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Note

Facile synthesis of acacetin-7-*O*-β-D-galactopyranoside

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ABSTRACT

Acacetin-7-*O*-β-D-galactopyranoside (**1**), a natural flavonoid isolated from flower heads of *Chrysanthemum morifolium*, has been reported to inhibit the replication of HIV in H9 cells. We achieved the total synthesis of compound **1** by employing a one-pot synthesis of the aglycon. The key reactions in this approach include the modified Baker–Venkataraman reaction and regio- and stereoselective *O*-glycosylations.

Acacetin-7-*O*-β-D-galactopyranoside (**1**) was first isolated in 1994 by Lee and co-workers from a methanol extract of the flower heads of *Chrysanthemum morifolium*[1] along with several other flavonoids. The flavonoids were evaluated for the inhibition of HIV growth in H9 cells. A typical example of this group of flavonoids is acacetin-7-*O*-β-D-galactopyranoside **1**, which is a glycoside incorporating an aglycon moiety and a galactopyranoside sugar in its structure.

It has recently become more apparent that most of the important classes of drugs, especially those derived from natural products, are glycosides having a sugar moiety linked to an aglycon through an *O*- or *C*-glycosidic bond.[2] In our continued efforts to use natural products only as synthetic templates and thereby replace the original plant sources with synthetic ones, we have developed a synthetic approach providing access to acacetin-7-*O*-β-D-galactopyranoside in good yields. The approach is facile and flexible and thus can be applied to the synthesis of other related flavonoids by simple substitution of the desired groups. The starting materials used are simple and cheaply available from commercial sources, thus making our approach economically effective.

Synthesis of aglycon: 2-*p*-methoxybenzyl-5,7-dihydroxychromone (2)

Recently, one-pot syntheses of various kinds of flavones utilizing a modified Baker–Venkataraman rearrangement[3,4] have received considerable attention. Of particular relevance here is a work by Boumendjel et al. who succeeded in the syntheses of flavones by refluxing 2,6-dihydroxyacetophenone with one equivalent of benzoyl chloride in the presence of K_2CO_3 in dry acetone, resulting in a moderate yield of the desired flavones (52%). However, the reaction also produced a small amount of the corresponding phenolic ester as a by-product.[5]

More interestingly, Buckle et al. have recently reported a one-pot syntheses of flavones by heating 2-hydroxyacetophenone with 3 equiv of benzoyl chloride using a K_2CO_3/acetone system resulting in an improved yield of the desired flavone to 65%. Nevertheless, a 3-benzoyl substituted flavone was produced in 20% yield as a by-product of the reaction.[6]

Inspired by the two reports above, we embarked on the synthesis of compound **1** with a vision to employ this one-pot strategy for the synthesis of our desired aglycon **2**. Gratifyingly, the K_2CO_3/acetone system using 1.5 equiv of *p*-methoxybenzoyl chloride under argon atmosphere gave us the best results as it led exclusively to the desired aglycon **2** in a 72% yield. The structure of aglycon **2** was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopies, and further verified by MS and IR spectroscopic measurements. The mass spectrum of **2** was characterized by a molecular ion peak at *m/z* 285.27 (M+1). The IR spectrum showed sharp peaks at 1737 cm^{-1} and 1651 cm^{-1} indicating the presence of a carbonyl

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group and carbon–carbon double bonds, respectively. A broader peak at 3161 cm^{-1} indicated the presence of –OH groups.

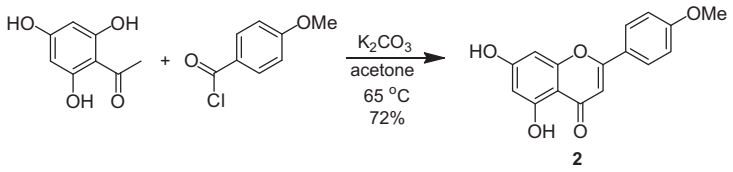
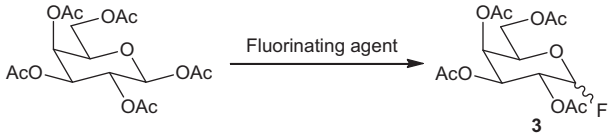


Table 1



Entry	Fluorinating agent	Solvent	Yield[a] (%)	α/β[b]
1	70% HF–pyridine	No solvent	82	96/4
2	DAST	CH_2Cl_2	87	67/33

[a] Isolated yield.
[b] Determined by ^1H NMR analysis.

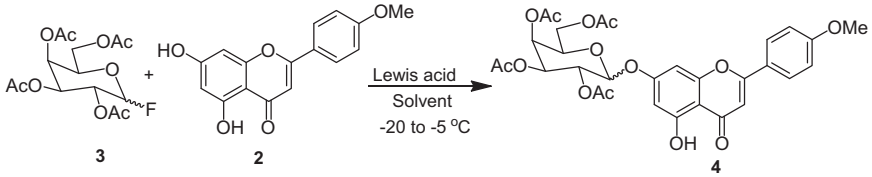
Synthesis of the glycosyl donor 3

Having succeeded in the synthesis of the desired glycosyl acceptor **2**, the next task was to prepare the glycosyl donor to be used in the glycosylation. Halogenated sugars are known and have been applied successfully in various glycosylation reactions. In particular, fluorinated sugars are good candidates. The thermal and chemical stabilities conferred by the strength of the carbon–fluorine bond are advantageous, resulting in the successful employment of fluorinated sugars as glycosyl donors under various reaction conditions.[7] With this concept in mind, we embarked on the fluorination of 1,2,3,4,6-pentaacetylated-β-D-galactopyranoside. The glycosyl fluorides were prepared using conventional methods either by treating the *O*-pentaacetylated-β-D-galactopyranoside with 70% HF–pyridine or with diethylaminosulfur trifluoride (DAST). Treatment with 70% HF–pyridine for 4 h at room temperature afforded the thermodynamically stable α anomer along with the β anomer in an α/β ratio of 96:4. On the other hand, treatment with DAST afforded the two anomers in an α/β ratio of 67:33 (Table 1). The use of DAST as a fluorinating agent was particularly important when the desired anomer was β because the procedure allowed the isolation of the β anomer after recrystallization from ethanol. The ^1H NMR spectrum for the α anomer featured a characteristic doublet signal of the anomeric proton at 5.87 ppm with a coupling constant $J = 2.8$ Hz, which is typical for an equatorial–axial coupling of H-1–H-2, whereas the β anomer was characterized by a doublet signal at 5.70 ppm, $J = 8.4$ Hz, signifying axial–axial coupling of H-1–H-2. These observations are in agreement with the reported data in the literature.[8,9]

Regio- and stereoselective *O*-glycosylation of aglycon 2 with glycosyl fluoride 3

Aglycon **2** was treated with 1 equiv of acetylated 1-fluoro-D-galactopyranoside **3** in the presence of 10 equiv (by weight) of 4 Å molecular sieves in dichloromethane. The reaction was catalyzed by 0.1 equiv of Lewis acid to give the corresponding β glycosides in good to high yields (Table 2). Glycosylation was found to be highly regioselective with glycosylation at the –OH group on C-7 predominating over glycosylation at the –OH on C-5. This regioselectivity for –OH on C-7 can be explained by both steric effects as well as electronic effects. The –OH group at C-7 is less sterically hindered compared with the –OH group at C-5, thus making it more favorable toward glycosylation. Moreover, the –OH group at C-7 is more electronically favored toward glycosylation owing to the fact that the neighboring carbonyl group at C-4 renders the –OH at C-5 less reactive toward glycosyl donors. Screening of Lewis acids indicated that $BF_3{\cdot}Et_2O$ and $ZnCl_2$ were more effective in catalyzing the reaction than others tested. The phenomenon that β glycosyl donors are less stable, and hence more reactive, toward glycosyl acceptors was observed. The stereochemistry of the

Table 2



Entry	Anomeric config. of **3**	Solvent	Lewis acid	Yield[a] (%)	α/β[b]
1	α	CH_2Cl_2	$BF_3{\cdot}Et_2O$	68	12:88
2	α	CH_2Cl_2	$SnCl_4$	64	16:84
3	β	CH_2Cl_2	$ZnCl_2$	76	4:96
4	β	CH_2Cl_2	$BF_3{\cdot}Et_2O$	78	3:97
5	α and β (1:1)	CH_3CN	$ZnCl_2$	69	8:92

[a] Isolated yield after column chromatography.
[b] Ratio was determined by ^1H NMR analysis.