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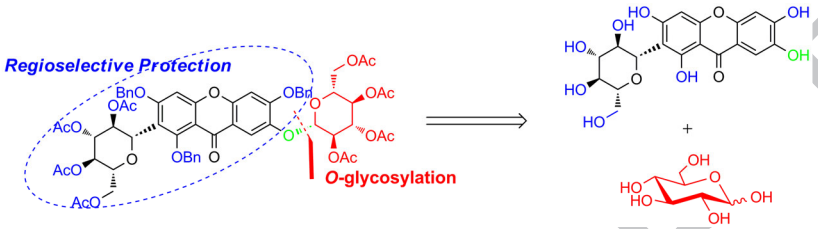

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ABSTRACT

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.

1. 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 (**Figure 1**)

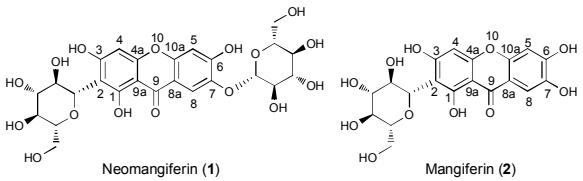


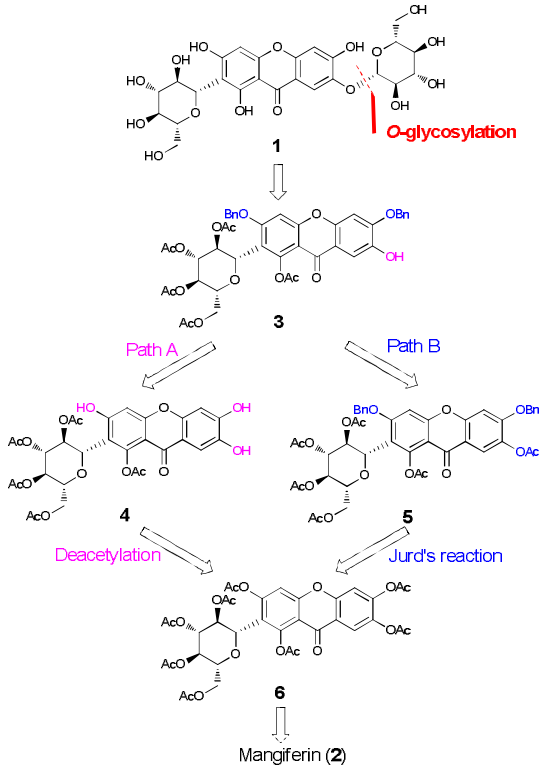
Figure 1. Structures of Neomangiferin (1) and Mangiferin (2).

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 towards 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 coexist with neomangferin in Zhi-Mu but also occurs abundantly in many other plants such as *Mangifera indica*, *Belamcanda chinensis*, *Foliaum pyrrosiae* and *Coffea pseudozanguebariae*[7], and thus relatively easy to obtain from nature.

2. 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-

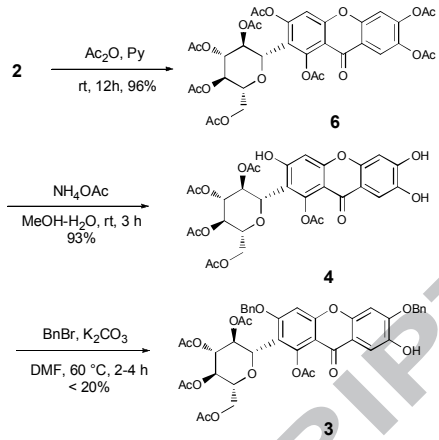
di-acetyl **6** to 3,6-di-benzyl **5** according to Jurd's method reported for flavones in 1958,[11] followed by selective deacetylation.[12]



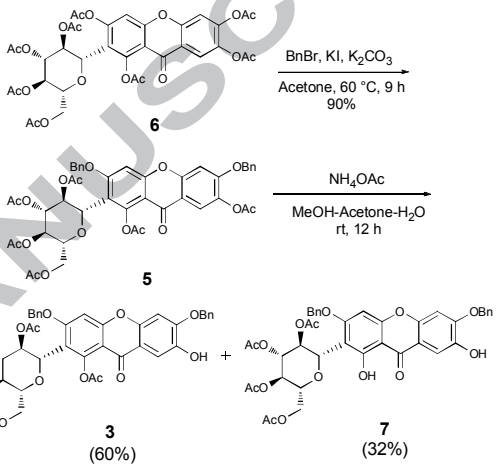
Scheme 1. Retrosynthetic Analysis of Neomangiferin (**1**)

Our synthesis commenced with Path A to investigate the reactivity differences of 3,6,7-hydroxyl groups (**Scheme 2**). Treatment of mangiferin (**2**) with Ac_2O/pyridine at rt afforded peracetyl ester **6** in 96% yield,[13] for which the rotamers were observed by ^1H NMR and ^{13}C NMR.[14] Selective removal of 3,6,7-tri-*O*-acetyl groups was then achieved with NH_4OAc in MeOH/H_2O,[12a] providing the desired compound **4** (93%) with the 1-OAc intact, which might be stabilized due to the steric hindrance. Unfortunately, the following benzylation of polyphenol **4** with benzyl bromide in the presence of potassium carbonate produced 3,6-dibenzyl ether 3 only in less than 20% yield,[15] and further adjustment of the reaction conditions did not make any improvement to reduce the tri-benzylated byproduct. This result suggested that the activities of 3,6,7-hydroxyl groups were not different enough to achieve the selective and efficient benzylation of 3,6-hydroxyl groups. As the yield of **3** was too low for the practical synthesis of neomangiferin, path A was abandoned.

Path B involved the Jurd's method reported for the protection of flavones,[16] in which the acetyl groups para to a carbonyl group could be directly converted to benzyl groups.[17] Because of the structure similarity of xanthones and flavones, this approach was tested with compound **6** first. Treatment of peracetyl ester **6** with BnBr in the presence of K_2CO_3 and KI afforded the expected intermediate **5** in an excellent yield of 90%. Following selective deprotection of 7-OAc conducted under the mild condition as in path A provided the desired 3,6-dibenzyl ether **3** in 60% yield with the formation of byproduct **7** in 32% yield, in which the 1-OAc was also removed (**Scheme 3**). Although the yield of 3 by Path B is significantly improved compared with Path A, we consider the formation of **3** is still not selective enough for the practical synthesis of neomangiferin.



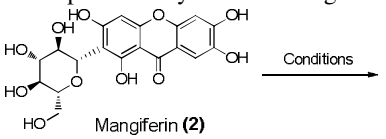
Scheme 2. Synthesis of 3,6-dibenzyl ether **3** by path A

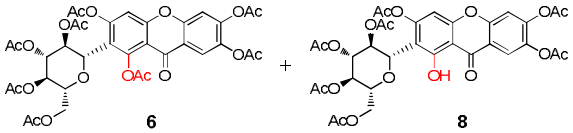


Scheme 3. Synthesis of 3,6-dibenzyl ether **3** in path B

To further improve the selectivity and yield, the activity order of different hydroxyl and acetyl groups was taken into consideration according to Jurd's conclusions. As the group transformation will occur in the following sequence, 3,6,7-OH, 1-OH, 3,6-OAc, 7-OAc, 1-OAc, which means 3,6,7-OH will react most qucikly and 1-OAc will be the last one to be converted, we thought compound **8** would be a suitable intermediate for the selective benzylation of 3,6-OAc by the Jurd's method and the simultaneous benzylation of 1-OH, leaving only the 7-OAc for following deacetylation. Various conditions for the synthesis of 3,6,7-tri-acyl ester **8** were explored, and the results are summarized in **Table 1**. Treatment of **2** with acetic anhydride in the presence of pyridine gave only trace amount of desired **8** with **6** as the major product,[13b] even when DMAP was introduced[18] (**Table 1**, entries 1 and 2). Attempts to carry out the acetylation under acidic conditions, including $BF_3{\cdot}Et_2O$,[19] TfOH, TFA, and MSA, yielded no expected product at all (**Table 1**, entries 3-6). Fortunately, we found that the yield of **8** was increased when NaOAc was used instead of pyridine (**Table 1**, entries 7).[20] And when the Ac_2O/AcOH system was used, the major product **8** was finally obtained in an excellent 94% yield (**Table 1**, entries 8 and 9).[21]

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%

[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).

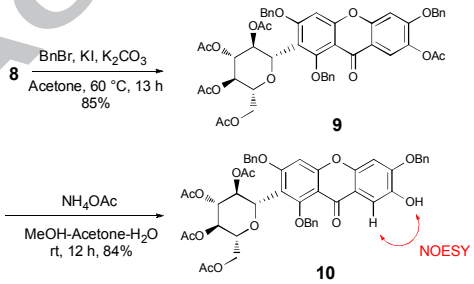
[e]The reaction was complex and no desired **6** or **8** was detected.

[f]Amount of NaOAc (1.2 equiv/OH).

[g]Amount of Ac_2O (1.3 equiv/OH).

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

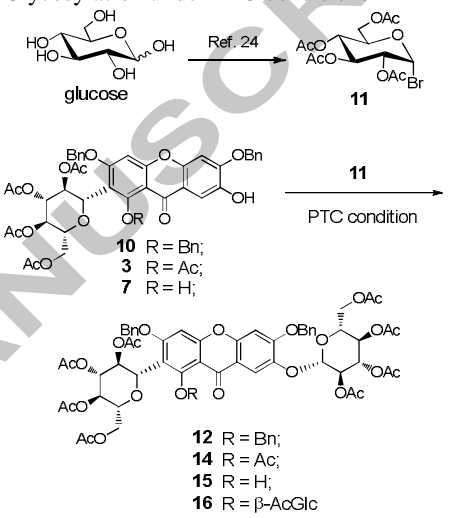
Jurd's reaction was conducted with **8** again (**Scheme 4**). Treatment of **8** with BnBr in the presence of K_2CO_3 and KI provided the 1,3,6-tri-*O*-benzyl ether **9** in 85% yield, leaving the 7-OAc intact as expected. Subsequent removal of the acetyl group of 7-OAc by NH_4OAc smoothly afforded compound **10** with a free 7-OH group, which was confirmed by NOESY analysis. We consider the synthesis of compound **10** is highly selective and efficient, which can be used for the practical semi-synthesis of neomangiferin. Moreover, this developed protecting strategy might also be available for the modification of other xanthones.



Scheme 4. Synthesis of glycosylation acceptor **10**

After the glycosylation acceptor **10** was obtained, the formation of 7-*O*-glycosidic linkage was attempted following the general method reported for flavones.[22] Under the phase-transfer catalysis (PTC) conditions (TBAB, 5% NaOH, CH_2Cl_2, reflux),[23] glycosylation of the accepter **10** with *α*-D-glucopyranosyl bromide **11**[24] produced the desired 7-*O*-*β*-D-glucoside **12** in 59% yield (**Table 2**, entry 1), and further optimization of the reaction conditions increased the yield to 78%, with no *α*-glucoside product detected (**Table 2**, entry 2). In contrast, when using **3** as the accepter, glycosylation can also took place smoothly, providing slightly less product **14** (**Table 2**, entry 3). We also tried to using compound **7** directly to see if regioselective glycosylation could be achieved. However, the expected 7-*O*-*β*-D-glucoside was obtained in only 39% yield, with 1,7-di-*O*-*β*-D-glucoside **16** (31%) as the main byproduct (**Table 2**, entry 4). Therefore, compound **10** should be the most proper accepter for efficient synthesis of neomangiferin.

Table 2. Glycosylation under PTC conditions

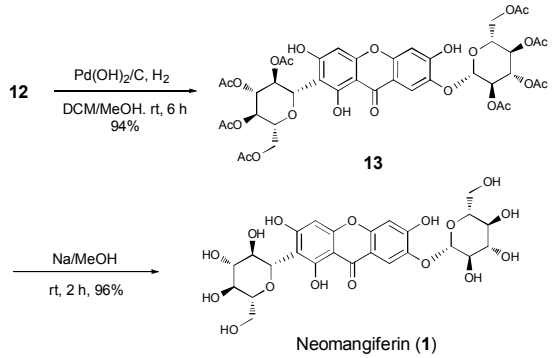


Entry	reagent and solvent	T (°C)	Result[a,b]
1	**10** (1eq), **11** (2 eq), TBAB, 5% NaOH (4 eq), CH_2Cl_2	38	**12** (59%)
2	**10** (1eq), **11** (3 eq), TBAB, 5% NaOH (7 eq), $CHCl_3$	60	**12** (78%)
3	**3** (1eq), **11** (3 eq), TBAB, 5% NaOH (7 eq), $CHCl_3$	60	**14** (73%)
4	**7**(1eq), **11** (3 eq), TBAB, 5% NaOH (7 eq), $CHCl_3$	60	**15** / **16** (39%/31%)

[a]Isolated yield.

[b]7-α-glucosides were not obtained.

Finally, catalytic hydrogenolysis of the glucoside **12** with $Pd(OH)_2/C$ in CH_2Cl_2/MeOH,[25] followed by removal of the acetate ester,[26] smoothly gave the target molecule **1** in 90% yield for two steps (**Scheme 5**). The ^1H NMR and ^{13}C NMR spectra of the synthesized neomangiferin (**1**) were identical to those reported for the isolated natural product,[27] and the structure was confirmed by 2D NMR.



Scheme 5. Complement of the synthesis of neomangiferin **1**

3. Conclusion

In conclusion, we have achieved the concise semi-synthesis of neomangiferin starting from mangiferin for the first time. The synthesis proceeded in 6 steps with a 47% overall yield, featuring a regioselective protecting strategy based on Jurd's method and a formation of 7-O-glycosidic linkage under PTC conditions. The efficiency and regioselectivity of our protection strategy may make it practical for the general structural modification and synthesis of xanthone derivatives.

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Supplementary data

Supplementary data related to this article can be found at http:// dx.doi.org/10.xxxx/xxxxx.

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