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# FIRST TOTAL SYNTHESIS OF (±)-GLYFLAVANONE-A

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## ABSTRACT

First convergent synthesis (±)-glyflavanone-A (**1**), a novel pyranoflavanone natural product, starting from phloroacetophenone and *p*-anisaldehyde is described.

*Key Words:* Pyranoflavanone; Glyflavanone-A; Total synthesis

In a previous paper[1] of this series, we reported a facile and convergent method for the synthesis of naturally occurring pyranoflavanones from readily available prenylated acetophenone derivatives. In continuation of our ongoing research program[2] on the total synthesis of bioactive prenylflavonoids, we herein describe the first total synthesis of (±)-glyflavanone-A (**1**),[3] a natural pyranoflavanoid isolated recently from the leaves of shrub *Glycosmis citrifolia* (Willd.) Lindl. during a reinvestigation of the chemical constituents of the plant which is used in folk medicine for the treatment of certain skin disorders, i.e., itch, scabies, boils and ulcers. Along with **1**,

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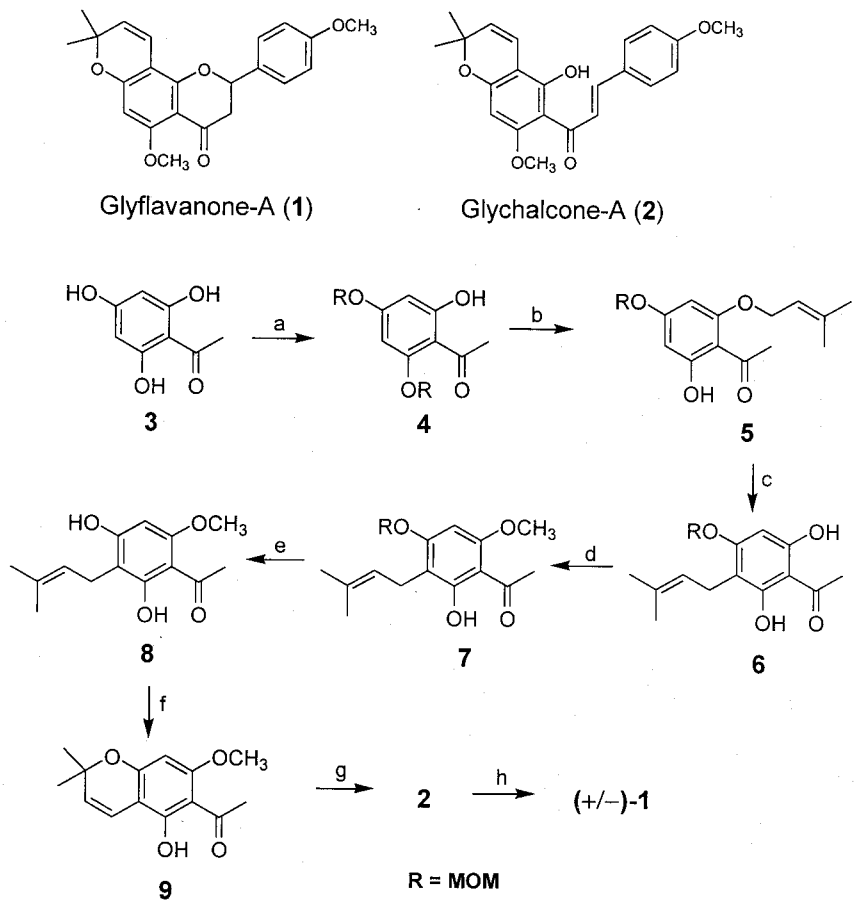


***Scheme 1.*** Reagents and Conditions: a) MOMCl, $K_2CO_3$, acetone, reflux, 0.5 h; b) prenyl bromide, $K_2CO_3$, acetone, reflux, 4 h; chromatography on silica gel; c) *N*,*N*-dimethylaniline, Ar, reflux, 4 h; d) $(CH_3O)_2SO_2$, acetone, $K_2CO_3$, reflux, 0.5 h; e) MeOH, 3 N HCl, reflux, 15 min; f) DDQ, Dioxane, benzene, reflux, 4 h; g) *p*-anisaldehyde, KOH, EtOH, r.t. 36 h; h) NaOAc, EtOH, reflux, 24 h. (MOM = methoxymethyl; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone).

glychalcone A (**2**),[3] a possible biosynthetic precursor of **1**, was also identified. The chemical structures of **1** or **2** were elucidated by extensive spectroscopic analysis. Outlined in Scheme 1 is the synthetic sequence that features an efficient DDQ-mediated oxidative pyranocyclization of the corresponding prenylated phloroacetophenone derivatives.

Selective methoxymethylation of phloroacetophone (**3**) (MOMCl, $K_2CO_3$, acetone) produced **4**[4,2j] in 63% yield, which was treated with prenyl bromide in the presence of $K_2CO_3$ in dry acetone to give the prenyl ether **5** in 91% yield after chromatographic purification on silica gel.[5] Thermal Claisen rearrangement (*N*,*N*-dimethylaniline, reflux)[6] of the prenyl ether **5** afforded the desired *para*-rearranged prenyl acetophenone **6** in 80% yield. Selective *O*-methylation of **6** ($MeO_2SO_2$, $K_2CO_3$, acetone, 86%) followed by demethoxymethylation (3 N HCl, MeOH, 1 : 5, v/v) of the resulting intermediate **7** gave **8** (75% from **6**). DDQ-mediated oxidative pyranocyclization (1.0 equiv., benzene, reflux)[7] of prenyl acetophenone **8** led to chromene **9** (81%, m.p. 117–120°C), which was condensed with *p*-anisaldehyde in an alcoholic aqueous solution of KOH to give the desired glychalcone-A (**2**) in 82% yield as a colorless oil. The chalcone **2** was cyclized in the usual manner (NaOAc, EtOH, reflux) to afford the title compound (±)-glyflavanone-A (**1**) in 70% isolated yield. The synthetic (±)-**1** and **2** have shown identical spectroscopic properties as those reported for the natural products, respectively.[3,8]

## EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and were uncorrected. IR spectra were recorded on a Nicolet 170 FT-IR spectrophotometer as a KBr discs. $^1$H NMR Spectra were recorded on a Bruker AC-80 or an AM-400 instrument in a $CDCl_3$ solution with TMS as an internal standard. Mass Spectra were measured on a ZAB-HS or HP-5988 mass spectrometer. Elemental analyses were performed with a MOD-1106 elemental analyzer. Purification of reagents and solvents was affected according to standard methods. Prior to concentration under reduced pressure, all extracts were dried over anhydrous $Na_2SO_4$. Flash column chromatography was performed on silica gel (200–300 mesh).

### 2-Hydroxy-4-methoxymethoxy-6-prenyloxyacetophenone (5)

To a mixture of **4** (500 mg, 1.79 mmol) and anhydrous $K_2CO_3$ (400 mg, 2.90 mmol) in dry acetone (20 ml) was added prenyl bromide (0.3 ml, 2.60 mmol). The resulting reaction mixture was refluxed for 4 h with stirring, cooled to ambient temperature, and filtered. The filtrate was evaporated and the residue was chromatographed on silica gel with pet. ether–ethyl acetate (v/v, 9 : 1) to give **5** as a white solid (500 mg, 91%), m.p. 39–41°C. $^1$H NMR (80 MHz) δ 1.74 and 1.78 (each 3H, s, C(C$H_3$)$_2$), 2.59 (3H, s, COC$H_3$), 3.45

(3H, s, $OCH_3$), 4.53 (2H, d, $J = 6.6$ Hz, $CH_2$), 5.15 (2H, s, $OCH_2O$), 5.48 (1H, t, $J = 6.6$ Hz, C*H*=), 6.03 and 6.17 (each 1H, d, $J = 2.1$ Hz, *H*-3,5), 13.62 (1H, s, *OH*, exchangeable with deuterium); MS *m*/*z*: 280 ($M^+$), 235, 225, 193, 151, 69, 45.

### 2,6-Dihydroxy-3-prenyl-4-methoxymethoxyacetophenone (6)

A solution of **5** (600 mg, 2.14 mmol) in *N*,*N*-dimethylaniline (15 ml) was refluxed under argon for 4.5 h. The reaction mixture was cooled to room temperature, acidified with 3 N HCl, and extracted with ethyl acetate ($3 \times 20$ ml). The combined organic phases were successively washed with 3 N HCl, 10% aqueous $NaHCO_3$ solution, water and brine, dried and concentrated. The residue was chromatographed on silica gel with pel. Ether–ethyl acetate (4 : 1) as an eluent to afford **6** as colorless needles (550 mg, 90%), m.p. 116–119°C. IR: 3400–3100, 1613, 1591, 1517, 1429, 1367, 1279, 1225, 1146, 1081, 1050, 996, 966, 904, 805 $cm^{-1}$; $^1$H NMR (80 MHz) δ 1.71 and 1.80 (each 3H, s, $C(CH_3)_2$), 2.66 (3H, s, $COCH_3$), 3.31 (2H, d, $J = 7.3$ Hz, $CH_2$), 3.45 (3H, s, $OCH_3$), 5.18 (3H, brs, $OCH_2O$ and $C_H$=), 6.17 (1H, s, *H*-5), 9.80 (1H, s, O*H*), 11.13 (1H, s, O*H*); MS *m*/*z*: 280 ($M^+$), 235, 233, 225, 193, 151, 69, 45.

### 2-Hydroy-3-prenyl-4-methoxymethoxy-6-methoxyacetophenone (7)

A mixture of **6** (400 mg, 1.43 mmol), anhydrous $K_2CO_3$ (360 mg, 2.60 mmol) and $Me_2SO_4$ (0.20 ml, 2.12 mmol) in dry acetone (15 ml) was refluxed for 30 min with stirring. The mixture was cooled and filtered. The filtrate was evaporated and the residue was chromatographed on silica gel with pet. ether–ethyl acetate (20 : 1) to give **7** as a colorless oil (360 mg, 86%). $^1$H NMR (80 MHz) δ 1.69 and 1.80 (each 3H, s, $C(CH_3)_2$), 2.64 (3H, s, $COCH_3$), 3.31 (2H, d, $J = 7.2$ Hz, $CH_2$), 3.50 and 3.89 (3H, s, $OCH_3 \times 2$), 5.26 (3H, brs, $OCH_2O$ and $C_H$=), 6.22 (1H, s, *H*-5), 13.99 (1H, s, *OH*, disappeared after deuterium exchange).

### 2,4-Dihydroxy-3-prenyl-6-methoxyacetophenone (8)

To a solution of **7** (160 mg, 0.54 mmol) in methanol (10 ml) was added 2.0 ml of 3 N HCl, the resulting mixture was refluxed after 15 min, then poured into cold water and extracted with dichloronethone ($3 \times 20$ ml). The combined organic phases were washed with water and brine, dried and

concentrated. Then the residue was chromatographed on silica gel with pet. ether–ethyl acetate (9 : 1) to give **8** as a colorless oil (120 mg, 88%). IR: 3400–3100, 1615, 1567, 1469, 1445, 1365, 1286, 1265, 1172, 1145, 1107, 1081, 1024, 984, 911, 804 $cm^{-1}$; $^1H$ NMR (80 MHz) δ 1.79 and 1.84 (each 3H, s, $C(CH_3)_2$), 2.63 (3H, s, $COCH_3$), 3.39 (2H, d, $J = 7.1$ Hz, $CH_2$), 3.86 (3H, s, $OCH_3$), 5.29 (1H, t, $J = 7.1$ Hz, $CH=$), 5.92 (1H, s, *H*-5), 6.23 (1H, s, *OH*), 14.38 (1H, s, *OH*); MS *m*/*z*: 250 ($M^+$), 235, 217, 207, 195, 179, 167, 123, 91, 69, 43.

### 2,2-Dimethyl-5-hydroxy-7-methoxy-6-acetylchromene (9)

To a mixture of **9** (100 mg, 0.4 mmol) and DDQ (90 mg, 0.4 mmol) in dry benzene (5 ml) was added three drops of dry dioxane and the resulting solution was brought to reflux for 4.5 h. The reaction mixture was cooled and filtered. The filtrate was concentrated in vacuum and the resulting residue was chromatographed on silica gel with pet. ether–ethyl acetate (10 : 1) to give **9** as pale yellow needles (80 mg, 81%), m.p. 117–120°C IR: 3400–3100, 1640, 1623, 1597, 1500, 1447, 1424, 1391, 1358, 1320, 1268, 1204, 1157, 1125, 1025, 889, 830, 807 $cm^{-1}$; $^1H$ NMR (80 MHz) δ 1.46 (6H, s, $CH_3 \times 2$), 2.62 (3H, s, $COCH_3$), 3.87 (3H, s, $OCH_3$), 5.46 (1H, d, $J = 10.0$ Hz, *H*-3), 5.90 (1H, s, *H*-8), 6.67 (1H, d, $J = 10.0$ Hz, *H*-4), 14.29 (1H, s, *OH*, exchangeable with deuterium); MS *m*/*z*: 248 ($M^+$), 233, 215, 200, 160, 149, 115, 77, 43.

### Glychalcone-A (2)

To a mixture of the chromene **9** (50 mg, 0.20 mmol) and *p*-anisaldehyde (30 mg, 0.22 mmol) in 1.4 ml of ethanol was added a mixture of KOH (700 mg, 12.5 mmol) in water (0.6 ml) and ethanol (0.7 ml) at 0°C with stirring. After stirring for 36 h under argon at 25°C, the reaction mixture was poured into ice-water, acidified to pH 2 with 3 N HCl and extracted with dichloromethane (3 × 10 ml); the combined organic phases were washed with water and brine, dried and concentrated. The residue was chromotographed on silica gel with pet. ether–ethyl acetate (9 : 1) as an eluent to give **1** as a yellowish oil (60 mg, 81%). IR: 3400, 1622, 1557, 1511, 1462, 1422, 1361, 1287, 1145 $cm^{-1}$; $^1H$ NMR (80 MHz) δ 1.47 (6H, s, $C(CH_3)_2$), 3.87 and 3.93 (each 3H, s, $OCH_3 \times 2$), 5.47 (1H, d, $J = 10.0$ Hz, *H*-3″), 5.94 (1H, s, *H*-5′), 6.71 (1H, d, $J = 10.0$ Hz, *H*-4″), 6.94 (2H, d, $J = 8.8$ Hz, *H*-3,5), 7.58 (2H, d, $J = 8.8$ Hz, *H*-2,6), 7.77 (1H, d, $J = 15.6$ Hz, *H*-α), 7.89 (1H, d,

$J = 15.6$ Hz, *H*-β), 14.73 (1H, s, O*H*); M/S *m/z*: 366 ($M^+$), 351, 232, 218, 217; Anal. calcd for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found: C, 71.98; H, 6.11.

### (±)-Glyflavanone-A (1)

A solution of chalcone **2** (60 mg, 0.16 mmol) and sodium acetate (400 mg, 4.88 mmol) in ethanol (5 ml) with three drops of water was refluxed for 24 h. The reaction mixture was poured into cold water and extracted with ethyl acetate ($3 \times 20$ ml). The combined organic phases were washed with brine and dried. After evaporation of the solvent in vacuum, the residue was chromatographed on silica gel with pet. ether–ethyl acetate (9 : 1) as an eluent to obtain **1** as a yellowish oil (400 mg 70%). IR: 2922, 1666, 1605, 1583, 1516, 1450, 1253, 1206, 1114 $cm^{-1}$; $^1H$ NMR (400 MHz) δ 1.44 and 1.46 (each 3H, s, $C(CH_3)_2$), 2.79 (1H, dd, $J = 16.4$, 3.1 Hz, *H*-$3_{eq}$), 3.01 (1H, dd, $J = 16.4$, 13.1 Hz, *H*-$3_{ax}$), 3.84 and 3.90 (each 3H, s, $OCH_3 \times 2$), 5.37 (1H, dd, $J = 13.1$, 3.1 Hz, *H*-2), 5.46 (1H, d, $J = 10.0$ Hz, *H*-3″), 6.05 (1H, s, *H*-6), 6.58 (1H, d, $J = 10.0$ Hz, H-4″), 6.95 (2H, d, $J = 8.4$ Hz, *H*-3′,5′), 7.39 (2H, d, $J = 8.4$ Hz, *H*-2′,6′); M/S *m/z*: 366 ($M^+$), 351, 251, 232, 217, 203, 149, 134, 119, 91, 77. Anal. calcd for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found: C, 72.44; H, 5.96.

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