A Facial One-step Approach to Stereospecific Spirocyclic Diols from α-Hydroxyepoxides

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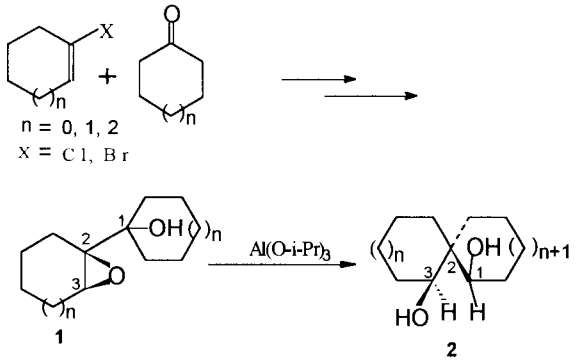
A new 1-step method for synthesis of stereospecific spirocyclic diols from α -hydroxyepoxides with aluminum isopropoxide was reported, which was stereospecific, simple and highly effective. The stereochemical assignment of some products was also discussed.

Synthesis of spirocyclic diols recently has been attracting the increasing interesting of organic chemists in asymmetry fields,[1-4] because some of the chiral spirocyclic diols, such as the chiral spiro[4.4]nonane-1,6-diol and spiro[5.5]undecane-1,7-diol, have been used as chiral ligands to modified aluminum hydride reagents to give high stereoselectivity for the reduction of aromatic ketones.[5] Though there have been reported some synthetic methods of this kind of spirocyclic diols,[1-6] they do not seem very effective because they generally went through the preparation of the corresponding spirocyclic dione, maximum yield of which has been as low as 26% for the synthesis of spiro[5.5]undecane-1,7-diol.[1] Recently, our independent studies in this field has brought about the discovery of a new short, effective and stereospecific approach to this kind of diols without preparation of the dione intermediates.



Scheme 1.

As indicated in Scheme **1**, the tertiary α -hydroxyepoxide **1** (prepared from chloro- or bromo-cycloalkene and cyclic ketone in two steps[7]), when treated with excess of aluminum isopropoxide at refluxing temperature of 2-propanol or THF, smoothly afforded the main *cis,trans* form of spirocyclic diols **2** in good yield. This reaction finished in 1-step a overall process of two reactions, the semi-pinacol rearrangement[8] and the Meerwein-Pondorf-Verley type reduction,[9] and has never been reported until present. The valuable features of this method included that, in some cases the stereochemitry of three diastereoisomeric centers, C-1, and C-2 and C-3, were successfully controlled, and in other cases at lest two centers, C-2 and C-3, controlled with C-1 being unequally diastereoisomerized. In addition, the procedure was quite simple and convenient, and effective to different sizes of spirocyclic diols, and also the reagent was very cheap and easily available.

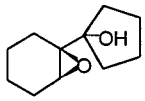
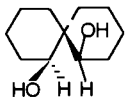
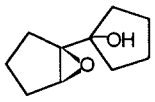
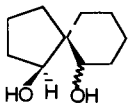
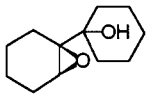
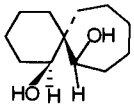
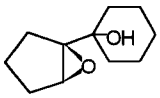
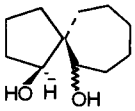
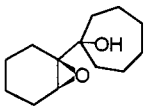
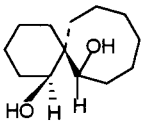
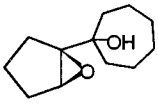
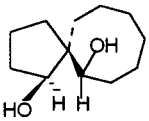
Listed in Table **1** were six examples we conducted. The racemic α -hydroxyepoxides of Runs **1**, **3**, **5** and **6** under the above conditions afforded only one spirocyclic diol product, respectively. We were unable to isolate other components from the reaction mixture except for Run **3**, in which a by-product of lower polarity was isolated in the yield up to 35% and was charaterized by spectroscopy to be the typical ring-cleavage product (the allylic alcohol) of epoxide.[10] This fact suggested that all three diastereoisomeric centers (C-1, C-2 and C-3) of these products were controlled stereochemically. Under the same conditions, however, the epoxide substrates of Runs **2** and **4** gave respectively a mixture of two isomers and no other components could be isolated from the reaction mixture, suggesting two diastereoisomeric centers of these products were controlled stereochemically but one remained diastereoisomerized.

The facts that Runs **3** and **4** exhibited lower yields of spirocyclic diols than others in Table **1** and a by-product was formed in considerably high yield in Run **3** suggested that the cyclo-enlargement of the cyclohexanols of Runs **3** and **4** would be less effective than that of other sizes of cycloalkanols. In addition, the formation of a couple of epimers of Runs **2** and **4** would suggest that the stereochemical control is more effective with cyclohexene oxisde derivative than with cyclopentene oxide.

As with the stererochemistry assignments, we initially investigated Runs**1**, **3**, **5** and **6** which all gave a singlet product. The ^{1}NMR spectra of these products exhibited a singlet or a doublet or a double doublet ($J \leq 2.5$Hz) for H-3 and the doublet (J >8 Hz) or a double doublet (J = 11, 4.4 Hz) for H-1. This observation suggested the axial (or similar) location of C_3-OH and the equatorial (or similar) of C_1-OH in these products. Furthermore the product of Run **1** could be acetalized readily with acetone/TsOH and the obtained acetal also showed the ^{1}H NMR singlet at δ 3.54 *ppm* for H-3 and a doublet at δ 3.39 *ppm* (J = 11, 4.2 Hz) for H-1. The molecular model examination suggested the existence of a *cis,trans* relative configuration in the product of Run **1**. Thus we deduced that the products of Runs **3**, **5** and **6** would exhibit the *cis,trans* configuration, though we have not made the detail investigation one by one.

To establish the stereochemistry of the epimeric isomers of Runs **2** and **4**, the mixture of two isomers of Run **2**, as an example, was made into acetal derivatives with acetone/TsOH. The primary 2D NOESY technique investigation indicated that the relative stereochemistry for the major isomer was the *cis,trans* form and the minor was the *cis,cis*. After all, we felt, in our investigation scope, that the relative stereochemistry of the main products obtained in the present method would be *cis,trans* form. A further exact investigation about the stereochemistry and the mechanism of this reaction, and its application to asymmetric organic reaction are still being

Table 1. The Synthesis of Spirocyclic Diols from α-Hydroxyepoxides with Aluminum Isopropoxide[a]

Run	Substrate	Product	Yield/% (Isomeric Ratio [b])
1			98(>99/<1)
2			80(68/32)
3			60(>99/<1)
4			50(76/24)
5			98(>99/<1)
6			77(>99/<1)

[a] The products were synthesized by the described procedure in text, and their structures were established mainly on the basis of NMR and mass spectroscopy. [b]The ratios of epimers were determined by ^{1}H NMR or GC-MS.

continued.
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References and Notes

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