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A HIGHLY STEREOSELECTIVE SYNTHESIS OF AN AZASPIROLACTAM RELATED TO CEPHALOTAXUS ALKALOIDS

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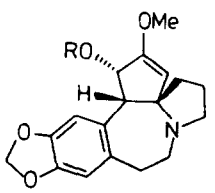
Abstract: Azaspirolactam (5) has been stereoselectively synthesised from nitrostyrene derivative (2) in high yield by sequential cycloaddition, Michael addition and reductive cyclisation reactions; the stereochemistry of compound (5) is confirmed by X-ray analysis of azaspirothiolactam (6).

There is considerable interest in the synthesis of 1-azaspirocycles especially when a high level of stereoselectivity can be achieved in the formation of the spiro centre.[1] Currently much work in this area is motivated by the promising anti-tumour activity found in naturally-occurring and semi-synthetic harringtonines, which are ester derivatives of Cephalotaxus alkaloids.[2] A stereoselective, total synthesis of cephalotaxine (1)[3] and model studies[4] directed towards this target have recently been reported. This communication describes a high-yielding, stereoselective route to azaspiro system (5), a compound which contains the requisite stereochemistry at the spiro centre and suitable functionality for elaboration to the cephalotaxine skeleton (Scheme).



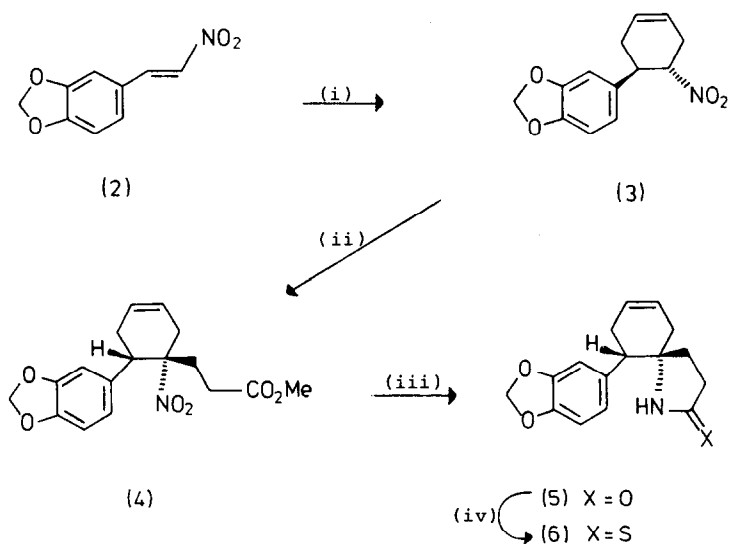
(1) R=H Cephalotaxine

R = —C(=O)—C(OH)(CH$_2$CO$_2$Me)—(CH$_2$)$_2$C(OH)(CH$_3$)$_2$ Harringtonine

Nitrostyrene derivative (2)[5] reacted with butadiene sulphone at 130°C in a bomb to yield compound (3).[6] Michael addition of methyl acrylate to the anion derived from (3) yielded nitroester (4)[7] as a single stereoisomer in high yield; this is the crucial step in determining the stereochemistry at the incipient spiro centre. A high degree of stereoselectivity in the alkylation of the anion of (3) was expected due to the presence of the bulky phenyl group on the adjacent carbon atom.

Cyclisation of compound (4) to 1-azaspirolactam (5)[8] occurred on refluxing an ethanolic solution of (4) with zinc and hydrochloric acid. Crystals of lactam (5) suitable for X-ray analysis could not be obtained, but treatment of lactam (5) with phosphorous pentasulphide yielded thiolactam (6) which crystallised in a form suitable for X-ray structure determination.[9] The X-ray structure of compound (6) (Figure) confirms the stereochemistry about the spiro centre that arises from the highly stereoselective Michael addition, (3)→(4).

Thus we have developed an expedient, and potentially versatile, sequence, (2)→(5), to yield azaspiro system (5) stereoselectively in 56% overall yield.



Scheme: Reagents and Conditions

(i) butadiene sulphone (5 eq.), hydroquinone (trace), toluene, 130°C, 144 h.

(ii) methyl acrylate (1 eq.), triton B, THF-t-BuOH, 20°C, 48 h.

(iii) Zn, HCl, ethanol, reflux, 18 h.

(iv) phosphorous pentasulphide, toluene, reflux, 3 h.

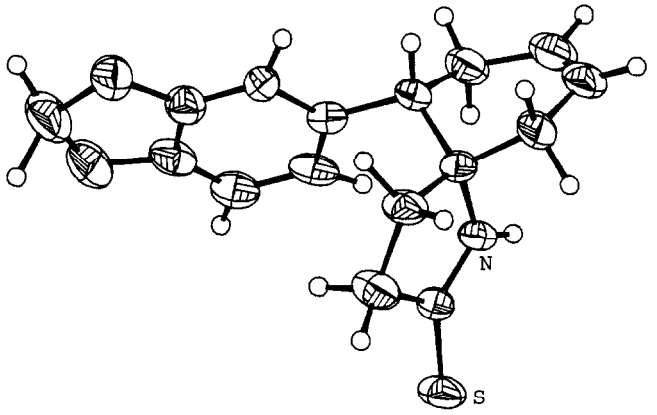


Figure: X-Ray Crystal structure of Compound (6)

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6. Compound (3), (92% yield), identical (m.p. and i.r.) with reported data for compound (3) previously prepared (72% yield) from (5) and butadiene.[5]

7. All new compounds gave satisfactory C, H and N elemental analysis. Compound (4) (75% yield), mp 98-100°C (from methanol); m/z 286 (M^+-NO_2); i.r. (nujol) ν_{max} 1735, 1530, 1482, 1373, 1315, 1252, 1210 1179, 1170, 1061, 930, 829, 815, 662, 647 cm^{-1}; δ_H ($CDCl_3$) 6.75-6.6 (3H, m), 5.9 (2H, s), 5.8 (2H, m), 3.7 (3H, s), 3.4 (1H, d) and 2.8-2.1 (8H, m) ppm δ_C ($CDCl_3$) 172.3, 147.6, 146.6, 133.3, 126.0, 124.0, 121.7, 108.1, 107.9, 100.9, 91.9, 51.7, 46.3, 31.9, 30.5, 28.5 and 27.5 ppm.

8. Compound (5) (81% yield), mp 179-181°C; m/z 271 (M^+); i.r. (nujol), ν_{max} 3160, 1673, 1255, 1232, 1032, 930 cm^{-1}; δ_H ($CDCl_3$) 6.9 (NH, s) 6.8-6.7 (2H, m), 5.9 (2H, s), 5.8-5.6 (2H, m) and 2.8-1.8 ppm (9H, m) δ_C ($CDCl_3$) 178.0, 148.0, 146.2, 134.6, 126.9, 124.2, 121.6, 108.6, 107.8, 100.6, 59.9, 47.9, 39.7, 32.0, 30.0 and 29.8 ppm.

9. Compound (6) (50% yield), mp 157-160°C (from toluene); m/z 287 (M^+); i.r. (nujol) ν_{max} 3130, 1500, 1480, 1238, 1220, 1162, 1045, 942, 858, 781 and 680 cm^{-1}; X-ray analysis, crystals are monoclinic, space group $P2_1/n$; a = 12.006(4), b = 8.995(5), c = 14.032(3) Å, α = 90.00 β = 67.41(2) γ = 90.00°, determined from 1389 observed reflections recorded on a CAD4 diffractometer using Cu radiation, refined to R 0.0548 and R_w 0.0423.

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