Syntheses of Knerachlin A and Knerachlin B

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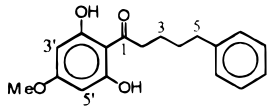
The first total syntheses of knerachlin A and knerachlin B are described, starting from 2,4,6-trihydroxyacetophenone and 2,6-dihydroxyacetophenone, respectively. The key step in the synthesis is the condensation of ketone **5** with cinnamaldehyde.

Diarylpentanoids, a group of compounds having the general structure Ar-C_5-Ar, have been isolated from some traditional medicines.[1,2] Experiments have shown that some of these compounds have interesting physiological actions, they can be antiinflammatory, antifungicidal, and antioxidative agents,[3] as well as inhibitors useful as antirheumatic and antiatherosclerotic agents.[4] Knerachlin A and knerachlin B, two new natural products having strong antibacterial activity, were isolated from *Knema furfuracea*, used in traditional medicine in tropical Africa, Asia, and Australasia.[5] Their structures were elucidated on the basis of spectral data as 5-phenyl-1-(2,6-dihydroxy-4-methoxyl)-phenyl-1-pentanone **(1)** and 5-phenyl-1-(2,6-dihydroxy)-phenyl-1-pentanone **(2)**, respectively. Their syntheses have not been reported so far. In this paper, we wish to describe the total syntheses of **1** and **2**.



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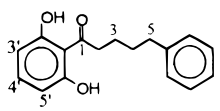

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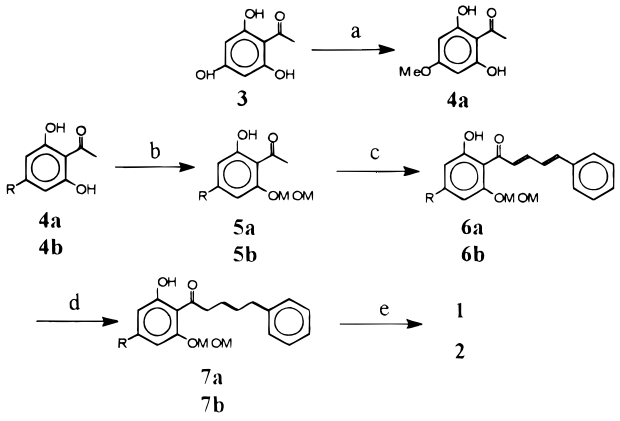
The 2,4,6-trihydroxyacetophenone **3** was treated with Me_2SO_4 and anhydrous K_2CO_3 in Me_2CO under reflux for 2 h to generate **4a** in 56%. Compound **4a** was protected with MOMCl in anhydrous K_2CO_3 and Me_2CO under reflux to give **5a**. The condensation of compound **5a** and cinnamaldehyde in a solution of NaOH in aqueous EtOH at room temperature afforded **6a**. Compound **1** was obtained by selective hydrogenation of **6a** using Pd/C as a catalyst, followed by refluxing in HCl−H_2O−MeOH. The synthesis of **2** was carried out in the same way as that of **1**, starting from **4b**. The synthetic route is outlined in Scheme 1.

The structures of the synthetic compounds were determinated by their IR, MS, and ^{1}H-NMR spectral data. The spectral data of **1** and **2** were consistent with those of the natural products.[5]

Scheme 1[a]



[a] Key: (a) Me_2SO_4, K_2CO_3, acetone, reflux; (b) MOMCl, K_2CO_3, acetone, reflux; (c) cinnamaldehyde, NaOH, EtOH−H_2O, room temperature; (d) H_2−Pd, EtOH, room temperature; (e) 3N HCl−MeOH, reflux.

Experimental Section

General Experimental Procedures. Melting points were measured on a Kofler hot stage and are uncorrected. IR spectra were obtained on a FT-170-SX spectrometer. ^{1}H-NMR spectra were recorded on a Varian FT-80A instrument in $CDCl_3$ solution, and chemical shifts were recorded in ppm units using Me_4Si as internal standard. MS were measured on a ZAB-HS spectrometer by direct inlet at 70 eV and by FAB.

2,6-Dihydroxy-4-methoxyacetophenone (4a). A solution of 2,4,6-trihydroxyacetophenone **3** (2.0 g, 11.9 mmol), Me_2SO_4 (1.1 g, 7.9 mmol) and anhydrous K_2CO_3 (0.96 g, 7.1 mmol) in Me_2CO (40 mL) was stirred under reflux for 2 h. The reaction solution was filtered and evaporated under reduced pressure to give a solid residue that was purified by flash column chromatography on Si gel (petroleum ether−EtOAc, 10:1) to yield recovered **3** (0.81 g) and **4a** (0.716 g) in 56% yield (based on unrecovered starting material) as a colorless solid: mp 132.5−134 °C (MeOH, lit[6] mp 136−137 °C); ^{1}H NMR(DMSO-d_6) δ 2.56 (3H, s, $COCH_3$), 3.72 (3H, s, OCH_3), 5.93 (2H, s, H-3′ and H-5′).

2-Hydroxy-4-methoxy-6-(methoxymethoxy)acetophenone (5a). A mixture of **4a** (200 mg, 1.09 mmol), MOMCl (266 mg, 3.3 mmol), and anhydrous K_2CO_3 (414 mg, 3.0 mmol) in Me_2CO (20 mL) was stirred under reflux for 2 h. Evaporation of the solution, which was filtered after reaction, afforded **5a** (195 mg, 86%) as a white powder: mp 59−61.5 °C (EtOAc−H_2O); IR ν max 3010, 2941, 1615, 1572 cm^{-1}; ^{1}H NMR δ 2.62 (3H, s, $COCH_3$), 3.49 (3H, s, OCH_2OCH_3), 3.78 (3H, s, OCH_3), 5.22 (2H, s, OCH_2OCH_3), 6.08 and 6.11 (each 1H, br s, $W_{1/2}$ = 2.5 Hz, H-3′ and H-5′); EIMS m/z [M]$^+$ 226 (83), 211 (6), 195 (12), 181 (28), 152 (100), 95 (22).

2-Hydroxy-6-(methoxymethoxy)acetophenone (5b). A mixture of **4b** (200 mg, 1.32 mmol), MOMCl (421 mg, 5.28 mmol), anhydrous K_2CO_3 (729 mg, 5.28

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mmol), and Me_2CO (20 mL) was stirred under reflux for 2 h. The reaction mixture was treated as described for **5a** to give **5b** (219 mg, 85%): a light yellowish liquid; IR ν max 3020, 2930, 1620, 1580 cm^{-1}; ^1H NMR δ 2.76 (3H, s, $COCH_3$), 3.53 (3H, s, OCH_2OCH_3), 5.29 (2H, s, OCH_2OCH_3), 6.6 (2H, d, J = 8.2 Hz, H-3′ and H-5′), 7.32 (1H, t, J = 8.2 Hz, H-4′); EIMS m/z $[M]^+$ 196 (27), 165 (6), 153 (1), 122 (27), 108 (6), 77 (8), 45 (100).

5-Phenyl-1-[2-hydroxy-4-methoxy-6-(methoxymethoxy)phenyl]-2,4-pentadien-1-one (6a). To a solution of NaOH (110 mg, 2.69 mmol) in EtOH (3 mL) and H_2O (1 mL) was added **5a** (390 mg, 1.73 mmol) and cinnamaldehyde (225 mg, 1.73 mmol) at room temperature. After being stirred for 2 h, the reaction mixture was treated with 10 mL of H_2O, extracted with EtOAc (3 ×10 mL), and the EtOAc extract dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by Si gel column chromatography, eluted with petroleum ether−EtOAc (v/v 10:1) to give the yellowish solid **6a** (375 mg, 64%): IR ν max 3410, 2943, 1621, 1581, 1152, 1057 cm^{-1}; ^1H NMR δ 3.58 (3H, s, OCH_2OCH_3), 3.64 (3H, s, OCH_3), 5.29 (2H, s, OCH_2OCH_3), 6.12 (2H, s, H-3 and H-5), 7.0−7.9 (9H, m); EIMS m/z $[M]^+$ 340 (28), 295 (10), 167 (100), 129 (90).

5-Phenyl-1-[2-hydroxy-6-(methoxymethoxy)-phenyl]-2,4-pentadien-1-one (6b). To a solution of NaOH (99 mg, 2.47 mmol) in EtOH (2.6 mL) and H_2O (1.0 mL) was added **5b** (200 mg, 1.02 mmol) and cinnamaldehyde (135 mg, 1.02 mmol) at room temperature, and the mixture was stirred for 4 h. Workup and purification of the reaction mixture were the same as for **6a** to afford **6b**, a yellowish gum (215 mg, 68%); IR ν max 3060, 2953, 1677, 1648, 1626, 1577, 1453, 1232 cm^{-1}; ^1H NMR δ 3.54 (3H, s, OCH_3), 5.31 (2H, s, OCH_2-OCH_3), 6.6−7.8 (12H, m); EIMS m/z $[M]^+$ 310 (17), 265 (14), 187 (3), 157 (7), 115 (39), 91 (10), 45 (100).

5-Phenyl-1-[2-hydroxy-4-methoxy-6-(methoxymethoxy)phenyl]-1-pentanone (7a). Compound **6a** (170 mg, 0.5mmol) and Pd/C (50 mg) in EtOH (10 mL) were stirred under a hydrogen atmosphere at room temperature for 4 h. The reaction mixture was filtered off, then evaporated under reduced pressure to give an oily residue. The residue was purified by flash column chromatography on Si gel with petroleum ether−EtOAc (v/v 10:1) to yield **7a** (160 mg, 93%) as a light yellowish oil: IR ν max 3061, 2938, 2859, 1621, 1595, 1429, 1209, 1158, 1058 cm^{-1}; ^1H NMR δ 1.66−1.84 (4H, m), 2.67 (2H, t, J = 6.8 Hz, $CH_2C_6H_5$), 3.07 (2H, t, J = 6.8 Hz, CH_2CO), 3.49 (3H, s, OCH_2OCH_3), 3.62 (3H, s, OCH_3), 5.21 (2H, s, OCH_2OCH_3), 6.13−6.18 (each 1H, d, J = 2.5 Hz, H-3′ and H-5′), 7.24 (5H, br s, C_6H_5); EIMS m/z $[M]^+$ 344 (15), 289 (18), 211 (13), 152 (61), 117 (26), 91 (35), 45 (100).

5-Phenyl-1-[2-hydroxy-6-(methoxymethoxy)-phenyl]-1-pentanone (7b). The reaction and workup sequences of **6b** (167 mg, 0.54 mmol) were the same as for **6a** to afford **7b** (155 mg, 93%) as a yellowish oil: IR ν max 3060, 2931, 1625, 1599, 1452, 1233, 1046 cm^{-1}; ^1H NMR δ 1.70−1.9 (4H, m), 2.71 (2H, m, $CH_2C_6H_5$), 3.14 (2H, m, CH_2CO), 3.52 (3H, s, OCH_2OCH_3), 5.26(2H, s, OCH_2OCH_3), 6.58 (1H, br s, $W_{1/2}$ = 2.5 Hz), 6.68 (1H, br s, $W_{1/2}$ = 2.5 Hz), 7.25 (5H, br s, C_6H_5); EIMS m/z $[M]^+$ 314 (5), 282 (6), 181 (9), 151 (9), 137 (37), 91 (32), 45 (100).

5-Phenyl-1-(2,6-dihydroxy-4-methoxyphenyl)-1-pentanone (1). Compound **7a** (125 mg, 0.363 mmol) was dissolved in 3 N HCl (2 mL) and MeOH (1 mL). After stirring 30 min at 100 °C, the mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the extract dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by Si gel column chromatography eluted with petroleum ether−EtOAc (v/v 10:1) to give **1** (85 mg, 78%), as colorless needles: mp 100−102 °C (EtOAc−H_2O, lit[5] mp 101−102 °C); IR ν max 3236, 3060, 3023, 2931, 1628, 1587, 1206, 1161, 1080 cm^{-1}; ^1H NMR δ 1.65−1.83 (4H, m, 2 CH_2), 2.66 (2H, t, J = 7.0 Hz, $CH_2C_6H_5$), 3.11 (2H, t, J = 7.0 Hz, CH_2CO), 3.79 (3H, s, OCH_3), 5.95 (2H, s, H-3′ and H-5′), 7.23 (5H, br s, C_6H_5); FABMS m/z $[M^+ + H]$ 301; *anal.* C 71.96%, H 6.71%, Calcd for $C_{18}H_{20}O_4$, C 72.24%, H 6.98%.

5-Phenyl-1-(2,6-dihydroxyphenyl)-1-pentanone (2). The reaction and workup of **7b** was the same as for **7a**. Compound **7b** (100 mg, 0.318 mmol) afforded **2** (71 mg, 83%), colorless needles: mp 107−109 °C (EtOAc−H_2O, lit.[5] mp 107−108 °C); IR ν max 3326, 3026, 2930, 2857, 1630, 1596, 1452, 1232, 1040 cm^{-1}; ^1H NMR δ 1.72−1.81 (4H, m, 2 CH_2), 2.69 (2H, t, J = 7.1 Hz, $CH_2C_6H_5$), 3.18 (2H, t, J = 6.8 Hz, CH_2CO), 6.40 (2H, d, J = 8.2 Hz, H-3′ and H-5′), 7.14−7.34 (6H, m, H-4′ and C_6H_5). FABMS m/z $[M^+ + H]$ 271 *anal.* C 75.53%, H 6.71%, calcd for $C_{17}H_{18}O_3$, C 75.70%, H 6.95%.

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