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The First Total Synthesis of Isoliquiritin

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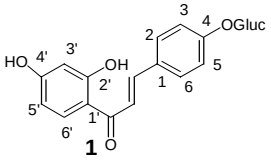
Abstract: A first total synthesis of isoliquiritin was accomplished starting from *p*-hydroxybenzaldehyde and 2,4-dihydroxyacetylphenone. The key step is condensation reaction. In synthetic process need not protect the hydroxy group of reacting substance.

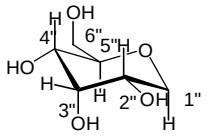
Keywords: Synthesis, isoliquiritin, flavonoid glycosides.

Isoliquiritin **1** was isolated from the roots of *G. uralensis* and also from other plants, and has been reported to exhibit antitumour, anti-HIV, curing hepatitis activities[1, 2], use as anti-allergic drug[4], and for sweetening[3]. It has been used for a strong inhibitor of hyaluronidase[4].



1

Gluc=



The synthesis of isoliquiritin (4-glucopyranoxy-2′,4′-dihydroxy chalcone) has not been reported, because there is no suitable synthetic methods for these compounds. It may have two reasons: (1) If we synthesize the chalcone then glucosylation, it is difficult to get target compound, because the glucosylation is difficult to 4-OH but easy to 4′-OH. (2). The reaction of 2,4-dihydroxyacetylphenone with compound **3** to give the desired nautral product **1** by normal methods[5] (condensation of acetylphenone with suitably substituted benzaldehyde in alkaline condition to give the chalcone) is not feasible because of the deacetylation in alkaline condition may give many by-products. Herein we introduce a facile and feasible synthetic method (as shown in **Scheme 1**) for the synthesis of isoliquiritin. This route involved the preperation of compound **3** and **3** was condensed with ketone **4** to give chalcone **5**. Isoliquiritin was obtained by deacetylation of chalcone **5.** In synthetic course it did not need to protect the hydroxy group of reacting substance. So this method for synthesis of isoliquiritin is facile and effect.

The compound **3 (**prepared from *p*-hydroxybenzaldehyde and α-acetylbromo-

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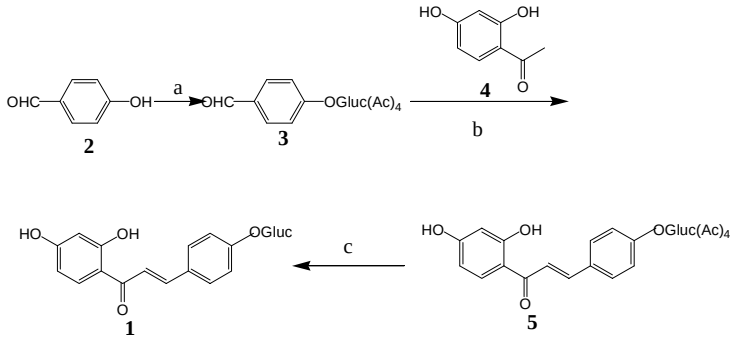
glucose by using anhydrous K_2CO_3 in a solvent mixture of DMF/acetone (3:2 v/v) and dodecyltrimethylammonium bromide (DTMAB) as a phase transfer catalyst) was condensed with 2, 4-dihydroxyacetylphenone (**4)** in the mixture of H_3BO_3, piperidine and SiO_2 in diglyme under 120°C for 8 h, to gave the chalcone **5** in 33% yield. Chalcone **5** was deacetylated by using anhydrous $Zn(OAc)_2$ in methanol in good yield to give isoliquiritin (The spectra data is in accordance with that of the natural sample which was reported in the literature[1,6]).

Scheme 1



Reagents and conditions: a) α-acetylbromoglucose/DMF/acetone (3;2 v/v)/K_2CO_3/DTMAB, reflux, 5 h, 80~85%; b) H_3BO_3/piperidine/SiO_2/diglyme, 120°C, 8 h, 33%; c) $Zn(OAc)_2$/MeOH, reflux, 7 h, 95%.

References and Notes

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6. The spectra data of **1**: Amorphous yellow powder, IR: (KBr cm^{-1}) 3346, 2927, 1780, 1594, 1511, 1420, 1370, 1315, 1228, 1117,1072,1029; ^1H NMR (400 MHz, DMSO-d_6 δ_{ppm}): 13.53(s,1H, -OH), 8.19 (d,1H, *J*=9.0Hz, H-6′),7.87 (d,1H, *J*=15.2Hz, H-β), 7.87 (d,2H, *J*=9.0Hz, H-2, 6), 7.77 (d,1H, *J*=15.2Hz, H-α), 7.08 (d,2H, *J*=9.0Hz, H-3, 5), 6.41 (dd, 1H, *J*=9.0,2.3Hz, H-5′), 6.28 (d,1H, *J*=2.3Hz, H-3′),4.98(d,1H, *J*=7.2Hz,H-1″) ,5.37(d,1H, *J*=4.3 Hz,2″-OH),5.50 (m,1H, 3″-OH), 5.10 (d,1H, *J*=5.0Hz,4″-OH), 4.6 (m,1H, 6″-OH), 3.68-3.70 (m,1H, H-6″a), 3.42-3.47 (m,1H, H-6″b), 3.38-3.40 (m,1H, H-5″), 3.22-3.30(m,1H, H-2″) ,3.22-3.30(m,1H, H-3″),3.15-3.19(m,1H, H-4″); ^{13}C NMR (50 MHz, DMSO-d_6 δ_{ppm}):191.5(C=O), 119.1(C-α),143.6(C-β),113.0(C-1″) ,165.1(C-2″),102.3(C-3″),165.8(C-4″),108.2(C-5″) , 133.1(C-6″),128.4(C-1),130.8(C-2),116.5(C-3),159.5(C-4),116.5(C-5),130.8(C-6),100.0(C-1″),73.2(C-2″),77.2(C-3″),69.7(C-4″),76.6(C-5″),60.7(C-6″);FAB-MS(*m/z*) 457 $(M+K)^+$, 295 $(M+K-162)^+$.

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