Highly Enantioselective Asymmetrization of *meso*-1,2-Diols through a Novel and Efficient Reaction Cycle

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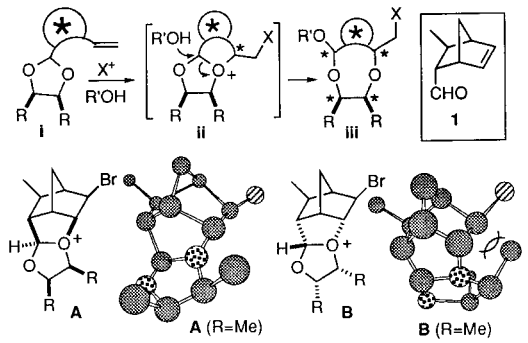
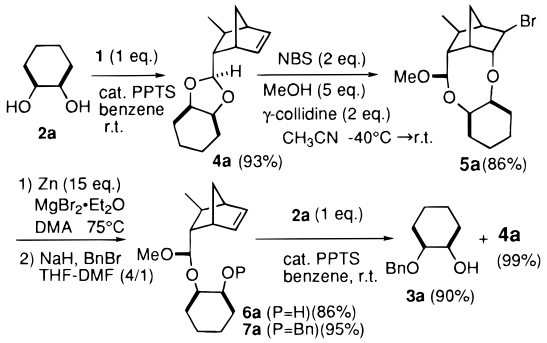
Enantiodifferentiation of the σ-symmetric diols (including *meso*-diols) is an important area in organic synthesis. Many enantiodifferentiation methodologies have been developed so far. They are widely divided into two groups. One is the group using enzymes as a tool[1] and the other is one using chemical methods.[2] Although both of them have proved to be very useful in asymmetrization of prochiral diols, no successful report on highly enantioselective asymmetrization of acyclic *meso*-1,2-diols has appeared, to the best of our knowledge. We present here a conceptionally novel and highly enantioselective asymmetrization of *meso*-1,2-diols, which is very powerful not only for cyclic diols but also for acyclic ones.

Recently, we have developed a new asymmetric synthesis of optically active 1,4- and 1,5-diols, where intramolecular haloetherification of chiral ene acetals, prepared from C_2-symmetric optically active diols and ene aldehydes, is characterized as a crucial step. The reaction of an ene acetal proceeds via an oxonium ion intermediate.[3] This finding suggested that if a large energy difference existed among the possible intermediates **ii** formed from the ene acetal **i** derived from the proper chiral nonracemic ene aldehyde and symmetric *meso*-diol, the reaction may proceed through the most stable intermediate resulting in the discrimination of the two oxygen atoms of the *meso*-diol (Scheme 1). We selected (1*R*,2*R*,3*S*,4*S*)-3-methyl-5-norbornene-2-carboxaldehyde (**1**) as a chiral ene aldehyde for the following four reasons: (1) **1** is easily prepared by asymmetric Diels−Alder reaction;[4] (2) acetalization would proceed stereoselectively to give the *cis* isomer;[5] (3) a newly produced chiral center (* center in **ii**) would be formed stereospecifically in the haloetherification because the double bond is fixed in the ring; and most importantly (4) sterically rigid forms of the oxonium ion intermediates would be expected to cause a large energy difference. The consideration for point 4 was supported from the consideration of the discriminating process for the two oxygen atoms of the acetal. As described later, because acetalization of **1** with *meso*-diols proceeded stereoselectively to give *cis*-ene acetals, two possible *cis* intermediates,[6] **A** and **B**, are depicted. As shown from the conformations of the intermediates **A** (R = Me) and **B** (R = Me), a large steric repulsion not only between the substituents and the bicyclo[2.2.1]heptane skeleton but also between the 1,3-dioxolane skeleton and the bicyclo[2.2.1]heptane skeleton is observed in endo isomer **B**, whereas such repulsion is not observed in exo isomer **A**. This suggests a large energy difference, in other words a large stability difference, between the two *cis* intermediates **A** and **B**, realizing an extremely high discrimination between the two oxygen atoms of the acetal.

Scheme 1



Scheme 2



To realize the concept above, *meso*-cyclohexane-1,2-diol (**2a**) was examined as a substrate (Scheme 2). The *cis*-ene acetal **4a**, readily synthesized as a single isomer in 93% yield from **1** and **2a**, is subjected to an intramolecular haloetherification to give the mixed acetal **5a** via an oxonium ion intermediate (refer to intermediate **A** in Scheme 1). As expected, it was determined to be a single isomer by ^{1}H NMR data. This showed that the discriminating process proceeded in a quite highly stereoselective manner. Dehaloetherification of **5a** using Zn and $MgBr_2$·Et_2O afforded the acetal **6a** in good yield. Protection of the hydroxy group of **6a** as a benzyl ether followed by transacetalization with one equivalent of *meso*-diol **2a** afforded the monoprotected diol **3a** in good yield. At the same time, **4a**

(1) For examples, see: (a) Fadel. A.; Arzel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 283−291. (b) Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769−3826. (c) Theil, F. *Chem. Rev.* **1995**, *95*, 2203−2227. (d) Banfi, L.; Guanti, G. *Synthesis* **1993**, 1029−1056. (e) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071−1140. (f) Bolando, W.; Frössl, C.; Lorenz, M. *Synthesis* **1991**, 1049−1072.

(2) For recent examples for 1,2-diols, see: (a) Maezaki, N.; Sakamoto, A.; Soejima, M.; Sakamoto, I.; Xia, L.; Tanaka, T.; Ohishi, H.; Sakaguchi, K.; Iwata, C. *Tetrahedron: Asymmetry* **1996**, *7*, 2787−2790. (b) Maezaki, N.; Soejima, M.; Takeda, M.; Sakamoto, A.; Matsumori, Y.; Tanaka, T.; Iwata, C. *Tetrahedron* **1996**, *52*, 6527−6546. (c) Maezaki, N.; Soejima, M.; Sakamoto, A.; Sakamoto, I.; Matsumori, Y.; Tanaka, T.; Ishida, T.; In, Y.; Iwata, C. *Tetrahedron: Asymmetry* **1996**, *7*, 29−32. (d) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430−431. (e) Maezaki, N.; Soejima, M.; Takeda, M.; Sakamoto, A.; Tanaka, T.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1994**, 1345−1346. (f) Suemune, H.; Watanabe, K.; Kato, K.; Sakai, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1767−1770. (g) Harada, T.; Wada, I.; Oku, A. *J. Org. Chem.* **1989**, *54*, 2599−2605. (h) Mukaiyama, T.; Tomioka, I.; Shimizu, M. *Chem. Lett.* **1984**, 49−52. For recent examples for 1,3-diols, see: (a) Davis, A. P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 591−594. (b) Prasad, K.; Underwood, R. L.; Repic, O. *J. Org. Chem.* **1996**, *61*, 384−385. (c) Harada, T.; Oku, A. *Synlett* **1994**, 95−104. (d) Suzuki, T.; Uozumi, Y.; Shibasaki M. *J. Chem. Soc., Chem. Commun.* **1991**, 1593−1595. (e) Appelt, A.; Willis, A. C.; Wild, S. B. *J. Chem. Soc., Chem. Commun.* **1988**, 938−940. (f) Mukaiyama, T.; Tanabe, Y.; Shimizu, M. *Chem. Lett.* **1984**, 401−404. (g) Ichikawa, J.; Asami, M.; Mukaiyama, T. *Chem. Lett.* **1984**, 949−952. (h) Nara, M.; Terashima, S.; Yamada, S. *Tetrahedrn* **1980**, *36*, 3161−3170. For recent example for 1,4-diols, see: Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1994**, 611−614.

(3) For intramolecular haloetherification of ene acetals, see: (a) Fujioka, H.; Kitagawa, H.; Matsunaga, N.; Nagatomi, Y.; Kita, Y. *Tetrahedron Lett.* **1996**, *37*, 2245−2248. (b) Fujioka, H.; Kitagawa, H.; Nagatomi, Y.; Kita, Y. *J. Org. Chem.* **1996**, *61*, 7309−7315.

(4) Prepared in three steps: (i) asymmetric Diels−Alder reaction of the commercially available *N*-crotonyl-(4*S*)-isopropyl-2-oxazolidinone and cyclopentadiene according to Evans's method (Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256.); (ii) $LiAlH_4$ reduction in THF at room temperature (97%); (iii) Swern oxidation (73%).

(5) There are some reports showing that acetalization of an aldehyde and a *cis*-diol tends to form a *cis*-acetal as a major product under kinetic control. For review, see: Clode, D. M. *Chem. Rev.* **1979**, *79*, 491−513.

(6) Because it is known that *cis*-bicyclo[3.3.0]octane is more stable than the corresponding *trans* isomer, two *cis* intermediates **A** and **B** are shown.

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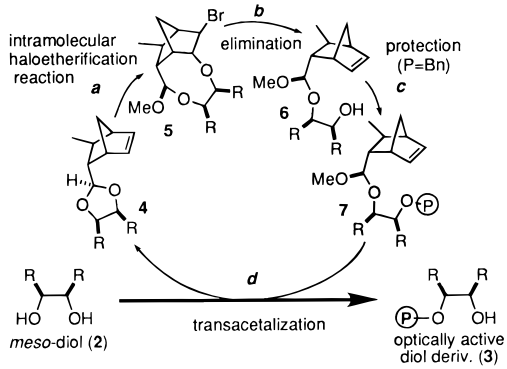
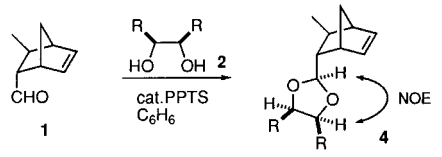
Scheme 3



Reaction conditions: [a] NBS (1.5 eq.), MeOH (5eq.),CH_3CN, -40~0°C. [b] Zn, $MgBr_2$•Et_2O, dimethylacetamide. [c] NaH, BnBr, THF-DMF (4/1). [d] **2** (1.0 eq.), cat. PPTS, C_6H_6.

Table 1. Acetalization of **1** with *meso*-Diol (**2**)



Entry	*meso*-Diol	Product	Yield of **4**
1	**2a**: R = -$(CH_2)_4$-	**4a**	93%
2	**2b**: R = -$(CH_2)_3$-	**4b**	99%
3	**2c**: R = -$(CH_2)_6$-	**4c**	96%
4	**2d**: R = -CH_2OCH_2-	**4d**	99%
5	**2e**: R = CH_3	**4e**	99%
6	**2f**: R = ^{n}Pr	**4f**	99%
7	**2g**: R = CH_2OBn	**4g**	91%
8	**2h**: R = ^{i}Pr	**4h**	83%

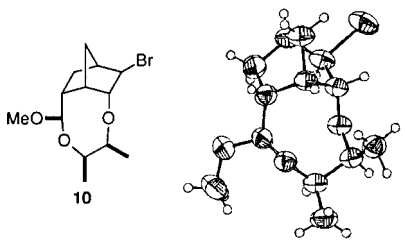
was regenerated quantitatively. The optical purity of **3a** was determined to be 97% ee by HPLC analysis with a Daicel Chiralpak AD. The absolute stereochemistry of **3a** was determined by comparison of its specific rotation [+16.6° (*c* 1.03, $CHCl_3$)] with the reported value [+16.5° (*c* 1.10, $CHCl_3$)],[7] and it agreed with the structure expected from the consideration of the stabilities of the intermediates in Scheme 1.

After once being converted to **4a**, the success of an asymmetrization of **2a** giving optically active **3a** in highly enantiomeric excess and simultaneous regeneration of **4a** must promise an efficient reaction cycle for asymmetrization of *meso*-1,2-diols **2** to their optically active derivatives **3** as depicted in Scheme 3.

The applicability of this method to many kinds of *meso*-1,2-diols, cyclic and acyclic ones, was then examined. The result for **2a** is also shown for comparison. Attempts at acetalization

(7) Naemura, K.; Takeuchi, S.; Hirose, K.; Tobe, Y.; Kaneda, T.; Sakata, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 213−219.

(8) X-ray analysis was performed on the mixed acetal **10** obtained by the same intramolecular haloetherification of the ene acetal derived from *meso*-2,3-butanediol **2e** and (±)-5-norbornene-2-carboxyaldehyde:



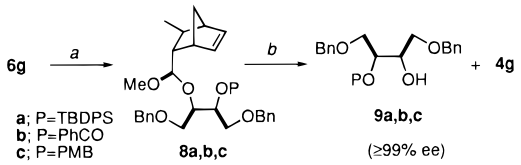
(9) The ee value of silyl ether **9a** was determined by ^{1}H NMR analysis of its acetate because **9a** was decomposed under the HPLC analysis conditions. Ee values of **9b** and **9c** were determined by HPLC analysis (Chiralpak AD; hexane/^{i}PrOH = 93/7).

Table 2. Reaction Cycle for Asymmetrization

Entry	Substr	Yield, %					Ee of **3**,[a] %
		5	**6**	**7**	**3**	**4**	
1	**4a**	86	86	95	90	99	97
2	**4b**	99	83	93	90	93	98
3	**4c**	95	89	98	95	99	≥99
4	**4d**	95	96	99	94	96	≥99
5	**4e**	89	93	96	99	95	97
6	**4f**	87	89	98	97	94	≥99
7	**4g**	90	86	91	91	96	≥99
8	**4h**	87	81	90	90	93	≥99

[a] Determined by HPLC analysis (Chiralpak AD).

Scheme 4



Reaction condition: [a] For **8a**: TBDPSCl, imidazole, DMF (86%); For **8b**: PhCOCl, pyr (99 %); For **8c**: *p*-$MeOC_6H_4CH_2Br$, NaH, DMF (86 %). [b] **2g** (1 eq.), cat. PPTS, C_6H_6, rt {**9a** (91%), **4g** (96%); **9b** (89%), **4g** (87%); **9c** (97%), **4g** (90%)}.

of **1** with *meso*-1,2-diols **2a**−**h** were successful and gave only single diastereomers, *cis* isomers **4a**−**h**, almost quantitatively in each case (Table 1). The stereochemistry of **4a**−**h** was determined by their NOE measurements.

The results subjecting the ene acetals **4** to the asymmerization reaction cycle (Scheme 3) are shown in Table 2. Intramolecular haloetherification of **4** gave the mixed acetals **5** as a single isomer by ^{1}H NMR level in every case. Dehaloetherification, benzylation, and transacetalization afforded the optically active **3** and **4**. Every reaction step proceeded in high yields. The optical purity of **3** was extremely high (≥97% ee) irrespective of ring size and the presence of an oxygen atom in the cyclic systems (entries 1−4) and of the kind of substituent in acyclic ones (entries 5−8). The absolute stereochemistry of the compounds was deduced from the mechanistic consideration in Scheme 1 and the following ones: that of cyclic monoprotected diols **3b**−**d** was determined by assuming the same sense of stereoselection as observed for **3a** and that of acyclic ones **3e**−**h** was determined from the consideration of X-ray crystallographic structure of the analog of **5e**.[8]

The other feature of the method is easy choice of a proper protective group. For example, in the case of the diol **2g** having a benzyl group, the silyl, acyl, or *p*-methoxybenzyl (MPB) group can also be used as a protective group. Thus **6g** was converted to the silyl, acyl- and *p*-methoxybenzyl compounds **9a**−**c**, whose ee values were estimated to be >99%,[9] in good yields without any problem (Scheme 4).

In summary, we have developed a new asymmetrization method for *meso*-1,2-diols. Characteristic points of the method are (i) asymmetrization with an extremely highly enantiomeric excess, (ii) wide applicability not only to cyclic 1,2-diols but also to acyclic ones for which no successful report has appeared yet, (iii) ready protection with proper group, and (iv) high efficiency through the asymmetrization reaction cycle.

Acknowledgment. This paper is dedicated to Professor Yoshito Kishi on the occasion of his 60th birthday.

Supporting Information Available: Preparation of aldehyde **1**, general procedures from **2** to **3** via **4**−**6** and **7**, ^{1}H NMR and ^{13}C NMR data for **5a**−**h**, **7a**−**h**, and **8a**−**c**, and HPLC analysis data for **3a**−**h** and **9a**−**c**, X-ray experimental data for **10** (12 pages). See any current masthead page for ordering and Internet access instructions.

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