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A novel $AlEt_3$-promoted tandem reductive rearrangement of 1-benzyloxy-2,3-epoxides: new route to 2-quaternary 1,3-diol units†

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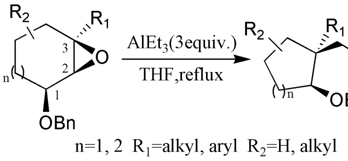
Received (in Cambridge, UK) 11th October 2002, Accepted 8th January 2003
First published as an Advance Article on the web 25th February 2003

A novel and highly stereoselective tandem rearrangement–reduction reaction of 1-benzyloxy-2,3-epoxide, under the promotion of triethylaluminum ($AlEt_3$), has been developed to construct a quaternary stereocenter and the hydroxymethyl attached to the carbon center in one-step.

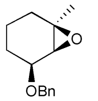
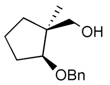
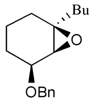
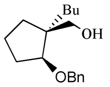
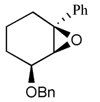
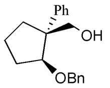
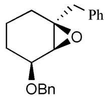
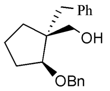
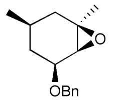
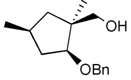
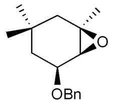
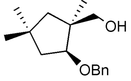
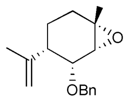
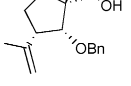
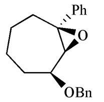
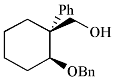
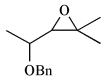
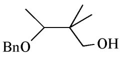
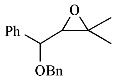
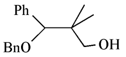
Stereoselective construction of 2-quaternary 1,3-diol units, especially those bearing the hydroxymethyl attached to a quaternary carbon center, is of particular importance in organic synthesis for they are widespread in natural products such as terpenes and steroids.[1] However synthesis is generally difficult to achieved. In connection with our studies on the chemistry of α-hydroxy epoxides, in which a tandem rearrangement–reduction reaction of tertiary α-hydroxy epoxide under the promotion of Al(*i*-PrO)$_3$ has been reported,[2] recent work has uncovered that the benzyl ether of secondary α-hydroxy epoxide, *i.e.* the 1-benzyloxy-2,3-epoxide, can undergo a novel tandem reaction in the presence of excessive $AlEt_3$ to form the benzyl ether of the 2-quaternary 1,3-diol unit (Scheme 1). This reaction involvs the first C–C rearrangement similar to that reported by Yamamoto,[3] who employed a complex MABR (methylaluminumbis(2,6-di-*tert*-butylphenoxide)) as reagent and the 1-*tert*-butyldimethylsilyloxyl-2,3-epoxide as substrate. The second process involves the concerted intramolecular hydride transformation from the ethyl group of $AlEt_3$ to C2, with ethylene being released. To our knowledge, this kind of tandem reductive rearrangement was the first observed in the reactions either for the secondary 1-hydroxy-2,3-epoxide or for $AlEt_3$.[4] In a previous report, $AlEt_3$ was used as the catalyst for polymerization or alkylating agent, and its reduction to carbonyl usually appeared as a side reaction,[5] but here it acted as both Lewis acid and as reduction agent. It was interesting that we did not isolate the products formed through the usual ethyl substitution of $AlEt_3$. The distinctive value of this reaction lays in the construction of both the quaternary stereocenter and the hydroxymethyl attached to the carbon center one step. Herein, we wish to report our experimental results.

Since cyclopentane and cyclohexane structures are the extensively existing frameworks of many important natural products, the 1-benzyloxy-2,3-epoxides with the corresponding cycohexane and cycloheptane units were chosen to examine this reaction. Instead of *tert*-butyldimethylsilyloxyl compounds,[3] we used the benzyl ether epoxides because they are applicable to more reaction media than the *tert*-butyldimethylsilyloxyl compounds. Thus, the 1-benzyloxy-2,3-epoxides were prepared racemically (except for entry 5[6] and 7[7]) from the corresponding allylic alcohols through epoxidation with *m*-CPBA or *t*-BuO_2H–[VO(acac)$_2$] followed by protection of high yields (75–92%). A general transformation was indicated in Scheme 1, a hydroxy group with NaH–BnBr,[8] and then subjected to the reductive rearrangement reaction, in a standard procedure,[9] to afford the major 2-quatenary 1,3-diol monoether products and all the experimental results were tabulated in Table 1. Particularly remarkable is the high level of diastereoselectivity of this reaction. The relative stereochemistry of the hydroxymethyl and benzyloxyl of the products were assigned to be *syn* form by NOESY spectroscopy.



Scheme 1

Table 1 Reductive rearrangement of 1-benzyloxy-2,3-epoxide promoted by $AlEt_3$ leading to 2-quaternary 1,3-diol unit[a]

Entry	Substrates	Products	Yield (%)	Time/h
1			92	11
2			86	14
3			91	7
4			80	10
5			85	9
6			75	16
7			83	11
8			84	6
9			91	15
10			86	6

[a] Isolated yield.

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† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b2/b209948a/

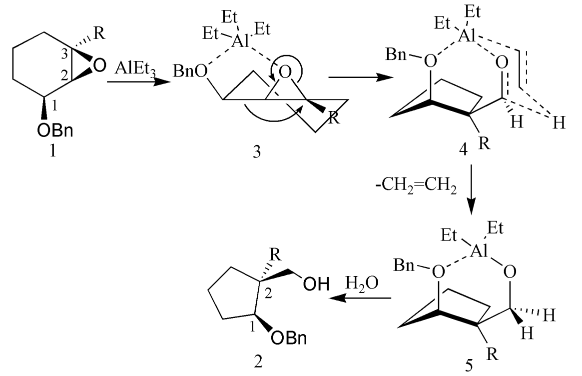
DOI: 10.1039/b209948a

Further investigation indicated that this tandem reaction was highly dependent upon the temperature and the properties of solvent. A refluxing temperature solvent proved to be essential, and performance at rt would lead the reaction to completion in 4–5 days. Among the solvents tested, THF demonstrated to be most efficient, while the mixed THF–hexane or the pure hexane solvents would lead to the formation of complex products (unidentified). In addition, employment of excessive (3 equiv.) AlEt$_3$ was necessary, as the complete transformation of substrate using 1 equiv. of reagent would take several days.

From Table 1 it could be seen, that entries 1–4 with substrates incorporating the different R substitutents (Me, n-Bu, Ph and Bn, respectively) at C3 all proceeded smoothly under the general reaction conditions, and similarly, entries 5–7 with the different substitutions at the cyclohexane rings still worked well. No apparent substitution or steric effects were observed in the above examples. In entry 8, the substrate with a bigger cycloheptane moiety also gave the good result. The facilities of entries 1–8 demonstrated the very extensive and practical applications of this tandem reaction to the synthesis of natural products containing five and/or six-membered ring structures bearing a chiral quaternary carbon. It was particularly notable that the product of entry 7, which contains three contagious chiral centers, would be an applicable and versatile chiral synthon for synthesis of a series of complex natural products, such as daucane sesquiterpenes,[10] dammarane-euphane triterpenoids,[11] and sesterterpenoid variecolin.[12]

To expand the scope of this reaction, the acyclic systems (entries 9 and 10) were examined, which still exhibited good stereocontrol as well as high yields of products. Though we did not assign the relative stereochemistry of the substrates of entries 9 and 10, both examples gave only one product, indicating the highly stereocontrol of this reaction for open-chain substrates. However, the substrates without protection of hydroxy proved to give very low yields of the products.[13]

On the basis of the above results and literature reports,[3] the mechanism of triethylaluminium promoted reductive rearrangement was proposed as showed in Scheme 2, which involved two concerted steps. The first would be the coordination of AlEt$_3$ with two oxygen atoms of benzyl ether and the epoxy, which activates the O–C3 bond and leads to its cleavage. This was accompanied by migration of C1 to C3 from the opposite site of the epoxy group and leads to the formation of the intermediate **4**. The concerted bond cleavage and carbon shift process resulted in the *syn* configuration of benzyl ether and hydroxymethyl in the final products. The second step would be the hydride shift from the ethyl to that carbon corresponding to C2 in the substrate as shown in the intermediate **4**. This was accompanied by the release of ethylene to form the intermediate **5**, which afforded the final product **2** after quenching with water. The favorable elements for hydride transformation rather than ethylation of the potential carbonyl could be the formation of a chair-like six-membered ring transition state incorporating the ethyl (intermediate **4**) and elimination of the ethylene. On the other hand, the severe steric hindrance caused by the newly formed quaternary center also avoids the ethylation process.



Scheme 2

In summary, the AlEt$_3$-promoted reductive rearrangement described here provides an efficient and highly stereocontrolled method for achieving 2-quatenary 1,3-diol derivatives. The applicable scope, synthetic application and chiral and/or catalytic features for this tandem reaction are currently under investigation.

This work was supported by NSFC (No. 29972019, 29925205 and QT program), FUKTME of China, the Young Teachers' Fund of Ministry of Education and the Fund of Ministry of Education (No. 99209).

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9 General procedure: a solution of AlEt$_3$ (4 M in THF, 0.27 ml) was added dropwise to a solution of the epoxide of entry 1 (Table 1) (80 mg, 0.36 mmol) in 3 ml dry THF under an argon atmosphere. The reaction mixture was stirred under reflux for 11 h, after which TLC analysis showed the reaction was complete. Then the reaction mixture was poured into 2 N HCl (10 ml) and extracted with diethyl ether (3×50 ml). The combined extracts were dried over anhydrous Na$_2$SO$_4$. The crude product was purified on silica gel (petroleum–ethyl acetate 9:1) afforded the desired product (72 mg, 92% yield).

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13 Unpublished results.