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Total synthesis of puerarin, an isoflavone *C*-glycoside☆

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Abstract—We completed the first total synthesis of puerarin (**1**), an isoflavone *C*-glycoside. The key intermediate, β-D-glucopyranosyl-2,6-dimethoxybenzene (**9**), was obtained by coupling of a lithiated aromatic reagent (**3**) with pyranolactone (**2**) in 56% yield. Condensation of (**16**) with *p*-methoxybenzaldehyde gave the chalcone (**17**). The protected chalcone (**18**) was cyclized to (**19**) in the presence of $Tl(NO_3)_3$. Demethylation of (**19**) was accomplished by refluxing with TMSI in CH_3CN to give puerarin (**1**).

Puerarin (**1**), a naturally occurring isoflavone *C*-glycoside, was isolated from *Pueraria lobota*,[1] one of the most popular Chinese herbal medicine, traditionally used to reduce febrile symptoms,[2] and also used as an anti-inebriation agent.[3] It also has hypoglycemic activity,[4] and increases coronary artery blood flow.[5] Recent studies showed that puerarin suppresses alcohol drinking in alcohol preferring (P) rats, high alcohol drinking (HAD) rats, and monkeys.[6] Because the glycosidic C–C bond is not cleavable under normal physiological conditions, the pharmacological profile of *C*-glycoside of isoflavone differs significantly from its corresponding *O*-glycoside and aglycone. Although the 7,4′-di-*O*-methyl analog of puerarin was synthesized previously,[7] the total synthesis of puerarin has not been reported. In order to fully explore its pharmacological properties and to establish structure–activity relationships, we developed a synthetic approach to puerarin (**1**).

The key intermediate in our synthetic approach outlined in Scheme 1 is the β-D-glucopyranosyl-2,6-dimethoxybenzene (**9**). In review of the literature, a vast array of methods are available for carbon–carbon bond formation at the anomeric carbon, however, in many cases the sugar ring is attached to the less-hindered position.[8] Grignard reaction of 2,6-dimethoxyphenylmagnesium bromide with tetraacetyl-α-D-glucosyl chloride was reported to gave β-*C*-glycoside (**9**) and its corresponding α-isomer.[7] However, we had to use 12 equiv. of Grignard reagent and the stereoselectivity was poor. α-Isomer was the major product and the overall yield was approximately 30%. In addition, isolation of (**9**), a highly water soluble and magnesium complexed product, was a nightmare. We tried to reduce the equivalents of Grignard reagent, unfortunately it resulted a complex mixture. In order to improve the yield of the key intermediate (**9**), a β-isomer of D-glucopyranosyl-2,6-dimethoxybenzene, we employed coupling reaction of a lithiated aromatic reagent (**3**) with a benzyl protected glycopyranolactone (**2**) followed by hydride reduction using TESH and $BF_3{\cdot}Et_2O$ to give predominately the β-isomer (**6**).[9a] Interestingly, it was reported in the literature that the same lithium reagent (**3**) failed to react with (**2**) to give the corresponding (**6**).[9b] It was assumed that the failure of the reaction might result from enolization of the lactone. In our hands, β-*C*-glycoside (**6**) was obtained stereoselectively in 56% overall yield upon coupling of lactone (**2**) with 1.6 equivalents of lithium reagent (**3**), and followed by hydride reduction with TESH in the presence of $BF_3{\cdot}Et_2O$. Hydrogenolysis of (**6**) using Pd/C as catalyst in methanol gave (**9**) in almost quantitative yield. The spectroscopic and physical data were identical to the product (**9**) obtained from Grignard reaction and no trace of α-isomer was found.

We also tried to react pyranolactone (**2**) with various sterically hindered lithium reagents. The mono-methoxy analog (**10**) was reported by coupling of 2-methoxy phenylmagnesium bromide (**12**) and tetraacetyl-α-D-glucosyl bromide (**11**).[10] When we repeated the same

Keywords: puerarin; total synthesis; natural product; isoflavone *C*-glycoside.

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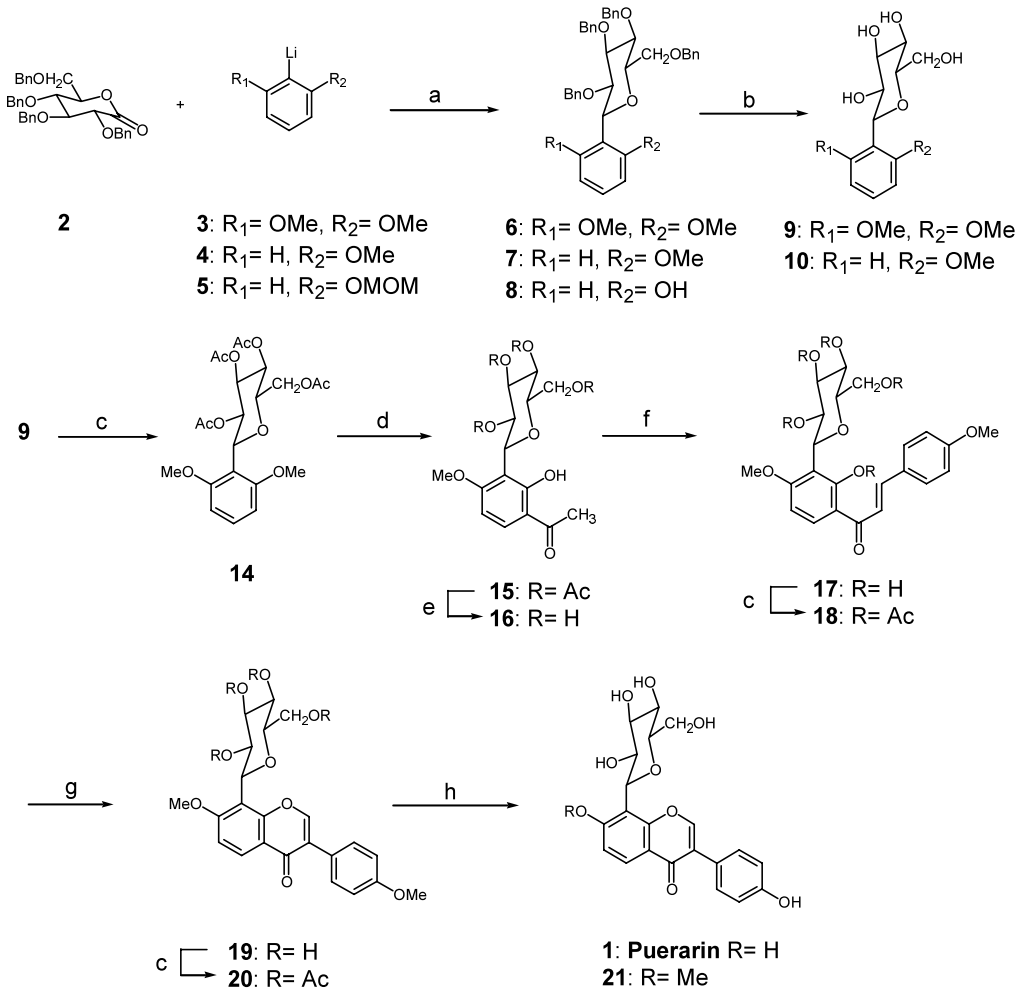
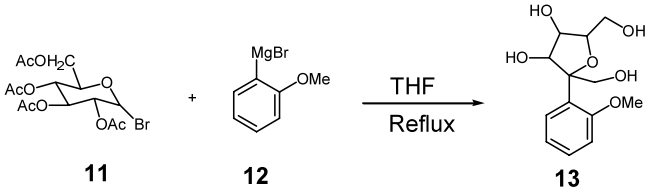


Scheme 1. *Reagents and conditions*: (a) THF, −78 to −10°C; 2. TESH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78°C to rt; (b) Pd/C, H_2; (c) Ac_2O, Py; (d) $AlCl_3$, AcCl, Et_2O; (e) 1. Na, MeOH; 2. H+ resin; (f) *p*-$MeOC_6H_4CHO$, NaOH, EtOH; (g) 1. $Tl(NO_3)_3$, MeOH/$CH(OCH_3)_3$; 2. 10% HCl, MeOH, reflux; (h) TMSI, CH_3CN, reflux, 5 days.

Grignard reaction, the major product showed the same ^1H and ^{13}C NMR data as reported in the literature. But a close examination of its DEPT spectrum, we found two methylene carbons in the sugar region and proved to be a *C*-glucofuranoside (**13**) as revealed by COSY, HMQC and HMBC analyses (Scheme 2). Apparently, it was derived from sugar ring contraction under refluxing Grignard reaction condition.



Scheme 2.

Following the previous coupling procedure, using lithium reagent (**4**), the corresponding β-*C*-glycoside (**7**) was obtained in 65% yield after reduction with TESH and $BF_3{\cdot}Et_2O$. Hydrogenolysis of (**7**) proceeded smoothly to give (**10**). The structure of (**10**) was confirmed unambiguously by DEPT, COSY, HMQC and HMBC analyses and no trace of α-isomer was present. In the case of MOM protected aryl lithium (**5**), it reacted smoothly with pyranolactone (**2**) to yield β-*C*-glycoside (**8**). MOM group was cleaved by $BF_3{\cdot}Et_2O$ during the reduction.

Following the literature procedure,[7] acetylation of glycoside (**9**) gave tetraacetate (**14**). Reaction of tetraacetate (**14**) in anhydrous ether with acetyl chloride in the presence of anhydrous $AlCl_3$ gave the acyl compound (**15**). During the acylation the methoxyl group *ortho* to the acyl group was also demethylated. After removal of acetyl groups, compound (**16**) was condensed with *p*-methoxybenzaldehyde to give chalcone (**17**). Subsequent acetylation provided protected chalcone (**18**). Oxidative rearrangement of (**18**) with $Tl(NO_3)_3$ in a mixed solvent of methanol and trimethyl orthoformate (1:1 v/v), followed by refluxing in methanol with 10% HCl gave desired 7,4′-di-*O*-methylpuerarin (**19**) in 84% yield.[7] Subsequent demethylation encountered many difficulties. Several conditions of demethylation of (**19**) were attempted and

unsuccessful. For instance, treatment of (**19**) with BBr_3,[11] BCl_3,[12] Ph_2PLi in THF,[13] pyridinium tribromide in xylene,[14] EtSNa in DMF,[15] refluxing in concentrated HBr,[16] 48% HBr with NaI at 110°C,[17] NaCN in DMSO at 125°C,[18] and $AlBr_3$ in refluxing EtSH.[19] We noticed that upon refluxing of (**19**) with Me_3SiI in $CHCl_3$[20] for 4 days gave a small amount of 7-*O*-methylpuerarin (**21**), unfortunately, a prolonged reflux failed to improve the yield and further demethylation at C-7 position never happened. Finally, when CH_3CN was used as solvent, refluxing with Me_3SiI for 5 days, starting material **19** was consumed and converted to the desired target compound (**1**)[21] in 35% yield along with partially demethylated 7-*O*-methylpuerarin (**21**) in 39% yield after column chromatography. Further prolonging the reaction time did not improve the yield. The overall yield of the synthesis of (**1**) was 10%. The spectroscopic and physical data were identical to the natural sample of puerarin (**1**). In order to improve the yield at the final step, other protecting groups are being examined.

Acknowledgements

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21. Spectral data for compound **1**: solid, mp: 184–186°C; HRMS *m/e* for $C_{21}H_{20}O_9$+H calcd 417.1185, found 417.1174, **^{1}H NMR** (CD_3OD, 300 MHz, ppm), δ 3.40–3.60 (3H, m), 3.72–3.87 (2H, m), 4.12 (1H, s, br), 5.09 (1H, d, $J=9.9$ Hz, H-1″), 6.85 (2H, d, $J=8.7$ Hz, H-2′ and H-6′), 6.99 (1H, d, $J=9$ Hz, H-6), 7.37 (2H, d, $J=8.4$ Hz, H-3′ and H-5′), 8.06 (1H, d, $J=8.7$ Hz, H-5), 8.20 (1H, s, H-2); **^{13}C NMR** (CD_3OD, 75.4 MHz, ppm), δ 62.74, 71.68, 72.98, 75.63, 79.98, 82.72, 113.1, 116.23, 116.58, 118.45, 124.16, 125.48, 128.07, 131.34, 154.46, 158.64, 162.97, 178.25.