Diastereoselective epoxide rearrangements using lithium amide bases: first stereocontrolled synthesis of 4-deoxyconduritols

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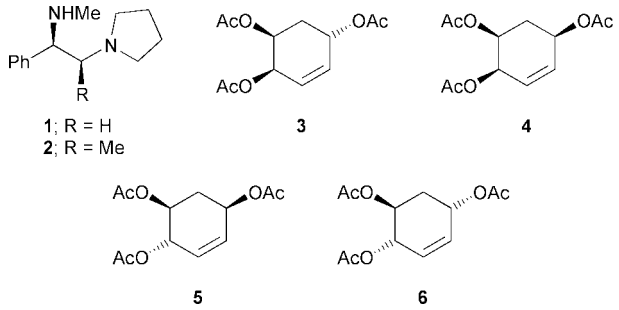
Two novel and completely diastereoselective lithium amide-mediated rearrangements of diprotected 4,5-dihydroxycyclohexene oxides and their use in the synthesis of 4-deoxyconduritols are described.

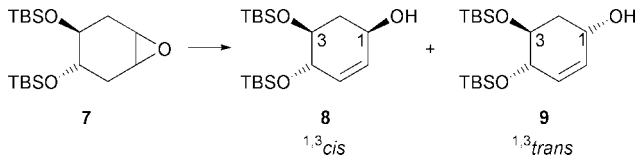
Conduritols and structurally related cyclitols possess a range of useful biological activity (including glycosidase inhibition)[1] and the stereocontrolled synthesis of such compounds continues to attract considerable attention.[2] As part of our research programme into the synthesis of polyhydroxylated cyclohexenes using chiral bases derived from **1** and **2**, we became



interested in the preparation of the triacetates of 4-deoxyconduritols **3**–**6**. Although the preparation of *racemic* **3**, **4** and **6** has been reported,[3–6] there exists no general, stereocontrolled method for the synthesis of 4-deoxyconduritols. Previously, we have described[7,8] the preparation of precursors to **3** and **4** in > 90% ee using the chiral base-mediated asymmetric desymmetrisation of *meso*-4,5-dihydroxycyclohexene oxides. In this paper, we describe a related but conceptually distinct lithium amide epoxide rearrangement approach to the synthesis of **5** and **6**.

In order to synthesise **5** and **6** with the required stereochemistry, we needed to study the rearrangement of *chiral* 4,5-dihydroxycyclohexene oxides like **7** using lithium amide bases (Scheme 1). Such a reaction is intrinsically different to our previously reported epoxide rearrangements: (i) the reaction is not a desymmetrisation; (ii) the reaction can proceed to give two possible *diastereomeric* allylic alcohol products (**8** and **9**) depending on the reacting conformation adopted by the epoxide (*vide infra*); (iii) any optical activity in the allylic alcohols produced must arise either from enantioenriched starting epoxide **7** or from a kinetic resolution of *racemic* **7** using a chiral base.

The rearrangement of cyclohexene oxides to allylic alcohols proceeds *via* lithium amide abstraction of a proton that is *cis* and



Scheme 1

pseudo-axial to the epoxide.[9] When such criteria are imposed on the two possible conformations (**A** and **B**) of **7** then it can be seen from Fig. 1 that removal of the highlighted (*cis* and pseudo-axial) proton in each conformation leads to different *diastereomers* of allylic alcohols: reaction *via* conformation **A** (diaxial silyloxy groups) generates **8** (^{1,3}*cis* stereochemistry); reaction *via* **B** (diequatorial silyloxy groups) gives **9** (^{1,3}*trans* stereochemistry). Thus, we anticipated that by controlling the reacting conformation, we would be able to synthesise allylic alcohols with either ^{1,3}*cis* or ^{1,3}*trans* relative stereochemistry. The successful implementation of this novel strategy is the subject of the present communication.

Racemic **7** was readily synthesised from cyclohexa-1,4-diene in 48% yield over three steps. The reaction of **7** with 2 equiv. of the lithium amide bases generated from *racemic* diamine **2** and diisopropylamine (Scheme 1) was studied under different conditions (Table 1). Reaction of **7** with the lithium amide base from **2** in THF, our usual solvent, generated a 32 : 68 mixture of allylic alcohols **8** and **9**† (Entry 1) which were readily separated by column chromatography. They were identified by conversion of **8** into the previously unreported 4-deoxyconduritol triacetate **5** (*vide infra*). The major product (**9**) must have arisen through reaction *via* conformation **B** (see Fig. 1).

Using *rac*-**2** and by changing the solvent to either Et_2O or cyclopentane, the coordinating ability of the solvent is reduced and only allylic alcohol **8** was formed (Entries 3 and 4). With these solvents, preferential reaction *via* conformation **A** is presumably promoted by intramolecular chelation of the silyloxy group and epoxide oxygen by the lithium cation. For

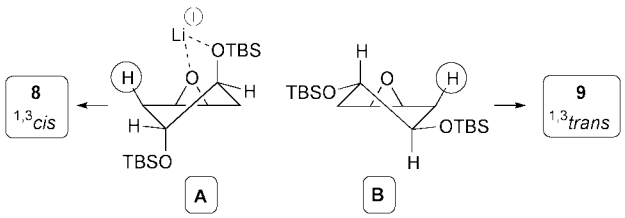


Fig. 1

Table 1 Diastereoselectivity of the lithium amide-mediated rearrangement of **7** using *rac*-**2** and LDA

Entry	Base	Solvent[a]	^{1,3}*cis* : *trans*[b]	Yield (%) of **8**[c]	Yield (%) of **9**[c]
1	**2**	THF	32 : 68	30	61
2	**2**	THF (+2 equiv. LiBr[d])	44 : 56	33	47
3	**2**	Et_2O	≥98 : 2	88	—
4	**2**	Cyclopentane	≥98 : 2	89	—
5	LDA	THF	83 : 17	82	—
6	LDA	Et_2O	95 : 5	85	—

[a] *Reaction conditions*: 2 equiv. diamine *rac*-**2** or $^{i}Pr_2NH$, 2 equiv. BuLi, solvent, 0 °C to rt over 2 h, 70 h, rt; [b] Ratio determined by ^{1}H NMR spectroscopy on the crude product mixtures; [c] Isolated yield after column chromatography; [d] Diamine was deprotonated using MeLi·LiBr rather than BuLi.

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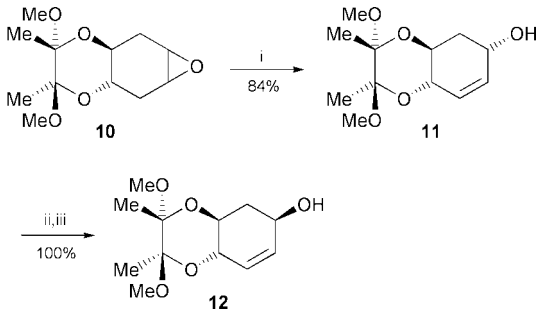

Scheme 2 *Reagents and conditions*: i, 2 equiv. *rac*-**2** + 2 equiv. BuLi, THF, 0 °C to rt over 2 h then 70 h at rt; ii, PCC, CH_2Cl_2 (100%); iii, $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 10 min (100%).

similar reasons, carrying out the reaction in THF with added lithium bromide led to a lowering of the ^{1,3}*trans* diastereoselectivity (Entry 2). The use of TBDPS and TES as protecting groups gave essentially the same results.

We have also investigated the use of LDA for these diastereoselective rearrangement reactions. In THF, a very good isolated yield (82%) of allylic alcohol **8** was obtained (Entry 5). The reaction must proceed preferentially *via* the chelated conformation **A** which is in stark contrast to the result obtained with diamine *rac*-**2** (Entry 1) indicating that LDA is a far better coordinator than *rac*-**2** in THF. Use of LDA in Et_2O led to a slight improvement in ^{1,3}*cis* selectivity (Entry 6) but this did not mirror the improvement in ^{1,3}*cis* selectivity observed with *rac*-**2** on moving from THF to Et_2O where none of the ^{1,3}*trans* diastereomer was observed (Entry 3).

From a synthetic viewpoint, reaction of **7** with the lithium amide derived from *rac*-**2** in cyclopentane generated **8** as the sole diastereomer which was isolated in 89% yield (Entry 4). Conversion of **8** into unknown triacetate **5**‡ was accomplished by deprotection with TBAF and subsequent acetylation (88% yield over the two steps).

Although it was possible to generate allylic alcohol **9** in 61% isolated yield (Entry 1), we wondered if it was possible to have a completely diastereoselective synthesis of an allylic alcohol with ^{1,3}*trans* stereochemistry (reaction only *via* the diequatorial conformation **B**). Thus, we used the Ley butane-2,3-diacetal protecting group[10] to lock the conformation equivalent to **B** in epoxide **10** (Scheme 2).

Racemic **10** was prepared from cyclohexa-1,4-diene in 56% yield. Reaction of **10** with the lithium amide of *rac*-**2** generated only one diastereomer of allylic alcohol in 84% yield and it was identified as the expected **11** by conversion into known[3] triacetate **6** (TFA–water deprotection followed by acetylation, 80% yield). Use of LDA produced allylic alcohol **11** in a slightly improved 89% isolated yield. In passing, we also note that it is possible to carry out a PCC oxidation–Luche reduction sequence to convert **11** into its diastereomer **12** with complete stereocontrol (axial attack of hydride in the conformationally locked intermediate enone explains the stereoselectivity). Finally, we present our preliminary findings on the kinetic resolution of **10** as a route to enantiomerically enriched allylic alcohols.[11] Reaction of *racemic* **10** with 0.7 equiv.[12] of the chiral base from (1*R*,2*S*)-**2** generated **11** in 32% yield (63% ee) and recovered *ent*-**10** in 51% yield (44% ee).

In summary, we have described two novel, completely diastereoselective and stereodivergent lithium amide-mediated epoxide rearrangement reactions (**7** → **8** and **10** → **11**). Mechanistically, our results can only be adequately explained in terms of the removal of a proton which is *cis* and pseudo-axial to the epoxide (see Fig. 1) as proposed by Rickborn and Thummel.[9] In addition, we have also reported the first example of a kinetic resolution on chiral 4,5-dihydroxycyclohexene oxides which, coupled with the oxidation–reduction sequence in Scheme 2, provides a concise approach to enantiomerically enriched 4-deoxyconduritols **5** and **6**.

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Notes and references

† All novel compounds have been fully characterised including microanalysis or HRMS.

‡ Data for novel triacetate **5**: pale yellow oil, R_F(1:1 petrol–Et_2O) 0.3; $\nu_{max}(CHCl_3)/cm^{-1}$ 1740 (C=O) and 1685; δ_H(270 MHz; $CDCl_3$) 5.85 (1H, ddd, *J* 1, 3 and 10, =CH), 5.72 [1H, ddd, *J* 2, 2 and 10 (appearing as a doublet of triplets), =CH], 5.53–5.44 (2H, m, CHOAc), 5.06 (1H, ddd, *J* 4, 7 and 12, CHOAc), 2.42 (1H, dddd, *J* 1, 4, 6 and 12, CH_AH_B), 2.07 (3H, s, Me), 2.06 (3H, s, Me), 2.05 (3H, s, Me) and 1.86 [1H, ddd, *J* 9, 12 and 12 (appearing as a triplet of doublets), CH_AH_B]; δ_C(67.5 MHz; $CDCl_3$) 170.5, 170.2, 170.1, 130.1, 127.7, 70.7, 69.7, 67.6, 32.4 and 21.0; *m/z* (CI, NH_3) 274 [100%, $(M + NH_4)^+$] and 197 (30) [Found: $(M + NH_4)^+$, 274.1288. $C_{12}H_{16}O_6$ requires *M* + H, 274.1291].

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12 Since we usually use 2 equiv. of chiral lithium amide bases for epoxide rearrangement reactions, we decided to use 0.7 equiv. of chiral base for the kinetic resolution. When 0.5 equiv. of chiral base was used, we obtained a 26% yield of allylic alcohol **11** (64% ee).