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Baker's yeast reduction of α-alkyl-α-hydroxy-β-keto esters[1]

Didier Buisson,[a,*] Xavier Baucherel,[b] Eric Levoirier[b] and Sylvain Juge[b,*,†]

[a]*Groupe de Métabolisme et Biosynthèse, Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, UMR 8601 CNRS, Université René Descartes, 45 Rue des Saints-Pères, 75270 Paris Cedex 06, France*

[b]*Unité mixte Université Cergy Pontoise-ESCOM, EP CNRS 1822, Synthèse Organique Sélective et Chimie Organométallique, Université Cergy Pontoise, 5 mail Gay Lussac, 95031 Cergy-Pontoise, France*

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Abstract

Cyclic or acyclic α-alkyl-α-hydroxy-β-keto esters were reduced by baker's yeast with high stereospecificity. In the former case, one enantiomer of the racemic mixture was transformed into optically active *trans*-dihydroxy compounds, while the remaining α-hydroxy-β-keto ester was enantiopure.

Keywords: microbial reactions; resolution; hydroxy esters; diols.

The microbial reduction of α-substituted β-keto esters is a useful method to obtain the corresponding enantiopure β-hydroxy esters with two chiral carbons in good yield. Examples of such reductions concerning α-alkyl compounds, including cyclic keto esters are reported. However, only a few examples with α-substitution by heteroatoms (chloro,[2–5] sulfur,[6,7] amino,[8–12] hydroxy[13,14] or acetoxy[15]) are described. Moreover, the corresponding β-hydroxy esters with three functional groups can be versatile synthons.

To this purpose, baker's yeast is the commonly used microorganism because it is quite cheap and easily available. It is known that baker's yeast reduction of ethyl 3-oxobutanoate affords the corresponding (3*S*)-hydroxy ester with high enantiomeric excess,[16] while ethyl 3-oxopentanoate gives (3*R*)-hydroxypentanoate with low optical purity.[17] The presence of substituent in the α-position increases the stereoselectivity and enantiopure (*S*)-hydroxy esters are obtained. However, the diastereoselectivity of the reduction of α-substituted β-keto esters depends on the nature of the substituent. For example, ethyl α-methyl acetoacetate is preferentially reduced into the corresponding *syn*-(3*S*)-hydroxy ester,[18] while reduction of ethyl α-hydroxy acetoacetate gives the *anti*-(3*S*)-hydroxy ester.[13] On the other hand, the α,α-dialkyl acetoacetates are not,[19] or slowly,[20] reduced. Therefore, we decided to study the reduction of α-alkyl-α-hydroxy-β-keto esters. As no enolization occurs, the resolution of the racemic substrate could be expected when only one enantiomer is reduced.

* Corresponding authors. E-mail: dbuisson@biomedicale.uni-paris5.fr (D. Buisson)

† E-mail: sylvain.juge@chim.u-cergy.fr

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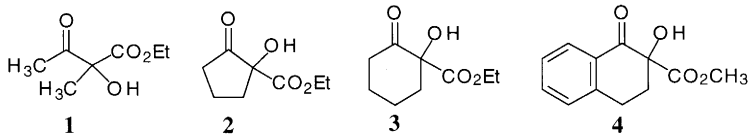
We report herein the baker's yeast reduction of α-alkyl-α-hydroxy-β-keto esters **1**–**4** and we describe the preparation of the corresponding dihydroxy esters in good to excellent enantiomeric excesses.



1 **2** **3** **4**

The α-hydroxy-β-keto esters **1**–**4** were obtained by catalytic oxidation of the corresponding α-alkyl keto esters by molecular oxygen.[21] Baker's yeast reductions were performed under the usual conditions.[22] The enantiomeric excesses of dihydroxy esters produced were determined by GC analysis of their (*S*)-*O*-acetyllactyl derivatives.[23] As only the secondary hydroxy group reacts with acetyllactyl chloride, the e.e. of the residual keto ester cannot be measured by direct derivatization. Therefore, the e.e. was determined after $NaBH_4$ reduction into a diastereomeric mixture of α,β-dihydroxy esters and consequent derivatization with (*S*)-*O*-acetyllactyl chloride. The results are summarized in Table 1.

Table 1
Baker's yeast reduction of α-hydroxy-β-keto esters **1**–**4**

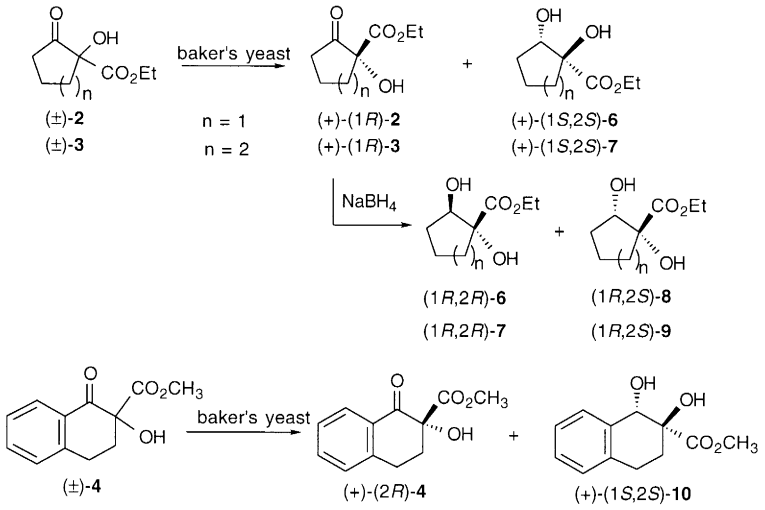
α-Hydroxy-β-keto ester					α,β-Dihydroxy esters					
Starting substrate	Reduction Time (h)	Residual Yield(%)	e.e.(%)	$[\alpha]_D$[b]	*syn or cis* Yield(%)	e.e.(%)	*anti or trans*	Yield(%)	e.e.(%)	$[\alpha]_D$[b]
(±)-**1**	5	0	-	-	50[a]	96	**5** (2*S*,3*S*)	50[a]	96	-
(±)-**2**	15	45	98	+ 12	0	-	**6** (1*S*,2*S*)	40	96	+ 21
(±)-**3**	18	27	99	+ 134	5	100	**7** (1*S*,2*S*)	58	63	+ 5
(±)-**4**	72	49	>95	+ 13	0	-	**10** (1*S*,2*S*)	43	86	+ 3

[a] Determined by GC, [b] (*c* 1, $CHCl_3$)

The microbial reduction of **1** was fast and both enantiomers were reduced. No resolution of this racemic substrate was observed and a mixture of two dihydroxy esters **5** with a high enantiomeric excess (96% e.e.) was obtained (Table 1; Scheme 2). Unfortunately, no chromatographic separation of diastereomers could be achieved. Their absolute configuration was assumed to be (3*S*), by comparison with the baker's yeast reduction of ethyl α-methyl acetoacetate[18] and ethyl α-hydroxy acetoacetate.[13]

In the case of the cyclic compounds (Scheme 1), the expected kinetic resolution was observed. The enantiospecificity of the reduction of compound **3** was good and excellent for the reduction of **2** and **4**. Only 50% of the ketoester was transformed. We obtained optically active α-hydroxy β-keto esters (+)-**2**, (+)-**3** and (+)-**4** in 27–49% yields (Table 1). The absolute configuration (*R*) of (+)-**4** was determined by direct comparison with the literature data,[24] and in the case of (+)-**3**, after derivatization into the corresponding benzoate.[25] Reduction of (+)-**2** with $NaBH_4$ afforded a mixture of the corresponding diastereomeric *cis*:*trans*-dihydroxy esters **6**, **8** in a 1:9 ratio, while (+)-**3** led to **7** and **9** in a 2:8 ratio (Scheme 1). These *trans*-dihydroxy esters **6** and **7** were the enantiomers of the microbial reduction products (+)-**6** and (+)-**7**, as demonstrated by GC analysis of their acetyllactate derivatives. The enantiomeric excess of the residual keto esters (+)-**2** and (+)-**3** were excellent (98 and 99%, respectively). $NaBH_4$ reduction of (+)-**4** was not efficient enough to obtain the corresponding diols **10** and no measurement of e.e. was achieved. However, the value of optical rotation for (+)-**4** ($[\alpha]_D$ +13 (*c* 1, $CHCl_3$)) indicated a good enantiomeric purity compared to the literature value ($[\alpha]_D$ −11.3 (*c* 0.55, $CHCl_3$) for 82% e.e.).[26]

The *trans*-configuration of the hydroxy groups in the cyclic dihydroxy esters produced was established by NMR data and confirmed for the cyclopentane derivative, by comparison with the spectrum of (±)-**8**



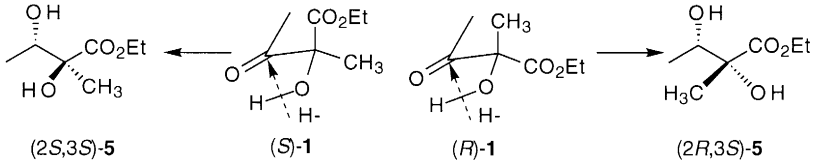
Scheme 1.

previously reported.[27] Consequently, the (*S*)-cyclic keto esters **2**, **3** and **4** were preferentially reduced into *trans*-diols (1*S*,2*S*)-**6**,[28] **7**[29] and **10**,[30] respectively, and the (*S*)-configuration of the reduction was established. The best result was achieved in the case of the reduction of **2** into (1*S*,2*S*)-**6**, which was obtained in 40% yield and 96% e.e. (Table 1).

The total yields of residual keto and dihydroxy esters were excellent (about 90%) compared to the yields of the reduction of the keto esters without hydroxy group,[19,31] suggesting no degradation of the α-hydroxy compounds by yeast.

The stereospecificity of these microbial reductions was in agreement with the proposed model[32] which postulates a reducible conformation with an axial position for the carboxyl group. It may be pointed out that a hydrogen bond between the hydroxy and the carbonyl groups for compounds **2**–**4**, obviously leads to such conformation. This hydrogen bond has been suggested by Sato et al.[13] to explain the inversion in the enantiospecificity observed in baker's yeast reduction of acyclic α-methyl and α-hydroxy-β-keto esters. Consequently, all cyclic β-keto esters are reduced with the same stereospecificity.

For each enantiomer of acyclic **1**, the postulated hydrogen bond involves a conformation with the methyl or the carboxylate group in an opposite face to the incoming hydride equivalent (Scheme 2). In this conformation, (*S*)-**1** can be fitted into the proposed model, suggesting the same enzyme which reduces (*S*)-**1** or cyclic keto esters. This hypothesis will be verified after purification of enzymes from baker's yeast involved in these reductions.



Scheme 2.

In conclusion, our study shows that baker's yeast reduction of α-hydroxy-α-substituted-β-keto esters is efficient to prepare optically pure α,β-dihydroxy esters. A combination of microbial and chemical reductions affords other isomers. Work is in progress with other microorganisms to obtain all possible stereomers.

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22. A suspension of baker's yeast Sigma Type II (4 g) in H_2O (200 ml) was stirred at 30°C for 15 min before addition of glucose (0.5 g). After 15 min the keto ester (200 mg) in ethanol (1 ml) was added. After the time indicated in Table 1 the suspension was filtered through Celite pad. The filtrate was saturated with NaCl and extracted with EtOAc. The organic phase was washed with brine and concentrated. Untransformed keto ester and dihydroxy compound were purified by column chromatography.
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24. See lit.[26] $[\alpha]_D$ −11 (*c* 0.55, $CHCl_3$) for (*S*) enantiomer (82% ee).
25. Benzoate derivative is obtained by reaction of (*R*)-**3** with benzoyl chloride (6 equiv.) in presence of triethylamine (6 equiv.) and DMAP (1 equiv.). $[\alpha]_D$ +77 (*c* 0.255, THF), lit.[26] $[\alpha]_D$ +72 (*c* 1, THF) for methyl ester.
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28. ^1H NMR (500 MHz, $CDCl_3$) δ ppm, *J* Hz: 1.32 (3H, t, *J*=7.2, CH_3), 1.70–1.95 (4H, m, $2H_4$, $1H_3$ and $1H_5$), 2.15 (1H, m, H_3), 2.28 (1H, m, H_5), 2.47 (1H, s, OH), 3.10 (1H, s, OH), 4.11 (1H, m, H_2), 4,31 (2H, q, *J* =7.2, CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ ppm: 174.8 (CO), 84.0 (C_1), 81.7 (C_2), 62.4 (CH_2), 35.3 (C_5), 32.8 (C_3), 20.8 (C_4), 14.5 (CH_3).
29. ^1H NMR (250 MHz, $CDCl_3$) δ ppm, *J* Hz: 1.32 (3H, t, *J*=7.2, CH_3), 1.45–1.65 (4H, m, H_4 and H_5) 1.65–1.81 (2H, m), 1.82–1.95 (1H, m), 1.96–2.05 (1H, m) 2.76 (1H, s, OH), 3.42 (1H, s, OH), 3.63 (1H, m, H_2), 4.27 (2H, q, *J*=7.2, CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ ppm: 175.0 (CO), 77.0 (C_1), 74.6 (C_2), 61.9 (CH_2), 33.4 and 29.6 (C_3, C_6), 22.3 and 21.8 (C_4, C_5), 14.1 (CH_3).
30. mp 136–138°C, ^1H NMR (250 MHz, MeOH) δ ppm, *J* Hz: 1.93 (1H, m, H_{3eq}), 2.20 (1H, ddd, $J_{3ax–3eq}$=14.1, $J_{3ax–4ax}$=11.7, $J_{3ax–4eq}$=6.1, H_{3ax}), 2.67 (1H, ddd, $J_{4eq–4ax}$=15, $J_{4eq–3ax}$=11.7, $J_{4eq–3eq}$=2.55, H_{4eq}), 2.85 (1H, ddd, $J_{4ax–4eq}$=15, $J_{4ax–3ax}$=11.7, $J_{4ax–3eq}$=6), 3.66 (3H, s, CH_3), 7–7.1 (3H, m, ArH), 7.16–7.25 (1H, m, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ ppm: 176.2 (CO), 137.3 (C), 131.7, 129.4, 128.7 and 127.0 (CH, Ar), 77.1 (C1), 73.0 (C2), 52.5 (CH_3), 26.1 and 25.7 (C_3 and C_4).
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