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ASYMMETRIC DIHYDROXYLATIONS VIA CHIRAL OXAZOLIDINES

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Summary: The title compounds, new chirally masked α,β unsaturated aldehydes, undergo diastereoselective dihydroxylation reactions with 45-60% diastereoisomeric excesses; chromatographic purification of the major diols, di-O-protection and auxiliary removal afford optically pure α,β dialkoxy aldehydes.

Enantiomerically pure di-O-protected α,β dihydroxy aldehydes, starting materials for the synthesis of several interesting sugars[1] and more complex polyhydroxylated targets,[2] are usually obtained through chemical modifications of chiral substances of natural or biotechnological origin.

Here we describe the synthesis of these compounds through the asymmetric dihydroxylation of chirally masked α,β unsaturated aldehydes, fulfilling the following requirements:

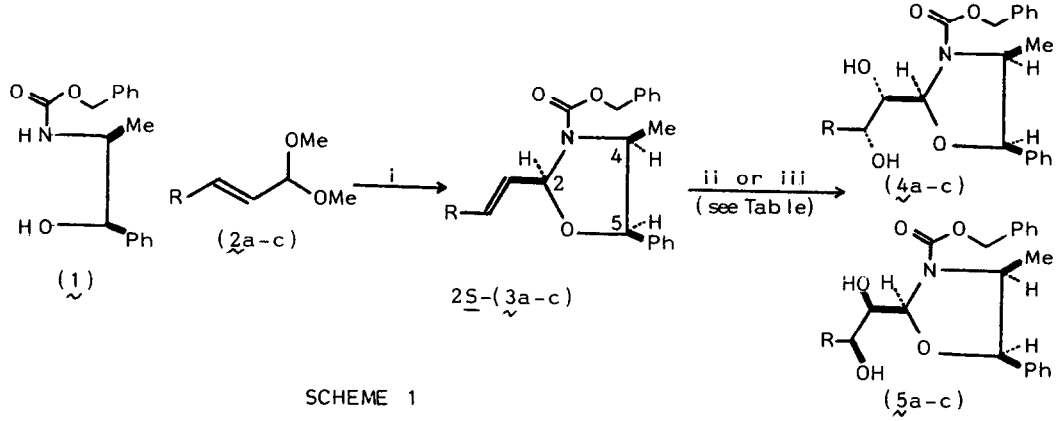
1) Fair degree of π-face differentiation; 2) Easy separation of the desired optically pure diastereomer; 3) Simple removal and recycling of the chiral directing group; 4) Commercial availability of both the enantiomeric forms of the chiral auxiliary.

The reaction of L-N-Benzyloxycarbonyl-norephedrine (1)[3] with the unsaturated dimethylacetals (2a-c) in the presence of pyridinium p-toluene-sulfonate afforded the (2S)-2-alkenyl-3-benzyloxycarbonyl-oxazolidines (3a-c)[4] in high yield and in a highly diastereoselective manner (scheme 1, Table).

The absolute configuration of compounds (3a-c) was determined by n.O.e. difference measurements.[5]

Catalytic OsO_4 dihydroxylation[6] of (3a) and (3b) afforded the diols (4a-b) and (5a-b) with diastereomeric excesses of 54-55% (see Table).

In contrast, the α,β unsaturated ester (3c) showed the opposite diastereoface preference either by OsO_4 or MnO_4^- dihydroxylation [6,7] (see Table).



SCHEME 1

i) Py·PTSA (0.3 mol. eq.), C_6H_6, molecular sieves 4Å, reflux, 3-40 h (88-92%)
ii) OsO_4 (0.05 mol. eq.), $Me_3\overset{+}{N}-\bar{O}$ (1.5 mol. eq.), acetone/H_2O 8/1, 25°C, 20-25 h
iii) $KMnO_4$ and $n\text{-}C_{16}H_{33}\overset{+}{N}Me_3\bar{B}r$ (3-4 mol. eq.), CH_2Cl_2, -40°C, 20-25 h.

TABLE: Stereochemistry of formation and dihydroxylation of the oxazolidines (3a-c).

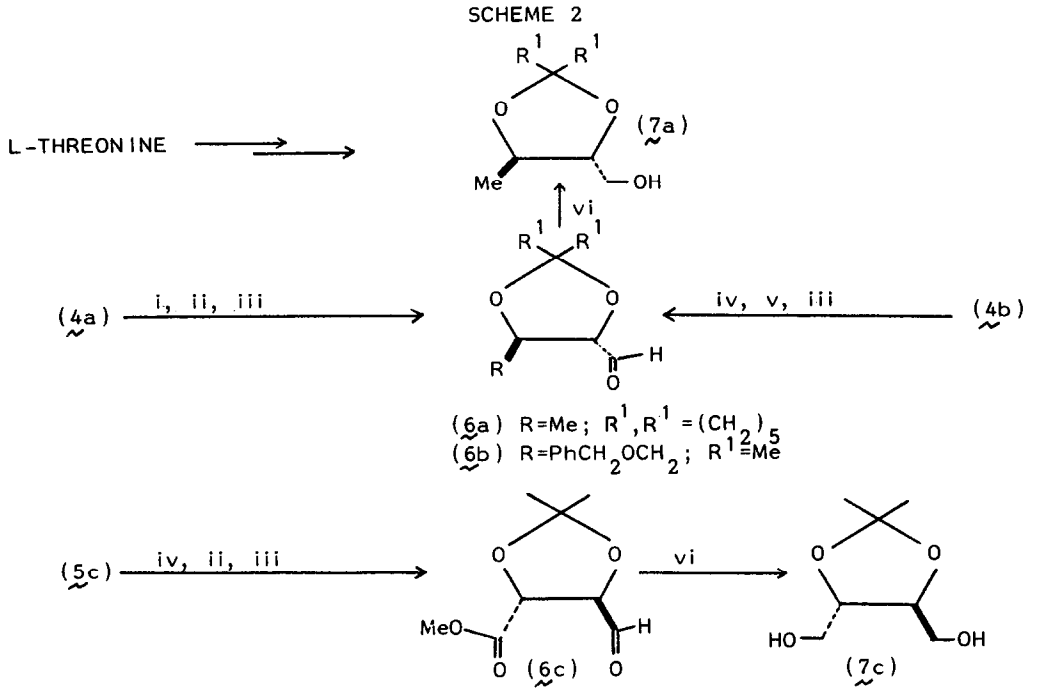
		Ring formation		Dihydroxylation	
(2)[a]		2S(3)/2R(3)[b,c]	yield% (3)	(4)/(5)[b,c]	yield% (4+5)
a	R= Me	7/1	86	3.4/1[e]	76
b	R= $PhCH_2OCH_2$[d]	5/1	92	3.5/1[e]	88
c	R= MeO_2C[d]	10/0	90	1/2.7[e]	95
				1/4.0[f]	60

a) The acetals were prepared from the corresponding aldehydes according to Ref. 8; b) Measured by ^1H NMR of the crude mixture; c) The major diastereoisomer could be obtained free of the minor one by chromatography. d) The parent aldehydes were prepared according to Refs. 9a and 9b ; e) Cat. OsO_4 dihydroxylation; f) MnO_4^- dihydroxylation.

Ketalization of the pure major diols (4a), (4b), and (5c), Cbz removal by standard hydrogenation or treatment with DIBAL at -78°C and subsequent mild acidic hydrolysis released the desired optically pure aldehydes (6a-c) together with L-norephedrine hydrochloride (scheme 2). The optical purity and the absolute configuration of the aldehydes was deduced comparing the chiroptical properties of authentic samples [10] with (6b) and with the reduced products (7a) and (7c).

It must be emphasized that while (6a) [1d] and (6b) [11] are known key intermediates for the total synthesis of L-daunosamine and other rare sugars, (6c) can be a useful highly functionalized new chiral building block.

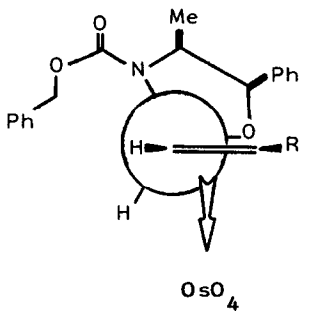
SCHEME 2



i) Cyclohexanone(3 mol. eq.), Py·PTSA (1 mol. eq.), C_6H_6, molecular sieves 4Å reflux, 10 h, (90%); ii) H_2, 10% Pd/C, THF/MeOH 3/1, 30 min, (95%); iii) 0.1 M HCl (2 mol. eq.), CH_2Cl_2, (95%); iv) acetone, PTSA, $CuSO_4$, 20 h, (90-94%); v) DIBAL (2 mol. eq.), CH_2Cl_2, -78°C, 30 min, (75%); vi) $NaBH_4$, MeOH, 0°C, (90%)

The diastereofacial preference observed in the dihydroxylation of (2a) and (2b) may be rationalized in terms of the known preferred C=C-C-O s-cis[12] more reactive conformation for such electrophilic additions (see figure).

We are currently investigating the reasons of the opposite stereoselectivity observed in the case of (3c).



Figure

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3.Prepared by treatment of norephedrine with benzyloxycarbonylchloride under standard Schotten-Baumann conditions (75-85%).

4.Unlike the previously reported 3-methyloxazolidines (P.Mangeney, A.Alexakis, J.F. Normant, Tetrahedron, 40, 1803 (1984)), compounds (3) are stable to water, that is an indispensable reagent in catalytic OsO_4 dihydroxylations.

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10.Authentic (7a), $[\alpha]_D^{25}$ +10° (c=1, $CHCl_3$), was obtained starting from L-threonine (see Ref. 1d) by $NH_2 \rightarrow OH$ substitution ($NaNO_2$, H_2SO_4, H_2O), methyl ester formation, di-O-protection and $LiAlH_4$ reduction.

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