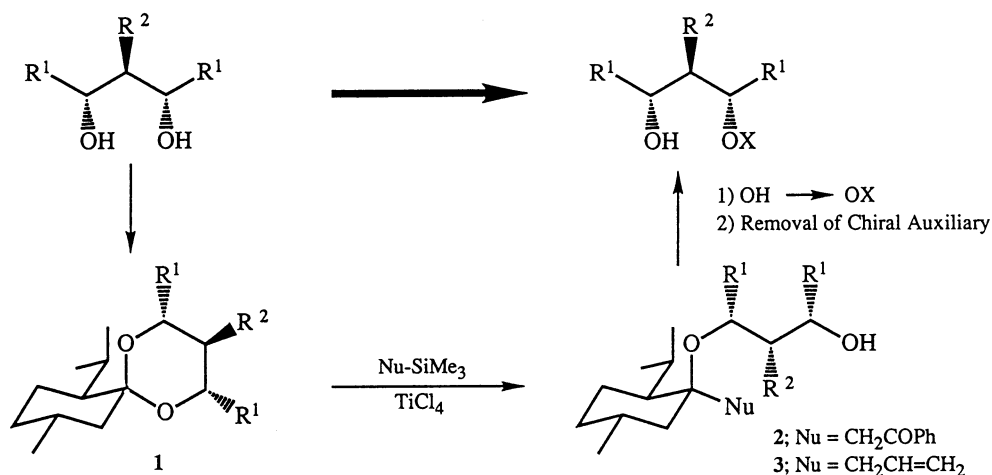


Enantiodifferentiating Functionalization of Prochiral Diols by Highly Stereoselective Ring-Cleavage Reaction of Spiroacetals Derived from *l*-Menthone with Allyltrimethylsilane-Titanium Tetrachloride

Toshiro HARADA,* Yoshifumi IKEMURA, Hiroyuki NAKAJIMA, Takayuki OHNISHI, and Akira OKU*
 Department of Chemistry, Kyoto Institute of Technology
 Matsugasaki, Sakyo-ku, Kyoto 606

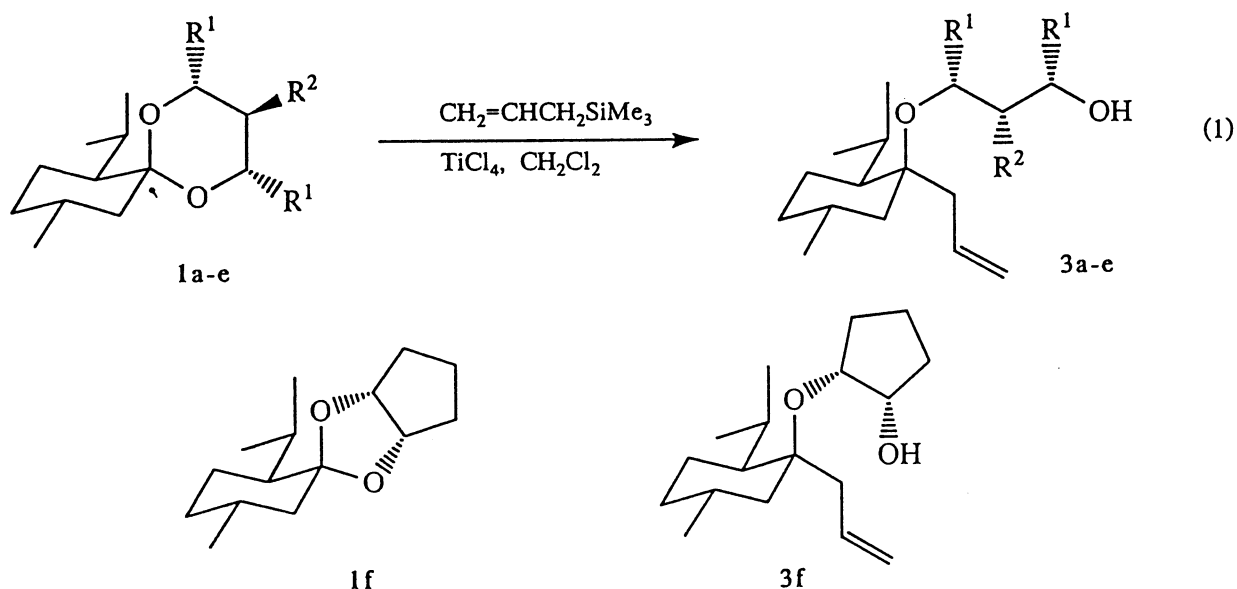
Enantiodifferentiating transformation of prochiral diols possessing σ -symmetry was realized by the utilization of titanium tetrachloride-promoted selective ring-cleavage reaction of spiroacetals derived from the diols and *l*-menthone with allyltrimethylsilane.

Enantiodifferentiating transformation of a prochiral hydroxyl group of diols possessing σ -symmetry provides versatile chiral building blocks which can be incorporated into diverse target structures.¹⁾ We recently reported a novel nonenzymatic method for this transformation which can be applied to various prochiral diols such as 2-substituted 1,3-diols,²⁾ and *meso*-1,2-, 1,3-, and 1,4-diols.^{3,4)} As shown in Scheme 1,⁵⁾ spiroacetal **1** prepared from prochiral diols and *l*-menthone undergoes a highly stereoselective ring-cleavage reaction on the equatorial C-H bond upon treatment with acetophenone enol trimethylsilyl ether (Nu-SiMe₃ = CH₂=C(Ph)OSiMe₃) and titanium tetrachloride to afford keto alcohol **2**, which can be readily converted to the appropriate enantiomerically pure material. We wish to report here an alternative method for the stereoselective ring-cleavage reaction of spiroacetal **1** where allyltrimethylsilane-titanium tetrachloride reagent⁶⁾ was employed (Scheme 1; Nu-SiMe₃ = CH₂=CHCH₂SiMe₃). The present method not only improves the efficiency of the ring-cleavage reaction but also broadens the scope of the enantiodifferentiating transformation of prochiral diols.



Scheme 1.

When acetophenone enol trimethylsilyl ether was employed, spiroacetals derived from 1,3-*meso*-diols (**1**; R^1 = alkyl, R^2 = H) underwent ring-cleavage reactions less efficiently in comparison with those derived from 2-substituted 1,3-propanediols (**1**; R^1 = H, R^2 = alkyl) due to the lower reactivity of the sterically hindered 4,6-disubstituted 1,3-dioxane moiety.³⁾ For example, ring-cleavage reaction of **1a** (R^1 = n-Hex, R^2 = H) and **1b** (R^1 = Me, R^2 = H) under the standard reaction conditions ($\text{CH}_2=\text{C}(\text{Ph})\text{OSiMe}_3$ (1.05 equiv.), TiCl_4 (1.05 equiv.), CH_2Cl_2 , -85°C , 1 h) gave the corresponding product **2a** and **2b** in 65% and 70% yield, respectively. Unfortunately, employment of an excess amount of the reagents or higher reaction temperature resulted in the further aldol reaction of the ring-cleavage product **2**. In contrast to this, we found that titanium tetrachloride-promoted reaction of **1** with an excess amount of allyltrimethylsilane gave the corresponding ring-cleavage product **3** in high yields irrespective of the structure of the starting spiroacetals (Eq. 1, Table 1).

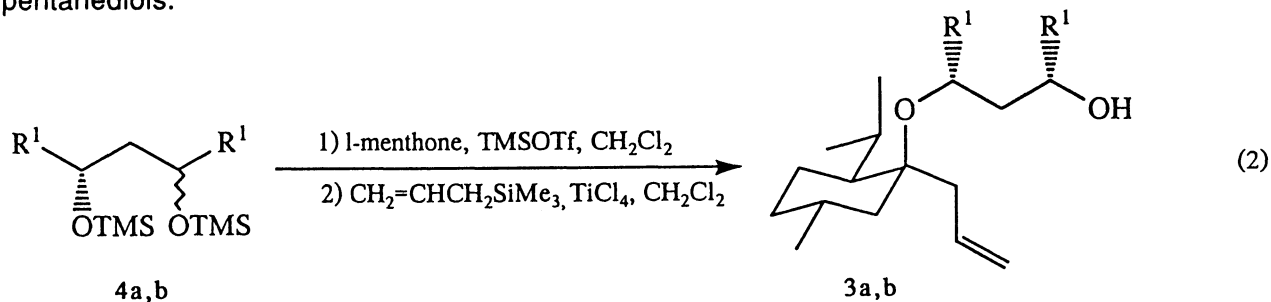


To a solution of spiroacetal **1** (1 mmol) and allyltrimethylsilane (10 mmol) in CH_2Cl_2 (10 mL) was added titanium tetrachloride (1.1 mmol) at -85°C and the resulting yellow solution was stirred for 24 h. After addition of pyridine (0.3 mL) at -85°C followed by aqueous work-up (aq KF/hexane-ethyl acetate (1:1))⁷⁾ ring-cleavage product **3** was isolated by silica gel flash chromatography.

Results summarized in Table 1 show that not only spiroacetals derived from *meso*-1,3-diols (**1a-c**) but also those from 2-substituted 1,3-propanediols (**1d,e**) and *meso*-1,2-diol (**1f**) underwent a highly stereoselective ring-cleavage reaction on equatorial C-O bonds to give **3** as the sole stereoisomer detectable by 200 MHz $^1\text{H-NMR}$ analysis.

It should be noted that acetal formation of bis(trimethylsilyl) ether **4** derived from *meso*-1,3-diols and the subsequent ring-cleavage reaction can be performed successively by a single flask operation (Eq. 2). Thus, after treatment of **4a** (R^1 = n-Hex) with *l*-menthone (1.1 equiv.) in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (10 mol%) in CH_2Cl_2 (1 M) at -40°C

for 18 h, the resulting mixture was cooled to $-85\text{ }^{\circ}\text{C}$, diluted with CH_2Cl_2 , and then subjected to the titanium tetrachloride-promoted ring-cleavage reaction with allyltrimethylsilane to give **3a** in 71% yield with a high stereoselectivity ($>95\%$ de). As reported previously, acetalization of *l*-menthone proceeded exclusively only with *meso*-**4b** ($\text{R}^1 = \text{Me}$) when a mixture of *dl*- and *meso*-**4b** was employed. Therefore, **3b** (91%) was directly obtained by a single flask operation from the 1:1 mixture of *dl*- and *meso*-**4b** which can be readily prepared from commercially available 1,3-pentanediols.



After protection of the hydroxyl group of ring-cleavage product **3** as benzyl ether ($\text{KN}(\text{TMS})_2$, BnBr , THF), the resulting benzyl ether was treated with 5% trifluoroacetic acid in CH_2Cl_2 at a room temperature⁹) to give chiral benzyl derivative **5** which was not accessible by our previous method (Eq. 3). As shown in Table 2, chiral benzyl derivatives **5** of high optical purities were obtained in high yields. Absolute configurations of **5b** and **5d** were determined after converting them to the known MTPA ester derivatives.^{2,3)}

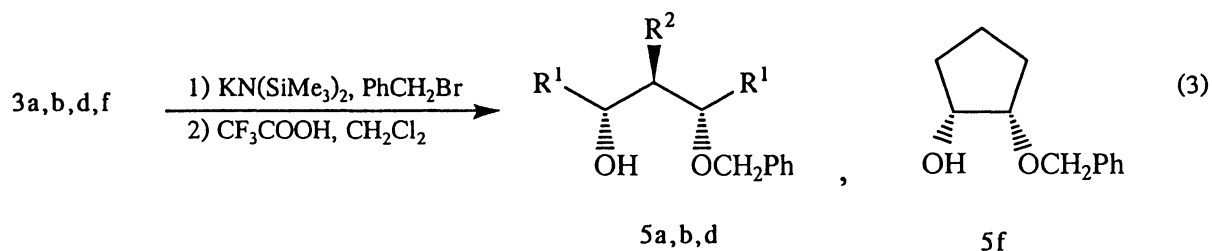


Table 1. Ring-Cleavage Reaction of Spiroacetal **1a**)

Entry	Spiroacetal	Product	Yield / %	de / % ^{b)}
1	1a ; $\text{R}^1 = \text{n-Hex}$, $\text{R}^2 = \text{H}$	3a	100	>95
2	1b ; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$	3b	95	>95
3c)	1b	3b	66	>95
4	1c ; $\text{R}^1 = \text{Me}_3\text{SiO}(\text{CH}_2)_2$, $\text{R}^2 = \text{H}$	3c	56	>95
5	1d ; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$	3d	84	>95
6	1e ; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{iso-Pr}$	3e	72	>95
7	1f	3f	62	>95

a) Unless otherwise noted, reactions were performed as described in the text.

b) The value was determined by 200 MHz ^1H -NMR analysis. c) The reaction was performed by using 1.5 equiv. of allyltrimethylsilane.

Table 2. Transformation of Ring-Cleavage Products to Chiral Derivatives **5**

Entry	Ring-cleavage product	Product	Yield / %	ee / % ^{a)}	[α] _D (CHCl ₃)
1	3a ; R ¹ = n-Hex, R ² = H	5a	75	>95	+31.5 (c 0.76)
2	3b ; R ¹ = Me, R ² = H	5b	85	>95	+52.9 (c 0.79)
3	3d ; R ¹ = H, R ² = Ph	5d	72	>95	+24.8 (c 1.00)
4	3f	5e	95	>95	+13.6 (c 0.096)

a) The value was determined by 200 MHz ¹H-NMR analysis of the corresponding (-)-MTPA ester.

We described an enantiodifferentiating transformation of prochiral diols to the synthetically useful chiral building block **5**. Since ring-cleavage products **3** are stable not only under basic conditions but also under moderately acidic conditions,¹⁰⁾ 1-allylneomenthyl group in **3** is a potential protecting group for alcohols and, therefore, ring-cleavage products **3** themselves can be utilized as versatile chiral building blocks.

This work was supported partially by Grant-in-Aid for Scientific Research on Priority Areas from Japan Ministry of Education, Science and Culture (No. 01649510).

References

- 1) J. W. Scott "Asymmetric Synthesis," ed by J. D. Morrison and J. W. Scott, Academic Press, New York (1984), Vol. 4, Chap. 1; S. Hanessian, "Total Synthesis of Natural Products: 'Chiron' Approach," Pergamon Press, Oxford (1983).
- 2) T. Harada, T. Hayashiya, I. Wada, N. Iwa-ake, and A. Oku, *J. Am. Chem. Soc.*, **109**, 527 (1987).
- 3) T. Harada, K. Sakamoto, Y. Ikemura, and A. Oku, *Tetrahedron Lett.*, **29**, 3097, (1988).
- 4) T. Harada, I. Wada, and A. Oku, *J. Org. Chem.*, **54**, 2599 (1989).
- 5) Only transformation of 2-substituted 1,3-propanediols and *meso*-1,3-diols are shown in Scheme 1.
- 6) A. Hosomi, M. Endo, and H. Sakurai, *Chem. Lett.*, **1976**, 941.
- 7) M. T. Reetz, "Organotitanium Reagents in Organic Synthesis," Springer-Verlag, Berlin (1986), p. 100.
- 8) We previously reported the preparation of **5d** but its optical purity was less satisfactory; T. Harada, I. Wada, and A. Oku, *Tetrahedron Lett.*, **28**, 4181 (1987).
- 9) H. C. Beyerman and J. S. Bontekoe, *Proc. Chem. Soc.*, **1961**, 249.
- 10) For example, **3** was stable in acetic acid or 1 M aq HCl-THF at a room temperature.

(Received June 4, 1990)