CHEMISTRY LETTERS, pp. 1589-1592, 1989.

Enzyme-Mediated Enantioface-Differentiating Hydrolysis of Enol Esters

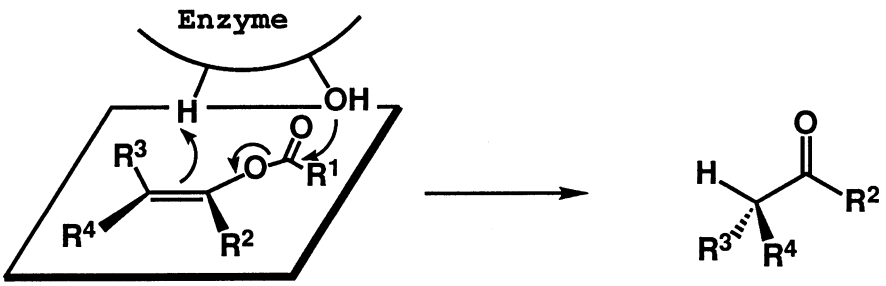
Kazutsugu MATSUMOTO and Hiromichi OHTA*
Department of Chemistry, Keio University, Hiyoshi, Yokohama 223

A new type of enzymatic hydrolysis has been disclosed. A kind of yeast, *Pichia miso*, hydrolyzed enol esters such as 3-acetoxy-1-p-methoxybenzyloxy-2-methoxymethoxy-2-alkenes with differentiation of the enantiotopic face to afford optically active α-substituted ketones.

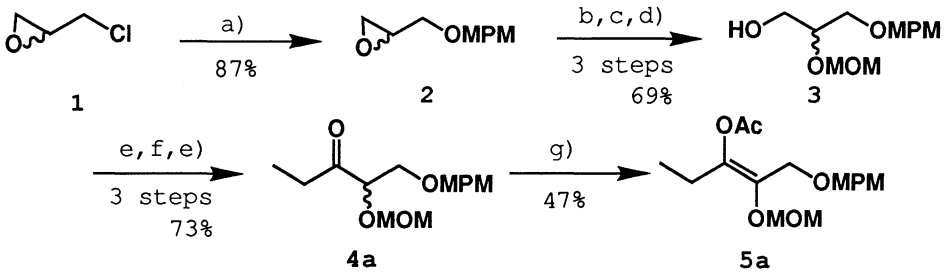
Optically active glycerol derivatives are considered to be versatile chiral building blocks in asymmetric synthesis.[1] For example, dihydroxyketone of type **4a** has been shown to be the key intermediate[2] in the synthesis of mycinolide IV.[3] Thus, preparation of chiral glycerol derivatives is an important problem, but relatively few methods have been developed, which are based on transformation of natural products, such as D-mannitol,[2,4] and L-ascorbic acid.[5]

In recent years, it has been established that enzymatic transformation of organic compounds is a useful technique for the synthesis of chiral molecules.[6] Enzymatic hydrolysis is, especially, advantageous because it requires no co-factors. Hitherto known biochemical hydrolysis can be classified into three categories, i.e., resolution of racemates, enantioselective reaction of meso compounds and asymmetrization of compounds with a prochiral center, all of which are based on the recognition of chiral centers by the enzyme system. In this paper, we present a simple synthesis of optically active glycerol derivatives via a new type of enzymatic hydrolysis, i.e., enantioface differentiating hydrolysis of enol esters.

Scheme 1 illustrates the conception of this reaction. If protonation occurs with selection of enantiotopic face of the C=C double bond in a concerted



Scheme 1.

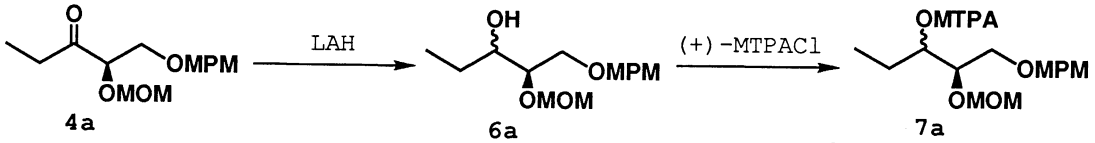


a) MPMOH, NaH / THF-DMF; b) AcONa / AcOH-DMF
c) MOMCl, $^{i}Pr_2NEt$ / CH_2Cl_2; d) NaOH / MeOH
e) Swern oxidn.; f) EtMgBr / THF
g) LDA, Ac_2O / THF

MOM = CH_3OCH_2-

MPM = CH_3O-C$_6$H$_4$-CH_2-

Scheme 2.



(+)-MTPA = MeO-C(CF$_3$)(Ph)-CO-

Scheme 3.

manner with the elimination of the acyl group without inclusion of an intermediary enol, then the carbon α to carbonyl should be enriched with either R or S configuration.

The substrate **5a** was readily prepared according to Scheme 2. Reaction of epichlorohydrin and p-methoxybenzylalcohol followed by protection and deprotection afforded glycerol derivative (**3**), which was transformed to ketone **4**. Treatment of **4** with LDA and acetic anhydride at -78 °C resulted (E)-enol acetate (**5a**).[7] The stereochemistry of this compound was determined by ^{1}H-NMR.[8] Although a lot of stock cultures and commercially available enzymes hydrolyzed **5a**, only a few microorganisms catalyzed the stereoselective protonation, *Pichia miso* IAM 4682 being the best. Fourty ml of sterilized nutrient medium of pH 6.8[9] was inoculated with *P. miso* and incubated for 2 days at 30 °C. To this suspension 38.5 μl of **5a** was added and the incubation was continued for additional 1 day. After the extraction of the broth with ethyl acetate, resulting mixture was purified by preparative TLC on silica gel to give optically active **4a** in a yield of 83%, $[\alpha]_D^{25}$ +14.7° (c 1.54, $CHCl_3$).[10] The absolute configuration of the product is R as determined by comparing the specific rotation with that of an authentic sample derived from D-mannitol.[11] The optical purity was determined to be 85%e.e. by HPLC analysis[12] of the MTPA ester **7a** which was derived from **4a** via reduction and esterification (Scheme 3).

The reaction of **5a** were examined under various conditions. It has become

Table 1. Asymmetric Hydrolysis of 5[a)]

5 4

	R^1	R^2	Yield/%	$[\alpha]_D$/°[b)]	ee/%[c)]
a	Me	Et	83	+14.7	85
b	Et	Et	78	+13.4	82
c	Pr	Et	45	+5.3	45
d	t-Bu	Et	0	——	——
e	MeO	Et	82	+12.9	81
f	Me	Me	50	+11.2	55
g	Me	Pr	86	+10.5	87
h	Me	Bu	54	+10.4	90
i	Me	pentyl	26	+9.5	84
j	Me	i-Pr	0	——	——
k	Me	3-butenyl	84	+11.6	86

a) Sub. concn. 0.1%, incubation for 24 h at 30 °C.
b) Measured in $CHCl_3$ at r.t.(c 0.8-1.7).
c) Determined by HPLC analysis after derivation to MTPA esters as shown in Scheme 3.

apparent that the initial concentration of **5a** has little effect to the chemical and optical yield even when it is as high as 1.0%. Hydrolysis proceeded very fast and has essentially completed in 3 hours when the concentration of the substrate was 0.1%. It was also confirmed that non-enzymatic hydrolysis nor racemization of the product occurred under the incubation conditions.

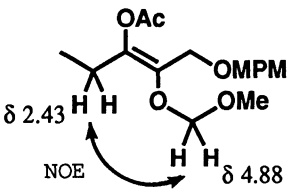
This reaction could be applied to other substrates (Table 1). Except for the substrates having a too bulky group, the hydrolysis proceeded to afford optically active compounds in analogy with **5a**. In particular, enol acetate having a butyl group (**5h**) was converted to the ketone **4h** in the highest optical yield. The substrate with a terminal double bond (**5k**) also resulted the corresponding chiral ketone **4k** in a good yield.

In conclusion, a new type of asymmetric hydrolysis of enol esters has been realized with differentiation of the enantiotopic face of C=C double bond by incubation with *P. miso* and optically active glycerol derivatives were effectively prepared by this new method. The present method can be also successfully applied to cyclic systems.[13)]

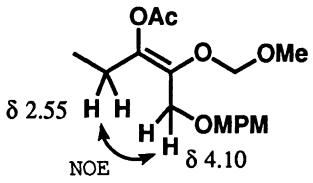
We are grateful to Sapporo Bioscience Foundation for the financial support of this work.

References

1) J. Jurczak, S. Pikul, and T. Bauer, Tetrahedron, 42, 447 (1986).
2) K. Tomooka, K. Matsumoto, K. Suzuki, and G. Tsuchihashi, 52nd National Meeting of the Chemical Society of Japan, Kyoto, April 1986, Abstr., No. 2Y 02.
3) K. Suzuki, T. Matsumoto, K. Tomooka, K. Matsumoto, and G. Tsuchihashi, Chem. Lett., 1987, 113.
4) E. Baer and H. O. L. Fischer, J. Biol. Chem., 128, 463 (1939).
5) M. E. Jung and T. J. Shaw, J. Am. Chem. Soc., 102, 6304 (1980).
6) Recent reviews: J. B. Jones, Tetrahedron, 42, 3351 (1986); H. Ohta, Yuki Gosei Kagaku Kyokai Shi, 46, 726 (1988); H. Yamada and S. Shimizu, Angew. Chem., Int. Ed. Engl., 27, 622 (1988).
7) As minor products, 3,4-unsaturated compound and (Z)-isomer of **5a** also formed. Spectral data of **5a**: ^{1}H NMR (CCl_4) δ 0.98 (t, J=7.8 Hz, 3H), 1.95 (s, 3H), 2.43 (q, J=7.8 Hz, 2H), 3.40 (s, 3H), 3.74 (s, 3H), 3.97 (s, 2H), 4.28 (s, 2H), 4.88 (s, 2H), 6.74 (d, J=8.7 Hz, 2H), 7.15 (d, J=7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.7, 21.2, 22.2, 56.2, 57.4, 64.4, 72.3, 97.0, 115.0, 130.2, 131.7, 142.1, 144.3, 160.5, 169.5; IR (neat) 2925, 1750, 1605, 1580, 1510, 1460, 1365, 1300, 1240, 1210, 1150, 1070, 1030, 1000, 920, 820, 750 (cm^{-1}); MS m/z (rel. intensity) 264 (3.9, $(M-AcOH)^+$), 219 (0.2), 189 (2.4), 175 (0.1), 137 (2.0), 121 (100).
8) The configuration of the major product was assigned to be E by NOE experiment. Irradiation at δ_H 2.43 (2H) caused enhancement at δ_H 4.88 (2H) and vice versa. On the other hand, the NOE between δ_H 2.55 (2H) and δ_H 4.10 (2H) was observed for the minor olefin.



the major product



the minor product

9) The medium consists of glucose 10 g, polypeptone 7 g, and yeast extract 5 g in 1000 ml of 0.2 M phosphate buffer. Under these conditions, no spontaneous hydrolysis of substrates was observed.
10) Spectral data of **4a**: ^{1}H NMR (CCl_4) δ 0.97 (t, J=7.2 Hz, 3H), 2.54 (q, J=7.2 Hz, 2H), 3.30 (s, 3H), 3.60 (d, J=4.5 Hz, 2H), 3.75 (s, 3H), 4.02 (t, J=4.5 Hz, 1H), 4.37 (s, 2H), 4.5 - 4.8 (m, 2H), 6.75 (d, J=8.4 Hz, 2H), 7.12 (d, J=8.4 Hz, 2H); IR (neat) 2900, 1720, 1600, 1580, 1510, 1450, 1400, 1350, 1300, 1240, 1170, 1150, 1100, 1030, 910, 820, 750 (cm^{-1}); MS m/z (rel. intensity) 282 (0.5, M^+), 264 (2.8), 237 (0.8), 181 (8.9), 137 (16), 121 (100).
11) $[\alpha]_D^{25}$ -18.1° (c 0.98, $CHCl_3$).
12) Conditions for HPLC analysis: Column, Develosil ODS-5 (0.46 cm x 25 cm); Solvent, MeOH/H_2O (70/30), 0.5 ml/min; Retention time, 154, 161, 170, and 183 min corresponding to the diastereomers.
13) H. Ohta, K. Matsumoto, S. Tsutsumi, and T. Ihori, J. Chem. Soc., Chem. Commun., 1989, 485.

(Received June 16, 1989)