Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 17 Sep 2007.

To cite this article: Wenfei Tan , Wei-Dong Z. Li , Chusheng Huang , Yulin Li & Yacheng Xing (1999) Facile Syntheses of 3′,4′-Methylenedioxy- 2″,2″-dimethylpyrano-[5″,6″:7,8]-flavoneand (±)-Ponganone III, Two Pyranoflavanoids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:19, 3369-3377, DOI: 10.1080/00397919908085964

To link to this article: http://dx.doi.org/10.1080/00397919908085964

SYNTHETIC COMMUNICATIONS, 29(19), 3369-3377 (1999)

FACILE SYNTHESES OF 3',4'-METHYLENEDIOXY-2",2"-DIMETHYLPYRANO-[5",6":7,8]-FLAVONE AND (±)-PONGANONE III, TWO PYRANOFLAVANOIDS

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Facile syntheses of two naturally occurring pyranoflavanoids, 3',4'-methylenedioxy-2",2"-dimethylpyrano-[5",6":7,8]-flavone (**1**) and (±)-ponganone III (**2**), have been achieved through the key intermediate chromene **6** by a DDQ-induced oxidative cyclization.

Pyranoflavanoids, a unique class of flavanoids characterized by the presence of a 2,2-dimethyl-2*H*-pyrano subunit, have been extensively investigated in recent years due to their interesting pharmacological properties.[1-3] Although several methods have been developed[4-8] for the synthesis of pyranoflavanoids, the lack of a general and efficient way still remains. In connection with our on-going program on the synthesis of flavanoids, herein we present the first facile syntheses of 3',4'-methylenedioxy-2",2"-dimethylpyrano-[5",6":7,8]-flavone (**1**) and ponganone III (**2**), two naturally occurring pyranoflavanoids isolated from

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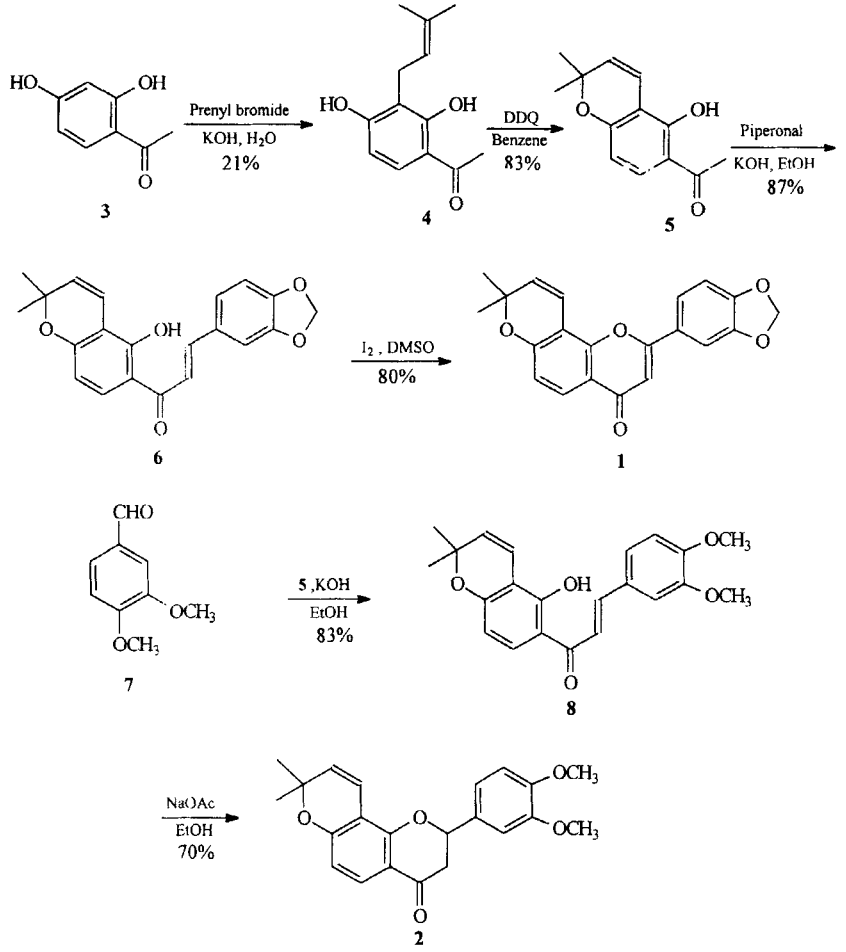
Dahlstedtia pinnata[9] and *Pongamia pinnala*[10] respectively. The synthetic route is outlined in the following scheme:



Scheme

Prenylation of 2,4-dihydroxyacetophenone (**3**) with prenyl bromide in aqueous potassium hydroxide produced the desired C_3-prenylated acetophenone **4** (21%, m.p. 157-158°C)[11] along with 4-hydroxy-prenylated product (40%) and C_5-prenylated 2,4-dihydroxyacetophenone (23%). Acetophenone **4** was converted

into the key intermediate chromene **5** (83%, m.p. 101-104°C) by the treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 1.0 equiv.) in benzene under reflux. Condensation of **5** with piperonal proceeded in an aqueous alcoholic KOH gave the corresponding chalcone **6** (87%, m.p. 142-144°C), which was treated[12] with sublimed iodine in DMSO under reflux to afford the desired pyranoflavanoid **1** (80%, m.p. 232-234°C). The synthetic **1** has identical spectral data with these of natural product.[9] The semi-synthesis of compound **1** using derivant of flavanone as starting material was once reported, but the procedure was limited because the yield was poor and the starting material was not easily obtained as commercial supply.[6] In the same way, alkaline condensation of **5** and 3,4-dimethoxybenzaldehyde (**7**) which was obtained by methylating 3,4-dihydroxybenzaldehyde with dimethyl sulfate gave the chalcone **8** in 83% yield. The chalcone **8,** a precursor of ponganone III (**2**) is also a new natural pyranoflavanoid. It was isolated from the roots of *Lonchocarpus subglaucescens*[13] and its synthesis has not been reported before. The chalcone **8** was cyclized by refluxing in a solution of sodium acetate in ethanol to afford (±)-ponganone III (**3**) in 70% yield. The spectral data of synthetic **2** and **8** are identical with those of reported respectively.[10,13] Thus, a general and facile approach for the synthesis of pyranoflavanoids has been developed based on an efficient preparation of pyrano acetophenone **5** as the key intermediate by a DDQ-induced oxidative cyclization.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are

uncorrected. IR spectra were recorded on a Nicolet 170 FT - IR spectrophotometer as a KBr discs. Unless otherwise stated, ^{1}H NMR spectra were recorded on an AC-80 instruments in $CDCl_3$ 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 effected according to standard methods. Prior to concentration under reduced pressure, all extracts were dried over anhydrous sodium sulfate. Column chromatography was performed on silica gel (200-300 mesh).

Prenylation of 2,4-dihydroxyacetophenone (3)

To a cold (0°C) mixture of **4** (1.52 g, 10 mmol) and potassium hydroxide (1.12 g, 20 mmol) in water (15 mL) was added dropwise prenyl bromide (1.49 g, 10 mmol). The resulting mixture was stirred at 0°C for 1 h and then at 25°C for 12 h. The reaction mixture was poured into ice-water, acidified to pH 2 with 3N HCl and extracted with ether. The combined ether extracts were successively washed with water and brine, dried and concentrated. The residue was chromatographed on silica gel with petrol ether-ethyl acetate (20:1, 8:1) as an eluent to afford **4** as white plates (470 mg, 21%, m.p. 157-158°C, lit.[11] 157-158°C) along with 4-prenyloxy-2-hydroxyacetophenone (colorless thick needles, 900 mg, 40%) and 2,4-dihydroxy-5-prenylacetophenone (white plates, 520 mg, 23%).

2,4-Dihydroxy-3-prenylacetophenone **(4)**: ^{1}H NMR: 1.73 & 1.80 (each 3H, s, C(CH_3)$_2$), 2.52 (3H, s, COCH_3), 3.32 (2H, d, J = 6.8 Hz, CH_2), 5.31 (1H, t, J = 6.8 Hz, CH=), 6.38 (1H, d, J = 9.0 Hz, *H*-5), 7.46 (1H, d, J = 9.0 Hz, *H*-6), 12.54

(1H, s, O*H*, disappeared after deuterium exchange); 4-Prenyloxy-2-hydroxyacetophenone: ^{1}H NMR: 1.67 & 1.72 (each 3H, s, C(CH_3)$_2$), 2.41 (3H, s, COCH_3), 4.44 (2H, d, J = 8.0 Hz, CH_2), 5.38 (1H, t, J = 8.0 Hz, C*H*=), 6.38 (2H, m, *H*-3 and *H*-5), 7.46 (1H, d, J = 9.0 Hz, *H*-6), 13.14 (1H, s, O*H*, disappeared after deuterium exchange); 2,4-Dihydroxy-5-prenylacetophenone: ^{1}H NMR: 1.70 & 1.73 (each 3H, s, C(CH_3)$_2$), 2.45 (3H, s, COCH_3), 3.17 (2H, d, J = 7.0 Hz, CH_2), 5.31 (1H, t, J = 7.0 Hz, C*H*=), 6.27 (1H, s, *H*-3), 7.46 (1H, s, *H*-6), 12.53 (1H, s, O*H*, disappeared after deuterium exchange).

2,2-Dimethyl-5-hydroxy-6-acetylchromene (5)

A mixture of **4** (220 mg, 1 mmol) and DDQ (230 mg, 1 mmol) in dry benzene was added 3-5 drops of dry dioxane and the resulting solution was refluxed for 4-5 h. The reaction mixture was cooled and filtered. The solide residue was washed with ethyl acetate several times. The filtrate was evaporated in vacuum. The residue was chromatographed on silica gel with petrol ether-ethyl acetate (15:1) to give **6** as pale yellow needles (180 mg, 83%), m.p. 101-104°C; IR: 3090, 2976, 1615, 1424, 1366, 1329, 1276, 831, 807 cm^{-1}; ^{1}H NMR: 1.47 (6H, s, C(CH_3)$_2$), 2.56 (3H, s, COCH_3), 5.60 (1H, d, J = 10.0 Hz, *H*-3), 6.35 (1H, d, J = 8.8 Hz, *H*-8), 6.74 (1H, d, J = 10.0 Hz, *H*-4), 7.53 (1H, d, J = 8.8 Hz, *H*-7), 12.99 (1H, s, OH, disappeared after deuterium exchange); MS *m/z*: 218(M$^+$), 203, 184, 161, 132, 128, 94, 77, 43.

3',4'-Methylenedioxy-2'-hydroxy-6",6"-dimethylchromeno-[2",3":4',3']-chalcone (6)

To a cold mixture of the chromene **5** (50 mg, 0.23 mmol) and piperonal (40mg,

0.27 mmol) in 1.4 mL of ethanol was added a cooled solution of potassium hydroxide (700 mg, 12.5 mmol) in water (0.6 mL) and ethanol (0.7 mL) with stirring. The resulting mixture was stirred under argon at 25°C for 36 h. Then the reaction mixture was poured into ice-water, acidified to pH 2 with 3N HCl and extracted with dichloromethane (3×10mL), the combined organic phases were washed with water and brine, dried and concentrated. The residue was chromatographed on silica gel with petrol ether-ethyl acetate (9:1) as an eluent to give chalcone **6** as pale yellow plates (70 mg, 87%), m.p. 142-144°C; IR: 3053, 2921, 1636, 1359 cm^{-1}; ^1H NMR: 1.48 (6H, s, $C(CH_3)_2$), 5.60 (1H, d, J = 10.0 Hz, *H*-3"), 5.96 (2H, s, OCH_2O), 6.39 (1H, d, J = 8.8 Hz, *H*-5'), 6.76 (1H, d, J = 10.0 Hz, *H*-4"), 7.46 (1H, d, J = 8.8 Hz, *H*-6'), 7.42 (1H, d, J = 15.3 Hz, *H*-α), 7.83 (1H, d, J = 15.3 Hz, *H*-β), 6.80-7.25 (3H, m, H-2,5,6), 13.51 (1H, s, OH disappeared after deuterium exchange); MS *m/z*: 350(M^+), 335, 229, 202, 187; Anal. Calad. for $C_{21}H_{18}O_5$: C, 71.90; H,5.1; Found: C, 71.48; H, 4.92.

3',4'-Methylenedioxy-2",2"-dimethylpyrano-[5",6":7,8]-flavone (1)

A mixture of 2'-hydroxychalcone **6** (50 mg, 0.14 mmol) and a crystal of iodine (catalytic amount) in DMSO (5 mL) was refluxed for 15 min. The reaction mixture was cooled and poured into a cold 20% solution of sodium thiosulphate. The solution was extracted with ethyl acetate, the combined organic phases were washed with water and brine, dried and concentrated. The residue was chromatographed on silica gel with petrol ether-ethyl acetate (4:1) to afford the desired flavone **1** as yellow solid (40 mg, 80%), m.p. 232-234°C; IR: 1630, 1580,1500, 1440, 1390, 1360, 1295, 1030, 980, 930, 890cm^{-1}; ^1H NMR: 1.55 (6H,

s, $CH(CH_3)_2$), 5.60 (1H, d, J = 10.0 Hz, *H*-3"), 6.05 (2H, s, OCH_2O), 6.60 (1H, s, *H*-3), 6.75 (1H, d, J = 10.0Hz, *H*-4"), 6.82 (1H, d, J = 8.0Hz, *H*-6), 7.95 (1H, d, J = 8.0 Hz, *H*-8), 6.91-7.43 (3H, m, Ar*H*); MS *m/z*: 348(M^+), 333, 231, 187, 167; Anal. Calad. for $C_{21}H_{16}O_5$: C, 72.41; H,4.63; Found: C, 72.12; H, 4.53.

3,4-Dimethoxy-2'-hydroxy-6",6"-dimethylchromeno-[2",3":4',3']-chalcone (8)

To a cold mixture of the chromene **5** (50 mg, 0.23 mmol) and **7** (40 mg, 0.24 mmol) in 1.4 mL of ethanol, was added a cooled solution of potassium hydroxide (700 mg, 12.5 mmol) in water (0.6 mL) and ethanol (0.7 mL) with stirring. The mixture was stirred under argon at 25°C for 36 h. Then the reaction mixture was poured into ice-water, acidified to pH 2 with 3N HCl and extracted with dichloromethane (3×10mL), the combined organic phases were washed with water and brine, dried and concentrated. The residue was chromatographed on silica gel with petrol ether-ethyl acetate (9:1) as an eluent to give chalcone **8** as a yellowlish oil (70 mg, 83%). IR: 2918, 1631, 1582, 1509, 1264, 1112 cm^{-1}; ^1H NMR(400 MHz): 1.48 (6H, s, $C(CH_3)_2$), 3.93 & 3.97 (each 3H, s, OCH_3 ×2), 5.61 (1H, d, J = 10.0 Hz, *H*-3"), 6.77 (1H, d, J = 10.0 Hz, *H*-4"), 6.40 (1H, d, J = 8.8 Hz, *H*-5'), 7.74 (1H, d, J = 8.8 Hz, *H*-6'), 6.92 (1H, d, J = 8.2 Hz, *H*-5), 7.17 (1H, d, J = 1.9 Hz, *H*-2), 7.26 (1H, dd, J = 8.2 and 1.9 Hz, *H*-6), 7.43 (1H, d, J = 15.4 Hz, *H*-α), 7.85 (1H, d, J = 15.4 Hz, *H*-β), 13.80 (1H, s, 2'-O*H*); MS *m/z*: 366(M^+), 351, 187, 164, 149, 131; Anal. Calad. for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05; Found: C, 72.53; H, 5.95.

Synthesis of (±)-ponganone III (2)

A solution of chalcone **8** (60 mg, 0.16 mmol) and sodium acetate (400 mg, 4.9

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 ×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 petrol ether-ethyl acetate (9:1) as an eluent to obtain **2** as a yellowlish oil (40 mg 70%). IR: 2929, 1681, 1595, 1516, 1269, 1111, 1026, 809 cm^{-1}; ^1H NMR(400 MHz): 1.45 & 1.48 (each 3H, s, $C(CH_3)_2$), 2.83 (1H, dd, J = 17.0 and 3.0 Hz, *H*-3eq), 3.05 (1H, dd, J = 17.0 and 17.0 Hz, *H*-3ax), 3.92 & 3.93 (each 3H, s, OCH_3 ×2), 5.43 (1H, dd, J = 17.0 and 3.0 Hz, *H*-2), 5.59 (1H, d, J = 10.0 Hz, *H*-4"), 6.51 (1H, d, J = 8.8 Hz, *H*-6), 6.65 (1H, d, J = 10.0 Hz, *H*-3"), 6.92 (1H, d, J = 8.6 Hz, *H*-5'), 7.02 (2H, m, *H*-2',6'), 7.75 (1H, d, J = 8.8 Hz, *H*-5); MS *m/z*: 366(M^+), 351, 202, 187, 164, 149, 131; Anal. Calad. for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05; Found: C, 72.38; H, 5.98.

ACKNOWLEDGEMENTS

This work was financially supported by the National Natural Science Foundation of China (29472044).

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(Received in the USA 17 February 1999)