First Total Synthesis of (±)-Puyanin and (±)-4'-*O*-Methylbonannione

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A facile approach for the first total synthesis of two naturally occurring geranylated flavonoids, (±)-puyanin (**1**) and (±)-4'-*O*-methylbonannione (**2**) has been obtained with total yields of 27% and 17.8%, respectively. The key steps were regioselective cyclization of geranylated trihydroxychalcone and regioselective geranylation of 2,4,6-trihydroxyacetophenone.

Keywords puyanin, 4'-*O*-methylbonannione, natural products, geranylated flavonoids, total synthesis

Introduction

Natural flavanones exist widely in the plant kingdom and exhibit many important biological and pharmacological activities such as antibacterial,[1,2] antifungal,[3] antitumor[4] and hypotensive.[5] Prenylated flavanones are a unique class of flavonoids characterized by the presence of a prenylated side chain (*i.e.* prenyl, geranyl) in the flavonoid skeleton[6,7] and the flavanones having prenyl or geranyl groups showed greater activity than the normal flavanones.[8] Studies on synthesis of geranylated flavanones have been reported by some researchers.[7,9,10,11] We report herein a facile synthetic approach (Scheme 1) for the synthesis of both C-8 and C-6 geranylated flavanoids puyanin (**1**) and 4'-*O*-methylbonannione (**2**) isolated from the leaf extracts of *Glycosmis* collected in Thailand and Malaysia[12] (Figure 1). The *Glycosmis* plants are widely distributed in tropical and subtropical regions, and some of the species were used as indigenous medicines. 4'-*O*-Methylbonannione (**2**) had also been isolated from the fruits of *Schizolaena hystrix* (Sarcolaenaceae) and possessed activity against the A2780 human ovarian cancer cell line and displayed weak cytotoxicity, its IC_{50} value is 17 μg/mL.[13] As far as we know, the total synthesis of (±)-puyanin (**1**) and (±)-4'-*O*-methylbonannione (**2**) has not been reported yet.

Results and discussion

In continuation of our ongoing program on the studies of flavanoids,[14,15] we recently reported a strategy to synthesize the compounds of (±)-puyanin (**1**) and (±)-4'-*O*-methylbonannione (**2**), specific procedures go as follows. 4,6-Bis[(methoxy) methoxy]-2-hydroxy-3-(1'-geranyl)-acetophenone (**5**), which is readily prepared from 2,4,6-trihydroxyacetophenone by the geranylation according to some researchers' report[11,16] and selective bismethoxymethylation, was condensed with *p*-methoxybenzaldehyde to afford chalcone **6** in 75% yield. Cyclization of chalcone **6** by treatment with NaOAc in EtOH was followed by demethoxymethylation to give the title (±)-puyanin (**1**) (m.p. 158—162 ℃) in 64% yield. The 4'-*O*-methylbonannione (**2**) was synthesized as isomeric mixture in 51% yield from chalcone **6** by a two-step sequence: (1) demethoxymethylation (MeOH, 3 mol/L HCl, 65%); (2) cyclization (EtOH, NaOAc and H_2O, 78%). Cyclization of chalcone **8** resulted in a mixture of (±)-**1** and (±)-**2** in a ratio of 5∶1 (Scheme 2). It is interesting to note that the ^1H and ^{13}C NMR data of the isomeric pair **1** and **2** were almost same. Because cyclization of **6** was followed by demethoxymethylation to give single (±)-puyanin (**1**), we can distinguish (±)-**2** from (±)-**1** by comparing ^1H NMR of two com-

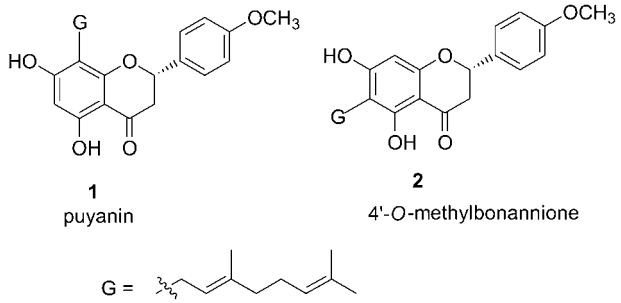

Figure 1 Structures of compounds **1** and **2**

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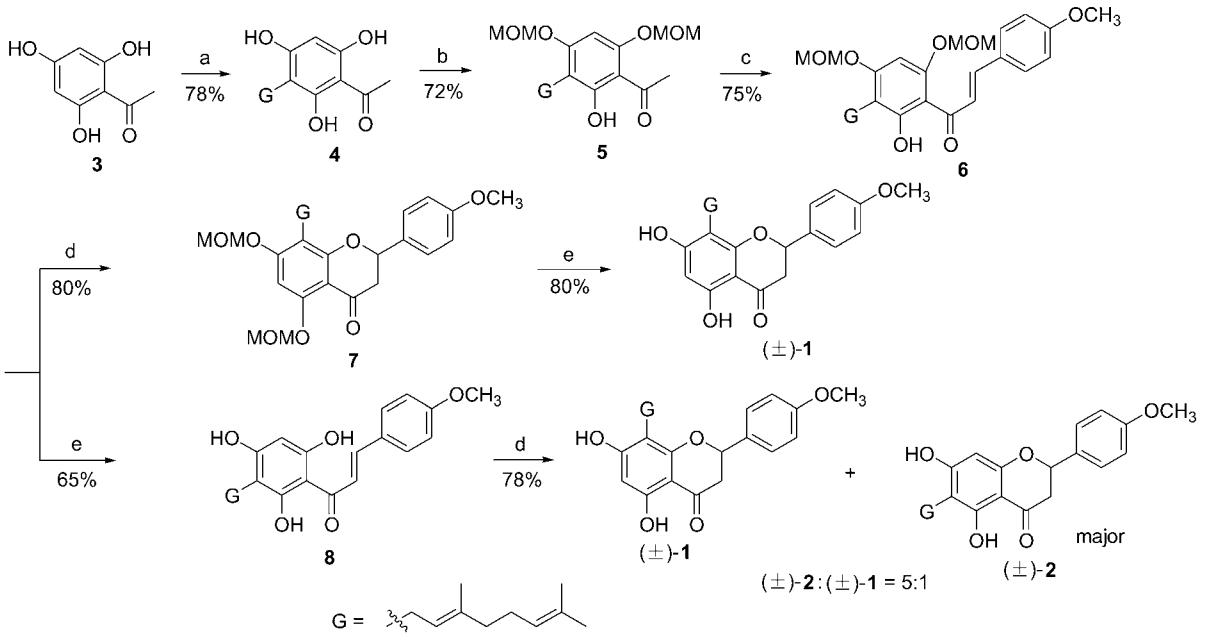
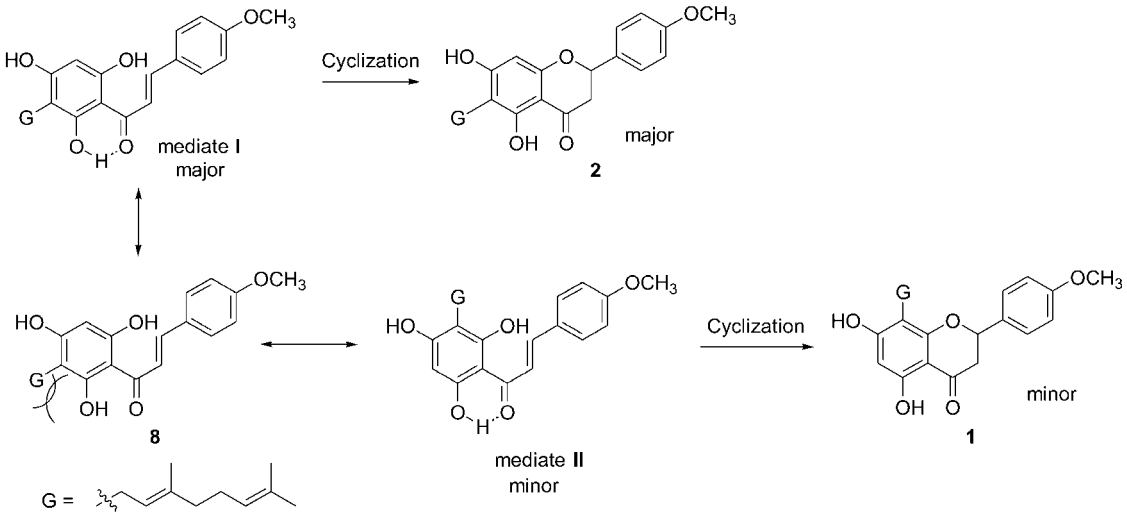
Scheme 1 Synthetic routes used to prepare (±)-**1** and (±)-**2**



Reagents and conditions: (a) geranyl bromine, anhydrous K_2CO_3, acetone, reflux; (b) anhydrous K_2CO_3, acetone, MOMCl, reflux; (c) *p*-methoxybenzaldehyde, KOH, H_2O-EtOH (V∶V=2∶3), under nitrogen, 0—20 ℃; (d) EtOH, NaOAc, reflux; (e) MeOH, 3 mol/L HCl, reflux.

Scheme 2 Possible cyclization mechanism of chalcone **8**



pounds. The synthetic C-8 geranylated flavanone (±)-puyanin (**1**) and C-6 geranylated flavanone (±)-4'-*O*-methylbonannione (**2**) have identical spectral data with those of natural products.[12,13]

Experimental

General experimental procedures Melting points were determined on X-5 melting point apparatus and uncorrected. For column chromatography, 200—300 mesh silica gel and GF_{254} were used. IR spectra were obtained on an FTIR-8430S spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400 instrument in $CDCl_3$ solution using TMS as the internal standard. MS were measured on an Agilent 5975C MSD spectrometer by direct inlet at 70 eV.

3-Geranyl-2,4,6-trihydroxyacetophenone (4) A solution of **3** (504 mg, 3 mmol), anhydrous K_2CO_3 (207 mg, 1.5 mmol) and geranyl bromine (518 mg, 2.4 mmol) in dry acetone (30 mL) was heated at reflux for 6 h, and then cooled to room temperature. The reaction mixture was filtered and evaporated under reduced pressure to give a residue that was purified by flash column chromatography on silica gel (petroleum ether-EtOAc, V∶V=4∶1) to yield **4** (711 mg, 78% yield) as a deep red gum. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.58, 1.66, 1.79 (s, 9H, $3CH_3$), 2.04—2.13 (m, 4H, 4'-2H and 5'-2H), 2.66 (s, 3H, $COCH_3$), 3.35 (d, J=7.2 Hz, 2H, 1'-2H), 5.05 (t,

J＝11.2 Hz, 1H, ＝CH), 5.25 (t, *J*＝13.2 Hz, 1H, ＝CH), 5.90 (s, 1H, ArH), 7.09 (s, 1H, OH), 9.55 (s, 1H, OH), 11.67 (s, 1H, OH); IR (KBr) ν_{max}: 3313, 2925, 1629, 1604, 1436, 1365, 1288, 1149, 1070 cm^{-1}; EIMS *m/z* (%): 304 ([M^+], 38), 289 (3), 261 (9), 235 (25), 219 (22), 181 (100).

4,6-Bis[(methoxy)methoxy]-2-hydroxy-3-(1'-geranyl)acetophenone (5) To a stirred mixture of **4** (608 mg, 2 mmol) and anhydrous K_2CO_3 (1.932 g, 14 mmol) in dry acetone (40 mL) was added dropwise MOMCl (400 mg, 5 mmol). The mixture was heated at reflux for 1.5 h, then cooled to room temperature, filtered, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (*V*∶*V*＝6∶1) to afford **5** (564 mg, 72% yield) as a light yellow liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.56, 1.64, 1.77 (s, 9H, $3CH_3$), 1.92—2.05 (m, 4H, 4'-2H and 5'-2H), 2.65 (s, 3H, $COCH_3$), 3.31 (d, *J*＝7.2 Hz, 2H, 1'-2H), 3.48, 3.51 (s, 6H, $2OCH_3$), 5.06—5.25 (m, 4H, $2OCH_2O$, 2'-H and 6'-H), 6.38 (s, 1H, ArH), 13.82 (s, 1H, OH); IR (KBr) ν_{max}: 2973, 2921, 1614, 1485, 1423, 1407, 1373, 1272, 1232, 1155, 1107, 1043, 962 cm^{-1}; EI-MS *m/z* (%): 392 ([M^+], 4), 347 (10), 273 (7), 269 (3), 225 (3), 69 (10), 45 (100).

4',6'-Bis[(methoxy)methoxy]-2'-hydroxy-4-methoxy-3'-(1''-geranyl)chalcone (6) To a stirred mixture of KOH (2.8 g, 50 mmol) in H_2O-EtOH (6.7 mL, *V*∶*V*＝2∶3) cooled to 0 ℃ in an ice bath was added dropwise a solution of **5** (392 mg, 1 mmol) and *p*-methoxybenzaldehyde (149.6 mg, 1.1 mmol, prepared from *p*-hydroxybenzaldehyde) in EtOH (2 mL) cooled to 0 ℃ under nitrogen. The reaction mixture was kept in ice bath for 1 h, then at ambient temperature for 24 h. The resulting mixture was poured into ice water (5 mL), and the solution was adjusted to pH 3—4 with 3 mol/L HCl, then extracted with CH_2Cl_2 (5 mL×3). The combined organic layers were washed with H_2O and saturated brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (*V*∶*V*＝6∶1) to give chalcone **6** (392 mg, 75% yield) as a deep yellow liquid. ^{1}H NMR (400 MHz) *δ*: 1.56, 1.64, 1.78 (s, 9H, $3CH_3$), 1.94—2.06 (m, 4H, 4''-2H and 5''-2H), 3.34 (d, *J*＝7.2 Hz, 2H, 1''-2H), 3.35, 3.48, 3.84 (s, 9H, $3OCH_3$), 5.06—5.26 (m, 4H, $2OCH_2O$, 2''-H and 6''-H), 6.38 (s, 1H, 5'-H), 6.92 (d, *J*＝6.8 Hz, 2H, 3-H, 5-H), 7.53—7.56 (d, *J*＝6.8 Hz, 2H, 2-H, 6-H), 7.83 (s, 2H, H_α, H_β), 13.86 (s, 1H, OH); IR (KBr) ν_{max}: 2918, 2854, 1604, 1577, 1512, 1423, 1316, 1288, 1230, 1172, 1066, 960 cm^{-1}; EI-MS *m/z* (%): 510 ([M^+], 3), 465 (5), 422(6), 355 (9), 299 (37), 219 (18), 165 (31), 149 (16), 121 (17), 91 (100).

5,7-Bis[(methoxy)methoxy]-4'-methoxy-8-(1''-geranyl)flavanone (7) To a solution of **6** (153 mg, 0.3 mmol) in EtOH (3.5 mL) were added NaOAc (353 mg, 4.3 mmol) and H_2O (one drop). The mixture was heated at reflux for 24 h. After the mixture was cooled to ambient temperature, H_2O (5 mL) was added and the mixture was extracted with Et_2O (10 mL×3). The combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum ether-EtOAc (*V*∶*V*＝2∶1) to give flavanone **7** (122.4 mg, 80% yield) as a light yellow oil. ^{1}H NMR (400 MHz) *δ*: 1.57, 1.64, 1.65 (s, 9H, $3CH_3$), 1.85—2.04 (m, 4H, 4''-2H and 5''-2H), 2.79 (dd, *J*＝3.0, 16.6 Hz, 1H, $H_{3\beta}$), 2.99 (dd, *J*＝13.0, 16.6 Hz, 1H, $H_{3\alpha}$), 3.31 (d, *J*＝7.2 Hz, 2H, 1''-2H), 3.49, 3.54, 3.83 (s, 9H, $3OCH_3$), 5.06—5.10 (m, 1H, *J*＝7.2 Hz, ＝CH), 5.17 (t, *J*＝7.0 Hz, 1H, ＝CH), 5.24, 5.26 (s, 4H, $2OCH_2O$), 5.35 (dd, *J*＝2.8, 12.8 Hz, 1H, 2-H), 6.57 (s, 1H, 6-H), 6.93 (d, *J*＝8.8 Hz, 2H, 3'-H, 5'-H), 7.38 (d, *J*＝8.4 Hz, 2H, 2'-H, 6'-H); IR (KBr) ν_{max}: 2960, 2910, 1681, 1595, 1515, 1444, 1334, 1253, 1151, 1068, 1037 cm^{-1}; EI-MS *m/z* (%): 510 ([M^+], 3), 465 (5), 387 (17), 355 (18), 343 (23), 331 (12), 209 (8), 161 (41), 134 (24), 45 (100).

(±)-Puyanin(5,7-dihydroxy-4'-methoxy-8-(1''-geranyl)flavanone (1) To a stirred solution of **7** (51 mg, 0.1 mmol) in MeOH (2 mL) was added dropwise 3 mol/L HCl (0.4 mL). The solution was heated at reflux for 45 min, then H_2O (5 mL) was added, and the solution was extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petoleum ether-EtOAc (*V*∶*V*＝8∶1) to give **1** (33.7 mg, 80% yield) as a yellow amorphous solid. m.p. 158—162 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.59, 1.66, 1.71 (s, 9H, $3CH_3$), 2.01—2.09 (m, 4H, CH_2), 2.80 (dd, *J*＝3.0, 17.0 Hz, 1H, $H_{3\beta}$), 3.06 (dd, *J*＝13.0, 17.2 Hz, 1H, $H_{3\alpha}$), 3.32 (d, *J*＝7.2 Hz, 2H, 1''-2H), 3.84 (s, 3H, OCH_3), 5.00—5.06 (m, 1H, ＝CH), 5.21 (t, *J*＝6.8 Hz, 1H, ＝CH), 5.36 (dd, *J*＝3.2, 13.0 Hz, 1H, 2-CH), 6.02 (s, 1H, 6-H), 6.25 (s, 1H, 7-OH), 6.95 (d, *J*＝8.8 Hz, 2H, 3'-H, 5'-H), 7.38 (d, *J*＝8.4 Hz, 2H, 2'-H, 6'-H), 12.02 (s, 1H, 5-OH); ^{13}C NMR ($CDCl_3$, 80 MHz) *δ*: 195.5 (C-4), 162.9 (C-7), 161.1 (C-5), 158.8 (C-4'), 137.7 (C-3''), 130.9 (C-1'), 126.6 (C-2'), 126.5 (C-6'), 122.7 (C-6''), 120.4 (C-2''), 113.0 (C-3',5'), 105.1 (C-8), 102.1 (C-10), 95.8 (C-6), 77.7 (C-2), 59.5 (OMe), 42.2 (C-3), 38. (C-4''), 26.0 (C-5''), 25.5 (C-8''), 21.1 (C-1''), 16.6 (C-9''), 15.1 (C-10''); IR (KBr) ν_{max}: 3232, 2929, 1635, 1585, 1515, 1436, 1375, 1296, 1253, 1174, 1074, 1031 cm^{-1}; EI-MS *m/z* (%): 422 ([M^+], 12), 299 (100), 219 (33), 205 (13), 177 (6), 165 (77), 134 (16), 91 (11), 69 (14), 55 (5).

2',4',6'-Trihydroxy-4-methoxy-3'-(1''-geranyl)chalcone (8) To a stirred solution of **6** (255 mg, 0.5 mmol) in MeOH (10 mL) was added dropwise 3 mol/L HCl (2 mL). The solution was heated at reflux for 15 min, then H_2O (10 mL) was added, and the solution was extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was

purified by silica gel column chromatography eluting with petroleum ether-benzene-EtOAc-formic acid (*V*∶*V*∶*V*∶*V*=3∶2∶2∶0.05) to give chalcone **8** (137 mg, 65% yield) as a yellow gum. m.p. 124——126 ℃; ^{1}H NMR (400 MHz) δ: 1.59, 1.66, 1.83 (s, 9H, 3CH_3), 2.05—2.14 (m, 4H, 4''-2H and 5''-2H), 3.41 (d, *J*=6.8 Hz, 2H, 1''-2H), 3.85 (s, 3H, OCH_3), 5.03—5.29 (m, 2H, 2''-H, 6''-H), 5.88 (s, 1H, 5'-H), 5.97 (s, 1H, OH), 6.93 (d, *J*=4.8 Hz, 2H, 3-H, 5-H), 7.55—7.59 (d, *J*=4.8 Hz, 2H, 2-H, 6-H), 7.82—7.90 (s, 2H, H_α, H_β), 8.48 (s, 1H, OH), 11.68 (s, 1H, OH); IR (KBr) ν_{max}: 3306, 2917, 1626, 1605, 1547, 1515,1454, 1345, 1288, 1232, 1138, 1080 cm^{-1}; EI-MS *m/z* (%): 422 ([M$^+$], 28), 337 (10), 299 (100), 219 (80), 165 (76), 134 (28), 121 (22), 69 (31), 41 (26).

(±)-4'-*O*-Methylbonannione [5,7-dihydroxy-4'-methoxy-6-(1''-geranyl)flavanone, 2] and (±)-puyanin [5,7-dihydroxy-4'-methoxy-8-(1''-geranyl)flavanone, 1] To a solution of **8** (42.2 mg, 0.1 mmol) in EtOH (1 mL) were added NaOAc (41 mg, 0.5 mmol) and H_2O (three drop). The mixture was heated at reflux for 24 h. After the mixture was cooled to ambient temperature, H_2O (5 mL) was added and the mixture was extracted with Et_2O (5 mL×3). The combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum ether-benzene-EtOAc-formic acid (*V*∶*V*∶*V*∶*V*=3∶2∶1.5∶0.05) to give a mixed flavanone of **2** and **1** in a ratio of 5∶1 (33 mg, 78% yield) as pale yellow solid. Five-sixths of this mixture is 4'-*O*-methylbonannione. m.p. 140—145 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.59, 1.69, 1.80 (s, 9H, 3CH_3), 2.04—2.11 (m, 4H, CH_2), 2.78 (dd, *J*=3.2, 17.2 Hz, 1H, $H_{3\beta}$), 3.09 (dd, *J*=13.0, 17.2 Hz, 1H, $H_{3\alpha}$), 3.37 (d, *J*=6.8 Hz, 2H, 1''-2H), 3.83 (s, 3H, OCH_3), 5.00—5.06 (m, 1H, =CH), 5.25 (t, *J*=7.2 Hz, 1H, =CH), 5.34 (dd, *J*=3.2, 13.0 Hz, 1H, 2-CH), 5.98 (s, 1H, 8-H), 6.33 (s, 1H, 7-OH), 6.94 (d, *J*=8.4 Hz, 2H, 3'-H, 5'-H), 7.38 (d, *J*=8.4 Hz, 2H, 2'-H, 6'-H), 12.40 (s, 1H, 5-OH); ^{13}C NMR ($CDCl_3$, 80 MHz) δ: 196.3 (C-4), 164.0 (C-7), 161.2 (C-5), 159.8 (C-4'), 139.4 (C-3''), 132.1 (C-8''), 130.5 (C-1'), 126.5 (C-2',6'), 121.0 (C-2''), 113.0 (C-3', 5'), 105.1 (C-6), 103.1 (C-10), 95.4 (C-8), 77.6 (C-2), 55.3 (OMe), 42.1 (C-3), 38.5 (C-5''), 26.0 (C-6''), 24.6 (C-8''), 21.7 (C-1''), 16.7 (C-9''), 16.5 (C-8''); IR (KBr) ν_{max}: 3406, 3120, 2921, 2850, 1627, 1585, 1517, 1460, 1379, 1296, 1253, 1172, 1089 cm^{-1}; EI-MS *m/z* (%): 422 ([M]$^+$, 31), 337 (15), 299 (100), 219 (73), 203 (13), 177 (11), 165 (70), 134 (27), 121 (27), 91 (34), 79 (12), 69 (40), 55 (24).

Conclusion

In summary, the present synthetic method provides a selective and facile route for the synthesis of C-6 and C-8 prenylated natural flavanoids, by which two geranylated natural flavanoids (±)-puyanin (**1**) and (±)-4'-*O*-methylbonannione (**2**) were first synthesized. The research on the total synthesis of (±)-**1** and (±)-**2** does not only have theoretical importance, but also have the potential medical prospect.

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