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Letter

A chemoenzymatic synthesis of aromatic carboxylic acid vinyl esters

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Abstract

The practical synthesis of vinyl *p*-coumarate (vinyl 4-hydroxycinnamate) and vinyl ferulate (vinyl 4-hydroxy-3-methoxycinnamate) was accomplished via a transesterification to the corresponding aromatic acid using vinyl acetate and a catalytic amount of $PdCl_2$, followed by the lipase-catalyzed regioselective alcoholysis in EtOH. © 1999 Elsevier Science B.V. All rights reserved.

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Flavonoid glucosides are very important compounds that are widely distributed in natural products. They are used as food ingredients, in cosmetics, and in various other commodities. Flower colors — types of plant pigments such as sugar-containing flavonoids and anthocyanins — are often present in an acylated form with *p*-coumaric acid and ferulic acid at a specific hydroxy (–OH) group of their sugar moieties [1]. These pigments are reported to be stable in plant tissues because of their intra- and inter-molecular hydrophobic interaction caused by acylation with an aromatic carboxylic acid [2–4]. To investigate the structure-stability relationship between the flavonoid aglycon and aromatic acid moiety, we previously reported the synthesis of arbutin cinnamate and isoquercitrin cinnamate via acylation by lipase-catalyzed transesterification with vinyl cinnamate as an acyl donor [5,6]. The transesterification of the flavonoid glucosides with other aromatic acid vinyl esters as acyl donors (in particular, vinyl *p*-coumarate and vinyl ferulate) are needed for detailed study with respect to the contribution of the aromatic carboxylic acid. Here, we describe a synthetic method for the preparation of aromatic carboxylic acid vinyl esters as acyl donors for the enzyme-catalyzed transesterification.

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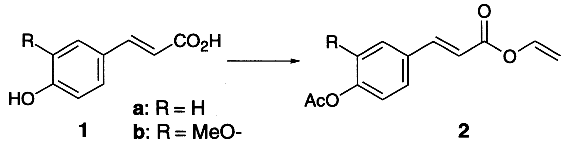
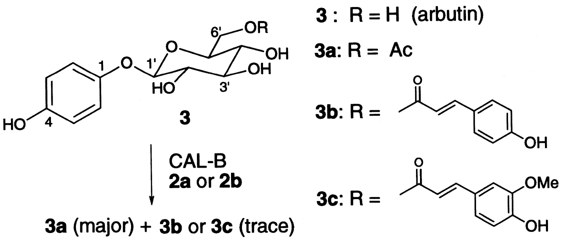
Aromatic acids, **1a** (*p*-coumaric acid) and **1b** (ferulic acid) were readily converted to the corresponding vinyl esters (**2a,b**) by $PdCl_2$-catalyzed transesterification with vinyl acetate, lithium acetate, and copper dibromide [7,8]. As a typical run, to a solution of vinyl acetate (0.4 mol) was added $PdCl_2$ (0.2 mmol), AcOLi (19.5 mmol), $CuBr_2$ (0.5 mmol) and two drops of water at room temperature. The reaction mixture was heated to 70°C and then the aromatic carboxylic acid (**1a** or **1b**) (40 mmol) was added. After stirring for 24 h at 70°C, the mixture was filtered and washed with ethyl acetate, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (*n*-hexane: EtOAc = 10:1) to give a white powder (isolated yield: **2a**, 61%; **2b**, 65%). Selected NMR data: **2a**; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 2.31$ (s, 3H), 4.63 (dd, 1H, $J = 6.2$, 1.4 Hz), 4.97 (dd, 1H, $J = 13.9$, 1.4 Hz), 6.47 (d, 1H, $J = 16.2$ Hz, 7.14 (dd, 1H, $J = 14.0$, 6.2 Hz), 7.56 (d, 2H, $J = 8.6$ Hz), 7.76 (d, 1H, $J = 15.9$ Hz), **2b**; ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 2.33$ (s, 3H), 3.87 (s, 3H), 4.64 (dd, 1H, $J = 6.6$, 1.4 Hz), 4.97 (dd, 1H, $J = 13.7$, 1.6 Hz), 6.40 (d, 1H, $J = 15.9$ Hz), 7.10 (m, 3H), 7.42 (dd, 1H, $J = 13.8$, 6.2 Hz), 7.74 (d, 1H, $J = 15.9$ Hz). The data showed that the phenolic hydroxyl moiety in the produced vinyl esters **2** was acetylated (by a side reaction) (Scheme 1).

The lipase-catalyzed transesterification to arbutin (**3**) was carried out with the acetylated vinyl ester **2a** or **2b** as the acyl donor using our previously reported method [5]. Consequently, 6′-acetylarbutin (**3a**) was the major product and the corresponding 6′-*p*-coumarate (**3b**) or 6′-ferulate ester (**3c**) was present as a very small amount in the product. This result shows that the lipase (Chirazyme L-2, cf., C-2, lyo, lipase fraction B from *Candida antarctica*, Roshe Diagnostics,) preferentially catalyzes the transesterification of the acetyl group, which is a much smaller acyl group compared with the aromatic acid group (Scheme 2).



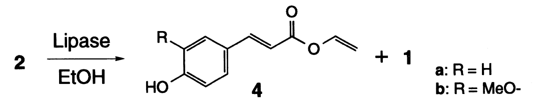
Scheme 1.



Scheme 2.

Since the deacylation of **2** by an alkaline hydrolysis [9,10] gave the corresponding aromatic acid which hydrolyzed both the acetyl and vinyl groups, we have investigated the regioselective hydrolysis of **2** using an enzyme under mild conditions. Six bacterial lipases (Amano-A, Amano-AY, Amano-F, Amano-M, Amano-PS, and Chirazyme) were selected and tested for their deacylating activities toward the acetyl group of **2a,b** in EtOH.

Table 1
Enzymatic regioselective alcoholysis of **2** in EtOH



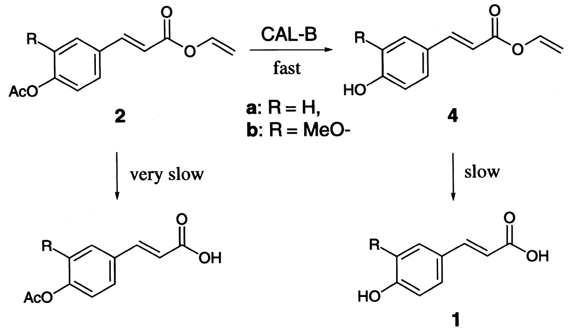
Lipase	**2a**		**2b**	
	4a (%)[b]	**1a** (%)[c]	**4b** (%)[b]	**1b** (%)[c]
Amano-A	55	11	43	21
Amano-AY	46	14	50	15
Amano-F	43	9	39	22
Amano-M	32	15	41	18
Amano-PS	85	0	78	0
Chirazyme[d]	64	6	67	5

[a] Incubated in EtOH at 37°C for 48 h.

[b] Isolated yield.

[c] The isolated yield of the by-product (also alcoholysis of vinyl ester moiety).

[d] Chirazyme, L-2, cf., C2, lyo, lipase from fraction B from *Candida antarctica*.



Scheme 3.

As shown in Table 1, Amano-PS (lipase from *Pseudomonas cepacia*) was found to catalyze the regioselective hydrolysis of the acetyl group of **2** in high yield.

As a typical run, to 40 ml of EtOH was added **2** (10 mmol), Amano-PS (1.0 g), and molecular sieves 4A (500 mg, heat-dried) at room temperature. The reaction mixture was stirred for 48 h at 37°C. The mixture was filtered and washed with EtOH, then concentrated under reduced pressure. The crude mixture was purified by silica-gel chromatography (*n*-hexane: EtOAc = 20: 1 ~ 3: 1) to afford a white powder (**4a**; 85%, **4b**; 78%). Selected NMR data: **4a**; ^{1}H NMR (270 MHz, DMSO-d_6): $\delta = 4.66$ (dd, 1H, $J = 6.2$, 1.4 Hz), 4.94 (dd, 1H, $J = 13.8$, 1.4 Hz), 6.42 (d, 1H, $J = 15.9$), 6.79 (d, 2H, $J = 7.8$ Hz), 7.34 (dd, 1H, $J =$ 14.3, 6.2 Hz), 7.57 (d, 2H, $J = 8.6$ Hz), 7.68 (d, 1H, $J = 15.9$ Hz), **4b**; ^{1}H NMR (270 MHz, DMSO-d_6): $\delta = 3.82$ (s, 3H), 4.69 (dd, 1H, $J = 6.2$, 1.4 Hz), 4.95 (dd, 1H, $J = 13.8$, 1.4 Hz), 6.55 (d, 1H, $J = 16.2$ Hz), 6.80 (d, 1H, $J = 8.1$ Hz), 7.17 (dd, 1H, $J = 8.1$, 1.6 Hz), 7.36 (m, 3H), 7.69 (d, 1H, $J = 15.7$ Hz). However, other lipases (Amano-A, AY, F, M, and CAL-B) also catalyzed the hydrolysis of the vinyl moiety to give the corresponding aromatic acid (**1a,b**) as a by-product. The acetylated aromatic acid (only alcoholysis of vinyl moiety) was not detected by a TLC analysis within 5 d after incubation in all cases. These results show that these lipases preferentially deacylate the acetyl group of **2** and that the reaction rate of the alcoholysis of **2** would be faster than the rate of the alcoholysis from the deacetylated vinyl ester **4** into the starting material (aromatic acid) **1** (Scheme 3).

The optimum temperature of the enzymatic regioselective deacylation was 37°C. The deacylation in other solvents (methanol, 1-propanol, 2-propanol, and *n*-butanol) took a very much longer time (5–7 days) under the same conditions. The use of ethanol as a solvent was effective for increasing the yield of the deacetylated vinyl ester **4**. According to the preceding papers [5,6], arbutin **3** was acylated by the lipase-catalyzed (Chirazyme) transesterification with **4** as the acyl donor and gave the corresponding aromatic carboxylic acid ester (yield, **3b**: 69%, **3c**: 62%). Thus, our present method is very effective and useful for preparing vinyl esters of aromatic carboxylic acid having a phenolic hydroxy group. The application of these aromatic acid vinyl esters to synthesize a wide variety of acylated flavonoids such as plant pigments is currently under investigation and will be reported in our following paper.

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