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

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Received May 14, 2008

Key Words : Desilylative-alkylation, Galangin, Flavonoid

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,

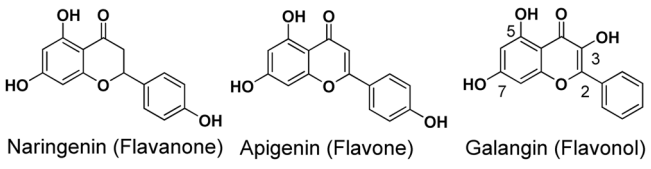


Figure 1. Structures of naringenin (flavanone), apigenin (flavone) and galangin (flavonol).

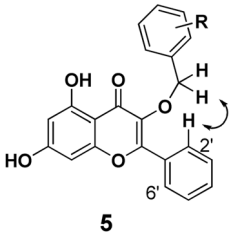
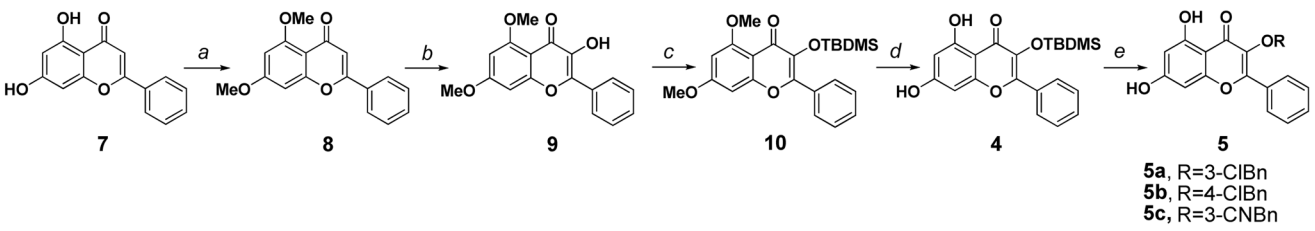
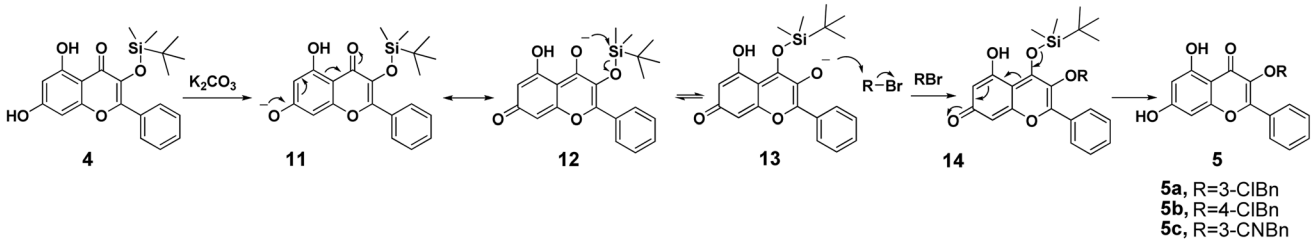


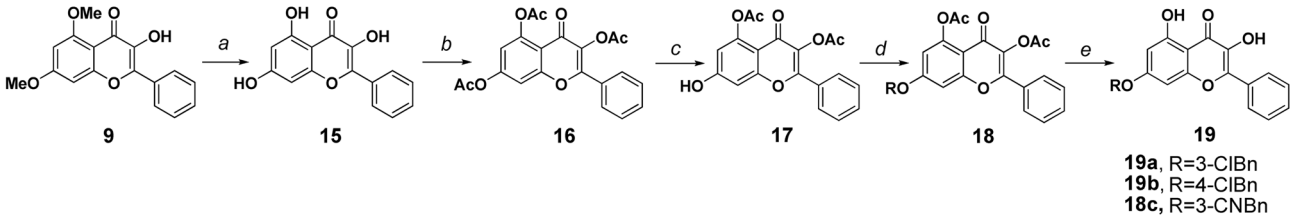
Figure 2. 2D-NOESY result of the compound **5**.



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

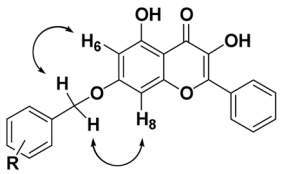


Figure 3. 2D-NOESY result of compound **19**.

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.

Acknowledgments. This work was supported by grant KRF-2007-313-C00476 from the Korea Research Foundation, Republic of Korea (MOEHRD, Basic Research Promotion Fund) and by grants from Biogreen 21 (Korea Ministry of Agriculture and Forestry), and the second Brain Korea 21 (Korea Ministry of Education). JK and HSL are supported by the second Brain Korea 21.

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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.