MASSEY UNIVERSITY

DEPARTMENT OF CHEMISTRY
AND BIOCHEMISTRY

The Addition of Heterocyclic Amines to a Nitro-alkene.

A thesis presented in partial fulfilment of the requirements
for the degree of

Master of Science

at Massey University.

Andrew Duncan Johnston.
August 1992.

To my family for their
support and patience.

Acknowledgements.

I wish to express my sincere thanks to Dr Margaret Brimble who, in her role as supervisor, has provided me with invaluable assistance, guidance and encouragement throughout the course of this work. In addition, she has introduced me to an area of research that has proved stimulating, thought-provoking and immensely rewarding and for this I am extremely grateful.

I would also like to acknowledge the support provided by my family and friends, for their encouragement when things became a little trying.

It remains for me to thank Dr Mark Brimble for his assistance in proof reading this thesis, and especially my friends and colleagues David Reid and Michael Nairn who in addition to helping with the proof reading have made life in the laboratory bearable.

CONTENTS

CHAPTER 1 **INTRODUCTION**

CHAPTER 2 **DISCUSSION**

ABBREVIATIONS

DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP = 4-dimethylaminopyridine
DMF = *N,N*-dimethylformamide
DMSO = dimethylsulphoxide
equiv = equivalent
m-CPBA = *meta*-chloroperoxybenzoic acid
N.M.R = nuclear magnetic ressonance
THF = tetrahydrofuran
t.l.c = thin layer chromatography
TMS = trimethylsilyl

CHAPTER 1

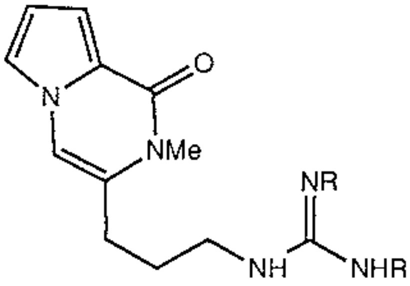
INTRODUCTION

This thesis is concerned with the synthesis of analogues of the insect feeding deterrent peramine (1), in which the key step involves the use of a Michael addition to a nitro-alkene. The introduction therefore consists of three parts:

1. The isolation and synthesis of the insect antifeedant peramine (1).
2. The use of nitro-alkenes as Michael acceptors.
3. Pyrazine ring systems related to peramine (1) and other natural products.

1.1 The Isolation and Synthesis of the Insect Antifeedant Peramine (1).

The resistance of perennial ryegrass *Lolium perenne L* to the Argentine stem weevil *Listrontus bonariensis* arises from the principal insect feeding deterrent peramine (1), a pyrrolopyrazine alkaloid produced by the fungal endophyte *Acremonium lolii* [1]. The Argentine stem weevil is a major pest of ryegrass pastures, maize, wheat, barley, and brassica crops in New Zealand. The adult Argentine stem weevil produces window like grazing scars on leaves, but generally causes little permanent damage to established pastures. The larvae however, are more destructive. Eggs are laid on the leaf sheath tissue and hatch to produce tunnelling larvae that burrow into the middle of the grass tiller. The larvae can also transfer from tiller to tiller, killing from three to five tillers as they mature. It has been shown that endophyte infected grass suffers less damage by adult weevil and has fewer eggs and larvae than do the uninfected plants.



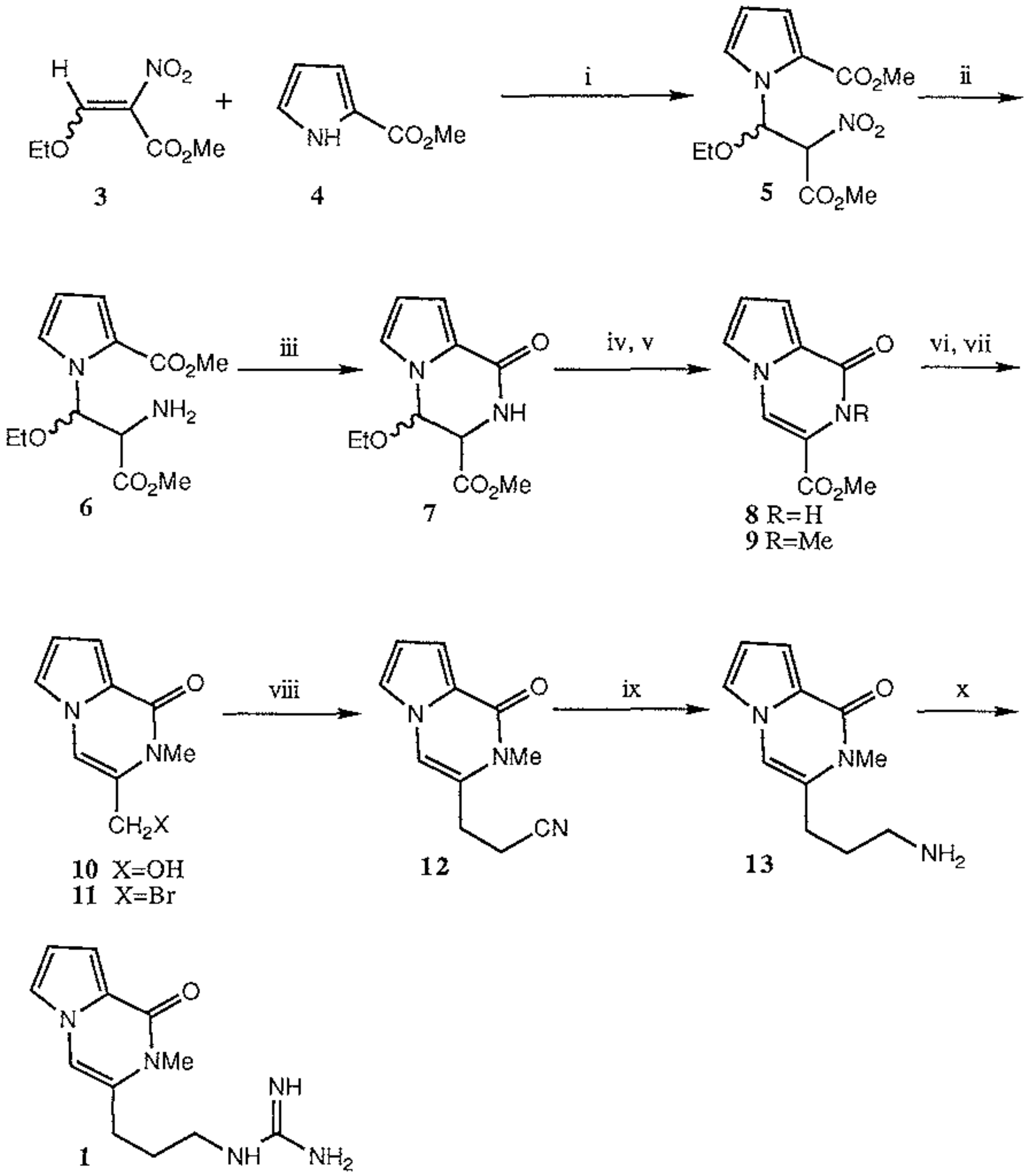
1. R=H
2. R=Ac

In 1986 Rowan and co-workers determined the structure of the diacetylated derivative of peramine (2) spectroscopically and found it to be the guanidinium alkaloid 3-(3'-guanidinylpropyl)-2-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one[2]. Thus peramine (1) contains two interesting structural features, a saturated diketopiperizine ring system and a guanidino group. These features prompted two independent chemical syntheses.

The first synthesis of peramine (1) was reported by Brimble[3] (Scheme 1) making use of a Michael addition of a pyrrole anion to a nitro-alkene to effect the key *N*-alkylation step. The nitro-alkene (3) underwent smooth Michael addition with the potassium salt of methylpyrrole-2-carboxylate (4) to give the Michael addition product (5) as a mixture of stereoisomers. The nitro group of the Michael adduct was reduced to the corresponding amine (6) using sodium borohydride/cobalt chloride. The amine then underwent cyclisation to the lactam (7) upon heating under reflux in toluene for twenty four hours. Treatment of the lactam with excess potassium hydride in tetrahydrofuran (THF) at room temperature effected elimination of the ethoxy group to give the secondary unsaturated lactam (8). Further treatment of the secondary unsaturated lactam with potassium hydride in dimethylformamide followed by the addition of methyl iodide afforded the tertiary lactam (9).

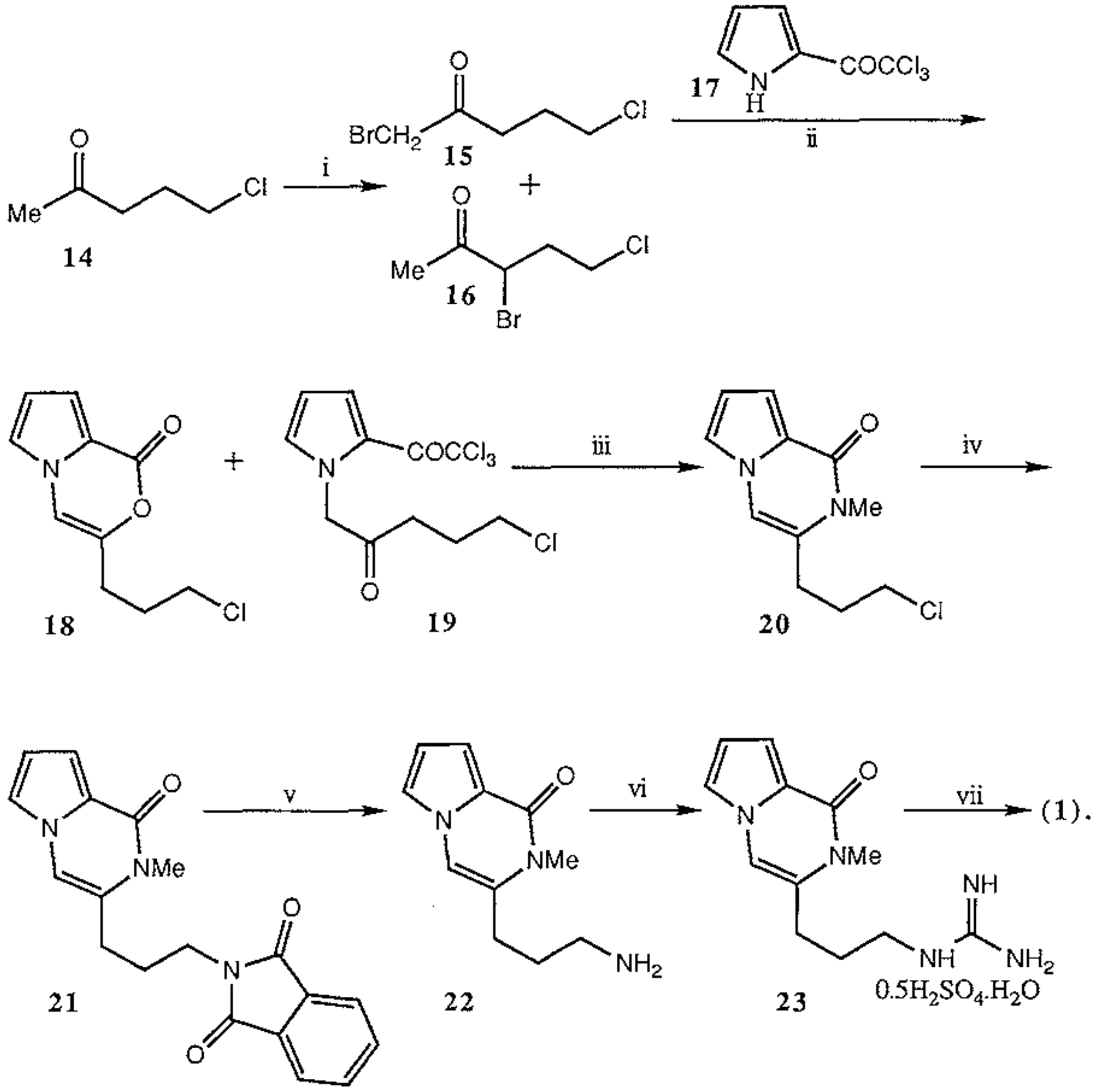
The elaboration of the C-3 carbomethoxy group to the appropriate guanidino group was then achieved in five steps as follows. The ester (9) was reduced to the alcohol (10) using sodium borohydride in methanol. The alcohol was converted to the unstable bromide (11) *via* the mesylate and then quickly added to a solution of cyanomethyl cuprate at -40°C to -20°C in tetrahydrofuran to give the nitrile (12). The nitrile was reduced using sodium borohydride/cobalt chloride in methanol to afford the amine (13), which was converted to the guanidino derivative peramine (1) using S-methylthiouronium hydrogen sulphate.

A second synthesis of peramine by the American chemical company Du Pont[4] soon followed (Scheme 2), in which *N*-alkylation of 2-(trichloroacetyl)pyrrole (17) with 1-bromo-5-chloro-2-pentanone (15) gave the pyrrolo[2,1-*c*]oxazin-1-one (18). Compound (19) was readily converted to (18) upon re-exposure to the alkylation conditions. Treatment of the pyrrolo[2,1,*c*]oxazin-1-one (18) with methylamine followed by aqueous hydrochloric acid afforded the desired 3-(3-chloropropyl)-2-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (20). Use of the Ing-Manske modification of the Gabriel synthesis[5] allowed conversion of the chloride (20) to the amine (22), which was then converted to peramine sulphate (23) upon treatment with 2-methyl-2-thiopseudourea sulphate in water. The sulphate was converted to the free base (1) using ion exchange chromatography.



Reagents and conditions: (i) **4**, KH, THF, then **3**, 0°C (82%); (ii) $NaBH_4$(5.0 equiv), $CoCl_2$ (2.0 equiv.),MeOH, room temp. (63%); (iii) toluene, reflux, 24h, (88%); (iv) KH, THF, room temp, (80%); (v) KH, DMF, MeI, (76%); (vi) $NaBH_4$, MeOH, 12h, (72%); (vii) $MeSO_2Cl$ (1.1 equiv.), Et_3N, CH_2Cl_2, -60°C 0.25h then LiBr (3.0 equiv.), THF, -60°C to -40°C, 0.5h; (viii), MeCN (5.0 equiv.), ^{n}BuLi (5.1 equiv.), 0.5h, -78°C then $CuBrMe_2S$ (5.2 equiv.), -78°C to -40°C, 0.5h then (**11**) (1.0 equiv.), -40°C to -20°C, (58% overall.); (ix) $NaBH_4$ (5.0 equiv.), $CoCl_2$ (2.0 equiv.), MeOH (62%); (x) *S*- methylthiouronium hydrogen sulphate (5.0 equiv.), room temp., 48h.

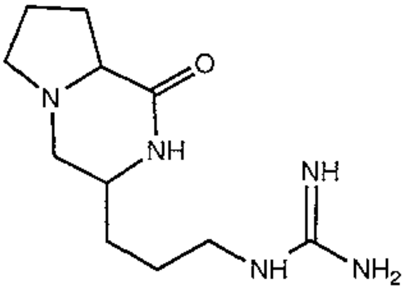
Scheme 1.



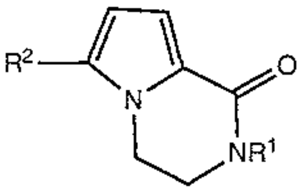
Reagents and conditions: (i) Br_2, MeOH, room temp, 2h, **15** (62%), **16** (28%); (ii) K_2CO_3, CH_3COCH_3, room temp, 18h, **18** &**19** (62%); (iii) CH_3NH_2, THF, 0°C, 3h, then 1N HCl, room temp, 2h, (45%); (iv) potassium phthalimide, DMF, 77-82°C, 1.5h, (81%); (v) $H_2NNH_2.H_2O$ (3.0 equiv.), EtOH, reflux 0.5h then 1N HCl, reflux 2.0 min, (84%); (vi) $(CH_3SC(=NH)NH_2)_2.H_2SO_4$, H_2O, 90°C, 15h, (49%); (vii) basic ion exchange, H_2O/CH_3OH, (98%).

Scheme 2.

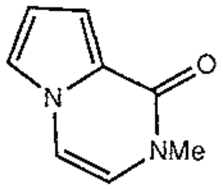
Alternative synthetic approaches to the 2-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one ring system of peramine (1) developed by Brimble *et al*[6],also yielded a series of analogues which could be examined for their feeding deterrent activity with the aim of constructing structure-activity relationships. Feeding deterrent assays[7] using a number of these peramine analogues (24, 25a-c, 26, 27) suggested the importance of the pyrrolopyrazine ring system rather than the propylguanidinyl side chain.



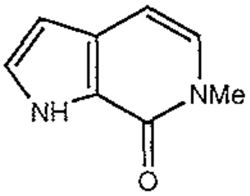
24 Cycloprolylargenine.



25(a) R^1=H, R^2=H
(b) R^1=Me, R^2=H
(c) R^1=Me, R^2=Br



26 Unsaturated Lactam



27

Thus, cycloprolylarginine (24) proved to be inactive as a feeding deterrent indicating that the specific pyrrolopyrazine ring system rather than the propylguanidinyl sidechain was important for feeding deterrent activity. The simple heterocyclic lactam (25a) also proved inactive as a feeding deterrent, however *N*-methylation of the lactam (25a) to give *N*-methyl lactam (25b) showed some antifeedant activity as did the bromolactam (25c) and the unsaturated lactam (26). The 6-methyl-1H-pyrrolo[2,3-*c*]pyrazin-7(6*H*)-one (27) ring system was also found to be inactive in the feeding deterrent assays. These results suggest minimal but precise structural requirements for feeding deterrent activity. However all these analogues (25b, 25c, 26) proved to be less active than peramine (1) itself suggesting some importance of the guanidinyl side chain in obtaining the full biological response.

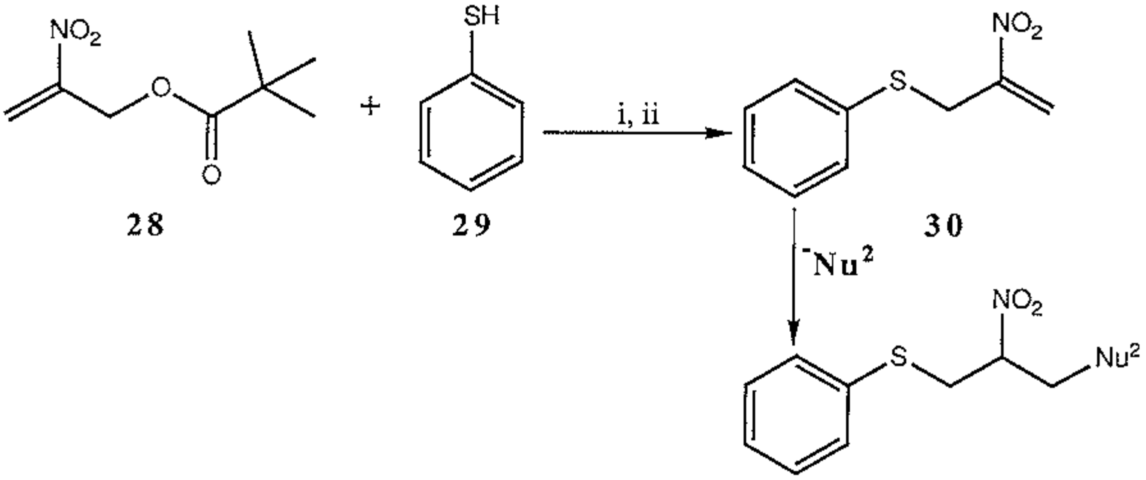
In light of these interesting biological results obtained with the analogues above, it was decided to embark on a programme involving synthesis of pyrazine ring systems related to peramine (1). Any new compounds synthesized in the work would be tested in the feeding deterrent assays already developed for peramine (1) itself. Generation of analogues for this purpose would also provide an extension to the use of the key Michael addition reaction using nitro-alkene (3) as a Michael acceptor for other heterocyclic anions.

1.2 The Use of Nitro-Alkenes as Michael Acceptors.

The nitro group is a powerful electron withdrawing group, therefore nitro-alkenes undergo 1,4-addition reactions with many different nucleophiles. The synthesis and reactions of nitro-alkenes has been extensively reviewed[8,9,10] and the recent review by Barrett[9] details the use of conjugated nitro-alkenes as Michael acceptors according to the type of nucleophile used. These categories include Michael additions using sulphur and oxygen centred nucleophiles, carbon centred nucleophiles, and nitrogen centred nucleophiles. This approach will be adopted here.

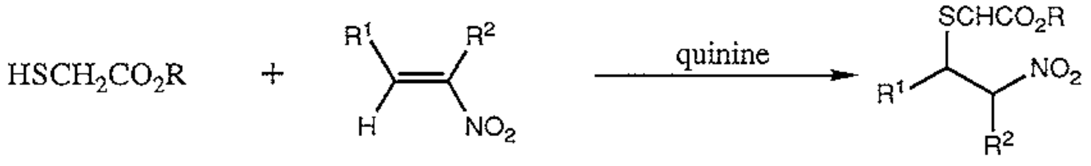
1.2.1. Oxygen and Sulphur-Centred Nucleophiles.

A number of examples using sulphur centred nucleophiles have been reported. The following examples are representative. Seebach and co-workers[11] have coupled 2-nitro-3-(pivaloyloxy)propene (28) with thiophenol (29) to afford the Michael adduct (30), which also contains a nitro-alkene functionality ready to react with another nucleophile (Scheme 3). Kobayashi and co-workers[12] have coupled thiols (31) with substituted and unsubstituted β-nitrostyrenes (32) in the presence of quinine catalysts to give the Michael adducts (33) in varying enantiomeric excess (Scheme 4). The optimum example reported involves the addition of thioglyconic acid (31, R=H) to (2-nitroethenyl)benzene (32, $R^1=C_6H_5$, $R^2=H$) affording the Michael adduct (33, R, $R^2=H$, $R^1=C_6H_5$) in 86% yield and in 58% ee.



Reagents and conditions: (i) **29**, ^{n}BuLi, THF, -78°C, 10 min then **28**, THF, 0.5h then -78 → 30°C, 0.17h, (62%).

Scheme 3.



31 $R=H, Me$

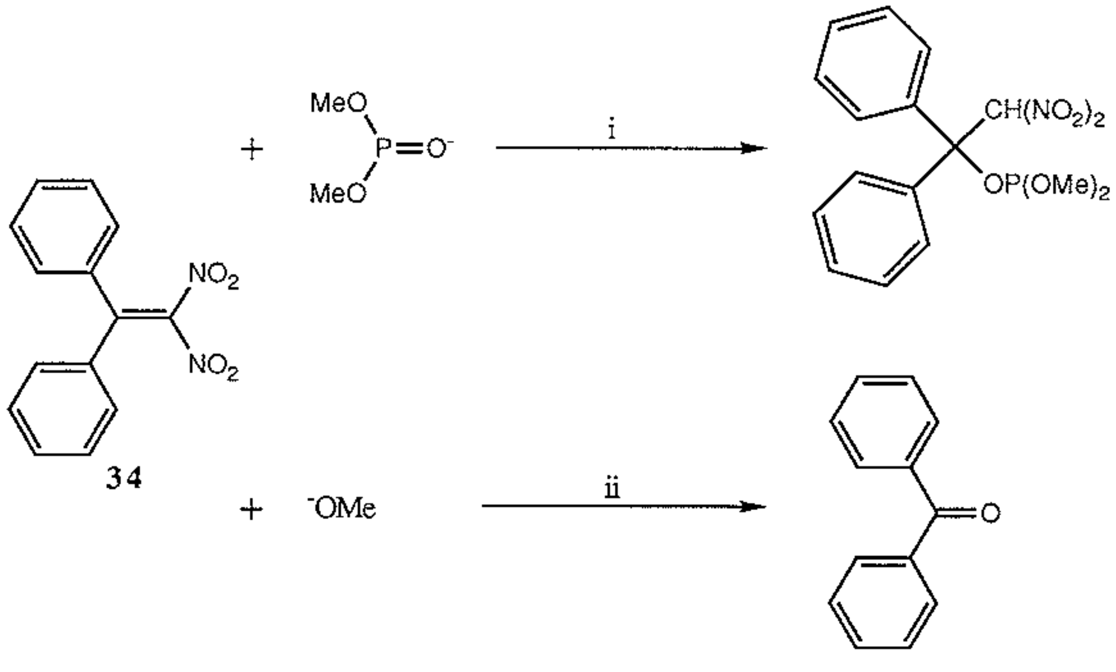
32 $R^1=C_6H_5, R^2=H, Me.$ $R^1=2\text{-}MeOC_6H_4,$ $MeOCO(CH_2)_4, R^2=H.$

33 $R^1=2\text{-}MeOC_6H_4, C_6H_5,$ $MeOCO(CH_2)_4$ $R^2=H, Me, R=H, Me$

Reagents and conditions: Toluene, room temp, Ar atmosphere, 0.25h, (86%).

Scheme 4.

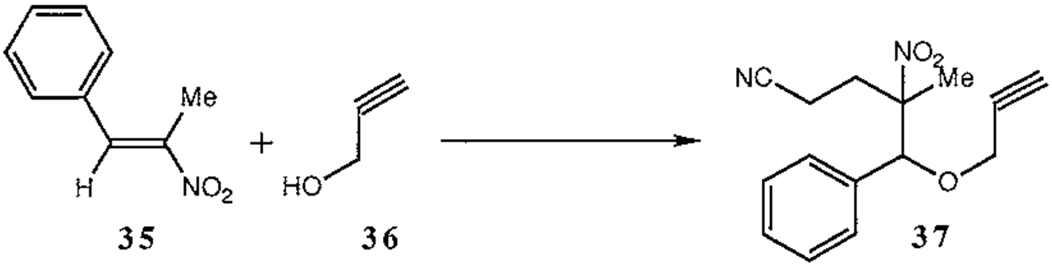
The addition of oxygen nucleophiles to nitro-alkenes can be demonstrated by the following examples. Russell and co-workers[13] have reacted 1,1-diphenyl-2,2-dinitroethene (34) with a number of nucleophiles including $(MeO)_2P(=O)^-K^+$ and $(EtO)_2P(=O)^-K^+$ to give the corresponding Michael adducts (Scheme 5). In this case, reaction with more basic nucleophiles, (eg ^-OMe) yielded only benzophenone arising from hydrolysis of the nitro-alkene.



Reagents and conditions: (i) Me_2SO, N_2 atmosphere, room temp, 0.5h, then 5% HCl, (75%); (ii) MeOH, N_2, room temp, 48h, (73%).

Scheme 5.

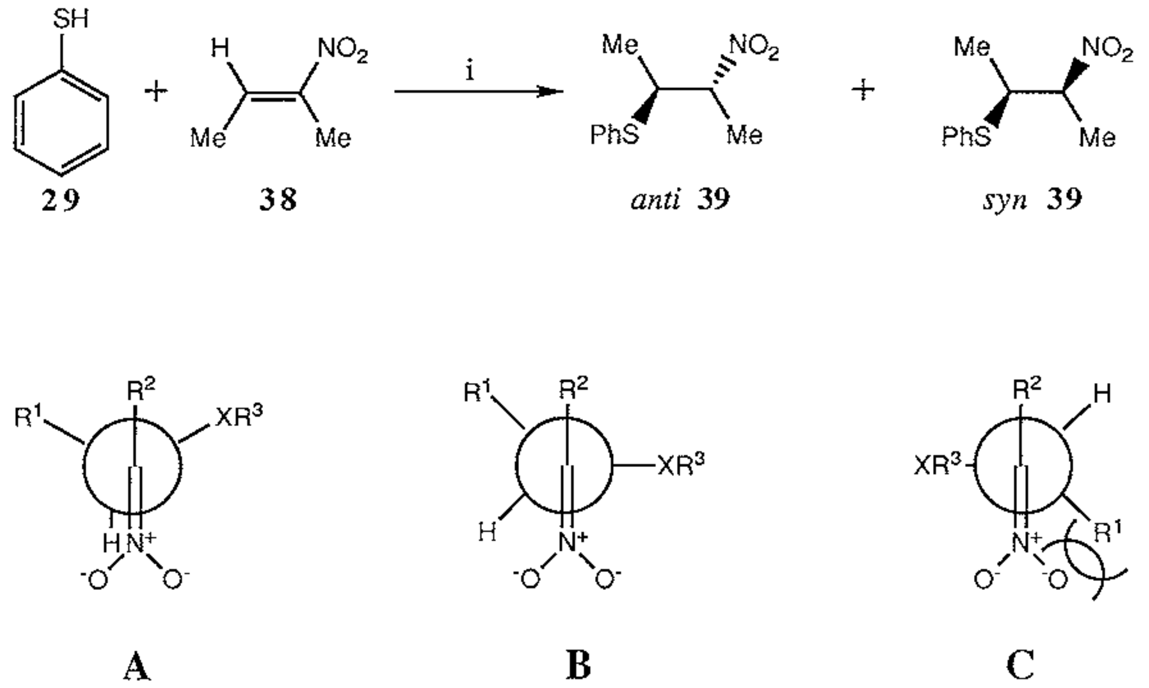
A further example involved the reaction of β-methyl-β-nitrostyrene (35) with 3-propynol (36) followed by a second Michael reaction using acrylonitrile to give the *bis* adduct (37) in 74% overall yield[14] (Scheme 6).



Scheme 6.

More recently attention has shifted toward control of the stereochemistry during additions of sulphur and oxygen centred nucleophiles to nitro-alkenes. Kamimura and co-workers[15] have compared the addition of thiolate anions to nitro-alkenes followed by protonation at room temperature or -78°C. For example, when thiophenol (29) was added to 2-nitro-2-butene (38) in the presence of triethylamine, the Michael adduct (39) was formed in 98% yield (Scheme 7). However the product (39) consists of a mixture of the two diastereomers, *syn* -(39) and *anti* -(39) in a ratio of 60:40 respectively. If, however, the reaction is carried out at room temperature followed by protonation at -78°C the *syn* / *anti* ratio becomes 9:91 respectively.

The authors suggested that the stereochemistry is determined in the protonation of the nitronate anion step, whereas the substituents on the nucleophile (R^3X) have no effect on the stereochemistry. There are three possible conformations of the intermediate nitronate anion (A, B, and C, Scheme 7). If A were the preferred confomer the diastereoselectivity should depend on the relative steric bulkiness between R^1 and R^3X. The authors, however, found this not to be the case in that varying the size of R^1 and R^3 lead to no significant change in the diastereoselectivity. Conformer B should be preferred over conformer C due to steric repulsion between R^1 and the nitro group in C. As R^3 covers one face of the nitronate derivative in conformer B, the proton attacks only from the opposite side of the R^3X group leading to the *anti* product.

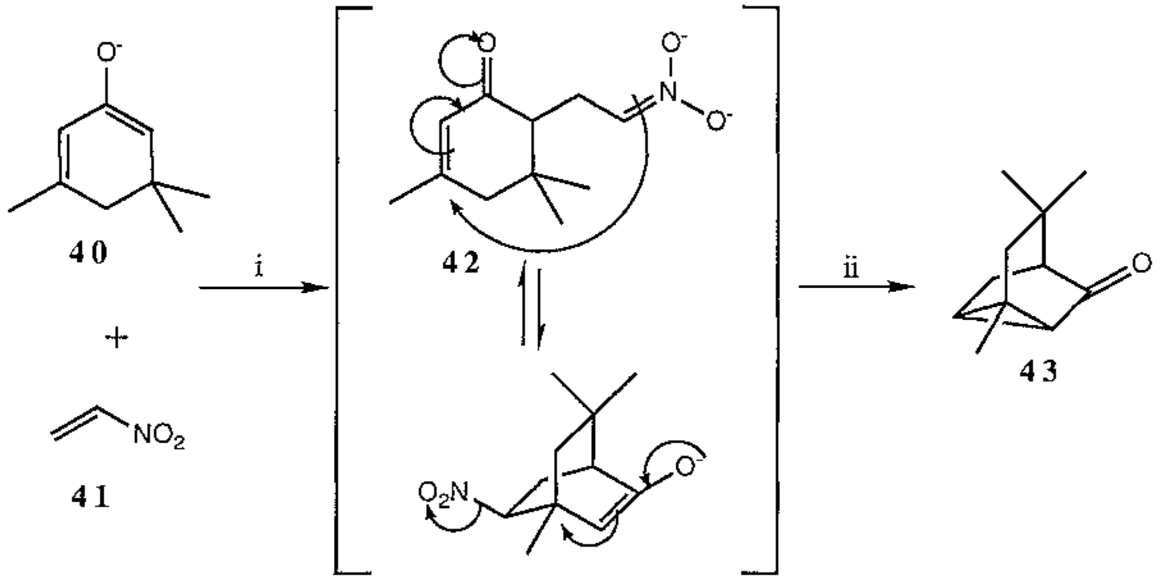


Reagents and conditions: (i) Et_3N (0.1 equiv.), MeCN, room temp., 1h then 1N HCl, room temp. (95%); **or**, CH_3CO_2H, -78°C, (75%).

Scheme 7.

1.2.2 Carbon-Centred Nucleophiles.

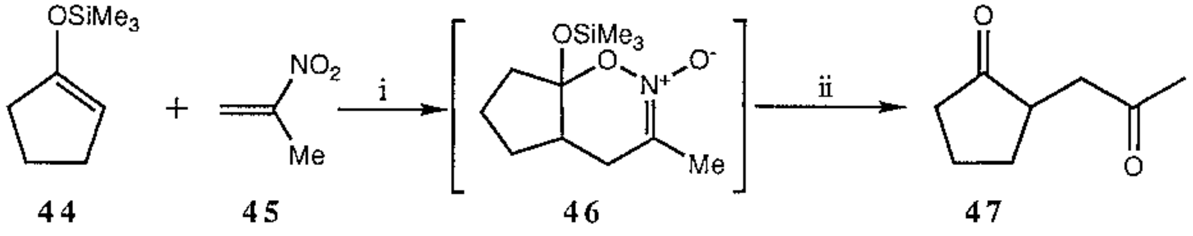
By far the largest body of work involving Michael additions of nitro-alkenes involves the addition of carbon centred nucleophiles. Cory and co-workers[16] have shown nitro-alkenes to be efficient reagents to effect a bicycloannulation in three steps (Scheme 8). Thus the enolate (40) undergoes conjugative addition to nitro-alkene (41), and the resulting nitronate undergoes a second intramolecular Michael addition to the α,β-unsaturated ketone (42) to afford the tricyclo-octanone (43). In this example the nitro group has dual character, acting first as an electron withdrawing group to aid the initial Michael addition, and then as a leaving group.



Reagents and conditions: (i) THF, -78°C, then **41**,HMPA, room temp; (ii) reflux 16h, (58%).

Scheme 8.

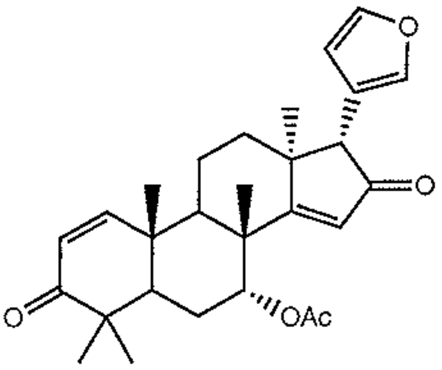
Yoshikoshi and co-workers[17] have used the condensation of enol silanes with nitro-alkenes to obtain 1,4-dicarbonyl species. In this case the nitro group is considered to be synthetically equivalent to the carbonyl group, due to the ease of conversion to ketones *via* the Nef reaction. Thus the conjugate addition of silyl enol ether (44) to nitro-alkene (45) in the presence of the Lewis acids $TiCl_4$ or $SiCl_4$ at -78°C, gave nitronate (46) as the product (Scheme 9). As the nitronate has a structure similar to a Nef reaction intermediate, the adduct was readily hydrolysed by treatment with water at reflux to afford the 1,4-dione (47) in a one pot operation .



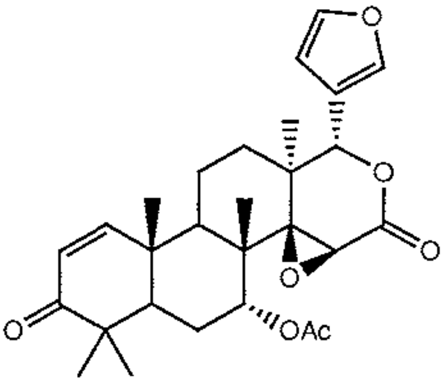
Reagents and conditions: (i) $SnCl_4$, CH_2Cl_2, -78°C; (ii) H_2O, reflux, (79%).

Scheme 9.

A more recent example of addition of enol silanes to nitro-alkenes involves the synthesis of compounds related to the insect antifeedants azadiradion (48) and gedunin (49)[18]. Azadiradion (48) and gedunin (49) are members of the Limonoid family, isolated from the neem tree *Azadirachta indica.*

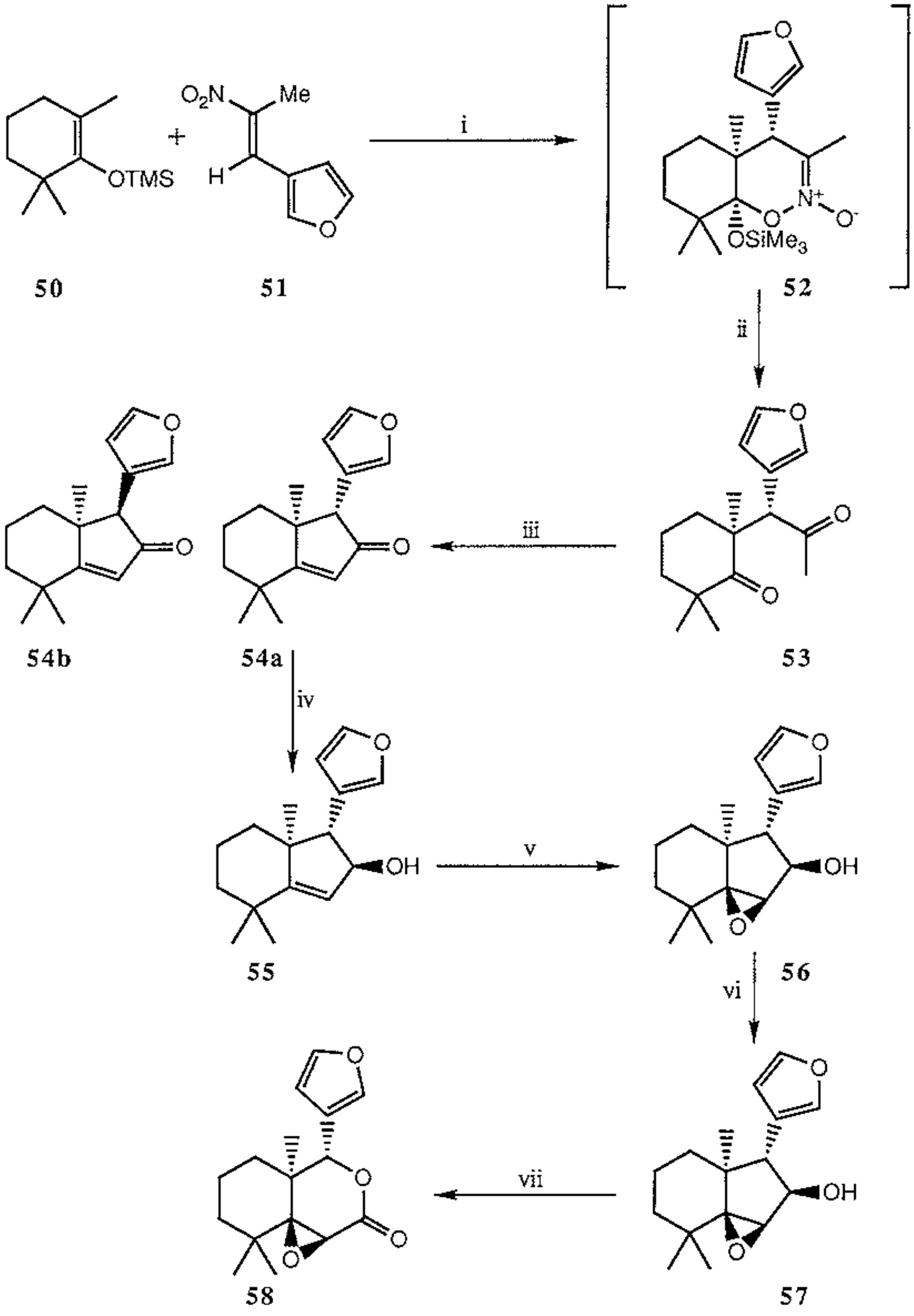


48 Azadiradion



49 Gedunin

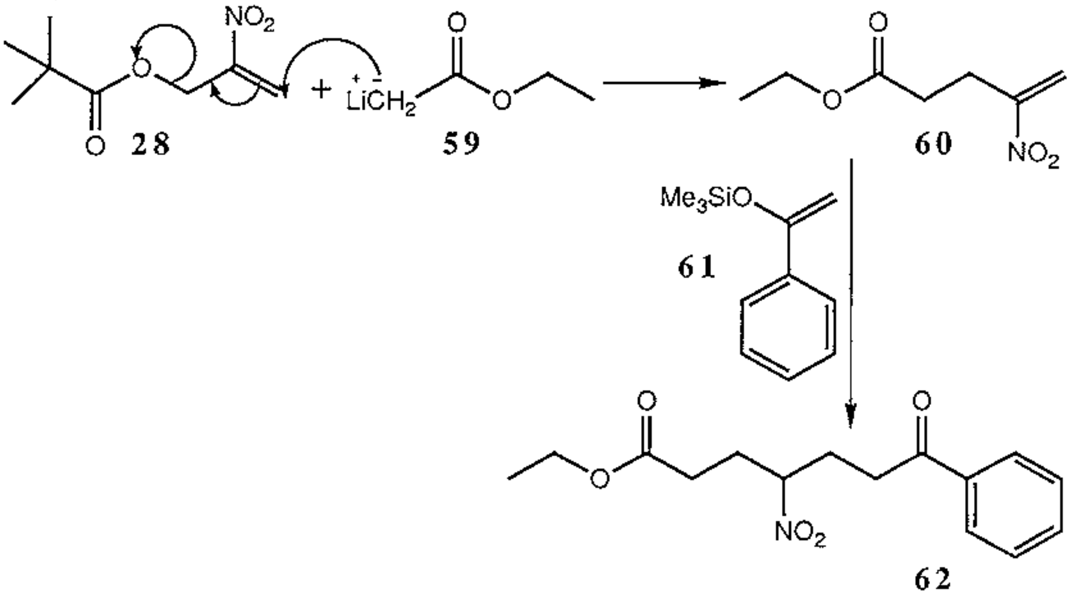
Mateos and co-workers[18] have synthesized structural subunits related to these compounds. Thus the addition of enol silane (50) to nitro-alkene (51) in the presence of titanium tetrachloride afforded the cyclic silyl nitronate (52) which gives the diketone (53) upon treatment with water in 75% yield (Scheme 10). The condensation of the diketone (53) in the presence of potassium hydroxide at 86°C, followed by elimination of water afforded a mixture of the two cyclopentanones (54a) and (54b) in a 4:1 ratio respectively. Reduction of (54a) using lithium aluminium hydride afforded, stereospecifically the allylic β-alcohol (55) in 97% yield. Stereospecific epoxidation of the allylic β-alcohol (55) with m-chloroperoxybenzoic acid (mCPBA) afforded the epoxide alcohol (56) in 75% yield. The authors suggested that the epoxidation proceeded from the β face due to the *syn* effect caused by hydrogen bonding of the reactants. Oxidation of the epoxide alcohol (56) with Jones reagent gave the epoxyketone (57), which upon Bayer-Villiger oxidation with *m*-chloroperoxybenzoic acid afforded the epoxylactone (58) in 60% yield. Epoxylactone (58) is a structural subunit related to Gedunin (49).



Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, N_2 atmosphere, -78°C, 0.25h; (ii) Na_2CO_3 (10%), -78°C → 25°C, 2h; (ii) H_2O, room temp, 2h, (75%); (iii) KOH, EtOH, N_2 atmosphere, reflux 40 min, **54a** (64%), **54b** (17%); (iv) $LiAlH_4$, $(C_2H_5)_2O$, N_2 atmosphere, 0°C, then Na_2SO_4, 1h, room temp, (97%); (v) mCPBA, CH_2Cl_2, -40°C, 3h, (75%); (vi) Jones reagent, CH_3COCH_3, 0°C, 1h, (96%); (vii) mCPBA, CH_2Cl_2, room temp, 5.5h, (60%).

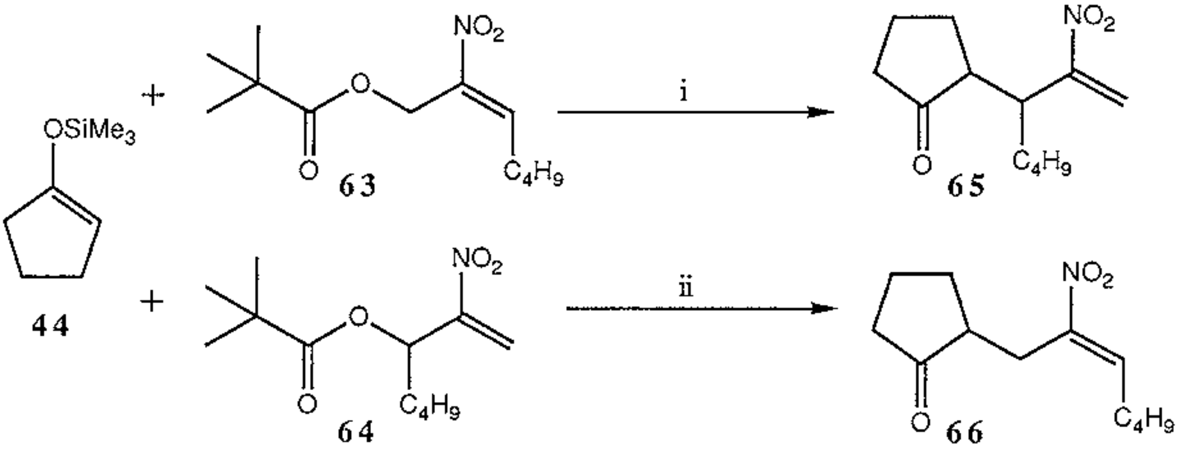
Scheme 10

Seebach and co-workers[9] have sequentially coupled pivaloate nitro-alkenes with two different nucleophiles. An example of this involves the reaction of nitro-alkene (28) with the enolate derived from ethyl acetate (59) to afford the nitro-alkene (60) in 87% yield. Further reaction of (60) with enol silane (61) afforded the *bis*-adduct (62) in 70% yield (Scheme 11).



Scheme 11.

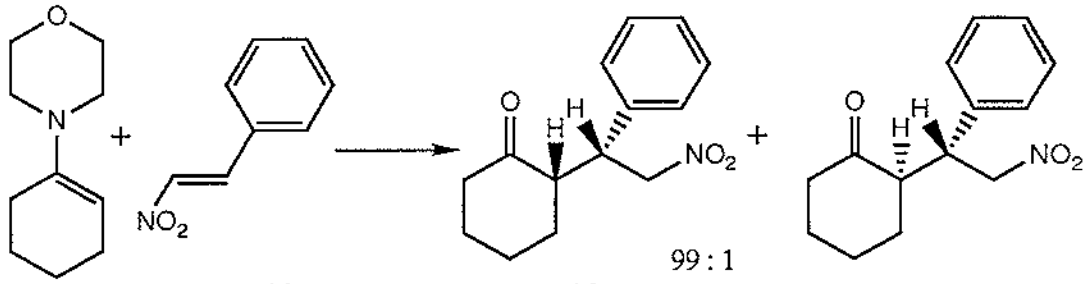
A further example of multiple coupling involves the addition of silyl ether (44) to the two isomeric nitro-heptenyl pivaloates (63) and (64) to afford the Michael adducts (65) and (66) in 73% and 75% yield respectively (Scheme 12). These results establish that the nitroallylations do not occur by direct S_N2 substitution but involve an addition elimination mechanism. The Michael adduct (66) was obtained only as the *Z* isomer, presumably on account of thermodynamic control[19].



Reagents and conditions: (i) THF, -78°C, 3h, (73%); (ii) THF, -78°C, 3h, (75%).

Scheme 12.

The Michael addition of enamines and enol silanes is a useful method to produce γ-nitro ketones with reasonable to excellent diastereoselectivity. Seebach[20,21] have reported the condensation of (E)-β-nitrostyrene with cyclic lithium enolates and enamines to preferentially produce the *erythro* adduct. Examples of these reactions include the addition of the morpholine enamine (67) to nitro-alkene (68) in ether at room temperature to afford the Michael adduct (69) in excellent diastereoselectivity (99:1) (Scheme 13).

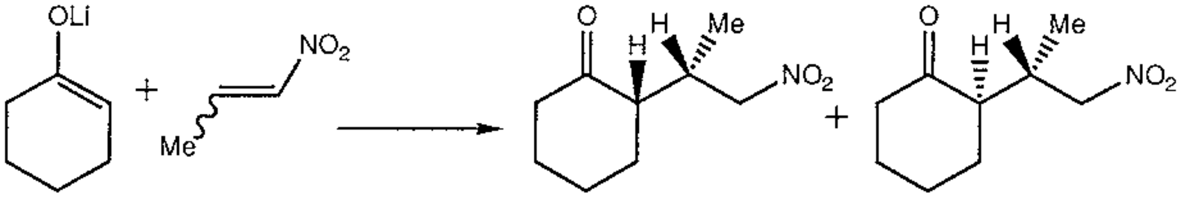


67 **68** **69**

Reagents and conditions: (i) $(C_2H_5)_2O$, room temp, 3 → 48h, (88%).

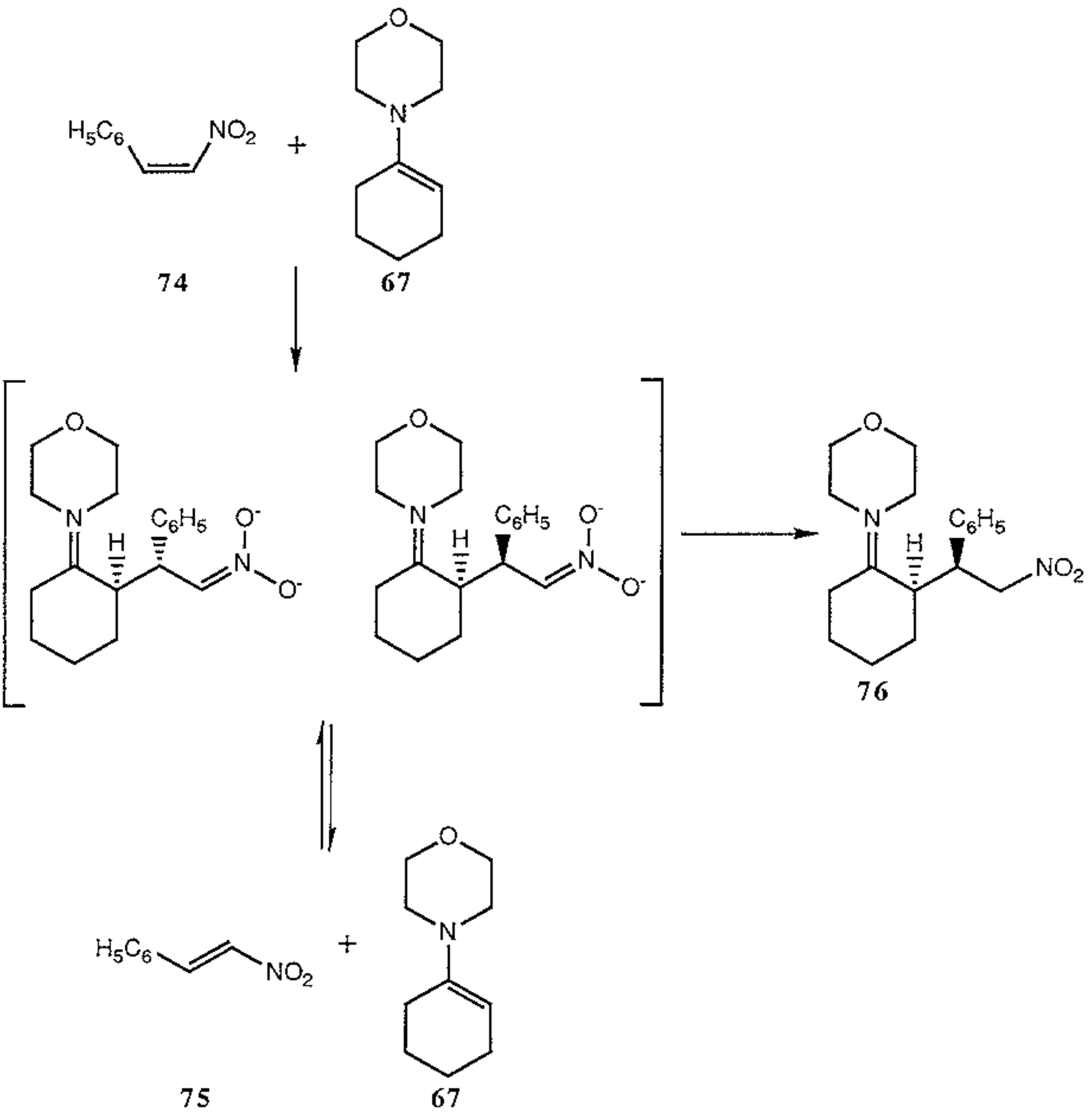
Scheme 13.

Further work by Seebach[22] demonstrated that (E)- and (Z)-1-nitropropene (71) react with cyclohexanone enolate (70) to produce both (72) and (73) (Scheme 14). The (E)-nitro-alkene preferentially produced the *erythro* diastereomer (72) (89:11), and the (Z)-nitro-alkene preferentially produced the *threo* diastereomer (73) (88:12).



70	**71**	*Erythro* **72**	*Threo* **73**
	E	89	11
	Z	12	88

In contrast, the addition of analogous enamines with (E)- or (Z)-nitroalkenes preferentially produced the *threo* isomer. An example of this involves the addition of morpholinocyclohexene (67) with both (Z)- and (E)-nitrostyrene (74) and (75) to afford enamine (76) in over 90% diastereomeric purity (Scheme 15).



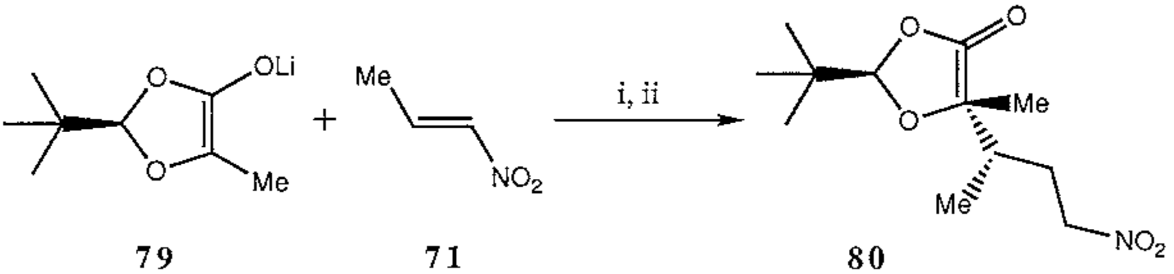
Scheme 15.

The following mechanism has been proposed by the authors[23]: with the (Z)-nitro-alkene (74) as starting material, the first step might be isomerisation to the more thermodynamically stable (E)-nitro-alkene (75), and has been established by N.M.R. experiments to be an intermediate. The conversion of the (E)-nitro-alkene into the major product (76) might be rationalised by postulating a favoured *gauche* conformation (77) (Scheme 16), for the reactive π systems in the transition state. Hydrolysis of the enamine (76) affords the nitro ketone (78).

77 **78**

Scheme 16.

Seebach has extended these studies to several cyclic enolates, with the following examples being representative. The addition of lithium enolate (79) to (E)-nitropropene (71) afforded the Michael adduct (80) in 58% yield and 93% diastereoselectivity[24] (Scheme 17).

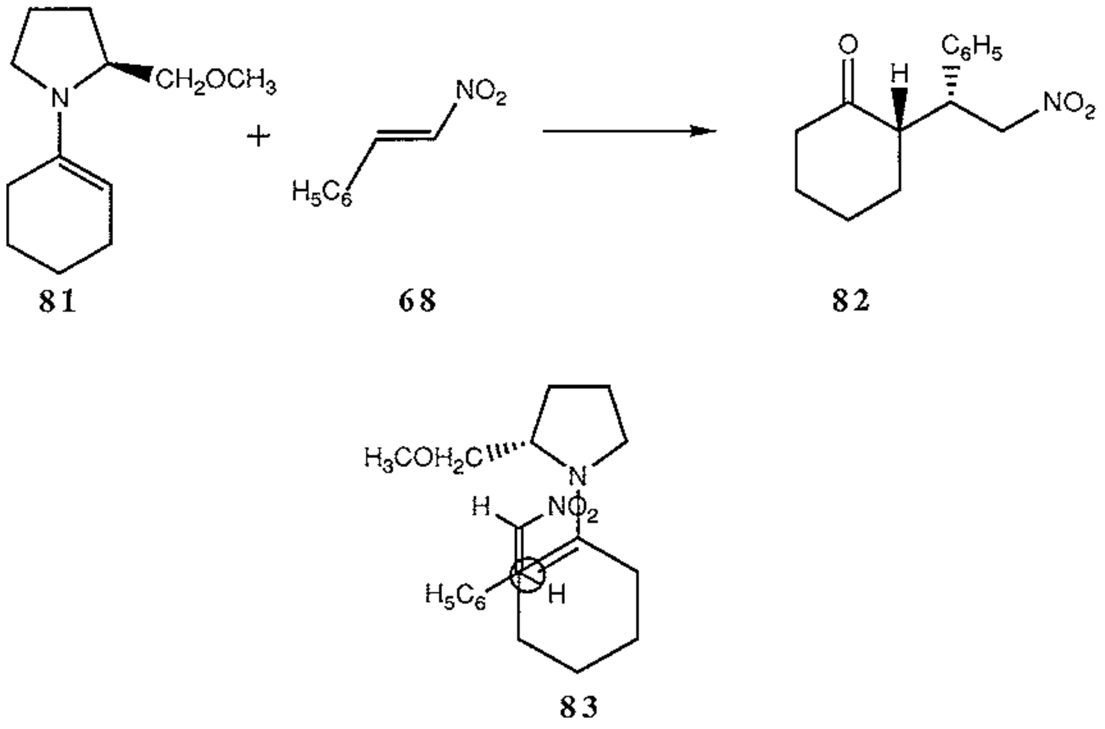


79 **71** **80**

Reagents and conditions: (i) LiN(^{i}Pr)$_2$, THF, -78°C, then **79**, 0.5h, then 0.5-0.75h, -78°C; (ii) **71**, -100°C-178^{0}C, 1.5h, then AcOH, THF, -78 → -40°, 0.25h (58%).

Scheme 17.

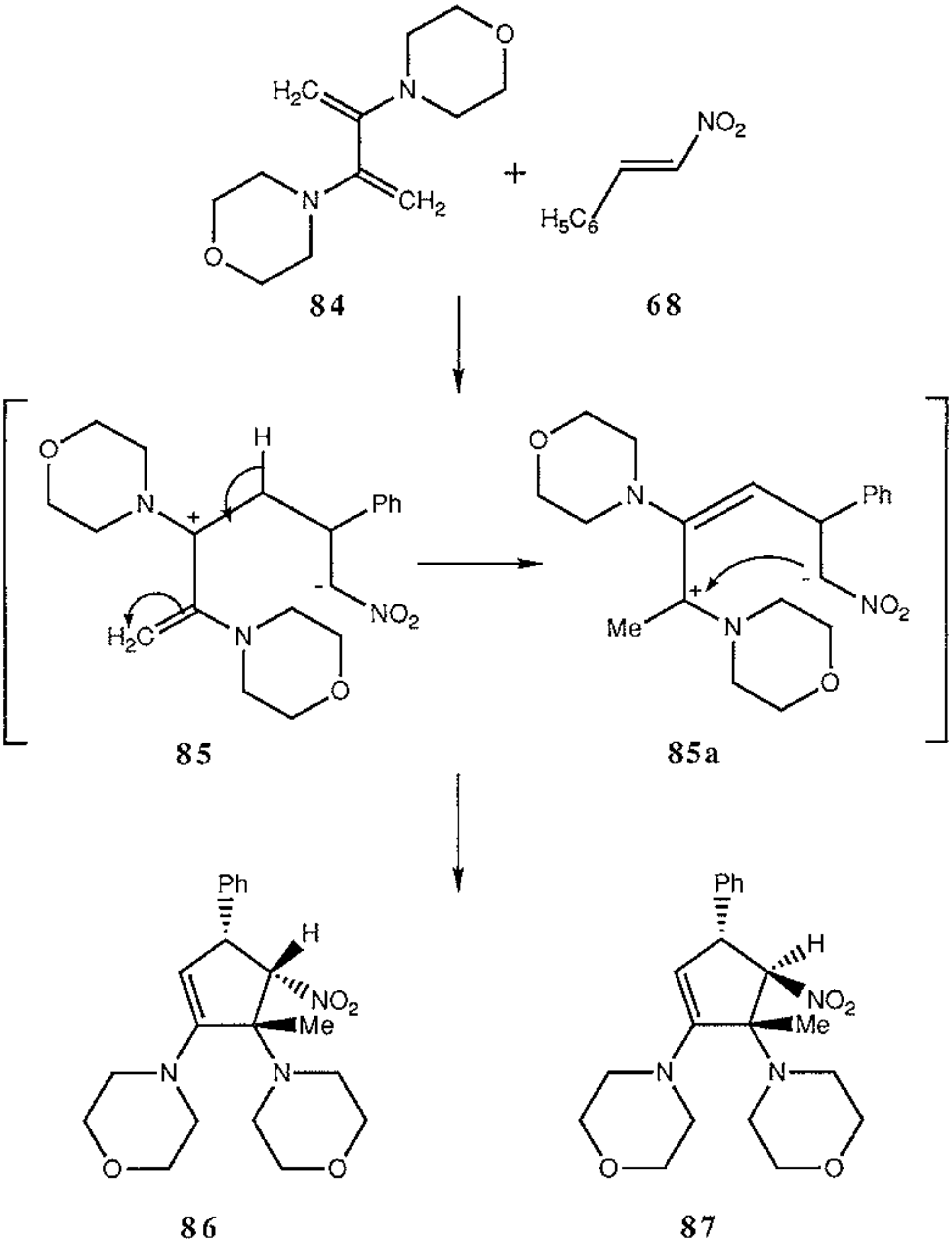
An extension of these studies furnished a second example as follows. The addition of chiral enamine (81) to (E)-β-nitrostyrene (68) afforded the ketone (82) as a single diastereomer in 97% ee (Scheme 18). The authors have suggested that this excellent diastereoselectivity resulted from reaction *via* the favoured transition state (83)[25].



Reagents and conditions: **68** Et_2O,-80^0C, Ar atmosphere, then **81** (1.0 equiv.) then -80 → 25°C, 6h.

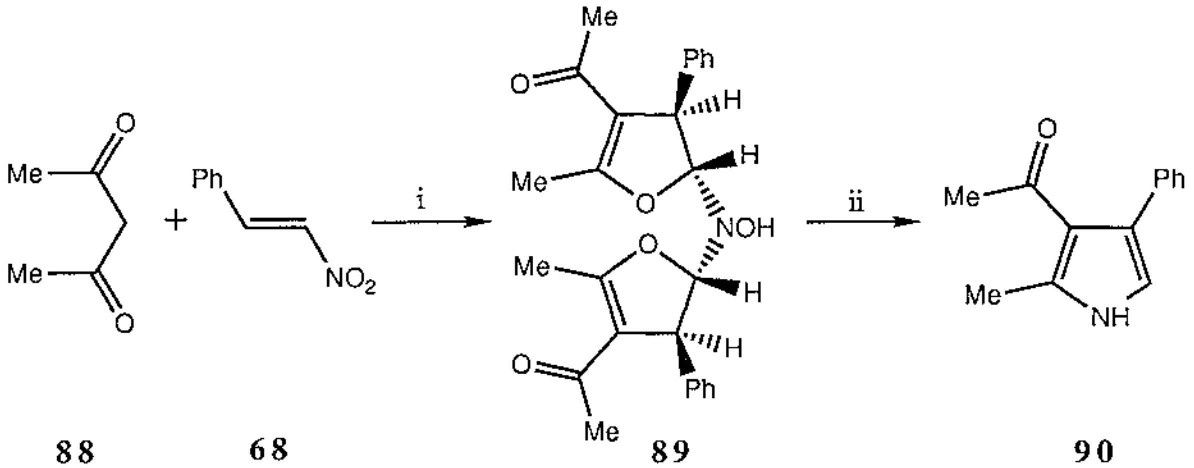
Scheme 18.

Destro and co-workers[26] have reported a synthesis of substituted cyclopentanones from the reaction of nitro-alkenes with dienamines. For example, 2,3-dimorpholino-1,3-butadiene (84) was added to β-nitrostyrene (68) to afford the cyclic Michael adducts (86) and (87) in 51% and 15% yield respectively (Scheme 19). The following mechanism has been proposed by the authors. The dipolar intermediate (85) formed by the attack of the enamine carbon to the activated π system of the alkene, is extensively stabilised by resonance and undergoes isomerisation to (85a) then cyclisation to the cyclopentene ring. During this process the stereochemistry of the nitro-alkene double bond is lost and this leads to the less hindered (86) and more hindered (87) diastereomers.



Reagents and conditions: THF, room temp, 24-48h, **87** (51%), **86** (15%).
Scheme 19.

Nitro-alkenes have been used widely in the synthesis of pyrroles[9]. The following examples are representative. Gomez-Sanchez and co-workers[27] have added pentane-2,4-dione (88) to β-nitrostyrene (68) in methanol containing sodium methoxide (0.2 mol eq) to afford the Michael adduct (89). Subsequent treatment of the adduct (89) with ammonia afforded the pyrrole (90) in 60% yield (Scheme 20).

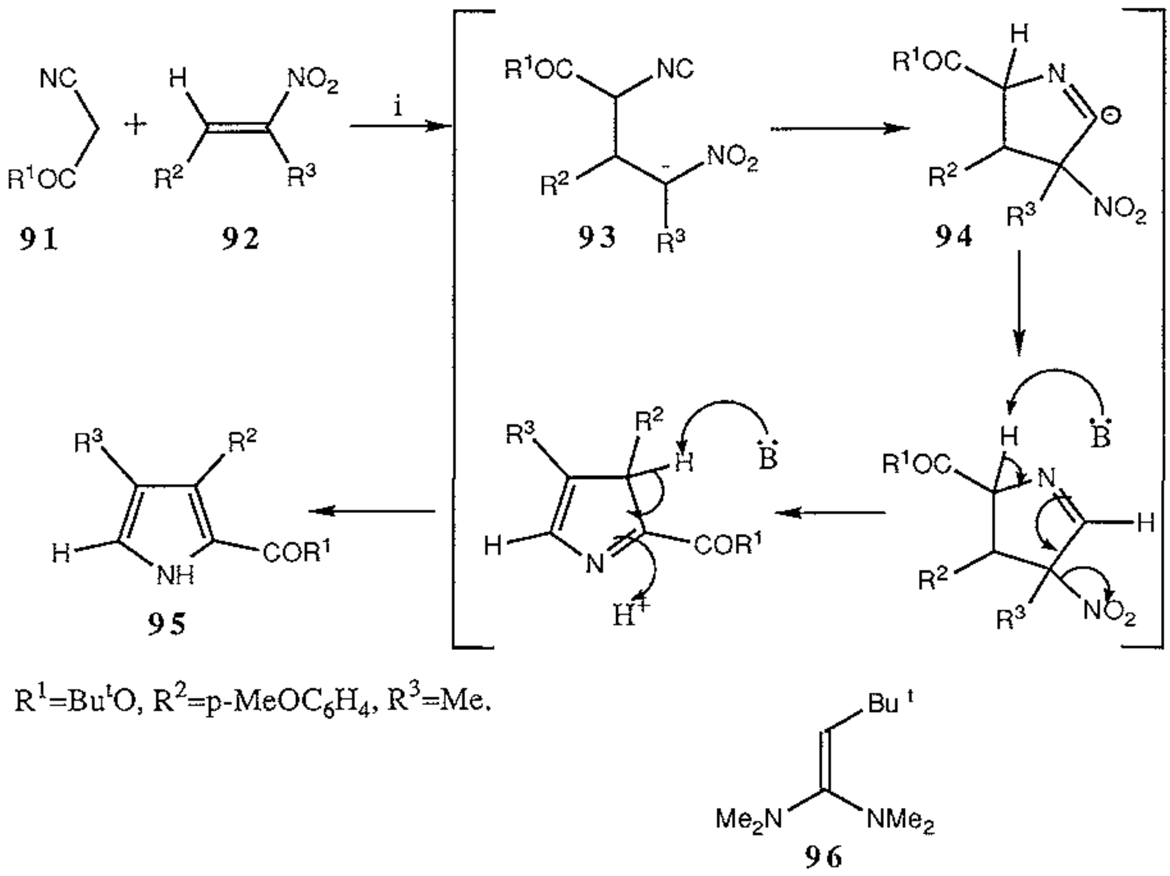


88 **68** **89** **90**

Reagents and conditions: (i) MeOH, MeO^- (0.2 equiv.), 0°C, 5 min, (68%); (ii) MeOH, NH_3 (gas), 0°C, 0.5h, (60%).

Scheme 20.

A further example of pyrrole synthesis involving nitro-alkenes has been furnished by Barton and co-workers[28]. In this case a α-isocyanoacetate ester is added to a nitro-alkene in the presence of base to afford 5-substituted pyrroles. Thus, the addition of the β-nitrostyrene derivative (92) to a mixture of ^{t}butyl-α-isocyanoacetate (91) and the guanidine base (96) in tetrahydrofuran/propan-2-ol at room temperature afforded the pyrrole (95) in 90% yield (Scheme 21). The following mechanism has been proposed by the authors. Base catalysed Michael addition of the α isocyanoacetate (91) to the nitro-alkene (92) followed by cyclisation of the nitronate anion (93) onto the isocyano group leads to the pyrroline (94). Base catalysed expulsion of nitrite from the pyrroline (94) and double bond rearrangement would finally give the pyrrole (95).



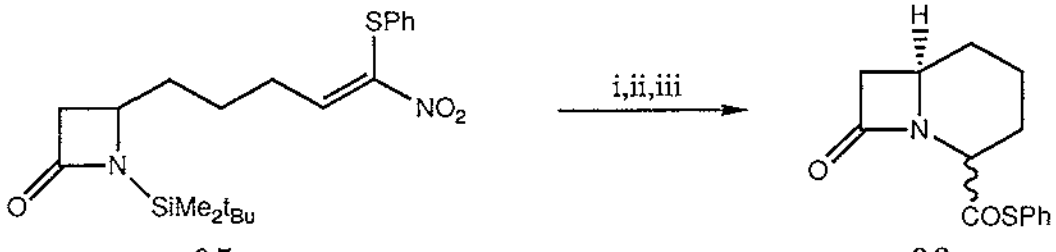
R^1=Bu^{t}O, R^2=p-MeOC$_6$H$_4$, R^3=Me.

Reagents and conditions: THF, 2-propanol, room temp, **96**, (90%).

Scheme 21.

1.2.3 Nitrogen-Centred Nucleophiles.

The addition of nitrogen centred nucleophiles to nitro-alkenes can be used to prepare bicyclic β-lactams[29]. Thus 4-(4-pentenyl)-2-azetidinone (97) undergoes intramolecular Michael addition, in the presence of HF-pyridine in dichloromethane (*N*-desilylation) followed by treatment with KO^{t}Bu and ozone to afford the bicyclic β-lactam (98) as a mixture of diastereomers in 53% yield (Scheme 22).

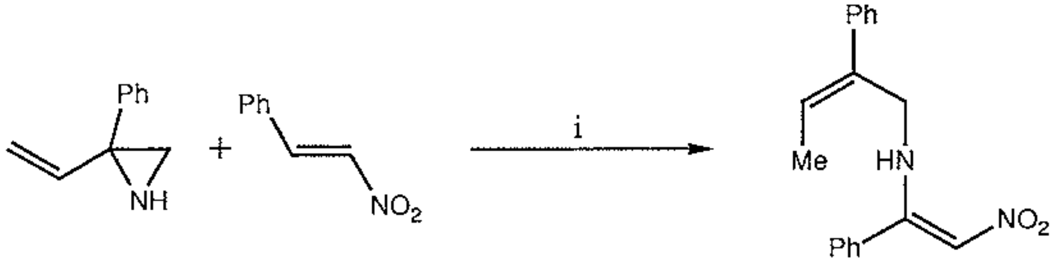


97 **98**

Reagents and conditions: (i) HF, C_5H_5N, CH_2Cl_2, -78 → 0°C; (ii) ^tBuOH, THF, ^tBu OK, (1.0 equiv.), -30°C; (iii) O_3, CH_2Cl_2, -78°C, (53% overall).

Scheme 22

A further example involving addition of a nitrogen centred nucleophile to a nitro-alkene involves the addition of vinylaziridine (99) to β-nitrostyrene (68) on heating to afford the unsaturated nitro-enamine (100) in over 90% yield[30] (Scheme 23). The product probably arose *via* initial nitrogen centred attack and subsequent retro-ene azetidine fragmentation.



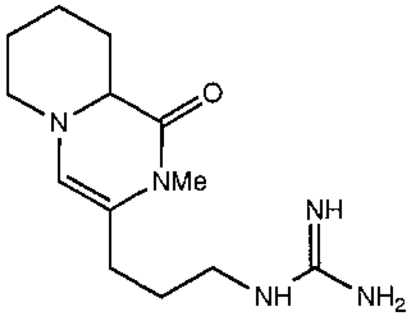
99 **68** **100**

Reagents and conditions: (i) C_6H_5, reflux, 6 days, (90%).

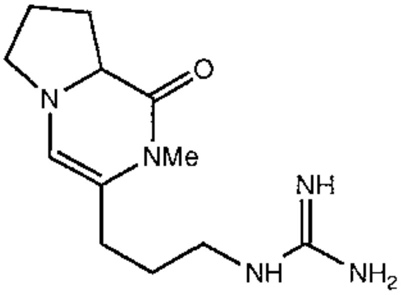
Scheme 23.

1.3 Pyrazine Ring Systems Related to Peramine (1) and Other Natural Products.

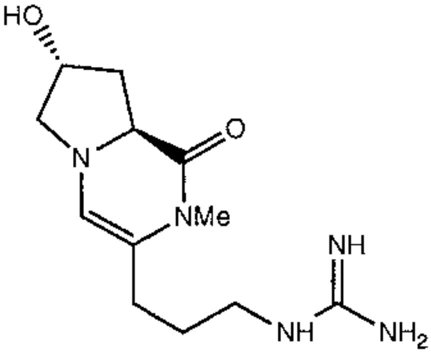
The aim of the present work was to synthesize analogues of peramine (1) for biological testing in insect feeding deterrent assays to establish structure-activity relationships. The target molecules were piperidinoperamine (101), prolylperamine (102), hydroxyprolylperamine (103), indoloperamine (104), and indolinoperamine (105).



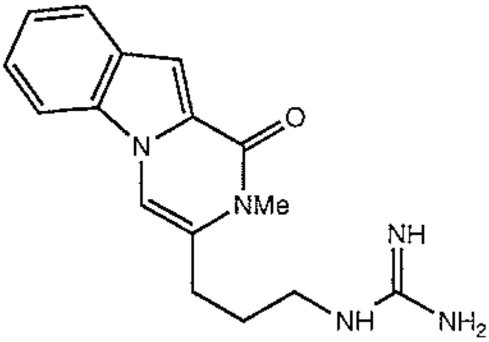
101 Piperidinoperamine



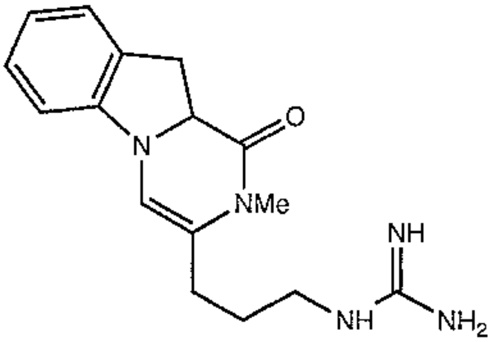
102 Prolylperamine



103 Hydroxyprolylperamine



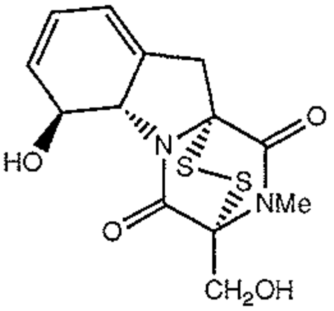
104 Indoloperamine



105 Indolinoperamine

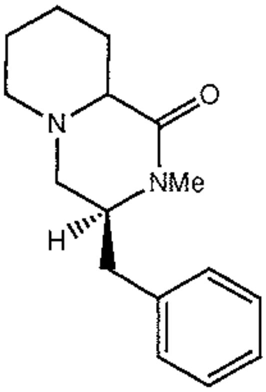
Initially the synthesis of the oxopiperazine ring systems present in each of these analogues would be undertaken, and the guanidinyl sidechain attached later. The synthesis of the novel oxoketopiperizine ring system would not only allow testing of the ring systems for their structure-activity relationships, but also extend the Michael addition reaction of a pyrrole anion to nitro-alkene (3) used in the synthesis of peramine (1), to other heterocyclic nucleophiles.

There are a number of natural products with pyrazine ring systems similar to that of peramine (1) and the synthetic analogues mentioned above. Gliotoxin (106) is a potent antibiotic produced by the fungus *Gliocadium fimbriatum*, and shows remarkable fungicidal and bactereocidal action against a number of pathogenic microorganisims[31]. Gliotoxin (106) displayed lethal action against aphids as a contact poison, and has a lethal dose toward mammals in the range of 45 to 65 mg/kg (rat). Gliotoxin (106) contains a similar ring system to indolinoperamine (104). Despite the fact that Kishi and co-workers have already synthesized gliotoxin (106)[32], the synthetic methodology presently developed toward indolinoperamine (104) may well be extended to synthesize gliotoxin in the future.



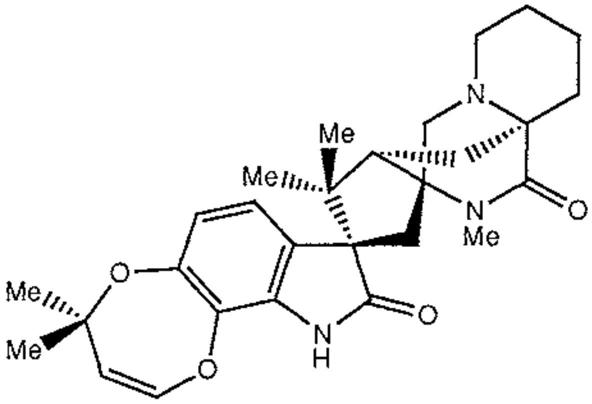
106 Gliotoxin

Verruculotoxin (107) is a tremorgenic mycotoxin isolated from green peanuts infected with the mold *Penicillium verruculosum* [33],which contains a ring system similar to piperidinoperamine (101). Verruculotoxin (107), containing the octahydro-2*H*-pyrido[1,2-*a*]pyrazine ring system has already proved to be a popular synthetic target in that three syntheses[34,35,36] of this natural product have been reported to date.



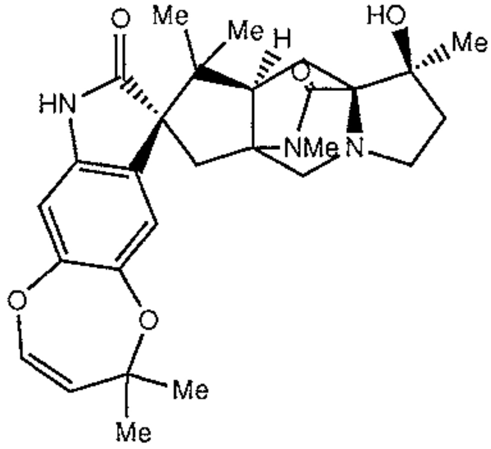
107 Verruculotoxin

Marcfortine A (108) is a complex mycotoxic alkaloid isolated from the mycelium of the *Penicillium roqueforti* strain B26[37]. Marcfortine A (107) was the first fungal alkaloid to possess a seven membered ring formed by the linkage of an isoprene unit to two phenolic hydroxy groups on the tryptophan unit, and has a ring subunit similar to that of piperidinoperamine (101).



108 Marcfortine A

Paraherquamide (109) is a mycotoxic alkaloid isolated from the mold *Penicillium parahhrquei* [38,39]. Paraherquamide is structurally related to the marcfortines, and also contains a ring system similar to that of prolylperamine (102). The unusual structures of these oxindole alkaloids and the recent discovery by a Merck group that paraherquamide (107) has potent antiparasitic properties has prompted synthetic interest in these molecules[40].



109 Paraherquamide