New synthetic strategies towards cephalotaxus alkaloids

John Michael Gardiner

Gardiner, John Michael (1988) New synthetic strategies towards cephalotaxus alkaloids. Doctoral thesis, Durham University.

NEW SYNTHETIC STRATEGIES
TOWARDS CEPHALOTAXUS ALKALOIDS

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

DECLARATION

The work described in this thesis was carried out by the author, in the Department of Chemistry, University of Durham, between October 1985 and August 1988. It has not been submitted in part, or in whole, for a higher degree in this, or any other University.

MEMORANDUM

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 spirolactam ester 6-(3,4-dimethoxy-6-carbomethoxymethylphenyl)-2-oxo-1-azaspiro[4.5]dec-8-ene. On reduction with DIBAL-H at -78°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 (±) 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:

My supervisor, Dr. Martin R. Bryce, for his encouragement, advice and boundless optimism.

Dr. Ray Matthews and Mr. John Banks for NMR services, Dr. Mike Jones and Mr. Vince McNeilly for obtaining mass spectra, and to Mr. Dave Hunter and Mr. Ralph Plumb for their assistance, particularly with high pressure work.

Professor M.B. Hursthouse, R.L. Short and P.A. Bates (Queen Mary College, London), for performing X-ray structural analyses.

The North of England Cancer Research Campaign for generous financial support for this work.

Mrs Susan Little for enduring the typing of this thesis, and the impatience of the author.

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*[1], the only genus of the family Cephalotaxaceae of the order Coniferae.

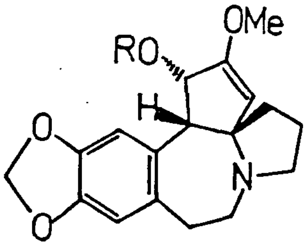
There are eight known species of this genus, *C.harringtonia, C.mannii, C.fortunei, C.hainanensis, C.wilsonia, C.oliveri, C.lanceolata* and *C.sinensis.*[2]

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[3]. 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*.

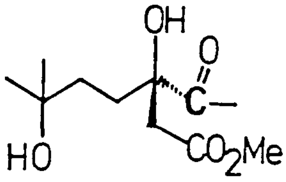
The discovery in 1961 that alkaloid extracts of *C.harringtonia* were active against sarcoma 180 tumour[4], prompted the considerable efforts which led to the isolation and full structural characterisation of *1-19* over the following two decades.

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



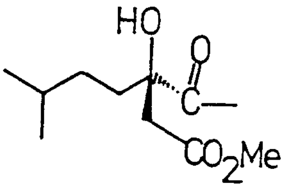
1. R = H (-) cephalotaxine

R =



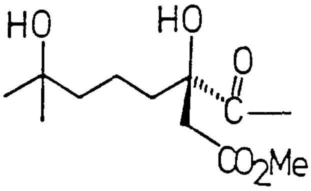
2 Harringtonine

R =



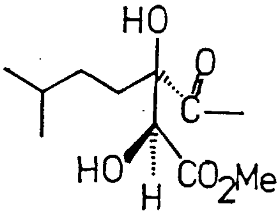
3 Deoxyharringtonine

R =



4. Homoharringtonine

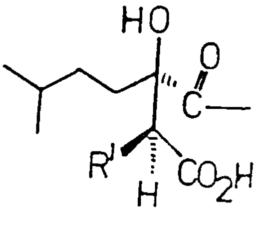
R =



5 Isoharringtonine

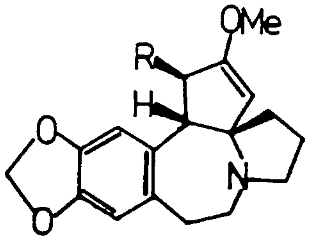
6 R = Ac Acetyl-cephalotaxine

7 R = Ac (+)Acetyl-cephalotaxine



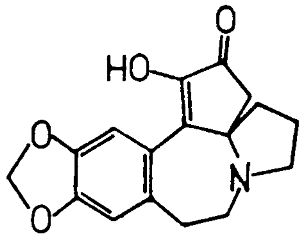
8 R' = OH Isoharringtonic acid

9 R' = H Deoxyharringtonic acid

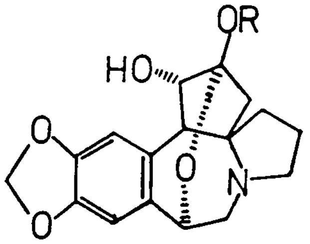


10 R = OH Epicephalotaxine

11 R = =O cephalotaxinone

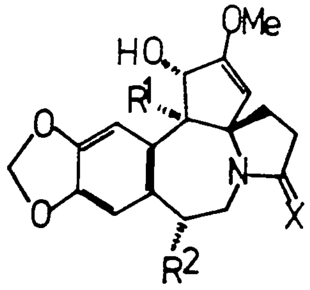


12 Demethylcephalotaxinone



13 R = Me Drupacine

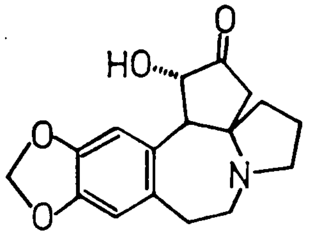
14 R = H Demethylneodrupacine



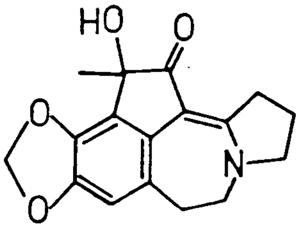
15 $X = H_2$ $R^1 = R^2 = OH$
11-hydroxycephalotaxine

16 $X = H_2$ $R^1 = OH$ $R^2 = H$
4-hydroxycephalotaxine

17 $X = O$ $R^1 = R^2 = H$
cephalotaxinamide



18 Demethyl cephalotaxine



19 Hainansine

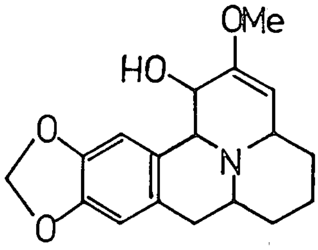
Unfortunately, the alkaloid content of *Cephalotaxus* plants is low, and supplies of plant material are limited[8]. Further, of the total alkaloid extract, only a small percentage generally constitutes the active harringtonines. For example, in *C. fortunei*, this varies from 0.02% of the root alkaloid 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[9] 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[5] revised this structure, largely on the basis of the olefinic singlet in the proton NMR spectrum, suggesting either structure *21* or *1*.



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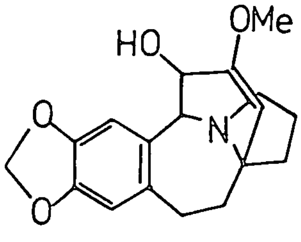


21

The structural assignment was partly resolved by Abraham et al[10] in 1969, whose X-ray structure analysis of cephalotaxine methiodide indicated structure *1*. 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[11,12], and this lends credence to postulated biosynthetic pathways (see 1.5).

The absolute configuration was determined five years later by Arora et al[13], from an X-ray study of the p-bromobenzoate of cephalotaxine, and further confirmation was provided by these workers later study[14] 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[4,15] 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[2,8].

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[4].

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[16], 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_{50} 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 isoharringtone, 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[2,3,8].

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[4].

Inhibition of DNA biosynthesis appears to result from competitive binding to DNA polymerase α, 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.

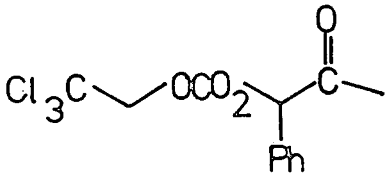
The role of the cephalotaxine ring skeleton in activity of its esters, has been postulated to be related to interaction with biological hosts via the 'triangular' arrangement of the nitrogen, and the oxygens on ring E[8] (cf. general enzymic binding). The role of side chain functionality is as yet unclear.

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,5, (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 funtionalities, 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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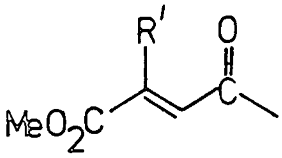
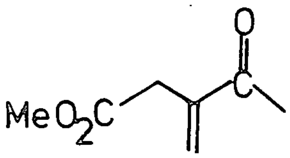


23 $R^1 = H$

24 $R^1 = CH_2CH_2CHMe_2$



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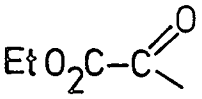

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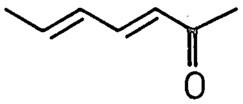

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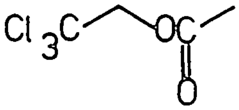

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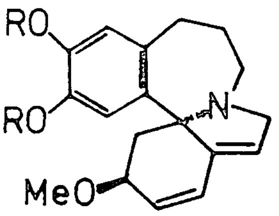
Some unnatural ester side chains

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.

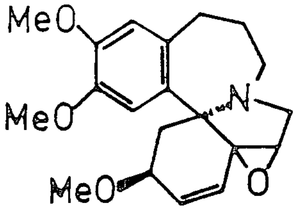
1.5 Biosynthesis of *Cephalotaxus* alkaloids

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



29 R = R = Me

30 R - R = $-CH_2-$



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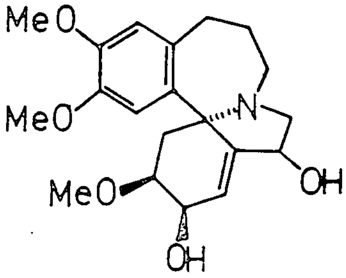

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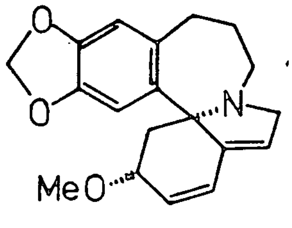
Good evidence has been produced for a biosynthetic pathway to the related erythrina alkaloids, e.g. erythraline, *33*, from tyrosine[20,21], via 1-benzylisoquinoline derivative, e.g. *34*[22] followed by oxidative intramolecular coupling of macrocylic intermediates, e.g. dibenzazonine, *35*[23].



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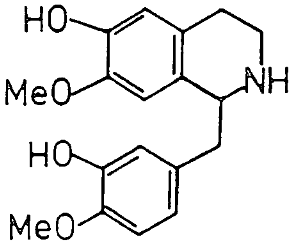

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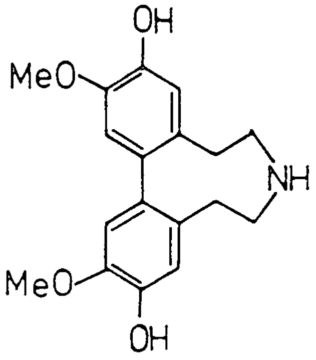

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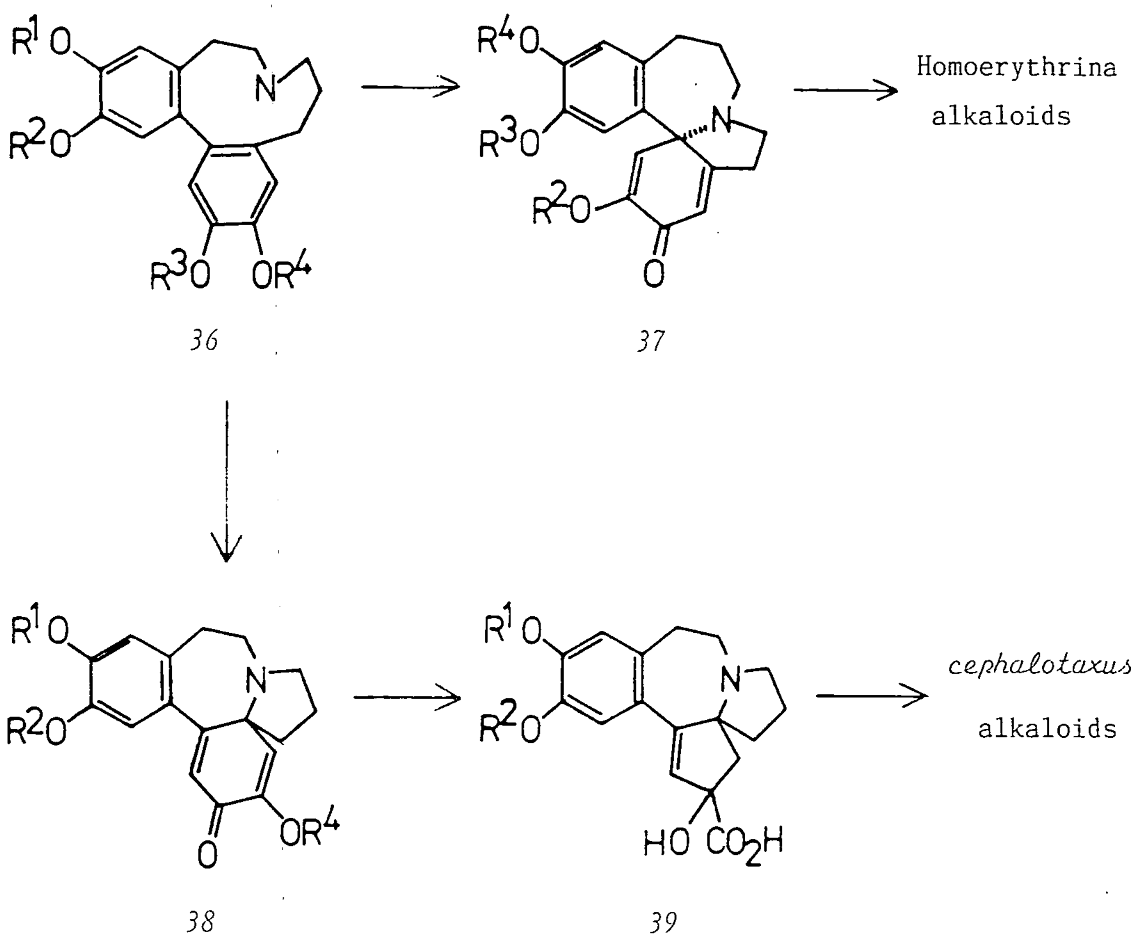
On this basis, Fitzgerald et al[24] postulated a similar biosynthetic origin of homoerythrina alkaloids from a 1-phenethylisoquinoline precursor, which Powell[25] subsequently observed, could provide entry to cephalotaxine intermediates *38* and *39*, by an alternative ring closure of dibenzacine, *36a*.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

SCHEME I



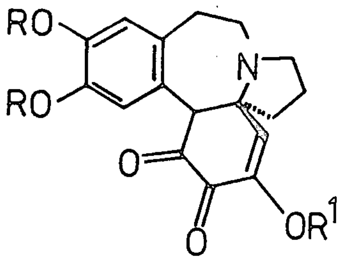
a $R^1 = R^4 = H$ $R^2 = R^3 = Me$

b $R^1 = R^2 = R^4 = Me$ $R^3 = H$

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

Biosynthetic studies have also now established 40 and 41 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[27,31].



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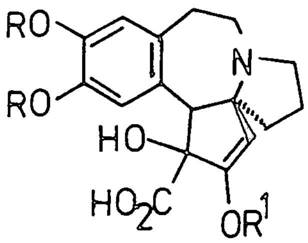

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1.6 Synthetic approaches to Cephalotaxine

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 (±)-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.

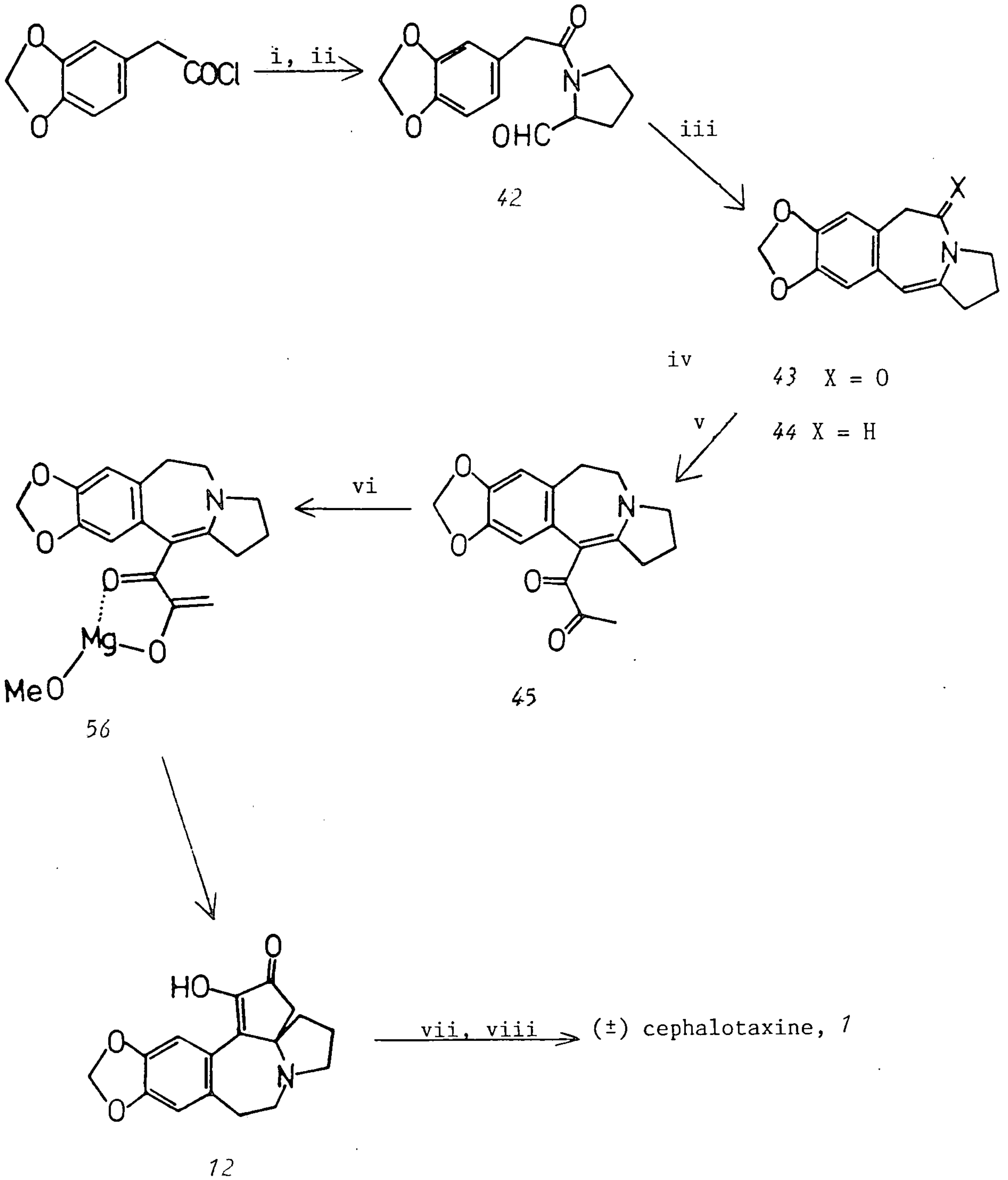
The first two total syntheses were reported simultaneously in 1972, employing completely different synthetic strategies[32].

i Weinreb and Auerbach synthesis

The first key synthetic step in this synthetic strategy[33,34] (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.

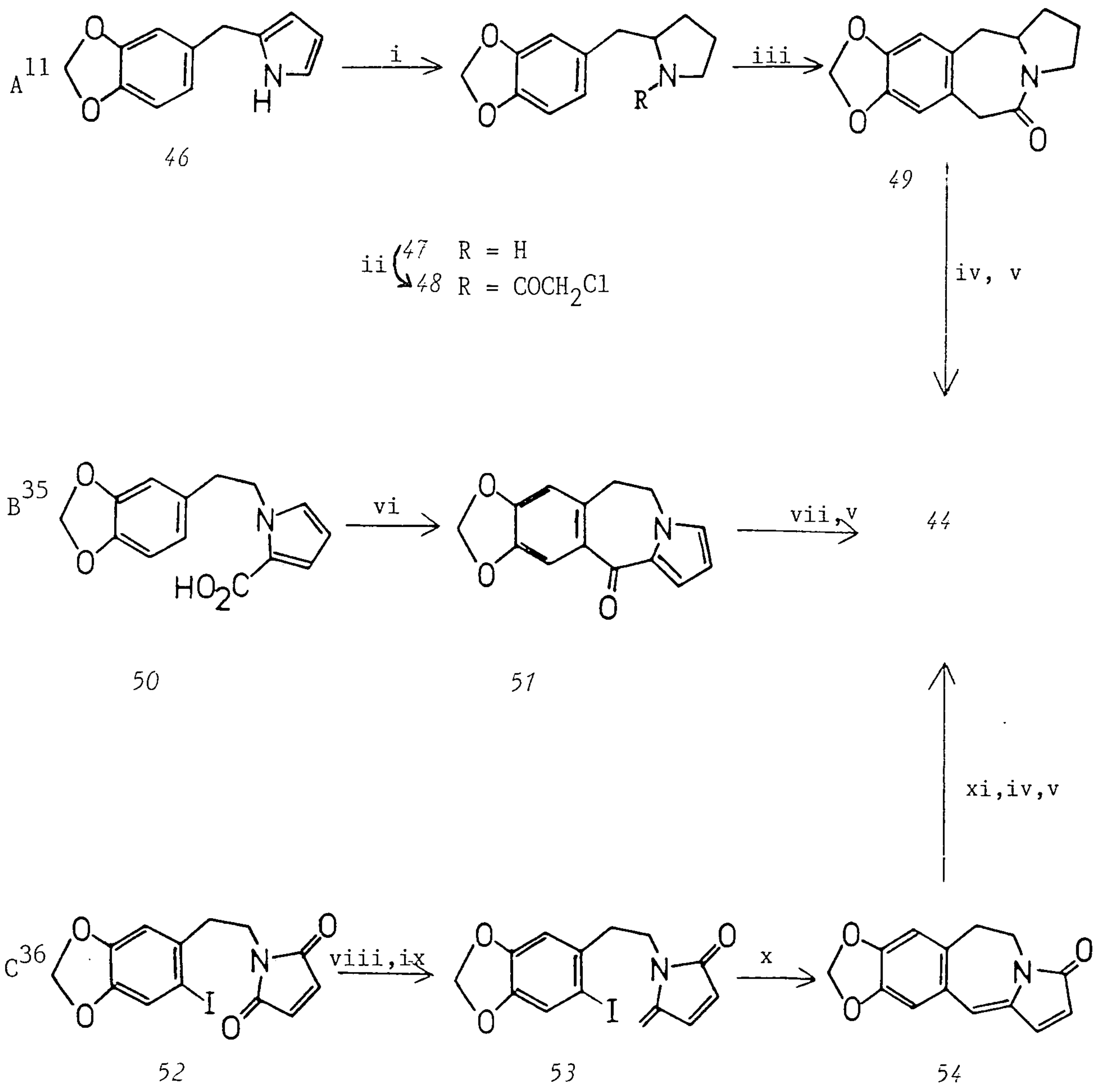
This enamine, *44*, was also an intermediate target for several other groups whose routes to *44* are outlined in scheme III[11,35,36].

SCHEME II

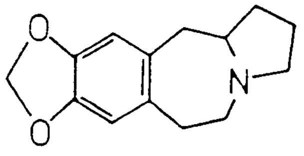


i 1-prolinol/K_2CO_3, ii DMSO/DCC (55%), iii $BF_3.Et_2O$ (87%),
iv LAH (100%), v pyruvic acid-ethyl chloroformate mixed anhydride (73%),
vi $Mg(MeO)_2$ (58%), vii $(MeO)_2$ CMe_2/pTsOH (45%), viii $NaBH_4$ (85%).

SCHEME III



i $Rh/Al_2O_3/H_2$(75%), ii $ClCOCH_2Cl/Et_3N$ (82%), iii hν (25%), iv LAH (65%), v $Hg(OAc)_2$, vi $(CF_3CO_2)O/SnCl_4$ (88%), vii H_2/C, viii MeMgI, ix pTsOH (70%), x hν/Et_3N (46%), xi H_2/PtO_2.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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, *12*, thus obtained, is actually the racemate of the naturally occurring alkaloid, demethylcephalotaxinone. This was conveniently methylated, under thermodynamic control, to provide racemic cephalotaxinone, *11*, 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 (±)-cephalotaxinone, *11*, to (±)-cephalotaxine, 1, is known to be stereospecific[25].

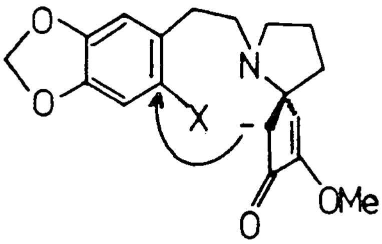
ii Semmelhack et al synthesis

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

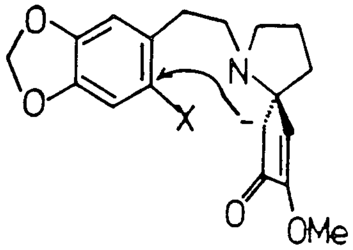
Semmelhack et al constructed the 1-azaspirocyclic subunit, *63*, in several steps from pyrrolidone, and *63*, reacted with *64* to provide the immediate cephalotaxinone precursor, *65* (scheme IV). The key step in the synthesis of azaspirocycle *63*, is the modified acyloin condensation of *60* to give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

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

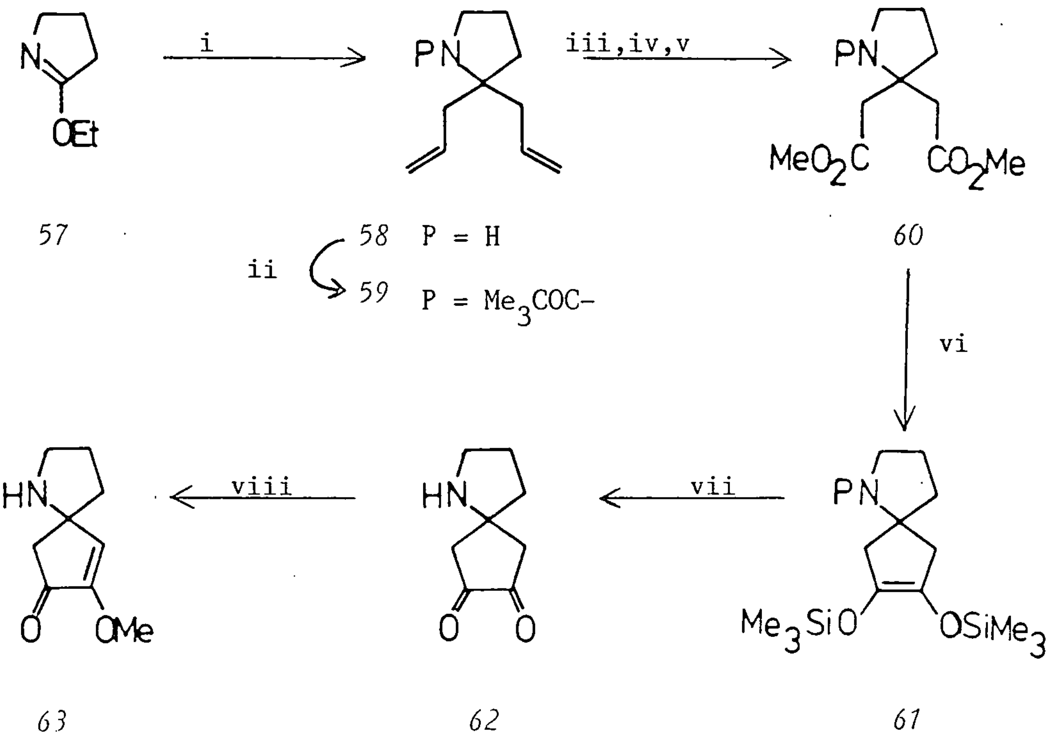


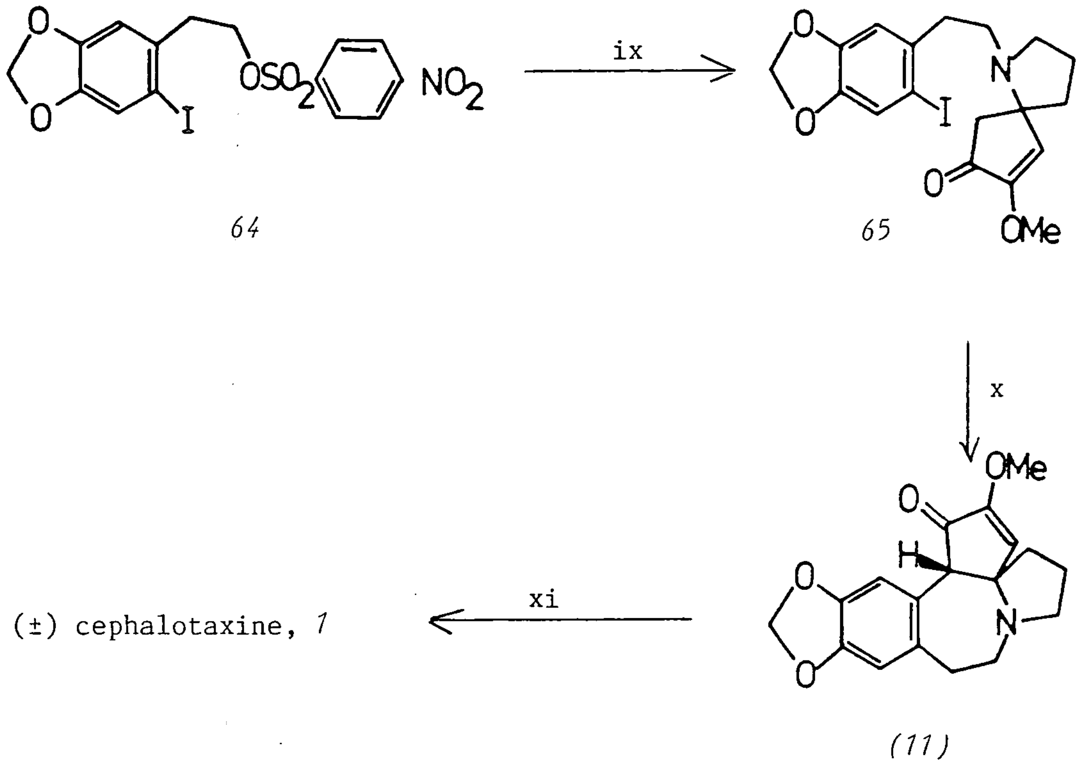
66A



66B

SCHEME IV





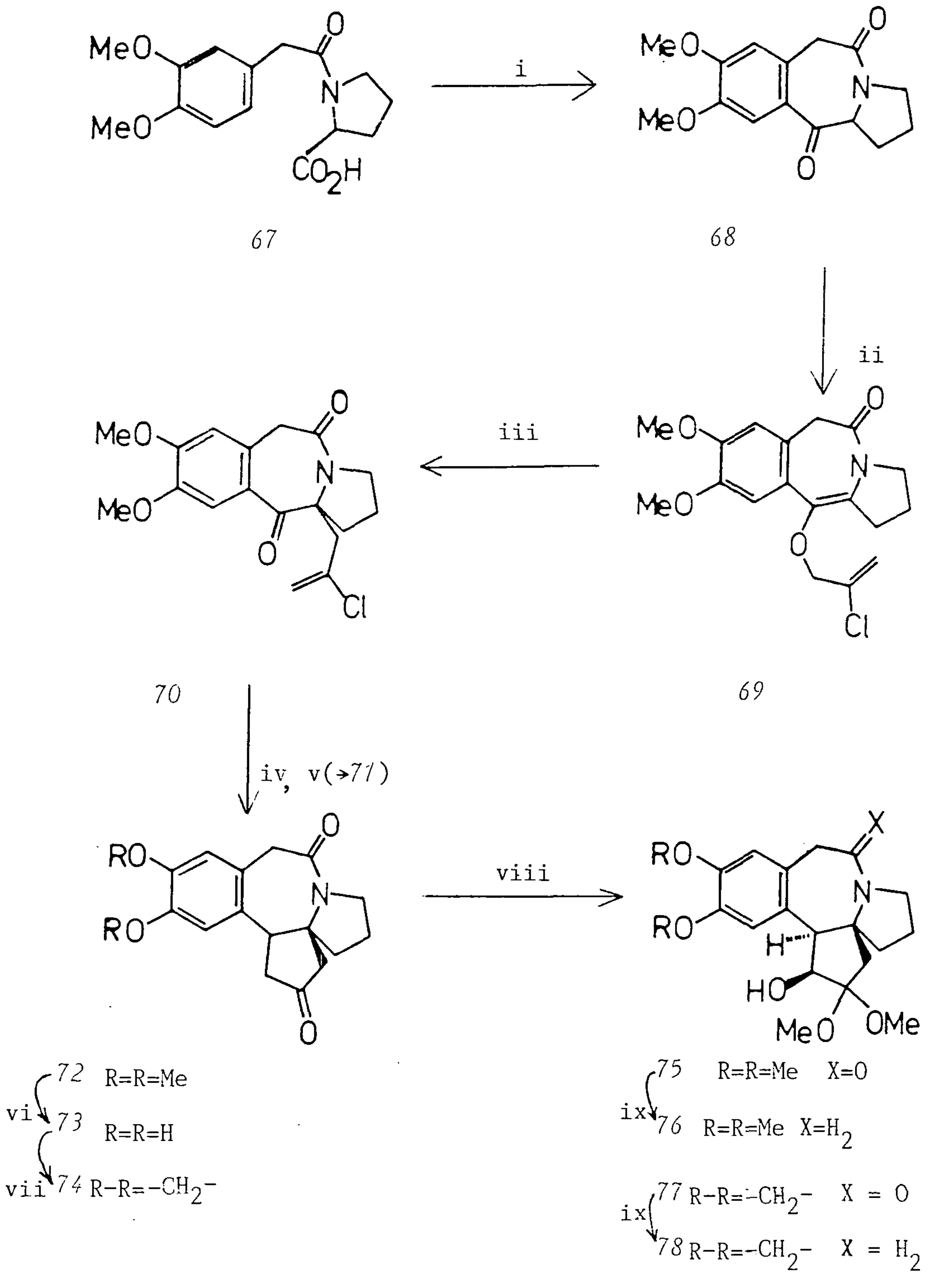
i allyl magnesium bromide (84%), ii Me_3COCON_3 (95%), iii O_3, iv Ag_2O/base, v $(MeO)_3CH/H^+$ (60%), vi Na-K, Me_3SiCl, vii Br_2/-78°C, vii CH_2N_2 (50%), ix *63* (70%), x hv/$KOBu^t$ (94%), xi DIBAL-H (76%)

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[39] (outlined in scheme V) starts from the dimethoxy compound *67*, leading to both cephalotaxine, *1*, and the 3,4-dimethoxy analogue, *79*.

SCHEME V



76 or *78* ⟶ cephalotaxine (91%) or dimethoxycephalotaxine (78%)
1 *79*

i PPA/55°C (74%), ii 2,3-dichloroprop-1-ene (91%), iii 150°C (97%), iv $NaBH_4$ (100%), v 90% H_2SO_4, 55°C (69%), vi BBr_3/-78°C (79%), vii CH_2Br_2/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.

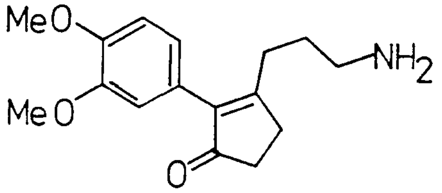
Final conversion of these intermediates to (±)-3,4-dimethoxycephalotaxine, *79* , and (±)-cephalotaxine, *1*, respectively, is then easily achieved in two steps, in good yields.

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 (±)-cephalotaxine from Hanaoka's tetracyclic intermediate, *68*, is 10% over nine steps, compared to 16% from Weinreb's elaboration of *44*to (±)-cephalotaxine in only three steps. The only reason Hanaoka's route to (±) 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[40].

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.



80

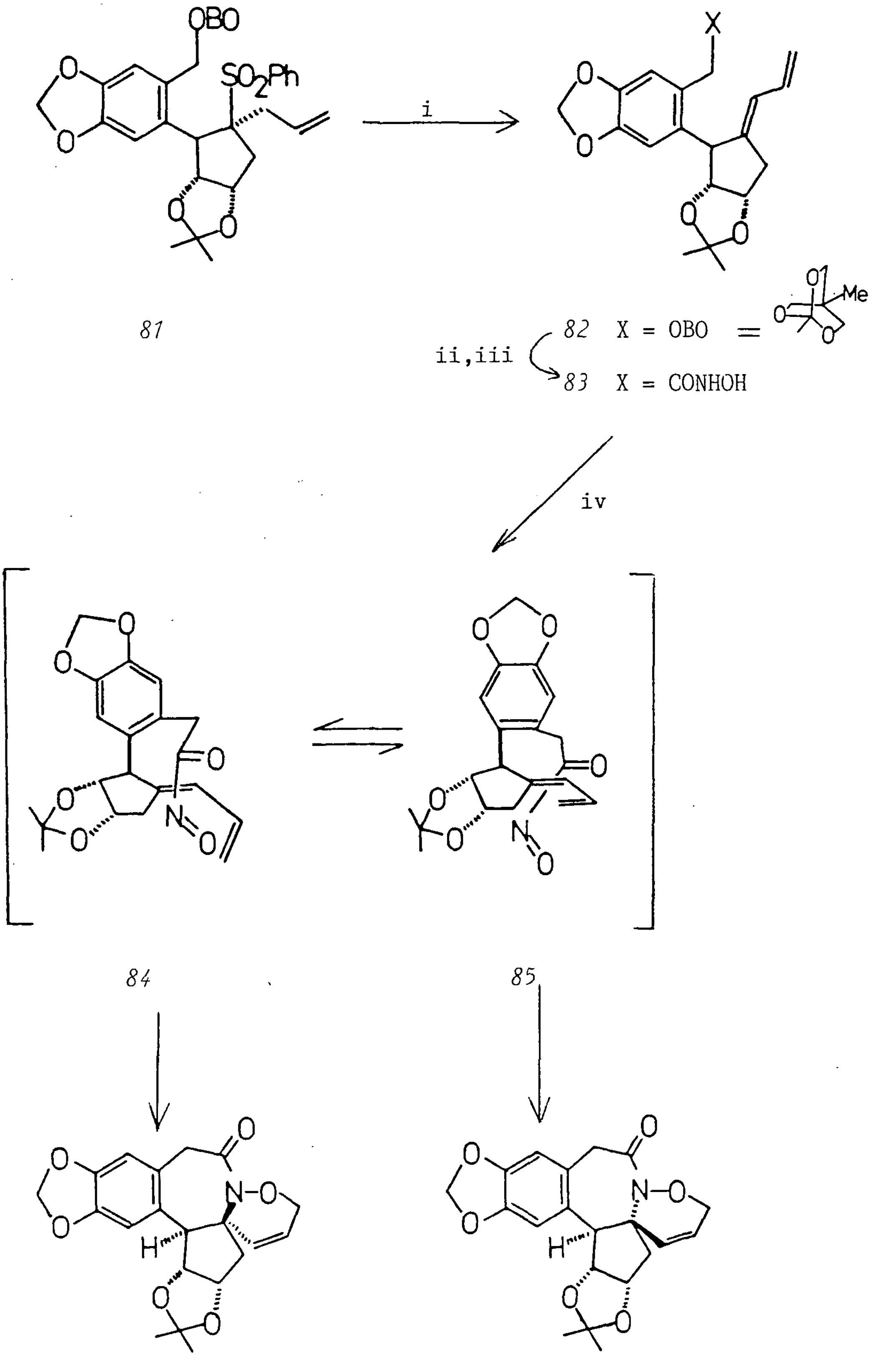
The alternative strategy (scheme VI) envisaged from related precursors, was a [4 + 2]Π cycloaddition of the nitroso derivative of *83* with the internal diene. This would construct ring C, and an easily modifiable ring D, and was expected, from precedents, to occur in a stereospecific manner, leading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

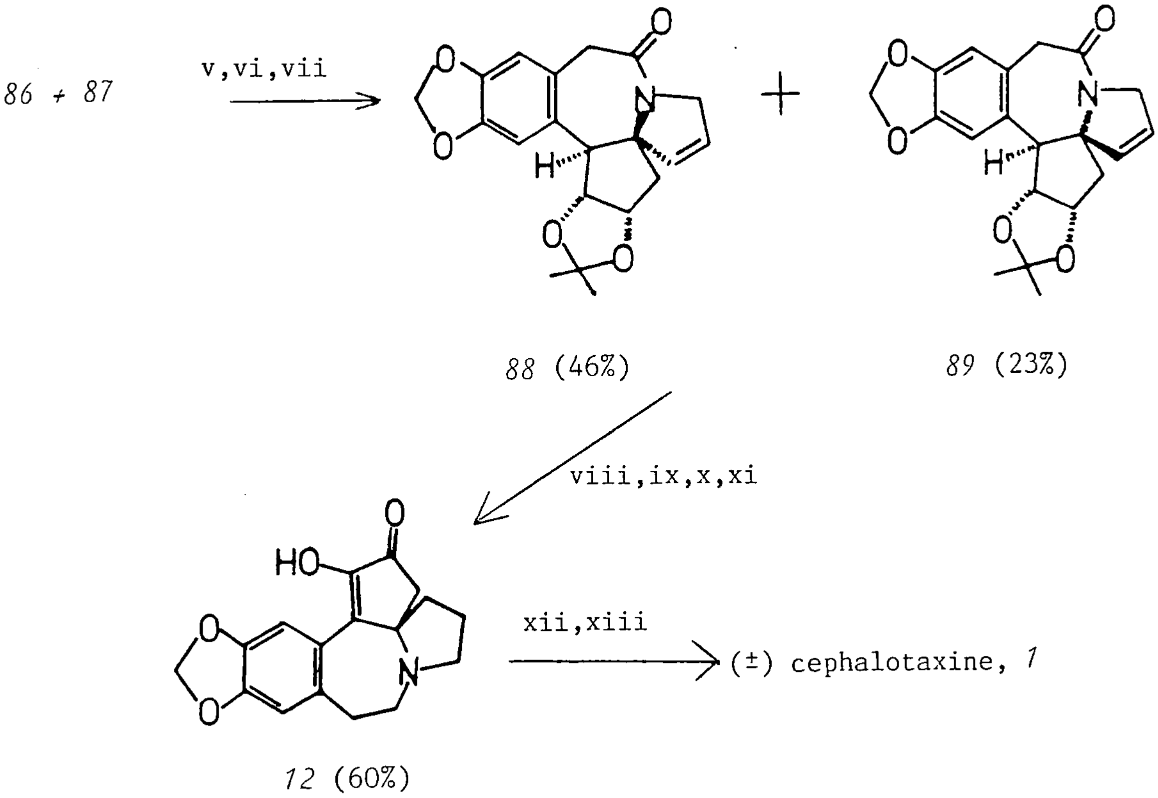
However, the cycloaddition provided an isomeric mixture, which on subsequent N-O cleavage with sodium-mercury amalgam, mesylation and then intramolecular amide alkylation, yielded a 2:1 mixture of the cephalotaxine precursor, *88*, and the diastereomer, *89*, respectively.

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 (±)-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-BuLi, ii pTsOH, iii NH_2OH, iv HIO_4, v Na-Hg/EtOH, vi $MsCl/Et_3N$, vii NaH, viii H_2/Pd, ix BH_3.THF, x HCl, xi Swern oxidation, xii pTsOH, xiii $NaBH_4$ (97%).

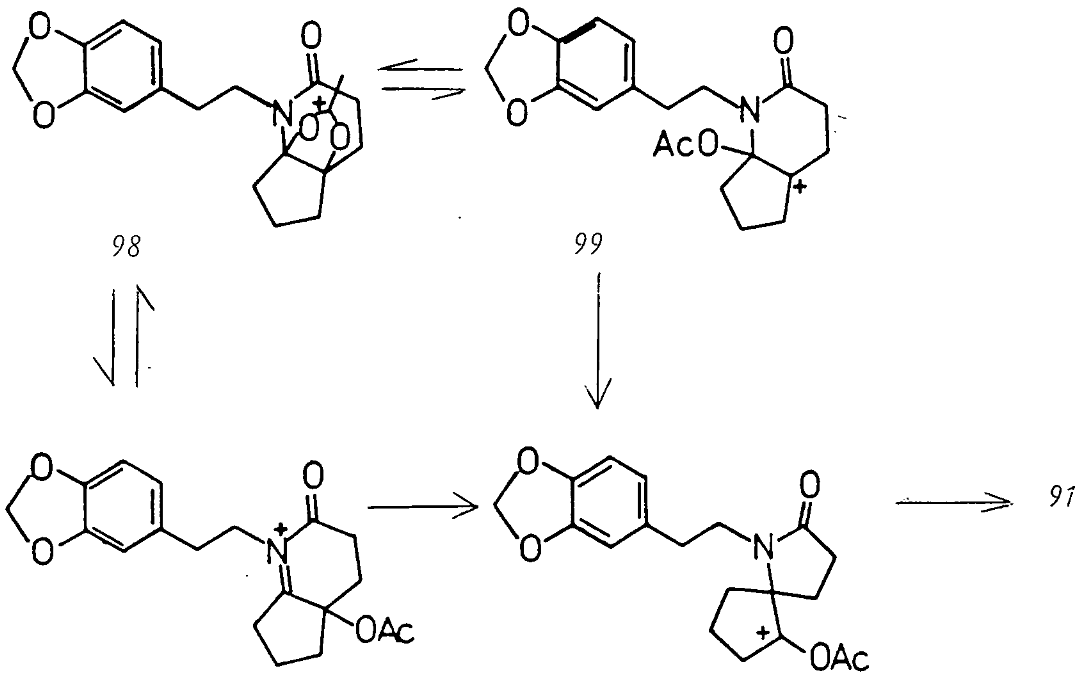
of both precursors leading to a single racemic intermediate, *12,* which is then converted to (±)-cephalotaxine by essentially the same methodology employed by Weinreb et al[33,34].

v Keuhne et al synthesis

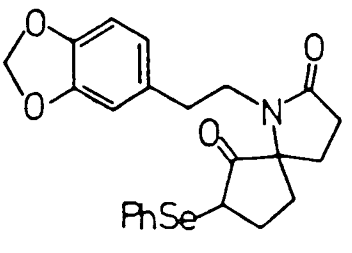
A fifth total synthesis has been presented recently[42], and has now been published[43] (scheme VII).

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

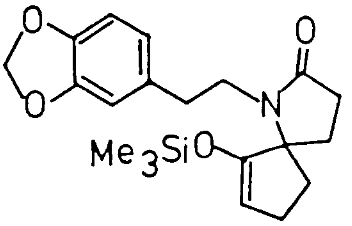
The mechanism postulated by Kuehne et al, involves two rearrangement pathways from the bridging acetal carbocation intermediate, *98,* via either *99* or *100* , to the cationic spiro intermediate *101* . This then adds acetate, and is then converted to the keto system, *91*. Support for both rearrangement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

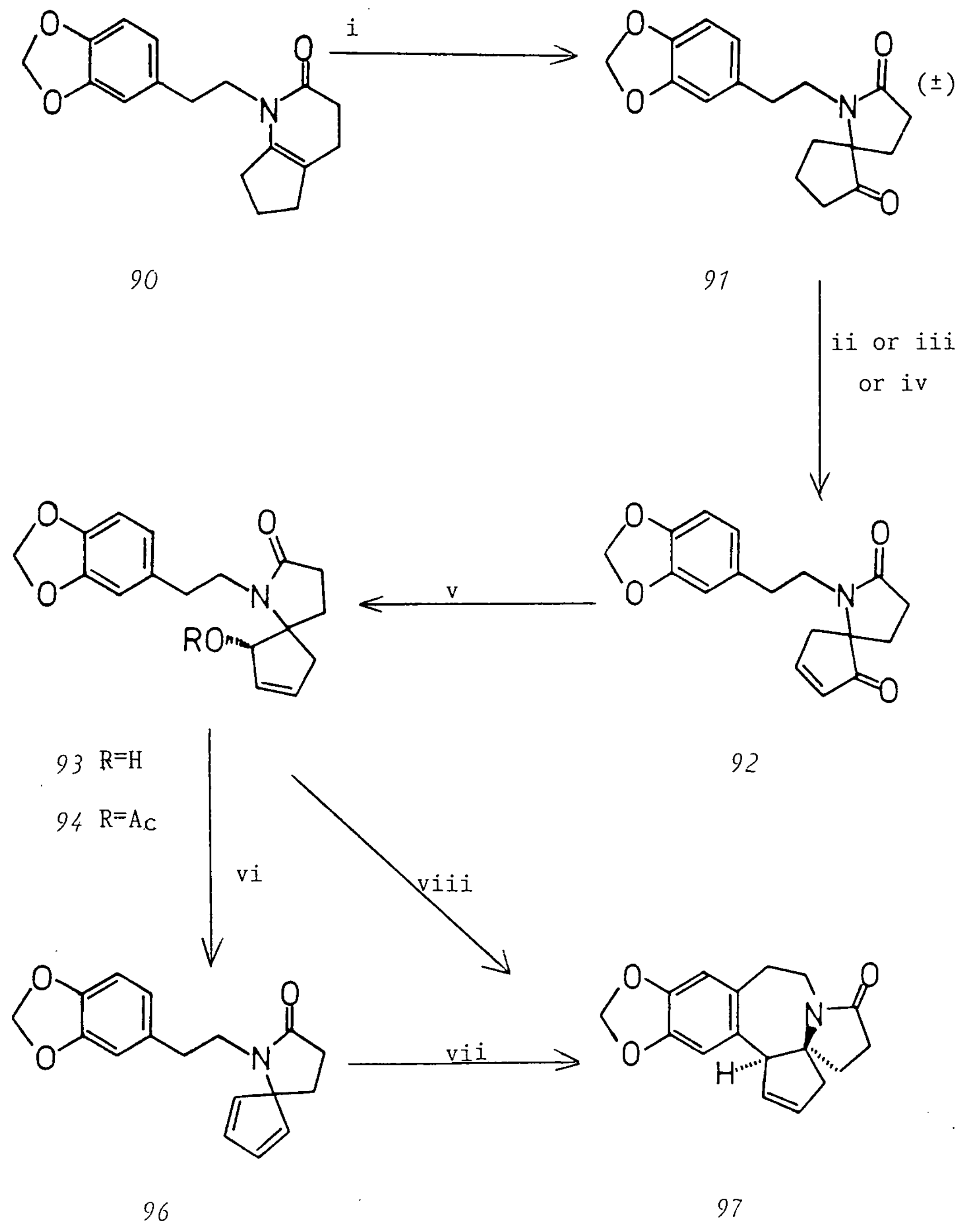


103



102

SCHEME VII



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

Meerwein-Pondorff reduction of the α ,β-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[40].

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.

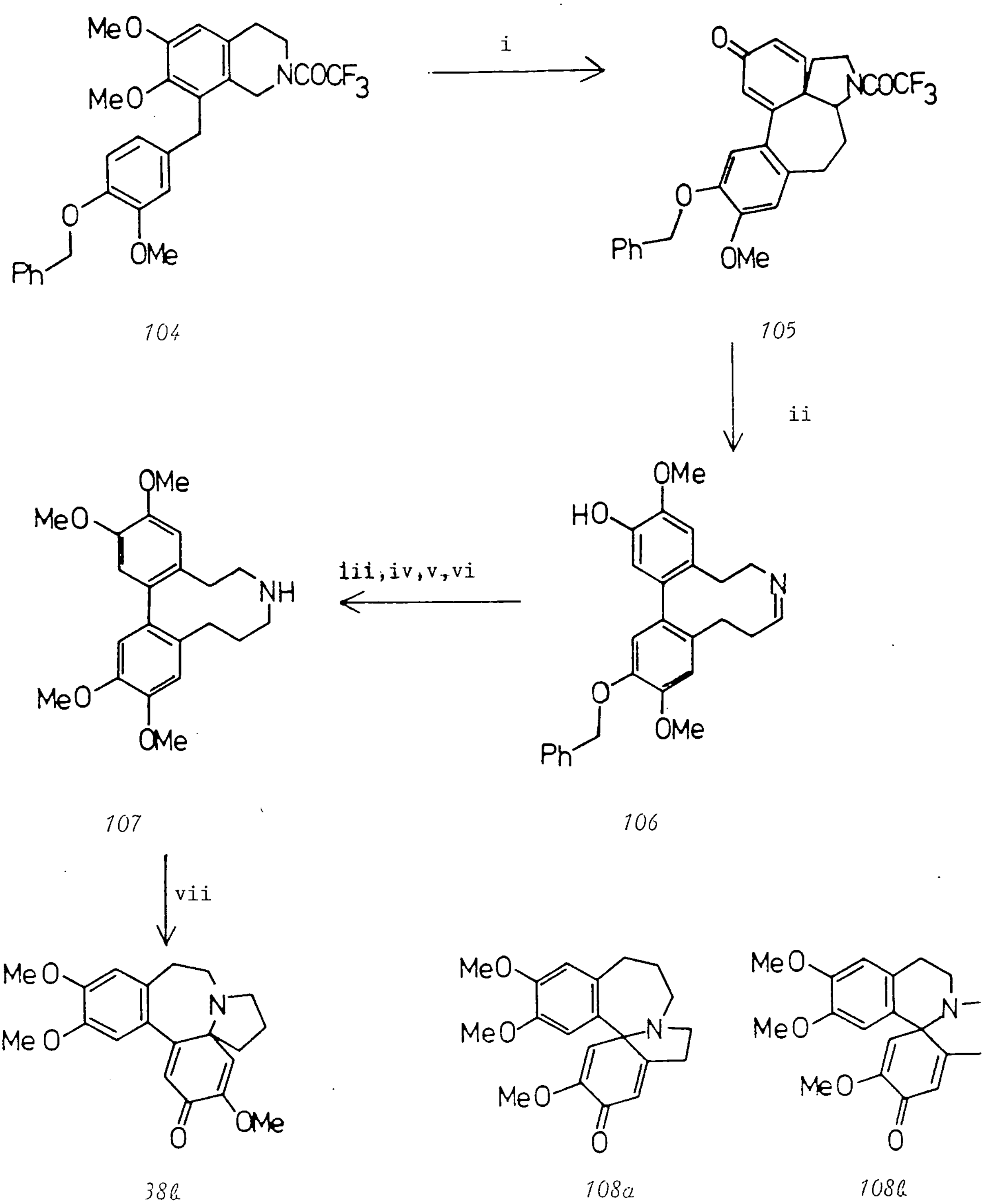
Kupchan et al[44,45] converted the hypothetical biogenetic intermediate 1-phenethyl tetrahydroisoquinoline, *104* to *105* by intramolecular oxidative coupling. This was ring expanded by treatment with base, to *106*, then elaborated to intermediate *107* in four steps, in ca. 70% overall yield (scheme VIII).

Oxidation with potassium ferricyanide then provided the coupled product *38b*, 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 *38b* , led either to *108a*[46], or a mixture of *108a* and *108b*[47].

vii Other synthetic routes in progress

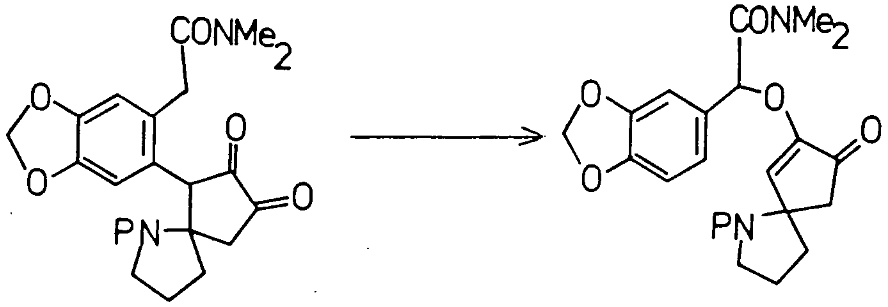
Several other groups are also currently trying to synthesize cephalotaxine. Hill and co-workers[48] are investigating routes via the same 1-azaspirocyclic intermediate as we have prepared (see 2.2), including possible aziridinium expansion methodology (see 3.1.iv).

SCHEME VIII



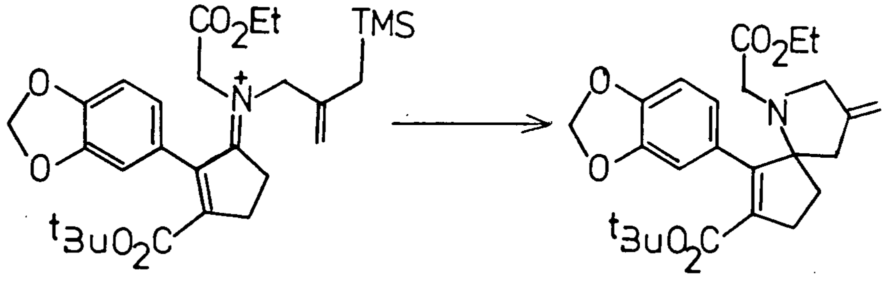
i VO$_2$/CF$_3$CO$_2$H, ii NaOH, iii NaBH$_4$, iv (CF$_3$CO$_2$) O, v CH$_2$N$_2$,
vi Pd/H$_2$, vii K$_3$Fe(CN)$_6$ (10%).

Raucher's group[49] 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.



109 *110*

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



111 *112*

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

Similarly, Bryson et al[53] 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.

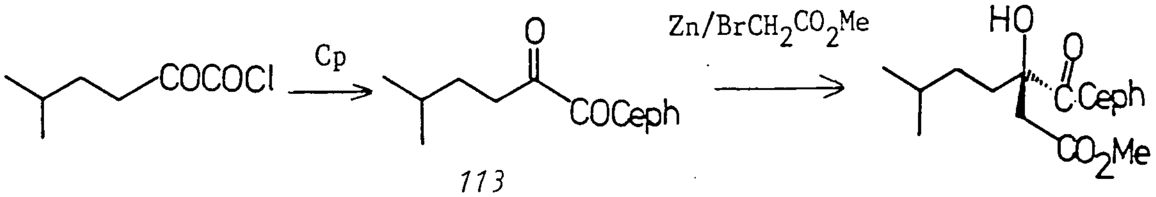
A variety of approaches are now available for the conversion of cephalotaxine to any of its four antitumour esters, which we will here only briefly review. Unfortunately, few of these are asymmetric, and thus separation of diastereomers is usually required.

Initial attempts at acylation of cephalotaxine with a fully formed acid substituent, were uniformly unsuccesful[7,54], 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[55] and co-workers reported the reasonably short route to deoxyharringtonine and its C2' epimer, summarized in scheme IX.

SCHEME IX



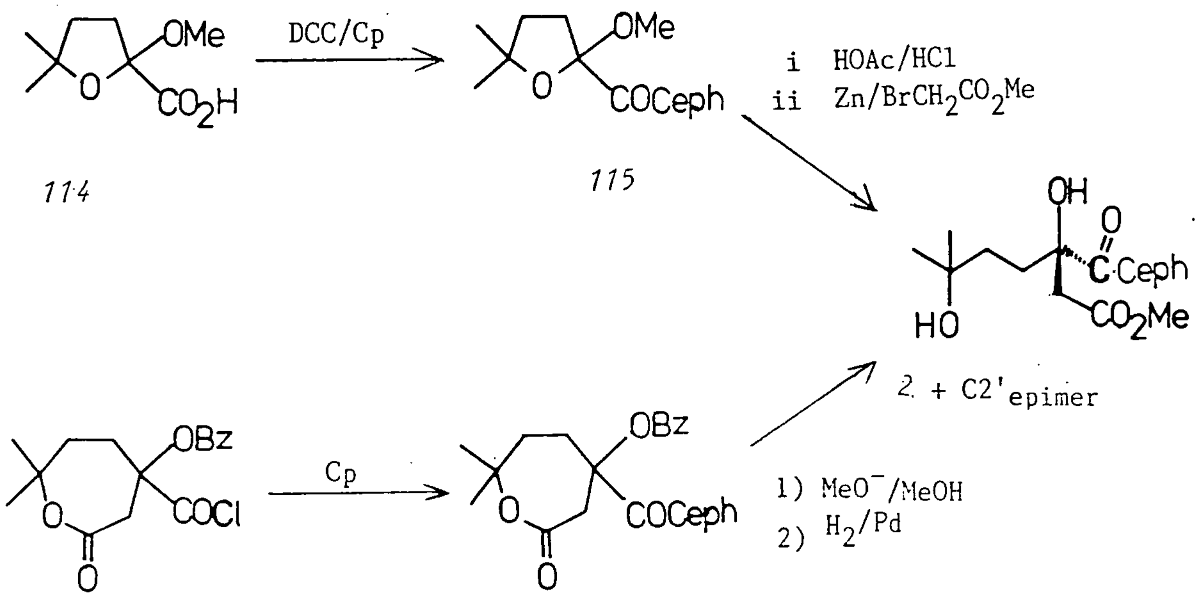
113

3 + C2' epimer

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*[56] or *116* [57] are outlined in scheme X, both providing harringtonine along with its C2' epimer.

SCHEME X



114

115

2 + C2'epimer

116

117

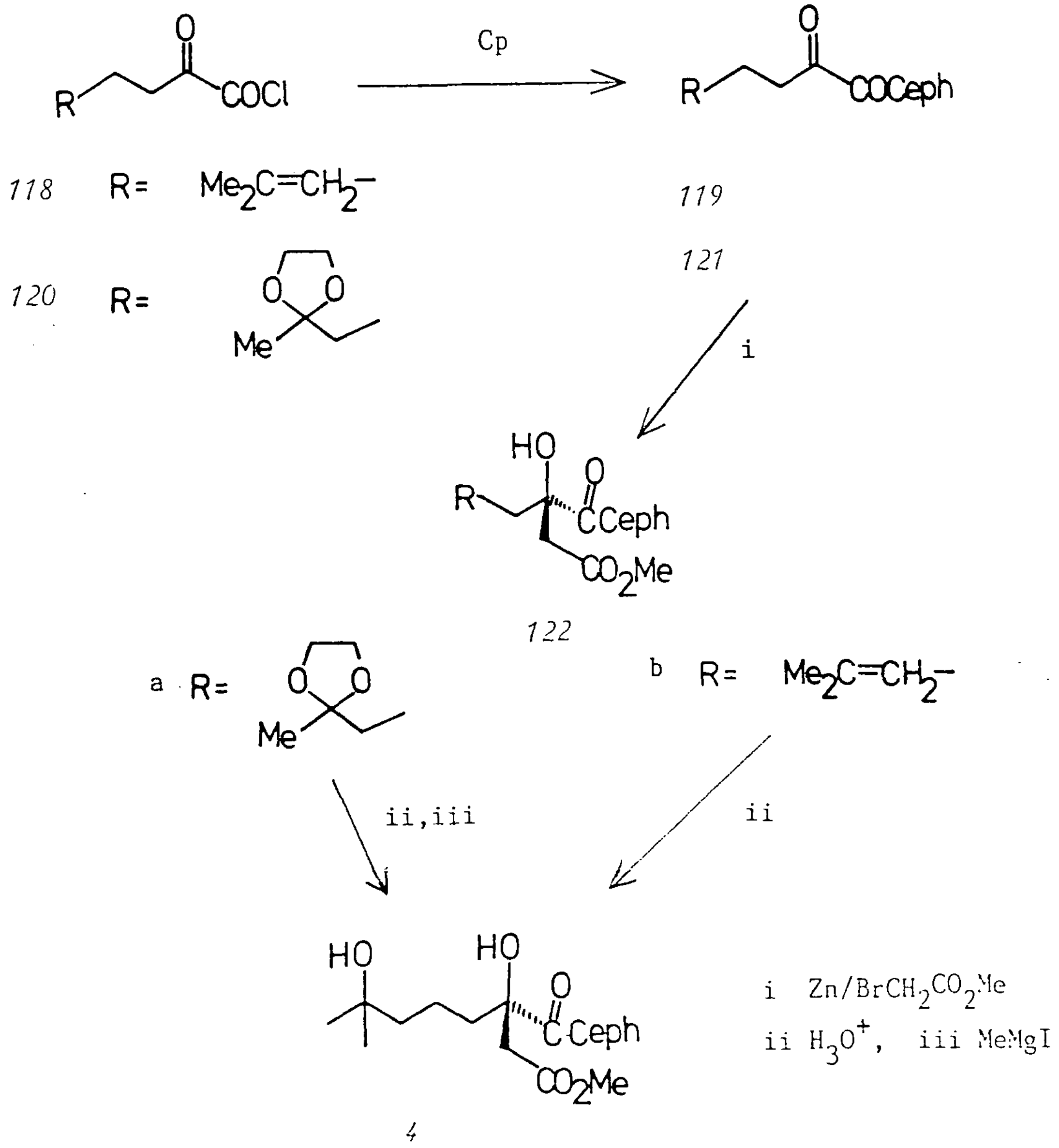
Throughout schemes IX to XIII, 'Cp' refers to parent cephalotaxine, *1* , and 'ceph' to the cephalotaxyl nucleus attached to the ester acyl oxygen.

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 α-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.

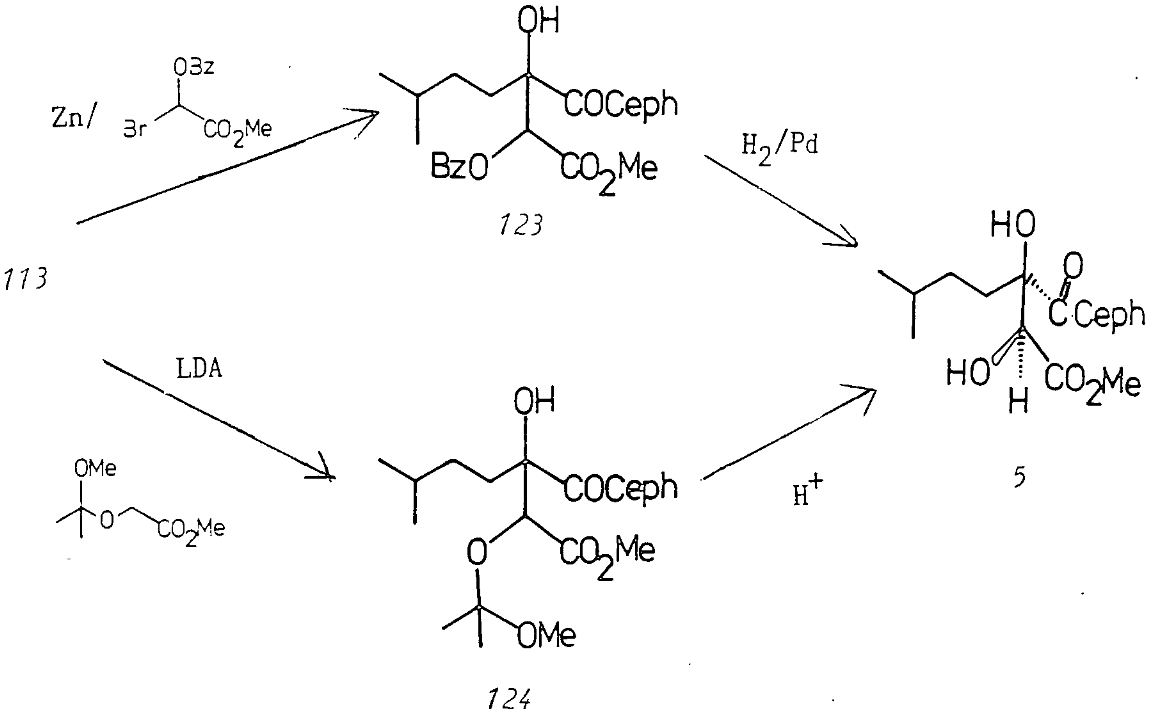
SCHEME XI



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



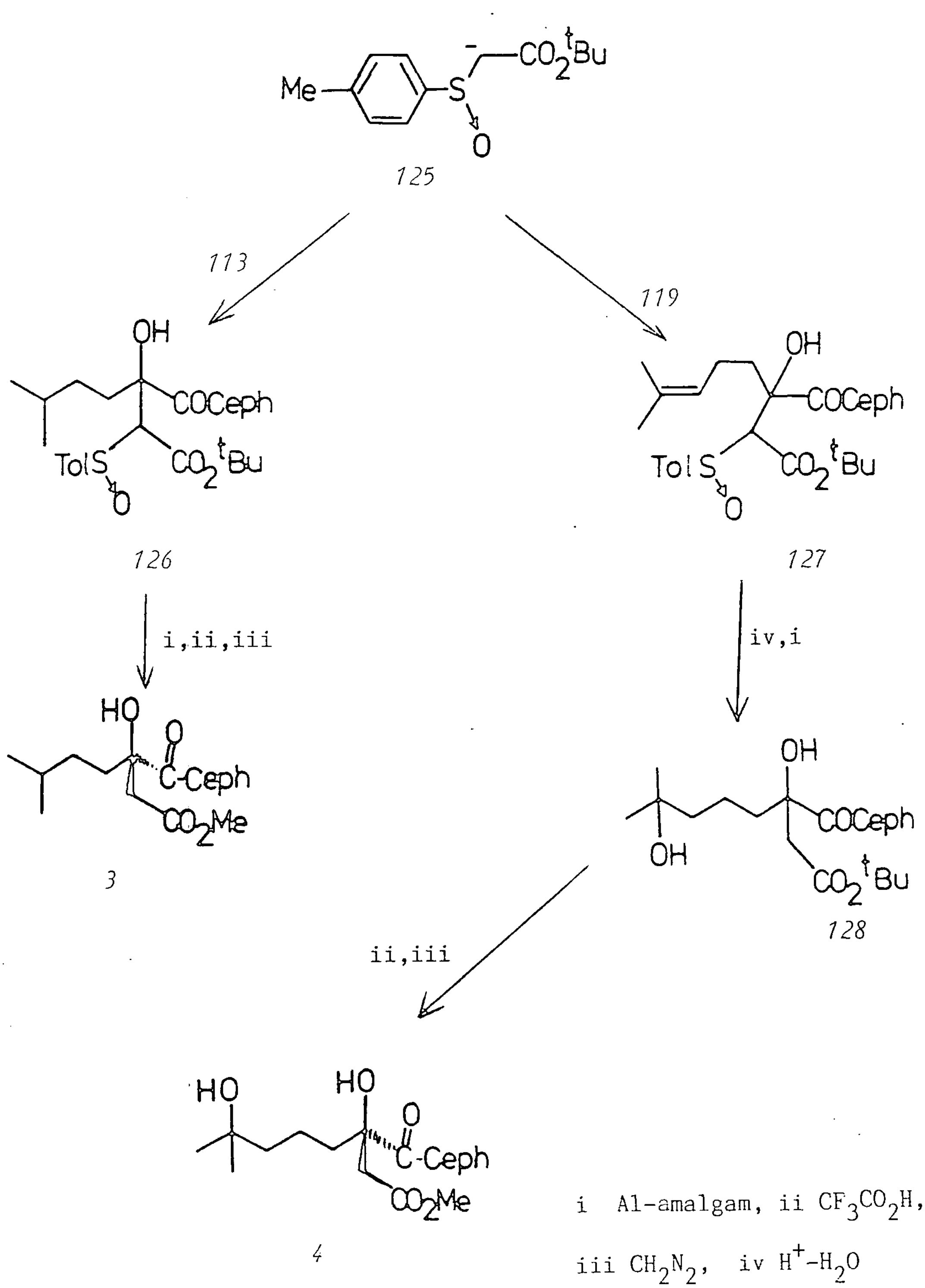
v Asymmetric syntheses of deoxy- and homoharringtonine

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-α-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



i Al-amalgam, ii CF_3CO_2H,

iii CH_2N_2, iv H^+-H_2O

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[58,59].

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 α-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.

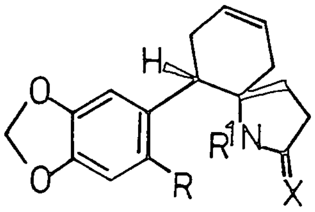
1.8 Retrosynthetic analysis of cephalotaxine

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[25].

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^1 = 2C fragment, H

X = O,H_2

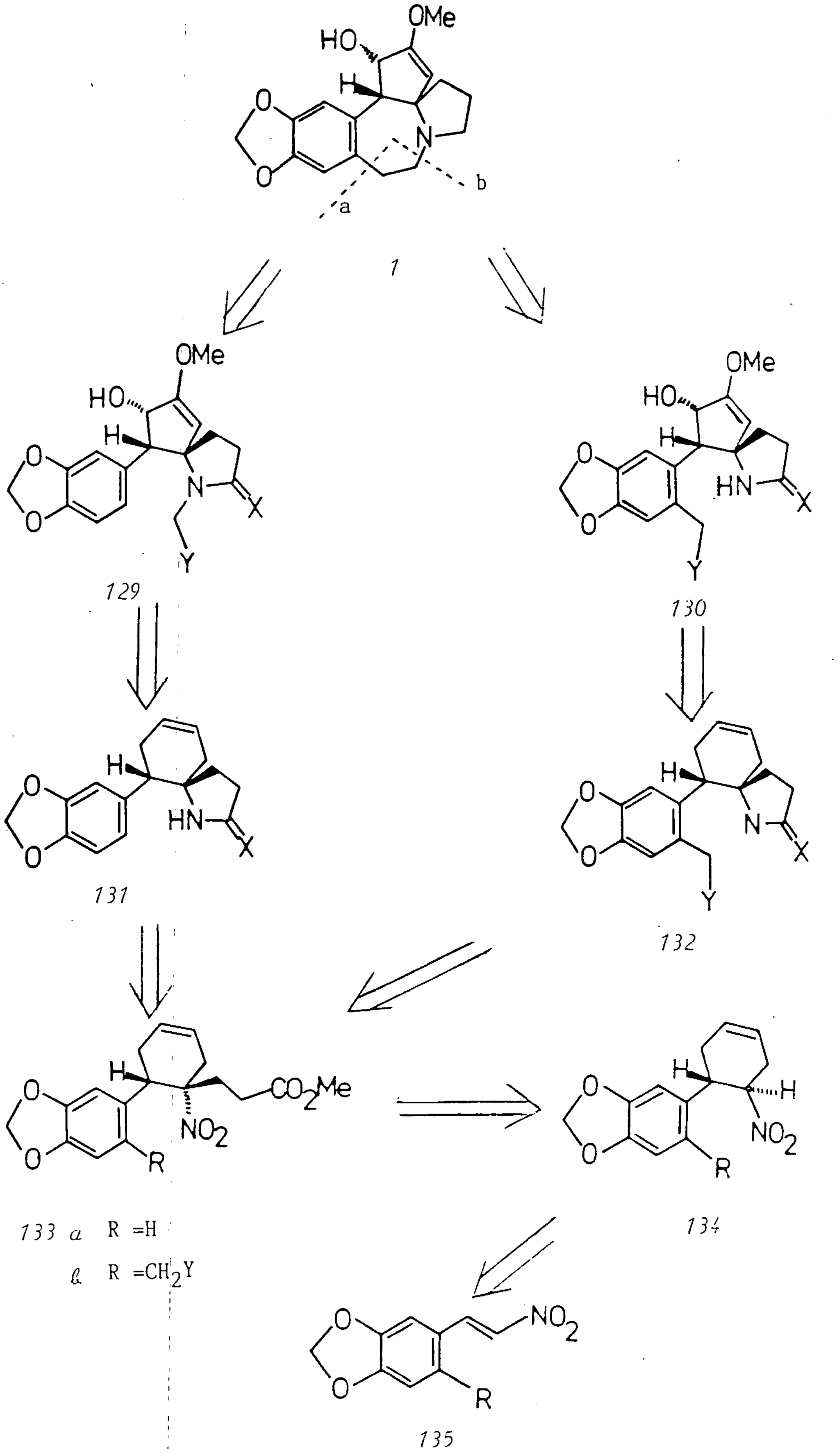
There are two types of such intermediate, viz those arising from C-aryl disconnection (a), and those from C-N disconnection (b). These intermediates represent different strategies, which, however, retrosynthetically converge with intermediates *133a* and *133b* (scheme XIV).

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[39,40,43]. Hence, we have a variety of pre-targets through which to direct ring E elaboration.

SCHEME XIV


OMe
HO
H
O
O
N
a
b
1
129
X
Y
HN
130
131
132
CO$_2$Me
NO$_2$
R
H
133 a R =H
b R =CH$_2$Y
134
135

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[39] and 8-oxo-cephalotaxine[43], 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.

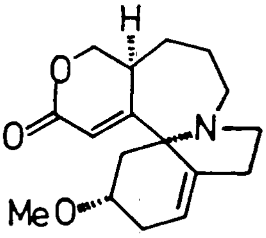
With the recent flurry of new synthetic approaches, to cephalotaxine, it is expected that the next few years will witness increasing reports of synthetically modified cephalotaxine ring systems.

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[60] alkaloids (e.g. *33*), the 1-azaspiro [6.5] dodecane homoerythrina[24] (e.g. *31*) and phellibilidine[61] alkaloids (e.g. phellibilidine *138*), the 1-azaspiro [5.4] decane spirobenzyl isoquinolines (e.g. *191*) and the 1-azaspiro [4.4] nonane brevianamide[62] alkaloids (e.g. brevianamide A, *139*), and other fused indole alkaloids e.g. austamide *140*[63-65] and aristoteline *141*[66].



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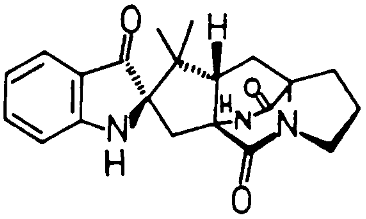

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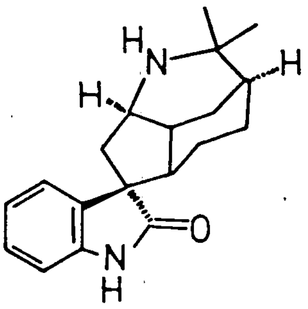

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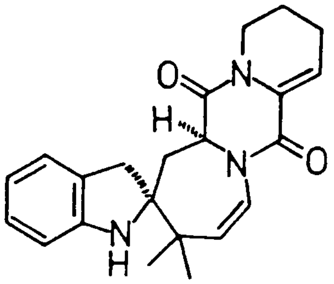

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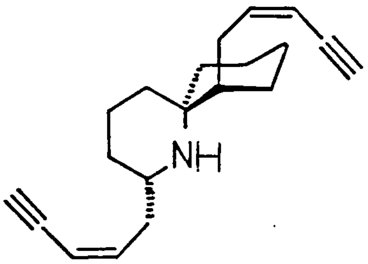
Simple bicyclic azaspirocyclic alkaloids which are of current interest include, most importantly, the 1-azaspiro [5.5] undecane histrionicotoxins [67,68] and the 2-azaspiro [5.5] undecane nitramine alkaloids[69]. However, their apparent structural simplicity belies considerable synthetic challenges.

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*.



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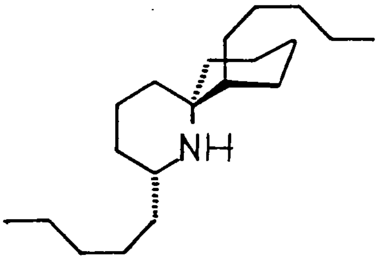
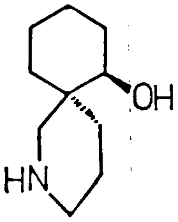


143

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.



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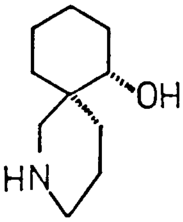

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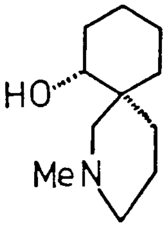


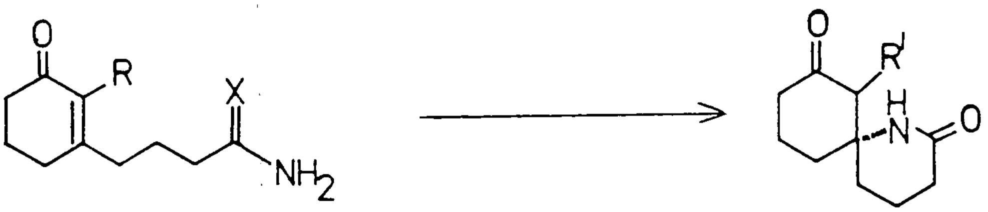
146

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 rearrangements 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[70] to spirocyclizations. These, and other approaches, are now considered in turn.

i Intramolecular Michael cyclizations.

Kishi et al[71] 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[72].



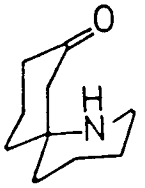
147 R = butyl X=O

148 R = butyl X= n-pentyl

150 R = H X = H_2

152 R' = ⋯⋯ Bu

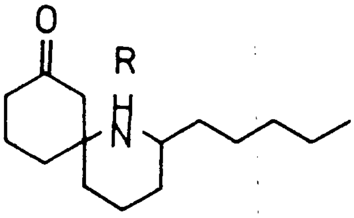
149 R' = ▬ Bu



151

In closely related work, Corey et al[73] found no stereo-selection in the uncatalysed cyclization of *152* to *153*, while Godleski et al[74] 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[40].



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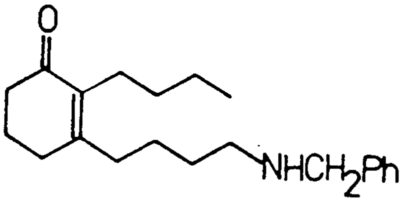

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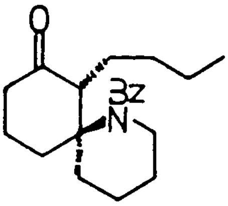
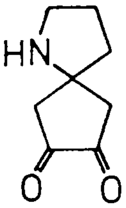


155

Interestingly, Semmelhack et al[38] 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.



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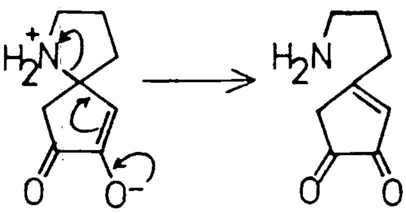
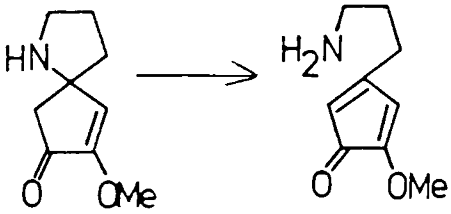


156 *157*

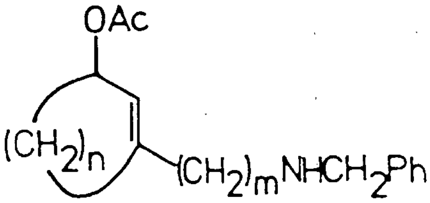


63 *158*

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

ii <u>Metal assisted cyclizations</u>

Metal assisted spirocyclization of substrates *159*, clearly related to those above, has provided entry not only to the 1-azaspiro [5.5] undecane skeleton, *160a*, but also to the 1-azaspiro [4.5] - and 1-azaspiro [5.4] - decanes *160b* and *160c* respectively, and 1-azaspiro [4.4] nonane, *160d* skeletons[51,52].



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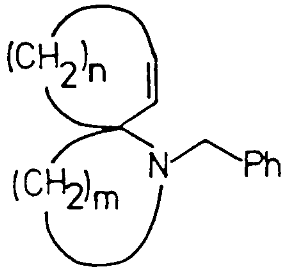
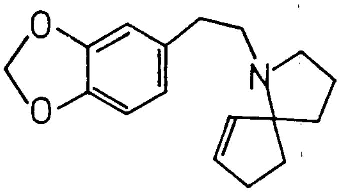


160a n = 3 m = 4
b n = 3 m = 3
c n = 2 m = 4
d n = 2 m = 3

Similarly, Carruthers et al[75] have recently found palladium (*0*) catalysed cyclization of amino-cyclohexyl acetate *159ℓ* (n = 3, m = 4), to azaspirocycle *160a*, 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[76a 76b].



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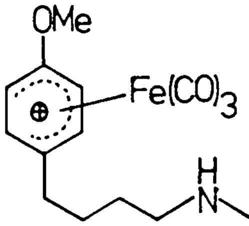

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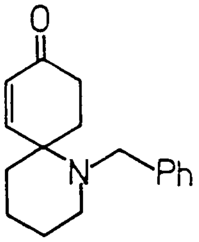


163

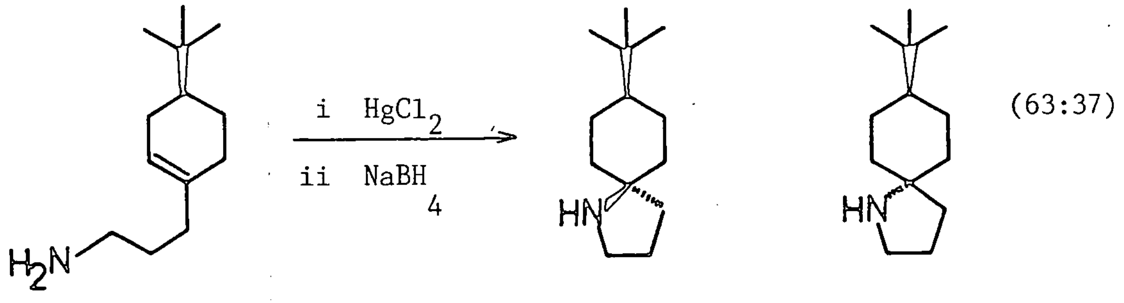
Azaspirocyclization of a cyclohexadienylium iron tricarbonyl complex, *162*, followed by oxidative decomplexation and hydrolysis, has also provided entry to the 1-azaspiro [5.5] undecane ring system, *163*[77].

iii Halo and mercuricyclizations

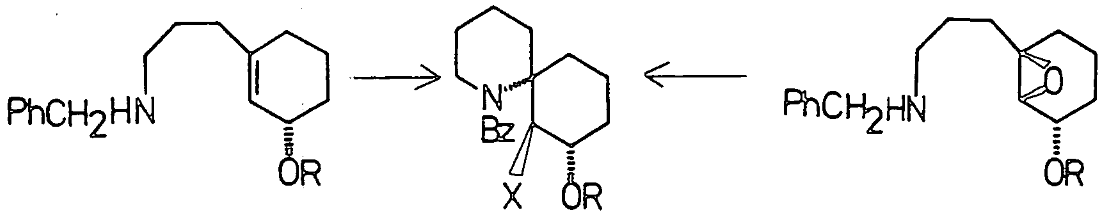
The mechanistically similar methodologies of mercuricyclization and iodocyclization, provide another entry to azaspirocycles, with the possibility of stereoselection.

The mercuricyclization of the amino-olefin *164* provides some selection of *165* over *166*[70,78]; while iodocyclization of *167* leads to good selectivity, providing the single azaspirocycle *168* [79,80].

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*.



164 165 166

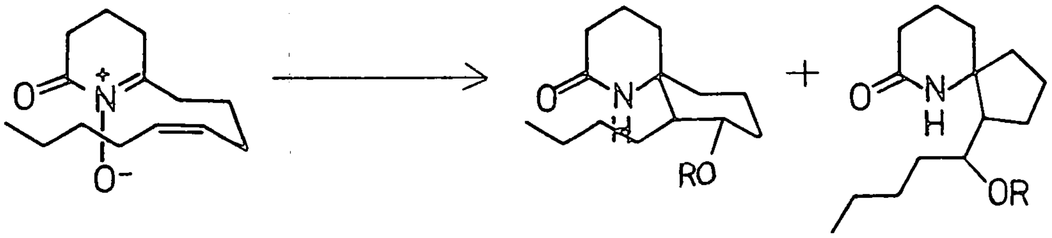


167 168 X = I 169

170 X = OH

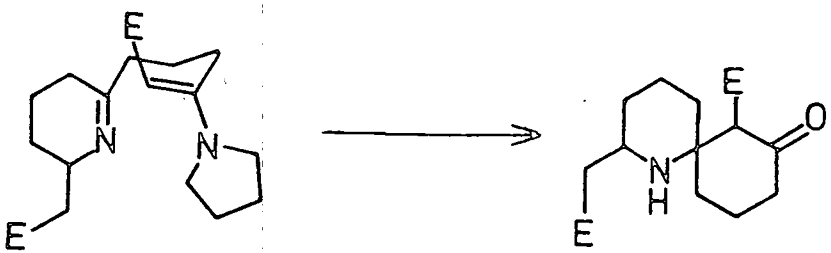
iv Acyliminium cyclizations

Evans et al[81,82] 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*.



171 172 (40%) 173 (30%)

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

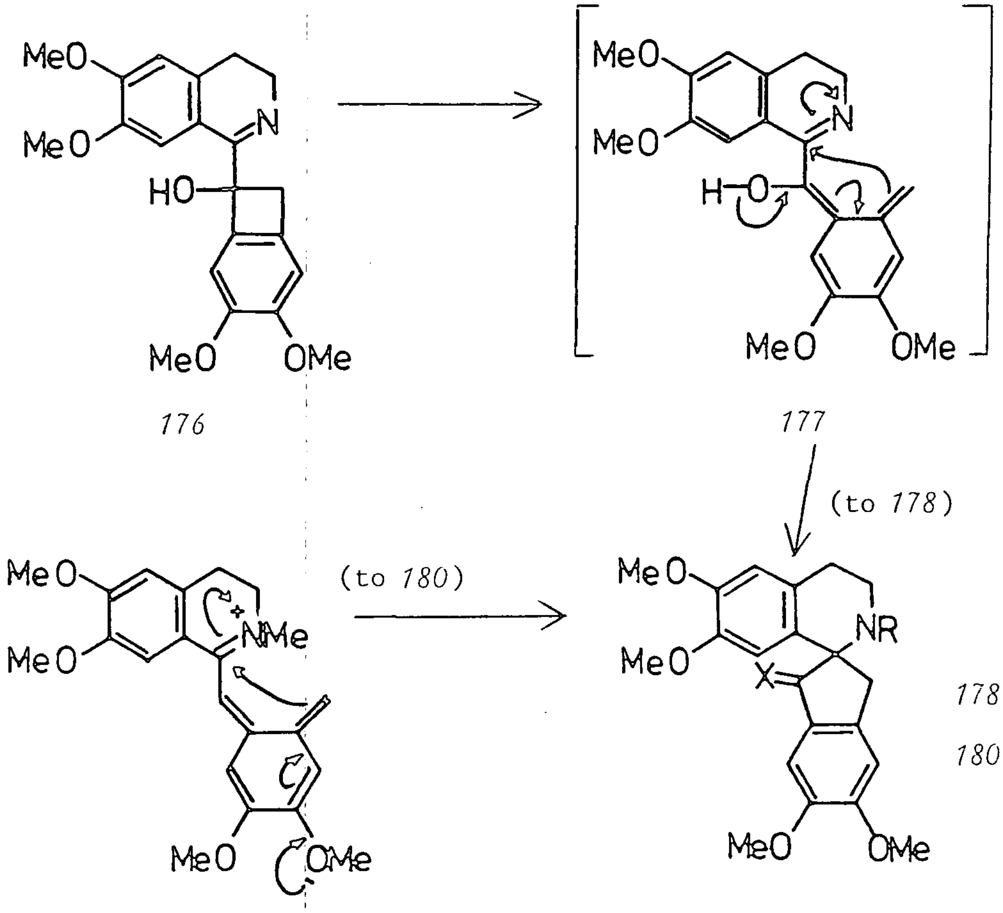


174 *175*

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*[86,87].

Analogously, the intermediate iminium o-quinonoid system *179* undergoes spirocyclization to *180*, by a similar process.[88,90]



176 *177* *179*

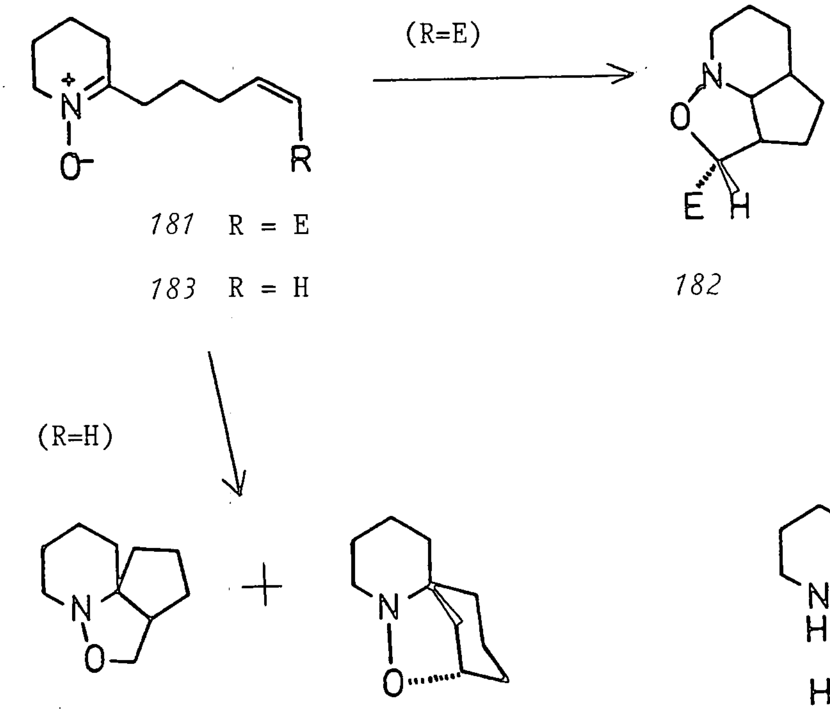
178 R = H X = O

180 R = Me X = CH_2

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*[91], and *183* to a mixture of *184* and *185*[92]. The latter compound was then converted to the simple 1-azaspirocycle *186*.



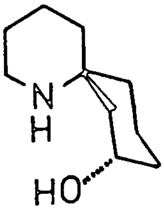
181 R = E

183 R = H

182

184

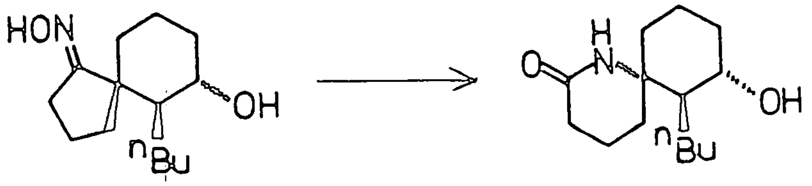
185



186

vi Rearrangements

One of the earliest syntheses of a histrionicotoxin derivative, reported by Corey et al[93], utilized the Beckmann rearrangement of the carbospirocyclic oxime *187*, to the spirolactam *188*.



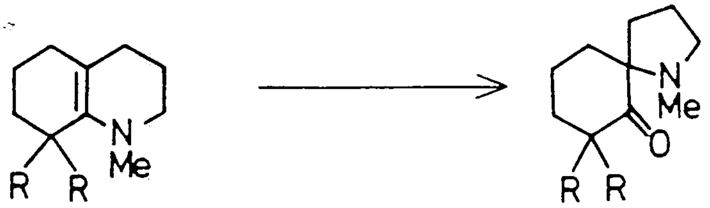
187

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[94], though yields were poor.

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

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[96].



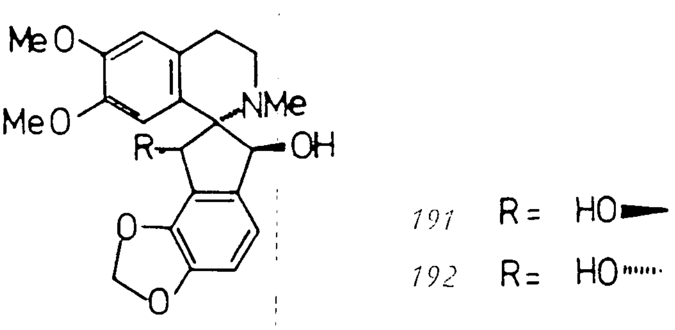
189a R=R=Me

189b R=R=H

190a 58%

190b 20%

Spirobenzylisoquinoline alkaloids, containing a benzo-fused 1-azaspiro [5.4] decane substructure, have also been obtained by re-arrangements. Approaches to ochrobirine[97], corydaine[98], fumaricine[99], raddeamine, *191*,[100] and yenhusomine, *192*,[100] 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.



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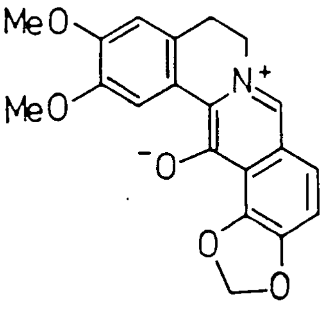
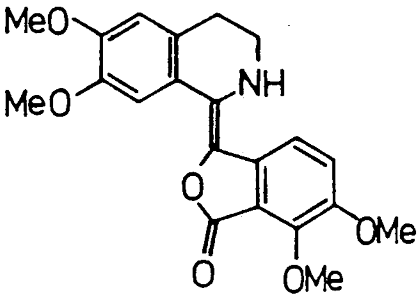


193

A completely different rearrangement to a spirobenzylisoquinoline occurred when DIBAL-H reduced *194* to *195*[101].



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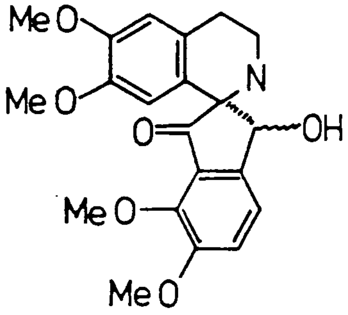
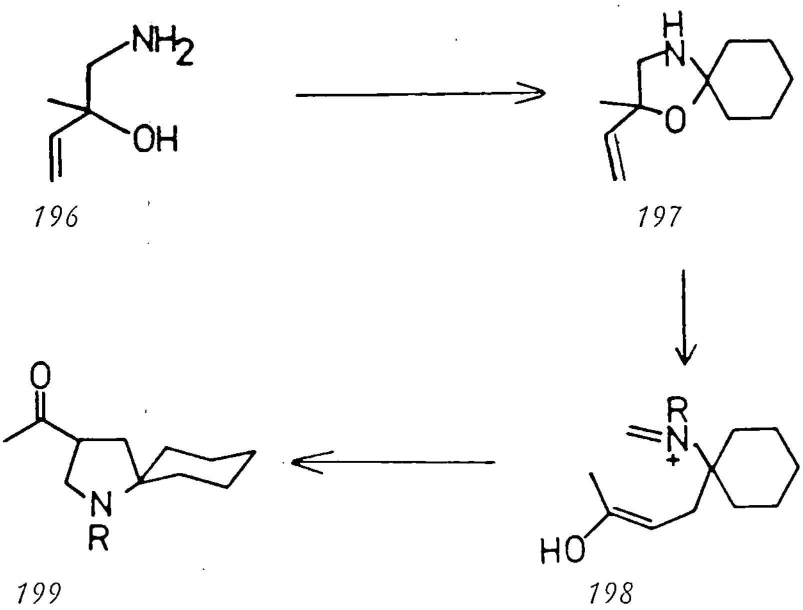


195

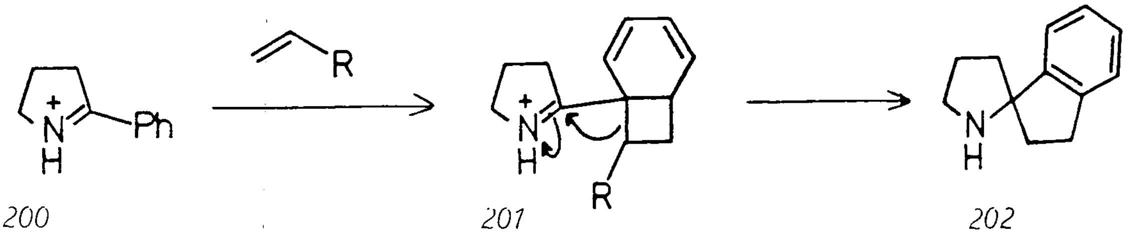
An elegant approach to 1-azaspirocycles, was reported by Overman et al[102], involving insertion of cyclohexanone into *196*, yielding intermediate *197*, which underwent a [3,3] sigmatropic rearrangement, (a cationic aza-Cope rearrangement) after treatment with alkyliodide, as the key step. The final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



vii Photochemical routes

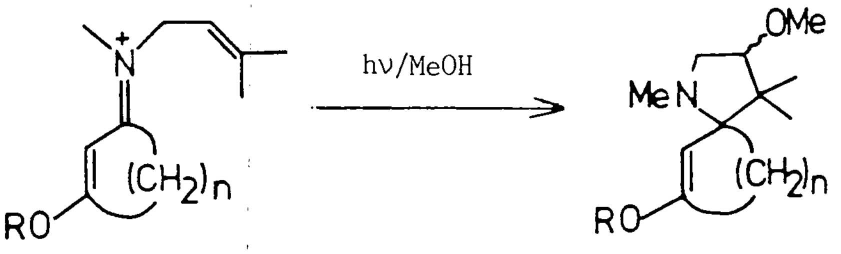
A few photochemical routes to 1-azaspirocycles have been reported, other than the photo rearrangements to spirobenzylisoquinolines described above.

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



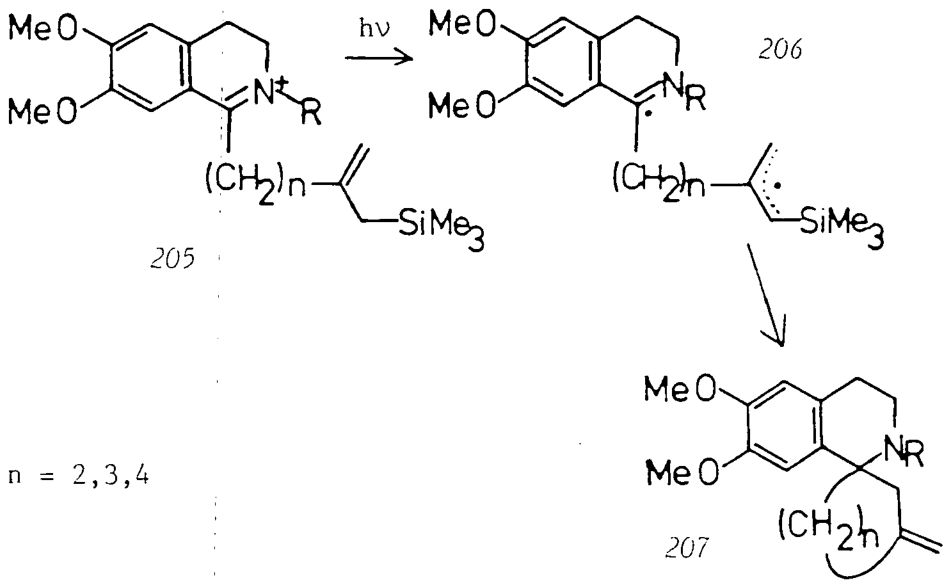
200 *201* *202*

Another approach involving photo-promoted intramolecular nucleophilic attack on an iminium functionality, yields spiroamine *204* from *203*[105].



203 *204*

Similarly, isoquinoliniums, *205*, undergo electron transfer induced photospirocyclization to spiroisoquinolines *207*, via intermediate diradicals *206*[106,107].



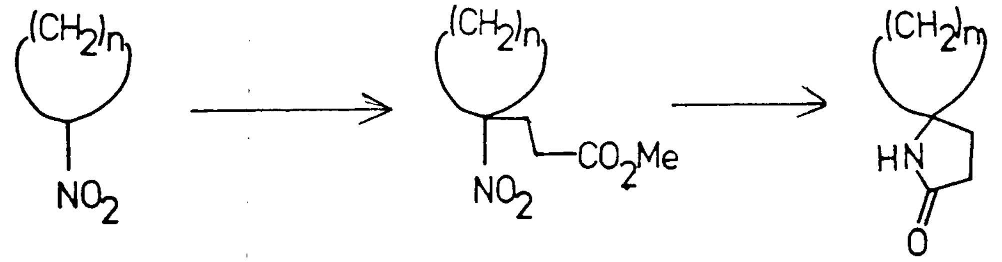
205 *206* *207*

n = 2,3,4

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 *210*[108,109] (see chapter 6).



n = 4,5

208a n = 4

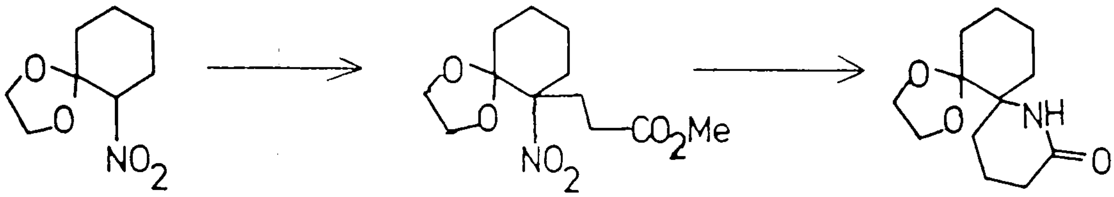
208b n = 5

209 n = 4

210 n = 5

Subsequently, this methodology - including an intermediate homologation - was applied to the nitrocyclohexonone ketal *211*, providing the 1-azaspiro [5.5] undecane, *213* [110,111].

Similar methodology has also recently been applied to synthesis of spirofused porphyrin-pyrrolidone type compounds[42].



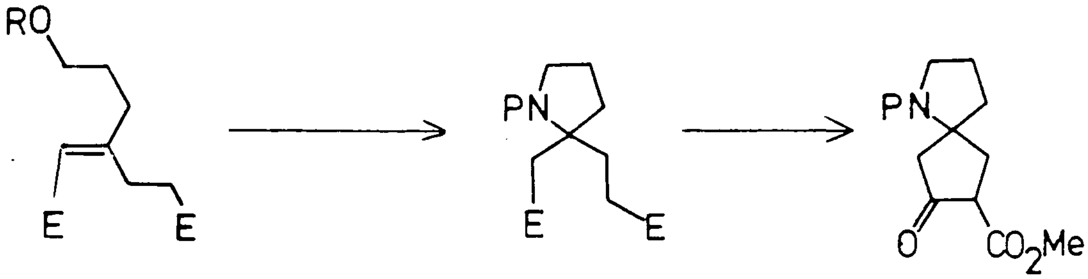
211

212

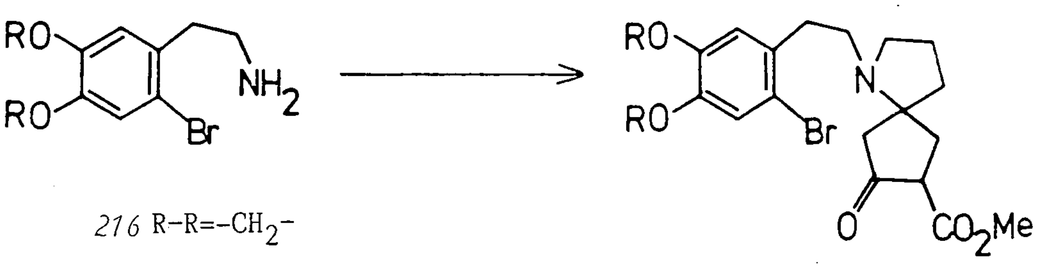
213

ix Miscellaneous methodologies

Amongst other general approaches to azaspirocyclic ring systems[113,114], one of particular relevance to our work was reported by Bryson et al.[53] 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*.



214 *215*



216 R-R=$-CH_2-$

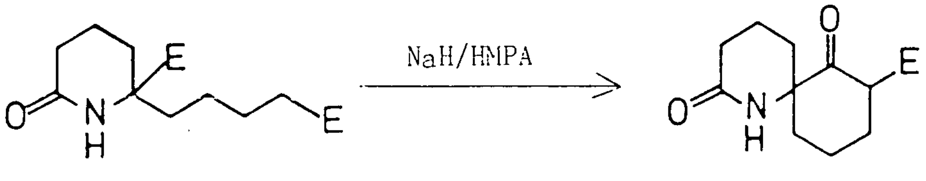
217 R=R=Me

218 R-R=$-CH_2-$

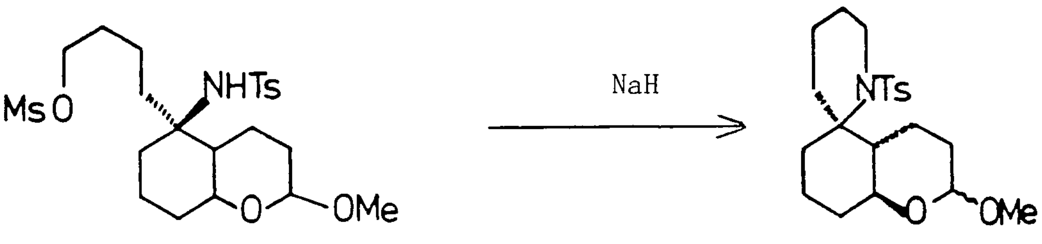
219 R=R=Me

Other spirocyclizations utilizing Dieckmann closure reactions, have included the cyclization of *220* to *221*[111].

Intramolecular nucleophilic displacement with amide anions has also been employed, effecting spirocyclization of *222* to *223*[96].



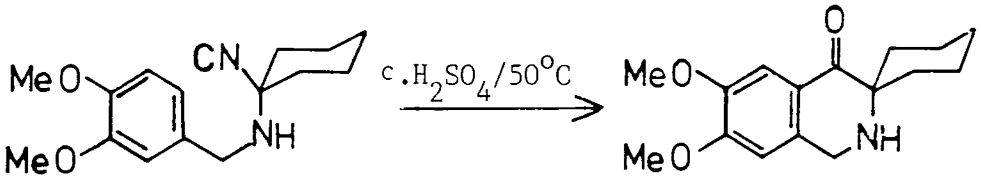
220 *221*



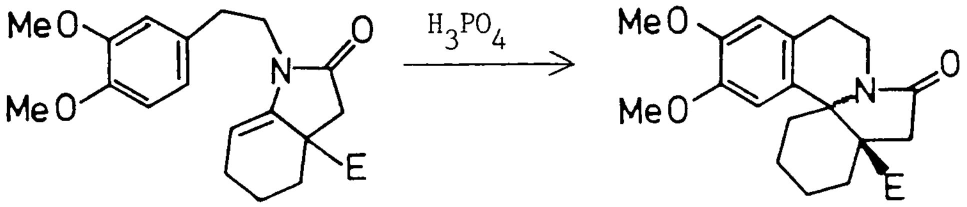
222 *223*

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[115,116].

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



224 *225*



226 *227*

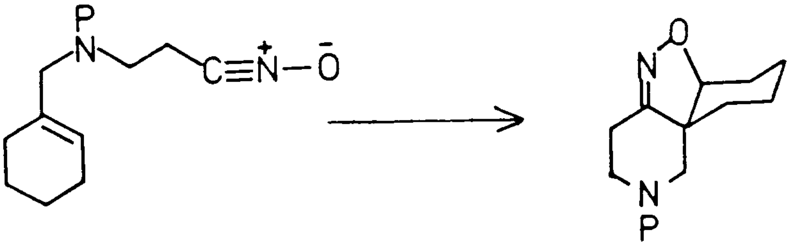
Pictet-Spengler type reactions have also provided occasional entry to azaspirocycle containing alkaloids, e.g. erythrina[121] and spirobenzylisoquinoline[122-124] alkaloids.

x 2-Azaspirocycles

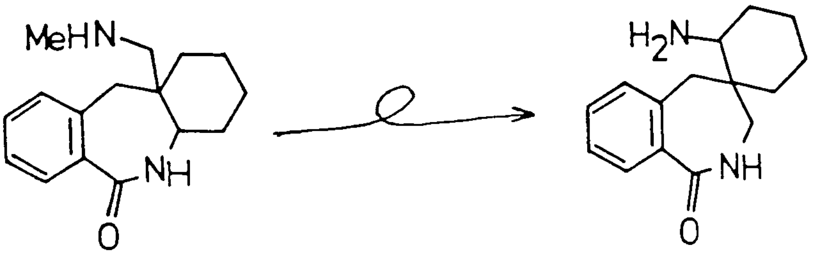
2-Azaspirocyclic compounds are far less common among natural products than 1-azaspirocycles, and consequently there have been far fewer reports of synthetic methodologies for construction of 2-azaspirocycle based ring systems.

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

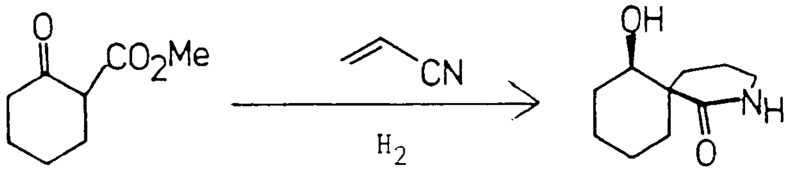
228 *229*



230 *231*



232 *233*

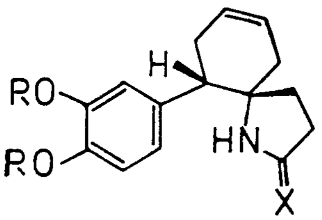


234 *235*

2.2 Construction of the spiro centre

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

The first intermediates in this scheme are the β-nitrostyrenes *237* and *238*, which are readily available by addition - condensation reaction of the corresponding aldehyde with nitromethane anion[133-137], as are a wide variety of analogues[138,139].

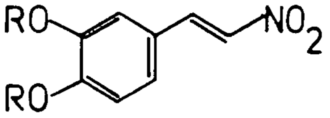


131a R-R=$-CH_2-$ X=O

131b R-R=$-CH_2-$ $X=H_2$

236a R=R=Me X=O

236b R=R=Me $X=H_2$

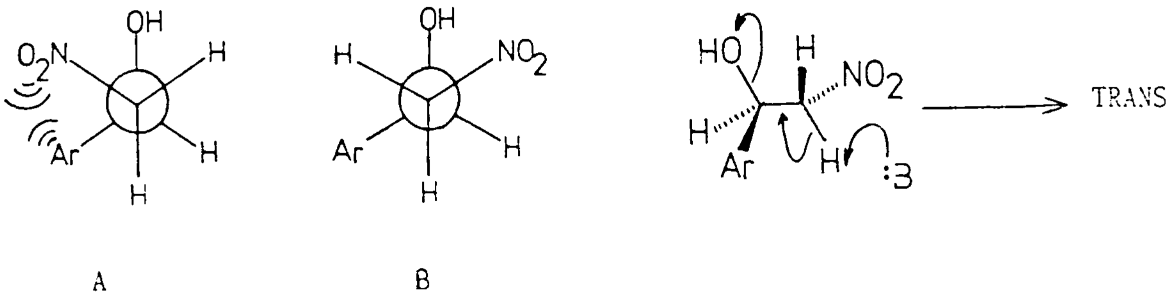


237 R-R=$-CH_2-$

238 R-R= Me

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

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



- fig. 1 -

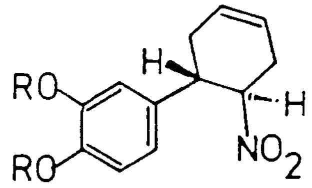
The next envisaged synthetic step was the construction of a six-membered ring E via cycloaddition methodology. The cycloaddition of 3,4-methylenedioxy - β-nitrostyrene, *237*, with butadiene, has been used as an early step in approaches to phenanthridine analogues,[143,144] and lycorine[145]. Similar reactions have also been reported with simple substituted butadienes and nitrostyrene *237*[146]. 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)[147], for cycloaddition to both *237* and *238*, largely due to the convenience of using a stable solid, rather than gaseous butadiene. Butadiene sulphone cheleotropically 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.

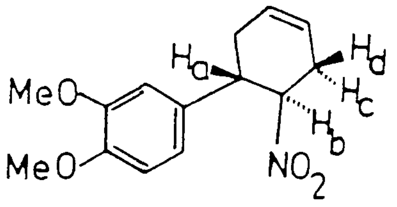
The trans geometry of β-nitrostyrenes is known to be preserved in Diels-Alder cycloadditions[148]. A racemic mixture of trans cycloadducts therefore results, because, clearly, the transition states for addition to either Re or Si face of the dieneophile, are degenerate.

The trans geometry is clearly evidenced by 250MHz 'H NMR decoupling experiments on the dimethoxy analogue, *240*; these data also provide some useful assignments (fig.2). Decoupling of the H_c-H_d region of methylene resonances, collapses the H_b signal (4.9-5.0ppm) to a simple doublet, with J_{ab}=11.1Hz, consistent only with an anti configuration.



239 R-R= $-CH_2-$ (92%)

240 R=R= Me (90%)



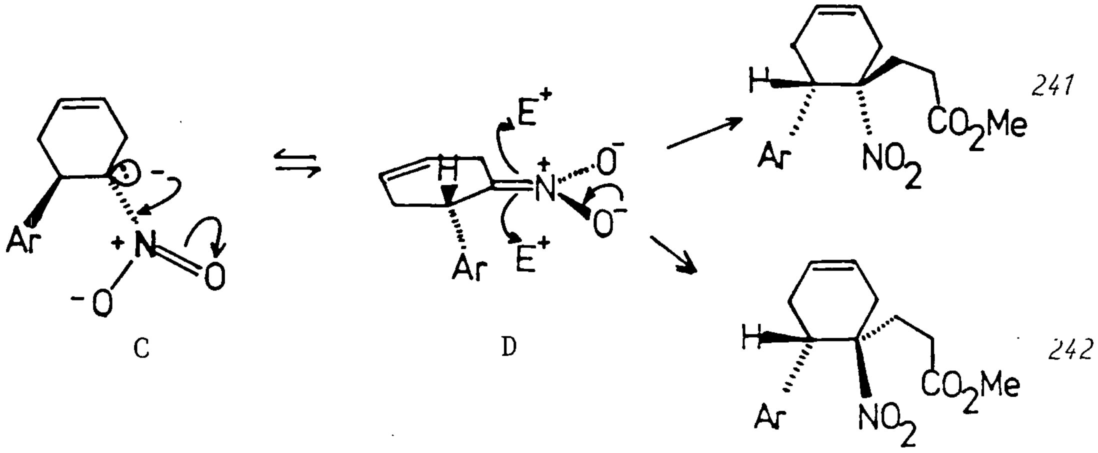
- *fig 2* -

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[149] donors, reacting with acceptors bearing no α or β substituents[150-152]. A variety of bases[153-157] 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.[156].

As a consequence of nitronate planarity[158-160], the stereochemistry at the α 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 *241*. The high stereospecificity in favour of *241* was indeed confirmed by X-ray structure analysis of a derivative of *131a*.

The highly stereospecific establishment of the quaternary centre of *241*, 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[161,162] 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 ν_{co} 1690 cm^{-1} in the IR spectrum.

To confirm beyond doubt the relative stereochemistry provisionally assigned above for *241*, 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).

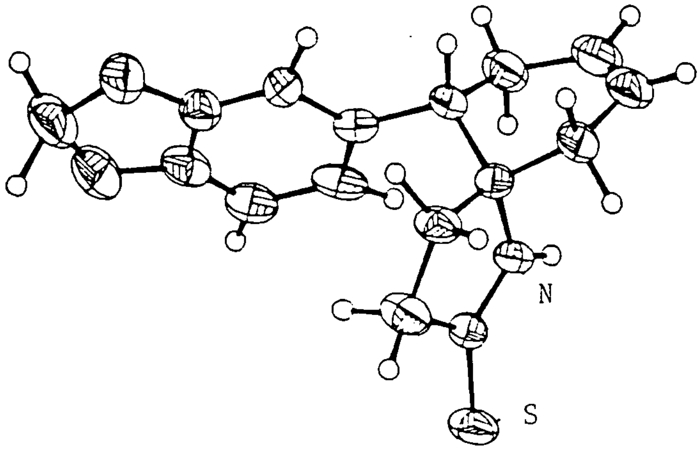
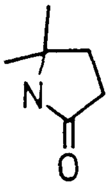


fig 4 X-ray structure of thiolactam, 253

2.3 Spirolactam modification and reduction

The standard reagants for reduction of amides and lactams, are lithium aluminium hydride (LAH)[163-167], or derivatives e.g. LiAlH(OMe)$_3$[168]. Simple γ-lactams, e.g. *243*[169], fused γ-lactams, e.g. *244* and simple spirolactams, e.g. *188*[94], have all been efficiently reduced with LAH. Several other direct methods are available, viz aluminium hydride, AlH_3[167], sodium acyloxyborohydride[170], $TiCl_4$-$NaBH_4$[171], $TiCl_4$-LAH[172] and diisobutylaluminium hydride (DIBAL-H)[173].



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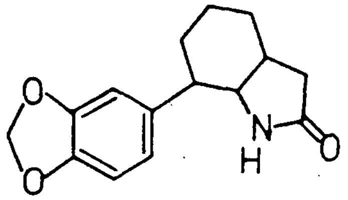

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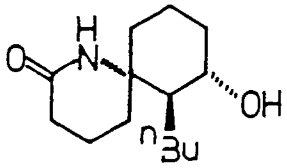
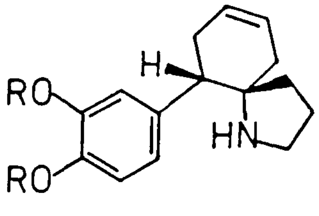


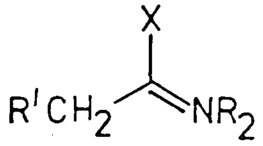
188

Our initial attempts to reduce spirolactam *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= $-CH_2-$

246 R=R=Me



R = Me,Et

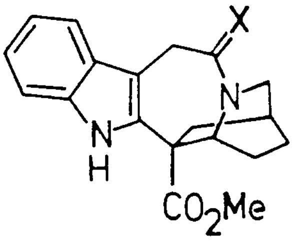
247 X = Cl

248 X = OR

249 X = SR

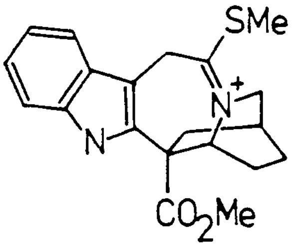
Indirect methods of reduction have been developed via substituted iminium salts of type *247*[174], *248*[175,176] and *249*[177,178], which are reduced in good yields, under mild conditions, with either sodium borohydride or sodium cyanoborohyride.

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[179,180] 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[181].



250 X = O

252 X = H$_2$



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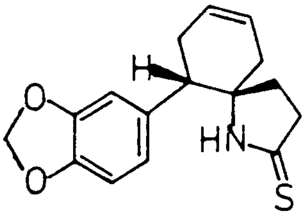


253

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

To allow further assignment of ^{13}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.

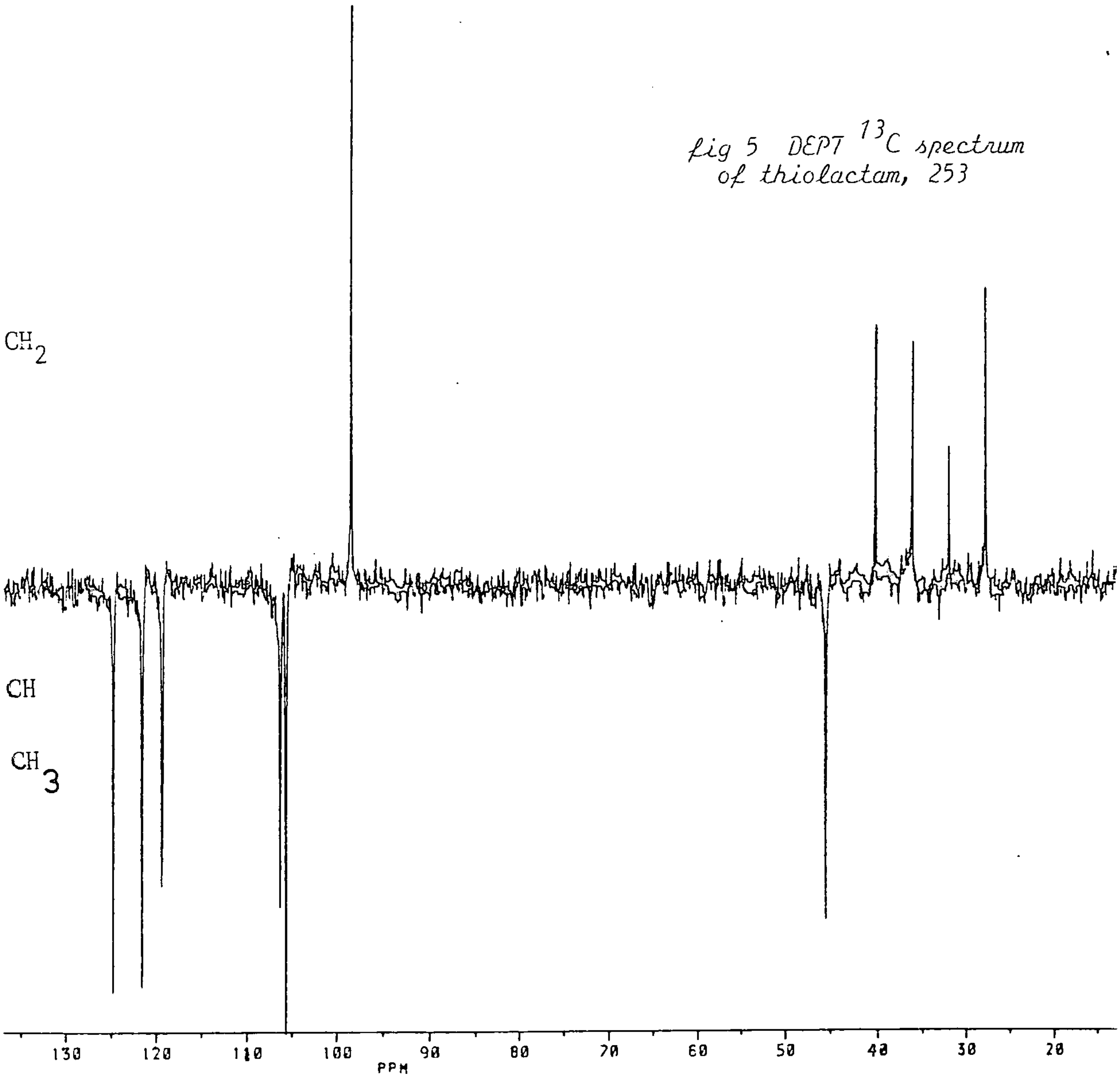
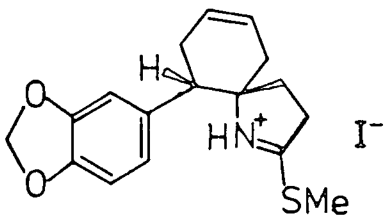


fig 5 DEPT ^{13}C spectrum of thiolactam, 253

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}H NMR showed a singlet (three protons) at ca. 2.5ppm, and the ^{13}C NMR showed seventeen discrete peaks. All data are consistent with retention of the thiomethyl group.



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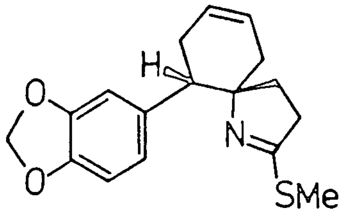


255

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[111,112].

A wider variety of ring E analogues are potentially available. Substituted analogues could be obtained using substituted butadienes or butadiene sulphones[188-190]. Of more potential significance, is the possibility of using a chiral diene which, coupled with the strong regiocontrol exerted by the nitro group[191,192], could lead to regioselective products, of the absolute stereochemistry appropriate to (-) cephalotaxine. These, and other possibilities, will be more fully discussed below.

CHAPTER THREE

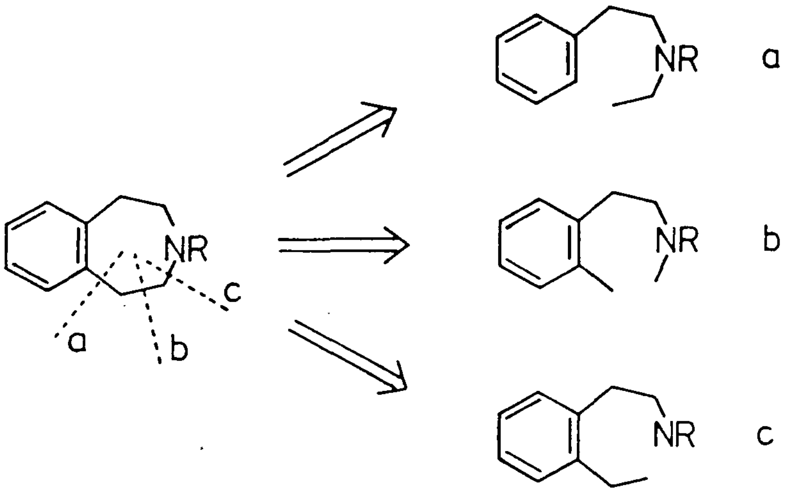
3-BENZAZEPINES : APPROACHES TOWARDS CEPHALOTAXINE RING C VIA ELECTROPHILIC CYCLIZATION

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[194], 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.

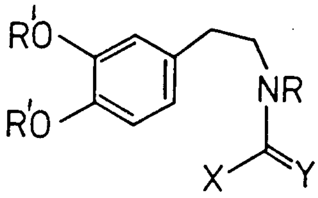
From a retrosynthetic point of view, the overwhelming majority of methods available, are based on disconnection 'a' rather than 'b' or 'c' (fig.6).



- *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.



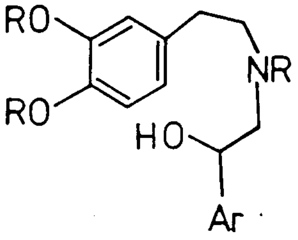
R = H,
alkyl,
tosyl,
R^3=OH
Cl
R^4 = Me,Et

	R'=R'	X	Y
257	$-CH_2-$	CH_2Cl	H_2
258	Me	"	"
259	$-CH_2-$	"	O
260	Me	"	"
261	$-CH_2-$	CR^1R^2OH	H_2
262	Me	"	"
263	$-CH_2-$	COR^3	"
264	Me	"	"
265	$-CH_2-$	$CH(OR^4)_2$	"
266	Me	"	"

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 (∿180°C)[195-199]. 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[200]. 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*.



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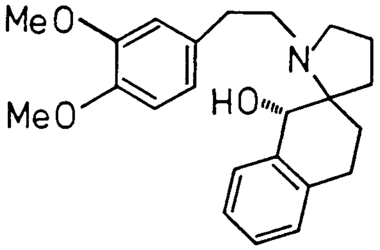

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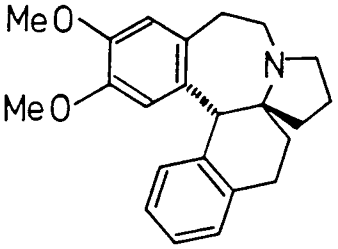


269

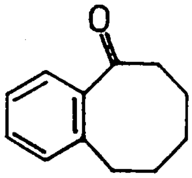
A wide variety of substitution patterns have been employed, and the commonest reaction conditions use polyphosphoric acid (PPA), hydrobromic acid or trifluoracetic-sulphuric acid mixtures, as the catalyst[201-213].

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 α to the hydroxy group[215].

While this methodology provides quite an efficient route, it has two distinct disadvantages; (1) it appears to require an aromatic group α 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[216]. It has provided efficient entry to six-membered[217-219], as well as seven-membered [220,221] and eight-membered[222] 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



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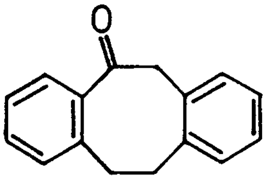

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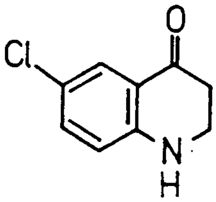


272

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

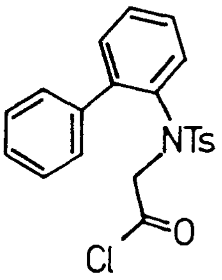
Other strong acids, such as methanesulphonic acid, have also effected such cyclization reactions. At least in carbocyclic systems[225], conc. sulphuric acid has been used to cyclize the corresponding methylester to isoquinolones[226-228], though no examples of application to 3-benzazepines have been 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[229,230]. 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)[231,232].

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[233-236].

However, it was subsequently reported that low reaction temperatures, typically -70°C, with excess aluminium chloride, could lead to good yields of 3-benzazepinones[237-239]. Similar low temperature reaction, at -10°C, was used to efficiently cyclize *273* to the benzofused 3-benzazepine *274*[240].



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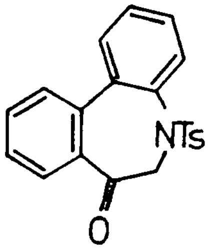

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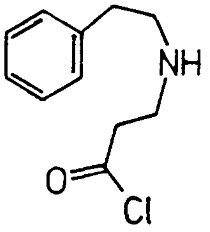
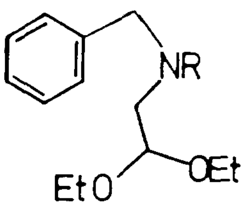


275

It is relevant to note that *275* is cyclized efficiently to the 3-benzazocine analogue by Friedel-Crafts reaction, in dichloromethane at reflux[241]. 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[242] and Bobbitt[243-246] syntheses of isoquinolines. Use of boron trifluoride as Lewis acid catalyst has also been extensively used to cyclize acetals[247], and the corresponding free aldehydes have been cyclized with mineral acids, to tetrahydroisoquinolines[248-251].

This methodology has found some use in the synthesis of 3-benzazepines[252-254], and Lewis acid catalysed cyclization of dimethylacetals[255-257] is one of the commonest routes of entry to isopavine alkaloids[258,194] e.g. *277* → *278*.



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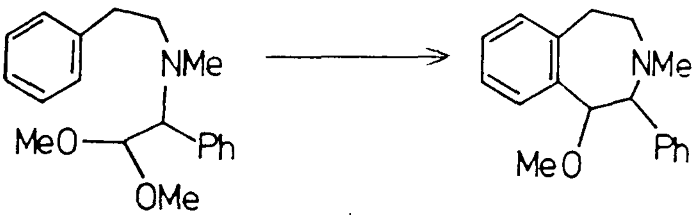


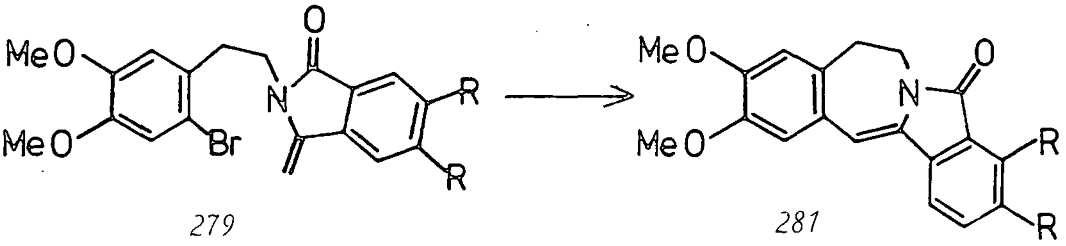
277 *278*

ii Photochemical cyclizations

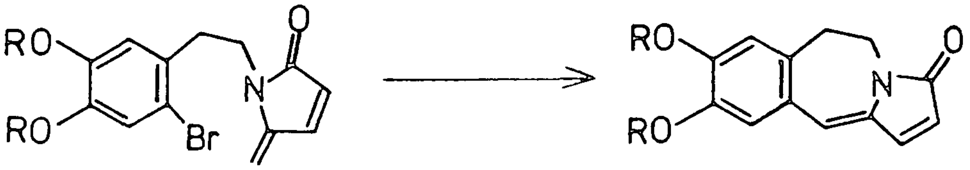
A number of photochemical approaches to 3-benzazepines have been developed, some being utilized further in synthetic studies towards cephalotaxine. Haloaryl-enolate photocyclizations[259] have been specifically applied to construction of the cephalotaxinone 3-benzazepine ring by Semmelhack's group[37,38](1.6.ii).

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[260].

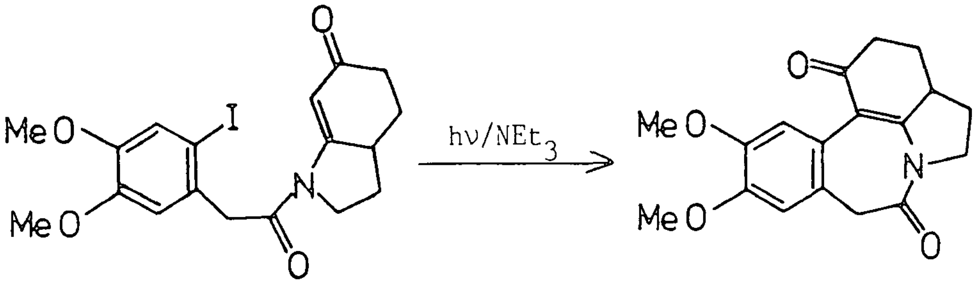
For example, Snieckus et al[261,262] have shown that *279* and *280* can be photocyclized to *281* and *282* respectively. Similarly, the enamido ketone *283* and enamino-ketone *284* can be photocyclized to 3-benzazepines *285*[263,264] and *286* [265,266]. Photocyclization can also be effected in analogous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



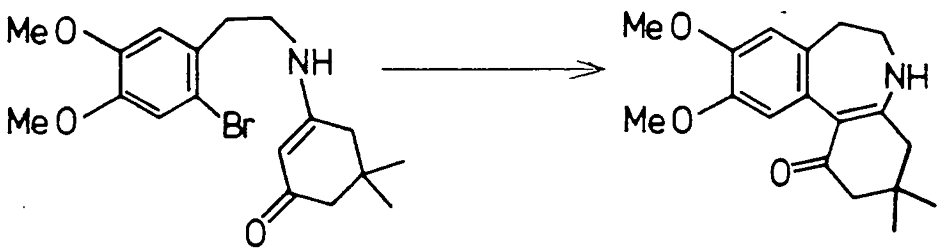
279 *281*



280 *282*



283 *285*



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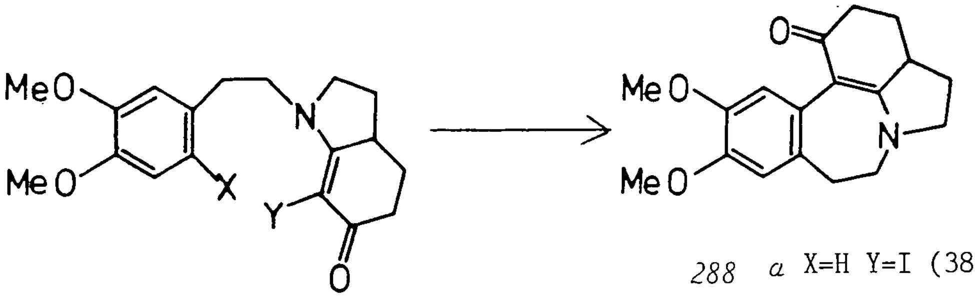
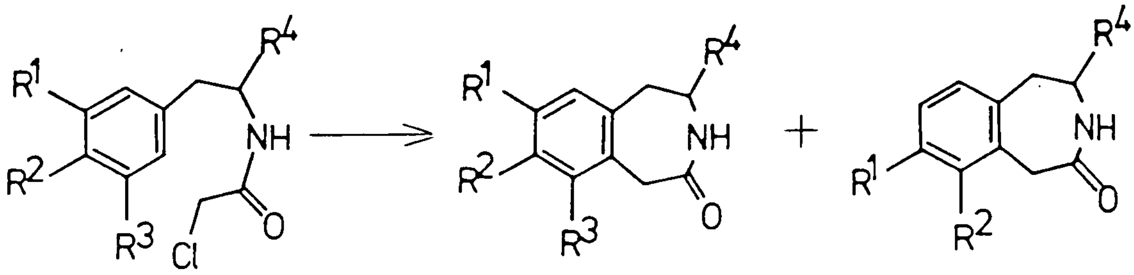


287

288 *a* X=H Y=I (38%)

b X=I Y=H (50%)

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[268], as more complicated deep-seated photo-rearrangements to unusual cyclic products competed[269-272]. Further complications result from formation of isomeric 3-benzazepines, as shown by a collation of results for various substrates (fig.7),



a $R^1=R^2=OMe$ $R^3=R^4=H$	27%	6%
b $R^1=R^2=R^3=OMe$ $R^4=H$	10%	-
c $R^1=R^3=OH$ $R^3=R^4=H$	-	-
d $R^1=OH$ $R^2=R^3=H$ $R^4=CO_2H$	70%	-

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[273]. The related tertiary amide, *48*, similarly provided moderate yield of the potential cephalotaxine intermediate *49*[11].(see 1.6.i).

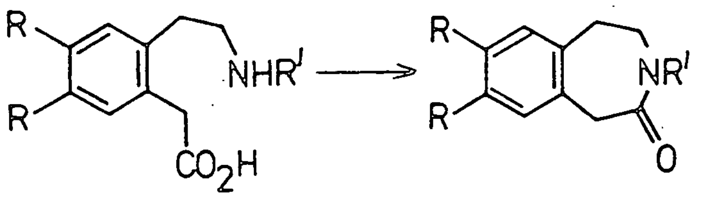
iii C-N bond forming ring closures

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[274], amide-acid[275], and amide-alcohol[276-278] condensations, and several other less common examples[279-281].

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

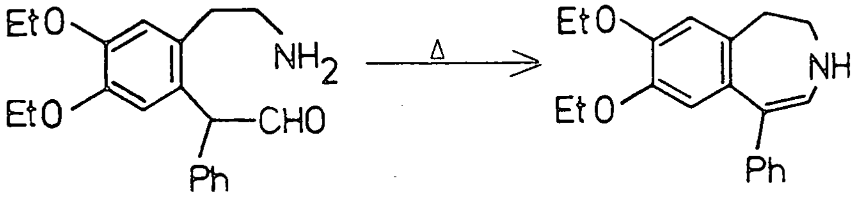


289 290

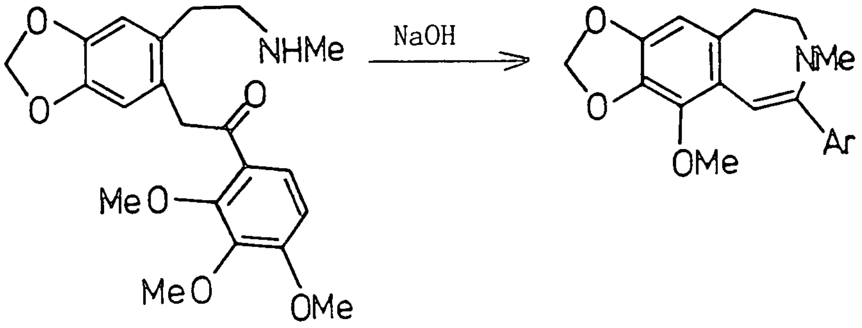
a R=R=R^1=H
b R=R=MeO R^1=H.CH$_2$Ph
c R-R= -CH$_2$- R^1=H,CH$_2$Ph

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

Amino-acids, *289*, can also be reductively cyclized with borane, directly providing the parent 3-benzazepines, *295* [288].

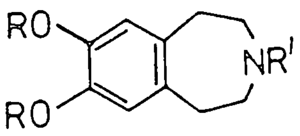


291 292



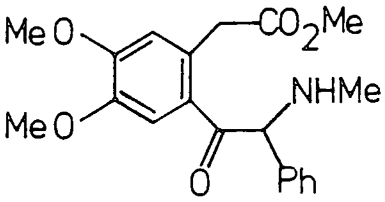
(84%)

293 294



295 R=R=Me,-CH$_2$-

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[289-290]. The high stereoselectivity being accounted for on the basis of Cram's rule[291], for hydride attack on rotamer *296a*.



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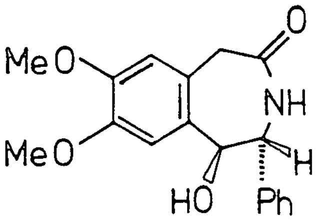

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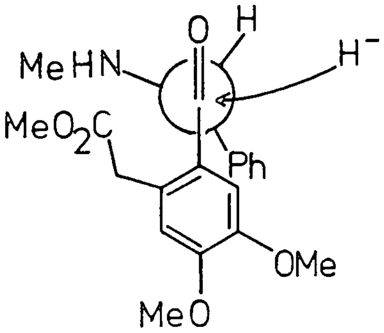
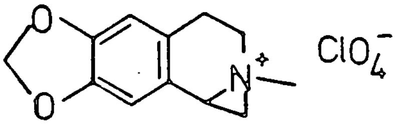


296 a

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[292,293]. Subsequently, this methodology was applied to isoquinoline fused aziridinium salts e.g. *298*,[294] *299*[295] and *300* [296], 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[297].



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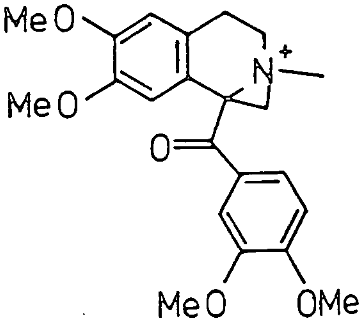

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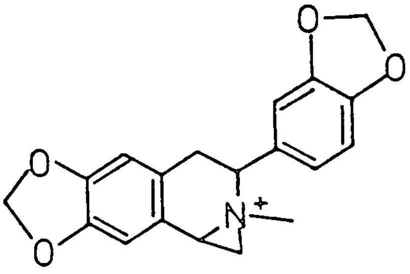
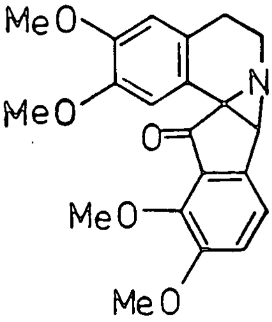


299

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[298-300], e.g. *301* → (±) cis-alpinigenine, *302a* and (±) cis-alpinine, *302b*. Related expansions have been effected either photolytically[301], under acid catalysis[302,299], with ethylchloroformate[303], or by hydrogenolysis[304].



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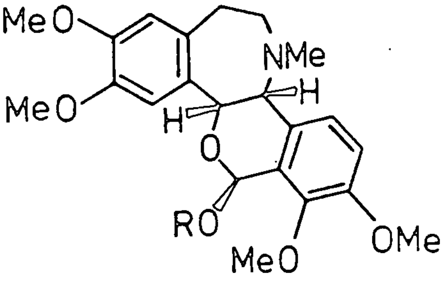
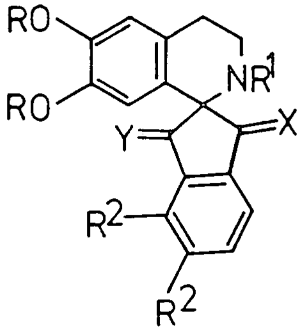


a R=H
b R=Me

302

A number of reports of rearrangement expansions of spirobenzylisoquinolines, *303*, leading to the 3-benzazepines, *304*[305,306], in good yield, have appeared which were then elaborated to rheadan alkaloids[307,308]. 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[309].



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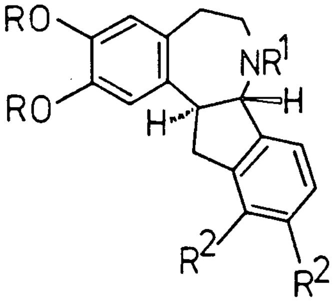


304

a R=Me $R^1=R^2=H$ X=Y=O

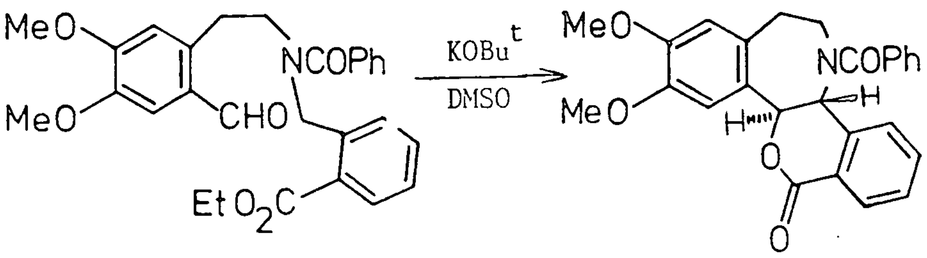
b R=R=$-CH_2-$ $R^1=R^2=H$ X=Y=O

c R^1=R=Me $Y=H_2$ R^2=OMe X=H,OMs

v <u>Miscellaneous other 3-benzazepine syntheses</u>

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 α anion of *305* on the aromatic aldehyde[310], subsequent lactonisation providing reasonable overall yield of *306*.

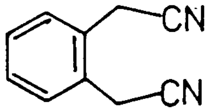


(56%)

305

306

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



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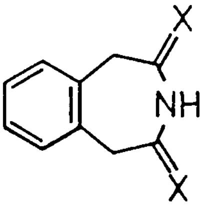
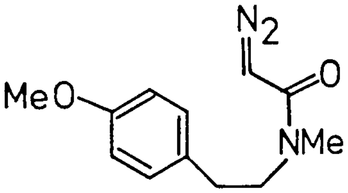


308 *a* X=H

b X=O

Beckmann rearrangement of the oxime of β-tetralone[315], and Schmidt rearrangement of β-tetralone directly[316], have both provided modest yields (20-30%) of 3-benzazepinone.

More recently, an example of an efficient entry to the 3-benzazepinone system, *311* has been described[317]; acid catalysed cyclization of *309* yields spirodienone intermediate *310*, which in two steps rearranges and rearomatizes to *311*.



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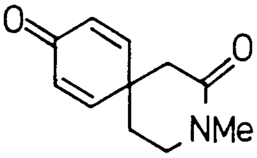

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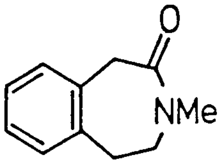


311

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

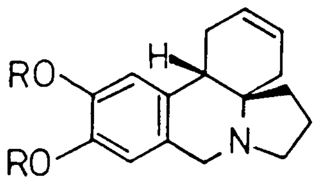
i Discussion

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[318,319] 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[320](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[321-322]. This is essentially a special case of the Mannich reaction, involving reaction of 2-phenethylamines and aldehydes or acetals[323]. 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[324]. However, with phenolic systems, the reaction may occur under neutral[325] or basic[326], 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*.

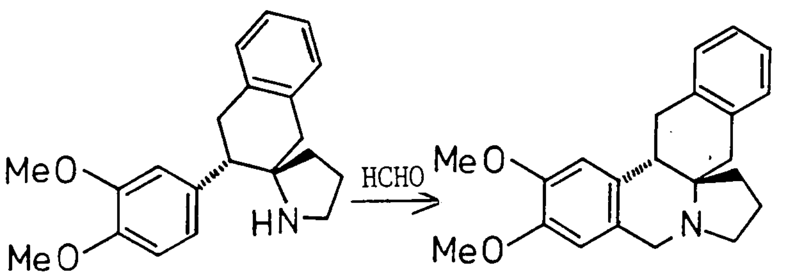


312 R=R= $-CH_2-$

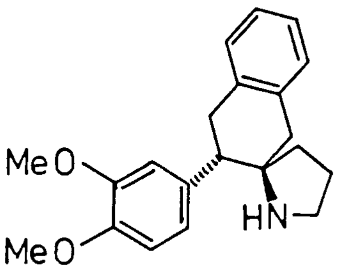
313 R=R=Me

(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[215]. In contrast, the trans, non-spirofused, system *317* is readily cyclized to the isoquinoline analogue *378*[325].



314 *315*



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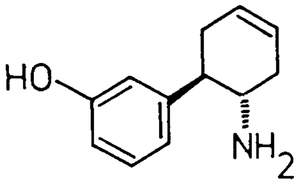

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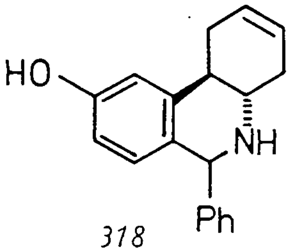
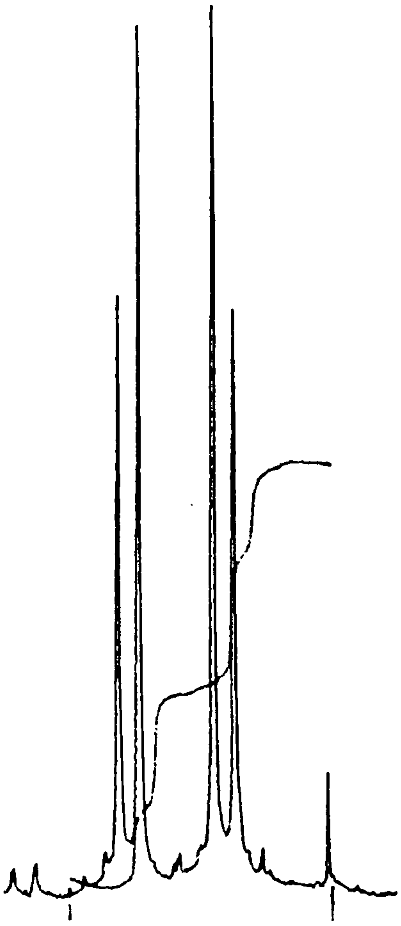


318

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 $J_{ab} = -14Hz$, is characteristic of protons on a centre adjacent to unsaturation, further confirming these as the new methylene bridge protons.



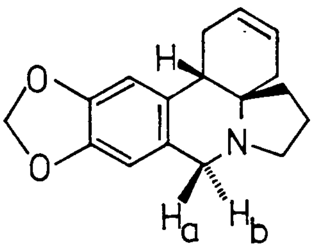


fig 8 AB spin system of 312

To help with further assignments, a DEPT ^{13}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}C NMR changes during construction of a seven-membered ring C (see chapter 4).

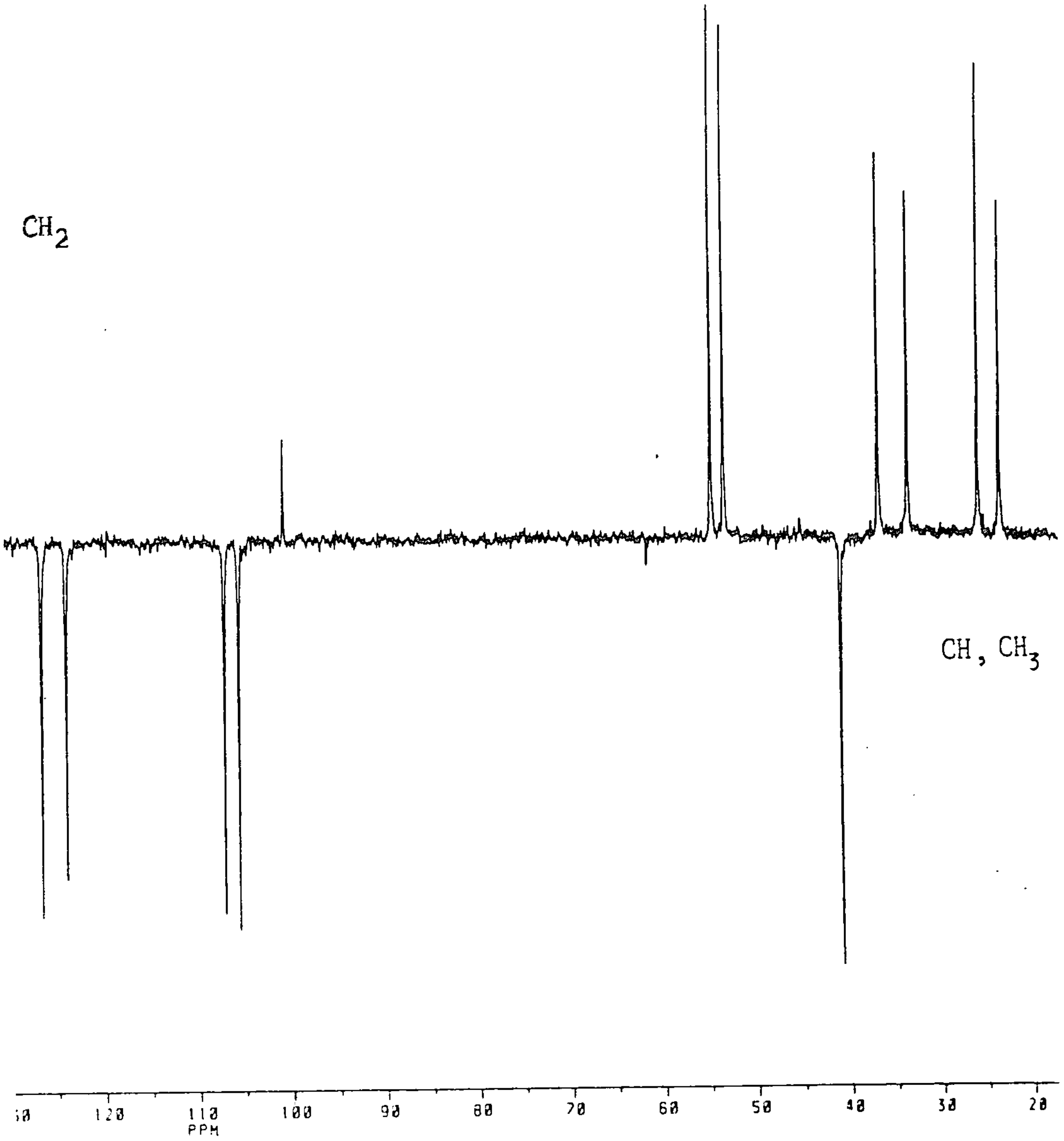
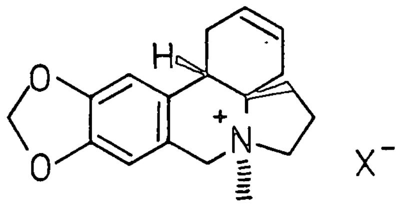


fig 9 DEPT ^{13}C spectrum of 312

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_6

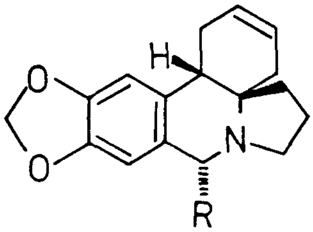
The favoured nitrogen geometry is expected to be as indicated, with the methyl group pointing away from the sterically cluttered 'top face'. However, while tertiary alkyl ammonium centres are configurationally stable, and numerous isomeric mixtures have been resolved since the turn of the century[327],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

While structurally related alkaloids such as lycorine and β-dihydrocaranine, yield mixtures of both nitrogen stereochemistries,[329] the rigid geometrical constraints at nitrogen, resulting from the spiro-fusion 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*.



320

Stereoselectivity in Pictet-Spengler type syntheses of isoquinolines has been the subject of a number of recent publications[330,331].

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

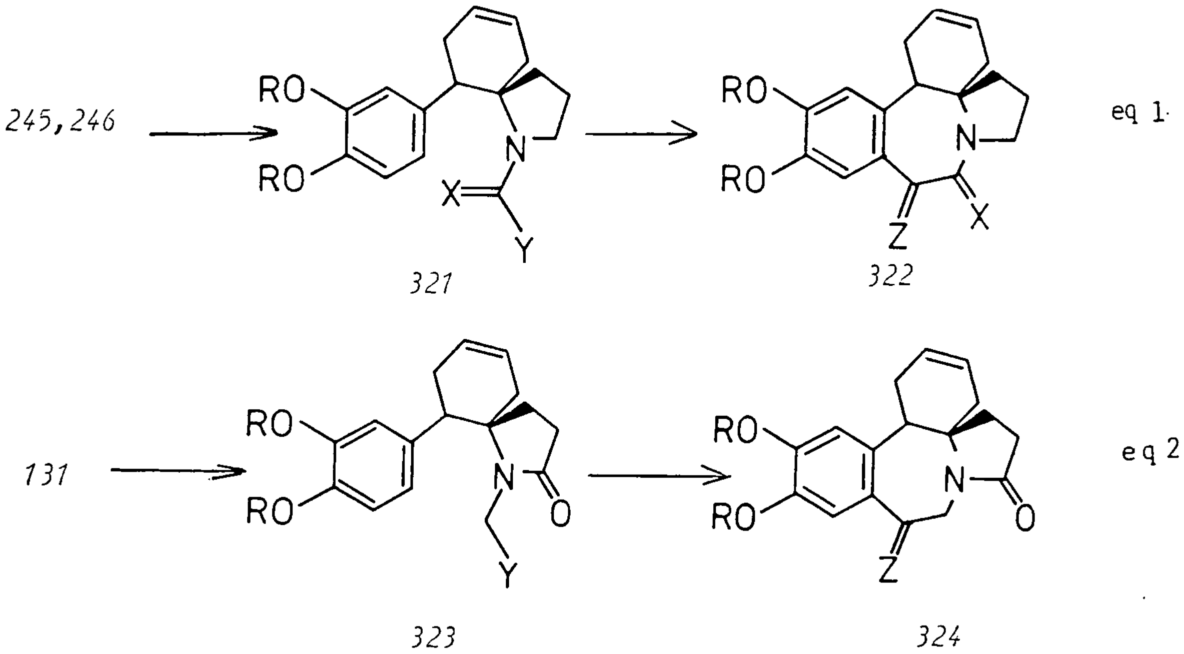
iii C-N bond forming ring closure

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).



$X = O, H_2$

$Y = CH_2Cl,\ CH_2OH,\ CO_2H,\ COCl,\ CHO,\ CH(OR)_2$

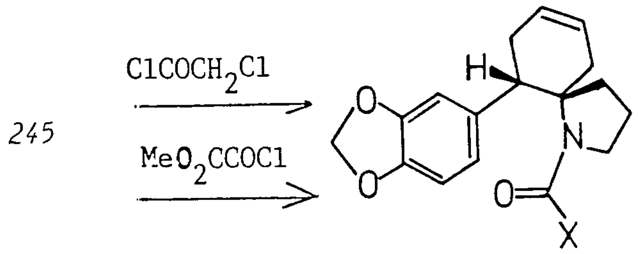
$Z = O,\ H_2,\ OR$

fig 10

i <u>Spiro-pyrrolidine derivatives</u>

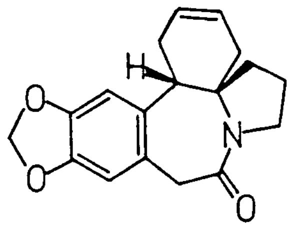
Entry to intermediates of type *321* should be readily provided by reaction of *245* with suitably functionalized acid chlorides. Our initial targets were derivatives *325* and *326*, which were both obtained in >95% yield, by reaction of *245* with either chloroacetyl chloride, or methyl-oxalylchloride,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



325 X = CH_2Cl

326 X = CO_2Me



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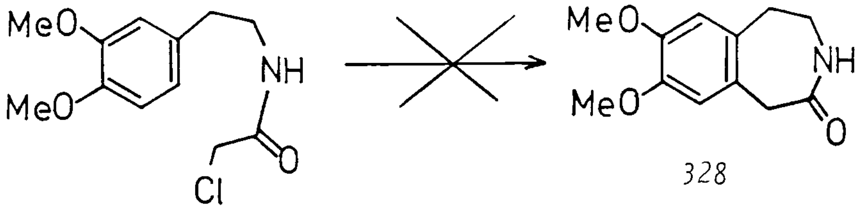
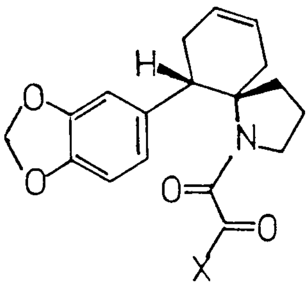


260 (R = H)

328

However, model studies on the N-2-chloroacetyl-phenethylamine, *260*(R=H) following the general procedure of Nair and Malik[200], 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.

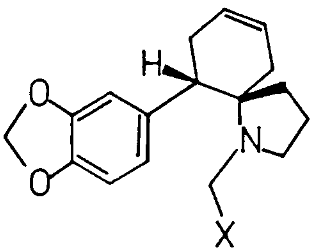


329 *a* X = OH

b X = Cl

But concurrent with our initial publication describing the synthesis of spiro-lactam *131a*, Hill's group published[48] 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 *327* (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

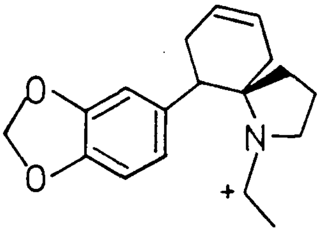
333 X = CH_2Cl

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, spiropyrrolidine *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-hydrooxyphenethylamine-type systems, has almost exclusively been effected on substrates possessing aromatic substituents α to the hydroxy group e.g.*267*. In *332* there is no such α-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}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[163].

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[333,334].

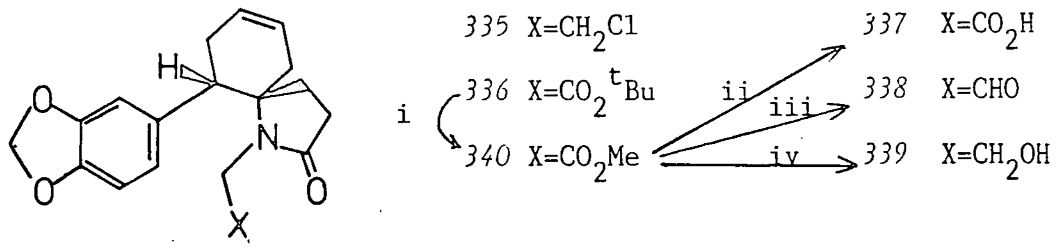
More recently, the use of alkali metal hydroxides, in phase transfer catalysed reactions with tetra-alkyl ammonium salts has been developed[335-337]. Potassium fluoride on activated alumina has proved an efficient heterogeneous base[338-340], far more active than KF itself, or KF on other supports such as silica, celite[341] 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[342].

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$^+$, ii NaOH/EtOH, iii DIBAL-H/-78°C, iv LiBH$_4$-ether

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

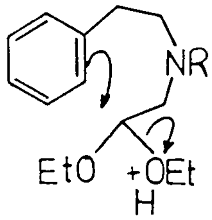
Based on the cyclization strategies to 3-benzazepines, involving electrophilic substitution, reviewed above (3.1.i), our target intermediates were the lactam-acid, *337*, lactam-aldehyde, *338*, and lactam-alcohol, *339*.

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[343]. 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 *339*, 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°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 cyclialkylation 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*.



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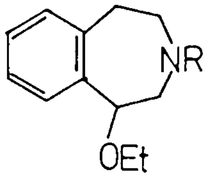
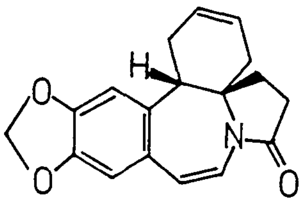


342

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 ν_{CO} 1708 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.



343

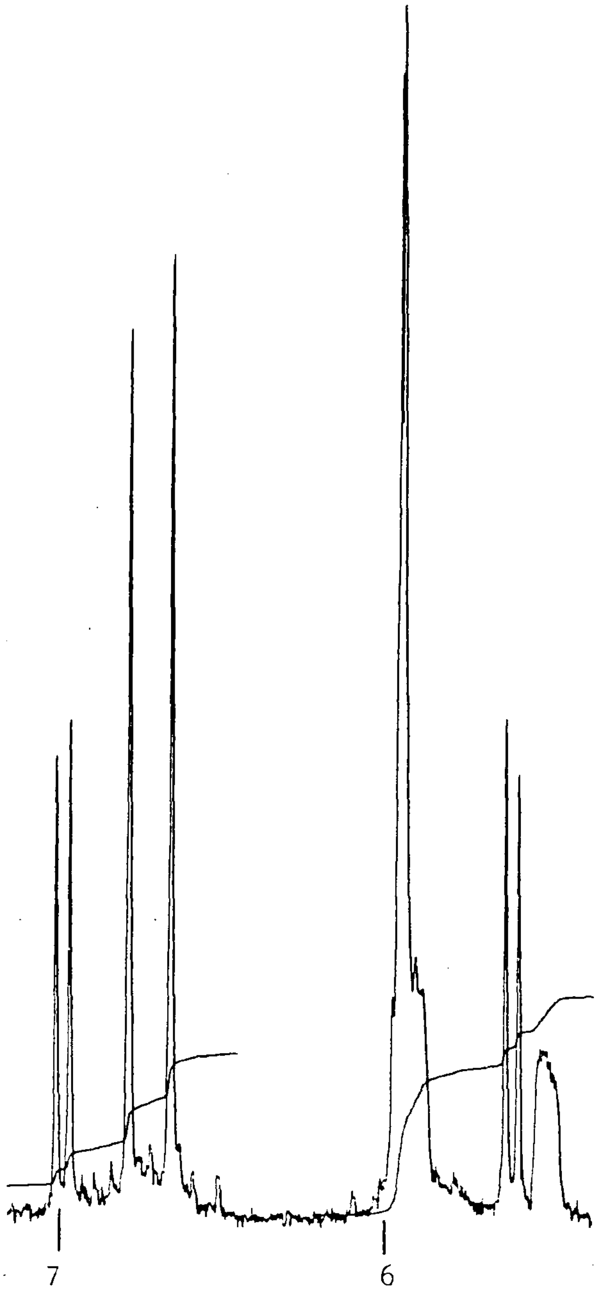


fig 11 250MHz proton NMR of 343

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, $J_{AX} \simeq 11Hz$, is also consistent with values for cis substituted double bonds.

The ^{13}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}C NMR).

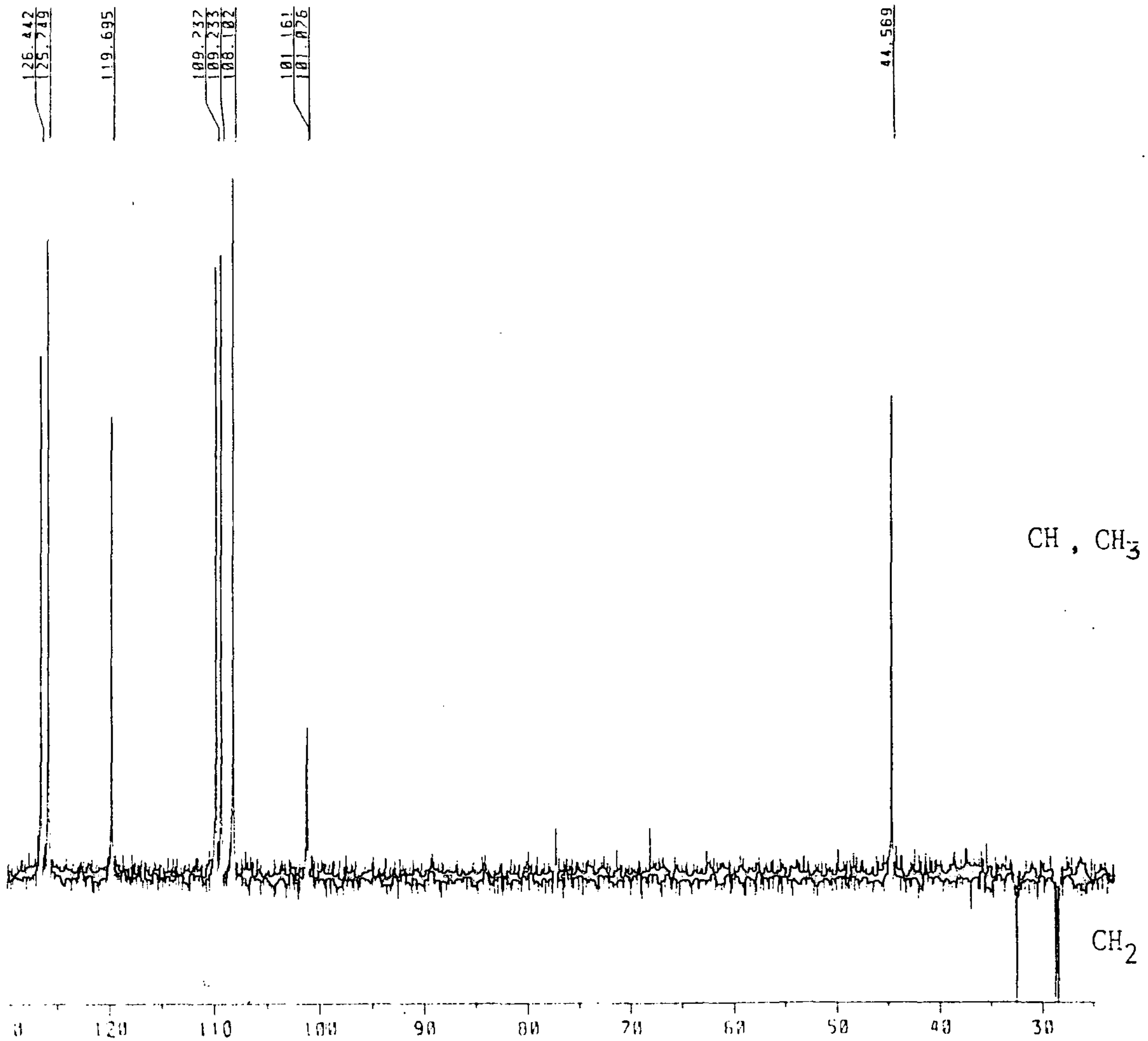
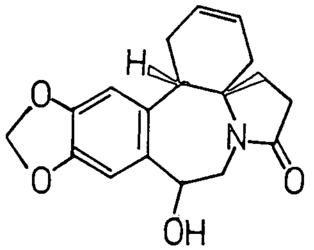


fig 12 DEPT ^{13}C spetrum of 343

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 ν_{CO} = 1663 cm^{-1} and a strong alcoholic O-H stretch at 3460 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 '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).

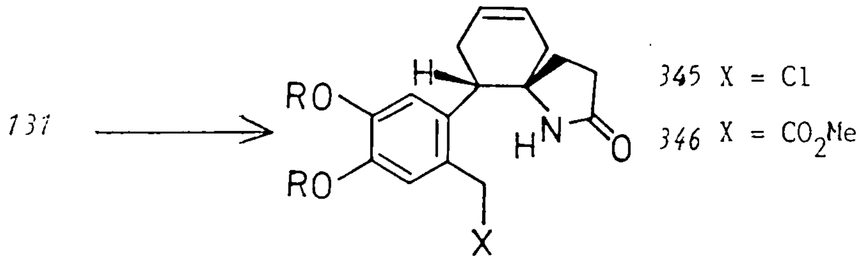
Here, we will describe work towards our desired 3-benzazepine intermediate, based on the retrosynthesis envisaged via *130* and *132* (scheme XIV, 1.8) ['category iii' methodology (3.1)].

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

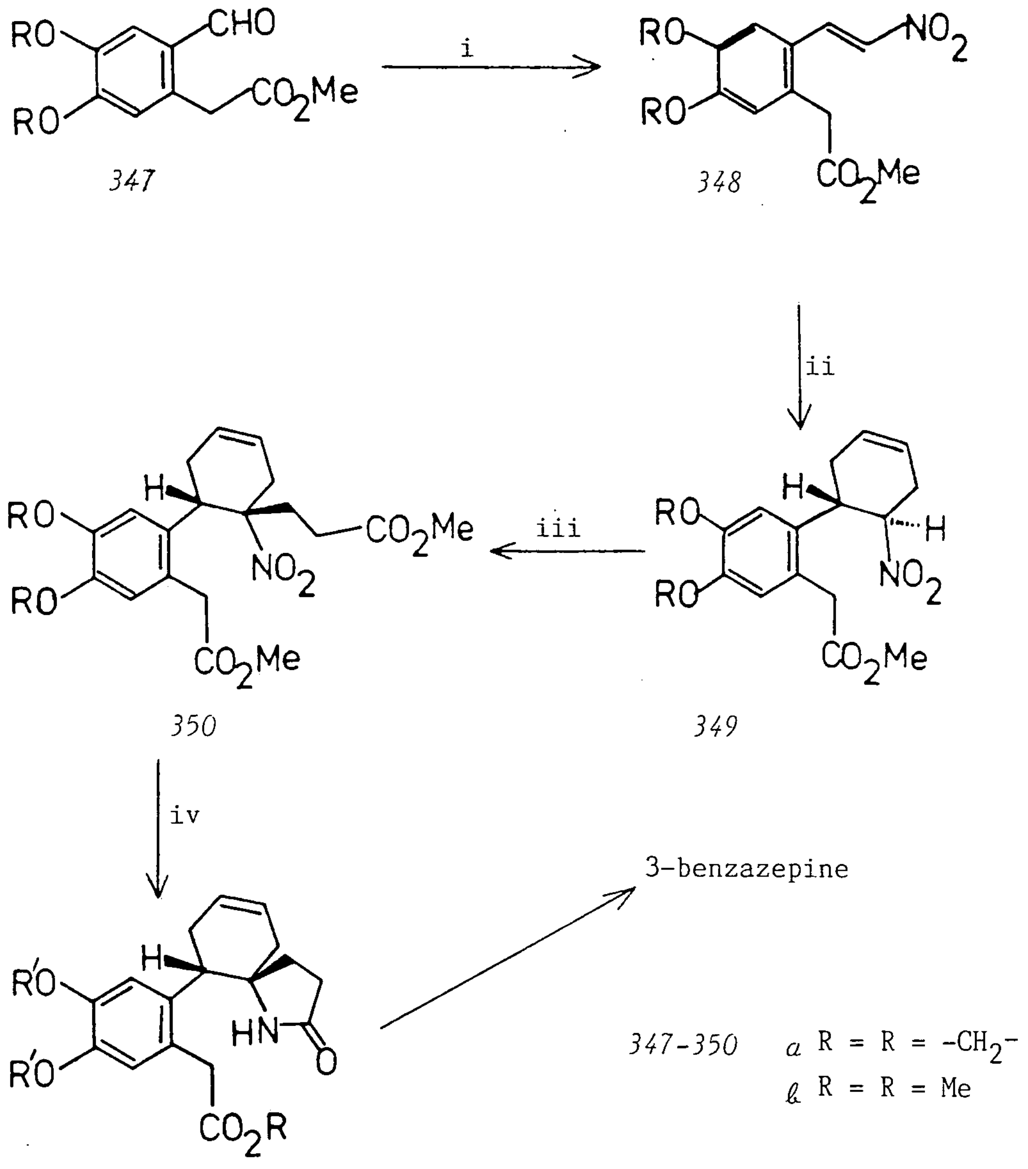
Implicit in our earlier retrosynthetic analysis (scheme XIV) is that this approach will retain the key stereospecific azaspirocyclization steps described above (2.2)

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[344], 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*.



345 X = Cl
346 X = CO_2Me

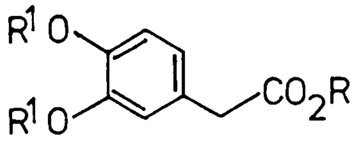
SCHEME XV



351 R' = R' = Me

i $MeNO_2/K_2CO_3$, ii butadiene sulphone, iii Me acrylate/triton-B, iv Zn/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

b R' = R' = Me R = Me

ii Discussion

Our first synthetic requirement was the formylation of *353b* to the aromatic aldehyde, *347b* . A number of methods are available for the introduction of aldehydic functionality into aromatic systems. The original method was the classical Gatterman formylation[345,346], and variations upon it[346,347-349], 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[350,351], 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[353] with dimethylformamide or N-methylformanilide[353-356], 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[357], a powerful formylating agent, or Lewis acid catalysed reaction with dichloromethyl methylether. The latter is reported[358] to have much wider scope than any other aromatic formylation methodology, and appears to be both experimentally mild and clean[359].

We found that using titanium tetrachloride as the Lewis acid catalyst[360], reaction of *353b* with dichloromethyl methyl ether, led only to recovery of crude starting material, *353b*. However, on changing the Lewis acid to aluminium trichloride, yields of 80-90% of the crystalline aldehyde, *347ℓ*, were obtained. The reaction proved particularly expedient, as recrystallisation from diethyl ether at -78°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 *347ℓ* with nitromethane, under essentially the same conditions which were successful with 6-nitropiperonal (4.2.ii), resulted in repeatably poor yields (ca 40%) of *348ℓ*. Potassium carbonate as catalytic base, under reflux conditions, led to a very crude product mixture, from which only ca.30% of nitrostyrene derivative *348ℓ* was isolated.

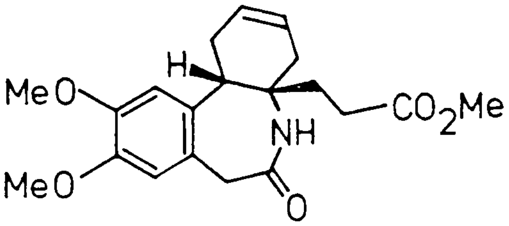
Use of the standard procedure successful with piperonal, (see 2.2), though lengthy, (taking 3-4 days to go to completion, as judged by t.l.c.), had the advantages of providing reasonable yields (70-75%) of *348ℓ*, of sufficient purity to be used directly for the subsequent cycloaddition reaction.

The use of butadiene sulphone as butadiene synthetic equivalent (see 2.2), again proved convenient for cycloaddition to *348ℓ*. 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 *349ℓ*, sufficiently pure for further use.

Michael addition of methyl acrylate to the anion of *349ℓ*, 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°C, if necessary. By analogy with compound *241*, the single product, *350ℓ* , must possess the single relative stereochemistry indicated (scheme XV).

The elaboration of intermediate *350ℓ* 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 γ-lactam ring, than the possible isomeric Σ-lactam, *353* as we would expect from entropic factors determining ring closure[361]. 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.

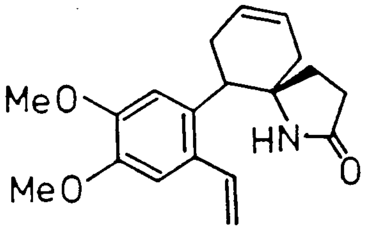


353c

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 ν_{max} ca. 1690 cm^{-1} is again consistent only with a smaller ring lactam (cf. five-membered lactam analogue *236a* [2.2]), (ν_{max} for a seven-membered lactam expected 40-50 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 351. For example, the carbethoxy group of 351c could be converted to a more favourable leaving group, e.g. tosylate, to be displaced by an internal nitrogen nucleophile.



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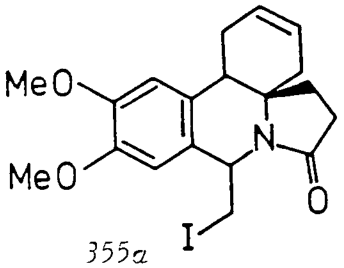
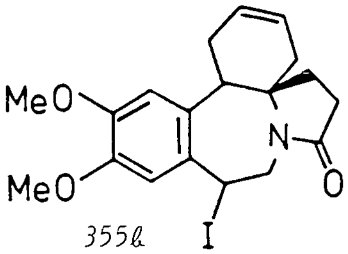


355a

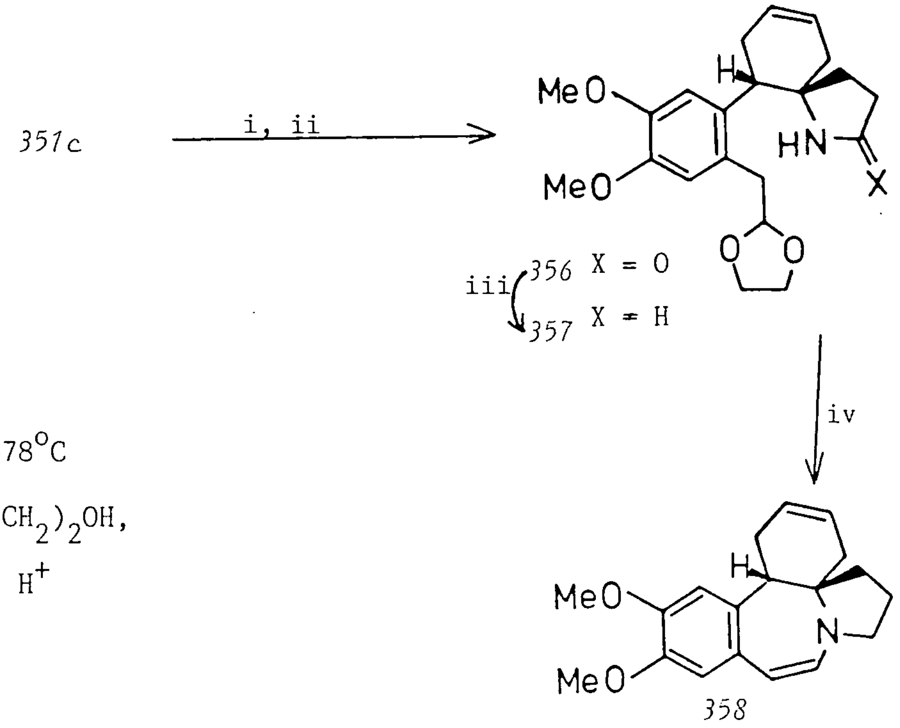


355b

Lactams undergo halogen assisted intramolecular cyclizations onto olefins[362], the use of N-nucleophiles in general being of current interest. However, entropic factors[361] would favour cyclization of lactam-olefin 354 to 355arather 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°C

ii pTsOH/HO(CH$_2$)$_2$OH,

iii LAH, iv 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.

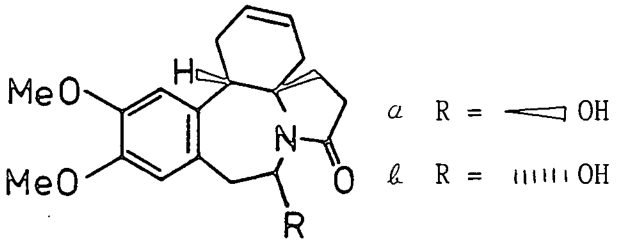
However, treatment of ester *351c* with DIBAL-H at -78°C, under essentially the same conditions successful in reducing the tertiary lactam-ester, *337*, (3.3) to the corresponding aldehyde, *338*, led, repeatably, only to the recovery of small quantities of material from bisulfite extraction. This was difficult to rationalize unless the majority of material was non-aldehydic. Though unchanged ester was recovered in small quantity, is 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, *351c*. The IR of the crude mixture showed a new carbonyl absorption at ν_{CO} 1670 cm^{-1}, inconsistent with an aldehyde group, and a strong, sharp band at 3280 cm^{-1} , possibly due to an intramolecularly bonded hydroxyl group. Careful chromatographic separation returned ca.40% of unchanged ester, *351c*, and ca.40% yield of a second material. The IR of this new material showed a single carbonyl peak at ν_{CO} 1670 cm^{-1}, and the sharp band at 3280 cm^{-1}.

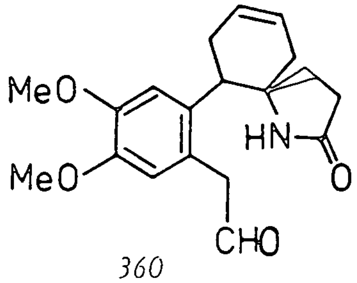
An unexpected observation was the complete absence of any lactam N-H stretch at ca. 3200 cm^{-1}, confirmed by 250 MHz proton NMR data. These initial observations suggested that cyclization had occured onto the lactam nitrogen.

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}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.



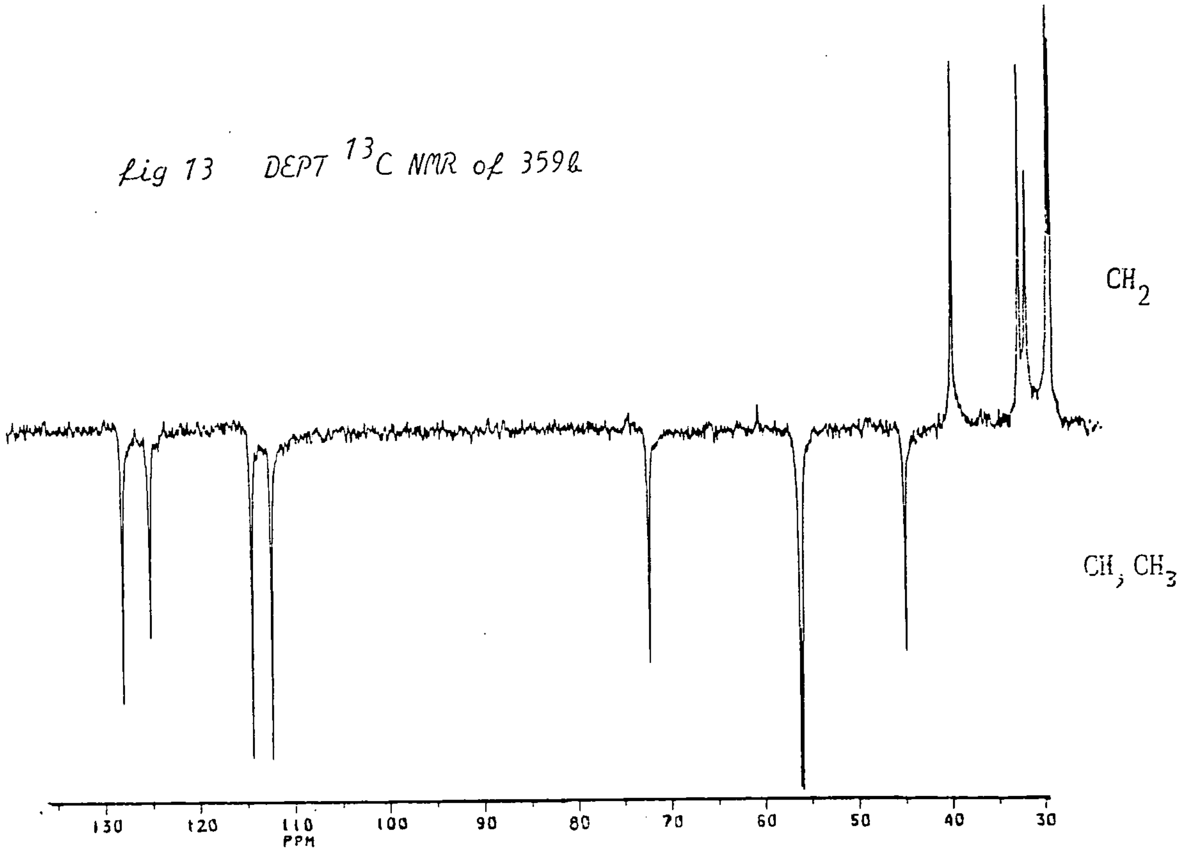
359



360

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}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 bulkyl 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.

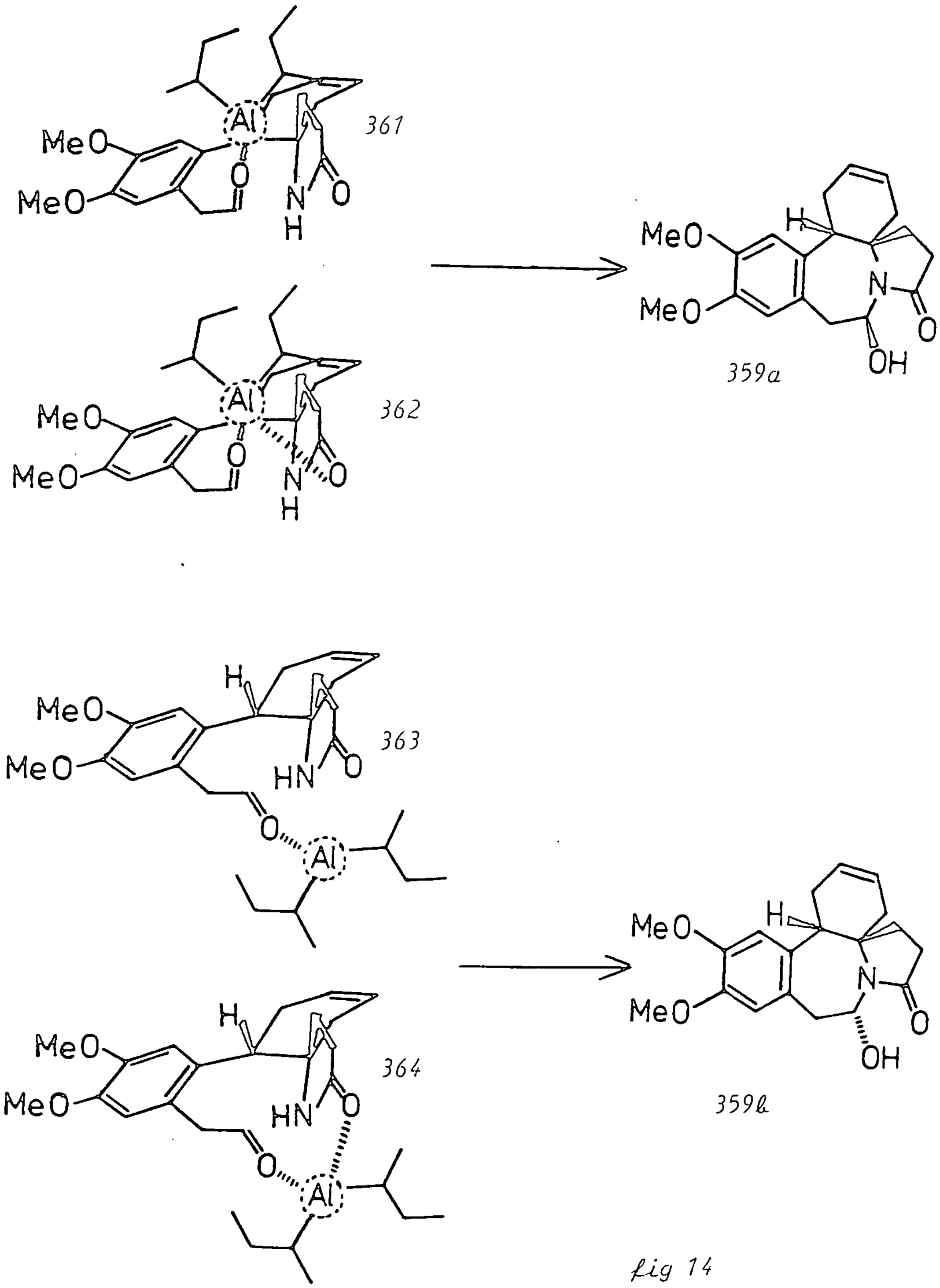


fig 14

DIBAL-H is known to regioselectively monoreduce cyclic imides to α-hydroxy lactams, and to reduce carbonyls by hydride transfer to the least hindered carbonyl face[363]. 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.

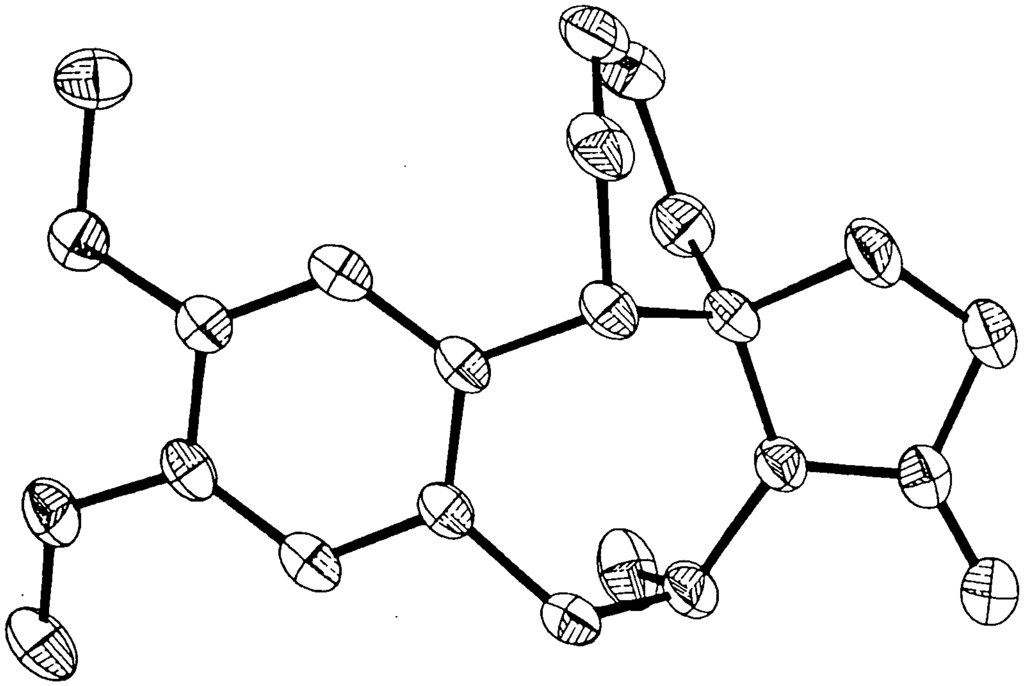


fig 15 X-ray structure of 359b : view from above benzene ring

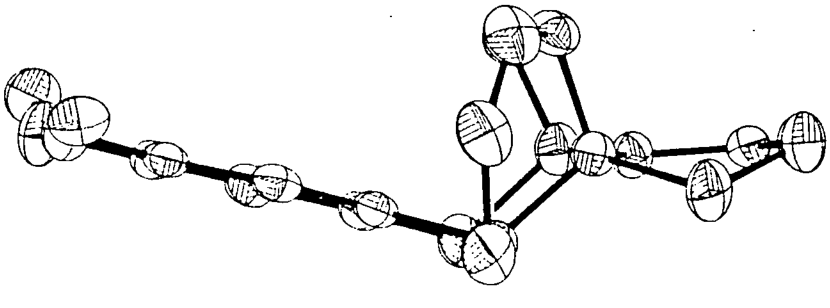
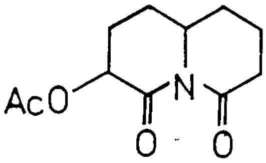


fig 16 X-ray structure of 359b : view in plane of benzene ring

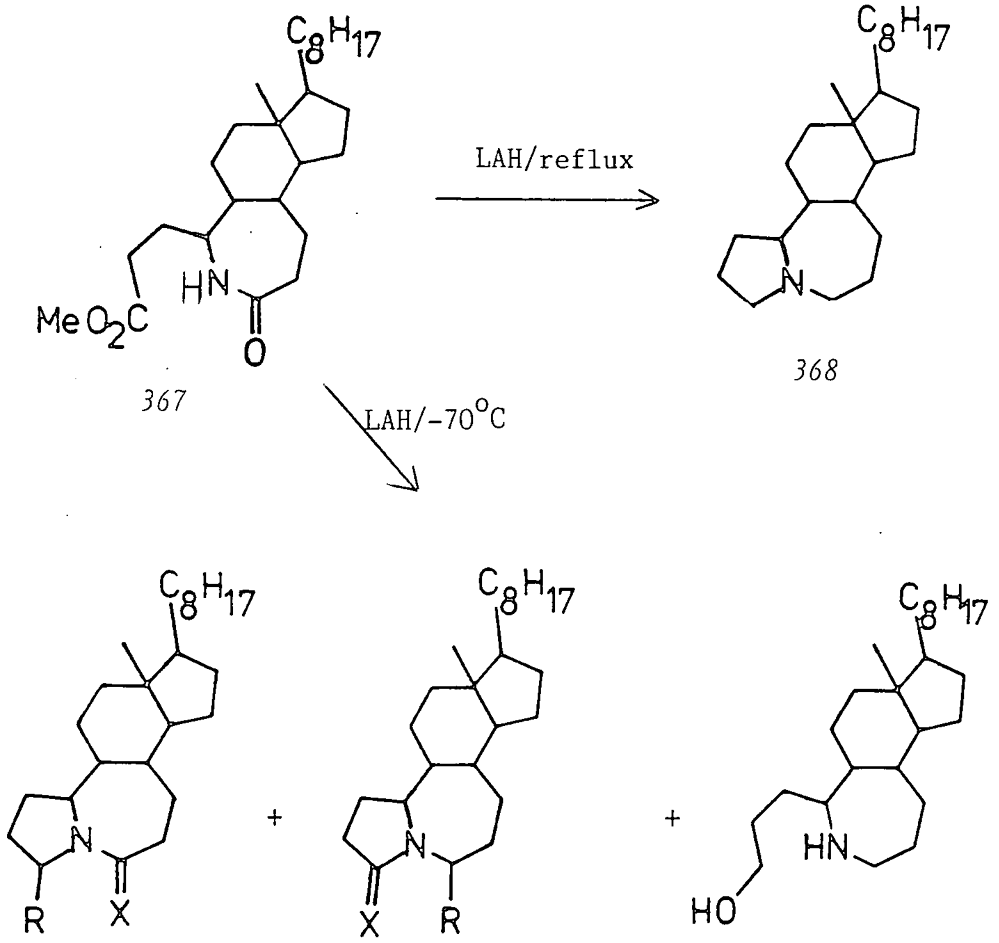
A further observation is that this relative configuration allows for hydrogen bonding between the hydroxyl and lactam carbonyl groups, forming a favourable chair-like six-membered ring. In contrast, the alternative configuration at the hydroxyl bearing carbon, would involve a much more twisted six-membered ring if such hydrogen bonding were to occur. This structure *359ℓ*, is consistent with the observed sharp OH stretch at 3280 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 dicyclocarbodiimide are known routes to small, e.g. β-lactam[364] and medium lactams, e.g. bicyclic imide *366*[365], reductive lactam-ester cyclizations with hydride reagents are rare. Treatment of lactam-ester *367* with LAH in THF at reflux, was reported to provide the bicyclic fully reduced amine *368*[366]. Reaction at -70°C yielded a complex mixture of all the possible regio- and stereo isomeric α-hydroxy lactams, *369-372*, and the reduced acyclic product *373*, in 18% yield. In contrast to this, our reaction of DIBAL-H with *357c* provides a single regioisomeric product α-hydroxy lactam, *359ℓ*, 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 *357c* 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 *374*. This is in sharp contrast to the efficient reductive five-membered ring closure of *367* under the same conditions described above[366].



367

368

369 R = HO

370 R = HO

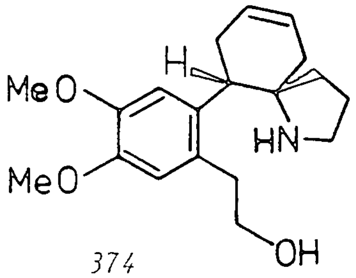
371 R = HO

372 R = HO

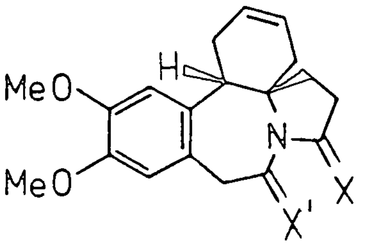
373

Trial reactions of *359ℓ* 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 *359ℓ*. LAH reduction to the amine will be utilized at an appropriate stage in the elaboration of ring E.



374



365 X = X' = O

375 X = X' = H_2

376 X = OH X' = O

Attempts to convert the α-hydroxy lactam, *359b*, to the imide, *365*, using chromium trioxide-pyridine[367], have so far led only to good recovery of unoxidized *359b*.

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[368].

4.2 Aza-cephalotaxine analogues

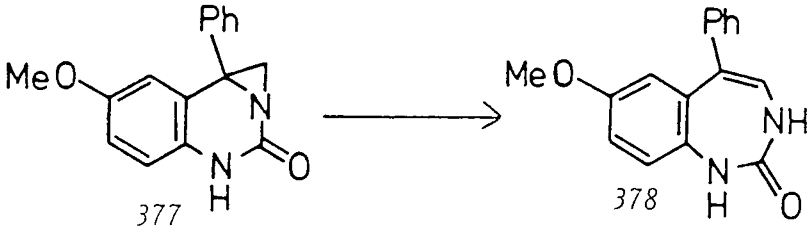
Much interest in the synthesis of benzazepine containing ring systems has been motivated by the range of physiological properties exhibited by some of these alkaloids. Similarly, benzodiazepine containing ring systems - though much rarer in natural products - also frequently show interesting biological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

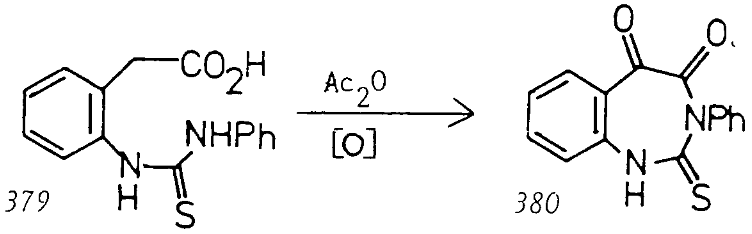
There have been no reports of synthetic work directed towards aza-cephalotaxine analogues. We considered these an obvious class of interesting analogues, that could be readily obtained by minor modifications of our synthetic strategy.

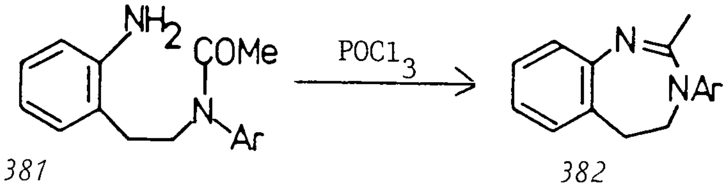
i 1,3-benzodiazepines

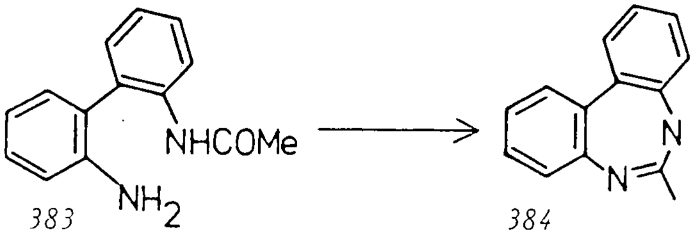
There have been far fewer reported synthetic approaches to benzodiazepines than to benzazepines, and 1,3-benzodiazepines, in particular, have been little investigated.

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



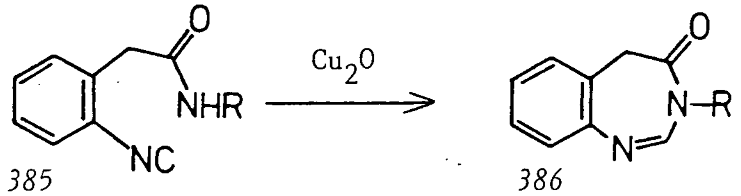






Formation of this one carbon bridge, from substrates already containing the requisite carbon containing functionality, is also available from copper (I) oxide promoted reaction of carbylamines e.g. *385*→*386*[376].

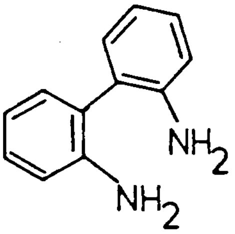
More significantly, a number of methodologies involving one carbon insertions into diamines, or amine-amides, have been developed. The



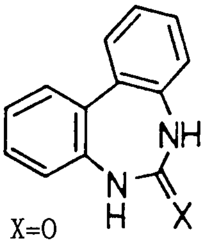
385 *386*

(favoured by bulky R)

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

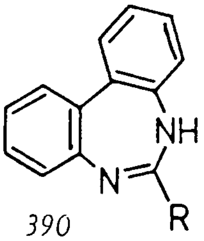


387



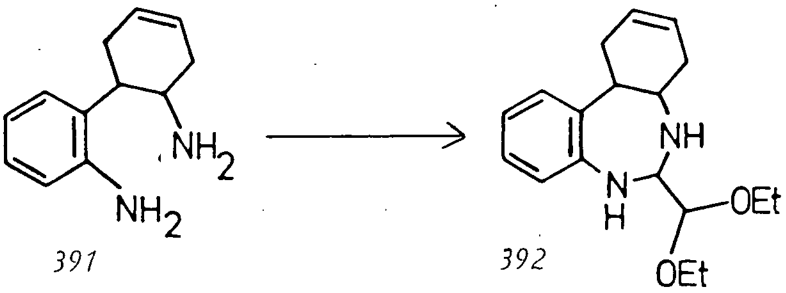
388 X=O

389 X=S

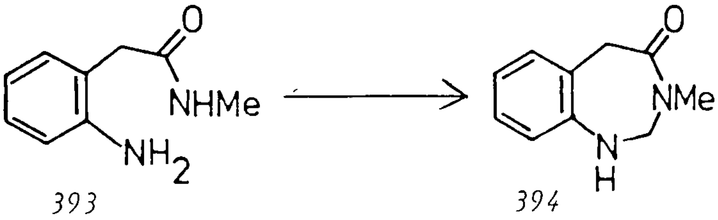


390

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



391 *392*

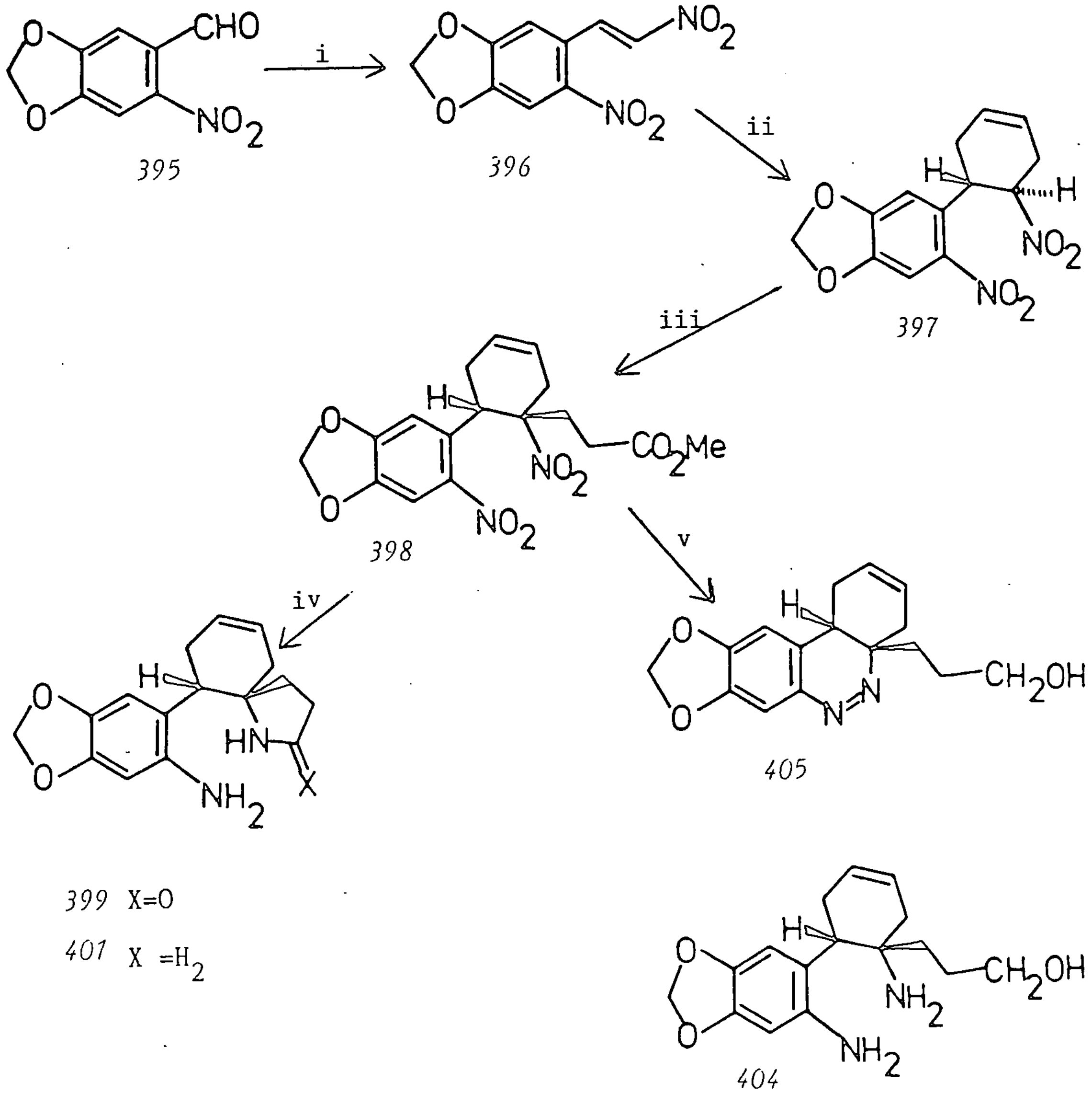


393 *394*

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 schemeXVII As we started this work, the condensation of 6-nitropiperonal with nitromethane, using potassium fluoride as base (dehydrating the intermediate β-hydroxy nitro compound with acetic anhydride), was reported[386]. In our hands, these conditions provided very good yields of nitrostyrene *396*(≥ 90%), of sufficient purity -

SCHEME XVII



395

396

397

398

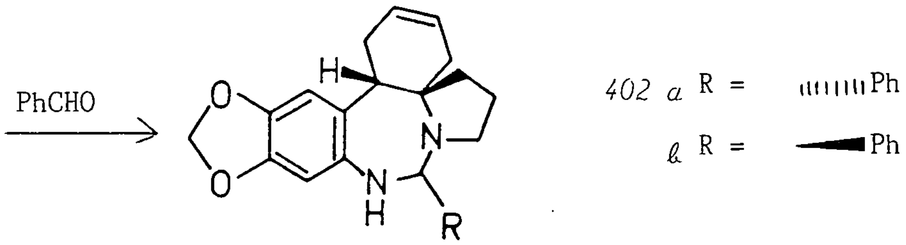
399 X=O

401 X $=H_2$

405

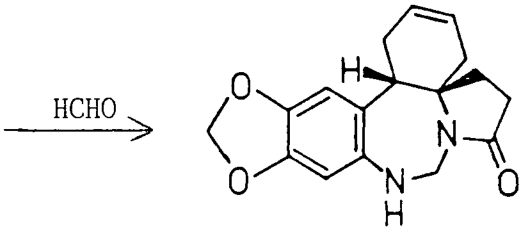
404

401

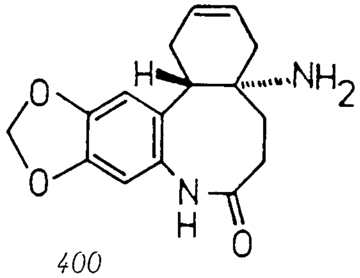


402 a, b

399



403



400

i $MeNO_2/KF/Ac_2O$, ii butadiene sulphone, iii Methyl acrylate/triton-B, iv Zn/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 γ-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 γ-lactam structure *399* was provided by the IR spectrum, which showed a single lactam carbonyl at ν_{max} 1690 cm^{-1} , consistent with a small ring lactam . (Medium ring lactams, such as an eight-membered system, would have ν_{max}, C=O at lower frequency.) Comparison of ^{13}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[387], 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 *402ℓ* 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 *359ℓ* (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.

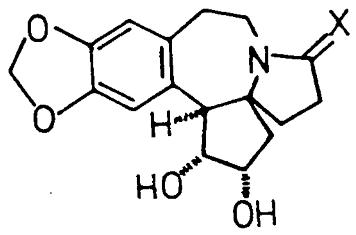
CHAPTER FIVE

PROGRESS TOWARDS FIVE MEMBERED RING E

5.1 Modifications of ring E

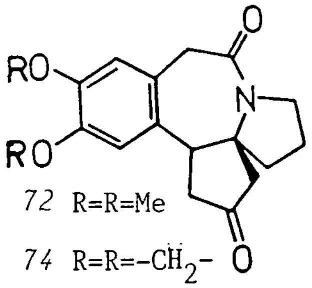
With the efficient, stereospecific construction of the azaspirocyclic moiety (2.2), and the mild, high yielding entry to the 3-benzazepine ring central to cephalotaxine (4.1) both achieved, the only remaining synthetic hurdle is appropriate elaboration of the cyclohexene ring E towards the oxidized cyclopentene 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*[39], or the 1,2-cis diol ring E of *406*[40] or *407*[43], 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_2

407 X = 0



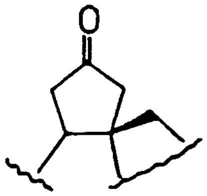
72 R=R=Me

74 R=R=-CH_2-

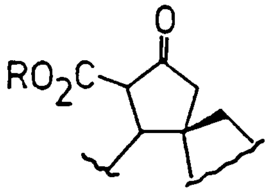
i Ring opening-ring closure strategies

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.

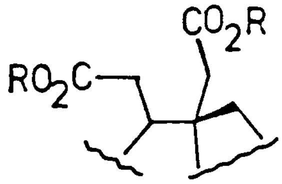
Oxidative ring opening of cyclic olefins, can be effected directly on the unsaturated substrate, or the trans- or cis-1,2-diol derivatives. Ozonolysis is perhaps the most well known of these methods and can lead



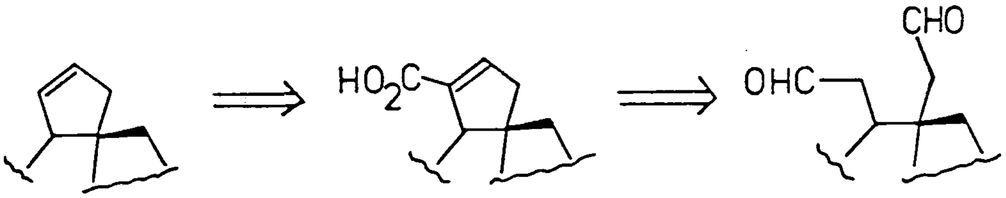
434



433 + regioisomer



409



408

410

to either diacid or dialdehyde products[388], by utilizing oxidative or reductive (e.g. Zn/HCl or Et_3PO) 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[389]). Direct oxidation of olefinic substrates to diacids, can also be achieved using Lemieux-von Rudloff[390] conditions (periodate salt, catalytic potassium permanganate), or with potassium permanganate, and quaternary ammonium salts[391], or dicyclohexyl-18-Crown-6[392] 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.

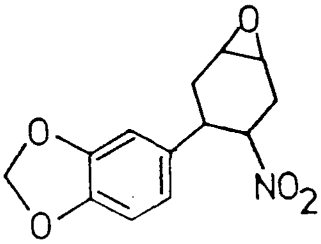
Oxidation attempts with potassium permanganate and dicyclohexyl-18-Crown-6 (5% molar catalyst through to stoichiometric) in benzene on the nitrocyclohexene *239*, or the lactam *131a*, led similarly to complex mixtures. The reaction mixture had darkened over ca. 10 minutes, indicating oxidation was occuring. 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[393]. 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[394]). Other reagent systems have also been reported to efficiently cleave diols viz acidic sodium bismuthate[395], lead tetra-acetate[396], pyridinium chlorochromate[400], and polymer supported periodate[401].

Initially, we decided to utilize the trans,-1,2-diol derivative of *239* or *131a* as substrates for oxidative clearage 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 reagants are known[402], but MCPBA[403] is currently the reagent of choice for epoxidation of isolated olefins, though this may soon be replaced by magnesium monoperoxyphthalate[404].

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



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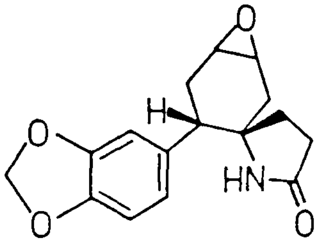
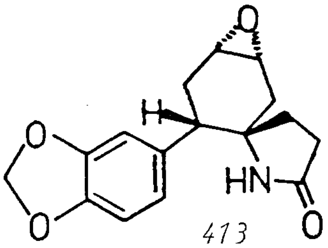


412

Notably, in both cases, the epoxide was obtained as a mixture of two isomers (nearly coincident on t.l.c., but occassionally 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



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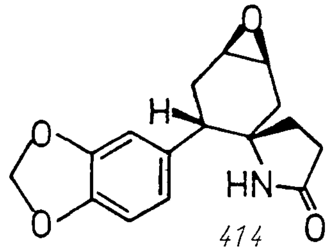
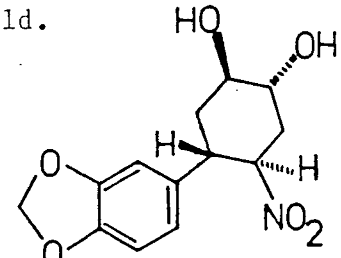


414

isomers indicated little selection between these isomers, consistent with the relative insensitivity of peracids to steric influences[405].

Treatment of epoxides *411* and *412* with 1% aq. sulphuric acid provided the expected[406] trans-1,2-diols, *415* and *416* in 80-90% yields. The trans-1,2-diol, *415*, had also been obtained from the starting olefin *239*, by reaction with hydrogen-peroxide and formic acid, in ca.60% yield.



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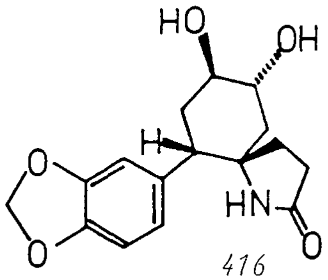


416

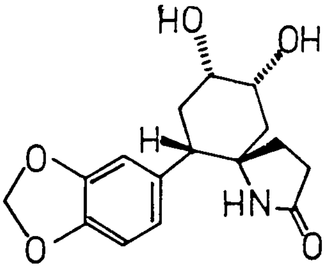
Periodate clearage of diols is usually carried out at, or below, ambient temperature[407], in a variety of protic solvents[408]. A water-methanol mixture proved most convenient for dissolving lactam-diol*416* But, treatment of *416* with periodic acid under progressively more vigorous conditions - including 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 *416*, 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[409], or thallium (I) acetate[410], 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[411] also yield cis-diols, osmium tetroxide oxidation has proved the most general and efficient of cis-hydroxylation methodologies[412]. A number of variations utilizing catalytic osmium tetroxide with a primary oxidant have been developed[413] (including now an asymmetric reagent system[414]), of which we chose the general methodology of van Rheenen et al[415] 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[416], or osmium organometallic[417] locating the large osmium centre in the hindered region close to the lactam ring.



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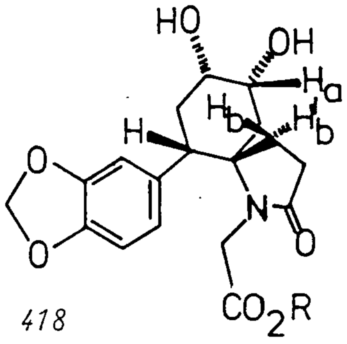
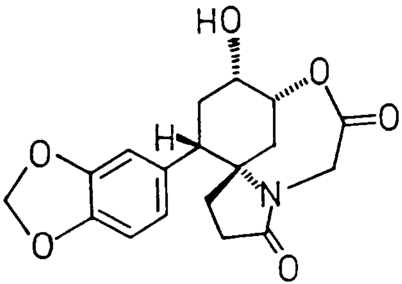


418

a R=Me

ℓ R=H

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[418] 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.



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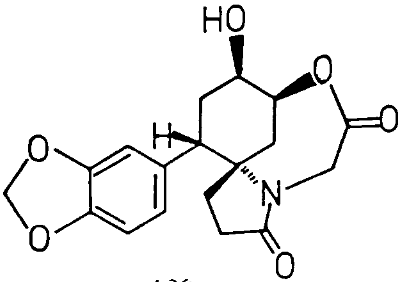
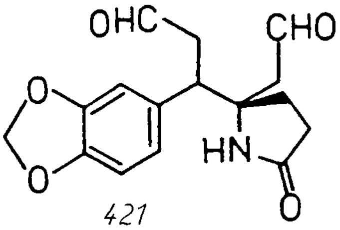


420

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.



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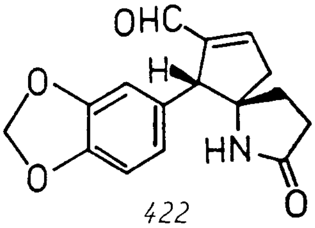

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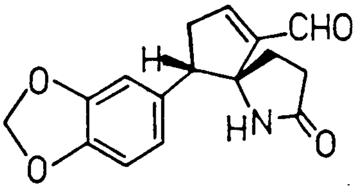
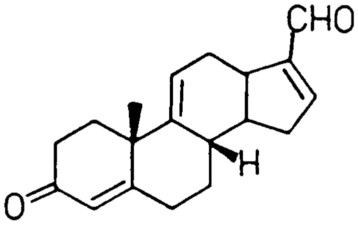


423

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[419] regioselectively obtained *424* from the corresponding dialdehyde, using catalytic piperidine acetate. More recently, Inubishi et al [420,421] have cyclized dialdehyde *425*to regioisomer *426*, with either basic alumina or catalytic piperidine acetate. Further, these workers[420,421] 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[422].



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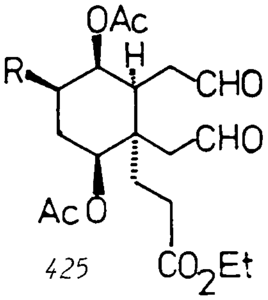

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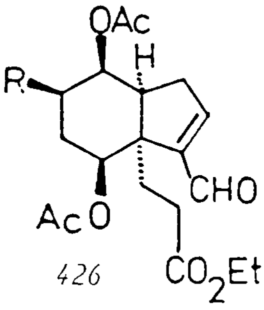

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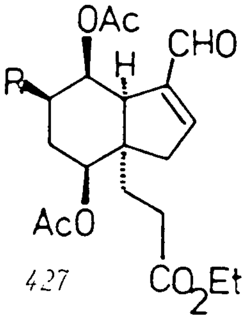

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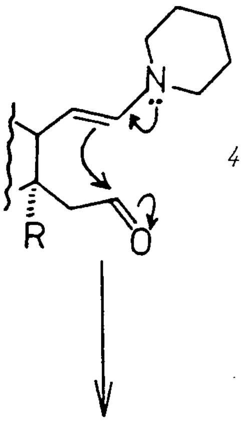
Inubishi et al[420] considered that with catalytic piperidine acetate, the piperidine enamine of the less hindered aldehyde, *428*, is formed, and then nucleophilically attacks the remaining free carbonyl; loss of the imminium substituent then provides the less hindered aldehyde product *426*. Basic 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 carbanion of the more hindered methylene group becomes the major nucleophile, resulting in the more hindered aldehyde, *427*.



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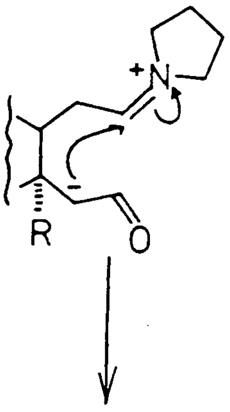

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427

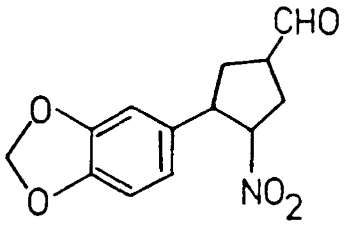
These reports aid us in predicting and choosing the regiochemistry of aldol cyclization of our dialdehyde, *421*. If we assume that the methylene group bonded to the quaternary spiro centre is more hindered than that linked to the tertiary benzylic centre, then we would expect treatment of *421* with 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, *359b*, 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[40] and Kuehne et al[43].

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[423]. 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 it dimethyl acetal, *431*.



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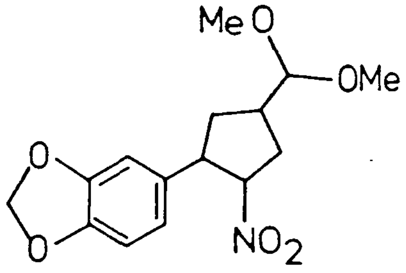

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Our interest then turned towards the well known epoxide to carbonyl rearrangements, catalysed primarily by Lewis acids[424] (boron-trifluoride etherate, magnesium bromide or aluminium chloride), but also by a variety of miscellaneous reagants[425]. 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[426], or with lithium bromide-alumina in toluene[427].

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.

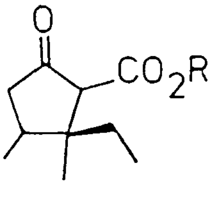
iii Summary and future work

A cis-hydroxylation, periodate clearage, 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[428-430], should shorten further the overall synthetic scheme.

Oxidation of dialdehyde intermediates e.g. 421, 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[431,432]. This is attractive because regiocontrol 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[39]. It also avails other possible strategies, to be discussed below.

432



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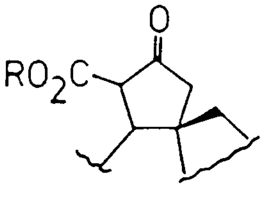

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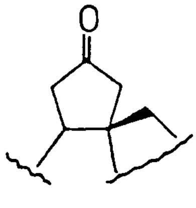


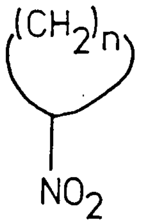
CHAPTER SIX

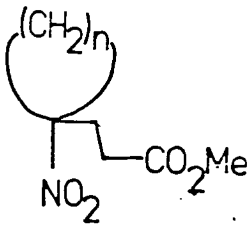
MODEL 1-AZASPIROCYCLES

6.1 Model Azaspirocycles

i Synthesis of model spirolactams

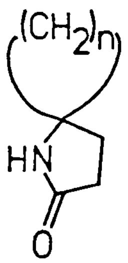
Our initial problems in cleanly reducing the spirolactam *131a* (2.2), led us to investigate the behaviour of model spirolactams. The obvious strategy to adopt for synthesis of model spirolactams, was the application of the Michael alkylation-reductive cyclization methodology (2.2), to simple nitrocycloalkanes.





208a n=4

208b n=5



209 n=4

210 n=5

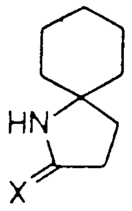
We found that nitrocyclohexane and nitrocyclopentane were both efficiently converted to the respective spirolactams, *209* and *210*, using this approach. Subsequently, good precedent for this type of strategy was found[108,109], using hydrogenolysis to effect reductive cyclization of *208a* and *208b* 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).

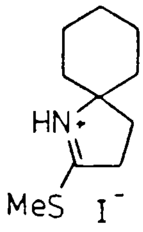
Conversion of the lactam 210 to the thiolactam, 435, was effected in good yield with phosphorus pentasulphide, and treatment of 435 with methyl iodide (in the dark), afforded near quantitative yields of the salt 436. If the methylation reaction is not protected from light, a yellow to orange, rather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



435 X=S

437 X=H_2



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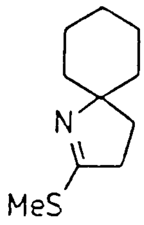

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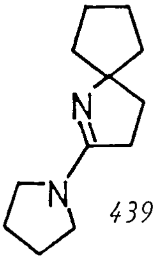
Thiolactim ethers, e.g. 438, are potentially versatile intermediates, as the β-carbon is susceptible to electrophilic attack and the α carbon to nucleophilic attack. The use of bifunctional reagants bearing both electrophilic and nucleophilic functionalities, has thus provided an annulation strategy onto thiolactim ethers[479].

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 *210* 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).



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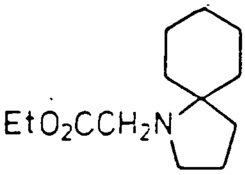

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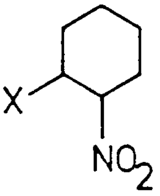
iii Future work

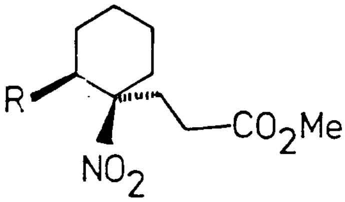
Methodologies for synthesis of substituted 1-azaspirocycles is an area of some current interest (see 2.1), and more particularly, stereospecific or enantiospecific approaches are keenly being investigated.

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



441 X = R

442 X = R



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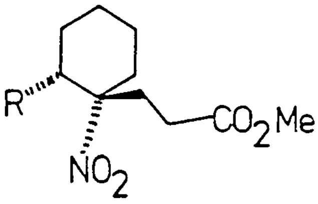

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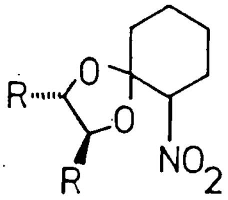
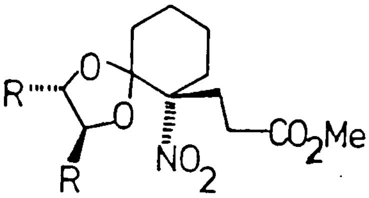
The utility of such an approach for asymmetric synthesis is clearly limited by the problems of obtaining enantiomerically pure β-chiral nitro cycloalkanes (single βconfiguration).

A potentially more viable strategy for enantioselective azaspirocyclic 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 auxilliary providing the enantiomerically pure 1-azaspirolactam, 447.



445



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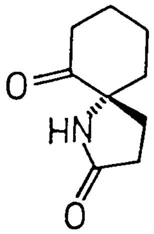

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CHAPTER SEVEN

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[161,162].

7.2 Experimental Procedures

i CHAPTER 2

Trans-1-(3,4-methylenedioxyphenyl)-2-nitroethene (237) was prepared following the literature procedure[135] from piperonal and the anion of nitromethane in 97% yield, m.pt. 161-164°C (from ethanol) (lit.[133] 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.[140] 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.[143,145] 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 $C_{14}H_{17}NO_4$ C 63.9, H 6.5, N 5.3; found C 63.8, H 6.6, N 4.8%; m/e 263 (El; M^+); ν_{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^{-1}; $\delta_H(CDCl_3)$

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); $\delta_C(CDCl_3)$ 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 ($MgSO_4$) 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 $C_{17}H_{19}NO_6$ C 61.3, H 5.7, N 4.2; found C 61.6, H 5.7, N 4.0%. m/e 286 (EI. M^+-NO_2) or 287 (CI), M^+ 333 absent; ν_{max} (nujol) 1735, 1530, 1352, 1315, 1250, 1210, 1180, 1170, 1030, 979, 956, 930, 899, 830, 815, 662 and 646 cm^{-1}; $\delta_H(CDCl_3)$ 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); $\delta_C(CDCl_3)$ 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 $C_{18}H_{23}NO_6$ 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; ν_{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^+); ν_{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 *241l*, 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^+); ν_{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 δ30.0ppm 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^+). ν_{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 (131b) -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 ($MgSO_4$) and evaporated at reduced pressure to yield compound *131b* as a viscous, pale yellow oil (2.73 g, 90%) Calculated for $C_{16}H_{19}NO_2$ 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; ν_{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 cm^{-1}; δ_H(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); δ_C(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 $C_{16}H_{20}ClNO_2$ 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 (236b) - This compound was prepared from lactam *236a*, under the same conditions as compound *131b*, 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. ν_{max} (neat) 3020, 2940, 2895, 2830, 1587, 1506, 1445, 1260, 1235, 1145, 1033, 810, 766, 695 and 655 cm^{-1}; δ_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); δ_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 methyliodide (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%; ν_{max} (KBr) 3430 (broad), 3030, 2990, 2910, 2780, 1575, 1505, 1490, 1448, 1240, 1040, 930, 855, 818 and 680 cm^{-1}; δ_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); δ_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 ($MgSO_4$) and evaporated *in vacuo* to leave a gelatinous, clear oil (80 mg, 47%). Calculated for $C_{17}H_{19}NSO_2$ m/e 301.11365; found 301.11435; ν_{max} ($CDCl_3$-CCl_4) 3020, 2890, 1585, 1500, 1485, 1440, 1315, 1250, 1230, 1100 and 1045 cm^{-1}; δ_H($CDCl_3$) 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-CH_3), 2.35-2.10 (4H, m), 1.92 (1H, m) and 1.55 (2H, m); δ_C($CDCl_3$) 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 $C_{17}H_{19}NO_2$ C 75.8, H 7.1, N 5.2; found C 76.2, H 7.2, N 4.9% m/e 270 (CI; M^+); ν_{max} (KBr) 3020, 2890, 2770, 1480, 1435, 1365, 1322, 1312, 1270, 1234, 1205, 1158, 1130, 1112, 1040, 932, 845 and 656 cm^{-1}; δ_H($CDCl_3$) 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); δ_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^+); ν_{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,5,6,10b-hexahydrocyclopenta[e] phenanthridinium salts: (a) *Iodide(319a)* - 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, *319a* (300 mg, 95%) as a pale yellow powder mp 201-202°C. Calculated for $C_{18}H_{22}NO_2I$ C 51.55, H 5.4, N 3.4; found C 51.48, H 5.7, N 3.0%.
(b) *hexafluorophosphate (319b)* - Methiodide salt *319a*, (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 *319b* (50 mg, 96%) as a white powder. Calculated for $C_{18}H_{22}NO_2PF_6$ 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_2. After completion of this addition, the mixture was allowed to warm to r.t. overnight. The reaction mixture was then poured into acidic (H_2SO_4) 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 ($MgSO_4$), 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%; ν_{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); ν_{max}(KBr) 3020, 2960, 2890, 1655, 1481, 1438, 1395, 1330, 1248, 1230, 1178, 1150, 1115, 1094, 1037, 930, 858, 802, 662 cm^{-1}; δ_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); δ_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 (H_2SO_4) ice water (100 ml, pH3) and extracted with chloroform (3 x 150 ml). The combined extracts were washed sequentially with (i) 10% aq. K_2CO_3 (200 ml), (ii) brine (100ml), dried ($MgSO_4$), filtered and evaporated to yield amide-ester *326*(0.66 g, 99%) as a white solid mp 105-107°C m/e 343 (EI, M^+), 344 (CI); Calculated for $C_{19}H_{21}NO_5$ C 66.47, N 6.12, H 4.08; found C 66.43, H 6.29, N 3.83%; ν_{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 cm^{-1}; $\delta_H(CDCl_3)$ 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 $\simeq$16Hz), 2.5-2.3 (2H, m), 2.2-2.0 (1H, m), 1.9-1.5 (4H, m),; $\delta_C(CDCl_3)$ 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), K_2CO_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, M^+), 344 (CI) Calculated for $C_{20}H_{25}NO_4$ C 69.97, H 7.29, N 4.08; found C 70.30, H 7.52, N 3.19%; ν_{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 cm^{-1}; $\delta_H(CDCl_3)$ 7.24 (1H, s), 6.86 (1H, d), 6.68 (1H, d, J = 7.9Hz), 5.9 (2H, d, J = 8Hz), 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); δ_C ($CDCl_3$) 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°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_2CO_3 (30 ml) (ii) brine (30 ml), dried ($MgSO_4$), 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); δ_H($CDCl_3$) 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 = 8.2Hz), 2.6 (1H, t, J= 5.5Hz), 2.52-2.11 (6H, m), 1.93-1.82 (2H, m), 1.61-1.5 (2H, m), 1.25-1.18 (1H, m); δ_C($CDCl_3$) 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 ($MgSO_4$), 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 *333* from mass spectral and NMR data. Elemental analysis could not be obtained. m/e 319 (EI, M^+), 320 (CI); $\delta_C(CDCl_3)$ 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 (336) - To a stirring solution of lactam *131a* (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 ($MgSO_4$), filtered and evaporated to leave a gum. Chromatography (alumina column, 20 x 4.5 cm) eluting with ethyl acetate, provided N-alkylated product *336* (4.2 g, 97%) as a white solid; mp 126-128°C; m/e 385 (EI, M^+), 330 (CI, M^+-isobutenyl). Calculated for $C_{22}H_{27}NO_5$ C 68.39, H 7.26, N 3.86; found C 68.00, H 7.12, N 3.94 %; ν_{max} (KBr) 3130, 2985, 1745, 1690, 1488 1443, 1415, 1388, 1367, 1255, 1235, 1559, 1040, 940, 850, 810, 778, 745, 670 cm^{-1}; δ_H ($CDCl_3$) 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); $\delta_C(CDCl_3)$ 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-carbotertbutoxymethyl-6-(3,4-dimethoxyphenyl)-2-oxo-1-azaspiro[4.5]dec-8-ene (323) [R = Me, Y = $CO_2{}^{+}Bu$], 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^+), 346 (CI, M^+-isobutenyl). Calculated for $C_{23}H_{31}NO_5$ C 68.83, H 7.73, N 3.49· found C 68.48, H 7.87, N 2.92%;ν_{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^{-1}; $\delta_H(CDCl_3)$ 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_2SO_4 (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_2CO_3 (2 x 30 ml) (ii) brine (50 ml), dried (MgSO$_4$), 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^+), 344 (CI); Calculated for $C_{19}H_{21}NO_5$ C 66.47, H 6.12, N 4.08; found C 66.03, H 5.94, N 3.73%; ν_{max} (KBr) 3020, 2895, 1752, 1690, 1503, 1487, 1440, 1412, 1385, 1340, 1308, 1252, 1237, 1210, 1176, 1118, 1098, 1037, 930, 811, 668 cm^{-1} ; $\delta_H(CDCl_3)$ 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); $\delta_C(CDCl_3)$ 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 ($MgSO_4$), 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°C; m/e 283 (EI, M^+-46), 330 (CI); Calculated for $C_{18}H_{19}NO_5$ C 65.65, H 5.78, N 4.26 m/e329.12632 ; found C 63.72, H 6.13, N 3.63%, m/e 329.11114 ; ν_{max} (KBr) 3480, 2900, 1735, 1635, 1487, 1440, 1283, 1170, 1035, 928, 870, 850, 810, 655, 580 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°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°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. Na_2CO_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 ($MgSO_4$), 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, M^+), 314 (CI), Calculated for $C_{18}H_{19}NO_4$ 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 ; ν_{max}(KBr) 3023 2900, 1732, 1685, 1507, 1491, 1443, 1412, 1385, 1341, 1306, 1254, 1240, 1178, 1100, 1041, 933, 860, 813, 670 cm^{-1}; $\delta_H(CDCl_3)$ 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 ($MgSO_4$), 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,M^++1), 316 (CI); ν_{max}(KBr) 3460, 3030, 2908, 1168, 1508, 1489, 1444, 1408, 1342, 1310, 1253, 1248, 1218, 1180, 1040, 932, 865, 854, 813, 778, 665 cm^{-1}; $\delta_H(CDCl_3)$ 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); $\delta_C(CDCl_3)$ 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. K_2CO_3 (10 ml), dried ($MgSO_4$), 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, M^+), 296 (CI); Calculated for $C_{18}H_{17}NO_3$ m/e 295.12084; found m/e 295.03494, ν_{max}(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 cm^{-1}; $\delta_H(CDCl_3)$ 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); $\delta_C(CDCl_3)$ 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 coincidant peaks. δ_CDEPT ($CDCl_3$) (CH_2CH_3) 126.4, 125.7, 119.7, 109.7, 109.2, 108.1, (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 ($MgSO_4$), filtered and evaporated to yield a white fluffy solid (56 mg , 93%), tentatively assigned structure *344* from spectral data; mpt 141-144°C; m/e 313, 295 (EI, M^+, M^+-18); 314, 296 (CI); Calculated for $C_{18}H_{19}NO_4^{‡}$ m/e 295.12084; found m/e 295.12240 ; ν_{max}(KBr) 3430, 2890, 1665, 1500, 1487, 1445, 1412, 1378, 1350, 1249, 1100, 1036, 930, 860, 810, 654 cm^{-1}; $\delta_H(CDCl_3)$ 6.79-6.65 (2H, m), 5.94-5.71 (4H, m), 3.45 (1H, m), 2.86-1.67 (11H, m);$\delta_C(CDCl_3)$ 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.

iii CHAPTER FOUR

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. Na_2CO_3 (2 x 200 ml), (ii) brine (100 ml), then dried ($MgSO_4$), 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 $C_{11}H_{14}O_4$ C 62.86, H 6.67; found C 63.09, H 7.12%; ν_{max} (neat) 2989, 2943, 2827, 1734, 1602, 1589, 1511, 1461, 1437, 1418, 1263, 1156, 1028, 950, 891, 841, 808, 788, 762, 703, 600, 538 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°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°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°C for 30 minutes, before being allowed to stir at 20°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 ($MgSO_4$), filtered and evaporated yielding a deep orange gum. Washing this with cold (-20°C) diethyl ether (3 x 20 ml) yielded aldehyde *347b* (13.3 g, 78%) as a dark orange solid, mpt 99.5-101.5°C. Calculated for $C_{12}H_{14}O_5$; C 60.50 %, H 5.88%, found C 60.36%, H 5.81%; m/e 238 (EI M^+), 239 (CI); ν_{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 cm^{-1}; δ_H ($CDCl_3$) 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); δ_C($CDCl_3$) 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 (348b) - To a suspension of aldehyde, *347b*, (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°C, diluted with methanol (5 ml), and the yellow solid filtered off. The solid was washed with portions of cold water and dried, yielding *348b* as a yellow powder (8.80 g, 74%); mpt 121-122°C; m/e 281 (EI,M^+), 282 (CI); Calculated for $C_{13}H_{15}NO_6$ C 55.52 %, H 5.39%, N 4.98%; found C 55.84%, H 5.54%, N 4.83%; ν_{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 cm^{-1}; δ_H($CDCl_3$) 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); δ_C($CDCl_3$) 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 (349b) - Nitrostyrene, *348b*, (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^{o}C for 7 days. The cooled, dark mixture was filtered and evaporated to yield a dark gum. Recrystallization from methanol (150 ml) provided *349b* (3.5 g, 74%), as a pale brown crystalline solid. mpt 148.5 - 149.5^{o}C; m/e 335 (EI,M^+), 353 (CI, $+NH_4^+$); Calculated for $C_{17}H_{21}NO_6$ C 60.89%, H 6.27%, N 4.18%; found C 61.20%, H 6.48%, N 3.90%; ν_{max} (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^{-1}; $\delta_H(CDCl_3)$ 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); $\delta_C(CDCl_3)$ 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 (350b) - To a stirring solution of nitro-ester *349b* (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_2CO_3 (ii) brine, then dried ($MgSO_4$), 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, *350b*, (1.97 g, 87%), as a white powder; mpt 100.5-101.5°C; m/e 421 (EI, M^+), 421 (CI); Calculated for $C_{21}H_{27}NO_8$ C 59.86%, H 6.41%, N 3.33%; found C 60.03%. H 6.54%, N 2.86%: ν_{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^{-1} ; $\delta_H(CDCl_3)$ 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); $\delta_C(CDCl_3)$ 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 (351b) - (a) To a stirring solution of nitro-diester *350b* (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 mxiture 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 ($MgSO_4$), filtered and evaporated to yield 6-(3,4-dimethoxy-6-carbohydroxymethylphenyl)-2-oxo-1-azaspiro [4.5]dec-8-ene, *351a* (157 mg, 38%), identified spectral data m/e 345 (EI, M^+), 346 (CI); ν_{max} (KBr) 3400 (OH), 3220 (NH), 1715 (Acid C=O), 1645 (lactam, C=O) cm^{-1}; (b) Crude lactam-acid, *351a*, (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_2CO_3, (ii) brine, then dried ($MgSO_4$), filtered and evaporated. Lactam-ester, *351b*, (47 mg, 90%) was obtained as a white powder. (Overall yield from *350b*, 34%); mp 163-165°C; m/e 359 (EI, M^+), 360 (CI); Calculated for $C_{20}H_{25}NO_5$ C 66.9, H 7.0, N 3.9; found C 66.7, H 7.0, N 3.2%; ν_{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^{-1}; δ_C($CDCl_3$) 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 (351c) - To a stirring solution of nitro-diester *350b* (1.013 g, 2.4 mmol) in ethanol (50 ml) and concentrated hydrocloric 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 ($MgSO_4$), filtered and evaporated to yield lactam-ester, *351c* (790 mg, 91%), as a white powder; mp 172.5-174.5°C; m/e 373 (EI, M^+), 374 (CI); Calculated for $C_{21}H_{27}NO_5$

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; ν_{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 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°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°C, then quenched by addition of brine (30 ml), and warmed to r.t. over 30 mins. The aqueous layer was separated and extracted withethyl acetate (3 x 100 ml), and the combined organic phases then washed with brine (10 ml), dried ($MgSO_4$), 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, *359b* , (183 mg, 91%) as a white solid; mp 133-135°C, m/e 329, 311 (EI, M^+, M^+-18), 330, 312 (CI); Analysis calculated for C H NO_4; C 69.30%, H 6.99%, N 4.26%, found C 69.62%, H 7.32%, N 4.01%; ν_{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 cm^{-1}; δ_H($CDCl_3$) 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); δ_C ($CDCl_3$) 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;

δ_CDEPT ($CDCl_3$) (CH_1,CH_3) : 127.9, 125.1, 114.3, 112.3, 72.2, 56.1, 55.8, (CH_2) : 44.8, 39.7, 32.4, 31.6, 29.2, 28.9 ppm.

7,8-dimethoxy-cyclohexeno[3,4-b]-pyrrolidino[1,2-a]-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 α-hydroxy-lactam, *359b*, (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°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°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 (Na_2SO_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); ν_{max} (KBr) 2958, 2910, 1625, 1610, 1579, 1495, 1460, 1440, 1410, 1380, 1335, 1261, 1095, 1041, 865, 800, 700, 658 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, *351c* (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°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 (Na_2SO_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, 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 $C_9H_6N_2O_6$ C 45.38, H 2.52, N 22.76; found C 45.08, H 2.42, N 11.53%; ν_{max} (KBr) 3105, 3060, 2917, 1638, 1600, 1510, 1482, 1430, 1340, 1274, 1031, 975, 957, 913, 872, 857, 809, 759, 735, 595, 557, 505 408 cm^{-1} ; δ_H ($CDCl_3$) 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); δ_C($CDCl_3$) 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^+), CI (310, M + NH_4^+); Calculated for $C_{13}H_{12}NO_6$ C 53.43, H 4.11, N 4.59; found C 53.44, H 4.08, N 9.33% ν_{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^{-1}; δ_H ($CDCl_3$) 7.34 (1H, s), 6.83 (1H, s), 6.1 (2H, s), 5.81-5.76 (2H, dt, J_d = 6.1, J_t= 10.2 Hz), 5.0-4.97 (1H, dt, J_d = 6.2, J_t = 10.2 Hz) 4.19-4.17 (1H, dt, J_d = 5.6, J_t = 10.8 Hz), 2.78-274 (4H, m); δ_C($CDCl_3$) 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, $M^{+}-NO_2$), 396 (CI, M+NH_4^+); Calculated for $C_{17}H_{18}N_2O_8$ C 53.97, H 4.76, N 7.41; found C 53.95, H 4.95, N 7.02%; ν_{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 cm^{-1}; δ_H ($CDCl_3$) 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); δ_C($CDCl_3$) 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 protions over 15 mins. The temperature rose to ca. 55°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 ($MgSO_4$), 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 234-236°C; m/e 286 (EI, M^+), 287 (CI); Calculated for $C_{16}H_{18}N_2O_3$ C 67.13, H 6.29, N 9.79; found C 66.96, H 6.41, N 9.53%; ν_{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 cm^{-1}; δ_C ($CDCl_3$) 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 ($MgSO_4$), 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 $C_{16}H_{18}N_2O_3$ m/e 286.13172; found m/e 286.12822; m/e = 287 (CI); ν_{max}(KBr) 3400, 3020, 2900, 1615, 1501, 1470, 1435, 1362, 1288, 1263, 1193, 1033, 930, 860, 818, 739, 656 cm^{-1} ; δ_H ($CDCl_3$) 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); δ_C ($CDCl_3$) 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^n.) 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^+), 299 (CI); Calcualted for $C_{17}H_{18}N_2O_3$ C 68.46, H 6.04, N 9.4; found C 68.36 H 5.92, N 8.92%; ν_{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^{-1}. δ_C ($CDCl_3$) 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_2CO_3 (10 ml), then brine (10 ml). The organic solution was then dried (Na_2SO_4), 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 $C_{16}H_{20}N_2O_2$ 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 benzaldehyde (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 ≃ 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).

iv CHAPTER FIVE

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^{o}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 protions of (a) saturated aq. sodium bisulfite; (b) water, dried ($MgSO_4$), and filtered through a pad of $MgSO_4$. Evaporation yielded crude epoxide, *411*, as a pale yellow solid, with IR indicating presence of m-chlorobenzoic acid impurity (carbonyl stretch at ν_{max} 1700 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 121-123^{o}C; m/e 263 (EI, M^+), 281 (CI, $M+NH_4^+$) . Calculated for $C_{13}H_{13}NO_5$ C 59.32, H 4.94, N 5.32; found C 59.00, H 4.78, N 4.83%; ν_{max} (KBr) 3005, 2910, 1609, 1547, 1504, 1486, 1440, 1373, 1244, 1190, 1106, 1034, 925, 897, 876, 832, 806, 632, 409 cm^{-1}; δ_H ($CDCl_3$) 6.72-6.59 (3H, m), 5.92 (1H, s), 4.87-4.76 (1H, dt, J_d = 4.5 J_t = 11.4 HZ), 3.42 (1H, s), 3.25 (1H, s), 3.13-3.01 (1H, dt, J_d = 7, J_t = 11.8 Hz), 2.87-2.80 (1H, d, J = 14 HzO, 2.49-2.4 (2H, m), 2.18-2.01 (1H, t, J $\simeq$14 Hz); δ_C($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°C, whereupon a white precipitate formed. The solution was filtered, and washed sequentially with 10 ml protions of (i) 10% aq. sodium bisulfite, (ii) 10% aq. Na_2CO_3, (iii) brine, then dried ($MgSO_4$), 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, *413* and *414* mp 150-153°C; m/e 287 (EI, M^+), 288 (CI),; Calculated for $C_{16}H_{17}NO_4$ C 66.90, H 5.92, N 4.88; found C 66.87, H 6.03m N 4.45%; ν_{max} (KBr) 3000, 2970, 2930, 2890, 1690, 1483, 1439, 1397, 1247, 1185, 1094, 1028, 923, 863, 818, 800, 701, 649, 610, 504, 458 cm^{-1}; $\delta_H(CDCl_3)$ 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); $\delta_C(CDCl_3)$ 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 (415) - 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°-60°C for 30 mins, over which period it became homogeneous. Most of the formic acid was then removed *in vacuo*, and the residue (monoformyl 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, *415*, (0.4 g, 70%) as a white solid, mp 190-192°C; m/e 281 (EI, M^+), 299 (CI, $M+NH_4^+$); Calculated for $C_{13}H_{15}NO_6$ C 55.52, H 5.34, N 4.98; found C 55.76, H 5.39, N 4.63%; ν_{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 cm^{-1}; δ_H $(CDCl_3)$ 7.41 (1H, s), 7.36-7.32 (2H m), 6.55 (2H, m), 5.65 (1H, dt, J_d = 3.8, J_t = 11.8 Hz), 4.6 (1H, s),

4.51 (1H, s), 4.19-4.08 (1H, δt, J_{δ} = 3.5, J_t = 12.4 Hz), 3.18-3.07 (1H, t, J = 12.5 Hz), 2.89-2.44 (4H, m); δ_C ($CDCl_3$) 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_2SO_4 (20 ml) added. The mixture was stirred at r.t. for 10 hrs, then evaporated to yield a crude white solid. Chromatogrpahy (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^+), 306 (CI); Calculated for $C_{16}H_{29}NO_5$ C 62.95, H 6.23, N 4.59; found C 62.92, H 6.63, N 4.29%; ν_{max} (KBr) 3395, 2930, 2895, 1660, 1500, 1490, 1443, 1411, 1285, 1255 1042, 939, 828, 671, 520 cm^{-1}.

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_2CO_3; (b) brine, dried ($MgSO_4$), 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^+), 306 (CI); Calculated for $C_{16}H_{19}NO_5$ C 62.9, H 6.2, N 4.6; ; found C 60.6, H 6.2, N 4.1% ; ν_{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^{-1}.

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-methylmorpholine 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_2SO_4) 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_2CO_3, (ii) brine, dried ($MgSO_4$), filtered and evaporated to give cis-diol *418a*, (514 mg, 93%) as a white solid. mp 85-87°C; m/e 377 (EI, M^+), 378 (CI); Calculated for $C_{19}H_{24}NO_7$ 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 :ν_{max} (KBr) 3400 3920, 1745, 1665, 1487, 1438, 1411, 1247, 1220, 1035, 930, 848, 805, 744, 700, 643, 505 cm^{-1}; δ_H ($CDCl_3$) 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); δ_C ($CDCl_3$) 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 ($MgSO_4$), 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 $C_{16}H_{16}NO_4$ (M^++1) m/e 286.10793; found m/e 286.10279; δ_H ($CDCl_3$) 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_C ($CDCl_3$) 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.

v CHAPTER SIX

1-(2-Carbomethoxyethyl)-1-nitrocyclohexane (208b) - 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_2CO_3 (iii) water, then dried ($MgSO_4$) and evaporated to yield an oil which on distillation afforded compound *208b* (14.1 g, 85%., bpt, 80°C at 0.5 mm Hg. Calculated for $C_{10}H_{17}NO_4$ C 55.8, H 7.9, N 6.5; found C 55.8, H 8.2, N 6.3%; ν_{max} (neat) 2940, 2861, 1743, 1537, 1445, 1350, 1305, 1203, 1175, 992, 897 and 845cm^{-1}; δ_H ($CDCl_3$) 3.82 (3H, s), 2.5 (6H, m), 1.85 (5H, m) and 1.6 (3H, s); δ_C ($CDCl_3$) 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 *208b* (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% aqeous 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 ($MgSO_4$) and evaporated to yield compound *210* as a white powder (3.0 g, 75%). Analytical samples of*210* mp 134-135°C (lit.[109] mp 132.2-132.3°C) were obtained by vacuum sublimation (70 -90°C at 0.5 mm Hg) or column chromatography on Al_2O_3 (eluent ethyl acetate: methanol 4:1 v/v). Calculated for $C_9H_{15}NO$ 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^+); ν_{max} (KBr)

3200, 2920, 2860, 1690, 1455, 1428, 1376, 1344, 1280, 1264, 1215, 1170, 1005, 988, 935, 900, 850, 744, 653, 611 and 512 cm^{-1} ; δ_H ($CDCl_3$) 7.98 (NH, s), 2.39 (2H, t), 1.88 (2H, t), 1.56-1.45 (10 H, m); δ_C ($CDCl_3$) 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 *210* (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°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% Na_2CO_3 solution, (iii) water, then dried ($MgSO_4$) 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 144.5-146°C; Calculated for $C_9H_{15}N_5$ 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, M^+); ν_{max} (KBr) 3030, 3000, 2930, 2845, 1540 (C=S) 1445, 1418, 1370, 1340, 1292, 1258, 1180, 1105, 1076, 796 cm^{-1}; δ_H ($CDCl_3$) 9.52 (NH, s), 2.96 (2H, t), 1.99 (2H, t), 1.65 (6H, m) and 1.44 (4H, m); δ_C ($CDCl_3$) 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 *210* (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°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. Na_2CO_3 (ii) NaCl solution, dried ($MgSO_4$) and evaporated to yield compound *437* as a pale yellow oil (0.5 g, 80%). Calculated for $C_9H_{17}N$ m/e 139.1361;

found 139.1346; ν_{max} (neat) 3250, 2920, 2850, 1450, 1105 and 920 cm^{-1}; δ_H ($CDCl_3$) 2.96 (2H, broad s, CH_2 adjacent to NH), 1.9 (2H, m and 1.7-1.2 (13H, m); δ_C ($CDCl_3$) 61.7, 45.2, 38.1, 36.5, 25.9, 25.4 and 23.9 ppm

2-Thio-1-azaspiro[4.5]decane-S-methiodide salt (436) - Thiolactam *435*, (0.96 g, 5.7 mmol) was dissolved in dry tetrahydrofuran (150 ml) and methyliodide (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 $C_{10}H_{18}NSI$ 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, M^+); ν_{max} (KBr) 3000, 2920, 2858, 2800, 1590, 1452, 1400, 1348, 1263, 1182 and 1065 cm^{-1}; δ_H ($CDCl_3$) 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); δ_C ($CDCl_3$) 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 K_2CO_3 solution (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. analysis [Al_2O_3 plate, eluent hexane:ethyl acetate (1:1 v/v)] to be pure product although satisfactory microanalytical data could not be obtained. Calculated for $C_{10}H_{17}NS$ 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. ν_{max} (neat) 2925, 2858, 1595, 1450. 1309, 1290, 1175, 1155, 1080 and 1055 cm^{-1} ; δ_H ($CDCl_3$) 2.48 (2H, t), 2.28 (3H, s) and 1.68-1.23 (12 H, m); δ_C ($CDCl_3$) 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 bromoethylacetate (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; ν_{max} (neat 2940, 2860, 2800, 1760, 1450, 1370, 1180 and 1040 cm^{-1} δ_H ($CDCl_3$) 4.24 (2H, q), 3.85 (1H, s), 3.42 (1H, s), 2.27-1.10 (19H, m); δ_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 *208b* 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); ν_{max} (neat) 2960, 2880, 1743, 1538, 1440, 1360, 1200, 1180 and 845 cm^{-1}; δ_H ($CDCl_3$) 3.65 (3H, s), 2.5 (2H, m), 2.1 (4H, s) and 1.8 (6H, m); δ_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.[109] 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^+); ν_{max} (KBr) 3160, 3078, 2940, 2870, 1688, 1463, 1434, 1380, 1260, 1035, 945, 930, 780, 645, 555, 520 and 420 cm^{-1}; δ_H ($CDCl_3$) 7.22 (NH, s), 2.32 (2H, t), 1.94 (2H, t) and 1.65 (8H, m); δ_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[43].

While attempts to obtain the imide functionality by oxidation of *359b* were unsuccessful (4.1), an alternative ring closure may provide this unknown 8-oxo-10-oxo substituion (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 β-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;

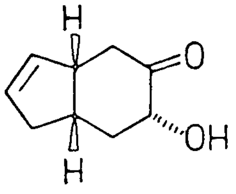
(ii) alternative strategies, constructing ring E early as a five membered ring;

(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[39,40,43], 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*.

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



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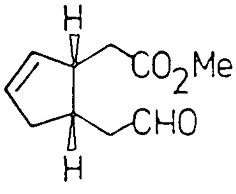

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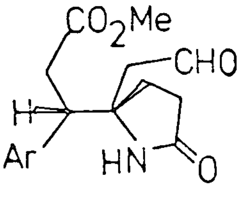

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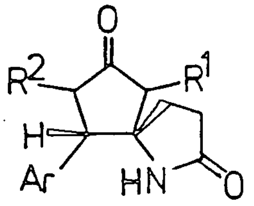
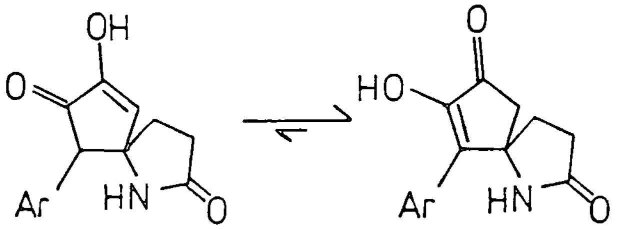


451 R1=H R^2 = CO_2Me

452 R^1=CHO R^2= H

453 R^1=R^2=H

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

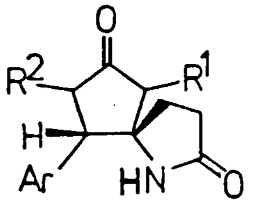


454 *455*

This is functionality appropriate to demethylcephalotaxinone, *12*, ring E intermediates of this type have already been converted to cephalotaxine ring E[40].

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 β-nitrostyrene intermediates (see 2.2, 4.1 and 4.2), represented generally as *456*, to the β-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 *77*[39].



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

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

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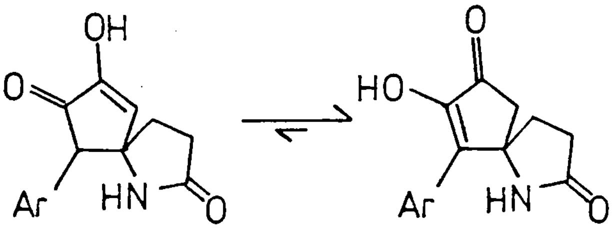

454 *455*

This is functionality appropriate to demthylcephalotaxinone *12*, ring E intermediates of this type have already been converted to cephalotaxine ring E[40].

ii Alternative strategies for five-membered ring E

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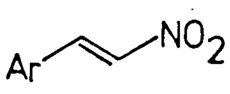

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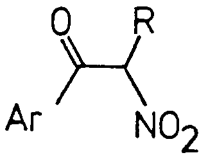
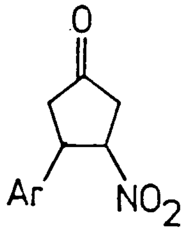


457 R=H

458 $R=CH_2C(Cl)CH_2$



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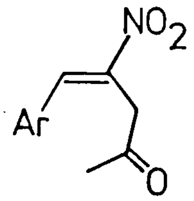
Reduction of *458* to the alcohol, and acid catalysed cyclization[39, 439] should similarly yield cyclopentanone intermediate, *459*.

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



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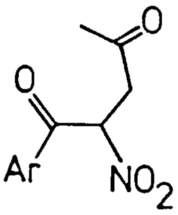

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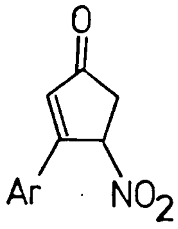
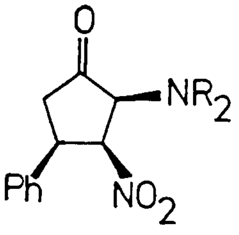


462

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



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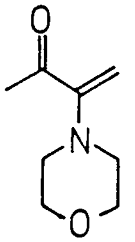

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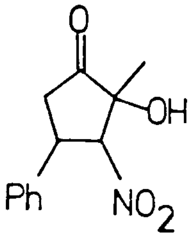

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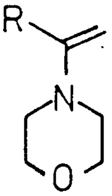
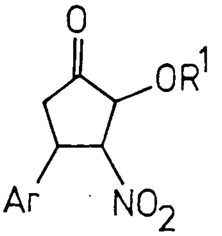


466 *a* R=CHO

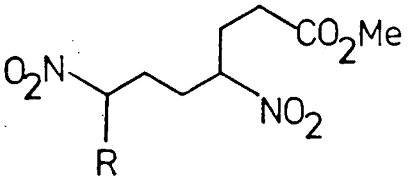
b R=CH(OMe)$_2$



467 *a* R^1=H

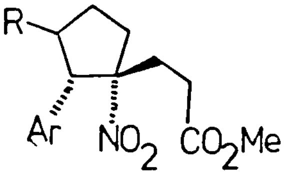
b R^1=Me

A partly convergent strategy can be devised, in which dinitro-ester *468* (prepared by monoalkylation of 1,4-dinitrobutane) condenses with a β-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* [443-445].



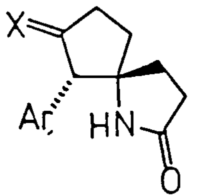
468 R=H

469 R= =CHAr



470 *a* R= ''''''NO$_2$

b R= ▬NO$_2$



471 X= ∼∼∼ NH$_2$

472 X= = O

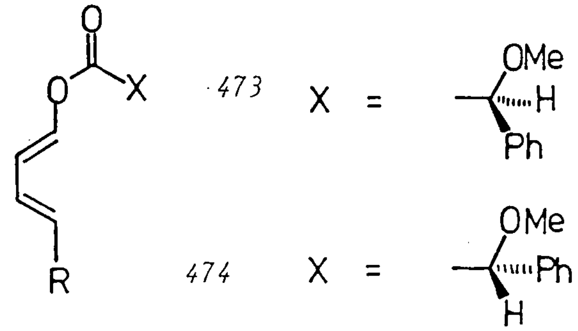
iii <u>Asymmetric construction of E?</u>

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[193], generally utilizing chiral auxiliaries attached to the dieneophile, or, less commonly, the diene[446]. With nitrostyrenes - which contain two prochiral olefin carbons - asymmetric cycloaddition to a diene, requires Π-face-selective addition to the diene, exo or endo specificity, and regiocontrol.

Nitroalkenes are known to be highly regioselective dieneophiles[440, 191,192,447], and we might expect endo positioning of the aromatic group. Π-Face-selectivity could be provided by an appropriate chiral diene substituent, preferentially 'shielding' one face of the diene. Trost et al[448] 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 Π-stacking effects and steric interactions.

Taking into account the regiospecifity 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.

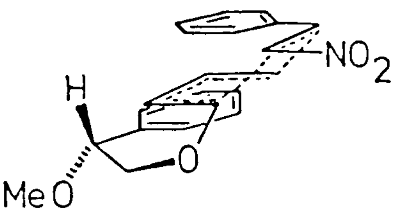


473 X =

474 X =

a R=H

b R= alkyl



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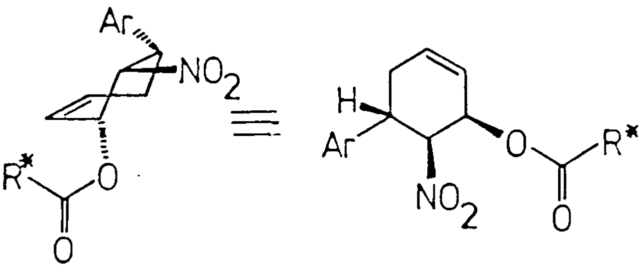

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APPENDIX II

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 (Univeristy 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 (Braunschweigh, 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 (Univeristy 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 Oranometallics 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 Alberto, 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 (Unviersity 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^3	1399.1
Space group	P21/n
Z	4
Dc/gcm-^{3}	1.364
Linear abs. coeff./cm-^{1}	20.108
F(000)	608

Data Collection

CAD4 diffractometer , Cu radiation , λ = 1.5418Å, ω-2θ scan mode

Scan width (0.8+0.15tanθ)° , Scan speed 1.3-6.77°min-1

θ min, θ max/deg	3, 65
Total Data	2671
Total Unique	2384
Total Observed ($I \geq 3\sigma I$)	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 $C_{16}H_{17}NO_2S$ (*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 $C_{16}H_{17}NO_2S$ *(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 (*359a*)

Crystallographic Studies

Crystal data: $C_{19}H_{23}N_1O_4$. M = 329.40, monoclinic, space group $P2_1/c$ (No. 14), a = 13.176(2), b = 7.094(1), c = 17.646(2) Å, β = 101.55(1)°, U = 1615.9(4) $Å^3$, z = 4, Dc = 1.354 g cm^{-3}, F(000) = 704, λ = 0.71069 Å, μ(Mo-K_α) = 0.9 cm^{-1}, crystal size (.73 x .32 x .45 mm).

Data collection: Unit cell parameters and intensity data were obtained by following previously detailed procedures[a], using a CAD4 diffractometer operating in the ω-2θ scan mode, with graphite monochromated Mo-K_α radiation. A total of 2834 unique reflections were collected ($3 \leqslant 2\theta \leqslant 50°$). The segment of reciprocal space scanned was: (h) 0 → 15, (k) 0 → 8, (l) -21 → 21.

Structure solution and refinement: The structure was solved by the application of routine direct methods (SHELX-86[b]), and refined by full-matrix least-squares (SHELX-76[c]). 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 $\Sigma w(|F_o| - |F_c|)^2$ 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.

[a] M.B. Hursthouse, R.A. Jones, K.M.A. Malik and G. Wilkinson, J.Am.Chem.Soc., 1979, 101, 4128.

[b] G.M. Sheldrick, SHELX-86 Program for Crystal Structure Solution, University of Gottingen, 1986.

[c] G.M. Sheldrick, SHELX76 Program for Crystal Structure Determination and refinement, University of Cambridge, 1976.

TABLE III.C

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

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) 359l

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) 359l

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)	2.687	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(17)-N(1)	1.945
HO(2)-N(1)	2.546	H(21)-C(1)	2.045
H(22)-C(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)	2.069	H(32)-C(2)	2.068
C(4)-C(2)	2.427	C(5)-C(2)	3.196
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)	2.576	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)	2.466	C(9)-H(31)	2.973
C(4)-H(32)	2.092	C(8)-H(32)	2.826
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
C(10)-C(4)	2.594
C(16)-C(4)	3.159
H(6)-C(5)	2.129
C(8)-C(5)	2.974
C(10)-C(5)	2.985
H(52)-H(51)	1.568
H(6)-H(51)	2.360
H(6)-H(52)	2.511
C(9)-H(52)	2.740
H(7)-C(6)	1.972
H(82)-C(6)	3.008
C(10)-C(6)	3.339
C(7)-H(6)	1.974
H(81)-C(7)	2.030
C(9)-C(7)	2.509
C(11)-C(7)	3.150
C(8)-H(7)	2.133
H(82)-H(7)	2.512
C(10)-C(8)	2.550
H(11)-C(8)	2.474
C(9)-H(81)	2.058
C(10)-H(81)	2.624
H(11)-H(81)	2.088
H(9)-H(82)	2.313
H(11)-C(9)	2.720
C(16)-C(9)	2.943
C(17)-C(9)	3.198
C(15)-H(9)	2.639
H(162)-H(9)	2.252
C(12)-C(10)	2.439
C(14)-C(10)	2.414
H(162)-C(10)	2.714
C(13)-C(11)	2.403
C(15)-C(11)	2.397
H(182)-C(11)	2.777
C(12)-H(11)	2.032
H(182)-H(11)	2.288
C(14)-C(12)	2.393
C(18)-C(12)	2.383
H(183)-C(12)	2.631
C(15)-C(13)	2.427
H(192)-C(13)	2.479
C(16)-C(14)	2.506
C(19)-C(14)	2.832
H(193)-C(14)	2.807
C(16)-H(14)	2.643
C(19)-H(14)	2.550
H(193)-H(14)	2.260
H(162)-C(15)	2.025
H(17)-C(16)	2.038
C(17)-H(161)	2.036
C(17)-H(162)	2.035
H0(2)-C(17)	1.992
H(182)-H(181)	1.568
H(183)-H(182)	1.568
H(193)-H(191)	1.568
H(9)-C(4)	2.075
C(15)-C(4)	3.211
C(17)-C(4)	2.633
C(7)-C(5)	2.483
C(9)-C(5)	2.500
C(17)-C(5)	3.344
C(6)-H(51)	2.025
C(6)-H(52)	2.025
C(7)-H(52)	2.995
C(10)-H(52)	2.703
C(8)-C(6)	2.496
C(9)-C(6)	2.835
C(11)-C(6)	3.463
H(7)-H(6)	2.239
H(82)-C(7)	2.031
C(10)-C(7)	3.183
H(11)-C(7)	2.556
H(81)-H(7)	2.363
H(9)-C(8)	2.082
C(11)-C(8)	2.868
H(82)-H(81)	1.568
H(9)-H(81)	2.431
C(11)-H(81)	2.598
C(9)-H(82)	2.058
C(11)-C(9)	2.570
C(15)-C(9)	2.536
H(162)-C(9)	2.768
C(10)-H(9)	1.992
C(16)-H(9)	2.725
H(11)-C(10)	2.049
C(13)-C(10)	2.815
C(16)-C(10)	2.527
C(17)-C(10)	3.192
C(14)-C(11)	2.747
C(18)-C(11)	2.817
H(183)-C(11)	2.787
C(18)-H(11)	2.503
H(183)-H(11)	2.353
C(15)-C(12)	2.794
H(182)-C(12)	2.657
H(14)-C(13)	2.027
C(19)-C(13)	2.372
H(193)-C(13)	2.728
H(161)-C(14)	2.511
H(192)-C(14)	2.757
C(15)-H(14)	2.048
H(161)-H(14)	2.288
H(192)-H(14)	2.478
H(161)-C(15)	2.025
C(17)-C(15)	2.541
H(162)-H(161)	1.568
H(17)-H(161)	2.245
H(17)-H(162)	2.377
H0(2)-H(17)	2.286
H(183)-H(181)	1.568
H(192)-H(191)	1.568
H(193)-H(192)	1.568

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