First total synthesis of (R,S)-8-geranyl-5,7-dihydroxyflavanone

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8-Geranyl-5,7-dihydroxyflavanone, a geranylflavanone natural product isolated from Helichrysum hypocephalum, has been synthesized in racemic form for the first time from in six steps including geranylation, hydroxyl protection, condensation, cyclization and deprotection, starting from 2,4,6-trihydroxyacetophenone and benzaldehyde.

Geranylflavonoids are a large group of natural products separated from many traditional medicinal plants in recent years. Many of them have been reported to have physiological effect such as hypotensive, antibacterial, antitumor, etc. In all these geranylflavonoids, known so far, the C-8 geranyl substituted flavanones have not been synthesized. We report herein a general synthetic route for this type of natural products.

8-Geranyl-5,7-dihydroxyflavone was isolated from Helichrysum hypocephalum and its structure elucidated as 1. In this paper, we report for the first time the total synthesis of this compound in five steps. The synthetic route is outlined in Scheme I.

Treatment of 2,4,6-trihydroxyacetophenone 2 and geranyl bromide with anhydrous potassium carbonate in dry acetone under reflux yielded the main product 3a and three by-products 3b, 3c and 3d in 78%, 5%, 5% and 1% yields, respectively. The product 3a was regioselectively protected by chloromethyl methyl ether (MOMCl) to give 4 in 65% yield. Compound 4 was condensed with benzaldehyde in a mixture of aqueous potassium hydroxide in ethanol at 0°C to room temperature with stirring for 36 hr to give the chalcone 5 in 71% yield. Compound 5 was refluxed in a solution of sodium acetate in ethanol for 24 hr to form 6 in 80% yield, followed by hydrolysis with 3N HCl in methanol to afford (R,S)-1. The spectral data of 1 were consistent with those given in literature.

Note

Experimental Section

General. Melting points were measured on a Kofler hot stage and are uncorrected. IR spectra were obtained on FT-170-sx spectrometer. 1H NMR spectra were obtained on Varian FT-80A and AM-400M instruments in CDCl3 solution (chemical shifts in δ, ppm) using Me4Si as internal standard. Mass spectra were measured on ZAB-HS and MAT44S spectrometers by direct inlet at 70eV.

2,4,6-Trihydroxy-3-geranylacetophenone 3a. A mixture of phloracetophenone 2 (1.000 g, 6 mmoles), geranyl bromide (0.604 g, 2.78 mmoles) and anhydrous potassium carbonate (0.415 g, 3.00 mmoles) in dry acetone (3.5 mL) was refluxed under thorough stirring for 6 hr. The reaction mixture was filtered and evaporated under reduced pressure to give an oily residue that was purified by flash column chromatography on Si gel (petroleum ether: EtOAc=10:1) to afford the unreacted 2 (228 mg) and 3a (1.100 g), 3b (71 mg), 3c (75 mg), as well as 3d (25 mg) in 78%, 5%, 5% and 1% yields (based on unrecovered starting material) respectively.

Compound 3a: a light yellow powder, mp105-106°C (lit9 mp 119-120°C, according to lit9 3a is a yellow oil) 1H NMR (CDCl3): δ 1.60 (s, 3H), 1.67 (s, 3H), 1.82 (s, 3H), 1.80-2.20 (m, 4H), 2.68 (s, 3H), 2.32 (d, J=7.0Hz, 2H), 5.17 (t, J=6.8Hz, 1H), 5.26 (t, J=7.0Hz, 1H), 5.90 (s, 1H), 6.97 (s, 1H), 9.55 (s, 1H) and 11.67 (s, 1H; IR (KBr): 3403, 3235, 1644, 1614, 1567, 1556, 1436, 1258, 1128 and 815 cm-1; MS (%): m/z 304 (M+, 30), 289 (3), 261 (9), 235 (25), 219 (22) and 181 (100).

3b: Colourless fine crystals (EtOAc-petroleum ether), mp 145-147°C (lit11 mp 147-150°C).

3c: A white waxy substance (lit11 waxy substance).

3d: Colourless fine crystals (EtOAc-pet. ether), mp 71-74°C; 1H NMR (CDCl3): δ 1.62 (s, 6H), 1.70 (s, 6H), 1.74 (s, 3H), 1.83 (s, 3H), 1.90-2.20 (m, 8H), 2.65 (s, 3H), 3.41 (d, J=7.0Hz, 2H), 4.56 (d, J=6.8Hz, 2H), 5.05-5.60 (m, 4H), 5.92 (s, 1H), 6.25 (s, 1H) and 14.41 (s, 1H; IR (KBr): 3165, 1644, 1614, 1567, 1449, 1367, 1285, 1262, 1220, 1160, 1097 and 815 cm-1; MS (%): m/z 440 (M+, 1), 304 (30), 261 (3), 235 (6), 181 (100), 137 (2) and 69 (25).
4, 6-Dimethoxymethoxy-2-hydroxy-3-(1'-geranyl)acetophenone 4. A mixture of 3a (304 mg, 1 mmoles), MOMCl (200 mg, 2.5 mmoles) and anhydrous K$_2$CO$_3$ (966 mg, 7 mmoles) in dry acetone (20 mL) was stirred well under reflux for 1.5 hr. Evaporation of the solution, which was filtered after reaction, afforded 5 (255 mg, 65% yield) as a deep red gum; $^1$H NMR (400 MHz CDCl$_3$): $\delta$ 1.58 (s, 3H), 1.64 (s, 3H), 1.79 (s, 3H), 1.90-2.15 (m, 4H), 2.66 (s, 3H), 3.32 (d, $J$=7.0 Hz, 2H), 3.48 (s, 3H), 3.58 (s, 3H), 5.06 (t, $J$=6.5 Hz, 1H), 5.19 (t, $J$=7.0 Hz, 1H), 5.24 (s, 2H), 5.27 (s, 2H), 6.40 (s, 1H) and 13.85 (s, 1H). IR (KBr): 2967, 2918, 1617, 1486, 1428, 1406, 1373, 1273, 1231, 1152, 1107, 1070, 1044 and 962 cm$^{-1}$; MS (%): m/z 392 (M$^+$, 4), 347 (10), 273 (7), 269 (3), 225 (3), 69 (10) and 45 (100). HREIMS: m/z 392.2210 [M$^+$] (Calcd for C$_{22}$H$_{24}$O$_6$ 392.2199).

4', 6'-Dimethoxymethoxy-2'-hydroxy-3'-(1''-geranyl)chalcone 5. A well stirred solution of 4 (132 mg, 0.34 mmoles) and benzaldehyde (36 mg 0.34 mmoles) in ethanol (2 mL) cooled to 5°C was added dropwise a solution of potassium hydroxide (1g) in 2mL water-ethanol mixture (2:3) cooled to 0°C under Ar atmosphere. The reaction was carried out for 3 hrs in ice-bath, then stirred for another 33 hr at room temperature. The mixture was poured into ice-water and the solution adjusted pH to 3-4 with dilute HCl, and extracted with diethyl ether. After work-up, the mixture was separated by Si gel column chromatography using pet. ether-EtOAc (10:1) as eluant. The purified chalcone 5 (116 mg) was a red gum, yield 71%; $^1$H NMR: $\delta$ 1.60 (s, 3H), 1.68 (s, 3H), 1.82 (s, 3H), 1.95-2.15 (m, 4H, m), 3.37 (d, $J$=7.0 Hz, 2H), 3.51 (s, 3H), 3.54 (s, 3H), 5.00-5.30
(m, 6H), 6.43 (s, 1H), 7.37-7.65 (m, 5H), 7.75 (d, J=16.0Hz, 1H), 7.99 (d, J=16.0Hz, 1H) and 13.78 (s, 1H); IR (KBr): 2981, 2914, 1613, 1581, 1567, 1448, 1424, 1316, 1229, 1153, 1067 and 1043 cm⁻¹; MS (%): m/z 480 (M⁺, 7), 435 (48), 347 (27), 325 (20), 273 (24), 269 (13), 249 (15), 217 (23), 195 (15), 131 (81), 69 (31) and 45 (100); HREIMS: m/z 480.2483 [M⁺] (Calc. for C₂₉H₂₆O₆ 480.2511).

(R,S)-5,7-dimethoxymethoxy-8-(1'-geranyl)flavanone 6. A solution of 5 (41 mg, 0.085 mmole) and 100 mg anhydrous sodium acetate in EtOH (1 mL) and water (one drop) was refluxed with diethyl ether. After work-up, the mixture was separated by column chromatography to give the unreacted 5 (10 mg) and the yellow crystals of 6 (24.7 mg) in 80% yield, mp 54-55 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.57 (s, 3H), 1.63 (s, 6H), 1.92-2.05 (m, 4H), 2.63 (dd, J=16.5, 3.0Hz, 1H), 2.99 (dd, J=16.5, 12.9Hz, 1H), 3.34 (d, J=6.7Hz, 2H), 3.48 (s, 3d), 3.54 (s, 3H), 5.06 (t, J=7.0Hz, 1H), 5.17 (t, J=6.7Hz, 1H), 5.25 (s, 2H), 5.27 (s, 2H), 5.41 (dd, J=12.9, 3.0Hz, 1H), 6.58 (s, 1H) and 7.26-7.47 (m, 5H); MS (%): m/z 480 (M⁺, 4), 357 (20), 335 (6), 307 (9), 269 (3), 253 (6), 231 (3), 179 (3), 135 (3), 131 (10), 69 (18) and 45 (100); IR (KBr): 2961, 2914, 1718, 1681, 1599, 1578, 1482, 1449, 1335, 1268, 1154, 1105, 1070 and 1041 cm⁻¹.

(R,S)-5,7-dihydroxy-8-(1'-geranyl)flavanone 1. A solution of 6 (24.7 mg, 0.063 mmole) in MeOH (5 mL) and 3N HCl (1 mL) was refluxed for 30 min, then added some water and extracted with EtOAc. After work-up, the extract was purified by Si gel column chromatography (PE-EtOAc, 10:1) to give colourless crystals of (R,S)-1 in 20% yield, mp 106-108°C; ¹H NMR (400MHz, CDCl₃): δ 1.60 (s, 3H), 1.68 (s, 3H), 1.74 (s, 3H), 2.05-2.11 (m, 4H), 2.85 (dd, J=17.2, 3.0Hz, 1H), 3.07 (dd, J=17.2, 13.0Hz, 1H), 3.35 (d, J=7.2Hz, 2H), 5.05 (t, 1H), 5.17 (t, J=7.2Hz, 1H), 5.43 (dd, J=13.0, 3.0Hz, 1H), 6.05 (s, 1H), 6.20 (s, 1H), 7.39-7.48 (m, 5H) and 12.01 (s, 1H); IR (KBr): 3382, 3260, 2968, 2908, 1635, 1603, 1500, 1438, 1379, 1341, 1292, 1221, 1154, 1075 and 1029 cm⁻¹; MS (%): m/z 392 (M⁺, 13), 325 (5), 309 (5), 281 (4), 270 (20), 269 (100), 255 (4), 231 (5), 221 (3), 219 (94), 203 (5), 177 (13), 165 (39), 97 (7), 77 (6), 55 (10) and 41 (14); HREIMS: m/z 392.2000 [M⁺] (Calc. for C₂₅H₂₁O₄ 392.1987).

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Reference
7 Bohm F & Abraham W R, Phytochemistry, 18, 1979, 1851.