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Studies on the Regio- and Enantioselectivity of the Lipase-catalyzed Transesterification of 1'- and 2'-Naphthyl Alcohols in Organic Solvent

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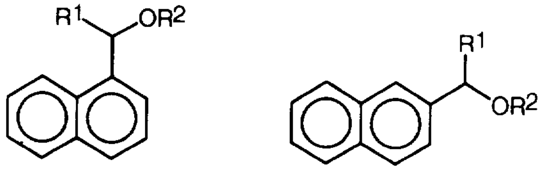
Abstract: The *Pseudomonas cepacia* lipase preferentially acylates the 2'-regioisomers of a few 1'- and 2'-naphthyl alcohols; in the case of compounds **3a**, **3c**, **4a**, **4c** the (R)-alcohols (65->98% ee) and the (S)-acetates (62-98% ee) are formed.

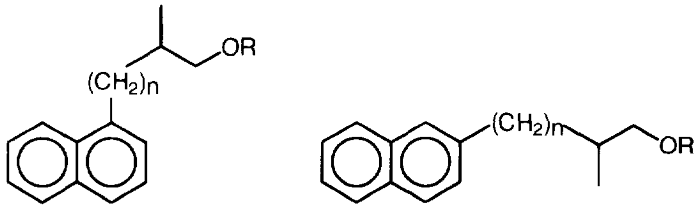
Recently, we have reported the results from our studies on the regio- and enantioselectivity of the *Pseudomonas fluorescens (P. cepacia)* lipase (PFL)-catalyzed irreversible transesterification[1] of 2-substituted-1,4-butanediols[2] in organic solvents. We have extended these studies to naphthyl alcohols that can be easily prepared as 1'- or 2'-regioisomers, where the aromatic portion of the molecule could influence[3] the regio- and stereochemical demand of the active site of the enzyme.[4]



1 **2**

a. $R^1 = CH_3$, $R^2 = H$
b. $R^1 = CH_3$, $R^2 = Ac$
c. $R^1 = R^2 = H$
d. $R^1 = H$, $R^2 = Ac$

We first investigated 1-(1'- and 2'-naphthyl)ethanols **1a** and **2a**, potentially useful as chiral auxiliaries,[5] that can be prepared in optically active form by several biocatalytic approaches such as reduction of the parent naphthyl methyl ketones by means of microorganisms[6,7] or enzymatic hydrolysis of suitable esters.[8] We found that, under the same conditions of temperature, solvent, enzyme/substrate ratio, etc.,[9] the 1-(1'-naphthyl)ethanol **1a** was not a substrate (5% of the acetate **1b** formed in 72 h), whereas the regioselective acylation of the 2'-isomer **2a** affords the nearly enantiomerically pure alcohol (S)-(-)-**2a** and acetate (R)-(+)-**2b**.[10] Opposite results in terms of regioselectivity were obtained on naphthylmethanols **1c** and **2c**, since the 1'-isomer was completely acylated in 5 hours and the 2'-isomer reacted in about 5% after 5 days. This result could not be fully interpreted by the existing models of the active sites proposed for known lipases. The 1'-and 2'-isomers may react by positioning the aromatic ring in different regions of the enzyme active site and consequently the size and the nature of the alcohol counterpart can play a significant role on the regio- and stereochemical outcome. For the above considerations, we prepared two other pairs of naphthyl alcohols, namely compounds **3a**, **4a**, **3c**, **4c**,[11] considering that 2-methyl alkanols have proven to be excellent substrates for the enzymatic resolution process.[12]



3 **4**

a. n = 0, R = H b. n = 0, R = Ac
c. n = 1, R = H d. n = 1, R = Ac

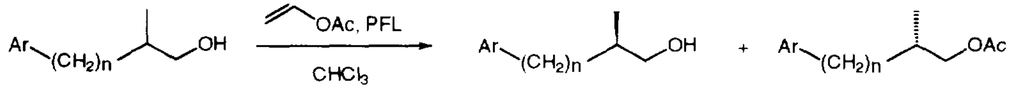
The results from the irreversible transesterification of all the naphthyl alcohols[13] are reported in the Table and show that the isomers **3a** and **4a**, as well as **3c** and **4c** react at different rates, the 2'-isomer being always more reactive. The stereochemical outcome of the resolution of the racemic naphthyl alcohols[14,15] here reported is identical to that found for the phenyl analogs.[16]

TABLE. PFL-catalyzed Transesterification of Naphtyl Alcohols

Substrate	*Product*	*Time (h)*	*Yield (%)*	*ee (%)*[a]	*Config.*[b]	*E*[c]
1a	**1b**	72	5	-	-	-
2a	**(+)-2b**	27	40	>98	R	196
2a	**(-)-2a**	96	30	>98	S	
1c	**1d**	5	98	-	-	-
2c	**2d**	120	5	-	-	
3a	**(-)-3b**	86	35	72	S	9
3a	**(+)-3a**	97	43	70	R	
4a	**(-)-4b**	16	32	62	S	6
4a	**(+)-4a**	22	31	65	R	
3c	**(+)-3d**	4	30	>98	S	150
3c	**(+)-3c**	23	34	>98	R	
4c	**(+)-4d**	3	40	92	S	45
4c	**(+)-4c**	7	40	85	R	

[a] The acetates were converted into the alcohols by reaction with $LiAlH_4$ and the ee established by NMR (ref. 14, 15). [b] Configurations assigned by optical rotation or by NMR (Ref. 15). [c] According to Sih, C. J.; Wu, S.-H. *Topics in Stereochemistry* **1989**, *19*, 63.

In fact, the secondary alcohol **2a** has the same (S)-configuration as the lipase-resolved 1-phenylethanol[17] and from the 2-methyl naphthyl alcohols **3a**,**4a** and **3c**,**4c** the (R)-alcohols and (S)-acetates were formed.[16] The ee values obtained for the latest products confirm that the enantioselectivity is higher when the stereogenic center is separated from the aromatic nucleus by a methylene group.[4a] All the above results are consistent with the presence of one or more aromatic amino acids at the active site of the *Pseudomonas cepacia* lipase that, by electronic interactions with the aromatic moiety of the susbstrate can strongly influence the stereochemical outcome of the transesterification process in organic solvents.[18]



Ar = Ph, 1-Naphth, 2-Naphth

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References and Notes

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9. The lipase used in this study was a gift from Amano, Japan and has been named PFL in accord to all previous works in our laboratory. The highest ee for the unreacted alcohol was generally reached at 60% conversion to the acetate, whereas very high ee were obtained for acetate if the acetylation was stopped at 40%. The mode of stirring the reaction (oscillatory in our case) seems also a critical factor for the reproducibility of results.
10. Similar results have very recently appeared while this manuscript was in preparation: Gaspar, J.; Guerrero, A. *Tetrahedron: Asymmetry* **1995**, *6*, 231.
11. The alcohol **3a** was prepared from commercial 1-naphthyl methyl ketone by Wittig reaction with methoxymethyltriphenylphosphonium salt and acidic hydrolysis to 2-naphthylpropanal that was subsequently reduced with sodium borohydride (35% overall). Starting from 2-naphthylacetic acid , the corresponding ethyl 2-naphthyl acrylate was prepared (Sunjic, V.; Habus, H.; Comisso, G.; Moimas, F. *Gazz. Chim. Ital.* **1989**, *119*, 229), hydrogenated (Pd-C, 10%) and reduced with $LiAlH_4$ to afford **4a** in 23% overall yield. The alcohol **3c** and **4c** were prepared from 1- and 2-naphthyl aldehydes by a Wittig-Horner condensation with triethyl phosphonopropionate followed by hydrogenation and $LiAlH_4$ reduction (42%).
12. Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. in *Biocatalysis in Non-conventional Media* Tramper, J.; Vermüe, M. H.; Beeftink, H. H.; von Stockar, U. Eds. Elsevier, Amsterdam **1992**, 533.
13. To a solution of the alcohol (1.2 mmol) in chloroform (2.5 mL), vinyl acetate (0.42 mL, 4.8 mmol) and PFL (16.8 mg, 31.6 U/mg) were added and the mixture stirred at 30 °C for the time necessary for the required conversion.
14. The ee of the alcohols was established by ^{1}H-NMR (500 MHz) of the (R)-MTPA ester (Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543) and the resonances for the CH_2OCO or *CH*OCO groups of all the derivatives were considered for this purpose. Racemic **2a**: two quartets centered at 6.25 and 6.29 ppm. (R)-**2a** (from the acetate **2b**) and (S)-**2a** : only a quartet at 6.29 and 6.25 ppm, respectively (98% ee). Racemic **3a**: two groups of signals between 4.30 and 4.47 ppm and 4.64 and 4.765 ppm. (R)-(+)-**3a**: two groups of signals at 4.35 and 4.40 ppm (15:85, 70% ee); (S)-(-)-**3a** (from the acetate **3b**): two groups of signals at 4.35 and 4.40 ppm (86:14, 72% ee). A similar pattern was observed for racemic and (R)-(+)-**4a**, except that the resonances were at 4.36, 4.43, 4.53, and 4.63 ppm.
15. (-)-**2a** is the (S)-alcohol (see for instance Fluka catalogue); for (R)-(+)-**3a** and (R)-(+)-**4a** see Ref. 16b. The (R) configuration to (+)-**3c** and (+)-**4c** was assigned comparing position and multiplicity of the CH_2OCO group of their (R)-MTPA esters with the same derivative of the known (R)-3-phenyl-2-methylpropanol (Ref. 4a; Ferraboschi, P; Casati, S.; Santaniello, E. *Tetrahedron: Asymmetry* **1994**, *5*, 19). The groups of signals at 4.045-4.090, 4.090-4.190, 4.215-4.260 ppm from the racemic alcohol were simplified in the spectrum of the (R)-alcohol (the multiplet at 4.090-4.190 was not detectable). Racemic **3c**: three groups of signals at 4.14-4.185, 4.195-4.295, 4.30-4.345 ppm in the ratio 0.5:1:0.5. (R)-(+)-**3c**, $\{[\alpha]_D$ +12.5 (*c* 1 in $CHCl_3$)$\}$: the multiplet at 4.195-4.295 was not detectable (>98% ee); (S)-(-)-**3c** $\{$from the (S)-(+)-acetate **3d**, $[\alpha]_D$ +27 (*c* 1 in $CHCl_3$)$\}$: only the group of signals at 4.195-4.295 was present (>98% ee). A similar pattern was observed for racemic, (R)-(+) **4c** $\{[\alpha]_D$ +9.8 (*c* 1 in $CHCl_3$)$\}$ and (S)-(-)-**4c** $\{$from the (S)-(+)-acetate **4d**, $[\alpha]_D$ +11 (*c* 1 in $CHCl_3$)$\}$, except that the resonances were at 4.08-4.13, 4.13-4.24, and 4.26-4.32 ppm.
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18. Similar observations have been recently reported; see: Nakamura, K.; Kawasaki, M.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3053.

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