Part I
Biomimetic Total Synthesis of Alkaloids

Biomimetic Organic Synthesis, First Edition. Edited by Erwan Poupon and Bastien Nay.

1
Biomimetic Synthesis of Ornithine/Arginine and Lysine-Derived Alkaloids: Selected Examples

Erwan Poupon, Rim Salame, and Lok-Hang Yan

1.1
Ornithine/Arginine and Lysine: Metabolism Overview[1)]

1.1.1
Introduction: Three Important Basic Amino Acids

- L-Ornithine (L-**1**) (L-Orn, Figure 1.1) is a non-proteinogenic amino acid produced from L-glutamic acid (**4**) in plants and from L-arginine (**2**) in animals. L-Ornithine plays a central role in the urea cycle in terrestrial vertebrates [1].
- L-Arginine: With its guanidine residue, L-Arginine (L-**2**) (L-Arg, R) is a highly basic amino acid. It is encoded by DNA and is the direct precursor of L-ornithine (L-**1**), urea, and also nitric oxide. It is also be encountered in some natural products (see below) [1, 2].
- L-Lysine (L-**3**) (L-Lys, K): is the only amino acid to have two different biosynthetic pathways. One is the aspartate (**5**) pathway present in bacteria, plants, and algae. The other starts from α-ketoglutarate (**6**) and is present in fungi [3, 4]. Lysine is an essential amino acid for humans.

Scheme 1.1 reflects some of the biochemical relations between L-ornithine (L-**1**)/L-arginine (L-**2**) and L-lysine (L-**3**). It is of course not the aim of this chapter to provide further details concerning their respective biosynthesis.[2)] Only important metabolic intermediates, helpful for a better comprehension of the following sections, have been stressed.

1) These three amino acids (Figure 1.1) share common chemical reactivity and are implicated in more or less similar biosynthetic pathways. We thus decided, in an effort to establish useful comparisons, to garner lysine and arginine/ornithine derived natural substances in a single chapter.
2) The interested reader is referred to classical biochemistry textbooks.

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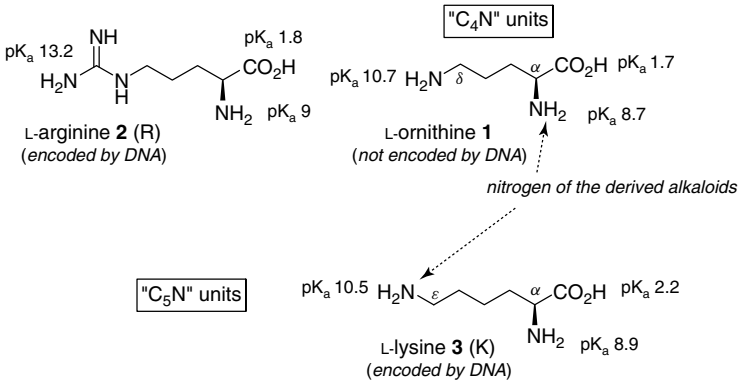
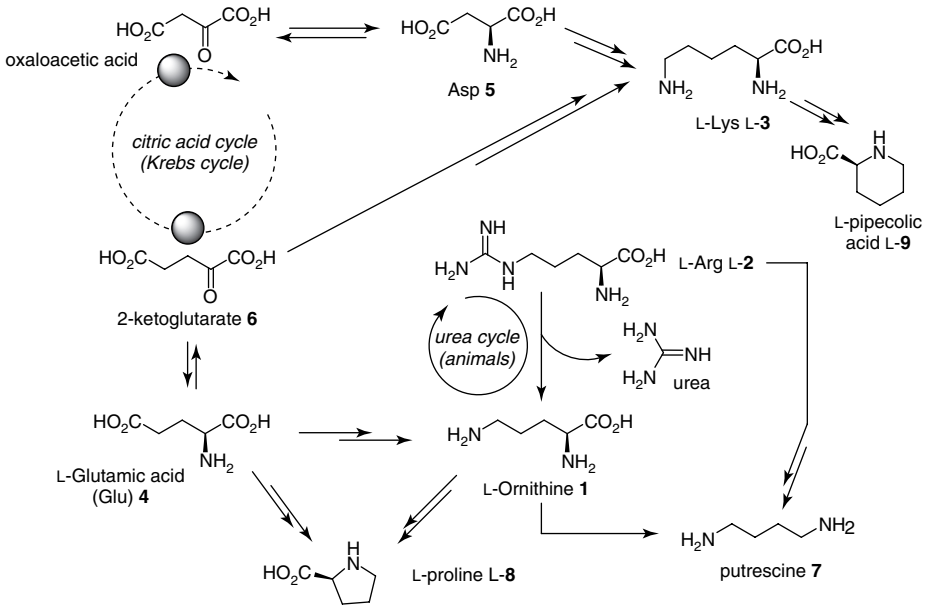


Figure 1.1 Structure of the amino acids.



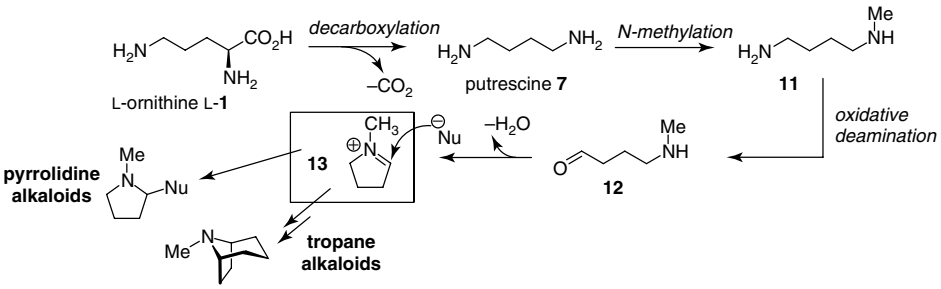
Scheme 1.1 Place of the three amino acids in primary metabolism.

1.1.2
From Primary Metabolism to Alkaloid Biosynthesis

The parallel between L-ornithine (L-**1**) and L-lysine (L-**3**) metabolism concerning their catabolism/biotransformation and subsequent chemical reactivity to form alkaloids is obvious (even if the incorporated nitrogen atom is different, that is, incorporation of the α-amino group for ornithine and ε-amino group for lysine). Mainly, both amino acids will be able to undergo decarboxylation to the corresponding diamine [putrescine **7** (C_4) and cadaverine **10** (C_5), respectively] and then oxidative deamination into aminoaldehydes (see below). Thereby, rather stable amino acids are turned into highly reactive units suitable for natural organic chemistry.

1.1.2.1 L-Ornithine Entry into Secondary Metabolism[3)]

The diamine putrescine (**7**) can be formed directly from the decarboxylation of L-ornithine (**1**) (Scheme 1.2); it can also be derived from L-arginine (**2**) [6] after decarboxylation and transformation of the guanidine functional group. Putrescine (**7**) is then mono-*N*-methylated[4)] by putrescine *N*-methyltransferase (PMT). This reaction is the first purely "secondary metabolite" step and **11** is the first specific metabolite towards alkaloids. *N*-Methylputrescine (**11**) may then be oxidatively deaminated by diamine oxidase to 4-methylaminobutanal (**12**), which generates the *N*-methyl-Δ^1-pyrrolinium cation **13**, a cornerstone electrophilic intermediate and a central precursor of numerous alkaloids belonging to the pyrrolidine or tropane groups when the reaction with an appropriate nucleophile occurs.

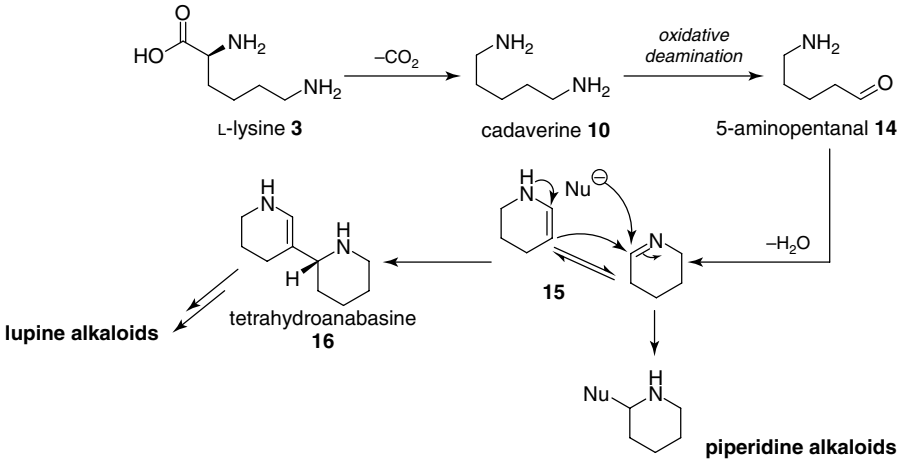


Scheme 1.2 Key elements of ornithine metabolism towards alkaloids.

1.1.2.2 L-Lysine Entry into Secondary Metabolism[5)]

Decarboxylation of L-lysine (L-**3**) into the diamine cadaverine (**10**) (Scheme 1.3) followed by oxidative deamination leads to aminopentanal **14**, which can cyclize into tetrahydropyridine **15**.[6)] This latter is most likely the universal intermediate

3) The fundamental first steps of ornithine (or lysine) catabolism towards alkaloids now constitute a classic in biosynthesis textbooks. See, among others, Reference [5].
4) This important step has been widely studied. PMT is closely related to spermidine synthase. See Reference [7] for a valuable review.
5) The interested reader is referred to classical biochemistry textbooks.
6) Synonymous terms: 2,3,4,5-tetrahydropyridine = Δ^1-piperideine (imine form); 1,2,3,4-tetrahydropyridine = Δ^2-piperideine (enamine form).



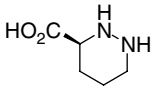
Scheme 1.3 Key elements of lysine metabolism toward alkaloids.

to lysine-derived piperidine alkaloids. This imine is too unstable and reactive to be isolated as such from plant material. Nucleophilic addition reactions at the imine function with suitable nucleophiles help stabilize **15** and are at the origin of various piperidine alkaloids. Dimerization into tetrahydroanabasine (**16**) is an important alternative in the lysine metabolism (the enamine form of **15** being the nucleophile). This latter reaction is spontaneous at physiological pH (*vide infra*) though stereospecific coupling involves an appropriate enzymic intervention in plants [8]. Tetrahydroanabasine (**16**) (which is probably also quite unstable as such *in vivo*) can then undergo various transformations and is at the origin of a class of alkaloids known as "*lupine alkaloids*" (Section 1.4.2).

1.1.3
Closely Related Amino Acids

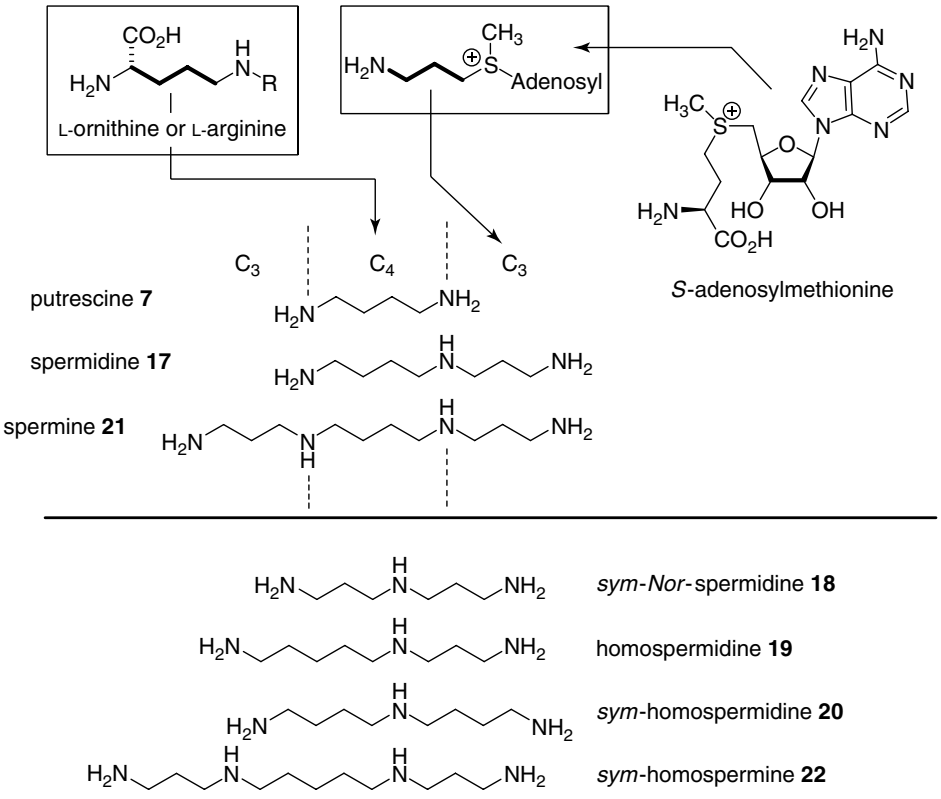
- L-Proline: (L-**8**) (L-Pro, P, Scheme 1.1) is one of the 20 amino acids of the genetic code but the only one with a secondary amine function. It is biosynthesized from L-glutamic acid [9]. L-Proline recently increased in importance with the successful development of organocatalysis.
- L-Pipecolic acid: Unlike L-proline (L-**8**), L-pipecolic acid (L-**9**) (Scheme 1.1) is a non-proteogenic amino acid. It derives from L-lysine and is at the origin of several classes of secondary metabolites. Biosynthetic and biomimetic aspects of pipecolic acid are discussed below.[7)]

7) Other close amino acids exist; of particular interest are piperazic acids (structure shown here). Their biosynthesis from lysine is discussed in Chapter 10 (Indole-Oxidized and Complex Peptide Alkaloids); see also Reference [10].



1.1.4
The Case of Polyamine Alkaloids

Cases where a C_4N_2 building block is incorporated [i.e., the polyamine putrescine (**7**)] include "polyamine alkaloids" (Scheme 1.4). Comprehensive review articles, especially by M. Hesse and colleagues, have appeared detailing the massive amount of work done in the field of these secondary metabolites during the last 20 years [11, 12]. Essentially, six basic backbone components, namely, putrescine (**7**), spermidines (**17**, **18**), homospermidines (**19**, **20**), spermine (**21**), and homospermine (**22**), participate in the skeleton of polyamine alkaloids. Figure 1.2 gives examples of cyclic polyamine alkaloids [piriferine (**23**), celacinnine (**24**), aphelandrine (**25**), and lipogrammistin A (**26**)], organized according to the classification of M. Hesse and colleagues (see Reference [11]). Interestingly, cadaverine units are very rarely present in such cyclic molecules. Despite interesting biomimetic syntheses [13], polyamine alkaloids will not be covered in this chapter (except for the biosynthesis of pyrrolidine alkaloids; see Section 1.3.1).



Scheme 1.4 Main polyamine backbones encountered in polyamine alkaloids.

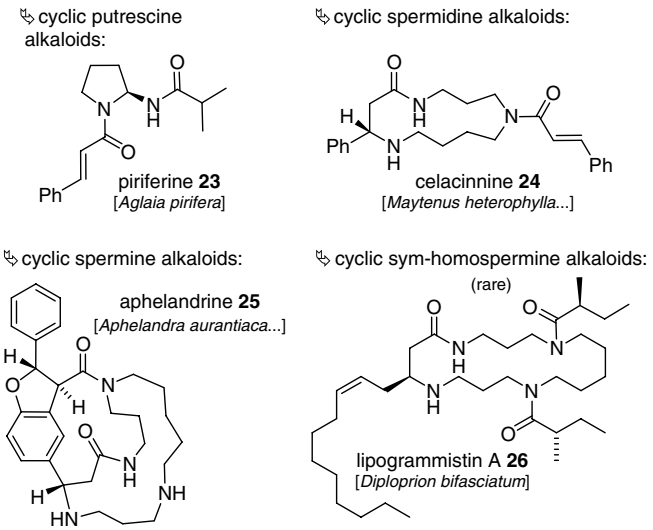


Figure 1.2 Representative polyamine alkaloids.

1.1.5
Biomimetic Synthesis of Alkaloids

Ionic iminium/enamine reactions are central to the construction of the title alkaloids, especially the Mannich reaction. This is probably one reason why biomimetic strategies have been particularly efficient in this class of secondary metabolites. We will, of course, approach in this chapter only some of the multifaceted aspects of the biomimetic chemistry of L-lysine or L-ornithine/arginine derived secondary metabolites. We will select topics and examples that are not covered (or not with the scrutiny we think opportune) in other review articles. This is especially the case when dealing with the manipulation of small reactive C_4 and C_5 units derived from the three amino acids. Some selected examples are presented in the following sections and organized as follows:

- biomimetic syntheses from L-lysine and L-ornithine/L-arginine or C_4, C_5 reactive units presumably derived from the amino acids;
- selected examples of biomimetic syntheses of more complex structures.[8)]

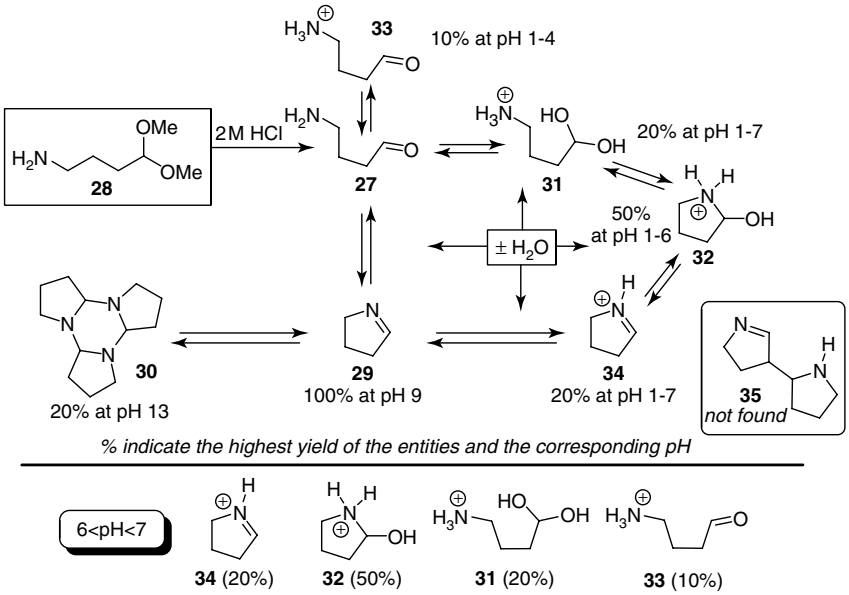
8) For the implementation of highly complex metabolisms within marine sponges and involving, according to biosynthetic proposals, L-lysine, L-arginine, and L-proline see Chapter 7 (Biomimetic Synthesis of Marine Pyrrole-2-aminoimidazole and Guanidinium Alkaloids).

1.2
Biomimetically Related Chemistry of Ornithine- and Lysine-Derived Reactive Units

1.2.1
Ornithine-Derived Reactive Units

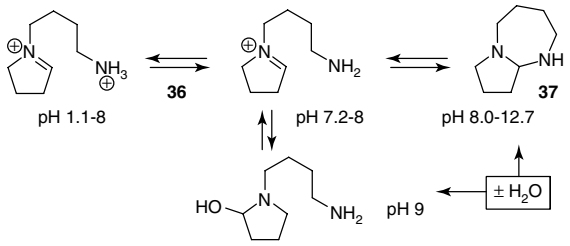
1.2.1.1 Biomimetic Behavior of 4-Aminobutyraldehyde

The Christophersen group studied the evolution of aqueous solutions of 4-aminobutyraldehyde (**27**) [prepared from aminobutyraldehyde dimethyl acetal (**28**), Scheme 1.5] by ^{1}H NMR over a wide pH range (1–12) [14]. Entropic factors explain the rapid formation of cyclic imine **29**, which can trimerize into **30**. When in aqueous solution, different species are in equilibrium and are depicted in Scheme 1.5. Along with aminobutanal **27**, two neutral (pyrrolidine **29** and trimer **30**), and four protonated entities (**31**–**34**) were detected and tracked as a function of pH. Around physiological pH, the four protonated species predominate. Owing to the rapid emergence of acid-catalyzed aldol condensation products, the authors cautiously avoided concentrated solution. As we will detail in a coming section, no dimeric structure such as **35** has been characterized from the mixtures.



Scheme 1.5 Biomimetic reactions from 4-aminobutyraldehyde (**27**).

With substituted nitrogen atom, for example, with a biosynthetically relevant aminobutyl side chain (Scheme 1.6), the formation of the pyrrolidinium ring is nearly exclusive, with **36** predominant among several other entities [15].

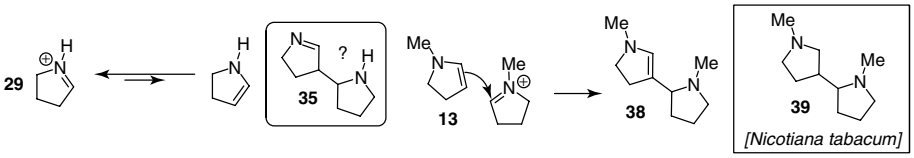


Scheme 1.6 Biomimetic behavior of a substituted pyrrolidinium ion.

Notably, aminal **37** is a bicyclic compound that is formed spontaneously at basic pH.[9)]

1.2.1.2 **Dimerization**

Whereas dimerization of six-membered ring enamines is a major outcome (as we will discuss in detail when dealing with lysine-derived units), the dimerization of the corresponding five-membered ring systems such as **29** is by far less described in the literature. The chemistry of these molecules is, correspondingly, simpler than that of lysine, probably because of a lesser propensity to react as an enamine (Scheme 1.7).



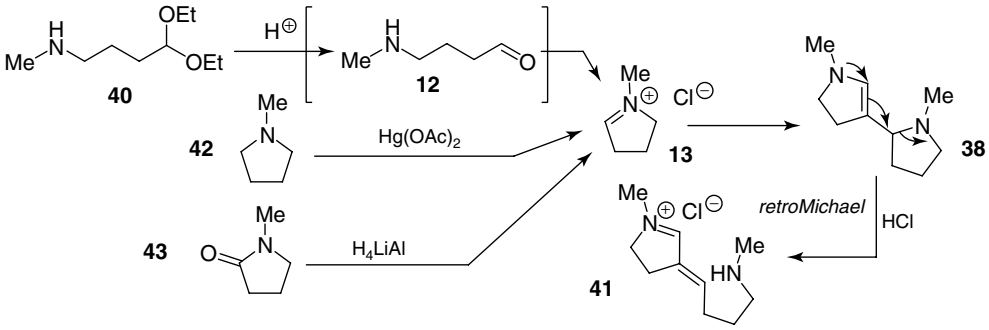
Scheme 1.7 Dimerization in the pyrrolidine series.

The dimer type **35** has never been described, although it has been postulated in some biosynthesis (Section 1.3.3). In the case of *N*-methyl substituted **13**,[10)] dimerization has been observed and dimer **38** characterized. Notably, the corresponding reduced dimer **39** has been detected as a mixture of diastereomers from the root system of *Nicotiana tabacum*, as well as monomeric **13** [18]. In fact, at physiological pH (around 7.2 in a growing tobacco plant), the coexistence of imine and enamine forms of **13** should provide the opportunity for more or less spontaneous condensations.

In the laboratory (Scheme 1.8), starting from *N*-methyl-4-aminobutanal diethyl acetal (**40**) in acidic conditions, deprotection affords **12**, which cyclizes into biosynthetic intermediate **13**, which in turn can dimerize into **38**. The product of a retro-Michael reaction, **41**, has also been fully characterized; it was usually observed as an impurity in the course of the synthesis of monomers **13** [19]. Alternative

9) Diazabicyclononane **37** was isolated earlier from *in vitro* chemical or enzymic conversion of spermidine with pea seedling diamine oxidase (PSDO); see Reference [16].

10) Is monomeric **29** too reactive and unstable? *N*-Monomethylputrescine (**11**) is in fact an early and central precursor of many alkaloids as the first specific metabolite *en route* to alkaloids such as nicotine or tropanes via *N*-methylpyrrolinium (**13**) (which could therefore be more stable than **15**); see References [5, 17].



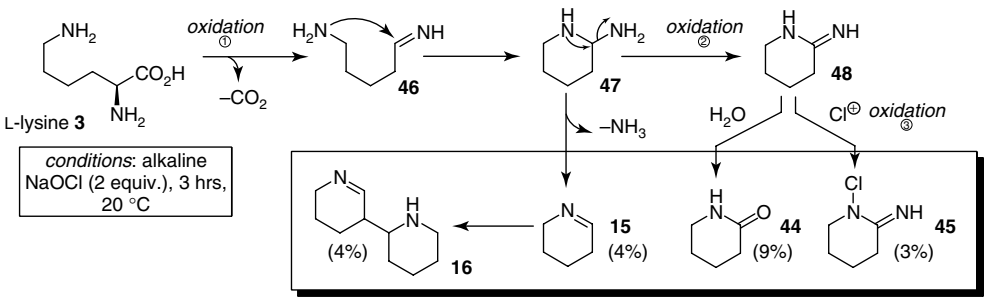
Scheme 1.8 Biomimetic dimerization in the pyrrolidine series.

procedures toward **13** consist of the oxidation (e.g., with mercuric diacetate [20]) of *N*-methylpyrrolidine (**42**) or the reduction of lactam **43** with aluminum hydrides [21].

1.2.2 Lysine-Derived Reactive Units

1.2.2.1 Oxidative Degradation of Free L-Lysine

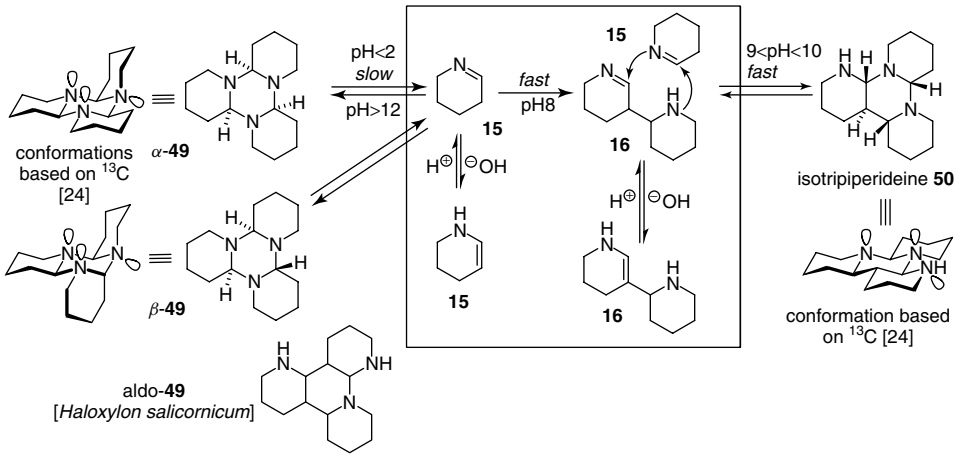
Despite a seemingly simple pathway, mimicking the fundamental L-lysine (and L-ornithine) catabolism pathways in the laboratory is far from trivial. Only a few publications report on the direct oxidation of L-lysine. In 1966, B. Franck and colleagues oxidized L-lysine with alkaline NaOCl in water (Scheme 1.9) [22]. Cyclic oxidation products were identified and compared with authentic samples. Scheme 1.9 highlights the possible pathways toward the isolated compounds; it may be assumed that the cyclic oxidation products arise from L-lysine by one (intermediates **46**, **47**), two (intermediate **48**) or three oxidation steps (**15**, **16**, **44**, **45**). Despite an incomplete conversion of L-lysine and the complex mixtures obtained, this simple reaction is of great interest as a totally biomimetic reaction that mimics (i) the decarboxylation/oxidative deamination steps and (ii) the spontaneous evolution of the resulting reactive species (**15**, dimer **16**, lactam **44**).



Scheme 1.9 Cyclic oxidative products of L-lysine.

1.2.2.2 Clemens Schöpf's Heritage: 50 Years of Endocyclic Enamines and Tetrahydroanabasine Chemistry

Numerous compounds resulting from the self-condensations of endocyclic enamines, which are closely related to metabolic pathways, have been described, especially in the pioneering work of Schöpf, starting from the late 1930s.

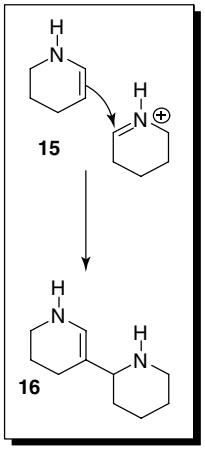


Scheme 1.10 Evolution of tetrahydropyridine.

The simplest compound, that is, Δ^1-piperideine (**15**), does not exist in monomeric forms but, instead, trimeric assemblies of types α- and β-**49** and **50** have been isolated (Scheme 1.10).[11] Structures **16**, **49**, and **50** were characterized by Schöpf in 1948 [23] and the configurations and conformations studied by the Kessler group in 1977 by ^{13}C NMR [24]. At neutral or slightly basic pH (~8), and as in nature, monomers **15** dimerize into tetrahydroanabasine (**16**) (which can be isolated as a dihydrobromide crystalline salt in the laboratory [25]). As early as 1956, Schöpf and colleagues clearly demonstrated the importance of pH on the kinetic and yield of conversion of **15** into **16**. Studies were conducted with pioneering and clear-sighted biosynthetic considerations (*zellmöglichen Bedingungen*, see Scheme 1.11) [26]. Tetrahydroanabasine also reacts in solution at pH 9 with imine **15** and gives in almost quantitative yield trimer **50**, also called isotripiperideine [23]. Consequently, trimer **50** is, in turn, in equilibrium with tetrahydroanabasine **16** and free Δ^1-piperideine **15** [27] and can, therefore, be considered as a stable, protected form of tetrahydroanabasine with interesting synthetic potential.

Aldotripiperideine (aldo-**49**) is another trimer that results from a rearrangement of α-tripiperideine in acidic conditions or in basic conditions at pH 9.2 at 100 °C. Interestingly, aldo-**49** was isolated from *Haloxylon salicornicum* as a natural substance [28].

11) Besides, they constitute a suitable way to store piperideine as a crystalline solid on a 100 g scale.

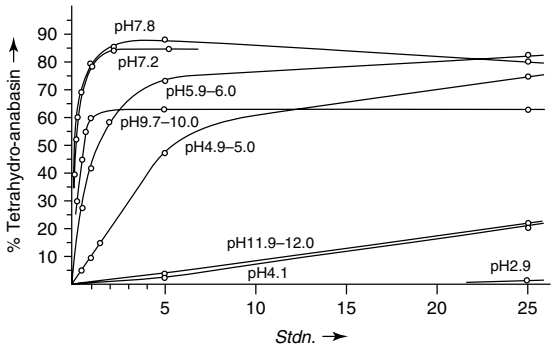


261. Clemens Schöpf, Franz Braun und Alfred Komzak[1] : Der Übergang von Δ^1-Piperidein in Tetrahydro-anabasin under zellmöglichen Bedingungen

(mitbearbeitet ven Hermann Koop)

[Aus dem Institut für organische Chemie der Technischen Hochschule Darmstadt]

(Eingegangen am 11. April 1956)



Ausb. an Tetrahydro-anabasin in % d.Th. beim Aufbewahren einer 0.1m Lösung von Δ^1-Piperidein in verdünnten Pufferlösungen bei 25°

Scheme 1.11 Schöpf's pioneering works.

1.2.2.3 Spontaneous Formation of Alkaloid Skeletons from Glutaraldehyde

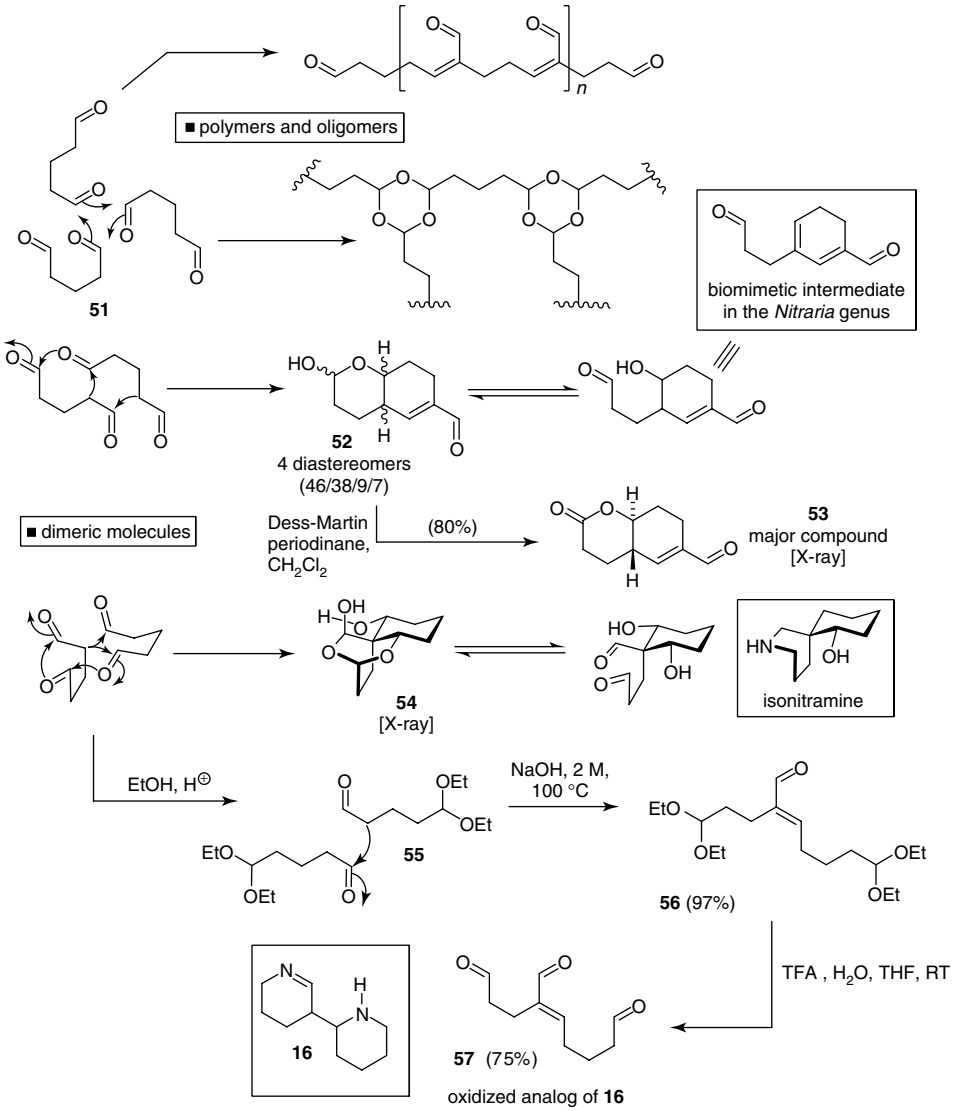
Glutaraldehyde (**51**) is a well-known crosslinking agent in biochemistry or histology and is used as a biocide.[12] It can also be advantageously seen as a convenient surrogate of lysine by considering a hypothetical oxidative deamination on aminopentanal **14**.[13]

Simple reactions (Scheme 1.12) were recently disclosed, highlighting an impressive propensity of **51** to mimic several lysine metabolism elements [29]. Whereas **51** was known to polymerize[14] according to different mechanisms and kinetics (Scheme 1.12) depending, for example, on the pH, very few studies previously described compounds resulting from self-condensations into small molecules. Products formed during the treatment of **51** in an aqueous solution at pH 8.5 and 60 °C were investigated. A double homoaldolization followed by crotonization of one of the aldol adducts can easily explain the formation of bicyclic **52**. This compound was previously described but no information was available concerning its stereochemistry [30]. Oxidation of **52** with Dess–Martin periodinane permitted crystallization of the major diastereomer **53**. Compound **52** is, interestingly, related to a biosynthetic intermediate postulated in the course of the biosynthesis of

12) The numerous applications of glutaraldehyde have been extensively reviewed: see Reference [8] in Reference [29].

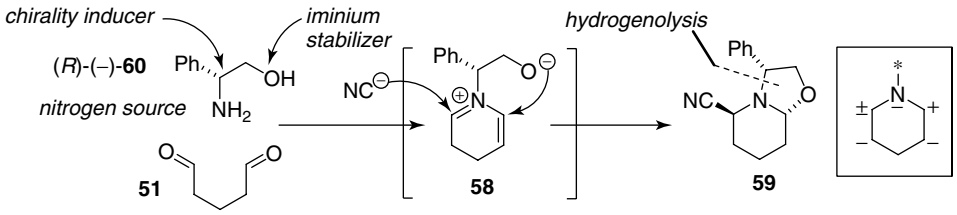
13) Of course, one needs to keep in mind that in plants reactive functional groups such as aldehydes will most likely be masked in a transitory way; they are, in this chapter, presented in their reactive form for simplicity.

14) Glutaraldehyde is quite stable as an aqueous solution, where it exists as several hydrates with the slow formation of oligomers and polymers (Scheme 1.12). It undergoes rapid polymerization in neat conditions with a catalytic amount of water.



Scheme 1.12 Various condensations of glutaraldehyde.

Nitraria alkaloids (Section 1.4.3). From the same mixture, a crystalline compound **54** that displayed a tricyclic structure with a spiranic quaternary carbon and contiguous acetal and hemiacetal functions was isolated. This intriguing molecule has a striking analogy with known simple spiroalkaloids such as nitramine also isolated from different species of the *Nitraria* genus and its plausible mechanism of formation totally parallels the postulated biosynthesis of such natural substances [31]. Diethoxypentanal **55**, which is easily available from monoprotection of **51**, has



Scheme 1.13 Cyanophenyloxazolopiperidine: a convenient building block.

been treated in a boiling sodium hydroxide solution to furnish quantitatively compound **56** by aldolization/crotonization as a single *(E)*-stereoisomer. Deprotection in acidic conditions gave **57**, an interesting oxidized analog of tetrahydroanabasine.

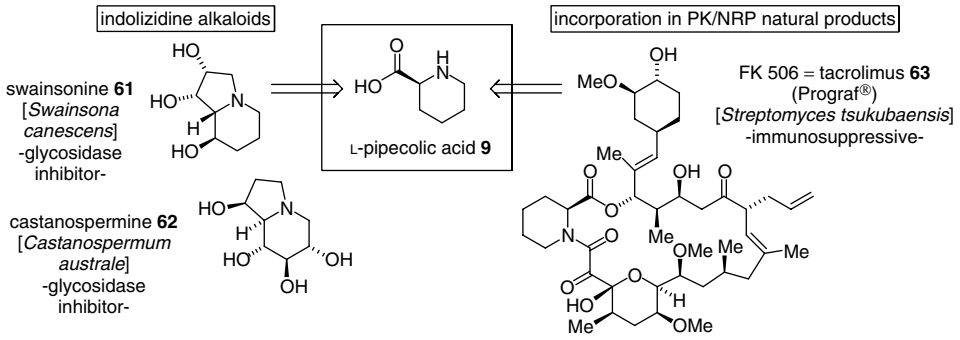
Glutaraldehyde (**51**) has been widely used for the synthesis of various heterocycles through the formation of dihydropyridine-type intermediates. The most powerful applications are probably the so-called "CN(*R,S*)"[15] method (Scheme 1.13) with the use of the chiral non-racemic *N*-cyanomethyloxazolidine ring system integrated in a piperidine structure as an ideal way to stabilize dihydropyridine **58** into compound **59** [prepared in a single step from glutaraldehyde **51**, *(R)*-(−)-phenylglycinol (**60**) and a source of cyanide ions in water]. This strategy, developed by the Husson and Royer groups, permitted the total synthesis of many alkaloids in a diastereoselective manner. Some of them are closely related to biomimetic strategies. This strategy has been extensively reviewed over the years [32]. As, interestingly, naturally occurring piperidine alkaloids bearing α-side chains are either in the *(R)* or *(S)* configuration, the possibility of using building blocks such as **59** to modulate the stereochemistry at α or α' positions constituted a real breakthrough in piperidine total synthesis.

1.2.3 Biomimetic Access to Pipecolic Acids

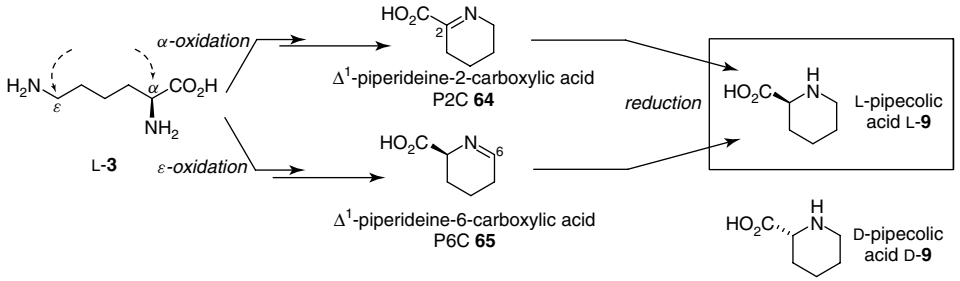
1.2.3.1 Pipecolic Acids: Biosynthesis and Importance

L-Pipecolic acid (L-**9**) was first identified in 1952 as a constituent of leguminous plants [33]. It is now recognized as a universal lysine-derived entity present in plants, animals, and microorganisms [34]. In natural substances, L-**9** is a key element in molecules as diverse as swainsonine (**61**) or castanospermine (**62**) (small indolizidine alkaloids known for their glycosidase-inhibiting properties, Scheme 1.14) or FK 506/tacrolimus (**63**) (a polyketide/non-ribosomal peptide hybrid clinically approved as an immunosuppressant). Over the years, many studies have sought to establish the biosynthetic routes to L-**9**. Different metabolic pathways (with different proposed mechanisms [35]) are involved in the formation of L-**9** (Scheme 1.15). Chemically speaking, these basic routes are distinguishable at the loss of the amino group of lysine **3**. The reality of immediate precursors, that is, piperideine carboxylic acids **64** (known as *P2C*) and **65** (*P6C*), has been

15) Named after the French Centre National de la Recherche Scientifique (CNRS).



Scheme 1.14 Selected example of pipecolic acid derived alkaloids and pipecolic acid containing secondary metabolites.

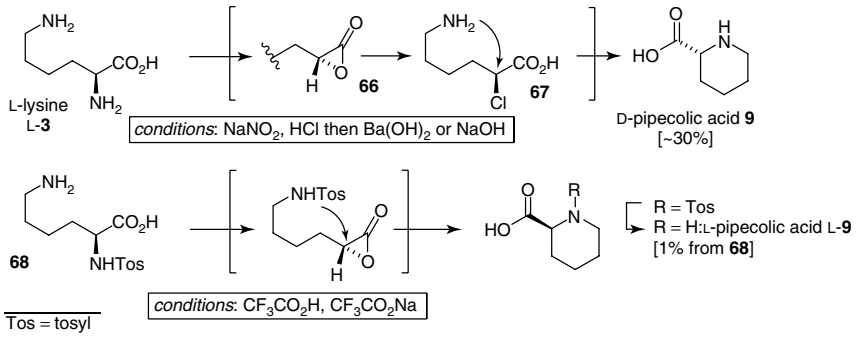


Scheme 1.15 Biosynthesis of pipecolic acid.

demonstrated by many feeding experiments and will not be further developed in the present chapter as many research and review articles are available [33]. The reverse pathways converting L-pipecolic acid (L-**9**) into (P6C **65**) [36] or lysine (**3**) [37] are also known. D-Pipecolic acid (D-**9**) was also reported and derives from D-lysine (whereas L-**9** can be biosynthesized from both L- and D-lysine (**3**) [38]) and was found as a constituent of a few natural substances.

1.2.3.2 **Biomimetic Access to Pipecolic Acids**

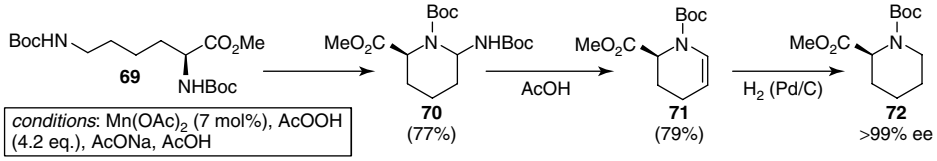
The chemical synthesis of pipecolic acid has been a subject of great interest. Powerful methods of asymmetric piperidine synthesis have been developed toward this aim [39] and have been reviewed [40]. We only outline, in this section, reactions directly involving L-lysine (**3**) (or protected L-**3**) to access **9** in a somewhat biomimetic way. In the 1970s, a first conversion of L-lysine (**3**) into optically active pipecolic acids was disclosed by Yamada and colleagues (Scheme 1.16) [41]. Sodium nitrite–hydrochloric acid was used as a deaminating agent of L-lysine, followed by barium or sodium hydroxide treatment to afford D-pipecolic acid (D-**9**) with more than 90% optical purity and satisfactory overall yield. Net retention of configuration was explained by the formation of lactonic intermediate **66** followed by halogeno-acid **67**. On the other hand, L-lysine could be converted directly into natural L-pipecolic acid starting from ε-tosyl-l-lysine (**68**) but in very low yield (~1%)



Scheme 1.16 Yamada's biomimetic access to pipecolic acids.

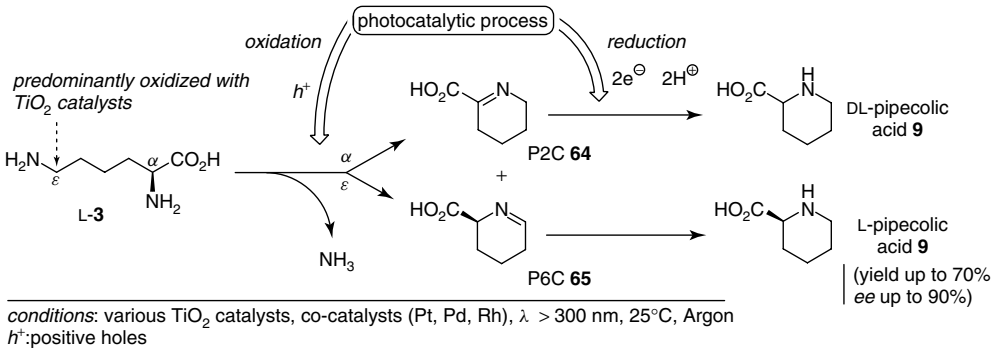
in strong acidic conditions. This work by Yamada and colleagues is not "truly" biomimetic, but is worth mentioning as it converts in a single step the acyclic skeleton of L-**3** into the piperidine ring of **9**.

In 2004, the fully protected L-lysine **69** was converted into aminal **70** by selective oxidation of the side chain using a $Mn(OAc)_2$/peracetic acid system by the Rossen group (Scheme 1.17) [42]. No epimerization occurred under the buffered oxidation conditions. Treatment under mild acidic conditions gave enamide **71**, which could be reduced to L-pipecolate **72**. This study constitutes one of the rare examples of biomimetic conversion of a side chain amino group into an aldehyde oxidation state (obtained as the cyclic *N,N*-acetal **70**).



Scheme 1.17 Rossen's biomimetic synthesis of pipecolate derivatives.

But one of the most interesting examples was probably the work disclosed by the Ohtani group (Scheme 1.18). The photocatalytic redox synthesis of pipecolic acid was achieved in a one-step procedure directly from unprotected L-lysine [43]. Several catalytic systems [various TiO_2/co-catalyst (Pt, Rh, Pd)] were investigated to define the best conditions in terms of selectivity (oxidation of ε-amino versus α-amino – which influences the final optical purity of pipecolic acid), yields, and rates. The mechanism was proved to proceed via (i) oxidation of L-lysine with positive holes, leading to P2C (**64**) and P6C (**65**), depending on the oxidized nitrogen and (ii) reduction of the imines with electron, with both steps taking place at the surface of the catalyst. Titanium oxides were shown to predominantly oxidize the ε-amino group, permitting enantiomeric excess up to 90%. The ins and outs of the multiple combinations of catalysts/co-catalysts were studied; the interested reader is referred to the original article for details. With the recourse to catalysis



Scheme 1.18 Totally biomimetic synthesis of pipecolic acid by photocatalysis.

and the release of ammonia as the only by-product of the reaction, this synthesis is indubitably a green chemistry process and a beautiful achievement.[16)]

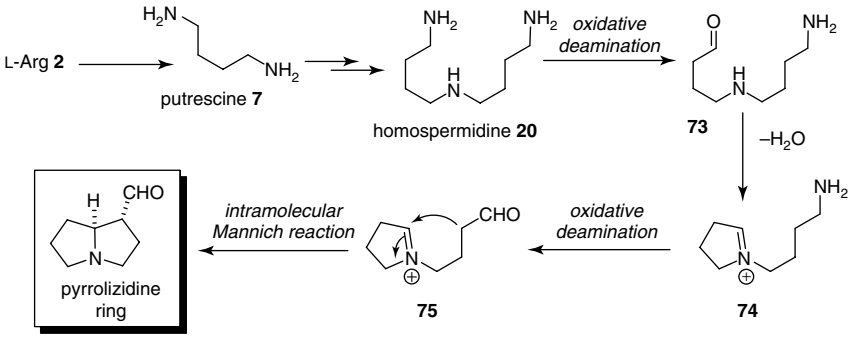
1.3
Biomimetic Synthesis of Alkaloids Derived from Ornithine and Arginine

1.3.1
Biomimetic Access to the Pyrrolizidine Ring

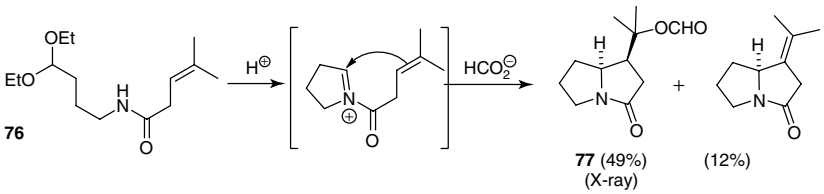
The pyrrolizidine nucleus consists of two fused pyrrolidine cycles; similarities between both biosyntheses may therefore be expected. These alkaloids are biosynthesized from homospermidine, which comes from putrescine (**7**) (Scheme 1.19). Oxidative deamination and subsequent formation of a first five-membered cycle (**74**) through dehydration is followed by an intramolecular Mannich reaction exploiting the enolization capacity of the remaining aldehyde of **75**. Biosyntheses of such alkaloids have been reviewed, as well as their structure elucidation, chemistry, and pharmacology [44].

The direct conversion of an acyclic precursor into a pyrrolizidine-type bicyclic structure was accomplished by the Marson group in 2000 (Scheme 1.20) [45]. Treatment of compound **76** in acidic conditions permitted the deprotection of the masked aldehyde, formation of the Δ^1-pyrrolidine, and subsequent formation of bicyclic **77** by an aza-Prins type cyclization. Such a cationic cyclization (radical cyclizations to pyrrolizidine are known) is closely related to biosynthetic pathways and was the first example of a non-enzymic synthesis of the pyrrolizidine ring from an acyclic precursor. The relative configuration of **77**, which was the sole diastereomer isolated, was ascertained by X-ray crystallography.

16) The term "*biomimetic*" does not appear in this article and no references to biosynthesis are made.



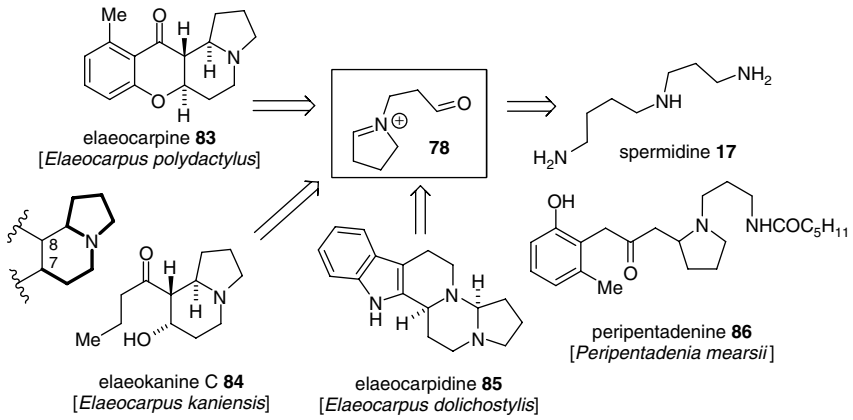
Scheme 1.19 Pyrrolizidine ring biosynthesis.



Scheme 1.20 Biomimetic access to the pyrrolizidine ring.

1.3.2
Biomimetic Syntheses of *Elaeocarpus* Alkaloids

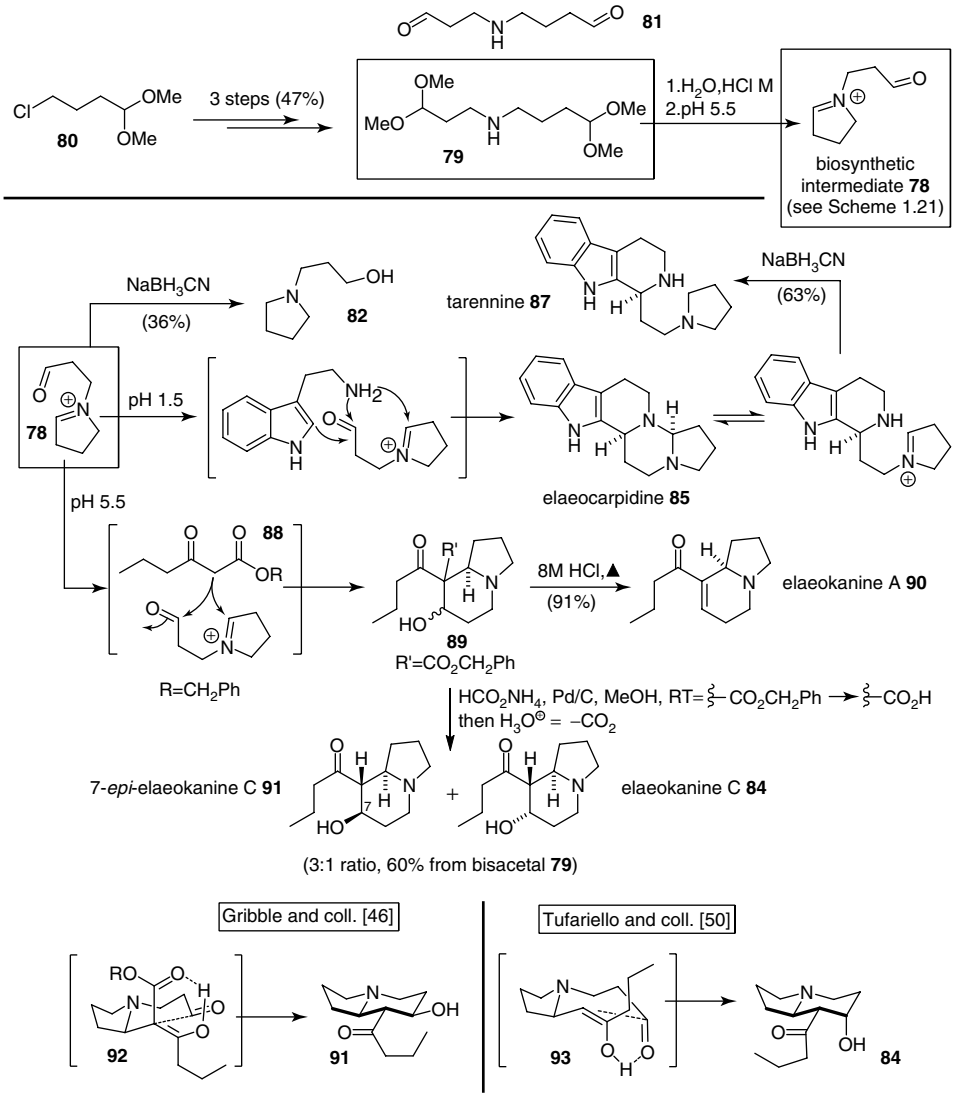
Homologous to intermediate **75** derived from homospermidine and implicated in the biosynthesis of indolizidine alkaloids, intermediate **78** (Scheme 1.21) has been postulated to be at the origin of interesting natural substances. Biomimetically speaking, aldehydic intermediate **78** was prepared in the laboratory by the Gribble group in the 1980s (Scheme 1.22) [46]. Bis-acetal **79** was prepared in three steps from chloroacetal **80** in 47% overall yield. It constitutes a stable protected equivalent of intermediate **81**, which under acidic conditions can be deprotected to give *in situ* **78**. In fact, non-isolated **81** when buffered at pH 5.5 presumably generates pyrrolinium aldehyde **78**. This latter was reduced to pyrrolidine **82** or more interestingly trapped by various nucleophiles in a biomimetic manner, thus giving a very interesting unified access to a group of alkaloids isolated from different species of *Elaeocarpus* and *Peripentadiena* (commonly known as *Elaeocarpus alkaloids* [47], see examples on Scheme 1.21, **83**–**86**). Most of them share a common indolizidine backbone functionalized at positions 7 and 8. Onaka, in the early 1970s, suggested intermediate **78** as the universal precursor of these natural substances [48]. The isolation some years after of alkaloids such as peripentadenine (**86**) [49] ascertained a spermidine (**17**) metabolism pathway. Although numerous syntheses of *Elaeocarpus* alkaloids have been reported [47], we deliberately delineate herein syntheses based on the *in situ* generation of intermediate **78**.



Scheme 1.21 *Elaeocarpus* alkaloids.

Trapping of intermediate **78** with tryptamine gave a straightforward isohypsic synthesis of (±)-elaeocarpidine (**85**) in a stereoselective cascade of reaction from acetal **79** by just adjusting the pH of the solutions (Scheme 1.22) [46]. The elaeocarpidine aminal function was then reduced with sodium cyanoborohydride to give tarennine (**87**). In turn, trapping of intermediate **78** with β-keto ester **88**, thus engaged in a tandem Mannich/aldol condensation, gave **89** as a mixture of two major diastereomers (axial and equatorial hydroxyl at C7) in 62% overall yield. Compound **89** appeared to be a common intermediate for the synthesis of both (±)-elaeokanine A (**90**) and C (**84**). Decarboalkoxylation in strong acidic conditions was accompanied with dehydration at position 7 and gave rise to (±)-elaeokanine A (**90**) in 91% yield. Milder conditions were necessary to carry out the synthesis of (±)-elaeokanine C (**84**). The conditions were carefully studied by the authors, who finally chose catalytic transfer hydrogenation with ammonium formate and palladium in methanol to afford the desired reaction. Although some degree of selectivity was expected, the outcome of the reaction clearly showed a preference for the wrong isomer, with a predominance of (±)-7-epi-elaeokanine C (**91**) over (±)-elaeokanine C (**84**) despite a good overall yield of 60% from bis-acetal **79**. This experiment and its outcome in terms of stereochemistry can be rationalized when considering transition state **92** in which an equatorial hydroxyl is to be expected. This supposition was compared to a similar case studied by Tufariello and Ali [50] a few years before with the intramolecular kinetic aldol reaction of a ketone instead of a β-ketoester. In the latter, a stereocontrol, totally in favor of the axial configuration, could have been governed by transition state **93**. Returning to a biosynthesis hypothesis and taking into account these findings, one can suggest that should such a pathway occur in Nature the decarboxylation step has to be prior to the aldol reaction.

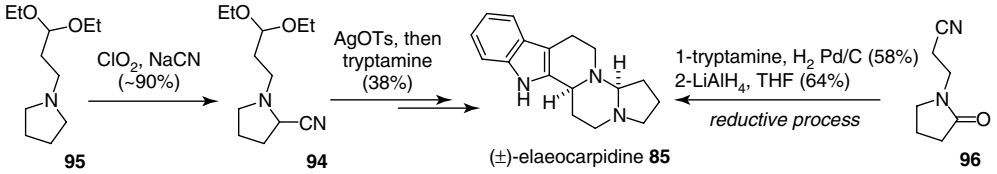
Starting from readily accessible acetal **79**, it is worth noting how simple starting materials (tryptamine, ketoesters) and reaction conditions (aqueous solutions at



Scheme 1.22 *Elaeocarpus* alkaloids: biomimetic synthesis.

various pH) enabled the design of a divergent pathway to *Elaeocarpus* alkaloids following, and thereby reinforcing, previously proposed biosynthetic hypotheses.

Concomitant with Gribble's work, the Hortmann group used α-cyanopyrrolidine **94** as a surrogate of **79** (Scheme 1.23) [51]. It was prepared by oxidative cyanation of the corresponding pyrrolidine **95** with chlorine dioxide (as an alternative to classical mercury acetate oxidation or modified Polonovski reaction). Compound **94** was used in a total synthesis of (±)-elaeocarpidine (**85**). Lactam **96** was prepared by Lévy and colleagues for the synthesis of **85** [52]. It was engaged in a reductive



Scheme 1.23 *Elaeocarpus* alkaloids: alternative biomimetic synthesis.

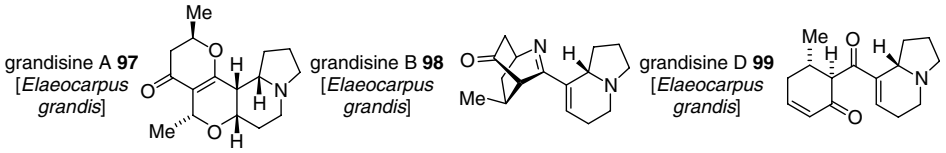


Figure 1.3 Other *Elaeocarpus* alkaloids.

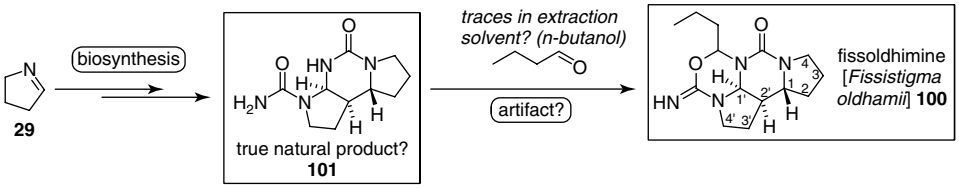
Pictet–Spengler reaction under catalytic hydrogenation conditions. The recourse to trivalent functional groups (lactam of **96**) where divalent ones (imine) are needed places this former approach at the borderline of biomimetic synthesis.

The *Elaeocarpus* alkaloid group gained constant interest with the discovery of new structures (see examples **97**–**99** in Figure 1.3) along with interesting biological properties (such as selective γ-opioid receptor affinity for grandisine-type alkaloids) [53]. These complex structures also stimulated state of the art total syntheses [54].

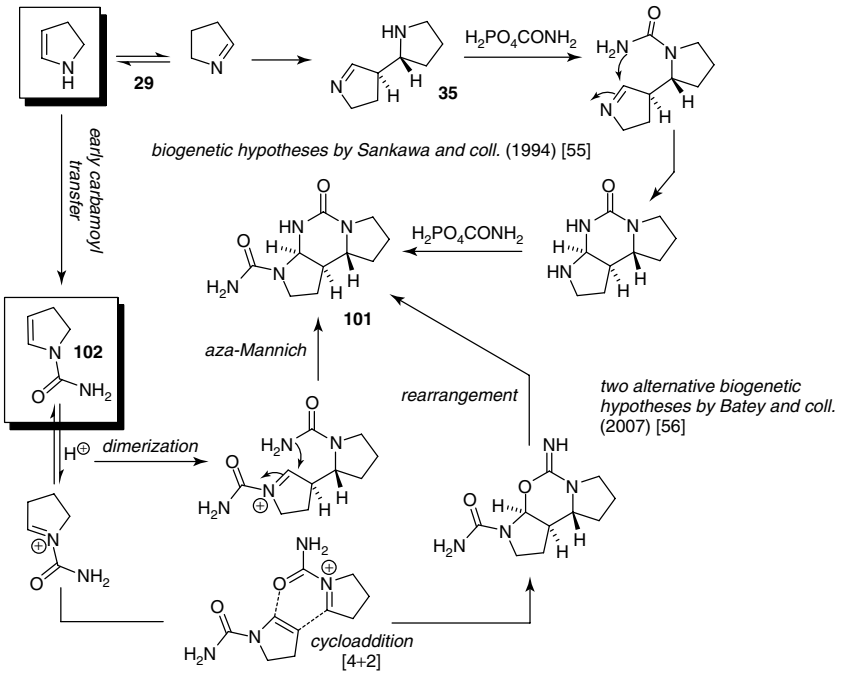
1.3.3
Biomimetic Synthesis of Fissoldhimine

Fissoldhimine (**100**) was isolated in 1994 by Sankawa *et al.* [55] from fresh stems of *Fissistigma oldhamii* (Annonaceae), a shrub mainly found in Southern China and Taiwan (Scheme 1.24). Its structure was unambiguously confirmed by X-ray analysis. Since *n*-butanol was used to extract this basic molecule from an alkaline solution, it was suggested that fissoldhimine was an artifact resulting from the aminoacetalization of compound **101** (which may therefore be the ''true'' natural product) with a molecule of *n*-butanal presumably present in *n*-butanol.[17] The authors proposed a biosynthetic pathway (Scheme 1.25) to fissoldhimine (**100**/**101**) from two molecules of cyclic enamine **29** that came from L-ornithine via a dimerization (see above). R. A. Batey and colleagues revisited the hypotheses in 2007 when disclosing the first biomimetic investigations toward fissoldhimine [56].

17) Defined as spontaneously formed natural products, artifacts are closely related to biomimetic chemistry (see Chapter 24 of this book).

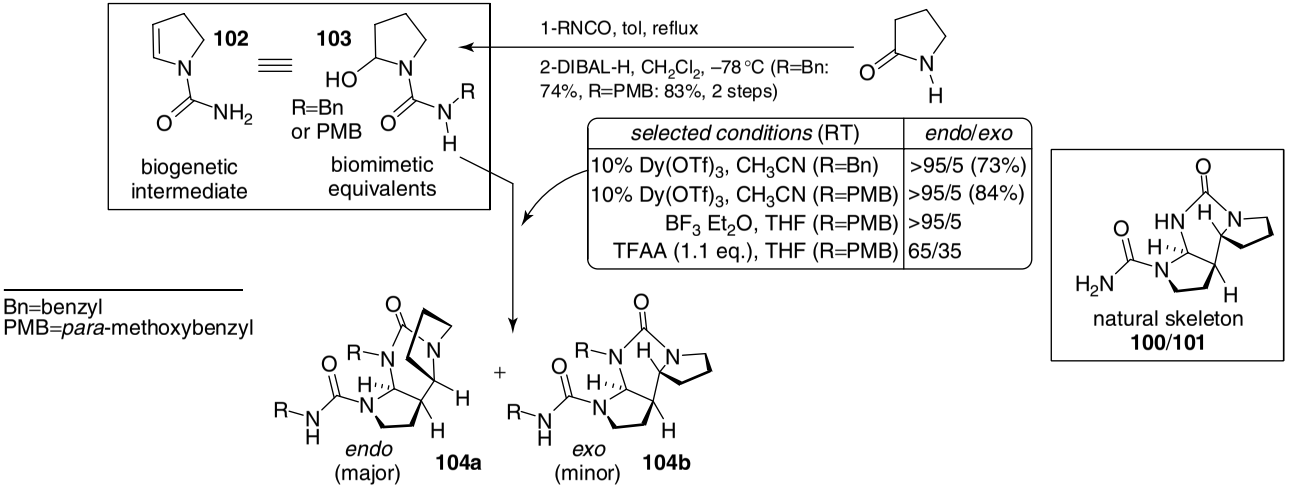


Scheme 1.24 Fissoldhimine: possible structures.



Scheme 1.25 Biosynthetic hypotheses.

Benzyl- or *para*-methoxybenzyl-protected urea **103** (Scheme 1.26) was used as biomimetic equivalent of biosynthetic intermediate **102** postulated in Scheme 1.25. The best conditions, the authors found, for the formation of the desired *exo*-dimer **104b** were the use of trifluoroacetic anhydride in THF (*endo*/*exo*: 2 : 1 ratio) but separation of the two diastereomers was impossible. In addition, final deprotection of the urea nitrogens was also problematic (removal of the benzyl group was unsuccessful and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone)-mediated deprotection of PMB groups resulted in the deprotection of only one of the nitrogens). Despite obtaining an *endo* relative stereochemistry that contrasts with the *exo* stereochemistry of natural fissoldhimine **100**/**101**, this example is interesting as it opens the way to discussions concerning the biosynthesis and the implication of enzymes, particularly since fissoldhimine was shown, by X-ray, to be a racemate in nature! Another point is that an early carbamoyl transfer is likely, in direct

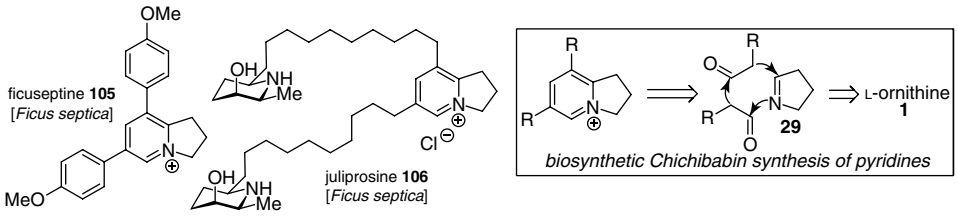


Scheme 1.26 Biogenetically inspired heterodimerization toward fissoldhimine.

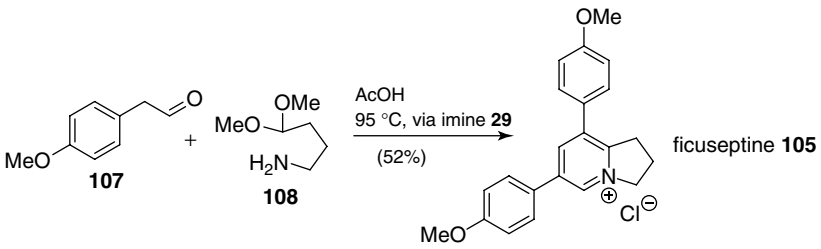
correlation with the critical difficulty of dimerization of imine **29** as already evoked (see above, Scheme 1.5).

1.3.4
Biomimetic Synthesis of Ficuseptine, Juliprosine, and Juliprosopine

As we will now discuss, imine **29** was successfully engaged by the Snider group [57] in a biomimetic synthesis of two dihydroindolizinium alkaloids: ficuseptine (**105**) [58] and juliprosine (**106**) [59] (Scheme 1.27). Biosynthetic considerations led to the postulation of a Chichibabin pyridine synthesis type reaction as a cornerstone convergent step for both **105** and **106**. Mixing aldehyde **107** (which is presumably a tyrosine metabolite in Nature) with imine **29**, generated *in situ* from **108**, in acetic acid provided ficuseptine (**105**) in a single step in 52% yield (Scheme 1.28).

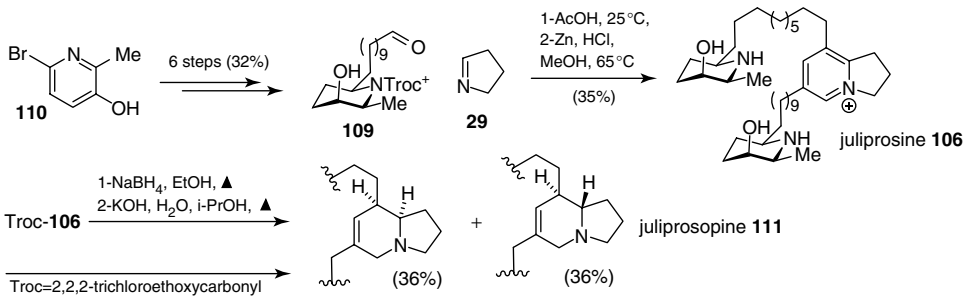


Scheme 1.27 Ficuseptine (**105**) and juliprosine structures (**106**), and plausible biogenesis.



Scheme 1.28 Ficuseptine: biomimetic synthesis.

This strategy appeared to be as effective (Scheme 1.29) when dealing with more complex juliprosine (**106**) in terms of side chains engaged in the pyridine formation (probably of polyketide origin in Nature). Aldehyde **109** was prepared in six steps from bromopyridinol **110** and reacted with preformed imine **29** at room temperature in acetic acid to give Troc-**106**, from which juliprosine **106** was liberated by protecting group removal. Juliprosopine (**111**) [60], a reduced tetrahydropyridine counterpart of juliprosine was then targeted by the authors as a final destination. Exposure of Troc-**106** to sodium borohydride gave a separable 1 : 1 mixture of diastereomers. Prior to this last step, model studies concluded that the natural stereochemistry of **111** should be trans. Therefore, the trans isomer was deprotected to afford juliprosopine (**111**), for which the stereochemistry was in consequence clarified 25 years after its isolation. It is striking in terms of



Scheme 1.29 Juliprosine (**106**) and juliprosopine (**111**) biomimetic synthesis.

evolutionary convergence that a pivotal biosynthetic (and synthetic!) reaction can give rise to different natural substances in different plants. These examples once again raise questions about the intervention of enzymes in such biosyntheses.

1.3.5
Biomimetic Synthesis of Arginine-Containing Alkaloids: Anchinopeptolides and Eusynstyelamide A

1.3.5.1 Natural Products Overview

Original dihydroxybutyrolactams were isolated from marine ascidian *Eusynstyela latericius* collected in the Australian Great Reef and named eusynstyelamides A–C (**112**–**114**, Figure 1.4) by the Tapiolas group in 2009 [61]. They are in fact closely related to other natural substances, namely, anchinopeptolides A–D (**115**–**118**) and surprisingly cycloanchinopeptolide C (**119**) (with its central core consisting in a tricyclic 5-12-4 ring system) isolated earlier from a marine sponge [62]. Biosynthetically, they might all arise from dimerization of monomeric modified α-ketoacid-containing peptides (dipeptides or tripeptides in the case of eusynstyelamides and anchinopeptolides, respectively) by an aldol reaction (formation of the carbon–carbon bond) and an addition to the amide (Figure 1.4, box). Biomimetic syntheses of these two classes of alkaloids have been performed by the Snider group.

1.3.5.2 Biomimetic Synthesis

(±)-Anchinopeptolide D (118) The aldol dimerization of protected modified tripeptide **120** (synthesis not described herein) was undertaken (Scheme 1.30) [63]. Treatment of **120** with potassium hydroxide in MeOH afforded a mixture of three isomeric compounds (Boc-**118**, Boc-**121**, **122**), two of which were deprotected to afford **118** (anchinopeptolide D) and **121** (epi-anchinopeptolide D). Equilibration studies clearly demonstrated epimerization at the hemiaminal center: heating pure Boc-**118** or Boc-**121** for 1 h resulted in a 2 : 1 mixture of Boc-**118** and Boc-**121**. Equilibration of the aldol stereocenter occurred more slowly (from pure Boc-**118**

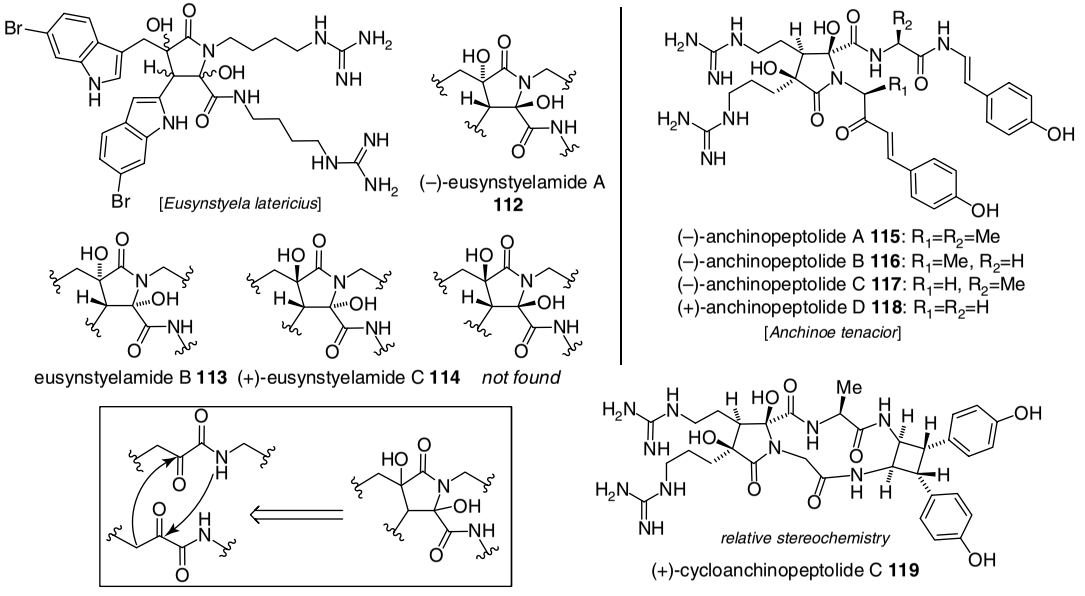
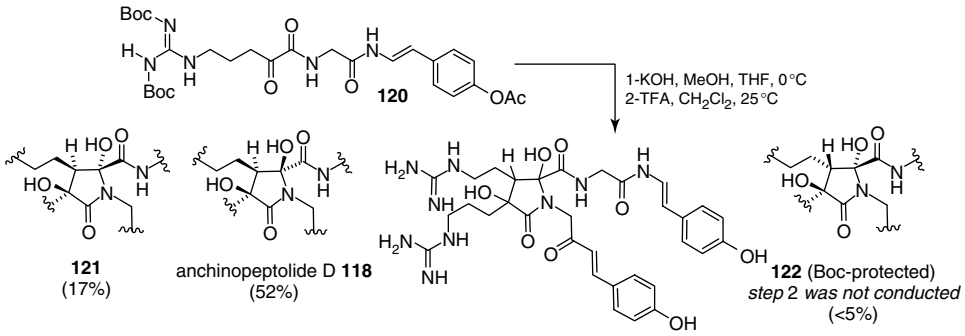


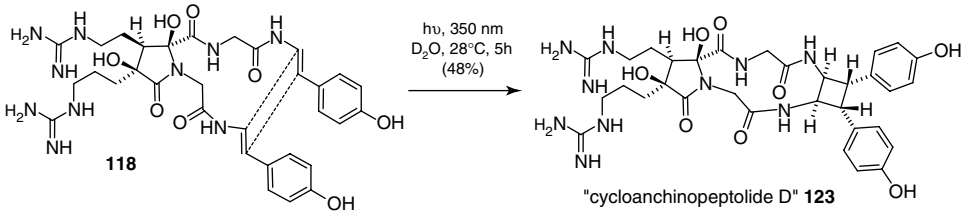
Figure 1.4 Eusynstyelamides and anchinopeptolides.



Scheme 1.30 Biomimetic synthesis of anchinopeptolides.

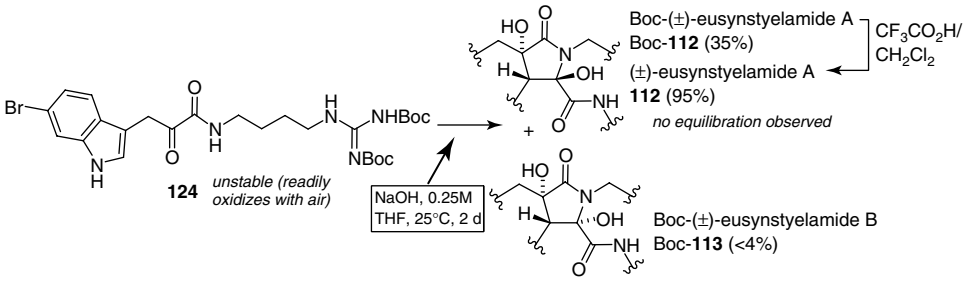
or Boc-**121**, 17 h of heating in KOH THF–MeOH provided a 6 : 3 : 1 mixture of Boc-**118**, Boc-**121**, and **122**).

"(±)-Cycloanchinopeptolide D" (123) A head to head [2 + 2] cycloaddition between the two double bonds of the plausibly tyrosine-derived part of anchinopeptolide C (**117**) may explain the formation of the cyclobutane ring of cycloanchinopeptolide C (**119**). To confirm this hypothesis, access to analog **123** (unnatural "cycloanchinopeptolide D") was targeted (Scheme 1.31). Careful choice of the photochemical conditions, especially the solvent, permitted the obtaining of **123** avoiding, thereby, the isomerization of the double bonds. Indeed, in water, irradiation of a 0.005 M solution of **118** at 350 nm afforded cycloanchinopeptolide D (**123**) in 48% yield. In water, a hydrophobic effect may cause the nonpolar chain to pack closely and favor the [2 + 2] cycloaddition *versus* the *trans/cis* isomerization.



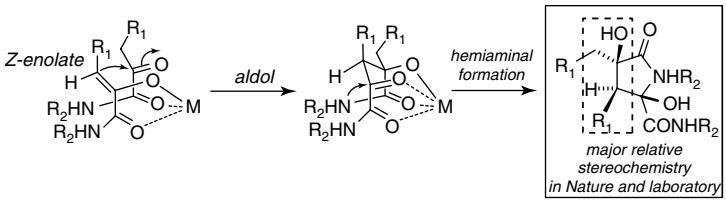
Scheme 1.31 Biomimetic synthesis of cycloanchinopeptolide D.

(±)-Eusynstyelamide A (112) Adopting a similar philosophy, access to **112** was possible (Scheme 1.32) [64] from unstable dipeptide **124** (prepared in four steps), which could undergo butyrolactam core formation under basic conditions. The obtaining of Boc-protected-**112** as a major compound (37%) was accompanied by small amounts of Boc-**113** (<4%). Deprotection of Boc-**112** afforded eusynstyelamide A (**112**). At this stage, chemical and reactivity observations stimulated interesting thoughts. As previously mentioned, anchinopeptolide D (**118**) was shown to equilibrate into a mixture of epimeric compounds. The question of



Scheme 1.32 Biomimetic synthesis of eusynstyelamide A.

whether eusynstyelamides B (**113**) and C (**114**) are natural products or artifacts spontaneously generated during extraction was logically posed. In fact, when the isolation of eusynstyelamides was conducted, some samples, carefully processed, of the sponge contained only eusynstyelamide A (**112**) whereas some others contained the two isomeric eusynstyelamides A (**112**) and B (**113**) (1 : 1 ratio) or the three isomeric compounds [eusynstyelamides A–C (**112**–**114**), 2 : 6 : 1 ratio]. Additionally, no evidence of equilibration was observed by the authors as confirmed by Snider and colleagues with synthetic eusynstyelamide A (**112**). Indeed, synthetic **112** did not equilibrate under various conditions (acidic, storage in CD_3OD) and decomposed in basic conditions. The formation of Boc-eusynstyelamide A (Boc-**112**) as the major isomer from monomeric **124** is consistent with the isolation of eusynstyelamide A (**112**) as a unique compound from some sample of raw material. In the laboratory, the aldol reaction gave rise to a major isomer with high selectivity according to the proposed mechanism (Scheme 1.33) and may be correlated with the fact that it is the main relative stereochemistry observed in the two series of alkaloids. The influence of the side chains when comparing the eusynstyelamide and anchinopeptolide series is probably prominent in controlling both the equilibration propensity and the stereochemical outcome of the aminal formation.

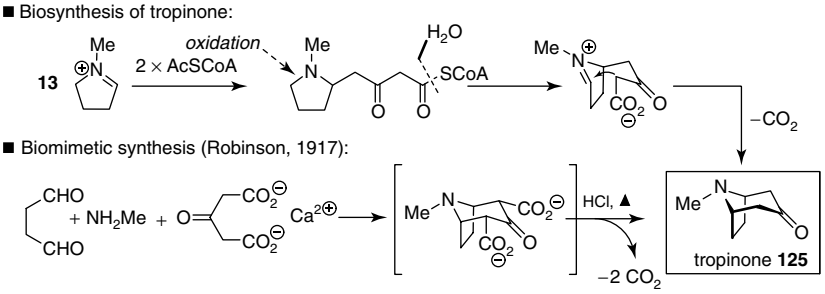


Scheme 1.33 Dimerization: a plausible mechanism.

1.3.6
A Century of Tropinone Chemistry

The biomimetic synthesis of tropinone (**125**) by Robinson in 1917 [65] is probably among the most renowned synthesis of organic chemistry. More than many other,

it has been analyzed, cited and is usually presented as the first biomimetic total synthesis and as a pioneering multicomponent reaction (Scheme 1.34). We will therefore not develop further this textbook classic. The reaction was revisited by Schöpf in the 1930s with an in-depth study of the reaction conditions [66] and has been adapted to other target molecules many times since then. Questions interfacing biosynthesis and chemistry arose continuously concerning tropane alkaloids; they were compiled and analyzed by O'Hagan and Humphrey in a review article [67]. The now well-established biosynthesis of the tropinone (**125**) skeleton is depicted in Scheme 1.34.



Scheme 1.34 Tropinone biosynthesis and landmark biomimetic synthesis.

Nearly one century later, this reaction still stimulates interesting discoveries. By way of an example, a solid-phase version was developed as an interesting means of generating tropane analogs in a combinatorial way [68]. The use of siloxy(allyl)silane was also reported in place of acetonedicarboxylates (avoiding thereby the double thermal decarboxylation step) and afforded tropinone in good yield [69]. Asymmetric syntheses of substituted tropinones, some using biomimetically related intramolecular Mannich reactions have also been disclosed [70]. The Mannich reaction and the Robinson–Schöpf condensation are absolute musts in the chemical toolbox for biomimetic synthesis of alkaloids [71].[18)]

1.4
Biomimetic Synthesis of Alkaloids Derived from Lysine

1.4.1
Alkaloids Derived from Lysine: To What Extent?

A list (if not a classification *sensu stricto*) according to the number of carbons that have been incorporated via the C_5N units originating from L-Lys can be drawn

18) "Time can never diminish the exquisite beauty of Robinson's total synthesis of tropinone. The simplicity of this remarkable synthesis, the splendor of the cascade and the stunning analysis that led to its conception will always stand out, marking this endeavor as a true classic in total synthesis, and inspiring new generations of chemists" [72].

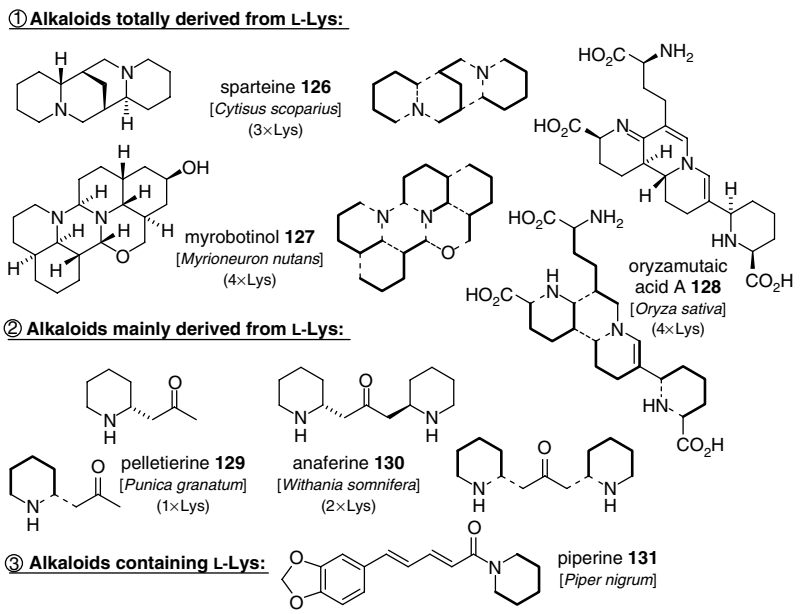


Figure 1.5 Lysine-derived alkaloids: selected examples.

up – some examples are given in Figure 1.5. One may then distinguish, more or less artificially, between three categories, that is, alkaloids: (i) exclusively derived from L-Lys[19] [e.g., sparteine (**126**), myrobotinol (**127**),[20] oryzamutaic acid A (**128**)[21], (ii) mainly derived from L-Lys [e.g., pelletierine (**129**) and anaferine (**130**)], and (iii) containing L-Lys [e.g., piperine (**131**)]. For each of the two first groups, examples of biomimetic syntheses will be discussed in this section.

1.4.2 Lupine Alkaloids

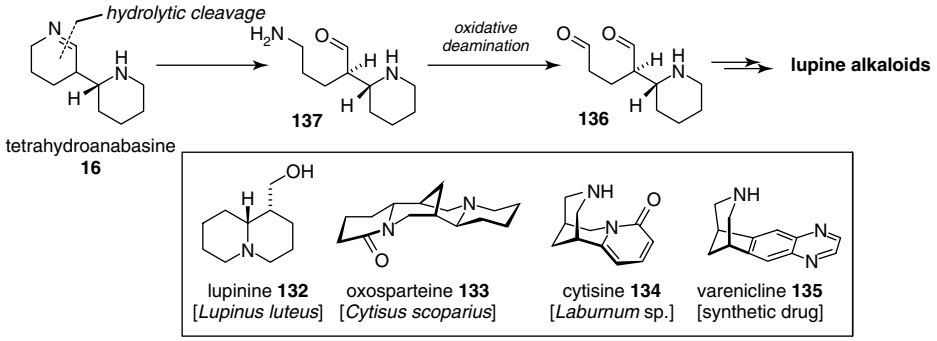
1.4.2.1 Overview and Biosynthesis Key Steps

The "lupine alkaloids" are an important and biosynthetically homogeneous group of natural substances found especially, but not only, in the *Lupinus* genus (Fabaceae). The vast majority of them are structurally characterized by a quinolizidine rings and they are classified in ten or so main subgroups defined by the central skeleton. Lupinine (**132**) (the simplest alkaloid of this group), sparteine (**126**),

19) Every single carbon atom of the alkaloids comes from L-Lys. It is, at this point, striking to see how complex structures can arise from a single amino acid.

20) See below for comments on this intriguing new family of alkaloids.

21) Oryzamutaic acid A (128) is one of the rare alkaloids that contain four molecules of L-lysine [22]. It is a novel yellow pigment isolated from the endosperm of an *Oryza sativa* (rice) mutant. Its rather elaborate architecture presumably incorporates several types of units derived from L-lysine, including lysine itself. It undoubtedly constitutes an appealing target for biomimetic synthesis! [73].



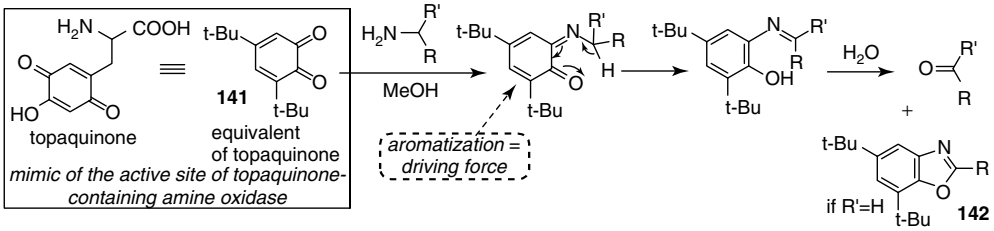
Scheme 1.35 Lupine alkaloids: origin and examples.

oxosparteine (**133**), and cytisine (**134**) are probably among the most well-known structures of lupine alkaloids (Scheme 1.35). The existence of multiple higher oxidized derivatives of lupine alkaloids and transformed skeletons thereof explains part of the diversity within this class of natural substances. They are of great interest for their biological properties such as nicotine-like properties. Varenicline (**135**) (Chantix®, Champix®), a synthetic drug that acts as a partial agonist of $\alpha_4\beta_2$-subtype of the nicotinic acetylcholine receptors, is directly inspired by the structure of natural cytisine. This drug is prescribed to treat smoking addiction in many countries in the USA and Europe. Many comprehensive reviews of interest have been published over the years covering many aspects of lupine alkaloids [74]. The suggestion that the quinolizidine is built up from L-lysine has now been widely confirmed by incorporation studies and chiral non-racemic intermediate **136** arising from selective hydrolysis of **16** (via intermediate **137**) appears to be a cornerstone in lupine alkaloid metabolism. The biosyntheses of alkaloids such as lupinine (**132**) or sparteine (**126**) are now textbook examples of L-lysine metabolism in plants.

1.4.2.2 Biomimetic Synthesis of Lupine Alkaloids

A unified biomimetic strategy starting from tetrahydroanabasine (**16**) was beautifully designed by Koomen and colleagues for the total synthesis of representative lupine alkaloids [75, 76]. Four natural substances, that is, lupinine (**132**), epilupinine (**138**), aminolupinane (**139**), and sparteine (**126**), as well as anabasine (**140**), were retrosynthetically traced back to the common precursor tetrahydroanabasine.

Mimic of the Fundamental Oxidative Deamination Step Topaquinone (2,4,5-trihydroxyphenylalanine) was identified as the covalently bound active site cofactor of copper-containing amine oxidases in the early 1990s [77]. These enzymes catalyze the fundamental two-electron oxidative deamination of primary amines into the corresponding aldehyde along with ammonia. The formation of a Schiff base that undergoes proton abstraction with aromatization as a driving force is implicated in the intimate mechanism of the enzyme. Several model studies of topaquinone or more generally quinoprotein enzymes have been



Scheme 1.36 Topaquinone and a topaquinone-mimic.

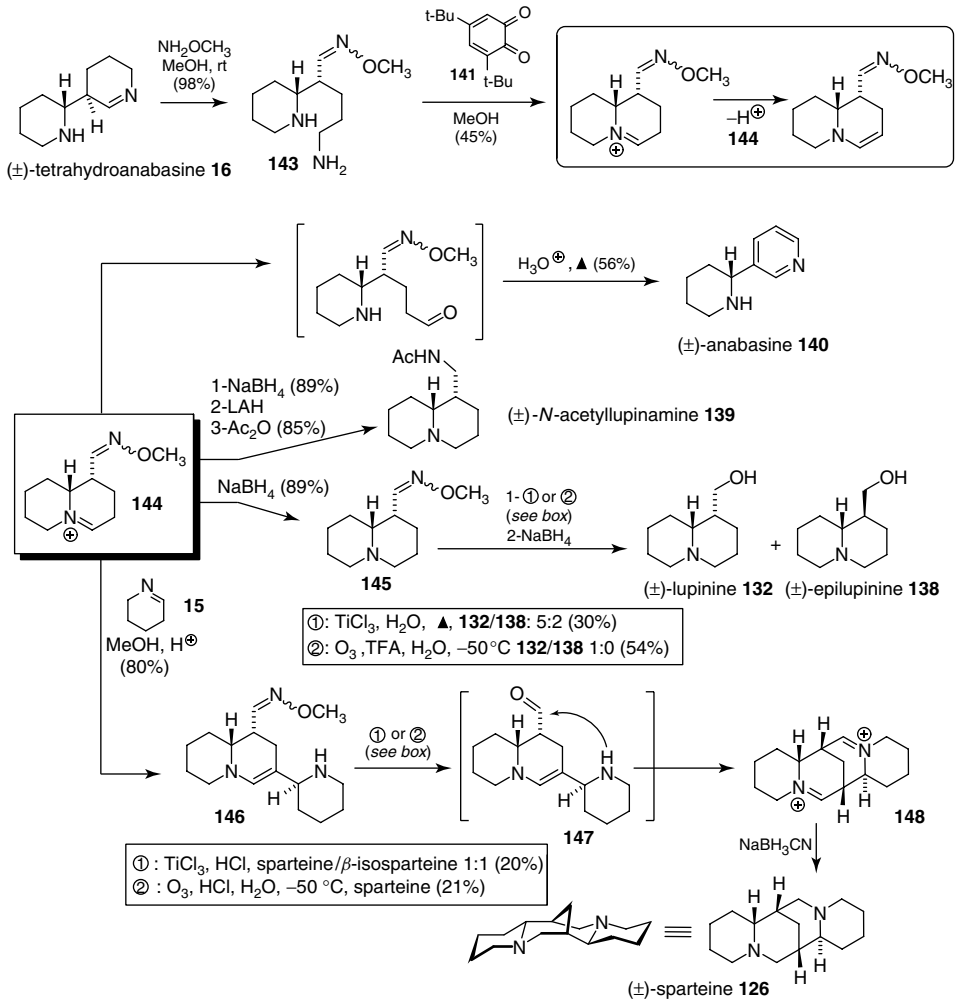
made but are beyond the scope of this chapter [77, 78]. Commercially available and stable di-*tert*-butyl-*o*-quinone **141** was successfully used as a topaquinone surrogate to achieve the desired oxidative deamination without any overoxidation to benzoxazoles of type **142** (Scheme 1.36). Quinone **141** was used to oxidize compound **143**, which resulted from the opening of tetrahydroanabasine (**16**) with methoxyamine (compound in which the stereochemistry was preserved), to give iminium or enamine **144** depending on the pH (Scheme 1.37).

Reduction of **144** gave a stable quinolizidine (Scheme 1.37), which was further reduced to aminolupinane (**139**, isolated as its acetate). Hydrolysis of the oxime of **145**, necessary to access lupinine, had to be performed under mild conditions to avoid epimerization of the intermediate aldehyde into the more stable epilupinine skeleton. Ozonolysis of **145** at low temperature followed by sodium borohydride reduction yielded exclusively lupinine (**132**). Under more vigorous conditions, a mixture of lupinine (**132**) and epilupinine (**138**) was obtained. The pathway to sparteine required participation of another tetrahydropyridine molecule (**15**). Reaction of **144** with **15** gave **146**, the oxime group of which was split under mild conditions to furnish aldehyde **147**, which is a direct precursor of the sparteine skeleton in which both the piperidine ring and the aldehyde occupy an axial position that can cyclize to **148**. Reduction of **148** furnished sparteine **126** but, as already observed with lupinine, oxime cleavage under more drastic conditions was accompanied with a loss of stereoselectivity, giving isomeric β-isosparteine along with sparteine. This synthesis clearly demonstrated that the whole pathway from tetrahydroanabasine (**16**) to polycyclic sparteine (**126**) can be efficiently mimicked in the laboratory. Finally, simple hydrolytic conditions from **144** surprisingly gave rise to anabasine (**140**) in a single step.[22)]

1.4.2.3 A Biomimetic Conversion of *N*-Methylcytisine into Kuraramine

Many examples of semi-synthetic conversions of lupine alkaloids have been disclosed over the years [74]; only one recent example will be given. Kuraramine (**149**) was isolated in 1981 from *Sophora flavescens* [79]. An obvious biosynthetic

22) Biosynthetically speaking, anabasine (**140**), for example, found in *Nicotiana sp.*, is derived from tetrahydropyridine and nicotinic acid and not from tetrahydroanabasine, nor does tetrahydroanabasine (**16**) derive from the reduction of anabasine (**140**).

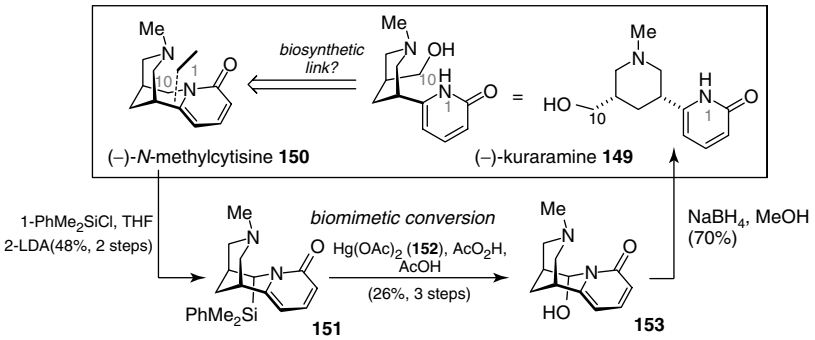


Scheme 1.37 Biomimetic unified access to lupine alkaloids.

relationship with *N*-methylcytisine (**150**) which could involve a N(1)–C(10) oxidative cleavage has been postulated and strengthened by a biomimetic conversion (Scheme 1.38). Indeed, in 2010, Gallagher *et al.* [80] first silylated **150** into **151**, which in turn was submitted to a Fleming–Tamao oxidation (**153**) followed by sodium borohydride reduction to give (−)-**149** in 18% overall yield.

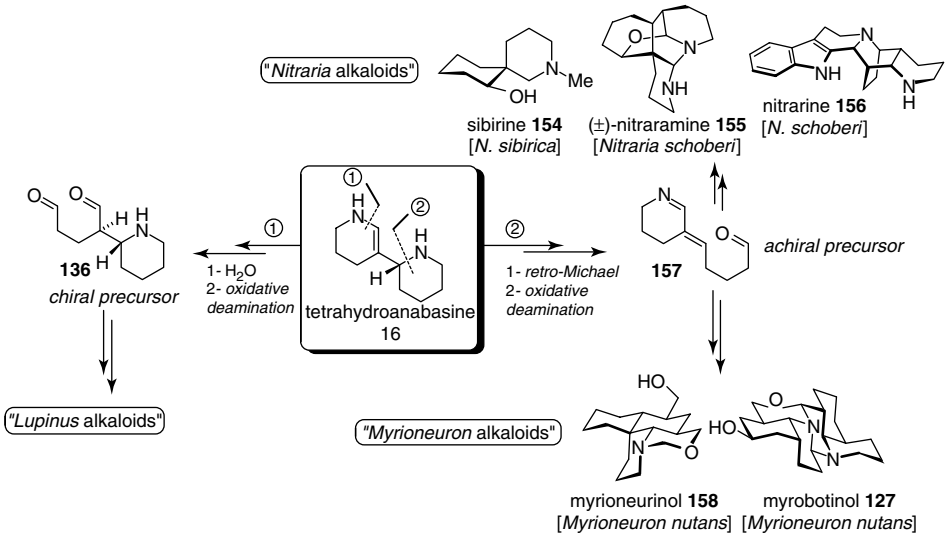
1.4.3
Biomimetic Synthesis of *Nitraria* and *Myrioneuron* Alkaloids

Mainly from the steppes of Uzbekistan, intriguing alkaloids [such as sibirine (**154**), nitraramine (**155**), and nitrarine (**156**)] have been isolated from *Nitraria* species



Scheme 1.38 Biomimetic synthesis of kuraramine from *N*-methylcytisine.

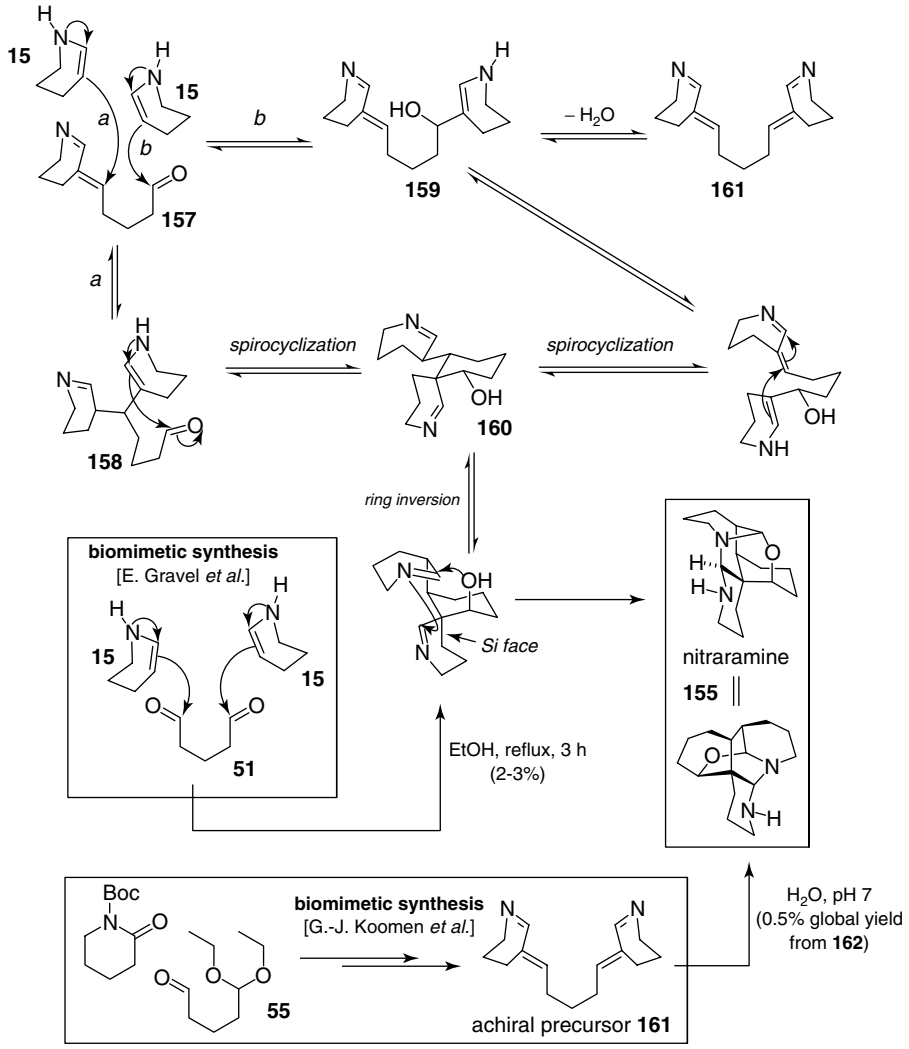
(Nitrariaceae). In the 1990s, an unusual lysine-derived metabolism was postulated by Koomen and colleagues to account for the biosynthesis of these often-complex molecules (Scheme 1.39) [81]. Often isolated as racemic mixtures, they may arise from an alternative opening/rearrangement of tetrahydroanabasine as compared to the "classical" *Lupinus* pathway (Scheme 1.39, pathway ① and Scheme 1.35 above). Central to this hypothesis is the formation of compound **157**, referred to as the "*key intermediate*" in *Nitraria* metabolism, by a retro-Michael reaction followed by an oxidative deamination (pathway ②).



Scheme 1.39 *Nitraria* and *Myrioneuron* alkaloids: origin and selected examples.

1.4.3.1 **Biomimetic Syntheses of Nitraramine**

Nitraramine (**155**) is probably one of the most original and intricate structures among lysine-derived alkaloids (Scheme 1.40). It has been isolated from *Nitraria*



Scheme 1.40 Biosynthetic hypotheses of nitraramine and total biomimetic synthesis.

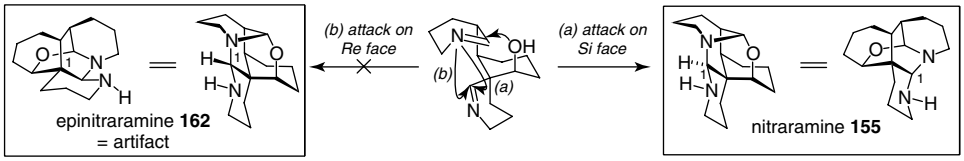
as a racemate. With several heterocycles (three peripheral cycles in a chair-like conformation and three central cycles in a boat-like conformation) and six contiguous stereogenic centers (one of which is a quaternary spiro center) this molecule, despite its rather modest molecular weight, can be seen as a real challenge for organic chemists.

The Koomen group proposed a biogenetic hypothesis according to which nitraramine might result from the assembly of lysine-derived simple precursors (Scheme 1.40), through a series of simple reactions. From key intermediate **157** as a pivotal achiral precursor, the addition of a piperideine molecule (**15**) could

then afford compound **158** (or **159**). An intramolecular spirocyclization reaction could then give rise to the spiro quaternary center (intermediate **160**) found in the natural product. A ring inversion on the newly created cyclohexane of **160** is then needed to explain two ring-closures by imine trappings that end the cascade toward nitraramine **155**.

The Koomen group targeted compound **161** in their beautiful pioneering total synthesis of nitraramine in 1995 (Scheme 1.40). Achiral synthetic **161** was then treated in neutral conditions in water and afforded the natural compound in a global sequence of a dozen steps from **55** and a piperidone (0.5% yield) [82]. In 2005, a second straightforward synthesis strongly reinforced the Koomen hypotheses [83]. In view of the fact that **157** can be obtained from the reaction of enamine **15** with glutaraldehyde (**51**) followed by dehydration, we set up a biomimetic total synthesis of nitraramine by a one-pot sequence. In fact, from simple starting materials **15** and **51** the reaction cascade quickly takes place. By treating one equivalent of **15** with two equivalents of **51** in boiling ethanol, nitraramine (**155**) was obtained in a low yield that competed with the Koomen total synthesis and also with quantities available from natural sources.

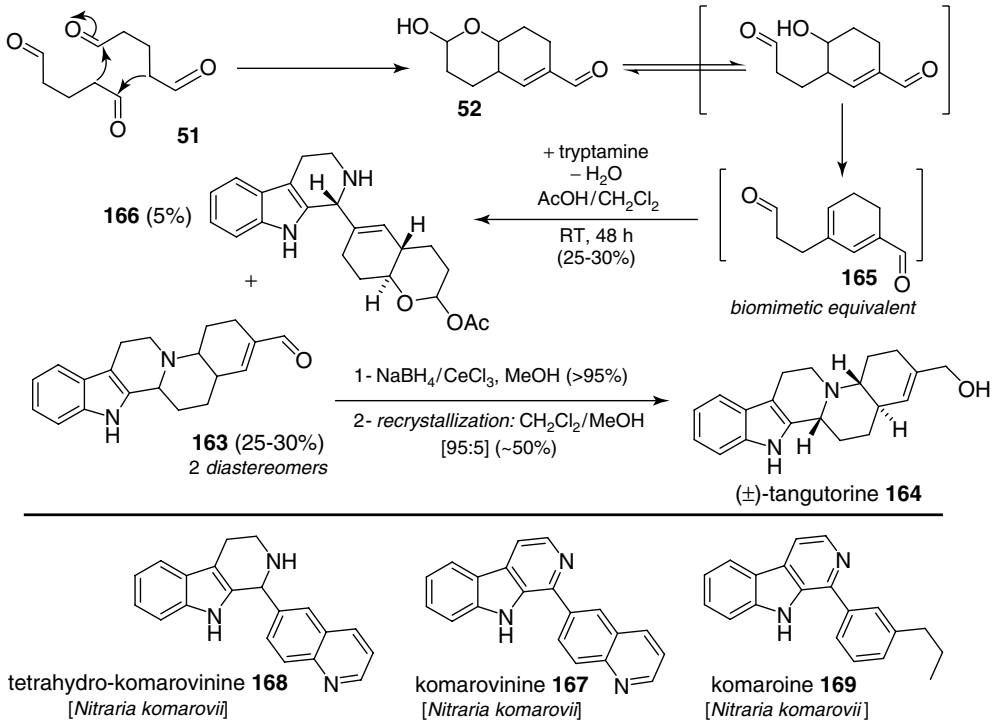
Interestingly, this second total synthesis of nitraramine showed that the natural substance previously described as epinitraramine (**162**) was actually an artifact resulting from the protonation of nitraramine in the NMR tube (Scheme 1.41). In fact, ^{1}H NMR spectra of protonated nitraramine (with traces of hydrochloric acid liberated from $CDCl_3$) differ slightly from those of **155** as a free base. Thereby, the absence of **162** reflects the high stereoselectivity of the cascade reaction. Finally, the success of the total synthesis of **155**, despite low yields, raises interesting questions concerning the implication of enzymes in the biosynthesis of such alkaloids.



Scheme 1.41 Epinitraramine is an artifact.

1.4.3.2 **Biomimetic Syntheses of Tangutorine**

As seen above (Scheme 1.12), the self-condensation of glutaraldehyde (**51**) furnishes bicyclic compound **52**. A simple condensation of **52** with tryptamine under acidic conditions allowed the synthesis of **163**, which is a direct precursor of tangutorine (**164**), another alkaloid isolated from a *Nitraria* species (Scheme 1.42) [84]. Indeed, reduction of **163** with sodium borohydride gave tangutorine (**164**) after recrystallization to isolate the major diastereomer of the (75 : 25) mixture [85]. The reaction course with tryptamine could be rationalized by assuming the *in situ* formation of intermediate **165**. Interestingly, compound **166**, resulting from a direct Pictet–Spengler reaction of the aldehyde function of **52** with tryptamine, was also isolated from the reaction. It is reminiscent of the structure of many alkaloids from

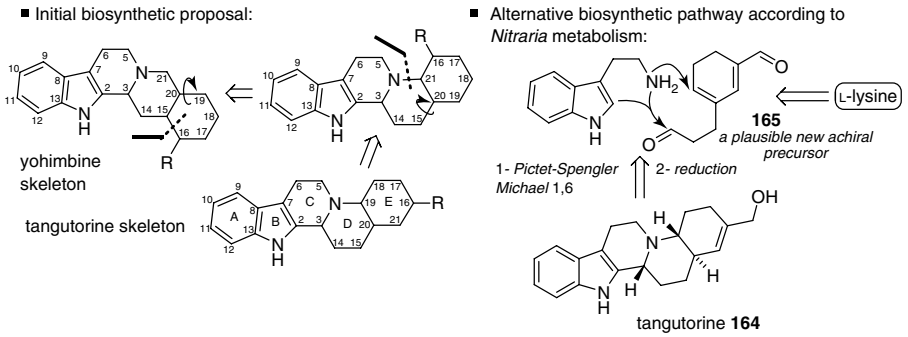


Scheme 1.42 Biomimetic synthesis of tangutorine.

the *Nitraria* genus in terms of carbon skeleton [see examples such as komarovinine (**167**), tetrahydro-komarovinine (**168**), and komaroine (**169**)], demonstrating thereby the impressive uniqueness of lysine metabolism in the *Nitraria* genus. It was therefore possible to postulate intermediate **165** as another achiral cornerstone metabolic intermediate along with already mentioned **157**. Both intermediates may, at least in part, contribute to explain the occurrence of many *Nitraria* alkaloids as racemates in Nature (this is especially the case for indolic *Nitraria* alkaloids).

This straightforward strategy also cast doubt on the previously proposed biosynthetic pathway to tangutorine (**164**), involving a complex rearrangement of a yohimbine-type indolomonoterpenic precursor, proposed by Jokela and colleagues (Scheme 1.43) [86]. These hypotheses appeared unlikely both in terms of chemical reactivity and chemotaxonomy.

In 2010, one of us published a comprehensive review covering the state of knowledge and detailing the isolation, structure determination (and revision), and the biomimetic syntheses of *Nitraria* alkaloids [87]; the interested reader is directed to this article as well as to older reviews [86]. Many achievements in biomimetic synthesis of *Nitraria* alkaloids have been disclosed by the Koomen group [88] and the Husson group [89]. Some of them beautifully addressed the issues of efficiency and selectivity in total synthesis.



Scheme 1.43 Comparison of two biosynthetic proposals for tangutorine.

More recently, a phytochemical study of *Myrioneuron nutans* (a species collected in Vietnam from a small genus within the Rubiaceae family) by Bodo and colleagues at the Museum National d'Histoire Naturelle in Paris revealed the presence of a new class of alkaloids that was named "*Myrioneuron* alkaloids." Interestingly, these new alkaloids are closely related to the *Nitraria* alkaloids despite the taxonomic distance of the two families. Their biosynthesis is also discussed in the aforementioned review article. Representative structures [myrioneurinol (**158**) and myrobotinol (**127**)] are presented in Scheme 1.39 [90]; they constitute ideal targets for total synthesis inspired by biosynthetic pathways.

1.4.3.3 Endocyclic Enamines Overview: Biomimetic Observations

From five- to seven-membered rings, the propensity of enamines to dimerize is schematically represented in Figure 1.6. Only two cases with biosynthetic consequences seem to be favorable for dimerization (**16** and **38**). Especially at neutral pH (e.g., "physiological" conditions), dimerization is spontaneous and therefore likely. This intrinsic reactivity pattern has probably partly governed Darwinian selection and the subsequent development of two metabolic pathways from tetrahydroanabasine (Scheme 1.39) [91, 92].

1.4.4 Biomimetic Synthesis of Stenusine, the Spreading Agent of *Stenus comma*

Rove beetles *Stenus comma* (Coleoptera, Staphylinidae) synthesize the alkaloid stenusine (**170**) (Figure 1.7) in their pygidial glands as an escape mechanism on

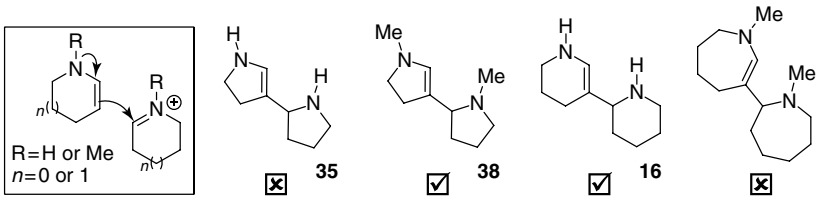


Figure 1.6 Dimerization issue and evolutive consequences.

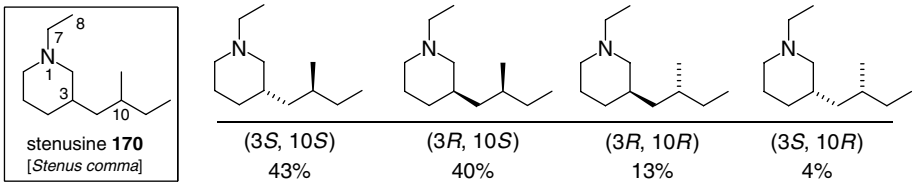
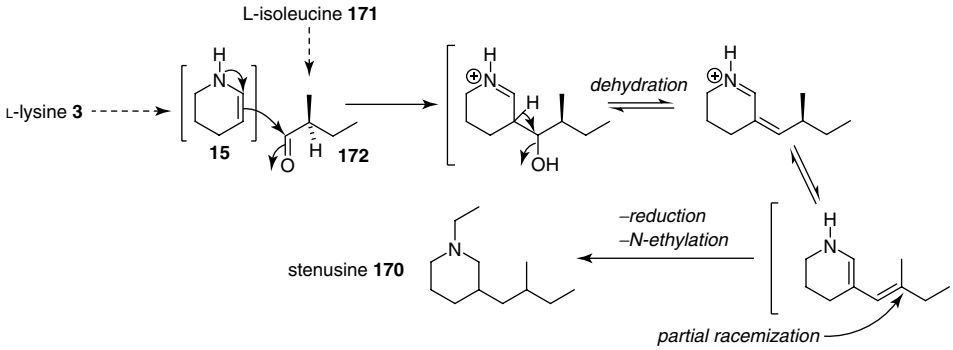


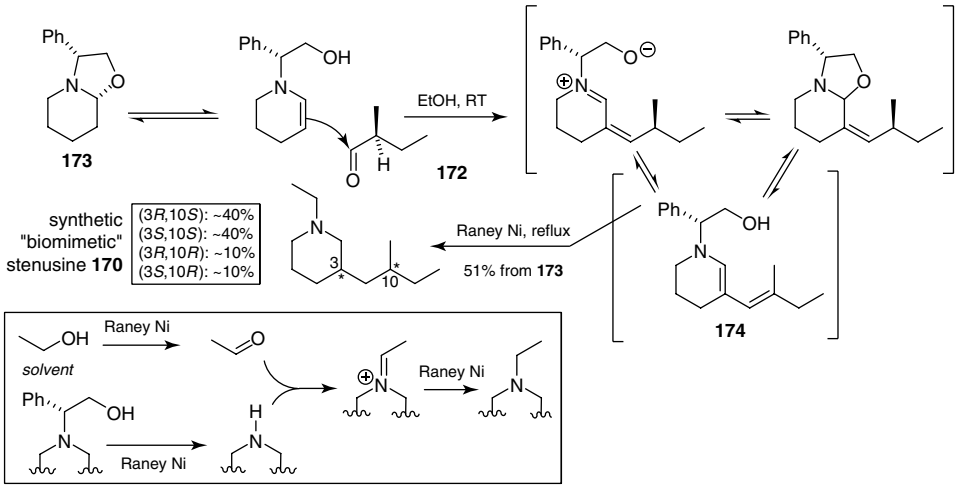
Figure 1.7 Stenusine: structure and stereochemical particularities.

water surfaces. The beetle propels itself over the water by expelling an oily substance with a high spreading capacity. Since the isolation and structure determination of stenusine (**170**) as the main component of the propulsion fluid, and a toxic chemical substance by Schildknecht *et al.* [93], numerous syntheses have been developed based on racemic and asymmetric strategies. Importantly, the enantioselective syntheses of isomeric (2*S*,3*S*)-stenusine and (2*S*,3*R*)-stenusine by Enders *et al.* [94] accompanied by chiral GC analysis for synthetic and natural samples revealed a strange fact. Indeed, stenusine is in fact a mixture of the four possible enantiomers in a ratio of 43 : 40 : 13 : 4 = (*S*, *S*) : (*S*, *R*) : (*R*, *R*) : (*R*, *S*) with a predominance (83 : 17) of the two epimers with a *(S)*-configuration on the side chain. It is unusual that an organism produces a natural compound as a mixture of the two pairs of enantiomers in a particular ratio. Husson, Kunesch, and colleagues proposed a very appealing biogenetic scheme for stenusine (**170**) that explained both the origin and the stereochemical particularities (Scheme 1.44) [95]. The essence of the biogenetic scenario is that stenusine derives most likely from L-lysine and L-isoleucine (**171**) and could be considered as the biological condensation of two of their metabolites, namely piperideine (**15**) and methylbutyraldehyde (**172**). Intermediates resulting from the iminium/enamine equilibrium could explain the formation of enantiomers at the C3 center and the partial racemization on the side chain leading after reduction and *N*-ethylation to stenusine.



Scheme 1.44 Putative biosynthetic pathway to stenusine.

Phenyloxazolopiperidine **173**, a stable equivalent of piperideine (**15**), was used to test the chemical basis of the hypothesis (Scheme 1.45). Reaction of **173** with *(S)*-2-methylbutyraldehyde (**172**) in ethanol at room temperature was conducted.



Scheme 1.45 Biomimetic synthesis of stenusine.

In the absence of air and after consumption of **173**, addition of Raney nickel to the mixture directly led to the formation of stenusine in an impressive succession of reactions (oxazolidine ring opening, condensation with aldehyde, dehydration, reduction, debenzylation, oxidation of ethanol to ethanal, Schiff base formation, and reduction to give the *N*-ethyl group). Perhaps the most significant feature of the reaction was the total lack of stereoselectivity when starting from chiral non-racemic **173** and *(S)*-**172!** The total synthesis was not shadowed for all that: in fact, comparison of the optical rotations of natural stenusine (**170**) and synthetic stenusine brought striking support to the biosynthetic hypothesis (Figure 1.8), which was confirmed when a ^{13}C NMR quantitative evaluation of the stereomeric composition of the Mosher acid salt of synthetic stenusine gave quite similar proportions.

The isolation of small amounts of aldehyde **175** or amounts up to 60% in boiling ethanol in the presence of air and molecular sieves provided strong support for the enticing sequence depicted in Scheme 1.45, and particularly for the occurrence enamine **174**. A mechanism involving formation of an oxetane (**176**) and double β-cleavage was proposed that could account for the formation of **175** (Scheme 1.46).

The story ended a few years later when Lusebrink and colleagues disclosed feeding experiments that clearly confirmed the biosynthetic scheme proposed earlier (Scheme 1.47) [96]. Deuterium-labeled amino acids and acetate combined

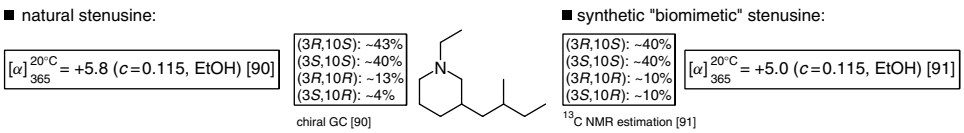
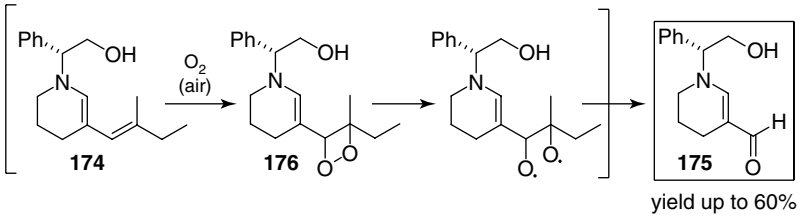
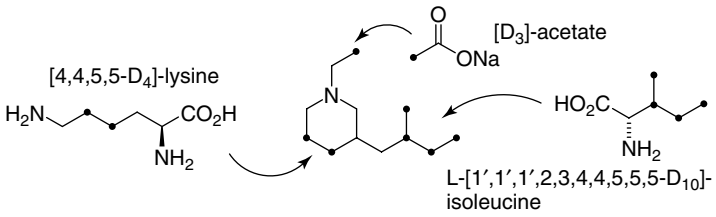


Figure 1.8 Natural and "biomimetic" stenusine: data comparisons.



Scheme 1.46 Biomimetic synthesis of stenusine: side reaction.



Scheme 1.47 Stenusine biosynthesis.

with GC/MS analysis showed that lysine forms the piperidine ring of stenusine, the side chain originates from isoleucine, and the *N*-ethyl group from acetate.[23)]

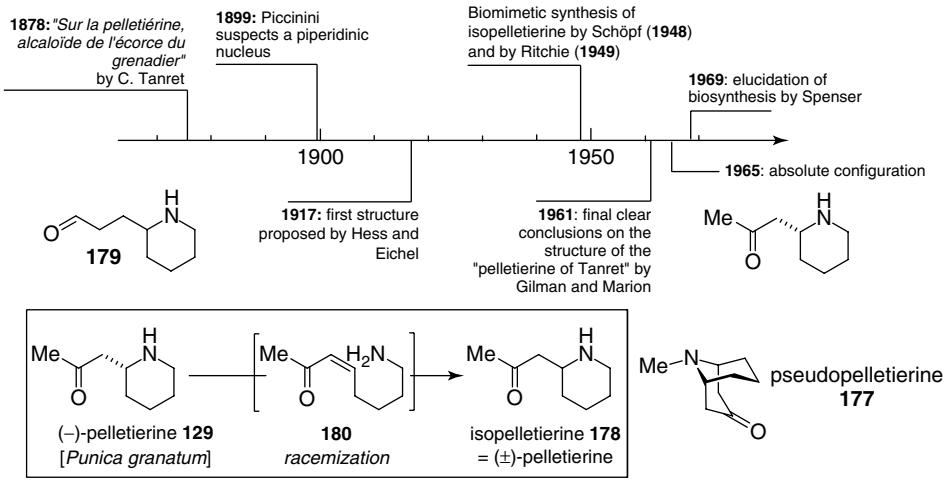
1.5
Pelletierine-Based Metabolism

1.5.1
Pelletierine: A Small Alkaloid with a Long History

Pelletierine (**129**)[24)] (Scheme 1.48) was isolated by Tanret in 1878 [97] from pomegranate (*Punica granatum* L.) (stem and root traditionally used as an anthelmintic against tapeworms) as a volatile, optically active compound along with three other alkaloids: methylpelletierine, pseudopelletierine (**177**), and isopelletierine (**178**). Pelletierine (**129**) was described as a colorless oil and its structure was regarded by Hess and Eichel in 1917 as an aldehyde: that is, 3-(2-piperidyl)propionaldehyde (**179**) [98]. However, its exact structure has long been debated. Among many studies worldwide, a Japanese team isolated pelletierine from pomegranate root bark following Hess' procedure, made a comparison with data provided by Hess and Eichel and concluded that the so-called pelletierine (**129**) was in fact isopelletierine (**178**) or 1-(2-piperidyl)-2-propanone [99]. NMR and IR studies by Gilman and Marion in 1961 were conducted on a

23) Piperidinic alkaloids isolated from insects usually have a polyketide and/or fatty acid origin; the case of stenusine is thereby remarkable. Alkaloids with a non-amino acid origin are discussed in Chapter 8.

24) Named in honor of Joseph Pelletier, French pharmacist and chemist (1788–1842).



Scheme 1.48 Pelletierine story from its discovery.

sample of pelletierine sulfate isolated by Tanret himself and showed the presence of a ketone instead of an aldehyde, confirming that the pelletierine of Tanret was 1-(2-piperidyl)-2-propanone [100]. From this point, (−)-pelletierine (**129**) is referred to as (−)-1-(2-piperidyl)-2-propanone and isopelletierine (**177**) (a term that should be avoided) to racemic pelletierine. The curious history of this small molecule has been brilliantly analyzed with an historical perspective in the 1960s [101]. Later, both the absolute configuration (D) [102] and biosynthesis, via L-lysine (**3**), were disclosed [103].

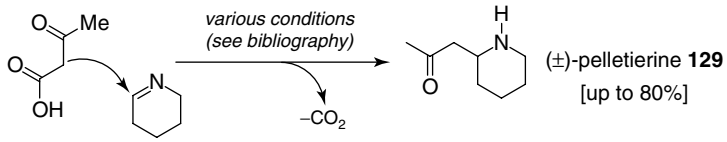
Part of the questioning concerning the exact structure of pelletierine (**129**) found its roots in the epimerization that is now a well-known phenomenon with **129** and is believed to be a base-catalyzed reaction operating via retro-Michael intermediate **180**. Also found in pomegranate, pseudopelletierine (**177**), the existence of which unlike pelletierine has never been questioned, is the higher homolog of tropinone (**125**).

1.5.2
Biomimetic Synthesis of Pelletierine and Pseudopelletierine

1.5.2.1 Pelletierine (129)[25)]

A Mannich reaction of acetoacetic acid followed by decarboxylation was early-on assumed to be at the origin of the propanone side chain of pelletierine (**129**) (Scheme 1.49). This was verified independently by Ritchie and colleagues and Schöpf in 1949 [104] and was proved to be biosynthetically totally correct 30 years

25) Compared to coniine, a similar structure in terms of complexity, pelletierine has been by far less studied in terms of asymmetric syntheses.



Scheme 1.49 Pelletierine biomimetic conditions.

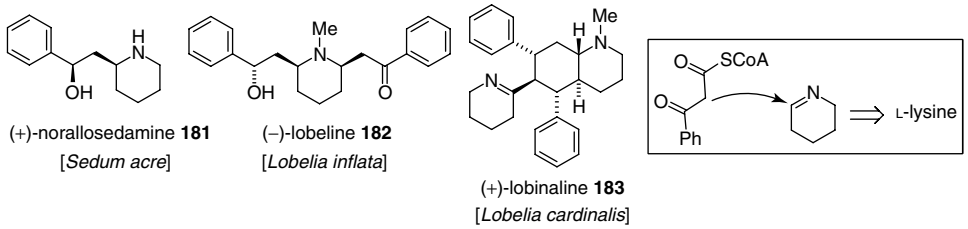
later by incorporation experiments *in vivo* [102]. Many improvements of these pioneering syntheses were subsequently disclosed (including the study of competitive dimerization of piperideine (**15**) into tetrahydroanabasine (**16**) [105]) as well as other ''non-biomimetic'' syntheses, including asymmetric strategies [106]. Pelletierine was also used as a starting material for biomimetic Claisen–Schmidt reactions known as the ''*pelletierine condensation*'' by different groups [107].

1.5.2.2 **Pseudopelletierine**

Pseudopelletierine (**177**) was prepared by the same biomimetic Mannich-type reaction as for tropinone but starting from glutaraldehyde (**51**) by Robinson in 1924, Schöpf in 1937, and reinvestigated by Cope in 1951 [108].

1.5.3 ***Lobelia* and *Sedum* Alkaloids**

Lobelia and *Sedum* alkaloids are closely related to pelletierine in terms of structures and biosynthesis. Examples are given in Scheme 1.50 (**181**–**183**); the central piperidine ring of these alkaloids is known to derive from L-lysine. Interesting reviews have been published by Bates [109] and Felpin and Lebreton [110] to which the reader can refer advantageously. Numerous total syntheses have also been disclosed [111].

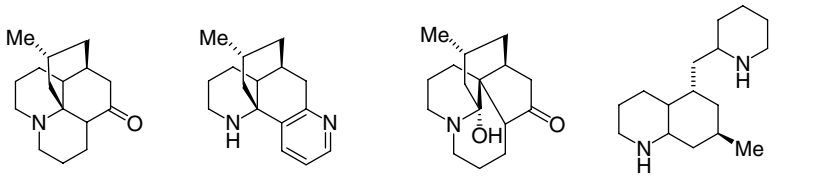


Scheme 1.50 *Sedum* and *Lobelia* alkaloids: selected structures and biosynthesis.

1.5.4 ***Lycopodium* Alkaloids**

1.5.4.1 **Overview, Classification, and Biosynthesis**

A significant number (>250 in 2010) of alkaloids with original and intricate structures are found in the *Lycopodium* genus. This genus has over 500 species



lycopodine **184** [*Lycopodium clavatum*] lycodine **185** [*Lycopodium annotinum*] fawcettimine **186** [*Lycopodium fawcetti*] phlegmarine **187** [*Lycopodium phlegmaria*]

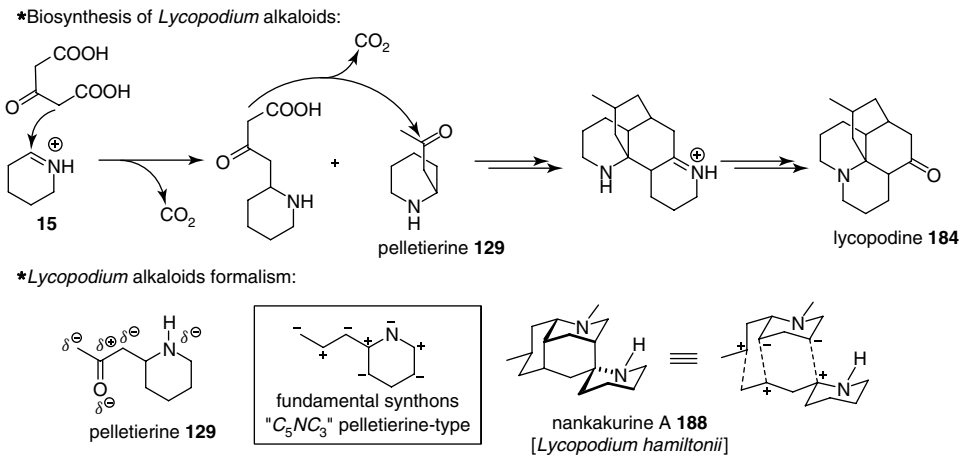
Figure 1.9 Examples of *Lycopodium* alkaloids.

and only around 10% of the species have been studied for their alkaloid content. Biological activities of such compounds can also be promising, as exemplified by well known huperzine A, which exhibits potent anticholinesterase activity. These alkaloids have attracted a great deal of interest from biogenetic and biological points of view as well as for providing challenging targets for total synthesis, especially because of their scarcity. W. A. Ayer has divided the *Lycopodium* alkaloids into four classes: lycopodine, lycodine, fawcettimine, and miscellaneous, with lycopodine (**184**), lycodine (**185**), fawcettimine (**186**), and phlegmarine (**187**) as representative compounds, respectively, for each class (Figure 1.9). Owing to the number of alkaloids now described, the classification has become tricky, especially with the isolation of highly complex structures (especially in the last ten years). Many comprehensive reviews have been published covering extraction, structure determination, biosynthetic hypotheses, total syntheses, and biological properties [112].

Based on biosynthetic considerations, another classification of *Lycopodium* alkaloids may be considered. In fact, even if the biosynthesis of the alkaloids is still not completely understood with very few feeding experiments conducted up to now, research groups have provided evidence for a lysine origin of these alkaloids. Furthermore, such as in the case of the biosynthesis of lycopodine (**184**) demonstrated by Spenser and colleagues (Scheme 1.51) [113], pelletierine units or analogs thereof are integrated in the structure. Therefore, *Lycopodium* alkaloids can be formally seen as pelletierine-type (propylpiperidine units[26] – $C_5N–C_3$) derived alkaloids and could then be classified according to the number of such units in the final natural substance, as proposed as early as 1960 by Conroy[27] [114]. As a consequence, some alkaloids may result from the condensation of two [e.g., nankakurine A (**188**), huperzine A (**189**), lyconadin A (**190**)], three [e.g., himeradine A (**191**), lycoperine A (**192**)], or even four [complanadine D (**193**)] pelletierine-type units as determined by the number of piperidine cycles in the molecules for the less rearranged skeletons (Scheme 1.52). At least chemically speaking, *Lycopodium* alkaloids can be

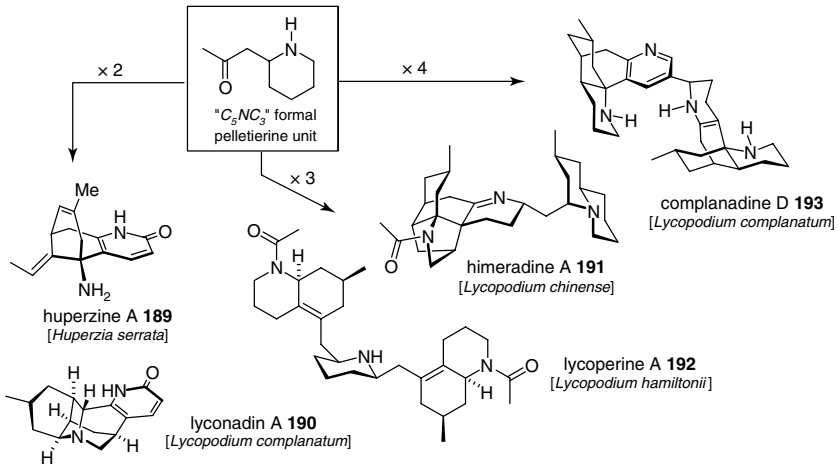
26) Whether this unit comes from pelletierine itself or from the *de novo* condensation of a piperideine of type **15** with C_3-acetone-type equivalent such as acetonedicarboxylic acid.

27) Conroy anticipated a $C_5–C_3$ common pattern in *Lycopodium* alkaloids but proposed a totally polyketide origin for it.



Scheme 1.51 Biosynthetic origin and analogy with pelletierine.

considered as being biosynthetically derived from simple more or less oxidized pelletierine-type units [see the example of nankakurine (**188**) in Scheme 1.51].



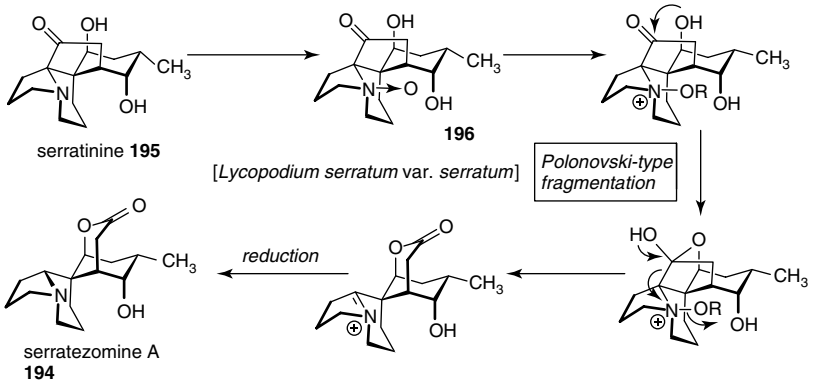
Scheme 1.52 A classification based on the formal analogy with pelletierine.

From the 1960s to the 1980s, the emergence of new strategies capable of addressing the *Lycopodium* alkaloid challenges permitted the total syntheses of complex structures by pioneering groups. This includes, among many others, work by Wenkert *et al.* [115], Evans [116], Heathcock *et al.* [117], and Schumann *et al.* [118], which often display interesting biomimetically related steps. Recent total syntheses of *Lycopodium* alkaloids were reviewed in 2009 (covering up to 2008) [112c, 119]. Most of them constitute the state of the art in total synthesis. Concerning biomimetic chemistry, we focus in this chapter on:

- Recent relevant ''biomechanistic'' conversions of alkaloids that permitted structure elucidation and the establishment of clear biosynthetic links. They constitute ideal examples of chemical predisposition in the world of natural substances. These studies exemplify magnificently the interconnection of numbers of *Lycopodium* alkaloids and highlight how simple reactions can explain part of both the diversity and complexity within this large family of alkaloids, which all derive from simple building blocks.
- Recent total synthesis that may feature at least one biomimetic step (usually a cascade reaction to form polycyclic skeletons).

1.5.4.2 **Biomimetic Rearrangement of Serratinine into Serratezomine A**

Serratezomine A (**194**) (Scheme 1.53) has been isolated from *Lycopodium serratum* var. *serratum* by the Kobayashi group [120], which proposed a biogenetic origin from serratinine (**195**), also found in this plant, through its *N*-oxide form **196** followed by a Polonovski-type fragmentation (Scheme 1.53).

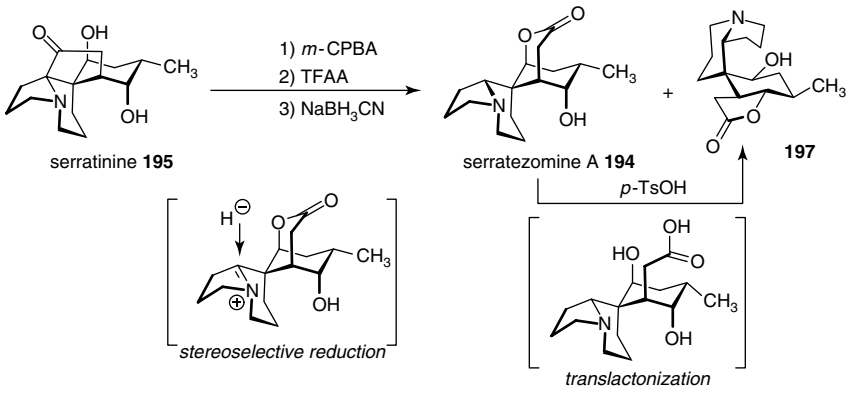


Scheme 1.53 Plausible biosynthetic correlation between serratinine and serratezomine A.

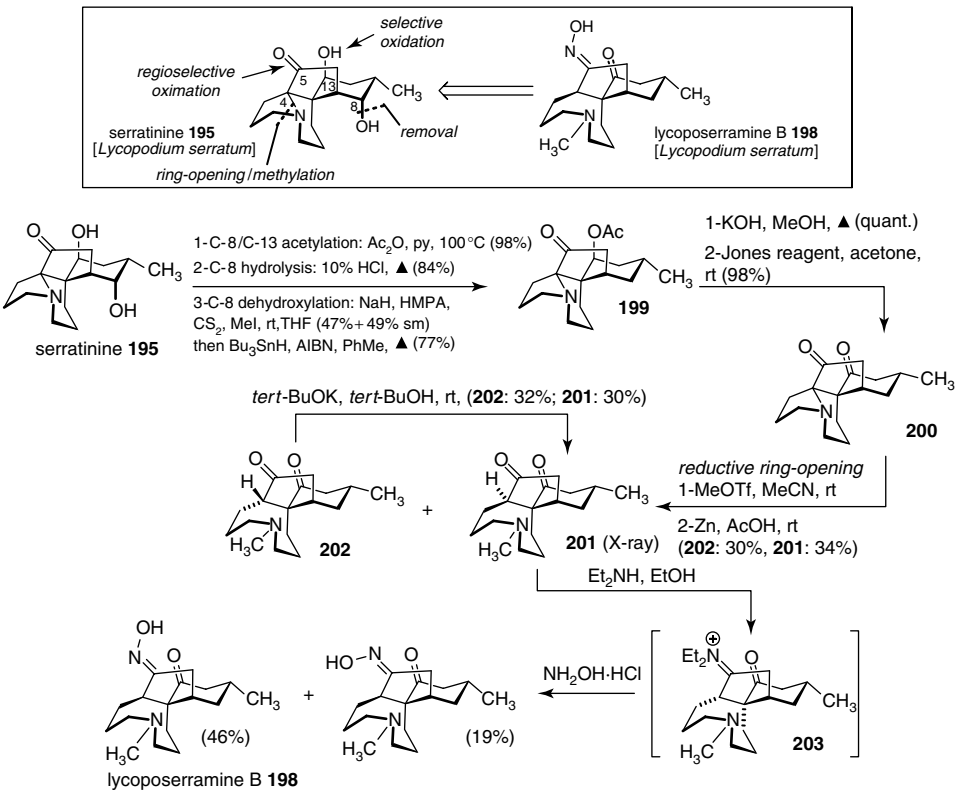
To verify this proposal (Scheme 1.54), the conditions of a modified Polonovski reaction (also known as the Polonovski–Potier reaction) were applied to serratinine (**195**): treatment with *m*-chloroperbenzoic (*m*-CPBA) acid followed by addition of trifluoroacetic anhydride and then sodium cyanoborohydride gave two compounds [121]. One of them was identified as serratezomine A (**194**) and was predominant at lower temperature (−50 and −20 °C) while the amount of the other (**197**) increased with temperature (0–20 °C). Formation of this latter indicates an acid-catalyzed-cleavage of the lactone ring.

1.5.4.3 **Biomimetic Conversion of Serratinine into Lycoposerramine B**

More recently, an alkaloid possessing an oxime function, lycoposerramine B (**198**, Scheme 1.55), was isolated from *Lycopodium serratum*. To confirm its structure, which was inferred by classical spectroscopic analysis, its semi-synthesis from serratinine (**195**) (for which the absolute configuration was known) was successfully attempted [122]. The retrosynthetic analysis (see box in Scheme 1.55) consisted of



Scheme 1.54 Biomimetic conversion of serratinine into serratezomine A.

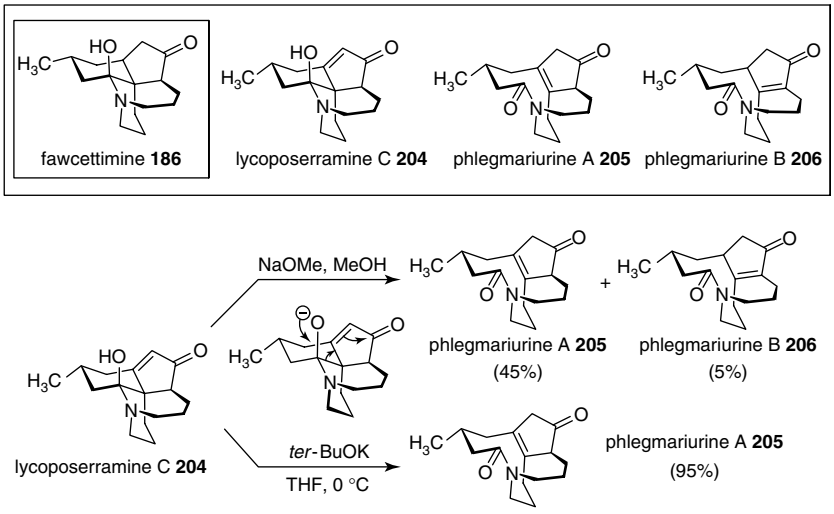


Scheme 1.55 Biomimetic conversion of serratinine into lycoposerramine B.

a removal of the hydroxyl group at C8, oxidation of the secondary hydroxyl at C13, ring-opening at the C4-N bond, and regioselective oxidation at C5. A monoacetate was first prepared starting from serratinine (**195**) in a two-step sequence followed by a Barton–McCombie dehydroxylation. After acetate removal and oxidation to **200**, the reductive ring-opening reaction was then conducted and yielded two C4 epimeric compounds (**201** and **202**; the latter could be epimerized in basic conditions). To selectively convert the carbonyl at C5 into an oxime, **201** was first treated with diethylamine (steric hindrance at C13 probably explains the selectivity). On the putative intermediate **203**, hydroxylamine reacted preferentially with the more reactive iminium function at C5. The major isomer was identical with natural lycoposerramine B (**198**) (including CD spectra).

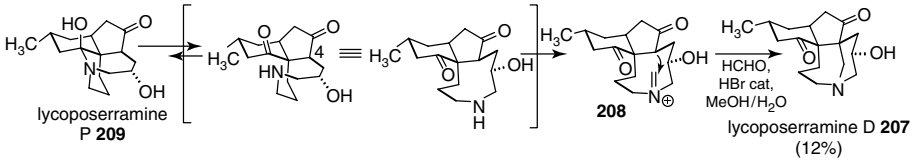
1.5.4.4 Biomimetic Interrelations within the Lycoposerramine and Phlegmariurine Series

Several alkaloids belonging to the fawcettimine group were isolated from *Lycopodium serratum* by the Takayama group, including several lycoposerramines [B (**198**) and C (**204**)] and related phlegmariurines A (**205**) and B (**206**) (Scheme 1.56) [123]. Lycoposerramine C could be converted into phlegmariurines A and B by ring opening in the presence of a base (whereas potassium *tert*-butylate furnished exclusively **205**, a mixture of **205** and **206** was obtained when treating with sodium methoxide). CD curves of semi-synthetic and natural phlegmariurine A were compared and shown to be identical, demonstrating thereby the same absolute configuration.



Scheme 1.56 Biomimetic conversions in the lycoposerramine/phlegmariurine series.

The structure of lycoposerramine D (**207**) (Scheme 1.57) revealed the presence of an isolated methylene carbon that corresponds to an extra carbon compared to common C_{16}-type *Lycopodium* alkaloids. A Mannich reaction involving iminium

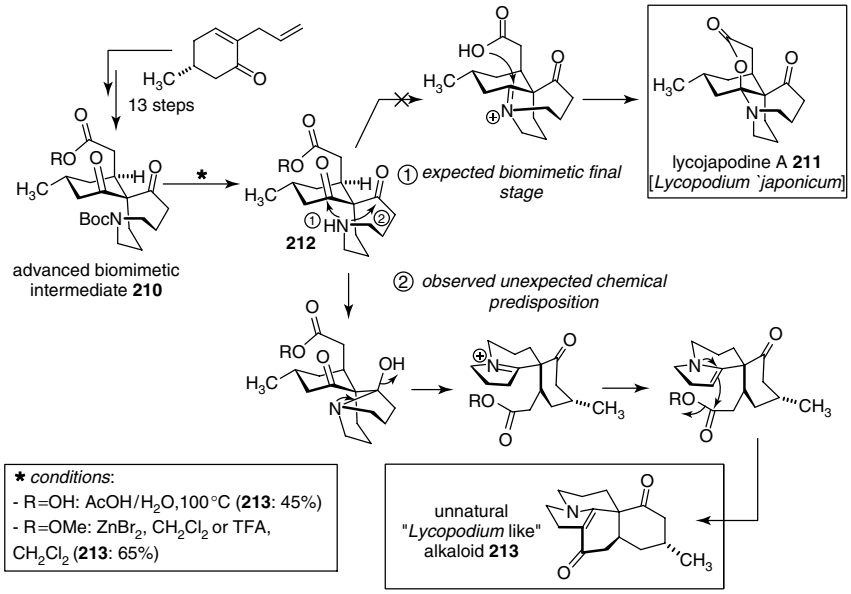


Scheme 1.57 Biomimetic conversion of lycoposerramine P into lycoposerramine D.

208 could easily explain the biosynthesis of lycoposerramine D (**207**) from lycoposerramine P (**209**), another alkaloid isolated and characterized concomitantly. This hypothesis was clearly ascertained as, when treated with formaldehyde, lycoposerramine P (**209**) yielded a semi-synthetic lycoposerramine D (**207**) that was totally identical to its natural counterpart [123a].

1.5.4.5 When Chemical Predisposition Does Not Follow Biosynthetic Hypotheses: Unnatural "*Lycopodium*-Like" Alkaloids

Yang and coworkers described an original work featuring a total synthetic dead end that unexpectedly gave interesting results (Scheme 1.58) [124]. The total synthesis of advanced intermediate **210** towards the total synthesis of lycojapodine A (**211**) was achieved but failed to give, through a possible biomimetic cascade, the desired carbinolamine lactone of the target molecule. Two competitive cyclizations can occur on such a diketone. But in fact, whatever the conditions tested, the initial 6/9 bicycle of **212** underwent the "wrong" pathway, leading after an impressive imine/enamine cascade to unnatural compound **213**. This unexpected

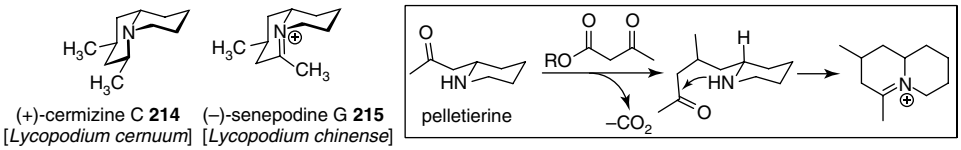


Scheme 1.58 Unexpected results: an interesting dead end in the course of the total synthesis of lycojapodine A.

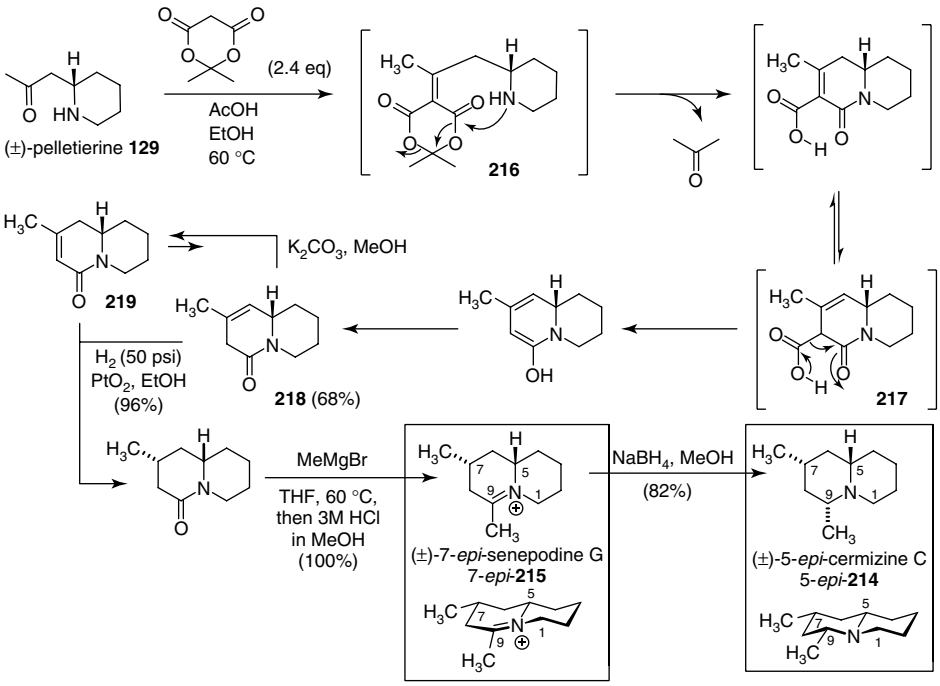
chemoselectivity may facilitate a better understanding of the biosynthesis and rearrangements of complex *Lycopodium* alkaloids.

1.5.4.6 **Total Synthesis of Cermizine C and Senepodine G**

Among others, two small quinolizidine alkaloids, namely cermizine C (**214**) and senepodine G (**215**) (Scheme 1.59), were isolated from the club moss *Lycopodium cernuum* and *Lycopodium chinense*, respectively, as minor compounds (respectively 0.00008 and 0.00005%) by the Kobayashi group [125]. Simple biosynthetic hypotheses may be put forward to explain the formation of senepodine G, a possible direct precursor of cermizine C through iminium reduction.



Scheme 1.59 Cermizine C and senepodine G: structure and plausible biosynthesis.

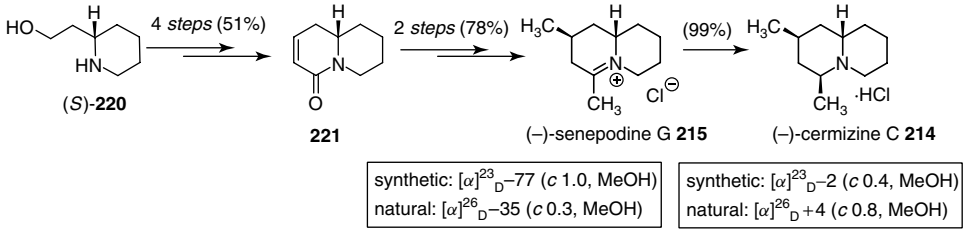


Scheme 1.60 Biomimetic synthesis of epi-senepodines from pelletierine.

Snider and colleagues set out to synthesize these two alkaloids [126]. Despite no mention of biosynthesis, their first approach started from pelletierine (**129**) and is worth noting as an interesting example of the conversion of one simple natural product into another (Scheme 1.60). A Knoevenagel reaction between the

ketone of (±)-pelletierine and Meldrum's acid (a synthetic surrogate of biosynthetic acetate-derived building blocks) afforded intermediate **216**, which would cyclize to give directly the corresponding quinolizidine skeleton in a beautiful cascade of reactions. Indeed, **217** was not isolable but furnished β,γ-isomer **218**, which equilibrated in basic conditions to a mixture of α,β-isomer **219** and **218** (3 : 1). Hydrogenation of the double bonds of **218** and **219** followed by alkylation furnished (±)-7-epi-senepodine G (7-epi-**215**), which provided (±)-5-epi-cermizine C (5-epi-**214**) after stereospecific reduction using sodium borohydride (axial attack from the less hindered top face).

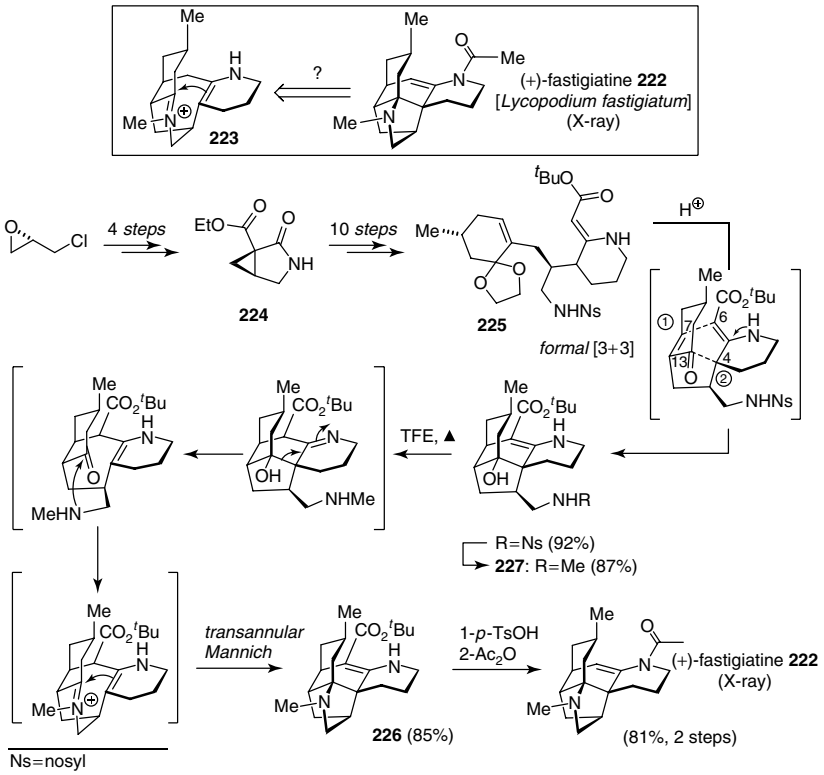
An alternative synthetic scheme starting from *(S)*-**220** via unsaturated lactam **221** enabled the synthesis of (−)-senepodine G (**215**) and (−)-cermizine C (**214**) (Scheme 1.61). Discrepancies in the comparison of optical rotation signs and magnitudes between natural and synthetic samples were also discussed by the authors. Very small amounts of natural compounds and the small value of the optical rotation clearly make the establishment of the absolute configuration of senepodine G and cermizine C difficult (although probably closely biosynthetically related, they were isolated from two different species).



Scheme 1.61 Biomimetic synthesis of senepodine G and cermizine C.

1.5.4.7 **Biomimetic Steps in the Total Synthesis of Fastigiatine**

Fastigiatine (**222**, Scheme 1.62) was isolated as a minor alkaloid from *Lycopodium fastigiatum* in 1985 by the MacLean group [127]. The first total synthesis of this complex alkaloid was only accomplished in 2010 by the Shair group (Scheme 1.62) [128]. Despite being non-biomimetic in essence, the strategy beautifully demonstrated that such a total synthesis not only implied the development of highly efficient chemical transformations but also permitted interesting biosynthetic proposals, that is, ring formation implying an intermediate of type **223**. The approach relies on the readily available cyclopropane **224**, which was converted in ten steps into intermediate **225**. The latter underwent an impressive sequence of reactions including a transannular Mannich reaction in acidic conditions to give **226** featuring the core of the alkaloid. Two steps consisting of functional manipulations of the skeleton afforded (+)-fastigiatine (**222**) in 15 steps from **224** with an average 30% yield. The suitability of intermediate **227** to easily undergo an amazing cascade to build in one step the challenging skeleton of fastigiatine encouraged the author to propose an intermediate such as **223** as the plausible biosynthetic intermediate toward these molecules.



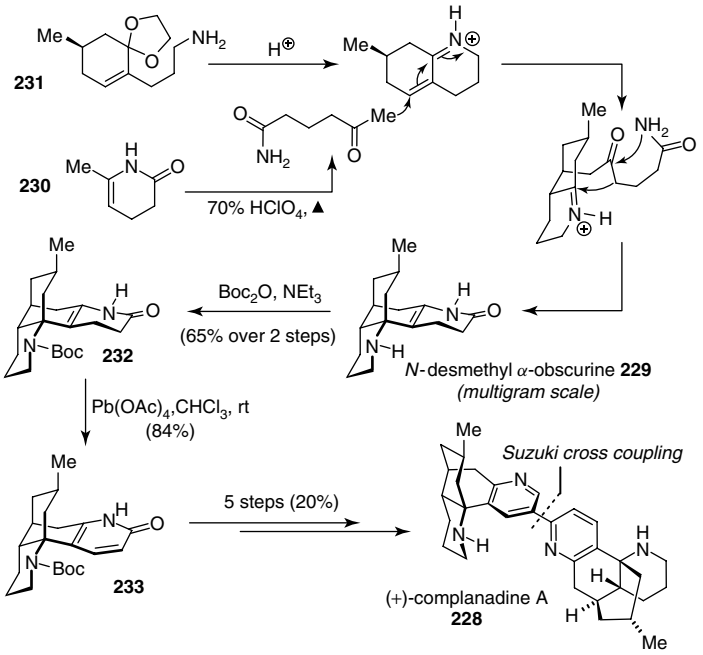
Scheme 1.62 A biomimetic cascade as a crucial step in the total synthesis of fastigiatine.

1.5.4.8 **Biomimetic Steps in the Total Synthesis of Complanadine A**

Earlier in 2010, a similar cascade reaction with evident biomimetic relevance was highlighted in the beautiful total synthesis of complanadine A (**228**) by Sarpong and colleagues (Scheme 1.63). [119c,d] who exploited a synthesis previously described by Schumann and Naumann [129]. *N*-Desmethyl α-obscurine (**229**) was prepared in a one-pot procedure from enamide **230** and enantiomerically pure **231**.

The next step consisted of an oxidation of lactam **232** to the corresponding pyridone **233** in a somewhat biomimetic way using lead tetraacetate. Such a pyridone nucleus is shared by many *Lycopodium* alkaloids such as huperzine A (**189**) and lyconadin A (**190**) (Scheme 1.52).

These few highlights of selected total syntheses conclude this section dedicated to *Lycopodium* alkaloids and also conclude this chapter devoted to the rich chemistry of alkaloids derived from ornithine and lysine. The exploration of the chemistry of these natural products is still ongoing. With the discovery of new complex structures – but in minute amounts – along with promising biological activities (e.g., neurotrophic properties for certain *Lycopodium* alkaloids), new synthetic strategies will undoubtedly be needed to secure enough material for biological purposes. Toward this end, no doubt biomimetic considerations will be able to



Scheme 1.63 Total synthesis of complanadine A by the Sarpong group.

answer synthetic problems. As mentioned above, organic synthesis is endowed with highly efficient biomimetic reactions such as the Mannich reaction and the Robinson–Schöpf condensation to tackle the access to more and more complex structures.

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