

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

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Received September 25, 1996[®]

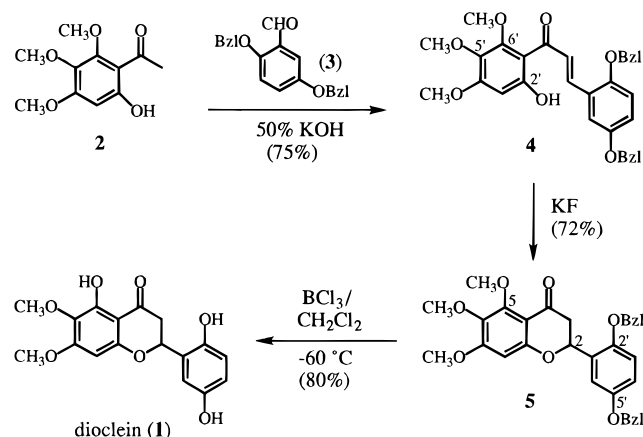
Synthesis of (*R,S*)-dioclein, a bioactive flavanone isolated from the root bark of *Dioclea grandiflora* Mart. ex Benth., is described.

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in the treatment of kidney stones and prostate gland disorders (Agra, M. F. Universidade Federal de Paraiba, Brazil, unpublished results).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 CHCl₃-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, [α]_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 H₃PO₄ 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 K₂CO₃ dissolved in CH₃CN 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

Scheme 1



ethers, along with the selective removal of the labile C-6 methyl ether, was accomplished in 80% yield using BCl₃ in CH₂Cl₂. The spectral (UV, IR, ¹H and ¹³C NMR, and MS) and chromatographic (TLC) properties of synthetic (*R,S*)-dioclein were identical to those of the natural product.³

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 spectrophotometer, and the frequencies were reported in cm⁻¹. ¹H- and ¹³C-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 Et₂O (3 × 50 mL). The combined ethereal extracts were washed with brine, dried over anhydrous MgSO₄, 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 Me₂CO) as deep orange crystals; *anal.* C 72.78%, H 5.89%, calcd for C₃₂H₃₀O₇, C 72.98%, H 5.75%; EIMS *m/z* [M]⁺ 526; IR 3515 (OH), 1676 (conj C=C), 1625

[®] Abstract published in *Advance ACS Abstracts*, April 1, 1997.

(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 $[\text{M}]^+$ 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, ArOCH₃), 3.87 (s, 3 H, ArOCH₃), 3.84 (s, 3 H, ArOCH₃), 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 $\text{C}_{17}\text{H}_{16}\text{O}_7$, C 61.43%, H 4.86%; found C 61.23%, H 4.78%; mp 214–216 °C; HRFABMS m/z $[\text{M} + \text{H}]^+$ 333.0982 (100) (calcd for $\text{C}_{17}\text{H}_{16}\text{O}_7$, 333.0974); IR 1645 (ArC=O), 1558 (Ar), 1506 (Ar), 1456 (Ar), 1290, 1201, 1111, and 808 cm^{-1} ; ^1H NMR (250 MHz, $\text{Me}_2\text{CO}-d_6$) 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, $\text{Me}_2\text{CO}-d_6$) 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

- (1) Andrade Lima, D. *Plantas da Caatingas*; Academia Brasileira de Ciências: Rio de Janeiro, Brazil, 1989; p 112.
- (2) Batista, J. S.; Almeida, R. N.; Bhattacharyya, J., *Abstracts of Papers*, II. Congress de la Federacion Farmaceutica Sudamericana, Montevideo, Uruguay, 1993; p 168.
- (3) Bhattacharyya, J.; Batista, J. S.; Almeida, R. N. *Phytochemistry* **1995**, *38*, 277–278.
- (4) Batista, J. S.; Almeida, R. N.; Bhattacharyya, J. *J. Ethnopharmacology* **1995**, *45*, 207–210.
- (5) Seshadri, T. R. *The Chemistry of the Flavonoid Compounds*; Geissman, T. A., Ed.; MacMillan: New York, 1962; p 156.
- (6) Narashimachari, N.; Seshadri, T. R. *Proc. Ind. Acad. Sci.* **1948**, *27A*, 223–230.
- (7) Compound **3** was prepared from 2,5-dihydroxybenzaldehyde (Aldrich Chemical Co.) using standard Williamson ether conditions.
- (8) Mani, R. I.; Herbert, L.; Manise, D. *J. Tenn. Acad. Sci.* **1991**, *66*, 1.
- (9) Jain, A. C.; Sharma, B. N. *Phytochemistry* **1973**, *12*, 1455–1458.
- (10) Harwood, L. M.; Loftus, G. C.; Oxford, A.; Thomson, C. *Synth. Commun.* **1990**, *20*, 649–657.

NP960659B