product (**32**–**33**, 16 : 84, Table 3, entry 1). Bicyclic alcohol **32** and allylic alcohol **33** arising from the rearrangement of epoxide **28** are inseparable by flash chromatography. However, allylic alcohol **33** is easily removed by palladium-catalysed isomerisation[29] to ketone **34**, allowing isolation of the bicyclic alcohol **32**. Deprotection of bicyclic alcohol **32** gave triol **35**, which was clearly not *meso* {8 resonances in ^{13}C NMR, $[\alpha]_D^{23}$ +3.1 (*c* 1.0, $CHCl_3$)}. When TMEDA was used as ligand, *only* allylic alcohol **33** was detected. The proportion of bicyclic alcohol **32** [*e.g.* with Pr^{i}Li, Table 3 entry 6; $[\alpha]_D^{23}$ +11.1 (*c* 1.0, $CHCl_3$)] increased when (−)-sparteine **3** was used, although the reaction still favoured allylic alcohol **33** (**32**–**33**, 45 : 55). Changes in product profile when using an organolithium with (−)-sparteine **3** compared with TMEDA **15** have been earlier observed by Beak *et al.*[30] These previous results together with the current findings suggest that the nature of organolithium complexes formed with TMEDA **15** can be very different to the corresponding complexes formed using (−)-sparteine **3**. TMEDA **15** is less hindered compared with (−)-sparteine **3**, and so it was considered that the use of the more sterically demanding (−)-α-isosparteine **4**[5] would further favour the formation of the bicyclic alcohol **32**. Indeed, the use of (−)-α-isosparteine **4** and Bu^{s}Li did result in an 87 : 13 ratio in favour of bicyclic alcohol **32**, with the alcohol **32** being produced in 83% ee (Table 3, entry 5). When the allylic alcohol **33** was removed by palladium-catalysed isomerisation an isolated yield of 56% of the bicyclic alcohol **32** was achieved. With Pr^{i}Li the ratio was slightly less favourable at 72 : 28 (Table 3, entry 6).

Allylic alcohols were not observed as byproducts in the rearrangements of epoxides **1**, **7** and **27**, either in the absence of ligands, or in the presence of TMEDA or sparteine. The observation of allylic alcohol **33** in the desymmetrisation of epoxide **28** indicates that appropriate positioning of ring substituents can significantly alter the reaction course in these rearrangements. Our results with epoxide **28** using TMEDA and the sparteines show that different diamines can be used to direct the reaction to different products.[30] Although allylic alcohol **33** may be (partly) formed by a β-deprotonation–elimination process, the fact that the ees are similar for bicyclic alcohol **32** and allylic alcohol **33** [at least when using (−)-sparteine **3**] suggest that they may both be derived from α-lithiation of epoxide **28** (compare **1**-**Li**, Scheme 1) followed by transannular or adjacent C–H insertion, respectively.[31] Whilst the difference in ees of the bicyclic alcohol **32** and allylic alcohol **33** are greater with (−)-α-isosparteine **4** (Table 3, entries 5 and 6) than with (−)-sparteine **3**, we have previously observed partitioning to different products of enantiomeric α-lithiated epoxides in the presence of chiral (non racemic) bases, giving rise to two products of different ees.[5] Intriguingly, the use of bisoxazoline (−)-**19** (Fig. 2) with epoxide **28** changes the selectivity, producing only the allylic alcohol **33**, albeit in modest yield and ee (Table 3, entry 7). The fact that the allylic alcohol **33** in this latter reaction has the same sign of specific rotation as **33** produced from the reaction in the presence of (−)-sparteine **3** (Table 3, entry 3) was surprising, as the predominant sense of asymmetric induction on α-deprotonation is opposite with the sparteines and bisoxazoline (−)-**19** in all the previous epoxide substrates (**1**, **7** and *N*-Boc-7-azanorbornene oxide).[5,23] The result with epoxide **28** and bisoxazoline (−)-**19** could indicate that the ligand induces a β-deprotonation–elimination process with this substrate.

The results of examining other functionalised medium-sized cycloalkene-derived epoxides **36**–**38** proved unsuccessful (the preparation and characterisation of epoxides **36**–**38** (Fig. 5) are described in the ESI).† When epoxide **36** was treated with

Table 2 Effect of experimental conditions on the rearrangement of epoxide **27**

Entry	RLi	Ligand	*T*/°C	**29** Yield (%)[a]	**29** Ee (%)[b]
1	Bu^{s}Li	—	−78	31[c]	—
2	Bu^{s}Li	**3**	−78	47	+72
3	Pr^{i}Li	**3**	−78	54	+80
4	Bu^{s}Li	**3**	−90	58	+76
5	Pr^{i}Li	**3**	−90	70	+84
6	Bu^{s}Li	**4**	−90	52	+78
7	Pr^{i}Li	**4**	−90	48	+82

[a] Isolated yields. [b] Determined by chiral HPLC. [c] 47% based on recovered starting material.

Table 3 Effect of experimental conditions on the rearrangement of epoxide **28**

Entry	RLi	Ligand	*T*/°C	Yield (%)[a] of **32**–**33**	**32**–**33**	**32** Ee (%)[b]	**33** Ee (%)[b]
1	Bu^{s}Li	—	−90	43	16 : 84	—	—
2	Bu^{s}Li	**15**	−90	70	0 : 100	—	—
3	Bu^{s}Li	**3**	−90	60	45 : 55	+71	+62
4	Pr^{i}Li	**3**	−90	44	45 : 55	+73	+70
5	Bu^{s}Li	**4**	−90	75	87 : 13	+83	+61
6	Pr^{i}Li	**4**	−90	44	72 : 28	+85	+60
7	Bu^{s}Li	**19**	−78	34[c]	0 : 100	—	+37

[a] Isolated yields. [b] Determined by chiral HPLC. [c] 48% based on recovered starting material.

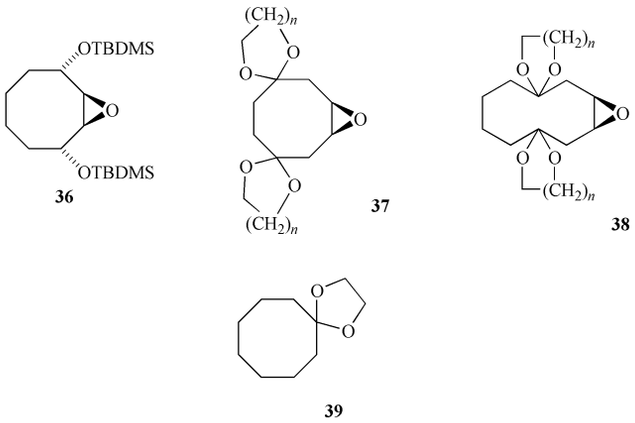
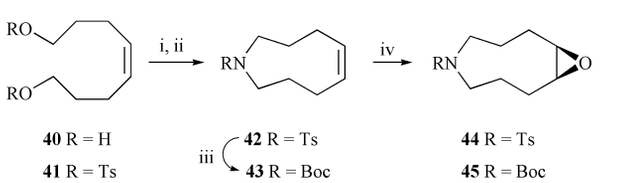


Fig. 5 Epoxides **36**–**39**.

organolithium (Pr^iLi or Bu^sLi), at −78 °C, both in the presence of a diamine ligand [(−)-sparteine **3** or TMEDA **15**] and in the absence of such a ligand decomposition occurred and no single compound could be isolated. The reasons for this are unclear, although a silyloxy substituent β to the lithiated epoxide (*cf.*, **1-Li**, Scheme 1) may provide an alternative reaction pathway; perhaps eliminating to form an unstable allene oxide[26b,32] or being eliminated under attack from a second equivalent of organolithium.[33] Epoxides **37** (n = 1 or 2) also underwent decomposition to an uncharacterisable mixture of products, whereas solid epoxides **38** (n = 1 or 2) were insoluble in hexane or Et_2O at low temperatures and were inert to the reaction conditions (decomposition was observed in THF or benzene). That the dioxolane protecting group might be unstable to the reaction conditions is confirmed by treating acetal **39**[34] with Pr^iLi·(−)-sparteine **3** in Et_2O. Decomposition was observed. Quenching the reaction after 2.5 h at −78 °C showed that decomposition was already underway. We recovered 50% of the substrate mass (as a 1 : 1 mixture of cyclooctanone–**39**).

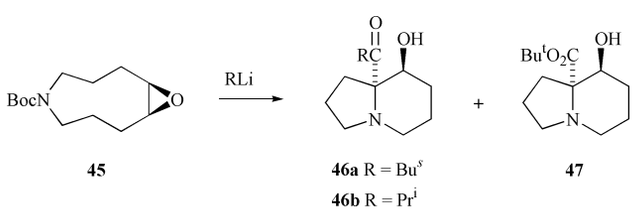
In the second strategy, examining heterocycloalkene-derived achiral epoxides, an important aspect of the study of transannular reactions of a medium-sized heterocycle concerns the potential problem of preparing the substrate.[35] However, application of methodology[36] used in the synthesis of the azacycloundecene system found in manzamine C led to a highly satisfactory route to the azacyclic epoxide **44** (Scheme 8). Thus,



Scheme 8 *Reagents and conditions:* i, TsCl, pyridine, 0 °C (5 h) to 25 °C (15 h), 74%; ii, $TsNH_2$, NAOH, Bu_4NI, toluene–H_2O, reflux, 5 h, 62%; iii, Na naphthalenide, THF, −78 °C, then HCl(g), then Et_3N, Boc_2O, DMAP, CH_2Cl_2, 25 °C, 64% from **42**; iv, $MeCO_3H$, Na_2CO_3, NaOAc, CH_2Cl_2, 0 °C (10 min) to 25 °C (15 h), 82% (R = Ts), 87% (R = Boc).

cyclisation under dilute conditions of the ditosylate **41** of the known diol **40** (readily available from cycloocta-1,5-diene **5**)[37] gave the reduced azonine **42** in 62% yield; to our knowledge this is the most efficient cyclisation reported to a simple reduced azonine.[35]

Subjection of the epoxide **44** derived from reduced azonine **42**, to typical asymmetric rearrangement conditions[1] [Bu^sLi (2.4 equiv.) and (−)-sparteine **3** (2.5 equiv.) in Et_2O at −78 °C for 5 h, followed by warming to 25 °C over 15 h] led only to the recovery of starting epoxide **44**, whereas quenching the reaction with D_2O led to essentially complete *o*-deuterium incorporation into the tosyl group to give **44-D** (64%). An attempt to induce reaction at the epoxide group subsequent to *ortho*-deprotonation using double the quantities of reagents indicated above led to no identifiable products; an alternative protecting group was therefore required. In order to avoid deprotonation of the aromatic ring, the protected epoxide **44a** [R = 2,4,6-triisopropylbenzenesulfonyl (trisyl)] was prepared by an analogous route to the tosyl-protected epoxide **44**. However, epoxide **44a** proved unreactive [the preparation and characterisation of **44**, **44-D** and epoxide **44a** are described in the ESI].† Removal of the tosyl group from **41** using sodium naphthalenide[36] and immediate Boc reprotection of the amine hydrochloride salt, gave the reduced azonine **43** (64%). Epoxidation provided **45**, which could potentially undergo deprotonation with an organolithium either α to the epoxide oxygen, or α to nitrogen. Beak has reported a 6-*exo*-*tet* cyclisation onto an epoxide *via* deprotonation α to NBoc; the deprotonation site was however also benzylic in this case.[38] Beak has also reported that the rate of deprotonation of Boc-protected azacycles decreases in moving from pyrrolidine to piperidine to perhydroazepine.[39] In the event, reaction of the epoxide **45** with Bu^sLi (2.4 equiv. in Et_2O at −78 °C for 5 h, followed by warming to 25 °C over 15 h) led to an inseparable 1 : 1 mixture of epimers (due to the stereogenic centre in the Bu^s group, *vide infra*) of ketone **46a** (48%, 70% based on recovered epoxide **45**, Scheme 9).



Scheme 9

In contrast, reaction of the epoxide **45** with Bu^sLi, under the same conditions but in the presence of TMEDA (2.5 equiv.), led to the formation of ester **47** as the major product (**47**–**46a**, 8 : 1 by ^1H NMR analysis; 74% isolated yield of **47**). Using (−)-sparteine **3** as the ligand in an otherwise identical experiment gave an equal mixture of **46a** and **47** (66% ee for **47**). The absolute configurations of the predominant octahydroindolizinol enantiomers are not known but can be tentatively assigned as shown in Scheme 9 by analogy with the selectivity for deprotonation at the *R* configured epoxide stereocentre with (−)-sparteine **3** observed in our earlier epoxide studies. Experiments were then carried out to examine the possibility of increasing both the proportion and ee of ester **47** formed from epoxide **45** (Table 4).

Maintaining the reaction at −78 °C for 18 h and then quenching at this temperature gave ester **47** in improved ee (74%, Table 4, entry 1), but the ketone **46a** predominated. However, repeating the same procedure at −98 °C significantly improved the proportion of ester **47** (**47**–**46a**, 5 : 1) and increased the ee of **47** to 79% (entry 2). Using Pr^iLi at −98 °C gave mainly the ester **47** (**47**–**46b**, 10 : 1) and with the highest level of asymmetric induction (89% ee, entry 3), as also observed with our earlier work on cycloalkene-derived epoxides.[5] Using (−)-α-isosparteine **4** as ligand with either Bu^sLi or Pr^iLi slowed the reaction considerably (entries 4 and 5), particularly in conjunction with Bu^sLi; the ees were also reduced compared with the corresponding (−)-sparteine **3** reactions. In an attempt to allow Pr^iLi–(−)-α-isosparteine **4** to completely consume the epoxide **45**, the reaction was left for 40 h at −98 °C (entry 6), but it still remained only 50% complete after this time and no change in the ee of ester **47** was observed. The use of catalytic amounts of ligand was also investigated (entries 7–9) with interesting results. Using 24 mol% (−)-sparteine **3** (10 mol% with respect to Pr^iLi) high levels of ee (82%) were still achieved, but the reaction was found to be much slower. In contrast (−)-α-isosparteine **4** was more

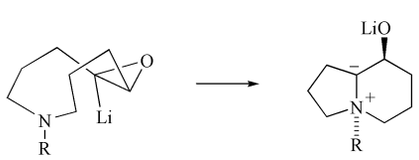
Table 4 Effect of experimental conditions on the rearrangement of epoxide **45**

Entry[a]	Ligand	RLi	**45**–**46**–**47**[b]	Yield of **47** (%)[c]	Ee of **47** (%)[d]
1[e]	**3**	Bu^{s}Li	0 : 62 : 38	32 (20)	+74
2	**3**	Bu^{s}Li	8 : 15 : 77	58 (50)	+79
3	**3**	Pr^{i}Li	21 : 7 : 72	57 (49)	+89
4	**4**	Bu^{s}Li	83: 0: 17	14	+64
5	**4**	Pr^{i}Li	65 : 3 : 32	29	+79
6[f]	**4**	Pr^{i}Li	54 : 4 : 42	40	+78
7[g]	**3**	Pr^{i}Li	30 : 26 : 44	36	+82
8[g]	**4**	Pr^{i}Li	52 : 5 : 43	33	+77
9[f,g]	**4**	Pr^{i}Li	25 : 12 : 63	54	+89

[a] Ratio of ligand–RLi–epoxide **45**, 2.45 : 2.4 : 1 and carried out at −98 °C with a reaction time of 18 h unless otherwise indicated. [b] Ratios determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of **47** as measured by ^{1}H NMR analysis using methyl diphenylacetate as an internal standard. Isolated yields given in parentheses. [d] Determined by GC (Chrompack chirasil-dex 25 m × 0.32 mm ID column; 6 psi, 120 °C). [e] Carried out at −78 °C. [f] Reaction time 40 h. [g] Ratio of ligand–RLi–epoxide **45**, 0.24 : 2.4 : 1.

effective when used in a catalytic fashion (entry 8), with no apparent change in the ee (compare entry 5). Repeating this last reaction but leaving it for 40 h at −98 °C allowed the reaction to proceed further to completion and also gave a much higher level of ee (entry 9). For ease of experimental procedure in all the reactions with (−)-α-isosparteine **4** in the current work, an additional equivalent of organolithium was used to remove the water of hydration from the ligand, rather than the previously used[5] pre-treatment of the ligand with CaH_2 and addition *via* cannula to the reaction mixture. The effect of the presence of LiOH on the ee and yield in the rearrangement of cyclooctene oxide **1** was examined: Pr^{i}Li (1.4 equiv.)–(−)-α-isosparteine **4** (0.2 equiv., pre-treated with CaH_2), Et_2O, −98 °C to 25 °C, gave bicyclic alcohol **2** (86% yield, 84% ee); Pr^{i}Li (1.4 equiv.)–(−)-α-isosparteine **4** (0.2 equiv.), Et_2O, −98 °C to 25 °C (80% yield, 79% ee). These results indicate a slight reduction occurs in ee and yield using the *in situ* method.

The structures of octahydroindolizinols **46** and **47** were assigned by extensive spectroscopic investigations and were later further supported by X-ray crystallographic analysis of ketone **46b**.[7] A mechanistic explanation for the formation of the octahydroindolizinols is that they arise *via* lithiation α to the epoxide oxygen to give **48**, followed by transannular reaction with the *N*-lone pair to give an ammonium ylide **49** and subsequent [1,2] migration of the exocyclic *N*-substituent (Scheme 10); direct insertion of the lithiated epoxide into the exocyclic



48 **49**

Scheme 10

C–N bond is also possible. Incorporation of the organolithium to give the ketones **46** could occur before or after the transannular reaction. The latter process seems most likely, since reducing the equivalents of organolithium from 2.5 improves (at the expense of conversion of starting epoxide **45**) the ratio of ester **47**–ketone **46**, and in a separate experiment ester **47** could be quantitatively converted to ketone **46b** using Pr^{i}Li (1.1 equiv., −78 °C for 1 h, followed by warming to 0 °C over 2 h).

In summary, the α-deprotonation transannular C–H insertion of substituted cyclooctene oxides provide enantioselective access to functionalised bicyclo[3.3.0]octan-2-ols in good yields and ees (84–89%). In particular, the ready availability of bicyclic alcohol **9** (4 steps from cycloocta-1,5-diene **5**) suggests it can be considered as an attractive new precursor in asymmetric synthesis, especially in polycyclopentanoid construction. With hexahydroazonine oxide **45** a novel insertion of the corresponding lithiated epoxide into a C–N bond occurs leading to a new and enantioselective entry to the important octahydroindolizinols framework.

Experimental

General details

All reactions requiring anhydrous conditions were conducted in flame- or oven-dried apparatus under an atmosphere of argon. Syringes and needles for the transfer of reagents were dried at 140 °C and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from sodium benzophenone ketyl, (chlorinated) hydrocarbons, amines and DMF from CaH_2. Internal reaction temperatures are reported unless stated otherwise. Reactions were monitored by TLC using commercially available glass-backed plates, pre-coated with a 0.25 mm layer of silica containing a fluorescent indicator (Merck). Organic layers were dried over $MgSO_4$ unless stated otherwise. Column chromatography was carried out on Kieselgel 60 (40–63 μm). Light petroleum refers to the fraction with bp 40–60 °C. $[\alpha]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded as thin films unless stated otherwise. Peak intensities are specified as strong (s), medium (m) or weak (w). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless stated otherwise with Varian Gemini 200, Bruker AC200, Bruker WM250, Bruker WH300, JEOL EX400, Bruker AM500 or Bruker AMX500 spectrometers. Chemical shifts are reported relative to $CHCl_3$ [δ_H 7.26, δ_C(central line of t) 77.0]. Coupling constants (J) are given in Hz. Chiral stationary phase HPLC was performed using a Daicel Chiralpak AD column (4.6 mm × 250 mm) on a Gilson system with 712 Controller Software and a 118 UV–VIS dectector set at 254 nm unless stated otherwise. Retention times for major ($t_R$mj) and minor ($t_R$mn) enantiomers (mj and mn refer to sparteine reactions) are given in minutes.

(5*R**,6*S**)-5,6-Bis(*tert*-butyldimethylsilyloxy)cyclooctene 6[9]

OsO_4 (4% w/w in H_2O; 0.37 cm^3, 49.1 μmol) was added to a stirred solution of cycloocta-1,5-diene **5** (2.0 cm^3, 16.1 mmol) and NMO (2.07 g, 17.7 mmol) in THF–acetone–H_2O (90 cm^3, 1 : 1 : 1) at 0 °C. The solution was allowed to warm to room temperature and stirred for 16 h before being cooled to 0 °C and saturated aq. $NaHSO_4$ (60 cm^3) added. The solution was stirred for a further 1 h, and then the aqueous layer was extracted with EtOAc (3 × 150 cm^3). The combined organic layers were washed with H_2O (2 × 50 cm^3) and brine (50 cm^3), and then these washes were back extracted with EtOAc (3 × 50 cm^3), before all the organic layers were combined, dried, and evaporated under reduced pressure to give an off-white solid. Purification of the residue by column chromatography (50% EtOAc in light petroleum) gave (1*R**,2*S**)-cyclooct-5-ene-1,2-diol (682 mg, 29%) as a white solid; mp 103–105 °C (lit.,[40] 104.5–106 °C); R_f 0.2 (50% EtOAc in light petroleum); ν_{max}(KBr)/cm^{-1}

3306br, 2928s, 1041m, 1029m and 734w; δ_H(200 MHz) 5.80–5.55 (2 H, m, C(1)H and C(2)H), 4.04–3.98 (2 H, m, C(5)H and C(6)H) and 2.58–1.75 (10 H, m, C(1)OH, C(2)OH, C(3)H_2, C(4)H_2, C(7)H_2 and C(8)H_2).

TBDMSCl (703 mg, 4.66 mmol) was added to a stirred solution of (1*R**,2*S**)-cyclooct-5-ene-1,2-diol (270 mg, 1.90 mmol) and imidazole (672 mg, 9.88 mmol) in DMF (5 cm^3) at 25 °C. After 18 h the solution was diluted with CH_2Cl_2 (30 cm^3) and washed with H_2O (2 × 20 cm^3), saturated aq. $CuSO_4$ (2 × 20 cm^3) and brine (20 cm^3). The organic layer was dried, and evaporated under reduced pressure. Purification of the residue by column chromatography (light petroleum) gave the *alkene* **6** (561 mg, 80%) as a clear oil; R_f 0.5 (light petroleum); ν_{max}/cm^{-1} 3017w, 2930s, 2857s, 1472m, 1252m, 1051s and 832s; δ_H(200 MHz) 5.80–5.50 (2 H, m, C(1)H and C(2)H), 3.93–3.83 (2 H, m, C(5)H and C(6)H), 2.91–1.41 (8 H, m, C(3)H_2, C(4)H_2, C(7)H_2 and C(8)H_2), 0.88 (18 H, s, SiCMe_3) and 0.03 (12 H, s, SiMe).

(1*R**,4*S**,5*R**,8*S**)-9-Oxabicyclo[6.1.0]nonane-4,5-diol 8

MCPBA (50% w/w pure; 70.0 g, 203 mmol) was added portionwise to a stirred solution of cycloocta-1,5-diene **5** (15 cm^3, 366 mmol) and Na_2CO_3 (42.0 g, 396 mmol) in CH_2Cl_2 (1400 cm^3) at 0 °C. The solution was allowed to warm to 25 °C with stirring over 17 h, before being cooled to 0 °C and aq. NaOH (2 mol dm^{-3}, 500 cm^3) was added slowly. The organic layer was separated, washed with H_2O until the washings were neutral, dried, and evaporated under reduced pressure. Reduced pressure distillation gave the monoepoxide (20.0 g, 54%) as a clear liquid; bp 102 °C (40 mmHg) [lit.,[11] 64–66 °C (6 mmHg)]; R_f 0.61 (50% Et_2O in light petroleum); ν_{max}/cm^{-1} 3006s, 2910s, 2838m, 1657w, 1486m, 1446m and 1429m; δ_H(200 MHz) 5.61–5.57 (2 H, m, C(4)H and C(5)H), 3.08–3.03 (2 H, m, C(1)H and C(8)H) and 2.46–2.00 (8 H, m, C(2)H_2, C(3)H_2, C(6)H_2 and C(7)H_2).

OsO_4 (4% w/w in H_2O; 2 cm^3, 0.3 mmol) was added to a stirred solution of the above monoepoxide (10 g, 80.0 mmol) and NMO (24.0 g, 205 mmol) in THF–H_2O (200 cm^3, 1 : 1) at 0 °C. The solution was allowed to warm to 25 °C and stirred for 15 h before being cooled to 0 °C. Excess $Na_2S_2O_4$ was added. After filtration the solution was concentrated under reduced pressure and transferred to a liquid–liquid extractor and continuously extracted with EtOAc for 24 h, then with CH_2Cl_2 for 72 h. The combined organic phases were dried and evaporated under reduced pressure. Purification of the residue by column chromatography (5% MeOH in CH_2Cl_2) gave the *epoxydiol* **8** (9.2 g, 73%) as a white solid; mp 132–135 °C; R_f 0.25 (10% MeOH in CH_2Cl_2); ν_{max}(KBr)/cm^{-1} 3296br s, 2986s, 2961s, 1461m, 1100m and 792s; δ_H(200 MHz, d_6-DMSO) 4.54 (2 H, d, *J* 4.4, C(4)OH and C(5)OH), 3.78 (2 H, dt, *J* 8.0 and 4.4, C(4)H and C(5)H), 2.89–2.79 (2 H, m, C(1)H and C(8)H) and 1.88–1.31 (8 H, m, C(2)H_2, C(3)H_2, C(6)H_2 and C(7)H_2); δ_C(50 MHz, d_6-DMSO) 74.6 (COH), 55.2 (CH), 30.5 (CH_2) and 23.0 (CH_2).

(1*R**,4*S**,5*R**,8*S**)-4,5-Bis(*tert*-butyldimethylsilyloxy)-9-oxabicyclo[6.1.0]nonane 7

Method 1. MCPBA (50% w/w pure; 1.40 g, 4.05 mmol) was added to a stirred solution of alkene **6** (1.00 g, 2.70 mmol) and Na_2CO_3 (0.57 g, 5.38 mmol) in CH_2Cl_2 (70 cm^3) at 0 °C. The ice bath was removed and the solution was stirred for 30 min before NaOH (2 mol dm^{-3}; 160 cm^3) was slowly added. The organic layer was separated and washed with H_2O until the washings were neutral, before drying and evaporation under reduced pressure. Purification of the residue by column chromatography (5% Et_2O in light petroleum) gave the *epoxide* **7** (1.01 g, 97%) as a clear oil which solidified on standing in the refrigerator over several days; mp 37–38 °C; R_f 0.4 (10% Et_2O in light petroleum); ν_{max}/cm^{-1} 2928s, 2856s, 1472s, 1462s, 1388m, 1362m, 1252s, 1109s, 1047s, 1005s, 957s, 833s, 775s and 672m; δ_H(500 MHz, 85 °C, d_8-toluene) 3.98–3.95 (2 H, m, C(4)H and C(5)H), 2.64–2.61 (2 H, m, C(1)H and C(8)H), 1.84–1.49 (8 H, m, C(2)H_2, C(3)H_2, C(6)H_2 and C(7)H_2), 0.94 (18 H, s, 2 × CMe_3), 0.09 (6 H, s, 2 × SiMe) and 0.04 (6 H, s, 2 × SiMe); δ_C(125 MHz, 85 °C, d_8-toluene) 77.6 (COSi), 54.5 (*C*OC), 31.3 (CH_2), 26.0 (2 × SiC*Me*$_3$), 22.8 (CH_2), 18.2 (2 × Si*C*Me_3), −4.6 (2 × $SiCH_3$) and −4.9 (2 × $SiCH_3$); *m*/*z* (CI) 387 (55%), 371 (95), 239 (100), 132 (75) and 107 (45) (Found: M + H^+, 387.2758. $C_{20}H_{43}O_3Si_2$ requires *M*, 387.2751).

Method 2. Epoxydiol **8** (4.1 g, 26 mmol), TBDMSCl (9.9 g, 65 mmol) and imidazole (33.5 g, 131 mmol) were stirred at 25 °C in DMF (15 cm^3) for 18 h. The solution was diluted with water (200 cm^3) and CH_2Cl_2 (200 cm^3). The aqueous layer was extracted with CH_2Cl_2 (4 × 100 cm^3), dried, and evaporated under reduced pressure to give a clear oil. Purification of the residue by column chromatography (10% Et_2O in light petroleum) gave the *epoxide* **7** (10 mg, 98%) as a clear oil which solidified on standing in the refrigerator over several days.

General procedure for the reaction of RLi with epoxides 7, 27 and 28

Distilled ligand (2.5 equiv.) was added dropwise over 10 min to a stirred solution of RLi (2.4 equiv.) in solvent at low temperature [for (−)-α-isosparteine·H_2O, RLi (4.9 equiv.) was added dropwise over 10 min to a stirred solution of (−)-α-isosparteine·H_2O (2.5 equiv.)]. After stirring for 1 h at low temperature a solution of epoxide (1 equiv.) in solvent was added over 15 min. The solution was then stirred at low temperature for a further 5 h, before being allowed to slowly warm to 25 °C overnight. The reaction was cooled to 0 °C and H_3PO_4 (0.5 mol dm^{-3}) was added dropwise. The organic layers were washed with saturated aq. $NaHCO_3$ (×2) and brine, dried and evaporated under reduced pressure, followed by column chromatography (10% Et_2O in light petroleum) of the residue.

Products from rearrangement of epoxide 7 following the general procedure

(2*S,5*S**,6*S**)-5,6-Bis(*tert*-butyldimethylsilyloxy)bicyclo-[3.3.0]octan-2-ol 9.** R_f 0.32 (20% Et_2O in light petroleum); ν_{max}/cm^{-1} 3392br w, 2955s, 2930s, 2858s, 1472m, 1257m, 1067m, 833s and 774s; δ_H(400 MHz) 3.99–3.92 (1 H, m C(6)H), 3.76 (1 H, d, *J* 3.2, C(2)H), 3.34 (1 H, br s, OH), 2.48–2.44 (1 H, m, C(1)H), 2.29–2.09 (3 H, m, C(3)H, C(4)H and C(7)H), 1.99–1.89 (2 H, m, C(4)H and C(8)H), 1.82–1.70 (2 H, m, C(7)H and C(8)H), 1.61–1.56 (1 H, m, C(3)H), 0.97 (9 H, s, C(CH_3)$_3$), 0.90 (9 H, s, C(CH_3)$_3$), 0.18 (3 H, s, $SiCH_3$), 0.17 (3 H, s, $SiCH_3$), 0.14 (3 H, s, $SiCH_3$) and 0.13 (3 H, s, $SiCH_3$); δ_C(100 MHz) 96.1 (COSi), 79.6 (COH), 73.0 (COSi), 58.6 (CH), 37.8 (CH_2), 36.4 (CH_2), 29.4 (CH_2), 25.7 (2 × SiC*Me*$_3$), 19.8 (CH_2), 18.0 (Si*C*Me_3), 17.9 (Si*C*Me_3), −2.7 (SiMe), −2.9 (SiMe), −4.5 (SiMe) and −4.9 (SiMe); *m*/*z* (CI) 387 (85%), 255 (100), 239 (25), 140 (45), 138 (50), 121 (95), 92 (45) and 91 (45) (Found: M + H^+, 387.2745. $C_{20}H_{43}O_3Si_2$ requires *M*, 387.2751). The ee was determined on the 2,6-dibenzoylated derivative† of the corresponding triol **12** by chiral HPLC (30 : 70 EtOH–hexane, 0.3 cm^3 min^{-1}) $t_R$mj, 21.3; $t_R$mn, 23.0. $[a]_D^{22}$ +26.4 (*c* 1, $CHCl_3$) for sample of 73% ee.

(5*S,6*R**)-1-*sec*-Butyl-5,6-bis(*tert*-butyldimethylsilyloxy)-cyclooctene 10 (R = Bu^s).** An unseparated mixture of stereoisomers at the *sec*-butyl 2-position; R_f 0.80 (20% Et_2O in light petroleum); ν_{max}/cm^{-1} 2956s, 2929s, 2857s, 1472m, 1462m, 1252m, 1072m, 834s and 774s; δ_H(400 MHz) 5.45–4.97 (1 H, m, C(2)H), 3.97–3.80 (2 H, m, C(5)H and C(6)H), 2.87–0.72 (17 H, m), 0.92–0.87 (18 H, m, 2 × CMe_3) and 0.09–0.02 (12 H, m, 4 × SiMe); δ_C(100 MHz) 145.8 (C$_2$*C*=CH), 123.9 (C$_2$C=*C*H), 123.0 (C$_2$C=*C*H), 81.1 (CHO), 81.0 (CHO), 68.7 (CHO), 44.1 (CH_2), 43.1 (CH_2), 41.8 (CH_2), 39.2 (CH_2), 38.9 (CH_2), 34.9 (CH_2), 34.3 (CH_2), 29.7 (CH_2), 27.0 (SiC*Me*$_3$), 26.7 (SiC*Me*$_3$),

25.4 (CH_2), 20.0 (CH_2), 19.9 (CH_2), 19.4 (Si*C*Me$_3$), 18.8 (Si*C*Me$_3$), 11.7 (Me), 11.5 (Me), −4.6 (SiMe), −4.7 (SiMe), −4.8 (SiMe) and −5.0 (SiMe); *m*/*z* (CI) 444 (M + NH_4^+, 5%), 295 (15), 180 (40) and 163 (100).

(5*S,6*R**)-5,6-Bis(*tert*-butyldimethylsilyloxy)-1-isopropylcyclooctene 10 (R = Pr^i).** R_f 0.90 (light petroleum); ν_{max}/cm^{-1} 2929s, 2858s, 1639w, 1475s, 1463s, 1387s, 1360s, 1255s and 1122s; δ_H(250 MHz) 5.04 (1 H, br d, *J* 12.5, vinyl-H), 3.97 (1 H, br d, *J* 5.3, CH(O)), 3.81 (1 H, dd, *J* 10 and 1.5, CH(O)), 3.09 (1 H, sept, *J* 7.2, C=C-C*H*Me$_2$), 2.52 (1 H, qd, *J* 12.2 and 4.5, C*H*$_A$H$_B$), 2.36 (1 H, tt, *J* 13.4 and 3.8, CH$_A$*H*$_B$), 2.30 (1 H, m, C*H*$_A$H$_B$), 2.15 (1 H, dd, *J* 13.0 and 3.8, CH$_A$*H*$_B$), 2.00–1.40 (4 H, m, 4 × CH$_A$H$_B$), 1.11 (3 H, d, *J* 7.1, C*Me*$_A$Me$_B$), 1.00 (3 H, d, *J* 7.1, CMe$_A$*Me*$_B$), 0.95 (9 H, s, CMe$_3$), 0.90 (9 H, s, CMe$_3$), 0.11 (3 H, s, Si*Me*$_A$Me$_B$), 0.09 (3 H, s, SiMe$_A$*Me*$_B$), 0.06 (3 H, s, Si*Me*$_A$Me$_B$) and 0.05 (3 H, s, SiMe$_A$*Me*$_B$); δ_C(100 MHz) 149.9 (=C), 124.5 (=CH), 80.7 (CO), 77.6 (CO), 39.2, 35.2, 28.5, 26.5 (C*Me*$_3$), 26.2 (C*Me*$_3$), 25.0, 22.8 (*C*Me$_3$), 22.3 (*C*Me$_3$), 20.5, 19.0, 18.5, −4.0 (Si*Me*$_A$Me$_B$), −4.4 (SiMe$_A$*Me*$_B$), −4.4 (Si*Me*$_A$-Me$_B$) and −4.6 (SiMe$_A$*Me*$_B$); *m*/*z* (CI) 412 (5%), 281 (30) and 149 (100) (Found: M$^+$, 412.3194. $C_{23}H_{48}O_2Si_2$ requires *M*, 412.3193).

(4*S,5*R**)-4,5-Bis(*tert*-butyldimethylsilyloxy)cyclooctanone 11.** R_f 0.41 (20% Et_2O in light petroleum); ν_{max}/cm^{-1} 2956s, 2940s, 1705m, 1483m, 1461m, 1253m, 1061m, 836s and 776s; δ_H(400 MHz) 3.86–3.78 (1 H, m, C(4)H), 3.67–3.58 (1 H, m, C(5)H), 2.90–2.84 (1 H, m, C(2)H), 2.53–2.47 (1 H, m, C(8)H), 2.30–2.23 (2 H, m, C(6)H and C(8)H), 2.17–2.12 (1 H, m, C(2)H), 2.00–1.94 (2 H, m, C(3)H and C(6)H), 1.90–1.83 (1 H, m, C(3)H), 1.78–1.71 (1 H, m, C(7)H), 1.51–1.44 (1 H, m, C(7)H), 0.91 (9 H, s, SiCMe$_3$), 0.88 (9 H, s, SiCMe$_3$), 0.08 (3 H, s, SiMe), 0.05 (3 H, s, SiMe), 0.03 (3 H, s, SiMe) and 0.02 (3 H, s, SiMe); δ_C(100 MHz) 210.3 (C=O), 77.2 (COSi), 74.1 (COSi), 43.2 (2 × CH_2), 35.5 (CH_2), 33.7 (CH_2), 25.8 (2 × SiC*Me*$_3$), 22.3 (CH_2), 18.1 (2 × Si*C*Me$_3$), −4.6 (SiMe), −4.7 (SiMe), −4.9 (SiMe) and −5.0 (SiMe); *m*/*z* (CI) 387 (100%), 272 (25), 255 (55), 132 (55), 74 (45) and 72 (70) (Found: M + H$^+$, 387.2749. $C_{20}H_{43}O_3Si_2$ requires *M*, 387.2751).

(1*S*,2*S*,5*S*,6*S*)-Bicyclo[3.3.0]octane-1,2,6-triol 12

HF (40% w/w in H_2O; 0.9 cm^3, 20 mmol) was added to a stirred solution of bicyclic alcohol **9** [40 mg, 0.10 mmol (80% ee, Table 1, entry 6)] in MeCN (6 cm^3). After 1 h the reaction was neutralised with the minimum amount of aq. $NaHCO_3$, and the solvent was evaporated under reduced pressure. Purification of the residue by column chromatography (EtOAc) gave the *triol* **12** (16 mg, quant.) as a white solid; R_f 0.1 (EtOAc); ν_{max}/cm^{-1} 3291br s, 2956m, 2948m, 1463m, 1358m, 1227m, 1125m, 1080m, 1037s and 742m; δ_H(500 MHz, CD_3OD) 4.26–4.23 (1 H, m, C(6)H), 3.93–3.90 (1 H, m, C(2)H), 2.28–2.22 (2 H, m, C(5)H and C(8)H), 2.04–1.93 (2 H, m, C(3)H and C(7)H), 1.85–1.78 (1 H, m, C(4)H), 1.71–1.57 (3 H, m, C(4)H, C(7)H and C(3)H) and 1.48–1.42 (1 H, m, C(8)H); δ_C(100 MHz, CD_3OD) 92.3 (COH), 80.8 (COH), 74.5 (COH), 56.0 (CH), 35.6 (CH_2), 34.9 (CH_2), 31.7 (CH_2) and 20.3 (CH_2); *m*/*z* (CI) 176 (100%), 159 (10) and 122 (5) (Found: M + NH_4^+, 176.1287. $C_8H_{18}NO_3$ requires *M*, 176.1287).

(1*S*,2*S*,5*S*,6*S*)-2,6-Diacetylbicyclo[3.3.0]octan-1-ol 13

Ac_2O (0.25 cm^3, 2.65 mmol) was added to triol **12** (75 mg, 0.47 mmol) in pyridine (1 cm^3) and stirred at 25 °C for 16 h. The reaction was diluted with EtOAc (15 cm^3) and washed with saturated $CuSO_4$ solution (2 × 10 cm^3) and brine (2 × 10 cm^3). The organic layers were dried and evaporated under reduced pressure. Purification of the residue by column chromatography (50% Et_2O in light petroleum) gave the *tertiary alcohol* **13** (87 mg, 76%) as a clear oil (Found: C, 59.4; H, 7.5. $C_{12}H_{18}O_5$ requires C, 59.5; H, 7.5%); R_f 0.10 (50% Et_2O in light petroleum); ν_{max}/cm^{-1} 3460br m, 2966m, 1735s, 1374m, 1240s and 1038m; δ_H(400 MHz) 5.37–5.34 (1 H, m, C(6)H), 5.02–4.80 (1 H, m, C(2)H), 3.87 (1 H, s, OH), 2.55–2.51 (1 H, m, C(5)H), 2.13 (3 H, s, $COCH_3$), 2.06 (3 H, s, $COCH_3$) and 2.11–1.43 (8 H, m, C(3)H$_2$, C(4)H$_2$, C(7)H$_2$ and C(8)H$_2$); δ_C(100 MHz) 173.2 (CO), 170.5 (CO), 90.3 (COH), 86.0 (CHOAc), 77.7 (CHOAc), 53.8 (CH), 33.8 (CH_2), 32.1 (CH_2), 31.7 (CH_2), 21.1 (CH_2), 20.8 (*Me*CO), 20.6 (*Me*CO).

(1*R*,2*S*,5*R*,6*S*)-(−)-2,6-Diacetylbicyclo[3.3.0]octane 14[14,41]

ClCOCO$_2$Me (0.045 cm^3, 0.49 mmol) was added dropwise to a solution of tertiary alcohol **13** (70 mg, 0.29 mmol) and DMAP (60 mg, 0.49 mmol) in THF (4 cm^3). A white precipitate formed. After 30 min the reaction was diluted with EtOAc (20 cm^3) and washed with saturated aq. $NaHCO_3$ (2 × 15 cm^3) and H_2O (15 cm^3). The organic layer was dried and evaporated under reduced pressure to give the crude oxalyl ester (110 mg). The crude oxalyl ester was dissolved in toluene (4 cm^3) and AIBN (7.5 mg) and Bu_3SnH (0.15 cm^3, 0.56 mmol) were added. The reaction was heated at reflux for 1 h, cooled and evaporated under reduced pressure. Purification of the residue by column chromatography (25% Et_2O in light petroleum gradient to 50% Et_2O in light petroleum) gave the *diacetate* **14** (27 mg, 41%, 60% based on recovered tertiary alcohol **13**) as a clear oil; R_f 0.71 (Et_2O); $[\alpha]_D^{22}$ −78.7 (*c* 1.0, $CHCl_3$) [lit.,[14] $[\alpha]_D^{20}$ +104.3 (*c* 1.0, $CHCl_3$) for (1*S*,2*R*,5*S*,6*R*) isomer]; ν_{max}/cm^{-1} 2962m, 1734s, 1375m, 1240s and 1057m; δ_H(400 MHz) 5.12–5.07 (2 H, m, C(2)H and C(6)H), 2.74–2.69 (2 H, m, C(1)H and C(5)H), 2.06 (6 H, s, Me), 1.83–1.67 (4 H, m, C(3)H$_2$ and C(7)H$_2$) and 1.64–1.48 (4 H, m C(4)H$_2$ and C(8)H$_2$); δ_C(100 MHz) 170.8 (C=O), 77.2 (*C*HOAc), 44.6 (CH), 32.2 (CH_2), 22.8 (CH_2) and 21.1 (*Me*CO).

6-(*tert*-Butyldimethylsilyloxy)cyclooct-3-enone 22

9-Oxabicyclo[4.2.1]non-3-en-1-ol **21**[26] (200 mg, 1.43 mmol), TBDMSCl (258 mg, 1.51 mmol) and imidazole (204 mg, 3.0 mmol) in DMF (4 cm^3) were stirred at 25 °C for 18 h. The solution was then diluted with CH_2Cl_2 (25 cm^3) and washed with H_2O (2 × 20 cm^3), saturated aq. $CuSO_4$ (2 × 20 cm^3) and brine (20 cm^3). The organic layer was dried and evaporated under reduced pressure. Purification of the residue by column chromatography (20% Et_2O in light petroleum) gave the *enone* **22** (310 mg, 85%) as a pale yellow oil; R_f 0.34 (20% Et_2O in light petroleum); ν_{max}/cm^{-1} 3026m, 2954s, 2857s, 1705s, 1462s, 1361m, 1254s, 1075s, 836s and 776s; δ_H(400 MHz) 5.73–5.59 (2 H, m, C(3)H and C(4)H), 3.95–3.89 (1 H, m, C(6)H), 3.18 (1 H, dd, *J* 15.8, 5.5, C(2)H), 3.11 (1 H, dd, *J* 15.8 and 5.8, C(2)H), 2.70 (1 H, dd, *J* 10.0 and 2.1, C(8)H), 2.66 (1 H, dd, *J* 10.0 and 2.2, C(8)H), 2.36–2.17 (2 H, m, C(5)H$_2$), 2.04–1.85 (2 H, m, C(7)H$_2$), 0.88 (9 H, s, SiCMe$_3$), 0.06 (3 H, s, SiMe) and 0.04 (3 H, s, SiMe); δ_C(100 MHz) 212.8 (C=O), 127.8 (C_H=CH), 125.9 (C_H=CH), 70.3 (COSi), 44.8 (CH_2), 37.9 (CH_2), 34.5 (CH_2), 32.4 (CH_2), 25.7 (SiC*Me*$_3$), 18.0 (*C*Me$_3$) and −4.9 (2 × SiMe) the carbonyl carbon was not observed; *m*/*z* (CI) 272 (100%), 140 (100) and 126 (45) (Found: M + H$^+$, 255.1778. $C_{14}H_{27}O_2Si$ requires *M*, 255.1780).

6-(*tert*-Butyldimethylsilyloxy)cyclooct-3-enol 23

L-Selectride (1.0 mol dm^{-3} in THF; 0.70 cm^3, 0.70 mmol) was added dropwise to a stirred solution of enone **22** (57 mg, 0.22 mmol) in THF at −78 °C. The reaction was stirred for 1 h before being allowed to warm to 25 °C. It was diluted with Et_2O (20 cm^3) and washed with H_2O (2 × 20 cm^3) and brine (20 cm^3). The organic layers were dried and evaporated under reduced pressure. Purification of the residue by column chromatography (35% Et_2O in light petroleum) gave the *alcohol* **23** (49 mg, 85%), an inseparable mixture of isomers, as an oil; R_f 0.1 (20% Et_2O in

light petroleum); ν_{max}/cm^{-1} 3352br m, 3022m, 2932s, 2858s, 1463m, 1361m, 1253m, 1067s, 836s and 774s; δ_H(400 MHz) 5.75–5.66 (2 H, m, C(3)H and C(4)H), 3.87–3.76 (2 H, m, C(1)H and C(6)H), 2.43–2.18 (4 H, m, C(2)H_2 and C(5)H_2), 1.92–1.55 (5 H, m, C(7)H_2, C(8)H_2 and COH), 0.88 (9 H, s, SiCMe_3), 0.06 (3 H, s, SiMe) and 0.04 (3 H, s, SiMe); δ_C(100 MHz) 129.6 (C_H=CH), 129.2 (C_H=CH), 127.8 (C_H=CH), 127.3 (C_H=CH), 71.8 (CO), 71.6 (CO), 71.4 (CO), 34.8 (CH_2), 34.6 (CH_2), 34.5 (CH_2), 34.0 (CH_2), 30.4 (CH_2), 30.1 (CH_2), 29.8 (CH_2), 25.8 (SiCMe_3), 18.1 (SiCMe$_3$) and −4.9 (2 × SiMe); *m*/*z* (CI) 257 (M + H$^+$, 35%), 126 (100%), 109 (60) and 72 (45).

(4*R**,7*R**)- and (4*R**,7*S**)-4,7-Bis(*tert*-butyldimethylsilyloxy)-cyclooctene compounds 24 and 25

Method 1. $LiAlH_4$ (122 mg, 3.22 mmol) in THF (5 cm^3) was added dropwise to a stirred solution of 9-oxabicyclo[4.2.1]non-3-en-1-ol **21** [26] (451 mg, 3.22 mmol) in THF (15 cm^3) at −78 °C. The reaction was stirred for 4 h before being allowed to warm to room temperature overnight. It was then diluted with Et_2O (100 cm^3) and washed with H_2O (3 × 100 cm^3). The combined aqueous layers were evaporated under reduced pressure. Purification of the residue by flash chromatography (5% MeOH in CH_2Cl_2) gave an inseparable mixture of *cis*- and *trans*-cyclooct-6-ene-1,4-diol (381 mg, 83%) as an off-white solid; R_f 0.2 (5% MeOH in CH_2Cl_2); ν_{max}/cm^{-1} 3368br m, 2923m, 2851s, 1459m, 1261m, 1031m and 800m; δ_H(400 MHz, CD_3OD) 5.78–5.66 (2 H, m, C(6)H and C(7)H), 3.76–3.69 (2 H, m, C(1)H and C(4)H), 2.46–2.25 (4 H, m, C(5)H_2 and C(8)H_2) and 1.93–1.36 (4 H, m, C(2)H_2 and C(3)H_2); δ_C(100 MHz, CD_3OD) 130.1 (*C*H=CH), 129.5 (*C*H=CH), 72.6 (CHOH), 72.4 (CHOH), 35.5 (CH_2), 35.2 (CH_2), 31.6 (CH_2) and 31.1 (CH_2).

Cyclooct-6-ene-1,4-diol (381 mg, 2.68 mmol), TBDMSCl (1.62 g, 10.7 mmol) and imidazole (1.46 g, 21.5 mmol) were stirred in DMF (20 cm^3) at 25 °C for 18 h. The solution was then diluted with CH_2Cl_2 (100 cm^3) and washed with H_2O (2 × 80 cm^3), saturated aq. $CuSO_4$ (2 × 80 cm^3) and brine (80 cm^3). The organic layer was dried and evaporated under reduced pressure. The title compounds were removed from other impurities by column chromatography (10% Et_2O in light petroleum) and then separated from one another by further chromatography (light petroleum gradient to 5% Et_2O in light petroleum). First eluted *trans-bis ether* **24** (417 mg, 42%) as a clear liquid. R_f 0.15 (1% Et_2O in light petroleum); ν_{max}/cm^{-1} 3026w, 2930s, 2858s, 1463m, 1361m, 1255m, 1063s, 836s and 774s; δ_H(400 MHz) 5.73–5.65 (2 H, m, C(1)H and C(2)H), 3.85–3.82 (2 H, m, C(4)H and C(7)H), 2.34–2.21 (4 H, m, C(3)H_2 and C(8)H_2), 1.87–1.83 (2 H, m, C(5)H and C(6)H), 1.42–1.35 (2 H, m, C(5)H and C(6)H), 0.89 (18 H, s, 2 × C(CH_3)$_3$), 0.06 (6 H, s, 2 × SiCH_3) and 0.05 (6 H, s, 2 × SiCH_3); δ_C(100 MHz) 128.3 (C_H=CH), 72.0 (COSi), 34.6 (CH_2), 30.4 (CH_2), 25.8 (2 × SiC*C*H$_3$), 18.1 (2 × Si*C*Me$_3$) and −4.8 (4 × SiMe); *m*/*z* (CI) 371 (5%), 239 (100), 132 (50), 74 (45) and 72 (60) (Found: M + H$^+$, 371.2801. $C_{20}H_{43}O_2Si_2$ requires *M*, 371.2801). Second eluted *cis-bis ether* **25** (378 mg, 38%) as a clear liquid. R_f 0.05 (1% Et_2O in light petroleum); ν_{max}/cm^{-1} 3020w, 2930s, 2858s, 1472m, 1361m, 1254m, 1068s, 836s and 774s; δ_H(400 MHz) 5.68–5.60 (2 H, m, C(1)H and C(2)H), 3.77–3.72 (2 H, m, C(4)H and C(7)H), 2.45–2.38 (2 H, m, C(3)H and C(8)H), 2.21–2.15 (2 H, m, C(3)H and C(8)H), 1.85–1.77 (2 H, m, C(5)H and C(6)H), 1.57–1.49 (2 H, m, C(5)H, and C(6)H), 0.90 (18 H, s, 2 × SiCMe_3), 0.06 (6 H, s, 2 × SiMe) and 0.05 (6 H, s, 2 × SiMe); δ_C(100 MHz) 128.7 (*C*H=CH), 71.8 (COSi), 35.1 (CH_2), 30.2 (CH_2), 25.8 (2 × SiC*Me*$_3$), 18.1 (2 × Si*C*Me$_3$) and −4.8 (4 × SiMe); *m*/*z* (CI) 371 (20%), 256 (55), 239 (100), 132 (40), 124 (25) and 107 (35) (Found: M + H$^+$, 371.2807. $C_{20}H_{43}O_2Si_2$ requires *M*, 371.2801).

Method 2. Alcohol **23** (3.40 g, 13.3 mmol), TBDMSCl (3.00 g, 19.9 mmol) and imidazole (2.70 g, 39.7 mmol) were stirred in DMF (40 cm^3) at 25 °C for 18 h. The solution was then diluted with CH_2Cl_2 (300 cm^3), washed with H_2O (2 × 250 cm^3), saturated aq. $CuSO_4$ (2 × 250 cm^3) and brine (250 cm^3). The organic layer was dried and evaporated under reduced pressure. Purification of the residue by column chromatography as in Method 1 gave *trans-bis ether* **24** (1.10 g, 22%) and *cis-bis ether* **25** (2.08 g, 42%).

(1*R**,3*R**,6*R**,8*S**)-3,6-Bis(*tert*-butyldimethylsilyloxy)-9-oxabicyclo[6.1.0]nonane 26

MCPBA (50% w/w pure; 173 mg, 0.38 mmol) was added to a stirred solution of *trans*-bis ether **24** (94 mg, 0.25 mmol) and Na_2CO_3 (80 mg, 0.75 mmol) in CH_2Cl_2 (10 cm^3) at 0 °C. The ice bath was removed and the solution was stirred for 1 h, before NaOH (2 mol dm^{-3}, 10 cm^3) was slowly added. The organic layer was separated and washed with H_2O until the washings were neutral, dried and evaporated under reduced pressure. Purification of the residue by column chromatography (5% Et_2O in light petroleum) gave the *epoxide* **26** (96 mg, 98%) as a clear oil; R_f 0.3 (10% Et_2O in light petroleum); ν_{max}/cm^{-1} 2954s, 2857s, 1472m, 1361w, 1255m, 1085s, 1060s, 866s, 835s and 775s; δ_H(400 MHz) 4.05–4.01 (1 H, m, C(3)H or C(6)H), 3.95–3.89 (1 H, m, C(3)H or C(6)H), 3.19–3.14 (1 H, m, C(1)H or C(8)H), 2.91–2.86 (1 H, m, C(1)H or C(8)H), 2.34–2.28 (2 H, m, C(2)H and C(7)H), 2.02–1.95 (1 H, m, C(4)H or C(5)H), 1.79–1.71 (1 H, m, C(4)H or C(5)H), 1.63–1.55 (1 H, m, C(4)H or C(5)H), 1.45–1.30 (3 H, m, C(2)H, C(4)H or C(5)H, and C(7)H), 0.89 (9 H, s, C(CH_3)$_3$), 0.88 (9 H, s, C(CH_3)$_3$), 0.07 (3 H, s, SiCH_3), 0.06 (3 H, s, SiCH_3), 0.05 (3 H, s, SiCH_3) and 0.04 (3 H, s, SiCH_3); δ_C(100 MHz) 69.2 (CHOSi), 69.1 (CHOSi), 53.2 (*C*OC), 53.0 (*C*OC), 35.7 (CH_2), 34.3 (CH_2), 29.8 (CH_2), 29.1 (CH_2), 25.8 (SiC*Me*$_3$), 25.7 (SiC*Me*$_3$), 18.1 (Si*C*Me$_3$), 18.0 (Si*C*Me$_3$), −4.8 (SiCH_3), −4.9 (2 × SiCH_3) and −5.0 (SiCH_3); *m*/*z* (CI) 387 (35%), 255 (10), 239 (100), 132 (15) and 107 (15) (Found: M + H$^+$, 387.2747. $C_{20}H_{43}O_3Si_2$ requires *M*, 387.2751).

(1*R**,3*R**,6*S**,8*S**)-3,6-Bis(*tert*-butyldimethylsilyloxy)-9-oxabicyclo[6.1.0]nonane 27 and (1*R**,3*S**,6*R**,8*S**)-3,6-bis(*tert*-butyldimethylsilyloxy)-9-oxabicyclo[6.1.0]nonane 28

MCPBA (50% w/w pure; 114 mg, 0.33 mmol) was added to a stirred solution of *cis*-bis ether **25** (80 mg, 0.22 mmol) and Na_2CO_3 (70 mg, 0.66 mmol) in CH_2Cl_2 (10 cm^3) at 0 °C. The ice bath was removed and the solution was stirred for 2 h, before NaOH (2 mol dm^{-3}, 10 cm^3) was slowly added. The organic layer was separated and washed with H_2O until the washings were neutral, dried, and evaporated under reduced pressure. The title compounds were removed from other impurities by column chromatography (5% Et_2O in light petroleum) and then separated from one another by further chromatography (gradient elution, 20% CH_2Cl_2 in light petroleum gradient to 100% CH_2Cl_2). First eluted *cis*,*trans-epoxide* **28** (46 mg, 54%) as a clear oil which solidified on standing in the refrigerator over several days; mp 41–43 °C; R_f 0.30 (50% CH_2Cl_2 in light petroleum); ν_{max}/cm^{-1} 2955s, 2857s, 1464m, 1368w, 1255m, 1094s, 1038s, 864m, 835s and 775s; δ_H(400 MHz) 4.05–3.95 (2 H, m, C(3)H and C(6)H), 3.26–3.21 (2 H, m, C(1)H and C(8)H), 2.37–2.24 (2 H, m, C(2)H and C(7)H), 2.02–1.91 (2 H, m, C(4)H and C(5)H), 1.41–1.26 (4 H, m, C(2)H, C(4)H, C(5)H and C(7)H), 0.90 (18 H, s, 2 × CMe_3), 0.08 (6 H, s, 2 × SiMe) and 0.06 (6 H, s, 2 × SiMe); δ_C(125 MHz, 90 °C, d_8-toluene) 70.6 (COSi), 52.5 (*C*OC), 35.4 (CH_2), 30.2 (CH_2), 26.2 (2 × SiC*Me*$_3$), 18.4 (2 × Si*C*Me$_3$), −4.6 (2 × SiMe) and −4.7 (2 × SiMe); *m*/*z* (CI) 387 (20%), 255 (45), 239 (25), 132 (90), 91 (35), 74 (80) and 72 (100) (Found: M + H$^+$, 387.2753. $C_{20}H_{43}O_3Si_2$ requires *M*, 387.2751). Second eluted *all cis-epoxide* **27** (23 mg, 27%) as a clear oil which solidified on standing in the refrigerator over several days; mp 30–32 °C; R_f 0.25 (50% CH_2Cl_2 in light petroleum); ν_{max}/cm^{-1} 2930s, 2857s, 1472m, 1384w, 1257m, 1098s, 1074s, 866m, 836s and 774s; δ_H(400 MHz) 3.87–3.79 (2 H, m,

C(3)H and C(6)H), 2.87–2.84 (2 H, m, C(1)H and C(8)H), 2.35–2.24 (2 H, m, C(2)H and C(7)H), 1.88–1.75 (2 H, m, C(4)H and C(5)H), 1.59–1.43 (4 H, m, C(2)H, C(4)H, C(5)H and C(7)H), 0.89 (18 H, s, 2 × CMe_3), 0.07 (6 H, s, 2 × SiMe) and 0.06 (6 H, s, 2 × SiMe); δ_C(100 MHz) 69.4 (COSi), 53.0 (*C*OC), 36.0 (CH_2), 30.4 (CH_2), 25.8 (2 × SiC*Me*$_3$), 18.1 (2 × Si*C*Me$_3$) and −4.8 (4 × SiMe); *m*/*z* (CI) 387 (40%), 255 (60), 239 (75), 201 (30), 132 (100), 107 (35), 91 (35) and 74 (45) (Found: M + H^+, 387.2750. $C_{20}H_{43}O_3Si_2$ requires *M*, 387.2751).

Products from rearrangement of epoxide 27 following the general procedure

(1*R,2*S**,4*R**,5*S**,7*S**)-4,7-Bis(*tert*-butyldimethylsilyloxy)-bicyclo[3.3.0]octan-2-ol 29.** R_f 0.3 (10% Et_2O in light petroleum); ν_{max}/cm^{-1} 3331br m, 2929s, 2858s, 1472w, 1361w, 1256m, 1123m, 1054m, 836s and 775s; δ_H(400 MHz) 4.28–4.25 (1 H, m, C(7)H), 4.13–4.07 (2 H, m, C(2)H and C(4)H), 3.11–3.08 (1 H, m, OH), 2.48–2.39 (2 H, m, C(1)H and C(5)H), 1.94–1.74 (6 H, m, C(3)H_2, C(6)H_2 and C(8)H_2), 0.90 (9 H, s, SiCMe_3), 0.89 (9 H, s, SiCMe_3), 0.08 (6 H, s, 2 × SiMe), 0.05 (3 H, s, SiMe) and 0.04 (3 H, s, SiMe); δ_C(100 MHz) 75.8 (CHO), 72.1 (CHO), 71.6 (CHO), 47.2 (CH), 45.4 (CH), 43.3 (CH_2), 35.8 (CH_2), 35.0 (CH_2), 25.8 (2 × SiC*Me*$_3$), 18.1 (Si*C*Me$_3$), 18.0 (Si*C*Me$_3$), −4.6 (2 × SiMe), −4.8 (SiMe), and −5.0 (SiMe); *m*/*z* (CI) 387 (100%), 329 (15), 270 (20), 132 (10), 105 (15) and 92 (15) (Found: M + H^+, 387.2756. $C_{20}H_{43}O_3Si_2$ requires *M*, 387.2751). The ee was determined on the diol (derived from 2,4-dinitrobenzoylation followed by desilylation using BF_3·Et_2O)† by chiral HPLC (60 : 40 EtOH–hexane, 0.75 cm^3 min^{-1}) $t_R$mj, 18.0; $t_R$mn, 26.4.

(4*R,7*S**)-1-*sec*-Butyl-4,7-bis(*tert*-butyldimethylsilyloxy)-cyclooctene 30 (R = Bu^s).** As an unseparated mixture of stereoisomers at the *sec*-butyl 2-carbon; R_f 0.8 (10% Et_2O in light petroleum); ν_{max}/cm^{-1} 2965s, 2922s, 2850s, 1472m, 1462m, 1072m, 839s and 743s; δ_H(400 MHz) 5.35–4.84 (1 H, m, C(2)H), 4.18–3.46 (2 H, m, C(4)H and C(7)H), 2.81–0.78 (17 H, m), 0.91–0.83 (18 H, m, 2 × SiCMe_3) and 0.08–0.01 (12 H, m, 4 × SiMe); δ_C(100 MHz) 144.8 (C_2*C*=CH), 144.0 (C_2*C*=CH), 123.8 (C_2C=*C*H), 121.0 (C_2C=*C*H), 73.7 (CHO), 72.3 (CHO), 72.1 (CHO), 71.8 (CHO), 44.1 (CH), 43.1 (CH_2), 41.8 (CH_2), 37.8 (CH_2), 36.8 (CH_2), 36.0 (CH_2), 32.3 (CH_2), 30.4 (CH_2), 25.9 (SiC*Me*3), 25.7 (SiC*Me*$_3$), 20.0 (CH_2), 19.2 (CH_2), 18.1 (Si*C*Me$_3$), 18.0 (Si*C*Me$_3$), 12.3 (Me), 12.1 (Me), −4.6 (SiMe), −4.7 (SiMe), −4.8 (SiMe) and −5.0 (SiMe).

(4*R,7*S**)-4,7-Bis(*tert*-butyldimethylsilyloxy)-1-isopropyl-cyclooctene 30 (R = Pr^i).** R_f 0.8 (10% Et_2O in light petroleum); ν_{max}/cm^{-1} 2956s, 2934s, 1472w, 1467m, 1067m, 954m, 839s and 699s; δ_H(400 MHz) 5.41–4.84 (1 H, m, C(2)H), 4.20–3.62 (2 H, m, C(4)H and C(7)H), 2.87–0.09 (15 H, m), 0.91–0.83 (18 H, m, 2 × SiC$(CH_3)_3$) and 0.06–0.02 (12 H, m, 4 × $SiCH_3$); δ_C(100 MHz) 146.5 (C_2*C*=CH), 145.9 (C_2*C*=CH), 123.8 (C_2C=*C*H), 119.9 (C_2C=C_H), 78.7 (CHO), 73.6 (CHO), 72.6 (CHO), 71.9 (CHO), 43.2 (CH), 41.7 (CH_2), 37.5 (CH_2), 37.3 (CH_2), 36.0 (CH_2), 35.9 (CH_2), 35.7 (CH_2), 34.9 (CH_2), 32.1 (CH_2), 31.9 (CH_2), 31.5 (CH_2), 30.7 (CH_2), 30.4 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 26.0 (SiC*Me*$_3$), 25.9 (SiC*Me*$_3$), 25.8 (SiC*Me*$_3$), 24.6 (Me), 22.4 (Me), 21.9 (Me), 21.7 (Me), 18.4 (Si*C*Me$_3$), 18.2 (Si*C*Me$_3$), 18.1 (Si*C*Me$_3$), −4.6 (2 × SiMe), −4.8 (SiMe) and −5.0 (SiMe); *m*/*z* (CI) 430 (M + NH_4^+, 5%), 281 (10), 166 (45) and 149 (100).

(1*R,2*S**,4*R**,5*S**,7*R**)-Bicyclo[3.3.0]octane-2,4,7-triol 31**

HF (40% w/w in H_2O; 0.1 cm^3, 4 mmol) was added to a stirred solution of bicyclic alcohol (+)-**29** (12 mg, 0.031 mmol) in MeCN (2 cm^3). After 1 h the reaction was neutralised with the minimum amount of aq. $NaHCO_3$ and evaporated under reduced pressure. Purification of the residue by column chromatography (20% MeOH in CH_2Cl_2) gave the *meso triol* **31** (4.5 mg, quant.) as a solid; $[\alpha]_D^{23}$ 0.0 (*c* 0.9, EtOH); R_f 0.45 (20% MeOH in CH_2Cl_2); ν_{max}/cm^{-1} 3302br s, 2948m, 1468m, 1361m, 1123m, 1037s and 667m; δ_H(400 MHz, CD_3OD) 4.14–4.06 (3 H, m, C(2)H, C(4)H and C(7)H), 2.57–2.47 (2 H, m, C(1)H and C(5)H) and 1.99–1.63 (6 H, m, C(3)H_2, C(6)H_2 and C(8)H_2); δ_C(100 MHz, CD_3OD) 80.2 (CHO), 74.7 (CHO), 45.9 (CH), 40.7 (CH_2) and 36.0 (2 × CH_2); *m*/*z* (CI) 176 (95%) and 159 (100) (Found: M + H^+, 159.1026. $C_8H_{15}O_3$ requires *M*, 159.1021).

Products from rearrangement of epoxide 28 following the general procedure

(2*S*,4*R*,7*S*)-4,7-Bis(*tert*-butyldimethylsilyloxy)cyclooct-2-enol 33. Data from Table 3, entry 2: R_f 0.2 (20% Et_2O in light petroleum); ν_{max}/cm^{-1} 3315br w, 2931s, 2850s, 1471m, 1358m, 1249s, 1048s, 835m and 774s; δ_H(400 MHz) 5.60 (1 H, dd, *J* 12.1, 5.7, C(2)H), 5.53 (1 H, dd, *J* 12.1, 5.5, C(3)H), 4.98–4.92 (1 H, m, C(1)H), 4.69–4.63 (1 H, m, C(4)H), 3.82–3.77 (1 H, m, C(7)H), 2.02–1.89 (3 H, m, C(6)H and C(8)H_2), 1.75–1.59 (4 H, m, C(5)H_2, C(6)H and COH), 0.89 (9 H, s, SiCMe_3), 0.88 (9 H, s, SiCMe_3), 0.06 (6 H, s, 2 × SiMe) and 0.05 (6 H, s, 2 × SiMe); δ_C(100 MHz) 133.2 (*C*=C), 133.1 (*C*=C), 70.0 (CHO), 68.6 (CHO), 66.0 (CHO), 45.2 (CH_2), 33.6 (CH_2), 32.9 (CH_2), 25.8 (2 × SiC*Me*$_3$), 18.1 (2 × Si*C*Me$_3$), −4.8 (2 × SiMe) and −4.9 (2 × SiMe); *m*/*z* (CI) 387 (30%), 255 (100), 237 (15) and 132 (20) (Found: M + H^+, 387.2748. $C_{20}H_{43}O_3Si_2$ requires *M*, 387.2751).

In all other cases a mixture of bicyclic alcohol **32** and allylic alcohol **33** were formed. The ee of both alcohols was measured by derivatisation to the diols (derived from 3,5-dinitrobenzoylation followed by desilylation using BF_3·Et_2O)† by chiral HPLC (60 : 40 EtOH–hexane, 0.75 cm^3 min^{-1}). For bicyclic alcohol **32** derivative: $t_R$mj, 10.4; $t_R$mn, 11.7. For allylic alcohol **33** derivative: $t_R$mj, 15.3; $t_R$mn, 22.7. This mixture was treated with 10% Pd/charcoal in EtOAc under an atmosphere of H_2 for 1 h. After filtration the mixture was evaporated under reduced pressure. Purification of the residue by column chromatography (10% Et_2O in light petroleum) gave bicyclic alcohol **32** and ketone **34**.

(1*R*,2*S*,4*S*,5*S*,7*S*)-4,7-Bis(*tert*-butyldimethylsilyloxy)bicyclo-[3.3.0]octan-2-ol 32. R_f 0.2 (10% Et_2O in light petroleum); ν_{max}/cm^{-1} 3369br w, 2955s, 2929s, 2856s, 1472w, 1361w, 1254m, 1048s, 835s and 774s; δ_H(400 MHz) 4.52–4.47 (1 H, m, C(4)H), 4.33–4.29 (1 H, m, C(7)H), 3.88–3.64 (1 H, m, C(2)H), 2.88–2.81 (1 H, m, C(5)H), 2.52–2.45 (1 H, m, C(1)H), 1.90–1.21 (6 H, m, C(3)H_2, C(6)H_2 and C(8)H_2), 0.88 (9 H, s, SiCMe_3), 0.87 (9 H, s, SiCMe_3), 0.05 (6 H, s, 2 × SiMe) and 0.04 (6 H, s, 2 × SiMe); δ_C(100 MHz) 77.4 (CHO), 75.4 (CHO), 72.5 (CHO), 50.5 (CH), 43.9 (CH), 42.6 (CH_2), 40.6 (CH_2), 37.1 (CH_2), 25.8 (2 × SiC*Me*$_3$), 18.1 (2 × CMe_3), −4.5 (2 × $SiCH_3$) and −4.8 (2 × $SiCH_3$); *m*/*z* (CI) 387 (55%), 346 (20), 272 (100), 255 (50), 132 (90) and 90 (25) (Found: M + H^+, 387.2752. $C_{20}H_{43}O_3Si_2$ requires *M*, 387.2751).

(3*R*,6*S*)-3,6-Bis(*tert*-butyldimethylsilyloxy)cyclooctanone 34. R_f 0.7 (10% Et_2O in light petroleum); ν_{max}/cm^{-1} 2929s, 2857s, 1702m, 1472w, 1253m, 1077m, 836s and 775m; δ_H(400 MHz) 3.89–3.84 (1 H, m, C(3)H), 3.78–3.75 (1 H, m, C(6)H), 2.97–2.92 (1 H, m, C(2)H), 2.47–2.38 (2 H, m, C(2)H, and C(4)H or C(5)H), 2.26–2.18 (2 H, m, C(4)H_2, or C(4)H and C(5)H, or C(5)H_2), 1.93–1.85 (2 H, m, C(4)H or C(5)H, and C(7)H), 1.75–1.62 (1 H, m, C(7)H), 1.17–1.08 (2 H, m, C(8)H_2), 0.89 (9 H, s, SiCMe_3), 0.88 (9 H, s, SiCMe_3), 0.09 (3 H, s, SiMe), 0.08 (3 H, s, SiMe), 0.04 (3 H, s, SiMe) and 0.03 (3 H, s, SiMe); δ_C(100 MHz) 212.0 (C=O), 72.7 (CHO), 70.7 (CHO), 48.9 (CH_2), 41.3 (CH_2), 30.4 (CH_2), 29.7 (CH_2), 28.7 (CH_2), 25.7 (2 × SiC*Me*$_3$), 18.0 (2 × Si*C*Me$_3$), −4.8 (2 × SiMe) and −4.9 (2 × SiMe); *m*/*z* (CI) 404 (80%), 387 (100), 272 (60), 255 (35), 197 (15), 132 (25) and

91 (20) (Found: M + H^+, 387.2752. $C_{20}H_{43}O_3Si_2$ requires *M*, 387.2751).

(1*R*,2*S*,4*S*,5*S*,7*R*)-(+)-Bicyclo[3.3.0]octane-2,4,7-triol 35

HF (40% w/w in H_2O; 0.1 cm^3, 4 mmol) was added to a stirred solution of bicyclic alcohol **32** (10 mg, 0.026 mmol) in MeCN (2 cm^3). After 1 h the reaction was neutralised with the minimum amount of aq. $NaHCO_3$, and evaporated under reduced pressure. Purification of the residue by column chromatography (20% MeOH–CH_2Cl_2) gave the *triol* **35** (4 mg, quant.) as a solid; $[\alpha]_D^{23}$ +3.1 (*c* 1.1, EtOH); R_f 0.45 (20% MeOH–CH_2Cl_2); ν_{max}/cm^{-1} 3273br s, 2958m, 1469m, 1364m, 1228m, 1123m, 1055s and 682m; δ_H(400 MHz, CD_3OD) 4.46–4.42 (1 H, m, C(4)H), 4.30–4.27 (1 H, m, C(2)H), 3.85–3.83 (1 H, m, C(7)H), 2.88–2.81 (1 H, m, C(5)H), 2.53–2.48 (1 H, m, C(1)H) and 1.92–1.40 (6 H, m, $C(3)H_2$, $C(6)H_2$ and $C(8)H_2$); δ_C(100 MHz, CD_3OD) 77.6 (CHO), 75.7 (CHO), 72.9 (CHO), 51.2 (CH), 45.5 (CH), 42.1 (CH_2), 41.2 (CH_2) and 35.5 (CH_2); *m*/*z* (CI) 176 (100%) and 159 (60) (Found: M + H^+, 159.1019. $C_8H_{15}O_3$ requires *M*, 159.1021).

(*Z*)-1,8-Bis(4-methylbenzylsulfonyloxy)oct-4-ene 41

TsCl (46.3 g, 0.24 mol) was added to a stirred solution of (*Z*)-oct-4-ene-1,8-diol **40**[37] (7.0 g, 48.6 mmol) in pyridine (100 cm^3) at 0 °C. The reaction mixture was allowed to stir at 25 °C for 2 h then re-cooled to 0 °C and diluted with Et_2O (100 cm^3). H_2O (100 cm^3) was added dropwise, then the organic layer was separated and washed with H_2O (50 cm^3) then sat. aq. $CuSO_4$ solution (3 × 50 cm^3), dried and then evaporated under reduced pressure. Purification of the residue by column chromatography (30% Et_2O–light petroleum) gave the *ditosylate* **41** (16.3 g, 74%) as a viscous, colourless oil; R_f 0.31 (50% Et_2O in light petroleum); ν_{max}/cm^{-1} 2957m, 1923w, 1734w, 1654w, 1598m, 1454m, 1354s, 1307m, 1292m, 1173s, 1097s and 1018m; δ_H(400 MHz) 7.79 (4 H, d, *J* 8.3, 4 × ArH), 7.36 (4 H, d, *J* 8.3, 4 × ArH), 5.29 (2 H, t, *J* 4.6, 2 × =CH), 4.02 (4 H, t, *J* 6.3, 2 × CH_2O), 2.46 (6 H, s, 2 × Me), 2.06–2.01 (4 H, m, 2 × CH_2) and 1.72–1.65 (4 H, m, 2 × CH_2); δ_C(125 MHz) 144.7 (2 × Ar, quat.), 133.1 (2 × Ar, quat.), 129.8 (4 × ArH), 129.1 (2 × =CH), 127.9 (4 × ArH), 69.8 (2 × CH_2O), 28.6 (2 × =C–*C*), 23.0 (2 × CH_2) and 21.6 (2 × Me); *m*/*z* (CI) 453 (MH^+, 100%), 452 (42), 341 (12) and 281 (5) (Found: M + NH_4^+, 470.1672. $C_{22}H_{32}NO_6S_2$ requires *M*, 470.1671).

(*Z*)-*N*-(4-Methylbenzylsulfonyl)-2,3,4,7,8,9-hexahydroazonine 42

A 2 L three-necked round-bottomed flask was equipped with a reflux condenser and two 100 cm^3 dropping funnels. The flask was charged with toluene (600 cm^3), Bu_4NI (1.14 g, 3.1 mmol), NaOH (18.6 g, 0.46 mol) and H_2O (44 cm^3). One dropping funnel was charged with a solution of ditosylate **41** (1 g, 2.21 mmol) in toluene (125 cm^3) and the other with a suspension of $TsNH_2$ (644 mg, 3.76 mmol) in toluene (125 cm^3). Both funnels were allowed to drip at the same rate over a period of 2 h into the well-stirred reaction; a gentle reflux (100 °C) was maintained during this time and for a further 2 h (note: during the addition, occasional heating of the $TsNH_2$ in toluene mixture was required in order to maintain a solution). After cooling to 25 °C the organic layer was separated and the aqueous layer was then extracted with Et_2O (3 × 50 cm^3). The combined organic layers were washed with brine (100 cm^3), dried and evaporated under reduced pressure. Purification of the residue by column chromatography (30% Et_2O in pentane) gave the *azacycle* **42** (383 mg, 62%) as a colourless, crystalline solid (Found: C, 64.4; H, 7.7; N, 4.9. $C_{15}H_{21}NO_2S$ requires C, 64.5; H, 7.6; N, 5.0%); R_f 0.61 (50% Et_2O in light petroleum); mp 105 °C (diethyl ether–pentane); ν_{max}(KBr)/cm^{-1} 3004m, 2965m, 2941m, 2920m, 2900m, 2856m, 1596m, 1461m, 1339s, 1298m, 1178m, 1156s, 1134s, 1095s, 972s, 879m, 808m and 689s; δ_H(400 MHz) 7.69 (2 H, d, *J* 8.2, 2 × ArH), 7.29 (2 H, d, *J* 8.2, 2 × ArH), 5.49 (2 H, t, *J* 5.6, 2 × =CH), 2.95 (4 H, t, *J* 6.3, 2 × CH_2), 2.43–2.39 (7 H, m, 2 × CH_2, Me) and 1.86–1.78 (4 H, m, 2× CH_2); δ_C(125 MHz) 143.2 (Ar, quat.), 134.3 (Ar, quat.), 130.1 (2 × ArH), 129.5 (2 × ArH), 127.6 (2 × =CH), 53.3 (2 × CH_2N), 28.3 (2 × CH_2), 22.2 (2 × CH_2) and 21.5 (Me); *m*/*z* (CI) 280 (MH^+, 77%), 126 (100) and 124 (87, [M − Ts]$^+$) (Found: M + H^+, 280.1371. $C_{15}H_{22}NO_2S$ requires *M*, 280.1371).

(*Z*)-*N*-(*tert*-Butoxycarbonyl)-2,3,4,7,8,9-hexahydroazonine 43

A freshly prepared solution of sodium naphthalenide in THF (40 cm^3, 15.5 mmol) was added dropwise to a stirred solution of Pr^iLi azacycle **42** (688 mg, 2.5 mmol) in THF (10 cm^3) at −78 °C until a permanent blue colouration was apparent and the starting material had been completely consumed as indicated by TLC. HCl gas was bubbled through the mixture for a couple of minutes and the solvent evaporated under reduced pressure. The residue was then triturated several times with 10% Et_2O–light petroleum to remove the naphthalene. The salt was dissolved in CH_2Cl_2, the NaCl was filtered off and the solvent was removed under reduced pressure. The trituration procedure was then repeated as above to give *(Z)-5-azacyclononene hydrochloride* (408 mg) as a pale yellow, hygroscopic solid, which was used directly in the next step without further purification; ν_{max} (Nujol)/cm^{-1} 3391br w, 2607m, 2392w, 2320w, 1715w, 1651w, 1576m, 1062m, 949m, 819m and 728m; δ_H(500 MHz) 9.18 (2H, br s, NH_2), 5.66–5.59 (2 H, m, 2 × =CH,), 3.22–3.15 (4 H, m, 2 × CH_2), 2.46–2.40 (4H, m, 2 × CH_2) and 1.89–1.83 (4 H, m, 2 × CH_2); δ_C(50 MHz) 130.1 (2 × =C), 44.2 (2 × CH_2N), 23.4 (2 × CH_2) and 22.6 (2 × CH_2); *m*/*z* (EI) 125 (MH^+, 20%), 124 (13) and 96 (100) (Found: M + H^+, 125.1204. $C_8H_{15}N$ requires *M*, 125.1204).

Et_3N (515 mm^3, 3.69 mmol) was added dropwise to a stirred solution of the amine hydrochloride (408 mg, approx. 2.5 mmol) in CH_2Cl_2 (16.5 cm^3) at 25 °C and the mixture was stirred for 10 minutes. Boc_2O (806 mg, 4.3 mmol) and DMAP (30 mg, 0.25 mmol) were then added, and after 15 h the solution was cooled to 0 °C and treated with ethylenediamine (1 cm^3) then stirred for 0.5 h. Et_2O (60 cm^3) and $KHSO_4$ (1 mol dm^{-3}, 40 cm^3) were added and the organic layer was separated. The organic layer was then washed with 1 M $KHSO_4$ (3 × 40 cm^3), sat. aq. $NaHCO_3$ (40 cm^3), brine (40 cm^3), dried and evaporated under reduced pressure. Purification of the residue by column chromatography (20% Et_2O in light petroleum) gave the *(Z)-N-(tert-butoxycarbonyl)-5-azacyclononene* **43** (370 mg, 67%, as a 1 : 1 mixture of rotamers by ^1H NMR analysis) as a colourless oil; R_f 0.68 (30% Et_2O in light petroleum); ν_{max}/cm^{-1} 3007m, 2972s, 2919s, 2859m, 1697s, 1483m, 1412m, 1364s, 1351s, 1317m, 1227m, 1171s, 1114m, 1026w, 867w and 720w; δ_H(500 MHz) 5.54–5.45 (2 H, m, 2 × =CH), 3.14–3.08 (4 H, m, 2 × NCH_2), 2.24–2.20 (4 H, m, 2 × =CCH_2), 1.90–1.84 (2 H, m, 2 × CH_2 of rotamer A), 1.81–1.76 (2 H, m, 2 × CH_2 of rotamer B) and 1.47 (9 H, s, 3 × Me); δ_C(125 MHz) 156.4 (C=O, quat.), 130.1 and 129.5 (=C), 78.9 ($C(CH_3)_3$, quat.), 52.6 and 51.9 (C-N), 28.6 (Me), 26.9 and 25.9 (=C-*C*), 22.6 and 22.5 (CH_2); *m*/*z* (CI) 226 (MH^+, 12%), 187 (25), 170 (39), 126 (48), 121 (43), 106 (35) and 74 (100) (Found: M + H^+, 226.1807. $C_{13}H_{24}NO_2$ requires *M*, 226.1807).

N-(*tert*-Butoxycarbonyl)-(1*R**,9*S**)-5-aza-10-oxabicyclo[7.1.0]-decane 45

Peracetic acid (36% w/w in dilute AcOH; 0.490 cm^3, 2.62 mmol) was added to a stirred mixture of alkene **43** (370 mg, 1.64 mmol), Na_2CO_3 (696 mg, 6.57 mmol) and NaOAc (7 mg, 0.08 mmol) in CH_2Cl_2 (8.2 cm^3) at 0 °C. The reaction was warmed to 25 °C and stirred for a further 15 h. Et_2O (30 cm^3) was added and the organic layers were washed with water (20 cm^3), saturated aq. $NaHCO_3$ (2 × 20 cm^3), brine (20 cm^3), dried and

evaporated under reduced pressure. Purification of the residue by column chromatography (40% Et_2O in light petroleum) gave the *epoxide* **45** (344 mg, 87%, as a 1 : 1 mixture of rotamers by ^1H NMR analysis) as a colourless, crystalline solid; R_f 0.24 (40% Et_2O in light petroleum); mp 44–45 °C (Et_2O–light petroleum) (Found: C, 64.9; H, 9.75; N, 5.9. $C_{13}H_{23}NO_3$ requires C, 64.7; H, 9.6; N, 5.8%); ν_{max}/cm^{-1} 2973s, 2921s, 2863m, 1686s, 1482s, 1412s, 1391m, 1352s, 1256m, 1231m, 1174s, 1084m and 1064m; δ_H(500 MHz) 3.53–3.41 (2 H, m, CHO), 3.03–2.90 (4 H, m, 2 × CH_2N), 2.13–2.03 (3 H, m, 3 × CH*H*), 1.98–1.79 (3 H, m, 3 × C*H*$_H$), 1.46 (9 H, s, CMe_3) and 1.41–1.29 (2 H, m, 2 × CH_2); δ_C(100 MHz) 156.2 (C=O, quat.), 79.4 (*C*Me_3, quat.), 58.2 and 58.07 (CHO), 54.5 and 53.7 (C-N), 28.5 (Me), 24.9, 24.7, 24.4 and 23.9 (CH_2); *m*/*z* (CI) 242 (MH^+, 9%), 186 (4, [M − Bu^t]$^+$) and 142 (100) (Found: M + H^+, 242.1756. $C_{13}H_{24}NO_3$ requires *M*, 242.1756).

Octahydro-1-*tert*-butoxycarbonylindolizin-8-ol 47

From Table 4, entry 3: Freshly distilled (−)-sparteine **3** (0.70 cm^3, 0.30 mmol) in Et_2O (1 cm^3) was added dropwise over 0.5 h to a stirred solution of Pr^iLi (1.09 mol dm^{-3} in light petroleum; 0.270 cm^3, 0.29 mmol) in Et_2O (1 cm^3) at −98 °C. The reaction mixture was allowed to stir for 1 h at −98 °C before the epoxide **45** (30 mg, 0.12 mmol) in Et_2O (1 cm^3) was added dropwise over 0.5 h. The reaction mixture was stirred for 18 h at this temperature and then H_3PO_4 (0.5 mol dm^{-3} in H_2O; 1 cm^3) was added slowly dropwise. After warming to room temperature the organic layer was removed and the aqueous layer was extracted with Et_2O (3 × 5 cm^3). The combined organic extracts were dried and then evaporated under reduced pressure. Purification of the residue by column chromatography (50% Et_2O in light petroleum gradient to 100% Et_2O) gave the ester **47** (14.8 mg, 49%); R_f 0.56 (70% Et_2O in light petroleum); $[\alpha]_D^{21}$ +48.6 (*c* 0.3 in $CHCl_3$); mp 47–48 °C (diethyl ether–light petroleum); ν_{max}/cm^{-1} 3489br w, 2938s, 2855m, 1724s, 1367m, 1248m, 1159s, 1132m and 1102s; δ_H(200 MHz) 4.08 (1 H, apparent s, CH), 3.14–2.71 (4 H, m, 2 × CH_2), 2.54 (1 H, br s, OH), 2.23–2.06 (2 H, m, CH_2), 1.84–1.63 (6 H, m, 3 × CH_2) and 1.46 (9 H, s, 3 × Me); δ_C(50 MHz) 173.7 (C=O, quat.), 80.8 (*C*–C=O, quat.), 71.3 (*C*$(CH_3)_3$, quat.), 65.9 (CHO), 51.2 (CH_2), 45.1 (CH_2), 31.5 (CH_2), 28.5 (CH_2), 28.1 (3 × Me), 20.5 (CH_2) and 18.8 (CH_2); *m*/*z* (CI) 242 (MH^+, 100%) and 140 (30) (Found: M + H^+, 242.1756. $C_{13}H_{24}NO_3$ requires *M* 242.1756). Data for by-products:

Octahydro-1-*sec*-butylcarbonylindolizin-8-ol 46a. R_f 0.48 (3 : 6 : 1, Et_2O–light petroleum–Et_3N); ν_{max}/cm^{-1} 3401br w, 2938s, 2875m, 1698m, 1462w, 1370w, 1058w and 985w; δ_H(300 MHz) 4.14 (1 H, apparent t, *J* 2.3, CH), 3.17–2.70 (5 H, m, 2 × CH_2 and CH), 2.15–1.19 (11 H, m, 5 × CH_2 and OH), 1.06 (3 H, d, *J* 6.7, Me), 1.02 (3 H, d, *J* 6.8, Me), 0.89 (3 H, t, *J* 7.3, Me) and 0.88 (3 H, t, *J* 7.5, Me); δ_C(50 MHz) 218.8, 218.1 (C=O, quat.), 68.2 (*C*-C=O, quat.), 66.2, 65.9 (CHO), 51.5, 51.3 (CH_2), 45.2, 45.0 (CH_2), 42.3, 42.1 (CH), 29.1, 29.0 (CH_2), 28.9, 28.3 (CH_2), 27.5, 26.6 (CH_2), 21.0, 20.7 (CH_2), 18.4, 18.3 (CH_2), 17.5 (Me), 11.7 and 11.5 (Me).

Octahydro-1-isopropylcarbonylindolizin-8-ol 46b. R_f 0.62 (60% Et_2O in MeOH); ν_{max}/cm^{-1} 3387br w, 2933s, 2890m, 1703s, 1455m, 1380m, 1147m, 1075m, 1005m, 976w and 958w; δ_H(300 MHz) 4.21–4.19 (1 H, m, CH), 3.24–3.15 (1 H, m, CH), 3.11–2.96 (3 H, m, CH_2 and CH), 2.79–2.74 (1 H, m, CH), 2.21–2.11 (1 H, m, CH), 1.93–1.75 (4 H, m, 2 × CH_2), 1.70–1.55 (1 H, m, CH), 1.46–1.32 (2 H, m, CH_2), 1.07 (3 H, d, *J* 6.7, Me) and 1.03 (3 H, d, *J* 6.7, Me); δ_C(50 MHz) 218.0 (C=O, quat.), 77.1 (*C*-C=O, quat.), 65.9 (CHO), 51.3 (CH_2), 45.2 (CH_2), 35.2 (CH), 29.1 (CH_2), 28.7 (CH_2), 20.7 (CH_2 and Me), 20.1 (Me) and 18.1 (CH_2); *m*/*z* (CI) 212 (MH^+, 18%), 126 (62), 72 (96) and 70 (100) (Found: M + H^+, 212.1648. $C_{12}H_{22}NO_2$ requires *M*, 212.1650).

Crystal data for **46b** are available: CCDC 182/1138. Crystal data are available in .cif format from the RSC website, see http://www.rsc.org/suppdata/cc/1999/309/.[7b]

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