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Remote Asymmetric Induction for Chiral 1,4-Diols Using a Chiral Acetal Derived from Chiral Hydrobenzoin

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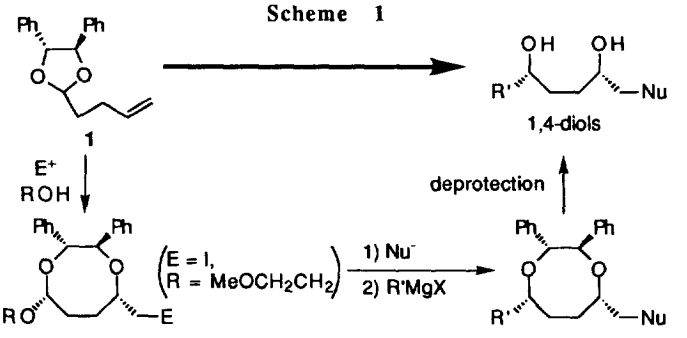
Abstract: A new route to chiral 1,4-diols has been developed in a 4 step sequence from the ene acetal, prepared from 4-pentenal and chiral hydrobenzoin, involving a remote asymmetric induction as a key step.

The development of new methodology for asymmetric synthesis is a challenging target in organic chemistry, and extensive studies have been reported so far. However, methods for reactions where the stereochemistry is controlled from a remote position are somewhat limited, the importance of these reactions notwithstanding.[1] As a part of our study on asymmtric synthesis using chiral C_2-symmetric acetals,[2] we now present an unprecedented example of remote double asymmetric induction leading to the stereoselective synthesis of optically active 1,4-diols.

The overall transformation is shown in Scheme 1. In the first step, an 8-membered acetal having two new chiral centers is produced in a highly stereoselective manner by halo-ether reaction to the double bond in the presence of alcohol. Then, after substitution of iodide by nucleophile the alkoxy group is diastereoselectively converted to an alkyl group by Grignard substitution. Finally, the deprotection of the diphenyl ethylene unit gives chiral 1,4-diols. The first step is a remote asymmetric induction reaction whereby two new chiral centers are constructed in a one-pot operation and the final 1,4-diol has two chiral centers remote from each other. The asymmetric synthesis developed here using C_2-symmetric acetals is recognized as an unprecedented method as it involves two types of reactions: 1) asymmetric induction on a neighboring prochiral center, and 2) an asymmetric reaction involving cleavage of the C-O bond of the acetal, which functions as the chiral synthetic equivalent of a carbonyl group. Although asymmetric synthesis using chiral acetals derived from C_2-symmetric diols has previously been studied, the reported methods invariably involve only one of the reaction modes described above.[3]

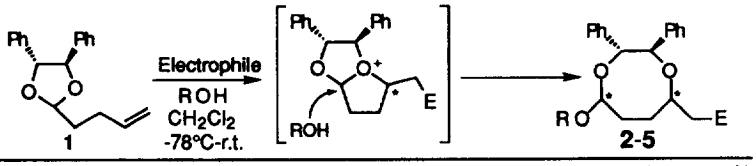
Scheme 1



We reacted the ene acetal **1**, prepared from 4-pentenal and chiral hydrobenzoin,[4] with the electrophiles NBS and $I(coll)_2ClO_4$[5] in the presence of ROH. The reaction gave the 8-membered acetals (**2-5**) as 4 inseparable stereoisomers via the bicyclic oxonium ion intermediate.[6,7] The results are shown in Table 1. In the case where $I(coll)_2ClO_4$ was used, the reaction proceeded in good yield with high stereoselectivity (entries 2-4).

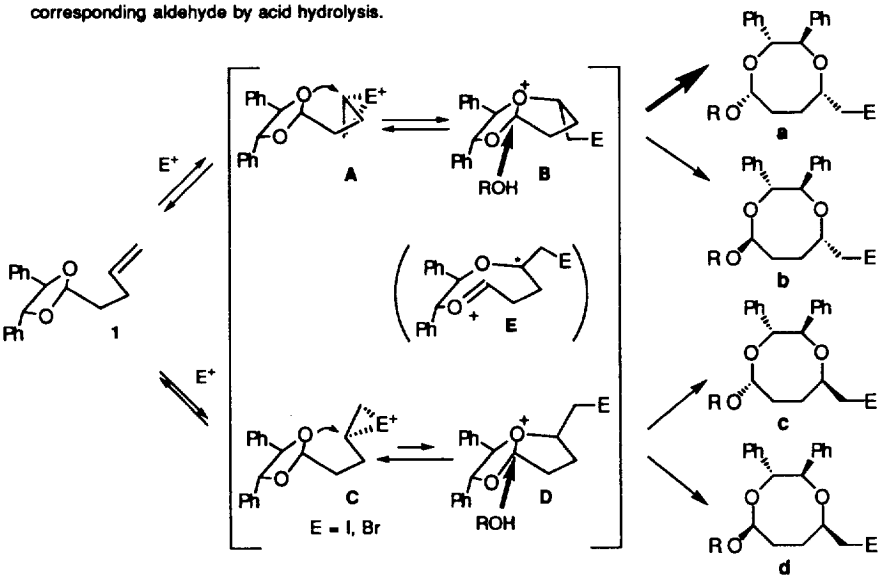
The optimal conditions were found to be the addition of $I(coll)_2ClO_4$ (1.5eq.) to a 0.1 mol CH_2Cl_2 solution of the ene acetal **1** (1eq.) and alcohol (5eq.) at -78°C, then warming to room temperature over 12h.

Table 1. The reaction of 1 with electrophile in the presence of alcohol



Entry	Electrophile	R	Product	Yield	Selectivity[a] (a:b:c:d)[b]
1	NBS	Me	2 (E=Br)	95%	74:8:18:0
2	$I(coll)_2ClO_4$	〃	3 (E=I)	86%	85:3:12:0
3	〃	Bn	4 (E=I)	74%	90:10[c]
4	〃	$MeOCH_2CH_2$	5 (E=I)	90%	86:2:11:1

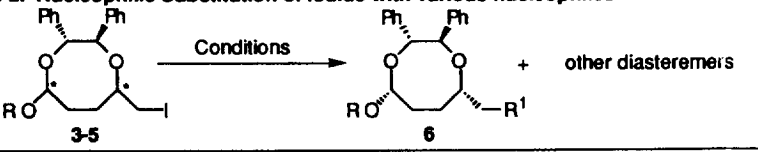
a) Determined by ^1H NMR studies and HPLC analysis. b) For **a**, **b**, **c**, and **d**, see the Scheme shown below. c) The ratio of **a**+**b**:**c**+**d**, determined by converting the product to the corresponding aldehyde by acid hydrolysis.



The relative stereochemistries of the major products (**a**) were determined by ^1H NMR, NOE, and by converting **5** to a known compound.[8] The relative stereochemistries of the other products (**b**, **c**, **d**) were tentatively assigned by assuming the reaction mechanism as shown in the lower part of Table 1. Thus, the addition of the halo cation to the double bond followed by attack of one of the acetal oxygen atoms on the halonium ion **A** or **C** forms the bicyclic oxonium ion intermediate **B** or **D**. Subsequent SN2-type displacement of the oxonium ion oxygen of **B** and **D** and/or the attack of an alcohol to the 8-membered ion intermediate **E** derived from **B** or **D** would occur to give the 8-membered acetal (**a**>**b**, **c**>**d**).[7] In view of the fact that this reaction gives rise exclusively to 8-membered acetal **a** as a product, we think that transition state **B** should be more favorable than **D** (**a**+**b**>**c**+**d**).[9]

The substitution of iodide in compounds **3**, **4**, and **5** with various nucleophiles was successful using known procedures. The results are summarized in Table 2. From the products containing 4 diastereoisomers the major diastereomer **6** was isolated in a pure state by simple SiO_2 column chromatography (entries 3-5). We next studied the nucleophilic replacement of the alkoxy group of **6a-c** with carbon nucleophiles. When a methoxyethoxy group was used as an alkoxy group (RO), Grignard reagents reacted at the acetal carbon and substitution occurred in good yield and with complete retention of the stereochemistry (Scheme 2),[10] whereas with other alkoxy groups the results were disappointing (with MeMgI; **6a**, 43%; **6b**, 0%). The stereochemistries of compounds **7a-d** were determined by X-ray crystallography of the *p*-bromobenzoate derivative **8** derived from **7d** by hydroboration-oxidation followed by *p*-bromobenzoylation. The reason for the good yield and complete retention can be attributed to the formation of complex A. In the case of the Lewis acidic conditions ($TiCl_4$/allyltrimethylsilane/CH_2Cl_2/-78°C) usually used in the cleavege of acetals, the reaction gave complex mixtures.

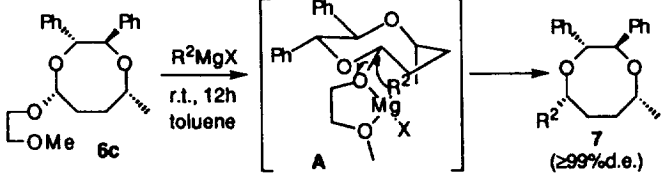
Table 2. Nucleophilic Substitution of Iodide with various nucleophiles

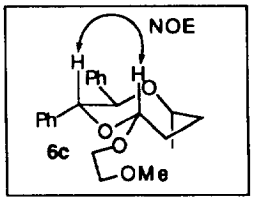


Entry	Substrate	Conditions	Product	Yield[a)]
1	**3** (R=Me)	$LiAlH_4$, THF	R^1=H (**6a**)	85%
2	**4** (R=Bn)	〃	R^1=H (**6b**)	88%
3	**5** ($R=MeOCH_2CH_2$)	〃	R^1=H (**6c**)	94% (72%[b)])
4	〃	NaCN, DMF	R^1=CN (**6d**)	92% (70%[b)])
5	〃	NaH, $CH_2(CO_2Et)_2$	$R^1=CH(CO_2Et)_2$ (**6e**)	93% (65%[b)])

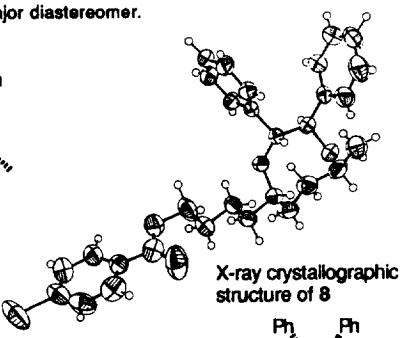
a) Combined yields of 4 diastreomers. b) Isolated yields of major diastereomer.

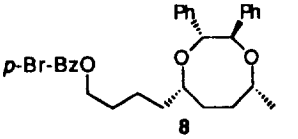
Scheme 2





R^2MgX	Product	Yield
MeMgI	**7a**	96%
EtMgBr	**7b**	87%
AllylMgBr	**7c**	92%
MgBr	**7d**	86%



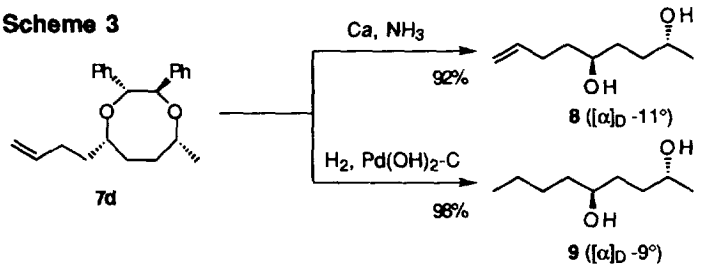


As highly stereoselective construction of compounds **7a-d** had been achieved, we finally examined the removal of the diphenyl ethylene unit using catalytic hydrogenolysis or the Birch reduction. Both processes proceeded smoothly and afforded the corresponding chiral 1,4-diols in good yields (Scheme 3).

In conclusion, a new asymmetric synthesis of chiral 1,4-diols has been developed based on a remote double asymmetric process as the key step. In the reaction the acetal acts firstly as a nucleophile and then as an

electrophile in a one-pot operation and the two remote stereogenic centers are built up simultaneously in a highly stereoselective manner. Further study along the lines presented here is in progress.

Scheme 3



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1. For reviews, see: (a) Mikami, K.; Shimizu, M.; *J. Synth. Org, Chem. Jpn.* **1993**, *51*, 3. (b) Thomas, E. J. *Chemtracts: Org. Chem.* **1994**, *7*, 207.
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3. For reviews on the asymmetric synthesis using the chiral C_2-symmetric acetals, see: (a) A. Alexakis and P. Mangeny, *Tetrahedron: Asymmetry*, **1990**, *1*, 477. (b) H. Fujioka and Y. Kita, "Studies in Natural Product Chemistry", ed by Atta-ur-Rahman, Elsevier, Amsterdam, 1994; Vol 14, pp 469.
4. Chiral hydrobenzoin is readily available in both enantiomeric forms by asymmetric synthesis or resolution; for asymmetric synthesis, see, Wang, Z. -M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302, and for resolution of *dl*-hydrobenzoin, see "Optical Resolution Procedures for Chemical Compounds" ed by P. Mewman, Optical Information Center, Manhattan College, Riverdale, New York, 1984, Vol. 3, pp 353.
5. Bis(*sym*-collidine)iodine(I) perchlorate ($I(coll)_2ClO_4$) is often used in halolactonization. Preparation: Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190.
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7. The high stereoselectivity in the alcohol displacement reactions (**a>b**, **c>d**, see Table 1) might be assumed to favor the direct SN2-type reaction from bicyclic ion.
8. The stereochemistries of the alkoxy group of the major products were determined from NOE experiment on **6c** (see Scheme 2) derived from **5a**. The stereochemistries of the halomethyl substituent were determined by converting **5** to (*R*)-enriched-pentane-1,4-diol {$[\alpha]_D^{23}$ -10 (*c*=0.46, MeOH) lit. $[\alpha]_D^{21}$ -13.4 (*c*=1.05, MeOH); Kitahara, T.; Mori, K.; Matsui, M. *Tetrahedron Lett.* **1979**, *32*, 3021.} in a three-step sequence: 1) acid hydrolysis, 2) $LiAlH_4$ reduction, and 3) hydrogenolysis.
9. The reason is not clear yet, but the preference of transition state **B** might be due to the repulsion between the halomethyl substituent and the anion species which might exist on the convex side of the cation.
10. For the reaction of a Grignard reagent and an acetal, see: Yuan, T. -M.; Yeh, S. -M.; Hsieh, Y. -T.; Luh, T. -Y. *J. Org. Chem.* **1994**, *59*, 8192 and references therein.

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