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

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ABSTRACT

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.

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.

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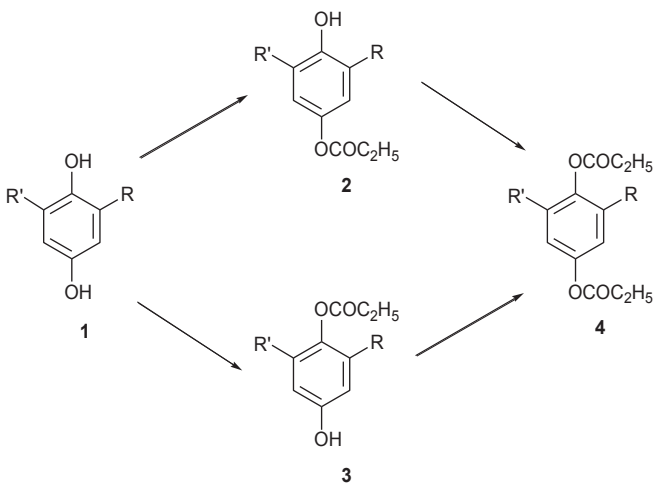
2. Results and discussion

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.

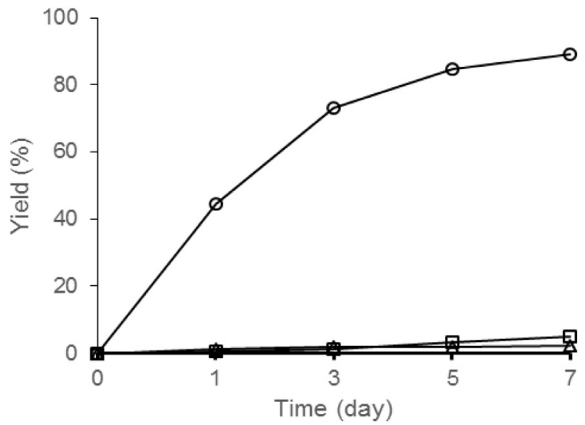


Fig. 1. Reaction profile of the *B. cepacia* lipase-catalyzed acylation of *t*-butylhydroquinone (**1e**) with vinyl propanoate in diisopropyl ether. Symbols: circle, **2e**; triangle, **3e**; square, **4e**.

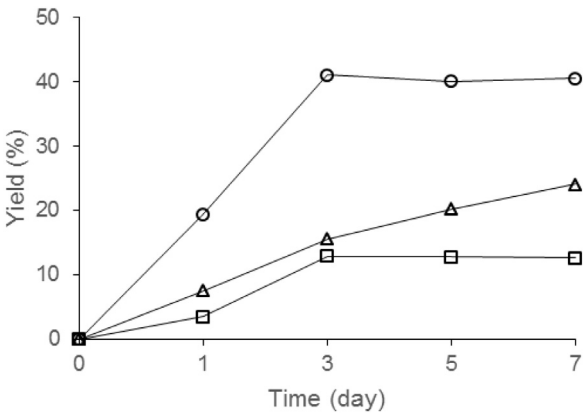


Fig. 2. Reaction profile of the *B. cepacia* lipase-catalyzed acylation of methoxyhydroquinone (**1f**) with vinyl propanoate in diisopropyl ether. Symbols: circle, **2f**; triangle, **3f**; square, **4f**.

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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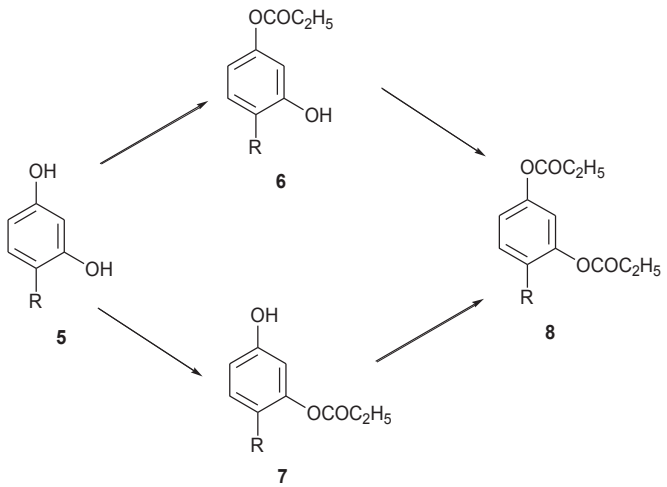
all the lipases were used in the immobilized form. Some of the results obtained after 1 day of incubation are shown in Table 2. Of the enzymes tested, *Candida antractica* lipase B (CAL-B)[11] and lipoprotein lipase from *Pseudomonas* sp. (Toyobo) were active enough toward the acylation of the phenolic hydroxy groups of **1a**. In terms of regioselectivity, the former lipase was the best, while the latter enzyme showed poor selectivity. The screening of lipases was also conducted with a substituted resorcinol, i.e., 4-ethylresorcinol (**5a**), employing the same acyl donor (Scheme 2). The acylations of **5a** were slower than those of the hydroquinone **1a**. Some of the results obtained after 3 days of incubation are shown in Table 3. Of the lipases with tolerable activity toward **5a**, *B. cepacia* lipase showed a very low regioselectivity, while the acylations catalyzed by CAL-B and *Chromobacterium viscosum* lipase proceeded regiospecifically: the 1-*O*-acyl derivative (**6a**) was obtained as the sole product. In this case also, the hydroxy group remote from the substituent was preferentially acylated. These results indicate that CAL-B was an enzyme of choice for the direct acylation of phenolic hydroxy groups in terms of both activity and regioselectivity. Accordingly, further studies were conducted using this lipase. As far as we know, this lipase has not so far been employed for such a purpose with success.

Table 2
Enzymatic propanoylation of methylhydroquinone (**1a**) with vinyl propanoate using various lipases[a]

Lipase source	Yield (%)			Convn. (%)
	2a	3a	4a	
Candida antarctica B[b]	51	18	17	86
Burkholderia cepacia[c]	14	17	4	35
Alcaligenes sp.[d]	3	4	1	8
Achromobacter sp.[e]	3	5	1	9
Porcine pancreas[f]	4	5	1	10
Chromobacterium viscosum[g]	9	13	2	24
Pseudomonas sp.[h]	26	26	44	96

[a] Reactions were conducted using **1a** (0.1 mmol), vinyl propanoate (0.3 mmol) and an immobilized lipase (40 mg) in diisopropyl ether (240 μl) at 45 °C for 1 day.
[b] Boehringer Mannheim (BioCatalytics) Chirazyme L-2.
[c] Amano lipase PS.
[d] Meito lipase PL.
[e] Meito lipase AL.
[f] Sima lipase Type II.
[g] Asahikasei lipase.
[h] Toyobo lipoprotein lipase.



Scheme 2. Lipase-catalyzed regioselective propanoylation of 4-substituted resorcinols (**5**). R: a, Me; b, Et; c, $(CH_3)_3CCH_2C(CH_3)_2-$; d, Bn; e, Cl; f, Br.

Table 3
Enzymatic propanoylation of 4-ethylresorcinol (**5a**) with vinyl propanoate using various lipases[a]

Lipase source	Yield (%)		
	6a	7a	8a
Candida antarctica B[b]	37	0	0
Burkholderia cepacia[c,d]	24	20	7
Alcaligenes sp.[e]	8	0	0
Achromobacter sp.[f]	7	0	0
Chromobacterium viscosum[g]	27	0	0

[a] Reactions were conducted using **5a** (0.1 mmol), vinyl propanoate (0.3 mmol) and an immobilized lipase (40 mg) in diisopropyl ether (240 μl) at 45 °C for 3 days.
[b] Boehringer Mannheim (BioCatalytics) Chirazyme L-2.
[c] Amano lipase PS.
[d] Convn.: 51%.
[e] Meito lipase PL.
[f] Meito lipase AL.
[g] Asahikasei lipase.

Although a large number of experimental data have already been accumulated on the effect of organic solvents on lipase-catalyzed reactions,[12] it is still difficult to predict the solvent effect, especially on regioselectivity. Therefore, the practical way is to select an appropriate solvent through screening experiments. The effect of solvents was investigated on the CAL-B-catalyzed acylation of **1a** with vinyl propanoate (see Supplementary data). Acylations were reasonably fast in hydrocarbons and ethers, while they proceeded extremely slowly and less regioselectively in such polar solvents as acetone and acetonitrile. The lipase was most active in diisopropyl ether among the solvents examined with a tolerable regioselectivity. Thus, the CAL-B-catalyzed acylation of a number of hydroquinones (**1**) carrying different substituents on the benzene ring was examined using vinyl propanoate in diisopropyl ether at 45 °C. As is usual with this type of reaction, the product distribution can be time-dependent. Fig. 3 shows the time-course of the propanoylation of methoxyhydroquinone (**1f**) as a typical example. The starting hydroquinone was consumed abruptly during the first 6 h, then decreased gradually, and finally disappeared after 24 h. The amount of the 4-*O*-acyl derivative (**2f**) increased steeply at first, then reached a maximum after ca. 12 h and then turned to a gradual decrease, while that of 1-*O*-acyl derivative (**3f**) increased gradually at first, then reached a maximum after ca. 6 h and then turned to a slight but steady decrease. The initial rates of formation of **2f** and **3f** determined after 1 h of incubation were 6.1×10^{-7} and 8.5×10^{-8} mol h^{-1} (mg of lipase)$^{-1}$, respectively: the former was ca. 7 times faster than the latter. On the other hand, 1,4-di-*O*-acyl derivative (**4f**) was not observed during the first 4 h, then increased

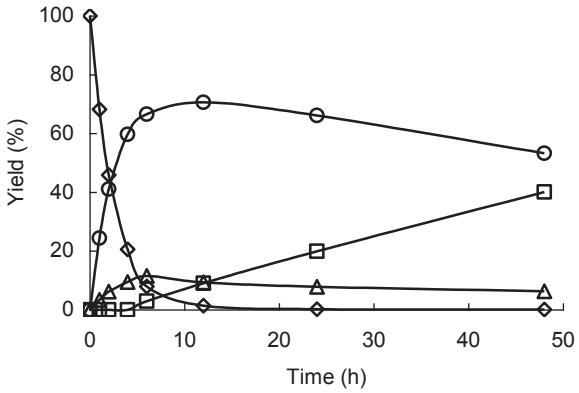


Fig. 3. Reaction profile of the CAL-B-catalyzed acylation of methoxyhydroquinone (**1f**) with vinyl propanoate in diisopropyl ether. Symbols: diamond, **1f**; circle, **2f**; triangle, **3f**; square, **4f**.

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almost linearly, and finally it became the major product after 72 h. Thus, the product distribution proved to be dependent largely on the reaction time. Accordingly, the results obtained after 1 day of incubation are taken up for discussion and compiled in Table 4. In all the cases, the 4-*O*-acyl derivative (**2**) was obtained as the main product, and the 1-*O*-acyl derivative (**3**) and/or the 1,4-di-*O*-acyl derivative (**4**) were also produced in various amounts depending on the substituent existed. When the substituent was changed from methyl (in **1a**) to ethyl (in **1c**), the proportion of the 4-*O*-acyl derivative in the reaction products increased to a considerable extent. With isopropylhydroquinone (**1d**) the 1-*O*-acyl derivative (**3d**) was not observed, and the 4-*O*-acyl derivative (**2e**) was produced as the exclusive product with *t*-butylhydroquinone (**1e**). Thus, the selectivity toward the hydroxy group remote from the substituent increased with the increase in the bulk of the substituent, i.e., methyl to isopropyl/*t*-butyl. This implies that the enhancement of steric demand of the substituent must be one of the contributory factors for the observed regioselectivity. The behavior of methoxyhydroquinone (**1f**) resembles that of **1c**, which implies also the importance of steric requirement in activity and regioselectivity. With fluorohydroquinone (**1h**) the regioselectivity deteriorated to a great extent, though its activity toward the acylation was as high as those of the alkyl-substituted hydroquinones. The other halogen substituents (in **1i** and **1j**) reduced the activity of hydroquinone, with a moderate regioselectivity. The effect of halogen substituents on the activity and regioselectivity in the acylation of hydroquinones seems rather complicated, indicating that besides the steric effect other factors, such as the electronic effect, must be taken into consideration.

Table 4
CAL-B-catalyzed propanoylation of substituted hydroquinones (**1**) with vinyl propanoate[a]

Substrate	R	R′	Yield (%)			Convn. (%)
			2	3	4	
1a	CH_3	H	51	18	17	86
1c	CH_3CH_2	H	73	8	12	93
1d	$(CH_3)_2CH$	H	75	0	16	91
1e	$(CH_3)_3C$	H	93	0	0	93
1f	CH_3O	H	71	10	19	100
1h	F	H	39	33	19	91
1i	Cl	H	41	16	5	62
1j	Br	H	47	22	8	77

[a] Reactions were conducted using **1** (0.1 mmol), vinyl propanoate (0.3 mmol) and CAL-B (40 mg) in diisopropyl ether (240 μl) at 45 °C for 1 day.

Next, the CAL-B-catalyzed propanoylation of a number of resorcinols (**5**) carrying alkyl, aralkyl or halogen substituents on the benzene ring was examined under the same reaction conditions as above. In general, the reactions were retarded largely compared with those of hydroquinones having the similar substituents. Thus, the results obtained after 3 days of incubation are compiled in Table 5.

Table 5
CAL-B-catalyzed propanoylation of substituted resorcinols (**5**) with vinyl propanoate[a]

Substrate	R	Yield (%) of **6**[b]
5a	CH_3	82
5b	CH_3CH_2	37
5c	$(CH_3)_3CCH_2C(CH_3)_2$	23
5d	$C_6H_5CH_2$	37
5e	Cl	74
5f	Br	69

[a] Reactions were conducted using **5** (0.1 mmol), vinyl propanoate (0.3 mmol) and CAL-B (40 mg) in diisopropyl ether (240 μl) at 45 °C for 3 days.
[b] The 3-*O*-propanoate (**7**) and 1,3-di-*O*-propanoate (**8**) were not detected in all the cases.

Quite interestingly, however, the acylation proceeded regiospecifically independent of the substituent, yielding the 1-*O*-acyl derivative (**6**) as the exclusive product and none of the 3-*O*-acyl derivative (**7**) nor the 1,4-di-*O*-acyl derivative (**8**). The steric factor of substituents in the substituted resorcinols had a much larger effect on its activity than that in the substituted hydroquninones. With 4-methylresorcinol (**5a**) the acylation proceeded most 'smoothly' among the resorcinols examined. It was retarded in the presence of bulkier substituents (in **5b** and **5c**), and no reaction took place with 4-*t*-butylresorcinol. This is probably because of the less accessibility of the lipase even toward the hydroxy group at position 1, to say nothing of the hydroxy group at position 3. The acylation of halogen-substituted resorcinols (**5e** and **5f**) proceeded at the rate between those of **5a** and the other alkyl-substituted resorcinols.

For the purpose of comparison, some typical non-enzymatic procedures for the acylation of phenolic hydroxy groups were also tried in the propanoylation of 4-ethylresorcinol (**5b**) (see Supplementary data). These chemical acylations were much inferior in terms of regioselectivity to the present enzymatic procedure.

3. Conclusion

CAL-B proved to be a tolerably active biocatalyst, compared to other lipases, for the direct acylation of the phenolic hydroxy groups of substituted hydroquinones and resorcinols. More importantly, the CAL-B-catalyzed acylation reactions take place generally in a highly regioselective manner: the hydroxy group remote from the substituent is preferentially acylated. In particular, they are regiospecific toward substituted resorcinols. In the case of substituted hydroquinones, the selectivity toward the hydroxy group remote from the substituent increases with the increase in the bulk of the substituent. The main or, in some cases, exclusive products obtained through the direct acylation of those dihydroxybenzenes are the regioisomers of those produced through the CAL-B-catalyzed deacylation of dihydroxybenzenes acylated at both phenolic hydroxy groups.[4] This should be of significant importance from a synthetic standpoint, because either regioisomer of monoacylated derivatives of dihydroxybenzenes can easily be obtained by choosing either acylation or deacylation mediated by the easily available single biocatalyst.

4. Experimental

4.1. General

^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were collected on a Varian Unity 500 spectrometer using DMSO-d_6 as a solvent with TMS as an internal standard. UV spectra were recorded on a Shimadzu UV-1600PC spectrometer. Melting points were determined on a Yamato MP-21 apparatus and are uncorrected. The liquid chromatograph employed was a Shimadzu LC-10AD instrument, equipped with a Rheodyne 7125 sample injector and a Shimadzu SPD-10A variable wavelength UV monitor. A Shimadzu C-R8A data processor was used for data acquisition and processing. TLC was run on precoated silica gel plates (Merck).

All the hydroquinones and resorcinols used in this study, except ethyl-, isopropyl- and fluorohydroquinoes, were purchased from Tokyo Chemical Industry Co. or Aldrich. All organic solvents were distilled following standard protocols and dried over molecular sieves prior to use.

4.2. Enzymes

Lipase B from *Candida antarctica* (CAL-B) was supplied by Boehringer Mannheim (BioCatalytics) as an immobilized form

(Chirazyme L-2), which had a specific activity of 3.2 U/mg lyophilized powder with tributyrin at 25 °C. The following lipases were obtained from Amano Pharmaceutical Co., Meito Sangyo Co., Asahi Chemical Industry Co., or Sigma: ex *B. cepacia* (Amano PS), *Alcaligenes* sp. (Meito PL), *Achromobacter* sp. (Meito AL), porcine pancreas (Sigma Type II), *Chromobacterium viscosum* (Asahikasei LP). Lipoprotein lipase from *Pseudomonas* sp. was supplied by Asahi Chemical Industry Co. All the enzymes were employed as immobilized forms on Celite. The preparation of immobilized *B. cepacia* lipase is described as a typical example. *B. cepacia* lipase (Amano PS; 400 mg) was dissolved in 10 ml of 0.1 M phosphate buffer (pH 7.0) and mixed with Celite No. 535 (Johns-Mansville Co.; 1 g), and the mixture was lyophilized using an Eyela FDU-830 freeze-dryer overnight.

4.3. Preparation of hydroquinones

*4.3.1. Ethylhydroquinone (**1c**).* This hydroquinone was prepared through the Clemmensen reduction of acetylhydroquinone according to the literature method;[13] mp 112–113 °C ($CHCl_3$) [lit.[13], mp 113–114 °C]; ^{1}H NMR δ 1.08 (3H, t, J=7.5 Hz, CH_3), 2.44 (2H, q, J=7.5 Hz, CH_2), 6.37 (1H, dd, J=8.5 and 3.0 Hz, H-5), 6.47 (1H, d, J=3.0 Hz, H-3), 6.54 (1H, d, J=8.5 Hz, H-6), 8.46 (1H, s, OH), 8.51 (1H, s, OH).

*4.3.2. Isopropylhydroquinone (**1d**).* Coupling of 2-isopropylphenol with diazotized sulfanilic acid followed by reduction yielded 2-isopropyl-4-aminophenol, which was then converted through diazotization to 2-isopropyl-1,4-quinone followed by reduction to the hydroquinone according to the literature method;[13] mp 129.5–131 °C ($CHCl_3$–pertoleum ether) [lit.[13], mp 129–131 °C]; ^{1}H NMR δ 1.10 (6H, d, J=7.0 Hz, $(CH_3)_2CH$), 3.12 (1H, septet, J=7.0 Hz, CH), 6.36 (1H, dd, J=9.0 and 3.0 Hz, H-5), 6.51 (1H, d, J=3.0 Hz, H-3), 6.54 (1H, d, J=9.0 Hz, H-6), 8.47 (1H, s, OH), 8.50 (1H, s, OH).

*4.3.3. Fluorohydroquinone (**1h**).* This hydroquinone was prepared through the oxidation of 2-fluorophenol with potassium persulfate according to the literature method;[13] mp 123–124 °C ($CHCl_3$) [lit.[13], mp 122–123 °C]; ^{1}H NMR δ 6.39 (1H, ddd, J=9.0, 3.0 and 1.5 Hz, H-5), 6.51 (1H, dd, J=13.0 and 3.0 Hz, H-3), 6.73 (1H, dd, J=10.0 and 9.0 Hz, H-6), 8.94 (1H, s, OH), 9.06 (1H, s, OH).

4.4. Preparation of authentic 4-*O*-momopropanoyl derivatives of hydroquinones

The 4-*O*-monopropanoates of hydroquinones were obtained as the major products of the CAL-B-catalyzed acylation of each hydroquinone. The preparation of the 4-*O*-propanoyl derivative (**2c**) of ethylhydroquinone (**1c**) is described as a typical example. To a solution of **1c** (204 mg, 1.5 mmol) and vinyl propanoate (490 μl, 4.5 mmol) in dry diisopropyl ether (3.6 ml) was added CAL-B (300 mg), and the mixture was stirred at 45 °C for 3 days. TLC showed the disappearance of the parent hydroquinone in the reaction mixture. The enzyme was filtered off and the filtrate was evaporated in vacuo. From the residual oil the monopropanoate **2c** was isolated as the major product by preparative TLC using hexane–EtOAc (2:1, v/v) as a developing solvent to give an oil (261 mg, 90%). The structure of **2c** was unambiguously determined by 2D NMR (HMQC, HMBC): cross-peaks of the proton of 1-OH with the carbons at C-1, C-2 and C-6 appeared in the HMBC spectrum.

*4.4.1. 4-O-Propanoylmethylhydroquinone (**2a**).* Mp 62–64 °C; ^{1}H NMR δ 1.11 (3H, t, J=7.5 Hz, CH_2CH_3), 2.09 (3H, s, $ArCH_3$), 2.53 (2H, q, J=7.5 Hz, CH_2), 6.70 (1H, dd, J=8.5 and 2.5 Hz, H-5), 6.74 (1H, d, J=8.5 Hz, H-6), 6.79 (1H, d, J=2.5 Hz, H-3), 9.30 (1H, s, OH); ^{13}C NMR δ 9.1 (CH_2CH_3), 16.1 ($ArCH_3$), 27.0 (CH_2), 114.8 (C-6), 119.5 (C-5), 123.6 (C-3), 124.9 (C-2), 142.6 (C-4), 153.1 (C-1), 173.1 (C=O). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.88; H, 6.46.

*4.4.2. 4-O-Propanoyl-2,6-dimethylhydroquinone (**2b**).* Oil; ^{1}H NMR δ 1.25 (3H, t, J=7.5 Hz, CH_2CH_3), 2.14 (6H, s, $ArCH_3$), 2.55 (2H, q, J=7.5 Hz, CH_2), 4.68 (1H, s, OH), 6.68 (2H, s, Ar); ^{13}C NMR δ 9.1 (CH_2CH_3), 16.0 ($ArCH_3$), 27.7 (CH_2), 121.1 (C-3, C-5), 124.1 (C-2, C-6), 143.3 (C-4), 149.8 (C-1), 173.8 (C=O). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.15; H, 7.46.

*4.4.3. 4-O-Propanoylethylhydroquinone (**2c**).* Oil; ^{1}H NMR δ 1.105 (3H, t, J=7.5 Hz, $COCH_2CH_3$),1.11 (3H, t, J=7.5 Hz, $ArCH_2CH_3$), 2.51 (2H, q, J=7.5 Hz, $ArCH_2CH_3$), 2.53 (2H, q, J=7.5 Hz, $COCH_2CH_3$), 6.70–6.73 (1H, distorted dd, J=8.5 and 2.5 Hz, H-5), 6.74–6.76 (1H, distorted d, J=8.5 Hz, H-6), 6.79 (1H, d, J=2.5 Hz, H-3), 9.30 (1H, s, OH); ^{13}C NMR δ 9.6 ($COCH_2CH_3$), 14.6 ($ArCH_2CH_3$), 23.2 ($ArCH_2CH_3$), 27.5 ($COCH_2CH_3$), 115.5 (C-6), 120.0 (C-3), 122.4 (C-5), 131.4 (C-2), 143.3 (C-4), 153.1 (C-1), 173.6 (C=O). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.81; H, 7.38.

*4.4.4. 4-O-Propanoylisopropylhydroquinone (**2d**).* Oil; ^{1}H NMR δ 1.11 (3H, t, J=7.5 Hz, CH_2CH_3), 1.13 (6H, d, J=7.0 Hz, $CH(CH_3)_2$), 2.53 (2H, q, J=7.5 Hz, CH_2), 3.18 (1H, septet, J=7.0 Hz, $CH(CH_3)_2$), 6.70–6.72 (1H, distorted dd, J=8.5 and 2.5 Hz, H-5), 6.75–6.76 (1H, distorted d, J=8.5 Hz, H-6), 6.80 (1H, d, J=2.5 Hz, H-3), 9.33 (1H, s, OH); ^{13}C NMR δ 9.1 (CH_2CH_3), 22.5 ($CH(CH_3)_2$), 26.6 ($CH(CH_3)_2$), 27.0 (CH_2), 115.2 (C-6), 119.2 (C-3), 119.4 (C-5), 135.3 (C-2), 143.1 (C-4), 152.0 (C-1), 173.1 (C=O). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.93; H, 7.55.

*4.4.5. 4-O-Propanoyl-t-butylhydroquinone (**2e**).* Oil; ^{1}H NMR δ 1.11 (3H, t, J=7.5 Hz, CH_3), 1.32 (9H, s, $C(CH_3)_3$), 2.53 (2H, q, J=7.5 Hz, CH_2), 6.73–6.75 (1H, distorted dd, J=8.5 and 2.0 Hz, H-5), 6.75–6.77 (1H, distorted d, J=8.5 Hz, H-6), 6.80 (1H, d, J=2.0 Hz, H-3), 9.39 (1H, s, OH); ^{13}C NMR δ 9.1 (CH_3), 27.0 (CH_2), 29.3 ($C(CH_3)_3$), 34.5 ($C(CH_3)_3$), 116.3 (C-6), 119.65 (C-3), 119.7 (C-5), 136.3 (C-2), 142.7 (C-4), 153.5 (C-1), 173.2 (C=O). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.33; H, 8.42.

*4.4.6. 4-O-Propanoylmethoxyhydroquinone (**2f**).* Oil; ^{1}H NMR δ 1.12 (3H, t, J=7.5 Hz, CH_2CH_3), 2.54 (2H, q, J=7.5 Hz, CH_2), 3.73 (3H, s, OCH_3), 6.49 (1H, dd, J=8.5 and 2.5 Hz, H-5), 6.70 (1H, d, J=2.5 Hz, H-3), 6.75 (1H, d, J=8.5 Hz, H-6), 8.97 (1H, s, OH); ^{13}C NMR δ 9.1 (CH_2CH_3), 27.0 (CH_2), 55.9 (OCH_3), 106.7 (C-3), 113.5 (C-5), 115.2 (C-6), 143.0 (C-4), 144.3 (C-1), 148.0 (C-2), 173.1 (C=O). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.17. Found: C, 61.40; H, 6.21.

*4.4.7. 4-O-Propanoylacetylhydroquinone (**2g**).* Oil; ^{1}H NMR δ 1.14 (3H, t, J=7.5 Hz, CH_2CH_3), 2.59 (2H, q, J=7.5 Hz, CH_2), 2.62 (3H, s, $COCH_3$), 6.99 (1H, d, J=9.5 Hz, H-6), 7.31 (1H, dd, J=9.5 and 2.5 Hz, H-5), 7.60 (1H, d, J=2.5 Hz, H-3), 11.73 (1H, s, OH). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.40; H, 6.03.

*4.4.8. 4-O-Propanoylfluorohydroquinone (**2h**).* Oil; ^{1}H NMR δ 1.11 (3H, t, J=7.5 Hz, CH_3), 2.55 (2H, q, J=7.5 Hz, CH_2), 6.76 (1H, ddd, J=8.5, 2.5 and 1.5 Hz, H-5), 6.94 (1H, dd, J=9.5 and 8.5 Hz, H-6), 7.02 (1H, dd, J=11.5 and 2.5 Hz, H-3), 9.88 (1H, s, OH); ^{13}C NMR δ 9.0 (CH_3), 27.0 (CH_2), 110.7 (C-3), 117.5 (C-5), 117.9 (C-6), 142.8 (C-1), 149.5 (C-4), 151.5 (C-2), 172.9 (C=O). Anal. Calcd for $C_9H_9FO_3$: C, 58.70; H, 4.93. Found: C, 58.96; H, 5.09.

*4.4.9. 4-O-Propanoylchlorohydroquinone (**2i**).* Mp 77–79 °C; ^{1}H NMR δ 1.11 (3H, t, J=7.5 Hz, CH_3), 2.54 (2H, q, J=7.5 Hz, CH_2), 6.87–6.91 (1H, distorted dd, J=8.5 and 2.5 Hz, H-5), 6.92–6.95 (1H, distorted d, J=8.5 Hz, H-6), 7.15 (1H, J=2.5 Hz, H-3), 10.18 (1H, s, OH); ^{13}C NMR δ 9.5 (CH_3), 27.5 (CH_2), 117.1 (C-6), 120.0 (C-2),

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122.0 (C-3), 123.9 (C-5), 143.3 (C-4), 151.6 (C-1), 173.4 (C=O). Anal. Calcd for $C_9H_9ClO_3$: C, 53.88; H, 4.52. Found: C, 53.83; H, 4.77.

*4.4.10. 4-O-Propanoylbromohydroquinone (**2j**).* Mp 76–79 °C; ^{1}H NMR δ 1.11 (3H, t, J=7.5 Hz, CH_3), 2.54 (2H, q, J=7.5 Hz, CH_2), 6.93–6.95 (1H, distorted dd, J=8.5 and 2.0 Hz, H-5), 6.97–6.95 (1H, distorted d, J=8.5 Hz, H-6), 7.30 (1H, dd, J=2.5 and 0.5 Hz, H-3), 10.3 (1H, s, OH); ^{13}C NMR δ 9.0 (CH_3), 26.9 (CH_2), 108.8 (C-2), 116.3 (C-6), 122.1 (C-5), 126.2 (C-3), 143.0 (C-4), 152.1 (C-1), 173.0 (C=O). Anal. Calcd for $C_9H_9BrO_3$: C, 44.11; H, 3.70. Found: C, 44.32; H, 3.77.

4.5. Preparation of authentic 1-*O*-momopropanoyl derivatives of hydroquinones

As they were the minor products of the lipase-catalyzed direct propanoylation of hydroquinones, the authentic samples of the 1-*O*-monopropanoates of hydroquinones were prepared in much higher yields through the lipase-catalyzed deacylation of each 1,4-*O*-dipropanoylhydroquinone.[4] The preparation of the 1-*O*-propanoyl derivative (**3c**) of ethylhydroquinone (**1c**) is described as a typical example. To a solution of 1,4-di-*O*-propanoylethylhydroquinone (**4c**) (125 mg, 0.5 mmol) and 1-propanol (113 μl, 1.5 mmol) in dry diisopropyl ether (1.1 ml) was added CAL-B (100 mg), and the mixture was stirred at 45 °C for 1 h. The enzyme was filtered off and the filtrate was evaporated in vacuo. From the residual oil the monopropanoate **3c** was isolated as the major product by preparative TLC using hexane–EtOAc (2:1, v/v) as a developing solvent to give an oil (56 mg, 68%). The structure of **3c** was unambiguously determined by 2D NMR (HMQC, HMBC): cross-peaks of the proton of 4-OH with the carbons at C-3, C-4 and C-5 appeared in the HMBC spectrum.

*4.5.1. 1-O-Propanoylmethylhydroquinone (**3a**).* Oil; ^{1}H NMR δ 1.14 (3H, t, J=7.5 Hz, CH_2CH_3), 2.00 (3H, s, $ArCH_3$), 2.57 (2H, q, J=7.5 Hz, CH_2), 6.57 (1H, dd, J=8.5 and 3.0 Hz, H-5), 6.63 (1H, d, J=3.0 Hz, H-3), 6.80 (1H, d, J=8.5 Hz, H-6), 9.30 (1H, s, OH); ^{13}C NMR δ 9.3 (CH_2CH_3), 16.0 ($ArCH_3$), 26.9 (CH_2), 113.3 (C-5), 117.2 (C-3), 122.7 (C-6), 130.7 (C-2), 141.5 (C-1), 155.0 (C-4), 172.8 (C=O). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.41; H, 6.75.

*4.5.2. 1-O-Propanoyl-2,6-dimethylhydroquinone (**3b**).* Oil; ^{1}H NMR δ 1.15 (3H, t, J=7.0 Hz, CH_2CH_3), 1.97 (6H, s, $ArCH_3$), 2.60 (2H, q, J=7.0 Hz, CH_2), 6.46 (2H, s, Ar), 9.17 (1H, s, OH). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.81; H, 7.19.

*4.5.3. 1-O-Propanoylethylhydroquinone (**3c**).* Oil; ^{1}H NMR δ 1.07 (3H, t, J=7.5 Hz, $COCH_2CH_3$), 1.14 (3H, t, J=7.5 Hz, $ArCH_2CH_3$), 2.35 (2H, q, J=7.5 Hz, $ArCH_2$), 2.58 (2H, q, J=7.5 Hz, $COCH_2$), 6.57 (1H, dd, J=8.5 and 2.5 Hz, H-5), 6.64 (1H, d, J=2.5 Hz, H-3), 6.80 (1H, d, J=8.5 Hz, H-6), 9.31 (1H, s, OH). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.83; H, 7.11.

*4.5.4. 1-O-Propanoylisopropylhydroquinone (**3d**).* Oil; ^{1}H NMR δ 1.10 (6H, d, J=7.0 Hz, $CH(CH_3)_2$), 1.14 (3H, t, J=7.5 Hz, CH_2CH_3), 2.57 (2H, q, J=7.5 Hz, CH_2), 2.84 (1H, septet, J=7.0 Hz, $CH(CH_3)_2$), 6.57 (1H, dd, J=8.5 and 3.0 Hz, H-5), 6.68 (1H, d, J=3.0 Hz, H-3), 6.79 (1H, d, J=8.5 Hz, H-6), 9.30 (1H, s, OH). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.48; H, 7.61.

*4.5.5. 1-O-Propanoyl-t-butylhydroquinone (**3e**).* Oil; ^{1}H NMR δ 1.14 (3H, t, J=7.5 Hz, CH_3), 1.24 (9H, s, $C(CH_3)_3$), 2.58 (2H, q, J=7.5 Hz, CH_2), 6.58 (1H, dd, J=8.5 and 3.0 Hz, H-5), 6.74 (1H, d, J=3.0 Hz, H-3), 6.77 (1H, d, J=8.5 Hz, H-6), 9.29 (1H, s, OH); ^{13}C NMR δ 9.0 (CH_3), 27.7 (CH_2), 30.0 ($C(CH_3)_3$), 34.2 ($C(CH_3)_3$), 113.1 (C-6), 113.6 (C-3), 125.1 (C-5), 141.3 (C-2), 141.6 (C-4), 154.7 (C-1), 173.1 (C=O). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.45; H, 8.01.

*4.5.6. 1-O-Propanoylmethoxyhydroquinone (**3f**).* Oil; ^{1}H NMR δ 1.11 (3H, t, J=7.5 Hz, CH_2CH_3), 2.52 (2H, q, J=7.5 Hz, CH_2), 3.69 (3H, s, OCH_3), 6.29 (1H, dd, J=8.5 and 2.5 Hz, H-5), 6.48 (1H, d, J=2.5 Hz, H-3), 6.82 (1H, d, J=8.5 Hz, H-6), 9.45 (1H, s, OH); ^{13}C NMR δ 9.2 (CH_2CH_3), 26.7 (CH_2), 55.7 (OCH_3), 100.6 (C-3), 106.4 (C-5), 123.0 (C-6), 131.9 (C-1), 151.6 (C-4), 156.3 (C-2), 172.5 (C=O). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.17. Found: C, 61.28; H, 6.25.

*4.5.7. 1-O-Propanoylacetylhydroquinone (**3g**).* Oil; ^{1}H NMR δ 1.17 (3H, t, J=7.5 Hz, CH_2CH_3), 2.56 (2H, q, J=7.5 Hz, CH_2), 2.60 (3H, s, $COCH_3$), 6.91 (1H, d, J=9.5 Hz, H-6), 7.17 (1H, dd, J=9.5 and 2.5 Hz, H-5), 7.32 (1H, d, J=2.5 Hz, H-3), 9.17 (1H, s, OH). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.34; H, 5.77.

*4.5.8. 1-O-Propanoylfluorohydroquinone (**3h**).* Oil; ^{1}H NMR δ 1.12 (3H, t, J=7.5 Hz, CH_3), 2.59 (2H, q, J=7.5 Hz, CH_2), 6.59 (1H, ddd, J=8.5, 2.5 and 1.0 Hz, H-5), 6.69 (1H, dd, J=12.5 and 2.5 Hz, H-3), 7.04 (1H, dd, J=9.0 and 8.5, H-6), 9.92 (1H, s, OH); ^{13}C NMR δ 9.1 (CH_3), 26.6 (CH_2), 103.6 (C-3), 111.4 (C-5), 124.4 (C-6), 129.8 (C-1), 153.9 (C-2), 156.4 (C-4), 172.3 (C=O). Anal. Calcd for $C_9H_9FO_3$: C, 58.70; H, 4.93. Found: C, 58.41; H, 4.84.

*4.5.9. 1-O-Propanoylchlorohydroquinone (**3i**).* Oil; ^{1}H NMR δ 1.15 (3H, t, J=7.5 Hz, CH_3), 2.60 (2H, q, J=7.5 Hz, CH_2), 6.75 (1H, dd, J=9.0 and 2.5 Hz, H-5), 6.89 (1H, d, J=2.5 Hz, H-3), 7.07 (1H, d, J=9.0 Hz, H-6), 9.92 (1H, s, OH). Anal. Calcd for $C_9H_9ClO_3$: C, 53.88; H, 4.52. Found: C, 53.99; H, 4.61.

*4.5.10. 1-O-Propanoylbromohydroquinone (**3j**).* Oil; ^{1}H NMR δ 1.15 (3H, t, J=7.5 Hz, CH_3), 2.59 (2H, q, J=7.5 Hz, CH_2), 6.79 (1H, dd, J=8.5 and 3.0 Hz, H-5), 7.04 (1H, d, J=3.0 Hz, H-3), 7.06 (1H, d, J=8.5 Hz, H-6), 9.92 (1H, s, OH). Anal. Calcd for $C_9H_9BrO_3$: C, 44.11; H, 3.70. Found: C, 43.94; H, 3.72.

4.6. Preparation of authentic 1,4-di-*O*-propanoyl derivatives of hydroquinones

Authentic samples of the 1,4-di-*O*-propanoates of hydroquinones were prepared by the reaction of each hydroquinone with propanoyl chloride in pyridine. The dipropanoylation of methylhydroquinone (**1a**) is described as a typical example. To a stirred solution of **1a** (420 mg, 3.0 mmol) in dry pyridine (20 ml) was added dropwise from a syringe propanoyl chloride (564 mg, 6.3 mmol), and the mixture was stirred at 100 °C for 3 days. 1-(2-Aminoethyl)piperazine (81 mg, 0.63 mmol) was added and the mixture was stirred for 30 min. Then 0.5 M HCl (60 ml) was added and the mixture was extracted with EtOAc (3×20 ml), the organic extracts were washed successively with 1 M NaOH (3×30 ml), water (30 ml), and brine (30 ml), and dried over Na_2SO_4. After evaporation of the solvent in vacuo, the residual oil was purified by column chromatography using hexane–EtOAc (2:1, v/v) as an eluent to give the dipropanoate 4**a** as white crystals (415 mg, 59%).

*4.6.1. 1,4-di-O-Propanoylmethylhydroquinone (**4a**).* Mp 47–50 °C; ^{1}H NMR δ 1.13 (3H, t, J=7.5 Hz, CH_2CH_3), 1.16 (3H, t, J=7.5 Hz, CH_2CH_3), 2.10 (3H, s, $ArCH_3$), 2.59 (2H, q, J=7.5 Hz, CH_2), 2.63 (2H, q, J=7.5 Hz, CH_2), 6.98 (1H, dd, J=8.5 and 3.0 Hz, H-5), 7.06 (1H, d, J=3.0 Hz, H-3), 7.08 (1H, d, J=8.5 Hz, H-6). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.89; H, 6.72.

*4.6.2. 1,4-di-O-Propanoyl-2,6-dimethylhydroquinone (**4b**).* Oil; ^{1}H NMR δ 1.13 (3H, t, J=7.5 Hz, CH_2CH_3), 1.18 (3H, t, J=7.5 Hz, CH_2CH_3), 2.07 (6H, s, $ArCH_3$), 2.57 (2H, q, J=7.5 Hz, CH_2), 2.67 (2H, q, J=7.5 Hz,

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CH_2), 6.88 (2H, s, Ar). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.30; H, 7.44.

*4.6.3. 1,4-di-O-Propanoylethylhydroquinone (**4c**).* Oil; ^{1}H NMR δ 1.10 (3H, t, J=7.5 Hz, $COCH_2CH_3$), 1.13 (3H, t, J=7.5 Hz, $COCH_2CH_3$), 1.16 (3H, t, J=7.5 Hz, $ArCH_2CH_3$), 2.46 (2H, q, J=7.5 Hz, $ArCH_2$), 2.59 (2H, q, J=7.5 Hz, $COCH_2$), 2.63 (2H, q, J=7.5 Hz, $COCH_2$), 6.99 (1H, dd, J=8.5 and 3.0 Hz, H-5), 7.07 (1H, d, J=3.0 Hz, H-3), 7.09 (1H, d, J=8.5 Hz, H-6). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.12; H, 7.48.

*4.6.4. 1,4-di-O-Propanoylisopropylhydroquinone (**4d**).* Oil; ^{1}H NMR δ 1.125 (6H, d, J=7.0 Hz, $CH(CH_3)_2$), 1.13 (3H, t, J=7.5 Hz, CH_2CH_3), 1.16 (3H, t, J=7.5 Hz, CH_2CH_3), 2.60 (2H, q, J=7.5 Hz, CH_2), 2.65 (2H, q, J=7.5 Hz, CH_2), 2.95 (1H, septet, J=7.0 Hz, $CH(CH_3)_2$), 6.98 (1H, dd, J=8.5 and 3.0 Hz, H-5), 7.07 (1H, d, J=3.0 Hz, H-3), 7.09 (1H, d, J=8.5 Hz, H-6). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.35; H, 7.82.

*4.6.5. 1,4-di-O-Propanoyl-t-butylhydroquinone (**4e**).* Oil; ^{1}H NMR δ 1.13 (3H, t, J=7.5 Hz, CH_2CH_3), 1.17 (3H, t, J=7.5 Hz, CH_2CH_3), 1.28 (9H, s, $C(CH_3)_3$), 2.59 (2H, q, J=7.5 Hz, CH_2), 2.65 (2H, q, J=7.5 Hz, CH_2), 7.01 (1H, dd, J=9.0 and 2.5 Hz, H-5), 7.06 (1H, d, J=2.5 Hz, H-3), 7.07 (1H, d, J=9.0 Hz, H-6). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.76; H, 8.02.

*4.6.6. 1,4-di-O-Propanoylmethoxyhydroquinone (**4f**).* Oil; ^{1}H NMR δ 1.13 (3H, t, J=7.5 Hz, CH_2CH_3), 1.14 (3H, t, J=7.5 Hz, CH_2CH_3), 2.58 (2H, q, J=7.5 Hz, CH_2), 2.60 (2H, q, J=7.5 Hz, CH_2), 3.74 (3H, s, OCH_3), 6.70 (1H, dd, J=8.5 and 2.5 Hz, H-5), 6.94 (1H, d, J=2.5 Hz, H-3), 7.10 (1H, d, J=8.5 Hz, H-6). Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.66; H, 6.57.

*4.6.7. 1,4-di-O-Propanoylacetylhydroquinone (**4g**).* Oil; ^{1}H NMR δ 1.14 (3H, t, J=7.5 Hz, CH_2CH_3), 1.15 (3H, t, J=7.5 Hz, CH_2CH_3), 2.50 (3H, s, $COCH_3$), 2.62 (2H, q, J=7.5 Hz, CH_2), 2.63 (2H, q, J=7.5 Hz, CH_2), 7.27 (1H, d, J=8.5 Hz, H-6), 7.41 (1H, dd, J=8.5 and 3.0 Hz, H-5), 7.67 (1H, d, J=3.0 Hz, H-3). Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.79; H, 6.33.

*4.6.8. 1,4-di-O-Propanoylfluorohydroquinone (**4h**).* Mp 78–79 °C; ^{1}H NMR δ 1.13 (3H, t, J=7.5 Hz, CH_3) 1.15 (3H, t, J=7.5 Hz, CH_3), 2.60 (2H, q, J=7.5 Hz, CH_2), 2.65 (2H, q, J=7.5 Hz, CH_2), 7.04 (1H, ddd, J=8.5, 2.5 and 1.5 Hz, H-5), 7.31 (1H, dd, J=11.0 and 2.5 Hz, H-3), 7.34 (1H, dd, J=9.0 and 8.5 Hz, H-6). Anal. Calcd for $C_{12}H_{13}FO_4$: C, 60.00; H, 5.45. Found: C, 60.13; H, 5.50.

*4.6.9. 1,4-di-O-Propanoylchlorohydroquinone (**4i**).* Oil; ^{1}H NMR δ 1.13 (3H, t, J=7.5 Hz, CH_3), 1.17 (3H, t, J=7.5 Hz, CH_3), 2.60 (2H, q, J=7.5 Hz, CH_2), 2.66 (2H, q, J=7.5 Hz, CH_2), 7.19 (1H, dd, J=8.5 and 2.5 Hz, H-5), 7.36 (1H, d, J=8.5 Hz, H-6), 7.47 (1H, d, J=2.5 Hz, H-3). Anal. Calcd for $C_{12}H_{13}ClO_4$: C, 56.15; H, 5.11. Found: C, 56.22; H, 4.88.

*4.6.10. 1,4-di-O-Propanoylbromohydroquinone (**4j**).* Mp 58–60 °C; ^{1}H NMR δ 1.13 (3H, t, J=7.5 Hz, CH_3), 1.17 (3H, t, J=7.5 Hz, CH_3), 2.60 (2H, q, J=7.5 Hz, CH_2), 2.66 (2H, q, J=7.5 Hz, CH_2), 7.22 (1H, dd, J=8.5 and 2.5 Hz, H-5), 7.34 (1H, d, J=8.5 Hz, H-6), 7.59 (1H, d, J=2.5 Hz, H-3). Anal. Calcd for $C_{12}H_{13}BrO_4$: C, 47.86; H, 4.35. Found: C, 48.06; H, 4.26.

4.7. Preparation of authentic 1-*O*-momopropanoyl derivatives of 4-substituted resorcinols

The 1-*O*-monopropanoates of 4-substituted resorcinols were obtained as the major products of the CAL-B-catalyzed acylation of each resorcinol. They were prepared in the same manner as described above for the preparation of 4-*O*-monopropanoates of hydroquinones.

*4.7.1. 1-O-Propanoyl-4-methylresorcinol (**6a**).* Mp 68–70 °C; ^{1}H NMR δ 1.11 (3H, t, J=7.5 Hz, CH_2CH_3), 2.09 (3H, s, $ArCH_3$), 2.55 (2H, q, J=7.5 Hz, CH_2), 6.43 (1H, dd, J=9.0 and 2.5 Hz, H-6), 6.51 (1H, d, J=2.5 Hz, H-2), 7.04 (1H, d, J=9.0 Hz, H-5), 9.56 (1H, s, OH); ^{13}C NMR δ 9.1 (CH_2CH_3), 15.6 (CH_3Ar), 27.0 (CH_2), 108.3 (C-2), 111.9 (C-6), 121.5 (C-4), 130.7 (C-5), 149.3 (C-1), 155.9 (C-3), 172.7 (C=O). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.82; H, 6.82.

*4.7.2. 1-O-Propanoyl-4-ethylresorcinol (**6b**).* Oil; ^{1}H NMR δ 1.11 (3H, t, J=7.5 Hz, $COCH_2CH_3$), 1.12 (3H, t, J=7.5 Hz, $ArCH_2CH_3$), 2.51 (2H, q, J=7.5 Hz, $COCH_2$), 2.55 (2H, q, J=7.5 Hz, $ArCH_2$), 6.46 (1H, dd, J=8.5 and 2.5 Hz, H-6), 6.52 (1H, d, J=2.5 Hz, H-2), 7.05 (1H, d, J=8.5 Hz, H-5), 9.55 (1H, s, OH); ^{13}C NMR δ 9.6 ($COCH_2CH_3$), 14.8 ($ArCH_2CH_3$), 23.0 ($ArCH_2CH_3$), 27.6 ($COCH_2CH_3$), 109.0 (C-2), 112.5 (C-6), 128.1 (C-4), 129.7 (C-5), 149.7 (C-1), 156.1 (C-3), 173.2 (C=O). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.75; H, 7.24.

*4.7.3. 1-O-Propanoyl-4-t-octylresorcinol (**6c**).* Oil; ^{1}H NMR δ 0.70 (9H, s, $C(CH_3)_3$), 1.11 (3H, t, J=7.5 Hz, CH_2CH_3), 1.36 (6H, s, $C(CH_3)_2$), 1.91 (2H, s, $CH_2C(CH_3)_3$), 2.53 (2H, q, J=7.5 Hz, CH_2CH_3), 6.46 (1H, d, J=2.5 Hz, H-2), 6.48 (1H, dd, J=7.5 and 2.5 Hz, H-6), 7.12 (1H, d, J=7.5 Hz, H-5), 9.57 (1H, s, OH); ^{13}C NMR δ 9.1 (CH_2CH_3), 27.1 (CH_2CH_3), 30.9 ($C(CH_3)_2$), 31.4 ($C(CH_3)_3$), 32.2 ($C(CH_3)_3$), 38.3 ($C(CH_3)_2$), 51.5 ($CH_2C(CH_3)_3$), 109.3 (C-2), 111.6 (C-6), 127.7 (C-5), 131.9 (C-4), 149.3 (C-1), 156.9 (C-3), 172.6 (C=O). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.17; H, 9.47.

*4.7.4. 1-O-Propanoyl-4-benzylresorcinol (**6d**).* Oil; ^{1}H NMR δ 1.10 (3H, t, J=8.0 Hz, CH_3), 2.55 (2H, q, J=8.0 Hz, CH_2CH_3), 3.85 (2H, s, CH_2Ph), 6.47 (1H, dd, J=8.0 and 2.5 Hz, H-6), 6.56 (1H, d, J=2.5 Hz, H-2), 7.02 (1H, d, J=8.0 Hz, H-5), 7.14–7.27 (5H, m, Ph), 9.73 (1H, s, OH); ^{13}C NMR δ 9.6 (CH_3), 27.6 (CH_2CH_3), 35.4 (CH_2Ph), 109.2 (C-2), 112.6 (C-6), 125.7 (C-4), 126.4 (C-4′), 128.9 (C-2′), 129.3 (C-3′), 131.1 (C-5), 141.7 (C-1′), 150.1 (C-1), 156.1 (C-3), 173.2 (C=O). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.24; H, 6.24.

*4.7.5. 1-O-Propanoyl-4-chlororesorcinol (**6e**).* Oil; ^{1}H NMR δ 1.10 (3H, t, J=7.5 Hz, CH_3), 2.56 (2H, q, J=7.5 Hz, CH_2), 6.57 (1H, dd, J=8.5 and 2.5 Hz, H-6), 6.70 (1H, d, J=2.5 Hz, H-2), 7.32 (1H, d, J=8.5 Hz, H-5), 10.32 (1H, s, OH). Anal. Calcd for $C_9H_9ClO_3$: C, 53.88; H, 4.52. Found: C, 54.03; H, 4.43.

*4.7.6. 1-O-Propanoyl-4-bromoresorcinol (**6f**).* Oil; ^{1}H NMR δ 1.12 (3H, t, J=7.5 Hz, CH_3), 2.58 (2H, q, J=7.5 Hz, CH_2), 6.54 (1H, dd, J=8.5 and 2.5 Hz, H-6), 6.73 (1H, d, J=2.5 Hz, H-2), 7.49 (1H, d, J=8.5 Hz, H-5), 10.56 (1H, s, OH). Anal. Calcd for $C_9H_9BrO_3$: C, 44.11; H, 3.70. Found: C, 44.37; H, 3.59.

4.8. Preparation of authentic 3-*O*-momopropanoyl derivatives of 4-substituted resorcinols

Authentic samples of the 3-*O*-monopropanoates of 4-substituted resorcinols were prepared through the lipase-catalyzed deacylation of each 1,4-*O*-dipropanoylresorcinol. They were prepared in the same manner as described above for the preparation of 1-*O*-monopropanoates of hydroquinones.

*4.8.1. 3-O-Propanoyl-4-methylresorcinol (**7a**).* Oil; ^{1}H NMR δ 1.14 (3H, t, J=7.5 Hz, CH_2CH_3), 1.97 (3H, s, $ArCH_3$), 2.59 (2H, q, J=7.5 Hz, CH_2), 6.44 (1H, d, J=2.0 Hz, H-2), 6.57 (1H, dd, J=8.5 and 2.0 Hz, H-

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6), 7.03 (1H, d, *J*=8.5 Hz, H-5), 9.43 (1H, s, OH). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.76; H, 6.67.

*4.8.2. 3-O-Propanoyl-4-ethylresorcinol (**7b**).* Oil; ^{1}H NMR δ 1.05 (3H, t, *J*=7.5 Hz, $ArCH_2CH_3$), 1.14 (3H, t, *J*=7.5 Hz, $COCH_2CH_3$), 2.34 (2H, q, *J*=7.5 Hz, $ArCH_2CH_3$), 2.59 (2H, q, *J*=7.5 Hz, $COCH_2CH_3$), 6.43 (1H, d, *J*=2.5 Hz, H-2), 6.61 (1H, dd, *J*=8.5 and 2.5 Hz,H-6), 7.06 (1H, d, *J*=8.5 Hz, H-5), 9.45 (1H, s, OH); ^{13}C NMR δ 9.2 ($COCH_2CH_3$), 14.8 ($ArCH_2CH_3$), 22.1 ($ArCH_2CH_3$), 27.1 ($COCH_2CH_3$), 109.6 (C-2), 113.3 (C-6), 125.7 (C-4), 129.8 (C-5), 149.2 (C-3), 156.3 (C-1), 172.6 (C=O). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.79; H, 7.05.

*4.8.3. 3-O-Propanoyl-4-t-octylresorcinol (**7c**).* Oil; ^{1}H NMR δ 0.69 (9H, s, $C(CH_3)_3$), 1.16 (3H, t, *J*=7.5 Hz, CH_2CH_3), 1.28 (6H, s, $C(CH_3)_2$), 1.71 (2H, s, $CH_2C(CH_3)_3$), 2.60 (2H, q, *J*=7.5 Hz, CH_2CH_3), 6.40 (1H, d, *J*=2.5 Hz, H-2), 6.57 (1H, dd, *J*=9.0 and 2.5 Hz, H-6), 7.14 (1H, d, *J*=9.0 Hz, H-5), 9.41 (1H, s, OH). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.54; H, 9.39.

*4.8.4. 3-O-Propanoyl-4-benzylresorcinol (**7d**).* Oil; ^{1}H NMR δ 1.05 (3H, t, *J*=7.5 Hz, CH_3), 2.50 (2H, q, *J*=7.5 Hz, CH_2CH_3), 3.69 (2H, s, CH_2Ph), 6.46 (1H, d, *J*=2.5 Hz, H-2), 6.60 (1H, dd, *J*=8.5 and 2.5 Hz, H-6), 7.03 (1H, d, *J*=8.5 Hz, H-5), 7.10–7.25 (5H, m, Ph), 9.53 (1H, s, OH). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.81; H, 6.45.

*4.8.5. 3-O-Propanoyl-4-chlororesorcinol (**7e**).* Oil; ^{1}H NMR δ 1.01 (3H, t, *J*=7.5 Hz, CH_3), 2.55 (2H, q, *J*=7.5 Hz, CH_2), 6.69 (1H, dd, *J*=8.5 and 2.5 Hz, H-6), 6.70 (1H, d, *J*=2.5 Hz, H-2), 7.02 (1H, d, *J*=8.5 Hz, H-5), 10.17 (1H, s, OH). Anal. Calcd for $C_9H_9ClO_3$: C, 53.88; H, 4.52. Found: C, 53.74; H, 4.46.

*4.8.6. 3-O-Propanoyl-4-bromoresorcinol (**7f**).* Oil; ^{1}H NMR δ 1.10 (3H, t, *J*=7.5 Hz, CH_3), 2.57 (2H, q, *J*=7.5 Hz, CH_2), 6.65 (1H, dd, *J*=8.5 and 2.5 Hz, H-6), 6.65 (1H, d, *J*=2.5 Hz, H-2), 7.42 (1H, d, *J*=8.5 Hz, H-5), 10.36 (1H, s, OH). Anal. Calcd for $C_9H_9BrO_3$: C, 44.11; H, 3.70. Found: C, 44.22; H, 3.96.

4.9. Preparation of authentic 1,3-di-*O*-propanoyl derivatives of 4-substituted resorcinols

Authentic samples of the 1,3-di-*O*-propanoates of 4-substituted resorcinols were prepared by the reaction of each resorcinol with propanoyl chloride in pyridine. They were prepared in the same manner as described above for the preparation of 1,4-di-*O*-propanoates of hydroquinones.

*4.9.1. 1,3-di-O-Propanoyl-4-methylresorcinol (**8a**).* Oil; ^{1}H NMR δ 1.12 (3H, t, *J*=7.5 Hz, CH_2CH_3), 1.15 (3H, t, *J*=7.5 Hz, CH_2CH_3), 2.09 (3H, s, $ArCH_3$), 2.57 (2H, q, *J*=7.5 Hz, CH_2), 2.62 (2H, q, *J*=7.5 Hz, CH_2), 6.94 (1H, dd, *J*=8.5 and 2.5 Hz, H-6), 6.96 (1H, d, *J*=2.5 Hz, H-2), 7.30 (1H, d, *J*=8.5 Hz, H-5). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.17; H, 7.07.

*4.9.2. 1,3-di-O-Propanoyl-4-ethylresorcinol (**8b**).* Oil; ^{1}H NMR δ 1.11 (3H, t, *J*=7.5 Hz, $COCH_2CH_3$), 1.12 (3H, t, *J*=7.5 Hz, $COCH_2CH_3$), 1.16 (3H, t, *J*=7.5 Hz, $ArCH_2CH_3$), 2.47 (2H, q, *J*=7.5 Hz, $ArCH_2$), 2.58 (2H, q, *J*=7.5 Hz, $COCH_2$), 2.63 (2H, q, *J*=7.5 Hz, $COCH_2$), 6.92 (1H, d, *J*=2.5 Hz, H-2), 6.98 (1H, dd, *J*=8.5 and 2.5 Hz, H-6), 7.33 (1H, d, *J*=8.5 Hz, H-5). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.32; H, 7.07.

*4.9.3. 1,3-di-O-Propanoyl-4-t-octylresorcinol (**8c**).* Oil; ^{1}H NMR δ 0.70 (9H, s, $C(CH_3)_3$), 1.12 (3H, t, *J*=7.5 Hz, CH2CH3), 1.17 (3H, t, *J*=7.5 Hz, CH_2CH_3), 1.34 (6H, s, $C(CH_3)_2$), 1.77 (2H, s, $CH_2C(CH_3)_3$), 2.58 (2H, q, *J*=7.5 Hz, CH_2CH_3), 2.63 (2H, q, *J*=7.5 Hz, CH_2CH_3), 6.89 (1H, d, *J*=2.5 Hz, H-2), 6.96 (1H, dd, *J*=8.5 and 8.5 Hz, H-6), 7.41 (1H, d, *J*=8.5 Hz, H-5). Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.73; H, 9.31.

*4.9.4. 1,3-di-O-Propanoyl-4-benzylresorcinol (**8d**).* Oil; ^{1}H NMR δ 1.08 (3H, t, *J*=7.5 Hz, CH_3), 1.16 (3H, t, *J*=7.5 Hz, CH_3), 2.52 (2H, q, *J*=7.5 Hz, CH_2CH_3), 2.59 (2H, q, *J*=7.5 Hz, CH_2CH_3), 3.86 (2H, s, CH_2Ph), 6.96 (1H, d, *J*=2.5 Hz, H-2), 6.99 (1H, dd, *J*=7.5 and 2.5 Hz, H-6), 7.17 (1H, d, *J*=7.5 Hz, H-5), 7.18–7.31 (5H, m, Ph). Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 72.94; H, 6.49.

*4.9.5. 1,3-di-O-Propanoyl-4-chlororesorcinol (**8e**).* Oil; ^{1}H NMR δ 1.13 (3H, t, *J*=7.5 Hz, CH_3), 1.17 (3H, t, *J*=7.5 Hz, CH_3), 2.60 (2H, q, *J*=7.5 Hz, CH_2), 2.66 (2H, q, *J*=7.5 Hz, CH_2), 7.13 (1H, dd, *J*=8.0 and 2.5 Hz, H-6), 7.23 (1H, d, *J*=2.5 Hz, H-2), 7.62 (1H, d, *J*=8.0 Hz, H-5). Anal. Calcd for $C_{12}H_{13}ClO_4$: C, 56.15; H, 5.11. Found: C, 55.98; H, 5.29.

*4.9.6. 1,3-di-O-Propanoyl-4-bromoresorcinol (**8f**).* Oil; ^{1}H NMR δ 1.11 (3H, t, *J*=7.5 Hz, CH_3), 1.16 (3H, t, *J*=7.5 Hz, CH_3), 2.59 (2H, q, *J*=7.5 Hz, CH_2), 2.64 (2H, q, *J*=7.5 Hz, CH_2), 7.05 (1H, dd, *J*=8.5 and 2.5 Hz, H-6), 7.20 (1H, d, *J*=2.5 Hz, H-2), 7.73 (1H, d, *J*=8.5 Hz, H-5). Anal. Calcd for $C_{12}H_{13}BrO_4$: C, 47.86; H, 4.35. Found: C, 47.78; H, 4.17.

4.10. General procedure for the lipase-catalyzed acylation of hydroquinones and resorcinols in an analytical scale

A solution of a dihydric phenol (0.1 mmol) and vinyl propanoate (32.7 μl, 0.3 mmol) in anhydrous diisopropyl ether (240 μl) was stirred with an immobilized lipase preparation (40 mg) in an incubator. After filtering off the enzyme and evaporation of the filtrate, the residue was subjected to NMR analysis to determine the conversion and product distribution, as the ^{1}H NMR spectra of the starting diol and its authentic propanoates (two isomeric monopropanoates and dipropanoate) are available with each hydroquinone or resorcinol. In the reactions of substituted hydroquinones (**1a**–**j**), the proton signals used for the purpose were different from compound to compound. The $ArCH_3$ proton signals together with the $COCH_2CH_3$ signals were utilized with **1a**. The proton signals appearing as a singlet were employed in the following cases: **1b**, $ArCH_3$; **1e**, $C(CH_3)_3$; **1f**, OCH_3; **1g**, $COCH_3$. The proton signals (H-5, H-2 or H-6) in the aromatic region were used with **1c**, **1d** and **1h**–**j**. In the reactions of 4-substituted resorcinols (**5a**–**f**), the proton signals (H-5, H-2 or H-6) in the aromatic region were mainly employed for the purpose. The whole content of the reaction mixture was used up for one analysis, and several discrete reaction mixtures were used at different reaction times.

4.11. HPLC monitoring of the propanoylation of methoxyhydroquinone (1f)

A solution of **1f** (42 mg, 0.3 mmol) and vinyl propanoate (98 μl, 0.9 mmol) in diisopropyl ether (720 μl) was stirred with CAL-B (120 mg) at 45 °C in a 1-ml vial. Aliquots (*ca.* 10 μl) of the reaction mixture were withdrawn at frequent intervals, diluted with ether, and filtered through a PTFE membrane filter. After evaporation of ether, the residue was dissolved in acetonitrile (1 ml), and subjected to HPLC analysis under the following conditions: column, Ascentis RP-Amide (4.6 mm i.d.×250 mm); mobile phase, 34% aq acetonitrile containing H_3PO_4 (0.01 M); flow rate, 1.0 ml min^{-1}; column temperature, 30 °C; detection, UV at 280 nm. The t_R's of relevant compounds are as follows: **1f**, 2.7 min; **3f**, 7.8 min; **2f**, 8.7 min; **4f**, 31.9 min. The absorbances of these compounds at 280 nm were obtained separately by usual UV measurements using their methanolic solutions and the factors were determined based on the absorbance of **1f** as follows: **2f**, 1.13; **3f**, 1.25; **4f**, 0.79. The peak areas obtained on HPLC were corrected using these factors.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.04.033.

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