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Asymmetric Synthesis Using C_2-Symmetric Diols: Use of (5*R*,6*R*)-3-Acetoxy-5,6-diphenyl-1,4-dioxan-2-one as a Chiral Synthetic Equivalent of 1,2-Ethanediol 1,2-Dicarbocation†

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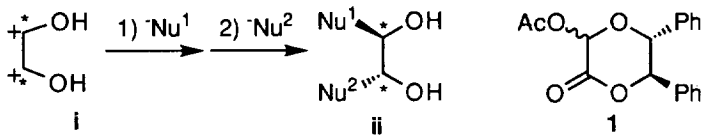
Abstract: A new route to chiral diol systems has been developed based on double nucleophilic addition to the cationic ions fixed on a 6-membered ring system using chiral hydrobenzoin as an auxiliary.

The development of the stereoselective synthesis of chiral 1,2-disubstituted 1,2-diols is a very important subject in the organic synthetic area and many methodologies have been devised so far. Most of them consist of the diastereoselective addition to the carbonyl functionality bearing a chiral alkoxy group next to it.[1] Recently the asymmetric dihydroxylation of olefins has been rapidly developing.[2]

We present here a new approach to the chiral 1,2-diol systems. The concept is illustrated in Scheme 1. Thus, stereoselective double nucleophilic addition to the chiral 1,2-ethanediol 1,2-dicarbocation **i** would afford the chiral 1,2-diols **ii**. To realize this idea, we studied the reaction using acetoxydiphenyldioxanone **1** as a synthetic equivalent of **i** and succeeded in developing a new reaction path to the chiral 1,2-diols.



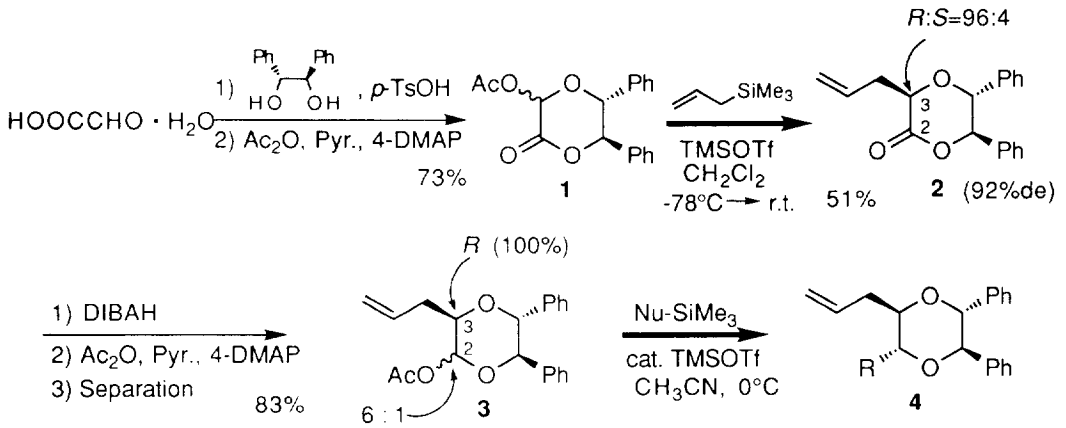
i ii 1

Scheme 1

Compound **1** was prepared from chiral hydrobenzoin and glyoxalic acid in two steps, condensation (1.5 eq. of glyoxalic acid/1 eq. of chiral hydrobenzoin/cat. *p*-TsOH/Bz./reflux) and acetylation (Ac_2O/Pyr./cat. 4-DMAP), as a 6 to 1 diastereomixture of the acetoxy group in 73% yield. Initially, racemic hydrobenzoin was used to study the stereoselectivities of the reactions.[3] The first nucleophilic additions to **1** were studied using allyltrimethylsilane under various reaction conditions (Lewis acid: TMSOTf, BF_3•Et_2O, $SnCl_4$; solvent: CH_2Cl_2, $ClCH_2CH_2Cl$, CH_3CN). The best stereoselectivity was attained using $Me_3SiOSO_2CF_3$ (TMSOTf) (1 eq.) as a Lewis acid in CH_2Cl_2 and the desired product was obtained in 92% de. Although introduction of other nucleophiles is still under investigation, highly diastereoselective allylation was attained for **1**. The second nucleophilic addition was then studied. The precursor **3** of the cationic species was prepared as a 6 to 1 mixture of acetate by reduction of **2** with DIBAH followed by acetylation. During this stage, minor 3*S*-isomer of **3** was removed by a simple SiO_2 column chromatography separation (hexane/AcOEt=8/1) and 3*R*-one **3** was obtained in a pure state. Nucleophilic addition of allyltrimethylsilane to **3** was carried out in the presence of a cat. amount of TMSOTf at 0°C (Scheme 2). As shown in the Table, use of CH_2Cl_2 as a reaction solvent resulted in fruitless (entry 2), but the reaction proceeded in an extremely highly stereoselective manner (≧99% de) to giv **4a** in

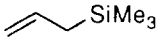
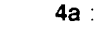
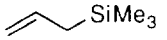
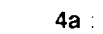
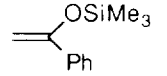
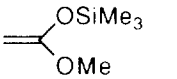
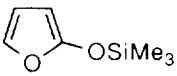
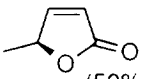
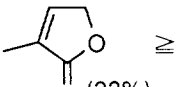
† This paper is dedicated to Professor Dr. Richard Neidlein on the occasion of his 65th birthday.

good yield using CH_3CN as the solvent (entry 1). Other silicon-containing nucleophiles (silyl enol ether, silyl ketene acetal) similarly reacted with **3** in a highly diastereoselective manner. The use of 2-(trimethylsiloxy)furan as a nucleophile gave two products; **4d** (52%) was obtained by the reaction at the C-5 position of the furan ring and **4e** (22%) was obtained by the reaction at the C-3 position of the furan ring and successive isomerization,[4] in highly stereoselective manners (≧99% de), respectively (entries 3-5).



Scheme 2

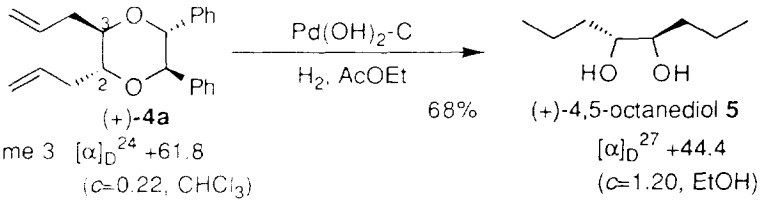
Table. Nucleophilic Addition to Dioxane Acetate **3**

Entry	Nu-$SiMe_3$	Products (Yield)	De(%)[b]
1		**4a** : R=  (89%)	≧99
2[a]		**4a** : R=  (20%)	≧99
3		**4b** : R=CH_2COPh (70%)	≧99
4		**4c** : R=CH_2CO_2Me (80%)	≧99
5		**4d** : R=  (52%), **4e** : R=  (22%)	≧99[c]

a) The reaction was carried out in CH_2Cl_2. b) Determined by ^1H NMR.
c) De of **4d** and **4e** were ≧99%, respectively.

The stereochemistries of the products were determined as follows. Hydrogenation of the diallyl compound **4a**, prepared from optically active **1** derived from (*R*, *R*)-(+)-hydrobenzoin, with $Pd(OH)_2$-C in AcOEt under medium pressure afforded (+)-4,5-octanediol **5**. Comparison of its specific rotation {$[\alpha]_D^{27}$ +44.4 (*c*=1.20, EtOH)} with the value of (+)-4,5-octanediol {$[\alpha]_D^{20}$ +43.1 (*c*=1.10, EtOH)}, prepared by the reaction of *trans*-4-octene and AD-mix-β which is supposed to give (*R*,*R*)-diol,[5] suggested that **4** has a 2*R*,3*R* configuration (Scheme 3). The stereochemistry of the first introduced allyl group (3*R* configuration) was

unequivocally confirmed by an X-ray analysis of the major product **4d** in entry 5. Thus, the X-ray analysis of **4d** proved the 3*R*-configuration and the *trans* relationship between the C-2 and C-3 substituents including the *R*-configuration of the butenolide unit (Fig.1).[6] The stereochemistries of the products in entries 3 and 4 were tentatively assigned from mechanistic analogy.

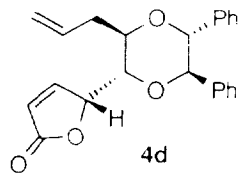


(+)-**4a**

Scheme 3 $[\alpha]_D^{24}$ +61.8 (*c*=0.22, $CHCl_3$)

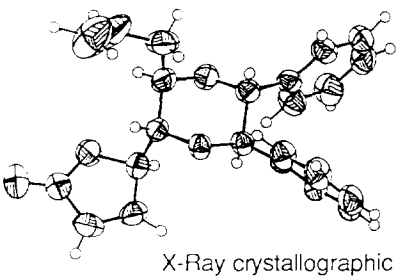
(+)-4,5-octanediol **5**

$[\alpha]_D^{27}$ +44.4 (*c*=1.20, EtOH)



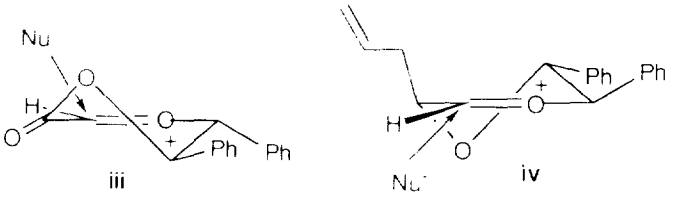
4d

Fig. 1



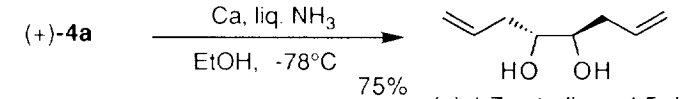
X-Ray crystallographic structure of **4d**

These results point out that the first introduction of an allylic unit occurred from the *re*-face of the oxonium ion intermediate **iii** formed from **1** and the second nucleophiles were introduced from *re*-face of the oxonium ion intermediate **iv** formed from **3**. These stereoselections could be rationalized as follows. Both intermediates **iii** and **iv** would exist as the conformers depicted in Scheme 4, where two bulky phenyl groups occupy pseudo-equatorial positions, and the nucleophilic addition would proceed from the *re*-face in a highly stereoselective manner for a stereoelectronic effect on the intermediate **iii**, then the second attack would proceed in an extremely high stereoselection from the *re*-face for steric repulsion of the next allylic group in addition to the stereoelectronic effect on intermediate **iv** (Scheme 4).[7]



Scheme 4

Advantages of our method are i) the protection of the diol unit of the formed products with 1,2-diphenylethylene group which promises further transformation of compounds **4** much easier and reproduction of diols at proper stage and ii) the availability of several cleaving methods for the benzyl ether derivatives.[8] Indeed Birch reduction of (+)-**4a** with Ca metal afforded a diol (+)-**6** with intact olefinic functions (Scheme 5).



Scheme 5

(+)-1,7-octadiene-4,5-diol (+)-**6**
$[\alpha]_D^{22}$ +42.4(*c*=0.83, EtOH)

In conclusion, the methodlogy described here is an unprecedented approach to chiral 1,2-disubstituted 1,2-diol systems based on double stereoselective nucleophilic addition to the cationic ions fixed on a 6-membered ring system using chiral hydrobenzoin as an auxiliary. Since both enantiomers of chiral hydrobenzoin are available,[9] our method allows one to synthesize optically active *vic*-diols in both enantiomeric forms.

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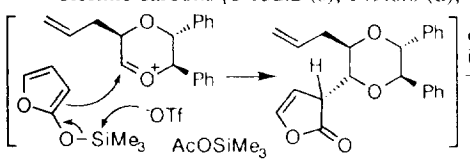
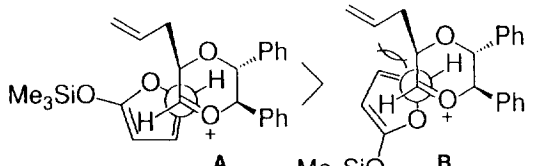
References and Notes

1. Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828; Cram, D. J.; Kopecky, K. R.; *J. Am. Chem. Soc.* **1959**, *81*, 2748; Still, W. C.; McDonard III, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031; Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.
2. For recent reviews, see: Lohray, B. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1317; Johnson, R. A.; Sharpless, K. B.Catalytic Asymmetric Dihydroxylation. In *Catalytic Asymmetrc Synthesis*; Ojima, I., Ed; VCH: Weinheim, Germany, 1993; pp 227-272. For recent examples, see: Lohray, B. B.; Nandanan, E.; Bhushan, V. *Tetrahedron Lett.* **1994**, *35*, 6559; Corey, E. J.; Noe, M. C.; Grogan, M. J. *Tetrahedron Lett.* **1994**, *35*, 6427; Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278; Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sancéau, J-Y.; Bennani, Y. *J. Org. Chem.* **1993**, *58*, 1991 and references cited therein.
3. Single stereoisomer, (5*R*,6*R*)-one, was depicted for easy understanding of the stereochemistry of the each reaction.
4. The formation of **4e** is rationalized as shown below. ^{13}C NMR of **4e** indicates the presence of four olefinic carbons [δ 132.2 (s), 149.6.0 (d), 134.0 (d), 118.4 (t)] except aromatic ones.



IR ν max(KBr) : 1755cm^{-1}.
^{1}H-NMR (270 MHz, $CDCl_3$) :
4.36(1H, dt, *J*=7.3, 1.3Hz, H-3),
4.70(1H, dd, *J*=1.3Hz, H-2),
4.97(2H, s, H-4'),
7.86(1H, d, *J*=1.3Hz, H-3').

5. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K-S.; Kwong, H-L.; Morikawa, K.; Wang, Z-M.; Xu, D.; Zhang, X-L. *J. Org. Chem.* **1992**, *57*, 2768.
6. Although stereochemical course of the reaction have not been ascertained, the stereoselective formation of the *R*-configuration of the butenolide unit of **4d** might be rationalized as follows. That is, transition state **A** leading to the *R*-isomer is more favorable than transition state **B** leading to *S*-isomer because of the steric factor. (*cf.* Jefford, C. W.; Jaggi, D.; Bernardinelli, G.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4041.)



7. *cf.* Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.
8. Greene, T. W.; Wuts, P. G. M."Protective Groups in Organic Synthesis, Second Eddition", John Wiley and Sons, New York, 1991.
9. Chiral hydrobenzoin is readily available in both enantiomeric forms by asymmetric synthesis (ref. 5) or resolution; for resolution of *dl*-hydrobenzoin, see "Optical Resolution Procedures for Chemical Compounds" ed by P. Mewman, Optical Information Center, Manhattan College, Riverdale, New York 10471, Vol. 3, 1984, pp 353.

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