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NOVEL APPROACH TO STEREOISOMERICALLY FULL SET OF OPTICALLY PURE 2,3-EPOXYESTERS FROM TARTARIC ACIDS

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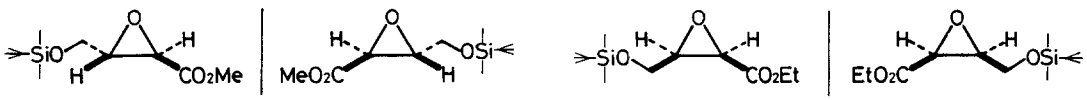
Abstract: Four possible stereoisomers of 4-(t-butyldimethylsilyloxy)-2,3-epoxybutanoic acid esters have been synthesized highly efficiently in both diastereomerically and enantiomericaly pure state from tartaric acids.

It is not too much to say that chiral epoxy functionality is one of the most potent frameworks in organic synthesis as a precursor for two contiguous stereochemically defined asymmetric centers because of its proneness to open the ring with both carbon and heteroatom nucleophiles under highly wide range of reaction conditions.[1] In this context, heavy emphasis is being placed on the importance of Sharpless method for asymmetric epoxidation[2] which can provide 2,3-epoxyalcohol with high enantiomeric homogeneity in every possible diastereomeric constitution, even if some limitations still remain therein.[3] Optically active 2,3-epoxyesters, which are currently required for our research projects, are also within our reach relying on such method[2] and subsequent oxidation of alcohol moiety.[4] However, we are now able to disclose herein extremely facile protocol for the synthesis of such compounds (1 and 2) including their antipodes in optically pure form from natural and unnatural tartaric acid diesters itself which are irreplaceable for the Sharpless method[2] as chiral auxiliary.[5]

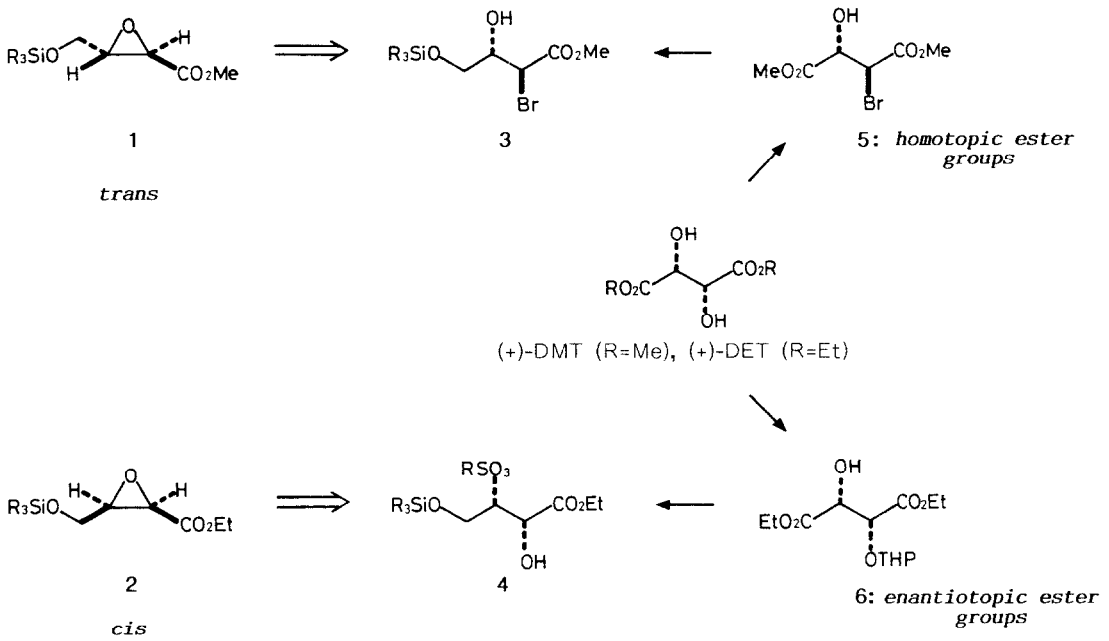


1 antipode of 1 2 antipode of 2

trans *cis*

As recognized from Scheme 1, during the route to 1, double chirality conversions at either of the internal carbons of (+)-DMT must be executed, while that to 2 should involve single inversion process. Thus, immediate precursors for the *trans*-epoxide 1 and *cis*-epoxide 2 were set as bromohydrin (3) and hydroxysulfonate (4), respectively. Another requisite pathway commonly involved in both routes should be a transformation by which only one of the ester groups of (+)-DMT or (+)-DET can be reduced into hydroxymethyl group. Especially noting in this context is that the route to 1 requires a reduction of either of the ester groups of bromohydrin succinate diester (5), while the route to 2 should achieve highly selective or exclusive, if possible, reduction of the ester group α to the hydroxyl group of (+)-DET-mono-THP ether (6) because the ester groups of 5 are *"homotopic"* in nature and, in contrast to it, those of 6 are essentially *"enantiotopic"* as far as the internal C(2) and C(3) functionalities in 5 and 6 serve as latent *trans*- and *cis*-epoxides, respectively. Realization of these requirements are described below.

Scheme 1



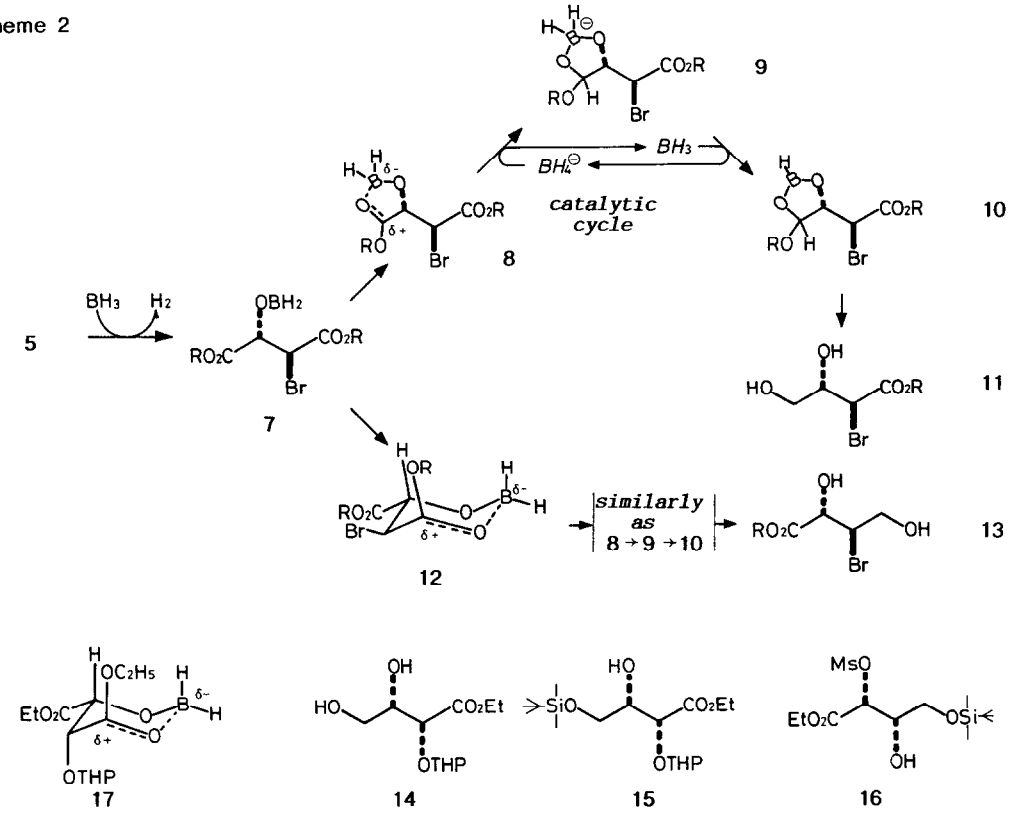
The bromohydrin 5 required for the synthesis of 1 was prepared in molar-scale according to K. Mori's directions with slight modification,[6] being provided as shelf-storable fine needles: mp 41-41.5 °C; $[\alpha]_D^{26}$ -46.6° (c 1.57, CH_2Cl_2). As has already been discussed (vide supra), the next thing to be achieved is a reduction of either of the ester groups of 5. This challenging task has been answered expeditiously by our previous method for selective reduction of α-hydroxy ester which was amazingly successful in the case of (*S*)-malic acid diester.[7] Thus, treatment of 5 with borane-dimethylsulfide complex [1 mole eq/THF/rt, 2 h] effected the formation of oxyborane intermediate (7) (Scheme 2) and, then, with catalytic amount of $NaBH_4$ (5 mole%) for additional 2 h, 7 led to a mixture of methyl *(2S,3S)*-2-bromo-3,4-dihydroxybutanoate (11) and methyl *(2R,3R)*-3-bromo-2,4-dihydroxybutanoate (13) in the ratio 4 : 1,[8] which, without purification,[9] was reacted with t-butyldimethylchlorosilane [1 eq/THF/imidazole/0°C→rt, 20 min]. After aqueous workup and purification by SiO_2 chromatography, a mixture of the corresponding TBDMS-ethers (3 + 13-OSi(t-Bu)Me_2) was obtained in 76% yield, which, on exposure to base [MeONa (1.1 eq)/MeOH/0°C→rt, 2 h], ended up with the formation of epoxide, converging to the single isomer, methyl *(2R,3S)*-4-(t-butyldimethylsilyloxy)-2,3-epoxybutanoate 1 in 95% yield (SiO_2 chromatography and distillation): by 90-91°C/0.7 Torr; $[\alpha]_D^{20}$ -24.7° (c 6.95, $CHCl_3$) and -39.7° (c 4.39, Et_2O); its ^{1}H-NMR, ^{13}C-NMR, TLC, and glass-capillary GLC (30 m) gave no sign of diastereoisomer at all.[10] This also implies that, when we take account of the given reaction conditions for a series of transformations and of an enantiomeric purity of 5, 1 should have been derived keeping the enantiomeric homogeneity of 5.

Mono-protected (+)-DET as THP-ether seems appropriate for the synthesis of *cis*-epoxide 2 for some reasons.[11] Thus, mono-*O*-THP-(+)-DET (6) was submitted to the reaction conditions for selective reduction of α-hydroxy ester [BH_3·SMe_2(1.05 eq)/THF/rt, 2h and, then, $NaBH_4$(5 mole%)/rt, 2h] to give diol (14) almost exclusively, which was reacted with TBDMS-Cl [1 eq/THF/imidazole/rt, 0.5 h], leading to the corresponding primary silyl ether (15) in 71% yield after SiO_2 chromatography. The

secondary hydroxyl group in **15** was sulfonylated in the usual manner [MsCl/Et_3N/Et_2O/0°C, 2 h] to afford mesylate in 95% yield and, then, the THP-group was splitted off selectively according to the Shibasaki's procedure,[12] giving rise to α-hydroxy-β-mesyloxyester (**4**) in 94% yield after SiO_2 chromatography: α-mesyloxy-β-hydroxyester (**16**), which is destined to lead to the antipode of **2**, was also separated on this chromatography only in small amount (**4** : **16** = 40 : 1). Thus, we had an immediate precursor of **2** in hand, which must be enantiomericaly homogeneous and was subjected to final endeavour to realize epoxidation that competes necessarily with E2-type elimination pathway. At the present time, EtONa in ethanol gave acceptable result to provide **2** in 43% yield after SiO_2 chromatography and distillation: $[\alpha]_D^{27}$ -10.1° (c 8.86, $CHCl_3$) and -14.4° (c 7.19, Et_2O); several diagnoses of diastereomeric contamination, which were executed in the case of **1**, turned out to leave no problem at all.[13]

The site-selectivity observed in the reduction of **5** or **6** can be given a mechanistic rationale on the basis of kinetically controlled formation of boron-coordinated 5- and 6-membered intermediates (**8** and **12**) to which transfer of hydride (H^-) from added BH_4^- occurs rather quickly to furnish dihydrodioxyborate species (**9**). While the BH_4^- is to be shifted to BH_3 through such crucial reaction, **9** is capable of transferring H^- to thus-generated BH_3, reviving BH_4^- to perform catalytic cycle as shown in Scheme 2. In 6-membered intermediates such as **12** and **17**, there exists destabilizing 1,3-diaxial interaction. In **12**, however, stabilizing dipole-dipole interaction between C-Br and C=O bonds seems to be operating, while, in the case of **17**, such is to be small owing to a dihedral angle (60°) between the THPO-C-C and C-C=O planes. Thus, the site-selectivity has been upgraded to 40 : 1 in the reduction of **6** as compared with **5** (4 : 1).

Scheme 2



The present method for the synthesis of optically pure *trans*- and *cis*-4-(t-butyldimethylsilyloxy)-2,3-epoxybutanoic acid esters is of great synthetic utility because it offers extremely simple routes to highly potent C_4 chiral building blocks ready for further elaborations directed to complex molecules. Synthetic efforts using 1 or 2 including their antipodes[14] are currently our major concern.

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References and Notes

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5) a) J. G. Hill, K. B. Sharpless, C. M. Exon, and R. Regenye, Org. Synth., **63**, 66 (1984); b) R. M. Hanson and K. B. Sharpless, J. Org. Chem., **51**, 1922 (1986).

6) K. Mori and H. Iwasawa, Tetrahedron, **36**, 87 (1980); we used (+)-DMT instead of (+)-DET, employing AcCl/MeOH in place of HBr/EtOH for transesterification pathway.

7) S. Saito, T. Hasegawa, M. Inaba, R. Nishida, T. Fujii, S. Nomizu, and T. Moriwake, Chem. Lett., 1389 (1984).

8) Determined by GLC analysis for acetonide derivatives prepared by treating a mixture of 11 and 13 with acetone-2,2-dimethoxypropane-TsOH system at rt for 12 h.

9) After quenching the reaction with MeOH, thus-generated $B(OMe)_3$ and excess MeOH must be eliminated as thoroughly as possible by azeotropic distillation with benzene under reduced pressure. Otherwise the yield of succeeding reaction (silyl protection) took a big drop.

10) ^{1}H-NMR (100 MHz, $CDCl_3$) δ 0.07 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $C(CH_3)_3$), 3.31-3.36 (1H, m, C(3)-H), 3.45 (1H, d, J=1.95 Hz, C(2)-H), 3.70-4.00 (2H, m, OCH_3); ^{13}C-NMR (25 MHz, $CDCl_3$) δ -5.4 ($Si-(CH_3)_2$), 18.27 ($\underline{C}$-Me_3), 25.78 ($C(\underline{C}H_3)_3$), 49.95 (C(2)), 52.34 (OCH_3), 58.19 (C(3)), 61.21 (OCH_2), 169.46 (C=O).

11) One of ideas to force the reduction into proceeding via 5-membered intermediate like 8 may be to make 1,3-diaxial interactions in 17 larger (see Scheme 2). Steric bulkiness of ester alkoxyl group may play an important role in this connection, which will be discussed elsewhere.

12) Y. Ogawa and M. Shibasaki, Tetrahedron Lett., **25**, 663 (1984).

13) ^{1}H-NMR (100 MHz, $CDCl_3$) δ 0.07 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$), 0.89 (9H, s, $C(CH_3)_3$), 1.30 (3H, t, J=7.2 Hz, $CH_2C\underline{H}_3$), 3.26-3.42 (1H, m, C(3)H), 3.70 (1H, d, J=4.6 Hz, C(2)H), 3.73 (1H, dd, J=4.9 and 11.7 Hz, C(4)H), 3.95 (1H, dd, J=5.6 and 11.7 Hz, C(4)H), 4.10-4.37 (2H, m, $OC\underline{H}_2Me$); ^{13}C-NMR (25 MHz, $CDCl_3$) δ -5.45 ($SiCH_3$), -5.26 ($SiCH_3$), 14.18 ($CH_2\underline{C}H_3$), 18.27 ($\underline{C}Me_3$), 25.83 ($C(CH_3)_3$), 51.85 (C(2)), 57.31 (C(3)), 60.58 ($SiOCH_2$), 61.50 ($O\underline{C}H_2CH_3$), 167.80 (C=O).

14) $[\alpha]_D^{27}$ +24.7° (c 5.33, $CHCl_3$) and +38.1° (c 6.03, Et_2O) for the antipode of 1; $[\alpha]_D^{27}$ +9.90° (c 2.27, $CHCl_3$) and +14.39° (c 4.45, Et_2O) for the antipode of 2.

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