Part One
Strained Heterocycles in the Synthesis of Natural Products

1
Aziridines in Natural Product Synthesis

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1.1
Introduction

The aziridinyl ring has attracted considerable attention over the last 20 years. A number of reviews dedicated to the synthesis of aziridines has appeared, dealing mainly with the preparation of this small heterocycle [1] and its reactions [2]. Very few have focused on natural product synthesis using aziridines.

This review is devoted to the occurrence of the aziridine moiety in the total synthesis of natural products (Table 1.1). Aziridines can be present in the natural product itself, or can serve as intermediates in the course of the natural product synthesis. Only the synthesis of truly natural products will be discussed here, and the synthesis of analogs or non-natural products will not be developed [3]. This review covers the literature from 1986, and follows the previous review [4] focused on aziridines in natural product synthesis.

1.2
Synthesis of Natural Products Containing Aziridine Units

The ability of aziridines to undergo highly stereo- and regioselective ring-opening reactions has been exploited in nature. A number of natural products possessing an aziridine ring have been shown to possess potent biological activity, which is closely associated with the reactivity of the strained heterocycle.

1.2.1
### Synthesis of Aziridine-2,3-Dicarboxylic Acid

Among natural products containing aziridines, C_2-symmetric aziridine-2,3-dicarboxylic acid **4**, a metabolite of *Streptomyces* MD 398-A1 [5a] was prepared in enantiopure form in few steps from L-(+)-diethyl tartrate [5b]. An optimized synthetic pathway to aziridine-2,3-dicarboxylate precursor **3** of naturally-occurring aziridine **4** was published later, removing the epimerization tendency

Table 1.1 Aziridine-based natural products.

Serial No.	Trivial name	Structure	Source	Isolation [Ref]	Biological activity	Synthesis [Ref]
1	Aziridine-2,3-dicarboxylic acid		*Streptomyces MD 398-A1*	[5a]	Antibacterial activity	[5b, 6]
2	(Z)-Dysidazirine		*Dysidea fragilis*	[7a]	Cytotoxicity, antifungal activity	[7b, 8]
3	FR-900482		*Streptomyces sandaensis*	[9a]	Antibacterial, anticancer activity	[10–15]
4	FR-66979		*Streptomyces sandaensis*	[9b]	Antibacterial, anticancer activity	[15, 16]
5	Mitomycin A		*Streptomyces cuesipitasus*	[17b]	Antibacterial, anticancer activity	[18, 19]
6	Mitomycin C		*Streptomyces cuesipitasus*	[17a]	Antibacterial, anticancer activity	[19, 20]
7	Mitomycin K		*Streptomyces verticillatus*	[17c]	Antibacterial, anticancer activity	[21, 22]
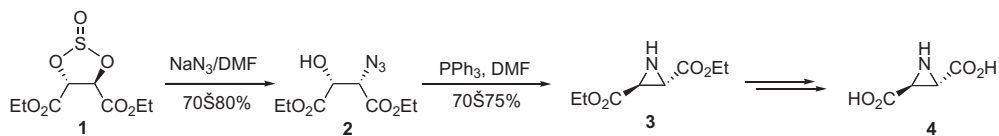
Scheme 1.1 Aziridine-2,3-carboxylic acid.
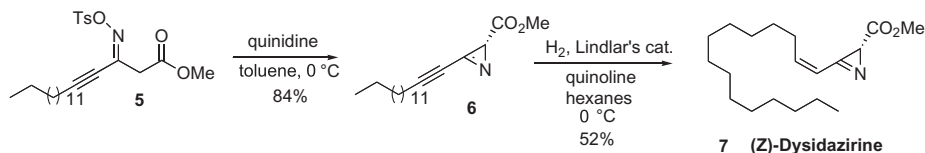
Scheme 1.2 (*Z*)-Dysidazirine.

of synthetic intermediates by using *anti*-3-azido-2-hydroxy-succinate **2** (Scheme 1.1) [6].

1.2.2
Synthesis of (*Z*)-Dysidazirine

While the first enantioselective synthesis of antifungal active (*Z*)-dysidazirine **7** isolated from the marine sponge *Dysidea fragilis* [7a] was achieved by a Darzens-type synthesis of *cis-N*-sulfinylaziridine carboxylic acid [7b], a very recent synthesis includes the transformation of tosylated imine **5** into azirine carboxylate **6** as a key step (Scheme 1.2) [8].

1.2.3
Syntheses of Mitomycins

In the field of total synthesis of natural products containing an aziridine ring, most efforts of synthetic organic chemists have been dedicated to mitomycins, a class of very potent antibacterial and anticancer compounds isolated [17] from extracts of genus *Streptomyces*, a filamentous gram-positive soil bacterium. The most abundant mitomycins in nature are represented in Scheme 1.3. Mitomycin C [17a], besides mitomycin A [17b] and K [17c], has become the most effective drug of the series against non-small-cell lung carcinoma and other soft and solid tumors [23]. Despite significant medicinal features, syntheses of this class of compounds (furthermore in racemic form) have been reported only four times over the past 30 years [24].

Since the first synthesis of a mitomycin by Kishi [18], only few organic chemists have succeeded to achieve a total synthesis of a mitomycin since serious difficulties occurred during the construction of both reactive quinone and aziridine rings with the elimination of methanol from the 9a position (Scheme 1.3). Mitomycins A and
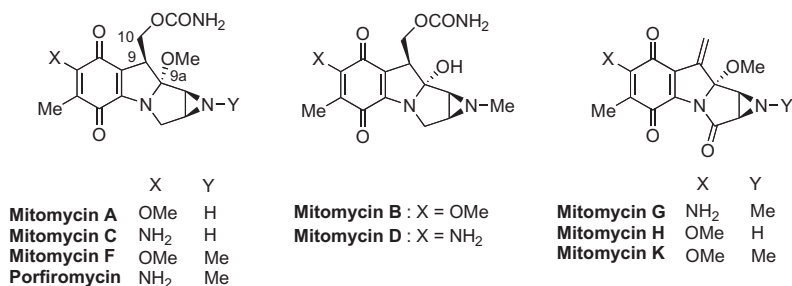
**Scheme 1.3** General mitomycins.
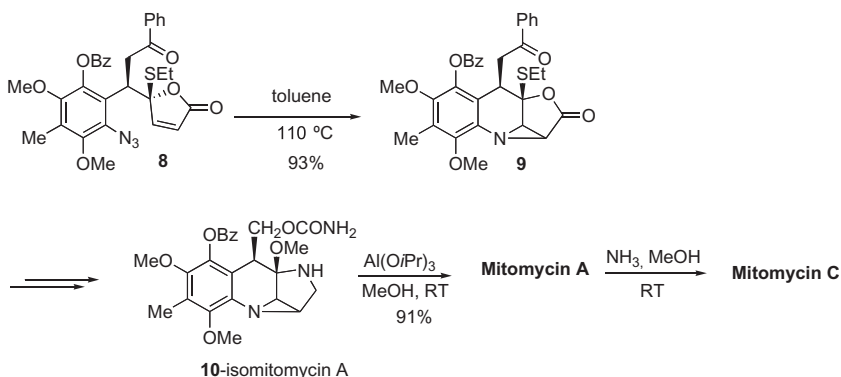

Scheme 1.4 Mitomycin A and C.

C were successfully synthesized by Fukuyama and co-workers in 18 steps from a readily available chalcone [19]. An intramolecular azide-olefin cycloaddition on **8** gave exclusively tetracyclic aziridine **9**. Isomitomycin intermediate **10** was then obtained in few steps providing mitomycin A by a subsequent reaction with Al(*i*-OPr)$_3$. A final ammonolysis step gave mitomycin C (Scheme 1.4).

Subsequent improvement for the total synthesis of mitomycin C was reported later by the same authors using highly reactive bridgehead iminium species in the key steps [20]. The required C-9a methoxy group was introduced under mild acidic conditions to give **13** in 60% yield via highly strained iminium ion **12** which was obtained from compound 11 through acidic treatment. Transformation of the aromatic ring of **13** using hydrogenolysis followed by oxidation with DDQ afforded the desired quinone ring of isomitomycin A in 77% yield. Isomitomycin A was then converted to (±)-mitomycin C via isomitomycin C **15** in 85% yield by treatment with NH$_3$ in methanol (Scheme 1.5).

Danishefsky and colleagues have designed a short total synthesis of the densely functionalized mitomycin K from parent mitomycins A and C by elimination of the carbamate at position 10 [21]. Introduction of *N*-methyl aziridine from an olefin was achieved in only 3 steps by 1,3-dipolar cycloaddition. Reaction of meth-
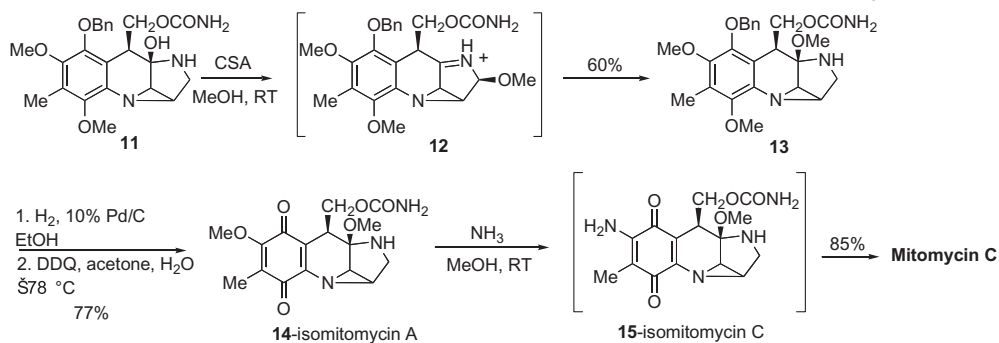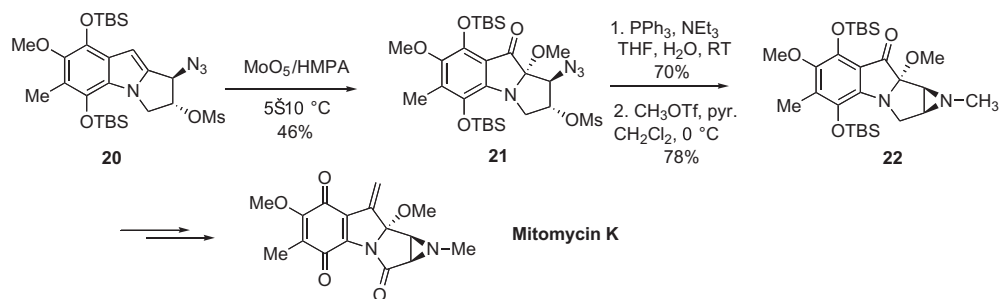
Scheme 1.5 Mitomycin C.
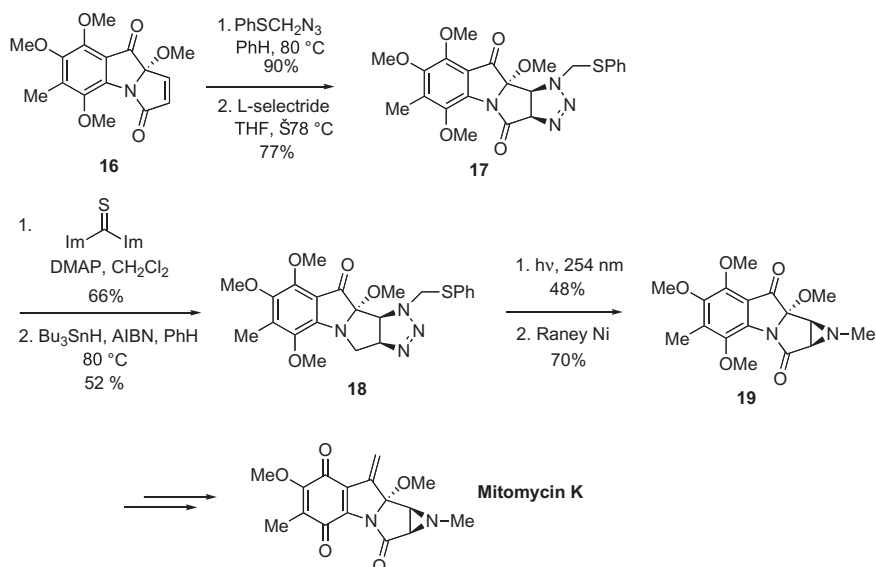
Scheme 1.6 Mitomycin K.

ylthiophenyl azide with imide **16** provided triazoline **17** which was then transformed to **18** in two steps. *N*-methylaziridine **19**, an advanced intermediate to mitomycin K, was obtained by irradiation at 254 nm (Scheme 1.6).

A facile method was set up for the transformation of azidomitosenes **20** into mitomycins (introduction of the C9a methoxy group) by using an oxidation reaction of the C9-9a double bond with $MoO_5 \cdot$ hexamethylphosphoramide (HMPA). Specifically, oxidation of **20** afforded in 46% **21** from which the fused *N*-methylaziridine ring could be constructed. **22** led to the mitomycin K in two steps. (Scheme 1.7) [22].

Scheme 1.7 Mitomycin K.
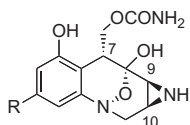
**FR-66979**, R = CH$_2$OH
FR-900482, R = CHO

Scheme 1.8 FR-66979 and FR-900482.

1.2.4
Syntheses of FR-900482 and FR-66979

Antitumor antibiotic natural products FR-900482 and FR-66979 (Scheme 1.8) isolated from *Streptomyces sandaensis* [9] are structurally related to mitomycin C and possess similar biological activities. They have proven to be less toxic than mitomycins in clinical cancer chemotherapeutics. In addition of the biomedical potential, the uncommon structure and the synthetic problem related to the construction of both aziridine ring and the hemiacetal functionality of FR-900482 and FR-66979 have attracted the attention of a number of synthetic chemists. Although several approaches have been explored to construct these highly functionalized structures, only six total syntheses have been accomplished and two formal syntheses [10, 25] have been reported to date.

The first total synthesis of (±)-FR-900482 was realized in 41 steps from readily available *N*-benzylamine [11]. In this strategy, the authors introduced the aziridine ring at the end of the synthesis to prevent any lability of the three-membered ring under acidic condition. Azide **24** was prepared by ring opening of epoxide **23** with NaN$_3$ followed by the transformation of the resulting alcohol to a mesylate. Upon oxidative treatment of **24** to exchange the PMB-protecting group on the aromatic ring for a dimethyl acetal, reduction of azide **25** by PPh$_3$ in the presence of a base furnished aziridine **26** which was then advanced to the target compound (Scheme 1.9). An enantioselective total synthesis of (+)-FR-900482 was reported later on by the same group with a slight modification of the initial route [12].
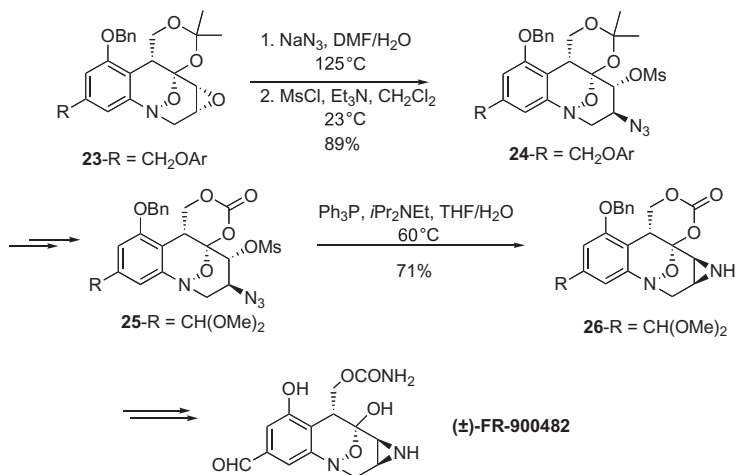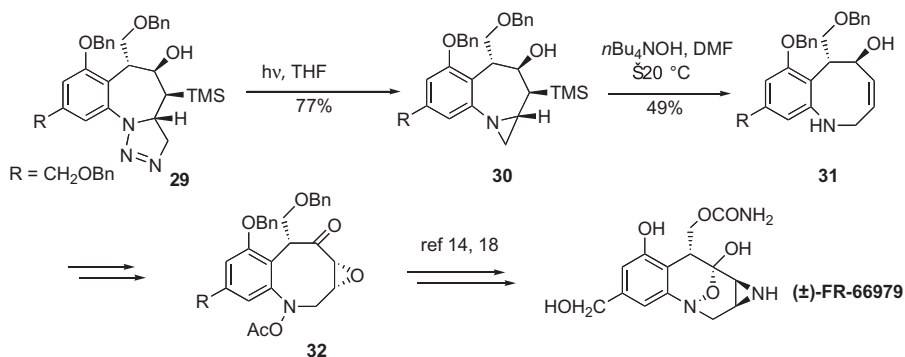
Scheme 1.9 (±)-FR-900482.
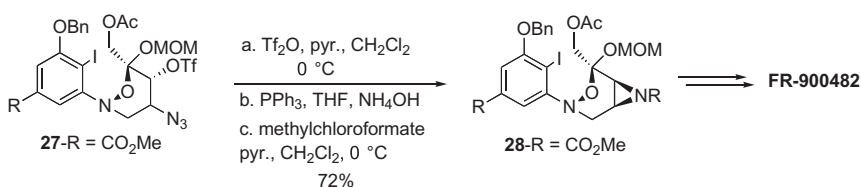
Scheme 1.10 (±)-FR-900482.

Danishefsky reported a total synthesis of racemic FR-900482 [13] in which the installation of the 9,10-aziridine ring was carried out following the precepts founded by Kishi and colleagues in their synthesis of mitomycins [26]. Compound **27** was treated in sequence with Tf_2O and pyridine, PPh_3, NH_4OH and finally methylchloroformate to furnish aziridine **28** in 72% overall yield (Scheme 1.10).

Naturally occurring FR-66979 has been synthesized in racemic form with a method comprising an original homo-Brook-mediated aziridine fragmentation of compound **30** providing the eight-membered ring benzazocenol **31**. The aziridine ring and the end of the total synthesis [16] were achieved subsequently from epoxide **32** following a described procedure (Scheme 1.11) [11].

The first enantioselective synthesis of the enantiomer of FR-900482 was developed by Terashima [27] starting from FK-973 [10], the more stable semisynthetic triacetyl derivatives of FR-900482. In the same time, a second total synthesis of both enantiomers was accomplished in a convergent manner in a 57 steps sequence using classical methods for the introduction of the aziridine ring [14].

Shorter enantioselective total syntheses of (+)-FR-900482 and (+)-FR-66979 were reported by Williams and co-workers and described the installation of the labile

Scheme 1.11 (±)-FR-66979.
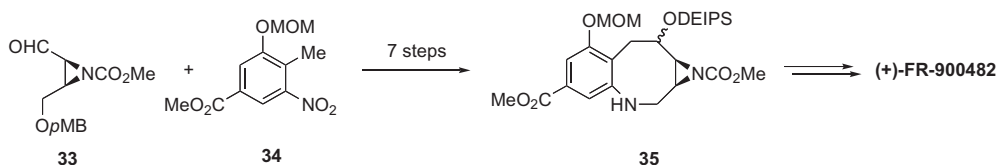
Scheme 1.12 (+)-FR-900482.

aziridine ring in the very beginning of the synthesis. In this purpose, aziridine **35** was prepared in 7 steps from compounds **33** and **34** (Scheme 1.12) [15].

1.3
Synthesis of Natural Products Involving the Transformation of an Aziridine Moiety

1.3.1
Nucleophilic Ring-Opening of Aziridines for Natural Product Synthesis

The usefulness of aziridines in organic synthesis is greatly related to their facility to undergo nucleophilic ring opening to relieve ring strain. In the case of "unactivated" alkyl-substituted or unsubstituted aziridines, acid catalysis is usually required. Conversely, it is well known that aziridines bearing nitrogen electron-withdrawing substituents such as carbonyl, sulfonyl, sulfinyl, phosphoryl, and phosphinyl are activated towards nucleophilic ring opening as the developing negative charge on nitrogen is stabilized. A wide array of nucleophiles can be used and in most cases, the regio- and stereoselectivity of the ring opening is predictable, a matter of paramount relevance when it comes to design a synthetic plan. While selectivity issues are highly dependent on the substrate and the reaction conditions, steric congestion is often at the origin of regioselectivity (nucleophilic attack occurring at the less congested terminus) and stereoselectivity is frequently

related to a ring opening resulting from an *anti* attack (stereospecific S_N2). A tremendous body of work has been disclosed in the field and the subject has been comprehensively reviewed. The use of nucleophilic ring opening of aziridines in the context of natural product synthesis, illustrated hereafter through representative examples, provides a good indication of the reaction's synthetic potential.

### 1.3.1.1 Carbon-Centered Nucleophiles

Nucleophilic ring opening of aziridines with carbon nucleophiles is mainly achieved using organometallic reagents. In spite of an early report in the 1970s [28], this type of reaction only started to become customary in natural product synthesis following seminal reports in the late 1980s concerning the use of organocuprate or Grignard reagents to open *N*-alkyl aziridines in the presence of BF_3 Et_2O [29] or to open *N*-tosyl aziridines (with no need of Lewis acidic activation) [30].

Ring opening of aziridines with organocopper reagents has proved useful for a number of syntheses. In a first example, as part of their studies on the synthesis of carbapenem antibiotics using aziridine ring openings [2a], Tanner and co-workers developed an enantioselective entry to naturally occurring (+)-PS-5 (Scheme 1.13) [31]. Reaction of $LiEt_2Cu$ with chiral *trans*-2,3-aziridino alcohol **36** afforded in 70% yield sulfonamido alcohol **37** which proved suitable for β-lactam ring construction and was advanced to a known intermediate of (+)-PS-5. As a result of the complexation of the reagent to the free C-1 hydroxyl group, nucleophilic attack occurred highly regioselectively at the C-2 carbon, in a behavior analogous to that of related epoxy alcohols. Ring opening took place with inversion of configuration and thus provided the requisite stereochemistry for the stereogenic centers of the final product. Interestingly, the related ring opening of the analogous 3-benzyloxyethyl substituted aziridino alcohol using excess Me_3Al took place at the C-3 carbon [32], a transformation that proved useful for the preparation of non-natural 1β-methylcarbapenem antibiotics [33].

In addition to cuprates, addition of Grignards has also been often used, most of the time under copper catalysis. For instance, Harrity and co-workers disclosed a formal synthesis of (–)-dihydropinidine wherein the tetrahydropyridine ring was constructed through a two-step [3 + 3] annelation sequence involving the reaction between alkylmagnesium reagents such as **38** bearing a pendant 1,3-dioxolane moiety and terminal *N*-sulfonyl aziridines (Scheme 1.14) [34]. Specifically, **38** was reacted with aziridine **39** in the presence of 20 mol % CuBr to afford intermediate **40**, which, upon acidic hydrolysis without intermediate purification, led to piperidine **41** in 78% overall yield.
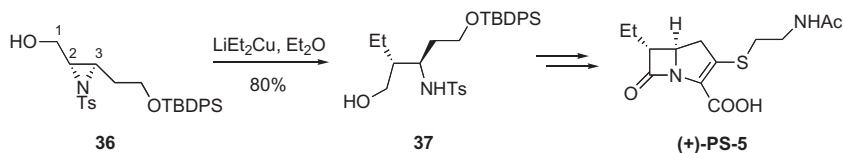

Scheme 1.13   (+)-PS-5.
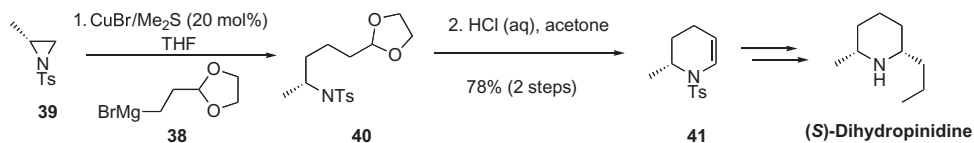
Scheme 1.14 (–)-Dihydropinidine.
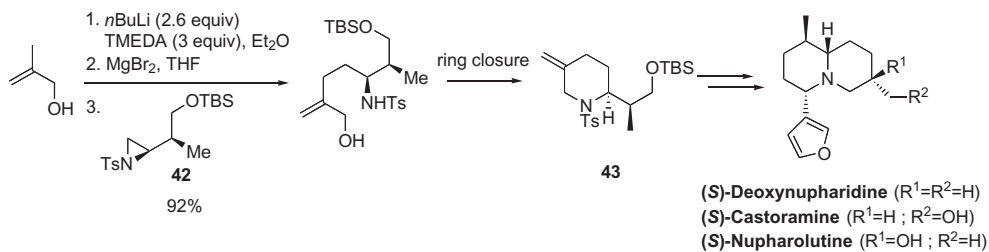
Scheme 1.15 Nuphar alkaloids.

In a related [3 + 3] annelation strategy, the allylmagnesium reagent obtained following deprotonation/transmetallation of methallyl alcohol was found to react with terminal *N*-sulfonyl aziridines, but this time with no need of copper salt addition (Scheme 1.15). The resulting 1,5-aminoalcohol could undergo ring closure to piperidines using palladium catalysis or Mitsunobu conditions, thus affording 2-alkylpiperidines with an exo methylene moiety at C-5, in what represents an improved approach to the related [3 + 3] cycloaddition reaction between aziridines and palladium-trimethylenemethane (Pd-TMM) species (see Section 1.3.2.4). In its application to synthesis, nucleophilic ring opening of enantiopure aziridine **42** and subsequent cyclization led to piperidine **43** that could be advanced to *nuphar* alkaloids (–)-deoxynupharidine, (–)-castoramine and (–)-nupharolutine [35, 36]. The same approach has also been used for the construction of the spiropiperidine motif in the formal synthesis of (±)-perhydrohistrionicotoxin [37].

Copper-bromide promoted coupling of arylmagnesium derivatives with terminal enantiopure *N*-butoxycarbonyl (*N*-Boc) aziridines is pivotal in the design of a very recent approach to renieramycin alkaloids based on the use of aziridines derived from (*S*)-serine as linchpins to bring together both tetrahydroisoquinoline parts of the target molecules (Scheme 1.16) [38]. First, homologation of densely substituted arylmagnesium **44** was effected by nucleophilic ring opening of enantiopure terminal *N*-Boc aziridine **45**. Intermediate **46** was then further elaborated through a Pictet–Spenger reaction involving aziridine **47**. The right and left part of the molecules were connected through a second copper -promoted coupling between **48** and arylgrignard **49** which afforded **50**, reaction of which with benzyloxyacetaldehyde led to a bistetrahydroisoquinoline common intermediate to (–)-renieramycins M and G and (–)-jorumycin, three alkaloids with potent antitumor antibiotic activities.
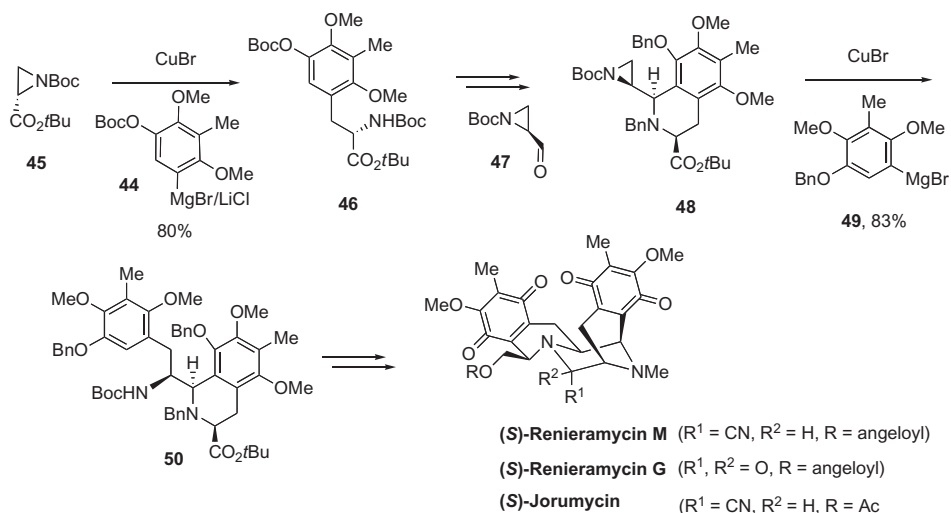
Scheme 1.16 Renieramycins.
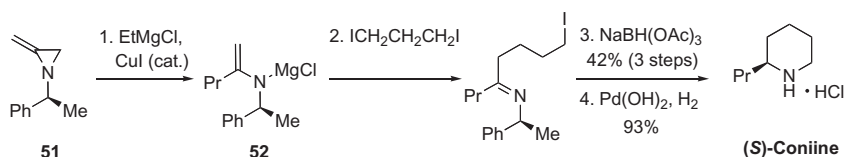
Scheme 1.17 (*S*)-Coniine.

Interestingly, copper-catalyzed nucleophilic ring opening of *N*-alkyl 2-methyleneaziridines by Grignard reagents does not require Lewis-acidic activation of the heterocycle if carried out at room temperature (Scheme 1.17). It results in the highly regioselectivity formation of a metalloenamine that can then be alkylated in the presence of electrophiles. Building on this chemistry, a concise synthesis of the hemlock alkaloid (*S*)-coniine was achieved from enantiopure methyleneaziridine **51** using a multicomponent strategy involving: ring opening, alkylation of the resulting metalloenamine **52** with a 1,3-difunctionalized electrophile, and diastereoselective reduction followed by *in situ* cyclization [39].

In addition to organocopper and organomagnesium reagents, ring opening of aziridines by lithium carbanions has also been used for synthetic purposes. The reaction between α-(phenylsulfonyl) lithio anions and *N*-phosphinyl or *N*-sulfonyl aziridines plays a key role in the strategy developed by Craig and co-workers for the synthesis of pyrrolidine-containing alkaloids (+)-monomorine I [40], (+)-preussin [41] and (±)-lepadiformine [42], built around the base-mediated 5-*endo*-trig intramolecular addition of amides onto vinylic sulfones. The case of (±)-lepadiformine is illustrative (Scheme 1.18). Ring opening at the least-substituted carbon of *N*-SES aziridine **53** by PhSO$_2$CH$_2$Li led to 3-amino sulfone **54**. *In situ* generation
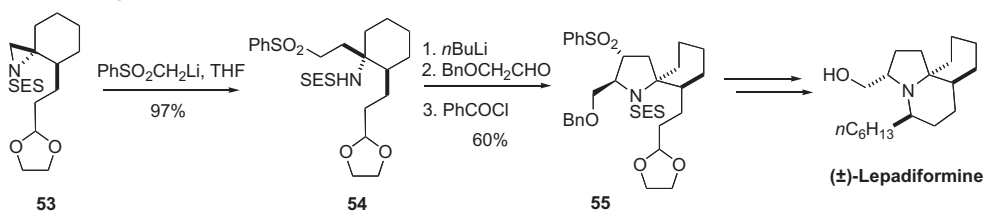
Scheme 1.18 (±)-Lepadiformine.
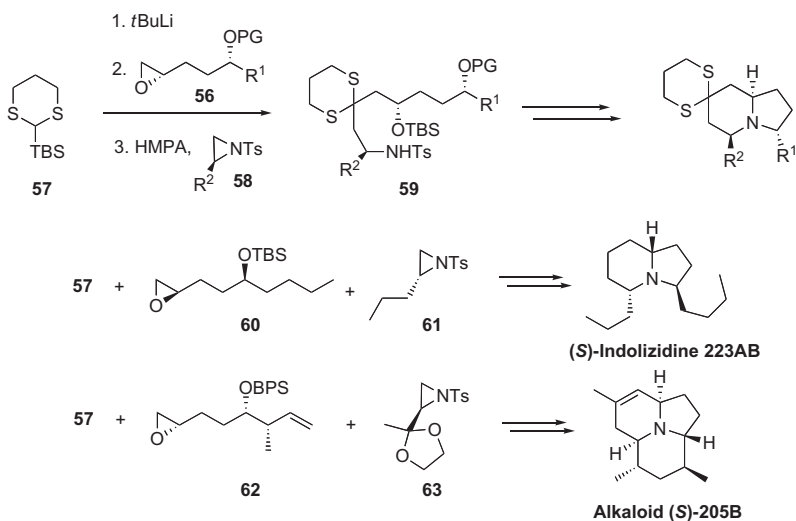
Scheme 1.19 (–)-Indolizidine 223AB and alkaloid (–)-205B.

of the requisite vinylic sulfone from this precursor enabled pyrrolidine formation following 5-*endo*-trig cyclization and afforded **55** that was advanced to the target compound.

Smith III and Kim have designed a very elegant strategy for the construction of indolizidine alkaloids using a three-component linchpin coupling involving a lithiated silyl dithiane, an epoxide and a *N*-tosyl aziridine (Scheme 1.19) [43, 44]. Nucleophilic ring opening of 5-alkoxy epoxides **56** by the lithio anion **57** of 1,3-dithiane resulted in the formation of a lithium alcoholate intermediate that underwent a solvent-controlled Brook rearrangement upon addition of HMPA. The lithiated dithiane derivative thus produced, could then be used to effect the nucleophilic ring opening of *N*-tosyl aziridines **58**, to afford, in fine, stereodefined 1,5-amino alcohols **59** that are suitable for indolizidine construction. This convergent approach has already proved successful for the preparation of (–)-indolizidine 223AB from enantiopure epoxide **60** and aziridine **61**, and for the preparation of alkaloid (–)-205B from enantiopure epoxide **62** and aziridine **63**.
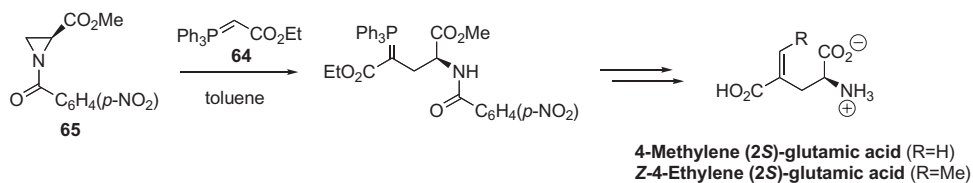
Scheme 1.20 Alkylideneglutamic acids.
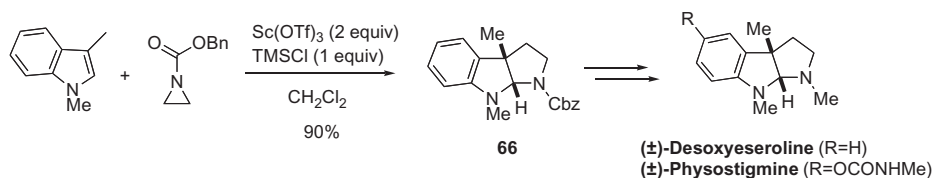
**Scheme 1.21** (±)-Physostigmine.

Ring opening of aziridines with carbon nucleophiles other than carbanions, though less common, has also proved useful for the synthesis of natural products. In an early example, Baldwin and co-workers disclosed an access to γ-alkylidene glutamates based on the reaction of carbonyl stabilized Wittig reagent **64** with enantiopure *N*-acyl and *N*-sulfonyl aziridine-2-carboxylates derived from serine (Scheme 1.20) [45]. For instance, the enantiopure ylide resulting from ring opening of aziridine **65** at the less-substituted carbon was further modified to provide 4-methylene (2*S*)-glutamic acid and *Z*-4-ethylene (2*S*)-glutamic acid.

Nakagawa and co-workers disclosed a concise approach to Calabar alkaloids based on the nucleophilic ring opening of *N*-benzyloxy-aziridine by 1,3-dimethylindole and subsequent intramolecular interception by nitrogen of the resulting indolenium (Scheme 1.21) [46]. In the optimized conditions involving activation of the aziridine by Sc(OTf)$_3$ in the presence of trimethylsilyl chloride (TMSCl), adduct **66** was obtained in 90% yield. This intermediate could be advanced to (±)-desoxyeseroline, a known intermediate of naturally occurring physostigmine.

Potassium cyanide was recently used efficiently for the ring opening of mono-substituted allylglycine derived *N*-sulfonyl aziridine **67** (used as mixture of diastereoisomers) (Scheme 1.22) [47]. The resulting β-aminonitrile moiety of adduct **68** could then be used for the construction of the 2-amino-tetrahydropyrimidine ring required to complete the synthesis of tetrahydrolathyrine.

1.3.1.2 Nitrogen-Centered Nucleophiles

Ring opening of aziridines with nitrogen nucleophiles, mainly amines and azides, has attracted considerable attention from organic chemists as a result of the increasing interest in diamine compounds for synthetic and pharmaceutical purposes. Quite surprisingly however, its use for the synthesis of natural products has so far been limited. As probable reasons, one might put forward both a limited
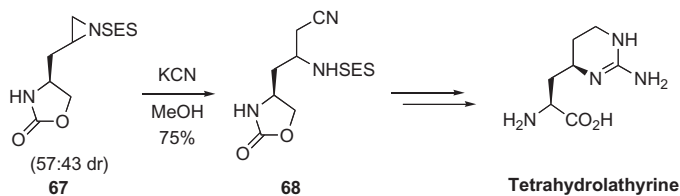
Scheme 1.22 Tetrahydrolathyrine.
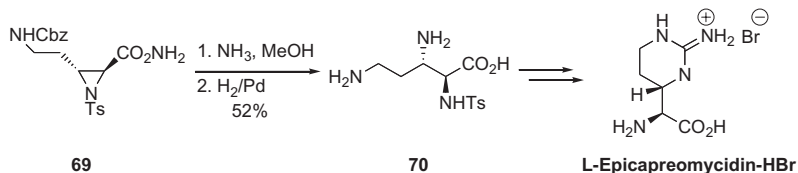
**Scheme 1.23** L-*epi*-Capreomycidin.

number of targets bearing the diamino moiety and the fact that amines are generally not inert to mainstream Lewis or Brønsted acidic aziridine ring opening promoters. Nonetheless, specially in the field of amino acid synthesis using aziridine-2-carboxylates as substrates, some elegant applications have been disclosed.

Amines are sufficiently nucleophilic to attack aziridines without the presence of a promoter. Shiba and co-workers took advantage of it to perform the ring opening of enantiopure *trans*-*N*-tosyl aziridine-2-carboxylate **69** with ammonia (Scheme 1.23) [48]. The attack took place regioselectively at C-3 in an S_N2 manner and thus afforded diamine **70** in 52% yield which was then converted into the hydrobromide salt of naturally occurring L-epicapreomycidin.

The reaction between amino acid carboxylates and *N*-tosyl aziridine-2-carboxylates has been used for the preparation of peptidyl derivatives (Scheme 1.24). In spite of moderate levels of regioselectivity, ring opening in methanol of aziridines **71** and **72** by nucleophilic attack of L-histidine at C-3 in the presence of 1M sodium hydroxide, was used for the preparation of FR900490 [49], feldamycin [50] (from **71**) and melanostatin [50] (from **72**).

In another related example, sodium pipecolinate was found to react highly efficiently with monosubstituted enantiopure *N*-tosyl aziridine **73** (Scheme 1.25). The corresponding piperidine adduct was obtained in 88% yield and was used to prepare verruculotoxin [51].

Other nucleophiles that have been used for the opening of aziridines without promoter are imidazole and 1,2,4-oxadiazolidine-3,5-dione (Scheme 1.26). Their reaction with (*S*)-serine derived enantiopure aziridine **74**, which has also proved useful in the context of ring opening with carbon nucleophiles (see Section 1.3.1.1), was carried out by Baldwin and co-workers to synthesize (*S*)-β-pyrazolylalanine and (*S*)-quiscalic acid [52].
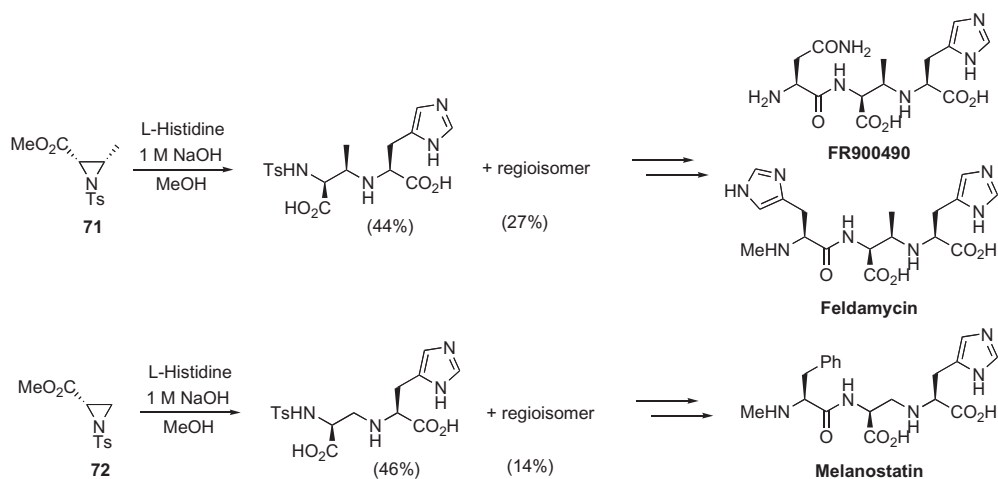
Scheme 1.24 FR-900490, feldamycin and melanostatin.
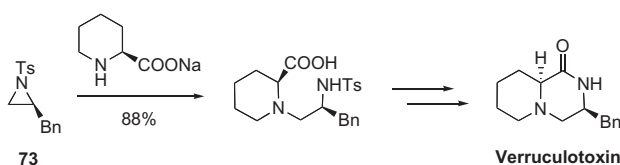
Scheme 1.25 Verruculotoxin.
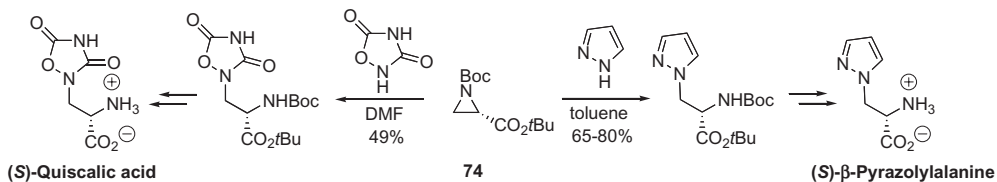
Scheme 1.26 (*S*)-β-Pyrazolylalanine.

From another perspective, as part of their studies on palladium-catalyzed dynamic kinetic asymmetric transformations, Trost and co-workers have developed a strategy towards pyrrolopiperazinones based on an annulation reaction between 5-bromopyrrole-2-carboxylate esters and vinyl aziridines (for a related cycloaddition reaction between vinyl aziridines and isocyanates see Section 1.3.2.4) (Scheme 1.27) [53]. In this transformation, following an asymmetric allylic alkylation step wherein the nitrogen of the pyrrole behaves as a good nucleophile for the regioselective ring opening of the aziridine, the pendant ester group serves as electrophile for lactam formation. Specifically, enantioselective palladium-catalyzed annulation
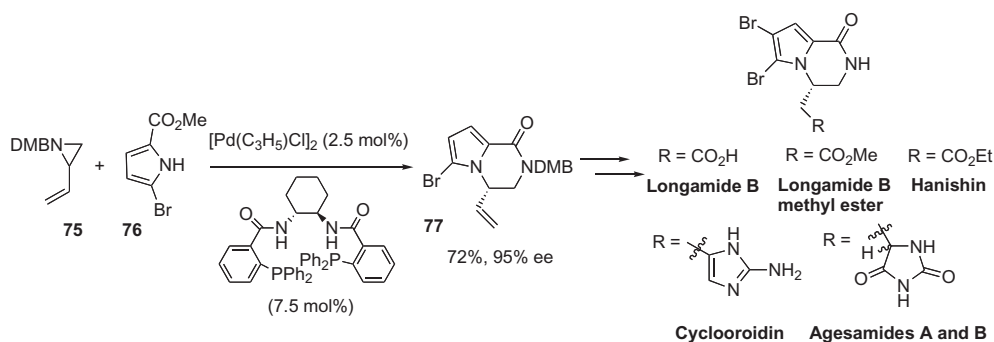
Scheme 1.27 Longamides and agesamides.
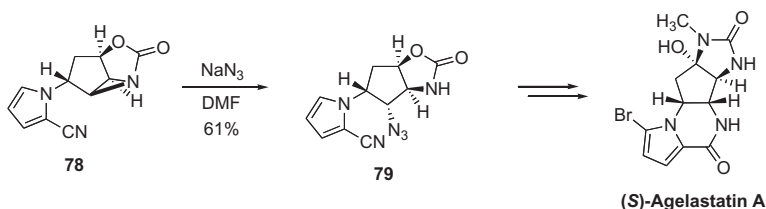
Scheme 1.28 (–)-Agelastatin A.

of racemic **75** and **76** provided pyrrolopiperazinone **77** in 72% yield and 95% enantiomeric excess. **77** was then found to be a suitable intermediate for the synthesis of pyrrole alkaloids longamide B (and thus longamide B methyl ester, hanishin and cyclooroidin) and agesamides A and B.

Finally, as illustrated in the synthesis of (–)-agelastatin A disclosed by Yoshimitsu, Ino and Tanaka, azides are also efficient nucleophiles to perform the ring opening of aziridines (Scheme 1.28) [54]. In the present example, unlike basic nitrogen nucleophiles such as ammonia and benzylamine that led to exclusive addition to the oxazolidinone core of **78**, sodium azide attacked the aziridine ring selectively to produce the azidated product **79** following cleavage of the weak outer bond of the tricyclic system.

1.3.1.3 Oxygen-Centered Nucleophiles
Nucleophilic ring opening of aziridines with oxygen nucleophiles provides direct access to amino alcohol units that are ubiquitous in nature. In general, aziridines, that show a lower reactivity towards this type of nucleophiles than structurally related epoxides, require activation of the nitrogen atom to undergo ring opening either by attachment of an electron-withdrawing group or by Brønsted or Lewis acids.

Ring opening using water as nucleophile leads directly to hydroxy amine derivatives and was promoted by strong organic Brønsted acids such as *p*-toluenesulfonic
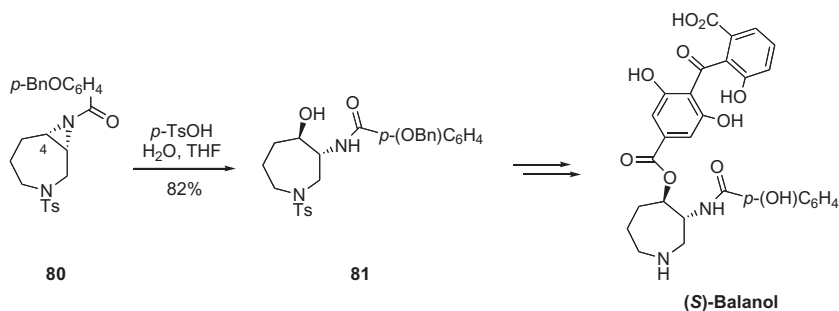
Scheme 1.29 (–)-Balanol.
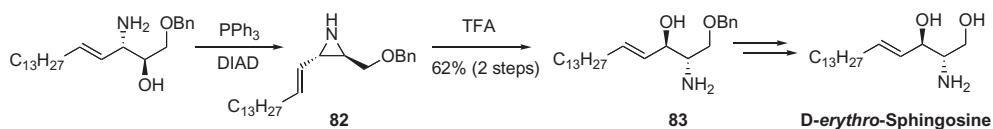
Scheme 1.30 D-*erythro*-Sphingosine.

acid (TsOH) and trifluoroacetic acid (TFA). Tanner and co-workers used this strategy in their synthesis of (–)-balanol (Scheme 1.29) [55–57], wherein treatment of enantiomerically pure *N*-acyl aziridine **80** with water in the presence of TsOH resulted in the near-exclusive ring opening at C-4 and led in 71% yield to amino alcohol **81** that was advanced to the natural product. The remarkable regioselectivity of the opening seemed to be related to both conformational and electronic effects of the fused bicyclic aziridine as it proved general for other nucleophiles and for ring opening of the analogous epoxide.

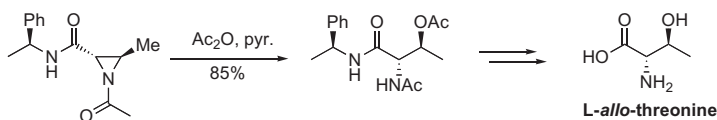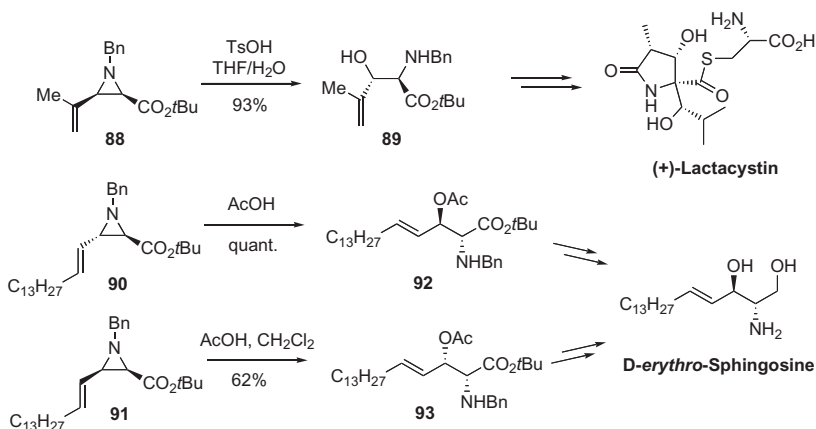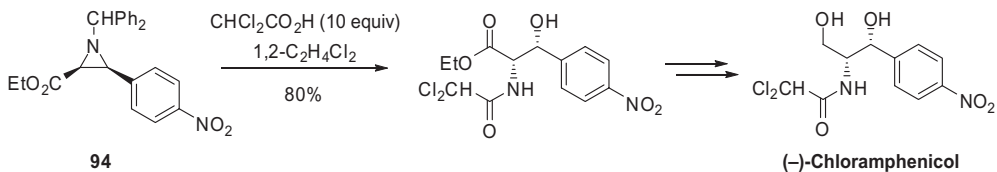Olofsson and Somfai used a TFA-mediated ring opening of a vinyl aziridine by water to synthesize D-*erythro*-sphingosine in enantiomerically pure form (Scheme 1.30) [58]. Specifically, crude unprotected aziridine **82** prepared from the parent vinylic 1,2-amino alcohol by Mitsunobu ring closure afforded regio- and stereoselectively *anti* amino alcohol **83** in 62% yield.

In the same vein, Trost and Dong performed the regio- and stereoselective hydrolytic ring opening of enantiopure fused bicyclic tosyl aziridine **84** on route to the non-natural (+) enantiomer of agelastatin A (Scheme 1.31) [59, 60][1]. Of the several conditions examined (CAN or BF$_3$ Et$_2$O in aqueous acetonitrile, variable amounts of TFA in aqueous acetone or dioxane at different temperatures), only treatment with TFA in dioxane/water under microwave heating (150 °C) gave high (84%) reproducible results. Interestingly, as the synthetic plan required oxidation

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1) Intermediate **84** is prepared from achiral starting materials using enantioselective catalytic reactions with chiral ligands available in both enantiomeric forms.

Synthesis of the natural (–) enantiomer of agelastatin should thus mirror the sequence used for the (+) enantiomer.

Scheme 1.31 (+)-Agelastatin A.

Scheme 1.32 Actinomycin D.

of the hydroxy amine to the corresponding α-amino ketone, direct oxidative ring opening was also developed. Reaction of **84** in DMSO in the presence of 0.7 equiv In(OTf)₃ led directly to **85** in 91% yield through a mechanism believed to involve attack of DMSO to the In(III) activated aziridine.

Nucleophilic ring opening of aziridines using carboxylate anions is rather common in the context of total synthesis. Very popular is the opening of aziridines containing 2-carboxylate or 2-carboxamide functionalities as it generally occurs regioselectively at C-3 and affords α-amino acid derivatives. Carboxylic acids themselves can operate this reaction in neutral conditions. For instance, Okawa and co-workers disclosed a total synthesis of cyclic peptide actinomycin D wherein ester bond formation between two dipeptide fragments was achieved in 45–55% yield through nucleophilic ring opening of 2-carboxamide-*N*-acyl aziridine **86** by the acid moiety of dipeptide **87** (Scheme 1.32) [61].

Alternatively, Cardillo and co-workers operated the ring opening of a similar aziridine in milder conditions using acetic anhydride in the presence of pyridine (Scheme 1.33) [62].

A nice illustration of the synthetic complementarity between opening by carboxylate and hydrolytic ring opening of *N*-benzyl aziridine-2-carboxylates can be found in the work of Ishikawa and co-workers (Scheme 1.34) [63]. Treatment of enantiopure *cis*-aziridine **88** with TsOH in the presence of water led in excellent

Scheme 1.33   L-*allo*-Threonine.

Scheme 1.34   (+)-Lactacystin and D-*erythro*-sphingosine.


Scheme 1.35   (–)-Chloramphenicol.

regio- and stereoselectivity to hydroxy amine **89** that was then used to prepare a known intermediate of (+)-lactacystin. However, when a similar approach was projected to access D-*erythro*-sphingosine, ring opening under analogous conditions of *cis*- or *trans*-aziridines **90** and **91** occurred with lower regioselectivity, a result that also contrasts with the opening of **82** in Somfai's approach (see above Scheme 1.30). Conversely, reaction with acetic acid was completely regio- and stereoselective and afforded acetoxy amines **92** and **93** that were used to reach the desired target.

Interestingly, Loncaric and Wulff evidenced that in the case of *N*-benzhydryl aziridine-2-carboxylate **94**, treatment with excess carboxylic acid resulted not only in ring opening at the benzylic position, but also in the subsequent *in situ* deprotection and acetyl transfer (Scheme 1.35). This sequence was elegantly exploited to prepare (–)-chloramphenicol enantioselectively [64].
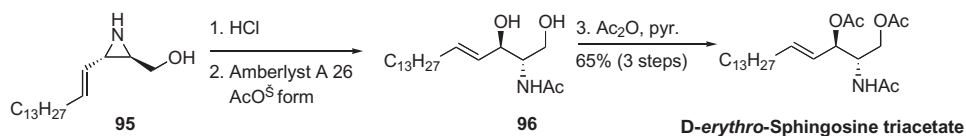
Scheme 1.36 D-*erythro*-Sphingosine triacetate.
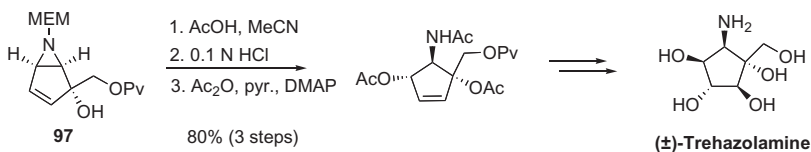

Scheme 1.37 (±)-Trehazolamine.
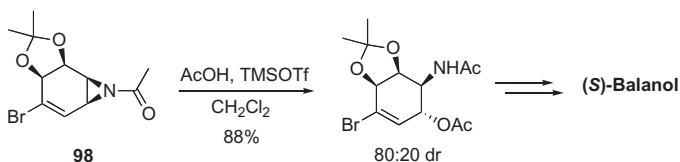

Scheme 1.38 (–)-Balanol.

A similar mechanism might be operating in the ring opening of unprotected aziridine **95** to afford *erythro*-sphingosine *N*-acetate **96** following treatment in refluxing benzene first with HCl and then with amberlyst A 26 in the acetate form (Scheme 1.36) [65].

Worthy of note, in addition to the above mentioned examples starting form aziridine-2-carboxylates, some examples of nucleophilic ring opening by acetates of fused bicyclic vinyl aziridines have been disclosed. In an approach to potent trehalase inhibitor (±)-trehazoline, Mariano and co-workers used acetic acid to achieve the ring opening of bicyclic *N*-MEM aziridine **97** obtained by photocyclization of 1-MEM-3-pivaloylmethylpyridinium perchlorate (Scheme 1.37) [66]. The use of a chiral inductor for the aziridination instead of the MEM group provided an enantiodivergent formal synthesis of the natural (+) and unnatural (–) enantiomers.

Similarly, in order to determine the optical rotation of a well established intermediate to (–)-balanol with absolute optical purity, Hudlicky and Sullivan carried out the ring opening of bicyclic *N*-acetyl vinyl aziridine **98** with acetic acid in the presence of trimethylsilyl triflate (TMSOTf) (Scheme 1.38) [67]. While nucleophilic attack of the acetate occurred unsurprisingly at the allylic position, only moderate levels of diastereoselectivity were achieved.
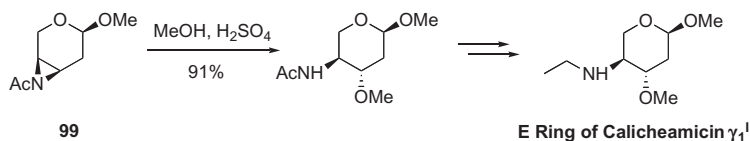
Scheme 1.39 Calicheamicin.
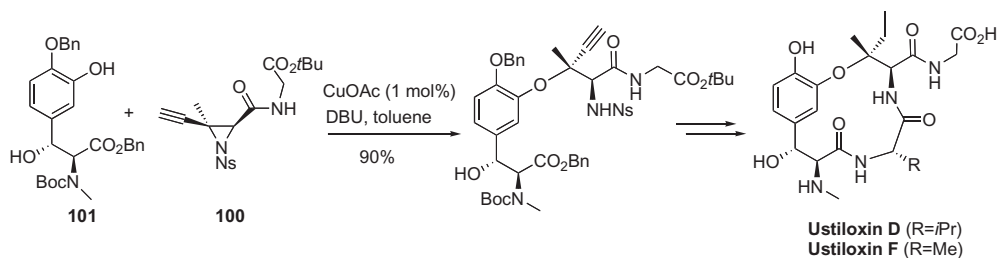
Scheme 1.40 Ustiloxins.

The use of nucleophilic ring opening of aziridines with alcohols for the synthesis of natural products has been rather limited so far. As previously, activation by Brønsted or Lewis acids is generally required. In an example of the first type, opening of *N*-acyl aziridine **99** by methanol promoted by sulfuric acid was found to be highly regio- and stereoselective, presumably as a result of conformational constraints of the bicyclic structure (Scheme 1.39) [68]. The resulting amino ether was used for the synthesis of E ring monosaccharide unit of calicheamicin γ_1^I. In an example of the second type, Lewis-acidic activation with $BF_3 \cdot Et_2O$ was used to promote the addition of allyl alcohol to a 2,3-aziridino-γ-lactone in the synthesis of the non-natural enantiomer of polyoxamic acid [69].

From a different angle, Jouillé and co-workers have developed a highly convergent route to ustiloxins through the copper-catalyzed ethynyl aziridine ring opening by phenol derivatives (Scheme 1.40) [70, 71]. In a representative application to the synthesis of cyclopeptide ustiloxins D and F, 2-carboxamide-aziridine **100** was coupled regio- and stereoselectively with β-hydroxy tyrosine derivative **101** in 90% yield.

Remarkably, clean regio- and stereoselective nucleophilic ring opening of enantiopure 2-carboxylate-*N*-nosyl aziridine **102** by methanol, useful to synthesize β-methoxytyrosine, could be carried out with no activation, probably due to the fact that the electron-rich phenol moiety weakens the C–N benzylic bond (Scheme 1.41) [72]. As a matter of fact, in the presence of TFA or copper salts, the diastereoselectivity of the reaction was moderate, as ring opening seemed to be occurring both via S_N1 and S_N2 mechanisms.

In a last example involving this time nucleophilic ring opening in basic conditions, aziridino alcohol **103** led to the regio- and stereoselective formation of the known intermediate of bestatin **104**, upon treatment with formaldehyde in the
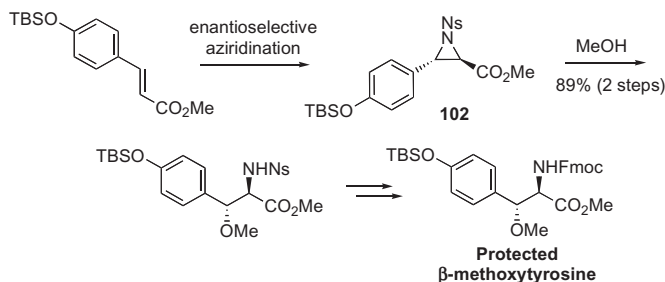
Scheme 1.41 β-Methoxytyrosine.
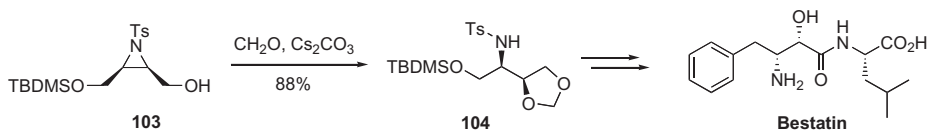
**Scheme 1.42** Bestatin.
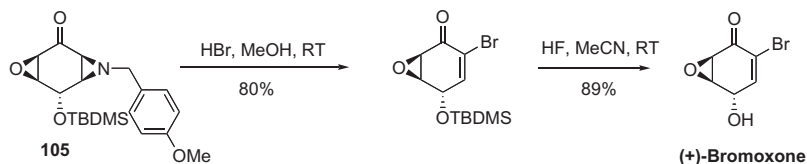
Scheme 1.43 (+)-Bromoxone.

presence of cesium carbonate via internal attack of the hydroxide anion of the hemiacetal formed *in situ* (Scheme 1.42) [73].

### 1.3.1.4 **Halogen Nucleophiles**

Ring opening of aziridines by halogen nucleophiles has been used only very recently for the purpose of natural product synthesis. Hydrogen bromide has been extensively used in the ring opening of aziridines to generate vicinal bromo amines. In the context of the synthesis of (+)-bromoxone, Maycock and co-workers described the use of 0.1 M HBr in MeOH to open selectively without any activation on the aziridine nitrogen *N*-PMB-aziridine **105** in the presence of an epoxide. The strategy was successfully applied to install the vinyl bromide moiety of the naturally occurring (+)-bromoxone (Scheme 1.43) [74].

Ring opening of aziridine **106** with tetraethylammonium chloride and TFA afforded with inversion and a total regio- and stereoselectivity the desired tetrahydroquinoline core of the virantmycin (Scheme 1.44) [75].
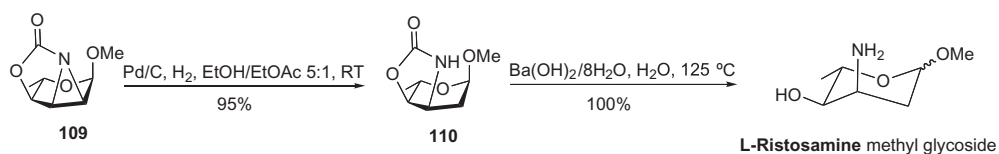
In the total synthesis of chlorodysinosin A, Hanessian and co-workers used cerium (III) chloride, an inexpensive and non-toxic inorganic salt to promote selec-
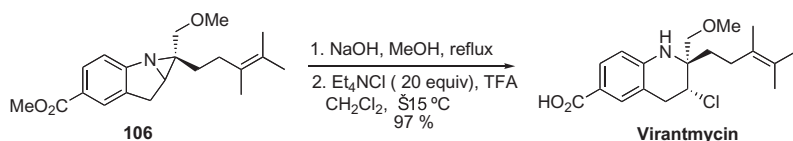
Scheme 1.44 Virantmycin.
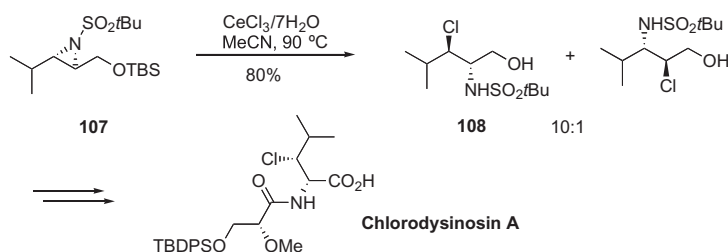
Scheme 1.45 Chlorodysinosin A.

Scheme 1.46 ʟ-Ristosamine.

tive ring opening of *N*-Bus aziridine **107** to form the corresponding 3-chloro sulfonamide **108** with an excellent regioselectivity (Scheme 1.45) [76].

1.3.1.5 Reductions

Reductive ring opening of aziridines can be highly regioselective by using catalytic hydrogenation. A very selective C–N bond cleavage was achieved on aziridine **109** using palladium on charcoal to produce carbamate protected ʟ-ristosamine derivative **110**, a useful synthon which after carbamate deprotection afforded ʟ-ristosamine methyl glycoside, a 2,3,6-trideoxy-3-amino-hexopyranose member of 2,6-dideoxy sugars. A similar series of transformation successfully afforded ʟ-daunosamine methyl glycoside (Scheme 1.46) [77].

1.3.2
Cycloaddition Reactions and Rearrangements

Aziridines have been used as partners in various cycloaddition reactions in order to obtain cyclic adducts. Intramolecular [3 + 2] cycloadditions of aziridines with olefinic moieties have been reported, as well as the [2,3]-Wittig rearrangement of vinylaziridines.

1.3.2.1 **Aziridines in [3 + 2] Cycloadditions**

Aziridinyl esters are known to be precursors of azomethine ylides [78] and to react with olefinic moieties in a [3 + 2] cycloaddition reaction. This key step was used by Takano and co-workers in the total synthesis of acromelic acid A (Scheme 1.47) [79]. Aziridine **111** reacted under thermal conditions to form the corresponding pyrrolidinyl cycloadduct stereoselectively, an advance intermediate to acromelic acid A.

The same key step has also been used [80] by the same authors in a total synthesis of (–)-kainic acid, as depicted in Scheme 1.48. This key step has also been used in a synthesis of the unnatural *N*-demethyl mesembrine [81].

Related to these [3 + 2] cycloaddition reactions, the thermal rearrangement of vinylaziridines such as **112** bearing an electron-withdrawing group (prepared through triazene pyrolysis) into pyrrolines was used by Hudlicky and co-workers in a formal synthesis of various pyrrolizidinyl heterocycles such as (±)-supinidine, (±)-isoretronecanol and (±)-trachelantamidine (Scheme 1.49) [82].

The same key step was applied by the same authors to the preparation of bicyclic compound **113**, which is an advanced intermediate in the synthesis of (±)-retronecine and (±)-heliotridine, as well as (±)-platynecine, (±)-hastanecine, (±)-turnefor-cidine and (±)-dihydroxyheliotridane (Scheme 1.50) [83].
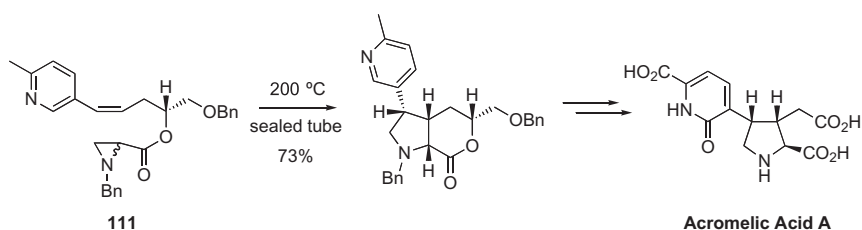
Scheme 1.47   Acromelic acid A.
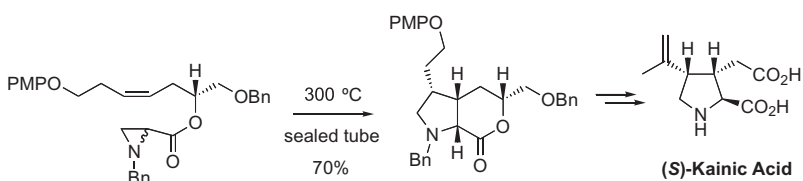
Scheme 1.48   (–)-Kainic acid.
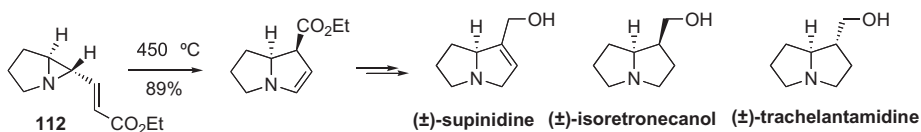
Scheme 1.49   (±)-Supinidine, (±)-isoretronecanol and (±)-trachelantamidine.

Scheme 1.50 Retronecine.

Scheme 1.51 Indolizidine 209D.
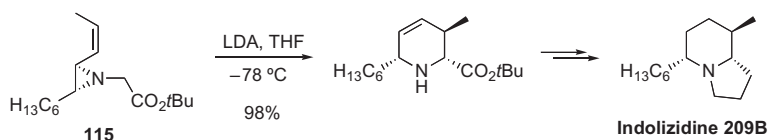
Scheme 1.52 Indolizidine 209B.
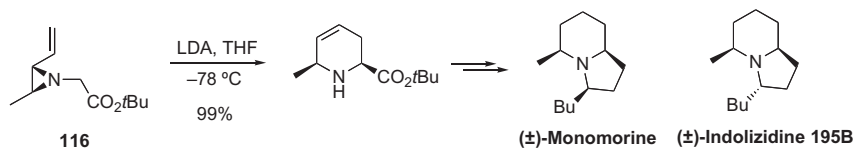
Scheme 1.53 (±)-Monomorine and (±)-indolizidine 195B.

1.3.2.2 Aziridines in [2,3]-Wittig Rearrangements

The utility of the [2,3]-Wittig rearrangement of vinyl aziridines [84] in natural product synthesis was largely demonstrated by Somfai and co-workers. For example, an enantioselective total synthesis of indolizidine 209D was achieved using the [2,3]-Wittig rearrangement of the enolate derived from aziridine **114** (Scheme 1.51) as a key step [85, 86].

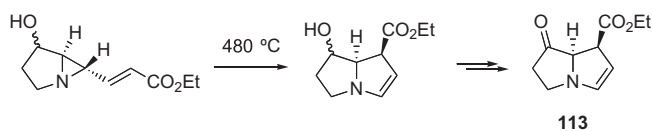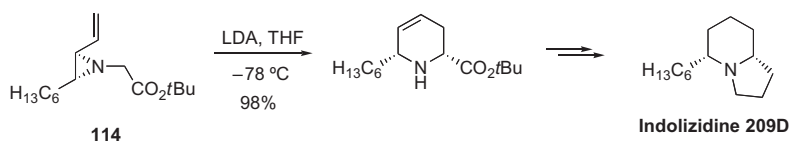The same key step was applied to the total synthesis of the indolizidine 209B. In this case, the [2,3]-Wittig rearrangement of the enolate derived from the substituted vinylaziridine **115** was used (Scheme 1.52) [86].

The total synthesis of racemic monomorine and indolizidine 195B have also been achieved using the [2,3]-Wittig rearrangement of vinyl aziridine **116** by the same authors (Scheme 1.53) [87].

1.3.2.3 Aziridines in Iodide-Mediated Rearrangements

Another way to realize the rearrangement of vinyl aziridines into pyrrolines is the S_N2' ring opening of vinyl aziridines with iodide ion followed by ring closure. This
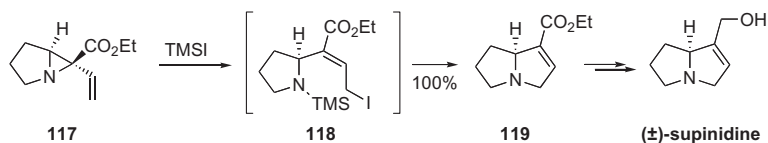
Scheme 1.54 (±)-Supinidine.
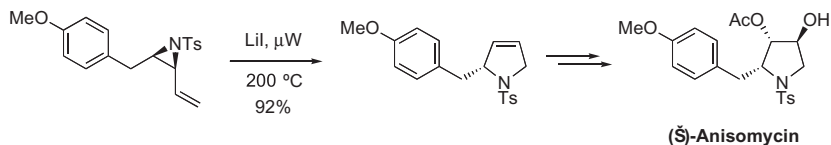
Scheme 1.55 (–)-Anisomycin.
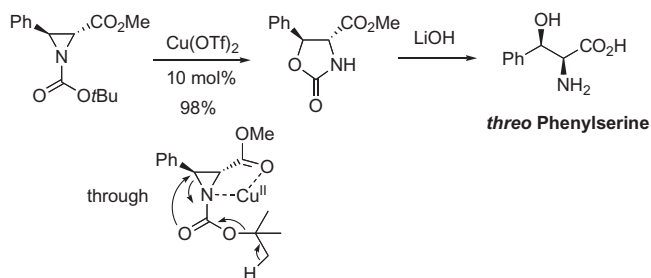
Scheme 1.56 *threo*-Phenylserine.

methodology was early recognized by Hudlicky and co-workers as an efficient way to achieve the synthesis of pyrrolizidinyl alkaloids (Scheme 1.54) [82, 88]. The S_N2' ring opening of aziridine **117** afforded the iodo compound **118** which gave the bicyclic compound **119** upon ring closure.

A similar reaction was later applied by Somfai in a formal synthesis of (–)-anisomycin (Scheme 1.55) [89].

1.3.2.4 Aziridines in Miscellaneous Rearrangements

The Lewis acid-mediated rearrangement of *N*-acyl aziridines into oxazolidin-2-ones was used in a straightforward synthesis of *threo* phenylserine (Scheme 1.56) [90]. Interestingly this rearrangement was shown to occur with retention of the configuration. By contrast, the same rearrangement, when applied to *N*-acyl aziridines, leads to the oxazoline formation (and not the oxazolidinone). This was applied to the total synthesis of (non-natural) Bn-protected (*L*)-*threo* sphingosine [58].

The stereoselective Lewis acid-catalyzed rearrangement of aziridinyl alcohols **120** and **121** into β-amino aldehydes was applied in a total synthesis of (±)-crinane and (±)-mesembrine (Scheme 1.57) [91].
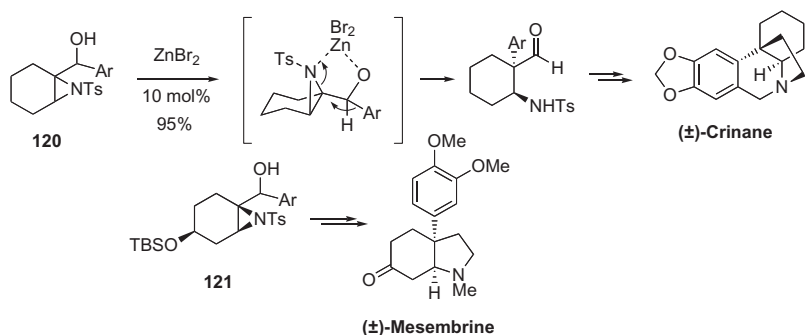
Scheme 1.57 (±)-Crinane and (±)-mesembrine.
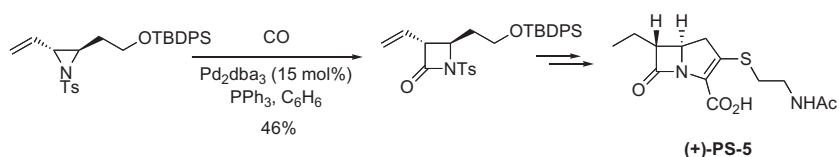
Scheme 1.58 (+)-PS-5.
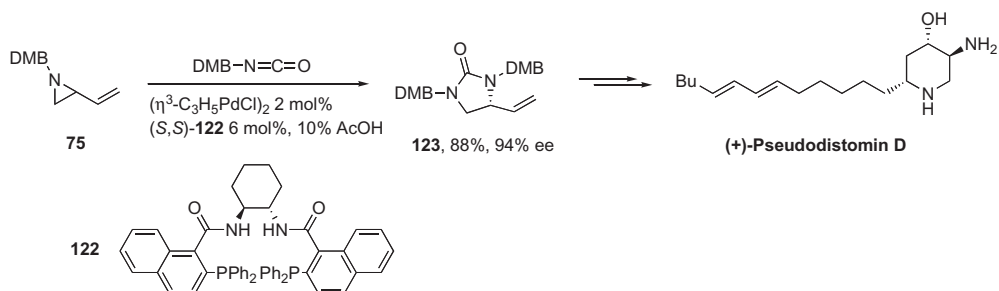
Scheme 1.59 (+)-Pseudodistomin D.

Vinylaziridines have been reported to undergo carbon monoxide insertion under palladium (0) catalysis. This method allowed the formation of β-lactams and was applied by Tanner and Somfai for the total synthesis of the carbapenem (+)-PS-5 (Scheme 1.58) [92].

The insertion of isocyanates can also been achieved under palladium (0) cataly-sis, leading to imidazolidin-2-ones. This strategy was used by Trost and co-workers in the total synthesis of (+)-pseudodistomin D (Scheme 1.59) [93]. The insertion occurred enantioselectively in the presence of chiral ligand **122** to afford enan-tioenriched imidazolidin-2-one **123**.

(−)-Pseudoconhydrin was prepared by Harrity and co-workers through a [3 + 3] cycloaddition strategy involving the aziridine **124** and a palladium-trimethylenemethane complex (Scheme 1.60) [94].
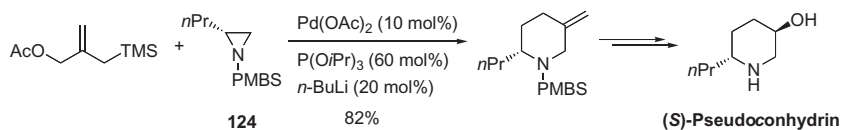
Scheme 1.60 (−)-Pseudoconhydrin.
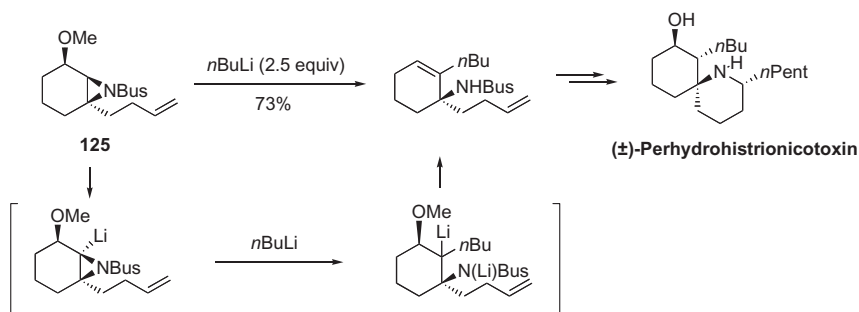
Scheme 1.61 (±)-Perhydrohistrionicotoxin.
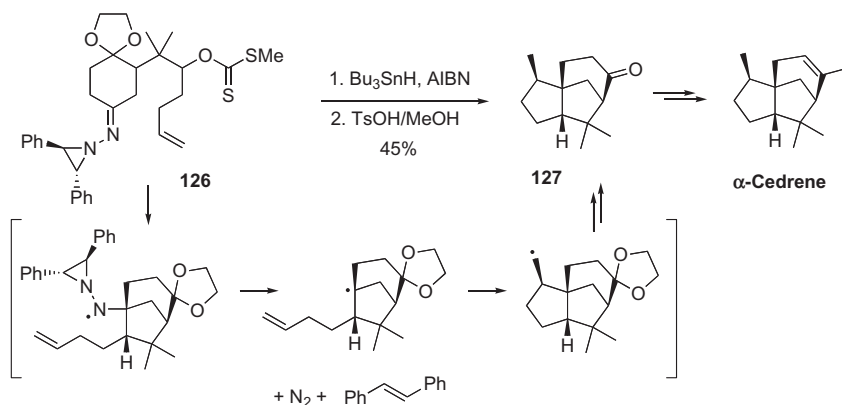
Scheme 1.62 α-Cedrene.

A formal synthesis of (±)-perhydrohistrionicotoxin has been reported through an interesting carbenoid rearrangement of a lithiated aziridine prepared by deprotonation of **125**, insertion of the resulting carbenoid into BuLi and subsequent β-elimination (Scheme 1.61) [95].

An elegant synthesis of α-cedrene was reported using the ability of aziridinyl hydrazones to behave as alkyl radical acceptors/precursors. Hydrazone **126** underwent a radical cascade upon reduction of the xanthate moiety to afford after hydrolysis tricyclic compound **127** (Scheme 1.62) [96].

1.3.3
Synthesis of Natural Products Involving the Transformation
of an Aziridinium Moiety

The chemistry of aziridiniums has been reviewed recently [97]. In this section only the examples where a true aziridinium ion is involved will be reviewed, since the activation of aziridines under Brønsted conditions has been developed in Section 1.3.1. Aziridiniums are prepared mainly through intramolecular substitution of a leaving group by nitrogen atom engaged in an aziridinyl moiety. Their reactivity is mainly related to ring enlargement reactions.

Biomimetic syntheses of (–)-vincadifformine and (–)-tabersonine have been reported by Kuehne and co-workers through the ring opening reactions of the aziridinium derived from the pentacyclic chloro compound **128** (Scheme 1.63) [98].

The *in situ* mesylation of amino alcohol **129** followed by the reaction with dibutylcuprate was reported by Tanner and Somfai to occur with retention of the configuration. This was explained by a mechanism involving the intramolecular displacement of mesylate by nitrogen. Ring opening of the resulting aziridinium ion **130** with dibutylcuprate afforded an advanced intermediate in the total synthesis of depentylperhydrohistrionicotoxin derivatives (Scheme 1.64) [99].

Aziridinium ion **132** formed through iodoamination of **131** followed by nucleophilic anchimeric assistance by the vicinal tertiary amine was intramolecularly opened by a proximal ester moiety to afford (+)-croomine in an elegant single step (Scheme 1.65) [100].
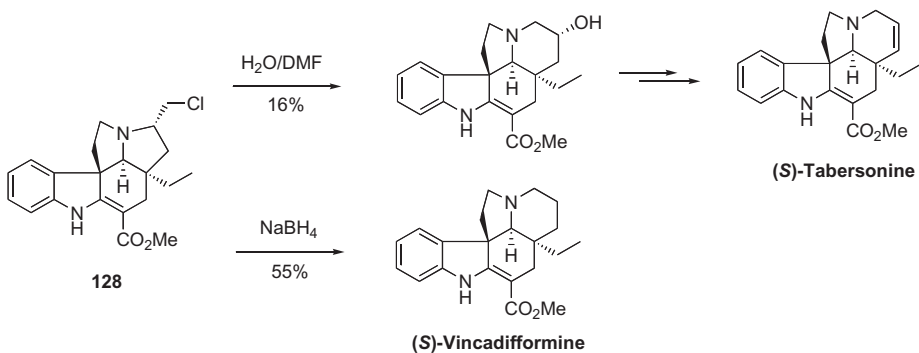
Scheme 1.63 (–)-Vincadifformine and (–)-tabersonine.
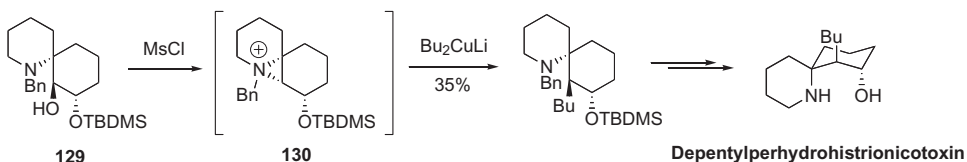
Scheme 1.64 Depentylperhydrohistrionicotoxin.
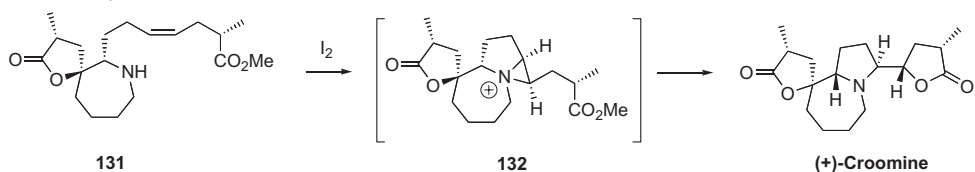
Scheme 1.65 (+)-Croomine.
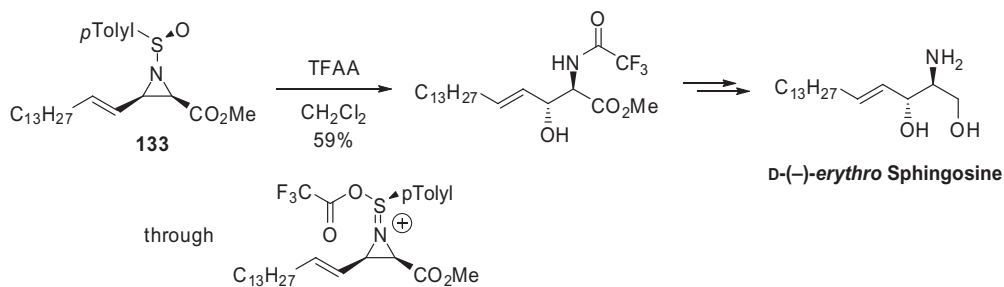
Scheme 1.66 D-(–)-*erythro*-Sphingosine.
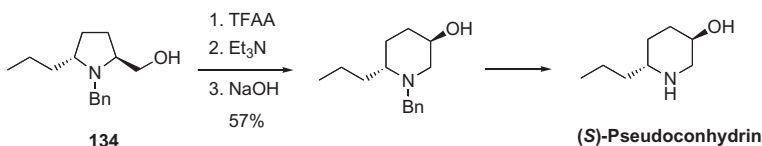
Scheme 1.67 (*S*)-Pseudoconhydrin.

The formation of an aminoalcohol unit through the Pummerer-like rearrangement of *N*-sulfinylaziridine **133** was used in a total synthesis of D-(–)-*erythro*-sphingosine by Davis and co-workers (Scheme 1.66) [101].

The stereoselective rearrangement of pyrrolidine-2-methanols into 3-hydroxypiperidines has been extensively studied by Cossy and co-workers [97], and has found several efficient applications in total synthesis. The substituted prolinol **134** has served in the total synthesis of (–)-pseudoconhydrin (Scheme 1.67) [102].

The synthesis of the piperidinyl core of (–)-velbanamine [103], as well as the synthesis or formal synthesis of various drugs such as (–)-zamifenacin [104], (–)-paroxetine [105] and reboxetine [106] have also been reported using the same type of methodology.

1.4
Conclusion

The aziridines have been named "the epoxides' ugly cousins" [2], and in fact the reactions of aziridines have received little interest compared with those of epox-

ides. However, the use of aziridines in the total synthesis of natural products has attracted increasing interest over the past 15 years. Besides the considerable amount of work devoted to aziridine-containing natural products (mitomycins and azinomycins) as well as to related synthetic targets, the aziridine ring has been used as an efficient precursor for the synthesis of 1,2-amino alcohols and other polyfunctionalized structures. Undoubtedly this synthetic potential is directly related to the ability to prepare stereo- and enantioselectively the aziridinyl core and will increase in the future.

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