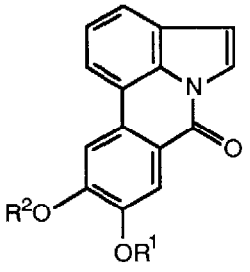
Tetrahedron Letters,Vol.30,No.42,pp 5807-5808,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A DIRECT SYNTHESIS OF PYRROLOPHENANTHRIDONE ALKALOIDS

David St C. Black*, Paul A. Keller, Naresh Kumar
School of Chemistry, The University of New South Wales,
Kensington, N.S.W. 2033. Australia

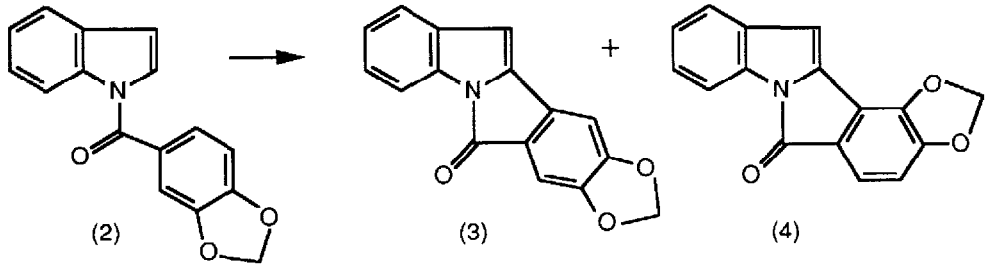
Abstract: *Pyrrolophenanthridone alkaloids were easily synthesized by palladium acetate catalyzed arylation of N-acylindolines (5a-c) followed by dehydrogenation.*

Hippadine (1a), pratorimine (1b), pratorinine (1c) and pratosinine (1d) comprise a series of pyrrolophenenthridone alkaloids[1] isolated from the bulbs of several *Crinum* species (*Amaryllidaceae*). These alkaloids are quite widely distributed in this species and possess significant biological activity. Hippadine (1a) reversibly inhibits fertility in male rats with a remarkable decrease both in testicular weight and in DNA content.[2] The structures of these alkaloids have been established by spectroscopic means and the previous controversy about the structure of pratorimine (1b) and pratorinine (1c) settled by X-ray crystallographic analysis.[3] Although lengthy syntheses of hippadine (1a)[4,5] and pratorimine (1b)[6] have been reported, there is still no general method for the synthesis of these structurally related alkaloids. We now report a new direct synthesis of these pyrrolophenanthridone alkaloids based on palladium catalyzed arylation of N-acylindolines (5) as shown in Scheme 1.



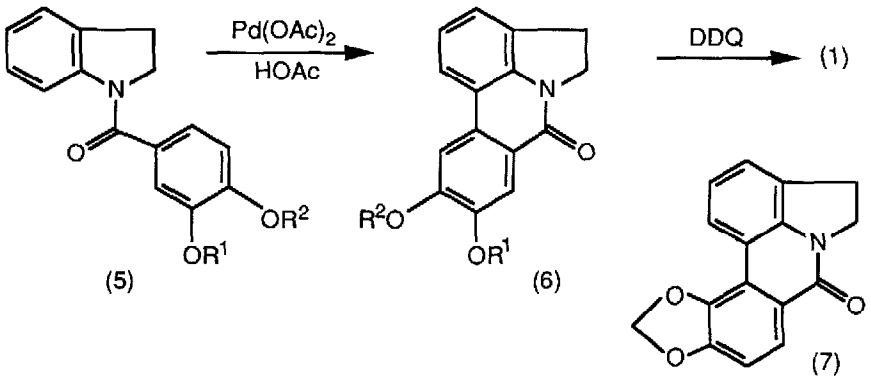
1,5,6	R^1	R^2
a	- CH_2 -	
b	H	Me
c	Me	H
d	Me	Me
e	CH_2Ph	Me
f	Me	CH_2Ph

Initially, it was found that palladium (II) acetate catalyzed intramolecular arylation of N-piperonyl indole (2) occurred exclusively[7] at the indole C2 position to give a mixture of the two regioisomers (3) and (4).



Successful cyclization on to the benzene ring was achieved by carrying out the reaction on the related indoline. In a typical experiment, the N-acylindoline (5a) (0.1 mmol), derived from piperonyl chloride and indoline, was heated with palladium (II) acetate (0.1 mmol) in glacial acetic acid at 115-120° for 5 h to give a mixture of the dihydrophenanthridone (6a; 15%) and the structural isomer (7; 10%). Quantitative dehydrogenation (of the mixture) with dicyanodichloroquinone in dioxan gave hippadine (1a) and its structural isomer.

Similarly, the N-acylindolines (5d, e, f) underwent cyclization respectively to the dihydrocompounds (6d; 50%), 6e; 25%), 6f; 25%)[8]. In each case, only a single isomer was observed. Dehydrogenation of compounds (6d, e, f) gave pratosinine (1d) and the benzyl ethers (1e, f) respectively. Although the yields obtained in the cyclization step are not high, the route is very direct, short and effective.



Scheme 1

Acknowledgement: This research was supported by the Australian Research Grants Scheme.

References and Notes:

1. M.F. Grundon, *Natural Product Reports*, 1989, **6**, 85.
2. S.C. Chattopadhyay, U. Chattopadhyay, P.P. Mathur, K.S. Saini and S. Ghosal, *Planta Med.*, 1983, **49**, 252.
3. J.A. Maddry, B.S. Joshi, A.A. Ali, M.G. Newton, and S.W. Pelletier, *Tetrahedron Letts.*, 1985, **26**, 4301.
4. K. Hayakawa, T. Yasukouchi, and K. Kanematsu, *Tetrahedron Letts.*, 1987, **28**, 5895.
5. S. Prabhakar, A.M. Lobo, and M.M. Marques, *J. Chem. Res. (S).*, 1987, 167.
6. B.S. Joshi, H.K. Desai and S.W. Pelletier, *J. Natural Products*, 1986, **49**, 445.
7. T. Itahara, *Synthesis*, 1979, 151.
8. Selected spectroscopic data: **6e**; m.p. 190-92°; ^{1}H n.m.r. δ ($CDCl_3$) 3.44 (t, *J* 8.2 Hz, 2H), 4.08, (s, 3H), 4.49 (t, *J* 8.2 Hz, 2H), 5.31 (s, 2H), 7.22 (t, *J* 7.5 Hz, 1H), 7.30 (d, *J* 7.2 Hz, 1H), 7.33 (d, *J* 7.4 Hz, 1H) 7.39 (t, *J* 7.6 Hz, 1H), 7.52 (d, *J* 7.6 Hz, 1H), 7.58 (s, 1H), 7.83 (d, 7.9 Hz, 1H), 8.05 (s, 1H); MS *m/z* 357 (M^+, 42%), 266 (100), 238 (38). **1e**; m.p. 181-82°; ^{1}H n.m.r. δ ($CDCl_3$). 4.12 (s, 3H), 5.32 (s, 2H), 6.89 (d, *J* 3.5 Hz, 1H) 7.33 (bt, 1H), 7.41 (t, *J* 7.6 Hz, 2H), 7.48 (t, *J* 7.7 Hz, 1H), 7.53 (d, *J* 7.5 Hz, 2H), 7.69 (s, 1H), 7.75 (d, *J* 7.7 Hz, 1H), 7.98 (d, *J* 7.7 Hz, 1H), 8.05 (d, *J* 3.6 Hz, 1H), 8.09 (s, 1H); MS *m/z* 355 (M^+, 40%), 264 (42), 236 (24).

(Received in UK 25 August 1989)