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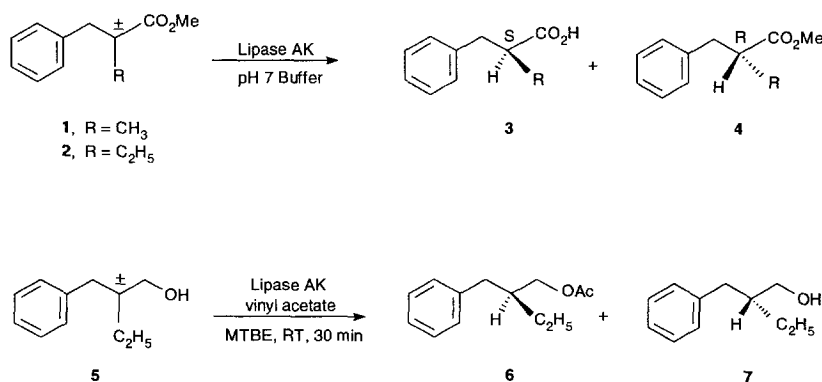
## DIFFERENCES IN REACTIVITY AND ENANTIOSELECTIVITY IN LIPASE REACTIONS WITH CARBOXYLIC ESTERS AND ALCOHOLS BEARING THE SAME STEREOGENIC CENTER

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**Abstract:** The reaction rate and stereochemical outcome of lipase reactions obtained with carboxylic esters and alcohols, which contain the same stereogenic center, can be modulated by changing the mode of the lipase reaction, *i.e.* ester hydrolysis versus alcohol acetylation.

The enantiomers of ( $\pm$ )-2-benzylpropionic acid have been previously prepared using a lipase catalyzed hydrolysis. Treatment of methyl ( $\pm$ )-2-benzylpropionate **1** in water with Lipase AK provided the (*R*)-methyl ester **4** and the (*S*)-acid **3** with >95% ee and in excellent yield.<sup>1</sup> In the course of our work we required a resolution of ( $\pm$ )-2-benzylbutyric acid. In contrast to the successful lipase resolution of ( $\pm$ )-1, lipase



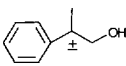
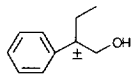
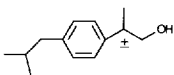
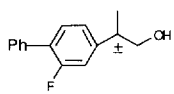
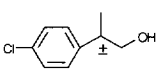
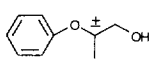
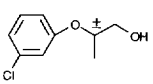
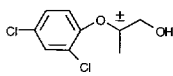
hydrolysis of ethyl ( $\pm$ )-2-benzylbutyrate **2** afforded disappointing results.<sup>2</sup> This prompted us to replace the carbomethoxy group with a carbinol group and study the lipase reaction in the reverse direction, *i.e.* acetylation in organic solvent. We were pleased to discover that Lipase AK (50 weight percent) performed favorably in the transesterification reaction of ( $\pm$ )-alcohol **5**<sup>3</sup> with vinyl acetate (2 equiv) and gave the

(*S*)-acetate **6** and (*R*)-alcohol **7** in excellent fashion<sup>4</sup> (MTBE solvent, room temperature, 30 min,  $E^5 = 42$ ). Since the enzymatic hydrolysis of esters of ( $\pm$ )-arylpropionic and ( $\pm$ )-phenoxypropionic acids using lipases has generally resulted in rather low enantioselectivities, we extended the study to the carbinol derivatives of these compounds. The results are shown in the Table. From lipase screening, we found PPL (Sigma) to be the lipase of choice for the acetylation of carbinols with vinyl acetate in MTBE solvent. Only in the case of the unsubstituted phenyl  $\alpha$ -methyl compound (entry 1) did we observe very low enantioselectivity. Substitution of the ethyl group for a methyl group enhanced selectivity (entry 2). When the PPL acetylation was performed with the carbinol derivatives of ibuprofen (entry 3) and flurbiprofen (entry 4), the reaction proceeded with high enantioselectivity.<sup>6</sup> The outcome with the phenoxy carbinols (entries 6, 7, and 8) was less dramatic. Nevertheless, our results are generally better or equal to those reported by other workers with lipase hydrolysis of ( $\pm$ )-phenoxypropionic esters,<sup>7</sup> enantioselective esterification of ( $\pm$ )-phenoxypropionic acids with alcohols,<sup>8</sup> and lipase catalyzed irreversible transesterification using vinyl ester of ( $\pm$ )-2-phenoxypropanoic acid.<sup>9</sup> This application of converting an ester to a carbinol may be of general applicability for resolution of  $\alpha$ -substituted carboxylic esters which are resistant or non-selective towards lipase hydrolysis.<sup>10</sup>

#### References and Notes

1. Delinck, D. L.; Margolin, A. L. *Tetrahedron Lett.* **1990**, *31*, 6797.
2. OF-360 afforded 69% conversion at 5 h with no selectivity in the acid product or recovered methyl ester. PPL, Lipase AK, and PS-30 gave <10% conversion to acid (6 d, room temperature). Lipase N (Amano) yielded 36% conversion to acid at 96 h, room temperature with  $ee_{(s)}$  32% and  $ee_{(p)}$  53% ( $E = 4$ ). The difficulty encountered in the lipase hydrolysis of ( $\pm$ )-**2** in this study is in agreement with those reported by other workers with the same compound, see Colombo, M.; DeAmici, M.; DeMicheli, C.; Pitre, D.; Carrea, G.; Riva, S. *Tetrahedron: Asymmetry* **1991**, *2*, 1021.
3. The results found with lipase acylation of ( $\pm$ )-2-benzylbutanol **5** are similar to those reported in ref. 1 for ( $\pm$ )-2-benzylpropanol.
4. Enantiomeric excess of (*R*)-alcohol was determined by HPLC using Chiralcel OD column (Daicel) with a mobile phase of 4% isopropanol in hexane. The enantiomeric excess of the (*S*)-acetate was determined by LAH reduction to the (*S*)-alcohol and chiral HPLC analysis. The stereochemical assignments of the products are based on the studies reported in ref. 1 for ( $\pm$ )-2-benzylpropanol.
5. Chen, C.-S.; Fujimoto, Y.; Gidraukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
6. Wu, S.-H.; Guo, Z.-W.; Sih, C.J. *J. Am. Chem. Soc.* **1990**, *112*, 1990. To obtain high enantioselectivity ( $E > 100$ ) the lipase hydrolysis was carried out on the activated  $\beta$ -chloroethyl ester of flurbiprofen and required purified *Candida* lipase. Use of the crude *Candida* preparation gave  $E = 10$ . These workers observed the same enhancement in selectivity with a series of phenoxypropionic esters.

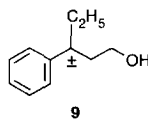
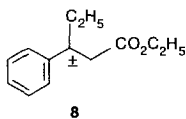
TABLE

Entry	Substrate <sup>a</sup>	Rxn Time, h	ee <sub>s</sub>	ee <sub>p</sub>	c <sup>d</sup>	E
1		19	ND	ND	0.56	<1
2		21	0.69 <sup>b</sup>	ND	0.52	9
3		24	0.90 <sup>b</sup>	ND	0.48	>100
4		24	0.95 <sup>c</sup>	ND	0.51	81
5		14	0.94 <sup>b</sup>	ND	0.49	>100
6		4	0.35 <sup>c</sup>	0.84 <sup>c</sup>	0.29	18
7		2	0.21 <sup>b</sup>	0.87 <sup>c</sup>	0.19	22
8		2	0.20 <sup>b</sup>	ND	0.20	11

<sup>a</sup> Reaction carried out in MTBE (50mg/mL) with 50% by weight PPL and 2 molar equivalent of vinyl acetate at room temperature. <sup>b</sup> Ee determined with Chiralpak-AD column (Daicel) using 4% IPA in hexane. <sup>c</sup> Ee determined with Chiralcel-OD column using the same mobile phase.

<sup>d</sup> Conversion calc'd by HPLC analysis or  $c = ee_s/ee_s + ee_p$  when available.

7. The workers in reference 6 obtained  $E = 2$  and  $E = 1$  for lipase hydrolysis of the methyl esters of 2-(3-chlorophenoxy)-propionic acid and 2-(2,4-dichlorophenoxy)-propionic acid using crude *Candida* lipase. After lipase purification, the  $E$  values increased to 12 and 14, respectively.
8. Chen, P.-Y.; Wu, S.-H.; Wang, K.-T. *Biotechnology Lett.* **1993**, *2*, 181.
9. Miyazawa, T.; Kurita, S.; Ueji, S.; Yamada, T.; Kuwata, S. *Biotechnology Lett.* **1992**, *10*, 941.
10. We also studied ethyl ( $\pm$ )-3-phenylpentanoate **8**. Similar to **2**, lipase hydrolysis of **8** also proved unsatisfactory. Transformation of ester **8** to alcohol **9** and subsequent lipase acetylation under the identical conditions described for **5** gave, after 1 h, 44% conversion. However, in comparison to alcohol **5**, the enantioselectivity of the reaction was low ( $ee_{(s)}$  34% and  $ee_{(p)}$  44%,  $E = 3$ ). In the case of  $\beta$ -ethyl substituted carbinol **9**, where the stereogenic center is one bond further removed from the acyl-enzyme tetrahedral complex, chiral recognition of the substrate by the lipase is less discriminatory.



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