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

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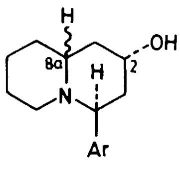
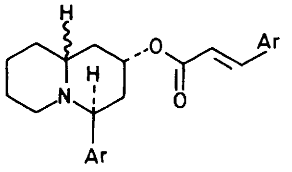
(±)-Lasubine I and (±)-subcosine I were synthesised by a route involving as a key step a 1,3-dipolar cycloaddition.

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.

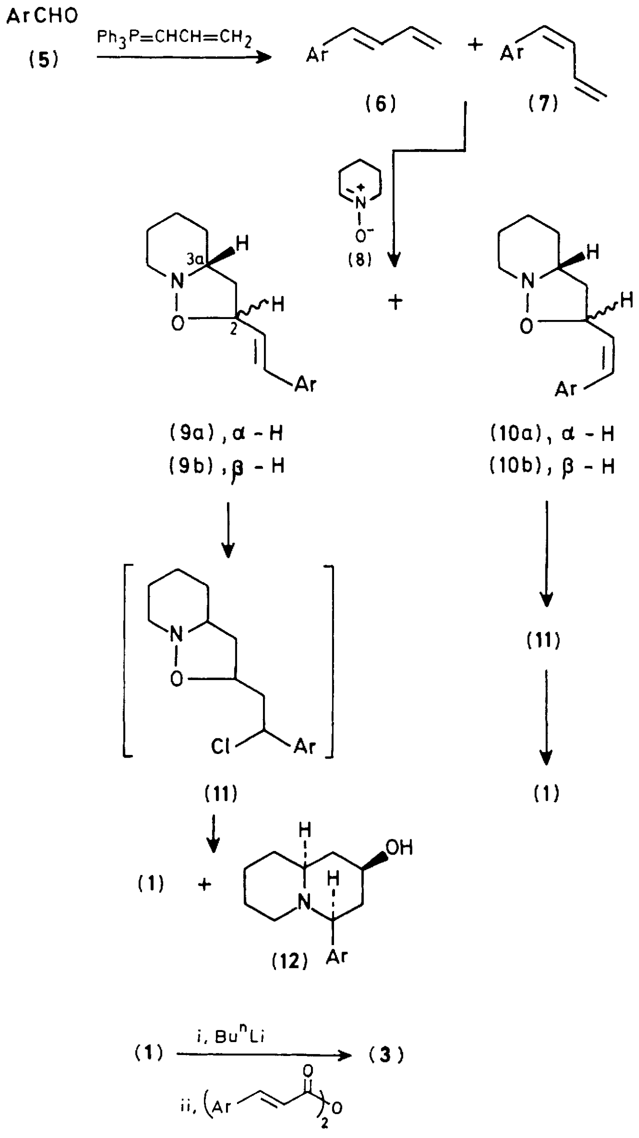


(1), β-H
(2), α-H



(3), β-H
(4), α-H

Ar = 3,4-(MeO)$_2$C$_6$H$_3$



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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.

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References

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

‡ All yields refer to isolated and purified materials.