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History, chemistry and biology of alkaloids from *Lobelia inflata*

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This review is dedicated to Professor Guillaume Le Baut on the occasion of his retirement

Contents

Keywords: Lobeline; *Lobelia inflata*; Alkaloids; Central nervous system.

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1. Introduction

Piperidine alkaloids constitute a large family of compounds, many of which are of great interest for their various biological activities.[1] A search of the chemical and patent

literature reveals thousands of references concerning this simple ring system, both in clinical and pre-clinical states.[2] Due to the extension of life expectancy in industrial countries, neurological disorders, like Alzheimer's or Parkinson's diseases, pose an important public health problem. Thus, the discovery of effective agents for the treatment of these pathologies is one of the major challenges in medicine for the future.[3,4] In this context, *Lobelia inflata* alkaloids (Fig. 1) and, in particular, (−)-lobeline **1**, the most active of them, represent a new class of promising therapeutic agents acting on the central nervous system (CNS).

This review documents a brief history of the uses of *Lobelia inflata*, describing the fascinating saga of this plant from its original use by native Americans. Biosynthetic routes to *Lobelia* alkaloids are then discussed, followed by an overview of their chemistry, with particular emphasis on asymmetric syntheses. The last section of the review includes a discussion on the bioactivity of (−)-lobeline **1** and its application for the future.

2. History

There can be few plants with a history as rich as that of *Lobelia inflata*. It is a plant native to northern North America that grows in meadows, waste places, fields and open woods.[5] *Lobelia inflata* is medically the most important variety of the Lobelia family, which consists of more than 50 species including in particular *L. cardinalis*, *L. erinus*, *L. spitaca*, *L. siphilitica*, *L. puberula* and *L. appendiculata*.

Among this family, *Lobelia inflata* contains the greatest concentration of more than 20 piperidine alkaloids[6] (see Figure 1 for the identification of **1**–**20**). (−)-Lobeline **1** is the major and the most biologically active alkaloid of the plant. *Lobelia inflata* is an annual or biannual plant, which grows to 2 feet tall and blooms from June through October. The flowers are very small, white to pale blue, with three oval petals facing downward and two sharply-pointed petals pointing up. The fruit is an inflated pod, resembling a small balloon, which is easily compressible and contains an innumerable number of minute brown seeds.

The story of *Lobelia inflata* can be traced back over many centuries. The herb is actually named in honour of the famous French physician and botanist Matthias De Lobel (1570–1616), who was attached to the court of King James I. Its specific name, *inflata*, is due to its inflated seed pods. *Lobelia inflata* is also known as Indian tobacco, because the native Americans (the Penobscot tribes) smoked the dried leaves as a substitute for tobacco, to produce the effect of alkaloids on the central nervous system (CNS).

Lobelia inflata was extensively used by the people of New England, long before the time of Samuel Thomson (superintendent of Indian affairs in North America from 1756 to 1774), its assumed discoverer. The credit for the introduction of *Lobelia* into medical practice is due to Dr. Manasseh Cutler and Dr. Samuel Thomson. As early as 1773, Thomson became aware of its power to procure vomiting and, during 1791, he first became practically acquainted with its ability to afford relief in diseases like colic, rheumatism and fever. Thomson and Cutler claimed to have used *Lobelia* for the treatment of asthma in the period 1805–1809. Thus, during the 19th century, *Lobelia* was one of the most medically important plants, used as a valuable remedy for asthma. *Lobelia* can, however, be a deadly poison in sufficient quantities. Indeed, Thomson fatally poisoned one of his patients (Ezra Lovett) by the use of *Lobelia*. Nevertheless, *Lobelia*, in the ordinary sense of the term, is not a poison. Undoubtedly, its injudicious use has, and might, produce death, but the same is true for many other drugs that are not ordinarily considered as poisons.

Interest in this class of molecules, and, in particular, in lobeline **1**, the potent alkaloid of this family, has increased in recent years, due to their remarkable biological profile. Thus, lobeline **1**, the principal alkaloid of *Lobelia*, is currently the subject of renewed interest for the treatment of drug abuse and neurological disorders.[7]

3. Biosynthesis

The study of *Lobelia* alkaloid biosynthesis in the 1960s and 1970s principally concerned the most important of them, lobeline **1**. For this reason, we present in this review the biosynthetic pathway of lobeline **1** in more detail. An overview of the biosynthesis of other *Lobelia* alkaloids is also presented, with particular attention being paid to lobinaline **19**.

The extensive research into the explanation of the biosynthetic pathway of piperidinic alkaloids started with Robinson's hypothesis.[8] Robinson postulated that lysine **21** is the precursor of the piperidinic ring in many of the naturally occurring piperidine derivatives via the tetrahydropyridine **22**. Thus, it was shown that lysine **21** furnished the nucleus of various piperidine alkaloids like anabasine **23**,[9,10] and sedamine **24**,[11] a related structural analogue of lobeline **1** (Scheme 1).

Lobeline **1** presents an interesting biosynthetic problem due to the substitutions at the C2 and C6 positions of the piperidine ring by two related substituents. The two key precursors generally accepted are lysine **21** and phenylalanine **25**. It has also been suggested that piperidine alkaloids could be derived from benzoic acid and acetate or from acetate alone[12] like coniine[13,14] **26** (Scheme 2). Different tracer studies with sodium [1-^{14}C]-acetate, however, seem to reject this hypothesis for *Lobelia* alkaloids. Indeed, sodium [1-^{14}C]-acetate was fed to *Lobelia syphilita* and no labelled lobeline **1** was isolated, while in a separate experiment administration of [1-^{14}C]-lysine yielded active lobeline **1**.[15]

The possible pathway for the biosynthesis of the side chains is outlined in Scheme 3. Phenylalanine **25** is converted into *trans*-cinnamic acid **28** by the enzyme phenylalanine ammonia-lyase (PAL).[16] This enzyme has been isolated from a plant source.[17] The hydroxylation of **28** by the addition of a molecule of water gave 3-hydroxy-3-phenylpropanoic acid **29**, which has been isolated from

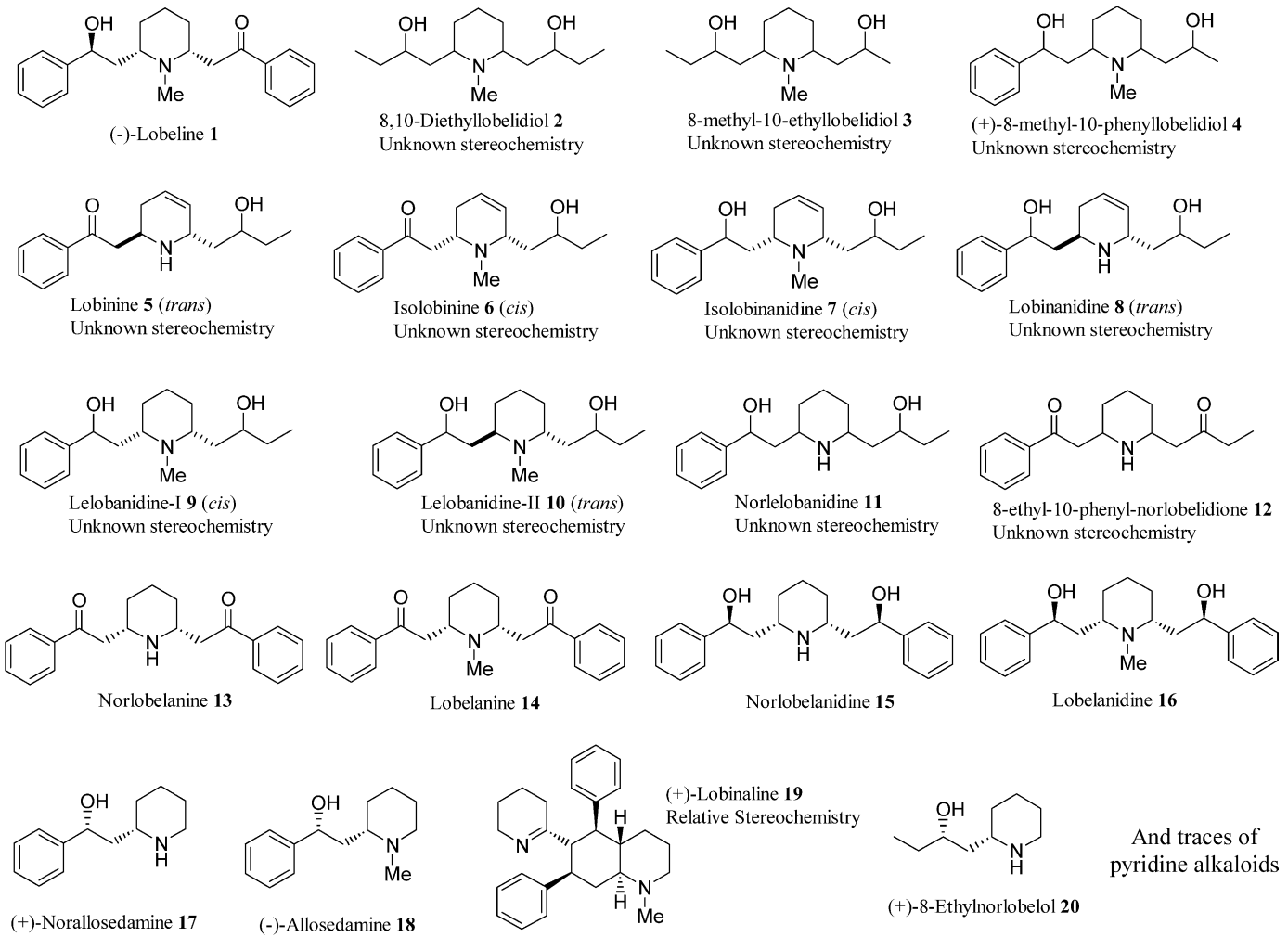
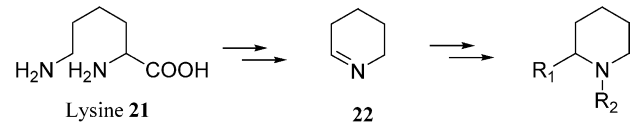
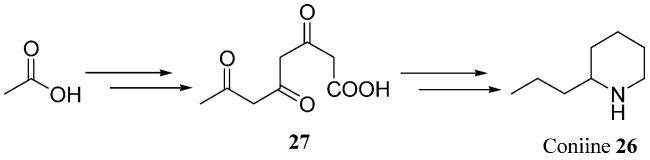


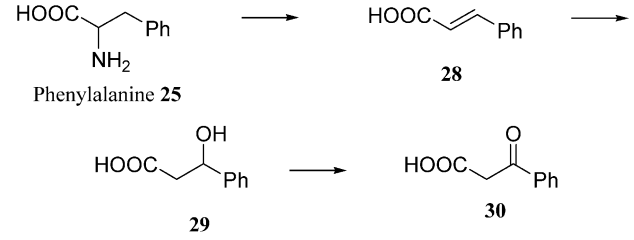
Figure 1. Alkaloids from *Lobelia inflata*.



Scheme 1.



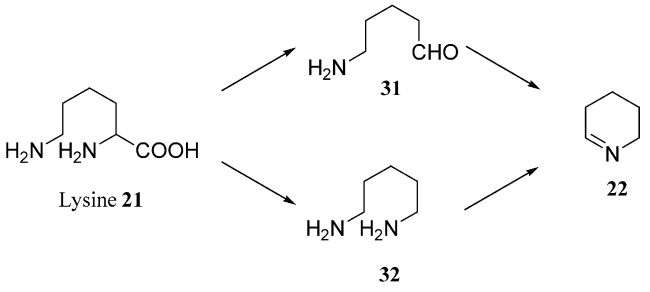
Scheme 2.



Scheme 3.

Lobelia inflata.[6] β-Oxidation gave benzoylacetic acid **30**, an important intermediate in the biosynthesis. Feeding experiments have been used to show that phenylalanine **25**, *trans*-cinnamic acid **28**, and 3-hydroxy-3-phenylpropanoic acid **29** are all intermediates in the biosynthetic route and have consequently validated this pathway.[18]

The formation of 2,3,4,5-tetrahydropyridine **22**, the potential intermediate in the biosynthesis of lobeline **1** or other piperidinic alkaloids, is unclear. Two possible pathways are the subject of some dispute (Scheme 4). In the first route, lysine furnished the 2,3,4,5-tetrahydropyridine **22** via 5-aminopentanal **31**.[19] The asymmetrical incorporation of substituents into the piperidine ring of a number of alkaloids favours this hypothesis.[20] It has been shown, however, that the substituents of lobeline **1** were symmetrically incorporated into lysine **21**.[16]

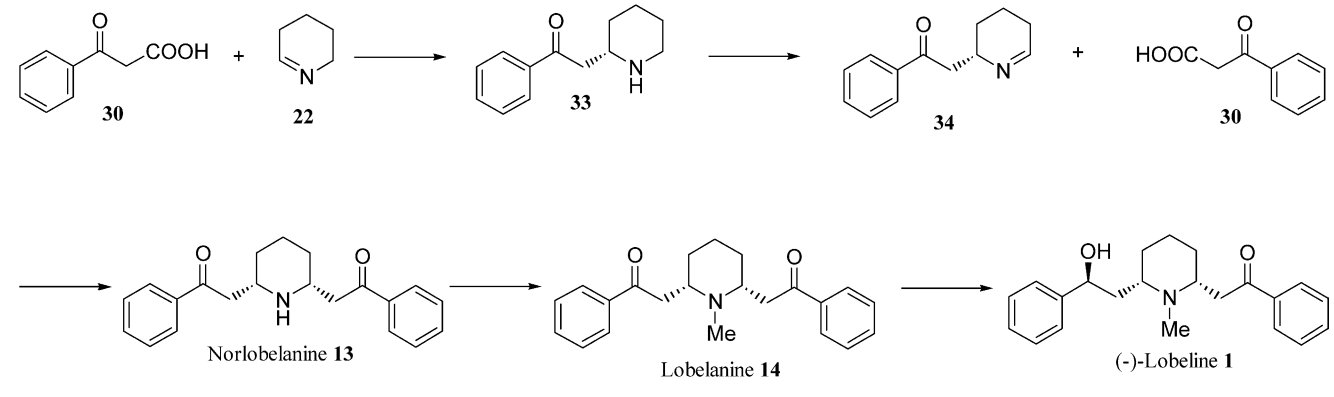


Scheme 4.

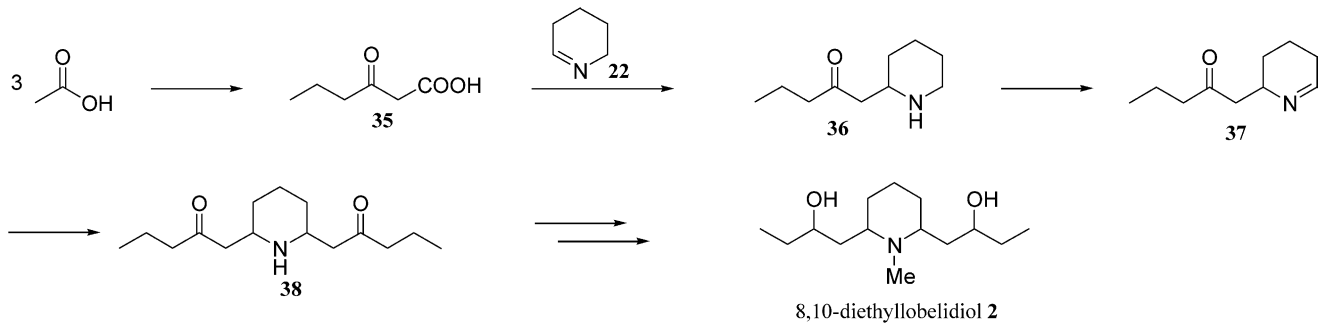
The second pathway suggested the formation of 2,3,4,5-tetrahydropyridine **22** via cadaverine **32** (pentane-1,5-diamine). Although cadaverine **32** was incorporated into lobeline **1** and stimulated the production of alkaloids like anabasine **23**,[21,22] tracer studies have suggested that it was not a normal intermediate between lysine **21** and 2,3,4,5-tetrahydropyridine **22**. Indeed, [2-^{14}C]-lysine gave 2,3,4,5-tetrahydropyridine **22** with all the radioactivity at the C2 position.[23]

Condensation of 2,3,4,5-tetrahydropyridine **22** with benzoylacetic acid **30** furnished the amino ketone **33**, which on oxidation via **34** and reaction with another molecule of benzoylacetic acid **30**, gave norlobelanine **13** (Scheme 5). *N*-Methylation of **13** yielded lobelanine **14**. The role of lobelanine **14** in the biosynthesis of lobeline **1** has been shown in feeding experiments by incorporation of labelled lobelanine **14** into lobeline **1** in high yield.[24] Thus, the symmetrical the incorporation of lysine **21** into lobeline **1** (vide supra) could be explained by the intervention of the symmetrical intermediate lobelanine **14**. Consequently, a large volume of evidence has been gathered in favour of **31** as a possible intermediate in the formation of **22**. The last step in this process is the reduction of one of the carbonyl groups. Nevertheless, the biosynthesis of lobeline **1** has been poorly studied and the enzymes responsible for the final stages in the biosynthesis of lobeline **1** have not been characterised.

The biosynthetic pathways of other *Lobelia* alkaloids have been studied in less detail, but it seems that the side chains without phenyl groups are derived from acetate. Specific tracer studies with [1-^{14}C]-acetate are in total agreement with the foregoing hypothesis.[18] The 3-oxohexanoic acid **35**, derived from three units of acetate, reacted with 2,3,4,5-tetrahydropyridine **22** to yield **36**. Formation of the imine **37** and subsequent condensation of another molecule of **35** generated the dione **38**. Demethylation of the side chains, *N*-methylation and reduction of the carbonyl functions gave 8,10-diethyllobelidiol **2** (Scheme 6).

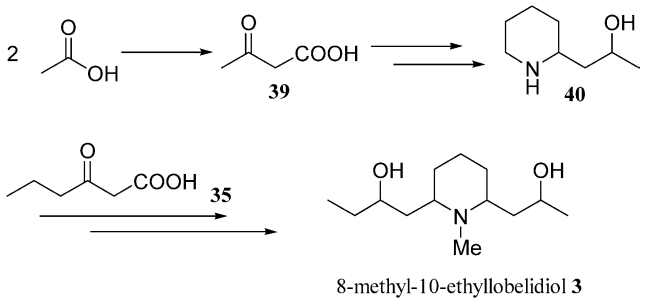


Scheme 5.



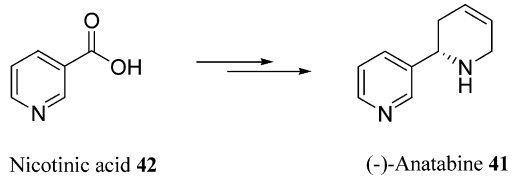
Scheme 6.

When the side chains are ethyl substituents, they are derived from two units of acetate to give 3-oxobutanoic acid **39** (Scheme 7). A similar biosynthetic cascade generated, for example, 8-methyl-10-ethyllobelidiol **3**.



Scheme 7.

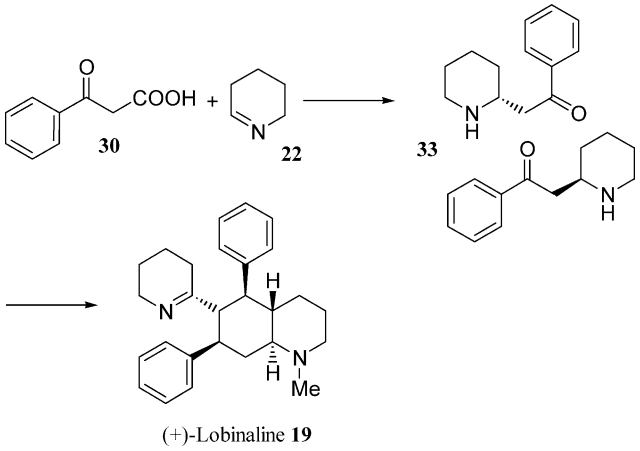
For **5** to **8**, in which the core is a tetrahydropyridine ring, the biosynthetic pathways have not been studied. In the case of anatabine **41**, however, an alkaloid of tobacco plants, the tetrahydropyridine ring is derived from nicotinic acid **42**[25] (Scheme 8). Moreover, pyridine alkaloids have been detected in *Lobelia inflata*.



Scheme 8.

The case of lobinaline **19** is an interesting problem, because of its particular structure in comparison with other *Lobelia* alkaloids. It should be noted that lobinaline **19** is the major alkaloid of *Lobelia cardinalis*. In spite of its original structure, it has been shown that lobinaline **19** derives from lysine **21** and phenylalanine **25**.[26] In fact, various tracer experiments, have shown that lobinaline **19** is formed simply by dimerisation[27] (Scheme 9) of phenacylpiperidine **33**, which is also an intermediate in the biosynthetic pathway of lobeline **1**.

Publications concerning the biosynthesis and isolation of lobeline-related alkaloids continue to appear at a steady rate. Studies in this area are presumably ongoing and we wait with anticipation for more detailed information about the latter stages of the biosynthetic route.



Scheme 9.

4. Chemistry of *Lobelia* alkaloids

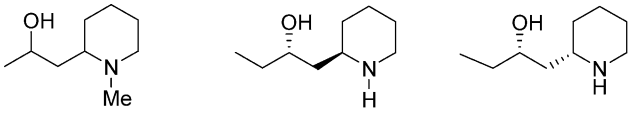
Only a few of the *Lobelia* alkaloids have been synthesised. In this review, we will describe the synthesis of *Lobelia* alkaloids, paying particular attention to the stereoselective asymmetric strategy. Thus, we will present the total syntheses of allosedamine **18**, 8-ethylnorlobelol **20**, lobeline **1** and its related alkaloids lobelanine **14** and lobelanidine **16**. It should be noted that the syntheses of sedamine **24** (found in *Sedum acre*, but not in *Lobelia inflata*) where its diastereoisomer, allosedamine **18**, was a minor product, are not presented here (Fig. 2). Recently, *Sedum* alkaloids have been reviewed by Bates and Sa-Ei.[28]

4.1. Synthesis of (+)-8-ethylnorlobelol

(+)-8-Ethylnorlobelol **20**, a minor alkaloid of *Lobelia inflata*, was first isolated by Wieland[6] et al. in 1939. These

Figure 2.

workers described the molecular formula as $C_9H_{19}NO$ and postulated the structure as an *N*-methylpiperidine derivative **43**. This structural assignment was revised twenty years later, however, by Schöpf[29] who, at the same time, established the absolute configuration as (2*R*,8*S*), but without reporting experimental evidence (Fig. 3). Thus, for many years, the absolute configuration was accepted as that described by Schöpf. Recently, Hootelé et al.[30] questioned this assignment and correctly revised the absolute configuration to (2*S*,8*S*). This assertion of Hootelé was confirmed, a short time later, by Takahata's group,[31] with the first asymmetric total synthesis of (+)-**20**.



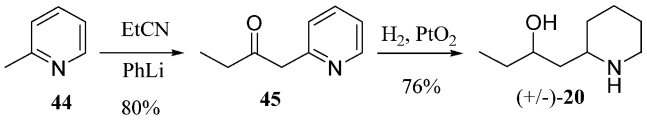
43 Structure proposed by Wieland *et al.*

20 Structure and absolute configuration (2*R*,8*S*) reported by Schölpf *et al.*

20 (2S,8S) corrected by Hootelé *et al.*

Figure 3.

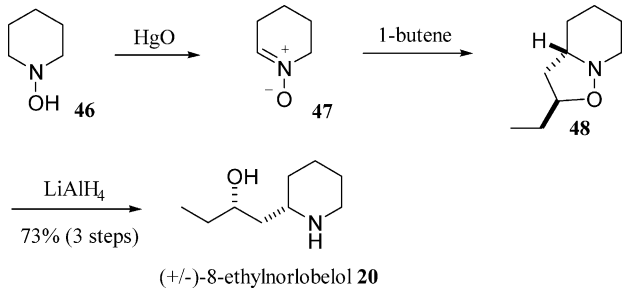
4.1.1. Non-stereoselective racemic approach. Kracher[32] and co-workers described (Scheme 10) the first racemic synthesis of (+/−)-**20** by the reaction of α-picoline **44** with propionitrile to give, after acidic work-up, the ketopyridine **45** in good yield (80%). This short and efficient synthesis was achieved by catalytic hydrogenation over platinum oxide of the pyridine ring and the carbonyl group in one step to afford (+/−)-**20**. In these studies, the pharmacological profile of some related analogues was also investigated, but no results were disclosed for (+/−)-**20**.



44 **45** (+/-)-**20**

Scheme 10.

4.1.2. Stereoselective racemic approach. More recently, Hootelé et al. have reported a very short diastereoselective synthesis of (+/−)-**20** (Scheme 11). Their approach exploited the advantageous properties of [2−3]-dipolar cycloaddition, which occurs with regio- and stereocontrol. Thus, the side chain was introduced by a regio- and stereoselective nitrone–alkene cycloaddition between 2,3,4,5-tetrahydropyridine-1-oxide **47** and 1-butene. The isoxazolidine **48** could easily be converted to (+/−)-**20** by cleavage of the N–O bond with $LiAlH_4$.



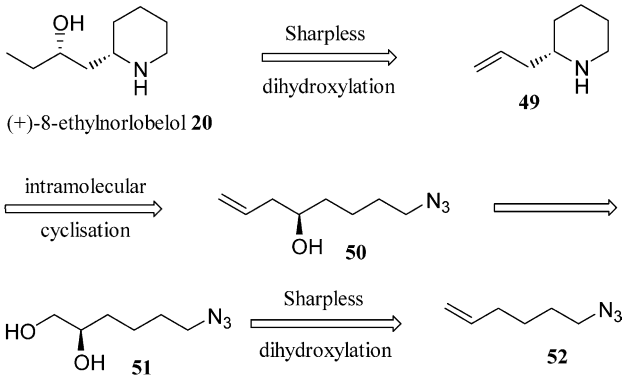
46 **47** **48**

(+/-)-8-ethylnorlobelol **20**

Scheme 11.

In these studies, Hootelé also reported experimental evidence to assign the natural enantiomer as (2*S*,8*S*) (Fig. 3). Consequently, they correctly revised the absolute configuration previously established by Schöpf.

4.1.3. Asymmetric approach. To date, the synthesis of (+)-8-ethylnorlobelol reported by Takahata et al. constitutes an interesting challenge as the only asymmetric synthesis. Retrosynthetically, the Takahata synthesis was achieved using three key reactions (Fig. 4). The Sharpless dihydroxylation of 5-hexenylazide **52** followed by an intramolecular aminocyclisation and a second Sharpless dihydroxylation constitute the three crucial steps of this synthesis to provide (+)-8-ethylnorlobelol **20**. This strategy was also applied to the synthesis of numerous piperidine derivatives and some ant defence alkaloids.[33,34]

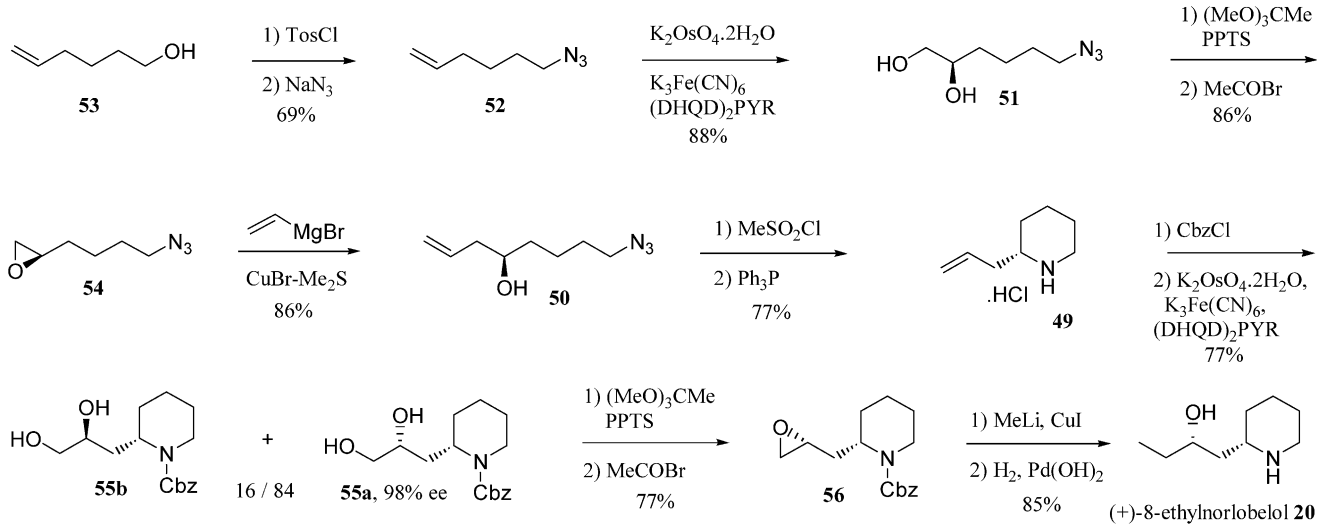


(+)-8-ethylnorlobelol **20**

49 **50** **51** **52**

Figure 4.

The synthesis started from the commercially-available 5-hexenol **53** (Scheme 12). Tosylation of the hydroxyl group followed by substitution with sodium azide furnished **52** in 69% yield over two steps. The Sharpless asymmetric dihydroxylation of 5-hexenylazide **52** generated the diol **51** in 88% yield with 88% ee. The intermediate **51** was converted into the epoxide **54** by the Sharpless one-pot two-step protocol in 86% yield. Regioselective copper-mediated Grignard allylation of the epoxide **54** afforded the alcohol **50** in good yield (86%). Treatment of the free hydroxyl group of **50** with mesyl chloride and subsequent reduction of the azide by the Staudinger reaction led to an intramolecular cyclisation with total inversion of configuration to give the desired 2-propenylpiperidine **49** (77% yield) as its hydrochloride salt. Protection of the piperidine as a benzyl carbamate followed by a second asymmetric dihydroxylation reaction of the terminal olefin led to a mixture of two diastereoisomers **55a/55b** in an 84/16 mixture, separable by chromatography on silica gel. The major diastereoisomer **55a** was found to be >98% ee. The resulting diol **55a** was converted into the epoxide **56** by the Sharpless one-pot two-step protocol using the same conditions as before for the transformation of **51** into the epoxide **54**. Regioselective copper-mediated Grignard methylation of the epoxide **56** and subsequent hydrogenolysis of the benzyl carbamate completed the total synthesis of (+)-8-ethylnorlobelol **20**. The melting point and specific rotation are in total agreement with those reported for the natural product. This assignment confirmed that proposed a short time earlier by Hootelé et al.



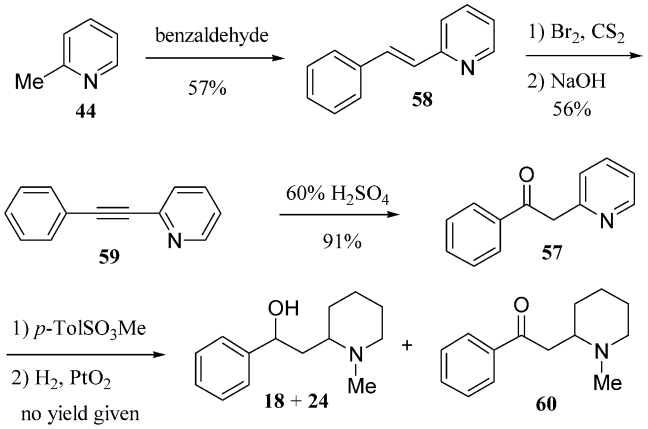
Scheme 12.

4.2. Synthesis of allosedamine

Although its biological properties are obsolete,[35] (−)-allosedamine has attracted attention as an interesting challenge and a valuable synthetic target for chemists.

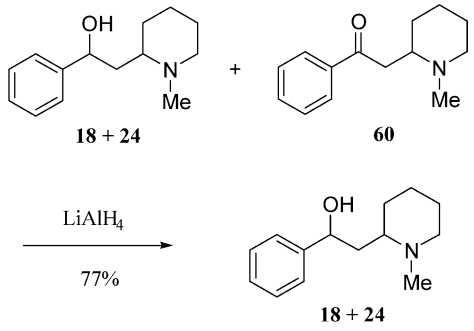
4.2.1. Non-stereoselective racemic approach. Before the 1960s, the piperidine core was often derived from a pyridine ring. The pyridine strategy provided an efficient and short route to piperidinic alkaloids, but yielded a mixture of diastereoisomers.

(−)-Allosedamine **18** was isolated from *Lobelia inflata*,[6,29] and the structural identification was reported by Marion[36] and co-workers on the basis of the first racemic synthesis (Scheme 13). It should be noted that these authors actually reported the structure of sedamine **24** (not found in *Lobelia* plants), which is a diastereoisomer of allosedamine **18**. These researchers envisaged the phenacylpyridine **57** as a key intermediate in their approach. The compound **57** was prepared by condensation of α-picoline **44** on benzaldehyde to give the alkene **58** after spontaneous elimination of a molecule of water. Bromination of the double bond and subsequent elimination in a basic medium furnished the acetylene **59** in 32% yield over the three steps. Hydration of the triple bond by treatment with concentrated sulphuric acid generated the expected key intermediate **57**. Methylation of the pyridine ring followed by catalytic hydrogenation gave a mixture of **18** and **60**. These products could be separated by the formation of the picrate salt derivatives, but with a rather low total yield.



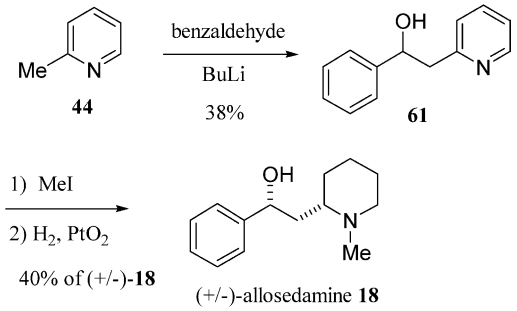
Scheme 13.

In order to avoid the formation of the picrate salt derivatives in the separation of **18** and **60**, Beyerman[37] and co-workers advocated treating the mixture with $LiAlH_4$ and, allosedamine **18** and sedamine **24** were then isolated as the single products (Scheme 14).



Scheme 14.

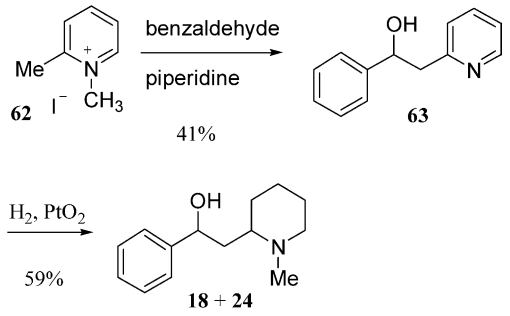
In their studies, however, the same workers also reported a simpler and shorter racemic synthesis starting from α-picoline **44** and benzaldehyde (Scheme 15). They found



Scheme 15.

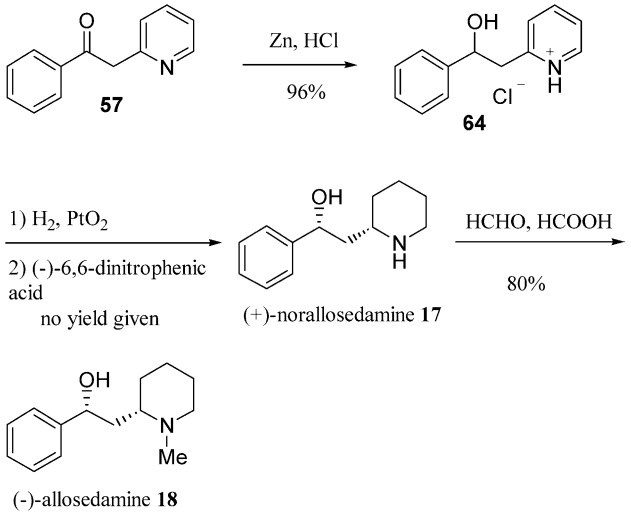
that the addition of α-picollyllithium to benzaldehyde furnished **61** without the elimination of a molecule of water, contrary to an acidic condensation. Subsequent *N*-methylation and catalytic hydrogenation gave a mixture of the two diastereoisomers, allosedamine **18** and sedamine **24**, which could be separated by fractional crystallisation.

Stanek[38] and co-workers observed the facile addition of 1,2-dimethylpyridinium iodide **62** to benzaldehyde to yield **63**, which on subsequent reduction furnished a mixture of **18** and **24** that were not separated (Scheme 16). In further studies, Beyerman[39] optimised the conditions described by Stanek to obtain the mixture of (+/−)-**18** and (+/−)-**24** in a better yield.



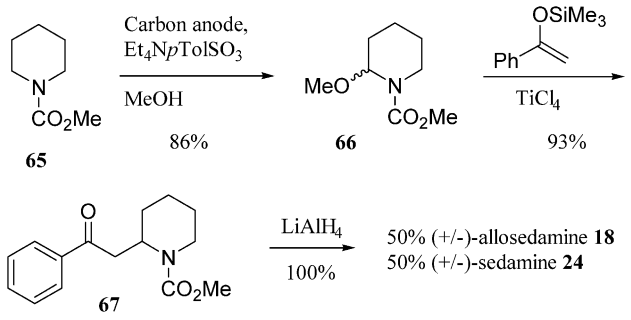
Scheme 16.

Starting from the phenacylpyridine **57**, Schöpf et al. isolated a mixture of norallosedamine **17** and its diastereoisomer by successive reduction of the carbonyl group with Zn and of the pyridine ring by catalytic hydrogenation over platinum oxide (Scheme 17). From this mixture, (+/−)-norallosedamine **17** was obtained in a pure form and was resolved by sequential crystallisations with (+)-6,6-dinitrophenic acid to give (+)-**17**. Compound (+/−)-**17** similarly treated with (−)-6,6-dinitrophenic acid gave (−)-**17**. Successive degradation of (+)-**17** led the authors to assign the absolute configuration as (2*S*,8*R*)-8-phenylnorlobelol **17**. Methylation of (+)-**17** under Eschweiler-Clarke conditions gave (−)-allosedamine **18**, the configuration of which is (2*S*,8*R*).



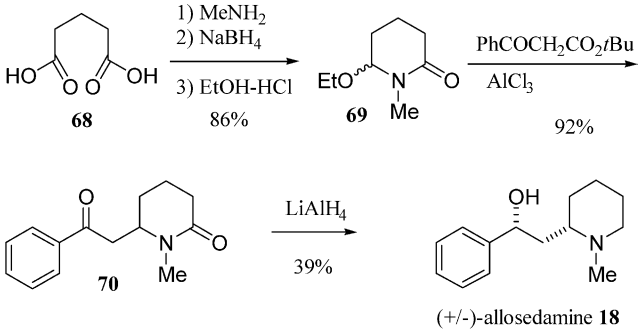
Scheme 17.

Introduction of the side chain via alkylation of an *N*-acyliminium precursor, formed in situ, also emerged as a suitable approach to achieve the synthesis of allosedamine **18** (Scheme 18). This strategy was advantageously used by Shono and co-workers.[40] The addition of 2-methoxypiperidine **66**, generated from **65** by anodic oxidation, to a silyl enol ether of acetophenone in the presence of $TiCl_4$, resulted in the isolation of **67** with high yield (93%). The non-stereoselective reduction of **67** with $LiAlH_4$ gave a mixture of (+/−)-sedamine **24** and (+/−)-allosedamine **18**, which were separated and identified by Schöpf's method.



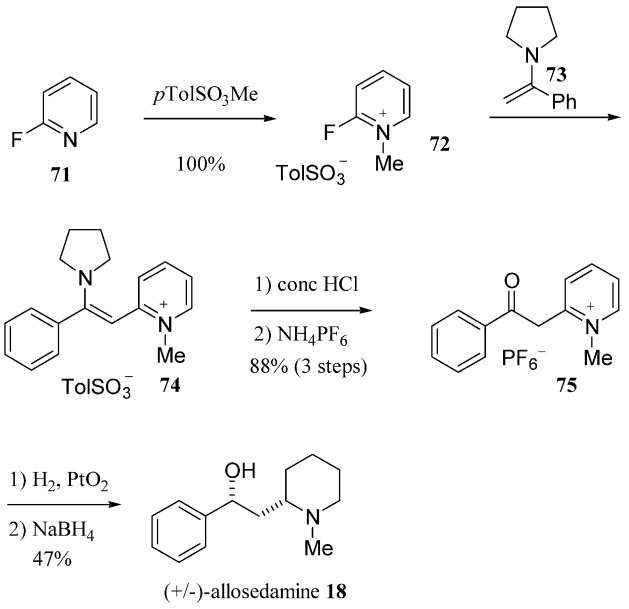
Scheme 18.

C–C bond formation between the piperidine precursor and the phenacyl side chain was also reported by Ozawa[41] in a similar approach (Scheme 19). 2-Ethoxy-6-piperidone **69**, readily prepared in two steps from glutaric acid **68**, was subjected to *C–C* bond formation with *tert*-butyl benzoylacetate and aluminum chloride to afford **70** after acidic hydrolysis. Reduction of the lactam and ketone functions with $LiAlH_4$ generated a mixture of sedamine **24** and (+/−)-allosedamine **18**, which were readily separated by column chromatography on silica gel.



Scheme 19.

More recently Meth-Cohn[42] and co-workers have developed a practical method for a short access to (+/−)-allosedamine **18** and related alkaloids via the pseudo Vilsmeier reagent **72**, which can easily be obtained by *N*-methylation of 2-fluoropyridine **71** (Scheme 20). The resulting iminium salt **72** was subjected to the enamine **73** to give **74**, which on acidic hydrolysis liberated the masked carbonyl group. Catalytic hydrogenation of the pyridinium ring of **75** followed by carbonyl reduction with $NaBH_4$ gave an equal mixture of diastereoisomers (+/−)-**18** and (+/−)-**24**, from which (+/−)-allosedamine **18** was isolated in a pure form after flash chromatography. It should be noted

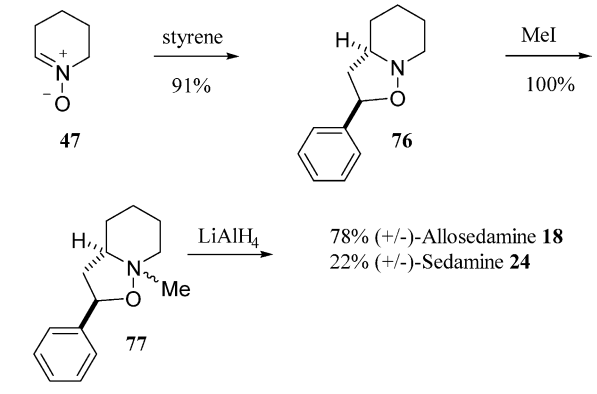


Scheme 20.

that the researchers developed an enzymatic resolution for some alkaloids to obtain chiral compounds. No experimental details were described, however, for (+/−)-allosedamine **18**. In addition, the application of this methodology to the synthesis of anti-Alzheimer agents was recently disclosed in a patent[43] by the same authors.

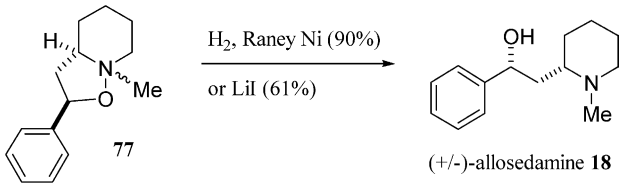
4.2.2. Stereoselective racemic approach. Tufariello[44] and, a few years later, Hootelé[45] developed a similar efficient route based on a regio- and stereoselective [2+3]-dipolar cycloaddition (Scheme 21). This strategy was widely used by Hootelé as an elegant route for various piperidinic derivatives including (+/−)-allosedamine **18** (vide supra).[46] Tufariello reported that the condensation of 2,3,4,5-tetrahydropyridine-1-oxide **47** with styrene afforded the isoxazolidine **76**, which upon *N*-methylation to **77** and subsequent treatment with $LiAlH_4$ furnished a mixture of (+/−)-allosedamine **18** (78%) and (+/−)-sedamine **24** (22%) with excellent overall yield. From this observation, the authors concluded that the cycloaddition step lacked stereoselectivity, to generate the isoxazolidine **76** in a 78/22 mixture of diastereoisomers.

In their studies, however, Hootelé et al. repeated the



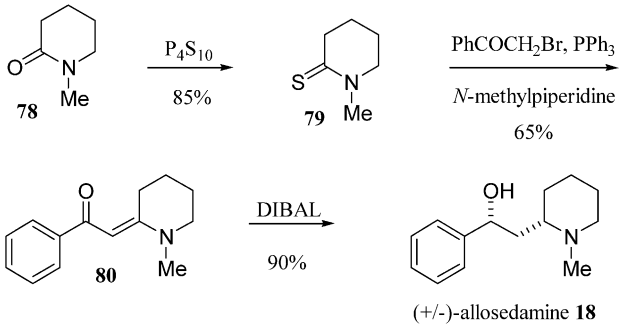
Scheme 21.

cycloaddition step in similar conditions and were surprised to note that analysis by gas–liquid chromatography of **76** revealed 97% of diastereoisomeric excess. This high diastereoselectivity resulted from an *exo* addition. Subsequent experiments showed that the reduction step with $LiAlH_4$ occurred with partial epimerisation. In order to overcome the critical step of the *N–O* bond cleavage without epimerisation, Hootelé et al. showed that hydrogenolysis of **77** with H_2/Raney nickel was the method of choice to generate (+/−)-allosedamine **18** as the sole product in high yield (Scheme 22). Liguori and co-workers[47] reported a valuable alternative to *N–O* bond cleavage in very mild experimental conditions by the use of LiI (Scheme 22). The yield was lower (61%) but the process was compatible with numerous functional groups.



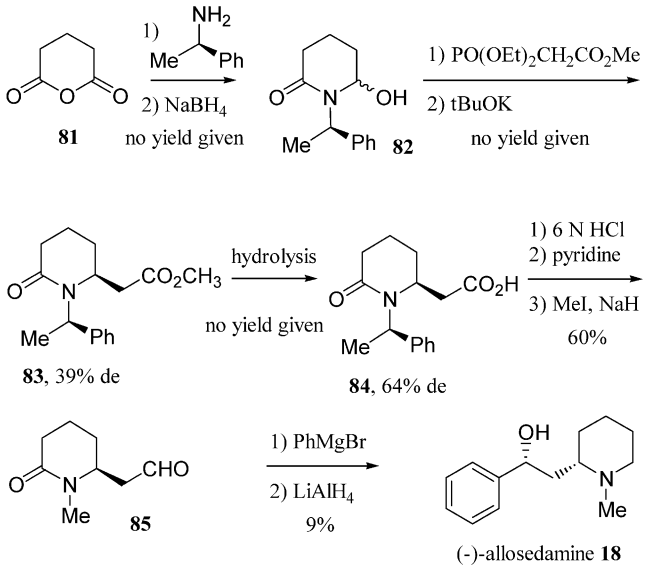
Scheme 22.

Ghiaci and Adibi[48] have reported more recently a straightforward synthesis of (+/−)-**18** by a judicious use of the Eschenmoser reaction (Scheme 23). The thiolactam **79**, easily prepared from the corresponding lactam **78**, reacted with phenacyl bromide to give the phenacylpiperidine **80** in good yield (65%). Reduction of **80** was conducted with a variety of reducing agents including $NaBH_4$, DIBAL-H, $LiAlH_4$ and H_2/Pt–C. DIBAL-H appeared to be the best reducing reagent and led exclusively to (+/−)-allosedamine **18**, probably via a chelated-type structure in the transition state.



Scheme 23.

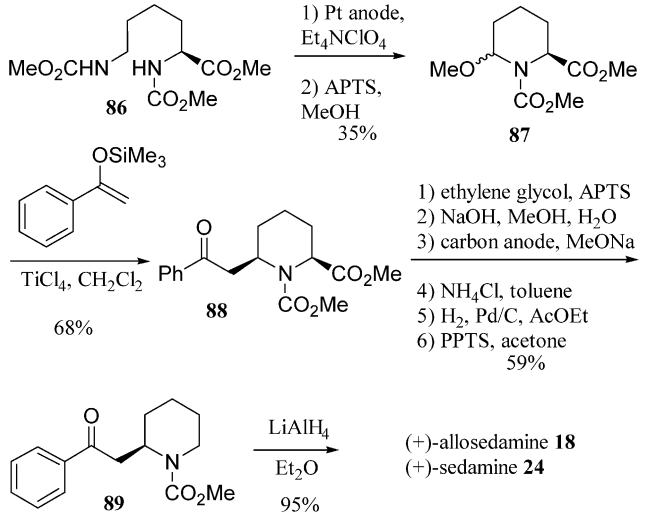
4.2.3. Asymmetric approach. The first asymmetric synthesis of **18** was described by the Wakabayashi[49] group and involved an asymmetric intramolecular Michal reaction (Scheme 24). Thus, treatment of glutaric anhydride **81** with (*R*)-(+)-α-phenylethylamine in harsh conditions followed by reduction with $NaBH_4$ generated the 6-hydroxy lactam **82**. A Wittig type condensation carried out on **82** and subsequent basic treatment gave **83** with modest selectivity (c.a. 39% de). Hydrolysis of the ester **83** to the acid **84**, however, and subsequent recrystallisation enhanced the de to 64%. The conversion of **84** into the aldehyde **85** was



Scheme 24.

achieved by standard methods. Addition of Grignard reagent on the carbonyl group of **85** and reduction of the lactam function gave the expected mixture of **18** and **24** in an equal ratio with low yield. Pure (−)-allosedamine **18** was isolated after chromatography on alumina. Unfortunately, the authors failed to quote the yields of the first steps for the synthesis, so it is not possible to comment on the efficiency of their route.

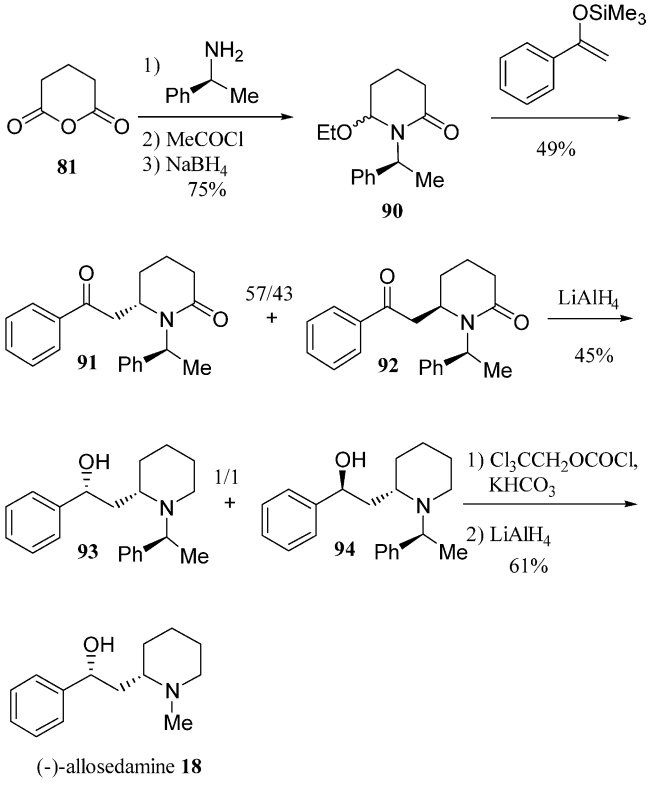
Alkylation of an *N*-acyliminium precursor with the formation of a *C–C* bond has also been applied in an asymmetric approach. Tanaka[50] and co-workers reported the stereoselective alkylation (ca. 10:1) of **87**, easily prepared from the lysine derivative **86**, by a silyl enol ether (α-trimethylsiloxystyrene; APTS) in the presence of $TiCl_4$ (Scheme 25). The expected derivative **88** was then isolated in 68% yield. These workers considered it prudent to protect the ketone group to perform the decarbonylation in a four-step sequence. After removal of the acetal group, the ketocarbamate **89** was subjected to reductive non-



Scheme 25.

stereoselective conditions to give an equal mixture of (+)-allosedamine **18** and (+)-sedamine **24**.

For their part, Naito[51] and co-workers opted for an *N*-phenylethyl chiral auxiliary to direct the stereoselectivity, but with low diastereoselectivity. The *N*-acyliminium precursor **90** was prepared by treatment of glutaric anhydride **81** with phenylethylamine followed by reduction of the imide and trapping of the resulting hydroxy-lactam by ethanolysis. Compound **90** was submitted to the silyl enol ether of acetophenone in the presence of $TiCl_4$ to give **91** and **92** with low diastereoselectivity (respectively in a 57/43 ratio) and modest yield (49%). The main diastereoisomer **91** was subjected to reduction with $LiAlH_4$ to give a 1:1 mixture of diastereoisomers, **93** and **94**, which were separated by medium-pressure column chromatography. Dealkylative carbamoylation and subsequent treatment with $LiAlH_4$ of **93** afforded (−)-allosedamine **18** in 61% yield (Scheme 26).



Scheme 26.

The first highly diastereo- and enantioselective synthesis of (−)-allosedamine **18** was achieved by Oppolzer.[52] The strategy involved an elegant chiral application of the widely used nitrone/styrene cycloaddition, followed by a reductive *N–O* cleavage (Fig. 5). It should be noted that this strategy was successfully applied to the synthesis of various pyrrolidine and piperidine alkaloids.[53–55]

The synthesis started from the known aldehyde[56] **97** (obtained in two steps from ε-caprolactone with 66% overall yield) which was acetalised with propane-1,3-diol (Scheme 27). A subsequent Me_3Al-mediated condensation of **98** with sultam (now known as Oppolzer's auxiliary)

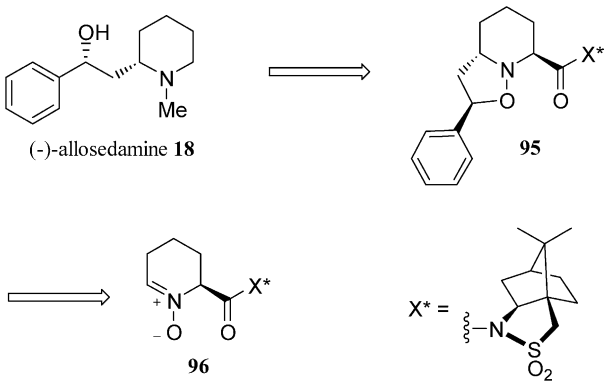


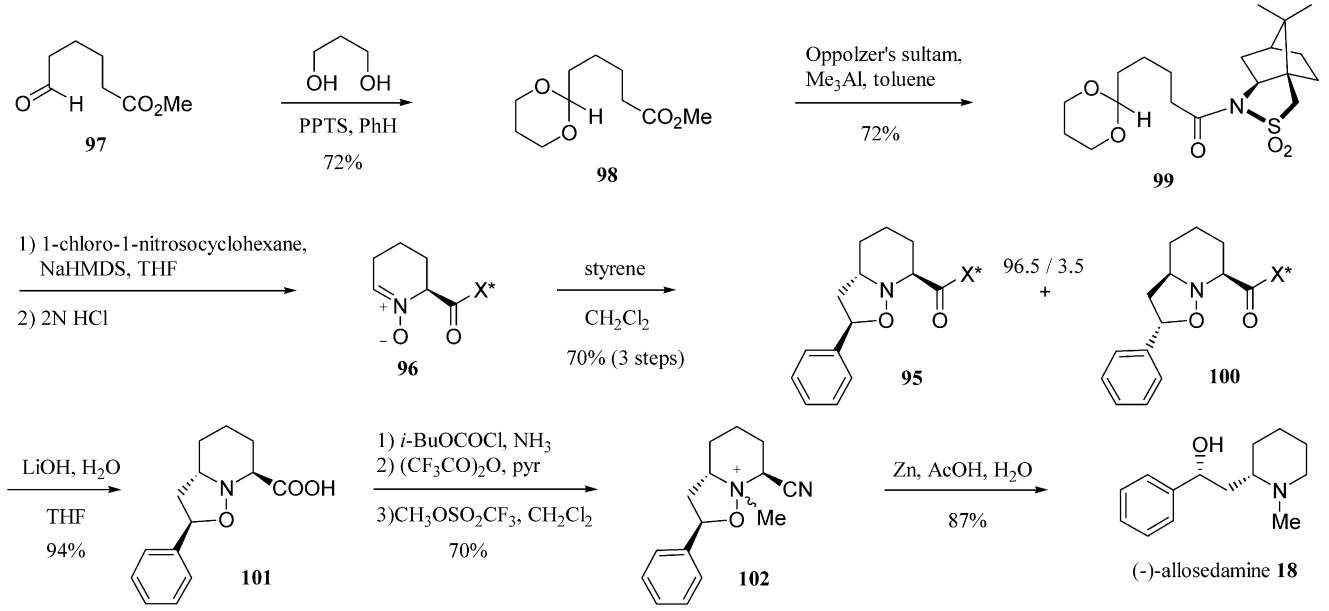
Figure 5.

afforded **99** in 72% yield. Compound **99** was deprotonated with NaHMDS and the resulting (*Z*)-enolate was trapped with 1-chloro-1-nitrosocyclohexane. Hydrolysis of the non-isolated acetal in acidic media gave the corresponding tetrahydropyridine *N*-oxide **96**, which was used without further purification in the next step. Thus, the crude dipole **96** reacted with styrene (dipolarophile) as a [3+2] cycloaddition with high stereoselectivity to give the cycloadduct **95**, contaminated by <3.5% of the diastereoisomeric cycloadduct **100**. The mixture was efficiently separated after flash chromatography and subsequent crystallisation. Cleavage of the chiral auxiliary with basic hydrolysis furnished the carboxylic acid **101** with recovery of the sultam auxiliary. The next step required the removal of the COOH group. Neither Barton's decarboxylation[57] nor Rapoport's decarbonylation,[58–60] however, afforded the desired product. An alternative method consisted of the transformation of the COOH group into a CN function, followed by a reductive α-aminonitrile decyanation. Thus, conversion of carboxylic acid **101** into the amide and subsequent dehydration of the resulting carboxamide generated the nitrile function. Unfortunately, the reductive decyanation failed again. In order to achieve the required transformation, the above results forced the researchers to plan an alternative strategy involving the methylation of nitrogen before the decyanation and *N*–*O*-cleavage. *N*-Methylation was performed with methyl triflate to give the ammonium triflate **102** as a 7/1 mixture of diastereoisomers. Treatment of the ammonium triflate **102** with activated Zn dust and HCl led not only to the *N*–*O*-cleavage, but also, in the meantime, removed the CN group in good yield (87%). Thus, the total synthesis of (−)-allosedamine **18** was achieved in nine steps and 21% overall yield from a known product (11 steps and 14% overall yield from a commercially available product).

Very recently, in connection with our programme towards the synthesis of natural products having biological activity on the central nervous system, we have reported an efficient and stereoselective synthesis of (−)-allosedamine **18**.

In our synthesis,[61] the chiral moiety at C2 was derived from a chiral homoallylic alcohol **105**. One of the key steps of this synthesis was to obtain the chiral homoallylic alcohol **105** with high enantiomeric excess. Previously, we have also used chiral homoallylic alcohols in the synthesis of various pyrrolidinic,[62,63] piperidinic,[64] and tetrahydropyridinic[65] alkaloids with high stereoselectivity. The second chiral centre was induced by the free hydroxyl group with a stereocontrolled epoxidation. Formation of the piperidine ring was achieved by an intramolecular cyclisation reaction (Fig. 6).

Thus, to obtain the chiral homoallylic alcohol **105** with high ee constituted the first challenge of this synthesis (Scheme 28). Numerous methods to synthesise homoallylic alcohols have been described in the literature.[66] We, however, have developed a new access to these intermediates that is applicable on a multigramme scale.[67] Thus, the chiral homoallylic alcohol **105** was obtained by a 2-step procedure which involved a condensation of allylmagnesium bromide on the commercial Weinreb amide **106** followed by an enantioselective reduction of the prochiral ketone[68–70] **107** with (+)-DIP-chloride™.[71] Thus, the



Scheme 27.

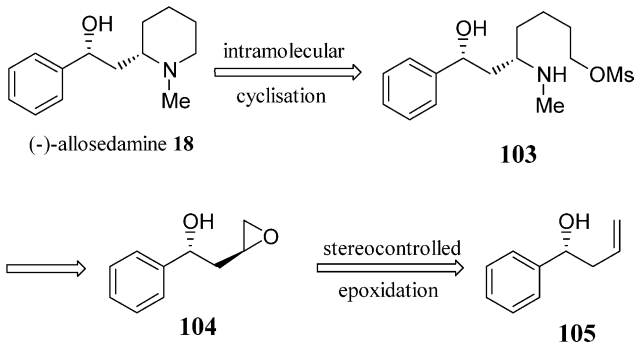


Figure 6.

alcohol **105** was isolated in good yield (84% in two steps) with high ee (>99%). For example, the direct allylboration of benzaldehyde with *B*-allyldiisopinocamphenylborane ($^{l}Ipc_2Ball$) gave **105** in similar yields, but resulted in a decrease in optical purity (95% ee).

A stereocontrolled epoxidation of the double bond by the Cardillo[72,73] procedure generated the second chiral centre of allosedamine with total diastereoselectivity to give the *syn* epoxy alcohol **104**. This procedure, which involved passage via the iodocarbonate **109**, was found to be better than the Sharpless protocol[74,75] using $VO(acac)_2$ and *t*BuOOH (*cis*/*trans*: 4/1). Protection of the benzylic hydroxyl function, followed by a regioselective opening of epoxide with allyl cuprate, generated **110**. The new hydroxyl function was converted into an amine. This step was found to be problematic when the conversion of the hydroxyl function into the amine occurred via an azide, according to the Mitsunobu protocol.[76] Indeed, the instability of the azide, which can spontaneously cyclise with the double bond as a [3+2] cycloaddition,[77,78] led to a complete decomposition of the product. Fortunately, persistent experimentation was rewarded when conversion into the amine **111** was found to occur in good yield (73% in two steps) by displacement of the corresponding mesylate with methylamine. The protection of the secondary amine into *tert*-butyl carbamate followed by hydroboration–oxidation of the double bond furnished the primary alcohol **112**. Activation of the hydroxyl group into the corresponding mesylate and subsequent treatment in methanolic acidic conditions led not only to the Boc cleavage, but also to the removal of the TBS protection to give a product which spontaneously cyclised during the basic treatment.

Thus, (−)-allosedamine **18** was efficiently obtained in 13 steps with an overall yield of 29%.

Riva, Passarella and co workers[79] reported a straightforward synthesis of (−)-allosedamine **18** based on three successive enzymatic resolutions of *N*-Boc-piperidine-2-ethanol **113** (Fig. 7).

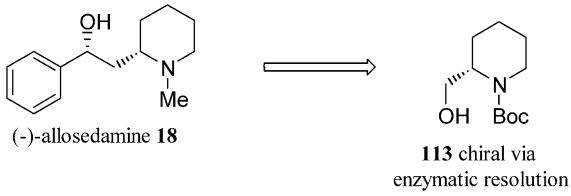
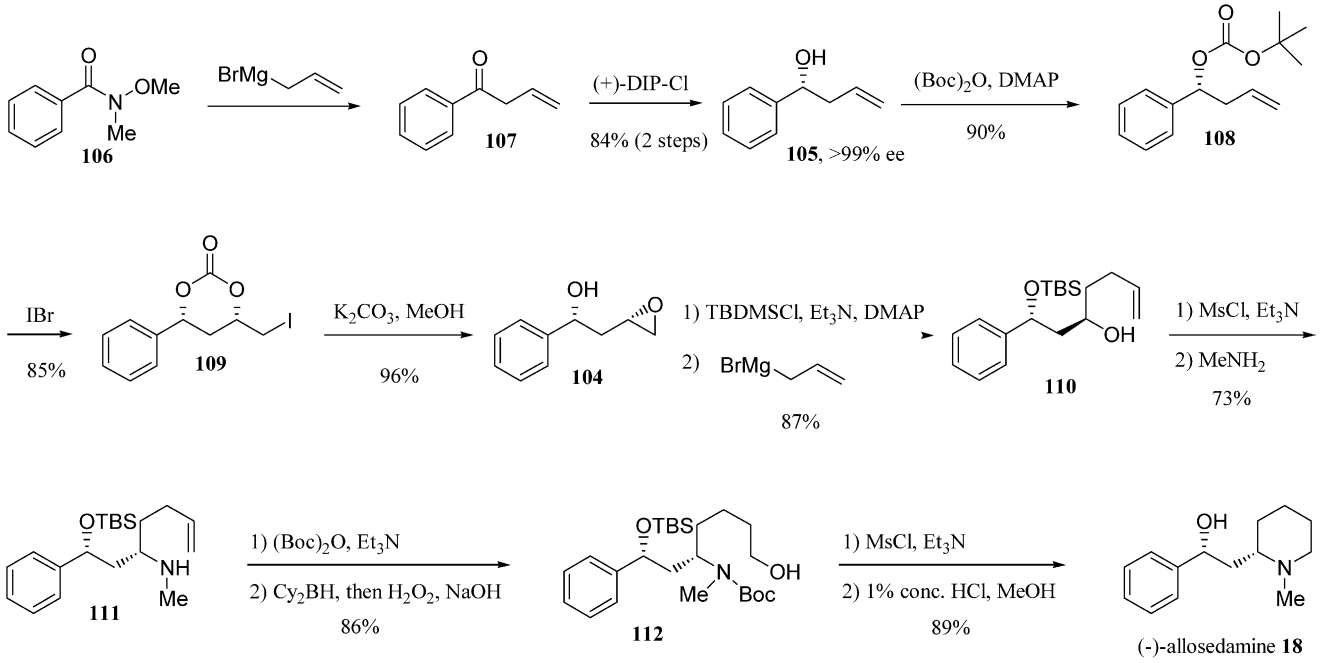
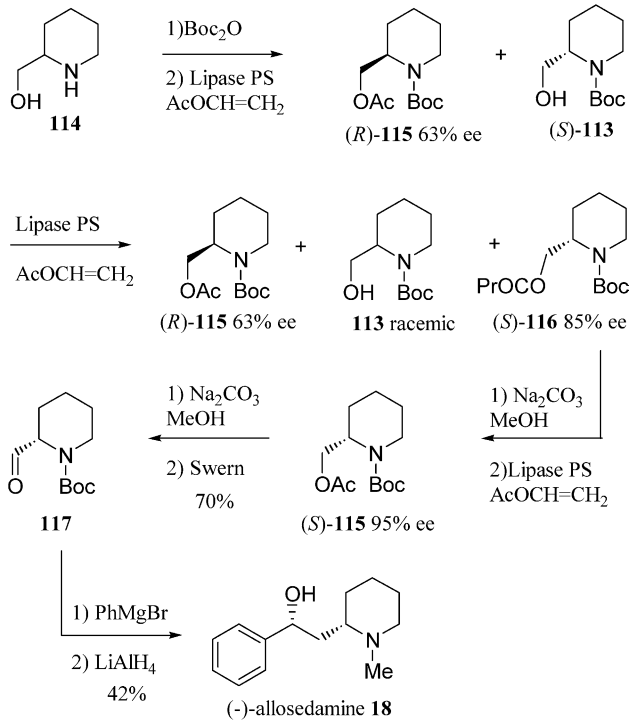


Figure 7.

Racemic commercially available piperidine-2-ethanol **114** was first protected as the corresponding *tert*-butyl carbamate and then submitted to the first enzymatic resolution with Lipase PS to give the acetate (*R*)-**115** with 63% ee and the alcohol (*S*)-**113** at 45% conversion (Scheme 29). After work-up, the crude mixture was then submitted to pancreatic lipase to give a separable mixture of the unreacted acetate (*R*)-**115**, the unreacted almost racemic alcohol **113** and the ester (*S*)-**116** with 85% ee. Compound **116** was chemically hydrolysed and was then again



Scheme 28.



Scheme 29.

submitted to a third enzymatic resolution with pancreatic lipase to give the acetate (*S*)-**115** with 95% ee. It should be noted that this sequence can be carried on multigramme scale, but the authors failed to quote a yield for this four-step process. The acetate protecting group of (*S*)-**115** was hydrolysed under basic condition and the resulting primary alcohol was oxidised by the Swern protocol to give the aldehyde **117** in 70% yields over two steps. The remaining steps, addition of phenylmagnesium bromide with low diastereoselectivity (3:2 dr) followed by the reduction of the *tert*-butyl carbamate with $LiAlH_4$ furnished (−)-allosedamine **18** in nine steps from the commercially available racemic piperidine-2-ethanol **114**.

Very recently, Raghavan and Rajender[80] have reported the total synthesis of (−)-allosedamine **18** via a diastereoselective addition of the sulphinyl anion **118** to the imine **119** followed by a bromohydration of the olefin **120** using the sulphinyl function as an internal nucleophile (Fig. 8).

Their synthesis began with the condensation of the sulphinyl anion **118** with the imine **119** in favour of the desired isomer **120** (3/1 dr) with 61% yield after separation of the diastereoisomers by column chromatography (Scheme 30). The next step involved a high-yielding stereo- and regioselective bromohydration of **120** using the sulphinyl group as an internal nucleophile via the transition state **A** to furnish **121**. After removal of the bromine atom, the free hydroxyl group was protected as the acetate derivative **122** and the nitrogen was alkylated with butenyl nosylate to give **123**. Subsequent treatment of **123** with trifluoroacetic anhydride in the presence of Et_3N (Pummerer rearrangement) followed by Wittig olefination generated the diethylenic substrate **124** in good yield (75%). In order to construct the piperidine core of (−)-allosedamine **18**,

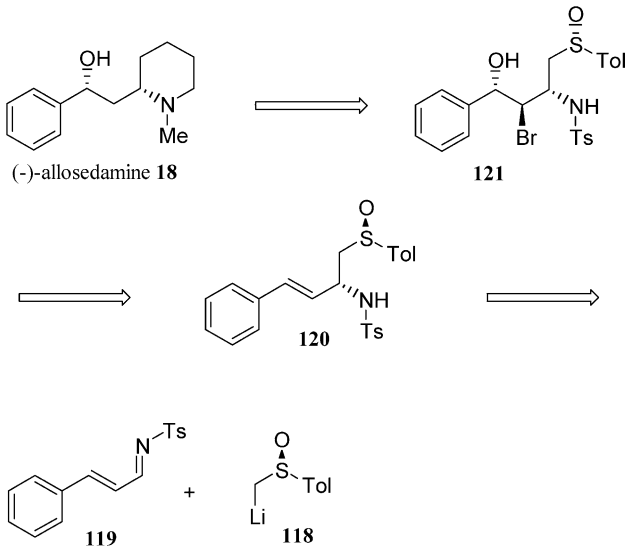


Figure 8.

compound **124** was subjected to a first-generation Grubbs' catalyst **125** to give **126** in 80% yield via a ring-closing metathesis reaction. Concomitant deprotection of the tosylate and acetate protecting groups and subsequent reduction of the double bond gave (+)-norallosedamine **17**. Finally, reductive methylation of the secondary nitrogen using HCHO and $NaBH_3CN$ gave (−)-allosedamine **18** in 12 steps and 11% overall yield.

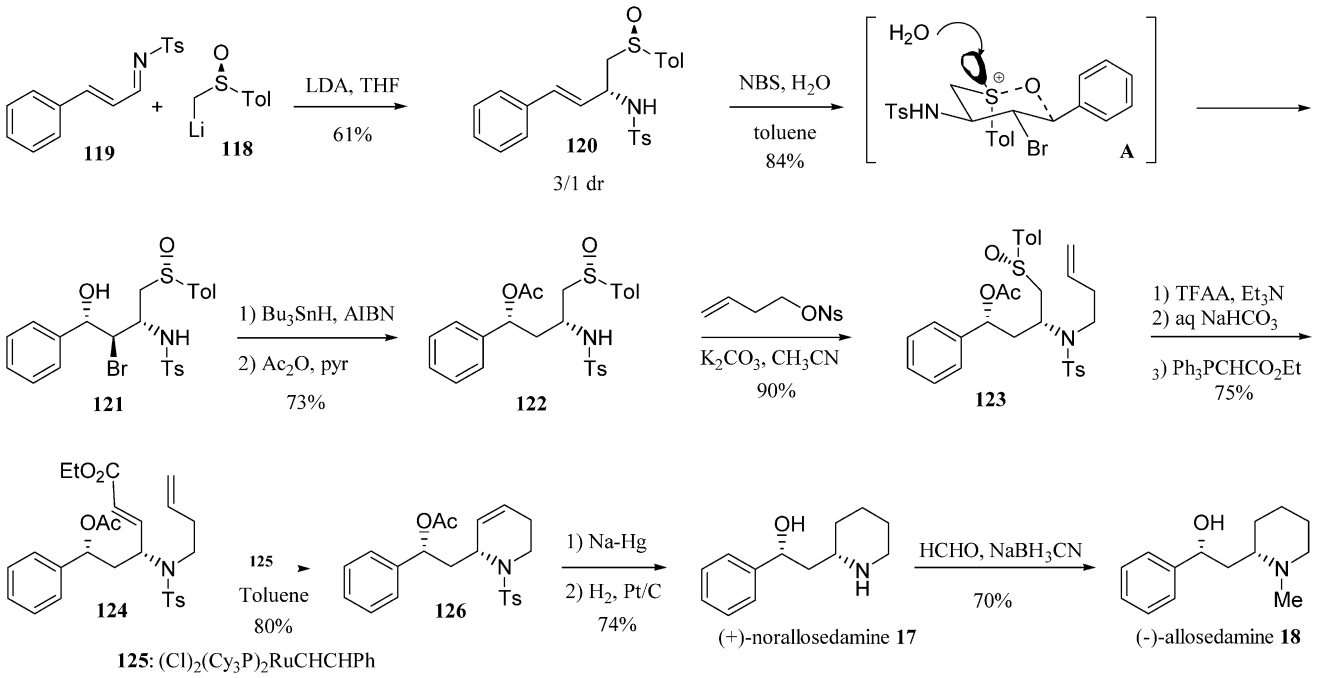
4.3. Synthesis of lobeline and related alkaloids

4.3.1. Chemical properties. Before discussing the chemistry of lobeline **1** and the related alkaloids, lobelanine **14** and lobelanidine **16**, it will be of interest to first consider some of their chemical properties.

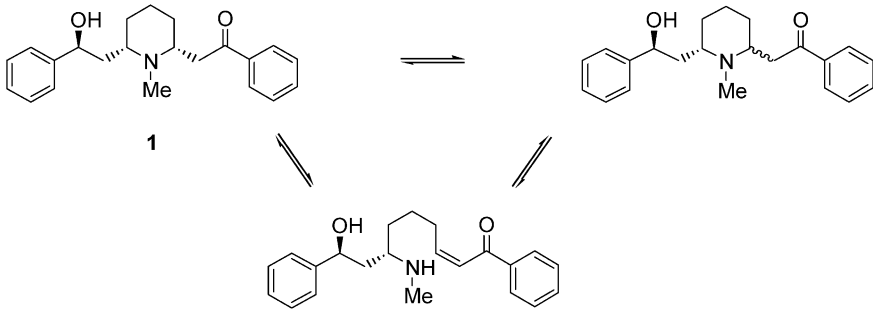
A problem occurred with lobeline, as with other ketopiperidine alkaloids. It was known that ketopiperidines are configurationally unstable and epimerise readily (Scheme 31). The mutarotation of (−)-lobeline is an interesting phenomenon, probably due to a retro Michael reaction that was studied during the 1960s. The rate of mutarotation of *cis*-(−)-lobeline **1** to a mixture of *cis* and *trans*-(−)-lobeline **1** is increased in hydrophilic solvents and in the presence of hydroxyl ions.[81] More recently, Marazano et al. noted that (−)-lobeline hydrochloride exists in solution as a single stereoisomer (vide infra). This shows that ketopiperidines are configurationally stable when the nitrogen lone pair is not available as its hydrochloride form. In our laboratory, we have paid particular attention to the mutarotation and it should be noted that, in its crystalline form, without solvent, no mutarotation occurred for *cis*-(−)-lobeline **1**.

Lobeline was first isolated by W. M. Procter Jr. in 1838.[1] Several incorrect characterisations of lobeline were proposed before Wieland[82] reported the correct chemical structure in 1929. This work was the starting point of extensive research into a better understanding of its complex pharmacological properties (vide infra).

To date, five total syntheses of lobeline **1** have been



Scheme 30.

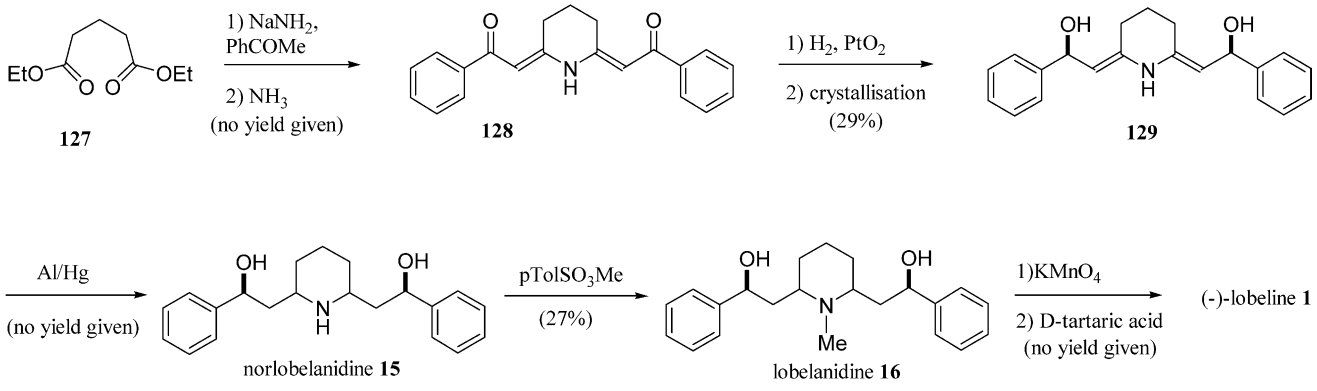


Scheme 31.

reported, among which, two involve the racemic form and three use asymmetric strategies. Wieland, Scheuing and Winterhalder, however, showed that lobelanidine **16** could be converted into lobeline **1** by a mild oxidation of a hydroxyl group. Moreover, lobelanine **14** could be reduced to lobelanidine **16** by catalytic hydrogenation over platinum oxide. Thus, a synthesis of lobelanine **14** and lobelanidine **16** constituted a formal synthesis of lobeline **1**.

4.3.2. Racemic approach to lobeline and related alkaloids. The work concerning the racemic approach was published before the 1950s and the yield of each step was not always given. For this reason, it is difficult to comment on the efficiency of the different routes, although it is important to report the intellectual design.

The first synthesis of lobeline **1** was described by Wieland et al.[83] (Scheme 32). The synthesis started with an ingenious



Scheme 32.

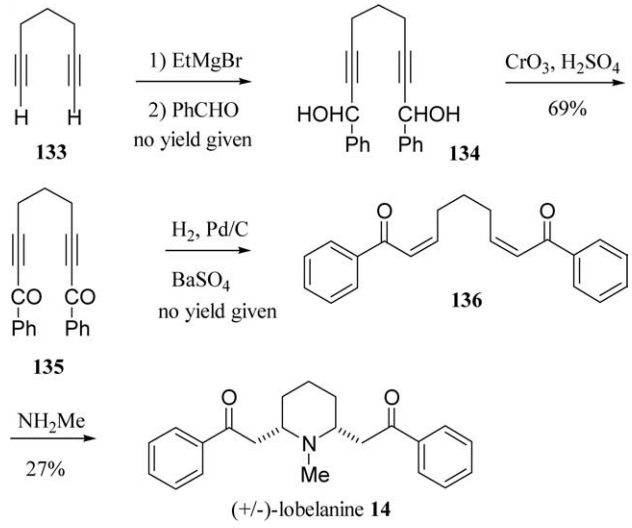
double Claisen condensation between ethyl glutarate **127** and acetophenone, followed by treatment with ammonia to build the piperidine ring in **128**. The carbonyl groups were reduced by catalytic hydrogenation over platinum oxide to give a mixture of two diastereoisomers that were separated by crystallisation. The corresponding β-norlobelanidiene **129** was treated with an aluminum amalgam to yield norlobelanidine **15**, which was converted into its methylated derivative by treatment with *p*TolSO$_3$Me. The lobelanidine **16** produced was converted into lobeline **1** by treatment with an oxidising agent such as permanganate. The lobeline **1** obtained as the reaction product was separated from the unchanged starting material. (+/−)-Lobeline **1** was then resolved by D-tartaric acid giving (−)-lobeline **1**, which was found to be identical in every respect with the naturally occurring base. The value of the optical rotation indicated the presence of the two epimers (*cis* vs *trans*) in an approximate 1/1 ratio.

Simultaneously with Wieland, Scheuing and Winterhalder[84] disclosed their work on the total synthesis of lobeline **1** (Scheme 33). Their strategy involved the synthesis of the diphenylethynylpyridine **131** that could be obtained by a known method[85] from 2,6-lutidine **130**. Hydration of **131** with concentrated sulphuric acid furnished the diphenacylpyridine **132**. Alkylation of the pyridine ring with *p*TolSO$_3$Me gave a quaternary salt that could easily be reduced to lobelanidine **16** with 5 mol of H$_2$. A mild oxidation of **16** by potassium permanganate gave a mixture of the (+/−)-lobeline **1** and the unreacted starting material, which were separated by crystallisation.

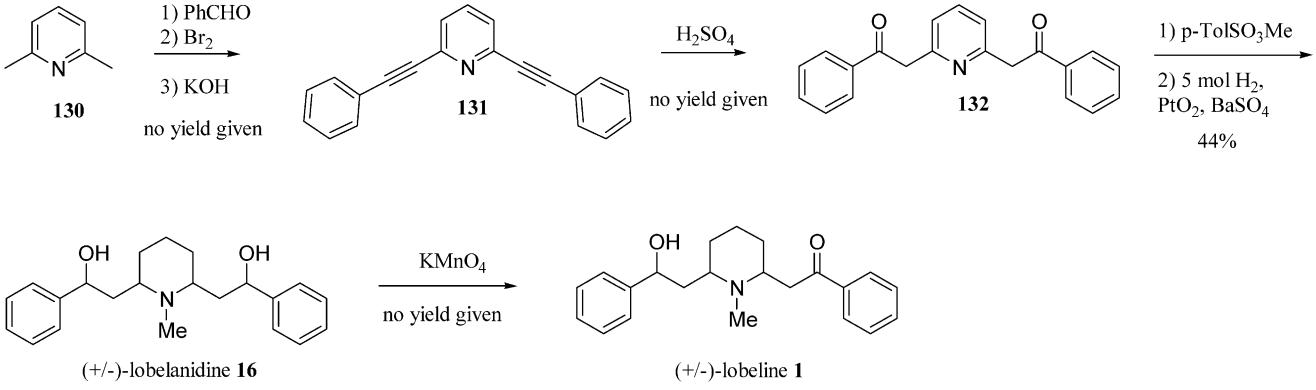
By an exceptional one-pot multistep process, the synthesis of lobelanine **14** was achieved by Schöpf and Lehmann[86] in 1935 (Scheme 34). This elegant strategy involved a Mannich condensation and a Robinson type biomimetic reaction. Thus, a mixture of glutaric dialdehyde, benzoylacetic acid and methylamine hydrochloride was stirred for several days to give lobelanine **14** in one step, in 90% yield.

Parker advantageously exploited a double aza-Michael addition to build the piperidine core (Scheme 35). Hepta-1,6-diyne **133**, treated with 2 equiv of EtMgBr, reacted with benzaldehyde to give the diols **134** as a mixture of two diastereoisomers. Oxidation by chromium trioxide in an acidic medium, however, gave the symmetrical diketone **135**. The next stage, involving catalytic hydrogenation, produced the expected Michael acceptor **136** as a symmetrical *Z*,*Z*-dienone. The addition of methylamine to **136** proceeded stereospecifically to furnish *cis*-lobelanine **14**.

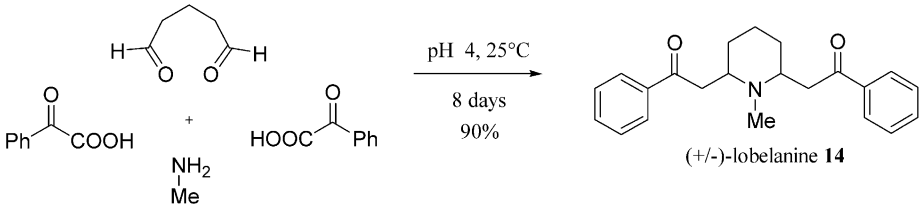
4.3.3. Asymmetric approach. In the course of designing a synthesis for a natural product, it can be profitable to



Scheme 35.



Scheme 33.



Scheme 34.

consider how its structure may have arisen in nature. Inspired by a biogenetic process, Schöpf and Müller in the mid-1960s described the first asymmetric total synthesis of (−)-lobeline.[87] It was anticipated that (−)-sedamine **24** would provide (−)-lobeline **1** by alkylation at C6 (Fig. 9). Moreover, it was reasoned that the phenacylpyridine[88] **57** should be an ideal starting material to access (−)-sedamine **24**.

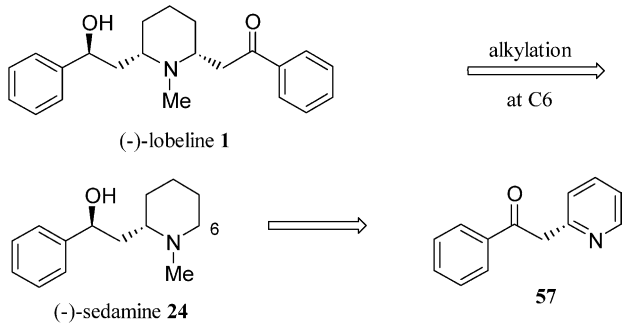
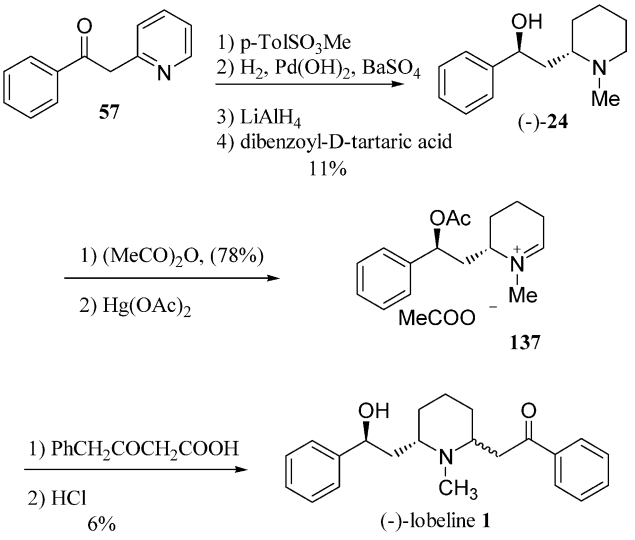


Figure 9.

The first aim was to synthesise (−)-**24** by using phenacylpyridine **57** as the readily available starting material (Scheme 36). With compound **57** in hand, (−)-**24** was obtained by the classical chemical transformation and resolution of (+/−)-**24** with dibenzoyl-D-tartric acid. Compound (−)-**24** was acetylated to give the corresponding *O*-acetyl derivative (78%), which was treated with mercuric acetate in acetic acid according to the procedure of Leonard et al.[89] Guided by the presumed biosynthetic pathway, the resulting iminium salt **137** was reacted with benzoyl acetic acid to yield the expected *O*-acetyl lobeline. A last hydrolysis of the acetate group enabled (−)-lobeline **1** to be isolated in an elegant fashion as a mixture of two epimers, even though the yield was low.



Scheme 36.

In the Marazano[90] synthesis, the piperidine ring of (−)-lobeline **1** was derived from a chiral pyridinium salt that was alkylated twice on the C2 and C6 positions by the Reformatsky reagent (Fig. 10). Alkylation of pyridinium

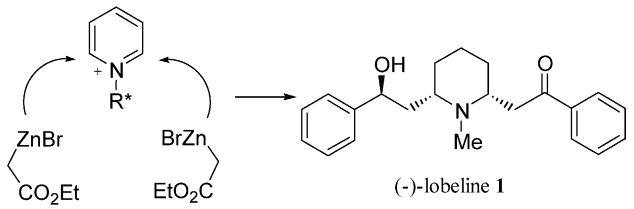


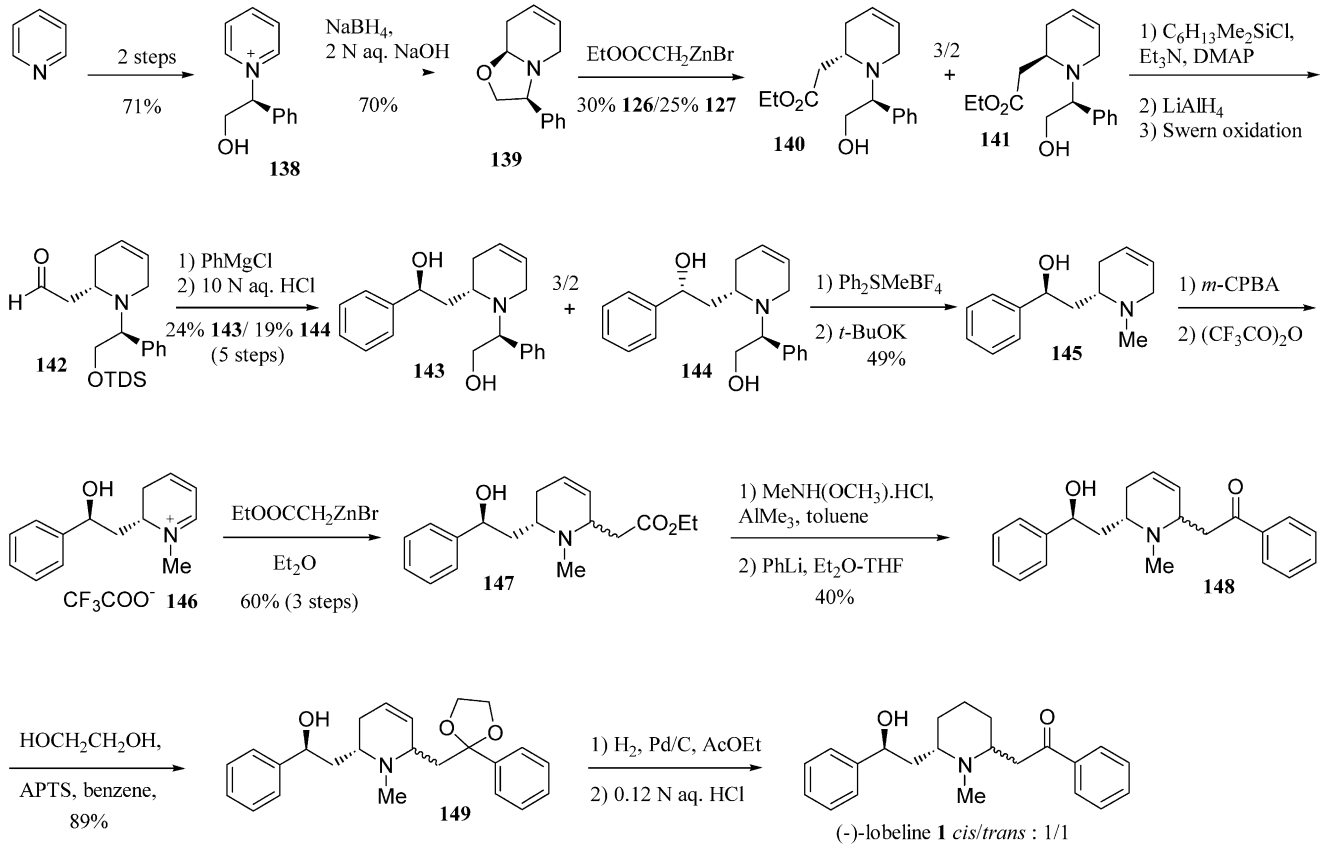
Figure 10.

salts has been extensively studied by Marazano to synthesise various piperidinic or tetrahydropyridinic alkaloids.[91] Thus, this methodology was successfully applied to the total synthesis of (−)-lobeline **1**.

The Marazano synthesis involved the formation of the chiral pyridinium salt **138** obtained in two steps from commercial products[92] (71% overall yield) (Scheme 37). The chiral pyridinium salt **138** was reduced to the oxazolidine **139**, which was opened by the Reformatsky reagent to give two diastereoisomers **140** and **141** with low selectivity (3/2 ratio, respectively) in 30% yield. Nevertheless, the diastereoisomers **140** and **141** were easily separated by chromatography on silica gel, which permitted the preparation of **140** on a large scale. The primary hydroxyl group was protected as a silyl derivative and the ester function was transformed into the unstable aldehyde **142** in two steps involving a reduction by $LiAlH_4$ followed by an oxidation with the Swern protocol. Addition of Grignard reagent to **142** and subsequent deprotection of the hydroxyl function in acidic conditions gave a mixture of two diastereoisomers **143** and **144** in a 3/2 ratio that were easily separated by chromatography on silica gel. The next step required the removal of the phenylethanol auxiliary and the methylation of nitrogen. The researchers used a quaternisation–elimination strategy in a two-step sequence. Thus, quaternisation with the powerful alkylating reagent diphenylmethylsulphonium tetrafluoroborate and subsequent removal of the chiral auxiliary by treatment with *t*BuOK provided 4,5-dihydrosedamine **145**. It should be noted that this route also allowed an access to (−)-sedamine **24** or (−)-allosedamine **18** by reduction of the double bond. The formation of the unstable iminium salt **146** in two steps by a modified Polonowski protocol followed by the addition of Reformatsky reagent gave **147** as an unseparable mixture of diastereoisomers. The next step was performed on the mixture of epimers. It is interesting to note that this alkylation step is similar to the formation of norlobelanine **13** in the biosynthetic pathway (vide supra). Thus, Marazano elegantly drew inspiration from a natural process.

Transformation of the ester function into a Weinreb amide followed by the addition of PhLi furnished the dehydrolobeline **148** as two epimers *cis*/*trans* in a 15/85 ratio. All attempts to selectively reduce the double bond in the presence of the free carbonyl group failed. The authors therefore used a protection of the carbonyl group to give the dioxalane **149**. Hydrogenation of the double bond followed by hydrolysis of the resulting dioxalane gave (−)-lobeline **1** in an equilibrium mixture of two epimers *cis*/*trans* in a 1/1 ratio.

Retrosynthetically, we used a similar strategy for the



Scheme 37.

synthesis of (−)-allosedamine **18** in the construction of (−)-lobeline **1** (vide supra) (Fig. 11). The synthesis involved the use of the *syn* epoxyalcohol **104**, which was a common chiral intermediate in the synthesis of (−)-allosedamine **18**. Formation of the piperidine ring was achieved by an intramolecular Michael reaction.

The synthesis began with the *syn* epoxyalcohol **104** previously described in the synthesis of (−)-allosedamine **18** (vide supra), (Scheme 38). Conversion into the *trans* isomer by the Mitsunobu protocol furnished the diastereoisomer **151** with total inversion of configuration. The key intermediate **152** was essentially obtained using the same cascade of reactions previously described (vide supra). A Dess–Martin oxidation into the aldehyde **153** followed by a Wittig olefination led to the enone **154**. Finally, removal of the TBS and the Boc groups in acidic media generated the enone **155**, which spontaneously cyclized during the basic treatment. Thus, (−)-lobeline **1** was obtained in an equilibrium mixture of two epimers *cis*/*trans* in a 1/1 ratio.

Thus, the highly enantioselective synthesis of (−)-lobeline requires 16 steps from benzaldehyde and gives 14% overall yields. This efficient route could be applied to the preparation of interesting analogues for biological screening.[93]

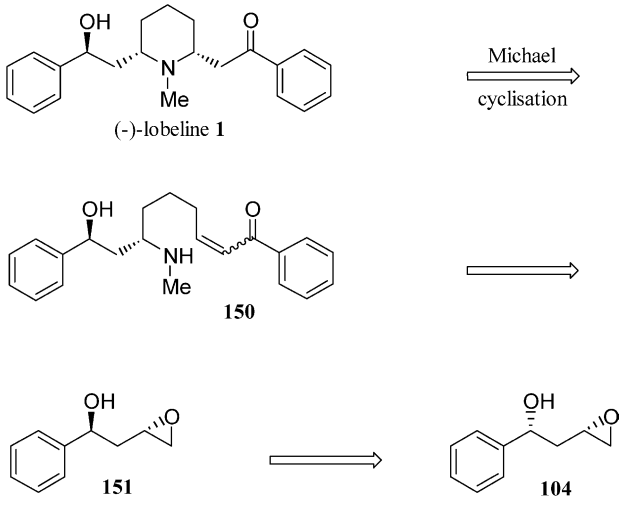
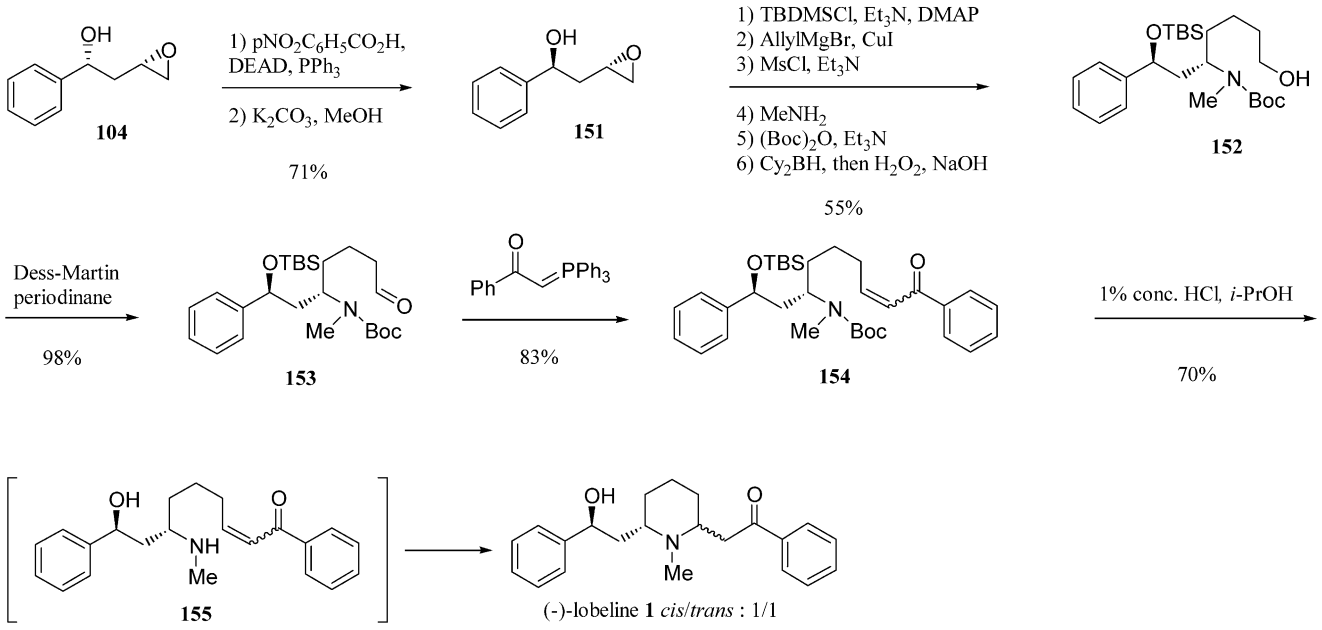


Figure 11.

5. Biology

(−)-Lobeline **1** appears to be the most biologically active alkaloid of *Lobelia* plants and consequently has been the subject of several pharmacological studies. Biological investigations over the last 25 years have shown that many of the medicinal properties empirically discovered by native Americans have a scientific basis. Each of the major effects, namely respiratory stimulant, drug deterrent, cognition enhancement in neurological disorders, as well as other minor biological properties reported for lobeline **1**, will be considered in turn, followed by its mode of action and the structure–activity relationship studies.



Scheme 38.

5.1. Biological activity of lobeline

5.1.1. Respiratory stimulant. For a very long time, the most important use for this drug has been in the treatment of respiratory problems. For this class of disease, no remedy was more highly valued by physicians in the late 19th century. Indeed, lobeline **1** was known as a powerful respiratory stimulant.[94] This important property has been explained by the activation of the carotid and aortic body chemoreceptors[95] at therapeutic doses. Larger doses may induce a cough. Lobeline **1** relaxes the tissues and favours expectoration when a large quantity of mucus is secreted. The potent action of this alkaloid on the respiratory system has therefore been used with success in numerous applications. Chronic pneumonia, asthma, bronchitis and laryngitis are all conditions in which lobeline **1** has been of great service.[5] It seems that the treatment of asthma reported by Thomson and Culter (see Section 2) constitutes the first modern therapeutic application.

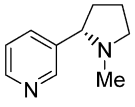
Lobeline **1** has also been advantageous for the treatment of victims who have been electrocuted or asphyxiated by toxic gases.[96] Moreover, it was useful in the case of the paralysis of respiratory centres after drug poisoning with alcohol, soporifics or morphine or after narcosis.[97] Lastly, **1** has also been used to treat asphyxia in newborn infants.[98]

Due to its unpredictable effects and the development of more effective agents, however, its use has become obsolete. Nevertheless, lobeline **1** is still officially listed in several pharmacopoeias.

5.1.2. Drug abuse. Lobeline **1** has been reported as a useful agent to treat dependency on drugs such as cocaine, amphetamine, caffeine, phenylcycline, opiates, barbiturates, benzodiazepines, cannabinoids, hallucinogens, alcohol and, especially, nicotine **156** (Fig. 12).[99] The most promising area in this field is the ability of **1** to be a substitute of nicotine **156**. Lobeline **1** produces several physiological effects similar to those produced by nicotine **156**. The use of **1** as a smoking deterrent was reported in 1936,[100] but several later studies led to a dispute between positive[101] and negative[102] reports. Numerous countries have sold drugs containing lobeline **1** such as: Nicoban™, Bantron™, CigArest™, NicFit™ and Smoker's Choice™. In 1993, however, the FDA claimed the inefficacy of these products and removed them from the market.

Nevertheless, a renewed interest in the treatment of smoking cessation with drugs containing **1** has resurfaced with the clinical experiments of Schneider and co-workers.[103] Their studies have shown that its inability to be an effective agent for smoking cessation was essentially due to its weak bioavailability. In a recent patent,[104] studies on a new formulation of drugs to deliver an effective amount of **1** to sublingual mucosa have been reported. In addition, the remarkable studies of Dwoskin and Crooks[105] reported the potential of **1** as a pharmacotherapy for the abuse of psychostimulants (e.g., amphetamine and methamphetamine). Thus, the development of new drugs providing lobeline **1** or its analogues with better availability is under investigation.

5.1.3. Lobeline as a treatment for CNS disorders. The most promising bioactivity of lobeline **1** concerns its use as an agent in the treatment of CNS diseases and pathologies. The effect of **1** on the CNS was extensively exploited by the native Americans, who smoked the dried leaves of *Lobelia* plants. Several studies have shown that **1** improves memory[106] in rodents, probably due to its involvement in cholinergic mechanisms of neurotransmission (vide infra).



(-)-nicotine **156**

Figure 12.

This pharmacological profile may be of great importance in the treatment of learning disorders like Alzheimer's disease (AD), the most common cause of dementia in the elderly. Indeed, two years ago, the cholinergic hypothesis was claimed to explain the cognitive symptoms of AD.[107] Thus, the development of new agents that selectively interact with cholinergic receptors could offer a new opportunity for AD therapy. AD is characterised by a gradual and progressive decline in intellectual function and behavioural abnormalities.

Lobeline **1** also appears to improve the performance of rats in sustained attention tasks,[108] and it could, therefore, be useful for the treatment of attention deficit hyperactivity disorder. This disorder afflicts children as well as adults and is characterised by inattention, restlessness, impulsiveness and hyperactivity. The agents acting via nicotinic acetylcholine receptors (nAChR) have not been extensively investigated as anxiolytic agents. Lobeline **1** has, however, been examined for its ability to decrease anxiety without cognitive impairment and without contributing to a depressive state.[109]

5.1.4. Other biological activities. In the 19th century, physicians used the emetic properties of lobeline **1** in cases of alimentary intoxication. Indeed, **1** causes direct central stimulation of the vomiting centre in the CNS and irritation of the gastrointestinal system. Lobeline **1** has many physiological effects often similar to those produced by nicotine **156** and, by stimulation of the autonomic ganglia, **1** produces sympathetic and parasympathetic effects.[110]

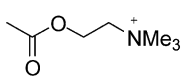
Sympathetic effects result in an increase in blood pressure (hypertension) and tachycardia. Bradycardia and hypotension have also been reported, however, in rats anesthetised with urethane and pentobarbital.[111] Parasympathetic effects, manifested in the gastrointestinal system, result in an increase in salivation and diarrhea.

After treatment with lobeline **1**, a slight suppression of appetite has been reported and its use of has therefore been suggested for the treatment of eating disorders such as obesity.[112]

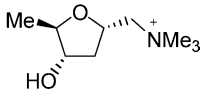
In a recent patent, Yerka described a method for increasing hydration and lubrication of lacrimal,[113] vaginal[114] and cervical tissues by the administration of lobeline **1**. The invention is useful for treating dry eye disease and corneal injury, as well as vaginal dryness and vulvar pain.

5.2. Mode of action

The neurotransmitter[115] acetylcholine **157** acts on acetylcholine receptors (AChR), which can be divided into muscarinic (mAChR) and nicotinic (nAChR) receptors based, on the agonist activities of the alkaloids, muscarine **158** and nicotine **156** (Fig. 13). nAChR are members of the superfamily of ligand-gated ion channels including γ-aminobutyric acid ($GABA_A$), *N*-methyl-D-aspartate (NMDA), serotonin ($5\text{-}HT_3$) and glycine receptors.[116] The nAChR have been the focus of intense research in recent years,[117] due to their involvement in cognitive, motor and behavioural systems.[118] Thus, modulation of cholinergic



acetylcholine **157**



L-muscarine **158**

Figure 13.

transmissions could be useful for the therapy of several CNS disorders, like Parkinson's disease and AD. nAChR are found on skeletal muscles at the neuromuscular junction and at numerous sites in the central and peripheral nervous system. Neuronal nAChR have a pentameric structure composed of α (α_2–α_9) and β (β_2–β_4) subunits with a considerable array of combinations.[119] Each of which displays specific physiological processes when a ligand acts on it. Thus, multiple populations of nAChR exist, but, in the brain, the $\alpha_4\beta_2$ and α_7 subunits are prevalent. Lobeline **1** displays a very low affinity for the α_7 subtype ($K_i >$ 10,000 nM) but a high affinity for $\alpha_4\beta_2$ ($K_i = 1$–5 nM).[120] A similar profile is observed for nicotine **156**.

Although the determination of the nAChR pharmacophore is an exceedingly difficult task, some of the pharmacophoric elements are generally accepted[121,122]:

- A donor of hydrogen bonds, like a quaternised nitrogen atom or a tertiary amine protonated at physiological pH.
- An acceptor of hydrogen bonds, like a pyridine or a carbonyl function.
- A distance between the donor and acceptor elements of 4.6–6.3 Å, according to the binding models studied.

In their pioneering work, Beers and Reich[123] considered that the structure of **1** could adopt a conformation that is in agreement with the nAChR pharmacophore. According to Barlow and Johnson's[124] observations, however, **1** possesses two potential hydrogen bond acceptors. Indeed, the phenyl-2-ketoethyl and phenyl-2-hydroxyethyl groups could bind through hydrogen bonds to the receptors, even though the keto moiety has been reported to be a better hydrogen bond acceptor.[125]

Many similar effects for nicotine **156** and lobeline **1**, like tachycardia and hypertension,[126] anxiolytic activity[127] and improvement of learning and memory,[128] have been recorded. Contrary to **156**, however, lobeline **1** does not increase locomotor activity[129] or produce conditioned place preference.[130] In addition, and again in contrast with nicotine **156**, chronic treatment with lobeline **1** does not increase the number of nicotinic receptors in mouse brain regions.[131]

Thus, **1** possesses no obvious structural resemblance to nicotine and is currently considered as an agonist,[115] an antagonist,[132] as well as a mixed agonist/antagonist,[133] at nicotinic receptors. These properties have been attributed to its particular structure, which could possess an agonist part (the keto portion) and an antagonist part (the hydroxyl portion).[124]

Nicotine **156** and lobeline **1** evoked dopamine (DA) release from rat striatial slices.[134] Unlike **156**, however, lobeline-induced DA release was calcium-independent and was

insensitive to mecamylamine, a non-competitive nicotinic receptor antagonist that blocks the ion channel of the receptor.[115] In addition, at weak concentrations that had no effect alone, lobeline **1** blocked nicotine-evoked DA release, indicating, in this case, that it acted as an antagonist at nAChR.[135] All of this work suggests that **156** and **1** act on nAChR via a non-common CNS mechanism. Thus, the pharmacological effect of **1** can either be mediated by minor subset populations of nAChR or through a non-nicotinic mechanism. It is also possible that **1** causes an allosteric effect at the nAChR, leading to a modification of its properties. In a recent paper, Dwoskin and Crooks[132] have proposed a novel mechanism of action for **1**, namely that it inhibited DA uptake into rat striatial synaptic vesicles by acting at the tetrabenzine binding site on vesicular monoamine transporter-2 (VMAT2). The induced inhibition of synaptic vesicular DA transport modified the concentration of DA in the cytosol and vesicles and, consequently, altered dopaminergic neurotransmission. The concentration of dopamine in the synaptic cleft and the activation of postsynaptic dopamine receptors diminished. Thus, by acting as an indirect antagonist of DA receptors, lobeline **1** antagonises the effect of psychostimulants (amphetamine and methamphetamine) which produce their effects, in part, by activation of the dopaminergic system. In this context, **1** and its analogues could represent a novel class of therapeutic agents with a great potential for the treatment of psychostimulant abuse. Thus, these recent studies suggest that **1** acts as an antagonist at the nAChR on the pre-synaptic dopaminergic nerve terminal and/or as an inhibitor at the tetrabenzine site on VMAT2 on synaptic vesicle membranes.

5.3. Structure–affinity relationships

In order to assess the contribution of the different structural components of the natural molecule **1** in binding to nAChR receptors, a wide range of lobeline-like structures **14**, **16**, **60**, **159–190** have been screened (Table 1).[136] Some structurally simplified analogues of lobeline with single arms have been synthesised to determine the usefulness of the phenyl-2-ketoethyl and phenyl-2-hydroxyethyl part. In every case, removal of one of the side chains resulted in a dramatic decrease in affinity, for nAChR. In addition, the absence of the piperidine ring in **175** resulted in a marked reduction in affinity in comparison with **60**. These data suggest the important contribution of both arms and the piperidine ring in the interaction with the receptors. Total deoxygenation of either side chain in **176**, **179**, **180** abolished affinity, suggesting an interaction of at least one oxygen with the receptor. Indeed, compounds **181** to **186**, where only one oxygen function (ketone or hydroxyl) was present, showed an enhanced affinity, in comparison with the totally deoxygenated compounds **177**, **179**, **180**. All of these affinity values are, however, modest in relation to those of lobeline **1**.

Thus, if the presence of one oxygen function is sufficient for binding, the asymmetrical derivatives **1**, **188** and **189** seem to be optimal. Surprisingly, lobelanine **14** and lobelanidine **16** display modest affinity for nAChR, although both oxygen functions are present. These results suggest that the presence of both oxygens is not a sufficient condition for high affinity binding. Each of the ketone and hydroxyl functions seemed to play an important role in receptor recognition. Protection of the hydroxyl group as its tosylate derivative **188** resulted in the conservation of affinity, but this result is unclear at the moment. Replacement of the hydroxyl group by a chloro function (**189**) retained the affinity of lobeline **1**. The potential of halogen atoms (Cl or F) is now well established in medicinal chemistry, due to their ability to participate in hydrogen bonding. Researchers have also envisaged the formation of the quaternary amine by intramolecular cyclisation, however, under the conditions of the binding assay. In order to study this possibility, the *N*-methylammonium salt **190** was prepared, but it displayed a 500-fold drop in affinity binding relative to lobeline **1**.

In their studies, Glennon and co-workers[136a] measured the analgesic activity of **180**, **183**, **187** and **1**, which displayed a broad range of affinities (Table 2). The analgesic effect produced was comparable for the four compounds. In the light of these results, it appears that the oxygen atoms are not required for the activity and that there was no relationship between the binding affinity for the $\alpha_4\beta_2$ receptor and the analgesic potency.

Terry's group[136b] also evaluated **1**, **159** and **161** for their mAChR affinity and for their ability to inhibit acetylcholinesterase (AChE) (Table 3). Although **1**, **159** and **161** display a lower affinity for mAChR, in comparison with nAChR, they are not inactive.

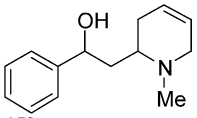
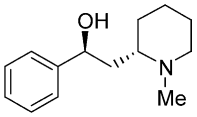
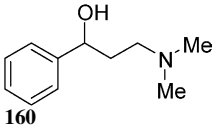
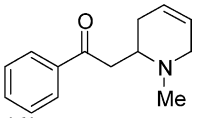
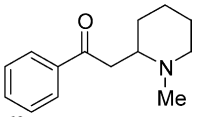
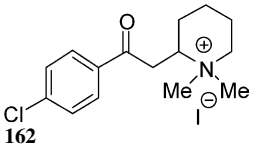
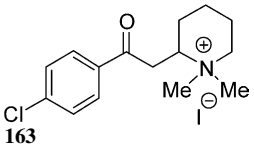
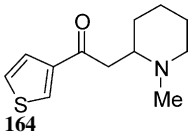
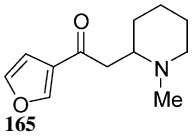
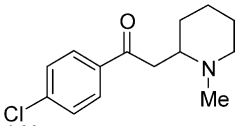
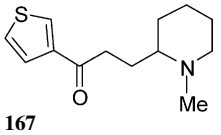
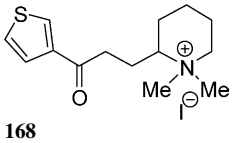
In the study of AChEI activity, lobeline **1** was found to be the more potent, although the standard for comparison (physostigmine, $IC_{50}=0.25$ μM) was 300-fold more potent. The authors concluded that the complex pharmacological activities of **1** could be mediated via nAChR, mAChR or other ion channel receptors and by inhibition of the enzyme AChE.

The inhibition of [^{3}H] DA uptake into the dopaminergic presynaptic terminal (inhibition of dopamine transporter 'DAT' activity) by several compounds was also evaluated by Crooks and Dwoskin[136c] (Table 4). Surprisingly, the inhibition of DAT was inversely proportional to the affinity value at nAChR. Deoxygenated compounds that displayed low affinity for nAChR interacted selectively with DAT, suggesting that oxygen atoms are not required for an optimal inhibition. This high selectivity for DAT interaction might be useful for the development of a novel class of therapeutic agents for the treatment of psychostimulant abuse.

6. Conclusion

Due to the extension of life expectancy in industrial countries and the prevalence of neurological disorders like Alzheimer's disease or Parkinson's disease, the discovery of effective agents for the treatment of these pathologies is one of the major challenges in medicine for the future. Biological and chemical studies of *Lobelia inflata* alkaloids and, in particular, (−)-lobeline **1**, have increased over the last few years. Lobeline **1** might serve as a useful lead for

Table 1. nAChR receptor affinity of various lobeline analogues

Chemical structure	nAChR receptor affinity K_i, nM, radioligand	Reference
 **159**	15 000, [^{3}H]cytisine	136b
 **24**	$>$10 000, [^{3}H]nicotine	136a
 **160**	$>$10 000, [^{3}H]nicotine	136a
 **161**	5400, [^{3}H]cytisine	136b
 **60**	2200, [^{3}H]nicotine $>$100 000, [^{3}H]cytisine	136a 136d
 **162**	$>$100 000, [^{3}H]cytisine	136d
 **163**	$>$100 000, [^{3}H]cytisine	136d
 **164**	10 400, [^{3}H]cytisine	136d
 **165**	5990, [^{3}H]cytisine	136d
 **166**	$>$100 000, [^{3}H]cytisine	136d
 **167**	24 600, [^{3}H]cytisine	136d
 **168**	29 000, [^{3}H]cytisine	136d

(*continued on next page*)

Table 1 (*continued*)

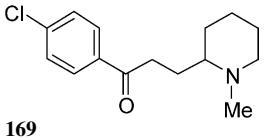
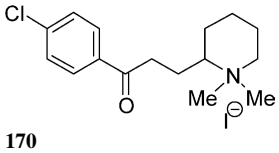
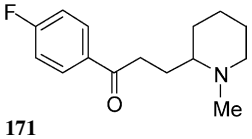
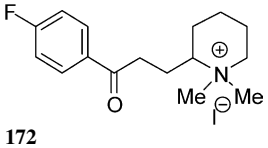
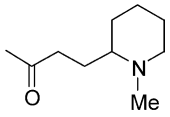
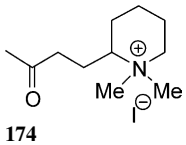
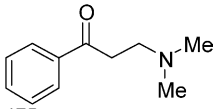
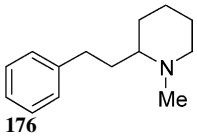
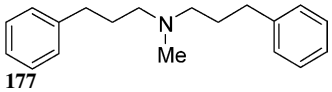
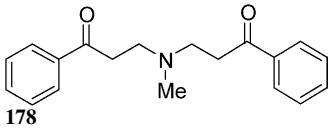
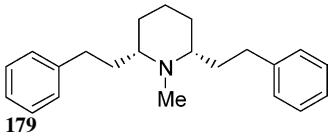
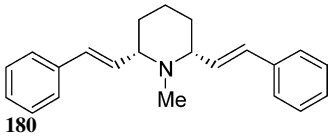
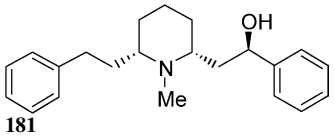
Chemical structure	nAChR receptor affinity K_i, nM, radioligand	Reference
 **169**	> 100 000, [^{3}H]cytisine	136d
 **170**	62 600, [^{3}H]cytisine	136d
 **171**	23 400, [^{3}H]cytisine	136d
 **172**	> 100 000, [^{3}H]cytisine	136d
 **173**	3700, [^{3}H]cytisine	136d
 **174**	1800, [^{3}H]cytisine	136d
 **175**	5900, [^{3}H]nicotine	136a
 **176**	2490, [^{3}H]nicotine	136a
 **177**	> 10 000, [^{3}H]nicotine	136a
 **178**	> 10 000, [^{3}H]nicotine	136a
 **179**	> 10 000, [^{3}H]nicotine 14 300, [^{3}H]nicotine	136a 136c
 **180**	> 10 000, [^{3}H]nicotine	136c
 **181**	160, [^{3}H]nicotine 340, [^{3}H]nicotine	136c 136a

Table 1 (*continued*)

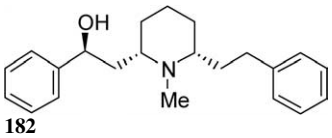
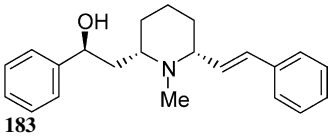
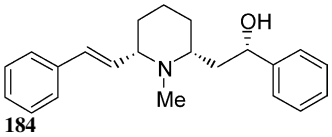
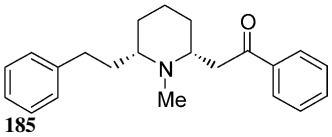
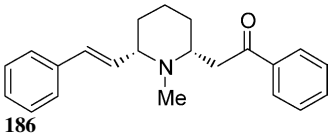
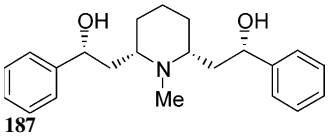
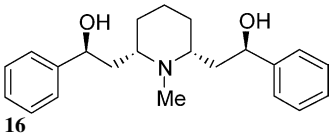
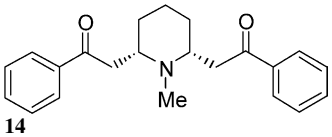
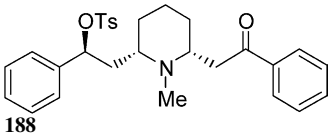
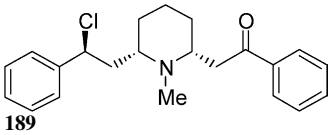
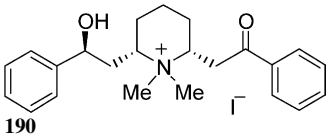
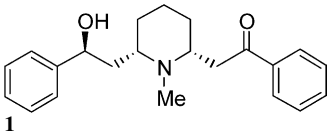
Chemical structure	nAChR receptor affinity K_i, nM, radioligand	Reference
 **182**	235, [^{3}H]nicotine	136a
 **183**	1315, [^{3}H]nicotine	136a
 **184**	4200, [^{3}H]nicotine	136c
 **185**	110, [^{3}H]nicotine	136a
 **186**	1085, [^{3}H]nicotine 130, [^{3}H]nicotine	136a 136c
 **187**	930, [^{3}H]nicotine	136c
 **16**	300, [^{3}H]nicotine	136a
 **14**	7800, [^{3}H]nicotine 11 000, [^{3}H]nicotine	136a 136c
 **188**	4.1, [^{3}H]nicotine	136c
 **189**	5, [^{3}H]nicotine	136a
 **190**	2035, [^{3}H]nicotine	136a
 **1**	4.3, [^{3}H]nicotine 4, [^{3}H]nicotine 16, [^{3}H]nicotine	136c 136a 136b

Table 2. Analgesic activity of **180**, **183**, **187** and **1**

Compound	Analgesic effect ED_{50} (μmol)/animal
1	23
180	27
183	32
187	38

Table 3. mAChR receptor affinity and inhibition of acetylcholinesterase for **1**, **159** and **161**

Compound	mAChR receptor affinity K_i, μmol, radioligand	AChRI activity IC_{50} (μmol)
1	37	76
159	55	5000
161	16	230

Table 4. Inhibition of DAT activity

Compound	Inhibition of DAT activity [^{3}H]-dopamine uptake, K_i (μmol)
1	45
14	25
179	3
180	0.8
181	8.9
184	1.3
186	3
187	54
188	39

the developement of new therapeutic agents that act on nAChR in a novel fashion. In addition, the non-nAChR-mediated pharmacological effects of lobeline **1** might provide new opportunities for a better understanding of neuronal disorders. Chemical studies in this area are probably at this prebiotic state.

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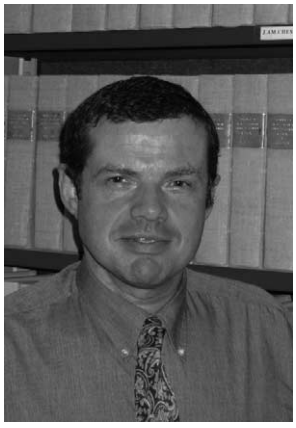
Biographical sketch



Jacques Lebreton was born in Guérande (France) in 1960. He received his PhD degree (1986) from the University of Paris XI-Orsay under the supervision of Professor Eric Brown (Le Mans). His thesis work included the total synthesis of C-nor D-homosteroids. In 1986, he started his first post-doctoral fellowship with Professor James A. Marshall at the University of South Carolina working on the [2,3]-Wittig rearrangement and its application in total synthesis. Following a second post-doctoral fellowship with Professor Robert E. Ireland at the University of Virginia working on the total synthesis of monensine, he joined in 1990 the laboratories of CIBA-GEIGY (Novartis) in Basle, where he worked in Dr. Alain De Mesmaeker's group in the area of antisense oligonucleotides. In 1994, he joined the CNRS and spent a few years in the group of Dr. Jean Villéras (UMR-CNRS 6513, Nantes) exposed to organometallic chemistry. In 1998, he was promoted to Professor at the University of Nantes. His major research interests are organometallic chemistry, synthesis of bioactive molecules (HIV, cancer and central nervous system diseases) and synthesis of labelled molecules to study biological processes.

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