

**Intramolecular Hydrogen Shift in Reduction of β -Mercuro Ketal.
Preparation of Optically Active *sec-tert*-1,3-Diols**

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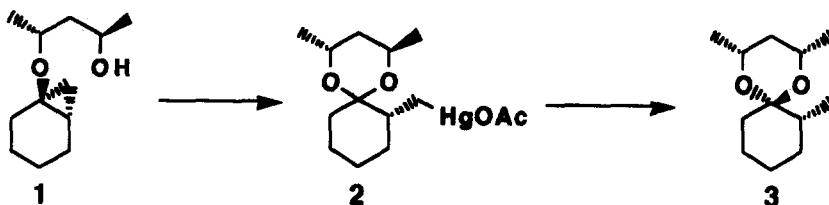
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Abstract: Intramolecular hydrogen shift of β -radical ketal was found in the reduction of optically active β -mercuro ketal. The addition of olefins to this hydrogen transferred radical proceeded regio and diastereo differentiatingly and afforded optically active *sec-tert*-1,3-diols.

Recently we established the preparation method of optically active cyclopropyl ethers by using diastereoface differentiating Simmons-Smith reaction of enol ethers having a chiral 1,3-diol.² One of the synthetically useful conversion of these diastereomerically pure products is oxymercuration with mercuric acetate, which cleft the cyclopropyl ether regioselectively without losing any diastereomeric purity, followed by treatment with sodium borohydride and methyl acrylate resulted in three carbon elongation.^{2a,3} During the study of this conversion, it was found that the competitive reaction giving diastereomerically pure side product was taken place. In this communication we report determination of the structure of this side product and optimization of its yield.

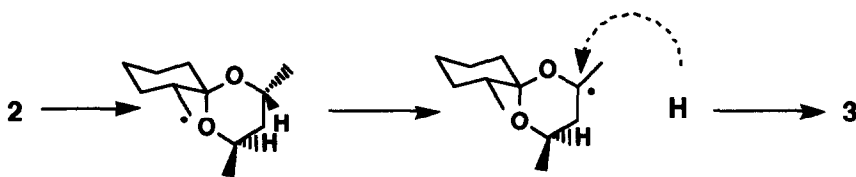
Scheme 1.



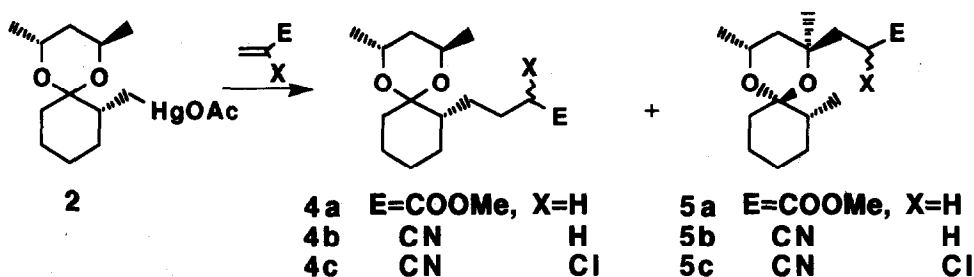
When diastereomerically pure **2** prepared from optically pure **1** was reduced with sodium borohydride in dichloromethane-water, a single diastomer (**3**) was obtained (isolated yield, 25.3%). Unexpectedly, hydrolysis indicated that the structure of the diol moiety of **3** was not originally employed *R,R* but *meso*. In the reverse, the spectra of the major product of acetalization with 2-methylcyclohexanone and *meso*-2,4-pentanediol (major/minor=7/3) were identical with those of **3**. Thus, the structure of **3** was assigned to be thermodynamically more stable acetal within two diastereomers as shown in scheme 1.

The reasonable formation mechanism of **3** should be 1) reduction of **2** afforded radical species, 2) hydrogen transfer to give more stable radical, 3) and then hydrogen addition to this from less hindered side (scheme 2).⁴ The efficiency and high stereospecificity of this hydrogen transfer and hydrogen addition process suggested that the ketone part in **2** could be a template for regio- and diastereodifferentiating conversion of the 1,3-diol part into the other optically active diols. Under this concept we next tried addition of several olefins to this hydrogen transferred radical species.

Scheme 2.



Scheme 3.



Reductive carbon chain elongation of **2** with sodium borohydride and 30 equivalents of methyl acrylate in dichloromethane-water produced normal adduct (**4a**) in 19.1% yield with side product (**5a**) in 10.6% yield. The ¹H-NMR and ¹³C-NMR spectrum of **5a** suggested its homogeneity and that methyl acrylate was added on one of the ether carbon of the chiral auxiliary in the substrate. Cosy and Noesy spectra of **5a** supported the planner structure of **5a** shown in scheme 3, but did not include enough stereochemical informations. Finally, the full structure of **5** was determined by X-ray diffraction analysis of the nitrile analog (**5b**).

Two molecules are involved in the asymmetric unit and are confirmed to have the same chirality. Absolute configuration was not determined in the course of X-ray analysis but deduced from the configuration of starting material **2**. The ORTEP drawing and structure of **5b** were shown in figure 1.⁵

Figure 1. ORTEP-drawing of two crystallographically independent molecules and structure of **5b**

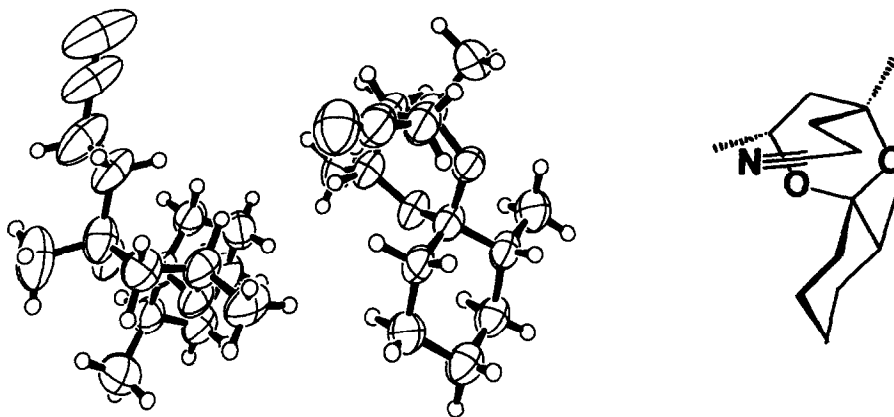


Table 1. The product yield with different amounts of some olefins.^a

E, X	Olefin equiv.	product yield(%)			products ratio
		4	5	total	5 / 4
COOMe, H	1	9.9	38.7	46.9	3.92
	3	12.0	38.5	50.5	3.21
	10	10.5	21.4	31.9	2.04
	30	11.9	10.6	22.5	0.89
CN, H	1	2.0	46.0	48.0	23.0
	3	23.0	20.0	43.0	0.87
	10	32.4	19.2	51.6	0.59
CN, Cl	1	17.8 ^b	38.6 ^b	56.4	2.17
	5	40.1 ^b	19.3 ^b	59.4	0.48

a) The reaction was carried out with ca. 150 mg of substrate (**2**) in 4 ml of dichloromethane at room temperature.

b) The products were 1 : 1 mixtures of diastereomers at terminal carbon.

Next we optimized the reaction conditions to get **5** as a major product. The yields of **4** and **5** with several types of olefins of different amounts were shown in table 1. If large excess amounts of olefins were employed to trap the radical before hydrogen transfer, contents of **4** in the reaction mixture were more than 50 % in all three cases. On the other hand, by the use of only 1 equivalent of methyl acrylate or acrylonitrile contents of **5** in the adducts was 83 % or 96 %, respectively. With the better radical acceptor, 2-chloroacrylonitrile, the total adducts yield was better than the other two cases, but a ratio of contents of **5** was low. The low total yield by the use of large excess amount of methyl acrylate could attribute to the consumption of methyl acrylate by the competitively proceeding polymerization.

In conclusion, the reaction rate of the hydrogen shift in the present study was faster than the addition of hydrogen or acrylonitrile to the radical, and competitive with 2-chloroacrylonitrile addition. In connection with handy synthesis of optically active 1,3-diol by enantiodifferentiating hydrogenation with tartaric acid modified Raney nickel catalysis,⁶ the present reaction is considered to be a new synthetic tool for optically active *sec-tert*-1,3-diols, of which diol moieties were protected by acetal. The application of this reaction to natural product synthesis will be published shortly.

References and Notes

1. Those who respond to X-ray analysis.
2. (a) Sugimura, T.; Futagawa, T.; Tai, A. *Tetrahedron Lett.* **1988**, *29*, 5775. (b) Sugimura, T.; Futagawa, T.; Yoshikawa, M.; Tai, A. *Tetrahedron Lett.* **1989**, *30*, 3807. (c) Sugimura, T.; Yoshikawa, M.; Futagawa, T.; Tai, A. *Tetrahedron* **1990**, *46*, 5955.
3. This procedure was successfully applied to the total synthesis of (+)-africanol. Sugimura, T.; Futagawa, T.; Tai, A., *Chem. Lett.* **1990**, 2991 and 2995.
4. For a general review of a radical reaction, "Advances in Free Radical Chemistry, Vol. 1" Ed. by Tanner, D. D. (1990) JAI press Inc. (London).
5. Crystal data of **5b**: C₁₅H₂₅N₁O₂, monoclinic, P2₁, Z=4, a=16.672(2), b=7.295(2), c=13.360(1) Å, β=107.18(1), V=1552.2(4) Å³, Mr=251.37, Dx=1.08 g/cm³, μ(CuKα)=5.54 cm⁻¹, Final R=0.082 for 2484 unique reflections with |F_o| larger than 3σ|F_o|. Structure was solved with Auto-Solve mode in TEXSAN (X-ray Structure Analysis Package supplied by RIGAKU corp.), and refined by least-squares procedure.
6. Tai, A.; Kikukawa, T.; Sugimura, T.; Inoue, Y.; Osawa, T.; Fujii, S. *J. Chem. Soc., Chem. Commun.* **1991**, 795.

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