Tetrahedron Vol 47, No 44, pp 9131-9166, 1991
Printed in Great Britain

0040-4020/91 $3 00+ 00
Pergamon Press plc

TETRAHEDRON REPORT NUMBER 301

Medium Ring Nitrogen Heterocycles

P. Andrew Evans and Andrew B. Holmes*

University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U K

(*Received* 17 *June* 1991)

Contents

1. Introduction

Monocyclic medium ring nitrogen heterocycles are an extremely important class of compounds, which occur in a range of natural and unnatural products The medium sized rings, in particular the eight- and nine-membered rings, are generally the most difficult to prepare using conventional cyclisation methods [1] Current synthetic methodology for the preparation of this class of compounds still remains very specific, with limited attention having been paid to stereocontrol [2]

The term medium ring, introduced by Prelog and Brown,[3] is usually applied to alicyclic compounds having a ring size in the range 8 to 11 However, 7-membered and 12-membered rings are often included for comparison purposes, particularly when analysing the conformational effects within these systems

Pioneering work by Ruzicka[4] and Ziegler[5] in the twenties and thirties provided the foundations of our present knowledge of macrocyclisation reactions The search for synthetic methods for the preparation of such systems has been a major objective ever since Most of the evidence available regarding the difficulties associated with the formation of medium rings comes from preparative studies [1,3]

The rate of cyclisation is obviously determined by the activation energy for the process This will be controlled by the ground state energy of the acyclic precursor and the energy of the transition state whose conformation can reasonably be expected to resemble that of the cyclic product. The relative ease of cyclisation is therefore also determined by the probability of end-to-end encounters The activation energy will also reflect the strain energy of the ring to be formed It was previously thought that the strain in both small and large rings was determined by the Baeyer angle strain However, since larger rings do not have to be planar, there was no justification for applying this theory to these rings A real understanding of the strain of medium sized rings evolved only after it was realised that three factors were involved [1,6] (1) torsional effects in single bonds (Pitzer strain), (2) deformation of ring bond angles from their preferred angles (Baeyer strain), and (3) transannular strain (non-bonded interactions) which occurs when atoms across the ring are forced into close proximity This strain will be reflected in the enthalpy of activation for the cyclisation

An entropic contribution to the activation energy for cyclisation emerges in the probability with which atoms placed at the chain termini will come within bonding distance There is a negative ΔS contribution from the reduction in rotational freedom of the open chain single bonds when they approach the ring-like transition state The frequency of such steric interactions will decrease rapidly with chain length This effect will thus tend to lower the cyclisation rate, as the number of methylene groups separating the reaction centres increases

The entropic factor promoting intermolecular rather than intramolecular cyclisation in large rings can be counteracted in part by utilising high-dilution conditions This was first described by Ziegler [1] However, medium ring formation is in many instances the most difficult to achieve, even under high dilution conditions, which supports the view that this is mainly a consequence of an enthalpic factor Modifications of the structure of the chain, with the introduction of other structural features such as *gem*-dimethyl groups, heteroatoms, or aromatic rings profoundly affects the ease of these reactions

Medium ring stereocontrol emerges as a realistic possibility in determining the relative stereochemistry of non-adjacent stereocentres in medium rings, and in acyclic target molecules derived from them, largely due to the pioneering work of Still and Galynker [7] Regio- and stereochemical transannular reactions occur occasionally in medium rings, and are often synthetically useful [8]

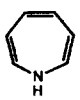
In this Report we detail the occurrence of medium ring nitrogen heterocycles (Section 2) and then summarise the synthetic methods (Section 3) which have been applied to their construction

2. Natural and Unnatural Azepines, Azocines and Azonines

The series of azepines, azocines and azonines which constitute the parent ring systems of the seven-, eight- and nine-membered azacycles[2] respectively are the primary concern of this review The azepines are the largest class in the series which is probably due to their relative ease of formation, and usefulness as both synthetic intermediates and therapeutic agents Owing to the difficulties associated with the preparation of such systems, there is an almost exponential decay in knowledge through the series In particular, information on saturated nine-membered rings is almost non-existent

2 1 *Azepines*

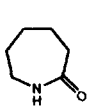
There are four tautomeric forms, designated as 1*H*-, 2*H*-, 3*H*- and 4*H*-azepine, which may be drawn to represent azacycloheptatriene 1*H*-Azepine **(1)** is a very unstable red oil (even at –78 °C in $CDCl_3$ solution) which rearranges in the presence of acid or base to the marginally more stable colourless 3*H*-azepine **(2)** The stability of 1*H*-azepines is enhanced by electron-withdrawing substituents, especially at the 1-position as these decrease the electron density in the 8π antiaromatic ring system Owing to the instabilities of such systems, reduced and partly reduced azepines are more common [2(a)]



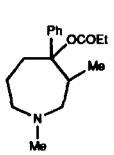
(1)

(2)

Caprolactam **(3)** is without doubt the most useful and important azepine derivative This seven-membered lactam has been used extensively as a precursor in the manufacture of nylon 6 [9] Interestingly, simple *C*-substituted caprolactams are known to possess significant CNS activity,[10] and hexahydroazepin-4-ol derivatives have useful analgesic properties For example proheptazine **(4)** has twice the analgesic effect of morphine and is only marginally addictive [11] Similarly, *N*-substituted hexahydroazepines have found use as antitussives, mydriatics, antispasmodics and oral hypoglycaemics [2(a)]

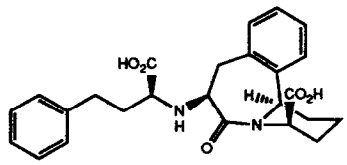


(3)



(4)

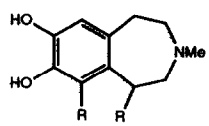
Noteworthy are the inhibitors of angiotension-converting enzyme, which incorporate the azepin-2-one ring Thus the tricyclic product (**5**) is a potent *in vitro* antihypertensive agent.[12]



(**5**)

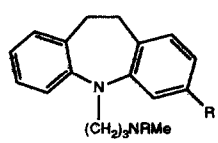
The pharmacological value of benzazepines however, is not as significant as their aza-analogues, the benzdiazepines Anticonvulsant, antiarrhythmic, anti-inflammatory and analgesic activity has been noted for several 1-, 2- and 3-benzazepines [13]

A novel class of dopamine receptor antagonists and neuroleptics is represented by the 7,8-dihydroxy-1,2,3,5-tetrahydro-3*H*-3-benzazepines (**6**). Interestingly, the 1-phenyl derivative (**6b**) is a potent antagonist of both central and peripheral dopamine receptors [14]



(**6**) a R = SPh R = H
b R = H R = Ph

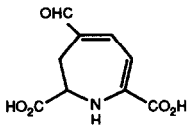
The most useful pharmacological agents based on the azepine nucleus are the 10,11-dibenz[*b,f*]azepines, such as desipramine (**7a**), imipramine (**7b**) and clomipramine (**7c**), which are widely used as antidepressants [15]



(**7**) a R = H R = H
b R = Me R = H
c R = Me R = Cl

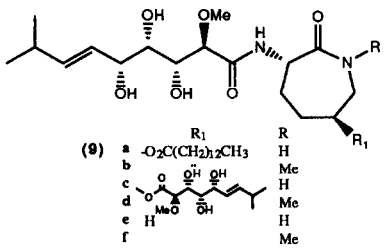
The diversity of azepine-containing natural products which have been isolated has stimulated considerable attention within this area These can be subdivided into two classes, monocyclic and polycyclic azepines Monocyclic azepines made a somewhat late appearance, however they have proved to be an interesting class of compounds.

Muscaflavin (**8**) is a yellow pigment which was isolated from the highly coloured poisonous mushroom *Amantita muscaria* by Musso [16]

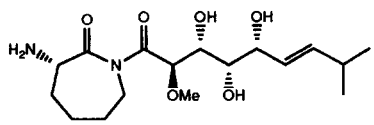


(8)

The bengamides A-E (**9a-f**) and isobengamide E (**10**) (Figure 8) were isolated by Crews[17] from an undescribed Jaspidae sponge which predominates throughout Fiji in the coral reef communities The bengamides are based on the azepin-2-one ring, which is derived from cyclised lysine and δ-hydroxylysine units Bengamides A-D (**9a-d**) are disubstituted *trans*-10-amino-13-hydroxy-azepin-2-ones derivatives The amino and hydroxyl side chains are acylated The *N*-acyl side chain in each case is the 2-methoxy-3,4,5-trihydroxy-8-methyl-non-6(*E*)-enoyl group The azepin-2-one may also be *N*-methylated In the isobengamide (**10**) the *N*-acyl group is on the ring nitrogen to form an unsymmetrical imide

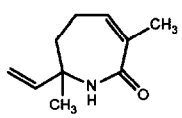


		R
(9) a	$-O_2C(CH_2)_{12}CH_3$	H
b		Me
c		H
d		Me
e		H
f		Me



(10)

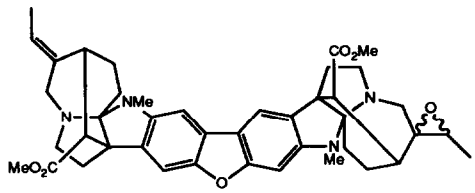
The seven-membered lactam (+)-acacialactam (**11**) was recently isolated by Sekine[18] from the seeds of *Acacia concinna* DC (Leguminosae) These seeds are used as a source of folk medicine for skin diseases in Thailand and the tropical countries The structure was assigned as an azepin-2-one, containing a quaternary carbon bearing vinyl and methyl substituents at the 7-position Another interesting feature is the α,β–unsaturated amide The absolute stereochemistry and biological activity are currently under investigation



(11)

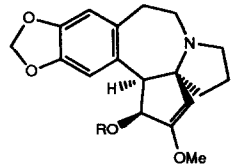
Polycyclic azepines are more abundant than the corresponding monocyclic azepines The following examples therefore constitute only a representation of the array of such molecules which occur within this class

Peceyline (**12**) was isolated by Cavé and Wenkert[19] from the Apocynaceae plant *Petchia ceylanica* Wight, which is indigenous to the lowlands of Sri Lanka They assigned its structure as a dimeric indoline alkaloid containing two seven-membered azacycles buried in complex polycyclic structures which are fused to a dibenzofuran system The structure of peceyline (**12**) was proposed to be as depicted or the isomer with the epoxide and double bond interchanged The related natural products peceylamine and pelankine were also isolated and assigned



(12)

The alkaloid cephalotaxine (**13a**) was isolated by Paudler[20] from *Cephalotaxus fortunei* and *drupacea*, and the structure was assigned by Powell [21] *C drupacea*, a small tree which is found predominantly in China and Japan, is commonly known as cow's tail pine or Japanese plum-yew *C fortunei* is known as the Chinese plum-yew and is found in northern China Cephalotaxine (**13a**) possesses a unique structure, having two spiro-fused five membered rings, both of which are annelated to a benzazepine system While the parent compound cephalotaxine (**13a**), is biologically inactive, a range of naturally occuring ester derivatives such as harringtonine (**13b**) and related semi-synthetic derivatives, were found to exhibit promising antitumour activity

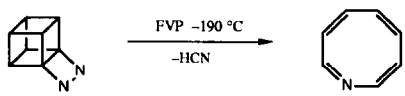


(13) a R = H

b R = C(OH)-C(=O)OCH2CO2Me-(CH2)2C(OH)Me2

2 2 *Azocines*

The azocines are a diverse class of compounds The many methods utilised to prepare such systems, especially the highly unsaturated azocines, are specific and often consist of a single example Only a limited systematic or comparative study of azocines as a class has been conducted However, the relative stability of the eight-membered rings and their bicyclic valence tautomers, and the potential aromaticity of the 10π-electron systems has been assessed The fully unsaturated azocines are π-equivalent heterocyclic analogues of cyclooctatetraene Addition of two electrons to this system or the removal of a proton from (a CH_2 position of) a dihydroazocine leads to dianion or monoanion formation respectively, each of which is an aromatic 10π-electron system [2(b)]

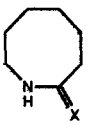


(14) (15)

The parent azocine (**15**) was isolated at −190 °C from the flash vacuum pyrolysis (FVP) of the 'diazabasketene' (**14**), it is unstable and decomposes to a coloured tarry material at −50 °C, and must be

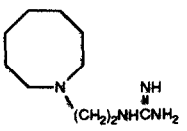
handled in KOH-coated glassware [22] Therefore, the more commonly encountered azocines are substituted, and fully or partly reduced Even so, the azocines have not been as extensively studied as the corresponding azepines, probably owing to the difficulties associated with their preparation They have also found considerable utility as synthetic intermediates and therapeutic agents.

The azocin-2-one (**16a**) may be polymerised to nylon 7 Pyrolysis of this material in the presence of KOH *in vacuo* at 300-350 °C slowly regenerates the monomeric lactam [2(b)] The azocin-2-one (**16a**) and its derivatives have also been employed in the synthesis of homopolymers,[23] copolymers,[24] and as polymerisation catalysts [25]

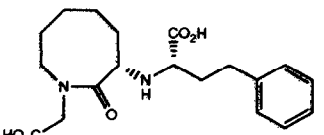


(16) a X = O
b X = S

Interestingly, the azocin-2-one (**16a**) and its thiolactam derivative (**16b**) possess significant CNS activity [26,27] Simple *N*-substituted octahydroazocines such as [2-(octahydro-1-azocinyl)ethyl]guanidine (**17**) and its salts, especially the sulphate,[28] exibit anti-hypertensive activity. Other anti-hypertensive agents are those based on the azocin-2-one ring system (**18**) [29] The *N*-substituted octahydroazocines also have significant utility as antimalarials,[30] antitussives,[31] nasal decongestants,[32] calcium channel antagonists[33] and analgesics [34]

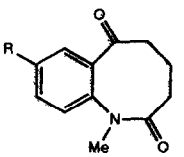


(17)



(18)

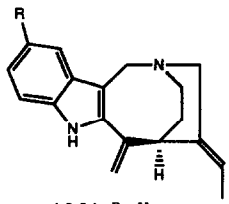
The current pharmacological knowledge of the benazocinones is still very much in its infancy However, the 1-benzazocindione (**19**) has been utilised as a sedative and anticonvulsant.[35]



(19) R = H Cl

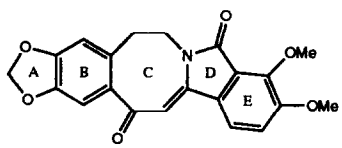
There are only a limited number of natural products which incorporate the azocine ring Most of these are complex polycyclic molecules

The alkaloids 10-hydroxy- (**20b**) and 10-methoxyapparacine (**20c**) were isolated from the leaves of *Ochrosia oppositifolia*.[36] The structure consists of a bridged azocine fused to an indole The molecule also contains two exocyclic double bonds, with the ethylidene group at the 20-position having the (*E*)-configuration Assignment of the double bond configuration in the parent apparacine (**20a**) followed from these studies



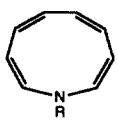
(20) a R = H
b R = OH
c R = OMe

The alkaloid magallanesine (**21**), the first naturally occurring isoindolobenzazocine, was isolated from *Berberis darwinii* Hook in southern Chile, and had its structure assigned by Shamma [37] However, it has recently been suggested that magallanesine (**21**) may have been obtained as an artefact of the isolation [38] Magallanesine (**21**) consists of a pentacyclic nucleus with a characteristic benzazocine ring system in which the nitrogen is present as a vinylogous imide The D and E rings consist of a dimethoxyphthalamide unit fused to the benzazocine

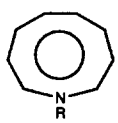


(21)

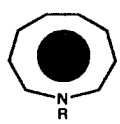
2 3 *Azonines*



(22) a R = CO_2Et
b R = COMe
c R = SO_2Ph



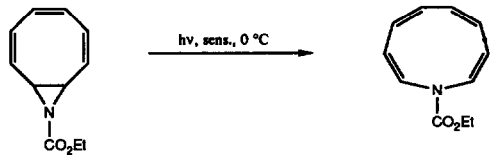
(23) a R = H
b R = Li^+
c R = Na^+



(24) a R = Me
b R = Et
c R = Bz

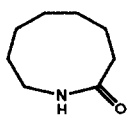
The nine-membered family of π-excessive heterocycles is commonly referred to as the *heteronins* They have been extensively studied with interest centered on their potential toward 10π-aromatic properties A variety of azonines is known and has been classified as antiaromatic (**22**), aromatic (**23**) and non-aromatic (**24**) The parent system (**22a**) may be prepared in a photoinduced electrocyclic opening from its bicyclic valence tautomer (**25**) There are five tautomeric forms, designated as 1*H*-, 2*H*-, 3*H*-, 4*H*- and 5*H*-azonine which may be drawn to represent azocyclononatetraene 1*H*-azonine (**23a**) is known as a very unstable oil Hence, azonines are more abundant in substituted, reduced and partly reduced form [2(c)]

Owing to the difficulties encountered during the preparation of these systems there is considerably less knowledge available compared with the azepines and azocines However, a limited number of azonines have found some utility as synthetic intermediates and therapeutic agents

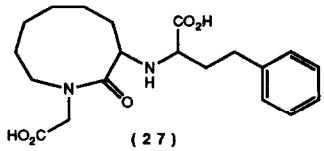


(25) (22a)

The azonin-2-one (**26**) and its derivatives have been employed as homopolymers,[23] copolymers[39] and as polymerisation catalysts[40] The azonin-2-one (**26**) also possesses significant CNS activity[26]



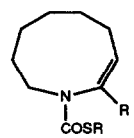
(26)



(27)

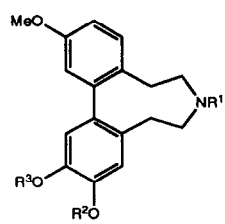
Inhibitors of angiotension-converting enzyme which incorporate the azonin-2-one ring (**27**) and possess significant antihypertensive activity are also notable[29] The *N*-substituted octahydroazonines also have significant utility as antimalarials[30] and analgesics[34]

The azonines have found considerable utility in the area of agrochemicals in the form of herbicides The carbothiolates (**28**) have been used as selective herbicides against grasses in cabbage and rice fields[41]



(28) R = H, Cl
R = Me Et, Pr etc

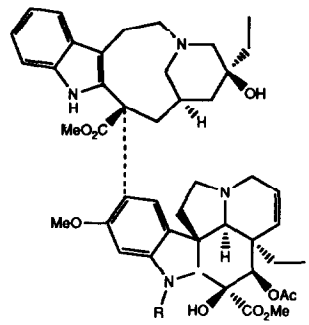
There are only a limited number of natural products which incorporate the azocine ring, most of which are complex polycyclic molecules (see Section 3 4)



(29) a $R^1 = R^2 = R^3 = Me$
b $R^2 = R^3 = Me$, $R^1 = H$
b $R^1 = R^2 = Me$, $R^2 = H$

The alkaloids laurifonine (**29a**), laurifine (**29b**) and laurifinine (**29c**) were isolated in India from the leaves of *Cocculus laurifolia* DC and the structure was assigned by Bhakuni [42] The alkaloids demonstrated hypotensive activity, indeed it was this factor which led to their isolation The natural products consist of a dibenz[*d,f*]azonine base having the same substitution pattern, but differing only in which groups are methylated

The alkaloids vinblastine (**30a**) and vincristine (**30b**) were isolated from *Catharanthus roseus* by Svoboda[43] and the structures were assigned by Neuss [44] They possess significant antitumour activity and have been widely used clinically As with other members of the family, the structures are dimeric

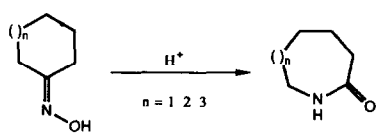


(30) a Me
b CHO

3. A Survey of the Syntheses of Medium Ring Azacycles

3 1 *Introduction and General Methods*

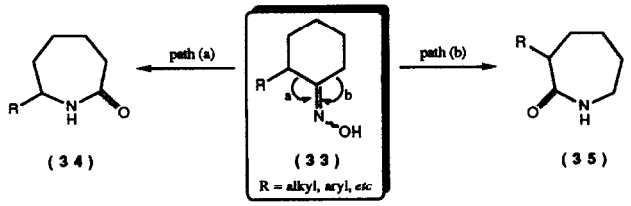
The following review concentrates on some of the methods described for the formation of azepines, azocines and azonines, and emphasises the difficulties encountered A small number of general methods exists for the preparation of such systems, and these are discussed together for brevity



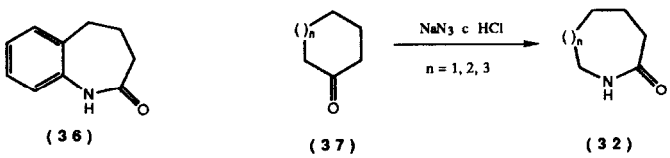
(31) (32)

The Beckmann rearrangement is the acid mediated isomerisation of oximes to amides, and was first reported by Beckmann in 1886,[45] and comprehensively reviewed most recently by Gawley [46] The lactams (**32**) are obtained from the rearrangement of the alicyclic oximes (**31**) This process has been successfully demonstrated for cases where n = 1, 2, 3 and has proven a highly efficient and fairly versatile process Indeed, the transformation through to lactams is unproblematic in simple substrates

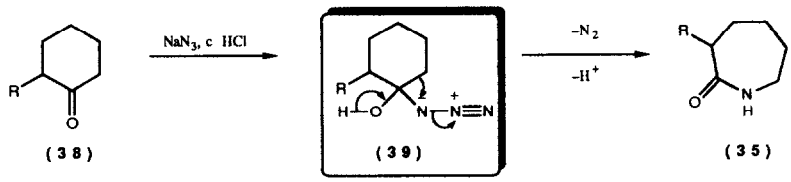
The problem arises in the case of unsymmetrical oximes (**33**), owing to the possibility of two pathways, which often result in a mixture of products Although the *anti*-rearrangement is favoured, with the more substituted carbon migrating [path (a)], both pathways can occur There is some evidence to suggest that bulky substituents (*e g* benzyl) at the α-position exert stereocontrol on the rearrangement [47] This forms the less hindered oxime,



anti to the benzyl group, promoting path (a), and the formation of **(34)** The choice of reagents to facilitate the process is also important, since this affects the selectivity Similarly, 1-benzazepinones **(36)** and their homologues may also be prepared using this reaction Generally, aryl migration is preferred, due to the formation of a delocalised cation as a reactive intermediate [48] However, many cases are known in which substantial alkyl migration also occurs, resulting in a mixture of benzazepinones



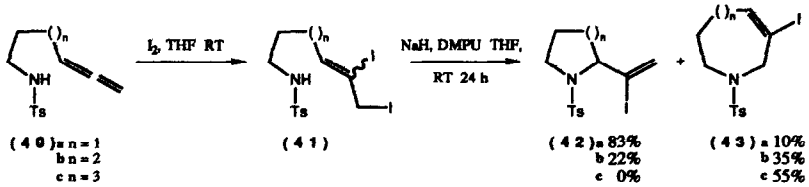
The Schmidt reaction[49] of alicyclic ketones **(37)** to lactams **(32)** is also noteworthy The process is again highly efficient, but unsymmetrical ketones often give a mixture of products However, α-substituted cyclic ketones **(38)** invariably yield 3-substituted lactams **(35)**, involving migration of the less substituted carbon (see **39**) [50] This process complements the Beckmann rearrangement, which favours the alternative rearrangement products



Although these processes are on the whole fairly efficient and versatile, the limited selectivity and the inherent lack of flexibility in the ring expansion has created the need for a more flexible process

Gallagher and co-workers[51] have recently reported a general approach to this class of compounds which involves a novel intramolecular cyclisation involving displacement of an allylic iodide by an *N*-sulphonyl amine Addition of iodine to the *N*-sulphonyl allenic amines **(40)** afforded the allylic iodides **(41)** in essentially quantitative yield, as a 1 1 mixture of (*E*)- and (*Z*)-isomers Treatment of the sulphonamide **(41)** with sodium hydride in the presence of *N*,*N*′-dimethylpropylene urea (DMPU) resulted in cyclisation to give the 'exo' product **(42)** and/or the 'endo' product **(43)** In the case of **(41a)**, the pyrrolidine **(42a)** was favoured over the azepine **(43a)** However, the azocine **(43b)** was the predominant product in the case of **(41b)**, with no strong preference for the 6- over the 8-membered azacycle The (*E*)-alkene stereochemistry in both the azepine

(43a) and the azocine (43b) was exclusive However, in the remaining example, the azonine (43c) was formed as an equal mixture of (*E*)- and (*Z*)-isomers This methodology provides access in moderate yields to functionalised monocyclic medium ring azacycles incorporating latent functionality



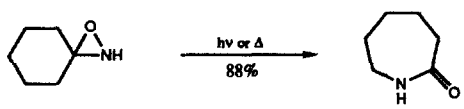
3 2 *The Synthesis of Azepines and Derivatives*

The synthetic methodology that has evolved for the preparation of azepines can be subdivided into two classes, the monocyclic and polycyclic systems The inherent problems associated with the preparation of such systems is clearly illustrated in the following survey

Intramolecular nucleophilic displacements of halogens from ω-halohexyl amines are the most direct route to saturated azepines Hexamethyleneimine was first prepared by this route This method has been to some extent superceded, although it is still used for highly substituted derivatives and for benzazepines.[2(a)]

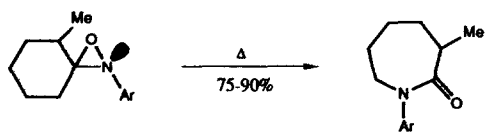
A general route to azepin-2-ones is the intramolecular cyclisation of ε-aminohexanoic acids [52] For caprolactam (3) the yields are low and superior methods are available These methods have very little utility in higher homologues Suprisingly, only limited methodology is known for the preparation of *C*-substituted azepin-2-ones

The thermally or photochemically induced ring expansion of oxaziridines to azepin-2-ones is fairly well documented. Thus flash pyrolysis of the oxaziridine (44)[53]affords caprolactam (3) in 88% yield



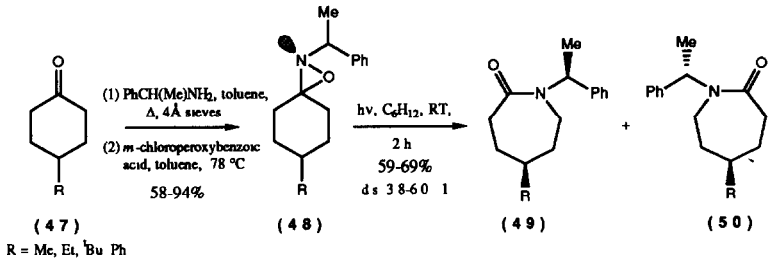
(44) (3)

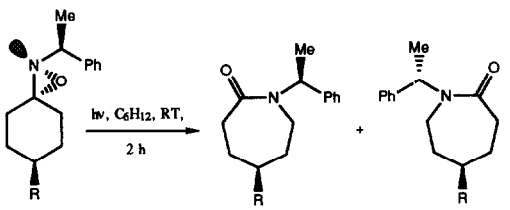
The migration tendency was poorly understood for a long time, and is now thought to be under stereoelectronic control rather than dependent on migratory preferences In both the thermal and photochemical processes it has been demonstrated that the substituent *trans* to the nitrogen lone pair of the bicyclic oxaziridine preferentially undergoes migration to a formally electron deficient nitrogen atom.[54] This is clearly illustrated in the following examples In the 2-aryloxaziridine (45) acid amide formation proceeds under mild conditions Heating the oxaziridine (45) (75 °C, 45 min) is sufficient to convert it to the 3-substituted lactam (46) in 75-90% yields [2(a)] This reaction can be thought of as a supplement to the Beckmann rearrangement in which it is often the more substituted carbon that migrates to form the alternatively substituted lactams



(45) (46)

The photochemical oxazıridine to amide reaction was pioneered by Lattes and coworkers [54,55] This has been supplemented by the work of Aubé[56] on the stereoselective preparation of azepin-2-ones A series of prochiral ketones (**47**) was converted into a series of oxazıridines (**48**) under standard conditions The oxazıridines (**48**) were obtained as a mixture of four possible stereoisomers which were then subjected to the photochemical rearrangement The diastereoisomeric lactams (**49**) and (**50**) were obtained as a mixture which

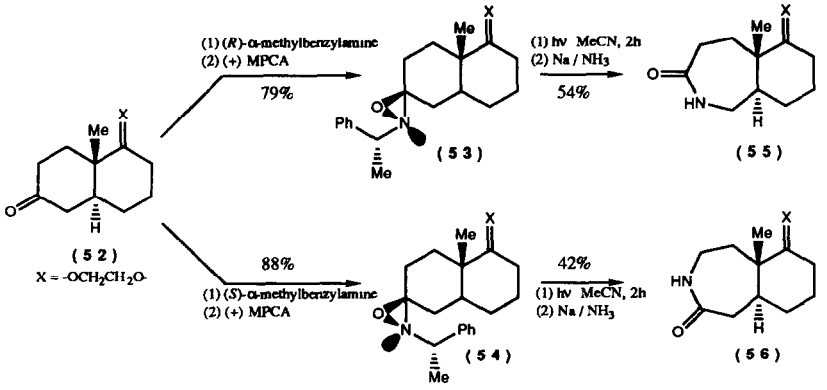




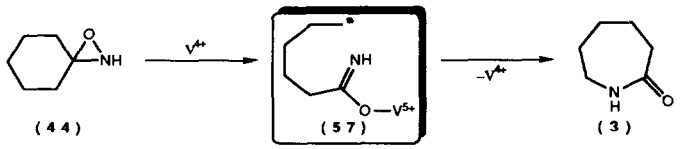
was separable by flash chromatography The ratio of oxazıridines (**48**) was highly dependent on imine sterochemistry For imines derived from cyclohehanone and α–methylbenzylamine, there is a clear preference for equatorial delivery of oxygen to an imine with approach *anti* to the phenyl substituent in a conformation having the benzylic hydrogen in the "inside" position The oxazıridine relative stereochemistry dictates the formation of a particular diastereoisomeric lactam The intrinsic selectivity of the rearrangement was determined by the photolysis of the major oxazıridine stereoisomer (**51**) The corresponding lactams (**49**) and (**50**) were obtained in a ratio of 93 7 (R = ^{t}butyl) and 94 6 (R = phenyl) This represents a 13 1 preference for the migration of the methylene group *anti* to the lone pair on nitrogen, in accord with the stereoelectronic theory proposed by Lattes

A more recent addition to this work[57] has realised direct regiochemical control in the ring expansion Oxidation of the imine derived from the enantiomerically pure ketone (**52**) and (*R*)-α-methylbenzylamine with monoperoxycamphoric acid [(+)-MPCA] affords the oxazıridine (**53**) as a single isomer The diastereomeric imine derived from ketone (**52**) and (*S*)-α-methylbenzylamine gave the oxazıridine (**54**) also as a single isomer Photolysis of the oxazıridine (**53**) was reported to give the lactam (**55**), while rearrangement of (**54**) was reported to give mainly (**56**) (5 3 1) However, these results are contrary to the stereoelectronic theory of the ring expansion (it is the bond *anti* to the nitrogen lone pair which migrates), and the transformations ought to be interchanged, the oxazıridine (**53**) should lead to lactam (**56**), and (**54**) to (**55**) The virtues of such a protocol are three-fold It effects remote regiochemical control, it is possible to obtain either regioisomer by a simple change in reagent stereochemistry, and it simultaneously allows optically active lactams to be obtained

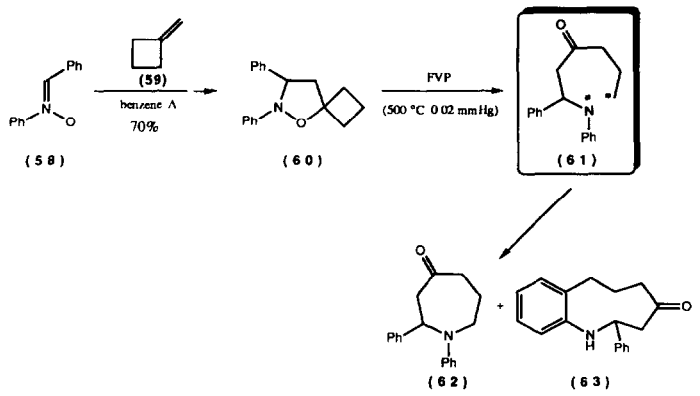
from racemic ketones The methodology is clearly useful, even though it has not been applied to higher homologues



The reaction of a catalytic amount of vanadium(IV) with the oxygen of the oxaziridine (**44**) leads to a related N-O cleavage The radical species (**57**) then recombines, with elimination of the metal ion in a ring expansion reaction, to afford caprolactam (**3**) in almost quantitative yield [58]

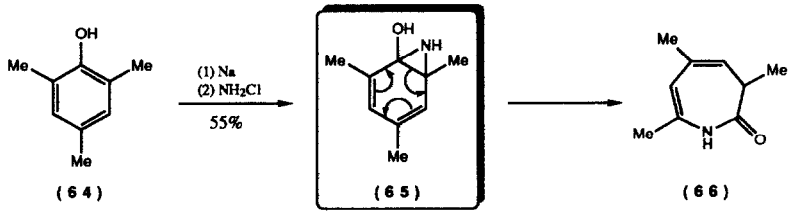


The thermal rearrangement of an isoxazolidine derivative (**60**) to the azepin-4-one (**62**) in moderate yield was recently described by Goti and Brandi [59] The isoxazolidine (**60**) was prepared as the sole regioisomer from the cycloaddition reaction of the nitrone (**58**) with methylenecyclobutane (**59**) The cycloadduct (**60**) was then subjected to FVP conditions to facilitate N-O bond cleavage and generate the diradical (**61**)



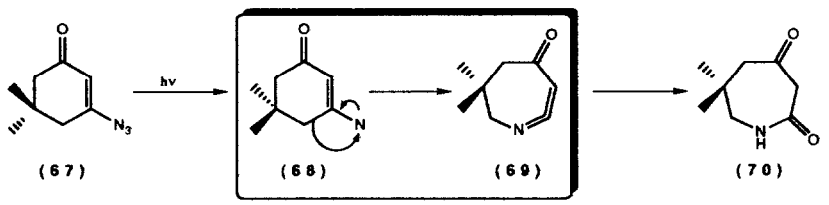
Recombination of (**61**) furnishes the azepin-4-one (**62**) in moderate yield and the 1-benzazonin-4-one (**63**) through radical recombination at the *ortho* position of the *N*-phenyl ring The former process is relatively facile, although its major limitation is its specific nature

Paquette[60] ring expanded a benzenoid species to an azepin-2-one (**66**) in 55% yield The azirıdine reactive intermediate (**65**) undergoes rearrangement to afford the lactam (**66**) The substrates used are symmetrical and aromatic, which is a limitation on the development of such a process



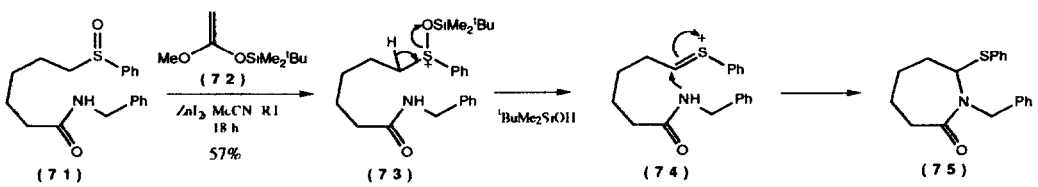
(**64**) (**65**) (**66**)

The photoinduced ring expansion of the azidocyclohexenone (**67**) *via* the nitrene (**68**) and its insertion product (**69**) to the azepindione (**70**) was described by Sato [61] The reaction was found to proceed more efficiently when it was carried out in wet benzene rather than aqueous THF [62] The nature of the solvated intermediate in the thermolysis and photolysis of aryl azides is however an unresolved issue This method has also been successfully applied to the preparation of benzazepines from naphthyl azides, and pyridoazepines from quinolyl and isoquinolyl azides [63,64]



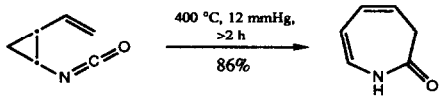
(**67**) (**68**) (**69**) (**70**)

Kita and co-workers[65] have reported the use of a novel sila-Pummerer rearrangement of ω-amidosulphoxides (**71**) to generate the reactive intermediate (**74**) which cyclised to the α-phenylthioamide (**75**) in moderate yield This is a particularly good reaction, owing to its mild nature, since it overcomes the problems associated with the more conventional method The role of the ketene acetal (**72**) is that of a mild silylating agent to produce the sila-Pummerer intermediate (**73**)



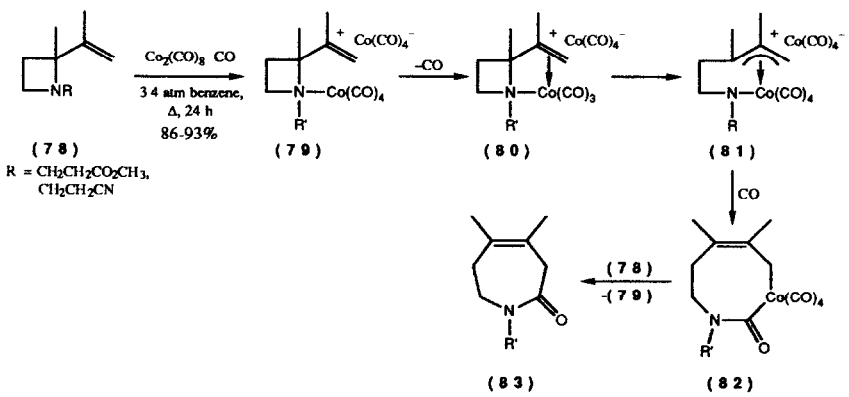
(**71**) (**73**) (**74**) (**75**)

The Cope rearrangement of cyclopropane derivatives (**76**) bearing *cis*-substituted vinyl and isocyanate groups has also been used to good effect in preparing azepin-2-ones (**77**) [66] More highly substituted cyclopropanes may be used with comparable yields [66(d)] Owing to the amount of unsaturation present in the products and the difficulties associated with the isocyanates this reaction has not been exploited any further

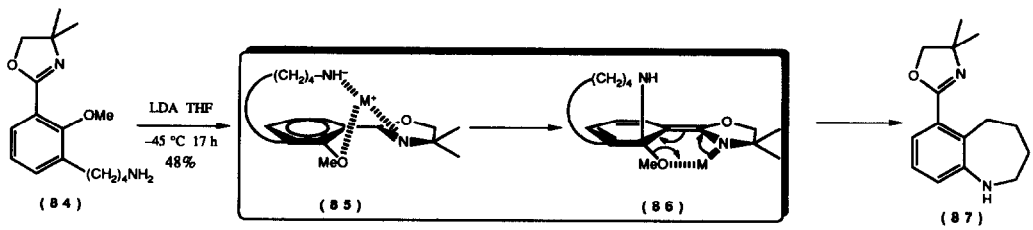


(**76**) (**77**)

Alper[67] has developed the cobalt-mediated carbonylation of 2-vinylazetidines (**78**) to afford ring-expanded seven-membered lactams Treatment of the 2-vinylazetidine (**78**) with $Co_2(CO)_8$ in benzene under pressure resulted in the formation of an ionic dicobalt complex (**79**), which was followed by the loss of carbon monoxide and π-complexation of the vinyl group to form the adduct (**80**) Ring opening forms a π-allyl complex (**81**) which then cyclises to with migratory insertion of CO to form the metallocycle (**82**) Reductive elimination affords (**83**) This is a relatively new method, which promises substantial synthetic utility

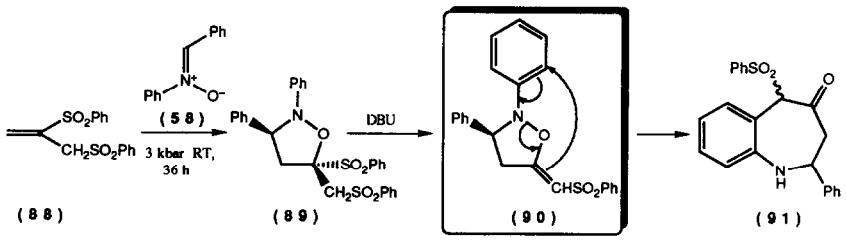


The preparation of benzazepines is generally more straightforward, owing to the rigid effect of the aryl ring on the mode of cyclisation One such method capitalises on the reactivity of an *ortho*-metallated oxazoline to promote displacement of a methoxy group by an ω–aminoalkyl side chain [68] Treatment of the amine (**84**) with LDA at –45 °C afforded the benzazepine (**87**) in 48% yield The reaction was proposed as being a nucleophilic displacement of the *o*-methoxy group on the aryloxazoline (**84**) *via* an addition-elimination process The side

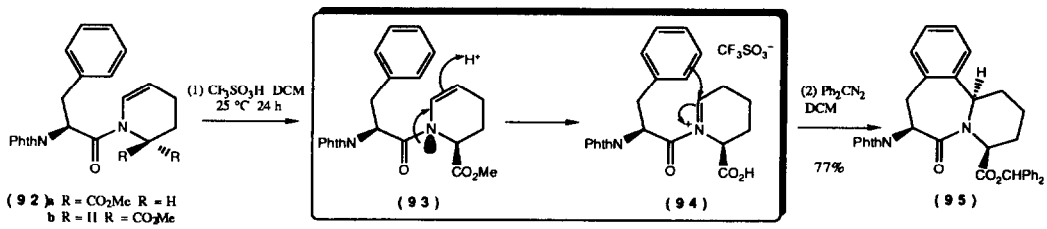


chain must therefore be long enough to approach the aryl ring from an angle close to tetrahedral This enables the metal ion to coordinate both to the methoxy group and to the two nitrogen atoms **(85)**

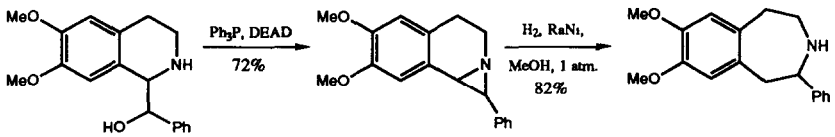
The cycloaddition-cyclisation reaction, developed by Padwa[69] to prepare the benzazepin-4-one **(91)**, is an elegant approach to this class of compounds The dipolarophile **(88)** was treated with the *N*-phenyl-*C*-phenylnitrone **(58)** to afford the cycloadduct **(89)** in 92% yield as a single stereoisomer The high pressure technique was particularly rewarding, owing to the commonly encountered reversibility of such cycloaddition reactions at high temperatures [70] The high pressure also reverses the selectivity in the cycloaddition reaction The cycloadduct **(89)** was treated with DBU to afford a 1 2 mixture of *cis* and *trans*-1,2,3,5-tetrahydro-2-phenyl-5-phenylsulphonyl-4*H*-1-benzazepin-4-one **(91)** presumably *via* a hetero-Cope rearrangement of the 5-methylene isoxazolidine **(90)** [71]



Intramolecular *N*-acyl iminium ion cyclisations can be employed to form seven-membered rings Thus Flynn[12] cyclised the enamide **(92a)** at room temperature using triflic acid This was followed by re-esterification of the acidic product with Ph_2CN_2 to furnish the required optically pure benzhydryl ester **(95)**, a tricyclic dipeptide mimic The stereoselectivity of the cyclisation may result from a preference for a pseudoequatorial orientation of the phthalamide moiety **(94)** in the transition state Interestingly, the diastereomeric enamide **(92b)** was resistant to the cyclisation under similar conditions

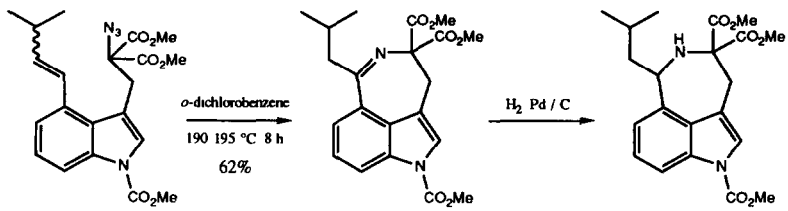


Employing an aziridine in a ring expansion reaction is not a new concept, it was described earlier in this section Pfister[72] recently demonstrated the utility of this reaction in the preparation of an antihypertensive agent (**98**) Treatment of the amino alcohol (**96**) under Mitsunobu conditions[73] with concomitant inversion of stereochemistry at C_2 afforded the aziridine (**97**) Selective hydrogenolysis of the more activated C_1-N bond with Raney nickel gave the 3-benzazepine (**98**) Enantiomerically pure 3-benzazepines may also be prepared



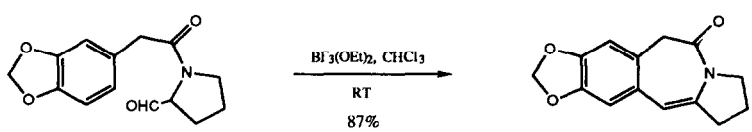
(**96**) (**97**) (**98**)

The intramolecular azide cycloaddition of (**99**) to generate the seven-memberd cyclic imine (**100**) formed the basis of Kozikowski's total synthesis of clavicipitic acid [74] Dipolar additions of azides to olefins are well precedented, and the intermediate triazolines generated in the initial [3+2] reaction have been shown to lose nitrogen with the formation of aziridines and/or imines [75] The imine (**100**) was catalytically hydrogenated to afford the amine (**101**) The fact that none of the aziridine was produced was attributed both to the strain associated with generating such a three-membered ring fused to a fairly constrained seven-membered ring and to a hydrogen migration made favourable by benzylic stabilisation [76] The regiochemistry of the [3+2] cycloaddition reaction was explained by the geometric and steric constraints imposed on the reaction as a consequence of its intramolecular nature [77]



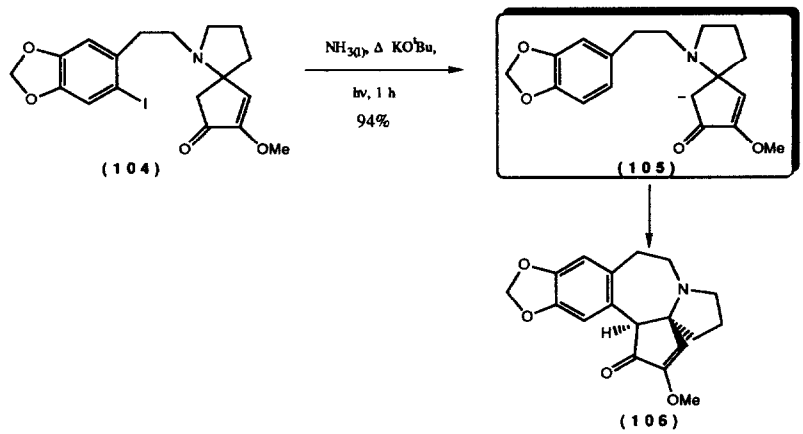
(**99**) (**100**) (**101**)

Cephalotaxine (**13a**) has stimulated considerable attention, owing to its unique structure and the biological activity associated with its esters Weinreb[78] closed the seven-membered ring of the precursor (**102**) by an elegant Lewis acid-catalysed electrophilic aromatic substitution reaction to give the crystalline tetracyclic enamide (**103**) The intermediate carbinol was not observed, neither was any of the *ortho* cyclised product

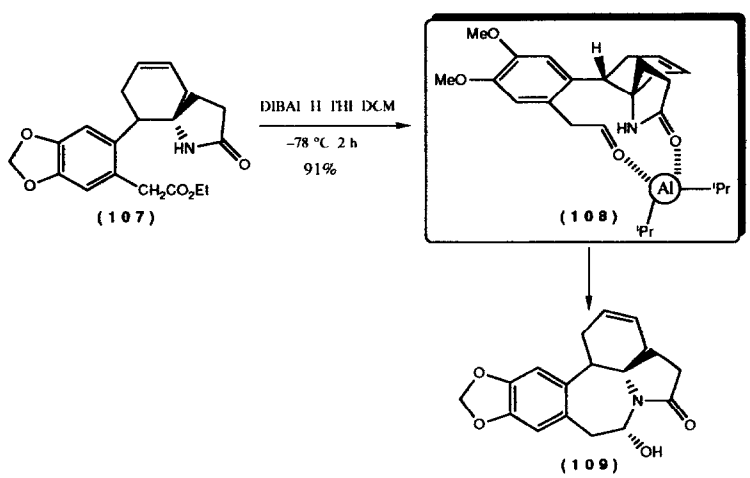


(**102**) (**103**)

Semmelhack[79] effected the same bond closure with a key $S_{RN}1$ reaction The aryl ketone (**104**) was suspended in liquid ammonia at reflux and potassium *tert*-butoxide (7 mol equiv) was added There was no apparent change but, upon external irradiation the solution turned faintly yellow Irradiation was continued for 1 hour to afford cephalotaxinone (**106**) in 94% yield. It was determined that the large excess of base was required in order to maintain the high equilibrium concentration of the anion (**105**), since decreasing the amount of base led to a reduction in cyclisation product

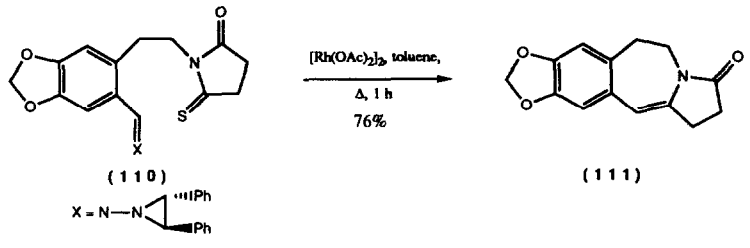


The intramolecular cyclisation of the amide aldehyde (**108**) was the method of seven-membered ring construction in Bryce's synthetic[80]approach to cephalotaxine (**13a**) This was based on a similar strategy used by Kishi[81] to prepare the key polycyclic azocine in the total synthesis of (±)-austamide Treatment of the lactam ester (**107**) with DIBAL (2 2 mol equiv) at –78 °C furnished the *N,O*-hemiacetal (**109**) in excellent yield The



stereoselectivity observed in the cyclisation was attributed to the involvement of the aluminium complex (**108**) (either monodentate or bidentate) Such a complex would activate the aldehyde oxygen to nucleophilic attack by the lactam nitrogen and control the stereochemistry

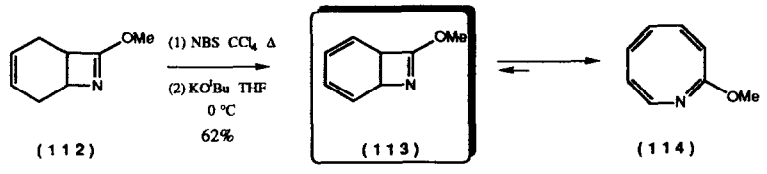
Danishefsky and co-workers[82] developed an elegant approach to various benzazepine substructures by the sulphide contraction method Treatment of the hydrazone (**110**) with rhodium(II) acetate dimer in refluxing toluene gave the key tetracyclic intermediate (**111**) in good yield. The cyclisation is likely to have occurred by insertion of a carbenoid into the thio-amide to yield a thiocarbonyl ylide species, which would extrude sulphur with formation of the double bond This is a particularly elegant approach, and has been used for the synthesis of other benzazepine natural products [83,84]



(110) (111)

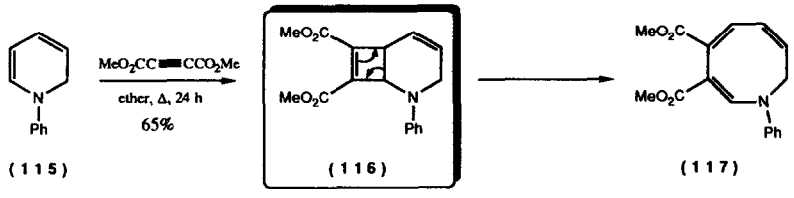
3 3 *The Synthesis of Azocines and Derivatives*

The most thoroughly investigated azocines are the 2-methoxyderivatives (**114**) which were first prepared and studied by Paquette [85] These molecules were prepared by thermally induced ring-opening of the corresponding bicyclic valence tautomers (*e g* **113**) which can be prepared by a bromination/dehydrobromination sequence This method proved to be a reasonably good and versatile route to 2-methoxyazocines (**114**)



(112) (113) (114)

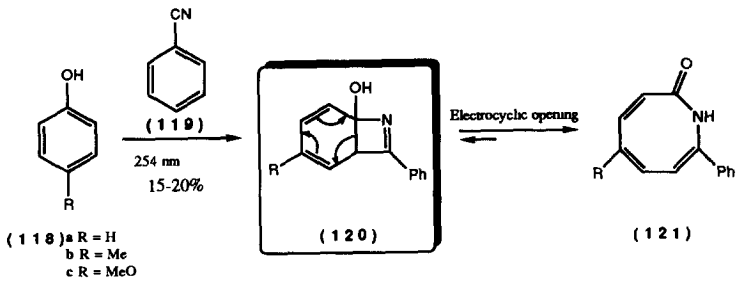
A related electrocyclic ring-opening strategy was reported by Acheson [86] The [2+2] cycloaddition of dimethyl acetylenedicarboxylate to 1-phenyl-1,2-dihydropyridine (**115**) gave 1,2-dihydroazocine (**117**) *via*



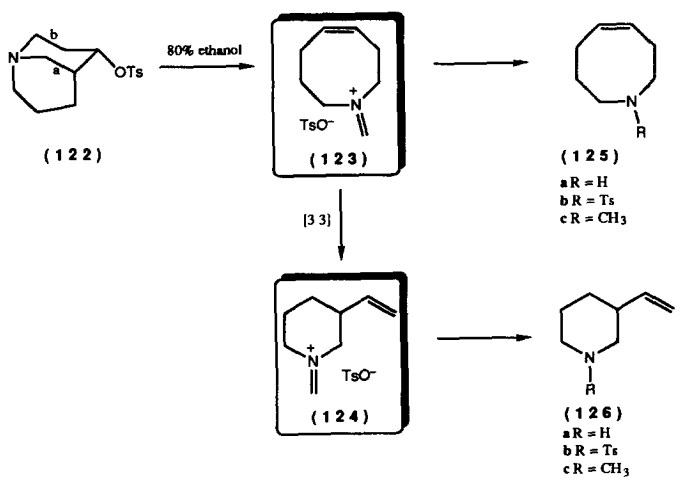
(115) (116) (117)

intermediacy of the cyclobutapyridine (**116**),[87] which was observed by n m r [86] The reaction is able to tolerate functionality at the 1, 3 and 4 positions on the 1,2-dihydropyridine (**115**), making it a fairly general and efficient process

The photocycloaddition of phenol derivatives (**118**) to benzonitrile (**119**) to afford substituted azocin-2-ones (**121**) was shown by Al-Jalal[88] to produce (**120**) as the major photoproduct Electrocyclic ring-opening and ketonisation of the enol gave the fully unsaturated lactam (**121**) Although the yields are poor, the method is direct

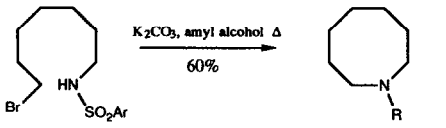


The hexahydroazocine (**125**) was formed by Grob[89] using his classsical fragmentation reaction An ethanolic solution of 1-azabicyclo[3 3 1]nonyl-4-endo tosylate (**122**) fragments to produce a quantitative yield of formaldehyde and amines (**125a**) and (**126a**) The amines (**125a**) and (**126a**) were isolated as their *N*-tosyl derivatives (**125b**) and (**126b**) in the ratio 12 88, which infers the preferential cleavage of bond b However, when the intermediate immonium salts (**123**) and (**124**) were reduced *in situ* with sodium borohydride, the amines (**125c**) and (**126c**) are formed in the ratio 94 6 The explanation given was unclear, and an alternative is given below The immonium ion (**123**) is the kinetic product which in the absence of



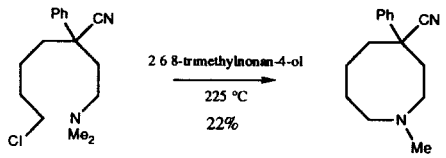
sodium borohydride, can undergo sigmatropic rearrangement to the thermodynamically more stable immonium ion (**124**) This then hydrolyses to the amine (**126a**) In the presence of sodium borohydride however, the immonium ion (**123**) is reduced before rearrangement can occur, enabling azocine (**125c**) formation A similar fragmentation has been utilised for the preparation of azepines

Cyclisation reactions have been used to prepare heptamethyleneimine (**128b**) and its derivatives Thus, treatment of the 7-bromoheptylsulphonamide (**127**) in amyl alcohol, under high dilution conditions with potassium carbonate, afforded azocine (**128a**), this can then be hydrolysed to the free base (**128b**) [90]



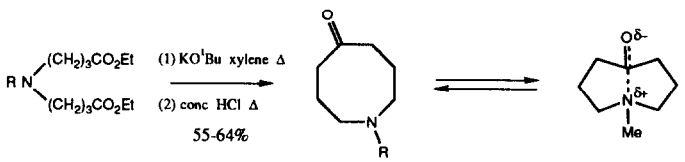
(**127**) (**128**)a R = SO_2Ar b R = H

Other cyclisations of open-chain precursors include the work of Tyson[91] on the cyclisation and dechloromethylation of the acyclic ω–chloro-amine (**129**) When a solution of the this compound (**129**) was heated in 2,6,8-trimethylnonan-4-ol at 225 °C, 1-methyl-4-phenyl-4-cyanoazacyclooctane (**130**) was produced in modest yield In fact, this is half the yield obtained in the preparation of the corresponding seven-membered nitrile by a similar process This serves to demonstrates the difficulties encountered in cyclisation reactions leading to eight-membered rings



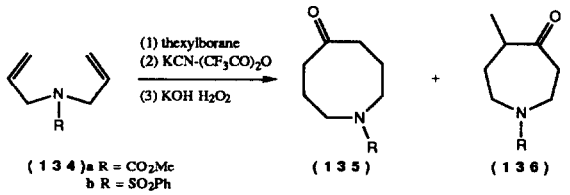
(**129**) (**130**)

The Dieckmann cyclisation was pioneered by Leonard[92] as a route to medium ring heterocycles Treatment of the diester (**131**) with potassium *tert*-butoxide under high dilution conditions, followed by hydrolysis and decarboxylation afforded the amino ketones (**132**) in moderate yields The *N*-methyl compound has an unusually low carbonyl stretching frequency, which can be ascribed to a transannular interaction between the carbonyl group and the nitrogen lone pair as depicted in (**133**)

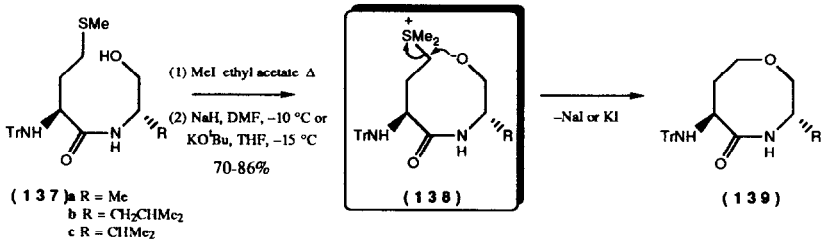


(**131**) (**132**)a R = Me b R = *p* Tol c R = Bn (**133**)

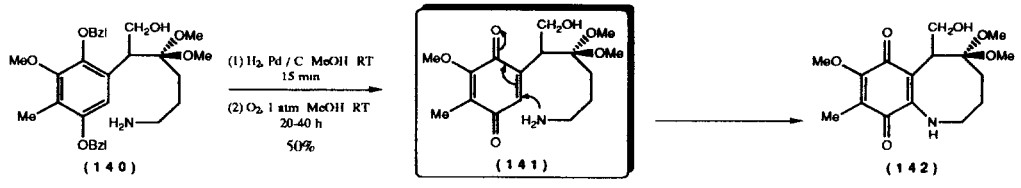
Garst[93] developed a tandem hydroboration and carbonylation of the *N,N*-bis allyl amine derivatives **(134)** to form the eight-membered amino ketones **(135)** This method complements the Dieckmann cyclisation for the preparation of similar substrates, but suffers from the disadvantage that the intramolecular hydroboration kinetically favours formation of the six-membered cyclic borane which necessarily leads to more of the seven-membered product **(136)** than **(135)**



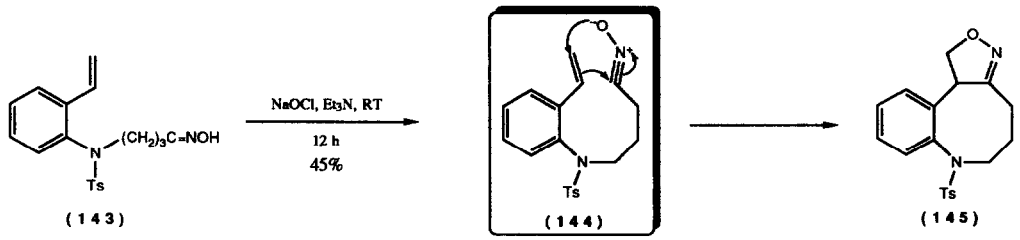
The preparation of peptide surrogates has become an important area of interest, and lactams are particularly attractive as they can contain a guaranteed amide conformation Barlos and co-workers[94] prepared an eight-membered ether lactam **(139)** by intramolecular alkoxide displacement of a sulphonium salt **(138)** Treatment with sodium hydride in dimethylformamide at −10 °C or potassium *tert*-butoxide in THF at −15 °C gave the 1,4-oxazocin-5-one **(139)** in excellent yield The surprising feature of this process is the relative ease of cyclisation, and it is likely that the amide behaves as a conformational restraint to facilitate the cyclisation



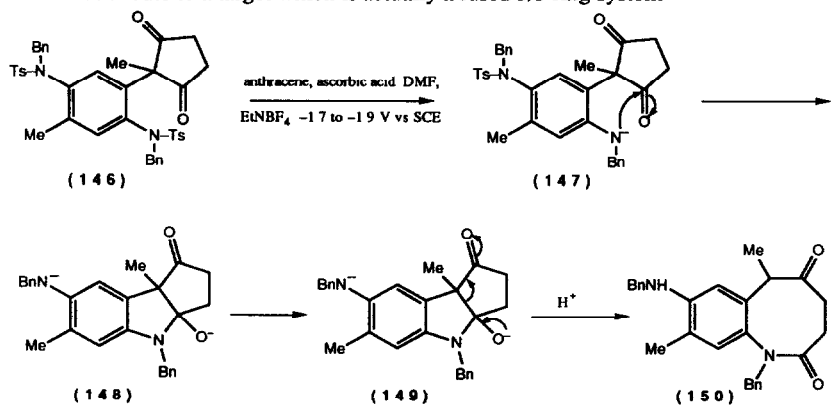
The mitomycins are an important class of quinonoid compounds, which exhibit potent antibiotic and antitumour activity Many of the approaches to the pyrrolo[1,2-*a*]indole ring system have involved a transannular cyclisation of an eight-membered ring Kishi[95] was the first to devise such an approach Hydrogenolysis of the masked hydroquinone **(140)**, followed by treatment with oxygen under pressure, gave the eight-membered quinone **(142)** in good yield The cyclisation clearly involves the formation of the benzoquinone **(141)**, followed by intramolecular 'Michael-type' cyclisation onto the quinone moiety The Michael reaction was rather efficient for eight-membered ring formation in this special case This approach formed the basis of the first total synthesis of the mitomycins [94(b)]



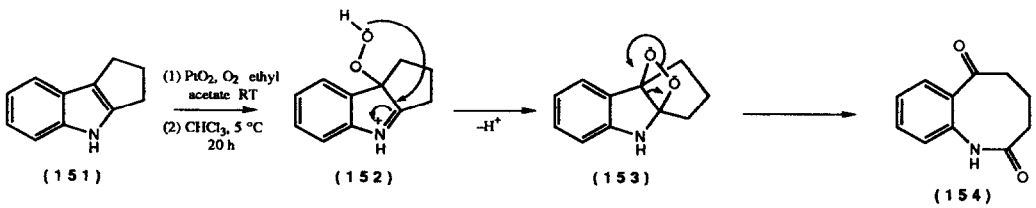
In a similar eight-membered precursor approach to the mitomycins Kozikowski[96] demonstrated the utility of an intramolecular nitrile oxide cycloaddition to prepare the key 1-benzazocine system **(145)** Oxidation of the (*E*)/(*Z*)-mixture of oximes **(143)** generated the nitrile oxide **(144)** *in situ* This underwent cycloaddition to afford the isoxazoline **(145)** in moderate yield



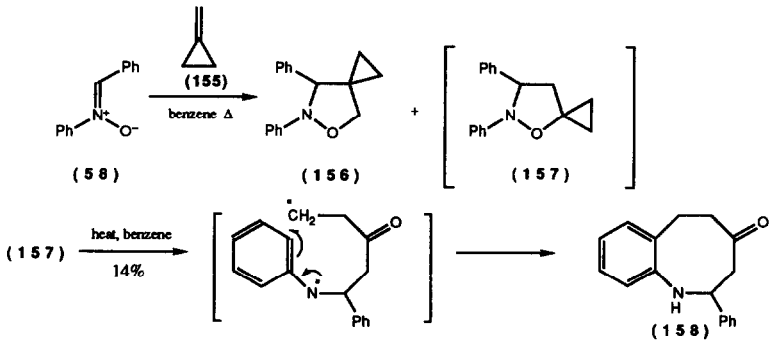
Ban[97] also adopted the 'medium ring strategy' to the mitomycins Electrochemical detosylation of an *N*-tosyl group gave the 1-benzazocine **(150)** A criss-cross annulation pathway was proposed in which ring closure of the anion **(147)** gave the tricycle **(148)** followed by fragmentation **(149)** to the medium ring This seems a rather circuitous route to a target which is actually a fused 5/5 ring system



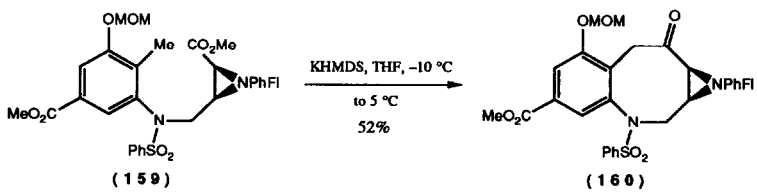
The benzazocinone **(154)** was prepared by Witkop[98] utilising a novel fragmentation of the dioxetan **(153)** derived from hydroperoxide **(152)**, the product of oxygenation of the indole **(151)** The conversions are highly efficient processes, making them ideal for the synthesis of such systems



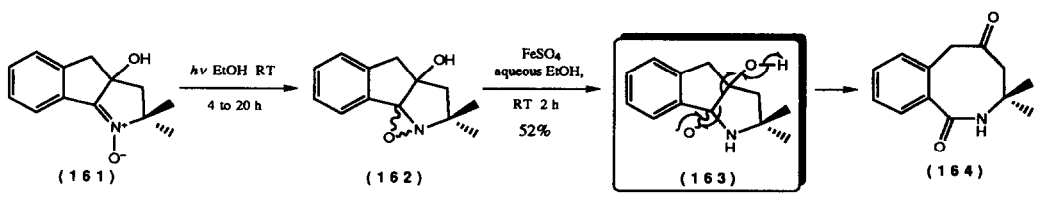
Goti's azepinone (62) synthesis by thermolysis of isoxazolidinones derived from methylenecyclobutane has already been mentioned A side reaction involves radical recombination through the *ortho* position of the *N*-phenyl substituent This minor pathway can also produce eight-membered rings from the major adduct (157) (which is not isolable) derived from the cycloaddition of the nitrone (58) to methylenecyclopropane (155) [59] Owing to the very modest yields this route is mainly of academic interest



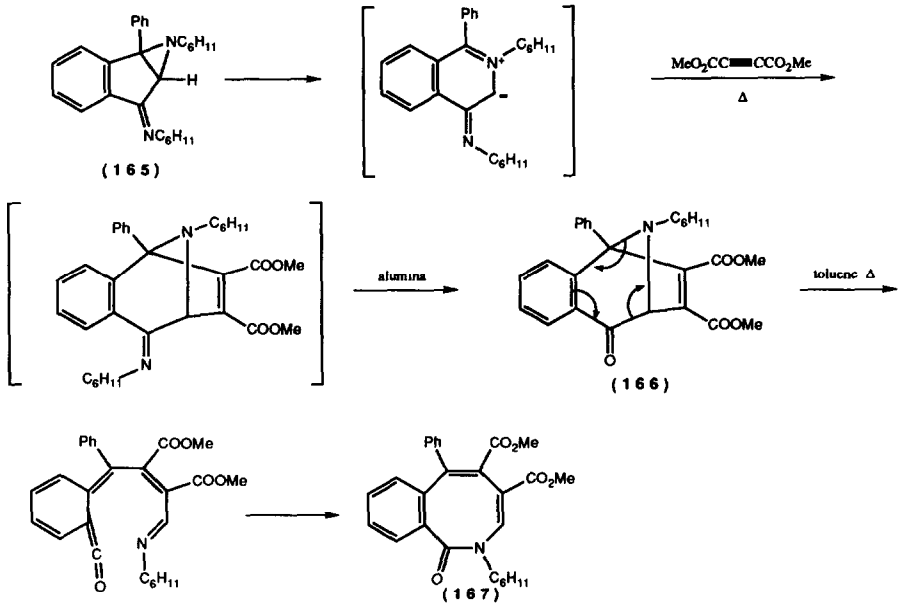
In an approach to the core nucleus of the antineoplastic agents FR900482 and FK973, Rapoport[99] employed the 1-benzazocin-5-one (160) as the precursor This was prepared by an intramolecular acylation of a tolyl group by an ester tethered through nitrogen Intramolecular condensations to form eight-membered rings are generally inefficient processes However, the severe conformational constraints imposed by the fused benzene and aziridine rings serve to facilitate this particular example



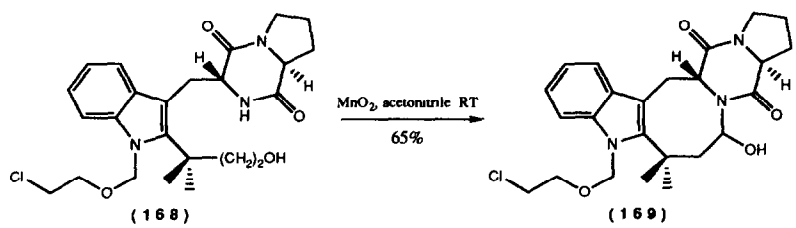
The three atom ring expansion of a tricyclic oxaziridine (161) to afford the 2-benzazocinone (164), was accomplished by Black [100] Photorearrangement of the nitrone (161) gave a mixture of *cis*- and *trans*-oxaziridines (162) These underwent an iron(II) sulphate-induced fragmentation *via* the alkoxy radical (163) The reaction does not proceed to completion unless a stoichiometric amount of iron(II) sulphate is present



A complex series of rearrangements of the aziridine-imine (**165**) was used by Padwa[101] to prepare the 2-benzazocine (**167**) Presumably ring-opening of (**165**) gave an azomethine ylide which underwent 1,3-dipolar cycloaddition to form an imine which hydrolysed on alumina to the ketone (**166**). Thermal cycloreversion of this intermediate would generate a ketene which could reclose *via* an eight-electron electrocyclic pathway to give (**167**) At present the pathway is of mechanistic interest only as its preparative value cannot be assessed

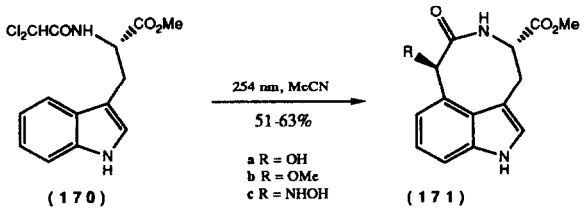


In the course of the total synthesis of (±)-austamide Kishi[81] prepared the key polycyclic azocine (**169**) *via* an intramolecular cyclisation of an amido-aldehyde generated by oxidation of the alcohol (**168**) with excess manganese dioxide in acetonitrile The ease of the cyclisation was certainly enhanced by the number of conformational constraints in the substrate (**168**) This particular approach has been widely used for a variety of polycyclic natural products

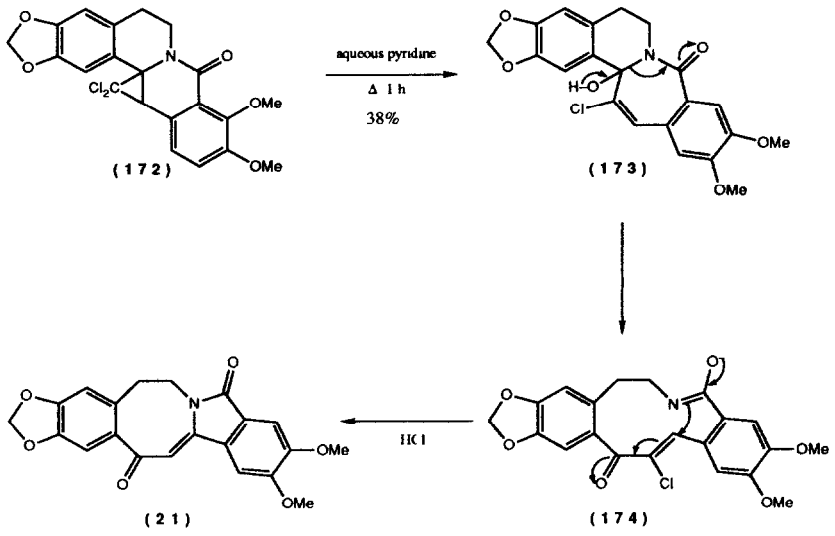


Moody[102] applied a novel intramolecular photocyclisation of a haloacetyl tryptophan derivative (**170**) to give the 7-substituted pyrrolobenzazocinone (**171**) in the total synthesis of (–)-indolactam V The displacement of the initially formed 7-chloro-derivative occurring under the reaction conditions When the photolysis reaction

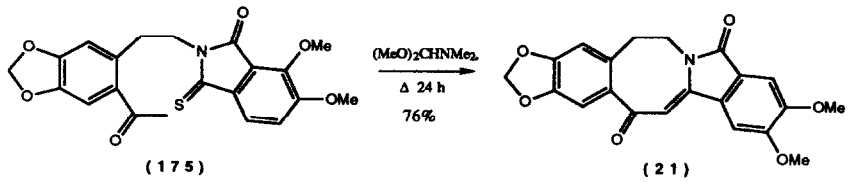
was worked up in the presence of other nucleophiles such as methanol and hydroxylamine, the corresponding derivatives (**171b**) and (**171c**) were formed in good yield The results obtained for the monochloro derivative were inferior Also no competing cyclisation to the indole 2-position was observed The reaction exhibits a remarkable degree of stereoselectivity at the 7-position, since the incoming nucleophile is exclusively *trans* to the ester group



Several years before Shamma had isolated magallanesine (**21**) from natural sources,[37] he had obtained it as a rearrangement product of the dichlorocarbene adduct of oxyberberine [103] Thus treatment of the dichlorocarbene adduct (**172**) in aqueous pyridine gave the natural product (**21**) Presumably cyclopropyl ring opening of (**172**) led to the allyl alcohol (**173**) which fragmented the central bond to afford an eleven-membered ring (**174**) This in turn reclosed in a Michael sense, followed by elimination of chloride, to furnish the keto-lactam (**21**)

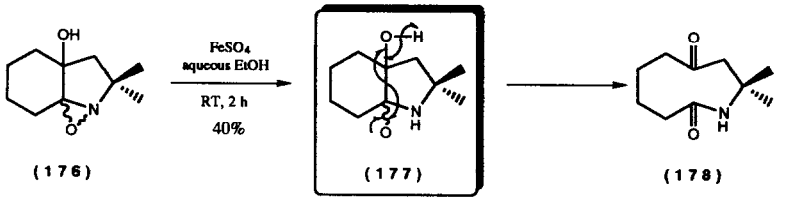


Danishefsky[83] also synthesised magnallanesine (**21**) using an intramolecular aldol condensation of the chemoselectively activated thio-phthalimide

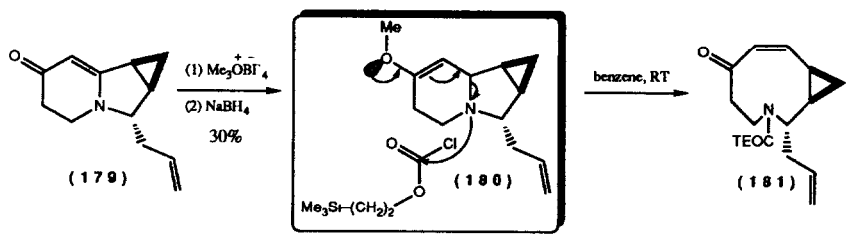


3 4 *The Synthesis of Azonines and Derivatives*

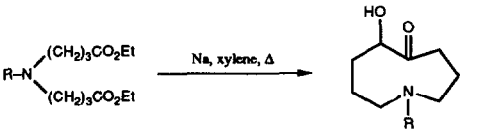
The novel three atom ring expansion of cyclic oxaziridines **(162)** developed by Black (Section 3 3) can also be applied to the preparation of azoninones **(178)** [100] Treatment of the *cis-* and *trans-* mixture of oxaziridines **(176)** with a stoichiometric amount of iron(II) sulphate gave the azonindione **(178)** in moderate yield This demonstrates the difficulties encountered in the preparation of these systems.



During the total synthesis of (±)-indolizomycin, Danishefsky[104] prepared the key azoninone nucleus **(181)** by a novel fragmentation sequence Treatment of the dihydropyridone **(179)** with trimethyloxonium fluoroborate afforded the iminium salt, which was reduced directly with sodium borohydride to give the enol ether amine **(180)** Acylation with 2-(trimethylsilyl)ethyl chloroformate in benzene at room temperature activated the nitrogen to leave in a fragmentation reaction to yield the azoninone **(181)** in 30% overall yield The poor yield for the transformation again illustrates the intrinsic difficulties associated with the preparation of these systems

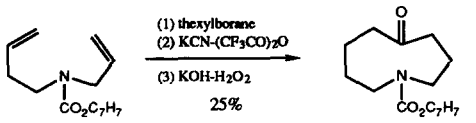


Leonard and coworkers[91b,c] have demonstrated the synthetic utility of the acyloin condensation of the diesters **(127)** to produce 1-azonin-5-ol-6-ones **(182)** Although a relatively moderate yield was obtained for the transformation, the procedure is direct and simple The extent of transannular interaction between N and C=O for the *N*-tolyl compound **(182b)** was considerably less than for the simple *N*-methyl compound **(182a)** This may be due to steric interference of the aryl group, or by the delocalising ability of the aryl group, or a combination of both these factors



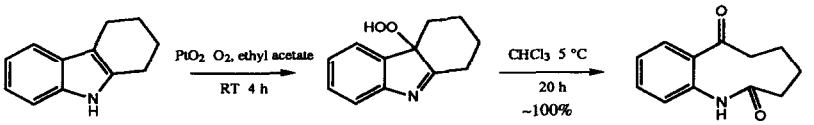
(127) (182) a R = Me b R = *p*-Tolyl

The azonin-5-one (**184**) may be prepared from a *N,N'*-propenyl-butenyl-amide (**183**), by the novel hydroboration-CO insertion process[92] discussed earlier in Section 3 3 Again, the modest yields reflect the difficulty in cyclising such acyclic precursors



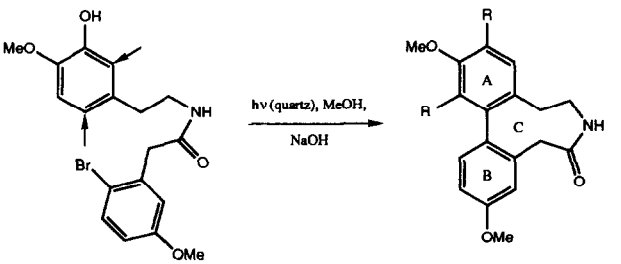
(183) (184)

The Witkop hydroperoxide fragmentation of the indolenine (**186**), prepared by oxygenation of the indole (**185**), is as equally effective in preparing the 1-benzazonine (**187**) as the lower homologue (**154**), and indicates the preparative value of this route to benz-fused medium ring nitrogen heterocycles [105]



(185) (186) (187)

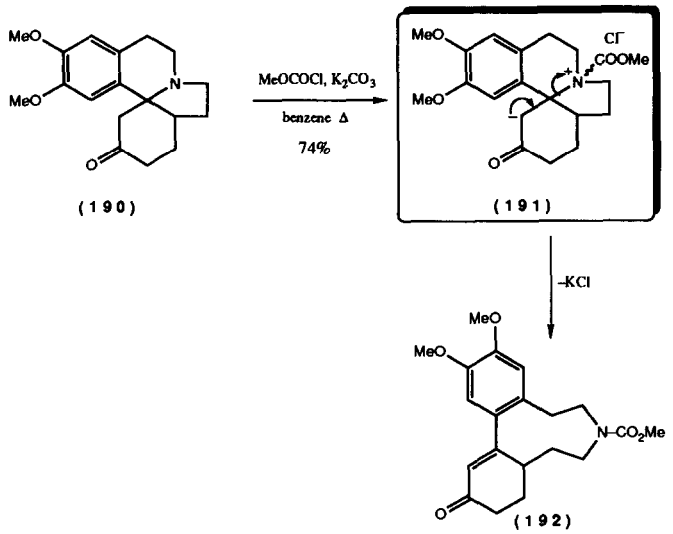
Ito[106] showed that the $S_{RN}1$ ring closure is also an effective route to the alkaloids neodihydrothebaine and bractazonine Substitution takes place at the *ortho*- as well as the *para*-position with respect to the phenolic



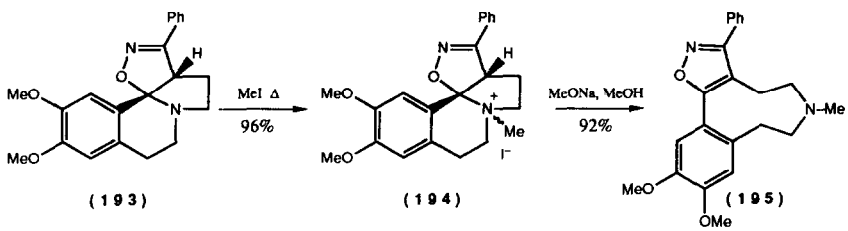
(188) (189) a R = H R = OH b R = OH, R = H

function in ring A Irradiation of the amide **(188)** in sodium hydroxide and methanol gave the dibenz[*d,f*]azonin-1-ol **(189a)** in 19% yield, and the dibenz[*d,f*] azonin-3-ol **(189b)**, in 38% yield This example illustrates the difficulties associated with the formation of unsymmetrical azonines, where there is the possibility of more than one pathway for cyclisation

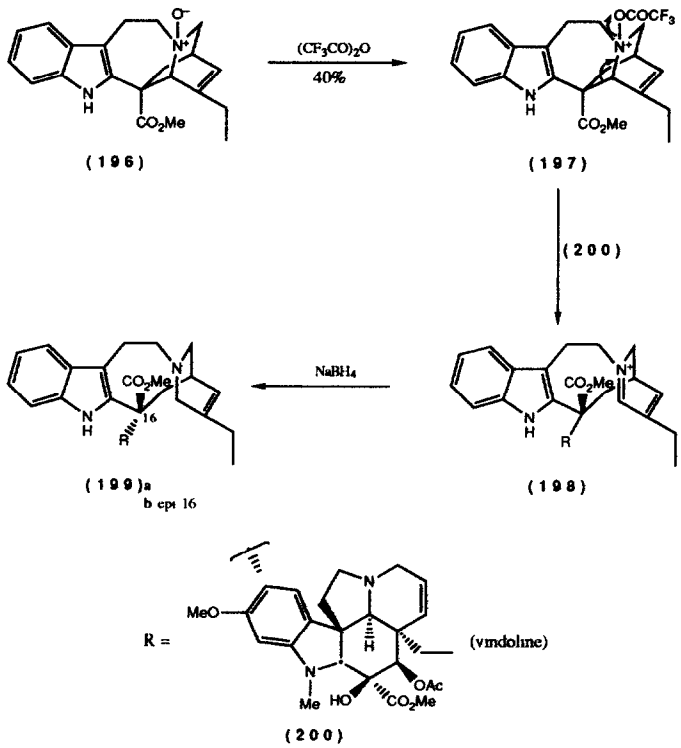
The total synthesis of the alkaloids laurifonine **(29a)** and laurifine **(29b)** was achieved by Bremner[107] using a chloroformate-mediated fragmentation Treatment of the erythrinan-3-one **(190)** with potassium carbonate and methyl chloroformate in refluxing benzene, afforded the dibenzazonine **(192)** in good yield The fragmentation was a model for the Danishefsky procedure already reported



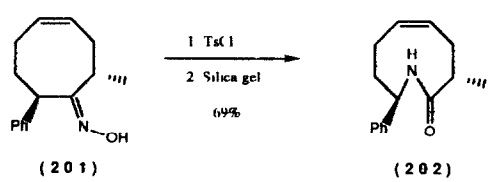
Wentland[108] recently prepared novel macrocyclic isoxazolo[4,5-*g*][3]benzazonine derivatives **(195)** by a quaternisation-elimination sequence This approach is similar to that used by Bremner above Quaternisation of the isoxazoline derivative **(193)** with an excess of methyl iodide gave the quaternary salt **(194)** Base-catalysed elimination is driven by the aromatisation of the heterocycle, and delivers the nine-membered ring **(195)** in excellent yield This is an extremely efficient process, providing latent functionality in the form of an isoxazoline, and thus enabling further manipulation of the system



Potier[109] applied a modified Polonovski reaction[110] in the synthesis of the vinblastine family of alkaloids This allowed the construction of the dimeric indole-indoline skeleton **(199a)** by aromatic electrophilic substitution induced by a fragmentation reaction Treatment of the *N*-oxide of catharanthine **(196)** with trifluroacetic anhydride and vindoline **(200)** *in situ* gave, after reduction with sodium borohydride, the dimeric indole-indoline skeleton **(199a)** in 40% yield The epimeric product **(199b)** was also isolated, with the yields and relative proportions of the two very much dependent on the experimental conditions Although only a moderate yield was obtained for this process, it is clearly an elegant and effective method of constructing this complex and clinically important class of molecules

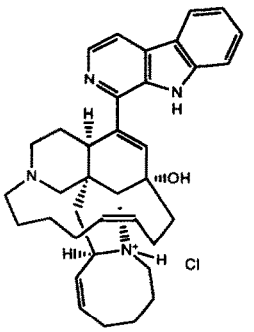


The Beckmann rearrangement has been applied to the synthesis of nine-membered lactams [111] It worked

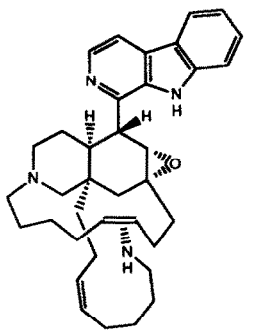


surprisingly well for the expansion of the *anti*-oxime **(201)** to the lactam **(202)** which has been constructed as a dipeptide component of a novel β–turn mimic [112]

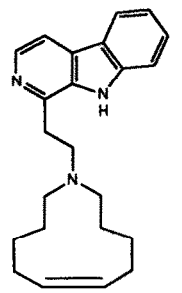
The manzamines are an intriguing family of complex policyclic antibiotic alkaloids isolated from marine sponges Manzamine A **(203)** containing an eight-membered ring was the first compound to be reported [113] This was quickly followed by reports of manzamines B **(204)** and C **(205)** containing eleven-membered rings,[114] and manzamines E and F which are related to manzamine A [115,116] Substantial synthetic effort has been devoted to the "tricyclic heart" of manzamines E and F,[117] but only one group has so far concerned itself with the synthesis of the medium ring portion



(203)

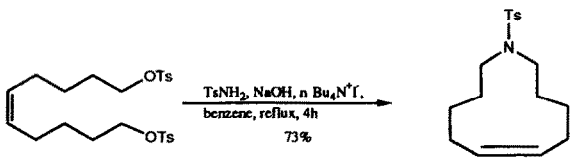


(204)



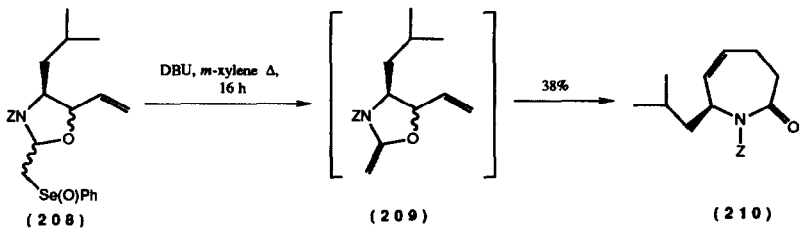
(205)

Manzamine C **(205)** was prepared by Nakagawa and Hino [118] The key ring closure reaction of the *Z*-bis tosylate **(206)** was conducted under phase transfer conditions to produce the eleven-membered ring product **(207)** remarkably efficiently This closure cannot be due to the template effect of the *Z*-double bond as the corresponding *E*-isomer closed with almost equal efficiency



(206) **(207)**

Very recently we have extended the Claisen ring expansion approach to include medium ring nitrogen heterocycles Thus pyrolysis of the selenoxide **(208)** in refluxing xylene generated the ketene aminal **(209)** (not isolated) which underwent Claisen rearrangement *in situ* to produce the seven-membered lactam **(210)** [119] The moderate yields in the seven-membered series arise from the strained transition state involved, but early indications are that this approach can be applied to efficient syntheses of larger sized medium ring lactams [120]



(208) (209) (210)

4. Summary

Although there are many methods for the preparation of azepines, azocines and azonines, as illustrated, they remain specific and often inefficient There are only two reactions which can be considered as being truly general for this class of compounds, the Beckmann and Schmidt rearrangements Therefore, the need for general, versatile and stereoselective methods still remains

5. References

1 Illuminati, G , Mandolini, L *Acc Chem Res* **1981**, *14*, 95
2 (a) Smalley, R K In *Comprehensive Heterocyclic Chemistry*, Katritzky, A R , Rees, C W , Eds , Pergamon Oxford, **1984**, Vol 7, Ch 5, p 491
(b) Moore, J A , Anet, F A L *ibid* Vol 7, Ch 5, p 653
(c) Anastassiou, A G *ibid* Vol 7, Ch 5, p 709
3 Sicher, J *Progr Stereochem* **1962**, *3*, 202
4 Ruzicka, L , Stoll, M , Schinz, H *Helv Chim Acta* **1926**, *9*, 249
5 Ziegler, K , Eberle, H , Ohlinger, H *Liebigs Ann Chem* **1933**, *504*, 94
6 Prelog, V *Pure Appl Chem* **1963**, *6*, 545
7 (a) Still, W C , Galynker, I *Tetrahedron* **1981**, *37*, 202
(b) Still, W C , MacPherson, L J , Harada, T , Callahan, J F , Rheingold, A L *ibid* **1984**, *40*, 2275
8 March, J In *Advanced Organic Chemistry*, Wiley-Interscience New York, **1985**
9 Boyer, J H In *Nitrenes*, Lwowski, W, Ed ,, Interscience New York, **1970**, p 163
10 Duong, T , Prager, R H , Tippett, J M , Ward, A D , Kerr, D I B *Aust J Chem* **1976**, *29*, 2667
11 Diamond, J , Bruce, W F , Tyson, F T *J Med Chem* **1964**, *7*, 57
12 Flynn, G A , Giroux, E L , Dage, R C *J Am Chem Soc* **1987**, *109*, 7914
13 Vejdelek, Z , Svátek, E , Holubek, J , Metys, J , Bartosová, M , Protiva, M *Collect Czech Chem Commun* **1981**, *46*, 148
14 Kaiser, C , Ali, F E , Bondinell, W E , Brenner, M , Holden, K G , Ku, T W Oh, H J , Ross, S T , Yim, N C F , Zirkle, C L , Hahn, R A , Sarau, H M , Setler, P E , Wardell, Jr , J R *J Med Chem* **1980**, *23*, 975
15 Kricka, L J , Ledwith, A *Chem Rev* **1974**, *74*, 101
16 Dopp, H , Musso, H *Chem Ber* **1973**, *106*, 3473
Ardenne, R , von Dopp, H , Musso, H , Steglich, W *Z Naturforsch , C* **1974**, *29*, 637
17 Adamczeski, M , Quiñoà, E , Crews, P *J Am Chem Soc* **1989**, *111*, 647
Synthesis of bengamide E Chida, N , Tobe, T , Ogawa, S *Tetrahedron Lett* , **1991**, *32*, 1063

18 Sekine, T , Arita, J , Saito, K , Ikegami, F , Okonogi, S , Murakoshi, I *Chem Pharm Bull* **1989**, *37*, 3164
19 Kunesch, N , Cavé, A , Hagaman, E W , Wenkert, E *Tetrahedron Lett* **1980**, *21*, 1727
20 Paudler, W W , Kerley, G I , McKay, J *J Org Chem* **1963**, *28*, 2194
21 Powell, R G , Weisleder, D , Smith, Jr , C R., Wolff, I A *Tetrahedron Lett* **1969**, 4081
22 McNeill, D W , Kent, M E , Hedaya, F , D'Angelo, P F , Schissel, P O *J Am Chem Soc* **1971**, *93*, 3817
23 Hall, H K *J Am Chem Soc* **1958**, *80*, 6404
24 Pikler, A , Jambrich, M , Simo, R , Mihaly, F , Kristofic, M , Konc, J , Pitonak, A *Czech CS* 234,969/ 5 Jan 1987 *Chem Abstr* **1987**, *107*, P177975a
25 Zahorovsky, S , Herman, O *Czech* 152,683/15 Apr 1974 *Chem Abstr* **1974**, *81*, P121378k
26 Elison, C , Lien, E J , Zinger, A P , Hussain, M , Tong, G L , Golden, M *J Pharm Sci* **1971**, *60*, 1058
27 Lien, E J , Lien, L L , Tong, G L , *J Med Chem* **1971**, *14*, 846
28 Blicke, F F , Doorenbos, N J *J Am Chem Soc* **1954**, *76*, 2317, Maxwell, R A , Mull, R P , Plummer, A J *Experientia* **1959**, *7*, 267
29 Thorsett, E D , Harris, E E , Aster, S D , Peterson, E R , Snyder, J P , Springer, J P , Hirshfield, J , Tristram, E W , Patchett, A A , Ulm, E H , Vassil, T C *J Med Chem* **1986**, *29*, 251
30 Klayman, D L , Scovill, J P , Bartosevich, J F , Mason, C J , *J Med Chem* **1979**, *22*, 1367
31 Malhotra, S , Koul, S K , Sharma, R L , Anand, K K , Gupta, O P , Dhar, K L *Indian J Chem , Sect B* **1988**, *27B*, 937
32 Wright, G C , Halliday, R P , Davis, C S *J Pharm Sci* **1970**, *59*, 105
33 Palfreyman, M G , Dudley, M W , Cheng, H C , Mir, A K , Yamada, S , Roeske, W R , Obata, T , Yamamura, H I *Biochem Pharmacol* **1989**, *38*, 2459
34 Clark, C R , Halfpenny, P R , Hill, R G , Horwell, D C , Hughes, J , Jarvis, T C , Rees, D C , Schofield, D *J Med Chem* **1988**, *31*, 831
35 Okamoto, T , Kobayashi, T , Yamamoto, H *Japan* 74 45,8746/6 Dec 1974 *Chem Abstr* **1975**, *83*, P9836y
36 Akhter, L , Brown, R T , Moorcroft, D *Tetrahedron Lett* **1978**, 4137
37 Valencia, E , Fajardo, V , Freyer, A J , Shamma, M *Tetrahedron Lett* **1985**, *26*, 993
38 Shamma, M , Rahimizadeh, M *J Nat Prod* **1986**, *47*, 1
39 Werner and Pfleiderer *Neth Appl* 6,408,333/25 Jan 1965 *Chem Abstr* **1965**, *63*, P1953e
40 Kralicek, J , Kubanek, V , Kondelikova, J *Chem Abstr* **1975**, *83*, 193771x
41 Fischer, A , Kiefer, H , Koenig, K H *Ger Offen* 1,917,534/8 Oct 1970 *Chem Abstr* **1970**, *73*, P130909w
42 Uprety, H , Bhakuni, D S *Tetrahedron Lett* **1975**, 1201
43 Neuss, N , Gorman, M , Svoboda, G H , Maciak, G , Beer, C T *J Am Chem Soc* **1959**, *81*, 4754 Svoboda, G H *Lloydia* **1961**, *24*, 173
44 Neuss, N , Gorman, M , Boaz, H E , Cone, N J *J Am Chem Soc* **1962**, *84*, 1509 Neuss, N , Gorman, M , Hargrove, W , Cone, N J , Biemann, K , Buchi, G , Manning, R E *J Am Chem Soc* **1964**, *86*, 1440
45 Beckmann, E *Chem Ber* **1886**, *89*, 988
46 Gawley, R E *Org React* **1987**, *35*, 1
47 Jensen, B L , Woods, M A *J Heterocycl Chem* **1979**, *16*, 1317
48 Kukla, M J *J Heterocycl Chem* **1977**, *14*, 933
49 Schmidt, Z *Angew Chem* **1923**, *36*, 511 Wolff, H *Org React* **1946**, *3*, 307

50 Moore, J A ; Mitchell, E In *Heterocyclic Compounds*, Elderfield, R C , Ed , Wiley· New York, **1967**, Vol 9, p 224
51 Shaw, R , Anderson, M , Gallagher, T *Synlett* **1990**, 584
52 Blade-Font, A *Tetrahedron Lett* **1980**, *21*, 2443
53 Schmidz, E , Striegler, H , Heyne, H U , Hilgetag, K P , Dilcher, H , Rusche, J *J Prakt Chem* **1977**, *319*, 195
54 Oliveros, E , Rivière, M , Lattes, A. *J Heterocycl Chem* **1980**, *17*, 1593
55 Lattes, A., Oliveros, E , Rivière, M , Belzecki, C , Mostowitz, D , Abramskj, W , Piccinni-Leopardi, C , Germain, G , Van Meerssche, M *J Am Chem Soc* **1982**, *104*, 3929
56 Aubé, J , Burgett, P M , Wang, Y *Tetrahedron Lett* **1988**, *29*, 151
Aubé, J , Wang, Y , Hammond, M , Tanol, M , Takusagawa, F , Velde, D V *J Am Chem Soc* **1990**, *112*, 4879
57 Aubé, J , Hammond, M *Tetrahedron Lett* **1990**, *31*, 2963
58 Schmidz, E , Striegler, H , Heyne, H U , Hilgetag, K P , Dilcher, H , Lorenz, R *J Prakt Chem* **1977**, *319*, 274
59 Cordero, F M , Goti, A , De Sarlo, F , Guarna, A , Brandi, A *Tetrahedron* **1989**, *45*, 5917
A radical cyclisation induced by a photo-excited enone has also been used to construct an eight-membered lactam Schell, F M , Cook, P M , Hawkinson, S W , Cassady, R E , Thiessen, W E *J Org Chem* **1979**, *44*, 1380
60 Paquette, L A *J Am Chem Soc* **1962**, *84*, 4987
61 Sato, S *Bull Chem Soc Jpn* **1968**, *41*, 2524
62 Tamura, Y , Yoshimura, Y , Kita, Y *Chem Pharm Bull* **1972**, *20*, 871
63 Hollywood, F , Khan, Z.U , Scriven, E F V , Smalley, R K , Suschitzky, H , Thomas, D R , Hull, R *J Chem Soc , Perkin Trans 1* **1982**, 431
64 Iddon, B , Meth-Cohn, O , Scriven, E F V , Suschitzky, H., Gallagher, P T *Angew Chem , Int Ed Engl* **1979**, *18*, 900
65. Kita, Y , Tamura, O , Miki, T , Tamura, Y *Tetrahedron Lett* **1987**, *28*, 6479
66 (a) Doering, W von E , Goldstein, M J *Tetrahedron* **1959**, *5*, 53
(b) Vogel, E , Erb, R , Lenz, G , Bothner-By, A A *Ann Chem* **1965**, *682*, 1
(c) Brown, I , Edwards, O E , McIntosh, J M , Vocelle, D *Can J Chem* **1969**, *47*, 2751
(d) Sasaki, T , Eguchi, S , Ohno, M *J Am Chem Soc* **1970**, *92*, 3192
67 Roberto, D , Alper, H *J Am Chem Soc* **1989**, *111*, 7539
68 Meyers, A I , Reuman, M , Gabel, R.A *J Org Chem* **1981**, *46*, 783
69 Padwa, A , Kline, D N , Norman, B H *Tetrahedron Lett* **1988**, *29*, 265
70 Dicken, C M , DeShong, P *J Org Chem* **1982**, *47*, 2047
71 Tufariello, J J , Ali, S A , Klingele, H O *J Org Chem* **1979**, *44*, 4213
Blechert, S *Liebigs Ann Chem* **1985**, 673
Zecchi, G , Parpani, P *J Org Chem* **1987**, *52*, 1417
72 Pfister, J R *Heterocycles* **1986**, *24*, 2099
73 Pfister, J R *Synthesis* **1984**, 969
Hall, C R , Williams, N E *J Chem Soc , Perkin Trans 1* **1981**, 2746
74 Kozikowski, A P , Greco, M N *J Org Chem* **1984**, *49*, 2310

75 Logothetis, A L *J Am Chem Soc* **1965**, *87*, 749
Scheiner, P *J Am Chem Soc* **1968**, *90*, 988
Scheiner, P *Tetrahedron* **1968**, *24*, 2757
Padwa, A *Angew Chem , Int Ed Engl* **1976**, *15*, 123
Pearson, W H *Tetrahedron Lett* **1985**, *26*, 3527
Hudlicky, T , Seoane, G , Lovelace, T C. *J Org Chem* **1988**, *53*, 2094
Taber, D F , Deker, P B , Fales, H M , Jones, T H , Lloyd, H.A *J Org Chem* **1988**, *53*, 2968
76 Smith, P A S , Chou, S P *J Org Chem* **1981**, *46*, 3970
77 Huisgen, R *J Org Chem* **1976**, *41*, 403
Houk, K N , Sims, J.; Duke, R E , Strozier, A J , George, J K *J Am Chem Soc* **1973**, *95*, 7287
78 Weinreb, S.M , Auerbach, J *J Am Chem Soc* **1975**, *97*, 2503
79 Semmelhack, M F ; Chong, B P , Stauffer, R D , Rogerson, T D , Chong, A , Jones, L D *J Am Chem Soc* **1975**, *97*, 2507
80 Gardiner, J.M , Bryce, M R , Bates, P A , Hursthouse, M B *J Org Chem* **1990**, *55*, 1261
81 Hutchinson, A J ; Kishi, Y *J Am Chem Soc* **1979**, *101*, 6786
82 Fang, F G , Maier, M E , Danishefsky, S J , Schulte, G. *J Org Chem* **1990**, *55*, 831
83 Fang, F G , Feigelson, G B , Danishefsky, S J *Tetrahedron Lett* **1989**, *30*, 2743
84 Fang, F G , Danishefsky, S J *Tetrahedron Lett* **1989**, *30*, 2747
85 Paquette, L A , Kakihana, T *J Am Chem Soc* **1968**, *90*, 3897
Paquette, L A *Angew Chem , Int Ed Engl* **1971**, *10*, 11
86 Acheson, R M , Paglietti, G ; Tasker, P A *J Chem Soc , Perkin Trans 1* **1974**, 2496
87 Acheson, R M , Wright, N D , Tasker, P A *J Chem Soc , Perkin Trans 1* **1972**, 2918
Lehman, P G. *Tetrahedron Lett* **1972**, 4863
88 Al-Jalal, N *J Chem Res (S)* **1989**, 110
89 Grob, C A , Kunz, W , Marbet, P R *Tetrahedron Lett* **1975**, 2613
90 Muller, A , Srepel, E , Funder-Fritzsche, E , Dicher, F *Monatsh Chem* **1952**, *83*, 386
91 Diamond, J , Bruce, W F , Gochman, C , Tyson, F T *J Org Chem* **1960**, *25*, 65
92 (a) Leonard, N J , Oki, M , Chiavarelli, S *J Am Chem Soc* **1955**, *77*, 6234.
(b) Leonard, N J , Oki, M *ibid* **1955**, *77*, 6241
(c) Leonard, N J , Sato, T *J Org Chem* **1969**, *34*, 1066
93 Garst, M E , Bonfiglio, J N , Marks, J *J Org Chem* **1982**, *47*, 1494
94 Carlos, K , Papaioannou, D , Patrianakou, S , Sanida, C , Tsegenidis, T *J Chem. Soc , Chem Commun* **1987**, 474
95 (a) Nakatsubo, F , Cocuzza, A J , Keeley, D E , Kishi, Y *J Am Chem Soc* **1977**, *99*, 4835
(b)Fukuyama, T , Nakatsubo, F , Cocuzza, A J , Kishi, Y *Tetrahedron Lett* **1977**, 4295
96 Kozikowski, A P , Mugrage, B M *J Chem Soc , Chem Commun* **1988**, 198
97 Oda, K , Ohnuma, T , Ban, Y *J Org Chem* **1984**, *49*, 953
98 Witkop, B , Patrick, J B , Rosenblum, M *J Am Chem Soc* **1951**, *73*, 2641
99 Jones, R J , Rapoport, H *J Org Chem* **1990**, *55*, 1144
100 Black, D St.C , Johnstone, L M *Angew Chem , Ind Ed Engl* **1981**, *20*, 670
101 Padwa, A , Sackman, P , Shefter, E , Vega, E *J Chem Soc , Chem Commun* **1972**, 680
102 Mascal, M , Moody, C J *J Chem Soc , Chem Commun* **1988**, 587
103 Manikumar, G , Shamma, M *J Org Chem* **1981**, *46*, 386
104 Kim, G , Chu-Moyer, M Y , Danishefsky, S J *J Am Chem Soc* **1990**, *112*, 2003
105 Witkop, B *J Am Chem Soc* **1950**, *72*, 1428
Witkop, B , Patrick, J B *ibid* **1951**, *73*, 2196
106 Theuns, H.G , Lenting, H B M , Salemink, C A , Tanaka, H , Shibata, M , Ito, K , Lousberg, R J J Ch *Heterocycles* **1984**, *22*, 2007

107 Bremner, J B , Dragar, C *Heterocycles* ***1985***, *23*, 1451
108 Wentland, M P ; *Tetrahedron Lett* **1989**, *30*, 1477
109 Potier, P , Langlois, N , Langlois, Y , Guéritte, F , *J Chem Soc , Chem Commun* **1975**, 670 Mangeney, P , Andriamialisoa, R Zo , Langlois, N , Langlois, Y , Potier, P *J Am Chem Soc* **1979**, *101*, 2243
110 Polonovski, M , Polonovski, M *Bull Soc Chim Fr* **1927**, 1190
111 Wilson, S R , Sawicki, R A *J Org Chem* **1979**, *44*, 330
112 Olson, G L , Voss, M E , Hill, D E , Kahn, M , Madison V S , Cook, C M *J Am Chem Soc* **1990**, *112*, 323
113 Sakai, R , Higa, T , Jefford, C W ; Bernardinelli, G *J Am Chem Soc* **1986**, *108*, 6404
114 Sakai, R , Kohmoto, S , Higa, T , Jefford, C W , Bernardinelli, G. *Tetrahedron Lett* **1987**, *28*, 5493
115 Ichiba, T., Sakai, R , Kohmoto, S , Saucy, G , Higa, T *Tetrahedron Lett* **1988**, *29*, 3083
116 Nakamura, H., Deng, S , Kobayashi, J -I , Ohizumi, Y , Tomotake, Y , Matsuzaki, T., Hirata, Y *Tetrahedron Lett* **1987**, *28*, 621
117 Brands, K M J , Meekel, A A P , Pandit, U K *Tetrahedron* **1991**, *47*, 2005 and references cited therein
118 Torisawa, Y , Hashimoto, A , Nakagawa, M , Hino, T *Tetrahedron Lett* **1989**, *30*, 6549
119 Evans, P A , Holmes, A B., Russell, K *Tetrahedron Asymmetry* **1990**, *1*, 593
120 Evans, P A , Holmes, A B , Russell, K manuscript in preparation

Acknowledgement
We thank the S.E R C for the award of a CASE studentship (P A E.) and ICI Pharmaceuticals for generous financial support We thank Dr K Russell for his interest in the research which made this review possible