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Semi-synthesis of neomangiferin from mangiferin

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ABSTRACT

Neomangiferin, a natural xanthone derivative bearing both *O*- and *C*-glucosides, was isolated from the leaves of *Gentiana asclepiadea* L. and has shown potential anti-diabetic activity. We describe herein the first semi-synthesis of neomangiferin from the natural *C*-glucoside mangiferin and glucose. The developed synthesis presents a facile protection strategy using Jurd's method to distinguish the different phenolic hydroxyl groups. Following this strategy, the regioselective protection of 1,3,6-hydroxyl groups was accomplished and neomangiferin was prepared by glycosylation under the phase-transfer catalysis conditions.

Introduction

Xanthones are natural polyphenolic compounds with the dibenzo-γ-pyrone framework,[1] which are mainly present in higher plants, lichens, fungi, and bacteria.[2] Hundreds of xanthone derivatives, including xanthone glycosides, xanthonolignoids, prenylated xanthones, and others, have been reported during the past ten years.[3] These compounds exhibit a wide spectrum of activities such as cytotoxic, anti-inflammatory, antimicrobial, and antifungal effects.[4] Neomangiferin (**1**) or mangiferin-7-*O*-β-D-glucoside, is a representative xanthone glycoside, which was first isolated from *Gentiana asclepiadea* by Michel and Andre in 1977[5] and now mainly obtained from *Rhizome Anemarrhenae* (Zhi-Mu in Chinese),[6] an important traditional herbal medicine with good hypoglycemic activity. As a natural derivative of the bioactive xanthonoid mangiferin (**2**),[7a] neomangiferin was found to have significant effect in lowering blood glucose level of KK-Ay mice, an animal model of non-insulin-dependent diabetes mellitus (NIDDM).[8] No changes were seen when investigated in normal mice, indicating that this compound is useful in treating NIDDM. Moreover, neomangiferin can also improve the kidney functions and prevent diabetic nephropathy, thus reducing the diabetes complication.[8d] Despite the good activity, its shortage in nature remains the main limiting factor for further study. Therefore, we expect to develop an efficient synthetic route of preparing neomangiferin for pharmacological use (Fig. 1).

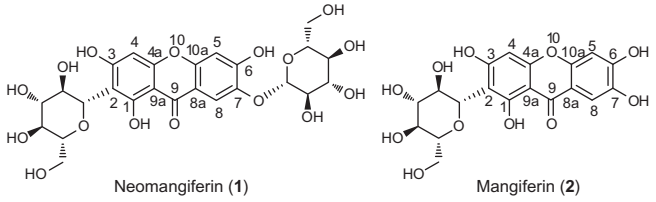

Figure 1. Structures of neomangiferin (**1**) and mangiferin (**2**).

So far, only a few synthetic methods for the preparation of xanthone glycosides have been reported. In 2010, Yu and co-workers accomplished the first total synthesis of *C*-glycoside mangiferin (**2**),[9] but studies toward the synthesis of xanthones bearing both *O*- and *C*-glycosides like neomangiferin (**1**) have not been described. Moreover, due to the lack of an effective method to distinguish the phenolic hydroxyl groups at different locations, derivatization of mangiferin was confined to multiple modifications such as 3,6,7-etherification, heptasulfation, and polyacylation or some easily obtainable single-modifications including 3-alkylation, 6′-acylation, and 6′-glycosylation.[10] For these reasons, the total synthesis and semi-synthesis of neomangiferin, a polyphenolic diglucosylxanthone, is challenging. Herein, we report the first concise synthesis of **1** from mangiferin **2**, which not only coexists with neomangiferin in Zhi-Mu but also occurs abundantly in many other plants such as *Mangifera indica*, *Belamcanda chinensis*, *Folium pyrrosiae*, and *Coffea pseudozanguebariae*,[7] and thus relatively easy to obtain from nature.

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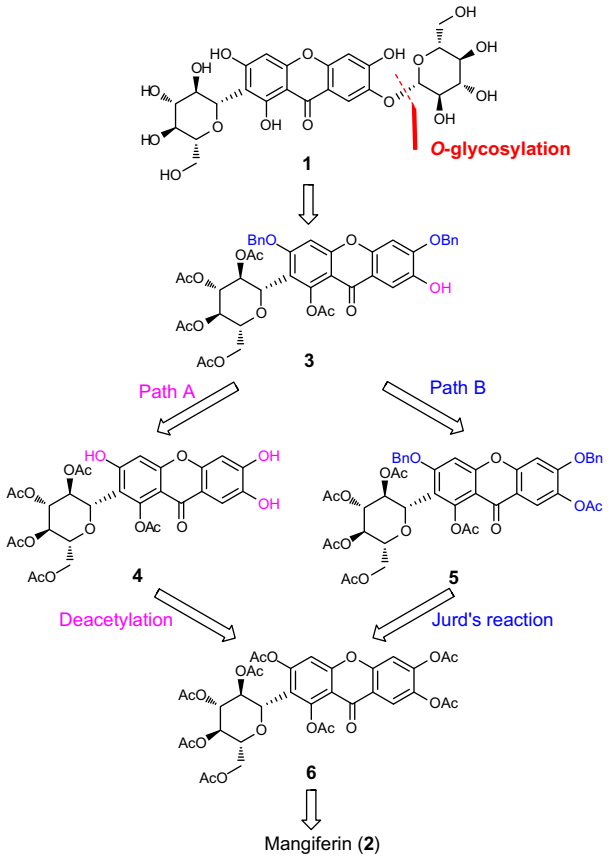
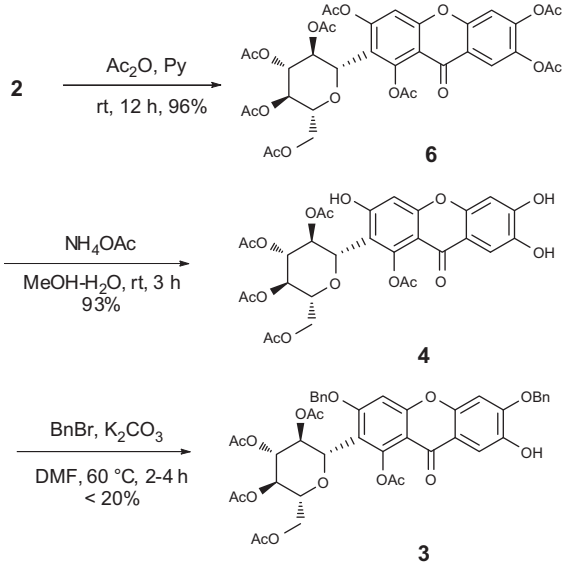


Scheme 1. Retrosynthetic analysis of neomangiferin (**1**).

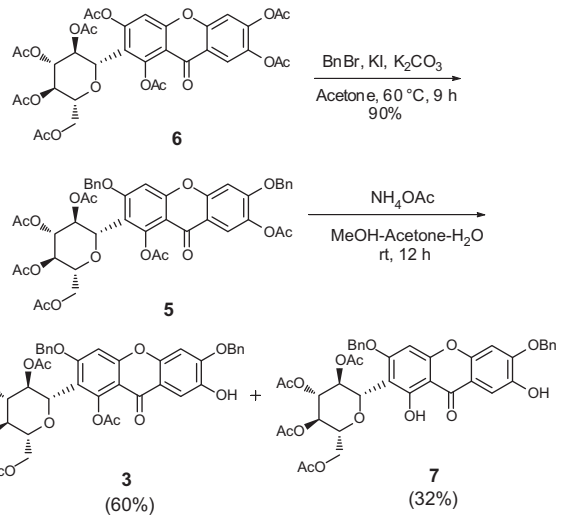


Scheme 2. Synthesis of 3,6-dibenzyl ether **3** by path A.

Results

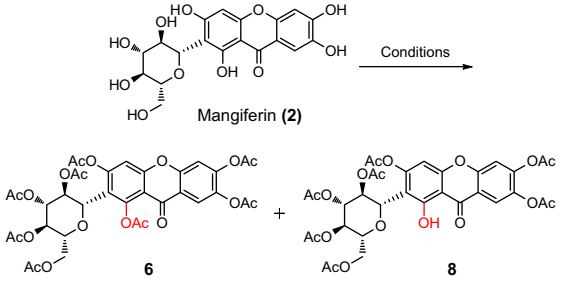
Our retrosynthetic analysis of neomangiferin (**1**) is outlined in Scheme 1. The 7-*O*-glucoside would be obtained by coupling 3,6-di-*O*-benzyl-7-hydroxy-mangiferin (**3**) with α-glucopyranosyl bromide under general phase-transfer catalysis (PTC) conditions or by the promotion of silver salts. Therefore, the key step for our synthesis is the selective protection of 1,3,6-hydroxyl groups in mangiferin, leaving the 7-hydroxyl group free for glycosylation. Two pathways were designed as shown in Scheme 1. In path A, compound **3** would be produced through the selective benzylation of partially acetylated mangiferin **4** based on the different reactivity of phenolic hydroxyl groups. And path B would feature a group transformation from 3,6-di-acetyl **6** to 3,6-di-benzyl **5** according to Jurd's method reported for flavones in 1958,[11] followed by selective deacetylation.[12]

Our synthesis commenced with Path A to investigate the reactivity differences of 3,6,7-hydroxyl groups (Scheme 2). Treatment



Scheme 3. Synthesis of 3,6-dibenzyl ether **3** in path B.

Table 1
Results of partial acetylation of mangiferin (**2**)



Entry	Conditions	Yield of **6** + **8**[b]
1	Ac_2O,[a] pyridine, rt, 12 h	96% + trace[c]
2	Ac_2O,[a] DMAP, pyridine, 60 °C, 0.5 h	98% + 0%
3	Ac_2O,[a] $BF_3{\cdot}Et_2O$,[d] rt, 12 h	[e]
4	Ac_2O,[a] TfOH,[d] rt, 12 h	[e]
5	Ac_2O,[a] TFA,[d] rt, 12 h	[e]
6	Ac_2O,[a] MSA,[d] rt, 12 h	[e]
7	Ac_2O,[a] NaOAc,[f] 80 °C, 3 h	44% + 46%
8	Ac_2O/AcOH (v/v = 1/1),[g] NaOAc,[f] 120 °C, 3 h	16% + 80%
9	Ac_2O/AcOH (v/v = 1/2),[g] NaOAc,[f] 120 °C, 3 h	Trace[c] + 94%

DMAP = 4-dimethylamiopyridine, TFA = trifluoroacetic acid, MSA = methanesulfonic acid.

[a] Amount of Ac_2O (1.25 equiv/OH).
[b] Yield of isolated product.
[c] Detected by TLC.
[d] Amount of acid (0.08 equiv).
[e] The reaction was complex and no desired **6** or **8** was detected.
[f] Amount of NaOAc (1.2 equiv/OH).
[g] Amount of Ac_2O (1.3 equiv/OH).