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Asymmetric Baeyer-Villiger Oxidation of Cyclobutanones

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Abstract: The asymmetric Baeyer-Villiger oxidation of racemic cyclobutanones **1**, **2**, and **3** and a prochiral cyclobutanone **4** under Sharpless oxidation conditions resulted in the enantiomeric lactones **5** *ee* 34%, **6** *ee* 53%, **7** *ee* 75% and **8** 40% *ee* respectively. Copyright © 1996 Elsevier Science Ltd

Baeyer-Villiger oxidation of cyclic ketones is a convenient and widely used method for the synthesis of lactones and/or hydroxy carboxylic acids[1]. Different catalytic[2] and biocatalytic[3] processes have been developed to perform this reaction. Surprisingly, a possibility to obtain enantiomeric lactones by asymmetric chemical oxidation of racemic or prochiral ketones using chiral catalysts has been so far neglected (with two exceptions only: cyclic ketones have been oxidized 1) with chiral Pt catalyst and H_2O_2 up to 58% *ee*[4] and 2) with chiral Ni and Cu complexes and O_2 in the presence of oxygen acceptor up to 69% *ee* [5]). In the present study we have investigated the asymmetric Baeyer-Villiger oxidation of cyclobutanones by a "Sharpless catalyst"[6] in order to develop a method for the synthesis of enantiomeric γ-hydroxy acids (and the corresponding lactones). It has been shown previously that these compounds might be of interest due to their biological activity.[7]

The racemic ketones **1**, **2** and **3**, and a prochiral cyclobutanone **4** were chosen as model compounds by us. The results are presented in the Table.[8]

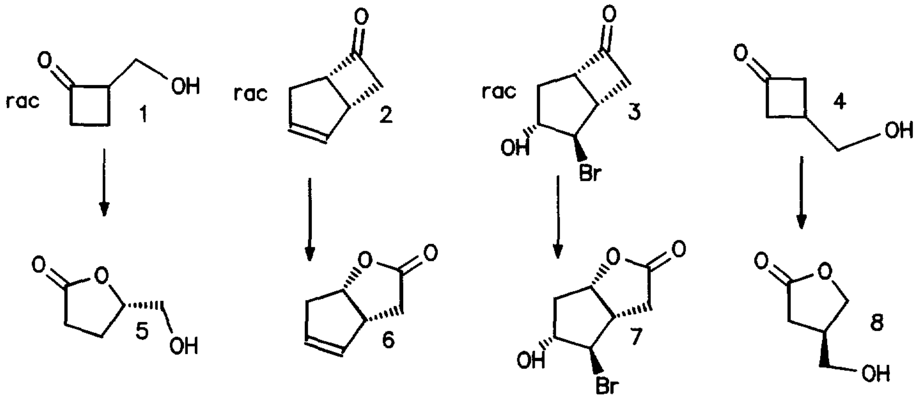

***Table*. Enantioselective Baeyer-Villiger Oxidation of Cyclobutanones 1-4**

Compound	Product	DMT		DET		DIPT	
		Conversion%	*ee*%	Conversion%	*ee*%	Conversion%	*ee*%
1	**5**	-	-	35 (4.5h)[a]	37	35 (6h)[a]	34
2	**6**	-	-	7	53	8(-5°C,48h)	34
3	**7**	49	34	40[b,e]	75	28[c,d]	67
4	**8**	9(-5°C,96 h)	27	14(-5°C,96h)	40	22(-5°C,96h, 31h RT)	33

[a] 1.5 times more diluted catalyst solution was used; at usual conditions the conversion was 51% and *ee* 33% in the case of DIPT.
[b] molecular sieves (4Å powder) were added; without the additive the conversion was 41% and *ee* 73%;
[c] the same result was obtained at the ratio of ketone:DIPT:$Ti(Oi\text{-}Pr)_4$:*t*-BuOOH 1:2.4:2:1.5;
[d] when MCPBA was used as an oxidant the conversion was 20% and *ee* 38% at the ratio of the reagents 1:1.8:1.8:0.6 (MCPBA);
[e] when 1 eq. of water was added the conversion was 4% and *ee* 41%

The enantioselectivity of the oxidation depends on the substrate and the oxidation conditions (oxidant composition, temperature, water content). For different substrates enantioselectivity varies from 27% *ee* to 75% *ee*. It is noteworthy that the existence of OH group in the substrate is not essential for determining the stereoselectivity. So, the oxidation of ketone **2**, which does not bear a OH group, resulted in lactone **6** in 53%*ee*, while hydroxyketones **1** and **4** resulted in lactones **5** and **8** only in 34% *ee*. The best enantioselectivity (75%*ee*) was obtained for the most bulky ketone (ketone **3**). This result suggests a possible steric influence on the oxidation selectivity. It should be mentioned that the oxidation of both ketones **1** (racemic, kinetic control) and **4** (prochiral, thermodynamic control) resulted in similar selectivity.

The oxidation was performed at Sharpless oxidation conditions.[9] In these conditions *tert*-butylhydroperoxide is used as the oxidizing agent. Although *tert*-butylhydroperoxide is not a common Baeyer-Villiger oxidant, the α-branched ketones **1** and **3** with OH-group were readily converted into lactones **5** and **7**, respectively, while the reaction of the α-unbranched ketone **4** resulting in lactone **8** was considerably slower. We tried to modify the catalyst replacing *t*-BuOOH by a common Baeyer-Villiger oxidant - *m*-chloroperbenzoic acid. In these modified conditions the oxidation of ketone **3** proceeds only in moderate enantioselectivity (38 % *ee*) and unsatisfactory isolated yield of the product. This result, however, seems promising enough to continue a search for new oxidants for tartaric acid ester-Ti complex.

Different tartaric acid esters were used as the asymmetric component in the catalyst. The highest selectivity was obtained for (+)-diethyltartrate (DET), while the catalyst with (+)-diisopropyltartrate (DIPT) was slightly and with (+)-dimethyltartrate (DMT) considerably less selective. As expected the reaction rate for the esters was in the following order: DMT > DET > DIPT. When DMT was used as the chiral inductor a partial decomposition of the catalyst in the course of the oxidation reaction was observed. It is known that traces of water may influence the Sharpless oxidation reaction.[9] Our experiments, in which special measures to avoid the traces of water in the reaction mixture were not used, revealed slightly lower selectivity as compared to the experiments with molecular sieves. On the other hand, with the addition of 1 equivalent of water[10] to the catalyst both the oxidation rate and enantioselectivity were drastically reduced.

The observation that the order of the addition of the oxidant and the ketone did not influence the enantioselectivity refer to the possible complexation of both compounds, the substrate and the oxidant, to the catalyst.

All substrates were prepared according to known procedures.[11] The reaction products were identified by ^{1}H and ^{13}C NMR spectroscopy and/or by comparing with literature data.[12] The ratio of the formed enantiomers was determined from the ratio of diastereomers of the corresponding *S*-O-methylmandelic acid esters by HPLC[13] (in the case of **5** and **7**) or/and ^{13}C NMR spectroscopy[14] (in the case of **7** and **8**), and in the case of compound **6** from the comparison of the value of $[\alpha]_D^{20}$ with that from literature[15]. The absolute configuration of the oxidation products was determined in the case of **6** on the basis of the sign of the optical rotation of the compound[15] and, in the case of **7**, on the basis of the ^{13}C NMR spectra of the corresponding *S*-O-methylmandelic acid esters (according to [16]), and of the sign of the optical rotation of the unreacted ketone **3**.[17] The possibility of the determination of the absolute configuration of chiral primary alcohols from ^{13}C NMR spectra of O-methylmandelic acid esters of these compounds is currently under study and will be published elsewhere. Our suggestions are referred in note [18].

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8. A typical experiment: To a solution of Ti(O*i*-Pr)$_4$ (1.5 mmoles) in 6 mL of CH$_2$Cl$_2$ tartaric acid ester (1.8 mmoles) was added and the mixture was stirred for 15 min at -20°C. After addition of a cyclobutanone (1 mmol in 2 mL of CH$_2$Cl$_2$) the mixture was stirred for additional 30 min. Now, *t*-BuOOH (1.5 mmoles in toluene, ~ 3.4M solution) was added and the mixture was kept at -20°C for 44 h.The reaction was quenched by stirring with citric acid monohydrate solution (1.5 mmoles in a mixture of 10% acetone in ether) at 20°C for 1 h. The reaction mixture was filtered through a path of celite and purified by column chromatography on silica gel.

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12. NMR spectra (^{1}H, ^{13}C, also 2D FT ^{1}H-^{1}H and ^{1}H-^{13}C COSY correlation diagrams were measured in CDCl$_3$ solution on a Bruker AMX-500 instrument.**5**: ^{1}H NMR δ 2.10 (dddd, *J*= 6.8, 8.0, 10.0, 12.9 Hz, H-3); 2.23 (dddd, *J*= 5.8, 7.7, 10.0, 12.9 Hz, H-3); 2.49 (ddd, *J*= 8.0, 10.0, 17.9 Hz, H-2); 2.57 (ddd, *J*= 5.8, 10.0, 17.9 Hz, H-2); 3.60 (dd, *J*= 4.6, 12.5 Hz, H-5); 3.83 (dd, *J*= 2.8, 12.5 Hz, H-5); 4.60 (dddd, *J*= 2.8, 4.6, 6.8, 7.7 Hz, H-4); ^{13}C NMR δ 22.96 (t, C-3), 28.56 (t, C-2), 63.74 (t, C-5), 80.95 (d, C-4), 178.15 (s, C-1).
6: According to Grieco, P.A. *J. Org. Chem.*, **1972**, *37*, p. 2363. **7**: According to [19]. **8** (C$_6$D$_6$ was added to obtain first order ^{1}H NMR spectrum): ^{1}H NMR δ 2.37 (dd, *J*= 5.9, 17.7 Hz H-2); 2.59 (dd, *J*= 9.0, 17.7, Hz, H-2); 2.74 (m, H-3); 3.61 (dd, *J*= 6.4, 10.8 Hz, H-5); 3.65 (dd, *J*= 5.6, 10.8 Hz, H-5); 4.20 (dd, *J*= 5.2, 9.2 Hz, H-4); 4.39 (dd), *J*= 7.5, 9.2 Hz, H-4); ^{13}C NMR δ 30.78 (t, C-2), 36.89 (d, C-3), 62.74 (t, C-5), 70.80 (t, C-4), 177.95 (s, C-1).

13. Conditions: a LKB liquid chromatograph equipped with a UV spectrometric detector (2158 Uvicord SD; 254 nm. A column Zorbax Sil 4.6x250 mm). Eluent hexane:*i*-PrOH:water for **5** 79.2:20:0.8 and for **7** 93.95:5:0.05.

14. *S*-O-methylmandelic acid ester of *S*-**5**: ^{1}H NMR δ 1.91 (dddd, *J*= 6.7, 7.8, 10.0, 13.0 Hz, H-3); 2.25 (dddd, *J*= 6.0, 7.8, 10.0, 13.0 Hz, H-3); 2.45 (ddd, *J*= 6.0, 10.0, 17.9 Hz, H-2); 2.45 (ddd, *J*= 7.8, 10.0 17.9 Hz, H-2); 4.22 (dd, *J*= 5.6, 12.2 Hz, H-5); 4.33 (dd, *J*= 3.1, 12.2 Hz, H-5); 4.64 (dddd, *J*= 3.1, 5.6, 6.8, 7.8 Hz, H-4); ^{13}C NMR δ 23.59 (t, C-3), 27.83 (t, C-2), 65.53 (t, C-5), 76.83 (d, C-4), 176.21 (s, C-1). *S*-O-methylmandelic acid ester of *R*-**5**: ^{1}H NMR δ 1.67 (dddd, *J*= 6.3, 7.6, 10.0, 13.0 Hz, H-3); 2.15 (dddd, *J*= 6.0, 7.9, 10.2, 13.0 Hz, H-3); 2.21 (ddd, *J*= 6.0, 10.0, 17.9 Hz, H-2); 2.31 (ddd, *J*= 7.6, 10.2, 17.9 Hz, H-2); 4.29 (dd, *J*= 4.3, 12.2 Hz, H-5); 4.29 (dd, *J*= 3.0, 12.2 Hz, H-5); 4.65 (dddd, *J*= 3.0, 4.3, 6.3, 7.9 Hz, H-4); ^{13}C NMR δ 23.28 (t, C-3), 27.70 (t, C-2), 65.30 (t, C-5), 76.86 (d, C-4), 176.41 (s, C-1).
S-O-methylmandelic acid ester of *R*-**8**: ^{1}H NMR δ 2.23 (dd, *J*= 6.6, 17.8 Hz, H-2); 2.57 (dd, *J*= 9.1, 17.8 Hz, H-2); 2.83 (m, H-3); 3.89 (dd, *J*= 5.8, 9.4 Hz, H-4); 4.22 (dd, *J*= 7.6, 9.4 Hz, H-4; 4.11 (dd, *J*= 6.6, 11.3 Hz, H-5); 4.21 (dd, *J*= 5.6, 11.3 Hz, H-5); ^{13}C NMR δ 30.72 (t, C-2), 34.31 (d, C-3), 64.66 (t, C-4), 69.69 (t, C-5), 175.70 (s, C-1).
S-O-methylmandelic acid ester of *S*-**8**: ^{1}H NMR δ 2.15 (dd, *J*= 6.5, 17.8 Hz, H-2); 2.50 (dd, *J*= 9.0, 17.8 Hz, H-2); 2.83 (m, H-3); 3.98 (dd, *J*= 5.7, 9.5 Hz, H-4); 4.29 (dd, *J*= 7.6, 9.5 Hz, H-4); 4.15 (dd, *J*= 6.5, 11.3 Hz, H-5); 4.17 (dd, *J*= 5.7, 11.3 Hz, H-5); ^{13}C NMR δ 30.64 (t, C-2), 34.36 (d, C-3), 64.68 (t, C-4), 69.75 (t, C-5), 175.71 (s, C-1).

15. In the best case the measured $[\alpha]_D^{20}$ for **6** was -60°, while the reference sample of 1*S*,5*R*-2-oxabicyclo[3.3.0]oct-6-en-3-one had $[\alpha]_D^{20}$=-113°. The reference value was taken as a basis for calculating the *ee* values.

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17. The unreacted **3** had $[\alpha]_D^{20}$=-38° (see Table 1, DET), which reveal the excess of a compound with the absolute configuration of 1*R*,2*S*,3*S*,5*R*. Consequently, lactone **7** should predominantly have the absolute configuration of 1*S*,2*R*,3*R*,5*S* according to: Newton, R.F., Paton, J., Reynolds, D., Young S., Roberts, S.M. *Chem. Commun.*, **1979**, p. 908-909; Kanger, T. P., Kabat, M., Wicha, E., Lopp, M., Lille Ü. *Zh.Org.Khim.*, **1990**, *26*, pp. 1711-1714. The same result was obtained when calculated from the corresponding *S*-O-methylmandelic acid esters according to[16].

18. The dominating absolute configuration of primary alcohols was suggested as *S*-**5** and *R*-**8** on the bases of ^{1}H and ^{13}C of *S*-O-methylmandelic acid esters of these compounds by using molecular modelling (Hyperchem MM^{+}) and aromatic ring current effect calculations (JAHMA v 1.2[19]). A good qualitative fit with the experimental data on the basis of Haigh-Mallion model[20] was observed.

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