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Optimisation of enantioselectivity for the chiral base-mediated rearrangement of bis-protected *meso*-4,5-dihydroxycyclohexene oxides: asymmetric synthesis of 4-deoxyconduritols and conduritol F

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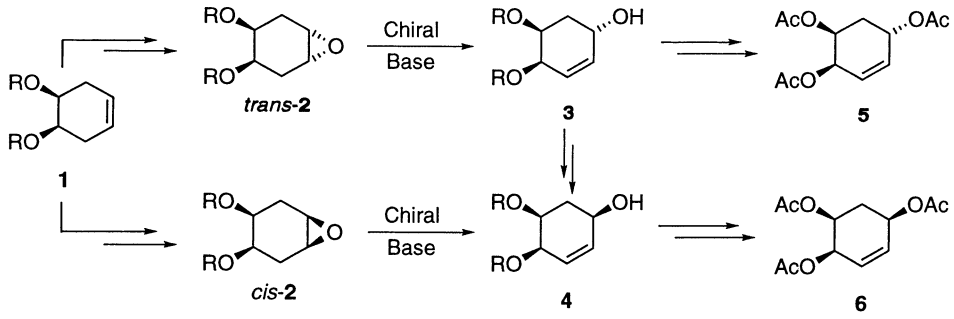
Abstract—A strategy based on diastereoselective epoxidation of a cyclohexene followed by chiral lithium amide-mediated epoxide rearrangement has been used to synthesise an allylic alcohol building block of >95% ee. The key step is the enantioselective rearrangement of a bis-protected *meso*-4,5-dihydroxycyclohexene oxide. A range of protecting groups and chiral base structures were surveyed in order to find the optimum protocol for high enantioselectivity. Using a *tert*-butyldimethylsilyloxy protecting group and a norephedrine-derived chiral base, a 93% yield of an allylic alcohol of >95% ee was achieved. To demonstrate the synthetic utility, this allylic alcohol was subsequently transformed into 4-deoxyconduritols and (+)-conduritol F.

1. Introduction

The first example of the use of a chiral lithium amide base as a reagent for asymmetric synthesis was described in 1980 by Whitesell and Felman.[1] Since then, research into chiral base chemistry has grown dramatically and chiral bases can now be regarded as genuinely useful reagents for organic synthesis. There are three main classes of desymmetrisation reactions[2] mediated by chiral lithium amide bases: (i) rearrangement of epoxides to allylic alcohols; (ii) deprotonation of cyclic ketones and related substrates and (iii) aromatic and benzylic functionalisation of tricarbonyl (η^6-arene) chromium complexes; these areas have been comprehensively reviewed.[3,4]

Whitesell and Felman's seminal contribution in 1980[1] described the chiral base-mediated rearrangement of cyclohexene oxide to cyclohex-2-en-1-ol (36% optical purity), a reaction that had previously been known in the racemic sense for some time.[5] Over the last 20 years, the use of chiral bases in epoxide rearrangements has been studied extensively from a methodology (Asami,[6] Murphy,[7] Hodgson,[8] Singh,[9] Andersson,[10] Ahlberg[11] and ourselves[12]), synthetic (Asami,[13] Mori,[14] Leonard,[15] Hodgson,[16] Singh,[17] Koskinen[18] and ourselves[19]), mechanistic (Morgan,[20] Hodgson[21] and Collum[22]) and theoretical perspective (Ahlberg[11,23]). In addition, Asami,[6d,e] Alexakis,[24] Andersson[10] and Ahlberg[11a,c] have had much success in the development of epoxide rearrangement reactions using sub-stoichiometric amounts of



Scheme 1.

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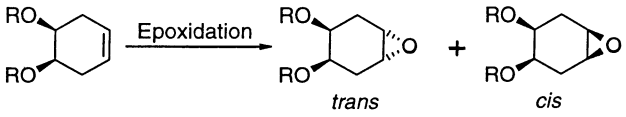
Table 1. Synthesis of *meso*-cyclohexene oxides



Entry	R	Alkene	Epoxidation method	*trans*/*cis*[a]	Epoxide	Yield (%)[b]
1	TES	**7**	*m*-CPBA, CH_2Cl_2[c]	39: 61	*trans*-**8**	38
2	TES	**7**	*m*-CPBA, cyclohexane[d]	85: 15	*trans*-**8**	n.d.
3	TES	**7**	Dioxirane[e]	98: 2	*trans*-**8**	74
4	TBS	**9**	*m*-CPBA, CH_2Cl_2[c]	56: 44	*trans*-**10**	51
5	TBS	**9**	*m*-CPBA, cyclohexane[d]	93: 7	*trans*-**10**	81
6	TBS	**9**	Dioxirane[e]	98: 2	*trans*-**10**	n.d.
7	TBDPS	**11**	*m*-CPBA, CH_2Cl_2[c]	98: 2	*trans*-**12**	92
8	$-C(Me)_2-$	**13**	*m*-CPBA, CH_2Cl_2[c]	90: 10	*trans*-**14**	77

[a] Ratio determined by ^1H NMR spectroscopy on the crude product mixture.
[b] Isolated yield after chromatography.
[c] *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 16–46 h.
[d] *m*-CPBA, $NaHCO_3$, cyclohexane, rt, 16–20 h.
[e] Oxone®, trifluoroacetone, Na_2·EDTA, MeCN–water, $NaHCO_3$, 0°C, 2–3 h.

chiral bases. Specifically, Andersson[10] and Ahlberg[11b,c] have shown that cyclohexene oxide can be rearranged to (*R*)- or (*S*)-cyclohex-2-en-1-ol of ≥96% ee using 5–10 mol% of chiral lithium amide base in the presence of approximately 2 equiv. of achiral (bulk) base.

Our own interest in epoxide rearrangements using chiral bases has focused on methodology and synthetic applications. In particular, over the last few years, we have been developing a general strategy for the diastereo- and enantiocontrolled synthesis of polyhydroxylated cyclohexanes.[12a,19c,e] The essence of the approach is captured in Scheme 1. The key step is the chiral base-mediated rearrangement of bis-protected *meso*-4,5-dihydroxycyclohexene oxides (such as *trans*- and *cis*-**2**) to the corresponding allylic alcohols (**3** and **4**, respectively). Allylic alcohols **3** and **4** can then be used to synthesise 4-deoxyconduritols (such as **5** and **6**), conduritols and related cyclitols[25] as such compounds possess a range of useful biological activity.[26]

Ideally, we wanted to discover a high yielding, diastereoselective way of synthesising *each* of epoxides *trans*- and *cis*-**2** as this would enable us to study the enantioselectivity of the epoxide rearrangements on single epoxide diastereomers. Previously, we have noted that for the bis *tert*-butyldimethylsilyl protected epoxides *trans*- and *cis*-**2** (R=TBS), the *cis* epoxide rearranged to the corresponding allylic alcohol with higher enantioselectivity than its *trans* counterpart.[12a] However, despite considerable efforts, we have been unable to develop a high yielding diastereoselective entry into bis protected epoxides *cis*-**2**. Fortunately, this was unimportant as we have now developed (i) a good method for generating epoxides *trans*-**2** stereoselectively; (ii) a highly enantioselective chiral base-mediated rearrangement of epoxides *trans*-**2** to allylic alcohols **3** (using a new chiral lithium amide base, developed independently by Ahlberg et al.[11] and ourselves[12b]) and (iii) a simple oxidation–reduction sequence for converting allylic alcohol **3** into the diastereomeric allylic alcohol **4**.[19e]

In this paper, we describe in full all of the optimisation studies on the preparation and chiral base-mediated rearrangement of bis-protected *meso*-4,5-dihydroxycyclohexene oxides *trans*-**2**. Furthermore, to showcase the methodology, allylic alcohol **3** (R=TBS, ≥89% ee) is used in the first asymmetric synthesis of 4-deoxyconduritols **5** and **6** and a new synthesis of the tetraacetate of naturally ocurring (+)-conduritol F is also presented.

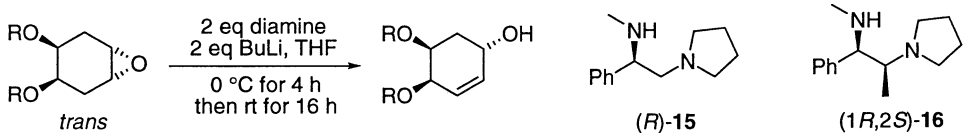
2. Results and discussion

2.1. Epoxide synthesis

The first step to be investigated in the approach outlined in Scheme 1 was the epoxidation of diprotected *cis*-4,5-dihydroxycyclohexenes **1** to give *trans*- and *cis*-**2**. Previously, we have communicated[27,28] some of the details on our study of the diastereoselectivity of epoxidation of alkenes **1**. In the present work, we were particularly interested in synthesising epoxides *trans*-**2** equipped with different protecting groups with a view to discovering which protecting group would give the highest enantioselectivity upon chiral base rearrangement (vide infra). Thus, four alkenes (**7**, **9**, **11**, and **13**) were prepared from the known[12a,29,30] 1,2-diol precursor using standard conditions (see Section 4). The results of their epoxidation are summarised in Table 1.

Our standard method for epoxidation involves treatment of the alkenes with *m*-CPBA in sodium hydrogencarbonate-buffered dichloromethane (room temperature, 16–46 h). The relative stereochemistry of the epoxides reported in Table 1 was elucidated using a combination of X-ray crystallography (of epoxide *trans*-**12**) and chemical correlation. Use of the standard *m*-CPBA/dichloromethane conditions with alkenes **11** and **13** gave high stereoselectivity in favour of the *trans* epoxides and hence good to excellent isolated yields of epoxides *trans*-**12** and *trans*-**14** (Table 1, entries 7 and 8). In contrast, with sterically less demanding silyl protecting groups (R=TES or TBS), the *m*-CPBA/dichloromethane conditions were considerably less *trans*-stereoselective and furnished much lower (≤51%) yields of epoxides *trans*-**8** and *trans*-**10** (Table 1,

Table 2. Enantioselective rearrangement of *meso*-cyclohexene oxides



Entry	R	Epoxide	Diamine	Alcohol	Yield (%)[a]	ee (%)[b]
1	TES	*trans*-**8**	(*R*)-**15**	(1*S*,4*R*,5*S*)-**17**	91	70
2	TBS	*trans*-**10**	(*R*)-**15**	(1*S*,4*R*,5*S*)-**18**	71	76
3	TBS	*trans*-**10**	(1*R*,2*S*)-**16**	(1*S*,4*R*,5*S*)-**18**	94	94
4	TBS	*trans*-**10**	(1*R*,2*S*)-**16**	(1*S*,4*R*,5*S*)-**18**	93[c]	>95[c]
5	TBDPS	*trans*-**12**	(*R*)-**15**	(1*S*,4*R*,5*S*)-**19**	76	68
6	TBDPS	*trans*-**12**	(1*R*,2*S*)-**16**	(1*S*,4*R*,5*S*)-**19**	85	84
7	$-C(Me)_2-$	*trans*-**14**	(*R*)-**15**	(1*S*,4*R*,5*S*)-**20**	39	48
8	$-C(Me)_2-$	*trans*-**14**	(1*R*,2*S*)-**16**	(1*S*,4*R*,5*S*)-**20**	56	26

[a] Isolated yield after chromatography.
[b] Enantiomeric excess determined by formation of Mosher's esters.
[c] Reaction carried out with 3.8 g of epoxide *trans*-**10** (10.5 mmol) added slowly to the chiral base solution which was kept between 0 and −10°C during the addition (see Section 4).

entries 1 and 4). We have suggested that a hydrogen bonding *cis*-directing effect with sterically less demanding silyl protecting groups (eg R=TES and TBS) disrupts the usual sterically controlled *trans*-stereoselective epoxidations in these systems.[27]

Interestingly, it appears that the proposed hydrogen bonding interaction can be minimised by carrying out the epoxidations in cyclohexane, a result which has some related literature precedent in five-ring systems but has not been fully explained.[6b] Thus, epoxidation of alkenes **7** and **9** with *m*-CPBA in cyclohexane gave significantly improved *trans* stereoselectivity (Table 1, entries 2 and 5) when compared to the dichloromethane results (Table 1, entries 1 and 4). Finally, the most stereoselective way of synthesising epoxides *trans*-**8** and *trans*-**10** (Table 1, entries 3 and 6) involved the use of Yang's dioxirane[31] (generated in situ from trifluoroacetone and Oxone®). However, we encountered difficulties when attempting to scale up the dioxirane epoxidations above 100 mg of epoxide and so this method was less useful.

From a synthetic viewpoint, our optimised methods for the preparation of the required *trans* epoxides are summarised as follows. The dioxirane method[31] gave a 74% isolated yield of epoxide *trans*-**8** (Table 1, entry 3); the *m*-CPBA/cyclohexane method gave an 81% isolated yield of epoxide *trans*-**10** (Table 1, entry 5) and the *m*-CPBA/dichloromethane method gave a 92% isolated yield of epoxide *trans*-**12** (Table 1, entry 7) and a 77% isolated yield of epoxide *trans*-**14** (Table 1, entry 8). For the large-scale synthesis of *trans* epoxides, the *m*-CPBA reactions were the most useful.

2.2. Optimisation of enantioselectivity for epoxide rearrangement using chiral lithium amide bases

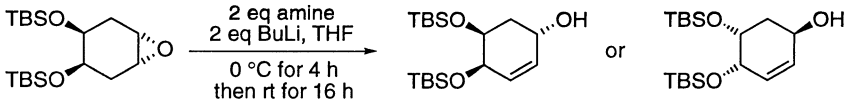
With four *trans* epoxides in hand, we were ready to study their chiral base-mediated rearrangement and the effect on the enantioselectivity of (i) the hydroxyl protecting group and (ii) the chiral base structure was assessed. Thus, we selected Singh's[9a] diamine (*R*)-**15** and the norephedrine-derived diamine (1*R*,2*S*)-**16**, independently developed by Ahlberg et al.[11] and ourselves,[12b] in order to screen the effect of the hydroxyl protecting group on enantioselectivity. Diamines (*R*)-**15**[32a] and (1*R*,2*S*)-**16**[12c] were easily prepared using our aziridinium ion-based methods for diamine synthesis.[32]

The preferred conditions for epoxide rearrangement in our group involve adding a THF solution of the epoxide to 2 equiv. of the chiral lithium amide base (generated from the diamine and butyllithium in THF at 0°C). Then, the reaction mixture is allowed to warm slowly from 0°C to room temperature over 4 h followed by stirring at room temperature for a further 16 h. The rearrangements are typically quenched with aqueous ammonium chloride and subjected to a standard acidic work-up (see Section 4 for full details). Using these conditions, epoxides *trans*-**8**, *trans*-**10**, *trans*-**12** and *trans*-**14** were rearranged using the chiral bases derived from diamines (*R*)-**15** and (1*R*,2*S*)-**16** and the results are presented in Table 2. The enantiomeric excess[33] and the absolute stereochemistry[34] of the allylic alcohols were determined by formation of diastereomeric Mosher's esters.[12a]

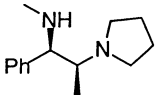
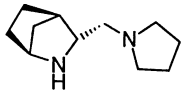
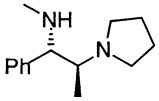
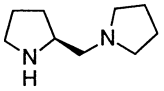
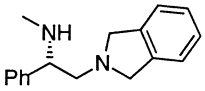
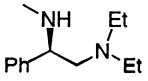
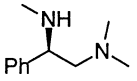
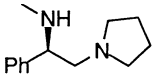
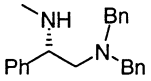
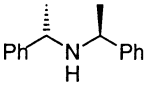
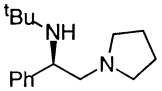
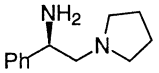
A comparison of the results obtained with Singh's diamine (*R*)-**15** for the four protecting groups (Table 2, entries 1, 2, 5 and 7) indicates that the *tert*-butyldimethylsilyl protecting group is optimal in terms of enantioselectivity: epoxide *trans*-**10** gave allylic alcohol (1*S*,4*R*,5*S*)-**18** with 76% ee (Table 2, entry 2). Epoxide *trans*-**14**, with the isopropylidene acetal protecting group, was rearranged with the lowest (48%) enantioselectivity (Table 2, entry 7). Presumably the reacting conformation of the epoxide in *trans*-**14** is somewhat distorted when compared to the conformations of the other epoxides (*trans*-**8**, *trans*-**10** and *trans*-**12**) which lack a ring-fused protecting group and this results in the lower observed enantioselectivity with epoxide *trans*-**14**.

For the silyl protected epoxides *trans*-**10** and *trans*-**12**, improved enantioselectivity was obtained using the norephedrine-derived base (1*R*,2*S*)-**16** compared with

Table 3. Enantioselective rearrangement of epoxide *trans*-**10** with different chiral bases

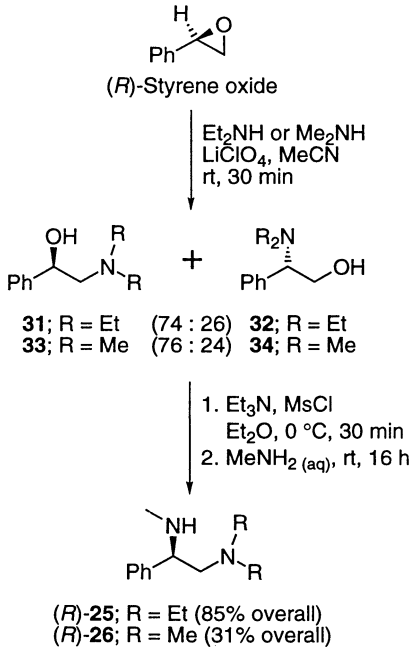


trans-**10** (1*S*,4*R*,5*S*)-**18** (1*R*,4*S*,5*R*)-**18**

Entry	Amine/diamine	Alcohol	Yield (%)[a]	ee (%)[b]
1	 (1*R*,2*S*)-**16**	(1*S*,4*R*,5*S*)-**18**	93	>95
2	 **21**	(1*R*,4*S*,5*R*)-**18**[c]	90	95
3	 (1*S*,2*S*)-**22**	(1*R*,4*S*,5*R*)-**18**	97	86
4	 (*S*)-**23**	(1*R*,4*S*,5*R*)-**18**	98	84
5	 (*S*)-**24**	(1*R*,4*S*,5*R*)-**18**	53	84
6	 (*R*)-**25**	(1*S*,4*R*,5*S*)-**18**	93	84
7	 (*R*)-**26**	(1*S*,4*R*,5*S*)-**18**	90	80
8	 (*R*)-**15**	(1*S*,4*R*,5*S*)-**18**	71	76
9	 (*S*)-**27**	(1*R*,4*S*,5*R*)-**18**	95	35
10	 (*S*,*S*)-**28**	(1*R*,4*S*,5*R*)-**18**	65	20
11	 (*R*)-**29**	(1*S*,4*R*,5*S*)-**18**	62	18
12	 (*R*)-**30**	(1*S*,4*R*,5*S*)-**18**	81	12

[a] Isolated yield after chromatography.
[b] Enantiomeric excess determined by formation of Mosher's esters.
[c] Reaction carried out using 0.2 equiv. of diamine **21** and 1.8 equiv. of diisopropylamine in the presence of DBU.[10]

Singh's base (*R*)-**15** (Table 2, compare entries 2 and 3 or entries 5 and 6). In contrast, rearrangement of the isopropylidene acetal-protected epoxide *trans*-**14** with diamine (1*R*,2*S*)-**16** proceeded with a poor 26% enantioselectivity (Table 2, entry 8). It is clear from Table 2 that the highest enantioselectivity for rearrangement is achieved using a *tert*-butyldimethylsilyl protecting group and the norephedrine-dervied diamine (1*R*,2*S*)-**16**: our optimised conditions for the rearrangement are presented in Table 2, entry 4. On a 10.5 mmol scale of epoxide *trans*-**10**, slow addition of this epoxide (as a THF solution) to the chiral lithium amide solution was required in order to maintain an internal reaction temperature of between 0 and −10°C and in this way, a 93% isolated yield of allylic alcohol (1*S*,4*R*,5*S*)-**18** of >95% ee was obtained. This reaction was simple to carry out, reliable and reproducible allowing multi-gram quantities of allylic alcohol (1*S*,4*R*,5*S*)-**18** to be synthesised. It is important to emphasise that the preparation of diamine (1*R*,2*S*)-**16** is very simple (two steps with no intermediate purification)[12c] and the diamine can be easily recovered (≥70% yield) using a simple acid-base extraction during the work-up (see Section 4).



Scheme 2.

Using the *tert*-butyldimethylsilyl protected epoxide *trans*-**10** as a model substrate, a detailed and systematic study on the effect of chiral lithium amide base structure on enantioselectivity has also been carried out. The full results (in descending order of enantioselectivity) are presented in Table 3. Most of the diamines studied were structurally related to Singh's[9a] diamine (*R*)-**15** but we also decided to include Andersson's[10] diamine **21**, Asami's[6a,b] diamine (*S*)-**23** and Whitesell's[1] amine (*S*,*S*)-**28**. Diamines (*S*)-**23** and (*S*,*S*)-**28** are commercially available and we have previously described the preparation of diamines (1*S*,2*S*)-**22**,[12c] (*S*)-**24**, (*S*)-**27**, (*R*)-**29** and (*R*)-**30**.[32b]

The known[35] diamines (*R*)-**25** and (*R*)-**26** were prepared using a new synthesis as delineated in Scheme 2. Thus, (*R*)-styrene oxide was reacted with either diethylamine or dimethylamine in the presence of lithium perchlorate according to Chini's procedure[36] to give a mixture of regioisomeric amino alcohols (**31**[37] and **32**[37] or **33**[38] and **34**[39]). After chromatography, each mixture was separately treated with mesyl chloride and then methylamine (our usual diamine forming conditions[32]) to give either diamine (*R*)-**25** (85% yield over two steps) or (*R*)-**26** (31% yield over two steps).

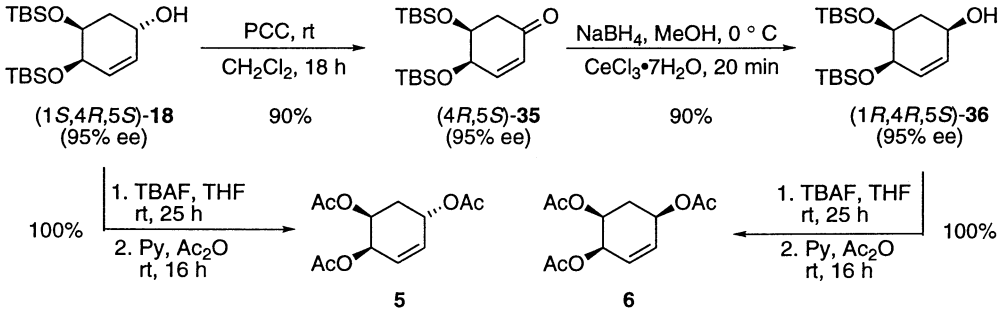
For the rearrangement of epoxide *trans*-**10**, it is possible to improve on the enantioselectivity observed with Singh's diamine (*R*)-**15** (76% ee; Table 3, entry 8) by varying the chiral base structure. For example, replacement of the pyrrolidinyl group in (*R*)-**15** by an iso-indolinyl group, a dimethylamino group or a diethylamino group (Table 3, entries 5–7) all gave improved enantioselectivity (up to 84% ee). However, even better results were obtained using pyrrolidinyl-substituted diamines with increased steric bulk as in the norephedrine-derived chiral diamines (1*R*,2*S*)-**16** and (1*S*,2*S*)-**22** (Table 3, entries 1 and 3). Of these, diamine (1*R*,2*S*)-**16** is preferred.

The use of a *N*-methyl substituent on the secondary nitrogen is essential for high enantioselectivity (Table 3, entries 11 and 12) as Singh has previously noted for the rearrangement of cyclohexene oxide itself.[9a] Our results also confirm that Whitesell's[1] base (*S*,*S*)-**28**, the base of choice for ketone deprotonations,[3] is not appropriate for epoxide rearrangement reactions (Table 3, entry 10). We note in passing that Asami's base (*S*)-**23** also performs well in the rearrangement of epoxide *trans*-**10** (Table 3, entry 4). Probably the most useful chiral base system available to synthetic chemists at the present time is Andersson's diamine **21** used in sub-stoichiometric amounts together with excess LDA and DBU.[10] We can confirm that this base system is also very successful for the rearrangement of epoxide *trans*-**10**—in our hands, a 90% isolated yield of allylic alcohol (1*R*,4*S*,5*R*)-**18** of 95% ee was obtained using diamine **21** (Table 3, entry 2).

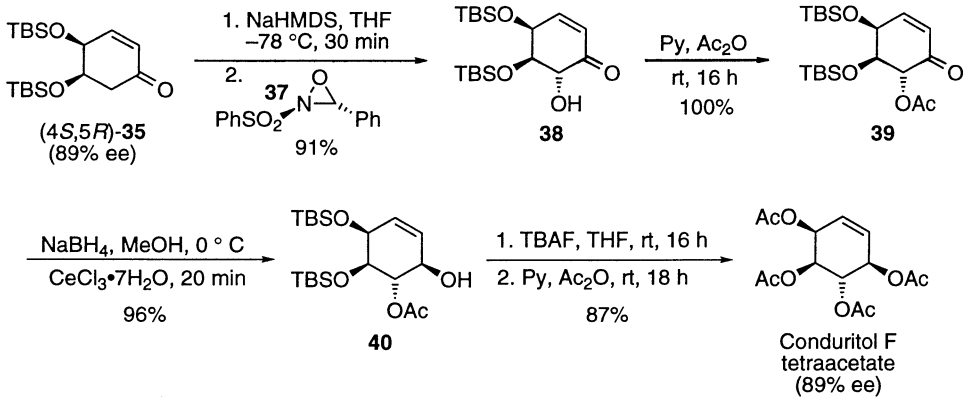
In summary, this is the first systematic study of an epoxide rearrangement that directly compares the enantioselectivity of most of the widely-used chiral lithium amide bases on one substrate at the same time. Our results demonstrate that diamine (1*R*,2*S*)-**16** provides high enantioselectivity (>95%) for the rearrangement of epoxide *trans*-**10**. Given that Ahlberg and co-workers[11b,c] have recently described its successful use in sub-stoichiometric amounts for epoxide rearrangement, this easily synthesised diamine could have great potential in the future. However, at present, the use of sub-stoichiometric amounts of Andersson's diamine **21** represents the most versatile reagent system for epoxide rearrangements and epoxide *trans*-**10** was not an exception.

2.3. Asymmetric synthesis of 4-deoxyconduritols and conduritol F

The epoxidation and chiral base-mediated rearrangement



Scheme 3.



Scheme 4.

studies had shown that multi-gram quantities of highly enantioenriched allylic alcohol (1*S*,4*R*,5*S*)-**18** could be prepared. Next, we wanted to convert this compound into its diastereomer (1*R*,4*R*,5*S*)-**36** and utilise both compounds in some synthetic studies. Although a Mitsunobu approach was briefly considered, it was found that a simple oxidation-reduction approach was most efficacious (Scheme 3).

Allylic alcohol (1*S*,4*R*,5*S*)-**18** (>95% ee) was oxidised using PCC in dichloromethane to give enone (4*R*,5*S*)-**35** (>95% ee) in 90% yield. Then, reduction under Luche conditions[40] generated a 90% yield of allylic alcohol (1*R*,4*R*,5*S*)-**36** (>95% ee) as a single, different (by ^{1}H NMR spectroscopy) diastereoisomer. The reduction is completely diastereoselective and presumably results from axial attack on a preferred conformation of enone (4*R*,5*S*)-**35** (with one silyloxy group in a pseudo-axial position and the other silyloxy group in an equatorial position), as depicted in Fig. 1 (R=H).

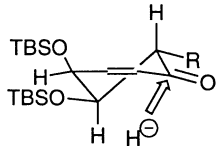


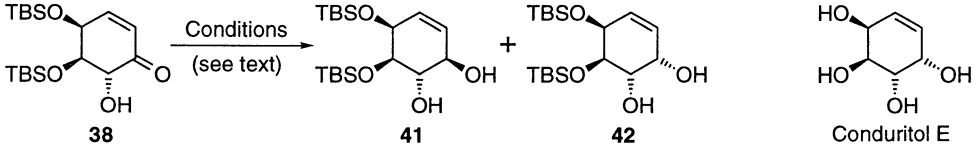
Figure 1.

As a trivial illustration of the utility of allylic alcohols (1*S*,4*R*,5*S*)-**18** and (1*R*,4*R*,5*S*)-**36** in synthesis, they were converted into 4-deoxyconduritols **5** and **6**, respectively. This was accomplished in quantitative yield by treatment of each of (1*S*,4*R*,5*S*)-**18** and (1*R*,4*R*,5*S*)-**36** with TBAF followed by standard acetylation (Scheme 3). This is the first asymmetric synthesis of 4-deoxyconduritols **5** {$[\alpha]_D=-236.1$ (*c* 3.5 in $CHCl_3$)} and **6** {$[\alpha]_D=-54.0$ (*c* 3.5 in $CHCl_3$)}; the spectroscopic data of **5** and **6** were consistent with literature data on the racemates.[41,42]

Finally, the general strategy described in this paper has been used in a concise asymmetric synthesis of the tetraacetate of (+)-conduritol F.[25a,b] In order to synthesise the naturally occurring enantiomer, enone (4*S*,5*R*)-**35** was required. Enone (4*S*,5*R*)-**35** (89% ee[43]) was prepared by rearrangement of epoxide *trans*-**10** with the chiral lithium amide base derived from diamine (1*S*,2*R*)-**16** and subsequent PCC oxidation. The synthesis of the tetraacetate of (+)-conduritol F is shown in Scheme 4.

For the α-hydroxylation of enone (4*S*,5*R*)-**35**, the use of lead tetraacetate[44] (in refluxing toluene) and Davis' oxaziridine[45] (on a preformed sodium enolate) were explored. We were never able to obtain more than a 57% yield of acetoxy enone **39** using lead tetraacetate and thus preferred the oxaziridine methodology. Deprotonation of enone (4*S*,5*R*)-**35** with sodium hexamethyldisilazide at low temperature and enolate trapping with Davis' oxaziridine **37** produced a 91% yield of a single diastereoisomer (by ^{1}H NMR spectroscopy) of hydroxy ketone **38**. Interestingly, no β-elimination of the silyloxy group was observed. The relative stereochemistry of **38** was established by completing the synthesis of the tetraacetate of (+)-conduritol F (vide infra) and comparing the ^{1}H and ^{13}C NMR spectroscpic data with that of all of the conduritol tetraacetates. The sense of diastereoselectivity in the formation of **38** presumably arises by attack *trans* to the bulky silyloxy groups on the almost planar six-membered ring enolate.

Next, we wanted to reduce the ketone in hydroxy ketone **38** and for high diastereoselectivity, it was necessary to protect the hydroxyl group (vide infra). Acetylation of hydroxy ketone **38** (to give **39**) and then Luche reduction[40] afforded allylic alcohol **40** as the only diastereomeric product in 96% yield. Axial attack of hydride on a preferred conformation of the enone (see Fig. 1; R=OAc) accounts for the stereoselectivity in a similar fashion to the reduction of enone (4*R*,5*S*)-**35** described previously (see Scheme 3). Finally,



Scheme 5.

TBAF deprotection and a final acetylation (87% for the two steps) yielded (+)-conduritol F tetraacetate (89% ee). The synthetic material exhibited $[\alpha]_D$=+46.9 (*c* 1.0 in $CHCl_3$) (lit.,[46] $[\alpha]_D$=+45.6 (*c* 1.1 in $CHCl_3$)) and was identical spectroscopically to the tetraacetate of (+)-conduritol F.[25a,b,40]

We briefly attempted to divert the synthesis from hydroxy ketone **38** to conduritol E (Scheme 5). Direct Luche reduction[40] of hydroxy ketone **38** gave a 59:41 mixture of diastereomeric 1,2-diols **41** and **42**[47] (corresponding to conduritol F and E stereochemistry, respectively). In this case we suggest that the preferred attack shown in Fig. 1 (R=OAc) is disrupted by complexation of the reagent to the hydroxyl group (R=OH) such that chelation-controlled reduction is competitive leading to a stereorandom reaction. The diastereoselectivity could be further improved in favour of conduritol E stereochemistry by carrying out a reported chelation-controlled *cis*-selective reduction using lithium aluminium hydride-aluminium trichloride ((i) 4 equiv. $AlCl_3$, Et_2O, rt, 5 min; (ii) 2 equiv. $LiAlH_4$, Et_2O, rt, 1 min; (iii) water).[48] In this way, an 80:20 mixture of 1,2-diols **41** and **42**[47] were obtained. However, we could not find conditions for complete diastereoselectivity in the synthetic route to conduritol E.

3. Conclusion

In summary, several features of our optimised route to key intermediates (eg allylic alcohol (1*S*,4*R*,5*S*)-**18** and enone (4*R*,5*S*)-**35**) for polyhydroxylated cyclohexane synthesis are described. The first step is the highly diastereoselective epoxidation of alkene **9** in cyclohexane which generates an 81% isolated yield of epoxide *trans*-**10**. Then, after a survey a wide range of chiral bases for the enantioselective rearrangement of epoxide *trans*-**10**, the second crucial step in the strategy, it was found that diamines (1*S*,2*R*)-**16** or **21** were optimal. For example, rearrangement of epoxide *trans*-**10** using 2 equiv. of diamine (1*S*,2*R*)-**16** gave a 93% yield of allylic alcohol (1*S*,4*R*,5*S*)-**18** of >95% ee. We believe that since allylic alcohol (1*S*,4*R*,5*S*)-**18**, enone (4*R*,5*S*)-**35** and their enantiomers can be readily synthesised in multi-gram quantities, they should be considered as useful building blocks for the synthesis of polyhydroxylated cyclohexane-based natural and unnatural products.[49]

4. Experimental

4.1. General

Water is distilled water. THF was dried over sodium-benzophenone and distilled before use. CH_2Cl_2 was dried over calcium hydride and distilled before use. Petrol refers to the fraction of petroleum ether boiling in the range 40–60°C and was redistilled before use. All non-aqueous reactions were carried out under oxygen-free nitrogen using oven-dried glassware. Flash column chromatography was carried out using ICN Biomedicals GmbH 33–63 silica (60 Å) or Fisher Matrex silica 60. Thin layer chromatography was carried out on commercially available Merck F_{254} aluminium-backed silica plates. *n*-Butyllithium was titrated against diphenylacetic acid before use. *m*-CPBA (approx. 70% pure) was used as supplied by Aldrich Chemical Company Ltd.

Proton (270 MHz) and carbon (67.9 MHz) NMR spectra were recorded on a 270 MHz spectrometer using an internal deuterium lock. All samples were recorded as solutions in deuteriated chloroform and chemical shifts are quoted in parts per million downfield of tetramethylsilane. Coupling constant (*J*) values are given in Hz. Carbon NMR spectra were recorded with broad band proton decoupling.

Melting points were measured on a digital melting point apparatus. Infra red spectra were recorded on an FT IR spectrometer as solutions in chloroform. Chemical ionisation and high resolution mass spectra were recorded on an Autospec spectrometer. Optical rotations were recorded on a polarimeter (using the sodium D line; 589 nm) at 20°C and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}.

The synthesis of diamines (1*R*,2*S*)-**16**,[12c] (1*S*,2*S*)-**22**,[12c] (*S*)-**24**,[32b] (*R*)-**15**,[32a] (*S*)-**27**,[32b] (*R*)-**29**[32b] and (*R*)-**30**[32b] has been reported previously. Diamine **21** was a gift from Professor P. G. Andersson and diamines (*S*)-**23** and (*S*,*S*)-**28** are commercially available from Aldrich Chemical Company Ltd. Diprotected alkenes **9**[12a] and **13**[30] were prepared using literature procedures.

4.1.1. (4*R,5*S**)-4,5-Dihydroxycyclohexene.** Cyclohexa-1,4-diene (25.0 g, 0.301 mol) was added to a stirred solution of KIO_3 (16.1 g, 75.2 mmol) and I_2 (38.2 g, 0.150 mol) in AcOH (500 mL) at rt under N_2. The resulting mixture was stirred at 60°C for 4 h. After cooling, KOAc (29.5 g, 0.301 mol) was added and the mixture heated at reflux for 4 h. After cooling, water (10 mL) was added and the solvent was evaporated under reduced pressure over a period of 3 h. Et_2O (200 mL) was added and the organic layer was washed with saturated $Na_2SO_{3(aq)}$ until the brown colour was removed, dried ($MgSO_4$) and evaporated under reduced pressure to give a crude mixture of mono and diacetate. To this crude mixture was added Amberlite IRA(OH) resin (150 g), MeOH (300 mL) and THF (150 mL) and the resulting suspension was stirred at rt for 16 h. The mixture was filtered through Celite and the resin washed well with hot MeOH (90 mL). The filtrate was evaporated under reduced pressure and purification by recrystallisation from $CHCl_3$–petrol gave known[12a,29,30] (4*R**,5*S**)-4,5-dihydroxycyclohexene (25.4 g, 74%) as white crystals, mp 78–80°C (lit.,[29] 79°C), data identical to those reported previously.[29,30]

4.1.2. (4*R,5*S**)-4,5-Bis(triethylsilyloxy)cyclohexene 7.** Triethylsilyl chloride (3.23 mL, 19.1 mmol) was added dropwise to a stirred solution of imidazole (3.4 g, 48.4 mmol) and (4*R**,5*S**)-4,5-dihydroxycyclohexene (1.1 g, 9.6 mmol) in DMF (22 mL) at rt under N_2. After stirring for 22 h, water (10 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL) and the combined organic extracts were washed with brine (3×20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by chromatography (50:1 petrol–Et_2O) gave alkene **7** (3.08 g, 93%) as a colourless oil, R_F (30:1 petrol–Et_2O) 0.7; IR (film) 2954, 1076, 1007, 737 cm^{-1}; ^1H NMR (270 MHz,

$CDCl_3$): δ 5.62–5.61 (m, 2H), 3.96–3.92 (m, 2H), 2.37–2.27 (m, 4H), 1.09–1.00 (m, 18H), 0.75–0.57 (m, 12H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 124.5, 70.7, 32.9, 7.2, 5.2; MS (CI, NH_3) *m/z* 343 $(M+H)^+$, 313, 234, 132; HRMS (CI, NH_3) *m/z* calcd for $C_{18}H_{38}O_2Si_2$ $(M+H)^+$ 343.2489, found 343.2490.

4.1.3. (4*R,5*S**)-4,5-Bis(*tert*-butyldiphenylsilyloxy)cyclohexene 11.** *tert*-Butyldiphenylsilyl chloride (1.08 mL, 4.2 mmol) was added dropwise to a stirred solution of imidazole (600 mg, 8.8 mmol) and (4*R**,5*S**)-4,5-dihydroxycyclohexene (200 mg, 1.8 mmol) in CH_2Cl_2 (22 mL) at rt under N_2. After stirring for 20 h, water (5 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (2×10 mL) and the combined organic extracts were washed with brine (3×10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by chromatography (10:1 petrol–Et_2O) gave alkene **11** (993 mg, 94%) as a white solid, mp 92–96°C; R_F (10:1 petrol–Et_2O) 0.7; IR (Nujol) 1105 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 7.70–7.66 (m, 8H), 7.43–7.21 (m, 12H), 5.59 (s, 2H), 3.92 (t, 2H, *J*=5 Hz), 2.32–2.24 (m, 2H), 1.89–1.81 (m, 2H), 1.08 (s, 18H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 136.0, 135.9, 134.9, 134.1, 129.4, 127.5, 127.4, 124.2, 71.7, 32.2, 27.0, 19.3 (some signals not resolved); MS (CI, NH_3) *m/z* 608 $(M+NH_4)^+$, 374, 157; HRMS (CI, NH_3) *m/z* calcd for $C_{38}H_{46}O_2Si_2$ $(M+NH_4)^+$ 608.3380, found 608.3380.

4.2. General method for *m*-CPBA epoxidation

Solid $NaHCO_3$ (3.8 mmol) and *m*-CPBA (approx. 70% pure material, 2.9 mmol) were added in portions to a stirred solution of the alkene (0.6 mmol) in solvent (5 mL) at rt under N_2. After 16–20 h at rt, 20% $Na_2SO_{3(aq)}$ (5 mL) was added and the two layers separated. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL) and the combined organic extracts were washed with 20% $Na_2SO_{3(aq)}$ (20 mL), 5% $NaHCO_{3(aq)}$ (20 mL), water (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Analysis of the crude product by ^1H NMR spectroscopy revealed the ratio of diastereoisomers (see Table 1) and the crude product was then purified by chromatography.

4.2.1. (1*S,2*R**,4*R**,5*S**)-4,5-Bis(triethylsilyloxy)cyclohexene oxide *trans*-8 (Table 1, entry 3).** 1,1,1-Trifluoracetone (0.57 mL, 6.38 mmol) was added via a pre-cooled syringe to a stirred solution of di-TES protected alkene **7** (200 mg, 0.58 mmol) and Na_2EDTA (2.5 mL of a 4×10^{-4} M aqueous solution, 0.001 mmol) in MeCN (4 mL) at 0°C. Then, a mixture of Oxone® (1.78 g, 6.38 mmol) and solid $NaHCO_3$ (378 mg, 4.5 mmol) was added in portions over 1 h. After stirring at 0°C for a further 1 h, the reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 98:2 mixture of epoxides *trans*- and *cis*-**8** (by ^1H NMR spectroscopy). Purification by chromatography (20:1 petrol–Et_2O) gave epoxide *trans*-**8** (155 mg, 74%) as a colourless oil, R_F (20:1 petrol–Et_2O) 0.35; IR (film) 2954, 1462, 1103, 1003, 741 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 3.69–3.65 (m, 2H), 3.16–3.15 (m, 2H), 2.12–1.97 (m, 4H), 0.94 (t, 18H, *J*=8.5 Hz), 0.63–0.54 (m, 12H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 68.5, 52.2, 31.2, 6.8, 4.8; MS (CI, NH_3) *m/z* 359 $(M+H)^+$, 329; HRMS (CI, NH_3) *m/z* calcd for $C_{18}H_{38}O_3Si_2$ $(M+H)^+$ 359.2438, found 359.2439.

4.2.2. (1*S,2*R**,4*R**,5*S**)-4,5-Bis(*tert*-butyldimethylsilyloxy)cyclohexene oxide *trans*-10 (Table 1, entry 5).** Using the general method for *m*-CPBA epoxidation, $NaHCO_3$ (490 mg, 5.8 mmol), *m*-CPBA (1.0 g, 4.0 mmol) and di-TBS protected alkene **9** (1.0 g, 2.9 mmol) in cyclohexane (40 mL) gave, after 18 h, a crude product which contained a 93:7 mixture of epoxides *trans*- and *cis*-**10**. Purification by chromatography (20:1 petrol–Et_2O) gave known[12a] epoxide *trans*-**10** (806 mg, 81%) as a colourless oil, data identical to those reported previously.[12a]

4.2.3. (1*S,2*R**,4*R**,5*S**)-4,5-Bis(*tert*-butyldiphenylsilyloxy)cyclohexene oxide *trans*-12 (Table 1, entry 7).** Using the general method for *m*-CPBA epoxidation, $NaHCO_3$ (172 mg, 2.1 mmol), *m*-CPBA (518 mg, 2.1 mmol) and di-TBDPS protected alkene **11** (688 mg, 1.2 mmol) in CH_2Cl_2 (30 mL) gave, after 20 h, a crude product which contained a 98:2 mixture of epoxides *trans*- and *cis*-**12**. Purification by chromatography (10:1 petrol–Et_2O) gave epoxide *trans*-**12** (649 mg, 92%) as a waxy white solid, mp 68–70°C; R_F (10:1 petrol–Et_2O) 0.4; IR (film) 2927, 1276 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 7.67–7.62 (m, 8H), 7.43–7.21 (m, 12H), 3.78–3.76 (m, 2H), 3.00 (br s, 2H), 2.12–1.97 (m, 2H), 1.76–1.71 (m, 2H), 1.08 (s, 18H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 136.0, 135.9, 135.8, 134.4, 133.7, 129.6, 129.5, 127.5, 69.9, 51.8, 30.7, 27.0, 19.3; MS (CI, NH_3) *m/z* 624 $(M+NH_4)^+$, 607, 529, 351; HRMS (CI, NH_3) *m/z* calcd for $C_{38}H_{46}O_3Si_2$ $(M+NH_4)^+$ 624.3329, found 624.3330.

4.2.4. (1*S,2*R**,4*R**,5*S**)-4,5-Bis(isopropylidenedioxy)cyclohexene oxide *trans*-14 (Table 1, entry 8).** Using the general method for *m*-CPBA epoxidation, $NaHCO_3$ (500 mg, 6.0 mmol), *m*-CPBA (1.48 g, 6.0 mmol) and acetal protected alkene **13** (500 mg, 3.2 mmol) in CH_2Cl_2 (10 mL) gave, after 46 h, a crude product which contained a 90:10 mixture of epoxides *trans*- and *cis*-**14**. Purification by chromatography (EtOAc) gave epoxide *trans*-**14**[50] (418 mg, 77%) as a colourless oil, R_F (EtOAc) 0.6; IR (film) 3033, 2937, 1519, 1425, 1382, 1060, 979, 929 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 4.27–4.19 (m, 2H), 3.20–3.19 (m, 2H), 2.42–2.34 (m, 2H), 2.12–2.04 (m, 2H), 1.45 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$): 107.4, 71.2, 50.1, 28.0, 27.5, 24.6; MS (CI, NH_3) *m/z* 171 $(M+H)^+$, 155; HRMS (CI, NH_3) *m/z* calcd for $C_9H_{14}O_3$ $(M+H)^+$ 171.1021, found 171.1019. Diagnostic signals for epoxide *cis*-**14**: ^1H NMR (270 MHz, $CDCl_3$): δ 1.52 (s, 3H), 1.26 (s, 3H).

4.3. General method for epoxide rearrangement (Tables 2 and 3)

n-Butyllithium (1.2–1.6 M solution in hexane, 1.12 mmol) was added dropwise to a stirred solution of diamine (or amine) (1.12 mmol) in THF (2 mL) at 0°C under N_2. After 30 min at 0°C, a solution of the epoxide (0.56 mmol) in THF (3 mL) was added dropwise via a cannula and the mixture

was warmed to rt over 4 h. After 16 h at rt, saturated $NH_4Cl_{(aq)}$ (5 mL) was added followed by Et_2O (20 mL) and the two layers separated. The aqueous layer was extracted with Et_2O (2×20 mL) and the combined organic extracts were washed with 2% $HCl_{(aq)}$ (3×20 mL), saturated $NaHCO_{3(aq)}$ (3×20 mL) and brine (15 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

4.3.1. (1*S*,4*R*,5*S*)-4,5-Bis(triethylsilyloxy)cyclohex-2-enol (1*S*,4*R*,5*S*)-17 (Table 2, entry 1). Using the general method for epoxide rearrangement, *n*-butyllithium (0.76 mL of a 1.6 M solution in hexane, 1.12 mmol), diamine (*R*)-**15** (228 mg, 1.12 mmol) and epoxide *trans*-**8** (200 mg, 0.56 mmol) in THF (5 mL) gave the crude product. Purification by chromatography (7:3 Et_2O–petrol) gave allylic alcohol (1*S*,4*R*,5*S*)-**17** (182 mg, 91%, 70% ee by Mosher's ester formation) as a colourless oil, $[\alpha]_D=-88.3$ (*c* 1.0 in $CHCl_3$); R_F (3:1 petrol–Et_2O) 0.3; IR (film) 3375, 2954, 1122, 1032, 741 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.76 (dd, 1H, *J*=3, 10.5), 5.67–5.62 (m, 1H), 4.46–4.41 (m, 1H), 4.13–4.04 (m, 2H), 2.28–2.26 (m, 1H), 1.90 (br s, 1H), 1.56 (ddd, 1H, *J*=2, 6, 13 Hz), 0.98–0.92 (m, 18H), 0.69–0.57 (m, 12H).

4.3.2. (1*S*,4*R*,5*S*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-cyclohex-2-enol (1*S*,4*R*,5*S*)-18 (Table 2, entry 4 and Table 3, entry 1). Using the general method for epoxide rearrangement, a solution of epoxide *trans*-**10** (3.78 g, 10.5 mmol) in THF (15 mL) was added dropwise via a cannula over 20 min to a solution of *n*-butyllithium (13.4 mL of a 1.6 M solution in hexane, 21.0 mmol) and diamine (1*R*,2*S*)-**16** (4.6 g, 21.0 mmol) in THF (15 mL) at −10°C (to ensure that the internal reaction temperature did not exceed 0°C at any time during the addition). After stirring for the usual length of time and standard work-up, purification by chromatography (7:3 Et_2O–petrol) gave allylic alcohol (1*S*,4*R*,5*S*)-**18** (3.5 g, 93%, >95% ee by Mosher's ester formation) as a white solid, $[\alpha]_D=-100.8$ (*c* 1.0 in $CHCl_3$) (lit.,[12a] $[\alpha]_D=-87.1$ (*c* 0.6 in $CHCl_3$) for allylic alcohol (1*S*,4*R*,5*S*)-**18** of 76% ee), data identical to those reported previously.[12a] The aqueous layer was basified with K_2CO_3 and extracted with Et_2O (2×30 mL). The combined organic extracts were dried (Na_2SO_4), evaporated under reduced pressure and purified by Kugelrohr distillation to give the known diamine (1*R*,2*S*)-**16** (3.25 g, 70% recovery) as a colourless oil.

4.3.3. (1*S*,4*R*,5*S*)-4,5-Bis(*tert*-butyldiphenylsilyloxy)cyclohex-2-enol (1*S*,4*R*,5*S*)-19 (Table 2, entry 6). Using the general method for epoxide rearrangement, *n*-butyllithium (0.45 mL of a 1.5 M solution in hexane, 0.66 mmol), diamine (1*R*,2*S*)-**16** (144 mg, 0.66 mmol) and epoxide *trans*-**12** (200 mg, 0.33 mmol) in THF (5 mL) gave the crude product. Purification by chromatography (7:3 Et_2O–petrol) gave allylic alcohol (1*S*,4*R*,5*S*)-**19** (169 mg, 85%, 84% ee by Mosher's ester formation) as a white solid, $[\alpha]_D=-72.2$ (*c* 1.0 in $CHCl_3$); mp 52–58°C; R_F (3:1 petrol–Et_2O) 0.3; IR (Nujol) 3379 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.73–7.64 (m, 8H), 7.44–7.22 (m, 10H), 5.54 (dd, 1H, *J*=3.5, 10), 5.39 (dd, 1H, *J*=3.5, 10 Hz), 4.23–4.21 (m, 2H), 4.15–4.11 (m, 1H), 2.27 (ddd, 1H, *J*=5, 10, 12 Hz), 1.43–1.12 (m, 2H), 1.08 (s, 9H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 136.1, 136.05, 135.95, 134.6, 124.3, 134.0, 133.8, 130.9, 130.0, 129.7, 129.55, 129.5, 127.6, 127.5, 127.4, 69.9, 69.1, 65.8, 35.9, 27.1, 27.0, 19.35, 19.25 (some signals not resolved); MS (CI, NH_3) *m/z* 624 $(M+NH_4)^+$, 351; HRMS (CI, NH_3) *m/z* calcd for $C_{38}H_{46}O_3Si_2$ $(M+NH_4)^+$ 624.3329, found 624.3334; Anal. calcd for $C_{38}H_{46}O_3Si_2$: C, 75.20; H, 7.64. Found: C, 75.01; H, 7.91.

4.3.4. (1*S*,4*R*,5*S*)-4,5-Bis(isopropylidenedioxy)cyclohex-2-enol (1*S*,4*R*,5*S*)-19 (Table 2, entry 7). Using the general method for epoxide rearrangement (note: the wash with 2% $HCl_{(aq)}$ during the work-up was omitted), *n*-butyllithium (1.1 mL of a 1.6 M solution in hexane, 1.8 mmol), diamine (*R*)-**15** (360 mg, 1.8 mmol) and epoxide *trans*-**14** (150 mg, 0.9 mmol) in THF (5 mL) gave the crude product. Purification by chromatography (EtOAc) gave allylic alcohol (1*S*,4*R*,5*S*)-**20**[51] (58 mg, 39%, 48% ee by Mosher's ester formation) as a colourless oil, $[\alpha]_D=-25.3$ (*c* 0.4 in $CHCl_3$); R_F (EtOAc) 0.4; IR (film) 3440, 2970 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): δ 5.91 (td, 1H, *J*=0.5, 10 Hz), 5.73–5.67 (m, 1H), 4.51–4.38 (m, 3H), 2.52–2.43 (m, 1H), 2.14 (br s, 1H), 1.72–1.63 (m, 1H), 1.37 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$): 133.9, 126.9, 108.5, 72.6, 71.3, 63.0, 35.1, 27.6, 26.3; MS (CI, NH_3) *m/z* 171 $(M+H)^+$, 155; HRMS (CI, NH_3) *m/z* calcd for $C_9H_{14}O_3$ $(M+H)^+$ 171.1021, found 171.1025.

4.3.5. (*R*)-*N*-Methyl-1-phenyl-2-(1-*N*,*N*′-diethyl)ethanamine (*R*)-25. $LiClO_4$ (931 mg, 8.8 mmol) was added to a stirred solution of (*R*)-styrene oxide (1.0 mL, 8.8 mmol) in MeCN (2 mL) at rt under N_2. After 10 min at rt, diethylamine (0.9 mL, 8.8 mmol) was added dropwise and the solution stirred for a further 30 min. Then, Et_2O (10 mL) and water (10 mL) were added, the layers separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by chromatography (5:2 CH_2Cl_2–MeOH) gave a 74:26 mixture (by ^1H NMR spectroscopy) of amino alcohols **31** and **32** (1.43 g, 85%) as a yellow oil, R_F (10:1 CH_2Cl_2–MeOH) 0.1. Diagnostic signal for known[37] amino alcohol **31**: ^1H NMR (270 MHz, $CDCl_3$): δ 4.71 (dd, 1H, *J*=3.5, 10.5 Hz); diagnostic signals for known[37] amino alcohol **32**: ^1H NMR (270 MHz, $CDCl_3$): δ 4.03–3.94 (m, 2H), 3.69–3.64 (m, 1H).

MsCl (0.53 mL, 6.8 mmol) was added dropwise to a stirred solution of a 74:26 mixture of amino alcohols **31** and **32** (750 mg, 3.9 mmol) and Et_3N (1.8 mL, 12.9 mmol) in Et_2O (15 mL) at 0°C under N_2. A white precipitate formed. After 30 min at 0°C, Et_3N (1.2 mL, 8.7 mmol) was added and the mixture was allowed to warm to rt. Then, $MeNH_{2(aq)}$ (40%; 4.8 mL, 65.5 mmol) was added and the two-phase mixture was stirred vigorously for 16 h at rt. The layers were separated and the aqueous layer was extracted with Et_2O (2×20 mL). The combined organic extracts were washed with 5% $NaHCO_{3(aq)}$ (30 mL) and water (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave known[35] diamine (*R*)-**25** (806 mg, 100%) as a colourless oil, $[\alpha]_D=-156.2$ (*c* 0.9 in $CHCl_3$) (lit.,[35] $[\alpha]_D=-135.4$ (*c* 1.9 in $CHCl_3$)), data identical to those reported previously.[35]

4.3.6. (*R*)-*N*-Methyl-1-phenyl-2-(1-*N*,*N*′-dimethyl)ethanamine (*R*)-26. $LiClO_4$ (931 mg, 8.8 mmol) was added to a stirred solution of (*R*)-styrene oxide (1.0 mL, 8.8 mmol) in MeCN (2 mL) at rt under N_2. After 10 min at rt, dimethylamine (4.4 mL of a 2 M solution in THF, 8.8 mmol) was added dropwise and the solution stirred for a further 30 min. Then, Et_2O (10 mL) and water (10 mL) were added, the layers separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by chromatography (10:1 CH_2Cl_2–MeOH) gave a 76:24 mixture (by ^1H NMR spectroscopy) of amino alcohols **33** and **34** (650 mg, 41%) as a yellow oil, R_F (10:1 CH_2Cl_2–MeOH) 0.3. Diagnostic signal for known[38] amino alcohol **33**: ^1H NMR (270 MHz, $CDCl_3$): δ 4.65 (dd, 1H, J=3.5, 10.5 Hz); diagnostic signal for known[39] amino alcohol **34**: ^1H NMR (270 MHz, $CDCl_3$): δ 3.89 (dd, 1H, J=8.5, 10.5 Hz).

MsCl (0.35 mL, 4.5 mmol) was added dropwise to a stirred solution of a 76:24 mixture of amino alcohols **33** and **34** (500 mg, 3.0 mmol) and Et_3N (1.4 mL, 10.0 mmol) in Et_2O (10 mL) at 0°C under N_2. A white precipitate formed. After 30 min at 0°C, Et_3N (0.8 mL, 5.7 mmol) was added and the mixture was allowed to warm to rt. Then, $MeNH_{2(aq)}$ (40%; 3.2 mL, 43.7 mmol) was added and the two-phase mixture was stirred vigorously for 16 h at rt. The layers were separated and the aqueous layer was extracted with Et_2O (2×20 mL). The combined organic extracts were washed with 5% $NaHCO_{3(aq)}$ (30 mL) and water (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave known[35] diamine (*R*)-**26** (403 mg, 75%) as a colourless oil, $[\alpha]_D$=−90.0 (*c* 0.9 in EtOH) (lit.,[35] $[\alpha]_D$=+93.8 (*c* 2.0 in EtOH) for diamine (*S*)-**26**), data identical to those reported previously.[35]

4.3.7. (4*R*,5*S*)-4,5-Bis(*tert*-butyldimethylsilyloxy)cyclohex-2-enone (4*R*,5*S*)-35. PCC (1.8 g, 8.37 mmol) was added to a stirred solution of allylic alcohol (1*S*,4*R*,5*S*)-**18** (2.0 g, 5.58 mmol, >95% ee) in CH_2Cl_2 (50 mL) at rt under N_2. After 18 h at rt, the solvent was evaporated under reduced pressure and the residue purified by chromatography (3:1 petrol–Et_2O) to give known[12a] enone (4*R*,5*S*)-**35** (1.8 g, 90%, >95% ee) as a white solid, $[\alpha]_D$= −108.1 (*c* 0.6 in $CHCl_3$) (lit.,[12a] $[\alpha]_D$=+109.8 (*c* 0.65 in $CHCl_3$) for (4*S*,5*R*)-**35** of 92% ee), data identical to those reported previously.[12a]

4.3.8. (1*R*,4*R*,5*S*)-4,5-Bis(*tert*-butyldimethylsilyloxy)cyclohex-2-enol (1*R*,4*R*,5*S*)-36. $CeCl_3{\cdot}7H_2O$ (1.88 g, 5.05 mmol) was added to a stirred solution of enone (4*R*,5*S*)-**35** (1.8 g, 5.05 mmol) in MeOH (50 mL) at rt under N_2. After cooling to 0°C, $NaBH_4$ (380 mg, 10.1 mmol) was added in portions over 10 min and the mixture was stirred for a further 10 min. Then, Et_2O (20 mL) and water (20 mL) were added, the layers separated and the aqueous layer was extracted with Et_2O (2×20 mL). The combined organic extracts were washed with brine (20 mL) and water (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give known[12a] allylic alcohol (1*R*,4*R*,5*S*)-**36** (1.7 g, 90%, >95% ee) as a white solid, $[\alpha]_D$=−35.4 (*c* 1.00 in $CHCl_3$) (lit.,[12a] $[\alpha]_D$=+20.6 (*c* 0.6 in $CHCl_3$) for (1*S*,4*S*,5*R*)-**36** of 92% ee), data identical to those reported previously.[12a]

4.3.9. (1*S*,4*R*,5*S*)-4,5-Bis(acetyloxy)cyclohex-2-en-1yl acetate 5. A solution of allylic alcohol (1*S*,4*R*,5*S*)-**18** (100 mg, 0.28 mmol, >95% ee) in TBAF (2 mL of a 1 M solution in THF) was stirred at rt under N_2 for 25 h. The solvent was evaporated and the residue dissolved in pyridine (2 mL) and Ac_2O (1 mL) at rt under nitrogen. After stirring at rt for 72 h, 2 M $HCl_{(aq)}$ (10 mL) and Et_2O (20 mL) were added, the layers separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic extracts were washed with 2 M $HCl_{(aq)}$ (2×10 mL), saturated $NaHCO_{3(aq)}$ (3×10 mL) and water (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by chromatography (1:1 petrol–Et_2O) gave triacetate **5** (73 mg, 100%, >95% ee) as a pale yellow oil, $[\alpha]_D$=−236.1 (*c* 3.5 in $CHCl_3$), data identical to those reported previously for the racemate.[41]

4.3.10. (1*R*,4*R*,5*S*)-4,5-Bis(acetyloxy)cyclohex-2-en-1-yl acetate 6. A solution of allylic alcohol (1*R*,4*R*,5*S*)-**36** (100 mg, 0.28 mmol, >95% ee) in TBAF (2 mL of a 1 M solution in THF) was stirred at rt under N_2 for 25 h. The solvent was evaporated and the residue dissolved in pyridine (2 mL) and Ac_2O (1 mL) at rt under nitrogen. After stirring at rt for 72 h, 2 M $HCl_{(aq)}$ (10 mL) and Et_2O (20 mL) were added, the layers separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic extracts were washed with 2 M $HCl_{(aq)}$ (2×10 mL), saturated $NaHCO_{3(aq)}$ (3×10 mL) and water (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by chromatography (1:1 petrol–Et_2O) gave triacetate **6** (73 mg, 100%, >95% ee) as a pale yellow oil, $[\alpha]_D$=−54.0 (*c* 3.5 in $CHCl_3$), data identical to those reported previously for the racemate.[42]

4.3.11. (4*S*,5*R*,6*S*)-4,5-Bis(*tert*-butyldimethylsilyloxy)-6-hydroxycyclohex-2-enone 38. A solution of enone (4*S*,5*R*)-**36** (100 mg, 0.28 mmol, 89% ee) in THF (3 mL) was added dropwise to a stirred solution of NaHMDS (0.42 mL of a 1 M solution in THF, 0.42 mmol) in THF (2 mL) at −78°C under N_2. After 30 min at −78°C, a solution of oxaziridine **37** (110 mg, 0.42 mmol) in THF (5 mL) was added dropwise via a cannula. After a further 20 min at −78°C, saturated $NH_4Cl_{(aq)}$ (2 mL) and Et_2O (2 mL) were added. After warming to rt, the two layers were separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic extracts were washed with water (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by chromatography (4:1 petrol–Et_2O) gave hydroxy enone **38** (95 mg, 91%) as a white solid, $[\alpha]_D$=−118.9 (*c* 0.2 in $CHCl_3$); mp 78–80°C; R_F (4:1 petrol–EtOAc) 0.2; IR ($CHCl_3$) 3498, 1685, 1095, 839 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.92 (dd, 1H, J=6, 10 Hz), 6.09 (d, 1H, J=10 Hz), 4.56 (d, 1H, J=10 Hz), 4.35 (dd, 1H, J=3.5, 6 Hz), 3.75 (dd, 1H, J=3.5, 10 Hz), 3.19 (br s, 1H), 0.92 (s, 9H), 0.88 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 199.7, 147.8, 127.6, 74.8, 74.3, 68.5, 25.9, 25.7, 18.3, 18.0, −4.3, −4.4, −4.6, −4.7; MS (CI, NH_3) *m*/*z* 390 $(M+NH_4)^+$, 373, 241; HRMS (CI, NH_3) *m*/*z* calcd for $C_{18}H_{36}O_4Si_2$ $(M+NH_4)^+$ 390.2496, found 390.2495.

4.3.12. (4*S*,5*R*,6*S*)-6-Acetoxy-4,5-bis(*tert*-butyldimethylsilyloxy)cyclohex-2-enone 39. A solution of hydroxy enone **38** (50 mg, 0.13 mmol) in pyridine (2 mL) and Ac_2O (2 mL) was stirred at rt under N_2 for 16 h. Then, saturated $NaHCO_{3(aq)}$ (10 mL) and Et_2O (10 mL) were added, the layers separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic extracts were washed with saturated $NaHCO_{3(aq)}$ (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give acetoxy enone **39** (55 mg, 100%) as a pale yellow solid, mp 88–94°C; R_F (4:1 petrol–Et_2O) 0.4; IR (CH_2Cl_2) 1692, 1597, 1422 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.90 (dd, 1H, J=6, 10 Hz), 6.06 (d, 1H, J=10 Hz), 5.75–5.65 (m, 1H), 4.37 (dd, 1H, J=3, 5.5 Hz), 4.04 (dd, 1H, J=3, 10 Hz), 2.18 (s, 3H), 0.93–0.85 (m, 18H), 0.15–0.09 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 193.8, 170.0, 146.7, 129.0, 75.4, 71.8, 68.5, 25.7, 20.9, 18.1, −4.1, −4.6, −4.8 (some signals not resolved); MS (CI, NH_3) m/z 432 $(M+NH_4)^+$, 415, 357, 355, 283, 225; HRMS (CI, NH_3) m/z calcd for $C_{20}H_{38}O_5Si_2$ $(M+NH_4)^+$ 432.2602, found 432.2604.

4.3.13. (1*R*,4*S*,5*R*,6*S*)-6-Acetoxy-4,5-bis(*tert*-butyldimethylsilyloxy)cyclohex-2-en-1-ol 40. $CeCl_3{\cdot}7H_2O$ (60 mg, 0.16 mmol) was added to a stirred solution of acetoxy enone **39** (62 mg, 0.15 mmol) in MeOH (2.5 mL) at rt under N_2. After cooling to 0°C, $NaBH_4$ (22 mg, 0.6 mmol) was added in portions over 10 min and the mixture was stirred for a further 10 min. Then, Et_2O (10 mL) and water (10 mL) were added, the layers separated and the aqueous layer was extracted with Et_2O (2×10 mL). The combined organic extracts were washed with brine (10 mL) and water (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give alcohol **40** (60 mg, 96%) as a yellow oil, R_F (4:1 petrol–Et_2O) 0.1; IR (Nujol) 3485, 1749 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.75–5.72 (m, 2H), 5.13 (dd, 1H, J=5, 8 Hz), 4.22 (dd, 1H, J=2, 3.5 Hz), 4.05–3.95 (m, 1H), 3.81 (dd, 1H, J=3.5, 8 Hz), 2.83 (br s, 1H), 2.11 (s, 3H), 0.92–0.88 (m, 18H), 0.13, (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 172.0, 129.1, 128.9, 75.1, 70.2, 68.8, 65.8, 26.0, 25.8, 22.6, 18.1, 4.2, −4.3, −4.5, −4.8 (one signal not resolved); MS (CI, NH_3) m/z 434 $(M+NH_4)^+$, 399, 285; HRMS (CI, NH_3) m/z calcd for $C_{20}H_{40}O_5Si_2$ $(M+NH_4)^+$ 434.2758, found 434.2761.

4.4. Conduritol F tetracetate

A solution of alcohol **40** (55 mg, 0.13 mmol) in TBAF (5 mL of a 1 M solution in THF) was stirred at rt under N_2 for 16 h. The solvent was evaporated and the residue dissolved in pyridine (2 mL) and Ac_2O (1 mL) at rt under nitrogen. After stirring at rt for 18 h, 2 M $HCl_{(aq)}$ (10 mL) and Et_2O (20 mL) were added, the layers separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic extracts were washed with 2 M $HCl_{(aq)}$ (2×10 mL), saturated $NaHCO_{3(aq)}$ (3×10 mL) and water (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by chromatography (2:1 petrol–EtOAc) gave known[46] conduritol F tetracetate (37 mg, 87%, 89% ee) as a colourless oil, $[\alpha]_D$=+46.9 (c 1.0 in $CHCl_3$) (lit.,[46] $[\alpha]_D$=+45.6 (c 1.1 in $CHCl_3$)), data identical to those reported previously.[46]

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