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On the Asymmetric Dihydroxylation of (2S,3R) 5-Phenylpent-4-en-2,3-diol Derivatives

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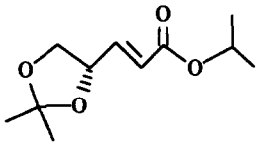
Abstract. Sharpless OsO_4 asymmetric dihydroxylation of derivatives of the unsaturated (2S,3R) diols **2** affords products **7a,b** and **10** and the diastereoisomers **8a,b** and **11**, respectively, in ratios depending upon the nature of the ligand (dihydroquinine and dihydroquinidine 4-chlorobenzoates), the mode of hydroxyl groups protection and the pattern of double bond substitution.

A recent report[1] on the steric outcome of the asymmetric olefin dihydroxylation (AD) of the sugar precursor **1**, using a new class of dihydroquinidine/dihydroquinine-based ligands, induces us to present the results of AD experiments on 1,3-dioxolane **6** and diacetate **9**, obtained from diols **2**. Since the latter compounds are structurally related to **1**, the results obtained in the present study might offer further information on the factors governing the mode of functionalization of olefins bearing stereogenic center(s) adjacent to the double bond[2,3] and give access to (regiospecifically protected) C-6--C-5 tetrols **3** and **4**, masked forms of 6-deoxy and 6-deoxy-3-*C*-methyl hexoses of the *L*-series.



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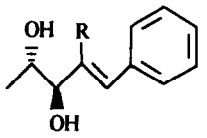
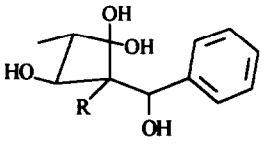


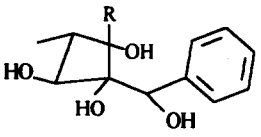
2a R=H
2b R=Me

Diols **2** are easily accessible by baker's yeast mediated decarboxylative incorporation of pyruvate into the C-6--C-3 moiety of cinnamaldehyde, followed by reduction of the intermediate (R) hydroxyketone.[4] They have been used as starting materials alternative to carbohydrates in the preparation of 2,3,6-trideoxy and 2,3,6-trideoxy-3-aminosugars of the *L*-series[5] and of a variety of optically active natural products belonging to quite different structural classes.[6] The synthetic pathways involved incorporation into the final products either of a C-6 carbon framework obtained by oxidative degradation of the aromatic ring of derivatives of **2** or of C-4 and

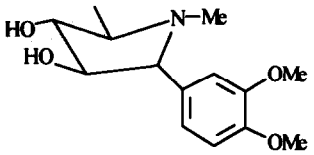
C-5 carbonyl compounds bearing two oxygen-substituted carbon atoms in alpha and beta positions, extruded by ozonolysis of the isopropylidene derivatives of **2**.



3 R=H, Me

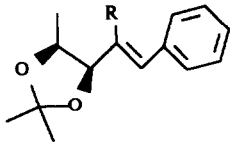


4 R=H, Me

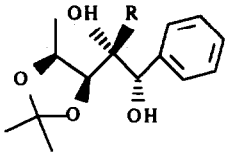


5

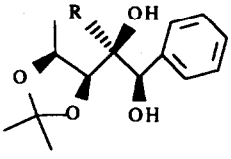
In our interest in new synthetic applications of diols **2** we desired to obtain, in partially protected forms, all the possible stereoisomeric tetrols formally accessible by the different modes of oxidative functionalization of the double bond present in derivatives of **2**. As indicated above, these products could be used not only as starting materials for 6-deoxyhexoses of the *L*-series but also for cyclic, heteroatom containing compounds, including analogs of codonopsine **5**.[7,8]



6 a R=H
b R=Me



7 a R=H
b R=Me



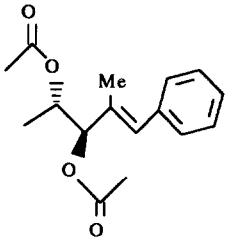
8 a R=H
b R=Me

To this end, we submitted to the Sharpless OsO_4-mediated AD both the isopropylidene and the diacetyl derivatives of **2**. The experiments were performed in the presence of the 4-chlorobenzoates of dihydroquinidine and dihydroquinine (DHQD-CLB and DHQ-CLB), reported, by the time the study was initiated, amongst the most effective ligands,[9] and, for shake of comparison, also in the absence of chiral bases.

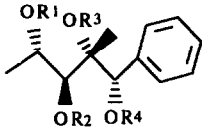
Table 1. Product distribution in the osmate-mediate conversion of **6** into diols **7** and **8**

Entry	Ligand	R in **6**	Ratio **7** : **8**
1	no one	H	3.2 : 1
2	"	Me	2.8 : 1
3	DHQ-CLB	H	13.3 : 1
4	"	Me	32 : 1
5	DHQD-CLB	H	1 : 2.4
6	"	Me	1 : 1.5

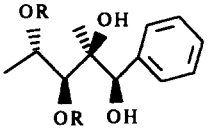
The *syn* 1,3-dioxolanes **6a,b** afford with the potassium osmate (VI) dihydrate/$K_3Fe(CN)_6/K_2CO_3$/*t*-BuOH-H_2O system,[9] under the above mentioned conditions, products **7a,b** and **8a,b** in the ratios reported in **Table 1**. Product distribution and structural assignement are based on GLC analyses and on NMR studies. The major diastereoisomers **7a** and **7b**, obtained in the presence of DHQ-CLB (entries 3 and 4 (**Table 1**)), were directly separated in pure form out of the reaction mixture by crystallization. The relative stereochemistry of **7a** was deduced from the ^1H NMR data. The values of the vicinal coupling constants $J(H_3,H_4)$ and $J(H_4,H_5)$ of 9.8 and 1.7 Hz respectively suggest that the molecule has a rather rigid conformation; H_3 and H_4 are *anti* oriented while H_4 and H_5 are *gauche* and antiperiplanar to the OH-5 and OH-4 groups respectively as suggested by the small value of $J(H_4,H_5)$. Moreover the irradiation of CH_3-2 produces significant NOEs on H-4 (8.5%) ad OH-4 (4.0%) indicating that OH-4 lies on the same side of CH_3-2 group. In addition, by irradiation of H-3 NOEs were observed for OH-4 (6.4%) and OH-5 (4.0%) confirming the spatial proximity of these groups. All these observations allow to establish unequivocally the 4R,5S stereochemistry of **7a**. The interpretation of vicinal coupling constants and NOEs are less clear for compound **8a**, due most probably to some conformational mobility of the molecule; on the other hand the configuration of C_4 and C_5 for **8a** must be opposite to that of **7a** because of the *syn* steric course of the dihydroxylation reaction. Products **7b** and **8b** lack the hydrogen in position 4, thus information about their relative stereochemistry can be deduced only from NOE experiments. The irradiation of CH_3-4 in the case of **8b** produces NOEs on OH-4 (8%), H-3 (5.5%), H-2 (4.5%), CH_3-2 (1%), H-5 (1.5%) and OH-5 (2.4%), clearly showing that CH_3-4 is spatially close to the H-2 and CH_3-2 groups. The same experiment carried out on **7b** shows enhancements for OH-4 (7%), H-5 (6%) and CH_3-2 (1.5%) and no effects for H-2 and H-3 , in agreement with an orientation of CH_3-4 *anti* to H-3 and *syn* to H-5.



9



10 **a** $R^2=R^4=Ac$; $R^1=R^3=H$
b $R^1=R^4=Ac$; $R^2=R^3=H$
c $R^1=R^2=R^4=Ac$; $R^3=H$
d $R^2=R^4=Ac$; $R^1=R^3=C(M2)_2$
e $R^2=R^4=H$; $R^1=R^3=C(Me)_2$



11 R=Ac

Subsequently, diols **2a,b** were acetylated and submitted to the hydroxylation reaction. However, of the two materials, only **9**, arising from trisubstituted **2b**, was transformed, giving rise to products **10** and **11** in the ratios reported in **Table 2**. At first sight, the composition of the reaction mixture resulted quite intriguing. This was due to the fact that the diol obtained as major diastereisomer from **9** is constituted by a ca. 1:1 mixture of

10a and of the regioisomeric material **10b**. These materials are formed by formal 1,4 and 1,3-acetate shifts, respectively, at some stage of the sequence. In fact, in **10a** the acetate group migrated from position 2 to 5, whereas in **10b** migration took place from position 3 to position 5. Regioisomeric **10a** and **10b**, obtained in crystalline form after separation by column chromatography, give rise upon acetylation to triacetate **10c**. The position of acetate esters has been deduced from the ^{1}H NMR spectra of **10a-c** on the basis of the chemical shifts of the proton α to the acetoxy group, while the stereochemistry of **10c** was assigned by chemical correlation with **7b**. To this end, the latter material was deprotected by acid hydrolysis to tetrol **3** (R = Me), directly converted into a triacetate, which resulted identical in every respect to **10c**.

The reasons of the acetate migration accounting for the formation of **10a** and **10b**, are, at present, unclear. However, the obtainment in the AD of **9** of **10a** and **10b**, differing in the mode of hydroxyl groups protection, is of some synthetic interest. Indeed, product **10a** is quantitatively converted into the 1,3-dioxane **10d**, providing, in turn, by basic hydrolysis, the diol **10e**. By AD of derivatives of **2b** are thus available tetraoxygenerated materials bearing two free hydroxyl groups in positions 4 and 5 (**8b**), 2 and 4 (**10a**), 3 and 4 (**10b**) and 3 and 5 (**10e**), respectively.

Comparison of the results of AD of the 1,3-dioxolanes **6a** and **6b** with those recently reported[1] relative to **1** [10:1, 1:1 and 2.6:1 diastereoisomeric ratios] indicates rough similarities as far as the figures relative to **6a** are concerned [entries 3, 5 and 1 of **Table 1**], but a much higher inductive effect by the added alkaloid derivative in the case of the trisubstituted olefin **6b** [entry 4 of **Table 1**]. The diacetate of **2a** was resistent to hydroxylation even under forcing conditions, *i.e.*, 72 h at reflux. Conversely, the trisubstituted analog **9** is undergoing readily hydroxylation in a mode largely dictated by its intrinsic stereochemistry, as shown by the results of **Table 2**. Indeed, already in the absence of added chiral base the 3,4-*anti* diastereoisomer is obtained in 10:1 ratio with the 3,4-*syn* material. Moreover, DHQD-CLB which assists the formation from **6a** and **6b** of an excess of the 3,4-*syn* educts, in the case of **9** fails in the scope [entry 3 of **Table 2**], being obtained a substantial excess of the 3,4-*anti* material.

Table 2. Product distribution in the osmate-mediated conversion of **9** into diols **10** and **11**

Entry	Ligand	Ratio **10:11**
1	no one	10 : 1
2	DHQ-CLB	32 : 1
3	DHQD-CLB	3.5 : 1

Seen together, the above results thus indicate the significant dependence of the mode of oxidative functionalization of structurally related olefins, bearing oxygen-substituted stereogenic carbons adjacent to the double bond, from the mode of hydroxyl groups protection and the pattern of olefin substitution. We will refer in due course on some synthetic applications of the above mentioned materials derived from yeast generated **2** through Sharpless AD.

Acknowledgment. We wish to thank Mrs. Rosanna Bernardi for her contribution in the GLC analysis and MURST for support.

EXPERIMENTAL SECTION

^1H NMR spectra were recorded with a Bruker AC-250 or a Bruker CXP-300 instrument in the FT mode with tetramethylsilane as internal standard. Optical rotations were measured in a 1 dm cell of 1 ml capacity by using a Jasco DIP-181 polarimeter. If no otherwise stated we refer to $[\alpha]^D_{20}$ measured in $CHCl_3$, c = 1. GLC analyses were performed on a DANI 8610 instrument, FID detector, with a fused silica capillary column (crosslinked 5% Ph,Me silicone), 25 m x 0.2 mm i.d. x 0.33 nm film thickness. H_2 carrier gas, 50.7 cm.$^{-1}$ Temperature program: 40 °C (i) (20 °C/min) to 175 °C (2 min) (1 °C/min) to 250 °C.

General Procedure of Asymmetric Hydroxylation[9]

To a stirred mixture made up of the ligand DHQ-CLB or DHQD-CLB (when indicated), 0.6 mmol, $K_3Fe(CN)_6$, 30 mmol, and K_2CO_3, 30 mmol, *t*-BuOH, 50 ml, H_2O, 50 ml, potassium osmate (VI) dihydrate, 0.02 mmol, at 23 °C is added the olefinic substrate, 10 mmol, in 10 ml *t*-BuOH. The reaction mixture is stirred until the reaction is complete (TLC) (usually 4-20 h). After addition of Na_2SO_3, 7 g, the aqueous phase was separated and extracted twice with CH_2Cl_2, 50 ml. The residue obtained upon evaporation of the combined organic extracts was taken up with 200 ml of ethyl acetate, 200 ml, and etracted with dil H_2SO_4, Na_2CO_3 sat. sol. and water. The crude material obtained upon evaporation of the dried solution is submitted to the GLC analysis. The indicated transformation products are obtained in crystalline form either by direct crystallization from hexane or by SiO_2 column chromatographic separation with hexane-ethyl acetate. The yields rane from 80 to 95%.

(2S,3S,4R,5S) 2,3-isopropylidenedioxy-4,5-dihydroxy-5-phenylpentane **7a** *and (2S,3S,4S,5R) 2,3-isopropylidenedioxy-4,5-dihydroxy-5-phenylpentane* **8a**

7a: obtained from **6a** (DHQ-CLB), m.p. 68 °C, $[\alpha]^D_{20}$ +20.9°. Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.54; H, 7.99. Found: C, 66.48; H, 7.89. ^1H NMR (DMSO-d_6) δ 1.13 (3H, σ, CH_3), 1.28 (3H, d, CH_3-2, $J(CH_3,H_2)$ 6.5 Hz), 1.29 (3H, s, CH_3), 3.42 (1H, ddd, H-4, $J(H_3,H_4)$ 9.8, $J(H_4,H_5)$ 1.7, $J(H_4$,OH-4) 9.0 Hz), 4.11 (1H, dd, H-3, $J(H_2,H_3)$ 5.6 Hz), 4.26 (1H, dq, H-2), 4.75 (1H,dd, H-5, $J(H_5$,OH-5) 6.0 Hz), 4.48 (1H, d, OH-4), 5.17 (1H, d, OH-5). **8a** (in the mixture with **7a**): ^1H NMR (DMSO-d_6) δ 1.19 (3H,d, CH_3-2, $J(H_2,CH_3)$ 6.2 Hz), 1.21 (3H, s, CH_3), 1.41 (3H, s, CH_3), 3.48 (1H, ddd, H-4, $J(H_3,H_4)$ 4.0, $J(H_4,H_5)$ 5.6, JH_4,OH-4) 5.6 Hz), 3.73 (1H, dd, H-3, $J(H_2,H_3)$ 4.0 Hz), 4.14 (1H, dq, H-2), 4.45 (1H, d, OH-4), 4.48 (1H, d, H-5), 5.27 (1H, d, OH-5, $J(H_5$,OH-5) 4.8 Hz).

(2S,3S,4R,5S) 2,3-isopropylidenedioxy-4,5-dihydroxy-4-methyl-5-phenylpentane **7b** *and (2S,3S,4S,5R) 2,3-isopropylidenedioxy-4,5-4-methyl-5-phenylpentane* **8b**

7b: obtained from **6b** (DHQ-CLB), m.p. 78-80 °C, $[\alpha]^D_{20}$ +22°. Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.86. Found: C, 67.61; H, 8.84. ^1H NMR (DMSO-d_6) δ 0.84 (3H, s, CH_3-4), 1.25 (3H, s,CH_3), 1.31 (3H, d, CH_3-2, $J(H_2,CH_3)$ 6.6 Hz), 4.23 (1H, d, H-3, $J(H_2,H_3)$ 6.3 Hz), 4.25 (1H, s, OH-4), 4.33 (1H, dq, H-2), 4.39 (1H,d, H-5, $J(H_5$,OH-5) 4.8 Hz), 5.35 (1H, d, OH-5), 7.16-7.44 (5H, m, C_6H_5). **8b** (in the mixture with **8a**): ^1H NMR (DMSO-d_6) δ 0.92 (3H, s, CH_3-4), 1.21 (3H, d, CH_3-2, $J(CH_3,H_2)$ 6.5 Hz), 1.22 (3H, s, CH_3), 1.43 (3H, s, CH_3), 3.52 (1H, d, H-3, JH_2,H_3) 5.2 Hz), 4.07 (1H, dq, H-2), 4.20 (1H, s, OH-4), 4.68 (1H, d, H-5, $J(H_5$,OH-5) 3.9 Hz), 5.12 (1H, d, OH-5), 7.16-7.44 (5H, m, C_6H_5).

(2S,3S,4R,5S) 3,5-diacetoxy-2,4-dihydroxy-4-methyl-5-phenylpentane **10a** *and the 2,5-diacetoxy-3,4-dihydroxy isomer* **10b**

The crude hydroxylation mixture from **9**, on chromatography with increasing amounts of ethyl acetate in hexane, affords first **10a**, m.p. 111 °C. $[\alpha]^D_{20}$ +7.8°. Anal. Calcd. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.95; H, 7.11. ^1H NMR ($CDCl_3$) δ 1.16 (3H, s, CH_3-4), 1.20 (3H, d, CH_3-2, JH_2,CH_3) 6.4 Hz), 2.09 (3H, s, $COCH_3$), 2.10 (3H, s, $COCH_3$), 3.43 (1H, s, OH-4), 3.54 (1H, d, OH-2, J(HP2,OH-2) 3.5 Hz), 4.10 (1H, dqd, H-2), 5.10 (1H,d, H-3, JH_2,H_3) 9.5 Hz), 5.56 (1H, s, H-5), 7.3-7.45 (5H, m, C_6H_5). Subsequently is eluted **10b**, m.p. 87-89 °C, $[\alpha]^D_{20}$ +36.8°. Anal. Calcd. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: 61.84; H, 7.10. ^1H NMR ($CDCl_3$) δ 0.98 (3H, s, CH_3-4), 1.38 83H, d, CH_3-2, $J(H_2,CH_3)$ 6.2 Hz), 2.07 (3H, s, $COCH_3$), 2.15 (3H, s, $COCH_3$), 2.61 1H, s, OH-4), 3.14 (1H,d, OH-3, $J(H_3$,OH-3) 5.5 Hz), 3.68

(1H, t, H-3, J(H_2,H_3) 5.0 Hz), 5.19 (1H, qd, H-2), 5.90 (1H, s, H-5), 7.3-7.43 (5H, m, C_6H_5).

(2S,3S,4R,5S) 2,3,5-triacetoxy-4-hydroxy-4-methyl-5-phenylpentane **10c**

This material was obtained upon treatment of **10a** and **10b** with Ac_2O, 10 mol. eq., in pyridine overnight, followed by aqueous work up. Thick oil. The products obtained in the two experiments showed $[\alpha]^D_{20}$ -11.6° and -11.5°, respectively, and identical ^1H NMR spectra ($CDCl_3$) δ 1.02 (3H s, CH_3-4), 1.25 (3H, d, CH_3-2, J(H_2,CH_3-2) 6.1 Hz), 2.05 (3H, s, $COCH_3$), 2.06 (3H, s, $COCH_3$), 2.11 (3H, s, $COCH_3$), 2.75 (1H, s, OH-4), 5.27-5.37 (2H, m, H-2 and H-3), 5.57 (1H, s, H-5), 7.23-7.43 (5H, m, C_6H_5).

Conversion of **7b** *into* **10c**

Product **7b**, 2.66 g, 10 mmol, in 50% methanolic 2N HCl is stirred at room temperature overnight. The reaction mixture is concentrated in the cold under vacuum, diluted with water and extracted four times with CH_2CCl_2. The residue obtained upon evaporation of the dried organic phase is dissolved in 10 ml of dry pyridine and treated with 10 ml of Ac_2O. After standing overnight at room temperature, aqueous work up and chromatography through a short path of SiO_2, afforded **10c**, $[\alpha]^D_{20}$ -11.4° in 75% overall yield. The ^1H NMR spectrum is superimposable to that of the material prepared from **10a** and **10b**.

(2S,3S,4R,5S) 3,5-dihydroxy-2,4-isopropylidenedioxy-4-methyl-5-phenylpentane **10e**

The diacetate diol **10a**, 3.1 g, 10 mmol, in 30 ml of dry acetone and 30 ml of 2,2-dimethoypropane is refluxed 30 min in the presence of 100 mg of 4-toluenesulfonic acid. The reaction mixture is diluted with ethyl acetate and washed with $NaHCO_3$ sol.. The residue obtained upon evaporation of the solvent is chromatographed through a short SiO_2 path to give **10d**, oil, 3.2 g, 88%, $[\alpha]^D_{20}$ +12.4°. ^1H NMR ($CDCl_3$) δ 1.17 (3H, d, CH_3-2, J(H_2,CH_3-2) 6.2 Hz), 1.26 (3H,s, CH_3-4), 1.41 (3H, s, CH_3), 1.42 (3H, s, CH_3), 2.05 (3H, s, $COCH_3$), 2.09 (1H, s, $COCH_3$), 4.00 (1H, dq, H-2, J(H_2,H_3) 9.5 Hz), 5.05 (1H, d, H-3), 5.36 (1H, s. H-5), 7.24-7.43 (5H, m, C_6H_5). Product **10d**, 2.6 g, 7.5 mmol, in 20 ml of methanol is treated with 20 ml of 1N NaOH at 30-40 °C for 1 h. The reaction miture is diluted with water and extracted three times with CH_2Cl_2. The residue obtained upon evaporation of the dried organic extract is chromatographed through a short path of SiO_2 to afford **10e**, oil, 2.1 g, 80%, $[\alpha]^D_{20}$ +10.3°. ^1H NMR ($CDCl_3$) δ 1.19 (3H, s, CH_3-4), 1.28 (3H, d, CH_3-2, J(H_2,CH_3-2) 6.2 Hz), 1.39 (3H, s, CH_3), 1.47 (3H, s, CH_3), 2.20 (1H,s br, OH), 2.90 (1H,s br, OH), 3.66 (1H, d, H-3, J(H_2,H_3) 9.5 Hz), 3.90 (1H, dq, H-2), 4.49 (1H, s, H-5), 7.26-7.39 (5H, m, C_6H_5).

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