Isomerisations of cycloalkene- and bicycloalkene-derived achiral epoxides by enantioselective α-deprotonation

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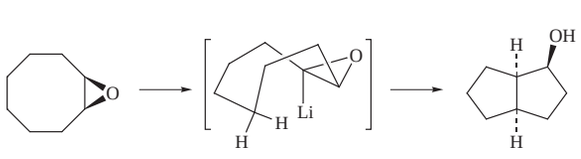
Enantioselective α-deprotonation–rearrangement of *cis*-cyclooctene oxide 1 using organolithiums in the presence of (−)-sparteine 4 or (−)-α-isosparteine 5 gives the (−)-alcohol 2 in good yields and ees. The use of C_2-symmetric bisoxazolines (−)-6a–d as ligands allows access to the (+)-alcohol 2. (−)-α-Isosparteine 5 functions as an efficient asymmetric ligand catalyst in the rearrangement of 1. The α-deprotonation process can be extended to other cycloalkene-derived achiral epoxides 7, 9, 11, 15 and 19. Lithium amide-induced transformations of rigid bicycloalkene-derived epoxides (25, 34 and 42) are described, providing insight into the rearrangement mechanisms which operate following α-lithiation in such systems. The enantioselective α-deprotonation–rearrangement of bicycloalkene-derived epoxides (25, 29 and 42) to ketones (28, 33 and 44 respectively) is described.

Enantioselective desymmetrisation of achiral materials is an attractive and powerful concept in asymmetric synthesis. A number of strategies already demonstrate the viability of this concept and its application in targeted syntheses to provide compounds with high ee.[1] Achiral epoxides represent an important class of substrates for new desymmetrisation methodologies because they are easily prepared with predictable stereochemistry from alkenes. The enantioselective rearrangement of achiral epoxides to allylic alcohols using chiral, nonracemic lithium amides has been well researched, and it has been assumed that these reactions proceed by β-deprotonation/elimination.[2] Enantioselective rearrangements which proceed *via* metallation of the epoxide ring (α-deprotonation) have not, prior to our studies discussed in detail in this paper,[3] been specifically (or deliberately)[2d] examined. Such metallated epoxides undergo a variety of interesting and potentially synthetically useful rearrangements by C–H insertion, either in a transannular manner to give bi- or tri-cyclic alkoxides and/or into adjacent C–H bonds to give enolates (or allylic alkoxides).[4]

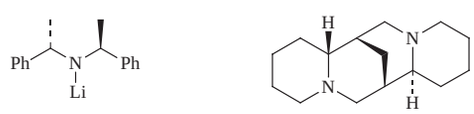
We initially studied the transannular desymmetrisation of medium-sized cycloalkene oxides and used *cis*-cyclooctene oxide **1** as a representative substrate (Scheme 1). Following



1 **1-Li** (−)-**2**

Scheme 1

Whitesell and White's observation of clean rearrangement of epoxide **1** to alcohol **2** using LDA in Et_2O at reflux,[5] we examined the use of a chiral, nonracemic lithium amide [lithium (*S*,*S*)-bis(1-phenylethyl)amide **3**][2] to achieve the rearrangement enantioselectively. It was not obvious that chiral, nonracemic lithium amides would be capable of enantioselective desymmetrisation by α-deprotonation since, unlike β-deprotonation (or α-deprotonation using organolithiums), the process has been demonstrated to be reversible with simple lithium amides.[4] Reversible α-deprotonations occur when the rate of reprotonation from the generated amine competes with the insertion step. For asymmetric synthesis, since enantioselectivity will be determined by kinetically controlled enantiotopic α-proton selection *via* diastereomeric transition states, then reversible deprotonation could compromise ee. For example, in the presence of a nonracemic base, **1-Li** and its enantiomer could undergo C–H insertion (or protonation to return epoxide **1**) at different rates. In the event, reaction of epoxide **1** with lithium amide **3** (2.5 equiv.) in Et_2O at reflux for 2 d led to a chromatographically inseparable mixture (74%) of bicyclic alcohol **2**[6] and cyclooct-2-en-1-ol[7] (90 : 10 by ^{1}H NMR respectively). The ee of the alcohol **2** (10%) was determined on the 2,4-dinitrobenzoate derivative by chiral HPLC. The low enantioselectivity for formation of the (2*S*)-alcohol **2** [assigned by comparison of order of elution on HPLC with dinitrobenzoate samples where the absolute configuration of the predominant enantiomer was known (*vide infra*)], together with cogeneration of cyclooct-2-en-1-ol, led us to consider the combination of an organolithium with a chiral, nonracemic ligand as an alternative method for enantioselective epoxide desymmetrisation.



3 (−)-**4**

Lithium amide **3** and (−)-sparteine **4**

In 1977 Boeckman reported that the epoxides **1** and **7** rearrange cleanly to the bicyclic alcohols **2** and **8** respectively (Schemes 1 and 2), on treatment with Bu^{n}Li (3 equiv.) in Et_2O–hexane (at −78 °C for 3 h followed by warming to room temperature).[8] As Hoppe *et al*. had found that highly enantioselective deprotonation α to oxygen in carbamates is possible using Bu^{s}Li in combination with (−)-sparteine **4** in Et_2O,[9] we initially applied these conditions[9a] to the epoxide **1**, to give the (−)-alcohol **2** in good yield and ee (Table 1, entry 1). The absolute configuration of the major enantiomer of the alcohol **2** obtained in this reaction is shown in Scheme 1 and was established by comparison of the direction of the specific rotation with that previously reported for alcohol **2** of known absolute

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configuration.[10] The predominant sense of asymmetric induction in the reaction of epoxide **1** corresponds to selective removal of the hydrogen at the *R*-configured carbon of the epoxide ring. The enantioselectivity may be explained by considering a sparteine–RLi–epoxide complex, where the C–H bond on the epoxide *R* stereocentre is held closer to the organolithium than the *S* stereocentre, minimising non-bonded interactions between sparteine and the epoxide (Fig. 1). Sampling established that there was no change in the ee of alcohol **2** during the course of this reaction suggesting that the gradual generation of the lithium alkoxide of alcohol **2** does not influence the asymmetric induction (chiral alkoxides can effect enantioselective deprotonations).[11] Importantly, the combination of the diamine with the organolithium did not compromise yield or clean conversion of the epoxide **1** exclusively to the *endo cis*-fused bicyclic alcohol **2**. No cyclooct-2-en-1-ol was observed. Variation in the nature of the organolithium, the solvent and the ligand were then examined with the epoxide **1**.

A secondary organolithium is essential to obtain a good level of ee in this transformation; use of Bu^{n}Li or Bu^{t}Li proceeded to give the alcohol **2** in similar yields to Bu^{s}Li, but with low and no ee respectively (Table 1, entries 2 and 3). The latter observation with Bu^{t}Li parallels observations made by Beak *et al.* in the enantioselective deprotonation of *N*-Boc pyrrolidine[12] and lends support to the argument that a tertiary organolithium is not able to form a complex with (−)-sparteine **4** that can effect enantiotopic proton selection. Pr^{i}Li,[13] which unlike Bu^{s}Li does not contain a stereogenic centre,[14] gave an improved ee (entry 4). Use of the secondary organolithiums in hydrocarbon solvents (pentane, toluene or cumene) gave similar levels of ee to those found using Et_2O, but reduced yields of the alcohol **2**. Quenching the reaction of the epoxide **1** with Bu^{s}Li and (−)-sparteine **4** in Et_2O after 5 h at −78 °C gave a similar yield and ee of alcohol **2** to an otherwise identical reaction which had been allowed to warm to room temperature after 5 h at −78 °C (entry 1). These results imply that the deprotonation is operative at −78 °C. Lowering the reaction temperature to −98 °C further improved ees (entries 5 and 6).

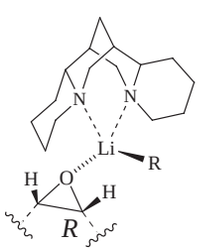
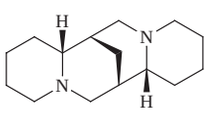


Fig. 1

Although (−)-sparteine **4** is not quite C_2-symmetric, it can be considered as functioning like a C_2-symmetric ligand.[15] For example, interchanging the alkyl group of the organolithium and the epoxide in models of our suggested transition state for epoxide asymmetric α-deprotonation (Fig. 1) still results in the epoxide *R* stereocentre being positioned closest to the lithium–carbon bond. The C_2-symmetric lupine alkaloid (−)-α-isosparteine **5** was investigated by Zschage and Hoppe in 1992 as an alternative to (−)-sparteine **4** as a chiral ligand in the BuLi-mediated deprotonation of an allylic carbamate where, following transmetallation with $Ti(OPr^i)_4$ and reaction with butanal, it induced 16% ee [(−)-sparteine **4** gave 31% ee] in the resultant homoallylic alcohol.[16] More recently, Kang and co-workers have reported (−)-α-isosparteine **5** as a superior ligand



(−)-**5**

(−)-α-Isosparteine **5**

to (−)-sparteine **4** in several asymmetric transformations: [2,3] Wittig rearrangements *via* enantioselective deprotonation using Bu^{s}Li in hexane,[17] as well as in Pd-catalysed allylic alkylations and addition of 2-lithio-1,3-dithiane to aldehydes.[18] In contrast, Beak and co-workers found (−)-α-isosparteine **5** to be a poor ligand for enantioselective deprotonation of *N*-Boc pyrrolidine using Bu^{s}Li in Et_2O [10% yield and 61% ee, compared with 87% yield and 96% ee using (−)-sparteine **4**].[19]

In the present study, reactions of epoxide **1** with Bu^{s}Li and with Pr^{i}Li starting at −78 °C in the presence of (−)-α-isosparteine **5** [prepared by $AlCl_3$-promoted isomerisation of (−)-sparteine **4**[20] and dried as a solution in Et_2O over CaH_2 prior to use[17]] gave improved ees of (−)-alcohol **2** (76% and 81% respectively, Table 1, entries 7 and 8) compared with the

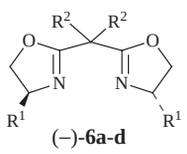
Table 1 Effect of experimental conditions on the yields and enantioselectivities of formation of alcohol **2** from epoxide **1** using Ligand/RLi in Et_2O

Entry	Ligand	RLi	Ligand : RLi : Epoxide **1**	*T*/°C	Yield (%)	Ee (%)[a]
1	**4**	Bu^{s}Li	1.45 : 1.4 : 1	−78	81	−70
2	**4**	Bu^{n}Li	1.45 : 1.4 : 1	−78	74	−31
3	**4**	Bu^{t}Li	1.45 : 1.4 : 1	−78	74	0
4	**4**	Pr^{i}Li	1.45 : 1.4 : 1	−78	75	−78
5	**4**	Bu^{s}Li	1.45 : 1.4 : 1	−98	79	−73
6	**4**	Pr^{i}Li	1.45 : 1.4 : 1	−98	74	−83
7	**5**	Bu^{s}Li	1.45 : 1.4 : 1	−78	77	−76
8	**5**	Pr^{i}Li	1.45 : 1.4 : 1	−78	92	−81
9	**5**	Bu^{s}Li	1.45 : 1.4 : 1	−98	72	−72
10	**5**	Pr^{i}Li	1.45 : 1.4 : 1	−98	55	−77
11	**6a**	Bu^{s}Li	1.45 : 1.4 : 1	−78	28	14
12	**6b**	Bu^{s}Li	1.45 : 1.4 : 1	−78	38	3
13	**6c**	Bu^{s}Li	1.45 : 1.4 : 1	−78	61	55
14	**6d**	Bu^{s}Li	1.45 : 1.4 : 1	−78	66	66
15	**6d**	Pr^{i}Li	1.45 : 1.4 : 1	−78	65	60
16	**4**	Pr^{i}Li	2.50 : 2.4 : 1	−98	86	−84
17	**4**	Bu^{s}Li	0.50 : 1.4 : 1	−98	58 (73)[b]	−69
18	**4**	Bu^{s}Li	0.50 : 1.4 : 1	−98	53 (76)[b]	−55
19	**4**	Pr^{i}Li	0.20 : 1.4 : 1	−98	62	−73
20	**4**	Pr^{i}Li	0.01 : 1.4 : 1	−98	63	−31
21	**5**	Pr^{i}Li	0.50 : 1.4 : 1	−98	44	−84
22	**5**	Pr^{i}Li	0.20 : 1.4 : 1	−98	86	−84
23	**5**	Pr^{i}Li	0.10 : 1.4 : 1	−98	78	−80
24	**5**	Pr^{i}Li	0.01 : 1.4 : 1	−98	71	−69

[a] Determined by chiral HPLC, negative values correspond to enrichment in (−)-alcohol **2**. [b] Yield in parentheses based on recovered epoxide **1**.

analogous reactions using (−)-sparteine **4** (70% ee and 78% ee respectively, entries 1 and 4). On lowering the reaction temperature to −98 °C, epoxide **1** with (−)-α-isosparteine **5** gave slightly lower enantioselectivity (compare entries 9 and 10 with 7 and 8), which may be due to the partially heterogeneous nature of these particular reaction mixtures at −98 °C.

As (+)-sparteine[21] is not as readily available as (−)-sparteine, most sparteine-based methods for asymmetric induction do not allow easy conversion of an achiral substrate into either enantiomer of a chiral product.[22] Also, modification/simplification of the sparteine skeleton to improve ees (if required), and/or to attempt to evaluate the factors which influence enantioselectivity, is a major challenge.[19] C_2-Symmetric bisoxazolines **6** have been widely used as ligands in asymmetric synthesis and their substituents R^1 and R^2 are easily varied depending on the precursor amino acid/alcohol and substituted malonic acid used.[23] Denmark and co-workers recently reported the use of bisoxazolines **6a**–**c** [as well as (−)-sparteine **4**] as effective ligands to



(−)-**6a-d**

6a (R^1 = Bu^t, R^2 = Et), **6b** (R^1 = Bu^t, R^2 = Bu^i)

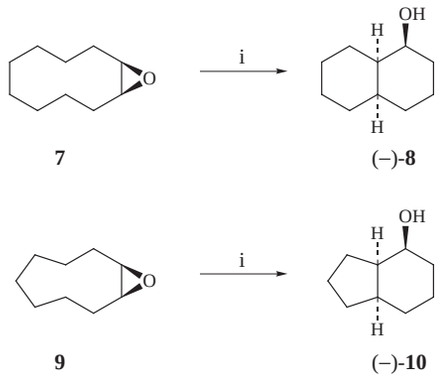
6c (R^1 = Pr^i, R^2 = Et), **6d** (R^1 = Pr^i, R^2 = Bu^i)

(−)-Bisoxazolines **6a-d**

induce selectivity between enantiotopic faces of imines in the addition of organolithiums.[24] Denmark's work led us to examine whether such ligands can induce selectivity between enantiotopic hydrogen atoms in the α-deprotonation of epoxides such as **1** using organolithiums (Table 1).

Although the diethyl- and diisobutyl-substituted *tert*-leucine-derived ligands **6a** (R^1 = Bu^t, R^2 = Et) and **6b** (R^1 = Bu^t, R^2 = Bu^i) gave some of the highest ees in Denmark's study,[24] they proved unsatisfactory with Bu^{s}Li and epoxide **1**, giving (+)-alcohol **2** in low ees (Table 1, entries 11 and 12). These results may indicate that the *tert*-butyl groups of ligands **6a**,**b** impede efficient coordination of the epoxide **1** [unlike (planar) imines] in an organolithium-ligand complex. However, use of the analogous valine-derived ligands **6c** (R^1 = Pr^i, R^2 = Et) and **6d** (R^1 = Pr^i, R^2 = Bu^i) with Bu^{s}Li and epoxide **1** gave (+)-alcohol **2** in 55% ee and 66% ee respectively (entries 13 and 14). The improved ee observed with Bu^{s}Li when using ligand **6d** compared with **6c** might be due to a greater preference for the reaction to proceed *via* aggregates in which the epoxide **1** is oriented so as to place its methylene groups away from the sterically more demanding diisobutyl-substituted bisoxazoline bridge of ligand **6d**. In contrast to our results, in the addition of organolithiums to imines[24] bisoxazoline ligands **6a**–**c** gave the same sense of asymmetric induction as (−)-sparteine **4**. The combination of ligand **6d** with Pr^{i}Li instead of Bu^{s}Li gave (+)-alcohol **2** in slightly lower ee (60%, entry 15); this is in contrast to our studies using (−)-sparteine **4** (entries 1 and 4).

Within the scope of our initial study with epoxide **1**, the best conditions for formation of alcohol **2** in terms of yield and ee were found to be Pr^{i}Li (2.4 equiv.) and (−)-sparteine **4** (2.5 equiv.) at −98 °C (entry 16). In contrast to *cis*-cyclooctene oxide **1**, for the enantioselective rearrangement of *cis*-cyclodecene oxide **7**[25] (prepared from *cis*-cyclodecene) to (−)-alcohol **8**[26] (of known absolute configuration)[27] using Bu^{s}Li starting at −78 °C, (−)-sparteine **4** was found to be a more effective ligand than (−)-α-isosparteine **5** (71% yield, 51% ee, and 83% yield, 38% ee respectively; ees were determined by HPLC on the 2,4-dinitrobenzoate derivative). Using Pr^{i}Li (2.4 equiv.) and (−)-sparteine **4** (2.5 equiv.) at −98 °C gave



7 (−)-**8**

9 (−)-**10**

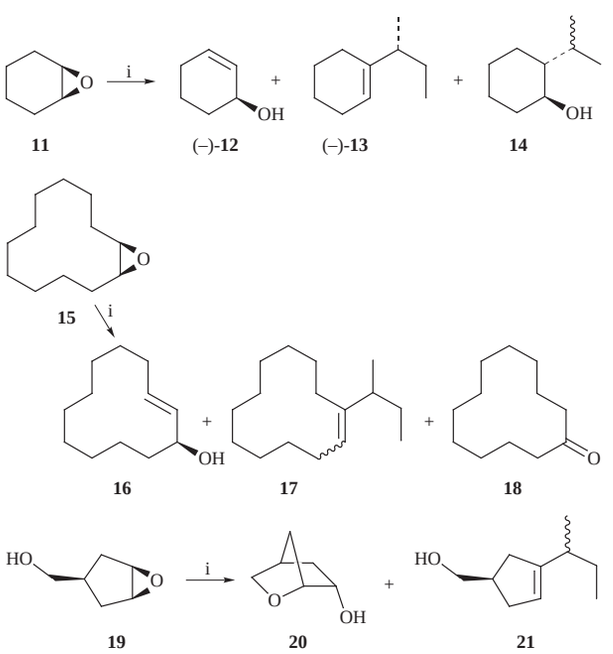
Scheme 2 *Reagents and conditions:* i, Pr^{i}Li (2.4 equiv.), (−)-sparteine **4** (2.5 equiv.), Et_2O, −98 °C (5 h) to 25 °C (15 h)

(−)-alcohol **8** in 97% yield and 77% ee (Scheme 2). These latter conditions were also effective for the enantioselective desymmetrisation of *cis*-cyclononene oxide **9** (prepared in 4 steps from *cis*-cyclooctene)[28] to give the (−)-alcohol **10** in 77% yield and 83% ee (determined by HPLC on the 2,4-dinitrobenzoate) (Scheme 2). The base-induced rearrangement of cyclononene oxide **9** had not been studied before and the selectivity for generating a single bicyclic isomer is noteworthy. However, reaction of 6,7,8,9,10,11-hexahydro-5*H*-benzocyclononene oxide with LDA is known to give 8,9-benzobicyclo[4.3.0]nonen-2-ol,[29] this is a similar outcome to that obtained with epoxide **9** in that the hydroxy group is positioned on the six- (rather than the five-) membered ring. Inspection of molecular models of *cis*-cyclononene oxide **9** indicates that the transannular C–H bond which undergoes insertion can position itself closer to the intermediate carbon lithium bond than the C–H bond from which insertion would lead to bicyclo[4.3.0]nonan-9-ol. Oxidation of (−)-alcohol **10** using PCC in the presence of SiO_2[30] gave a ketone (93%) with ^{13}C NMR (and ^{1}H NMR) spectral data consistent with that published for *cis*-bicyclo[4.3.0]nonan-2-one.[31] Moreover, the ^{13}C NMR (and ^{1}H NMR) spectral data for (−)-alcohol **10** match that published for the product obtained from exhaustive reduction of bicyclo[4.3.0]non-1(6)-en-2-one,[31] which provides evidence (assuming reduction from the *exo* face of the intermediate *cis*-bicyclo[4.3.0]nonan-2-one) that alcohol **10** is *endo* and *cis*-fused, as expected.[4] The absolute stereochemistry of the predominant enantiomer of (−)-alcohol **10** was assigned by analogy with alcohols **2** and **8**, and was consistent with the negative Cotton effect observed in the CD spectrum for *cis*-bicyclo[4.3.0]nonan-2-one obtained from (−)-alcohol **10**.[10,27]

We also studied the possibility of achieving transannular desymmetrisation with asymmetric catalysis. In the absence of (−)-sparteine **4**, no reaction was observed between epoxide **1** and either Bu^{s}Li or Pr^{i}Li (at −98 °C for 5 h). At −78 °C for 5 h both Bu^{s}Li and Pr^{i}Li gave some alcohol **2** {38% [~5% after 10 min (following complete addition of the epoxide **1**)] and 11% respectively}; we had earlier established that the reaction between epoxide **1** and Bu^{s}Li in the presence of (−)-sparteine **4** was essentially complete after 5 h at −78 °C [75%, 36% conversion to (−)-alcohol **2** was observed after 10 min (following complete addition of the epoxide **1**)]. For the reaction of epoxide **1** with Bu^{s}Li starting at −98 °C it was possible to reduce the quantity of (−)-sparteine **4** and still achieve asymmetric induction, although ees of, and conversions to, (−)-alcohol **2** were reduced in these cases (Table 1, entries 17, 18). The combination of 0.2 equiv. of (−)-sparteine **4** with Pr^{i}Li starting at −98 °C gave (−)-alcohol **2** in good ee (62% yield, 73% ee, entry 19) and even using only 0.01 equiv. of (−)-sparteine **4** in the reaction of epoxide **1** with Pr^{i}Li at −98 °C gave moderately enantioenriched (−)-alcohol **2** (31% ee, entry 20). However, the gradual erosion in ee on reducing the proportion of the chiral ligand with either Bu^{s}Li or Pr^{i}Li suggests that

(−)-sparteine **4** does not function efficiently as a catalyst at −98 °C. By comparison, (−)-α-isosparteine **5** is much more effective as a catalyst for enantioselective deprotonation of epoxide **1** (Table 1, entries 21 to 24; the reaction mixtures were homogeneous in these cases). Beak has speculated that the reduced reactivity of (−)-α-isosparteine **5** compared with (−)-sparteine **4** in the enantioselective deprotonation of *N*-Boc pyrrolidine may be due to the greater steric hindrance of the Bu^{s}Li-ligand complex in the case of (−)-α-isosparteine **5** (due to both peripheral rings extending towards the organolithium).[19] In the present case with epoxide **1**, the rate of deprotonation does not seem to be significantly altered when using (−)-α-isosparteine **5** instead of (−)-sparteine **4** (Table 1, entries 7–10), and indeed additional steric hindrance in the complex formed between (−)-α-isosparteine **5** and the lithium alkoxide of alcohol **2** following deprotonation–rearrangement may aid dissociation of the ligand and thus promote catalysis. The observation of significant asymmetric induction when using as little as 1 mol% (−)-α-isosparteine **5** is encouraging for the further development of catalytic asymmetric processes using nitrogen donor ligands with organolithiums.

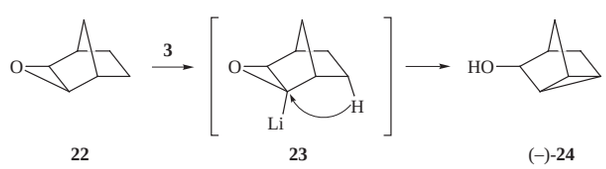
As examples of reactions of Bu^{s}Li/(−)-sparteine **4** with cycloalkene oxides which are outside the medium-ring classification, we have briefly examined the reactions of cyclohexene oxide **11**, *cis*-cyclododecene oxide **15** and epoxyalcohol **19** (Scheme 3). Kissel and Rickborn observed that cyclohexene



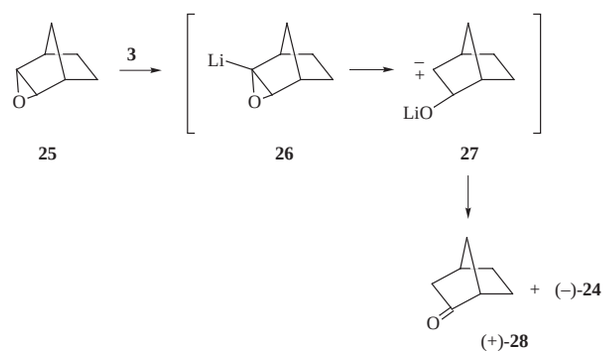
Scheme 3 *Reagents and conditions:* i, Bu^{s}Li, (−)-sparteine **4**, Et_2O, −78 °C to 25 °C

oxide **11** was converted to a mixture of cyclohex-2-en-1-ol **12** and cyclohexanone (89:11 respectively) on treatment with Bu^{n}Li in Et_2O–hexanes at reflux after 4 h,[32] whereas Boeckman reported that cyclohexene oxide **11** reacts to give a mixture of cyclohex-2-en-1-ol **12** and cyclohexanone and recovered epoxide **11** (29:56:15 respectively) on treatment with Bu^{n}Li (3 equiv.) in Et_2O–hexane at −78 °C for 3 h followed by warming to room temperature.[8] In contrast, we found that reaction of cyclohexene oxide **11** with Bu^{s}Li/(−)-sparteine **4** (1.5 equiv.) in Et_2O at −78 °C gave mainly (−)-(*R*)-1-(butan-2-yl)cyclohexene **13**[33] (33%, ee not known, absolute configuration known),[34] and (−)-(*S*)-cyclohex-2-en-1-ol **12**[35] [24%, 20% ee (determined by HPLC on the 2,4-dinitrobenzoate)] along with lesser amounts of the addition product **14** (13%, 50:50 mixture of diastereomers). The formation of (−)-alkene **13**, which represents an alkene synthesis by organolithium reductive alkylation of an epoxide, finds precedence in early work by Crandall and Lin[36] and the process has recently been investigated in more detail by Mioskowski *et al.*[37] If (−)-(*S*)-cyclohex-2-en-1-ol **12** [as well as (−)-alkene **13**] derives from α-lithiated cyclohexene oxide, then the reaction displays the same (but reduced) preference for removal of the hydrogen at the *R*-configured carbon of the epoxide ring as observed earlier with the medium-sized cycloalkene oxides. *cis*-Cyclododecene oxide **15** has been isomerised to *trans*-cyclododec-2-en-1-ol **16** (62%) using Bu^{n}Li in Et_2O[38] and Boeckman also reported that cyclododecene oxide reacts to give cyclododec-2-en-1-ol along with cyclododecanone **18** and recovered epoxide (80:10:10 respectively).[8] Reaction of *cis*-cyclododecene oxide **15** (prepared in two steps from *cis*,*trans*,*trans*-1,5,9-cyclododecatriene)[39] with Bu^{s}Li/(−)-sparteine **4** (1.5 equiv.) in Et_2O at −78 °C gave mainly (−)-*trans*-cyclododec-2-en-1-ol **16**[7] [38%, 58% ee (determined by HPLC on the 2,4-dinitrobenzoate), absolute configuration of predominant enantiomer not known], the alkene **17** (24%, *E*:*Z* = 75:25) and cyclododecanone **18**[40] (12%). The geometry of the major and minor isomers of alkene **17** were assigned by comparison of the ^{1}H and ^{13}C NMR data with those for (*E*)- and (*Z*)-5-(butan-2-yl)dec-5-ene {for the latter isomers δ_H 2.02–1.89 [(*E*)- =CC*H*Me] and 2.54 [(*Z*)- =CC*H*Me] were particularly useful in the assignment}.[37] Reaction of epoxyalcohol **19** (prepared in five steps from dimethyl malonate and *cis*-1,4-dichlorobut-2-ene)[41] with Bu^{s}Li/(−)-sparteine **4** (2 equiv.) in Et_2O at −78 °C gave the (−)-alcohol **20** [21%, 23% ee (determined by HPLC on the 2,4-dinitrobenzoate), absolute configuration of predominant enantiomer not known], known as the racemate,[42] and the alkene **21** (20%, ~50:50 mixture of diastereomers as judged by ^{13}C NMR analysis). The formation of alcohol **20** is unusual: to the best of our knowledge the insertion of a lithium alkoxide into a lithiated epoxide has not been reported.

Before examining asymmetric rearrangements of bicycloalkene oxides we made a direct comparison of the effect of epoxide stereochemistry on product outcome, by individual treatment of *exo*-norbornene oxide **22** and *endo*-norbornene oxide **25** (the latter prepared in 4 steps from norbornene)[43] with LDA (2.5 equiv.) in Et_2O at 0 °C for 16 h to give nortricyclanol **24**[44] [90% (paralleling an original observation by Crandall),[44a] no norcamphor **28** observed] and a mixture of norcamphor **28**[45] (55%) and nortricyclanol **24** (14%, **28**:**24** = 80:20 by ^{1}H NMR analysis of the crude product mixture) respectively (Schemes 4 and 5). For lithiated *exo*-norbornene oxide **23** transannular C–H insertion may proceed readily as hydride migration is able to assist the breaking of the C–O bond (by



Scheme 4



Scheme 5

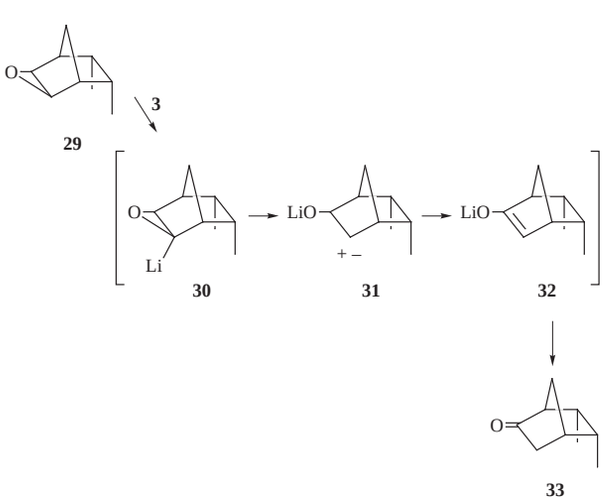
attack at the C–O σ* orbital). In contrast, lithiated *endo*-norbornene oxide **26** could proceed to carbene **27** which then partitions between insertion into the adjacent LiOC–H bond to give the enolate of norcamphor **28** (mainly) and transannular C–H insertion to give nortricyclanol **24**.

Because epoxides such as **22** cannot suffer from competing elimination to generate allylic alcohols we first examined the asymmetric rearrangement using nonracemic lithium amides. Treatment of *exo*-norbornene oxide **22** in Et_2O from −78 °C to 25 °C with bases which can effect the rearrangement of epoxides to allylic alcohols in high ees {lithium (*S*)-2-[(pyrrolidin-1-yl)methyl]pyrrolidide (1.8 equiv.) or dilithiated (1*R*,2*S*)-norephedrine (3 equiv.)}[2] gave nortricyclanol **24** in poor yields (22% and 29% respectively) and low ees (1% and 8% respectively by HPLC on the 2,4-dinitrobenzoate). However, using lithium (*S*,*S*)-bis(1-phenylethyl)amide **3** (1.8 equiv.) in Et_2O from 0 °C to 25 °C gave the (−)-alcohol **24** in 73% yield and 49% ee (Scheme 4). Commencing the reaction with **3** in Et_2O at −78 °C, rather than at 0 °C, gave essentially the same result (65% yield, 47% ee), suggesting that the reaction does not operate below 0 °C. The use of other solvents with **22** was less satisfactory (benzene, 0 °C to 25 °C, 76% yield, 31% ee; pentane, −78 °C to 25 °C, 64% yield, 25% ee). The presence of lithium halides, which have been shown to improve enantioselectivity in other lithium amide reactions,[46] did not alter enantioselectivity in the present case (**3**/LiCl, Et_2O, −78 °C to 25 °C, 68% yield, 45% ee; **3**/LiBr, Et_2O, −78 °C to 25 °C, 59% yield, 46% ee). Evaluation of Bu^{s}Li (1.4 equiv.)/(−)-sparteine **4** (1.45 equiv.) at 0 °C indicated that it is another reagent combination for the desymmetrisation of *exo*-norbornene oxide **22** (16% yield, 34% ee). Improved yields and ees were found when reducing the temperature of the reaction from 0 °C to −78 °C in Et_2O (Bu^{s}Li, 43% yield, 49% ee; Pr^{i}Li, 63% yield, 46% ee); although using Bu^{s}Li in benzene was less satisfactory in terms of ee (0 °C to 25 °C, 67% yield, 24% ee), yields were improved using Bu^{s}Li in pentane without degradation of ee (73% yield, 52% ee). The absolute configuration of the major enantiomer of the alcohol **24** obtained with either lithium (*S*,*S*)-bis(1-phenylethyl)amide **3** or RLi/(−)-sparteine **4** was the same, as shown in Scheme 4, and was established by comparison of the direction of the specific rotation with that previously reported for alcohol **24** of known absolute configuration.[47] The sense of asymmetric induction with both base **3** and RLi/(−)-sparteine **4** parallels that observed in our medium-ring study (*vide supra*).

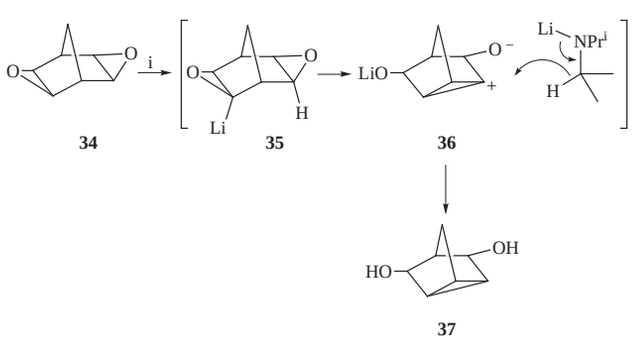
Although we had established that the asymmetric rearrangement of *exo*-norbornene oxide **22** is possible using chiral lithium amides, it was not clear that such an initial enantiodiscrimination process would lead to enantio-enriched ketones. First, rearrangement of a lithiated epoxide to a ketone (*e.g.* **29** to **33**, Scheme 6)[48] is likely to be slower than in the examined case of transannular C–H insertion (compare Schemes 4 and 6), giving more time for reprotonation. In the presence of a non-racemic base, a lithiated epoxide **30** and its enantiomer could undergo rearrangement to an enolate **32** (or protonation to return to the epoxide **29**) at different rates, potentially compromising the initial, kinetically controlled, enantioselective deprotonation. Second, even if a single lithiated epoxide enantiomer **30** was formed it might rearrange to partially or fully racemised enolate **32** if enolate formation occurs competitively by two mechanisms: α-ring opening and insertion of the carbene **31** into the LiOC–H bond (shown in Scheme 6) and electrocyclic β-ring opening (there is experimental evidence in support of both mechanisms).[4,49] In the event, treatment of epoxide **29** (prepared in five steps from the Diels–Alder cycloadduct of cyclopentadiene and maleic anhydride)[48] with base **3** (1.85 equiv.) in Et_2O at 0 °C for 24 h gave (−)-ketone **33** [58%, 35% ee by HPLC after reduction (L-Selectride®)[50] and 3,5-dinitrobenzoate derivatisation of the resulting, known[51] *endo*-alcohol]. Reaction in a variety of solvents at 40 °C was less satisfactory [Et_2O: 87%, 18% ee; pentane: 74%, 6% ee; THF: 62%, 2% ee; THF/LiCl (2 equiv.): 85%, 0% ee].

Reaction of *endo*-norbornene oxide **25** with base **3** gave (+)-norcamphor **28**[45] [40%, 32% ee by chiral HPLC after reduction (L-Selectride®)[50] and 3,5-dinitrobenzoate derivatisation of the resulting *endo*-norborneol[50,52]] along with (−)-nortricyclanol **24**[48] {20%, 38% ee [**28**:**24** = 80:20 by ^{1}H NMR analysis of the crude product mixture (the same ratio observed using LDA, *vide supra*)], Scheme 5}. The absolute configuration of the major enantiomer of the norcamphor **28** obtained in this reaction is as shown in Scheme 5, and was established by comparison of the direction of the specific rotation with that previously reported for norcamphor **28** of known absolute configuration.[53] Assuming that (+)-norcamphor **28** and (−)-nortricyclanol **24** derive from a common enantio-enriched lithiated epoxide **26** (Scheme 5), then this result has important mechanistic consequences because it provides evidence that α-ring opening occurs *en route* to the enolate of norcamphor (however *vide infra*). The lower ee observed for (+)-norcamphor **28** compared with (−)-nortricyclanol **24** suggests minor competing electrocyclic β-ring opening and/or [probably more likely (*vide infra*)] that base **3** is effecting different partitioning of lithiated epoxide **26** and its enantiomer (and/or carbene **27** and its enantiomer) to norcamphor **28** and nortricyclanol **24**. The selectivity for removal of the hydrogen at the *R*-configured carbon of the epoxide ring of *endo*-norbornene oxide **25** with base **3** is the same as that observed with *exo*-norbornene oxide **22**. The absolute configuration of the major enantiomer of ketone **33** obtained from epoxide **29** is tentatively assigned by analogy and is shown in Scheme 6. CD spectra obtained for (−)-ketone **33** and (+)-norcamphor **28** are consistent with this assignment.

We also examined the reaction of *exo*,*exo*-norbornadiene diepoxide **34** (prepared from norbornadiene using dimethyldioxirane)[54] with LDA (2.5 equiv.) at 0 °C for 16 h which gave *meso*-nortricyclandiol **37**[55] (56%, Scheme 7). In this case, as



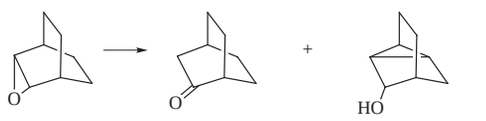
Scheme 6



Scheme 7 *Reagents and conditions:* i, LDA (2.5 equiv.), Et_2O–hexane, 0 °C to 25 °C, 16 h

with *exo*-norbornene oxide **22**, hydride migration may assist transannular C–H insertion from the presumed first-formed lithiated intermediate **35**. However, rather than leading to a highly strained cyclopropyl containing spiro-epoxide, subsequent (or nearly concerted) rupture of the remaining epoxide ring could generate a cyclopropyl cation **36**, which then undergoes reduction by LDA.

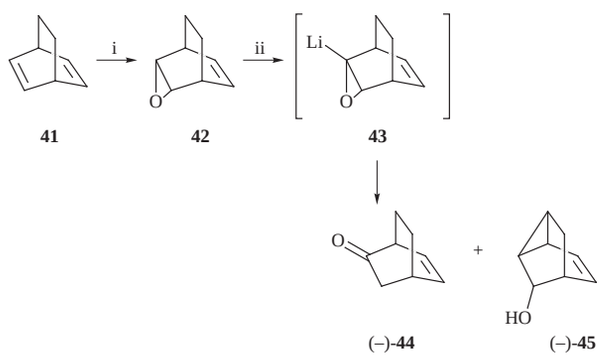
Crandall and co-workers reported the lithium amide induced rearrangement of bicyclo[2.2.2]octene oxide **38** to give mainly bicyclo[2.2.2]octanone **39** (Scheme 8).[48] This result indicates



38 **39** **40** [**39** : **40** = 95 : 5]

Scheme 8[48] *Reagents and conditions:* i, LDA (2.5 equiv.), Et_2O–hexane, reflux, 20 h

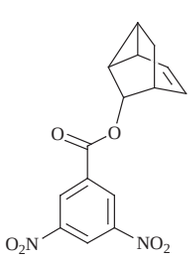
that, aside from epoxide stereochemistry, the propensity for transannular C–H insertion is very sensitive to the distance between the lithiated epoxide and transannular C–H bonds. By analogy with bicyclo[2.2.2]octene oxide **38**, structurally related and known *endo*-mono-epoxide **42**[56] was anticipated to rearrange to ketone **44** (Scheme 9), which has been used in the



41 **42** **43** (–)-**44** (–)-**45**

Scheme 9 *Reagents:* i, $MeCO_3H$ (1.1 equiv.), Na_2CO_3, CH_2Cl_2; ii, lithium amide, Et_2O–hexane

synthesis of breynolide (the aglycon derivative of the potent orally active hypocholesterolemic glycoside breynin A),[57] loganin,[58] and the naturally occurring juvenile hormone juvabione.[59] The *endo*-mono-epoxide **42** was prepared (76%) from bicyclo[2.2.2]octadiene **41**[60] using peracetic acid. The predominant stereochemistry [*cis*:*trans* (epoxide to alkene), 94:6] was initially assigned from the original literature,[56] together with the fact that di-epoxidation of bicyclo[2.2.2]octadiene is known to give a single di-epoxide[61] and NOE studies of *endo*-mono-epoxide **42** (see Experimental section); the stereochemistry was confirmed later by X-ray crystallographic analysis of 3,5-dinitrobenzoate **46** (*vide infra*)]. The sense and magnitude



46

3,5-Dinitrobenzoate **46**

of the diastereoselectivity in this epoxidation is not readily explained, although it may be an example of alkene-directed epoxidation.[62] In contrast to bicyclo[2.2.2]octene oxide **38**,

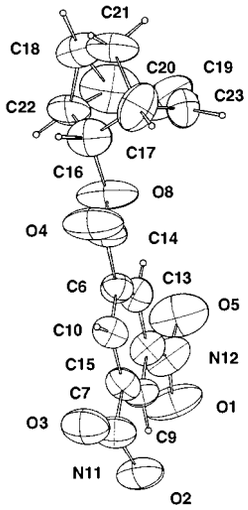
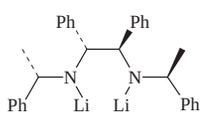


Fig. 2 Molecular structure of 3,5-dinitrobenzoate **46** (thermal ellipsoids are at the 50% level)

reaction of mono-epoxide **42** with LDA (2.5 equiv.) in Et_2O at reflux for 16 h gave a mixture of ketone **44**[63] (29%) and (mainly) alcohol **45**[64] [55%, **44**:**45** = 41:59 by ^1H NMR analysis of the crude product mixture (33:67 at −10 °C), Scheme 9]. Thermolysis of alcohol **45** resulted in a retro Diels–Alder reaction to give the known 1-(cyclohexa-2,4-dienyl)acetaldehyde (32%).[65] The structure of alcohol **45** was unambiguously confirmed by X-ray crystallographic analysis of the derived 3,5-dinitrobenzoate **46** (Fig. 2). In the rearrangement of mono-epoxide **42** the double bond in mono-epoxide **42** may promote C–H insertion by π–C–H σ* orbital overlap in the lithiated epoxide **43** (and/or at the carbene stage); bicyclo[2.2.2]octene oxide **38**, which lacks such a promoting effect, proceeds entirely to a carbene which then partitions between (mainly) insertion into the adjacent LiOC–H bond resulting in the enolate of ketone **39**, and transannular C–H insertion (exclusively *cis*[4a] to OLi) to give alcohol **40** (Scheme 8).

Reaction of mono-epoxide **42** with base **3** in Et_2O at 0 °C for 16 h reproducibly gave a mixture of mainly (−)-ketone **44** [40%, 19% optical purity (*op*), major enantiomer shown in Scheme 9][58] along with (−)-alcohol **45** (30%, 16% ee, **44**:**45** = 57:43, 66:34 at reflux). The absolute stereochemistry of the predominant enantiomer of alcohol **45** formed in this reaction was tentatively assigned as shown in Scheme 9 by comparison of CD spectra of (−)-ketone **44** and tricyclo[3.2.1.$0^{2,7}$]oct-3-en-6-one,[66] the latter being obtained (66%) by oxidation of alcohol **45** using PCC in the presence of SiO_2.[30] For the case of mono-epoxide **42**, if one again assumes that α-ring-opening operates, then the major ketone enantiomer (−)-**44** formally arises from the opposite sense of asymmetric induction found with base **3** and *endo*-norbornene oxide **25**. No reaction was observed between mono-epoxide **42** and chiral, nonracemic base **47**[67] in Et_2O at 0 °C for 16 h. However, reaction at 20 °C for 8 h gave a mixture of mainly ketone (+)-**44** (50%, 12% *op*) along with alcohol (−)-**45** (15%, 20% ee, **44**:**45** = 73:27). Although bases **3** and **47** both provide ketone **44** as the major product, we had earlier observed that ketone **44** was the minor product when LDA was used as the base in Et_2O. The nature of the base therefore has a significant effect in determining the ratio of ketone **44** to alcohol **45**. The bases **3** and **47** either retard



47

Lithium amide **47**

transannular insertion or accelerate enolate formation from lithiated epoxide **43** and/or the derived carbene (compared with LDA). The results also indicate that bases **3** and **47** generate (in low ees) opposite enantiomers of ketone **44** but the same enantiomer of alcohol **45**. Therefore, bases **3** and **47** effect different partitioning of lithiated epoxide **43** and its enantiomer (and/or the corresponding carbene and its enantiomer) to ketone **44** and alcohol **45**.

In summary, the reaction of cyclooctene oxide **1** (as a representative medium-sized cycloalkene oxide) by enantioselective α-deprotonation–rearrangement to give the bicyclic alcohol **2** has been achieved in up to 86% yield and 84% ee using Pr^iLi and (−)-sparteine **4**. Easily modified bisoxazoline ligands **6** have been shown to induce enantioselective deprotonation, allowing straightforward access to either enantiomer of bicyclic alcohol **2**. Catalytic enantioselective α-deprotonation was best achieved using (−)-α-isosparteine **5** (0.2 equiv.), to give the bicyclic alcohol **2** in 86% yield and 84% ee (even 0.01 equiv. of **5** gave **2** in 71% yield and 69% ee). An unusual intramolecular insertion of a lithium alkoxide into a lithiated epoxide has been observed with alcohol **19**.

In the LDA-induced transformations of bicycloalkene-derived epoxides (a) the first direct comparison of the effects of epoxide stereochemistry have been examined: in the norbornyl system the results are consistent with concerted transannular rearrangement under stereoelectronic control for *exo*-norbornene oxide **22**, and rearrangement first to a carbene for *endo*-norbornene oxide **25**; (b) with *exo*,*exo*-norbornadiene diepoxide **34** a novel rearrangement–concomitant reduction process has been observed; and (c) the presence of a double bond in bicyclo[2.2.2]octyl systems such as **42** results in transannular C–H insertion as the dominant reaction pathway. Asymmetric access to ketones (**28**, **33** and **44**) in modest ees has been achieved using chiral, nonracemic lithium amides **3** and **47**. Variation of the lithium amide in the reaction of monoepoxide **42** has a significant influence on the ratio of products obtained from the putative intermediate lithiated epoxide **43**.

Experimental

General details

All reactions requiring anhydrous conditions were conducted in flame-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, and amines 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). Column chromatography was carried out on Kieselgel 60 (40–63 μm). Light petroleum refers to the fraction with bp 40–60 °C. $[a]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}. CD spectra were measured with a JASCO J600 Spectropolarimeter; the dissymmetry factor *g* (ratio of circular dichroic to isotropic absorbance at the same wavelength) is listed for samples where the concentration was difficult to measure. IR spectra were recorded as thin films unless stated otherwise. Peak intensities are specified as strong (s), medium (m) or weak (w). ^1H 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 are given in min.

Typical procedure (A) for organolithium/(−)-sparteine 4 induced enantioselective rearrangement of achiral epoxides

(−)-*endo*-*cis*-Bicyclo[3.3.0]octan-2-ol 2. Freshly distilled (−)-sparteine **4** (1.13 cm^3, 4.9 mmol) was added dropwise over 0.5 h to a stirred solution of Pr^iLi[13] (1.2 mol dm^{-3} in light petroleum; 4.0 cm^3, 4.8 mmol) in Et_2O (8 cm^3) at −98 °C. The reaction mixture was allowed to stir for 1 h at −98 °C before cyclooctene oxide **1** (Aldrich, 252 mg, 2.0 mmol) in Et_2O (2 cm^3) was added dropwise over 0.5 h. The reaction mixture was stirred for 5 h at this temperature and then warmed slowly to ambient temperature overnight. The reaction mixture was then cooled to 0 °C before HCl (2 mol dm^{-3} in water; 10 cm^3) was added dropwise. The organic layer was washed with saturated aq. $NaHCO_3$ (2 × 10 cm^3), brine (10 cm^3), dried ($MgSO_4$) and then evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 30% Et_2O in light petroleum) to give a colourless oil, the *alcohol* **2**[6] (217 mg, 86%); R_f 0.43 (50% Et_2O in light petroleum); $[a]_D^{21}$ −19.0 (*c* 1.0 in $CHCl_3$) {lit. for 2*S* isomer,[10] $[a]_D^{25}$ −104 (*c* 4.4 in $CHCl_3$); lit. for 2*S* isomer,[68] $[a]_D^{25}$ −18 (*c* 3.980 in $CDCl_3$); lit. for 2*R* isomer,[69] $[a]_{589}$ +29.9 (*c* 1.094 in EtOH)}; δ_H(400 MHz) 4.15 (1 H, m, C*H*OH), 2.45–2.35 (2 H, m, 2 × CH) and 1.80–1.05 (11 H, m, 5 × CH_2 and OH). The ee of the 2,4-dinitrobenzoate derivative was determined to be 84% by HPLC (50 : 50 EtOH–hexane, 1 cm^3 min^{-1}), $t_R$mn, 6.8; $t_R$mj, 13.2.

(−)-*N*,*N*′-Bis[(1*S*)-1-(hydroxymethyl)-2-methylpropyl)]-2,2-bis(2-methylpropyl)propane-1,3-diamide

2,2-Bis(2-methylpropyl)propanedioyl dichloride[23] (2.9 g, 11.4 mmol) in CH_2Cl_2 (5 cm^3) was added to a stirred solution of L-valinol[70] (2.48 g, 24.0 mmol) and Et_3N (8.0 cm^3, 57 mmol) in CH_2Cl_2 (25 cm^3) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and then stirring was maintained for 4 h. The reaction mixture was then diluted with CH_2Cl_2 (10 cm^3) and poured into saturated aq. NH_4Cl (50 cm^3). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic layers were successively washed with HCl (1 mol dm^{-3}; 10 cm^3), saturated aq. $NaHCO_3$ (10 cm^3) and brine (10 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the solid white residue by recrystallisation gave white needles, the title *diamide* (3.68 g, 83%); mp 134–136 °C (from CH_2Cl_2–acetone); $[a]_D^{21}$ −43.3 (*c* 1.0 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3357s, 3219s, 2961s, 2876s, 2678m, 2497m, 1659s, 1529s, 1389m, 1170m, 1053s and 1038s; δ_H(300 MHz) 7.88 (2 H, br d, *J* 6.1, 2 × NH), 3.76–3.71 (6 H, m, 2 × CH_2O, 2 × CHN), 3.21 (2 H, br s, 2 × OH), 2.01–1.94 (2 H, m, 2 × CH), 1.82 (4 H, d, *J* 6.6, 2 × CH_2), 1.69–1.60 (2 H, m, 2 × CH), 1.00 (6 H, d, *J* 6.8, 2 × Me), 0.99 (6 H, d, *J* 6.8, 2 × Me), 0.90 (6 H, d, *J* 6.5, 2 × Me) and 0.89 (6 H, d, *J* 6.5, 2 × Me); δ_C(50 MHz) 175.5 (C=O, quat.), 63.9 (CH_2O), 57.9 (CHN), 55.0 (*C*C=O, quat.), 49.0 (CH_2), 28.9 (CH), 25.5 (CH), 23.4 (Me), 23.2 (Me), 19.5 (Me) and 18.8 (Me); *m*/*z* (CI) 387 (M + H^+, 35%), 301 (15), 258 (28), 170 (22), 147 (40), 104 (55), 86 (100), 72 (95), 58 (82) and 44 (59) (Found: M + H^+, 387.3223. $C_{21}H_{43}N_2O_4$ requires *M*, 387.3223).

(−)-(4*S*,4′*S*)-2,2′-(diisobutylmethylene)bis[4-(1-methylethyl)-4,5-dihydrooxazole] 6d

MsCl (0.794 cm^3, 10.3 mmol) was added to the above diamide (1.8 g, 4.7 mmol) and Et_3N (2.86 cm^3, 20.5 mmol) in CH_2Cl_2 (50 cm^3) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and was stirred for a further 3 h. The reaction mixture was then poured into saturated aq. NH_4Cl (50 cm^3). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 cm^3). The combined organic layers were washed with brine (50 cm^3), dried (Na_2SO_4), and concentrated under reduced pressure to afford the crude bis-mesylate as a yellow oil. The crude bis-mesylate was treated with a mixture of NaOH (0.5 mol dm^{-3} in water; 50 cm^3) and

MeOH (50 cm^3) at reflux for 3 h. The cooled mixture was then concentrated to half the original volume. The resulting residue was extracted with CH_2Cl_2 (3 × 60 cm^3) and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give a thick pale yellow oil. Purification of the oil by column chromatography (6% acetone in CH_2Cl_2) gave a colourless oil, the *bis*(*oxazoline*) **6d** (1.25 g, 74%); R_f 0.25 (9% acetone in CH_2Cl_2); $[a]_D^{21}$ −125.3 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 2957s, 2871s, 1657s, 1470s, 1386m, 1306m, 1267m, 1000s, 974s and 889m; δ_H(300 MHz) 4.17–4.09 (2 H, m, 2 × CH), 3.94–3.86 (4 H, m, 4 × CH), 1.99 (4 H, d, *J* 6.1, 2 × CH_2), 1.87–1.76 (2 H, m, 2 × CH), 1.73–1.60 (2 H, m, 2 × CH), 0.92 (6 H, d, *J* 6.3, 2 × Me), 0.92 (6 H, d, *J* 6.3, 2 × Me), 0.86 (6 H, d, *J* 6.6, 2 × Me) and 0.84 (6 H, d, *J* 6.6, 2 × Me); δ_C(50 MHz) 168.0 (C=N, quat.), 71.8 (CH), 69.2 (CH_2), 45.0 (*C*C=N, quat.), 40.8 (CH_2), 32.3 (CH), 24.7 (CH), 24.0 (Me), 23.1 (Me), 18.9 (Me) and 17.5 (Me); *m*/*z* (CI) 351 ($M + H^+$, 82%), 240 (35), 123 (25), 86 (48) and 74 (100) (Found: $M + H^+$, 351.3012. $C_{21}H_{39}N_2O_2$ requires *M*, 351.3012).

cis-Cyclodecene oxide 7

cis-Cyclodecene (Fluka, 1.43 cm^3, 9.0 mmol) was added to MCPBA (50% w/w pure; 3.42 g, 9.9 mmol) in CH_2Cl_2 (20 cm^3). The mixture was stirred at room temperature for 18 h, washed successively with NaOH (2 mol dm^{-3} in water; 3 × 10 cm^3), water (10 cm^3) and brine (10 cm^3). The organic layer was dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography (5% Et_2O in light petroleum) to give a colourless oil, *cis*-cyclodecene oxide **7**[25] (1.35 g, 97%); R_f 0.43 (20% Et_2O in light petroleum); δ_H(400 MHz) 2.97 (2 H, m, 2 × CHO), 1.99 (2 H, m, 2 × H of CH_2CHO), 1.81–1.69 (2 H, m, 2 × H of CH_2CHO) and 1.62–1.38 (12 H, m, 6 × CH_2).

(−)-*endo*-*cis*-Bicyclo[4.4.0]decan-2-ol 8

Following the typical procedure (A), *cis*-cyclodecene oxide **7** (308 mg, 2 mmol) gave white needles, the *alcohol* **8**[26] (299 mg, 97%); R_f 0.41 (50% Et_2O in light petroleum); $[a]_D^{21}$ −17.2 (*c* 1.0 in $CHCl_3$) {lit. for 2*S* isomer,[27] $[a]_D$ −22 ($CHCl_3$)}; δ_H(200 MHz) 3.67 (1 H, ddd, *J* 11, 4 and 4, C*H*OH) and 1.90–1.14 (17 H, m, 7 × CH_2, 2 × CH and OH). The ee of the 2,4-dinitrobenzoate derivative was determined to be 77% by HPLC (50 : 50 EtOH–hexane, 1 cm^3 min^{-1}), $t_R$mj, 8.7; $t_R$mn, 10.7.

(−)-*endo*-*cis*-Bicyclo[4.3.0]nonan-2-ol 10

Following the typical procedure (A), *cis*-cyclononene oxide **9**[28] (280 mg, 2 mmol) gave a semi-solid, the *alcohol* **10** (217 mg, 77%); R_f 0.26 (50% Et_2O in light petroleum); $[a]_D^{21}$ −27.2 (*c* 1.0 in $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3600s, 3440br s, 2930s, 2860s, 1462m, 1444m, 1258s, 1120w, 1060s, 1041s, 960m, 894w and 857w; δ_H(200 MHz) 3.96 (1 H, m, C*H*OH), 2.26 (1 H, m, CH) and 1.97–1.05 (14 H, m, 6 × CH_2, CH and OH); δ_C(50 MHz) 71.4 (COH), 46.3 (*C*HCHOH), 40.1 (*C*HCHCHOH), 31.5 (CH_2), 29.3 (CH_2), 27.0 (CH_2), 23.9 (CH_2), 21.3 (CH_2) and 21.2 (CH_2). The ee of the 2,4-dinitrobenzoate derivative was determined to be 83% by HPLC (50 : 50 EtOH–hexane, 1 cm^3 min^{-1}), $t_R$mn, 9.7; $t_R$mj, 11.8.

(−)-*cis*-Bicyclo[4.3.0]nonan-2-one

Alcohol **10** (25 mg, 0.18 mmol) in CH_2Cl_2 (1 cm^3) was added to PCC (115 mg, 0.53 mmol) and SiO_2 (120 mg) in CH_2Cl_2 (4 cm^3). After 1 h Et_2O (20 cm^3) was added and the resultant suspension filtered through Celite 545 (Fluka) and evaporated under reduced pressure. Purification of the residue by column chromatography (30% diethyl ether–light petroleum) gave a colourless oil, the title *ketone*[31] (23 mg, 93%); R_f 0.58 (50% Et_2O in light petroleum); $[a]_D^{26}$ −69.6 (*c* 1.15 in $CHCl_3$); CD $\Delta\varepsilon_{max}$(MeOH)/dm^3 mol^{-1} cm^{-1} (λ/nm) −0.493 (294); CD $\Delta\varepsilon_{max}$($CHCl_3$)/dm^3 mol^{-1} cm^{-1} (λ/nm) −0.532 (296); δ_H(200 MHz) 2.66–2.52 (1 H, m, CH) and 2.49–1.29 (13 H, m, 6 × CH_2 and CH).

(−)-Cyclohex-2-en-1-ol 12, (−)-1-(butan-2-yl)cyclohexene 13 and 2-(butan-2-yl)cyclohexan-1-ol 14

Following the typical procedure (A), (−)-sparteine **4** (3.6 cm^3, 15.7 mmol), Bu^{s}Li (1.3 mol dm^{-3} in cyclohexane; 11.5 cm^3, 15 mmol) and cyclohexene oxide **11** (Aldrich, 1.01 cm^3, 10 mmol) gave a residue which was purified by column chromatography (gradient elution, 10% to 50% Et_2O in pentane). The first to elute was a colourless oil, the *alkene* **13**[33] (0.45 g, 33%); R_f 0.83 (10% Et_2O in light petroleum); $[a]_D^{20}$ −0.9 (*c* 1.0 in $CHCl_3$) {lit. for 1-(2*R*) isomer,[34a] $[a]_D^{22}$ −4.06 (neat)}; ν_{max}/cm^{-1} 2929s, 2837s, 1665w, 1461m and 1376m; δ_H(200 MHz) 5.38 (1 H, br s, =CH), 2.07–1.80 (5 H, m, 2 × CH_2 and CH), 1.69–1.47 (4 H, m, 2 × CH_2), 1.43–1.16 (2 H, m, CH_2), 0.96 (3 H, d, *J* 6.9, Me) and 0.80 (3 H, t, *J* 7.4, Me); δ_C(125 MHz) 142.2 (C=, quat.), 120.5 (=CH), 43.5 (CH), 28.1 (CH_2), 25.7 (CH_2), 25.3 (CH_2), 23.6 (CH_2), 23.4 (CH_2), 19.7 (Me) and 12.5 (Me). Second to elute was a colourless oil, the *addition product* **14** (0.21 g, 13%); R_f 0.51 (50% Et_2O in light petroleum); ν_{max}/cm^{-1} 3339s, 2929s, 2857s, 1450m, 1380w and 1058m; δ_H(200 MHz) 3.50–3.30 (1 H, m, C*H*OH), 2.03–1.34 (7 H, m, CH and 3 × CH_2), 1.33–1.05 (5 H, m, 2 × CH_2 and CH), 0.88 (3 H, t, *J* 5.6, Me) and 0.76 (3 H, d, *J* 6.9, Me); δ_C(50 MHz) 71.4 (CH), 71.4 (CH), 51.1 (CH), 48.7 (CH), 36.3 (CH_2), 33.7 (CH), 32.7 (CH), 27.8 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 25.6 (CH_2), 25.1 (CH_2), 25.0 (CH_2), 24.0 (CH_2), 23.5 (CH_2), 17.1 (Me), 14.1 (Me), 13.5 (Me), 12.8 (Me) and 12.3 (Me). Third to elute was a colourless oil, cyclohex-2-enol **12**[7] (0.24 g, 24%); R_f 0.25 (50% Et_2O in light petroleum); $[a]_D^{20}$ −30.4 (*c* 1.0 in $CHCl_3$) {lit.,[35] $[a]_D$ +130.6 (*c* 1.21 in $CHCl_3$) for >99% ee of (*R*)-cyclohex-2-enol}; δ_H(200 MHz) 5.86–5.64 (2 H, m, 2 × CH=), 4.15 (1 H, br s, C*H*OH) and 2.20–1.40 (7 H, m, 3 × CH_2 and OH). The ee of the 2,4-dinitrobenzoate derivative was determined to be 20% by HPLC (4 : 96 EtOH–hexane, 0.2 cm^3 min^{-1}), $t_R$mj, 133.5; $t_R$mn, 148.8.

cis-Cyclododecene oxide 15

MCPBA (50% w/w pure; 1.37 g, 4.0 mmol) was added to a stirred solution of *cis*-cyclododecene[71] (0.60 g, 3.6 mmol) in CH_2Cl_2 (30 cm^3) at 0 °C and the reaction mixture was then allowed to warm to ambient temperature over 17 h. The reaction mixture was diluted with CH_2Cl_2 (10 cm^3), filtered, washed with saturated aq. $NaHCO_3$ (5 × 30 cm^3) and brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by column chromatography (10% Et_2O in light petroleum) and subsequent bulb-to-bulb distillation (85 °C/0.05 mmHg) gave a colourless oil, *cis*-cyclododecene oxide **15**[39] (0.41 g, 62%); R_f 0.45 (15% Et_2O in light petroleum); δ_H(200 MHz) 2.89 (2 H, d, *J* 9.7, 2 × CHO), 1.96–1.72 (2 H, m, 2 × H of CH_2CHO) and 1.70–1.15 (18 H, m, 2 × H of CH_2CHO and 8 × CH_2).

(−)-*trans*-Cyclododec-2-en-1-ol 16, 1-(butan-2-yl)cyclododecene 17 and cyclododecanone 18

Following the typical procedure (A) above, *cis*-cyclododecene oxide **15** (0.164 g, 0.9 mmol) gave a residue which was purified by column chromatography (10% Et_2O in pentane) and subsequent bulb-to-bulb distillation (60 °C/0.1 mmHg). First to elute was a colourless oil, the *alkene* **17** (47.3 mg, 24%, *E* : *Z* = 75 : 25, by ^{1}H NMR analysis of the isomeric =CHs in the δ 5.4–5.1 region); R_f 0.82 (10 % Et_2O in light petroleum); ν_{max}/cm^{-1} 2927s, 2860m, 2342w and 1467m; δ_H(200 MHz) 5.41 (0.25 H, t, *J* 7.4, =CH), 5.12 (0.75 H, t, *J* 7.7, =CH), 2.54 (0.25 H, ap. sxt, *J* 7.1, CHC=, *Z*), 2.23–1.83 (4.75 H, m, 2 × CH_2C= and CHC=), 1.62–1.14 (18 H, m, 9 × CH_2), 1.06–0.94 (3 H, m, *Me*CH) and 0.94–0.74 (3 H, m, *Me*CH_2); δ_C(125 MHz) 143.9 (C=, quat. *Z*), 140.7 (C=, quat. *E*), 126.4 (=CH, *E*), 123.7 (=CH, *Z*), 39.7 (CH, *Z*), 36.1 (CH, *E*), 30.0 (CH_2, *E*), 29.0 (CH_2, *Z*), 28.2 (CH_2, *E*), 27.5 (CH_2, *Z*), 27.1 (CH_2, *E*), 26.9 (CH_2, *E*),

26.5 (CH_2, *E*), 26.4 (CH_2, *Z*), 26.0 (CH_2, *Z*), 25.9 (CH_2, *E*), 25.5 (CH_2, *E*), 25.3 (CH_2, *E*), 25.2 (CH_2, *Z*), 25.1 (CH_2, *Z*), 24.7 (CH_2, *Z*), 24.7 (CH_2, *E*), 24.6 (CH_2, *Z*), 24.2 (CH_2, *Z*), 24.1 (CH_2, *E*), 23.3 (CH_2, *E*), 22.8 (CH_2, *Z*), 22.4 (CH_2, *Z*), 20.6 (Me, *Z*), 18.9 (Me, *E*), 12.4 (Me, *E*) and 12.1 (Me, *Z*). Second to elute was a white solid, cyclododecanone **18**[40] (20.2 mg, 12%); R_f 0.33 (10% Et_2O in light petroleum); mp 53–54 °C (lit.,[40] 57–58 °C); δ_H(200 MHz) 2.55–2.35 (4 H, m, 2 × CH_2), 1.80–1.55 (4 H, m, 2 × CH_2) and 1.46–1.08 (14 H, m, 7 × CH_2). Third to elute was a colourless oil, *trans*-cyclododec-2-enol **16**[7] (63.0 mg, 38%); R_f 0.38 (50% Et_2O in light petroleum); $[\alpha]_D^{20}$ −1.8 (*c* 1.0 in $CHCl_3$); δ_H(200 MHz) 5.72–5.34 (2 H, m, 2 × CH=), 4.24–4.04 (1 H, m, CH), 2.40–2.15 (1 H, m), 2.15–1.90 (1 H, m), 1.90–1.70 (1 H, m) and 1.70–1.04 (15 H, m). The ee of the 3,5-dinitrobenzoate derivative was determined to be 58% by HPLC (EtOH, 1 cm^3 min^{-1}), $t_R$mj, 17; $t_R$mn, 31.

(−)-*endo*-2-Oxabicyclo[2.2.1]heptan-6-ol 20 and 3-(butan-2-yl)-cyclopent-3-ene-1-methanol 21

Following typical procedure A above, epoxyalcohol **19**[41] (57 mg, 0.5 mmol) gave a residue which was purified by column chromatography (30% Et_2O in pentane). First to elute was a colourless oil, the *alkene* **21** (15.2 mg, 20%); R_f 0.36 (50% Et_2O in light petroleum); $[\alpha]_D^{20}$ −0.5 (*c* 1.5 in $CHCl_3$); ν_{max}/cm^{-1} 3350m, 2962s, 2929s and 2874m; δ_H(200 MHz) 5.26 (1 H, br s, =CH), 3.68–3.36 (2 H, m, CH_2OH), 2.60–2.26 (2 H, m, CH_2), 2.26–1.92 (2 H, m, CH_2), 2.60–1.92 (1 H, m, CH), 1.54–1.15 (3 H, m, CH_2 and CH), 1.00 (3 H, d, *J* 6.8, Me) and 0.83 (3 H, t, *J* 7.4, Me); δ_C(125 MHz) 148.2 (C=, quat.), 148.3 (C=, quat.), 121.2 (=CH), 67.5 (CH_2OH), 39.7 (CH), 39.6 (CH), 36.8 (CH), 36.7 (CH), 35.3 (CH_2), 35.2 (CH_2), 35.1 (CH_2), 27.9 (CH_2), 18.9 (Me), 18.9 (Me), 11.7 (Me) and 11.6 (Me); *m*/*z* (CI) 172 ($[M + NH_4]^+$, 20%), 155 ($[MH^+]$, 50), 137 (40), 123 (100), 121 (25), 108 (22) and 107 (88); Second to elute was a colourless oil, the *alcohol* **20**[42] (8.6 mg, 21%); R_f 0.38 (80% EtOAc in light petroleum); $[\alpha]_D^{20}$ −1.4 (*c* 0.86 in $CHCl_3$); ν_{max}/cm^{-1} 3360s, 2930s, 2248w, 1723m and 1455m; δ_H(500 MHz) 4.20–4.14 (2 H, m, C*H*OH and CH_2OCH), 3.70–3.61 (2 H, m, CH_2OCH), 2.65–2.60 [1 H, m, C(4)H], 2.59–2.45 [1 H, m, *exo*-H of C(5)H_2], 2.29–2.23 [1 H, m, *syn*-H of C(7)H_2], 2.11–2.05 [1 H, m, *anti*-H of C(7)H_2], 1.69–1.63 (1 H, m, OH) and 1.56–1.52 [1 H, m, *endo*-H of C(5)H_2]; ^{1}H NMR NOE experiments: irradiation at δ 3.65 saw enhancement at 4.15 (1.2%) and at 2.25 (3%); irradiation at 2.25 saw enhancement at 4.15 (2.6%); irradiation at 2.10 saw enhancement at 4.15 (1%) and at 2.65 (3%); δ_C(125 MHz) 78.6 (CHO), 65.7 (CHO), 64.6 (CH_2), 36.4 (CH), 34.9 (CH_2) and 34.5 (CH_2). The ee of the 3,5-dinitrobenzoate derivative was determined to be 23% by HPLC (50:50 EtOH–hexane, 1 cm^3 min^{-1}), $t_R$mj, 9.6; $t_R$mn, 10.9.

Typical procedure (B) for lithium amide-induced rearrangement of achiral epoxides

(−)-Tricyclo[2.2.1.0^{2,6}]heptan-3-ol 24. Bu^{n}Li (2.2 M in hexanes; 0.82 cm^3, 1.8 mmol) was added to a stirred solution of (*S*,*S*)-bis(1-phenylethyl)amine[72] (400 mg, 1.85 mmol) in Et_2O (7.5 cm^3) at 0 °C. After 0.5 h, a solution of *exo*-norbornene oxide **22** (Aldrich, 110 mg, 1.0 mmol) in Et_2O (3 cm^3) was added and the reaction mixture was allowed to warm to ambient temperature over 20 h. The mixture was then diluted with Et_2O (20 cm^3), washed successively with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (gradient elution, 20 to 40% Et_2O in light petroleum) gave an amorphous solid, *nortricyclanol* **24**[44] (80 mg, 73%); R_f 0.29 (50% Et_2O in light petroleum); $[\alpha]_D^{20}$ −13.3 (*c* 1.0 in $CHCl_3$) {lit.,[47a] $[\alpha]_D^{25}$ −40 ($CHCl_3$); lit.,[47b] $[\alpha]_D^{20}$ −22.3 (*c* 1.0 in $CHCl_3$) for material determined (by HPLC of the phenylcarbamate derivative) to have 54.7% ee}; δ_H(400 MHz) 3.78 (1 H, s, C*H*OH), 1.76 (1 H, s, br, CH), 1.73 (1 H, d, *J* 11, CH), 1.62 (1 H, br s, OH), 1.31 (1 H, d, *J* 10, H of CH_2), 1.23 (1 H, d, *J* 10, H of CH_2), 1.19–1.11 (3 H, m, CH_2 and CH) and 1.01 (1 H, dt, *J* 5 and 0.7, CH). The ee of the 2,4-dinitrobenzoate derivative was determined to be 49% by HPLC (10:90 EtOH–hexane, 1 cm^3 min^{-1}) $t_R$mn, 16.5; $t_R$mj, 18.4.

(−)-5-*endo*-6-*endo*-5,6-Dimethylbicyclo[2.2.1]heptan-2-one 33

Following typical procedure B above, epoxide **29**[48] (100 mg, 0.8 mmol) gave a residue which was purified by column chromatography (10% Et_2O in pentane) to give greasy, colourless plates, the *ketone* **33**[48] (58 mg, 58%); R_f 0.30 (20% Et_2O in light petroleum); $[\alpha]_D^{20}$ −18 (*c* 1.0 in $CHCl_3$); CD $\Delta\varepsilon_{max}$(MeOH)/dm^3 mol^{-1} cm^{-1} (λ/nm) +0.030 (306) and −0.018 (275); δ_H(200 MHz) 2.46 (2 H, s, 2 × CH), 2.32 (2 H, m, 2 × CH), 2.12 (2 H, dt, *J* 16, 1, CH), 1.90 (1 H, dd, *J* 16, 4, CH), 1.72 (2 H, d, *J* 1, 2 × CH), 0.90 (3 H, d, *J* 6, Me) and 0.82 (3 H, d, *J* 6, Me). The ee of the 3,5-dinitrobenzoate derivative following reduction (L-Selectride®)[50] to the known[51] 2-*endo*-5-*endo*-6-*endo*-5,6-dimethylbicyclo[2.2.1]heptan-2-ol [δ_H(200 MHz) 4.33 (2 H, m, 2 × CHO), 2.13 (4 H, m, 4 × CH), 1.77 (2 H, dt, *J* 11 and 5, CH), 1.44 (1 H, s, CH), 1.35 (2 H, s, 2 × CH), 1.15 (3 H, d, *J* 7, Me) and 0.96 (3 H, d, *J* 6.5, Me)] was determined to be 35% by HPLC (EtOH, 0.5 cm^3 min^{-1}) $t_R$mn, 14.6; $t_R$mj, 17.8.

(−)-Tricyclo[2.2.1.0^{2,6}]heptan-3-ol 24 and (+)-bicyclo[2.2.1]-heptan-2-one 28

Following typical procedure B above, *endo*-norbornene oxide **22**[43] (200 mg, 1.8 mmol) gave a residue which was purified by column chromatography (10% Et_2O in pentane). First to elute was a white solid, *norcamphor* **28**[45] (80 mg, 40%); R_f 0.38 (80% EtOAc in light petroleum); $[\alpha]_D^{20}$ +7.8 (*c* 0.55 in $CHCl_3$) {lit.,[53] $[\alpha]_D^{20}$ +17.0 (*c* 4.368 in $CHCl_3$)}; CD $\Delta\varepsilon_{max}$(MeOH)/dm^3 mol^{-1} cm^{-1} (λ/nm) −0.104 (304) and +0.063 (275); δ_H(200 MHz) 2.64 (2 H, m, *J* 14, 2 × CH), 2.08 (1 H, dd, *J* 14, 4, CH), 1.79 (4 H, m, 4 × CH) and 1.56 (3 H, m, 3 × CH). The ee of the 3,5-dinitrobenzoate derivative following reduction (L-Selectride®)[50] to the known[50,52] *endo*-bicyclo[2.2.1]heptan-2-ol [δ_H(200 MHz) 4.23 (1 H, m, CHO), 2.26 (1 H, m, CH), 2.16 (1 H, m, CH), 1.54 (1 H, m, CH), 1.32 (5 H, m, 5 × CH) and 0.84 (1 H, m, CH)] was determined to be 32% by HPLC (30:70 EtOH–hexane, 0.5 cm^3 min^{-1}) $t_R$mj, 22.0, $t_R$mn, 26.9. Second to elute was a colourless oil, *nortricyclanol* **24**[44] (40 mg, 20%); $[\alpha]_D^{20}$ −15.8 (*c* 0.55 in $CHCl_3$). The ee of the 3,5-dinitrobenzoate derivative was determined to be 38% by HPLC (5:95 EtOH–hexane, 0.5 cm^3 min^{-1}) $t_R$mn, 44.9; $t_R$mj, 46.8.

exo,*exo*-Tricyclo[2.2.1.0^{2,6}]heptane-3,5-diol 37

Bu^{n}Li (2.2 mol dm^{-3} in hexanes; 0.82 cm^3, 1.8 mmol) was added to a stirred solution of diisopropylamine (0.26 cm^3, 2.0 mmol) in Et_2O (7.5 cm^3) at 0 °C. After 0.5 h, *exo*,*exo*-norbornadiene diepoxide **34**[54] (100 mg, 0.8 mmol) was added in Et_2O (1 cm^3). After 16 h, the mixture was washed successively with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (50% Et_2O in pentane) gave a waxy white solid, meso-*nortricyclandiol* **37**[55] (56 mg, 56%); R_f 0.31 (Et_2O); ν_{max}/cm^{-1} 3350br (OH); δ_H(400 MHz) 4.16 (2 H, d, *J* 6, 2 × CHO), 2.89 (2 H, d, *J* 6.5, 2 × OH), 1.94 [1 H, s, C(4)H], 1.50 (2 H, d, *J* 5, CH_2), 1.34 [2 H, s, 2 × C(2/6)H] and 1.30 (1 H, t, *J* 5.5, C(1)H) [note: C(4)H is misassigned in the lit.];[55b] δ_C(125 MHz) 80.0 (CH), 39.3 (CH), 27.9 (CH_2), 16.9 (CH) and 13.8 (CH).

endo-2,3-Epoxybicyclo[2.2.2]oct-5-ene 42

A solution of peracetic acid (38% w/v in acetic acid; 5.1 cm^3, 29 mmol) was added dropwise to a vigorously stirred mixture of bicyclo[2.2.2]octa-2,5-diene **41**[60] (2.8 g, 26 mmol) and Na_2CO_3 (8.4 g) in CH_2Cl_2 (200 cm^3) at 0 °C and the reaction mixture was allowed to reach ambient temperature. After 15 h the mixture was filtered and the filtrate was washed with saturated aq. $NaHCO_3$, dried ($MgSO_4$) and carefully evaporated under

reduced pressure. Purification of the residue by bulb-to-bulb distillation gave a colourless semi-solid, the endo-*monoepoxide* **42** (2.45 g, 76%, *endo*:*exo* = 93:7, by ^{1}H NMR analysis of the isomeric HC=CHs in the δ 6.5–5.8 region); bp (sublimes) 95–100 °C/30 mmHg (lit.,[56] mp 120–123 °C); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 1260m (COC) and 916s (COC); δ_H(200 MHz) 6.43 (0.15 H, dd, *J* 5 and 3, *exo*-HC=CH), 5.88 (1.85 H, dd, *J* 5 and 3, *endo*-HC=CH), 3.25–3.15 (2 H, m, 2 × CHO), 3.05–2.85 (2 H, m, 2 × CH), 1.60–1.40 (2 H, m, 2 × CH) and 1.35–1.20 (2 H, m, 2 × CH); ^{1}H NMR NOE experiments: irradiation at δ 3.2 saw enhancement at 1.5 (3.8%), irradiation at 1.5 saw enhancement at 3.2 (2.3%); δ_C(50 MHz) 128.2 (=CH), 48.0 (CH), 32.5 (CH) and 21.5 (CH_2).

2-(Cyclohexa-2,4-dien-1-yl)acetaldehyde

A solution of racemic alcohol **45** (50 mg, 0.4 mmol) in *tert*-butylbenzene (0.5 cm^3) was heated in a sealed tube at 200 °C for 24 h. The resultant solution was purified by column chromatography (10% Et_2O in pentane) to give a colourless oil, the title *aldehyde*[65] (16 mg, 32%); R_f 0.60 (40% Et_2O in light petroleum); δ_H(400 MHz) 9.78 (1 H, t, *J* 2, CHO), 5.97–5.90 (2 H, m, 2 × HC=), 5.80–5.75 (1 H, m, =CH), 5.71 (1 H, dd, *J* 9 and 4, HC=), 2.90–2.82 (1 H, m, CH), 2.58–2.47 (2 H, m, 2 × CH), 2.42–2.37 (1 H, m, CH) and 2.06–1.98 (1 H, m, CH); δ_C(100 MHz) 201.9 (C=O), 129.0 (=CH), 125.2 (=CH), 124.8 (=CH), 124.1 (=CH), 48.0 (CH_2), 28.3 (CH_2) and 27.5 (CH).

X-Ray structure determination of *endo*-tricyclo[3.2.1.0^{2,7}]oct-3-en-6-yl 3,5-dinitrobenzoate 46

Crystal data. $C_{15}H_{12}N_2O_6$, M = 316.07. Monoclinic, a = 24.581(1), b = 6.537(1), c = 18.055(5) Å, β = 98.15(3), V = 2872.52(2) Å^3 (by least-squares refinement on diffractor angles for 25 automatically centred reflections, λ = 1.5418 Å), space group $C2/c$ (C^6_{2h}, No. 15), Z = 8, D_x = 1.463 g cm^{-3}. Pale yellow plate. Crystal dimensions: 0.12 × 0.12 × 0.03 mm, μ(Cu-Kα) = 9.361 cm^{-1}. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc*., *Perkin Trans. 1*, available *via* the RSC web pages (http://www.rsc.org/authors). Any request to the CCDC for the material should quote the full literature citation and the reference number 207/224.

Data collection and processing. Enraf-Nonius Mach 3 diffractometer, $\omega/2\theta$ mode using the Enraf-Nonius Express control software, Cu-Kα radiation; 2772 reflections measured ($0 \leqslant \theta \leqslant 65°$, $-h$ to h, -1 to k, -1 to l), 833 reflections observed, $I > 3\sigma(I)$, [merging R = 0.033]. No absorption correction applied, *ca*. 4% decrease in intensity standards during data collection.

Structure analysis and refinement. Direct method (SIR 92).[73] Full-matrix least-squares refinement with the hydrogen atoms placed geometrically and robust resistant 3 term (3.88, 2.21, 2.87) Chebyschev polynomial weighting scheme.[74] Final R and R_w values are 0.079 and 0.010. Unobserved reflections were not included. Programs used and the source of scattering factor data are given in ref. 75. 209 Parameters were refined, the maximum electron density in the difference map (ρ_{max}) was 0.44 e Å^{-3} and ρ_{min} −0.21 e Å^{-3}. Standard deviations in bond lengths and angles range from 0.008 to 0.021 Å and 0.1 to 0.9°.

(−)-Bicyclo[2.2.2]oct-5-en-2-one 44 and (−)-*endo*-tricyclo-[3.2.1.0^{2,7}]oct-3-en-6-ol 45

Following typical procedure B above, endo-*monoepoxide* **42** (200 mg, 1.8 mmol) gave a residue which was purified by column chromatography (10% Et_2O in pentane). The first to elute was a colourless oil, the *ketone* **44**[63] (80 mg, 40%, 19% optical purity); R_f 0.29 (20% Et_2O in light petroleum); $[\alpha]_D^{25}$ −98.8 (*c* 0.51 in $CHCl_3$) {lit.,[58] $[\alpha]_D^{23}$ −520 (*c* 0.26 in $CHCl_3$) for >98% ee material}; CD λ_{max}(hexane)/nm (*g*) 296 (-2.12×10^{-2}); δ_H(200 MHz) 6.51 (1 H, t, *J* 7, HC=), 6.20 (1 H, t, *J* 7, HC=), 3.15 (1 H, d, *J* 6, CH), 3.05–2.95 (1 H, m, CH), 2.05 (2 H, d, *J* 3, 2 × CH) and 1.9–1.2 (4 H, m, 4 × CH). Second to elute was a colourless greasy solid, the *alcohol* **45** (60 mg, 30%); mp 90 °C (lit.,[64a] 38–40 °C); $[\alpha]_D^{25}$ −11.4 (*c* 0.82 in $CHCl_3$); R_f 0.15 (20% Et_2O in light petroleum); ν_{max}/cm^{-1} 3300br (OH) and 3040m (CH); δ_H(400 MHz) 6.33–6.31 (1 H, m, HC=), 5.72–5.68 (1 H, m, HC=), 4.09 (1 H, br s, CHO), 2.77 (1 H, q, *J* 6, CH), 1.75 (2 H, m, 2 × CH), 1.55 (1 H, m, CH), 1.48 (1 H, m, CH), 1.27 (1 H, m, OH) and 0.83 (1 H, d, *J* 11, CH); δ_C(125 MHz) 127.4 (=CH), 123.5 (CH), 70.3 (CH), 37.3 (CH), 26.0 (CH_2), 21.2 (CH), 17.0 (CH) and 15.7 (CH); *m*/*z* (EI) 122 (M^+, 60%), 91 (70) and 78 (100) (Found: M^+, 122.0730. $C_8H_{10}O$ requires M, 122.0732). The ee of the 3,5-dinitrobenzoate derivative **46** was determined to be 16% by HPLC (25:75 EtOH–hexane, 0.5 cm^3 min^{-1}) $t_R$mn, 23.5; $t_R$mj, 25.1.

(+)-Tricyclo[3.2.1.0^{2,7}]oct-3-en-6-one

A solution of alcohol (−)-**45** (34 mg, 0.3 mmol) in CH_2Cl_2 (0.5 cm^3) was added dropwise to a stirred suspension of PCC (150 mg, 0.7 mmol) and SiO_2 (150 mg) in CH_2Cl_2 (3 cm^3). After 2 h Et_2O (5 cm^3) was added and the resultant suspension filtered through Celite 545 (Fluka) and evaporated under reduced pressure. Purification of the residue by column chromatography (10% Et_2O in pentane) gave a colourless oil, the title *ketone*[66] (22 mg, 66%); R_f 0.19 (20% Et_2O in light petroleum); $[\alpha]_D^{23}$ +19.1 (*c* 0.11 in $CHCl_3$); CD λ_{max}(hexane)/nm (*g*) 306 ($+1.13 \times 10^{-2}$); δ_H(400 MHz) 6.04 (1 H, dd, *J* 9 and 5, HC=), 6.95 (1 H, dt, *J* 7.5 and 3, =CH), 2.62–2.60 (1 H, m, CH), 2.35–2.25 (3 H, m, 3 × CH), 1.58–1.56 (1 H, m, CH) and 1.31 (1 H, d, *J* 11, CH).

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