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

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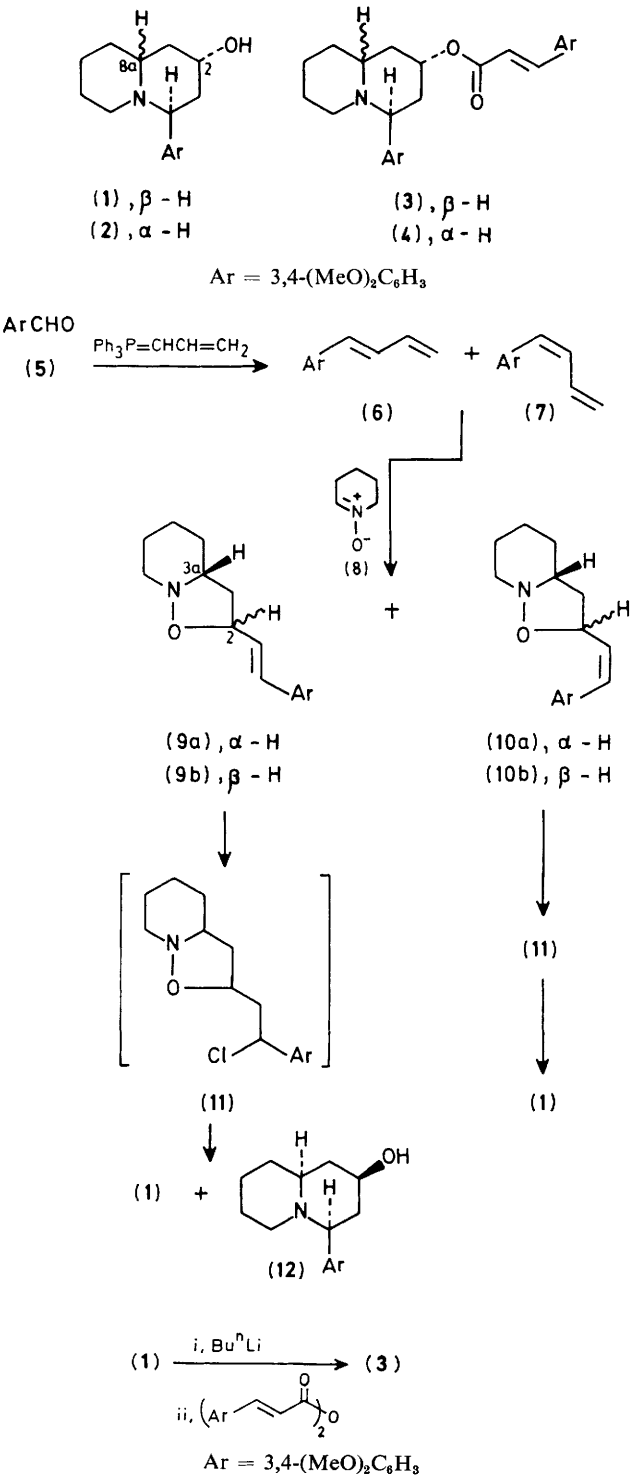
(±)-Lasubine I and (±)-subcosine I were synthesised by a route involving as a key step a 1,3-dipolar cycloaddition.

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 ^{1}H and ^{13}C n.m.r. comparison as well as t.l.c. behaviour. Finally, the lithium salt of (**1**) (Bu^{n}Li, 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 ^{1}H 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 nitrone. We believe that the present methodology should provide an efficient general route for the synthesis of lactonic Lythraceae alkaloids.

We are indebted to Professor E. Fujita for kindly providing samples of natural lasubine I and II, and subcosine I and II.

Received, 2nd June 1983; Com. 711

References

1 K. Fuji, T. Yamada, E. Fujita, and H. Murata, *Chem. Pharm. Bull.*, 1978, **26**, 2515.
2 J. P. Ferris, C. B. Boyce, and R. C. Brinner, *Tetrahedron Lett.*, 1966, 5129.
3 A. Rother and A. E. Schwarting, *Lloydia*, 1975, **36**, 477.
4 J. J. Tufariello and Sk. Asrof Ali, *Tetrahedron Lett.*, 1978, 4647.

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

‡ All yields refer to isolated and purified materials.