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Synthesis of pelargonidin 3-*O*-6″-*O*-acetyl-β-D-glucopyranoside, an acylated anthocyanin, via the corresponding kaempferol glucoside

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Abstract—The first total synthesis of pelargonidin 3-*O*-6″-*O*-acetyl-β-D-glucopyranoside, an acylated anthocyanin of magenta-colored *Verbena* flowers, was successfully carried out. The key intermediate, protected kaemferol 3-*O*-glucoside, was constructed by the Baker–Venkataraman rearrangement from a glucosyloxyacetophenone followed by Zn–Hg reduction to the corresponding acylated anthocyanin.

Glycosyl flavonoids, such as anthocyanins, flavonols, and flavones, show a wide range of biological activities such as flower color development,[1] protection against UV light,[2] and insect stimulants.[3] They also have medicinal properties as antioxidants,[4] hepatoprotectant,[5] and inhibitors against influenza virus sialidase.[6] Despite their potential importance, the synthetic methodology of glycosyl flavonoids was extremely limited.[7,8] In particular, the synthesis of acylated anthocyanin has never been performed.[7] Thus, we have focused our attention on the synthesis of acylated anthocyanin and 3-*O*-glucosyl flavonol as a precursor of acylated anthocyanin. There are two critical points on the synthesis of glycosyl flavonoids. One is the formation of the flavonoid nucleus and the other is regio and stereoselective glycosylation to the nucleus. Direct glycosylation to the flavonoid skeleton is a very powerful and useful method, but this method has been limited because the preparation of suitably protected flavonoids is difficult and this glycosylation reaction sometimes gives a low yield due to hydrogen bonding. Therefore, only a few approaches for 3-*O*-glucosyl flavonol using quercetin[8b,c,e] and kaempferol[8f] have been reported. To overcome the problem, we studied the efficient and flexible synthesis of the flavonoid skeleton via cyclization after glycosylation. Retrosynthetic analysis of pelargonidin 3-*O*-6″-*O*-acetyl-β-D-glucopyranoside (**1**),[9] an acylated anthocyanin of magenta-colored *Verbena* flowers, is shown in Figure 1. Our strategy has two challenging issues: [1] The effective β-glucosylation of the low nucleophilic OH of 2-hydroxyacetophenone (**6**) predicted by a hydrogen bonding to the carbonyl group and [2] transformation of the acylated flavonol **13** to the corresponding anthocyanin **1** by metal reduction.

We developed a high β-selective glucosylation of an α-ketoalcohol **6** and realized the construction of 3-*O*-glucosyl flavonol **11** and **13** using a building block having a sugar moiety.[10] By a direct metal reduction[7c,e] of kaempferol 3-*O*-6″-*O*-acetyl-β-D-glucopyranoside (**13**),[5b] we could transform to the corresponding anthocyanin **1**. Here we report the first total synthesis of pelargonidin 3-6″-*O*-acetyl-β-D-glucoside (**1**)[9] (Scheme 1).

Tri-MOM ether **3** protected with MOMCl from phloroglucinol (**2**) (53%) was lithiated with *n*-BuLi, and then condensed with benzyloxyacetoaldehyde to give alcohol **4** (77%). Alcohol **4** was oxidized with TPAP to give acetophenone **5** (99%), which was converted by acidic hydrolysis, selective silyl protection to the di-TBS, and hydrogenolysis using $Pd(OH)_2$ (**6**, 76%, three steps).

Keywords: Acylated anthocyanin; Pelargonidin 3-*O*-6″-*O*-acetyl-β-D-glucopyranoside; Kaempferol 3-*O*-6″-*O*-acetyl-β-D-glucopyranoside.
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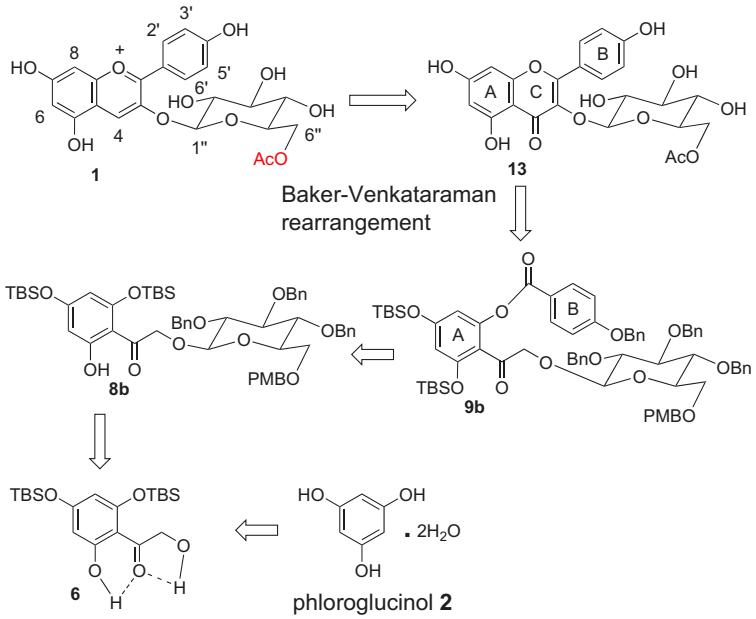
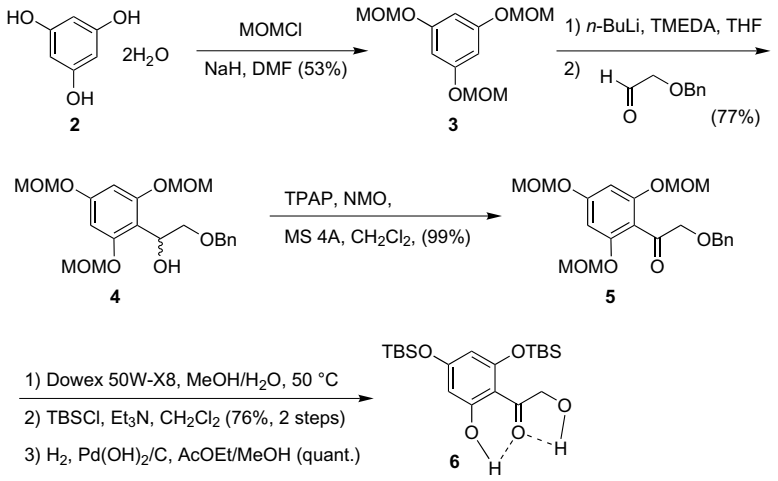


Figure 1. Structure and retrosynthetic analysis for pelargonidin 3-*O*-6″-*O*-acetyl-β-D-glucopyranoside (**1**).



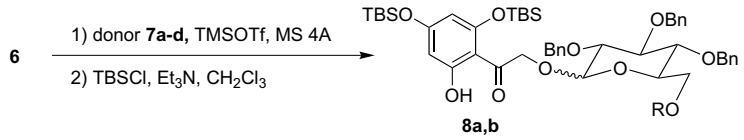
Scheme 1.

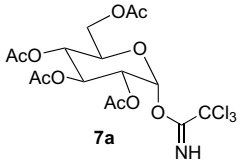
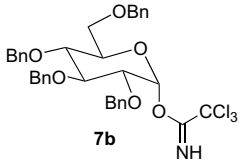
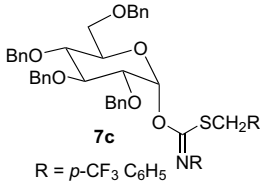
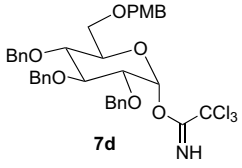
Glucosylation of **6** was examined using various glucosyl imidates **7a**–**d** in the presence of a catalytic amount of TMSOTf and MS 4A (Table 1).[11,12] The acetyl-protected sugar **7a** gave no glucosylated product, but the starting alcohol remained, while benzyl-protected sugar **7b**, **c** gave glucoside **8a**. Using acetonitrile or propionitrile as a solvent the desired β-glucoside was predominantly obtained in spite of no neighboring participation.[13] Because TBS-protecting groups were partially removed during the glucosylation, re-silylated reaction with TBSCl was carried out for work-up handling. Although silylation of **8a**,**c** was performed, one hydroxyl group remained to be free. This might be due to the strong hydrogen bond formation between the carbonyl group and phenolic hydroxyl group.

Esterification of the free *ortho*-hydroxyl group was carried out according to Wandless's condition (Scheme 2).[10c] Compound **8a** and *p*-*O*-benzyloxybenzoic acid were mixed with EDCI and DMAP in the presence of TsOH at rt to give ester **9a** in 61% yield. Successively **9a** was heated at 120 °C with pyridine and K_2CO_3. The Baker–Venkataraman type sequential cyclization–dehydration reaction occurred to give kaempferol 3-*O*-glucoside derivative **10** (42%).[10c] Hydrogenolysis of **10** with H_2–$Pd(OH)_2$/C gave kaempferol 3-*O*-glucoside (**11**) quantitatively.[5b,14,15]

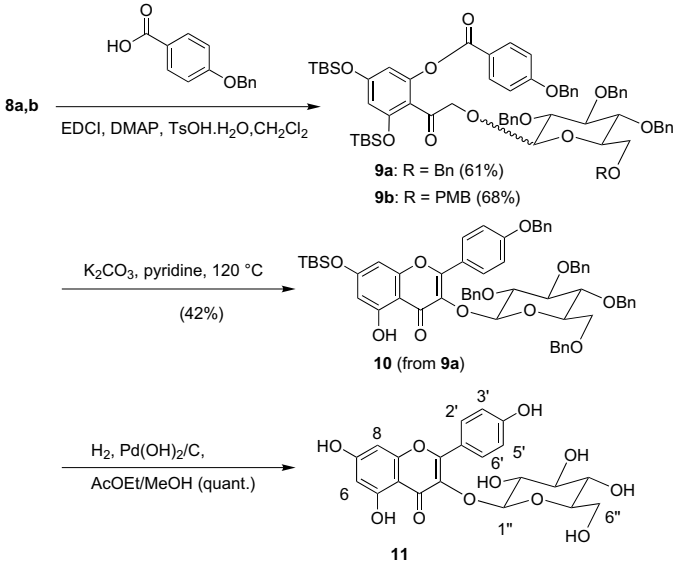
For the synthesis of 6″-O-acetylated glucosyl flavonol, we designed 7-*O*-*p*-methoxybenzyl-2,3,4-tri-*O*-benzyl-glucosyl imidate (**7d**) (Table 1, entry 4). Compound **8b** was obtained by the glycosylation of **6** with **7d** followed by re-silylation giving **8b** in 66% yield (β/α = 94/6). According to the same process as for **9a**,**b** was obtained in 68% yield (Scheme 2), and then cyclization toward a flavonol, re-silylation with TBSCl–Et_3N, treatment with

Table 1. Glucosylation with imidates **7a**–**d** in the presence of TMSOTf[a]

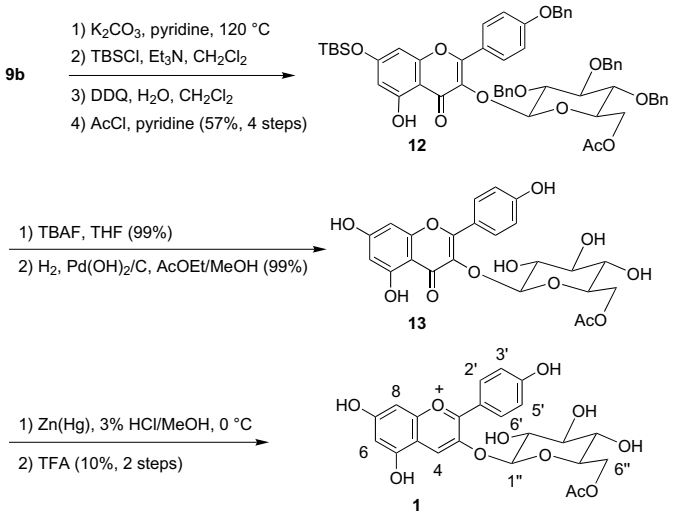


Entry	Donor	Solvent	Temperature (°C)	Glucoside	Yield[b] (%)	α/β[c]
1	 **7a**	CH_2CI_2	−78 to 0	—	0	—
2	 **7b**	MeCN	−40	**8a**	57	11/89
3	 **7c** R = *p*-CF_3 C_6H_5	EtCN	−40	**8a**	65	11/89
4	 **7d**	MeCN	−40	**8b**	66	6/94

[a] Compound **6** was used without purification, after hydrogenolysis.
[b] Isolated yield.
[c] α/β ratio was determined by ^1H NMR spectra.



Scheme 2.



Scheme 3.

$DDQ/H_2O/CH_2Cl_2$ for the removal of PMB, and acetylation gave acetate **12**[16,17] in an overall 57% yield for the four steps (Scheme 3). Deprotection of TBS and benzyl groups gave kaempferol 3-*O*-6″-*O*-acetyl-β-D-glucopyranoside (**13**)[14,15a] in quantitative yield. The product **13** was identical to that isolated from the flower of *Arnica chamissonis* and the needles of *Picea abies*. Finally metal reduction of **13** with Zn(Hg) in 3% HCl(gas) MeOH solution gave the corresponding anthocyanin, pelargonin 3-*O*-6″-*O*-acetyl-β-D-glucopyranoside (**1**)[9,14] in 10% yield,[18] which was found as a pigment in magenta *Verbena hybrida* petals. Here, we succeeded in the first synthesis of a natural acylated anthocyanin.

Our synthetic route has flexibility to synthesize versatile 3-*O*-glycosyl-flavonols and anthocyanins by changing the sugar moiety and/or the benzaldehyde structure.

In summary, we succeeded in the first total synthesis of pelargonidin 3-*O*-6″-*O*-acetyl-β-D-glucopyranoside (**1**), an acylated anthocyanin of the *Verbena* flower, via the corresponding kaempferol glucoside. This synthetic protocol might render a useful construction method for other flavonoid glucosides including anthocyanins and flavonol glucosides.

Acknowledgments

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13. It is well known that glycosylation using MeCN as a solvent has the tendency to give β-linked glucoside: Ratcliffe, A. J.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 747–750.
14. The synthetic **1**,[9] **11**,[15] and **13**[15a] were identical to the natural ones. For NMR analysis of **1**, we found a misassignment. The assignments of H-2″ and H-3″ should be reversed.[9] Data for **1**: ^{1}H NMR (500 MHz, 5% CF_3CO_2D in DMSO-d_6) δ 8.83 (s, 1H, H-4), 8.55 (d, $J = 8.9$ Hz, 1H, H-2′,6′), 7.02 (d, $J = 8.9$ Hz, 1H, H-3′,5′), 6.94 (d, $J = 2.3$ Hz, 1H, H-8), 6.70 (d, $J = 2.3$ Hz, 1H, H-6), 5.35 (d, $J = 8.0$ Hz, 1H, H-1″), 4.38 (dd, $J = 12.0$, 1.7 Hz, 1H, H-6a″), 3.98 (dd, $J = 12.0$, 8.0 Hz, 1H, H-6b″), 3.75 (ddd, $J = 9.0$, 8.0, 1.7 Hz, 1H, H-5″), 3.43 (dd, $J = 9.0$, 8.0 Hz, 1H, H-2″), 3.35 (t, $J = 9.0$ Hz, H-3″), 3.17 (t, $J = 9.0$ Hz, H-4″), 1.97 (s, 3H, OAc), HRMS (FAB) calcd for $C_{23}H_{23}O_{11}$ (M^+) 475.1240. Found: 475.1244; Data for **11**: ^{1}H NMR (600 MHz, CD_3OD) δ 8.09 (d, $J = 9.0$ Hz, 2H, H-2′,6′), 6.93 (d, $J = 9.0$ Hz, 2H, H-3′,5′), 6.42 (d, $J = 2.2$ Hz, 1H, H-6 or H-8), 6.23 (d, $J = 2.2$ Hz, 1H, H-6 or H-8), 5.27 (d, $J = 7.3$ Hz, 1H, H-1″), 3.73 (dd, $J = 11.9$, 2.5 Hz, 1H, H-6″), 3.57 (dd, $J = 11.9$, 5.5 Hz, 1H, H-6″), 3.48 (dd, $J = 9.1$, 7.3 Hz, 1H, H-2″), 3.45 (t, $J = 9.1$, 1H, H-3″), 3.35 (t, $J = 9.1$ Hz, 1H, H-4″), 3.24 (ddd, $J = 9.1$, 5.5, 2.5 Hz, 1H, H-5″); Data for **13**: ^{1}H NMR (600 MHz, CD_3OD) δ 8.06 (d, $J = 8.8$ Hz, 2H, H-2′,6′), 6.90 (d, $J = 8.8$ Hz, 2H, H-3′,5′), 6.44 (d, $J = 2.2$ Hz, 1H, H-6 or H-8), 6.24 (d, $J = 2.2$ Hz, 1H, H-6 or H-8), 5.20 (d, $J = 7.3$ Hz, 1H, H-1″), 4.21 (dd, $J = 11.8$, 2.2 Hz, 1H, H-6″), 4.10 (dd, $J = 11.8$, 5.9 Hz, 1H, H-6″), 3.48 (dd, $J = 9.1$, 7.3 Hz, 1H, H-2″), 3.46 (t, $J = 9.1$ Hz, 1H, H-3″), 3.42 (ddd, $J = 9.1$, 5.9, 2.2 Hz, 1H, H-5″), 3.33 (t, $J = 9.1$ Hz, 1H, H-4″), 1.87 (s, 3H, OAc).
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16. A minor α-linked glucoside disappeared during the reaction and the purification.
17. Data for **12**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.59 (s, 1H), 8.01 (d, $J = 8.8$ Hz, 2H, H-2′,6′), 7.2–7.4 (m, 20H, Bn), 6.96 (d, $J = 9.2$ Hz, 2H, H-3′,5′), 6.38 (d, $J = 1.6$ Hz, 1H, H-6 or H-8), 6.28 (d, $J = 1.6$ Hz, 1H, H-6 or H-8), 5.51 (d, $J = 7.7$ Hz, 1H, H-1″), 5.11 (d, 1H, $J = 11.0$ Hz, Bn), 5.10 (s, 2H, Bn), 4.99 (d, $J = 10.7$ Hz, 1H, Bn), 4.81 (d, $J = 11.0$ Hz, 1H,Bn), 4.78 (d, $J = 10.7$ Hz, 1H, Bn), 4.77 (d, $J = 11.0$ Hz, 1H, Bn), 4.51 (d, $J = 11.0$ Hz, 1H, Bn), 4.09 (dd, $J = 12.0$, 2.2 Hz, 1H, H-6″), 3.98 (dd, $J = 12.0$, 4.0 Hz, 1H, H-6″), 3.76 (t, $J = 9.1$ Hz, 1H, H-3″), 3.64 (dd, $J = 9.1$, 7.7 Hz, 1H, H-2″), 3.52 (t, $J = 9.1$ Hz, 1H, H-4″), 3.39 (ddd, $J = 9.1$, 4.0, 2.2 Hz, 1H, H-5″), 1.76 (s, 3H, OAc), 0.98 (s, 9H, Si*t*-Bu), 0.25 (s, 6H, $SiMe_2$).
18. The low yield was due to deacetylation. The main product was pelargonidin 3-*O*-glucoside (yield: 15%), which was identical to the natural one: Yoshida, K.; Sato, Y.; Okuno, R.; Kameda, K.; Isobe, M.; Kondo, T. *Biosci. Biotech. Biochem.* **1996**, *60*, 589–593.