Unexpected Desilylative-alkylation of 3-*O*-*tert*-Butyl-dimethylsilyl Galangin

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Biological activities of flavonoids have led to the creation of many therapeutic forms of plant flavonoids.[1] Data on the chemical structures of a variety of flavonoids have been obtained, and the fundamental mechanisms of action of flavonoids as antioxidants, anti-inflammatories, cardiotonics, radioprotectors, antitumor agents and antiviral agents have been identified.[2] However, little effort has been expended on synthetic flavonoid analogues presumably due to the difficulties in controlling the regiochemistry of the flavonoids. As a part of our ongoing efforts directed at the structure-activity relationship studies (SARs) of naturally occurring flavonoids, we have been interested in the regioselective alkylation of flavanones (naringenin, **1**, Fig. 1) and flavones (apigenin, **2**, Fig. 1).[3] Herein, we report our recent attempts on the regioselective alkylation of a flavonol, galangin (**3**, Fig. 1).

The flavonol has an additional hydroxyl group at the 3 position of the ring C (Fig. 1), which is known to be the primary site of alkylation.[5] Thus, we envisaged that 3-*O*-protected galangin would be selectively converted into the 7-*O*-alkyl galangin under alkylating conditions, and set out to synthesize the key intermediate **4** starting from the commercially available chrysine **7** (Scheme 1).

Treatment of chrysine **7** with Me_2SO_4 and K_2CO_3 in acetone provided the 5,7-di-*O*-methyl chrysine **8**, which was subjected to the α-hydroxylation conditions[6] to give the 5,7-di-*O*-methyl galangin **9** in 60% yield. Protection of the 3-OH group with TBDMSCl and DMAP in anhydrous pyridine followed by Lewis acid-mediated demethylation provided the key intermediate **4**, which was smoothly transformed into the alkylated product **5** upon treatment with substituted benzyl bromides (3-ClBnBr, 4-ClBnBr and 3-CNBnBr) and K_2CO_3 in acetone. However, under the alkylation conditions, the TBDMS protecting group was lost, and the NOESY analysis of **5** showed that there was no nOe correlation between the benzylic and A-ring protons (H6 and H8) (Fig. 2),[7] which implied that the alkylation did not take place at the 7-*O* position. Instead, the benzylic protons of **5** showed strong nOe correlation with aromatic protons at the B-ring, which confirms that the alkylation site is 3-*O* rather than 7-*O*. Protection of the 3-hydroxy group of **9** with TBDPSCl instead of TBDMSCl was attempted to provide more stable silyl ether but resulted in the same desilylative alkylation product **5** (data not shown).

Based on this result, we presumed that the unexpected 3-*O*-alkylated products were formed *via* desilylative-alkylation mechanism (Scheme 2). The flavonoid is deprotonated with K_2CO_3 to give an anion **11**, which resonanced to the corresponding chromen-4-ol anion **12**. The alkoxide ion then attacks the nearby TBDMS group to result in silyl migration (3-*O* to 4-*O*). The enolate anion at the 3-position **13**, thus formed, attacks benzylic bromide to provide the 3-*O*-alkyl product **14**, which resonances back to the stable aromatic form with concurrent loss of the TBDMS group upon aqueous work-up.

In order to verify the desilylative-alkylation mechanism.

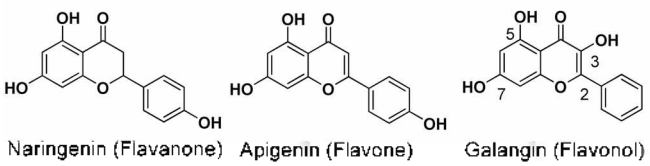


Figure 1. Structures of naringenin (flavanone), apigenin (flavone) and galangin (flavonol).

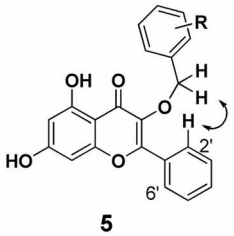
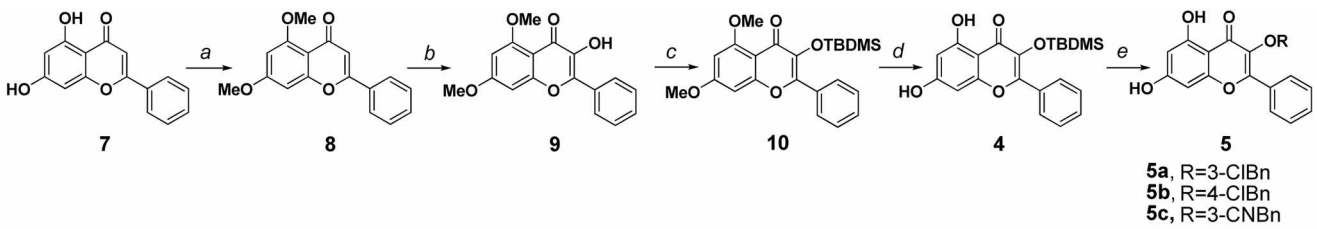
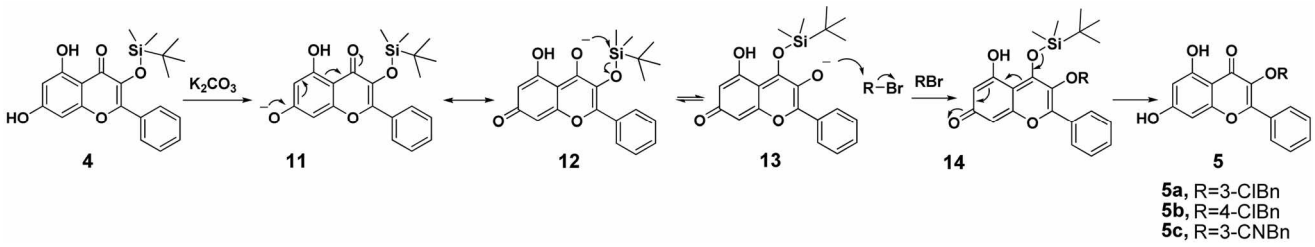


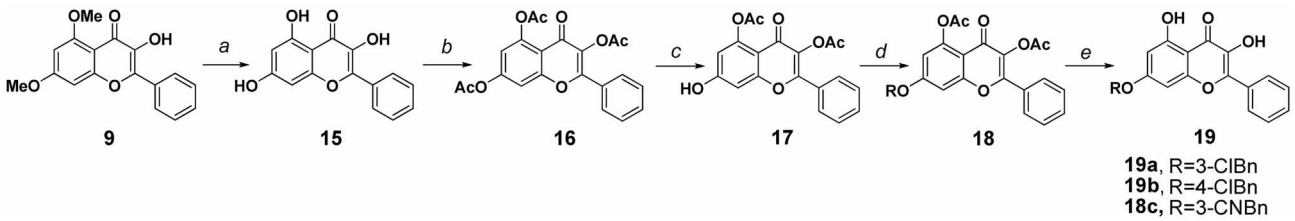
Figure 2. 2D-NOESY result of the compound **5**.



Scheme 1. Synthesis of 3-*O*-alkyl galangin. *Reagents and Conditions*: a) Me_2SO_4, K_2CO_3, acetone, rt; b) LDA, $B(OMe)_3$, AcOH, H_2O_2, THF, −78 °C; c) TBDMSCl, DMAP, pyr, 60 °C; d) BBr_3, CH_2Cl_2, rt; e) RBr, K_2CO_3, acetone, rt.



Scheme 2. Proposed mechanism of desilylative-alkylation.



Scheme 4. Synthesis of 7-*O*-alkyl galangin. *Reagents and Conditions*: a) BBr_3, CH_2Cl_2, rt; b) Ac_2O, pyr, rt; c) Imidazole, PhSH, NMP, 0 °C; d) RBr, K_2CO_3, acetone, rt; e) NH_3/MeOH, rt

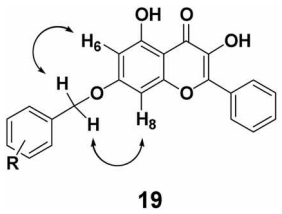


Figure 3. 2D-NOESY result of compound **19**.

we installed a different protecting group at the 3-*O* position (Scheme 3). Thus, 3,5-di-*O*-acetyl galangin **17** was prepared by peracetylation of galangin **15** followed by regioselective deacetylation[8] of 7-*O*-acetyl group. Alkylation of **17** with substituted benzyl bromides and K_2CO_3 in acetone provided the corresponding alkylated product **18** without loss of the acetyl protecting group.

Treatment of **18** with methanolic ammonia gave the free galangin derivative **19**[9] of which NOESY analysis (Fig. 3) showed that the benzylic protons strongly correlate with A-ring protons (H6 and H8) but not with the C-ring aromatic protons. This result is clear evidence that the alkylation proceeded at the 7-*O* position.

In summary, in our recent attempt to synthesize 7-*O*-alkyl galangin through alkylation of 3-*O*-*tert*-butyl-dimethyl-silylgalangin, we observed a clean transformation to the unexpected 3-*O*-alkyl product. A rational explanation to this unusual finding was proposed as the desilylative-alkylation mechanism, and the key role of the 3-*O*-silyl protecting group was demonstrated by the alkylation of 3,5-di-*O*-acetyl galangin which gave the 7-*O*-alkyl product.

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7. *Preparation of compound* **5**: To a stirred mixture of **4** (100 mg, 0.26 mmol) and K_2CO_3 (40 mg, 0.29 mmol) in acetone (6 mL) was added 3-cyano benzyl bromide (59mg, 0.29 mmol) in a dropwise fashion. The reaction mixture was stirred at rt for 2 days, neutralized with 1 N HCl solution, and then extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and after filtration, the filtrate was concentrated under reduced pressure to give a dark yellow syrup. Purification by flash chromatography on silica gel, eluted with a mixture of hexane/EtOAc (2:1 v/v), provided **5c** as a yellow powder (62%): ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 12.6 (s, 1H, -OH), 8.01 (dd, J = 7.4, 1.4 Hz, 2H), 7.56-7.51 (m, 3H), 7.37 (s, 1H), 7.34-7.30 (m, 3H), 6.51 (d, J = 1.8 Hz, 1H), 6.30 (d, J = 1.8 Hz, 1H), 5.14 (s, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 179.6, 165.2, 163.3, 158.2, 157.6, 139.6, 138.5, 132.8, 132.7, 132.5, 131.9, 131.4, 130.2, 129.5, 129.4, 119.1, 113.1, 106.1, 99.7, 94.9, 94.7, 73.7.
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9. *Preparation of compound* **19**: To a solution of **17** (200 mg, 0.56 mmol) and K_2CO_3 (312 mg, 2.26 mmol) in acetone (10 mL) was added 3-cyano benzyl bromide (332 mg, 1.69 mmol). The reaction mixture was stirred for 3 h at rt and then filtered washing with acetone. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (Hex:EtOAc = 2:1) to give **18c** as an off-white powder (53%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.81 (m, 2H), 7.75 (s, 1H), 7.67-7.69 (m, 2H), 7.48-7.55 (m, 5H), 6.91 (d, J = 2.4 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 5.18 (s, 2H), 2.44 (s, 3H), 2.31 (s, 3H). A mixture of **18c** (140 mg, 0.3 mmol) obtained above and methanolic ammonia (7 mL) was stirred for 5 h at rt. The reaction mixture was concentrated under reduced pressure to give **19c** as a yellow powder (73%): ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.27-8.35 (m, 2H), 7.96 (s, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H), 7.68 (t, J = 7.9 Hz, 1H), 7.51-7.61 (m, 3H), 6.89 (s, 1H), 6.50 (s, 1H), 5.41 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d6) δ 176.9, 164.2, 160.9, 156.6, 146.7, 138.3, 137.9, 132.9, 132.3, 131.5, 131.2, 130.5, 130.2, 128.9, 127.9, 118.9, 111.9, 104.9, 98.5, 93.4, 69.1.