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1,5-Benzodithiepan-3-one 1,5-Dioxide: A Novel Chiral Auxiliary for Asymmetric Desymmetrization of *meso*-1, 2-Diols

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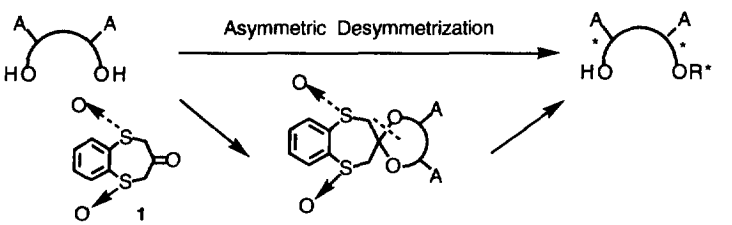
Abstract: A novel C_2-symmetric bis-sulfoxide **1** was synthesized as a chiral auxiliary for asymmetric desymmetrization of *meso*-1,2-diols. *cis*-Cyclohexane-1,2-diol and *cis*-cyclopentane-1,2-diol were desymmetrized *via* acetalization with **1** followed by base-promoted acetal cleavage with high diastereoselectivity (>96% *d.e.*).

Asymmetric desymmetrization of σ-symmetric diols is an area of chemistry that has recently received increasing attention as a method for synthesizing useful chiral building blocks for various natural products. Considerable effort has been devoted to the development of efficient methods. [1-4] We investigated a novel chemical asymmetric desymmetrization of σ-symmetric diols *via* acetalization with a chiral β-ketosulfoxide followed by a diastereoselective acetal cleavage reaction, which is formally equivalent to asymmetric desymmetrization. [2] Although other groups have also developed chiral auxiliaries for this purpose, [3,4] an inevitable problem with the previous auxiliaries has been the formation of two diastereomeric isomers in acetalization. To solve this problem, we designed a new chiral auxiliary **1** with C_2-symmetry. To the best of our knowledge, this is the first use of a C_2-symmetric chiral auxiliary for the asymmetrization of σ-symmetric diols.

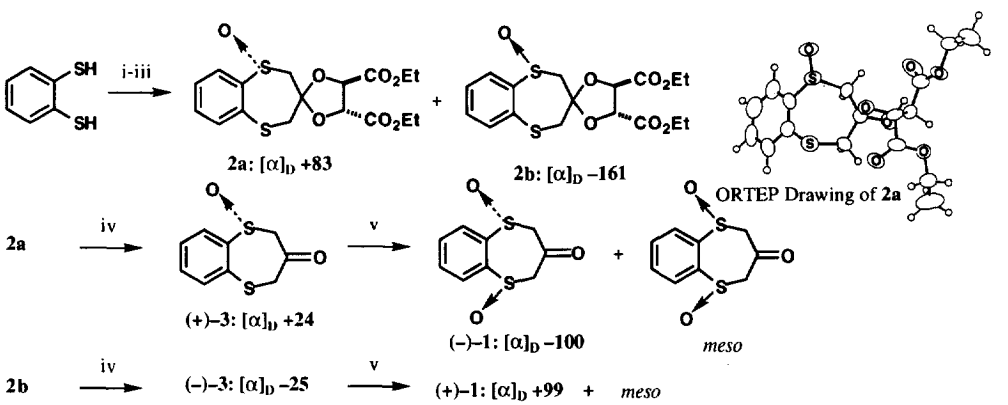
In this communication, we report the synthesis of the novel C_2-symmetric cyclic bis-sulfoxide **1** and its application as a chiral auxiliary for asymmetric desymmetrization of *meso*-1,2-diols.



Scheme 1

RESULTS AND DISCUSSION

Both enantiomers of the chiral auxiliary **1** were prepared starting from 1,2-benzenedithiol, [5] as shown in Scheme 2. Condensation of 1,2-benzenedithiol with 1,3-dichloroacetone in the presence of dimethylaminopyridine (DMAP) gave 1,5-benzodithiepan-3-one in good yield. Acetalization with the bis-trimethylsilyl ether of (+)-diethyl tartrate by Noyori's method [6] was followed by oxidation of one of the sulfides with one equivalent of *m*-chloroperbenzoic acid (MCPBA) to give the separable diastereomeric isomers **2a** and **2b**. [7] Base-promoted deacetalization of **2a** with potassium hexamethyldisilazide (KHMDS) gave the ketosulfoxide (+)-**3**, which was oxidized by dry ozonization [8] to give the bis-sulfoxide (−)-**1** along with *meso*-bis-sulfoxide [(−)-**1**: *meso* = ~2 : 1]. [7] The enantiomers (+)-**1** was prepared from **2b** using the same procedure. The absolute configurations of (+)-**1** and (−)-**1** were unambiguously determined by an X-ray single crystal structure analysis of **2a**. [9]

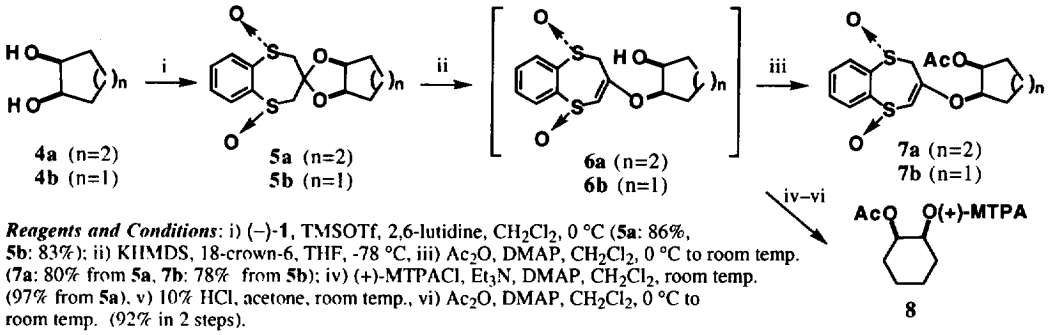


Reagents and Conditions: i) 1,3-dichloroacetone, DMAP, CH_2Cl_2, −30 °C (76%); ii) diethyl L-tartrate bis-trimethylsilyl ether, TMSOTf, CH_2Cl_2, room temp. (97%); iii) MCPBA, CH_2Cl_2, −78 °C (**2a**: 45%, **2b**: 52%); iv) KHMDS, THF, −78 °C [(+)-**3**: 83%, (−)-**3**: 72%]; v) O_3, SiO_2, −78 °C to −20°C [(−)-**1**: 36% (conversion yield 43%); *meso*: 18%, (+)-**1**: 35% (conversion yield 44%); *meso*: 17%].

Scheme 2

With the chiral auxiliary in hand, the asymmetric desymmetrization of **4a** and **4b** was examined. *meso*-1,2-Diols **4a** and **4b** were acetalized with (−)-**1** in the presence of TMSOTf and 2,6-lutidine at 0 °C in good yield to give the acetals **5a** and **5b**, respectively. [10] On treatment with lithium hexamethyldisilazide (LiHMDS) and 12-crown-4, base-promoted acetal fission of **5a** proceeded to give the alcohol **6a**, which was immediately acetylated to prevent recyclization. [11] The diastereomeric excess of the resulting **7a** was very poor (Table 1, entry 1). Interestingly, the counter cation in the base had a remarkable effect. Selectivity was dramatically increased in the order Li<<Na<K (entries 1–3). The best enantiomeric excess was achieved using three equivalents of KHMDS in THF, which led to the formation of the acetate **7a** in 91% chemical yield and >96% *e.e.* (entry 3). [12] No solvent effect was observed (entries 4 and 5). The resulting alcohol **6a** could be converted into (1*S*,2*R*)-**8** without a loss of enantiomeric excess (>96% *e.e.*). [13] The efficiency of the chiral

auxiliary (−)-**1** was demonstrated by asymmetrization of *cis*-cyclopentane-1,2-diol **4b** to give the acetate **7b** with high diastereoselectivity (entry 6). [12]



4a (n=2)
4b (n=1)

5a (n=2)
5b (n=1)

6a (n=2)
6b (n=1)

7a (n=2)
7b (n=1)

8

Reagents and Conditions: i) (−)-**1**, TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (**5a**: 86%, **5b**: 83%); ii) KHMDS, 18-crown-6, THF, -78 °C, iii) Ac_2O, DMAP, CH_2Cl_2, 0 °C to room temp. (**7a**: 80% from **5a**, **7b**: 78% from **5b**); iv) (+)-MTPACl, Et_3N, DMAP, CH_2Cl_2, room temp. (97% from **5a**), v) 10% HCl, acetone, room temp., vi) Ac_2O, DMAP, CH_2Cl_2, 0 °C to room temp. (92% in 2 steps).

Scheme 3

Table 1. Diastereoselective Acetal Cleavage of **5a** and **5b**.

Entry	Substrate	Conditions (equiv.)	Product	Yield (%)[b]	*d.e.* (%)[c]
1	**5a**[a]	LiHMDS (5), 12-crown-4 (5), THF, −78 °C	**7a**	79	8
2	**5a**[a]	NaHMDS (3), 15-crown-5 (3), THF, −78 °C	**7a**	83	90
3	**5a**	KHMDS (3), 18-crown-6 (3), THF, −78 °C	**7a**	91	>96
4	**5a**[a]	KHMDS (3), 18-crown-6 (3), DME, −78 °C	**7a**	75	>96
5	**5a**[a]	KHMDS (3), 18-crown-6 (3), toluene, −78 °C	**7a**	80	>96
6	**5b**	KHMDS (3), 18-crown-6 (3), THF, −78 °C	**7b**	78	>96

[a] Racemic **5** was used. [14] [b] Isolated yield after acetylation. [c] Determined by ^{1}H-NMR spectroscopy.

In conclusion, a novel C_2-symmetric bis-sulfoxide was synthesized for the asymmetric desymmetrization of *meso*-1,2-diols. An efficient differentiation of the enantiotopic group in *meso*-1,2-diols was accomplished using the bis-sulfoxide as a chiral auxiliary. Further studies are in progress to explore the full scope of this methodology and its application to the synthesis of various natural products.

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11. After the addition of the base, the reaction was quenched with acetic anhydride at –78 ℃, and the mixture was transferred into saturated NH_4Cl aqueous solution. The work-up was essential to prevent undesirable recyclization of the product. The partially acetylated product was filtrated through a short pad of silica gel and then completely acetylated with acetic anhydride and DMAP.
12. The absolute configurations of the cleaved alcohols **6a** and **6b** were determined by Mosher's method after conversion into the corresponding MTPA esters; Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519; *Idem. J. Org. Chem.* **1969**, *34*, 2543–2549.
13. The chiral auxiliary (–)-**1** was recovered in 95% chemical yield without decreasing the enantiomeric excess (>98% *e.e.*).
14. By the same procedure as in the case of chiral **5a**, racemic **5a** was synthesized from the racemic **3**, which was prepared by oxidation of 1,5-benzodithiepan-3-one with MCPBA.

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