ARTICLE

OBC
www.rsc.org/obc

Enantioselective alkylative double ring-opening of epoxides derived from cyclic allylic ethers: synthesis of enantioenriched unsaturated diols †

David M. Hodgson,*[a] Matthew A. H. Stent,[a] Bogdan Štefane[a] and Francis X. Wilson[b]

[a] *Dyson Perrins Laboratory, Department of Chemistry, University of Oxford, South Parks Road, Oxford, OX1 3QY, UK. E-mail: david.hodgson@chem.ox.ac.uk; Fax: +(44) 01865 275674; Tel: +(44) 01865 275697*

[b] *Roche Discovery (Welwyn), 40 Broadwater Road, Welwyn Garden City, Herts, AL7 3AY, UK*

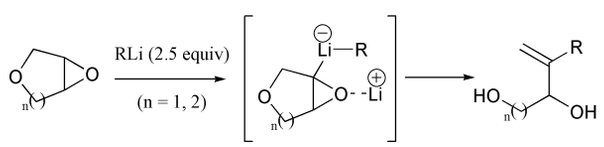
Received 17th December 2002, Accepted 3rd February 2003
First published as an Advance Article on the web 17th February 2003

A screen of external chiral ligands has led to enantioselective organolithium-induced alkylative double ring-opening of 3,4-epoxytetrahydrofuran **1** with *n*-BuLi to give 3-methyleneheptane-1,2-diol **3** in 75% yield and 55% ee in the presence of bisoxazoline **10**, and in up to 60% ee in the presence of (−)-sparteine **2**. Extending the alkylative double ring-opening reaction to epoxides derived from oxabicyclo[*n*.2.1]alkenes (*n* = 2, 3) results in the formation of cycloalkenediols, which, when carried out in the presence of (−)-sparteine **2** affords products in up to 85% ee.

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,[1–3] and base-induced enantioselective transformations of such epoxides are a focus of current interest.[4–8]

We recently reported that dihydrofuran and dihydropyran epoxides on treatment with two equivalents of an organolithium in THF undergo an alkylative double ring-opening, giving substituted acyclic alkenediols (Scheme 1).[9,10] This process likely proceeds *via* α-deprotonation and insertion into the resulting lithiated epoxide (carbenoid) of a second equivalent of organolithium (possibly by a 1,2-metallate shift),[11] followed by elimination.

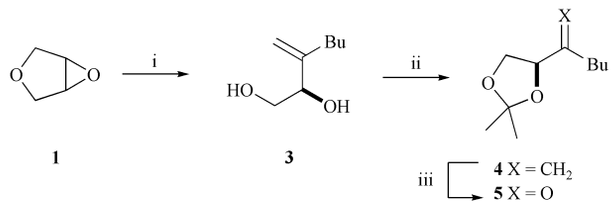


Scheme 1

In conjunction with our studies into the enantioselective deprotonations of cycloalkene- and heterocycloalkene-derived epoxides[5–8] we sought to develop the above alkylative desymmetrisation reaction of epoxides into an enantioselective entry to acyclic and cyclic unsaturated diols.[12] For such an asymmetric process using an organolithium with an external chiral (enantio-enriched or -pure) ligand, it seems probable that any enantioselectivity would originate from the initial discrimination between the enantiotopic C–H groups on the epoxide ring by deprotonation with an organolithium–ligand complex.[8] However, the exact fates of the individual enantiomeric lithiated epoxide (carbenoid) intermediates might be different in the presence of a chiral, non-racemic ligand.[5] Therefore, the efficiency of the reaction both in terms of yield and ee may not necessarily reflect the (enantio)selectivity of the initial deprotonation step.

Results and discussion

Our initial investigations focused on the alkylative desymmetrisation of the simplest available achiral epoxide derived from a cyclic allylic ether: 3,4-epoxytetrahydrofuran ‡ **1** (Scheme 2). THF is not normally used as a solvent in external chiral ligand controlled transformations using organolithiums, since THF itself often acts as a more effective ligand[13] resulting in products with no or little enantioenrichment; therefore, we were pleased to observe that the non-ligand mediated reaction with Bu^{n}Li proceeded with identical yields (90%) in Et_2O or toluene to that originally observed[9,10] in THF. However, application of our typical conditions for asymmetric epoxide lithiation (dropwise addition of a solution of epoxide to a preformed organolithium–ligand complex at −78 °C in Et_2O, followed by slow warming over 16 h)[5–7] gave poor results for a Bu^{n}Li–(−)-sparteine **2** complex (2.5 equiv. each), with only 16% of 3-methyleneheptane-1,2-diol **3** isolated, in 43% ee (Table 1, entry 1); no other characterisable material was isolated from this reaction. Under the same conditions, but switching to toluene as solvent, gave an identical yield and similar ee (40%) of alkenediol **3** (Table 1, entry 2). Using the less sterically encumbered achiral diamine TMEDA as an additive in Et_2O also resulted in a reduced yield (50%) of alkenediol **3** compared to the ligand-free process, although the effect was less severe than with (−)-sparteine.



1 **3**

Scheme 2 *Reagents and conditions:* i, Bu^{n}Li–**2**, Et_2O, −78 °C (5 h) to 25 °C (16 h); ii, 2,2-dimethoxypropane, PTSA, benzene, 25 °C, 14 h; iii, O_3, CH_2Cl_2, −78 °C, 5 min, then DMS, −78 °C to 25 °C, 2 h.

The absolute stereochemistry of the major enantiomer of 3-methyleneheptane-1,2-diol (−)-**3**, obtained with (−)-sparteine **2**, is as shown in Scheme 2 and was established by polarimetric

† Electronic supplementary information (ESI) available: the preparation and characterisation of derivatives for ee determinations. See http://www.rsc.org/suppdata/ob/b2/b212404a/

‡ The IUPAC name for 3,4-epoxytetrahydrofuran is 3,6-dioxabicyclo-[3.1.0]hexane.

DOI: 10.1039/b212404a

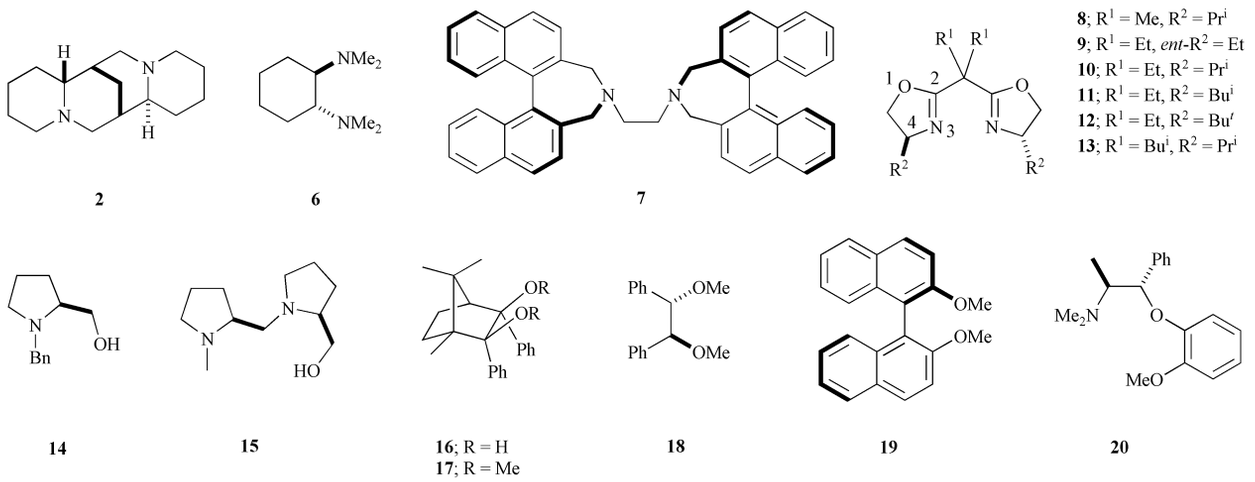


Fig. 1 External chiral ligands screened.

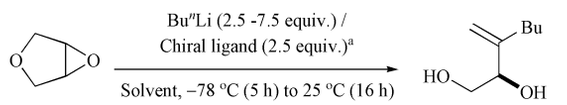
comparison for ketone **5** {$[a]_D^{22}$ −44.1 (*c* 1.57 in CH_2Cl_2), lit.,[14] $[a]_D^{20}$ +63.2 (*c* 2.2 in CH_2Cl_2) for *R* isomer}. (−)-3-Methyleneheptane-1,2-diol **3** was converted to ketone **5** by a protection–ozonolysis sequence (Scheme 2). The sense of asymmetric induction observed in enediol **3** using RLi–**2** with epoxide **1** parallels all our previous observations on enantioselective α-deprotonation of epoxides[8] [medium-sized (8, 9 and 10-membered) cycloalkene epoxides,[5] silyloxysubstituted cyclooctene epoxides,[6] and norbornene§ epoxide[5] and (*N*-Boc)-7-azanorbornene epoxide[7]] using sparteine, where proton removal at the *R*-epoxide stereocentre is consistently seen. Products from similar α-deprotonation–alkylation 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 sparteine.

Due to the low yield and modest ee obtained initially obtained using (−)-sparteine **2**, we screened some alternative external chiral ligands. As the organolithium has a dual function of both a base and a nucleophile in the reaction we chose to investigate ligands (Fig. 1) known to mediate either enantioselective deprotonations or additions of organolithiums.[15] When using Bu^{n}Li in the presence of (−)-sparteine **2**, we established that reaction in Et_2O at −78 °C was complete within 5 min; however, for ease of reproducibility, and as no degradation of yield or ee was observed with extended reaction times, all reactions were maintained at −78 °C for 5 h and then allowed to warm to room temperature over 16 h. Reactions were conducted in Et_2O, except for those using bisoxazoline ligands (*vide infra*) or ligands containing a potentially coordinating ether linkage, where toluene was used.

At the start of the ligand study, two other bis(tertiary amines) **6**[16] and **7**[17] were also found to give low yields of alkenediol and in lower ees compared with (−)-sparteine **2** (Table 1, entries 3 and 4). We previously introduced C_2-symmetric bisoxazolines as ligands for alkyllithiums in enantioselective deprotonation (of cyclooctene oxide).[5,8,18] The ready availability of the amino alcohol precursors to the bisoxazolines allows for variation of steric bulk of the linking (R^1) and ring C-4/4′ (R^2) substituents (**8**–**13**, Fig. 1). In the current ligand study with epoxide **1** the best yield and ee combination was obtained with bisoxazoline **10**, for which toluene was slightly better than Et_2O as solvent (compare Table 1, entry 8: 49% yield, 49% ee; and entry 7: 44% yield, 42% ee, respectively). Amino alkoxides from **14**[19,20] and **15**,[21] bis(alkoxide) from **16**[20] and amino ether **20**[22] all gave moderate yields of alkenediol in conjunction with a poor ee. Diethers **17**,[20] **18**[23] and **19**[23] afforded only racemic material, albeit in good yield.

§ The IUPAC name for norbornene is bicyclo[2.2.1]heptene.

Table 1 Screen of ligands in the reaction of 3,4-epoxytetrahydrofuran with Bu^{n}Li



1 3

Entry	Ligand	Bu^{n}Li (equiv.)	Solvent	Yield (%)	ee (%)[b]
1	**2**	2.5	Et_2O	16	−43
2	**2**	2.5	Toluene	16	−40
3	**6**	2.5	Et_2O	34	−20
4	**7**	2.5	Et_2O	7	−14
5	**8**	2.5	Toluene	28	+38
6	**9**	2.5	Toluene	34	−44
7	**10**	2.5	Et_2O	44	+42
8	**10**	2.5	Toluene	49	+49
9	**11**	2.5	Toluene	45	+23
10	**12**	2.5	Toluene	40	+18
11	**13**	2.5	Toluene	22	+40
12[c]	**14**	5.0	Et_2O	56	−11
13[c]	**15**	5.0	Et_2O	63	+20
14[c]	**16**	7.5	Et_2O	40	−29
15	**17**	2.5	Toluene	67	0
16	**18**	2.5	Toluene	60	+6
17	**19**	2.5	Toluene	56	0
18	**20**	2.5	Toluene	43	+20

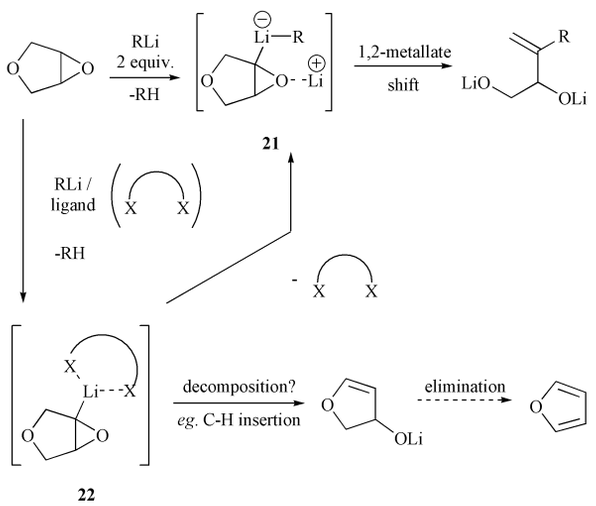
[a] Absolute configuration of predominant enantiomer obtained with (–)-sparteine **2** is shown. [b] Determined by chiral HPLC on the bis(3,5-dinitrobenzoate) derivative.† A positive value indicates that the major enantiomer was the first to elute. [c] Alcohols **14**, **15** and **16** required additional equivalents of Bu^{n}Li to form the reactive complex.

At this point, the dual role of the organolithium in the current transformation led us to consider probing the equimolar ratio of organolithium and ligand used. The general trend of an inverse relationship between enantioselectivity and yield in the above ligand screen (Table 1) is consistent with an analysis where complete (1 : 1) complexation of the organolithium and ligand, whilst potentially maximising selectively in the deprotonation, leads to a reduction in the 'effective concentration' of available nucleophile. This could occur by ligand complexation of the oxiranyl anion (*ie.* **22**, Scheme 3) retarding the formation of metallate complex **21**, and then intermediate **22** undergoing competitive decomposition (*e.g.*, *via* C–H insertion)[8,24] to ultimately give furan (or dihydrofuran-3-one), although attempts to detect these byproducts (*e.g.*, by trapping with dieneophiles or NMR studies of reactions conducted in d_8-toluene) failed.

Table 2 Reaction of 3,4-epoxytetrahydrofuran with Bu^{n}Li in the presence of varying quantities of ligand

Entry	Ligand (equiv.)	Bu^{n}Li (equiv.)	Solvent	Yield (%)	ee (%)[a]
1[b]	**2** (2.5)	2.5	Et_2O	16	−43
2	**2** (1.0)	3.5	Et_2O	22	−60
3	**2** (0.2)	2.7	Et_2O	41	−54
4	**2** (0.05)	2.5	Et_2O	56	−45
5[b]	**2** (2.5)	2.5	Toluene	16	−40
6	**2** (1.0)	3.5	Toluene	49	−47
7	**2** (0.2)	2.7	Toluene	63	−38
8[b]	**10** (2.5)	2.5	Toluene	49	+49
9	**10** (1.0)	3.5	Toluene	75	+55
10	**10** (0.2)	2.7	Toluene	67	+32

[a] Determined by chiral HPLC on the bis(3,5-dinitrobenzoate) derivative. A positive value indicates that the major enantiomer was the first to elute. [b] Results from Table 1.

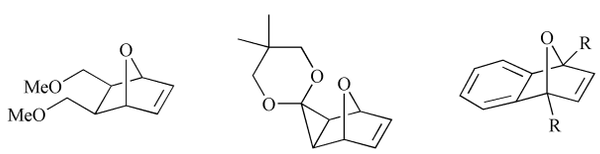


Scheme 3

Regardless of the validity of the above argument it was found that, when sub-stoichiometric quantities of (−)-sparteine **2** or bisoxazoline **10** were used, enantioselectivities were pleasingly maintained at reasonable levels whilst improvements in yield were observed (Table 2). For both **2** and **10** the optimum ees are observed with 1 equiv. ligand and 3.5 equiv. Bu^{n}Li (Table 2, entries 2, 6 and 9). In the case of (−)-sparteine **2** the yield remains poor; reducing further the quantity of this ligand results in an increase in yield (entries 3 and 4), however, ee is gradually reduced (although, interestingly, the ee is maintained at levels equivalent to the stoichiometric reaction when as little as 5 mol% (−)-sparteine **2** is used; Table 2, entry 4). Ligand acceleration using **10** is not as efficient as with **2** and ee drops significantly with further reduction in the quantity of **10** as, presumably, the background (ligand-free) reaction begins to compete more effectively. In the absence of a ligand the rate of reaction was considerably slowed by cooling to −98 °C (2.5 equiv. Bu^{n}Li, Et_2O; 30% yield after 1 h); however, initiating a (−)-sparteine-mediated reaction at −98 °C gave no increase in selectivity (a small increase in yield was observed; 5 mol % (−)-sparteine, 2.5 equiv. Bu^{n}Li: 61% yield, 43% ee; *cf.* Table 2, entry 4). Extension to other organolithiums[9,10] was generally unsatisfactory, *e.g.* with epoxide **1** and (−)-sparteine **2** (0.2 equiv.) the following organolithiums (2.7 equiv.) gave enediols in the yields and ees indicated: MeLi (12% yield, 15% ee), Pr^{i}Li (37% yield, 46% ee), $TMSCH_2Li$ (61% yield, 26% ee) and PhLi (16% yield, 46% ee).†

The increase in yield when the proportion of organolithium relative to ligand is increased (Table 2) is in line with our above hypothesis (Scheme 3) regarding the fate of the lithiated intermediate. That an increase in ee is *also* observed (on reducing the quantity of ligand from 2.5 to 1.0 equiv.), is potentially also consistent with this argument, as the major lithiated epoxide enantiomer arising from a ligand-accelerated deprotonation is likely to be more closely associated with ligand than the lithiated intermediate arising from a non-selective (non-ligand mediated) deprotonation. If the ligand-mediated reaction requires decomplexation of the ligand from the lithiated epoxide before formation of the metallate species (*i.e.* **22** ⟶ **21**, Scheme 3), then, assuming decomplexation is aided by the presence of ligand-free organolithium, it follows that reducing the relative proportion of ligand to alkyllithium will be beneficial.

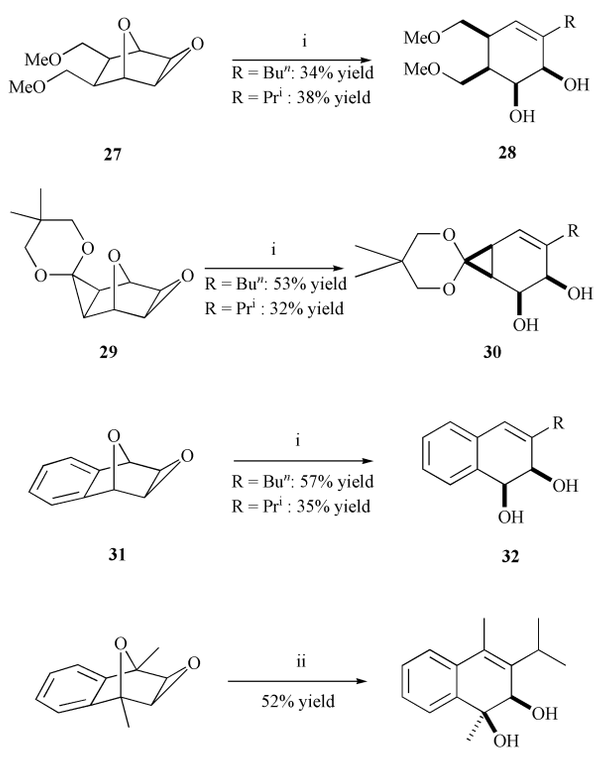
With the above results in hand (and considering the hypothesis outlined in Scheme 3), we next turned our attention to epoxides derived from 7-oxabicyclo[2.2.1]heptenes. For these substrates a competing C–H insertion (or β-elimination) pathway could not operate, due to the unfavourable formation of a bridgehead double bond. A number of readily available symmetrical 7-oxabicyclo[2.2.1]heptenes (*e.g.*, **23**, **24** and **25**, Fig. 2) have previously been utilised in other desymmetrisation processes by Lautens,[25] Waymouth[26] and Nakamura.[27]



23 **24** **25**; R = H **26**; R = Me

Fig. 2 7-Oxabicyclo[2.2.1]heptenes.

The epoxides of alkenes **23**, **24** and **25**[28] were readily prepared (75–82% yield), exclusively as the *exo*-isomers, by epoxidation using *in situ* generated methyl(trifluoromethyl)dioxirane.[29] The resulting epoxides **27**, **29** and **31** were first reacted with Bu^{n}Li as well as Pr^{i}Li in the absence of a ligand. The desired cyclohexenediols **28**, **30** and **32** were obtained in 32–57% yield (Scheme 4). We also chose to examine the dimethyl-substituted



Scheme 4 *Reagents and conditions:* i, Bu^{n}Li or Pr^{i}Li (2.5 equiv.), THF, −78 °C (5 h) to 25 °C (16 h); ii, Pr^{i}Li–TMEDA (2.5 equiv.), Et_2O, −78 °C (5 h) to 25 °C (16 h).

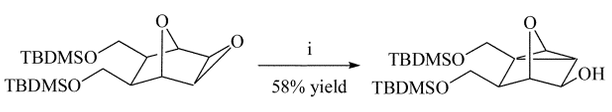
Table 3 Asymmetric alkylative double ring-opening of 7-oxabicyclo-[2.2.1]heptene-derived epoxides

Entry	Substrate	R	Ligand	Yield (%)	ee (%)[a]
1	**27**	Bu^n	**2**	46	34
2	**27**	Bu^n	**10**	34	−40
3	**27**	Pr^i	**2**	34	63
4	**29**	Bu^n	**2**	57	27
5	**29**	Pr^i	**2**	49	59
6	**31**	Bu^n	**2**	51	50
7[b]	**31**	Pr^i	**2**	44	74
8	**33**	Pr^i	**2**	42	56

[a] Determined by chiral HPLC. [b] Using toluene or cumene as alternative solvents gave **32** in 42% yield, 71% ee, and 45% yield, 69% ee, respectively.

epoxide **33** (prepared from alkene **26**[30] in 79% yield). This relatively more hindered epoxide failed to react with either Bu^{n}Li or Pr^{i}Li in the absence of a ligand; however, addition of the achiral diamine TMEDA to the reaction of **33** with Pr^{i}Li in Et_2O gave the expected substituted cyclohexenediol **34** in 52% yield (Scheme 4). The cyclohexenediols **28**, **30**, **32** and **34** were the sole products isolated from these reactions (the mass balance presumably comprising volatile, or water soluble or polar baseline materials).

Interestingly, under otherwise identical conditions, the bis(*tert*-butyldimethylsilyl) analogue of **27** (*i.e.* epoxide **35**, Scheme 5) on treatment with Bu^{n}Li gave only the tricyclic alcohol **36** (58% yield) arising from a transannular carbenoid insertion.[5–8] One possible explanation for the divergent reactivity of epoxides **27** and **35** might be that following lithiation of the epoxide ring of **35** a subtle electronic effect of the silyl ethers could encourage the observed transannular C–H insertion by making that C–H bond more nucleophilic. Alternatively, the steric demands of the silyl protecting groups might disfavour formation of the ate complex (*cf.* **21**, Scheme 3) which leads to incorporation of the organolithium.



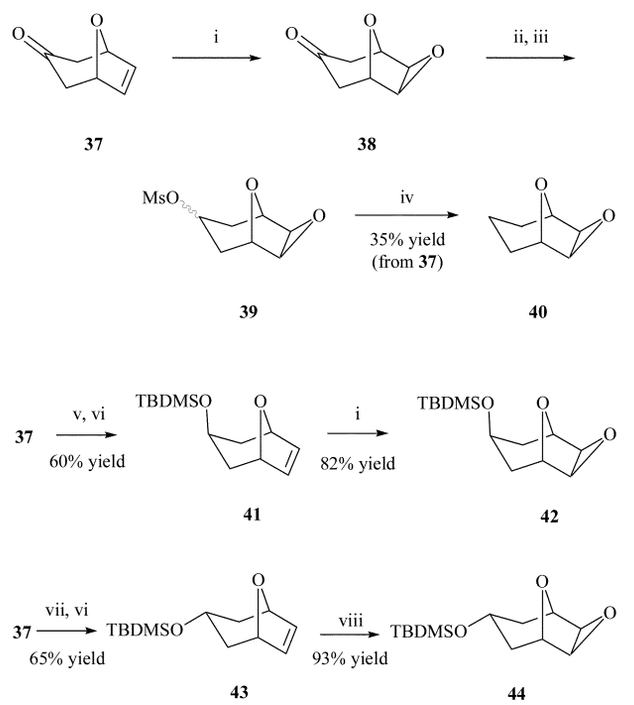
35 **36**

Scheme 5 *Reagents and conditions:* i, Bu^{n}Li (2.5 equiv.), THF, −78 °C (5 h) to 25 °C (16 h).

In contrast to the reactivity of 3,4-epoxytetrahydrofuran, the (−)-sparteine-mediated reactions of the 7-oxabicyclo[2.2.1]-heptene-derived epoxides (**27**, **29**, **31** and **33**) gave similar yields of enantioenriched cyclohexenediols (**28**, **30**, **32** and **34**) to the non-ligand mediated reactions, and ees up to 74% were observed (Table 3).

When benzo-fused substrate **31** was reacted with an excess (3.5 equiv.) of Bu^{n}Li–(−)-sparteine some isomerisation (~10%) of the double bond in the product was observed to the exocyclic position; this presumably occurs *via* partial (base-induced) allylic deprotonation of the alkoxide of **32**. Consequently, the quantity of organolithium–ligand complex was reduced (to 2.1 equiv.) in the reactions with Bu^{n}Li shown in Table 3; alkene isomerisation was not observed under these later conditions. For Pr^{i}Li reactions an excess (3.5 equiv.) was always used. As similar yields but slightly lower ees were observed with Pr^{i}Li and benzo-fused substrate **31** at −78 °C in aromatic hydrocarbon solvents compared with ether (toluene 42% yield 71% ee, cumene 45% yield 69% ee, ether 44% yield 74% ee), the latter solvent was studied exclusively with the other [2.2.1] substrates (Table 3). The asymmetric alkylative double ring-opening reaction of diether **27** with Bu^{n}Li was also conducted in the presence of bisoxazoline **10** (2.1 equiv. of Bu^{n}Li and **10**); compared with using **2** this resulted in a slight increase in ee being combined with a decrease in yield (Table 3, entry 2). Where a comparison is possible, use of the secondary organolithium (Pr^{i}Li) consistently resulted in greater enantioselectivity than the primary organolithium (Bu^{n}Li, *e.g.*, compare Table 3, entries 1 and 3, 4 and 5, and 6 and 7); this is in line with previous observations concerning other epoxide deprotonations.[5–8] The reduced enantioselectivity observed in the reaction of **33** when compared to **31** (*cf.* Table 3, entries 7 and 8) indicates that the methyl substituents of **33** may reduce the difference between the transition states in the suggested[8] ternary epoxide–sparteine–organolithium complexes for deprotonation at the enantiotopic C–H groups of the epoxide.

We next turned our attention to 8-oxabicyclo[3.2.1]octene-derived epoxides. Three substrates (**40**, **42** and **44**) were selected for examination, and were projected to be available from well-known 8-oxabicyclo[3.2.1]oct-6-en-3-one **37**[31,32] (Scheme 6).

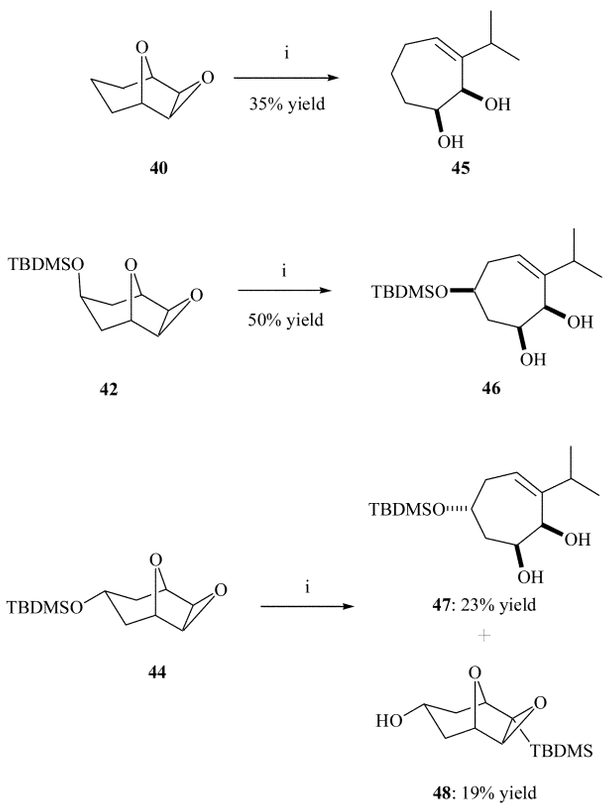


Scheme 6 *Reagents and conditions:* i, 1,1,1-Trifluoroacetone, Oxone, $NaHCO_3$, MeCN, H_2O, 0 °C, 4 h; ii, $LiAlH_4$, THF, −78 °C, 4 h; iii, MsCl, Et_3N, CH_2Cl_2, 0 °C to 25 °C (16 h); iv, $LiAlH_4$, THF : Et_2O (1 : 5), 65 °C, 6.5 h; v, Sm, ICH_2CH_2I, Pr^{i}OH, THF, 65 °C, 3.5 h; vi, TBDMSCl, imidazole, DMF, 25 °C, 16 h; vii, L-Selectride, THF, −78 °C, 1 h then NaOH, H_2O_2; viii, $MeCO_3H$, $NaCO_3$, CH_2Cl_2, 25 °C, 20 h.

Similar to the bicycloheptene epoxides examined earlier, the bicyclooctene epoxides do not present (bridgehead) double bond formation as a possible competing reaction pathway. However, the 3-carbon bridge introduces some potential conformational mobility at the rear of the epoxide and the epimeric silyl ethers **42** and **44** were designed to also probe steric (and any stereoelectronic) effects on product profile/ee, for which the 'unsubstituted' epoxide **40** would act as a suitable substrate for comparison. In the event, synthesis of deoxygenated parent compound **40** did not prove straightforward: desulfurisation of the dithioacetal derived from ketone **37**, or Clemmensen reduction of ketone **37**, or dehydration of the corresponding epoxy alcohol, or Barton deoxygenation of the xanthate derivative all failed to give the desired material. An acceptable method was eventually developed involving treatment of a solution of the epoxy mesylate **39** in THF–Et_2O (1 : 5) with $LiAlH_4$ at reflux for 6.5 h; the desired epoxy oxabicyclo[3.2.1]octane **40** being obtained in 35% yield over four steps from **37**, with negligible hydride ring-opening of the epoxide ring being observed

(Scheme 6).[33] In contrast to **40**, diastereomeric ethers **41** and **43** were readily prepared *via* known, highly stereoselective reductions of the ketone functionality in **37**,[34] followed by protection and epoxidation.

Attempted reaction of epoxides **40**, **42** and **44** with Pr^{i}Li in THF all failed in the absence of a ligand; however, on addition of TMEDA to the reaction mixtures in Et_2O the expected cycloheptenediols **45**, **46** and **47** were obtained in moderate yields (Scheme 7). Epoxysilane **48** was also isolated from the reaction of *endo*-ether **44**, this product likely arises *via* a retro-[1,5]-Brook migration of the silyl group in the putative oxiranyl anion intermediate.[35,36] The asymmetric alkylative double ring-opening reaction of epoxides **40**, **42** and **44** with Pr^{i}Li–(−)-sparteine was then studied, and the reaction conditions were varied with a view to maximising ees/yields of the cycloalkene diols (Table 4).



Scheme 7 *Reagents and conditions:* i, Pr^{i}Li–TMEDA (3.5 equiv.), Et_2O, −78 °C (5 h) to 25 °C (16 h).

Because of the modest yields of cycloheptenediols in Et_2O with epoxides **40**, **42** and **44** (Table 4, entries 1, 6 and 14), other solvents were examined. In contrast to 3,4-epoxytetrahydrofuran **1** and benzo-fused substrate **31** studied earlier, it was found that using aromatic hydrocarbon solvents with the bicyclooctene epoxides resulted in improved yields of cycloheptenediols with the additional benefit of improved ees (entries 3, 9 and 16). Lowering the initial reaction temperature (in cumene) resulted in slight increase in ee only for *exo*-ether **42** (entry 11), however yields were uniformly reduced (entries 4, 11 and 17). Alternatively, yields could be improved (in cumene) at the expense of ee by initiating reactions at temperatures slightly higher than −78 °C. The observations with epoxide **44** of different ees for the cycloheptenediol **47** and the Brook rearrangement product **48** (*e.g.*, Table 4, entry 16; 84% and 40% ee, respectively) provides another example of enantiomeric partitioning:[8] in the presence of the chiral ligand sparteine, the relative proportions of the enantiomeric lithiated epoxides of **44** proceeding to **47** and **48** are different.

Enantioselective nucleophilic ring-opening of unsaturated oxa- and (to a lesser extent) aza-bicyclic compounds, principally being developed by Lautens,[26,37,38] results in cycloalkenes bearing the nucleophile in an *allylic* position. The results described herein represent, to the best of our knowledge, the first enantioselective generation–intermolecular nucleophile trapping of a lithium carbenoid[39] (*cf.* Scheme 1).[12] Proceeding *via* double ring-opening, the chemistry comprises an intermolecular C–C single bond forming reaction with cogeneration of unsaturation and two functional group reorganisations, leading to nucleophile incorporation at a *vinylic* position and synthetically valuable 1,2-diol functionality. It provides a new and enantioselective access to unsaturated diols in a regio-, stereo- and enantio-controlled fashion, and thus has the potential to be a powerful method for organic synthesis. A recent report by O'Brien indicates ways in which the sparteine framework might be modified so as to improve on the yields and ees reported herein.[40] Extensions of the current process to other epoxides,[24] organolithiums and manipulation of the adducts towards targets of biological interest,[41] are also under investigation.

Table 4 Asymmetric alkylative double ring-opening reaction of 8-oxabicyclo[3.2.1]octene-derived epoxides

Entry	Substrate	Solvent	Temp. (°C)	Yield (%)	ee (%)[a]
1	**40**	Et_2O	−78	31	63
2	**40**	Toluene	−78	28	79
3	**40**	Cumene	−78	44	85
4	**40**	Cumene	−90	34	80
5	**40**	Cumene	−61	58	73
6	**42**	Et_2O	−78	41	50
7	**42**	Pentane	−78	21	46
8	**42**	Hexane	−78	49	56
9	**42**	Toluene	−78	58	66
10	**42**	Cumene	−78	46	69
11	**42**	Cumene	−90	34	74
12	**42**	Cumene	−61	58	65
13	**42**	Cumene	−42	36	ND
14[b]	**44**	Et_2O	−78	21	71
15[b]	**44**	Toluene	−78	59	77
16[b]	**44**	Cumene	−78	54	84
17[b]	**44**	Cumene	−90	23	83
18[b]	**44**	Cumene	−61	33	ND

[a] Determined by chiral HPLC or chiral GC. ND = Not determined. [b] **48** was also observed: entry 14: 16% (66% ee); entry 15: 13% (64% ee); entry 16: 10% (40% ee); entry 17: 0%; entry 18: 18% (ee ND).

Experimental

General

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 under argon; CH_2Cl_2, pentane, hexane, toluene and cumene from CaH_2 under argon. External reaction temperatures are reported unless stated otherwise. Reactions were monitored by TLC using commercially available aluminium-backed plates, precoated 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}. Melting points were determined using a Gallenkamp hot stage apparatus and are uncorrected. Elemental analysis was performed by Elemental Microanalysis Limited, Okehampton, Devon, UK. 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 Bruker JEOL EX400 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. OH signals were assigned by the absence of cross-peaks in ^1H–^{13}C correlation spectra. Chiral stationary phase HPLC was performed using a Daicel Chiralcel OD column (4.6 mm × 250 mm) or Daicel Chiralpak AD column (4.6 mm × 250 mm) on a Gilson System with 712 Controller Software and a 118 UV–vis detector set at 254 nm. Chiral GC was performed using on a ThermoQuest CE Instruments TRACE GC, running Chrom-Card for TRACE software, fitted with a CYDEX-β column at the stated temperature–temperature gradient. Retention times for major (t_R mj) and minor (t_R mn) enantiomers are given in minutes.

Typical experimental procedure for ligand mediated alkylative desymmetrisation: (+)-3-methyleneheptane-1,2-diol 3

To a stirred solution of (4*S*)-2,2′-(1-ethylpropylidene)bis[4-(1-methylethyl)-4,5-dihydrooxazole] **10**[42] (0.28 g, 0.93 mmol) in toluene (3 cm^3) at −78 °C was added dropwise Bu^{n}Li (1.9 mol dm^{-3} in hexanes, 1.7 cm^3, 3.3 mmol). After stirring at −78 °C for 1 h a solution of 3,4-epoxytetrahydrofuran **1**[43] (80 mg, 0.93 mmol) in toluene (3 cm^3) was added dropwise over 10 min. The reaction mixture was stirred at −78 °C for 5 h and then allowed to warm to 25 °C over 16 h. HCl (1 mol dm^{-3}, 5 cm^3) was added and the layers separated, the organic phase was washed with further HCl (1 mol dm^{-3}, 5 cm^3), the combined aqueous washings extracted with Et_2O (10 cm^3), the combined organic layers dried, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (75% Et_2O in light petroleum) gave 3-methyleneheptane-1,2-diol **3**[9,10] as a colourless oil (0.10 g, 75%); $[a]_D^{25}$ +9.0 (*c* 1.0 in $CHCl_3$). The ee of the bis(3,5-dinitrobenzoate)† was determined to be 55% by chiral HPLC (OD Column, 80% EtOH in heptane, 1.0 cm^3min^{-1}, t_R mj, 24.0; t_R mn, 34.0).

(−)-4-(1-Methylenepentane)-2,2-dimethyl-1,3-dioxolane 4

To a solution of (−)-3-methyleneheptane-1,2-diol **3** (0.274 g, 1.69 mmol, prepared following Table 2, entry 3) in 2,2-dimethoxypropane (5 cm^3) and dry benzene (10 cm^3) at 25 °C was added anhydrous PTSA (15 mg, 79 μmol). After 14 h water (30 cm^3) was added and the mixture extracted with Et_2O (3 × 30 cm^3). The combined organic extracts were dried, filtered and concentrated under reduced pressure, yielding pure *dioxolane* **4** (0.300 g, 88%); R_f 0.60 (90% Et_2O in light petroleum); $[a]_D^{25}$ −29.1 (*c* 1.1 in $CHCl_3$); ν_{max}/cm^{-1} 2933m, 1456w, 1370m, 1215m, 1158m, 1065s, 903m and 862m; δ_H(400 MHz) 5.13 (1 H, s, C=CH), 4.88 (1 H, s, C=CH), 4.51 (1 H, dd, *J* 8.0 and 6.5, OCH), 4.10 (1 H, dd, *J* 8.0 and 6.5, OCH), 3.60 (1 H, dd, *J* 8.0 and 8.0, OCH), 2.08–1.91 (2 H, m, CH_2), 1.47–1.40 (2 H, m, CH_2), 1.44 (3 H, s, CCH_3), 1.39 (3 H, s, CCH_3), 1.37–1.28 (2 H, m, CH_2), and 0.90 (3 H, t, *J* 7.5, CH_3); δ_C(100 MHz) 146.8 (*C*=CH), 110.4 ($C(CH_3)_2$), 109.1 (C=*C*H), 78.9 (OCH), 69.1 (OCH_2), 31.3 (CCH_3), 30.0 (CCH_3), 26.3 (CH_2), 25.7 (CH_2), 22.5 (CH_2) and 13.9 (CH_3); *m*/*z* [CI + (NH_3)] 202 (M + NH_4^+, 20%), 185 (M + H^+, 100), 169 (55) and 127 (70) (Found: M + NH_4^+, 202.1806. $C_{11}H_{24}NO_2$ requires 202.1807).

(−)-1-(2,2-Dimethyl-1,3-dioxolan-4-yl)-1-pentanone 5[14]

Ozone was bubbled through a solution of (−)-4-(1-methylenepentane)-2,2-dimethyl-1,3-dioxolane **4** (0.151 g, 0.748 mmol) in CH_2Cl_2 (15 cm^3) at −78 °C until a blue colour persisted (*ca.* 5 min). The excess ozone was than removed by bubbling oxygen through the solution until the blue colour disappeared. After addition of Me_2S (0.4 cm^3) at −78 °C, the reaction mixture was warmed to 25 °C for 2 h and then concentrated under reduced pressure. Purification of the residue by column chromatography (90% Et_2O in light petroleum) gave *ketone* **5** as a colourless oil (0.119 g, 85%); R_f 0.27 (90% Et_2O in light petroleum); $[a]_D^{22}$ −44.1 (*c* 1.57 in CH_2Cl_2) {lit. for pure *R* isomer,[14] $[a]_D^{20}$ +63.2 (*c* 2.2 in CH_2Cl_2)}; ν_{max}/cm^{-1} 2960m, 1718s, 1385m, 1373m,1261m, 1216m, 1153m, 1072s and 849m; δ_H(400 MHz) 4.40 (1 H, dd, *J* 7.8 and 5.7, OCH), 4.17 (1 H, dd, *J* 8.7 and 7.8, OCH), 3.94 (1 H, dd, *J* 8.7 and 5.7, OCH), 2.58 (1 H, t, *J* 7.1, C=OCH_2), 2.57 (1 H, t, *J* 7.1, C=OCH_2), 1.57–1.48 (2 H, m, CH_2), 1.46 (3 H, s, CCH_3), 1.36 (3 H, s, CCH_3), 1.34–1.25 (2 H, m, CH_2), 0.88 (3 H, t, *J* 7.5, CH_3); δ_C(100 MHz) 211.0 (C=O), 110.8 ($C(CH_3)_2$), 80.2 (OCH), 66.5 (OCH_2), 38.2 (CCH_3), 26.0 (CCH_3), 25.0 (CH_2), 24.9 (CH_2), 22.2 (CH_2) and 13.8 (CH_3).

***exo,exo*-2,3-Bis(methoxymethyl)-5,6-epoxy-7-oxabicyclo [2.2.1]heptane 27**

To a solution of *exo*-2,3-bis(methoxymethyl)-7-oxabicyclo [2.2.1]hept-5-ene **23**[26] (1.15 g, 6.24 mmol) and Na_2EDTA (400 μmol dm^{-3} in H_2O, 31 cm^3, 13 μmol, 0.002 equiv.) in MeCN (47 cm^3) at 0 °C was added trifluoroacetone (6.2 cm^3, 69 mmol, 11 equiv.) from a pre-cooled syringe. The resulting homogeneous mixture was treated with a mixture of Oxone® (19.2 g, 31.2 mmol, 5 equiv.) and $NaHCO_3$ (4.20 g, 50.0 mmol, 8 equiv.) portionwise over 15 minutes, and then stirred at 0 °C for 4.5 h.[29] H_2O (240 cm^3) was added and the mixture extracted with CH_2Cl_2 (3 × 240 cm^3). The combined organic layers were dried, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (Et_2O) gave *epoxide* **27** as a white solid (1.02 g, 82%); R_f 0.15 (Et_2O); mp 66–67 °C (Found: C, 59.7; H, 8.2. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.1%); ν_{max}/cm^{-1} (KBr) 2997m, 2932m, 2894m, 1486m, 1461m, 1038s and 964s; δ_H(400 MHz) 4.38 (2 H, s, C(1)–H and C(4)–H), 3.35 (2 H, dd, *J* 8.8 and 5.2, 2 × C*H*H), 3.32 (6 H, s, 2 × CH_3), 3.31 (2 H, s, C(5)–H and C(6)–H), 3.29–3.24 (2 H, m, 2 × CH*H*′) and 2.14–2.07 (2 H, m, C(2)–H and C(3)–H); δ_C(100 MHz) 76.7 (C(1) and C(4)), 70.0 (2 × CH_2), 58.8 (2 × CH_3), 49.8 (C(5) and C(6)) and 43.2 (C(2) and C(3)); *m*/*z* [APCI +] 223 (M + Na^+, 10%), 201 (M + H^+, 30), 169 (40), 155 (50), 137 (100), 123 (100) and 109 (90).

(+)-(1*RS*,2*SR*,5*RS*,6*RS*)-3-Butyl-5,6-bis(methoxymethyl) cyclohex-3-ene-1,2-diol 28 (R = Bu^n)

Following the general procedure above, *exo,exo*-2,3-bis-(methoxymethyl)-5,6-epoxy-7-oxabicyclo[2.2.1]heptane **27** (80 mg, 400 μmol) in Et_2O was reacted with Bu^{n}Li (2.40 mol dm^{-3} in hexanes, 0.35 cm^3, 840 μmol, 2.1 equiv.) in the presence of (−)-sparteine **2** (0.20 cm^3, 840 μmol, 2.1 equiv.). Column chromatography (75% Et_2O in light petroleum) gave *enediol* **28** (R = Bu^n) as a colourless oil (48 mg, 46%); R_f 0.15 (75% Et_2O in petrol); $[a]_D^{25}$ +28.7 (*c* 1.00 in $CHCl_3$); ν_{max}/cm^{-1} 3370s br, 2926s, 1458m and 1100s; δ_H(500 MHz) 5.32 (1 H, d, *J* 3.2, C(4)–H), 4.37 (1 H, d, *J* 10.0, OH), 3.97 (1 H, br s, C(2)–H), 3.84–3.80 (1 H, m, C(1)–H), 3.60–3.52 (2 H, m, C(6)–CH_2), 3.44–3.36 (2 H, m, C(5)–CH_2), 3.39 (3 H, s, OCH_3), 3.36 (3H, s, OCH_3), 2.99 (1 H, d, *J* 10.0, OH), 2.56 (1 H, br s, C(6)–H), 2.35 (1 H, dq, *J* 7.5 and 3.0, C(5)–H), 2.32–2.26 (1 H, m, C*H*H), 2.08–2.02 (1 H, m, CH*H*′), 1.54–1.23 (4 H, m, 2 × CH_2) and 0.91 (3 H, t, *J* 7.0, CH_3); δ_C(125 MHz) 140.3 (C(3)), 122.6 (C(4)), 71.6 (C(6)–CH_2), 71.2 (C(5)–CH_2), 69.1 (C(2)), 67.4 (C(1)), 58.8 (OCH_3), 58.7 (OCH_3), 39.1 (C(5)), 36.6 (C(6)), 32.9 (CH_2), 30.0 (CH_2), 22.4 (CH_2) and 13.9 (CH_3); *m*/*z* [CI + (NH_3)] 259 (M + H^+, 20%), 241 (100) and 193 (35) (Found: M + H^+, 259.1907. $C_{14}H_{27}O_4$ requires 259.1909). The ee of the bis(3,5-dinitrobenzoate)† was determined to be 34% by chiral HPLC (OD Column, 80% EtOH in heptane, 1.0 cm^3min^{-1}, t_R mj, 19.0; t_R mn, 41.8).

(+)-(1*RS*,2*SR*,5*RS*,6*RS*)-5,6-Bis(methoxymethyl)-3-isopropyl cyclohex-3-ene-1,2-diol 28 (R = Pr^i)

Following the general procedure above, *exo,exo*-2,3-bis-(methoxymethyl)-5,6-epoxy-7-oxabicyclo[2.2.1]heptane **27** (80

mg, 400 μmol) in Et_2O was reacted with Pr^iLi (1.55 mol dm^{-3} in light petroleum, 0.64 cm^3, 1.00 mmol, 2.5 equiv.) in the presence of (−)-sparteine **2** (0.23 cm^3, 1.00 mmol, 2.5 equiv.). Column chromatography (75% Et_2O in light petroleum) gave *enediol* **28** (R = Pr^i) as a pale yellow oil (33 mg, 34%); R_f 0.15 (75% Et_2O in light petroleum); $[\alpha]_D^{25}$ +33.2 (*c* 1.00 in $CHCl_3$); ν_{max}/cm^{-1} 3382m br, 2893s, 1460m, 1387m and 1100s; δ_H(400 MHz) 5.28 (1 H, br d, *J* 3.6, C(4)–H), 4.33 (1 H, d, *J* 10.0, OH), 4.0–4.04 (1 H, m, C(2)–H), 3.81 (1 H, ddd, *J* 10.0, 4.4 and 2.8, C(1)–H), 3.60–3.51 (2 H, m, C(6)–CH_2), 3.41 (2 H, dq, *J* 9.6 and 4.0, C(5)–CH_2), 3.38 (3 H, s, OCH_3), 3.35 (3 H, s, OCH_3), 3.03 (1 H, d, *J* 10.4, OH), 2.61 (1 H, sept., *J* 7.0, C*H*$(CH_3)_2$), 2.57–2.53 (1 H, m, C(6)–H), 2.33 (1 H, ddd, *J* 14.0, 7.2 and 2.8, C(5)–H), 1.06 (3 H, d, *J* 7.0, CH(CH_3)$_2$) and 1.05 (3 H, d, *J* 7.0, CH(CH_3)$_2$); δ_C(100 MHz) 145.6 (C(3)), 120.3 (C(4)), 71.6 (CH_2), 71.5 (CH_2), 68.6 (C(2)), 67.9 (C(1)), 58.9 (OCH_3), 58.8 (OCH_3), 38.9 (C(5)), 36.7 (C(6)), 29.4 (*C*H$(CH_3)_2$), 22.4 (CH(*C*H_3)$_2$) and 20.9 (CH(*C*H_3)$_2$); *m*/*z* [CI + (NH_3)] 262 (M + NH_4^+, 25%) and 245 (M + H^+, 100) (Found: M + H^+, 245.1756. $C_{13}H_{25}O_4$ requires 245.1753). The ee of the bis-(3,5-dinitrobenzoate)† was determined to be 63% by chiral HPLC (OD Column, 80% EtOH in heptane, 1.0 cm^3 min^{-1}, t_R mj, 16.8; t_R mn, 42.2).

exo-8-Oxatricyclo[3.2.1.0^{2,4}]oct-6-en-3-one neopentyl acetal 24

A mixture of 6,6-dimethyl-4,8-dioxaspiro[2,5]oct-1-ene[44] (7.15 g, 51.0 mmol) and furan (37 cm^3, 510 mmol, 10 equiv.) were heated together at 60–70 °C in a sealed tube for 7 days. Following concentration under reduced pressure the residue was purified by column chromatography (50% Et_2O in light petroleum) giving *alkene* **24** as a white solid (4.20 g, 40%); R_f 0.20 (50% Et_2O in light petroleum); mp 88–90 °C (light petroleum) (Found: C, 68.9; H, 8.0. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%); ν_{max}/cm^{-1} (KBr) 2995s, 2957s, 2866m, 1474m, 1381s, 1109s and 1079s; δ_H(400 MHz) 6.59 (2 H, s, C(6)–H and C(7)–H), 5.06 (2 H, s, C(1)–H and C(5)–H), 3.60 (2 H, s, CH_2), 3.52 (2 H, s, CH_2), 1.55 (2 H, s, C(2)–H and C(4)–H) and 1.02 (6 H, s, 2 × CH_3); δ_C(100 MHz) 138.3 (C(6) and C(7)), 104.4 (C(3)), 77.2 (C(1) and C(5)), 76.6 (CH_2), 76.2 (CH_2), 33.2 (C(2) and C(4)), 30.6 (*C*$(CH_3)_2$) and 22.4 (2 × CH_3); *m*/*z* [APCI +] 209 (M + H^+, 45%) and 123 (100).

exo,exo-6,7-Epoxy-8-oxatricyclo[3.2.1.0^{2,4}]octan-3-one neopentyl acetal 29

To a solution of *exo*-8-oxatricyclo[3.2.1.0^{2,4}]oct-6-en-3-one neopentyl acetal **24** (4.20 g, 20.2 mmol) and Na_2EDTA (400 μmol dm^{-3} in H_2O, 100 cm^3, 40 μmol, 0.002 equiv.) in MeCN (150 cm^3) at 0 °C was added trifluoroacetone (20 cm^3, 220 mmol, 11 equiv.) from a pre-cooled syringe. The resulting homogeneous mixture was treated with a mixture of Oxone® (62.0 g, 101 mmol, 5 equiv.) and $NaHCO_3$ (13.6 g, 162 mmol, 8 equiv.) portionwise over 30 minutes, and then stirred at 0 °C for 1.5 h.[29] H_2O (600 cm^3) was added and the mixture extracted with CH_2Cl_2 (3 × 500 cm^3). The combined organic layers were dried, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (Et_2O) gave *epoxide* **29** as a white solid (3.40 g, 75%); R_f 0.20 (Et_2O); mp 151–153 °C (Found: C, 64.3; H, 7.2. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.2%); ν_{max}/cm^{-1} (KBr) 2960m, 2872w, 1458m, 1111s and 1029s; δ_H(400 MHz) 4.59 (2 H, s, C(1)–H and C(5)–H), 3.54 (2 H, s, CH_2), 3.51 (2 H, s, C(6)–H and C(7)–H), 3.48 (2 H, s, CH_2), 1.64 (2 H, s, C(2)–H and C(4)–H) and 0.99 (6 H, s, 2 × CH_3); δ_C(100 MHz) 92.5 (C(3)), 76.2 (CH_2), 76.0 (CH_2), 72.8 (C(1) and C(5)), 53.0 (C(6) and C(7)), 30.5 (*C*$(CH_3)_2$), 29.8 (C(2) and C(4)) and 22.3 (2 × CH_3); *m*/*z* [APCI +] 225 (M + H^+, 100%), 157 (30), 139 (40) and 111 (70).

(+)-(1*RS*,4*SR*,5*RS*,6*RS*)-3-Butyl-4,5-dihydroxybicyclo[4.1.0]hept-2-en-7-one neopentyl acetal 30 (R = Bu^n)

Following the general procedure above, *exo,exo*-6,7-epoxy-8-oxatricyclo [3.2.1.0^{2,4}]octan-3-one neopentyl acetal **29** (80 mg, 360 μmol) in Et_2O was reacted with Bu^nLi (2.40 mol dm^{-3} in hexanes, 0.31 cm^3, 750 μmol, 2.1 equiv.) in the presence of (−)-sparteine **2** (0.17 cm^3, 750 μmol, 2.1 equiv.). Column chromatography (75% Et_2O in light petroleum) gave *enediol* **30** (R = Bu^n) as a colourless oil (57 mg, 57%); R_f 0.20 (75% Et_2O in light petroleum); $[\alpha]_D^{25}$ +21.5 (*c* 1.00 in $CHCl_3$); ν_{max}/cm^{-1} 3437s br, 2958s, 2871s, 1470s, 1435s, 1254m, 1135s and 1065s; δ_H(400 MHz) 5.59 (1 H, d, *J* 5.6, C(2)–H), 4.15 (1 H, dt, *J* 9.6 and 5.6, C(5)–H), 3.90 (1 H, dd, *J* 12.0 and 5.6, C(4)–H), 3.74 (1 H, d, *J* 12.0, OH), 3.57–3.46 (3 H, m, OCH_2 and OC*H*H), 3.26 (1 H, d, *J* 10.8, OCH*H*), 3.06 (1 H, d, *J* 9.6, OH), 2.14–2.10 (2 H, m, CH_2), 1.92 (1 H, dd, *J* 9.6 and 5.6, C(6)–H), 1.81 (1 H, dd, *J* 10.4 and 5.6, C(1)–H), 1.47–1.25 (4 H, m, 2 × CH_2), 1.22 (3 H, s, CCH_3), 0.90 (3 H, t, *J* 7.2, CH_3) and 0.80 (3 H, s, CCH_3); δ_C(100 MHz) 138.8 (C(3)), 126.0 (C(2)), 92.6 (C(7)), 77.2 (OCH_2), 76.0 (OCH_2), 68.1 (C(4)), 66.2 (C(5)), 34.8 (CH_2), 30.6 (*C*$(CH_3)_2$), 30.1 (CH_2), 28.7 (C(6)), 25.2 (C(1)), 22.9 (C(*C*H_3)$_2$), 22.4 (CH_2), 21.8 (C(*C*H_3)$_2$) and 13.9 (CH_3); *m*/*z* [CI + (NH_3)] 300 (M + NH_4^+, 10%), 283 (M + H^+, 10), 265 (100), 148 (50) and 131 (65) (Found: M + NH_4^+, 300.2178. $C_{16}H_{30}NO_4$ requires 300.2175). The ee of the bis(3,5-dinitrobenzoate)† was determined to be 27% by chiral HPLC (OD Column, 80% EtOH in heptane, 1.0 cm^3min^{-1}, t_R mj, 19.9; t_R mn, 26.3).

(+)-(1*RS*,4*SR*,5*RS*,6*RS*)-4,5-Dihydroxy-3-isopropylbicyclo[4.1.0]hept-2-en-7-one neopentyl acetal 30 (R = Pr^i)

Following the general procedure above, *exo,exo*-6,7-epoxy-8-oxatricyclo [3.2.1.0^{2,4}]octan-3-one neopentyl acetal **29** (80 mg, 360 μmol) in Et_2O was reacted with Pr^iLi (1.40 mol dm^{-3} in light petroleum, 0.64 cm^3, 890 μmol, 2.5 equiv.) in the presence of (−)-sparteine **2** (0.20 cm^3, 890 μmol, 2.5 equiv.). Column chromatography (75% Et_2O in light petroleum) gave *enediol* **30** (R = Pr^i) as a colourless oil (47 mg, 49%); R_f 0.20 (75% Et_2O in light petroleum); $[\alpha]_D^{25}$ +35.0 (*c* 1.00 in $CHCl_3$); ν_{max}/cm^{-1} 3432s br, 2958s, 2870m, 1471m, 1434m, 1136m and 1064s; δ_H(400 MHz) 5.63 (1 H, d, *J* 5.6, C(2)–H), 4.16–4.11 (1 H, m, C(5)–H), 4.00 (1 H, dd, *J* 12.0 and 5.6, C(4)–H), 3.80 (1 H, d, *J* 12.0, OH), 3.57–3.47 (3 H, m, OCH_2 and OC*H*H), 3.25 (1 H, d, *J* 11.2, OCH*H*), 3.09 (1 H, d, *J* 9.2, OH), 2.41 (1 H, sept., *J* 6.8, C*H*$(CH_3)_2$), 1.93 (1 H, dd, *J* 10.4 and 6.0, C(6)–H), 1.83 (1 H, dd, *J* 10.4 and 5.6, C(1)–H), 1.22 (3 H, s, CCH_3), 1.08 (3 H, d, *J* 6.8, CH(CH_3)$_2$), 1.03 (3 H, d, *J* 6.8, CH(CH_3)$_2$) and 0.80 (3 H, s, CCH_3); δ_C(100 MHz) 144.6 (C(3)), 115.1 (C(2)), 92.7 (C(7)), 77.2 (OCH_2), 76.0 (OCH_2), 67.3 (C(4)), 66.4 (C(5)), 32.8 (*C*H$(CH_3)_2$), 30.5 (*C*$(CH_3)_2$), 29.0 (C(6)), 25.1 (C(1)), 22.8 (C(*C*H_3)$_2$), 22.3 (CH(*C*H_3)$_2$), 21.8 (CH(*C*H_3)$_2$) and 21.7 (C(*C*H_3)$_2$); *m*/*z* [ES +] 291 (M + Na^+, 100%), 251 (50) and 172 (25) (Found: M + Na^+, 291.1573. $C_{15}H_{24}NaO_4$ requires 291.1572). The ee of the bis(3,5-dinitrobenzoate)† was determined to be 59% by chiral HPLC (OD Column, 80% EtOH in heptane, 1.0 cm^3min^{-1}, t_R mj, 18.9; t_R mn, 23.7).

(−)-(1*RS*,2*SR*)-3-Butyl-1,2-dihydronaphthalene-1,2-diol 32 (R = Bu^n)

Following the general procedure above, *exo*-1,4–2,3-diepoxy-1,2,3,4-tetrahydronaphthalene **31**[28] (80 mg, 360 μmol) in Et_2O was reacted with Bu^nLi (1.90 mol dm^{-3} in hexanes, 0.55 cm^3, 1.1 mmol, 2.1 equiv.) in the presence of (−)-sparteine **2** (0.24 cm^3, 1.1 mmol, 2.1 equiv.). Column chromatography (50% Et_2O in light petroleum) gave *enediol* **32** (R = Bu^n) as a white solid (55 mg, 50%); R_f 0.20 (50% Et_2O in light petroleum); mp 62–63 °C(Et_2O–light petroleum); $[\alpha]_D^{25}$ −47.1 (*c* 0.79 in $CHCl_3$);ν_{max}/cm^{-1} ($CHCl_3$) 3292s br, 2928s, 2858m, 1456m and 1099m; δ_H(400 MHz) 7.56–7.52 (1 H, m, C(8)–H), 7.28–7.22

(2 H, m, C(6)–H and C(7)–H), 7.08–7.04 (1 H, m, C(5)–H), 6.26 (1 H, s, C(4)–H), 4.70 (1 H, br s, C(1)–H), 4.10 (1 H, br s, C(2)–H), 2.65 (1 H, br d, *J* 9.2, OH), 2.38–2.28 (2 H, m, CH_2), 1.92 (1 H, br s, OH), 1.60–1.50 (2 H, m, CH_2), 1.47–1.38 (2 H, m, CH_2) and 0.98–0.94 (3 H, m, CH_3); δ_C(100 MHz) 141.1 (C(3)), 134.8 (C(8a)), 132.3 (C(4a)), 128.1 (ArC–H), 127.5 (ArC–H), 126.3 (ArC–H), 126.1 (ArC–H), 123.8 (C(4)), 71.4 (C(1)), 70.4 (C(2)), 34.1 (CH_2), 30.3 (CH_2), 22.5 (CH_2) and 14.0 (CH_3); *m*/*z* [CI + (NH_3)] 236 (M + NH_4^+, 80%) and 218 (M^+, 75) (Found: M + NH_4^+, 236.1649. $C_{14}H_{22}NO_2$ requires 236.1651). The ee was determined to be 51% by chiral HPLC (OD Column, 10% EtOH in hexane, 0.3 $cm^{-3}min^{-1}$, t_R mn, 19.7; t_R mj, 22.4).

(−)-(1*RS*,2*SR*)-3-Isopropyl-1,2-dihydronaphthalene-1,2-diol 32 (R = Pr^i)

Following the general procedure above, *exo*-1,4–2,3-diepoxy-1,2,3,4-tetrahydronaphthalene **31**[28] (80 mg, 360 μmol) in Et_2O was reacted with Pr^iLi (1.10 mol dm^{-3} in light petroleum, 1.6 cm^3, 1.8 mmol, 3.5 equiv.) in the presence of (−)-sparteine **2** (0.40 cm^3, 1.8 mmol, 3.5 equiv.). Column chromatography (50% Et_2O in light petroleum) gave *enediol* **32** (R = Pr^i) as a white solid (45 mg, 44%); R_f 0.30 (80% Et_2O in light petroleum); mp 78–79 °C(EtOH); $[\alpha]_D^{25}$ −104.5 (*c* 1.00 in $CHCl_3$);ν_{max}/cm^{-1} (KBr) 3306s br, 2959s, 2866m, 1454m, 1263m, 1112m and 1086s; δ_H(400 MHz) 7.59–7.57 (1 H, m, C(8)–H), 7.29–7.23 (2 H, m, C(6)–H and C(7)–H), 7.09–7.07 (1 H, m, C(5)–H), 6.28 (1 H, s, C(4)–H), 4.71 (1 H, m, C(1)–H), 4.15 (1 H, d, *J* 4.2, C(2)–H), 2.66–2.57 (1 H, m, C*H*(CH_3)$_2$), 1.21 (3 H, d, *J* 7.0, CH_3) and 1.19 (3 H, d, *J* 7.0, CH_3); δ_C(100 MHz) 146.9 (C(3)), 135.1 (C(8a)), 132.1 (C(4a)), 128.0 (ArC–H), 127.6 (ArC–H), 126.4 (ArC–H), 126.0 (ArC–H), 122.0 (C(4)), 71.8 (C(1)), 69.3 (C(2)), 32.6 (*C*H(CH_3)$_2$), 21.8 (CH_3) and 21.3 (CH_3); *m*/*z* [CI + (NH_3)] 222 (M + NH_4^+, 10%), 206 (20), 187 (100), 170 (50) and 155 (40) (Found: M + NH_4^+, 222.1489. $C_{13}H_{20}NO_2$ requires 222.1494). The ee was determined to be 74% by chiral HPLC (OD Column, 20% EtOH in hexane, 0.3 $cm^{-3}min^{-1}$, t_R mn, 15.7; t_R mj, 17.7).

exo-1,4-Dimethyl-1,4:2,3-diepoxy-1,2,3,4-tetrahydro naphthalene 33

To a solution of 1,4-dimethyl-1,4-epoxy-1,4-dihydronaphthalene **26**[30] (3.83 g, 22.2 mmol) and Na_2EDTA (400 μmol dm^{-3} in H_2O, 110 cm^3, 44 μmol, 0.002 equiv.) in MeCN (170 cm^3) at 0 °C was added trifluoroacetone (22 cm^3, 245 mmol, 11 equiv.) from a pre-cooled syringe. The resulting homogeneous mixture was treated with a mixture of Oxone® (68.4 g, 111 mmol, 5 equiv.) and $NaHCO_3$ (15.0 g, 178 mmol, 8 equiv.) portionwise over 30 minutes, and then stirred at 0 °C for 2.5 h.[29] H_2O (600 cm^3) was added and the reaction mixture extracted with CH_2Cl_2 (3 × 500 cm^3). The combined organics were dried, filtered and concentrated under reduced pressure giving an off-white solid. Recrystallisation (EtOAc–hexanes) gave *epoxide* **33** as a white solid (3.30 g, 79%); R_f 0.35 (50% Et_2O in light petroleum); mp 86–87 °C(EtOAc–hexanes) (Found: C, 76.3; H, 6.5. $C_{12}H_{12}O_2$ requires C, 76.6; H, 6.4%); ν_{max}/cm^{-1} (KBr) 3055m, 2982m, 2936m, 1455s, 1386s, 1286s, 1143s and 978m; δ_H(400 MHz) 7.25–7.19 (4 H, m, 4 × ArH), 3.35 (2 H, s, C(2)–H and C(3)–H) and 1.82 (6 H, s, 2 × CH_3); δ_C(100 MHz) 148.8 (C(4a) and C(8a)), 126.9 (C(6) and C(7)), 119.6 (C(5) and C(8)), 83.2 (C(1) and C(4)); 58.8 (C(2) and C(3)) and 13.7 (2 × CH_3); *m*/*z* [CI + (NH_3)] 206 (M + NH_4^+, 20%), 189 (M + H^+, 100), 173 (65), 159 (90) and 90 (40) (Found: M + H^+, 189.0915. $C_{12}H_{13}O_2$ requires 189.0915).

(−)-(1*RS*,2*RS*)-1,2-Dihydro-1,4-dimethyl-3-isopropyl naphthalene-1,2-diol 34

Following the general procedure above, *exo*-1,4-dimethyl-1,4:2,3-diepoxy-1,2,3,4-tetrahydronaphthalene **33** (0.100 g, 531 μmol) in Et_2O was reacted with Pr^iLi (1.50 mol dm^{-3} in light petroleum, 0.89 cm^3, 1.3 mmol, 2.5 equiv.) in the presence of (−)-sparteine **2** (0.31 cm^3, 1.3 mmol, 2.5 equiv.). Column chromatography (50% Et_2O in light petroleum) gave *enediol* **34** as a white solid (52 mg, 42%); R_f 0.25 (50% Et_2O in light petroleum); mp 108–109 °C (Et_2O–light petroleum) (Found: C, 77.2; H, 8.8. $C_{15}H_{20}O_2$ requires C, 77.5; H, 8.7%); $[\alpha]_D^{25}$ −108.6 (*c* 1.00 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3306m br, 2964s, 2930m, 1390m, 1330m, 1090s and 1001s; δ_H(500 MHz) 7.70–7.68 (1 H, m, ArH), 7.32–7.25 (3 H, m, 3 × ArH), 3.83 (1 H, d, *J* 8.0, C(2)–H), 3.15 (1 H, sept., *J* 7.0, C*H*(CH_3)$_2$), 3.09 (1 H, s, OH), 2.08 (3 H, s, C(4)–CH_3), 1.44 (1 H, d, *J* 8.0, OH), 1.32 (3 H, s, C(1)–CH_3), 1.17 (3 H, d, *J* 7.0, CH(CH_3)$_2$) and 1.12 (3 H, d, *J* 7.0, CH(CH_3)$_2$); δ_C(125 MHz)) 140.9 (C=C), 140.1 (C=C), 133.9 (C(8a)), 127.6 (ArC–H), 127.3 (ArC–H), 126.5 (C(4a)), 125.0 (ArC–H), 123.8 (ArC–H), 73.5 (C(1)), 71.0 (C(2)), 29.0 (*C*H(CH_3)$_2$), 25.3 (C(1)–CH_3), 21.1 (CH(*C*H_3)$_2$), 19.9 (CH(*C*H_3)$_2$) and 13.7 (C(4)–CH_3); *m*/*z* [CI + (NH_3)] 250 (M + NH_4^+, 10%), 232 (M + H^+, 20), 215 (100), 199 (90) and 183 (25) (Found: M + NH_4^+, 250.1805. $C_{15}H_{24}NO_2$ requires 250.1807). The ee was determined to be 56% by chiral HPLC (OD Column, 5% EtOH in heptane, 0.3 $cm^{-3}min^{-1}$, t_R mj, 23.7; t_R mn, 27.0).

exo-2,3-Bis(*tert*-butyldimethylsilyloxymethyl)-7-oxabicyclo [2.2.1]hept-5-ene

To a solution of crude *exo*-2,3-bis(hydroxymethyl)-7-oxabicyclo[2.2.1]hept-5-ene[26] (~11 mmol) in DMF (5.5 cm^3) was added TBDMSCl (4.10 g, 27.2 mmol, 2.5 equiv.) and imidazole (3.70 g, 54.5 mmol, 5 equiv.). After stirring for 16 h the reaction mixture was partitioned between Et_2O (20 cm^3) and H_2O (10 cm^3). The organic layer was washed with H_2O (2 × 10 cm^3), dried, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, 5% Et_2O in light petroleum) gave the *bis(silyl ether)* as a colourless oil (3.04 g, ~60%); R_f 0.25 (5% Et_2O in light petroleum); ν_{max}/cm^{-1} 2930s, 2857s, 1472m, 1256s, 1114m, 1081s and 837s; δ_H(400 MHz) 6.36 (2 H, s, C(5)–H and C(6)–H), 4.82 (2 H, s, C(1)–H and C(4)–H), 3.77 (2 H, dd, *J* 10.0 and 5.6, 2 × C*H*H), 3.56–3.51 (2 H, m, 2 × CH*H*), 1.82–1.75 (2 H, m, C(2)–H and C(3)–H), 0.91 (18 H, s, 2 × C(CH_3)$_3$), 0.07 (6 H, s, 2 × $SiCH_3$) and 0.06 (6 H, s, 2 × $SiCH_3$); δ_C(100 MHz) 135.5 (C(5) and C(6)), 80.4 (C(1) and C(4)), 62.3 (2 × CH_2), 42.4 (C(2) and C(3)), 25.9 (2 × C(*C*H_3)$_3$), 18.2 (2 × *C*(CH_3)$_3$) and −5.3 (4 × $SiCH_3$).

exo,exo-2,3-Bis(*tert*-butyldimethylsilyloxymethyl)-5,6-epoxy-7-oxabicyclo[2.2.1]heptane 35

To a solution of *exo*-2,3-bis(*tert*-butyldimethylsilyloxymethyl)-7-oxabicyclo[2.2.1]hept-5-ene (3.04 g, 7.90 mmol) and Na_2-EDTA (400 μmol dm^{-3} in H_2O, 40 cm^3, 16 μmol, 0.002 equiv.) in MeCN (60 cm^3) at 0 °C was added trifluoroacetone (7.8 cm^3, 87 mmol, 11 equiv.) from a pre-cooled syringe. The resulting homogeneous mixture was treated with a mixture of Oxone® (24.3 g, 39.5 mmol, 5 equiv.) and $NaHCO_3$ (5.31 g, 63.2 mmol, 8 equiv.) portionwise over 30 minutes, and then stirred at 0 °C for 2 h.[29] H_2O (300 cm^3) was added and the reaction mixture extracted with CH_2Cl_2 (3 × 250 cm^3). The combined organics were dried, filtered and concentrated under reduced pressure, purification of the residue by column chromatography (SiO_2, 20% Et_2O in light petroleum) gave the *epoxide* **35** as a colourless oil which solidified on standing (2.67 g, 84%); R_f 0.25 (20% Et_2O in light petroleum); mp 38–40 °C (Found: C, 59.9; H, 10.4. $C_{20}H_{40}O_4Si_2$ requires C, 60.0; H, 10.1%); ν_{max}/cm^{-1} 2955s, 2930s, 2857s, 1472m, 1257s, 1083s and 837s; δ_H(400 MHz) 4.39 (2 H, s, C(1)–H and C(4)–H), 3.65 (2 H, dd, *J* 10.0 and 5.6, 2 × C*H*H), 3.52–3.48 (2 H, m, 2 × CH*H*), 3.32 (2 H, s, C(5)–H and C(6)–H), 2.05–1.89 (2 H, m, C(2)–H and C(3)–H), 0.89 (18 H, s,

2 × $C(CH_3)_3$), 0.05 (6 H, s, 2 × $SiCH_3$) and 0.04 (6 H, s, 2 × $SiCH_3$); δ_C(100 MHz) 76.5 (C(1) and C(4)), 60.4 (2 × CH_2), 50.0 (C(5) and C(6)), 45.9 (C(2) and C(3)), 25.8 (2 × C(CH_3)$_3$), 18.1 (2 × $C(CH_3)_3$) and −5.4 (4 × $SiCH_3$); *m/z* [APCI +] 423 (M + Na^+, 10%), 401 (M + H^+, 15), 269 (70), 155 (100) and 137 (40).

1,7-Bis(*tert*-butyldimethylsiloxymethyl)-3-oxatricyclo [2.2.1.0^{2,6}]heptan-5-ol 36

To a solution of *exo,exo*-2,3-bis(*tert*-butyldimethyl silyloxymethyl)-5,6-epoxy-7-oxabicyclo[2.2.1]heptane **35** (80 mg, 200 μmol) in THF (5 cm^3) at −78 °C was added Bu^{n}Li (2.00 mol dm^{-3} in hexanes, 0.25 cm^3, 500 μmol, 2.5 equiv.) dropwise. The mixture was stirred at −78 °C for 5 h and then allowed to warm to 25 °C over 16 h. Phosphate buffer (pH 7, 5 cm^3) was added and the mixture extracted with EtOAc (2 × 10 cm^3). The combined organic layers were dried, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO_2, 50% Et_2O in light petroleum) gave the *tricyclic alcohol* **36** as a colourless oil (46 mg, 58%); R_f 0.20 (50% Et_2O in light petroleum); ν_{max}/cm^{-1}3435m br, 2930s, 2857s, 1472s, 1390m, 1256s, 1086s, 837s and 776s; δ_H(400 MHz) 4.02 (1 H, s, C(4)–H), 3.99 (1 H, d, *J* 4.0, C(2)–H), 3.93 (1 H, br d, *J* 11.0, C(5)–H), 3.73 (2 H, d, *J* 5.6, C(1)–CH_2), 3.60 (1 H, dd, *J* 10.0 and 5.6, C(7)–CH_2), 3.40 (1 H, t, *J* 9.6, C(7)–CH_2), 1.97 (1 H, dd, *J* 9.6 and 5.6, C(6)–H), 1.72 (1 H, d, *J* 11.0, OH), 1.48 (1 H, d, *J* 4.0, C(7)–H), 0.88 (9 H, s, C(CH_3)$_3$), 0.87 (9 H, s, C(CH_3)$_3$), 0.04 (6 H, s, 2 × $SiCH_3$) and 0.02 (6 H, s, 2 × $SiCH_3$); δ_C(100 MHz) 76.8 (C(4)), 74.3 (C(5)), 59.8 (C(7)–CH_2), 58.8 (C(1)–CH_2), 54.8 (C(2)), 45.5 (C(6)), 31.4 (C(1)), 25.8 (2 × C(CH_3)$_3$), 22.5 (C(7)), 18.2 ($C(CH_3)_3$), 18.1 ($C(CH_3)_3$), −6.4 (2 × $SiCH_3$) and −6.5 (2 × $SiCH_3$); *m/z* [CI + (NH_3)] 418 (M + NH_4^+, 20%) and 401 (M + H^+, 100) (Found: M + H^+, 401.2543. $C_{20}H_{41}O_4Si_2$ requires 401.2543).

6,7-Epoxy-8-oxabicyclo[3.2.1]octan-3-ol

To a solution of *exo*-6,7-epoxy-8-oxabicyclo[3.2.1]octan-3-one **38**[45] (4.37 g, 24.2 mmol) in THF (175 cm^3) at −78 °C was added $LiAlH_4$ (1.0 mol dm^{-3} in THF, 12 cm^3, 12 mmol, 2 equiv. hydride). After 4 h at −78 °C the temperature was raised to 0 °C and the reaction quenched according to the procedure of Fieser and Fieser[46] (0.46 cm^3 H_2O, 0.46 cm^3 15% aqueous NaOH and 1.4 cm^3 H_2O). The resulting granular precipitate was removed by filtration through Celite and was then washed with hot EtOAc (500 cm^3). The combined organic extracts were concentrated under reduced pressure to give an inseparable 9 : 1 diastereomeric mixture (^{1}H NMR) of *alcohol* as a pale yellow gum (3.57 g, quant.,); R_f 0.20 (EtOAc); ν_{max}/cm^{-1} 3401s br, 2953s, 1275s and 1081s; δ_H(400 MHz, major diastereoisomer) 4.27 (2 H, d, *J* 4.2, C(1)–H and C(5)–H), 4.12–4.02 (1 H, m, C(3)–H), 3.50 (2 H, s, C(6)–H and C(7)–H), 2.26 (1 H, br s, OH), 2.00 (2 H, dd, *J* 14.0 and 6.4, C(2)–H and C(4)–H) and 1.66 (2 H, ddd, *J* 14.0, 10.2 and 4.2, C(2)–H and C(4)–H); δ_C(100 MHz, major diastereoisomer) 71.8 (C(1) and C(5)), 62.5 (C(3)), 52.6 (C(6) and C(7)) and 35.7 (C(2) and C(4)); δ_H(400 MHz, minor diastereoisomer) 4.19 (2 H, d, *J* 4.2, C(1)–H and C(5)–H), 4.12–4.02 (1 H, m, C(3)–H), 3.67 (2 H, s, C(6)–H and C(7)–H), 2.26 (1 H, br s, OH), 2.18 (2 H, dt, *J* 15.4 and 4.2, C(2)–H and C(4)–H) and 1.57 (2 H, dd, *J* 15.4 and 0.8, C(2)–H and C(4)–H); δ_C(100 MHz, minor diastereoisomer) 71.0 (C(1) and C(5)), 62.2 (C(3)), 54.2 (C(6) and C(7)) and 33.7 (C(2) and C(4)); *m/z* [CI + (NH_3)] 160 (M + NH_4^+, 100%) (Found: M + NH_4^+, 160.0972. $C_7H_{14}NO_3$ requires 160.0974).

3-(Methylsulfonyl)-6,7-epoxy-8-oxabicyclo[3.2.1]octane 39

To a solution of 6,7-epoxy-8-oxabicyclo[3.2.1]octan-3-ol (3.57 g, 24.2 mmol) in CH_2Cl_2 (120 cm^3) at 0 °C was sequentially added Et_3N (14 cm^3, 97 mmol, 4 equiv.) and MsCl (4.7 cm^3, 61 mmol, 2.5 equiv.). The resulting mixture was allowed to warm to 25 °C over 16 h, then diluted with CH_2Cl_2 (150 cm^3) and washed with H_2O (150 cm^3), HCl (2.0 mol dm^{-3} in H_2O, 150 cm^3), saturated aqueous $NaHCO_3$ (150 cm^3) and brine (150 cm^3). The organic layer was dried, filtered and concentrated under reduced pressure to give an inseparable 9 : 1 diastereomeric mixture (^{1}H NMR) of mesylate **39** as a yellow solid (4.83 g, 90%); R_f 0.40 (EtOAc); ν_{max}/cm^{-1} (KBr) 3006m, 2829m, 1355s, 1172s, and 1045s; δ_H(400 MHz, major diastereoisomer) 5.06 (1 H, tt, *J* 10.6 and 6.6, C(3)–H), 4.34 (2 H, d, *J* 4.4, C(1)–H and C(5)–H), 3.60 (2 H, s, C(6)–H and C(7)–H), 3.02 (3 H, s, CH_3), 2.19 (2 H, dd, *J* 14.0 and 6.6, C(2)–H and C(4)–H) and 1.99 (2 H, ddd, *J* 14.0, 10.6 and 4.4, C(2)–H and C(4)–H); δ_C(100 MHz, major diastereoisomer) 72.4 (C(3)), 71.5 (C(1) and C(5)), 52.1 (C(6) and C(7)), 38.7 (CH_3) and 33.0 (C(2) and C(4)); δ_H(400 MHz, minor diastereoisomer) 4.98–4.95 (1 H, m, C(3)–H), 4.26 (2 H, d, *J* 4.2, C(1)–H and C(5)–H), 3.72 (2 H, s, C(6)–H and C(7)–H), 3.14 (3 H, s, CH_3), 2.28 (2 H, dt, *J* 17.0 and 4.2, C(2)–H and C(4)–H) and 1.95 (2 H, d, *J* 17.0, C(2)–H and C(4)–H); δ_C(100 MHz, minor diastereoisomer) 73.5 (C(3)), 70.3 (C(1) and C(5)), 53.5 (C(6) and C(7)), 38.7 (CH_3) and 31.5 (C(2) and C(4)); *m/z* [CI + (NH_3)] 238 (M + NH_4^+, 100%) and 142 (20) (Found: M + NH_4^+, 238.0744. $C_8H_{16}NO_5S$ requires 238.0749).

exo-6,7-Epoxy-8-oxabicyclo[3.2.1]octane 40

To a suspension of 3-(methylsulfonyl)-6,7-epoxy-8-oxabicyclo-[3.2.1]octane **39** (4.50 g, 20.4 mmol) in Et_2O (510 cm^3) and THF (60 cm^3) at reflux was added $LiAlH_4$ (1.0 mol dm^{-3} in THF, 41 cm^3, 41 mmol, 8 equiv. hydride). After 6.5 h the reaction mixture was cooled to 0 °C and quenched according to the procedure of Fieser and Fieser[46] (1.6 cm^3 H_2O, 1.6 cm^3 15% aqueous NaOH and 4.7 cm^3 H_2O). The resulting granular precipitate was removed by filtration through Celite and was then washed with hot EtOAc (500 cm^3). The combined organics were concentrated under reduced pressure and then purified by column chromatography (70% Et_2O in light petroleum) to give a pale yellow solid which was further purified by bulb-to-bulb distillation (75 °C, 0.2 mbar) to give *epoxide* **40** as a white solid (1.00 g, 39%); R_f0.10 (50% Et_2O in petrol); mp 89–91 °C; ν_{max}/cm^{-1} (KBr) 2949m, 1464m, 1442m, 1395m, 1292m, 1092m and 1026s; δ_H(400 MHz) 4.15 (2 H, d, *J* 4.0, C(1)–H and C(5)–H), 3.57 (2 H, s, C(6)–H and C(7)–H), 1.92–1.83 (2 H, m, C(2)–H and C(4)–H), 1.78–1.65 (1 H, m, C(3)–H) and 1.56–1.48 (3 H, m, C(2)–H, (C(3)–H and C(4)–H); δ_C(100 MHz) 71.9 (C(1) and C(5)), 52.9 (C(6) and C(7)), 25.1 (C(2) and C(4)) and 16.3 (C(3)); *m/z* [CI + (NH_3)] 144 (M + NH_4^+, 100%) (Found: M + NH_4^+, 144.1024. $C_7H_{14}NO_2$ requires 144.1025).

(−)-(1*RS*,2*SR*)-3-Isopropylcyclohept-3-ene-1,2-diol 45

Following the general procedure above, *exo*-6,7-epoxy-8-oxabicyclo[3.2.1]octane **40** (80 mg, 634 μmol) in cumene was reacted with Pr^{i}Li (1.40 mol dm^{-3} in light petroleum, 1.6 cm^3, 2.2 mmol, 3.5 equiv.) in the presence of (−)-sparteine **2** (0.51 cm^3, 2.2 mmol, 3.5 equiv.). Column chromatography (60 to 90% Et_2O in light petroleum, 10% steps) gave *enediol* **45** as a white solid (47 mg, 44%); R_f 0.30 (Et_2O); mp 100–102 °C; $[\alpha]_D^{23}$ −43.0 (*c* 0.66 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3339s br, 2965m, 2920s, 2878m, 1466m, 1444m, 1302m, 1264m, 1071m and 1045s; δ_H(400 MHz) 5.75 (1 H, dd, *J* 8.8 and 4.8, C(4)–H), 4.20 (1 H, br s, C(2)–H), 3.64 (1 H, ddd, *J* 11.0, 4.2 and 1.6, C(1)–H), 2.49–2.21 (4 H, m, C(5)–H, C$H(CH_3)_2$ and 2 × OH), 2.18–2.07 (1 H, m, C(7)–H), 2.04–1.95 (1 H, m, C(5)–H), 1.94–1.85 (1 H, m, C(7)–H), 1.74–1.66 (1 H, m, C(6)–H), 1.49–1.36 (1 H, m, C(6)–H), 1.02 (3 H, d, *J* 6.8, CH_3) and 1.01 (3 H, d, *J* 6.8, CH_3); δ_C(100 MHz) 146.0 (C(3)), 128.2 (C(4)), 75.9 (C(2)), 73.0 (C(1)), 36.2 ($CH(CH_3)_2$), 34.1 (C(7)), 26.4 (C(5)), 25.8 (C(6)), 21.5

(CH_3) and 21.4 (CH_3); *m/z* [CI + (NH_3)] 188 (M + NH_4^+, 100%), 186 (40), 170 (M + H^+, 85), 154 (40), 153 (40) and 137 (90) (Found: M + NH_4^+, 188.1653. $C_{10}H_{22}NO_2$ requires 188.1651). The ee of the bis(3,5-dinitrobenzoate) † was determined to be 85% by chiral HPLC (OD Column, 80% EtOH in hexane, 0.75 cm^3min^{-1}, t_R mn, 31.3; t_R mj, 40.3).

exo-3-(*tert*-Butyldimethylsilyloxy)-8-oxabicyclo[3.2.1]oct-6-ene 41

A mixture of *exo*-8-oxabicyclo[3.2.1]oct-6-en-3-ol[34] (0.350 g, 2.77 mmol), TBDMSCl (0.520 g, 3.47 mmol, 1.25 equiv.) and imidazole (0.470 g, 6.93 mmol, 2.5 equiv.) in DMF (1.5 cm^3) was stirred for 16 h and then partitioned between Et_2O (10 cm^3) and H_2O (10 cm^3). The organic layer was separated and washed with H_2O (2 × 10 cm^3), dried, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (10% Et_2O in light petroleum) gave *silyl ether* **41** as a colourless oil (0.515 g, 77%); R_f 0.25 (10% Et_2O in light petroleum); ν_{max}/cm^{-1} 2953s, 2857m, 1254m, 1113s, 1089s, 1047m and 964s; δ_H(400 MHz) 6.11 (2 H, s, C(6)–H and C(7)–H), 4.76 (2 H, d, *J* 3.8, C(1)–H and C(5)–H), 3.89 (1 H, tt, *J* 9.6 and 6.4, C(3)–H), 1.77 (2 H, dd, *J* 13.2 and 6.4, C(2)–H and C(4)–H), 1.67 (2 H, ddd, *J* 13.2, 9.6 and 3.8, C(2)–H and C(4)–H), 0.88 (9 H, s, $C(CH_3)_3$) and 0.03 (6 H, s, 2 × $SiCH_3$); δ_C(100 MHz) 130.9 (C(6) and C(7)), 78.1 (C(1) and C(5)), 64.5 (C(3)), 35.8 (C(2) and C(4)), 25.8 ($C(CH_3)_3$), 18.0 ($C(CH_3)_3$) and −4.6 (2 × $SiCH_3$); *m/z* [CI + (NH_3)] 258 (M + NH_4^+, 25%), 241 (M + H^+, 100) and 183 (10) (Found: M + H^+, 241.1621. $C_{13}H_{25}O_2Si$ requires 241.1624).

exo,exo-3-(*tert*-Butyldimethylsilyloxy)-6,7-epoxy-8-oxabicyclo-[3.2.1]octane 42

To a solution of *exo*-3-(*tert*-butyldimethylsilyloxy)-8-oxabicyclo[3.2.1]oct-6-ene **41** (0.780 g, 3.25 mmol) and Na_2EDTA (400 μmol dm^{-3} in H_2O, 16 cm^3, 6.5 μmol, 0.002 equiv.) in MeCN (24 cm^3) at 0 °C was added trifluoroacetone (3.2 cm^3, 35 mmol, 11 equiv.) from a pre-cooled syringe. The resulting homogeneous mixture was treated with a mixture of Oxone® (9.99 g, 16.3 mmol, 5 equiv.) and $NaHCO_3$ (2.18 g, 26.0 mmol, 8 equiv.) portionwise over 30 minutes, and then stirred at 0 °C for 4 h.[29] H_2O (300 cm^3) was added and the reaction mixture extracted with CH_2Cl_2 (3 × 300 cm^3). The combined organic layers were dried, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (50% Et_2O in light petroleum) gave *epoxide* **42** as colourless oil which crystallised on standing (0.640 g, 77%); R_f 0.20 (50% Et_2O in light petroleum); mp 47.5–48.0 °C (Found: C, 61.1; H, 9.5. $C_{13}H_{24}O_3Si$ requires C, 60.9; H, 9.4%); ν_{max}/cm^{-1} (KBr) 2957s, 2856s, 1472s, 1394m, 1260s and 1157m; δ_H(400 MHz) 4.27 (2 H, d, *J* 4.4, C(1)–H and C(5)–H), 4.07 (1 H, tt,*J* 10.4 and 6.4, C(3)–H), 3.51 (2 H, s, C(6)–H and C(7)–H), 1.89 (2 H, dd, *J* 14.0 and 6.4, C(2)–H and C(4)–H), 1.75 (2 H, ddd, *J* 14.0, 10.4 and 4.4, C(2)–H and C(4)–H), 0.87 (9 H, s, $C(CH_3)_3$) and 0.04 (6 H, s, 2 × $SiCH_3$); δ_C(100 MHz) 71.9 (C(1) and C(5)), 63.2 (C(2)), 52.7 (C(6) and C(7)), 36.2 (C(2) and C(4)), 25.7 ($C(CH_3)_3$), 18.0 ($C(CH_3)_3$) and −4.7 (2 × $SiCH_3$); *m/z* [CI + (NH_3)] 274 (M + NH_4^+, 100%), 257 (M + H^+, 30) and 241 (85) (Found: M + NH_4^+, 274.1844. $C_{13}H_{28}NO_3Si$ requires 274.1838).

(−)-(1*RS*,2*SR*,4*SR*)-4-(*tert*-Butyldimethylsilyloxy)-7-isopropylcyclohept-6-ene-1,2-diol 46

Following the general procedure above, *exo,exo*-3-(*tert*-butyldimethylsilyloxy)-6,7-epoxy-8-oxabicyclo[3.2.1]octane **42** (80 mg, 310 μmol) in cumene was reacted with Pr^iLi (1.40 mol dm^{-3} in light petroleum, 0.79 cm^3, 1.1 mmol, 3.5 equiv.) in the presence of (−)-sparteine **2** (0.25 cm^3, 1.1 mmol, 3.5 equiv.). Column chromatography (50 to 70% Et_2O in light petroleum, 10% steps) gave *enediol* **46** as a colourless oil (43 mg, 46%); R_f 0.45 (Et_2O); $[\alpha]_D^{24}$ −13.5 (*c* 1.00 in $CHCl_3$);ν_{max}/cm^{-1} 3381s br, 2957s, 2858s, 1464m, 1256s and 1089s; δ_H(400 MHz) 5.40 (1 H, t, *J* 6.0, C(6)–H), 4.14 (1 H, br s, C(1)–H), 3.89–3.84 (1 H, m, C(4)–H), 3.77–3.73 (1 H, m, C(2)–H), 3.25 (1 H, br s, OH), 2.58–2.44 (2 H, m, C(5)–H and OH), 2.37 (1 H, sept, *J* 6.8, $CH(CH_3)_2$), 2.22–2.05 (3 H, m, 2 × C(3)–H and C(5)–H), 1.05 (3 H, d, *J* 6.8, $CH(CH_3)_2$), 1.04 (3 H, d, *J* 6.8, $CH(CH_3)_2$), 0.89 (9 H, s, $C(CH_3)_3$), 0.08 (3 H, s, $SiCH_3$) and 0.06 (3 H, s, $SiCH_3$); δ_C(100 MHz) 147.4 (C(7)), 119.8 (C(6)), 75.8 (C(1)), 71.5 (C(2)), 67.4 (C(4)), 42.5 (C(3)), 35.6 ($CH(CH_3)_2$), 34.8 (C(5)), 25.7 ($C(CH_3)_3$), 22.0 ($CH(CH_3)_2$), 21.9 ($CH(CH_3)_2$), 18.0 ($C(CH_3)_3$), −4.9 ($SiCH_3$) and −5.1 ($SiCH_3$); *m/z* [CI + (NH_3)] 318 (M + NH_4^+, 25%), 301 (M + H^+, 90), 283 (100), 151 (20) and 135 (30) (Found: M + H^+, 301.2202. $C_{16}H_{33}O_3Si$ requires 301.2199). The ee of the bis(3,5-dinitrobenzoate) † was determined to be 69% by chiral HPLC (OD Column, 80% EtOH in hexane, 0.75 cm^3min^{-1}, t_R mn, 21.8; t_R mj, 27.5).

endo-3-(*tert*-Butyldimethylsilyloxy)-8-oxabicyclo[3.2.1]oct-6-ene 43

A mixture of *endo*-8-oxabicyclo[3.2.1]oct-6-en-3-ol[34] (1.15 g, 9.12 mmol), TBDMSCl (1.72 g, 11.4 mmol, 1.25 equiv.) and imidazole (1.55 g, 22.8 mmol, 2.5 equiv.) in DMF (4.5 cm^3) was stirred for 16 h and then partitioned between Et_2O (20 cm^3) and H_2O (10 cm^3). The organic layer was washed with H_2O (2 × 10 cm^3), dried, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (10% Et_2O in light petroleum) gave *silyl ether* **43** as a colourless oil (1.76 g, 80%); R_f 0.35 (10% Et_2O in light petroleum); ν_{max}/cm^{-1} 2949s, 2856m, 1472w, 1256m and 1074s; δ_H(400 MHz) 6.20 (2 H, s, C(6)–H and C(7)–H), 4.68 (2 H, d, *J* 4.0, C(1)–H and C(5)–H), 4.05 (1 H, m, C(3)–H), 2.16 (2 H, ddd, *J* 14.5, 5.4 and 4.0, C(2)–H and C(4)–H), 1.51 (2 H, d, *J* 14.5, C(2)–H and C(4)–H), 0.86 (9 H, s, $C(CH_3)_3$) and −0.02 (6 H, s, 2 × $SiCH_3$); δ_C(100 MHz) 133.6 (C(6) and C(7)), 77.8 (C(1) and C(5)), 64.5 (C(3)), 36.1 (C(2) and C(4)), 25.6 ($C(CH_3)_3$), 17.7 ($C(CH_3)_3$) and −5.0 (2 × $SiCH_3$); *m/z* [CI + (NH_3)] 258 (M + NH_4^+, 10%), 241 (M + H^+, 100) and 132 (10) (Found: M + H^+, 241.1621. $C_{13}H_{25}O_2Si$ requires 241.1624).

endo,exo-3-(*tert*-Butyldimethylsilyloxy)-6,7-epoxy-8-oxabicyclo-[3.2.1]octane 44

To a solution of *endo*-3-(*tert*-butyldimethylsilyloxy)-8-oxabicyclo[3.2.1]oct-6-ene **43** (1.47 g, 6.11 mmol) and Na_2CO_3 (2.60 g, 24.5 mmol, 4 equiv.) in CH_2Cl_2 (30 cm^3) at 0 °C was added AcO_2H (40% in AcOH, 2.1 cm^3, 12 mmol, 2 equiv.) over 15 minutes. The mixture was allowed to warm to room temperature whilst stirring over 15 h, the mixture was then recooled to 0 °C and further quantities of peracetic acid (2 cm^3) and CH_2Cl_2 (5 cm^3) were added. After stirring for a further 5 h the reaction mixture was diluted with CH_2Cl_2 (50 cm^3) and the mixture was washed with NaOH (2.0 mol dm^{-3} in H_2O, 75 cm^3), and then with H_2O until the washings were neutral. The organic layer was dried, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (50% Et_2O in light petroleum) gave *epoxide* **44** as a colourless oil which crystallised on standing (1.46 g, 93%); R_f 0.25 (50% Et_2O in light petroleum); mp 28–29 °C (Found: C, 60.8; H, 9.5. $C_{13}H_{24}O_3Si$ requires C, 60.9; H, 9.4%); ν_{max}/cm^{-1} 2949s, 2855s, 1296m, 1259s, 1203m and 1084s; δ_H(400 MHz) 4.21 (2 H, d, *J* 4.4, C(1)–H and C(5)–H), 3.99 (1 H, m, C(3)–H), 3.64 (2 H, s, C(6)–H and C(7)–H), 2.10 (2 H, dt, *J* 14.0, and 4.4, C(2)–H and C(4)–H), 1.53 (2 H, d, *J* 14.0, C(2)–H and C(4)–H), 0.86 (9 H, s, $C(CH_3)_3$) and 0.02 (6 H, s, 2 × $SiCH_3$); δ_C(100 MHz) 77.3 (C(1) and C(5)), 62.9 (C(3)), 54.6 (C(6) and C(7)), 34.6

(C(2) and C(4)), 25.6 (C(CH_3)$_3$), 17.7 (C(CH$_3$)$_3$) and −5.1 (2 × SiCH$_3$); *m/z* [CI + (NH$_3$)] 257 (M + H$^+$, 100%), 241 (95) and 132 (25) (Found: M + H$^+$, 257.1567. $C_{13}H_{25}O_3Si$ requires 257.1573).

(−)-(1*RS*,2*SR*,4*RS*)-4-(*tert*-Butyldimethylsilyloxy)-7-isopropyl cyclohept-6-ene-1,2-diol 47 and (+)-*endo,exo,endo*-6-(*tert*-butyldimethylsilyl)-6,7-epoxy-8-oxabicyclo[3.2.1] octan-3-ol 48

Following the general procedure above, *endo,exo*-3-(*tert*-butyl dimethylsilyloxy)-6,7-epoxy-8-oxabicyclo[3.2.1]octane **44** (80 mg, 310 μmol) in cumene was reacted with Pr^{i}Li (1.40 mol dm^{-3} in light petroleum, 0.79 cm^3, 1.1 mmol, 3.5 equiv.) in the presence of (−)-sparteine **2** (0.25 cm^3, 1.1 mmol, 3.5 equiv.). Column chromatography (50 to 70% Et$_2$O in light petroleum, 10% steps) gave two products.

First to elute was a colourless oil, *silyl epoxide* **48** (10 mg, 10%); R_f 0.40 (Et$_2$O); $[\alpha]_D^{25}$ +138.2 (*c* 0.84 in CHCl$_3$); ν_{max}/cm^{-1} 3434m br, 2952s, 2856m, 1471m, 1247m and 1089m; δ_H(400 MHz) 4.65 (1 H, d, *J* 3.2, C(5)–H), 4.33 (1 H, t, *J* 4.4, C(3)–H), 4.22 (1 H, s, C(7)–H), 4.19 (1 H, d, *J* 4.4, C(1)–H), 2.18 (1 H, d, *J* 11.2, C(4)–H), 1.89 (1 H, br s, OH), 1.83 (1 H, dd, *J* 13.2 and 4.4, C(2)–H), 1.72–1.63 (2 H, m, C(2)–H and C(4)-H), 1.02 (9 H, s, C(CH$_3$)$_3$), 0.18 (3 H, s, SiCH$_3$) and 0.00 (3 H, s, SiCH$_3$); δ_C(100MHz) 86.3 (C(6)), 83.4 (C(5)), 80.5 (C(7)), 80.4 (C(1)), 73.7 (C(3)), 41.1 (C(4)), 34.1 (C(2)), 27.3 (C(CH_3)$_3$), 17.5 (C(CH$_3$)$_3$), −5.2 (SiCH$_3$) and −5.8 (SiCH$_3$); *m/z* [CI + (NH$_3$)] 274 (M + NH$_4^+$, 100%), 257 (M + H$^+$, 15), 132 (20), 102 (75) and 90 (45). The ee was determined to be 40% by chiral GC (120 °C, t_R mj, 159.2; t_R mn, 166.2).

Second to elute was a colourless oil, *enediol* **47** (51 mg, 54%); R_f 0.35 (Et$_2$O); $[\alpha]_D^{25}$ −58.8 (*c* 1.00 in CHCl$_3$); ν_{max}/cm^{-1} 3378s br, 2956s, 2857s, 1472m, 1253s and 1083s; δ_H(400 MHz) 5.48 (1 H, dd, *J* 8.0 and 5.2, C(6)–H), 4.25 (1 H, br s, C(1)–H), 4.09–4.00 (2 H, m, C(2)–H and C(4)–H), 2.47 (1 H, dd, *J* 15.2 and 5.2, C(5)–H), 2.35 (1 H, sept, *J* 7.0, CH(CH$_3$)$_2$), 2.28–2.17 (2 H, m, C(3)–H and C(5)–H), 2.05–1.91 (3 H, m, C(3)–H and 2 × OH), 1.04 (3 H, d, *J* 7.0, CH(CH_3)$_2$), 1.03 (3 H, d, *J* 7.0, CH(CH_3)$_2$), 0.86 (9 H, s, C(CH$_3$)$_3$), 0.04 (3 H, s, SiCH$_3$) and 0.03 (3 H, s, SiCH$_3$); δ_C(100 MHz) 146.0 (C(7)), 122.6 (C(6)), 75.7 (C(1)), 69.0 (C(2)), 67.8 (C(4)), 41.6 (C(3)), 35.7 (CH(CH$_3$)$_2$), 34.3 (C(5)), 25.7 (C(CH_3)$_3$), 21.6 (CH(CH_3)$_2$), 21.5 (CH(CH_3)$_2$), 18.0 (C(CH$_3$)$_3$) and −5.0 (2 × SiCH$_3$); *m/z* [CI + (NH$_3$)] 318 (M + NH$_4^+$, 90%), 301 (M + H$^+$, 20), 283 (15), 186 (100), 168 (30), 151 (50) and 135 (30) (Found: M + NH$_4^+$, 318.2460. $C_{16}H_{36}NO_3Si$ requires 318.2464). The ee was determined to be 84% by chiral HPLC (AD Column, 20% EtOH in hexane, 0.75 cm^{-3} min^{-1}, t_R mn, 43.9; t_R mj, 51.5) following derivatisation † as the bis(3,5-dinitrobenzoate) and desilylation using BF$_3$.Et$_2$O.

Acknowledgements

We thank the EPSRC and Roche for a CASE award (to M.A.H.S.), the European Union for a Marie Curie Fellowship (HPMF-CT-2002–01589 to B.Š.), the EPSRC National Mass Spectrometry Service Centre for mass spectra, and H. Sintim for providing ligands **7**, **18** and **19**.

References

1 (*a*) M. C. Willis, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1765–1784; (*b*) K. Mikami and A. Yoshida, *J. Synth. Org. Chem. Jpn.*, 2002, **60**, 732–739.
2 E. Schoffers, A. Golebiowski and C. R. Johnson, *Tetrahedron*, 1996, **52**, 3769–3826.
3 E. N. Jacobsen, *Acc. Chem. Res.*, 2000, **33**, 421–431.
4 P. O'Brien, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1439–1458.
5 D. M. Hodgson, G. P. Lee, R. E. Marriott, A. J. Thompson, R. Wisedale and J. Witherington, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2151–2161.
6 D. M. Hodgson, I. D. Cameron, M. Christlieb, R. Green, G. P. Lee and L. A. Robinson, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2161–2174.
7 D. M. Hodgson, C. R. Maxwell and I. R. Matthews, *Tetrahedron: Asymmetry*, 1999, **10**, 1847–1850.
8 For recent reviews, see: (*a*) D. M. Hodgson and E. Gras, *Synthesis*, 2002, 1625–1642; (*b*) D. M. Hodgson, E. Gras and K. Tomooka, in *Topics in Organometallic Chemistry: Organolithiums in Enantioselective Synthesis*, ed. D. M. Hodgson, Springer-Verlag, Heidelberg, 2003, vol. 5, in press.
9 D. M. Hodgson, M. A. H. Stent and F. X. Wilson, *Org. Lett.*, 2001, **3**, 3401–3403.
10 D. M. Hodgson, M. A. H. Stent and F. X. Wilson, *Synthesis*, 2002, 1445–1453.
11 (*a*) A. N. Kasatkin and R. J. Whitby, *Tetrahedron Lett.*, 2000, **41**, 5275–5280; (*b*) P. Kocienski and C. Barber, *Pure Appl. Chem.*, 1990, **62**, 1933–1940.
12 Preliminary communication: D. M. Hodgson, C. R. Maxwell, T. J. Miles, E. Paruch, M. A. H. Stent, I. R. Matthews, F. X. Wilson and J. Witherington, *Angew. Chem., Int. Ed.*, 2002, **41**, 4313–4316; *corrigendum*, 2002, **41**, 4611.
13 J. F. Remenar, B. L. Lucht and D. B. Collum, *J. Am. Chem. Soc.*, 1997, **119**, 5567–5572.
14 M. Larchevêque and Y. Petit, *Synthesis*, 1986, 60–64.
15 For reviews on organolithium-ligand combinations, see: (*a*) K. Tomioka, *Synthesis*, 1990, 541–549; (*b*) D. Hoppe and T. Hense, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2282–2316; (*c*) A. Basu and S. Thayumanavan, *Angew. Chem., Int. Ed.*, 2002, **41**, 716–7386; (*d*) D. M. Hodgson and M. A. H. Stent, in *Topics in Organometallic Chemistry: Organolithiums in Enantioselective Synthesis*, ed. D. M. Hodgson, Springer-Verlag, Heidelberg, 2003, vol. 5, in press.
16 E.-U. Würthwein, K. Behrens and D. Hoppe, *Chem. Eur. J.*, 1999, **5**, 3459–3463.
17 J.-P. Mazaleyrat and D. J. Cram, *J. Am. Chem. Soc.*, 1981, **103**, 4585–4586.
18 D. M. Hodgson and G. P. Lee, *Tetrahedron: Asymmetry*, 1997, **8**, 2303–2306.
19 T. Mukaiyama, K. Soai and S. Kobayashi, *Chem. Lett.*, 1978, 219–222.
20 S. Itsuno, H. Yanaka, C. Hachisuka and K. Ito, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1341–1342.
21 T. Mukaiyama, K. Soai, T. Sato, H. Shimizu and K. Suzuki, *J. Am. Chem. Soc.*, 1979, **101**, 1455–1460.
22 S. Manabe, *Chem. Commun.*, 1997, 737–738.
23 M. Shindo, K. Koga and K. Tomioka, *J. Org. Chem.*, 1998, **63**, 9351–9357.
24 D. M. Hodgson, T. J. Miles and J. Witherington, *Synlett*, 2002, 310–312.
25 (*a*) M. Lautens and S. Ma, *J. Org. Chem.*, 1996, **61**, 7246–7247; (*b*) M. Lautens, C. Dockendorff, K. Fagnou and A. Malicki, *Org. Lett.*, 2002, **4**, 1311–1314; (*c*) M. Lautens, J.-L. Renaud and S. Hiebert, *J. Am. Chem. Soc.*, 2000, **122**, 1804–1805; (*d*) M. Lautens, K. Fagnou and M. Taylor, *Org. Lett.*, 2000, **2**, 1677–1679; (*e*) M. Lautens, K. Fagnou and S. Hiebert, *Acc. Chem. Res.*, 2002, **36**, 48–58.
26 D. B. Millward, G. Sammis and R. M. Waymouth, *J. Org. Chem.*, 2000, **65**, 3902–3909.
27 M. Nakamura, A. Hirai and E. Nakamura, *J. Am. Chem. Soc.*, 2000, **122**, 978–979.
28 L. G. French and T. P. Charlton, *Heterocycles*, 1993, **35**, 305–313.
29 D. Yang, M.-K. Wong and Y.-C. Yip, *J. Org. Chem.*, 1995, **60**, 3887–3889.
30 M. S. Newman, H. M. Dali and W. M. Hung, *J. Org. Chem.*, 1975, **40**, 262–264.
31 J. Mann and L.-C. de Almeida Barbosa, *J. Chem. Soc., Perkin Trans. 1*, 1992, 787–790.
32 H. Kim and H. M. R. Hoffmann, *Eur. J. Org. Chem.*, 2000, 2195–2201.
33 For similar chemoselectivity, see: L. E. Martínez, W. A. Nugent and E. N. Jacobsen, *J. Org. Chem.*, 1996, **61**, 7963–7966.
34 R. Dunkel, M. Mentzel and H. M. R. Hoffmann, *Tetrahedron*, 1997, **53**, 14929–14936.
35 W. H. Moser, *Tetrahedron*, 2001, **57**, 2065–2084.
36 M. E. Jung and C. J. Nichols, *J. Org. Chem.*, 1996, **61**, 9065–9067.
37 M. Lautens, C. Gajda and P. Chiu, *J. Chem. Soc., Chem. Commun.*, 1993, 1193–1194.
38 P. Chiu and M. Lautens, *Top. Curr. Chem.*, 1997, **190**, 1–85.
39 G. Boche and J. C. W. Lohrenz, *Chem. Rev.*, 2001, **101**, 697–756.
40 M. J. Dearden, C. R. Firkin, J.-P. R. Hermet and P. O'Brien, *J. Am. Chem. Soc.*, 2002, **124**, 11870–11871.

41 D. M. Hodgson, J.-M. Galano and M. Christlieb, *Chem. Commun.*, 2002, 2436–2437.
42 S. E. Denmark, N. Nakajima, O. J.-C. Nicaise, A.-M. Faucher and J. P. Edwards, *J. Org. Chem.*, 1995, **60**, 4884–4892.
43 P. L. Barili, G. Berti and E. Mastrorilli, *Tetrahedron*, 1993, **49**, 6263–6276.
44 S. Yamago, M. Nakamura, X. Q. Wang, M. Yanagawa, S. Tokumitsu and E. Nakamura, *J. Org. Chem.*, 1998, **63**, 1694–1703.
45 B. Föhlisch and O. Herrscher, *Tetrahedron*, 1985, **41**, 1979–1983.
46 L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, John Wiley and Sons, New York, 1967, vol. 1, p. 584.