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NITRONE CYCLOADDITION. A ROUTE TO THE LUPIN CLASS OF ALKALOIDS[1]

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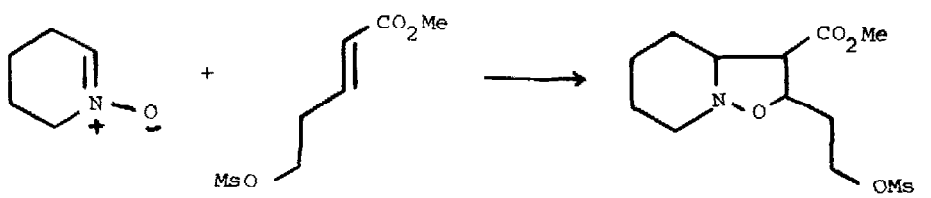
Several recent studies have emphasized the use of nitrones in the synthesis of alkaloidal systems.[2] We now report the use of 2,3,4,5-tetrahydropyridine-1-oxide (1) in the synthesis of dl-lupinine and dl-epilupinine[3]. The central feature of this synthesis is the use of a nitrone cyclization procedure to form an essential carbon-carbon bond. The overall result is an efficient annelation procedure.

To achieve the stated goals, we sought to investigate the reaction of 2,3,4,5-tetrahydropyridine-1-oxide with the methanesulfonate of methyl (E)-5-hydroxy-2-pentenoate (2). In order to prepare the desired methanesulfonate, 3-buten-1-ol was converted to its tetrahydropyranyl ether, which was then



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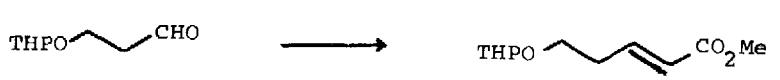
ozonized in toluene at -78°, and the resultant ozonide hydrogenated over 10% palladium-on-carbon to afford an 88% yield of the aldehyde tetrahydropyranyl ether 4. The later was exposed to trimethyl phosphonoacetate in a modified



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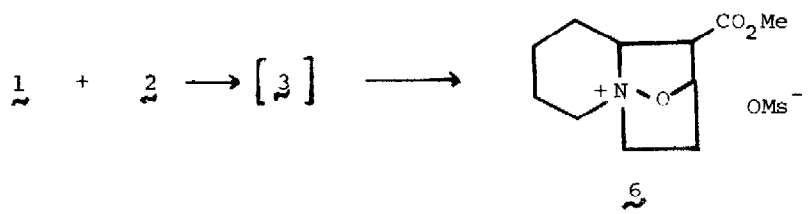
Wittig procedure to give the ester tetrahydropyranyl ether 5 in 81% yield. An nmr spectrum of this ester (bp 90-2°/0,7mm) indicated it to possess trans-

stereochemistry ($CDCl_3$, δ 5.8 ppm (d,1,J = 16 Hz). The ester was deprotected using p-toluenesulfonic acid in methanol, and the resultant alcohol was converted into the methanesulfonate 2 in 98% yield through the use of methanesulfonyl chloride and triethylamine.

When the methanesulfonate 2 was exposed to 2,3,4,5-tetrahydropyridine-1-oxide in toluene at 0-5° for 60 hrs., the salt 6 (mp 174-175.5°) was isolated in 74% yield. This transformation apparently proceeds via the adduct



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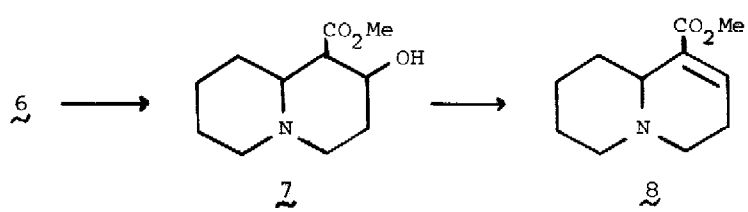
3, which cyclizes spontaneously. The ir spectrum of the salt (6) exhibits the expected carbonyl stretching band at 5.82μ, and the corresponding nmr spectrum (MeOD, δ 1.42-2.1(m,7), 2.32(m,2), 2.68(s,3), 3.74(s,3), 3.75(m,1), 4.08(m,3), 4.14(m,1), and 5.65 ppm (d,1,J = 4 Hz)) is consistent with the structural assignment. The salt was reduced to the hydroxy ester 7 with zinc and acetic acid to give hydroxyester 7 in 80% yield. The hydroxyester was then dehydrated[2d] with phosphorus oxychloride in pyridine to give the unsat-



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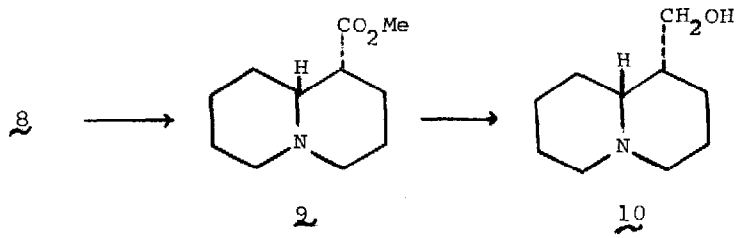
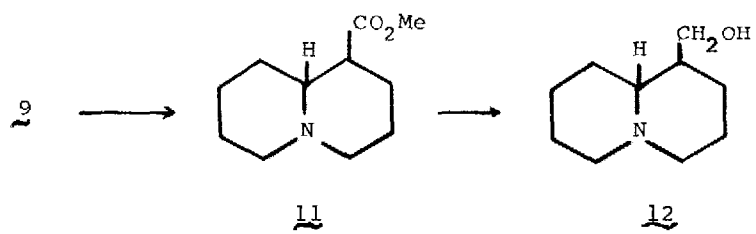
urated ester 8 in 75% yield. This ester, bp 80°/1.5mm., showed absorption at 5.82μ in its ir spectrum, and its nmr spectrum ($CDCl_3$) displayed a three-proton singlet at δ 3.77 ppm (methyl ester) and a one-proton multiplet at δ 6.93 ppm (vinyl proton). Its uv spectrum (ethanol) showed absorption at 215.5mμ (ε13800). Reduction of the unsaturated ester using platinum oxide afforded methyl lupinate (9)[3d], which was converted into dl-lupinine (10) by reduction with lithium aluminum hydride in ether[5]. The dl-lupinine exhibited ir, nmr, and mass spectra identical with an authentic sample

of (-)-lupinine (6).



Methyl lupinate was epimerized to methyl epilupinate (11) with sodium methoxide in methanol. The methyl epilupinate then converted into epilupinine[3f] (12) by reduction with lithium aluminum hydride in ether.



The synthetic sequence described herein demonstrates that the regioselectivity of nitrone cycloadditions to unsaturated centers is sufficient, in many cases, to justify their incorporation in synthetic planning. Moreover, the approach utilized emphasizes the potential usefulness of nitrone-based routes in the generation of six- as well as five-membered rings[1].

REFERENCES AND NOTES:

1. This work was supported in part by funds from the National Institutes of Health (CA 14611) and further assisted by funds provided by the National Science Foundation to the Department of Chemistry for the purchase of a Varian T-60 NMR Spectrometer.
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