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A Convenient Synthesis of 6-Hydroxyharman.

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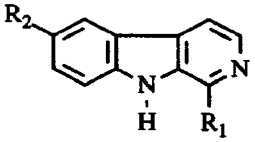
Abstract: *A three-step synthesis of 6-hydroxyharman and 6-hydroxynorharman from benzene and pyridine blocks is described. The preparation of the two α-substituted β-carbolines is based on a new synthetic methodology which involves reactions such as Directed Ortho Metalation and Heteroring Cross-Coupling.*

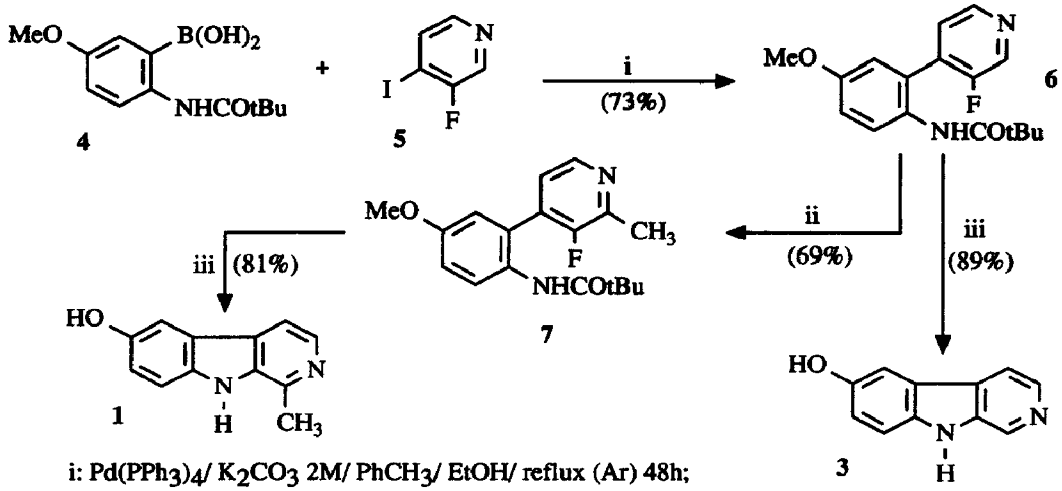
Among the few known 6-hydroxy-β-carbolines are Eudistomins which possess interesting antiviral activity.[1] 6-Hydroxyharman (1) (Scheme 1), was isolated in 1978 by Blomster[2] from roots of *Grewis mollis*. Isoharmine (2) was isolated in 1970 by Willaman and Li[2] from *Virola* species and in 1990 by Ayoub and Rashan[3] from seeds of *Peganum harmala*. It was synthesized by methylation of 6-hydroxyharman (1) with diazomethane.[2] Our group recently published a new convergent route to β-carbolines[4] and α-substituted β-carbolines[5] starting from simple benzene and pyridine reagents. This fruitful strategy was extended to 6-hydroxyharman (1) and 6-hydroxynorharman (3) starting from 4-methoxyaniline.



$R_1 = CH_3$; $R_2 = OH$ (1)
$R_1 = CH_3$; $R_2 = OMe$ (2)
$R_1 = H$; $R_2 = OH$ (3)

Scheme 1

The boronic acid 4 was prepared by metalation-boronation[4] of 4-methoxy-pivaloylaminobenzene in 42% yield and 3-fluoro-4-iodopyridine (5) was obtained in 94% yield by metalation-iodination[4,7] of 3-fluoropyridine. Palladium-catalyzed cross-coupling between the boronic acid 4 and the iodopyridine 5 using a Suzuki procedure[6] afforded the biaryl 6 in 73% yield. Regioselective metalation of 6 by n-butyllithium in THF at low temperature and reaction of the resulting lithio derivative with methyliodide afforded the corresponding 2-methylpyridine 7 in 69% yield (Scheme 2). Cyclization[4] of 6 and 7 to the expected β-carbolines 3 and 1[8] was achieved by treatment with boiling pyridinium chloride at 215°C. Under these conditions, hydrolysis of the methoxy group was observed.



i: $Pd(PPh_3)_4$/ K_2CO_3 2M/ $PhCH_3$/ EtOH/ reflux (Ar) 48h;
ii: 1) nBuLi/ THF/ -78°C/ 1h30min 2) CH_3I/ 1h 3) H_3O^+;
iii: 1) Pyridinium chloride/ 215°C/ 15 min 2) NH_4OH/ 0°C.

Scheme 2

The reported synthesis of 6-hydroxylated β-carbolines (**1**, **3**) relies on selective key steps such as metalation, cross-coupling and cyclization. It is fully convergent, highly regioselective and allows interesting overall yields respectively of 41% and 65%.

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7. Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. Adv. Heterocycl. Chem. **1991**, *52*, 187-304.
8. The main physical data of compound **1** are: mp: 222-223°C; IR (KBr) 3360, 3190, 2960, 2920, 2860, 1605, 1480, 1450, 1430, 1405, 1295, 1185, 835, 825, 815. ^1H NMR (DMSO-d^6) δ (ppm) 2.67 (s, 3H, CH_3); 5.10 (s, 1H, OH); 6.95 (dd, 1H, J= 8.9 and 2.2 Hz); 7.25 (d, 1H, J= 8.9 Hz); 7.46 (d, 1H, J= 8.9 Hz); 7.92 (d, 1H, H_4, J= 5.1 Hz); 8.40 (d, 1H, H_3, J= 5.1 Hz); 8.90 (s, 1H, NH). Anal. Calcd for $C_{12}H_{10}N_2O$ (198.23): C, 72.71; H, 5.08; N, 14.13. Found: C, 72.43; H, 5.14; N, 13.89.

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