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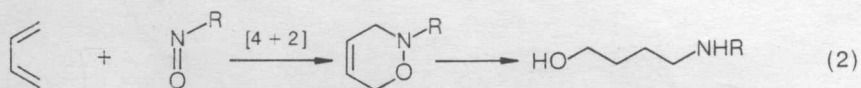
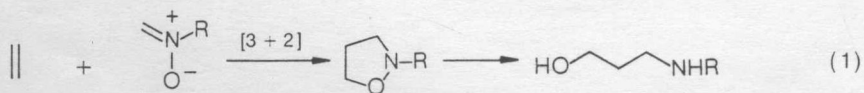
中國書院

TOTAL SYNTHESIS OF NITROGEN-CONTAINING NATURAL PRODUCTS VIA CYCLOADDITION REACTIONS

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1 INTRODUCTION

Thermally induced heterocycloaddition such as 1,3-dipolar cycloaddition (ref. 1) and hetero Diels-Alder reaction (refs. 2, 3), both 6π electron pericyclic reactions in which the two new σ -bonds are formed simultaneously, provide a versatile route to a wide variety of heterocyclic compounds. Of these pericyclic reactions, only the $[3 + 2]$ dipolar cycloaddition of nitrones (ref. 4) and the Diels-Alder reactions involving nitroso compounds as heterodienophiles (ref. 5) can afford cyclic hydroxylamines as shown in eqns. (1) and (2), in which both the nitrogen and oxygen atoms are ring members. A synthetically important feature common to these two types of cycloadditions is introduction of nitrogen and oxygen functionality at the same time with a high degree of regiochemical and stereochemical control. Subsequent reduction of these $[3 + 2]$ and $[4 + 2]$ cycloadducts viz. tetrahydro-1,2-oxazoles (isoxazolidines) and tetrahydro-1,2-oxazines, respectively, can easily be achieved by using a wide variety of reducing agents, such as zinc in acetic acid, sodium or aluminum amalgam in ethanol, or hydrogen over catalysts, and normally result in cleavage of the N-O bond leading to the formation of corresponding acyclic γ - and δ -amino alcohols as shown in the following eqns. (1) and (2).



These amino alcohols thus generated can be utilized as key building blocks for the construction of a variety of nitrogen-containing natural products including alkaloids. In the early 1980s, when we began a program to develop general utility of the cycloaddition-N-O bond cleavage approach to natural product synthesis, this approach had only received isolated attention although both nitron and nitroso cycloadditions themselves were well known reactions. However, the popularity of the nitron usage in the synthesis of alkaloids and related natural products has been sharply increased in recent years due to development of mechanistic and synthetic aspects of 1,3-dipolar cycloaddition.

The purpose of this chapter is to review our recent work on the development of both nitron and nitroso methodologies for preparing nitrogen-containing natural products including alkaloids, antibiotics, and a pheromone.

2 INDOLIZIDINE ALKALOIDS

Our initial efforts in the area of the indolizidine alkaloid synthesis were centered around using cyclic nitrones in the 1,3-dipolar cycloaddition since cyclic nitrones have an advantage in being fixed in the E configuration over acyclic nitrones which exist in E/Z equilibrium.

2.1 Tylophorine and Septicine

We first chose tylophorine (10), the major alkaloid of *Tylophora* species from Sri Lanka (ref. 6), as a synthetic target which possesses as a parent system the phenanthroindolizidine nucleus. Tylophorine has been synthesized in racemic form through numerous approaches (ref. 7), and recently two optically active preparations have been reported (ref. 8). All of these syntheses have been accomplished by utilizing synthetic routes starting from phenanthrene derivatives except for two routes (refs. 7d, 7f) involving oxidative coupling.

Our approach (ref. 9) to tylophorine and its biogenetic congener, septicine (9), based on the dipolar [3 + 2] cycloaddition, involved reaction between 1-pyrrolidine 1-oxide (2) and 3,4-dimethoxystyrene (1) to give a diastereomeric mixture of 3 and 4 in a ratio of 5:2 (by GC), favoring the trans isomer 3 in nearly quantitative yield (Fig. 1). Catalytic hydrogenation of this mixture resulted in N-O bond cleavage to afford the amino alcohol 5 (86%) as a mixture of two isomers (α - and β -OH in formula 5). Acylation of 5 afforded the amide alcohol 6 along with a minor amount of the amide ester 7. The crude mixture of the products was hydrolysed under alkaline conditions to produce 6 in 70% yield based on 5. Oxidation with Collins reagent followed by intramolecular aldol condensation converted 6 into the lactam 8 in 65%

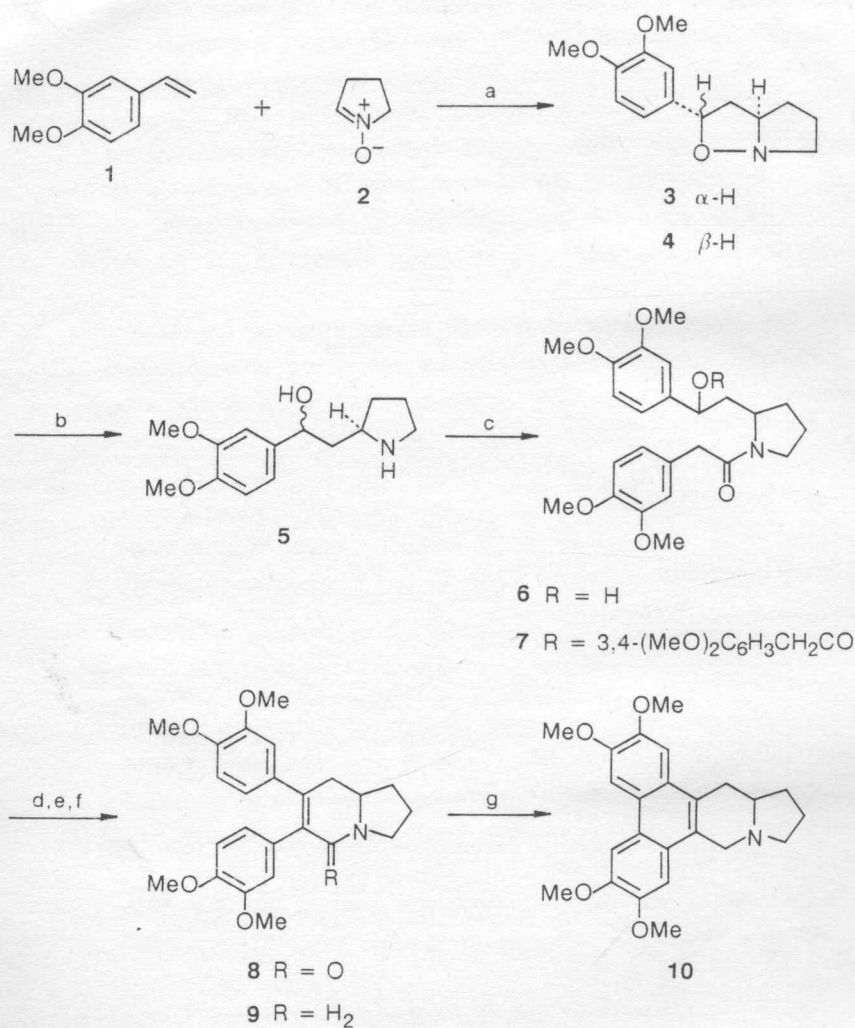
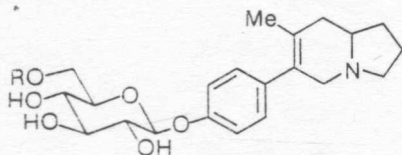


Fig. 1 (a) toluene, reflux; (b) H_2 , Pd/C, MeOH; (c) 3,4-(MeO) $_2$ - $C_6H_3CH_2COCl$, K_2CO_3 , CH_2Cl_2 , r.t., then K_2CO_3 , MeOH, H_2O , reflux; (d) $CrO_3 \cdot 2Py$, CH_2Cl_2 , r.t.; (e) KOH, EtOH, reflux; (f) AlH_3 , THF-Et $_2O$, r.t.; (g) $h\nu$, I_2 , CH_2Cl_2 .

yield. Reduction of 8 with alane afforded (\pm)-septicine (9) (ref. 10) in 88% yield, which was subjected to UV irradiation to provide (\pm)-tylophorine (10) in 43% yield.

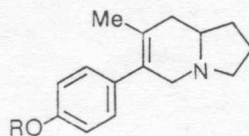
2.2 Ipalbidine

The *Ipomoea* alkaloids, isolated from the seeds of *Ipomoea alba* and *Ipomoea muricata*, comprise two glycoside alkaloids ipalbine (11) (ref. 11) and ipomine (12) (refs. 12-14) and their aglycone ipalbidine (13) (ref. 10). A unique structural feature of this class of alkaloids is that the C-methyl group is found on the hexahydroindolizidine nucleus. They are the only examples of naturally occurring indolizidine alkaloids (ref. 15). We envisaged a synthetic approach to ipalbidine (13) via the bicyclic ketone (15) which can be directly transformed into O-methylipalbidine (14), a synthetic precursor of ipalbidine (ref. 16).



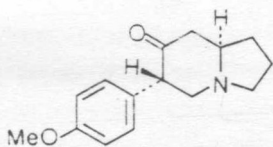
11 R = H

12 R = p-coumaroyl



13 R = H

14 R = Me



15

As a part of preliminary experiments (ref. 17) aimed at constructing the bicyclic ketone system by the nitronone based approach, cycloaddition of the nitronone 2 with the 2-phenyl-3-butenone 16 was carried out to give three adducts 17, 18, and 19 in 17, 31, and 32% yields, respectively (Fig. 2). Reductive treatment of the minor product 17 (6:5 diastereomeric mixture) with zinc in aqueous acetic acid resulted in the formation of 20 which possesses the equivalent functionality on the indolizidine ring system to that possessed by the indolizidinone 15.

Because of low selectivity in the formation of the cycloadduct 17, we abandoned the above approach to the bicyclic ketone intermediate 15. Thus an alternative nitronone based approach to 15 was next elaborated as shown in Fig. 3 (ref. 18).

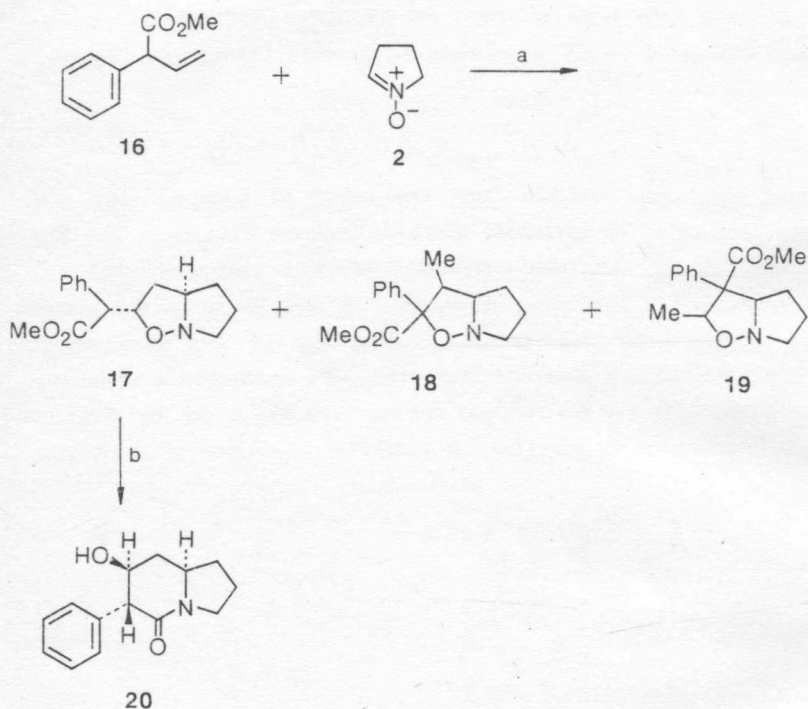


Fig. 2 (a) toluene, reflux; (b) Zn, aq. AcOH, 120 °C.

The reaction of the nitron **2** with *p*-methoxy(allyl)benzene (**21**) in refluxed toluene produced the cycloadduct **22** in 70% yield as a single diastereoisomer. The high regioselectivity and stereoselectivity observed in this reaction are rationalized on the basis of the preference for dipole LUMO control (ref. 19) and exo-oriented transition state (ref. 20), respectively, when non-conjugated, electron-rich olefins such as **21** are used as dipolarophiles. Subsequent N-O bond cleavage of **21** by hydrogenation afforded the γ -amino alcohol **23** (82%), which was heated with formic acid in toluene to give N,O-diformylated compound **24**. For selective hydrolysis of the O-formate group, **24** was exposed to ammonia in methanol to give the N-formylcarbinol **25** in 69% yield from **23**. Collins oxidation of **25** yielded the formylketone **26** (72%).

For the construction of the indolizidine skeleton, we then considered application of internal aldol condensation to **26**. Compared with the case in the aldol cyclization previously employed in the tylophorine (and also julandine, see below) synthesis [eqn. (3)], the type of aldol reaction required in the present case [eqn. (4)] is unusual as the amide C=O group is normally unreactive as the electrophilic partner (ref. 21). After several unsuccessful

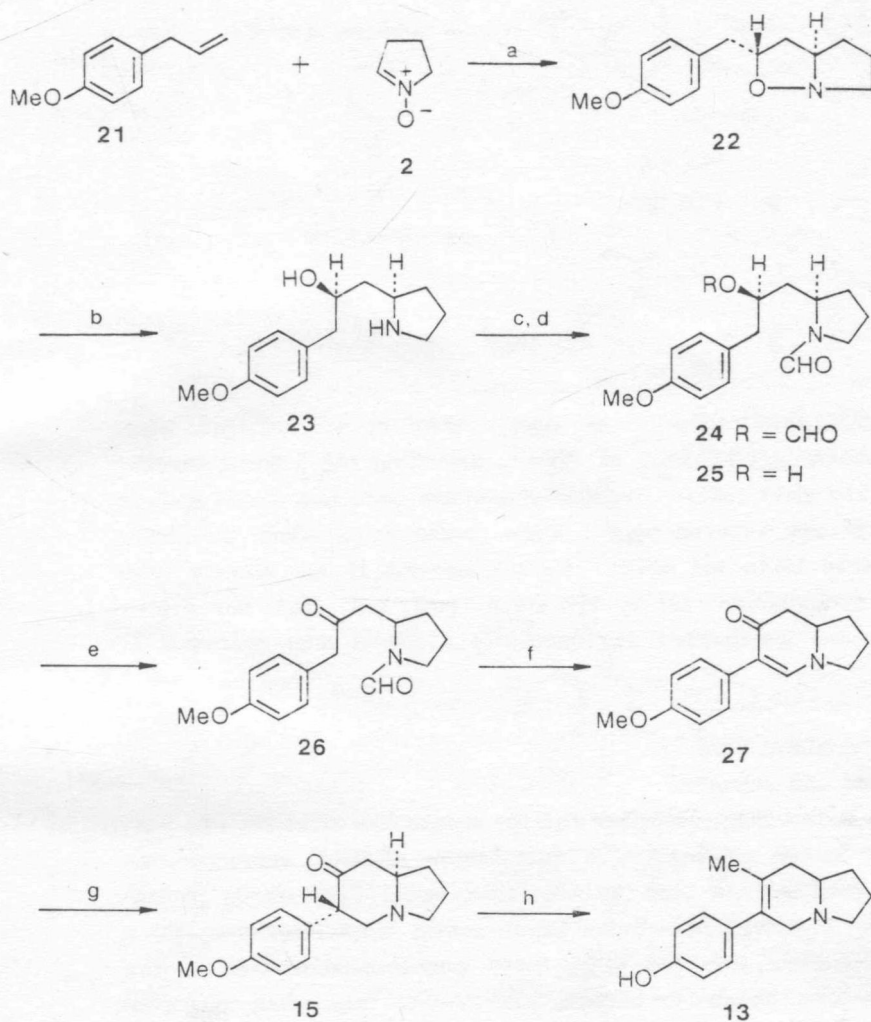
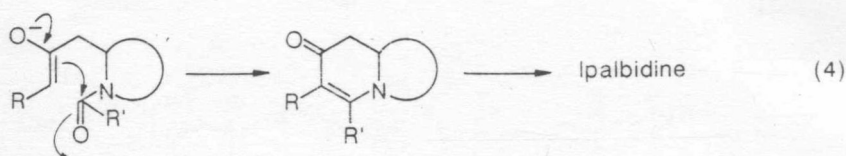
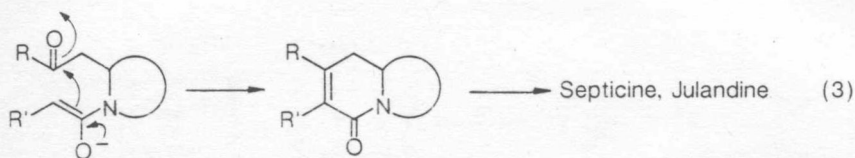


Fig. 3 (a) toluene, reflux; (b) H_2 , Pd/C, MeOH; (c) HCO_2H , toluene, reflux; (d) NH_3 , MeOH, r.t.; (e) $CrO_3 \cdot 2Py$, CH_2Cl_2 , r.t.; (f) $Al(t-BuO)_3$, xylene, reflux; (g) Li, NH_3 , THF, $-78^\circ C$; (h) refs. 10d and 16a.

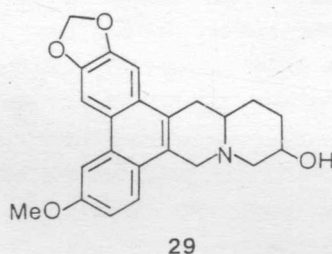
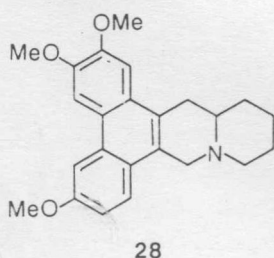


attempts, however, the intramolecular aldol cyclization was attained when heated with aluminum *tert*-butoxide in xylene, providing the bicyclic enaminone 27 albeit in low yield (36%). Eventually selective reduction of the olefinic double bond of 27 was achieved by the Birch procedure to afford the objective bicyclic ketone 15 in 54% yield. Since compound 15 has already been converted into (\pm)-ipalbidine (13) by two steps (refs. 10d, 16a), our preparation of the ketone intermediate 15 constitutes a formal total synthesis of racemic 13.

3 QUINOLIZIDINE ALKALOIDS

3.1 Cryptopleurine and Julandine

The nitron methodology described for the indolizidine alkaloids was next planned to apply to the synthesis of a quinolizidine alkaloid, cryptopleurine (28) (ref. 22), first isolated from an Australian laurel *Cryptocarya pleuro-sperma* (ref. 23). Cryptopleurine forms together with cryptopleuridine (29) a rare group of alkaloids with the *trans*-fused phenanthroquinolizidine ring system and has been shown to possess unique and interesting biological properties including cytotoxic (ref. 24), vesicant (ref. 23), and antitumor (ref. 25) activities, and, thus, is responsible for considerable recent synthetic attention (ref. 26).



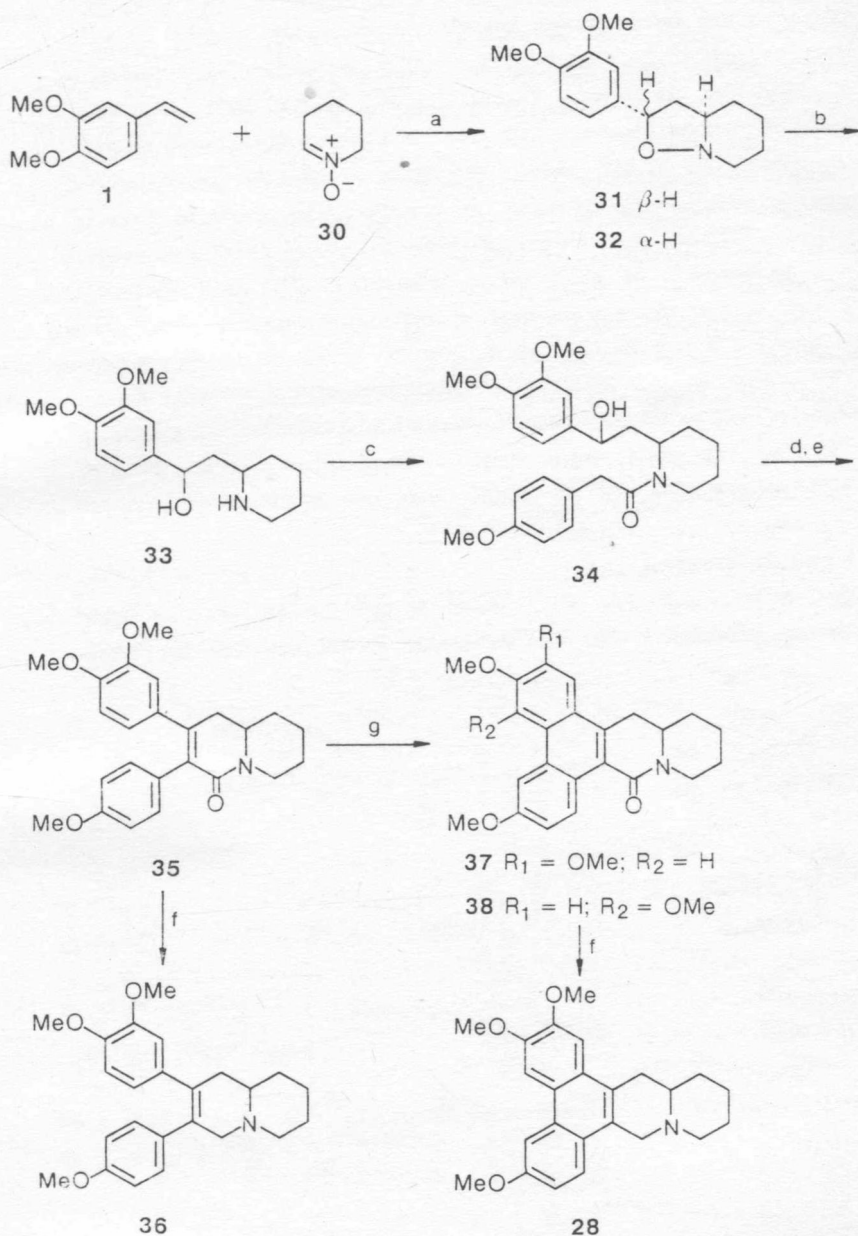
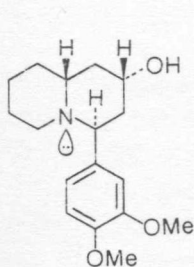


Fig. 4 (a) toluene, reflux; (b) Zn, aq. AcOH, 50 °C; (c) p-MeO-C₆H₄CH₂COCl, K₂CO₃, MeCN, r.t. then K₂CO₃, H₂O, MeOH, reflux; (d) CrO₃·2Py, CH₂Cl₂, r.t.; (e) NaOEt, EtOH, reflux; (f) LiAlH₄, THF, reflux; (g) hν, I₂, dioxane.

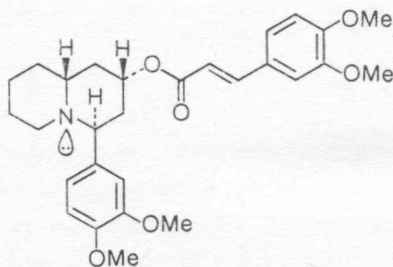
Our synthesis of cryptopleurine (28) and its seco base julandine (36) began with the 1,3-dipolar cycloaddition reaction of the cyclic nitrone 30 with 3,4-dimethoxystyrene (1) (Fig. 4) (ref. 27). The cycloadducts, actually a 20:1 mixture of *trans* and *cis* isomers 31 and 32, so obtained (93%) was subjected to reductive N-O bond cleavage with zinc in aqueous acetic acid to give the cyclic amino alcohol 33 in 90% yield. Acylation of 33 afforded 34 along with the N,O-diacylated product, however, in practice, the crude mixture of these products was, without separation, subjected to brief treatment under alkaline condition to produce 34 as a single product in 64% yield from 33. Oxidation of 34 with Collins reagent followed by intramolecular aldol condensation yielded the bicyclic lactam 35 (55% yield from 34) which on LiAlH_4 reduction provided (\pm)-julandine (36) (ref. 28). Irradiation of the bicyclic lactam 35 in the presence of iodine yielded two fluorescent photocyclisation products 37 and 38 in 48 and 14% yield, respectively. The major product 37 was converted to (\pm)-cryptopleurine (28) by LiAlH_4 reduction in 95% yield.

3.2. Lasubine I and Subcosine I

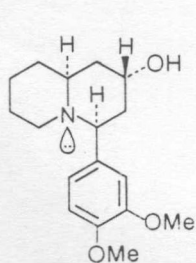
Other target molecules which we decided to synthesize are the new quinolizidine alkaloids lasubine I (39) and subcosine I (40) with the *cis*-fused



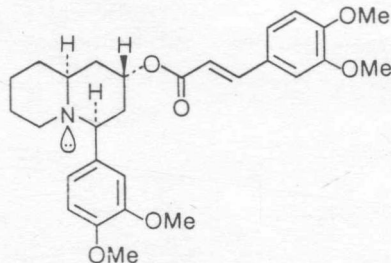
39 Lasubine I



40 Subcosine I



41 Lasubine II



42 Subcosine II

quinolizidine ring system, which have been isolated (ref.29) from the leaves of *Lagerstroemia subcostata* Koehne along with lasubine II (41) (ref. 30) and subcosine II (42) with the trans-fused quinolizidine ring system. Our first synthesis of 39 and 40 based on nitronc cycloaddition (ref. 30) has been achieved as follows (ref. 31).

1,3-Cycloaddition between 1-(3,4-dimethoxyphenyl)butadiene (43), a 9:5 mixture of the E and Z isomers, and the nitronc 30 gave the corresponding E and Z cycloadducts 44 (trans/cis = 10:3) and 45 (trans/cis = 5:1) in 49 and 22% yields, respectively (Fig. 5). With the E isomer 44 in hand, we attempted to transform it directly to lasubine I (39). Thus hydrogen chloride was added to the olefin moiety of 44 to generate the chloride as a diastereomeric mixture of 46 and 47, which, without separation, underwent hydrogen-

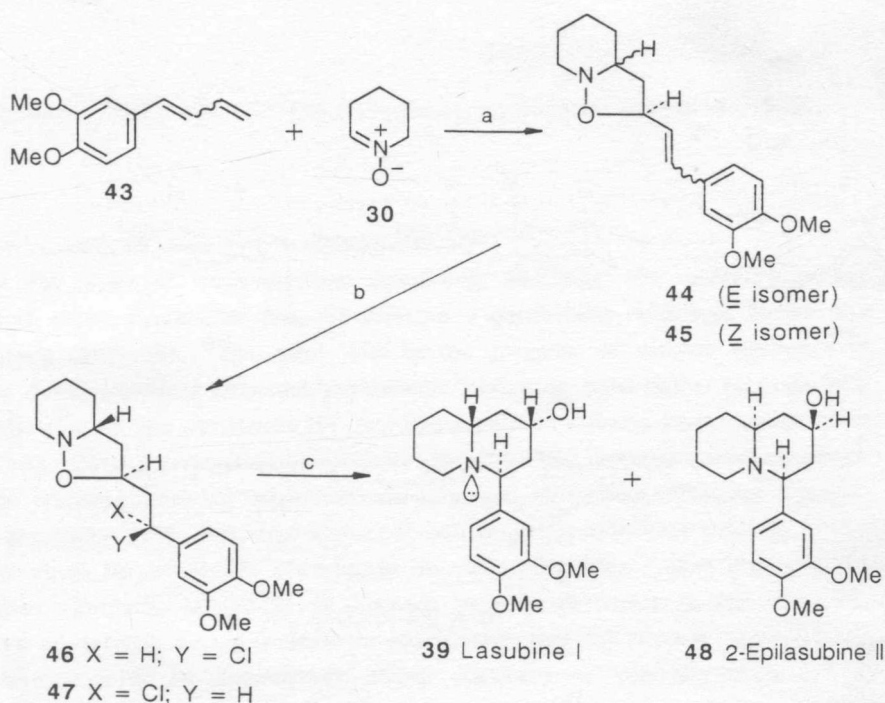


Fig. 5 (a) toluene, reflux; (b) HCl, CHCl₃, 0-5 °C; (c) H₂, Pd/C, Py-MeOH.

ation to afford (\pm)-lasubine I (39) in 44% yield from 44 along with (\pm)-2-epilasubine II (48) as a minor product (14% yield).

The formation of both alkaloids 39 and 48 must arise via both chlorides 46 and 47, respectively (Fig. 6). Subsequent reductive N-O bond cleavage furnishing the amino alcohols 49 and 50 followed by in situ ring closure via S_N2 displacement may afford lasubine I (39) and 2-epilasubine II (48), respectively. In the case of the reaction leading to lasubine I, the initially formed conformer 39', which has a trans-fused quinolizidine ring and an axial aryl group should be thermodynamically disfavored because of strong non-bonded interactions between the aromatic hydrogens at C-2' and/or C-6' and the two axial quinolizidine hydrogens at C-2 and/or C-6. Thus 39' epimerizes to the thermodynamically more stable cis-fused quinolizidine conformation 39 by nitrogen inversion.

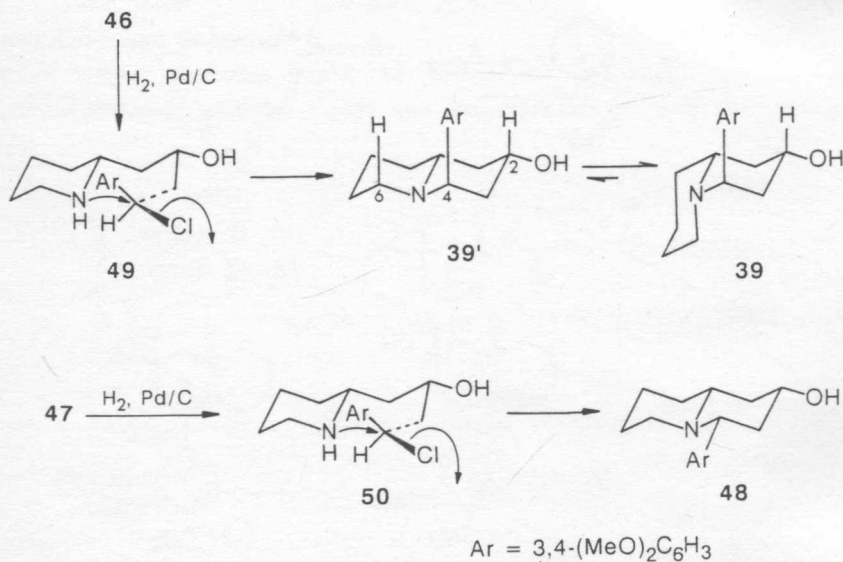
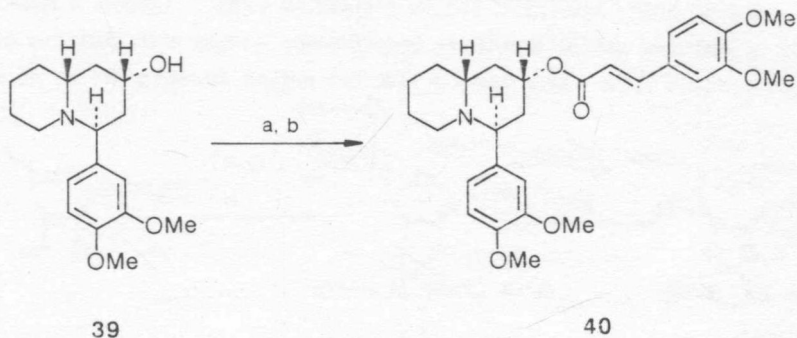


Fig. 6 Formation of lasubine I (39) and 2-epilasubine II (48).

Treatment of the lithium salt of synthetic lasubine I (39) with 3,4-dimethoxycinnamic anhydride gave (\pm)-subcosine I (40) in 48% yield. Thus the first total synthesis of (\pm)-subcosine I was achieved by utilizing 1,3-dipolar cycloaddition of a nitron as a key step.



(a) *n*-BuLi, THF, -78 °C; (b) 3,4-dimethoxycinnamic anhydride, THF, r.t.

4 (+)-NEGAMYCIN AND (-)-3-EPINEGAMYCIN

In the area of cycloaddition reactions, inducing the chirality under control of chiral auxiliaries has represented a continuing challenge during the last decade (ref. 32). Our next goal in the program of nitron methodology was the development of efficient asymmetric induction with chiral nitrones and its application to the synthesis for (+)-negamycin in natural form. Negamycin (51) (ref. 33), a structurally unique peptide-like natural product which exhibits striking activity against Gram-negative bacteria, including *Pseudomonas aeruginosa* (ref. 34), has attracted considerable synthetic interest (refs. 35, 36) since its structure elucidation in 1971 (ref. 36). Our strategy for the chiral synthesis of (+)-51 is outlined retrosynthetically in Fig. 7. The key step envisioned would involve an enantioselective 1,3-dipolar cycloaddition of a nitron with an appropriate chiral auxiliary to the allylamine. This cycloaddition would simultaneously create two new asymmetric centers adaptable to the 3*R*,5*R* stereochemistry of (+)-51.

Of reported chiral inductor groups in asymmetric nitron cycloaddition (ref. 38), carbohydrate derivatives initially developed by Vasella (ref. 39) seemed to be most applicable. Accordingly, our first objective was to develop the efficient chiral N-glycosyl nitrones and to demonstrate acceptable diastereoselection during the cycloaddition.

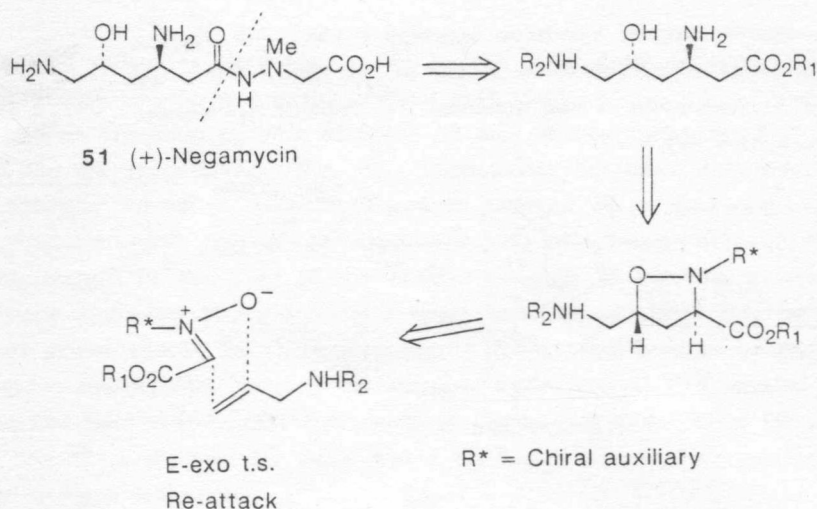


Fig. 7 Retrosynthetic analysis of (+)-negamycin (51).

4.1 Asymmetric 1,3-Dipolar Cycloaddition

Treatment of known 1-O-benzyl-D-ribo-furanose (52) with 1,1-dimethoxycyclohexane was followed by methylation and hydrogenation, affording 53 (70% overall yield), which was then quantitatively converted to the oxime 54. The nitron 55, generated in situ by the reaction of 54 with methyl glyoxylate, was allowed to react with the allylamine derivative 56 (toluene, reflux) to furnish an inseparable mixture of the (3R,5R)-trans (57a) and (3S,5R)-cis (57b) adducts in total yield of 91%. The mixture was subjected to LiAlH₄ reduction, hydrolysis to remove the chiral auxiliary (diluted HCl, MeOH), and N-benzylation to give the trans (3R,5R)-58a and cis (3S,5R)-58b alcohols in a ratio of 4:9 (total overall yield: 46% from 57a + 57b), after chromatographic separation. The ee of the products was determined as the Mosher's (+)-MTPA ester (ref. 40), proving to be 73.6% (Fig. 8) (ref. 41).

This result indicates that the asymmetric induction observed with D-ribosyl nitron 55 is less than satisfactory. A much better result was obtained by employing the D-glosyl template shown in Fig. 9 (ref. 42). D-Gulono-γ-lactone (D-59) was converted to 2,3:5,6-O-cyclohexylidene-D-gulo-furanose (D-60) by treatment with 1,1-dimethoxycyclohexane followed by DIBAL reduction in 88% yield from D-59. Compound D-60 was converted quantitatively to the oxime D-61. The nitron D-62, generated in situ by the reaction of D-61 with methyl glyoxylate as a mixture of E and Z isomers, was allowed to react with the allylamine derivative 56 to produce a mixture of the 3R,5R-trans (D-63a) and 3S,5R-cis (D-63b) adducts in 84% yield. After

removal of the D-gulosyl auxiliary group by acid hydrolysis, the diastereomeric mixture of the products was subjected to N-benylation followed by LiAlH_4 reduction to provide the chromatographically separable trans alcohol ($3R,5R$)-58a and cis alcohol ($3S,5R$)-58b in a ratio of 2:3 (55% overall yield from D-63a + D-63b). Thus utilization of the D-gulosyl chiral template in this process resulted in a highly stereobiasd synthesis of 58a and 58b in 93.7% ee and 94.2% ee [determined as the (+)-MTPA ester (ref. 40)], respectively.

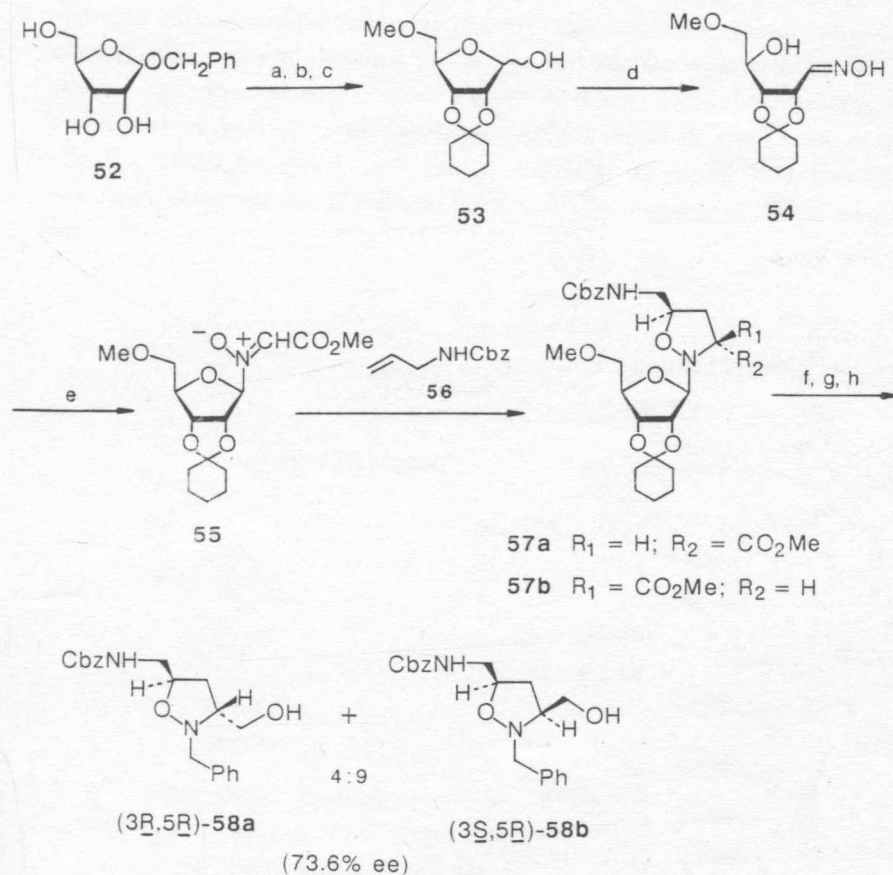


Fig. 8 (a) 1,1-dimethoxycyclohexane, TsOH , benzene, reflux; (b) MeI , NaH , glyme, 40°C ; (c) H_2 , Pd/C , MeOH ; (d) $\text{NH}_2\text{OH}\cdot\text{HCl}$, Py , r.t.; (e) methyl glyoxylate, toluene, MS 4A, reflux; (f) HCl-MeOH , 40°C ; (g) LiAlH_4 , Et_2O , r.t.; (h) PhCH_2Br , K_2CO_3 , DMF , 50°C .

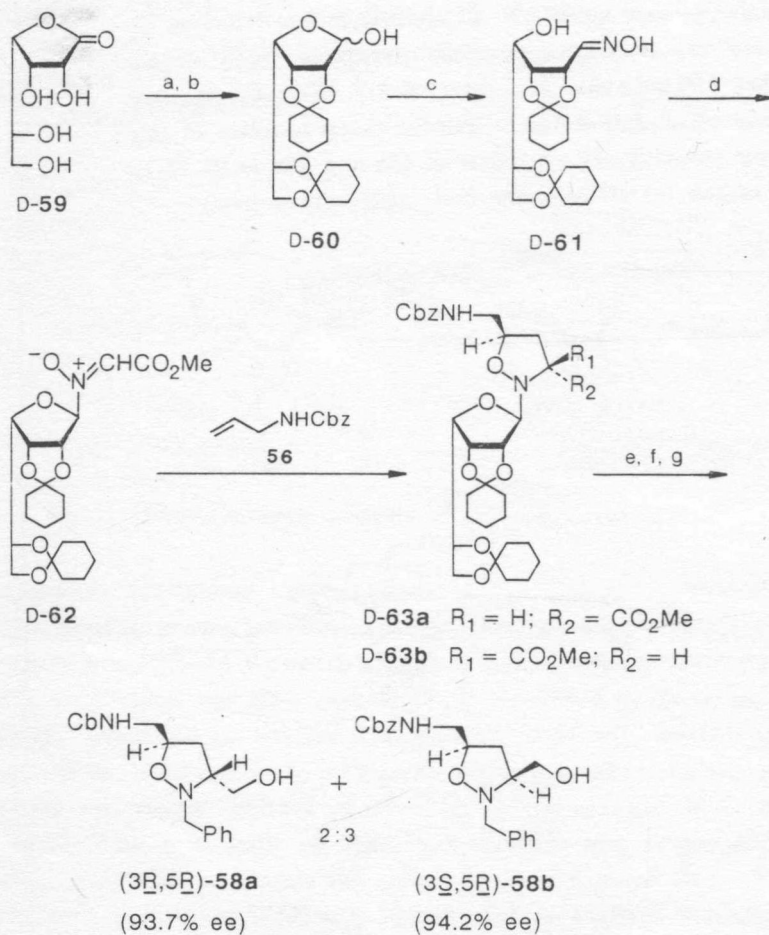


Fig. 9 (a) 1,1-dimethoxycyclohexane, TsOH, benzene, reflux; (b) DIBAL, toluene-THF, -78°C ; (c) $\text{NH}_2\text{OH}\cdot\text{HCl}$, Py, r.t.; (d) methyl glyoxylate, toluene, reflux; (e) HCl-MeOH , 90°C ; (f) PhCH_2Br , K_2CO_3 , DMF, 50°C ; (g) LiAlH_4 , Et_2O , r.t.

Both trans (D-63a) and cis (D-63b) products obtained in this cycloaddition using the nonconjugated olefin 56 as the dipolarophile must arise applying Diels-Alder terminology) from the exo transition state since endo transition state would be greatly restricted by suffering from unfavorable

steric interactions between the CH_2NHCbz group in the incoming dipolarophile 56 and the furan ring oxygen atom of the nitron D-62; the E isomer of the nitron D-62 thus yields the trans adduct D-63a, while the Z isomer yields the cis adduct D-63b. The facial selectivity observed in this cycloaddition with both E and Z nitrones may be interpreted in terms of "O-endo" transition state model (A) (ref. 39b) as shown in Fig. 10, wherein, by analogy to recent reports (ref. 43), the electron-donating group (secondary alkyl) rather than the polar group (alkoxy) is perpendicular to the plane of the nitrogen-carbon double bond to permit the maximum orbital overlap of the participating centers, leading to the favored re face approach at the prochiral olefin. An alternative "O-exo" transition state model (B) should be disfavored due to serious nonbonded interactions between the furan ring oxygen and the CHCO_2Me group (ref. 44). A similar approach to a prochiral diene has been observed in pericyclic cycloaddition reaction of chiral sugars (ref. 45).

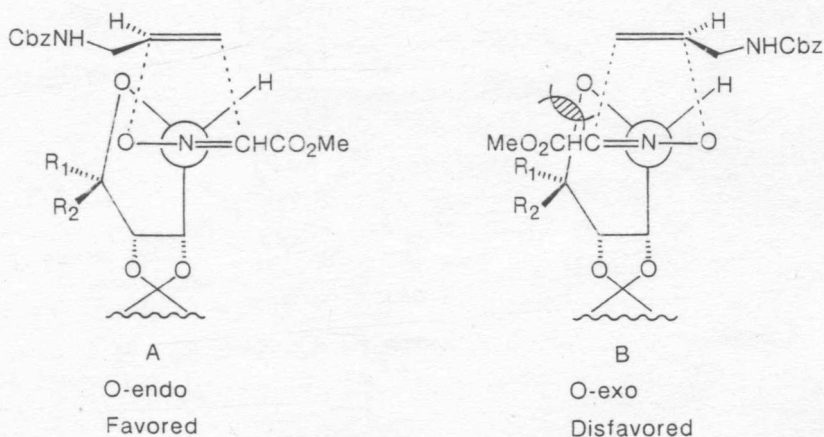


Fig. 10

Due to the above demonstrated capacity of the D-gulosyl auxiliary to create the chiral centers with high selectivity, opposite enantiomeric chiral induction by the asymmetric nitron cycloaddition was then investigated. In this regard, as an easily available and inexpensive enantiomeric chiral template the L-gulosyl nitron L-62 was prepared from D-glucuronolactone (64) according to Fig. 11. The cycloaddition of L-62 with 56 (affording a mixture of L-63a and L-63b) followed by separation by silica gel chromatography gave