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# Desymmetrization of Unsaturated *meso*-1,2-Diols *via* an Intramolecular Haloetherification of Ene Acetals: A Remarkable Kinetic Control

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**Abstract**

Haloetherification reaction of the chiral ene acetals derived from unsaturated *meso*-1,2-diols and chiral non-racemic norbornene aldehyde proceeded in an intramolecular manner with an unexpectedly high kinetic control. This method has been successfully employed for the desymmetrization of unsaturated *meso*-1,2-diols leading to their optically pure derivatives. © 1998 Elsevier Science Ltd. All rights reserved.

*Keywords*: Asymmetric synthesis; Diols; Acetals; Etherification

Desymmetrization of the σ-symmetric diols including *meso*-diols in an enantio-differentiating manner is an extremely useful process to get enantiomerically pure compounds and many methodologies have been developed so far [1–26; for review, see 1–5]. Recently, we reported a new desymmetrization method of *meso*-1,2-diols as shown in Scheme 1 [27]. The intramolecular haloetherification of the ene acetals **3**, prepared by the acetalization of chiral norbornene aldehyde **2** with *meso*-1,2-diols **1**, gave the mixed acetals **4** as a single isomer. Successive dehaloetherification, protection, and trans-acetalization with **1** afforded the optically active mono-protected derivatives **6** and the regenerated ene acetals **3**. This method is synthetically quite useful because it involves an efficient desymmetrization reaction cycle from *meso*-diols **1** to the optically active **6** *via* three different types of acetal derivatives (**3**, **4**, **5**) with the regeneration of the first chiral ene acetals **3**. However, since the crucial step of this desymmetrization cycle is an intramolecular haloetherification reaction, only saturated diols were examined in that study.

It was envisaged that if the methodology could be extended to the diols having olefins in the same molecule, namely unsaturated ones, the method would find application for the construction of more useful chiral building blocks. However, similar haloetherification reaction of the ene acetals derived from unsaturated diols (*i.e.* presence of double bond in **1**) was anticipated to bring about a competition between the intra- and intermolecular reaction pathway. We report here the remarkable kinetic control observed between these two processes and various unsaturated optically active diol derivatives that have been obtained by our desymmetrization reaction cycle.

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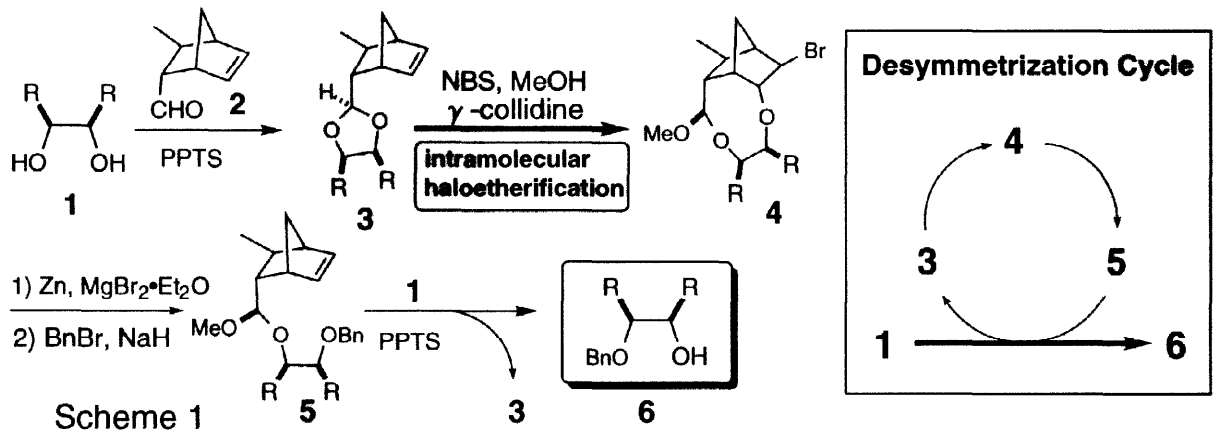
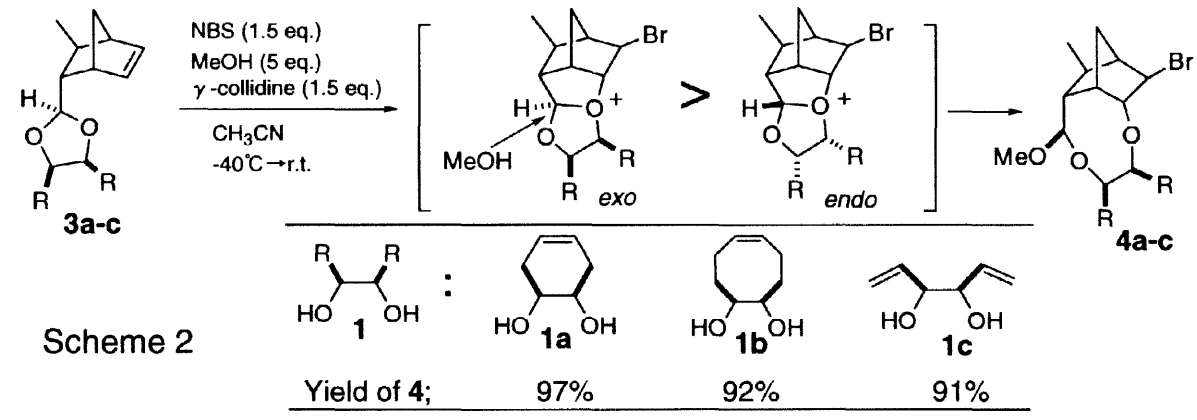



To begin with, we first investigated the reaction of 4-cyclohexene-1,2-diol **1a** in order to examine the possibility of the use of unsaturated diols in our desymmetrization method. Haloetherification reaction of **3a** [1] derived from **1a** in the presence of MeOH, to our surprise, proceeded only in an intramolecular fashion to give the 8-membered acetal **4a** in a quite high yield. Interestingly, product arising out of the reaction of cyclohexene olefin was not at all observed.[2] The degree of the desymmetrization of two oxygen atoms of acetal **3a** was determined to be 100% by NMR experiment. Its stereochemistry was established by converting it to the known compound *via* hydrogenation [27]. This extremely high stereoselectivity in haloetherification reaction is probably due to a large stability difference between the two *cis*-intermediates, since *endo*-isomer has 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 as discussed in our earlier paper [27].

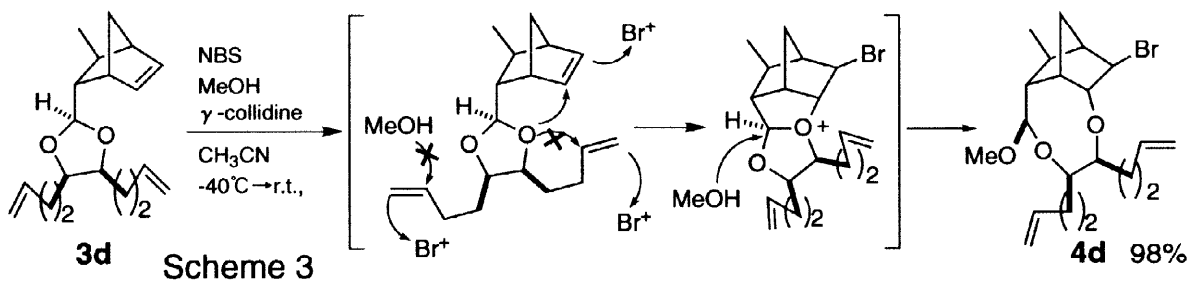



[1] Ene acetals **3** reported in this paper were obtained as a single isomer and their stereochemistry were determined to be *cis* by NOE experiment.

[2] Typical experimental procedure for haloetherification: To a stirred solution of **3** (0.1 mmol) in $CH_3CN$ (1 mL) were added MeOH (5 equiv.), γ-collidine (1.5 equiv.), and NBS (1.5 equiv.) at -40°C under $N_2$. The mixture was allowed to warm to room temperature. After completion of the reaction (TLC check), aqueous saturated $Na_2S_2O_3$ was added into the mixture. Extraction with EtOAc, usual workup and purification by silica gel column chromatography (hexane/EtOAc) afforded the mixed acetal **4**.

In order to show the versatility of the remarkable kinetic control of this haloetherification reaction, we then examined the reactions of the acetals **3b** [1] and **3c** [1] derived from 5-cyclooctene-1,2-diol **1b** and 1,5-hexadiene-3,4-diol **1c**. In both cases, high kinetic control was observed and the desired products **4b** and **4c** were obtained in extremely high yields through the intramolecular reaction. High selectivities in these haloetherification reaction could be due to the preference of the intramolecular reaction over that of the intermolecular one, in addition to the high reactivity of norbornene olefin to form the bromonium ion because of its non-hyperconjugated character (Scheme 2).

To ascertain the high reactivity of norbornene olefin, we chose the ene acetal derived from 1,9-decadiene-5,6-diol **3d**.[1] In this case, since both the norbornene olefin and the diol olefin are equidistant from the acetal oxygen and in addition, both olefins are expected to form a 5-membered transition state with the acetal oxygen, it is of great interest to examine their relative reactivities. As expected, the reaction proceeded exclusively with the norbornene olefin to give the desired product in high yield. This chemoselective haloetherification reaction is quite noteworthy from synthetic point of view (Scheme 3).

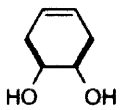
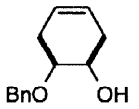
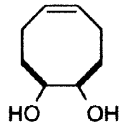
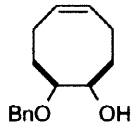
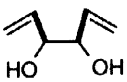
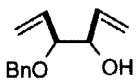
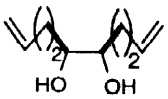
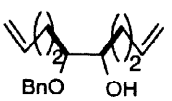



Scheme 3

Having achieved the desymmetrization of unsaturated *meso*-diols **1** in quite high diastereoselectivity by remarkable kinetic control of haloetherification reaction of ene acetals **3**, we then focussed our attention on the conversion of the mixed acetals **4** to the optically active monoprotected diol derivatives **6** as per the procedure reported previously by us [3] (refer to Scheme 1). Table 1 shows the results of overall conversion of *meso*-diols **1** to their optically active derivatives **6** including the yields of acetalization and intramolecular haloetherification. It should be pointed out that $MgBr_2 \cdot Et_2O$, which has been reported by us as an additive during the dehaloetherification reaction, was found to be inffective in the present case. On the other hand, $ZnCl_2$ proved to be an efficient additive for the dehaloetherification of the mixed acetals **4**. A point worth mentioning is that both the acid labile allylic ether moieties present in **4c** remained intact under the reaction conditions. The subsequent two step sequence, *viz.*, protection of the hydroxy group as benzyl ether and transacetalization with the starting *meso*-diols **1**, afforded the desired optically pure unsaturated *meso*-1,2-diol derivatives **6**, with the regeneration of the ene acetals **3** (84~90%), whose optical purities were ascertained by HPLC analysis.

[3] Typical experimental procedure for dehaloetherification: To a stirred solution of **4** (0.1 mmol) in $CH_3CON(CH_3)_2$ (1 ml) were added $ZnCl_2$ (6 equiv.) and Zn (20 equiv.) under $N_2$. The mixture was stirred at around 80°C. After completion of the reaction (TLC), the mixture was diluted with ether and filtered through a celite pad. The filtrate was evaporated in vacuo and purified by silica gel column chromatography (hexane/EtOAc) to afford **5**.

Table 1. Desymmetrization of *meso*-1,2-diols **1** to their optically active derivatives **6**

| Entry | 1 | | Yield (%) 3 | 4 | 5 | 6 | | Yield(%) | E.e.(%)[a] |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  | **a** | 86 | 97 | 84 |  | **a**[b] | 90 | ≥99 |
| 2 |  | **b** | 86 | 92 | 82 |  | **b**[b] | 89 | ≥99 |
| 3 |  | **c** | 84 | 91 | 79 |  | **c**[b] | 97 | ≥99 |
| 4 |  | **d** | 81 | 98 | 76 |  | **d** | 97 | ≥99 |

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

[b] Specific rotation: **6a** $[\alpha]^{27}_{D}$ +45.8° (*c* 0.30, $CHCl_3$), **6b** $[\alpha]^{20}_{D}$ -5.9° (*c* 0.34, $CHCl_3$), **6c** $[\alpha]^{20}_{D}$ +57.6° (*c* 0.93, $CHCl_3$).

In conclusion, we have developed an efficient desymmetrization reaction of unsaturated *meso*-1,2-diols with a high degree of kinetic control. Chemoselective haloetherification of norbornene olefin in presence of other double bonds is a highly remarkable finding, as the unreacted olefin moiety could be exploited for further elaboration, leading to the synthesis of a variety of optically active compounds.

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