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Facile and Regioselective Synthesis of Phenylpropanoid-Substituted Flavan-3-ols

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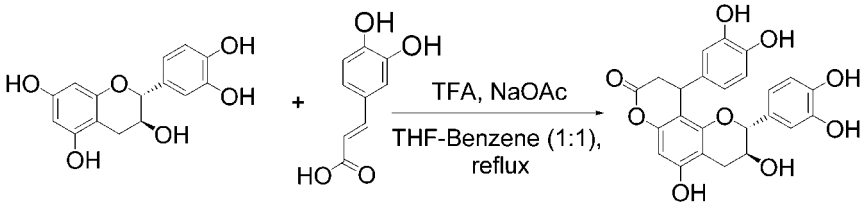
ABSTRACT



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A highly efficient, facile, one-pot regioselective synthesis of a series of phenylpropanoid-substituted flavan-3-ols is described. The mechanism involves dienone–phenol rearrangement followed by a Michael-type reaction.

The importance of new lead compounds for the development of novel pharmaceuticals has recently been increasing, along with the increase of incidence of deadly illnesses such as AIDS, cancers, hepatitis, etc. In this regard, tannins have attracted scientific interest because of their wide range of biological actions[1] such as selective inhibition of HIV replication.[2] The oriental Chinese and Japanese medicines use tannin-containing plant extracts as astringents, diuretics, antiinflammatory, antiseptic, and haemostatic pharmaceutics, and against diarrhoea and stomach and duodenal tumors.[3] Phenylpropanoid-substituted flavan-3-ols are a kind of tannin (proanthocyanidins) that occurs in plants of a woody habit as minor constituents. As a part of our research on hepatoprotective natural medicines,[4] we have isolated a series of flavan-3-ols and phenylpropanoid-substituted flavan-3-ols,[5] which showed potent hepatoprotective activity against D-galactosamine (D-GalN)/tumor necrosis factor-α (TNF-α)-induced cell death in primary cultured mouse hepatocytes. Interestingly, their protective activity was dramatically improved by the presence of a phenylpropanoid group on the flavan-3-ol skeleton.[6] Thus, phenylpropanoid-substituted flavan-3-ols might be attractive candidates for new lead compounds for biological testing. However, isolation of pure components in sufficient scale from natural resources is very difficult, because they are polar and often present as a complex mixture. Thus, appropriate synthetic methods are desired.

Until now, there has been no reliable method for the synthesis of phenylpropanoid-substituted flavan-3-ols. Non-

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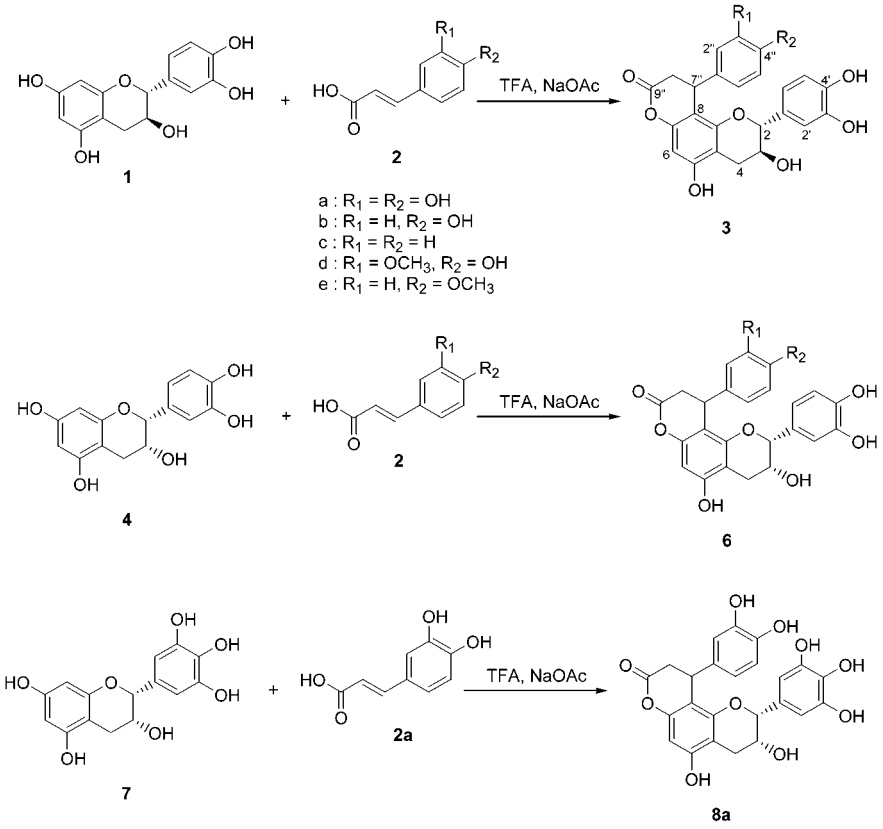
Table 1. Reaction Conditions and Yields for the Synthesis of Various Phenylprapanoid-Substituted Flavan-3-ols



entry	substrates	conditions	yield (%)[a]
1	**1** + **2a**	THF, 12 h	35
2	**1** + **2a**	dioxane, 31 h	23
3	**1** + **2a**	THF−benzene (1:1), 31 h	90
4	**1** + **2a**	DMSO, 4 h	decomposition
5	**1** + **2b**	THF, 12 h	31
6	**1** + **2c**	THF, 48 h	decomposition
7	**1** + **2d**	THF, 24 h	19
8	**1** + **2e**	THF, 48 h	decomposition
9	**4** + **2a**	THF, 6 h	65
10	**4** + **2a**	THF−benzene (1:1), 12 h	51
11	**4** + **2a**	dioxane, 12 h	12
12	**4** + **2b**	THF, 12 h	27
13	**4** + **2c**	THF, 48 h	decomposition
14	**7** + **2a**	THF, 24 h	9

[a] Yields were determined by ^{1}H NMR spectra, as a 1:1 epimeric mixture at the 7″ position.

aka et al. tried to synthesize cinchonains Ia and Ib (**6a**) from epicatechin (**4**) and caffeic acid (**2a**) with BF_3 etherate or dilute hydrochloric acid, but they did not obtain any desired product. The only successful method was a coupling using a catalytic amount of *p*-TsOH in dry dioxane.[7] However, this method suffered many drawbacks such as unwanted side products, tedious separation, and very low yields (<1%).

We assumed the reaction mechanism involved esterification of epicatechin (**4**) with caffeic acid (**2a**) followed by Michael reaction,[8] or vice versa. Several conditions for esterification were attempted, but they gave no satisfactory results. Use of DCC and DMAP in various solvents and reaction conditions led to decomposition of the starting material and/or poor yields, and *p*-TsOH also led to decomposition in most cases. Protection of the catechol groups[9] in both flavan-3-ol and caffeic acid for selective esterification also failed. Thus, a second approach to initially form the carbon−carbon bond between flavan-3-ol and phenylpropanoid was tried. In this regard, treatment of caffeic acid (**2a**) and catechin (**1**) with TFA and sodium acetate in

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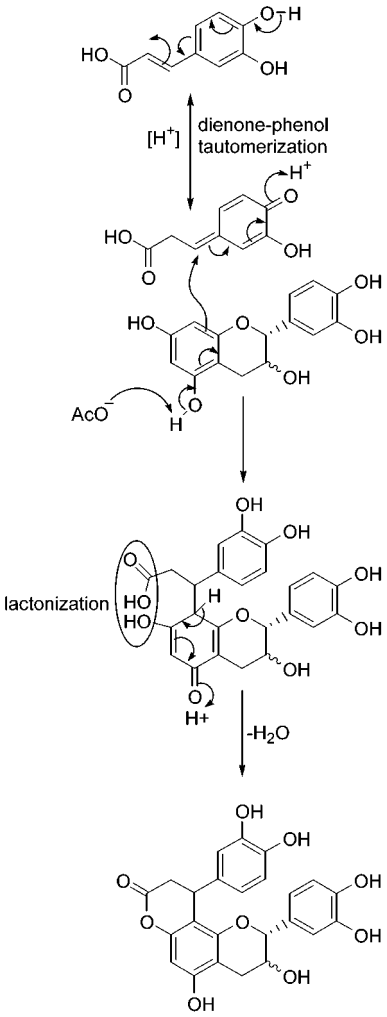

Figure 1. Plausible mechanistic pathway of the coupling reaction.

THF regioselectively gave the desired products **3a** as a 1:1 epimeric mixture on C-7″ (Table 1, entry 1).[10,11] The reaction was highly dependent on the solvents used, and in general, THF and THF−benzene (1:1) showed good selectivity (entries 1, 3, 5, 9, 10); dioxane gave an epimeric mixture of three coupled products without selectivity (entries 2, 11), while DMSO gave only a trace amount of the target compound together with mostly decomposed products (entry 4). This is in agreement with the results obtained by Nonaka[7] et al., who got a mixture of at least six different products in dry dioxane. Similarly, phenylpropanoid-substituted epicatechin **6a** was obtained from epicatechin (**4**) and caffeic acid (**2a**) (entries 9−11). However, gallocatechin (**7**) was unstable under the conditions and underwent decomposition; the yield of **8a** was only 9% (entry 14). Good yields were obtained with *p*-hydroxycinnamic acid (**2b**) as well as caffeic acid (**2a**) (entries 3, 5, 9, 12), while cinnamic acid (**2c**) and *p*-methoxycinnamic acid (**2e**) gave no coupling product. These results would indicate the importance of the *p*-hydroxyl functionality for the reaction and could be rationalized by the mechanism in Figure 1. The *p*-hydroxyl group should provide anchimeric assistance through a typical dienone−phenol tautomerism,[12] to give an intermediate which then reacts with flavan-3-ol as a Michael acceptor. The fact that the reaction failed to proceed in the absence of TFA, even after prolonged treatment under similar conditions, is in agreement with the mechanism. Under acidic conditions, phenolic compounds are very susceptible to the dienone−phenol tautomerization. Cinnamic acid (**2c**) and *p*-methoxycinnamic acid (**2e**), which lack the phenolic hydroxyl group and cannot form the intermediate through dienone−phenol rearrangement, failed to undergo a coupling reaction.

Selective attack through the C-8 position of the flavan-3-ols to the electron-deficient β-position of the dienone intermediate and subsequent ring closure by lactonization led to the final product. The regioselectivity of this coupling reaction can be rationalized on the basis of the charge density on the B-ring of flavan-3-ols using PM3 calculations.[13] The calculated charge density at the C-8 position is higher by −0.053 than at the C-6 position, indicating higher nucleophilicity of the C-8 position. Thus, the C-8 position of flavan-3-ols preferentially adds to the δ-position of the $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl group produced through the dienone−phenol rearrangement to give the product in high yield.

In conclusion, we have described a facile, one-step procedure for construction of phenylpropanoid-substituted flavan-3-ols. Biological activities of the synthesized compounds are now under investigation and will be reported elsewhere.

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(10) **General procedure:** A mixture of catechin (**1**, 200 mg, 0.688 mmol), caffeic acid (**2a**, 182 mg, 1.008 mmol) and 1 equiv of NaOAc (56.4 mg, 0.688 mmol) was dissolved in THF (8 mL) under an Ar atmosphere. To the solution, 6 equiv of TFA (300 μL, 3.90 mmol) was added, and the mixture was refluxed with stirring. The progress of reaction was continuously monitored by checking the disappearance of the flavan-3-ol spot on TLC every hour. The reaction was then quenched by adding saturated sodium bicarbonate solution (10 mL), and the mixture was extracted with ethyl acetate (30 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered, concentrated, and purified by preparative TLC (EtOAc−hexane, 3:7) to afford **3a** (280 mg, 90%).

(11) The products were identified by comparing the NMR data with those in the literature. (a) Reference 5. (b) Reference 7. (c) Chen, H. F.; Tanaka, T.; Nonaka, G.; Fujioka, T.; Mihashi, K. *Phytochemistry* **1993**, *33*, 183−187. (d) David, J. M.; Yoshida, M.; Gottlieb, O. R. *Phytochemistry* **1994**, *35*, 545−546.

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(13) PM3 calculation was done with **CS MOPAC Pro** imprimented in **CS Chem 3D Pro** Program 1996−1999 Cambridge Soft Corporation.