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Preparation of Optically Active α-Hydroxy Ketone Derivatives by Enzyme-Mediated Hydrolysis of Enol Esters

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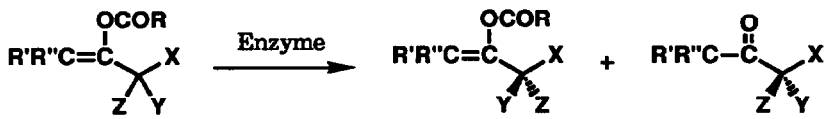
Summary: A new method of preparation of optically active α-hydroxy ketone derivatives has been developed. Incubation of (*Z*)-3-propionyloxy-4-benzyloxy-2-pentene (**1a**) with lipase OF gave optically pure (*R*)-enol propionate **1a**, which in turn was converted without racemization to (*R*)-ketone **2a** by the aid of $LiAlH_4$.

Optically active α-hydroxy ketone derivatives are important intermediates in asymmetric organic synthesis. Naturally occuring α-hydroxy and amino acids are important chiral sources for such class of compounds, but they are hardly sufficient to supply for a variety of compounds.

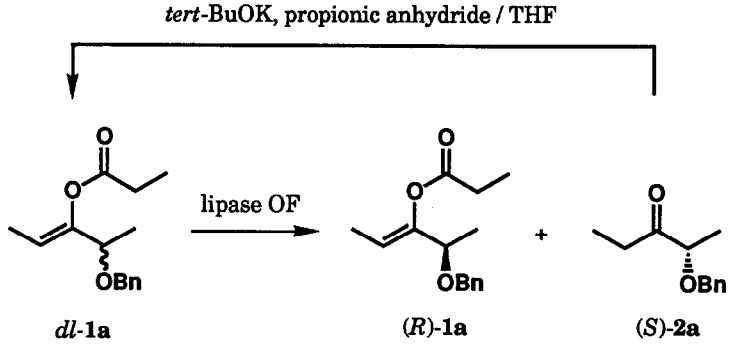
In the previous papers, we have reported a new type of enzyme-mediated kinetic resolution *via* hydrolysis of enol esters (Scheme 1).[1] Enzymatic hydrolysis of enol esters directly affords optically active ketone derivatives when the enzyme system distinguishes the configuration of α-position. In this paper, we applied this methodology to the preparation of optically active α-hydroxy ketone



Scheme 1.

derivatives. When this type of compounds are employed as chiral synthons, it is sometimes desirable that α-hydroxy group is protected with an appropriate group, such as benzyl which is stable to acidic and basic conditions. While utilization of an esterase in enantioselective hydrolysis of α-acyloxyketones[2] have been demonstrated to be successful, ketones obtained here are limited to those which have free hydroxy and acyloxy groups. On the other hand, in the enol ester method, any protection for the α-hydroxy group can be chosen in principle.

(*Z*)-Enol propionate **1a** was selected as the representative substrate, which was prepared as a single isomer by treatment of racemic ketone **2a** with *tert*-BuOK and propionic anhydride in THF (73% yield). The stereochemistry of **1a** was determined by NOE experiment of ^1H NMR.[3] At first, enzymatic hydrolysis of **1a** was carried out by incubation with *Bacillus coagulans* which had been demonstrated to have the ability of enantioselective hydrolysis of acyclic enol esters.[1a] Unfortunately, the trial was revealed to be impractical because the hydrolysis proceeded slowly with low selectivity.



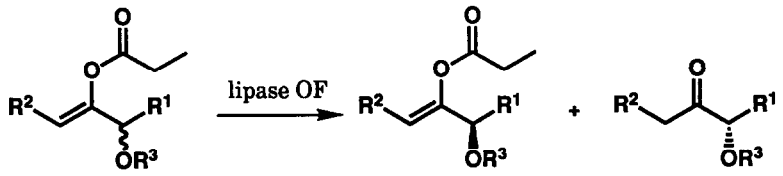
Scheme 2.

Thus we screened the enzyme system to hydrolyze **1a** with sufficient recognition of the configuration. Finally, lipase OF (from *Candida cylindracea*, commercially available from Meito Sangyo Co., Ltd.) was selected as the best. Representative experimental procedure is as follows. Eighty μl (82 mg) of *dl*-**1a** and 18 mg of the enzyme were added to 40 ml of 0.2 M phosphate buffer (pH 6.5) and stirred for 48 hr at 30 °C. The products were extracted with ethyl acetate and purified with preparative TLC to afford optically pure (*R*)-enol propionate **1a**[4] and optically active (*S*)-ketone **2a**[5] (16% ee) in 12 % and 72 % yields, respectively. The yield of (*R*)-**1a** was improved to 26% (95% ee) when the reaction time was shortened to 18 hr. The reaction also proceeded smoothly using the substrate and the enzyme in five-fold concentration. Since (*S*)-**2a** was easily converted to racemic **1a** by treatment with *tert*-BuOK and propionic anhydride, optically pure (*R*)-**1a** could be efficiently obtained by repeating enzymatic hydrolysis. The absolute configurations of the resulting compounds were determined by comparing the optical rotations with that of an authentic sample derived from (*S*)-ethyl lactate.[6] The ee's were determined by HPLC analysis with CHIRALCEL OJ (Daicel Chemical Industries, Ltd.).[7] When (*S*)-**2a** of higher optical purity is required, it can be obtained by shortening the incubation time. Thus 3-hr incubation afforded (*S*)-**2a** of 70% ee.

This reaction could be applied to various compounds (Table 1). While an enol ester having a terminal double bond (**1d**) was hydrolyzed wihtout enantioselectivity, the hydrolysis of other substrates having various alkyl groups proceeded to afford optically active compounds similarly to **1a**. In paticular, changing R^1 from methyl to ethyl (**1b**) and propyl (**1c**) increased the selectivity. Thus, enantiomerically pure (*R*)-**1b** and **1c**, which are difficult to prepare in usual methods were easily obtained. Some variations are possible for the protection of the hydroxy group, *i.e.*, α-methoxybenzyloxy (R^3=MPM, **1h**) and benzyloxymethoxy (R^3=BOM, **1g**) enol esters gave satisfactory results.

The chiral enol esters thus obtained must be transformed to the corresponding ketones to be utilized further as chiral building blocks. Hydrolysis of optically pure (*R*)-**1a** even under a weakly basic condition (K_2CO_3 in MeOH) brought about the decreasing of the ee of the resulting ketone. After some trials, we found that treatment of (*R*)-**1a** with $LiAlH_4$ in THF is the way of choice, which afforded optically pure (*R*)-**2a**[8] in 95% yield without any racemization.

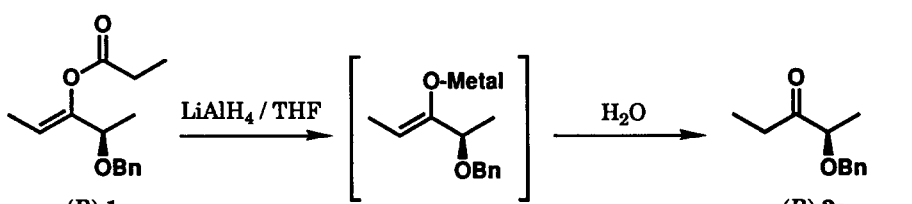
Table 1. Enzymatic Hydrolysis of Enol Esters.[a)]



dl-**1** (*R*)-**1** (*S*)-**2**

					Enol ester			Ketone			
	R^1	R^2	R^3	Time/h	Yield/%	$[\alpha]_D$[b)]	ee/%[c)]	Yield/%	$[\alpha]_D$[d)]	ee/%[c)]	E[e)]
a	Me	Me	Bn	3	73		23	20	-28	70	7
				18	26		95	57		42	8
				48	12	+69	>99	72		16	
b	Et	Me	Bn	48	27	+89	>99	54	-34	53[k)]	12[f)]
c	Pr	Me	Bn	168[g)]	27	+84	>99[h)]	36	-31	51	12[i)]
d	Me	H	Bn	48	2		<1	75		<5	
e	Me	Et	Bn	72	15	+71	>99[h)]	70	- 7.8	26	7[f)]
f	Me	Bu	Bn	30[g)]	12	+64	96[j)]	65	- 6.5	18[k)]	4
g	Me	Me	BOM	12	28	+123	>99	48	-13	56	12[l)]
h	Me	Me	MPM	12	20	+79	>99[h)]	71	- 8.2	26	7[f)]

a) Incubation was performed using 0.2% of substrates in 0.2 M phosphate buffer (pH 6.5) at 30 °C. The ratio of substrate/enzyme (w/w) was 4.5/1 unless otherwise noted. b) Measured in $CHCl_3$ at r. t. (c 0.6 - 1.3). c) Determined by HPLC analysis with CHIRALCELL OJ unless otherwise noted. d) Measured in $CHCl_3$ at r. t. (c 0.8 - 1.5). e) E value was calculated by ln[(1-C)(1-ee(S))]/ln[(1-C)(1+ee(S))], C=ee(S)/(ee(P)+ee(S)).[9)] f) Calculated at C=0.14 - 0.20. g) The ratio of substrate/enzyme (w/w) was 1.0. h) Determined by HPLC analysis after derivation to the ketone with $LiAlH_4$. i) Calculated at C=0.43. j) Determined by the method in note k) after derivation to the ketone. k)Determined by HPLC analysis of the corresponding MTPA ester of the reduced alcohol (more polar isomer) using Develosil ODS-5 (Nomura Chemical Co., Ltd.). Reduction of ketone was performed with DIBAL in THF. l) Calculated at C=0.28.



(*R*)-**1a** (*R*)-**2a**

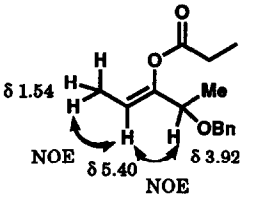
>99% ee Yield 95%, >99% ee

Scheme 3.

In conclusion, optically pure α-hydroxy ketone derivatives were easily obtained by enzyme-mediated hydrolysis of enol esters. Application of this method to the synthesis of natural products is described in the following paper.

References and Notes

1) a) K. Matsumoto and H. Ohta, *Chem. Lett.*, 1109 (1989); b) T. Sugai, H. Kakeya, M. Morooka, S. Ohba and H. Ohta, *Tetrahedron*, **45**, 6135 (1989).
2) For example, H. Ohta, M. Ikemoto, H. Ii, Y. Okamoto and G. Tsuchihashi, *Chem. Lett.*, 1169 (1986).
3) The configuration of **1** was assigned to be *Z* by 400 MHz ^{1}H NMR experiment (solvent, $CDCl_3$; TMS as internal standard). Irradiation at δ_H 3.92 (1H) caused enhancement at δ_H 5.40 (1H) and *vice versa*. Irradiation at δ_H 3.92 (1H), however, did not cause enhancement at δ_H 1.54 (3H).



1a

4) $[\alpha]_D^{26}$ +68.5° (c 0.89, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7.57 Hz, 3H), 1.30 (d, J = 6.84 Hz, 3H), 1.54 (d, J = 6.84 Hz, 3H), 2.49 (q, J = 7.57 Hz, 2H), 3.92 (q, J = 6.84, 1H), 4.41 (d, J = 12.0, 1H), 4.66 (d, J = 12.0 Hz, 1H), 5.40 (q, J = 6.84 Hz, 1H), 7.23 - 7.40 (m, 5H); IR (neat) 2980, 2940, 2870, 1760, 1690, 1495, 1450, 1350, 1290, 1150, 1080, 1005, 820, 735, 700 cm^{-1}; MS, m/z (rel. intensity) 249 (3, M^++1), 142 (52), 141 (36), 105 (46), 91 (100), 86 (37), 57 (77).
5) $[\alpha]_D^{26}$ - 5.0° (c 1.12, $CHCl_3$); ^{1}H NMR (CCl_4) δ 0.97 (t, J = 8.0 Hz, 3H), 1.24 (d, J = 7.0 Hz, 3H), 2.50 (q, J = 8.0 Hz, 2H), 3.76 (q, J = 7.0 Hz, 1H), 4.42 (s, 2H), 7.0 - 7.5 (m, 5H); IR (neat) 3000, 2960, 2900, 1720, 1500, 1455, 1400, 1370, 1330, 1210, 1110, 1060, 1030, 970, 800, 740, 700 cm^{-1}; MS, m/z (rel. intensity) 192 (5, M^+), 181 (24), 149 (5), 135 (13), 105 (68), 91 (100), 77 (17), 57 (33).
6) Authentic sample of (*S*)-**2**: $[\alpha]_D^{24}$ -45.9° (c 1.16, $CHCl_3$).
7) Conditions for HPLC analysis. **1** : solvent, hexane/2-propanol=180/1; flow rate, 0.08 ml/min; retention time, 128 and 136 min corresponding to the enantiomers. **2** : solvent, hexane/2-propanol =180/1; flow rate, 0.1 ml/min; retention time 214 and 229 min.
8) $[\alpha]_D^{23}$ +44.0° (c 0.94, $CHCl_3$).
9) C. -S. Chen, Y. Fujimoto, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc.*, **104**, 7294 (1982).

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