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Recent advances in the synthesis of nicotine and its derivatives

Florence F. Wagner and Daniel L. Comins*

Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204, USA

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1. Introduction

(*S*)-Nicotine (**1**) is present together with a number of minor alkaloids in tobacco and a wide variety of other plants. Dried leaves of the tobacco plants *Nicotiana rustica* and *N. tabacum* contain as much as 2–8% of (*S*)-nicotine.[1] Interest in the actions of nicotine has remained high over the past century, primarily because of the widespread exposure of people to nicotine through recreational use of tobacco products. First isolated in 1828,[2] the correct structure of nicotine was not proposed until 1883 by Pinner.[3] Pictet and Rotschy are accredited with first synthesizing the alkaloid in 1904.[4] Whidby and Seeman reported in 1976 that the preferred (>90%) configuration of the *N*-methyl group in nicotine is (*R*) under a variety of experimental conditions.[5] In fresh *N. tabacum*, the alkaloid mixture typically consists of 93% (*S*)-nicotine (**1**), 3.9% (*S*)-anatabine (**2**), 2.4% (*S*)-nornicotine (**3**), and 0.5% (*S*)-anabasine (**4**) (Fig. 1).[6]

A large scale application of nicotine was its use as an insecticide, as approximately 2800 tons of (*S*)-nicotine were used as a crop protectant per year.[7] Aqueous solutions of nicotine sulfate are still used throughout the world as insecticides.[8] More recently, nicotine has attracted much attention because of its potential pharmacological effects on central nervous system (CNS) diseases. In particular, (*S*)-nicotine may have beneficial effects in the treatment of Parkinson's disease (PD), Alzheimer's disease (AD), Tourette's syndrome,

* Corresponding author. E-mail: daniel_comins@ncsu.edu

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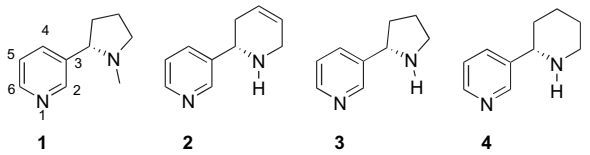


Figure 1. Alkaloid mixture in fresh *Nicotiana tabacum*.

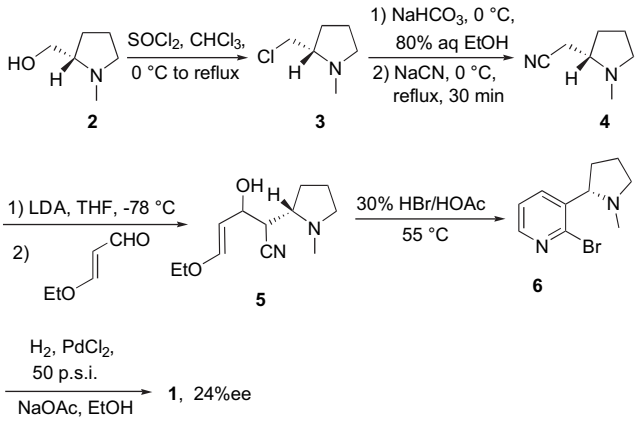
schizophrenia, attention-deficit hyperactivity disorder (ADHD), smoking cessation, epilepsy, and depression.[9] An estimated 4.5 million Americans have AD. The number of Americans diagnosed with AD has more than doubled since 1980 and still continues to grow. By 2050, the number of individuals with AD could range from 11.3 million to 16 million.[10] PD affects over 1 million people in the US alone. One person in 200 will get PD during their lifetime; this risk increases with age since one in every 100 persons over 60 years of age has Parkinson's. Both neurodegenerative disorders have emerged as a major public health concern as a consequence of the post World War II baby boom and the changes in the global population age profile.

Neuronal nicotinic acetylcholine receptors (nAChRs) exert an important modulatory influence in the CNS. This action represents an attractive therapeutic opportunity for CNS disorders. Nicotine, the prototypical agonist of nAChRs, unfortunately activates all subtypes of nAChRs. Moreover, nicotine's well-known potential for abuse and its toxic effects on the gastro intestinal and cardio vascular systems prevents its use as a drug for CNS disorders. Researchers are busy synthesizing analogues with nAChR subtype selectivity. The goal is to develop drugs that have medicinal benefits for the safe and effective treatment of CNS disorders without adverse side-effects.[11] In addition to some historical background, this review covers the literature over the last 10 years (1997–2006) on the synthetic approaches to nicotine and nicotine analogues.

2. Progress toward the enantioselective syntheses of nicotine and nornicotine

Since the first synthesis by Pictet in 1904,[5] a plethora of clever syntheses of nicotine has been accomplished. Most of the early literature (1969–1996) on the preparation of nicotine and its analogues describes the use of a pyridine derivative as starting material onto which the pyrrolidine ring was constructed.[12]

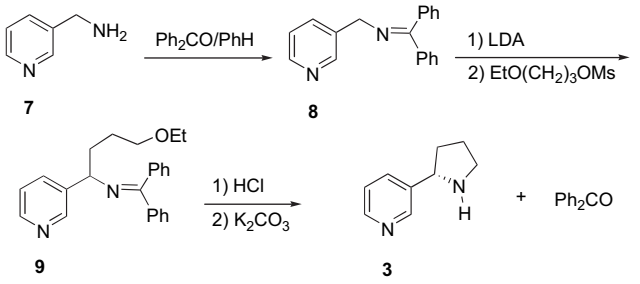
Chavdarian and co-workers reported in 1982 the first synthesis of optically active nicotine.[13] This synthesis was unique since an optically active starting material was used as the pyrrolidine source onto which the pyridine ring was built (Scheme 1). The synthesis starts with L-proline, which is converted to amino alcohol **2**. Sequential treatment of **2** with thionyl chloride and sodium cyanide afforded **4** via chloride **3**. Addition of the lithium anion of **4** with 3-ethoxyacrolein led to **5**, which underwent cyclization upon treatment with a mixture of HBr/HOAc to give 2-bromonicotine (**6**). Removal of the halogen by hydrogenolysis completed the synthesis of nicotine (**1**); however, the product was obtained in only 24% ee.



Scheme 1. First synthesis of optically active nicotine by Chavdarian.

As studies on the affinity of nicotine and its derivatives for nAChRs progressed, it was generalized that the affinity of the (*S*) enantiomer was 10–100 times higher than that of the (*R*) enantiomer.[14] Synthetic efforts were then aimed toward enantioselective syntheses, or the isolation of both enantiomers through resolution.

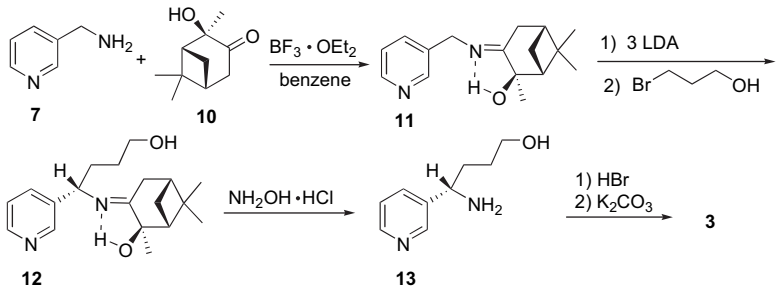
In 1996, Crooks and Deo developed a simple route to nornicotine (**3**).[15] Reaction of 3-(aminomethyl)pyridine (**7**) with benzophenone provides the imine **8** (Scheme 2). Deprotonation of the Schiff's base with LDA, followed by addition of methanesulfonic acid 3-ethoxypropyl ester, affords α-alkylated imine **9**. Hydrolysis and basification to form the pyrrolidine ring complete the synthesis of **3**. The Crooks group followed up in 1999 with an asymmetric version for the synthesis of (*S*)- and (*R*)-nornicotine (**3**) with moderately high optical purity via alkylation of a chiral 2-hydroxy-3-pinanone ketimine template (Scheme 3).[16]



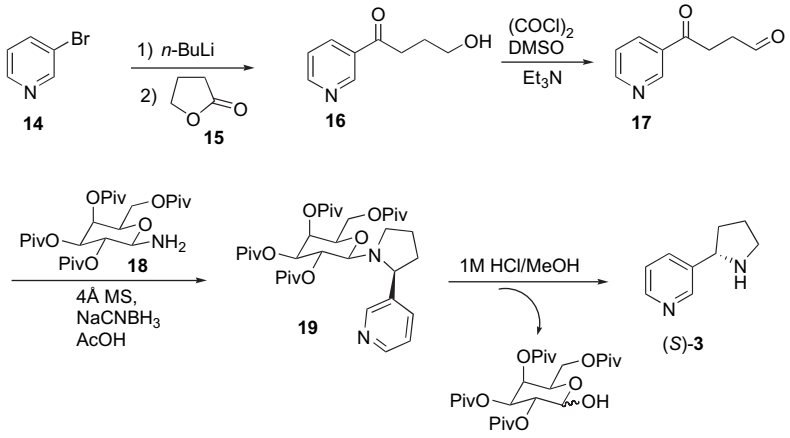
Scheme 2. Crooks' racemic synthesis of nornicotine.

In 1999, Loh and co-workers reported a four-step stereoselective synthesis of (*S*)-nornicotine.[17] Hydroxyketone **16** was obtained by lithium-halogen exchange of 3-bromopyridine (**14**) with *n*-BuLi followed by treatment with lactone **15** (Scheme 4). A Swern oxidation gave aldehyde **17**. The diastereoselective reductive amino cyclization with 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosylamine (**18**) afforded compound **19**. The chiral auxiliary was then cleaved by acidic hydrolysis to complete the synthesis of (*S*)-nornicotine with an optical purity greater than 98%.

Until recently, the most economical way to obtain the desired enantiomer of nicotine and its analogues was via the resolution of a racemic mixture. In 1982, Jacob reported



Scheme 3. Crooks' enantioselective synthesis of nornicotine.



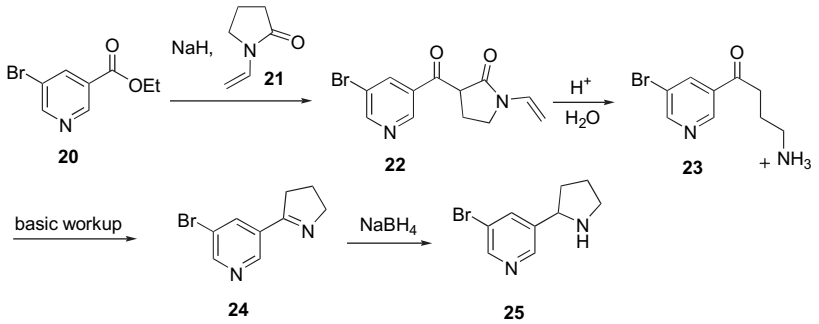
Scheme 4. Loh's synthesis of (*S*)-nornicotine using 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosylamine as a chiral auxiliary.

the preparation of 5-bromonornicotine (**25**) and its subsequent resolution to get both isomers in high enantiomeric purity (Scheme 5).[18a] The enolate of *N*-vinylpyrrolidinone[18b] (**21**) was condensed with ethyl 5-bromonicotinate (**20**). The hydrolysis of the enamine, decarboxylation, and cyclization affords 5-bromomyosmine (**24**). Reduction with $NaBH_4$ gave racemic 5-bromonornicotine (**25**), which was converted to its ammonium salt with enantiomerically pure organic acids. After several recrystallizations and conversion to the free base, each enantiomer of **25** was obtained with an optical purity greater than 95%.

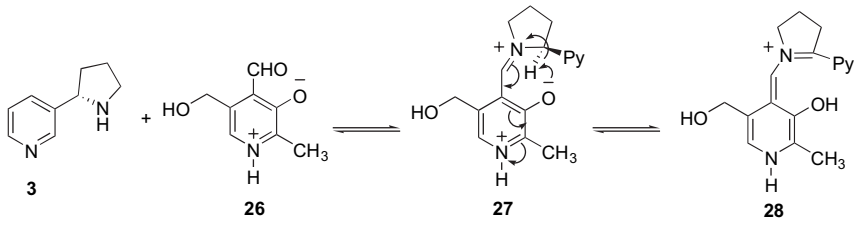
Seeman and co-workers followed with the resolution of (±) nornicotine.[19] The racemic mixture was acylated with optically pure (−)-menthyl chloroformate. The diastereomers were separated and the carbamate was removed using an acid-catalyzed procedure. Each enantiomer was obtained in optical purity greater than 99%.

For practical purpose, a racemic mixture of nicotine can be of use, and racemizations of natural material were developed. In 1996, Jacob reported the racemization of nornicotine using a pyridoxal catalyst (Scheme 6).[20]

In 1982, Bowman and Tsujino separately reported two convenient methods for the racemization of (*S*)-nicotine. Bowman treated (−)-(**1**) with NaH in *p*-xylene to give (±)-(**1**).[21] Tsujino observed that (*S*)-nicotine was completely racemized by refluxing with a catalytic amount of Me_3COK.[22]



Scheme 5. Synthesis of 5-bromonornicotine by Jacob.

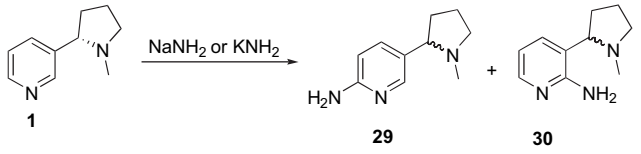


Scheme 6. Racemization of nornicotine using a pyridoxal catalyst.

3. Methodologies for the synthesis of substituted nicotines

Nicotine and its analogues have been a synthetic challenge to the chemist. Few examples of efficient enantioselective syntheses of nicotine and substituted nicotines have been reported. The selective chemical functionalization of nicotine at the pyridine or on the pyrrolidine ring has been difficult to control.[23] More specifically, formation or preservation of the chiral pyrrolidine ring has stimulated a great deal of synthetic activity in recent years. As previously stated, individual enantiomers were usually obtained by resolution via the crystallization of diastereomeric salts.[24] In an attempt to avoid the use of a resolution to obtain enantiopure analogues, chemists have been investigating the substitution reactions of natural nicotine.

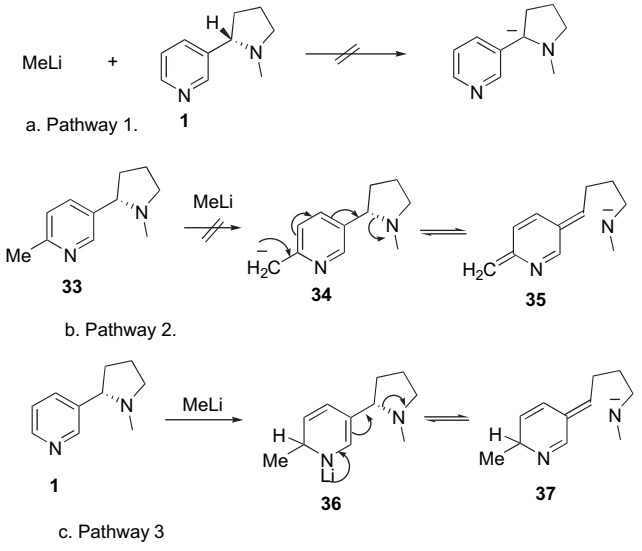
Early work on the reactivity of nicotine showed that the chiral pyrrolidine ring is easily racemized. The reactivity of (*S*)-nicotine toward amide bases was explored by Tschitschibabin and Kirssanov in 1924 (Scheme 7).[25] A mixture of 6- and 2-aminonicotines (**29** and **30**) was prepared by treatment with sodium or potassium amide. Under the reaction conditions, the pyrrolidine was racemized. This early work demonstrated that the Chichibabin reaction, of enormous importance in pyridine chemistry, could not be applied to the enantioselective preparation of nicotine derivatives.



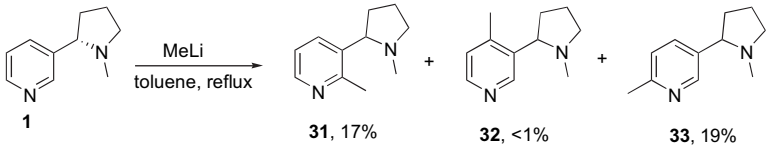
Scheme 7. Reaction of natural nicotine with sodium or potassium amide.

The addition of alkyllithiums to nicotine has been used to prepare derivatives.[26–28] In 1981, Seeman and co-workers studied the alkyllithium methylation of nicotine. The reaction of **1** with 2 equiv of methyllithium in refluxing toluene afforded **31**, **32**, and **33** in 17%, <1%, and 19% yields, respectively, with 32% of recovered nicotine (Scheme 8). In 1983, they followed up with another report discussing possible pathways for the loss of optical purity observed during the methyllithium reaction that could occur according to three different pathways (Scheme 9).[27] It was shown that the starting material does not racemize under the reaction conditions (Scheme 9, pathway 1) as the recovered nicotine was nearly optically pure. The methylated nicotine could also racemize (Scheme 9, pathway 2), but the treatment of methylnicotine of high optical purity with methyllithium (or other alkyl- or aryl-lithiums) did not lead to racemization.[28] It is noteworthy that **33** is also optically stable in the presence of LDA. It was postulated that an equilibrium might exist between intermediate **36** and ring-opened intermediate **37** leading to racemization (Scheme 9, pathway 3). Other alkyllithium reagents, i.e., Et, *i*-Pr, *n*-Bu, sec-Bu, *t*-Bu, and vinyl, add regiospecifically to nicotine to provide 6-substituted nicotines of low optical purity.[28]

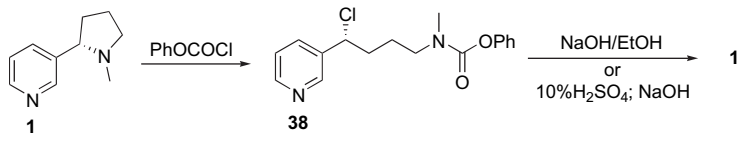
The radical alkylation and hydroxyalkylation of nicotine have been studied.[23a,29] In general, yields are low and a mixture of isomers is produced with the 6-alkylnicotines predominating. The radical substitution method appears to proceed without racemization. The reaction of nucleophiles



Scheme 9. Proposed mechanisms for the loss of optical purity in the methylation of nicotine with methyllithium.



Scheme 8. Organometallic methylation of nicotine.

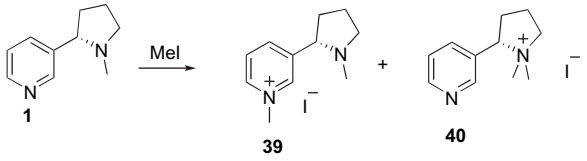


Scheme 10. Pyrrolidine ring-opening with phenyl chloroformate.

with *N*-acylpyridinium salts has proven to be a valuable method for the synthesis of substituted pyridines.[30,31] The *N*-acyl salts are generally formed in situ by the addition of a chloroformate to a solution of the pyridine. Addition of a nucleophile, i.e., an organometallic, gives a dihydropyridine intermediate, which is easily oxidized to the substituted pyridine.

In 1999, Cosford and Bleicher demonstrated that the pyrrolidine would ring-open with inversion of configuration upon reaction with chloroformates, so the pyrrolidine nitrogen prevented useful pyridinium salt formation. They found that chloride **38** would subsequently convert back to **1** on treatment with base with net retention of configuration (Scheme 10).[32]

Selective N-alkylation can also be difficult as nicotine's two nitrogen atoms are nucleophilic and can compete for electrophiles.[23b] When treating nicotine with iodomethane, a 2.5:1 ratio of monoalkylated products **39** and **40** is observed (Scheme 11);[33] however, larger alkyl halides are reported to selectively alkylate nicotine at the pyridine nitrogen.[23b]



Scheme 11. Alkylation of nicotine with iodomethane.

The examples above demonstrated that regioselective chemical functionalization of the pyridine ring of nicotine was difficult to achieve using known pyridine substitution chemistry.[23,33] For many years, the development of enantioselective preparations of synthetic nicotine derivatives using nicotine as a starting material was hindered due to this deficiency.

4. New approaches to the synthesis of nicotine and analogues

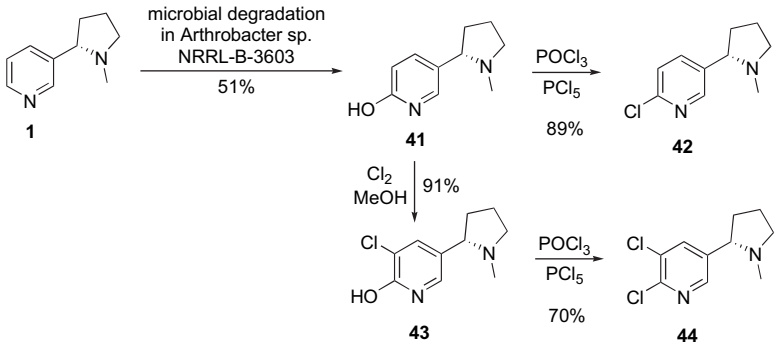
The enantioselective formation of nicotine and substituted nicotines was recently marked by three milestones: (1) the biotransformation of (*S*)-nicotine by Roduit, (2) the enantioselective syntheses of tobacco alkaloids reported by Lebreton and later by Helmchen, and (3) the enantioselective preparation of substituted nicotines directly from natural (*S*)-nicotine by Comins and co-workers. These and other recent advances in nicotine chemistry are described below.

4.1. Biotransformation of (*S*)-nicotine

Roduit and co-workers successfully used (*S*)-nicotine for the regiospecific synthesis of enantiopure analogues. In 1997, they optimized the biotransformation of **1** to (*S*)-6-hydroxynicotine (**41**) using *Arthrobacter oxydans* NRRL-B-3603 as the micro-organism (Scheme 12).[34] Using this method, (*S*)-6-hydroxynicotine was isolated in 51% yield, and up to 30 g/L could be produced. Using known pyridine substitution chemistry, they were able to convert **41** to (*S*)-6-chloronicotine (**42**) and (*S*)-5,6-dichloronicotine (**44**) in good yields with total retention of optical activity.

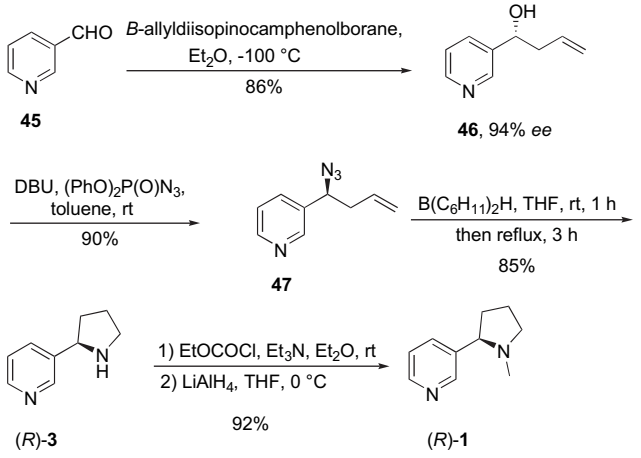
4.2. Enantioselective synthesis of tobacco alkaloids by Lebreton

In 2000, Lebreton and co-workers described a short synthesis of (*R*)-nicotine (Scheme 13).[35] Allylation of 3-pyridinecarboxaldehyde (**45**) with *B*-allyldiisopinocamphenylborane afforded homoallylic alcohol **46** in high optical purity. Chiral azide **47** was obtained from alcohol **46** in one step with inversion of stereochemistry. The pyrrolidine ring was constructed using an intramolecular hydroboration–cycloaddition of chiral azido-olefin **47** to yield (*R*)-nornicotine (**3**), which was methylated via the formation and reduction of an intermediate *N*-ethyl carbamate. (*R*)-Nicotine was



Scheme 12. Roduit's semi-synthetic transformation of (*S*)-nicotine.

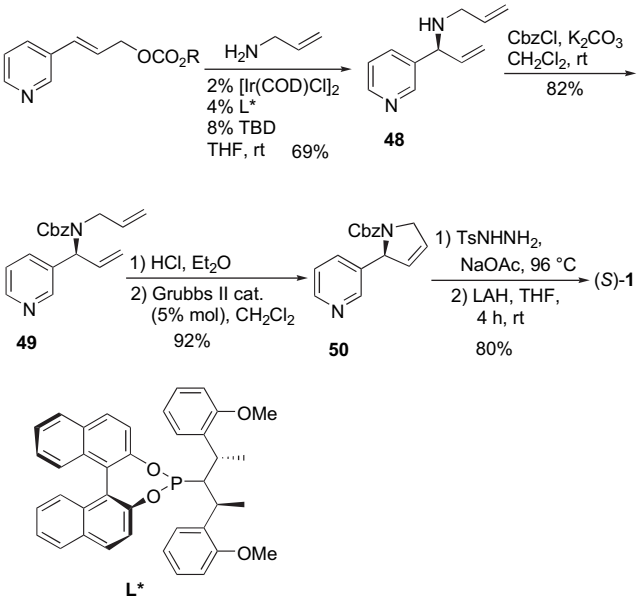
obtained in optical purity greater than 92% and in 60% overall yield.



Scheme 13. Short synthesis of (*R*)-nicotine by Lebreton.

4.3. Enantioselective synthesis of (*R*)- and (*S*)-nicotine by Helmchen

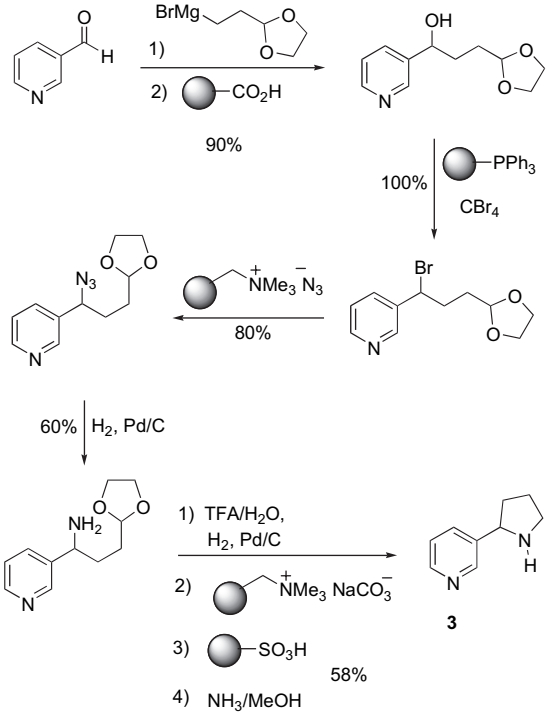
In 2005, Helmchen and co-workers reported the synthesis of nicotine in greater than 99% ee via an asymmetric Ir-catalyzed allylic amination followed by a ring-closing metathesis as shown in Scheme 14.[36] To avoid racemization, which occurs under catalytic hydrogenation, diimide reduction of dehydronicotine **50** was carried out. In the final step, LAH reduction afforded enantiopure (*S*)-**1**. This route was also used to prepare (*R*)-**1** by changing the chiral ligand.



Scheme 14. Enantioselective synthesis of (*S*)-nicotine by Helmchen.

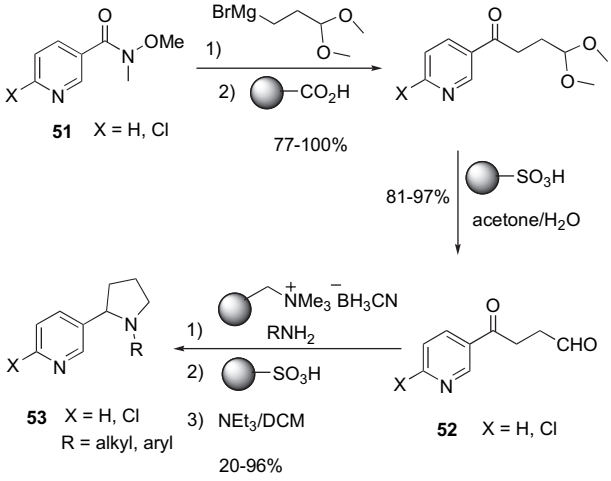
4.4. Ley's synthesis of nornicotine and nicotine derivatives

Ley and co-workers applied the sequential use of solid-supported reagents and scavengers to the synthesis of nornicotine, nicotine, and various functionalized derivatives.[37] Their preparation of racemic nornicotine is depicted in Scheme 15.

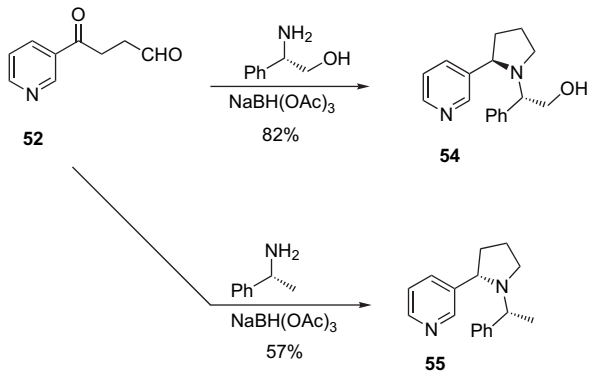


Scheme 15. Ley's synthesis of racemic nornicotine.

The five-step sequence was carried out without conventional work-up procedures or chromatography and provided nornicotine of >90% purity. A second approach to the nicotine structural motif started with the Weinreb amide **51** (Scheme 16). This route provides ready access to racemic pyrrolidine *N*-substituted analogues **53**. The same group explored a modification of their synthetic route, which uses a chiral amine to control the reduction step (Scheme 17). The use of enantiopure 2-phenylglycinol or α-methylbenzylamine with ketoaldehyde **52** and sodium triacetoxyborohydride produced nicotine derivatives **54** and **55**, respectively. These reactions gave essentially a single diastereomer of each compound.



Scheme 16. Synthesis of pyrrolidine *N*-substituted analogues.



Scheme 17. Diastereoselective preparation of **54** and **55**.

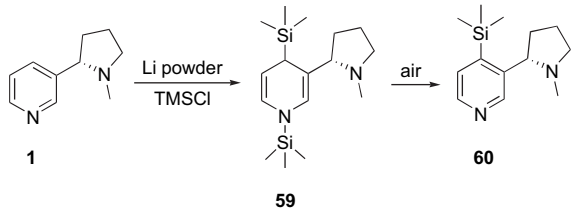
A method for removal of the chiral appendage from the pyrrolidine nitrogen was not reported.

4.5. Comins' C-4 regiospecific substitution of the pyridine ring of nicotine

In 2005, the Comins' group discovered that pivaloyl chloride and nicotine formed an *N*-acylpyridinium salt in situ without competitive pyrrolidine ring-opening. Attack of dialkyl cuprates on the *N*-pivaloylpyridinium salt of nicotine (**56**) led to the exclusive formation of *N*-pivaloyl-1,4-dihydronicotines **57a–h** as single diastereomers in most cases[38] (Scheme 18). Subsequent rearomatization of dihydropyridines **57a–h** with elemental sulfur in refluxing toluene yielded 4-substituted nicotines **58a–h** without loss of optical purity. This work represents the first example of a method for substituting the C-4 position of nicotine in a regiospecific manner. The method is convenient, inexpensive, amenable to scale-up, and allows several different types of substituents to be introduced.

4.6. Comins' reductive disilylation of nicotine

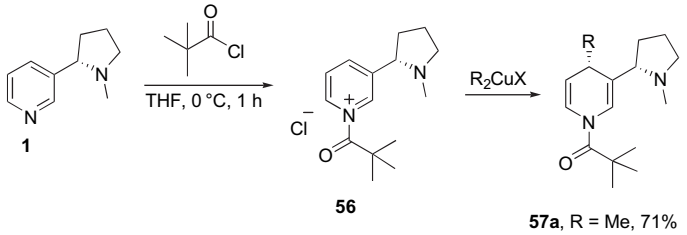
The reductive disilylation of nicotine with lithium powder in the presence of TMSCl affords 1,4-bis(trimethylsilyl)-1,4-dihydronicotine **59** in 95% yield after vacuum distillation (Scheme 19).[39] Several reactions of **59** were investigated and the results are summarized in Scheme 20. This method provides derivatives of nicotine with good to high enantiomeric purity in a regiospecific and inexpensive manner. Various C-5 substituted nicotines (i.e., **64**), known to often have nAChR subtype selectivity, are now available using this two-step procedure. The dihydronicotines of the type **61–63** should also prove to be valuable synthetic building blocks and intermediates to other nicotine analogues.



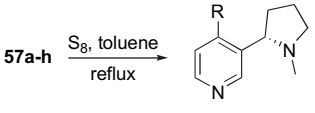
Scheme 19. Reductive disilylation of (*S*)-nicotine.

4.7. Comins' regioselective metalation of the pyridine ring of (*S*)-nicotine

In another approach to nicotine analogues, Comins and coworkers synthesized a variety of novel, as well as known, C-2 and C-6 substituted nicotines directly from (*S*)-nicotine in moderate to high yield using directed lithiation methods.[40] The choice of base was found to play a crucial role in accessing the desired lithiopyridine intermediates in a regioselective manner.

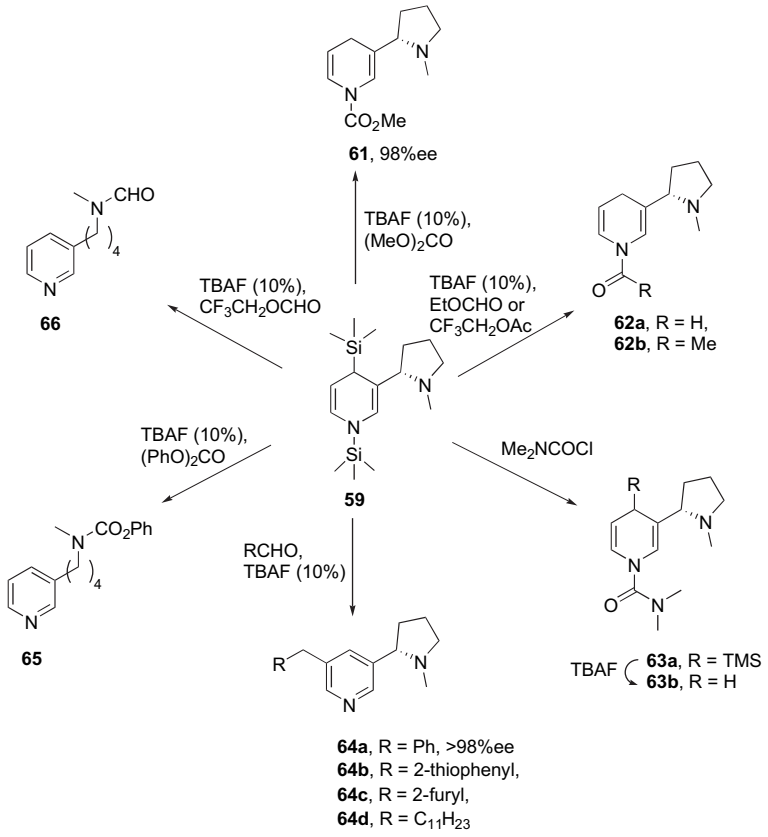


57a, R = Me, 71%
57b, R = Ph, 79%
57c, R = *n*-Bu, 40%
57d, R = Bn, 64%
57e, R = furan, 77%
57f, R = $BnOCH_2$, 76% (52% dr)
57g, R = *t*-$BuOCH_2$, 58%
57h, R = $PhMe_2Si$, 81% (68% dr)



58a, R = Me, 79%
58b, R = Ph, 59%
58c, R = *n*-Bu, 93%
58d, R = Bn, 64%
58e, R = 2-furanyl, 74%
58f, R = $BnOCH_2$, 60%
58g, R = *t*-$BuOCH_2$, 68%
58h, R = $PhMe_2Si$, 80%

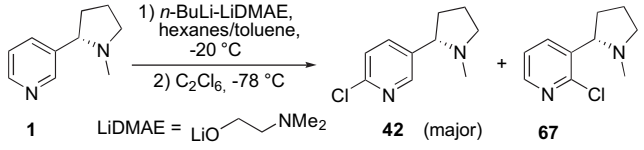
Scheme 18. Synthesis of C-4 substituted nicotine derivatives via an *N*-acylpyridinium salt of (*S*)-nicotine.



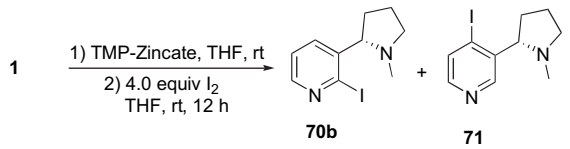
Scheme 20. Transformations of dihydronicotine derivative **59**.

The reaction of nicotine with *n*-BuLi–LiDMAE[41] resulted in selective deprotonation at the C-6 position of the pyridine ring (Scheme 21) without erosion of optical purity. The synthesis of **42** was successfully performed on a large scale (20 mmol) in excellent yield. Likewise, various other electrophiles were installed at the C-6 position of the pyridine ring (Scheme 22). This direct substitution method was the first example of a synthetically useful lithiation of (*S*)-nicotine. Its success prompted the investigation of other directed metalations of nicotine and derivatives.

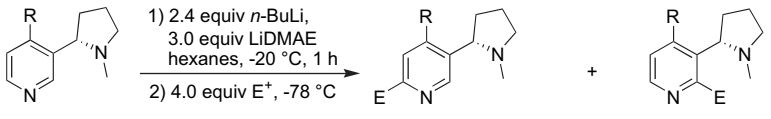
On metalation of nicotine using lithium di-*tert*-butyltetramethylpiperidinozincate (Kondo's TMP-Zincate)[42] followed by addition of iodine, (*S*)-2-iodonicotine (**70b**) and (*S*)-4-iodonicotine (**71**) were formed in unoptimized 19% and 24% yields, respectively (Scheme 23).[40] The two isomers



Scheme 21. Formation of (*S*)-6-chloronicotine via directed lithiation.



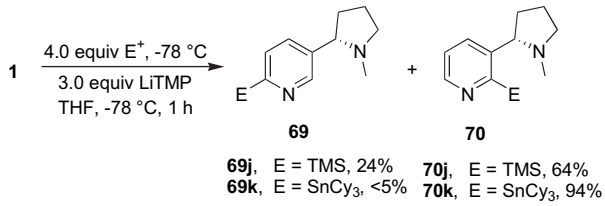
Scheme 23. Regioselectivity in the metalation of nicotine with TMP-zincate.



Scheme 22. Lithiation and substitution of nicotine and nicotine derivatives using *n*-BuLi–LiDMAE as base.

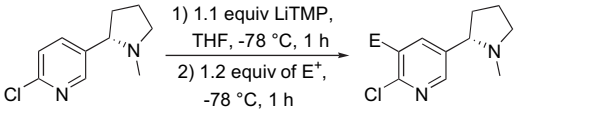
are readily separated by chromatography, thus the method provides access to these potentially valuable iodonicotines.

Reaction of nicotine with LiTMP was also investigated (Scheme 24). When nicotine was added to a solution containing 3.0 equiv of LiTMP and chlorotrimethylsilane (TMSCl), the C-2 substituted nicotine **70j** was obtained as the major product in 64% yield along with the C-6 substituted **69j** in 24% yield. Interestingly, the use of tricyclohexyltin chloride as the electrophile in this reaction affords the 2-substituted product **70k** in excellent yield. To help rationalize these results, it is proposed that LiTMP coordinates at the pyrrolidine nitrogen in the transition state. The C-2 position of the pyridine ring is selectively deprotonated versus the C-6 position, although the reaction is likely reversible. The reason for the high regioselectivity observed on trapping with tricyclohexyltin chloride is unclear at this time.



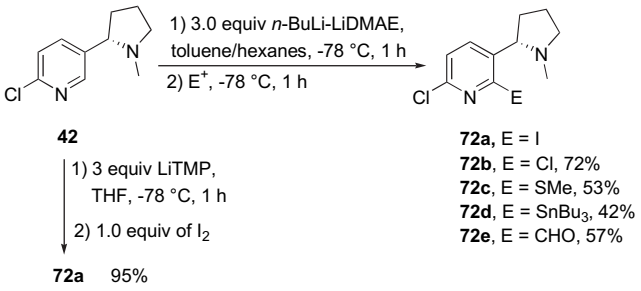
Scheme 24. Electrophile-dependent regioselectivity in the reaction of nicotine with LiTMP as base.

The development of a convenient preparation of 6-chloronicotine (Scheme 21) opened the door to additional directed *ortho*-metalation (DoM) reactions directed by the chlorine atom. Taking this approach, Comins and co-workers reported the regioselective substitution of (*S*)-6-chloronicotine (**42**) via directed lithiation of the pyridine ring.[40] Initially, Gribble's lithiation[43] of halopyridines with LDA was attempted without success. Fortunately, the stronger base, LiTMP, was effective. Deprotonation of **42**, using LiTMP in THF at −78 °C, followed by addition of the appropriate electrophile, afforded the C-5 substituted derivatives **44** and **71a–f** (Scheme 25). This convenient reaction allows the regioselective introduction of various functional groups at C-5 of **42**.



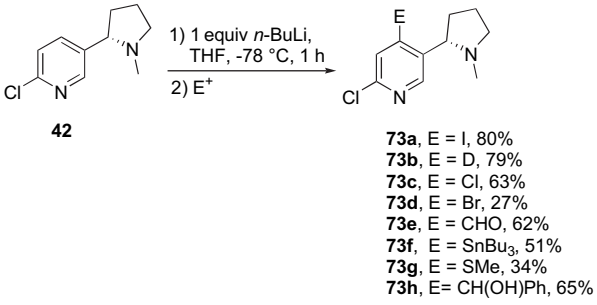
Scheme 25. Substitution at the C-5 position of the pyridine ring of (*S*)-6-chloronicotine using LiTMP as base.

Treatment of 6-chloronicotine with 3.0 equiv of LiTMP followed by the addition of only 1.0 equiv of iodine resulted in the near quantitative formation of (*S*)-6-chloro-2-iodonicotine (**72a**) via a proposed halogen dance mechanism[40] (Scheme 26). Although other C-2 substituted 6-chloronicotines can likely be prepared from **72a** using lithium-halogen exchange or cross-coupling reactions, a direct route from **42** was developed. Treatment of 6-chloronicotine with *n*-BuLi–LiDMAE in toluene at −78 °C, followed by addition of the electrophile, afforded the desired products **72b–e** in moderate to good yield.

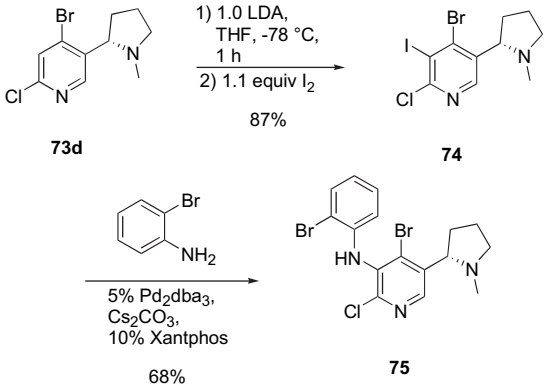


Scheme 26. Substitution at the C-2 position of the pyridine ring of (*S*)-6-chloronicotine using *n*-BuLi–LiDMAE as base.

Remarkably, regiospecific formation of 4-substituted 6-chloronicotines **73a–h** was achieved by simple treatment of 6-chloronicotine with 1.1 equiv of *n*-BuLi in THF at −78 °C and subsequent addition of electrophiles (Scheme 27).[40] This directed lithiation is obviously effected by intramolecular coordination of *n*-butyllithium to the pyrrolidine nitrogen during the deprotonation step. This method not only provides a two-step synthesis of 4,6-disubstituted nicotines, but also allows the preparation of polyhalo derivatives that can be used for sequential lithium-halogen exchange and cross-coupling reactions. For example, 4-bromo-6-chloronicotine (**73d**) can be lithiated at C-5 with LDA and treated with iodine to afford trihalonicotine **74** (Scheme 28).[44] Regioselective palladium-catalyzed amination of **74**



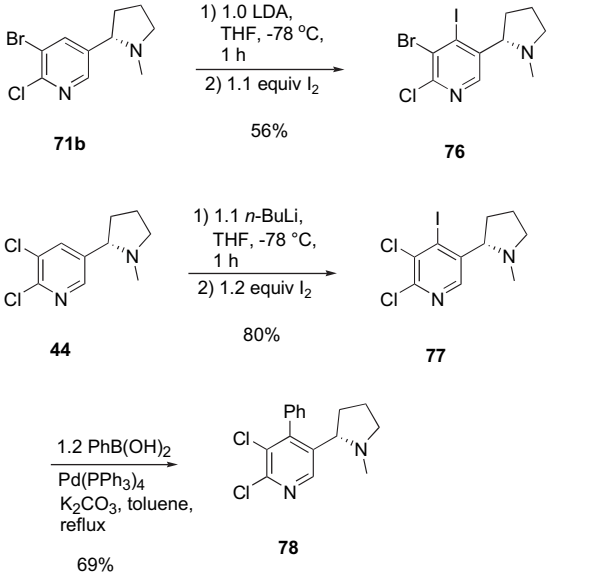
Scheme 27. Regiospecific substitution at the C-4 position of the pyridine ring of (*S*)-6-chloronicotine.



Scheme 28. Regioselective amination of a polyhalonicotine.

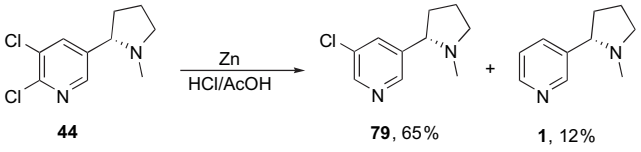
with 2-bromoaniline gives the C-5 amino derivative **75** in good yield.

Alternatively, the bromochloronicotine **71b** and dichloronicotine **44** can be lithiated with LDA or *n*-BuLi at C-4 and iodinated to provide trihalo derivatives **76** and **77** in good yields (Scheme 29). A Suzuki cross-coupling of **77** with phenylboronic acid afforded the 4-phenyl derivative **78** in good yield.[44]



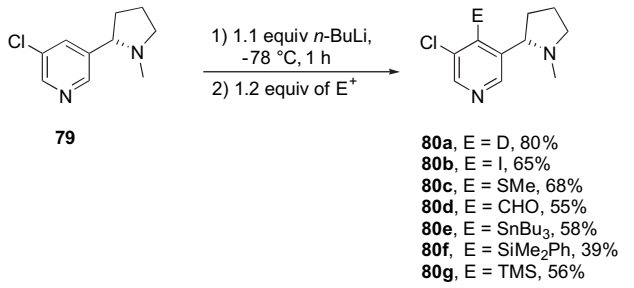
Scheme 29. Preparation of polyhalonicotines.

Comins and Wagner[40] developed a methodology for the synthesis of 4,5-disubstituted nicotines. (*S*)-5,6-Dichloronicotine was treated with zinc powder in a 1.0 M solution of HCl in acetic acid to afford (*S*)-5-chloronicotine (**79**) in 65% yield (Scheme 30).



Scheme 30. Regioselective C-6 dehalogenation of 5,6-dichloronicotine.

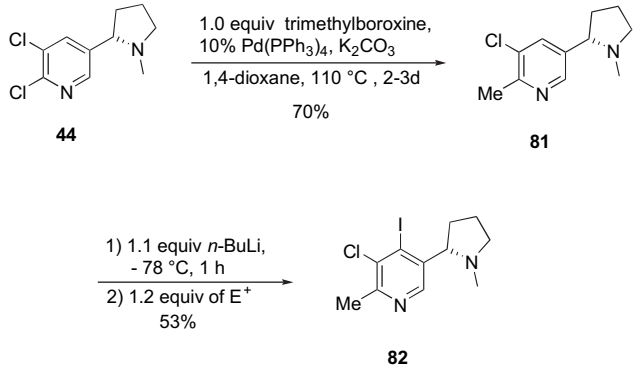
(*S*)-5-Chloronicotine (**79**) was treated with 1.1 equiv of *n*-BuLi in THF at −78 °C to effect a DoM reaction at C-4. Upon addition of electrophiles, C-4 substituted 5-chloronicotine derivatives **80a–g** were obtained in moderate to good yield (Scheme 31). Gros and co-workers recently



Scheme 31. Regioselective substitution at the C-4 position of the pyridine ring of (*S*)-5-chloronicotine.

reported the lithiation/substitution of (*S*)-nicotine at C-4 using $TMSCH_2Li$ (2 equiv) as the base.[45]

A halogen at C-6 of nicotine is more reactive toward cross-coupling than the same halogen at C-5. This was demonstrated by the conversion of dichloronicotine **44** to the 6-methyl derivative **81** (Scheme 32). Conversion of **81** to the iodonicotine **82** was carried out via C-4 lithiation with *n*-BuLi. It is interesting that this conversion can be carried out in the presence of a relatively acidic methyl group at C-6.[44]



Scheme 32.

5. Synthesis of anti-Parkinson's drug SIB-1508Y

(*S*)-(−)-5-Ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine maleate (SIB-1508Y, **83**, Fig. 2), also known as Altinicline, was discovered and developed at SIBIA Neurosciences Inc.[32,46] SIB-1508Y possesses the nicotine core structure that is substituted at the C-5 position with an acetylene group. This fairly simple compound is an agonist of human neuronal nAChRs. Functional assay studies led to the preclinical development of **83** for the treatment of Parkinson's disease (PD); although, clinical trials in PD patients were stopped in Phase II in 1999. SIB-1508Y is still the subject of ongoing research and its reported syntheses represent inventive and useful ways to construct or substitute the nicotine ring system.

5.1. First synthesis of SIB-1508Y

The first synthesis of SIB-1508Y was reported by Cosford and co-workers in 1998.[46] Ethyl 5-bromonicotinate was treated with the enolate of 1-vinylpyrrolidinone to form ketone **22** (Scheme 33). The subsequent hydrolysis of the enamide and decarboxylation allowed the ring closure of the intermediate to afford imine **24**. Compound **24** was then reduced with $NaBH_4$ in the presence of CBz-D-proline (complex **84**), and the pyrrolidine nitrogen was methylated to

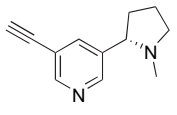
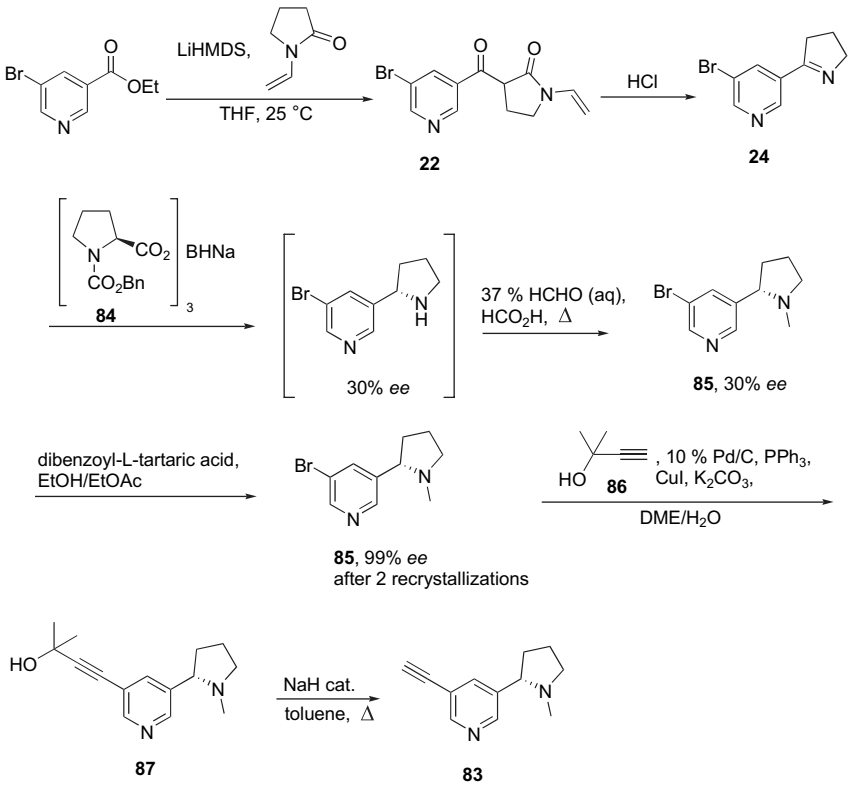


Figure 2. Anti-Parkinson's nicotine analogue SIB-1508Y.



Scheme 33. Cosford's synthesis of SIB-1508Y.

give enantiomerically enriched 5-bromonicotine (**85**) (30% ee) in good yield. Two consecutive recrystallizations as its diastereomeric dibenzoyl-L-tartrate salt furnished **85** in >99% ee. The palladium-catalyzed Sonogashira cross-coupling reaction with 2-methyl-3-butyn-2-ol (**86**) provided protected ethyne **87** in 92% yield. Finally, base-catalyzed deprotection of the acetylene afforded **83**. Soon after, Cosford described a method for the racemization of enriched (*R*)-**85**, which was isolated from their classical resolution procedure.[32] This allowed the (*R*) isomer byproduct to be converted to (*S*)-**85** via their resolution method. This route left room for improvement since the enantiomerically pure material was obtained after several costly fractional crystallizations.

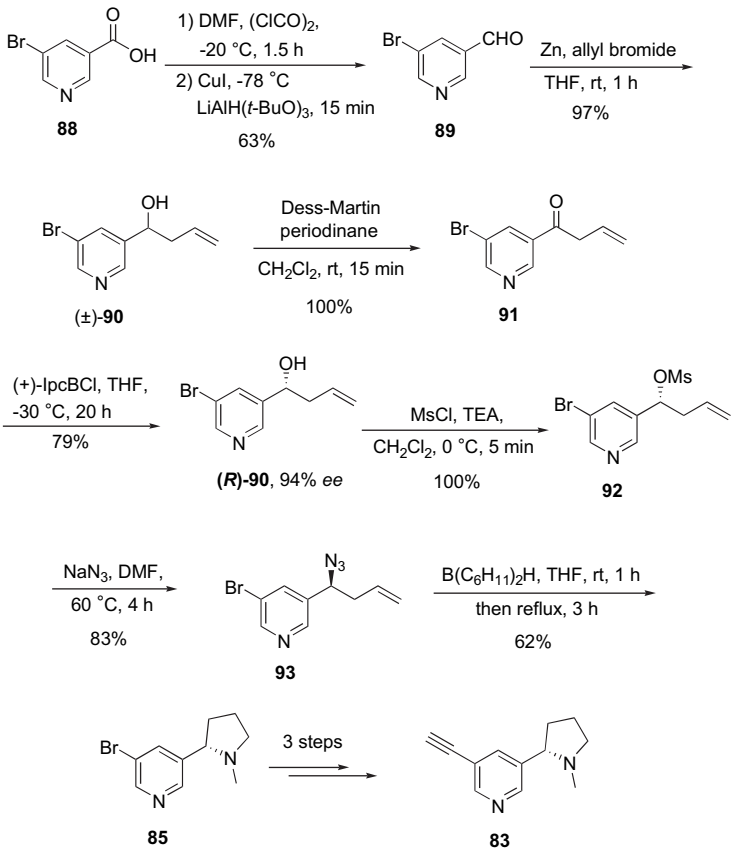
5.2. First enantioselective synthesis of SIB-1508Y

In 2001, Lebreton and co-workers offered a clever enantioselective construction of the pyrrolidine ring of 5-bromonicotine (**85**) (Scheme 34).[47] 5-Bromonicotinic acid (**88**) was converted to the corresponding aldehyde **89**. Allylation with allyl bromide in the presence of zinc gave racemic allyl alcohol **90**, which was subsequently oxidized under Dess–Martin oxidation conditions to ketone **91**. The enantiomerically pure alcohol (*R*)-**90** was obtained using diisopinocamphenylchloroborane as the reducing agent. Nucleophilic displacement of the corresponding mesylate **92** by azide occurred with complete inversion of configuration. An intramolecular hydroboration–cycloaddition tandem reaction[47b] of azido-olefin **93** completed the formation of **85** in 94% ee. SIB-1508Y was synthesized in 10 steps with an overall 18% yield and constituted the first enantioselective synthesis of the nAChR agonist.

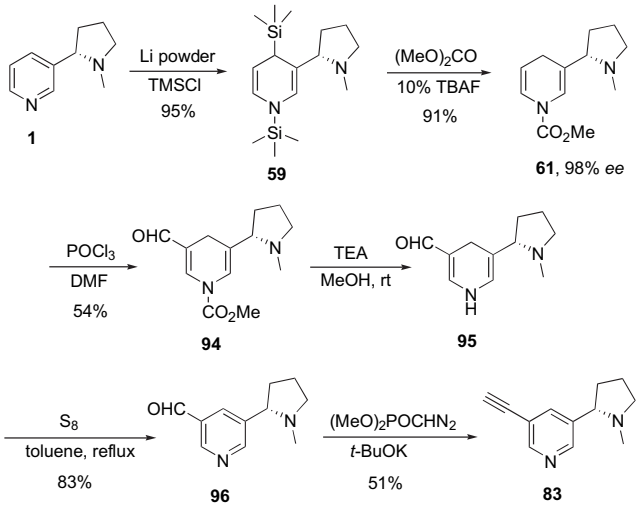
5.3. Synthesis of SIB-1508Y from natural nicotine

In 2006, the Comins' group reported a novel approach to the synthesis of SIB-1508Y using (*S*)-nicotine as an inexpensive starting material (Scheme 35).[48] This route avoids the use of fractional crystallization of a diastereomeric salt, as the chiral integrity of the pyrrolidine ring is conserved throughout the synthesis. Treatment of (*S*)-nicotine with lithium powder and chlorotrimethylsilane afforded 1,4-bis(trimethylsilyl)-1,4-dihydronicotine (**59**) in high yield.[38,39] Acylation of **59** with methyl carbonate in the presence of TBAF (10%) gave the 1-acyl-1,4-dihydronicotine **61** (98% ee). Formylation[49] of **61** under Vilsmeier–Haack conditions provided the desired C-5 aldehyde **94**. The *N*-carbomethoxy group was removed under mild conditions (TEA, MeOH, rt, 1 d) to provide, after rearomatization using elemental sulfur in refluxing toluene, 5-formylnicotine (**96**). The synthesis was completed by using the Seyferth–Gilbert homologation[50] to convert **96** to **83**. SIB-1508Y was synthesized in six steps with an overall 20% yield and constituted its first enantioselective synthesis directly from natural nicotine.

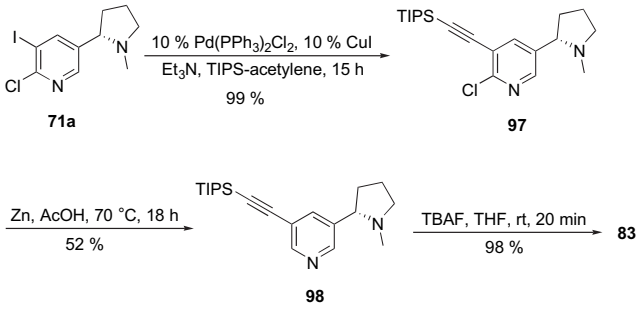
This synthesis was followed with a second generation, five-step preparation of the nAChR agonist. (*S*)-6-Chloro-5-iodonicotine (**71a**), obtained in only two steps from natural nicotine,[40] was submitted to Sonogashira cross-coupling conditions using [(triisopropyl)silyl]acetylene. Compound **97** was obtained in quantitative yield. The reaction of **97** with a hot mixture of Zn/AcOH afforded dehalogenated product **98** in 52% yield. The deprotection of the acetylene moiety using tetrabutylammonium fluoride (TBAF) completed the synthesis of SIB-1508Y (**83**). This synthesis represents the shortest enantioselective synthesis of this



Scheme 34. The first enantioselective synthesis of SIB-1508Y by Lebreton.



Scheme 35. Comins' first synthesis of SIB-1508Y from natural nicotine.



Scheme 36. Comins' expedient five-step synthesis of SIB-1508Y from natural nicotine.

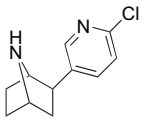


Figure 3. Epibatidine.

nicotine analogue, in only five steps and 32% overall yield (Scheme 36).[51]

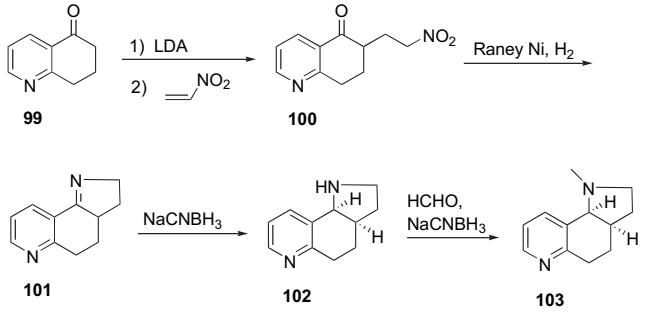
6. Synthesis of conformationally constrained nicotine derivatives

Interest in nicotine analogues with modified pyrrolidine structures increased after the isolation of the very active alkaloid, epibatidine (Fig. 3), isolated from the skin of a South American frog by Daly in 1992.[52a] Despite its toxicity, epibatidine has prompted important research in the synthesis of conformationally constrained nicotine analogues.[52b,c]

6.1. Bridged and conformationally constrained derivatives

In 1978, Leete and co-workers opened this field of nicotine research with the first synthesis of a 'bridged nicotine', a hexahydropyrroloisoquinoline.[12d] In 1983, Seeman and

co-workers reported the preparation of bridged nicotine **103** (Scheme 37).[53] Their synthesis starts with the formation of the enolate of 7,8-dihydro-5(6*H*)-quinolone (**99**) followed by the addition of nitroethylene. The Michael adduct, nitro ketone **100**, was isolated and subsequently reduced with H_2 and Raney nickel to afford bridged myosmine **101**. Its reduction with sodium cyanoborohydride gave bridged nornicotine **102**, which was converted to its nicotine analogue **103** by reductive methylation with sodium cyanoborohydride in the presence of formaldehyde. Only one ring-juncture epimer was isolated.



Scheme 37. Seeman's synthesis of bridged nicotine **103**.

Seeman concluded that this synthetic approach should also be applicable to the preparation of the isomeric nicotinoid **104** from isoquinolone **105** (Fig. 4). Glassco and co-workers reported the synthesis of **104** using this route[54a] while Vernier and co-workers published the synthesis of **106** in 1998.[54b] Analogue **106** was shown to be active in animal models for PD and pain.

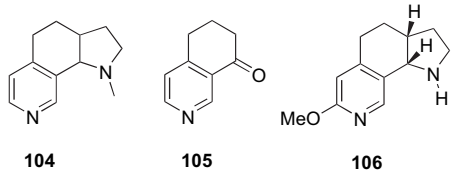
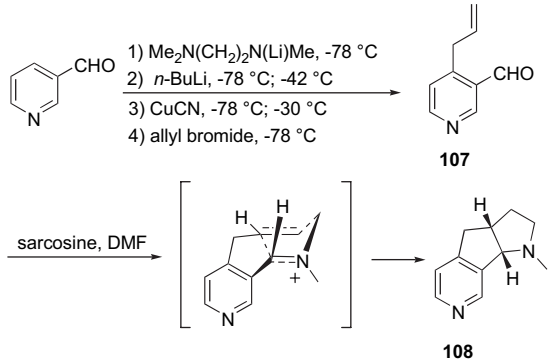


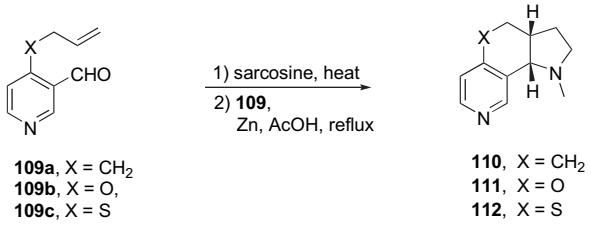
Figure 4.

Along the same vein, in 2002 and 2004, Zhai and co-workers reported a new synthesis of an annulated nicotine derivative via a one-pot assembly of 4-allyl-3-pyridinecarboxaldehyde (Scheme 38).[55,56] Ortho lithiation of 3-pyridinecarboxaldehyde via an α-amino alkoxide intermediate[57] followed by



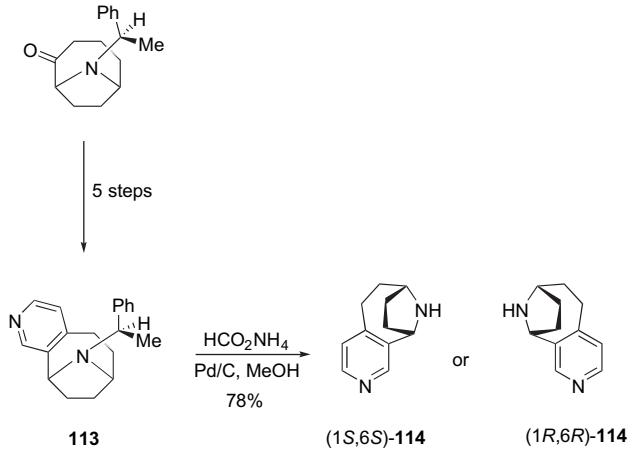
Scheme 38. Nicotine analogues by intramolecular [3+2] cycloaddition.

alkylation with allyl bromide gave 4-allyl-3-pyridinecarboxaldehyde (**107**). An intramolecular azomethine ylide-alkene [3+2] cycloaddition using sarcosine effected the formation of the annulated analogue **108**. In 2006, Zhai's group followed with the synthesis of bridged nicotines **110**–**112** using a similar [3+2] cycloaddition as depicted in Scheme 39.[58]



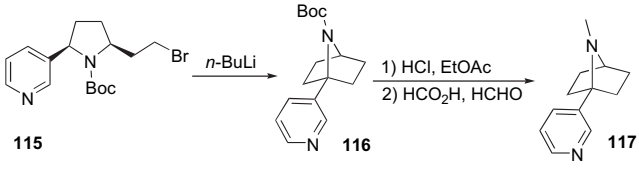
Scheme 39. Nicotine analogues by intramolecular [3+2] cycloaddition.

In 1986, Kanne and co-workers reported the synthesis of the highly potent bridged nicotinoid (±)-**114**.[59] In 2006, Carroll and co-workers modified this procedure to prepare each enantiomer of **114** (Scheme 40).[60] Benzylamine was replaced by (*R*)-(+)-methylbenzylamine to generate both diastereomers of **113**, which were subsequently converted to (+) and (−)-**114**.



Scheme 40. Carroll's enantioselective synthesis of **114**.

In 1999, Rapoport and co-workers designed and synthesized conformationally constrained bicyclic nicotine analogue **117** derived from D- and L-glutamic acid (Scheme 41).[61] The key step in this approach is an intramolecular anionic cyclization at the benzylic position to form azabicyclo intermediate **116**. Bromide **115** was formed in 10 steps from L-glutamic acid. Using *n*-BuLi to deprotonate the benzylic position an intramolecular cyclization took place to afford Boc-protected nicotine analogue **116**. Deprotection to the free amine and methylation gave the target molecule **117**.



Scheme 41. Rapoport's synthesis of conformationally constrained bicyclic analogues of nicotine from L-glutamic acid.

The other enantiomer was obtained by starting with D-glutamic acid using the same reaction sequence.

6.2. Fused, annulated, and spirocyclic analogues

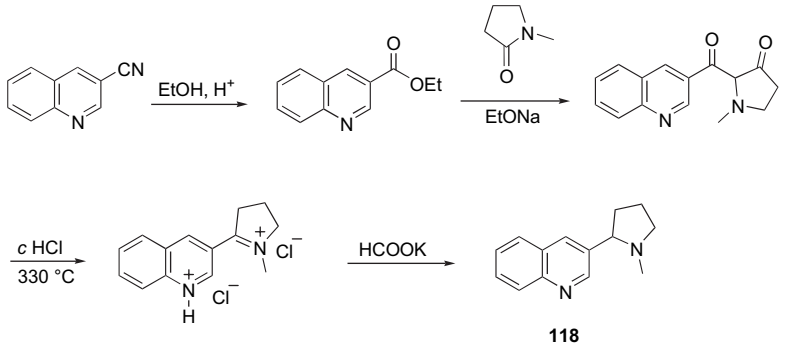
The first synthesis of a benzo-fused nicotine, compound **118**, was reported by Ide in 1970.[62] This procedure was later used and modified by Glennon and co-workers for the synthesis of fused nornicotines and nicotines (Scheme 42).[63]

In 2000, to further enhance the conformational restriction, Rapoport designed and synthesized fused nicotine analogue **124** (Scheme 43).[64] The construction of the fused framework was achieved by an intramolecular Heck reaction of compound **119**. Ozonolysis of **120** gave ketone **121**, which was hydrolyzed and reduced to **123** using a Wolf–Kishner reaction. Finally, **123** was methylated to yield fused nicotine analogue **124**.

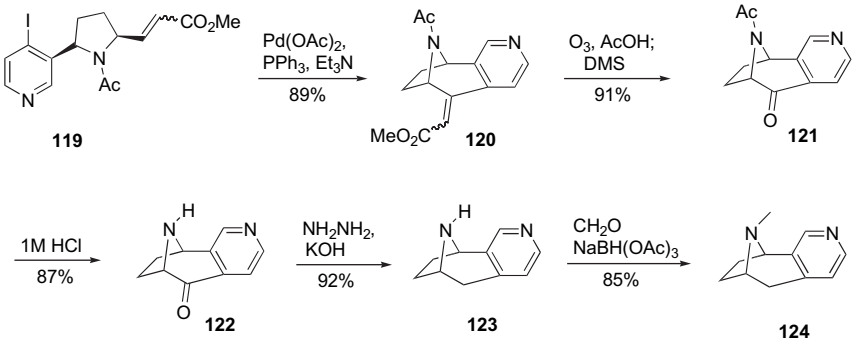
In 2001, Rapoport's group followed with an enantiospecific synthesis of annulated nicotine analogue **128** (Scheme 44).[65] Chloropyridine **125** was formed in eight steps and high yield from glutamic acid. The intramolecular cyclization of the ester enolate at C-4 via an S_NAr mechanism gave bicyclic compound **126**. The ester was hydrolyzed, converted to the acyl chloride, and condensed with 2-mercaptopyridine *N*-oxide. The subsequent radical decarboxylation gave the *N*-Boc-protected nicotine analogue **127**, which was converted in two steps to the N-methylated nicotine target **128**.

In 2002, Ullrich and co-workers reported the enantioselective synthesis of 7-(3-pyridyl)-1-azabicyclo[2.2.1]heptane (**133**) (Scheme 45).[66] A Stille cross-coupling reaction between 3-stannylpyridine **129** and acyl chloride **130** was employed to generate pyridyl ketone **131**. Reductive amination with either enantiomer of α-methylbenzylamine provided benzylamines **132** in good de. The subsequent cleavage of the benzyl group by hydrogenolysis and then ring formation complete the synthesis of **133** in five steps with an optical purity of 90%.

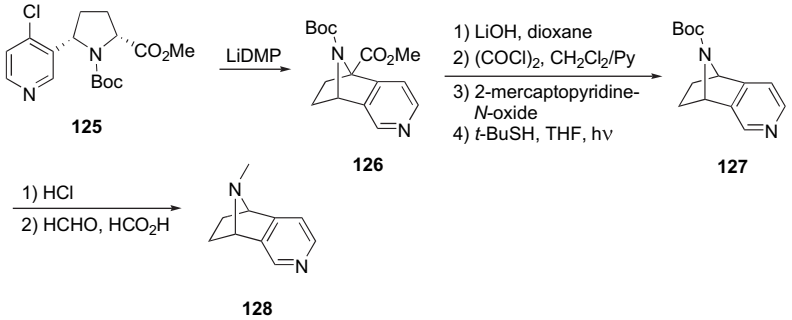
Ullrich followed with the design of tetracyclic nicotine-like compounds such as **139** (Scheme 46) and spiro-annulated



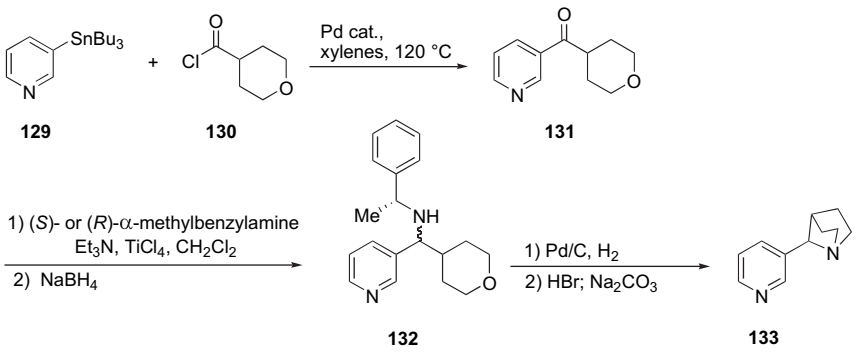
Scheme 42. Synthesis of fused nicotine analogue **118**.



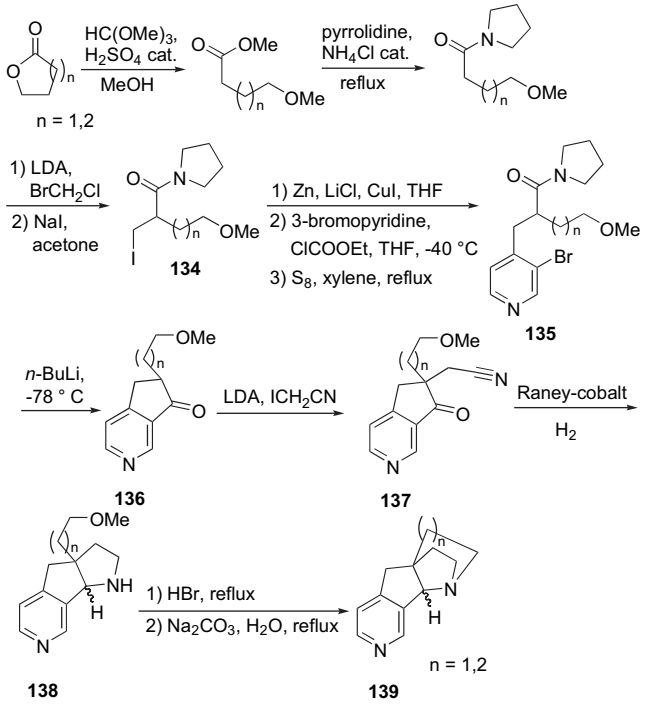
Scheme 43. Annulated nicotine analogues by Rapoport.



Scheme 44. Rapoport's synthesis of conformationally constrained bicyclic nicotine analogue **128**.



Scheme 45. Ullrich's synthesis of nicotinoid **133**.



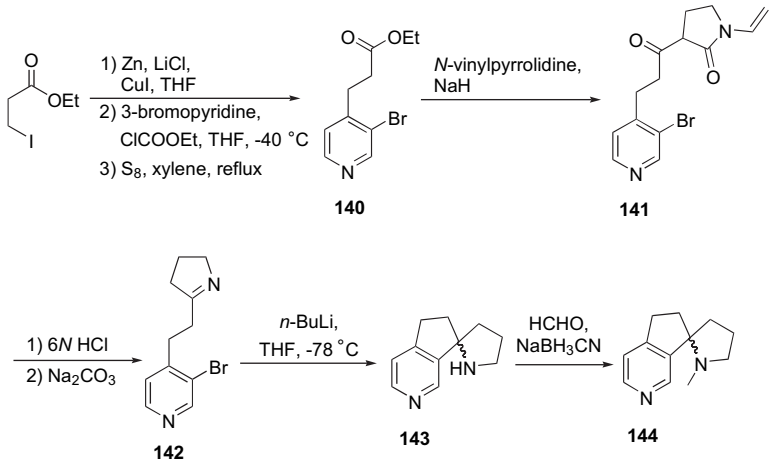
Scheme 46. Ullrich's synthesis of analogue **139**.

nicotine analogues such as **144** (Scheme 47).[67] The bridged analogues were synthesized from a pyridine derivative onto which the azabicyclic system was built. The regioselective 1,4-addition of the organocopper reagent of **134** to the *N*-acylpyridinium salt of 3-bromopyridine, followed by rearomatization with elemental sulfur, led to pyridine **135**. Lithium-halogen exchange initiated the intramolecular cyclization with the amide. Installment of the acetonitrile group followed by hydrogenation led to a cascade reaction forming the annulated pyrrolidines. After ether cleavage, the last cyclization to the azabicyclic ring system completed the synthesis of **139**.

Using a very similar approach, spiro-annulated analogues **144** were designed (Scheme 47). A β-iodocarboxylic acid ester was converted to an organocopper reagent and added to the *N*-acylpyridinium salt of 3-bromopyridine to form compound **140** after rearomatization. The ester was transformed to cyclic imine **142** via ketone **141**. Lithium-halogen exchange afforded nornicotine analogues **143** that were methylated to afford spiro-annulated nicotine analogues **144**.

7. Conclusions

This review has presented recent progress in the synthesis of nicotine and analogues along with some seminal earlier work. Significant advances have been made in the last 10 years that have increased the availability of analogues for pharmacological study. These and further efforts are crucial to the understanding of the nicotinic pharmacophore and to the development of drugs for the treatment of various CNS diseases.



Scheme 47. First synthesis of a spiro-annulated analogue of nicotine.

The progress made in stereoselective syntheses and the application of modern synthetic methods have clearly advanced the field. The new reactions of (*S*)-nicotine allow all positions on the pyridine ring to be substituted in a regioselective manner. These methods will allow a plethora of interesting and potentially useful compounds based on nicotine. These methods will undoubtedly be applied to the preparation of potential pharmaceuticals, insecticides, synthetic intermediates, and novel ligands for catalytic asymmetric synthesis.

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Biographical sketch

Florence Février Wagner was born in 1980 in Argenteuil, France. She graduated in Chemistry from CPE Lyon (Lyon School of Chemistry, Physics and Electronics) in 2003. Between her junior and senior year at CPE Lyon, she joined Scynexis (Durham, NC) as an intern for one year. She then pursued and received her Ph.D. degree in Chemistry from North Carolina State University in 2006 under the supervision of Prof. Daniel L. Comins. Since then, she has been working as a scientist at Metastatix, Inc. (Tucker, GA). Her current research interest is focused on the development of CXCR4 inhibitors for the treatment of metastatic cancer and various inflammatory and autoimmune diseases, such as HIV.

Professor Daniel L. Comins received his B.A. degree in Chemistry in 1972 from the State University of New York at Potsdam and his Ph.D. in 1977 from the University of New Hampshire under the direction of Robert E. Lyle. During 1977–1979, he was a Postdoctoral Associate in the laboratories of Professor A.I. Meyers at Colorado State University working on the total synthesis of the antitumor alkaloids *N*-methylmaysenine and maysine. He joined the faculty of Utah State University in 1979, became an Associate Professor in 1984, and moved to North Carolina State University as a Full Professor in 1989. His research interests include heterocyclic chemistry, synthetic methodology, and total synthesis of natural products. In 1995 and again in 1999, he was elected to the Advisory Board of the International Society of Heterocyclic Chemists. He is or has been a member of the Editorial Advisory Boards of *Progress in Heterocyclic Chemistry*, *Letters in Organic Chemistry*, and *Current Topics in Medicinal Chemistry*. Professor Comins is currently an Associate Editor of the *Journal of Organic Chemistry*. In 1998, he became a Japan Society Promotion of Science (JSPS) Research Fellow. Recently, he was the recipient of the 2005 North Carolina ACS Distinguished Lecturer Award.