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Preparation of a New Chiral Building Block for Synthesizing Broadly Varied Types of Tertiary Alcohols

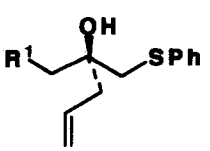
Toshiyuki ITOH,[a*] Hiroyuki OHARA,[a] Yumiko TAKAGI,[a*]
Naoki KANDA,[a] and Kenji UNEYAMA[b]

a) Department of Chemistry, Faculty of Education,
Okayama University, Okayama 700, Japan
b) Department of Applied Chemistry, Faculty of Engineering
Okayama University, Okayama 700, Japan

Abstract: Preparation of chiral phenyl glycidyl sulfide **1**, which is a useful chiral building block for tertiary alcohol derivatives, is achieved *via* lipase-catalyzed reaction as a key step.

Optically active tertiary alcohol derivatives are widespread in physiologically important compounds. Therefore, these compounds have been the challenging targets for asymmetric synthesis. Effort to construct a chiral tertiary hydroxyl moiety has focused on finding a way to introduce an alkyl group to a chiral ketone with high diastereoselectivity.[1] Another reasonable way would be for the synthesis to start from a chiral building block that possesses tertiary hydroxyl group with a certain chirality.[2] To obtain both enantiomers of tertiary alcohols, we noted the optically pure phenyl glycidyl sulfide (**1**). Because the subsequent reaction with a variety of nucleophiles gives optically pure β-hydroxy sulfide **2**, which can be transformed again into new optically active epoxide with retention of the chiral center.[3] Further, the subsequent nucleophilic ring-opening of the newly formed epoxide can lead to a wide variety of optically active tertiary alcohols. It is therefore expected that both enantiomeric forms of a tertiary alcohol **3** might be obtained by the exchange of the order of two nucleophilic ring-opening reactions of the optically active phenyl glycidyl sulfide **1**. We describe here an enantioselective synthesis of the optically active **1**.

1



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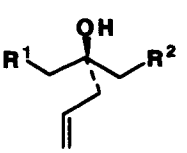

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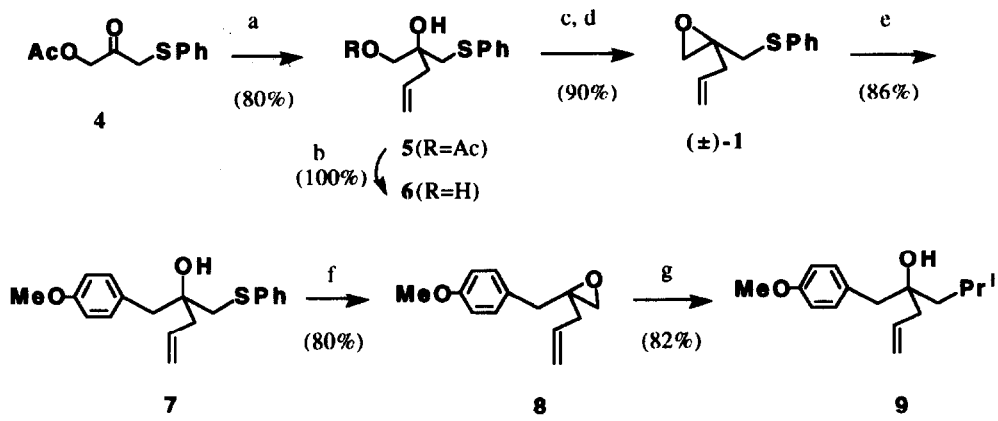
Scheme 1



(a) allylbromide, $SnCl_2$-Al, THF-H_2O=1:1, RT; (b) LiOH, THF-H_2O=3:1, RT;
(c)TsCl, py, CH_2Cl_2, RT; (d) NaOH-MeOH, -10°C; (e) 4'-$MeOC_6H_4MgBr$, 20 mol% CuI,
THF - Me_2S = 20:1, -15°C; (f) Et_3OBF_4, CH_2Cl_2 then NaOH, 0°C;
(g) i-PrMgBr, 20 mol% CuI, HF - Me_2S = 20:1, -30°C.

Initially we attempt to confirm the usefulness of **1** as a chiral synthon for tertiary alcohols. Racemic epoxide **1** was prepared from 1-acetoxy-3-phenylthio-2-propanone **4**[3] through the four steps shown in Scheme 1. Nucleophilic ring-opening of (±)-**1** with 4'-methoxyphenyl magnesium bromide in the presence of 20 mol% of CuI(I) at -15°C in a THF-Me_2S mixed solvent afforded β-hydroxy sulfide **7** in 86% yield. Treatment of **7** with Meerwein reagent followed by 2M-NaOH aqueous solution provided the epoxide **8** in 80% yield.[3] Grignard reaction of **8** with isopropyl magnesium bromide gave tertiary alcohol **9** in 82% yield (Scheme I). It is believed that no racemization occur during these reaction sequences. Since glycidyl sulfide **1** possesses allyl group, this compound is useful for the synthesis of tetrahydrofuran derivatives.[4]

The synthetic strategy of this optically active epoxide is based on the use of a lipase-catalyzed reaction. The enzymatic reaction is well recognized as an excellent and easy procedure for preparation of enantiomerically pure products.[5] Ease of the reaction is a very desirable feature of the synthesis especially for a building block. Since enzymatic resolution of a racemic ester is a well-established procedure,[5a] we initially tried to resolve racemic acetate **5** by lipase-catalyzed hydrolysis. Unfortunately, we were enable to find an enzyme that hydrolyzed the acetate with enantioselectivity. Our final preparation of the optically active glycidyl sulfide **1** is shown in Scheme 2. The starting material of our synthesis was optically active glycidol monoacetate (R)-**13** which was obtained through a lipase-catalyzed reaction according to Seu et al.[6]

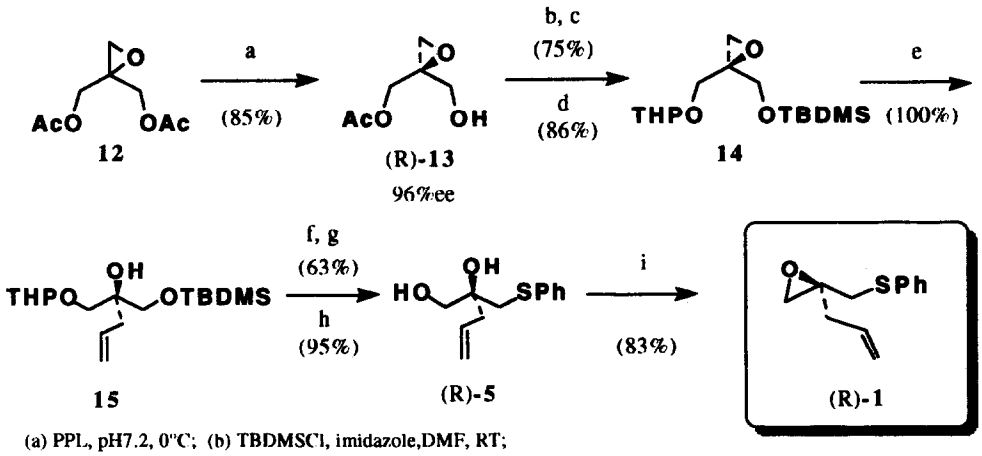
The prochiral diacetate **12** was treated with porcine pancreatic lipase (PPL, Sigma type II) to afford the monoacetate (R)-**13**, $[\alpha]^{23}_D$ -4.3°(c1.2, Et_2O), 96%ee, in 85% yield. (R)-**13** was converted to t-butyldimethylsilyl ether, then hydrolyzed with the acetoxy group. Hydoroxyl group of the resulting glucidol was protected as tetrahydropyranyl ether (THP) to afford epoxide **14**. Ring-opening reaction of **14** with vinyl magnesium bromide in the presence of 20 mol% of CuI gave **15** in quantitative yield. After deprotection of the

t-butyldimethylsilyl group, **15** was converted to β-hydroxy sulfide (R)-**5** in 63% yield using a two-step procedure involving substitution reaction by diphenyldisulfide followed by deprotection of the tetrahydropyranyl group. (R)-**5** was monotosylated and treated with methanolic sodium hydroxide to furnish optically active glycidyl sulfide (R)-**1**, $[\alpha]^{21}_D$ +6.0°(c0.77, $CHCl_3$), in 83% yield. The enantiomeric excess of **1** was confirmed as 86%ee by capillary GPC analysis (Chiraldex G-TA, ϕ 0.25mm × 20m, 100°C, He). Therefore, %ee of the starting (R)-**13** was slightly diminished during the reaction sequence, though it has not yet been determined of which reaction caused this loss of optical purity.

We succeeded the preparation of a new chiral building block, (R)-**1**, with high enantiomeric excess from the glycidol monoacetate (R)-**13**, which itself was easily obtained through an enzymatic reaction from the corresponding prochiral diacetate.

The applicability of **1** is now obvious as demonstrated in scheme 1, and it is believed that this optically active chiral building block **1** can become a useful precursor of optically active tertiary alcohols. Further research is being done on refining the synthetic path to achieve an optically pure **1**.

Scheme 2



(a) PPL, pH7.2, 0°C; (b) TBDMSCl, imidazole,DMF, RT;
(c) LiOH, THF-H_2O, RT; (d) DHP, PPTS, RT;
(e) Vinyl MgBr,10 mol% CuI, THF-Me_2S (20:1), - 15°C; (f) TBAF, THF, RT;
(g) PhSSPh (5eq.), Bu_3P, py; (h) p-TsOH.H_2O, MeOH, RT;
(i) TsCl, py, CH_2Cl_2, RT. then NaOH-MeOH, -10°C.

$[\alpha]^{21}_D$ +6.0°
(c0.77, $CHCl_3$)
86%ee

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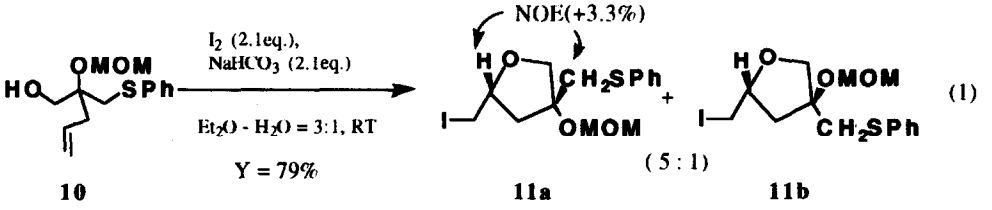
4. An example of the synthetic application is shown in equation 1. Diol **10** was treated with iodine in an ether-H_2O (3:1) mixed solvent in the presence of $NaHCO_3$ to provide **11** in 79% yield. The *cis*:*trans* ratio was determined by ^1H NMR analysis as 5:1 and the stereochemistry was confirmed by NOE experiment after separation of each isomer by silica gel TLC. NMR experiments were performed at the SC-NMR Laboratory of Okayama University.



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6. Seu, Y-B.; Kho, Y-H. *Tetrahedron Lett.*, **1992**, *33*, 7015. The reported %ee of (R)-**13**, $[\alpha]^{22}_D$ -4.0°(c1.0, Et_2O), was 92%ee.

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