Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1673–1677

TETRAHEDRON: *ASYMMETRY*

Synthesis and *Rhizopus oryzae* mediated enantioselective hydrolysis of α-acetoxy aryl alkyl ketones

Ayhan S. Demir,[a,b,*] Haluk Hamamci,[b,c] Cihangir Tanyeli,[a,b] Idris M. Akhmedov[a] and Fatos Doganel[b]

[a]*Department of Chemistry, Middle East Technical University, 06531 Ankara, Turkey*
[b]*Department of Biotechnology, Middle East Technical University, 06531 Ankara, Turkey*
[c]*Department of Food Engineering, Middle East Technical University, 06531 Ankara, Turkey*

Received 18 February 1998; accepted 24 April 1998

Abstract

$Mn(OAc)_3$ oxidation of aromatic ketones afforded the α-acetoxy ketones in good yield. Selective hydrolysis of the acetoxy ketones by the fungus *Rhizopus oryzae* yields (*R*)-hydroxy ketones in high enantiomeric excess.

1. Introduction

The α-hydroxy ketones are important structural units in many biologically active natural products and are also important synthons for the asymmetric synthesis of natural products.[1] Several methods have been developed for the preparation of optically active α-hydroxy ketones. For example, the stereoselective oxidation of optically active enolates,[2] oxidation of prochiral enolates using optically active oxaziridines,[3] selective oxidation of chiral titanium enolates and asymmetric oxidation of silyl enol ethers.[4] As an alternative to chemical methods, optically active α-hydroxy ketones are prepared enzymatically by reduction of α-diketones[5] and by kinetic resolution of racemic α-hydroxy and α-acetoxy ketones.[6]

Recently we have reported the synthesis of optically active α-hydroxy enones by lipase-catalyzed hydrolysis of α-acetoxy enones.[7] During the course of our studies on the biotransformation of acetoxy ketones to hydroxy ketones using different enzymes, we observed that *Rhizopus oryzae* has the versatility for the enantioselective hydrolysis of acetoxy ketones.

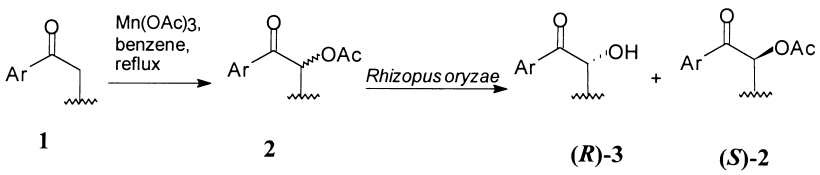
In this paper we present the enantioselective synthesis of hydroxy ketones from ketones via $Mn(OAc)_3$ mediated acetoxylation followed by enantioselective ester hydrolysis utilizing *Rhizopus oryzae*.

* Corresponding author. E-mail: asdemi1@pop.uky.edu

0957-4166/98/$19.00
PII: S0957-4166(98)00165-7

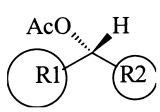
2. Results and discussion

In an initial reaction shown in Scheme 1, the oxidation of aromatic ketones **1** with four equivalents of manganese(III) acetate furnished the desired α-acetoxy ketones **2** in good yields (Table 1). In connection with ongoing research[8a–h] we found that the source of manganese(III) acetate is very important for the high yields of the reactions. The anhydrous manganese(III) acetate used in this oxidation was prepared from manganese(II) nitrate and acetic anhydride and dried using phosphorus pentoxide under vacuum prior to use.[8i–k]



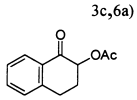
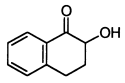
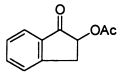
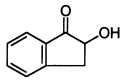
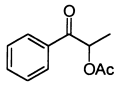
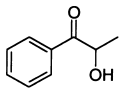
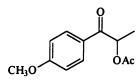
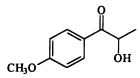
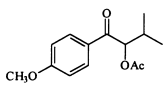
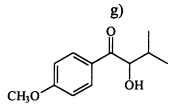
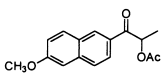
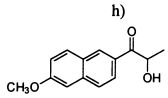
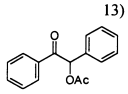
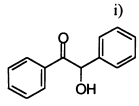
Scheme 1.

The first bioconversion was performed with tetralone in EtOH and the fungus was incubated in the presence of tetralone at 25°C. The conversion was monitored by TLC using authentic hydroxy ketone as a reference. After 26 h about 40–45% conversion of the product was observed. The product was separated using flash column chromatography and hydroxy ketone **3a** was isolated in 38% yield and in 35% ee. The configuration of the keto alcohol was assessed as (*R*) by comparison of its specific rotation with literature data.[3c,6a,9] Under similar conditions, neutralization of the reaction medium during the conversion with $CaCO_3$ solution increases the ee to 94%. Changing the reaction temperature and ethanol solvent for THF or DMSO did not improve the results. The use of excess $CaCO_3$ decreases the enantiomeric excesses. A variety of cyclic and acyclic aromatic acetoxy ketones are employed as substrates since the absolute stereochemistry of the resulting hydroxy ketones has been previously established. In an initial survey, *Rizhopus oryzae* appears to contain an esterase that is able to yield alcohols with configurations that exhibit a consistent pattern. The hydrolysis of aromatic acetoxy ketones with different R_1 and R_2 are examined. The results are given in Table 1 and show that the enantiomeric excess (ee) varied from 66% to 96%. It is apparent that higher ees are found in those alcohols which show the differences in the relative sizes of R_1 (aryl) and R_2 (alkyl), i.e. phenyl, methoxyphenyl, methoxynaphthyl groups versus methyl substituent (**3c**, **3d**, **3f**). The relatively smaller ee values are obtained with phenyl, methoxyphenyl versus phenyl and isopropyl (**3e**, **3g**). From these observations there is a change in the observed ees on changing alkyl groups from methyl to isopropyl and phenyl versus aryl. The control experiment with authentic optically active acetates under the conditions of the bioconversion reaction proved them to be configurationally stable and racemization is not responsible for their lower enantiomeric excesses. The enantiomeric excesses of recovered acetoxy ketones varied from 24 to 86% and were determined via their hydroxy ketones.[9]



The results show that *Rhisopus oryzae* mediated hydrolysis of acetoxy ketones provides hydroxy ketones with high enantiomeric excesses and enantiomerically enriched acetoxy ketones in good chemical yields. The enzymes favor the (*R*)-enantiomers in accordance with the suggested mechanism of hydrolase-catalyzed enantioselective hydrolysis of the acetoxy group to the hydroxy group.[10–14]

Table 1
Synthesis and *Rhizopus oryzae* mediated enantioselective hydrolysis of α-hydroxy aryl alkyl ketones

Acetoxy ketones **2**	React. Time (h)	Yield (%)	Hydroxy ketones **(*R*)-3**	Conv.[j] (%)	React. Time (h)	Yield (%)	Hydroxy ketones **(*R*)-3** ee[a] (%)	Acetoxy ketones **(*S*)-2** ee (%)	E[j]
3c,6a)  **a**	5	86	c)  **a**	45	84	39	94	77	75
8c)  **b**	3	82	d)  **b**	48	96	41	93	86	76
2b)  **c**	4	88	e)  **c**	41	120	40	96	67	98
 **d**	4	77	f)  **d**	47	120	38	94	83	85
 **e**	6	71	g)  **e**	27	144	34	66	24	6
 **f**	5	78	h)  **f**	38	142	41	89	55	30
13)  **g**	b) -	-	i)  **g**	32	146	36	70	33	8

a) Enantiomeric excess values are determined via their (*S*)-O-acetyllactyl ester derivatives by GC (capillary column HP-5 crosslinked 5%PhMe silicone)[15] and with the ^{1}H NMR shift reagent Eu(hfc)$_3$ and from the reported specific rotations of each chiral alcohols. b) Commercially available compound is used. c) (*R*)-2-acetoxy-1-tetralone derivative: $[\alpha]_D^{20}$= + 65.5 (c=1.46, $CHCl_3$), ee= 81.3%[3c]; this work: $[\alpha]_D^{20}$= + 76.1 (c=2.0, $CHCl_3$)[9b] d) (*S*)-**3b**[11]: $[\alpha]_D^{20}$= +21.0 (c=1.40, $CHCl_3$); this work: $[\alpha]_D^{20}$= -23.1(c=1.50, $CHCl_3$). e) (*R*)-**3c**: $[\alpha]_D^{20}$= +81.0 (c=1.50, $CHCl_3$)[12]; +83.7(c=2.0, $CHCl_3$)[2b]; this work: $[\alpha]_D^{20}$= +82.2(c=2.0, $CHCl_3$). f) (*S*)-**3d**[12]: $[\alpha]_D^{21}$= -33.4(c=1.05, MeOH); this work: $[\alpha]_D^{20}$= +33.6 (c=1.0, MeOH). g) (*S*)-**3e**[12]: $[\alpha]_D^{23}$= +37.5 (c=1.0, MeOH); this work: $[\alpha]_D^{20}$= -25.7 (c=1.0, MeOH). h) (*S*)-**3f**[12]: $[\alpha]_D^{23}$= -59.4 (c=1.05, MeOH); this work: $[\alpha]_D^{20}$= +54.2 (c=1.0, MeOH). i) (*R*)-**3g**[2b]: $[\alpha]_D^{20}$= -230.5 (c=1.0, benzene); this work: $[\alpha]_D^{20}$= -170.1 (c=1.0, benzene). J) Conversion values are calculated according to the ref. 16; E=enantiomeric ratio[16].

3. Experimental[15,16]

3.1. General procedure for the preparation of α-acetoxy ketones

A mixture of 10 mmol of manganese(III) acetate and 2.5 mmol of ketone in 50 ml of benzene was refluxed (the reaction was monitored by TLC) under a Dean–Stark trap. The mixture was cooled to

RT, diluted with ethyl acetate, was washed successively with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. The crude products were chromatographed on flash silica gel in ethyl acetate:hexane (1:3).

3.2. General procedure for the preparation of α-hydroxy ketones

Rhizopus oryzae (NRRL 395) was used for the experiments. It was cultivated on boiled rice and the fungal spores were transferred by loopfuls into the sterile flasks containing the medium and grown in a rotary shaker at 30°C for two days. The medium for fungal growth includes 15.0 g glucose syrup, 1.0 g $(NH_4)_2SO_4$, 0.30 g KH_2PO_4, 0.12 g $MgSO_4$ and 0.02 g $ZnSO_4$ diluted to 500 ml by distilled water. The medium was divided into five portions and sterilized in the autoclave for 15 minutes. Spores from the main plate were transferred into an Erlenmeyer flask containing 100 ml sterile medium. The fungus was inoculated at 30°C for two days in the rotary shaker and the substrate (1.7 mmol) dissolved in 2 ml EtOH. Shaking was resumed until approximately 40–45% of the racemic acetate had been hydrolyzed. During the hydrolysis the medium was neutralized with 10% $CaCO_3$ solution. The fungus was filtered out, washed with distilled water, and the combined aqueous phases extracted with ethyl acetate and the alcohol and unhydrolyzed acetate separated by flash column chromatography (EtOAc:hexane, 1:2).

*3.3. 2-Acetoxy-1-(4-methoxyphenyl)-1-propanone **2d***

Colorless semisolid. FR-IR: 1735, 1670, 1595 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.42 (d, J=7.0 Hz, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 8.72 (dd, J=14.0 and 6.8 Hz, 1H, CH), 6.94 (m, 2H, C_6H_4), 7.86 (m, 2H, C_6H_4). Anal. calcd for $C_{12}H_{14}O_4$ (222.24): C, 64.85; H, 6.34. Found: C, 65.12; H, 6.43.

*3.4. 2-Acetoxy-1-(4-methoxyphenyl)-3-methyl-1-butanone **2e***

Colorless semisolid. FT-IR: 1740, 1665, 1510 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.62 (d, J=7.0 Hz, 3H, CH_3), 1.14 (d, J=6.9 Hz, 3H, CH_3), 2.11 (m, 1H, CH), 2.14 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 5.92 (dd, J=13.7 Hz and 7.0 Hz, 1H, CH), 6.92 (m, 2H, C_6H_4), 7.88 (m, 2H, C_6H_4). Anal. calcd for $C_{14}H_{18}O_4$ (250.29): C, 67.18; H, 7.24. Found: C, 67.38; H, 7.33.

*3.5. 2-Acetoxy-1-(6-methoxy-2-naphthyl)-1-propanone **2f***

Colorless solid, m.p. 112–114°C. IR (KBr) 1720, 1680, 1610 cm^{-1}. ^1H NMR($CDCl_3$): δ 1.53 (d, J=6.8 Hz, 3H, CH_3), 2.10 (s, 3H, CH_3), 3.96 (s, 3H, OCH_3), 5.88 (dd, J=14 Hz and 7.0 Hz, 1H, CH), 7.18–7.32 and 7.62–8.39 (m, 6H, $C_{10}H_6$). Anal. calcd for $C_{16}H_{16}O_4$ (272.31): C, 70.57; H, 5.92. Found: C, 70.23; H, 5.71.

Acknowledgements

We thank the Middle East Technical University for grant (AFP-1997) and the Turkish State Planning Organization for grant (DPT-1997).

References

1. (a) Hanessian, S. *Total Synthesis of Natural products: The Chiron Approach*; Pergamon Press: New York, 1983; Chapter 2. (b) Whitesell, J. K.; Buchanan, C. M. *J. Org. Chem*. **1986**, *51*, 5443. (c) Chandhary, A. G.; Kingston, D. G. I. *Tetrahedron Lett*. **1993**, *34*, 4921. (d) Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *Acc. Chem. Res*. **1997**, *30*, 364.
2. (a) Gore, M. P.; Vederas, J. C. *J. Org. Chem*. **1986**, *51*, 3700. (b) Enders, D.; Bushan, V. *Tetrahedron Lett*. **1988**, *29*, 2437.
3. (a) Davis, F. A.; Hakue, M. S. *J. Org. Chem*. **1986**, *51*, 4083. (b) Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Hakue, M. S. *J. Am. Chem. Soc*. **1990**, *112*, 6679. (c) Davis, F. A.; Clark, C.; Kumar, A.; Chen, B. *J. Org. Chem*. **1994**, *59*, 1184.
4. (a) Adam, W.; Prechtl, F. *Chem. Ber*. **1994**, *127*, 667. (b) Adam, W.; Fell, R. T.; Stegman, V. R.; Saha-Moller, C. R. *J. Am. Chem. Soc*. **1998**, *120*, 708.
5. (a) Csuk, R.; Glanzer, B. I. *Chem. Rev*. **1991**, *91*, 49. (b) Nakamura, K.; Kondo, S.-I.; Kawai, Y.; Hida, K.; Kitano, K.; Ohno, A. *Tetrahedron: Asymmetry* **1996**, *7*, 409.
6. (a) Adam, W.; Diaz, M. T.; Fell, R. T.; Saha-Moller, C. R. *Tetrahedron: Asymmetry* **1996**, *8*, 2207. (b) Gala, D.; DiBenedetto, D. J.; Clark, J. E.; Murphy, B. L.; Schumacher, D. P.; Steinman, M. *Tetrahedron Lett*. **1996**, *37*, 611. (c) Ota, H.; Dobashi, G. (Yuki Gosei Kogyo Co., Ltd) Jpn Kokai Tokkyo Koho JP 62,208, 298 [87,208,298] (Cl. C12 p41/00), 12 Sep 1987, Appl. 86/49,983, 7 March 1986. CA 108: 148914v. (d) Adam, W.; Fell, R. T.; Saha-Moller, C. R.; Zhao, C. G. *Tetrahedron: Asymmetry* **1998**, *9*, 397. (e) Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Tetrahedron: Asymmetry* **1998**, *9*, 907.
7. Tanyeli, C.; Demir, A. S.; Dikici, E. *Tetrahedron: Asymmetry* **1996**, *7*, 2399.
8. (a) Demir, A. S; Saatçioglu, A. *Synth. Commun*. **1993**, *23*(5), 571. (b) Demir, A. S.; Jeganathan, A. *Synthesis*, **1992**, 235. (c) Demir, A. S.; Çamkerten, N.; Akgün, H.; Tanyeli, C.; Mahasneh, A. S.; Watt, D. S. *Synth. Commun*. **1990**, *20*(15), 2279. (d) Demir, A. S.; Sayraç, T.; Watt, D. S. *Synthesis* **1990**, 1119. (e) Demir, A. S.; Akgün, H.; Tanyeli, C.; Watt D. S. *Synthesis* **1991**, 719. (f) Demir, A. S.; Tanyeli, C.; Akgün, H.; Çaliskan, Z.; Özgül, E. *Bull. Chem. Soc. Fr*. **1995**, *132*, 423. (g) Demir, A. S.; Tanyeli, C.; Gülbeyaz, V.; Akgün H. *Turkish J. Chemistry* **1996**, *20*, 244. (h) Tanyeli, C.; Çaliskan, Z.; Demir A. S. *Synth. Commun*. **1997**, *27*(19), 3471. (i) Chretien, A.; Varga, G. *Bull. Soc. Chim. Fr*. **1936**, *3*, 2385. (j) Bauer, G. *Handbuch der Praeparativen Anorganischen Chemie*; Stuttgart, 1962, p. 1283. (k) Nikishin, G. I.; Vinogradov, M. G.; Verenchikov, S. P. *Izv. Akad. Nauk SSSR Ser. Khim*. **1969**, 1835; Bull. Acad. Sci. USSR Div. Chem. Sci. 1969, 1698.
9. (a) Racemization-free conversion of acetoxy ketones to hydroxy ketones: 3 mmol of acetoxy ketone in 30 ml of abs. methanol was refluxed for 2 h in the presence of a catalytic amount of conc. sulfuric acid. To the reaction mixture was added 100 ml of ethyl acetate, and the organic layer was washed with saturated $NaHCO_3$ and water and dried over $MgSO_4$. The crude products were purified by flash column chromatography. (b) Racemization-free conversion of hydroxy ketones to aceotoxy ketones: to the solution of 3 mmol of hydroxy ketone and 1 ml of dry pyridine in 20 ml of CH_2Cl_2 was added 1 ml of acetic anhydride at 0°C. The mixture was stirred at room temperature for 15 h, washed with 1 N HCl solution and brine, and dried over $MgSO_4$. The crude products were purified by flash column chromatography. Using DMAP instead of pyridine gives partial racemization of hydroxy ketones (see Ulku, D.; Tahir, M. N.; Tanyeli, C.; Demir, A. S.; Dikici, E. *Acta Cryst*. **1997**, *C53*, 1998).
10. (a) Cygler, M.; Grochulsky, P.; Kazlauskas, R. J.; Schrag, J. D.; Bouthillier, F.; Rubin, B.; Serrequi, A. N.; Gupta, A. K. *J. Am. Chem. Soc*. **1994**, *116*, 3180. (b) Maximo, M. F.; Van Der Lugt, J. P. *Biocatalysis* **1994**, *8*, 321. (c) Kasai, M.; Kawai, K.; Imuta, M.; Ziffer, H. *J. Org. Chem*. **1984**, *49*, 675.
11. Resnick, S. M.; Torok, D. S.; Lee, K.; Brand, J. M.; Gibson, D. T. *Appl. Environ. Microbiol*. **1994**, *60*, 3323.
12. Honda, Y.; Ori, A.; Tsuchihashi, G. *Bull. Chem. Soc. Jpn* **1987**, *60*, 1027.
13. Harada, K.; Shiono, S. *Bull. Chem. Soc. Jpn* **1984**, *57*, 1040.
14. Kenyon, J.; Patel, P. L. *J. Chem. Soc*. **1965**, 435.
15. (a) Monsadi, A.; Gessner, M.; Gunther, G.; Deger, W.; Singer, G. *J. High Res. Chromatography & Chromatography Commun*. **1987**, *10*, 67. (b) Slessor, K. N.; King, G. G. S.; Miller, D. R.; Winson, M. L.; Cutforth, T. L. *J. Chem. Ecol*. **1985**, *11*, 1659.
16. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. H. *J. Am. Chem. Soc*. **1982**, *104*, 7294.