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Secondary alcohols act as better nucleophiles than primary alcohols in the lipase-catalyzed regioselective deacylation of dihydroxybenzenes acylated at both phenolic hydroxyls

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Abstract—*Candida antarctica* lipase B (CAL-B) was found to be highly regioselective as well as active in the deacylation of resorcinols and hydroquinones acylated at both phenolic hydroxyls. Contrary to expectation, secondary alcohols acted as better nucleophiles than primary alcohols in these enzymatic deacylations.

Lipases have been recognized as very attractive catalysts for organic syntheses because of their stability, usability and broad substrate tolerance.[1] Moreover, since they are easily available from a variety of sources, especially bacteria and fungi, there must be a fair chance of finding a suitable enzyme for a transformation of interest in terms of catalytic activity and/or selectivity. They have been employed mainly for the preparation of homochiral compounds related to pharmaceuticals and agrochemicals through stereoselective hydrolysis, esterification or transesterification. Besides lipases' stereoselectivity, their regioselective properties have also been exploited for the preparation of compounds, which are not easily obtainable by chemical methodologies. For example, the lipase-catalyzed acylation or deacylation procedure has been applied to the synthesis of selectively protected derivatives of polyhydroxy compounds such as carbohydrates. Compared to such studies on alcoholic hydroxyls, there have been much less studies on phenolic hydroxyls. The ability of lipases to discriminate between hydroxy groups of this type should deserve further attention because of its importance in organic synthesis. Parmar and co-workers have reported on the lipase-catalyzed deacylation of peracetylated polyhydroxy acetophenones and related aromatic ketones.[2,3] When they were subjected to transesterification with 1-butanol as a nucleophile in the presence of porcine pancreatic lipase (PPL) or *Candida cylindracea* (*rugosa*) lipase (CRL) in organic solvents, it was found that deacylation took place predominantly at positions other than *ortho* to the ketonic group, generally the acetoxy group at the *para* position being preferentially cleaved over the one at the *meta* position. The authors concluded that the carbonyl group attached to the benzene ring plays an important role in the recognition of acetoxy groups in polyphenolic peracetates, and they postulated the formation of a transient Schiff's base-type complex with the lysine residue in the active site of PPL.[2d] Nicolosi and co-workers have reported on the regioselectivity observed in the *Pseudomonas cepacia* lipase (PCL)-catalyzed deacylation with 1-butanol of peracetylated flavonoids, which contain a carbonyl group attached to the benzene ring.[4] It is worth while to examine how substituents other than the carbonyl can affect the regioselectivity in the lipase-catalyzed deacylation of peracylated polyphenols. In this regard, Klibanov and co-workers have investigated the lipase-catalyzed deacylation of octylhydroquinone butanoylated at both phenolic hydroxyls using 1-butanol, and they even found the reversion of PCL's regioselectivity upon a change from toluene to acetonitrile as the reaction medium.[5]

These studies have prompted us to investigate the lipase-catalyzed deacylation of diacylated dihydroxybenzenes,

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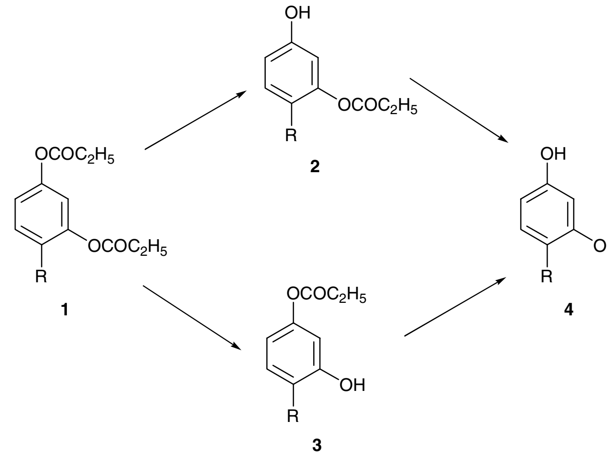
that is, resorcinols and hydroquinones, carrying several substituents other than the carbonyl. We found that in these deacylations, *Candida antarctica* lipase B (CAL-B) was more active than other lipases so far employed and moreover highly regioselective and, unexpectedly, that secondary alcohols acted as better nucleophiles than primary alcohols.

Initially, 4-substituted 1,3-di-*O*-propanoylresorcinols[6] (**1**) were subjected to deacylation with alcohols as nucleophiles in the presence of immobilized CAL-B[7] (Scheme 1).[8] These esters (**1**) can undergo enzymatic transesterification through two pathways to form either 3-*O*-propanoylresorcinols (**2**) or 1-*O*-propanoylresorcinols (**3**),[9] and finally to afford the parent resorcinols (**4**). The product distributions obtained after the incubation of **1** with 2-propanol (3 mol equiv) in diisopropyl ether at 45 °C are shown in Table 1. With resorcinol derivatives carrying alkyl or aralkyl substituents (**1a**–**c**), 3-*O*-propanoylresorcinols (**2a**–**c**) were obtained as the sole products of deacylation after 60 min of incubation, at the end of which 93–100% conversions were reached (entries 1, 4 and 5). The formation of neither the isomeric 1-*O*-propanoylresorcinols (**3a**–**c**) nor the parent resorcinols (**4a**–**c**) was detected. Thus, CAL-B was found to be active enough toward these diacylated dihydroxybenzenes and its activity seemed to be much higher than those of other lipases so far employed, taking it into consideration that the PPL or CRL-catalyzed deacylation of peracetylated polyhydroxy acetophenones and related aromatic ketones required several hours to even several days in order to reach a reasonable conversion.[2,10] Moreover, this lipase showed a complete regiospecificity in the deacylation of these compounds bearing no carbonyl group in diisopropyl ether. The deacylation of the resorcinol derivatives carrying halogen substituents (**1d** and **1e**) proceeded more smoothly, reaching completion after 15 min (entries 6 and 7). Although 3-*O*-propanoylresorcinols (**2d** and **2e**) were the major products (in 88–92% yield), the parent resorcinols (**4d** and **4e**) were also produced, while the isomeric 1-propanoylresorcinols (**3d** and **3e**) were not detected. These results indicate that of the two acyloxy groups the one remote from the substituent R and hence sterically less hindered was preferentially deacylated in the CAL-B-catalyzed deacylation of resorcinol derivatives. When the solvent was changed from diisopropyl ether to a more polar solvent, acetonitrile (entry 2), or to a more hydrophobic solvent, toluene (entry 3), regioselectivity was diminished to some extent in either case, but its reversal was never observed as in the PCL-catalyzed deacylation of the hydroquinone derivative mentioned above, as shown in Table 1 for the case of **1a**.



Scheme 1. CAL-B-catalyzed regioselective deacylation of 4-substituted 1,3-di-*O*-propanoylresorcinols (**1**). R: a, Et; b, $(CH_3)_3CCH_2C(CH_3)_2$-; c, Bn; d, Cl; e, Br.

Next, 2-substituted 1,4-di-*O*-propanoylhydroquinones (**5**) were subjected to deacylation with 2-propanol in the presence of CAL-B under the same reaction conditions (Scheme 2). The product distributions obtained from the substrates bearing an alkyl substituent (**5a**–**d**) are shown in Table 2, entries 1–4. After the incubation time of 60 min there remained (almost) no starting diacylated hydroquinones. With these hydroquinones acylated at both phenolic hydroxyls, loosened regioselectivity was observed, but the acyloxy group remote from the substituent R was preferentially deacylated to afford 1-*O*-propanoylhydroquinones (**6a**–**d**) as major products, as with the above-mentioned resorcinol derivatives. The steric demand of the R group seems to be greatly responsible for the regioselectivity observed. Thus, with methyl- and ethyllhydroquinone derivatives (**5a** and **5b**) the isomeric 4-*O*-propanoylhydroquinones (**7a** and **7b**) and the parent hydroquinones (**8a** and **8b**) were also produced in small amounts (entries 1 and 2).

Table 1. CAL-B-catalyzed deacylation of 4-substituted 1,3-di-*O*-propanoylresorcinols (**1**) with 2-propanol in diisopropyl ether[a]

Entry	Substrate	R	Time (min)	Products (%)		
				2	**3**	**4**
1	**1a**	CH_3CH_2	60	100	0	0
2	**1a**[b]		60	91.7	1.8	4.6
3	**1a**[c]		60	30.9	3.4	0
4	**1b**	$(CH_3)_3CCH_2C(CH_3)_2$	60	92.6	0	0
5	**1c**	$C_6H_5CH_2$	60	100	0	0
6	**1d**	Cl	15	87.7	0	12.3
7	**1e**	Br	15	91.7	0	8.3

[a] Reaction conditions: 0.1 mmol of **1**, 0.3 mmol of 2-propanol and 40 mg of CAL-B in 240 μl of anhydrous diisopropyl ether at 45 °C.
[b] In acetonitrile.
[c] In toluene.