General Synthetic Approach to the Quinolizidine Alkaloids *via* a [2+3]-Cycloaddition

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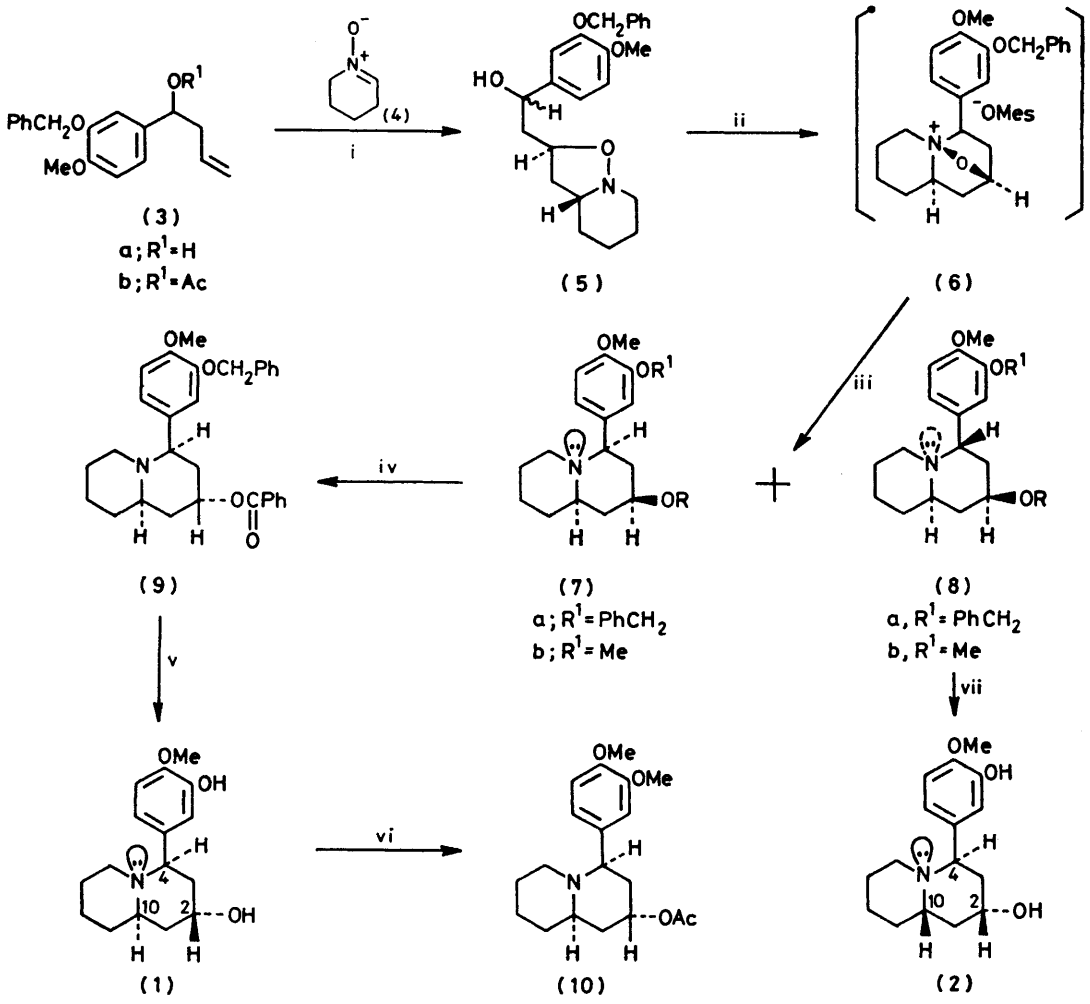
Summary Two naturally occurring arylquinolizidinols have been synthesized *via* a [2 + 3]-cycloaddition.

NATURALLY occurring quinolizidine alkaloids[1] possess both *trans*- and *cis*-quinolizidine configurations as shown in the two isomeric alkaloids (**1**) and (**2**).[2] Although these

alkaloids have been synthesized separately, there are few efficient routes[3] which lead to the formation of both alkaloids from a single precursor. We now describe a convenient route to both alkaloids employing the [2 + 3]-cycloaddition of a nitrone[4] to an alkene as the key step.

On heating the homoallylic alcohol (**3a**), readily derived from 3-benzyloxy-4-methoxybenzaldehyde with allylmagnesium bromide, with 3,4,5,6-tetrahydropyridine 1-oxide (**4**) in toluene under reflux for 3—4 h, the adduct (**5**)† was obtained quantitatively as two inseparable diastereomers. Adduct (**5**) was also obtained from the cycloaddition of the acetate (**3b**) to the nitrone (**4**) followed by alkaline hydrolysis. The adduct (**5**) was then treated with methanesulphonyl chloride in pyridine followed by reduction with Zn–50% aqueous acetic acid to give the expected two alcohols (**7a**; R=H) and (**8a**; R=H) through the quaternary salt (**6**). These alcohols were separated as the acetates (**7a**; R=Ac) [$\delta(CDCl_3)$ 4·86 (1H, m, $w_{1/2}$ = 19 Hz) and 2·95 (1H, dd, J 11 and 3 Hz); ν_{max} ($CHCl_3$) 2785 and 2740 cm^{-1} (Bohlmann band)] and (**8a**; R=Ac) [$\delta(CDCl_3)$ 5·20 (1H, m) and 4·14 (1H, t, J 6 Hz)] in 37·5 and 25·3% yield, respectively. The acetate (**8a**; R=Ac) was converted into the natural product (**2**) [m.p. 193—194 °C (lit.[2] 193—194 °C)] with the *cis*-quinolizidine configuration by successive hydrolysis and hydrogenolysis. The overall yield of the *cis*-quinolizidine (**2**) from (**3a**) was 20·2%.

The isomeric acetate (**7a**; R=Ac) was converted into the natural product (**1**) by inversion of its C-2 centre using the Mitsunobu reaction.[5] Thus, the acetate (**7a**) was hydrolysed to give the alcohol (**7a**; R=H), treatment of which with diethyl azodicarboxylate and triphenylphosphine in the presence of benzoic acid gave the benzoate (**9**)



SCHEME. All compounds depicted are racemic but, for convenience, only one enantiomer is shown. *Reagents*. i, toluene, reflux, ii, $MeSO_2Cl$, pyridine, iii, Zn–50% AcOH, then Ac_2O, pyridine, iv, NaOH, aq. MeOH, then $(EtO_2C–N=)_2$, Ph_3P, $PhCO_2H$, v, NaOMe, MeOH, then 10% Pd–C, H_2, vi, CH_2N_2, then Ac_2O, pyridine, vii, NaOH, aq. MeOH, then 10% Pd–C, H_2.

† The relative stereochemistry shown in adduct (**5**) at the future C-2 and C-10 was determined from its transformation into (**1**) and (**2**).

[$\delta(CDCl_3)$ 5·38 (1H, m) and 3·35 (1H, q, J 5 Hz)]. The natural product (**1**)‡ m.p. 94—95 °C (lit.[2] 94—95 °C); ν_{max} (KBr) 2800 and 2760 cm^{-1} (Bohlmann band)] was then obtained in 84·6% yield on sequential methanolysis and hydrogenolysis of (**9**). The *O*-methyl alkaloid derivatives (**7b**; R=Ac) and (**8b**; R=Ac), were similarly synthesised from veratraldehyde in yields of 36·3 and 23·0%, respectively.

The present method, employing the highly stereoselective [2 + 3]-cycloaddition of a nitrone,[6] should be generally applicable to the synthesis of 4-substituted *trans*- and *cis*-quinolizidine alkaloids.

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‡ The *trans*-quinolizidine (**1**) was further confirmed by transformation into (**10**) (M. Hanaoka, N. Ogawa, and Y. Arata, *Tetrahedron Lett.*, 1973, 2355; *Chem. Pharm. Bull.*, 1975, **23**, 2140). We thank Professor M. Hanaoka for kindly providing us with the spectral data (i.r. and ^{1}H-n.m.r.) of (**10**). We also thank Professor E. Fujita for valuable information and Dr. K. Ogasawara for helpful discussions.

§ All new compounds exhibited satisfactory spectroscopic and analytical (combustion and/or high-resolution mass spectral) data consistent with the structures shown.

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[3] A synthesis of the quinolizidine nucleus as *trans*- and *cis*-forms *via* unsymmetrical diene–nitrone cycloadditions has been reported: J. J. Tufariello and R. C. Gatrone, *Tetrahedron Lett.*, 1978, 2753.
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[6] R. Green, F. Tonnard, and R. Carrié, *Tetrahedron Lett.*, 1973, 453; J. J. Tufariello and S. A. Ali, *ibid.*, 1978, 4647.