A concise synthesis of \((\pm)-7\)-O-galloyltricetiflavan\(^{\dagger}\)

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\((\pm)-7\)-O-galloyltricetiflavan (1a) was synthesized successfully in five steps from the commercially available trihydroxyacetophenone (2) and trimethoxybenzoyl chloride (3). The flavone 4a was prepared in a one-pot reaction and it gave hex-O-methylflavan 6 followed by acylation and reduction. However, the demethylation of flavan 6, 5-O-acetylfavan 10 and 5-O-phenylacetylfavan 11 by BBr\(_3\) gave all the hydrolyzed fragments 7 and 8 as the major products. By contrast, in the same condition, hept-O-methylflavan 9 could provide the desired product \((\pm)-7\)-O-galloyltricetiflavan (1a) in 91% yield. The additional 5-O-B-Br\(_2\) complex may stabilize the ester bond during the demethylation process.

When flavan 6 was treated with BBr\(_3\) in dichloromethane at \(-40^\circ\text{C}\) or \(-78^\circ\text{C}\),\(^2\) the desired product 1a was generated in only 3% yield (based on HPLC-MS analysis), accompanied with 4-O-methyl gallic acid (7) and flavan 8 as the major products, indicating the ester bond of hex-O-methylflavan 6 is highly unstable under acidic conditions (Scheme 1).

Then, 5-O-methylflavan 9, 5-O-acetylfavan 10 and 5-O-phenylacetylfavan 11 were prepared as substrates to explore if they provided different results (Scheme 2). Similarly, 5-O-acetylfavan 10 and 5-O-phenylacetylfavan 11 were not tolerated under these reaction conditions, which gave the hydrolyzed products 7 and 8 as major products. In contrast, when flavan 9 was treated with BBr\(_3\) in dichloromethane at \(-40^\circ\text{C}\) to room temperature, the desired product \((\pm)-7\)-O-galloyltricetiflavan (1a) was generated in 91% yield and no hydrolyzed product was detected after 24 h. The structure of \((\pm)-7\)-O-galloyltricetiflavan (1a) was confirmed by \(^1\)H NMR, \(^13\)C NMR, and HR-MS spectrum, and they are consistent with the literature’s report.\(^4\)

We presumed that when BBr\(_3\) was added to the additional 5-O-methyl group to form the 5-O-B-Br\(_2\) complex, it may stabilizes the ester bond of 7-phenolic hydroxyl group. By contrast, the 5-O-acetyl or 5-O-phenylacetyl groups was more easily hydrolyzed and could not help stabilize the ester bond.

In conclusion, \((\pm)-7\)-O-galloyltricetiflavan (1a) was synthesized successfully in five steps from commercial available...
trihydroxyacetophenone (2) and trimethoxybenzoyl chloride (3). Flavone 4a was prepared in a one-pot reaction and it gave hex-O-methylflavan 6 followed by acylation and reduction. However, the demethylation of flavan 6 by BB₃ gave the hydrolyzed fragments 7 and 8 as major products. Similarly, neither 5-O-acetylflavan 10 nor 5-O-phenylacetylflavan 11 could provide the desired product. In contrast, hept-O-methylflavan 9 could give the desired product (±)-7-O-galloyltricetilflavan (1a) in 91% yield. The additional 5-O-B-Br₂ complex may stabilize the ester bond during the demethylation process. Our method could also provide an efficiently pathway to prepare other 7-O-acetylated flavans.

**Experimental section**

**General experimental procedures**

All reactions were performed in glassware containing a Teflon-coated stir bar. Solvents and chemical reagents were obtained from commercial sources and used without further purification. ¹H and ¹³C NMR spectra were recorded on Varian Mercury 500 MHz or 400 MHz, and the data were recorded using DMSO-d₆, CDCl₃ and CD₃OD as the solvents. Chemical shifts (δ) are reported in ppm downfield from an internal TMS standard. The reactions and products were analyzed by HPLC-MS. High-resolution mass spectra were obtained in ESI mode on a hybrid IT-TOF mass spectrometer. Flash column chromatography on silica gel (200–300 mesh) was used for the routine purification of reaction products. The column output was monitored by TLC on silica gel (100–200 mesh) precoated on glass plates (15 × 50 mm), and spots were visualized by a 5% vanillin sulfuric acid/ethanol solution.

**Synthesis of compounds 4a and 4b.** The two-phase mixture of a trihydroxyacetophenone (2, 4.0 g, 21.06 mmol) and an aryl chloride (3, 13.34 g, 56.14 mmol) in toluene (100 mL) and saturated aqueous K₂CO₃ (100 mL) was vigorously stirred at 60 °C for 30 min. Tetrabutylammonium hydrogen sulfate (7.3 g, 21.5 mmol) was added, and the mixture was stirred at 75 °C for an additional two hours. During this period, the organic layer turned orange, and an orange-brown liquid separated at the interface. The toluene layer was separated, and the orange-brown liquid was extracted with CHCl₃ (50 mL). The toluene and CHCl₃ solutions were washed with water (2 × 90 mL), dried with Na₂SO₄, filtrated and concentrated to give a brown oil (15.2 g). The mixture was redissolved in methanol (60 mL), CH₃ONa (2.19 g) in 30% yield. The CHCl₃ solution was concentrated to give compound 4a as a canary yellow solid (2.19 g) in 30% yield. The CHCl₃ solution was concentrated to give compound 4b as a yellow solid (5.76 g) in 50% yield.

**Scheme 1** The synthesis of intermediates of (±)-7-O-galloyltricetilflavan (1a).
3H), 3.65 (s, 7H). 13C NMR (125 MHz, DMSO-\textsubscript{d\textsubscript{6}}) \( \delta \) 191.7, 180.5, 165.5, 162.7, 162.1, 158.1, 153.7, 153.4, 143.4, 140.5, 132.8, 127.1, 120.5, 107.5, 106.8, 104.1, 99.9, 95.2, 60.9, 60.8, 57.0, 56.4. HRMS-ESI (\[m/z\]): [M + Na\textsuperscript{+}] calsd for C\textsubscript{29}H\textsubscript{32}NaO\textsubscript{11} 563.1888; found 563.1892.

5-Hydroxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4\textsubscript{H}-chromen-7-yl-3,4,5-trimethoxybenzoate (5). To a solution of compound 4a (2.15 g, 18.73 mmol) and anhydrous K\textsubscript{2}CO\textsubscript{3} (1.73 g, 12.78 mmol) in 150 mL of CH\textsubscript{2}Cl\textsubscript{2} was added palladium on carbon (5%, 1.00 g), and the mixture was stirred for 72 h under N\textsubscript{2}. Upon completion, the reaction contents were quenched by the addition of ice water (20 mL), the CH\textsubscript{2}Cl\textsubscript{2} was washed with water (25 mL) and brine (15 mL), dried with Na\textsubscript{2}SO\textsubscript{4}, filtered, and then concentrated to give a brown oil. After purification by flash silica gel column chromatography, compound 9 (0.62 g) was obtained as a white solid in 99.0% yield.

1H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.48 (s, 2H), 7.44 (s, 2H), 7.10 (s, 1H), 6.70 (d, \( J = 3.7 \) Hz, 2H), 3.95 (d, \( J = 6.6 \) Hz, 18H). 13C NMR (101 MHz, CDCl\textsubscript{3}) \( \delta \) 182.8, 164.6, 164.0, 162.0, 156.7, 156.3, 153.7, 153.2, 141.7, 126.1, 123.5, 108.9, 107.6, 105.9, 105.7, 103.8, 101.3, 61.1, 61.1, 56.4. HRMS-ESI (\[m/z\]): [M + Na\textsuperscript{+}] calsd for C\textsubscript{28}H\textsubscript{30}NaO\textsubscript{11} 561.1367; found 561.1369.

5-Hydroxy-2-(3,4,5-trimethoxyphenyl)chroman-7-yl-3,4,5-trimethoxybenzoate (9). To a solution of compound 6 (600 mg, 1.14 mmol) in 5 mL of dry DMF was added dimethyl sulfate (238 \( \mu \)L, 2.51 mmol) and anhydrous K\textsubscript{2}CO\textsubscript{3} (472 mg, 3.42 mmol), and the mixture was stirred for 5 h at 56 \( ^\circ \)C. The solution was concentrated, redissolved in EtOAc washed with water, dried with Na\textsubscript{2}SO\textsubscript{4}, filtered, and then concentrated to give a brown oil. After purification by flash silica gel column chromatography, compound 9 (0.62 g) was obtained as a white solid in 99.0% yield.

1H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.48 (s, 2H), 6.70 (s, 2H), 6.49 (d, \( J = 2.2 \) Hz, 1H), 6.36 (d, \( J = 2.2 \) Hz, 1H), 4.98 (dd, \( J = 10.8, 2.1 \) Hz, 1H), 3.98 (d, \( J = 1.0 \) Hz, 9H), 3.92 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 2.97–2.82 (m, 1H), 2.82–2.67 (m, 2H), 2.34–2.21 (m, 1H), 2.08–1.99 (m, 2H). 13C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 165.0, 158.4, 156.1, 153.4, 153.1, 150.2, 142.8, 137.6, 137.2, 137.2, 124.5, 108.7, 107.4, 103.2, 103.1, 96.9, 78.0, 61.0, 60.9, 60.4, 56.4, 56.2, 55.7, 29.7, 29.6, 19.8, 14.2. HRMS-ESI (\[m/z\]): [M + Na\textsuperscript{+}] calsd for C\textsubscript{29}H\textsubscript{32}NaO\textsubscript{11} 563.1888; found 563.1892.

Synthesis of (±)-7-O-galloyltriflavan (1a). Compound 9 (0.48 g, 0.88 mmol) was dissolved in dry CH\textsubscript{3}Cl\textsubscript{2} (20 mL), then BBr\textsubscript{3} (15.4 mL, 1.0 M in CH\textsubscript{3}Cl\textsubscript{2}) was added dropwise at \( -40 \) \( ^\circ \)C. The resultant red-brown solution was warmed to r.t. and stirred for 12 h under N\textsubscript{2}. Upon completion, the reaction contents were quenched by the addition of ice water (20 mL), the CH\textsubscript{3}Cl\textsubscript{2} was removed, and the water layer was extracted twice with ethyl acetate (50 mL). The combined organic extracts were then washed with water (25 mL) and brine (15 mL), dried with Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated. The residue was purified...
over Sephadex LH-20 gel to give (±)-7-O-galloyltricetiflavan (0.36 g) as a brown solid in 91% yield and in 98% purity (from HPLC-MS).

\[ ^{1}H \text{NMR (500 MHz, CD}_{2}\text{OD)} \delta 7.21 (s, 2H), 6.47 (s, 2H), 6.22 (d, J = 11.9 Hz, 2H), 4.84 (s, 1H), 2.79 (d, J = 17.2 Hz, 1H), 2.74–2.65 (m, 1H), 2.27–2.15 (m, 1H), 2.09–1.95 (m, 1H). \] 13C NMR (100 MHz, CD_{2}OD) \delta 167.0, 157.7, 157.2, 151.4, 146.8, 146.5, 140.3, 133.9, 133.6, 120.7, 110.4, 108.5, 106.1, 102.3, 101.4, 79.0, 30.4, 20.3. HRMS-ESI ([m/z]: [M + H]⁺) calcd for C_{32}H_{36}NaO_{11} 591.1842; found 591.1845.

5-Methoxy-2-(3,4,5-trimethoxyphenyl)chroman-7-yl-3,4,5-trimethoxybenzoate (10). To a solution of compound 6 (100 mg, 0.19 mmol) in 5 mL of dry acetone was added acetyl chloride (25 μL) and anhydrous K_{2}CO_{3} (52 mg, 0.38 mmol), and the mixture was stirred for 2 h and adjusted to pH = 5 with 2 M HCl (aq). The solution was concentrated, redissolved in EtOAc washed with water, dried with NaSO_{4}, filtered and concentrated to give a brown oil. After purification by silica gel column chromatography, compound 10 (91 mg) was obtained as a colorless oil in 85% yield.

\[ ^{1}H \text{NMR (500 MHz, CDCl}_{3}) \delta 7.42 (s, 2H), 6.74 (d, J = 2.2 Hz, 1H), 6.64 (s, 2H), 6.61 (d, J = 2.3 Hz, 1H), 4.98 (d, J = 10.6 Hz, 1H), 3.99–3.80 (m, 1H), 2.78–2.67 (m, 2H), 2.22 (d, J = 14.0 Hz, 1H), 2.06 (dt, J = 23.4, 9.5 Hz, 1H). \] 13C NMR (100 MHz, CDCl_{3}) \delta 168.8, 164.5, 156.4, 153.4, 153.1, 149.7, 149.5, 142.9, 137.7, 136.7, 124.2, 113.0, 108.5, 108.1, 107.4, 103.1, 78.2, 77.3, 61.0, 60.9, 56.4, 56.2, 29.2, 20.8, 20.1. HRMS-ESI ([m/z]: [M + Na]⁺) calcd for C_{36}H_{36}NaO_{11} 591.1837; found 591.1849.

5-(2-Phenylacetoyl)-2-(3,4,5-trimethoxyphenyl)chroman-7-yl-3,4,5-trimethoxybenzoate (11). To a solution of compound 6 (100 mg, 0.19 mmol) in 5 mL of dry acetone was added phenylacetyl chloride (50 μL) and anhydrous K_{2}CO_{3} (52 mg, 0.38 mmol), and the mixture was stirred for 2 h and adjusted to pH = 5 with 2 M HCl (aq). The solution was concentrated, redissolved in EtOAc washed with water, dried with NaSO_{4}, filtered, and concentrated to give a brown oil. After purification by silica gel column chromatography, compound 11 (110 mg) was obtained as a colorless oil in 93% yield.

\[ ^{1}H \text{NMR (500 MHz, CDCl}_{3}) \delta 7.54–7.33 (m, 7H), 6.76 (d, J = 2.3 Hz, 1H), 6.66 (s, 2H), 6.62 (d, J = 2.1 Hz, 1H), 4.97 (d, J = 10.3 Hz, 1H), 4.04–3.86 (m, 18H), 2.59 (dd, J = 10.7, 5.8 Hz, 2H), 2.23–2.11 (m, 1H), 2.09–1.94 (m, 2H). \] 13C NMR (100 MHz, CDCl_{3}) \delta 169.3, 164.6, 156.4, 153.4, 153.1, 149.6, 149.4, 142.9, 137.7, 136.6, 133.3, 129.4, 128.8, 128.8, 127.5, 124.2, 113.0, 108.5, 108.1, 107.4, 103.1, 78.2, 77.3, 61.0, 60.9, 56.4, 56.2, 41.4, 29.2, 19.9. HRMS-ESI ([m/z]: [M + Na]⁺) calcd for C_{38}H_{36}NaO_{11} 667.2150; found 667.2165.

Conflicts of interest
There are no conflicts to declare.

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References