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NEW SYNTHETIC STRATEGIES  
TOWARDS CEPHALOTAXUS ALKALOIDS

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(Graduate Society)

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University of Durham

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Thesis submitted for the degree of  
Doctor of Philosophy, September 1988



23 MAR 1989

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## ABSTRACT

*Thesis submitted for the degree of Doctor of Philosophy by John M. Gardiner (Graduate Society), September 1988, titled "New Synthetic Strategies towards Cephalotaxus alkaloids".*

Michael alkylation, with methyl acrylate, of nitrocyclohexenes bearing functionalized aromatic substituents at the 2-position, was found to be highly stereoselective. Subsequent dissolving metal reductive cyclization was highly efficient, and these two steps thus provided a stereospecific entry to a substituted 1-azaspirocyclic system, related to the cephalotaxine skeleton.

Application of this methodology to trans-4-(3,4-dimethoxy-6-carbomethoxymethylphenyl)-5-nitrocyclohexene afforded spiro lactam ester 6-(3,4-dimethoxy-6-carbomethoxymethylphenyl)-2-oxo-1-azaspiro[4.5]dec-8-ene. On reduction with DIBAL-H at  $-78^{\circ}\text{C}$ , this cyclized in high yield, with high stereoselectivity to the corresponding 3-benzazepine-2-ol system.

Similar methodology with trans-4-(3,4-methylenedioxy-6-nitrophenyl)-5-nitrocyclohexene, allowed for a formaldehyde insertion reaction to provide a 1,3-benzodiazepine analogue.

Preliminary studies hold promise for allowing modification of the cyclohexene ring to known pre-targets of cephalotaxine.

These findings bring the synthetic strategy towards providing a competitive route to ( $\pm$ ) cephalotaxine, and also a range of analogues, including the unknown 11-aza and 10-hydroxy-8-oxo systems.

## ACKNOWLEDGEMENTS

I would like to express my gratitude to the following:

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My parents, for their continuing support and help throughout my years in Durham.

And last, but not least, to those, particularly in labs 29 and 27, whose humour and friendship has been greatly valued, and will be missed.

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CHAPTER ONE

INTRODUCTION TO  
CEPHALOTAXUS ALKALOIDS



## 1.1 Occurrence and distribution

*Cephalotaxus* alkaloids are a structurally unique class of alkaloids, isolated from conifers of the genus *Cephalotaxus*<sup>1</sup>, the only genus of the family Cephalotaxaceae of the order Coniferae.

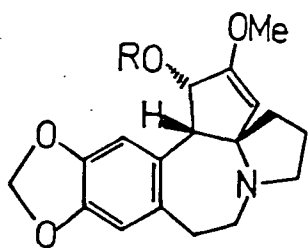
There are eight known species of this genus, *C.harringtonia*, *C.mannii*, *C.fortunei*, *C.hainanensis*, *C.wilsonia*, *C.oliveri*, *C.lanceolata* and *C.sinensis*.<sup>2</sup>

Though these evergreen shrubs are largely native to Eastern Asia, - the last six of the above being indigenous only to China - *C.harringtonia* and *C.mannii* are found in the western United States, western Canada, north east Argentina and western Uruguay, as well as south east Asia<sup>3</sup>. All species of *Cephalotaxus* are found mostly in humid valleys and forests, preferring elevations between 100 m and 2000 m.

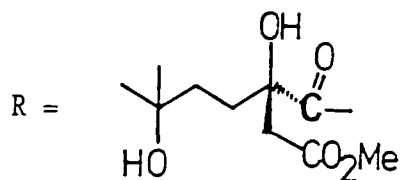
Since 1963, eighteen alkaloids of the *Cephalotaxus* series have been isolated from extracts of these plants. The most widespread being the parent alkaloid, cephalotaxine, 1, obtained from seven of the species. These alkaloids fall into two general categories; (i) those retaining the cephalotaxine nucleus, bearing an ester side chain, 2-9, and (ii) those involving modifications of the parent ring system, with or without acyl substituents, 10-19.

The discovery in 1961 that alkaloid extracts of *C.harringtonia* were active against sarcoma 180 tumour<sup>4</sup>, prompted the considerable efforts which led to the isolation and full structural characterisation of 1-19 over the following two decades.

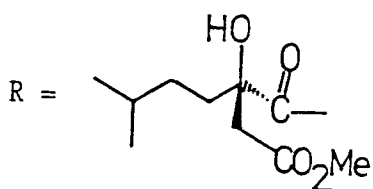
By the end of the 1960s, the four 'harringtonine' esters of cephalotaxine, 2-5, had been isolated, and their structures established<sup>5-7</sup>. All these esters were found to exhibit antitumour activity, furthermore, none of the alkaloids involving a modified ring system exhibits significant antitumour activity.



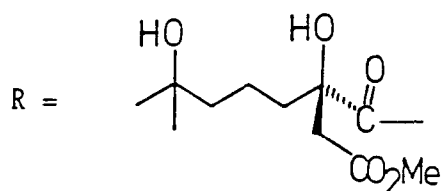
7. R = H (-) cephalotaxine



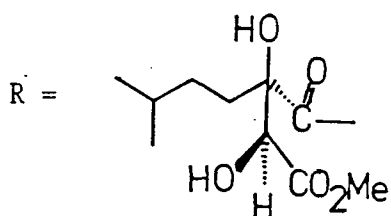
2 Harringtonine



3 Deoxyharringtonine



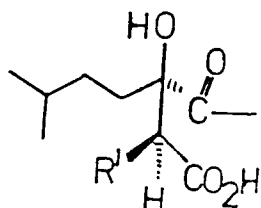
4 Homoharringtonine



5 Isoharringtonine

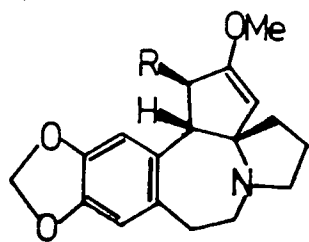
6 R = Ac Acetyl-cephalotaxine

7 R = Ac (+)Acetyl-cephalotaxine



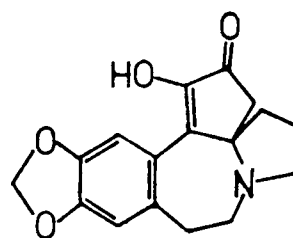
8 R' = OH Isoharringtonic acid

9 R' = H Deoxyharringtonic acid

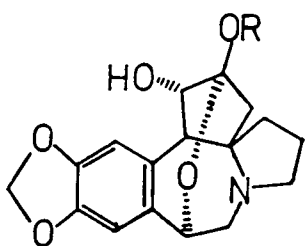


10 R = OH Epicephalotaxine

11. R = =O cephalotaxinone

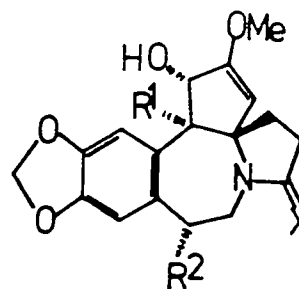


12 Demethylcephalotaxinone



13 R = Me Drupacine

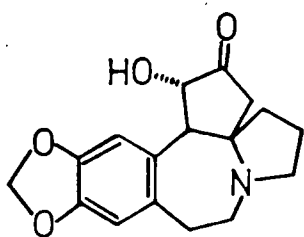
14 R = H Demethylneodrupacine



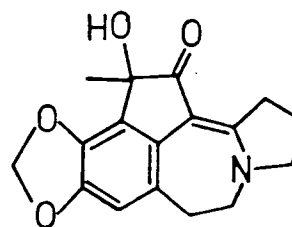
15 X = H<sub>2</sub> R<sup>1</sup> = R<sup>2</sup> = OH  
11-hydroxycephalotaxine

16 X = H<sub>2</sub> R<sup>1</sup> = OH R<sup>2</sup> = H  
4-hydroxycephalotaxine

17 X = O R<sup>1</sup> = R<sup>2</sup> = H  
cephalotaxinamide



18 Demethyl cephalotaxine



19 Hainansine

Unfortunately, the alkaloid content of *Cephalotaxus* plants is low, and supplies of plant material are limited<sup>8</sup>. Further, of the total alkaloid extract, only a small percentage generally constitutes the active harringtonines. For example, in *C. fortunei*, this varies from 0.02% of the root alkaloid extracts to 0.7% of leaf extracts. The richest source of harringtonines appears to be the roots of *C. harringtonia*,

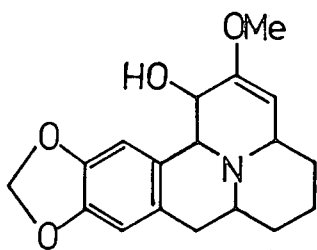
35.5% of whose alkaloid extract is harringtonines - though this is an exceptional example.

A program of cultivating *Cephalotaxus* plants as a source of harringtonine is further hampered by the slow growth rate of these plants. So despite the development of a large-scale extraction procedure, the viability of isolation of naturally occurring harringtonines as a major long term source is limited.

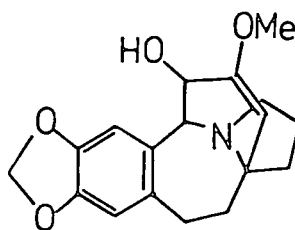
Consequently, attention has become directed towards synthetic routes to the cephalotaxine nucleus, and to the acyl moiety appropriate for subsequent elaboration to synthetic harringtonines. Later in this chapter, we will review in some detail synthetic approaches to the cephalotaxine nucleus through to July 1988, and briefly review partial synthesis of harringtonines from cephalotaxine.

## 1.2 Structure determination of cephalotaxine

The parent alkaloid, cephalotaxine, **1**, was first isolated by Paudler et al<sup>9</sup> in 1963, from *C. harringtonia* and *C. fortunei*. On the basis of their spectroscopic analyses, these workers provisionally assigned the structure **20**. Several years later, Powell et al<sup>5</sup> revised this structure, largely on the basis of the olefinic singlet in the proton NMR spectrum, suggesting either structure **21** or **1**.



**20**



**21**

The structural assignment was partly resolved by Abraham et al<sup>10</sup> in 1969, whose X-ray structure analysis of cephalotaxine methiodide indicated structure 7. However, their methiodide turned out to be racemic, though their starting cephalotaxine was optically active. This racemisation of cephalotaxine - requiring inversion of four chiral centres - was rationalized by postulating a series of macrocyclic equilibria, in which all four chiral centres could achieve planar geometry (as cations or double bonds, or through amine lone pair inversion).

Similar behaviour was later observed during synthetic approaches toward cephalotaxine<sup>11,12</sup>, and this lends credence to postulated biosynthetic pathways (see 1.5).

The absolute configuration was determined five years later by Arora et al<sup>13</sup>, from an X-ray study of the p-bromobenzoate of cephalotaxine, and further confirmation was provided by these workers later study<sup>14</sup> on cephalotaxine itself. Thus, natural (-) cephalotaxine was assigned the 3S, 4S 5R configuration.

### 1.3 Antitumour activity

#### i Experimental systems

Although all four harringtonine esters, 2-5, show some antitumour activity, harringtonine, 2, and homoharringtonine have been most investigated, by virtue of their higher activity.

A number of studies in the late 1970s<sup>4,15</sup> of the effects of these esters on experimental tumour systems, produced a large body of information on their range of activities, toxicity and mode of action. It was found that homoharringtonine was overall the most effective, active against a range of cancers including P388 lymphocytic leukemia, L1210 lymphoid leukemia, Lewis lung carcinoma, L615 and L7212 leukemias, sarcoma 180, walker carcinoma 256, colon tumour 38, epidermoid carcinoma of the nasopharynx, acute myelocytic leukemia, acute monocytic leukemia,

erythroleukemia and B16 melanoma<sup>2,8</sup>.

Harringtonine appears to have a similar range of activity, but is in general less potent, though this is in part dependent on experimental conditions.

## ii Pre-clinical studies

The promising experimental tumour studies led to pre-clinical and clinical evaluations, in both China and the United States, by the early 1980s<sup>4</sup>.

The investigations in pre-clinical trials with harringtonine and homoharringtonine (e.g. on tumour implanted mice), were particularly encouraging in relation to colon 38 tumour and P388 leukemia. Homoharringtonine effected complete tumour inhibition, and cures, against colon 38 tumour, which is resistant to most clinical antitumour agents. It also showed higher activity against P388 leukemia than the vinca alkaloids, vincristine and vinblastine, showing moderate activity even against vincristine and ellipticine resistant P388 lines. It was also as effective against cytosine arabinose resistant lines, as against non-resistant lines.

Further, homoharringtonine showed a strong synergism with the clinical agent 5-fluorouracil, combination therapy leading to cures against P388 lines which neither agent alone can cure.

Harringtonine and homoharringtonine were both found active against L1210 leukemia and B16 melanoma, in mice, both showing greater activity than the vinca alkaloids.

## iii Clinical studies

Phase I clinical trials commenced in China and the U.S.A. in 1977, and both harringtonine and homoharringtonine were found to be effective with patients suffering from either lymphocytic or non-lymphocytic



leukemia. Several trials found up to 75% of patients experienced some degree of remission, with as many as 20% showing complete remission.

Combination therapy with harringtonine or homoharringtonine, and arabinosyl cytosine, vincristine or prednisone, also showed reasonable results against leukemias, in trials in China.

Phase I trials also show that the toxicity of homoharringtonine or harringtonine, means that treatment is more effectively administered as a series of small doses, or by continuous infusion<sup>16</sup>, than by larger, less frequent doses.

The promising results of Phase I trials, has led to current Phase II trials in both China and the United States of America.

#### iv Toxicity

In all these studies, the toxicity of harringtonine and homoharringtonine has been an important, dose limiting consideration. The main target organs are the gastrointestinal tract, the heart, hematopoietic organs, and bone marrow, with quoted LD<sub>50</sub> values in the region of 5mg/kg.

Notably, the most active esters are the most toxic, homoharringtonine and harringtonine being 2-4 times more toxic than deoxyharringtonine and isoharringtonine, and the essentially inactive unnatural esters are at least a hundred times less toxic.

#### v Mode of action

It has been established that inhibition of protein and DNA biosynthesis in the cell, are the mechanisms accounting for the antitumour activity of the harringtonines<sup>2,3,8</sup>.

Studies to determine at what point in the biosynthesis inhibition occurs, are at variance. Several studies have indicated that initiation, but not elongation, of protein synthesis was inhibited. Another study, however, concluded that there was no inhibition of protein biosynthesis

initiation, but chain elongation was prevented by action blocking peptide bond formation, as well as amino acyl RNA binding<sup>4</sup>.

Inhibition of DNA biosynthesis appears to result from competitive binding to DNA polymerase  $\alpha$ , rather than any damage to the DNA template for replication. RNA biosynthesis is unaffected by harringtonines.

#### 1.4 Structure activity relationships : Unnatural esters

The correlation of structural features with biological activity, is important not only for understanding how the harringtonines function, but clearly also for the design of synthetic analogues likely to exhibit similar, or even improved activity.

The role of the cephalotaxine ring skeleton in activity of its esters, has been postulated to be related to interaction with biological hosts via the 'triangular' arrangement of the nitrogen, and the oxygens on ring E<sup>8</sup> (cf. general enzymic binding). The role of side chain functionality is as yet unclear.

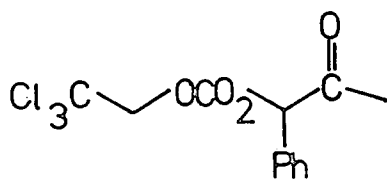
Amongst the harringtonines, it seems clear that the hydroxyl group furthest from the cephalotaxine nucleus is of some importance, and that the length of the side chain is of much less significance. Thus, both harringtonine and homoharringtonine show comparable levels of activity, while deoxyharringtonine (with no distant hydroxyl group) is approximately half as active, and isoharringtonine<sup>5</sup>, (with the hydroxyl group closer to the nucleus) is an order of magnitude less active.

It is also evident that the C2' configuration is important, as the harringtonine C2' epimer (S configuration) is at least two orders of magnitude less active than the natural isomer.

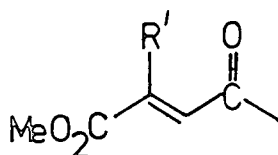
However, the inactivity of cephalotaxine alone, cephalotaxine acetate (with a non-chiral ester function) and the diester of the dicarboxylic acid side chain, obtained from harringtonine hydrolysis, shows that a combination of structural, and stereochemical, features - some residing

in the acyl moiety and some in the cephalotaxine nucleus - are jointly responsible for activity.

A large number of unnatural cephalotaxine esters have been synthesized, in an attempt to clarify structural requirements for activity. Of the fifty or so of these esters reported, with a diverse range of functionalities, only 22-28 have shown any activity at all. All these esters are at least an order of magnitude less active than harringtonine or homoharringtonine.

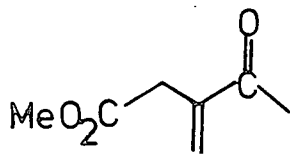


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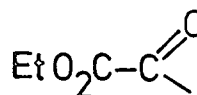


23 R<sup>1</sup> = H

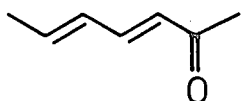
24 R<sup>1</sup> = CH<sub>2</sub>CH<sub>2</sub>CHMe<sub>2</sub>



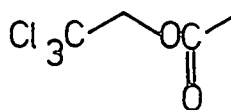
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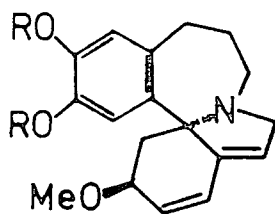
28

*Some unnatural ester side chains*

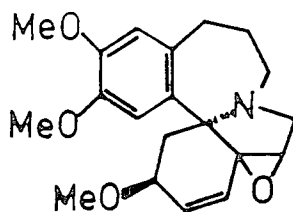
Unfortunately, these findings have not appreciably clarified structure activity relationships, as there are no obvious structural features common to these unnatural esters, or directly relevant to the natural esters. So, the design of simpler, potentially active cephalotaxine derivatives is as yet distant.

### 1.5 Biosynthesis of *Cephalotaxus* alkaloids

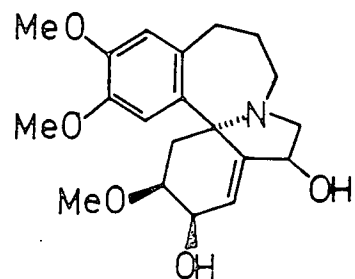
The occurrence of alkaloids of the structurally related homoerythrina series in plants of the *Cephalotaxus* genus, e.g. schelhammeridine, 29<sup>17</sup>, and the dimethoxy systems, wilsonine, 31<sup>5</sup>, fortuneine, 30<sup>18</sup>, and 2-epicephalofortuneine, 32<sup>19</sup>, suggests a common biosynthetic precursor to both classes of alkaloid.



29 R = R = Me



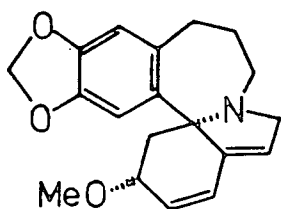
31



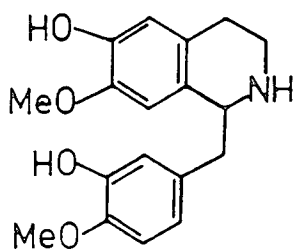
32

30 R - R = -CH<sub>2</sub>-

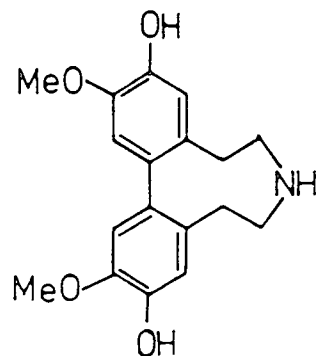
Good evidence has been produced for a biosynthetic pathway to the related erythrina alkaloids, e.g. erythraline, 33, from tyrosine<sup>20,21</sup>, via 1-benzylisoquinoline derivative, e.g. 34<sup>22</sup> followed by oxidative intramolecular coupling of macrocyclic intermediates, e.g. dibenzazoneine, 35<sup>23</sup>.



33



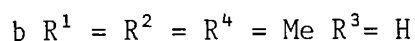
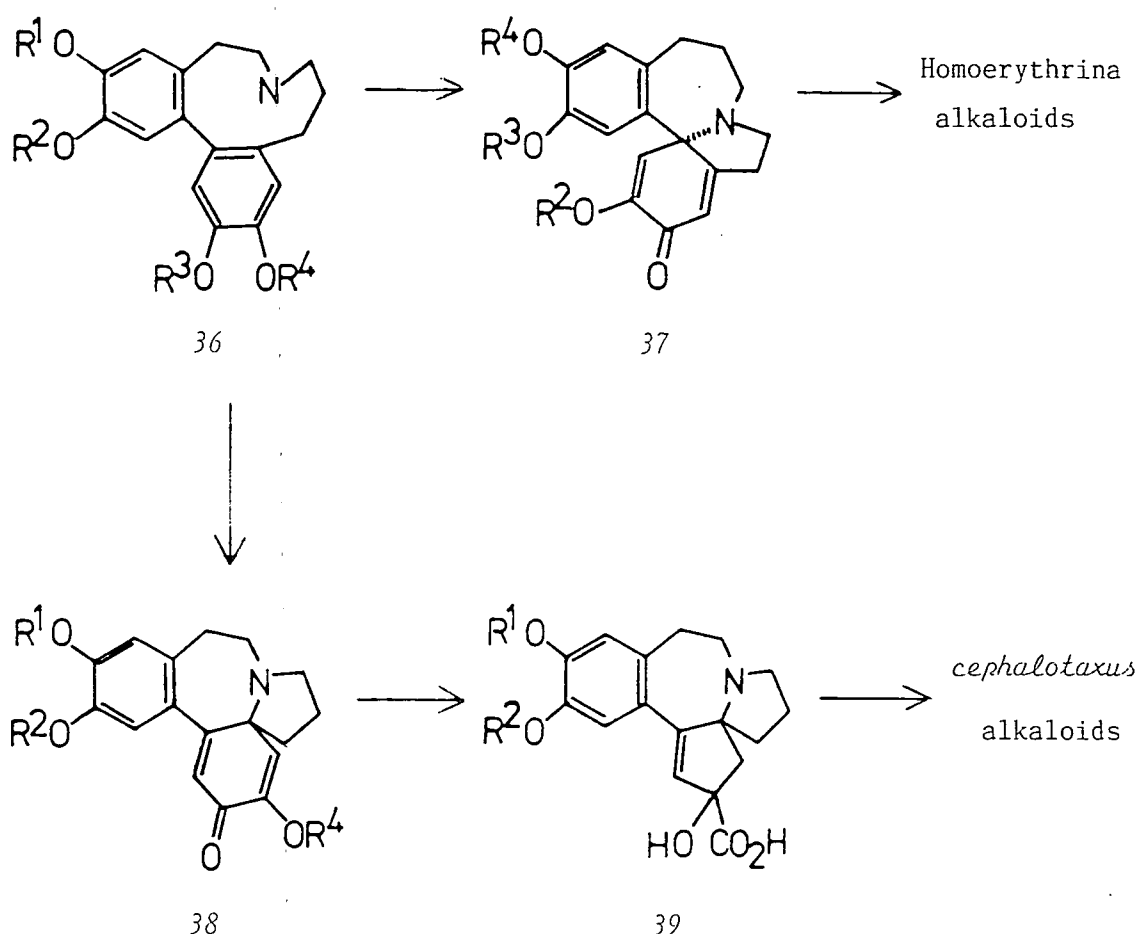
34



35

On this basis, Fitzgerald et al<sup>24</sup> postulated a similar biosynthetic origin of homoerythrina alkaloids from a 1-phenethylisoquinoline precursor, which Powell<sup>25</sup> subsequently observed, could provide entry to cephalotaxine intermediates 38 and 39, by an alternative ring closure of dibenzacine, 36*l*. (scheme I)

SCHEME I

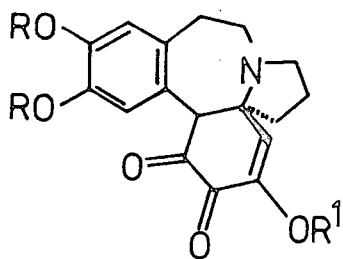


However, subsequent investigations have not confirmed the intermediacy of a macrocyclic ring closure step<sup>26-29</sup> though they have confirmed a 1-phenethylisoquinoline like precursor, derived from one molecule of tyrosine and one of phenylalanine<sup>28,30,31</sup>. Biomimetic synthetic studies (see later) have, however, given some support to a macrocyclic intermediate.

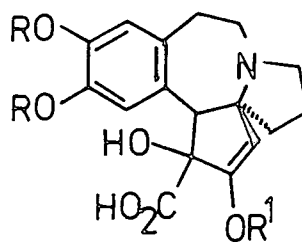
Biosynthetic studies have also now established 40 and 47 as likely intermediates, and have shown that cephalotaxine and cephalotaxinone are biogenetically interchangeable, with demethyl derivatives being biosynthetically derived from either of these.

Studies on the biosynthesis of the ester side chains of the

harringtonines, have indicated they are derived from L-leucine<sup>27,31</sup>.



40



41

### 1.6 Synthetic approaches to Cephalotaxine

The unusual ring system of the *Cephalotaxus* alkaloids, and the promising antitumour activity of its naturally occurring esters, has resulted in considerable synthetic efforts being directed towards the total synthesis of cephalotaxine, since the early 1970s.

Five total syntheses of ( $\pm$ )-cephalotaxine have been reported to date, along with a variety of partially successful synthetic approaches. We will review the completed total syntheses in some detail, and briefly cover those as yet incomplete syntheses.

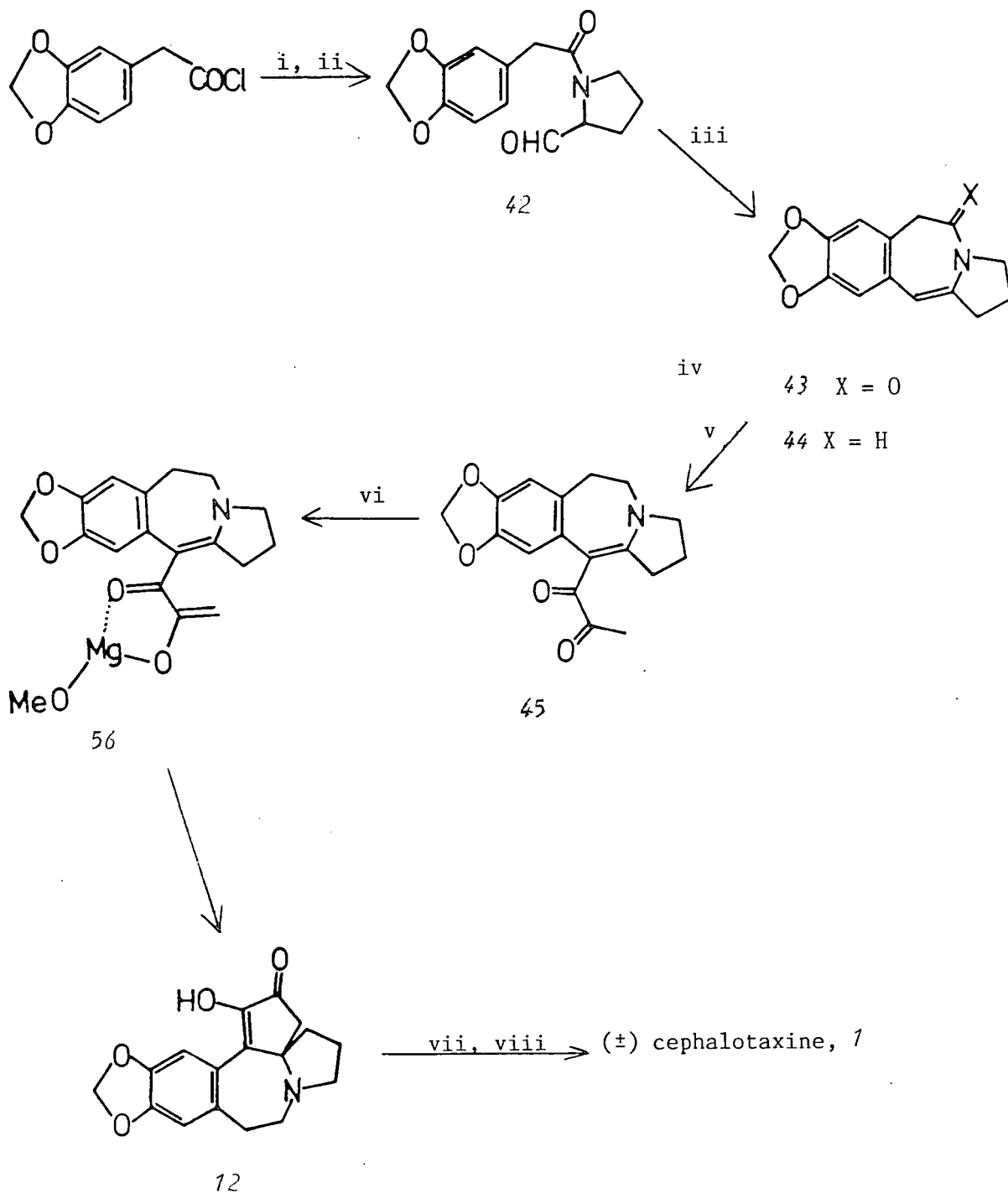
The first two total syntheses were reported simultaneously in 1972, employing completely different synthetic strategies<sup>32</sup>.

#### i Weinreb and Auerbach synthesis

The first key synthetic step in this synthetic strategy<sup>33,34</sup> (which is outlined in scheme II), was the early, efficient construction of the 7-membered ring, by Lewis acid catalysed cyclization of the amide-aldehyde 42, under very mild conditions. The resulting 3-benzazepinone, 43, was reduced with LAH to the enamine intermediate, 44, which proved to be moderately unstable.

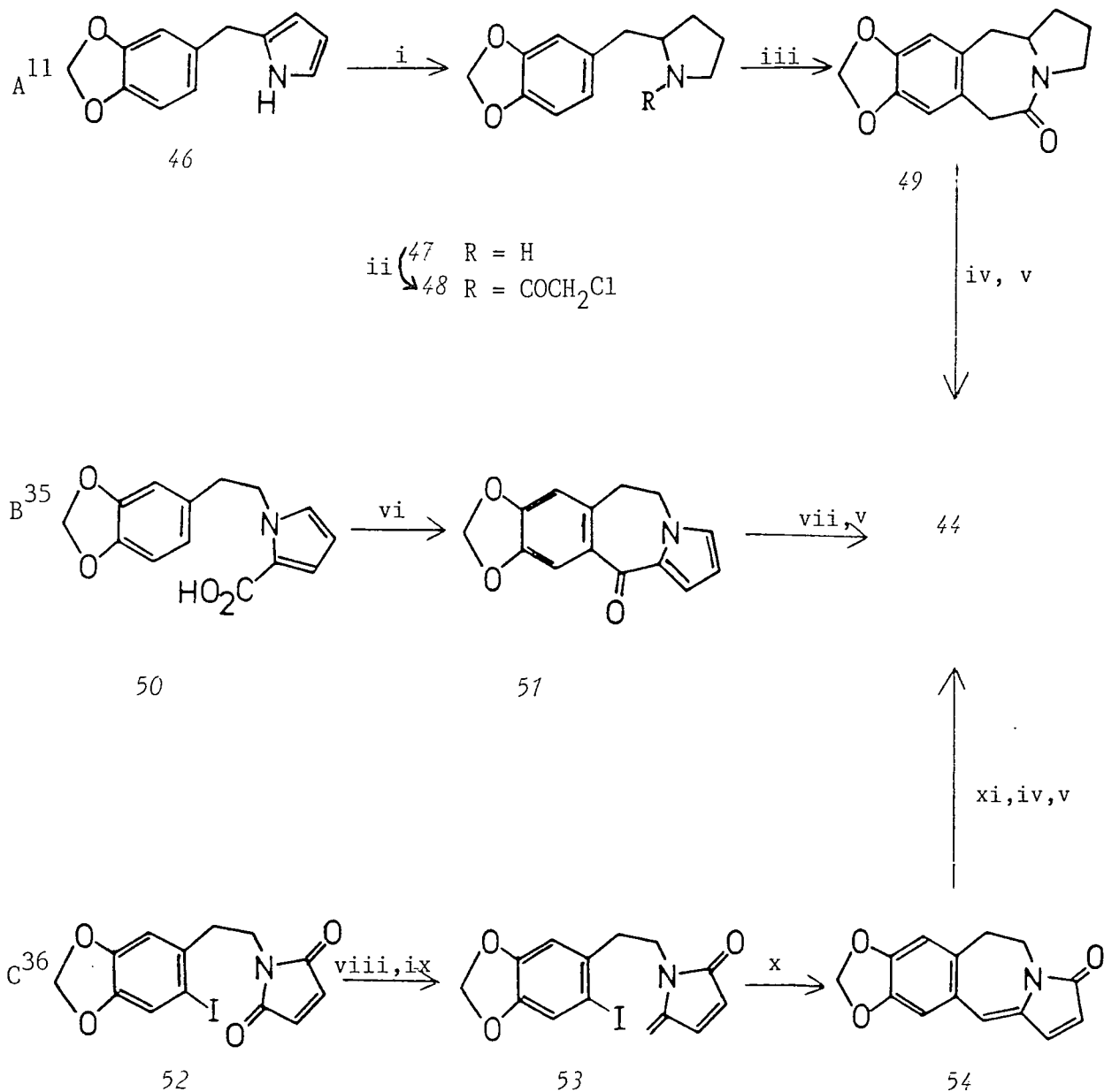
This enamine, 44, was also an intermediate target for several other groups whose routes to 44 are outlined in scheme III<sup>11,35,36</sup>.

SCHEME II



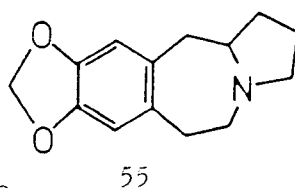
i 1-prolinol/ $K_2CO_3$ , ii DMSO/DCC (55%), iii  $BF_3 \cdot Et_2O$  (87%),  
 iv LAH (100%), v pyruvic acid-ethyl chloroformate mixed anhydride (73%),  
 vi  $Mg(MeO)_2$  (58%), vii  $(MeO)_2 CMe_2/pTsOH$  (45%), viii  $NaBH_4$  (85%).

SCHEME III



i  $\text{Rh}/\text{Al}_2\text{O}_3/\text{H}_2$  (75%), ii  $\text{ClCOCH}_2\text{Cl}/\text{Et}_3\text{N}$  (82%), iii  $h\nu$  (25%), iv LAH (65%),  
 v  $\text{Hg}(\text{OAc})_2$ , vi  $(\text{CF}_3\text{CO}_2)_2\text{O}/\text{SnCl}_4$  (88%), vii  $\text{H}_2/\text{C}$ , viii MeMgI, ix pTsOH (70%),  
 x  $h\nu/\text{Et}_3\text{N}$  (46%), xi  $\text{H}_2/\text{PtO}_2$ .

All these routes proceed via the fused tetrahydrobenzazepine, 55, which is then oxidized to 44 by mercuric acetate.





A common problem with all these routes, was finding a successful method for ring E annulation. A number of substituted enamine intermediates failed to cyclize. Eventually, the dicarbonyl intermediate, 45, (obtained by acylation of 44 with the mixed anhydride of pyruvic acid and ethylchloroformate) was found to undergo intramolecular Michael cyclization, using magnesium methoxide as base, probably via the rigid, magnesium-chelated enolate, 56.

The resulting pentacyclic system, 72, thus obtained, is actually the racemate of the naturally occurring alkaloid, demethylcephalotaxinone. This was conveniently methylated, under thermodynamic control, to provide racemic cephalotaxinone, 77, in moderate yield.

Thus, the enamine intermediate, 44, had been conveniently elaborated to cephalotaxinone in only three steps. Proceeding via demethylcephalotaxinone, which has no benzylic proton, allows the relative stereochemistry of benzylic and spiro centre to be correctly established, under the conditions of thermodynamically controlled methylation. The final step, viz the borohydride reduction of ( $\pm$ )-cephalotaxinone, 77, to ( $\pm$ )-cephalotaxine, 1, is known to be stereospecific<sup>25</sup>.

## ii Semmelhack et al synthesis

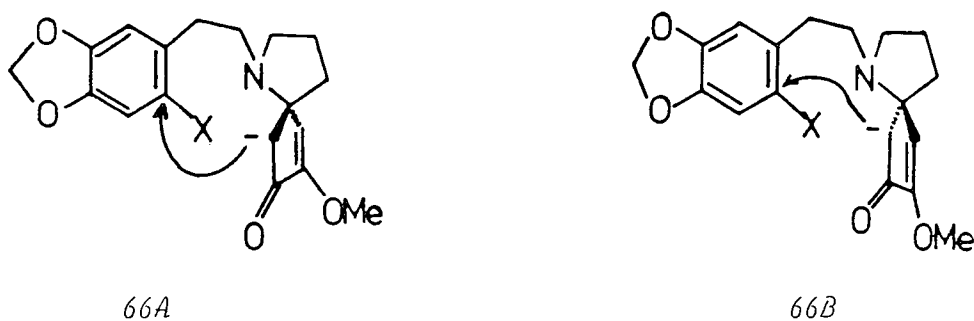
A conceptually different, convergent, synthetic strategy was reported by Semmelhack et al<sup>37,38</sup>, concurrent with Weinreb's<sup>33,34</sup> approach.

Semmelhack et al constructed the 1-azaspirocyclic subunit, 63, in several steps from pyrrolidone, and 63, reacted with 64 to provide the immediate cephalotaxinone precursor, 65 (scheme IV). The key step in the synthesis of azaspirocyclic 63, is the modified acyloin condensation of 60 to give 61.

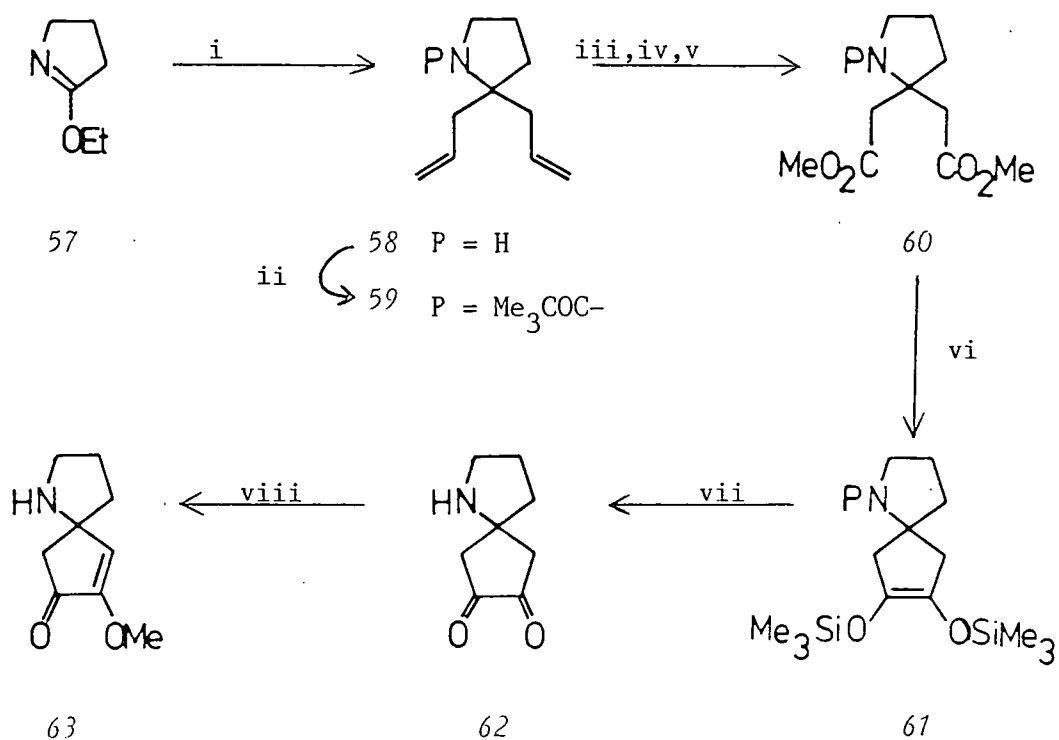
Overall, the pivotal synthetic step is the photocyclization of the enolate of 65, which occurs stereospecifically to provide ( $\pm$ )-cephalotaxinone, in very high yield. The stereospecificity is accounted for through a combination of the stereoelectronic requirements of the eno-

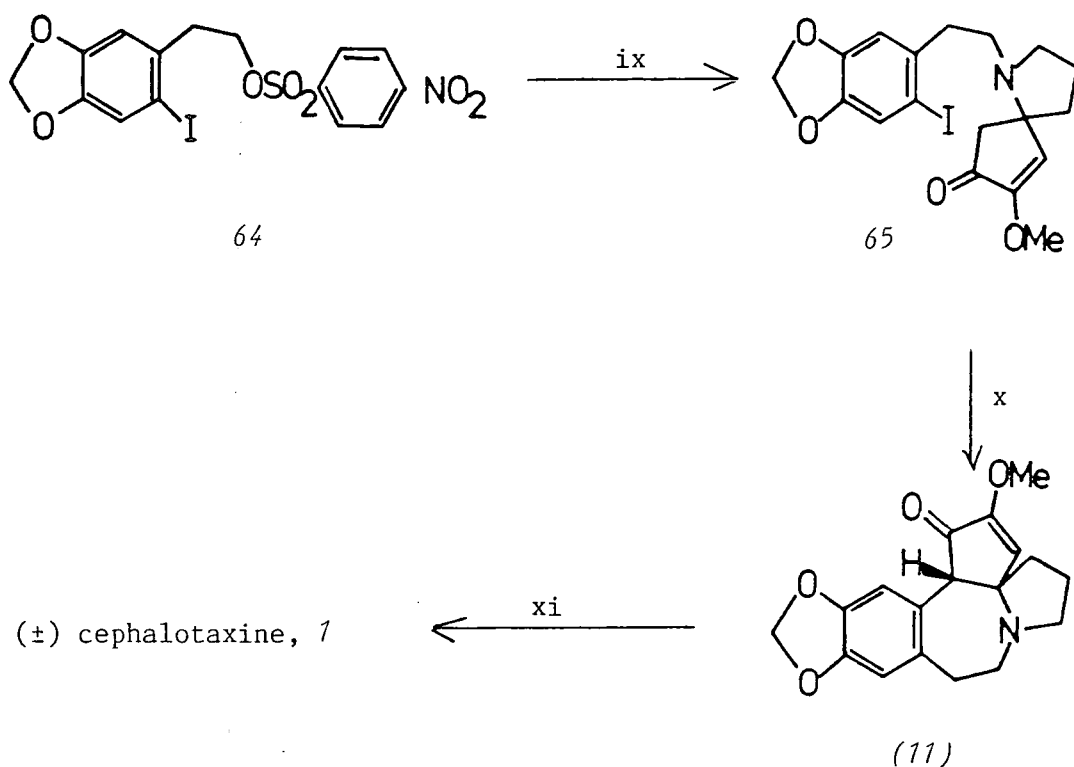
late nucleophile and aromatic electrophile, and the rigidity of the spiro centre. Enantiomer *66A* provides (+)-cephalotaxine, while enantiomer *66B* provides (-)-cephalotaxine, hence racemic cephalotaxine is obtained.

Semmelhack et al then reduced (±)-cephalotaxinone stereospecifically to (±)-cephalotaxine, using DIBAL-H.



SCHEME IV





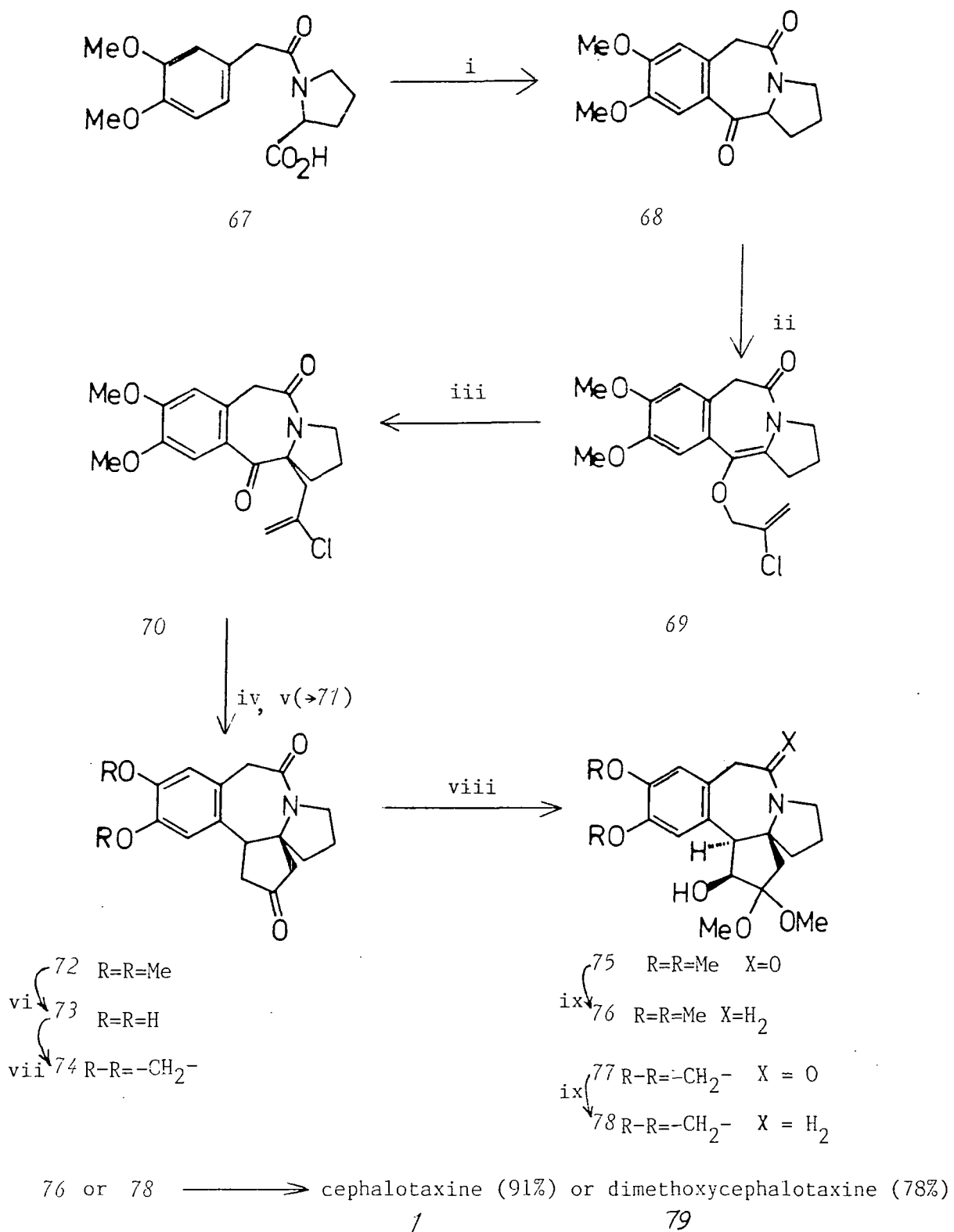
i allyl magnesium bromide (84%), ii  $\text{Me}_3\text{COCON}_3$  (95%), iii  $\text{O}_3$ ,  
 iv  $\text{Ag}_2\text{O}/\text{base}$ , v  $(\text{MeO})_3\text{CH}/\text{H}^+$  (60%), vi  $\text{Na}-\text{K}$ ,  $\text{Me}_3\text{SiCl}$ , vii  $\text{Br}_2/-78^\circ\text{C}$ ,  
 viii  $\text{CH}_2\text{N}_2$  (50%), ix 63 (70%), x  $\text{hv}/\text{KO}^\text{t}\text{Bu}$  (94%), xi DIBAL-H (76%)

Surprisingly, it was not until 1986 that the next total synthesis reached completion, though a number of partly completed syntheses were reported in the meantime. Since then, two further total syntheses have been published. This demonstrates the heightened interest in these alkaloids over recent years.

### iii Hanaoka et al synthesis

These workers' strategy, reported in 1986<sup>39</sup> (outlined in scheme V) starts from the dimethoxy compound 67, leading to both cephalotaxine, 1, and the 3,4-dimethoxy analogue, 79.

SCHEME V



i PPA/55°C (74%), ii 2,3-dichloroprop-1-ene (91%), iii 150°C (97%),  
 iv NaBH<sub>4</sub> (100%), v 90% H<sub>2</sub>SO<sub>4</sub>, 55°C (69%), vi BBr<sub>3</sub>/-78°C (79%),  
 vii CH<sub>2</sub>Br<sub>2</sub>/KF (33%), viii iodosobenzene (80%), ix LAH (85%), x pTsOH,

The benzazepine ring is established early, by acid catalysed electrophilic cyclization of the amide-acid, 67. This is a strategy, therefore, conceptually similar to Weinreb's synthesis, which proceeds via the structurally related intermediates 43 and 44.

The key steps for ring E annulation are the Claisen rearrangement of 69 to 70, and the subsequent stereospecific acid catalysed olefin cyclization of alcohol intermediate 71 to 72. It is important to note that this latter step is the key stereochemical step, and not the Claisen rearrangement which introduces only one (racemic) stereocentre.

Intermediate 72 can then be modified to the natural methylenedioxy functionality, by boron tribromide demethylation to the catechol, 73, followed by insertion of the methylene bridge with dibromomethane, to provide the methylenedioxy system, 74, in moderate yield.

Oxidative modification of the cyclopentanone ring E of 72, or 74, then leads stereospecifically to 75 or 77, respectively, as the bulky oxidant attacks from the least hindered face.

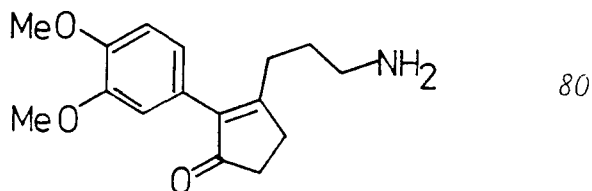
Final conversion of these intermediates to ( $\pm$ )-3,4-dimethoxycephalotaxine, 79, and ( $\pm$ )-cephalotaxine, 1, respectively, is then easily achieved in two steps, in good yields.

Although Hanaoka's synthesis is longer than Weinreb's, the extremely good yields for many of Hanaoka's conversions, compared with the moderate yields of Weinreb's steps, means that the overall yield of ( $\pm$ )-cephalotaxine from Hanaoka's tetracyclic intermediate, 68, is 10% over nine steps, compared to 16% from Weinreb's elaboration of 44 to ( $\pm$ )-cephalotaxine in only three steps. The only reason Hanaoka's route to ( $\pm$ ) cephalotaxine is overall lower yielding than Weinreb's, is the poor yield (33%) for methylene bridge insertion into catechol 73.

The last year (mid-87 to mid-88) has seen two new, elegant, total syntheses. The first of these is an intramolecular nitroso cycloaddition approach, reported by Fuchs et al<sup>40</sup>.

#### iv Fuchs et al synthesis

The Fuchs group's original efforts had been directed towards intramolecular Michael spirocyclization of the intermediate  $80^{41}$ , utilizing well known methodology for histrionicotoxin precursors (see 2.1.i). However, [4.4] spirocyclization attempts on  $80$  proved fruitless.



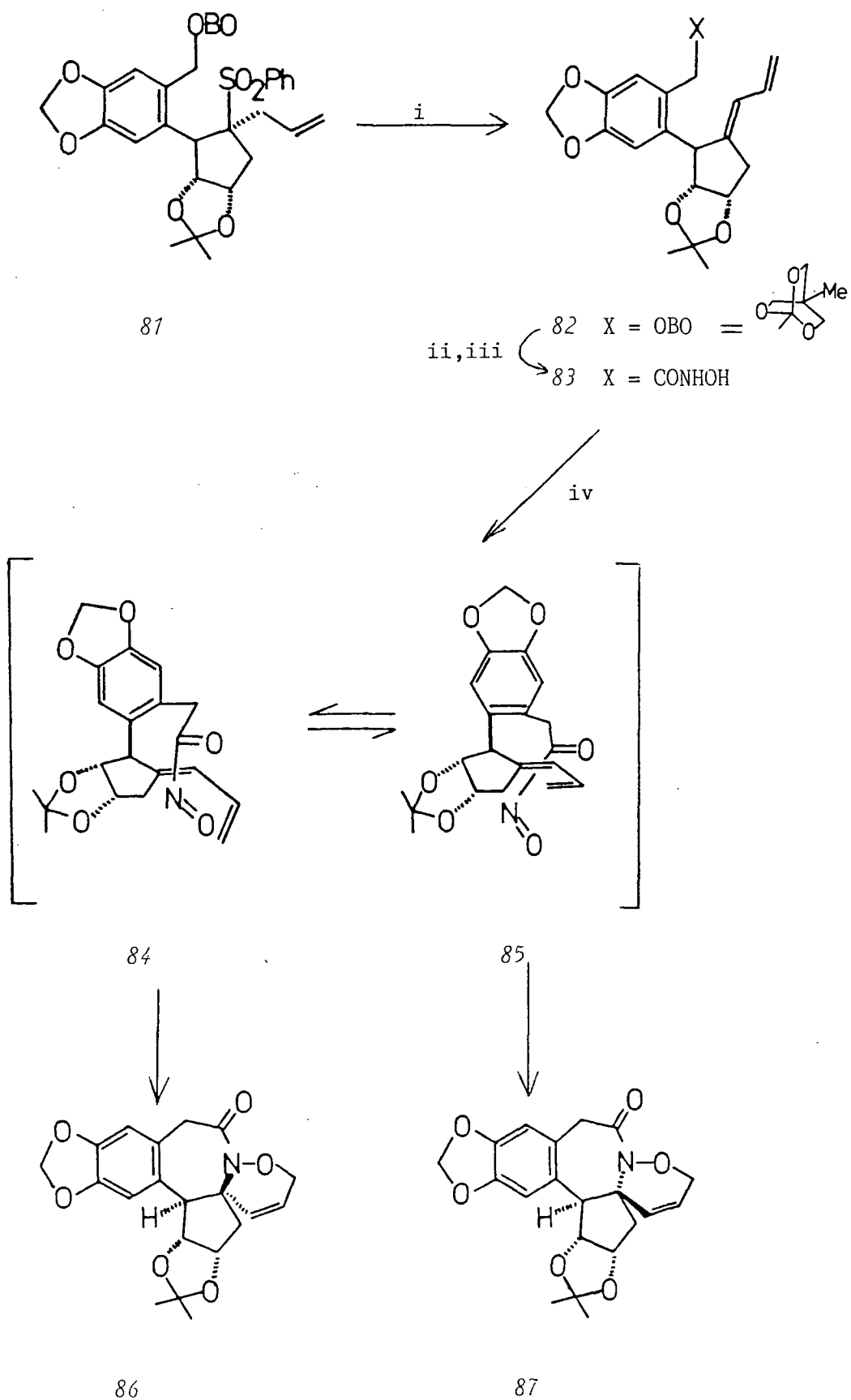
The alternative strategy (scheme VI) envisaged from related precursors, was a [4 + 2] $\pi$  cycloaddition of the nitroso derivative of  $83$  with the internal diene. This would construct ring C, and an easily modifiable ring D, and was expected, from precedents, to occur in a stereospecific manner, leading to cis ring E fusion to ring C, i.e. via intermediate  $84$ .

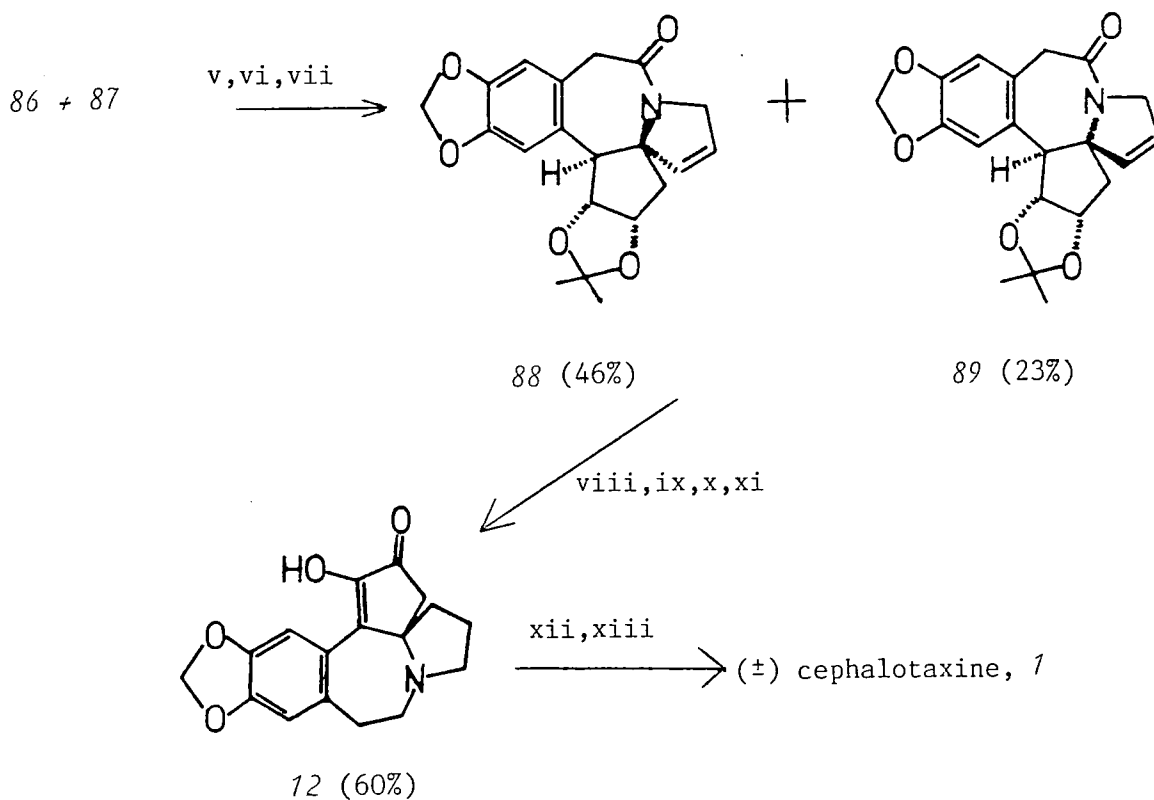
However, the cycloaddition provided an isomeric mixture, which on subsequent N-O cleavage with sodium-mercury amalgam, mesylation and then intramolecular amide alkylation, yielded a 2:1 mixture of the cephalotaxine precursor,  $88$ , and the diastereomer,  $89$ , respectively.

Fuchs observes that the minor isomer must arise from intramolecular cycloaddition via geometry  $85$ , with the dieneophile adding from the opposite face to the tethering moiety, which is unprecedented among intramolecular cycloadditions.

A further attractive feature of this synthesis is that by proceeding via demethylcephalotaxine, both cycloaddition products can be taken through to ( $\pm$ )-cephalotaxine. Reduction of the double bond and lactam carbonyl functionalities of  $88$  and  $89$ , followed by deprotection of the 1,2-cis diol, then Swern oxidation, leads to demethylcephalotaxinone,  $12$ . The loss of the benzylic proton results in the relative stereochemistries

SCHEME VI





i  $t\text{-BuLi}$ , ii  $p\text{TsOH}$ , iii  $\text{NH}_2\text{OH}$ , iv  $\text{HIO}_4$ , v  $\text{Na-Hg/EtOH}$ , vi  $\text{MsCl/Et}_3\text{N}$ ,  
 vii  $\text{NaH}$ , viii  $\text{H}_2/\text{Pd}$ , ix  $\text{BH}_3\cdot\text{THF}$ , x  $\text{HCl}$ , xi Swern oxidation, xii  $p\text{TsOH}$ ,  
 xiii  $\text{NaBH}_4$  (97%).

of both precursors leading to a single racemic intermediate, 12, which is then converted to ( $\pm$ )-cephalotaxine by essentially the same methodology employed by Weinreb et al<sup>33,34</sup>.

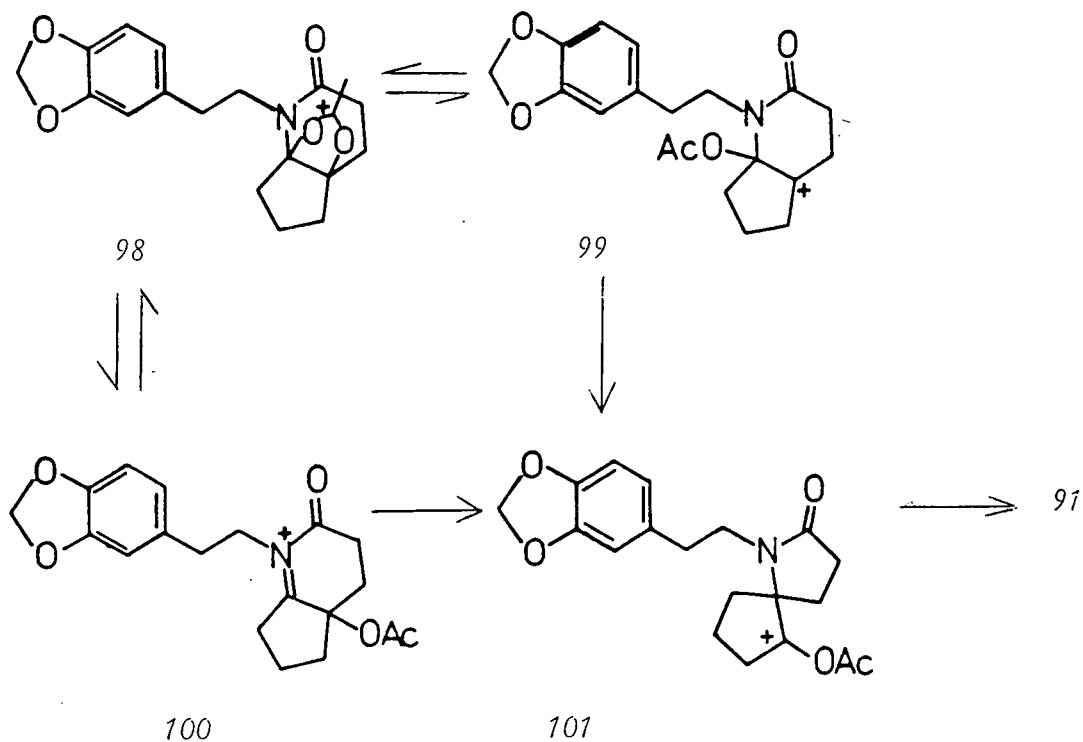
#### v Keuhne et al synthesis

A fifth total synthesis has been presented recently<sup>42</sup>, and has now been published<sup>43</sup> (scheme VII).

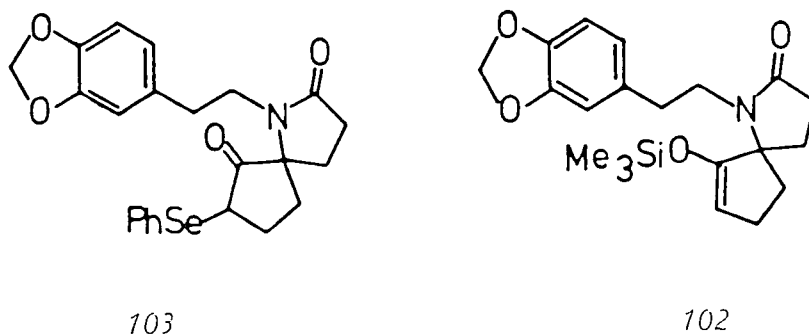
The first key step in this approach is the novel oxidative rearrangement of bicyclic enamide, 90 to the spiro piperidone, 91, which proceeds in good yield.



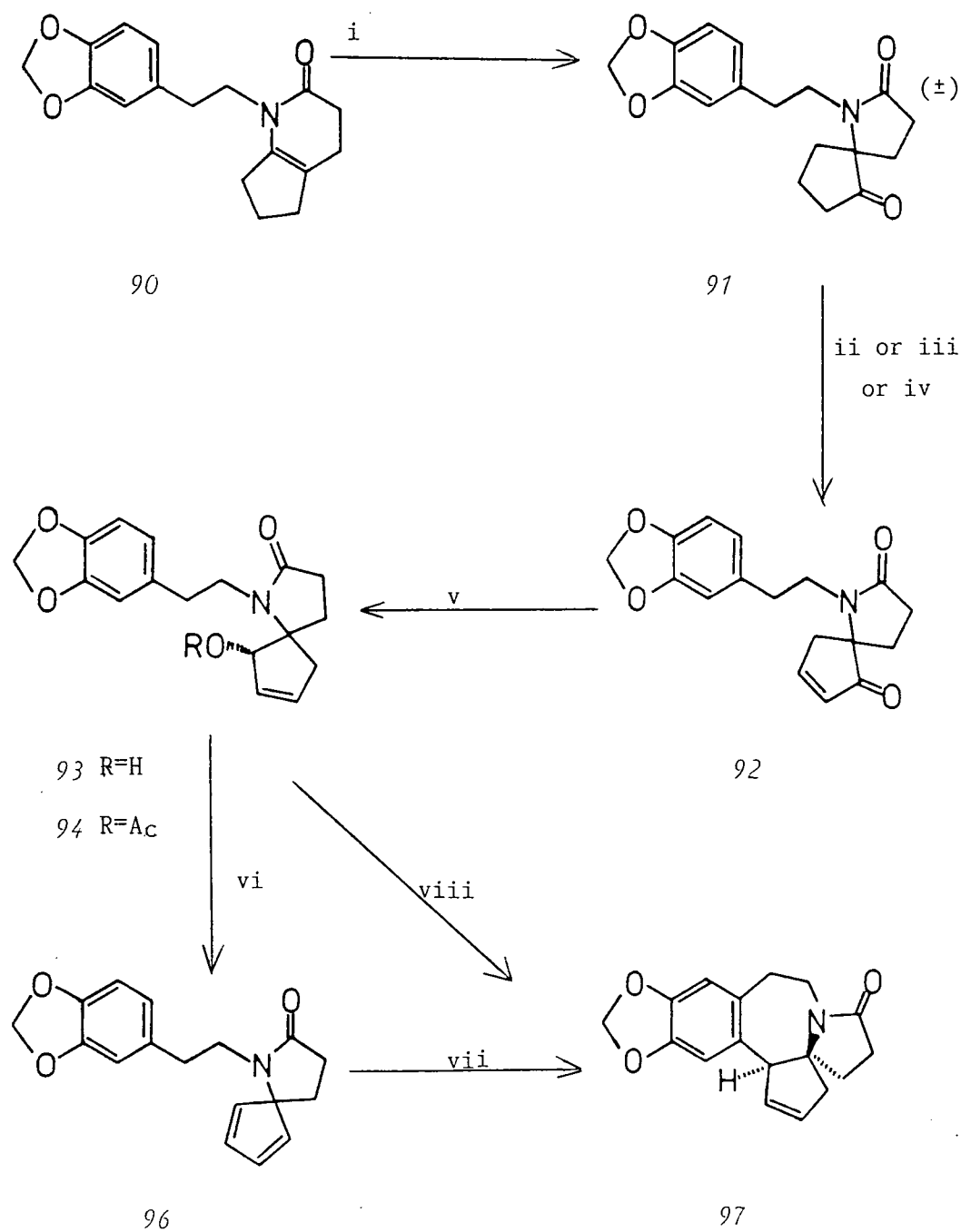
The mechanism postulated by Kuehne et al, involves two rearrangement pathways from the bridging acetal carbocation intermediate, 98, via either 99 or 100, to the cationic spiro intermediate 101. This then adds acetate, and is then converted to the keto system, 91. Support for both rearrangement pathways, was provided by labelling studies.



Introduction of the double bond in the carbocyclic ring (to become ring E) is achieved efficiently in two ways. These two methods share the common silyl enol ether intermediate 102, which is either converted to the selenyl ether, 103, and then oxidatively deselenated to 92, or directly oxidized to 92 by palladium diacetate and quinoline. (The overall yields being 88% and 92% respectively).



SCHEME VII



i  $\text{Pb}(\text{OAc})_4$  (80%), ii (a)  $\text{Me}_3\text{SiI}/\text{HMD}$ , (b)  $\text{PhSeCl}$ , (c)  $\text{HIO}_4$  (88%),  
 iii (a)  $\text{Me}_3\text{SiI}/\text{HMD}$ , (b)  $\text{PO}(\text{OAc})_2/\text{quinoline}$  (92%), iv (bisbenzotrile) $\text{PdCl}_2$   
 (68%), v  $\text{Al}(\text{OPr}^i)_3/\text{}^i\text{PrOH}$  (100%), vi  $\text{Pd}(\text{PPh}_3)_4$ , vii  $\text{CF}_3\text{CO}_2\text{H}$ , viii  $\text{SnCl}_4$  (100%).

Meerwein-Ponndorf reduction of the  $\alpha, \beta$ -unsaturated ketone, 92, is presumed to provide relative stereochemistry with hydroxyl and lactam functionalities trans. After acetolysis, closure of ring C is then achieved in two ways, most efficiently by Lewis acid catalysed cyclization with tin tetrachloride.

The cyclopentanone ring E is then modified via similar methodology to that employed by Fuchs et al<sup>40</sup>.

Overall, Kuehne's strategy has the attractive features of an efficient, novel rearrangement entry of the ringD-ringE azaspirocyclic moiety, and a mild, quantitative, stereospecific entry to the 3-benzazepine ring C.

#### vi Biomimetic approaches

A number of investigations directed towards biomimetic cephalotaxine synthesis, have been reported to be partly successful, though these do not appear to have been carried to the final target.

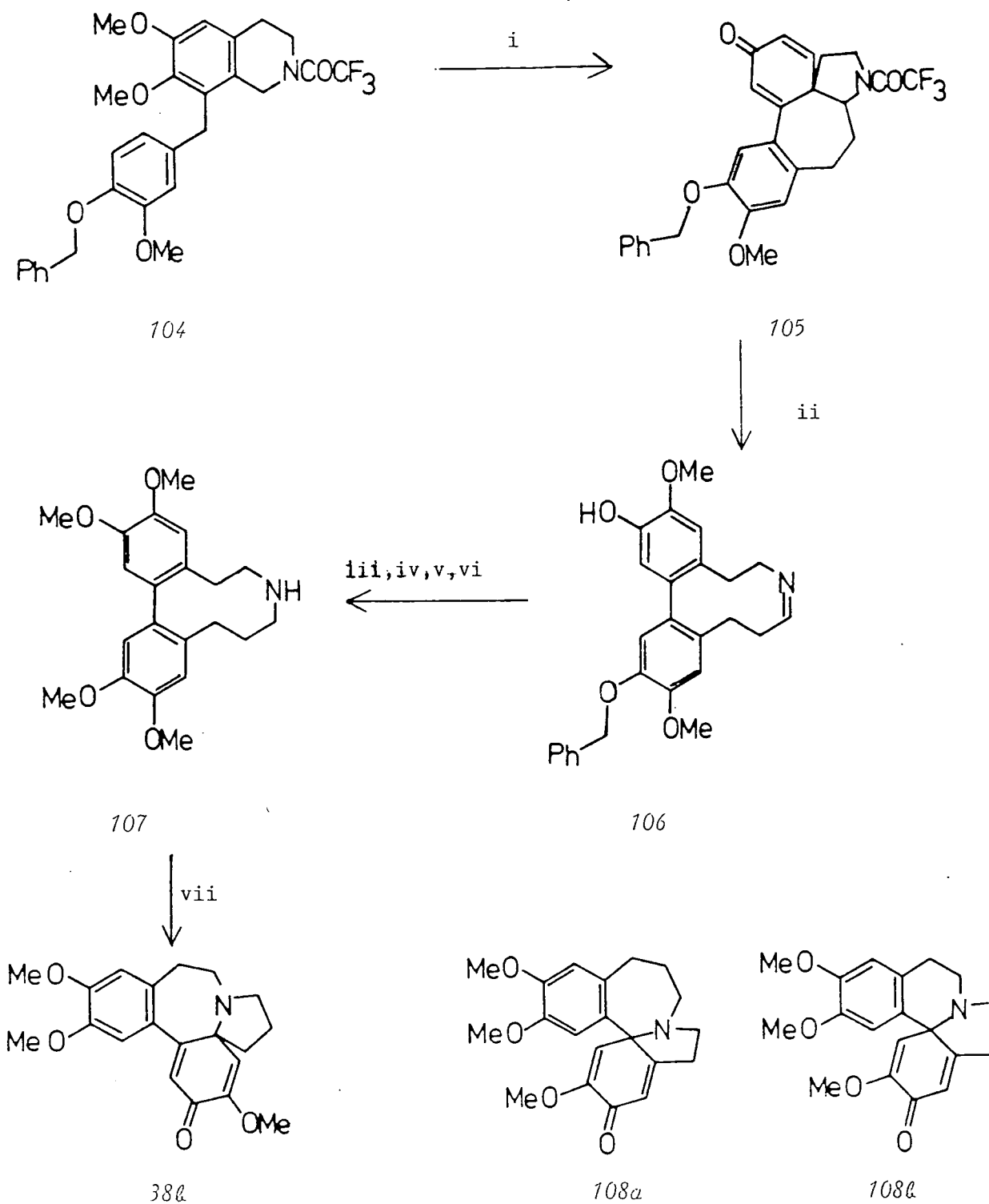
Kupchan et al<sup>44,45</sup> converted the hypothetical biogenetic intermediate 1-phenethyl tetrahydroisoquinoline, 104 to 205 by intramolecular oxidative coupling. This was ring expanded by treatment with base, to 106, then elaborated to intermediate 107 in four steps, in ca. 70% overall yield (scheme VIII).

Oxidation with potassium ferricyanide then provided the coupled product 38a, the assumed biosynthetic precursor of cephalotaxine (see 1.5). Unfortunately, the yield of this step was only 10%. Other attempts to convert intermediate 107 to 38a, led either to 108a<sup>46</sup>, or a mixture of 108a and 108b<sup>47</sup>.

#### vii Other synthetic routes in progress

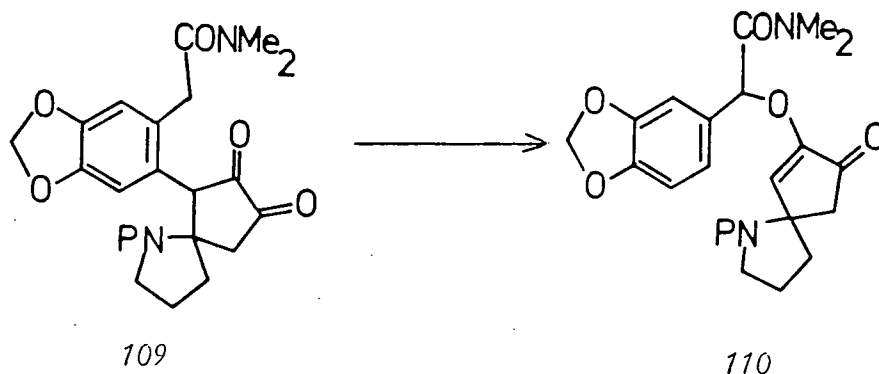
Several other groups are also currently trying to synthesize cephalotaxine. Hill and co-workers<sup>48</sup> are investigating routes via the same 1-azaspirocyclic intermediate as we have prepared (see 2.2), including possible aziridinium expansion methodology (see 3.1.iv).

SCHEME VIII

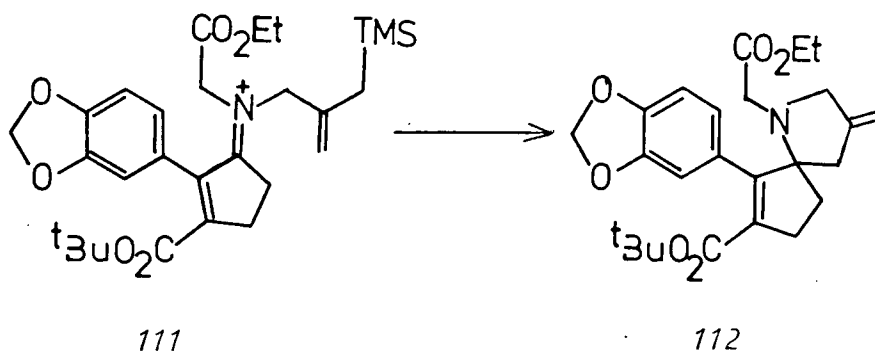


i  $\text{VO}_2/\text{CF}_3\text{CO}_2\text{H}$ , ii  $\text{NaOH}$ , iii  $\text{NaBH}_4$ , iv  $(\text{CF}_3\text{CO}_2)_2\text{O}$ , v  $\text{CH}_2\text{N}_2$ ,  
 vi  $\text{Pd}/\text{H}_2$ , vii  $\text{K}_3\text{Fe}(\text{CN})_6$  (10%).

Raucher's group<sup>49</sup> are investigating methodology via [3,3] sigmatropic rearrangement of intermediates like 109 to 110, to construct an appropriately functionalized azaspirocyclic subunit, with the facility to then construct ring C.



Further development of electron-initiated photocyclization of immonium salts (see 2.1.vii) by Mariano et al<sup>50</sup>, has provided the promising cephalotaxinone intermediate 112 from immonium salt 111.



Prior to these reports, Godleski et al<sup>51,52</sup> published a highly efficient synthesis of a 1-azaspirocyclic related to cephalotaxine (see 2.1.ii), but have not reported any further progress.

Similarly, Bryson et al<sup>53</sup> reported the synthesis of another 1-azaspirocyclic intermediate, still requiring ring C closure to establish the basic cephalotaxine ring system, though this route does not appear to have been developed further (see 2.1.ix).

## viii Conclusion

The intensive efforts of many groups towards the total synthesis of cephalotaxine over the last decade, seem likely to provide a considerable number of efficient routes to this target.

With such a variety of solutions to the synthetic challenges of the cephalotaxine ring system, in hand, the development of 'second generation' syntheses - particularly with a view to effecting asymmetric synthesis - should begin to emerge during the next decade.

### 1.7 Partial syntheses of harringtonines

It is the harringtonines 2-5, and not the parent alkaloid, 1, which show antitumour activity (see 1.3), so much effort has been directed towards partial syntheses of these esters from cephalotaxine.

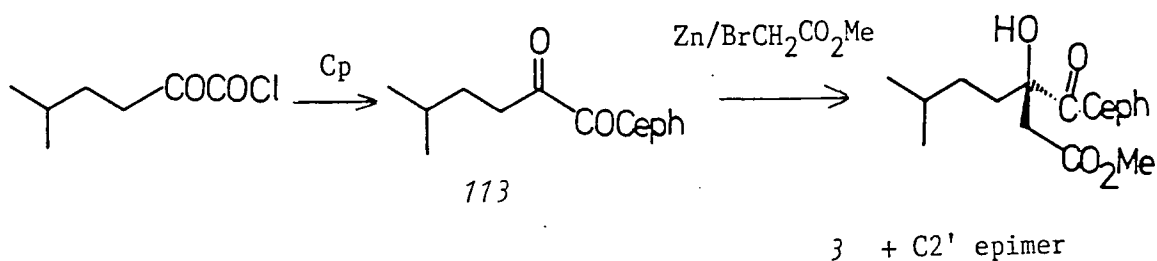
A variety of approaches are now available for the conversion of cephalotaxine to any of its four antitumour esters, which we will here only briefly review. Unfortunately, few of these are asymmetric, and thus separation of diastereomers is usually required.

Initial attempts at acylation of cephalotaxine with a fully formed acid substituent, were uniformly unsuccessful<sup>7,54</sup>, probably due to the steric hindrance of the cephalotaxine hydroxyl group. Thus, the following approaches established the acyl bond to the nucleus earlier in the construction of the side chain, which was then elaborated to the appropriate harringtonine functionality.

#### i Deoxyharringtonine

This derivative, 3, having the simplest of the ester side chains, was the first to yield to partial synthesis. Mikolajczak<sup>55</sup> and co-workers reported the reasonably short route to deoxyharringtonine and its C2' epimer, summarized in scheme IX.

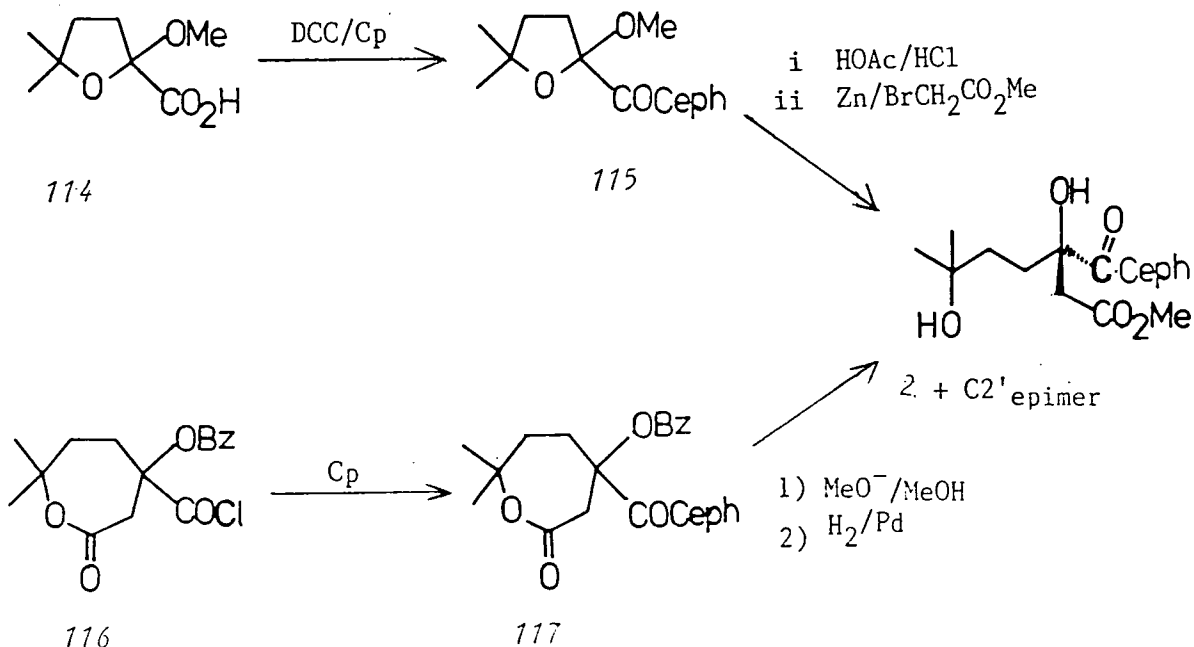
SCHEME IX



ii Harringtonine

Two different general approaches to partial synthesis of harringtonine have been reported, both involving protection of the C7' hydroxyl group, one as cyclic ether, and the other as cyclic acetal. These strategies, commencing from either 114<sup>56</sup> or 116<sup>57</sup> are outlined in scheme X, both providing harringtonine along with its C2' epimer.

SCHEME X



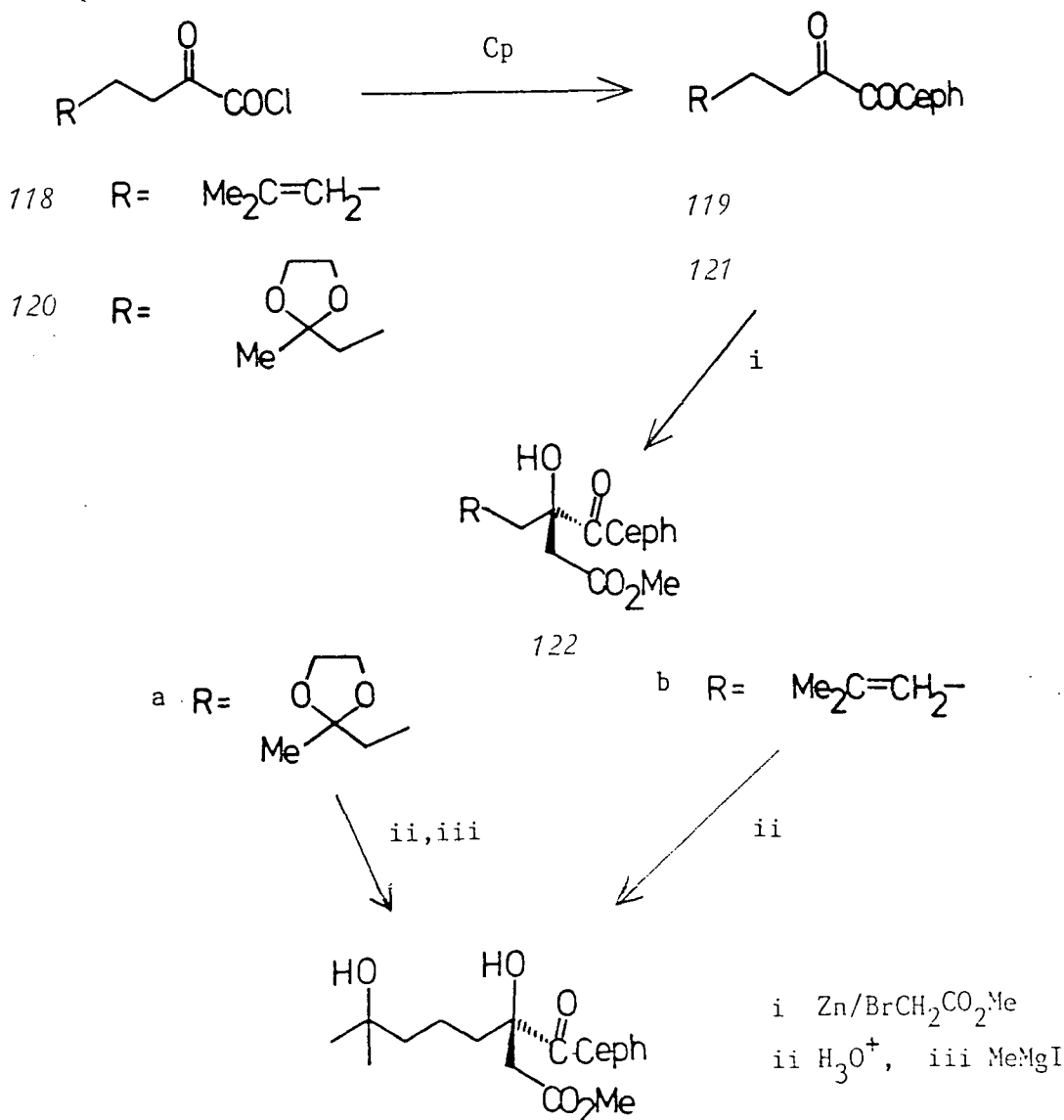
Throughout schemes IX to XIII, 'Cp' refers to parent cephalotaxine, 1, and 'ceph' to the cephalotaxyl nucleus attached to the ester acyl oxygen.

iii Homoharringtonine

This ester is undergoing the most extensive pre-clinical and clinical trials, so viable partial synthesis of this alkaloid is of particular importance.

The reported routes to homoharringtonine are strategically similar to those reported for deoxyharringtonine, involving  $\alpha$ -keto acid chloride intermediates, and Reformatsky methodology to introduce C2' functionality. The two major routes, commencing with olefin 118 and ketal 120 respectively, are outlined in scheme XI.

SCHEME XI

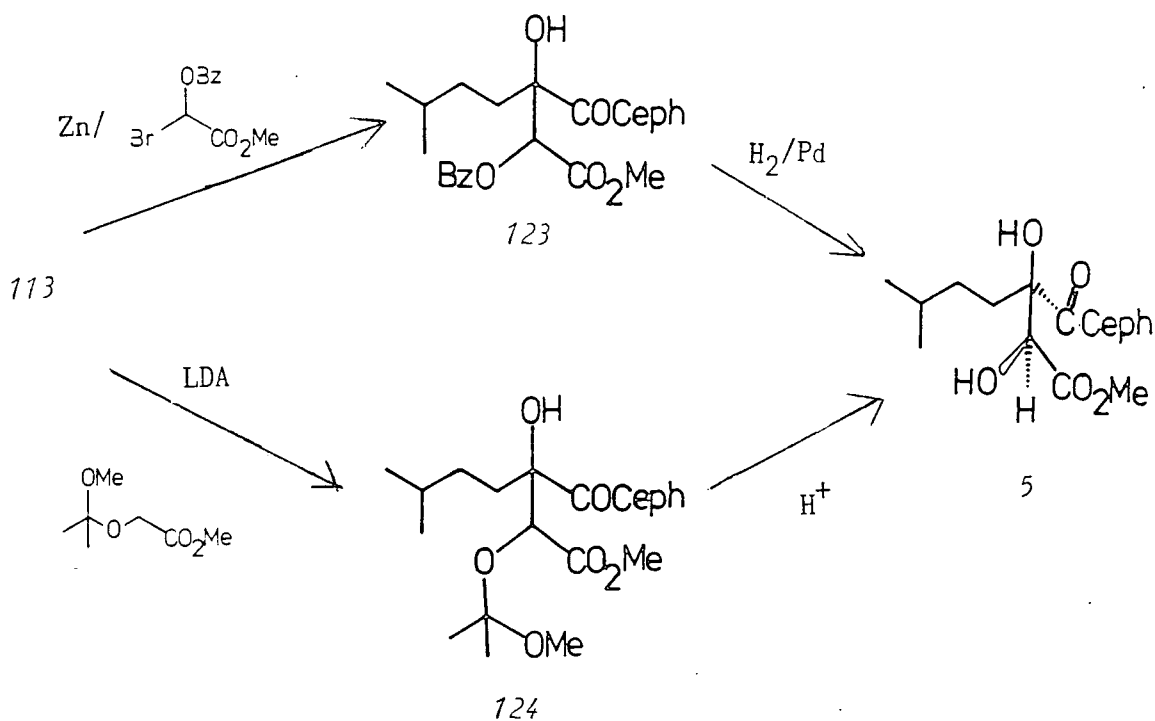




iv Isoharringtonine

Two similar routes have been reported, both proceeding from the deoxyharringtonine intermediate, 113, differing mainly in the choice of carbonyl alkylating agent and hydroxy' protecting group (scheme XII).

SCHEME XII



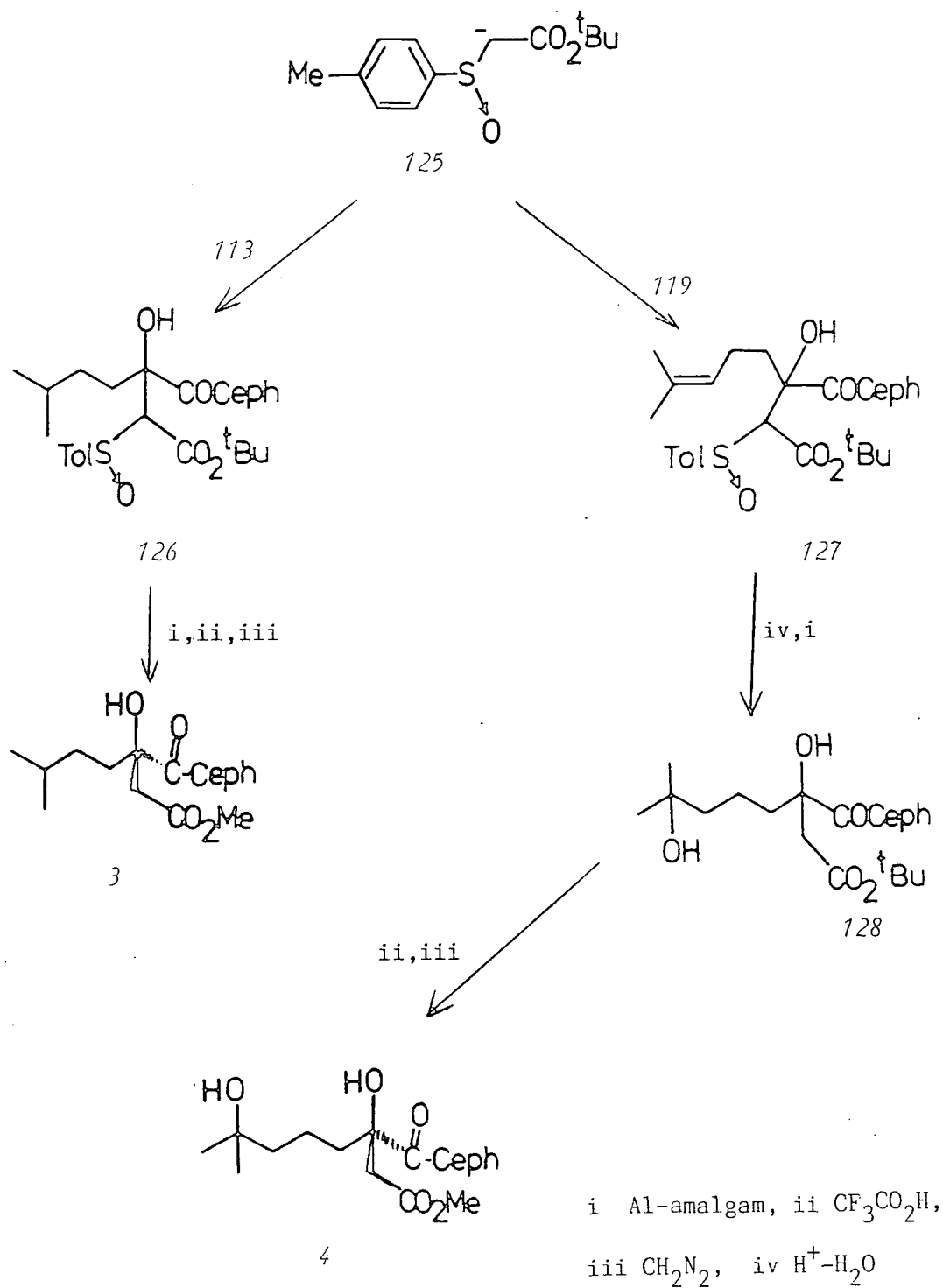
v Asymmetric syntheses of deoxy- and homoharringtonine

A totally synthetic source of harringtonine esters will only really become viable when asymmetric syntheses of both cephalotaxine, and asymmetric introduction of the acyl moiety, have been achieved.

To date, several asymmetric partial syntheses of cephalotaxine esters have been reported.

The first strategy involves stereoselective addition of the chiral (+)-R- $\alpha$ -sulfinyl ester anion, 125, to either 113 or 119 (intermediates above for deoxyharringtonine and homoharringtonine syntheses), which can then be elaborated to the natural deoxyharringtonine and homoharringtonine stereoisomers. (Scheme XIII).

SCHEME XIII



An alternative asymmetric synthesis of homoharringtonine has also been achieved by an apparently minor modification of the approaches above (1.7.iii), using a free carbonyl at C7'. The Reformatsky alkylation of the C2' carbonyl in this case is found to be stereospecific<sup>58,59</sup>.

This remarkable stereospecificity was accounted for by invoking a crown ether like arrangement of the dicarbonyl ester 128, one of the possible geometries providing a better cage-like complexation to the zinc, and this allows only for pro-R attack on the  $\alpha$ -keto functionality. Thus, only the natural C2' epimer is obtained.

## vi Conclusion

These reports hold good promise for the future development of efficient asymmetric partial syntheses of all the harringtonines. This then only leaves the major challenge of an asymmetric synthesis of cephalotaxine, to provide a true total synthesis of the naturally occurring harringtonines.

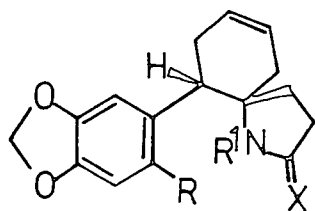
### 1.8 Retrosynthetic analysis of cephalotaxine

The main structural features of the cephalotaxine skeleton are; (1) the 1-azaspirocyclic subunit (fused annular to a 3-benzazepine ring, with defined stereochemical requirements), (2) the central 3-benzazepine ring, and (3) the oxidized cyclopentene ring.

The key 'higher level' features central to this retrosynthetic analysis are; (1) the recognition of the three stereocentres, and more specifically, the identification of the relative stereochemistry of two of these centres common to rings C and E, (2) the topological consequences of this relative stereochemistry, coupled with the rigidity of the spiro centre, leading to a pronounced bowl shape of cephalotaxine, 1, and therefore pentacyclic synthetic precursors.

That this topology might be important to the feasibility of certain steps in the ring synthesis, should be considered. It is certainly important to the stereochemistry of introducing the hydroxyl functionality: it is this bowl geometry which directs stereospecific reduction of the carbonyl to the required hydroxyl configuration<sup>25</sup>.

The design of our synthetic strategy hinged on the identification of a versatile azaspirocyclic intermediate of general form *136*, with the necessary functionality for possible elaboration towards ring C and E.



*136*

R=H, 2C fragment

R<sup>1</sup> = 2C fragment, H

X = O, H<sub>2</sub>

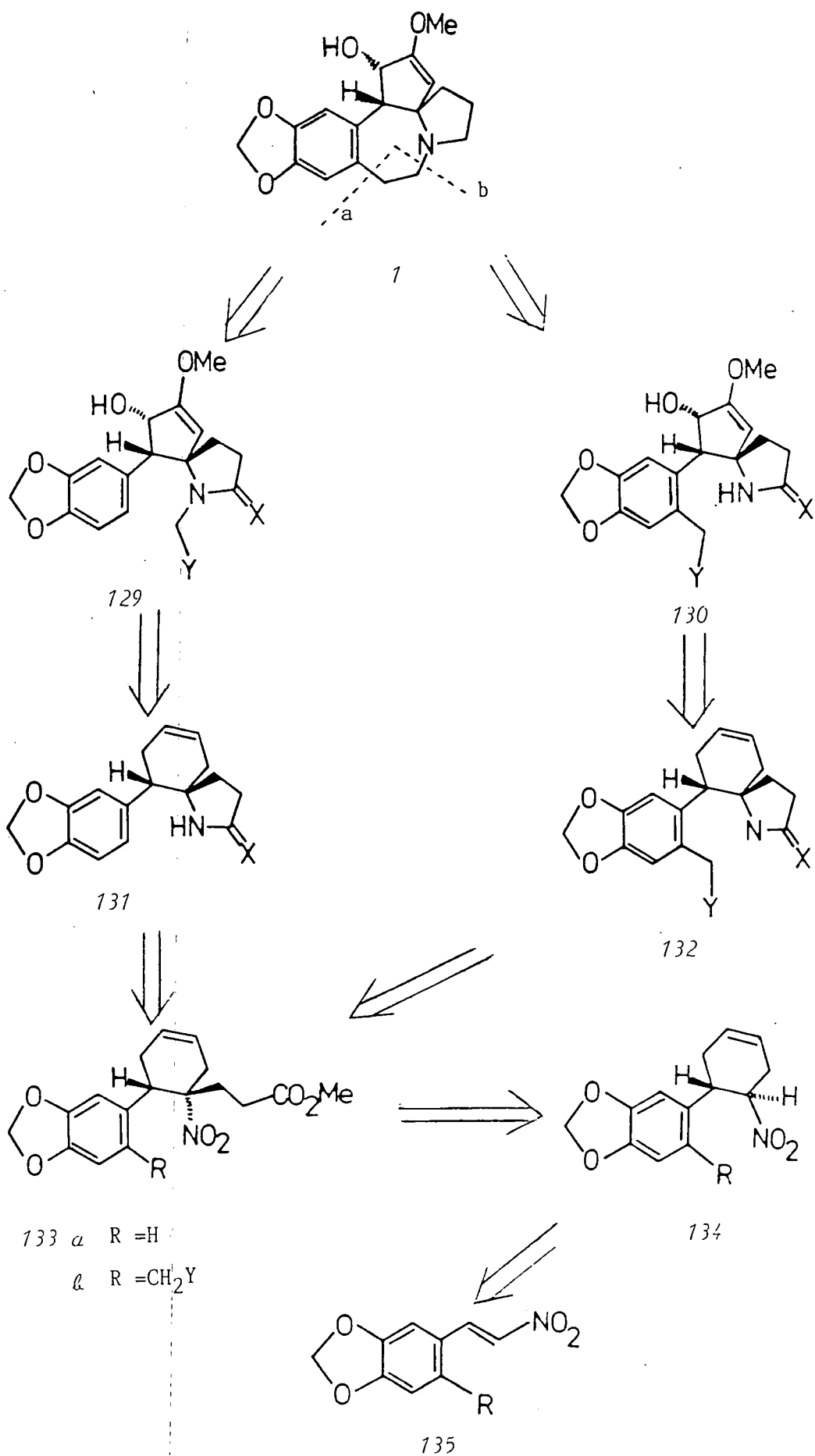
There are two types of such intermediate, viz those arising from C-aryl disconnection (a), and those from C-N disconnection (b). These intermediates represent different strategies, which, however, retrosynthetically converge with intermediates *133a* and *133b* (scheme XIV).

The intermediates *133* are pivotal to both the significant stereochemical, and consequently topological, retrosynthetic considerations of this general strategy.

The relative stereochemistry of *133*, with nitro and aromatic groups trans (which then determines the relative stereochemistry of these centres throughout the envisaged synthesis), could be derived from cis or trans *134*, as Michael addition to *134* should be stereocontrolled on the basis of steric considerations (see 2.2).

The modification of ring E, from the cyclohexene of our earlier devised intermediates, towards the appropriately functionalized cyclopentene, is not addressed in the retrosynthesis of scheme XI. The possibilities available will be covered in chapter 5. However, this problem has been assisted, since the outset of our work, by the variety of intermediate ring E systems that have now been carried through to cephalotaxine ring E<sup>39,40,43</sup>. Hence, we have a variety of pre-targets through which to direct ring E elaboration.

SCHEME XIV



## 1.9 Cephalotaxine analogues

The investigation of synthetic cephalotaxine ring analogues has seen little work, the only notable reports being the syntheses of 3,4-dimethoxycephalotaxine<sup>39</sup> and 8-oxo-cephalotaxine<sup>43</sup>, described in the last two years.

The types of modification which are worth exploring, fall into two major categories: (1) those with novel substitution in any of the rings, and, (2) those involving changes in ring size, or introduction of extra ring heteroatoms.

Category (1) clearly involves a wide range of analogues, with substitution possible in rings C,D, or E, and also on the aromatic nucleus. Also within this category is the cephalotaxine regioisomer, *137a*, which could then provide an alternative series of isomeric harringtonines, *137b*, for study.

Within category (2) there are clearly a number of ring size variations that are possible, and that may be of interest. Prime targets would be 6- or 8-membered ring C, 6-membered ring D, and 6-membered ring E, which will all be discussed further in the relevant sections of following chapters.

Further, of some interest is the introduction of an extra heteroatom in one of the rings, the most feasible being ring C. This is an area we have touched upon, and will be discussed in chapter 4.

The possibility of modifying our synthetic scheme to yield a range of interesting analogues, is one of the underlying aims of the work described here.

With the recent flurry of new synthetic approaches, to cephalotaxine, it is expected that the next few years will witness increasing reports of synthetically modified cephalotaxine ring systems.

CHAPTER TWO

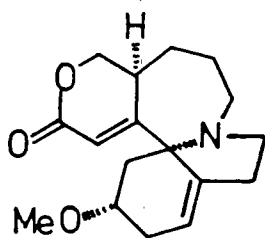
1-AZASPIROCYCLIC RING SYSTEMS:

REVIEW OF METHODOLOGY AND

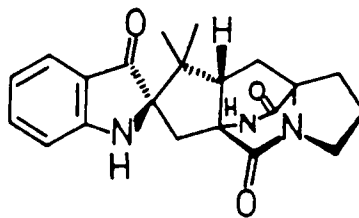
DISCUSSION OF RESULTS

## 2.1 Introduction - Synthetic approaches to azaspirocycles

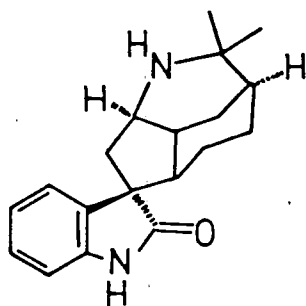
Azaspirocyclic ring systems are present in a variety of natural products, other than *cephalotaxus* alkaloids. These include the 1-azaspiro [5.5] undecane erythrina<sup>60</sup> alkaloids (e.g. 33), the 1-azaspiro [6.5] dodecane homoerythrina<sup>24</sup> (e.g. 31) and phellibilidine<sup>61</sup> alkaloids (e.g. phellibilidine 138), the 1-azaspiro [5.4]decane spirobenzyl isoquinolines (e.g. 191) and the 1-azaspiro [4.4] nonane brevianamide<sup>62</sup> alkaloids (e.g. brevianamide A, 139), and other fused indole alkaloids e.g. austamide 140<sup>63-65</sup> and aristoteline 141<sup>66</sup>.



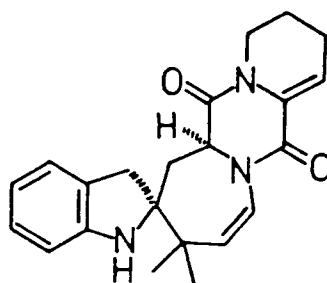
138



139



141

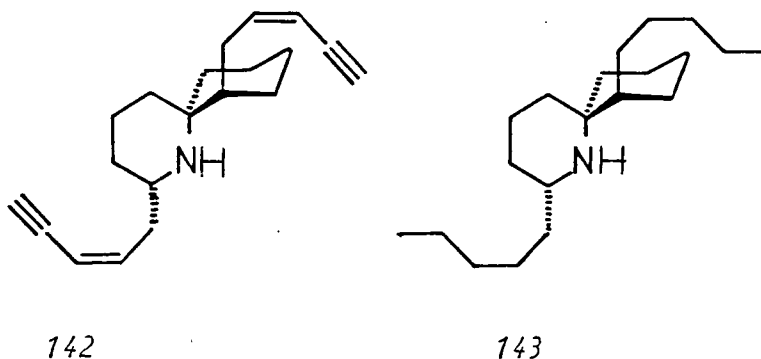


140

Simple bicyclic azaspirocyclic alkaloids which are of current interest include, most importantly, the 1-azaspiro [5.5] undecane histrionicotoxins<sup>67,68</sup> and the 2-azaspiro [5.5] undecane nitramine alkaloids<sup>69</sup>. However, their apparent structural simplicity belies considerable synthetic challenges.

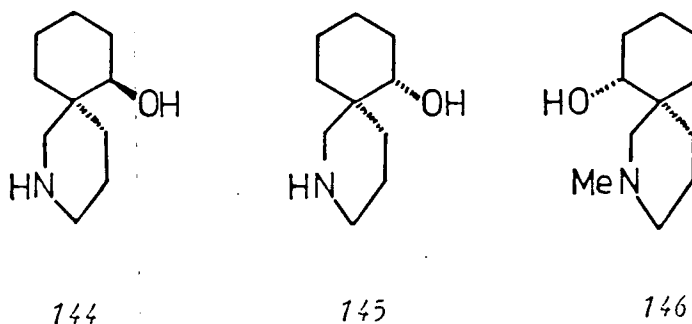


Since the mid-1970s, a number of new approaches to 1-azaspirocyclic ring systems have been developed, motivated largely by the unusual neurophysiological properties of histrionicotoxin 142, and its derivative, perhydrohistrionicotoxin 143.



Consequently, most reported synthetic efforts have been directed towards the 1-azaspiro [5.5] nonane skeleton of these alkaloids, or the 1-azaspiro [4.4] nonane framework of *cephalotaxus*, and brevianamide alkaloids.

Some attention has also been focused on the 2-azaspiro [5.5] undecane nitramine alkaloids, nitramine 144, isonitramine 145 and sibirine 146, largely due to their simplicity and their relationship to the histrionicotoxins. However, we will not consider this work in any detail.



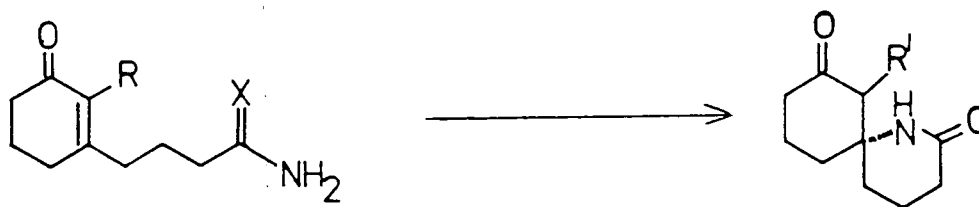
A range of methodologies have been employed, many of which are motivated by achieving stereospecificity in the formation of the spiro-centre, facilitating the possibility of asymmetric induction. Therefore it is not surprising that both intramolecular cycloadditions, and re-

arrangements have been employed. Other types of methodology have included catalytically-assisted intramolecular Michael additions, metal-assisted amine-olefin cyclizations, as well as the extension of iodocyclization reactions<sup>70</sup> to spirocyclizations. These, and other approaches, are now considered in turn.

i Intramolecular Michael cyclizations.

Kishi et al<sup>71</sup> reported the acid-catalysed Michael cyclization of amido-enone 147, with some degree of stereoselection, providing a 2:1 ratio of 148:149, reversed by basic equilibration to a 1:4 ratio.

A similar acid catalysed cyclization of the amino-enone, 150, generated in situ, to the spiroamine, 151, was effected in 94% yield by Magnus et al<sup>72</sup>.



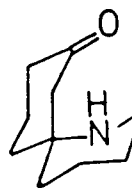
147 R = butyl X=O

148 R = butyl X= n-pentyl

150 R = H X = H<sub>2</sub>

152 R' = Bu

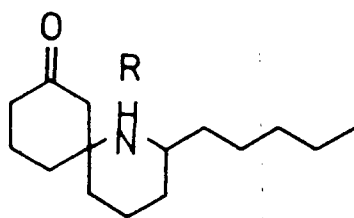
149 R' = Bu



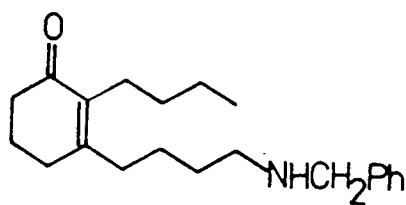
151

In closely related work, Corey et al<sup>73</sup> found no stereo-selection in the uncatalysed cyclization of 152 to 153, while Godleski et al<sup>74</sup> reported that trimethylsilyliodide catalysed cyclization of 154 provided 155 stereoselectively.

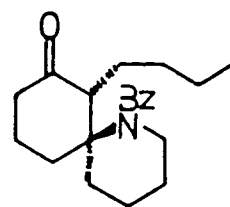
An attempted extension of this methodology to the synthesis of a 1-azaspiro [4.4] nonane precursor of cephalotaxine proved unsuccessful<sup>40</sup>.



153

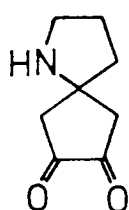


154

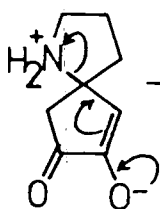


155

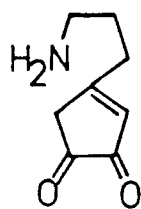
Interestingly, Semmelhack et al<sup>38</sup> found that azaspirocycle 62 was readily polymerized. They postulated that the zwitterionic form 156 underwent a retro-Michael reaction to 157, which was subsequently polymerized.



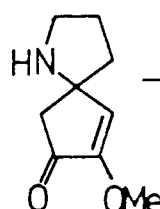
62



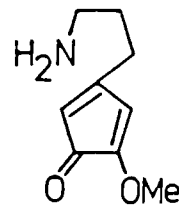
156



157



63

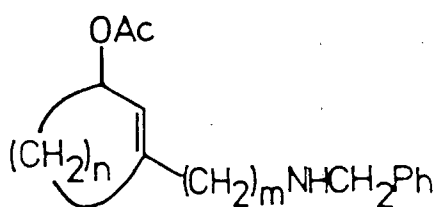


158

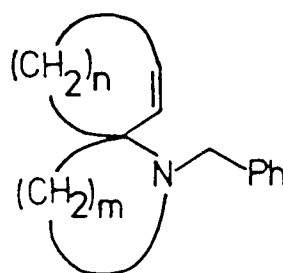
Similarly, they suggest that instability of 63 is due to a related retro-Michael elimination to 158.

## ii Metal assisted cyclizations

Metal assisted spirocyclization of substrates 159, clearly related to those above, has provided entry not only to the 1-azaspiro [5.5]



159



160a n = 3 m = 4

l n = 3 m = 3

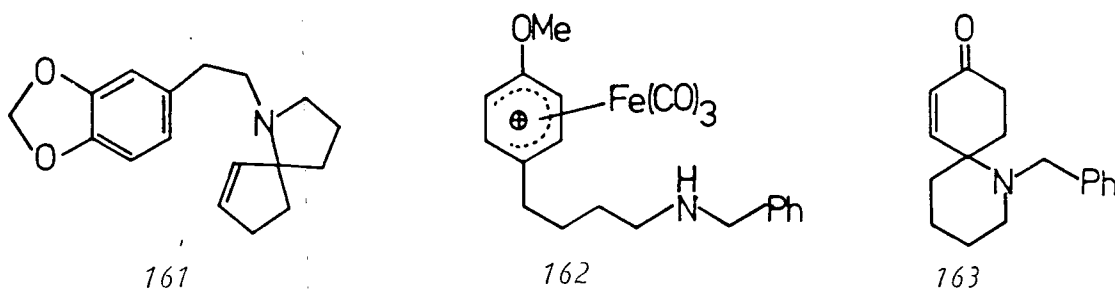
c n = 2 m = 4

d n = 2 m = 3

undecane skeleton, 160a, but also to the 1-azaspiro [4.5] - and 1-azaspiro [5.4] - decanes 160l and 160c respectively, and 1-azaspiro [4.4] nonane, 160d skeletons<sup>51,52</sup>.

Similarly, Carruthers et al<sup>75</sup> have recently found palladium (0) catalysed cyclization of amino-cyclohexyl acetate 159*g* ( $n = 3, m = 4$ ), to azaspirocycle 160*a*, to proceed smoothly in moderate yield.

This methodology has been extended to the synthesis of the cephalotaxine intermediate, 161, by these workers, the cyclization step itself being quantitative. Though further progress is yet to be reported, this approach holds the possibility of leading to an enantioselective synthesis, utilizing the potential of allyl palladium complexes for asymmetric synthesis<sup>76a,76b</sup>.



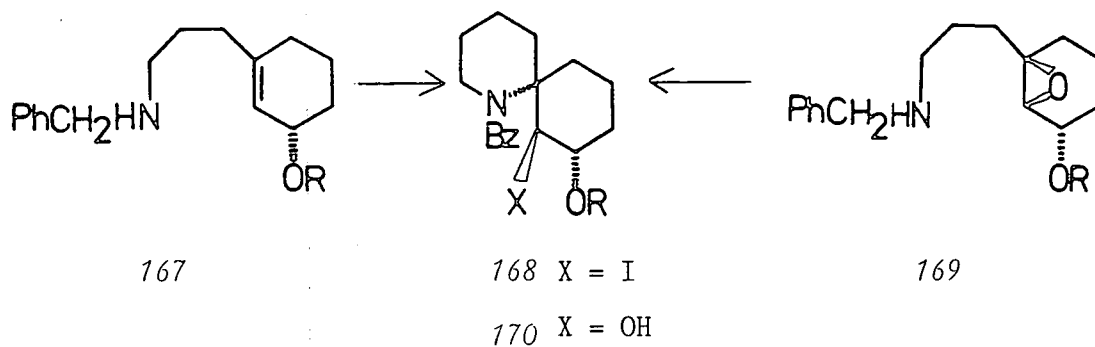
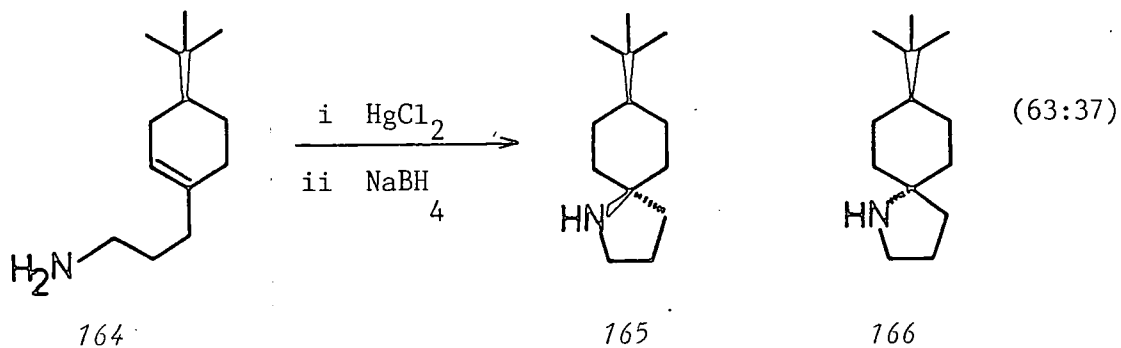
Azaspirocyclization of a cyclohexadienylum iron tricarbonyl complex, 162, followed by oxidative decomplexation and hydrolysis, has also provided entry to the 1-azaspiro [5.5] undecane ring system, 163<sup>77</sup>.

### iii Halo and mercuricyclizations

The mechanistically similar methodologies of mercuricyclization and iodocyclization, provide another entry to azaspirocycles, with the possibility of stereoselection.

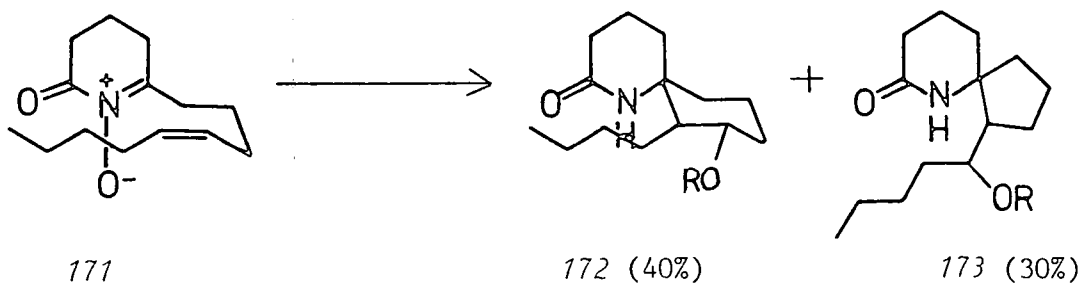
The mercuricyclization of the amino-olefin 164 provides some selection of 165 over 166<sup>70,78</sup>, while iodocyclization of 167 leads to good selectivity, providing the single azaspirocycle 168<sup>79,80</sup>.

A related, but uncatalysed, reaction is the spirocyclization of the epoxide 169, susceptible to attack by the amine internal nucleophile (cf. the activated double bond of 167 in halocyclization). This reaction is also stereoselective in affording 170.

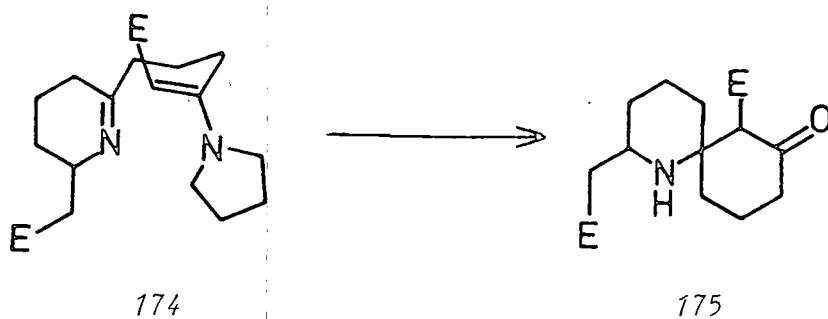


#### iv Acyliminium cyclizations

Evans et al<sup>81,82</sup> used a 'formate activated' exocyclic olefin as internal nucleophile to attack the endocyclic acyliminium double bond of 171, providing a mixture of spirocyclic products 172 and 173.



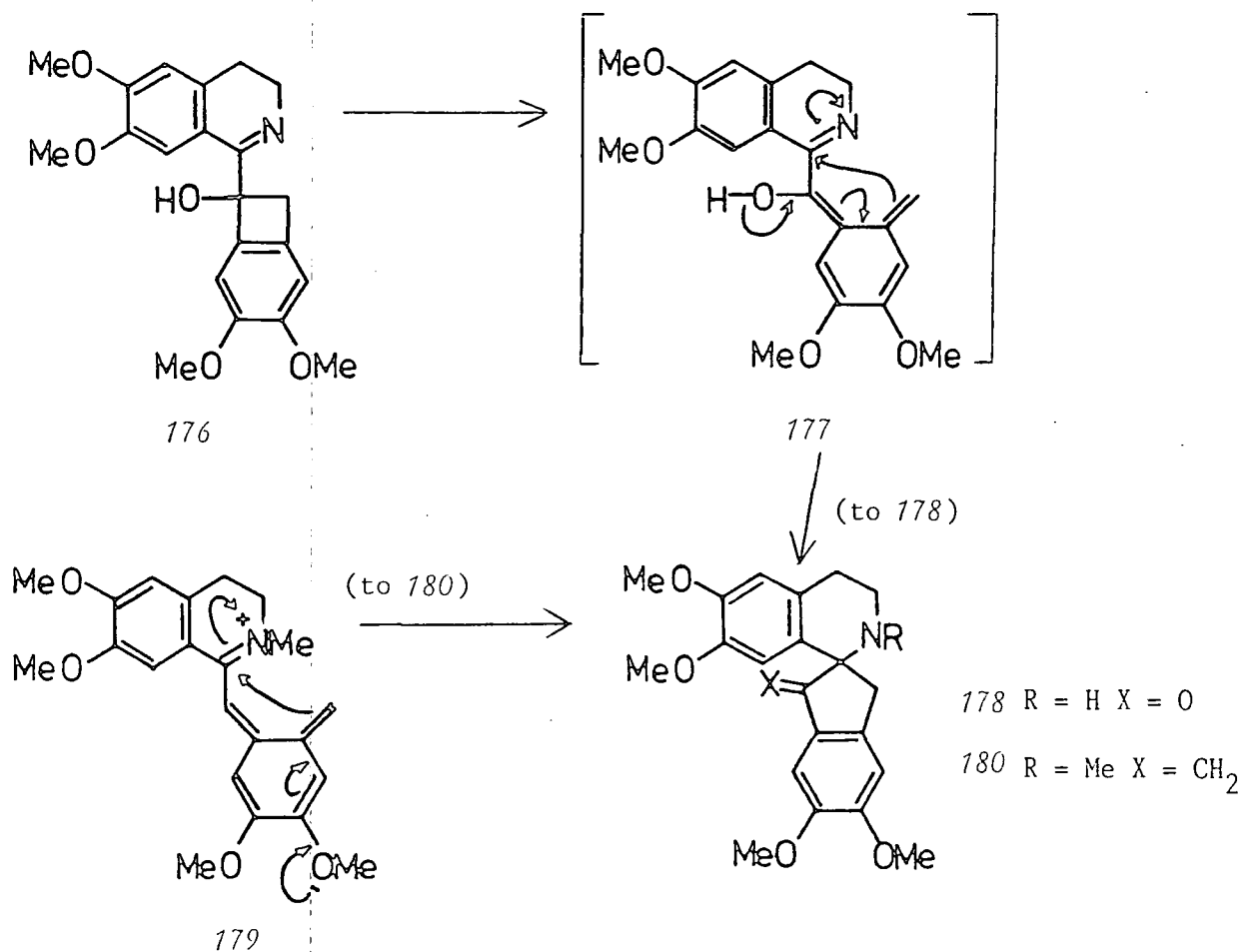
Similar activated olefin cyclizations onto acyl iminium intermediates have also been reported by Schoemaker et al<sup>83,84</sup>, while the analogous acid catalysed cyclizations of exocyclic enamines onto imines has been reported by Corey et al<sup>85</sup>, in the cyclization of 174 to 175.



Cyclizations of olefins onto internal imine or iminium functionalities have also been reported in the synthesis of spirobenzylisoquinolines. These proceed via ring opening of a benzocyclobutane, the resulting double bond - activated by virtue of the instability of the o-quinonoid intermediate - then attacking the imine or iminium carbon.

For example, the unstable 176 opens to the reactive o-quinonoid 177. Assistance from the hydroxyl group is then suggested to aid nucleophilic attack on the imine, generating azaspirocycle 178<sup>86,87</sup>.

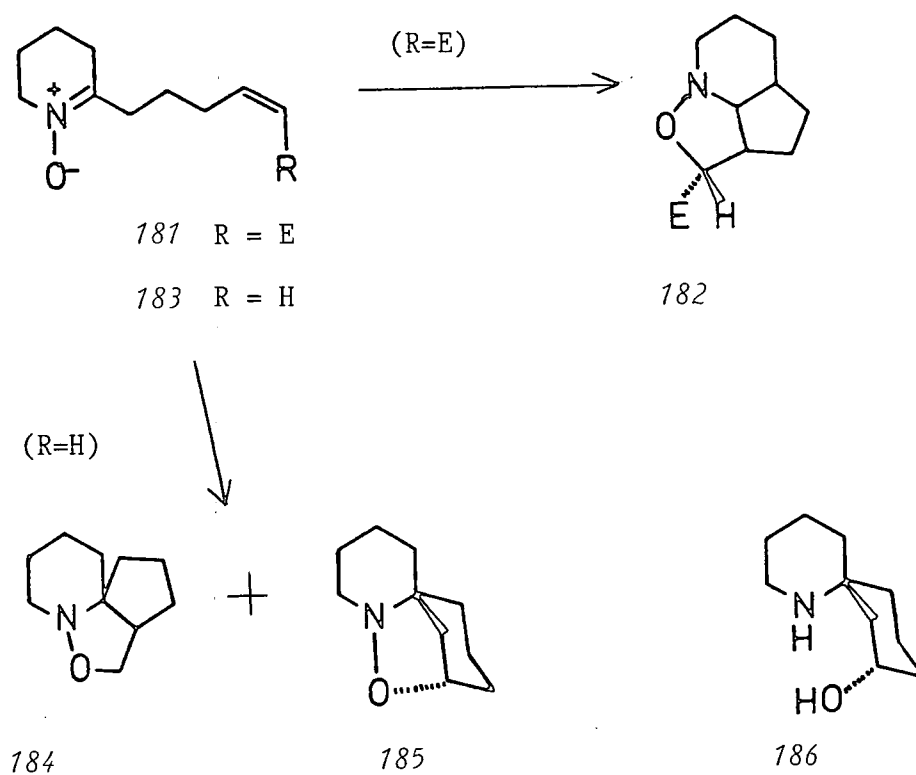
Analogously, the intermediate iminium o-quinonoid system 179 undergoes spirocyclization to 180, by a similar process.<sup>88,90</sup>



## v Intramolecular cycloadditions

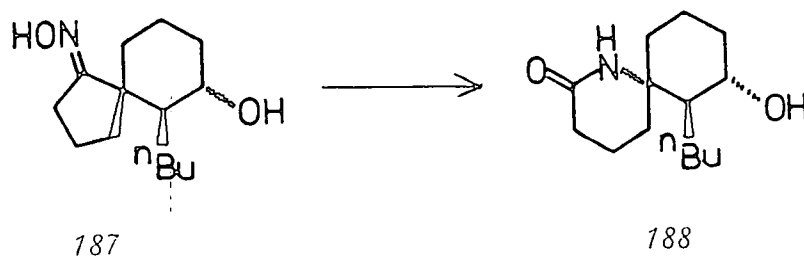
The use of intramolecular cyclizations is particularly attractive, because of the well-defined stereochemistry of such cyclizations.

Cycloaddition of nitrones to olefins have been used e.g. for 181→182<sup>91</sup>, and 183 to a mixture of 184 and 185<sup>92</sup>. The latter compound was then converted to the simple 1-azaspirocycle 186.



## vi Rearrangements

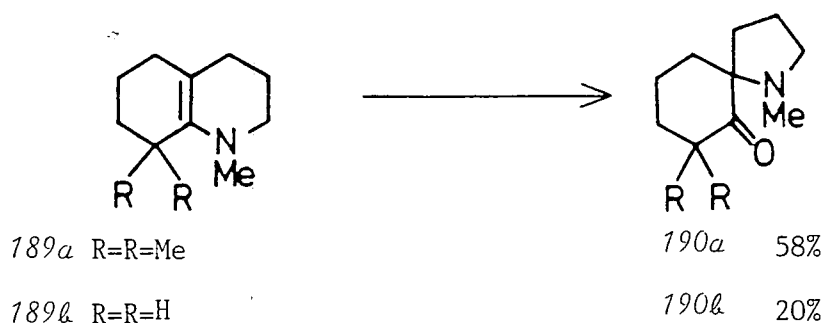
One of the earliest syntheses of a histrionicotoxin derivative, reported by Corey et al<sup>93</sup>, utilized the Beckmann rearrangement of the carbospirocyclic oxime 187, to the spiro lactam 188.



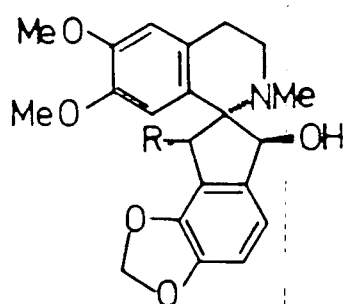
A similar approach to both the 1-azaspiro [5.5] undecane and 1-azaspiro [5.4] decane skeletons, by thionyl chloride induced Beckmann rearrangement, had been reported previously by Hill et al<sup>94</sup>, though yields were poor.

This Beckmann rearrangement methodology has been later used in the synthesis of substituted 1-azaspiro [5.5] undecanes<sup>95</sup>.

A variety of other rearrangement approaches to azaspirocycles have been reported since the mid-1970s. The novel base induced rearrangement of an intermediate iminium salt, from treatment of 189 with bromine, leads to system 190 in poor to moderate yields<sup>96</sup>.

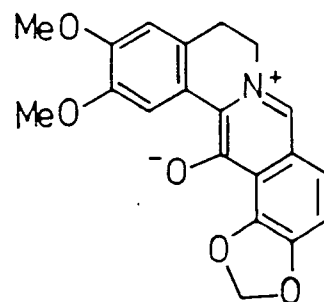


Spirobenzylisoquinoline alkaloids, containing a benzo-fused 1-azaspiro [5.4] decane substructure, have also been obtained by rearrangements. Approaches to ochrobirine<sup>97</sup>, corydaine<sup>98</sup>, fumaricine<sup>99</sup>, raddeamine, 191,<sup>100</sup> and yenusomine, 192,<sup>100</sup> all proceed via photo-rearrangement of a phenol betaine intermediate 193, to yield fused aziridine isoquinolines; aziridine opening then leads to the spiro fused products.



191 R= HO  $\blacktriangleright$

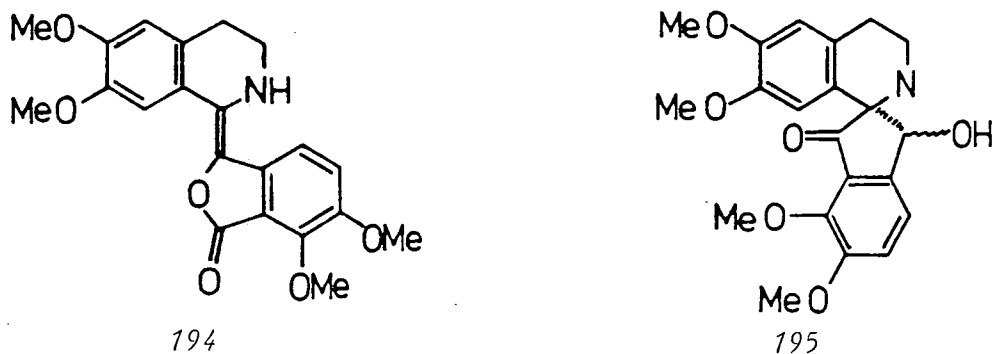
192 R= HO  $\cdots$



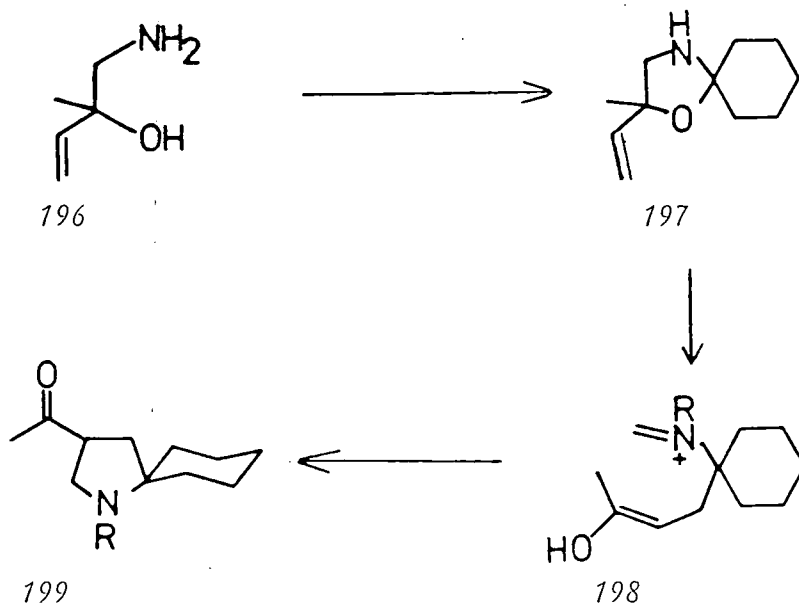
193



A completely different rearrangement to a spirobenzylisoquinoline occurred when DIBAL-H reduced 194 to 195<sup>101</sup>.



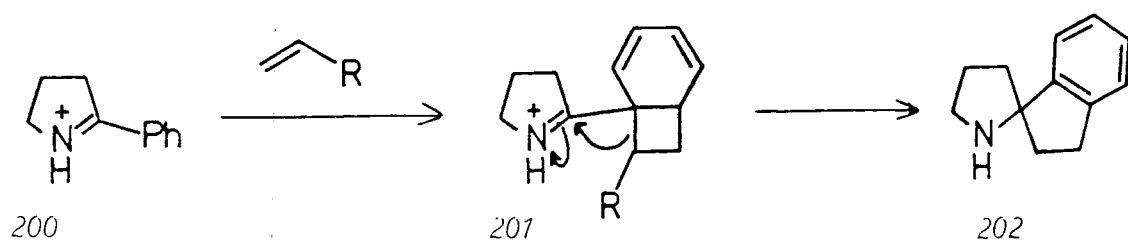
An elegant approach to 1-azaspirocycles, was reported by Overman et al<sup>102</sup>, involving insertion of cyclohexanone into 196, yielding intermediate 197, which underwent a [3,3] sigmatropic rearrangement, (a cationic aza-Cope rearrangement) after treatment with alkyl iodide, as the key step. The final cyclization involved the Mannich reaction of the rearranged intermediate 198, to yield 199 in 70% overall yield.



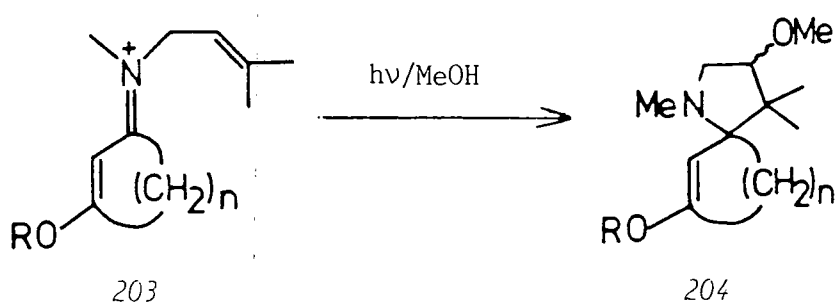
#### vii Photochemical routes

A few photochemical routes to 1-azaspirocycles have been reported, other than the photo rearrangements to spirobenzylisoquinolines described above.

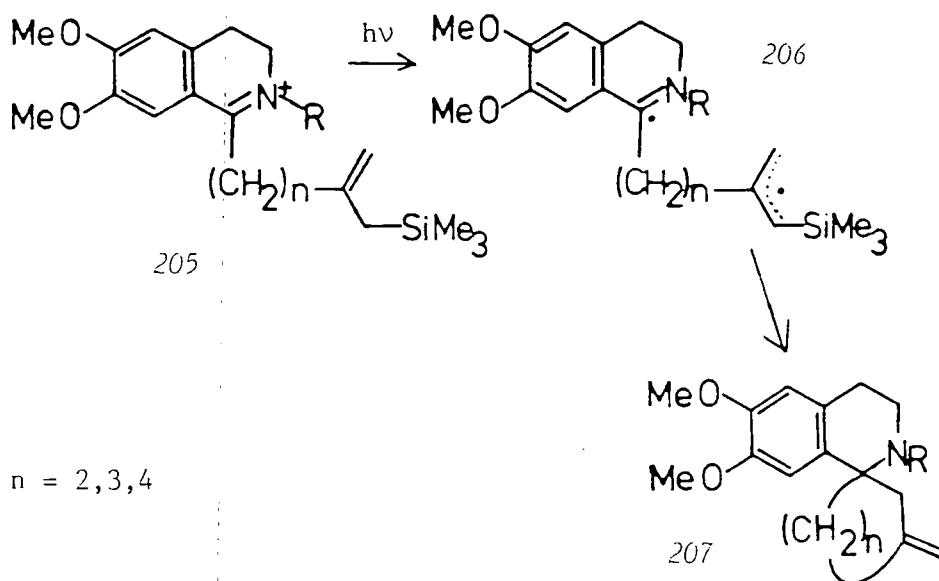
One approach utilizes a [2+2] $\pi$  arene-olefin cycloaddition, converting 200 to 201, which then undergoes rearrangement to the azaspirocycle 202<sup>103,104</sup>.



Another approach involving photo-promoted intramolecular nucleophilic attack on an iminium functionality, yields spiroamine 204 from 203<sup>105</sup>.



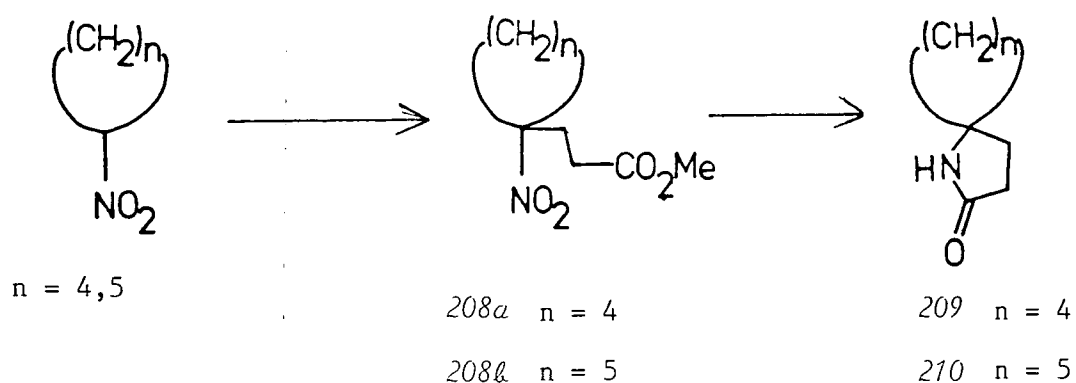
Similarly, isoquinoliniums, 205, undergo electron transfer induced photospirocyclization to spiroisoquinolines 207, via intermediate diradicals 206<sup>106,107</sup>.



viii Quaternization via intermolecular Michael addition

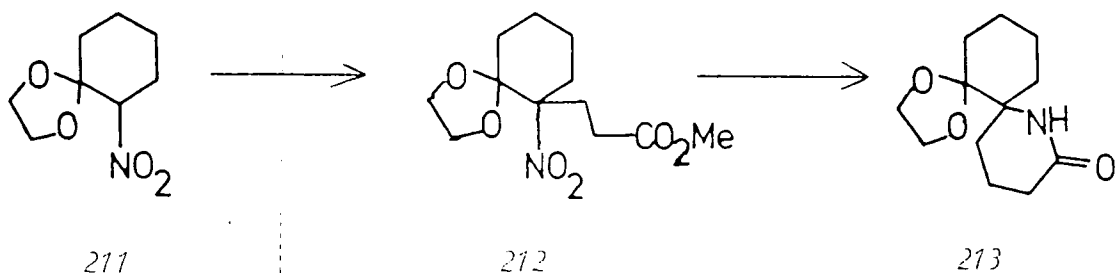
The use of intermolecular Michael additions to construct the quaternary centre, precursory to spirocyclization, has also been used, both generally to yield model azaspirocycles, and more specifically to yield 2-azaspirocyclic nitramine analogues.

Particularly relevant to the present work, is an early report that the alkylation of the anion of nitrocycloalkanes with methyl acrylate, followed by hydrogenolysis, gave good yields of the 1-azaspirocycles 209 and 270<sup>108,109</sup> (see chapter 6).



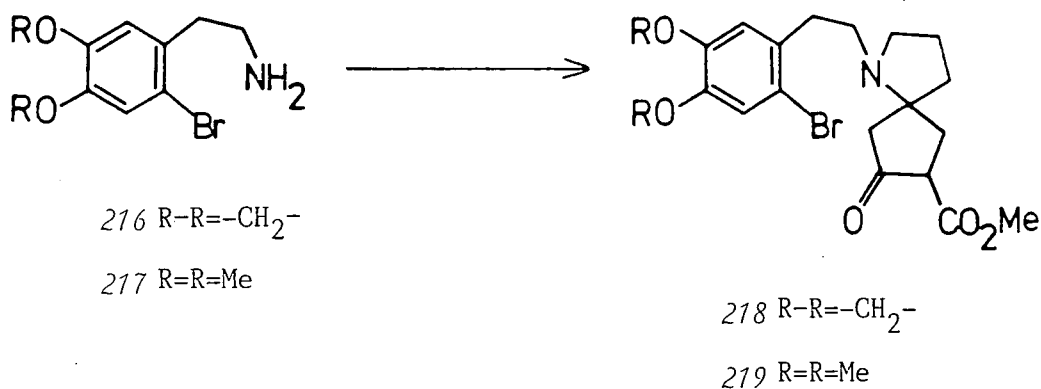
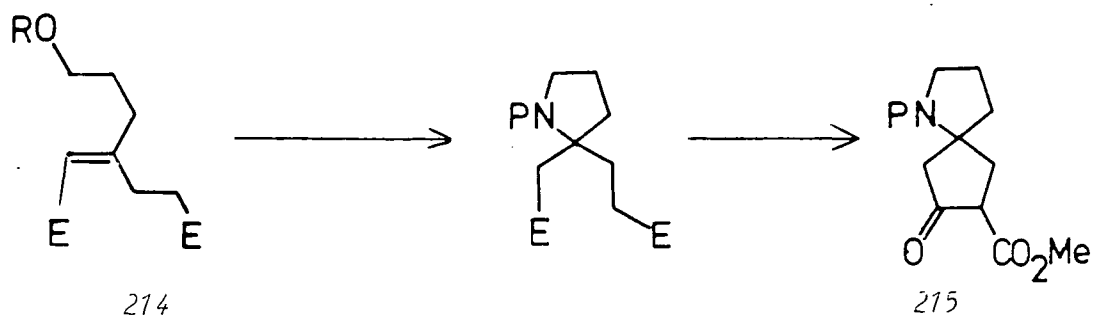
Subsequently, this methodology - including an intermediate homologation - was applied to the nitrocyclohexanone ketal 271, providing the 1-azaspiro [5.5] undecane, 273<sup>110,111</sup>.

Similar methodology has also recently been applied to synthesis of spirofused porphyrin-pyrrolidone type compounds<sup>42</sup>.



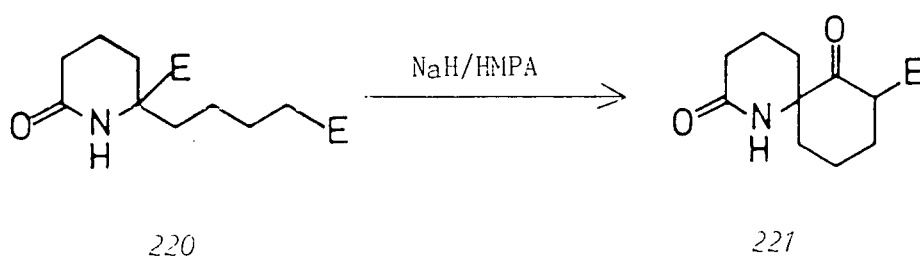
ix Miscellaneous methodologies

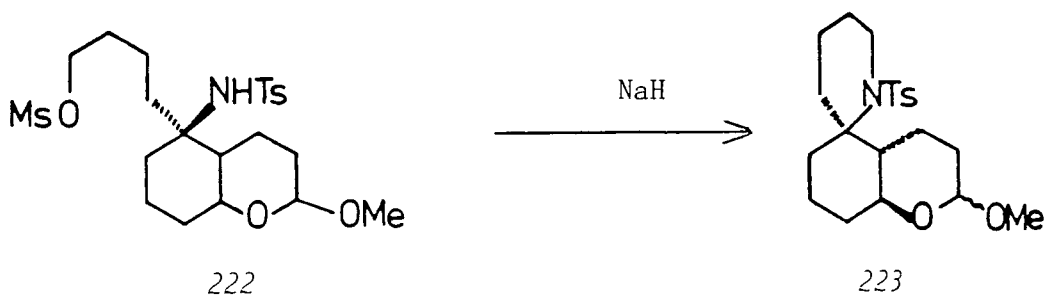
Amongst other general approaches to azaspirocyclic ring systems<sup>113,114</sup>, one of particular relevance to our work was reported by Bryson et al.<sup>53</sup> The general amine insertion - Dieckmann cyclization methodology of 214→215, has been extended to amines 216 and 217 to provide good yields of cephalotaxine and dimethoxy-cephalotaxine precursors 218 and 219.



Other spirocyclizations utilizing Dieckmann closure reactions, have included the cyclization of 220 to 221<sup>111</sup>.

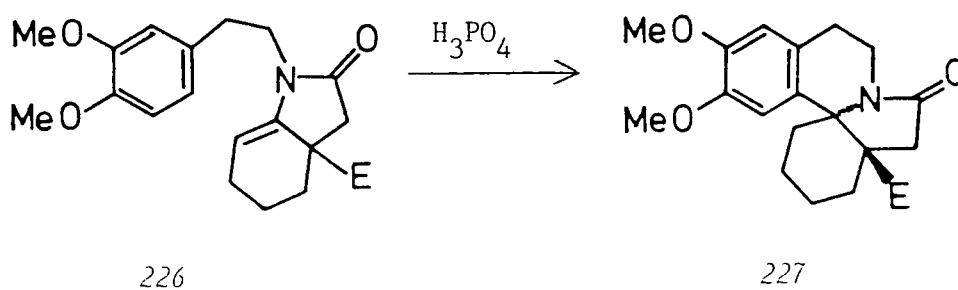
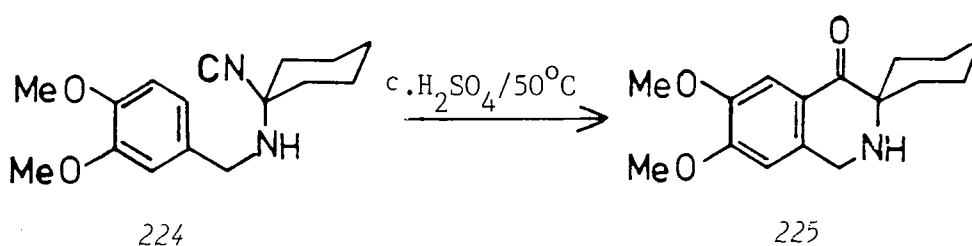
Intramolecular nucleophilic displacement with amide anions has also been employed, effecting spirocyclization of 222 to 223<sup>96</sup>.





Electrophilic cyclizations have provided entry to certain benzo-fused 1-azaspirocycles. For example, strong acid catalysed cyclialkylation of 224 yields the azaspirocycle 225 in good yield<sup>115,116</sup>.

Similarly, acid catalyzed cyclialkylation, e.g. of enamide 226, has also provided a general route to erythrina alkaloids<sup>117-120</sup> e.g. 227, which contain a further fused spiroisoquinoline structure.

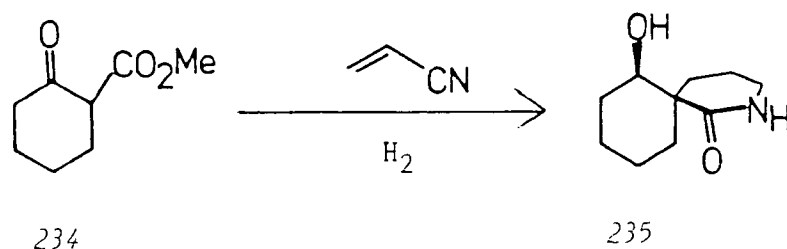
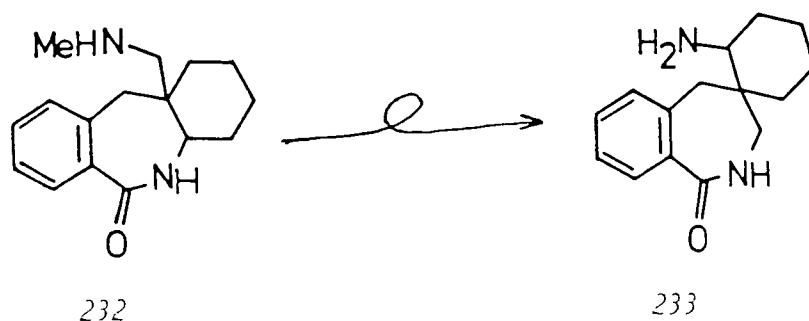
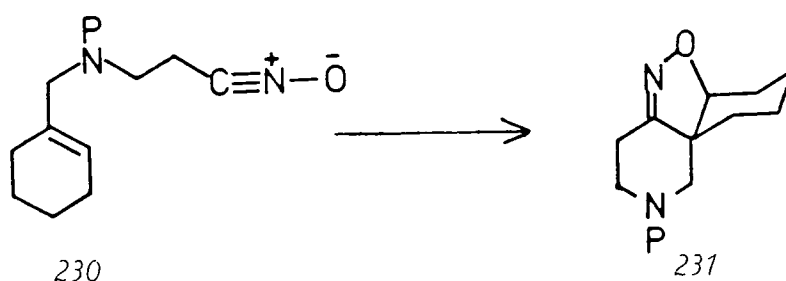
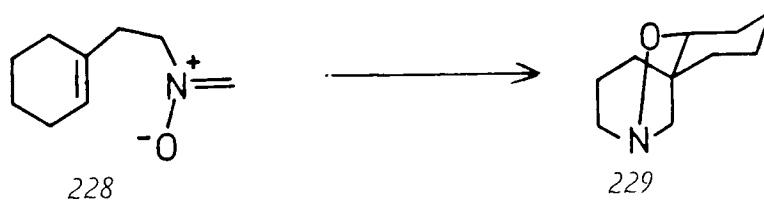


Pictet-Spengler type reactions have also provided occasional entry to azaspirocycle containing alkaloids, e.g. erythrina<sup>121</sup> and spirobenzylisoquinoline<sup>122-124</sup> alkaloids.

## x 2-Azaspirocycles

2-Azaspirocyclic compounds are far less common among natural products than 1-azaspirocycles, and consequently there have been far fewer reports of synthetic methodologies for construction of 2-azaspirocycle based ring systems.

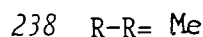
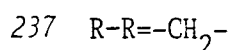
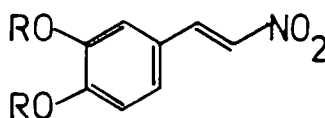
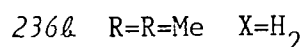
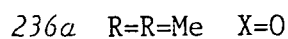
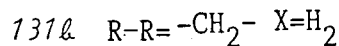
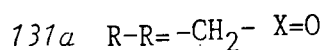
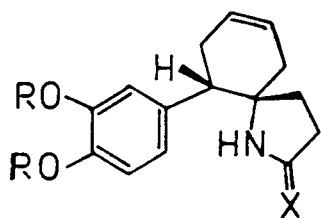
Reported approaches have included intramolecular nitronc cycloadditions, e.g. 228→229<sup>125</sup> intramolecular nitrile oxide cycloadditions e.g. 230→231<sup>126</sup>, thermal rearrangements e.g. 232→233<sup>127</sup>, Michael addition quaternizations, followed by reductive cyclization, e.g. 234→235<sup>128</sup>. A number of other recent methods have also appeared<sup>129-132</sup>.



## 2.2 Construction of the spiro centre

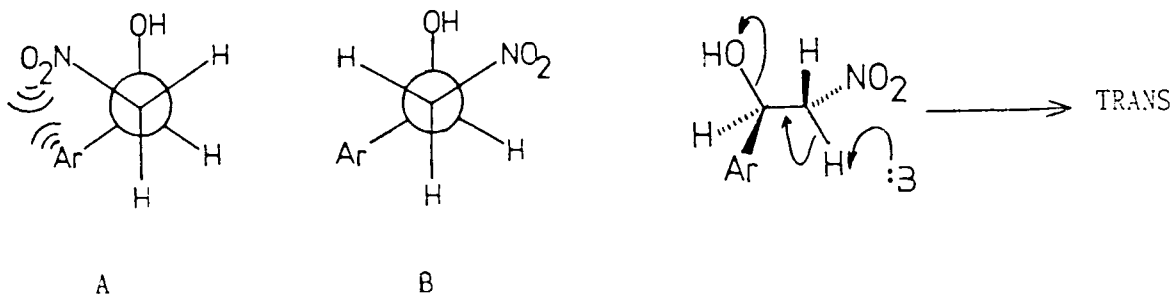
Our general retrosynthetic strategy for construction of azaspiro-cyclic intermediate, 131, and its dimethoxy analogue, 236, has been described above (see 1.8).

The first intermediates in this scheme are the  $\beta$ -nitrostyrenes 237 and 238, which are readily available by addition - condensation reaction of the corresponding aldehyde with nitromethane anion<sup>133-137</sup>, as are a wide variety of analogues<sup>138,139</sup>.



The nitromethane anion is generally generated by the use of amines, either as the free base<sup>140</sup>, or as the hydrochloride in the presence of potassium carbonate, liberating the free amine in situ<sup>141</sup>. The reaction occurs slowly, but efficiently, at room temperature.

The reaction is a two step process, proceeding with high trans stereospecificity,<sup>142</sup> because of the lower energy transition state for antiperiplanar, E2, elimination from rotamer A relative to rotamer B (fig.1).



- fig. 1 -

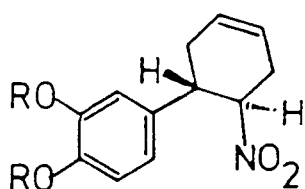
The next envisaged synthetic step was the construction of a six-membered ring E via cycloaddition methodology. The cycloaddition of 3,4-methylenedioxy -  $\beta$ -nitrostyrene, 237, with butadiene, has been used as an early step in approaches to phenanthridine analogues,<sup>143,144</sup> and lycorine<sup>145</sup>. Similar reactions have also been reported with simple substituted butadienes and nitrostyrene 237<sup>146</sup>. Reported yields have been ca. 60-70%, reaction generally requiring elevated temperatures for prolonged periods, with up to ten-fold excess of diene.

We have used the known butadiene synthetic equivalent, butadiene sulphone (3-sulpholene)<sup>147</sup>, for cycloaddition to both 237 and 238, largely due to the convenience of using a stable solid, rather than gaseous butadiene. Butadiene sulphonecheletropically eliminates sulphur dioxide to generate butadiene in situ, in the temperature range (110°C - 130°C) required for the cycloaddition reaction itself.

Further, this modification provided a significant improvement in yields of 239 and 240 over the literature procedures, and required only ca. three equivalents of sulphone reagent.

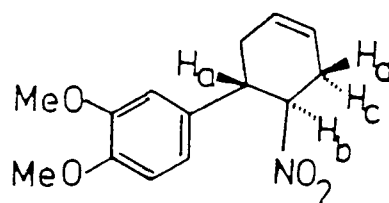
The trans geometry of  $\beta$ -nitrostyrenes is known to be preserved in Diels-Alder cycloadditions<sup>148</sup>. A racemic mixture of trans cycloadducts therefore results, because, clearly, the transition states for addition to either Re or Si face of the dieneophile, are degenerate.

The trans geometry is clearly evidenced by 250MHz <sup>1</sup>H NMR decoupling experiments on the dimethoxy analogue, 240; these data also provide some useful assignments (fig.2). Decoupling of the H<sub>c</sub>-H<sub>d</sub> region of methylene resonances, collapses the H<sub>b</sub> signal (4.9-5.0ppm) to a simple doublet, with J<sub>ab</sub>=11.1Hz, consistent only with an anti configuration.



239 R-R= -CH<sub>2</sub>- (92%)

240 R-R= Me (90%)



- fig 2 -

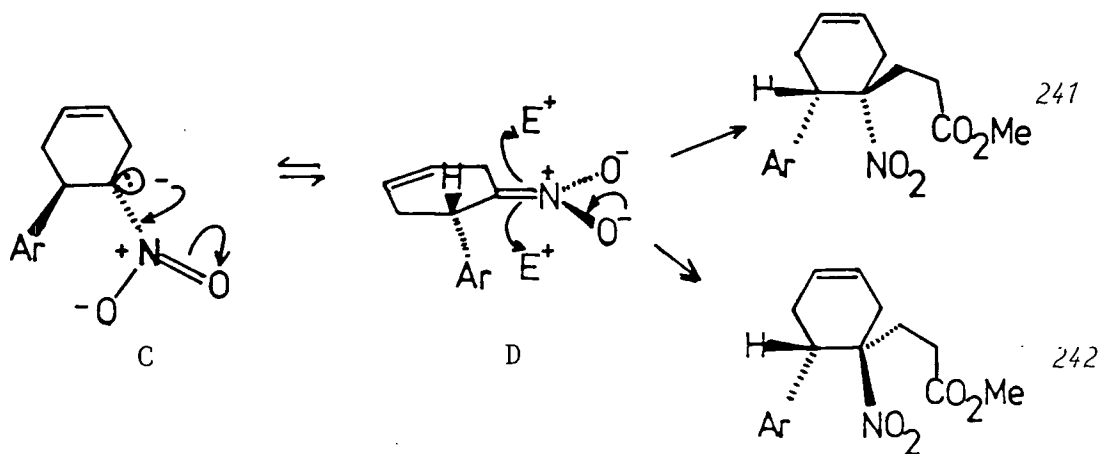


Confirmation of methylene assignments is provided by decoupling of the benzylic  $H_a$  (3.3–3.4ppm), where upon the upfield methylene multiplet (2.3–2.5ppm) is simplified to an AB like spin system.

The next synthetic step is the key step in constructing the quaternary centre, which is to become the spiro centre.

The anions from secondary nitroalkanes, e.g. 239 and 240, are known to be good Michael<sup>149</sup> donors, reacting with acceptors bearing no  $\alpha$  or  $\beta$  substituents<sup>150–152</sup>. A variety of bases<sup>153–157</sup> have been employed in these reactions, and recently the use of DBU has extended the utility of this reaction, by allowing efficient addition to substituted Michael acceptors<sup>156</sup>.

As a consequence of nitronate planarity<sup>158–160</sup>, the stereochemistry at the  $\alpha$  site is lost, and alkylation either with retention or inversion, is possible. In the case of our nitrocycloadduct, 239, the anion, C, is stabilized as nitronate, D, which a Michael electrophile, e.g. methyl acrylate, can attack, trans to the bulky aromatic group yielding 241, or cis to this group yielding 242 (fig.3)



- fig 3 -

Using triton B as the base, and methyl acrylate as the Michael acceptor, good yields (80–90%) of an addition product were obtained. All physical and spectroscopic data indicated the product to be of a

single relative stereochemistry, thus indicating the Michael reaction to be highly stereoselective.

As the ester chain is larger than the nitro group, we expected preferential Michael alkylation trans to the bulky aromatic substituent, leading to stereochemistry *247*. The high stereospecificity in favour of *247* was indeed confirmed by X-ray structure analysis of a derivative of *131a*.

The highly stereospecific establishment of the quaternary centre of *247*, now allowed construction of the azaspirocyclic intermediates *131*, by reduction-cyclization methodology.

The hydrogenation strategy employed by Hill et al and Moffet et al, for such cyclizations, is clearly inapplicable in our case, as retention of ring E unsaturation is essential to allow further ring E modification. However, the use of reducing metal conditions with activated zinc dust<sup>161,162</sup> and hydrochloric acid, led to efficient spirocyclization to lactams *131a* and *236a* (91% and 72% yields respectively), initially confirmed by the characteristic five-membered ring lactam carbonyl stretch at  $\nu_{\text{CO}}$  1690  $\text{cm}^{-1}$  in the IR spectrum.

To confirm beyond doubt the relative stereochemistry provisionally assigned above for *247*, we obtained a single crystal X-ray structure of thiolactam, *253*. (We were also interested in the general conformation resulting from spirofusion). This X-ray analysis confirmed our predicted relative stereochemistry (fig.4).

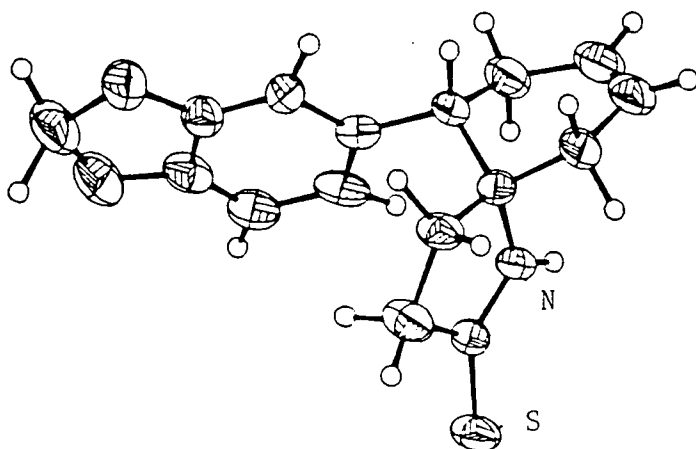
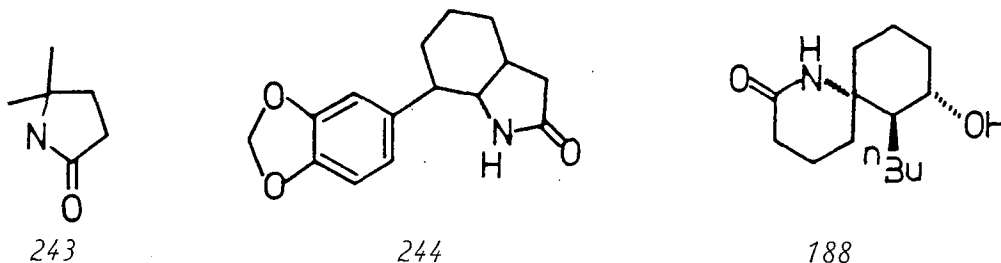


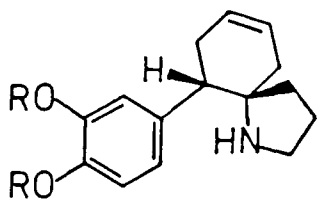
fig 4 X-ray structure of thiolactam, *253*

### 2.3 Spirolactam modification and reduction

The standard reagents for reduction of amides and lactams, are lithium aluminium hydride (LAH)<sup>163-167</sup>, or derivatives e.g.  $\text{LiAlH}(\text{OMe})_3$ <sup>168</sup>. Simple  $\gamma$ -lactams, e.g. 243<sup>169</sup>, fused  $\gamma$ -lactams, e.g. 244 and simple spiro-lactams, e.g. 188<sup>94</sup>, have all been efficiently reduced with LAH. Several other direct methods are available, viz aluminium hydride,  $\text{AlH}_3$ <sup>167</sup>, sodium acyloxyborohydride<sup>170</sup>,  $\text{TiCl}_4\text{-NaBH}_4$ <sup>171</sup>,  $\text{TiCl}_4\text{-LAH}$ <sup>172</sup> and diisobutylaluminium hydride (DIBAL-H)<sup>173</sup>.

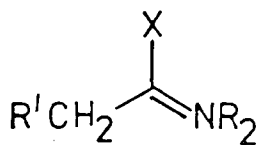


Our initial attempts to reduce spiro-lactam 131a with LAH, under a variety of conditions (culminating with one weeks' reflux in THF), returned 70-80% of unchanged lactam. Subsequently, changing the solvent from potassium dried THF to diethyl ether rigorously dried over sodium then LAH, resulted in clean, repeatable reduction to spiroamine 245 in >90% yield. The dimethoxy lactam, 236a, was reduced to 246 under the same conditions, in similar yield. The required reaction times of between 48 hours and 96 hours (following the reaction by t.l.c.) indicate a remarkable resistance of 131a and 236a to reduction.



245 R-R=  $-\text{CH}_2-$

246 R-R=Me



247 X = Cl

248 X = OR

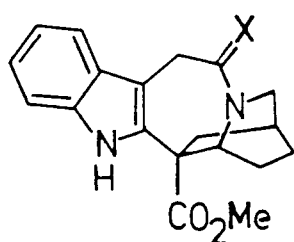
249 X = SR

R = Me, Et

Indirect methods of reduction have been developed via substituted iminium salts of type 247<sup>174</sup>, 248<sup>175,176</sup> and 249<sup>177,178</sup>, which are

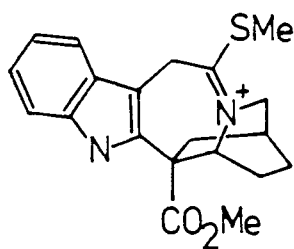
reduced in good yields, under mild conditions, with either sodium borohydride or sodium cyanoborohydride.

Alongside our attempts at LAH reduction of *131a*, we decided to explore alternative thioiminium methodology, which had proved successful with lactams which had been difficult to reduce with LAH. Okumura et al<sup>179,180</sup> had been unable to completely reduce *250* with LAH. However, thioiminium iodide salt, *251*, was easily reduced with sodium borohydride, or acidic sodium cyanoborohydride, to the amine *252*, by Sundberg et al<sup>181</sup>.

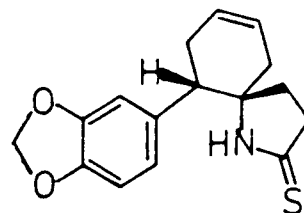


*250* X = O

*252* X = H<sub>2</sub>



*251*



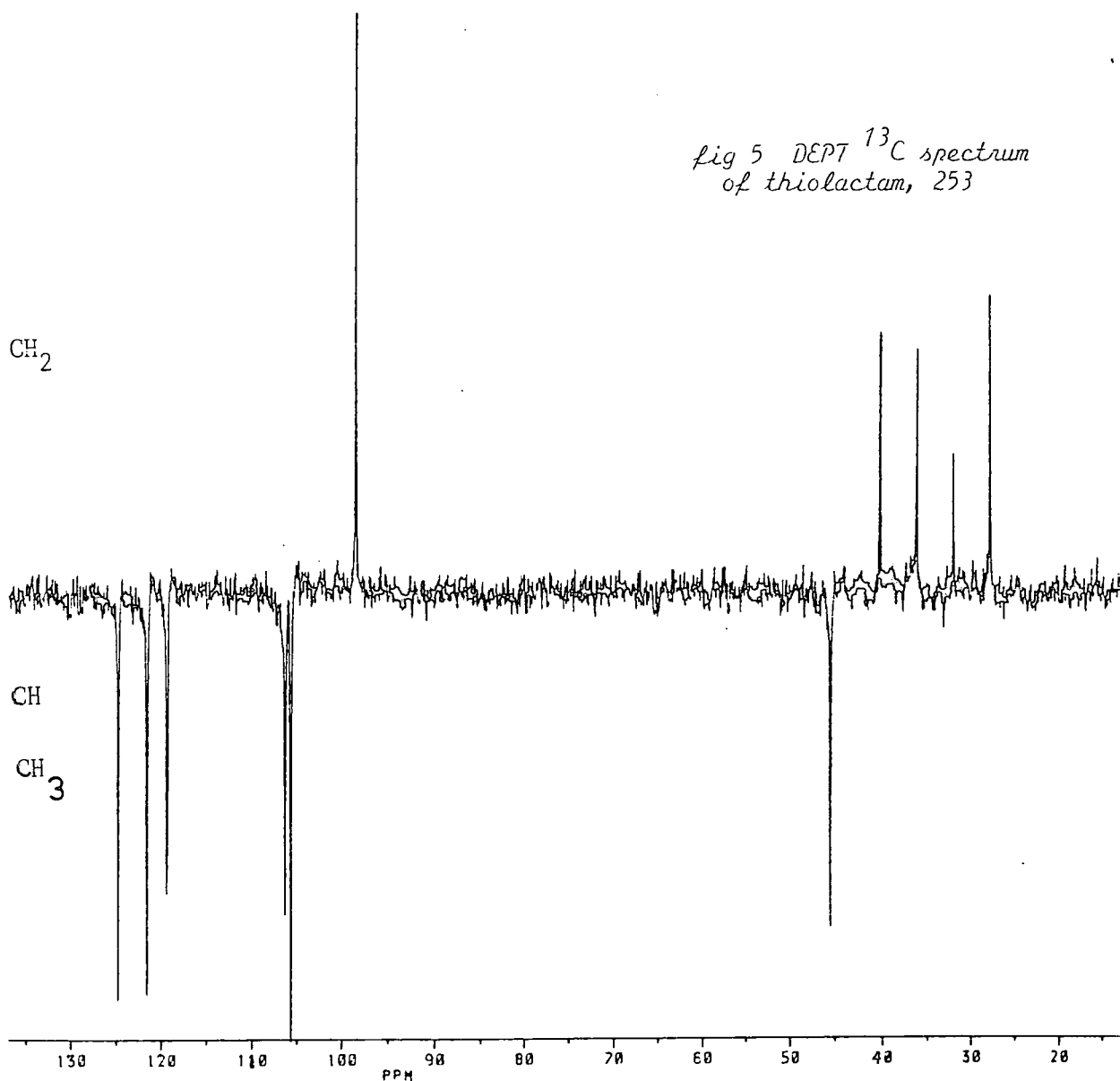
*253*

Amides can be converted to thioamides, using phosphorus pentasulphide<sup>182-184</sup>, or Lawesson's reagent<sup>185,186</sup> as the sulphur transfer source, either thermally or ultrasonically<sup>187</sup>. We found that using phosphorus pentasulphide gave better yields of thiolactam, *253*, from lactam *131a* than did Lawesson's reagent.

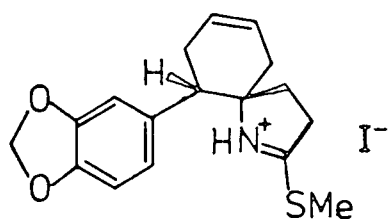
To allow further assignment of <sup>13</sup>C data for thiolactam, *253*, and so to aid our assignments for other spirofused systems, a DEPT spectrum was obtained (fig.5). The most useful information this provides is that the spiro carbon can definitely be identified at 69ppm (absent in DEPT), and the benzylic carbon identified at ca. 46ppm.

Treatment of *253* with methyl iodide gave near quantitative yields of methiodide salt, *254*. However, reaction of *254* with either sodium borohydride under neutral conditions, or sodium cyanoborohydride under acidic conditions, resulted in modest yields of a material, whose spectral data were inconsistent with a simple amine product.

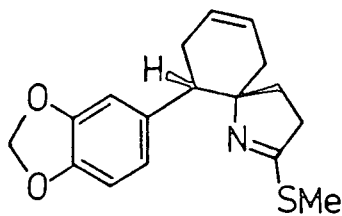
fig 5 DEPT  $^{13}\text{C}$  spectrum  
of thiolactam, 253



The mass spectrum of this product showed a molecular ion at  $m/e = 301$  in EI, and  $m/e = 302$  in CI, and no mass peak corresponding to the amine, 245. Further, the 250MHz  $^1\text{H}$  NMR showed a singlet (three protons) at ca. 2.5ppm, and the  $^{13}\text{C}$  NMR showed seventeen discrete peaks. All data are consistent with retention of the thiomethyl group.



254



255

On the basis of these data, a provisional structural assignment as thiolactimether, 255, was made, the product of simple deprotonation of salt 254. High resolution mass spectral analysis confirmed a molecular formula consistent with this structure.

This unexpected result, coupled with our successful reduction with LAH by this stage, terminated our investigations of this reduction methodology.

#### 2.4 Summary

A highly stereoselective, high yielding entry to our key 1-azaspirocyclic intermediates has been developed. The relative stereochemistry obtained, with the aromatic substituent, and nitrogen functionality in a cis arrangement, is that required for the cephalotaxine skeleton.

However, the benzylic proton can be equilibrated in the final synthetic stages, at least at the cephalotaxinone stage, so the importance of the stereospecificity does not lie only in its relevance to the final target stereochemistry. Its importance lies perhaps more in the role of this cis geometry in favourable reaction stereochemistry for the formation of ring C.

#### 2.5 Future analogues

A variety of possible modifications, in both ring size and functionality, of rings D and E can be envisaged on the general basis of the above methodology (chapter 2.2). Ring D homologation has been utilized in analogous simple 1-azaspiro [5.5] undecanes by several groups<sup>111,112</sup>.

A wider variety of ring E analogues are potentially available. Substituted analogues could be obtained using substituted butadienes or butadiene sulphones<sup>188-190</sup>. Of more potential significance, is the possibility of using a chiral diene which, coupled with the strong regio-

control exerted by the nitro group<sup>191,192</sup>, could lead to regioselective products, of the absolute stereochemistry appropriate to (-) cephalotaxine. These, and other possibilities, will be more fully discussed below.

CHAPTER THREE

3-BENZAZEPINES : APPROACHES  
TOWARDS CEPHALOTAXINE RING C  
VIA ELECTROPHILIC CYCLIZATION

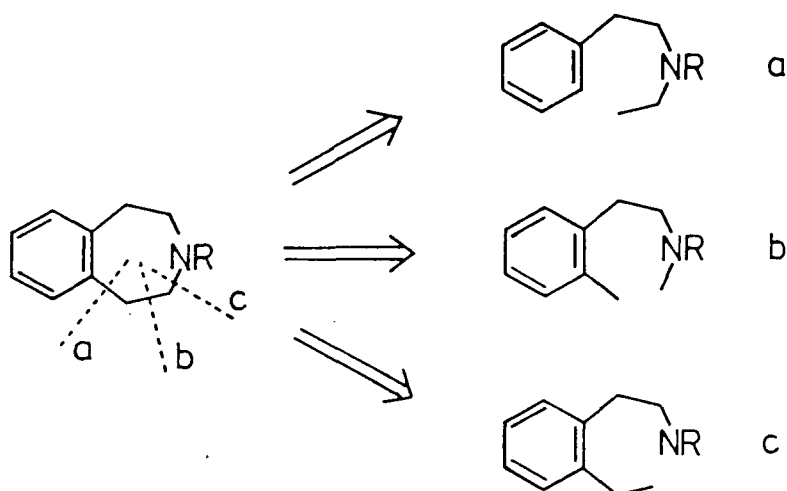


### 3.1 Synthetic methodology for 3-benzazepines : Review

The tetrahydro-3-benzazepine ring system is common to three major classes of alkaloids; the isopavine, rheadan and *cephalotaxus* alkaloids<sup>194</sup>, all of which probably share a 1-phenethylisoquinoline as biogenetic precursor (see 1.5).

Consequently, over a number of years, considerable effort has been directed towards synthesis of the 3-benzazepine ring system. This has defined many viable intermediates that are suitable for elaboration to this ring system. However, these largely fall within only a few mechanistic approaches, the vast majority being based on electrophilic aromatic substitution as the key cyclization step. Beyond this there are some reports of aziridine ring expansion methodologies (strictly not a cyclization approach), and of syntheses based on C-N bond formation for ring closure, as well as several photochemical approaches.

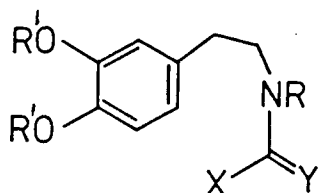
From a retrosynthetic point of view, the overwhelming majority of methods available, are based on disconnection 'a' rather than 'b' or 'c' (fig.6).



- fig 6 -

i Electrophilic cyclialkylations

The intermediates for electrophilic cyclialkylation possess, necessarily, functionalized ethyl substituents on the nitrogen atom which is to be included in the ring. There are basically six types of such intermediates that have proved successful for cyclizations to the 3-benzazepine ring, with the general structures 257-266. These will now be briefly considered in turn.



|     | R' = R'            | X                                 | Y              |
|-----|--------------------|-----------------------------------|----------------|
| 257 | -CH <sub>2</sub> - | CH <sub>2</sub> Cl                | H <sub>2</sub> |
| 258 | Me                 | "                                 | "              |
| 259 | -CH <sub>2</sub> - | "                                 | O              |
| 260 | Me                 | "                                 | "              |
| 261 | -CH <sub>2</sub> - | CR <sup>1</sup> R <sup>2</sup> OH | H <sub>2</sub> |
| 262 | Me                 | "                                 | "              |
| 263 | -CH <sub>2</sub> - | COR <sup>3</sup>                  | "              |
| 264 | Me                 | "                                 | "              |
| 265 | -CH <sub>2</sub> - | CH(OR <sup>4</sup> ) <sub>2</sub> | "              |
| 266 | Me                 | "                                 | "              |

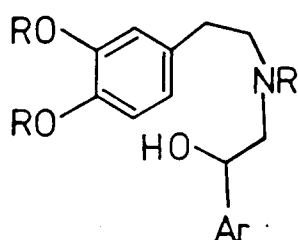
R = H,  
alkyl,  
tosyl,  
R<sup>3</sup> = OH  
Cl  
R<sup>4</sup> = Me, Et

The intramolecular Friedel-Crafts cyclization of N-2-chloroethylphenethylamine derivatives, 257, 258, requires very forcing conditions for efficient reaction, typically involving a day or so at elevated temperatures ( $\sim 180^{\circ}\text{C}$ )<sup>195-199</sup>. Nonetheless, this approach has received much attention, particularly in the pharmaceutical industry, when scale up to large quantities is necessary.

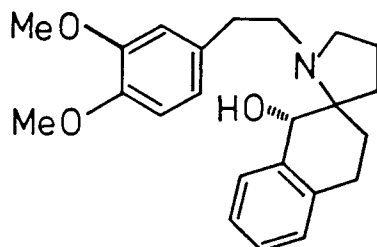
Similarly, N-2-chloroacetamide phenethylamine derivatives, 259, 260, have proved suitable substrates for Friedel-Crafts cyclization<sup>200</sup>. However, these also require long reaction times and elevated temperatures.

A particularly common approach to the 3-benzazepine ring system has involved the cyclization of N-2-hydroxyethyl phenethylamines, 261,

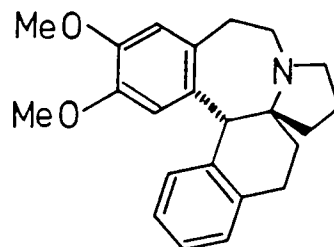
262, under acid catalysis. Almost all reported examples of this type of cyclization have utilized systems where  $R^1$  is hydrogen or an alkyl group, and  $R^2$  is an aromatic substituent. Thus, the general cyclization substrate is of form 267.



267



268



269

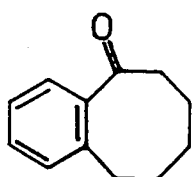
A wide variety of substitution patterns have been employed, and the commonest reaction conditions use polyphosphoric acid (PPA), hydrobromic acid or trifluoroacetic-sulphuric acid mixtures, as the catalyst<sup>201-213</sup>.

For example, complex polycyclic system 269, with a spiro fused 3-benzazepine analogous to the cephalotaxine ring system, is prepared from 268, in which again there is a phenyl substituent  $\alpha$  to the hydroxy group<sup>215</sup>.

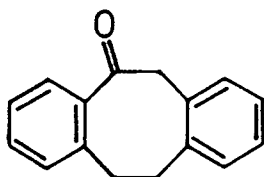
While this methodology provides quite an efficient route, it has two distinct disadvantages; (1) it appears to require an aromatic group  $\alpha$  to the hydroxy function to stabilize the intermediate cationic electrophile, and (2) strongly acidic conditions are necessary. Hence, its applicability to structurally varied benzazepine syntheses, or those bearing labile functionality, is limited.

Polyphosphoric acid catalysed cyclialkylation of carboxylic acids onto aromatic rings, is well known in carbocyclic chemistry<sup>216</sup>. It has provided efficient entry to six-membered<sup>217-219</sup>, as well as seven-membered<sup>220,221</sup> and eight-membered<sup>222</sup> carbocyclic rings, e.g. 270 and 271.

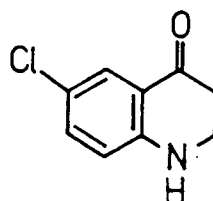
This approach has also found some use in analogous heterocyclic synthesis, for example in the preparation of the reduced isoquinolone



270



271



272

272<sup>223,224</sup>. This methodology has been used for construction of the 3-benzazepine ring, specifically in the preparation of the cephalotaxine intermediate 68<sup>38</sup> (see 1.6.iii). In general, these cyclizations require temperatures above ambient, and in some cases as high as 100°C.

Other strong acids, such as methanesulphonic acid, have also effected such cyclization reactions. At least in carbocyclic systems<sup>225</sup>, conc. sulphuric acid has been used to cyclize the corresponding methylester to isoquinolones<sup>226-228</sup>, though no examples of application to 3-benzazepines have been found.

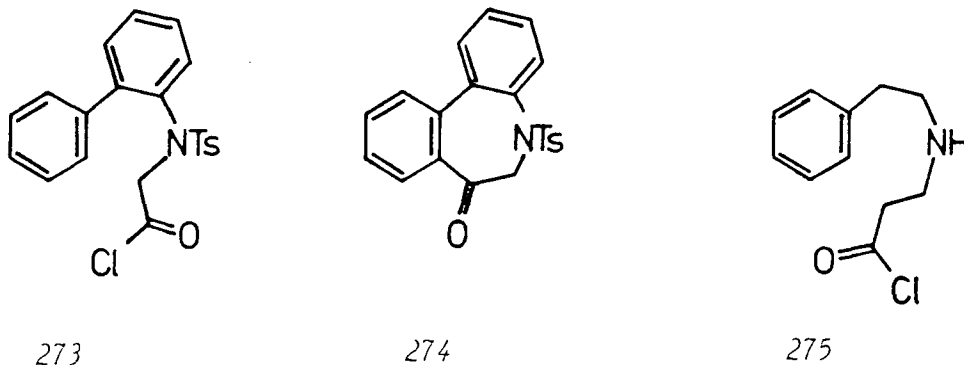
Intramolecular Friedel-Crafts acylation via acid chloride intermediates of type 263,264 ( $R^3=Cl$ ) seems initially an obvious approach to 3-benzazepine ring construction, with the potential to proceed under **relatively** mild reaction conditions.

Cyclialkylation of acid chlorides to carbocyclic systems is successful at temperatures in the 0-25°C range<sup>229,230</sup>. However, one drawback is that very high dilution techniques have been required to obtain good yields of larger than six-membered rings (especially eight-membered)<sup>231,232</sup>.

As an approach to 3-benzazepines this has been investigated over a number of years, and it was observed that at reaction temperatures much above 0°C, rapid loss of carbon monoxide occurred, leading to isoquinolines as major reaction products, rather than 3-benzazepines<sup>233-236</sup>.

However, it was subsequently reported that low reaction temperatures, typically -70°C, with excess aluminium chloride, could lead to good

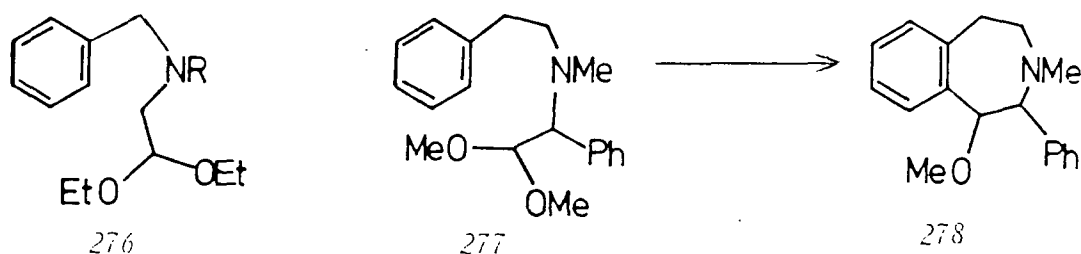
yields of 3-benzazepinones<sup>237-239</sup>. Similar low temperature reaction, at  $-10^{\circ}\text{C}$ , was used to efficiently cyclize 273 to the benzofused 3-benzazepine 274<sup>240</sup>.



It is relevant to note that 275 is cyclized efficiently to the 3-benzazocine analogue by Friedel-Crafts reaction, in dichloromethane at reflux<sup>241</sup>. Thus, the competitive loss of carbon monoxide appears only to be important when there is a favourable reaction pathway to a six-membered ring available.

Another type of electrophilic cyclialkylation involves the use of 2-carbon fragments on nitrogen, functionalized as dialkyl acetals, or free aldehydes. This methodology is widely used in isoquinoline syntheses, mineral acid catalysed cyclization of acetals, e.g. 276, being the basis of the Pomerantz-Fritz<sup>242</sup> and Bobbitt<sup>243-246</sup> syntheses of isoquinolines. Use of boron trifluoride as Lewis acid catalyst has also been extensively used to cyclize acetals<sup>247</sup>, and the corresponding free aldehydes have been cyclized with mineral acids, to tetrahydroisoquinolines<sup>248-251</sup>.

This methodology has found some use in the synthesis of 3-benzazepines<sup>252-254</sup>, and Lewis acid catalysed cyclization of dimethylacetals<sup>255-257</sup> is one of the commonest routes of entry to isopavine alkaloids<sup>258,194</sup> e.g. 277  $\rightarrow$  278.

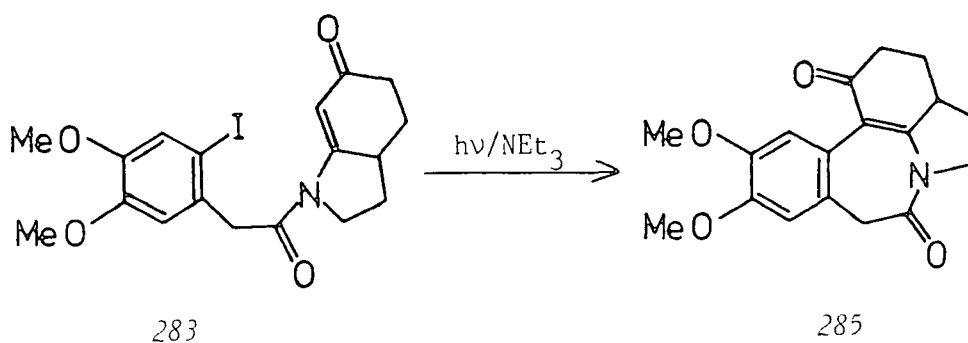
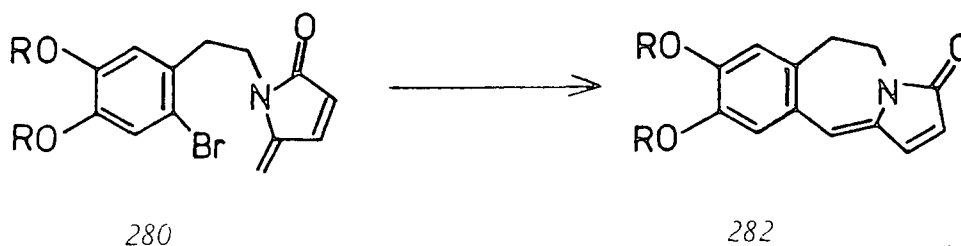
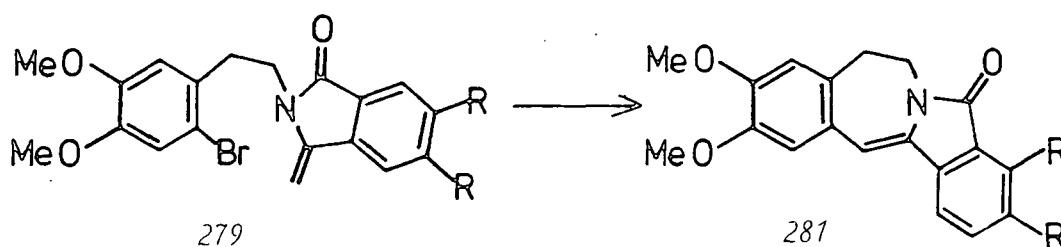


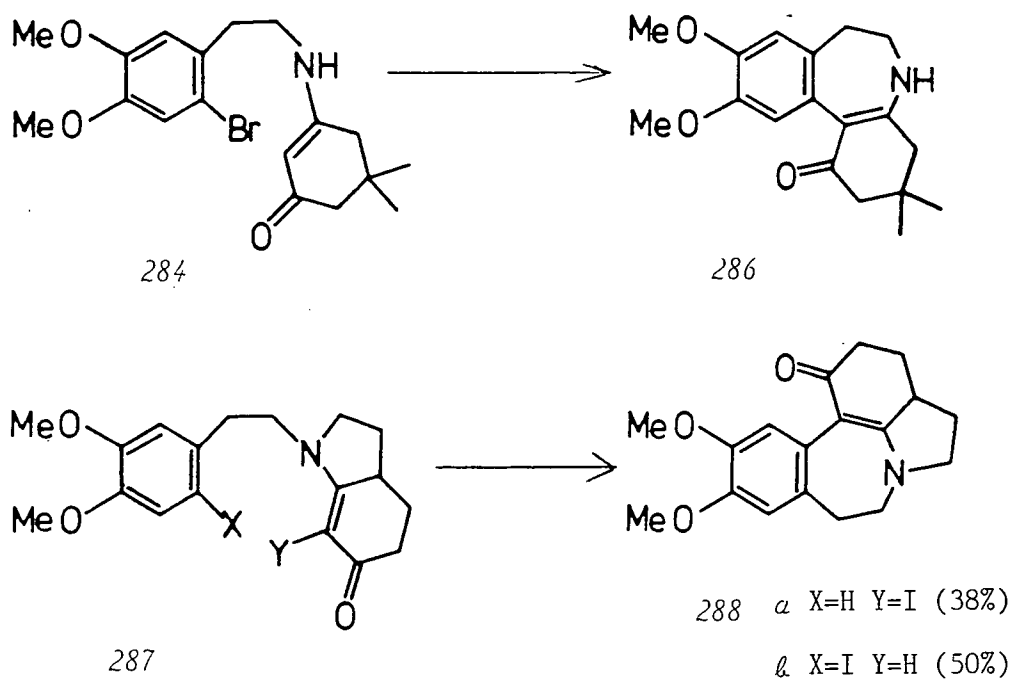
## ii Photochemical cyclizations

A number of photochemical approaches to 3-benzazepines have been developed, some being utilized further in synthetic studies towards cephalotaxine. Haloaryl-enolate photocyclizations<sup>259</sup> have been specifically applied to construction of the cephalotaxinone 3-benzazepine ring by Semmelhack's group<sup>37,38</sup> (1.6.ii).

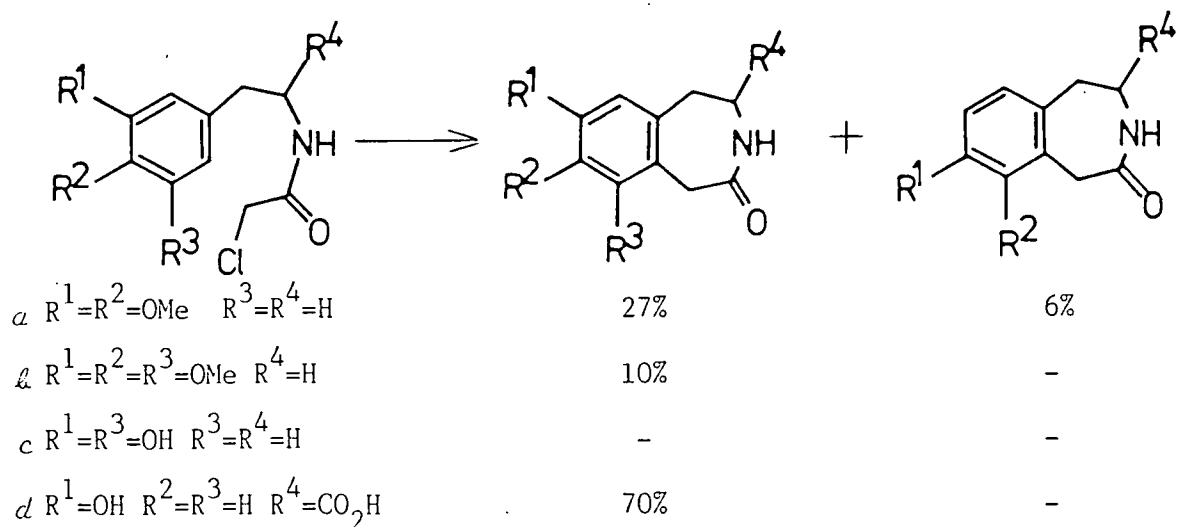
A related class of photocyclizations of aryl halides onto enamide, enamino or enamido-ketones, has also provided some reasonably efficient entries to 3-benzazepine containing systems<sup>260</sup>.

For example, Snieckus et al<sup>261,262</sup> have shown that 279 and 280 can be photocyclized to 281 and 282 respectively. Similarly, the enamido ketone 283 and enamino-ketone 284 can be photocyclized to 3-benzazepines 285<sup>263,264</sup> and 286<sup>265,266</sup>. Photocyclization can also be effected in analogous systems with the halogen located on the enamino $\beta$  olefin carbon. Thus both 287a and 287b provide the same 3-benzazepine, 288<sup>267</sup>.





A different photochemical strategy, viz the photocyclization of N-chloroacetyl phenethylamine derivatives, was thoroughly investigated by Witkop et al in the late 1960s. However, in few cases did good yields of 3-benzazepines result<sup>268</sup>, as more complicated deep-seated photo-rearrangements to unusual cyclic products competed<sup>269-272</sup>. Further complications result from formation of isomeric 3-benzazepines, as shown by a collation of results for various substrates (fig.7),



However, analogous photocyclization of N-methyl-3,4-dimethoxy phenethylamine, or the 3,4-methylenedioxy N-methyl system, provided moderate yields of the primary isomeric 3-benzazepine<sup>273</sup>. The related tertiary amide,<sup>48</sup> similarly provided moderate yield of the potential cephalotaxine intermediate <sup>49</sup><sup>11</sup>.(see 1.6.i).

### iii C-N bond forming ring closures

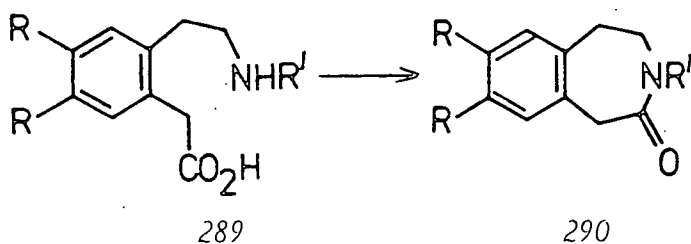
Methodologies for construction of 3-benzazepines from precursors bearing a functionalized 2-carbon fragment on the aromatic ring - C-N bond formation being the key cyclization step - have been much less utilized than the aryl-carbon bond forming cyclizations, of the 'disconnection a' strategies above.

This is probably due, in large part, to the ready availability of simple phenethylamines bearing 2-carbon, functionalized, fragments substituted onto nitrogen. Thus, as we have seen above, most simple 3-benzazepine syntheses constitute different types of cyclialkylations onto the aromatic nucleus. Consequently, syntheses of more complicated 3-benzazepine containing systems have been directed towards intermediates of these general types.

The use of C-N bond formation as the cyclization step, has found a variety of uses in tetrahydroisoquinoline syntheses. The types of reactions utilized include amide anion-mesylate displacement<sup>274</sup>, amide-acid<sup>275</sup>, and amide-alcohol<sup>276-278</sup> condensations, and several other less common examples<sup>279-281</sup>.

A few applications of these, and other, methodologies to 3-benzazepine synthesis have been reported. Condensation of amino acids <sup>289a-</sup><sup>289c</sup><sup>282,283</sup> being the most utilized, refluxing in high boiling solvents affording good yields of 3-benzazepinones <sup>290a-</sup><sup>290c</sup>. However, it is worth noting that 3-benzazepines are harder to prepare than the 1- or 2- isomers using this approach.

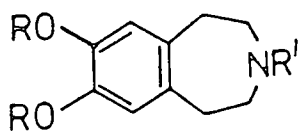
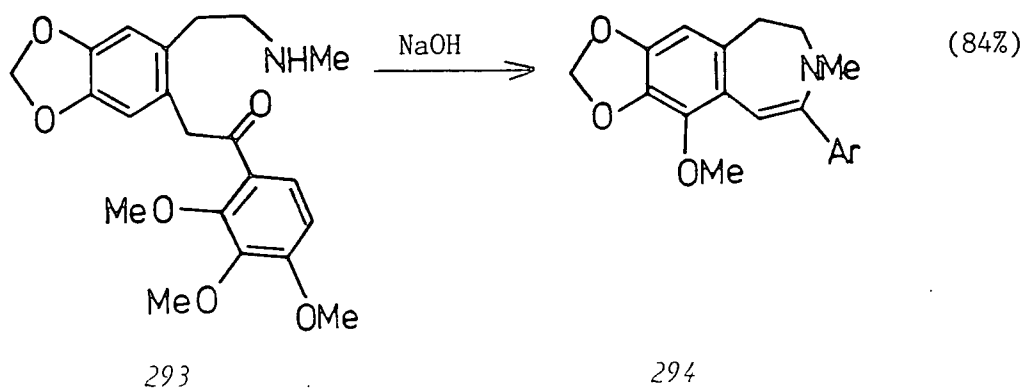
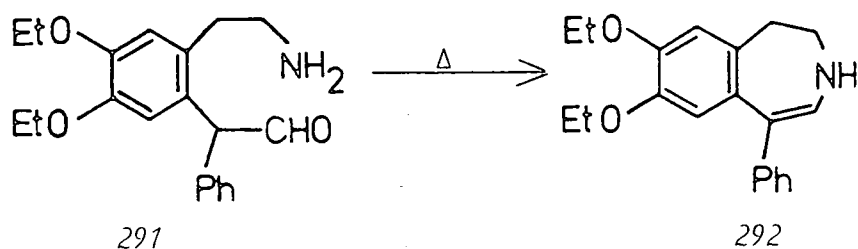




- a R=R=R<sup>1</sup>=H  
 b R=R=MeO R<sup>1</sup>=H·CH<sub>2</sub>Ph  
 c R-R= -CH<sub>2</sub>- R<sup>1</sup>=H, CH<sub>2</sub>Ph

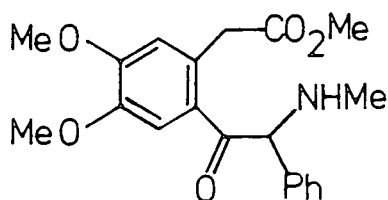
Amino-aldehydes, e.g. 291, have been thermally cyclized to 3-benzazepines<sup>284</sup>, e.g. 292, and amino-ketones have been cyclized by strong bases, e.g. 293→294<sup>285</sup>, a reaction which has been applied to synthesis of the 3-benzazepine rheadan alkaloids by Brossi and co-workers<sup>286,287</sup>.

Amino-acids, 289, can also be reductively cyclized with borane, directly providing the parent 3-benzazepines, 295<sup>288</sup>.

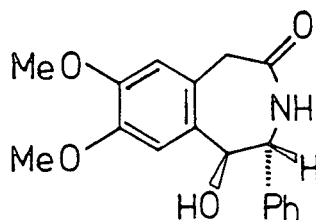


295 R=R=Me, -CH<sub>2</sub>-

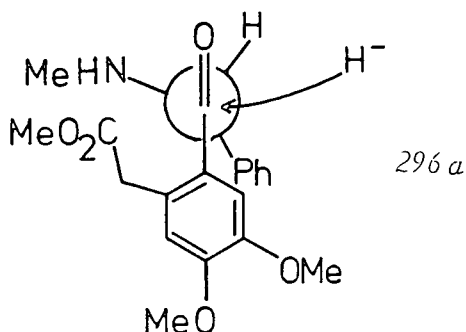
Reductive cyclization of amino-esters has also provided a highly efficient, stereoselective, entry to the 3-benzazepinone skeleton. Sodium borohydride reduction of amino-ester **296** yielding the cyclized racemic product, **297**, in very high yield<sup>289-290</sup>. The high stereoselectivity being accounted for on the basis of Cram's rule<sup>291</sup>, for hydride attack on rotamer **296a**.



**296**



**297**

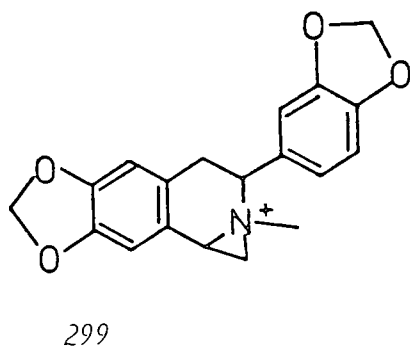
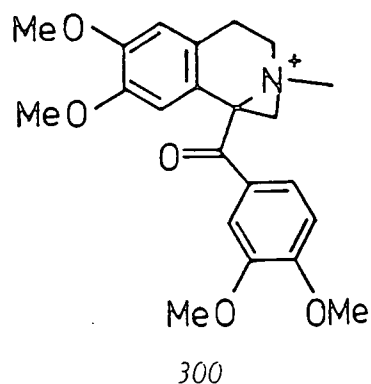
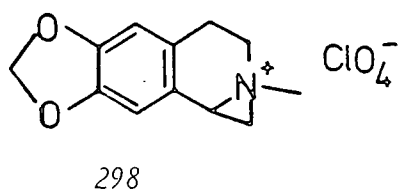


**296a**

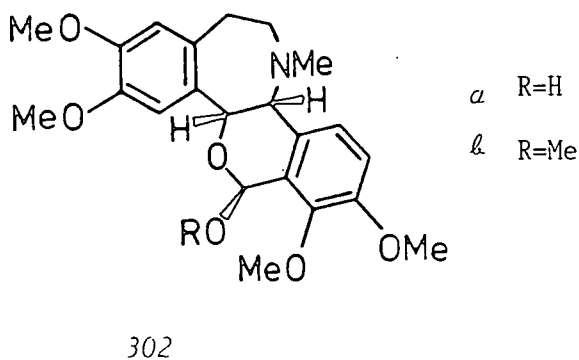
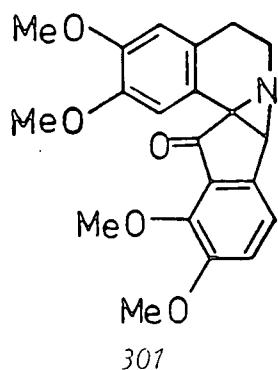
#### iv Aziridine-aziridinium ring expansion strategies

A completely different approach to 3-benzazepine ring formation is based on a number of mechanistically related fused-aziridine or fused-aziridinium ring openings. As such, this general approach does not constitute a cyclization methodology, but rather the expansion of already existent isoquinoline type rings to 3-benzazepines.

Ring expansions of simple fused aziridinium salts were first reported in the early 1960s by Leonard et al<sup>292,293</sup>. Subsequently, this methodology was applied to isoquinoline fused aziridinium salts e.g. **298**,<sup>294</sup> **299**<sup>295</sup> and **300**<sup>296</sup>, to furnish variable yields of 3-benzazepines (the latter example providing 82% yield of ring expanded product). Ring expansions with nucleophiles, e.g. methoxide, were found to be more favourable for ring expansion, than reductive aziridinium ring opening<sup>297</sup>.

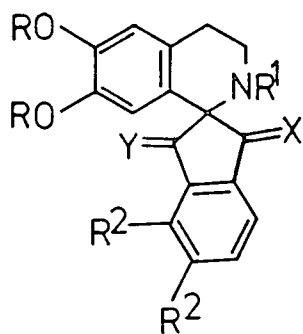


Ring expansions of isoquinoline fused aziridines have also recently found use as a route to 3-benzazepines, particularly in synthetic approaches to the rheadan alkaloids<sup>298-300</sup>, e.g. 301  $\rightarrow$  ( $\pm$ ) cis-alpinigenine, 302a and ( $\pm$ ) cis-alpinine, 302b. Related expansions have been effected either photolytically<sup>301</sup>, under acid catalysis<sup>302,299</sup>, with ethylchloroformate<sup>303</sup>, or by hydrogenolysis<sup>304</sup>.

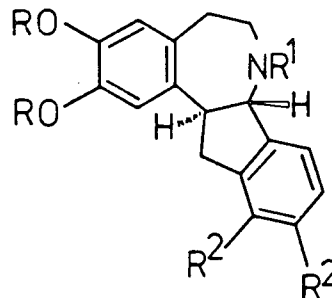


A number of reports of rearrangement expansions of spirobenzylisoquinolines, 303, leading to the 3-benzazepines, 304<sup>305,306</sup>, in good yield, have appeared which were then elaborated to rheadan alkaloids<sup>307,308</sup>. These reactions were brought about either reductively by acidic zinc (303a and 303b), or thermally (303c). Mechanistically, they were all postulated to proceed via fused aziridinium intermediates structurally akin to the aziridines, 301. Biomimetic studies have indicated a

relationship of these ring expansions to biosynthesis of rheadan alkaloid precursors<sup>309</sup>.



303



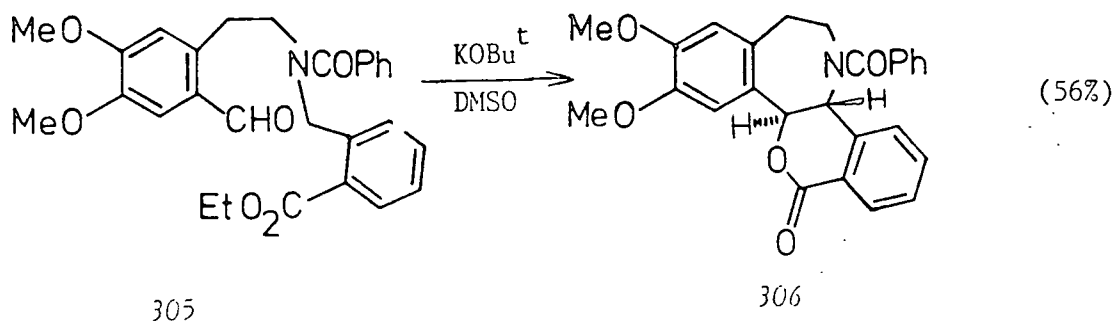
304

- a  $R=Me$   $R^1=R^2=H$   $X=Y=O$   
 b  $R=R=-CH_2-$   $R^1=R^2=H$   $X=Y=O$   
 c  $R^1=R=Me$   $Y=H_2$   $R^2=OMe$   $X=H,OMs$

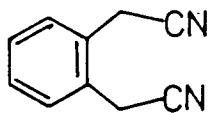
#### v Miscellaneous other 3-benzazepine syntheses

A number of other miscellaneous methodologies have been employed in the construction of the 3-benzazepine system.

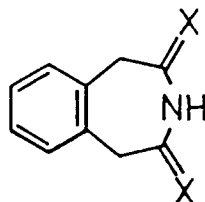
There is one example of a 'disconnection'b' type strategy for entry to the 3-benzazepine skeleton of readan alkaloids, the key step being intramolecular attack of the amide  $\alpha$  anion of 305 on the aromatic aldehyde<sup>310</sup>, subsequent lactonisation providing reasonable overall yield of 306.



Hydrogenation of dibenzylcyanides e.g. 307 affords directly the fully saturated 3-benzazepine, 308a<sup>311-313</sup>, while treatment with hydrobromic acid in acetic acid, (followed by sodium acetate) yields imides, e.g. 308b<sup>314</sup>.



307

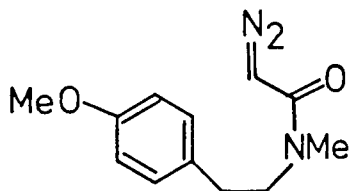


308 a X=H

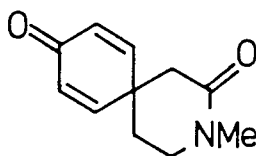
b X=O

Beckmann rearrangement of the oxime of  $\beta$ -tetralone<sup>315</sup>, and Schmidt rearrangement of  $\beta$ -tetralone directly<sup>316</sup>, have both provided modest yields (20-30%) of 3-benzazepinone.

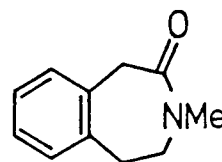
More recently, an example of an efficient entry to the 3-benzazepinone system, 317 has been described<sup>317</sup>; acid catalysed cyclization of 309 yields spirodienone intermediate 310, which in two steps rearranges and rearomatizes to 317.



309



310



311

## vi Conclusion

Several other 3-benzazepine syntheses employed directly in the synthesis of cephalotaxine, or of intermediates directed towards its synthesis, have not been discussed here. These are described elsewhere in chapters 1 and 4.

## 3.2 Cyclopentaphenanthridine analogues

### i Discussion

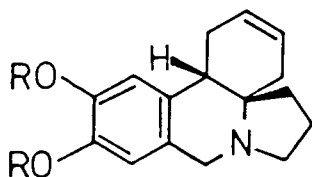
We have discussed (1.9) the importance of ring size cephalotaxine analogues, and the relevance of possible modifications of our general

synthetic strategy towards this aim.

The key role of ring C in determining the geometry of the cephalotaxine skeleton, suggests that alternative sizes of this ring are of some interest. In particular, the widespread occurrence of the tetrahydroisoquinoline framework in naturally occurring alkaloids<sup>318,319</sup> and the variety of synthetic methods available to this system, point towards six-membered ring C as an obvious analogue. This is also of interest because of the biosynthetic links between tetrahydroisoquinoline derivatives and *cephalotaxus* and closely related alkaloids<sup>320</sup> (see 1.5).

Our intermediate spiroamine, 247, containing essentially a 2-phenethylamine structure, should allow for elaboration to a tetrahydroisoquinoline system, via standard Pictet-Spengler cyclization<sup>321-322</sup>. This is essentially a special case of the Mannich reaction, involving reaction of 2-phenethylamines and aldehydes or acetals<sup>323</sup>. The mechanism proceeds via an intermediate imine or iminium salt, which undergoes Mannich-like electrophilic cyclization onto the aromatic nucleus. It is particularly successful with aromatic nuclei bearing activated substituents, usually proceeding under acid catalysis<sup>324</sup>. However, with phenolic systems, the reaction may occur under neutral<sup>325</sup> or basic<sup>326</sup> conditions.

We found that reaction of spiroamine 245 with formaldehyde, under hydrochloric acid catalysis, afforded good yields of the cyclopentaphenanthridine, 312. Similarly, the dimethoxyspiroamine, 246, was cyclized to the analogue 313.

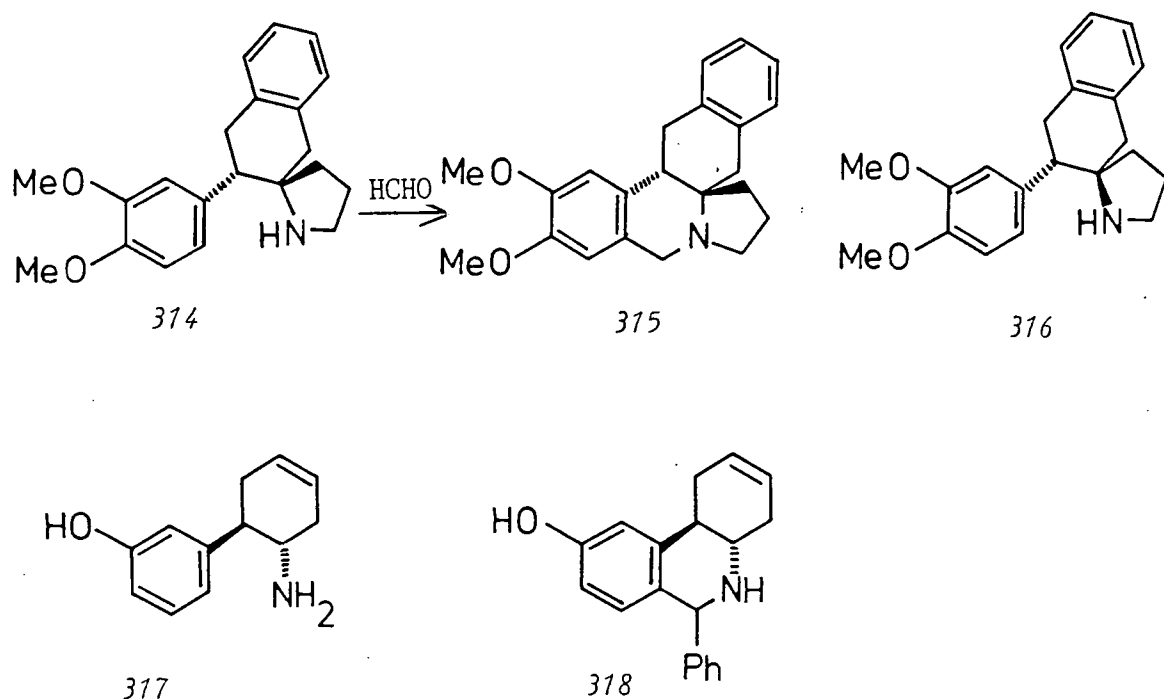


312 R=R= -CH<sub>2</sub>-

313 R=R=Me

(70-75%)

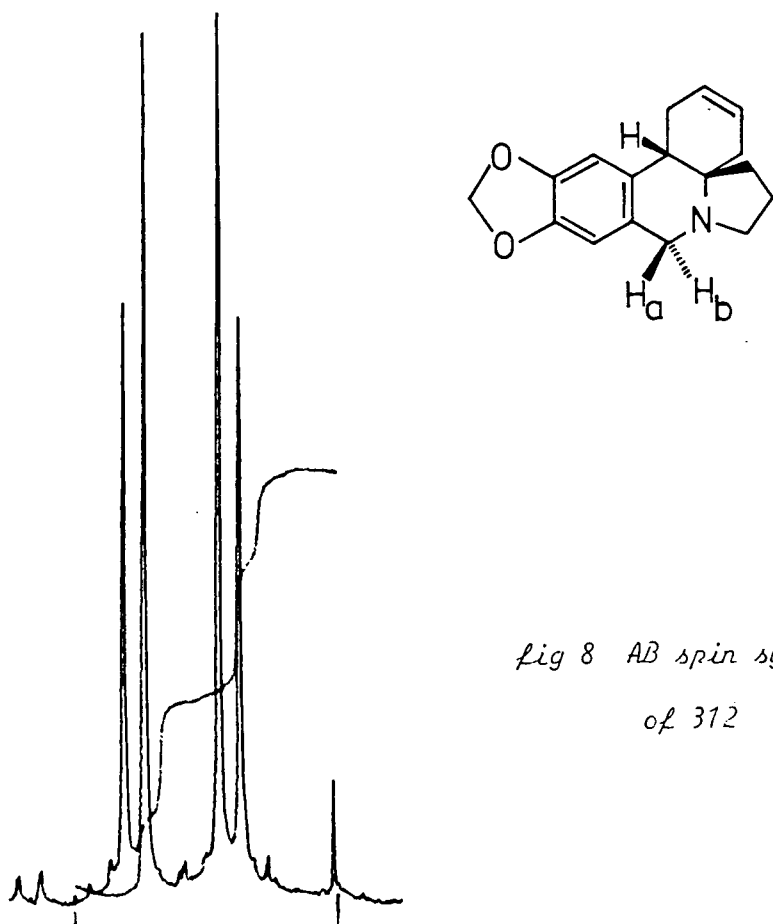
The ease and efficiency of this cyclization is partly a consequence of the relative stereochemistry of the spiroamines, 245 and 246. Molecular models indicate that a cis arrangement of the amino and aromatic functionalities, leads to a favourable isoquinoline conformation in the product, while a trans arrangement would lead to a significantly more strained six-membered ring. That this is, indeed, a significant consideration in systems containing a rigid spirofusion, is evidenced by the successful Pictet-Spengler cyclization of 314 to 315, and recovery of the trans isomer, 316, unchanged under the same conditions<sup>215</sup>. In contrast, the trans, non-spirofused, system 317 is readily cyclized to the isoquinoline analogue 318<sup>325</sup>.



This may be of importance, not only with regard to six-membered ring C formation, but to the possible effects of strain on seven-membered ring formation from spirofused precursors. (see 2.4).

As compound 312 is our first pentacyclic cephalotaxine analogue, we were interested in a detailed look at the NMR characteristics of this material.

The 250MHz proton NMR showed the geminal protons,  $H_a$  and  $H_b$  as an AB system centred at ca. 3.8ppm (a characteristic shift for these isoquinoline methylene protons) (fig.8). This confirms a single relative molecular configuration, resulting in a single diastereotopic relationship between  $H_a$  and  $H_b$ , and consequently the observed single AB spin system. The large geminal coupling constant of  $J_{ab} = -14\text{Hz}$ , is characteristic of protons on a centre adjacent to unsaturation, further confirming these as the new methylene bridge protons.



*fig 8 AB spin system  
of 312*

To help with further assignments, a DEPT  $^{13}\text{C}$  spectrum of 312 was obtained (fig.9), and compared with the DEPT spectrum of thiolactam, 253 (fig.5).

This comparison showed that the two new methylene carbons - the bridge to the aromatic ring, and the reduced, pyrrolidine methylene - are those resonating at 54.6ppm and 53.3ppm. The position of the



benzylic methine carbon was confirmed in the 40-45ppm region, and the now substituted aromatic carbon, absent in fig.8, was seen to be that resonating at ca.119 ppm in the thiolactam spectrum.

These data allowed clearer interpretation of  $^{13}\text{C}$  NMR changes during construction of a seven-membered ring C (see chapter 4).

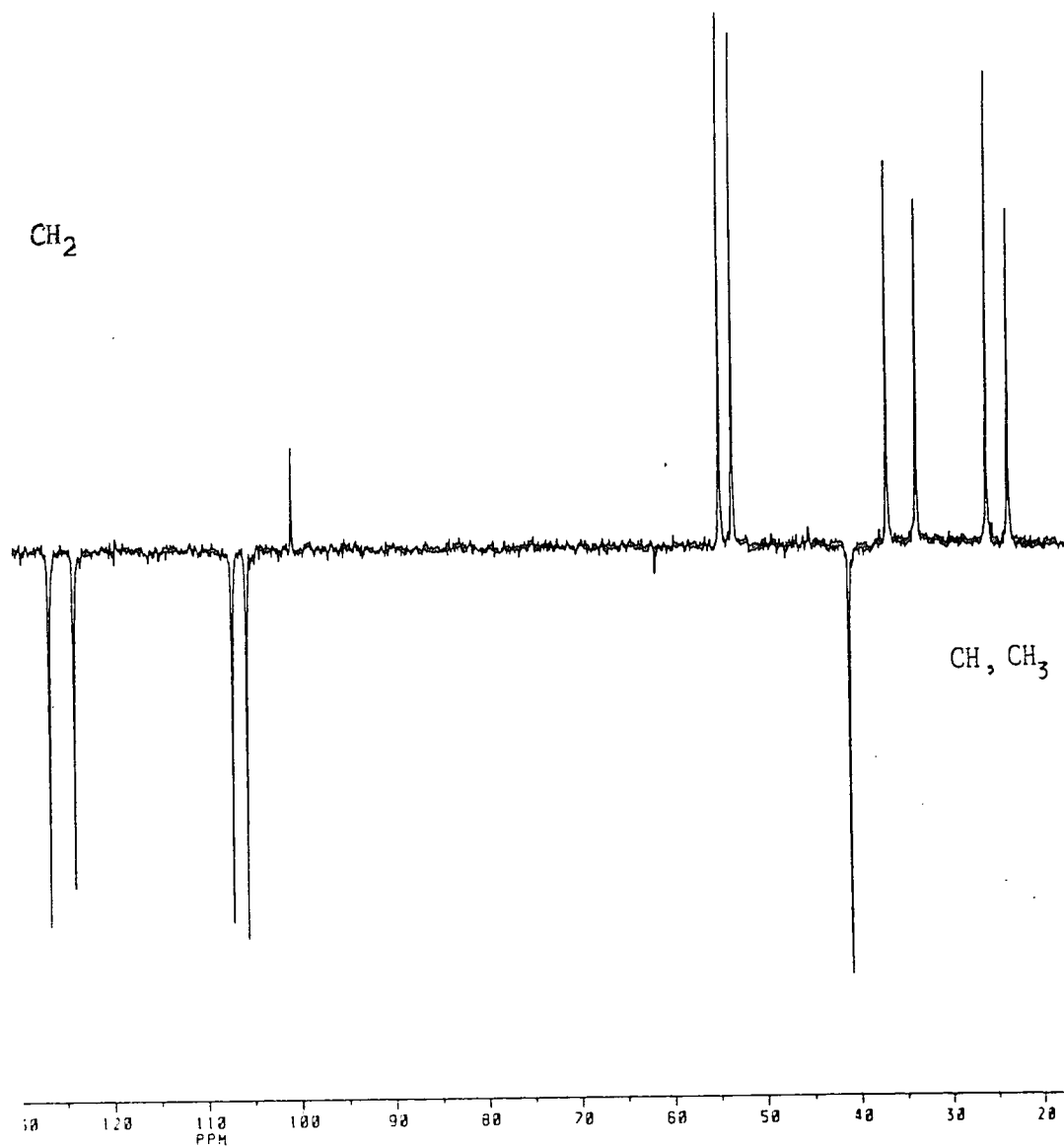
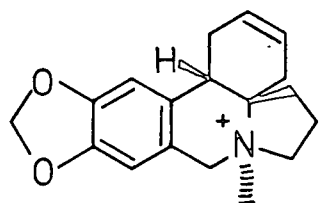


Fig 9 DEPT  $^{13}\text{C}$  spectrum of 312

The presence of the basic amino nitrogen in 312 and 313, may result in complications during the intended modification of ring E. Consequently protection of this nitrogen is desirable, most easily by quaternization to the hydrochloride or methiodide salts. We chose the methiodide, 319a which was obtained in very good yield by treatment of the amine 312 with methyl iodide. As iodide is a potential nucleophile which may interfere during reactions on ring E, exchange with the non-nucleophilic hexafluorophosphate anion was effected with aqueous hexafluorophosphoric acid, providing 319b in quantitative yield.



319 a X = I

b X = PF<sub>6</sub>

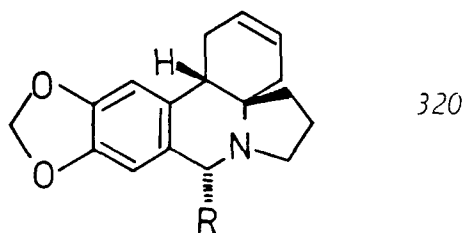
The favoured nitrogen geometry is expected to be as indicated, with the methyl group pointing away from the sterically cluttered 'top face'. However, while tertiary alkyl ammonium centres are configurationally stable, and numerous isomeric mixtures have been resolved since the turn of the century<sup>327</sup>, iodide ions can efficiently facilitate racemization by equilibrating via free amine. The obtained quaternized stereochemistry can be determined by either kinetic or thermodynamic criteria<sup>328</sup>.

While structurally related alkaloids such as lycorine and  $\beta$ -dihydrocaranine, yield mixtures of both nitrogen stereochemistries,<sup>329</sup> the rigid geometrical constraints at nitrogen, resulting from the spirofusion of our cyclopenta-phenanthridine, suggest that the alternative ammonium stereochemistry would involve significantly more strain in both the five- and six-membered rings of the indolazidine subunit, to a degree where only one stereochemistry will be observed.

## ii Future modifications

The only development of this section of work which is of interest, is to ascertain the degree of stereoselectivity possible - resulting from the conformational constraints resulting from the relative stereochemistry and rigid spirofusion - with increasingly bulky aldehydes in Pictet-Spengler reactions.

Models would suggest increasing preference for the relative stereochemistry of 320.



Stereoselectivity in Pictet-Spengler type syntheses of isoquinolines has been the subject of a number of recent publications<sup>330,331</sup>.

### 3.3 Electrophilic aromatic substitution strategies

With the efficient construction of the 1-azaspirolactam 131a, and 1-azaspiropyrrolidine, 245, intermediates now achieved (2.2, 2.3), a range of synthetic elaborations towards ring C became possible. The approaches fall broadly, within the general categorization identified at the start of this chapter, viz:

- i electrophilic cyclization
- ii photochemical cyclization
- iii C-N bond forming ring closure
- iv three-membered ring expansion

Essentially all our synthetic efforts have been within categories(i) and (iii), and so only brief mention of possible strategies within the remaining two categories will be given.

Our approach based on category (iii) methodology will be discussed in chapter 4. The bulk of discussions here will thus be related to potential electrophilic annulation (category (i)).

Spiro-pyrrolidine, 245, and spiro-lactam, 131a, offer different 'parallel' possibilities, represented schematically by equations 1 and 2 respectively (fig.10).

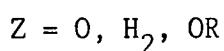
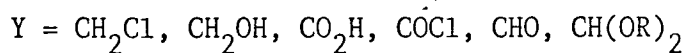
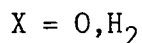
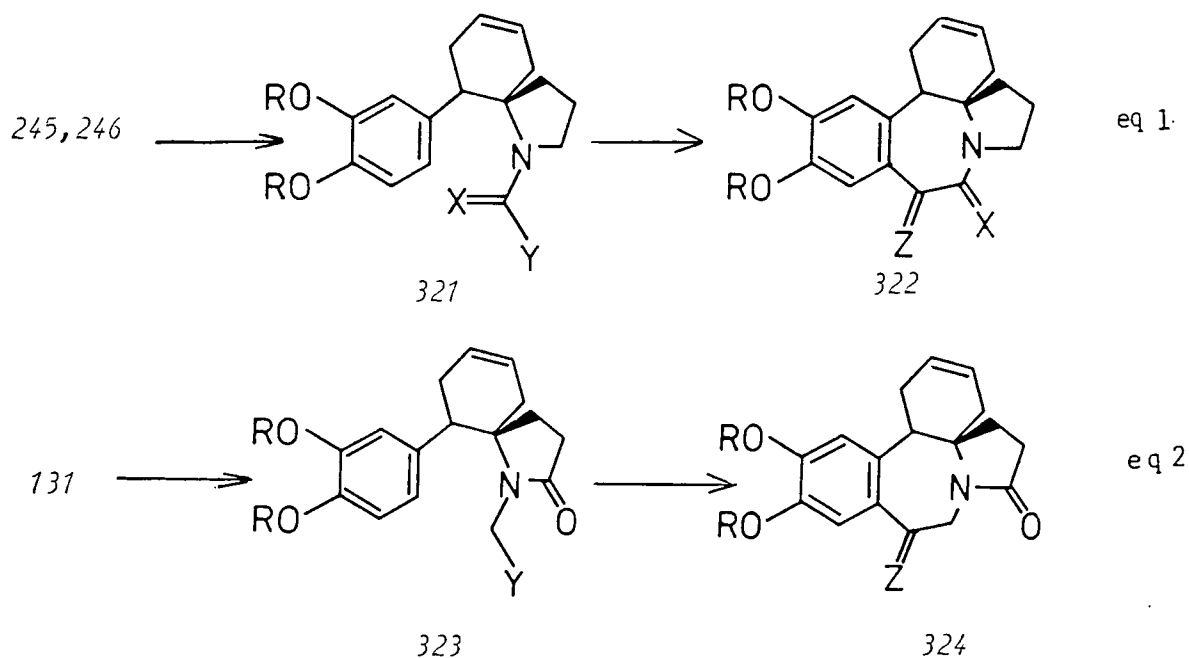


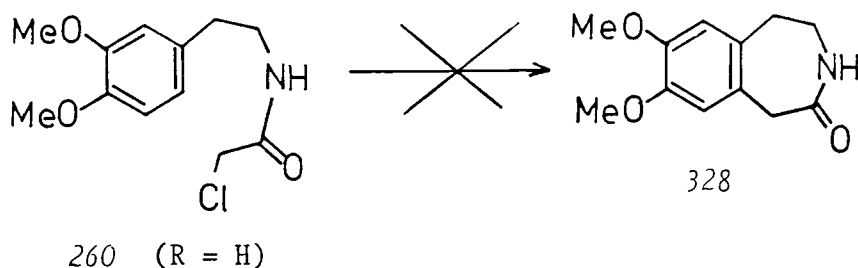
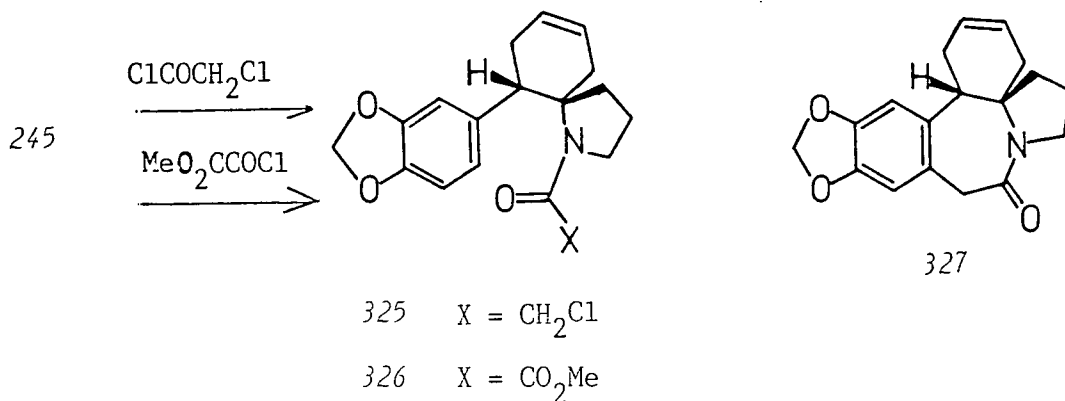
Fig 10

#### i Spiro-pyrrolidine derivatives

Entry to intermediates of type 321 should be readily provided by reaction of 245 with suitably functionalized acid chlorides. Our initial targets were derivatives 325 and 326, which were both obtained in >95% yield, by reaction of 245 with either chloroacetyl chloride, or methyl-oxalylchloride, in presence of triethylamine.

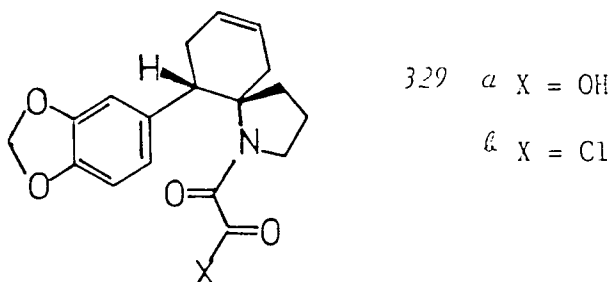
Derivative 325 is essentially a N-2-chloroacetyl-phenethylamine, and should thus be a suitable substrate for Friedel-Crafts cyclization

to the 3-benzazepinone, 327. It is also a potential substrate for Witkop photocyclization (3.1.ii).



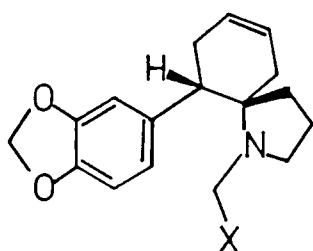
However, model studies on the N-2-chloroacetyl-phenethylamine, 260(R=H) following the general procedure of Nair and Malik<sup>200</sup>, led only to good recovery (>70%) of uncyclized 260 after chromatography. Consequently, preparation of 325 was not scaled up, and Friedel-Crafts cyclization with 325 was not attempted.

Two possible approaches to ring C from intermediate 326 were envisaged. Firstly, saponification to amido-acid 329a, followed by acid catalysed intramolecular aromatic acylation. Secondly, conversion of 329a to the acid chloride 329b, followed by Friedel-Crafts acylation.



But concurrent with our initial publication describing the synthesis of spiro-lactam *131a*, Hill's group published<sup>48</sup> an essentially identical route to this compound. In their paper, Hill et al reported that attempts at Lewis acid catalysed cyclization of either *329a* or *329b* were unsuccessful. This report further discouraged us from continuing this line of investigation.

Approaches via derivatives *321* ( $x = H_2$ ) seemed more promising, as many of the 'classical' approaches to 3-benzazepines (see 3.1.i) proceed via this sort of intermediate.



*330*  $X = CH(OEt)_2$

*331*  $X = CO_2Et$

*332*  $X = CH_2OH$

*333*  $X = CH_2Cl$

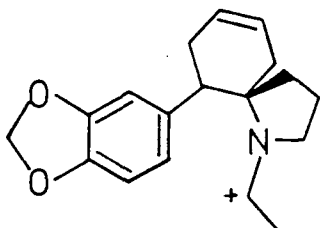
With a view to possible boron trifluoride cyclization of the diethyl acetal *330*, attempts were made to N-alkylate *245* with bromoacetaldehyde diethyl acetal, using sodium hydride or n-butyl lithium as base. Use of the latter led to a product mixture of at least three materials, while use of the former base did lead to isolation of some material, possibly product *330*, from IR and NMR evidence. However, yields were in the region of only 20-25% and attempts to optimize this have not yet been followed up.

In contrast, spiro-pyrrolidine *245* was very efficiently N-alkylated using bromoethylacetate, with potassium carbonate as base in presence of 18-Crown-6. The product amino-ester, *331*, was obtained pure in >99% yield following column chromatography.

While attempts at saponification of *331* to the amino acid involved some purification problems, the ester was cleanly reduced to the amino-alcohol *332*, in 99% yield, by LAH.

As described above (3.1.i), acid catalysed cyclization of 2-hydro-

oxyphenethylamine-type systems, has almost exclusively been effected on substrates possessing aromatic substituents  $\alpha$  to the hydroxy group e.g. 267. In 332 there is no such  $\alpha$ -substituent, and it is possible therefore, that competition from cyclization via the more stable secondary carbocation, 334, will complicate any products obtained.



334

In fact, it was found that treatment of 332 with PPA at room temperature for 20 hours, led to isolation of only a small percentage of material, suggested by mass spectral data, and t.l.c., to be largely unchanged alcohol. Reaction at elevated temperatures led only to a complex mixture by t.l.c., possibly due to side reactions, including opening of the methylenedioxy ring under such hot acidic conditions. 332

Other attempts at acid catalysed cyclization, e.g. with methanesulphonic acid/phosphorus pentoxide, also proved fruitless.

We then turned to dehydrative cyclization with phosphorus oxychloride, which afforded a single product, provisionally assigned on the basis of its mass spectrum ( $m/e = 310$ ) and  $^{13}\text{C}$  NMR (which showed a new peak at 44 ppm (C-Cl) replacing that at ca. 65 ppm (C-OH)), as the 2-chloroethyl derivative, 333 (ca. 70% yield), rather than the intended cyclized product.

This thus appears to be quite a convenient route to this potential Friedel-Crafts cyclization substrate, though this has not been developed further, as other cyclization methods appeared more promising (see 3.3.i and 4.1).

#### ii Spiro-lactam derivatives

The development of possible routes to ring C via electrophilic cyclization of N-substituted spiro-lactams, is more desirable than

approaches via N-substituted spiro-pyrrolidine derivatives, because the amide functionality constitutes effective 'protection' of the basic amino nitrogen. This may prove important in subsequent modifications of ring E, where some steps may be base sensitive.

A number of methods are available for the N-alkylation of amides, essentially involving deprotonation with strong base to the amide anion, which then nucleophilically displaces, for example, a halogen from the alkylating agent<sup>163</sup>.

The use of a sodium dispersion in toluene, or alcoholic alkali metal hydroxides, as bases for these reactions, has been known for over a century. Subsequently, sodium hydride has also found use as the base in this type of reaction<sup>333,334</sup>.

More recently, the use of alkali metal hydroxides, in phase transfer catalysed reactions with tetra-alkyl ammonium salts has been developed<sup>335-337</sup>. Potassium fluoride on activated alumina has proved an efficient heterogeneous base<sup>338-340</sup>, far more active than KF itself, or KF on other supports such as silica, celite<sup>341</sup> or molecular sieves. For KF-alumina, reaction on the alumina surface probably forms potassium aluminate and potassium hydroxide as the species responsible for the high basic activity<sup>342</sup>.

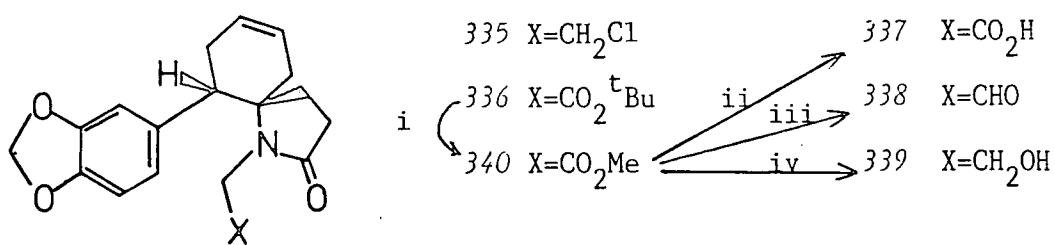
Our initial attempts at alkylation of 1-azaspirolactam *131a* were with 2-bromochloroethane as bifunctional alkylating agent, with preferential displacement of bromide expected to yield the N-2-chloroethyl lactam *335*. However, the use of potassium hydroxide, either as heterogeneous powder, or as a 50% solution, with tetrabutylammonium bromide or tetrabutylammonium hydrogen sulphate as phase transfer catalyst, under a variety of conditions, led in all cases to good recovery of lactam *131a*. In several cases, t.l.c. and mass spectra suggested some alkylation may have occurred, but only in very low yield.



Similarly, the use of sodium hydride, or potassium fluoride on activated alumina, as bases, led to, at best, low yields of alkylated materials, along with several other products.

Subsequently, N-substitution utilizing bromotertbutylacetate as alkylating agent was attempted (it is considerably more electrophilic than simple haloalkanes), with potassium tert-butoxide as base. Initial attempts at effecting this conversion at ambient temperatures in DMF, led only to good recovery of unsubstituted lactam, *131a*. However, performing the reaction in tert-butyl alcohol at reflux, led to 60% yield of the N-substituted lactam tert-butyl ester, *336*, and 40% recovery of starting lactam, completely separated by chromatography.

By increasing the molar ratio of both base and alkylating agent, to greater than two equivalents per lactam, the yield of alkylated lactam was improved to, reproducibly, >98%.



i MeOH/H<sup>+</sup>, ii NaOH/EtOH, iii DIBAL-H/-78<sup>o</sup>C, iv LiBH<sub>4</sub>-ether

The lactam ester, *336*, offered entry to a range of intermediates, bearing a functionalized two carbon substituent on nitrogen, as potential cyclialkylation substrates, analogous to the tertiary amino intermediates, *330-333*, above (3.3.i).

Based on the cyclization strategies to 3-benzazepines, involving electrophilic substitution, reviewed above (3.1.i), our target intermediates were the lactam-acid, *337*, lactam-aldehyde, *338*, and lactam-alcohol, *339*.

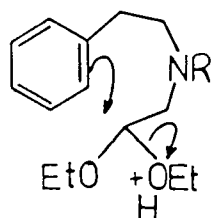
The selective reduction of esters in the presence of amides can be achieved under mild conditions with lithium borohydride. However, the

reactivity of tert-butyl esters is much less than that of, for example, methyl esters<sup>343</sup>. Thus, the tert-butyl ester, 336, was converted to the methyl ester, 340, by transesterification, essentially quantitatively. Ester 340 was then efficiently reduced to the lactam alcohol<sup>339</sup>, by treatment with lithium borohydride in ether (75-80%). This ester, 340, was also converted to the lactam acid 337 by saponification with alcoholic sodium hydroxide (ca. 85% yield), and to lactam-aldehyde 338 by treatment with DIBAL-H at  $-78^{\circ}\text{C}$  (ca. 60%).

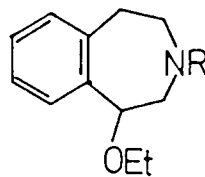
Preliminary investigations of PPA catalysed cyclization of the acid 337, or alcohol 339, were unsuccessful. Small yields of material were obtained, for which mass spectral data were not consistent with cyclization of either to the 3-benzazepine skeleton. However, this is not basis enough to rule out the possible use of these intermediates, particularly the lactam-acid 337, as there are a wide variety of catalysed reactions yet to be tested.

We next chose to attempt cyclization using the aldehyde, 338. As described above (3.1.i), the mineral or Lewis acid catalysed cyclization of dialkyl acetals, or free aldehydes, of amino systems related to lactam 338, has found some specific uses for construction of 3-benzazepine rings. Also, lactam-aldehydes relevant to 338 have been cyclized under Lewis acid catalysis, in the synthesis of cephalotaxine precursors (1.6.i).

Though both acetals and aldehydes react similarly, the former do not necessarily proceed via an intermediate free aldehyde. Rather, the protonated intermediate 341 can cyclize directly to 342.



341



342

Treatment of our lactam-aldehyde 338 with boron trifluoride diethyletherate as Lewis acid, provided a complex mixture. However, t.l.c. showed one particularly mobile component, and this could be almost completely separated by column chromatography.

The IR spectrum of this material showed a single carbonyl absorption at  $\nu_{\text{CO}}$  1708  $\text{cm}^{-1}$ , and the mass spectrum showed a molecular ion at  $m/e = 295$ . Its 250MHz proton NMR spectrum showed two sharp aromatic singlets, each integrating as single protons (fig.11). On this basis a provisional structural assignment as the 3-benzazepine 343 was made.

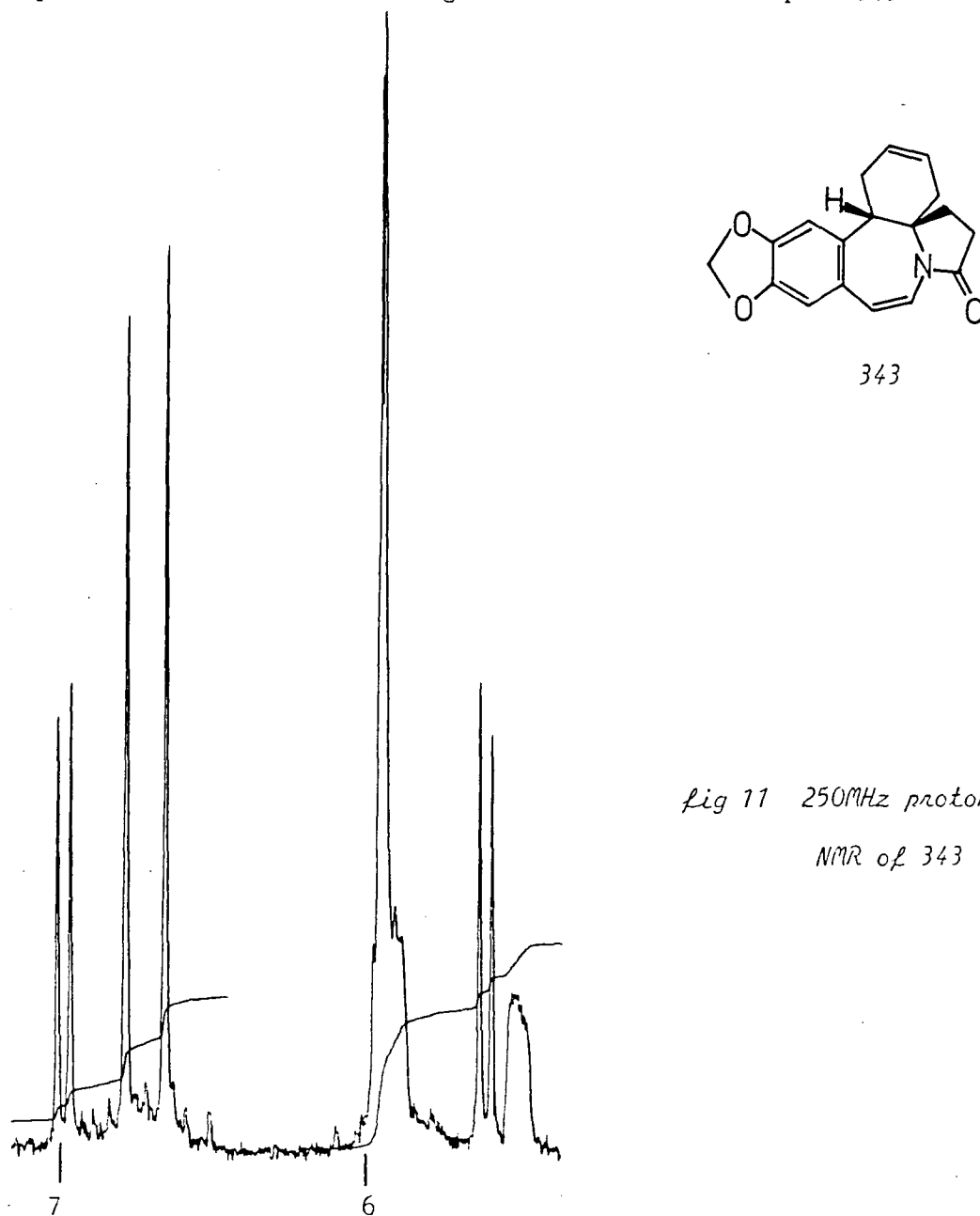


fig 11 250MHz proton  
NMR of 343

Further support for this assignment was provided by the two doublets at ca. 7 ppm and ca. 5.6ppm, appearing to constitute an AX spin system. This is consistent with the expected positions and couplings of the enamide protons. The coupling constant,  $J_{AX} \approx 11\text{Hz}$ , is also consistent with values for cis substituted double bonds.

The  $^{13}\text{C}$  NMR DEPT spectrum showed six carbons bearing an odd number of protons, in the 108 - 130 ppm regions (fig.12), which is again consistent with structure 343, with two unsubstituted aromatic sites, and four unsaturated methine carbons.

The benzylic methine shows at 44.6 ppm, and the methylene carbons of rings D and E show in the 28-33 ppm region (the peak at 33 ppm is suggested to be two coincident peaks, as it is particularly intense in the proton-decoupled  $^{13}\text{C}$  NMR).

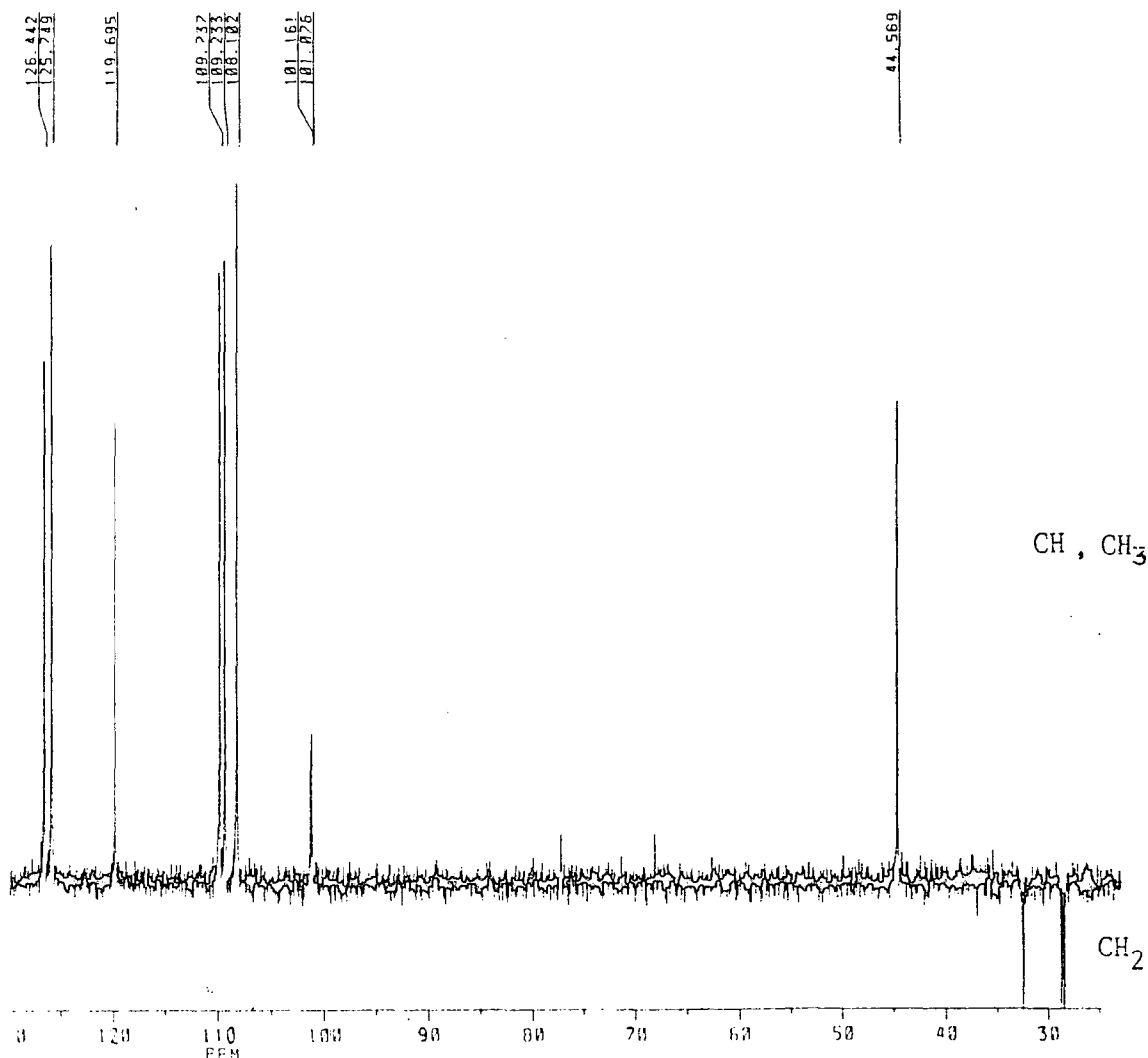
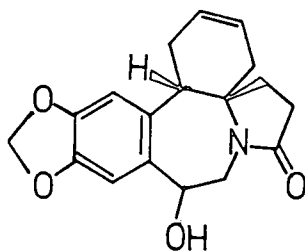


Fig 12 DEPT  $^{13}\text{C}$  spectrum of 343

Unfortunately, changing ratios of Lewis acid, or reaction time, did not significantly improve the yield of this product above 14%. Therefore, it does not appear to be a viable entry to the desired 3-benzazepine system, at this stage.

Treatment of lactam-aldehyde 338 with 4-6M hydrochloric acid provided a crude product, shown by t.l.c. to be largely one material. This showed a single carbonyl peak in the IR spectrum at  $\nu_{\text{CO}} = 1663 \text{ cm}^{-1}$  and a strong alcoholic O-H stretch at  $3460 \text{ cm}^{-1}$ . The CI mass spectrum showed an M+1 peak at  $m/e = 314$ , and a major peak at  $m/e = 296$  (corresponding to loss of water). In the EI spectrum the only high mass peak was at  $m/e = 295$ . These data, combined with two proton aromatic integration in the 250 MHz  $^1\text{H}$  NMR, suggested the 3-benzazepinol structure 344.



344

The crude yield of this material was ca. 80-90%, but scale-up, efficient purification and full structural confirmation (including hydroxy carbon stereochemistry), have yet to be completed.

### iii Summary

A range of spiro-pyrrolidine and spiro-lactam derivatives, bearing functionalized two carbon substituents on nitrogen, have been prepared, several in very good yield. These offer potential for a wide range of electrophilic cyclialkylation entries to the basic 3-benzazepine skeleton of cephalotaxine. Currently, two of the lactam derivatives appear to have provided 3-benzazepine products, though unambiguous structural confirmation and yield optimization are still awaited. The full scope of available methodologies towards 3-benzazepine ring closure, using these intermediates, is far from having been exhausted.

CHAPTER FOUR

ALTERNATIVE APPROACHES TO RING C :

3-BENZAZEPIN-2-OL and

1,3-BENZODIAZEPINE ANALOGUES

#### 4.1 Approaches to ring C via C-N bond forming ring closure

We have reviewed above (3.1) the general strategies available for 3-benzazepine formation, and have reported progress, based on electrophilic cyclialkylation, towards construction of the 3-benzazepine ring C of our target cephalotaxine intermediates (3.3).

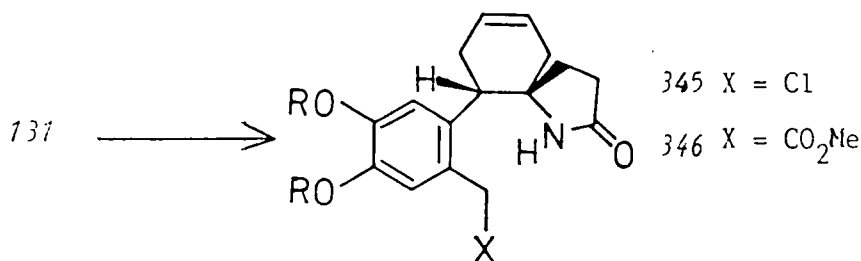
Here, we will describe work towards our desired 3-benzazepine intermediate, based on the retrosynthesis envisaged via 130 and 132 (scheme XIV, 1.8) ['category iii' methodology (3.1)].

Our intended ring forming reaction will involve some form of C-N bond formation. The few reported examples of this approach to 3-benzazepines have been described (3.1.iii), the majority utilizing amine-ester, amine-acid or amine-aldehyde condensations.

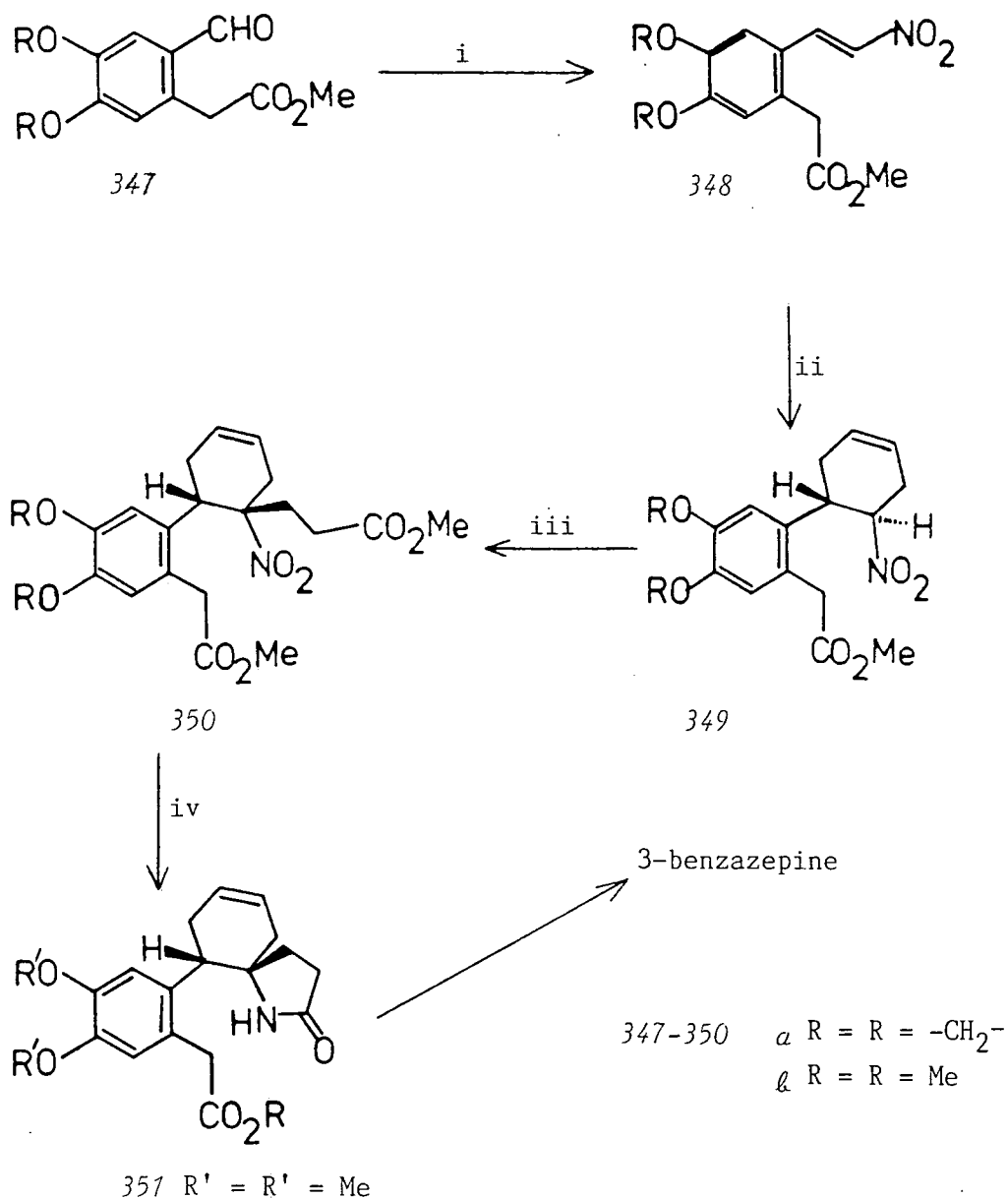
##### i Strategy

Implicit in our earlier retrosynthetic analysis (scheme XIV) is that this approach will retain the key stereospecific azaspirocyclization steps described above (2.2)

Our first consideration was whether to introduce the two carbon fragment on the aromatic ring at the start of the synthesis, or subsequent to spirocyclization. The latter approach would most easily be achieved by chloromethylation of lactam 131a to 345, followed by cyanation and hydrolysis-esterification<sup>344</sup>, to afford the potentially more versatile lactam-ester, 346. Unfortunately, standard chloromethylation attempts on 131a, with formaldehyde-hydrogen chloride, led only to good recovery of unchanged lactam, 131a. Chloromethylation was also unsuccessful with the precursor nitrocyclohexene, 239.



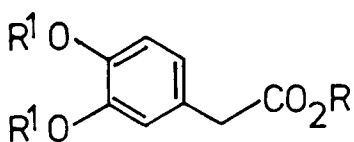
SCHEME XV



i  $\text{MeNO}_2/\text{K}_2\text{CO}_3$  , ii butadiene sulphone, iii Me acrylate/triton-B, iv  $\text{Zn}/\text{HCl}$

Thus, we approached the synthesis commencing with a starting material already bearing a two carbon aromatic substituent (see scheme XV). The required aldehyde, 347a, is not commercially available, and neither is the precursor 352. However, the acid of the dimethoxy analogue of 352, viz 353a, is available, and was therefore chosen. It was converted to the ester, 353b, in near quantitative yield by acidic methanol. Conversion to the natural methylene dioxy functionality can be achieved at a later stage in the synthesis.





352  $R' = R' = -CH_2-$   $R = Me$

353 a  $R' = R' = Me$   $R = H$

l  $R' = R' = Me$   $R = Me$

## ii Discussion

Our first synthetic requirement was the formylation of 353l to the aromatic aldehyde, 347l. A number of methods are available for the introduction of aldehydic functionality into aromatic systems. The original method was the classical Gatterman formylation<sup>345,346</sup>, and variations upon it<sup>346,347-349</sup>, using an HCN/HCl mixture under Lewis acid catalysis. The Gatterman-Koch formylation using instead CO and HCl, specifically fails with phenolic ether substrates. The Adams modification<sup>350,351</sup>, generating zinc chloride as the Lewis acid in situ, appears to have more particular applicability to formylation of phenolic ethers. However, our attempts at using various adaptations of this reaction system, resulted in extremely crude product mixtures.

Vilsmeier-type formylation<sup>353</sup> with dimethylformamide or N-methylformanilide<sup>353-356</sup>, and phosphorus oxychloride, is another approach applicable to activated systems like phenol ethers. However, again we found this method to provide very crude product mixtures, and a more efficient, cleaner method was therefore sought.

Two attractive methods are the use of formyl fluoride<sup>357</sup>, a powerful formylating agent, or Lewis acid catalysed reaction with dichloromethyl methylether. The latter is reported<sup>358</sup> to have much wider scope than any other aromatic formylation methodology, and appears to be both experimentally mild and clean<sup>359</sup>.

We found that using titanium tetrachloride as the Lewis acid catalyst<sup>360</sup>, reaction of 353l with dichloromethyl methyl ether, led only to recovery of crude starting material, 353l. However, on changing the Lewis acid to aluminium trichloride, yields of 80-90% of the crystalline

aldehyde, 347 $\ell$ , were obtained. The reaction proved particularly expedient, as recrystallisation from diethyl ether at  $-78^{\circ}\text{C}$  provided analytically pure product, with minimal loss of material. The reaction could also be scaled-up to provide 10-15 g batches of aldehyde.

The use of potassium fluoride as base for the condensation of 347 $\ell$  with nitromethane, under essentially the same conditions which were successful with 6-nitropiperonal (4.2.ii), resulted in repeatably poor yields (ca 40%) of 348 $\ell$ . Potassium carbonate as catalytic base, under reflux conditions, led to a very crude product mixture, from which only ca.30% of nitrostyrene derivative 348 $\ell$  was isolated.

Use of the standard procedure successful with piperonal, (see 2.2), though lengthy, (taking 3-4 days to go to completion, as judged by t.l.c.), had the advantages of providing reasonable yields (70-75%) of 348 $\ell$ , of sufficient purity to be used directly for the subsequent cycloaddition reaction.

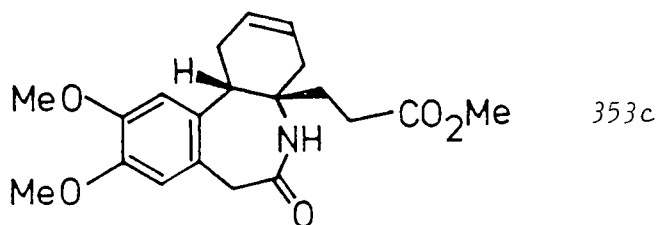
The use of butadiene sulphone as butadiene synthetic equivalent (see 2.2), again proved convenient for cycloaddition to 348 $\ell$ . However, a number of initial difficulties in obtaining reasonable yields were encountered, but a modification of the work-up used previously for 249, repeatably afforded satisfactory yields (70-75%) of 349 $\ell$ , sufficiently pure for further use.

Michael addition of methyl acrylate to the anion of 349 $\ell$ , proceeded under the conditions utilized previously (2.2), to afford a single major product (t.l.c.). This was obtained as a white powder in 75-88% yield, after chromatography of the crude reaction mixture, with further purification by recrystallization from diethyl ether at  $-78^{\circ}\text{C}$ , if necessary. By analogy with compound 241, the single product, 350 $\ell$ , must possess the single relative stereochemistry indicated (scheme XV).

The elaboration of intermediate 350 $\ell$  towards construction of rings C and D could now be approached. The most obvious approach to ring D,

is to employ the reductive cyclization methodology successful with analogous systems *241a* and *241b* (2.2).

Under the standard conditions of these previous zinc-hydrochloric acid reductions, a poor yield of a white powder (ca. 25%) was isolated: from mass spectral and IR data, this was provisionally assigned the lactam-acid structure, *351a*. The lactam carbonyl absorption being more consistent with a  $\gamma$ -lactam ring, than the possible isomeric  $\Sigma$ -lactam, *353* as we would expect from entropic factors determining ring closure<sup>361</sup>. This acid, *351a*, could be converted to its methyl ester, *351b*, in >90% yield by refluxing in acidic methanol. However, the poor yield of *351a* could not be significantly improved, probably largely due to the low solubility of the lactam-acid *351a* causing extraction problems.

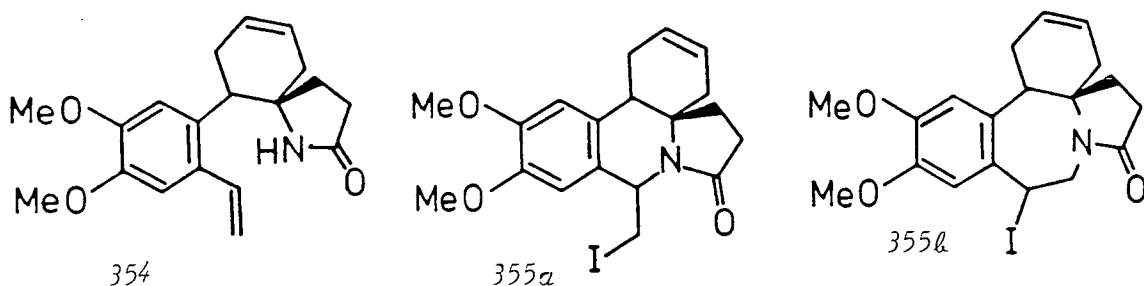


It was therefore decided to avoid basification at elevated temperature, and the crude acidic reaction mixture was instead basified with cold aqueous alkali. This then provided a white solid, whose spectral characteristics suggested it to be ethyl ester *351c*, transesterification of the methyl ester occurring under the reaction conditions. The yield at this stage was now 90% from the nitro-diester, *350*.

The lactam C=O stretch at  $\nu_{\max}$  ca.  $1690\text{ cm}^{-1}$  is again consistent only with a smaller ring lactam (cf. five-membered lactam analogue *236a* [2.2]), ( $\nu_{\max}$  for a seven-membered lactam expected  $40\text{--}50\text{ cm}^{-1}$  lower). The reductive cyclization of *350* is thus completely regioselective in construction of ring D, with no competitive cyclization to *353c*.

With the construction of ring D, and a functionalized two carbon fragment attached to the aromatic ring, a number of possibilities were

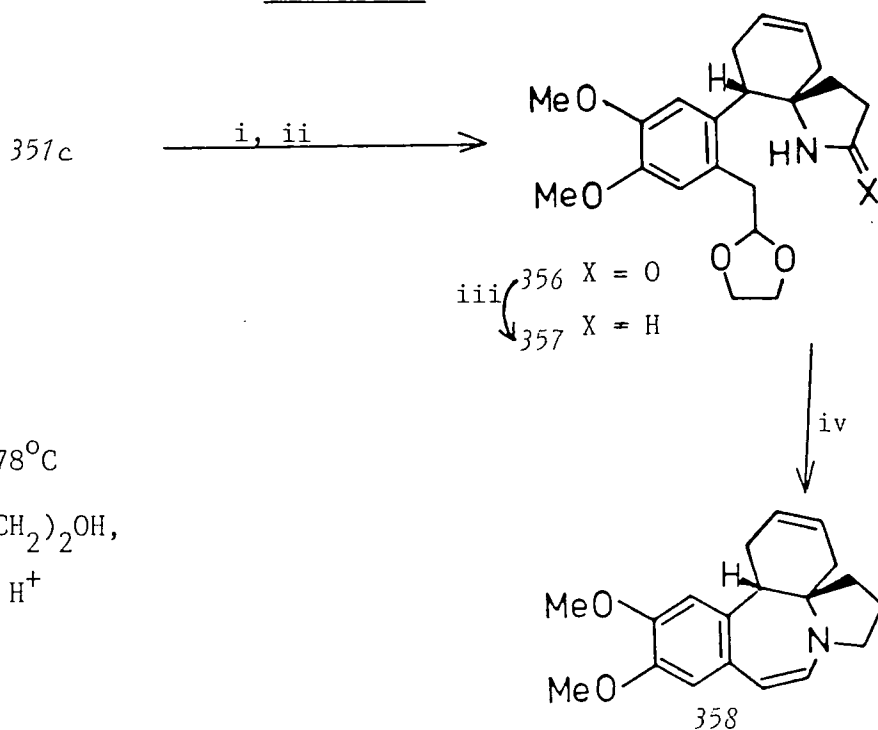
available for C-N bond formation to give the ring C appropriate to the cephalotaxine skeleton. Possible approaches could utilize either the lactam nitrogen, or the reduced amine nitrogen, as internal nucleophile, in derivatives of 357. For example, the carboxy group of 357c could be converted to a more favourable leaving group, e.g. tosylate, to be displaced by an internal nitrogen nucleophile.



Lactams undergo halogen assisted intramolecular cyclizations onto olefins<sup>362</sup>, the use of N-nucleophiles in general being of current interest. However, entropic factors<sup>361</sup> would favour cyclization of lactam-olefin 354 to 355a rather than 355b so such a strategy was ruled out.

The alternative strategy devised for formation of the seven-membered ring, is outlined in scheme XVI. This scheme envisages reduction of the

SCHEME XVI



- i DIBAL-H/ $-78^{\circ}\text{C}$
- ii pTsOH/ $\text{HO}(\text{CH}_2)_2\text{OH}$ ,
- iii LAH, iv  $\text{H}^+$

ethyl ester to aldehyde, protection of this aldehyde, and LAH reduction of the lactam to yield spiropyrrolidine intermediate 357. Deprotection of the aldehyde was then hoped to allow facile condensation to enamine 358. The route was particularly attractive, despite involving several steps, as the three steps prior to cyclization should all proceed very efficiently.

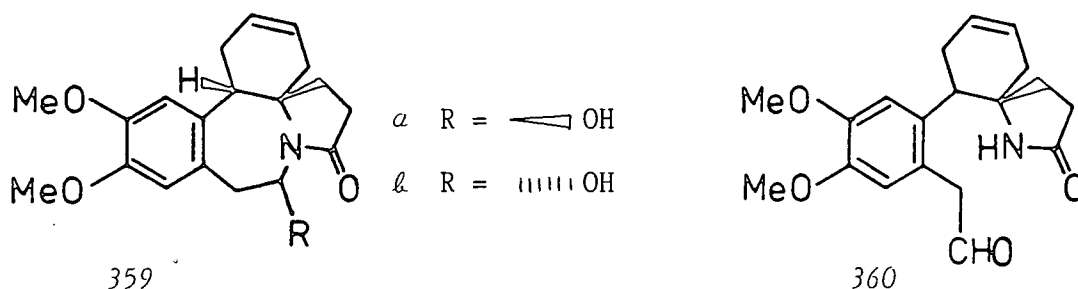
However, treatment of ester 357c with DIBAL-H at  $-78^{\circ}\text{C}$ , under essentially the same conditions successful in reducing the tertiary lactam-ester, 337, (3.3) to the corresponding aldehyde, 338, led, repeatably, only to the recovery of small quantities of material from bisulfite extraction. This was difficult to rationalize unless the majority of material was non-aldehydic. Though unchanged ester was recovered in small quantity, it was considered likely that most of the ester had been reduced to the aldehyde, presumably then undergoing further reaction in situ.

Consequently, bisulfite extraction of the reaction mixture was replaced by washing with brine, and then isolating all materials from the organic medium. Using 1.4 equivalents of DIBAL-H, the isolated product mixture consisted of two materials, one suggested by t.l.c. to be unchanged ester, 357c. The IR of the crude mixture showed a new carbonyl absorption at  $\nu_{\text{CO}}$   $1670\text{ cm}^{-1}$ , inconsistent with an aldehyde group, and a strong, sharp band at  $3280\text{ cm}^{-1}$ , possibly due to an intramolecularly bonded hydroxyl group. Careful chromatographic separation returned ca.40% of unchanged ester, 357c, and ca.40% yield of a second material. The IR of this new material showed a single carbonyl peak at  $\nu_{\text{CO}}$   $1670\text{ cm}^{-1}$ , and the sharp band at  $3280\text{ cm}^{-1}$ .

An unexpected observation was the complete absence of any lactam N-H stretch at ca.  $3200\text{ cm}^{-1}$ , confirmed by 250 MHz proton NMR data. These initial observations suggested that cyclization had occurred onto the lactam nitrogen.

The EI mass spectrum showed two major ions, at  $m/e = 329$  and  $311$ , correlating with ions at  $m/e = 330$  and  $312$  in the CI mass spectrum. These data are consistent with a preliminary structural assignment as **359**, (loss of water accounting for the lower of the mass peaks above). A rigid fused polycyclic framework is also consistent with the large number of notably sharp bands in the product IR spectrum, relative to acyclic precursors.

Further confirmation of structure **359** was provided by carbon-13 NMR data, which showed appearance of a peak at ca. 72 ppm. DEPT  $^{13}\text{C}$  NMR (fig.13) also confirmed this carbon bears an odd number of hydrogens, consistent with a secondary alcoholic carbon, as expected for cyclized product **359**. The above data, coupled with satisfactory elemental analysis led to a definite structural assignment as **359**. By increasing the ratio of DIBAL-H used to 2.1 equivalents, 80-90% yield of **359b**, and 5-10% recovery of **357c**, could be obtained after column chromatography.

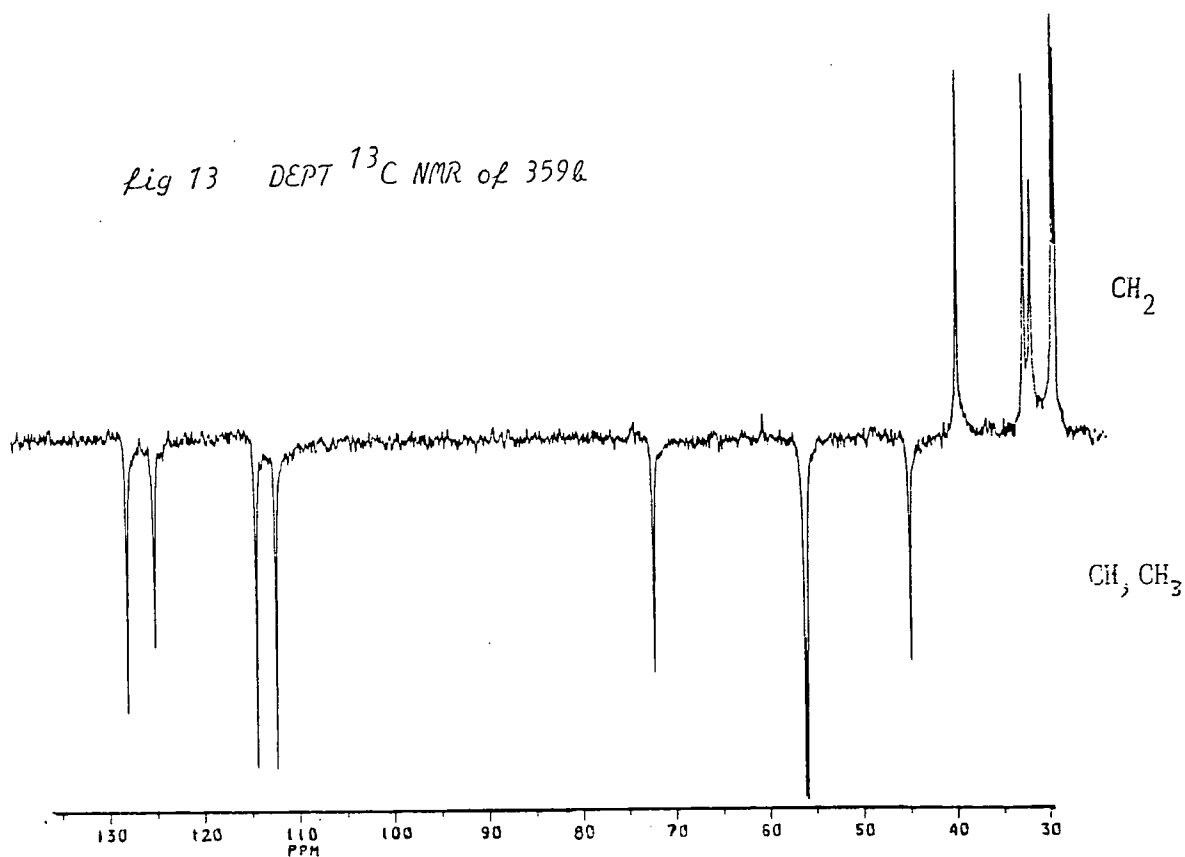


It is of further note, that all the spectroscopic evidence (and t.l.c.) indicate the cyclized product to be of a single relative stereochemistry. This reaction is therefore stereospecific in introduction of the new stereocentre formed on cyclization.

The reaction probably proceeds via a lactam-aldehyde intermediate, **360**, cyclization occurring through an aluminium monocoordinated, or chelated, complex, in which the aldehyde carbonyl is activated to nucleophilic attack by the lactam nitrogen. On this basis, we rationalized that either type of complexation would strongly disfavour intermediates,

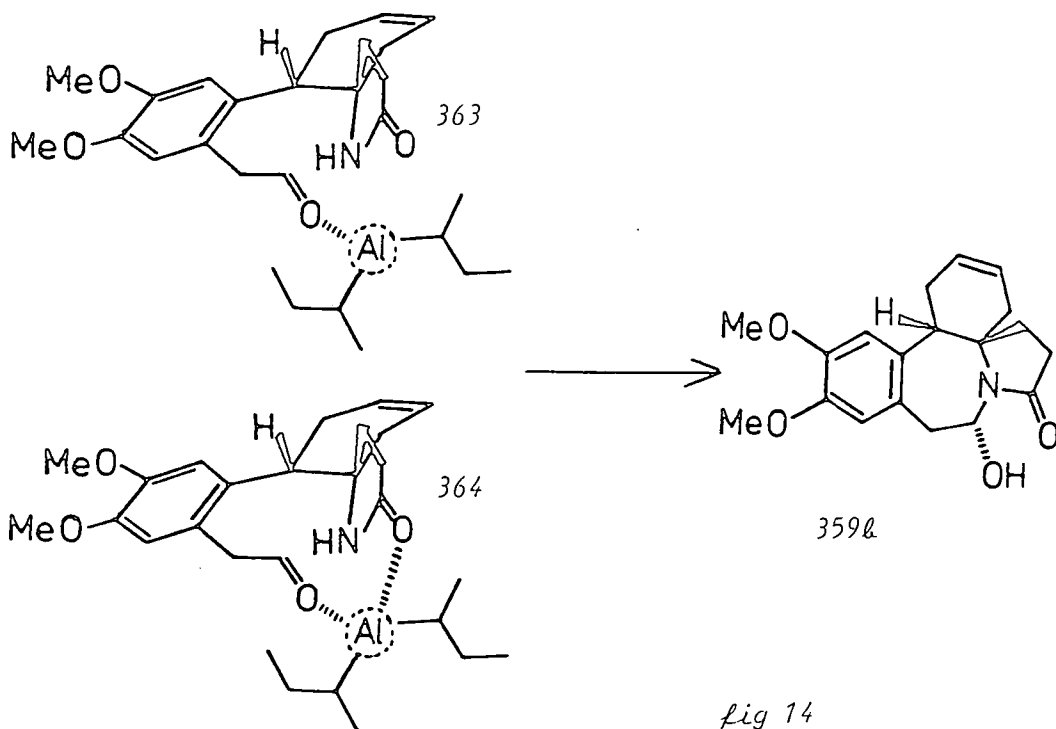
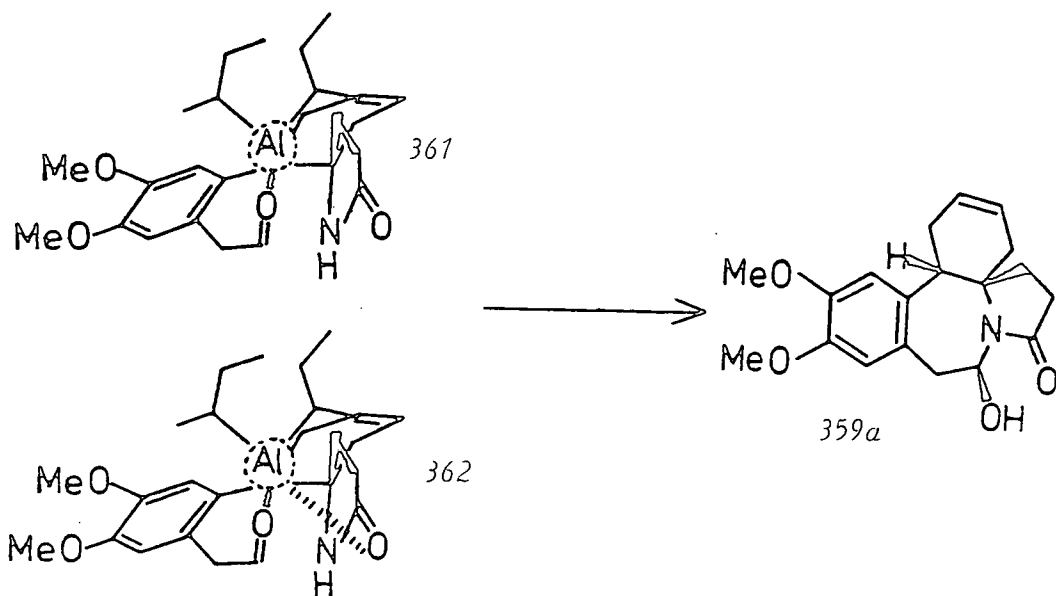


Fig 13 DEPT  $^{13}\text{C}$  NMR of 359b



i.e. 361 or 362, leading to the relative stereochemistry 359a, due to the considerable steric bulk of the coordinating diisobutylaluminium group. The geometry involved in these intermediates, coupled with the rigidity imparted by spiro-fusion, would result in extreme steric interactions between the organo-metallic group, and the lactam ring (fig.14). In contrast, intermediates 363 or 364 are far less sterically hindered, as the bulky organoaluminium group is in the open, unhindered "back face" of the molecule (fig.14). Therefore, if this is indeed the general mechanistic picture, we would expect to observe stereoselectivity in favour of the relative configuration of 359b.

An alternative, though less likely, mechanism could proceed via the imide 365, in which the stereochemistry would be determined by hydride transfer from DIBAL-H to one of the carbonyl groups.



DIBAL-H is known to regioselectively monoreduce cyclic imides to  $\alpha$ -hydroxy lactams, and to reduce carbonyls by hydride transfer to the least hindered carbonyl face<sup>363</sup>. So, should such a mechanism be involved we should observe high stereoselection in favour of 359a.

To confirm unambiguously that the product was the desired 3-benzazepinol ring, 359b, and to identify the relative configuration at the alcoholic carbon, an X-ray structure was obtained. This data, of course,



also gave us an insight into the conformation of this novel heterocyclic system.

The X-ray data confirm the skeletal structure, and confirm that the cyclization is highly stereoselective in favour of isomer 359b (fig.15) - the predicted product stereochemistry from the coordinated aldehyde intermediate, 363 or 364. An 'edge on' view (fig.16) shows also that the hydroxyl group consequently points away from the 'bowl' region enclosed by the aromatic and lactam rings. The 3-benzazepine ring shows buckling about the axis of the two carbons either side of the nitrogen.

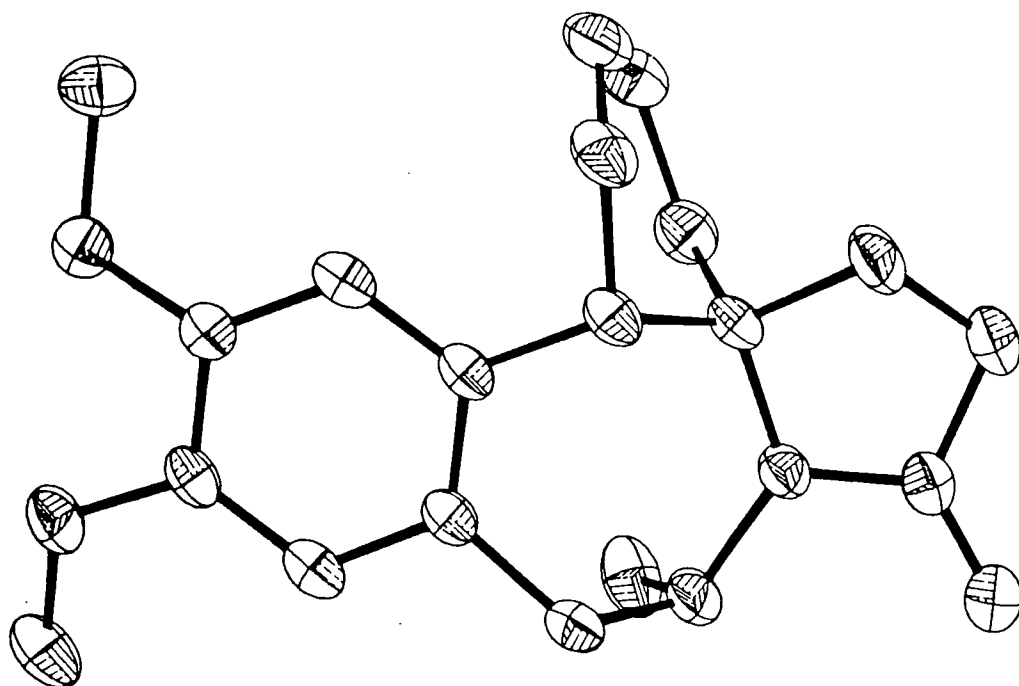


fig 15 X-ray structure of 359b : view from above benzene ring

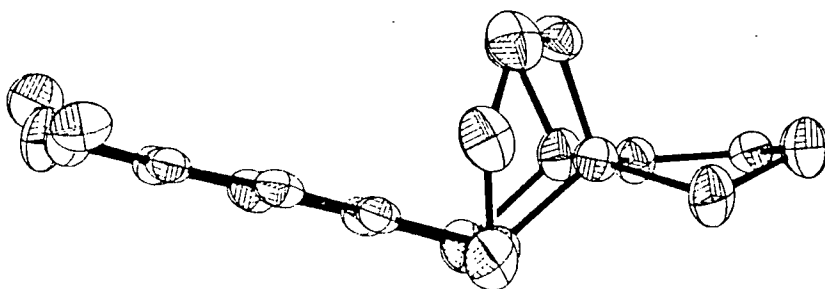
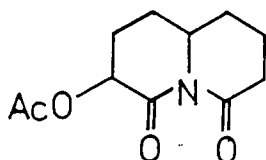


fig 16 X-ray structure of 359b : view in plane of benzene ring

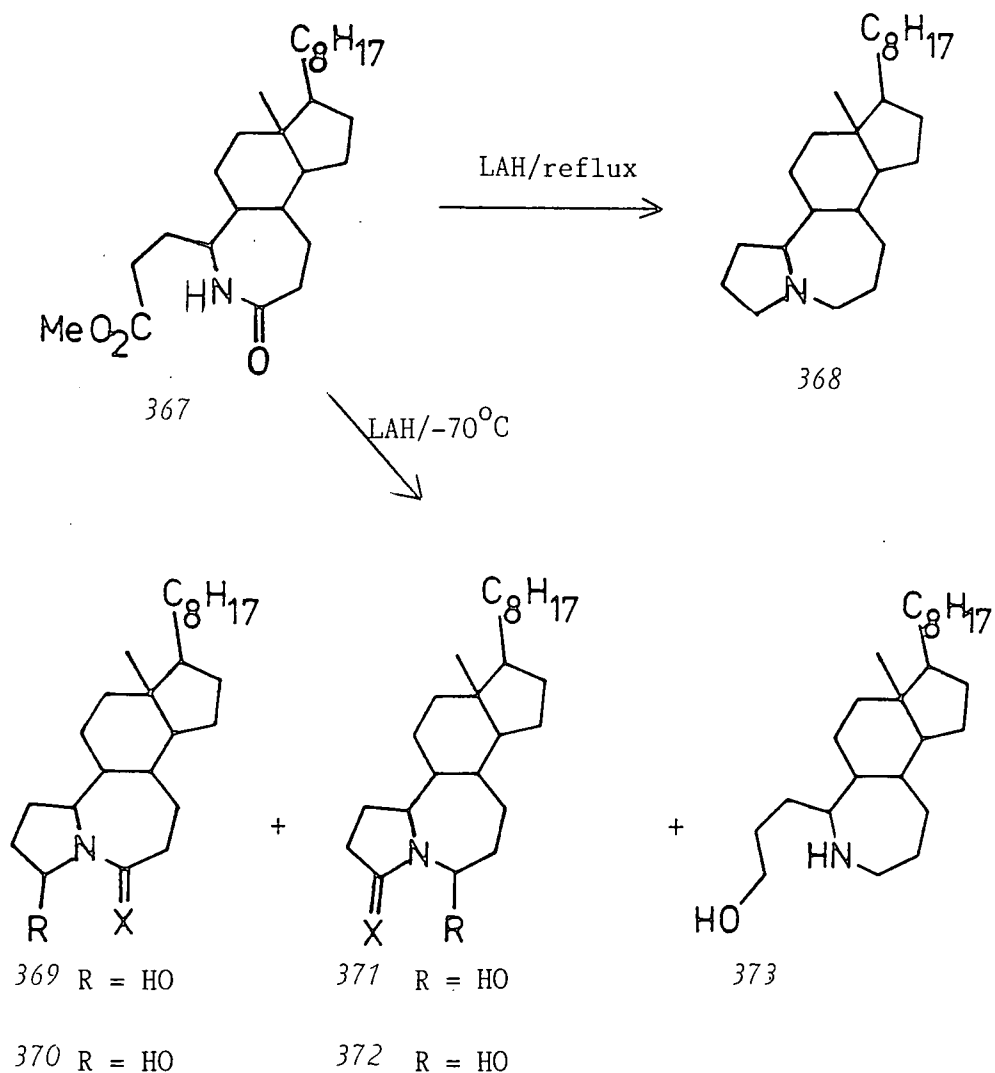
A further observation is that this relative configuration allows for hydrogen bonding between the hydroxyl and lactam carbonyl groups, forming a favourable chair-like six-membered ring. In contrast, the alternative configuration at the hydroxyl bearing carbon, would involve a much more twisted six-membered ring if such hydrogen bonding were to occur. This structure <sup>359d</sup>, is consistent with the observed sharp OH stretch at  $3280\text{ cm}^{-1}$  in the IR spectrum, characteristic of constrained intramolecular hydrogen bonding. This is also evidenced by non-bonded interatomic distances and bond angles.



366

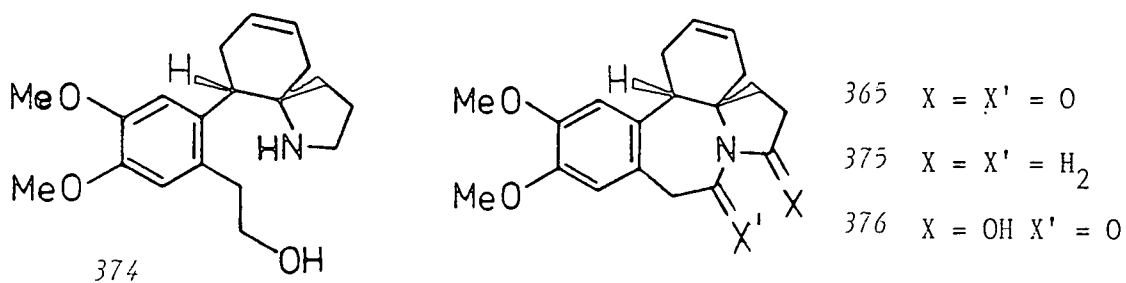
While lactam-acid or amide-acid condensations with dicyclocarbo-diimide are known routes to small, e.g.  $\beta$ -lactam<sup>364</sup> and medium lactams, e.g. bicyclic imide <sup>366</sup><sup>365</sup>, reductive lactam-ester cyclizations with hydride reagents are rare. Treatment of lactam-ester <sup>367</sup> with LAH in THF at reflux, was reported to provide the bicyclic fully reduced amine <sup>368</sup><sup>366</sup>. Reaction at  $-70^{\circ}\text{C}$  yielded a complex mixture of all the possible regio- and stereo isomeric  $\alpha$ -hydroxy lactams, <sup>369-372</sup>, and the reduced acyclic product <sup>373</sup>, in 18% yield. In contrast to this, our reaction of DIBAL-H with <sup>357c</sup> provides a single regioisomeric product  $\alpha$ -hydroxy lactam, <sup>359d</sup>, and no partly reduced acyclic material. Further, we are effecting a seven-membered ring annulation, which is less favourable than the five-membered ring annulation described above.

Also, we found that reaction of lactam-ester <sup>357c</sup> with LAH in THF at reflux, provided a single material (by t.l.c.), with a molecular ion consistent with the fully reduced, uncyclized amino alcohol <sup>374</sup>. This is in sharp contrast to the efficient reductive five-membered ring closure of <sup>367</sup> under the same conditions described above<sup>366</sup>.



Trial reactions of 359 $\mu$  with LAH, under prolonged reflux in THF, yielded largely one product (t.l.c.) indicated by mass spectral data to be the expected amine 375.

However, modification of ring E would be better undertaken while retaining the lactam functionality of 359 $\mu$ . LAH reduction to the amine will be utilized at an appropriate stage in the elaboration of ring E.



Attempts to convert the  $\alpha$ -hydroxy lactam, 359d, to the imide, 365, using chromium trioxide-pyridine<sup>367</sup>, have so far led only to good recovery of unoxidized 359d.

### iii Summary

This methodology has provided novel entry to the 3-benzazepine ring system, under very mild conditions, in good yield with very high stereospecificity. The stereospecificity is explained by invoking lactam nucleophilic attack on an aluminium coordinated internal aldehyde. Analogous use of bulky organo-aluminium coordinated aldehydes, to control intermolecular carbon nucleophile additions in an anti-Cram fashion, is of some current interest<sup>368</sup>.

## 4.2 Aza-cephalotaxine analogues

Much interest in the synthesis of benzazepine containing ring systems has been motivated by the range of physiological properties exhibited by some of these alkaloids. Similarly, benzodiazepine containing ring systems - though much rarer in natural products - also frequently show interesting biological properties. For example the 1,3-benzodiazepine neothramycin antitumour antibiotics<sup>369,370</sup>, and the 1,4 benzodiazepine sedatives chlorodiazepoxide and diazepam<sup>371</sup> (dominating the US sedatives market).

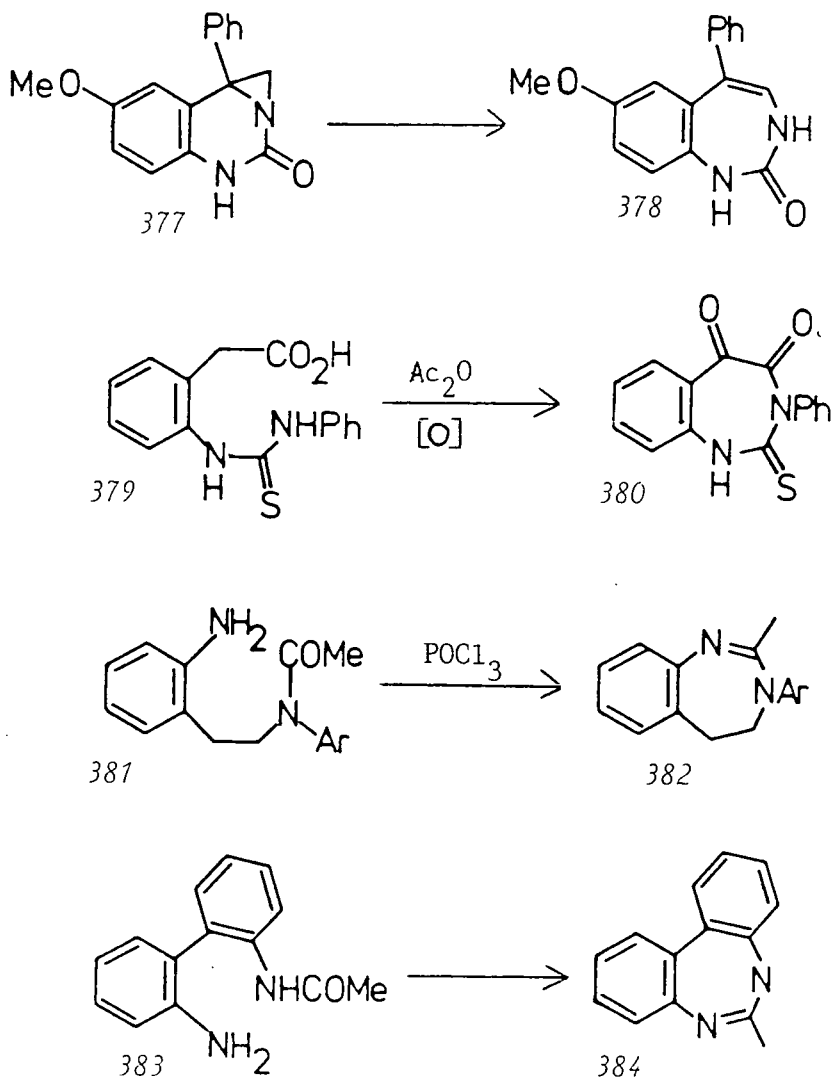
There have been no reports of synthetic work directed towards aza-cephalotaxine analogues. We considered these an obvious class of interesting analogues, that could be readily obtained by minor modifications of our synthetic strategy.

### i 1,3-benzodiazepines

There have been far fewer reported synthetic approaches to benzodiazepines than to benzazepines, and 1,3-benzodiazepines, in particular,

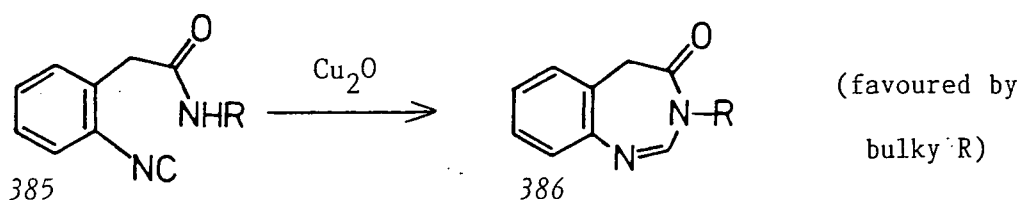
have been little investigated.

Among such approaches, thermal aziridine ring opening has been reported for the conversion of 377 to the 1,3-benzodiazepine 378<sup>372</sup>, and condensation cyclizations, e.g. 379 to 380, have been claimed in early literature<sup>373</sup>. More recently, condensation cyclization has been reported in forming the one carbon bridge between the nitrogen atoms, in the closure of 381 to 382<sup>374</sup>, and 383 to 384<sup>375</sup>.

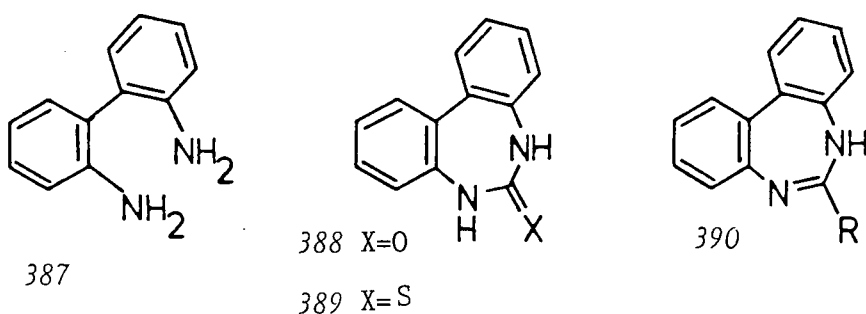


Formation of this one carbon bridge, from substrates already containing the requisite carbon containing functionality, is also available from copper (I) oxide promoted reaction of carbylamines e.g. 385→386<sup>376</sup>.

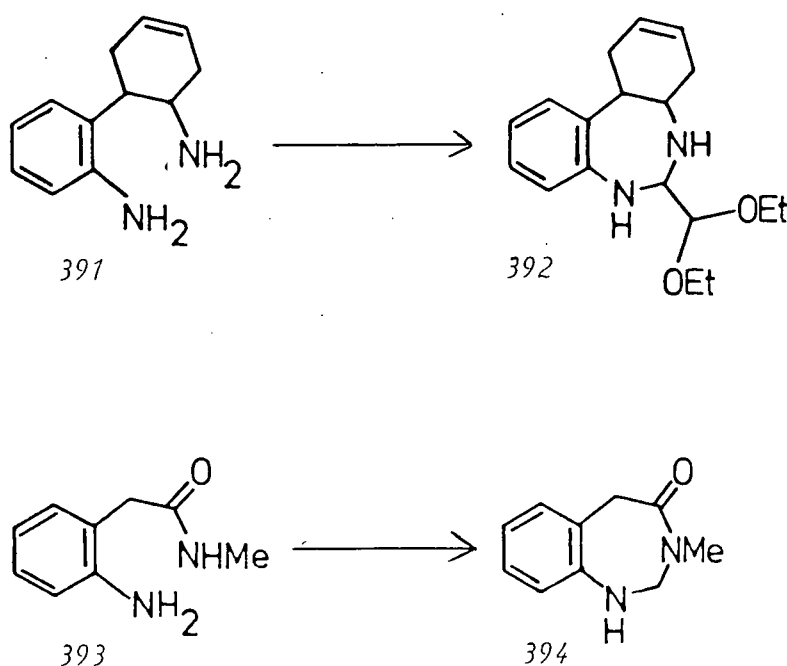
More significantly, a number of methodologies involving one carbon insertions into diamines, or amine-amides, have been developed. The



inserted carbon sources have included carbon monoxide, thiocarbonyl chloride, carbondisulphide and N,N-dicarbonyldimidazole<sup>377,378</sup>. Such reactions with the dibenzannelated system 387, have provided entry to the benzo-1,3-diazepines 388<sup>379</sup>, 389<sup>380</sup> and 390<sup>381-383</sup>.



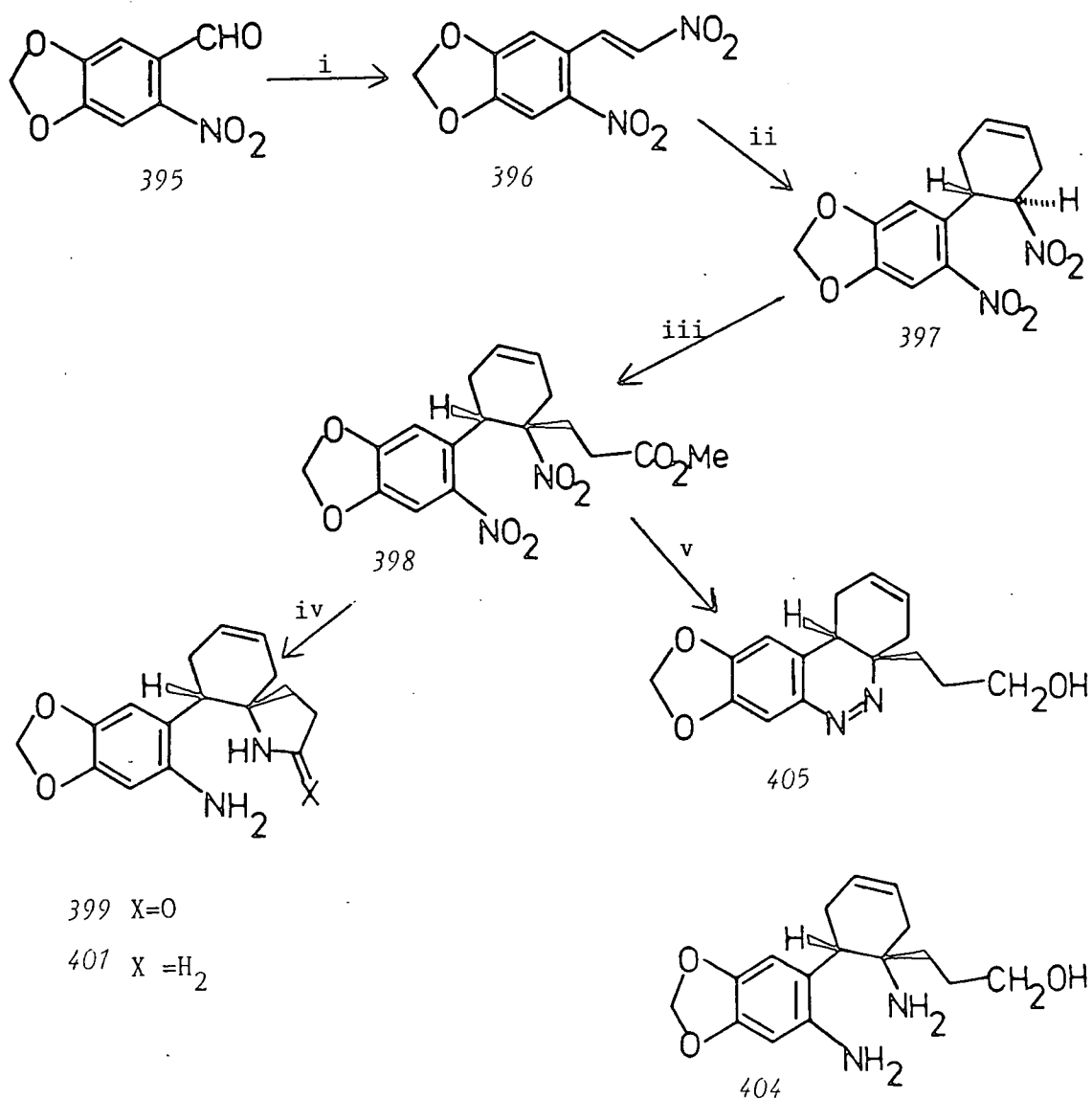
The use of aldehydes, including formaldehyde, has also been reported for insertion into both diamines e.g. 391<sup>375,384</sup> and amine-amides 392<sup>385</sup>, to yield 1,3-benzodiazepines 393 and 394 respectively.

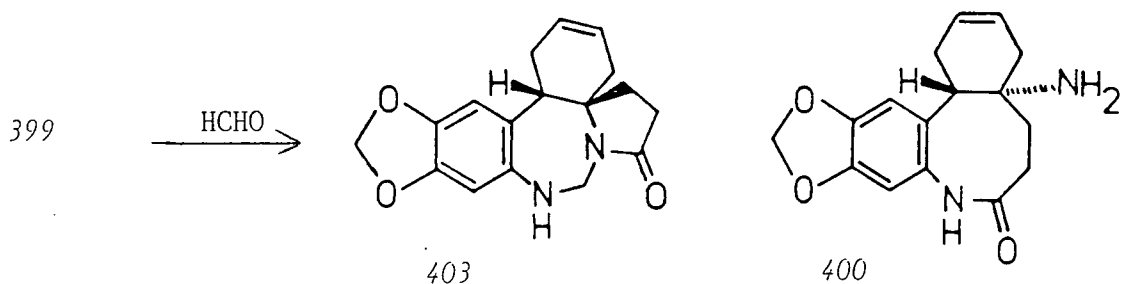
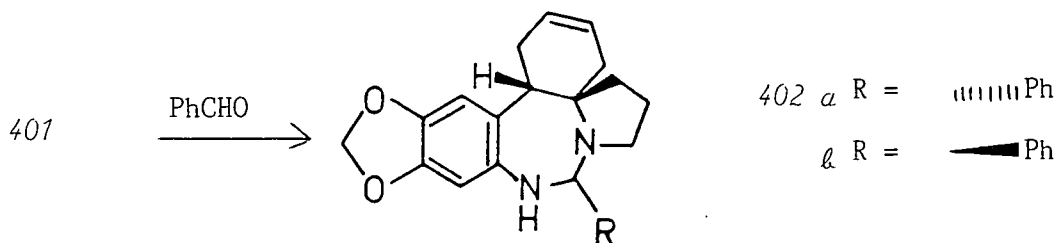


ii Progress towards aza-cephalotaxine

We considered that adaption of the general methodology described earlier (2.2), commencing with 6-nitropiperonal in place of piperonal, should provide an approach to 1,3-benzodiazepine cephalotaxine analogues, via an insertion cyclization step. We thus embarked on the synthetic approach outlined in scheme XVII. As we started this work, the condensation of 6-nitropiperonal with nitromethane, using potassium fluoride as base (dehydrating the intermediate  $\beta$ -hydroxy nitro compound with acetic anhydride), was reported<sup>386</sup>. In our hands, these conditions provided very good yields of nitrostyrene 396 ( $\geq 90\%$ ), of sufficient purity -

SCHEME XVII





i  $\text{MeNO}_2/\text{KF}/\text{Ac}_2\text{O}$ , ii butadiene sulphone, iii Methyl acrylate/triton-B,  
 iv  $\text{Zn}/\text{HCl}$ , v LAH

frequently analytical - to use directly.

The dinitro cyclohexenyl cycloadduct 397 was then obtained in 75-80% yield, by the standard reaction with butadiene sulphone. Michael addition with methyl acrylate proceeded smoothly to provide the dinitro ester 398 in 86% yield. Based on our reasoning in chapter 2, the single product obtained is assigned the relative stereochemistry, as shown in structure 398. This is consistent with all spectroscopic and chromatographic evidence. Compound 398 is our key intermediate for constructing the 5 membered ring D, and the 1,3-benzodiazepine ring C.

Our next step, dissolving metal reductive cyclization of 398, could yield either  $\gamma$ -lactam 399, or the isomeric azocine 400. However, the formation of five-membered rings is considerably favoured over competition from eight-membered ring closure. We thus expected selective formation of the desired amino-lactam 399. Indeed, reduction of 398, with zinc-hydrochloric acid, afforded selectively the five-membered lactam product 399. The reaction was, however, far less clean than the analogous cyclizations (2.2), producing a considerable quantity of dark red coloured



by products (possibly intermolecular reaction products?). Nonetheless, 55-60% yields of analytically pure product 399 were obtained after chromatography.

Confirmation of the  $\gamma$ -lactam structure 399 was provided by the IR spectrum, which showed a single lactam carbonyl at  $\nu_{\max}$  1690  $\text{cm}^{-1}$ , consistent with a small ring lactam. (Medium ring lactams, such as an eight-membered system, would have  $\nu_{\max}$ , C=O at lower frequency.) Comparison of  $^{13}\text{C}$  NMR shifts with those for the analogous methylenedioxySpirolactam 131a (2.2), show specifically the presence of the low intensity spiro carbon at 60.2 ppm, compared to 59.9 ppm for 131a (2.2). LAH reduction of 399 provided moderate yields of the diamine 401.

A number of approaches to inserting a one-carbon bridge between the nitrogens of 399 or 401 are available (see 4.2.i). Attempts at insertion of a simple methylene bridge into 401, by reaction with formaldehyde, led to a complex mixture, which appeared to decompose on attempted chromatography. The use of simple aldehydes, leading to 2-substituted benzodiazepines, was therefore considered.

Stirring 401 with benzaldehyde in ethanol<sup>387</sup>, provided, after chromatography, a mixture of two materials, one of which was a minor component. Notably, the CI mass spectrum of the mixture showed a single, very intense molecular ion at  $m/e = 361$ : this is consistent with the benzodiazepine structure 402. The single mass observed suggests that the second material in the mixture is isomeric. Presumably, therefore both diastereomers 402a and 402b are obtained - they could possibly be separated by further chromatography. Assignment of structure 402a as the major product, could be made on steric grounds.

This is in contrast to the stereoselectivity (in introduction of functionality at the 2 position of the seven-membered ring), observed in the DIBAL-H induced cyclization to 359b (4.1.ii).

A preliminary reaction of lactam-amine 399 with formalin at reflux,

provided a mixture of two materials, the major of which was obtained as a white solid. It showed a molecular ion at  $m/e = 299$ , with no peak at  $m/e = 287$  (shown by starting material) in the CI mass spectrum. The IR spectrum showed a much simpler NH region, with loss of the amide N-H absorption, and satisfactory elemental analysis was obtained. These data suggest that formaldehyde insertion has occurred, providing the 1,3-benzodiazepine derivative, 403.

Though this work is at an early stage, it appears to hold promise as a route to a variety of aza-cephalotaxine analogues - and ultimately aza-cephalotaxine itself - based on a 1,3-benzodiazepine ring C.

An alternative strategy towards construction of a diazepine ring C, had envisaged formation of this ring prior to ring D cyclization. We had hoped reduction of dinitro-ester 398 would provide the diamino-alcohol 404, then allowing possible insertion reactions between the two primary amino groups.

Reaction of 398 with LAH, gave a dark red mixture, from which an intensely yellow, single material was obtained by column chromatography. The mass spectrum of this product showed a molecular ion at four mass units lower than that expected for 404, but consistent with diaza structure 405.

The 250 MHz proton NMR spectrum was consistent with either 404 or 405 (assuming NH exchange for 404), but chemical evidence indicated we did not have the diamino structure 404: reaction with acidic formaldehyde or sodium hydroxide and dibromomethane, led only to good recovery of the starting material. High resolution mass spectral data confirmed the molecular formula consistent with azaphenanthridine 405. Thus, reductive diazotization - analogous to aromatic amine couplings - had occurred in reasonable yield (ca. 65%) to afford the unexpected diazocyclic 405.

iii Summary

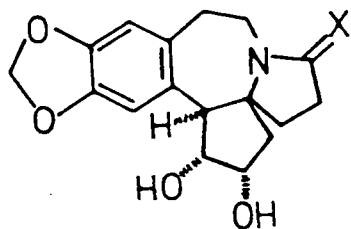
Adaptation of the azaspirocyclization methodology described above (2.2), starting from 6-nitropiperonal, has provided diaza intermediates 399 and 400, which preliminary investigations indicate allow entry to a range of aza-cephalotaxine analogues - a class of analogues as yet uninvestigated.

CHAPTER FIVE  
PROGRESS TOWARDS  
FIVE MEMBERED RING E

## 5.1 Modifications of ring E

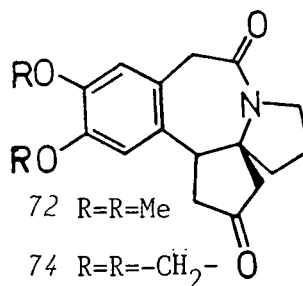
With the efficient, stereospecific construction of the azaspirocyclic moiety (2.2), and the mild, high yielding entry to the 3-benzazepine ring central to cephalotaxine (4.1) both achieved, the only remaining synthetic hurdle is appropriate elaboration of the cyclohexene ring E towards the oxidized cyclopentene ring E of the target. The necessary ring contraction should provide a functionalized cyclopentane intermediate, suitable for modification to the requisite ring E functionality. Two general strategies are available viz (i) ring opening - ring closure; (ii) rearrangement - contraction.

The most recent total syntheses of cephalotaxine reported, have assisted this challenge, as they provide the cyclopentanone ring E of 72 or 74<sup>39</sup>, or the 1,2-cis diol ring E of 406<sup>40</sup> or 407<sup>43</sup>, as pre-targets through which to route our ring E modifications, to yield a formal total synthesis. However, other methodologies are also being considered.



406 X = H<sub>2</sub>

407 X = O



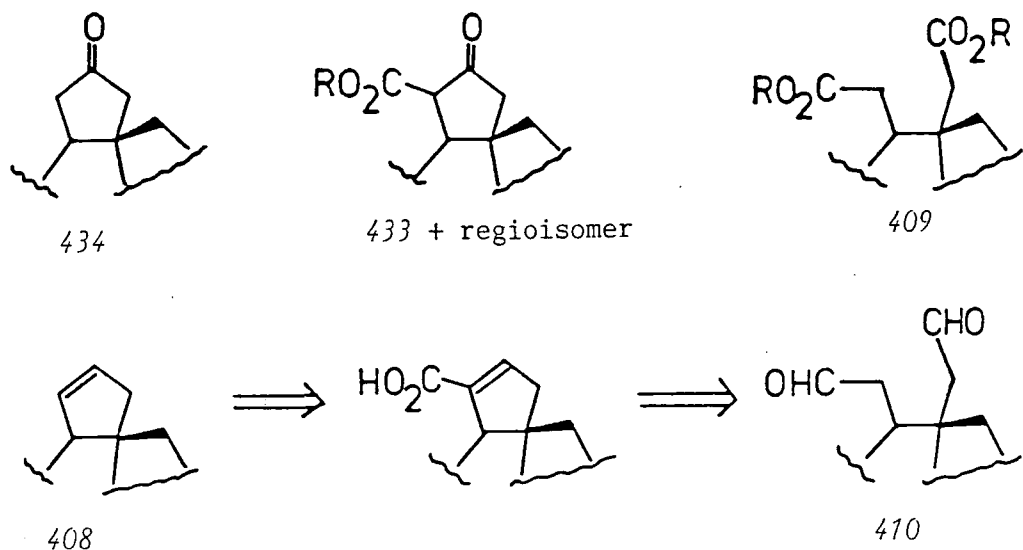
72 R=R=Me

74 R=R=-CH<sub>2</sub>-

### i Ring opening-ring closure strategies

There are two basic ring opening-ring closure retrosynthetic strategies from cyclopentenone ring E pre-targets 434 (cf. 72 or 74) or from cyclopentene pre-targets 408. The former of these relates formally to the diester, 409, and the latter to the dialdehyde 410, as ring opened derivatives, so they are essentially convergent routes.

Oxidative ring opening of cyclic olefins, can be effected directly on the unsaturated substrate, or the trans- or cis-1,2-diol derivatives. Ozonolysis is perhaps the most well known of these methods and can lead



to either diacid or dialdehyde products<sup>388</sup>, by utilizing oxidative or reductive (e.g. Zn/HCl or Et<sub>3</sub>PO) work-ups respectively. The utility of ozonolysis is generally limited by scale-up problems, and variable yields, particularly on reductive work-up (though DMS-MeOH appears to be effective<sup>389</sup>). Direct oxidation of olefinic substrates to diacids, can also be achieved using Lemieux-von Rudloff<sup>390</sup> conditions (periodate salt, catalytic potassium permanganate), or with potassium permanganate, and quaternary ammonium salts<sup>391</sup>, or dicyclohexyl-18-Crown-6<sup>392</sup> as phase transfer catalyst.

Attempts at oxidation of lactam 131a using Lemieux-von Rudloff procedures, (with various solvent mixtures), led to complex product mixtures. Treatment of the crude product mixture with acidic methanol, or dimethylsulphate and sodium carbonate, in the hope of purifying the diacid as its diester, led only to four or more major materials (by t.l.c.), which could not be separated.

Oxidation attempts with potassium permanganate and dicyclohexyl-18-Crown-6 (5% molar catalyst through to stoichiometric) in benzene on the nitrocyclohexene 239, or the lactam 131a, led similarly to complex mixtures. The reaction mixture had darkened over ca. 10 minutes, indicating oxidation was occurring. In this case, partial separation of the products after

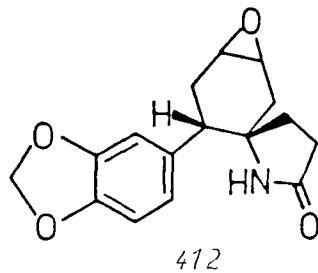
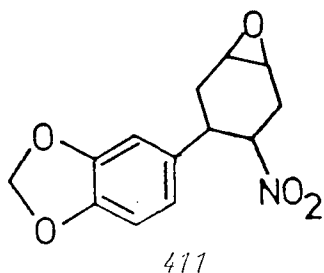
esterification was achieved, and the 250 MHz proton NMR data suggested ester functionalities, but also the presence of fragmentation products, probably due to over-oxidation.

The use of periodate salts or periodic acid is perhaps the most commonly used diol cleavage method<sup>393</sup>. In cyclic systems, both the cis- and trans- 1,2-diols are oxidatively cleaved to the dialdehyde in good yield, under mild conditions (though the cis-diol reacts faster<sup>394</sup>). Other reagent systems have also been reported to efficiently cleave diols viz acidic sodium bismuthate<sup>395</sup>, lead tetra-acetate<sup>396</sup>, pyridinium chlorochromate<sup>400</sup>, and polymer supported periodate<sup>401</sup>.

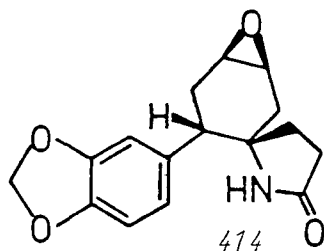
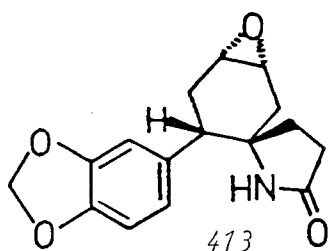
Initially, we decided to utilize the trans,-1,2-diol derivative of 239 or 131a as substrates for oxidative cleavage to the dialdehyde systems. This was largely because the trans-diol can easily be obtained from the epoxide, which we required also for attempting rearrangement-contraction of ring E (5.1.iii).

A variety of epoxidation reagents are known<sup>402</sup>, but MCPBA<sup>403</sup> is currently the reagent of choice for epoxidation of isolated olefins, though this may soon be replaced by magnesium monoperoxyphthalate<sup>404</sup>.

On treating 239 and 131a with MCPBA in chloroform, the epoxides 411 and 412 were obtained as white solids, in >90% yields after chromatography.

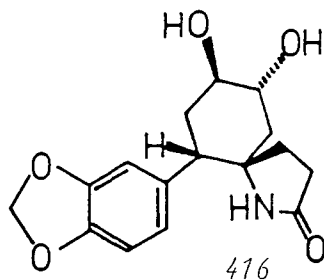
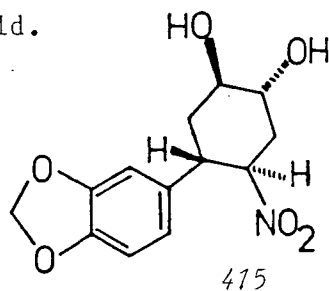


Notably, in both cases, the epoxide was obtained as a mixture of two isomers (nearly coincident on t.l.c., but occasionally partly separable by column chromatography). These are presumably the two possible epoxides derived from peracid addition from either face of the double bond, e.g. 413 and 414 from the lactam 131a. Carbon-13 NMR data of the mixture of



isomers indicated little selection between these isomers, consistent with the relative insensitivity of peracids to steric influences<sup>405</sup>.

Treatment of epoxides 471 and 472 with 1% aq. sulphuric acid provided the expected<sup>406</sup> trans-1,2-diols, 475 and 476 in 80-90% yields. The trans-1,2-diol, 475, had also been obtained from the starting olefin 239, by reaction with hydrogen-peroxide and formic acid, in ca.60% yield.



Periodate cleavage of diols is usually carried out at, or below, ambient temperature<sup>407</sup>, in a variety of protic solvents<sup>408</sup>. A water-methanol mixture proved most convenient for dissolving lactam-diol 476. But, treatment of 476 with periodic acid under progressively more vigorous conditions - including 48 hours at 50°C - led to yields of dialdehyde (as judged by proton NMR integration) between 10% and 30%. In contrast, trial reaction of trans-cyclohexane-1,2 diol using the mildest conditions applied to 476, gave >90% crude yield of adipaldehyde. A probable explanation is that a combination of the rigidity of the spiro-fusion, coupled, most importantly, with the aromatic substituent 'locking' the ring's chair conformation, constrains the hydroxyl groups in a rigid antiperiplanar arrangement. This makes formation of the intermediate periodate complex very difficult to achieve, on steric grounds. Trans-cyclohexane-1,2-diol can react via alternative ring conformations that



bring the hydroxyl groups in closer proximity. For *416* reaction via the corresponding boat-like intermediates is kinetically less achievable.

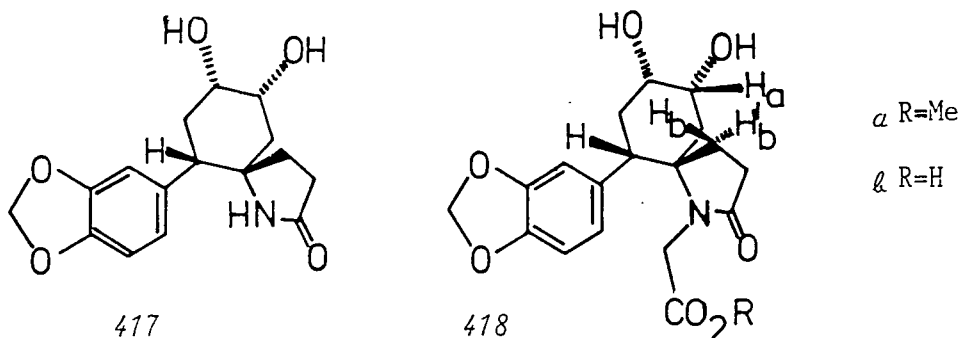
Use of the corresponding cis-1,2-diol *417* should obviate the problems encountered with the trans-1,2-diol, *416* as the hydroxyl groups of *417* will be 'locked' in a close arrangement, where periodate complexation is readily achieved. Several methods are available for the cis-hydroxylation of olefins. The Prevost reaction, using iodine and silver acetate<sup>409</sup>, or thallium (I) acetate<sup>410</sup>, in wet acetic acid has found some use. We found, however, that using iodine and silver acetate, with the nitrocyclohexene derivative *239*, led only to mixtures of products, whose IR spectra did not suggest significant amounts of the desired diol.

While basic potassium permanganate, and tetra-alkylammonium permanganates<sup>411</sup> also yield cis-diols, osmium tetroxide oxidation has proved the most general and efficient of cis-hydroxylation methodologies<sup>412</sup>. A number of variations utilizing catalytic osmium tetroxide with a primary oxidant have been developed<sup>413</sup> (including now an asymmetric reagent system<sup>414</sup>), of which we chose the general methodology of van Rheenen et al<sup>415</sup> with N-methylmorpholine oxide as primary oxidant.

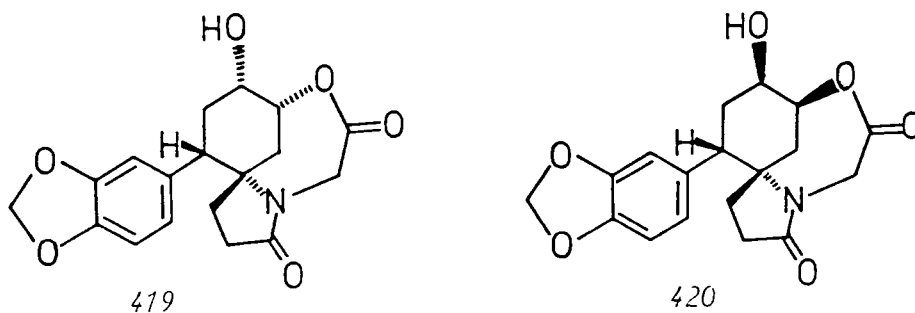
Changing the solvent system from water-acetone to acetone-tert-butanol was necessary due to the poor solubility of spirolactam *131a* in acetone or water. Reaction of spirolactam *131a* using ca.1% molar osmium tetroxide solution (90% aq. tert-butanol), led repeatedly to relatively poor yields of the cis-diol, *417* (ca. 40%). However, similar reaction with the N-alkylated derivative, *337*, led to yields of 85-95% of the corresponding cis-diol *418a*. This may be due to the poor solubility characteristic of lactam *131a* being exacerbated by the diol functionality (cf. trans diol - insolubility) leading to extraction difficulties. The finding that extraction with boiling ethyl acetate gave some yield improvement, supported this explanation.

It is noteworthy that both cis diols *417* and *418a* appear to be

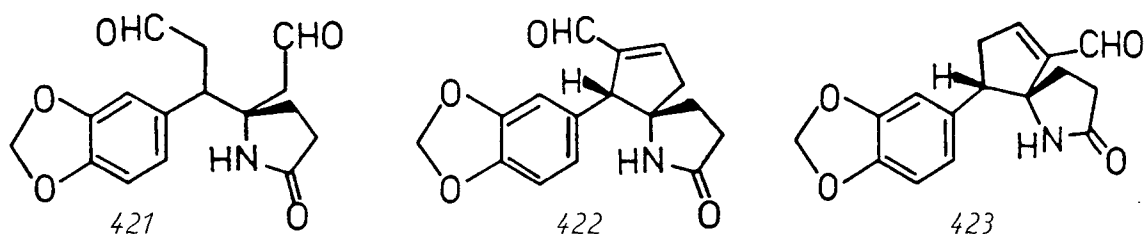
single isomers (from t.l.c. and spectroscopic data). We would expect to observe selectivity in favour of the isomers shown as the 'alternative' isomers would require the intermediate osmate ester<sup>416</sup>, or osmium organometallic<sup>417</sup> locating the large osmium centre in the hindered region close to the lactam ring.



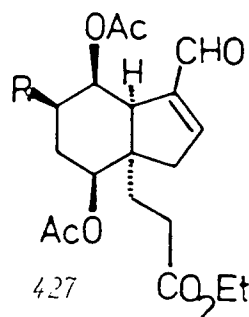
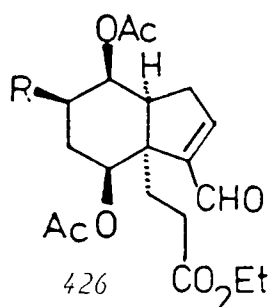
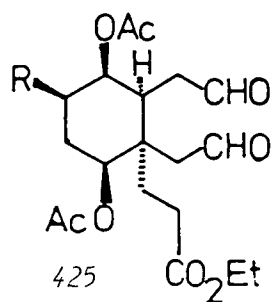
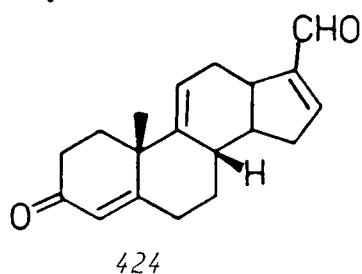
Attempts to confirm this stereochemistry by observing an NOE effect between  $H_a$  and  $H_b$ ,  $H_b^1$  methylene protons, proved fruitless. It would be interesting to provide chemical evidence for this predicted stereochemistry. Corey-Nicolaou lactonization<sup>418</sup> of acid 418l should provide lactone 419, while the alternative cis-diol stereochemistry should prohibit cyclization, as the product lactone, 420, would be extremely strained. However, these reactions have not yet been attempted.



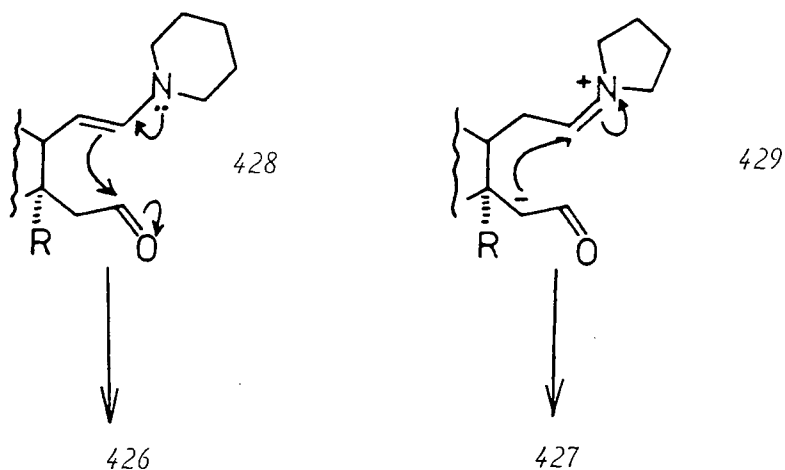
Reaction of the cis-diol 417, under the conditions unsuccessful with the corresponding trans-diol, 416, above, provided a crude off-white solid. Proton NMR was consistent with dialdehydic functionality (from aldehyde proton and methylene dioxy proton integrations), the yield of crude dialdehyde, 421, being 98%. Dialdehydes are frequently unstable to purification, and thus the crude material was used directly.



The major problem confronting intramolecular aldol condensation of 421, is how to control the regiochemistry of cyclization. Of the two possible regioisomeric products, 422 and 423, the former is that required for the ring E pre-target 408. Several examples of regiocontrolled intramolecular aldol condensation to cyclopentene-1-carboxaldehydes have been reported. Woodward et al<sup>419</sup> regioselectively obtained 424 from the corresponding dialdehyde, using catalytic piperidine acetate. More recently, Inubishi et al<sup>420,421</sup> have cyclized dialdehyde 425 to regioisomer 426, with either basic alumina or catalytic piperidine acetate. Further, these workers<sup>420,421</sup> found that treatment of dialdehyde 425 with excess pyrrolidine acetate in a polar solvent eg methanol, led to 8:1 selectivity in favour of the alternative regioisomer, 427. A regioselective tosic acid catalysed aldol cyclization has also recently been reported<sup>422</sup>.



Inubishi et al<sup>420</sup> considered that with catalytic piperidine acetate, the piperidine enamine of the less hindered aldehyde, 428, is formed, and then nucleophilically attacks the remaining free carbonyl; loss of the imminium substituent then provides the less hindered aldehyde product 426. Basic alumina provides the same regioisomer simply because the anion of the least hindered methylene group is preferentially formed. With excess pyrrolidine acetate, they concluded that the initially formed immonium salt, 429 (which rearranges to enamine 428 if only catalytic acetate is used), is the major reacting species. In this case the carb-anion of the more hindered methylene group becomes the major nucleophile, resulting in the more hindered aldehyde, 427.



These reports aid us in predicting and choosing the regiochemistry of aldol cyclization of our dialdehyde, 421. If we assume that the methylene group bonded to the quaternary spiro centre is more hindered than that linked to the tertiary benzylic centre, then we would expect treatment of 421 with basic alumina, or catalytic piperidine acetate, to provide predominantly regioisomer 422.

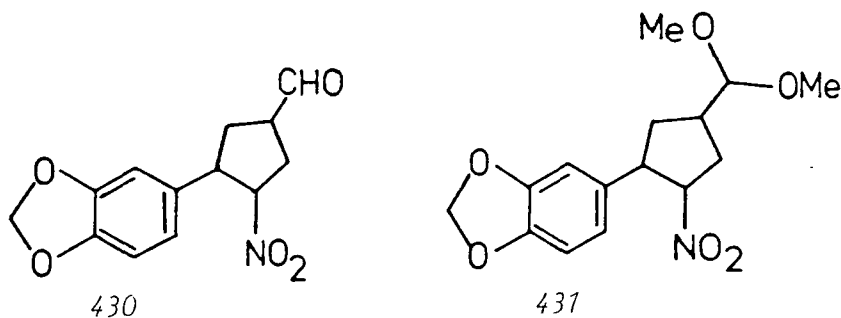
We found that slowly passing a chloroform solution of dialdehyde, 421, through a basic alumina column, provided a single material (t.l.c.) Spectroscopic data were consistent with an aldol product, and high resolution mass spectral analysis confirmed this. Attempts to confirm the

expected regiochemical assignment as 422, by observing an NOE enhancement between the aldehyde and benzylic protons, have so far produced no satisfactory results.

If this regiochemistry, 422, can be confirmed, by using the 3-benzazepinol analogue, 359d, described in chapter 4, we are within striking distance of a formal total synthesis, via the pre-targets 406a and 406b reported by Fuchs et al<sup>40</sup> and Kuehne et al<sup>43</sup>.

## ii Rearrangement-contraction strategies

Both cyclic olefins and cyclic fused epoxides are known to undergo rearrangements with ring contraction. Thallium (III) trinitrate (TTN) oxidative rearrangement of cyclic olefins occurs very rapidly in methanolic solution, providing the corresponding ring contracted carboxaldehyde in good yield<sup>423</sup>. Reaction of TTN with nitrocyclohexene derivative 239 provided a crude product, whose NMR and mass spectral data were inconsistent with either rearranged aldehyde 430, or its dimethyl acetal, 431.



Our interest then turned towards the well known epoxide to carbonyl rearrangements, catalysed primarily by Lewis acids<sup>424</sup> (boron-trifluoride etherate, magnesium bromide or aluminium chloride), but also by a variety of miscellaneous reagents<sup>425</sup>. There are several examples of fused epoxides yielding ring contracted carboxaldehydes as the major product. For example, cyclohexene oxide can be efficiently ring contracted with lithium bromide-tributylphosphine oxide in benzene<sup>426</sup>, or with lithium bromide-alumina in toluene<sup>427</sup>.

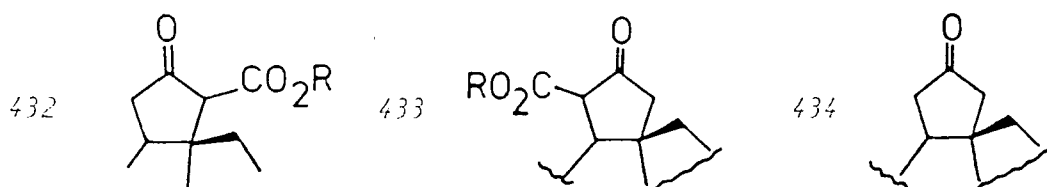
Our preliminary attempts at boron trifluoride dimethyl etherate catalysed rearrangement, of mixtures of isomeric epoxides 473 and 474, have yielded mixtures of a number of products. Stereoelectronic considerations would suggest the two epoxides, 473 and 474, should lead to alternative carboxaldehyde substitution configuration. The above finding, i.e. more than two products (none being epoxides), does not indicate only two diastereomers. Further, similar reaction of one epoxide also gave several products (by t.l.c.). However, further investigations in this area would still be worthwhile.

### iii Summary and future work

A cis-hydroxylation, periodate cleavage, aldol condensation methodology appears to have provided entry to a simple regioisomeric cyclopentenecarboxaldehyde product. From precedents, this is expected to be the regioisomer appropriate for elaboration into known cephalotaxine ring E pre-targets.

The use of catalytic osmium tetroxide with sodium periodate as primary oxidant, following precedents<sup>428-430</sup>, should shorten further the overall synthetic scheme.

Oxidation of dialdehyde intermediates e.g. 427, to the corresponding diacid, (or perhaps direct olefin cleavage to yield a diacid), is worth pursuing. This would then allow for Dieckmann type cyclization of the corresponding diester with potassium tert-butoxide, an established route to carbethoxy-cyclopentanones<sup>431,432</sup>. This is attractive because regio-control is not important, as both regioisomers of type 432 and 433 can be decarboxylated to the same cyclopentanone ring E intermediate, 434, which has already been elaborated to cephalotaxine ring E functionality<sup>39</sup>. It also avails other possible strategies, to be discussed below.



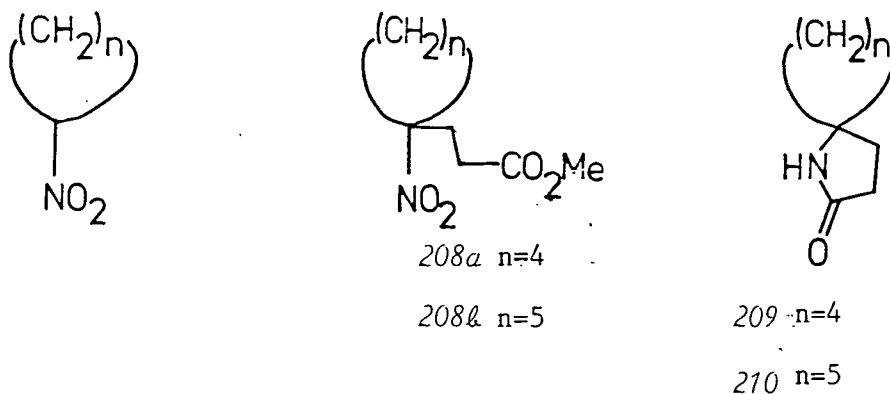
CHAPTER SIX

MODEL 1-AZASPIROCYCLES

## 6.1 Model Azaspirocycles

### i Synthesis of model spirolactams

Our initial problems in cleanly reducing the spirolactam *131a* (2.2), led us to investigate the behaviour of model spirolactams. The obvious strategy to adopt for synthesis of model spirolactams, was the application of the Michael alkylation-reductive cyclization methodology (2.2), to simple nitrocycloalkanes.



We found that nitrocyclohexane and nitrocyclopentane were both efficiently converted to the respective spirolactams, *209* and *210*, using this approach. Subsequently, good precedent for this type of strategy was found<sup>108,109</sup>, using hydrogenolysis to effect reductive cyclization of *208a* and *208b* to *209* and *210* respectively. Unfortunately, hydrogenolysis is clearly inapplicable to our cephalotaxine intermediates, though we find zinc-hydrochloric acid to be an efficient alternative reductive cyclization system.

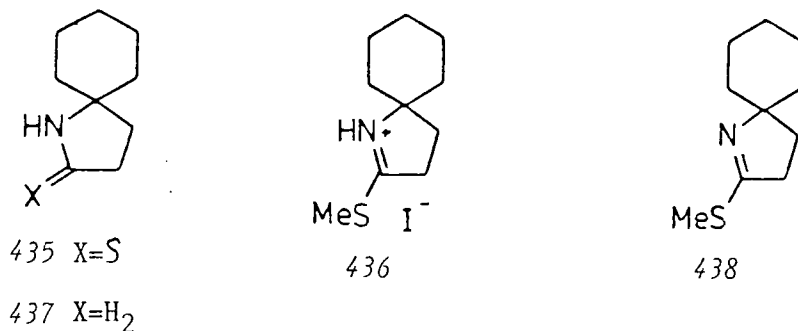
### ii Reduction and functionalization of model spirolactams

As we had found with spirolactam, *131a* (2.3), LAH initially provided inconsistent results with the model spirolactam, *210*. Consequently, we embarked upon a thiolactiminium route, in the hope of finding more efficient, milder reducing conditions. Many of these reactions were then carried out using *131a* (2.3).



Conversion of the lactam *210* to the thiolactam, *435*, was effected in good yield with phosphorus pentasulphide, and treatment of *435* with methyl iodide (in the dark), afforded near quantitative yields of the salt *436*. If the methylation reaction is not protected from light, a yellow to orange, rather than white, product is obtained.

As described above (2.3), hydride reduction of thioamide methiodide salts is known to yield amines under mild conditions. However, treatment of *436* with sodium borohydride yielded a crude material, whose mass spectral and IR characteristics were inconsistent with amine *437* (cf. reaction of thiolactam methiodide, *254*, in chapter 2.3). The structural assignment of the major product as thiolactim ether, *438*, was confirmed by deprotonation of *436* with aqueous potassium carbonate to yield *438*, identical by IR and mass spectral data with the product above. Further structural confirmation was provided by proton NMR, showing a three proton singlet at 2.28 ppm due to the S-methyl group, carbon-13 NMR evidencing the unsaturated carbon at 166.9 ppm, and the absence of an N-H stretch in the IR spectrum.



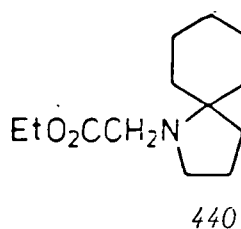
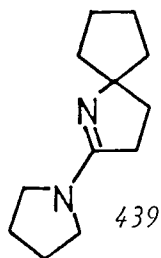
Thiolactim ethers, e.g. *438*, are potentially versatile intermediates, as the  $\beta$ -carbon is susceptible to electrophilic attack and the  $\alpha$  carbon to nucleophilic attack. The use of bifunctional reagents bearing both electrophilic and nucleophilic functionalities, has thus provided an annulation strategy onto thiolactim ethers<sup>479</sup>.

Reaction of *438* with pyrrolidine afforded a single product (as judged by t.l.c.). This was assigned as the product of nucleophilic displacement of the thiomethyl group viz the amidine *439*, on the basis

of high resolution mass spectral data, and the absence of the S-methyl resonance in its 250 MHz proton NMR. However, a pure sample of this product was not obtained.

While investigating these reactions, we found that rigorously dried diethyl ether as solvent, led to reproducible reduction of spirolactam 270 to spiropyrrolidine 437(80% yield). These experimental conditions were then successfully applied to spirolactam, 131a (2.3).

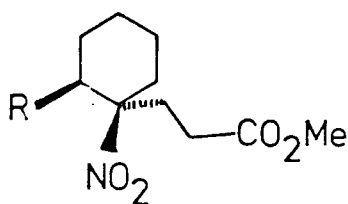
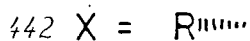
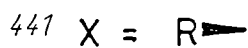
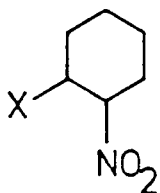
The spiropyrrolidine, 437, so obtained, could be alkylated with ethyl bromoacetate, using potassium carbonate as base. This provided the N-2-carbethoxy-spiropyrrolidine, 440, in yields of ca. 99%. This methodology was then applied to similar success, to the spiropyrrolidine 245, (3.3.i).



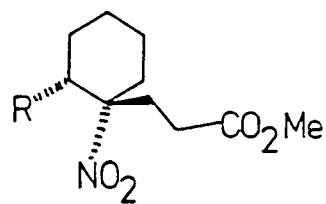
### iii Future work

Methodologies for synthesis of substituted 1-azaspirocycles is an area of some current interest (see 2.1), and more particularly, stereospecific or enantiospecific approaches are keenly being investigated.

Extrapolation of the highly stereospecific Michael alkylation of the substituted nitrocyclohexene, 239 (2.2), to  $\beta$ -chiral nitrocycloalkanes, should provide an enantiospecific route to substituted 1-azaspirocycles, provided the  $\beta$ -substituent is sufficiently bulky. Nitrocyclohexane derivatives 441 and 442 would yield stereoisomers 443 and 444 respectively (with (S)- and (R)- quaternary configurations respectively). Racemic  $\beta$ -substituted nitrocycloalkanes should stereospecifically provide the corresponding racemate.



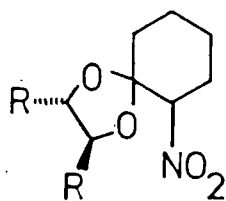
443



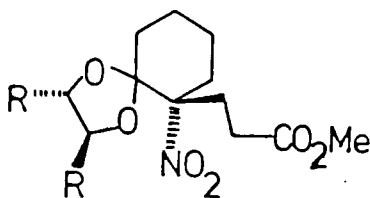
444

The utility of such an approach for asymmetric synthesis is clearly limited by the problems of obtaining enantiomerically pure  $\beta$ -chiral nitro cycloalkanes (single  $\beta$  configuration).

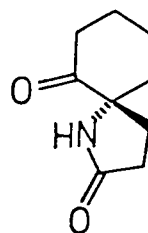
A potentially more viable strategy for enantioselective azaspiro-cyclic syntheses is the use of homochiral ketal nitrocycloalkanes e.g. 445. These could result in good asymmetric induction to provide 446, reductive cyclization followed by removal of the chiral auxiliary providing the enantiomerically pure 1-azaspirolactam, 447.



445



446



447

CHAPTER SEVEN

EXPERIMENTAL

## 7.1 Introduction - General Methods

Melting points were recorded on a Kofler hot-stage microscope apparatus, and are uncorrected. Infra-red spectra were recorded on Perkin Elmer 577 and 457 spectrophotometers. Proton NMR and carbon-13 NMR spectra, were recorded on a Bruker AC 250 instrument, operating at 250.134 MHz for protons and 62.896 MHz for the carbon nucleus. Chemical shifts given in ppm are relative to tetramethylsilane as internal standard. Mass spectra were obtained on a VG 7070E instrument, operating at 70eV, with ionization modes as indicated.

T.l.c. data were obtained using Merck pre-coated alumina (0.2 mm), or Merck pre-coated silica (alumina backed) sheets (0.2mm). Alumina sheets were used unless otherwise stated. For column chromatography, Merck Alumina (Activity II to III; 70-230 mesh) or Merck Silica gel (70-230 mesh) were employed, as indicated.

Throughout, 'dry' or 'freshly distilled' solvent refers to distillation from the following agents, under a nitrogen atmosphere:- diethyl ether (sodium metal, then LAH), THF (sodium metal, then LAH), chlorocarbons ( $P_2O_5$ ), benzene (sodium metal), toluene (sodium metal and/or LAH), acetonitrile ( $CaH_2$ ), t-butanol (anhydrous  $K_2CO_3$ ), methanol (magnesium methoxide).

Activated zinc dust refers to BDH Analar zinc powder, pre-treated with aq.HCl<sup>161,162</sup>.

## 7.2 Experimental Procedures

### i CHAPTER 2

*Trans-1-(3,4-methylenedioxyphenyl)-2-nitroethene (237)* was prepared following the literature procedure<sup>135</sup> from piperonal and the anion of nitromethane in 97% yield, m.pt. 161-164°C (from ethanol) (lit.<sup>133</sup> 158°C).

*Trans-1-(3,4-dimethoxyphenyl)-2-nitroethene (238)* prepared analogously to compound 237 from 3,4-dimethoxybenzaldehyde, was obtained in 92% yield, m p 143-144.5°C (from methanol) (Lit.<sup>140</sup> 140°C).

*Trans-4-(3,4-methylenedioxyphenyl)-5-nitrocyclohexene (239)* A mixture of compound 237 (10.0 g, 0.05 mol), butadiene sulphone (31.0 g, 0.25 mol), hydroquinone (0.35 g) and dry toluene (150 ml) was placed in a bomb (400 ml capacity) and heated at 130°C for six days. The crude product mixture was filtered and the filtrate evaporated *in vacuo* to leave a gum which was extracted with boiling ether (ca. 500 ml). This extract was filtered and evaporated and the residue was recrystallised from methanol, with cooling to 0°C, to yield pure product 239, as light tan crystals, (11.8 g, 92%) mp 99 - 101°C (lit.<sup>143,145</sup> 97-99°C). Yields are not significantly reduced when the reaction is scaled up three fold.

*Trans-4-(3,4-dimethoxyphenyl)-5-nitrocyclohexene (240)* was prepared analogously to 239, from compound 238 and butadiene sulphone, and isolated as a light tan crystalline solid, 90% yield (from methanol) mp 115-117°C. Calculated for C<sub>14</sub>H<sub>17</sub>NO<sub>4</sub> C 63.9, H 6.5, N 5.3; found C 63.8, H 6.6, N 4.8%; m/e 263 (E1; M<sup>+</sup>);  $\nu_{\max}$  (KBr) 3050, 2962, 2942, 2920, 2840, 1595, 1545, 1525, 1466, 1448, 1440, 1425, 1375, 1335, 1262, 1240, 1216, 1192, 1150, 1030, 862, 830, 770, 773, 715, 689, 670 and 642 cm<sup>-1</sup>;  $\delta_{\text{H}}$ (CDCl<sub>3</sub>)

6.79-6.75 (3H,m), 5.81-5.68 (2H,m), 4.90 (1H, m), 3.85 (3H, s), 3.82 (3H,s) 3.31 (1H, m), 2.76 (2H, m) and 2.43 (2H, m);  $\delta_{\text{C}}(\text{CDCl}_3)$  148.8, 148.0, 132.3, 126.3, 122.3, 119.1, 111.2, 110.5, 87.2, 55.5, 43.5, 32.9 and 31.0 ppm. Methoxy carbons coincident at 55.5 ppm.

*4-(2-Carbomethoxyethyl)-5-(3,4-methylenedioxyphenyl)-4-nitrocyclohexene (241a)* - To a stirred solution of compound 239 (10.0 g, 0.04 mol) dissolved in a mixture of *t*-butanol (200 ml) and THF (100 ml) was added sequentially methyl acrylate (3.9 g, 0.04 mol) and *N*-benzyltrimethylammonium hydroxide (Triton B) (2.0 ml, 4 mmol). This mixture was stirred at 20°C under nitrogen for 48 hrs during which time the mixture darkened and some solid precipitated. The solvent was evaporated *in vacuo* and the residue extracted with ether (3 x 300 ml); the extracts were filtered and washed sequentially with (i) dilute hydrochloric acid (300 ml), (ii) 10% sodium hydroxide solution (300 ml), (iii) water (2 x 300 ml). The ether layer was then dried ( $\text{MgSO}_4$ ) and evaporated. Addition of cyclohexane to the resulting solid and/or recrystallisation from methanol afforded product 241a, light tan crystals, (12.3 g, 92%) mp 98-100°C. Calculated for  $\text{C}_{17}\text{H}_{19}\text{NO}_6$  C 61.3, H 5.7, N 4.2; found C 61.6, H 5.7, N 4.0%.  $m/e$  286 (EI.  $\text{M}^+-\text{NO}_2$ ) or 287 (CI),  $\text{M}^+$  333 absent;  $\nu_{\text{max}}$  (nujol) 1735, 1530, 1352, 1315, 1250, 1210, 1180, 1170, 1030, 979, 956, 930, 899, 830, 815, 662 and 646  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CDCl}_3)$  6.75-6.60 (3H, m), 5.9 (2H, s), 5.8 (2H, m), 3.7 (3H, s), 3.4 (1H, d,  $J = 6.9$  Hz), 2.8-2.1 (8H, m);  $\delta_{\text{C}}(\text{CDCl}_3)$  172.3, 147.6, 146.8, 133.3, 126.0, 124.0, 121.7, 108.1, 107.9, 100.9, 91.9, 51.7, 46.3, 31.9, 30.7, 28.5 and 27.5 ppm.

*4-(2-Carbomethoxyethyl)-5-(3,4-dimethoxyphenyl)-4-nitrocyclohexene (241b)* - This compound was prepared analogously to 241a from 240, and isolated in 75% yield, mp 86-89°C (from methanol). Calculated for  $\text{C}_{18}\text{H}_{23}\text{NO}_6$  C 61.9, H 6.6, N 4.0; found C 62.0, H 6.6, N 3.5%

m/e 303 (CI,  $M^+-NO_2$ ),  $M^+$  349 absent;  $\nu_{max}$  (nujol) 1735, 1608, 1586, 1535, 1329, 1298, 1266, 1236, 1205, 1185, 1157, 1149, 1035, 1008, 980, 870, 837, 820, 773, 720 and 663  $cm^{-1}$ ;  $\delta_H(CDCl_3)$  6.76-6.74 (3H, m), 5.91-5.81 (2H, m), 3.83 (3H, s), 3.80 (3H, s), 3.67 (3H, s), 3.45 (1H, d, J = 6.3 Hz) and 2.81-2.16 (8H, m);  $\delta_C(CDCl_3)$  172.3, 148.5, 148.3, 132.0, 126.1, 123.9, 120.3, 111.3, 110.8, 91.9, 55.5, 51.7, 46.2, 31.7, 30.7, 28.5 and 27.7 ppm

*6-(3,4-Methylenedioxyphenyl)-2-oxo-1-azaspiro[4.5]dec-8-ene (131a) -*

Nitroester 241a (24.5 g, 0.07 mol) was dissolved in a mixture of absolute ethanol (600 ml) and concentrated hydrochloric acid (100 ml); to this solution was added, with stirring, zinc dust (80 g) (activated by pre-treatment with hydrochloric acid) in portions, causing the temperature of the mixture to rise to ca. 60°C. The mixture was then refluxed with stirring for 15 hrs, and while still hot, filtered *in vacuo* yielding a clear green filtrate which was basified with 20% aqueous sodium hydroxide solution (ca. 300 ml) and then refluxed for a further 3 hrs. The hot, basic solution was filtered and evaporated *in vacuo* nearly to dryness when the residue was dissolved in water (700 ml) and extracted into chloroform (3 x 300 ml). The organic layer was washed sequentially with (i) 10% aqueous hydrochloric acid (300 ml), (ii) 10% sodium chloride - 10% sodium carbonate solution (300 ml), (iii) water (300 ml) and then dried ( $MgSO_4$ ) and evaporated *in vacuo* to yield a sticky solid, which, on washing with ether gave compound 131a as a white powder (9.6 g, 96% crude yield). Further washing with ether and/or acetone yielded pure compound 131a (18.1 g, 91%) mp 179-181°C. Calculated for  $C_{16}H_{17}NO_3$  C 70.9, H 6.3, N 5.2; found C 70.7, H 6.5, N 4.9%; m/e 271 (EI), 272 (CI;  $M^+$ );  $\nu_{max}$  (nujol) 1675, 1480, 1302, 1255, 1232, 1094, 1033, 931, 852, 845, 820, 815, 766 and 691  $cm^{-1}$ ;  $\delta_H(CDCl_3)$  7.58 (NH, s), 6.81 (1H, s), 6.75 (2H, s) 5.90 (2H, s), 5.8-5.6 (2H, m) and 2.8-1.4 (9H, m);  $\delta_C(CDCl_3)$  178.0, 147.2, 146.2, 134.6, 126.9, 124.2, 121.6, 108.6, 107.8, 100.6, 59.9 (spiro-C), 47.9, 39.7,



32.1, 30.0 and 29.8 ppm.

*6-(3,4-Dimethoxyphenyl)-2-oxo-1-azaspiro[4.5]dec-8-ene (236a)* - This compound was prepared from *241b*, analogously to compound *131a* and was isolated as a white powder in 72% yield, mp 134-136°C (from acetone). Calculated for  $C_{17}H_{21}NO_3$  C 71.1, H 7.3, N 4.9; found C 71.3, H 7.8, N 4.4%

m/e 228 (CI), 287 (EI;  $M^+$ );  $\nu_{\max}$  (KBr) 3160, 3012, 2905, 1690, 1589, 1510, 1460, 1370, 1310, 1265, 1238, 1160, 1141, 1035, 800, 767, 670 and 648  $cm^{-1}$ ;  $\delta_H$ ( $CDCl_3$ ) 6.83-6.81 (3H, m), 6.44 (1H, s, NH), 5.86 (1H, m), 5.70 (1H, m), 3.86 (3H, s), 3.85 (3H, s), 2.80 (1H, t, J = 7.7 Hz), 2.5-1.9 (6H, m), 1.85 (1H, m) and 1.45 (1H, m);  $\delta_C$ ( $CDCl_3$ ) 177.8, 148.6, 148.0, 133.3, 127.1, 124.6, 120.8, 111.4, 110.9, 59.8, 55.7, 47.8, 39.7, 32.3 and 30.0 [probably two carbons at  $\delta 30.0$  ppm by analogy with compound *131a*].

*6-(3,4-Methylenedioxyphenyl)-2-thio-1-azaspiro[4.5]dec-8-ene (253)* - To a stirred solution of lactam *131a* (1.4 g, 5.2 mmol) in dry toluene or dry benzene (100 ml) under nitrogen was added phosphorus pentasulphide (3.0 g, 6.5 mmol) and the mixture was heated at reflux for 3 hrs, then cooled and dilute sodium hydroxide solution added to raise the pH to ca. 9 whence a thick yellow suspension formed. The mixture was extracted into toluene-petroleum ether (bp 40-60°C) (2:1 v/v) (3 x 100 ml) and the combined extracts washed sequentially with 100 ml portions of (i) 10% sodium chloride solution, (ii) 10% sodium carbonate solution and (iii) water, and then dried ( $MgSO_4$ ) and evaporated *in vacuo* to leave a solid which was recrystallised from toluene to afford colourless crystals of compound *253* (1.15 g, 80%), mp 157-160°C. Calculated for  $C_{16}H_{17}NO_2S$  C 66.9, H 5.9, N 4.9, S 11.2; found C 67.3, H 6.2, N 4.7, S 11.6%, m/e 287 (EI), 288 (CI;  $M^+$ ).  $\nu_{\max}$  (KBr) 3130, 1500, 1480, 1238, 1220, 1162, 1045, 942, 858, 781 and 680  $cm^{-1}$ ;  $\delta_H$ ( $CDCl_3$ ) 9.35 (1H, s, NH) 6.80 (1H, s), 6.75 (2H, s), 5.92 (2H, s), 5.85-5.68 (2H, m) and 2.68-1.82 (9H, m);  $\delta_C$ ( $CDCl_3$ ) 204.7, 147.4,

146.4, 133.7, 127.1, 123.9, 121.6, 108.6, 108.0, 100.7, 69.0, 47.7, 42.4, 38.3, 34.1, and 30.1 ppm.

*6-(3,4-Methylenedioxyphenyl)-1-azaspiro[4.5]dec-8-ene (131k)* - To a stirring suspension of lithium aluminium hydride (3.3 g, 86 mmol) in rigorously dried ether (distilled sequentially from sodium and lithium aluminium hydride) under nitrogen was added lactam *131a* (3.2 g, 11.8 mmol) in portions over 0.5 h at a rate sufficient to maintain gentle reflux. The reaction mixture was then heated and stirred at reflux for 4 days, then cooled and treated with water (6 ml) and 20% sodium hydroxide solution (9 ml). The mixture was warmed to room temperature, filtered and the filtrate washed sequentially with (i) 20% sodium hydroxide solution (50 ml) and (ii) water (50 ml), then dried ( $\text{MgSO}_4$ ) and evaporated at reduced pressure to yield compound *131k* as a viscous, pale yellow oil (2.73 g, 90%)  
Calculated for  $\text{C}_{16}\text{H}_{19}\text{NO}_2$  C 74.7, H 7.4, N 5.45, m/e 257.14158; found C 75.2, H 7.6, N 5.4%, m/e 257.13917;  $\nu_{\text{max}}$  (neat) 3320, 3020, 2960, 2895, 2830, 1608, 1505, 1487, 1437, 1409, 1373, 1332, 1292, 1245, 1125, 1110, 1046, 940, 870, 812, 730, 666 and 560  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 6.97 (1H, s, NH), 6.8-6.7 (3H, m), 5.89 (2H, s), 5.84 (1H, m), 5.69 (1H, m), 2.94 (2H, t,  $J = 6.42$  Hz), 2.74 (1H, t,  $J = 6.03$  Hz), 2.4 (2H, m), 2.07 (2H, m) and 1.8-1.5 (4H, m);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 147.3, 146.0, 137.8, 127.5, 126.1, 121.9, 109.0, 107.6, 100.7, 62.0, 47.2, 45.0, 37.4, 36.7, 31.6 and 24.9 ppm. The hydrochloride salt of amine (*18a*) was obtained from the amine and 5 M hydrochloric acid after 0.5 hrs at room temperature, as a white solid, mp ca. 200°C (dec) Calculated for  $\text{C}_{16}\text{H}_{20}\text{ClNO}_2$  C 65.4, H 6.8, N 4.8; found C 65.1, H 6.5, N 4.2%.

*6-(3,4-Dimethoxyphenyl)-1-azaspiro[4.5]dec-8-ene (236k)* - This compound was prepared from lactam *236a*, under the same conditions as compound *131k*, and isolated as an oil (yield varied between 80-90%).

Calculated for  $C_{17}H_{23}NO_2$  m/e 273.17288; found m/e 273.16895.  $\nu_{\max}$  (neat) 3020, 2940, 2895, 2830, 1587, 1506, 1445, 1260, 1235, 1145, 1033, 810, 766, 695 and 655  $cm^{-1}$ ;  $\delta_H(CDCl_3)$  7.04 (1H, s, NH), 6.87-6.74 (3H, m), 5.83 (1H, m), 5.67 (1H, m), 5.67 (1H, m), 3.83 (6H, s), 2.90 (1H, t, J = 6.39 Hz), 2.74 (1H, t, J = 6.26 Hz), 2.45 (2H, m) and 2.13-1.47 (7H, m);  $\delta_C(CDCl_3)$  147.8, 146.9, 136.1, 127.1, 125.5, 120.4, 111.5, 110.0, 61.4, 55.2, 46.6, 44.5, 37.1, 36.1, 31.1 and 24.3 ppm. The hydrochloride salt of amine (18b) was prepared from the amine and 5 M hydrochloric acid, white solid, mp ca. 200°C (dec). Calculated for  $C_{17}H_{24}ClNO_2$  C 54.9, H 7.8, N 4.5; found C 65.8, H 8.2, N 4.3%.

*6-(3,4-Methylenedioxyphenyl)-2-methylthio-1-azaspiro[4.5]deca-1,8-diene hydroiodide (254)* - Thiolactam, 253, (1.53 g, 5.3 mmol) was dissolved in dry THF (130 ml) and methyl iodide (6.7 g, 47 mmol) was added with stirring. The solution rapidly turned golden and a precipitate of salt 254 began to form within 0.5 hrs. After stirring for 15 hrs at 20°C the mixture was evaporated in vacuo and the solid was washed with ether (20 ml), filtered and dried to yield compound 254, a pale yellow solid (1.99 g, 87%) mp 185-186.5°C. Calculated for  $C_{17}H_{20}NSI$  C 47.6, H 4.7, N 3.3; found C 47.5, H 4.5, N 3.0%;  $\nu_{\max}$  (KBr) 3430 (broad), 3030, 2990, 2910, 2780, 1575, 1505, 1490, 1448, 1240, 1040, 930, 855, 818 and 680  $cm^{-1}$ ;  $\delta_H(CDCl_3)$  6.88-6.72 (3H, m), 5.95 (2H, s), 5.82-5.70 (2H, m), 3.4 (1H, m), 3.2 (1H, m), 2.7 (3H, s,  $SCH_3$ ), 2.6-1.8 (8H, m);  $\delta_C(CDCl_3)$  198.5 ( $\overset{+}{C}=N$ ), 149.8, 149.0, 134.3, 128.4, 124.3, 123.2, 109.9, 109.5, 102.7, 77.4, 49.6, 38.7, 37.9, 33.4, 30.6 and 16.0 ppm.

*6-(3,4-Methylenedioxyphenyl)-2-methylthio-1-azaspiro[4.5]deca-1,8-diene (255)* - Salt, 254, (244 mg, 0.56 mmol) was dissolved in dry tetrahydrofuran (100 ml) and sodium borohydride (38 mg, 1.0 mmol) was added. After 2 hrs when the solution was clear and colourless, 20% sodium

hydroxide solution (75 ml) was added and two layers left to separate. The THF layer was collected, dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo* to leave a gelatinous, clear oil (80 mg, 47%). Calculated for  $\text{C}_{17}\text{H}_{19}\text{NSO}_2$  m/e 301.11365; found 301.11435;  $\nu_{\text{max}}$  ( $\text{CDCl}_3\text{-CCl}_4$ ) 3020, 2890, 1585, 1500, 1485, 1440, 1315, 1250, 1230, 1100 and 1045  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 6.70-6.60 (3H, m), 5.90 (2H, s), 5.91-5.71 (2H, m), 2.80 (1H, m), 2.64 (1H, m), 2.47 (3H, s, S- $\text{CH}_3$ ), 2.35-2.10 (4H, m), 1.92 (1H, m) and 1.55 (2H, m);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 172.3 (C=N), 147.5, 146.3, 136.5, 127.2, 125.2, 122.2, 109.3, 107.6, 100.8, 77.2, 49.6, 40.3, 38.2, 35.2, 31.1 and 13.7 ppm.

*8,9-Methylenedioxy-1,4,4a,5,6,10b-hexahydrocyclopenta[e]phenanthridine* (312) - Amine 131b (3.0 g, 11.7 mmol) was added to a mixture of 37% formalin solution (60 ml) and 20% aqueous hydrochloric acid (120 ml). After 3 hrs at reflux the mixture was basified with 20% sodium hydroxide solution, extracted into chloroform and the chloroform extract was dried and evaporated to yield a yellow solid which was recrystallised from methanol (addition of water to a saturated methanol solution assisted crystallisation of the product) to yield compound 312; a white solid, (2.38 g, 75%) mp 88-90°C, Calculated for  $\text{C}_{17}\text{H}_{19}\text{NO}_2$  C 75.8, H 7.1, N 5.2; found C 76.2, H 7.2, N 4.9% m/e 270 (CI;  $\text{M}^+$ );  $\nu_{\text{max}}$  (KBr) 3020, 2890, 2770, 1480, 1435, 1365, 1322, 1312, 1270, 1234, 1205, 1158, 1130, 1112, 1040, 932, 845 and 656  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 6.97 (1H, s), 6.66 (1H, s), 5.90 (2H, s), 5.65 (1H, m), 5.4 (1H, m), 3.93 (1H, d, J = 13.5 Hz), 3.67 (1H, d, J = 13.5 Hz), 3.10 (1H, m), 2.78-2.54 (4H, m), 1.95-1.86 (3H, m), and 1.64-1.52 (3H, m);  $\delta_{\text{C}}$  146.4, 145.3, 132.7, 129.6, 126.6, 123.9, 107.1, 105.6, 100.7, 61.4, 54.6, 53.3, 40.8, 36.6, 33.3, 25.5 and 23.1 ppm.

*8,9-Dimethoxy-1,4,4a,5,6,10b-hexahydrocyclopenta[e]phenanthridine* (313) - By analogy with the preparation of compound 312, amine 236b yielded compound 313, 65% white powder, mp 121-124°C (from methanol-water).

Calculated for  $C_{18}H_{23}NO_2$  C 75.8, H 8.1, N 4.9; found C 75.4, H 8.4, N 4.2%;  
m/e 286 (CI;M<sup>+</sup>);  $\nu_{max}$  (KBr) 1610, 1512, 1464, 1366, 1344, 1320, 1283,  
1220, 1208, 1191, 1131, 1120, 1105, 1058, 861, 743 and 669  $cm^{-1}$ ;  $\delta_H(CDCl_3)$   
6.70 (1H, s), 6.66 (1H, s), 5.63 (1H, m), 5.38 (1H, m), 3.91 (1H, d, J =  
13.7 Hz), 3.83 (3H, s), 3.82 (3H, s), 3.75 (1H, d, J = 13.7 Hz), 3.01 (1H,  
m), 2.87-2.67 (3H, m), 2.54-2.47 (1H, m), 1.93-1.86 (3H, m), 1.66-1.56 (3H,  
m);  $\delta_C(CDCl_3)$  147.1, 146.5, 130.5, 127.7, 126.0, 123.4, 109.5, 108.1, 60.6,  
55.5, 53.5, 52.0, 40.3, 35.9, 30.8, 25.1 and 22.1 ppm.

*N*-methyl-8,9-methylenedioxy-1,4,4a,5,6,10*h*-hexahydrocyclopenta[*e*]phenanthridinium salts: (a) Iodide (319*a*) - To a solution of amine, 312, (0.2 g, 0.75 mmol) in dry methanol (20 ml), was added methyl iodide (640 mg, 4.5 mmol), and the mixture heated at reflux for 4 hrs. The methanol and excess methyl iodide were then removed *in vacuo*, and the crude product washed with diethyl ether, yielding methiodide salt, 319*a* (300 mg, 95%) as a pale yellow powder mp 201-202°C. Calculated for C<sub>18</sub>H<sub>22</sub>NO<sub>2</sub>I C 51.55, H 5.4, N 3.4; found C 51.48, H 5.7, N 3.0%.

(b) hexafluorophosphate (319*b*) - Methiodide salt 319*a*, (50 mg, 0.12 mmol), was dissolved in water (15 ml), and to this stirring solution was added excess hexafluorophosphoric acid, resulting in an immediate white precipitate. After 5 mins, this precipitate was filtered off, washed with cold water and dried *in vacuo*, to provide hexafluorophosphate 319*b* (50 mg, 96%) as a white powder. Calculated for C<sub>18</sub>H<sub>22</sub>NO<sub>2</sub>PF<sub>6</sub> C 50.23, H 5.20, N 2.89; found C 49.97, H 5.17, N 3.26%.

*N*-(2-chloroacetyl)-3,4-dimethoxyphenethylamine (260):- To a solution of 3,4-dimethoxyphenethylamine (4.5 g, 0.025 mol) in diethyl ether (150 ml) with triethylamine (10 ml), at -10°C, was added chloroacetylchloride (4.5 g, 0.04 mol) in diethyl ether (50 ml), dropwise with efficient stirring, over 2 hrs, under N<sub>2</sub>. After completion of this addition, the mixture was allowed to warm to r.t. overnight. The reaction mixture was then poured into acidic (H<sub>2</sub>SO<sub>4</sub>) ice water (150 ml, pH 3) and shaken vigorously, then extracted with chloroform (3 x 150 ml). The combined extracts were then washed sequentially with (i) 5% aq. sodium hydroxide (2 x 100 ml), (ii) 1M hydrochloric acid (100 ml) (iii) water (100 ml), dried (MgSO<sub>4</sub>), filtered and evaporated. The resulting sandy coloured solid was column chromatographed (alumina column, 20 x 4 cm) eluting with chloroform, to yield the

amide, 260 (4.44 g, 70%) as a pale brown solid mp 85-86.5°C. Calculated for  $C_{12}H_{16}NO_3Cl$  C 55.92, H 6.21, N 5.44, Cl 13.8; found C 56.36, H 6.45, N 5.10, Cl 14.2%;  $\nu_{\max}$  (KBr) 3230, 3072, 2995, 2935, 2828, 1639, 1577, 1510, 1460, 1433, 1418, 1334, 1259, 1238, 1204, 1157, 1139, 1038, 1026, 942, 853, 802, 761, 693, 630, 577, 440  $cm^{-1}$ .

*N*-(2-chloroacetyl)-6-(3,4-methylenedioxyphenyl)-1-azaspiro[4.5]dec-8-ene (325) - To a stirring solution of amine 245, (0.1g, 0.4mmol) in diethyl ether (40 ml), cooled to -15°C, was added, under  $N_2$ , chloroacetyl chloride (62 mg) in diethyl ether (8 ml), over several minutes, resulting in rapid formation of a white precipitate. The mixture was then allowed to warm to r.t., poured into acidic ( $H_2SO_4$ ) ice water (75 ml, pH3), and extracted with chloroform (3 x 70 ml). The combined extracts were washed sequentially with (i) 5% aq. sodium hydroxide (2 x 100 ml), (ii) 1M HCl (50 ml), (iii) brine (50 ml), dried ( $MgSO_4$ ), filtered and evaporated, to yield crude amide 325 (115 mg, 89%) as an off-white solid, which was not obtained analytically pure, but was characterized spectroscopically. m/e 333 (EI,  $M^+$ ), 334 (CI);  $\nu_{\max}$  (KBr) 3020, 2960, 2890, 1655, 1481, 1438, 1395, 1330, 1248, 1230, 1178, 1150, 1115, 1094, 1037, 930, 858, 802, 662  $cm^{-1}$ ;  $\delta_H$ ( $CDCl_3$ ) 6.77-6.6 (3H, m), 5.91 (2H, d, J = 3.62 Hz), 5.82 (2H, s), 3.87 (1H, br, s), 3.68-3.44 (3H, br s), 2.8 (1H, br, s), 2.45 (2H, m), 2.22-2.03 (3H, m), 1.8-1.6 (3H, m);  $\delta_C$ ( $CDCl_3$ ) 164.96, 147.6, 146.3, 137.2, 126.96, 125.5, 121.9, 108.7, 107.9, 100.8, 68.4, 49.0, 47.6, 44.2, 40.5, 34.2, 31.8, 21.7 ppm.

*N*-(2-carbomethoxyacetyl)-6-(3,4-methylenedioxyphenyl)-1-azaspiro[4.5]dec-8-ene, (326) - To a stirring solution of amine 245, (0.5 g, 1.9 mmol) in diethyl ether (40 ml) and triethylamine (1 ml), at ca. -15°C, was added methyloxalyl chloride (0.33 g, 3.1 mmol), in diethyl ether (8 ml), in small portions over 1 hr. The resulting white suspension was allowed

to warm to r.t. overnight, was poured into acidic ( $\text{H}_2\text{SO}_4$ ) ice water (100 ml, pH3) and extracted with chloroform (3 x 150 ml). The combined extracts were washed sequentially with (i) 10% aq.  $\text{K}_2\text{CO}_3$  (200 ml), (ii) brine (100ml), dried ( $\text{MgSO}_4$ ), filtered and evaporated to yield amide-ester 326 (0.66 g, 99%) as a white solid mp 105-107°C m/e 343 (EI,  $\text{M}^+$ ), 344 (CI); Calculated for  $\text{C}_{19}\text{H}_{21}\text{NO}_5$  C 66.47, N 6.12, H 4.08; found C 66.43, H 6.29, N 3.83%;  $\nu_{\text{max}}$  (KBr) 3022, 2967, 2890, 2775, 1742, 1660, 1502, 1488, 1443, 1418, 1378, 1255, 1213, 1160, 1122, 1102, 1048, 985, 971, 944, 906, 876, 853, 818, 764, 748, 732, 718, 705, 682, 658, 523, 508, 440, 418, 362  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 6.8-6.5 (3H, m), 5.8 (2H, s), 5.7 (2H, m), 3.7 (3H, s), 3.5-3.2 (3H, m), 2.9-2.6 (1H, t,  $J \approx 16\text{Hz}$ ), 2.5-2.3 (2H, m), 2.2-2.0 (1H, m), 1.9-1.5 (4H, m);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 163.4, 160.2, 147.6, 146.2, 136.6, 126.7, 125.2, 121.8, 108.5, 107.7, 100.6, 68.4, 52.0, 48.8, 46.6, 40.1, 32.7, 31.4, 21.8 ppm.

*N*-carbethoxyethyl-6-(3,4-methylenedioxyphenyl)-1-azaspiro[4.5]dec-8-ene (331) - A mixture of amine 245, (4.37 g, 0.017 mol),  $\text{K}_2\text{CO}_3$  (2.54 g, 0.018 mol), bromoethylacetate (3.00 g, 0.18 mol), and 18-Crown-6 (50 mg, 0.2 mmol) under dry nitrogen, in freshly distilled acetonitrile (300 ml), was heated at reflux for 18 hrs. The reaction mixture was cooled and filtered, the solvent removed *in vacuo*, and the crude residue chromatographed (alumina column, 25 x 4 cm), eluting with 1:1 hexanes-ethyl acetate. The pure amino-ester 331 (5.81g, 99%) was obtained as a white solid on prolonged drying under high vacuum mp 72-74°C. m/e 343 (EI,  $\text{M}^+$ ), 344 (CI) Calculated for  $\text{C}_{20}\text{H}_{25}\text{NO}_4$  C 69.97, H 7.29, N 4.08; found C 70.30, H 7.52, N 3.19%;  $\nu_{\text{max}}$  (neat) 3060, 3023, 2956, 2866, 2815, 2767, 2695, 1738, 1652, 1623, 1604, 1505, 1487, 1446, 1419, 1378, 1254, 1244, 1194, 1164, 1139, 1126, 1107, 1042, 962, 940, 935, 913, 876, 847, 805, 729, 712, 692, 667, 641, 535  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 7.24 (1H, s), 6.86 (1H, d), 6.68 (1H, d,  $J = 7.9\text{Hz}$ ), 5.9 (2H, d,  $J = 8\text{Hz}$ ), 5.85-5.72 (2H, m), 4.25-4.1 (2H, m), 3.61-3.56 (1H, d,



$J = 16.7$  Hz), 3.14–2.98 (2H, m), 2.6 (1H, t,  $J=6.2$  Hz), 2.49–2.32 (3H, m), 2.15 (2H, s), 1.9–1.81 (1H, m), 1.66–1.26 (5H, m), 1.27–0.92 (1H, m);  $\delta_C$  (CDCl<sub>3</sub>) 172.6, 146.9, 145.6, 137.8, 126.2, 126.4, 122.4, 109.8, 107.1, 100.4, 63.2, 60.1, 55.1, 53.6, 50.4, 40.2, 33.6, 31.6, 22.8, 14.1 ppm.

*N*-(2-hydroxyethyl)-6-(3,4-methylenedioxyphenyl)-1-azaspiro[4.5]dec-8-ene (332) - To a stirring suspension of LAH (480 mg, 20 mmol) in rigorously dried, freshly distilled diethyl ether (50 ml), was added amino-ester 331 (483 mg, 1.4 mmol) in small portions over 5 mins. The mixture was heated at reflux for 24 hrs, and was then cooled to ca.  $-5^{\circ}\text{C}$  in an ice/salt bath. Water (1 ml) was added dropwise, with efficient stirring, over 45 mins, followed by aq. sodium hydroxide (30% 3 ml) in portions over 20 mins. This mixture was then stirred and allowed to warm to r.t. over 2 hrs and the solution filtered from the inorganic residues. Water (25 ml) was added to the filtered solution, and was extracted with diethyl ether (3 x 50 ml). The combined extracts were washed sequentially with (i) 20% aq. Na<sub>2</sub>CO<sub>3</sub> (30 ml) (ii) brine (30 ml), dried (MgSO<sub>4</sub>), filtered and evaporated to leave amino-alcohol, 332 (420 mg, 99%) as a thick colourless oil. The product showed no significant impurities by t.l.c., but could be further purified by column chromatography (alumina column, 31 x 2 cm) eluting with 3:2 ethyl acetate-hexanes, returning 402 mg (95%) of a thick oil, assigned structure 332 from spectral data.  $m/e$  302 (EI,  $M^+ + 1$ ), 302 (CI);  $\delta_H$ (CDCl<sub>3</sub>) 6.8 (1H, s), 6.65 (2H, m), 5.8 (2H, s), 5.75 (2H, s), 3.44–3.3 (2H, m), 3.0 (1H, t,  $J = 8.2\text{Hz}$ ), 2.6 (1H, t,  $J= 5.5\text{Hz}$ ), 2.52–2.11 (6H, m), 1.93–1.82 (2H, m), 1.61–1.5 (2H, m), 1.25–1.18 (1H, m);  $\delta_C$ (CDCl<sub>3</sub>) 147.4, 145.9, 138.3, 127.5, 126.6, 122.4, 109.1, 107.7, 100.8, 63.8, 60.1, 52.8, 52.1, 49.2, 39.9, 32.4, 31.8, 22.1 ppm

*N*-(2-chloroethyl)-6-(3,4-methylenedioxyphenyl)-1-azaspiro[4.5]dec-8-ene (333) - To a solution of amino-alcohol 332 (65 mg, 0.2 mmol) in

toluene ( 5 ml) was added phosphorus oxychloride, and the mixture heated at reflux for 24 hrs. The cooled reaction mixture was then poured into water (10 ml) and stirred thoroughly. This mixture was basified with aq. sodium hydroxide (10%, 5 ml), and extracted with chloroform (3 x 40 ml). The combined extracts were washed with brine (20 ml), dried ( $\text{MgSO}_4$ ), filtered and evaporated. The crude product was chromatographed (alumina, column 42 x 1.5 cm) eluting with 2:1 cyclohexane-ethyl acetate, to yield a pale oil (56 mg, 69%), provisionally assigned as chloride <sup>333</sup> from mass spectral and NMR data. Elemental analysis could not be obtained.  $m/e$  319 (EI,  $\text{M}^+$ ), 320 (CI);  $\delta_{\text{C}}$ ( $\text{CDCl}_3$ ) 147, 145.9, 138.2, 128, 126.6, 122.3, 109.6, 107.4, 100.6, 64.1, 54.5, 53.6, 50.6, 44.0, 40.3, 32.5, 31.9, 22.7 ppm.

*N*-carbotertbutoxymethyl-6-(3,4-methylenedioxyphenyl)-2-oxo-1-azaspiro [4.5]dec-8-ene (<sup>336</sup>) - To a stirring solution of lactam <sup>131a</sup> (3.07 g, 11.3 mmol), in freshly distilled tert-butanol (150 ml), at 45°C, was added potassium tert-butoxide (2.67 g, 23.8 mmol), and the mixture warmed to 70°C to complete dissolution. To this solution was added bromo-tert-butylacetate (4.85 g, 24.9 mmol), in one portion, where upon a heavy white precipitate formed almost immediately. The mixture was then heated at 80°C for 15 hrs, and the tert-butanol then removed *in vacuo*. To the residue was added water (50 ml), and this was extracted with dichloromethane (3 x 150 ml). The combined extracts were washed with brine (50 ml), dried ( $\text{MgSO}_4$ ), filtered and evaporated to leave a gum. Chromatography (alumina column, 20 x 4.5 cm) eluting with ethyl acetate, provided N-alkylated product <sup>336</sup> (4.2 g, 97%) as a white solid; mp 126-128°C;  $m/e$  385 (EI,  $\text{M}^+$ ), 330 (CI,  $\text{M}^+$ -isobutenyl). Calculated for  $\text{C}_{22}\text{H}_{27}\text{NO}_5$  C 68.39, H 7.26, N 3.86; found C 68.00, H 7.12, N 3.94 %;  $\nu_{\text{max}}$  (KBr) 3130, 2985, 1745, 1690, 1488, 1443, 1415, 1388, 1367, 1255, 1235, 1559, 1040, 940, 850, 810, 778, 745, 670  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 6.7-6.5 (3H, m), 5.88 (2H, s), 5.82-5.69 (2H, m),

4.12-4.03 (1H, d, J = 17 Hz), 3.36-3.26 (1H, d, J = 8.7 Hz), 2.8-2.7 (1H, t, J = 6.6 Hz), 2.5-2.2 (4H, m), 2.1-1.98 (3H, m), 1.86-1.74 (1H, m), 1.37 (9H, s);  $\delta_{\text{C}}(\text{CDCl}_3)$  176.3, 168.7, 147.9, 146.7, 135.0, 127.1, 125.5, 122, 108.7, 108.5, 101.1, 81.7, 63.3, 48.6, 44.6, 35.9, 34.2, 31.4, 29.3, 18.0 ppm.

*N*-carbortertbutoxymethyl-6-(3,4-dimethoxyphenyl)-2-oxo-1-azaspiro[4.5]dec-8-ene (323) [R = Me, Y = CO<sub>2</sub><sup>t</sup>Bu], was prepared analogously to 336, starting from 236a (1.1 g, 3.8 mmol), in t-butanol (50 ml), with potassium tert-butoxide (871 mg, 7.8 mmol), and bromotert-butyl acetate (1.51 g, 7.74 mmol). Chromatography (alumina column, 25 x 2 cm), eluting with ethyl acetate afforded the product as a white solid (1.47 g, 96%), mp 126-127°C; m/e 401 (EI, M<sup>+</sup>), 346 (CI, M<sup>+</sup>-isobutenyl). Calculated for C<sub>23</sub>H<sub>31</sub>NO<sub>5</sub> C 68.83, H 7.73, N 3.49. found C 68.48, H 7.87, N 2.92%;  $\nu_{\text{max}}$  (KBr) 3075, 3025, 2970, 2925, 2831, 1740, 1688, 1590, 1517, 1461, 1413, 1368, 1336, 1260, 1250, 1240, 1224, 1149, 1027, 900, 862, 852, 830, 758, 742, 662 cm<sup>-1</sup>;  $\delta_{\text{H}}(\text{CDCl}_3)$  6.81-6.71 (3H, m), 5.9-5.77 (2H, m), 4.22-4.1 (1H, d, J=17.2Hz), 3.85 (6H, s), 3.5-3.43 (1H, d, J = 1.7 Hz), 2.87-2.81 (1H, t, J = 7.3 Hz), 2.56-2.31 (4H, m), 2.12-1.69 (4H, m), 1.44 (9H, s) ppm.

*N*-carbomethoxymethyl-6-(3,4-methylenedioxyphenyl)2-oxo-1-azaspiro[4.5]dec-8-ene, (340) - Tert-butyl ester 336 (2.78 g, 7.2 mmol) was dissolved in analar methanol (300 ml), and conc. H<sub>2</sub>SO<sub>4</sub> (2ml) added. The mixture was heated at reflux for 20 hrs, and then most of the methanol was removed *in vacuo*. Water was then added (100 ml), and then the combined extracts were washed sequentially with (i) 10% aq. Na<sub>2</sub>CO<sub>3</sub> (2 x 30 ml) (ii) brine (50 ml), dried (MgSO<sub>4</sub>), filtered and evaporated. The crude product was chromatographed (alumina column, 15 x 3 cm) eluting with ethyl acetate, to yield methyl ester 340 (2.48 g, 100%) as a white powder. mp 119-120°C; m/e 343 (EI, M<sup>+</sup>), 344 (CI); Calculated for C<sub>19</sub>H<sub>21</sub>NO<sub>5</sub> C 66.47, H 6.12,

N 4.08; found C 66.03, H 5.94, N 3.73%;  $\nu_{\max}$  (KBr) 3020, 2895, 1752, 1690, 1503, 1487, 1440, 1412, 1385, 1340, 1308, 1252, 1237, 1210, 1176, 1118, 1098, 1037, 930, 811, 668  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 6.75-6.61 (3H, m), 5.94 (2H, s), 5.91-5.76 (2H, m), 4.22, 4.15 (1H, d,  $J = 17.4$  Hz), 3.69 (3H, s), 3.49, 3.39 (1H, d,  $J = 17.8$  Hz), 2.88-2.83 (1H, t,  $J = 6.9$  Hz), 2.54-2.28 (4H, m), 2.18-2.08 (2H, m), 1.98-1.84 (1H, m), 1.72-1.58 (1H, m);  $\delta_{\text{C}}$ ( $\text{CDCl}_3$ ) 176.4, 170.0, 147.9, 146.8, 135.0, 127.1, 125.3, 122.0, 108.6, 108.4, 101.1, 63.5, 52.2, 48.4, 43.6, 35.5, 34.1, 31.4, 29.2 ppm.

*N*-hydroxycarbomethyl-6-(3,4-methylenedioxyphenyl)-2-oxo-1-azaspiro[4.5]dec-8-ene (337) - Methyl ester 340 (1.115 g, 3.25 mmol) was dissolved in ethanol (30 ml) and potassium hydroxide (2.20 mg, 3.93 mmol) added. The mixture was refluxed for 10 hrs, cooled and evaporated. To the residue was added aqueous acid (pH2) until the mixture was acidified to this pH. This was extracted with ethyl acetate (3 x 100 ml), the combined extracts washed with brine (50 ml), dried ( $\text{MgSO}_4$ ), filtered and evaporated to yield lactam-acid, 337 (850 mg, 80%) as an off white powder, which was not obtained analytically pure; mp 70.5-73 $^{\circ}\text{C}$ ; m/e 283 (EI,  $\text{M}^+$ -46), 330 (CI); Calculated for  $\text{C}_{18}\text{H}_{19}\text{NO}_5$  C 65.65, H 5.78, N 4.26 m/e 329.12632; found C 63.72, H 6.13, N 3.63%, m/e 329.11114;  $\nu_{\max}$  (KBr) 3480, 2900, 1735, 1635, 1487, 1440, 1283, 1170, 1035, 928, 870, 850, 810, 655, 580  $\text{cm}^{-1}$

6-(3,4-methylenedioxyphenyl)2-oxo-1-azaspiro[4.5]dec-8-ene-1-ethanal (338) - Methyl ester 340 (1.698 g, 4.95 mmol) in freshly distilled toluene (30 ml) was cooled to -78 $^{\circ}\text{C}$ , and DIBAL-H (4.5 ml, 1.5 M solution) was added in 1 ml portions at ca. 10 min intervals. After this addition was complete, the mixture was stirred at -78 $^{\circ}\text{C}$  for a further 3 hrs. It was then quenched with saturated aq. sodium bisulfite (50 ml), and allowed to warm to r.t., stirring for 2 hrs. The bisulfite layer was collected, and the organic phase extracted with further bisulfite solution (2 x 50 ml).

These extracts were combined, washed with diethyl ether (20 ml), and then basified to pH8-9 by careful addition of 20% aq.  $\text{Na}_2\text{CO}_3$  in small portions over 1 hr. The aqueous phase was then extracted with ethyl acetate (3 x 150 ml), the combined extracts washed with brine (30 ml), dried ( $\text{MgSO}_4$ ), filtered and evaporated. The product was washed with ether, which was removed under high vacuum to yield aldehyde 338 (812 mg, 56%) as an off white powder; which was not analytically pure; mpt 79-81°C; m/e 313 (EI,  $\text{M}^+$ ), 314 (CI), Calculated for  $\text{C}_{18}\text{H}_{19}\text{NO}_4$  C 66.85, H 6.69, N 3.90, m/e313.13408 ; found C 65.07, H 6.81, N 2.93%, m/e313.12770 ;  $\nu_{\text{max}}$  (KBr) 3023, 2900, 1732, 1685, 1507, 1491, 1443, 1412, 1385, 1341, 1306, 1254, 1240, 1178, 1100, 1041, 933, 860, 813, 670  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 9.44 (CHO, s), 6.77-6.61 (3H, m), 5.96 (2H, s), 5.9-5.57 (2H, m), 4.25, 4.18 (1H, d, J = 18.3 Hz), 3.5, 3.43 (1H, d, J = 17.8 Hz), 2.91-2.85 (1H, t, J = 6.6Hz), 2.58-2.51 (1H, m), 2.32-2.22 (2H, m), 2.18-1.99 (2H, m), 1.95-1.86 (1H, m), 1.77-1.63 (1H, m), 1.25-1.18 (1H, m). ppm

*N*-(2-hydroxy ethyl)-6-(3,4-methylenedioxyphenyl)-2-oxo-1-azaspiro[4.5]dec-8-ene (339) - To stirring methyl ester, 340 , (234 mg, 0.68 mmol) in diethyl ether (10 ml) was added lithium borohydride (30 mg, 1.4 mmol), and the mixture stirred for 20 hrs. Diethyl ether (50 ml) and water (15 ml) were added, and the mixture poured into a separating funnel. After removing the ether phase, the aqueous phase was extracted with further diethyl ether (2 x 50 ml), and the combined extracts were washed with brine (15 ml), dried ( $\text{MgSO}_4$ ), filtered and evaporated. On standing under diethyl ether (5 ml), then vacuum drying, the lactam-alcohol 339 (157 mg, 74%) was obtained as a white solid.

m/e 316 (EI,  $\text{M}^+ + 1$ ), 316 (CI);  $\nu_{\text{max}}$  (KBr) 3460, 3030, 2908, 1168, 1508, 1489, 1444, 1408, 1342, 1310, 1253, 1248, 1218, 1180, 1040, 932, 865, 854, 813, 778, 665  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 6.74-6.59 (3H, m), 5.93 (2H, s), 5.82 (2H, s),

3.71-3.66 (1H, m), 3.56-3.42 (2H, m), 3.02-2.95 (1H, m), 2.86-2.81 (1H, m), 2.5-2.24 (3H, m), 2.14-2.0 (2H, m), 1.91-1.72 (1H, m), 1.65-1.50 (1H, m), 1.23-1.11 (1H, m), 0.91-0.84 (1H, m);  $\delta_{\text{C}}(\text{CDCl}_3)$  177.9, 147.6, 146.5, 134.8, 126.8, 124.9, 121.7, 108.2, 100.8, 64.3, 62.4, 60.2, 48.0, 45.4, 36.5, 34.1, 31.5, 29.3 ppm.

*7,8-methylenedioxy-cyclohexeno[3,4-b]-(2-pyrrolidono)[1,5-a]-2,3-dihydro-3-benzazepine (343)* - To a stirring solution of lactam-aldehyde 338 (218 mg, 0.7 mmol), in dry chloroform (10 ml) was added boron trifluoride dimethyletherate (2 ml). The mixture was stirred at r.t., then poured into water (5 ml), and the organic phase separated. This was washed with 5% aq.  $\text{K}_2\text{CO}_3$  (10 ml), dried ( $\text{MgSO}_4$ ), filtered and evaporated. Silica gel t.l.c. showed several materials, the most intense of which was more mobile than the others. Chromatography (silica gel column, 30 x 1.5 cm), eluting with ethyl acetate provided the mobile product as a white powder (28 mg, 14%) mp 155-58°C m/e 295 (EI,  $\text{M}^+$ ), 296 (CI); Calculated for  $\text{C}_{18}\text{H}_{17}\text{NO}_3$  m/e 295.12084; found m/e 295.03494,  $\nu_{\text{max}}(\text{KBr})$  2910, 1842, 1708, 1664, 1560, 1508, 1490, 1445, 1376, 1350, 1332, 1279, 1242, 1200, 1183, 1162, 1081, 1035, 997, 937, 929, 869, 848, 821, 790, 773, 749, 677, 648, 458, 448  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CDCl}_3)$  7.0, 6.96 (1H, d,  $J = 10.6$  Hz), 6.78 (1H, s), 6.65 (1H, s), 5.94-5.89 (2H, m), 5.60-5.57 (1H, d,  $J = 10.5$  Hz), 6.5 (1H, m), 2.9-2.4 (6H, m), 2.1-1.6 (4H, m);  $\delta_{\text{C}}(\text{CDCl}_3)$  174.3, 146.9, 131.0, 127.1, 126.4, 120.4, 110.4, 109.9, 108.7, 101.8, 68.7, 45.2, 33.1, 29.3, 29.0; Peaks at 146.9 and 33.1 probably both two coincident peaks.  $\delta_{\text{C}}^{\text{DEPT}}(\text{CDCl}_3)$  ( $\text{CH}_2\text{CH}_3$ ) 126.4, 125.7, 119.7, 109.7, 109.2, 108.1, ( $\text{CH}_2$ ) 44.6, 33.1, 29.3, 29.0 ppm methylene dioxy peak shows inverted due to method of pulsing.

7,8-Methylenedioxy-cyclohexene[3,4-b]-(2-pyrrolidono)[1,5-a]-4-hydroxy-2,3,4,5-tetrahydro-3-benzazepine, (344) - Lactam-aldehyde, 338 (60 mg, 0.2 mmol) was dissolved in methanol (10 ml), and 6M hydrochloric acid (40 ml) added. The mixture became yellow and was stirred at r.t. for 48 hrs. The methanol was removed *in vacuo*, and the residual aqueous solution basified with aq. sodium hydroxide (2M), and saturated with sodium chloride. This was extracted with ethyl acetate (3 x 50 ml), and the combined extracts washed with brine (20 ml), dried ( $\text{MgSO}_4$ ), filtered and evaporated to yield a white fluffy solid (56 mg, 93%), tentatively assigned structure <sup>344</sup> from spectral data; mpt 141-144°C; m/e 313, 295 (EI,  $\text{M}^+$ ,  $\text{M}^+-18$ ); 314, 296 (CI); Calculated for  $\text{C}_{18}\text{H}_{19}\text{NO}_4$  m/e 295.12084; found m/e 295.12240 ;  $\nu_{\text{max}}$  (KBr) 3430, 2890, 1665, 1500, 1487, 1445, 1412, 1378, 1350, 1249, 1100, 1036, 930, 860, 810, 654  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 6.79-6.65 (2H, m), 5.94-5.71 (4H, m), 3.45 (1H, m), 2.86-1.67 (11H, m);  $\delta_{\text{C}}$ ( $\text{CDCl}_3$ ) 173.7, 146.2, 133.6, 130.3, 126.4, 125.7, 119.7, 109.7, 109.2, 108.1, 101.1, 68.1, 44.6, 32.4, 29.7, 28.6, 28.3 ppm. Two coincident peaks at 146.2 ppm.

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‡ Calculated for loss of water from molecular ion.

*3,4-dimethoxy-carbomethoxymethyl benzene (353b)*:- 3,4-Dimethoxyphenylacetic acid, 353a (20 g, 0.1 mol) was dissolved in methanol (350 ml), and concentrated sulphuric acid (15 ml) added. The mixture was heated at reflux for 20 hrs, cooled, and most of the methanol removed *in vacuo*. Water (100 ml) was added to the residue, which was extracted with 1:1 ethylacetate-diethyl ether (3 x 300 ml). The combined extracts were washed sequentially with (i) 20% aq.  $\text{Na}_2\text{CO}_3$  (2 x 200 ml), (ii) brine (100 ml), then dried ( $\text{MgSO}_4$ ), filtered and evaporated. Prolonged drying *in vacuo* yielded ester, 353b (20 g, 93%) as a pale golden oil, of sufficient purity for further use. Calculated for  $\text{C}_{11}\text{H}_{14}\text{O}_4$  C 62.86, H 6.67; found C 63.09, H 7.12%;  $\nu_{\text{max}}$  (neat) 2989, 2943, 2827, 1734, 1602, 1589, 1511, 1461, 1437, 1418, 1263, 1156, 1028, 950, 891, 841, 808, 788, 762, 703, 600,  $538\text{ cm}^{-1}$ .

*3,4-Dimethoxy-6-carbomethoxymethyl benzaldehyde (347b)* - To a solution of dimethoxyphenylacetic methyl ester, 353b, (15.1 g, 0.072 mol) in rigorously dried dichloromethane (300 ml), cooled to  $-10^\circ\text{C}$  under nitrogen, was added aluminium chloride (19.8 g, 0.148 mol), in small portions over 5 minutes, with efficient stirring. To the resulting deep red solution, was then added dichloromethylmethylether (12 g, 0.099mol), dropwise over one hour. Stirring was maintained at  $-5^\circ\text{C}$  for another hour, whereupon the solution became very deep green. The solution was then allowed to warm to room temperature, and was then warmed at  $35^\circ\text{C}$  for 30 minutes, before being allowed to stir at  $20^\circ\text{C}$  overnight. The deep green solution was then poured portionwise onto ice water (400 ml) and shaken vigorously, for 5-10 mins, during which time exothermic reaction melted much of the ice. The aqueous layer was separated, and extracted with dichloromethane (3 x 250 ml), and the



combined organic phases were washed sequentially with (i) 5% aq.

KOH (3 x 100 ml), (ii) brine (100 ml), The organic solution was then dried ( $\text{MgSO}_4$ ), filtered and evaporated yielding a deep orange gum. Washing this with cold ( $-20^\circ\text{C}$ ) diethyl ether (3 x 20 ml) yielded aldehyde 347g (13.3 g, 78%) as a dark orange solid, mpt  $99.5-101.5^\circ\text{C}$ . Calculated for  $\text{C}_{12}\text{H}_{14}\text{O}_5$ ; C 60.50 %, H 5.88%, found C 60.36%, H 5.81%; m/e 238 (EI  $\text{M}^+$ ), 239 (CI);  $\nu_{\text{max}}$  (KBr) 3020, 2940, 2850, 2745, 1735, 1688, 1610, 1578, 1535, 1460, 1440, 1410, 1390, 1360, 1342, 1298, 1284, 1253, 1218, 1190, 1178, 1128, 1011, 993, 900, 878, 848, 795, 763, 712,  $590\text{ cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 10.06 (CHO, s), 7.36 (1H, s), 6.79 (1H, s), 4.01 (2H, 2), 3.96 (3H, s), 3.95 (3H, s), 3.71 (3H, s);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 190.4, 171.3, 153.1, 148.1, 130.3, 127.2, 114.2, 113.8, 56.0, 55.9, 52.0, 37.7 ppm.

*Trans-1-(3,4-dimethoxy-6-carbomethoxymethylphenyl)-2-nitroethene* (348g) - To a suspension of aldehyde, 347g, (10.8 g, 42.4 mmol), potassium carbonate (238 g, 1.7 mmol) and methylamine hydrochloride (303 mg, 4.49 mmol), in methanol, was added nitromethane (5 ml, excess), and the mixture stirred at room temperature for 96 hrs, during which time a heavy yellow precipitate formed. The mixture was then cooled to  $-5^\circ\text{C}$ , diluted with methanol (5 ml), and the yellow solid filtered off. The solid was washed with portions of cold water and dried, yielding 348g as a yellow powder (8.80 g, 74%); mpt  $121-122^\circ\text{C}$ ; m/e 281 (EI,  $\text{M}^+$ ), 282 (CI); Calculated for  $\text{C}_{13}\text{H}_{15}\text{NO}_6$  C 55.52 %, H 5.39%, N 4.98%; found C 55.84%, H 5.54%, N 4.83%;  $\nu_{\text{max}}$  (KBr) 3108, 2957, 2918, 1735, 1603, 1528, 1497, 1467, 1441, 1331, 1278, 1230, 1220, 1205, 1180, 1116, 1041, 1012, 980, 968, 903, 868, 839, 763, 737, 694, 584, 543,  $501\text{ cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 8.27, 8.22 (1H, d, J = 13Hz), 7.54, 7.48 (1H d, J = 13 Hz), 7.0 (1H, s), 6.8 (1H, s), 3.9 (8H, m), 3.77 (3H, s);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 171.0, 152.5, 148.7, 136.3, 136.1, 129.8, 121.5, 114.0,

109.3, 56.1, 52.4, 38.3 ppm.

*Trans-4-(3,4-dimethoxy-6-carbomethoxymethylphenyl)-5-nitrocyclohexene (349k)* - Nitrostyrene, 348k, (4 g, 14.2 mmol), butadiene sulphone (15 g, 127 mmol), hydroquinone (0.3 g, 2.7 mmol) and toluene (75 ml), were charged in a 150 ml steel bomb, and heated at 135°C for 7 days. The cooled, dark mixture was filtered and evaporated to yield a dark gum. Recrystallization from methanol (150 ml) provided 349k (3.5 g, 74%), as a pale brown crystalline solid. mpt 148.5 - 149.5°C; m/e 335 (EI, M<sup>+</sup>), 353 (CI, +NH<sub>4</sub><sup>+</sup>); Calculated for C<sub>17</sub>H<sub>21</sub>NO<sub>6</sub> C 60.89%, H 6.27%, N 4.18%; found C 61.20%, H 6.48%, N 3.90%;  
ν<sub>max</sub> (KBr) 3035, 3003, 2956, 2935, 2841, 1740, 1610, 1550, 1521, 1470, 1453, 1443, 1377, 1277, 1251, 1231, 1210, 1188, 1103, 1090, 1020, 1009, 877, 681, 668, 562, 508 cm<sup>-1</sup>; δ<sub>H</sub>(CDCl<sub>3</sub>) 6.73 (1H, s), 6.68 (1H, s), 5.84-5.75 (2H, m), 5.1-4.9 (1H, m), 3.93, 3.85 (1H, m), 3.7 (3H, s), 3.6 (1H, d, J = 15.9Hz), 2.8 (2H, s), 2.58-2.51 (1H, m), 2.33-2.17 (2H, m); δ<sub>C</sub>(CDCl<sub>3</sub>) 172.2 148.0, 130.9, 127.0, 125.3, 122.5, 114.1, 109.2, 87.2, 56.1, 55.9, 52.1, 39.2, 38.2, 33.2, 31.6 ppm.

*4-(2-carbomethoxymethyl)-5(3,4-dimethoxy-6-carbomethoxymethylphenyl)-4-nitrocyclohexene (350k)* - To a stirring solution of nitro-ester 349k (1.8 g, 5.4 mmol), in tert-butanol (20 ml) and tetrahydrofuran (10 ml), was added methyl acrylate (1 g, 11.6 mmol) and triton-B (0.2 ml). The mixture was stirred at r.t. for 48 hrs, during which time the mixture darkened. The reaction mixture was then poured into dilute hydrochloric acid (25 ml) and chloroform (50 ml). The aqueous layer was separated and further extracted with chloroform (3 x 50 ml). The combined organic extracts were washed sequentially with 50 ml portions of (i) saturated Na<sub>2</sub>CO<sub>3</sub> (ii) brine, then dried (MgSO<sub>4</sub>), filtered and evaporated to yield a golden gum. Column chromatography (alumina

column, 22 cm x 3 cm) eluting with 1:1 hexane-ethyl acetate provided diester, 350*l*, (1.97 g, 87%), as a white powder; mpt 100.5-101.5°C; m/e 421 (EI, M<sup>+</sup>), 421 (CI); Calculated for C<sub>21</sub>H<sub>27</sub>NO<sub>8</sub> C 59.86%, H 6.41%, N 3.33%; found C 60.03%. H 6.54%, N 2.86%;  $\nu_{\max}$  (KBr) 2938, 2838, 1738, 1610, 1534, 1468, 1452, 1437, 1370, 1355, 1340, 1321, 1303, 1280, 1204, 1175, 1100, 1064, 1041, 1008, 984, 905, 875, 828, 755, 695, 658 cm<sup>-1</sup>;  $\delta_{\text{H}}$ (CDCl<sub>3</sub>) 6.89 (1H, s), 6.63 (1H, s), 5.97-5.88 (2H, m), 4.04, 3.97 (1H, d, J = 16 Hz), 3.87 (3H, s), 3.77 (3H, s), 3.69 (6H, s), 3.46-3.39 (1H, d, J = 16 Hz), 3.10, 3.02 (1H, d, J = 19 Hz), 2.78, 2.71 (1H, d, J = 17 Hz), 2.53-2.14 (7H, m);  $\delta_{\text{C}}$ (CDCl<sub>3</sub>) 172.5, 172.3, 148.4, 147.9, 131.5, 127.1, 125.5, 123.3, 113.8, 110.5, 91.3, 55.7, 52.1, 51.9, 41.1, 38.4, 33.1, 31.3, 29.2, 28.5 ppm. Methoxy methyls coincident at 55.7 ppm.

*6-(3,4-dimethoxy-6-carbomethoxymethylphenyl)-2-oxo[4.5]dec-8-ene (351*l*)* - (a) To a stirring solution of nitro-diester 350*l* (0.5 g, 1.19 mmol), in ethanol (20 ml) and conc. HCl (3.5 ml), was added activated zinc dust (3.3 g, excess) in small portions over 15 mins, with considerable exotherm. The mixture was then heated at reflux for 20 hrs. The hot solution was then filtered through celite to remove residual zinc, washed with hot ethanol (10 ml), basified to ca. pH 10 (25% aq. NaOH), and heated at reflux for a further 8 hrs. The cooled reaction mixture was then acidified to pH3 (2M HCl) and extracted with ethyl acetate (3 x 100 ml). The combined extracts were washed with brine (30 ml), dried (MgSO<sub>4</sub>), filtered and evaporated to yield *6-(3,4-dimethoxy-6-carbohydroxymethylphenyl)-2-oxo-1-azaspiro [4.5]dec-8-ene*, 351*a* (157 mg, 38%), identified spectral data m/e 345 (EI, M<sup>+</sup>), 346 (CI);  $\nu_{\max}$  (KBr) 3400 (OH), 3220 (NH), 1715 (Acid C=O), 1645 (lactam, C=O) cm<sup>-1</sup>; (b) Crude lactam-acid, 351*a*, (50 mg, 0.14 mmol) was dissolved in methanol (50 ml), and concentrated sulphuric

acid (0.5 ml) added. The mixture was heated at reflux for 20 hrs, then allowed to cool. Most of the methanol was then removed *in vacuo*, and to the residue was added water (30 ml). This mixture was then extracted with dichloromethane (3 x 75 ml), and the combined extracts washed sequentially with 30 ml portions of (i) 20% aq. Na<sub>2</sub>CO<sub>3</sub>, (ii) brine, then dried (MgSO<sub>4</sub>), filtered and evaporated. Lactam-ester, 351*l*, (47 mg, 90%) was obtained as a white powder. (Overall yield from 350*l*, 34%); mp 163-165°C; m/e 359 (EI, M<sup>+</sup>), 360 (CI); Calculated for C<sub>20</sub>H<sub>25</sub>NO<sub>5</sub> C 66.9, H 7.0, N 3.9; found C 66.7, H 7.0, N 3.2%;  $\nu_{\max}$  (KBr) 3180, 3010, 2930, 1850, 1738, 1687, 1607, 1516, 1437, 1367, 1329, 1309, 1284, 1263, 1227, 1157, 1095, 1011, 895, 870, 758, 665, 570, 520 cm<sup>-1</sup>;  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 178.2, 171.9, 148.2, 147.4, 132.2, 127.6, 124.5, 113.5, 110.2, 60.4, 55.7, 52.1, 41.8, 40.8, 38.7, 31.5, 30.9, 30.4 ppm. Methoxy carbons coincident at 55.7 ppm. Two aromatic carbons coincident at 110.2 ppm.

6-(3,4-dimethoxy-6-carbethoxymethylphenyl)-2-oxo-1-azaspiro[4.5]dec-8-ene (351*c*) - To a stirring solution of nitro-diester 350*l* (1.013 g, 2.4 mmol) in ethanol (50 ml) and concentrated hydrochloric acid (8 ml), was added activated zinc dust (9 g) in small portions over 20 mins, during which time the temperature rose to ca. 60°C. The mixture was then heated at reflux for 15 hrs. The hot solution was filtered through Celite to remove residual zinc, being washed through with glacial acetic acid (ca. 25 ml), and evaporated to give a pale gum. To this gum was added water (30 ml), and this was extracted with dichloromethane (3 x 100 ml). The combined extracts were washed sequentially with (a) saturated sodium bicarbonate (30 ml), (b) brine (20 ml), then dried (MgSO<sub>4</sub>), filtered and evaporated to yield lactam-ester, 351*c* (790 mg, 91%), as a white powder; mp 172.5-174.5°C; m/e 373 (EI, M<sup>+</sup>), 374 (CI); Calculated for C<sub>21</sub>H<sub>27</sub>NO<sub>5</sub>

C 67.56, H 7.24, N 3.7, m/e 373.18892 ; found C 66.72, H 6.95, N 3.2%  
m/e 373.18767;  $\nu_{\max}$  (KBr) 3190, 3060, 3015, 2930, 2840, 1732, 1688,  
1608, 1518, 1450, 1310, 1288, 1263, 1228, 1159, 1097, 1050, 1011, 942,  
758, 665, 640, 520  $\text{cm}^{-1}$ ;

*7,8-dimethoxy-cyclohexeno[3,4-b]-(2-pyrrolidono)[1,5-a]-4-hydroxy-2,3,4,5-tetrahydro-3-benzazepine (359b)* - To a solution of lactam-ester 351c (0.23 g, 0.62 mmol) in freshly distilled, dry toluene (40ml) and dichloromethane (30 ml), cooled to  $-78^{\circ}\text{C}$ , was added under nitrogen, DIBAL-H solution (0.9 ml, 1.5 M in toluene, 1.35 mmol) in small portions over 45 mins. After addition was completed, the reaction mixture was stirred for a further 2 hrs at  $-78^{\circ}\text{C}$ , then quenched by addition of brine (30 ml), and warmed to r.t. over 30 mins. The aqueous layer was separated and extracted with ethyl acetate (3 x 100 ml), and the combined organic phases then washed with brine (10 ml), dried ( $\text{MgSO}_4$ ), filtered and evaporated. The crude product was adsorbed on to alumina, and column chromatography (alumina column, 30 x 1.5 cm) eluting with ethyl acetate, then 95:5 ethyl acetate-methanol provided unreacted lactam-ester (12 mg, 5%) further elution with 9:1 ethyl acetate-methanol then provided 3-benzazepinol, 359d, (183 mg, 91%) as a white solid; mp  $133-135^{\circ}\text{C}$ , m/e 329, 311 (EI,  $\text{M}^+$ ,  $\text{M}^+-18$ ), 330, 312 (CI); Analysis calculated for  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_4$ ; C 69.30%, H 6.99%, N 4.26%, found C 69.62%, H 7.32%, N 4.01%;  $\nu_{\max}$  (KBr) 3270, 3020, 2970, 2925, 2875, 1665, 1608, 1518, 1460, 1450, 1438, 1415, 1380, 1358, 1338, 1310, 1298, 1280, 1261, 1222, 1212, 1199, 1163, 1112, 1096, 1074, 1041, 1017, 978, 940, 868, 856, 807, 783, 744, 688, 662, 633, 590, 528  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 6.91 (1H, s), 6.73 (1H, s), 6.07-5.91 (2H, m), 5.6 (1H, s), 3.88 (3H, s), 3.84 (3H, s), 3.21-3.15 (2H, m), 3.09-3.01 (2H, m), 2.67 (2H, br, s), 2.45-2.3 (3H, m), 1.86-1.76 (3H, m);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 176.1, 147.6, 147.3, 131.0, 128.1, 127.9, 125.0, 114.3, 112.3, 72.1, 65.0, 56.1, 55.8, 44.8, 39.6, 32.3, 31.5, 29.1, 28.8;

$\delta_{\text{C DEPT}} (\text{CDCl}_3)$  ( $\text{CH}_1, \text{CH}_3$ ) : 127.9, 125.1, 114.3, 112.3, 72.2, 56.1, 55.8, ( $\text{CH}_2$ ) : 44.8, 39.7, 32.4, 31.6, 29.2, 28.9 ppm.

*7,8-dimethoxy-cyclohexeno[3,4- $\beta$ ]-pyrrolidino[1,2- $\alpha$ ]-2,3,4,5-tetrahydro-3-benzazepine (375)* - To a stirring suspension of LAH (200 mg, 5.3 mmol) in rigorously dried, freshly distilled THF (15 ml) was added  $\alpha$ -hydroxy-lactam, <sup>359d</sup>, (30 mg, 0.1 mmol) at a rate sufficient to maintain gentle reflux. The stirring mixture was then heated at reflux for 48 hrs. It was then allowed to cool to r.t., then further cooled in an ice-salt bath to ca.  $-5^\circ\text{C}$ . Water (0.5 ml) was then cautiously added dropwise, with efficient stirring, over 30 mins, followed by sodium hydroxide solution (aq. 30%, 1 ml) in portions over 20 mins. The mixture was then allowed to stir a further 1 hr, warming to  $18^\circ\text{C}$ . The resulting solution was then filtered from the white inorganic residues, brine (10 ml) added, and the aqueous layer extracted with diethyl ether (3 x 30 ml). The combined organic phases were then washed with brine (10 ml), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated to yield a pale brown gum, tentatively assigned as amine 375 (21 mg, 80%) from spectral data;  $m/e$  300 (CI);  $\nu_{\text{max}}$  (KBr) 2958, 2910, 1625, 1610, 1579, 1495, 1460, 1440, 1410, 1380, 1335, 1261, 1095, 1041, 865, 800, 700,  $658 \text{ cm}^{-1}$ ;

*6-(3,4-dimethoxy-6-[2-hydroxyethyl]phenyl)-1-azaspiro[4.5]dec-8-ene (374)* - To a stirring suspension of LAH (0.5 g, 13 mmol) in rigorously dried, freshly distilled THF (20 ml), was added lactam-ester, <sup>357c</sup> (0.1 g, 0.3 mmol) at a rate sufficient to maintain gentle reflux. The reaction mixture was then heated at reflux for 48 hrs, before being allowed to cool to r.t. It was then cooled to ca.  $-5^\circ\text{C}$  in an ice-salt bath, and water (0.2 ml) added dropwise over 30 min.

Sodium hydroxide solution (30% aq. 0.8 ml) was then added in portions over 15 mins. The mixture was then allowed to warm to r.t., with stirring, over 1 hr, and the solution then filtered from the inorganic residues. Brine (10 ml) was added, and the mixture extracted with diethyl ether (3 x 30 ml), the combined extracts being washed with brine (10 ml), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and evaporated, to yield a t.l.c. homogeneous gum, whose mass spectrum was inconsistent with a benzazepine and which was not further investigated. m/e 319 (EI,  $\text{M}^{+2}$ ), 319 (CI).

*Trans-1-(3,4-methylenedioxy-6-nitrophenyl)-2-nitroethene, (396)*  
- 6-nitropiperonal (10.3 g, 53 mmol), potassium fluoride (0.7 g, 12 mmol), 18-Crown-6 (0.29 g, 1 mmol) and nitromethane (14.1 g, 230 mmol), were stirred in 2-propanol at room temperature for 5 hrs. Acetic acid (1 ml) was then added, and the 2-propanol and excess nitromethane evaporated *in vacuo*. To the resulting crude orange solid was then added acetic anhydride (100 ml) and sodium acetate (1.2 g, 0.015 mol). The mixture was stirred at r.t. for 12 hrs, and then poured into ice water (100 ml). This was allowed to warm to r.t. with stirring, and after several hours a yellow precipitate rapidly formed. This was filtered and thoroughly washed with cold water, and dried *in vacuo*, affording 396 as a yellow powder (11.38 g, 90%); mp 111-112.5°C. Calculated for  $\text{C}_9\text{H}_6\text{N}_2\text{O}_6$  C 45.38, H 2.52, N 22.76; found C 45.08, H 2.42, N 11.53%;  $\nu_{\text{max}}$  (KBr) 3105, 3060, 2917, 1638, 1600, 1510, 1482, 1430, 1340, 1274, 1031, 975, 95<sup>-</sup>, 913, 872, 857, 809, 759, 735, 595, 557, 505 408  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 8.53, 8.48 (1H, d, J = 13.5 Hz), 7.66 (1H, s), 7.41, 7.35 (1H, d, J = 13.5 Hz), 6.24 (2H, s);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 152.4, 150.4, 143.6, 139.2, 135.7, 122.4, 107.6, 106.5, 103.9 ppm.

*Trans-4-(3,4-methylenedioxy-6-nitrophenyl)-5-nitrocyclohexene*  
(307) - Compound 396 (9.7 g, 0.04 mol), butadiene sulphone (24.8 g, 0.2 mol), hydroquinone (0.2 g, 1.8 mmol) and toluene (150 ml) were charged in a 400 ml steel bomb, and heated at 130°C for 7 days. The cooled contents of the bomb were then filtered and evaporated, yielding a dark gum. This was extracted with boiling diethyl ether (4 x 100 ml), the hot extracts being filtered, then evaporated. The resulting tacky brown gum was then recrystallized from methanol (100ml), affording tan crystals of 397 (9.5 g, 75%); mp 135-136°C; m/e 292 (EI, M<sup>+</sup>), CI (310, M + NH<sub>4</sub><sup>+</sup>); Calculated for C<sub>13</sub>H<sub>12</sub>NO<sub>6</sub> C 53.43, H 4.11, N 4.59; found C 53.44, H 4.08, N 9.33%  $\nu_{\max}$  (KBr) 3045, 3000, 2905, 2850, 1618, 1555, 1505, 1485, 1427, 1400, 1372, 1344, 1308, 1251, 1220, 1198, 1161, 1118, 1040, 983, 932, 872, 821, 769, 724, 677, 593, 563 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 7.34 (1H, s), 6.83 (1H, s), 6.1 (2H, s), 5.81-5.76 (2H, dt, J<sub>d</sub> = 6.1, J<sub>t</sub> = 10.2 Hz), 5.0-4.97 (1H, dt, J<sub>d</sub> = 6.2, J<sub>t</sub> = 10.2 Hz) 4.19-4.17 (1H, dt, J<sub>d</sub> = 5.6, J<sub>t</sub> = 10.8 Hz), 2.78-2.74 (4H, m);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 151.9, 147.0, 144.4, 131.3, 126.4, 122.6, 106.1, 105.9, 103.1, 85.9, 38.7, 32.7, 31.5 ppm

*4-(2-carbomethoxymethyl)-5-(3,4-methylenedioxy-6-nitrophenyl)-4-nitrocyclohexene (398)* - Compound 397 (1.92 g, 6.6 mmol) was dissolved in THF (15 ml) and t-butanol (25 ml), methyl acrylate (0.75 g, 8.7 mmol), and triton-B (0.5 ml) added. The orange, solution rapidly darkened, and was stirred at r.t. for 48 hrs. The crude reaction mixture was evaporated onto alumina, and dried *in vacuo*. The mixture was then chromatographed (alumina column, 21 x 3 cm), eluting with hexanes, followed by 1:1 hexanes-ethyl acetate, affording 398 as a pale yellow-brown solid (2.13 g, 86%); mp 130-132°C; m/e 332 (EI, M<sup>+</sup>-NO<sub>2</sub>), 396 (CI, M+NH<sub>4</sub><sup>+</sup>); Calculated for C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>8</sub> C 53.97, H 4.76, N 7.41; found C 53.95, H 4.95, N 7.02%;  $\nu_{\max}$  (KBr) 3080, 2946, 2916,



2888, 1730, 1614, 1530, 1508, 1490, 1441, 1389, 1349, 1319, 1289, 1265, 1240, 1200, 1042, 930, 880, 823, 778, 762, 755, 670, 548  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 7.27 (1H, 2), 6.90 (1H, s), 6.09 (2H, s), 5.96-5.81 (2H, m), 4.48, 4.43 (1H, t,  $J = 11.6$  Hz), 3.66 (3H, s), 2.92-2.18 (8H, m);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 172.3, 151.3, 147.0, 145.3, 129.7, 126.2, 123.8, 107.8, 105.8, 103.0, 91.1, 52.0, 38.8, 32.7, 30.7, 30.4, 28.4 ppm.

6-(3,4-methylenedioxy-6-nitrophenyl)-2-oxo-1-azaspiro[4.5]dec-8-ene (399) - Dinitro-ester 398 (1.01 g, 2.7 mmol) was dissolved in ethanol (55 ml) and conc. HCl (6 ml). To this stirring solution was added activated zinc dust (5.8 g, excess) in small portions over 15 mins. The temperature rose to ca.  $55^{\circ}\text{C}$ , and the solution became a bright orange colour. This was then heated at reflux, for 12 hrs. The hot mixture was then filtered through a pad of Celite, which was washed through with hot ethanol. The solution was then evaporated *in vacuo*, 20% aq. NaOH (50 ml) added, and this then extracted with chloroform (3 x 100 ml). The combined organic extracts were washed with brine (50 ml), dried ( $\text{MgSO}_4$ ), filtered and evaporated to yield crude 399 as a pale orange, solid (550 mg, 72%). Chromatography (alumina column, 30 x 3 cm), eluting with 25:5, through 9:1, to 4:1 ethyl acetate-methanol, provided a pale pink solid, showing impurity by IR and t.l.c. Repeated chromatography (alumina column, 20 x 3 cm), eluting with 9:1 ethyl acetate-methanol, provided pure 399 (370 mg, 55%) as a pale straw powder. mp  $234\text{-}236^{\circ}\text{C}$ ; m/e 286 (EI,  $\text{M}^+$ ), 287 (CI); Calculated for  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3$  C 67.13, H 6.29, N 9.79; found C 66.96, H 6.41, N 9.53%;  $\nu_{\text{max}}$  (KBr) 3420, 3388, 3350, 3242, 3031, 2919, 2879, 1682, 1642, 1499, 1482, 1436, 1407, 1254, 1237, 1191, 1164, 1040, 933, 873, 678, 608,  $516\text{ cm}^{-1}$ ;  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 177.6, 146.5, 144.0, 141.4, 138.6, 127.4, 125.0, 107.5, 107.3, 101.0, 60.2, 45.4, 40.6, 37.5, 32.3, 30.3 ppm.

6,7-methylenedioxy-cyclohexeno[3,4-c]-3-(3-hydroxypropyl)-3,4-dihydrocinnoline (405) - LAH (0.8 g, 21 mmol) was suspended in diethyl ether (40 ml), and dinitro-ester 398 (500 mg, 1.3 mmol), added in small portions over 5 mins. The mixture was then warmed to reflux, whereupon the suspension became a sandy brown colour, progressively changing to a deep maroon colour, over 1-2 hrs. After 8 hrs reflux, the mixture was cooled in an ice-salt bath, and water (1 ml) added dropwise over 30 mins, 24% aq. NaOH (3 ml), was then added in 3 portions over 10 mins. The resulting mixture was then stirred for 30 mins, during which time it became a bright yellow colour. The yellow solution was filtered off from the precipitate, which was washed with several portions of diethyl ether. The organic solution was washed with brine (15 ml), dried ( $\text{MgSO}_4$ ), and filtered. Chromatography (alumina column, 26 x 2 cm), eluting with ethyl acetate, followed by 9:1 ethyl acetate-methanol, provided the bright yellow 405 (240 mg, 65%) as a gum. it could be temporarily solidified by rapid evaporation of a diethyl ether solution *in vacuo*, but reverted to a gum on several hours standing. Calculated for  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3$  m/e 286.13172; found m/e 286.12822; m/e = 287 (CI);  $\nu_{\text{max}}$  (KBr) 3400, 3020, 2900, 1615, 1501, 1470, 1435, 1362, 1288, 1263, 1193, 1033, 930, 860, 818, 739, 656  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 7.25 (1H, s), 6.47 (1H, s), 5.86 (2H, s), 5.52 (2H, s), 3.43-3.37 (2H, t, J = 5.8 Hz), 2.47-2.26 (1H, m), 2.12-2.0 (2H, m), 1.91-1.81 (1H, m), 1.65-1.46 (4H, m). 1.1 (1H, m);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 149.9, 146.7, 137.9, 126.1, 125.3, 122.0, 109.7, 105.1, 101.8, 63.3, 62.9, 32.0, 31.1, 30.9, 27.1, 26.3 ppm.

7,8-methylenedioxy-cyclohexeno[3,4-d]-(2-pyrrolidono)[1,5-c]-1,2,4,5-tetrahydro-1,3-benzodiazepine (403) - Lactam-amine 399 (70 mg, 0.25 mmol) was dissolved in ethanol (3 ml), and formaldehyde (0.3 ml, 3% aq. sol<sup>n</sup>.) was added. The mixture was stirred at 20°C for

1 hr, then heated at reflux for 10 hrs. The cooled mixture was then evaporated *in vacuo*, and chromatographed (alumina column, 25 x 1.5 cm), eluting with ethyl acetate, to afford the 1,3-benzodiazepine derivative 403 (52 mg, 71%) as a white solid; mp > 240°C; m/e 298 (EI, M<sup>+</sup>), 299 (CI); Calculated for C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> C 68.46, H 6.04, N 9.4; found C 68.36 H 5.92, N 8.92%;  $\nu_{\max}$  (KBr) 3018, 2693, 2892, 2873, 1690, 1483, 1412, 1308, 1257, 1190, 1172, 1153, 1118, 1084, 1039, 970, 932, 873, 852, 837, 804, 790, 752, 720, 702, 643, 488 cm<sup>-1</sup>.  $\delta_C$  (CDCl<sub>3</sub>) 172.5, 145.9, 145.4, 143.4, 128.4, 126.1, 125.9, 109.1, 108.7, 100.9, 68.9, 61.5, 55.6, 43.3, 30.4, 29.9, 29.0, 28.6 ppm.

*6-(3,4-methylenedioxy-6-aminophenyl)-1-azaspiro[4.5]dec-8-ene* (401) - LAH (0.7 g, 18 mmol) was suspended in freshly distilled THF (35 ml), and lactam-amine 399 (233 mg, 0.8 mmol) added at a rate sufficient to maintain gentle reflux. The mixture was then stirred at reflux, under nitrogen, for 56 hrs. The mixture was then cooled to ca. -5°C, and water (1 ml) added dropwise, with efficient stirring, over 30 mins. 30% aq. NaOH (3 ml) was then added in small portions over 10 mins. The mixture was stirred, while warming to r.t., over 2 hrs. The resulting solution was filtered off the solid residues, and washed with 10% aq. Na<sub>2</sub>CO<sub>3</sub> (10 ml), then brine (10 ml). The organic solution was then dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated to yield a pale brown gum, assigned structure 401 on the basis of high resolution mass spectral data (200 mg, 95%). T.l.c. evidence indicated a single major product. Calculated for C<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub> m/e 272.15248; found 272.14872; m/e 273 (CI).

*7,8-methylenedioxy-cyclohexeno[3,4-d]-pyrrolidino[1,2-c]-2-phenyl-1,2,4,5-tetrahydro-1,3-benzodiazepine* (402) - Assigned diamine 401 (74 mg, 0.27 mmol) was dissolved in ethanol (3 ml), and benzalde-

hyde (32 mg, 0.3 mmol) added. The mixture was stirred for 20 hrs at 20°C, then evaporated *in vacua*. Chromatography (alumina column, 25 x 1.5 cm), eluting with 1:1 hexanes-ethyl acetate, through to ethyl acetate, provided fractions containing two similar materials. The more mobile material (t.l.c.,  $rf \approx 0.3$  with 1:1 hexanes-ethyl acetate) appeared to be by far the major product as judged by t.l.c. From mass spectral data the products were provisionally assigned as the insertion reaction isomers, 402a and 402b (68 mgs, 70%). Calculated for  $C_{23}H_{24}N_2O_2$  m/e 360.18378; found m/e 360,17442; m/e 361 (CI).

*Trans-1-(3,4-methylenedioxyphenyl)-2-nitro-4,5-epoxycyclohexane (411)*

To a stirring solution of 239 (595 mg, 2.4 mmol) in dry dichloromethane (10 ml), was added MCPBA (700 mg, ca. 3.5 mmol) in dry dichloromethane (10 ml), in portions over 40 mins. The mixture was stirred at ambient temperature for 18 hrs, during which time some precipitate deposited. The reaction mixture was then cooled to ca.  $-10^{\circ}\text{C}$  in an ice-acetone bath, causing more *m*-chlorobenzoic acid to precipitate. This was filtered, and the precipitate washed with cold dichloromethane (10 ml). The filtrate was washed sequentially with 10 ml portions of (a) saturated aq. sodium bisulfite; (b) water, dried ( $\text{MgSO}_4$ ), and filtered through a pad of  $\text{MgSO}_4$ . Evaporation yielded crude epoxide, 411, as a pale yellow solid, with IR indicating presence of *m*-chlorobenzoic acid impurity (carbonyl stretch at  $\nu_{\text{max}}$   $1700\text{ cm}^{-1}$ ). Column chromatography (alumina, 23 cm x 3.5 cm) eluting with ethyl acetate afforded pure epoxide, 411, as a mixture of isomers (412 mg, 65%), as a white powder; mp  $121\text{--}123^{\circ}\text{C}$ ;  $m/e$  263 (EI,  $\text{M}^+$ ), 281 (CI,  $\text{M}+\text{NH}_4^+$ ). Calculated for  $\text{C}_{13}\text{H}_{13}\text{NO}_5$  C 59.32, H 4.94, N 5.32; found C 59.00, H 4.78, N 4.83%;  $\nu_{\text{max}}$  (KBr) 3005, 2910, 1609, 1547, 1504, 1486, 1440, 1373, 1244, 1190, 1106, 1034, 925, 897, 876, 832, 806, 632, 409  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 6.72–6.59 (3H, m), 5.92 (1H, s), 4.87–4.76 (1H, dt,  $J_{\text{d}} = 4.5$ ,  $J_{\text{t}} = 11.4$  Hz), 3.42 (1H, s), 3.25 (1H, s), 3.13–3.01 (1H, dt,  $J_{\text{d}} = 7$ ,  $J_{\text{t}} = 11.8$  Hz), 2.87–2.80 (1H, d,  $J = 14$  Hz), 2.49–2.4 (2H, m), 2.18–2.01 (1H, t,  $J \approx 14$  Hz);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 148.3, 147.5, 133.2, 121.3, 108.9, 101.6, 86.4, 53.3, 51.2, 43.8, 32.9, 31.5 ppm.

*6-(3,4-methylenedioxyphenyl)-8,9-epoxy-2-oxo-1-azaspiro[4.5]dec-8-ene (413, 414)* - To a stirring solution of spirolactam, 131a, (3.16 g, 11.7 mmol) in freshly distilled dichloromethane (35 ml), was added MCPBA (2.65 g, ca. 13 mmol) in dichloromethane (30 ml), in portions. The pale

yellow solution was stirred at ambient temperature for 15 hrs, then cooled to ca.  $-10^{\circ}\text{C}$ , whereupon a white precipitate formed. The solution was filtered, and washed sequentially with 10 ml portions of (i) 10% aq. sodium bisulfite, (ii) 10% aq.  $\text{Na}_2\text{CO}_3$ , (iii) brine, then dried ( $\text{MgSO}_4$ ), filtered and evaporated. The crude epoxide was chromatographed (alumina column, 27 cm x 4 cm), eluting with 85:15 ethyl acetate-methanol, to yield pure epoxide (3.12 g, 93%) as a mixture of isomers, 473 and 474 mp  $150-153^{\circ}\text{C}$ ; m/e 287 (EI,  $\text{M}^+$ ), 288 (CI),; Calculated for  $\text{C}_{16}\text{H}_{17}\text{NO}_4$  C 66.90, H 5.92, N 4.88; found C 66.87, H 6.03, N 4.45%;  $\nu_{\text{max}}$  (KBr) 3000, 2970, 2930, 2890, 1690, 1483, 1439, 1397, 1247, 1185, 1094, 1028, 923, 863, 818, 800, 701, 649, 610, 504,  $458\text{ cm}^{-1}$ ;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 8.83 (NH, s), 6.79-6.63 (3H, m), 5.94 (2H, s), 3.41-3.25 (2H, m), 2.75-2.69 (1H, dd,  $J_1 = 4.9$ ,  $J_2 = 12$  Hz), 2.5-1.63 (7H, m), 1.29-1.13 (1H, m);  $\delta_{\text{C}}$ ( $\text{CDCl}_3$ ) 179.5, 147.8, 146.9, 133.5, 122, 109.1, 108.4, 101.1, 59.8, 53.1, 50.4, 44, 40.4, 32.1, 30.5, 28.1 ppm.

*[Trans-4-(3,4-methylenedioxyphenyl)-5-nitro]-trans-1,2-dihydroxy cyclohexane (475)* - To a stirring mixture of 239 (0.5g, 2 mmol) and formic acid (1 g), was added hydrogen peroxide (1g, 30% aq.), and the mixture heated at  $55^{\circ}-60^{\circ}\text{C}$  for 30 mins, over which period it became homogeneous. Most of the formic acid was then removed *in vacuo*, and the residue (mono-formyl ester) hydrolysed by steam distillation, collecting ca. 70 ml aq. formic acid. The water was then evaporated (from the distillation flask) leaving a yellow-brown solid. Column chromatography (alumina column, 20 cm x 3 cm) eluting with 92:8 ethyl acetate-methanol provided trans-diol, 475, (0.4 g, 70%) as a white solid, mp  $190-192^{\circ}\text{C}$ ; m/e 281 (EI,  $\text{M}^+$ ), 299 (CI,  $\text{M}+\text{NH}_4^+$ ); Calculated for  $\text{C}_{13}\text{H}_{15}\text{NO}_6$  C 55.52, H 5.34, N 4.98; found C 55.76, H 5.39, N 4.63%;  $\nu_{\text{max}}$  (KBr) 3580, 3495, 3005, 2895, 1608, 1540, 1491, 1440, 1401, 1378, 1353, 1245, 1210, 1108, 1090, 934, 871, 849, 840, 826, 760, 721, 688, 635,  $438\text{ cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 7.41 (1H, s), 7.36-7.32 (2H m), 6.55 (2H, m), 5.65 (1H, dt,  $J_{\text{d}} = 3.8$ ,  $J_{\text{t}} = 11.8$  Hz), 4.6 (1H, s),

4.51 (1H, s), 4.19-4.08 (1H,  $\delta$ t,  $J_\delta = 3.5$ ,  $J_t = 12.4$  Hz), 3.18-3.07 (1H, t,  $J = 12.5$  Hz), 2.89-2.44 (4H, m);  $\delta_C$  (CDCl<sub>3</sub>) 147.2, 146.2, 133.9, 119.8, 107.2, 106.5, 100.3, 86.3, 67.9, 67.2, 40.5, 33.4, 32.5 ppm

*6-(3,4-methylenedioxyphenyl)-trans-8,9-dihydroxy-2-oxo-1-azaspiro [4.5]dec-8-ene (416)* - Lactam epoxides 413 and 414 (1.6 g, 5.6 mmol), were dissolved in methanol (30 ml), and 1% aq. H<sub>2</sub>SO<sub>4</sub> (20 ml) added. The mixture was stirred at r.t. for 10 hrs, then evaporated to yield a crude white solid. Chromatography (alumina column, 20 x 3 cm) eluting with 4:1 ethyl acetate-methanol, afforded pure trans-diol 416 (1.52 g, 89%), as a white powder; mp 155-156°C, m/e 305 (EI, M<sup>+</sup>), 306 (CI); Calculated for C<sub>16</sub>H<sub>29</sub>NO<sub>5</sub> C 62.95, H 6.23, N 4.59; found C 62.92, H 6.63, N 4.29%;  $\nu_{\max}$  (KBr) 3395, 2930, 2895, 1660, 1500, 1490, 1443, 1411, 1285, 1255 1042, 939, 828, 671, 520 cm<sup>-1</sup>.

*6-(3,4-methylenedioxyphenyl)-cis-8,9-dihydroxy-2-oxo-1-azaspiro [4.5]dec-8-ene (417)* - Lactam 131a (0.99 g, 3.65 mmol) was dissolved in THF (5 ml), t-butanol (35 ml) and acetone (10 ml), and N-methylmorpholine-N-oxide (442 mg, 3.78 mmol) added. To this stirring mixture was added osmium tetroxide (7 ml of 7 mg/ml solution in 90% aq. tert-butanol). After ca. 10 mins a slight darkening had occurred. The mixture was stirred at 30°C for 20 hrs, and then saturated aq. sodium bisulfite (15 ml) was added. The mixture was then stirred at r.t. for 30 mins, before being filtered through Celite. The resulting solution was evaporated, and acid brine (30 ml, pH 2) added. This was extracted with ethyl acetate (3 x 200 ml) and the combined extracts washed sequentially with 40 ml portions of (a) 20% aq. Na<sub>2</sub>CO<sub>3</sub>; (b) brine, dried (MgSO<sub>4</sub>), filtered and evaporated to yield crude cis diol, 417, (420 mg, 38%), as a white solid. Further extraction

with ethyl acetate, at reflux overnight, afforded a further 160 mg (14%) of crude diol. Column chromatography (silica gel column, 38 cm x 2 cm) eluting with 3:2 ethyl acetate-methanol, provided cis-diol, 417, (510 mg, 46%) as a white powder; mp 250.5 -252°C; m/e 305 (EI, M<sup>+</sup>), 306 (CI); Calculated for C<sub>16</sub>H<sub>19</sub>NO<sub>5</sub> C 62.9, H 6.2, N 4.6; ; found C 60.6, H 6.2, N 4.1% ;  $\nu_{\max}$  (KBr) 3555, 3290, 3165, 2910, 2860, 1664, 1500, 1488, 1395, 1318, 1262, 1190, 1103, 1068, 1046, 997, 947, 835, 812, 797, 651, 530, 513 cm<sup>-1</sup>.

*N*-(Carbomethoxymethyl)-6-(3,4-methylenedioxyphenyl)cis-8,9-dihydroxy-2-oxo-1-azaspiro[4.5]dec-8-ene (418a) - To a stirring solution of *N*-carbethoxy-lactam, 337, (0.5 g, 1.46 mmol) in acetone (10 ml), and tert-butanol (20 ml), was added *N*-methyldmorpholine *N*-oxide (185 mg, 1.58 mmol), followed by osmium tetroxide (10 ml, 1 mg/ml 90% aq. tert-butanol solution). The mixture was stirred at 30-35°C for 36 hrs, after which time it had darkened considerably. Saturated aq. sodium bisulfite (10 ml) was then added, the mixture stirred for 30 mins, then filtered through Celite and evaporated *in vacuo*. To the residue was added acidic (H<sub>2</sub>SO<sub>4</sub>) brine (20 ml, pH 1.5), which was then extracted with ethyl acetate (3 x 100 ml). The combined extracts were washed sequentially with 20 ml portions of (i) 10% aq. Na<sub>2</sub>CO<sub>3</sub>, (ii) brine, dried (MgSO<sub>4</sub>), filtered and evaporated to give cis-diol 418a, (514 mg, 93%) as a white solid. mp 85-87°C; m/e 377 (EI, M<sup>+</sup>), 378 (CI); Calculated for C<sub>19</sub>H<sub>24</sub>NO<sub>7</sub> C 60.5, H 6.1, N 3.7, m/e 377.14745; found C 59.6, H 6.2, N 3.1%, m/e 347.15561 :  $\nu_{\max}$  (KBr) 3400 3920, 1745, 1665, 1487, 1438, 1411, 1247, 1220, 1035, 930, 848, 805, 744, 700, 643, 505 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 6.68 (1H, m), 6.5 (2H, m), 5.89 (2H, s), 4.67, 4.60 (1H, d, J = 17.5 Hz), 4.06-3.65 (6H, m), 3.4 (2H, m), 3.1 (1H, t, J = 8.5 Hz), 2.18-1.86 (7H, m), 2.31-1.22 (1H, m);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 177.2, 169.6, 147.8, 146.8, 133.5, 122.0, 108.8, 108.5, 101.1, 67.8, 67.4, 66.2, 52.6, 46.4, 45.4, 40.0, 35.7, 34.9, 29.1 ppm.



7-Carboxaldehyde-6-(3,4-methylenedioxyphenyl)2-oxo-1-axaspiro[4.4]undec

-7-ene (422) - (a) To a stirring solution of cis-diol, 418a (212 mg, 0.7 mmol) in methanol (10 ml), was added periodic acid (135 mg, 0.7 mmol) in water (5 ml). The mixture was stirred at r.t. for 2 hrs, then saturated with sodium chloride, and extracted with ethyl acetate (3 x 75 ml). The combined extracts were washed with brine (20 ml), dried (MgSO<sub>4</sub>), filtered and evaporated (at <40°C) *in vacuo*, providing a gum, which on washing with diethyl ether and drying *in vacuo* yielded crude dialdehyde, 421 (208 mg, 98%) as a cream powder. The proton NMR showed two protons resonating at 9.8 ppm. The crude product was not purified further (see 5.1.i), and was used directly

(b) The crude dialdehyde, 421 (208 mg, 0.69 mmol) was dissolved in chloroform (1 ml) and loaded onto a column of basic alumina (30 cm x 1.5 cm). It was chromatographed (after allowing to stand on the column for 20 minutes), eluting with chloroform, to provide a single material, expected to be the aldol regioisomer, 422 (70 mg, 36%) as a gum. The product was obtained as an off white solid on triturating with diethyl ether, though on standing it became a gum.

Calculated for C<sub>16</sub>H<sub>16</sub>NO<sub>4</sub> (M<sup>+</sup>+1) m/e 286.10793; found m/e 286.10279;

δ<sub>H</sub> (CDCl<sub>3</sub>) 9.83 (CHO, s), 6.75 (1H, d, J = 7.9 Hz), 6.5-6.39 (2H, m).

5.94 (2H, s), 5.41 (1H, m), 2.57-2.45 (3H, m), 1.85-1.73 (4H, m);

δ<sub>C</sub> (CDCl<sub>3</sub>) 200.5, 177.1, 148.0, 146.7, 134.2, 121, 108.6, 101.2, 86.9,

71.4, 56.6, 54.2, 40.7, 32.3, 26.6 ppm. Two aromatic carbons coincident at 108.6 ppm.

*1-(2-Carbomethoxyethyl)-1-nitrocyclohexane (208k)* - Nitrocyclohexane (9.9 g, 0.08 mol) was dissolved in a mixture of dry tetrahydrofuran (100 ml) and *t*-butanol (200 ml); methyl acrylate (6.6 g, 0.08 mmol) and Triton-B (3 ml) were added and the mixture was stirred at 20°C for 48 hrs. The solvents were removed *in vacuo* and the residue extracted with ether (3 x 100 ml); the combined extracts were washed sequentially with 50 ml portions of (i) 1M HCl (ii) 20% aq. Na<sub>2</sub>CO<sub>3</sub> (iii) water, then dried (MgSO<sub>4</sub>) and evaporated to yield an oil which on distillation afforded compound 208k (14.1 g, 85%, bpt, 80°C at 0.5 mm Hg. Calculated for C<sub>10</sub>H<sub>17</sub>NO<sub>4</sub> C 55.8, H 7.9, N 6.5; found C 55.8, H 8.2, N 6.3%;  $\nu_{\max}$  (neat) 2940, 2861, 1743, 1537, 1445, 1350, 1305, 1203, 1175, 992, 897 and 845cm<sup>-1</sup>;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) 3.82 (3H, s), 2.5 (6H, m), 1.85 (5H, m) and 1.6 (3H, s);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 172.1, 90.7, 51.3, 35.0, 33.7, 27.9, 24.7 and 22.4 ppm.

*2-Oxo-1-azaspiro[4.5]decane (210)* - Nitroester 208k (5.7 g, 0.027 mmol) was dissolved in ethanol (200 ml) and conc. hydrochloric acid (30 ml). Activated zinc dust (20 g) was added in portions with stirring, and the mixture was stirred at reflux for 16 hrs, then filtered hot. The cooled filtrate was basified to pH 9 with 40% aqueous NaOH and then refluxed for a further 3 hrs. The mixture was again filtered hot and evaporated. The residue was dissolved in water (50 ml) and extracted into dichloromethane. The organic layer was dried (MgSO<sub>4</sub>) and evaporated to yield compound 210 as a white powder (3.0 g, 75%). Analytical samples of 210 mp 134–135°C (lit.<sup>109</sup> mp 132.2–132.3°C) were obtained by vacuum sublimation (70–90°C at 0.5 mm Hg) or column chromatography on Al<sub>2</sub>O<sub>3</sub> (eluent ethyl acetate: methanol 4:1 v/v). Calculated for C<sub>9</sub>H<sub>15</sub>NO C 70.6, H 9.8, N 9.2; found C 70.8, H 9.6, N 8.8%; Mass spec. m/e 153 (EI), 154 CI, M<sup>+</sup>);  $\nu_{\max}$  (KBr)

3200, 2920, 2860, 1690, 1455, 1428, 1376, 1344, 1280, 1264, 1215, 1170, 1005, 988, 935, 900, 850, 744, 653, 611 and 512  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 7.98 (NH, s), 2.39 (2H, t), 1.88 (2H, t), 1.56-1.45 (10 H, m);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 177.7, 59.5, 38.3, 32.7, 30.1, 25.2, 22.9 ppm

*2-Thio-1-azaspiro[4.5]decane (435)* - A mixture of lactam 270 (0.8 g, 4.7 mmol), phosphorous pentasulphide (2.4 g, 5.4 mmol) in dry benzene (80 ml) was stirred at reflux for 3 hrs and then cooled to  $0^{\circ}\text{C}$ . The mixture was basified to pH 9 with 20% aq. NaOH to yield a yellow precipitate. The mixture was extracted with toluene-petroleum ether (2:1 v/v) and the organic layer washed sequentially with some portions of (i) NaCl solution, (ii) 10%  $\text{Na}_2\text{CO}_3$  solution, (iii) water, then dried ( $\text{MgSO}_4$ ) and evaporated to yield the product as a white powder (0.89 g, 100%). Chromatography on an alumina column eluted with ethyl acetate:hexane mixtures (1:1 followed by 1:5 v/v) gave thiolactam 435 (0.64 g, 73%) mp  $144.5\text{--}146^{\circ}\text{C}$ ; Calculated for  $\text{C}_9\text{H}_{15}\text{N}_5$  C 63.9, H 8.9, N 8.3; found C 63.3, H 9.0, N 7.9%; Mass spec. m/e 169 (EI), 170 CI,  $\text{M}^+$ );  $\nu_{\text{max}}$  (KBr) 3030, 3000, 2930, 2845, 1540 (C=S) 1445, 1418, 1370, 1340, 1292, 1258, 1180, 1105, 1076, 796  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 9.52 (NH, s), 2.96 (2H, t), 1.99 (2H, t), 1.65 (6H, m) and 1.44 (4H, m);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 203.5, 69.4, 45.1, 37.7, 34.9, 25.6 and 23.8 ppm.

*1-Azaspiro[4.5]decane(437)* - Lithium aluminium hydride (0.9 g) was suspended in rigorously dried ether (25 ml) and lactam 270 (0.688 g, 4.5 mmol) was added in small portions at a rate sufficient to maintain gentle reflux. The mixture was then refluxed with stirring for 72 hrs, and then cooled to  $-5^{\circ}\text{C}$ . Water (1 ml) was added dropwise, followed by 20% aq. NaOH (3 ml) in portions over 1 hr and then water (1 ml). The clear solution was filtered and the organic layer washed sequentially with (i) 10% aq.  $\text{Na}_2\text{CO}_3$  (ii) NaCl solution, dried ( $\text{MgSO}_4$ ) and evaporated to yield compound 437 as a pale yellow oil (0.5 g, 80%). Calculated for  $\text{C}_9\text{H}_{17}\text{N}$  m/e 139.1361;

found 139.1346;  $\nu_{\max}$  (neat) 3250, 2920, 2850, 1450, 1105 and 920  $\text{cm}^{-1}$ ;  
 $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 2.96 (2H, broad s,  $\text{CH}_2$  adjacent to NH), 1.9 (2H, m and 1.7-1.2  
(13H, m);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 61.7, 45.2, 38.1, 36.5, 25.9, 25.4 and 23.9 ppm

*2-Thio-1-azaspiro[4.5]decan-5-methiodide salt (436)* - Thiolactam 435,  
(0.96 g, 5.7 mmol) was dissolved in dry tetrahydrofuran (150 ml) and methy-  
liodide (2.0 g, 14 mmol) was added. The solution was stirred at 20°C in  
the dark for 18 hrs. The resulting precipitate was filtered and washed  
with ether (50 ml) to afford pure methiodide salt 436 (1.73 g, 98%) as a  
white powder mp 199-200°C; Calculated for  $\text{C}_{10}\text{H}_{18}\text{NSI}$  C 38.6, H 5.8, N 4.5;  
found C 38.3, H 6.0, N 4.2%; Mass spec m/e 184 (EI,  $\text{M}^+$ );  $\nu_{\max}$  (KBr) 3000,  
2920, 2858, 2800, 1590, 1452, 1400, 1348, 1263, 1182 and 1065  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$   
( $\text{CDCl}_3$ ) 3.24 (2H, t), 3.05 (3H, s), 2.43 (2H, m), 2.22 (2H, t) and 1.90-  
1.30 (8H, m) (NH not observed);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 189.1, 37.1, 35.8, 31.7, 24.1,  
23.2 and 19.2 ppm (spiro carbon at ca. 77 ppm concealed by solvent peaks).

*2-Methylthio-1-azaspiro[4.5]deca-1-ene (438)* - Salt 436 (1.6 g,  
3.4 mmol) was suspended in ether (70 ml) to which 20% aqueous  $\text{K}_2\text{CO}_3$  solu-  
tion (50 ml) was added, and the mixture was stirred at room temperature  
for 1 hr. The ether layer was separated and worked up as usual to afford  
compound 438 as a pale yellow liquid (0.62 g, 99%), shown by t.l.c. ana-  
lysis [ $\text{Al}_2\text{O}_3$  plate, eluent hexane:ethyl acetate (1:1 v/v)] to be pure pro-  
duct although satisfactory microanalytical data could not be obtained.  
Calculated for  $\text{C}_{10}\text{H}_{17}\text{NS}$  C 65.6, H 9.3, N 7.65; m/e 183.1082; found C 62.7,  
H 8.9, N 6.6%, m/e 183.1038.  $\nu_{\max}$  (neat) 2925, 2858, 1595, 1450, 1309,  
1290, 1175, 1155, 1080 and 1055  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 2.48 (2H, t), 2.28 (3H,  
s) and 1.68-1.23 (12 H, m);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 166.9, 76.4, 37.7, 33.8, 25.6, 23.6  
and 13.6 ppm

*1-(1-Carboethoxymethyl)-1-azaspiro[4.5]decane (440)* - Compound 437 (209 mg, 1.5 mmol) was dissolved in dry acetonitrile (20 ml) and anhydrous potassium carbonate (209 mg, 1.5 mmol), 18-Crown-6 (3 mg) and bromoethyl-acetate (254 mg, 1.5 mmol) were added. The mixture was stirred and refluxed under nitrogen for 24 hrs. The mixture was cooled, filtered and evaporated and the residue chromatographed on an alumina column [eluant hexane:ethyl acetate (1:1 v/v)] to yield a pale yellow oil (335 mg, 99%). Satisfactory microanalytical data were not obtained, although all other data implied a pure sample. Calculated for  $C_{13}H_{23}NO_2$  m/e 225.1729; found 225.1667;  $\nu_{\max}$  (neat 2940, 2860, 2800, 1760, 1450, 1370, 1180 and 1040  $cm^{-1}$ );  $\delta_H$  ( $CDCl_3$ ) 4.24 (2H, q), 3.85 (1H, s), 3.42 (1H, s), 2.27-1.10 (19H, m);  $\delta_C$  ( $CDCl_3$ ) 172.0, 63.7, 60.5, 51.4, 50.3, 33.5, 32.3, 26.1, 24.2, 21.0 and 14.2 ppm.

*1-(2-Carbomethoxyethyl)-1-nitrocyclopentane (208a)* - This compound was prepared from nitrocyclopentane, analogously to compound 208 and isolated as an oil in 88% yield. Calculated for  $C_9H_{15}NO_4$  C 53.7, H 7.5, N 7.3; found C 54.0, H 7.6, N 7.3%; Mass spec. m/e 155 ( $M^+ - NO_2$ );  $\nu_{\max}$  (neat) 2960, 2880, 1743, 1538, 1440, 1360, 1200, 1180 and 845  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 3.65 (3H, s), 2.5 (2H, m), 2.1 (4H, s) and 1.8 (6H, m);  $\delta_C$  ( $CDCl_3$ ) 172.6, 99.3, 51.8, 37.2, 34.4, 29.8 and 24.4 ppm

*2-Oxo-1-azaspiro[4.4]decane (209)* - This compound was prepared from nitro-ester 208a, analogously to compound 210 in 50% yield, white powder, mp 127-129°C (after sublimation), (lit.<sup>109</sup> mp 125.6-126.2°C). Calculated for  $C_8H_{13}NO$  C 69.1, H 9.4, N 10.1; found C 68.9, H 9.6, N 9.6% Mass spec. m/e 140 (CI,  $M^+$ );  $\nu_{\max}$  (KBr) 3160, 3078, 2940, 2870, 1688, 1463, 1434, 1380, 1260, 1035, 945, 930, 780, 645, 555, 520 and 420  $cm^{-1}$ ;  $\delta_H$  ( $CDCl_3$ ) 7.22 (NH, s), 2.32 (2H, t), 1.94 (2H, t) and 1.65 (8H, m);  $\delta_C$  ( $CDCl_3$ )

177.9, 67.2, 39.1, 33.6, 31.0 and 23.1 ppm.

APPENDIX I

FUTURE WORK

## I.1 Ring C

Our methodology for construction of the seven-membered 3-benzazepine ring C (4.1), provides the unknown 8-oxo-10-hydroxy ring D-ring C functionality. Removal of the hydroxy group (e.g. by mesylation, base-elimination and reduction), would yield the 8-oxo functionality, first reported in 1988 by Kuehne et al<sup>43</sup>.

While attempts to obtain the imide functionality by oxidation of 359~~6~~ were unsuccessful (4.1), an alternative ring closure may provide this unknown 8-oxo-10-oxo substitution (i.e. acid-lactam with DCC condensation). Further, DIBAL-H reduction of this should regioselectively reduce one carbonyl (possibly in the seven-membered ring), stereoselectively. This would provide a route to the 8-oxo-10-hydroxy system with the alternative 10 position relative stereochemistry.

Larger ring C analogues of cephalotaxine are unknown. The application of the methodology described earlier (4.1) to 3,4-methylenedioxyphenyl propionic acid, could provide a route to an eight-membered ring C cephalotaxine analogue.

## I.2 Ring D

Methodology for six-membered lactam azaspirocycles, via Arndt-Eistert homologation of the intermediate ester, has been described (2.1). Four-membered lactam azaspirocycles, however, are unknown; alkylation of 239 with bromoethylacetate should provide an appropriate intermediate for  $\beta$ -lactam cyclization, which would provide an interesting class of analogues.

The use of substituted methyl acrylates (see 2.2) could provide ring D substituted analogues. However, the problem of stereocontrol arises, and the alkylation being anti to the aromatic group suggests little likelihood of selectivity in formation of new stereocentres.



### I.3 Ring E

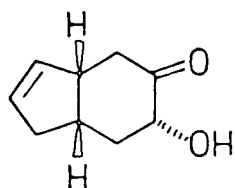
Clearly, as we have yet to construct ring E with the functionality present in cephalotaxine, initially work should be directed towards this goal, following three basic approaches, viz:

- (i) modification of the available cyclohexene ring E;
- (ii) alternative strategies, constructing ring E early as a five membered ring;
- (iii) asymmetric synthesis of a cyclohexene or other, ring E; elaboration towards (-) cephalotaxine.

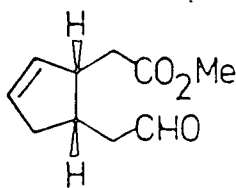
#### i Modifications of cyclohexene ring E

The general strategies available for entry to ring E pre-targets, already elaborated to cephalotaxine<sup>39,40,43</sup>, have been discussed above (5.1). Here, we will briefly describe other possible approaches to ring opened intermediates, and an alternative modification of cyclopentanone pre-target, 407.

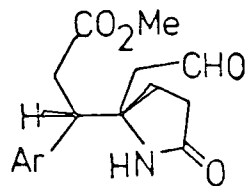
$\alpha$ -ketols are available from cyclic olefins<sup>433</sup>, cyclic 1,2-diols<sup>434,435</sup> or fused epoxides<sup>436</sup>, all functionalities which have already been obtained for ring E(5.1). Mild oxidative cleavage of cyclohexane -  $\alpha$ -ketols, e.g. 448, to ring opened ester-aldehydes, e.g. 449, has been reported<sup>437</sup>. This methodology therefore provides a potential route to intermediates such as 450, oxidation-esterification then cyclization affording  $\beta$ -keto-ester 451, or direct cyclization of 450 potentially providing  $\beta$ -keto-aldehyde, 452. Both 451 and 452 should provide access to the unsubstituted cyclopentanone ring E derivative.



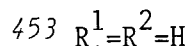
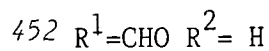
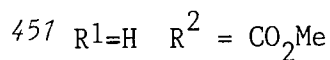
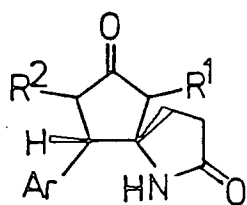
448



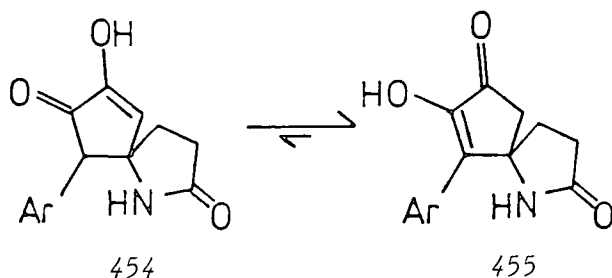
449



450



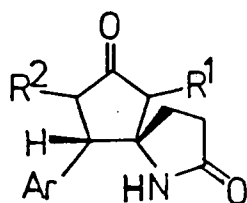
An alternative to the cyclopentanone modification of Hanaoka et al<sup>39</sup>, could be the application of Takeda's conversion of cyclohexanone to cyclohexa-1,2-dione<sup>438</sup>, to the cyclopentanone ring. This methodology converts cyclohexanones to  $\alpha$ -ketols, with the second oxygen introduced at the less hindered  $\alpha$ -position. In our intermediates, we might expect 453 to be converted to 454, tautomerizing to the further conjugated isomer 455.



This is functionality appropriate to demethylcephalotaxinone, 72, ring E intermediates of this type have already been converted to cephalotaxine ring E<sup>40</sup>.

## ii Alternative strategies for five-membered ring E

The early construction of ring E as a functionalized cyclopentane, would obviate modification of a cyclohexene ring E. A number of general annulation approaches can be envisaged: below are described four general strategies, three of which have precedents. The first of these involves modification of any of our  $\beta$ -nitrostyrene intermediates (see 2.2, 4.1 and 4.2), represented generally as 456, to the  $\beta$ -keto nitro derivative 457, (via epoxidation, reductive opening then oxidation, or epoxide oxidative rearrangement, for example). Alkylation with 2,3-dichloro-1-propene should then afford 458, which is very closely related to Hanaoka's intermediate 71<sup>39</sup>.

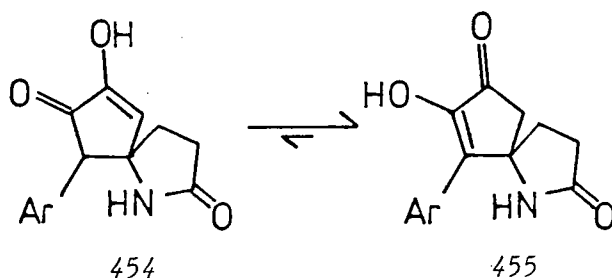


451  $R^1=H$   $R^2 = CO_2Me$

452  $R^1=CHO$   $R^2 = H$

453  $R^1=R^2=H$

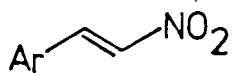
An alternative to the cyclopentanone modification of Hanaoka et al<sup>39</sup>, could be the application of Takeda's conversion of cyclohexanone to cyclohexa-1,2-dione<sup>438</sup>, to the cyclopentanone ring. This methodology converts cyclohexanones to  $\alpha$ -ketols, with the second oxygen introduced at the less hindered  $\alpha$ -position. In our intermediates, we might expect 453 to be converted to 454, tautomerizing to the further conjugated isomer 455.



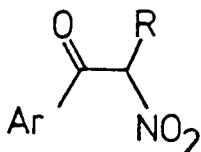
This is functionality appropriate to demethylcephalotaxinone<sup>12</sup>, ring E intermediates of this type have already been converted to cephalotaxine ring E<sup>40</sup>.

#### ii Alternative strategies for five-membered ring E

The early construction of ring E as a functionalized cyclopentane, would obviate modification of a cyclohexene ring E. A number of general annulation approaches can be envisaged: below are described four general strategies, three of which have precedents. The first of these involves modification of any of our  $\beta$ -introstyrene intermediates (see 2.2, 4.1 and 4.2), represented generally as 456, to the  $\beta$ -keto nitro derivative 457, (via epoxidation, reductive opening then oxidation, or epoxide oxidative rearrangement, for example). Alkylation with 2,3-dichloro-1-propene should then afford 458, which is very closely related to Hanaoka's intermediate 71<sup>39</sup>.

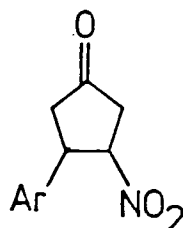


456



457 R=H

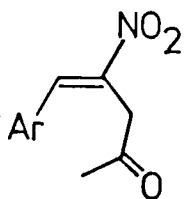
458 R=CH<sub>2</sub>C(Cl)CH<sub>2</sub>



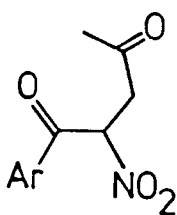
459

Reduction of 458 to the alcohol, and acid catalysed cyclization<sup>39, 439</sup> should similarly yield cyclopentanone intermediate, 459.

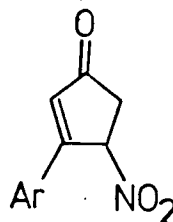
A related strategy is a Robinson-type annulation<sup>439</sup> to a cyclopentanone. The nitrostyrene, 460, should be available from an appropriate aromatic aldehyde and 4-nitro-butan-2-one. Conversion to the corresponding  $\beta$ -keto nitro intermediate, 461 (see above), should then allow for base-promoted cyclocondensation<sup>439</sup> to cyclopentenone 462.



460

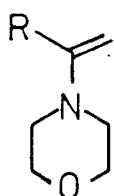
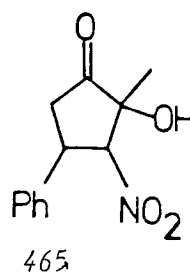
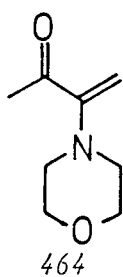
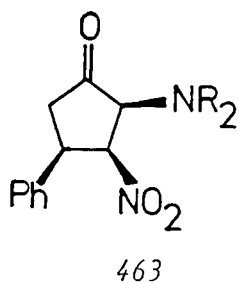


461

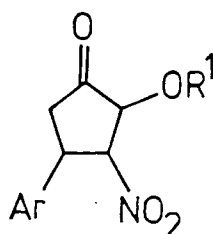


462

Enamines, e.g. 1-aminobutadiene, undergo (non-concerted) cycloadditions<sup>440</sup>, being particularly successful with nitrostyrene dieneophiles. Addition of 2,3-dimorpholino butadiene to  $\beta$ -nitrostyrene provided, after hydrolysis, reasonable yield of the amino-cyclopentanone, 463<sup>441</sup>. More recently, similar cycloaddition of the  $\alpha$ -ketoenamine 464 to  $\beta$ -nitrostyrene, yielded, after hydrolysis the  $\alpha$ -hydroxy-cyclopentanone, 465, in very good yield (and as a single diastereomer)<sup>442</sup>. The use of enamines 466a and 466b, could then provide mild entry to cyclopentanones 467a and 467b respectively (potentially diastereoselectively).

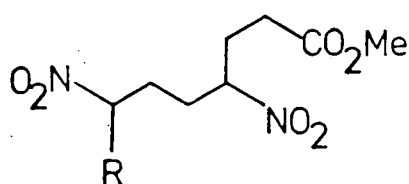


466 a R=CHO  
 & R=CH(OMe)<sub>2</sub>



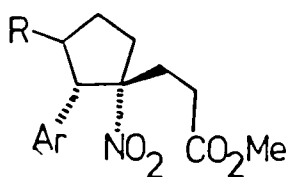
467 a R<sup>1</sup>=H  
 & R<sup>1</sup>=Me

A partly convergent strategy can be devised, in which dinitro-ester 468 (prepared by monoalkylation of 1,4-dinitrobutane) condenses with a  $\beta$ -nitrostyrene derivative, 456, to yield 469. Intramolecular Michael cyclization should then afford cyclopentones, 470a and 470b. Our reductive cyclization methodology (see 2.2) should then yield 471, and oxidation of 471 should provide cyclopentanone, 472<sup>443-445</sup>.



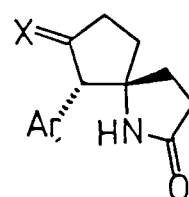
468 R=H

469 R= =CHAR



470 a R= .....NO<sub>2</sub>

& R= >NO<sub>2</sub>



471 X= ~~~~~NH<sub>2</sub>

472 X= = O

### iii Asymmetric construction of E?

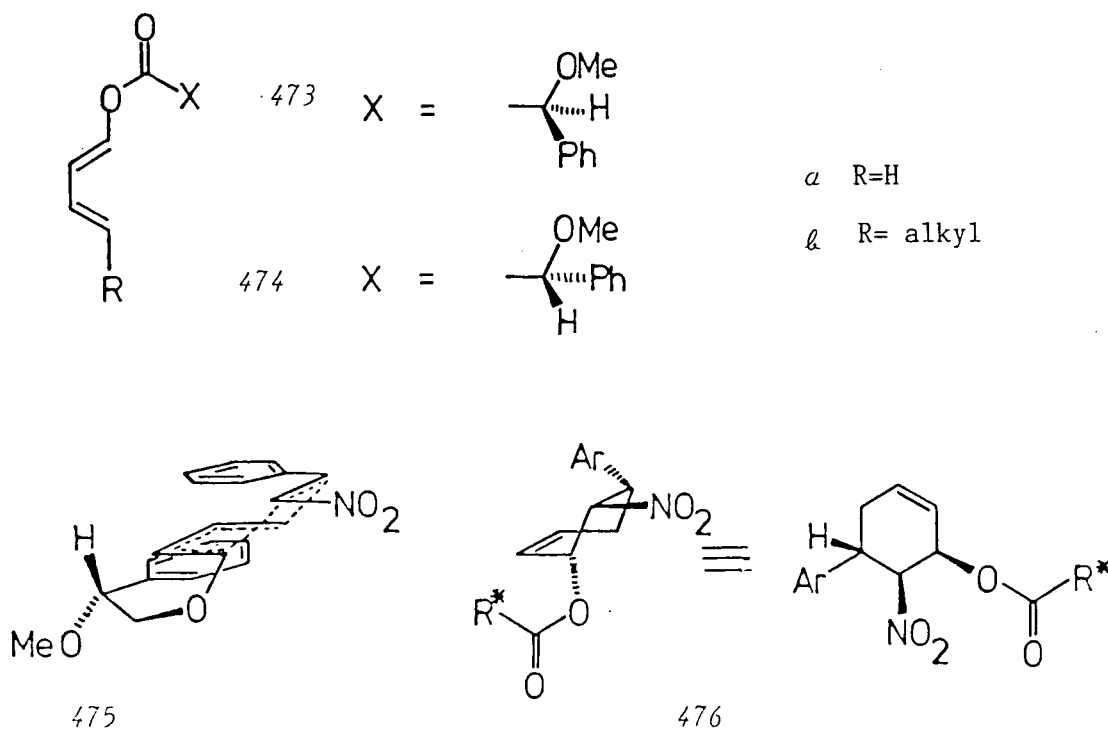
Asymmetric approaches to cephalotaxine synthesis are a remaining challenge. All current syntheses provide racemic cephalotaxine (1.6).

Asymmetric Diels-Alder reactions are of considerable current interest<sup>193</sup>, generally utilizing chiral auxiliaries attached to the dieneophile, or,

less commonly, the diene<sup>446</sup>. With nitrostyrenes - which contain two prochiral olefin carbons - asymmetric cycloaddition to a diene, requires  $\Pi$ -face-selective addition to the diene, exo or endo specificity, and regiocontrol.

Nitroalkenes are known to be highly regioselective dieneophiles<sup>440, 191,192,447</sup>, and we might expect endo positioning of the aromatic group.  $\Pi$ -Face-selectivity could be provided by an appropriate chiral diene substituent, preferentially 'shielding' one face of the diene. Trost et al<sup>448</sup> have reported reasonably good ee (75-80%) in addition of chiral dienes 473a and 473b to acrolein. They explained the face-selectivity from a combination of  $\Pi$ -stacking effects and steric interactions.

Taking into account the regiospecificity and endo-selectivity expected, coupled with Trost's observations, we would require the (*R*) enantiomer, 474. The favoured conformation of 474 could lead to cycloaddition preferentially via transition state 475, yielding stereoisomer 476, containing two asymmetric centres of configurations appropriate to natural (-) cephalotaxine.



APPENDIX II

LECTURES, COLLOQUIA AND CONFERENCES

The Board of Studies in Chemistry requires that each postgraduate research thesis contain an appendix listing:

- 1 all research colloquia, research seminars and lectures, arranged by the Department of Chemistry during the period of the residence as a postgraduate student.
- 2 all research conferences attended, and papers presented by the author, during the period when the research for the thesis was carried out.

II.1 Lectures and Colloquia organised by the Department of Chemistry during the period October 1985 - July 1988

- 17.10.85 \* Dr. C.J. Ludman (University of Durham)  
"Some Thermochemical Aspects of Explosions"
- 24.10.85 Dr. J. Dewing (UMIST)  
"Zeolites - Small Holes, Big Opportunities"
- 30.10.85 \* Dr. S.N. Whittleton (University of Durham)  
"An Investigation of a Reaction Window"
- 31.10.85 \* Dr. P. Timms (University of Bristol)  
"Some Chemistry of Fireworks"
- 5.11.85 Prof. M.J. O'Donnell (Indiana-Purdue University, U.S.A.)  
"New Methodology for the Synthesis of Amino Acids"
- 7.11.85 Prof. G.Ertl (Munich, W.Germany)  
"Heterogeneous Catalysis"
- 14.11.85 \* Dr. S.G.Davies (University of Oxford)  
"Chirality Control and Molecular Recognition"
- 20.11.85 \* Dr. J.A.H. McBride (Sunderland Polytechnic)  
"A Heterocyclic Tour on a Distorted Tricycle - Biphenylene"
- 21.11.85 Prof. K.H. Jack (University of Newcastle)  
"Chemistry of Si-Al-O-N Engineering Ceramics"
- 28.11.85 Dr. B.A.J. Clark (Kodak Ltd)  
"Chemistry and Principles of Colour Photography"
- 28.11.85 Prof. D.J. Waddington (University of York)  
"Resources for the Chemistry Teacher"
15. 1.85 Prof. N. Sheppard (University of East Anglia)  
"Vibrational and Spectroscopic Determinations of the Structures of Molecules Chemisorbed on Metal Surfaces"



23. 1.86 \* Prof. Sir Jack Lewis (University of Cambridge)  
"Some More Recent Aspects in the Cluster Chemistry of Ruthenium and Osmium Carbonyls"
29. 1.86 Dr. J.H. Clark (University of York)  
"Novel Fluoride Ion Reagents"
30. 1.86 \* Dr. N.J. Phillips (University of Loughborough)  
"Laser Holography"
12. 2.86 Dr. J. Yarwood (University of Durham)  
"The Structure of Water in Liquid Crystals"
12. 2.86 Dr. O.S. Tee (Concordia University, Montreal, Canada)  
"Bromination of Phenols"
13. 2.86 \* Prof. R. Grigg (Queen's University, Belfast)  
"Thermal Generation of 1,3-Dipoles"
19. 2.86 \* Prof. G. Procter (University of Salford)  
"Approaches to the Synthesis of Some Natural Products"
20. 2.86 \* Dr. C.J.F. Barnard (Johnson Matthey Group)  
"Platinum Anti-Cancer Drug Development"
26. 2.86 Ms. C. Till (University of Durham)  
"ESCA and Optical Emission Studies of the Plasma Polymerisation of Perfluoroaromatics"
27. 2.86 Prof. R.K. Harris (University of Durham)  
"The Magic of Solid-State NMR"
5. 3.86 \* Dr. D. Hathway (University of Durham)  
"Herbicide Selectivity"
5. 3.86 Dr. M. Schroder (University of Edinburgh)  
"Studies on Macrocyclic Compounds"
6. 3.86 \* Dr. B. Iddon (University of Salford)  
"The Magic of Chemistry"
12. 3.86 Dr. J.M. Brown (University of Oxford)  
"Chelate Control in Homogeneous Catalysis"
14. 5.86 Dr. P.R.R. Langridge-Smith (University of Edinburgh)  
"Naked Metal Clusters - Synthesis, Characterisation, and Chemistry"
9. 6.86 Prof. R. Schmutzler (Braunschweig, W. Germany)  
"Mixed Valence Diphosphorus Compounds"
23. 6.86 Prof. R.E. Wilde (Texas Technical University, U.S.A.)  
"Molecular Dynamic Processes from Vibrational Bandshapes"
- 16.10.86 \* Prof. N.N. Greenwood (University of Leeds)  
"Glorious Gaffes in Chemistry"
- 23.10.86 \* Prof. H.W. Kroto (University of Sussex)  
"Chemistry in Stars, Between Stars and in the Laboratory"

- 29.10.86 Prof. E.H.Wong (University of New Hampshire, U.S.A.)  
"Coordination Chemistry of P-O-P Ligands"
- 5.11.86 Prof. Döpp (University of Duisburg)  
"Cyclo-Additions and Cyclo-Reversions Involving Capto-Dative Alkenes"
- 6.11.86 \* Dr. R.M. Scrowston (University of Hull)  
"From Myth and Magic to Modern Medicine"
- 13.11.86 \* Prof. Sir Geoffrey Allen (Unilever Research)  
"Biotechnology and the Future of the Chemical Industry"
- 20.11.86 Dr. A. Milne and Mr. S. Christie (International Paints)  
"Chemical Serendipity - A Real Life Case Study"
- 26.11.86 Dr. N.D.S. Canning (University of Durham)  
"Surface Adsorption Studies of Relevance to Heterogeneous Ammonia Synthesis"
- 27.11.86 \* Prof. R.L.Williams (Metropolitan Police Forensic Science)  
"Science and Crime"
- 3.12.86 Dr. J. Miller (Dupont Central Research, U.S.A.)  
"Molecular Ferromagnets: Chemistry and Physical Properties"
- 8.12.86 Prof. T.Dorfmüller (University of Bielefeld, W.Germany)  
"Rotational Dynamics in Liquids and Polymers"
22. 1.87 Prof. R.H. Ottewill (University of Bristol)  
"Colloid Science: A Challenging Subject"
28. 1.87 Dr. W. Clegg (University of Newcastle -upon-Tyne)  
"Carboxylate Complexes of Zinc Charting a Structural Jungle"
4. 2.87 Prof. A. Thomson (University of East Anglia)  
"Metalloproteins and Magneto-optics"
5. 2.87 Dr. P. Hubberstey (University of Nottingham)  
"Demonstration Lecture on Various Aspects of Alkali Metal Chemistry"
11. 2.87 Dr. T. Shepherd (University of Durham)  
"Pteridine Natural Products: Synthesis and Use in Chemotherapy"
12. 2.87 Dr. P.J.Rodgers (I.C.I., Billingham)  
"Industrial Polymers from Bacteria"
17. 2.87 Prof. E.H.Wong (University of New Hampshire, U.S.A.)  
"Symmetrical Shapes from Molecules to Art and Nature"
19. 2.87 \* Dr. M. Jarman (Institute of Cancer Research)  
"The Design of Anti-Cancer Drugs"
4. 3.87 Dr. R. Newman (University of Oxford)  
"Change and Decay: A Carbon-13 CP/MAS NMR Study of Humification and Coalification Processes"

5. 3.87 \* Prof. S.V.Ley (Imperial College)  
"Fact and Fantasy in Organic Synthesis"
9. 3.87 \* Prof. F.G.Bordwell (Northeastern University, U.S.A.)  
"Carbon Anions, Radicals, Radical Anions and Radical Cations"
11. 3.87 Dr. R.D.Cannon (University of East Anglia)  
"Electron Transfer in Polynuclear Complexes"
12. 3.87 \* Dr. E.M. Goodger (Cranfield Institute of Technology)  
"Alternative Fuels for Transport"
17. 3.87 Prof. R.F.Hudson (University of Kent)  
"Aspects of Organophosphorus Chemistry"
18. 3.87 \* Prof. R.F.Hudson (University of Kent)  
"Homolytic Rearrangements of Free-Radical Stability"
3. 4.87 \* Prof. G.Ferguson (University of Guelph, Canada)  
"X-Ray Crystallography for the Organic Chemist"
6. 5.87 Dr. R. Bartsch (University of Sussex)  
"Low Co-ordinated Phosphorus Compounds"
7. 5.87 \* Dr. M. Harmer (I.C.I. Chemicals and Polymer Group)  
"The Role of Organometallics in Advanced Materials"
11. 5.87 Prof. S.Pasynkiewicz (Technical University, Warsaw)  
"Thermal Decomposition of Methyl Copper and Its Reactions with Trialkylaluminium"
27. 5.87 \* Dr. M. Blackburn (University of Sheffield)  
"Phosphonates as Analogues of Biological Phosphate Esters"
24. 6.87 \* Prof. S.M.Roberts (University of Exeter)  
"Synthesis of Novel Anti-Viral Agents"
26. 6.87 Dr. C.Krespan (E.I. Dupont de Nemours)  
"Nickel (0) and Iron (0) as Reagents in Organofluorine Chemistry"
- 15.10.87 \* Dr. M.J.Winter (University of Sheffield)  
"Pyrotechnics"
- 22.10.87 \* Prof. G.W.Gray (University of Hull)  
"Liquid Crystals and their applications"
- 29.10.87 \* Mrs S. van Rose (Geological Museum, London)  
"Chemistry of Volcanoes"
- 4.11.87 Mrs M. Mapletoft (Durham Chemistry Teachers' Centre)  
"Salter's Chemistry"
- 5.11.87 \* Dr. A.R.Butler (University of St.Andrews)  
"Chinese Alchemy"
- 12.11.87 \* Prof. D.Seebach (E.T.H., Zurich)  
"From Synthetic Methods to Mechanistic Insight"

- 26.11.87 \* Dr. D.H.Williams (University of Cambridge)  
"Molecular Recognition"
- 11.87 Dr. J.Davidson (Herriot-Watt University)  
"Metal Promoted Oligomerization Reactions of Alkynes"
- 3.12.87 \* Dr. J. Howard (I.C.I., Wilton)  
"Chemistry of Non-Equilibrium Processes"
- 10.12.87 Dr. C.J. Ludman (University of Durham)  
"Explosives"
- 16.12.87 Mr R.M.Smart (I.C.I.)  
"The Interaction of Chemicals with Lipid Bilayers"
- 19.12.87 \* Prof. P.G.Sammes (Smith, Kline and French)  
"Chemical Aspects of Drug Development"
21. 1.88 \* Dr. F.Palmer (University of Nottingham)  
"Luminescence"
28. 1.88 \* Dr. A.G.Cairns-Smith (University of Glasgow)  
"Clay Minerals and the Origin of Life"
9. 2.88 Mr Lacey (Durham Chemistry Teachers' Centre)  
"Double Award Science"
11. 2.88 \* Prof. J.J.Turner (University of Nottingham)  
"Catching Organometallic Intermediates"
18. 2.88 \* Dr. K. Borer (University of Durham Industrial Research Labs)  
"The Brighton Bomb - A Forensic Science View"
15. 2.88 \* Prof. A. Underhill (University of Bangor)  
"Molecular Electronics"
3. 3.88 \* Prof. W.A.G.Graham (University of Alberta, Canada)  
"Rhodium and Iridium Complexes in the Activation of  
Carbon-Hydrogen Bonds"
7. 3.88 \* Prof. H.F.Koch (Ithaca College, U.S.A.)  
"Does the E2 Mechanism Occur in Solution?"
16. 3.88 L.Bossons (Durham Chemistry Teachers' Centre)  
"GCSE Practical Assessment"
7. 4.88 \* Prof. M.P. Hartshorn (University of Canterbury, New Zealand)  
"Aspects of Ipso-Nitration"
13. 4.88 Mrs E. Roberts (SATRO Officer for Sunderland)  
"Links between Industry and Schools"
18. 4.88 Prof. C.A.Nieto de Castro (University of Lisbon and Imperial  
College)  
"Transport Properties of Non-Polar Fluids"
25. 4.88 Prof. D.Birchall (I.C.I. Advanced Materials)  
"Environmental Chemistry of Aluminium"
27. 4.88 Dr. R. Richardson (University of Bristol)  
"X-ray Diffraction from Spread Monolayers"

27. 4.88 \* Dr. J.A.Robinson (University of Southampton)  
"Aspects of Antibiotic Biosynthesis"
28. 4.88 Prof. A.Pines (University of California, Berkeley, U.S.A.)  
"Some Magnetic Moments"
11. 5.88 Dr. W.A.McDonald (I.C.I. Wilton)  
"Liquid Crystal Polymers"
11. 5.88 Dr. J. Sodeau (University of East Anglia)  
"Spray Cans, Smog and Society"
8. 6.88 Prof. J.P. Majoral (Université Paul Sabatier)  
"Stabilization Complexation of Short-Lived Phosphorus Species"
29. 6.88 Dr. M.E.Jones (Durham Chemistry Teachers' Centre)  
"GCSE Chemistry Post-mortem"
29. 6.88 \* Prof. G.A.Olah (University of Southern California, U.S.A.)  
"New Aspects of Hydrocarbon Chemistry"
6. 7. 88 Dr. M.E.Jones (Durham Chemistry Teachers' Centre)  
"GCE Chemistry A-Level Post-mortem"

\* Indicates colloquia attended by the author.

## II.2 Conferences attended

- 1 Stereochemistry Symposium, Sheffield, December 1985
- 2 Graduate Symposium, Durham, 16 April 1986
- 3 Graduate Symposium, Durham, 27 March 1987
- 4 Royal Society of Chemistry, Perkin Division,  
North East Regional Meeting, Newcastle upon Tyne,  
15 September 1987
- 5 Royal Society of Chemistry Annual Congress,  
Canterbury, 12-15 April 1988
- 6 Graduate Symposium Durham, 19 April 1988  
Lecture presented: "New Synthetic Approaches  
Towards Cephalotaxus Alkaloids."

APPENDIX III

X-RAY STRUCTURAL DATA

III.1 DATA for 6-(3,4-METHYLENEDIOXYPHENYL)-2-THIO-1-AZASPIRO[4.5]DEC-8-ENE (253)

|                                     |            |
|-------------------------------------|------------|
| Crystal system                      | Monoclinic |
| a/Å                                 | 12.006(4)  |
| b/Å                                 | 8.995(5)   |
| c/Å                                 | 14.032(3)  |
| α/deg                               | 90.00      |
| β/deg                               | 67.41(2)   |
| γ/deg                               | 90.00      |
| v/Å <sup>3</sup>                    | 1399.1     |
| Space group                         | P21/n      |
| Z                                   | 4          |
| Dc/gcm <sup>-3</sup>                | 1.364      |
| Linear abs. coeff./cm <sup>-1</sup> | 20.108     |
| F(000)                              | 608        |

Data Collection  
 -----

CAD4 diffractometer , Cu radiation ,  $\lambda = 1.5418\text{\AA}$  ,  $\omega$ -2 $\theta$  scan mode  
 Scan width  $(0.8+0.15\tan\theta)^\circ$  , Scan speed 1.3-6.77<sup>°</sup>min<sup>-1</sup>  
 $\theta_{\min}$ ,  $\theta_{\max}$ /deg 3, 65  
 Total Data 2671  
 Total Unique 2384  
 Total Observed ( $I \geq 3\sigma$ ) 1389

Refinement  
 -----

No. of parameters 239  
 Weighting scheme coeff. g 0.0005  
 Final R 0.0548  
 Final Rw 0.0423

TABLE III.A : BOND LENGTHS (Å) for C<sub>16</sub>H<sub>17</sub>NO<sub>2</sub>S (253)

|              |           |              |           |
|--------------|-----------|--------------|-----------|
| C(2)-S(1)    | 1.657(6)  | N(3)-C(2)    | 1.320(5)  |
| C(6)-C(2)    | 1.503(8)  | C(4)-N(3)    | 1.470(5)  |
| H(3)-N(3)    | 0.962(47) | C(5)-C(4)    | 1.528(8)  |
| C(7)-C(4)    | 1.523(7)  | C(11)-C(4)   | 1.562(7)  |
| C(6)-C(5)    | 1.521(8)  | H(51)-C(5)   | 1.004(40) |
| H(52)-C(5)   | 0.985(39) | H(61)-C(6)   | 0.901(41) |
| H(62)-C(6)   | 0.918(41) | C(8)-C(7)    | 1.495(7)  |
| H(71)-C(7)   | 1.089(40) | H(72)-C(7)   | 1.000(40) |
| C(9)-C(8)    | 1.310(7)  | H(8)-C(8)    | 1.017(46) |
| C(10)-C(9)   | 1.493(7)  | H(9)-C(9)    | 1.016(45) |
| C(11)-C(10)  | 1.529(8)  | H(101)-C(10) | 1.068(39) |
| H(102)-C(10) | 0.997(40) | C(12)-C(11)  | 1.509(7)  |
| H(11)-C(11)  | 0.981(32) | C(13)-C(12)  | 1.408(6)  |
| C(20)-C(12)  | 1.390(6)  | C(14)-C(13)  | 1.363(6)  |
| H(13)-C(13)  | 0.944(37) | O(15)-C(14)  | 1.387(6)  |
| C(18)-C(14)  | 1.370(6)  | C(16)-O(15)  | 1.436(7)  |
| O(17)-C(16)  | 1.407(7)  | H(161)-C(16) | 0.964(50) |
| H(162)-C(16) | 0.919(51) | C(18)-O(17)  | 1.370(6)  |
| C(19)-C(18)  | 1.361(7)  | C(20)-C(19)  | 1.399(7)  |
| H(19)-C(19)  | 1.035(39) | H(20)-C(20)  | 1.008(39) |



TABLE III.B : BOND ANGLES (DEG.) for C<sub>16</sub>H<sub>17</sub>NO<sub>2</sub>S (253)

|                    |           |                     |           |
|--------------------|-----------|---------------------|-----------|
| N(3)-C(2)-S(1)     | 127.3(4)  | C(6)-C(2)-S(1)      | 125.2(4)  |
| C(6)-C(2)-N(3)     | 107.5(4)  | C(4)-N(3)-C(2)      | 116.5(4)  |
| H(3)-N(3)-C(2)     | 115.7(30) | C(4)-N(3)-H(3)      | 127.3(31) |
| C(5)-C(4)-N(3)     | 101.7(4)  | C(7)-C(4)-N(3)      | 110.5(4)  |
| C(7)-C(4)-C(5)     | 112.2(4)  | C(11)-C(4)-N(3)     | 110.5(4)  |
| C(11)-C(4)-C(5)    | 114.2(4)  | C(11)-C(4)-C(7)     | 107.7(4)  |
| C(6)-C(5)-C(4)     | 105.7(4)  | H(51)-C(5)-C(4)     | 109.2(24) |
| H(52)-C(5)-C(4)    | 110.5(25) | H(52)-C(5)-H(51)    | 107.9(33) |
| C(6)-C(5)-H(51)    | 112.4(23) | C(6)-C(5)-H(52)     | 111.2(24) |
| C(5)-C(6)-C(2)     | 105.3(5)  | H(61)-C(6)-C(2)     | 108.1(30) |
| H(61)-C(6)-C(5)    | 112.3(28) | H(62)-C(6)-C(2)     | 110.4(27) |
| H(62)-C(6)-C(5)    | 111.3(29) | H(62)-C(6)-H(61)    | 109.4(41) |
| C(8)-C(7)-C(4)     | 113.5(5)  | H(71)-C(7)-C(4)     | 106.6(21) |
| H(72)-C(7)-C(4)    | 107.8(24) | H(72)-C(7)-H(71)    | 106.2(31) |
| C(8)-C(7)-H(71)    | 112.5(23) | C(8)-C(7)-H(72)     | 109.9(24) |
| C(9)-C(8)-C(7)     | 123.4(6)  | H(8)-C(8)-C(7)      | 117.1(28) |
| C(9)-C(8)-H(8)     | 119.4(28) | C(10)-C(9)-C(8)     | 122.9(6)  |
| H(9)-C(9)-C(8)     | 121.7(28) | C(10)-C(9)-H(9)     | 115.4(28) |
| C(11)-C(10)-C(9)   | 113.0(5)  | H(101)-C(10)-C(9)   | 112.5(23) |
| H(102)-C(10)-C(9)  | 109.8(25) | H(102)-C(10)-H(101) | 105.2(32) |
| C(11)-C(10)-H(101) | 104.7(23) | C(11)-C(10)-H(102)  | 111.2(26) |
| C(10)-C(11)-C(4)   | 109.8(4)  | C(12)-C(11)-C(4)    | 114.6(4)  |
| C(12)-C(11)-C(10)  | 112.8(4)  | H(11)-C(11)-C(4)    | 106.5(20) |
| H(11)-C(11)-C(10)  | 107.0(20) | C(12)-C(11)-H(11)   | 105.5(20) |
| C(13)-C(12)-C(11)  | 118.9(5)  | C(20)-C(12)-C(11)   | 122.0(5)  |
| C(20)-C(12)-C(13)  | 119.1(5)  | C(14)-C(13)-C(12)   | 117.6(5)  |
| H(13)-C(13)-C(12)  | 119.1(27) | C(14)-C(13)-H(13)   | 123.1(27) |
| O(15)-C(14)-C(13)  | 127.4(5)  | C(18)-C(14)-C(13)   | 122.6(5)  |
| C(18)-C(14)-O(15)  | 109.9(5)  | C(16)-O(15)-C(14)   | 104.7(5)  |
| O(17)-C(16)-O(15)  | 108.8(5)  | H(161)-C(16)-O(15)  | 107.1(32) |
| H(162)-C(16)-O(15) | 105.0(33) | H(162)-C(16)-H(161) | 121.5(49) |
| O(17)-C(16)-H(161) | 104.6(33) | O(17)-C(16)-H(162)  | 109.4(34) |
| C(18)-O(17)-C(16)  | 106.3(5)  | O(17)-C(18)-C(14)   | 110.0(5)  |
| C(19)-C(18)-C(14)  | 121.6(5)  | C(19)-C(18)-O(17)   | 128.2(5)  |
| C(20)-C(19)-C(18)  | 117.0(5)  | H(19)-C(19)-C(18)   | 121.3(24) |
| C(20)-C(19)-H(19)  | 121.7(24) | H(20)-C(20)-C(12)   | 120.6(24) |
| C(19)-C(20)-C(12)  | 122.1(5)  | H(20)-C(20)-C(19)   | 117.3(24) |

III.2. DATA FOR 7,8-DIMETHOXY-CYCLOHEXENO [3,4-b]-(2-PYRROLIDINO)[1,5-a]  
-4-HYDROXY-2,3,4,5-TETRAHYDRO-3-BENZAZEPINE (359d)

Crystallographic Studies

Crystal data:  $C_{17}H_{23}N_2O_4$ .  $M = 329.40$ , monoclinic, space group  $P2_1/c$  (No. 14).  $a = 13.176(2)$ ,  $b = 7.094(1)$ ,  $c = 17.646(2)$  Å,  $\beta = 101.55(1)^\circ$ ,  $U = 1615.9(4)$  Å<sup>3</sup>,  $z = 4$ ,  $D_c = 1.354$  g cm<sup>-3</sup>,  $F(000) = 704$ ,  $\lambda = 0.71069$  Å,  $\mu(\text{Mo-K}\alpha) = 0.9$  cm<sup>-1</sup>, crystal size (.73 x .32 x .45 mm).

Data collection: Unit cell parameters and intensity data were obtained by following previously detailed procedures<sup>a</sup>, using a CAD4 diffractometer operating in the  $\omega$ - $2\theta$  scan mode, with graphite monochromated Mo-K $\alpha$  radiation. A total of 2834 unique reflections were collected ( $3 \leq 2\theta \leq 50^\circ$ ). The segment of reciprocal space scanned was: ( $h$ )  $0 \rightarrow 15$ , ( $k$ )  $0 \rightarrow 8$ , ( $l$ )  $-21 \rightarrow 21$ .

Structure solution and refinement: The structure was solved by the application of routine direct methods (SHELX-86<sup>b</sup>), and refined by full-matrix least-squares (SHELX-76<sup>c</sup>). All the non-hydrogen atoms were refined anisotropically. All hydrogen atoms, except that of the hydroxyl group, were placed into calculated positions (C-H 0.96 Å;  $U = 0.10$ ). The hydroxyl hydrogen atom was allowed unrestricted isotropic refinement. The final residuals  $R$  and  $R_w$  were 0.052 and 0.062 respectively for the 227 variables and 2396 data for which  $F_o > 3\sigma(F_o)$ . The function minimised was  $\sum_w (|F_o| - |F_c|)^2$  with the weight,  $w$ , being defined as  $1/[\sigma^2(F_o) + 0.0007F_o^2]$ . All computations were made on a DEC VAX-11/750 computer.

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TABLE III.C

Bond lengths (Å) for C(19)H(23)N(1)O(4) 359d

|             |          |             |          |
|-------------|----------|-------------|----------|
| C(1)-O(1)   | 1.238(3) | C(17)-O(2)  | 1.412(4) |
| C(12)-O(3)  | 1.368(3) | C(18)-O(3)  | 1.425(3) |
| C(13)-O(4)  | 1.374(3) | C(19)-O(4)  | 1.405(4) |
| C(1)-N(1)   | 1.354(4) | C(4)-N(1)   | 1.485(3) |
| C(17)-N(1)  | 1.458(3) | C(2)-C(1)   | 1.492(4) |
| C(3)-C(2)   | 1.523(5) | C(4)-C(3)   | 1.550(5) |
| C(5)-C(4)   | 1.535(5) | C(9)-C(4)   | 1.554(5) |
| C(6)-C(5)   | 1.496(4) | C(7)-C(6)   | 1.327(5) |
| C(8)-C(7)   | 1.504(5) | C(9)-C(8)   | 1.535(5) |
| C(10)-C(9)  | 1.537(5) | C(11)-C(10) | 1.403(4) |
| C(15)-C(10) | 1.391(4) | C(12)-C(11) | 1.385(4) |
| C(13)-C(12) | 1.398(4) | C(14)-C(13) | 1.378(4) |
| C(15)-C(14) | 1.401(4) | C(16)-C(15) | 1.507(5) |
| C(17)-C(16) | 1.519(5) | HO(2)-O(2)  | 1.01(4)  |

TABLE III.D

Bond angles (deg.) for C(19)H(23)N(1)O(4) 359d

|                   |          |                   |           |
|-------------------|----------|-------------------|-----------|
| C(18)-O(3)-C(12)  | 117.2(3) | C(19)-O(4)-C(13)  | 117.3(3)  |
| C(4)-N(1)-C(1)    | 113.4(3) | C(17)-N(1)-C(1)   | 119.2(3)  |
| C(17)-N(1)-C(4)   | 126.9(3) | N(1)-C(1)-O(1)    | 125.4(3)  |
| C(2)-C(1)-O(1)    | 125.7(3) | C(2)-C(1)-N(1)    | 108.9(3)  |
| C(3)-C(2)-C(1)    | 102.9(3) | C(4)-C(3)-C(2)    | 104.4(3)  |
| C(3)-C(4)-N(1)    | 99.9(2)  | C(5)-C(4)-N(1)    | 112.5(3)  |
| C(5)-C(4)-C(3)    | 110.9(3) | C(9)-C(4)-N(1)    | 114.4(3)  |
| C(9)-C(4)-C(3)    | 110.9(3) | C(9)-C(4)-C(5)    | 108.1(3)  |
| C(6)-C(5)-C(4)    | 111.0(3) | C(7)-C(6)-C(5)    | 123.0(3)  |
| C(8)-C(7)-C(6)    | 123.6(3) | C(9)-C(8)-C(7)    | 111.3(3)  |
| C(8)-C(9)-C(4)    | 107.0(3) | C(10)-C(9)-C(4)   | 114.1(3)  |
| C(10)-C(9)-C(8)   | 112.2(3) | C(11)-C(10)-C(9)  | 121.8(3)  |
| C(15)-C(10)-C(9)  | 120.0(3) | C(15)-C(10)-C(11) | 118.2(3)  |
| C(12)-C(11)-C(10) | 122.0(3) | C(11)-C(12)-O(3)  | 124.9(3)  |
| C(13)-C(12)-O(3)  | 115.7(3) | C(13)-C(12)-C(11) | 119.4(3)  |
| C(12)-C(13)-O(4)  | 116.3(3) | C(14)-C(13)-O(4)  | 124.6(3)  |
| C(14)-C(13)-C(12) | 119.1(3) | C(15)-C(14)-C(13) | 121.7(3)  |
| C(14)-C(15)-C(10) | 119.7(3) | C(16)-C(15)-C(10) | 121.3(3)  |
| C(16)-C(15)-C(14) | 119.0(3) | C(17)-C(16)-C(15) | 114.2(3)  |
| N(1)-C(17)-O(2)   | 111.8(3) | C(16)-C(17)-O(2)  | 108.8(3)  |
| C(16)-C(17)-N(1)  | 112.8(3) | HO(2)-O(2)-C(17)  | 109.9(19) |

TABLE III.E  
Selected non-bonded distances (A) for C(19)H(23)N(1)O(4)

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Intramolecular:

|             |       |             |       |
|-------------|-------|-------------|-------|
| N(1)-O(1)   | 2.303 | C(2)-O(1)   | 2.432 |
| H(21)-O(1)  | 2.831 | H(22)-O(1)  | 2.658 |
| C(17)-O(1)  | 2.795 | H(17)-O(1)  | 2.333 |
| N(1)-O(2)   | 2.376 | C(1)-O(2)   | 3.265 |
| C(4)-O(2)   | 3.218 | C(5)-O(2)   | 3.267 |
| H(52)-O(2)  | 2.685 | C(15)-O(2)  | 2.822 |
| C(16)-O(2)  | 2.384 | H(161)-O(2) | 2.655 |
| H(17)-O(2)  | 1.955 | O(4)-O(3)   | 2.600 |
| C(11)-O(3)  | 2.441 | H(11)-O(3)  | 2.649 |
| C(13)-O(3)  | 2.342 | H(181)-O(3) | 1.920 |
| H(182)-O(3) | 1.985 | H(183)-O(3) | 1.990 |
| C(12)-O(4)  | 2.354 | C(14)-O(4)  | 2.437 |
| H(14)-O(4)  | 2.643 | H(191)-O(4) | 1.929 |
| H(192)-O(4) | 1.875 | H(193)-O(4) | 2.029 |
| C(2)-N(1)   | 2.317 | H(21)-N(1)  | 2.834 |
| C(3)-N(1)   | 2.323 | H(32)-N(1)  | 2.733 |
| C(5)-N(1)   | 2.511 | H(51)-N(1)  | 2.716 |
| H(52)-N(1)  | 2.697 | C(9)-N(1)   | 2.554 |
| H(9)-N(1)   | 2.659 | C(10)-N(1)  | 3.210 |
| C(15)-N(1)  | 3.190 | C(16)-N(1)  | 2.480 |
| H(162)-N(1) | 2.565 | H(171)-N(1) | 1.945 |
| HO(2)-N(1)  | 2.544 | H(21)-C(1)  | 2.045 |
| H(22)-O(1)  | 2.045 | C(3)-C(1)   | 2.358 |
| H(32)-C(1)  | 2.769 | C(4)-C(1)   | 2.374 |
| C(5)-C(1)   | 3.286 | C(17)-C(1)  | 2.425 |
| H(17)-C(1)  | 2.407 | HO(2)-C(1)  | 3.071 |
| H(31)-C(2)  | 2.048 | H(32)-C(2)  | 2.068 |
| C(4)-C(2)   | 2.427 | C(5)-C(2)   | 3.194 |
| H(51)-C(2)  | 2.895 | H(22)-H(21) | 1.568 |
| C(3)-H(21)  | 2.072 | H(31)-H(21) | 2.259 |
| C(4)-H(21)  | 2.836 | H(51)-H(21) | 2.558 |
| C(3)-H(22)  | 2.072 | H(31)-H(22) | 2.552 |
| H(32)-H(22) | 2.258 | C(5)-C(3)   | 2.540 |
| H(51)-C(3)  | 2.639 | C(6)-C(3)   | 3.103 |
| C(7)-C(3)   | 3.213 | C(8)-C(3)   | 2.871 |
| H(82)-C(3)  | 2.574 | C(9)-C(3)   | 2.556 |
| H(9)-C(3)   | 2.781 | H(32)-H(31) | 1.568 |
| C(4)-H(31)  | 2.092 | C(5)-H(31)  | 2.562 |
| H(51)-H(31) | 2.581 | C(6)-H(31)  | 2.715 |
| C(7)-H(31)  | 2.805 | C(8)-H(31)  | 2.822 |
| H(82)-H(31) | 2.444 | C(9)-H(31)  | 2.973 |
| C(4)-H(32)  | 2.092 | C(8)-H(32)  | 2.824 |
| H(82)-H(32) | 2.311 | C(9)-H(32)  | 2.586 |
| H(9)-H(32)  | 2.509 | H(51)-C(4)  | 2.059 |
| H(52)-C(4)  | 2.059 | C(6)-C(4)   | 2.498 |
| C(7)-C(4)   | 2.810 | C(8)-C(4)   | 2.482 |

|               |       |               |       |
|---------------|-------|---------------|-------|
| H(82)-C(4)    | 2.726 | H(9)-C(4)     | 2.075 |
| C(10)-C(4)    | 2.594 | C(15)-C(4)    | 3.211 |
| C(16)-C(4)    | 3.159 | C(17)-C(4)    | 2.633 |
| H(6)-C(5)     | 2.129 | C(7)-C(5)     | 2.483 |
| C(8)-C(5)     | 2.974 | C(9)-C(5)     | 2.500 |
| C(10)-C(5)    | 2.985 | C(17)-C(5)    | 3.344 |
| H(52)-H(51)   | 1.568 | C(6)-H(51)    | 2.025 |
| H(6)-H(51)    | 2.360 | C(6)-H(52)    | 2.025 |
| H(6)-H(52)    | 2.511 | C(7)-H(52)    | 2.995 |
| C(9)-H(52)    | 2.740 | C(10)-H(52)   | 2.703 |
| H(7)-C(6)     | 1.972 | C(8)-C(6)     | 2.496 |
| H(82)-C(6)    | 3.008 | C(9)-C(6)     | 2.835 |
| C(10)-C(6)    | 3.339 | C(11)-C(6)    | 3.463 |
| C(7)-H(6)     | 1.974 | H(7)-H(6)     | 2.239 |
| H(81)-C(7)    | 2.030 | H(82)-C(7)    | 2.031 |
| C(9)-C(7)     | 2.509 | C(10)-C(7)    | 3.183 |
| C(11)-C(7)    | 3.150 | H(11)-C(7)    | 2.556 |
| C(8)-H(7)     | 2.133 | H(81)-H(7)    | 2.363 |
| H(82)-H(7)    | 2.512 | H(9)-C(8)     | 2.082 |
| C(10)-C(8)    | 2.550 | C(11)-C(8)    | 2.868 |
| H(11)-C(8)    | 2.474 | H(82)-H(81)   | 1.568 |
| C(9)-H(81)    | 2.058 | H(9)-H(81)    | 2.431 |
| C(10)-H(81)   | 2.624 | C(11)-H(81)   | 2.598 |
| H(11)-H(81)   | 2.088 | C(9)-H(82)    | 2.058 |
| H(9)-H(82)    | 2.313 | C(11)-C(9)    | 2.570 |
| H(11)-C(9)    | 2.720 | C(15)-C(9)    | 2.536 |
| C(16)-C(9)    | 2.943 | H(162)-C(9)   | 2.768 |
| C(17)-C(9)    | 3.198 | C(10)-H(9)    | 1.992 |
| C(15)-H(9)    | 2.639 | C(16)-H(9)    | 2.725 |
| H(162)-H(9)   | 2.252 | H(11)-C(10)   | 2.049 |
| C(12)-C(10)   | 2.439 | C(13)-C(10)   | 2.815 |
| C(14)-C(10)   | 2.414 | C(16)-C(10)   | 2.527 |
| H(162)-C(10)  | 2.714 | C(17)-C(10)   | 3.192 |
| C(13)-C(11)   | 2.403 | C(14)-C(11)   | 2.747 |
| C(15)-C(11)   | 2.397 | C(18)-C(11)   | 2.817 |
| H(182)-C(11)  | 2.777 | H(183)-C(11)  | 2.787 |
| C(12)-H(11)   | 2.032 | C(18)-H(11)   | 2.503 |
| H(182)-H(11)  | 2.288 | H(183)-H(11)  | 2.353 |
| C(14)-C(12)   | 2.393 | C(15)-C(12)   | 2.794 |
| C(18)-C(12)   | 2.383 | H(182)-C(12)  | 2.657 |
| H(183)-C(12)  | 2.631 | H(14)-C(13)   | 2.027 |
| C(15)-C(13)   | 2.427 | C(19)-C(13)   | 2.372 |
| H(192)-C(13)  | 2.479 | H(193)-C(13)  | 2.728 |
| C(16)-C(14)   | 2.506 | H(161)-C(14)  | 2.511 |
| C(19)-C(14)   | 2.832 | H(192)-C(14)  | 2.757 |
| H(193)-C(14)  | 2.807 | C(15)-H(14)   | 2.048 |
| C(16)-H(14)   | 2.643 | H(161)-H(14)  | 2.288 |
| C(19)-H(14)   | 2.550 | H(192)-H(14)  | 2.478 |
| H(193)-H(14)  | 2.260 | H(161)-C(15)  | 2.025 |
| H(162)-C(15)  | 2.025 | C(17)-C(15)   | 2.541 |
| H(17)-C(16)   | 2.038 | H(162)-H(161) | 1.568 |
| C(17)-H(161)  | 2.036 | H(17)-H(161)  | 2.245 |
| C(17)-H(162)  | 2.035 | H(17)-H(162)  | 2.377 |
| H(2)-C(17)    | 1.992 | H(2)-H(17)    | 2.286 |
| H(182)-H(181) | 1.568 | H(183)-H(181) | 1.568 |
| H(183)-H(182) | 1.568 | H(192)-H(191) | 1.568 |
| H(193)-H(191) | 1.568 | H(193)-H(192) | 1.568 |

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