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SYNTHESIS OF ARCYRIAFLAVIN B

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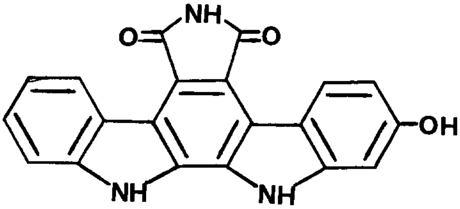
Summary : A flexible synthetic route is described to the substituted indolocarbazole systems present in the natural products arcyriaflavin B (1) and staurosporine(2).

In recent years the occurrence of the unusual indolocarbazole system has been reported in the natural products arcyriaflavins B (1) and C, isolated from the slime mould Arcyria denudata[1] and the antibiotic antihypertensive staurosporine(2) produced by Streptomyces staurosporeus.[2] We have now developed a general route to these little-explored systems which provides efficient incorporation of the substitution patterns of the natural products.



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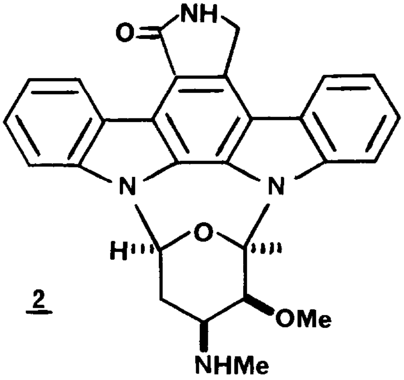

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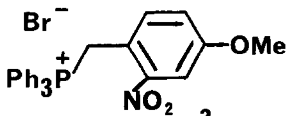
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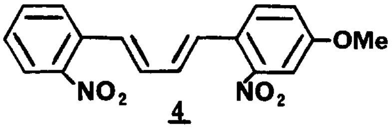
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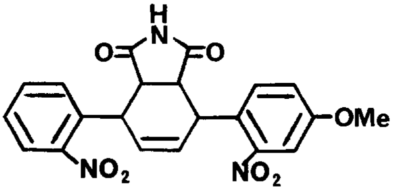
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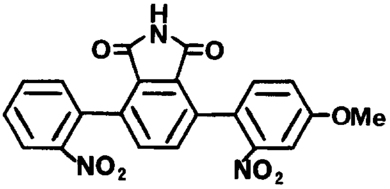
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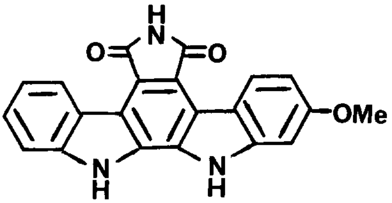
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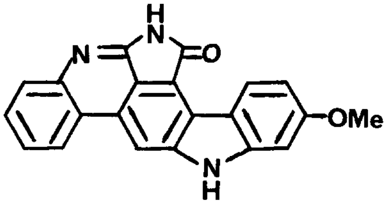
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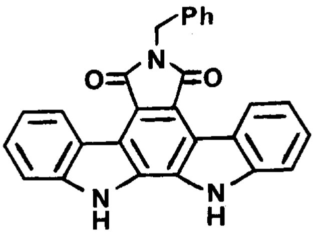
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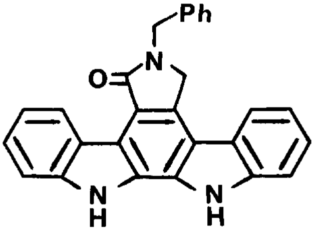
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For the synthesis of arcyriaflavin B the phosphonium bromide (3) was converted into the corresponding ylid (K_2CO_3/18-crown-6/CH_2Cl_2) which was condensed with o-nitrocinnamaldehyde to yield a (Z,E)-diene mixture (80%) which was quantitatively converted to the pure (E,E)-diene (4) orange prisms from toluene m.p. 171 - 172°, by room temperature treatment with iodine in toluene. Heating (4) with neat maleimide (120°; 24 hr) gave the Diels-Alder adduct (5) m.p. 238 - 239° after chromatographic purification (95%). Dehydrogenation of the adduct with DDQ in tert. butylbenzene gave the substituted terphenyl (6; 75 - 80%) m.p. 232 - 233° from ethanol. Deoxygenation[3] of (6) with triphenylphosphine (5 equ.) in refluxing collidine for 40 hours gave the hoped-for double nitrene insertion product (7; 65%) m.p. > 325°. Minor by-products included the mononitrene carbonyl insertion product (8) and the cognate regioisomer. The low solubility of the highly polar indolocarbazole (7) product complicated the seemingly trivial demethylation step but this was finally achieved by heating (7) in a sealed tube with neat pyridine hydrochloride to afford synthetic arcyriaflavin B (1; 87%) yellow needles from acetone m.p. > 325° whose spectroscopic properties corresponded closely with those recorded for the natural product.[5] The overall yield of arcyriaflavin B from 2-nitro-4-methoxybenzyl bromide[4] was 27%.

A cognate series of reactions using 1,4-di(o-nitrophenyl)butadiene and N-benzylmaleimide gave the N-benzylimide (9) in an overall yield of 55%. An alternative route more amenable to larger scale preparation involved the interaction of the diene with dimethyl acetylenedicarboxylate and dehydrogenation of the cyclohexadiene product with palladium black in mesitylene; the resulting terphenyl diester was converted via the N-benzylimide into (9). Clemmensen reduction of (9) gave in 71% yield the corresponding lactam (10) which is currently being employed as an intermediate in synthetic approaches to staurosporine.

The analytical and spectroscopic properties of all compounds were fully consistent with the designated structures.

We thank S.E.R.C. for a studentship award (to IH) and Roche Products Ltd. for support.

References and Notes

1. W. Steglich, B. Steffan, L. Kopanski and G. Eckhardt, Angew. Chem. Int. Ed. Engl., 1980, **19**, 459. See also L. Kopanski, G. R. Li, H. Besl and W. Steglich, Liebigs Ann. Chem., 1982, 1722.

2. A. Furusaki, N. Hashiba, T. Matsumoto, A. Hirano, Y. Iwai and S. Omura, J. Chem. Soc. Chem. Commun., 1978, 800.

3. J. I. G. Cadogan in "Organophosphorus Reagents in Organic Synthesis", Academic Press; New York 1979; p. 272. Use of collidine rather than the usual tert. butylbenzene as solvent gave much improved yields; use of triethyl phosphite produced much N-ethylated product.

4. Upjohn Company U.S.P. 2813128 (Chem. Abstr., 1958, **52**, 5477c).

5. Found for (1) M^+ 341.0802 ($C_{20}H_{11}N_3O_3$ requires M 341.0800. PMR (250 MHz in CD_3COCD_3) δ 6.92 (1H, dd, J = 8.6, 2.2 Hz), 7.10 (1H, d, J = 2.0 Hz), 7.34 (1H, ddd, J = 8.1, 7.1, 1.0 Hz), 7.52 (1H, ddd, J = 8.2, 7.1, 1.2 Hz), 7.67 (1H, d, J = 8.2 Hz), 8.72 (1H, s), 8.93 (1H, d, J = 8.7), 9.13 (1H, d, J = 8.1 Hz), 9.74 (1H, br.s), 10.83 (2H, br.s).

IR $\nu_{max.}$ (KBr), 3400 - 3100 (br.s), 3040 (sh), 2930 (sh), 1735 (m), 1690 (s), 1625 (m) cm^{-1}.

UV $\lambda_{max.}$ (MeOH (log ε), 230 (4.41), 272 (4.01), 282 (4.05), 324 (4.49), 415 (3.58) nm.

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