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Kinetic Resolution of Secondary Alcohols Mediated by Rabbit Gastric Lipase

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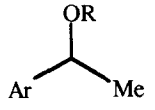
***Abstract**: Secondary benzylic alcohols were kinetically resolved by rabbit gastric lipase-mediated acylation with isopropenyl acetate. Among all the substrates tested, a high enantioselectivity was observed only for 1-[2-(6-methoxy)naphthyl]ethanol **3a** (E>500). Allylic alcohols **14a** and **15a** were also efficiently resolved (E = 26 and 51 respectively).* © 1997 Elsevier Science Ltd. All rights reserved.

We recently described the palladium-catalyzed nucleophilic substitution of enantiomerically pure esters of alcohols **1a**-**3a** by sodium dimethyl malonate.[1] Alcohols **1a** and **2a** are commercially available, in racemic and both enantiomeric forms. Racemic **3a** is easily prepared by hydride reduction of the corresponding ketone.[2] We wish to report our results concerning the preparation of enantiomerically pure **3a** and **3b**,[3] and various others optically active 1-arylethanols, by kinetic resolution mediated by rabbit gastric lipase (RGL).[4] We already used RGL in kinetic resolution of 2-hydroxyalkyldiphenylphosphines[5] and axially chiral cycloalkylidenethanols.[6]



a: R = H ; **b**: R = Ac

1	Ar = 1-naphthyl	**7**	Ar = 4-methoxyphenyl
2	Ar = 2-naphthyl	**8**	Ar = 4-bromophenyl
3	Ar = 2-(6-methoxy)naphthyl	**9**	Ar = ferrocenyl
4	Ar = phenyl	**10**	Ar = 3-quinolyl
5	Ar = 2-methoxyphenyl	**11**	Ar = 4-quinolyl
6	Ar = 3-methoxyphenyl	**12**	Ar = 4-isoquinolyl

Racemic 1-[2-(6-methoxynaphthyl)]ethanol **3a** (1g, 5 mmol) and isopropenyl acetate (1.5 g, 15 mmol) were dissolved in 30 mL ether and 200 mg of RGL were added. The resulting suspension was stirred at room temperature for 21.5 h and then filtered through Celite. After evaporation of the solvent, the residue was subjected to chromatography (silica gel, eluent = hexane / ethyl acetate 80:20) to give (*R*)-**3b** (0.51 g, 2.1 mmol, 42%), ee > 99.5% and (*S*)-**3a** (0.41 g, 2.0 mmol, 41%), ee = 78.5%. Enantiomeric excesses were determined by HPLC on a CHIRACEL OD-H column. The substrate conversion and the enantioselectivity factor E were calculated[7] to be 44% and > 500 respectively. This high value of E is superior to the reported value in the literature (E = 78),[3b] and to the results we obtained with some commercially available lipases. Saponification (KOH, MeOH) of (*R*)-**3b** gave enantiomerically pure (*R*)-**3a**.

Encouraged by this satisfactory result, we attempted the acylation of **3a** by succinic anhydride,[9] in order to avoid the separation of **3a** and **3b** by column chromatography. However, although the enzymatic activity was retained, the enantioselectivity of this resolution was very low (E = 2).

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Some other 1-arylethanols were tested in the acetylation by isopropenyl acetate: experimental conditions were the same as described above for **3a**. Results are collected in the Table.

These kinetic resolutions were performed in order to determine the factor E. Enantiomeric excesses of remaining substrates were not optimized. The present study demonstrate that RGL shown a high specificity for alcohol **3a**. For all other substrates, the E values were in the range 1.1 to 23. Utilization of RGL in the case of **1a**, **2a**, **4a**, **9a** and **11a** does not improve the results described in the literature.[10]

1a and **2a** showed moderate enantioselectivity with a very low enzymatic activity for the former (entries 1 and 2). The large difference on substrates **2a** and **3a** should be noted: the introduction of a methoxy substituent in the 6-position of **2a** enhances the enantioselectivity by a factor 20 at least. The enantiomers of 1-acenaphthenol **13a** were both rapidly esterified in the same conditions (entry 4).

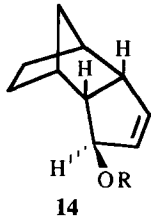
1-Phenylethanol **4a** was poorly resolved by RGL (entry 5) and introduction of a methoxy substituent in meta (**6a**) or para (**7a**) position resulted in a moderate enhancement of the enantioselectivity (entries 6 and 7). The results of entries 5 to 7 showed that the large difference observed between the enantioselectivities on **2a** and **3a** is not only due to an electronic effect. 1-(2-methoxyphenyl)ethanol **5a** was recovered unchanged after 5 days of reaction, maybe because of a strong hydrogen bond stabilization of the substrate.

The introduction of a para-bromo substituent is beneficial (entry 8), and the recovered 1-(4-bromo)-phenylethanol **8a** was enantiomerically pure at 60% conversion.

Both enantiomers of 1-ferrocenylethanol **9a** were acetylated with very similar rates and both the alcohol **9a** and the acetate **9b** were obtained with very low ee values (entry 9).

We investigated three heteroaromatic substrates **10a**-**12a**: (+)-1-(3-quinolyl)ethanol **10a** was previously obtained by asymmetric hydride reduction of 3-acetylquinoline,[11] but the enantioselectivity of the reaction was unknown. 1-(4-Quinolyl)ethanol **11a** was recently resolved via an immobilized lipase-catalyzed acetylation. [10d] To the best of our knowlegde, 1-(4-isoquinolyl)ethanol **12a** was described only in racemic form. Substrate **10a** gave a comparable result to the similarly substituted naphthalene derivative **2a** (entry 10), whereas **11a** and **12a** (entries 11 and 12) were slowly acetylated, with a lower enantioselectivity than **1a**. Introduction of a nitrogen atom on the aromatic moiety has little influence on this resolution.

Finally, we examined the kinetic resolution of allylic alcohols **14a** and **15a**.[12] Commercially available PPL and CCL lipases were not efficient in the acetylation of (±)-**14a**: the enzymatic activities were low (conversion of 17% and 33% respectively in 3 days) as well as the enantioselectivities (E = 5 and 3). RGL gave the best result for this substrate: (+)-**14a** (ee = 70%) and (-)-**14b** (ee = 85%) were obtained after 44h at 20°C in cyclohexane (c = 0.45, E = 26). The acetylation of the endo isomer (±)-**15a** was slower since after 5 days at 30°C (no acetate was detected after two days of reaction at 20°C), the conversion reached about the same value (c = 0.44). However, the enantioselectivity was enhanced: alcohol (+)-**15a** and acetate (-)-**15b** were isolated with 71% and 92% ee respectively (E = 51).[13]



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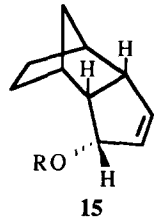
a: R = H



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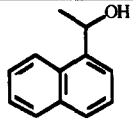
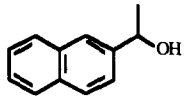
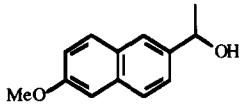
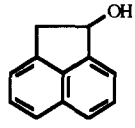
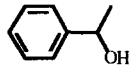
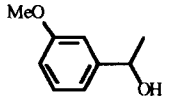
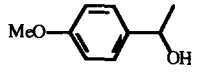
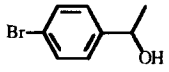
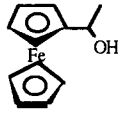
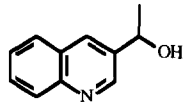
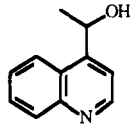
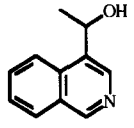
b: R = Ac

Table

Entry		Substrate	time (h)	ee alcohol (%) [a]	ee acetate (%) [a]	c (%) [b]	E [b]
1	**1a**		96	13	85	13.5	14
2	**2a**		19	59 [c]	85.5	41	23
3	**3a**		21.5	78.5	>99.5	44	>500
4	**13a**		24	80.5	2.5 [d]	97	2
5	**4a**		18	54	43.5 [d]	55.5	4
6	**6a**		18	92	63 [d]	59.5	14
7	**7a**		18	95 [c]	36	72.5	7
8	**8a**		18	>99.5	63 [d]	61	20
9	**9a**		18	6 [c]	4	60	1.1
10	**10a**		15	82.5	74.5 [d]	52.5	17
11	**11a**		17	7	68.5	9	6
12	**12a**		96	17 [e]	59 [e]	22	5

[a] Determined by HPLC unless otherwise noted. [b] The substrate conversion c and the enantioselectivity factor E were calculated[7] from standard equations. [c] Determined by HPLC after acetylation (Ac_2O, catalytic DMAP, Et_3N). [d] Determined by HPLC after saponification (KOH, MeOH). [e] Determined by ^1H NMR in the presence of $Eu(hfc)_3$.

In conclusion, enantioselectivities for kinetic resolution of a number of secondary alcohols have been determined in lipase-mediated acetylation. Rabbit gastric lipase was found to be highly superior in terms of enantioselection to common commercially available lipases in two cases (**3a** and **14a**). In the case of bicyclic aromatic substrates, influence of steric factors in enantioselection predominates since β-substituted aryl methyl carbinols showed higher selectivity than α-isomers.

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References and notes

1- Legros, J.Y.; Toffano, M.; Fiaud, J.C. *Tetrahedron* **1995**, *51*, 3235-3246.
2- 2-Acetyl-6-methoxynaphthalene was prepared according to: Arsenijevic, L.; Arsenijevic, V.; Horeau, A.; Jacques, J. *Org. Synth.* **1973**, *53*, 5-8.
3- 1-[2-(6-methoxynaphthyl)]ethanol was previously obtained optically active by: (a) asymmetric oxazaborolidine-catalyzed borane reduction of 2-acetyl-6-methoxynaphthalene: Corey, E.J.; Bakshi, R.K.; Shibata, S.; Chen, C.P.; Singh, V.K. *J. Am. Chem. Soc.* **1987**, *109*, 7925-7926, (b) kinetic resolution using XAD-8 immobilized lipoprotein lipase: Hsu, S.H.; Wu, S.S.; Wang, Y.F.; Wong, C.H. *Tetrahedron Lett.* **1990**, *31*, 6403-6406.
4- Moreau, H.; Gargouri, Y.; Lecat, D.; Junien, J.L.; Verger, R. *Biochim. Biophys. Acta* **1988**, *960*, 286-293. The Rabbit Gastric Lipase is a crude lipase extracted from rabbit stomach and was obtained from Sipsy-Jouveinal Company. It is a lyophilized power showing ≈ 20 U/mg (tributyrin as substrate).
5- Kagan, H.B.; Tahar, M.; Fiaud, J.C. *Bioorg. Med. Chem.* **1994**, *2*, 15-21.
6- Fiaud, J.C.; Gil, R.; Legros, J.Y.; Aribi-Zouioueche, L.; König, W.A. *Tetrahedron Lett.* **1992**, *33*, 6967-6970.
7- The substrate conversion c and the enantioselectivity factor E were calculated taking the following equations,[8] where ee_S and ee_P refer to the recovered alcohol substrate and the acetate product respectively:
$$c = ee_S/(ee_S + ee_P) \; ; \qquad E = \ln[(1-c)(1-ee_S)]/\ln[(1-c)(1+ee_S)]$$
8- (a) Chen, C.S.; Wu, C.H.; Girgaukas, G.; Sih, C.J. *J. Am. Chem. Soc.* **1987**, *109*, 2182-2187. (b) Kagan, H.B.; Fiaud, J.C. Kinetic Resolution. In *Topics in Stereochemistry*, Vol. 18, pp. 249-330, Eliel, E.L.; Wilen, S.H., Eds; John Wiley and Sons, Inc.; New York, 1988.
9- For other lipase-catalyzed acylations with succinic anhydride, see: (a) Terao, Y.; Tsuji, K.; Murata, M.; Achiwa, K.; Nishio, T.; Watanabe, N.;Seto, K. *Chem. Pharm. Bull.* **1989**, *37*, 1653-1655. (b) Gutman, A.L.; Brenner, D.; Boltanski, A. *Tetrahedron: Asymmetry* **1993**, *4*, 839-964. (c) reference 8.
10- For some recent exemples of lipase catalyzed resolutions of aryl methyl carbinols, see: (a) Ferraboschi, P.; Casati, S.; Manzocchi, A.; Santaniello, E. *Tetrahedron: Asymmetry* **1995**, *6*, 1521-1524. (b) Nakamura, K.; Kawasaki, M.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1079-1085. (c) Suginaka, K.; Hayashi, Y. Yamamoto, Y. *Tetrahedron: Asymmetry* **1996**, *7*, 1153-1158. (d) Nishikawa, T.; Yoshikai, M.; Obi, K.; Isobe, M. *Tetrahedron Lett.* **1994**, *35*, 7997-8000. For an efficient resolved of 1-ferrocenyl-ethanol: (e) Boaz, N.W. *Tetrahedron Lett.* **1989**, *30*, 2061-2064.
11- Seebach, D.; Daum, H. *Chem. Ber.* **1974**, *107*, 1748-1763.
12- For the synthesis of racemic **14a-b** and **15a-b**, see: Fiaud, J.C.; Legros, J.Y. *J. Org. Chem.* **1987**, *52*, 1907-1911.
13- *endo* 3-Hydroxydicyclopentadiene (dehydro analogue of **15a**) is also more efficiently resolved by lipase-mediated acetylation than the *exo* stereoisomer: Tanaka, K.; Ogasawara, K. *Synthesis* **1995**, 1237-1239 and references herein.

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