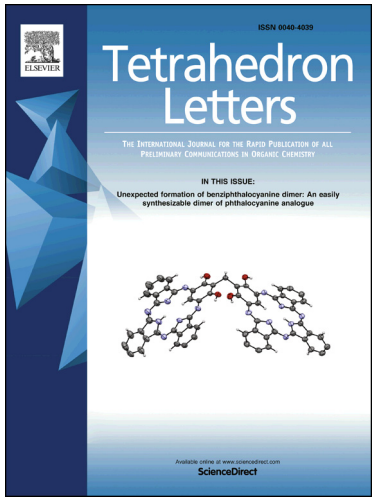

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Total Synthesis of two isoflavone *C*-glycosides (6-*tert*-butyl puerarin and 6-*tert*-butyl-4'-methoxypuerarin) through the deoxybenzoin pathway

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ABSTRACT

The total synthesis of two isoflavone *C*-glycosides (6-*tert*-butylpuerarin and 6-*tert*-butyl-4'-methoxypuerarin) was achieved through the deoxybenzoin pathway with overall yields of 14.6% and 14.2%. The key intermediate **12** was obtained by de-*tert*-butylation of **10** with trifluoroacetic acid and Friedel-Crafts acetylation of 2-*C*-*β*-D-glucopyranoside **11**. The ring closure of **12** with the $POCl_3$/DMF reagent resulted glucosyl isoflavone formation **13**, which was debenzylated and demethylated by BBr_3 to obtain **14** and **15**. This pathway represents a novel synthetic pathway based on Friedel–Crafts acetylation and Vilsmeier-Haack cyclization to achieve isoflavone *C*-glycosides in high yields.

KEYWORDS: *C*-glycoside; Isoflavone; 6-*tert*-butylpuerarin; deoxybenzoin pathway; 6-*tert*-butyl-4'-methoxypuerarin

Isoflavone *C*-glycosides, in which the sugar moiety is attached by a C–C bond directly to the isoflavone ring, are not easily hydrolyzed in acidic gastric juices compared with *O*-glycosides and aglycone. These glycosides exhibit various biological activities such as radioprotective,[1] anti-myocardial ischemic,[2] mitogenic, and colony-stimulating,[3] and antidiabetic[4] activities. Among these compounds, puerarin, which is found mainly in *Pueraria radix*, show strong anti-myocardial ischemic effects;[5] it expands the coronary artery and cerebrovascular system,[6] significantly reduces myocardial oxygen consumption,[7] and improves cardiac systolic function. To improve the efficacy of puerarin and enhance its concentration in the blood, 6-*tert*-butylpuerarin and 6-*tert*-butyl-4'-methoxypuerarin were totally synthesized to prevent the 7-*O*-*β*-D-glucuronide and 4'-*O*-sulfate formation of the compound in the liver.[8]

Numerous active *C*-glucosylflavonoids, such as vicenin-1,[9] flavocommelin,[10] saponarin,[11] and orientin,[12] were synthesized starting from *C*-glucosyl acetophenones. The condensation of *C*-glucosyl acetophenone **1** with 3,4-*bis*(benzyloxy)benzaldehyde led to the production of *C*-glucosylchalcone **2**, which yielded orientin (Scheme 1)[12] after I_2–dimethyl sulfoxide promoted intramolecular cyclodehydrogenation and a final debenzylation by hydrogenolysis. The synthetic pathway of *C*-glucosylisoflavonoids was highly similar to that of *C*-glucosylflavonoids. 8-*β*-D-glucopyranosylgenistein was synthesized via *C*-glucosylchalcone **3** formation by aldol condensation of *C*-glucosyl acetophenone **1** with 4-(benzyloxy)benzaldehyde. The oxidative rearrangement of chalcone **3** with thallium(III) nitrate yielded a dimethyl acetal **5**, which was then cyclizated by refluxing in 10% HCl and de-*O*-benzylated by hydrogenolysis to give the desired 8-*β*-

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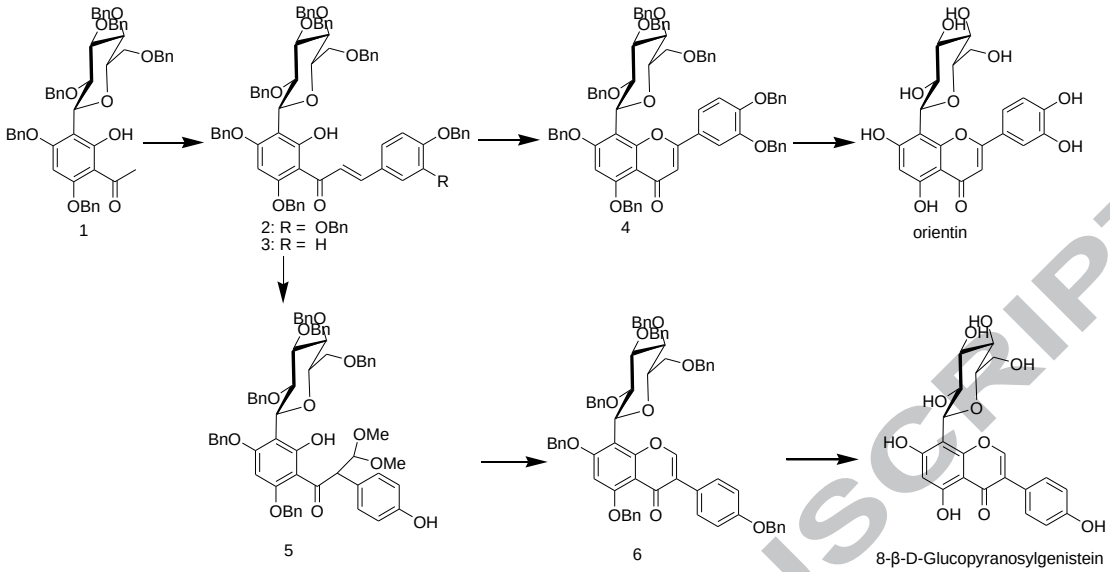


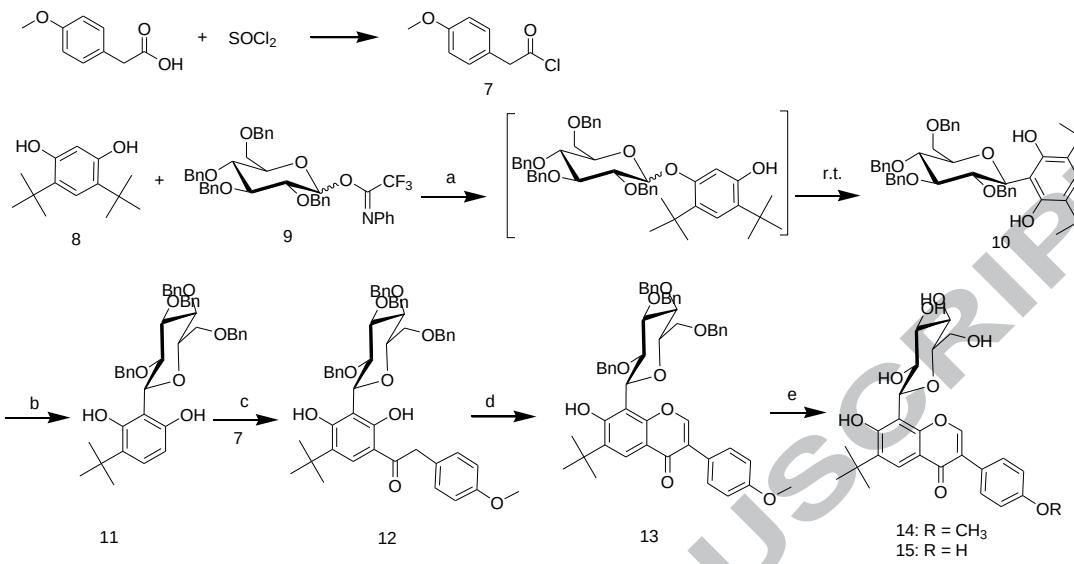
Scheme 1: Total synthesis of a flavone *C*-glycoside (orientin) and an isoflavone *C*-glycoside (8-*β*-D-glucopyranosylgenistein)

D-glucopyranosylgenistein (Scheme 1).[13]

However, previous literature reviews [13-17] showed that the synthesis of isoflavone *C*-glycosides only involves the chalcone pathway starting from *C*-glucosylacetophenone. Moreover, numerous aryl *C*-glycosides without acetyl groups were not used in synthesizing isoflavone *C*-glycosides, thereby limiting the synthesis of various isoflavone *C*-glycosides. Furthermore, highly toxic thallium (III) nitrate is used in the conventional total synthesis of isoflavone *C*-glycosides by oxidative rearrangement of chalcones.[13, 15-17] Therefore, a facile green synthesis method should be developed for synthesizing of *C*-glucosylisoflavonoids. In this paper, two isoflavone *C*-glycosides (6-*tert*-butylpuerarin and 6-*tert*-butyl-4'-methoxypuerarin) was totally synthesized through a simple deoxybenzoin route in five steps for overall yields of 14.6% and 14.2%.

Results and Discussion

Results are shown in Scheme 2. 4,6-di-*tert*-butylbenzene-1,3-diol (**8**) was reacted with 2,3,4,6-tetra-*O*-benzylglucopyranosyl trifluoroacetimidate (**9**) to obtain the desired 2-*C*-*β*- D-glucopyranoside **10** using the O→C glycoside rearrangement methods with TMSOTf as an activator at 0°C;[18, 19] moreover, the reaction mixture temperature was elevated gradually to ambient temperature. We tried to react 2,3,4,6-tetra-*O*-benzyl-glucopyranosyl trifluoroacetimidate with 1-(5-*tert*-butyl-2,4-dihydroxyphenyl)-2-(4-methoxyphenyl)ethanone, but the desired *C*-glycoside was not detected. This failure was due to the electron-withdrawing acyl group in the phenol acceptor that decreased the electron cloud density of the oxygen atoms in the phenolic hydroxyl group, thereby resulting in decreased reactivity with glycosyl donor. 1-(5-*tert*-butyl-2,4-dihydroxyphenyl)ethenone was used as the phenol acceptor, only a minimal amount of the corresponding *β*-*C*-glycoside [*δ*:13.20 (s, 1H; OH-6), 9.31 (s, 1H; OH-4), 7.59 (s, 1H; H-8), 2.59 (s, 3H; H-1), 1.38 (s, 9H; $(CH_3)_3C$)] was obtained.



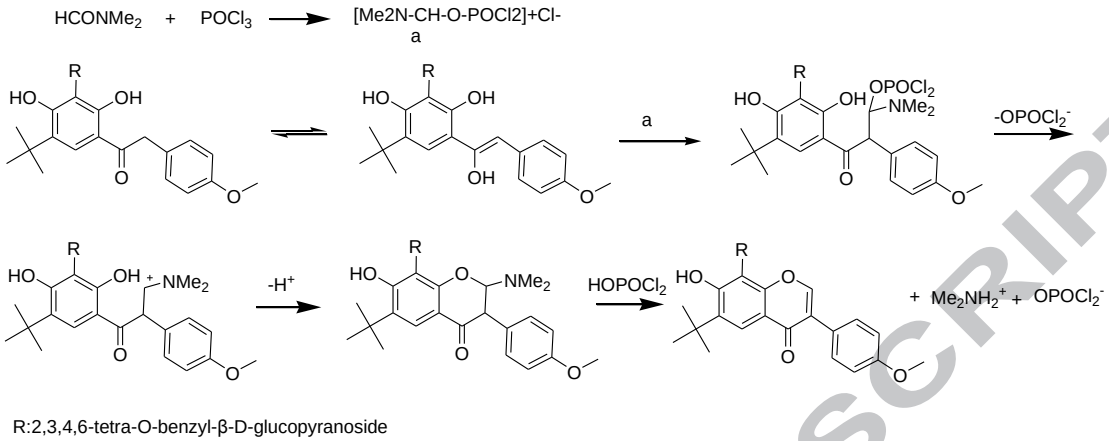
Scheme 2. Total synthesis of two isoflavone *C*-glycosides (6-*tert*-butyl puerarin and 6-*tert*-butyl-4'-methoxypuerarin). Reagents and conditions: a) TMSOTf, CH_2Cl_2, 0°C to room temperature (r.t.), 51.6%; b) CF_3COOH, $Na_2S_2O_4$, r.t., 66.2%; c) $AlCl_3$, Et_2O, r.t., 63.6%; d) $POCl_3$, DMF, 70°C, 68.3%; e) BBr_3, CH_2Cl_2, -78°C, **14** (95.5%), **15** (98.6%).

This low *C*-glycoside yield from this reaction was likely a result of the poor matching of the reactivities of the glycosyl donor and phenol acceptor.

Subsequent de-*tert*-butylation encounters many difficulties. Several conditions of de-*tert*-butylation of *β*-*C*-glycoside **10** have been attempted and were unsuccessful, such as treatment of **10** with HBr,[20] TfOH,[21] $AlCl_3$ in toluene,[22] $AlCl_3$ in dichloromethane,[23] sulfuric acid in toluene,[24] and $AlCl_3$ in nitromethane and toluene.[25] We noticed that 6-*tert*-butyl group can be removed from *β*-*C*-glycoside **10** by stirring at room temperature for 90 min in the presence of trifluoroacetic acid to allow it to synthesize **11**.[26] Subsequently, treating 4-methoxyphenylacetyl acid with thionyl chloride at room temperature for 4 h resulted in the corresponding acid chloride 7,[27] which was reacted with 2-*C*-*β*-D-glucopyranoside **11** in the presence of anhydrous aluminium chloride to result in deoxybenzoin **12** with a 63.6% yield.[18, 28] However, the desired deoxybenzoin was not detected when a de-*tert*-butyl product, which was obtained through the deprotection of the 4,6-di-*tert*-butyl groups in **10**, was reacted with **7** and anhydrous $AlCl_3$. This finding illustrated that the large steric hindrance of the tert-butyl substituent allows the acyl group to be selectively attached to C-6 in the *C*-glycoside **11**.

Upon obtaining the glucosylisoflavone **13** from **12**, we first tried to take advantage of the reaction of deoxybenzoin 12 in DMF with morpholine and triethyl orthoformate at 140 °C; however, a poor yield (12%) of **13** was obtained owing to the destruction of the sugar ring caused by high temperature.[29] An increased glucosylisoflavone yield (68.3%) **13** was prepared by treatment of **12** in DMF with the $POCl_3$/DMF reagent (prepared at 10°C) at 70 °C for 6 h.[30] The reaction mechanism could be as follows: The reaction of DMF with $POCl_3$ leads to the production of carbocation **a**, which

attacks the methylene carbon of deoxybenzoin **12** consecutively with a ring closure to produce glucosylisoflavone **13**, as outlined in Scheme 3. However, this method was



Scheme 3. Proposed reactions and mechanisms for converting deoxybenzoin **12** to glucosylisoflavone **13**

not suitable for any of the deoxybenzoins containing a phloroglucinol structure, because a carbonyl group in the phloroglucinol nucleus that is attacked by the DMF-$POCl_3$ reagent leads to nuclear formylation and polymerization.[30]

The subsequent debenzylation and demethylation of **13** with BBr_3 proceeded rapidly to yield 6-*tert*-butyl-4'-methoxypuerarin **(14)** and 6-*tert*-butyl puerarin **(15)** with 95.5% and 98.6% yields,[31-33] respectively. When isoflavone **13** and BBr_3 were stirred at -78 ° C for 1 h, the de-benzyl product **14** was first produced. The reaction system was then stirred at room temperature for 10 min to yield the demethylated product **15**. Under hydrogenolysis using 10% Pd–C, the debenzylation of **13** did not proceed because of the olefin reduction.[34-35]

Conclusion

Two isoflavone *C*-glycosides (6-*tert*-butyl puerarin and 6-*tert*-butyl-4'-methoxypuerarin) was totally synthesized through a novel synthetic pathway based on Friedel-Crafts acetylation and Vilsmeier-Haack cyclization in five steps with overall yields of 14.6% and 14.2%. The facile green deoxybenzoin route was developed to analyze *C*-glucosylisoflavonoids and applicable to the large-scale synthesis of various isoflavone *C*-glycosides.

Acknowledgment

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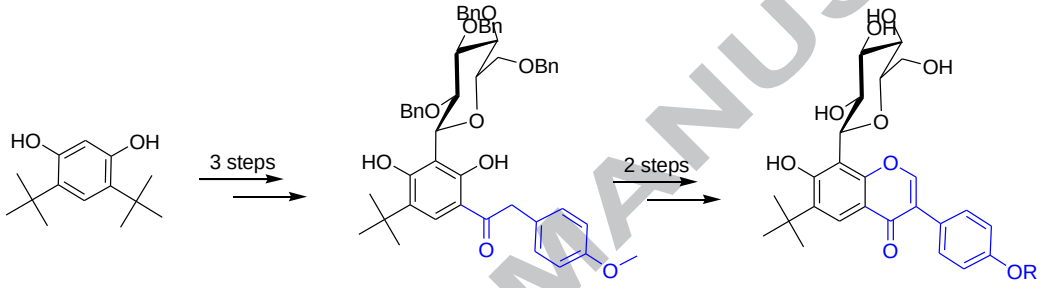
Research highlights

This was a novel synthetic pathway to achieve isoflavone *C*-glycosides.

The total synthesis of 6-*tert*-butyl puerarin was achieved.

The first total synthesis of 6-*tert*-butyl-4'- methoxypuerarin was achieved.

Graphical Abstract



6-*tert*-butyl-4'-methoxypuerarin: R = CH_3, Y: 14.2%
6-*tert*-butyl puerarin : R = H, Y: 14.6%