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# 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

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at Massey University.

*Andrew Duncan Johnston.*

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To my family for their  
support and patience.

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## ABBREVIATIONS

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

# CHAPTER 1

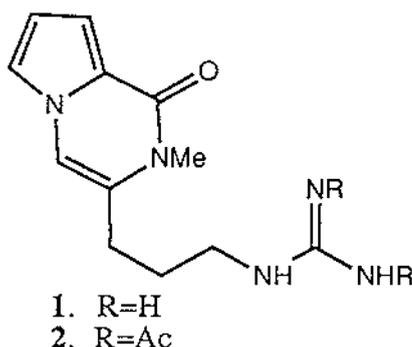
## INTRODUCTION

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 *Listronotus bonariensis* arises from the principal insect feeding deterrent peramine (1), a pyrrolopyrazine alkaloid produced by the fungal endophyte *Acremonium lolii*<sup>1</sup>. 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.



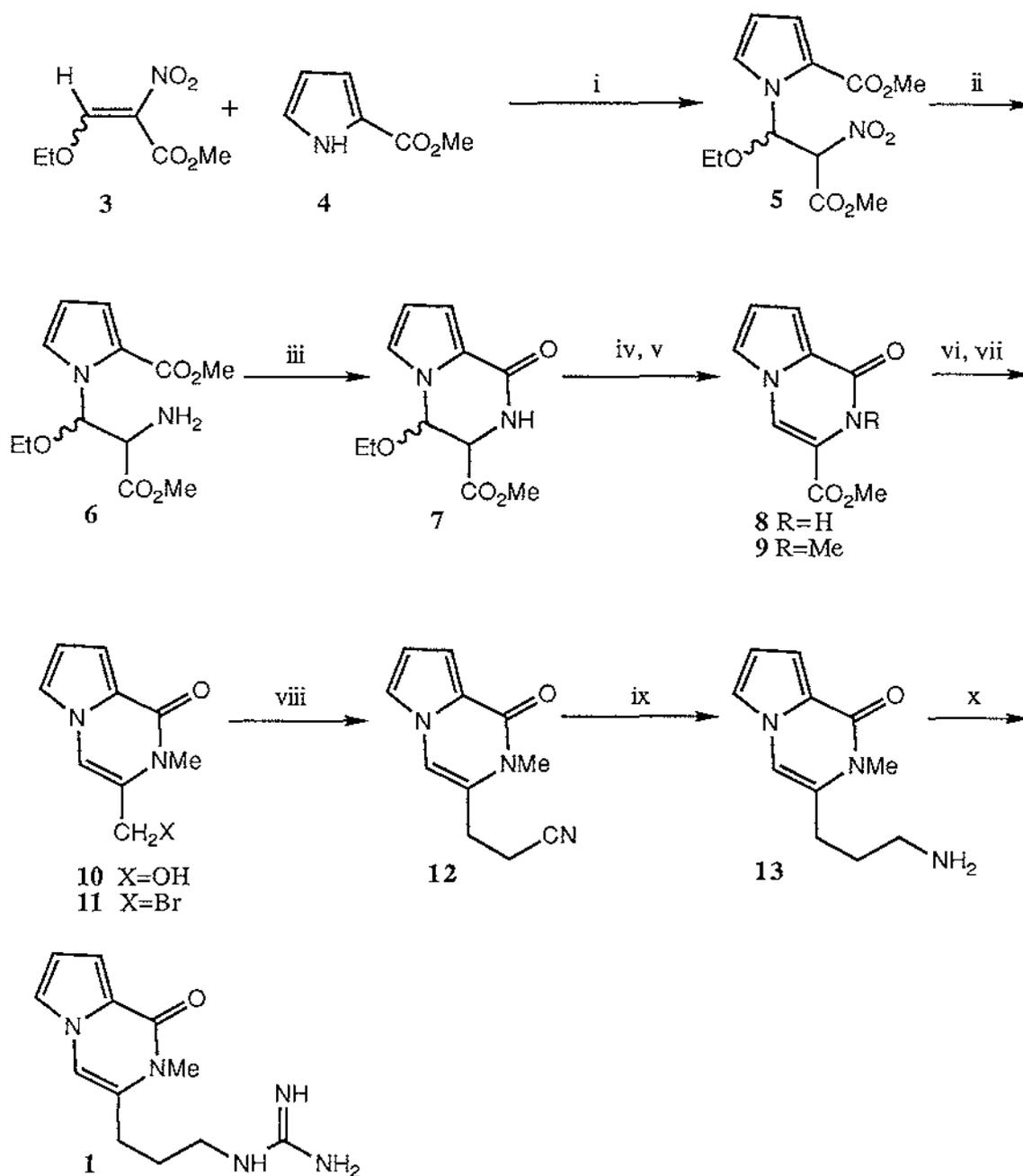
In 1986 Rowan and co-workers determined the structure of the diacetylated derivative of peramine (2) spectroscopically and found it to be the guanidinium alkaloid 3-(3'-guanidinylpropyl)-2-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one<sup>2</sup>. Thus peramine (1)

contains two interesting structural features, a saturated diketopiperazine ring system and a guanidino group. These features prompted two independent chemical syntheses.

The first synthesis of peramine (1) was reported by Brimble<sup>3</sup> (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).

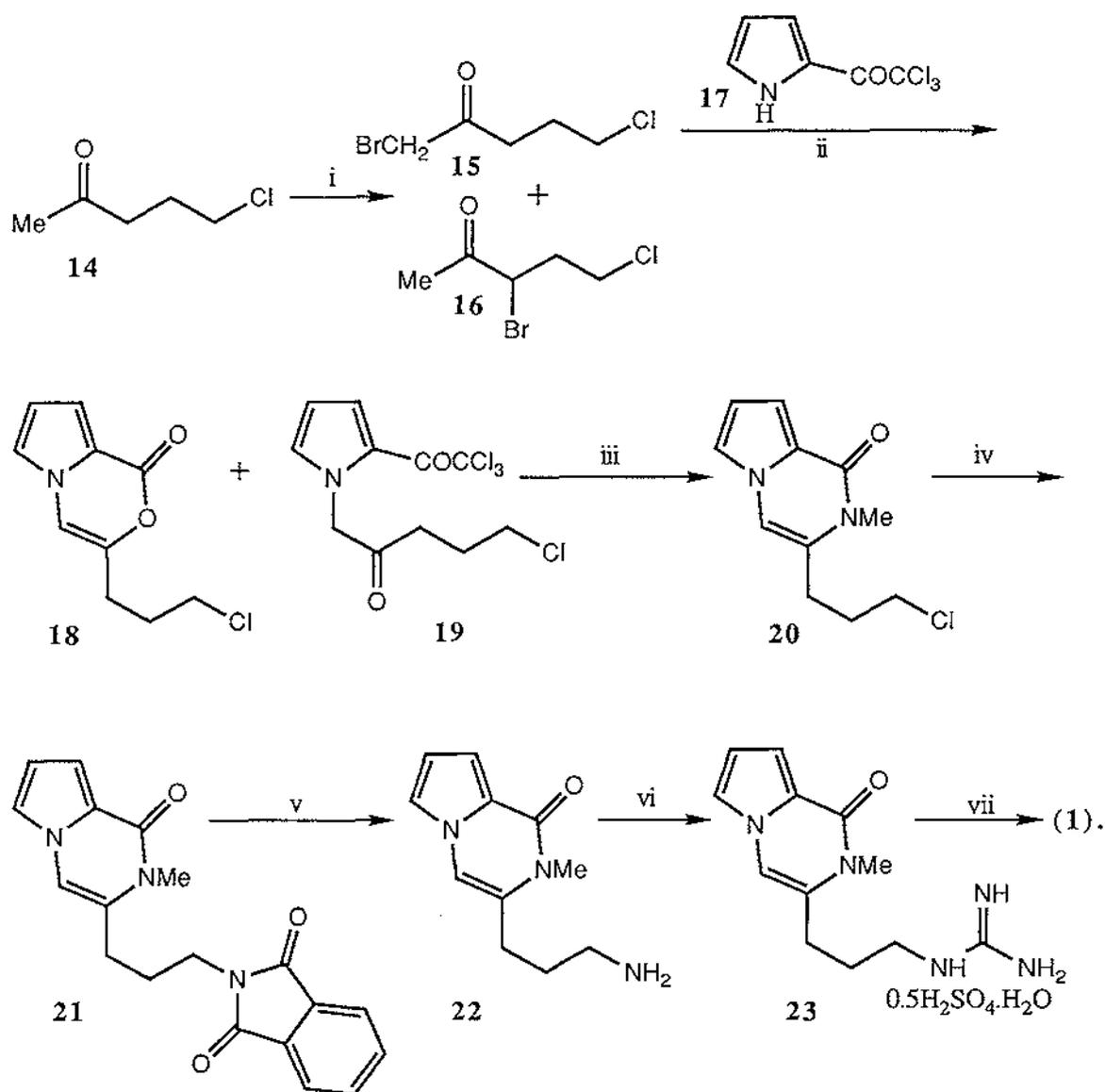
The elaboration of the C-3 carbomethoxy group to the appropriate guanidino group was then achieved in five steps as follows. The ester (9) was reduced to the alcohol (10) using sodium borohydride in methanol. The alcohol was converted to the unstable bromide (11) *via* the mesylate and then quickly added 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*-methylthiuronium hydrogen sulphate.

A second synthesis of peramine by the American chemical company Du Pont<sup>4</sup> 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<sup>5</sup> 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<sub>4</sub> (5.0 equiv), CoCl<sub>2</sub> (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<sub>4</sub>, MeOH, 12h, (72%); (vii) MeSO<sub>2</sub>Cl (1.1 equiv.), Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -60°C 0.25h then LiBr (3.0 equiv.), THF, -60°C to -40°C, 0.5h; (viii), MeCN (5.0 equiv.), <sup>n</sup>BuLi (5.1 equiv.), 0.5h, -78°C then CuBrMe<sub>2</sub>S (5.2 equiv.), -78°C to -40°C, 0.5h then (11) (1.0 equiv.), -40°C to -20°C, (58% overall.); (ix) NaBH<sub>4</sub> (5.0 equiv.), CoCl<sub>2</sub> (2.0 equiv.), MeOH (62%); (x) S- methylthiuronium hydrogen sulphate (5.0 equiv.), room temp., 48h.

**Scheme 1.**

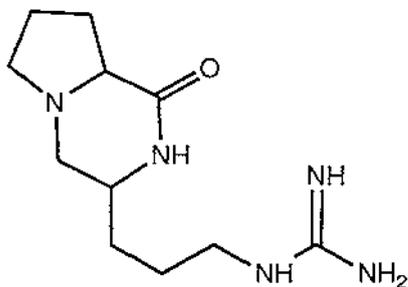


**Reagents and conditions:** (i)  $\text{Br}_2$ , MeOH, room temp, 2h, **15** (62%), **16** (28%); (ii)  $\text{K}_2\text{CO}_3$ ,  $\text{CH}_3\text{COCH}_3$ , room temp, 18h, **18** & **19** (62%); (iii)  $\text{CH}_3\text{NH}_2$ , THF,  $0^\circ\text{C}$ , 3h, then 1N HCl, room temp, 2h, (45%); (iv) potassium phthalimide, DMF,  $77\text{--}82^\circ\text{C}$ , 1.5h, (81%); (v)  $\text{H}_2\text{NNH}_2\cdot\text{H}_2\text{O}$  (3.0 equiv.), EtOH, reflux 0.5h then 1N HCl, reflux 2.0 min, (84%); (vi)  $(\text{CH}_3\text{SC}(\text{=NH})\text{NH}_2)_2\cdot\text{H}_2\text{SO}_4$ ,  $\text{H}_2\text{O}$ ,  $90^\circ\text{C}$ , 15h, (49%); (vii) basic ion exchange,  $\text{H}_2\text{O}/\text{CH}_3\text{OH}$ , (98%).

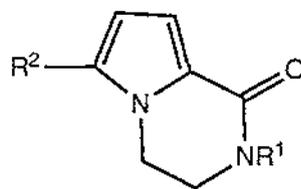
**Scheme 2.**

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*<sup>6</sup>, 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<sup>7</sup> using a number of these

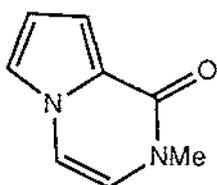
peramine analogues (24, 25a-c, 26, 27) suggested the importance of the pyrrolopyrazine ring system rather than the propylguanidinyl side chain.



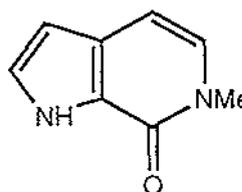
24 Cyclopropylarginine.



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, cyclopropylarginine (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.

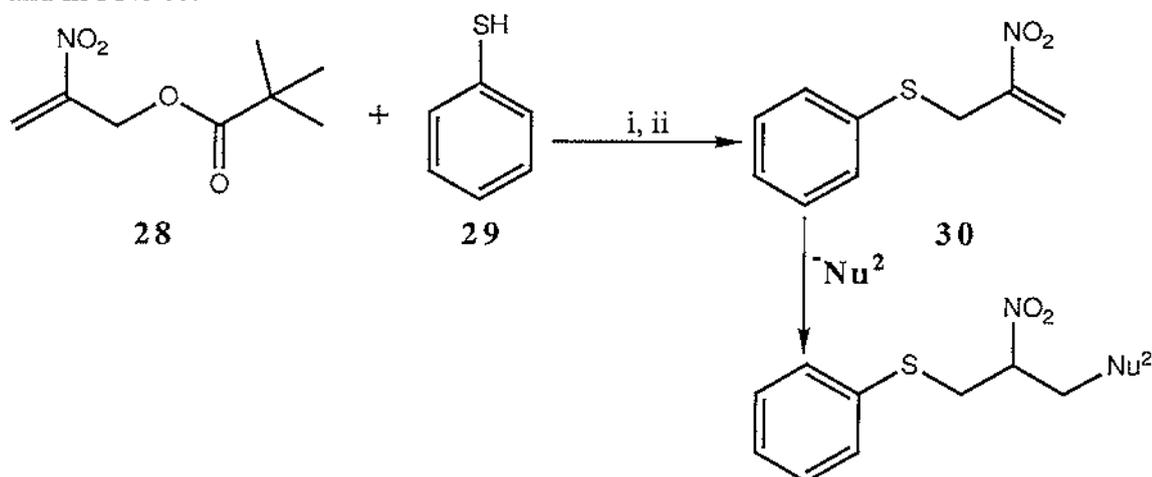
In light of these interesting biological results obtained with the analogues above, it was decided to embark on a programme involving synthesis of pyrazine ring systems related to peramine (1). Any new compounds synthesized in the work would be tested in the feeding deterrent assays already developed 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<sup>8,9,10</sup> and the recent review by Barrett<sup>9</sup> 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.

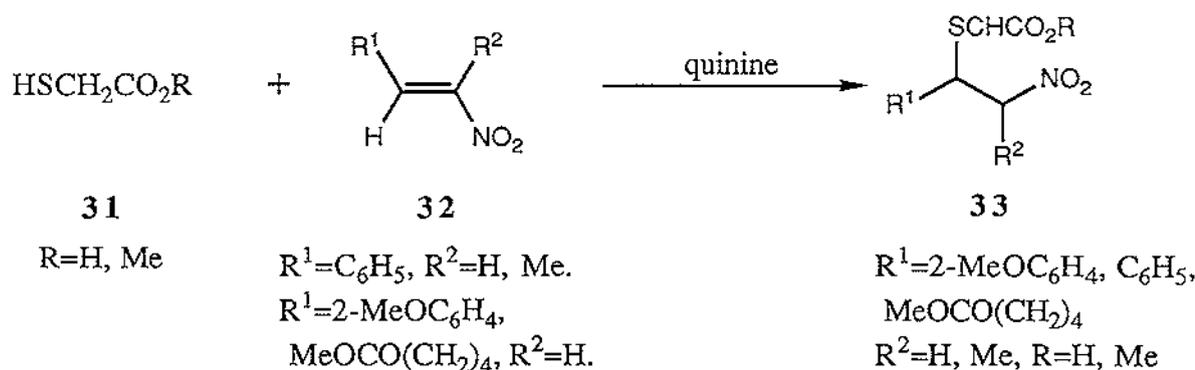
### 1.2.1. Oxygen and Sulphur-Centred Nucleophiles.

A number of examples using sulphur centred nucleophiles have been reported. The following examples are representative. Seebach and co-workers<sup>11</sup> 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<sup>12</sup> have coupled thiols (31) with substituted and unsubstituted  $\beta$ -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 thioglycolic acid (31, R=H) to (2-nitroethenyl)benzene (32, R<sup>1</sup>=C<sub>6</sub>H<sub>5</sub>, R<sup>2</sup>=H) affording the Michael adduct (33, R, R<sup>2</sup>=H, R<sup>1</sup>=C<sub>6</sub>H<sub>5</sub>) in 86% yield and in 58% ee.



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

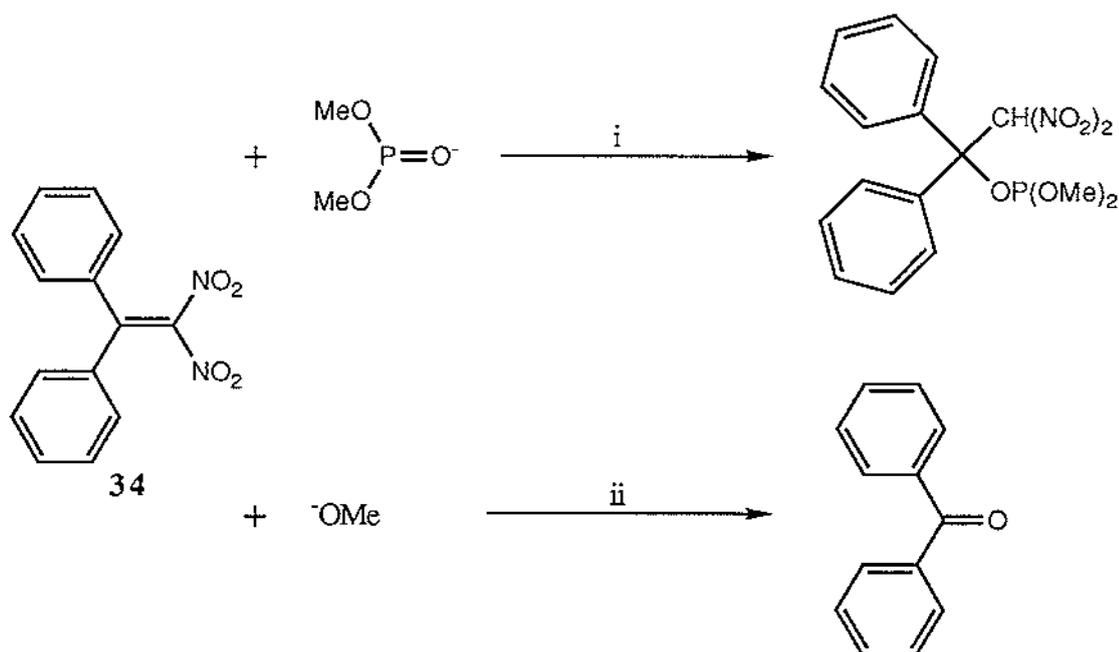
Scheme 3.



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

**Scheme 4.**

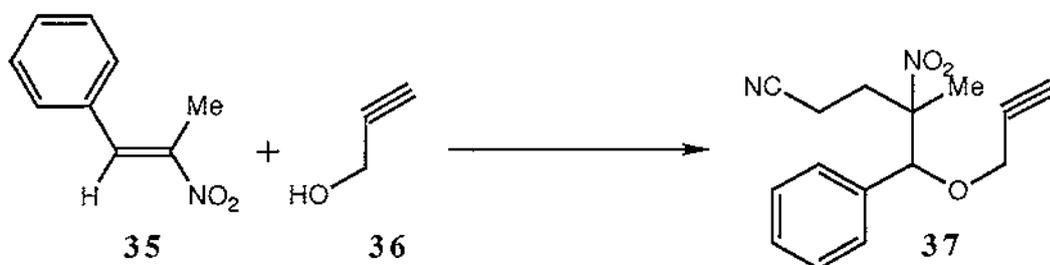
The addition of oxygen nucleophiles to nitro-alkenes can be demonstrated by the following examples. Russell and co-workers<sup>13</sup> have reacted 1,1-diphenyl-2,2-dinitroethene (34) with a number of nucleophiles including  $(\text{MeO})_2\text{P}(=\text{O})\cdot\text{K}^+$  and  $(\text{EtO})_2\text{P}(=\text{O})\cdot\text{K}^+$  to give the corresponding Michael adducts (Scheme 5). In this case, reaction with more basic nucleophiles, (eg  $\text{OMe}^-$ ) yielded only benzophenone arising from hydrolysis of the nitro-alkene.



*Reagents and conditions:* (i)  $\text{Me}_2\text{SO}$ ,  $\text{N}_2$  atmosphere, room temp, 0.5h, then 5% HCl, (75%); (ii)  $\text{MeOH}$ ,  $\text{N}_2$ , room temp, 48h, (73%).

**Scheme 5.**

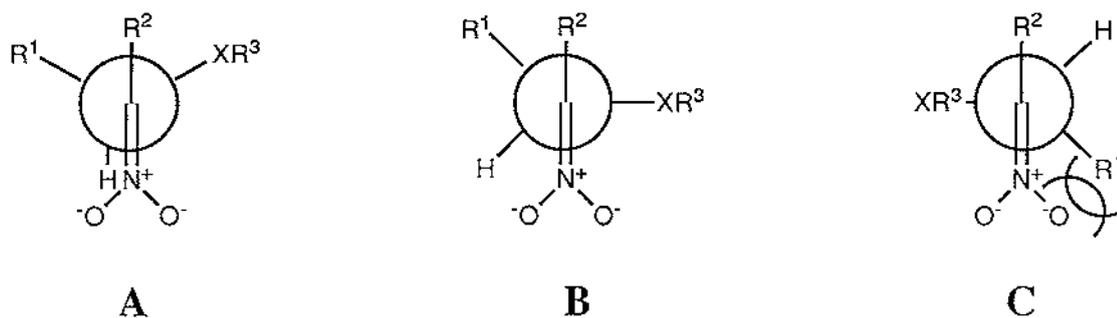
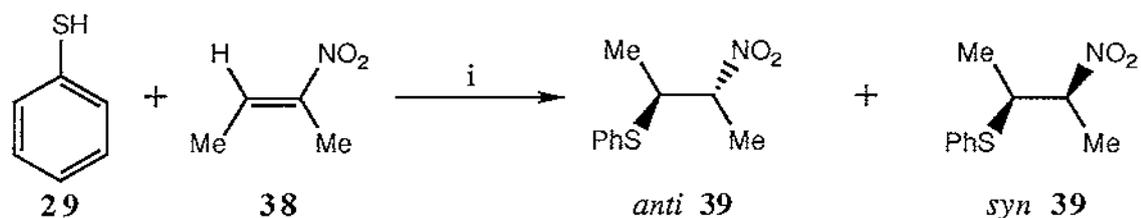
A further example involved the reaction of  $\beta$ -methyl- $\beta$ -nitrostyrene (35) with 3-propynol (36) followed by a second Michael reaction using acrylonitrile to give the *bis* adduct (37) in 74% overall yield<sup>14</sup> (Scheme 6).



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<sup>15</sup> have compared the addition of thiolate anions to nitro-alkenes followed by protonation at room temperature or  $-78^{\circ}\text{C}$ . 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  $-78^{\circ}\text{C}$  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 ( $\text{R}^3\text{X}$ ) 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 conformer the diastereoselectivity should depend on the relative steric bulkiness between  $\text{R}^1$  and  $\text{R}^3\text{X}$ . The authors, however, found this not to be the case in that varying the size of  $\text{R}^1$  and  $\text{R}^3$  lead to no significant change in the diastereoselectivity. Conformer B should be preferred over conformer C due to steric repulsion between  $\text{R}^1$  and the nitro group in C. As  $\text{R}^3$  covers one face of the nitronate derivative in conformer B, the proton attacks only from the opposite side of the  $\text{R}^3\text{X}$  group leading to the *anti* product.

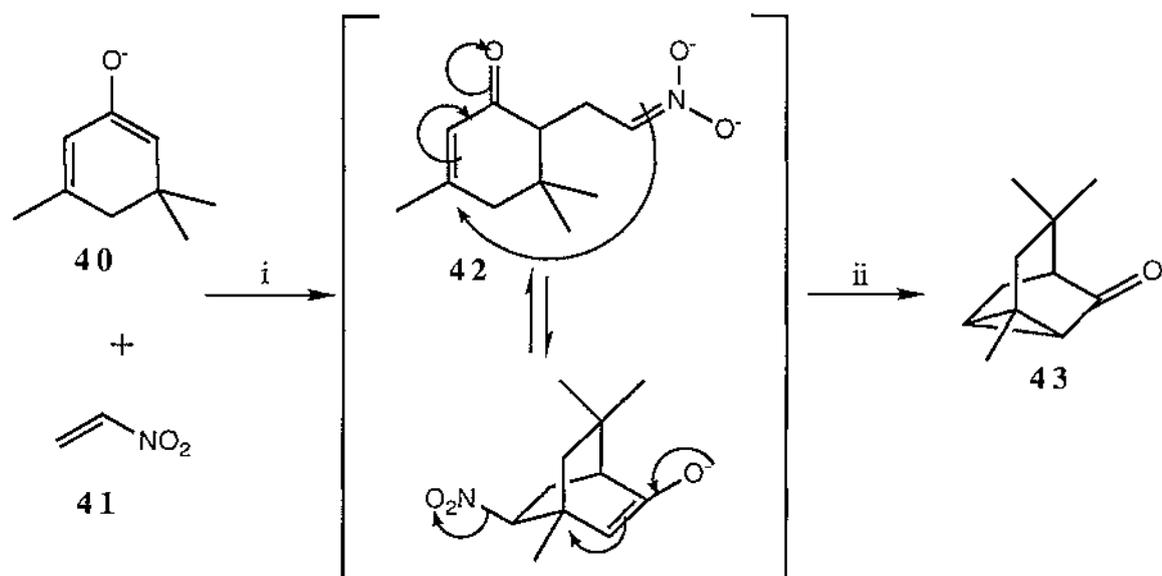


*Reagents and conditions:* (i) Et<sub>3</sub>N (0.1 equiv.), MeCN, room temp., 1h then 1N HCl, room temp. (95%); or, CH<sub>3</sub>CO<sub>2</sub>H, -78°C, (75%).

**Scheme 7.**

### 1.2.2 Carbon-Centred Nucleophiles.

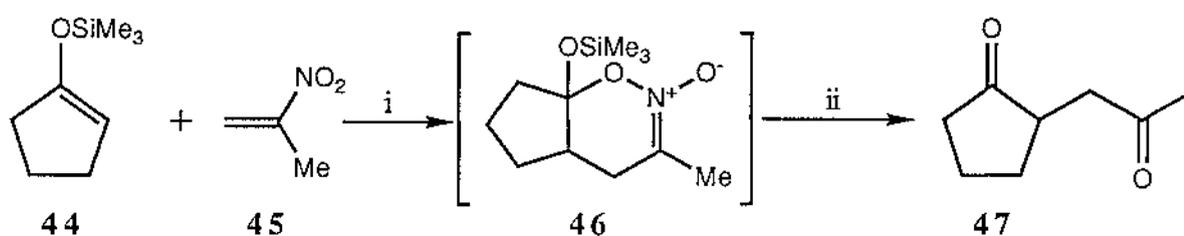
By far the largest body of work involving Michael additions of nitro-alkenes involves the addition of carbon centred nucleophiles. Cory and co-workers<sup>16</sup> have shown nitro-alkenes to be efficient reagents to effect a bicycloannulation in three steps (Scheme 8). Thus the enolate (**40**) undergoes 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,  $-78^{\circ}\text{C}$ , then 41, HMPA, room temp; (ii) reflux 16h, (58%).

Scheme 8.

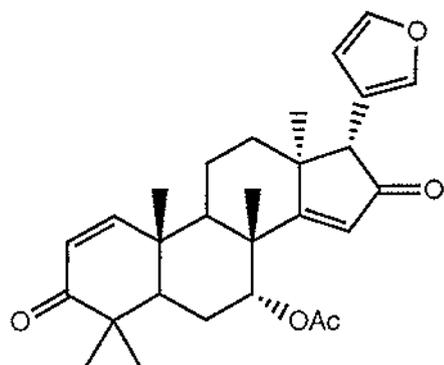
Yoshikoshi and co-workers<sup>17</sup> have used the condensation of enol silanes with nitroalkenes to obtain 1,4-dicarbonyl species. In this case the nitro group is considered to be synthetically equivalent to the carbonyl group, due to the ease of conversion to ketones *via* the Nef reaction. Thus the conjugate addition of silyl enol ether (44) to nitroalkene (45) in the presence of the Lewis acids  $\text{TiCl}_4$  or  $\text{SiCl}_4$  at  $-78^{\circ}\text{C}$ , 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.



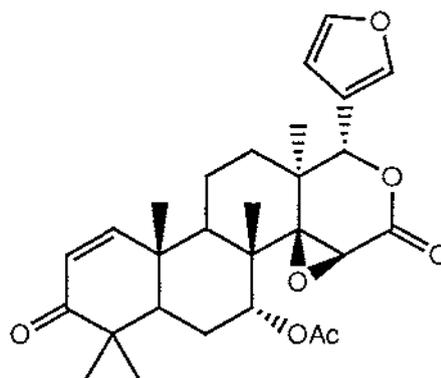
Reagents and conditions: (i)  $\text{SnCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^{\circ}\text{C}$ ; (ii)  $\text{H}_2\text{O}$ , reflux, (79%).

Scheme 9.

A more recent example of addition of enol silanes to nitroalkenes involves the synthesis of compounds related to the insect antifeedants azadiradion (48) and gedunin (49)<sup>18</sup>. Azadiradion (48) and gedunin (49) are members of the Limonoid family, isolated from the neem tree *Azadirachta indica*.

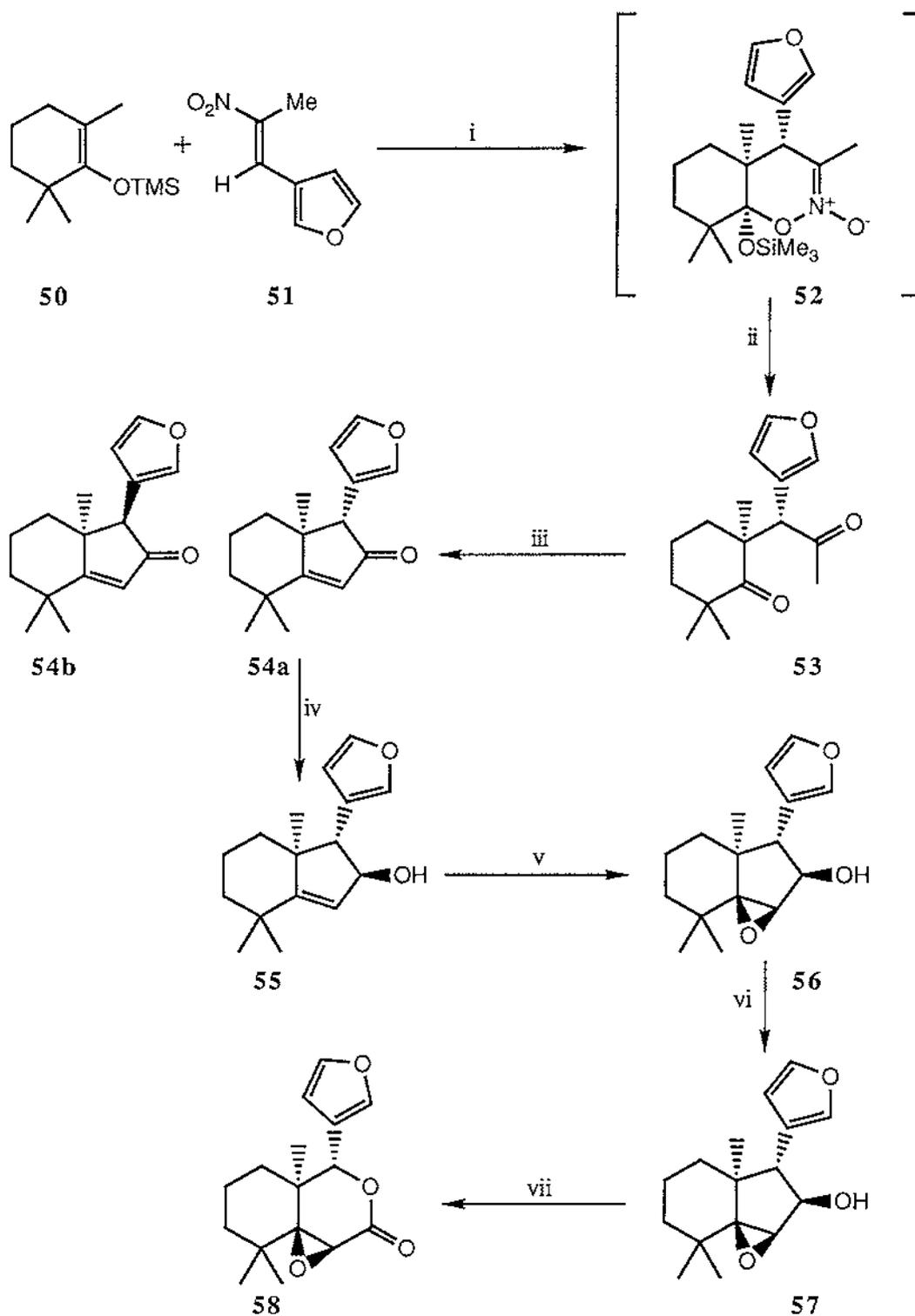


48 Azadiradion



49 Gedunin

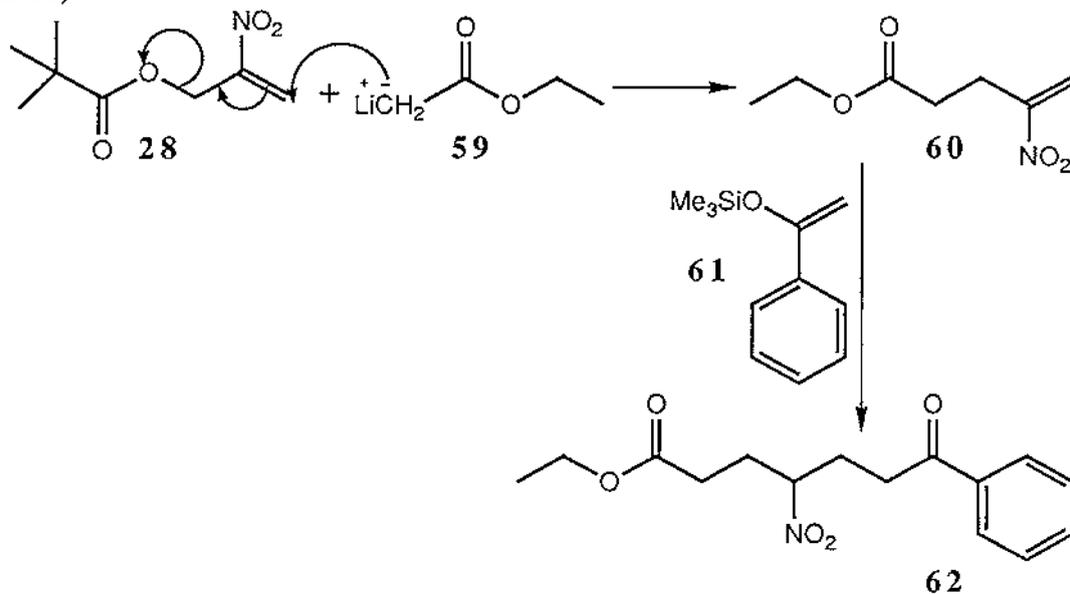
Mateos and co-workers<sup>18</sup> have synthesized structural subunits related to these compounds. Thus the addition of enol silane (50) to nitro-alkene (51) in the presence of titanium tetrachloride afforded the cyclic silyl nitronate (52) which gives the diketone (53) upon treatment with water in 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  $\beta$ -alcohol (55) in 97% yield. Stereospecific epoxidation of the allylic  $\beta$ -alcohol (55) with *m*-chloroperoxybenzoic acid (mCPBA) afforded the epoxide alcohol (56) in 75% yield. The authors suggested that the epoxidation proceeded from the  $\beta$  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 epoxy lactone (58) in 60% yield. Epoxy lactone (58) is a structural subunit related to Gedunin (49).



*Reagents and conditions:* (i)  $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{N}_2$  atmosphere,  $-78^\circ\text{C}$ , 0.25h; (ii)  $\text{Na}_2\text{CO}_3$  (10%),  $-78^\circ\text{C} \rightarrow 25^\circ\text{C}$ , 2h; (iii)  $\text{H}_2\text{O}$ , room temp, 2h, (75%); (iv)  $\text{KOH}$ ,  $\text{EtOH}$ ,  $\text{N}_2$  atmosphere, reflux 40 min, **54a** (64%), **54b** (17%); (v)  $\text{LiAlH}_4$ ,  $(\text{C}_2\text{H}_5)_2\text{O}$ ,  $\text{N}_2$  atmosphere,  $0^\circ\text{C}$ , then  $\text{Na}_2\text{SO}_4$ , 1h, room temp, (97%); (vi)  $\text{mCPBA}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-40^\circ\text{C}$ , 3h, (75%); (vii) Jones reagent,  $\text{CH}_3\text{COCH}_3$ ,  $0^\circ\text{C}$ , 1h, (96%); (viii)  $\text{mCPBA}$ ,  $\text{CH}_2\text{Cl}_2$ , room temp, 5.5h, (60%).

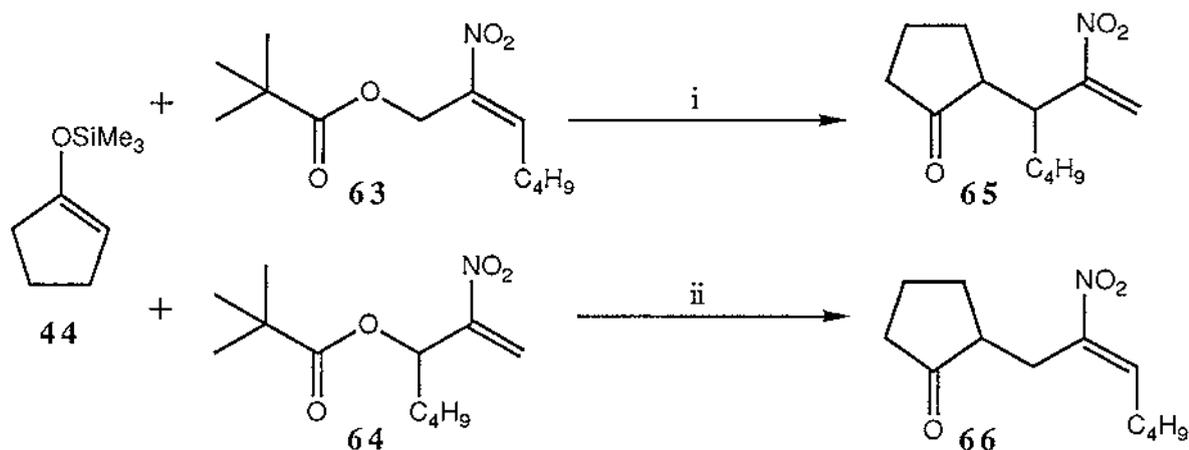
**Scheme 10**

Seebach and co-workers<sup>9</sup> 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.

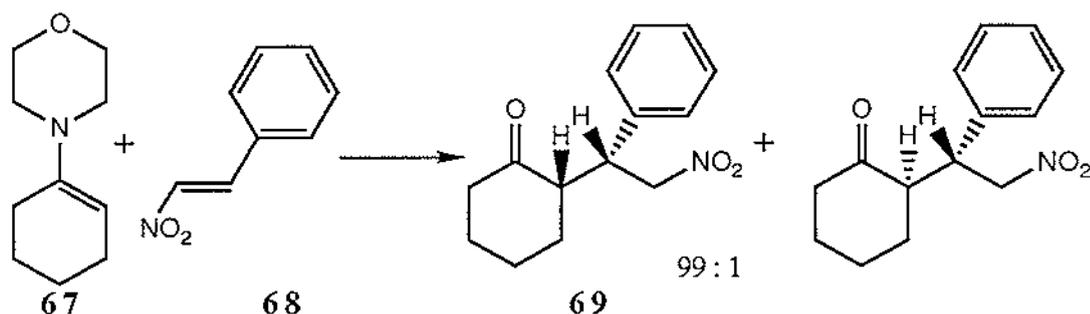
A further example of multiple coupling involves the addition of silyl ether (44) to the two isomeric nitro-heptenyl pivaloates (63) and (64) to afford the Michael adducts (65) and (66) in 73% and 75% yield respectively (Scheme 12). These results establish that the nitroallylations do not occur by direct S<sub>N</sub>2 substitution but involve an addition elimination mechanism. The Michael adduct (66) was obtained only as the *Z* isomer, presumably on account of thermodynamic control<sup>19</sup>.



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

Scheme 12.

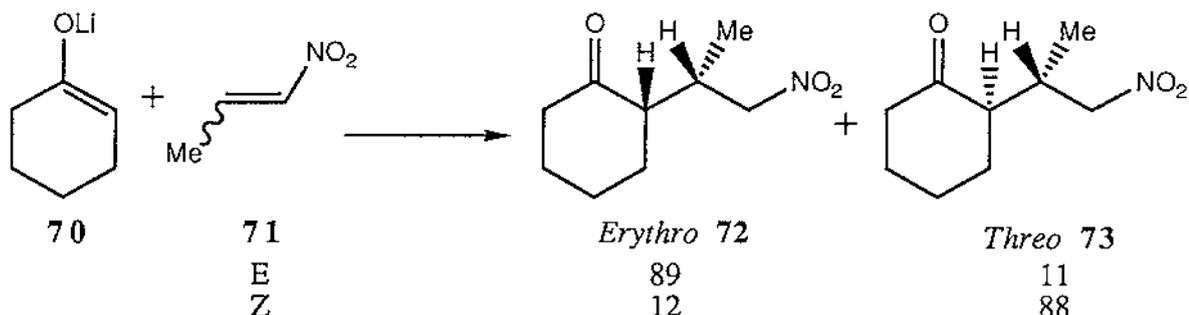
The Michael addition of enamines and enol silanes is a useful method to produce  $\gamma$ -nitro ketones with reasonable to excellent diastereoselectivity. Seebach<sup>20,21</sup> have reported the condensation of (*E*)- $\beta$ -nitrostyrene with cyclic lithium enolates and enamines to preferentially 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).



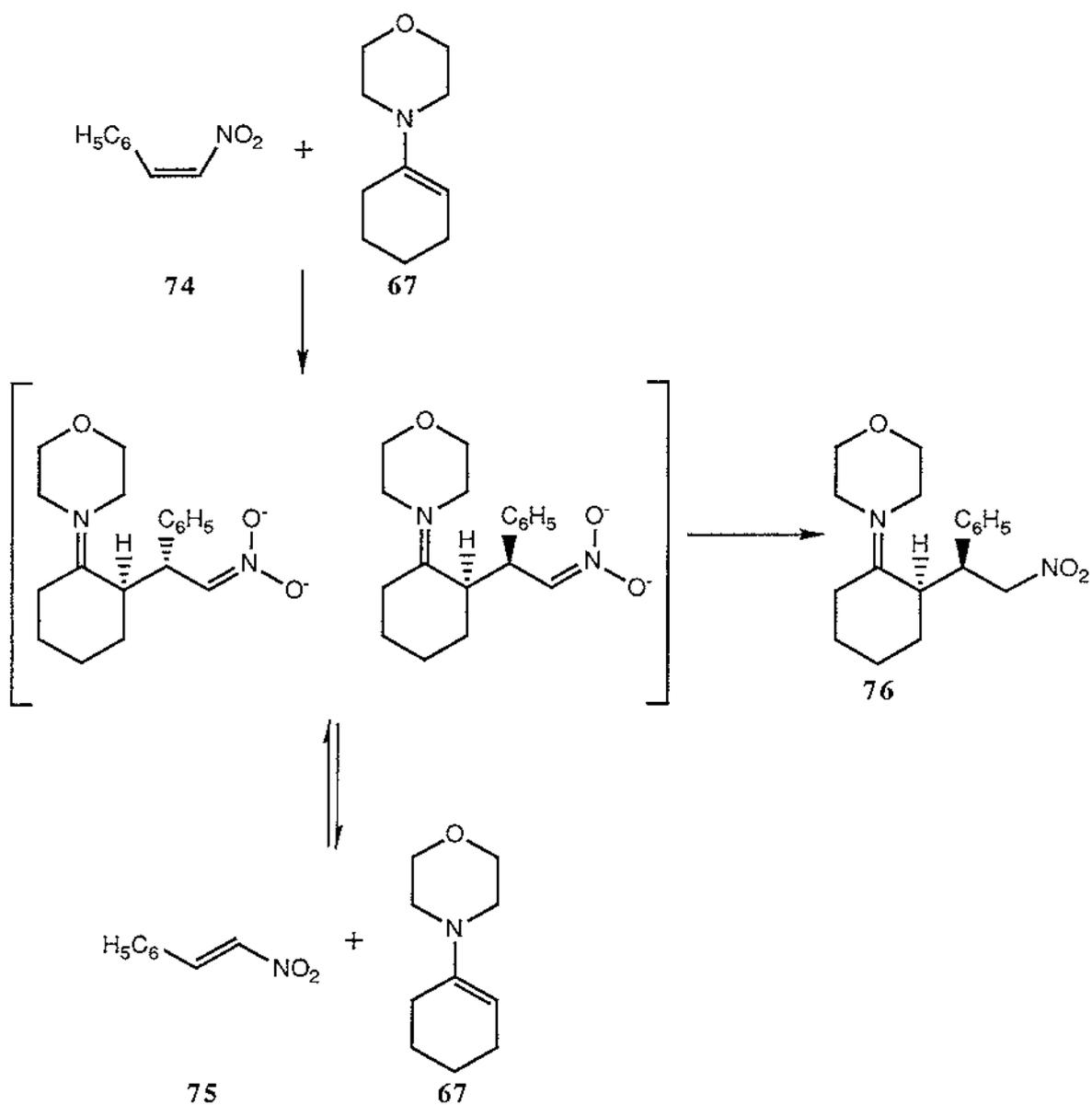
Reagents and conditions: (i)  $(C_2H_5)_2O$ , room temp, 3  $\rightarrow$  48h, (88%).

**Scheme 13.**

Further work by Seebach<sup>22</sup> 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).



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).



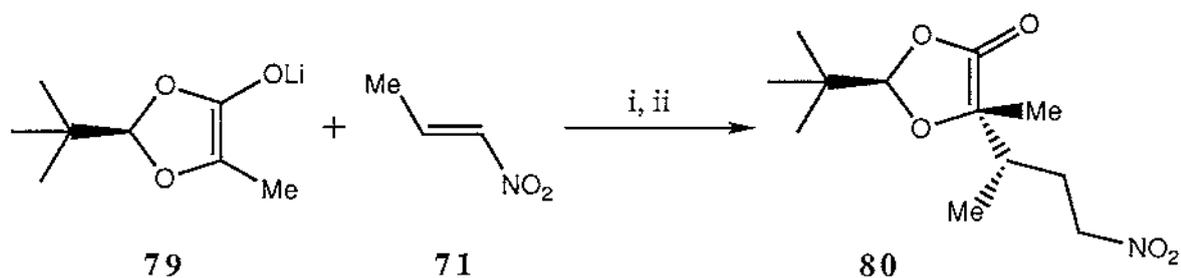
Scheme 15.

The following mechanism has been proposed by the authors<sup>23</sup>: 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  $\pi$  systems in the transition state. Hydrolysis of the enamine (76) affords the nitro ketone (78).



**Scheme 16.**

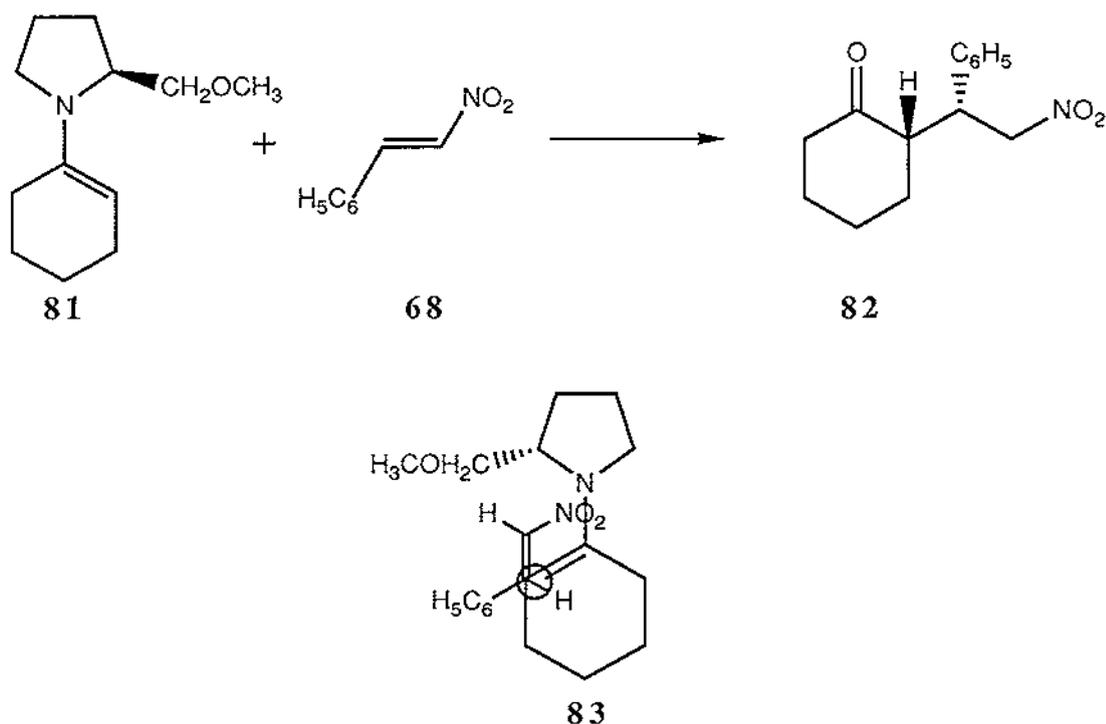
Seebach has extended these studies to several cyclic enolates, with the following examples being representative. The addition of lithium enolate (79) to (E)-nitropropene (71) afforded the Michael adduct (80) in 58% yield and 93% diastereoselectivity<sup>24</sup> (Scheme 17).



*Reagents and conditions:* (i)  $\text{LiN}(\text{tPr})_2$ , THF,  $-78^\circ\text{C}$ , then 79, 0.5h, then 0.5-0.75h,  $-78^\circ\text{C}$ ; (ii) 71,  $-100^\circ\text{C}$ - $-78^\circ\text{C}$ , 1.5h, then AcOH, THF,  $-78 \rightarrow -40^\circ$ , 0.25h (58%).

**Scheme 17.**

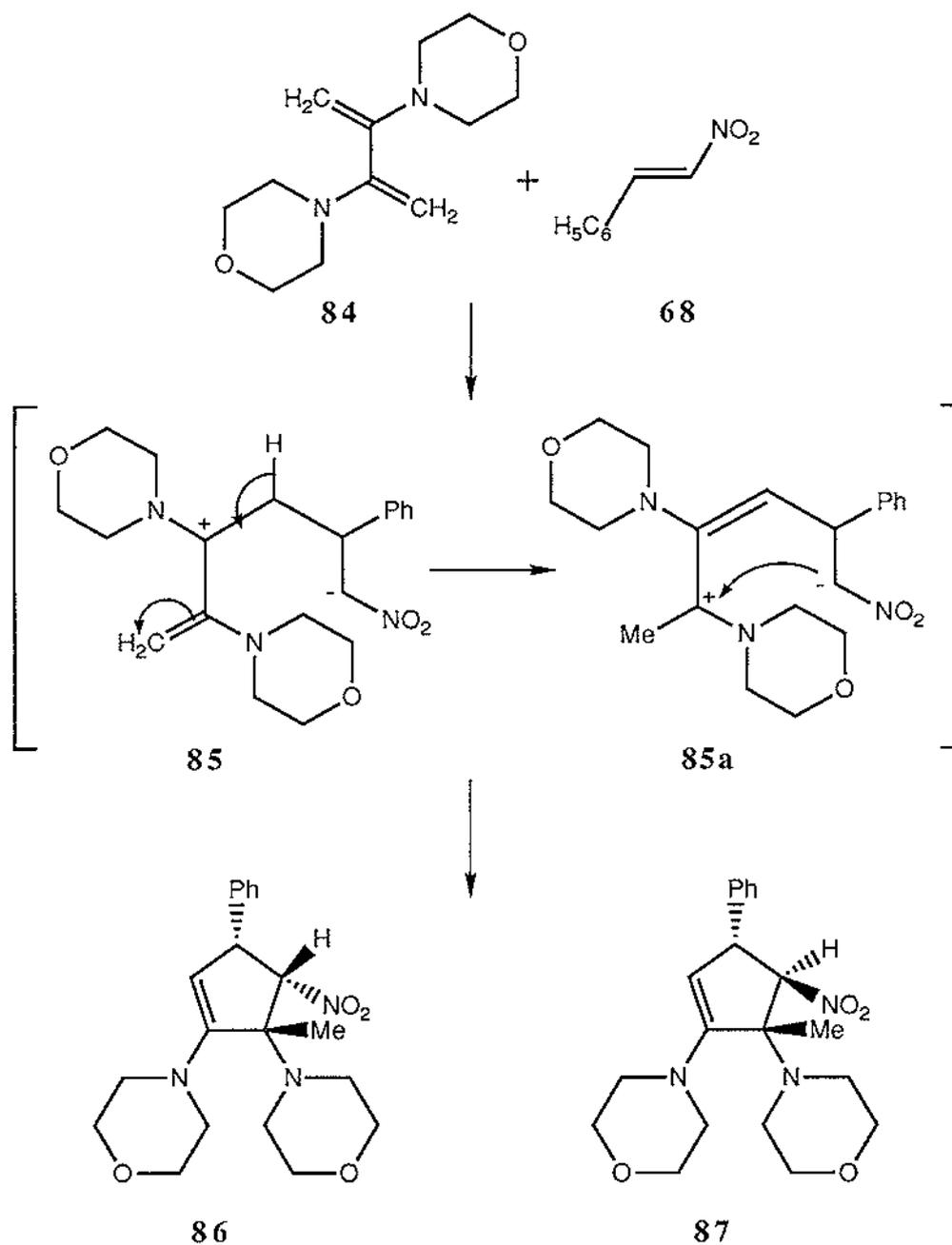
An extension of these studies furnished a second example as follows. The addition of chiral enamine (81) to (E)- $\beta$ -nitrostyrene (68) afforded the ketone (82) as a single diastereomer in 97% ee (Scheme 18). The authors have suggested that this excellent diastereoselectivity resulted from reaction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



*Reagents and conditions:* 68 Et<sub>2</sub>O, -80<sup>0</sup>C, Ar atmosphere, then 81 (1.0 equiv.) then -80 → 25<sup>0</sup>C, 6h.

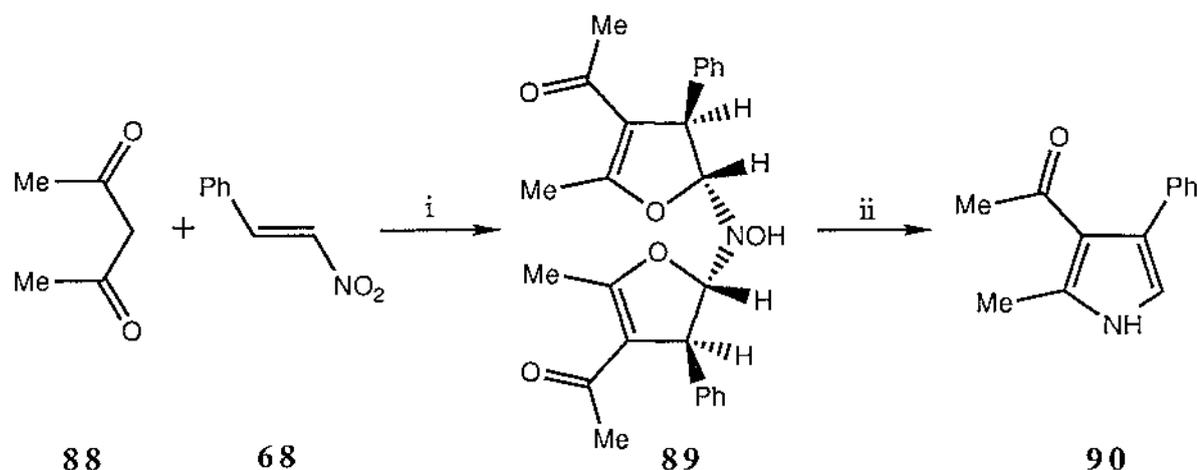
**Scheme 18.**

Destro and co-workers<sup>26</sup> 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.



**Scheme 19.**

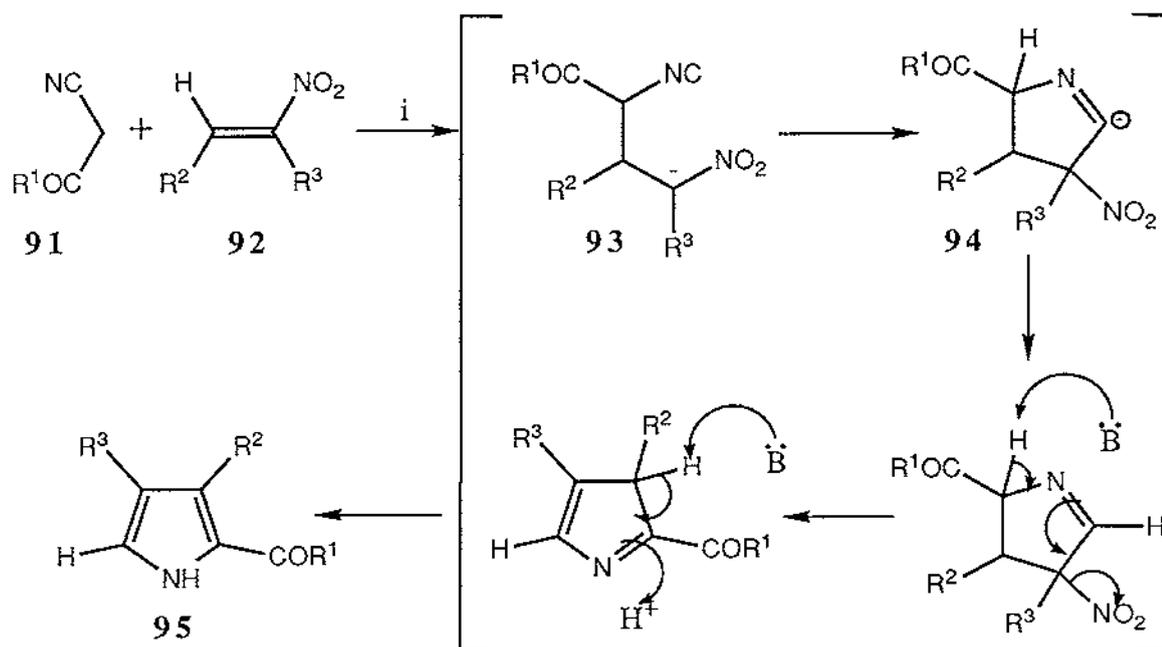
Nitro-alkenes have been used widely in the synthesis of pyrroles<sup>9</sup>. The following examples are representative. Gomez-Sanchez and co-workers<sup>27</sup> have added pentane-2,4-dione (88) to  $\beta$ -nitrostyrene (68) in methanol containing sodium methoxide (0.2 mol eq) to afford the Michael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



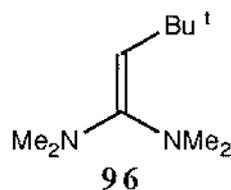
*Reagents and conditions:* (i) MeOH, MeO<sup>-</sup> (0.2 equiv.), 0°C, 5 min, (68%);  
(ii) MeOH, NH<sub>3</sub> (gas), 0°C, 0.5h, (60%).

**Scheme 20.**

A further example of pyrrole synthesis involving nitro-alkenes has been furnished by Barton and co-workers<sup>28</sup>. In this case a  $\alpha$ -isocyanoacetate ester is added to a nitro-alkene in the presence of base to afford 5-substituted pyrroles. Thus, the addition of the  $\beta$ -nitrostyrene derivative (92) to a mixture of <sup>t</sup>butyl- $\alpha$ -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  $\alpha$  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).



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

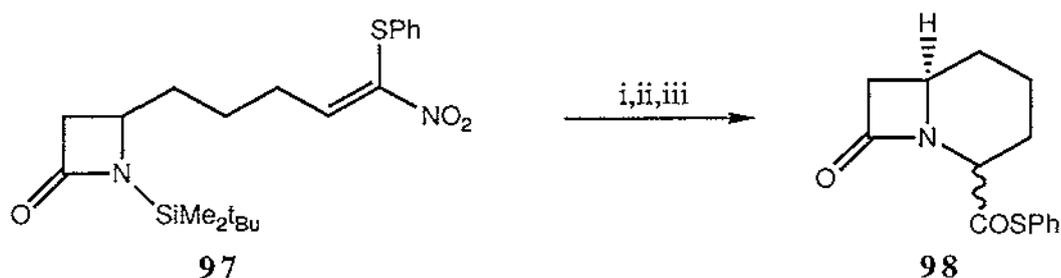


*Reagents and conditions:* THF, 2-propanol, room temp, **96**, (90%).

**Scheme 21.**

### 1.2.3 Nitrogen-Centred Nucleophiles.

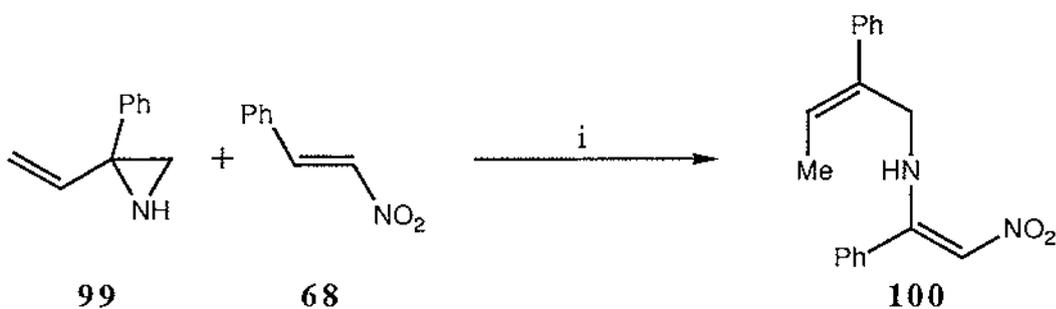
The addition of nitrogen centred nucleophiles to nitro-alkenes can be used to prepare bicyclic  $\beta$ -lactams<sup>29</sup>. Thus 4-(4-pentenyl)-2-azetidinone (**97**) undergoes intramolecular Michael addition, in the presence of HF-pyridine in dichloromethane (*N*-desilylation) followed by treatment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



*Reagents and conditions:* (i) HF, C<sub>5</sub>H<sub>5</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78 → 0°C; (ii) <sup>t</sup>BuOH, THF, <sup>t</sup>Bu OK, (1.0 equiv.), -30°C; (iii) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -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<sup>30</sup> (Scheme 23). The product probably arose *via* initial nitrogen centred attack and subsequent retro-ene azetidine fragmentation.

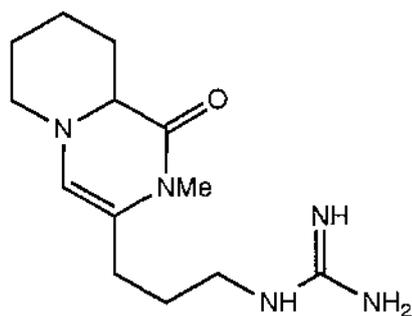


*Reagents and conditions:* (i) C<sub>6</sub>H<sub>5</sub>, reflux, 6 days, (90%).

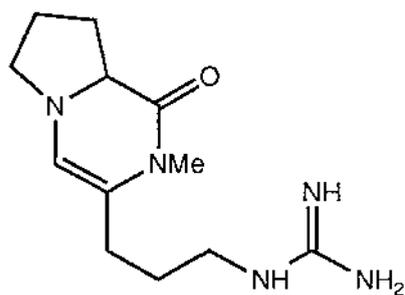
**Scheme 23.**

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

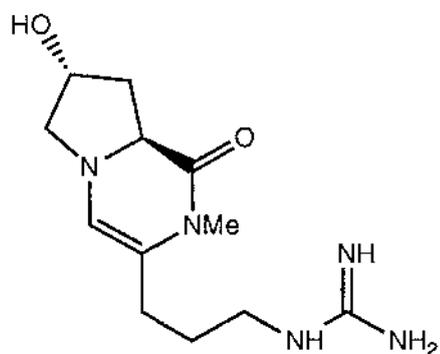
The aim of the present work was to synthesize analogues of peramine (1) for biological testing in insect feeding deterrent assays to establish structure-activity relationships. The target molecules were piperidinoperamine (101), prolylperamine (102), hydroxyprolylperamine (103), indoloperamine (104),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



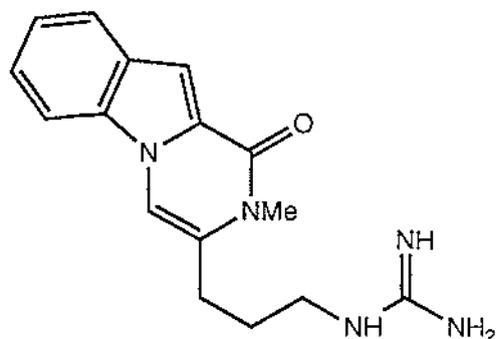
**101** Piperidinoperamine



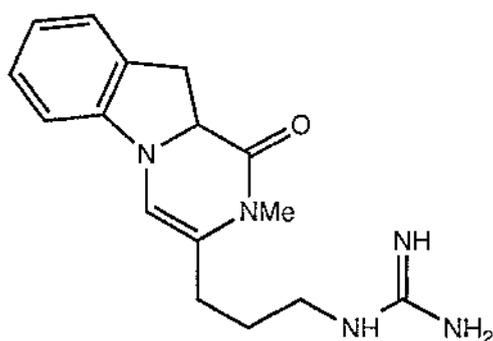
**102** Prolylperamine



**103** Hydroxyprolylperamine



**104** Indoloperamine

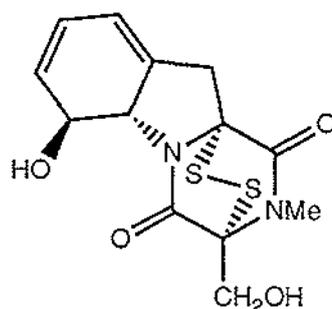


**105** Indolinoperamine

Initially the synthesis of the oxopiperazine ring systems present in each of these analogues would be undertaken, and the guanidiny sidechain attached later. The synthesis of the novel oxoketopiperazine 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.

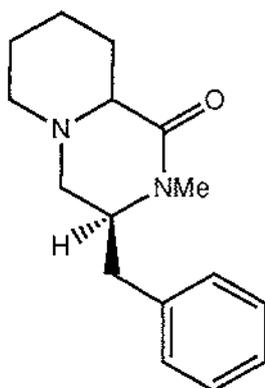
There are a number of natural products with pyrazine ring systems similar to that of peramine (1) and the synthetic analogues mentioned above. Gliotoxin (106) is a potent

antibiotic produced by the fungus *Gliocadium fimbriatum*, and shows remarkable fungicidal and bacteriocidal action against a number of pathogenic microorganisms<sup>31</sup>. 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)<sup>32</sup>, the synthetic methodology presently developed toward indolinoperamine (104) may well be extended to synthesize gliotoxin in the future.



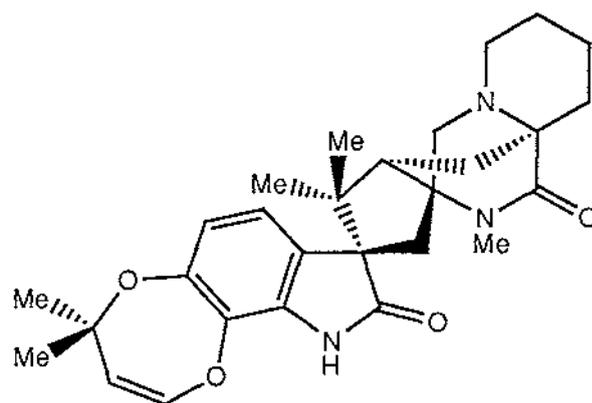
106 Gliotoxin

Verruculotoxin (107) is a tremorgenic mycotoxin isolated from green peanuts infected with the mold *Penicillium verruculosum*<sup>33</sup>, 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<sup>34,35,36</sup> of this natural product have been reported to date.



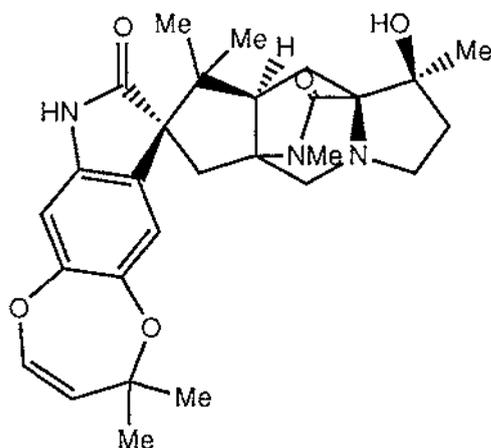
107 Verruculotoxin

Marcfortine A (108) is a complex mycotoxic alkaloid isolated from the mycelium of the *Penicillium roqueforti* strain B26<sup>37</sup>. 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*<sup>38,39</sup>. 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<sup>40</sup>.



109 Paraherquamide

## CHAPTER 2.

### DISCUSSION

#### 2.1 Synthetic Studies toward Indoloperamine using the Anion of Methyl-indole-2-carboxylate.

A facile entry to the pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one ring system present in peramine (1) has been reported by Brimble<sup>3</sup>, in which the key step involves the addition of pyrrole-anion (4) to nitro-alkene (3). The resulting nitro-adduct contains all the functionality required for elaboration to peramine (1) itself.

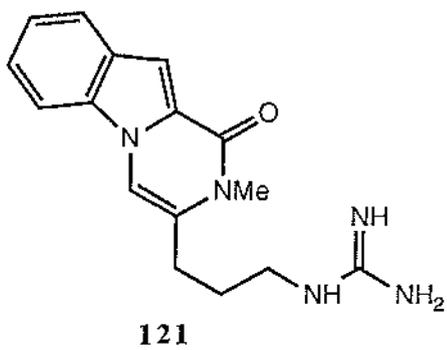
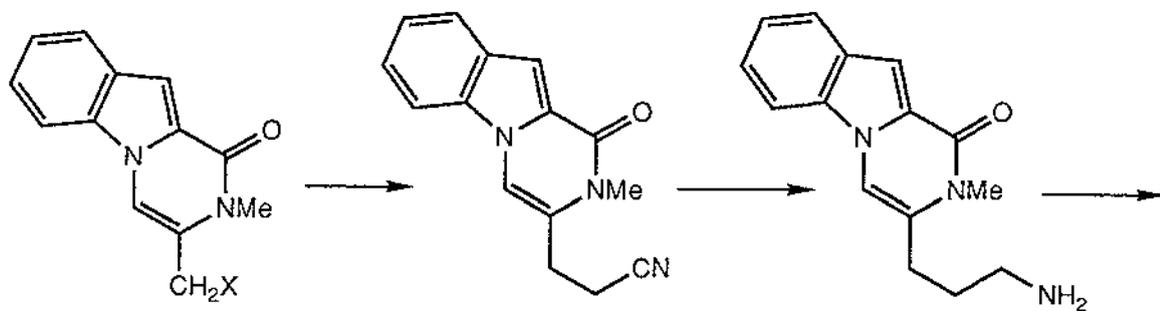
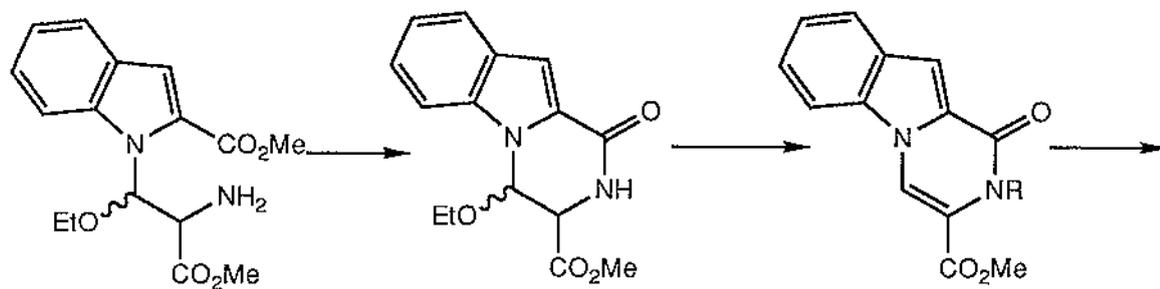
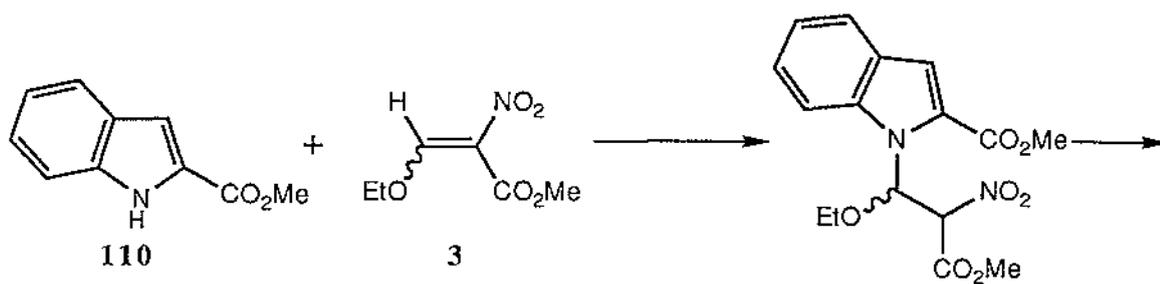
It was envisaged that extension of the synthetic methodology developed for peramine (1) could be applied to the synthesis of more complex ring systems related to peramine (1) and the natural products gliotoxin (106), verruculotoxin (107), and marcfortine A (108). Initial work was directed toward the synthesis of indoloperamine (121), in which the key step would be the addition of the anion of methyl indole-2-carboxylate (110) to nitro-alkene (3) (Scheme 24).

Generation of the anion of methyl indole-2-carboxylate (110) with potassium hydride in tetrahydrofuran (THF) at 0°C for 0.5 hours (the conditions used for methyl pyrrole-2-carboxylate<sup>3</sup>), followed by the addition of nitro-alkene (3) afforded only starting materials. A number of reagents and conditions were tried in an attempt to effect the successful Michael addition of the anion of (110) to nitro-alkene (3) (Table 1), however, in all cases only starting materials were recovered.

The failure of the Michael addition of the anion of (110) to nitro-alkene (3) could be attributed to the anion of (110) not being a sufficiently good nucleophile due to either electronic effects associated with the indole ring, steric effects, or a combination of both.

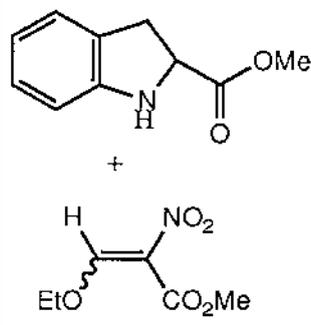
#### 2.2 Synthesis of the Hexahydropyrido[1,2-*a*]pyrazin-1(2*H*)-one Ring System.

Disappointed by the inability to effect the *N*-alkylation of the anion of (110) with nitro-alkene (3), attention then focused on the addition of methyl-2-piperidine-2-carboxylate to nitro-alkene (3) (Scheme 25). Methyl-2-piperidine-2-carboxylate, hydrochloride (112) was prepared by esterification of 2-piperidine carboxylic acid, hydrochloride (111) using thionyl chloride in methanol for two days according to the method of Yasutake *et al*<sup>41</sup> in 91% yield, m.p. 210-213°C. The melting point was in good agreement with the literature<sup>42</sup>.



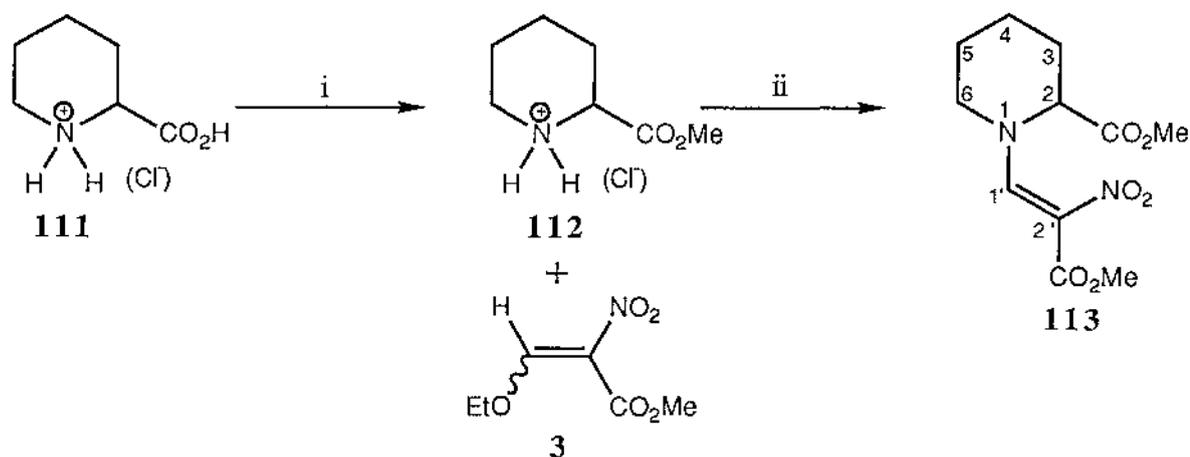
Scheme 24.

**Table 1.**

STARTING MATERIAL	REAGENTS and CONDITIONS	RESULT
	KH (1.5 equiv.), THF, 0°C, N <sub>2</sub> atmosphere.	Starting Materials
	KH (1.5 equiv.), THF, 18-Crown-6, 0°C, N <sub>2</sub> atmosphere.	Starting Materials
	KH (1.5 equiv.), DMSO, 0°C, N <sub>2</sub> atmosphere.	Starting Materials
	K <sub>Metal</sub> , THF, 0°C, N <sub>2</sub> atmosphere.	Starting Materials
	KO <sup>t</sup> Bu, 18-Crown-6, 0°C, N <sub>2</sub> atmosphere.	Starting Materials

Having successfully prepared methyl ester hydrochloride (112) its subsequent reaction with nitro-alkene (3) was investigated. Initial attempts involved liberation of the free base of (112) by treating with 2M NaOH (2.0 equiv.) in dichloromethane followed by aqueous workup to give the free base in 51% crude yield. The free base was then dissolved in toluene followed by the addition of nitro-alkene (3) to give the Michael adduct (113) in 41% overall yield.

In light of the poor yield of the Michael adduct (113) a one pot procedure was sought (Scheme 25). The best method was found to involve liberation of the free base of methyl ester hydrochloride (112) *in situ* by treatment with sodium acetate (2.0 equiv.) in methanol as solvent followed by nitro-alkene (3) (1.0 equiv.), to give the Michael adduct (113), after filtration and recrystallisation, as yellow prisms in 85% yield, m.p. 96.5-97°C.

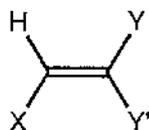


*Reagents and conditions:* (i) SOCl<sub>2</sub> (0.36 equiv.), MeOH (5.0 equiv.), room temp, 2 days 91%; (ii) NaOAc (2.0 equiv.), MeOH, room temp, 0.75 h (85%).

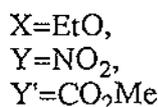
**Scheme 25.**

The product analysed correctly for  $C_{11}H_{16}N_2O_6$ , with a molecular ion at  $m/z$  272 in the mass spectrum supporting this molecular formula. The infrared spectrum exhibited two strong absorbances at 1742 and 1724  $cm^{-1}$  (C=O), indicating the presence of the two ester carbonyl groups, and an absorbance at 1619  $cm^{-1}$  (C=C), supporting the formation of an olefin. The  $^1H$  N.M.R spectrum exhibited a six proton singlet at  $\delta_H$  3.81 assigned to the two methoxy groups and a one proton singlet at  $\delta_H$  8.01 assigned to H-1', providing strong evidence for the formation of a nitro olefin. The  $^{13}C$  N.M.R spectrum was assigned on the basis of chemical shift with the aid of DEPT spectra. The resonances at  $\delta_C$  119.3 (singlet) and  $\delta_C$  149.9 (doublet) assigned to C-2' and C-1' respectively once again supported the formation of a nitro olefin. The clean high field  $^1H$  and  $^{13}C$  N.M.R spectra supported the formation of only one diastereomer from this reaction. The product was assigned the (Z)- stereochemistry by virtue of the fact that subsequent reduction of the nitro group resulted in formation of a lactam, which would not have occurred if the (E)- isomer had been formed (*vide infra*).

Reaction of a system containing a vinylic leaving group with a nucleophile may take place *via* a number of mechanistic routes. This discussion is based on a vinylic system substituted by a leaving group (X), and electron withdrawing  $\beta$  substituents (Y and Y') (3).



3

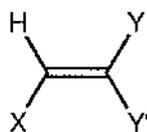


Nucleophilic attack at the  $\alpha$  carbon can give either substitution or addition products; the latter can undergo a subsequent elimination step (Scheme 26). This route is promoted when Y and Y' are electron withdrawing groups.

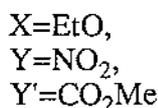
Evidence suggests that if Y and Y' are electron withdrawing groups, nucleophilic substitution is a multi-step process<sup>33,44,45</sup>. The stereochemistry of substitution is mainly dependent on the nature of the leaving group and the activating groups. Poor leaving groups give stereoconvergence. Complete stereoconvergence indicates that the same (E)- : (Z)- product ratio is obtained from both geometric isomers of the substrate. Partial stereoconvergence means that each isomeric precursor gives non-identical mixtures of (E)- and (Z)- products. For good leaving groups retention is observed if the activating groups are moderately delocalising, but if Y and Y' are strongly delocalising then stereoconvergence is often the result.

The product analysed correctly for  $C_{11}H_{16}N_2O_6$ , with a molecular ion at  $m/z$  272 in the mass spectrum supporting this molecular formula. The infrared spectrum exhibited two strong absorbances at 1742 and 1724  $cm^{-1}$  (C=O), indicating the presence of the two ester carbonyl groups, and an absorbance at 1619  $cm^{-1}$  (C=C), supporting the formation of an olefin. The  $^1H$  N.M.R spectrum exhibited a six proton singlet at  $\delta_H$  3.81 assigned to the two methoxy groups and a one proton singlet at  $\delta_H$  8.01 assigned to H-1', providing strong evidence for the formation of a nitro olefin. The  $^{13}C$  N.M.R spectrum was assigned on the basis of chemical shift with the aid of DEPT spectra. The resonances at  $\delta_C$  119.3 (singlet) and  $\delta_C$  149.9 (doublet) assigned to C-2' and C-1' respectively once again supported the formation of a nitro olefin. The clean high field  $^1H$  and  $^{13}C$  N.M.R spectra supported the formation of only one diastereomer from this reaction. The product was assigned the (Z)- stereochemistry by virtue of the fact that subsequent reduction of the nitro group resulted in formation of a lactam, which would not have occurred if the (E)- isomer had been formed (*vide infra*).

Reaction of a system containing a vinylic leaving group with a nucleophile may take place *via* a number of mechanistic routes. This discussion is based on a vinylic system substituted by a leaving group (X), and electron withdrawing  $\beta$  substituents (Y and Y') (3).

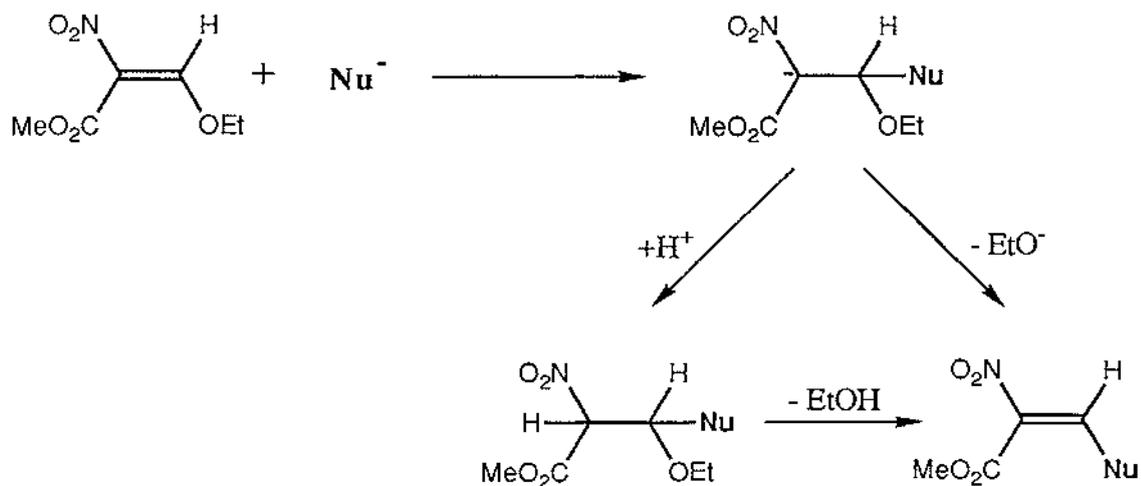


3



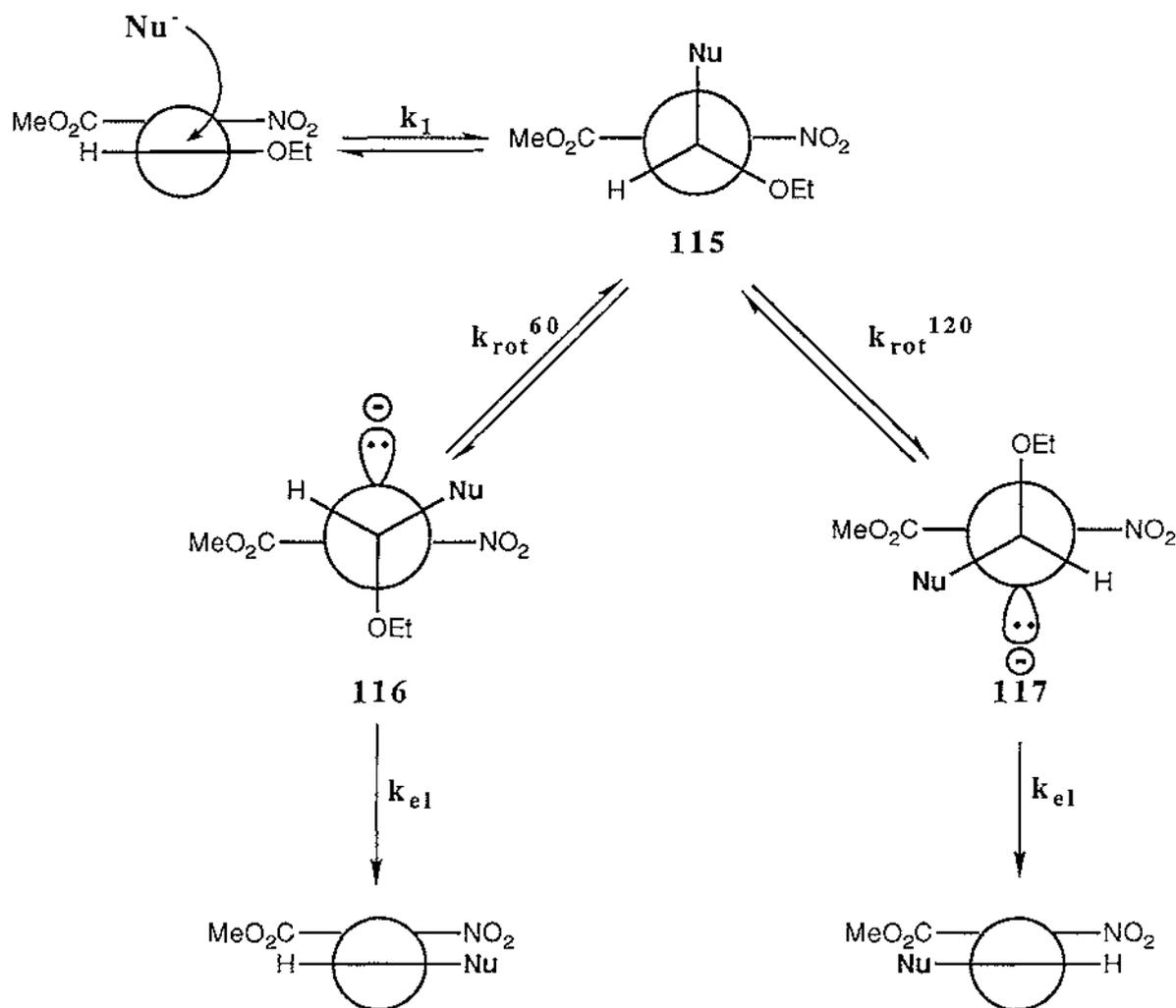
Nucleophilic attack at the  $\alpha$  carbon can give either substitution or addition products; the latter can undergo a subsequent elimination step (Scheme 26). This route is promoted when Y and Y' are electron withdrawing groups.

Evidence suggests that if Y and Y' are electron withdrawing groups, nucleophilic substitution is a multi-step process<sup>33,44,45</sup>. The stereochemistry of substitution is mainly dependent on the nature of the leaving group and the activating groups. Poor leaving groups give stereoconvergence. Complete stereoconvergence indicates that the same (E)- : (Z)- product ratio is obtained from both geometric isomers of the substrate. Partial stereoconvergence means that each isomeric precursor gives non-identical mixtures of (E)- and (Z)- products. For good leaving groups retention is observed if the activating groups are moderately delocalising, but if Y and Y' are strongly delocalising then stereoconvergence is often the result.



**Scheme 26.**

In general terms the mechanism can be illustrated as follows (Scheme 27).

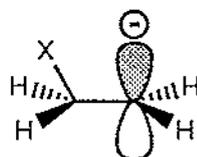


**Scheme 27.**

Nucleophilic attack generates a carbanionic species (115). For stereoelectronic reasons, the expulsion of  $X^-$  is only possible when the carbanionic orbital and the C-X bond are

parallel. Thus a  $60^\circ$  rotation gives conformer (116) and a  $120^\circ$  rotation gives conformer (117). Expulsion of  $X^-$  from conformer (116) leads to retention of stereochemistry while expulsion from (117) gives inversion. Both the rate of rotation and rate of expulsion of  $X^-$  are relevant to the stereochemistry and three situations can be envisaged;

1 If  $k_{el} > k_{rot}$ , expulsion of  $X^-$  from (116) and (117) takes place before further rotation. The steric ratio of the product mixture is determined by the relative rates of rotation. For example, when  $k_{rot}^{60} \gg k_{rot}^{120}$  stereochemistry is retained in the product, but when  $k_{rot}^{120} \gg k_{rot}^{60}$  then complete inversion is the result. The competition between  $60^\circ$  and  $120^\circ$  rotations can be explained in terms of two components of the rotational barrier: steric and hyperconjugative<sup>46</sup>. The hyperconjugative barrier arises from anionic hyperconjugation which is the nett difference between the stabilising interaction between  $C^-$  ( $2p$ ) and  $\sigma_{C-X}$ . By using the angle dependence of the hyperconjugative interaction, the rotational barrier for simple systems such as (118) was calculated<sup>46</sup>



118

It was shown that the hyperconjugative factor favours the  $60^\circ$  over the  $120^\circ$  rotation. When the hydrogens of the simple system are replaced with electron withdrawing groups it has been shown that the hyperconjugative barrier is reduced<sup>47</sup>. The steric barrier is a factor which favours the rotation leading to the lower steric interaction between eclipsing vicinal substituents.

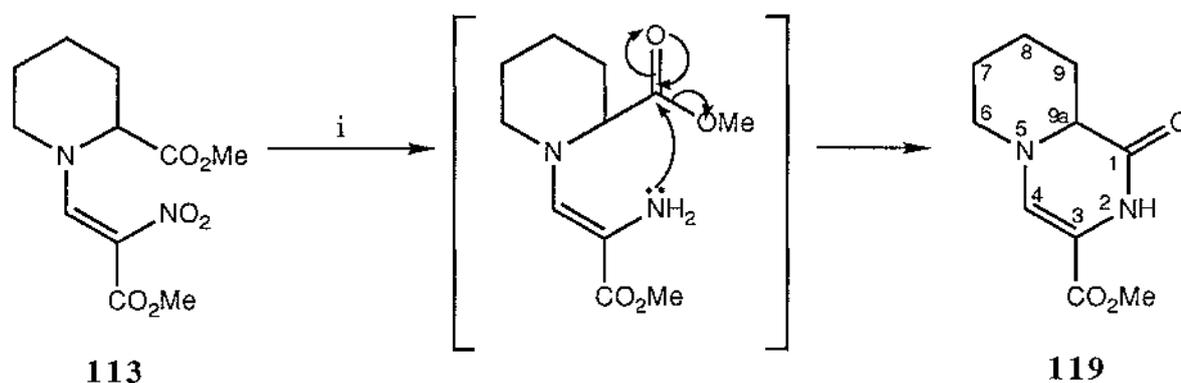
2 When rotation is faster than elimination ( $k_{rot} > k_{el}$ ), both precursors will give the same ratio of products (or a single product). Thus complete stereoconvergence is observed.

3 If  $k_{rot} \approx k_{el}$ , both rotational barriers and elimination rates influence the product ratios. This leads to partial stereoconvergence.

In the present case, the addition of methyl-2-piperidine-2-carboxylate (112) to nitroolefin (3) gives only the (Z)-adduct (113) despite the fact that a mixture of stereoisomers of alkene (3) was used. Thus, both the (E)- and (Z)- isomers of alkene (3) give the same (Z)-adduct (113). This observed stereoconvergence is consistent with the argument outlined

above for the case when rotation is faster than elimination, ( $k_{rot} \gg k_{el}$ ). A similar observation has been reported by Seebach<sup>19</sup>.

With the Michael adduct (113) in hand the next task was to effect cyclisation to the hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one ring system. Thus treatment of a solution of nitro-adduct (113) in tetrahydrofuran / *t*-butanol (2:1) with amalgamated magnesium and titanium tetrachloride using tetrahydrofuran as solvent, according to the method of George and Chandrasekaran<sup>48</sup> afforded the lactam (119) in 46% yield after purification by flash chromatography, presumably *via* the intermediate amine (Scheme 28). A number of reagents and conditions were evaluated in an attempt to optimise the yield of lactam (119) (Table 2), however, reduction using the titanium (II) species generated by the reduction of titanium tetrachloride with amalgamated magnesium was found to be the most satisfactory.

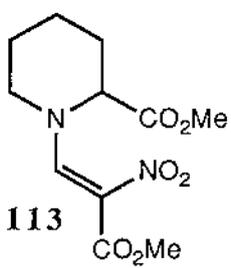
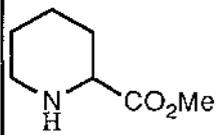
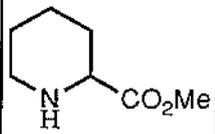
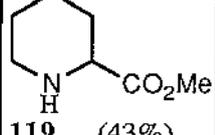


Reagents and conditions: Mg/Hg/TiCl<sub>4</sub>, THF/*t*BuOH (2:1), 0°C, 1h (46%).

Scheme 28.

The lactam (119) melted at 87-88°C and analysed correctly for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>, with a molecular ion at  $m/z$  210, confirming this as the molecular formula. The infrared spectrum showed a strong absorbance at 3271 cm<sup>-1</sup> assigned to the NH group, and two strong absorbances at 1740 and 1680 cm<sup>-1</sup> assigned to the ester and lactam carbonyl groups respectively. The <sup>1</sup>H N.M.R spectrum exhibited an upfield shift in the resonances assigned to the olefin from  $\delta_H$  8.01 in the Michael adduct (113) to  $\delta_H$  6.83 in the lactam (119), consistent with the replacement of the strongly electron withdrawing nitro group with an amide. A broad resonance at  $\delta_H$  7.36 was assigned to the secondary amide (NH). Moreover the presence of only one methoxy group at  $\delta_H$  3.74 suggested that cyclisation to the lactam (119) had occurred. The <sup>13</sup>C N.M.R spectrum was assigned on the basis of chemical shift with the aid of DEPT spectra. Resonances at  $\delta_C$  119.3 and  $\delta_C$  149.9 assigned to C-2' and C-1' in the Michael adduct (113) displayed an upfield shift resonating at  $\delta_C$  101.0 and  $\delta_C$  129.9 and assigned to C-3 and C-4 respectively in the lactam (119). The upfield shifts observed for these vinylic carbons once again is consistent with the replacement of the strongly electron withdrawing nitro group for a secondary amide.

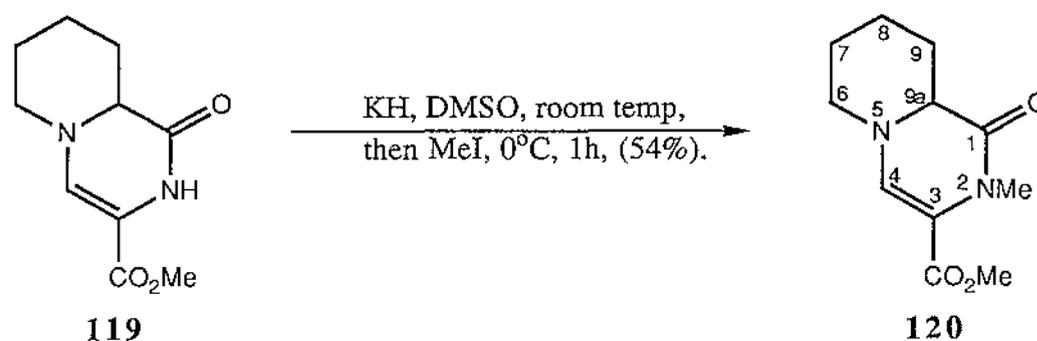
Table 2.

STARTING MATERIAL	REAGENTS and CONDITIONS	RESULT
 <p><b>113</b></p>	CoCl <sub>2</sub> (2.0 equiv.), NaBH <sub>4</sub> (5.0 equiv.), MeOH, room temperature, 0.5h <sup>50</sup> .	Baseline by t.l.c, difficult to isolate.
	LiBH <sub>4</sub> (3.0 equiv.), diglyme (4.0 ml/mmol substrate), MeOH (0.45 ml/mmol substrate), 0°C, 2h <sup>51</sup> .	Recovered starting material.
	NaBH <sub>4</sub> (2.5 equiv.)/Pd-C (4 mg/mmol substrate), THF (4 ml/mmol substrate), 0°C, 12h <sup>52</sup> .	
	Pd-C, H <sub>2</sub> , MeOH, room temp, 16h.	<b>119</b> (26%).
	Pd-C, H <sub>2</sub> , MeOH, room temp, 16h, then toluene, reflux, 2h.	<b>119</b> (33%).
	Raney Ni, H <sub>2</sub> , MeOH, room temp, 3.5h.	<b>119</b> (16%).
	NH <sub>4</sub> O <sub>2</sub> , CH (4.6 equiv.)/Pd-C, MeOH, room temp, Ar atmosphere <sup>53</sup> .	
	Ni <sub>2</sub> B/NaBH <sub>4</sub> , MeOH, room temp, 0.5h <sup>54</sup> .	
Mg/Hg/TiCl <sub>4</sub> , THF, <sup>t</sup> BuOH, 0°C, N <sub>2</sub> atmosphere, 1h <sup>48</sup> .	<b>119</b> (43%).	

With the secondary unsaturated lactam (119) in hand it was decided to effect *N*-methylation to the tertiary unsaturated lactam (120) as required for piperidinoperamine (101). Using dimethyl sulphoxide as solvent, sodium hydride (1.5 equiv.) was added to lactam (119) at room temperature, under a nitrogen atmosphere, followed by the addition of methyl iodide (1.0 equiv.) at 0°C affording the tertiary lactam (120) as a pale brown oil (54%) after purification by flash chromatography (Scheme 29).

The purified product was unstable, forming a dark oil on standing. The molecular ion at *m/z* 224.1158 in the high resolution mass spectrum supported the molecular formula C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>. The infrared spectrum exhibited two strong absorbances at 1750 and 1644 cm<sup>-1</sup> assigned to the ester and lactam carbonyl groups respectively, whilst the absence of an absorbance for an NH group suggested the formation of the tertiary amide. The <sup>1</sup>H N.M.R spectrum exhibited a three proton singlet at δ<sub>H</sub> 3.31 assigned to the *N*-methyl group, and a

three proton singlet at  $\delta_{\text{H}}$  3.67 assigned to the methoxy group. The  $^{13}\text{C}$  N.M.R spectrum exhibited a resonance at  $\delta_{\text{C}}$  31.7 (quartet) assigned to the N-methyl group supported the formation of the tertiary lactam (120).



**Scheme 29.**

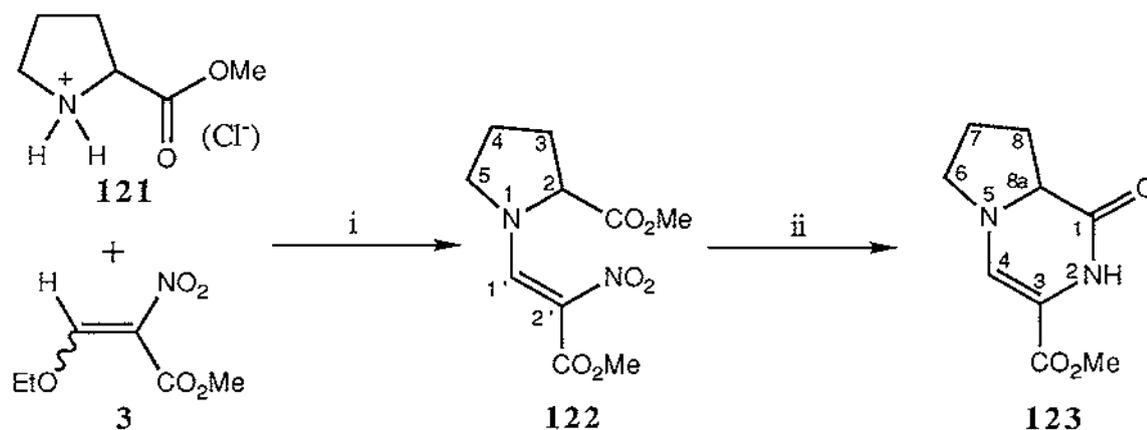
The synthesis of lactams (119) and (120) constitutes a synthesis of the ring systems present in piperidoperamine (101) and verruculotoxin (107). Future work could be directed to the conversion of lactams (119) and (120) to these synthetic targets. Work in this direction requires a method for the selective reduction of the ester to a primary alcohol, as the use of sodium borohydride (as used in the synthesis of peramine (1), (see page 3) was in this case unsuccessful.

### 2.3 Synthesis of the Tetrahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one Ring System.

Having successfully synthesized the hexahydropyrido[1,2-*a*]pyrazin-1(2*H*)-one ring system, attention shifted to the synthesis of the five membered ring analogue, namely the tetrahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one ring system using similar reaction conditions to those employed above (Scheme 30). Thus liberation of the free base of L-proline methyl ester hydrochloride (121) *in situ* by treatment with sodium acetate (2.0 equiv.) using methanol as solvent, followed by the addition of nitro-alkene (3) gave the Michael adduct (122) after aqueous workup and purification by flash chromatography in 98% yield as yellow prisms, m.p. 75-76°C.

The product analysed correctly for  $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_6$ , with a molecular ion at  $m/z$  258 supporting this molecular formula. The infrared spectrum exhibited two strong absorbances at 1744 and 1720  $\text{cm}^{-1}$  indicating the presence of two ester carbonyl groups, an absorbance at 1618  $\text{cm}^{-1}$  supporting the formation of an olefin, and an absorbance at 1565  $\text{cm}^{-1}$  due to the  $\text{NO}_2$  group. The  $^1\text{H}$  N.M.R spectrum exhibited a six proton singlet at  $\delta_{\text{H}}$  3.81 assigned to the two methoxy groups, and a one proton singlet at  $\delta_{\text{H}}$  8.29 assigned to 1'-H providing strong evidence for the formation of a nitro olefin. The  $^{13}\text{C}$

N.M.R spectrum exhibited resonances at  $\delta_C$  120.2 (singlet) and  $\delta_C$  147.3 (doublet) assigned to C-2' and C-1' respectively, again supporting the formation of a nitro olefin. The high field  $^1H$  and  $^{13}C$  N.M.R spectra suggested the formation of only one diastereomer from this reaction, which was assigned as the (*Z*)- isomer by virtue of the fact that subsequent reduction of the nitro group resulted in the formation of a lactam (123) (*vide supra*).



*Reagents and conditions:* (i) NaOAc (2.0 equiv.), MeOH, room temp, 0.75h, 98%  
(ii) Mg/Hg/TiCl<sub>4</sub>, THF/<sup>t</sup>BuOH (2:1), 0°C, 1h, 28%.

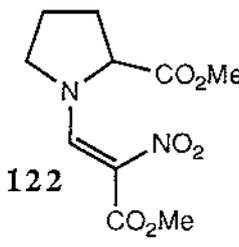
**Scheme 30.**

With the nitro-adduct (122) in hand, attention then focused on cyclisation of the nitro-adduct (122) to the lactam (123). Again a number of reagents and conditions were tried in an attempt to effect a facile reduction of the nitro group to an amine (Table 3), however the best conditions were once again those reported by George and Chandrasekaran<sup>48</sup>. Thus treatment of nitro-adduct (122) with amalgamated magnesium and titanium tetrachloride afforded the lactam (123) albeit only in 28% yield after purification by flash chromatography. The product was extremely unstable, darkening on standing within minutes of isolation.

Elemental analysis proved difficult to obtain for this compound, however the molecular ion at  $m/z$  196.0856 in the high resolution mass spectrum supported the molecular formula C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>6</sub>. The infrared spectrum showed a broad absorbance at 3430 cm<sup>-1</sup> assigned to the NH group, and two strong absorbances at 1739 and 1677 cm<sup>-1</sup> assigned to the ester and lactam carbonyl groups respectively. The  $^1H$  N.M.R spectrum exhibited an upfield shift in the resonances assigned to the olefin from  $\delta_H$  8.29 in the Michael adduct (122) to  $\delta_H$  7.08 in the lactam (123). This upfield shift is consistent with the absence of the deshielding effect of the nitro group, and with the upfield shifts observed upon reduction of Michael adduct (113) to form lactam (119) (see page 31). A broad one

proton singlet at  $\delta_{\text{H}}$  7.46 was assigned to the NH of the secondary amide confirming the formation of the lactam (123). The  $^{13}\text{C}$  N.M.R spectrum also exhibited upfield shifts from  $\delta_{\text{C}}$  120.2 and  $\delta_{\text{C}}$  147.3 assigned to the vinylic carbons C-2' and C-1' respectively in the Michael adduct (122) to  $\delta_{\text{C}}$  103.6 and  $\delta_{\text{C}}$  128.3 assigned to the vinylic carbons C-3 and C-4 in the lactam (123). This upfield shift is consistent with the absence of the deshielding effect of the nitro group upon formation of the lactam (123) as observed previously (see page 31). The apparent instability of lactam (123) together with the low yield in the reduction step hindered further work on this ring system.

**Table 3.**

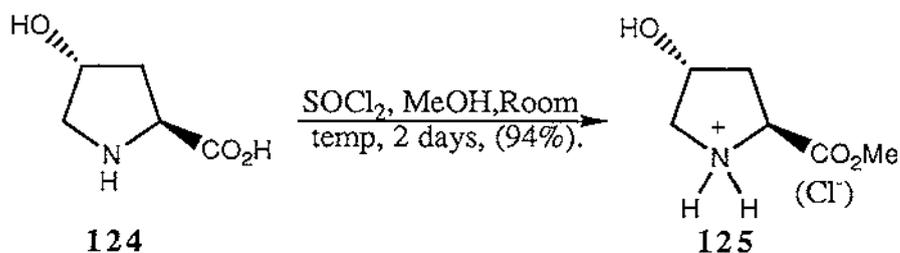
STARTING MATERIAL	REAGENTS and CONDITIONS	RESULT
 <p>122</p>	Zn/HCl, EtOH, reflux, 0.5h <sup>55</sup> .	Recovered starting material
	RuCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>3</sub> /H <sub>2</sub> , benzene/EtOH (1:1), room temp, 1h <sup>56</sup> .	Recovered starting material
	CrCl <sub>2</sub> , HCl (3%), THF, 3h <sup>57</sup> .	Recovered starting material
	Mg/Hg/TiCl <sub>4</sub> , THF, <sup>t</sup> BuOH, 0°C, N <sub>2</sub> atmosphere, 1h <sup>48</sup> .	<b>123</b> (28%).

#### 2.4 Synthesis of the (8a*S*,7*R*)-(-)-7-Acetoxytetrahydropyrrolo [1,2-*a*]pyrazin-1(2*H*)-one Ring System.

Having prepared the tetrahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one ring system albeit in low yield, attention then focused on the synthesis of the analogous hydroxytetrahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one ring system. It was envisaged that conditions used in the synthesis of the previous two ring systems could be employed in the present case. (2*S*,4*R*)-(-)-Methyl-4-hydroxypyrrolidine-2-carboxylate hydrochloride (125) was prepared by the esterification of (2*S*,4*R*)-(-)-4-hydroxy-2-pyrrolidine carboxylic acid (124) using thionyl chloride in methanol for two days according to the method of Yasutake *et al*<sup>41</sup> in 94% yield (Scheme 31). The melting point was in good agreement with the literature<sup>57</sup>.

Repeating the procedure used to obtain Michael adducts (113) and (123) from their respective amino acid esters (112) and (121) and nitro-alkene (3), this time using hydroxyproline methyl ester (125) afforded the Michael adduct (126) in 97% yield after purification by flash chromatography (Scheme 32). The product, yellow prisms, m.p. 81-83°C, was converted to its acetate derivative in 93% yield using acetic anhydride (1.5 equiv.), triethylamine (2.0 equiv.), 4-dimethylaminopyridine (catalytic) and

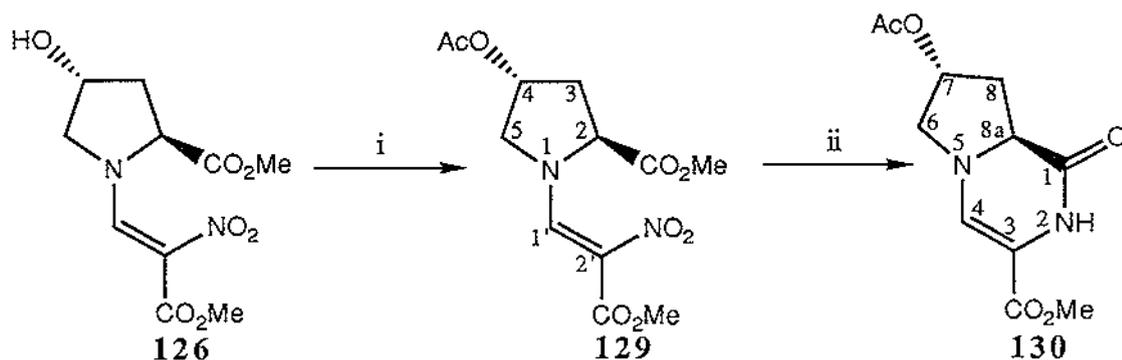
dichloromethane as solvent under a nitrogen atmosphere for one hour. The acetate (129) analysed correctly for  $C_{12}H_{16}N_2O_8$  with a molecular ion at  $m/z$  316 in the mass spectrum confirming this molecular formula. The infrared spectrum of the hydroxy adduct (126) exhibited a broad absorbance at  $3600-3200\text{ cm}^{-1}$  due to the hydroxy group, two strong absorbances at  $1743$  and  $1721\text{ cm}^{-1}$  assigned to the two ester carbonyl groups, and an absorbance at  $1616\text{ cm}^{-1}$  assigned to the nitro-olefin. These absorbances were in excellent agreement with those found in the previously synthesized Michael adducts (113) and (122). The  $^1\text{H}$  N.M.R spectrum of the hydroxy adduct (126) exhibited a two proton multiplet at  $\delta_{\text{H}}$  5.09 to 5.16 assigned to 4-H and the hydroxyl proton, and a broad one proton singlet at  $\delta_{\text{H}}$  8.36 assigned to the vinylic proton 1'-H, characteristic for the formation of a nitro-olefin. The  $^{13}\text{C}$  N.M.R spectrum of the hydroxy adduct exhibited resonances at  $\delta_{\text{C}}$  119.5 and  $\delta_{\text{C}}$  147.8 consistent with the shifts observed for the vinylic carbons C-2' and C-1' in the Michael adducts (113) and (122) (see pages 27 and 33). The high field  $^1\text{H}$  and  $^{13}\text{C}$  N.M.R spectra again suggested the formation of only one diastereomer from this reaction, which was assigned to the (Z)- isomer by virtue of the fact that subsequent reduction of the nitro group of acetate (129) resulted in the formation of a lactam (130). This stereochemistry is consistent with that observed on formation of the Michael adducts (113) and (122).



Scheme 31.

Having successfully prepared the Michael adduct (126), its reduction to the corresponding lactam (128) was investigated. Using methanol as solvent, Michael adduct (126) was reduced under a hydrogen atmosphere using palladium on charcoal (5%) as catalyst. Thin layer chromatographic analysis (t.l.c) suggested that the Michael adduct had undergone hydrogenolysis to give *trans*-hydroxyproline-2-carboxylate (127) (Scheme 32). This was confirmed by isolation of the ester (127) and analysis by  $^1\text{H}$  N.M.R spectroscopy and mass spectrometry.





*Reagents and conditions:* (i) Et<sub>3</sub>N, (CH<sub>3</sub>CO)<sub>2</sub>O, DMAP (catalytic), CH<sub>2</sub>Cl<sub>2</sub>, nitrogen atmosphere, room temp (93%); (ii) H<sub>2</sub>, Pd/C (5%), room temp, 16h, (71%).

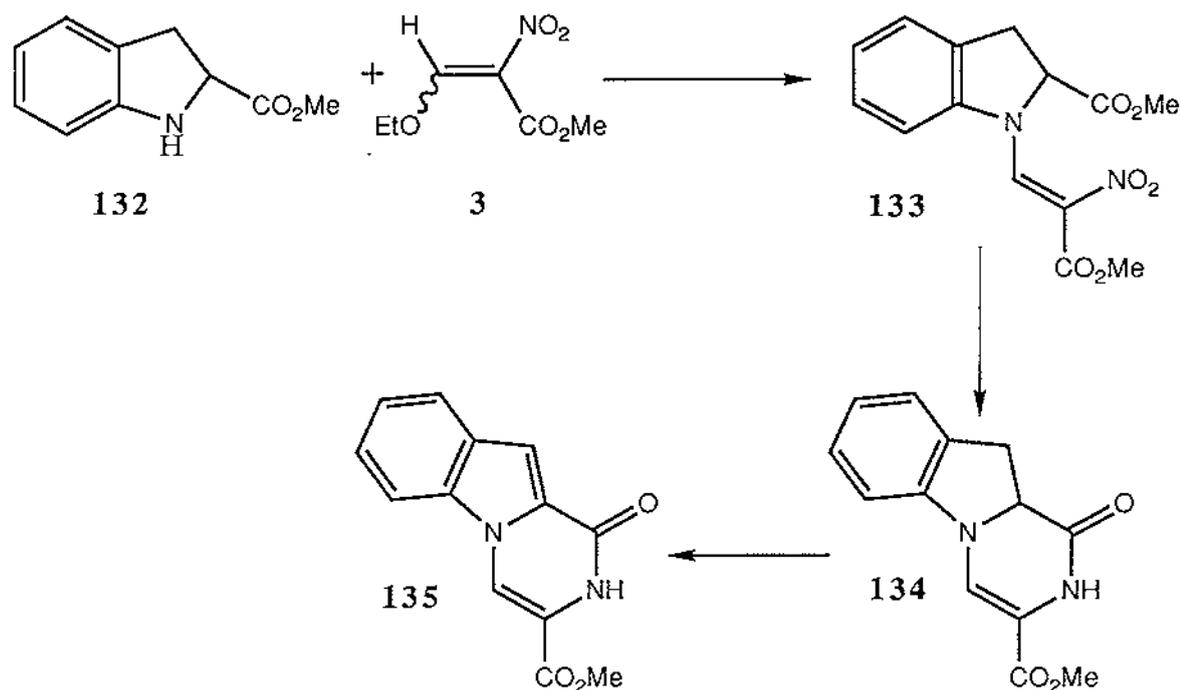
**Scheme 33.**

The acetoxylactam (130) was prepared in 71% yield after purification by flash chromatography as a pale yellow oil. The product was somewhat unstable, darkening on standing within twenty four hours of isolation. Elemental analysis proved difficult to obtain for this compound, however the molecular ion at  $m/z$  254.0897 in the high resolution mass spectrum supported the molecular formula C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub>. The infrared spectrum showed two strong absorbances at 1737 and 1683 cm<sup>-1</sup> assigned to the ester and lactam carbonyl groups respectively, and an absorbance at 1636 cm<sup>-1</sup> assigned to the olefin. The <sup>1</sup>H N.M.R spectrum exhibited a three proton singlet at  $\delta_H$  2.06 assigned to the acetoxy group, a three proton singlet at  $\delta_H$  3.75 assigned to the methoxy group, and a one proton multiplet at  $\delta_H$  5.22-5.32 assigned to 7-H. An upfield shift in the resonance assigned to the olefin from  $\delta_H$  8.37 in the Michael adduct (129) to  $\delta_H$  7.09 in the lactam (130) was again consistent with the upfield shifts observed previously upon formation of the lactams (119) and (123). The <sup>13</sup>C N.M.R spectrum exhibited a resonance at  $\delta_C$  20.9 (quartet) assigned to the methyl group of the acetate, a resonance at  $\delta_C$  52.1 (quartet) assigned to the methoxy group of the C-3 ester and three resonances at  $\delta_C$  165.1, 170.4, and 174.4 (singlets) assigned to the C-1, ester, and acetate carbonyl carbons respectively. Upfield shifts from  $\delta_C$  121.2 and  $\delta_C$  147.4 assigned to C-2' and C-1' respectively in the Michael adduct (129) to  $\delta_C$  103.2 and  $\delta_C$  127.1, assigned to C-3 and C-4 respectively in the lactam (130), were also consistent with the upfield shifts observed previously upon formation of the lactams (119) and (123) (see pages 31 and 34).

Having successfully synthesized the 7-Acetoxypyrrolidopyrazin-1(2H)-one ring system, attention then focused on the original aim of construction of the Indolo[1,2-*a*]pyrazin-1(2H)-one ring system present in Indoloperamine (104).

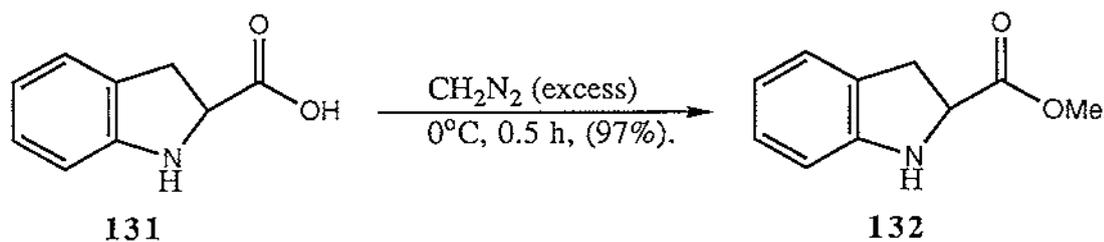
## 2.5 Synthesis of the 10-10a-Dihydroindolino[1,2-*a*]pyrazin-1(2*H*)-one and Indolo[1,2-*a*]pyrazin-1(2*H*)-one Ring Systems.

With the successful synthesis of the saturated five membered tetrahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one and saturated six membered hexahydropyrido[1,2-*a*]pyrazin-1(2*H*)-one ring systems in place using heterocyclic amines as nucleophiles for the key Michael addition, a new approach to the indolo[1,2-*a*]pyrazin-1(2*H*)-one ring system was postulated. This involved the use of methyl indoline-2-carboxylate (132) as a nucleophile for the key Michael addition step, followed by cyclisation to the indolinolactam (134) and subsequent aromatisation to give the indolinolactam (135) (Scheme 34). This would provide the 10,10a-dihydroindolinolactam (134) and a fully aromatic analogue (135) for biological testing in the insect antifeedant assays developed for peramine (1).

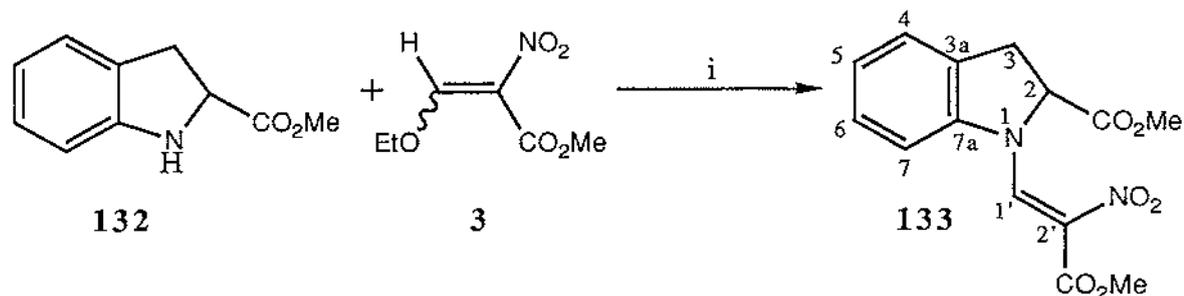


Scheme 34.

Methyl indoline-2-carboxylate (132) was prepared by the esterification of D,L-indoline-2-carboxylic acid (131) with ethereal diazomethane (excess) as a pale orange oil in 97% yield after purification by flash chromatography (Scheme 35). Having successfully prepared methyl ester (132), its subsequent reaction with nitro-alkene (3) was investigated. Using methanol as solvent, nitro-alkene (3) (1.0 equiv.) was added to a solution of the methyl ester (132) followed by stirring at room temperature for 0.5 hours to afford the Michael adduct (133) in 50% yield as pale yellow needles (Scheme 36).



Scheme 35.



*Reagents and conditions:* (i) NaOAc (2.0 equiv.), MeOH, room temp, 0.5h, (50%).

Scheme 36.

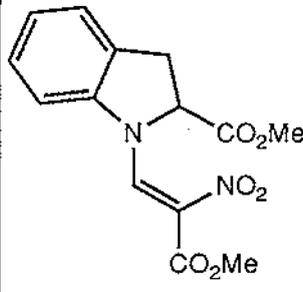
The product analysed correctly for  $C_{14}H_{14}N_2O_5$  with a molecular ion at  $m/z$  306 in the mass spectrum supporting this molecular formula. The infrared spectrum exhibited two strong absorbances at 1755 and 1709  $cm^{-1}$  assigned to the two ester carbonyl groups, an absorbance at 1627  $cm^{-1}$  supporting the formation of an olefin, and an absorbance at 1588  $cm^{-1}$  due to the nitro group. The  $^1H$  N.M.R spectrum exhibited three one proton double doublets at  $\delta_H$  3.34,  $\delta_H$  3.69 and  $\delta_H$  5.22 assigned to 3-H, 3-H', and 2-H respectively. This ABX system supported saturation at C-2 and C-3. Two three proton singlets at  $\delta_H$  3.74 and  $\delta_H$  3.87 indicated the presence of two methoxy groups, and a one proton singlet at  $\delta_H$  8.83 assigned to 1'-H provided strong evidence for the formation of a nitro olefin. The  $^{13}C$  N.M.R spectrum exhibited resonances at  $\delta_C$  34.0 (triplet), and  $\delta_C$  62.1 (doublet) assigned to C-3 and C-2 respectively once again supporting saturation between C-2 and C-3. Resonances at  $\delta_C$  53.1 and  $\delta_C$  53.2 were assigned to the two methoxy groups, and resonances at  $\delta_C$  127.8 and  $\delta_C$  138.4 assigned to C-2' and C-1' respectively, again supporting the formation of a nitro olefin.

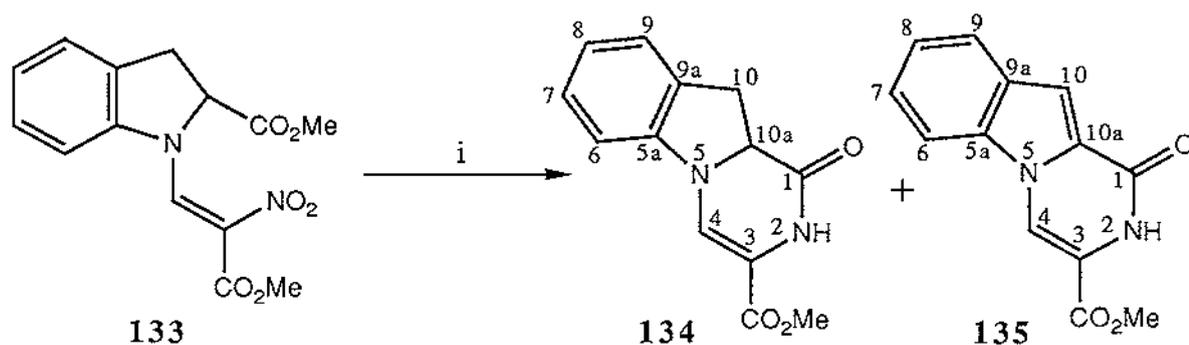
The high field  $^1H$  and  $^{13}C$  N.M.R spectra suggested the formation of only one diastereomer from this reaction, which was assigned as the (Z)- isomer, again by virtue of the fact that subsequent reduction of the nitro group resulted in formation of a lactam (134). This stereochemistry is again consistent with that observed upon formation of the Michael adducts (113), (122), and (126) (see pages 27, 33, and 35).

Having successfully prepared the Michael adduct (133), its reduction and cyclisation to the lactam (134) was investigated. Using methanol as solvent, Michael

adduct (133) was reduced under a hydrogen atmosphere using palladium on charcoal (5%) as catalyst. Thin layer chromatographic analysis (t.l.c) showed a complex mixture of products that could not be isolated upon attempted purification. A number of reagents and conditions were evaluated in an attempt to effect a facile reduction of the nitro group to an amine (Table 4), however, the best conditions were again those reported by George and Chandrasekaran<sup>48</sup> (Scheme 37).

Table 4.

STARTING MATERIAL	REAGENTS and CONDITIONS	RESULT
	Pd-C, H <sub>2</sub> , room temp, 16h	Complex mixture of products.
	NaBH <sub>4</sub> (5.0 equiv.), CoCl <sub>2</sub> , (2.0 equiv.), MeOH, room temp, 16h <sup>50</sup> .	<b>134</b> (9%).
	CrCl <sub>2</sub> , HCl (3%), THF, 3h <sup>57</sup> .	<b>134</b> (20%).
	Mg/Hg/TiCl <sub>4</sub> , THF, <sup>t</sup> BuOH, 0°C, N <sub>2</sub> atmosphere, 1h <sup>48</sup> .	<b>134</b> (38%), <b>135</b> (10%).



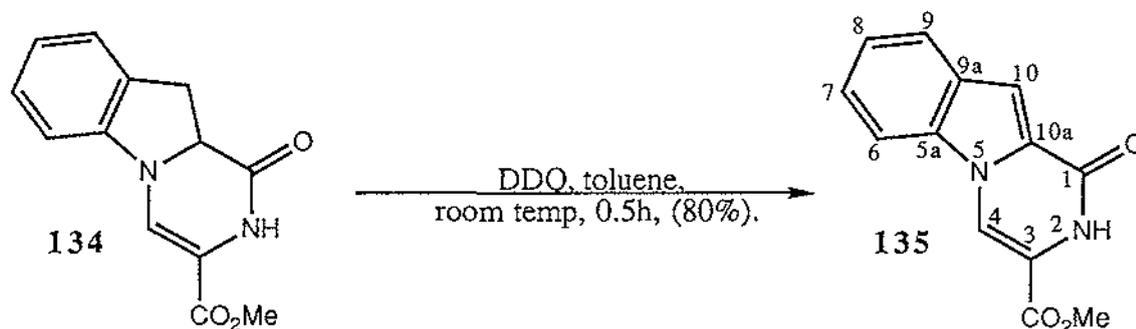
Reagents and conditions: (i) Mg/Hg/TiCl<sub>4</sub>, THF/ <sup>t</sup>BuOH (2:1), 0°C, N<sub>2</sub> atmosphere, 1h, **134** (38%), **135** (10%).

Scheme 37.

Thus, treatment of nitro-adduct (133) with amalgamated magnesium and titanium tetrachloride afforded a 4:1 mixture of lactam (134) and (135) respectively, in 48% overall yield, that were easily separated and purified by flash chromatography (Scheme 37). Analytical figures were difficult to obtain for lactam (134) as it slowly aromatised on standing to lactam (135), however the molecular ion at *m/z* 244.0895 in the high resolution mass spectrum supported the molecular formula C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>.

The  $^1\text{H}$  N.M.R spectrum for lactam (134) exhibited a two proton doublet at  $\delta_{\text{H}}$  3.24 and a one proton triplet at  $\delta_{\text{H}}$  4.57 assigned to 10-H, 10-H', and 10a-H respectively supporting saturation at C-10 and C-10a. An upfield shift from  $\delta_{\text{H}}$  8.83 assigned to the vinylic proton 1'-H in the Michael adduct (133) to  $\delta_{\text{H}}$  7.79 assigned to 4-H in the lactam (134) was again consistent with the upfield shifts observed previously upon reduction of the nitro group to form a lactam. Moreover, the presence of only one methoxy group at  $\delta_{\text{H}}$  3.72 (singlet, three protons), together with a resonance at  $\delta_{\text{H}}$  9.48 assigned to the NH of the secondary amide, suggested the formation of a lactam. The  $^{13}\text{C}$  N.M.R spectrum was assigned on the basis of chemical shifts with the aid of DEPT spectra. Resonances at  $\delta_{\text{C}}$  30.1 (triplet), and  $\delta_{\text{C}}$  59.6 (doublet) assigned to C-10 and C-10a respectively once again supported saturation at C-10 and C-10a. An upfield shift from  $\delta_{\text{C}}$  128.7 and  $\delta_{\text{C}}$  138.4 assigned to vinylic carbons C-2' and C-1' in the Michael adduct (133) to  $\delta_{\text{C}}$  108.1 and  $\delta_{\text{C}}$  108.9 assigned to vinylic carbons C-3 and C-4 respectively in the lactam (134) is again consistent with the replacement of the strongly electron withdrawing nitro group for a secondary amide, as observed previously (see pages 31, 34, and 38).

Having successfully prepared indolinolactam (134) its subsequent aromatisation to the indololactam (135) was investigated. Using toluene as solvent, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.0 equiv.) was added to a solution of 10,10a-dihydroindolinolactam (134) at room temperature to give the aromatic indololactam (135) in 80% yield as colourless needles after purification by flash chromatography (Scheme 38).



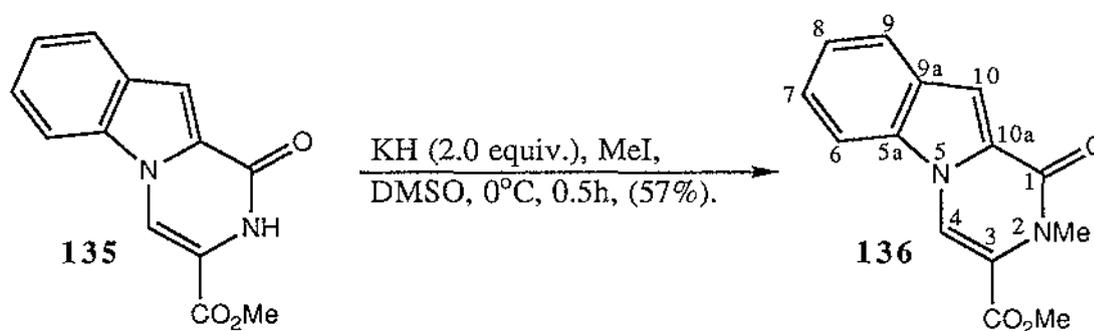
Scheme 38.

The product analysed correctly for  $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_3$  with a molecular ion at  $m/z$  242 in the mass spectrum supporting this molecular formula. The infrared spectrum exhibited absorbances at  $3187\text{ cm}^{-1}$  assigned to the NH group, and absorbances at  $1718$ , and  $1660\text{ cm}^{-1}$  assigned to the ester and lactam carbonyl groups respectively.

The  $^1\text{H}$  N.M.R spectrum exhibited a downfield shift from a two proton doublet at  $\delta_{\text{H}}$  3.24 assigned to 10-H and 10'-H in the 10-10a saturated lactam (134) to a one proton singlet at  $\delta_{\text{H}}$  7.53 assigned to 10-H in the 10-10a unsaturated lactam (135), supporting aromatisation at C-10 and C-10a. The  $^{13}\text{C}$  N.M.R spectrum also exhibited downfield

shifts from  $\delta_{\text{C}}$  30.1 and  $\delta_{\text{C}}$  59.6 assigned to C-10 and C-10a respectively in the indolino lactam (134) to  $\delta_{\text{C}}$  123.9 and  $\delta_{\text{C}}$  133.4 assigned to C-10 and C-10a respectively in the indolo lactam (135), supporting aromatisation at C-10 and C-10a.

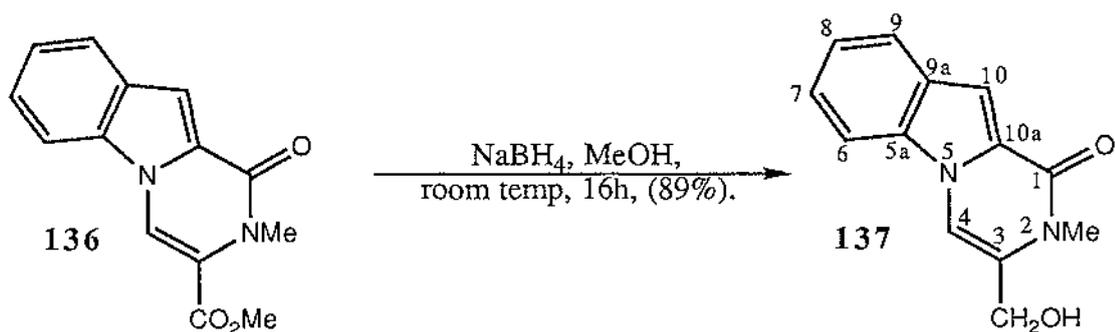
With the indolo[1,2-*a*]pyrazin-1(2*H*)-one ring system in hand, it was decided to effect N-methylation to the tertiary unsaturated lactam (136) as required for indoloperamine (104). Using dimethyl sulphoxide as solvent, potassium hydride (2.0 equiv.) was added to lactam (135) at room temperature under a nitrogen atmosphere, followed by the addition of methyl iodide (1.5 equiv.) at 0°C affording the tertiary lactam (136) as colourless needles (57%) after purification by flash chromatography (Scheme 39).



**Scheme 39.**

The product melted at 173-174 °C and analysed correctly for C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub> with a molecular ion at *m/z* 256 in the mass spectrum supporting this molecular formula. The infrared spectrum exhibited two strong absorbances at 1719 and 1651 cm<sup>-1</sup> assigned to the ester and lactam carbonyl groups respectively which were consistent with those found for peramine (1). Moreover the absence of an absorbance for an NH group suggested the formation of a tertiary amide. The <sup>1</sup>H N.M.R spectrum exhibited a three proton singlet at  $\delta_{\text{H}}$  3.39 assigned to the N-methyl group, and a three proton singlet at  $\delta_{\text{H}}$  3.88 assigned to the C-3 methoxy group, again consistent with those found for peramine (1). The <sup>13</sup>C N.M.R spectrum exhibited a resonance at  $\delta_{\text{C}}$  31.7 (quartet) assigned to the N-methyl group, supporting the formation of a tertiary amide. These resonances were in excellent agreement with those found for peramine (1).

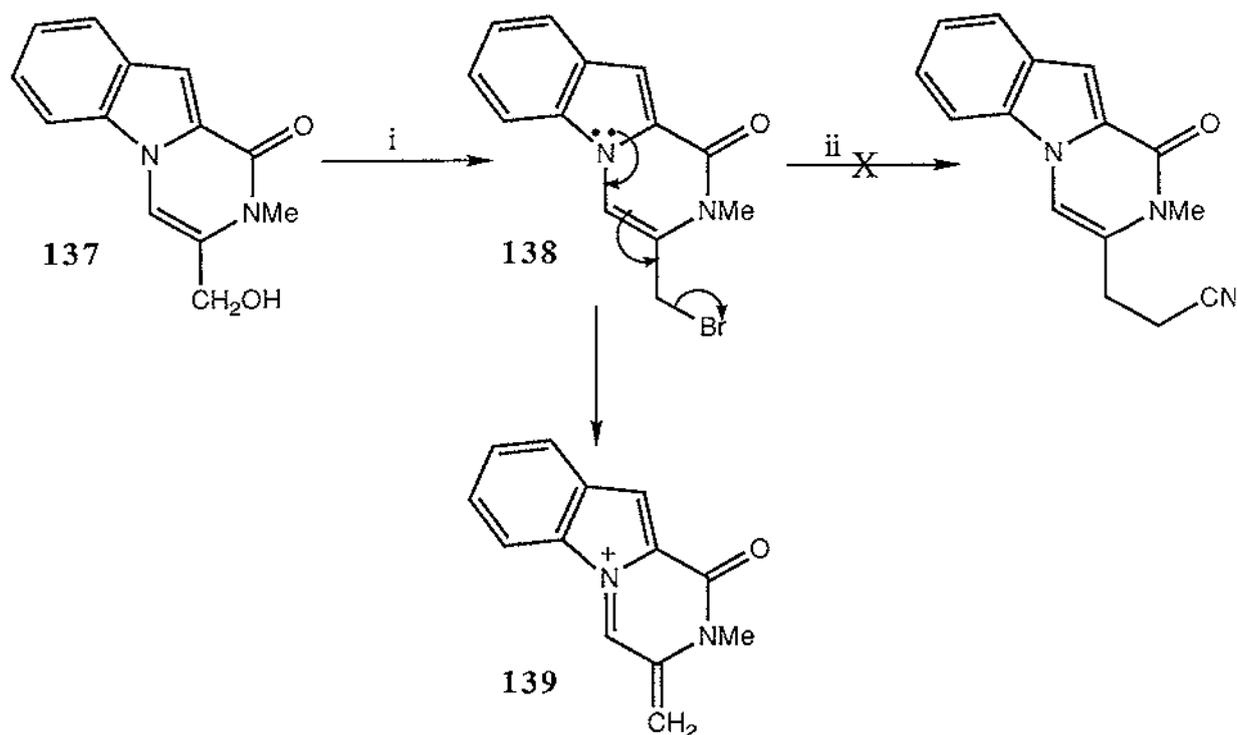
With the successful synthesis of the 3-methoxycarbonyl-2-methylindolo[1,2-*a*]pyrazin-1(2*H*)-one (136) ring system, it was envisaged that the synthetic methodology developed for the elaboration of the C-3 methoxycarbonyl group to the n-propylguanidino group as reported by Brimble *et al*<sup>3</sup> could be applied to the present work. The desired oxidation level was achieved by reduction of the ester (136) to the alcohol (137) in 89% yield using sodium borohydride in methanol as solvent to afford the alcohol (137) as colourless needles m.p. 190-191°C after purification by flash chromatography (Scheme 40).



**Scheme 40.**

The product analysed correctly for  $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2$  with a molecular ion at  $m/z$  228 in the mass spectrum supporting this molecular formula. The infrared spectrum exhibited an absorbance at  $3332\text{ cm}^{-1}$  assigned to the alcohol group, and a strong absorbance at  $1623\text{ cm}^{-1}$  assigned to the ester carbonyl group. The  $^1\text{H}$  N.M.R spectrum exhibited a two proton doublet at  $\delta_{\text{H}}$  4.47 assigned to  $\text{CH}_2\text{OH}$ , in excellent agreement with that found for peramine (1), and a broad one proton triplet at  $\delta_{\text{H}}$  5.51 (exchangeable with  $\text{D}_2\text{O}$ ) assigned to the alcohol proton. The  $^{13}\text{C}$  N.M.R spectrum exhibited a resonance at  $\delta_{\text{C}}$  58.8 (triplet) assigned to the  $\text{CH}_2\text{OH}$  supporting the formation of the alcohol (137). Extension of the sidechain then required conversion of the alcohol (137) into a suitable leaving group. The bromide (138) was generated *in situ* from the alcohol (137) with methanesulphonyl chloride and triethylamine using tetrahydrofuran as solvent at  $-60^\circ\text{C}$ , followed by displacement of the mesylate with excess lithium bromide at  $-60$  to  $-40^\circ\text{C}$ . The bromide (138) was subjected to aqueous workup to remove any salts present, and quickly added to a solution of cyanomethylcuprate at  $-40$  to  $-20^\circ\text{C}$  in tetrahydrofuran. The cyanomethylcuprate was generated by the addition of the corresponding organolithium reagent to copper(I) dimethylsulphide complex (Scheme 41).

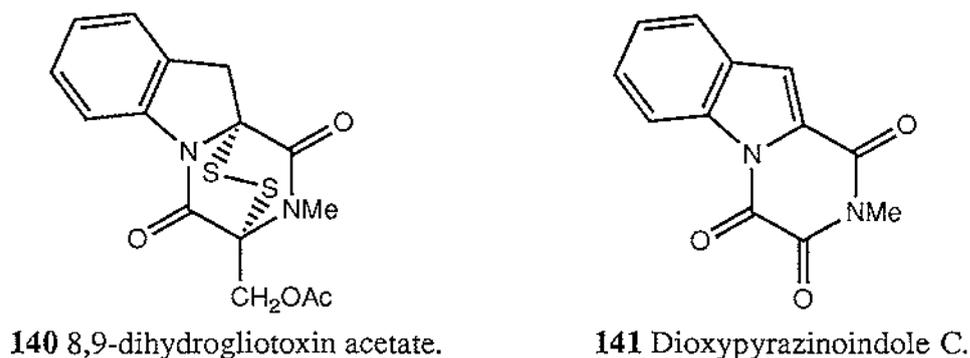
Thin layer chromatographic analysis showed baseline material that was difficult to isolate. The failure of this reaction was attributed to the bromide being too unstable to withstand the necessary workup, and undergoing intramolecular rearrangement, with displacement of the bromide. Subsequent thin layer chromatographic analysis of the bromide (138) after workup showed baseline material that was difficult to isolate, supporting the formation of the salt (139).



*Reagents and conditions:* (i) MsCl (1.1 equiv.), Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -60°C, 0.25h, then LiBr (3.0 equiv.), THF, -60 to -40°C, 0.5h; (ii) MeCN (5.0 equiv.), <sup>n</sup>BuLi (5.1 equiv.), 0.5h, -78°C, then CuBr.Me<sub>2</sub>S (5.2 equiv.), -78° to -40°C, 0.5h, then 138 (1.0 equiv.), -40 to -20°C, 1h.

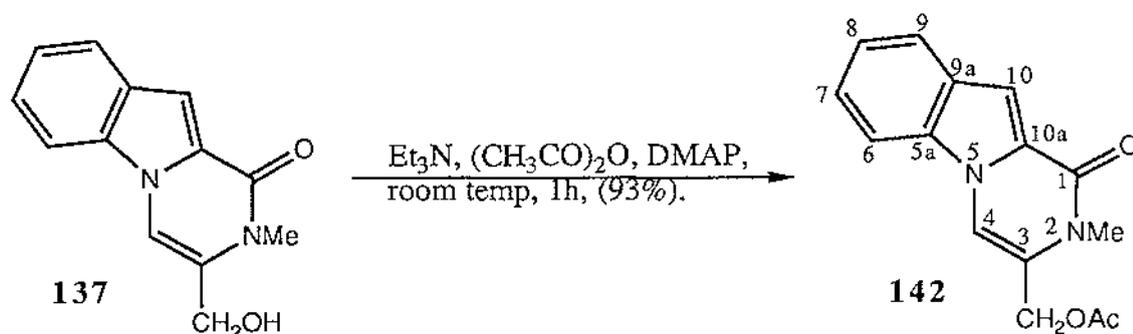
**Scheme 41.**

Disappointed by the inability to effect extension of the C-3 sidechain to the nitrile, attention then focused on the synthesis of 8,9-dihydrogliotoxin acetate (140) analogues, and dioxypyrazinoindole-C (141).



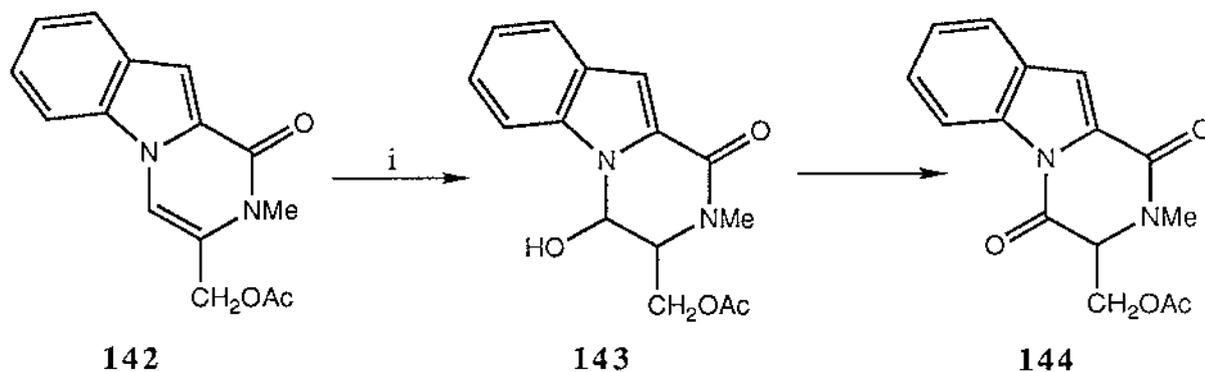
Thus the alcohol (137) was converted to the acetate derivative (142) in 85% yield using acetic anhydride (1.5 equiv.), triethylamine (2.0 equiv.), 4-dimethylaminopyridine

(catalytic), and dichloromethane as solvent, under a nitrogen atmosphere for 1hr (Scheme 42).



**Scheme 42**

The molecular ion at  $m/z$  270.1000 in the high resolution mass spectrum supported the molecular formula  $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$ . The  $^1\text{H}$  N.M.R spectrum exhibited a three proton singlet at  $\delta_{\text{H}}$  assigned to  $\text{COCH}_3$ , and a two proton singlet at  $\delta_{\text{H}}$  5.06 assigned to  $\text{CH}_2\text{OAc}$ , supporting the formation of the acetate (142). The  $^{13}\text{C}$  N.M.R spectrum exhibited resonances at  $\delta_{\text{C}}$  21.0 (quartet) assigned to  $\text{COCH}_3$  and at  $\delta_{\text{C}}$  61.7 (triplet) assigned to  $\text{CH}_2\text{OAc}$  again supporting the formation of the acetate derivative (142). With the acetate (142) in hand, attention shifted to elaboration of the C-4 alkene to a carbonyl group *via* the alcohol (143) as required for the 8,9-dihydrogliotoxin acetate analogue (144) (Scheme 43). Treatment of the acetate (142) with borane methyl sulphide complex using THF as solvent however, afforded only starting materials.



*Reagents and conditions:* (i)  $(\text{CH}_3)_2\text{S}\cdot\text{BH}_3$ , THF,  $0^\circ\text{C}$ , Ar atmosphere, 2.5h.

**Scheme 43.**

### **Summary.**

The present work constitutes a synthesis of the ring systems present in the peramine (1) analogues piperidinoperamine (101), prolylperamine (102), acetoxypolyperamine (142), indoloperamine (104), and indolinoperamine (105). Future work may be directed toward elaboration of the C-3 methoxycarbonyl group to the guanidino sidechain to afford the analogues of the natural product peramine (1).

## Chapter 3.

### EXPERIMENTAL

#### *General Details.*

Melting points were determined using a Kofler hot stage apparatus and are uncorrected.

Infrared spectra were recorded using a BIO-RAD FTS-7 or a BIO-RAD FTS-40 spectrophotometer as nujol mulls or thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers ( $\text{cm}^{-1}$ ) with the following abbreviations: s = strong, m = medium, w = weak, and br = broad.

$^1\text{H}$  nuclear magnetic resonance spectra were obtained at 270 MHz using a JOEL GX270 spectrometer.  $^1\text{H}$  nuclear magnetic resonance data are expressed in parts per million downfield from tetramethylsilane as an internal reference and are reported as position ( $\delta_{\text{H}}$ ), relative integral, multiplicity (s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, t = triplet, q = quartet, m = multiplet.), coupling constant ( $J$  Hz), and assignment.

$^{13}\text{C}$  nuclear magnetic resonance spectra were obtained at 67.8 MHz using a JOEL GX270 spectrometer.  $^{13}\text{C}$  nuclear magnetic resonance data are expressed in parts per million downfield from tetramethylsilane as an internal reference and are reported as position ( $\delta_{\text{C}}$ ), multiplicity in the single off resonance decoupled spectrum and assignment.

Mass spectra were recorded using a Varian VG70-250S double focusing magnetic sector mass spectrometer with an ionisation potential of 70eV. Major fragments are given as percentages relative to the base peak intensity.

Elemental Analyses were performed at the microanalytical laboratory, University of Otago, Dunedin.

Flash chromatography was performed according to the procedure of Still *et al*<sup>60</sup> using Merck Kieselgel 60 (230-400 mesh) with the indicated solvents.

Thin layer chromatography was performed using precoated silica gel plates (Merck

Kieselgel 60F<sub>254</sub>) and compounds were visualised by ultra-violet fluorescence, ninhydrin, iodine, or vanillin in methanolic sulphuric acid.

Solvents were dried and purified according to the methods of Perrin, Perrin and Amarego<sup>61</sup>.

***Methyl-2-nitro-3-ethoxyacrylate (3).***

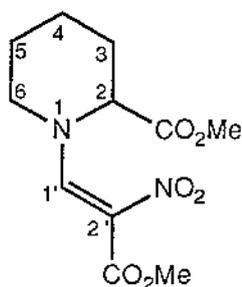
The *title compound* (3) was prepared from methyl nitroacetate<sup>58</sup>, triethylorthoformate and acetic anhydride according to the method of Kamlet<sup>59</sup> as a colourless liquid, b.p 119-121 °C / 1.0 mm Hg (lit<sup>59</sup>. b.p 119-121°C / 1.0 mm Hg).

***Methyl piperidine-2-carboxylate hydrochloride (112).***

The *title compound* (112) was prepared from 2-piperidine-carboxylic acid (111) (15.0 g, 105 mmol) and thionyl chloride (10 ml, 329 mmol), according to the method of Yasutake and co-workers<sup>41</sup> as a white crystalline solid (18.6 g, 91 %), m.p 214-218°C (lit<sup>42</sup> m.p 213-215°C).

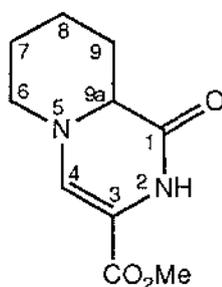
***(Z)-Methyl-1-(2'-methoxycarbonyl-2'-nitroethenyl)piperidine-2-carboxylate (113).***

To a solution of Methyl-piperidine-2-carboxylate hydrochloride (112) (5.0 g, 28 mmol) and sodium acetate (7.6 g, 56 mmol) in methanol (150 ml), was added a solution of the acrylate (3) (4.9 g, 56 mmol) in methanol (10 ml). The solution was stirred at room temperature for 0.75 h and the methanol removed at reduced pressure. The resultant yellow suspension was dissolved in ethyl acetate (100 ml), washed with water (3 x 25 ml), and dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of the solvent at reduced pressure afforded a yellow solid that was triturated with diethyl ether to give the *title compound* (113) (6.43 g, 85%) as yellow prisms. m.p. 96.5-97.5 °C. (Found: C, 48.3; H, 5.7; N, 10.3. C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O<sub>6</sub> requires: C, 48.5; H, 5.9; N, 10.3%).  $\nu_{\max}$  (Nujol) / cm<sup>-1</sup> 1742, 1724 (s, C=O) and 1619 (m, C=C);  $\delta_{\text{H}}$  (270 Mhz; CDCl<sub>3</sub>), 1.24-2.39 (6H, m, 3 x CH<sub>2</sub>), 3.32-3.91 (2H, m, CH<sub>2</sub>N), 3.81 (6H, s, 2 x CO<sub>2</sub>Me), 4.23 (1H, d, *J*, 5.2 Hz, CHN), 8.01 (1H, s, HC=C),  $\delta_{\text{C}}$  (67.8 MHz; CDCl<sub>3</sub>) 19.2, 24.7, 27.4 (t, C-3, C-4, C-5), 52.5 (q, OMe), 52.5 (d, C-2), 52.6 (t, C-6), 119.3 (s, C-2'), 149.9 (d, C-1'), and 162.9, 169.5 (s, 2 x CO<sub>2</sub>Me); *m/z* 272 (M<sup>+</sup>, 12%), 22.6 (M-NO<sub>2</sub>, 4), 213 (M-CO<sub>2</sub>Me, 100), 137 (24), and 85 (43).



**3-Methoxycarbonyl-5,6,7,8,9,9a-tetrahydropyrido[1,2-a]pyrazin-1-(2H)-one. (119).**

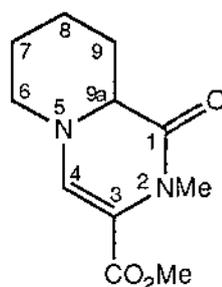
To a suspension of mercuric chloride (165 mg, 0.61 mmol) in dry tetrahydrofuran (8 ml), under nitrogen, was added magnesium powder (36 mesh, 268 mg, 11.04 mmol), and the reaction mixture stirred at room temperature for 0.15h. The turbid supernatant liquid was withdrawn by syringe and the amalgam washed with dry tetrahydrofuran (3 x 10ml). The amalgam was then suspended in dry tetrahydrofuran (16 ml), cooled to -10°C and titanium tetrachloride (1.05 g, 5.53 mmol) added slowly in one portion. To this was added a solution of (Z)-Methyl-1-(2'-methoxycarbonyl-2'-nitroethenyl)piperidine-2-carboxylate (113) (500 mg, 1.84 mmol) in dry tetrahydrofuran / t-butanol (2:1) (12 ml) and the reaction mixture stirred for 1 h at 0 °C. The reaction mixture was quenched with water (5 ml), diluted with diethyl ether (50 ml) and dried (Na<sub>2</sub>SO<sub>4</sub>). After filtration through a short pad of celite the solvent was removed at reduced pressure. The resultant black oil was purified by flash chromatography using hexane-ethyl acetate (1:2) as eluent affording the *title compound* (119) (177 mg, 46%) as an orange oil, which upon trituration using diethyl ether gave colourless needles, m.p. 87-88 °C (Found: C, 56.9; H, 6.4; N, 13.3, C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> requires: C, 57.1; H,6.7; N, 13.3%);  $\nu_{\max}$  (thin film) /cm<sup>-1</sup> 3271 (m, NH), 1740 (s, C=O, ester), and 1680 (s, C=O lactam);  $\delta_{\text{H}}$  (270 MHz, CDCl<sub>3</sub>) 1.51-2.25 (6H, m, 3 x CH<sub>2</sub>), 3.09-3.15 (1H, m, 6-H), 3.37-3.43 (1H, m, 6-H'), 3.74 (3H, s, OMe), 3.74-3.81 (1H, m, CHN), 6.83 (1H, s, HC=C), and 7.36 (1H, br s, NH);  $\delta_{\text{C}}$  (67.8 MHz, CDCl<sub>3</sub>) 24.1, 25.0, 27.7 (t, C-7, C-8, C-9), 51.3 (q, OMe), 53.2 (t, C-6), 59.1 (d, C-9a), 101.0 (s, C-3), 129.9 (d, C-4), and 162.6, 162.9 (s, C-1, C=O ester); *m/z* 210 (M<sup>+</sup>, 100%), 179 (M-OCH<sub>3</sub>, 15), and 123 (4).



**3-methoxycarbonyl-2-methyl-5,6,7,8,9,9a-hexahydropyrido[1,2-a]pyrazin-1-(2H)-one. (120).**

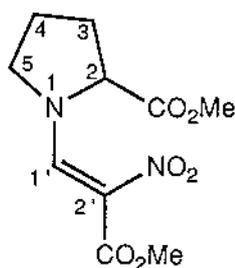
To a stirred solution of lactam (119) (104 mg, 0.50 mmol) in dry dimethyl sulphoxide (2 ml), under nitrogen was added sodium hydride (18 mg, 0.74 mmol). The resultant suspension was stirred for 0.5 h, cooled to 0 °C, then methyl iodide (71 mg, 0.50 mmol) added and the suspension disappeared. The resultant solution was stirred for a further 0.5 h, then aqueous sodium dihydrogen phosphate (1 ml) added, followed by 2M HCl (1 ml). The mixture was extracted with ethyl acetate (3 x 30 ml), washed with water (2 x 10 ml),

and dried ( $\text{Na}_2\text{SO}_4$ ). Removal of the solvent at reduced pressure afforded a brown oil, that was purified by flash chromatography using hexane-ethyl acetate (1:2) as eluent to give the *title compound* (120) as a pale brown oil. (Found  $M^+$ , 224.1158.  $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_3$  requires  $M$  224.1161);  $\nu_{\text{max}}$  (thin film) /  $\text{cm}^{-1}$  1750 (s, C=O, ester), and 1664 (s, C=O, lactam);  $\delta_{\text{H}}$  (270 MHz,  $\text{CDCl}_3$ ) 1.24-2.18 (6H, m, 3 x  $\text{CH}_2$ ), 2.19-3.11 (1H, m, 6-H), 3.32-3.42 (1H, m, 6-H'), 3.31 (3H, s, NMe), 3.67 (3H, s, OMe), 3.62-3.88 (1H, m, CHN), and 7.02 (1H, s, HC=C);  $\delta_{\text{C}}$  (67.8 MHz;  $\text{CDCl}_3$ ) 23.6, 24.8, 26.9 (t, C-7, C-8, C-9), 31.7 (q, NMe), 50.9 (q, OMe), 52.8 (t, C-6), 59.1 (d, C-9a) 106.5 (s, C-3), 135.0 (d, C-4), and 162.8, 164.2 (s, C-1, C=O, ester);  $m/z$  224 ( $M^+$ , 100%), 195 (M-NMe, 22), and 181 (88).



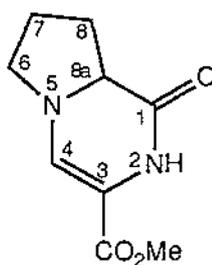
**(Z)-Methyl-1-(2'-methoxycarbonyl-2'-nitroethenyl)pyrrolidine-2-carboxylate (122).**

The *title compound* (122) was prepared from L-proline methyl ester hydrochloride (121) (1.0 g, 6 mmol), sodium acetate (1.65 g, 12.0 mmol), and nitroalkene (3) (1.06g, 6.0 mmol) using the procedure described for nitroalkene (113). Purification by flash chromatography using hexane-ethyl acetate (1:1) as eluent gave the *title compound* (122) (1.5 g, 98%) as yellow prisms, m.p. 75-76°C. (Found: C, 46.7; H, 5.6; N, 10.5,  $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_6$  requires: C, 46.5; H, 5.5; N, 10.8%);  $\nu_{\text{max}}$  (thin film) /  $\text{cm}^{-1}$  1744, 1722 (s, C=O), 1618 (m, C=C), and 1565 (w,  $\text{NO}_2$ );  $\delta_{\text{H}}$  (270 MHz,  $\text{CDCl}_3$ ) 2.02-2.34 (4H, m, 2 x  $\text{CH}_2$ ), 3.25-3.46 (2H, m,  $\text{CH}_2\text{N}$ , 3.74-3.96 (1H, m, CHN), 3.81 (6H, s, 2 x OMe), and 8.29 (1H, br s, HC=C);  $\delta_{\text{C}}$  (67.8 MHz,  $\text{CDCl}_3$ ) 24.4, 28.9 (t, C-3, C-4), 48.9 (t, C-5), 52.9, 53.1 (q, 2 x OMe), 66.6 (d, C-2), 120.2 (s, C-2'), 147.3 (d, C-1'), and 162.6, 170.6 (s, 2 x  $\text{CO}_2\text{Me}$ );  $m/z$  258 ( $M^+$ , 19%), 212 (M- $\text{NO}_2$ , 3), 199 (M- $\text{CO}_2\text{Me}$ , 100), 183 (13), 95 (19), 71 (50), and 43 (20).



**3-Methoxycarbonyl-6,7,8,8a-tetrahydropyrrolo[1,2-a]pyrazin-1-(2H)-one (123)**

The *title compound* (123) was prepared from nitroalkene (122) (490 mg, 1.90 mmol), using the procedure described for lactam (119). Purification by flash chromatography using hexane-ethyl acetate (1:2) as eluent afforded the *title compound* (123) as a pale yellow oil that decolourised on standing. (Found:  $M^+$ , 196.0856,  $C_9H_{12}N_2O_3$  requires  $M$ , 196.0848);  $\nu_{\max}$  (thin film) /  $cm^{-1}$ , 3430 (br, m, NH), 1739 (s, C=O, ester), and 1677 (s, C=O, lactam);  $\delta_H$  (270 MHz,  $CDCl_3$ ) 1.94-2.45 (4H, m, 2 x  $CH_2$ ), 3.48-3.55 (2H, m,  $CH_2N$ ), 3.75 (3H, s, OMe), 3.86-3.98 (1H, m, CHN), 7.08 (1H, s, HC=C), and 7.46 (1H, br s, NH);  $\delta_C$  (67.8 MHz,  $CDCl_3$ ) 23.0, 28.2 (t, C-7, C-8), 50.3 (q, OMe), 51.4 (t, C-6), 59.5 (d, C-8a), 103.6 (s, C-3), 128.3 (d, C-4), and 162.1, 162.6 (s, C-1, C=O, ester);  $m/z$  196 ( $M^+$ , 100%), 181 ( $M-CH_3$ , 6), 156 (36), 140 (44), and 108 (48).



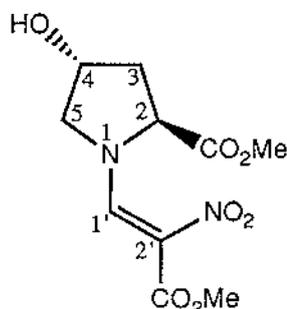
**(2S,4R)-(-)-Methyl-4-hydroxypyrrolidine-2-carboxylate. (125).**

The *title compound* (125) was prepared from (2S,4R)-(-)-4-Hydroxy-2-pyrrolidinecarboxylic acid (124) (5.0 g, 0.038 mmol) and thionyl chloride (10ml, 137 mmol), according to the method of Yasutake and co-workers<sup>41</sup> as a white crystalline solid (6.5 g, 94%), m.p. 160-162°C. (lit<sup>49</sup> m.p.162-164°C).

**(2S,4R)-(-)-(Z)-Methyl-4-hydroxy-1-(2'-methoxycarbonyl-2'-nitroethenyl)piperidine-2-carboxylate (126).**

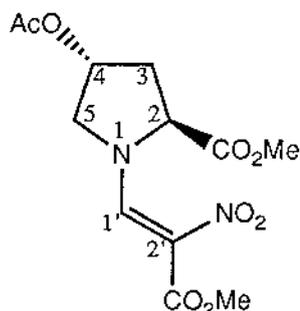
The *title compound* (126) was prepared from (2S,4R)-(-)-4-Hydroxypyrrolidine-2-carboxylate hydrochloride (125) (100 mg, 0.55 mmol), sodium acetate (150 mg, 1.10 mmol), and nitro acrylate (3) using the procedure described for nitro alkene (113). Purification by flash chromatography using hexane-ethyl acetate (1:1) as eluent gave the *title compound* (126) (142 mg, 97%) as yellow prisms, m.p. 81-83 °C.  $[\alpha]_D^{21}$  -420.5° (c, 0.394,  $CH_3Cl$ ). (Found (acetate): C, 45.4; H, 5.3; N, 8.6.  $C_{12}H_{12}N_2O_8$  requires: C, 45.6; H, 5.1; N, 8.9%);  $\nu_{\max}$  (Nujol) /  $cm^{-1}$  3480 (br, m OH), 1743, 1721 (s, C=O), and 1616 (m, C=C);  $\delta_H$  (270 MHz,  $CD_3OD$ ) 2.22-2.46 (2H, m,  $CH_2$ ), 3.37 (2H, d,  $J$  10.3 Hz,  $CH_2N$ ), 3.84 (3H, s, OMe), 4.50 (1H, m, CHN), 5.09-5.16 (2H, m, CH OH) and 8.36 (1H, br s, HC=C);  $\delta_C$  (67.8 MHz,  $CD_3OD$ ) 37.0 (t, C-3), 52.3, 53.1 (q, 2 x OMe),

59.1 (t, C-5), 64.6 (d, C-2), 69.4 (d, C-4), 119.5 (s, C-2'), 147.8 (s, C-1'), and 162.4, 170.7, (s, 2 x OMe);  $m/z$  274 ( $M^+$ , 13%), 215 ( $M-CO_2Me$ , 100), and 192 (13).



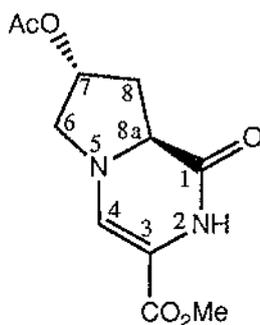
**(2*S*,4*R*)-(-)-(Z)-Methyl-4-acetoxy-1-(2'-methoxycarbonyl-2'-nitroethenyl)pyrrolidine-2-carboxylate (129).**

To a solution of the nitroalkene (126) (196 mg, 0.72 mmol) in dichloromethane (5 ml) was added triethylamine (148 mg, 1.46 mmol), acetic anhydride (112 mg, 1.09 mmol) and 4-dimethylaminopyridine (DMAP) (3 mg), and the reaction mixture allowed to stand at room temperature for 1 h. The reaction mixture was quenched with water (5 ml), extracted with dichloromethane (2 x 10 ml), washed with water (2 x 5 ml), and dried ( $Na_2SO_4$ ). Removal of the solvent at reduced pressure afforded a yellow oil that was purified by flash chromatography using hexane-ethyl acetate as eluent to give the *title compound* (129) (210 mg, 93%), as a pale yellow oil.  $[\alpha]_D^{21}$   $-269.7^\circ$  (c, 0.0640,  $CH_3Cl$ ). (Found: C, 45.4; H, 5.3; N, 8.6;  $C_{12}H_{16}N_2O_8$  requires: C, 45.6; H, 5.1; N, 8.9%);  $\nu_{max}$  (thin film) /  $cm^{-1}$  1735 (s, C=O, ester), and 1624 (m, C=C);  $\delta_H$  (270 MHz,  $CDCl_3$ ) 2.05 (3H, s, OAc), 2.24-2.59 (2H, m,  $CH_2$ ), 3.75-3.88 (2H, m,  $CH_2N$ ), 3.83 (6H, s, 2 x OMe), 4.64-4.70 (1H, m, CHN), 5.23-5.38 (1H, m, CHO), and 8.37 (1H, br s, HC=C);  $\delta_C$  (67.8 MHz,  $CDCl_3$ ) 20.7 (q,  $CH_3$ ), 34.4 (t, C-3), 52.6, 53.2 (q, 2 x OMe), 56.0 (t, C-5), 64.2 (d, C-2), 71.7 (d, C-4), 121.2 (s, C-2'), 148.4 (d, C-1'), 162.2, 170.0 (s, 2 x C=O, ester);  $m/z$  317 ( $MH^+$ , 8%), 316 ( $M^+$ , 8), 257 ( $M-CO_2Me$ , 12), 197 (46), 165 (76), 121 (100).



**(8a*S*,7*R*)-(-)-7-Acetoxy-3-methoxycarbonyl-6,7,8,8a-tetrahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one. (130).**

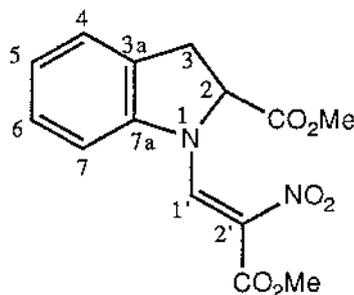
To a solution of nitroalkene (129) (990 mg, 3.13 mmol) in methanol (150 ml) was added 5% palladium on charcoal (20 mg), and the reaction flask flushed with hydrogen. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 16 h. After filtration through a short celite pad, the solvent was removed at reduced pressure to afford a brown oil, that was purified by flash chromatography using hexane-ethyl acetate as eluent to give the *title compound* (130) (566 mg, 71%) as a pale yellow oil that darkened on standing.  $[\alpha]_D^{21} -27.2^\circ$  (c, 0.206, MeOH). (Found:  $M^+$ , 254.0897.  $C_{11}H_{14}N_2O_5$  requires  $M$ , 254.0903);  $\nu_{\max}$  (thin film) /  $cm^{-1}$  3450 (m, NH), 1737 (s, C=O, ester), and 1683 (s, C=O, lactam);  $\delta_H$  (270 MHz,  $CDCl_3$ ) 2.06 (3H, s, OAc), 2.07-2.26 (2H, m,  $CH_2$ ), 3.03-3.08 (1H, m, 6-H), 3.30 (1H, dd,  $J_{6,6'}, 12.5$ ,  $J_{6,7}$ , 4.8 Hz, 6-H), 3.75 (3H, s, OMe), 4.00 (1H, t,  $J_{8a,8}$ , 7.8 Hz, 8a-H), 5.22-5.32 (1H, m,  $CHOAc$ ), and 7.09 (1H, s,  $HC=C$ );  $\delta_C$  (67.8 MHz,  $CDCl_3$ ), 20.9 (q,  $CH_3$ ), 36.4 (t, C-8), 52.1 (q, OMe), 52.4 (t, C-6), 58.3 (d, C-8a), 71.2 (d, C-7), 103.2 (s, C-3), 127.1 (d, C-4), and 165.1, 170.4, 174.4 (s, C-1, C=O, ester, acetate);  $m/z$  254 ( $M^+$ , 34%), 223 ( $M-CO_2Me$ , 6), 194 ( $M-HOAc$ , 95), 134 (43), 82 (49), 68 (100), and 43 (82).



**Methyl-1-(2'-methoxycarbonyl-2'-nitroethenyl)indoline-2-carboxylate (133).**

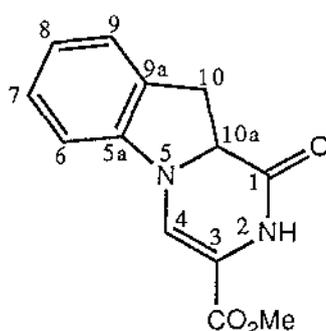
To a solution of DL-indoline-2-carboxylate (132) (526 mg, 2.96 mmol) in methanol (10 ml) was added a solution of the acrylate (3) (520 mg, 2.96 mmol) in methanol (1 ml). A yellow precipitate formed, and the resultant mixture was stirred for 1 h. The precipitate was filtered, washed with methanol (2 x 10 ml), and dried (air) to give the *title compound* (133) (456 mg, 50%) as pale yellow needles, m.p. 131.5-132 °C. (Found: C, 55.0; H, 4.7; N, 9.2%,  $C_{14}H_{14}N_2O_6$  requires: C, 54.9; H, 4.6; N, 9.2%);  $\nu_{\max}$  (Nujol) /  $cm^{-1}$  1588 (m,  $NO_2$ ), 1627 (m, C=C), 1709, and 1755 (s, 2 x C=O);  $\delta_H$  (270 MHz,  $CDCl_3$ ) 3.34 (1H, dd,  $J_{3,3'}$ , 16.9,  $J_{3',2}$ , 10.6 Hz, 3-H'), 3.74 (3H, s, OMe), 3.87 (3H, s, OMe), 5.22 (1H, dd,  $J_{2,3'}$ , 10.6,  $J_{2,3}$ , 3.3 Hz, 2-H), 7.15-7.35 (4H, m, Ar-H), and 8.83 (1H, m,  $HC=C$ );  $\delta_C$  (67.8 MHz,  $CDCl_3$ ) 34.0 (t, C-3), 53.1, 53.2 (q, 2 x OMe), 62.1 (d, C-2), 110.8, 125.8, 126.0, 128.8 (d, C-4, C-5, C-6, C-7), 128.7 (s, C-2') 134.5 (s, C-3a),

138.4 (d, C-1'), 143.2 (s, C-7a), and 162.6, 169.7 (s, C=O, ester);  $m/z$  306 ( $M^+$ , 52%), 247 ( $M-CO_2Me$ , 28), 171 (100), 118 (51).



**10-10a-Dihydro-3-methoxycarbonylindolino[1,2-a]pyrazin-1(2H)-one. (134)**

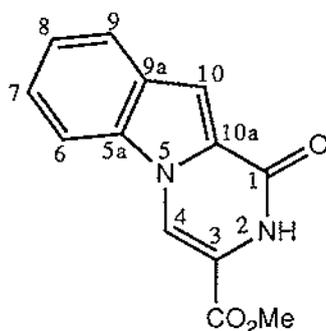
The *title compound* (134) was prepared from Nitroalkene (133) using the procedure described for lactam (119). Purification by flash chromatography using hexane-ethyl acetate (1:1) as eluent gave the *title compound* (134) (807 mg, 48%), as a pale yellow solid, m.p. 259-261 °C (changes form to needles 195-198 °C): (Found:  $M^+$ , 244.0859,  $C_{13}H_{12}N_2O_3$  requires  $M$ , 244.0848);  $\nu_{max}$  (Nujol) /  $cm^{-1}$  3187 (m, NH), 1718 (s, C=O.ester), 1660 (s, C=O lactam);  $\delta_H$  (270 MHz,  $CD_3OD$ ) 3.24 (1H, d,  $J$  10.5 Hz,  $CH_2$ ), 3.72 (3H, s OMe), 4.57 (1H, t,  $J$  10.5 Hz, CHN), 6.89 (1H, t,  $J$  7.3 Hz, 8-H or 7-H), 7.17 (1H, d,  $J$  7.3 Hz, 7-H or 8-H), 7.23 (1H, d,  $J$  7.3 Hz, 6-H or 9-H), 7.28 (1H, d,  $J$  7.3 Hz, 9-H or 6-H), 7.79 (1H, s, 4-H), and 9.48 (1H, s, NH);  $\delta_C$  (67.8 MHz,  $CD_3OD$ ) 30.1 (t, C-10), 51.4 (q, OMe), 59.6 (d, C-10a), 108.1 (s, C-3), 108.9, 120.0, 122.0, 125.4, 127.9 (d, C-4, C-6, C-7, C-8, C-9), 128.8 (s, C-9a), and 162.1, 163.2 (s, C-1, C=O, ester);  $m/z$  244 ( $M^+$ , 100%), 242 ( $M-2H$ , 24), and 156 (33).



**3-Methoxycarbonylindolino[1,2-a]pyrazin-1(2H)-one. (135).**

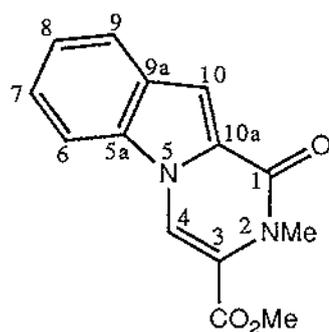
To a solution of lactam (134) (1.17 g, 4.8 mmol) in toluene (150 ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The reaction mixture was stirred for 0.5 h, filtered, and washed with toluene (2 x 25 ml), to give a tan solid that was purified by flash chromatography using ethyl acetate as eluent to afford the *title compound* (135) (928

mg, 80%) as colourless needles, m.p 270-271 °C; (Found: C, 64.3; H, 4.3; N, 11.6; C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub> requires: C, 64.5; H, 4.2; N, 11.6%);  $\nu_{\max}$  (Nujol) / cm<sup>-1</sup> 3187 (w, NH), 1669 (s, C=O, ester), and 1637 (s, C=O, lactam);  $\delta_{\text{H}}$  (270 MHz, CDCl<sub>3</sub>) 3.99 (3H, s, OMe), 7.40 (1H, t, *J* 7.8 Hz, 7-H or 8-H), 7.51 (1H, t, *J* 8.1 Hz, 8-H or 7-H), 7.53 (1H, s, 10-H), 7.76 (1H, d, *J* 8.1 Hz, 6-H or 9-H), 7.86 (1H, d, *J* 8.1 Hz, 9-H or 6-H), 8.21 (1H, s, 4-H), and 8.41 (1H, br s, NH);  $\delta_{\text{C}}$  (67.8 MHz, CDCl<sub>3</sub>) 53.0 (q, OMe), 106.4 (s, C-3), 106.4, 110.8, 112.5, 123.1, 123.9, 125.4 (d, C-4, C-6, C-7, C-8, C-9, C-10), 114.1, 127.5, 128.6, 133.4 (s, C-3, C-5a, C-9a, C-10a), 156.0 (s, C-1), and 162.0 (s, C=O, ester); *m/z* 242 (M<sup>+</sup>, 100%), 182 (M-CO<sub>2</sub>Me-H, 33), and 154 (27).



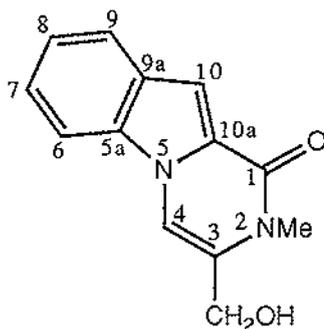
**3-methoxycarbonyl-2-methyl-indolo[1,2-a]pyrazin-1(2H)-one. (136)..**

To a solution of lactam (135) (300 mg, 1.22 mmol) in dry dimethylsulphoxide (10 ml) was added potassium hydride (100 mg, 2.45 mmol). The reaction mixture was stirred at room temperature for 0.5 h then methyl iodide (261 mg, 1.84 mmol) was added. After 0.5 h aqueous sodium dihydrogen phosphate (2 ml) and water (25 ml) were added and the reaction mixture extracted with ethyl acetate (3 x 50 ml). The organic extract was washed with water (2 x 20 ml), and dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of the solvent under reduced pressure afforded a pale cream solid that was purified by flash chromatography using hexane-ethyl acetate (1:1) as eluent to give the *title compound* (135) (181 mg, 57 %) as colourless needles, m.p. 173-174 °C; (Found: C, 65.4; H, 4.7; N, 10.9; C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub> requires: C, 65.6; H, 4.7; N, 10.9%);  $\nu_{\max}$  (Nujol) / cm<sup>-1</sup> 1719 (s, C=O, ester), and 1651 (s, C=O, lactam);  $\delta_{\text{H}}$  [(CD<sub>3</sub>)<sub>2</sub>SO] 3.39 (3H, s, NMe), 3.88 (3H, s, OMe), 7.36 (1H, s, 10-H), 7.37 (1H, t, *J* 8.2 Hz, 7-H or 8-H), 7.47 (1H, t, 8-H, or 7-H), 7.84 (1H, t, d, *J* 8.2 Hz, 6-H or 9-H), 8.26 (1H, d, 9-H or 6-H), and 8.69 (1H, s, 4-H);  $\delta_{\text{C}}$  [67.8 MHz, (CD<sub>3</sub>)<sub>2</sub>SO] 31.7 (q, NMe), 52.4 (q, OMe), 104.3, 112.2, 114.8, 122.2, 123.4, 124.6 (d, C-4, C-6, C-7, C-8, C-9, C-10), 117.7, 126.6, 127.9, 132.8 (s, C-3, C-5a, C-9a, C-10a), 156.2 (s, C-1), and 162.2 (s, C=O, ester); *m/z* 256 (M<sup>+</sup>, 100), 197 (M-CO<sub>2</sub>Me, 10).



**3-Hydroxymethyl-2-methylindolo[1,2-a]pyrazin-1(2H)-one.. (137).**

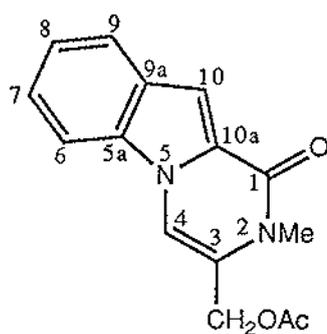
To a solution of ester (136) (181 mg, 0.71 mmol), in methanol (10 ml), under nitrogen was added sodium borohydride (540 mg, 14.27 mmol). The reaction mixture was left to stand at room temperature for 16 h. After quenching with water (5 ml) the methanol was removed by rotary evaporation and the residue extracted with ethyl acetate (3 x 25 ml). The organic extract was washed with water (2 x 5 ml) dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent removed at reduced pressure to give a pale yellow solid that was purified by flash chromatography using hexane-ethyl acetate (1:1) as eluent to give the *title compound* (137) (143 mg, 89%) as colourless needles, m.p. 190-191 °C (decomp); (Found: C, 68.2; H, 5.3; N, 12.0.  $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2$  requires: C, 68.4; H, 5.3; N, 12.3%);  $\nu_{\text{max}}$  (Nujol) /  $\text{cm}^{-1}$  3332 (br, w, OH), and 1623 (s, C=O, lactam);  $\delta_{\text{H}}$  [270 MHz,  $(\text{CD}_3)_2\text{SO}$ ] 3.53 (3H, s, NMe), 4.47 (1H, d,  $J$  4.1 Hz,  $\text{CH}_2\text{OH}$ ), 5.51 (1H, br t,  $J$  4.1 Hz, OH), 7.23 (1H, s, 10-H), 7.23 (1H, t,  $J$  7.8 Hz, 7-H or 8-H), 7.41 (1H, t,  $J$  7.8 Hz, 8-H or 7-H), 7.81 (1H, d,  $J$  7.8 Hz, 6-H or 9-H), 7.98 (1H, s, 4-H), and 8.03 (1H, d,  $J$  7.8 Hz, 9-H or 6-H);  $\delta_{\text{C}}$  [67.8 MHz,  $(\text{CD}_3)_2\text{SO}$ ] 28.6 (q, NMe), 58.8 (t,  $\text{CH}_2\text{OH}$ ), 101.1, 105.7, 111.4, 122.0, 122.2, 123.5 (d, C-4, C-6, C-7, C-8, C-9, C-10), 126.4, 126.7, 127.0, 131.7 (s, C-3, C-4a, C-9a, C-10a), and 156.7 (s, C-1);  $m/z$  228 ( $\text{M}^+$ , 100%), 231 (M- $\text{CH}_3$ , 14), 211 (M-OH, 35), and 197 (M- $\text{CH}_2\text{OH}$ , 8).



**3-Acetoxyethyl-2-methylindolo[1,2-a]pyrazin-1(2H)one. (142).**

The *title compound* (142) was prepared from alcohol (137) (50 mg, 0.22mmol), triethylamine (44 mg, 0.44mmol), and acetic anhydride (27 mg, 0.26 mmol) using the procedure described for alcohol (126). Removal of the solvent under reduced pressure

afforded a white crystalline powder, that was purified by flash chromatography using hexane-ethyl acetate (1:1) as eluent to give the *title compound* (142) as colourless plates (50mg, 85%), m.p. 208-210 °C; (Found  $M^+$ , 270.1000,  $C_{15}H_{14}N_2O_3$  requires  $M$ , 270.1004);  $\delta_H$  (270 MHz,  $CDCl_3$ ) 2.14 (3H, s, OAc), 3.58 (3H, s, NMe), 5.06 (2H, s,  $CH_2OAc$ ), 7.39 (1H, t,  $J$  8.2 Hz, 7-H or 8-H), 7.42 (1H, T,  $J$  8.2 Hz, 8-H or 7-H), 7.42 (1H, s, 10-H), 7.45 (1H, s, 4-H), 7.66 (1H, d,  $J$  8.2 Hz, 6-H or 9-H), and 7.83 (1H, d,  $J$  8.2 Hz, 9-H or 6-H);  $\delta_C$  (67.8 MHz,  $CDCl_3$ ) 21.0 (q,  $COCH_3$ ), 29.3 (q, NMe), 61.7 (t,  $CH_2OAc$ ), 103.5, 108.8, 110.4, 122.7, 122.8, 124.2 (d, C-4, C-6, C-7, C-8, C-9, C-10), 120.5, 126.9, 127.9, 132.2 (s, C-3, C-5a, C-9a, C-10a), 157.6 (s, C-1), and 170.4 (s, C=O, ester);  $m/z$  270 ( $M^+$ , 67%), 227 ( $M-COCH_3$ , 4), 211 ( $M-OCOCH_3$ , 100), and 183 (13).



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