

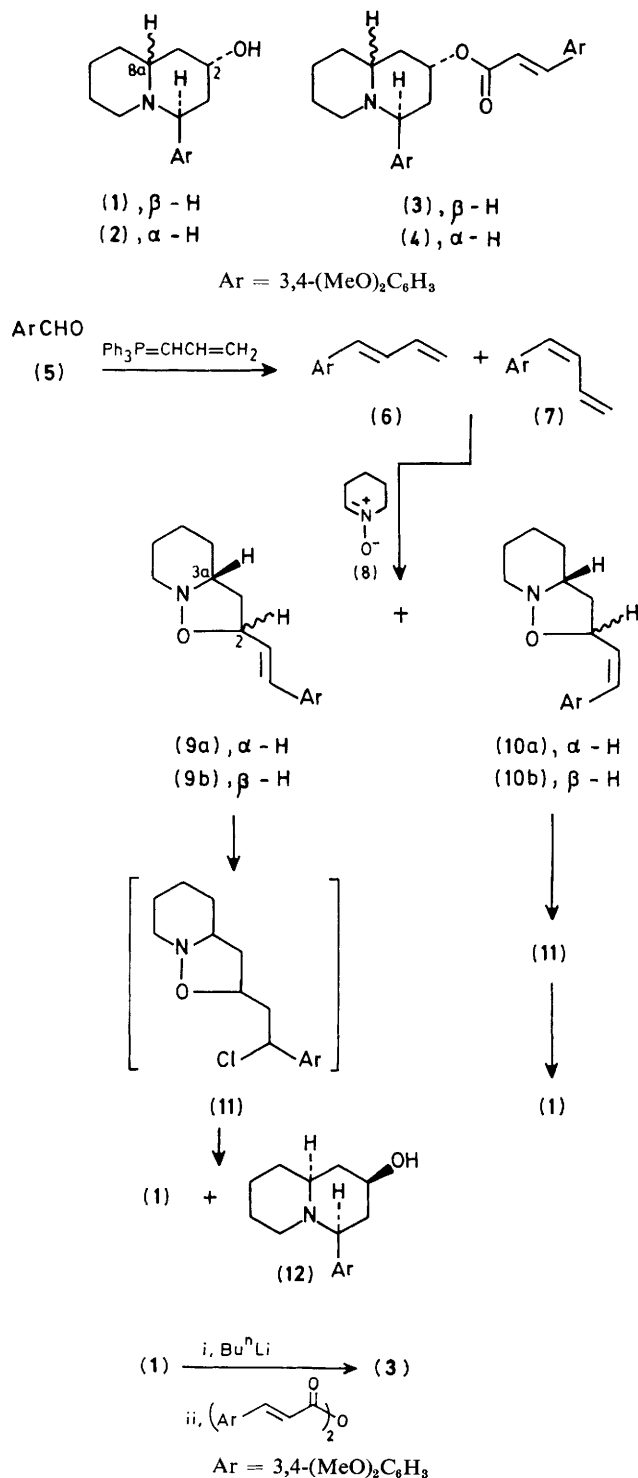
Synthesis of (±)-Lasubine I and (±)-Subcosine I

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(±)-Lasubine I and (±)-subcosine I were synthesised by a route involving as a key step a 1,3-dipolar cycloaddition.

The leaves of *Lagerstroemia subcostata* have been found to contain four new alkaloids, lasubine I (1) and II (2), and subcosine I (3) and II (4).¹ These alkaloids are structurally related



to phenolic 4-phenylquinolizidines which have been postulated as intermediates in the biosynthesis of the lactonic Lythraceae alkaloids.^{2,3} We report the first total synthesis of some of these alkaloids which utilises a 1,3-dipolar cycloaddition as a key step.

Treatment of 3,4-dimethoxybenzaldehyde (5) with the phosphorane derived from allyltriphenylphosphonium bromide gave an inseparable mixture of the *E*- and *Z*-isomers of 1-(3,4-dimethoxyphenyl)butadiene (6) and (7) in a ratio of 9:5.[†] The reaction of these isomers (6) and (7) with 2,3,4,5-tetrahydropyridine 1-oxide (8) in refluxing toluene followed by separation by column chromatography (silica gel, hexane-ethyl acetate, 5:1) yielded the corresponding *E*- and *Z*-cycloadducts (9) and (10) in 49 and 22% yields,[‡] respectively. These isomers (9) and (10) were shown by g.l.c. analysis to be a 10:3 mixture of diastereoisomers (9a) and (9b), and a 5:1 mixture of (10a) and (10b) with a preference for the formation of the *exo*-isomers (9a) and (10a) in each case.⁴

Hydrogen chloride was passed into a chloroform solution of (9) to give the chloride (11), which was, without isolation, subjected to *in situ* cyclisation via reductive N-O bond cleavage by hydrogenation over 10% Pd/C in ethanol furnishing (±)-lasubine I (1) and (±)-2-epilasubine II (12) in 44 and 14% yields [based on (9)], respectively. The *cis*-relationship between 2-H and 8a-H in these products arises from the corresponding configurations of C-2 and 3a-H in the *exo*-adducts (9a) and (10a), and other possible stereoisomers with 2-H *cis* to 8a-H arising from the minor adducts (9b) and (10b) were not isolated. With the same set of reactions and under the same conditions, (10) gave (±)-lasubine I (1) as the sole product though in low yield (35%). The synthetic (1) was found to be identical with natural (−)-(1) by ¹H and ¹³C n.m.r. comparison as well as t.l.c. behaviour. Finally, the lithium salt of (1) (BuⁿLi, tetrahydrofuran, −78 °C) was treated with 3,4-dimethoxycinnamic anhydride in the presence of 4-dimethylaminopyridine (dioxane, room temp., 24 h) to afford (±)-subcosine I (3) in 48% yield. The synthetic (±)-(3) thus obtained was identical with natural (−)-(3) in its ¹H n.m.r. spectral data and t.l.c. behaviour. Thus the first total synthesis of (±)-subcosine I has been achieved utilising a [3 + 2] dipolar cycloaddition of a nitron. We believe that the present methodology should provide an efficient general route for the synthesis of lactonic Lythraceae alkaloids.

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[†] Analysed by g.l.c. (2% OV-1, 160 °C).

[‡] All yields refer to isolated and purified materials.