A Facile Synthesis of 6-*C*-Prenylflavanones

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Received 6 January 1997; revised 11 April 1997

The first total synthesis of two natural 6-*C*-prenylflavanones, (±)-6-*C*-prenyleriodoctyol (**1**) and 6-*C*-prenylnaringenin (**2**), using the acetophenone derivative **6** as the key intermediate is described. This new efficient synthetic approach was mainly based on Claisen rearrangement and cyclization reaction.

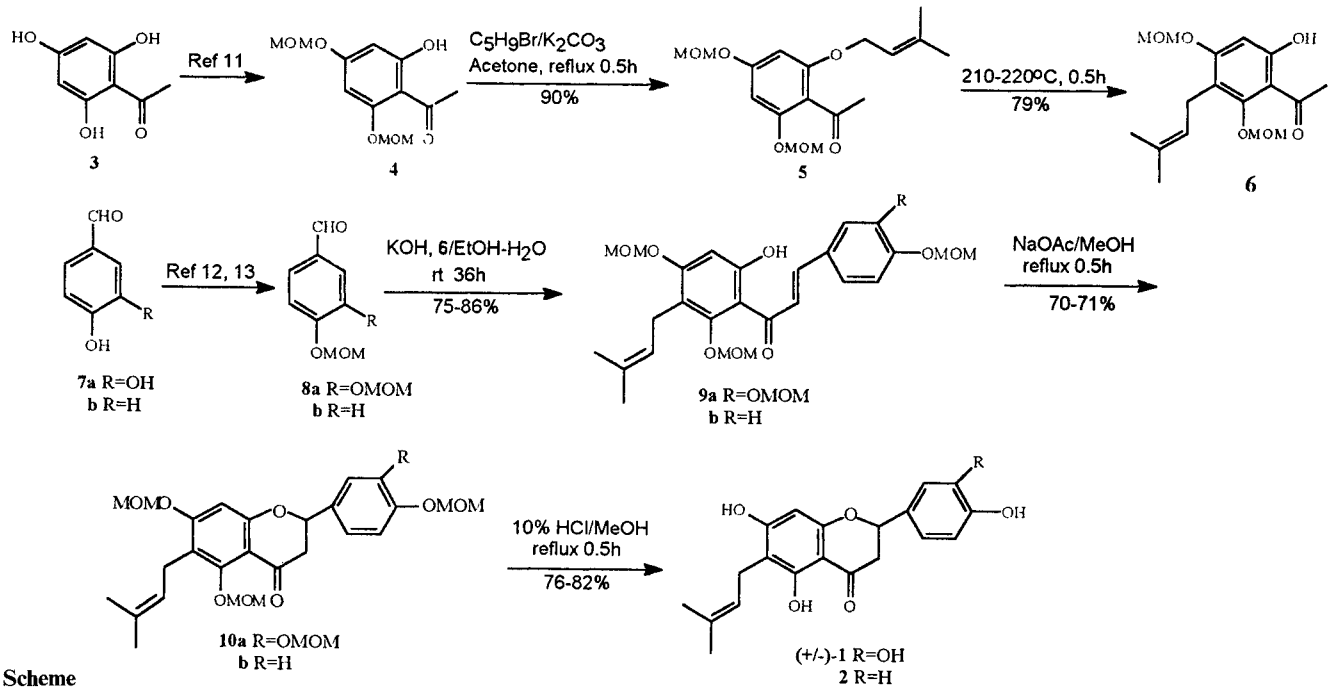
In recent years, the synthesis and pharmocology of prenylflavanones have been extensively investigated due to their wide range of biological activities.[1-6] In 1981, Bohlman et al. described the isolation and structural elucidation of 6-*C*-prenyleriodoctyol (**1**) from *Wyethia helenioids*.[7] This compound represents a new class of flavanones prenylated at C-6 in ring A. To our knowledge, no simple and high-yield way to synthesize 6-*C*-prenylflavanones, especially those with many hydroxy groups, has been reported in the past decades. Though the semisynthesis using polyhydroxyflavanones as starting materials has been reported,[8] this procedure was limited because of its poor yield and was not amenable to the large-scale preparation of 6-*C*-prenylflavanones.

Thus, in view of the biological interest in this new class of flavanones and in continuation of our study on the synthesis of prenylflavonoids, we felt it necessary to develop a new and efficient synthetic method for the preparation of 6-*C*-prenylflavanones. Herein we present the first total synthesis of two such compounds, (±)-6-prenyleriodoctyol (**1**) and 6-*C*-prenylnaringenin (**2**), of which the latter was isolated from *Wyethia glabra* by Mccormick et al.[9] The synthetic route is shown in the Scheme.

In order to prepare the key intermediate **6**, we first treated 2,4,6-trihydroxyphenylethanone (**3**) with prenyl bromide (4-bromo-2-methylbut-2-ene), then selectively protected the hydroxy group as the methoxymethyl ether. But we found that 2-hydroxy-4,6-bis(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenylethanone instead of compound **6** was obtained in this way.[10] Then we prepared the key intermediate **6** using the following strategy in which the Claisen rearrangement of ether **5** is the key step.

Treatment of 2,4,6-trihydroxyphenylethanone (**3**) with two equivalents of chloromethyl methyl ether gave the desired compound **4** in 68% yield.[11] Compound **4** was refluxed with prenyl bromide in the presence of potassium carbonate in anhydrous acetone to afford the ether **5** in 90% yield. A 79% yield of the prenylated acetophenone **6** was obtained by the Claisen rearrangement of the ether **5**.

The hydroxy-protected benzaldehydes **8a** and **8b** were prepared by methoxymethylation of precursors **7a** and **7b**, respectively.[12,13] Condensation of benzaldehyde **8** and acetophenone **6** proceeded in aqueous alcoholic alkali solution giving the chalcone **9**. Chalcone **9** was cyclized by refluxing in a solution of sodium acetate in ethanol to the flavanone **10**. It is noteworthy that the presence of some drops of water which dissolve the sodium acetate is essential for this cyclization reaction. The preparation of (±)-6-*C*-prenyleriodoctyol (**1**) and 6-*C*-prenylnaringenin (**2**) was achieved by demethoxymethylation of com-



Scheme

pounds **10a** and **10b** in a mixture of 10% aqueous hydrochloric acid and methanol (1:5, v/v), respectively.

In summary, a seven-step process has been described to prepare the 6-*C*-prenylflavanones **1** and **2**. The advantages of this approach are reasonable yields (the overall yield of **1** and **2** is 15% and 22%, respectively) and the ease with which the reaction can be carried out under mild conditions with readily available materials and reagents. This new, simple and convenient method should find applications in the synthesis of biologically active 6-*C*-prenylflavonoids and their analogs.

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. Petroleum ether used had bp 60–90 °C. Melting points were measured with a Kofler hot stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 80 spectrometer. Mass spectra were recorded on a HP-5988 mass spectrometer. IR spectra were recorded on a Nicolet 170 XFT-IR spectrameter. Elemental analysis was performed with a MOD-1106 elemental analyzer.

4,6-Bis(methoxymethoxy)-2-(3-methylbut-2-en-1-yloxy)phenylethanone (5):

To a stirred solution of phenol **4** (128 mg, 0.5 mmol) and K_2CO_3 (138 mg, 1 mmol) in acetone (10 mL) was added prenyl bromide (75 mg, 0.5 mmol). After refluxing for 2 h, the solution was filtered, and concentrated. The residue was purified by column chromatography on silica gel using petroleum ether and EtOAc (9:1, v/v) as eluent to give 146 mg (90%) of a colorless oil.

IR (neat): ν = 1701, 1604, 1433, 1225, 1151, 1112, 1072, 1023 cm^{-1}.

^{1}H NMR ($CDCl_3$, 80 MHz): δ = 1.67 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.40 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3) 4.42 (d, J = 7.6 Hz, 2H, CH_2), 5.06 (s, 2H, OCH_2O), 5.09 (s, 2H, OCH_2O), 5.32 (t, J = 7.6 Hz, 1H, CH=), 6.24 (d, J = 2.0 Hz, 1H, C_5–H), 6.36 (d, J = 2.0 Hz, 1H, C_3–H).

MS (70 eV): m/z = 324 (M^+), 296, 279, 256, 212, 182, 138, 109.

Anal. Calc. for $C_{17}H_{24}O_6$ (324.4): C, 62.95; H, 7.46; Found: C, 63.11; H, 7.68.

6-Hydroxy-2,4-bis(methoxymethoxy)-3-(3-methylbut-2-en-1-yl)phenylethanone (6):

The ether **5** (130 mg, 0.40 mmol) was heated at 200–210 °C under Ar for 2 h, then the product was purified by column chromatography on silica gel using petroleum ether and EtOAc (19:1, v/v) as eluent to give 102 mg (79%) of a pale yellow oil.

IR (neat): ν = 1621, 1598, 1272, 1154, 1067 cm^{-1}.

^{1}H NMR ($CDCl_3$, 80 MHz): δ = 1.63 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.25 (d, J = 7.3 Hz, 2H, CH_2), 3.42 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 5.01 (t, J = 7.3 Hz, 1H, CH=), 5.16 (s, 2H, OCH_2O), 5.19 (s, 2H, OCH_2O), 6.18 (s, 1H, C_5–H), 13.67 (s, 1H, OH).

MS (70 eV): m/z = 324 (M^+), 279, 247, 205, 151, 109, 99, 91.

Anal. Calc. for $C_{17}H_{24}O_6$ (324.4): C, 62.95; H, 7.46; Found: C, 63.02; H, 7.53.

(*E*)-1-[6′-Hydroxy-3′-(3-methylbut-2-en-1-yl)-2′,4′-bis(methoxymethoxy)]phenyl-3-[3,4-bis(methoxymethoxy)]phenylprop-2-en-1-one (9a); Typical Procedure:

To a cold solution of **6** (97 mg, 0.30 mmol) and **8a** (75 mg, 0.33 mmol) in EtOH (3.0 mL) was added dropwise a cooled solution of KOH (3.0 g, 53.6 mmol) in H_2O/EtOH (1.2 mL, 2.0 mL) at 0 °C under Ar. After stirring at r.t. for 36 h, the resulting mixture was poured into cold water, acidified to pH 2 with 3% HCl, and extracted with CH_2Cl_2 (2 × 25 mL). The organic phase was washed with sat. aq $NaHCO_3$ solution (30 mL) and H_2O (20 mL), dried ($MgSO_4$), filtered, and then concentrated in vacuo. The residue was chromatographed on silica gel [eluent: petroleum ether/EtOAc (4:1, v/v)] to give 120 mg (75%) of a viscous oil.

IR ($CHCl_3$): ν = 1628, 1572, 1551, 1467, 1269, 1157, 1080 cm^{-1}.

^{1}H NMR ($CDCl_3$, 80 MHz): δ = 1.67 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 3.26 (d, J = 7.5 Hz, 2H, CH_2), 3.63 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.97–5.45 (m, 9H, 4 × OCH_2O and CH=), 6.21 (s, 1H, $C_{5'}$–H), 6.83 (d, J = 8.0 Hz, 1H, C_5–H), 7.36 (m, 2H, C_2–H and C_6–H), 7.47 (d, J = 16.0 Hz, 1H, CH_α =), 8.13 (d, J = 16.0 Hz, 1H, CH_β =), 13.65 (s, 1H, OH).

MS (70 eV): m/z = 532 (M^+), 514, 487, 461, 429, 379, 276, 197.

Anal. Calc. for $C_{28}H_{36}O_{10}$ (532.6): C, 63.14; H, 6.81; Found: C, 63.28; H, 6.87.

Compound **9b**:

Condensation of **6** (97 mg, 0.3 mmol) and **8b** (55 mg, 0.33 mmol) via the same procedure led to 122 mg (86%) of **9b** as a brown oil.

IR ($CHCl_3$): ν = 1631, 1603, 1557, 1487, 1260, 1154 cm^{-1}.

^{1}H NMR ($CDCl_3$, 80 MHz): δ = 1.67 (s, 6H, 2 × CH_3), 3.21 (d, J = 7.0 Hz, 2H, CH_2), 3.45 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 5.11 (s, 2H, OCH_2O), 5.14 (s, 2H, OCH_2O), 5.15–5.17 (m, 3H, OCH_2O and CH=), 6.13 (s, 1H, $C_{5'}$–H), 6.86 (d, J = 8.5 Hz, 2H, C_3–H and C_5–H), 7.43 (d, J = 8.5 Hz, 2H, C_2–H and C_6–H), 7.54 (d, J = 16.0 Hz, 1H, CH_α =), 8.07 (d, J = 16.0 Hz, 1H, CH_β =), 13.23 (s, 1H, OH).

MS (70 eV): m/z = 472 (M^+), 454, 427, 410, 249, 203.

5,7,3′,4′-Tetrakis(methoxymethoxy)-6-(3-methylbut-2-en-1-yl)flavanone (10a); Typical Procedure:

A stirred solution of **9a** (106 mg, 0.20 mmol) and NaOAc (360 mg, 3.66 mmol) in EtOH (4.0 mL) containing 3 drops of H_2O was refluxed for 24 h. After cooling, the mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The organic phase was washed with H_2O and brine, dried ($MgSO_4$) and filtered. After removal of the solvent, the residue was purified by column chromatography on silica gel. Elution with petroleum ether/EtOAc (4:1, v/v) afforded the pure flavanone **10a**; yield: 75 mg (70%); pale yellow powder; mp 83–85 °C.

IR ($CHCl_3$): ν = 1687, 1603, 1471, 1262, 1160 cm^{-1}.

^{1}H NMR ($CDCl_3$, 80 MHz): δ = 1.67 (s, 6H, 2 × CH_3), 2.81 (dd, J = 3.0, 17.0 Hz, 1H, C_3–H), 3.07 (dd, J = 13.0, 17.0 Hz, 1H, C_3–H), 3.28–3.69 (m, 14H, 4 × OCH_3 and CH_2), 5.01–5.43 (m, 10H, 4 × OCH_2O and CH=, C_2–H), 6.11 (s, 1H, C_8–H), 6.81 (d, J = 8.0 Hz, 1H, $C_{5'}$–H), 6.96 (m, 2H, $C_{6'}$–H and $C_{2'}$–H).

MS (70 eV): m/z = 532 (M^+), 517, 502, 461, 411, 358, 201, 189, 135.

Anal. Calc. for $C_{28}H_{36}O_{10}$ (532.6): C, 63.14; H, 6.81; Found: C, 63.31; H, 6.94.

5,7,4′-Tris(methoxymethoxy)-6-(3-methylbut-2-en-1-yl)flavanone **(10b)**: yield: 67 mg (71%); yellowish oil.

IR ($CHCl_3$): ν = 1685, 1601, 1540, 1253, 1152, 1053 cm^{-1}.

^{1}H NMR ($CDCl_3$, 80 MHz): δ = 1.70 (s, 6H, 2 × CH_3), 2.47 (dd, J = 3.2, 17.0 Hz, C_3–H), 2.85 (dd, J = 13.0, 17.0 Hz, 1H, C_3–H), 3.20 (d, J = 7.8 Hz, 2H, CH_2), 3.35 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 5.02–5.33 (m, 8H, 3 × OCH_2O and CH=, C_2–H), 6.09 (s, 1H, C_8–H), 6.83 (J = 8.0 Hz, 2H, $C_{3'}$–H and $C_{5'}$–H), 7.36 (d, J = 8.0 Hz, 2H, $C_{2'}$–H and $C_{6'}$–H).

MS (70 eV): m/z = 472 (M^+), 457, 427, 410, 249, 203.

Anal. Calc. for $C_{26}H_{32}O_8$ (472.5): C, 66.08; H, 6.83; Found: C, 65.92; H, 6.66.

(±)-6-*C*-Prenyleriodoctyol (1); Typical Procedure:

To a cold solution of **10a** (53 mg, 0.10 mmol) in MeOH (5.0 mL) was added 10% aq HCl solution (1.0 mL). The mixture was refluxed for 30 min, poured into cold H_2O (20 mL) and extracted with CH_2Cl_2 (25 mL). The organic layer was washed with H_2O (30 mL) and sat. aq $NaHCO_3$ solution (50 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated. The residue was purified with column chromatography on silica gel using petroleum ether/EtOAc (4:1, v/v) as eluent to give **1** as a white solid; mp 185–186 °C (Lit.[7] mp 188 °C); yield: 27 mg (76%).

IR ($CHCl_3$): ν = 3489, 1661, 1602, 1584, 1503, 1286, 1159 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.69 (s, 6 H, 2 × CH_3), 2.76 (dd, J = 3.0, 17.0 Hz, 1 H, C_3–H), 3.07 (dd, J = 13.0, 17.0 Hz, 1 H, C_3–H), 3.35 (d, J = 7.5 Hz, 2 H, CH_2), 5.17 (t, J = 7.5 Hz, 1 H, CH=), 5.28 (dd, J = 3.0, 17.0 Hz, 1 H, C_2–H), 6.05 (s, 1 H, C_8–H), 6.83 (d, J = 8.0 Hz, 1 H, $C_{5'}$–H), 6.89 (dd, J = 2.0, 8.0 Hz, 1 H, $C_{6'}$–H), 6.95 (d, J = 2.0 Hz, 1 H, $C_{2'}$–H), 12.03 (s, 1 H, OH).

MS (70 eV): m/z = 356 (M^+), 341, 313, 301, 283, 204, 189, 165.

Anal: Calc. for $C_{20}H_{20}O_6$ (356.4): C, 67.41; H, 5.66; Found: C, 67.28; H, 5.74.

6-C-Prenylnaringenin **(2)**: yield: 28 mg (82%); pale yellow oil.

IR ($CHCl_3$): ν = 3376, 1653, 1600, 1537, 1438, 1152 cm^{-1}.

^1H NMR ($CDCl_3$, 80 MHz): δ = 1.67 (s, 6 H, 2 × CH_3), 2.50 (dd, J = 3.0, 17.0 Hz, 1 H, C_3–H), 2.81 (dd, J = 13.0, 17.0 Hz, 1 H, C_3–H), 3.18 (d, J = 8.2 Hz, 2 H, CH_2), 5.09 (t, J = 8.2 Hz, CH=), 5.17 (dd, J = 3.0, 13.0 Hz, 1 H, C_2–H), 6.03 (s, 1 H, C_8–H), 6.71 (d, J = 8.5 Hz, 2 H, $C_{3'}$–H and $C_{5'}$–H), 7.22 (d, J = 8.5 Hz, 2 H, $C_{2'}$–H and $C_{6'}$–H), 12.35 (s, 1 H, OH).

MS (70 eV): m/z = 340 (M^+), 325, 297, 285, 220, 205, 192, 165.

Anal. Calc. for $C_{20}H_{20}O_5$ (340.3): C, 75.74; H; 5.92; Found: C, 75.90; H, 6.04.

This work was supported by financial assistance from the Natural Science Foundation of China.

(1) Mitscher, L.A.; Park, Y.H.; Clark, D. *J. Nat. Prod.* **1990**, *43*, 259.
(2) Mitscher, L.A.; Gollapudi, S.R.; Khanna, I.K.; Trake, S.D.; Hanumaiah, T.; Ramaswamy, T.; Jagannadha Rao, K.V. *Phytochemistry* **1985**, *24*, 2885.
(3) Fomum, Z.T.; Ayafor, J.F.; Mbafor, J.T.; Mbi, C.M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1, 33.
(4) Maillard, M.; Gupta, M.P.; Hostettmann, K. *Plant Medica* **1987**, *53*, 563.
(5) Banerji, A.; Luthria, D.L. *Ind. J. Chem.* **1990**, *29B*, 163.
(6) Huang, L.; Fullas, F.; McGivney, R.J.; Brown, D.M.; Wani, M.C.; Wall, M.E. *J. Nat. Prod.* **1996**, *59*, 290.
(7) Bohlmann, F.; Zdero, C.; Robinson, H.; King, R.M. *Phytochemistry* **1981**, *20*, 2245.
(8) Khan, S.A.; Krishnamurti, M. *Ind. J. Chem.* **1984**, *23B*, 887.
(9) Mccormick, S.; Robson, K.; Bohin, B. *Phytochemistry* **1985**, *24*, 1614.
(10) Bu, X.; Li, Y. *J. Nat. Prod.* **1996**, *59*, 968.
(11) Sherif, E.A.; Islam, A.; Krishnamurti, M. *Ind. J. Chem.* **1982**, *21B*, 478.
(12) Yardly, J.P.; Fletcher, H. *Synthesis* **1976**, 244.
(13) Edwards, R.L.; Mir, I. *J. Chem. Soc.* (C) **1967**, 411.