

**On the Use of Epoxy Alcohol-Aldol Rearrangement
for Stereoselective Construction of Quarternary Carbon Centers**

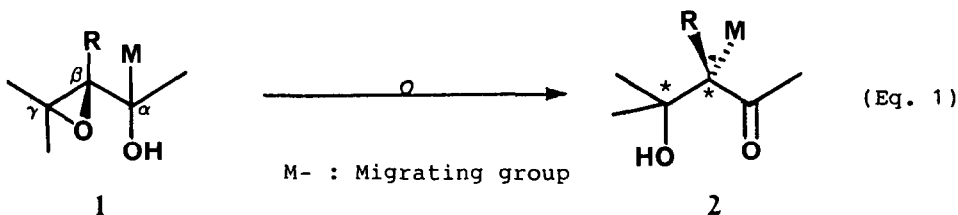
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Summary: A new method for the construction of quarternary carbon centers is reported, which is based on the Lewis acid-promoted 1,2-rearrangement of β,γ -epoxy alcohols giving α,α -disubstituted aldols stereospecifically in high yields.

Stereoselective construction of quarternary carbon centers is one of the significant problems in current organic synthesis, which has been the subject of extensive studies.¹⁾ Pertinent to this, several efficient methods have been devised for the introduction of the quarternary chirality including stereoselective alkylation,^{2a-c)} insertion reaction,^{2d)} and so on.

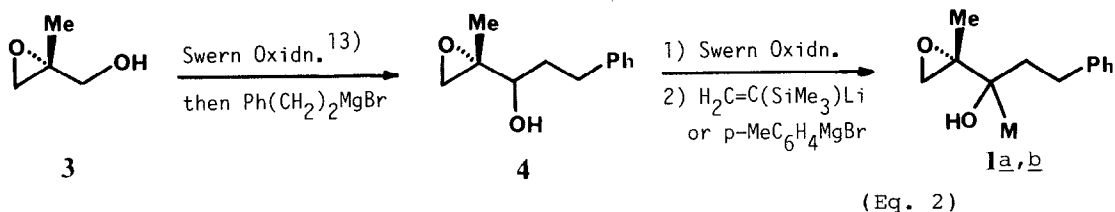
Epoxy alcohol-aldol rearrangement,³⁾ a newer method for the stereocontrolled aldol synthesis, has an expedient potentiality in this context as shown in Eq. 1. Provided stereospecific, the rearrangement of epoxy alcohols 1 having the β -substituent would give α,α -disubstituted β -hydroxy carbonyl compounds 2, which are hardly accessible by the conventional aldol condensations. Furthermore, ready availability of 1 in optically active



forms, e.g. from sugars⁴⁾ or by the Katsuki-Sharpless reaction,⁵⁾ would render this protocol an attractive approach to the chiral syntheses of 2. However, we must pay attention to the problem of stereo-randomization (racemization) which could be involved due to the apparent readiness of the formation of the tertiary carbocation at the β -position under the Lewis acidic conditions for the rearrangement. With these concerns in mind, we examined the rearrangement reactions of epoxy alcohols 1.

In this communication, we wish to describe the reaction profiles to show the promising scope as well as some limitations of the rearrangement-based approach to the construction of the quarternary carbon centers.

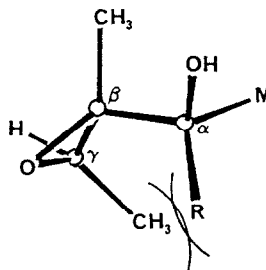
(R)-2-Methyloxiranemethanol **3** (87±1 %ee: not optimized),⁷⁾ which was obtained by the catalytic Sharpless epoxidation [TBHP, Ti(OiPr)₄ (10 mol %), D-(-)-DIPT (12 mol %)],^{5b)} was converted to chiral epoxy alcohols **1a** and **1b** in three steps, respectively. The conversion of **3** to **4** was performed in one-pot operation, because of the high volatility of the intermediary aldehyde.



Rearrangements of epoxy alcohols **1a,b** were smoothly effected by their treatment with BF₃·OEt₂ (2.0 equiv.) in CH₂Cl₂ at -78 °C to give aldols **2a,b** in excellent yields.⁶⁾ The reactions were almost instantaneous at -78 °C, much faster rates than the previous cases without the β-substituent which proceeded around -40 °C - 0 °C.³⁾ Gratifyingly, no racemization was observed under these conditions, which was assured by the fact that no decreases of the ee's were detectable for **2a** and **2b** (87±1 %ee) by their Mosher analyses.⁷⁾

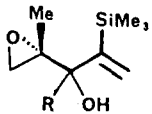
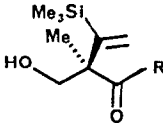
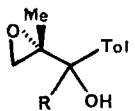
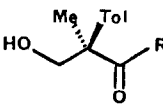
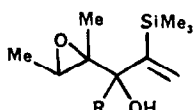
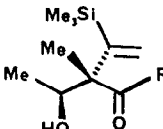
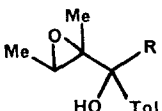
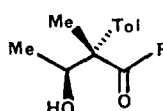
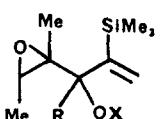
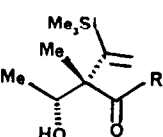
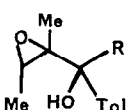
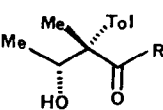
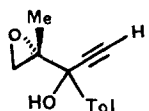
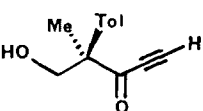
Rearrangements of non-terminal epoxy alcohols were also examined using the racemic materials **1c-f**. Under the conditions above stated, both of the trans epoxy alcohols **1c** and **1d** were uneventfully converted to the corresponding products in excellent yields. The products (**2c**, **2d**) were proven to be the single isomers,⁸⁾ respectively, which again ensured the stereospecificity of the rearrangements. On the other hand, the cases of cis isomers **1e** and **1f** were more or less problematic. For **1f**, some loss of the stereospecificity was observed, i.e. the product **2f** was accompanied by 11 % of the isomer **2d**. The reaction performed in CHCl₃ gave a slightly improved result (5 % of **2d**). This stereo-scrambling for the cis case indicates a limitation of the reaction. As shown in Fig. 1, severe steric interaction between the γ-methyl group and the α-substituent prevents the molecule from adapting the conformation requisite for the rearrangement (antiperiplanar arrangement of α-C-M and β-C-O).³⁾ For **1e**, however, this problem was overcome by its prior conversion to the corresponding TMS ether **1e'**³⁾ whose rearrangement gave aldol **2e** as a single isomer in 89 % yield.⁸⁾ Here, the use of Fig. 1 (iPrO)₂TiCl₂ as the Lewis acid was favorable, otherwise much lower yield of **2e** resulted.

An interesting example of the rearrangement is shown in run 7,⁹⁾ which depends on our previous finding of the very low migratory aptitude of the alkynyl groups in the related rearrangement.¹⁰⁾ For **1g** also, the ethynyl group functioned as the staying group, and the exclusive migration of the p-tolyl group led to the formation of **2g** in 97 % yield, which



(Only one isomer is depicted.)

Table 1. 11,12)

Run	Epoxy alcohol <u>1</u>	Product <u>2</u>	Yield ^{a)} (%)	Isomeric Purity(%)
1	 <u>1a</u>	 <u>2a</u>	86	— ^{d)}
2	 <u>1b</u>	 <u>2b</u>	100	— ^{d)}
3	 <u>1c</u>	 <u>2c</u>	88	>99 ^{e)}
4	 <u>1d</u>	 <u>2d</u>	85	>99 ^{e)}
5	 <u>1e</u> X=H <u>1e'</u> X=SiMe ₃	 <u>2e</u>	89 ^{b)}	>99 ^{e)}
6	 <u>1f</u>	 <u>2f</u>	87 ^{c)}	95 ^{e, f)}
7	 <u>1g</u>	 <u>2g</u>	97	— ^{d)}

a) Isolated yields. b) 1e' was used [(iPrO)₂TiCl₂ / Hexane, -78 °C, 5 min]. c) In CHCl₃, -40 °C, 30 min. d) 87±1 %ee, see text. e) Determined by HPLC (ZORBAX-SIL, Hexane / AcOEt) and 400 MHz ¹H NMR. f) Accompanied by 5% of 2d. R- = Ph(CH₂)₂-; Tol- = p-CH₃C₆H₄-.

is a potentially useful building unit with the chiral quarternary carbon, since the stereospecificity was again ascertained by the MTPA analysis.⁷⁾

Considering the ready accessibility of chiral epoxy alcohols, this rearrangement is a useful synthetic method for chiral quarternary carbons in various natural products. Further investigation on the use of the process for the natural product synthesis is now under way in our laboratory.

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References and Notes

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- 6) To a solution of **1a** (102 mg, 0.35 mmol) in CH_2Cl_2 (4 ml) was added $\text{BF}_3 \cdot \text{OEt}_2$ (99 mg, 0.70 mmol) in CH_2Cl_2 (1 ml) at -78°C . After stirred for 5 min, the mixture was poured into pH 7 buffer, and extractive workup followed by TLC separation gave **2a** in 86 % yield.
- 7) (*R*)-(+)-MTPA was used. Samples from the racemic alcohols gave baseline-separated spectra at 400 MHz ^1H NMR to allow the accurate estimation of the ee's; J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).
- 8) ^{13}C NMR (CDCl_3) of selected compounds follow: **2c**: δ 0.9, 13.6, 16.7, 30.3, 40.1, 62.6, 70.2, 126.1, 128.3, 128.4, 129.9, 141.0, 151.2, 215.2. **2d**: δ 12.5, 16.1, 21.0, 30.4, 40.1, 60.2, 71.3, 126.0, 126.4, 128.3, 128.4, 129.6, 136.4, 137.1, 140.8, 215.2. **2e**: δ 1.2, 17.4, 17.9, 30.2, 40.3, 62.6, 70.6, 126.1, 128.3, 128.5, 130.9, 141.1, 150.8, 213.5. **2f**: δ 17.3, 17.4, 21.0, 30.3, 40.4, 59.9, 71.4, 126.0, 127.6, 128.3, 128.4, 129.2, 135.0, 137.1, 140.9, 214.0.
- 9) Synthesis of **1g** from **3**: 1) Swern oxidn.¹³⁾ then $p\text{-CH}_3\text{C}_6\text{H}_4\text{MgBr}$ / THF, -78°C ; 2) Swern oxidn.; 3) $\text{LiC}\equiv\text{CH}$ / THF, -78°C .
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- 11) All new compounds exhibited satisfactory ^1H NMR, IR, and HRMS spectra.
- 12) **2a**: $[\alpha]_{\text{D}}^{27} +74^\circ$ (c 0.94, CHCl_3). **2b**: $[\alpha]_{\text{D}}^{25} +83^\circ$ (c 1.4, CHCl_3). **2g**: $[\alpha]_{\text{D}}^{26} +111^\circ$ (c 1.05, CHCl_3). **3**: $[\alpha]_{\text{D}}^{28} +5.4^\circ$ (c 4.7, CH_2Cl_2).
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