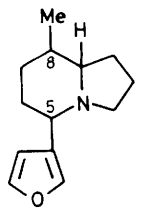
A Nitrone Cycloaddition to a 1,4-Disubstituted-buta-1,3-diene. A Synthesis of 5-(3-Furyl)-8-methyl-octahydroindolizine

Joseph J. Tufariello* and Andrew D. Dyszlewski

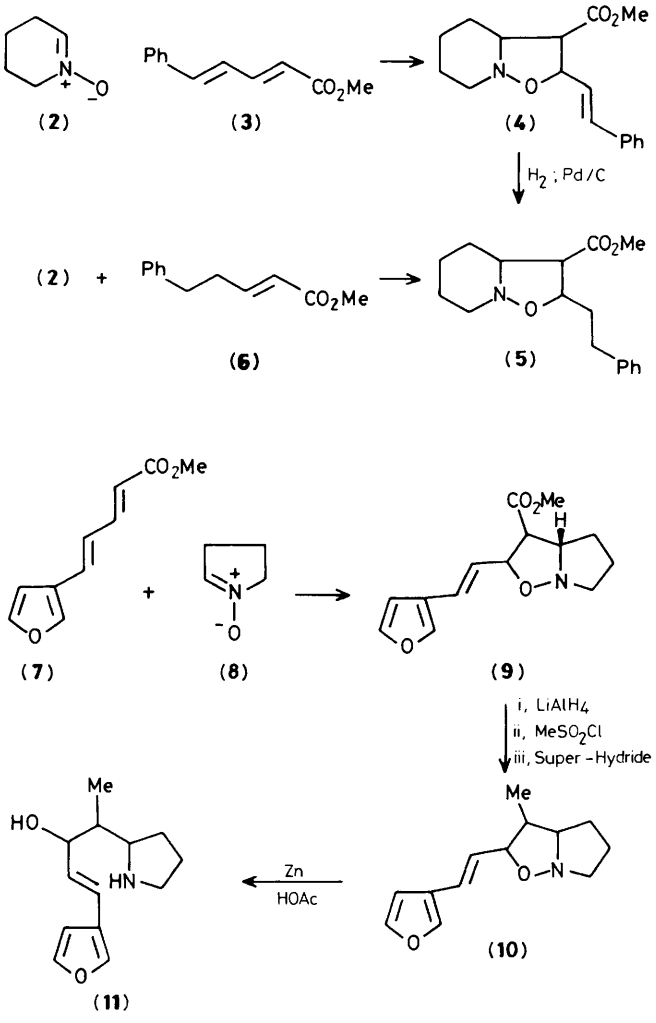
Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214, U.S.A.

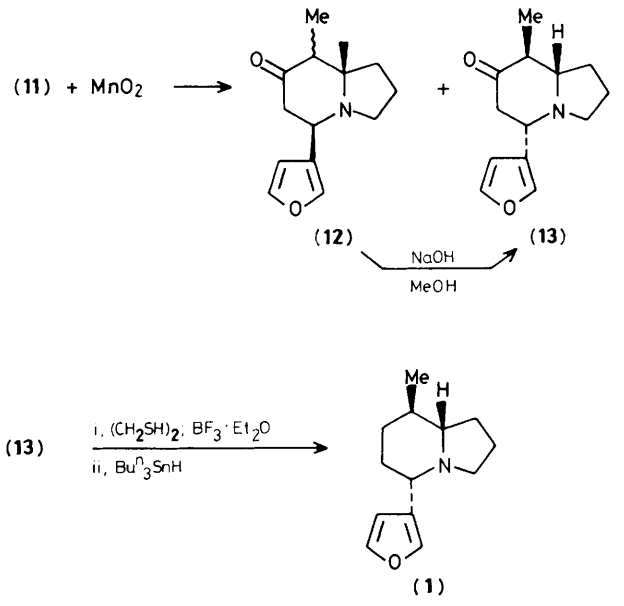
A new nitrone-based synthesis of the Nuphar indolizidine 5-(3-furyl)-8-methyloctahydroindolizine was accomplished by a regiospecific cycloaddition of a nitrone with a 1,4-disubstituted butadiene.

Castoreum, a perfume extract derived from the dried scent glands of the Canadian beaver (*Castor fiber* L.) was found to contain alkaloidal natural products of the Nuphar quinolizidine genus. Of particular interest was the detection, by g.c.–mass spectrometry, of a Nuphar alkaloid, 5-(3-furyl)-8-methyloctahydroindolizine (**1**).[1] The structural formula was determined solely by the fragmentation pattern displayed in the mass spectrum; therefore, the stereochemistry of the natural product was not assigned in the study. This alkaloid



(**1**)





has been the subject of two prior syntheses,[2] but we report herein a new stereospecific nitrone-based synthesis of this indolizidine alkaloid.

Nitrone additions to 1-substituted butadienes have been shown to be highly regiospecific. Indeed, several isoxazolidine intermediates have been converted into alkaloidal natural products.[3] Our attention has since focused on nitrone additions to 1,4-disubstituted buta-1,3-dienes. In principle, the cycloaddition to an unsymmetrically 1,4-disubstituted butadiene could proceed at either double bond to afford four regioisomeric adducts, each as a mixture of diastereoisomers. In order to determine the site selectivity and regiochemical mode of cycloaddition, we have shown that 3,4,5,6-tetrahydropyridine-1-oxide (**2**), when added to methyl (*E*,*E*)-5-phenylpenta-2,4-dienoate (**3**), gave a single regioisomeric product [*i.e.* (**4**)].[4] The adduct (**4**) was hydrogenated (H_2/Pd–C; 1 atm) and the reduction product [*i.e.* (**5**)] was identical with the adduct prepared by a nitrone cycloaddition to methyl (*E*)-5-phenylpent-1-enoate (**6**). The regiochemistry of this latter reaction is unambiguously known.[5]

Synthesis of the Nuphar indolizidine called for the synthesis of methyl (*E*,*E*)-5-(3-furyl)penta-2,4-dienoate (**7**),† which was accomplished by coupling furan-3-carbaldehyde (Aldrich) and trimethyl 4-phosphonocrotonate (NaH, dimethoxyethane, 82%). Cycloaddition of pyrroline-1-oxide (**8**) with two equivalents of diene (**7**) in refluxing benzene gave a 73% yield of adduct (**9**) as a diastereoisomeric mixture. The ^{1}H n.m.r. spectrum ($CDCl_3$) exhibited a doublet of doublets at δ 2.83 (*J* 6.0, 9.0 Hz) for the C-3 protons, an overlapping doublet of doublets centred at δ 4.73 (*J* 7.5, 9.0 Hz) for the C-2 protons, and an overlapping doublet of doublets for the β-vinyl protons at δ 5.83 (*J* 7.5, 15.3 Hz). Confirmation of this regiochemical assignment was accomplished by selective spin decoupling experiments. Decoupling of the β-vinyl protons at δ 5.83 caused the collapse of the C-2 protons into doublets (*J* 9.0 Hz) while double irradiation of the C-3 protons at δ 4.73 collapsed both the β-vinyl protons (*J* 15.3 Hz) and the C-3 protons (*J* 6 Hz) into doublets.

Ultimate confirmation of regiochemistry involved completion of the synthesis of the natural product. This was accomplished by reduction of adduct (**9**) ($LiAlH_4$, Et_2O), followed by mesylation ($MeSO_2Cl$, Et_3N) and nucleophilic displacement (Super Hydride, tetrahydrofuran) to afford the methyl substituted adduct (**10**) in 94% overall yield for the three steps. Reductive scission of the nitrogen–oxygen bond of (**10**) with zinc and 50% aqueous acetic acid gave the amino alcohol (**11**) in quantitative yield. Allylic oxidation of (**11**) with activated manganese dioxide[6] gave a 65% yield of a 7 : 3 *cis* to *trans* mixture of octahydroindolizine-7-ones (**12**) and (**13**). The isomers were separated by column chromatography on silica gel (chloroform). The first fraction contained the *trans* isomer (**13**) which displayed a methyl doublet at δ 1.03 (*J* 6.6 Hz) and a doublet of doublets for the axial C-5 proton at δ 3.30 (*J* 3.6, 11.5 Hz) in the ^{1}H n.m.r. spectrum ($CDCl_3$). The i.r. spectrum displayed a strong Bohlmann band[7] at 3.58 μm and a carbonyl stretch at 5.83 μm. The second fraction contained the *cis* isomer (**12**) with a ^{1}H n.m.r. spectrum ($CDCl_3$) that displayed a methyl doublet at δ 1.04 (*J* 6.6 Hz) and a C-5 equatorial proton at δ 4.45 (*J* 2.5, 6.5 Hz). The i.r. spectrum contained a carbonyl absorbance at 5.85 μm. Epimerization of the *cis* isomer (**12**) was easily accomplished by refluxing in 10% aqueous sodium hydroxide and methanol to give a 90% yield of a 4 : 1 mixture of *trans* (**13**) to *cis* (**12**) isomers.

The synthesis was completed by treatment of (**13**) with ethane-1,2-dithiol and boron trifluoride–diethyl ether at room temperature which gave a 95% yield of the thioacetal. Reduction with n-tributyltin hydride[8] gave a 70% yield of product (**1**). The mass spectrum of synthetic compound (**1**)

† All spectral data (^{1}H and ^{13}C n.m.r. and i.r.) and combustion analyses are in agreement with the structural assignments.

was identical to that of the natural product. The stereochemistry was confirmed by comparison of the ^{1}H and ^{13}C n.m.r. spectra of (**1**) synthesised independently by LaLonde.[2a] The i.r. spectrum also contained a Bohlmann band at 3.48 μm. In conclusion, we have shown that a site specific and regiospecific nitrone cycloaddition to a 1,4-disubstituted butadiene was instrumental in the synthesis of Nuphar indolizidine (**1**).

We thank the National Institutes of Health for financial support (GM 34053 and 25303). We also thank Professor R. T. LaLonde (S.U.N.Y. at Syracuse) for the spectra used in the structural confirmation. Finally we acknowledge the help of Diane Cicatello, Lawrence Teruel, and Lena ElChehabi for preparation of starting materials.

Received, 14th January 1987; Com. 042

References

1 B. Maurer and G. Ohloff, *Helv. Chim. Acta*, 1976, **59**, 1169.
2 (a) R. T. LaLonde, N. Muhammad, C. F. Wong, and E. R. Sturiale, *J. Org. Chem.*, 1980, **45**, 3664; (b) T. Ohnuma, M. Tabe, K. Shuya, and Y. Ban, *Tetrahedron Lett.*, 1983, **24**, 4249.
3 J. J. Tufariello and J. M. Puglis, *Tetrahedron Lett.*, 1986, **27**, 1265; J. J. Tufariello, H. Meckler, and K. P. A. Senaratne, *Tetrahedron*, 1985, **41**, 3447.
4 J. J. Tufariello and A. D. Dyszlewski, unpublished results.
5 J. J. Tufariello, in '1,3-Dipolar Cycloaddition Chemistry,' ed. A. Padwa, vol. 2, Wiley, New York, 1984, p. 82.
6 A. J. Faidiatdi, *Synthesis*, 1976, 65; p. 133.
7 T. A. Crabb, R. F. Neuwton, and D. Jackson, *Chem. Rev.*, 1971, **71**, 109.
8 C. G. Gutierrez, R. A. Stringham, T. Nitasaki, and K. G. Glasscock, *J. Org. Chem.*, 1980, **45**, 3393.