Pergamon

Tetrahedron Letters 40 (1999) 503–506

TETRAHEDRON LETTERS

Deracemization of *anti*-1,2-Diols Leading to *trans*-Epoxides via Oxazaborolidine-Mediated Enantiomer-Differentiating Ring-Cleavage of Acetal Derivatives

Toshiro Harada,* Tomohito Nakamura, Motoharu Kinugasa, and Akira Oku

Department of Chemistry, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan

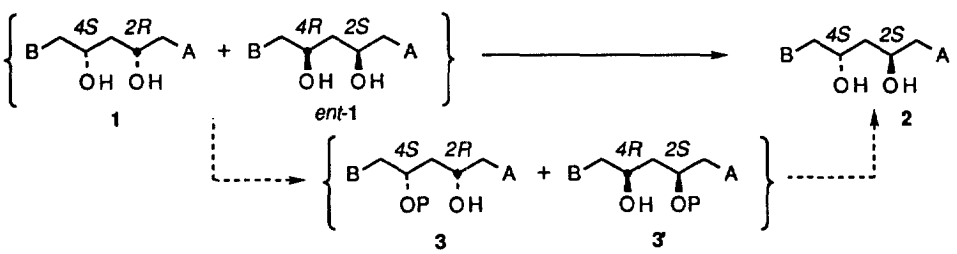
Received 24 September 1998; revised 4 November 1998; accepted 6 November 1998

Abstract: An enantioconvergent transformation of racemic *anti*-1,2-diols to enantiomerically enriched (71-96% ee) *trans*-epoxides is realized via chiral oxazaborolidine-mediated enantiomer-differentiating ring-cleavage reaction of the acetal derivatives.

Keywords: acetals; diols, asymmetric induction; asymmetric reactions; cleavage reactions

Of various strategies for asymmetric synthesis, enantioconvergent transformation of racemic substrates to enantiomerically pure products has been less studied but is of potential importance because it can expand the scope of substrates that hitherto has been limited to prochiral compounds [1]. We recently proposed a novel deracemization scheme in which both enantiomers (2*R*,4*S*)-**1** and (2*S*,4*R*)-*ent*-**1** are converted into the same enantiomer (2*S*,4*S*)-**2** by the inversion of specific stereogenic centers, 2*R* for **1** and 4*R* for *ent*-**1** (Scheme 1)[1] [2]. The deracemization scheme was realized through a stepwise process involving enantiomer-differentiating protection of the racemic diol by using *l*-menthone as a chiral auxiliary leading to **3** (from **1**) and **3'** (from *ent*-**1**) and carbinol carbon inversion by the Mitsunobu esterification [2]. One characteristic feature of the approach is that the racemic substrates and resulting isomeric intermediates are processed in parallel reactions without separation.

Scheme 1

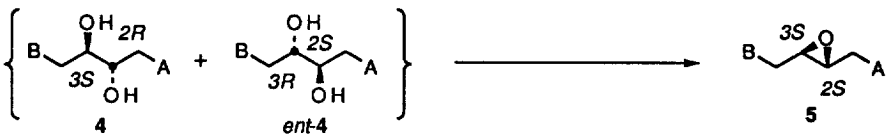


1. Groups A and B are arbitrarily chosen as highest-priority groups in Schemes 1 and 2.

0040-4039/99/$ - see front matter
PII: S0040-4039(98)02387-9

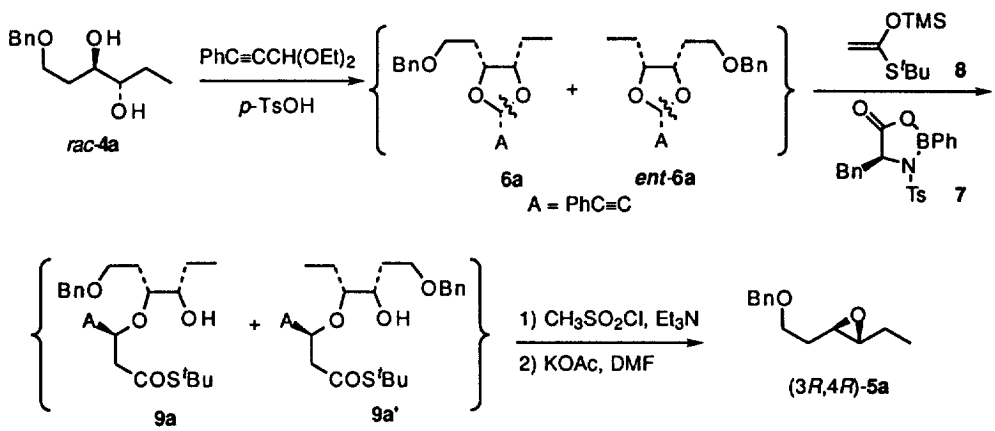
Chiral epoxides are versatile intermediates for the synthesis of enantiomerically pure complex molecules. Despite great advances in the asymmetric epoxidation of functionalized as well as unfunctionalized olefins, reliable methods for the preparation of unfunctionalized *trans*-epoxides are relatively rare [3,4]. Recently, an efficient catalytic method was reported by Shi et al. using a fructose-derived ketone as a catalyst [5]. A racemic *anti*-1,2-alkanediol could be transformed to (2*S*,3*S*)-*trans*-epoxide **5** in an enantioconvergent manner if diols **4** and *ent*-**4** undergo cyclization with a specific inversion of the *R* carbinol carbons (Scheme 2).[1] Herein, we wish to report a novel method for the asymmetric synthesis of *trans*-epoxides based on the deracemization of *anti*-1,2-alkanediols.

Scheme 2



1,3,4-Hexanetriol derivative *rac*-**4a** was stereoselectively transformed to *syn*-acetal *rac*-**6a** (*syn*:*anti* = 16:1) by transacetalization with 3,3-diethoxy-1-phenylpropyne under kinetically controlled conditions [6,7] in 85% yield (Scheme 3). We have recently reported an enantioselective ring-cleavage reaction of prochiral acetals **6'** derived from *meso*-1,2-diols: chiral oxazaborolidine **7**-mediated reaction of **6'** generally affords C-$O_{pro\text{-}R}$ bond-cleavage products with high selectivity (>90% ee) [6,7]. Upon application of a similar ring-cleavage to *rac*-**6a**, the C-O bonds adjacent to the ethyl and the benzyloxyethyl groups are expected to undergo selective cleavage respectively for **6a** and *ent*-**6a** to give protected derivatives **9a** and **9a'**. Indeed, treatment of *rac*-**6a** with **7** (1.2 equiv) and silyl ketene *S*,*O*-acetal **8** (1.5 equiv) in CH_2Cl_2 at -78 °C afforded a mixture of the ring-cleavage products (1.3:1) in 75% yield. Conversion of the mixture to the mesylates (CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C) followed by treatment with potassium acetate in DMF at 85 °C for 3 h gave *trans*-epoxide **5a** ($[\alpha]^{20}_D$ -23.8 (*c* 1.7, $CHCl_3$)) of 95% ee in 85% yield. The absolute configuration of **5a** was determined by converting it into the known (3*R*,4*R*)-3,4-epoxyhexan-1-ol [8].

Scheme 3



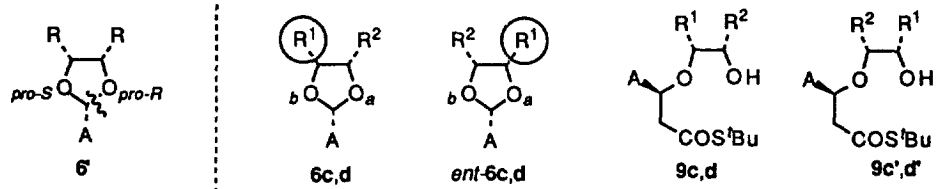


Table 1 Deracemization of 1,2-Diols Leading to *trans*-Epoxides [a]

entry	*rac*-4	*rac*-6 yield (*syn*:*anti*)	9 + 9' yield (ratio)	5 [b]	yield	ee [c]
1	*rac*-4a	85% (16:1)	75% (1.3:1)	(3*R*,4*R*)-5a [d]	80%	95%
2	*rac*-4b	68% (13:1)	41% (1.3:1)	(1*R*,2*R*)-5b [d]	79%	93% [e]
3	*rac*-4c	78% (7.6:1)	85% (1.7:1)	(2*R*,3*R*)-5c [f]	70%	85% [f]
4	*rac*-4d	60% (13:1)	84% (2.6:1)	(2*R*,3*R*)-5d [g]	87%	71%
5	*meso*-4e	62% (19:1)	80% [7]	(2*R*,3*R*)-5e [h]	84% [i]	96% [j]
6	*meso*-4f	60% (8:1)	80%	(3*R*,4*R*)-5f [g]	81% [k]	96%

[a] Unless otherwise noted, reaction conditions are as follows: transacetalization; 3,3-diethoxy-1-phenylpropyne (1.2-3 equiv), *p*-TsOH (0.1 equiv), molecular sieves 4A, CH_2Cl_2 (rt , 2-5 h), ring-cleavage; **8** (1.5-3 equiv), **7** (1.2-1.5 equiv), CH_2Cl_2 (-78 °C, 15 h), transformation to **6**; i) MsCl, Et_3N, CH_2Cl_2, rt, ii) NaOAc (5 equiv), DMF, 85 °C, 3-5 h. [b] Specific rotations are as follows: **5a**; $[\alpha]_D^{20}$ +23.8 (*c* 1.69, $CHCl_3$), **5b**; $[\alpha]_D^{20}$ -3.19 (*c* 3.30, $CHCl_3$), **5c**; $[\alpha]_D^{20}$ +27.0 (*c* 1.00, $CHCl_3$), **5d**; $[\alpha]_D^{20}$ +12.4 (*c* 0.62, $CHCl_3$), **5e**; $[\alpha]_D^{20}$ +8.80 (*c* 1.25, $CHCl_3$), **5f**; $[\alpha]_D^{20}$ +16.9 (*c* 1.76, $CHCl_3$). [c] Unless otherwise noted, enantioselectivity was determined by chiral HPLC (Chiracel OD for **5a,d** and Chiracel AD for **5f**. [d] For absolute configuration determination, see text. [e] The epoxide was converted to *trans*-2-cyclododecenol (see text). Enantioselectivity was determined by a HPLC (Chiracel AD) analysis of the benzoate derivative. [f] The epoxide was reduced with $LiAlH_4$. Enantioselectivity and absolute configuration were determined by ^{19}F NMR analysis of the MTPA ester derivative [11]. [g] Tentative assignment. [h] The absolute configuration was determined by specific rotation measurement [12]. [i] The mixture of ring-cleavage products was converted to the triflate (Tf_2O, pyridine) and then treated with LDA in THF. [j] The reaction of the epoxide with Me_2CuLi gave (2*S*,3*S*)-1,4-dibenzyloxy-3-methyl-2-butanol, whose ee was determined by ^1H NMR analysis of the MTPA ester derivative. [k] The cyclization of the mixture of mesylte was carried out by using K_2CO_3 in MeOH.

Deracemization of other 1,2-diols by using a similar reaction sequence is summarized in Table 1. *trans*-Epoxide of *cis,trans,trans*-1,5,9-cyclododecatriene, **5b** (93% ee), was prepared starting from commercially available diol *rac*-**4b**. For the determination of the absolute structure, **5b** was converted to *trans*-2-cyclododecenol in two steps (H_2, Pd/C, MeOH, and then, diethylaluminium 2,2,6,6-tetramethylpiperidide, hexane [9], 84% overall yield). As we anticipated, (1*R*,2*R*)-configuration was established by a 500 MHz ^{1}H NMR analysis of the MTPA derivative of the alcohol based on the modified Mosher method [10]. Somewhat lower enantioselectivity was observed in the desymmetrization of diols *rac*-**4c,d** (entries 3 and 4). For these diols, ring-cleavage reaction gave **9c,d** in preference to **9c',d'**. A similar reaction sequence can be successfully applied to an asymmetric synthesis of C_2-symmetric *trans*-epoxides. Thus, enantioselective ring-cleavage of *meso*-acetals **6e** and **6f** and subsequent cyclization afforded *trans*-epoxides **5e** (96% ee) and **5f** (96% ee), respectively (entries 5 and 6).

The lower ee observed for **5c,d** are most probably due to the lower level of C-O bond differentiation in the ring-cleavage step. The less preferable C-O_b bond cleavage of **6c,d** produces the enantiomer of **9c',d'** (*ent*-**9c',d'**) while that of *ent*-**6c,d** results in the formation of the enantiomer of **9c,d** (*ent*-**9c,d**). The major products **9c** (55%) and **9d** (61%) were obtained in yields exceeding 50%, suggesting that the C-O_b bond cleavage of *ent*-**6c,d** leading to *ent*-**9c,d** proceeded to some extent. It is probable that the sterically more demanding R^1 group (C_6H_{13} and C_3H_7 for *ent*-**6c** and **-6d**, respectively) adjacent to the C-O_a bond retarded the coordination of Lewis acid **7** and subsequent C-O_a bond cleavage, resulting in the competing cleavage of the less preferable C-O_b bond and lower levels of C-O bond differentiation. For **6c,d**, such effect may improve the selectivity in the cleavage. However, even complete selectivity may not contribute significantly to the ee of major product **9c,d**. In the case where R^1 and R^2 are approximately equal in their steric demands as in **6a,b**, the ring-cleavage proceeded with higher levels of C-O bond differentiation similar to those for *meso*-**6e,f** [6,7] leading to the *trans*-epoxide of >93% ee.

In summary, we have described deracemization of *anti*-1,2-diols leading to enantiomerically enriched *trans*-epoxides. The study disclosed the utility of oxazaborolidine-mediated ring-cleavage reaction of cyclic acetals in enantiomer differentiation of racemic 1,2-diols.[2]

References

[1] Nógrádi M. Stereoselective synthesis. VCH, New York, 1996:36-40.

[2] Harada T, Shintani T, Oku A. J. Am. Chem. Soc. 1995;117:12346-47.

[3] Johnson RA, Sharpless KB. In: Ojima I, editor. Catalytic asymmetric synthesis. VCH, New York, 1993:chapter 4.1.

[4] Jacobsen EN. In: Ojima I, editor. Catalytic asymmetric synthesis. VCH, New York, 1993:chapter 4.2.

[5] Wang Z-X, Tu Y, Frohn M, Zhang J-R, Shi Y. J. Am. Chem. Soc. 1997;119:112235-11235.

[6] Kinugasa M, Harada T, Oku A. J. Am. Chem. Soc. 1997;119:9067-9068.

[7] Kinugasa M, Harada T, Oku A. Tetrahedron Lett. 1998;39:4529-4532.

[8] Rossiter RE, Sharpless KB. J. Org. Chem. 1984;49:3707-3711.

[9] Yasuda A, Tanaka S, Oshima K, Yamamoto H, Nozaki H. J. Am. Chem. Soc. 1974;96:6513-6514.

[10] Ohtani I, Kusumi T, Kashman Y, Kakisawa H. J. Am. Chem. Soc. 1991;113:4092-4096.

[11] Weber B, Seebach D. Tetrahedron 1994;50:7473-7484.

[12] Nicolaou KC, Papahatjis DP, Claremon DA, Magolda RL, Dolle RE. J. Org. Chem. 1985;50:1440-1456.

2. This work was supported partially by a Grant-in-Aid for Scientific Research on Priority Area (10125218) from the Ministry of Education, Science, and Culture, Japan.