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Use of Enantiomerically Pure 7-Azabicyclo[2.2.1]heptan-2-ol as a Chiral Template for the Synthesis of Aminocyclitols

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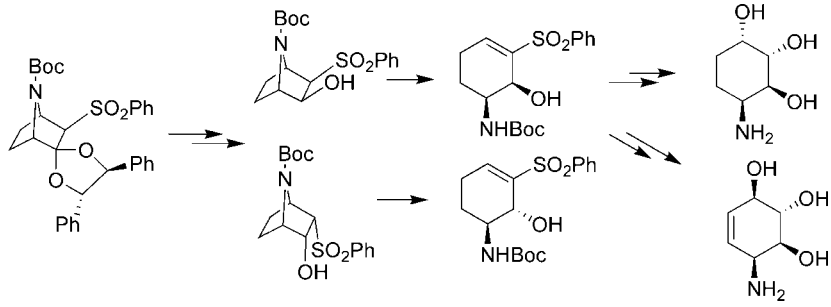
ABSTRACT



Using enantiopure 7-azabicyclo[2.2.1]heptane-2-ol, the synthesis of *cis*- as well as *trans*-2-aminocyclohexanols, dihydroconduramine E-1, and *ent*-conduramine F-1 has been described.

Various aminocyclitols, natural (**1**) as well as synthetic (Figure 1), possess the ability to mimic oligosaccharides,[1] making them potential candidates as inhibitors of glycosidases. In particular, conduramines **2** and **3**, apart from being used as probes for biological functions of oligosaccharides,[2,3] have also served as important synthetic precursors of amino- and diaminocyclitols[4] and for many other biologically active compounds.[5] Therefore, it is not surprising to see the considerable research interest by synthetic chemists toward the synthesis of aminocyclitols[6] and conduramines.[7]

Owing to our broad interest in the design, synthesis, and evaluation of new azasugars as glycosidase inhibitors,[8] it

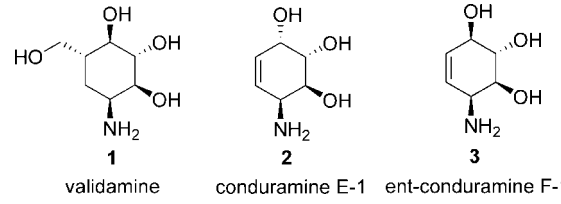


Figure 1. Some bioactive cyclic polyhydroxylated amines.

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(1) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300–2324.
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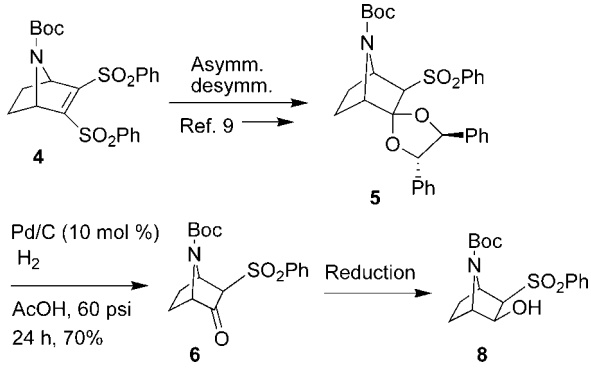
occurred to us that designing a chiral template to obtain aminocyclitols (natural and synthetic) would be an important contribution to this area. In this context, we envisioned the potential of substrate **8** for the synthesis of various aminocyclohexanols. Compound **8** could easily be obtained from optically pure 7-azabicyclo[2.2.1]hept-2-one **6**, synthesized by us a few years ago[9] via asymmetric desymmetrization of *meso*-**4** (Scheme 1). We had developed this strategy to synthesize (−)-epibatidine,[10] a powerful non-opiod analgesic.

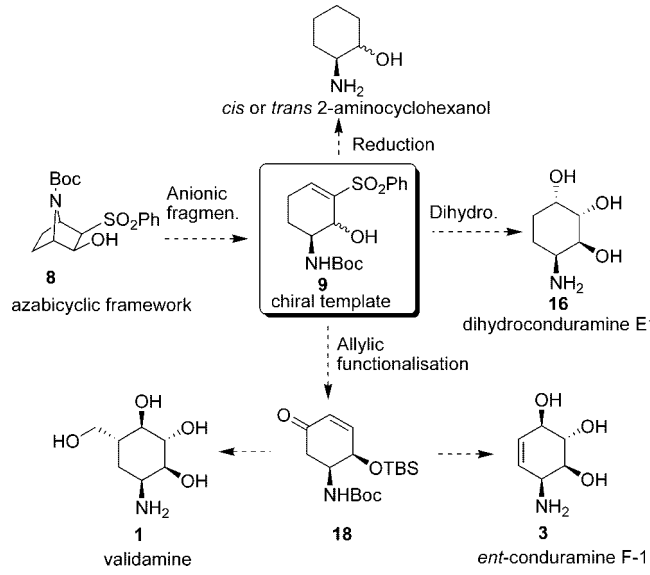
Scheme 1. Synthesis of Chiral Template **8**



The idea of utilizing **8** as a chiral template for the synthesis of aminocyclitols in general emerged from its rigid bicyclic structure[11] and suitably juxtaposed functionalities for its easy transformation to aminocyclohexenol derivative **9** useful for the synthesis of scores of aminocyclitols as described in Scheme 2. In this paper, we disclose our preliminary results on the successful demonstration of the synthesis and use of **8** as a chiral template for the synthesis of aminocyclitols.

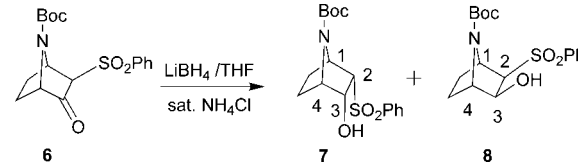
Desymmetrized compound **5** was obtained in 80% yield (99% de) by asymmetric desymmetrization of *meso*-**4** by employing our previously described protocol.[9] Removal of the ketal moiety from **5** by hydrogenation (Pd/C, 10 mol%, AcOH, 60 psi) provided **6** in 70% yield as a diastereomerically pure compound[12] along with the recovery of starting material **5** (30%) (Scheme 1).

Scheme 2. Imaginative Pathway for the Synthesis of Aminocyclitols



We hoped that reduction of **6** with lithium borohydride would furnish only **8**, owing to *endo*-attack of the hydride on carbonyl group. However, it unexpectedly gave a diastereomeric mixture of alcohols **7** and **8** (1:9) (Scheme 3).

Scheme 3. Reduction of Ketone



Fortunately, both diastereomers could be easily separated by silica gel column chromatography.

The relative configurations of both alcohols were unambiguously deduced from their ^{1}H NMR spectrum in $CDCl_3$. For illustration, the H-2 in **7** appeared as dd (J = 9.3, 4.4 Hz) coupling with bridgehead H-1 and H-3 whereas H-3 appeared as ddd (J = 9.6, 9.3, 4.6 Hz) coupling with H-2, bridgehead H-4 and -OH. The coupling with -OH (J = 9.6 Hz) was confirmed by D_2O exchange which simplified the coupling to dd (J = 9.3, 4.6 Hz). Similarly, in the case of **8**, the H-2 showed doublet (J = 6.5 Hz) coupling only with H-3, whereas H-3 appeared as dd (J = 9.7, 6.5 Hz) coupling with H-2 as well as O−H indicating the *endo*-orientation for H-3. This observation is in complete agreement with the

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(12) The observed NMR splitting pattern in **6** is because of restricted rotation about the NCO bond (rotamers). For similar observations, see: Pavri, N. P.; Trudell, M. L. *Tetrahedron Lett.* **1997**, *38*, 7993–7996.

literature reports[13,14] where no coupling is seen between bridgehead and the *endo*-proton in the 7-azabicyclo[2.2.1]heptane system. Since reduction of **6** at room temperature produced diastereomeric mixtures of the corresponding alcohols (**7** and **8**), it became obvious to us that there was an epimerization of H-2 during reduction. Therefore, it occurred to us to investigate the reduction at lower temperature with the hope that it might offer diastereoselectivity. However, to our surprise, the results showed complete reversal in the diastereoselectivity and the ratio of **7** and **8** with respect to temperature is shown in Table 1.

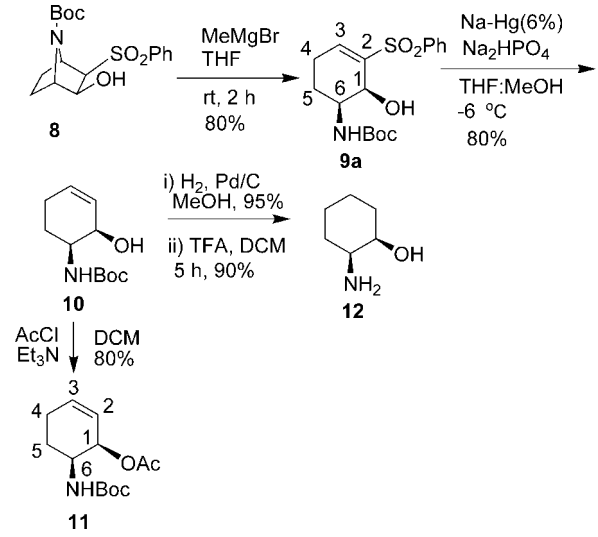
Table 1. Yields and Ratio of **7** and **8** during Reduction of Ketone

entry	T (°C)	ratio (**7**/**8**)	time	yield (%) (combined)
1	−78	7:3	30 min	75
2	−90	7.5:2.5	45 min	70
3	25	1:9	12 h	78

The formation of both **7** and **8**, possibly, could be rationalized by considering the base mediated (BH_4^-) epimerization of H-2 and the orientation of phenylsulfonyl group directing the face of hydride attack on the carbonyl group. While at room temperature, the thermodynamically more stable *exo*-phenylsulfonyl moiety directs the *endo*-attack of the hydride ion resulting **8** as the major product, **7** is formed in larger proportions at lower temperature due to kinetically more favored *endo*-phenylsulfone.

Initially, we tried the anionic rearrangement of **8** using bases such as LiHMDS and *n*-BuLi; however, they failed to give any product. Finally, ring opening of **8** succeeded by the addition of excess of methyl magnesium bromide[7f] in a THF solution at room temperature producing **9a** in 80% yield as a crystalline solid [mp 131 °C; $[\alpha]^{25}_D$ −69.0 (*c* 1.00, $CHCl_3$)] (Scheme 4). Owing to undefined couplings between the two stereochemical protons (H-1 and H-6) in the ^{1}H NMR of **9a** in $CDCl_3$, it proved difficult to assign relative configuration satisfactorily. Although **9a** was a good crystalline compound, it did not diffract properly for X-ray analysis. Therefore, we removed the phenylsulfonyl group from **9a** using 6% sodium amalgam in a buffered methanol and derivatized the free hydroxyl to corresponding *O*-acetate **11**. Luckily, this compound turned out to be a good crystalline solid (mp 66 °C) and produced the X-ray structure[15] (Figure 2) confirming the *cis*-1,6-amino alcohol configuration for **9a** (Scheme 4). Highly encouraged with the success of the ring-opening reaction of **8**, we considered that **7** could also be equally susceptible for rearrangement. However, reaction of **7** with methyl magnesium bromide under similar reaction conditions as described for **8** was not equally rewarding as

Scheme 4. Anionic Fragmentation of **8**



it failed to give any product. A close look at the structure of **7** indicated that in this molecule, the orientation of sulfone moiety is *endo* which may not allow the fragmentation due to the lack of antiperiplanarity between the bonds to be cleaved. Therefore, in order to support our observation, we epimerized the *endo*-sulfone moiety to *exo* using KHMDS as a base, which gave **13** in 70% yield. The epimerization of **7** was not successful using LiHMDS, possibly due to the chelation of the lithium between hydroxyl and sulfonyl oxygen. The structure of **13** was confirmed on the basis of ^{1}H NMR analysis in $CDCl_3$ as H-2 appeared as a doublet (J = 3.6 Hz) which is possible only when sulfone is *exo*-oriented. Subjecting **13** to the usual anionic rearrangement yielded **9b** in 70% yield [crystalline solid; mp 125 °C; $[\alpha]^{25}_D$ +14.6 (*c* 0.40, $CHCl_3$)] (Scheme 5). The stereochemistry of **9b** was confirmed by carrying out COSY experiments.

Since both **9a** as well as **9b** can be obtained from desymmetrized compound **6**, simple experimental manipulations such as sulfonyl group removal, reduction of the olefinic

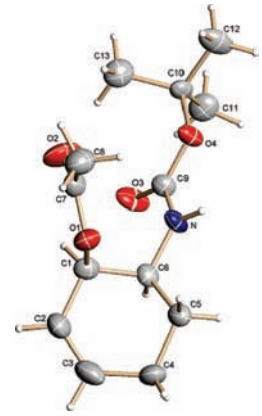


Figure 2. ORTEP diagram of **11**.

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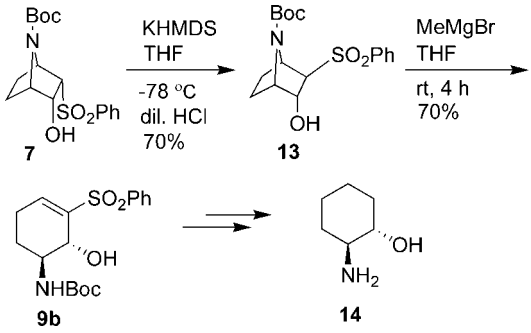
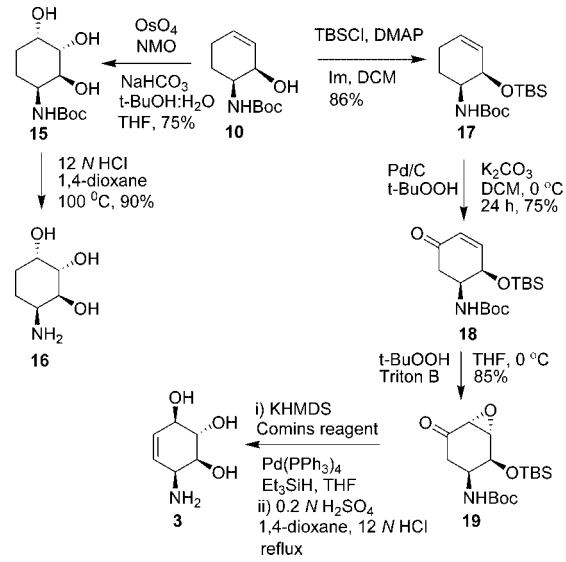
(15) Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-691970.

Scheme 5. Ring Opening of Epimerized Alcohol



Scheme 6. Synthesis of Dihydroconduramine E1 **16** and Epoxy Ketone **19**



double bond, and *N*-Boc deprotection produced *cis*- as well as *trans*-2-aminocyclohexanols (**12** and **14**), respectively. It may be important to mention that these compounds have been fascinating targets for synthesis due to their wide applicability as ligands in asymmetric syntheses[16] and as small molecular probes for quorum-sensing modulation.[17] Optically pure *trans*-1,2-aminocyclohexanol (**14**) is obtained by either the aminolysis of cyclohexene epoxides using enantiopure methylbenzylamine in the presence of trimethylaluminum[18] or enantioselective opening of the *meso*-epoxide by an appropriate nucleophile using chiral catalyst.[19,20] In contrast, optical resolution has been the only method available for the synthesis of enantiomerically pure *cis*-1,2-aminocyclohexanol (**12**).[21]

As we had obtained **10** in larger quantity initially, we proceeded to explore its synthetic utility in the synthesis of *ent*-conduramine F-1 (**3**) as well as dihydroconduramine E-1 (**16**). While conduramine **3**, also called norvalienamine, is as active as valienamine in inhibiting α-glucosidase from yeast,[22] compound **16** is unknown in all respects. Toward transforming **10** into **16**, we carried out OsO_4-catalyzed dihydroxylation of the olefinic bond which gave expected **15** in 75% yield as a single isomer and was characterized by detailed COSY, NOESY, and ^{13}CMR data. The observed dihydroxylation stereochemistry of **15** was in accordance with Donohae's[23] report. The carbamate deprotection using dilute HCl yielded **16** in 90% yield (Scheme 6) [mp 95 °C $[\alpha]^{25}_D$ +55 (*c* 0.5, H_2O)]. To explore its synthetic utility in the synthesis of **3**, the free hydroxy moiety of **10** was protected as the −OTBS ether (**17**, 86% yield). The allylic oxidation of **17** by stirring with Pd/C (10 mol %) and *t*-BuOOH in DCM at 0 °C furnished enone **18** in 75% yield.[24] The nucleophilic epoxidation of enone **18** using TBHP and Triton-B in THF at 0 °C yielded single product **19** in 85% yield as a crystalline solid [mp 110 °C $[\alpha]^{25}_D$ −45.0 (*c* 0.50, $CHCl_3$)]. The epoxy ketone **19** was fully characterized by ^{1}H NMR, ^{13}C NMR, and mass spectra. The stereochemistry of the epoxide was confirmed by detailed COSEY and NOESY studies. Compound **19** was transformed into the corresponding enol triflate by reaction with KHMDS/Comins reagent[25] which upon treatment with $Pd(PPh_3)_4$ and Et_3SiH produces the corresponding olefin derivative. One-pot epoxide ring opening and global deprotection by refluxing with 0.2 N H_2SO_4 and 10 N HCl in dioxane produced *ent*-conduramine F-1 (**3**) (Scheme 6). Optimization of the reactions conditions and the synthesis of corresponding analogues starting from **9b** are in progress and will be detailed appropriately in a full paper.

Acknowledgment. K.N.T. is thankful to UGC, New Delhi. for the award of research fellowship.

Supporting Information Available: Experimental details and NMR spectroscopic and mass spectroscopic data for the new compounds are given in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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