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Nobiletin metabolites: Synthesis and inhibitory activity against matrix metalloproteinase-9 production

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ABSTRACT

A divergent synthesis of nobiletin metabolites was developed through highly oxygenated acetophenone derivative. We used commercially available methyl 3,4,5-trimethoxybenzoate as a starting material for concise preparation of the key intermediate, 2′-hydroxy-3′,4′,5′,6′-tetramethoxyacetophenone (**I**). These metabolites showed strong inhibitory activity against matrix metalloproteinase-9 production in human lens epithelial cells.

Nobiletin (3′,4′,5,6,7,8-hexamethoxyflavone) (**1**), isolated from citrus fruits, has a broad spectrum of health-promoting properties including anticancer,[1] antimetastatic,[2] antiinflammatory,[3] antidiabetic,[4] and neurotrophic activities.[5] In particular, increasing attention has been paid to its antitumor metastatic activity due to the inhibition of gene expression and production of some matrix metalloproteinases (MMP-1, -3, and -9).[6] Recently, nobiletin metabolites have been found to possess potent antiinflammatory,[7] antitumor,[8] and neurotrophic activities,[9] which in some cases exceed those of the parent compound.

In the course of metabolic studies of **1**, 3′-demethylnobiletin (**2**),[10] 4′-demethylnobiletin (**3**),[11] and 3′,4′-didemethylnobiletin (**4**)[12] have been isolated from rodent urine and identified (Fig. 1). Because of the limited availability of these metabolites in nature, detailed investigations of the structure–activity relationship remain to be performed. We therefore initiated a divergent synthesis of nobiletin metabolites **2**–**4** to confirm their structures unambiguously. In the present study, we developed a versatile method for the synthesis of nobiletin metabolites and evaluated their inhibitory activity against MMP-9 production.

Syntheses of nobiletin and its derivatives reported thus far can be classified into two categories as depicted in Scheme 1, that is, (A) intramolecular Michael cyclization of 2′-hydroxychalcone followed by oxidative dehydrogenation;[9,13–16] and (B) C-ring construction via dehydration of 1-(2-hydroxyaryl)-3-arylpropane-1,3-dione.[17–21] Both approaches rely on 2′-hydroxyacetophenone **I** as a key compound. However, efficient synthesis of such a highly oxygenated acetophenone derivative has not been reported. With this context in mind, we commenced with the development of an alternative access to key compound **I**.

We chose commercially available permethyl gallate (**5**) as a starting material (Scheme 2). Our efforts concentrated on methoxylation of the 2,6-positions of **5** using the Ulmann-type reaction. Upon treatment with 2 equiv of NBS, ester **5** was brominated in quantitative yield. The resulting **6** was subjected to the CuBr-mediated Ulmann-type reaction with a large excess amount of sodium methoxide,[22] which gave rise to 2,6-dihydroxybenzoate (**7**) instead of the anticipated permethoxylated ester (**8**).[23]

Based on the result, we proposed a reaction mechanism including catalytic cycles of Cu salt: (i) oxidative addition; and (ii) reductive elimination (Scheme 3). In this cycle, we recognized that intermediate A, in which Cu(I) salt coordinates with the carboxyl group and methoxy group, could be prepared for demethylation to afford **7**. Thus, we assumed that this demethylation process is peculiar to the benzoate derivative.

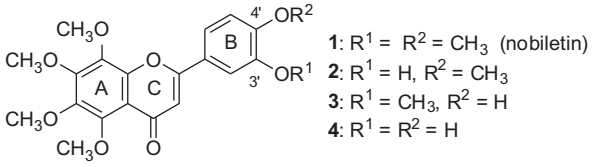

Figure 1. Structures of nobiletin and its metabolites.

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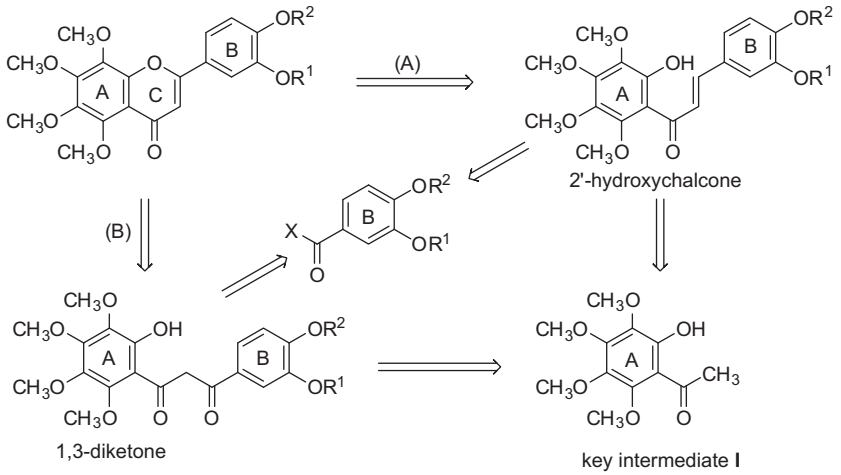
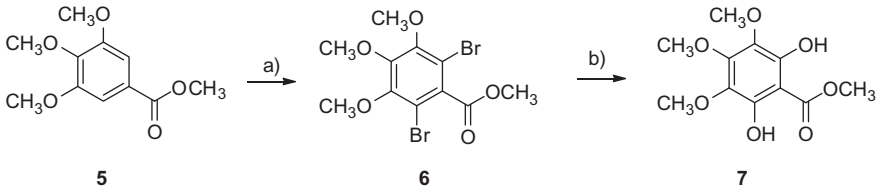
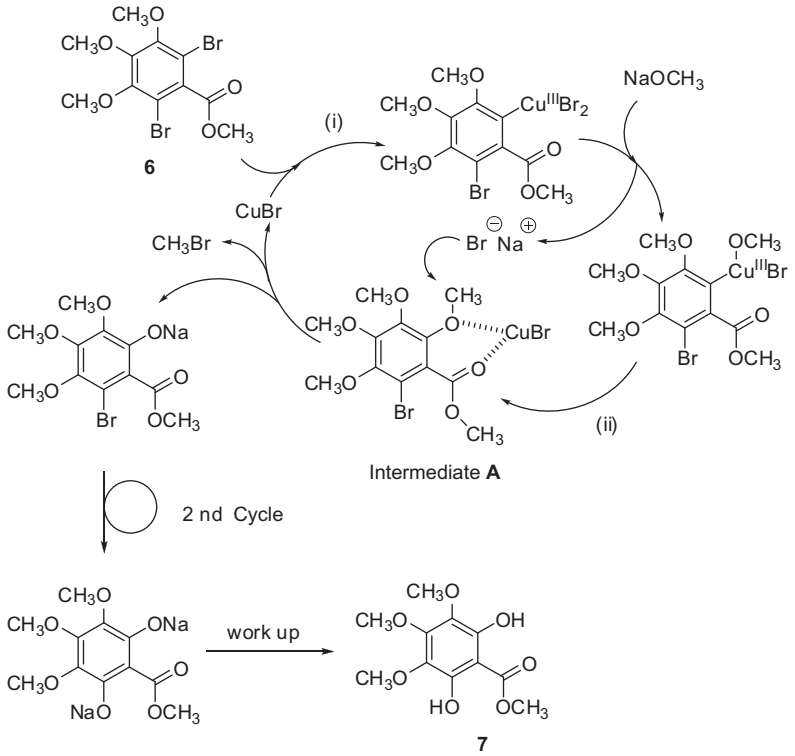


Scheme 1. Classification of polymethoxyflavone synthesis.



Scheme 2. Synthesis of 2,6-dihydroxybenzoate. Reagents and conditions: (a) NBS (2.4 equiv), DMF, 50 °C, quant.; (b) CuBr (0.1 equiv), NaOMe (20 equiv), methanol, reflux, 90%.



Scheme 3. Proposed reaction mechanism of Ulmann-type reaction.

Unfortunately, selective monoetherification of 2,6-dihydroxybenzoate **7** failed. We therefore examined subsequent permethylation of crude **7** to obtain **8** (Scheme 4). Alkaline hydrolysis of ester **8** provided carboxylic acid **9** in 96% yield in three steps.[24] To provide methyl ketone functionality, **9** was then treated with 2 equiv of methyllithium.[25] However, unexpected