# The First Enantioselective Syntheses of Axially Chiral Enantiomerically Pure Calix[4]resorcinarene Derivatives

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We report here our preliminary work that is designed to address the enantioselective synthesis of axially chiral, enantiomerically pure, calix[4]resorcinarene derivatives by the enantioselective generation of diastereoisomerically pure tetrakis(benzoxazines) followed by the removal of the chiral auxiliary. The key to our strategy involves the alkylation of the four residual phenolic groups that are present in diastereoisomerically and enantiomerically pure tetrakis(benzoxazines) **1** before removal of a chiral auxiliary, thus ensuring that diastereoisomerization is precluded as well as providing the necessary dissymmetry.

The chemistry of calixarenes[1] continues to be widely studied, and in particular the preparation in high yields of a range of calix[4]resorcinarene derivatives has provided interesting possibilities. The structures of the thermodynamic products place the eight phenolic hydroxyl groups on the upper rim of the $C_{4v}$ symmetric products and these compounds have been utilized in a wide range of syntheses.[2] Important recent work has also concentrated on stereochemical aspects of the chemistry of calixarenes. The dissymmetry generated by unsymmetrical substitution of calixarenes was recognized as being related to the nonplanar structures of the parent compounds,[3a] although a number of chiral calixarene conformers are racemized thermally by processes involving "through-the-annulus rotation".[3b] The first example of the optical resolution of such a compound was achieved with chiral liquid chromatography.[3c] A large number of axially chiral calixarene derivatives continues to be prepared as racemates, some of which have been resolved with chiral chromatographic procedures.[4] Lipase-catalyzed transesterification has been used recently to generate chiral calix[4]arenes with high enantiomeric excesses.[5] Diastereoselective functionalization has also been used to prepare chiral calixarene derivatives.[6] Included in this area has been the highly diastereoselective functionalization of calix[4]resorcinarene derivatives involving the formation of tetrakis(3,4-dihydro-2-*H*-1,3-benzoxazines) by the use of chiral nonracemic primary amines. The presence of substituents attached to the inter-ring methine carbon atoms precludes thermal racemization processes in calix[4]resorcinarene derivatives. The earlier publications suggest that the control of diastereoselection is capricious with classical Mannich protocols.[7] In our hands the best results are obtained using a bis(methoxymethyl ether), for example **2**, as a bis(iminium ion) precursor. Our experience shows that although the crystalline tetrakis(3,4-dihydro-2-*H*-1,3-benzoxazines) remain diastereoisomerically stable over long periods of time, they undergo rapid diastereoisomerization in solution in the presence of traces of acids.[7a] We had previously determined the handedness of the dihydro-2-*H*-1,3-benzoxazine rings in the dissymmetric structures in one of a pair of enantiomers by a single-crystal X-ray structure determination. In addition we established that the products were diastereoisomerized to an unequal mixture of diastereoisomers in acid-catalyzed reactions, via ring-opened iminium ions.[7a]

Recent studies of the *O*-benzylation of cyclophanes highlight the problems of control of regioselectivity and in the determination of the number of *O*-benzylation reactions that occur.[8] Our early attempts to achieve tetrakis(*O*-methylation) using a variety of conventional protocols failed. However, we were able to deprotonate all four phenolic hydroxy groups in a THF solution of the calix[4]resorcinarene **1**[7a] using 4 equiv of *n*-butyllithium at −78 °C. Methylation at low temperature with dimethyl sulfate then gave the tetramethyl ether **3** in 45% yield, while the use of methyl

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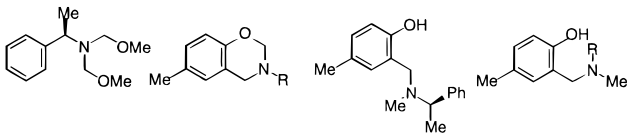
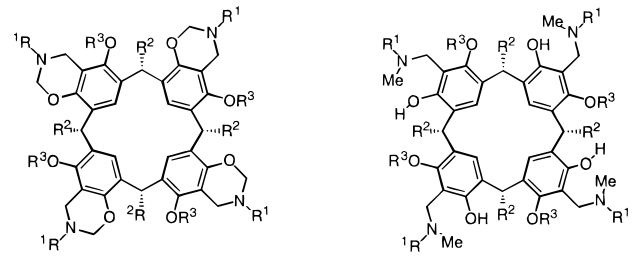
triflate gave **3** in 84% yield, in both cases as a single diastereoisomer. Methylation of the enantiomer of **1** gave its tetramethyl ether in similar yields. The purity of the enantiomers was established by the identity of the two sets of $^1$H and $^{13}$C NMR spectra, from their optical rotations, and from chiral hplc data. The methylation protocol is general and good yields of the related tetramethyl ethers have been obtained with analogues of **1** where the substituent $R^2$ is, for example, methyl, pentyl, and $\beta$-phenylethyl.



**2** **4**, R = (R)-α-methylbenzyl; **5** **6**, R = H
**7**, R = Me **8**, R = Me



**1**, $R^1$ = (R)-α-methylbenzyl, $R^2$ = undecyl, $R^3$ = H
**3**, $R^1$ = (R)-α-methylbenzyl, $R^2$ = undecyl, $R^3$ = Me
**11**, $R^1$ = $R^3$ = Me, $R^2$ = undecyl



**9**, $R^1$ = (R)-α-methylbenzyl, $R^2$ = undecyl, $R^3$ = Me
**10**, $R^1$ = H, $R^2$ = undecyl, $R^3$ = Me
**12**, $R^1$ = $R^3$ = Me, $R^2$ = undecyl

With a series of tetramethyl ethers in hand we were in a position to study the removal of the chiral auxiliaries. A number of possibilities was apparent on the basis of the known lability of the heterocyclic ring present in a number of derivatives of 3,4-dihydro-2-*H*-1,3-benzoxazine. The cleavage of the aminol ether functionality has been reported on a number of occasions. Our own studies had shown that reactions with electrophiles such as dichlorodimethylsilane allowed Mannich reactions to be conducted with nucleophilic aromatic heterocycles.[9] Burke and his collaborators had earlier shown that a series of 3,4-dihydro-2-*H*-1,3-benzoxazines gave phenolic dibenzylamines when the 3,4-dihydro-2-*H*-1,3-benzoxazines were allowed to stand with phenols in the condensed phase.[10] Both of these reaction types involved cleavage of the aminol ether to give an iminium ion. Because the degradative removal of the chiral auxiliary in the calix[4]-resorcinarene derivatives required four reactions to be carried out at each step, high yields were essential at each stage. We therefore decided to conduct a study of some model reactions before applying heterocyclic ring cleavage reactions to the chiral ether **3** and its enantiomer.

Since the 3,4-dihydro-2-*H*-1,3-benzoxazine ring system fragments to an iminium ion in the presence of protic acids, we expected that the conversion of the model compound **4** into **5** would be possible by a modification of the Eschweiler−Clarke procedure, in which the benzoxazine derivative was heated in 97% formic acid without the addition of formaldehyde. Experiment confirmed this reasoning, and the amine **5** was isolated in 85% yield. Hydrogenolysis of **5** to give **6** was achieved in 87% yield when carried out at atmospheric pressure with hydrogen in the presence of palladium hydroxide.[11] We reasoned that conversion of the secondary amine **6** into the tertiary benzylamine derivative would also be best carried out in two stages in the calix[4]resorcinarene series. As a model, the secondary amine **6** was converted into the 3,4-dihydro-2-*H*-1,3-benzoxazine **7** in 65% yield by treatment with formaldehyde and hence into the tertiary amine **8** in 89% yield by heating with 97% formic acid.

We were thus in a position to generate a number of axially chiral enantiomerically pure calix[4]resorcinarene derivatives from a wide range of enantiomeric tetramethyl ethers such as **3** and its enantiomer. When the calix[4]resorcinarene derivative **3** was heated under reflux in 97% formic acid it was rapidly converted into the ring-opened *N*-methyl compound **9** in 65% yield. Hydrogenolysis of **9** in the presence of hydrogen chloride and palladium hydroxide gave the tetrakis-secondary amine **10** in 75% yield, then, by reaction with formaldehyde, the tetra-*N*-methyl-3,4-dihydro-2-*H*-1,3-benzoxazine **11** in 87% yield, which is formally related to the racemic tetrakis(3,4-dihydro-2-*H*-1,3-benzoxazine) (±)-**11**, derived directly from methylamine followed by methylation. A second modified Eschweiler−Clarke reaction with 97% formic acid gave the tetrakis-tertiary amine **12** in 94% yield. The enantiomers of **9**, **10**, **11**, and **12** were obtained in comparable yields by using the same sequence of reactions. Finally, we were able to make use of the known retro-Mannich reactions of 3,4-dihydro-2-*H*-1,3-benzoxazines that have been studied previously.[12] We found that when the tetrakis(3,4-dihydro-2-*H*-1,3-benzoxazine) **3** was heated in an excess of morpholine, the heterocyclic ring underwent ring fragmentation and capture of morpholine to give an analogue of **12** in 35% yield, in which the dimethylamino groups had been replaced by morpholino residues.

The present study thus establishes the first enantioselective route to a number of axially chiral calix[4]resorcinarene derivatives with $C_4$ symmetry as single enantiomers. The presence of phenolic and secondary or tertiary amine functionalities provide these compounds with the potential to be used for a wide variety of purposes, for example, in molecular recognition phenomena. In addition they are capable of a wide range of further functional group interconversion reactions that will give additional axially chiral calix[4]resorcinarene derivatives. We are currently exploring these opportunities together with the development of a number of related compounds.

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**Supporting Information Available:** Experimental procedures and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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