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Total synthesis of apigenin 7,4′-di-*O*-β-glucopyranoside, a component of blue flower pigment of *Salvia patens*, and seven chiral analogues

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Abstract—We have succeeded in the first total synthesis of apigenin 7,4′-di-*O*-β-D-glucopyranoside (**1a**), a component of blue pigment, protodelphin, from naringenin (**2**). Glycosylation of **2** according to Koenigs–Knorr reaction provided a monoglucoside **4a** in 80% yield, and this was followed by DDQ oxidation to give apigenin 7-*O*-glucoside (**12a**). Further glycosylation of 4′-OH of **12a** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl fluoride (**5a**) was achieved using a Lewis acid-and-base promotion system ($BF_3{\cdot}Et_2O$, 2,6-di-*tert*-butyl-4-methylpyridine, and 1,1,3,3-tetramethylguanidine) in 70% yield, and subsequent deprotection produced **1a**. Synthesis of three other chiral isomers of **1a**, with replacement of D-glucose at 7 and/or 4′-OH by L-glucose (**1b**–**d**), and four chiral isomers of apigenin 7-*O*-β-glucosides (**6a**,**b**) and 4′-*O*-β-glucosides (**7a**,**b**) also proved possible.

Keywords: Glycosylation of phenol; Apigenin 7,4′-di-*O*-glucoside; Flavone; Antipode; L-Glucose; 2,6-Di-*tert*-butyl-4-methylpyridine; Lewis acid-and-base promotion.

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