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Synthesis of Carbohydrates and Related Polyhydroxylated Compounds Employing Asymmetric Dihydroxylation. 1. An Access to *Erythro*-diols

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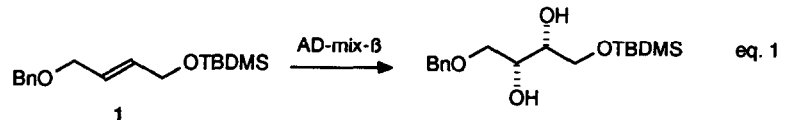
Abstract: Asymmetric dihydroxylation provides an easy access to tetrose: threose directly from the (*E*)-olefin **1**, and erythrose *via* an irreversible Payne-type rearrangement - opening process of the threitol cyclic sulfate **5**.

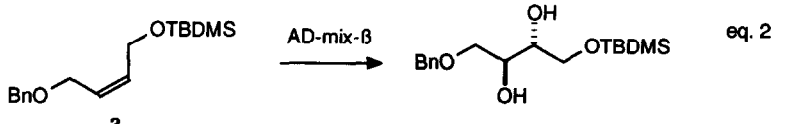
Since the discovery of the Sharpless asymmetric epoxidation, there have been numerous applications of the reaction to the synthesis of enantiomerically pure compounds.[1] One of the beneficiaries has been the synthesis of carbohydrates and related polyhydroxylated natural products.[2] In particular, the synthesis of tetroses proceeds virtually trouble-free.[2a] The key reactions of this work are the asymmetric epoxidation (AE) of C-4 allylic alcohols (e.g., 4-benzyloxy-2-buten-1-ol), followed by regioselective epoxide-opening reactions. Stereochemical control of the two chirality centers (thus four stereoisomers) was fully achieved by selecting from (*E*)- or (*Z*)-allylic alcohol substrates and from L-(+)- or D-(-)-tartrate ligands (four possible combinations).[3]

Impressive advances have recently been made in the asymmetric dihydroxylation (AD) reaction.[4] This process would seem to offer a more straightforward solution toward the synthesis of carbohydrate and related polyhydroxylated natural products since the products are diols and further transformations should be unnecessary.[5] Indeed, AD of 1,4-bis-*O*-protected (*E*)-2-butenediol **1** using AD-mix-β[6] directly yielded the protected D-threitol **2** in high chemical yield and enantiomeric purity (eq. 1).[7] On the other hand, AD of the corresponding (*Z*)-olefin **3** gave the protected erythritol **4** – perhaps not surprisingly – in practically racemic form (eq. 2),[7] exposing a weakness of the AD process in comparison with the AE process. While continuous efforts from the Sharpless group,[8] and others,[9] have made possible the AD of dissimilarly disubstituted cis olefins in up to 80% ee, a compound such as **3** would probably be an impossible substrate for AD since the two substituents are isosteric and the product diol is therefore pseudo-meso. Thus, an efficient method was sought to convert the *threo*-diol **2** to an *erythro*-diol compound, and a solution was found from the lessons learned from the epoxy alcohol chemistry.



1 2

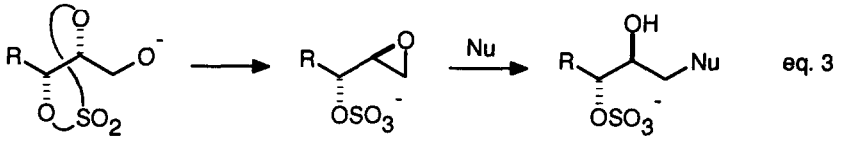
89% yield, >95% ee



3 4

94% yield, ca. 5% ee

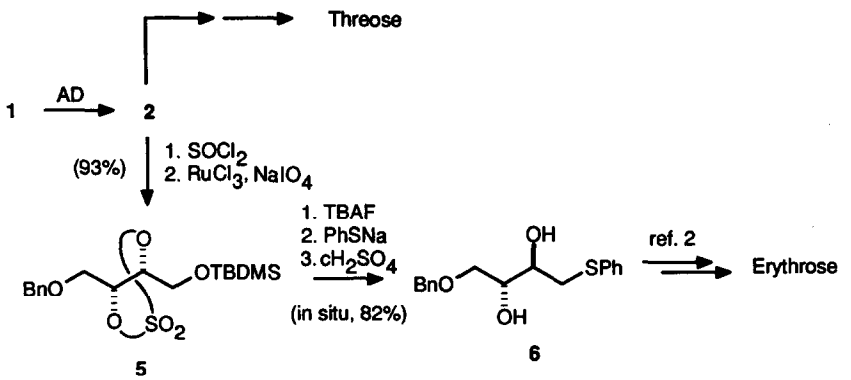
Vicinal diol cyclic sulfates have been said to be "like epoxides, only more reactive."[10] It was therefore envisaged that 2,3-cyclic sulfate-1-ols would undergo a Payne-type rearrangement, just like 2,3-epoxy-1-ols.[11] Unlike with epoxy alcohols, however, the rearrangement of 2,3-cyclic sulfate-1-ols would be irreversible, as the leaving group is a sulfate anion. A nucleophile added *after* the rearrangement is complete would open the epoxide cleanly at the terminal carbon (eq. 3).



Thus, the *threo*-diol **2** was converted to the cyclic sulfate **5** following a known procedure[10] (scheme I). Upon deprotection of the TBDMS group using F^-, the rearrangement took place *in situ*, as judged by TLC. Benzenethiolate nucleophile was then added, and the epoxide-opening product was hydrolyzed[12] to yield (2*R*,3*R*)-1-benzyloxy-4-phenylthio-2,3-butanediol **6** (82% yield from **5**).[13] The product **6** is an *erythro*-diol, the C-3 chirality center of the *threo*-diol **2** having been inverted during the Payne-type rearrangement. The phenylthio-diol compounds have been converted to carbohydrates *via* Pummerer rearrangement of the corresponding sulfoxides.[2]

Thus, the chemistry described above provides an access to both *threo*- and *erythro*-tetroses, starting from a single (*E*)-olefin and employing the asymmetric dihydroxylation reaction. It is also expected that this rearrangement-opening process will find use beyond carbohydrate synthesis and therefore broaden the synthetic utility of the AD reaction, as it compares very favorably with corresponding processes following an AE reaction.[11b] As alluded to earlier, the irreversible nature of this rearrangement makes the reaction easy to perform and highly regioselective. In addition, a wide variety of nucleophiles can be used as the reaction is run in aprotic solvent. The nucleophiles so far tried successfully in this process include ^-CN, $^-N_3$, ^-OAc, ^-I, and organometallic nucleophiles, all giving the respective *erythro*-diols in high yields. The scope of this process will be discussed shortly in a full account.

Scheme I



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3. There are other syntheses of tetroses employing AE as the key stereo-controlling step, but using different strategies from that of Masamune-Sharpless. See for example: (a) Yoshida, J.-I.; Maekawa, T.; Morita, Y.; Isoe, S. *J. Org. Chem.* **1992**, *57*, 1321. (b) Achmatowicz, B.; Raubo, P.; Wicha, J. *J. Org. Chem.* **1992**, *57*, 6593.
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5. Osmylation has been widely used for the stereoselective synthesis of (long-chain) polyhydroxylated compounds, often in enantiomerically pure forms even using achiral osmylating reagents. See for example: (a) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 2524. (b) Arjona, O.; Candilejo, A.; de Dios, A.; Fernández de la Pradilla, R.; Plumet, J. *J. Org. Chem.* **1992**, *57*, 6097. (c) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.

6. Purchased from Aldrich Chemical Co. For the composition of AD-mix-ß, see reference 4c.
7. (a) The enantiomeric purity of this compound was measured by first converting the diol product to the previously known 2,3-*O*-isopropyliden-1-ol (i. 2-methoxypropene, (±)-10-camphorsulfonic acid; ii. tetrabutylammonium fluoride) and comparing the optical rotation with the literature value (reference 2a). (b) The acetonide derived from **2**: $[\alpha]_D$ -8.15 (c 0.785, $CHCl_3$). Lit. $[\alpha]_D$ +7.8 for the enantiomer (92% ee). (c) The acetonide derived from **4**: $[\alpha]_D$ -0.19 (c 1,565, EtOH). Lit . $[\alpha]_D$ -3.7.
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13. Experimental procedure for the rearrangement-opening process: The cyclic sulfate **5** (0.47 g, 1.1 mmol) was dissolved in THF (10 mL) and tetrabutylammonium fluoride (trihydrate, 0.36 g, 1.15 mmol) was added. The mixture was stirred at rt under nitrogen. TLC taken after 15 min (SiO_2, Hexane-EtOAc 2:1) indicated a complete disappearance of the starting material and a presence of base-line material. After 30 min, a THF solution of PhSNa (prepared from PhSH [0.15 mL, 1.5 mmol] and NaH [60%, 36 mg, 1.5 mmol] in THF [5 mL]) was added *via* syringe. The mixture was stirred for 2 hr at rt. Concentrated sulfuric acid (0.055 ml, 2 mmol) was then added. Stirring for 30 min at rt was followed by an extractive work-up (EtOAc - $NaHCO_3$). The combined organic phases were dried (Na_2SO_4). The concentrated crude product was purified on a silica column (hexane - EtOAc 3:2) to yield the sulfide diol product **6** (0.27 g, 82% yield). mp. 108-109 °C (Lit. 107-108 °C). The IR and NMR spectra were identical to those previously reported in the literature (reference 2a). A small amount of the product **6** was peracetylated (Ac_2O-pyridine 1:2, 60°C, 1 hr) and the structure was confirmed by NMR spectroscopy.

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