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Novel Enzymatic Synthesis of 4-*O*-Cinnamoyl Quinic and Shikimic Acid Derivatives

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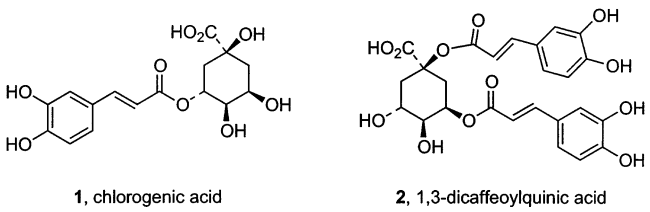
Abstract: The first direct synthesis of 4-*O*-cinnamoyl derivatives of quinic and shikimic acids were accomplished by regioselective esterification with *Candida antarctica* lipase A. For hydrocinnamic esters, enzymatic transesterification with vinyl esters gave excellent yields. However, more reactive acylating agents such as anhydrides were used to synthesize cinnamic derivatives of both acids. An inhibitory effect was observed with this lipase for *p*-methoxy, *p*-hydroxy, and *p*-acetoxy vinyl ester and anhydride derivatives (coumarate and ferulate derivatives).

Few studies have explored the role of secondary metabolic pathways in plant response to oxidative stress. Among them, emphasis is given to the phenylpropanoid biosynthetic pathway, which is responsible for the synthesis of a diverse array of flavonoids and other phenolic metabolites, such as tannins, hydroxycinnamate, and hydroxybenzoate esters.[1] Hydroxycinnamic acids, such as *p*-coumaric acid (4-hydroxycinnamic acid), caffeic acid (3,4-dihydroxycinnamic acid), and ferulic acid (4-hydroxy-3-methoxycinnamic acid), are largely derived from fruits, vegetables, grains, and coffee and are normally associated with quinic acid or sugars as esters.[1c,2] Lipid-soluble esters of phenolic compounds consist of hydroxycinnamates linked to sterols, terpene alcohols, or triterpenes.[3]

In recent years, the phenolic functionality has attracted much attention and has been studied by many researchers.[4] Cinnamic derivatives of quinic and shikimic acid present special relevance. Most intensely studied is 5-caffeoylquinic acid (chlorogenic acid, **1**, Figure 1), which has antibacterial, antimutagenic, antitumor, and antiviral properties.[5] It has been shown that a number of these phenolics act as antioxidants, with plural mechanisms involving free-radical scavenging and metal ion chelation.[4b,c] Their antioxidative action could prevent oxidative damage in vivo relating to various diseases such as cancer[4d,e] or cardiovascular diseases,[2a,6] as well as offering other curative properties (anti-inflammatory, astringent, antispasmodic, antibacterial, etc.).[4a,7] Recently, some of these phenolics[8] have been shown to present inhibitory effects on HIV-integrase (**2**, Figure 1).



1, chlorogenic acid **2**, 1,3-dicaffeoylquinic acid

FIGURE 1. Caffeoyl derivatives of quinic acid.

Most of the cinnamoyl derivatives described in the literature are related to quinic acid,[4−8] and only a few publications report on cinnamoyl shikimic acid derivatives.[2c,9] Most of these compounds are isolated from plant sources[1−9] or synthesized by random isomerization of the available acid.[8a,10] The occurrence in nature of phenolic esters with quinic and shikimic acids is extensive, since the presence of various hydroxyl groups in the molecule increases the number of possible esters. In fact, several new derivatives have been isolated over the past few years.[7b,11] Recently, Sefkow[12] described the first efficient synthesis of 1-, 3-, 4-, and 5-caffeoylquinic acids starting from suitably protected quinic acid precursors. Chemical synthesis of these esters is difficult due to phenolic acids

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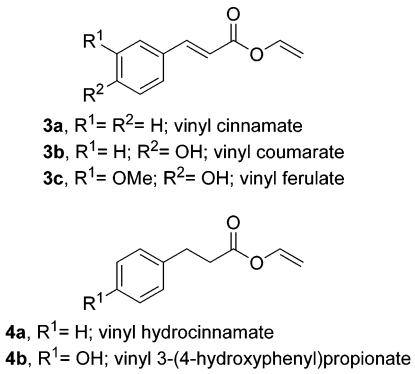

FIGURE 2. Cinnamic and hydrocinnamic vinyl ester derivatives.

being heat-sensitive and susceptible to oxidation under certain pH conditions.[13] In addition, selective functionalization of polyhydroxylated molecules requires several protection and deprotection steps. In this respect, using lipases for esterification may be a worthwhile synthetic pathway.[14] Enzymatic esterification of flavonoid glucosides[15] and glucosides[16] with cinnamate ester derivatives is described in the literature.

We previously reported[17] the regioselective enzymatic acylation of methyl shikimate with *Candida antarctica* lipase A (CAL-A). This lipase selectively catalyzes the acylation of methyl shikimate with alkyl and unsaturated vinyl esters at the secondary C-4 hydroxyl group. Taking into account the wide range of biological activities of phenolic derivatives of quinic and shikimic acids, and the difficulties in their syntheses, we described for the first time the one-step synthesis of C-4 cinnamate ester derivatives of both acids by lipase-catalyzed regioselective transesterification.

For the enzymatic acylation, vinyl cinnamate ester derivatives were used as acylating agents (Figure 2). Although the preparation of vinyl coumarate (**3b**) and vinyl ferulate (**3c**) is described in the literature[15] by the vinyl exchange reaction of vinyl acetate and the corresponding aromatic acid with mercury(II) acetate, in our experience better yields were obtained through esterification of the corresponding hydroxycarboxylic acid under basic conditions in the presence of palladium(II) acetate as catalyst.[18] Thus, vinyl coumarate (**3b**), vinyl ferulate (**3c**), vinyl hydrocinnamate (**4a**), and vinyl *p*-hydroxyphenylpropionate (**4b**) were synthesized in 79%, 77%, 57%, and 50% yield, respectively (Figure 2). Vinyl cinnamate (**3a**) is the only ester commercially available.

SCHEME 1

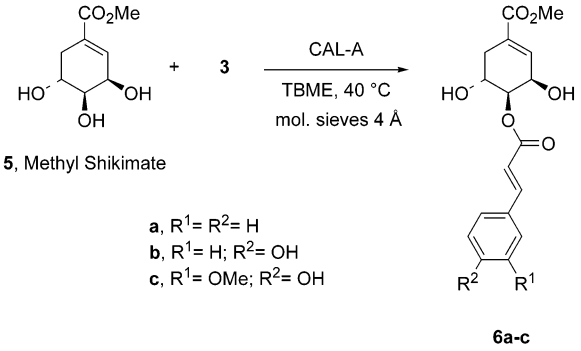

TABLE 1. Acylation of Methyl Shikimate with Vinyl Cinnamate Ester Derivatives Catalyzed by CAL-A

entry	vinyl ester[a]	*t* (h)	conv (%)[b]	C-4 acyl[b,c] (%)	yield (%)
1	**3a**	25	30	30 (**6a**)	
2	**3b**	72	NR[d]		
3	**3c**	72	NR[d]		
4	**4a**	4.5	100	100 (**7a**)	85
5	**4b**	8.5	50	mixture[e]	

[a] Ratio **5**/vinyl ester (1:10). [b] Based on ^{1}H NMR signal integration. [c] Isolated acyl derivative is indicated in parentheses. [d] NR, no reaction. [e] Mixture of mono- and diacylated compounds by ^{1}H NMR.

The enzymatic transesterification of methyl shikimate (**5**) was carried out with CAL-A at 40 °C with *tert*-butylmethyl ether (TBME) as solvent and in the presence of molecular sieves 4 Å (Scheme 1). CAL-A selectively catalyzes the acylation at the C-4 hydroxyl group with vinyl cinnamate (**3a**) (entry 1, Table 1), giving rise to methyl 4-*O*-cinnamoylshikimate (**6a**). However, the reaction did not evolve further, and a maximum 30% conversion was achieved after 25 h. The reactivity of vinyl coumarate (**3b**) and vinyl ferulate (**3c**) was lower, and no reaction occurred with these acylating agents (entries 2 and 3, Table 1). On the other hand, when vinyl hydrocinnamate (**4a**) was used, 100% conversion and total selectivity in the acylation of the C-4 hydroxyl were observed, methyl 4-*O*-hydrocinnamoylshikimate (**7a**, Figure 3) being isolated in 85% yield after flash chromatography (entry 4, Table 1).

The influence of the unsaturation in the vinyl esters is shown in entries 1 and 4 in Table 1, since CAL-A catalyzes the esterification of **5** with vinyl hydrocinnamate (**4a**) with a higher reaction rate than with vinyl cinnamate (**3a**). Finally, we investigated the acylation of methyl shikimate with a *p*-hydroxy-substituted derivative of **4a**. Under the same reaction conditions, the acylation of **5** with **4b** proceeded without regioselectivity, and a mixture of mono- and diacyl derivatives was obtained (entry 5, Table 1).

In view of the poor reactivity of vinyl esters, the corresponding anhydrides were used as acylating agents. Only the cinnamic anhydride (**8a**) had been prepared previously.[19] Following a similar procedure, we synthe-

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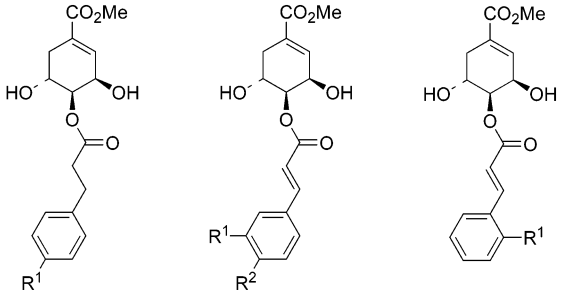
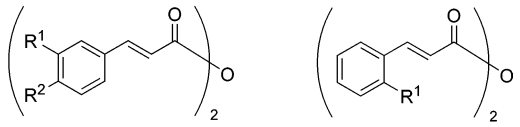


7a, R^1= H
7b, R^1= OH

10b, R^1= H; R^2= OAc
10c, R^1= OMe; R^2= OAc
10d, R^1= H; R^2= OMe
10e, R^1= H; R^2= F

11a, R^1= OAc
11b, R^1= OMe

FIGURE 3. Cinnamic and hydrocinnamic shikimic acid derivatives.



8a, R^1= R^2= H
8b, R^1= H; R^2= OAc
8c, R^1= OMe; R^2= OAc
8d, R^1= H; R^2= OMe
8e, R^1= H; R^2= F

9a, R^1= OAc
9b, R^1= OMe

FIGURE 4. Cinnamic anhydride derivatives.

TABLE 2. Acylation of Methyl Shikimate with Cinnamic Anhydride Derivatives Catalyzed by CAL-A

entry	acid anhydride[a]	*t* (h)	conv[b] (%)	C-4 acyl[b,c] (%)	C-3 acyl[b] (%)	diacyl[b] (%)
1	**8a**	18	100	90 (**6a**)	5	5
2	**8b**	24	NR[d]			
3	**8c**	32	NR[d]			
4	**8d**	32	NR[d]			
5	**8e**	18	100	95 (**10e**)	5	
6	**9a**	6	65	65[e]		
7	**9b**	24	NR[d]			

[a] Ratio **5**/acid anhydride (1:5). [b] Based on ^{1}H NMR signal integration. [c] Isolated acyl derivative is indicated in parentheses. [d] NR, no reaction. [e] Mixture of **11a** and methyl 4-*O*-acetylshikimate (ratio 2:1, respectively). The last one arises from reaction on the acetate ester function of **9a**.

sized a series of cinnamic anhydride derivatives **8** and **9** (Figure 4) by reaction of carboxylic acids with bis-(trichloromethyl)carbonate[20] (triphosgene). For effective synthesis, protection of the hydroxyl group (as acetyl) in the aromatic ring was necessary.

Methyl 4-*O*-cinnamoylshikimate (**6a**) was prepared in one step by esterification of **5** with cinnamic anhydride (**8a**) and CAL-A in the presence of molecular sieves 4 Å. The reaction takes place in 18 h at 40 °C with excellent regioselectivity toward the acylation of the C-4 hydroxyl group (entry 1, Table 2). To remove the acid generated, which inhibited the enzyme, a base should be added to the reaction mixture. However, we have observed that in basic media the acyl group migrates from the 4- to the 3- and 5-position. Because of this, an insoluble inorganic base such as potassium carbonate, which does not interfere with the enzyme and does not favor this migration, was added. For the synthesis of methyl 4-*O*-acetylcoumaroylshikimate (**10b**, Figure 3), the enzymatic transesterification reaction of **5** with a suitably protected coumaric anhydride derivative **8b** was carried out (entry 2, Table 2). In these conditions, CAL-A was unable to catalyze the acylation reaction. The same behavior was observed with 4-*O*-acetylferulic anhydride (**8c**) and 4-methoxycinnamic anhydride (**8d**) (entries 3 and 4, Table 2). At first, the low reactivity was ascribed to the poor solubility of the anhydrides in TBME, and as a result other solvents such as THF, 1,4-dioxane and acetone were used. However, no improvements were observed, and so these results could be attributed to an electronic and/or steric effect. The inhibitory effect of electron-donating *p*-substituents in cinnamic or benzoic acid derivatives has been previously reported.[21] This effect explains the absence of reactivity for **8d**, but not for **8b** and **8c**. In these cases the absence of reactivity can be ascribed to steric effects of the acetoxy group in the 4-position. This fact was confirmed by acylation of **5** with *p*-fluorocinnamic anhydride (**8e**), which has a smaller deactivated group in the 4-position. CAL-A gives rise to the corresponding ester **10e** (Figure 3) with high regioselectivity and in good isolated yield (entry 5, Table 2). As expected the enzymatic acylation of **5** with 2-acetoxycinnamic anhydride (**9a**) takes place in a short reaction time and with total selectivity, but two 4-*O*-acyl derivatives, **11a** (Figure 3) and methyl 4-*O*-acetylshikimate, in a ratio 2:1, respectively, were obtained (entry 6, Table 2). The latter arises from an acylation reaction on the ester function of **9a**. As with anhydride **8d**, the transesterification with 2-methoxycinnamic anhydride (**9b**) did not take place (entry 7, Table 2).

We extended the aforementioned methodology to synthesize cinnamate derivatives of quinic acid. First, we studied the acylation reaction of methyl quinate (**12**) with alkyl and unsaturated vinyl esters in the same conditions as previously described[17] for methyl shikimate. Thus, the reaction was carried out at 40 °C in the presence of molecular sieves 4 Å, 10 equiv of acylating agent, TBME as solvent, and catalyzed by CAL-A (Scheme 2). The transesterification takes place with total selectivity toward the C-4 hydroxyl group, C-4-acyl derivatives **14a**−**d** being isolated exclusively in 85−92% yield after flash chromatography. Lower conversions and no selectivity were observed if more polar solvents such as acetone, 1,4-dioxane, or acetonitrile were used.

Similarly, various cinnamate ester derivatives of quinic acid (**15** and **16**, Figure 5) were effectively synthesized from **12** and acyl donors such as vinyl hydrocinnamate (**4a**), vinyl *p*-hydroxyphenylpropionate (**4b**), cinnamic anhydride (**8a**), and *p*-fluorocinnamic anhydride (**8e**) by direct transesterification using CAL-A. The results are shown in Table 3.

It should be noted that in contrast with methyl shikimate, the reaction with a *p*-hydroxy-substituted

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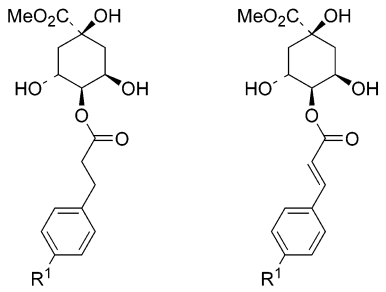

FIGURE 5. Cinnamic and hydrocinnamic quinic acid derivatives.

SCHEME 2

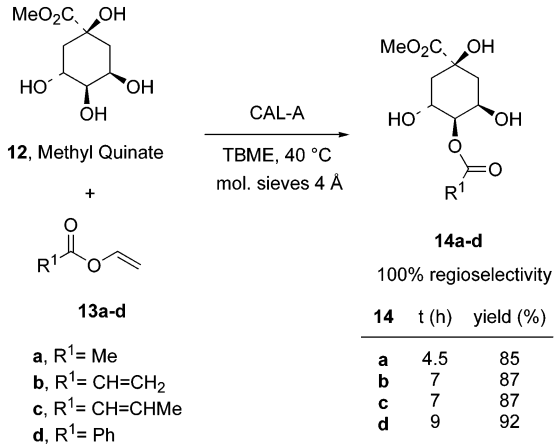

TABLE 3. Acylation of Methyl Quinate with Cinnamic Derivatives Catalyzed by CAL-A[a]

entry	acylating agent	*t* (h)	ratio **12**/ acyl agent	conv[b] (%)	yield[c] (%)
1	**4a**	7	1:10	100	90 (**15a**)
2	**4b**	24	1:10	86	73 (**15b**)
3	**8a**	21	1:5	100	91 (**16a**)
4	**8e**	21	1:5	100	90 (**16b**)

[a] C-4 acyl is formed exclusively. [b] Based on ^{1}H NMR signal integration. [c] Isolated compound is indicated in parentheses.

hydrocinnamate derivative **4b** has proceeded satisfactorily, and after 24 h at 40 °C (the reaction did not evolve further), the desired product **15b** was isolated by flash chromatography (entry 2, Table 3). The rate of esterification was lower than the rate of esterification with vinyl hydrocinnamate, indicating the inhibitory effect of the *p*-hydroxy substituent in the activity of the lipase (entry 1 vs entry 2, Table 3). We also tried the esterification reaction of quinic and shikimic acids with *C. antarctica* lipase B (CAL-B), since this lipase acylated the primary hydroxyl group of the sugar moiety in flavonoid glycosides with vinyl esters of phenolic acids.[15] However, the process did not yield the desired product, but hydrolysis of the vinyl esters and anhydrides took place.

In summary, 4-*O*-cinnamoyl derivatives of quinic and shikimic acids can be efficiently synthesized in a one-step enzymatic transesterification reaction with vinyl esters and anhydrides as acyl donors. *C. antarctica* lipase A allows the selective acylation of the C-4 hydroxyl group in methyl shikimate and methyl quinate, giving rise to a variety of cinnamate ester derivatives of both acids in excellent yields. In addition, this lipase is immobilized on a support and was recycled without loss of significant activity. This method allows easy access to a variety of aromatic quinic and shikimic esters, important secondary plant metabolites, and enables further investigation of their therapeutic and antimicrobial properties.

Experimental Section

General Methods. *C. antarctica* lipase A (CAL-A, chirazyme L-5, c-f, lyophilized, 25 U/g using 1-phenylacetate) was obtained from Roche. *C. antarctica* lipase B (CAL-B, Novozym 435, 7300 PLU/g) was a gift from Novo-Nordisk. TLC chromatograms were visualized by heating after spraying with a 5% aqueous sulfuric acid solution containing cerium sulfate (1%) and molybdophosphoric acid (2.5%). Column chromatography was performed over silica 60 Å (230−400 mesh) except for **6a**, **7a**, and **10e** in which silica 60 Å (32−63 μm) pH 7 was used. Molecular sieves 4 Å were dried at 180 °C in a vacuum over 2 h. Methyl shikimate (**5**) and methyl quinate (**12**) were dried in under high vacuum (10^{-5} mbar) before use.

Enzymatic Acylation of Methyl Shikimate (5) and Methyl Quinate (12). General Procedure. In a standard procedure, the acylating agent (ratios are indicated in Tables 1−3), dissolved in *tert*-butyl methyl ether (0.75 mL for vinyl esters and 1.5 mL for anhydrides), was added to an Erlenmeyer flask that contained triol **5** (13 mg, 0.069 mmol) or **12** (13 mg, 0.062 mmol), CAL-A (13 mg), potassium carbonate (2.5 equiv, only if anhydrides are used as acylating agents), and 4 Å molecular sieves (13 mg) under nitrogen. The suspension was shaken at 250 rpm and 40 °C (times are indicated in Tables 1−3). The mixture was filtered, and the organic solvent was evaporated. Then, the reaction crude was subjected to flash chromatography (10% CH_2Cl_2/Et_2O for **6a**; 30% CH_2Cl_2/Et_2O for **7a**; 15% CH_2Cl_2/Et_2O for**10e**; 3% MeOH/EtOAc for **14a**; 10% CH_2Cl_2/EtOAc for **14b** and **14c**; 15% CH_2Cl_2/EtOAc for **14d**; gradient eluent 30−60% EtOAc/CH_2Cl_2 for **15a** and **16b**; 50% EtOAc/CH_2Cl_2−EtOAc−5% MeOH/EtOAc for **15b**; and gradient eluent 40−70% EtOAc/CH_2Cl_2 for **16a**) to give **6a** (white solid, 86% yield), **7a** (colorless oil, 85% yield), **10e** (white crystalline solid, 88% yield), **14a** (white crystalline solid, 85% yield), **14b** (white solid, 87% yield), **14c** (colorless oil, 87% yield), **14d** (white solid, 92% yield), **15a** (white solid, 90% yield), **15b** (yellow oil, 73% yield), **16a** (white solid, 91% yield), and **16b** (white solid, 90% yield). For **6a**, **7a**, and **10e** silica 60 Å (32−63 μm) pH 7 was used to avoid migrations from C-4 to C-3. (This operation should be done almost immediately to minimize the contact with both the silica gel and the eluent). Then, the solvents were evaporated at 20 °C under reduced pressure. A practical synthesis was carried out in a 2 mmol scale of methyl shikimate (**5**) with cinnamic anhydride. Longer reaction time (24 h) was observed to retain the regioselectivity.

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Supporting Information Available: Experimental procedures for vinyl esters and anhydrides, complete ^{1}H and ^{13}C NMR spectral data, mp, IR, microanalysis, optical rotation, MS, and HRMS data for the new compounds. The level of purity is indicated by the inclusion of copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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