Saturated nitrogen heterocycles

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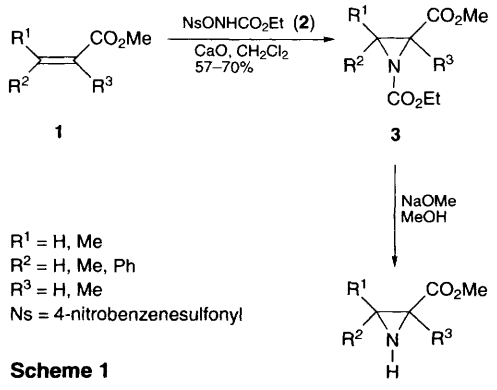
Reviewing the literature published in 1996
Continuing the coverage in *Contemporary Organic Synthesis*, 1996, **3**, 259

1 Introduction

This review covers the literature relating to saturated nitrogen heterocycles published in 1996. The classification of the chemistry described is similar to that described in the previous survey in *Contemporary Organic Synthesis*.[1]

2 Three-membered rings

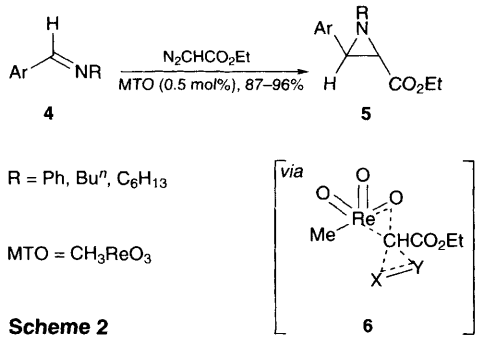
Aziridine-1,2-dicarboxylates **3** have been prepared by the addition of an excess of (ethoxycarbonyl)-nitrene (:NCO_2Et) to α,β-unsaturated esters **1** in 58–72% yield (**Scheme 1**).[2] The nitrene was



Scheme 1

conveniently generated from ethyl *N*-[(4-nitrophenylsulfonyl)oxy]carbamate **2** by α-elimination induced, crucially, by CaO or K_2CO_3; homogeneous bases such as triethylamine did not give the desired products. The ethoxycarbonyl protecting group was readily removed by treatment with sodium methoxide in methanol. When (1*R*, 2*S*, 5*R*)-menthyl *N*-[(4-nitrophenylsulfonyl)oxy]carbamate was used as a source of an enantiomerically pure nitrene, addition to **1** gave a 1:1 mixture of diastereomers, indicating that negligible asymmetric induction had taken place.

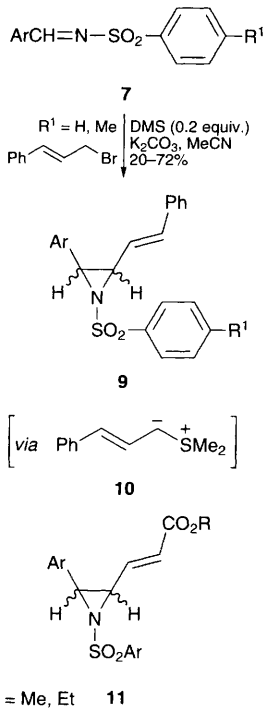
Espenson and Zhu have described the use of methylrhenium trioxide (MTO) to catalyse the addition of ethyl diazoacetate (EDA) to aromatic imines **4** (**Scheme 2**).[3] Addition of EDA and MTO (0.5 mol%) to the imine gave the aziridines **5** in 87–96% yield. Only the *trans* isomer was obtained, suggesting the intermediacy of species **6** in the reaction.



Scheme 2

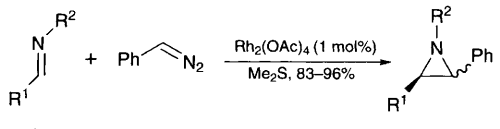
Li, Dai and Hou have described the preparation of (β-phenylvinyl) aziridines **9** by the reaction of *N*-sulfonylimines **7** and cinnamyl bromide **8** and K_2CO_3 in the presence of a catalytic amount of DMS (**Scheme 3**).[4] The reaction proceeds by attack of the sulfonium ylide **10** on imine **7** and gives a variable yield of the aziridine **9** (20–72%) as an approximately equimolar mixture of *cis* and *trans* isomers. This work was later extended to include the synthesis of *N*-sulfonyl-2-[(*E*)-(2-alkoxycarbonyl)-ethenyl]-3-arylaziridines **11** by the same reaction.[5] The *cis*:*trans* ratio of the products was improved to 8:1 by using a stronger base [$KN(SiMe_3)_2$] at −78 °C.

Aggarwal has described the synthesis of aziridines **13** from imines **12**, by a reaction also mediated by a sulfonium ylide (**Scheme 4**).[6] However, the sulfonium ylides are generated in this instance by the reaction of an aryldiazomethane with rhodium acetate in the presence of dimethyl sulfide. DMS was an essential additive, proving that aziridine



Scheme 3

formation was not a result of a simple metal carbenoid process. In all cases, a mixture of *trans* and *cis* aziridines (ratio = 3:1) was obtained. An SES [(β-trimethylsilyl)ethylsulfonyl] group was also found to be an effective replacement for the ubiquitous, but notoriously robust, *N*-tosyl protecting group. Other diazo compounds (*N*,*N*-diethyldiazoacetamide and ethyl diazoacetate) were found to undergo the aziridination reaction in similarly high

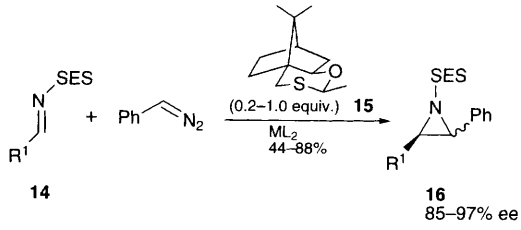


R^1 = Ph, *p*-ClC_6H_4, *p*-MeC_6H_4
R^2 = Ts, DPP, SES

DPP = *N*-diphenylphosphinyl
SES = β-(trimethylsilyl)ethanesulfonyl

Scheme 4

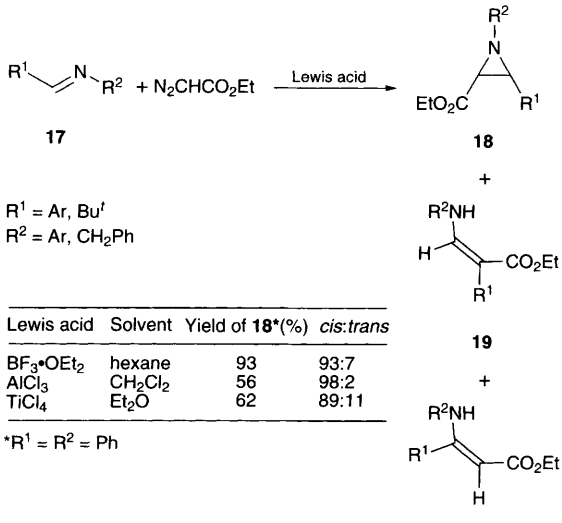
yields. The diazoamide gave predominantly the *trans* aziridine (2:1), and the diazo ester predominantly the *cis* aziridine; presumably results of kinetic and thermodynamic control respectively. These results led to the development of the first catalytic asymmetric aziridination of *N*-SES protected aromatic imines (**Scheme 5**). In the presence of sulfide **15** (0.2–1.0 equiv.), derived from (+)-camphorsulfonyl chloride, ML_2 (M = Rh, Cu) (L = OAc or acac) and phenyldiazomethane, aziridines **16** were obtained in 44–88% yield as a 3:1 mixture of *trans* and *cis* isomers in high enantiomeric excess (85–97% ee).



R^1 = Ph, *p*-ClC_6H_4, *p*-MeC_6H_4
M = Rh, Cu
L = OAc, acac

Scheme 5

Brookhart, Templeton and co-workers have described a synthesis of aziridines **18** from ethyl diazoacetate and various imines catalysed by several common Lewis acids (**Scheme 6**).[7] The formation of



R^1 = Ar, Bu^t
R^2 = Ar, CH_2Ph

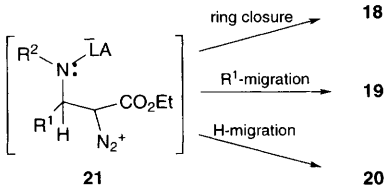
Lewis acid	Solvent	Yield of **18***(%)	*cis*:*trans*
BF_3•OEt_2	hexane	93	93:7
$AlCl_3$	CH_2Cl_2	56	98:2
$TiCl_4$	Et_2O	62	89:11

*R^1 = R^2 = Ph

Scheme 6

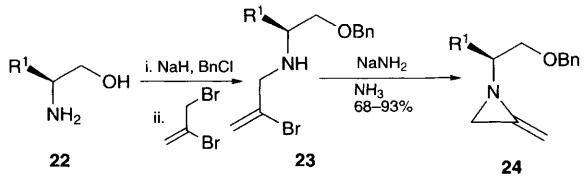
vinylogous carbamates **19** and **20** was a major competing side reaction. Best results were obtained by reducing the amount of Lewis acid ($BF_3 \cdot OEt_2$) (0.1 equiv.) and using hexane as the solvent. $AlCl_3$ and $TiCl_4$ gave results comparable to $BF_3 \cdot OEt_2$. The mechanism for the production of the aziridines was

proposed to be non-carbenoid, instead involving nucleophilic attack of ethyl diazoacetate onto the Lewis acid-complexed imine, to give **21** followed by ring closure and loss of nitrogen. The side-products **19** and **20** result from 1,2-migration of either the R^1 or the H substituent from **21** (**Scheme 7**).



Scheme 7

Shipman and co-workers have described the enantiospecific synthesis of chiral nonracemic methyleneaziridines **24** from homochiral β-amino alcohols **22** (**Scheme 8**).[8] Reaction of *O*-benzyl protected (*S*)-valinol **22** ($R^1 = Pr^i$) with 2,3-dibromopropene and cyclization with $NaNH_2$–NH_3 gave the methyleneaziridine **24** in 77% overall yield *via* **23**. No appreciable racemization occurred in the cyclization. Methyleneaziridines are potentially useful intermediates in asymmetric synthesis.

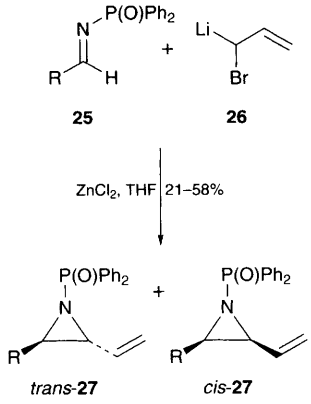


R^1 = Me, Ph, Pr^i, Me_2CHCH_2

Scheme 8

Sweeney and co-workers have described the carbenoid-like, $ZnCl_2$-catalysed Darzens-type addition of α-bromoallyllithium **26** to *N*-diphenylphosphinyl aldimines **25** (**Scheme 9**).[9] The reaction produced the expected aziridine **27** in variable yield, depending on the nature of R, but with good diastereoselectivity. The vinylaziridines obtained by this route underwent reasonably efficient and highly regioselective S_N2' reaction with a wide variety of diverse nucleophiles.

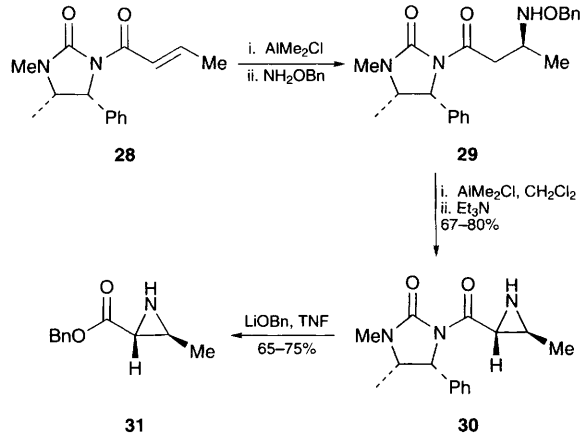
Cardillo and co-workers have described a practical, auxiliary-based approach to the synthesis of enantiomerically pure alkyl aziridine-2-carboxylates (**Scheme 10**).[10] Addition of *O*-benzylhydroxylamine to **28**, derived from Helmchen's auxiliary,



R	Yield (%)	*cis*:*trans*
Ph	58	1:10
4-BrC_6H_4	30	1:10
Bu^t	21	5:1

Scheme 9

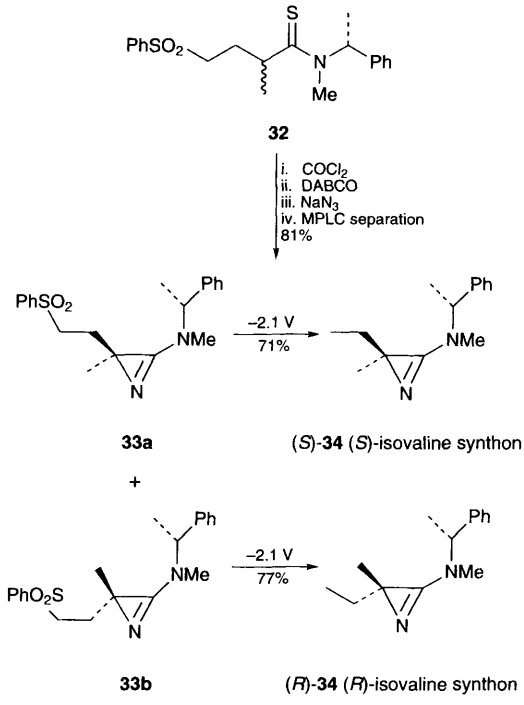
gives predominantly **29** or its diastereomer, depending on the Lewis acid used. Once purified to a single diastereomer, treatment with triethylamine and $AlMe_2Cl$ in dichloromethane gave the aziridine **30** in excellent yield as a single (*trans*) diastereomer. Significantly, the chiral auxiliary could be removed with lithium benzyloxide to give the corresponding benzyl ester **31**, without appreciable racemization.



Scheme 10

Heimgartner and Bucher have described the synthesis of optically active 3-amino-2*H*-azirines (*S*)-**34** and (*R*)-**34** (**Scheme 11**).[11] Sequential treatment of the thioamide **32** with phosgene, DABCO and sodium azide gave a separable mixture of 2*H*-azirines **33a** and **33b**. Separation by MPLC and electrochemical cleavage of the phenylsulfonyl group gave (*S*)-**34** and (*R*)-**34**. These compounds

were subsequently used as isovaline synthons in peptide coupling reactions with amino acids.

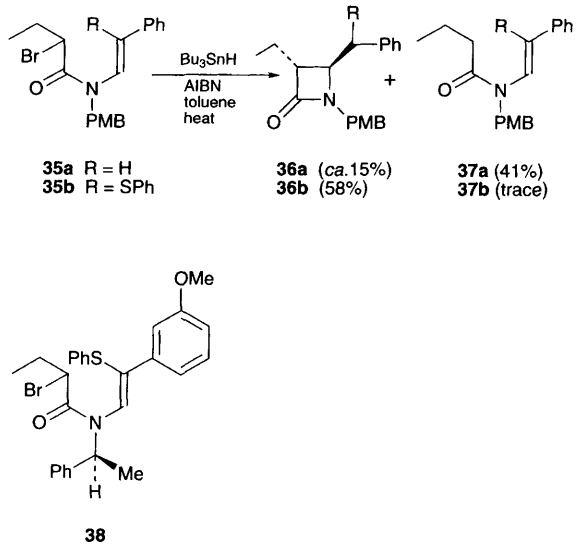


Scheme 11

3 Four-membered rings

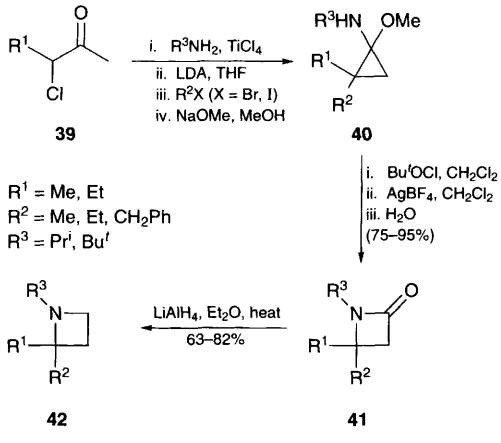
The ring strain energy in an isolated β-lactam has been determined experimentally for the first time by Abboud and co-workers.[12] The value of 119.4 ± 5.7 kJmol^{-1} is in excellent agreement with calculated values.

The synthesis of β-lactams by the radical cyclization of *N*-vinylic α-bromo amides has been described by Ishibashi, Ikeda and co-workers (**Scheme 12**).[13] Initial studies were carried out on **35a**, but only a small amount of the desired β-lactam **36a** was formed, together with the γ-lactam formed by 5-*endo-trig* cyclization and the simple reduction product **37a**. However, by strategically placing a radical-stabilizing phenylthio group at the terminus of the double bond (compound **35b**), the same reaction proceeded in much better yield to give the β-lactam **37b** in 58% yield, with much reduced amounts of the two side-products. Having served its purpose, the phenylthio group was removed from **37b** and the product converted into an intermediate for the synthesis of the carbapenem antibiotics (±)-PS-5 and (±)-thienamycin. In an attempt to make this same intermediate optically active, the radical cyclization was performed on **38**, containing the (*S*)-1-phenethylamine chiral auxiliary. However, the diastereoselectivity obtained was only modest (ratio of desulfurized β-lactams = 68:32).



Scheme 12

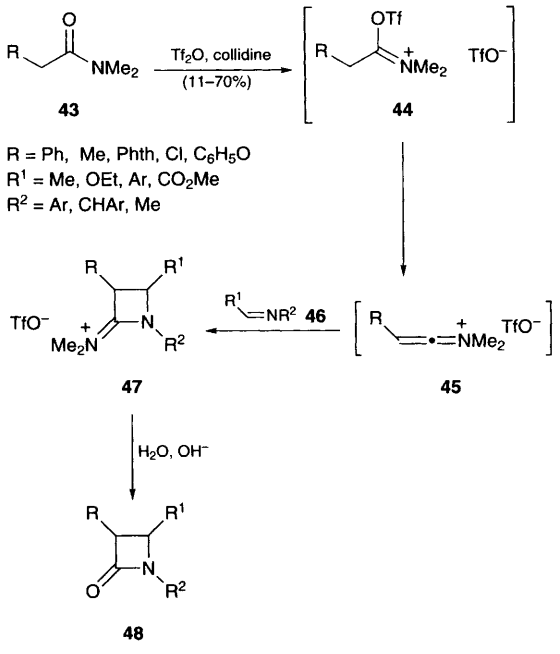
De Kimpe and co-workers have described the interesting ring enlargement transformation of 2,2-disubstituted 1-methoxycyclopropylamines to the rare 1,4,4-trialkyl β-lactams (**Scheme 13**).[14] Imination of α-chloroketone **39** with an amine and $TiCl_4$, followed by a highly regioselective alkylation and NaOMe-mediated Favorskii-type reaction, gave the cyclopropane **40** in good overall yield. The key ring enlargement was achieved by *N*-chlorination with *tert*-butyl hypochlorite, followed by ring expansion with $AgBF_4$ and hydrolysis, to give the β-lactams **41** in generally good yield (75–95%). Only the expected regioisomer, resulting from migration of the *gem*-disubstituted carbon centre, was obtained. Attempted reduction of β-lactams with $LiAlH_4$ usually results in cleavage to acyclic amino alcohols, but in this case the azetidines **42** were obtained in 63–82% yield.



Scheme 13

In a thorough investigation of the chemistry of 2-azetidiniminium salts, Battaglia and co-workers

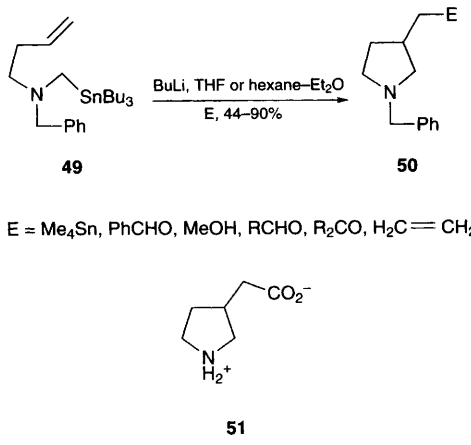
have described a novel synthesis of β-lactams **48** from *N*,*N*-disubstituted amides **43** and imines **46** (**Scheme 14**).[15] It is proposed that treatment of the amide **43** with trifluoromethanesulfonic anhydride in the presence of collidine results in the formation of a keteniminium trifluoromethanesulfonate (triflate) salt **45** *via* the α-triflyliminium triflate **44**. This electrophile reacts with the imine partner to give the 2-azetidiniminium triflate **47**, hydrolysis of which gives the β-lactam **48** in variable yield. The reaction yielded a mixture of *cis* and *trans* products, generally in favour of the *cis* product, but dependent on the steric and electronic nature of the substituents on the imine (R^1 and R^2), but substantially independent of those on the amide (R).



Scheme 14

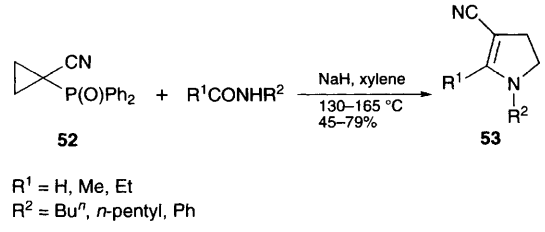
4 Five-membered rings

The synthesis of 3-alkylpyrrolidines by the anionic cyclization of α-aminostannanes has been reported by Coldham and Hufton (**Scheme 15**).[16] Treatment of stannane **49** (easily prepared from the homoallylic amine and ICH_2SnBu_3) with butyllithium and an electrophile gives the 3-substituted pyrrolidine **50** in 44–90% yield. A number of useful electrophiles (aldehydes, ketones, chloroformates, tetraalkylstannanes and alkyl halides) were used. This strategy was used to prepare (±)-**51**, a known γ-aminobutyric acid uptake inhibitor in just four steps from commercially available starting materials.



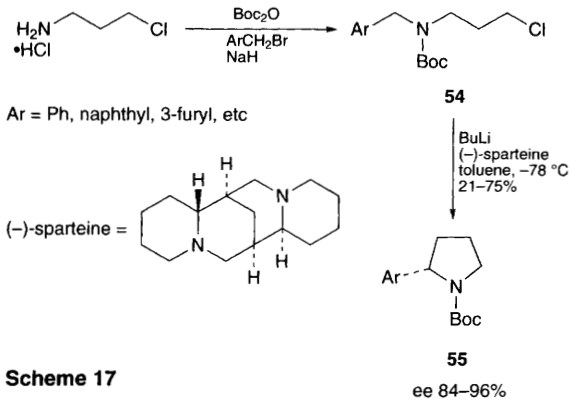
Scheme 15

Zhang and Zhao have described the synthesis of dihydropyrroles from cyanocyclopropylphosphine oxides (**Scheme 16**).[17] The reaction of (1-cyanocyclopropyl)diphenylphosphine oxide (**52**) with the sodium salt of a secondary amide at 130–165 °C in xylene gives the 2,3-dihydropyrroles **53** in good yields (45–79%). Primary amides and amides with bulky *N*-substituents did not afford the desired products, instead resulting in coupled but uncyclized products.



Scheme 16

Beak and co-workers[18] (**Scheme 17**) have described the synthesis of alkyl pyrrolidines by anionic cyclizations in a manner similar to that of Coldham and Hufton. Treatment of γ-chloro amines **54** with *n*- or *s*-butyllithium and (−)-sparteine in toluene at −78 °C results in the formation of (*S*)-2-aryl-Boc-pyrrolidines **55** in good yields (20–70%) and excellent ee (generally 84–96%). The reaction tolerates many substituted and heteroaromatic groups, with the lone exception of Ar=4-MeO, which curiously gave the product **55** in only 3% ee. The reaction can clearly involve either asymmetric deprotonation or asymmetric substitution on an already cyclized intermediate. Through deuterium labelling studies, it was shown that the pathway is asymmetric deprotonation, to form an enantiomerically enriched organolithium intermediate that cyclizes faster than it racemizes.



Scheme 17

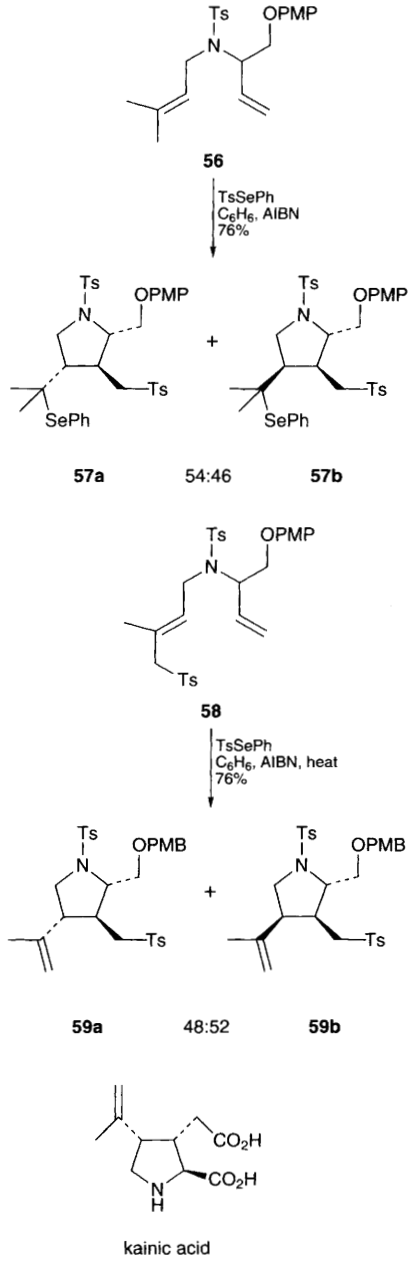
An approach to the kainic acid skeleton *via* radical cyclization of 4-aza-1,6-dienes has been reported by Bertrand, Nouguier and Gastaldi (**Scheme 18**).[19] Reaction of diene **56**, with TsSePh–AIBN in refluxing benzene gave the pyrrolidines **57a** and **57b** in approximately equimolar amounts, an unusual outcome considering that the classical radical cyclization of simple hex-5-enyl radicals normally greatly favours the formation of *cis* products. Since the phenylseleno group could not efficiently be converted into the kainic acid isopropenyl unit by oxidative elimination, the diene **56** was modified to **58**, incorporating an allylic sulfone, which suffered elimination under the reaction conditions to give **59a/b** (*ca.* 1:1 mixture) following radical cyclization.

Bachi and co-workers have described an alternative radical-based route to the kainic acid skeleton (**Scheme 19**).[20] Treatment of isonitrile **60** with ethanethiol and AIBN in toluene resulted in the formation of **61** *via* an imidoyl radical in 77% yield. Alternatively, a similar radical could be generated by treatment of the related isothiocyanate **63** with Bu_3SnH and ACN (a radical initiator), to give **64a/b** in the ratio 1.4:1 (yield >92%). Both **62** and **64a** were converted to kainic acid.

A radical cyclization of an α-amino radical onto an α,β-unsaturated ester has been used to construct pyrrolidines (**Scheme 20**).[21] The generation of the α-amino radicals in this case was achieved by a novel condensation of an aldehyde (R^3CHO) with benzotriazole and a homoallylic secondary amine **65**. The resulting aminoalkyl benzotriazole **66** is decomposed with SmI_2 to yield the α-amino radical which cyclizes in a 5-*exo*-*trig* fashion to give the 3-mono ($R^1=R^3=H$) or 2,3-di-substituted ($R^1=H$) pyrrolidine **67** in good yield (51–70%), but only when $R^2=CO_2Me$. Without this activating group, only products resulting from simple reduction or dimerization were obtained. The cyclized products were formed with modest diastereoselectivity (3:1–1:3, depending on R^3).

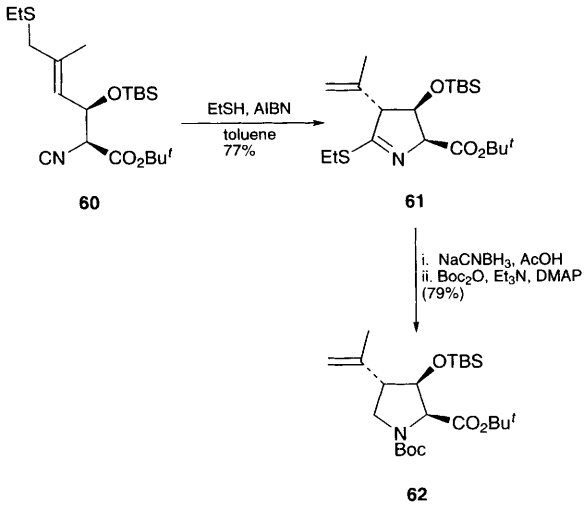
Harwood and Lilley have described a tandem azomethine ylide cycloaddition–Pummerer rearrangement strategy for the synthesis of enantiomerically pure 5-(hydroxymethyl)prolines (**Scheme 21**).[22] Starting with (5*S*)-5-phenylmorpholinone (**68**) as a chiral template and 2-(prop-2-enylthio)ethanal, **69** was produced *via* the azomethine ylide. Oxidation with MCPBA and sodium periodate gave a single diastereomeric sulfoxide which underwent Pummerer rearrangement with trifluoroacetic anhydride–benzyl alcohol to give **70** in 38% yield. Desulfurization and removal of the chiral template atoms then gave the enantiomerically pure amino acid **71**.

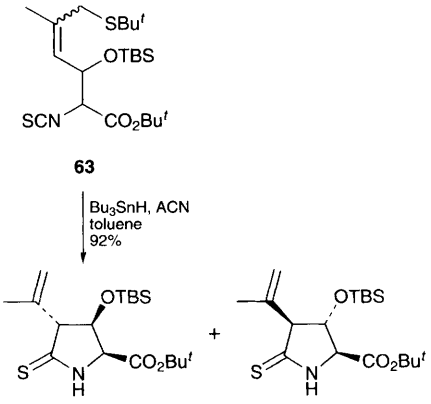
Overman and Tellew have reported the remarkably efficient synthesis of the 2,5-diazatricyclo-[5.2.1.$0^{4,10}$]decane ring system through application of an intramolecular azomethine ylide cycloaddition (**Scheme 22**).[23] Treatment of **72** and **73** with potassium *tert*-butoxide gave the adduct **74**, which, on refluxing in xylene with ammonium chloride (to



PMB = *p*-methoxybenzyl

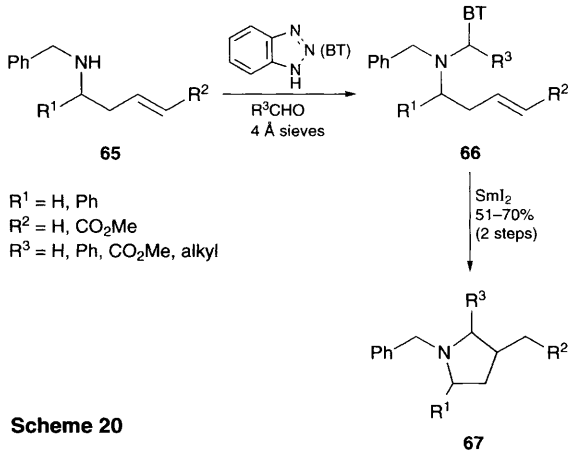
Scheme 18



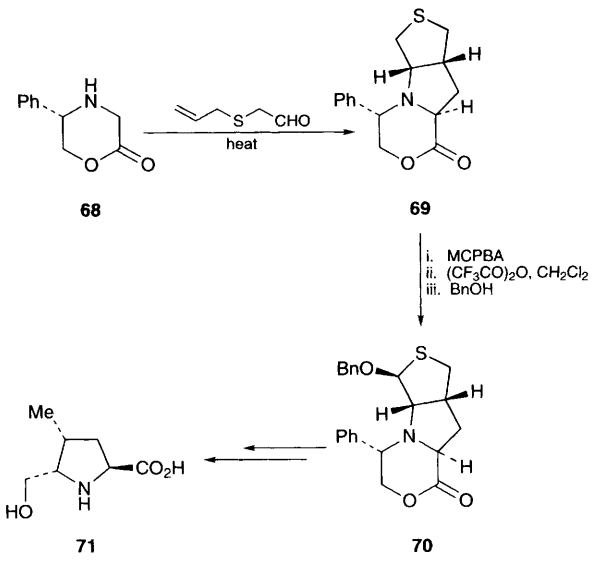


ACN = 1, 1′-azobis(cyclohexanecarbonitrile)

Scheme 19

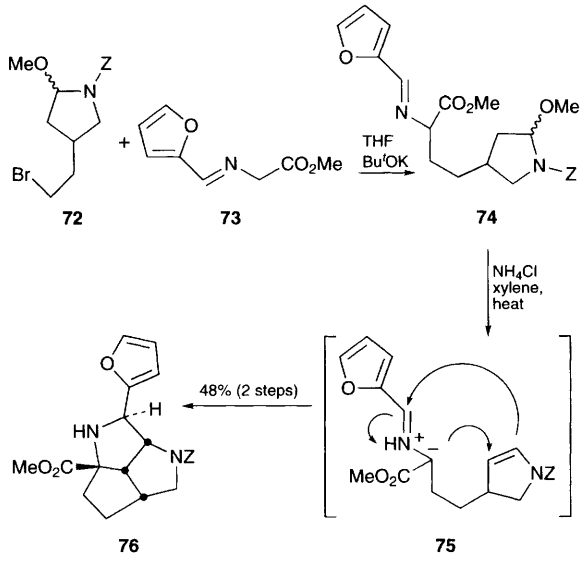


Scheme 20



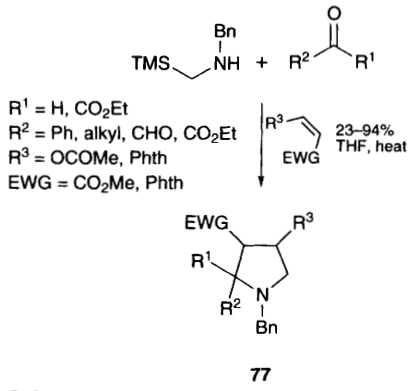
Scheme 21

catalyse elimination of methanol from the hemiaminal portion) gave **76** in 48% yield as a single regio- and all-*cis* stereo-isomer, *via* azomethine ylide **75**. The intramolecular nature of the reaction accounts for the observed regio- and stereochemistry and presumably the ease with which such an electron rich dipolarophile undergoes cycloaddition with the azomethine ylide.



Scheme 22

Torii and coworkers have described a particularly practical application of azomethine ylide methodology (**Scheme 23**).[24] Reaction of *N*-(trimethylsilylmethyl)benzylamine, a carbonyl compound and a dipolarophile in THF gave the pyrrolidine derivative **77** *via* the azomethine ylide. A number of structurally diverse aldehydes and ketones and dipolarophiles (including alkynes) were used. Such



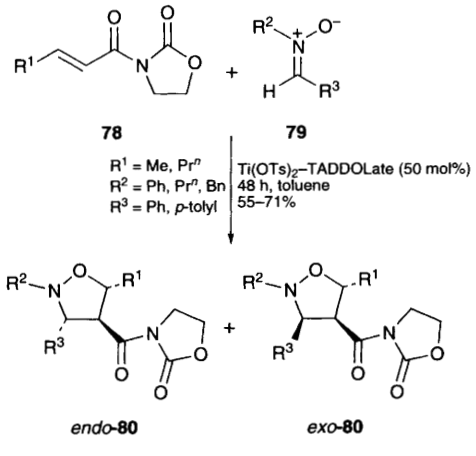
Scheme 23

multi-component reactions have potential in the synthesis of combinatorial libraries.

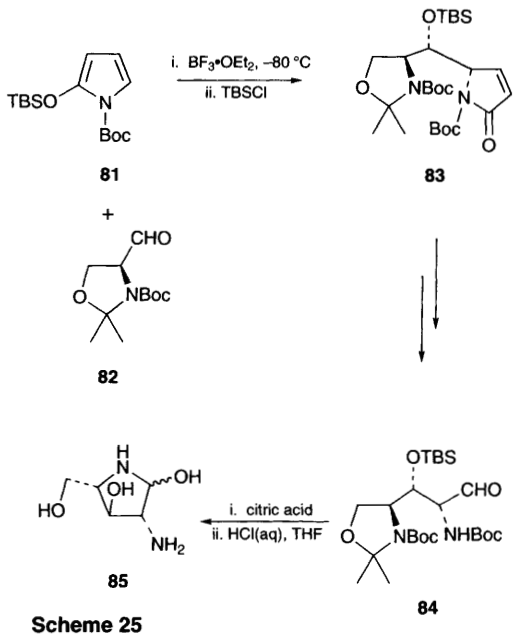
Jørgensen and co-workers have described an enantio- and diastereo-selective nitrone–alkene 1,3-dipolar cycloaddition reaction catalysed by the modified Seebach catalyst, $Ti(OTs)_2$ TADDOLate (TADDOL = α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol) (**Scheme 24**).[25] Best results (*endo*:*exo* ratio >95:5, ee of *endo* product = 93%) are obtained with the acrylate **78** (R = Me) and nitrone **79** ($R^2 = R^3 = Ph$). Indeed, with a variety of other substrates, the *endo*:*exo* ratio is always greater than 95:5, but the ee is heavily substrate dependent.

Rassu, Casiraghi and co-workers have described the synthesis of some diaza sugars, utilizing a Mukaiyama aldol reaction as the key step (**Scheme 25**).[26] Reaction of *N*-Boc-2-OTBS-pyrrole **81** with the Garner aldehyde **82** in the presence of $BF_3 \cdot OEt_2$ gave a 3:1 mixture of *syn*:*anti* aldol adducts in a total 80% yield, **83** being the major one. The aldol adducts were separated and converted separately by conventional means to 2,4-diamino-2,4-dideoxy-L-arabinose **85** and the corresponding ribose (from the minor *anti* aldol adduct).

Enantiomerically pure 3-substituted pyrrolidines have been synthesized by Pedrosa and co-workers using an auxiliary based strategy (**Scheme 26**).[27]



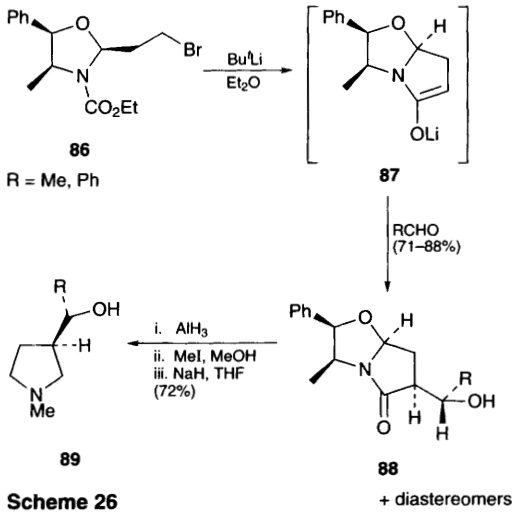
Scheme 24



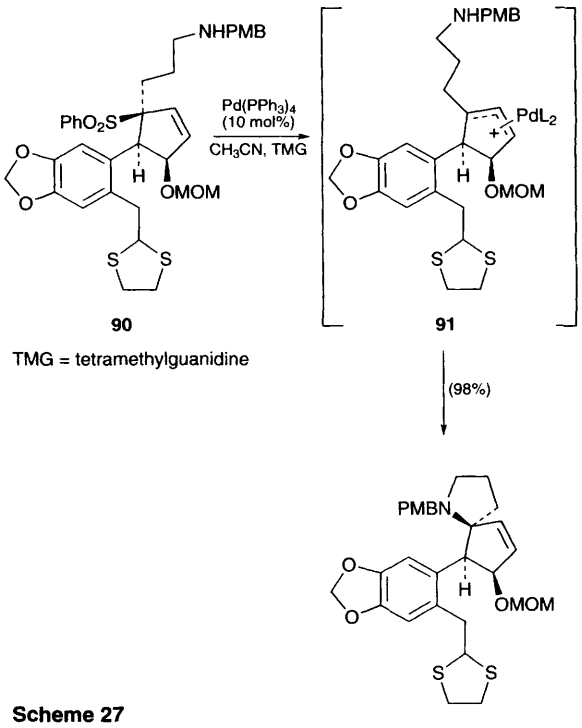
Scheme 25

Starting from the norephedrine-derived oxazolidine **86**, lithiation and addition of an aldehyde gave the bicyclic lactam **88**, *via* **87**. Although the chemical yields were excellent (71–88%), the diastereoselectivity was modest (*ca.* 2:1). Separation of the major diastereomer, reductive cleavage of the chiral auxiliary and subsequent transformations gave the 3-substituted pyrrolidine **89**.

The intramolecular addition of a pendant amino group to a π-allylpalladium intermediate was a key step in the synthesis of the spirocyclic ring system of the anticancer agent cephalotaxine (**Scheme 27**).[28] The π-allylpalladium complex **91**, which was formed by loss of the phenylsulfonyl group from **90** in the presence of palladium tetrakis(triphenylphosphine) and tetramethylguanidine (TMG) in refluxing acetonitrile, underwent spirocyclization to give selectively **92**. TMG was far superior to other bases, a result thought to be in part due to suppression of unwanted β-hydride elimination of **91**.



Scheme 26



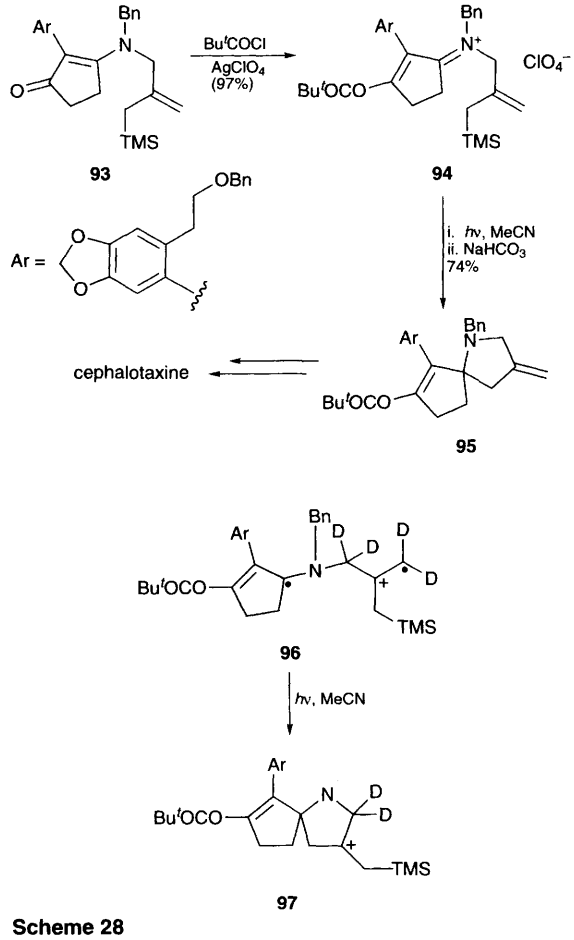
Scheme 27

Two other interesting strategies for the preparation of cephalotaxine have been disclosed by Mariano and co-workers (**Scheme 28**).[29] The first strategy involves a single electron transfer promoted photocyclization of the aryl-substituted silylallyliminium salt **94** (generated from **93**) to generate **95**. The reaction gave racemic **95** in 74% yield based on one recycle (47% conversion). The reaction is proposed to go by two separate pathways as shown by deuterium-labelling, the main one involving cation diradical cyclization of **96** to **97**. Mariano's alternative route for the synthesis of the cephalotaxine skeleton involved preparation of the ten-membered cyclic amine **100** (by conventional means from **98** and **99**) (**Scheme 29**) followed by TMSOTf-promoted transannular cyclization to give **101**, a previously established intermediate to the natural product.

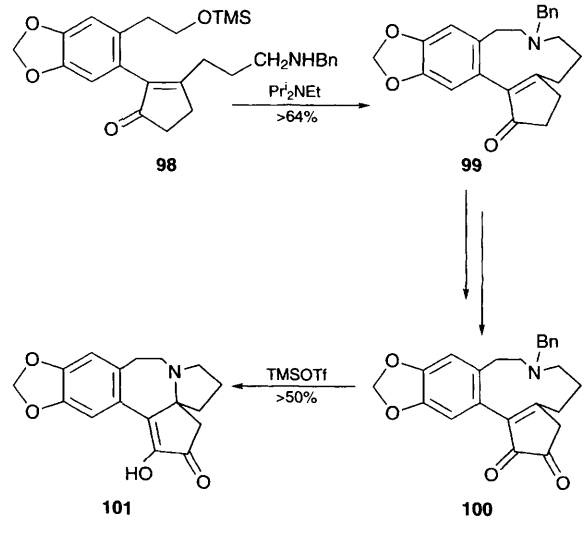
Two Michael addition reactions were used by Sosnicki and Liebscher to construct pyrrolidin-2-ylidene carboxylates (**Scheme 30**).[30] The first, addition of nitromethane anion to the α,β-unsaturated thioamide **102**, gave racemic **103**, following an alkylative Eschenmoser sulfur contraction reaction. Selective reduction of the nitro group with hydrogen and Raney Ni gave the final product **104** by a Michael addition–elimination sequence. A similar sequence of reactions from thiolactam **105** gave the disubstituted pyrrolidine **106**.

A novel tandem Michael–Henry reaction has been used to prepare 2-hydroxymethyl-3-hydroxy-4-nitro-pyrrolidines (**Scheme 31**).[31] Treatment of **107** (derived from L-serine), with $BzOCH_2CH_2NO_2$ (a precursor of nitroethylene) gave the Michael adduct, which, on oxidation, underwent a Henry (nitro-aldol) reaction to give a diastereomeric mixture of piperidines **108a/b** (ratio 3:1). Standard functional group interconversions on the major isomer gave **109**, a natural product isolated from *Castanospermum australe*.

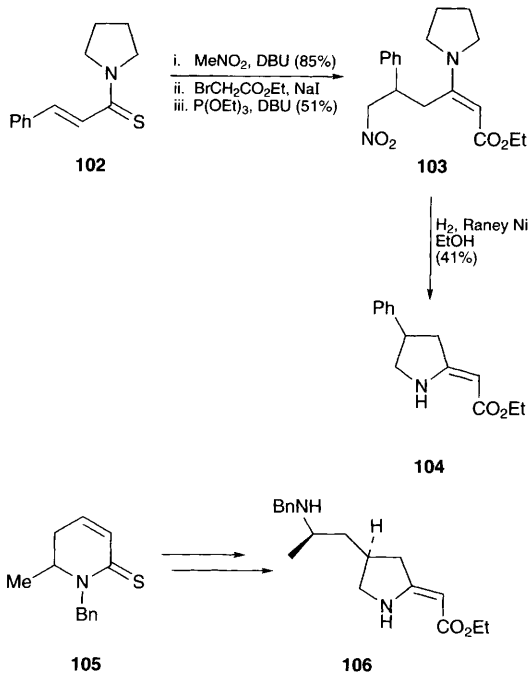
Mann and co-workers have described the regioselective ring-opening of phenylaziridines with allylsilanes promoted by $BF_3 \cdot OEt_2$ (**Scheme 32**).[32] For



Scheme 28



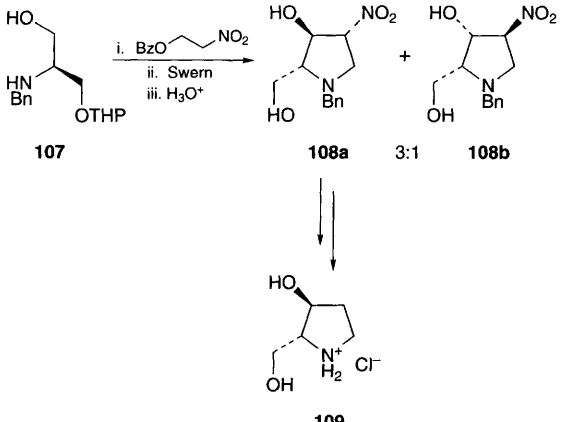
Scheme 29



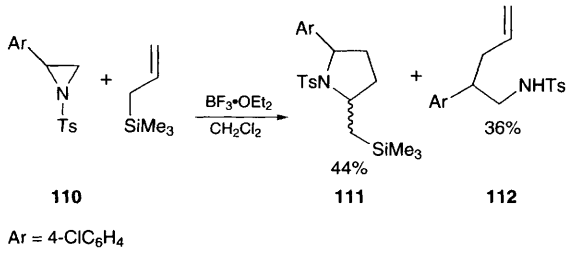
Scheme 30

example, **111** was obtained in 44% yield (as a 1:1 mixture of *cis*:*trans* isomers) from **110** and trimethylallylsilane, together with a lesser amount of the side product **112**. The reaction proceeds presumably by a simple S_E2' mechanism and a stabilized β-silyl cation intermediate.

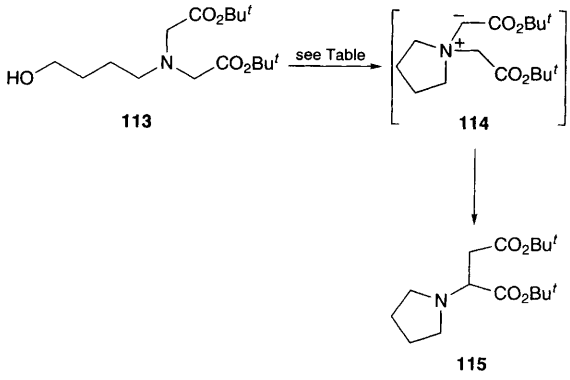
A serendipitous synthesis of pyrrolidines of type **115** has been described by Walker (**Scheme 33**).[33]



Scheme 31



Scheme 32



Conditions	Yield of **115**(%)
PPh_3 (1.0 equiv.), DEAD (1.0 equiv.)	40
Bu_3P (2.2 equiv.), ADDP (2.2 equiv.)	77

ADDP = 1,1′-(azodicarbonyl)dipiperidine

Scheme 33

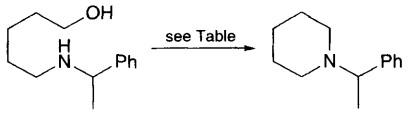
Under standard Mitsunobu conditions (PPh_3, DEAD), **113** is converted into **115** in 40% yield. Subsequent optimization (Bu_3P, ADDP) increased this to 77%. The compound arises through Stevens rearrangement of the putative species **114**, formed initially in the Mitsunobu reaction.

5 Six-membered rings

In studies on efficient use of the Mitsunobu reaction to synthesize heterocycles, Tsunoda and co-workers have described a synthesis of piperidines, including the natural product (+)-α-skytanthine (**Scheme 34**).[34] In a simple case (**116**→**117**), classical Mitsunobu-type reagents were found to be inferior to two new phosphorane reagents, cyanomethylene-tributyl- and -trimethyl-phosphorane (CMBP and CMMP). This was also true for the more demanding substrate (**118**) required for the synthesis of the natural product. In refluxing benzene, CMMP effected the formation of piperidines **119a** and **119b** in 81% overall yield from **118** in the ratio 92:8. The major isomer **119a** was subsequently converted to (+)-α-skytanthine.

Treatment of γ,δ-unsaturated aldimines **120** with bromine leads to 5-(bromomethyl)pyrrolin-1-ium bromides **121**, which on treatment with a sodium alkoxide suffer rearrangement to give the heavily functionalized piperidines **123**, presumably through the exotic aziridinium ion **122** (**Scheme 35**).[35] The *N*,*O*-aminal functionality can be readily reduced with sodium borohydride to give the piperidines **124**. However, on heating (preparative gas chromatography), an unusual rearrangement occurred that led to the formation of the 3-ketopiperidines **125**.

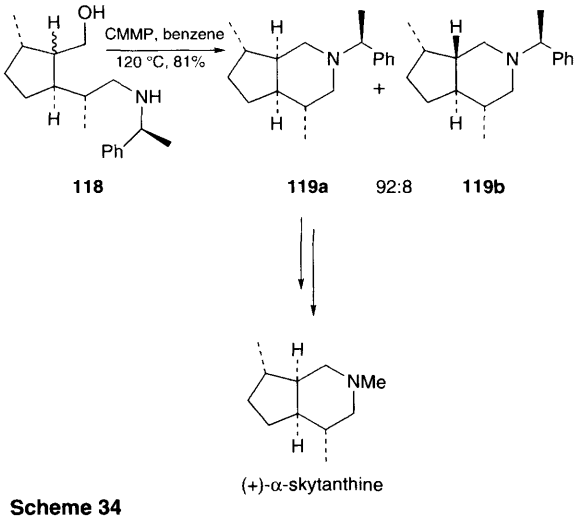
The synthesis of some piperidines by the aza[2,3]-Wittig rearrangement of certain vinylaziridines has been described by Somfai and co-workers (**Scheme 36**).[36] On treating the vinylaziridine **126** with base, a mixture of products was obtained which was dependent on the nature of the base and the anion



116 117

Conditions		Yield of **117** (%)
DEAD–PPh_3	(25 °C)	43
DHTD–PBu_3	(25 °C)	27
CMBP	(120 °C)	83
CMMP	(120 °C)	89

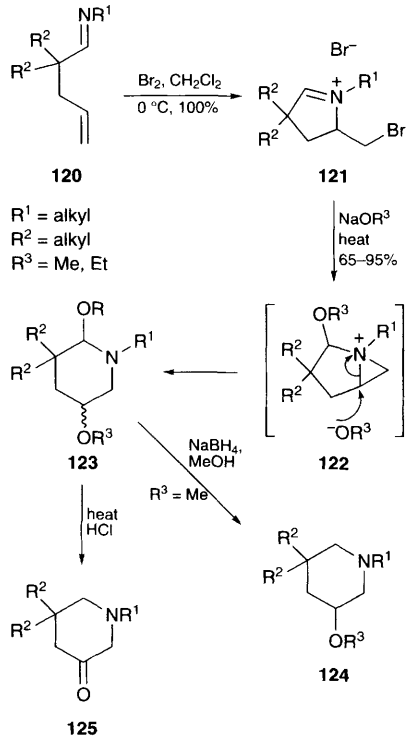
DHTD = 4,7-dimethyl-3,4,5,6,7,8-hexahydro-1,2,4,7-tetrazocine-3,8-dione



118 **119a** 92:8 **119b**

(+)-α-skytanthine

Scheme 34



120 **121**

R^1 = alkyl
R^2 = alkyl
R^3 = Me, Et

123 **122** **124** **125**

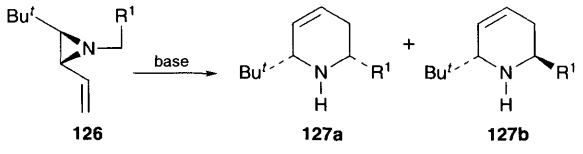
Scheme 35

stabilizing group (R^1) on the aziridine. Best results were obtained with $R^1 = CO_2Bu^t$ and LDA as the base; these gave rise to exclusively the *cis* diastereomer **127a** in 95% yield. These conditions were used to introduce a methyl substituent at the C-3 position of piperidine **130** by appropriately substituting the alkene in the substrate **129**. The aza[2,3]-Wittig rearrangement is stereospecific, so the stereochemistry at C-3 is completely determined by the geometry of the double bond in the starting material. The main limitation of this method would appear to be the synthesis of the aziridine starting materials, because in the present work they were obtained from epoxy alcohols by a multi-step sequence.

An intermolecular Mannich reaction has been used to prepare 2,3,4-substituted piperidines (**Scheme 37**).[37] Condensation of the diene–iron tricarbonyl complex **131** and amine **132** gave the imine **133**, which underwent a diastereoselective cyclization to give **134a** and **134b** in 58% and 7% yields respectively, each as a mixture of epimers at the 3-position. Removal of the iron tricarbonyl moiety and hydrolysis–reduction of the 4-ketal gave the natural products (±)-dienomycin C (from **134a**) and (±)-4-*epi*-dienomycin C.

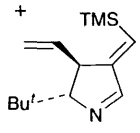
The condensation–rearrangement reaction between a reducing sugar and an amine – the Amadori reaction – has been used by Guzi and Macdonald to synthesize **136** (an intermediate in the synthesis of novel topoisomerase II inhibitors) (**Scheme 38**).[38] The key transformation involves heating **135** with TsOH in toluene at reflux to obtain **136** in 82% yield.

Comins has described a method of functionalization of a pyridine to produce chiral *N*-acyl-2,3-dihydro-4-pyridones (**Scheme 39**).[39] Treatment of



126 **127a** **127b**

R^1	Base	Yield (%) of **127a**	**127b**	**128**
CO_2Bu^t	LDA	95		
CN	$KN(SiMe_3)_2$	69	11	
C≡CTMS	Bu^sLi	29	42	24



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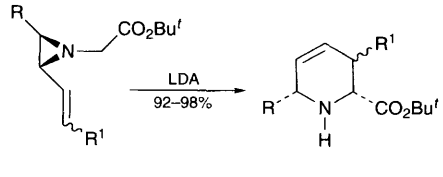
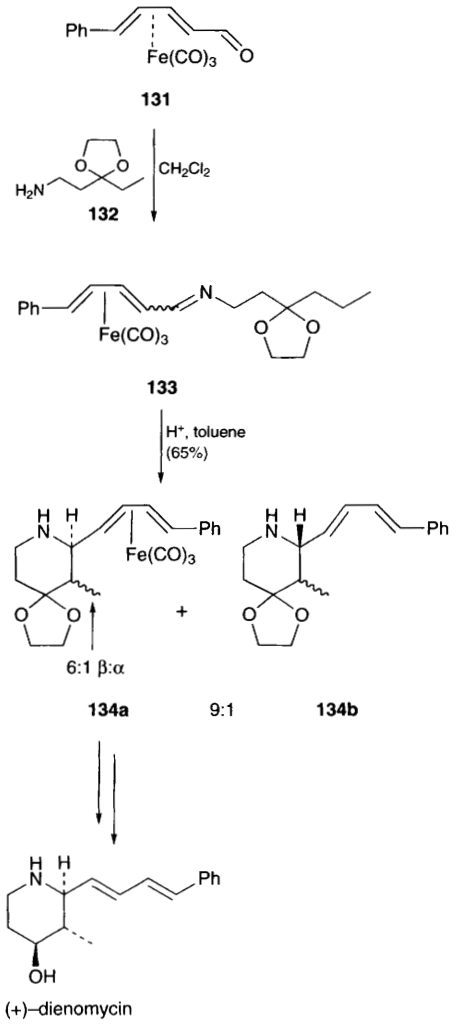


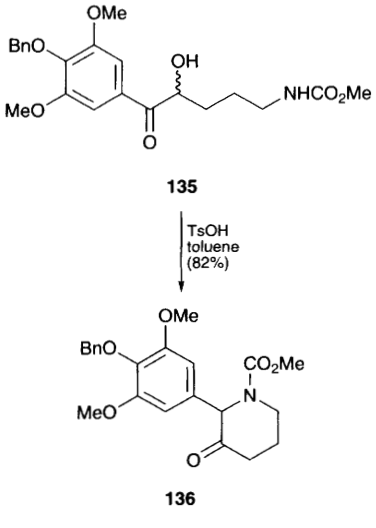
129 **130**

R^1 = H, α-Me, β-Me
R = alkyl

Scheme 36

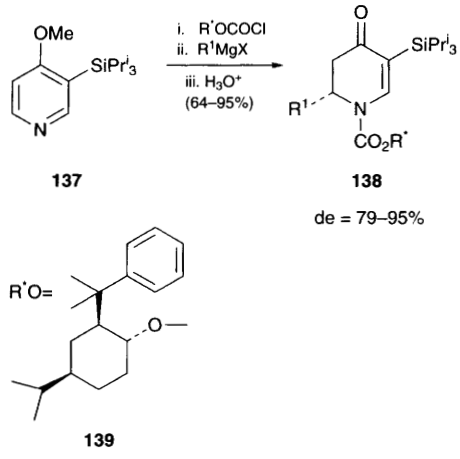


Scheme 37



Scheme 38

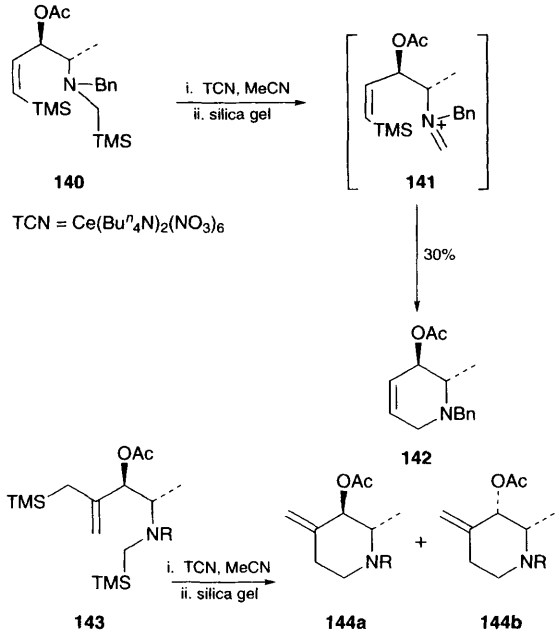
the pyridine **137** with R*OCOCl, a chiral chloroformate derived ultimately from limonene, followed by a Grignard reagent gave the dihydro-4-pyridones **138** in generally excellent yield and diastereoselectivity (80–95%). A number of enantiomerically pure R* groups were investigated, and it was found that **139** generally afforded the best diastereoselectivity. A reasonably wide variety of simple aryl and alkyl Grignard reagents were used successfully.



Scheme 39

Mariano and co-workers have described details of the oxidative Mannich cyclization of certain α-silylamines and -amides (**Scheme 40**).[40] Treatment of **140** with TCN gives a modest yield of the disubstituted piperidine **142** (30%), *via* the iminium ion **141**. No racemization or epimerization was observed. In contrast, the allylsilane **143** gives two piperidines **144a** and **144b** in improved yield under the same conditions, although both are of low enantiomeric purity. The problems of low yield and optical purity could be reduced to some extent by replacing the *N*-benzyl protecting group with a benzoate group, which was suggested to have the effect of suppressing a competitive aza-Cope side reaction, responsible for loss of the optical purity.

Murata and Overman have described the cyclization of *N,O*-acetals **145** and **148** to yield piperidines **147** and tetrahydropiperidines **149** respectively (**Scheme 41**).[41] These reactions developed from the NaI-promoted Mannich cyclization chemistry developed for the synthesis of the pumiliotoxin alkaloids, but differ in that if the reaction conditions are kept strictly anhydrous, a wide variety of much weaker nucleophiles can be used. Treatment of **145** with TMSX (X = Br, Cl) or $SiCl_4$ in acetonitrile or CH_2Cl_2 resulted in the formation of the 3-(1-haloalkylidene)piperidine **147** in excellent yield and as a single stereoisomer (when R = Me or H). Alternatively, with **148**, similar reaction conditions gave **149** in good yields. Non-halide nucleophiles (X = CN, N_3, OAc, OTf) were not successful, resulting instead in uncyclized side-products. The resulting vinyl halides should be valuable inter-



R	Yield of **144a** (%)	Yield of **144b** (%)
Bn	41 (24% ee)	34 (0% ee)
COPh	48 (50% ee)	0

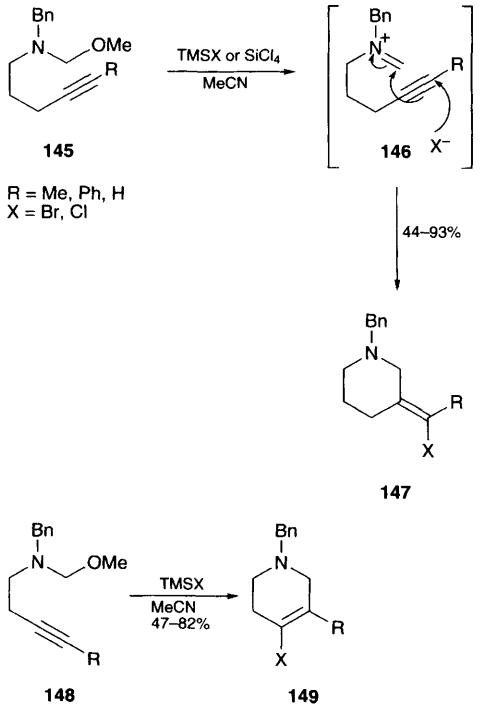
Scheme 40

mediates for the synthesis of more functionalized piperidines by a range of cross-coupling reactions.

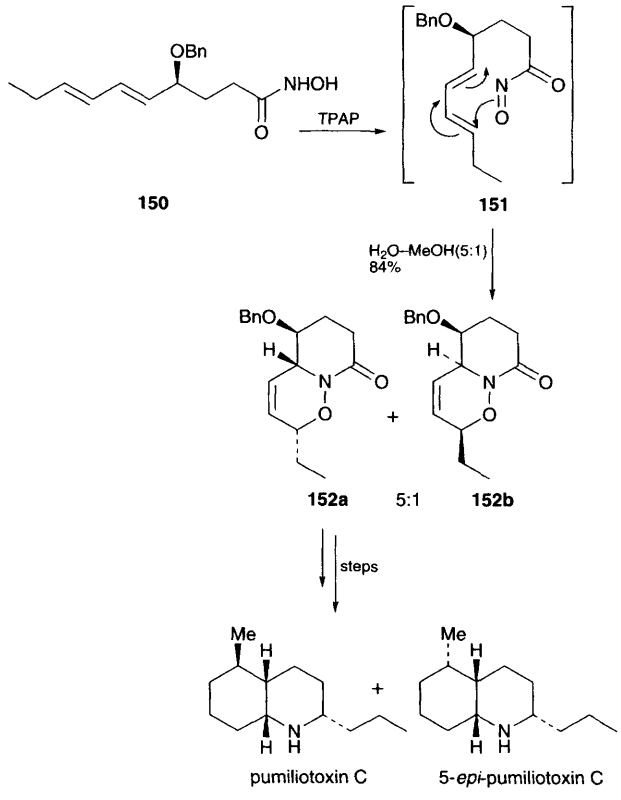
The total synthesis of (−)-pumiliotoxin C by Kibayashi and co-workers involved a novel acyl-nitroso Diels–Alder reaction under aqueous conditions (**Scheme 42**).[42] The hydroxamic acid **150** (synthesized from malic acid) was oxidized by TPAP (Pr_4NRuO_4) to the intermediate acylnitroso intermediate **151** which underwent Diels–Alder reaction to give predominantly the *trans* isomer **152a**. Although other groups have used similar Diels–Alder reactions to construct piperidines, the high stereoselectivity obtained in this study is noteworthy. A number of conventional steps then furnished (−)-pumiliotoxin C from **152a**.

McKervey and co-workers have described the first asymmetric N–H insertion reactions of an α-diazocarbonyl catalysed by a chiral rhodium catalyst (**Scheme 43**).[43] Diazoketone **153**, on treatment with the (*S*)-mandelic acid-derived rhodium catalyst Rh_2L_4, gave the piperidine **154a** in 45% ee as the major component of the reaction mixture. Other products resulting from C–H insertion (**154b**) and β-elimination (**154c**) were also obtained. The same reaction with **155** gave **156**, although the ee was only 15%.

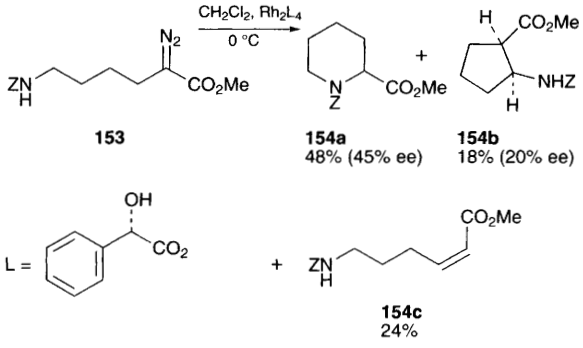
Ogasawara and co-workers have described the particularly efficient synthesis of (+)-pseudoconhydrine and (+)-*N*-methylpseudoconhydrine from 3-hydroxypyridine (**Scheme 44**).[44] Reduction of 3-hydroxypyridine with sodium borohydride in the presence of benzyl chloroformate afforded the versatile (but unstable) hydroxypiperidine **157** in 69% yield. This was then treated with methanol–HCl and the secondary alcohol was acetylated, to give the *N*,*O*-aminal **158**. Under $ZnCl_2$ catalysis, treatment of **158** with allylsilane gave a mixture of *trans* and *cis* 2,5-disubstituted piperidines, heavily in

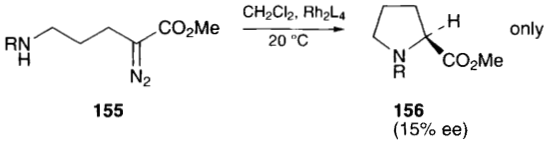


Scheme 41



Scheme 42

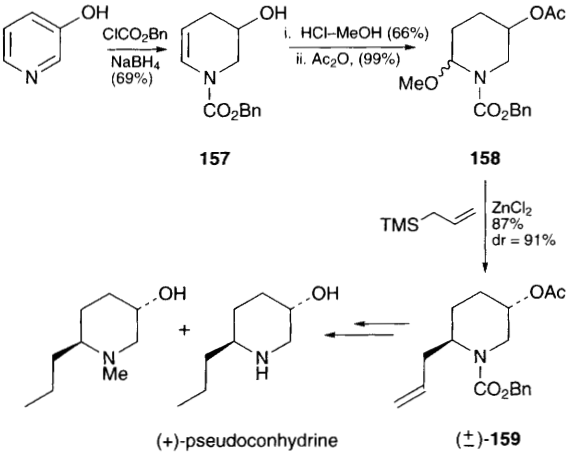




R = Z, Boc

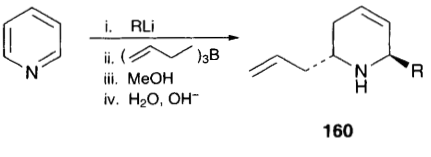
Scheme 43

favour of the *trans* isomer (±)-**159**. This compound was resolved enzymatically and converted to the two natural products by conventional means.



Scheme 44

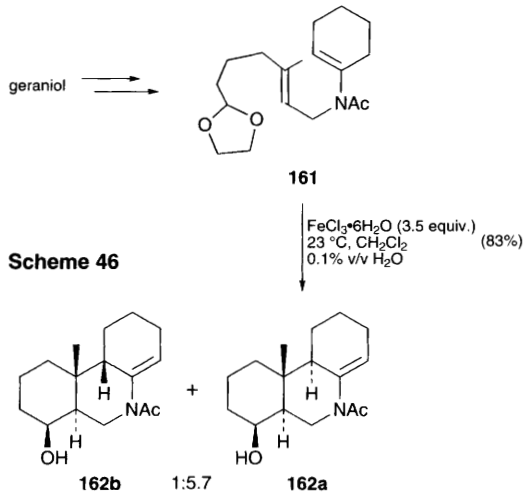
A similarly rapid functionalization of a common aromatic molecule to a piperidine was reported by Bubnov and co-workers (**Scheme 45**).[45] In this instance, pyridine itself was treated separately with RLi, allyl borane, methanol, and aqueous base in a one-pot procedure to afford (±)-**160** (R = H, Bu^n, Ph) in 50–60% yield.



R = Me, Bu^n, Ph

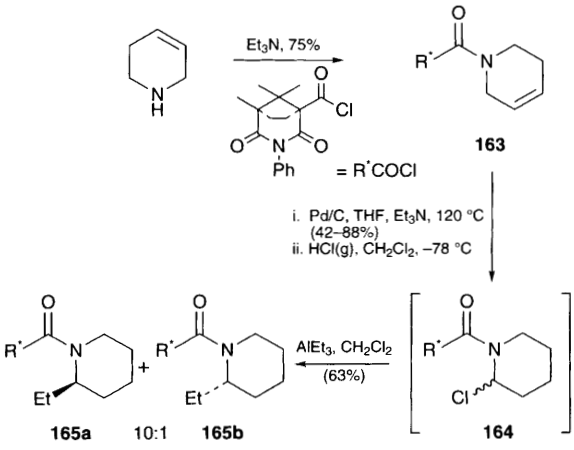
Scheme 45

Sen and Roach have described the conversion of **161**, obtained from geraniol in nine steps, to the tricycles **162a/b** by a cyclization reminiscent of the biological transformation of squalene to the steroid skeleton (**Scheme 46**).[46] The reaction conditions appear to be critical to the success of the reaction: *viz* alteration of either the amount or the nature of the Lewis acid (3.5 equiv. of $FeCl_3 \cdot 6H_2O$); the temperature (23 °C); the solvent (dichloromethane); and even the amount of adventitious moisture (0.1% v/v H_2O) led to drastically reduced amounts of product. With optimal conditions, a 5.7:1 mixture of **162a** and **162b** in a total yield of 83% could be obtained.



Scheme 46

Wanner and co-workers have described the use of a new chiral auxiliary in the asymmetric functionalization of 1,2,3,6-tetrahydropyridine (**Scheme 47**).[47] Formation of the amide **163**, followed by Pd/C-catalysed isomerization of the double bond and treatment with HCl gas gave the α-chloroamide **164**. Immediate treatment of this with $AlEt_3$ gave piperidines **165a/b** in 63% overall yield as a separable mixture of diastereomers (ratio *ca.* 10:1).



Scheme 47

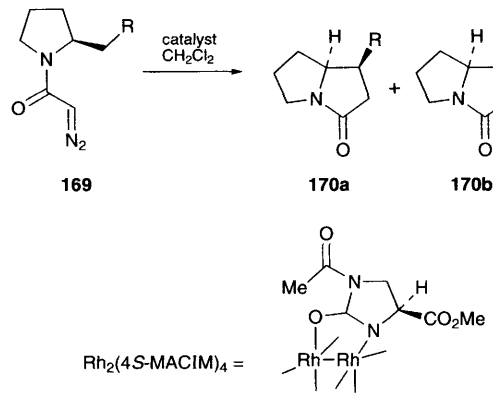
A photocyclization of an enamide has been used to generate trisubstituted piperidines (**Scheme 48**).[48]

Treatment of **166** with triethylamine and 2-phenyloxazole-4-carbonyl chloride gave the unstable enamide **167**. This was then refluxed with sodium borohydride under ultraviolet irradiation in acetonitrile–methanol to afford predominantly lactam **168a** and a small amount of the α-anomer **168b**. The methylthio grouping was oxidized to a methanesulfonyl group, which was then replaced by a three-carbon chain by reaction with allyltributylstannane, producing predominantly the α-isomer under most reaction conditions. This was subsequently homologated to the triacetate of the structure proposed for the natural product pseudodistomin A.

6 Pyrrolizidines, indolizidines and quinolizidines

The homochiral dirhodium catalyst $Rh_2(4S\text{-MACIM})_4$ has been used to catalyse the regioselective C–H insertion reaction of pyrrolidinediazoacetamides to form pyrrolizidines (**Scheme 49**).[49] For example, treatment of homochiral **169** (R = OMe) with $Rh_2(OAc)_4$ gave a modest yield of a mixture of the pyrrolidines **170a/b**. However, with $Rh_2(4S\text{-MACIM})_4$, the yields and diastereoselectivity improved. Similar results were obtained with R = Me; the 'mismatched case' with $Rh_2(4R\text{-MACIM})_4$ as the catalyst gave lower diastereoselectivity (75:25), and $Rh_2(OAc)_4$ by itself gave a much lower yield (32%). The intermediate **170a** (R = Me) was converted to the natural product (−)-heliotridane.

A sequential hydrogen atom abstraction–radical cyclization reaction was used by Robertson and co-workers to provide a different synthesis of the natural product (±)-heliotridane (**Scheme 50**).[50] Starting with **171**, treatment with AIBN and Bu_3SnH in refluxing benzene afforded the α-amino radical **172** (*via* 1,5-H atom transfer by the initial vinyl radical) which cyclized to give a 13:1 mixture of **173a** and **173b**. Thiophenol was added at the end of the reaction to facilitate the removal of the tin



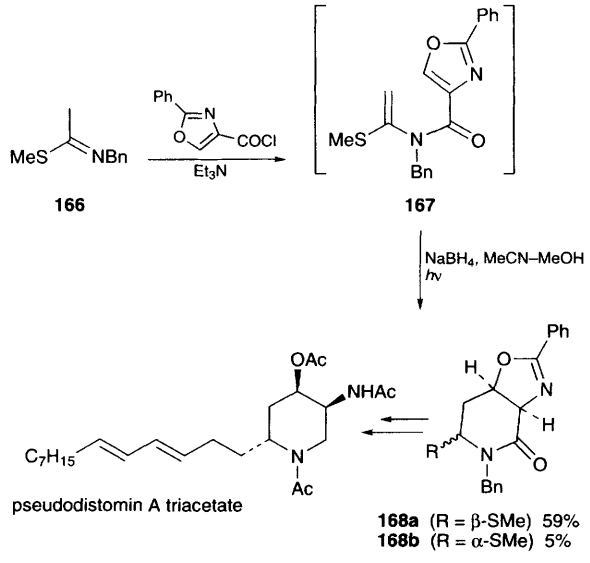
R	Catalyst	170a:170b	Total yield(%)
OMe	$Rh_2(OAc)_4$	53:47	45
OMe	$Rh_2(4S\text{-MACIM})_4$	97:3	88
Me	$Rh_2(OAc)_4$	18:82	32
Me	$Rh_2(4S\text{-MACIM})_4$	98:2	86
Me	$Rh_2(4R\text{-MACIM})_4$	75:25	

Scheme 49

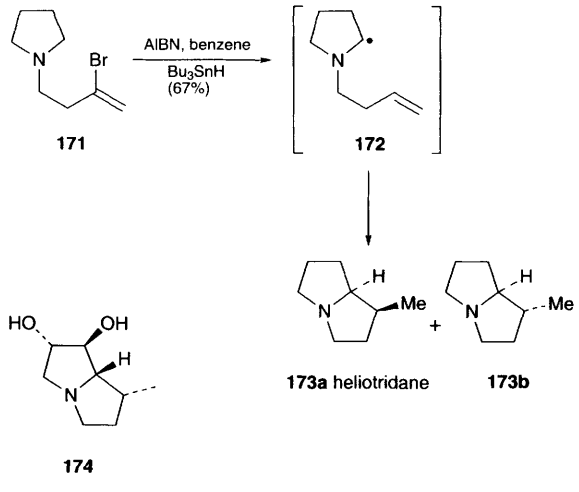
residues from the reaction mixture. Furthermore, the same strategy enabled the synthesis of **174**, a potential glycosidase inhibitor.

Viehe and co-workers have described the diastereoselective synthesis of trifluoromethyl-substituted pyrrolizidines by the addition of an azomethine ylide to a dipolarophile (**Scheme 51**).[51] For example, treatment of **175** with methyl triflate affords the trifluorothioamidium salt **176**, which on treatment with DBU and an electron deficient dipolarophile, for example methyl acrylate, afforded a diastereomeric mixture of the pyrrolidizines **177a/b** in good yield and excellent diastereoselectivity (95:5).

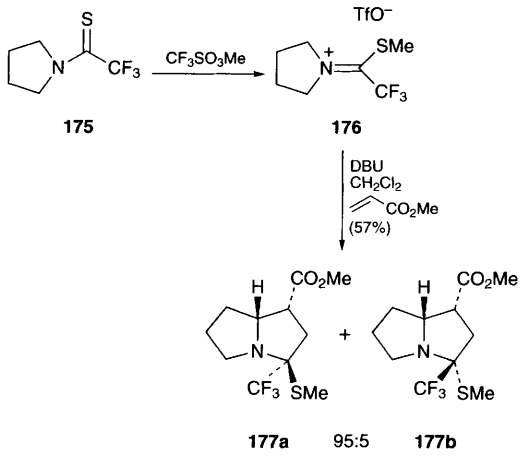
The key step in the synthesis of castanospermine by Mootoo and Zhao is the triple reductive amination of the triketone **178** with ammonium formate and sodium cyanoborohydride (**Scheme 52**).[52] This reaction yielded the perbenzyl ether of castano-



Scheme 48



Scheme 50



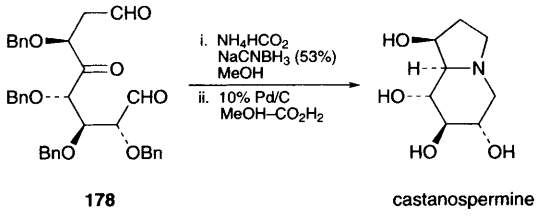
Scheme 51

spermine in 53% yield as a single diastereomer, and may be similar to the actual route by which the polyhydroxylated indolizidines are biosynthesized.

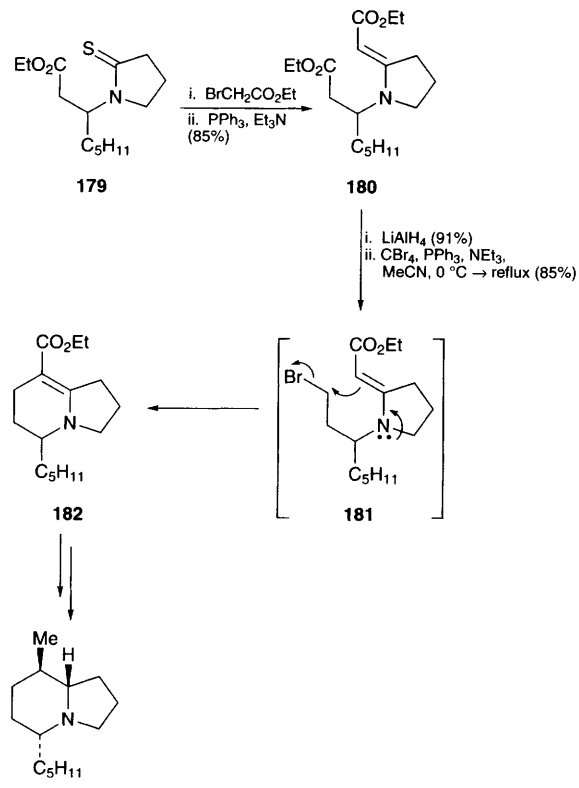
Indolizidine 209B has been made by Michael and Gravestock (**Scheme 53**).[53] Exposure of thioamide **179** to alkylative Eschenmoser sulfur contraction conditions gave the vinylogous carbamate **180** in 85% yield. This was converted to bromide **181**, which underwent a surprisingly smooth cyclization to give **182** upon refluxing the reaction mixture. Several steps were then employed to convert the vinylogous urethane moiety into the functionality present in (±)-209B.

Goti, Brandi and Cardona have described the synthesis of (+)-lentiginosine, another naturally occurring polyhydroxylated indolizidine (**Scheme 54**).[54] The key step involved the dipolar cycloaddition of the enantiomerically pure nitrone **183** with but-3-en-1-ol. When R = Bu^t, the cycloaddition is quite diastereoselective, affording **184** as the major component of a 10:2:1 mixture of diastereomers. Subsequent well-precedented manipulations converted **184** into (+)-lentiginosine.

Embedded in the *Erythrina* alkaloid skeleton is an indolizidine framework. This was constructed very elegantly by Padwa and co-workers using a tandem Diels–Alder *N*-acyliminium ion cyclization (**Scheme 55**).[55] Starting with **185**, treatment with Ac_2O–TsOH effected Pummerer rearrangement to afford the isobenzofuran **186**. Diels–Alder reaction and expulsion of ethanethiol (**186**→**187**) generated the *N*-acyliminium ion **188**, which was intercepted by the adjacent electron rich aromatic ring to afford



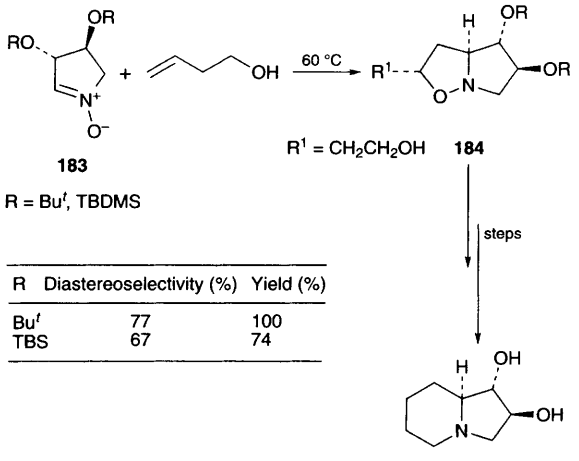
Scheme 52



Scheme 53

189, all in 70% overall yield from **185**. Analogues of the *Erythrina* skeleton were speculated to be accessible by simple alteration of the length of some of the tethers in **185**.

Mangeney and co-workers have described the transformation of the chiral auxiliary-substituted pyridine **190** to the quinolizidine skeleton (**Scheme 56**).[56] Addition of MeCu to the 4-position of the pyridine ring, followed by alkylation of the pyridyl anion with 4-chlorobutanoyl chloride, removal of the chiral auxiliary and Finkelstein Cl–I exchange gave **191** as a single enantiomer. A 6-*exo* radical cyclization under standard conditions then gave a

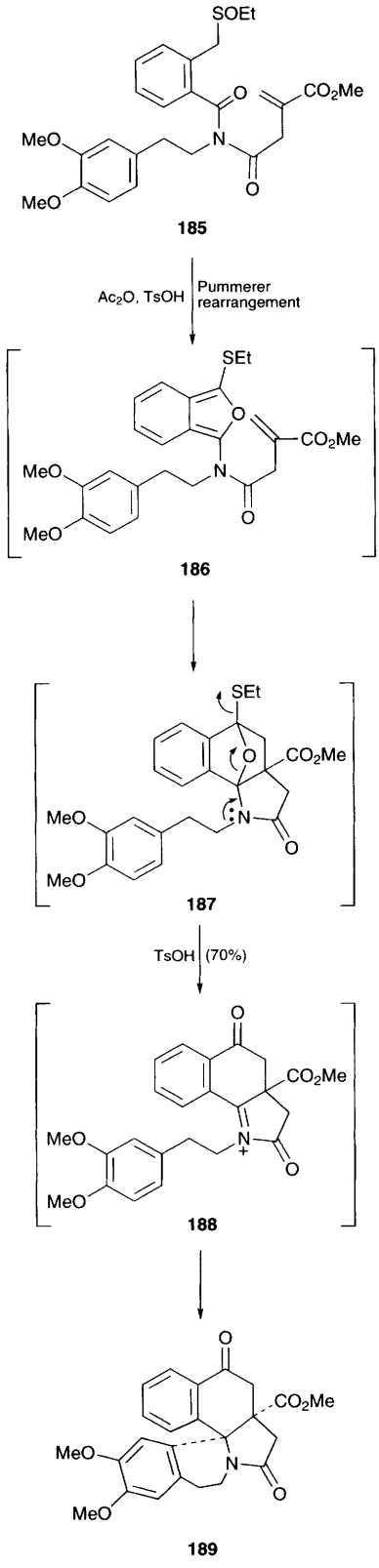


R = Bu^t, TBDMS

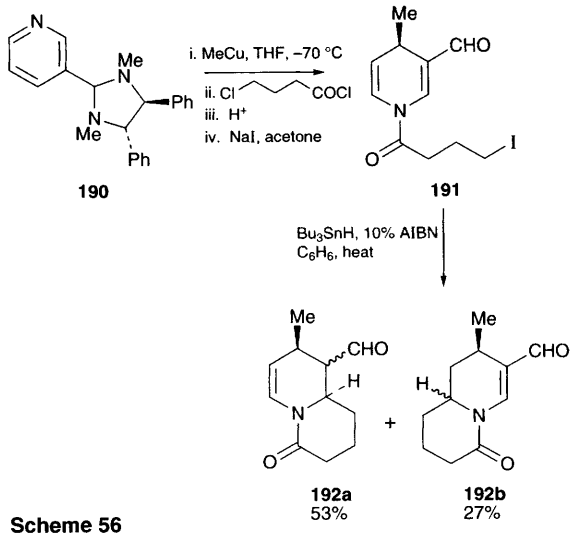
R	Diastereoselectivity (%)	Yield (%)
Bu^t	77	100
TBS	67	74

Scheme 54

mixture of regioisomers **192a** and **192b** in total 80% yield. Each regioisomer was also a mixture of epimers. The poor regioselectivity was solved by using Zn–CuI with ultrasound, instead of radical



Scheme 55



Scheme 56

conditions, to effect cyclization but the diastereoselectivity remained poor.

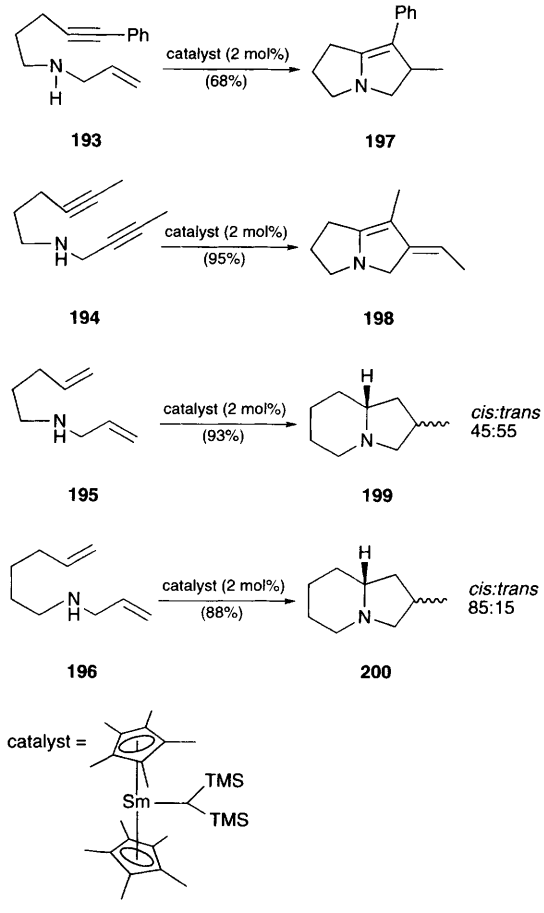
Marks and Li have described a powerful approach to the synthesis of the pyrrolizidine and indolizidine alkaloid skeletons in an organolanthanide-catalysed reaction (**Scheme 57**).[57] The substrates are remarkably simple (*e.g.* **193–196**), containing one or two each of an alkyne and alkene separated by an appropriate number of carbon atoms from a central nitrogen atom. The key hydroamination–bicyclization reactions were carried out in benzene at room temperature under strictly deoxygenated and anhydrous conditions with either $Cp^*_2SmCH(TMS)_2$ or $Me_2SiCp^*_2NdCH(TMS)_2$ ($Cp^* = \eta^5$-Me_5C_5) (2 mol%). Although simple alkaloids such as **199** and **200** can be readily made, the real power of the reaction lies in the preparation of unsaturated derivatives such as **197** and **198**, which are amenable to further functionalization. A catalytic cycle is proposed that involves covalent formation of an N–Sm bond, followed by intramolecular co-ordination to the acetylene. The C–N bond (first ring) is formed by metathesis, and the resulting Sm–C bond inserts into the remaining alkene (or alkyne) to give C–C bond formation (second ring).

The pyrrolizidine, indolizidine and quinolizidine frameworks have been synthesized by a photo-induced electron transfer (PET) reaction of 1-alkenyl-2-silyl-pyrrolidines and -piperidines (**Scheme 58**).[58] For example, irradiation of **201a** (itself obtained by a PET reaction of the acyclic precursor) with ultraviolet light ($\lambda > 280$ nm) and 1,4-dicyanonaphthalene (DCN) gave **202** as a 97:3 mixture of diastereomers in 90% yield. Interestingly, the homologue **201b** gave the products **202b** in similar yield, but with completely reversed stereochemistry, reminiscent of similar radical cyclization reactions.

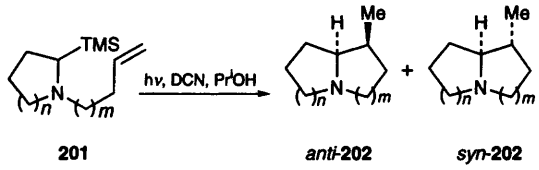
The indolizidine alkaloids 167B and 209D have been synthesized by Lee and co-workers using a radical cyclization approach (**Scheme 59**).[59] The primary bromide **203** was made in nine steps from (*S*)-proline. Treatment of **203** with Bu_3SnH–AIBN

gave **204** efficiently *via* a 6-*exo* cyclization. The homologue **206** was made analogously from **205**.

Tsai and co-workers have described the synthesis of pyrrolizidinones, indolizidinones and quinolizidinones by intramolecular cyclization of α-acylamino radicals onto acylsilanes (**Scheme 60**).[60] The substrates **207a–d** were refluxed with Bu_3SnH and AIBN in benzene to effect cyclization. The yields

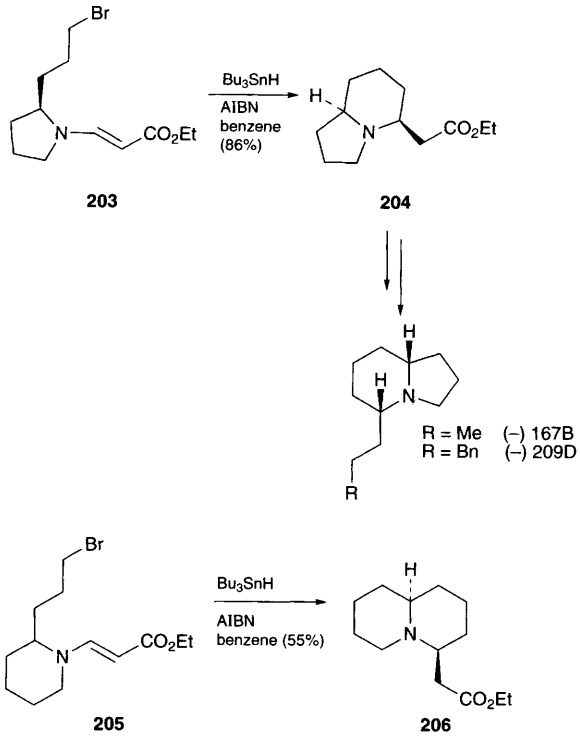


Scheme 57



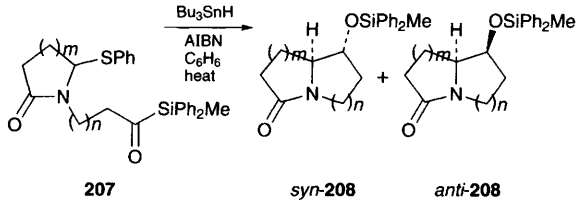
Entry	*n*	*m*	*anti*:*syn*	Yield (%)
a	1	1	97:3	90
b	2	2	0:100	88
c	1	2	2:98	85
d	2	1	95:5	87

Scheme 58



Scheme 59

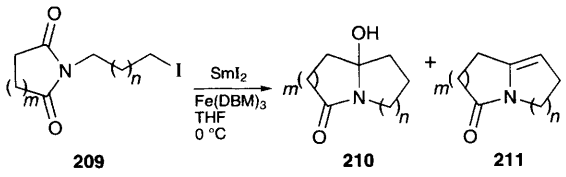
were good to moderate and the diastereoselectivity modest (see table). The *syn*:*anti* ratio varied between 1.9:1 and 3.8:1, with the indolizidinone and quinolizidinone alkaloids enjoying slightly more stereocontrol over the formation of the alcohol centre.



Entry	*m*	*n*	Yield (%) of *syn*	*anti*
a	1	1	34	18
b	1	2	63	16
c	2	1	58	23
d	2	2	57	15

Scheme 60

Ha and co-workers have described the SmI_2-mediated reductive cyclization of *N*-iodoalkyl cyclic imides to the pyrrolizidine and indolizidine skeletons (**Scheme 61**).[61] For example, the succinimide **209b** gave **211b** (56% yield) and the glutarimide



209 210 211

DBM = tris(dibenzoylmethane)

Entry	m	n	Yield (%) of 210	211
a	1	1	32	
b	1	2		56
c	2	1	35	
d	2	2		60

Scheme 61

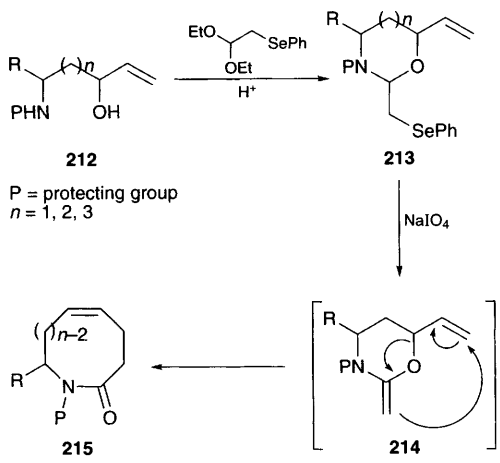
209d gave **211d** (60% yield) on treatment with SmI_2, $Fe(DBM)_3$ in THF.

7 Medium and large rings

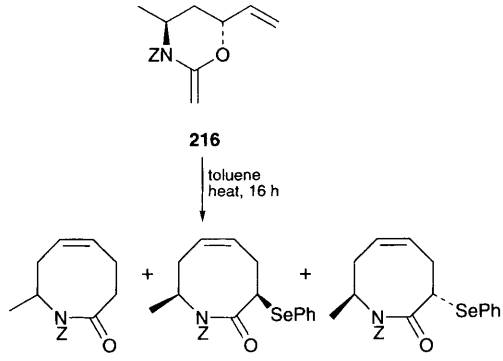
Holmes and co-workers have described details of the Claisen rearrangement of vinyl substituted *N,O*-ketene aminals into eight-, nine- and ten-membered lactams (*e.g.* **214→215**, **(Scheme 62)**.[62] The desired ketene acetals are prepared by classical selenoxide elimination from the corresponding selenide (*e.g.* **213**), prepared readily from 1,*n*-amino alcohols. Similar methodology has been used very successfully in the preparation of medium ring lactones from ketene acetals, but the analogous *N,O*-ketene aminals are much more electron rich, thereby making the lactam synthesis rather more prone to side-reactions. For example, **216** afforded only 17% of the desired product **217a**, together with 51% of a 9:1 mixture of selenides **217b** and **217c**, obtained by premature trapping of the *N,O*-ketene aminal with phenylselenenic acid. This side reaction could be usefully suppressed by the addition of a large amount of a highly reactive ketene acetal [$Me_3SiOC(OMe)=CH_2$] to scavenge the offending PhSeOH. The nine membered lactam **220** ($n=1$) was obtained in 54% overall yield from the amino alcohol **218** ($n=1$); and the simple ten-membered lactam **220** ($n=2$) from **218** ($n=2$) in 78% yield **(Scheme 63)**. The efficient formation of the eight-membered ketene acetal **219** ($n=2$) (58%) from the corresponding 1,5-amino alcohol is noteworthy.

The use of transition metal-catalysed ring closing metathesis (RCM) reactions of alkenes in all areas of organic chemistry is currently growing, owing to increased knowledge of the robust catalysts pioneered by the Grubbs and Schrock groups. Barrett and co-workers have applied this methodology to the synthesis of novel β-lactams containing fused medium sized rings **(Scheme 64)**.[63] Starting with 4-acetoxyazetidin-2-one **221**, two simple steps produced the bis-alkenes **222a–c**. Treatment with the molybdenum catalyst **223** (5 mol%) gave the seven-, eight- and nine-membered rings (**224a–c**) in 84%, 53% and 12% yield respectively.

In a partial solution to the difficult problem of the development of traceless linkers for solid phase combinatorial chemistry, van Maarseveen and



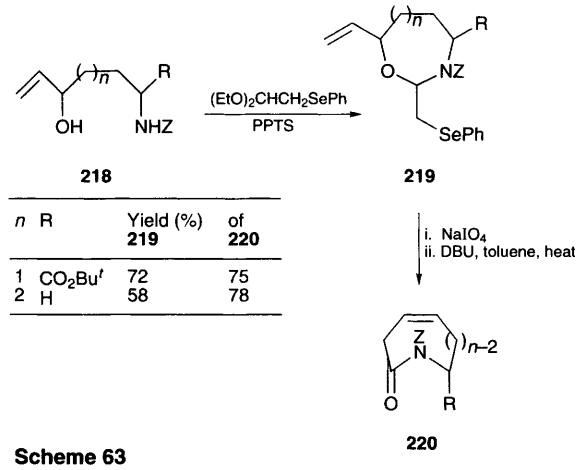
212 213 214 215



216 217a 217b 217c

Conditions	% Yield of 217a	217b	217c
No additive	17	46	5
$Me_3SiOC(OMe)=CH_2$(20 equiv.)	80	—	—

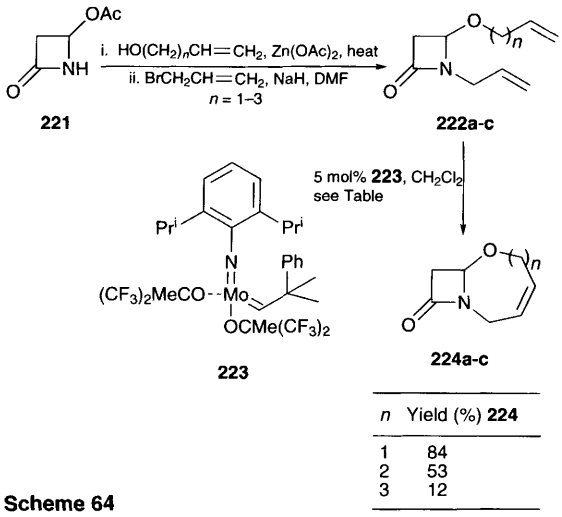
Scheme 62



218 219 220

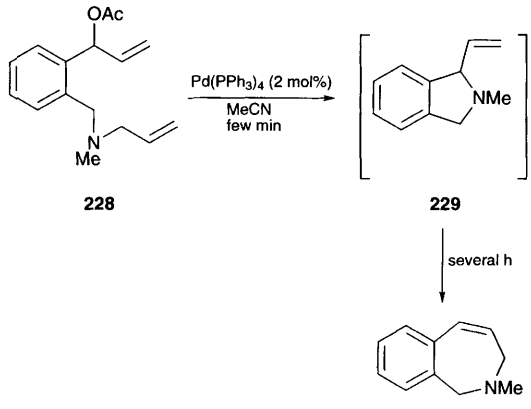
n	R	Yield (%) of 219	220
1	CO_2Bu^t	72	75
2	H	58	78

Scheme 63



n	Yield (%) **224**
1	84
2	53
3	12

Scheme 64



Scheme 66

co-workers have described the RCM–cleavage reaction of **225** to give the seven-membered lactam **227**, using the ruthenium catalyst **226** (**Scheme 65**).[64] Unfortunately, the yield for the reaction is only modest, and the reaction time long, even with 100 mol% of the catalyst.

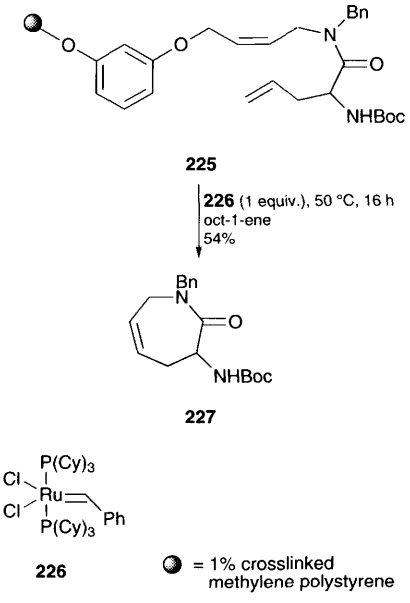
Pfeffer and Grellier have described the preparation of **230** from **228** through the application of an intramolecular palladium-catalysed tertiary amine–allyl coupling reaction (**Scheme 66**).[65] It was found that **229** is an intermediate in the reaction, which is slowly converted to **230**. A detailed catalytic cycle is proposed.

Yamamoto and co-workers have described efficient syntheses of several spermine-derived macrocyclic alkaloids (**Scheme 67**).[66] The key step is the antimony(III) ethoxide-promoted regioselective cyclization of **231** in benzene to the 17-membered lactam **233**. It is proposed that the antimony atom forms a chelate (**232**) with the four nitrogen atoms and the carbonyl group, thereby reducing the severe entropic penalty involved in cyclizing a large ring. Although titanium and zirconium alkoxides were also partially effective (19 and 23% yield with a related substrate), antimony(III) ethoxide was far more efficient. The key intermediate **233** was converted into the natural products (±)-verbacine, (±)-verbaskine and (±)-verbascenine.

The azocine ring in magallanesine has been constructed by Kurihara and co-workers by a novel [1,2]-Meisenheimer rearrangement of the azetidine *N*-oxide **235** (**Scheme 68**).[67] Starting with **234**, treatment with H_2O_2 formed the *N*-oxide **235**, which, when refluxed in THF, underwent the Meisenheimer rearrangement to give **236** in 64% yield. Hydrogenolysis of the N–O bond gave **237** in quantitative yield. The synthesis of magallanesine was then completed by palladium-catalysed cyclization of **238** under the carefully optimized conditions shown.

The seven-membered ring in a series of analogues of the dopamine D_1 antagonist SCH-23390 was formed by the methanesulfonic acid-catalysed cyclization of an acyclic precursor (**239**→**240**, **Scheme 69**).[68] The methylthio group was used to activate the aromatic ring toward cyclization; without it no cyclization occurred. The methylthio group was later removed with Raney nickel and replaced with the more versatile bromide group.

A similar type of structure is found in the *Amaryllidaceae* alkaloids. Kita and Zenk and co-workers have investigated the use of the hypervalent iodine(III) reagent phenyliodine(III) bis(trifluoroacetate) (PIFA) to form the spirocyclic azepine ring by an oxidative phenolic coupling (**241**→**242**, **Scheme 70**).[69] The solvent was found to play a particularly important role in the yield of the cyclization. Only poorly nucleophilic but polar solvents such as CF_3CH_2OH and $(CF_3)_2CHOH$, and to a lesser degree acetonitrile, gave acceptable yields. The amino protecting group was also found to affect the yield: trifluoroacetamido gave the best results.



Scheme 65

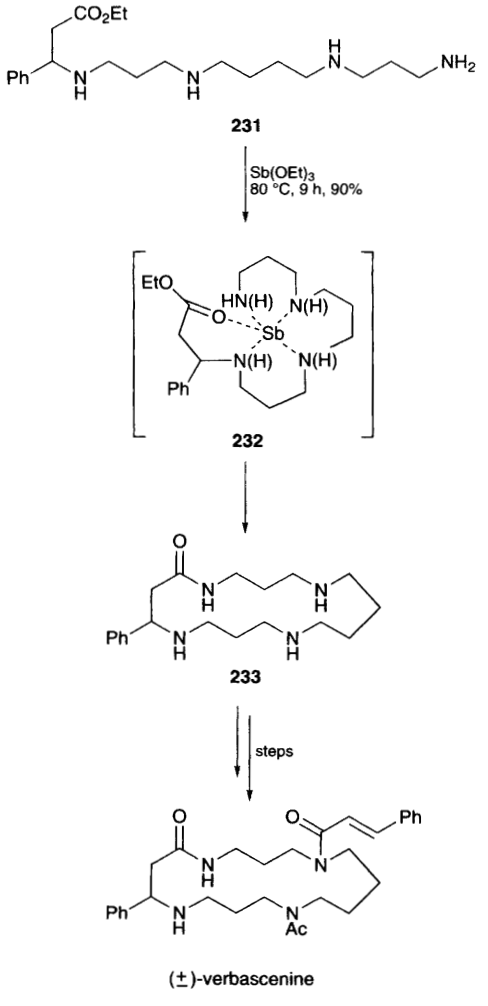
8 Tetrahydroquinolines and tetrahydroisoquinolines

Recent progress in the synthesis of 1,2,3,4-tetrahydroquinolines has been the subject of a comprehensive review by Katritzky, Rachwal and Rachwal.[70]

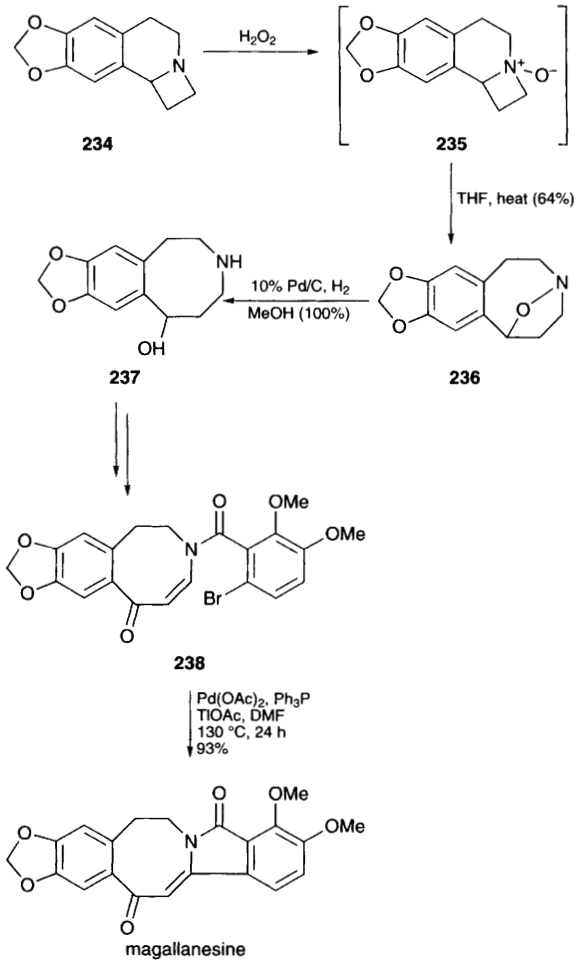
Kobayashi and Ishitani have described an interesting catalytic asymmetric aza Diels–Alder reaction for the synthesis of tetrahydroquinolines **245** (**Scheme 71**).[71] The imine **243**, an alkene, the chiral Yb complex **244** (10-20 mol%) [prepared from $Yb(OTf)_3$, (*R*)-(+)-BINOL and a hindered base] when mixed together in the presence of 4 Å molecular sieves gave the tetrahydroquinoline in 52-90% yield. The *cis*/*trans* ratio is excellent and ee values are in the range 61–91% for the *cis* isomer.

An efficient synthesis of 1,2,3,4-tetrahydroquinolines (*e.g.* **248**) from anilines has been reported by Beifuss and co-workers (**Scheme 72**).[72] The key reaction, [4+2] cycloaddition of a cationic 2-azabutadiene with an alkene proceeds with excellent regiochemistry in 67–92% yield in the presence of $SnCl_4$. In 1,2-disubstituted alkenes, the stereochemistry in the product reflects the geometry of the double bond, suggesting the mechanism is a concerted cycloaddition. The azadiene is obtained from *in situ* Lewis acid-mediated decomposition of the corresponding α-arylaminosulfone **248**. These are themselves readily available from amines **246**, aqueous formaldehyde and toluene-4-sulfinic acid by a Mannich-type reaction.

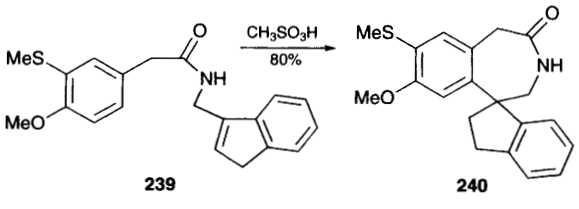
Solid-phase reactions of all types are currently of great interest owing to the application of combinatorial techniques to drug discovery. This is particularly true for syntheses of traditional medicinal chemistry templates such as tetrahydroisoquinolines. A strategy devised by Künzer and co-workers enables the synthesis of 1,2,6-trisubstituted tetrahydroisoquinolines from one fixed building block and four variable ones (**Scheme 73**).[73] Starting with



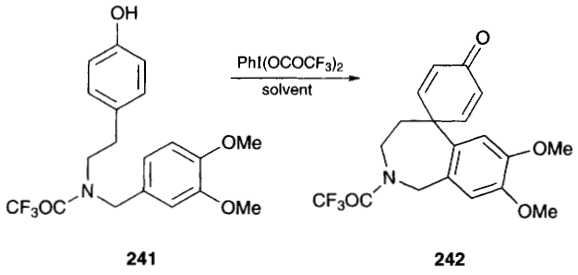
Scheme 67



Scheme 68



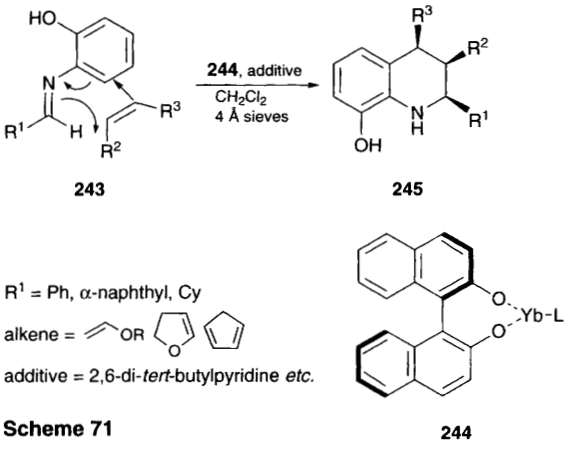
Scheme 69



241 242

Solvent	Yield (%)
DMF	18
CH_2Cl_2	30
MeCN	50
CF_3CH_2OH	61
$(CF_3)_2CHOH$	70

Scheme 70



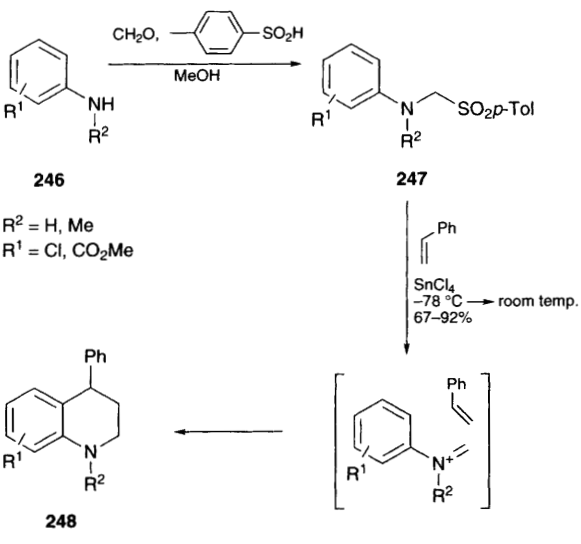
243 245 244

R^1 = Ph, α-naphthyl, Cy

alkene =

additive = 2,6-di-*tert*-butylpyridine *etc.*

Scheme 71

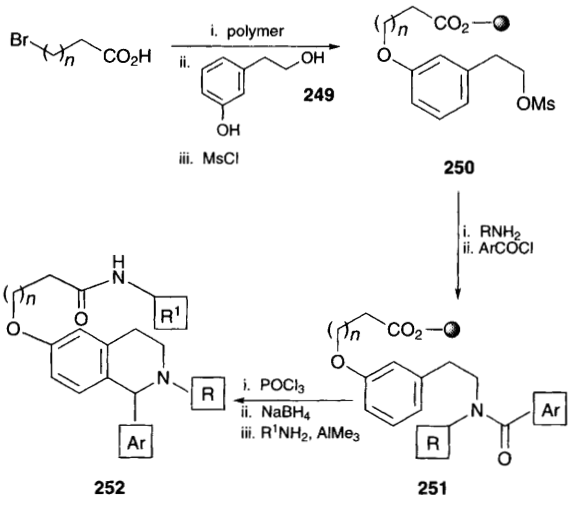


246 247 248

R^2 = H, Me

R^1 = Cl, CO_2Me

Scheme 72



252 251

Scheme 73

an ω-bromoacid, connection to the polystyrene resin (HEPS), addition of the fixed building block (*e.g.* **249**) and mesylation gave **250**. Displacement of the mesylate with an amine RNH_2 and acylation with ArCOCl gave **251**. The ring closure was effected classically with $POCl_3$ (Bischler–Napieralski reaction) followed by reduction. Cleavage from the resin and introduction of the 4th unit of diversity was achieved with R^1NH_2 and trimethylaluminium. This approach was used to make a 24-membered single compound library represented by **252**.

An interesting approach to the tetrahydroquinoline alkaloid virantmycin has been described by Morimoto, Shirahama and co-workers (**Scheme 74**).[74] The first key reaction involves the photochemical decomposition of azide **253** in toluene solution to give a nitrene intermediate, which adds stereospecifically to the alkene of the proximal α,β-unsaturated ester to give the aziridine **254** in 86% yield. A number of steps converted **254** into **255**, which was treated with tetraethylammonium chloride and TFA to effect highly regio- and stereoselective opening of the aziridine to give (±)-virantmycin. This work and a subsequent paper[75] elucidated for the first time the relative and absolute configuration of virantmycin.

9 Methods for the general synthesis of two or more ring sizes

The key reaction in a synthesis of the polyether hemibrevetoxin B by Yamamoto and co-workers was an intramolecular reaction of a γ-alkoxyallylstannane with an aldehyde to generate stereoselectively six- and seven-membered cyclic ethers. This methodology has now been extended to include the synthesis of piperidines and pyrrolidines (**Scheme 75**).[76] Starting with **256** (prepared in six steps from 4-aminobutan-1-ol), treatment with a Lewis acid at low temperature gave the piperidines **257a** and **257b** in good yield. The diastereoselectivity was found to be dependent on the nature of the Lewis acid used, but lies approximately

between 1:2 and 2:1. Remarkably, leaving out the Lewis acid and subjecting **256** to the purely thermal reaction (120 °C, 36 h) gave a 67% yield of virtually diastereomerically pure **257b** (>98:2). The analogous cyclization to give pyrrolidines also occurs, this time giving high *cis* selectivity (10:90) with either a Lewis acid ($TiCl_4$) or under purely thermal conditions.

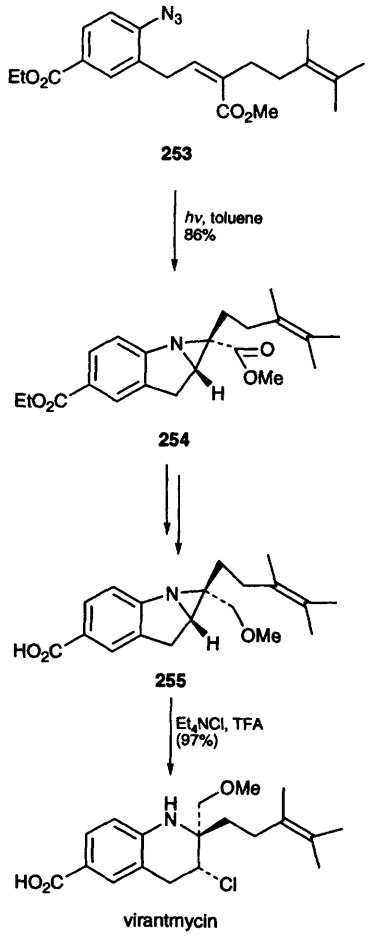
As mentioned earlier, metathesis reactions are becoming ever more fashionable. Blechert and co-workers have now described the first diastereoselective ring-closing metathesis (RCM) reaction, illustrated by the reaction of **260** (**Scheme 76**).[77] Treatment of **260** with the Grubbs *ruthenium* catalyst **226** (10 mol%) gives predominantly **261a** in 88% yield (92% de), whereas treatment with the Schrock molybdenum catalyst **223** (5–10 mol%) gives predominantly the *syn* diastereomer (97% yield, 72% de). The analogous reaction with the homologue to give piperidines (**262→263a/b**) was similarly efficient, but far less stereoselective (Ru catalyst: 4% de; Mo catalyst: 48% de).

The same research group has also described the RCM of amines bound to a solid support (Tentagel S or tritylpolystyrol) (**Scheme 77**).[78] As typical for many reactions on solid support, long reaction times are necessary. However, both piperidines and pyrrolidines could be made efficiently (for example **264→265** and **266→267**).

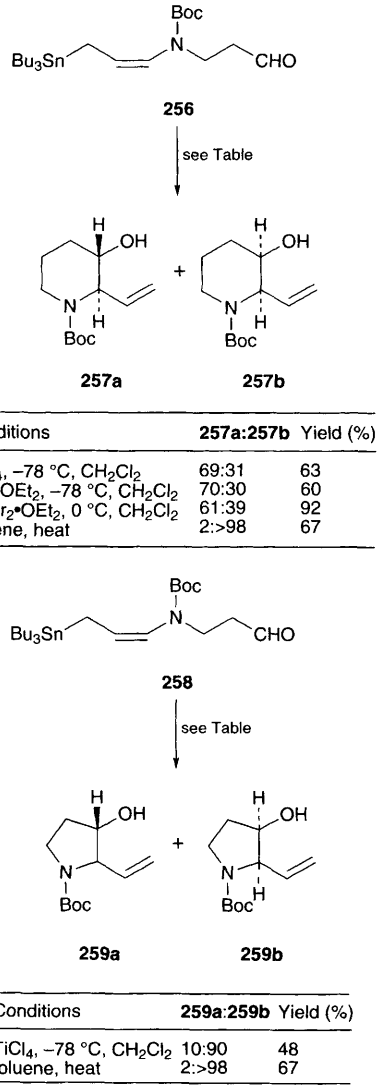
Finally Blechert and co-workers have described the formation of γ- and δ-lactams by RCM of vinyl- or allyl-glycine derivatives (**268→269** and **270→271**; **Scheme 78**).[79] In general the yields were slightly greater and the reaction times shorter for the synthesis of six-membered rings.

The discovery of an unexpected steroid-like side-product **274** in the conversion of **272** to **273** prompted Romero and co-workers to investigate further the synthesis of azasteroids (**Scheme 79**).[80] Their work culminated in the preparation of **276** (30% yield) by treatment of **275** with HCO_2H and $(CH_2O)_n$. Note that the four contiguous stereocentres created in this reaction have the correct steroidal *trans* disposition. This work is similar to that of Sen and Roach (**Scheme 46**).

Giese and co-workers have described the preparation of γ- and δ-lactams through the stereoselective photocyclization of glycine in dipeptides (**Scheme 80**).[81] The constrained dipeptides thus obtained are



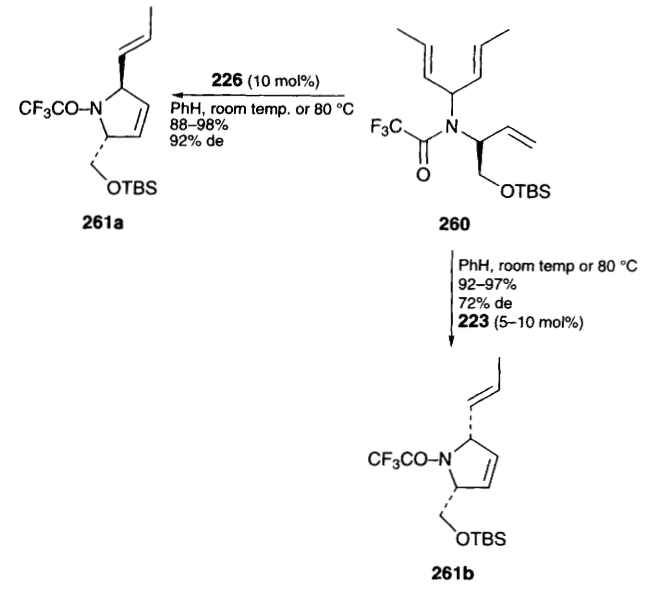
Scheme 74

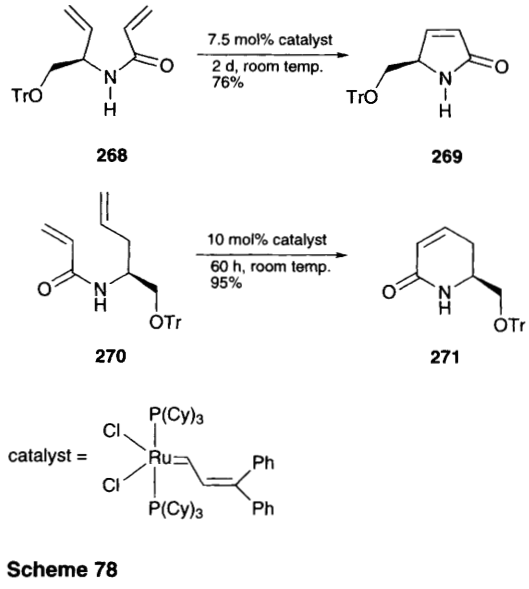


Conditions	257a:257b	Yield (%)
$TiCl_4$, –78 °C, CH_2Cl_2	69:31	63
BF_3•OEt_2, –78 °C, CH_2Cl_2	70:30	60
$MgBr_2$•OEt_2, 0 °C, CH_2Cl_2	61:39	92
toluene, heat	2:>98	67

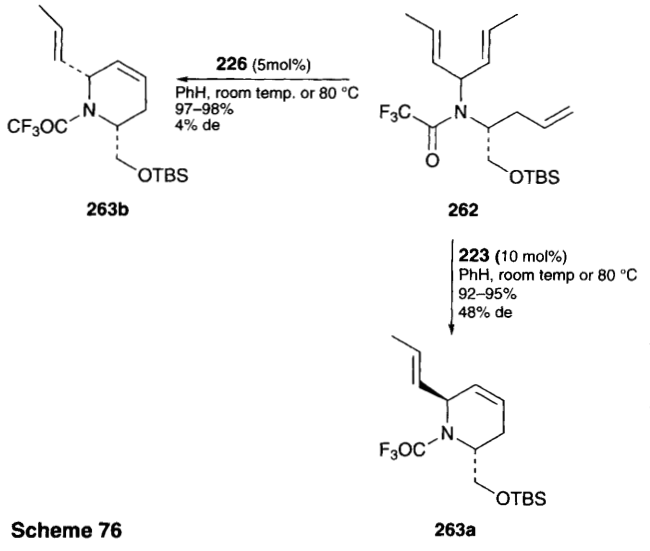
Conditions	259a:259b	Yield (%)
$TiCl_4$, –78 °C, CH_2Cl_2	10:90	48
toluene, heat	2:>98	67

Scheme 75

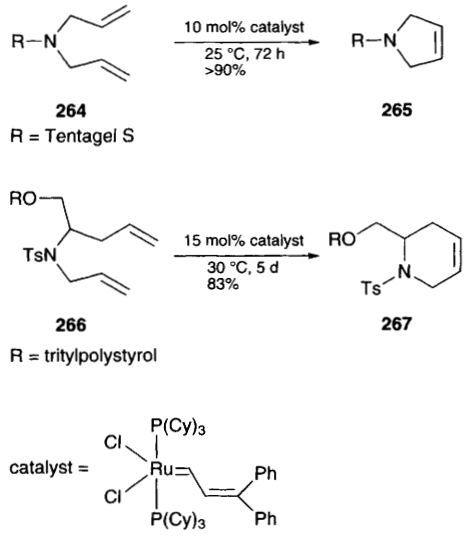




Scheme 78

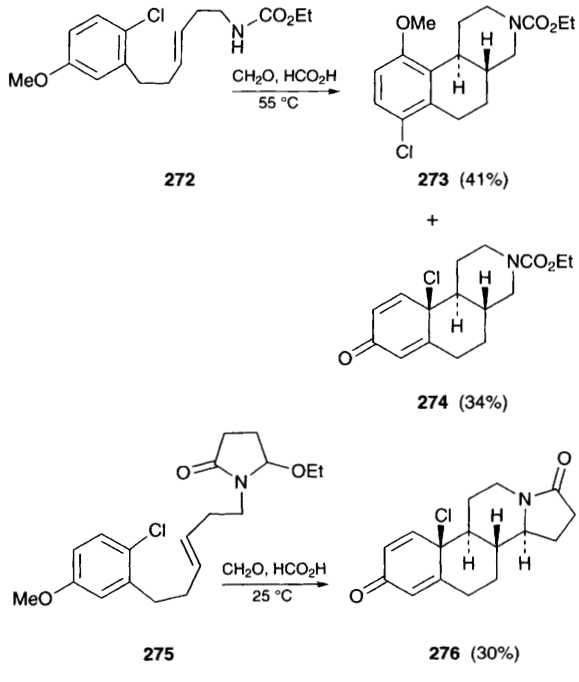


Scheme 76

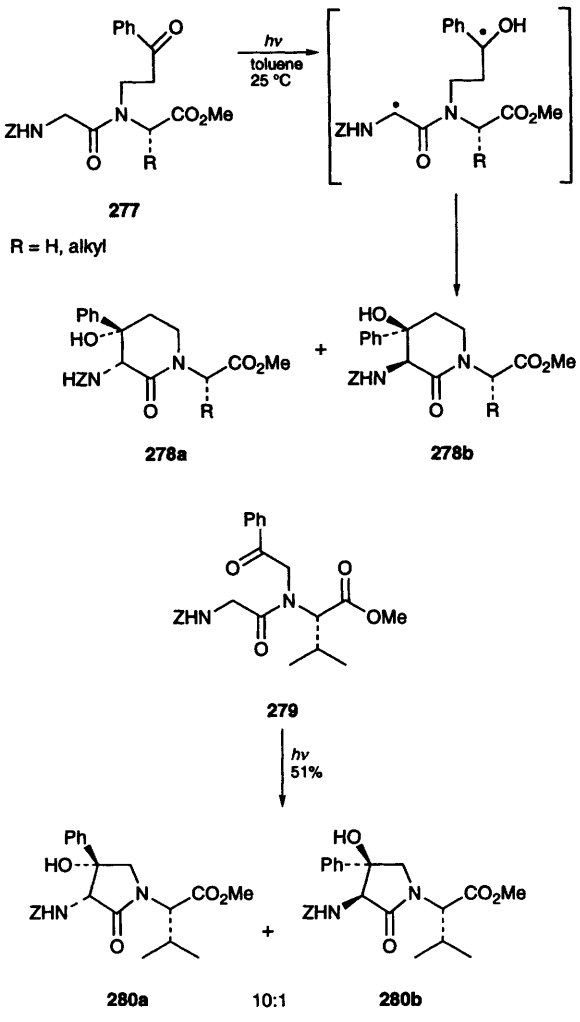


Scheme 77

closely related to the family of Freidinger lactams and thus may show potential as β-turn mimics. For example, irradiation of **277** (R = Me) in toluene resulted in the formation of a mixture of **278a** and **278b** in 48% and 22% yield respectively. Note that the two polar groups are both *cis* to each other, presumably because of an H-bonding interaction. With larger R substituents, the diastereoselectivity improved. In polar solvents this preference for *cis* diastereoselctivity was reduced. The γ-lactams (**280a/b**) are formed from **279** with slightly greater diastereoselectivity. The level of asymmetric induction in this transformation is remarkable, given the relative remoteness of the original chiral centre.

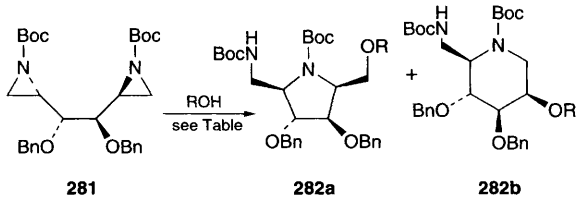


Scheme 79



Scheme 80

Duréault and co-workers have described the reaction of the interesting bis-aziridine **281** with oxygen nucleophiles (**Scheme 81**).[82] Depending on

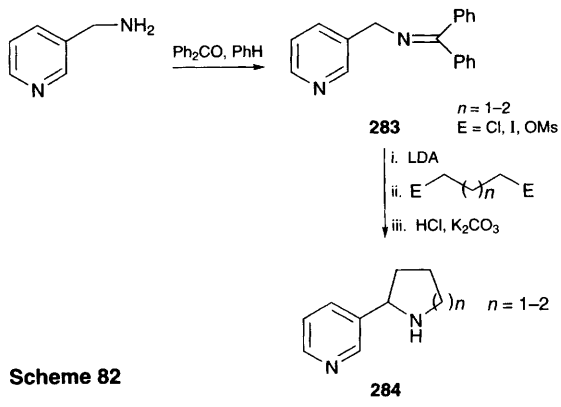


R	Conditions	% Yield of 282a	282b
$COCH_3$	20 °C, 2 h	55	27
$CH_2CH{=}CH_2$	$Yb(OTf)_3$ (10 mol%)	27	55
H	$Yb(OTf)_3$ (10 mol%)	27	50

Scheme 81

the choice of nucleophile and Lewis acid catalyst, either the azafuranose (**282a**) or the azapyranose (**282b**) product is favoured.

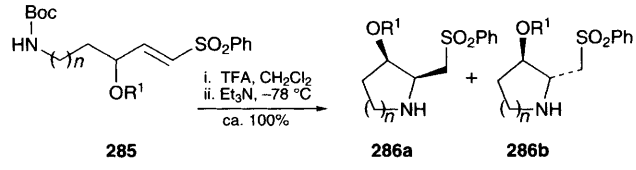
Deo and Crooks have described a simple synthesis of some of the minor tobacco alkaloids



Scheme 82

(**Scheme 82**).[83] Metallation of the Schiff base **283**, followed by the addition of a dielectrophile gave after workup the piperidine **284** ($n=2$) or the pyrrolidine **284** ($n=1$).

Carretero and co-workers have described the stereoselective synthesis of hydroxypyrrolidines and hydroxypiperidines by intramolecular conjugate addition of amines onto α,β-unsaturated sulfones (**285**→**286a/b**; **Scheme 83**).[84] The *cis*:*trans* ratio was

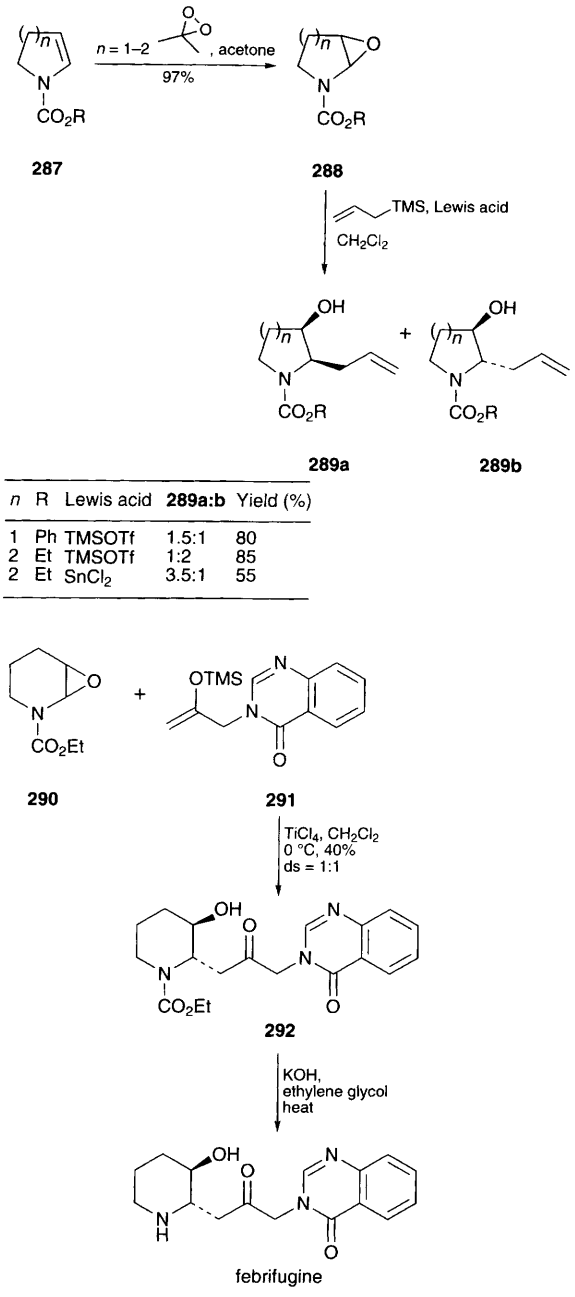


OR^1	n	286a:286b	OR^1	n	286a:286b
OH	1	80:20	OH	2	50:50
OCH_2OEt	1	44:56	OCH_2OEt	2	45:55
OTBS	1	40:60	OTBS	2	33:67
OTIPS	1	22:78	OTIPS	2	20:80

Scheme 83

found to vary with the nature of the oxygen protecting group R^1: bulkier groups generally leading to an increase in the amount of the *trans* isomer.

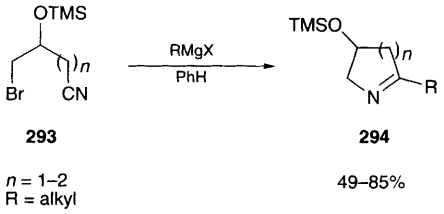
Burgess and co-workers have described the regio- and diastereo-selective opening of epoxides **288** derived from pyrrolidine- and piperidine ene carbamates (**Scheme 84**).[85] With allyltrimethylsilane as the nucleophile, the *syn*:*anti* ratio could be influenced by the nature of the Lewis acid, particularly in the piperidine series. This methodology was used to synthesize febrifugine, a *Hydrangea* alkaloid that possesses antimalarial and anticoccidal properties (**290**+**291**→**292**).



n	R	Lewis acid	**289a:b**	Yield (%)
1	Ph	TMSOTf	1.5:1	80
2	Et	TMSOTf	1:2	85
2	Et	$SnCl_2$	3.5:1	55

Scheme 84

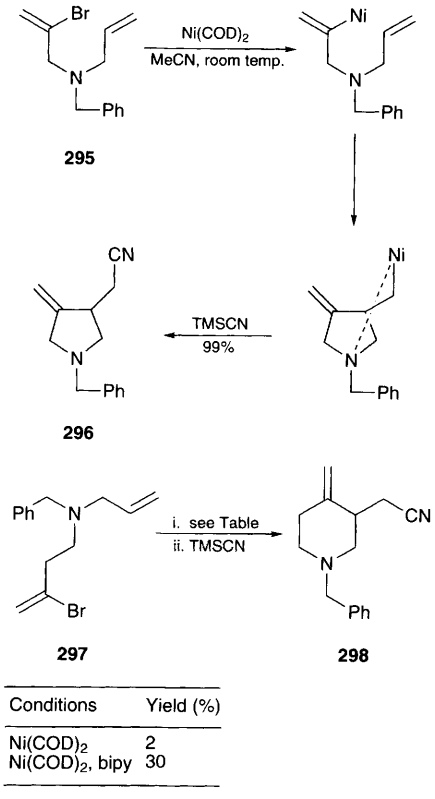
Fry and co-workers have described the synthesis of five- and six-membered cyclic imines by the addition of simple Grignard reagents to ω-bromonitriles (**293**→**294**, **Scheme 85**).[86] The diastereo-



Scheme 85

selective reduction of some of the six-membered imines derived from this reaction to piperidines was also investigated.

The nickel-promoted cyclization of certain allylamines to piperidines or pyrrolidines has been described by Delgado and co-workers (**Scheme 86**).[87] Treatment of **295** with $Ni(COD)_2$ and one of a wide range of electrophilic or nucleophilic quenching



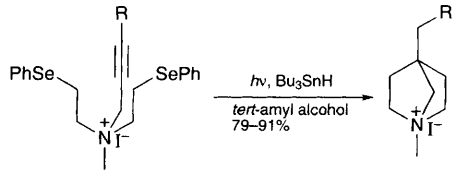
Conditions	Yield (%)
$Ni(COD)_2$	2
$Ni(COD)_2$, bipy	30

Scheme 86

agents (TMSCN, alkyl halides, acid chlorides, $NaBH_4$) gave the correspondingly substituted pyrrolidines **296** in quite good yields. The homologous reactions with **297** were less successful: the standard reaction conditions gave only 2% of the desired product **298**, and addition of 2,2′-bipyridine (to ligate the nickel atom) increased this to only 30%.

10 Miscellaneous

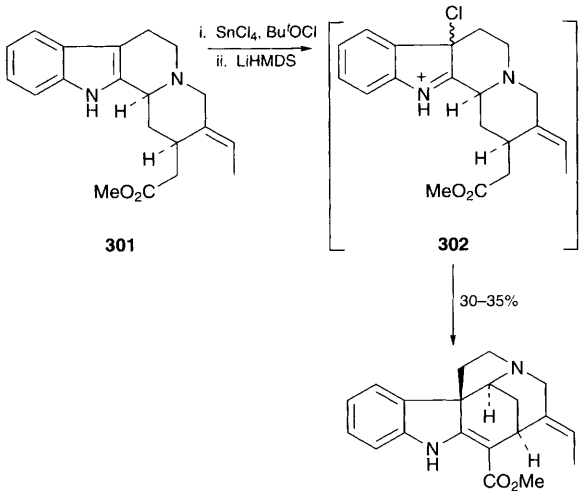
Della and Knill have described an interesting synthesis of the 1-azabicyclo[2.2.1]heptyl system (**Scheme 87**).[88] Treatment of **299** with Bu_3SnH–*hν* in



Scheme 87

tert-amyl alcohol effected the synthesis of **300** in 79% overall yield when R = H.

Finally, we conclude with the extraordinary biomimetic transformation of **301** directly into the natural product (±)-akuammicine as reported by Martin and co-workers (**Scheme 88**).[89] Treatment of **301** with $SnCl_4$ and *tert*-butyl hypochlorite gave initially an epimeric mixture of cationic chloroindolenines **302**, which on treatment with $LiN(SiMe_3)_2$ rearranged to akuammicine, in a similar manner to that demonstrated in the biosynthesis of other *Strychnos* alkaloids.



Scheme 88

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