Saturated nitrogen heterocycles

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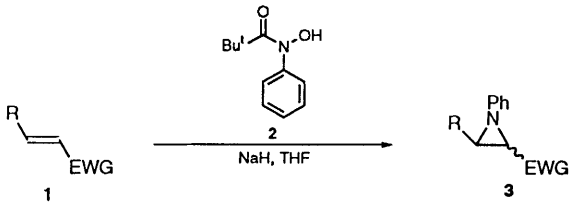
Reviewing the literature published between January 1992 and May 1993

1 Three- and four-membered rings

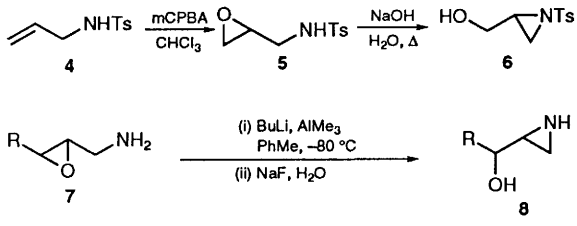
1.1 Aziridines

A useful new aziridination of alkenes has appeared. Thus, the *N*-arylhydroxamic acid **2** reacts efficiently with electron-deficient alkenes **1** to generate the functionalized aziridines **3**.[1] The mechanism of the transformation has not been fully resolved.

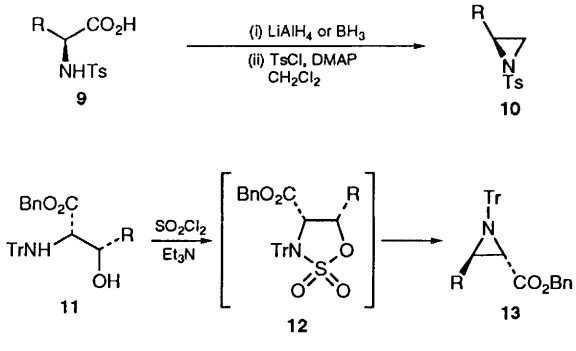


(EWG = Electron Withdrawing Group)

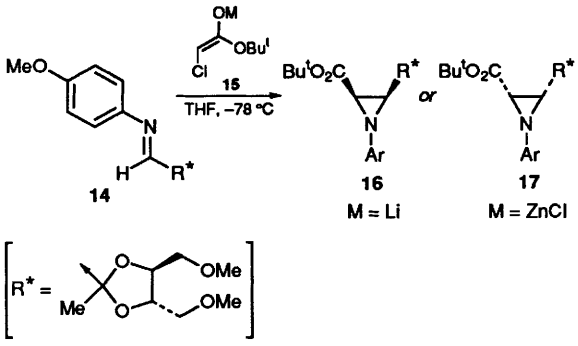
Two separate reports have described the utility of Payne-like rearrangements of aminomethyl oxiranes for aziridine synthesis. In the first of these,[2] the epoxide **5**, prepared by straightforward mCPBA oxidation of the allylsulfonamide **4**, rearranges in aqueous sodium hydroxide to afford the tosyl aziridine **6**. Predictably, no product from the alternative 4-*endo-tet* cyclization mode is observed. In the second report, Vaultier and co-workers[3] describe the trimethylaluminium-mediated rearrangement of the *N*-unsubstituted epoxy amines **7** into the aziridinemethanols **8** in good yield.[3] An alanate complex is a proposed intermediate.



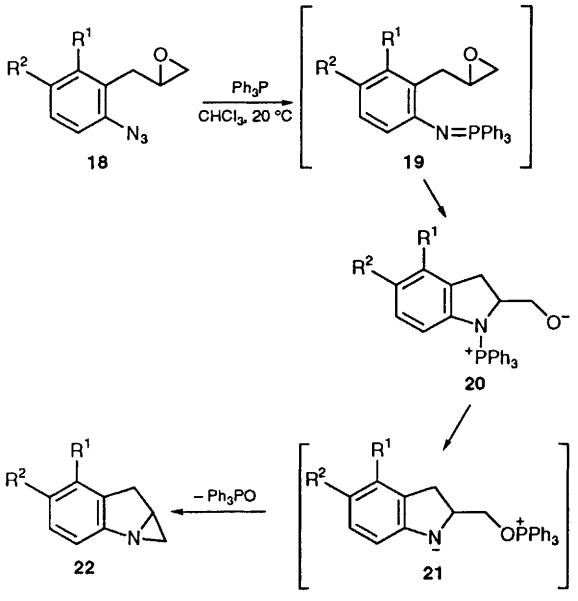
The synthesis of homochiral aziridines has featured prominently in several publications. Thus, Berry and Craig have highlighted a simple but nonetheless effective reduction/ring closure sequence for conversion of the α-amino acids **9** into the chiral monosubstituted aziridines **10**.[4] Yields are generally excellent. Continuing the 'chiral pool' theme, the trityl serine and threonine esters **11** [R = H, Me] are converted into the cyclic sulfamidates **12** using sulfuryl chloride and triethylamine. The sulfamidates **12** are inherently unstable and rearrange *in situ* to give the chiral aziridines **13**.[5]



Finally, Fujisawa and his group[6] have described remarkable metal-dependent diastereoselectivity in the condensation reactions of the chloroketene acetals **15** with the chiral imine **14**. The lithium enolate **15**, M = Li affords only the 2*R*,3*S* aziridine **16**, whilst metal exchange to a zinc enolate **15**, M = ZnCl generates only the 2*S*,3*R* isomer **17**.



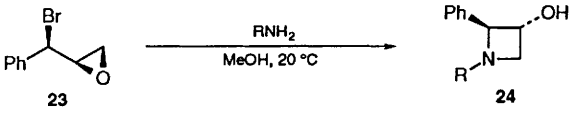
Molina *et al.* have achieved a short and regioselective entry into the fused azirino[1,2-a]indole ring system **22** (**Scheme 1**).[7] The method relies on generation of the intermediate iminophosporanes **19** from appropriate azide precursors **18**, followed by cyclization to the betaines **20** which then rearrange to **21**. Cyclization of **21** and concomitant elimination of phosphine oxide finally produces **22** in 45–95% yield.



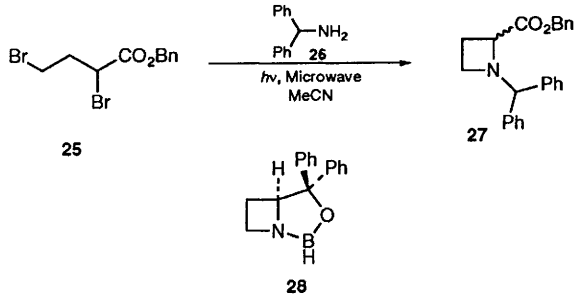
Scheme 1

1.2 Azetidines

Developments in the synthesis of β-lactams will be reviewed in a separate article in this Journal. Toda and co-workers[8] have exploited the efficient aminolysis of the epibromohydrin derivatives **23** to prepare homochiral 3-hydroxyazetidines like **24**.



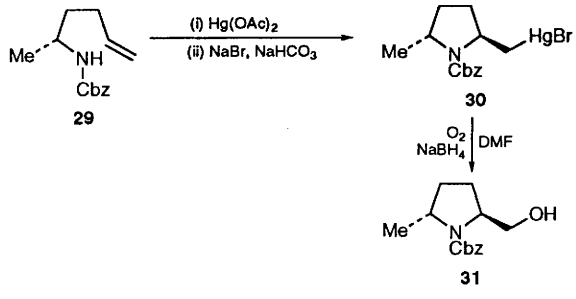
The benzhydryl azetidine-2-carboxylate **27** is a key intermediate in the synthesis of the oxazaborolidine catalyst **28** and, in a new twist to some standard chemistry, this intermediate has been prepared by bis-alkylation of benzhydrylamine **26** with the dibromobutyrate **25** under microwave irradiation.[9] The use of microwaves shortened the reaction time from 24 hours to 15 minutes and enhanced the yield considerably.



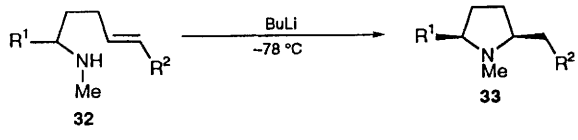
2 Five-membered rings with one nitrogen atom

2.1 Pyrrolidines

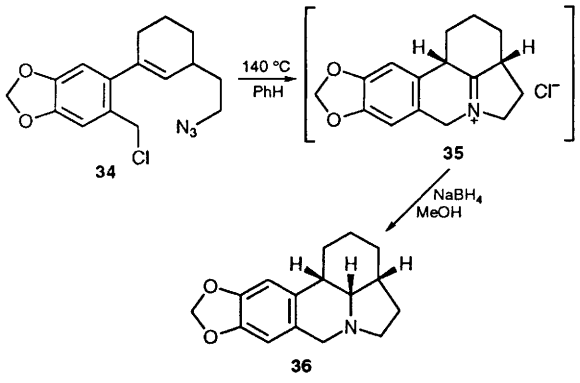
The intramolecular addition of nitrogen to double and triple bonds continues to extend the scope of available pyrrolidine syntheses. As part of a chirospecific synthesis of pyrrolizidines, Takahata and Momose[10] have exploited a selective amidomecuration of the terminal alkene in **29** to generate the *trans*-2,5-disubstituted species **30**. Demercuration then affords the prolinol **31**.



By contrast, butyllithium-mediated cyclization of the secondary amines **32** is remarkably selective in favour of the *cis*-2,5-disubstituted pyrrolidine products **33**.[11] The reaction proceeds optimally in the presence of only a catalytic amount of alkyllithium.

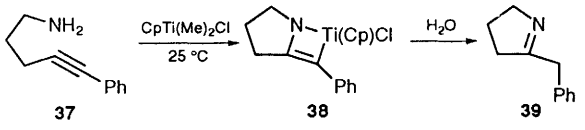


The intramolecular addition of azide to double bonds is a well established route to pyrrolidines, and Pearson *et al.* have now used the procedure in a concise synthesis of racemic γ-lycorane **36**.[12] Thus, thermolysis of the azide **34** first generated the transient iminium ion **35** which was reduced selectively *in situ* to generate lycorane **36** (**Scheme 2**).

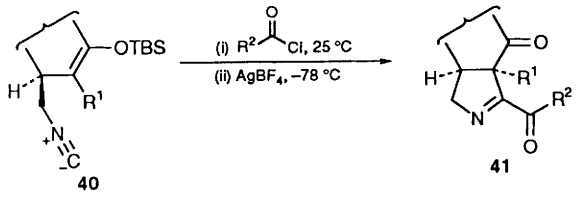


Scheme 2

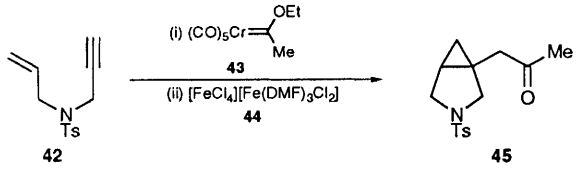
With suitable catalysis, amines will also add readily to *sp*-centres. Livinghouse and his colleagues have described the titanium-catalysed cyclization of the acetylenic amine **37** *via* a formal [2 + 2] cycloaddition of a metalloimine complex, generating the intermediate metallacycle **38**. Aqueous hydrolysis of **38** then liberates the Δ′-pyrroline **39** in excellent yield.[13]

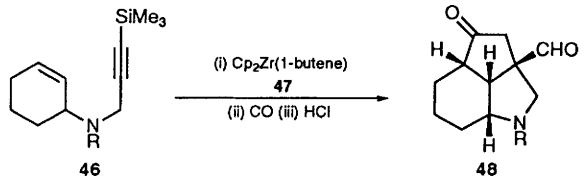


Moving from N–C to C–C bond forming reactions, Livinghouse *et al.* have also prepared more-functionalized pyrrolines using the cyclization of acyliminium ions. Thus, the 2,3-diacyl derivatives **41** are assembled in good yield by a one-pot acylation/silver-mediated cyclization of the isonitriles **40**.[14]

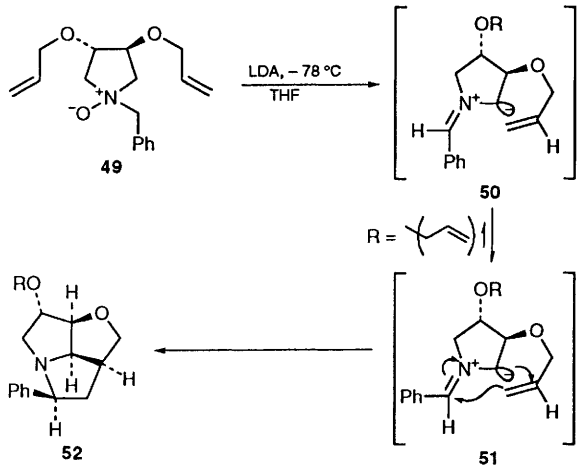


The enyne **42** reacts with Fischer carbene complexes like **43**, in the presence of the iron catalyst **44**, to generate the unusual bicyclic pyrrolidine **45**.[15] The reaction is assumed to proceed *via* two intermediate chromacyclobutanes. In a structurally related enyne cyclization, Mori and co-workers have shown that perhydroindole derivatives like **48** can be constructed, albeit in modest yields, by a reductive coupling of the silyl acetylene **46** promoted by the zirconium complex **47**.[16] The product **48**, R = Bn was then used in a formal synthesis of dendrobine.



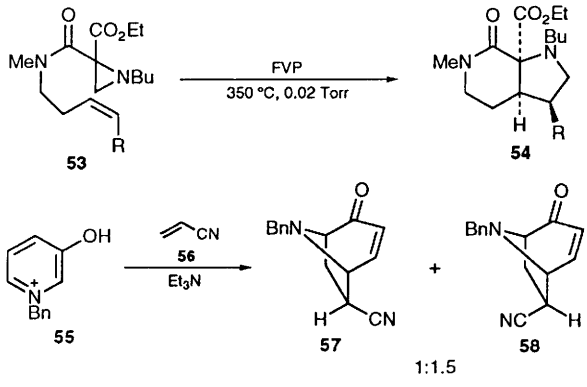


Several research groups have published details of new dipolar cycloaddition routes to pyrrolidines or embellishments of existing methods. Takano and his group[17] report that deprotonation of the C_2 symmetric *N*-oxide **49** produces the dipolar species **50** which presumably equilibrates to the isomer **51** before undergoing an intramolecular cycloaddition to afford the tricyclic pyrrolizidine-like structure **52** (**Scheme 3**).

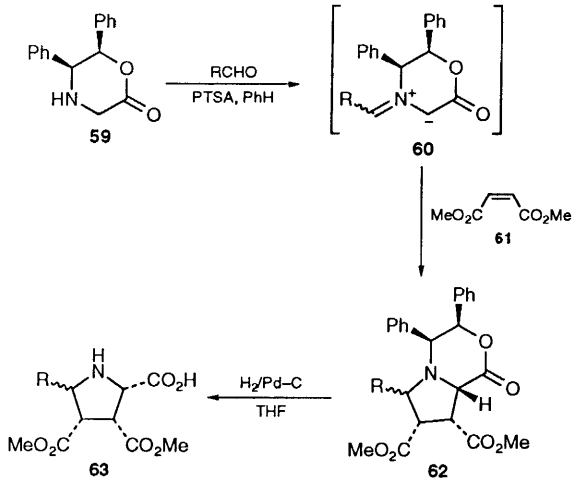


Scheme 3

This represents the first disclosure of an intramolecular 1,3-dipolar cycloaddition of a non-stabilized ylide generated from an amine oxide. At the other thermal extreme, Heathcock *et al.* have used flash vacuum pyrolysis to accelerate the intramolecular cycloaddition reactions of stabilized ylides with unactivated dipolarophiles.[18] Thus the aziridine **53** is converted into the functionalized bicyclic system **54** by brief heating at 350°C. Finally, Jung and his collaborators have exploited the 3-hydroxypyridinium salt **55** as a useful ylide precursor. Treatment of **55** with acrylonitrile **56** and triethylamine affords a roughly equal mixture of the diastereoisomeric azabicyclo[3.2.1]octenones **57** and **58**. The latter isomer, **58**, is an intermediate in the authors' synthesis of Bao Gong Teng A, a natural antiglaucoma agent.[19]

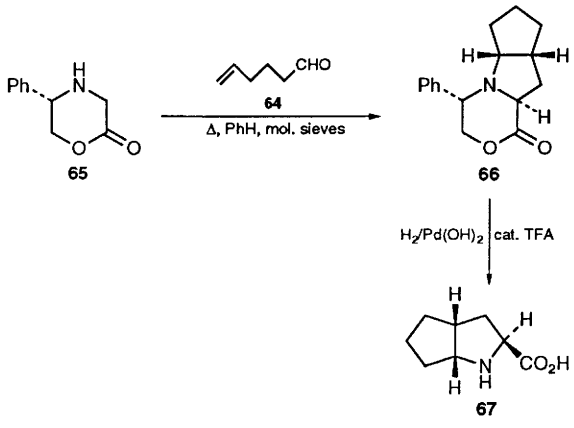


The synthesis of substituted prolines is a well represented area, and two related dipolar cycloaddition approaches are particularly worthy of note. Williams *et al.* have established the diphenylmorpholinone **59** as a valuable cycloaddition template. Reaction of **59** with an aldehyde generates a transient, stablized ylide **60** which is trapped *in situ* by, for example, dimethyl maleate **61** to afford the bicyclic adduct **62** (**Scheme 4**). The chiral auxiliary is then discarded by hydrogenation to give the tetrasubstituted pyrrolidine **63**.[20]

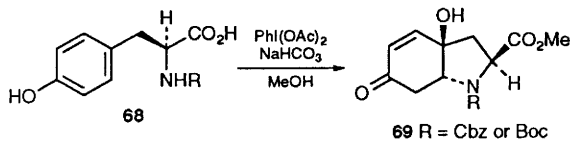


Scheme 4

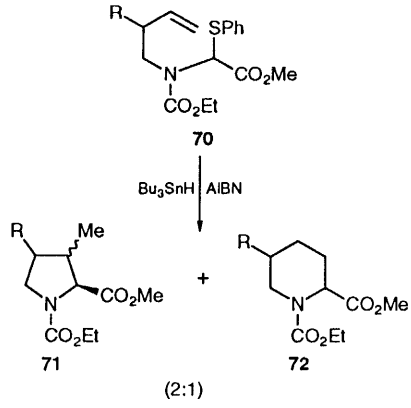
Harwood and Lilley have shown that the intramolecular variant of this cycloaddition sequence proceeds in high yield and with excellent diastereoselectivity, notably with unactivated alkenes as dipolarophiles.[21] Thus, the phenylmorpholinone **65** and 5-hexenal **64** afford the tricyclic pyrrolidine **66** in boiling benzene, and hydrogenation then liberates the bicyclic proline analogue **67**.



As part of a synthetic approach to the hydroindole core of *Stemona* alkaloids, Wipf and Kim have demonstrated an effective oxidative cyclization of tyrosine **68** by iodobenzene diacetate to yield the bicyclic enone **69**.[22] In the absence of sodium bicarbonate only *ipso* spirolactonization is observed.

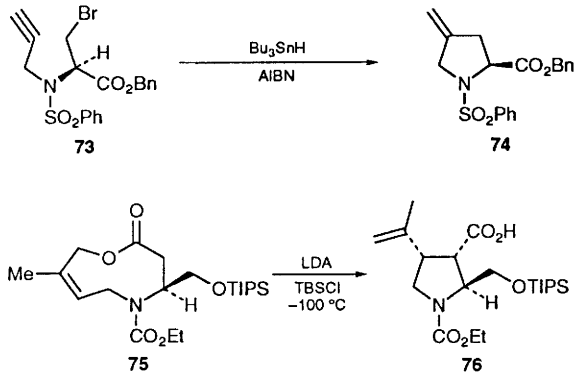


Radical cyclizations have also provided new entries to substituted prolines. The thioaminals **70** serve as precursors for carbon-centred glycine radicals, and their treatment with tributylstannane affords a mixture of the five- and six-membered products, **71** and **72**.[23]

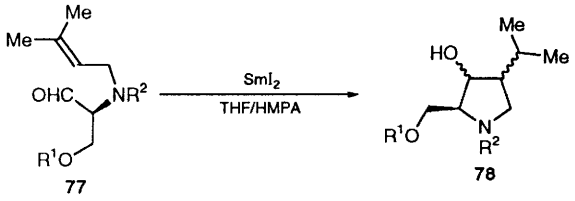


The transformation is reasonably tolerant of substituents although yields are variable.

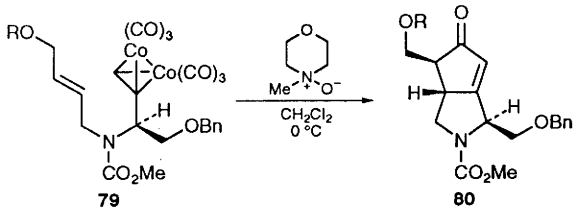
The homochiral 4-exomethyleneproline **74** has been prepared by a tributylstannane-promoted 5-*exo-dig* cyclization of the acetylene **73**.[24] The neuroexcitatory prolinoid kainic acid and its congeners have attracted continued synthetic attention. Thus, Knight and his co-workers have employed a particularly elegant transannular ester-enolate Claisen rearrangement reaction as part of their total synthesis of (−)-α-kainic acid.[25] Deprotonation of the nine-membered azalactone **75**, by LDA, followed by warming effects rearrangement *via* a boat-like transition state leading to the key functionalized pyrrolidine **76**.



Baldwin *et al.* have shown that samarium iodide cyclizes the alkene substituted aminoaldehydes **77** to diastereoisomeric mixtures of the kainoid precursors **78**;[26] an *N*-acyl substituent is apparently essential for the transformation to proceed.

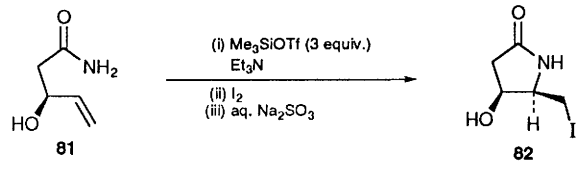


Finally, Takano and colleagues have developed conditions for the intramolecular Pauson–Khand cyclization of the dicobalt carbonyl protected acetylene **79**. The bicyclic enone product **80** is a key intermediate in the authors' enantiospecific synthesis of (−)-kainic acid.[27]

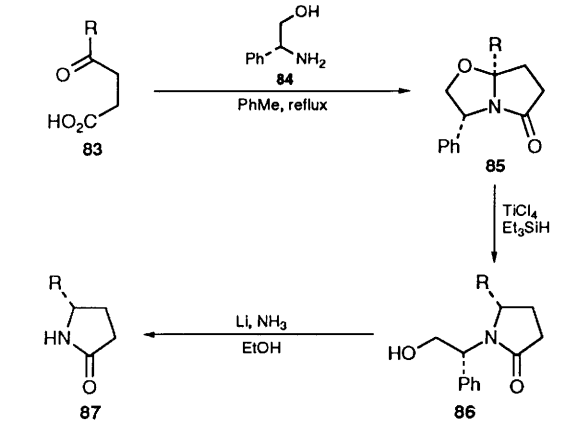


2.2 Pyrrolidinones

The intramolecular addition of amide nitrogen centres to unsaturated bonds is a popular route to γ-lactams. Knapp *et al.* have extended their earlier work in this area by developing an efficient, stereoselective iodolactamization of the primary amide **81** affording the hydroxypyrrolidinone **82** after removal of the transient protecting group.[28]

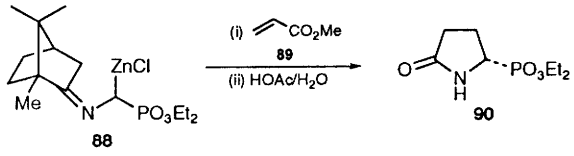


Although amide bond formation *per se* is outside the remit of this review, several noteworthy γ-lactam syntheses are appropriately included. A simple asymmetric synthesis of 5-substituted 2-pyrrolidinones which relies on the chiral auxiliary phenylglycinol **84** has been reported by Meyers *et al.* (**Scheme 5**).

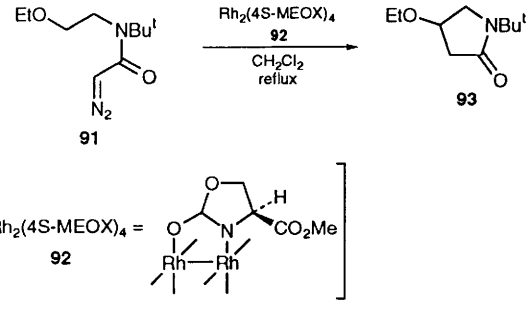


Scheme 5

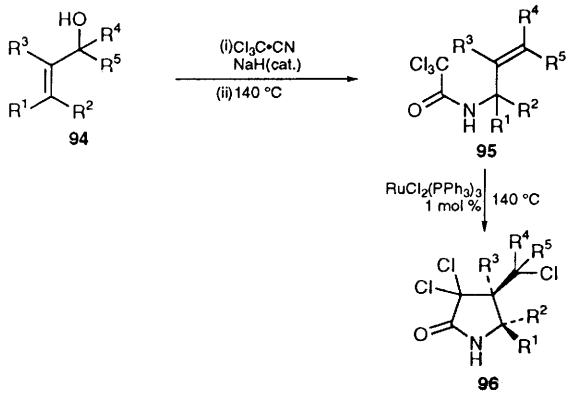
Condensation of **84** with γ-ketoacids **83** yields the bicyclic aminals **85**. Stereoselective reduction of **85** with alane or triethylsilane/Lewis acid next generates the substituted lactams **86**. Removal of the residual auxiliary, liberating the 5-substituted pyrrolidinones **87** is then achieved by a dissolving metal reduction.[29] Schöllkopf has described a synthesis of the novel 5-phosphonate **90** in the course of studies on phosphonoproline analogues. A Michael addition of the chiral metallated imine **88** to methyl acrylate **89** gives the homochiral lactam **90** after hydrolytic work-up. Zinc appears to be essential since the reaction fails when a lithiated imine is employed.[30]



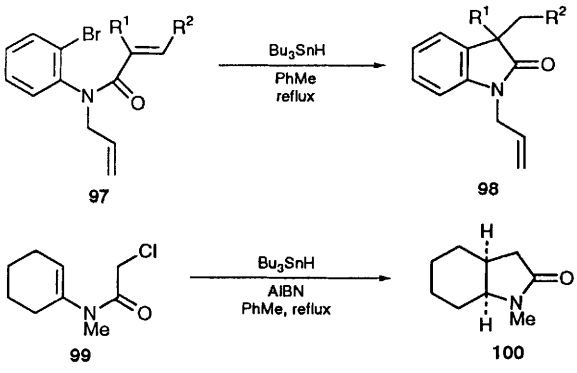
The use of transition metals is affording some effective new syntheses in this area. Thus, the chiral rhodium catalyst $Rh_2(4S\text{-MEOX})_4$ **92** almost quantitatively converts the diazoamide **91** into the lactam **93** with a moderately good e.e. (78%). The authors also describe several related catalysts which give varying amounts of azetidine by-products.[31]



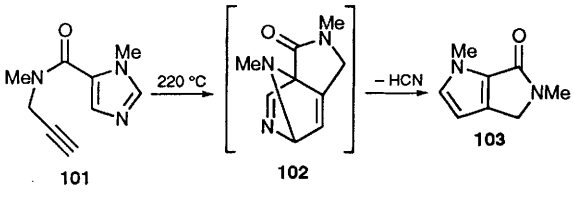
Many radical-based approaches to polyhalogenated pyrrolidinones have appeared in recent years, and three recent reports add to this list. Itoh and co-workers[32] have reported that *N*-allyl trichloroacetamides such as **95**, which are readily prepared from the appropriate allyl alcohols **94** by an Overman-type [3,3]-sigmatropic rearrangement, are converted into the pyrrolidinones **96** in good yield under ruthenium catalysis.

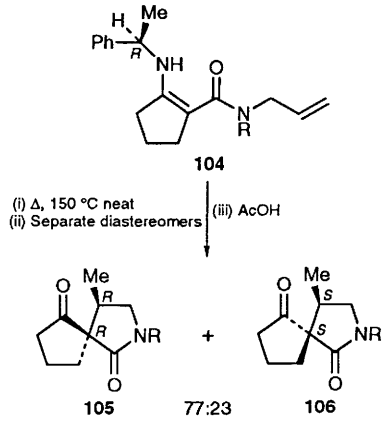


Jones and Storey have assembled the oxindoles **98** by a tin-mediated radical cyclization of the bromoanilide **97** although, in some cases, small amounts of corresponding dihydroquinolone products were formed by the alternative 6-*endo* cyclization.[33] No competitive addition to the isolated allyl double bond in **97** was obseved. Finally, Ikeda and his colleagues have documented the radical cyclization of *N*-vinyl chloroacetamides such as **99**, affording the bicyclic pyrrolidinone **100**. This chemistry has then been extended to a useful synthesis of perhydroerythrinane.[34]

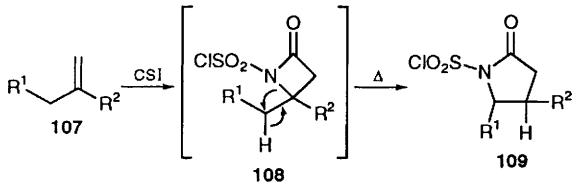


Two interesting pericyclic approaches to pyrrolidinones have emerged recently. In the first, the pyrrolo[3,4-b]pyrrolidinone **103** is assembled quickly and efficiently by a thermal intramolecular Diels–Alder reaction of the acetylenic imidazole **101**. The presumed intermediate adduct **102** is not observed and almost certainly extrudes HCN *in situ*.[35] In the second report, the homochiral aminoacrylamide **104** undergoes an asymmetric intramolecular ene reaction on heating at 150°C. Hydrolysis of the separated diastereoisomeric products then gives the enantiomeric spiropyrrolidinones **105** and **106** in a ratio of 77:23, corresponding to 52% e.e. for the ene reaction.[36]



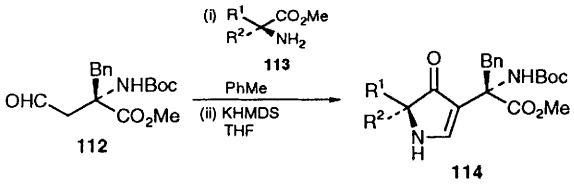


Ring expansion reactions are frequently serendipitous discoveries, and Black and his co-workers have now described such an expansion of β-lactams which may have considerable synthetic scope. The reaction of chlorosulfonyl isocyanate (CSI) with simple 1,1-disubstituted alkenes **107**, bearing at least one allylic proton is presumed to generate the classical β-lactam intermediates **108**. On heating the reaction mixture, however, only the sulfonyl pyrrolidinones **109** are isolated, in 60–70% yield.[37]



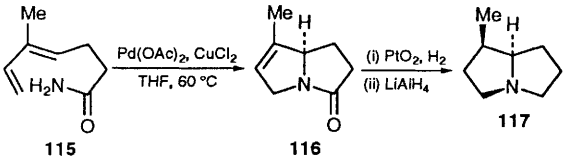
In an unrelated ring expansion, the *N*-phenylazetidinone **110** is converted stereospecifically into the iminopyrrolidinone **111** on treatment with cyanotrimethylsilane and aluminium chloride.[38]

Smith and Hirschmann have described a short synthesis of the homochiral 3-pyrrolidinones **114** which are readily assembled into oligomeric β-strand peptidomimetics.[39] The synthesis of **114** relies on imine formation between the aldehyde **112** and the unnatural amino acids **113**, followed by KHMDS-induced cyclization.



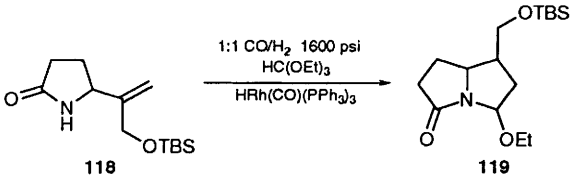
2.3 Pyrrolizidines and related compounds

A new route to pyrrolizidine alkaloids, developed by Andersson and Bäckvall,[40] relies on a palladium catalysed tandem cyclization of the dienyl amide **115** generating the bicyclic lactam **116** which was then converted into (±)-heliotridane **117**.

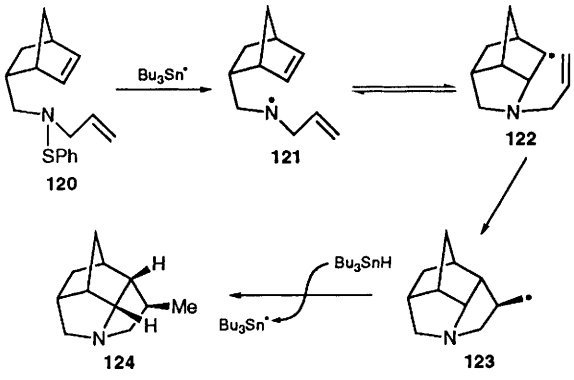


An intramolecular amidocarbonylation of the pyrrolidinone **118** proceeds under rhodium catalysis and very high pressures of carbon monoxide and

hydrogen (> 100 atmospheres) to give the aminal **119** as a 2 : 1 mixture of isomers. The isomers of **119** were then transformed into isoretronecanol and trachelanthamidine.[41]

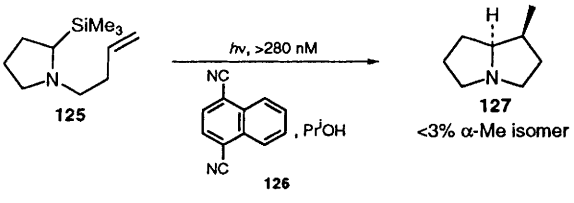


Significant developments in radical-mediated ring closure reactions have emerged. Bowman and his co-workers[42] have prepared the tetracyclic pyrrolizidine analogue **124** from the bicyclic sulfenamide **120** (**Scheme 6**). The reaction proceeds by generation of the aminyl radical intermediate **121** which then undergoes tandem cyclizations *via* **122** and **123** before abstracting hydride and regenerating the catalytic tin radical.

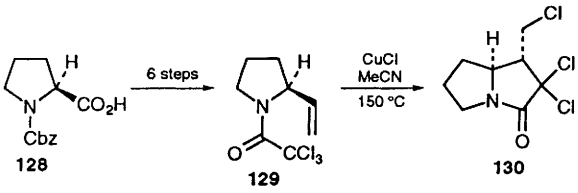


Scheme 6

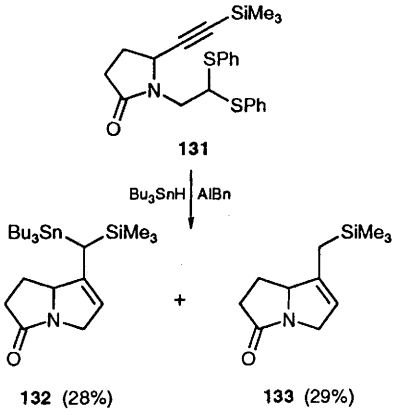
The α-amino radical generated by photolysis of **125** in the presence of 1,4-dicyanonaphthalene **126** as an electron-transfer agent cyclizes stereoselectively to afford the pyrrolizidine **127**. Less than 3% of the α-methyl isomer is produced during the ring closure.[43]



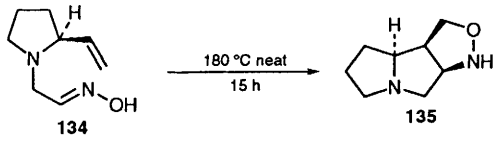
In a reaction analogous to the formation of the pyrrolidinone **96**, the vinyl pyrrolidine **129**, which is readily available from cbz-proline **128**, is shown to cyclize under copper (I) catalysis to generate the trichlorolactam **130** in 93% yield.[44] Dechlorination



and amide reduction then completes a synthesis of pseudoheliotridane. In the last radical cyclization example, the tin mediated cyclization of thioacetal **131** provides a 1 : 1 mixture of the bicyclic lactams **132** and **133**; the mixture has then been used to complete a synthesis of racemic supinidine.[45]



Finally, Hassner and his co-workers have described the intramolecular oxime-olefin cycloaddition reaction of the proline-derived vinyl pyrrolidine **134** to afford the tricyclic adduct **135**.[46] Despite the need to heat the oxime neat at 180°C for 15 hours, the product **135** is isolated in 56% yield, and has also been converted into supinidine.

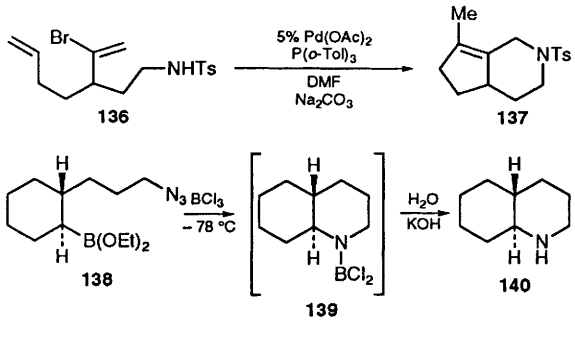


3 Six-membered rings with one nitrogen atom

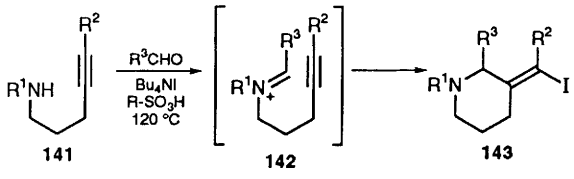
3.1 Piperidines

An excellent review of synthetic approaches to the *Daphniphyllum* alkaloids has appeared.[47] Amongst a wealth of chemistry, the review contains a valuable summary of fused piperidine ring constructions.

Returning to the theme of nitrogen addition to unsaturated bonds, Weinreb *et al.* have described a regioselective synthesis of the piperidine **137** by palladium-mediated sequential cyclizations of the aminodiene **136**.[48] The azidoboronates **138**, prepared *via* hydroboration of a suitable alkene with $HBCl_2$ and an alcohol, are readily cyclized by treatment with boron trichloride to give the intermediate dichloroboranes **139**. Basic hydrolysis efficiently liberates the bicyclic perhydroquinolines **140**.[49]

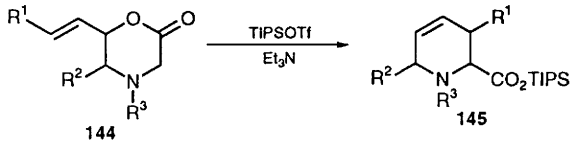


Overman and his colleagues have extended their existing work on the Mannich-like intramolecular addition reactions of alkynes to imines by demonstrating that the imines **142**, prepared by condensation of the amines **141** with a range of aldehydes, readily undergo an iodide-promoted cyclization to form the alkylidenepiperidines **143**.[50]



141 142 143

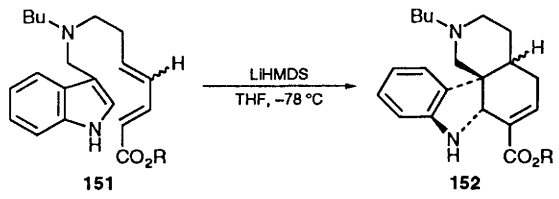
Angle and his group have published more details of their elegant, stereoselective pipecolic acid synthesis. Conversion of the oxazinones **144** into their corresponding TIPS ketene acetals facilitates a conformationally restricted Claisen rearrangement which proceeds by a boat-like transition state to generate the pipecolic acids **145**.[51] The procedure has also been applied to the synthesis of enantiomerically pure piperidine derivatives.



144 145

Angle has also described an unrelated synthesis of piperidines which relies on silver oxide oxidation of the phenol **146** to the quinonoid species **147**. Addition of zinc chloride then catalyses cyclization of the enecarbamate **147**, generating the intermediate **148** which can be isolated as a mixture of **149** and **150** in which the new enecarbamate **149** predominates (**Scheme 7**).[52]

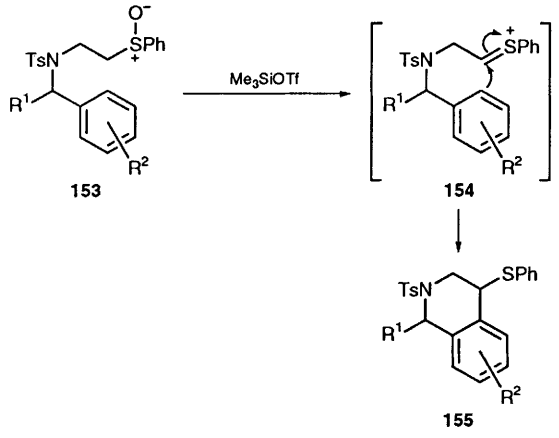
Finally, as part of a synthetic approach to manzamines, Markó and his group have detailed a remarkable anionic cyclization of the indole **151** to give the tetracyclic system **152**. Overall, the transformation is the equivalent of an indole-based IMDA reaction. The authors suggest a plausible mechanism involving kinetic addition of the indolyl anion to the dienoate followed by a fast, intramolecular Mannich reaction.[53]



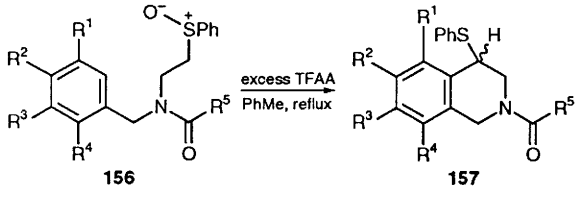
151 152

3.2 Tetrahydroisoquinolines and related compounds

Two similar reports of the utility of intramolecular Pummerer reactions in the synthesis of tetrahydroisoquinolines have appeared. In the first, by Craig and co-workers,[54] treatment of the β-aminosulfoxides **153** with TMS triflate generates the presumed thionium ion intermediates **154** which then cyclize to generate moderate yields of the tetrahydroisoquinolines **155**. Takano has described essentially the same cyclization of **156** to **157** catalyzed by TFAA.[55]

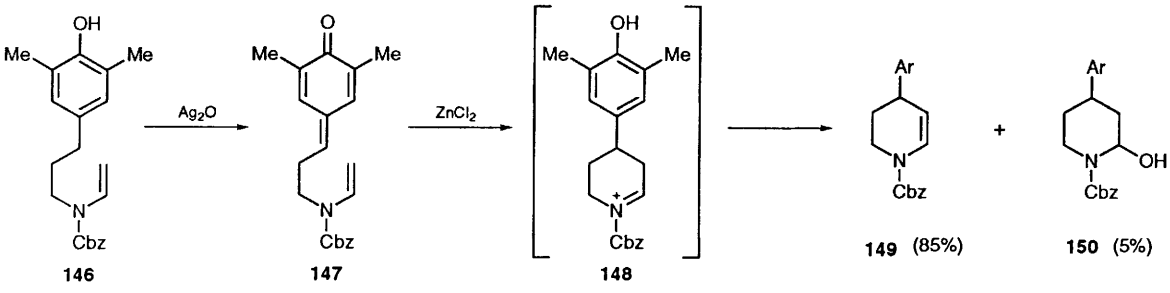


153 154 155



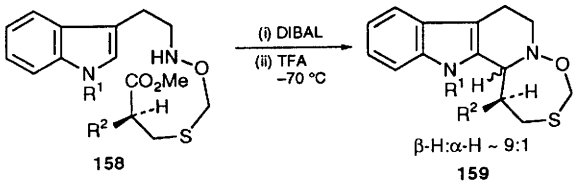
156 157

The venerable Pictet–Spengler reaction continues to show new facets. As part of a synthetic approach to tetracyclic eudistomins, a stereoselective synthesis of the tetrahydro-β-carbolines **159** has been achieved by reduction of the esters **158** followed by *in situ* cyclization of the resulting aldehydes with TFA.[56]



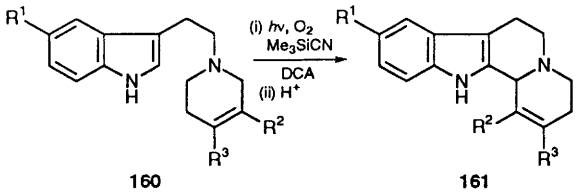
146 147 148 149 (85%) 150 (5%)

Scheme 7

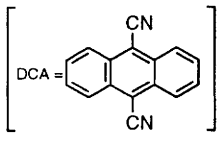


158 159

Photolysis of the tryptamine analogues **160** in the presence of TMSCN and 9,10-dicyanoanthracene **162** as a photosensitizer produces the tetracyclic indoloquinolizidines **161** after acidification. The reaction proceeds by cyanation to generate intermediate α-aminonitriles which afford Pictet-Spengler products on treatment with acid.[57]

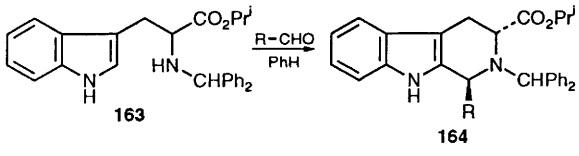


160 161



162

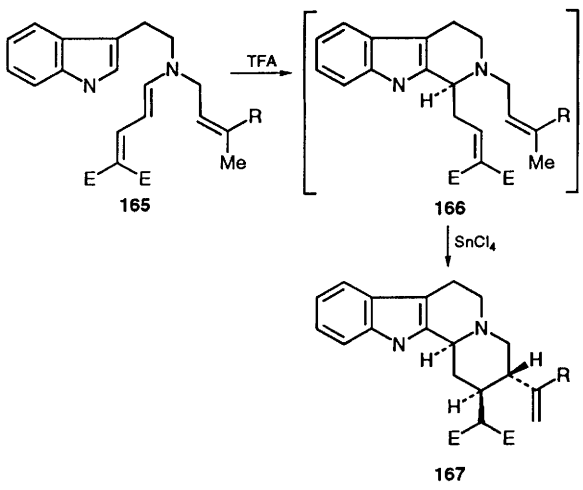
Appropriately substituted tryptophan derivatives can give excellent stereoselectivity in cyclocondensations with aldehydes. Thus the *N*-benzhydryl tryptophan isopropyl ester **163** condenses with aldehydes to generate the *trans* tetrahydro-β-carbolines **164** exclusively.[58]



163 164

Tietze and Wichmann have established a short and neat entry to corynanthe type alkaloids which relies on tandem Pictet-Spengler and intramolecular Michael reactions (**Scheme 8**).[59] Thus, treatment of the amino triene **165** with TFA generates the intitial cyclization product **166** which is not isolated. Exposure of **166** to tin tetrachloride then mediates a stereoselective Michael reaction producing the tetracyclic amine **167**. Interestingly, no single Brönsted or Lewis acid alone could be found to achieve both cyclizations.

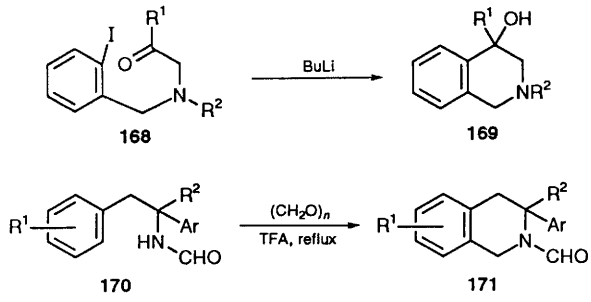
Two somewhat unusual tetrahydroisoquinoline syntheses have been published. Kihara and co-workers[60,61] have reported the lithiation and cyclization of **168** to generate the carbinol **169** on exposure to butyllithium (a so-called intramolecular Barbier reaction). Lastly, Maryanoff[62] has shown that reaction of the formyltryptamine **170** with paraformaldehyde generates a formyliminium ion which then cyclizes spontaneously to the formamide



165 166 167

Scheme 8

171. The reaction has not been extended to aldehydes other than formaldehyde.

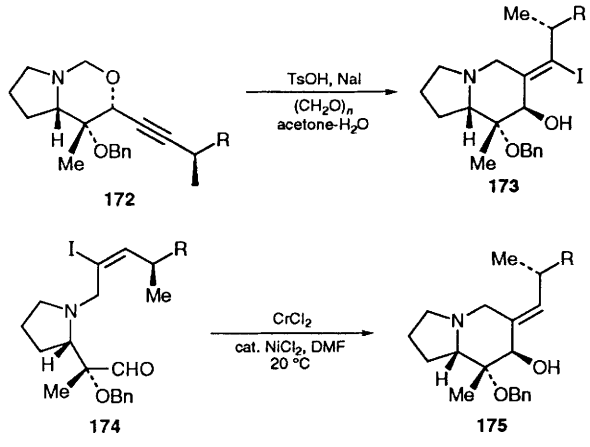


168 169 170 171

3.3 Indolizidines

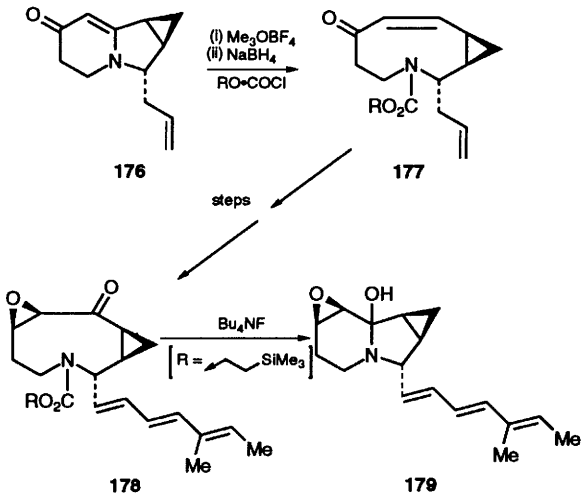
A comprehensive, 94-reference, review of synthetic approaches to castanospermine, its stereoisomers and analogues has appeared.[63]

The total syntheses of several complex indolizidines have recently been described. A pivotal step in the construction of the dendrobatid alkaloid (+)-allopumiliotoxin 339A by Overman[64] is the generation and cyclization of an iminium ion from **172** leading to the vinyl iodide **173**. In a second synthesis of allopumiliotoxin 339A, the vinyl iodide **174** is converted into an organochromium intermediate by Nozaki chemistry. The subsequent cyclization gives the advanced intermediate **175**.[65]



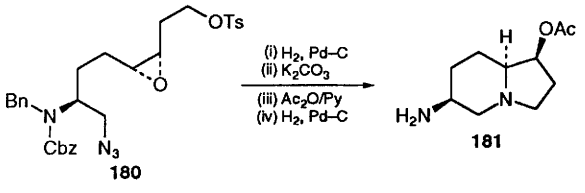
172 173 174 175

The elegant synthesis of indolizomycin by Danishefsky *et al.*[66] achieves the requisite pendant functionality by assembling and then fragmenting an indolizidine-like core unit (**Scheme 9**). Thus, the dihydropyridone **176** is ring enlarged to first give the azonine **177**. After further modification to **178**, deprotection of the ring nitrogen initiates a spontaneous transannular cyclization affording indolizomycin **179**.

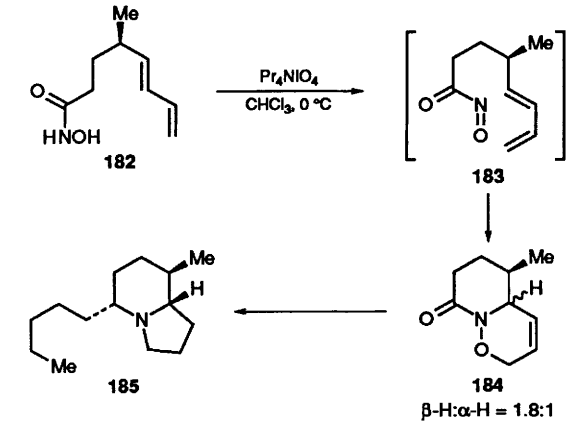


Scheme 9

An enantioselective synthesis of (−)-slaframine **181** exploits a chemoselective hydrogenation of the azide **180** followed by tandem cyclization of the resulting amine. Acetylation and deprotection then liberate the alkaloid **181**.[67]

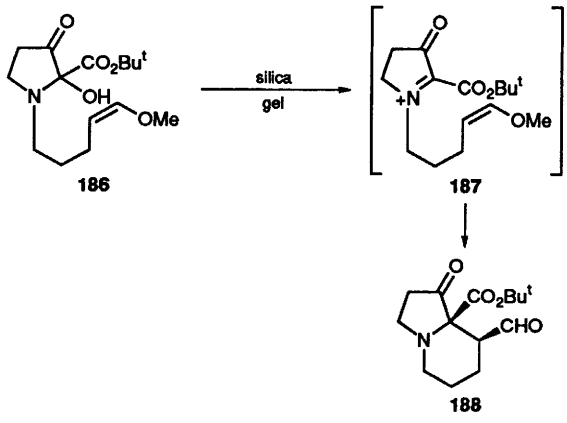


Oxidation of the homochiral hydroxamic acid **182** transiently generates the acylnitrosodiene **183** which then undergoes an IMDA cyclization, affording the key adduct **184** as a mixture of diastereomers (**Scheme 10**).[68] These intermediates **184** have been used as



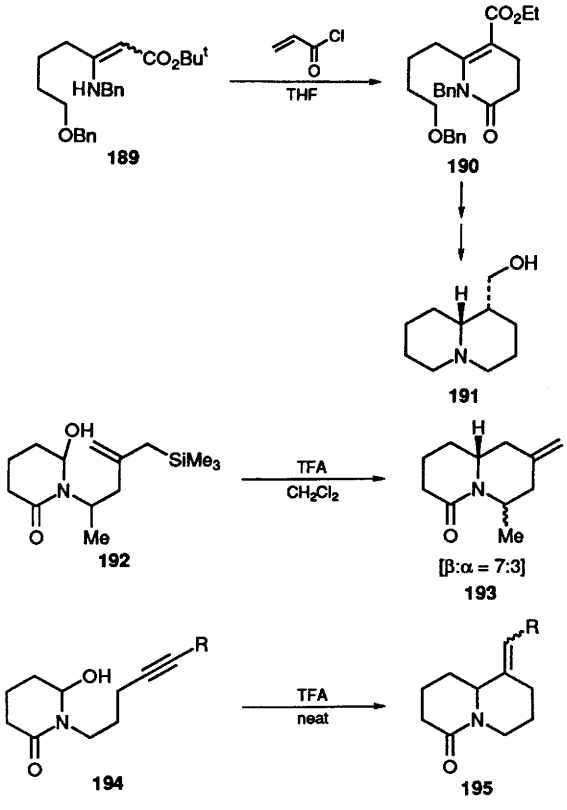
Scheme 10

common precursors for several of the gephyrotoxin alkaloids including 209B **185**. Wasserman *et al.*[69] have shown that the vicinal tricarbonyl derivative **186** is converted *via* the acyliminium ion **187** into the bicyclic amine **188** simply by the action of silica gel.



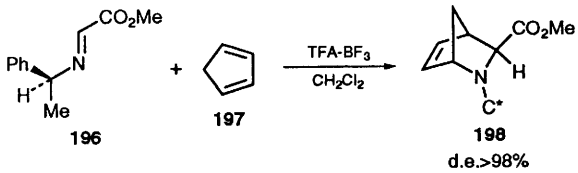
3.4 Quinolizidines

A useful aza-annulation has been devised as the key component of a stereocontrolled route to lupinine **191**. Reaction of the β-aminocrotonate **189** with acryloyl chloride generates only the lactam **190** in 80% yield.[70] Two related cyclizations of acyliminium ions derived from hemi-aminals have been used to assemble quinolizidines. In the first,[71] exposure of the hemi-aminal **192** to TFA promotes iminium ion formation and interception by the pendant allylsilane then affords the isomeric bicyclic lactams **193**. The second report uses identical conditions, but an acetylenic terminator rather than an allylsilane;[72] thus **194** affords the lactams **195**

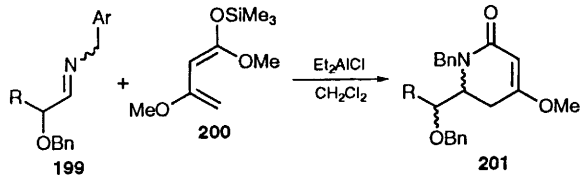


3.5 Aza Diels–Alder reactions

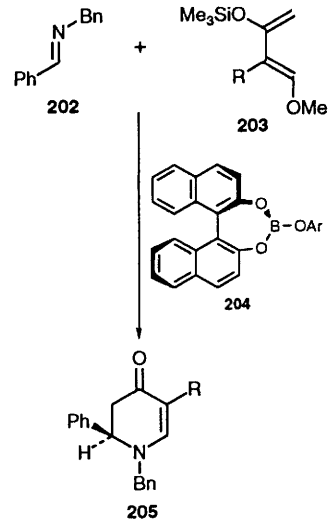
The synthesis of six-membered rings containing nitrogen has fuelled continued interest in aza-variants of [4 + 2] cycloadditions, with the majority of recent developments in the azadienophile domain. Abraham and Stella[73] have achieved near total diastereocontrol in the cycloaddition of the homochiral imine **196** with, for example, cyclopentadiene **197** to afford the adduct **198**. A critical development is the use of a catalytic mixture of TFA and BF_3 to optimize the process.



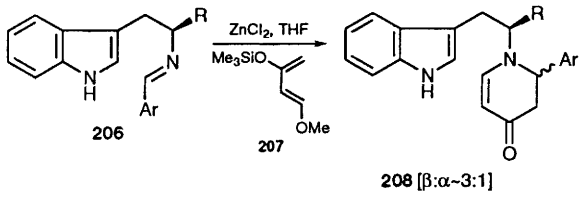
Diethylaluminium chloride has been established as an excellent catalyst for the cycloaddition reactions of α-alkoxyimines such as **199**.[74] Diastereoselectivity in the reaction of **199** with the diene **200**, to afford the lactams **201**, varies from moderate to very good.



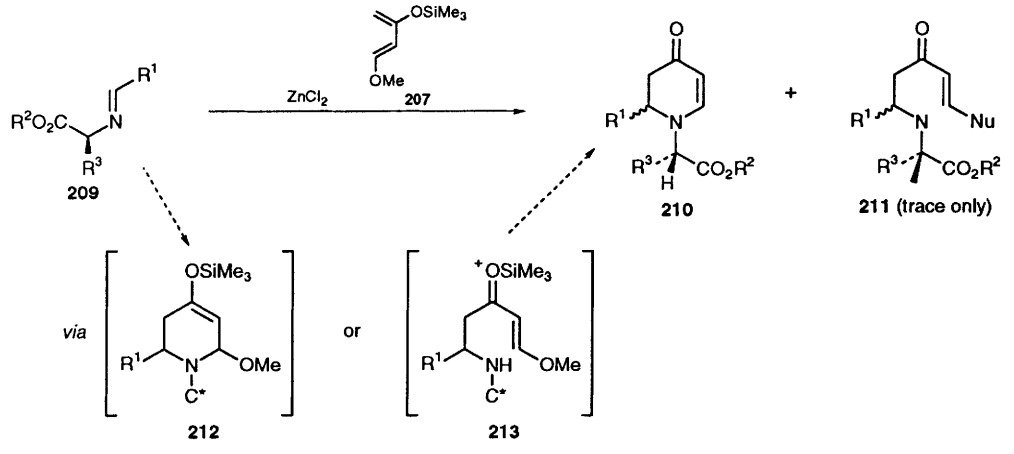
Variation of the diene substitution can result in a complete reversal of the cycloaddition regiochemistry. In contrast to the previous example, the imine **202** reacts with the dienes **203** to provide the 4-pyridone derivatives **205**. Use of the BINAP-based boronate **204** results in up to 90% e.e.[75,76]



Waldmann and his co-workers have demonstrated some useful levels of diastereocontrol in the zinc chloride catalysed reaction of the tryptophan-based imines **206** with Danishefsky's diene **207**.[77] The dihydropyridones **208** are isolated typically as *ca.* 3:1 mixtures. The actual mechanism of this, and related cycloadditions, is the subject of a study by the same research group.[78]



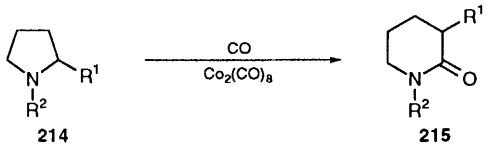
The imines **209** react with the diene **207** as in the previous example, to give the dihydropyridones **210** together with a trace impurity **211** arising from residual nucleophile incorporation. The authors have detected no intermediates akin to **212** which would be consistent with a concerted [4 + 2] cycloaddition. However, the observation of **211** is circumstantial evidence for a tandem Mannich–Michael sequence *via* intermediates such as **213** (**Scheme 11**).



Scheme 11

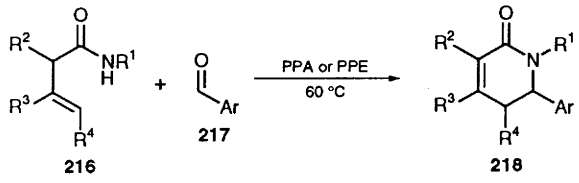
3.6 Piperidinones

Alper and his group[79] have continued their explorations of carbonylative ring expansion reactions by demonstrating an efficient, cobalt-mediated conversion of the pyrrolidines **214** into the δ-lactams **215**. The reaction is regioselective in that only the more substituted ring carbon migrates to CO.

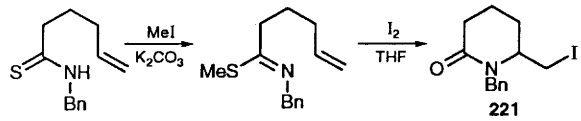


214 **215**

The alkenamides **216** react with aryl aldehydes **217** typically in hot polyphosphoric acid to afford the unsaturated lactams **218** in good yield and with useful levels of diastereoselectivity in the C–C bond forming process.[80] Momose and his colleagues[81] have disclosed that thioimidates **220**, prepared from the unsaturated thioamides **219**, undergo an efficient iodolactamization to provide the functionalized 2-piperidinones **221**.

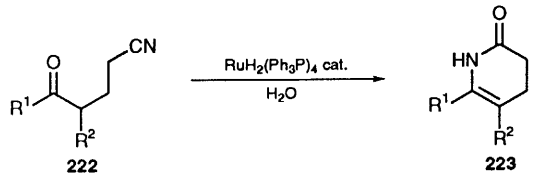


216 **217** **218**

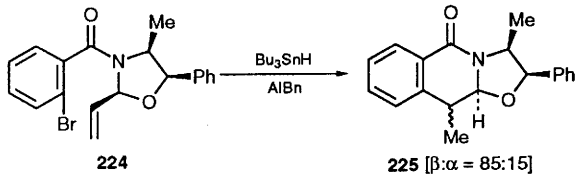


219 **220** **221**

The hydration–cyclization of γ-ketonitriles such as **222** under ruthenium hydride catalysis generates the ene-lactams **223** in high yield, and Murahashi *et al.*[82] have applied this procedure to a relatively short synthesis of (−)-pumiliotoxin C. Radical-initiated carbon–carbon bond formation is now almost ubiquitous in heterocyclic synthesis, and Gennari *et al.*[83] have described an enantioselective synthesis of the tricyclic lactams **225** by a tin hydride facilitated cyclization of the aryl bromide **224**.

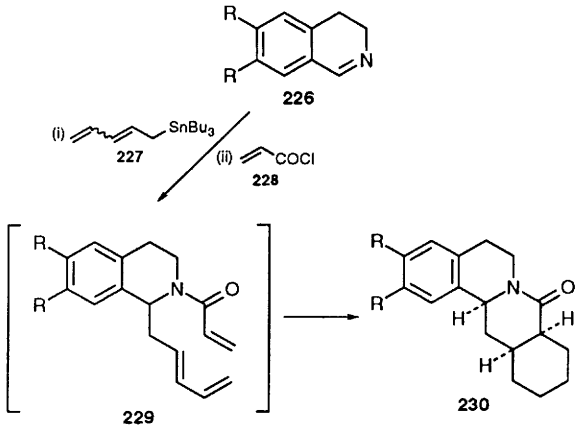


222 **223**



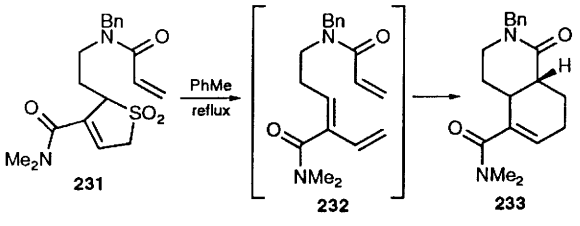
224 **225** [β:α = 85:15]

Although the Diels–Alder reaction primarily assembles C–C bonds, a corollary may be the generation of new heterocycles, and two research groups have recently used this protocol to advantage in alkaloid synthesis. Firstly, Yamaguchi and his co-workers[84] have achieved a quick entry to the yohimbane system which relies on nucleophilic addition of the dienylstannane **227** to a suitable cyclic imine **226** followed by *in situ* acylation with acryloyl chloride **228** to yield the bicycloannulated product **230**. The triene intermediates **229** are not observed (**Scheme 12**). In the second report, by Leonard and his group,[85] thermolysis of the sulfolene **231** liberates transiently the amidotriene **232** which rapidly cyclizes to generate the bicyclic amide **233**.



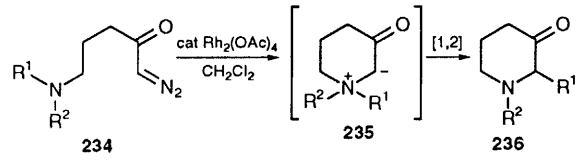
226 **227** **228** **229** **230**

Scheme 12

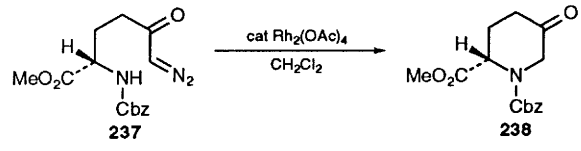


231 **232** **233**

A useful Stevens [1,2]-shift route to 3-piperidinones has emerged. Thus, West *et al.*[86] report that exposure of the aminopropyl diazoketones **234** to standard rhodium carbenoid conditions affords the cyclic aminoketones **236**, presumably by a [1,2]-alkyl shift of the intermediate ylides **235**. Using a similar protocol, the 5-oxopipecolic acids **238** have been assembled by a rhodium-mediated insertion of the carbenoid derived from the diazoketone **237**.[87]

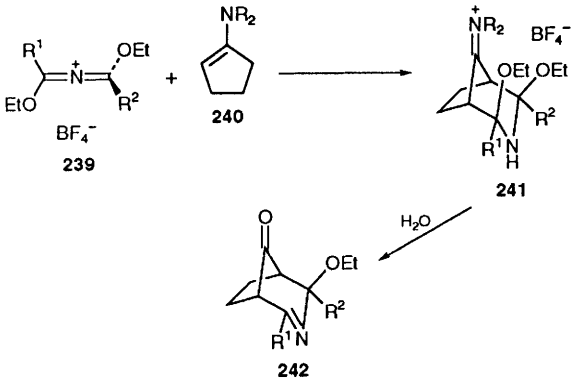


234 **235** **236**



237 **238**

Lastly, reaction of the azapropenylium salts **239** with the enamine **240** generates the bicyclic imines **241**, which are readily hydrolysed to the azabicyclo[3.2.1]octenones **242** (**Scheme 13**).[88]

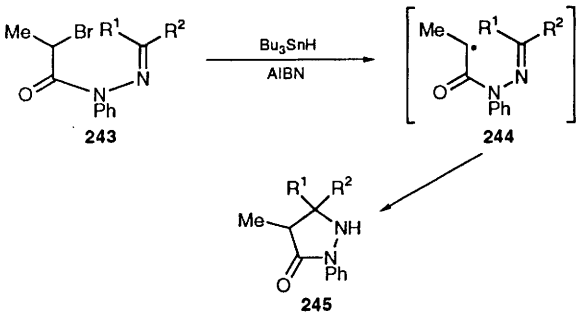


Scheme 13

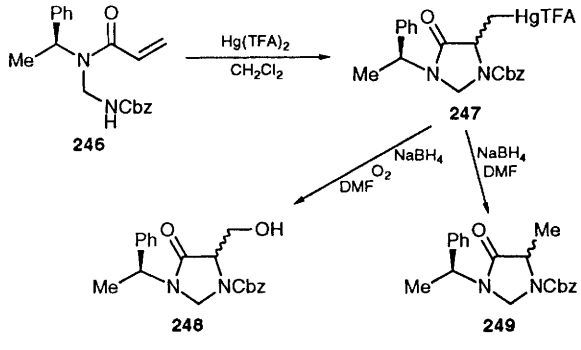
4 Rings with two or more nitrogen atoms

4.1 Five-membered rings

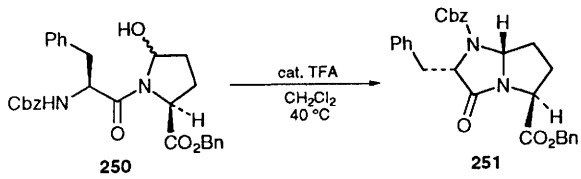
Treatment of the α-bromoacyl phenylhydrazones **243** with tributylstannane generates the radical intermediate **244** which then cyclizes to give the pyrazolidinones **245** rather than the anticipated diazetidinone 4-*exo-trig* products.[89] As part of a new



synthesis of α-amino acids (**Scheme 14**), the chiral amidal **246** has been converted into the organomercurial imidazolidinone **247**. This versatile intermediate can then either be demetallated reductively, affording **249**, or oxygenated, generating the alcohol **248**.[90] Baldwin and his co-workers have synthesized the conformationally restricted, bicyclic γ-lactam dipeptide analogue **251**, utilizing as the key transformation a cyclization of the acyliminium ion derived from the hemi-aminal **250**.[91]

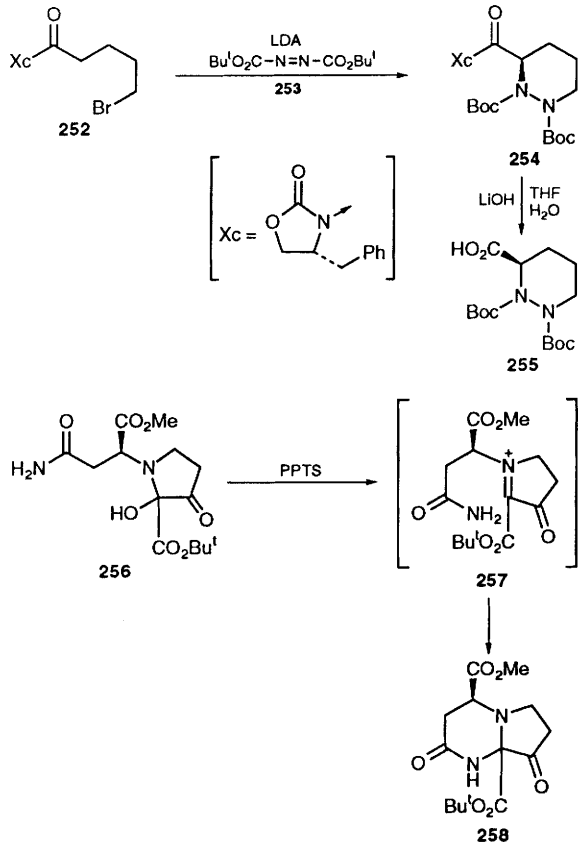


Scheme 14

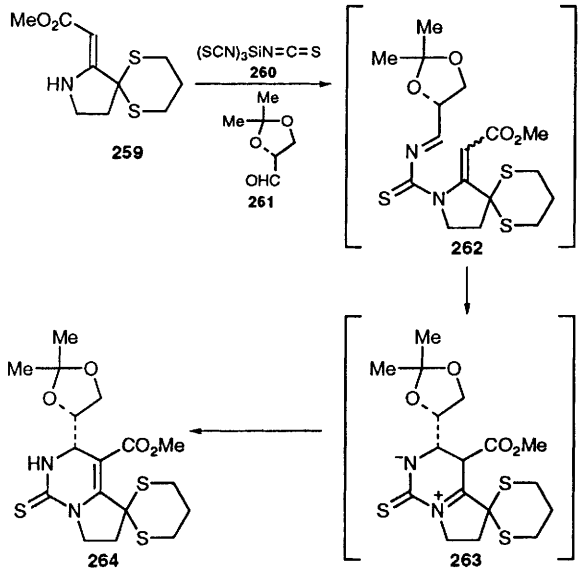


4.2 Six-membered rings

An efficient synthesis of both enantiomers of piperazic acid, a constituent of the anti-tumour antibiotic azinothricin, has been reported.[92] The lithium enolate of the bromovaleryl carboximide **252** adds to the azodicarboxylate **253** giving direct access to the piperazine **254**. Hydrolysis of **254** with lithium hydroxide then liberates bis-Boc (3*R*)-piperazic acid **255**. A further example of nucleophilic amide additions to acyliminium ions is provided by Wasserman and co-workers[93] as part of a synthetic route to azadethiacephams. The hemi-aminal **256** liberates the iminium ion **257** on heating with pyridinium tosylate and subsequent cyclization then provides the bicyclic amidal **258**.

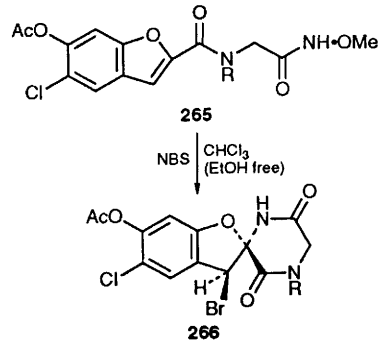


In the course of an impressive enantioselective synthesis of (−)-decarbamoylsaxitoxin, Hong and Kishi[94] have developed a remarkable trimolecular cyclization of the β-amino unsaturated ester of the aminocrotonate **259**, *R*-glyceraldehyde acetonide **261** and silicon tetraisothiocyanate **260** affording the cyclic thiourea **264** in 72% yield, **Scheme 15**. The reaction presumably proceeds by formation of the thiourea **262** which next undergoes a [3,3] cyclization, generating the zwitterion **263**. A proton shift then gives **264**.



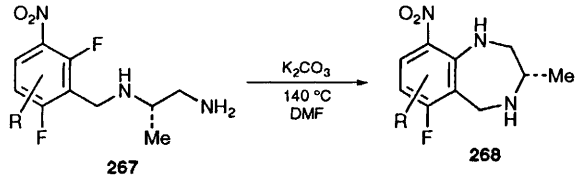
Scheme 15

Miknis and Williams[95] have shown that reaction of the benzofuran **265** with *N*-bromosuccinimide generates stereoselectively the spirodiketopiperazine **266**, an intermediate in the authors' completed synthesis of the fungal metabolite aspirochlorine.



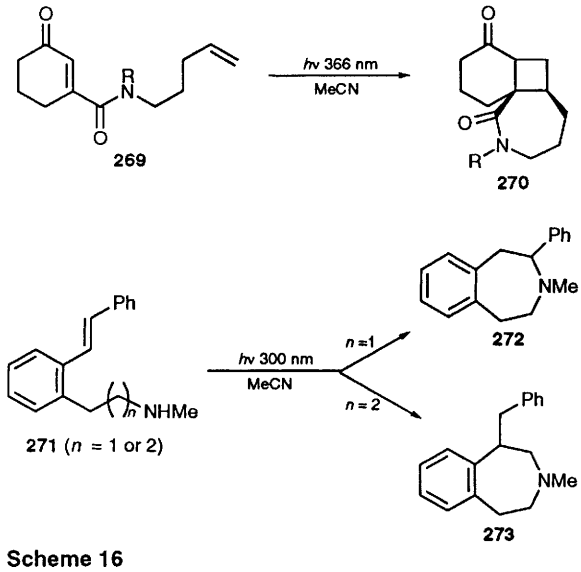
4.3 Seven-membered rings

As part of a programme to prepare analogues of the anti-HIV-1 agent TIBO, Parker and Coburn[96] have reported a regioselective synthesis of the benzodiazepines **268** by cyclization of the difluoronitrobenzenes **267**. No attack at the *para*-fluoro position is observed.



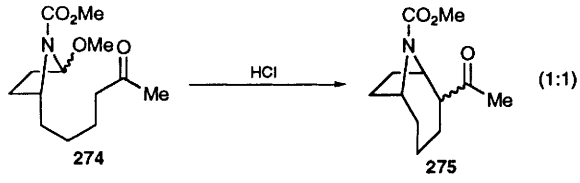
5 Seven-, eight-, and nine-membered rings

Two new azepane syntheses rely on photocyclization reactions. Thus, Piva and co-workers[97] have shown that photolysis of the vinylogous ketoamide **269** at 366 nm affords the tricyclic [2 + 2] cycloaddition product **270**. In a study of intramolecular stilbene amine photoadditions, Lewis and Reddy[98] have demonstrated that the substrates **271** show a clear preference for seven-membered rings formation regardless of amine side chain length. Thus photolysis at 300 nm leads to either **272** or **273** with no formation of six- or eight-membered by-products (**Scheme 16**).

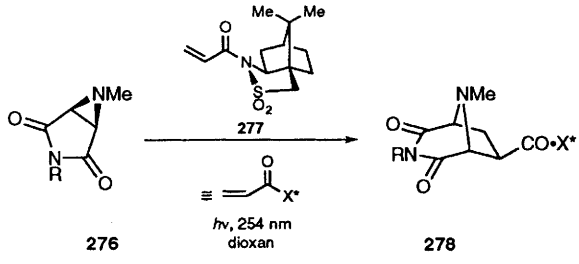


Scheme 16

Hydrogen chloride effects the cyclization of the keto-aminal **274** *via* an intermediate iminium ion, to provide the azepane **275** as a mixture of isomers.[99] The product **275** has then been used to complete a synthesis of (+)-anatoxin a.

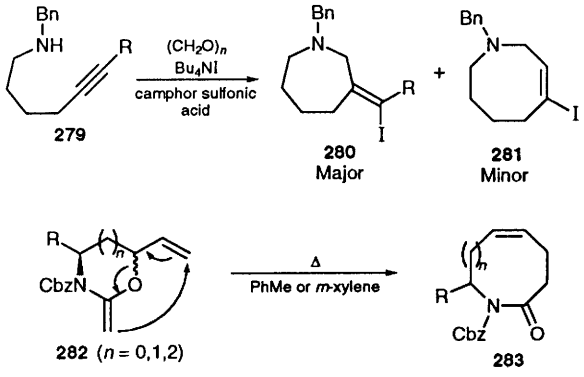


Garner and his group[100] have used a 1,3-dipolar cycloaddition reaction between the acryloyl sultam **277** and a dipole generated by photolysis of the aziridinylimide **276** to provide the adduct **278** in good yield. This chemistry forms the basis of an asymmetric synthesis of (−)-quinocarcin.

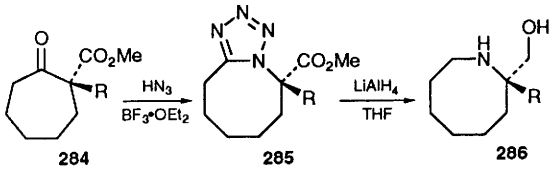


Overman *et al.* have established a useful, general route to medium-ring nitrogen heterocycles based on an iodide-promoted Mannich cyclization of alkynylamines such as **279**.[101] The product

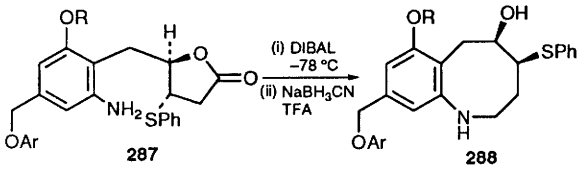
distribution favours the azepanes **280** over azocanes **281**. A general route to monocyclic medium-ring lactams has been reported by Holmes and co-workers.[102] The method relies on a Claisen rearrangement of the ketene aminals **282**, which are generated *in situ* by selenoxide elimination, to afford the lactams **283**. Yields are generally high for the assembly of seven-, eight-, and nine-membered rings.



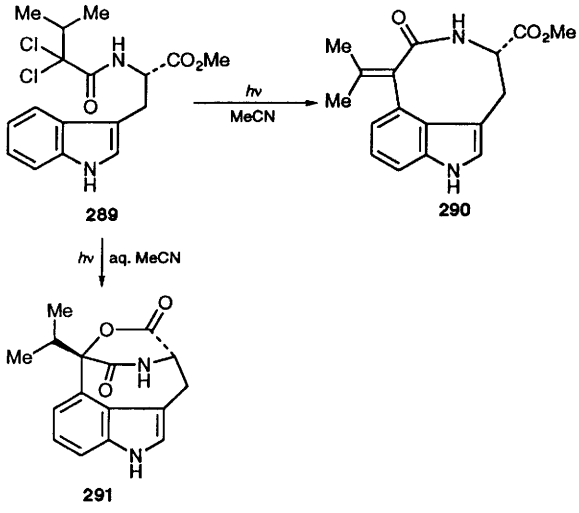
The reaction of optically active β-ketoesters such as **284** with hydrazoic acid and a Lewis acid generates the tetrazoloazocanes **285** *via* the Schmidt rearrangement.[103] The products **285** are then readily reduced by LAH to the homochiral azocane carbinols **286**.



As a key step in the synthesis of the fungal metabolite FR-900482, the lactone **287** was reduced to an intermediate aldehyde followed by a novel macrocyclic reductive alkylation to provide the benzazocane **288**.[104]



Finally, Moody and his group[105] have published full details of their synthesis of (−)-indolactam V. In the course of this work, the authors describe photocyclizations of the tryptophan-derived amide **289**. Photolysis in dry acetonitrile affords only the eight-membered lactam **290** but, in the presence of trace amounts of water, the major reaction product is the lactone **291**.



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