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Candida antarctica lipase B-mediated regioselective acylation of dihydroxybenzenes in organic solvents

Toshifumi Miyazawa *, Manabu Hamada, Ryohei Morimoto, Yuki Maeda

Department of Chemistry, Faculty of Science and Engineering, Konan University, Higashinada-ku, Kobe 658-8501, Japan

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Candida antarctica lipase B proved to be a highly active biocatalyst for the direct acylation of phenolic hydroxy groups of substituted hydroquinones and resorcinols, which have rarely been reported so far. More importantly, the acylation reactions took place generally in a markedly regioselective manner: the hydroxy group remote from the substituent was preferentially acylated. In the case of substituted hydroquinones, the selectivity increased with the increase in the bulk of the substituent. Interestingly, the 1-*O*-monoacylated derivatives were obtained as the sole products in the case of 4-substituted resorcinols.

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1. Introduction

Enzymatic methodologies have now come to constitute important alternatives or complements to chemical synthesis. Among a number of enzymes exploited for synthetic purposes, lipases (triacylglycerol hydrolases, EC 3.1.1.3) are recognized as a very attractive group of catalysts because of their stability, usability and broad substrate tolerance. 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. Lipases have been employed for the preparation of homochiral compounds mainly related to pharmaceuticals and agrochemicals through enantioselective hydrolysis in aqueous milieux or esterification/transesterification in organic solvents.[1] Besides the stereoselective nature of lipases, their regioselective properties have also been exploited for the preparation of compounds, which are not easily obtainable by pure chemical methods. The synthesis of selectively protected derivatives of compounds containing multiple hydroxy groups such as carbohydrates has been undertaken through the lipase-catalyzed acylation or deacylation procedure.[2] These enzymatic acyl-transfer approaches are more straightforward than the standard chemical methods, because they can protect or deprotect a hydroxy group in the presence of several others under optimized reaction conditions. Compared to such studies on alcoholic hydroxy groups, there have been much less studies on phenolic hydroxy groups. Several reports have dealt with the lipase-catalyzed deacylation of peracetylated polyhydroxybenzenes,[3,4] and flavones and related compounds[5] by transesterification with an alcohol such as *n*-butanol in organic media. On the other hand, only a few reports have dealt with the lipase-catalyzed regioselective direct acylation of phenolic hydroxy groups.[6] This is probably because a phenolic hydroxy group is generally far less nucleophilic than an alcoholic hydroxy group and/or because phenolic compounds are known to inhibit some enzymes.[7] Nicolosi and coworkers reported that in the *Burkholderia* (*Pseudomonas*) *cepacia* lipase-catalyzed acetylation of aromatic dihydroxy aldehydes and ketones with vinyl acetate in cyclohexane–*t*-amyl alcohol, the hydroxy group other than the one at position *ortho* to the carbonyl was selectively acylated. They attributed this high regioselectivity to the chelation of the carbonyl with the *o*-hydroxy group.[6a,8] Stimulated by this work, we set about examining the regioselectivity in the lipase-catalyzed acylation of the simplest members of polyphenols, i.e., dihydroxybenzenes (hydroquinones and resorcinols) carrying substituents other than the carbonyl. The preparation of regioselectively protected derivatives of polyphenolic compounds by direct acylation procedure should be an extremely challenging task. We envisaged that if the substituent group was sterically demanding enough regioselective reactions might occur even in the absence of a carbonyl. In fact, we found that of the lipases examined *Candida antarctica* lipase B was a highly active biocatalyst for the direct acylation of phenolic hydroxy groups and the reactions took place generally in a very regioselective manner.[9] The present paper reports the results of our investigation in detail.

* Corresponding author. Tel.: +81 78 431 4341; fax: +81 78 435 2539; e-mail address: miyazawa@konan-u.ac.jp (T. Miyazawa).

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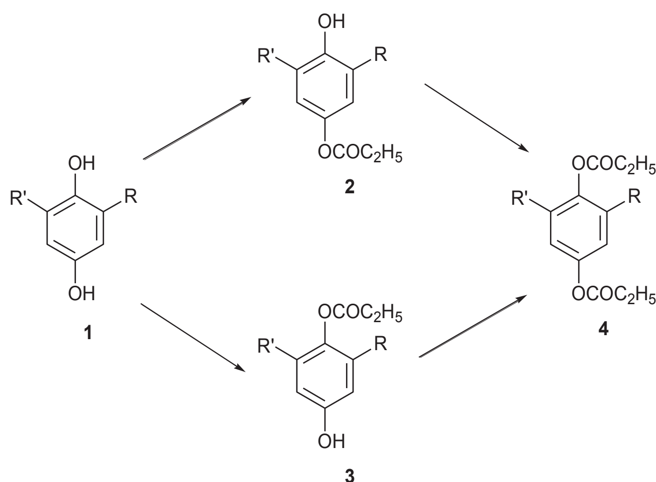
2. Results and discussion

Initially, several hydroquinones (**1**) bearing different substituents including the acetyl group on the benzene ring were subjected to enzymatic acylation under almost the same reaction conditions as those of the earlier work by Nicolosi and co-workers,[6a] employing vinyl propanoate (3 M equiv.) in the presence of immobilized *B. cepacia* lipase (Amano lipase PS) on Celite in cyclohexane–*t*-amyl alcohol (9:1, v/v) at 45 °C. As depicted in Scheme 1, the hydroquinone **1** can undergo acylation through two pathways to form either the 4-*O*-propanoyl derivative (**2**) or the 1-*O*-propanoyl derivative (**3**), and finally to afford the 1,4-di-*O*-propanoyl derivative (**4**). The product distributions after 3 days of incubation obtained through ^{1}H NMR analysis are compiled in Table 1. The phenolic hydroxy groups of all the hydroquinones (**1**) examined managed to be acylated, though the reactions were rather slow. The acylation of acetylhydroquinone (**1g**) was the slowest among those of the substituted hydroquinones examined, and besides the expected 4-*O*-acyl derivative (**2g**) the isomeric 1-*O*-acyl derivative (**3g**) was also produced in a fair amount, indicating the incompleteness of the lipase's regioselectivity even toward the aromatic dihydroxyketone. On the other hand, the reaction of *t*-butylhydroquinone (**1e**) proceeded in a highly regioselective manner beyond our expectations: the hydroxy group remote from the substituent was preferentially acylated, affording mainly the 4-*O*-acylted derivative (**2e**). This can be seen more clearly from the time-course of the propanoylation of **1e** followed through the quantification of products by HPLC analysis (Fig. 1). The yield of **2e** increased steadily with time and reached to ca. 90% after 7days. The reaction profile was almost the same with 2,6-dimethylhydroquinone (**1b**), though the 1,4-di-*O*-acylated product (**4b**) was not observed at all even after 7 days in this case. These results imply that the steric demand of the substituent(s) must be responsible for the observed high regioselectivity. When the steric bulk of a substituent became smaller, the reaction proceeded in a less regioselective manner, as can be seen from Fig 2 indicating the reaction profile of methoxyhydroquinone (**1f**). Although the 4-*O*-acyl derivative (**2f**) was still the main product, the isomeric 1-*O*-acyl derivative (**3f**) and the 1,4-di-*O*-acyl derivative (**4f**) were produced in fair amounts with time. The situation was almost the same with methylhydroquinone (**1a**) bearing the smallest substituent examined, though a larger amount of the 1,4-di-*O*-acylated derivative (**4a**) was produced with time in this case. Thus, we recognized a relationship between the steric demand of the substituent(s) and the regioselectivity in the *B. cepacia* lipase-catalyzed acylation.



Scheme 1. Lipase-catalyzed regioselective propanoylation of substituted hydroquinones (**1**). R: a, Me; b, Me; c, Et; d, *i*-Pr; e, *t*-Bu; f, MeO; g, Ac; h, F; i, Cl; j, Br. R′: a and c–j, H; b, Me.

Table 1
Burkholderia cepacia lipase-catalyzed propanoylation of substituted hydroquinones (**1**) with vinyl propanoate[a]

Substrate	R	R′	Yield (%)			Convn. (%)
			2	3	4	
1a	CH_3	H	41	27	30	98
1b	CH_3	CH_3	79	4	0	83
1e	$(CH_3)_3C$	H	73	2	1	76
1f	CH_3O	H	41	16	13	70
1g	CH_3CO	H	22	6	0	28

[a] Reactions were conducted using **1** (0.1 mmol), vinyl propanoate (0.3 mmol) and *Burkholderia cepacia* lipase immobilized on Celite (40 mg) in 240 µl of cyclohexane–*t*-amyl alcohol (9:1) at 45 °C for 3 days.

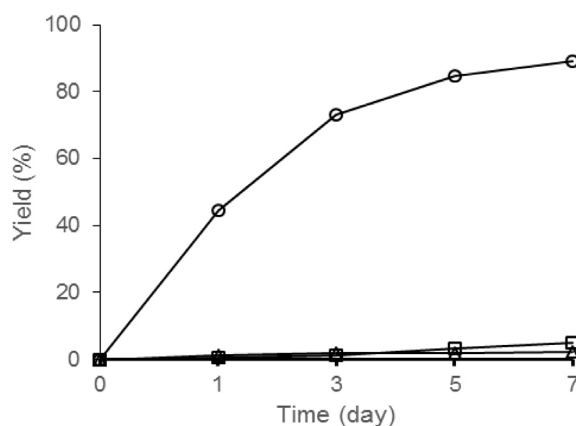


Fig. 1. Reaction profile of the *B. cepacia* lipase-catalyzed acylation of *t*-butylhydroquinone (**1e**) with vinyl propanoate in diisopropyl ether. Symbols: circle, **2e**; triangle, **3e**; square, **4e**.

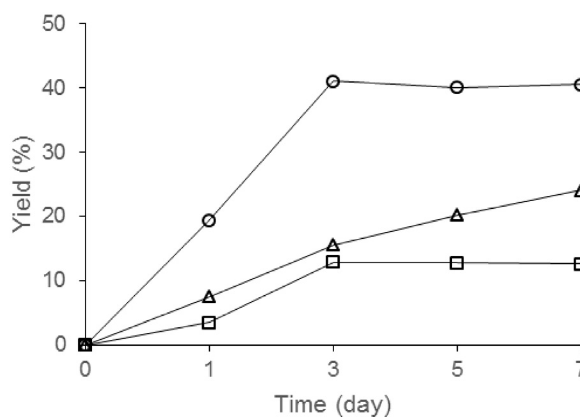


Fig. 2. Reaction profile of the *B. cepacia* lipase-catalyzed acylation of methoxyhydroquinone (**1f**) with vinyl propanoate in diisopropyl ether. Symbols: circle, **2f**; triangle, **3f**; square, **4f**.

Since *B. cepacia* lipase showed only a limited regioselectivity toward the hydroquinones bearing a smaller substituent, other lipases from microbial and pancreatic sources were screened to find out enzymes with better regioselectivity as well as better catalytic activity by choosing as a model compound methylhydroquinone (**1a**), which showed the poorest regioselectivity in the *B. cepacia* lipase-catalyzed acylation. The reaction was conducted using vinyl propanoate in diisopropyl ether[10] at 45 °C, and

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