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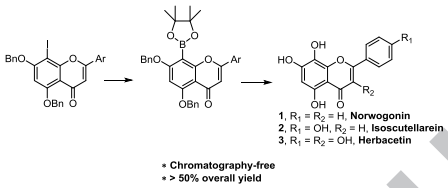

- Chromatography-free
- > 50% overall yield

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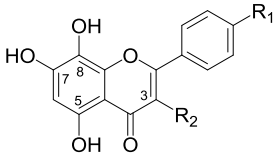
ABSTRACT

An expeditious synthesis of norwogonin, isoscutellarein, and herbacetin, has been accomplished by a strategy featuring a borylation of sterically hindered aryl iodide and a one-pot oxidation to generate the C-3 and C-8 OH groups. The total synthesis gives excellent yields and conventional flash column chromatography is not needed for purification.

1. Introduction

Flavones have antioxidant, anti-proliferative, anti-tumor, anti-microbial, antibacterial, anti-inflammatory activities, and are also used in cardiovascular disease and neurodegenerative disorders. Flavones have been an indispensable anchor for the development of new therapeutic agents, and some flavones have undergone clinical studies.[1] Norwogonin (**1**), isoscutellarein (**2**), and herbacetin (**3**) are a class of 5,7,8-trihydroxyflavone originally isolated from *Scutellaria baicalensis*, which is an active component of the Traditional Chinese Medicine (TCM) extract from Huang Qin. They have been reported to present anti-inflammatory,[2] insecticidal and antifungal,[3] anticancer,[4] antidepressant,[5] free radical scavenging, and antioxidant effects.[6] Additionally, they were found to exhibit potent influenza virus inhibitory activity *in vivo* and *in vitro*.[7]



1, $R_1 = R_2 = H$, **Norwogonin**
2, $R_1 = OH$, $R_2 = H$, **Isoscutellarein**
3, $R_1 = R_2 = OH$, **Herbacetin**

Figure 1. Chemical structures of norwogonin, isoscutellarein, and herbacetin.

The diverse biological activities exhibited by 5,7,8-trihydroxyflavones have made them of particular synthetic interest. Norwogonin (**1**), isoscutellarein (**2**), and herbacetin (**3**) only occur at low levels in natural plants, and this has negatively influenced further evaluation of their biological activities. Therefore, the chemical synthesis of **1**, **2**, and **3** would be a very important way of addressing the problem of their availability. As such, several methods for the synthesis of 5,7,8-trihydroxyflavones are available (Scheme 1, **A**), which broadly can be categorized into two groups involving oxidative cyclization of chalcones or acid-catalyzed cyclization of 1,3-diketones using 3,4,5-trimethoxyphenol or 2-hydroxy-3-alkoxy-4,5-trimethoxyacetophenone as the starting material[8] and selective bromination at the C-6 position of 5-hydroxy-7-methoxyflavone, followed by methanolysis with CuBr and MeONa.[9] Further deprotection and oxidation yielded the related 5,7,8-trihydroxyflavone and 3,5,7,8-tetrahydroxyflavone.

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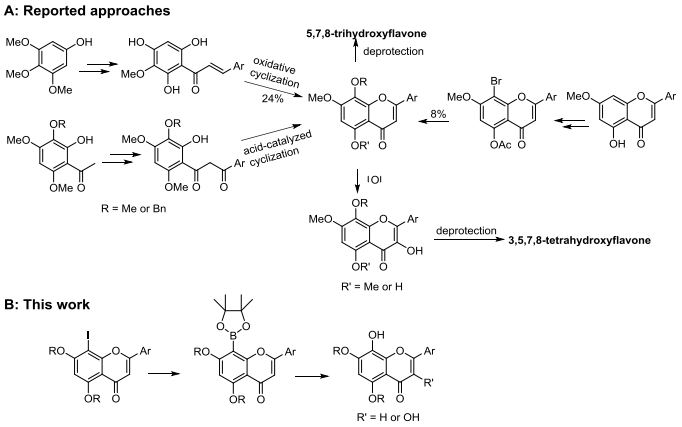
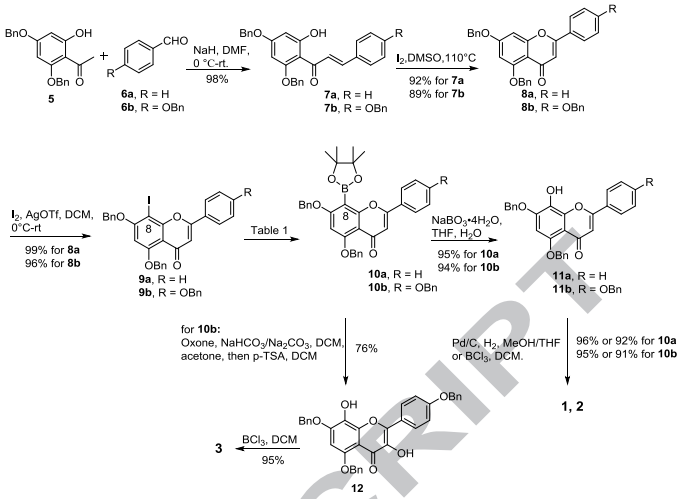


Scheme 1. Reported methods for the synthesis of 5,7,8-trihydroxyflavones (**A**) and our approach (**B**).

In general, these approaches suffered either from low overall yields and tedious work-up or from uncommercially available starting materials and harsh reaction conditions. In this paper, we introduce the C-8 OH groups of 5,7,8-trihydroxyflavone and 3,5,7,8-tetrahydroxyflavone *via* an borylation of 8-iodonated flavone and a subsequent oxidation.

2. Results and discussion

Our synthetic efforts (Scheme 2) commenced with 2,4-dibenzyloxy-6-hydroxy phenylacetone **5**. Condensation of **5** with benzaldehyde (**6a** or **6b**) was achieved *via* a Claisen-Schmidt reaction[10] to give the chalcone (**7a** or **7b**) in >95% yield. Chalcone (**7** or **7b**) was cyclized in the presence of catalytic iodine in DMSO at 110 °C to give benzyl-protected flavones (**8a** or **8b**) in high yields. 8-iodonated flavones (**9a** and **9b**) were readily prepared by reacting **8a** and **8b** with AgOTf/I_2 under mild conditions.[11] Borylation of **9a** and **9b** with classical Miyaura borylation reaction[12] employing bis(pinacolato)diboron (B_2pin_2) as boron source failed to yield corresponding boronic esters, only dehalogenated byproducts were obtained (Table 1, entries 1–2), which might be attributed to the large steric effect. The attempt to convert **9b** into **10b** with halogen-lithium exchange to form boronic acid and subsequent esterification with pinacol afforded a complex mixture (Table 1, entry 3).[13] We next screened the effect of the palladium source, ligand and boron source on the borylation reaction of the model substrate (**9b**). To our delight, simple variation of boron source showed that pinacolborane (pinBH) led to much improved reactivity. Several catalytic systems were found to be efficient for the borylation reaction of **9b**, while a $Pd(AcO)_2$/P(*o*-Tol)$_3$ system provided the highest yield (Table 1, entries 4–10). Borylation of **9a** with the same reaction condition also smoothly afforded corresponding boronic ester **10a** in 88% yield.



Scheme 2. Synthesis of norwogonin (**1**), isoscutellarein (**2**) and herbacetin (**3**).

Table 1
Borylation at C-8 position of **9b**

Entry	Reaction conditions	Yield/%
1	$PdCl_2$(dppf), B_2Pin_2, KOAc/DMSO, 80 ºC	0 [a]
2	$PdCl_2$(dppf), B_2Pin_2, TEA/dioxane, 90 ºC	0 [a]
3	(a) *n*-BuLi, (b) $B(OMe)_3$, (c) HCl, (d) pinacol	– [b]
4	$PdCl_2$(dppf), pinBH, TEA/dioxane, 90 ºC	23
5	$PdCl_2$(dppf), pinBH, TEA/dioxane, 70 ºC	28
6	$PdBr_2$, P(*o*-Tol)$_3$, pinBH, TEA/THF, 70 ºC	66
7	$PdCl_2$, PPh_3, pinBH, TEA/THF, 70 ºC	49
8	$Pd(AcO)_2$, P(*o*-Tol)$_3$, pinBH, TEA/THF, 60 ºC	85
9	$Pd(AcO)_2$, P(*o*-Tol)$_3$, pinBH, TEA/dioxane, 85 ºC	63
10	$Pd(AcO)_2$, PPh_3, pinBH, TEA/dioxane, 85 ºC	43

[a] >95% dehalogenated product was observed.
[b] Complex mixture.

With the boronic esters (**10a** and **10b**) in hand, the corresponding phenols (**11a** and **11b**) were obtained in high yields by oxidation with $NaBO_3 \cdot 4H_2O$[14] within 60 minutes. Removal of the benzyl groups of **11a** and **11b** by hydrogenolysis or BCl_3 furnished norwogonin (**1**)[15] and isoscutellarein (**2**)[16] in >90% yield. Oxidization of **10b** to generate C-3 and C-8 OH groups in one-pot was readily accomplished in 76% yield by treatment with dimethyldioxirane (DMDO),[17] generated *in situ* from Oxone and acetone at low temperature, followed by opening of the resulting epoxide with catalytic *p*-toluenesulfonic acid (*p*-TSA). Debenzylation of **12** with BCl_3 provided herbacetin (**3**) whose spectral data were in agreement with those reported in literature.[18] Additionally, the desired product in each step could be purified *via* recrystallization, and conventional flash column chromatography is not needed.

In summary, an exceedingly efficient synthesis of norwogonin, isoscutellarein, and herbacetin has been accomplished, which provided >50% overall yield. The most striking maneuver in this synthesis is the borylation of sterically hindered aryl iodides and a one-pot oxidation to generate the hydroxyl groups. This efficient and flexible entry should offer opportunities for the construction of many other norwogonin, isoscutellarein, and herbacetin analogues for chemical biology investigations.

Acknowledgments

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Supplementary Material

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- A new approach to 5,7,8-trihydroxyflavones is provided.
- Satisfactory yields of norwogonin, isoscutellarein, and herbacetin are obtained.
- Borylation of sterically hindered aryl iodides is developed.
- NO column chromatography is needed for purification.