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Synthesis of quercetin 3-*O*-(2″-galloyl)-α-L-arabinopyranoside

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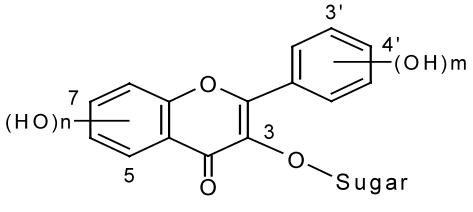
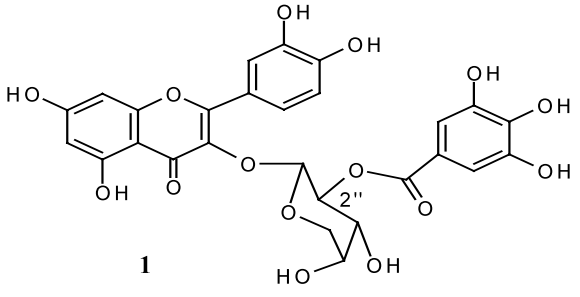
Abstract—Quercetin 3-*O*-(2″-galloyl)-α-L-arabinopyranoside, a plant flavonol glycoside showing HIV-1 integrase inhibition, antibacterial, and antioxidant activities, was synthesized, with the glycosylation of the flavonol 3-OH being explored.

More than 1000 flavonol *O*-glycosides have so far been isolated, mostly, from higher plants.[1] The majority of these structures (~80%) have a sugar linkage at the 3-OH,[1] and over 20% possess one or more acyl groups attached through the sugar residues, which further enhances the structural diversity.[1] While flavonol *O*-glycosides play a variety of important roles in the growth and development of plants,[1,2] e.g. as inter-species signaling molecules, they have also demonstrated a wide range of properties which might be beneficial to humans, such as antimicrobial, anti-cancer, and radical-scavenging activities.[1,2] In contrast to the wide occurrence and importance of flavonol glycosides, synthetic studies toward this important group of natural products are surprisingly rare.[3–5] Quercetin 3-*O*-(2″-galloyl)-α-L-arabinopyranoside **1**, representing a typical structure of a flavonol *O*-glycoside, has been isolated from *Lasiobema japonica*,[6] *Eucalyptus rostrata*,[7] and *Acer okamotoanum*.[8] This compound shows a potent antibacterial activity (against *E. coli* B at 100 ppm concentration)[6] and an antioxidant activity (against peroxidation of rabbit erythrocyte membrane ghost with $IC_{50}=34$ μM).[7] Moreover, inhibition against HIV-1 integrase ($IC_{50}=18.1$ μg/mL) is also demonstrated, which is the highest among ten of its congeners.[8] Here we report the synthesis of flavonol glycoside **1**.

Since the flavonol quercetin is commercially available, the synthesis of glycoside **1** should simply involve protective manipulation of the hydroxyls and glycosylation of the 3-OH of the quercetin derivatives. The 7-OH and 4′-OH of polyhydroxyflavones are known to have preferential reactivity toward nucleophilic substitution, thus using Jurd's procedure,[9] 7-*O*-benzylquercetin **2** and 7,4′-di-*O*-benzylquercetin **11** were readily obtained via controlled benzylation of quercetin pentacetate. Ketal protection of the *ortho*-3′,4′-OH on **2** would leave the 3 and 5-OHs free, and a selective glycosylation on the 3-OH was then expected due to the chelation of the 5-OH with the 4-carbonyl group.[3] We chose the lipophilic cyclohexylidene group to block the catechol with the intention of increasing the solubility of the quercetin derivative in the glycosylation solvents (Scheme 1). In the previous syntheses of flavonol *O*-gly-



n = 0-4, m = 0-3
Flavonol 3-*O*-glycosides



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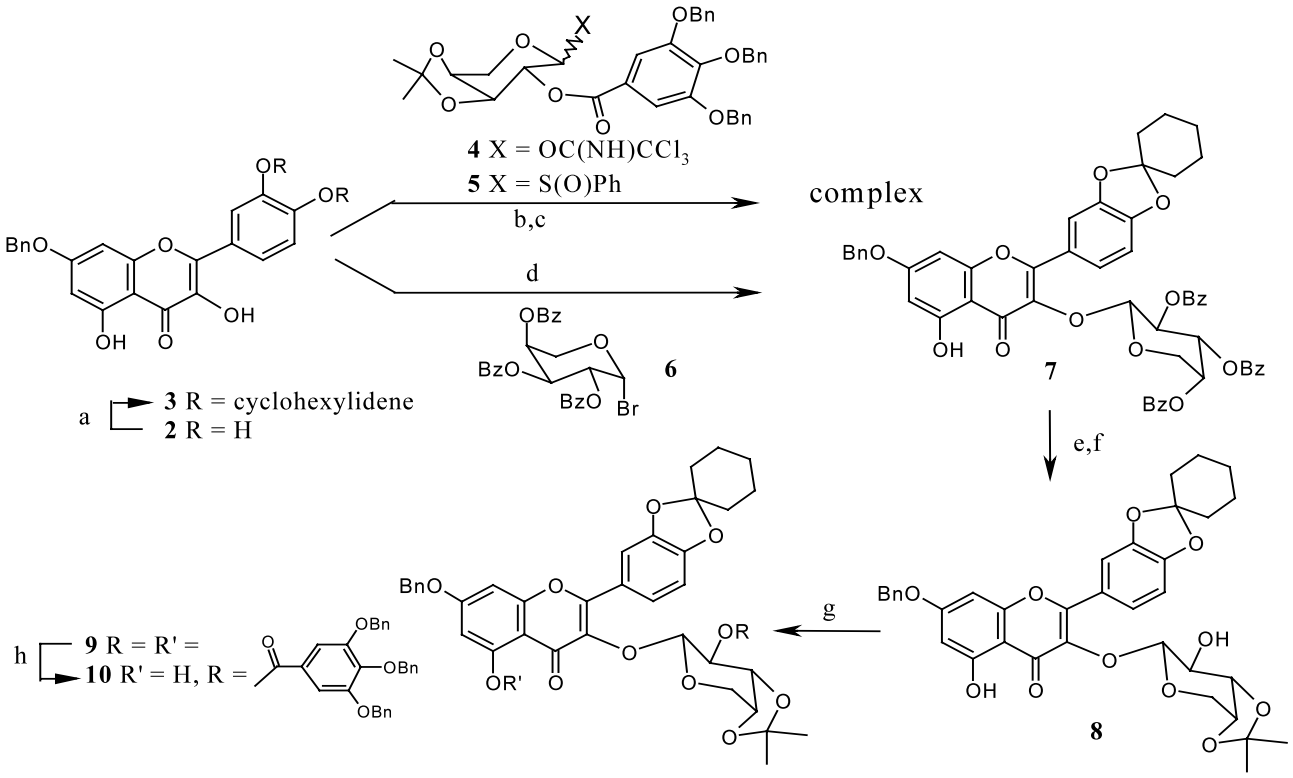
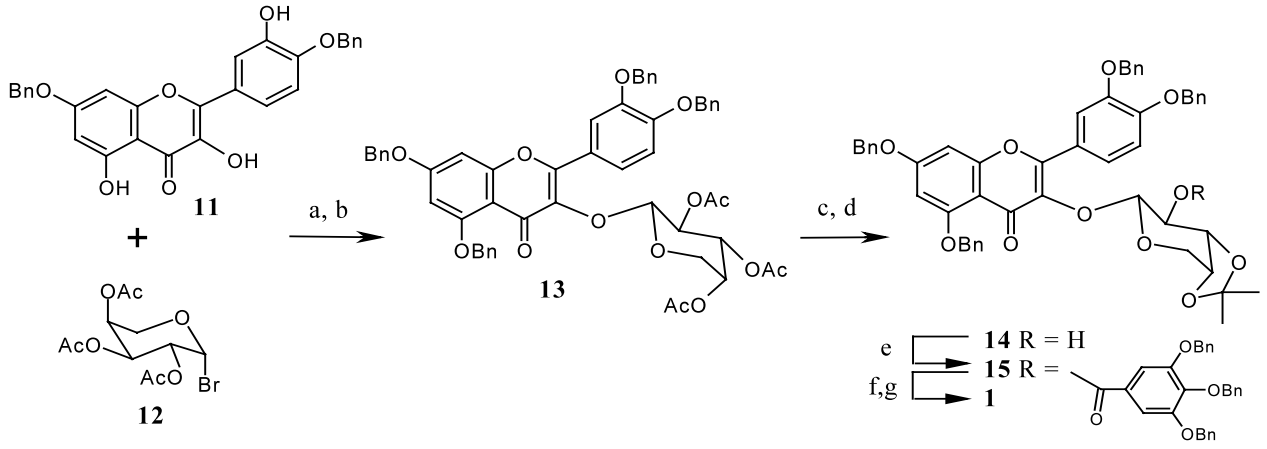


Scheme 1. *Reagents and conditions*: (a) cyclohexanone, PhMe, *p*-TsOH, reflux, 61%; (b) for **4**, TMSOTf or $BF_3{\cdot}OEt_2$, CH_2Cl_2, 4 Å MS; (c) for **5**, Tf_2O, DTBMP, CH_2Cl_2, 4 Å MS; (d) $Bu_4N^+Br^-$, $CHCl_3$/aq. K_2CO_3 (0.18 M) (v:v, 1:1), 42°C, 91%; (e) NaOMe, HOMe/CH_2Cl_2, rt; (f) DMP, CSA (10-camphorsulfonic acid), DMF, 91% (2 steps); (g) tribenzylgalloyl chloride, pyridine, DMAP, rt, 94%; (h) PhSH, DBU, DMF, 40°C, 92%.

cosides, all the glycosylation steps employed glycosyl bromides or chlorides under either Koenigs–Knorr conditions (promoted by silver salts)[3] or, later, under phase-transfer-catalyzed (PTC) alkaline conditions.[4] Although the glycosylation yields are comparable (normally lower than 50%) under these conditions, the PTC conditions greatly improved the workup procedure. Here, we intended first to glycosylate the phenolic 3-OH of **3** with arabinopyranosyl trichloroacetimidate **4** and sulfoxide **5**,[10] because glycosyl trichloroacetimidate and sulfoxide donors have recently been used successfully in the glycosylation of phenols.[11,12] However, attempts under various conditions failed, unavoidably leading to complex products, conceivably due to decomposition of the donors or the resulting products under the acidic conditions. We then turned to basic PTC conditions for glycosylation. Thus, treatment of 3,5-diol **3** with 2,3,4-tri-*O*-benzoyl-α-L-arabinopyranosyl bromide **6** under conditions similar to those in the literature (in the presence of 1.3 M aq. KOH) provided the desired α-glycoside **7** in 36% yield. However, when the reaction was carried out in dilute aq. KOH (0.18 M), the yield of **7** was increased to 81%. This yield was further improved to 91% when K_2CO_3 (0.18 M) was employed as a base.[13] These results might be attributed to the decrease of the side reactions of the glycosyl bromide **6** under basic conditions, i.e. elimination to give the glycal and cleavage of the acyl protecting groups. No β-anomer was detected under these PTC glycosylation conditions. After conversion of **7** into 5,2″-diol **8**, we expected to acylate the 2″-OH selectively with the tribenzylgalloyl group. However, no selectivity was achieved between the 5- and 2″-OHs under various acylation conditions (e.g., tribenzylgallic acid, DCC). Therefore, the 5,2″-di-acylated product **9** was prepared (94%) under forced conditions. Selective removal of the 5-*O*-tribenzylgalloyl group was then attempted and found to work well in the presence of PhSH and DBU in DMF at 40°C, giving **10** in excellent yield (92%).[14] Unfortunately, the final removal of the protecting groups from **10** was unsuccessful under various conditions;[15] and the 3′,4′-cyclohexylidene could not be removed without cleavage of the 3-*O*-glycosidic bond.

However, treatment of triol **11** with 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl bromide **12** under the above optimized PTC conditions, after blocking the remaining 5 and 3′-OH with benzyl groups,[16] gave the expected glycoside **13** in a satisfactory 60% yield (Scheme 2). Subjection of **13** to deacetylation and acetonization provided **14** with the 2-OH free (86%), which was acylated with tribenzylgalloyl chloride to provide **15** in 86% yield. Final removal of the protective groups on **15** was straightforward. Thus, the sugar propylidene residue was readily cleaved using 80% AcOH (86%), then the remaining seven benzyl groups on the phenolic hydroxyls were removed cleanly by hydrogenation over 10% Pd–C in a mixed solvent of ethanol and ethyl acetate (1:1) under normal pressure to furnish the target molecule **1** (94%). All the data recorded for **1** were identical with those reported.[6,17]



Scheme 2. *Reagents and conditions*: (a) $Bu_4N^+Br^-$, $CHCl_3$/aq. K_2CO_3 (0.12 M) (v:v, 1:1), 42°C; (b) BnBr, Ag_2O, AgOTf (cat.), DIPEA (cat.), DMF, 60% (2 steps); (c) NaOMe, HOMe/CH_2Cl_2, rt; (d) DMP, CSA, DMF, 86% (2 steps); (e) tribenzylgalloyl chloride, pyridine, DMAP, 86%; (f) 80% AcOH, THF, 86%; (g) H_2, 10% Pd–C, EtOH/EtOAc, 94%.

In summary, a structurally typical flavonol *O*-glycoside with interesting bioactivities was readily synthesized from 7,4′-di-*O*-benzylquercetin in seven steps and 36% overall yield. The conventional PTC glycosylation conditions have been improved by using much diluted aq. K_2CO_3 ($\sim$0.1 M). The present successful conditions for the selective removal of the phenolic acyl group (PhSH, DBU, DMF) and the unsuccessful attempts at glycosylation of the flavonol 3-OH under acidic conditions are worth further exploration.

Acknowledgements

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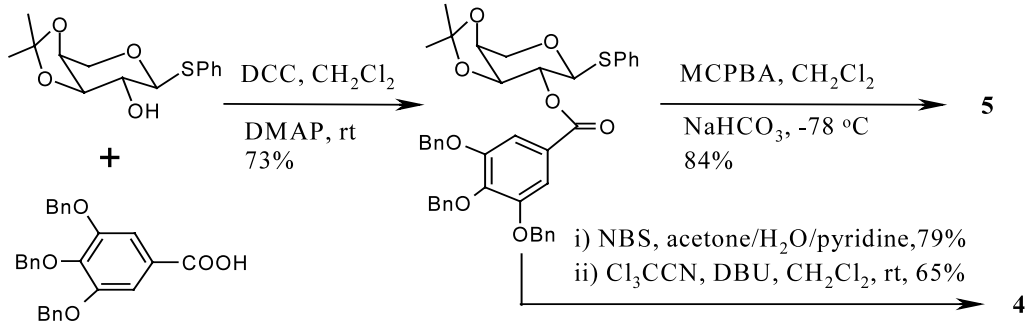
References

1. Harborne, J. B.; Baxter, H. *The Handbook of Natural Flavonoids*; John Wiley & Sons: Chichester, 1999; Vol. 1.
2. (a) Harborne, J. B. *The Flavonoids*: *Advances in Research since 1986*; Chapman and Hall: London, 1994; (b) Harborne, J. B. *The Flavonoids*: *Advances in Research since 1980*; Chapman and Hall: London, 1988; (c) Harborne, J. B.; Mabry, T. J. *The Flavonoids*: *Advances in Research*; Chapman and Hall: London, 1982; (d) Harborne, J. B.; Mabry, T. J.; Mabry, H. *The Flavonoids*; Chapman and Hall: London, 1975.
3. (a) Vermes, B.; Farkas, L.; Nógrádi, M. In *Topics in Flavonoid Chemistry and Biochemistry*; Farkas, L.; Gábor, M.; Kállay, F., Eds.; Elsevier: Amsterdam, 1975; pp. 162–170; (b) Farkas, L.; Vermes, B.; Mihály, N.; Kálmán, A. *Phytochemistry* **1976**, *15*, 1184; (c) Vermes, B.; Chari, V. M.; Wagner, H. *Helv. Chim. Acta* **1981**, *64*, 189.
4. (a) Demetzos, C.; Skaltsounis, A.-L.; Tillequin, F.; Koch, M. *Carbohydr. Res.* **1990**, *207*, 131; (b) Razanamahefa, B.; Demetzos, C.; Skaltsounis, A.-L.; Andriantisiferana, M.; Tillequin, F. *Heterocycles* **1994**, *38*, 357; (c) Demetzos, C.; Skaltsounis, A.-L.; Razanamahefa, B.; Tillequin, F. *J. Nat. Prod.* **1994**, *57*, 1234.
5. Enzymatic introduction of acyl groups onto the sugar moiety of flavonol glycosides has been reported, see: (a) Danieli, B.; De Bellis, P.; Carrea, G.; Riva, S. *Helv. Chim. Acta* **1990**, *73*, 1837; (b) Danieli, B.; Bertario, A.; Carrea, G.; Redigolo, B.; Secundo, F.; Riva, S. *Helv. Chim. Acta* **1993**, *76*, 2981.
6. Iwagawa, T.; Kawasaki, J.-I.; Hase, T.; Sako, S.; Okubo, T.; Ishida, M.; Kim, M. *Phytochemistry* **1990**, *29*, 1013.
7. Okamura, H.; Mimura, A.; Yakou, Y.; Niwano, M.; Takahara, Y. *Phytochemistry* **1993**, *33*, 557.
8. Kim, H. J.; Woo, E.-R.; Shin, C.-G.; Park, H. *J. Nat. Prod.* **1998**, *61*, 145.
9. Jurd, L. *J. Org. Chem.* **1962**, *27*, 1294.
10. Imidate **4** and sulfoxide **5** were prepared from phenyl 3,4 - *O* - isopropylidene - 1 - thio - α - L - arabinopyranoside employing the following approaches:



11. Mahling, J.-A.; Schmidt, R. R. *Synthesis* **1993**, 325.
12. Thompson, C.; Ge, M.; Kahne, D. *J. Am. Chem. Soc.* **1999**, *121*, 1237.
13. K_2CO_3 was found superior to KOH in a solid–liquid PTC glycosylation of phenols, see: Hongu, M.; Satio, K.; Tsujihara, K. *Synth. Commun.* **1999**, *29*, 2775.
14. The deprotection of the aryl acetate using literature conditions (PhSH, K_2CO_3, DMF, 40°C) gave **10** in 70% yield. Here, we found that using DBU as a base instead of K_2CO_3 increased the yield of **10** to 92%. See: Chakraborti, A. K.; Nayak, M. K.; Sharma, L. *J. Org. Chem.* **1999**, *64*, 8027.
15. Exhaustive attempts were taken following literature methods for cleavage of ketals, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: Chichester, 1999.
16. The presence of phenolic hydroxyls usually makes chromatography on silica gel difficult due to heavy adhesion.
17. Selected data for the key compounds. **13**: $[\alpha]_D^{19}=-87.9$ (*c* 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (brs, 1 H), 7.71 (d, 1 H, $J=8.5$), 7.59–7.32 (m, 20 H), 7.02 (d, 1 H, $J=8.5$), 6.53 (brs, 1 H), 6.44 (brs, 1 H), 5.80 (d, 1 H, $J=7.1$), 5.53 (t, 1 H, $J=8.6$), 5.38–5.15 (m, 8 H), 5.08 (brs, 2 H), 3.87 (d, 1 H, $J=12.9$), 3.58 (d, 1 H, $J=12.9$), 2.17 (s, 3 H), 2.05 (s, 3 H), 1.87 (s, 3 H). ESI-MS: 943.5 [M+Na$^+$]. Calcd for $C_{54}H_{48}O_{14}$: C, 70.42, H, 5.25; Found: C, 70.20, H, 5.53. **14**: $[\alpha]_D^{19}=-40.6$ (*c* 1.38, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (brs, 1 H), 7.74 (d, 1 H, $J=7.5$), 7.59–7.27 (m, 20 H), 7.00 (d, 1 H, $J=8.1$), 6.53 (brs, 1 H), 6.46 (brs, 1 H), 5.23 (s, 4 H), 5.21 (s, 2 H), 5.08 (s, 2 H), 4.97 (d, 1 H, $J=7.5$), 4.19 (m, 2 H), 4.01 (m, 2 H), 3.66 (dd, 1 H, $J=9.3$, 3.3), 1.54 (s, 3 H), 1.37 (s, 3 H). ESI–MS: 857.5 [M+Na$^+$]. Calcd for $C_{51}H_{46}O_{11}\cdot 0.5H_2O$: C, 72.58, H, 5.61; Found: C, 72.84, H, 5.75. **15**: $[\alpha]_D^{24}=-103.0$ (*c* 1.62, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (brs, 1 H), 7.65–7.23 (m, 36 H), 7.01 (d, 1 H, $J=8.5$), 6.51 (brs, 1 H), 6.36 (brs, 1 H), 6.00 (d, 1 H, $J=6.0$), 5.55 (m, 1 H), 5.32 (s, 2 H), 5.24 (s, 2 H), 5.14 (s, 4 H), 5.11 (s, 2 H), 5.10 (s, 2 H), 5.03 (s, 2 H), 4.37 (m, 2 H), 4.05 (d, 1 H, $J=11.3$), 3.81 (d, 1 H, $J=11.0$), 1.54 (s, 3 H), 1.37 (s, 3 H). ESI-MS: 1257.9 [M+H$^+$]. Calcd. for $C_{79}H_{68}O_{15}$: C, 75.46, H, 5.45; Found: C, 75.17, H, 5.66. **1**: $[\alpha]_D^{20}=-96.4$ (*c* 0.33, MeOH); IR: 3300, 1703, 1656, 1607, 1503 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.55 (brs, 1 H), 9.82 (brs, 1 H), 9.28 (brs, 1 H), 9.21 (brs, 2 H), 8.94 (brs, 1 H), 7.71 (d, 1 H, $J=7.4$), 7.49 (brs, 1 H), 7.03 (s, 2 H), 6.85 (d, 1 H, $J=8.2$), 6.40 (brs, 1 H), 6.19 (brs, 1 H), 5.59 (d, 1 H, $J=6.1$), 5.32 (t, 1 H, $J=6.9$), 5.07 (brs, 1 H), 4.88 (brs, 1 H), 3.71 (m, 3 H), 3.41 (m, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 177.32, 165.24, 164.41, 156.44, 148.87, 145.68, 145.21, 138.64, 133.28, 120.55, 120.97, 119.74, 115.80, 115.60, 109.13, 104.10, 98.92, 93.71, 72.45, 69.98, 67.14, 65.23. ESI-MS: 609.1 [M+Na$^+$].