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FIRST TOTAL SYNTHESIS OF (±)-KENUSANONE B

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The first total synthesis of a natural prenylflavanone, (±)-kenusanone B (**1**) has been achieved by condensation of acetophenone **4** and benzaldehyde **6** followed by cyclization and deprotection. Chloromethyl methyl ether was used as a facile protecting reagent of free hydroxy groups for the synthesis of polyhydroxylated flavanones.

In recent years the synthesis and pharmocology of prenylflavanones have been extensively investigated due to their wide range of biological activities[1]. Kenusanone B, a new natural polyhydroxylated prenylflavanone was isolated from the root bark of *E. Koreensis*, and identified[2] as 6, 8-bis(3-methyl-2-butenyl)-5, 7, 2', 4', 6'-pentahydroxy- (2S)-flavanone on the basis of spectral date (CD, NMR, MS, UV). Herein we present the first total synthesis of (±)-kenusanone B (**1**) in order to confirm the proposed structure and further more to evaluate its biological activities.

For the synthesis of polyhydroxylated flavonoids, protecting agents such as dimethyl sulfate[3], alkyl sulphate[4], acetic anhydride[5] were often used to protect the free hydroxy groups, but in most cases, deprotection was always accompanied with

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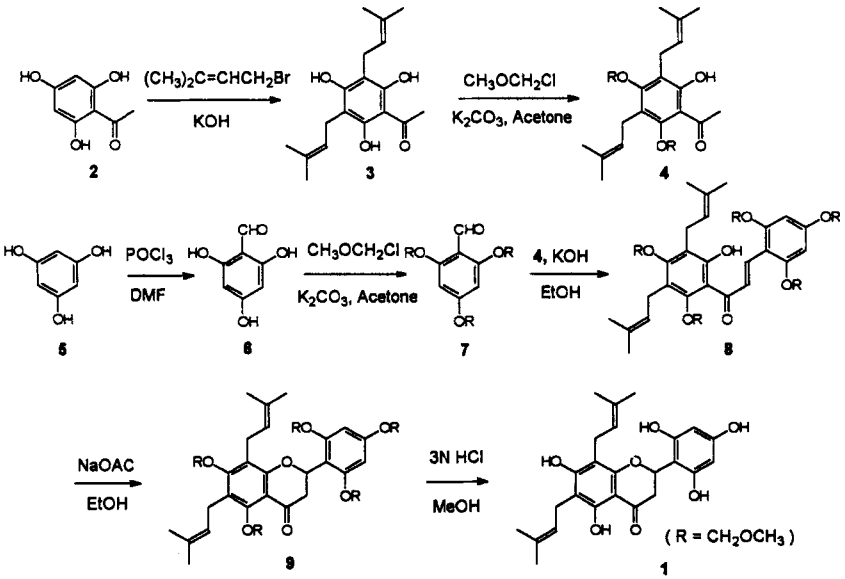
ring cleavage and the yields were poor. In this paper, the methoxy methyl ether protection group, which is stable under alkaline condition but easily cleaved by dilute acid, has been used for the synthesis of polyhydroxylated flavanone (±)-kenusanone B (**1**). Both methoxymethylation and demethoxy methylation of the flavanoids can be easily conducted under mild conditions with good yield. It seems that the methoxy methyl ether function may be the most suitable protecting group for the synthesis of polyhydroxylated flavanone which may have better biological activities[6] than those without hydroxy groups in the A and B rings of the flavanone. The synthetic pathway is outlined in the scheme.



The synthesis started with 2, 4, 6-trihydroxybenzaldehyde[7] (**2**) which was prenylated[8] with prenyl bromide in aqueous potassium hydroxide to afford **3** in 56% yield. Selective methoxymethylation of **3** with chloromethyl methyl ether in the presence of anhydrous potassium hydroxide in dry acetone gave **4** in 83%

yield. 2, 4, 6-Trihydroxybenzaldehyde (**6**) was usually prepared by Adams-Levine reaction[9] of 1, 3, 5-trihydroxybenzene (**5**) in the presence of zinc cyanide with a good stream of hydrogen chloride in dry ether. Here we found treatment of **5** with phosphoryl chloride in N, N-dimethylformamide (Vilsmeier-Hack reaction) can also afford the aldehyde **6** in good yield (88%). To our knowledge, this is the first time that **6** is prepared by this method. The method is simple to perform, implys easy workup and gives satisfactory yield. Methoxymethylation of compound **6** by the method described for **4** gave aldehyde **7** in 90% yield. Condensation of acetophenone **4** and aldehyde **7** proceeded in an aqueous alcoholic alkali give to chalcone **7** in 87% yield. **7** was cyclized by refluxing in a solution of sodium acetate in ethanol to afford flavanone **8** in 72% yield. It is noteworthy that the presence of some drops of water which dissolved sodium acetate is essential for the success of this cyclization reaction. The demethoxymethylation of flavanone **8** with 3N hydrochloric acid and methanol (1:5, v/v) gave compound **1** in 65% yield. The synthetic product is identical with the natural sample in spectral and physical properties except optical activity.

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 in KBr discs. Unless otherwise stated, ^{1}HNMR spectra were recorded at 80MHz on AC-80 instruments in $CDCl_3$ with internal TMS (δ scale).

Mass Spectra were dertermined on a ZAB-HS and HP-5988 mass spectrometer. Elemental analysis 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 with silica gel (200-300 mesh).

2-Hydroxy-3, 5-bis(3-methyl-2-butenyl)-2, 4, 6-trihydroxyacetophenone (3)

The solution of **2** (10 mmol, 1.68 g) in 10% aq. KOH (20 mmol, 1.12 g) was cooled to 0 °C and then prenyl bromide (20 mmol, 2.98 g) was added dropwise in 5 min with stirring. The mixture was stirred at room temperature for 1h, and poured into ice-water, acidified to PH=2, extracted with ethyl acetate. The extract was dried, evaporated and then chromatographed with benzene to give **3** in 56% yield (1.70 g) as pale yellow needles (benzene), mp 78-79^{0}C (lit[8]. 78-79^{0}C). ^{1}HNMR: 1.78 (s, 6H, CH_3×2), 1.83 (s, 6H, CH_3×2), 2.65 (s, 3H, $COCH_3$), 3.37 (d, 4H, J=7.0Hz, CH_2×2), 5.23 (t. 2H, J=7.0Hz, CH=×2), 6.30 (br s, 1H, OH, disappeared after deuterium oxide addition), 10.11 (br s, 2H, OH×2, disappeared after deuterium oxide addition).

2-Hydroxy-3, 5-bis(3-methyl-2-butenyl)-2, 4, 6-trimethoxymethoxyaceto phenone (4)

The mixture of **3** (3 mmol, 912 mg) , anhydrous potassium carbonate (3 g) and methoxy methyl chloride (7 mmol, 564 mg) in acetone (10 mL) was refluxed with

stirring for 30 min, the mixture was cooled and filtered, the filtrate was evapovated and the residue was chromotographed with petrol ether-acetone (19:1) gave **4** in 83% yield (976 mg) as a colorless oil. ^{1}HNMR: 1.68 (s, 6H, CH_3×2), 1.74 (s, 6H, CH_3×2), 2.69 (s, 3H, $COCH_3$), 3.35 (m, 4H, CH_2×2), 3.46, 3.55 (s, each 3H, OCH_3×2), 4.90, 4.96 (s, each 2H, OCH_2O×2), 5.18 (t, 2H, J=7.0Hz, CH=×2), 12.64 (s, 1H, OH, disappeared after deuterium oxide addition).

2, 4, 6-Trihydroxybenzaldehyde (6)

Phosphoryl chloride (10 mmol, 1.54 g) was added dropwise over 15 min to a stirred solution of 1, 3, 5-trihydroxybenzene (**5**) (10 mmol, 1.26 g) in DMF (20 mL) at 0 ^{0}C. The solution was then stirred at room temperature for 3h and poured into ice water. Next day, the product was separated by filtration, washed with water and dried, the aldehyde **6** was obtained as a red powder (1.36 g, 88%). ^{1}HNMR (d_6-acetone): 5.9 (s, 2H, H-3, 5), 10.1 (s, 1H, CHO).

2, 4, 6-Trimethoxymethoxybenzaldehyde (7)

The mixture of **6** (5.0 mmol, 770 mg), chloromethyl methyl ether (20 mmol, 1.61 g) and anhydrous potassium carbonate (8 g) in dry acetone (30 mL) was refluxed for 30 min, the mixture was cooled and filtered, the filtrate was evapovated and the residue was chromotographed with petrol ether-acetone (19:1) to give **7** (1.24 g, 87%) as a colorless oil. IR: 2957, 1683, 1601, 1452, 1393, 1147 cm^{-1}; ^{1}HNMR: 3.49 (s, 3H, OCH_3), 3.52 (s, 6H, OCH_3×2), 5.19 (s, 2H, OCH_2O), 5.25 (s, 4H, OCH_2O×2), 6.26 (br s, 2H, H-3, 5), 10.17 (s, 1H, CHO); m/z (EI-

MS): 286, 255, 224, 181, 150, 91, 45. Anal. Calcd. for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34; Found; C, 54.68; H, 6.28.

2'-Hydroxy-3', 5'-bis(3-methyl-2-butenyl) -4', 6', 2, 4, 6-pentamethoxy methoxy chalcone (8)

To a cold solution of the prenylacetophenone **4** (1.0 mmol, 392 mg) and benzaldehyde **7** (1.5 mmol, 429 mg) in 6 mL ethanol, a cooled solution of potassium hydroxide (3.0 g) in water (2.5 mL) and ethanol (3.0 mL) was added with stirring. The mixture was stirred under argon at room temperature for 36h. Then the whole was poured into ice-water, acidified to PH=2 with dilute hydrochloric acid, and extracted with dichloromethane (3×50 mL), the combined organic phase was washed with water and brine, dried and concentrated. The residue was chromatographed to give chalcone **8** as a reddish oil (594 mg, 90%). IR: 3204, 2925, 1605, 1551, 1450, 1157cm^{-1}; ^{1}HNMR: 1.72, 1.78 (s, each 6H, CH_3×2), 3.35-3.61 (m, 19H, CH_2×2 and OCH_3×5), 4.90, 4.99 (s, each 2H, OCH_2O), 5.20-5.38 (m, 8H, CH=×2 and OCH_2O×3), 6.58 (br s, 2H, H-3, 5), 8.10 (d, J=16.0Hz, 1H, CHα=), 8.38 (d, J=16.0Hz, 1H, CHβ=); m/z (EI-MS): 660, 629, 584, 521, 465, 409, 281, 177, 45. Anal. Cacld. for $C_{35}H_{48}O_{12}$: C, 63.62; H, 7.32; Found: C, 63.45; H, 7.38.

6, 8-Bis(3-methyl-2-butenyl)-5, 7, 2', 4', 6'-pentamethoxymethoxyflavanone (9)

The solution of chalcone **8** (0.5 mmol, 330 mg) and sodium acetate (500 mg) in

ethanol (5 mL) with three drops of water was refluxed for 24h. The reaction mixture was poured into cold water and extracted with ethyl acetate (3×20 mL). The combined organic layer was washed with brine and dried. After removal of the solvent, the residue was chromatographed to afford flavanone **9** as a yellow semi-solid (238 mg, 72%). IR: 2924, 1681, 1610, 1584, 1437, 1156 cm^{-1}; ^{1}HNMR: 1.69, 1.77 (s, each 6H, CH_3×2), 2.52 (dd, J=16.8Hz and 2.8Hz, 1H, H-3α), 3.27 (d, J=7.0Hz, 4H, CH_2×2), 3.45-3.60 (m, 15H, OCH_3×5), 3.92 (dd, J=12.7Hz and 16.8Hz, 1H, H-3β), 4.97 (s, 2H, OCH_2O), 5.10-5.29 (m, 10H, CH=×2 and OCH_2O×4), 5.95 (dd, J=2.8Hz and 12.7Hz, H-2), 6.59 (br s, 2H, H-3', 5'); m/z (EI-MS): 660, 617, 584, 483, 465, 411, 281, 91, 45. Anal. Cacld. for $C_{35}H_{48}O_{12}$: C, 63.62; H, 7.32; Found: C, 63.78; H, 7.28.

6, 8-Bis(3-methyl-2-butenyl)-5, 7, 2', 4', 6'-pentahydroxyflavanone (1):

To a solution of flavanone **9** (0.2 mmol, 132 mg) in methanol (5.0 mL), was added 3N hydrochloric acid (1.0 mL), the resulting mixture was refluxed for 20min, then poured into cold water and extracted with dichloromethane (3×20 mL). The combined organic phase was washed with water and brine, dried and concentrated. Then the residue was chromatographed to give (±)-kenusanone B (**1**) as a pale yellow amorphous powder (57 mg, 65%). IR: 3377, 1629, 1607, 1447, 1247, 1152 cm^{-1}; ^{1}HNMR (d_6-acetone): 1.72, 1.77, 1.79, 1.83 (s, each 3H, CH_3), 2.74 (dd, J=16.8Hz and 2.8Hz, 1H, H-3α), 3.34-3.44 (m, 4H, CH_2×2), 4.11 (dd, J=12.7Hz and 16.8Hz, 1H, H-3β), 5.05-5.23 (m like t, 2H, CH=×2), 5.90 (dd,

J=2.8Hz and 12.7Hz, H-2), 5.99 (br s, 2H, H-3', 5'), 6.47, 6.57, 7.27, 7.37 (br s, disappeared after deuterium oxide addition, each 1H, OH), 12.36 (s, disappeared after deuterium oxide addition, 1H, 5-OH); m/z (FAB-MS): 441, 440, 442, 385, 367, 307, 289, 273, 233, 154; Anal. Cacld. for $C_{25}H_{28}O_7$: C, 68.17; H, 6.41; Found: C, 68.42; H, 6.38.

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