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TOTAL SYNTHESIS OF COMPOUNDS RELATED TO THE HOMOERYTHRINA ALKALOIDS

Edward McDonald* and Apichart Suksamrarn
University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW.

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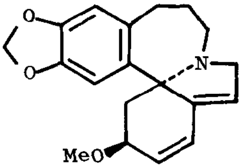
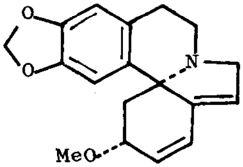


(1)



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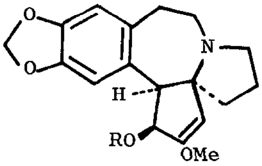
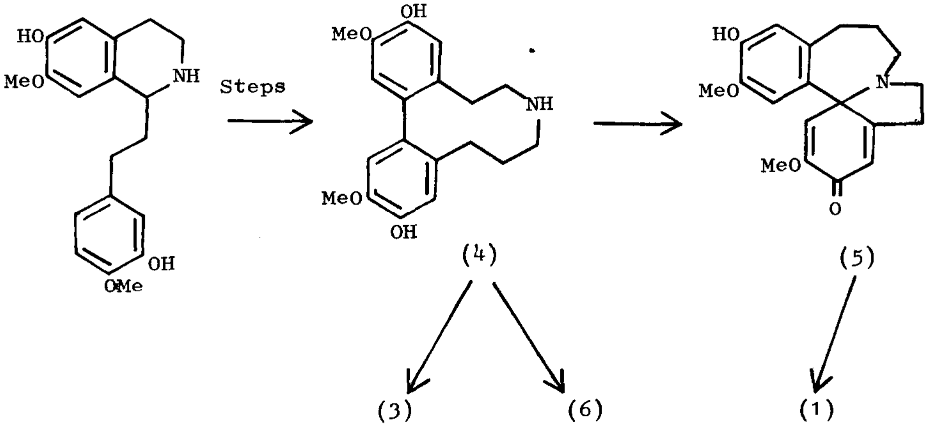


(3)

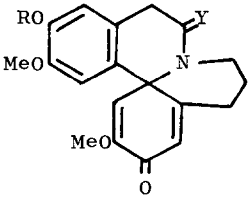
Schelhammeridine (1), the major alkaloid of *Schelhammera pedunculata*,[1] is structurally related to erythraline (2) which is known to be derived from a 1-benzylisoquinoline.[2] It is therefore reasonable by analogy to consider the hypothetical pathway shown (Scheme) for the biosynthesis of the *Schelhammera* alkaloids, and preliminary results are consistent with this.[3] Furthermore, alkaloids with the *Schelhammera* skeleton are found together with cephalotaxine (3) in *Cephalotaxus wilsoniana*[4] and both structural types may be derived from a common intermediate (Scheme) (but see ref. 5).



SCHEME

We now report syntheses of the dibenzazecine (4), the dienone (5)[6] and the isomeric dienone (6), whose skeleton has not yet been found in Nature.

The conversion of lactam (7)[7] to amine (6) required several steps. Reduction of the benzyl ether (8)[8] with LiAlH$_4$ in THF gave a mixture of epimeric alcohols (9) which, without purification, was treated under carefully controlled conditions with Jones' reagent in acetone (0-5°, 45 sec.) to give after p.l.c. the dienone amine (10). Several other oxidants were unsuccessful since benzylic oxidation occurs readily. Thus reaction of (9) with CrO$_3$-pyridine or CrO$_3$-3,5-dimethylpyrazole[9] gave the ketone (11), m.p. 196-198°, M$^+$, 431, δ 3.44, 4.40 (AB quartet, J=19Hz, ArCOCH$_2$N).

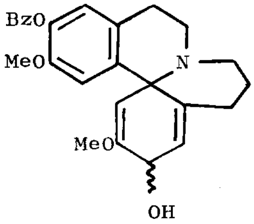


(6) Y = H$_2$, R = H

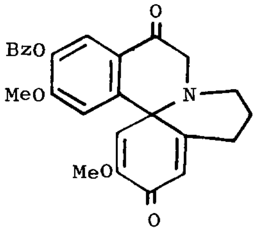
(7) Y = O, R = H

(8) Y = O, R = CH$_2$Ph

(10) Y = H$_2$, R = CH$_2$Ph



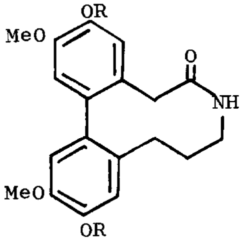
(9)



(11)

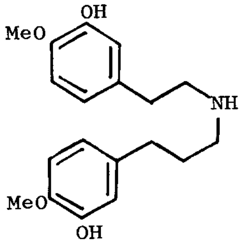
The benzyl protecting group of dienone (10) was removed by treatment with aqueous trifluoroacetic acid[10] (20°, 48 hours) to afford the required 6:6 fused dienone amine (6), $\nu_{max.}$ 3530, 1672, 1643, 1617 cm^{-1}, δ (CDCl$_3$-D$_2$O) 3.61 and 3.72 (each 3H, s, OMe); 6.16, 6.22, 6.36, 6.68 (each 1H, s, 2ArH and 2 dienone-H). In the region quoted this n.m.r. spectrum is extremely similar to that of the benzyl ether (10), demonstrating that no unwanted chemical change occurred during the debenzylation step.

In another set of reactions the dienone lactam (7) was first cleaved by chromous chloride reduction[2] to the azecine lactam (12), m.p. 244-245.5° in 89% yield. The corresponding dibenzyl ether (13) was reduced by $LiAlH_4$ in THF and the resultant amine was hydrogenolyzed (H_2/Pd-C/MeOH) to give the required phenolic dibenzazecine (4), m.p. 300-302° in 53% overall yield from (12): M^+, 329; $\delta(CD_3OD)$ 3.78 (6H, s, 2 x OMe), 6.56, 6.60, 6.74, 6.86 (each 1H, s, 4 x ArH).



(12) R = H

(13) R = Bz



(14)

Oxidation of (4) can give two possible dienones (5) and (6) but after treatment of (4) with alkaline ferricyanide, the chloroform extract of the reaction mixture contained an almost pure dienone (60% yield after p.l.c.). This compound, m.p. 134-135.5° is clearly different (t.l.c., ^{1}H-n.m.r.) from the 6:6 fused dienone (6) and so the cyclisation must have proceeded with high regiospecificity to generate the isomeric 5:7-fused dienone (5). The spectral properties of this compound are identical with those quoted for the dienone, m.p. 135-137°, prepared[6] in 4% yield by the similarly ambiguous oxidation of amine (14). These new results therefore confirm the revised structural formulation[6] of Kametani.

Routes to (4), (5) and (6) are therefore available for biosynthetic and synthetic studies on Schelhammera, Cephalotaxus and related alkaloids.

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