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Stereoselective Construction of Three- and Four-Contiguous Asymmetric Centers: Novel Possibility by Alkylative Rearrangement of Epoxy Silyl Ethers

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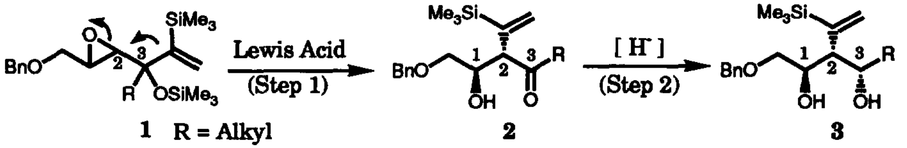
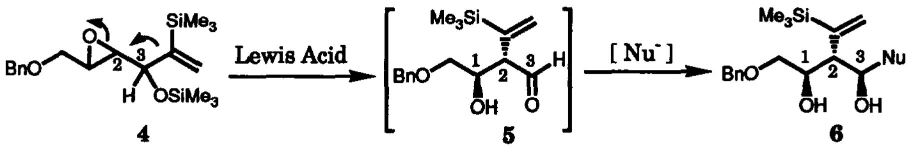
Summary: Stereospecific 1,2-rearrangement of epoxy silyl ethers in the presence of nucleophiles is described. The reaction affords 1,3-diols or corresponding mono-silylated ethers, which provides a route to establish three- or four-contiguous asymmetric centers in one step.

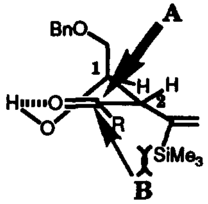
Previously, we reported a stereoselective synthetic method of 2-vinyl-1,3-diols which are versatile in natural product synthesis. The method depends on the rearrangement-reduction sequence (Scheme 1), starting from epoxy trimethylsilyl (TMS) ether **1**.[1] The TMS-vinyl group serves not only as a good migrating group in the 1,2-rearrangement (step 1) but also as a controlling element for dictating the hydride attack to **2** (step 2). Large steric bias posed by this group leads to highly selective formation of *2,3-syn*-diol **3** (see model I).



Scheme 1



Scheme 2



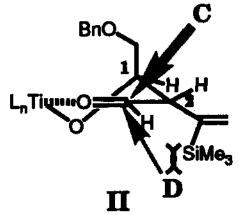
I (ref. 1)

Instead, if we start with epoxy silyl ether **4** with *secondary* silylether at C(3) (*cf. tertiary* in **1**), β-hydroxy aldehyde **5** would be formed by the rearrangement. And the subsequent nucleophilic addition would give 1,3-diol **6** with *2,3-anti* stereochemistry (*cf.* **3**). A potential problem foreseen was the instability of β-hydroxy aldehyde **5**, for which we planned to perform the rearrangement *in the presence of nucleophiles* to convert the aldehyde **5** *in situ* to 1,3-diol **6**.

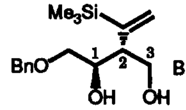
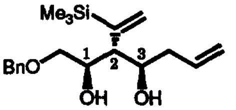
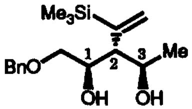
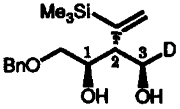
In this communication, we describe the aspect of this consecutive 1,2-rearrangement and nucleophilic addition, the synthetic potential and also some new implications on the reaction profiles.

The reaction of epoxy silylether **4** in the presence of Et_3SiH represents the stereospecificity of the 1,2-rearrangement step.[2] At -78 °C, to a mixture of epoxy silylether **4** and Et_3SiH (3 equiv.) in CH_2Cl_2 was added a solution of $TiCl_4$ (2.2 equiv.) in CH_2Cl_2, where the rearrangement and subsequent hydride attack proceeded immediately to afford 1,3-diol **6a** in 89% yield. The stereochemistry of **6a** was rigorously ***anti,*** which clearly showed the full inversion at C(2).[2]

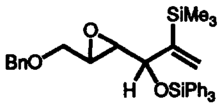
Moreover, the 2,3-relationship, that is, the diastereofacial selectivity of the nucleophilic attack could be highly controlled to be *anti*-selective. The reaction with allyltrimethylsilane (2 equiv.) and $TiCl_4$ (2.2 equiv., -78 °C / CH_2Cl_2; 15 min) afforded **6b** in 75% yield, where the 2,3-selectivity was *anti* / *syn* = 12 / 1.[2] Dimethylzinc (2 equiv., -78 °C / CH_2Cl_2; 15 min) was also an effective nucleophile to afford **6c** in excellent yield with high *anti* selectivity.[2] These selectivities are explained by invoking the titanium chelate model **II**. Interestingly, the use of Et_3SiD[3] in place of Et_3SiH led to the formation of **6d** with a "chiral methylene."[2]



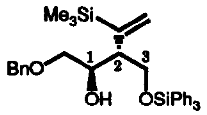
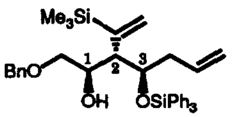
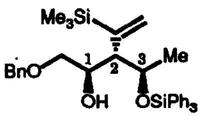
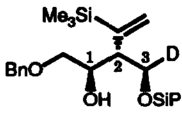
II

Product:				
	6a	**6b**	**6c**	**6d**
2,3-*anti* / *syn*	—	12 / 1	14 / 1	2,3-*anti* only
Yield (%)	89	75	89	74

Unexpectedly, similar reactions of triphenylsilyl (TPS) ether **7** provided a new mechanistically intriguing finding. Different from the TMS cases, ***the products were mono-silyl ethers 8a-d rather than 1,3-diols 6, where the TPS group exclusively located at C(3).*** The regiospecificity was confirmed by ^{1}H-NMR analysis of the acetate derivative of **8**. These results correspond to the conservation of O-Si bond during the reaction, which suggests the intermediacy of silyl oxonium species, rather than aldehyde, which is trapped by the nucleophiles.[4,5] Now, it is not evident whether the reaction proceeds *via* aldehyde **II** or silyl oxonium species in the TMS cases above.[5]

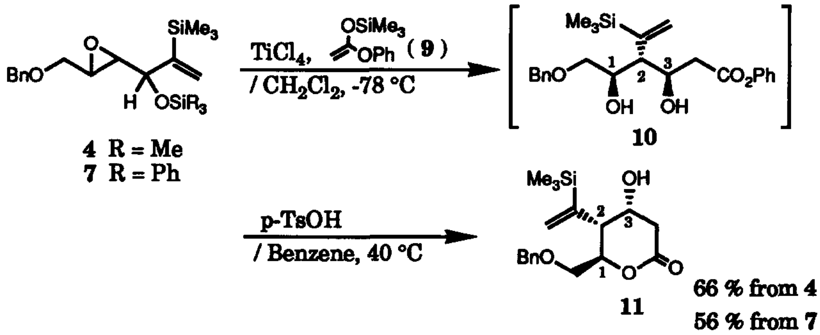


7

Nucleophile:	Et_3SiH		Me_2Zn	Et_3SiD
Product:				
	8a	**8b**	**8c**	**8d**
2,3-*anti* / *syn*	—	33 / 1	22 / 1	2,3-*anti* only
Yield (%)	82	88	60	85

It is also notable that the 2,3-selectivities of the TPS cases are higher than those of the corresponding TMS cases (*cf.* **6b** *vs.* **8b**, **6c** *vs.* **8c**). And the formation of mono-silyl ether is also synthetically useful since the selective protection of one of two *secondary* hydroxyl groups is realized.

Silyl ketene acetals[6] worked also well as the nucleophile in this type of reaction. In this case, the experimental procedure described above was not effective. Instead, the pre-mixing of $TiCl_4$ and epoxy silyl ether at -78 °C followed by the addition of silyl ketene acetal was favorable, which gave dihydroxy ester **10** in good yield.[7] It is noteworthy that no products containing the siloxy group were obtained even starting from TPS ether **7**. The product was isolated as lactone **11** after acid-treatment of the reacted product, since the attempted isolation of **10** by silica-gel TLC led already to the partial formation of lactone **11**. This lactone **11** was isomerically pure product with the stereochemistry depicted below, which means the excellent 2,3-selectivity.



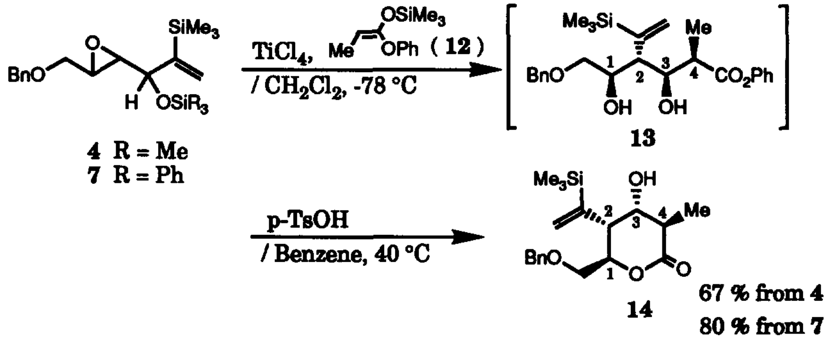
4 R = Me
7 R = Ph

10

11

66 % from **4**
56 % from **7**

Furthermore, use of prostereogenic silyl ketene acetal offers a new possibility for constructing four contiguous asymmetric centers as shown below. The reaction using (*E*)-ketene TMS acetal **12** provided lactone **14** as a sole isolable product. The 3,4-relationship of **13** is *syn* (3,4-*anti* in **14**), which suggests the open transition state concerned with the stage of the nucleophilic addition.[9] The alkoxyl part of ketene TMS acetal plays a significant role for the high 3,4-selectivity, since poor selectivity resulted from ketene TMS acetal of methyl propionate.



4 R = Me
7 R = Ph

13

14

67 % from **4**
80 % from **7**

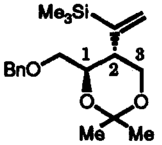
As described above, the stereoselective synthesis of the four-contiguous asymmetric centers was performed by the rearrangement with the silyl ketene acetal.

In summary, the 1,2-rearrangement-nucleophilic addition sequence described above provide a new possibility for establishing three- or four-contiguous asymmetric centers.

References and Notes

1) a) K. Maruoka, M. Hasegawa, H. Yamamoto, K. Suzuki, M. Shimazaki, and G. Tsuchihashi, *J. Am. Chem. Soc.*, **108**, 3827 (1986); b) K. Suzuki, M. Miyazawa, M. Shimazaki, and G. Tsuchihashi, *Tetrahedron*, **44**, 4061 (1988); c) K. Suzuki, M. Miyazawa, and G. Tsuchihashi, *Tetrahedron Lett.*, **28**, 3515 (1987).

2) The stereochemistry of the products is determined by the coupling constants of H(2) of the acetonide derivatives **15-18** which are as follows: **15**: $J_{H_1-H_2}$ = 11 Hz, **16**: $J_{H_1-H_2} = J_{H_2-H_3}$ = 11 Hz, **17**: $J_{H_1-H_2} = J_{H_2-H_3}$ = 10 Hz, **18**: $J_{H_1-H_2} = J_{H_2-H_3}$ = 11 Hz.



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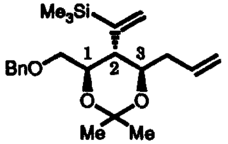

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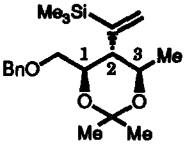

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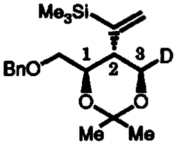
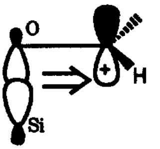


18

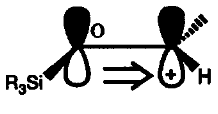
3) M. P. Doyle, C. C. McOsker, and C. T. West, *J. Org. Chem.*, **41**, 1393 (1976).

4) Unique characters of silyl ethers different from alkyl ethers are documented by *ab initio* method: S. Shambayati, J. F. Blake, S. G. Wierschke, W. L. Jorgensen, and S. L. Schreiber, *J. Am. Chem. Soc.*, **112**, 697 (1990).

5) In a formal sense, two types of silyl oxonium species are conceivable. One is III (σ-π* conjugation) and the other is IV (n-π* conjugation), although the contribution is not clear. Further study is in progress.



III

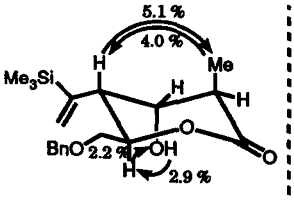


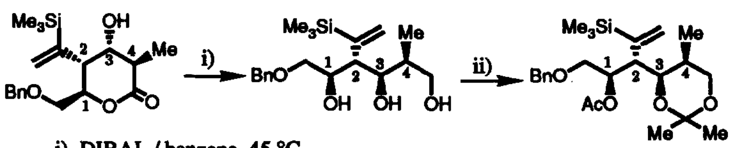
IV

6) N. Slougui and G. Rousseau, *Synth. Commun.*, **17**, 1 (1987).

7) Typical procedure by using silyl ketene acetal follows:
To a solution of TPS ether **7** (195 mg, 0.354 mmol) in CH_2Cl_2 (5 mL) at -78 °C was added $TiCl_4$ (1.0 M in CH_2Cl_2, 0.78 mL) and the mixture was stirred for 3 min. TMS ketene acetal **12** (162 mg, 0.728 mmol) was added to the mixture at -78 °C and stirring was continued for 6 min. After phosphate buffer (pH 7) was added, the mixture was filtrated through a Celite pad followed by extractive workup. After evaporation, the residue was dissolved in benzene (5 mL), and p-TsOH•H_2O (42 mg) was added. After stirring for 50 min at 40 °C, the reaction mixture was cooled and poured into $NaHCO_3$ solution. Extractive workup followed by preparative TLC (hexane / ethyl acetate = 2 / 1) gave lactone **14** (98.7 mg, 80.0 %).

8) Stereochemistry of **14** was confirmed by two methods: (1) NOE difference by 400 MHz ^{1}H-NMR. (2) Decoupling study on acetonide **19** ($J_{H_3-H_4}$ = 2 Hz).





i) DIBAL / benzene, 45 °C,
ii) $Me_2C(OMe)_2$, p-TsOH / DMF, 0°C; Ac_2O, DMAP / Pyr.

19

9) a) M. T. Reetz, K. Kesseler, and A. Jung, *Tetrahedron*, **40**, 4327 (1984); b) Also see: R. Noyori, S. Murata, and M. Suzuki, *Tetrahedron*, **37**, 3899 (1981); *cf.* c) Cyclic transition state: T. H. Chan, T. Aida, P. W. K. Lau, V. Gorys, and D. N. Harpp, *Tetrahedron Lett.*, **1979**, 4029.

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