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A NEW ROUTE TO HOMOCHIRAL *TRANS*-DISUBSTITUTED CYCLOPENTANES

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Summary: *Asymmetric epoxidation of cyano-substituted allylic alcohols gave epoxides of high optical purity. Subsequent base-promoted cyclization produced diastereomerically pure cyclopentane derivatives in moderate yield.*

The epoxyalcohol products of Sharpless' asymmetric epoxidation reaction[1,2] have found increasing use as intermediates in chiral synthesis[3,4] due to their typically high optical purity and to the regiochemical and stereochemical predictability of subsequent epoxide opening. The intramolecular opening of these epoxides has led to the synthesis of optically active cyclization products, most notably oxygen[5-12] and nitrogen[13-15] heterocycles. Only rarely, however, have optically active carbocycles been prepared in this way.[16,17] In the present study we show that the asymmetric epoxidation reaction is applicable to certain cyano-substituted allylic alcohols and that the resulting optically active epoxides are converted by strong base to diastereomerically pure carbocyclic products.

The base-promoted carbocyclic ring closure of (racemic) epoxynitriles has been systematically investigated by Stork and co-workers[18] who found, *inter alia*, that the action of sodamide on 6,7-epoxyoctanenitrile (**Ia**) (configuration not specified[20,21]) leads regiospecifically and stereoselectively to the *trans*-disubstituted cyclopentane **IIa**. We describe here the preparation of optically active **Ib** in both *cis* and *trans* forms and the cyclization of each to a single cyclopentane derivative.

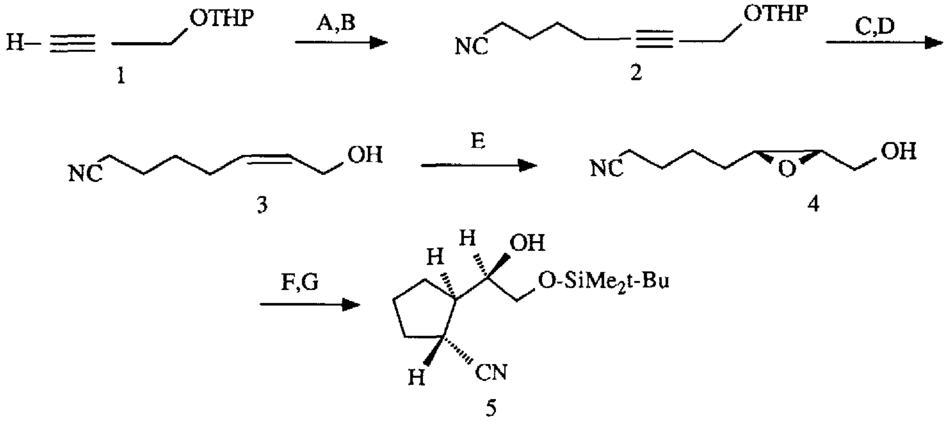
Ia
b

IIa

a $R = CH_3$

b $R = CH_2OH$

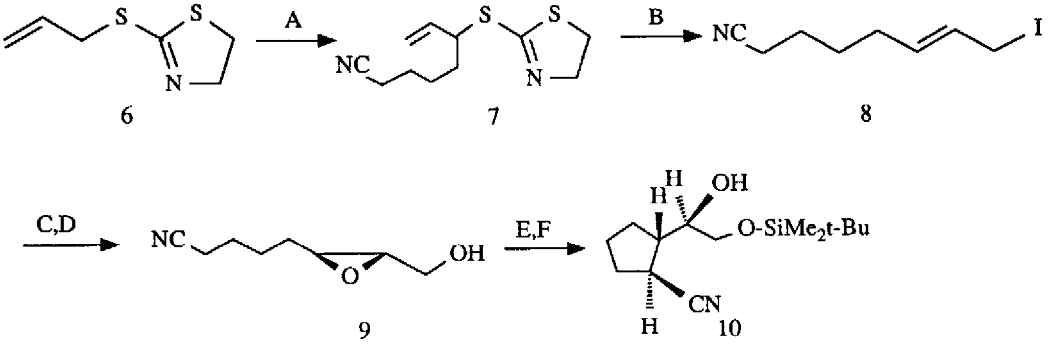
The synthesis in the *cis* series is outlined in Scheme I. Propargyl alcohol THP ether **1**, after chloroalkylation and cyanide substitution, produced acetylenic nitrile **2**. Conversion to the corresponding *cis* allylic alcohol **3** was accomplished by deprotection followed by controlled hydrogenation with Lindlar's catalyst. Asymmetric epoxidation of **3** by Sharpless' procedure using (+)-diisopropyl tartrate gave epoxide **4** in 72% yield. The acetate ester of **4** had $[\alpha]_D$ + 12.5° ($CHCl_3$) and its optical purity was found to be 96% by the chiral shift reagent method.[22] The TBDMS ether of **4**, on treatment with an excess of sodium hexamethyldisilazane in benzene at 25°C for 90 min. produced cyanocyclopentane **5** in 74% yield. The diastereomeric homogeneity of **5** was indicated by its apparent chromatographic uniformity as well as by its ^{13}C NMR spectrum which exhibited only a single peak for each distinguishable carbon atom. Analysis by high resolution mass spectrometry confirmed the expected molecular formula by presenting a molecular ion at m/e 212.1106 ($C_{10}H_{10}NO_2Si$) corresponding to [M--t-Bu].



A) n-BuLi, $Br(CH_2)_4Cl$, HMPA (80%). B) NaCN, HMPA (79%). C) PPTS, MeOH (95%).
D) H_2, Lindlar catalyst (88%). E) t-BuOOH, (+)DIPT, $Ti(O\text{-}iPr)_4$ (72%). F) TBDMS-Cl, imidazole (96%).
G) NaN $(SiMe_3)_2$ benzene, 25°C, 90 min. (74%).

SCHEME I

The initial steps of our synthesis in the *trans* series (Scheme II) are based on Hirai and Kishida's method[23] for constructing *trans* allylic iodides. The alkylation product **7** from 2-allylthio-2-thiazoline (**6**) and 5-bromopentanenitrile underwent N-methylation and spontaneous fragmentation to *trans* allylic iodide **8**. Routine transformations led to the corresponding allylic alcohol which, by Sharpless' procedure, gave epoxide **9** in 65% yield. The acetate ester of **9** had $[\alpha]_D$ -25.0° ($CHCl_3$) and its optical purity was found to be 94%. The TBDMS ether of **9** underwent cyclization to cyanocyclopentane 10 in 56% yield. Compound **9** appeared to be chromatographically homogeneous and its ^{13}C NMR spectrum showed only the expected number of signals. Its high resolution mass spectrum likewise exhibited a molecular ion at m/e 212.1104 ($C_{10}H_{10}NO_2Si$) for [M--t-Bu].



A) n-BuLi, Br$(CH_2)_4$CN, THF, -60°(62%). B) CH_3I (60%). C) NaOAc, HMPA, 25°; NaOH (54%). D) t-BuOOH, Ti(Oi-Pr)$_4$, (+)-DIPT (65%). E) TBDMS-Cl, imidazole (89%). F) $NaN(SiMe_3)_2$, benzene, 25°, 75 min. (56%).

SCHEME II

The cyano-carbon configurations given in **5** and **10** are based on Stork's findings for IIa. The other two chiral centers of these cyclization products are assigned based on Sharpless' asymmetric epoxidation rules and the assumption of inversion in the nucleophilic opening of epoxides.

In summary, we have found that, in the cases studied, the presence of a nitrile substituent was compatible with the Sharpless asymmetric epoxidation and that the subsequent base-promoted cyclization produced diastereomerically pure cyclopentane derivatives in moderate yield.

Acknowledgement. We wish to express appreciation to Professor K.B. Sharpless for supplying a considerable amount of helpful information, then unpublished, regarding the asymmetric epoxidation reaction..

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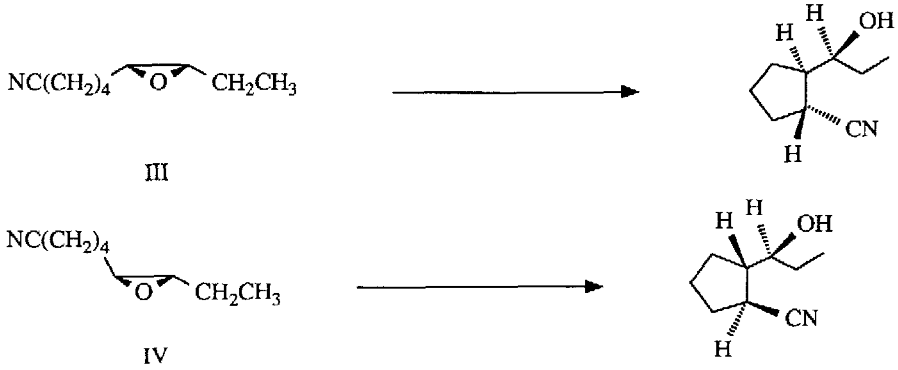
20. The epoxide stereochemistry is of particular significance because the regiochemistry of cyclization of 5,6-epoxynitriles is directly dependent on epoxide configuration.[19] As a preliminary to the present work, we synthesized (±)-cis- and (±)-trans-6,7-epoxynonanenitrile (III and IV, respectively) and verified that both yielded the expected disubstituted cyclopentanes when treated with sodium hexamethyldisilazane.



21. In a recent private communication, Professor Stork has disclosed that this epoxynitrile was cis, since it came from an alkene which was prepared by a Wittig reaction on the required cyanoaldehyde.

22. Tris[3-heptafluoropropylhydroxymethylene)-(-)-camphorato], europium III derivative (Aldrich) was employed. We are grateful to Mr. Mark Naylor for these determinations.

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