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DOUBLE ASYMMETRIC INDUCTION IN THE OSMYLATION OF γ-ALKOXY-α,β-UNSATURATED ESTERS.

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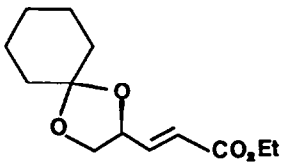
Abstract. OsO_4 promoted cis-dihydroxylation of enantiomerically pure (E)-α,β- unsaturated esters derived from alkoxyaldehydes occurs with noticeable levels (up to ≥ 45:1) of stereoselection when carried out in the presence of alkaloid derived ligands. Matching and mismatching substrate-ligand pairs have been identified.

The stereoselective version of the catalytic or stoichiometric cis-dihydroxylation of alkenes opens a straigthforward entry to polyols, important target molecules, either as such or as chiral building blocks.The pioneering works by Sharpless,[1] Kishi,[2] and Scork[3] highlighced two possible different approaches, namely osmylation in the presence of a chiral ligand[1] or osmylation of a chiral olefin.[2,3] Both routes have been the subject of recent papers.[4-15]

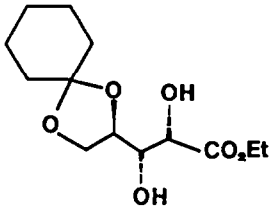
We reported[16] that double asymmetric induction[17] can be successfully employed in the stereoselective synthesis of optically active masked syn-α,β--dihydroxy aldehydes via diidroquinidine acetate promoted osmylation of chiral acecals of α,β-unsaturated aldehydes derived from (1S)-10-mercaptoisoborneol. In order to extend the scope of our approach, we have now examined the cis-hydroxylation of α,β-unsaturated esters deriving from easily available enantiomerically pure alkoxyaldehydes such as (R)-cyclohexylidenglyceraldehyde or (S)-benzyllactaldehyde. As suitable substrates we chose (R)-ethyl-4,5-O,O--cyclohexylidendioxy-2-(E)-pentenoate (1), and (S)-ethyl-4-benzyloxy-2-(E)--pentenoate (2) which were prepared as previously described.[18]

The osmylation of α,β-unsaturated ester (R)-(E)-(1) in the presence of chiral or achiral amines as ligands was first examined (Table 1). The stoichiometric reaction in the presence of quinuclidine (entry 2) proved to be more stereoselective than the corresponding catalytic process,[&] promoted either by an achiral (entry 1) or a chiral[4] (entry 6) base, affording (4) with

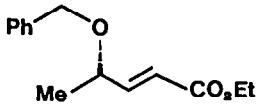
[&] To obtained a reasonably fast reaction the catalytic osmylations were carried out at 20°C (see Table 1).



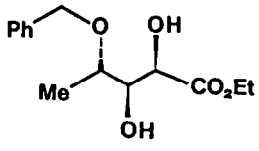
(R)-(E)-(1)



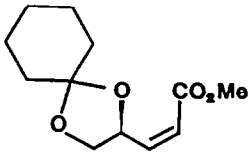
(4a) + (4b)



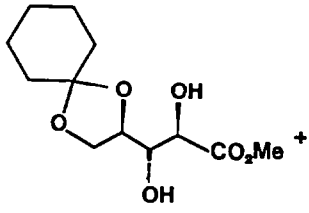
(S)-(E)-(2)



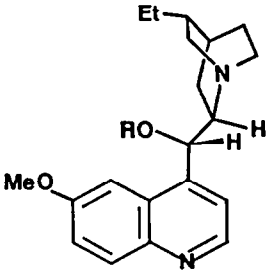
(5a) + (5b)



(R)-(Z)-(3)

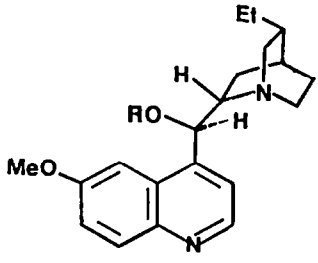


(6a) + (6b)



(7) R = Ac

(8) R = p-Cl-C_6H_4-CO



(9) R = Ac

(10) R = p-Cl-C_6H_4-CO

noticeable level of stereoselection in favor of isomer (4a).[§] The inerent diastereofacial selectivity of substrate (1) can be further improved by stoichiometric osmylation in the presence of matching[17] quinidine derived chiral ligands (7) or (8) (entries 3,4), while the mismatching[17] pair is represented by the combination of (1) and quinine derived ligand (9) (entry 5), which leads to a virtually stereorandom reaction.

The (S)-(E)-benzyloxy derivative (2) was found to be less stereoselective (entries 7-10, Table 1). However, a satisfactory level of stereoselection was achieved combining (2) with ligand (9) or (10) to give a predominance of (5a); once again the stoichiometric processes were more effective than the catalytic

Table I. Osmylation of α,β-unsaturated esters (1)-(3).

Entry	Olefin	Method[a]	Ligand	T(°C)	Yield %	Diastereomeric ratio anti:syn[b]
1	(E)-(1)	A	Me_3N	20	73	3:1
2	(E)-(1)	B	Quinuclidine	-20	40	10:1
3	(E)-(1)	B	(7)	-20	80	20:1
4	(E)-(1)	B	(8)	-20	80	≥45:1
5	(E)-(1)	B	(9)	-20	44	1:1.2
6	(E)-(1)	C	(8)	20	75	2.1:1
7	(E)-(2)	B	Quinuclidine	-20	51	4:1[c]
8	(E)-(2)	B	(9)	-20	50	6.5:1[c]
9	(E)-(2)	B	(10)	-20	88	11:1
10	(E)-(2)	C	(10)	20	83	2.9:1
11	(Z)-(3)	A	Me_3N	20	66	1:1[c]
12	(Z)-(3)	B	Quinuclidine	-20	43	1:1
13	(Z)-(3)	B	(7)	-20	100	1:1.5[c]
14	(Z)-(3)	B	(8)	-20	84	1:1.2
15	(Z)-(3)	B	(10)	-20	91	2.5:1

[a] Method A: Catalytic OsO_4 (0.1 mol equiv), $Me_3N{\rightarrow}O$ (2 mol equiv). Method B: Stoichiometric OsO_4, 2 mol equiv of achiral or chiral ligand. Method C: Catalytic OsO_4 (0.0015 mol equiv), chiral catalyst (0.0015 mol equiv), $Me_3N{\rightarrow}O$ (2 mol equiv). [b] As determined by ^1H NMR. [c] As determined by ^1H NMR on the cyclohexylidene derivative (see experimental).

§ Cis-dihydroxylation of (1) with $KMnO_4$ affords a (4a):(4b) 3:1 mixture with a diastereoselectivity comparable to that of the catalytic osmylation, albeit in much lower yield (20%).

ones.** It is generally accepted that cis-dihydroxylation of (E)-α,β-unsaturated esters bearing an alkoxy-substituted allylic stereocenter[3,13] occurs in an anti-fashion, affording 2,3-syn-3,4-anti products. This stereochemical outcome was confirmed in this case by ^{1}H NMR spectroscopy and by comparison of the NMR data with those of similar products of known stereochemistry.[13]

The decrease of stereoselectivity observed on passing from ester (1) to (2) is difficult to rationalize. However, it must be noted that an analogous trend was found in other electrophilic additions to double bonds featuring alkoxy--substituted allylic stereocenters, such as nitrile oxide cycloadditions.[18-20] The stronger donor ability of the CH_2OR group compared to methyl, or a direct through space interaction of the homoallylic oxygen lone pair with the olefin bond were suggested as responsible for this phenomenon.[19]

In order to have access to products with different relative stereochemistry, osmylation of (R)-methyl-4,5-O,O-cyclohexylidendioxy-2-(Z)-pentenoate (3)[18] was also studied. Unfortunately, both the catalytic and the stoichiometric reactions carried out in the presence of achiral bases were non stereoselective with (6a):(6b) ratios close to 1:1 (entries 11 and 12, Table 1); the use of chiral ligands such as (7),(8) and (10), and stoichiometric amounts of OsO_4, produced only a slight increase in stereoselectivity, which remains however synthetically useless (entries 13-15). Thus, analogous esters of different double bond configuration such as (R)-(E)-(1) and (R)-(Z)-(3) behave in a strikingly different mode. Although surprisingly, this was not completely unexpected[4,13-15]. Indeed according to Sharpless[4] (Z)-olefins give "poor results" with regard to asymmetric osmylation in the presence of chiral bases, and different trends in the cis-hydroxylation of chiral (E)- and (Z)-derivatives have also been found by Scolastico,[13] Vedejs,[14] and Fleming.[15] It is however interesting to note that the degree of stereoselectivity observed in the osmylation of (R)-(Z)-(3) is higher with ligand (10) than with (8), which are the mistaching and matching partners, respectively, of (R)-(E)-(1): thus, pair matching does not depend exclusively on the configuration of the allylic stereocenter but also on that of the double bond.

On proposing a tentative rationale for the stereochemical outcome of these osmylations of α,β-unsaturated esters, in our opinion two main factors should be taken into account: first, the complexed osmium-ligand reagent is very bulky and sterically demanding; and, second, the presence of different ligands on osmium influences the stereoselectivity of the reaction of (E)- and not of (Z)-esters. Therefore, in agreement with previous observations,[3] it seems possible that a less hindered and more conformationally mobile (E)-ester can accomodate the attack of the osmium-ligand reagent on a reactive conformation that makes

** For sake of comparison we want to point out that cis-dihydroxilation of ethyl-(E)-cynnamate in the presence of (9) affords a noticeable level (88% e.e.) of chiral discrimination,[16] in agreement with the higher stereoselection generally found for non-functionalized aryl-substituted olefins.[1,4]

diastereofacial discrimination possible.[$] This may not be the case for the (Z)-ester in which the intrinsic steric hindrance about the double bond allow the ester to react only in the conformation that features the allylic hydrogen nearly eclipsed to the alkene; inspection of molecular models indicates that the two diastereofaces of the olefin offer very similar bias to topface and bottomface attack, that are therefore virtually equivalent in energy.

Experimental

Infrared spectra were recorded on a Perkin-Elmer 247 instrument. ^{1}H and ^{13}C NMR spectra were obtained on Varian EM 390 and Varian XL-300 spectrometer in $CDCl_3$ as solvent. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed with a Perkin-Elmer 240 instrument. Silica gel was used for analytical and flash chromatography. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure. All reactions employing dry solvents were run under Argon.

Esters (1)-(3) were prepared as previously described;[18] chiral ligands (7)-(10) were obtained following Sharpless' procedures.[1,4]

General procedure for catalytic osmylation.

A) With trimethylamine-N-oxide dihydrate: to a stirred solution of ester (0.5 mmol) in a 9:1 THF:H_2O mixture (6 ml) cooled at 0°C, $Me_3N{\rightarrow}O.2H_2O$ (1.0 mmol) was added, followed by 0.05 mmol of 0.2 M solution of OsO_4 in toluene. The reaction mixture was stirred overnight at 20°C and was then quenched by the addition of solid $NaHSO_3$. Evaporation of the solvent followed by filtration on a short column of silica gel with Et_2O/MeOH mixtures gave the crude diols, that were further purified by flash chromatography.

B) With chiral ligands (8) and (10): the procedure reported by Sharpless[4] was followed. The reactions were performed on 0.5 mmol of esters. Flash chromatography was used for the final purification.

General procedure for stoichiometric osmylation.

The procedure was the same for achiral or chiral ligands. To a stirred solution of ester (0.5 mmol) and ligand (1 mmol) in toluene (2 ml) cooled at -20°C, 0.5 mmol of a 0.2 M solution of OsO_4 in toluene was added. After overnight stirring at -20°C, H_2O (1 ml) and solid $NaHSO_3$ were added, and the reaction mixture allowed to warm-up to room temperature. The above described work-up gave the diols.

Occasionaly the diols were converted into the corresponding O,O-cyclohexylidene derivatives to allow easier diastereoisomeric ratios determination with 1,1-diethoxycyclohexane or 1,1-dimethoxycyclohexane for (5a,b) and (6a,b), respectively, in the presence of catalytic p-toluenesulphonic acid.

Yields and diastereoisomeric ratios are reported in Table 1. Relevant ^{1}H NMR data for diols (4)-(6) are reported in this order: δ (ppm) H-C2, H-C3, H-C4;

[$] Different reactive conformations for osmylation of chiral (E)-allyl derivatives have been proposed.[2,3,13-15,20]

J_{2-3}; J_{3-4} (Hz).

Ethyl-2,3-dihydroxy-4,5-O,O-cyclohexylidendioxy pentanoate (4a,b). Eluant: diethylether. Found: C% 56.60; H% 8.14. $C_{13}H_{22}O_6$ requires: C% 56.92; H% 8.08. $[\alpha]_D^{22}$= 22.1 (c 1, $CHCl_3$) for ≥45:1 (4a):(4b) mixture. Relevant ^{1}H NMR data for (4a): 4.39 (d); 3.84 (dd); 4.00-4.13 (m); 1.4, 8.3; for (4b): 4.15 (d); 3.85 (dd); 4.05-4.15 (m); 2.7, 8.0.

Ethyl-2,3-dihydroxy-4-benzyloxypentanoate (5a,b). Eluant: diethylether:hexanes 7:3. $[\alpha]_D^{22}$= 20.15 (c 1, $CHCl_3$) for a (5a):(5b) 11:1 mixture. The ^{13}C NMR data were identical to those reported.[13] Relevant ^{1}H NMR data for (5a): 4.55 (d); 4.09 (dd); 3.65 (dq); 1.5, 9.0; for (5b): 4.20 (d); 3.78 (bd); 3.78 (bq); 1.8, 0.5.

Relevant ^{1}H NMR data for the cyclohexylylidene derivatives of (5a): 4.46 (d); 4.26 (dd); 3.70-3.80 (m); 6.0, 4.7; of (5b): 4.42 (d); 4.30 (dd); 3.68-3.77 (m); 6.5, 4.5.

Methyl-2,3-dihydroxy-4,5-O,O-cyclohexylidendioxypentanoate (6a,b). Eluant: diethylether. Found: C% 55.55; H% 7.80. $C_{12}H_{20}O_6$ requires: C% 55.37; H% 7.74. $[\alpha]_D^{22}$= 32.7 (c 0.6, $CHCl_3$) for (6a). $[\alpha]_D^{22}$= 6.3 (c 0.2, $CHCl_3$) for a 23:1 (6b): (6a) mixture. Relevant ^{1}H NMR data for (6a): 4.41 (d); 3.85 (dd); 4.09-4.18 (m); 3.5, 8.0; for (6b): 4.25 (d); 3.75 (dd); 4.18-4.29 (m); 5.0, 3.0. Relevant ^{1}H NMR data for the bis-cyclohexylidene derivative of (6a): 4.71 (d); 4.20 (dd); 4.02-4.11 (m); 5.7, 8.6; of (6b): 4.59 (d); 4.30 (dd); 4.13-4.24 (m); 7.0, 5.3.

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