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Allylic 4-Methoxybenzoates Display Excellent Reagent-Controlled Double Diastereoselection in the Sharpless Asymmetric Dihydroxylation: Application to Highly Selective Total Syntheses of Polyols

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Abstract: *The asymmetric dihydroxylation of several enantiomerically pure 4-substituted allylic 4'-methoxybenzoates proceeds with excellent reagent-controlled diastereoselectivities. This observation, coupled with the high enantio- and regioselectivity provided by the Sharpless asymmetric dihydroxylation of suitably protected dienes, has been used to accomplish the stereocontrolled total syntheses of several vic-polyols.* © 1997 Elsevier Science Ltd.

In recent years there has been an increased understanding of the important biological role of carbohydrates.[1] This has stimulated an interest in the synthesis of both natural and unnatural polyols. Progress in the stereocontrolled synthesis of these compounds from non-carbohydrate sources has been hindered by the lack of asymmetric reactions for vicinal polyol formation.[2] An exception is the use of the Sharpless asymmetric epoxidation for the synthesis of hexoses.[3,4]

The Sharpless asymmetric dihydroxylation (AD),[5] which directly produces diols with high enantioselectivity, has two limitations relevant to the total synthesis of carbohydrates: (1) low enantioselectivities are generally obtained in the dihydroxylation of allylic alcohols, and (2) reagent-controlled diastereoselectivity[6] under AD conditions with stereocenters proximal to the reaction site has been only moderate.[7,8] The first issue has recently been solved by the use of allylic 4-methoxybenzoate esters to afford the corresponding diols in very high enantiomeric purity.[9] The transition-state model,[10] which successfully predicted the utility of these compounds as dihydroxylation substrates, also suggested a solution to the second problem. It indicated that enantiomerically pure 4-substituted allylic 4'-methoxybenzoates should interact with the catalyst in a similar fashion and therefore afford products with excellent reagent-controlled diastereoselectivity that could be useful for carbohydrate total synthesis. This prediction has been confirmed experimentally by the results that are described herein.

Initial studies were conducted on the preparation of 6-deoxyhexoses. Commercially available (*E,E*)-2,4-hexadien-1-ol was transformed into the corresponding 4-methoxybenzoate ester **1** (4-MeOBzCl, TEA, DMAP (cat.), CH_2Cl_2, 23 °C, 2 h, 87%), which was subjected to asymmetric dihydroxylation with the $(DHQD)_2PYDZ$ ligand to afford diol **2** in 98% ee and 7 : 1 regioselectivity, $[\alpha]_D^{18}$ +7.1 (*c* 6.6, $CHCl_3$).[11]

The purified diol **2** was transformed into its acetonide **3**, $[\alpha]_D^{19}$ -4.6 (*c* 0.655, $CHCl_3$), under standard conditions (2-methoxypropene, $POCl_3$ (cat.), CH_2Cl_2, 0 °C to 23 °C, 1 h, 91%). As expected,[8] the OsO_4-NMO dihydroxylation of olefin **3** afforded 1.9 : 1 mixture of *anti* and *syn* products, as shown in Table 1. However,

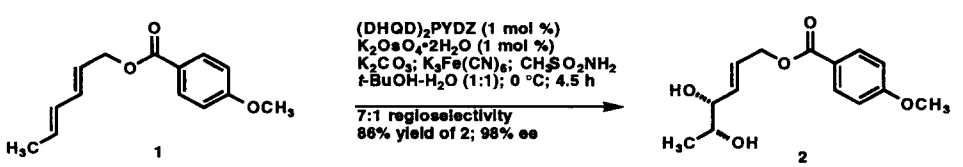

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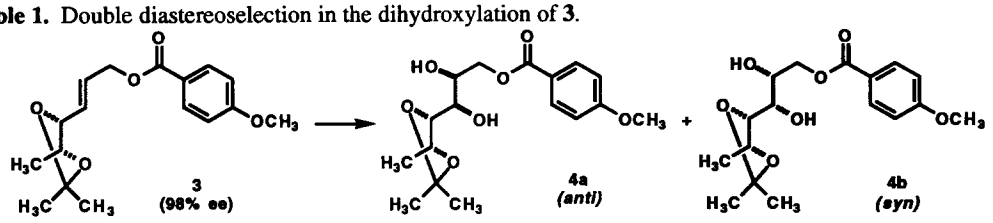
Table 1. Double diastereoselection in the dihydroxylation of **3**.

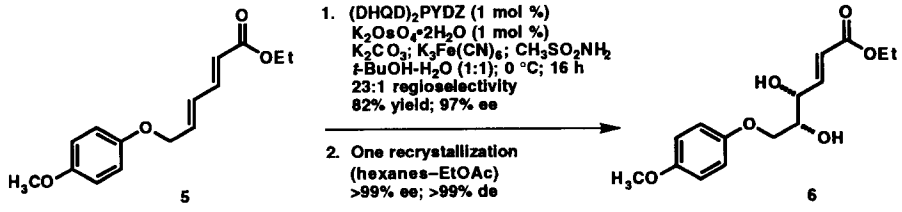


Dihydroxylation conditions	Isolated yield	Ratio of *anti* / *syn*
OsO_4; NMO acetone–H_2O (10:1)	88% of *anti* and *syn*	1.9 : 1
AD $(DHQ)_2PHAL$ (matched case)	86% of *anti*	54 : 1
AD $(DHQD)_2PYDZ$ (mismatched case)	86% of *syn*	1 : 35

AD conditions: Ligand (5 mol %), $K_2OsO_4 \cdot 2H_2O$ (1 mol %); K_2CO_3 (3 eq), $K_3Fe(CN)_6$ (3 eq), $CH_3SO_2NH_2$ (1 eq), *t*-BuOH-H_2O (1:1); 0 °C, 2.5 h

when olefin **3** was dihydroxylated under AD conditions in the presence of the $(DHQ)_2PHAL$ ligand (matched case), excellent diastereoselectivity was observed in favor of the *anti* (D-fucol) product **4a**, mp 87-89 °C, $[\alpha]_D^{20}$ +2.7 (*c* 0.62, MeOH). Use of the $(DHQD)_2PYDZ$ ligand (mismatched case) also resulted in excellent diastereoselection, but this time favoring the *syn* (6-deoxy-D-iditol) product **4b**, $[\alpha]_D^{22}$ +23.8 (*c* 1.94, MeOH).

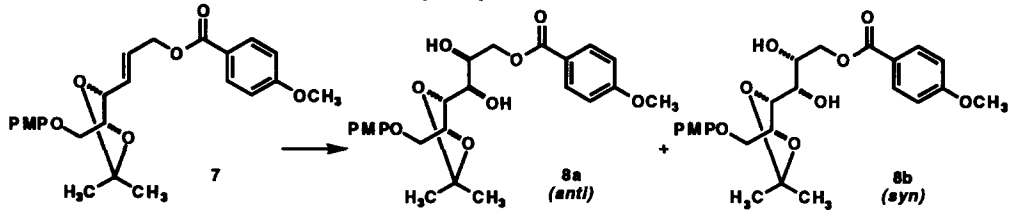
Encouraged by the success in the 6-deoxyhexose series, a similar approach to hexoses was undertaken. 4-Methoxyphenyl (PMP) ether **5**, which was chosen as a suitable starting material, was prepared from the corresponding alcohol[12] (4-MeOPhOH, Ph_3P, DEAD, THF, reflux, 1 h, 93%).[13] Diene **5** was subjected to the asymmetric dihydroxylation reaction using the $(DHQD)_2PYDZ$ ligand to afford diol **6** in 97% ee and 23 : 1 regioselectivity.[14] This mixture was recrystallized once to obtain pure **6** in >99% ee, mp 118 °C, $[\alpha]_D^{22}$ +35 (*c* 0.52, $CHCl_3$). This result is particularly noteworthy when one considers that the corresponding reaction with OsO_4-NMO affords an 11% yield of a 2.4 : 1 regioisomer mixture favoring racemic **6**.[15]



Diol **6** was transformed into protected 4-methoxybenzoate **7** in 87% overall yield, mp 69-70 °C, $[\alpha]_D^{27}$ +30.2 (*c* 1.32, $CHCl_3$), by the following sequence: (1) acetonide formation using 2-methoxypropene ($POCl_3$ (cat.), CH_2Cl_2, 0 °C to 23 °C, 3 h, 92%), (2) DIBAL-H reduction in CH_2Cl_2 (-78 °C to -42 °C, 45 min, >99%), and finally (3) acylation with 4-MeOBzCl (TEA, DMAP (cat.), CH_2Cl_2, 23 °C, 3 h, 95%).

Dihydroxylation of olefin **7** with OsO_4-NMO afforded a 2.5 : 1 mixture of *anti* to *syn* diol products, as shown in Table 2. The dihydroxylation under AD conditions using the $(DHQ)_2PHAL$ ligand (matched case) provided only the *anti* (D-galatitol) diastereomer **8a**, mp 126-127 °C, $[\alpha]_D^{23}$ +17.1 (*c* 0.896, $CHCl_3$). The corresponding reaction with the $(DHQD)_2PYDZ$ ligand (mismatched case) afforded a 90 : 1 mixture favoring the *syn* (D-iditol) product **8b**, mp 84-85 °C, $[\alpha]_D^{23}$ +22.4 (*c* 0.875, $CHCl_3$).

Table 2. Double diastereoselection in the dihydroxylation of **7**.



Dihydroxylation conditions	Isolated yield	Ratio of *anti* / *syn*
OsO_4; NMO acetone–H_2O (10:1)	96% of *anti* and *syn*	2.5 : 1
AD $(DHQ)_2PHAL$ (matched case)	93% of *anti*	>200 : 1
AD $(DHQD)_2PYDZ$ (mismatched case)	90% of *syn*	1 : 90

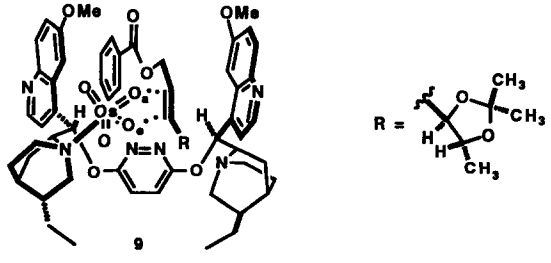
AD conditions: Ligand (5 mol %), $K_2OsO_4 \cdot 2H_2O$ (1 mol %); K_2CO_3 (3 eq), $K_3Fe(CN)_6$ (3 eq), $CH_3SO_2NH_2$ (1 eq), t-BuOH-H_2O (1:1); 0 °C, 6-11 h

The absolute and relative stereochemistries of products **4** and **8** were confirmed by chemical transformation of compounds **4a** and **8b** to 2,3,4,5-diisopropylidene-D-fucitol and D-iditol hexabenzoate respectively, followed by comparison of their ^1H NMR spectra and specific rotations to those of authentic samples.[16]

In both series (Tables 1 and 2) the intrinsic substrate preference is almost completely ignored, with the asymmetric catalyst determining the diastereoselectivity of the reaction. Any traces of the minor diastereomers are easily removed by chromatography and the products are differentially protected for further elaboration. The strategy outlined above allows for great flexibility and could be applied to the synthesis of a variety of carbohydrates. For example, the opposite enantiomers could be prepared in a similar fashion by using the $(DHQ)_2PHAL$ instead of the $(DHQD)_2PYDZ$ ligand for the initial dihydroxylation of **1** and **5**. The resulting products could also be used to prepare higher sugars (≥8 carbon atoms) by repeated bishomologation and asymmetric dihydroxylation sequences.

The proposed transition state geometry for the dihydroxylation of, for example, chiral olefin **3** with $(DHQD)_2PYDZ$-OsO_4 (mismatched case) is shown in expression **9** (the methoxy group of the substrate is omitted for clarity) and Figure 1.

The structural features of this complex are very similar to those present in the proposed transition state for the dihydroxylation of allyl 4-methoxybenzoate.[9] The 1,3-dioxolane portion of the olefinic substrate is easily accommodated in the open space of the front part of the binding pocket with no unfavorable steric interactions. The proposed transition state for the reaction of chiral olefin **3** with $(DHQ)_2PHAL$-OsO_4 (matched case) is very similar to the one depicted for the mismatched case.



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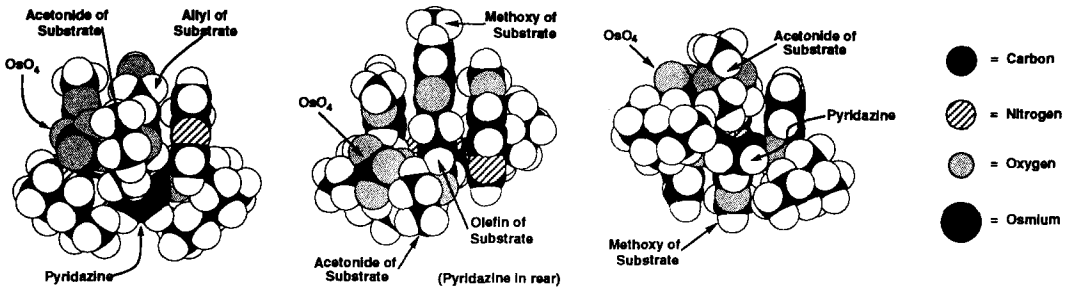

Figure 1. Three views of the proposed complex of olefin **3**, OsO_4 and $(DHQD)_2PYDZ$.

The superb diastereoselectivities described herein demonstrate the general usefulness of allylic 4-methoxybenzoates as substrates for the AD[17] and the mechanistic model used for their design.[18]

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