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ASYMMETRIC EPOXIDATION OF DIVINYL CARBINOL: A NEW APPROACH TO THE SYNTHESIS OF 2,6-DIDEOXYHEXOSES[1]

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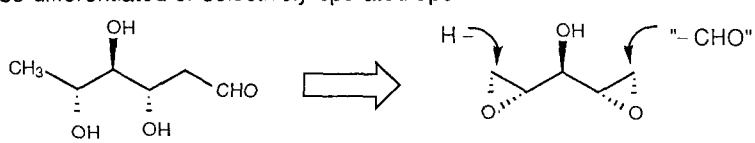
ABSTRACT: The high level of stereochemical control exhibited in the Sharpless epoxidation of prochiral divinyl alcohols has been exploited in short enantioselective syntheses of the dideoxy sugars D-digitoxose and D-olivose.

Recent communications have reported that the Sharpless epoxidation of prochiral divinyl alcohols proceeds with enantiotopic group and diastereotopic face selectivity.[2] This extremely high level of stereocontrol is a fundamental property of the Sharpless epoxidation/kinetic resolution.[3] The kinetic resolution aspect of the Sharpless reaction results from the fact that for a dl-pair of an allylic alcohol one face of one enantiomeric olefin is significantly more reactive than the other three olefin faces. Thus, one enantiomer is epoxidized with face selectivity and the other enantiomer is kinetically resolved. As explained by Schreiber,[2a,b] in the Sharpless epoxidation of divinyl carbinol[4] with (+)-DIPT the pro-S vinyl group is epoxidized with diastereofacial selectivity whereas the minor enantiomer (resulting from addition to the pro-R olefin) is kinetically resolved via a double addition process. We have carried out this reaction under catalytic conditions[5] (10% $Ti(OiPr)_4$, 12% (+)-DIPT,150% tBuOOH, crushed 4A molecular sieves, -20°C, 90 Hrs., distillative workup, 60% yield) to give **1** and now report the use of this reaction in the enantioselective syntheses of differentially protected D- digitoxose and D-olivose.[6]

1

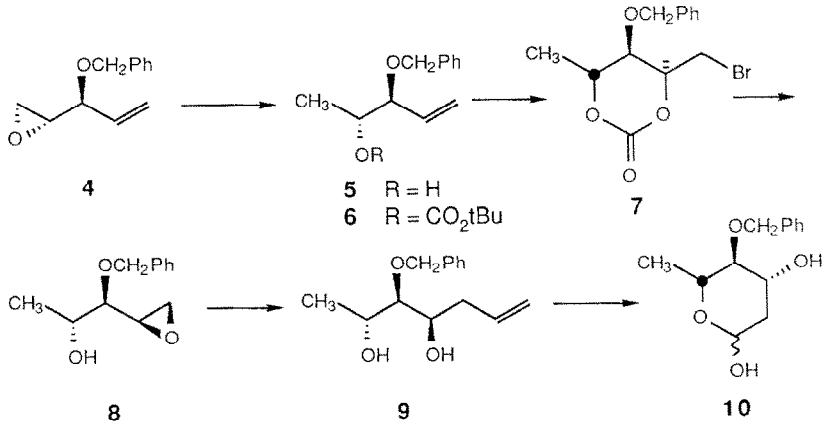
The target compound in this study was digitoxose. We required a synthesis that would be applicable to both the natural (D) and unnatural (L) enantiomers. A simplistic retrosynthetic analysis of D-digitoxose (**2**) involves nucleophilic ring opening of bis-epoxide **3** (a meso compound) with both hydride and an acyl anion equivalent. Control of absolute configuration can be achieved if the two enantiotopic epoxide groups can be differentiated or selectively operated upon.



2 **3**

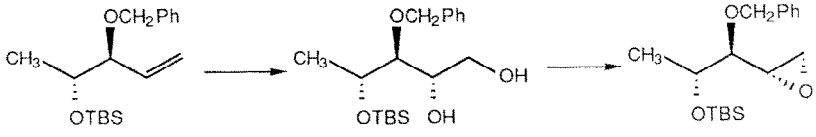
The group selectivity inherent in the Sharpless epoxidation of divinyl carbinol will readily allow for the differentiation of these enantiotopic epoxide groups. The synthesis of the enantiomeric L-sugars can be obtained using the enantiomeric (-)-tartrate.

Epoxide **1** was found to be very prone to Payne rearrangement[7]. During several attempts to protect the free alcohol group this rearrangement proved to be quite problematic. However, benzylation (NaH, benzyl bromide, Bu_4NI , THF)[2c] proceeded rapidly at room temperature to afford **4** without rearrangement of the epoxide. Treatment of **4** with excess LAH at 0°C afforded alcohol **5**[8] in 95% yield. The plan at this stage was to use the free hydroxyl group of **5** to direct the epoxidation of the double bond in a 1,3-syn fashion using the carbonate extension protocol.[9] In the event, **5** was converted into the carbonate **6** (NaH, BOC-ON, 85%). Treatment of **6** with bromine[10] and solid K_2CO_3 in CH_2Cl_2 at -50°C (65% yield) proceeded in a diastereoselective fashion (8:1) to give **7** ; however, the observed stereochemistry was opposite to that which was predicted.[11] Bromocarbonate **7** was readily converted into epoxide **8** upon treatment with excess K_2CO_3 in aqueous methanol. Epoxide ring opening of **8** was achieved by silylation (TMS-Cl, Et_3N), treatment of the resulting silyl ether with vinylmagnesium bromide in the presence of cuprous iodide, followed by desilylation (K_2CO_3, MeOH) to give **9** in 70% overall yield. Ozonolysis followed by reductive workup (MeSMe) afforded 4-O-benzyl-D- olivose (**10**)[12] in 90% yield.



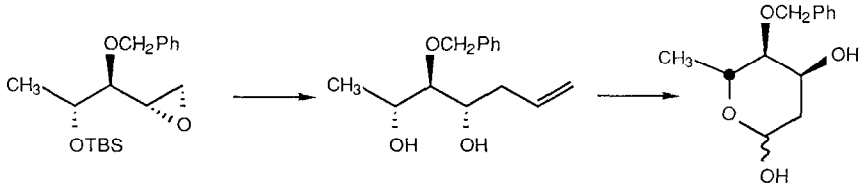
4 **5** R = H; **6** R = CO_2tBu **7** **8** **9** **10**

Silylation (TBS-Cl, DMAP, CH_2Cl_2) of **5** readily afforded **11**. Osmylation (cat. OsO_4, NMO; 85% overall from **5**) of **11** proceeded in a highly diastereoselective[13] fashion (12:1) to afford **12** as the major product. Selective tosylation (TsCl, py) of **12** followed by treatment with base (K_2CO_3, MeOH) afforded the desired α-epoxide **13** in 70% overall yield.



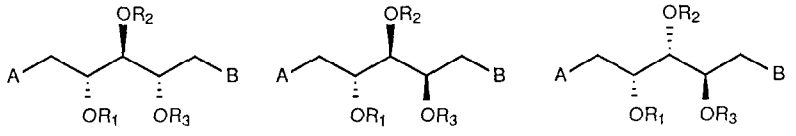
11 **12** **13**

The conversion of **13** into 4-O-benzyl-D-digitoxose (**15**), via **14** [$(CH_2{=}CH)_2CuCNLi_2$, $BF_3{\cdot}OEt_2$[14] -78°C; nBu_4NF; 75% overall] was achieved by methodology analogous to the conversion of **8** into **10** . Surprisingly, epoxide **13** was significantly less reactive than the isomeric epoxide (derived from silylation of **8**). Epoxide **13** was unreactive towards vinyl cuprates in the absence of $BF_3{\cdot}OEt_2$; however, epoxide ring opening occurred readily in the presence of $BF_3{\cdot}OEt_2$ at -78°C. Ozonolysis of **14** followed by reductive workup (MeSMe) afforded 4-O-benzyl-D-digitoxose **15**[15] in 90% overall yield.



13 **14** **15**

The methodology described in this paper is applicable , in principle, to the synthesis of six out of the eight possible stereoisomers (I, II and III and their enantiomers) of differentially protected 1,2,3-triols, where A and B are groups which can be introduced as nucleophiles.



I II III

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   (b) S.L.Schreiber, T.S.Schreiber, D.B.Smith, manuscript submitted for review.
   (c)S.Hatakeyama,K.Sakurai,and S.Takano, *J.Chem.Soc.Chem.Comm.*,**1985**,1759
   (d)B.Hafele,D.Schroter, and V.Jager, *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 87
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3. Recent reviews on the synthetic and mechanistic aspects of the Sharpless epoxidation: (a) B.E.Rossiter, in "Asymmetric Synthesis" Vol 5,pp 194-246 J.D.Morrison,ed.Academic Press,Inc. 1985 (b) M.G.Finn and K.B.Sharpless, in "Asymmetric Synthesis" Vol 5,pp 247-308 J.D.Morrison,ed.Academic Press,Inc. 1985
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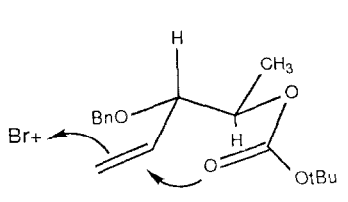
6. (a) For another Sharpless epoxidation approach to dideoxyhexoses, see: W.R.Roush and R.J.Brown, *J.Org.Chem.*,**1982**, *47*, 1371
   (b) For a recent review on the syntheses of carbohydrates from noncarbohydrate precursors see: G.J.McGarvey, M.Kimura , T.Oh and J.M.Williams, *J.Carbohydr. Chem.*, **1984**, *3*, 125
7. G.B.Payne, *J.Org.Chem.*,**1962**,*27*, 3819; C.H.Behrens and K.B.Sharpless, *Aldrichimica Acta*,**1983**,*16*, 67
8. HPLC analysis (CN-column and YMC chiral column) of the 3,5-dinitrobenzoate derivative of **5** indicated de≥97% and ee>99%. I wish to thank Dr. J.C.James for this data.
9. P.A.Bartlett,J.D.Meadows,E.G.Brown,A.Morimoto,and K.K.Jernstedt,*J.Org. Chem.* , **1982**,*47*, 4013
10. Attempted iodocarbonatization resulted in a very low yield of iodocarbonates,but the same level of distereoselectivity was observed.

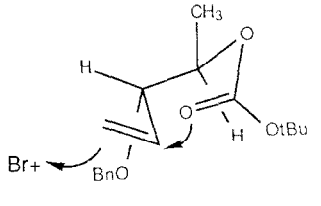
11. Based on the examples cited in Ref 9 the 1,3- diastereoselectivity was expected to be syn, not anti as experimentally observed. None of the examples in this paper has an oxygen substituent adjacent to the double bond. Apparently ,the benzyloxy substituent in **6** is effecting the stereochemical outcome of this reaction.

Of interest are the iodolactonization studies (A.R.Chamberlin, M. Dezube, P. Dussault, and M. C. McMills, *J.Am.Chem.Soc.* **1983**, *105*, 5819.) of allylic alcohols to form butyrolactones. In this study the major products generally had the two oxygen substituents syn to each other, as was observed in this case. For related studies in formation of five membered rings see: P.A.Bartlett, in "Asymmetric Synthesis" Vol 3, pp 411-454,J.D.Morrison,ed.AcademicPress,Inc.1984; see also Y.Tamaru, M.Mizutani, Y.Furukawa, S-i.Kawamura, Z-i.Yoshida, K.Yanagi, and M.Minobe, *J.Am.Chem.Soc,* **1984**,*106*, 1079; D.R.Williams and F.H.White,*Tetrahedron Lett.*, **1985**,*21*, 2529, *Tetrahedron Lett.*, **1986**, *22*, 2195. Interestingly iodo diol formation of allylic alcohols in acyclic systems proceeds with a high degree of diastereoselectivity; however, in these cases the reactions proceed with the opposite face selectivity. See A.R.Chamberlin and R.L.Mulholland,Jr. *Tetrahedron*, **1985**, *40*, 2297. For an example of a directing effect of a benzyloxy substituent in an intramolecular oxymercuration leading to a substituted tetrahydropyran (both oxygen substituents end up syn) see J-R Pougny, M.A.M.Nassr and P.Sinay,*J.Chem.Soc.Chem.Comm*, **1981**,375. I wish to thank Prof. S.L.Schreiber for a helpful discussion on this point.

A and B represent likely transition states leading to the major and minor products, respectively, of this reaction. In transition state A the vinyl group and benzyloxy substituent are eclipsed. Of interest are the the theoretical studies of S.D.Kahn and W.J.Herhe, *Tetrahedron Lett.*, **1985**,*26*, 3647. This study proses that the most reactive conformer of an allylic alcohol (ether) is that in which the vinyl group and oxygen group are eclipsed.



A



B

12. Characterized as its α-methyl glycoside. ^{1}H NMR 300 MHz: δ 1.25 d 3H; 1.64 m 1H; 2.0 bs 1H 2.11 m 1H; 3.00 t (J=9.3 Hz) 1H; 3.29 s 3H; 3.71 m 1H; 3.99 m 1H; 4.75 m 3H; 7.33 bs 5H.

13. J.K.Cha,W.J.Christ,and Y.Kishi, *Tetrahedron*, **1984**,*40*, 2247

14. B.H.Lipshutz, D.A.Parker, J.A.Kozlowski,and S.L.Nguyen, *Tetrahedron Lett.* , **1984**,*25*, 5959.

15. Characterized as its β-methyl glycoside. ^{1}H NMR 300 MHz: δ 1.30 d 3H; 1.60 m 1H; 2.17 m 1H; 2.37 bd 1H; 3.14 dd (J=9.3,3.0 Hz) 1H; 3.47 s 3H; 3.82 m 1H; 4.23 m 1H; 4.57 ABq 2H; 4.73 dd (J=9.6,2.1 Hz) 1H; 7.33 bs 5H.

ACKNOWLEDGEMENT

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