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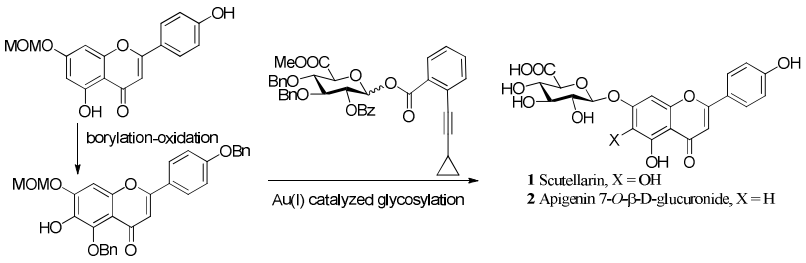

Abstract

A general protocol for direct glucuronic linkages formation featuring Au(I)-catalyzed appropriately protected glucuronyl o-alkynylbenzoate-involved glycosylation reaction, as well as a concise approach for easy access of scutellarein prominent for the mild and efficient hydroxyl group installation via borylation-oxidation sequence from flavanone derivative, has been established, based on which a novel route for scutellarin derivatives preparation has been devised. The developed strategies, among which the stepwise deprotection process was also included, guarantee the high whole synthetic efficiency, and definitely will find broad application in diversity-oriented synthesis of bioactive flavonoid glycosides.

Total Synthesis of Scutellarin and Apigenin 7-*O*-β-D-glucuronide

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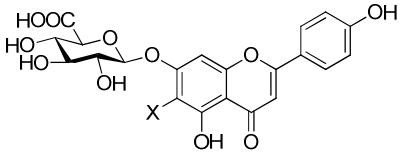
Abstract

A general protocol for direct glucuronic linkages formation featuring Au(I)-catalyzed appropriately protected glucuronyl o-alkynylbenzoate-involved glycosylation reaction, as well as a concise approach for easy access of scutellarein prominent for the mild and efficient hydroxyl group installation via borylation-oxidation sequence from flavanone derivative, has been established, based on which a novel route for scutellarin derivatives preparation has been devised. The developed strategies, among which the stepwise deprotection process was also included, guarantee the high whole synthetic efficiency, and definitely will find broad application in diversity-oriented synthesis of bioactive flavonoid glycosides.

1. Introduction

As a well-known traditional Chinese medicine herb, *Erigeron breviscapus* has been widely prescribed for the treatment of cerebrovascular diseases, such as cerebral hemorrhage, stroke, cerebral thrombosis, as well as myocardial infarction. The principle ingredients responsible for the broad pharmaceutical usages of *E. breviscapus* have been proven to scutellarin **1** as well as analogues such as apigenin 7-*O*-β-D-glucuronide **2**,[1] which indeed have been demonstrated to show numerous pharmaceutical activities, including antitumoral activity,[2] neuroprotection,[3] angiogenesis promotion,[4] as well as anti-HIV effects,[5] and presently are widely clinically used in China under different dosage forms. At present, scutellarin is solely acquired from *E. breviscapus* by direct extraction, thus with the demand increasing, on the one hand resulting in exhausted natural *E. breviscapus* source, on the other hand bringing about serious problems for concise quality control of products from different batches. In addition, the access of pure scutellarin directly from natural sources is by no means a simple problem due to the microheterogeneity. Thus, alternative approaches to get pure scutellarin are highly desired.

Figure 1. The chemical structures of scutellarin and its analogue.



1 Scutellarin, X = OH
2 Apigenin 7-*O*-β-D-glucuronide, X = H

In comparison to enzymatic method,[6] limited by enzyme accessibility, production

scale, as well as high production cost, the chemical synthesis holds the promise to solve the problem of scutellarin acquirement completely. Thus, the synthetic investigation towards scutellarin has been undertaken in as early as 1958 by Zemplén and coworkers,[7] and finally culminated in the first total synthesis in 1974.[8] Afterwards, with the new pharmaceutical effects of scutellarin being disclosed continuously, the interest, both from chemists and from pharmacologists, in synthetic investigation were refuelled, as exemplified by the appearance of quite a few approaches for scutellarin synthesis.[9] As all existing synthetic methods are heavily depend on expensive starting materials, including 2-hydroxy-4,5,6-trimethoxyacetophenone or scutellarein, and conventional glycosylation protocols, such as glycosyl bromide involved glycosylation under the effect of stoichiometric amounts of silver salts or phase transfer catalyst (PTC) conditions, they suffer from not only tedious synthetic sequence and accordingly compromised overall synthetic efficiency but also harsh reaction conditions, unacceptable synthetic cost, as well as restricted synthetic flexibility.[10] In line with our continuous interest in bioactive flavonoid glycosides synthesis,[11] we decided to launch a program to establish a practical approach for scutellarin derivatives synthesis.

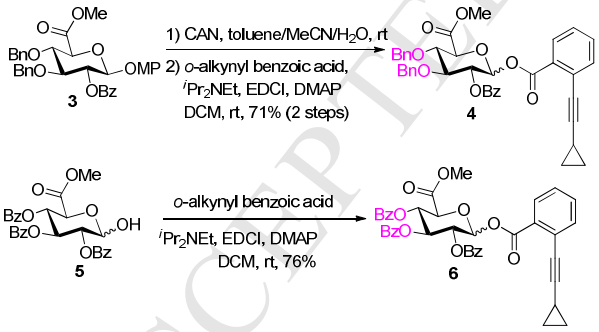
The scarce scutellarein aglycon and, in particular, the glycuronyl phenolic linkage which is notorious for unsatisfactory formation efficiency due to the diminished reactivity not only for glycosylation donor but also for acceptor, [12] poses considerable challenge for scutellarin derivatives synthesis, and also constitutes the underlying factors responsible for the sluggish development of the synthetic field. Thus, as prerequisites for efficient synthetic approach establishment, two pivotal problems, that is efficient glycosidic linkages construction with appropriate glucuronic donors and easy accessibility of scutellarein aglycon, should be solved first. The developed solutions should enjoy broad application scope, thus based on which the pining diversity-oriented synthesis of scutellarin derivatives could be expected.

2. Results and discussion

Glycuronyl residues are widely spread in nature, and, in particular, they are also comprised in drug derivatives used for drug metabolism study as reference compounds.[13] Nevertheless, the construction of glycuronic linkages in a highly efficient manner represents one of the most challenging problems in synthetic carbohydrate chemistry. The main difficulties associated with glycuronylation lie in the lowered reactivity of the glycosylation donors, originating from the strongly electron-withdrawing 5-CO_2R group, which frequently leads to orthoester or transacylating byproducts formations. To avoid the deleterious effect of the ester group in glycosylation reactions, a detour postglycosylation oxidation strategy has been devised.[14] However, the additional steps required for C-6-OH oxidation state adjustment after glycosidic linkage construction compromises the convergent extent of the synthesis and accordingly the synthetic efficiency. On the contrary, from a synthetic perspective, the alternative preglycosylation oxidation strategy featuring C-6-OH oxidation level manipulation prior to glycosidic linkages construction is more

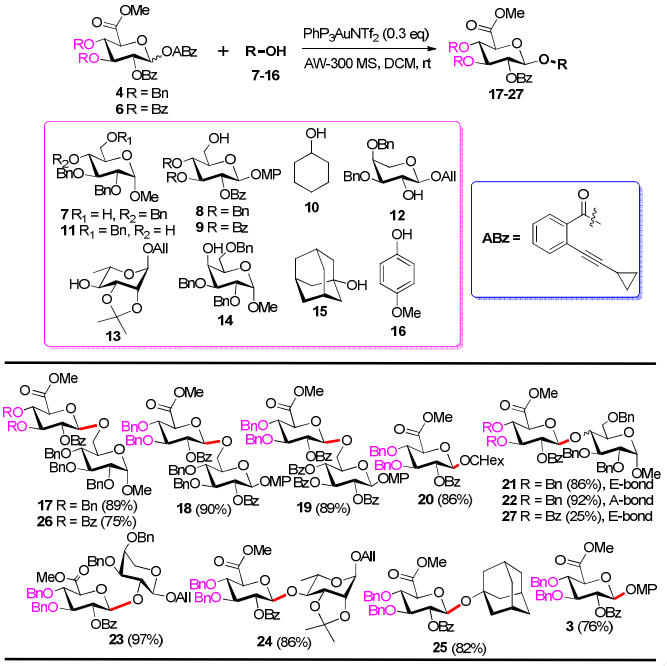
direct and appealing. Unsurprisingly, a variety of glycosylation protocols have been adopted to this strategy in attempts to set up an efficient approach for direct glycuronic linkage construction, however, only limited successes have been achieved.[15] Considering that the recently introduced Yu glycosylation[16] has shown impressive performances in challenging glycosidic linkages construction[17] and has not been tried in direct glycuronide synthesis,[18] we decided to check the feasibility of glucuronyl o-alkynylbenzoate donor in glucuronides synthesis with the hope to establish a general protocol for highly efficient and direct glucuronic linkages construction to facilitate not only the synthesis of scutellarin derivatives but also the synthesis of other bioactive compounds containing glucuronic acid residues. Inspired by the instructive work of Huang, wherein an extremely important statement in carbohydrate chemistry, that is the higher reactivity one donor has the more potential glycosylation capability it possesses, has been put forward and testified,[19] the glucuronyl o-alkynylbenzote donor **4** equipped with electron-donating benzyl groups on 3,4-*di*-OH was designed and synthesized. As a comparison, the donor **6** with all its 2,3,4-*tri*-OH blocked by electron-withdrawing benzoyl groups was also made (Scheme 1). On the 2-OH of both donors, an benzoyl group was selected so as to control the 1,2-*trans*-chirality of newly formed glycosidic linkages via the neighboring-group participating effect. Thus, with **3** [20] as starting material, ceric ammonium nitrate (CAN) mediated anomeric OH liberation and sequential dehydrative esterification with o-alkynylbenzoic acid afforded donor **4** (71%, for 2 steps); while the reference donor **6** was prepared under standard acylation conditions from lactol **5** (76%).[21]

Scheme 1. Synthesis of glucuronyl o-alkynylbenzoate donors **4** and **6**.



With both donors **4** and **6** in hand, they were put to condense with a variety of acceptors to evaluate their glycosylation potential (Table 1). Under the effect of catalytic amounts of Au(I) complex, all primary acceptors **7**-**9** were smoothly glycosylated with **4**, to deliver the desired disaccharides **17**-**19** with excellent yields (above 89%). Simple as well as complex sugar secondary alcohols **10**-**14** were proved to be vital substrates for donor **4** as well, providing glycosylation products **20**-**24** with good to excellent yields upon treated with standard glycosylation conditions (above 86% yields). It is worth noting that the glycosylation potential of **4** is so impressive that even the bulky and inert tertiary 1-adamantanol **15** could be efficiently glycosylated to afford the glycosylation product **25** in a good 82% yield. Furthermore,

Table 1. Direct glucuronic linkages construction with donors **4** and **6**.

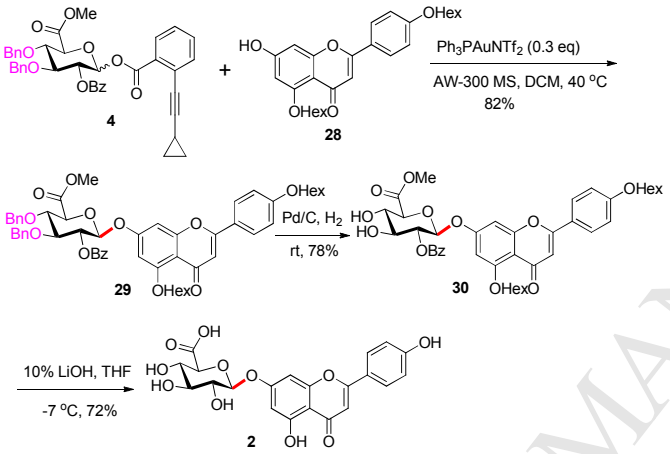


the coupling of **4** with phenolic acceptor **16** proceeded smoothly in spite of the decreased reactivity of the phenolic acceptor, and good yield of phenolic glycoside **3** [20] was obtained (76%), which boded well for the ensuing application of **4** in the synthesis of scutellarin and analogues thereof. As comparisons, donor **6** was evaluated subsequently to react with different acceptors. Although **6** could also condense with primary acceptor **7**, the glycosylation yield was diminished to 75%; while in terms of the secondary acceptor **11**, only low yield of product **27** was recorded (25%). With the assistance of 2-OBz, all glycosylation proceeded stereoselectively to afford only β-glycosides, as verified by the diagnostic anomeric protons of all glycosylation products, which all appear in doublet forms with J values ranging from 7.6 to 8.0 Hz. The conspicuous glycosylation capability difference between **4** and **6** highlights the profound effect of electron-donating protecting groups at 3,4-*di*-OH on the glycosylation potential of glucuronyl donors via offsetting the deactivating effect of C-6 ester group. Furthermore, in comparison to the widely adopted PTC glycosylation protocol in scutallerin derivative synthesis, the present Yu protocol shows evident advantages as to the substrate scope as well as the flexibility.

Inspired by the promising result of coupling between **4** and **16**, the application of **4** in the synthesis of scutellarin derivative apigenin 7-*O*-β-D-glucuronide **2** was subsequently investigated (Scheme 2). Effected by the low reactivity of acceptor **28** [22], presumably originating from the electron-withdrawing acyl protecting groups, the condensation between **4** and **28** proceeded inefficiently; under conventional conditions (0.3 equivalents of Au(I) complex, overnight) only 50% yield of **29** was obtained. Modification of the conventional glycosylation procedure by changing the addition manner of catalyst from one portion to two portions at an interval of 8 h and prolonging the reaction time to 16 h brought about an upsoar in yield, leading to an 82% yield for **29**. The two benzyl groups in **29** were removed by hydrogenolysis to

convert **29** to **30** (78%), which was then exposed to mild basic conditions (10% LiOH) to cleave all acytyl protecting groups and simultaneously saponify the methyl ester to provide **2** in a good 72% yield. The reaction temperature is vital for the final deprotection step, as high reaction temperature leads to a mixture of products, which can be ascribed to the labile property of electron-rich flavonoid residue to air under basic conditions as well as the propensity of glucuronyl moiety to undergo epimerization and elimination side reactions under harsh basic conditions.[23] The spectroscopic data of synthetic **2** was proved to identical to those of authentic sample.[1]

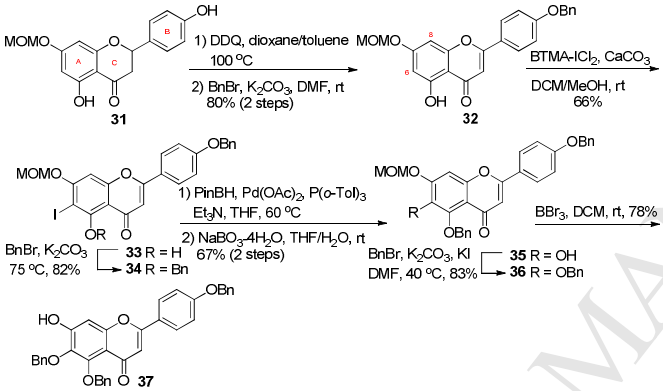
Scheme 2. Synthesis of scutellarin analogue **2**.



With the glycosylation protocol for glucuronic linkage construction settled, our attention was then shifted to the scutellarein access problem. To avoid the drawbacks of existing routes for scutellarein preparation, including tedious synthetic sequence, expensive starting materials, and harsh reaction conditions, a new approach with flavonoid compounds as starting materials was pursued (Scheme 3). Thus, starting from naringein derivative **31**,[24] flavone **32** was generated via a sequence of DDQ-mediated oxidation and selective 4'-OH benzylation (80%, for 2 steps). The regioselective C-6 iodination of **32** was subsequently effected by benzyltrimetylammonium dichloroiodate (BTMA-ICl_2) under the assist of the directing effect of the free 5-OH.[25] The directing effect of 5-OH is efficacious, so that the inherent propensity of flavone moiety to undergo regioselective C-8 iodination is completely overrode, and the C-6 iodinated flavone **33** was isolated as the only product (66%). After the 5-OH was blocked with benzyl group, compound 34 ready for C-6-OH installation was obtained. With **34** in hand, the substitution of iodide with hydroxyl group or its surrogates was investigated extensively. Impeded by the severe steric hindrance of the iodide atom imposed by the two flanked substituents, all attempts in copper- or palladium-catalyzed coupling with allyl alcohol, 1-trimethylsilyethanol, benzyl alcohol, and benzaldoxime under different conditions[26] uniformly met with failure, except for the try of coupling with sodium methoxide under the effect of CuBr, which indeed afforded the methyl protected scutellarein derivative.[9b] However, the methylated scutellarein can not serve as

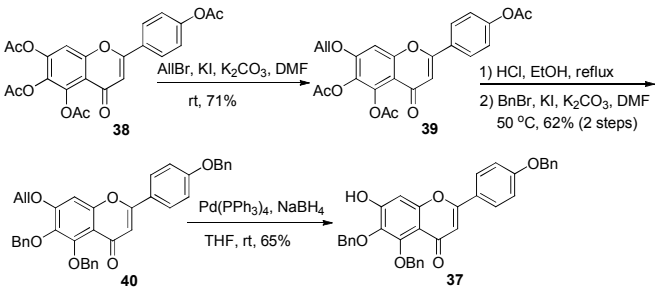
intermediate in the novel synthetic route, since the demethylation entails harsh reaction conditions. Finally, the borylation-oxidation sequence was invoked. Although the classic as well as the modified Miyaura borylation conditions failed to provide the desired borylation intermediate ($PdCl_2$(dpf), $(PinB)_2$ or $Pd(OAc)_2$, PCy_2(o-biph), PinBH),[27a-d] it was finally shown that the combination of $Pd(OAc)_2$/P(o-Tol)/PinBH effected the borylation efficiently to afford the boronic ester, which was directly exposed to oxidation conditions to afford phenol **35** ($NaBO_3$, 67% for 2 steps).[27e] Protection of the newly formed OH with benzyl group was followed by MOM removal with BBr_3, thus affording the appropriately protected scutellarein acceptor **37** (65%, for 2 steps).

Scheme 3. Synthesis of appropriately protected scutellarein **37** from naringenin derivative.



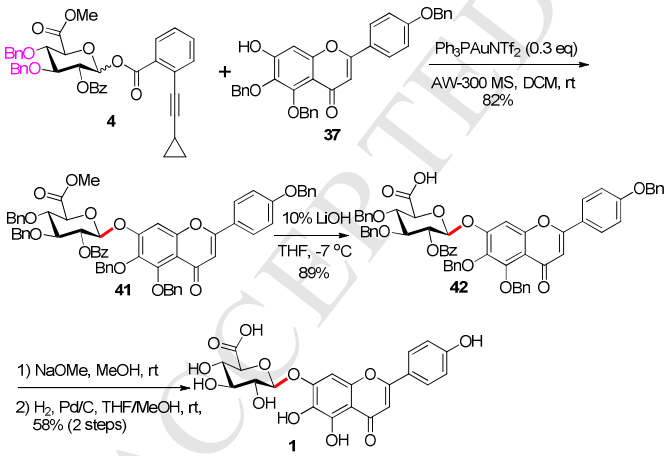
As the spectroscopic data of **33** could not provide convincing proofs to support the C-6 iodination in the above synthetic approach, to corroborate the chemical structure of the synthetic **37**, it was resynthesized with peracetylated scuteller-in **38** [28] as starting material (Scheme 4). The one-pot regioselective 7-OAc cleavage and simultaneous allylation afforded **39** smoothly (71%). The following replacement of acetyl groups with benzyl groups was achieved via acid-mediated deacetylation and ensuing benzylation to deliver the fully protected scutellarein **40** (62%, 2 steps), which was then exposed to palladium-catalyzed deallylation conditions to give **37** (65%). The 1H NMR comparison of synthetic **37** with different origins showed that actually identical spectra were obtained,[29] corroborating the structure of **37** as well as the reliability of the novel scutellarein synthesis approach.

Scheme 4. Determination of the chemical structure of **37** via resynthesizing with **38** as starting material.



With both glycosylation protocol and reliable access route to acceptor established, now the stage was set for the completion of the synthesis of scutellarin (Scheme 5). Benefited from the electron-donating benzyl protecting groups on acceptor **37**, its condensation with **4** proceeded without any event under standard conditions, and an excellent yield of fully protected scutallerin **41** was obtained (82%). In the final deprotection processes, the sequence of methyl ester saponification, benzoyl and benzyl groups removal was systematically screened, and finally resulted in the optimal protecting groups manipulation order of methyl ester saponification followed by benzoyl group cleavage prior to benzyl groups hydrogenolysis. Under mild basic conditions (10%, LiOH, -7 ^{o}C), the methyl ester in **41** was successfully saponified, to yield **42** (89%), which was then put to harsh basic conditions to remove the benzoyl group (NaOMe/MeOH, rt). The resultant debenzoylated acid intermediate was thenconverted to the target molecule **1**, upon treatment with conventional hydrogenolysis conditions (58%, for 2 steps). This deprotection sequence can exclude the possible side reactions to a maximum extent: the exposure of carboxyl group in the early stage of the deprotection process can prevent the possible epimerization as well as elimination processes of glucuronyl residue under harsh basic conditions required for benzyol group departure; while the final hydrogenolysis process can segregate the oxidation-labile multi-hydroxy-substituted flavone residue in **1** from the air during protecting group manipulation. Finally, the spectra comparison of the synthetic **1** with authentic compound was made, and fortunately, excellent accordance was observed.[1]

Scheme 5. The completion of the synthesis of **1**.



3. Conclusions

In summary, a novel and flexible approach toward scutellarin and its analogue featuring highly efficient and direct glucuronic linkage construction with glucuronyl o-alkynylbenzoate as donor as well as easy access of scutellarein from flavanone starting material has been established. Through the synthetic investigation, a general protocol for direct glucuronic linkage constructions with glucuronyl o-alkynylbenzoate donor carrying benzoyl group on its 2-OH and two benzyl groups on its 3,4-*di*-OH has been devised; meanwhile, capitalizing on the borylation-oxidation sequence, a

concise route for easy access of scutellarein has also been set up. In addition, the optimized stepwise deprotection sequence for scutellarin synthesis supressed the possible side reactions to a maximum extent guaranteeing the efficiency of the whole synthesis, which can find broad application in the synthesis of scutellarin analogues.[30]

Acknowledgements

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Highlights

1, A novel route for scutellarin and analogue thereof preparation.

2, Au(I)-catalyzed glycosylation by use of glucuronyl o-alkynyl benzoate as donors.

3, A concise approach for easy access of scutellarein prominent for the mild and efficient hydroxyl group installation via borylation- oxidation sequence from flavanone derivative.