A Convenient Synthesis of Hispidin from Piperonal

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An improved synthesis of hispidin (overall yield 24%) starting from the commercially available piperonal is reported. This three-step method is more effective and advantageous compared to the known six-step preparation.

Styrylpyrones are natural products accumulated in fungi and higher plants. The first styrylpyrone glycoside, namely equisetumpyrone A, was isolated from gametophytes and fertile sprouts of Equisetum arvense L., whose structure was recently elucidated. Its biosynthesis is still unknown and we propose that this styrylpyrone glycoside is formed through caffeoyl-CoA, which combines with malonate, and by hydroxylation of the resulting hispidin and subsequent glucosylation of the dihydroxyhispidin B. Hispidin, a naturally occurring styrylpyrone, whose structure was determined as 4-hydroxy-6-(3',4'-dihydroxystyrlyl)-2-pyrone (4) was first isolated from Polyergus hispidus in 1889. This biologically active trihydroxy-substituted styrylpyrone exhibits in vitro antimicrobial activity against Gram-positive organisms, and also the acid-fast Mycobacterium smegmatis.

To verify the proposed biosynthetic route of equisetumpyrone, we required sufficient amounts of hispidin. A cumbersome, multistep synthesis of hispidin was reported earlier; unfortunately, we encountered difficulties with this synthetic sequence and were, therefore, obliged to work out a more convenient method. We report here a three-step synthesis of hispidin (4) (24% overall yield), which starts from the commercially available piperonal (1), as displayed in the Scheme.

The condensation of piperonal (1) with 4-methoxy-6-methyl-2-pyrene in the presence of magnesium methoxide, analogous to the reported preparation of 4-methoxy-6-(4'-methoxystyrlyl)-2-pyrene, afforded the methylenedioxy styrylpyrone 2 in 52% yield. The selective demethylation of 2 with boron trichloride in dichloromethane at 40 °C gave the dihydroxy styrylpyrone 3 in 74% yield. The latter was converted to hispidin (4) in 64% yield by demethylation of the pyrone ether group with sodium thioethoxide in dimethylformamide at reflux.

The advantages of the present three-step route (Scheme) over the previous six-step one are: a) instead of 3,4-di(methoxymethoxy)benzaldehyde, which is prepared by alkylation of 3,4-dihydroxybenzaldehyde with expensive and toxic chloromethyl methyl ether, commercially available piperonal (1) is employed as the carbonyl component for condensation with methylnylpyrone, which proceeds in much higher yield (52% vs. 23%), and b) the methylenedioxy group of 2 is readily cleaved by boron trichloride to release the dihydroxy-substituted styrylpyrone methyl ether 3, which is effectively demethylated to hispidin (4) by sodium thioethoxide in dimethylformamide, an ether cleaving reagent employed for the first time for such an application. In contrast, several steps are required for the deprotection of 4-methoxy-6-[3',4'-di(methoxymethoxy)-styryl]-2-pyrene to hispidin, which was employed in the literature procedure.

Solvents were purified according to standard procedures. CHCl₃ was distilled from P₂O₅ and DMF from CaH₂. Melting points were determined on a Reichert Thermovar hot stage apparatus. IR spectra were recorded on a Perkin-Elmer 1420 spectrometer and the UV spectra on a Hitachi U-3200 spectrophotometer. ¹H and ¹³C NMR spectra were acquired on a Bruker AC 200 (200 MHz) or AC 250 (250 MHz) spectrometer. Chemical shifts refer to CDCl₃, DMSO-d₆, or CD₂OD. The FAB mass spectrum was obtained on a Finnigan MAT 8430 instrument by using glycerol as matrix. 4-Methoxy-6-methyl-2-pyrene was prepared according to the literature procedure by methylation of the commercially available 4-hydroxy-6-methyl-2-pyrene with dimethyl sulfate.

4-Methoxy-6-(3',4'-methylene dioxy styrlyl)-2-pyrene (2):
To a suspension of Mg(O)₂ (60.0 mmol, prepared from 1.46 g
of Mg-turnings) in anhyd. MeOH (40 mL) was added dropwise to a solution of piperonal (1: 3.00 g, 20.00 mmol) and 4-methoxy-6-methyl-2-pyrene (3.36 g, 24.00 mmol) in MeOH (40 mL) under an Ar atmosphere. The mixture was stirred under gentle reflux for 7 h, the solvent was removed by rotoevaporation (40 °C/20 Torr), the residue was dissolved in CH₂Cl₂ (25 mL) and treated with 3.3 M AcOH (30 mL) in H₂O. The aqueous layer was separated and extracted with CH₂Cl₂ (5 × 25 mL). The combined organic layers were washed with H₂O (6 mL), sat. NaH₂PO₄ solution (12 mL) and brine (6 mL), and dried (Na₂SO₄). After removal of the solvent (20 °C/20 Torr) the residue was recrystallized from MeOH (1 L) to afford 2.82 g (10.44 mmol, 52%) of styrylpyrone 2 as pale yellow needles; mp 234–235 °C (Lit.10 mp 236 °C).

IR (KBr): ν = 3070, 1715, 1625, 1605, 1550, 1505, 1440, 1405, 1250, 1155, 1030 cm⁻¹.

UV (MeOH): λₘₐₓ (log ε) = 223 (4.284), 251 (3.993), 363 nm (4.325).

¹H NMR (CDCl₃, 250 MHz): δ = 3.82 (s, 3 H, OCH₃), 5.47 (d, J = 2.2 Hz, 1 H, 3-H), 5.89 (d, J = 2.2 Hz, 1 H, 5-H), 5.99 (s, 2 H, OCH₃), 6.40 (d, J = 15.9 Hz, 1 H, 8'-H), 6.80 (d, J = 8.0 Hz, 1 H, 5'-H), 6.97 (dd, J = 8.0 Hz, 1 H, 6'-H), 7.00 (d, J = 1.5 Hz, 1 H, 2'-H), 7.41 (d, J = 15.9 Hz, 1 H, 7'-H).

Analytical data of 4-Methoxy-6-(3,4-dihydroxystyrlyl)-2-pyrene (3): A 1 M solution of BCl₃ in hexane (6.9 mL, 6.91 mmol) was added dropwise to a solution of styrylpyrone 2 (0.607 g, 2.23 mmol) in anhyd. CH₂Cl₂ (100 mL) under an N₂ atmosphere. Stirring was continued for 22 h at reflux and MeOH (10 mL) was added at 20 °C to the mixture. The solution was removed (20 °C/20 Torr) and the residue was recrystallized from MeOH (25 mL) to give 0.431 g (1.65 mmol, 74%) of styrylpyrone 3 as yellow needles, mp 256–257 °C (Lit.7 mp 257 °C).

IR (KBr): ν = 3600–2900, 1645, 1615, 1585, 1530, 1440, 1395, 1335, 1285, 1240, 1135, 1095, 1025, 950 cm⁻¹.

UV (MeOH): λₘₐₓ (log ε) = 220 (4.372), 253 (4.133), 371 nm (4.405).

¹H NMR (DMSO-d₆, 200 MHz): δ = 3.81 (s, 3 H, OCH₃), 5.58 (d, J = 2.1 Hz, 1 H, 3-H), 6.25 (d, J = 2.1 Hz, 1 H, 5-H), 6.66 (d, J = 16.0 Hz, 1 H, 8'-H), 6.76 (d, J = 8.2 Hz, 1 H, 5'-H), 6.94 (dd, J₁ = 8.2 Hz, J₂ = 1.7 Hz, 1 H, 6'-H), 7.03 (d, J = 1.7 Hz, 1 H, 2'-H), 7.15 (d, J = 16.0 Hz, 1 H, 7'-H).

¹³C NMR (DMSO-d₆, 50 MHz): δ = 56.2 (q, CH₂), 87.9 (d, C-3), 100.0 (d, C-5), 114.0 (d, C-2), 115.7 (d, C-5'), 116.0 (d, C-8'), 120.3 (d, C-6'), 126.6 (s, C-1'), 134.7 (d, C-7'), 145.5 (s, C-3'), 147.4 (s, C-4'), 158.9 (s, C-6), 162.7 (s, C-2'), 170.9 (s, C-4')

Hispinid (4): To a suspension of NaH (72.0 mg, 60% oil dispersion) in anhyd. DMF (1 mL) was added a solution of EtSH (107 mg, 1.73 mmol) in DMF (2 mL) under an N₂ atmosphere. The mixture was stirred for 5 min and a solution of styrylpyrone 3 (100 mg, 0.384 mmol) in DMF (3 mL) was added. Stirring was continued for 1 h at reflux, the mixture was cooled to 0 °C, acidified (pH 6) with 10% aq HCl and extracted with EtOAc (5 × 5 mL). The combined extracts were dried (Na₂SO₄) and the solvent removed (40 °C/20 Torr). The crude product was recrystallized from aq MeOH to yield 60.0 mg (0.244 mmol, 64%) of hispinid (4) as yellow needles, mp 258–259 °C (dec.) (Lit.9 mp 259 °C).

MS (FAB, Glycerol): m/z = 247 (M + H)⁺.

IR (KBr): ν = 3600–2900, 1635, 1585, 1530, 1425, 1355, 1275, 1250, 1185, 1140, 1100, 950 cm⁻¹.


¹H NMR (CD₂OD, 200 MHz): δ = 5.37 (d, J = 1.9 Hz, 1 H, 3-H), 6.07 (d, J = 1.9 Hz, 1 H, 5-H), 6.53 (d, J = 15.9 Hz, 1 H, 8'-H), 6.75 (d, J = 8.2 Hz, 1 H, 5'-H), 6.89 (dd, J₁ = 8.2 Hz, J₂ = 1.9 Hz, 1 H, 6'-H), 7.01 (d, J = 1.9 Hz, 1 H, 2'-H), 7.25 (d, J = 15.9 Hz, 1 H, 7'-H).

¹³C NMR (CD₂OD, 50 MHz): δ = 90.3 (d, C-3), 101.7 (d, C-5), 114.8 (d, C-2), 116.5 (d, C-5'), 116.8 (d, C-8'), 122.0 (d, C-6'), 128.7 (s, C-1'), 137.2 (d, C-7), 146.6 (s, C-3'), 148.6 (s, C-4'), 161.9 (s, C-6), 167.7 (s, C-2'), 173.3 (s, C-4').

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