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Asymmetric dihydroxylation of D-xylose-derived allyl ethers

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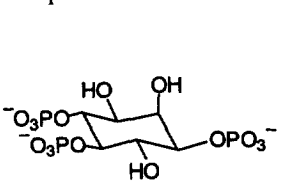
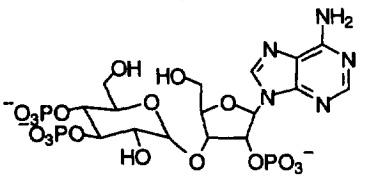
Abstract: The catalytic asymmetric dihydroxylation of several allyl 2-O-benzyl-α-D-xylosides with AD-mix β and PYR(DHQD)$_2$ shows poor diastereofacial selectivity if the 3- and 4-OH groups are unprotected or acetylated. Acetal, benzyl ethers and benzoyl esters enhance the diastereoselectivity which is opposite to that predicted by the "AD mnemonic" and which is completely lost using AD-mix α. © 1997 Elsevier Science Ltd

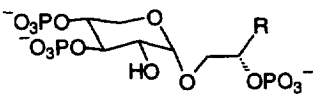
In connection with our research programme on the synthesis of analogues of the second messenger inositol 1,4,5-trisphosphate (IP_3), we needed some [(2*S*)-2-hydroxypropyl]-D-xylosides which could mimic adenophostin A,[1] a natural product having the highest known affinity for IP_3 receptor.[2] We chose to prepare these compounds from readily available allyl D-xylosides[3] and we were thus faced with the problem of diastereoselective dihydroxylation of allylic ethers.



***myo*-Inositol-1,4,5-trisphosphate**



Adenophostin A



Xylose-based mimics

Although allyl glycosides **1** are highly asymmetric, the stereogenic centres of the xylose moiety are too distant from the reacting double bond to influence significantly the diastereofacial selectivity on the terminal olefin. Thus we turned to the catalytic asymmetric dihydroxylation (AD). The Sharpless procedure has found wide applications for the enantioselective AD of prochiral olefins including allyl ethers.[4] The AD of chiral substrates has also been studied and some examples of sugar-substituted olefins via carbon–carbon bonds have been reported.[5] The AD of allyl ethers[6] and esters[7,8] have been studied but AD of chiral allyl ethers is less documented. We report in this letter our results in the AD of D-xylose-derived allyl ethers showing that poor to good diastereofacial selectivity can be obtained depending on the protecting groups used on the sugar moiety.

Our synthetic strategy in the synthesis of *myo*-inositol-1,4,5-trisphosphate mimics led us to introduce a protecting group at position 2 and to try to get the *S* configuration at position 7 of the expected diol. We started with the 2-O-benzyl ether **1a** which was treated according to the procedure of Sharpless,[4] using AD-mix β which is supposed to give the required 7*S* isomer according to the "AD mnemonic". Dihydroxylation proceeded well but, to our disappointment, almost equal amounts of both diastereomers (diastereoisomeric ratio (d.r.) 1.2:1) were obtained as seen from ^{13}C nmr which proved to be a reliable method for this analysis. Catalytic AD being a two phase reaction we suspected that compound **1a** could react in the aqueous phase with the osmium (VIII) species. This reaction in the absence of the chiral ligand led obviously to no selectivity as observed in the reaction of osmium tetroxide and N-methyl morpholine-N-oxide as the cooxidant (Table 1, entry 1). To lower its solubility

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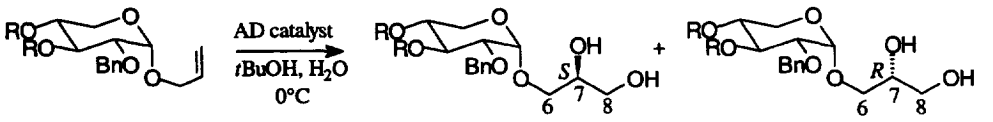
Table 1. Asymmetric dihydroxylation of allyl-D-xylosides **1** and **4**



1 **2** **3**

Entry	Compound	R	Reagent	d.r. ratio [c]
1	**1a**	H	OsO_4 cat, NMO	1:1
2	**1a**	H	AD-mix β [a]	1.2:1
3	**1b**	Ac	AD-mix β [a]	1.4:1
4	**1c**	$(CH_3)_2C$	AD-mix β [a]	2.1:1
5	**1d**	pMeOBn	AD-mix β [a]	2.3:1
6	**1e**	Bn	AD-mix β [a]	4.5:1
7	**1f**	Bz	AD-mix β [a]	4.3:1
8	**1g**	$C_6H_{11}CO$	AD-mix β [a]	5.6:1
9	**1e**	Bn	$(DHQD)_2PYR$, 1 mol%	2.7:1
10	**1e**	Bn	$(DHQD)_2PYR$, 4 mol%	5.2:1
11	**1e**	Bn	AD-mix β–$(DHQD)_2PYR$[b]	4.8:1
12	**1f**	Bz	AD-mix β–$(DHQD)_2PYR$[b]	8.1:1
13	**1f**	Bz	AD-mix α [a]	1.1:1
14	**4**	see Scheme	AD-mix β [a]	**5/6** 1.2:1[d]
15	**4**	see Scheme	AD-mix α [a]	**6/5** 1.3:1 [d]

a) Commercial reagents (Aldrich) were used according to Sharpless's recommended procedure.

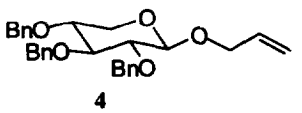
b) 1 mol% of each catalyst was used.

c) Ratio (major/minor diastereoisomers) determined by ^1H and ^{13}C nmr spectrocopy by averaging the integrals values of H-1 and C-1, C-8 signals respectively.

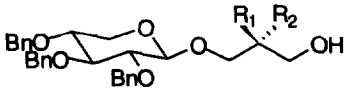
d) The absolute configuration at C-7 of **5** and **6** is presently unknown.

in the aqueous phase, compound **1a** was acetylated under standard conditions to give olefin **1b**. This compound was treated as above with AD-mix β to yield a d.r. of 1.4:1.

Alternatively compound **1a** was treated with dimethoxypropane in acidic acetone to provide the acetal **1c**. Slightly improved results were obtained (entry 4, d.r. 2.1:1). This improvement can be attributed to an enhancement of the lipophilicity of the substrate or to the introduction of a conformational bias in this substrate by formation of a *trans*-fused ring system. To shed light on this point, we prepared non-biased derivatives such as benzyl ethers **1d** and **1e**. Gratifyingly this d.r. increased to 4.5:1 with benzyl ethers as protecting groups (compound **1e**, entry 6). Finally the more synthetically useful compound **1f** was prepared and gave identical results (entry 7) with a d.r. ratio of 4.3:1. This d.r. enhancement in the AD of compounds **1d–f** could be attributed to stacking interactions between the aromatic rings of the protecting groups and those of the catalyst, which should contribute to the correct orientation of the substrate in the catalytic centre. This hypothesis is inconsistent with the results obtained with compound **1g** (entry 8) in which the aromatic rings were replaced by cyclohexyl rings. Thus the observed improvements are more likely the result of favourable hydrophobic interactions between the protecting groups and the catalyst and/or steric hindrances between these bulky groups which tend to favour one orientation of the substrate in the catalytic centre.

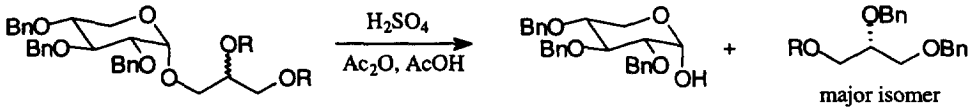


4



5 R_1 = OH, R_2 =H
6 R_1 = H, R_2 = OH

The importance of the ligand structure has been already pointed out.[4] We checked this point by submitting compound **1e** to AD using the $(DHQD)_2$/PYR reagent. The diastereomeric ratio decreased to 2.7:1 using 1 mol% of the catalyst but some improvements (5.2:1) were observed using 4 mol% of the catalyst. This showed that the nature of the ligand did not greatly influence the diastereomeric ratio but, not unexpectedly, the amount of catalyst seems to be important. Mixture of catalysts [$(DHQD)_2$PYR and $(DHQD)_2$PHAL 1 mol% of each] can be successfully used to improve the d.r. to 4.8:1 for compound **1e** and 8.1:1 for compound **1f** (entries 11 and 12). We attempted to reverse the diastereoselectivity using AD-mix α which is supposed to give the opposite facial selectivity as compared to AD-mix β. Surprisingly the d.r. dropped to 1.1:1, the major diastereoisomer being the one formed using AD-mix β. Thus compounds **1e–g** and AD-mix β form matched pairs. Assuming that the stereochemistry at the anomeric centre should play an important role, we investigated the AD of compound **4** using AD-mix β and AD-mix α. In both experiments, a modest diastereomeric induction was observed accompanied by a reversal of diastereoselectivity on going from AD-mix α to AD-mix β (see Table 1, entries 14, 15). This clearly indicates that none of these pairs are matched and that compound **4** is poorly "recognized" by the catalytic site.



2e, 3e R = H
7 R = Bn

2,3,4-tri-O-benzyl-D-xylose

8 R = Ac
9 R = H

Intrigued by the rather low selectivities in the AD of matched pairs **1e–g** and AD-mix β, we investigated thoroughly the absolute configuration of the dihydroxylation product **2e** and **3e**. For that purpose, the mixture was benzylated under standard conditions to give the benzyl ether **7**. This compound was submitted to acid hydrolysis to liberate the aglycon, isolated as its acetate **8**. Removal of the acetyl group gave the known di-O-benzyl *sn* glycerol **9**. Its optical rotation ($[\alpha]_D$ −11.2 (c 1, $CHCl_3$), compared with literature data ($[\alpha]_D$ −17.2 (c 1, $CHCl_3$),[9] indicated that this compound was a 82:18 mixture of *S*/*R* compound. *Thus we concluded that asymmetric dihydroxylation of compounds* ***1*** *gave mainly the 7R derivative, instead of the 7S derivative predicted by the AD mnemonic.*

In conclusion the asymmetric dihydroxylation of chiral allyl ethers strongly depends on the nature of the chiral substituent, and in our case of the protecting groups of the xylose moiety. Large hydrophobic protecting groups favour the diastereoselectivity which however remains poor, but the observed selectivity is opposite to that expected from AD-mnemonic. The selectivity is completely lost by simply changing the configuration of the asymmetric centre near the allylic reacting centre (going from α-anomer to β-anomer). This suggests that this substrate can bind to the catalyst by the two faces of the double bond or that the catalyst is highly selective and cannot accommodate this substrate. Olefins that cannot be "recognized" by the binding pocket of the catalyst should react in the so-called secondary cycle, i.e. with OsO4 in a two phase system. These results should be in favour of the "enzyme-like" concept[4,8] in the reaction of AD-mix, with a high substrate selectivity. Further experiments, needed for a better understanding of the observed results, in particular the AD-mnemonic failure, are currently being performed.

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