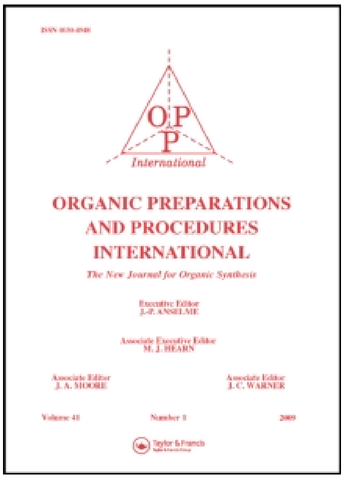

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RECENT SYNTHETIC APPLICATIONS OF NITRONES. A REVIEW

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RECENT SYNTHETIC APPLICATIONS OF NITRONES. A REVIEW

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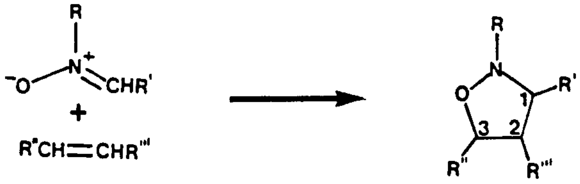
INTRODUCTION

A highly useful reaction of nitrones is the [3+2] cycloadditon with olefins to afford five-membered heterocycles. This reaction, which results in the formation of carbon-carbon bond with the concomitant strategic 1,3-disposition of the nitrogen and oxygen functionalities, serves as an attractive alternative to the classic Mannich reaction. The general subject of nitrones[1] as well as the specific aspect of their preparations, rearrangments, participation in 1,3-dipolar cycloaddition reactions, their uses in medicinal chemistry, and in alkaloid synthesis have been reviewed up to the late seventies.[2] Mechanistic aspects of the cycloaddition reaction has been studied by different groups.[3] The continuing interest in the cycloaddition reactions of nitrones has prompted this review which emphasizes synthetic applications which have appeared since 1978.

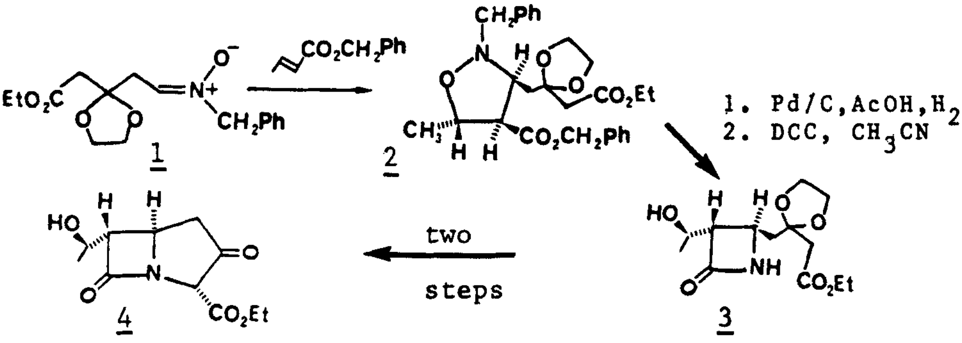


I. CYCLOADDITIONS

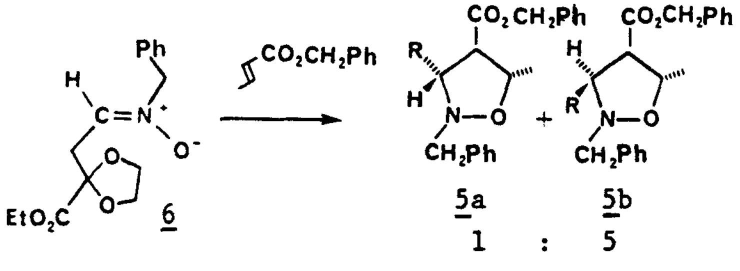
1. INTERMOLECULAR CYCLOADDITIONS

a. β-Lactams

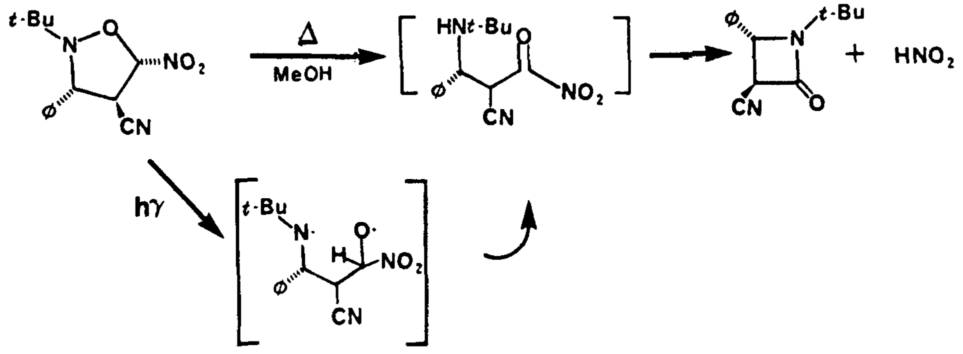
Thienamycin, a key member of the carbapenem antibiotics, was recently synthesized by two groups; both employed a nitrone-olefin cycloaddition reaction.[4] The predictable regio- and stereochemical outcome of this reaction allowed control of stereochemistry at three centers around the azetidinone ring system. Kametani, *et al.* reported that isoxazolidine **2** was the sole isomer obtained from the cycloaddition of nitrone 1 and benzyl



crotonate in benzene; an *endo*-crotonate-*E*-nitrone transition state was suggested. Isoxazolidine **2** was hydrogenated to a β-hydroxy-β-amino acid, which was cyclized to give **3**. Similar results were reported for the cycloaddition of nitrone **6** and benzyl crotonate in toluene, except that two isomeric isoxazolidines were produced. The key intermediates **5a** and **5b** were transformed into the azetidinone system.



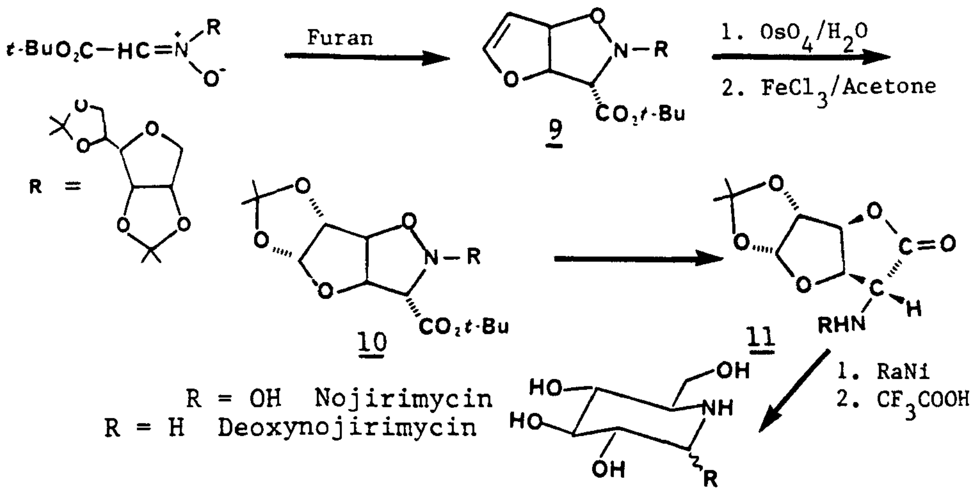
Thermal and photochemical reorganizations of isoxazolidines have resulted in the production of β-lactams.[5] A ring contraction involving a reactive acyl nitro species is presumed to be involved (Scheme 1). In the photolytic pathway, scission of the N-O bond followed by internal hydrogen atom transfer and cyclization was postulated. The presence of the nitro group was thought to be important.



Scheme 1

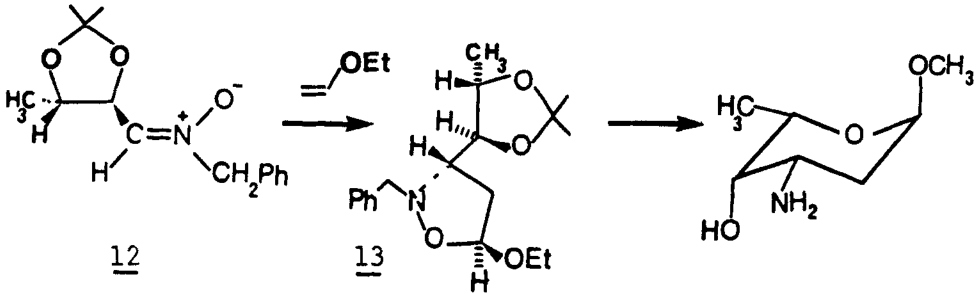
b. Carbohydrates

An interesting application of nitrone cycloaddition reaction is found in the total synthesis of nojirmycin, an antibiotic and one of the few naturally occurring aza analogs of glucose.[6] Nojirimycin and 1-deoxynojirimycin were elaborated from the nitrone-furan adduct **9**. Osmylation, protection followed by N-O bond cleavage and hydrolysis, gave the amino



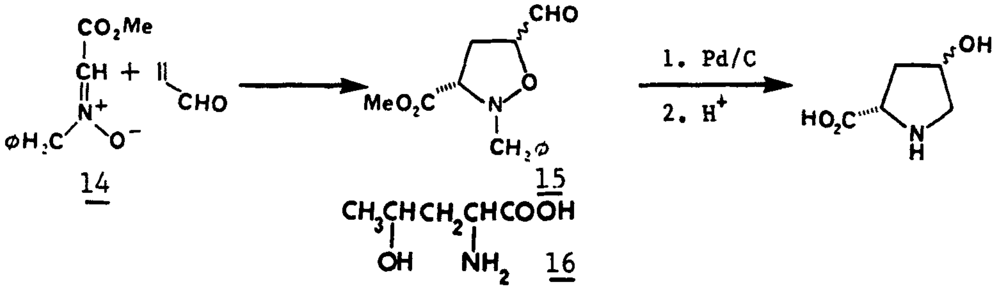
lactone **11**, which was transformed in a few steps to the natural products. The nitrone employed in this case is derived from a sugar derivative; asymmetric induction with such nitrones has been studied by Vasella.[7]

A high degree of diastereoselectivity was observed in the cycloaddition of nitrone **12** with excess ethyl vinyl ether at 35°.[8] The sole diastereomer **13** was subjected to N-O bond scission under catalytic hydrogenation in methanolic HCl to give the glycoside of daunosamine.



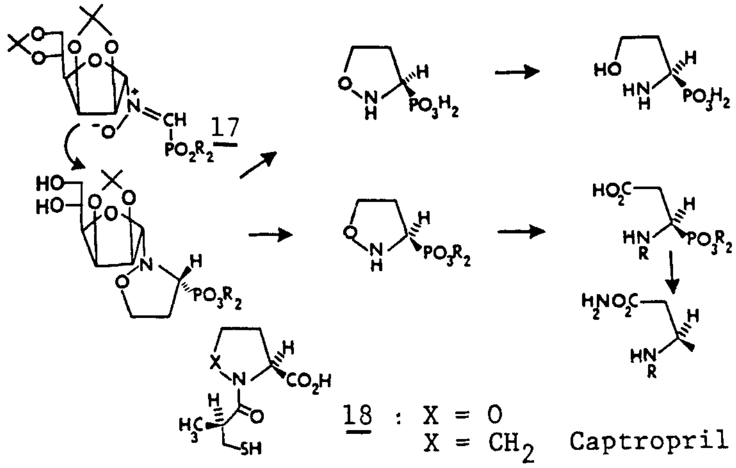
c. Amino Acids

The development of new methods for the preparation of amino acids continues to be a synthetic challenge. Cycloaddition of nitrone **14** with acrolein gave the isoxazolinidine **15**. Hydrogenolysis over palladium hydroxide followed by hydrolysis produced the *cis*- and *trans*-4-hydroxyprolines.[9] As expected a single regioisomer was formed as a stereoisomeric mixture. It was suggested that stereoisomers were the result of (*E*) and



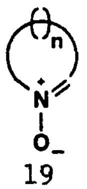
(*Z*) isomers of the starting nitrone.[16] The same cycloaddition reaction served as the key step in the synthesis of γ-hydroxy-β-amino acid **16**.

Asymmetric synthesis of α-aminophosphonic acids (analogs of α-amino acids) have been achieved by Vasella utilizing a new class of nitrones, C-phosphononitrones **17**.[10] The carbohydrate moiety attached to the nitrogen atom of the nitrone acts as a chiral auxiliary. Scheme 2 illustrates the synthesis of the α-aminophosphonic acid analogs of L-5-oxaproline, L-homoserine, L-aspartic acid, L-asparagine. An analogous process was utilized in the synthesis of D- and L-5-oxaproline **18**, a new captropril analogue.[11]



Scheme 2

d. Alkaloids



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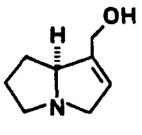
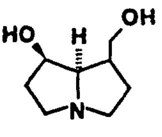
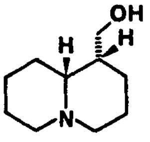


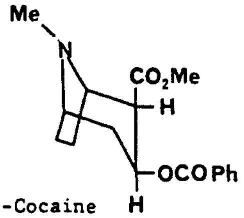
dl-Supinidine



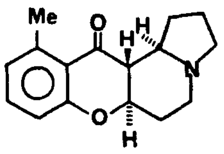
dl-Retronecine



dl-Lupinine



dl-Cocaine

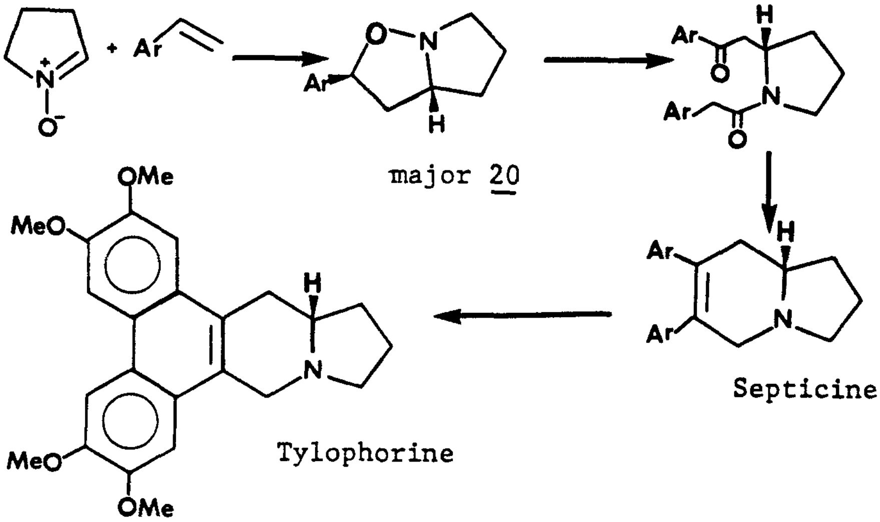


Elaeocarpine

Cyclic nitrones represented by the general formula **19** are commonly employed in the total synthesis of several classes of alkaloids. A recent account of the pioneerring work of Tufariello documents the diverse utility of these nitrones in the synthesis of senecio, indolizine, nuphar, and quinolizidine alkaloids.[2]

Indolizidine Alkaloids

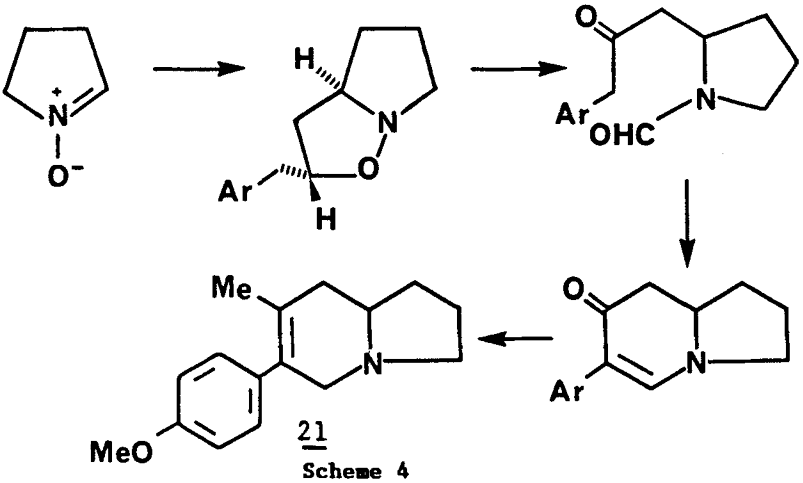
(±) Septicine and (±) tylophorine have a common parent system, aryl substituted indolizidine nucleus, and exhibit important biological activity. The key intermediate **20** required for the final photocyclization step was derived from a nitrone-olefin cycloaddition process (Scheme 3).[12]



Scheme 3

The aglycone of ipalbine and ipomine alkaloids possess an indolizidine system with methyl substitution. Cycloaddition of *p*-allyl anisole and 1-pyrroline 1-oxide gave isoxazolidines,[13] which was transformed to the N-formyl carbinol. Final cyclization to the bicyclic enamine was achieved with aluminum *t*-butoxide. The cyclized product was converted to the aglycone moiety **21** (Scheme 4).

Kametani reported[14] the total synthesis of elaeokanine A,B,C, utilizing a nitrone-olefin cycloaddition. While the regio- and stereochemical nature of the cycloaddition process provided the proper basic skeleton and correct stereochemistry at C-7 and C-8, the subsequent reaction sequence did not preserve the latter.



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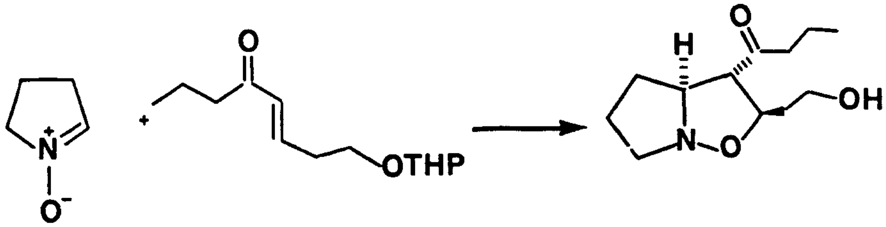
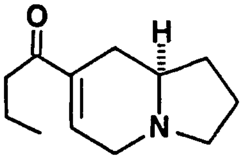
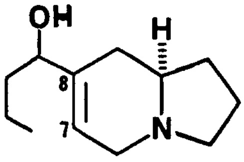
Scheme 4

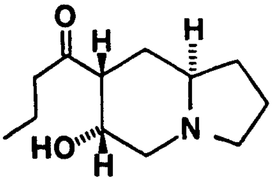




Elaeokanine A



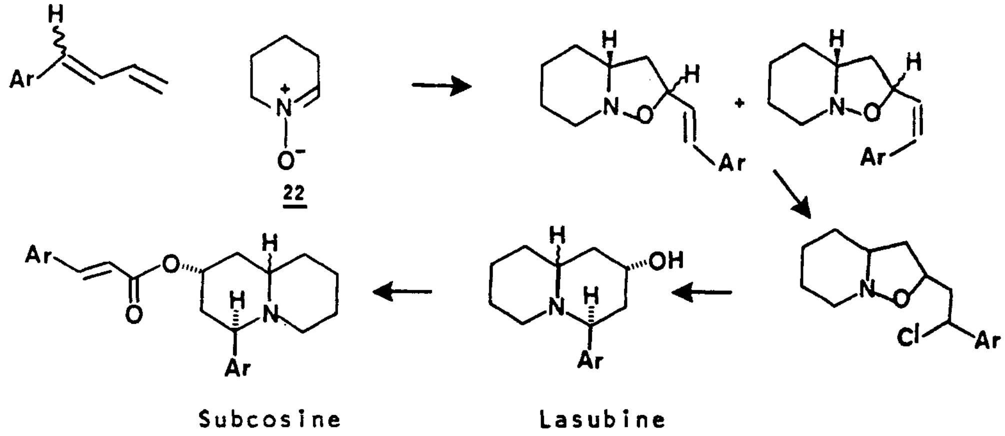
B



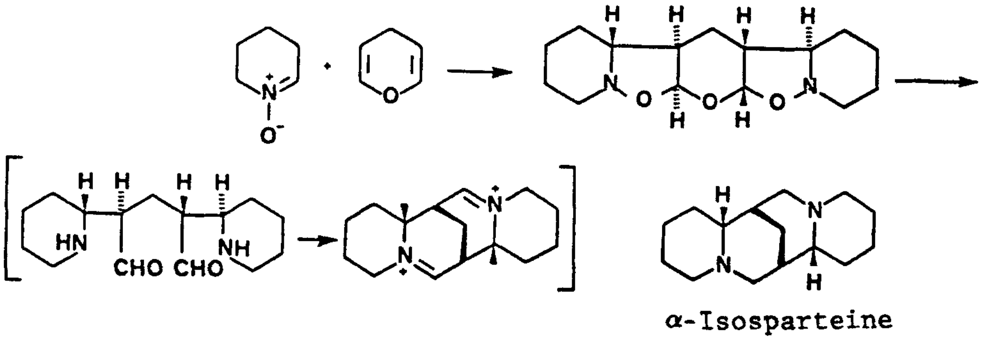
C

Quinolizidine Alkaloids

The regiospecific cycloaddition of (*E*) and (*Z*) dienes with nitrone 22 produced the isoxazolidines.[15] Reduction of the N-O bond places the hydroxyl at the appropriate carbon. Further elaboration gave the alkaloids (±)-lasubine I, (±)-subcosine I. These systems were approached by Takano by similar manner.[16]

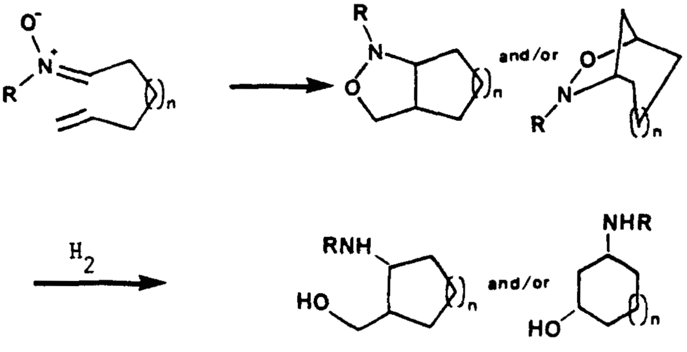


A short and facile preparation of the tetracyclic alkaloid, α-isosparteine, involves the cycloaddition of Δ^1-piperidine-1-oxide to 4H-pyran.[17] Catalytic hydrogenation of the adduct over Pd $(OH)_2$ gave the natural product. The stereochemical outcome in the cycloaddition resulted from the *exo*-addition product. No *endo*-product was observed due to the steric hindrance in the transition state of the *endo* mode of addition.



2. INTRAMOLECULAR CYCLOADDITIONS

Pioneering investigations of intramolecular nitrone-olefin cyclization were carried out by LeBel and coworkers in the late fifties and early sixties.[18] In these reactions, the olefin moiety can be an appendage either from the carbon atom or from the nitrogen atom of the nitrone. In general, the isoxazolidines that are derived from C-alkenyl nitrones (with the exception of cyclic nitrones) are potential precursors for the construction of carbocyclic systems (Scheme 5). On the other hand, the isoxazolidines derived from N-alkenyl nitrones will necessarily lead to nitrogen heterocycles (*vide infra*).

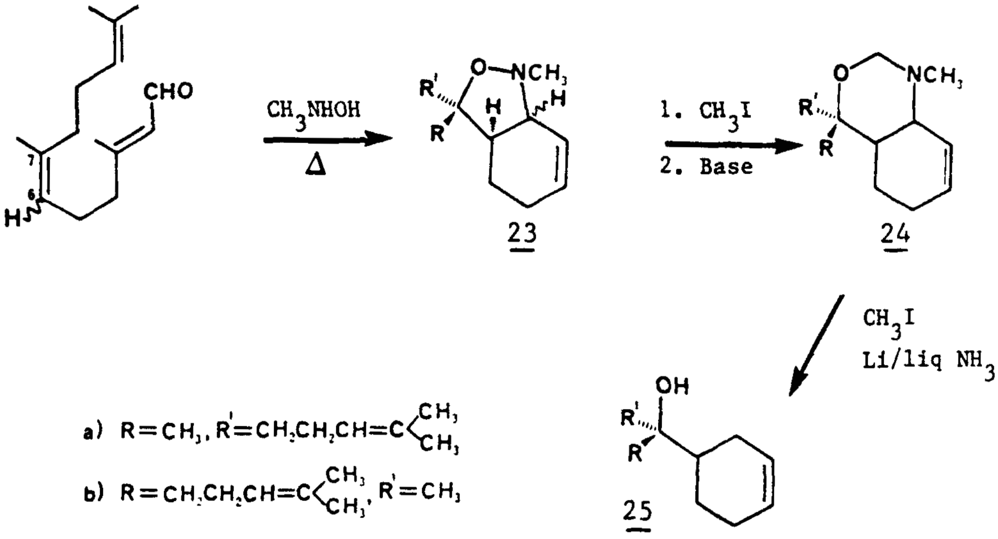


Scheme 5

a. C-Alkenyl Nitrones

i) Sesquiterpenes

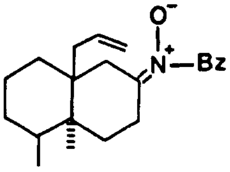
The stereospecificity of C-alkenyl nitrone cycloaddition reaction had been exploited for the synthesis of sesquiterpene bisabolol.[19] The diastereomeric mixture of isoxazolidines **23a** and **23b** was obtained from (*6Z*) and (*6E*)-farnesal and methylhydroxylamine. Reductive removal of the nitrogen led to the sesquiterpene **25**.



a) $R=CH_3, R'=CH_2CH_2CH=C(CH_3)_2$

b) $R=CH_2CH_2CH=C(CH_3)_2, R'=CH_3$

Intramolecular cycloadditions of exocyclic nitrones with the appropriate olefinic linkages furnished bridged bicycloalkanes fused to the isoxazolidines.[20] Application of this reaction is exemplified by the total synthesis of the sesquiterpene **26**, (12S)-7, 12-secoishwaran-12-ol. Nitrone **27** underwent smooth cycloaddition to give the key intermediate isoxazolidines **28** in high yields. Hydrogenation followed by hydrodeamination and dehydration gave the penultimate intermediate **29**, which was converted to the natural product in two steps.



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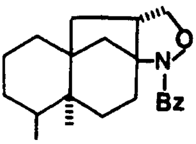

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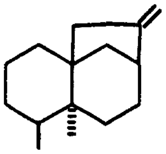

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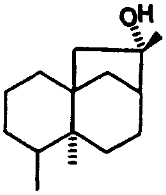

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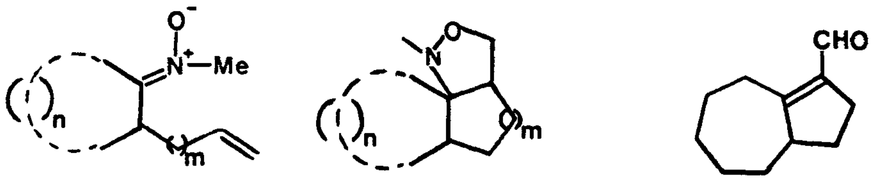
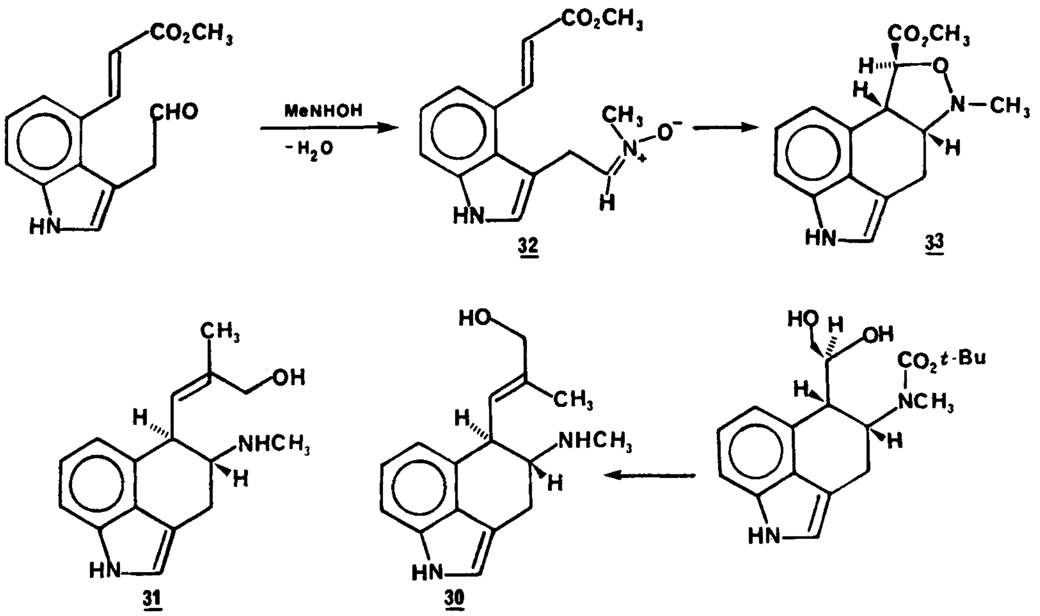
A related cycloaddition reaction was reported by Kakisawa and coworkers.[21] Perhydroazulene derivative and related systems were derived from the resulting isoxazolidine (Scheme 6).



Scheme 6

ii) Alkaloids

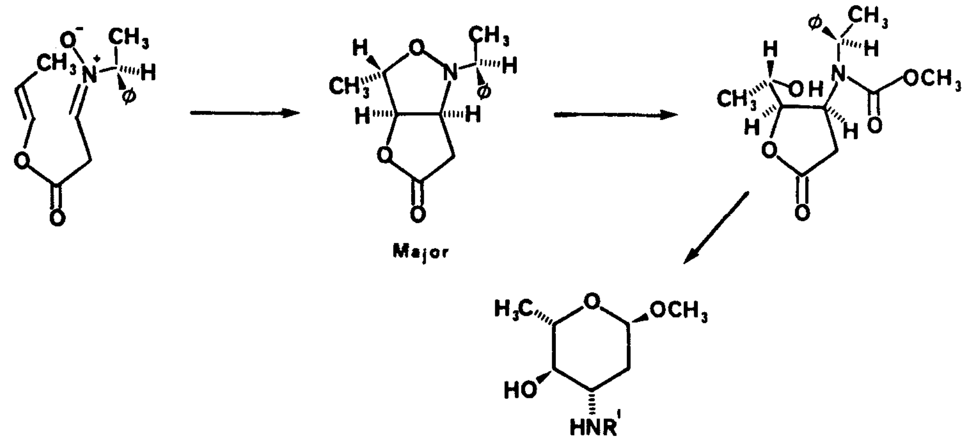
In a total synthesis of the ergot alkaloids chanaclavine I (**30**) and isochanaclavine (**31**) by Oppolzer, the key step involved a transient C-alkenylnitrone.[22] Nitrone **32** underwent a regio- and stereoselective intramolecular cycloaddition to a 1,2-disubstituted olefin. The isoxazoli-



dine 33 contains the proper basic skeleton for elaboration to the naturally occurring alkaloids.

iii) Aminosugars

Chiral synthesis of the sugar moities of the anthracycline antibiotics adriamycin, daunomycin, and carminomycin were achieved by Wovkulich and Uskokovic.[23] The nitrone-enol ester, generated by reaction of an enamine and optically pure α-methylbenzylhydroxylamine, underwent intra-

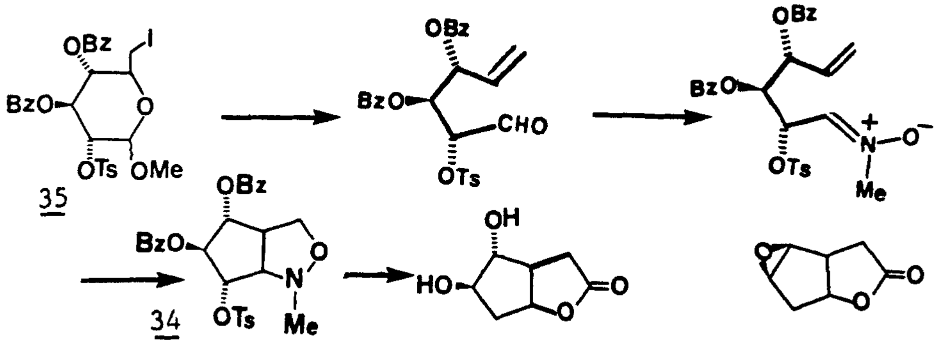


Scheme 7

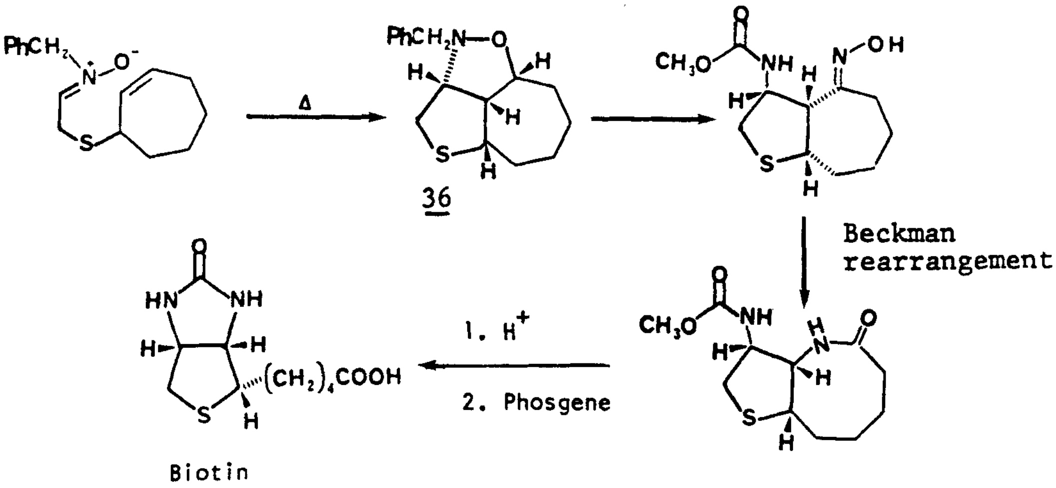
molecular cycloaddition to an adduct which has the desired relative stereochemistry at the chiral centers with appropriate heteroatoms in place. Reduction followed by protection of the amine gave a lactone carbamate, which was transformed to the sugar derivatives (Scheme 7).

iv) Miscellaneous

Isoxazolidine 34, obtained from the sugar derivative 35 in two steps,[24] was converted to various functionalized cyclopentane derivatives.



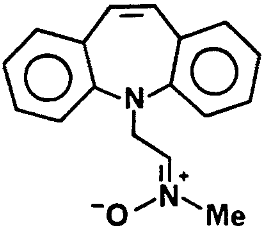
Noteworthy in these examples is the formation of the carbocycles with predictable stereochemistry at the various chiral centers. The starting carbohydrate nucleus served to introduce various functionalities and chirality in the carbocyclic system *via* the nitrone cycloaddition process.



Scheme 8

Isoxazolidines fused to heterocyclic system would be produced when a hetero atom links the cycloaddition partners.[25] Thus, in a single cycloaddition process of **36**, there was obtained the necessary framework with proper stereochemistry at all three centers of biotin.[26] The side-chain and nitrogens for the urea moiety were derived from the seven-membered ring of the isoxazolidine (Scheme 8).

An interesting variation in these cycloaddition reactions involves the nitrone and olefin linked by a nitrogen atom.[27] Nitrones such as **37**



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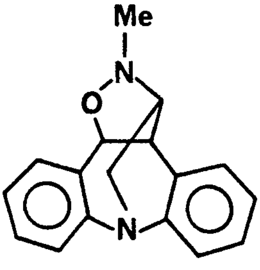

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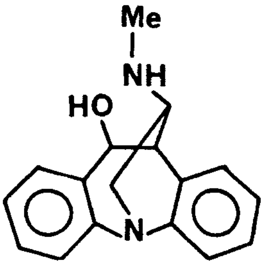
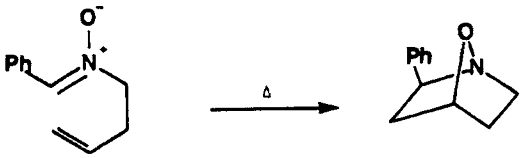


39

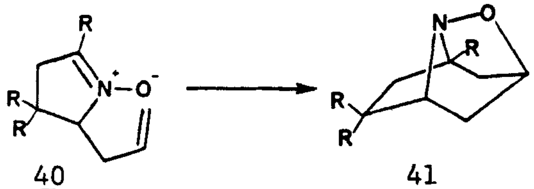
underwent cycloaddition to give the pentacyclic isoxazolidine **38** which in turn elaborated to functionalized dibenzazepines **39**. The corresponding carbon analogs had also been synthesized.

b. N-Alkenyl Nitrones

Intramolecular reactions involving N-alkenyl nitrones which lead to bridged bicyclic isoxazolidines have attracted little attention in total synthesis until recently.[28] In the first example, reported by Lumma, N-3-butenyl, C-phenyl nitrone cyclized to give the isoxazolidine exclusively.[29]

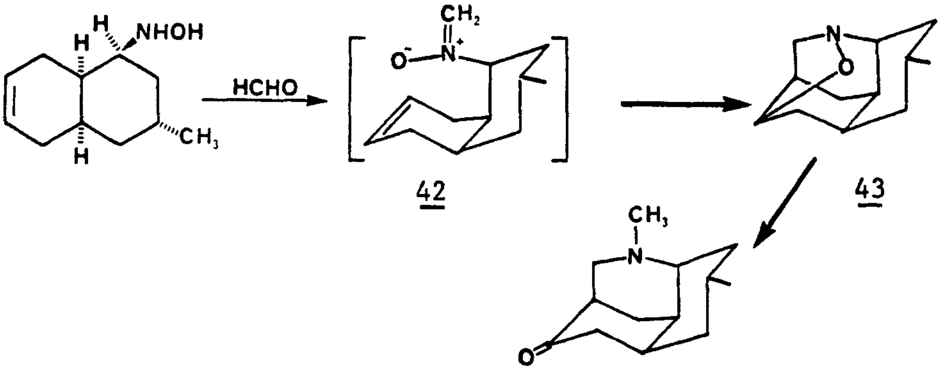


Analogous regiochemistry in the direction of addition was observed in the reaction of cyclic nitrone **40** → **41** leading to the tropane alkaloid skeleton.[30]



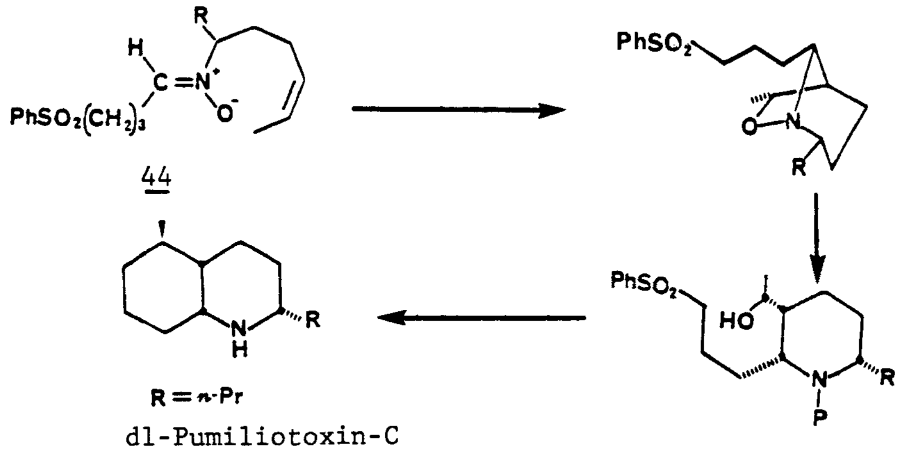
Alkaloids

An elegantly conceived total synthesis of **Lycopodium** alkaloid (+)-luciduline from an N-alkenyl nitrone has been reported.[31] A regiospecific intramolecular cycloaddition of nitrone **42**, from (+)-pulegone, resulted in the exclusive formation of the isoxazolidine **43**. Methylation followed by LAH reduction gave a N-methylamino alcohol which was oxidized to (+)-luciduline.



(+)-Luciduline

N-Alkenyl nitrones of the type **44** undergo smooth cyclization to the bridged bicyclic isoxazolidines; N-O bond scission lead to 2,3,6-*cis* substituted piperidines.[32] The relative stereochemistry of four chiral centers are controlled in a single cycloaddition process. This methodology was extended to the total synthesis of *dl*-pumiliotoxin-C from 2-pentanone and methyl phenyl sulfone (Scheme 9).

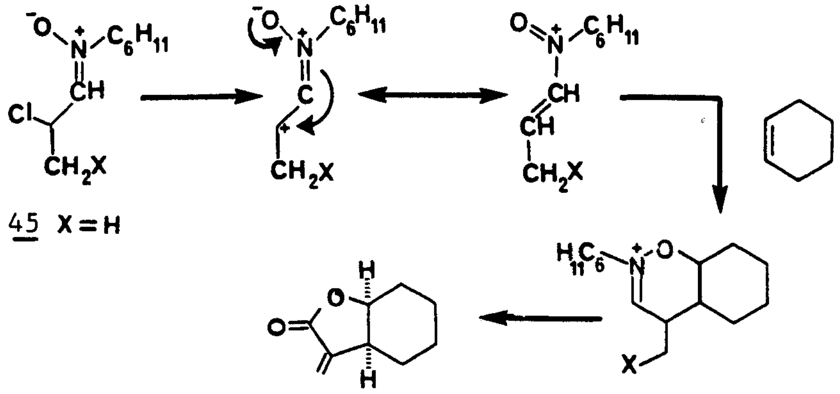


Scheme 9

II. [4+2] CYCLOADDITIONS OF NITRONES

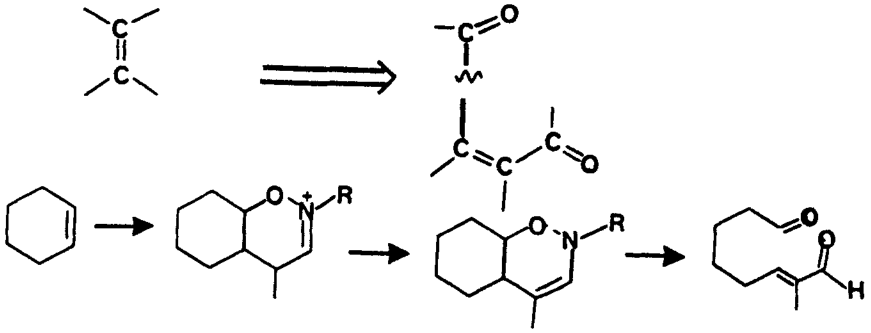
C-(1-chloroalkyl) nitrones, (e.g., 45) introduced by Eschenmoser,[33] can be efficiently utilized in organic synthesis. These nitrones serve as the precursors to the N-alkyl-N-vinyl nitrosonium cations, which participate in [4+2] cycloaddition process. This methodology was artfully applied in the synthesis of α-methylene lactones (Scheme 10) and in other useful synthetic transformations.

The sequence [2+4]-cycloaddition→deprotonation→[2'+4']cycloreversion was employed for the oxidative cleavage of olefinic double bonds with concomitant extension of the carbon chain at one of the double bond termini.

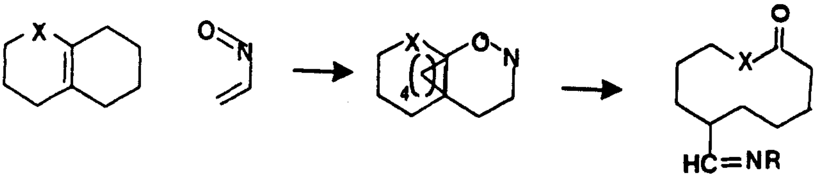


Scheme 10

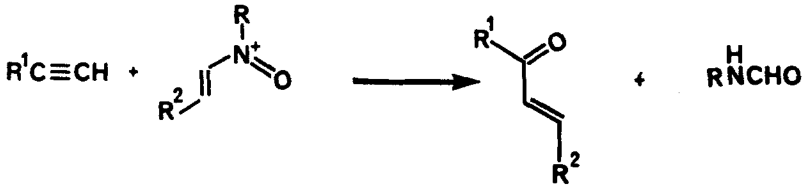
This indirect "carboxolytic" cleavage of double bonds proceeds in preparatively useful yields.[33]



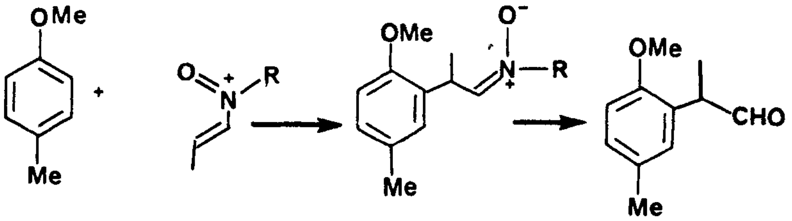
An extension of this methodology involving enol ethers as the cycloaddition partners provided a synthetic route to medium ring lactones. However, it is observed that these enol ether type double bonds cause difficulties in the initial cycloaddition process. Also the delicate cycloreversion process is limited by steric effects.[34]

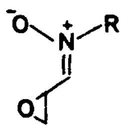


This cycloaddition, reversion process is also applied to acetylinic compounds to provied α,β-unsaturated carbonyl compounds.[35]



Simple variation in the reaction conditions of argentous ion induced α-chloro-aldonitrone/olefin reaction proceeds in substitution, thereby providing a method for β-γ-unsaturated aldehyde. Such substitution also occurs at activated aromatic nuclei. These reactions occur regiospecifically at the least substituted carbon.[36] Similar reactivity was observed for the epoxy nitrones (**46**).[37]





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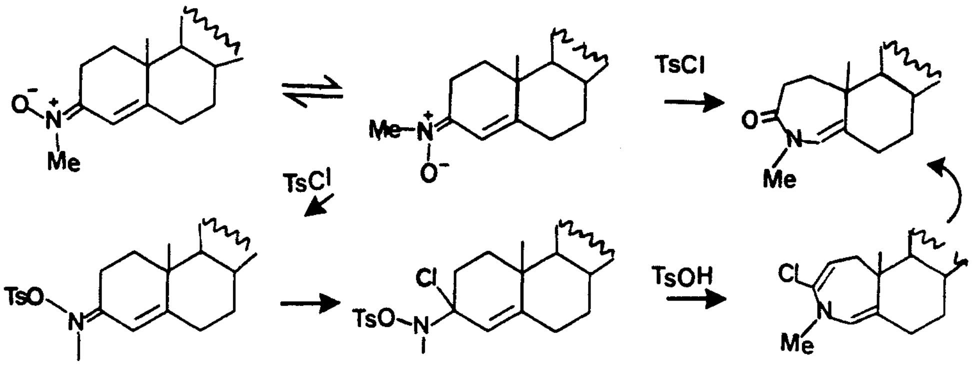
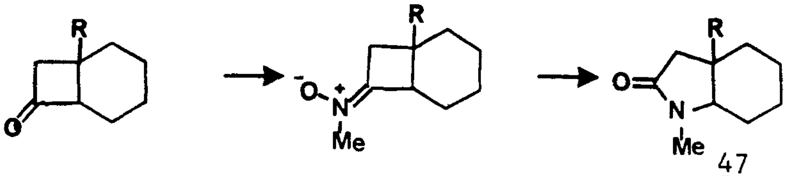
III. OTHER SYNTHETIC APPLICATIONS

Barton-Beckmann Rearrangement

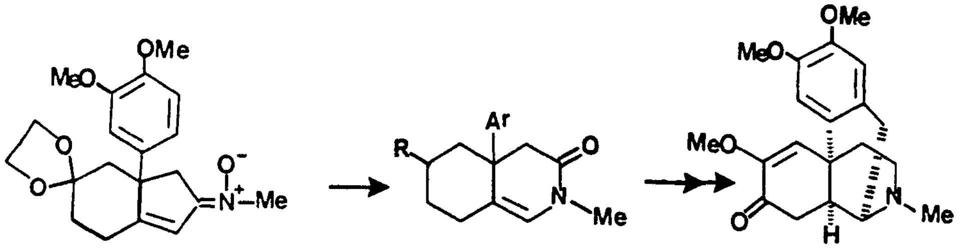
Ketonitrones undergo a Beckmann-type rearrangement on treatment with *p*-toluenesulfonyl chloride.[38] The outcome of this reaction, in contrast to the Beckmann rearrangement, does not depend on the stereochemistry of the nitrone since the (*Z*)-and (*E*)-nitrones interconvert rapidly under the conditions and both gave the same product. Such a rearrangement of bicyclo [4.2.0] octanones gave the perhydroindolone **47**, while the conventional Beckmann rearrangement would only lead to isoindole skeleton.[39]





47

More recently, McMurry applied this rearrangement in his synthesis of O-methylpallidinine.[40]



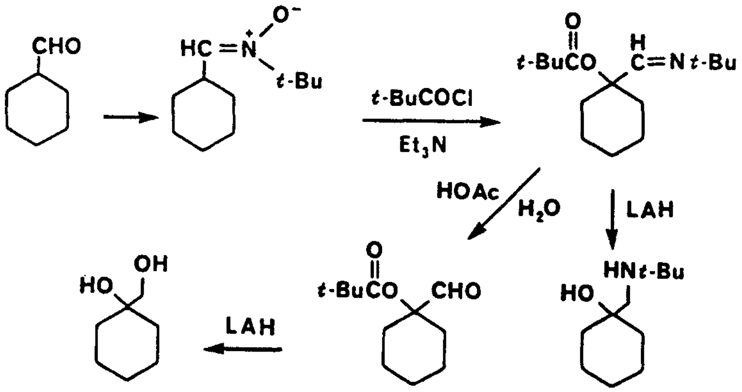
O-Methylpallidine

α-Oxygenation of Aldehydes and Cyclic Ketones

This process involves the treatment of the nitrones with acyl chloride in the presence of triethylamine to afford α-acyloxyimines by rearrangement of N-vinyl-O-acylhydroxylamine intermediates.[41] Hydrolysis yields the corresponding α-acyloxy carbonyl compounds (Scheme 11).

Other useful synthetic transformations[42-46] which need to be mentioned include the formation of olefins,[42] oxaziridines,[43] oxime-O-ethers[44] and oxazines.[45]

It is apparent that the nitrone-olefin cycloaddition process can serve as a powerful synthetic tool, and its full potential for diverse utility in synthesis is yet to be realized.



Scheme 11

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