Synthesis of (*R,S*)-Dioclein, a Bioactive Flavanone from the Root Bark of *Diocleia grandiflora*

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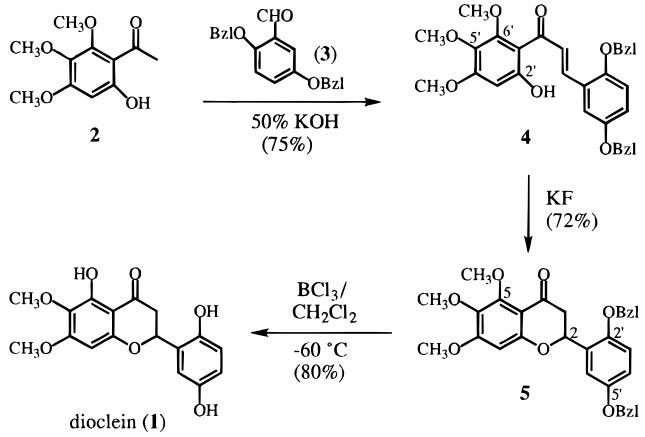
Synthesis of (*R,S*)-dioclein, a bioactive flavanone isolated from the root bark of *Dioclea grandiflora* Mart. ex Benth., is described.

Dioclea grandiflora Mart. ex Benth. (Leguminosae), a vine commonly known as "macuna", is used in the popular medicine of northeastern Brazil.[1] The root of this plant is used in the treatment of kidney stones and prostate gland disorders (Agra, M. F. Universidade Federal de Paraiba, Brazil, unpublished results). A preliminary pharmacological screening of the EtOH extract of the root-bark of *D. grandiflora* showed significant analgesic activity in rats and mice.[2] Subsequently, chemical investigation of the $CHCl_3$-soluble part of the EtOH extract of the root-bark of *D. grandiflora* resulted in the isolation of a new flavanone, dioclein (**1**), mp 160−162 °C, $[\alpha]_D$ − 88.7°, which also demonstrated the analgesic activity detected in the crude extract.[3,4] We required a source of dioclein for chemical corroboration of its structure as well as for further pharmacological studies. Here we report a three-step synthesis of (*R,S*)-dioclein, which represents the first synthesis of this natural product.

Flavanones are isomeric with the corresponding 2′-OH chalcones, and these isomers are easily interconverted using either acid or base. A common approach to the synthesis of flavanones is, therefore, to prepare the intermediate 2′-OH chalcone, with the other functional groups protected, and isomerize to the flavanone in acidic medium.[5] However, in the case of 5′- or 6′-hydroxychalcones, the flavanone is quite stable, and often the chalcone cannot be isolated.[6] Dioclein has a 5-OH group and was expected to be easily prepared from the appropriate chalcone as illustrated in Scheme 1. Surprisingly, this simple strategy proved to be troublesome.

In the first step, 2-hydroxy-4,5,6-trimethoxyacetophenone (**2**) was condensed with 2,5-bis(benzyloxy)benzaldehyde (**3**)[7] in the presence of 50% aqueous KOH to give 2,5-bis(benzyloxy)-2′-hydroxy-4′,5′,6′-trimethoxychalcone (**4**) in 75% yield.[8] We were disappointed to find that treatment of **4** with 60% aqueous KOH in EtOH at reflux for over 72 h gave no reaction. Similarly, traditional acidic conditions, such as 20% or 50% aqueous H_3PO_4 or 30% HBr in HOAc,[9] also failed to promote ring closure despite heating for several days at temperatures between 30 and 70 °C. Decomposition of the chalcone occurred whenever temperatures greater than 75 °C were used. Further work revealed that treatment of **4** with KF in MeOH under reflux for 24 h yielded flavanone **5** in 72% yield,[10] while K_2CO_3 dissolved in CH_3CN could be used to promote cyclization at room temperature in 68% yield, but required longer reaction times (>48 h). Deprotection of the 2′- and 5′-benzyl ethers, along with the selective removal of the labile C-6 methyl ether, was accomplished in 80% yield using BCl_3 in CH_2Cl_2. The spectral (UV, IR, ^1H and ^{13}C NMR, and MS) and chromatographic (TLC) properties of synthetic (*R,S*)-dioclein were identical to those of the natural product.[3]

Scheme 1



Experimental Section

General Experimental Procedures. Melting points were determined in a Thomas Hoover "Unimelt" apparatus and are uncorrected. IR were recorded with a Perkin-Elmer 1600 FT-IR spectrophtometer, and the frequencies were reported in cm^{-1}. ^1H- and ^{13}C-NMR spectra were recorded on a Bruker 250 MHz instrument, and EIMS were recorded on a Finnigan 4000 spectrometer.

2,5-Bis(benzyloxy)-2′-hydroxy-4′, 5′,6′-trimethoxychalcone (4). To a solution of 2-hydroxy-4,5,6-trimethoxyacetophenone (**2**) (0.80 g; 3.5 mmol) and 2,5-bis(benzyloxy)benzaldehyde (**3**) (1.12 g; 3.5 mmol) in absolute EtOH (50 mL) was added 16 mL of 50% aqueous KOH. The resulting mixture was stirred at room temperature for 48 h. The reaction mixture was acidified at 0 °C with 10% aqueous HCl and then extracted with Et_2O (3 × 50 mL). The combined ethereal extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The resulting solid residue was purified *via* column chromatography on Si gel (elution with hexanes−EtOAc, 9:1) to give 1.38 g of **4** (75%), which was homogeneous by TLC analysis [hexanes−EtOAc, 3:1; R_f (**4**) = 0.36, R_f (**2**) = 0.52, R_f (**3**) = 0.62]: mp 101−103 °C (recrystallized from Me_2CO) as deep orange crystals; *anal.* C 72.78%, H 5.89%, calcd for $C_{32}H_{30}O_7$, C 72.98%, H 5.75%; EIMS *m/z* $[M]^+$ 526; IR 3515 (OH), 1676 (conj C=C), 1625

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(conj C=O), 1557 (Ar), 1492 (Ar), 1454 (Ar), 1381, 1348, 1118, 821, and 737 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.22 (d, 1 H, J = 15.9 Hz), 7.93 (d, 1 H, J = 15.9 Hz), 7.28−7.46 (m, 11 H), 6.89−7.01 (m, 2 H), 6.29 (s, 1 H), 5.14 (s, 2 H, $PhCH_2$), 5.06 (s, 2 H, $PhCH_2$), 3.90 (s, 3 H, C4-OCH_3), and 3.82 (s, 6 H, 2 Ar-OCH_3).

2′,5′-Bis(benzyloxy)-5,6,7-trimethoxyflavanone (5) Using KF. Chalcone (**4**) (0.61 g, 1.15 mmol) was added to a stirred solution of KF (0.20 g) in MeOH (25 mL), and the mixture was refluxed for 24 h. The reaction mixture was diluted with H_2O and extracted with Et_2O (5 × 30 mL). The combined ethereal extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give an oily residue. Purification *via* column chromatography on Si gel (elution with hexanes−EtOAc, 9:1) afforded 0.44 g of **5** (72%), which was homogeneous by TLC analysis (hexanes−EtOAc, 2:1; R_f **4** = 0.52, R_f **5** = 0.40): mp 97−99 °C (recrystallized from Me_2CO) as cream-colored crystals; EIMS m/z $[M]^+$ 526; IR 1682 (ArC=O), 1600 (Ar), 1489 (Ar), 1454 (Ar), 1262, 1103, 821, and 737 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.29−7.47 (m, 11 Ar-H), 6.90 (d, 2 H, J = 1.4 Hz, two ArH), 6.36 (s, 1 H, C8-H), 5.07 (s, 2 H, $PhCH_2$), 5.06 (s, 2 H, $PhCH_2$), 5.05 (m, 1H, C2-H), 3.95 (s, 3 H, $ArOCH_3$), 3.87 (s, 3 H, $ArOCH_3$), 3.84 (s, 3 H, $ArOCH_3$), 2.83−2.88 (m, 2 H, C3-H).

2′,5′-Bis(benzyloxy)-5,6,7-trimethoxyflavanone (5) Using K_2CO_3. Chalcone (**4**) (38 mg, 0.07 mmol) was added to a stirred suspension of K_2CO_3 (20 mg, 0.14 mmol) in CH_3CN (1.0 mL), and the resulting mixture was stirred at room temperature for 48 h. The reaction mixture was then acidified with 10% aqueous HCl, saturated with NaCl, and extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude residue (36 mg) was chromatographed on Si gel (elution with hexanes−EtOAc, 9:1) to give 26 mg of **5** (68%), which was identical to that previously characterized.

Dioclein (1). To a solution of **5** (70 mg, 0.13 mmol) in CH_2Cl_2 (2.0 mL) cooled to −60 °C was added dropwise a solution of BCl_3 (530 μL, 0.53 mmol) in CH_2Cl_2 (1.0 mL). The resulting mixture was slowly warmed to room temperature over a 90 min period. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (1.0 mL) and then extracted with Et_2O (3 × 20 mL). The combined ethereal extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on Si gel (elution with hexane−EtOAc, 1:1) to yield 35 mg (80%) of racemic dioclein, which was homogeneous by TLC analysis (hexanes−EtOAc, 1:1; R_f **5** = 0.87, R_f **1** = 0.46): *anal.* calcd for $C_{17}H_{16}O_7$, C 61.43%, H 4.86%; found C 61.23%, H 4.78%; mp 214−216 °C; HRFABMS m/z $[M + H]^+$ 333.0982 (100) (calcd for $C_{17}H_{16}O_7$, 333.0974); IR 1645 (ArC=O), 1558 (Ar), 1506 (Ar), 1456 (Ar), 1290, 1201, 1111, and 808 cm^{-1}; ^1H NMR (250 MHz, Me_2CO-d_6) δ 8.18 (s, 1 H), 7.90 (s, 1 H), 7.01 (d, 1 H, J = 2.8 Hz, ArH), 6.66−6.79 (m, 2 H, ArH), 6.23 (s, 1 H, C8-H), 5.75 (dd, 1 H, J = 12.8, 3.2 Hz, C2-H), 3.90 (s, 3 H, Ar-OCH_3), 3.71 (s, 3 H, Ar-OCH_3), 2.79−3.12 (m, 2 H, C3-H); ^{13}C NMR (62.5 MHz, Me_2CO-d_6) 202.5 (s), 166.2 (s), 164.2 (s), 160.1 (s), 155.7 (s), 151.7 (s), 131.1 (s), 129.0 (s), 121.3 (d), 120.8 (d), 118.3 (d), 107.9 (s), 96.8 (d), 79.9 (d), 64.7 (q), 60.8 (q), 46.8 (t) ppm.

References and Notes

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