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

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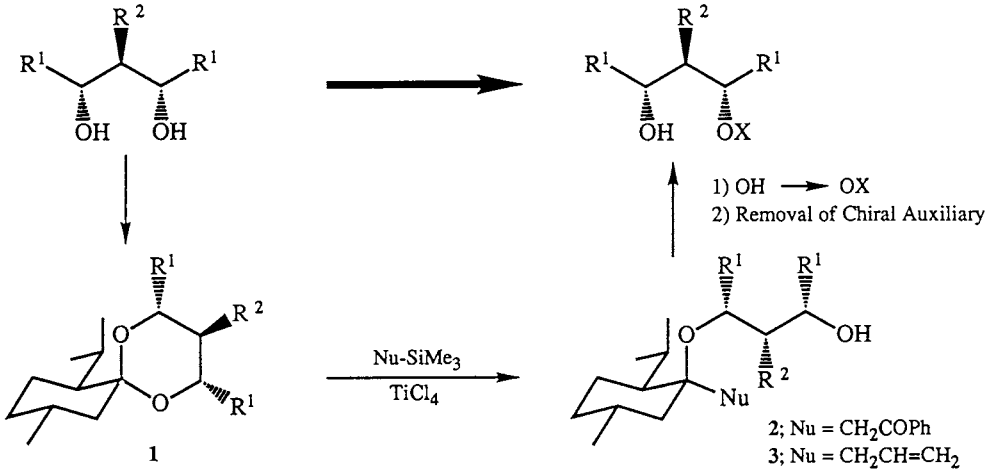
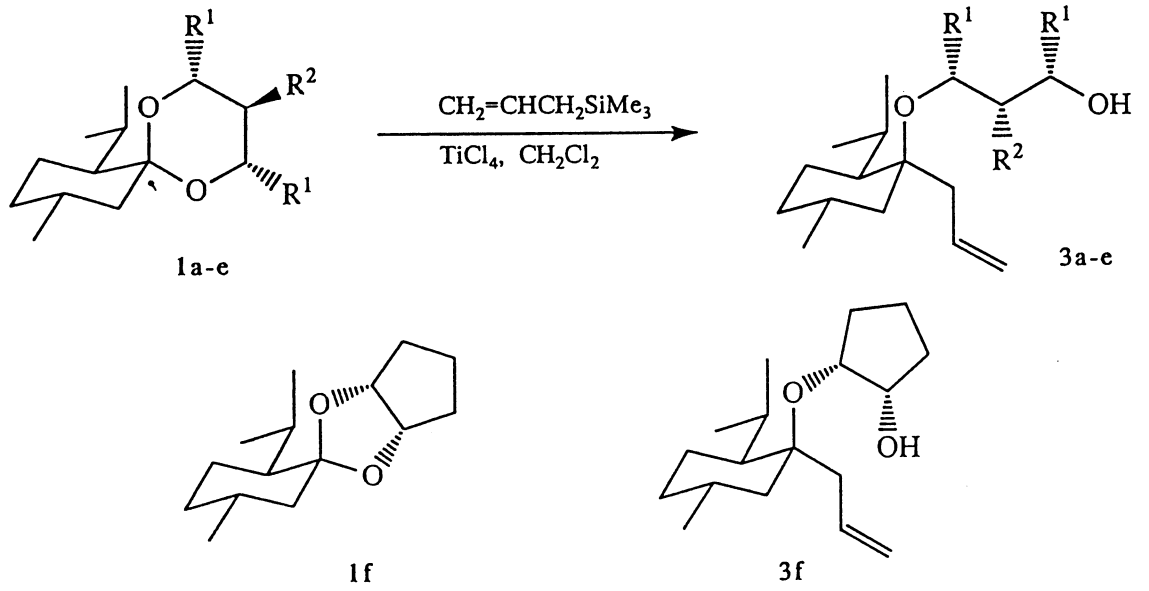
Enantiodifferentiating transformation of prochiral diols possessing σ-symmetry was realized by the utilization of titanium tetrachloride-promoted selective ring-cleavage reaction of spiroacetals derived from the diols and *l*-menthone with allyltrimethylsilane.

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-$SiMe_3$ = CH_2=C(Ph)O$SiMe_3$) 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 reagent[6] was employed (Scheme 1; Nu-$SiMe_3$ = CH_2=$CHCH_2SiMe_3$). 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 (CH_2=C(Ph)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).



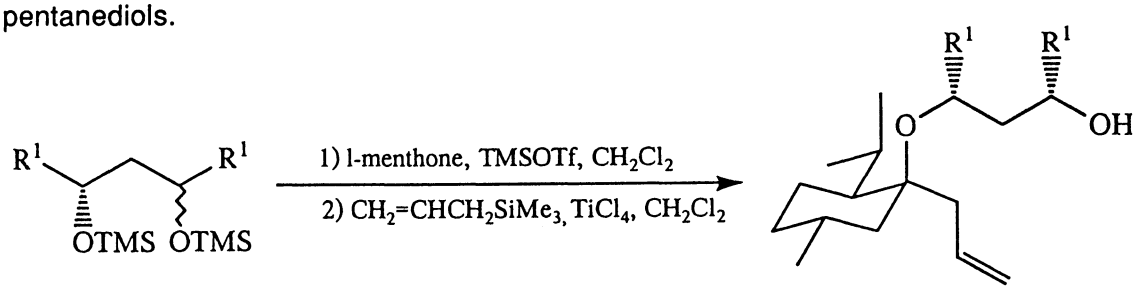
(1)

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}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

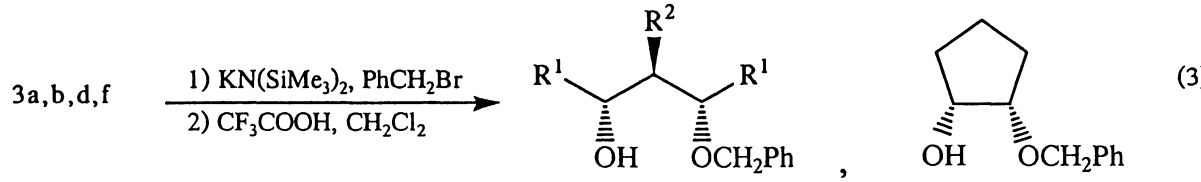
for 18 h, the resulting mixture was cooled to -85 °C, diluted with CH_2Cl_2, and then subjected to the titanium tetrachloride-promoted ring-cleavage reaction with allyltrimethylsilane to give **3a** in 71% yield with a high stereoselectivity (>95% de). As reported previously, acetalization of *l*-menthone proceeded exclusively only with *meso*-**4b** (R^1 = 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.



(2)

4a,b 3a,b

After protection of the hydroxyl group of ring-cleavage product **3** as benzyl ether ($KN(TMS)_2$, BnBr, THF), the resulting benzyl ether was treated with 5% trifluoroacetic acid in CH_2Cl_2 at a room temperature[9] 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]



(3)

5a,b,d 5f

Table 1. Ring-Cleavage Reaction of Spiroacetal **1**[a]

Entry	Spiroacetal	Product	Yield / %	de / %[b]
1	**1a**; R^1 = n-Hex, R^2 = H	**3a**	100	>95
2	**1b**; R^1 = Me, R^2 = H	**3b**	95	>95
3[c]	**1b**	**3b**	66	>95
4	**1c**; R^1 = $Me_3SiO(CH_2)_2$, R_2 =H	**3c**	56	>95
5	**1d**; R^1 = H, R^2 = Ph	**3d**	84	>95
6	**1e**; R^1 = H, R^2 = 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 ^{1}H-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)]	$[\alpha]_D(CHCl_3)$
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 ^{1}H-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.

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References

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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).
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10) For example, **3** was stable in acetic acid or 1 M aq HCl-THF at a room temperature.

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