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Desymmetrization of *meso*-1,2-Diols via Chiral Oxazaborolidine-Mediated Ring-Cleavage of Acetal Derivatives with Silyl Ketene *S,O*-Acetal

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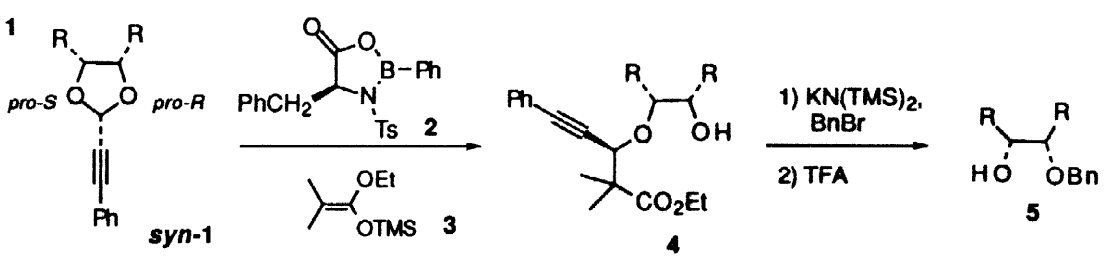
Abstract: Desymmetrization of *meso*-1,2-diols leading to enantiomerically enriched MOM and MEM ethers is realized via chiral oxazaborolidine-mediated enantioselective ring-cleavage reaction of the acetal derivatives with silyl ketene *S,O*-acetal.

Keywords: acetals; diols; asymmetric induction; amino alcohols

The non-enzymatic approach to enantiotopic group differentiation, or desymmetrization, of prochiral bifunctional compounds has been receiving increasing attention because of its utility in preparing chiral building blocks as well as in constructing multiple stereogenic centers [1,2]. We recently developed a method for desymmetrizing *meso*-1,2-diols [3-12] via a chiral Lewis acid-mediated enantioselective ring-cleavage of acetal derivatives *syn*-**1** (Scheme 1) [13]. *B*-Phenyl oxazaborolidine **2** [14,15] as a chiral Lewis acid was demonstrated to be highly effective in differentiating the C-O$_{pro\text{-}R}$ group of *syn*-**1** from the enantiotopic C-O$_{pro\text{-}S}$ in the reaction with silyl ketene acetal **3** derived from ethyl isobutyrate. Although the ring-cleavage products **4** can be readily converted into benzyl ethers **5**, application to asymmetric synthesis of desymmetrized derivatives with acid-sensitive protecting groups was hampered by the acidic conditions employed in the conversion. We wish to report herein desymmetrization of *meso*-1,2-diols leading to enantiomerically enriched MOM (CH_3OCH_2), MEM ($CH_3OCH_2CH_2OCH_2$) ethers **8**, and β–amino alcohol **11** via an enantioselective ring-cleavage reaction using silyl ketene *S,O*-acetal **6** as a nucleophile. We also describe the synthetically useful observation of an exclusive reaction of a *meso* acetal in the presence of a *dl* isomer.

Scheme 1



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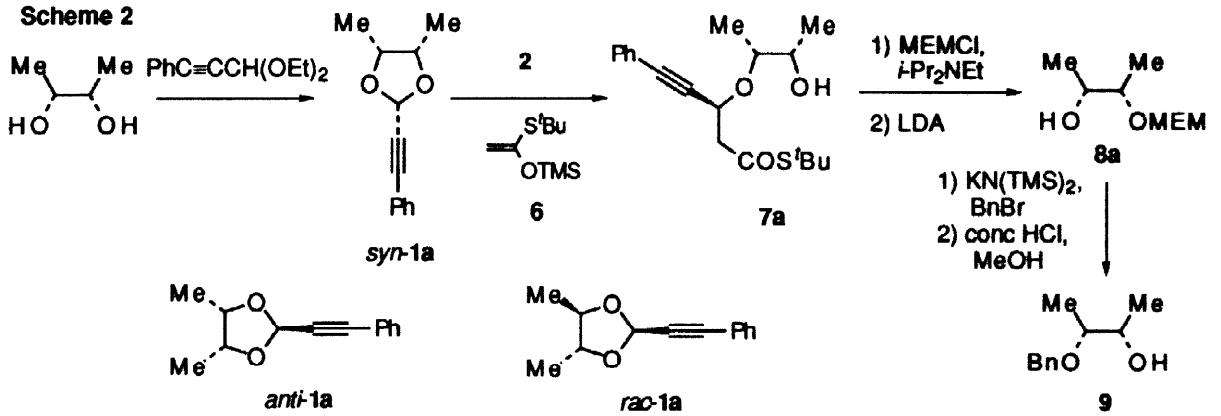


Treatment of *meso*-2,3-butanediol with 3,3-diethoxy-1-phenylpropyne (1.2 equiv) in the presence of *p*-TsOH (0.1 equiv) and molecular sieves 4A in CH_2Cl_2 at rt gave a 97:3 mixture of *syn*- and *anti*-**1a** in 92% yield (Scheme 2).[1] The mixture was subjected to ring-cleavage reaction by using silyl ketene *S,O*-acetal **6** (1.5 equiv) as a nucleophile. When the reaction was carried out in the presence of oxazaborolidine **2** (1.2 equiv) in CH_2Cl_2 at -78 °C, ring-cleavage product **7a** of 96% ee[2] was obtained in 97% yield.[3] The result shows that **2** serves as an efficient Lewis acid promoter also for the ring-cleavage using ketene *S,O*-acetal **6**.

After protection of the hydroxyl group of ring-cleavage product **7a** (95% ee) as MEM ether, the thiol ester moiety was removed by treatment with LDA in THF at 0 °C to give desymmetrized MEM ether derivative **8a** of 96% ee[2] in 74% overall yield. The absolute configuration of **8a** was determined by converting it into benzyl ether derivative (2*S*,3*R*)-**9** ($[\alpha]^{20}_D$ -25.8 (*c* 1.2, $CHCl_3$)) [13].

Several other *meso*-diols were successfully desymmetrized to the enantiomerically enriched MEM and MOM ethers **8** (>95% ee) via enantioselective ring-cleavage reaction with silyl ketene *S,O*-acetal **6** (Table 1). In the initial transacetalization, the *syn* isomers were selectively formed under kinetically controlled conditions (TsOH (0.1 equiv), molecular sieves 4A, CH_2Cl_2, rt) [17,18]. When the rate of acetalization is slow, competitive isomerization to the *anti* isomers made it difficult to obtain high *syn* selectivity at the higher conversion (entries 3-5). The ring-cleavage reaction was effected without lowering chemical yields and enantioselectivities for *syn*-**1d,e** with the benzyloxy and acetoxy groups to give **7d,e**, which were transformed to MOM ethers **8d,e** of potential utility as chiral building blocks (entries 4 and 5). For **7e** with acetoxy groups, removal of the thiol ester moiety was successfully achieved by using KOAc in DMF (80 °C). *meso*-Hydorobenzoin derivative *syn*-**1f** was less reactive and the yield of ring-cleavage product **7f** was low, even under enforced conditions (entry 6).

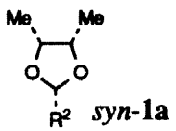
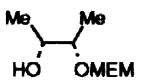
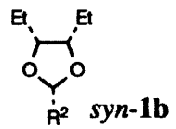
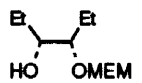
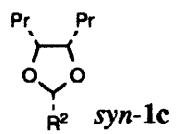
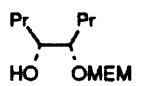
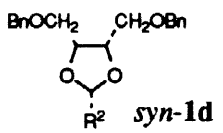
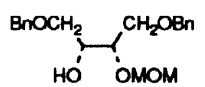
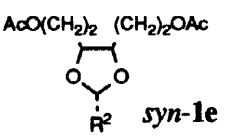
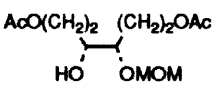
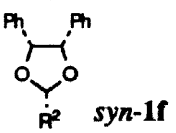
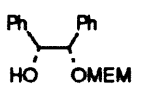
As observed in the reaction with ketene *O,O*-acetal **3** [13], isomeric acetals *anti*-**1** were not reactive and rigorous purification of the starting acetals was not necessary. Moreover, one can even use a mixture of *meso*- and *dl*-1,2-diols in the ring-cleavage reaction. Thus, transacetalization of a commercially available 2,3-butanediol, a 66:34 mixture of the *meso* and *dl* isomers, gave the corresponding acetals in 68% yield as a 63:3:34 mixture of *syn*-**1a**,

1. Stereochemistry of *syn*-**1a** was determined by a NOESY experiment.
2. The ee value was determined by ^1H NMR (500 MHz) analysis of the MTPA ester derivative [16].
3. Diastereoselectivity of the ring-cleavage reaction was also high (>95%). The stereochemistry of the carbon adjacent to the phenylethynyl group in **7a** was tentatively assigned based on the observed inversion of the configuration at the acetal carbon in the reaction using ketene *O,O*-acetal **3** [13].

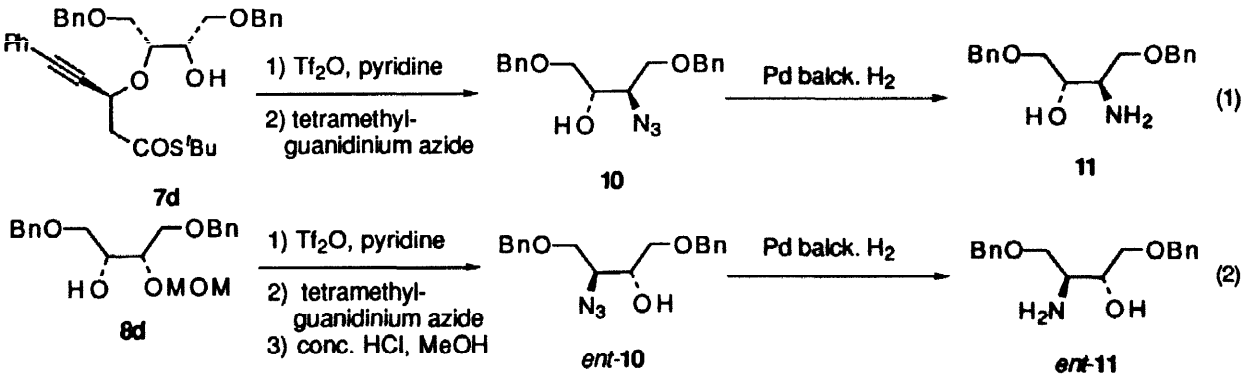
anti-**1a**, and *rac*-**1a**. Ring-cleavage of the mixture afforded **7a** of 96% ee[2] in 64% yield (97% yield based on *meso* acetals). The formation of the diastereomeric ring-cleavage product was not detected and the recovered acetal (36%) was a 7:93 mixture of *anti*- and *rac*-**1a**. The exclusive reaction of *meso* acetals is of considerable synthetic utility because a variety of 1,2-diols are easily accessible as a mixture of *meso* and *dl* isomers by reductive coupling of aldehydes. Indeed, the reaction of propanal mediated by SmI_2 [19] afforded a 40:60 mixture of *meso*- and *dl*-4,5-octanediol. The reaction of a stereo mixture of acetal **1c** (*syn*:*rac* = 36:64, *anti* < 1%), derived from the diol, gave ring-cleavage product **7c** (96% ee)[2] in 34% yield with the quantitative recovery of the *dl* isomer.

Because the thiol ester moiety can be removed under relatively mild conditions, the ring-cleavage products **7** themselves can be regarded as building blocks in asymmetric syntheses. Their potential utility was demonstrated in the asymmetric synthesis of β-amino alcohol **11**

Table 1
Asymmetric Synthesis of MEM and MOM ethers **8** by Desymmetrization of *meso*-1,2-Diols [a]

entry	acetals R^2 = PhC≡C	yield (%)	*syn*-selectivity (%)	ring-cleavage product	yield (%)	desymmetrized product	yield (%)	ee [b] (%)	$[\alpha]_D$ (*c*, $CHCl_3$)
1	 *syn*-**1a**	92	97	**7a**	97	 **8a**	74	96	+47.4 (1.1)
2	 *syn*-**1b**	98	93	**7b**	83	 **8b**	73	96	+35.3 (1.4)
3	 *syn*-**1c**	64	>97	**7c**	91	 **8c**	72	97	+22.1 (0.89)
4	 *syn*-**1d**	55 [c]	97	**7d**	80 [d]	 **8d** [e]	84	96	+13.8 (1.4)
5	 *syn*-**1e**	31	>97	**7e**	96	 **8e**	72 [f]	97	+15.3 (1.5)
6	 *syn*-**1f**	92	>97	**7f**	33 [g]	 **8f**	72 [h]	95	+94.2 (1.3)

[a] Unless otherwise noted, reaction conditions are as follows: transacetalization; 3,3-diethoxy-1-phenylpropyne (1.2 equiv), *p*-TsOH (0.1 equiv), molecular sieves 4A, CH_2Cl_2 (rt , 1-4 h), ring-cleavage; **6** (1.5 equiv), **2** (1.2 equiv), CH_2Cl_2 (-78 °C, 15 h), transformation to **8**; i) MEMCl (or MOMCl), *i*-Pr_2NEt, CH_2Cl_2, rt, ii) LDA (1.2-1.6 equiv), THF, 0 °C. [b] Unless otherwise noted, ee values were determined by ^1H NMR (500 MHz) analyses of MTPA ester derivatives. [c] Three equiv of 3,3-diethoxy-1-phenylpropyne was used. [d] Ring-cleavage was carried out by using **6** (3 equiv) and **2** (1.5 equiv). [e] The absolute configuration of **8d** was determined by the modified Mosher's method [20]. [f] Removal of the thiol ester moiety was effected by using KOAc (5 equiv) in DMF (80 °C, 2 h). [g] The reaction was performed at -50 °C for 5 h to give **7f** of 92% ee. [h] The reaction was carried out by using **7f** (95% ee), which was prepared in 19% yield by ring-cleavage reaction at -78 °C.



(eqs 1 and 2). Conversion of the ring-cleavage product **7d** into the triflate and subsequent reaction with tetramethylguanidinium azide [21] in acetonitrile gave azide **10** of 96% ee[4] in 79% overall yield. The second reaction most probably proceeded through a mechanism involving initial substitution of the azide anion followed by removal of the thiol ester moiety under slightly basic conditions. Hydrogenation of azide **10** using Pd black as a catalyst furnished amino alcohol **11** ($[\alpha]^{25}_D$ +11.8 (*c* 1.1, $CHCl_3$)) in 95% yield. On the other hand, desymmetrized MOM derivative **8d** (96% ee) was transformed by a similar reaction sequence to enantiomeric amino alcohol *ent*-**11** ($[\alpha]^{25}_D$ -10.9 (*c* 1.1, $CHCl_3$)) in 71% yield.[5]

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4. The ee value was determined by HPLC analysis with a Chiracel OD column.

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