Pergamon

Tetrahedron Letters, Vol. 38, No. 28, pp. 5051-5054, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01102-7

Direct Asymmetric α-Hydroxylation of β-Hydroxyketones

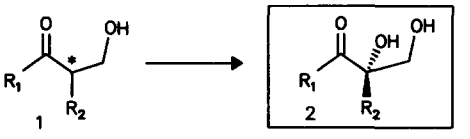
Margus Lopp*, Anne Paju, Tõnis Kanger, Tõnis Pehk[1],

Institute of Chemistry, Akadeemia tee 15, Tallinn EE0026, Estonia;

[1]Institute of Chemical Physics and Biophysics, Akadeemia tee 27, Tallinn EE0026, Estonia

Abstract. Direct oxidation of racemic β-hydroxyketones **1a-c** under Sharpless oxidation conditions resulted in the enantiomeric α,β-dihydroxyketones **2a** in 97% *ee*, **2b** in 86% *ee* and **2c** in 95% *ee* respectively, in 37-58% of isolated yield. The oxidation is assumed to proceed *via* an allylic enolate intermediate.

In our recent publication we showed that substituted racemic and prochiral cyclobutanones undergo Baeyer-Villiger oxidation while subjected to Sharpless oxidation conditions, resulting in enantiomeric lactones.[1] In the present study we have investigated the direct oxidation of α-substituted ketones with 5- and 6-membered ring and with an open chain (**1a, 1b** and **1c** respectively[2]) under Sharpless oxidation conditions. Surprisingly enough, we found that these ketones resulted in α,β-dihydroxyketones (**2a-c** respectively) instead of Baeyer-Villiger oxidation products under ordinary oxidation conditions. (Scheme 1). Since the enantiomerically pure α-hydroxyketones are of great importance as the chiral building blocks in the synthesis of several natural products[3], we have investigated the reaction in a more detail. The obtained results are presented in the Table.



a $R_1 = R_2 = -(CH_2)_3-$
b $R_1 = R_2 = -(CH_2)_4-$
c $R_1 = R_2 = CH_3$

Scheme 1

The stereoselectivity of hydroxylation depended on the substrate and varied from 86-97% *ee* in the best examples. The highest stereoselectivity (97% *ee*) was obtained in the case of α-hydroxymethyl cyclopentanone **1a**. It is noteworthy that the oxidation of the open chain ketone 1-hydroxy-2-methyl-3-butanone **1c** also occurs with high enantioselectivity (up to 95% *ee*). The oxidation of α-hydroxymethyl cyclohexanone proceeds with slightly lower selectivity (86% *ee*). We observed that the present direct oxidation process required bigger reagent/substrate ratio than both the ordinary Sharpless epoxidation process[4] and the lactonization of

cyclobutanones.[1] So, the best results were obtained at the ratio of the substrate/Ti(O*i*Pr)$_4$/(+)-DET/*t*-BuOOH 1/3/3.6/1.2. Also, the data revealed that the bigger excess of *t*-BuOOH in the reagent diminished the yield (cf. Table, No. 6 and No. 7). In this case a considerable amount of the substrate remained unchanged. The isolated yields of dihydroxyketone **2** were up to 37% for **2a**, up to 54% for **2c** and up to 58% for **2b**. In the case of **2b** it can be definitely stated that the conversions of racemic substrate **1b** >50% occurs without the enantiomeric purity of the of dihydroxylated product **2b** being reduced. (Table No. 4 and No.5).

In the case of cyclic substrates the formation of ω-hydroxy ketoacid **3** (oxidative cleavage product) was detected. The amount of isolated ketoacid **3** was slightly bigger in the case of 5-carbon ring than in the case of 6-carbon ring. (see Table, Nos. 1-6).

Table. Hydroxylation of β-hydroxyketones at Sharpless oxidation conditions.[5]

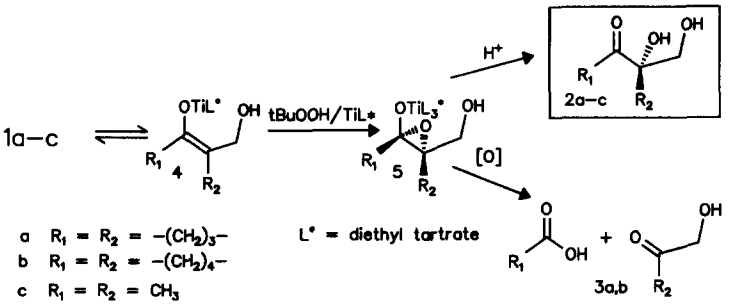
No	Compound	Conditions			Product				Recovered		
		Ti(O*i*Pr)$_4$/(+)DET	t-BuOOH	time	2			3	1		
		ratio (eq)	eq	h	yield %	$[\alpha]_D$[a]	*ee*%[b]	yield%	yield%	$[\alpha]_D$[c]	*ee*%[d]
1	**1a**	1.5/1.8	1.5	48	11	+53°	75	9	56	+21°	10
2	**1a**	2.4/2.9	1.2	46	32	+81°	97	12	33	+40°	24
3	**1a**	3/3.6	1.2	46	37	+79°	97	12	23	+32°	21
4	**1b**	1.5/1.8	1.5	46	20	+101°	86	5	54	0	0
5	**1b**	2.3/2.8	1.15	46	55	+101°	86	8	15	0	0
6	**1b**	3/3.6	1.2	46	58	+101°	86	8	3	0	0
7	**1b**	3/3.6	3	46	15	+96°	85	9	37	0	0
8	**1c**	3/3.6	1.2	46	29	-10°	95	-	49	+5°	15
9	**1c**	3/3.6	1.2	92	47	-10°	93	-	30	+10°	29
10	**1c**	3/3.6	1.2	168	54	-10°	91	-	21	+13°	35
11	**1d**	3/3.6	1.2	72	-	-	-	-	e	-	-
12	**1e**	3/3.6	1.2	72	-	-	-	-	e	-	-

a measured in 96% ethanol
b determined by HPLC and/or ^{1}H and ^{13}C NMR spectra of the primary *R*-(-)-α-methoxyphenylacetic acid mono esters
c measured in CH_2Cl_2
d determined by HPLC from the *R*-(-)-α-methoxyphenylacetic acid esters
e the substrate remained unchanged

It has been shown that the titanium enolates of ketones can be oxidized by *tert*-butylhydroperoxide affording α-hydroxy ketones with good diastereoselectivity.[6] It has also been found that the asymmetric dihydroxylation of methyl- and trimethylsilyl enol ethers with OsO_4 using *AD-mix*-catalysts results in α-hydroxy ketones with excellent enantioselectivity.[7] Salen Mn(III) complexes[8] and oxaziridines [9] have found to be efficent in the synthesis of α-hydroxy ketones.

Our present results can be rationalized on the assumption that β-hydroxy ketones form a kinetic enolate with the Sharpless reagent. The presence of β-hydroxy group and the branching of the substrate in α-position favour the formation of the allylic enolate **4** particularly. Then the oxidation of the formed allylic units proceed *via* the

Sharpless oxidation mechanism, resulting in the epoxides **5**. These epoxides rearrange in acidic media in α,β-dihydroxyketones **2** (Scheme 2).



Scheme 2

The assumption that the allylic intermediates are formed in the process of oxidation is supported by the fact that the existance of the OH-group in β-position is essential for oxidation. Thus, α-branched ketones, which do not bear β-hydroxy group (α-methylcyclopentanone **1d** and α-methylcyclohexanone **1e**) were not oxidized at ordinary reaction conditions. (see Table, No.11 and No.12).

The formation of an allylic achiral intermediate necessarily causes the racemization of the substrate. Indeed, we found that in the case of compound **1b** the unreacted substrate did not reveal optical activity.This points to the possible formation of enolate in the equilibrium process. However, in the case of compounds **1a** and **1c** the recovered substrate from the reaction mixture revealed optical activity (*ee* up to 35%). This is an indication that enantioselection does exists in the enolate formation step, but in the case of **1a** and **1c** the ketone/enolate equilibrium is shifted towards the ketone reducing the influence of the kinetic racemization.

The formation of α,β-dihydroxyketones **2** was accompanied by the oxidative cleavage of the C-C bond, resulting in ω-hydroxy ketoacids **3**. The excess of *t*-BuOOH (3 equivalents of *t*-BuOOH instead of usual 1.2 equivalents) diminishes the yield of ketone diol **2.** At the same time we did not observe any substantial increase in the amount of cleavage product **3**. Thus, one might assume that the excess of *t*-BuOOH supresses the formation of enolate **4** and, therefore, the subsequent oxidation.

The structure of the substrates and the products was determined by ^{13}C NMR. (at 500 MHz Bruker AMX-500 instrument. 2D ^{1}H-^{1}H and ^{1}H-^{13}C COSY correlations were applied when necessary). The characterictic chemical shifts are presented in [10]. The *ee* of the compounds were determined using R-(-) α-methoxyphenyl acetic acid esters of the compounds by HPLC and/ or by ^{13}C NMR spectra.[11] The absolute configurations of the compounds were not specially determined. The structures in Figs 1 and 2 correspond to Sharpless AE face-selection rule for (+)-DET.[12]

Acknowledgement.: This study was supported by the Estonian Science Foundation grants 2076 and 2293.

References and Notes.

1. Lopp M., Paju A., Kanger T., Pehk, T. *Tetrahedron Lett.*, **1996,** *37*, 7583-7486.

2. Compounds **1a** and **1b** were prepared according to Taylor R.J.K., Wiggins, K., Robinson, D.H. *Synthesis.*, **1990,** 589-590; **1c** was purchased from Aldrich.

3. Davis, F.A., Chen, B.-C. Chem.Rev., **1992,** *92*, 919-934.

4. Cao, Y., Hanson, R.M., Klunder, J.M., Ko, S.Y., Masamune ,H., Sharpless, K.B. *J.Am.Chem.Soc.*, **1987,** *109*, 5765.

5. A typical experiment: To a solution of $Ti(OiPr)_4$ (3 mmols) in CH_2Cl_2 (6 ml) (+)-diethyltartrate (DET, 3.6 mmoles) was added and the mixture was stirred for 15 min at -20°C. After addition of β-hydroxyketone **1** (1 mmol) in CH_2Cl_2 (2 ml) the mixture was stirred for 30 min. Now *t*-BuOOH (1.2 mmoles in toluene,~3.4 M solution) was added and the mixture was kept at -20°C for 46 h. The reaction was quenched by stirring with citric acid monohydrate solution (3 mmoles in a mixture of 10% acetone in ether) at room temperature for 1 h. The reaction mixture was filtered through a path of celite, the celite layer was washed with acetone and methanol. The solutes were concentrated and the residue was purified on silica gel.

6. Shultz, M Kluge, R., Scüβler, M., Hoffmann, G.. *Tetrahedron,* **1995**, *51*, 3175-3180.

7. Hashiyama, T, Morikawa, K., Sharpless, K.B. *J.Org.Chem.*, **1992,** *57*, 5067-5068.

8. Fukuda T., Katsuki T. *Tetrahedron Lett.*, **1996,** *25*, 4389-4392; Adam, W., Frell, R.T., Mock-Knoblauch C., Saha-Möller, C.H. *Tetrahedron Lett.*, **1996,** *36*, 6531-6534.

9. For example a recent work by Gala D., DiBenedetto D.J., Mergelsberg I., Kugelman, M. *Tetrahedron Lett.*, **1996,** *45*, 8117-8120.

10. ^1H and ^{13}C chemical shifts in $CDCl_3$, δ_{TMS}: **2a**: δ^1H 1.87 m and 1.93 m (H4), 2.07m (H3), 2.38 t 2*8.1 (H5), 3.62 d and 3.67 d 11.9 (H6), 3.18 bs (OH); δ ^{13}C 219.55 (C1), 78.78 (C2), 32.43 (C3), 17.23 (C4), 35.29 (C5), 64.95 (C6). **2b**: δ^1H 1.60 m (H3a) and 2.16 m (H3e), 1.67 m (H4a) and 1.81 m (H4e), 1.68 m (H5a) and 2.09 (H5e), 2.53 m and 2.55 m (H6ae), 3.66 d and 3.96 d 11.7 (H7), 2.77 and 4.31 bs (OH); $\delta^{13}C$ 212.59 (C1), 80.01 (C2), 37.40 (C3), 22.38 (C4), 27.70 (C5), 38.27 (C6), 66.71 (C7). **2c**: 3.64 d and 3.85 d 11.7 (H1), 1.29 s (2-CH_3), 2.28 s (H4); $\delta^{13}C$ 67.78 (C1), 79.82 (C2), 210.96 (C3), 23.82 (C4), 21.20 (2-CH_3).

11. ^1H and ^{13}C chemical shifts in $CDCl_3$ of *R*-(-)-α-methoxyphenylacetic acid mono esters of reaction products **2a** to **2c**, δ_{TMS}: **2a**, major isomer δ^1H 1.87 m and 1.89 m (H3), 1.73 m and 1.94 m (H4), 2.25 m and 2.27 m (H5), 4.08 d and 4.32 d 11.5 (H6), 3.42 s (OCH_3), 4.77 s ($CHOCH_3$), 7.35-7.41 m (Ph); $\delta^{13}C$ 216.41 (C1), 77.34 (C2), 32.84 (C3), 16.91 (C4), 34.95 (C5), 66.18 (C6), 57.42 (OCH_3), 82.28 (CHO), 135.82 (*s*-Ph), 127.18 (*o*-Ph), 128.64 (*m*-Ph), 128.87 (*p*-Ph), 170.45 (COO); minor isomer δ^1H 1.87 m and 1.89 m (H3), 1.71 m and 1.96 m (H4), 2.31 m and 2.35 m (H5), 4.06 d and 4.34 d 11.6 (H6), 3.40 s (OCH_3), 4.79 s ($CHOCH_3$), 7.35- 7.41 (Ph); $\delta^{13}C$ 216.44 (C1), 77.67 (C2), 32.86 (C3), 16.89 (C4), 34.73 (C5), 66.29 (C6), 57.41 (OCH_3), 82.19 (CHO), 135.89 (*s*-Ph), 127.17 (*o*-Ph), 128.68 (*m*-Ph), 128.88 (*p*-Ph), 170.54 (COO). **2b**, major isomer δ^1H 1.60 m and 2.13 m (H3), 1.62 m and 1.77 m (H4), 1.58 m and 2.02 m (H5), 2.17 m 2.31m (H6), 4.18 d and 4.57 d 11.7 (H-7), 4.09 s (OH), 3.40 s (OCH_3), 4.76 s ($CHOCH_3$), 7.34 m (*p*-Ph), 7.36 (*m*-Ph), 7.37 m (*o*-Ph); δ ^{13}C 210.23 (C1), 77.88 (C2), 38.20 (C3), 22.52 (C4), 27.58 (C5), 37.89 (C6), 68.39 (C7), 57.38 (OCH_3), 82.01 (CHO), 135.87 (*s*-Ph), 127.01 (*o*-Ph), 128.61 (*m*-Ph), 128.78 (*p*-Ph), 170.51 (COO); minor isomer δ^1H 1.61 m and 2.13 m (H3), 1.64 m and 1.77 m (H4), 1.64 m and 2.09 m (H5), 2.54 m (H6), 4.16 d and 4.60 d 11.7 (H7), 3.93 s (OH), 3.38 s (OCH_3), 4.76 s ($CHOCH_3$), 7.35 m (*p*-Ph), 7.37 (*m*-Ph), 7.41 (*o*-Ph); $\delta^{13}C$ 210.52 (C1), 77.95 (C2), 37.84 (C3), 22.42 (C4), 27.52 (C5), 38.23 (C6), 68.18 (C7), 57.31 (OCH_3), 82.16 (CHO), 135.81 (*s*-Ph), 127.12 (*o*-Ph), 128.65 (*m*-Ph), 128.88 (*p*-Ph), 170.51 (COO). **2c**, major isomer δ^1H 4.17 d and 4.34 d 11.7 (H1), 1.27 s (2-CH_3), 3.92 s (OH), 1.86 s (H4), 3.40 s (OCH_3), 4.75 s ($CHOCH_3$), 7.33-7.41 m (Ph); $\delta^{13}C$ 68.95 (C1), 77.59 (C2), 21.65 (2-CH_3), 208.76 (C3), 23.45 (C4), 57.38 (OCH_3), 82.09 (CHO), 135.98 (*s*-Ph), 127.09 (*o*-Ph), 128.69 (*m*-Ph), 128.89 (*p*-Ph), 170.23 (COO); minor isomer δ^1H 4.22 d and 4.32 d 11.7 (H1), 1.29 s (2-CH_3), 3.65 s (OH), 2.13 s (H4), 3.39 s (OCH_3), 4.75 s ($CHOCH_3$), 7.33-7.41 m (Ph); $\delta^{13}C$ 68.79 (C1), 77.76 (C2), 21.50 (2-CH_3), 209.16 (C3), 24.02 (C4), 57.35 (OCH_3), 82.33 (CHO), 135.87 (*s*-Ph), 127.09 (*o*-Ph), 128.69 (*m*-Ph), 128.92 (*p*-Ph), 170.31 (COO).

12. Finn, M.G., Sharpless, K.B. On the Mechanism of Asymmetric Epoxidation with Titanium-Tartrate Catalysts. In: *Asymmetric Synthesis;*Morrisson ,J.D., Ed.; Academic Press, New York, 1985; p. 247.

(*Received in UK* 2 *April* 1997; *revised* 3 *June* 1997; *accepted* 6 *June* 1997)