An Economical Synthesis of the Alkaloids, 3,4-Dimethoxy-ω-(2-piperidyl)-acetophenone, Julandine, and Cryptopleurine

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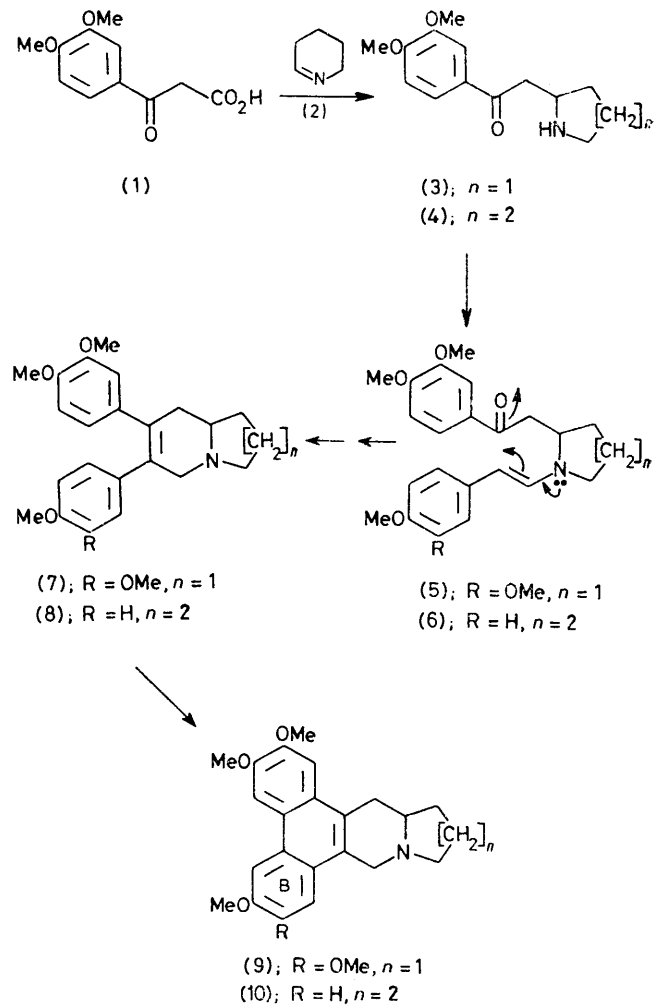
Summary Condensation of dimethoxybenzoylacetic acid with enzyme-generated (**2**) gives 3,4-dimethoxy-ω-(2-piperidyl)acetophenone (**4**), which by reaction with *p*-methoxyphenylacetaldehyde, and titanium(IV) chloride-catalysed cyclisation of the resultant enamine (**6**) leads to julandine (**8**); thallium(III) trifluoroacetate oxidation of (**8**) gives cryptopleurine (**10**).

THE alkaloids represented by cryptopleurine (**10**) and tylophorine (**9**) exhibit various interesting biological properties including anti-cancer action.[1,2] Exploitation of these properties in the synthesis of analogues depends on the efficient elaboration of these ring-systems and, based on biogenetic considerations, an economical synthesis of septicine (**7**) has been developed: (**1**) → (**3**) → (**5**) → (**7**);[3] treatment of septicine (**7**) with thallium(III) trifluoroacetate gave tylophorine (**9**) in high yield.[4] Extension of this route to the synthesis of cryptopleurine (**10**), though simple in principle, proved more difficult in practice, but with interesting consequences.

The key intermediate, 3,4-dimethoxy-ω-(2-piperidyl)-acetophenone (**4**), in the projected route is an alkaloid found in *Boehmeria platyphylla* and *B. cylindrica*.[2,5] It was easily synthesized by condensation of dimethoxybenzoylacetic acid (**1**)[3] with Δ^1-piperideine (**2**) generated *in situ* from cadaverine by pea-seedling diamine oxidase[6] (aqueous solution, pH 7; yield: 79%).

Condensation of phenacylpyrrolidines [as (**3**)] with substituted phenylacetaldehydes, in benzene without catalyst, rapidly affords the enamine [as (**5**)]. The rarely observed enamine–ketone condensation [see (**5**)] is, in this case effected simply in methanol at room temperature.[3,7] In the condensation of (**4**) and *p*-methoxyphenylacetaldehyde, however, the reaction failed, although enamine formation (n.m.r. analysis) was again rapid. On the other hand, cyclisation of the enamine (**6**) (and subsequent dehydration) could be achieved using selected Lewis acids: tin(IV) chloride and titanium(IV) chloride in benzene, and magnesium iodide in ether; reduction of the intermediate immonium salt (sodium borohydride in Pr^iOH) gave (**8**), according closely in properties with natural material from *B. platyphylla* and *B. cylindrica*[2,8] (the alkaloid is given the trivial name julandine for convenience).



Of the Lewis acids used above, titanium(IV) chloride (1 mol. equiv.), which has been noted[9] as a reagent which favours co-ordination to oxygen and is an efficient dehydrating agent, gave the highest yield of (**8**): 29%. Co-ordination to the ketonic oxygen rather than the enamine system

of (**6**) is obviously crucial to the success of the cyclisation, and the application of titanium chloride as a reagent in similar reactions is promising.

Thallium(III) trifluoroacetate has recently found application as an efficient coupling reagent for biaryls[10] and its use in the conversion of septicine (**7**) into tylophorine (**9**) has been noted above. The transformation of julandine (**8**) into cryptopleurine (**10**) was achieved similarly even though the linkage to ring B is notably *meta* to the methoxy-substituent [1 mol. equiv. of thallium(III) trifluoroacetate in trifluoroacetic acid; 20 min, room temperature; yield after recrystallisation: 69%]; as in the synthesis of tylophorine (**9**), only one of the possible coupling products was detected. [The synthetic (**10**) was identical to natural cryptopleurine, by comparison of i.r. and u.v. spectra, t.l.c., and, crucially for the manner in which the aromatic rings are linked, n.m.r. spectra.] The efficiency of the synthetic route through (**4**) and (**8**) to cryptopleurine (**10**) not only provides convenient access to these alkaloids which has application in biosynthetic studies, but also indicates that analogues of biological interest may be economically prepared.

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