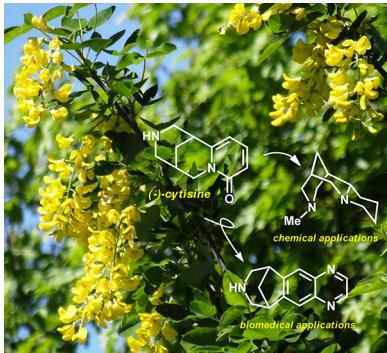


(*-*)-Cytisine and Derivatives: Synthesis, Reactivity, and Applications

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1. INTRODUCTION

(−)-Cytisine (−)-1, [(1*R*,5*S*)-1,2,3,4,5,6-hexahydro-1,5-methano-8*H*-pyrido[1,2*a*][1,5] diazocin-8-one (Figure 1), is an alkaloid

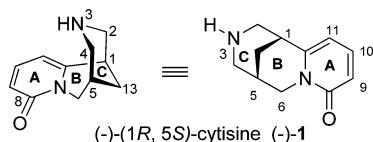


Figure 1. Structure and absolute configuration of (−)-cytisine. IUPAC numbering of the atoms.

extracted from various plants belonging to the Leguminosae (Fabaceae) family and particularly from the seeds of the common garden decorative tree *Laburnum anagyroides* (*Cytisus Laburnum*, Golden rain acacia).^{1–3} Its uses in traditional medicine started thousands of years ago: Indians in America

consumed *Laburnum* seeds for their emetic and purgative effects.^{4,5} In Europe, (−)-1 was used as a respiratory analeptic,⁶ a diuretic,⁷ or an insecticide.⁸ Moreover, during the second World War, the leaves of *Laburnum anagyroides* were used as tobacco substitute. (−)-Cytisine has been marketed in Central and Eastern Europe (trade name: Tabex) and used for over 40 years to treat tobacco dependence^{4,5,9} despite the lack of clinical studies. Whereas (−)-1 was isolated in the second half of the 19th century, its chemistry remained underdeveloped until the end of the 1990s. The renewed interest in this compound came from the identification of its biological properties. It was demonstrated that (−)-cytisine has a high affinity at nicotinic acetylcholine receptors (nAChRs)^{10–14} with high $\alpha 4\beta 2$ subtype selectivity. It behaves as a partial agonist¹⁵ with low nonspecific binding. These properties have made [³H]cytisine the most used radioligand until now for the study of nicotinic neurotransmission, and thus cytisine contributed significantly to the knowledge acquired in this research field over the last 30 years.

Thanks to the progress in pharmacology, physiology, and molecular biology of neuronal nicotinic receptors, the potential of nicotinic ligands for treatment of neurodegenerative disorders has been recognized¹⁶ and has stimulated the synthesis of a large number of ligands able to modulate their biological action. Moreover, the $\alpha 4\beta 2$ nAChRs subtype has been identified as being involved in the antinociceptive activity, and the agonists could control opiate-resistant pain.¹⁷ Within this context, (−)-cytisine appeared as a lead candidate to develop new molecules interacting more selectively with the nAChRs of the central nervous system (CNS) while displaying minimal side effects. Varenicline 3 (Figure 2) developed by Pfizer

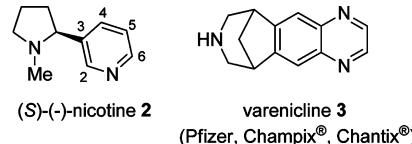


Figure 2. Structures of (−)-nicotine and varenicline.

laboratories¹⁸ (trade name Chantix in the USA, Champix in Canada and Europe) is the first successful example of this research.

Although commercially available from general suppliers, (−)-cytisine is currently an expensive chemical. However, recently, an adaptation of known described methods^{19,20} allowed its efficient and reproducible extraction from the seeds of *Laburnum anagyroides*^{21,22} easily available at low cost from seed producers. This method contributed significantly to the development of (−)-cytisine chemistry with the synthesis of various substituted derivatives (see sections 4–7) and of more complex structures including natural products (see sections 8 and 9). Recently, the unique tricyclic chiral arrangement of (−)-cytisine containing a bispidine moiety (rings B and C, Figure 1) enabled the synthesis of an equivalent of the (−)-sparteine enantiomer [i.e., (+)-sparteine surrogate] and thus was the key of original asymmetric transformations (see section 7.2).

A literature search revealed more than 1700 references concerning cytisine including more than 230 articles using [³H]cytisine. To date, no comprehensive review dedicated to this versatile alkaloid and its derivatives has been published. Only short reports are included in Michael's reviews on indolizidine and quinolizidine alkaloids.²³ O'Brien²⁴ and O'Neill et al.¹⁸

have focused their reviews on the syntheses of (−)-cytisine, and thus the synthetic approaches to (−)-1 and (+)-1 will be presented briefly. Recent structural modifications of cytisine as a lead for the development of drugs acting at nAChRs were summarized.²⁵ This Review intends to collect and discuss the widespread knowledge regarding (−)-cytisine and its natural or non-natural derivatives. Furthermore, an emphasis is put on the applications of (−)-cytisine to the synthesis of natural products and to asymmetric transformations. Some medicinal, biological, or pharmacological data and uses of (−)-cytisine derivatives will be mentioned when available. This Review covers the literature up to December 2012. The tetracyclic compounds with a cytisine core (i.e., anagyrine), the ammonium salts of (−)-1, are beyond the scope of this Review.

2. BACKGROUND

2.1. (−)-Cytisine: Natural Sources

Cytisine was first isolated in 1865 by Husemann and Marmé^{1,2} from the seeds of *Cytisus Laburnum Med.*, a small hardy tree common in central and southern Europe and cultivated for its golden-yellow flowers. The name “*Cytisus*” comes from the greek “*Kytisos*”, which was originally the name of a species of clover widespread on Kythnos, a Greek island.

(−)-Cytisine is a prevalent quinolizidine alkaloid^{23,26–30} in the plants belonging to the Leguminosae (or Fabaceae) family, including the genera *Laburnum*,^{31–34} *Thermopsis*,^{35,36} *Cytisus*,^{1,20} *Genista*,³⁷ and *Sophora*.³⁸ It was proved that ulexine,³⁹ a compound extracted from *Ulex europeus* L., sophorine⁴⁰ from *Sophora secundiflora*, and baptitoxine⁴¹ from *Baptisia tinctoria* are identical to (−)-cytisine. Among the various alkaloids present in several parts of these plants, (−)-1 is often the most abundant particularly in seeds. For example, (−)-1 represents 63% of alkaloids in the seeds of *Argyrolobium uniflorum*⁴² and 59% in those of *Templetonia Incana*.⁴³ In *Petteria ramentacea*, this percentage reaches 80%, and a similar amount (79%) was found in the flowers. Various concentrations dependent on the maturation state but also on the age of the plant and climatic conditions were found in several parts of the plant.⁴⁴ The yields of isolation from seeds of *Laburnum anagyroides* vary according to the literature. A reproducible process has been developed by Rouden’s group,²¹ and then by O’Brien et al.²² The extraction usually affords up to 1.5 g of pure (−)-cytisine from 100 g of seeds.

2.2. Biological Activity Profiles

The biological properties of (−)-cytisine have been summarized in recent Bulgarian and Polish reviews dealing with the treatment of nicotine addiction.^{4,5} In addition, (−)-cytisine has shown analgesic, antihypertensive, inotropic, antispasmodic, antioxidant, and insecticidal activities.

2.2.1. Toxicity. *Cytisus laburnum* is one of the most known toxic plants in poisoning centers.⁴⁵ The poisonous effects were long ago associated with cytisine,^{46–48} later attributed to its agonist interaction with nAChRs. Serious cases of poisoning are rare,^{4,45} the ingestion of *Laburnum* seeds usually causing gastrointestinal upset only. For horse, a lethal dose of seedpods containing *Laburnum anagyroides* was estimated to be 0.5 g/kg. The pharmacokinetics behavior of [³H]cytisine was studied in mice after intravenous and oral administration of a sublethal dose (2 mg/kg). In blood, (−)-cytisine has a half-life of 200 min, and its maximum level was reached after 2 h. Excretions in urine were 32% and 18%, respectively, 24 h after intravenous and oral administrations.¹¹ The brain levels of nicotine and (−)-cytisine were compared 5 min after subcutaneous injection in rats.

The results (cytisine = 0.17 nmol/g; nicotine = 2.2 nmol/g) indicated that (−)-cytisine can enter the brain only poorly relative to nicotine.⁴⁹ The authors suggested that the low partition coefficient of cytisine at physiological pH (in ethanol/H₂O: log $P_{\text{cytisine}} = -0.94$; log $P_{\text{nicotine}} = 1.2^{50}$) could explain this low blood brain barrier penetration. This hypothesis was discussed when cytisine was compared to varenicline 3 (Champix/Chantix) as a smoking cessation agent.⁵¹

In mice, cytisine hydrochloride is less toxic intravenously than nicotine hydrogen tartrate, but more toxic by intraperitoneal or oral administration. As compared to cytisine, *N*-methylcytisine hydroiodide (or caulophylline) is less toxic, whereas *N*-dimethylated ammonium iodide salt of cytisine is almost inactive. Cytisine and its methyl derivative are active as their N-protonated cations. The difference of pK_a [cytisine, pK_a = 7.92 (7.8 in a recent study⁵¹), *N*-methyl cytisine, pK_a = 7.04]⁵² may account in part for the stronger activity of cytisine.⁵² No antidote for cytisine exists. Therefore, only symptomatic treatment of *Laburnum* poisoning is possible. The effects of various drugs on the acute toxicity of cytisine were studied in mice. It was shown that diazepam, biperiden, and sodium hexobarbital, drugs acting on CNS, reduced the toxicity of the alkaloid.⁵³

2.2.2. Nicotinic Receptor Binding. Nicotinic acetylcholine receptors (nAChRs) belong to the family of ligand-gated ion channels.¹⁶ They have been divided into muscle-type receptors found at the skeletal neuromuscular junction and neuronal receptors found in the central and peripheral nervous system, but also in non-neuronal tissues. Neuronal nAChRs exert a modulatory influence on transmitter release, synaptic efficacy, and neuronal function. Seventeen nAChR subunits have been identified, and nicotinic receptors are pentameric combinations of these subunits. The heteromeric ($\alpha 4\beta 2(\beta 2)3$, ($\alpha 3\beta 2\beta 4)3$, and homomeric ($\alpha 7)5$ are the most important in the brain. They will be named $\alpha 4\beta 2$, $\alpha 3\beta 4$, and $\alpha 7$ below. The design of specific modulators is made difficult by the high number of subunits and by the various combinations of these subunits, the low abundance of some of them in the brain, and the lack of selective ligands to study the role of nAChRs under physiological and pathological conditions.

2.2.2.1. (−)-Cytisine, Ligand of nAChRs. The binding characteristics of [³H]cytisine to brain membrane preparations have been extensively studied since 1980.⁵⁴ Pabreza,¹⁰ Freedman,¹² Sloan,⁵⁵ and Anderson research groups¹⁴ demonstrated that the dissociation constant (K_D) of [³H]cytisine for rat brain nAChRs was less than 1 nM¹⁰ (0.145 nM).¹⁴ The specific binding represented 60–90% of total binding at all concentrations examined up to 15 nM. The density of [³H]cytisine binding sites in rat cortex ($B_{\max} = 4$ fmol/mg,¹⁰ 85–99 fmol/mg¹⁴ of tissue) was similar to the density of sites labeled with other nicotinic cholinergic agonist ligands, but the affinity of cytisine was higher ([³H]nicotine, $K_i = 0.89$ nM; $B_{\max} = 114$ fmol/mg; [³H]-methylcarbamylcholine, $K_i = 1.07$ nM, $B_{\max} = 63.8$).¹⁴ No decrease in the binding affinity of [³H]cytisine over a period of 8 months was observed when it was stored at −20 °C. (−)-Cytisine was a million-fold more selective for nicotinic over muscarinic receptors ($K_i > 400\,000$ nM). In human brain, similar results were found. In the four brain regions studied, [³H]cytisine labeled a single class of high-binding sites [K_i 0.25 nM, B_{\max} (thalamus): 40.9 fmol/mg protein],¹² which were identified as the $\alpha 4\beta 2$ nAChR subtype. Biodistribution of [³H]cytisine was also studied in mouse brain. After intravenous injection of the tracer, the radioactivity peaked at 30 min.⁵⁶ Its concentration was high in

the thalamus, intermediate in the superior colliculi, prefrontal cortex, and hippocampus, and low in the cerebellum in good agreement with the brain regional distribution predicted for nAChR agonist recognition sites. Binding was displaced by (-)-nicotine, not by (+)-nicotine.⁵⁶

With the advances in the knowledge of nAChRs, various binding studies of (-)-cytisine under different conditions (rat or human, tissues or cells) at the different nAChR subtypes were described (cf. ref 5 for a review). All of these binding data make [³H]-cytisine a crucial ligand for quantitation of neuronal nAChRs and suggested that cytisine derivatives, appropriately labeled with a positron emitting radionuclide, may be useful for the study of nicotinic neurotransmission in human CNS by positron emission tomography (PET).⁵⁷

2.2.2.2. (-)-Cytisine as Smoking Cessation Agent. Cytisine is a potent and competitive partial agonist at $\alpha 4\beta 2$ subunit, while at $\alpha 7$ it behaves as a full agonist with relatively lower potency.¹³ Its physiological and behavioral effects are complex and differ from those of nicotine.⁵⁸ Cytisine has weaker peripheral effects on the cardiovascular system. Its higher activity than nicotine and its low oral toxicity made cytisine a natural alternative to nicotine for smoking cessation (cf., Introduction). Excellent reviews have been published recently;^{4,5,9,59} therefore, this point will not be detailed here. Recently, Pfizer Co. reported an in-depth study of the preclinical properties of (-)-cytisine as compared to the partial agonists varenicline 3 (Pfizer, launched in 2006, Figure 2) and dianicline (Sanofi-Aventis, SSR 591813) (Figure 3), two other partial agonists of nAChRs developed for

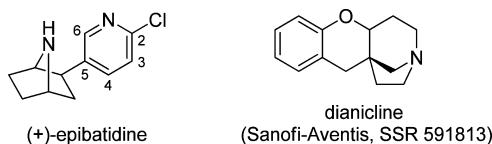


Figure 3. Structures of epibatidine and dianicline.

smoking cessation.⁵¹ The in vitro binding affinities of cytisine at five nAChR subtypes using [³H]-epibatidine (in HEK293 cells: $\alpha 4\beta 2$, $K_i = 2.0$ nM, $\alpha 3\beta 4$, $K_i = 480$ nM, $\alpha 6/\alpha 4\beta 4$, 329 nM) or [¹²⁵I]- α -bungarotoxin (K_i $\alpha 7$ in IMR32 cells, 5890 nM; $\alpha 1\beta 1\gamma\delta$ in Torpedo electroplax membrane, 492 nM) for competitive displacements were determined. The agonist efficacies of nicotine, varenicline, cytisine, and dianicline at human $\alpha 4\beta 2$ nAChR expressed in oocytes (female gametocyte) were compared. The lower efficacy of cytisine as compared to nicotine or varenicline was consistent with previous observations. Pharmacokinetics data and prediction of human steady-state brain concentrations showed that these concentrations were much higher for varenicline (32–131 nM) than for cytisine (2–10 nM). The authors suggested that this difference could not come only from the poor brain penetration of cytisine but also could be due to an active, non-P-glycoprotein brain efflux mechanism. The total brain concentrations at 2 h after per os injection of cytisine in wild type (FVB/N) and P-glycoprotein deficient mice were, respectively, 0.11 and 0.19 nmol/g, values that compare well with previous studies in rats. The study showed that, despite the high in vitro potency of cytisine, its brain concentration was not sufficient to affect $\alpha 4\beta 2$ nAChRs.

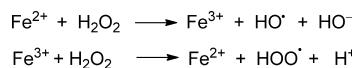
2.2.2.3. (+)-Cytisine. The non-natural enantiomer of cytisine (**(+)-1**) was synthesized in 2006.⁶⁰ Its affinity at the nAChRs of subtype $\alpha 4\beta 2$ was more than 260 times lower than that of (**(-)-1**) [**(+)-1** $K_i = 0.79 \pm 0.30 \mu\text{M}$; **(-)-1** $K_i = 3.0 \pm 0.65 \text{ nM}$]

under the same conditions of measurement]. It is worth noting that this difference between the affinities of enantiomers $(-)\text{-1}$ and $(+)\text{-1}$ is higher than that measured for enantiomers of nicotine because the estimated average affinity of (R) -nicotine is about 10 times lower than that of (S) -nicotine.⁶¹ No other biological property of $(+)\text{-1}$ was reported.

2.2.3. Miscellaneous Biological Activities. 2.2.3.1. Dop-

amine Neurotransmission. The Ferger group in 1998⁶² demonstrated that cytisine can induce a reduction of hydroxyl radical production in vitro. The authors suggested that the formation of complexes of cytisine with iron could inhibit the Fenton reaction⁶³ (Scheme 1) or remove the formed hydroxyl

Scheme 1. Fenton Reaction



radicals. In addition, *in vivo* experiments on mice showed that cytisine partially prevented the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced decrease in striatal dopamine concentration. They concluded that cytisine could be useful for the treatment of Parkinson's disease where the chelation of iron could prevent neuronal cell death.

More recently, the Abin-Carriquiry group⁶⁴ demonstrated the ability of cytisine to induce dopamine release in vivo by microdialysis and its capacity to reduce striatal dopamine depletion induced by 3,4-dihydroxyphenylacetic acid injection in the substantia nigra. By this protective effect, cytisine could become a lead for understanding the CNS plasticity mediated by nicotinic receptors.

2.2.3.2. Antidepressant Property. Numerous studies have suggested that targeting the nAChRs holds promise as a new therapeutic approach for the treatment of depression.⁶⁵ Specifically, Mineur et al.⁶⁶ observed antidepressant-like effects of cytisine in mouse models. The experiments supported the hypothesis that these effects might arise from the ability of cytisine to block $\alpha 4\beta 2$ nAChRs.

2.3. Biosynthesis

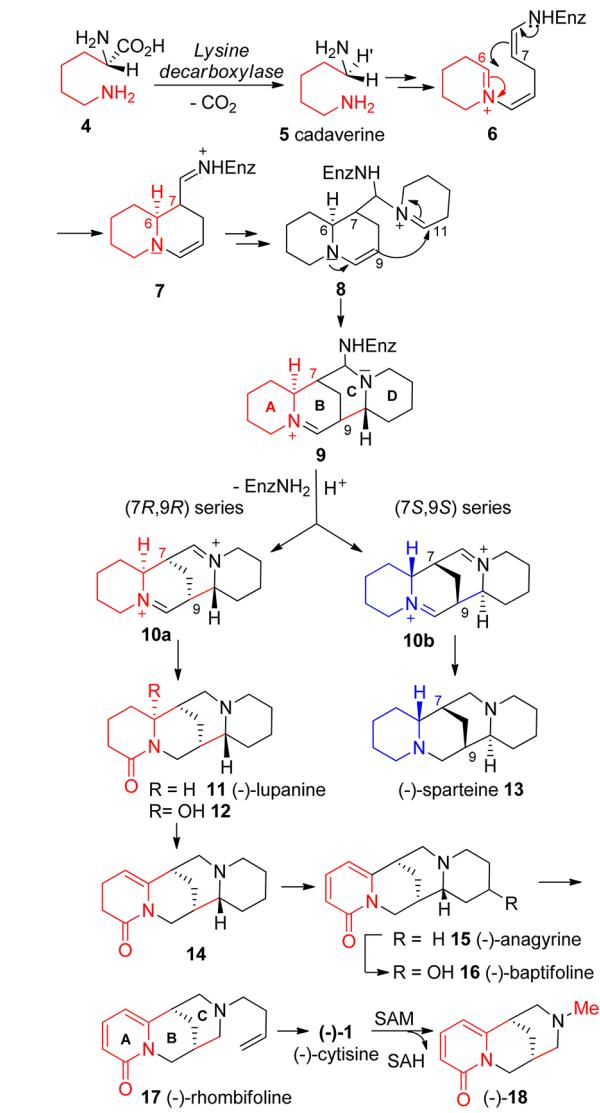
The first studies on the biosynthesis of $(-)$ -cytisine were reported in the 1960s.^{67,68} They were later confirmed by extensive research on the biosynthesis of various quinolizidine alkaloids of the lupines family, especially of that of sparteine (cf., refs 28,29,69–71 for reviews). Although not fully elucidated, the possible pathways for the biosynthesis of $(-)$ -cytisine and $(-)$ -*N*-methylcytisine are presented here with a special emphasis on the well-established routes.

The lupine alkaloids are synthesized in the green parts of the plants before being translocated to other organs. In the intact plants, they are stored as salts such as malates in the epidermal tissues, leaves, petioles, and stems. Unlike the tetracyclic alkaloids (i.e., sparteine, lupanine), which accumulate as two series of enantiomers, the α -pyridone-type alkaloids occur only as (7*R*,9*R*) enantiomers.

The first step of lupine alkaloids biosynthesis is the production of cadaverine **5** by decarboxylation of lysine **4**^{67,72} catalyzed by lysine decarboxylase, an enzyme located in chloroplast stroma.⁷³ Intermediates following cadaverine **5** have not been detected probably because they are bound to enzymes. However, the diiminium cations **10a** and **10b** were suggested as the most likely intermediate in the formation of the tetracyclic alkaloids.

The stereoselectivity of ring formations in the biosynthesis of sparteine 13 and lupanine 11 has been explained^{29,74,75} from reactions of the two postulated intermediates 6 and 8. The absolute configuration of C₆, C₇, C₉, and C₁₁ would be determined at the ring cyclization steps (6 → 7 and 8 → 9).^{74,76} An intramolecular attack from the 7-Re face to the 6-Re face of 6 to give 7 then 8 followed by the attack from the 9-Re face to the 11-Si face of 8 would lead to dicitcations 10. Scheme 2 presents the possible pathway for the formation of (−)-cytisine.

Scheme 2. Possible Pathway for the Formation of (−)-Cytisine in Genus *Thermopsis*

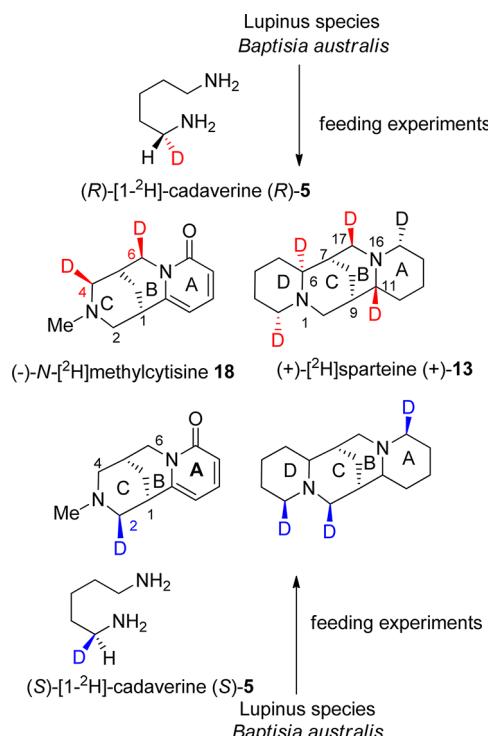


The (7R,9R) dication intermediate 10a (Scheme 2) would be converted into (−)-lupanine 11 released from the enzyme complex. 11 then was supposed to undergo specific enzyme-mediated oxidation/deshydration/dehydrogenation to afford sequentially 5,6-dehydrolupanine 14, anagyrine 15, and, finally, via rhombifoline 17, (−)-cytisine (−)-1. No (7S,9S)-α-pyridone-type alkaloids have been found, suggesting that the enzyme(s) responsible for dehydrogenation of ring A of lupanine to α-pyridone can convert only the (7R,9R)-(−)-lupanine. Compound 12 (6-hydroxylupanine) could be an intermediate between lupanine 11 and 14. Indeed, a 6β-hydroxylupanine isolated from *Bolusanthus speciosus* was shown to be an unstable compound prone to dehydration.⁷⁷

The presence of an S-adenosyl-L-methionine cytisine N-methyltransferase has been detected in crude enzyme preparations from *Laburnum anagyroides* plants and from cell cultures of *Laburnum alpinum* and *Cytisus canariensis*.⁷⁸ The transferase catalyzed the transfer of a methyl group from S-adenosyl-L-methionine (SAM) to cytisine, yielding N-methyl cytisine.⁷⁹ These experiments demonstrated that N-methyl cytisine is not directly formed from rhombifoline 17.

Incorporation of carbon-14 or deuterium into quinolizidine alkaloids of different plants using labeled [¹⁴C]cadaverine, [¹⁴C]lupanine, [¹⁴C]sparteine,⁶⁸ and (R)-[1-²H] and (S)-[1-²H]cadaverines^{74,75} established that the tricyclic alkaloids (cytisine and its N-methyl derivative) are formed from tetracyclic intermediates. Three cadaverine units are incorporated to about the same extent into lupanine,⁸⁰ precursor of cytisine (Scheme 3).

Scheme 3. Labeling Patterns in (+)-Sparteine and (−)-Methylcytisine in Feeding Experiments



This hypothesis was supported by feeding experiments with the enantiomeric [1-²H]cadaverines 5 into *Baptista australis*,^{76,81} from which (−)-N-methylcytisine and (+)-sparteine were the main isolated compounds. Deuterium from (R)-[1-²H]cadaverine dihydrochloride was retained at C₆ and C₄ of N-methylcytisine 18, whereas (S)-[1-²H]cadaverine isomer labeled carbon C₂. Comparison of these labeling patterns with those of (+)-sparteine 13 (Scheme 3) suggested that the outer ring D of a tetracyclic intermediate was cleaved and that ring A was converted into pyridone during the formation of (−)-N-methylcytisine 18.

By carrying out such a biomimetic approach, sparteine was obtained via chemical synthesis based on reactive precursor.⁸² To our knowledge, it has not yet been applied to the preparation of cytisine related compounds whose preparation via other routes would be difficult.

2.4. Early Chemistry for Structure Elucidation

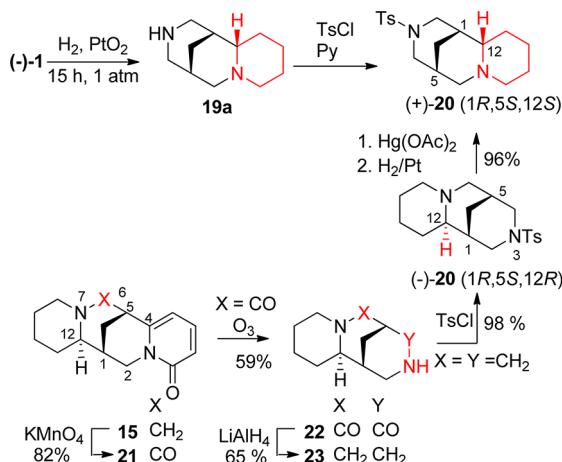
The correct molecular formula ($C_{11}H_{14}N_2O$) of cytisine was assigned in 1890.⁸³ The structure of the alkaloid was elucidated

after 40 years of intense research (cf., ref 27 for a review) focused mainly on analyses of the products (isolated as salts) formed in electrophilic substitutions and in degradations/reductions of either cytisine or its methyl or acetyl derivatives. It was fully characterized by spectroscopic analyses in the mid-1980s.

The purpose of this part is not to present the process that led to exact structure of cytisine but only to describe chemical transformations of (*-*)-1 leading to readily accessible substructures. This should stimulate research of more efficient and selective reactions to prepare these valuable compounds.

2.4.1. Absolute Configuration of (*-*)-Cytisine. The absolute configuration of (*-*)-1 was established⁸⁴ by chemical transformations. (*-*)-1 was reduced⁸⁵ into tetrahydrodeoxocytisine 19a, which was transformed into its *N*-tosyl derivative (+)-20 (Scheme 4).

Scheme 4. Synthesis of (1*R*,5*S*,12*S*)-*N*-Tosyl Tetrahydrodeoxocytisine from Cytisine



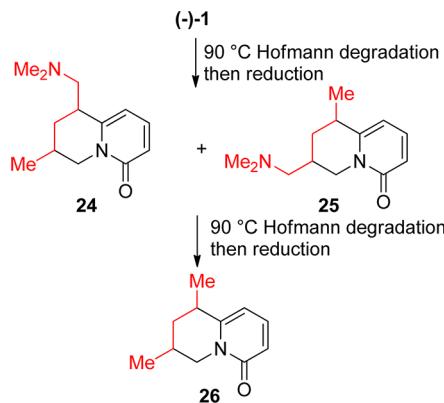
The protected compound (+)-20 was independently prepared from (*-*)-anagyrene 15 of known absolute configuration.⁸⁶ (*-*)-Anagyrene 15 was converted (Scheme 4) into bis-lactam 22 by treatment with potassium permanganate followed by ozonolysis. Lithium aluminum hydride reduction of 22 led to diamine 23. Tosylation of 23 afforded tosylate (*-*)-20. This latter was epimerized into tosylate (+)-20 by dehydrogenation with mercuric acetate followed by catalytic hydrogenation (Scheme 4).

2.4.2. Hofmann Degradations of (*-*)-Cytisine. The Hofmann exhaustive degradation of cytisine (*-*)-1 was investigated originally by Partheil.⁸⁷ Spath and Galinovsky⁸⁸ studied the degradation of (*-*)-1 sequentially, each Hofmann degradation being followed by a reduction step. Thus, pyridone 26 was obtained from the pyridone-amines 24 and 25 after two degradation–reduction sequences (Scheme 5).

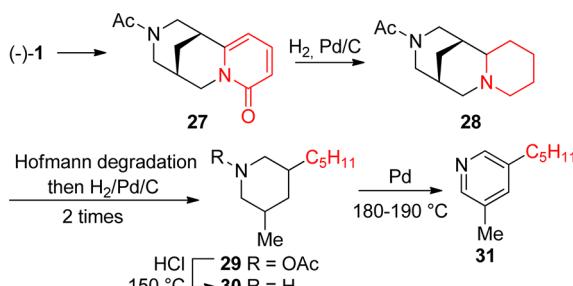
The same authors studied also the degradation of the fully reduced cytisine 28 in which the secondary amine was protected by an acetyl group.⁸⁹ After two Hofmann degradations of *N*-acetyl tetrahydrodeoxocytisine 28, each one followed by a reduction, they isolated 3-methyl-5-(*n*-pentyl)piperidine 30 after deprotection of the secondary amine. The structure of 30 was based on its dehydrogenation into the corresponding pyridine 31 (Scheme 6).

2.4.3. Oxidations of (*-*)-Cytisine. The structure of pyridone 26 (Scheme 5) was based on its ozonolysis into lactam 32 (Scheme 7) whose hydrolysis and oxidation afforded a mixture of meso and racemic dimethylglutaric acids.⁸⁸

Scheme 5. Hofmann Degradations of (*-*)-Cytisine



Scheme 6. Hofmann Degradation of *N*-Acetylcytisine

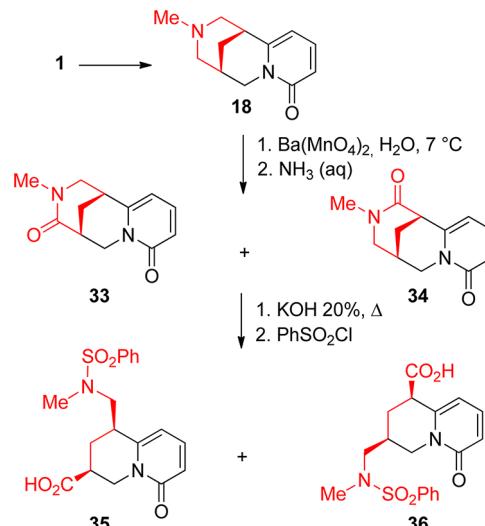


Scheme 7. Oxidation of a Cytisine Derivative



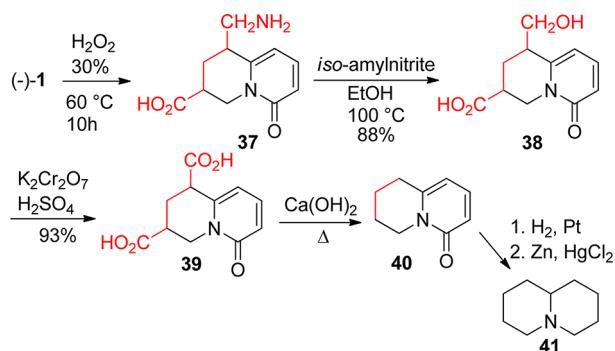
Several oxidations (not shown) provided additional evidence for the structure of (*-*)-1. Treatment of *N*-methyl cytisine 18 with barium permanganate⁹⁰ afforded a mixture of lactams 33 and 34, which were separated and characterized as their benzenesulfonyl derivatives 35 and 36, respectively (Scheme 8).

Scheme 8. Barium Permanganate Oxidation of *N*-Methylcytisine



A few years later, Polonovski and Lecoq^{20,91} studied the hydrogen peroxide oxidation of cytisine (−)-1. They identified the amino acid 37. Diazotation of 37 followed by potassium dichromate oxidation afforded the diacid 39, which was decarboxylated into pyridone 40. Reduction of this pyridone led to the known bicyclic amine 41 (Scheme 9).

Scheme 9. Hydrogen Peroxide Oxidation of Cytisine



Surprisingly, with the exception of the aromatic electrophilic substitutions, these chemical transformations (mainly degradations) have not been explored for synthetic purposes, although interesting structures have been synthesized.

2.5. Physicochemical Properties of (−)-Cytisine

2.5.1. Conformations. The conformations of the tricyclic skeleton of cytisine were established by means of careful studies of ¹H NMR,^{92,93} ¹³C NMR,^{92,94,95} ¹⁵N NMR⁹⁶ spectra in connection with X-ray data,^{92,97,98} FT-IR,^{93a,99} Raman⁹⁹ spectroscopic, and computational studies.¹⁰⁰

2.5.1.1. Conformation in the Solid State. In the solid state, X-ray crystallography⁹⁸ showed that cytisine adopts conformation **1a** (Figure 4) with an essentially planar pyridone ring. This

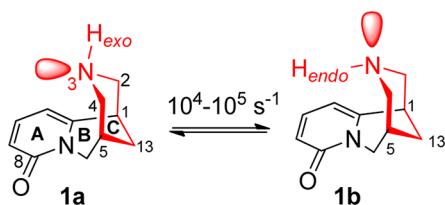


Figure 4. Conformations of (−)-cytisine.

planarity confers an envelope conformation on the adjacent ring B with the bridgehead carbon (C₁₃) out of the plane. Ring C adopts a conventional chair conformation. The N₃—H group forms a flattened pyramid with the nitrogen lone pair axial and its three substituents (C₂, C₄, and H). The sum of the three bond angles around N₃ indicated a tetrahedral geometry. Similar bond lengths, bond angles, and torsion angles were found for N-methylcytisine 18. As compared to cytisine, the ring C of N-methylcytisine has a chair form more rigid than that of cytisine.

In cytisine crystal, two independent molecules are in perpendicular positions with respect to each other.⁹² The equatorial hydrogen of the piperidine nitrogen of one molecule forms an intermolecular hydrogen bond with the piperidone oxygen of another molecule and stabilizes the crystal structure. These weak interactions O₈—H_{3'} (2.55 Å) and O_{8'}—H₃ (2.44 Å) form intermolecular angles of 144° and 145°. N-Methylcytisine has no similar intermolecular network.⁹⁸

IR and Raman spectra⁹⁹ for associated cytisine in the solid state were recorded, and the vibrational frequencies were computed for both conformers at the DFT level.¹⁰⁰ Among the two stable conformers **1a** and **1b**, only one **1a** is present in the solid state, where it is stabilized by intermolecular H-bonds (C=O···HN).

2.5.1.2. Conformation in Solution. The conformation of cytisine in solution is similar to that observed in the solid.⁹² Although flexibility was expected for ring C, the chair conformation was the only observed. Minimization of the steric effects between ring B and C could account for this observation.^{93b} The ¹H NMR spectra were consistent with a H-exo ⇌ H-endo (**1a** ⇌ **1b**) equilibrium and a N₃—H inversion rate in the range of 10⁴ and 10⁵ s⁻¹ (Figure 4). This was confirmed by quaternarization of N₃ with trifluoroacetic acid. The relaxation figures for the carbon atoms obtained at concentrations in the 0.1 M range reflected aggregation in solution.⁹²

FT-IR spectroscopy and particularly of the ν(C=O) frequency region^{99b} together with semiempirical (AM1 and PM3) computations¹⁰⁰ evidenced that **1a** and **1b** were present in apolar solvents in almost equal quantities, similar to the gas phase (see below).

Recently, from ¹H and ¹³C NMR analyses, Przybyl et al.¹⁰¹ suggested that N-acylcytisines in DMSO are in *cis*–*trans* equilibrium with ring C in chair and boat conformations (Figure 5).

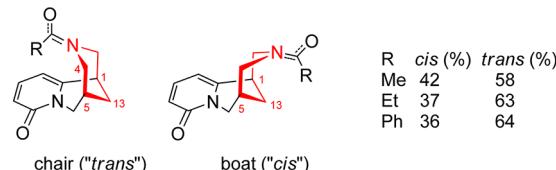


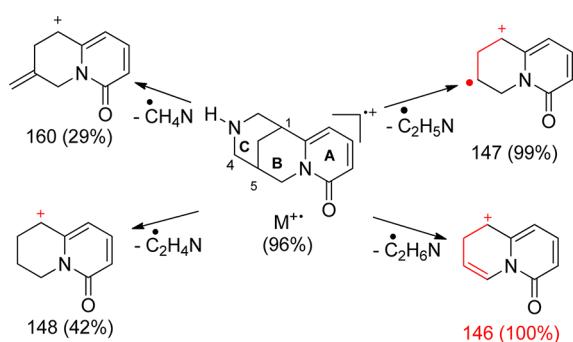
Figure 5. Conformations of N-acylcytisines.

2.5.1.3. Gas-Phase Structure. Geometrical parameters calculated at the semiempirical (AM1 and PM3), ab initio (HF/6-31G*),¹⁰⁰ and DFT¹⁰² levels for the conformations **1a** and **1b** in the gas phase were compared to those obtained on the basis of X-ray measurements.^{92,98} Unlike its methyl derivative **18**, where a single conformation is preferred strongly, the structural characterization of cytisine is more complex. Indeed, according to DFT, conformation **1b** (*endo*-H) is preferred by 1.04 kJ mol⁻¹ over **1a** (*exo*-H). The high energy barrier calculated for the NH inversion (15 kJ mol⁻¹) explains the existence of both isomers (*endo* and *exo*) observed in the gas phase and in apolar solvents. Their abundances **1a** and **1b** are almost the same in the mixture (40–60%, respectively).¹⁰³

The electronic structure has been investigated using photoelectron spectroscopy (PE).¹⁰² However, due to the broad and overlapped bands of the mixture of nearly isoenergetic conformers N—H *exo* and N—H *endo*, no information on the conformational equilibrium in the gas phase could be confidently derived from the PE spectrum.

2.5.2. Mass Spectrum. Detailed fragmentation pathways of cytisine molecular ion have been identified, and few characteristic fragment ions have been characterized.¹⁰⁴ The main fragmentation route of **1** (and five N-substituted derivatives) involves the cleavages of the C₁—C₂ and C₄—C₅ bonds, that is, the elimination of the C₂H₆N radical from ring C producing the base peak (146) (Scheme 10). The cleavage of the same bonds in the molecular ion with the simultaneous ejection of C₂H₅N leads to the abundant odd-electron distonic ion (*m/z* 147, 99%).

Scheme 10. Main Fragmentation of the Molecular Ion of Cytisine



which is also precursor of ions m/z 146, m/z 132, and m/z 93. The strong molecular ion (190.1, 96%) and the even-electron fragment (148, 42%) are characteristic of cytisine.

2.5.3. Thermochemistry. With the aim of standardization and certification of drugs based on cytisine, Kasenov et al.¹⁰⁵ measured different thermodynamic parameters of cytisine using calorimetric studies. They are summarized in Table 1. These data could be a valuable tool to estimate the probability and direction of reactions involving cytisine and derivatives or related naturally active substances.

The specific heat of cytisine was also measured, and the data were used to obtain the equation $C_p^\circ = f(T)$, which has the following form at 198–298 K: $C_p^\circ = (372.8 \pm 20.4) - (253.9 \pm 13.9) \times 10^{-3}T - (70.0 \pm 3.8) \times 10^5 T^{-2}$ J mol⁻¹ K⁻¹.

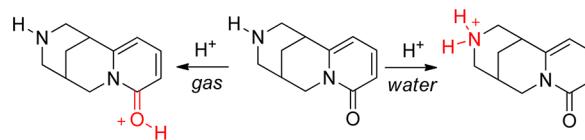
2.5.4. Protonation Sites. To understand interactions of cytisine with biological systems, ab initio calculations including two model compounds N-methyl-2-pyridone and piperidine have been performed to know the favored site of protonation in different environments.¹⁰⁶ Among the three functions considered as the possible sites of protonation of 1 (piperidine and piperidinone nitrogens, carbonyl oxygen), surprisingly the carbonyl oxygen is preferentially protonated in the gas phase, whereas, in water, the piperidine nitrogen is first protonated (Scheme 11).

3. CYTISINE SYNTHESES

The first total syntheses of (\pm)-cytisine were described more than 50 years ago. Intense research on the nicotinic neurotransmission in the 1990s boosted the need for new ligands of high affinity at the nAChRs (see section 2.2.2) and thus the development of original and flexible syntheses of cytisine. An excellent review on the synthetic routes to cytisine has been published in 2007.²⁴ The different syntheses are presented below with a special emphasis on the succession of the ring formations of the tricyclic structure and on the availability of the starting materials. Attempts to prepare nonracemic cytisine are gathered and compared at the end of this section.

The most common route to the tricyclic core of cytisine is the formation of C₆–N₇ bond of ring B resulting from the nucleophilic substitution of a leaving group by the nitrogen of a

Scheme 11. Protonation Sites of Cytisine



pyridine or of a dihydropyridinone, a strategy originally described by Van Tamelen.¹⁰⁷ The advent of metal-catalyzed aryl cross couplings has considerably improved this synthetic pathway. More recently, carbons in positions 1 and 12 were linked via an intermolecular 1,6-nucleophilic addition of a piperidinone (or piperidone enolate)⁶⁰ to a pyridone ring mediated by a base or via a palladium mediated Hartwig's α -arylation of a bromopyridone.¹⁰⁸ Only one paper presents a highly efficient synthesis of cytisine using a ring-closure metathesis to form ring A.¹⁰⁹ In two early syntheses by Bohlmann¹¹⁰ and Govindachari,¹¹¹ ring C was built from conveniently substituted quinoline-4-one derivatives. No recent work has used this strategy for the synthesis of cytisine or analogues. Scheme 12 summarizes the different routes later described in more detail.

3.1. Successive Formation of Rings A, then C

Bohlmann¹¹⁰ and Govindachari¹¹¹ completed the tricyclic structure of cytisine by the C-ring closure in 1955 and 1957, respectively. Both of the syntheses employed a trisubstituted starting pyridine (masked ring B) to build a quinolizidinone derivative. In Bohlmann's¹¹⁰ approach, quinolizidinone 45 was built in six steps from pyridine 42. Ring C was then formed from compound 45 under harsh conditions (Scheme 13).

In Govindachari's¹¹¹ synthesis (Scheme 14), the key trisubstituted pyridine 48 possessed a nitrile and an ester as masked amine and alcohol functions. Formation of the quinolizinone 49 and its functional transformations to 50 did not require high temperature and pressure. However, partial reduction of quinolizinone 50, then ring C construction to afford (\pm)-cytisine were low yielding steps.

3.2. Successive Formation of Rings C, then B (C₆–N₇ Bond)

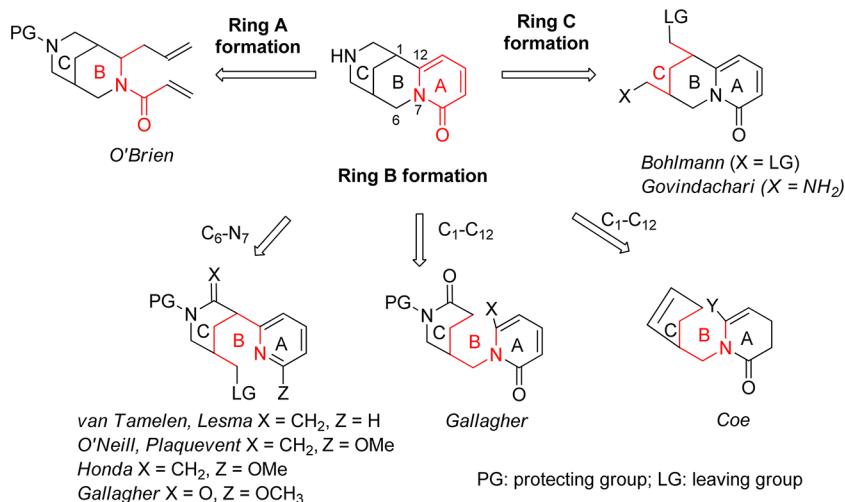
Van Tamelen in 1955^{107,112} used 2-methylpyridine 51 as the precursor of ring A of cytisine. Ring C was first appended. Nucleophilic displacement of a good leaving group by the pyridine nitrogen afforded ring B (Scheme 15). This approach of ring B was subsequently taken up in several other syntheses.

Guided by a biomimetic approach, van Tamelen and Baran¹⁰⁷ envisaged first the formation of ring C via a 2-fold Mannich condensation of benzylamine, formaldehyde, and 2-(2-pyridyl)-ethylmalonic acid. All attempts were unsuccessful. Starting from the elaborated precursor 52 (Scheme 16) prepared from pyridine 51, a tandem Mannich condensation–conjugate addition–decarboxylation reaction then enabled one to build ring C. A mixture of *cis* and *trans* ester 53 was formed. Epimerization of the *trans* to the *cis* isomer 53 was carried out to improve the yield of the ring-closure step. Functional transformation of *cis* ester 53 to bromide 54 allowed ring B formation via intramolecular nucleophilic substitution.

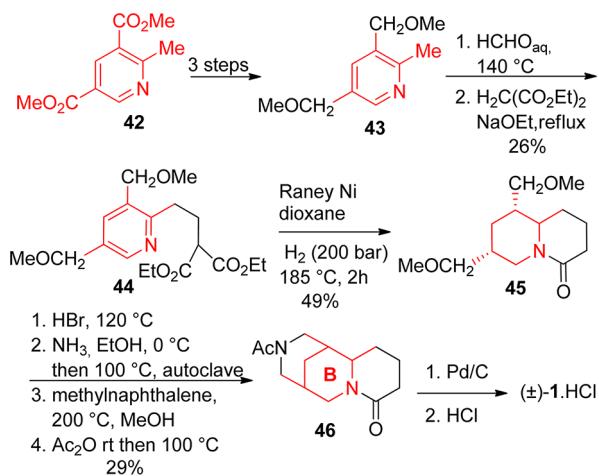
Table 1. Thermochemical Data of Cytisine

enthalpies	kJ mol^{-1}	enthalpies	kJ mol^{-1}
$\Delta_f H^\circ_{\text{liquid}}$	-189.7	$\Delta H^\circ_{\text{combustion}}$	-6144 \pm 232
$\Delta_f H^\circ_{\text{crystalline}}$	-226.3	$\Delta H^\circ_{\text{melt}}$	+36.6
$\Delta H^\text{m}_{\text{dissolution}}$	-0.65 \pm 0.01 (H ₂ O)	$\Delta H^\text{m}_{\text{dissolution}}$	+36.13 \pm 0.47 (96% EtOH)

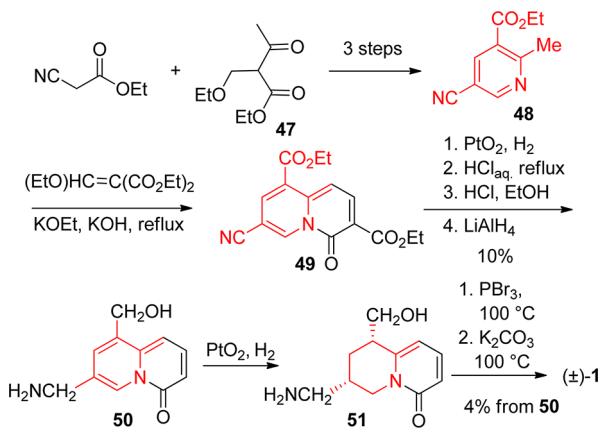
Scheme 12. Different Routes to the Tricyclic Core of Cytisine



Scheme 13. Bohlmann Synthesis

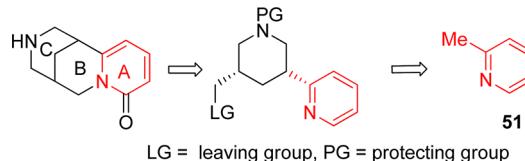


Scheme 14. Govindachari Synthesis



Oxidation and then deprotection of the secondary amine afforded cytisine (\pm)-1. This synthesis suffered from the low yielding preparation of the starting material 52 and from the difficult oxidation of the compound 55. Nevertheless, (-)-cytisine has been obtained unambiguously by resolution of the racemic compound with camphorsulfonic acid and comparison with the natural product (cf., section 3.6.1).

Scheme 15. Cytisine Synthesis: Van Tamelen Retrosynthetic Approach



3.3. Formation of Rings C (C₁–C₁₂ Bond), then B (C₆–N₇ Bond), a Convergent Approach

O'Neill¹¹³ and Plaquevent¹¹⁴ used van Tamelen's strategy to build ring B. Thanks to the discovery of palladium-catalyzed cross-coupling reactions to synthesize bis-pyridines (A–C ring connection) and to the possibility of selectively reducing one pyridine nucleus,¹¹⁵ their cytisine syntheses were more efficient and shorter. Last, to avoid the difficult oxidation of the pyridine ring, a methoxypyridine was used as the precursor of pyridone ring A. Scheme 17 summarizes the retrosynthetic analysis of this approach.

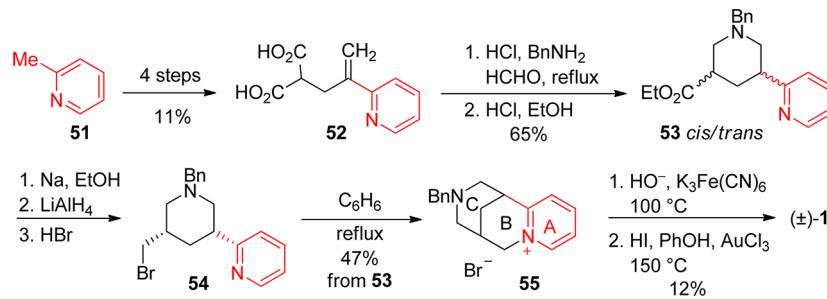
The first key step of the syntheses, the formation of the bond C₁–C₁₂ via heteroaryl cross-coupling reactions, is developed in Schemes 18 and 19.

3.3.1. Suzuki Couplings (Scheme 18). Palladium-catalyzed cross-coupling reactions in general and the Suzuki reaction in particular represent nowadays a powerful modern method to quickly assemble aromatic moieties. Various boron sources and conditions were tested for linking bromomethoxy-pyridine 57 with bromonicotinate 56. However, the yields in bipyridine 60, including the preparation of boron reagents, did not exceed 55%.¹¹³

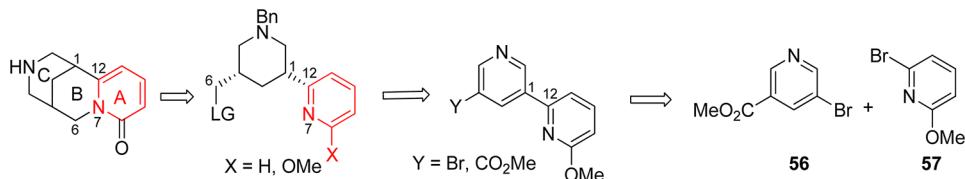
3.3.2. Stille Couplings (Scheme 18). The Stille reaction was tried as an alternative to the Suzuki coupling. S-Bromonicotinate 56 was readily transformed into its tri-n-butylstannane 59, and the coupling with bromomethoxy-pyridine 57 provided the desired bipyridine 60 in 50% yield.¹¹³ O'Neill et al. carried out also the reaction of 57 and 56 under the Stille–Kelly conditions avoiding the isolation of stannane 59 to synthesize 60 with about the same efficiency. Overall, the Stille methodology did not afford better yields as compared to the Suzuki reaction.

3.3.3. Negishi Coupling. Plaquevent et al.¹¹⁴ described the preparation of various substituted and functionalized bipyridines

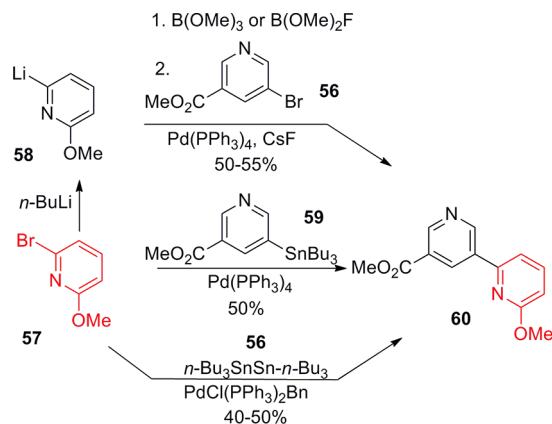
Scheme 16. Van Tamelen Synthesis



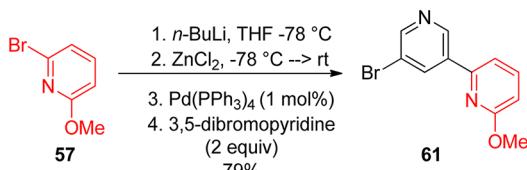
Scheme 17. O'Neill and Plaquevent's Retrosynthetic Approach to Cytisine



Scheme 18. Bipyridine Syntheses



Scheme 19. Bipyridine from Negishi Coupling



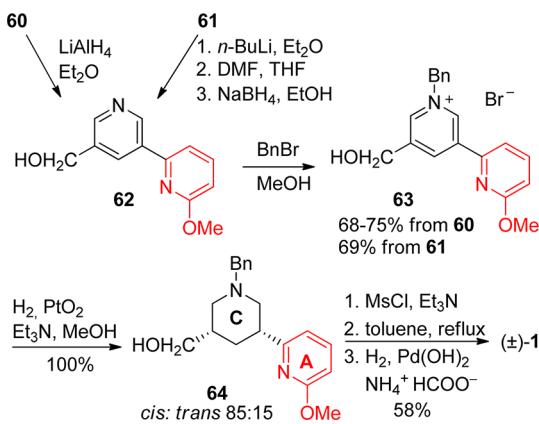
via a Negishi cross-coupling reaction. Using a low catalyst loading of $\text{Pd}(\text{PPh}_3)_4$ (1 mol %), zinc derivative of bromomethoxypyridine 57 reacted with an excess of dibromopyridine to afford pyridine 61 in 79% yield (Scheme 19). This makes the Negishi reaction the method of choice to create the C_1-C_{12} link between rings A and C of cytisine.

3.3.4. Formation of Cytisine from Bipyridines.

Formation of the diazabicyclo[3.3.1]nonane ring of cytisine was accomplished via the pyridinium alcohol 63. Selective N -benzylation of the less hindered pyridine ring of bipyridine 62 afforded 63, which was hydrogenated into 3,5-piperidine 64 as a *cis* and *trans* mixture (85:15). The *cis* isomer was transformed into its mesylate, which cyclized under reflux of toluene. Debenzylation provided (\pm)-cytisine (Scheme 20).

These approaches toward bipyridine were among the most efficient syntheses of (\pm)-cytisine from commercially available

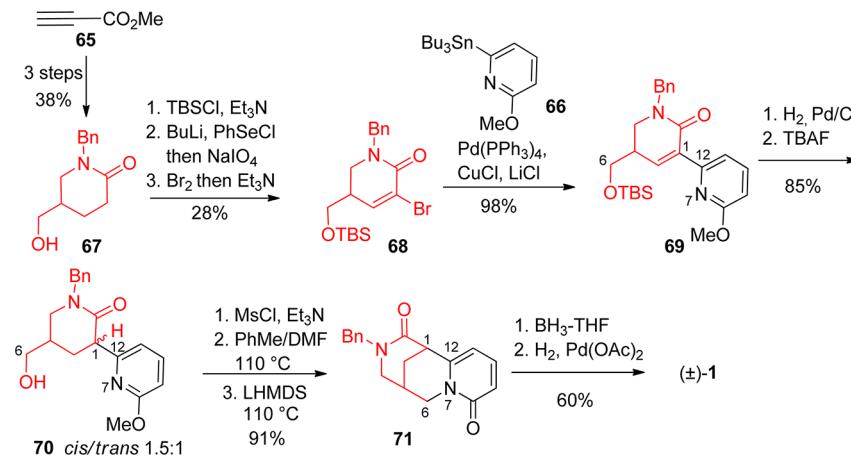
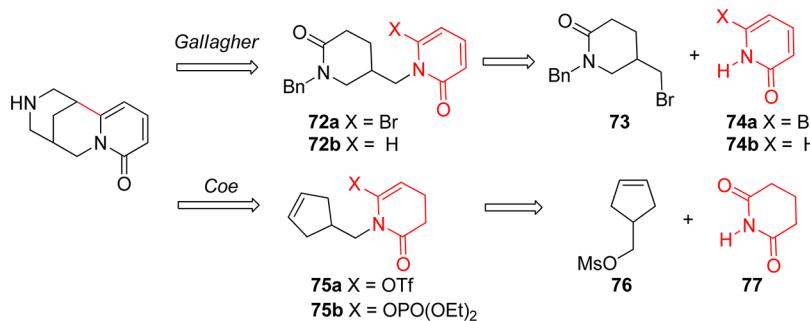
Scheme 20. Cytisine Syntheses of O'Neill and Plaquevent



compounds (7–8 steps) with overall yields from 20%¹¹³ to 31%.¹¹⁴ The main drawback of these routes was the poor selectivity (ratio *cis/trans*: 85:15) of the hydrogenation step of the bipyridines intermediates.

With the aim of developing a robust and flexible synthesis of cytisine to allow the preparation of analogues, Gallagher et al.¹¹⁶ in 2011 chose to assemble an adequately substituted dihydropyridone with a methoxypyridine. Compound 69 was prepared by reaction of dihydrobromopyridone 68, synthesized in six steps from methyl propiolate, with pyridine stannane 66 (Scheme 21). Hydrogenation of dihydropyridone 69 then desilylation afforded a mixture of *cis* and *trans* lactams 70 (ratio 1.5:1). Mesylation of the diastereoisomeric mixture 70, then thermal cyclization led to lactam 71 in 91% yield. This excellent yield was related to the facile isomerization of the *trans* to *cis* mesylate under basic conditions. A selective lactam reduction and N -debenzylation afforded (\pm)-cytisine. Cytisine was thus prepared according to a 14-step synthesis, the longest linear sequence from commercially available reagents and within 5% overall yield. The strategy for the construction of the cytisine skeleton is quite similar to the O'Neill and Plaquevent syntheses, particularly if one considers the type of reaction involved in the key steps to make the C_1-C_{12} and C_6-N_7 bonds.

Scheme 21. Gallagher's Cytisine Synthesis via a Pyridine–Dehydropiperidinone

Scheme 22. Retrosynthetic Analysis To Link C₁–C₁₂

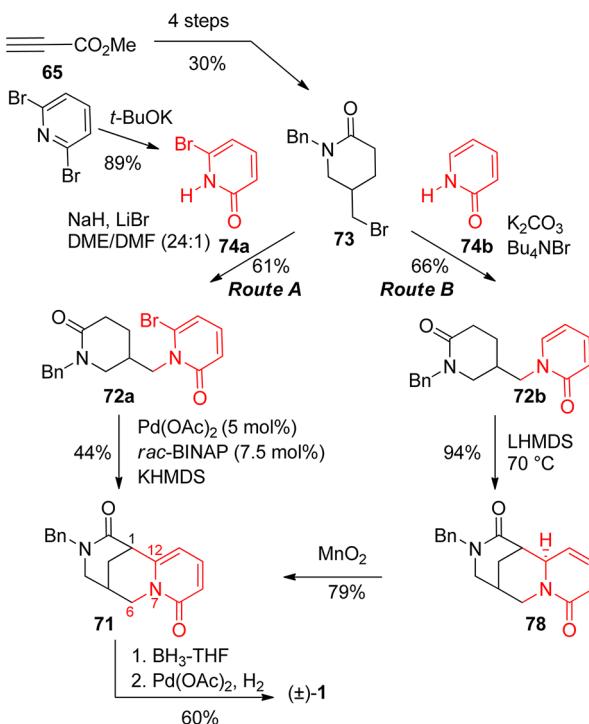
3.4. Formation of Ring C (C₆–N₇ Bond), then Ring B (C₁–C₁₂ Bond): A Convergent Approach

In the following original approaches, ring **B** was again the last ring built to complete the tricyclic structure of cytisine, but the C₁–C₁₂ bond was formed at last (Scheme 22). Three routes have been studied. Two of them used the intramolecular addition of a lactam enolate to a pyridone (Gallagher).^{60,108} The third one was based on an intramolecular Heck reaction (Coe).¹¹⁷

To avoid the hydrogenation of a bipyridine derivative, Gallagher et al.¹⁰⁸ synthesized N-substituted pyridones **72a** and **72b** (X = Br or X = H). The different steps of these convergent syntheses are shown in Scheme 23. The key starting material was bromomethylpiperidinone **73** prepared in four steps from methyl propiolate **65**. N-Alkylation of bromopyridone **74a** (route A) required a careful control of the experimental conditions to avoid O-alkylation and to obtain **72a** in reasonable yields. Palladium-mediated formation of C₁–C₁₂ bond afforded lactam **71**, which was selectively reduced, then deprotected to (±)-cytisine. This synthesis (overall yield 5%, eight steps) was slightly improved⁶⁰ by using pyridone **74b** instead of bromopyridone **74a** (Scheme 23, route B). Lactam **72b** underwent an unprecedented high yielding intramolecular 1,6-conjugated addition under basic conditions to form C₁–C₁₂ bond of ring **B**. An oxidation–reduction–deprotection sequence yielded (±)-cytisine in nine steps from methyl propiolate and about 9% overall yield. This new strategy was successfully applied to the synthesis of other tetracyclic lupine alkaloids (anagyrine and thermopsine).

Coe's strategy¹¹⁷ was based on the formation of C₁–C₁₂ bond of ring **B** using an intramolecular Heck reaction between

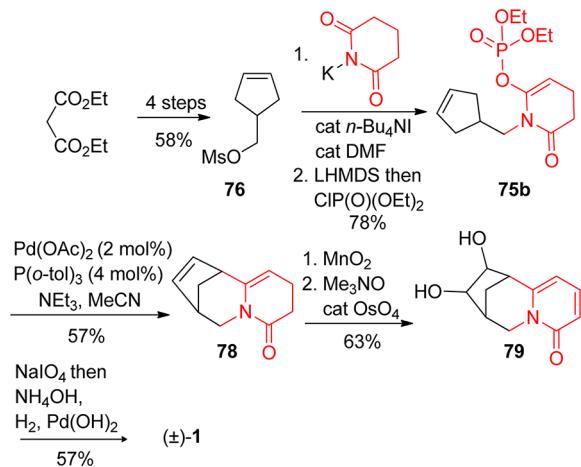
Scheme 23. Gallagher Approach



a ketene hemiaminal derived from glutarimide (A ring precursor) and a cyclopentenylmethyl substituent (Scheme 24).

Ketene hemiaminal triflates **75a** and, for the first time, ketene aminal dialkyl or diphenyl phosphates of glutarimide **75b** were

Scheme 24. Coe Synthesis



tested in an intramolecular Heck reaction. The best results were obtained with the diethylvinylphosphate ester **75b** (yield of **78**: 57%). The triflate gave a similar yield (52%), but its low yielding preparation (11%) limited its use for the synthesis. Dehydrogenation of the tricyclic lactam required the use of MnO_2 in large excess. The piperidine ring C was introduced in two steps. First, a standard dihydroxylation of the cyclopentene unit afforded diol **79** in 63% yield. This diol was then transformed into cytisine in a one-pot procedure (57% overall yield) involving oxidative cleavage, reductive amination. In this 10-step synthesis (9.2% overall yield), it should be noted that no protecting group was used (Scheme 24). This strategy was applied to synthesize carbon analogues of cytisine.¹¹⁸

3.5. Successive Formation of Rings C, then A

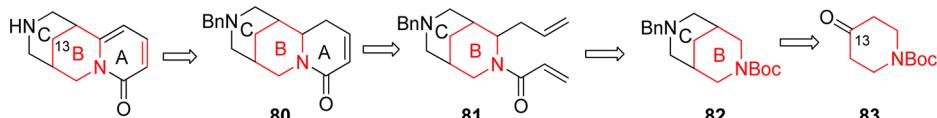
The strategy developed by O'Brien et al.¹⁰⁹ started with piperidinone **83** as ring B precursor. Ring C was first built using well-known and efficient reactions. A ring-closing metathesis of acrylamide **81** afforded dihydropyridinone **80**, a direct precursor of (\pm)-cytisine (Scheme 25).¹¹⁹

Key features of this new approach to (\pm)-cytisine were first a double Mannich reaction of *N*-Boc-piperidinone **83**, which gave *N*-Boc bispidine **82** after complete Wolff–Kishner reduction of the ketone. Allylation of the carbon α to the *N*-Boc group was carried out via a lithiation-transmetalation procedure using an allylphosphate instead of an allylbromide according to previously developed conditions.¹²⁰ The ring-closure metathesis of diallyl compound **81**, using Grubbs I catalyst, was efficient (89%), probably because of the rigid bispidine and the equatorial allyl group. Oxidation–*N*-debenzylation of **80** could be carried out in a one-pot procedure by heating **80** in toluene–cyclohexene at 100 °C in the presence of Pd/C. This linear synthesis is one of the shortest (six steps) and the most efficient preparation of (\pm)-cytisine (19% overall yield) from commercially available *N*-Boc piperidinone **83** (Scheme 26).

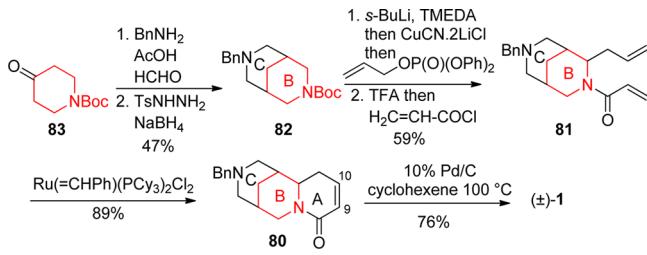
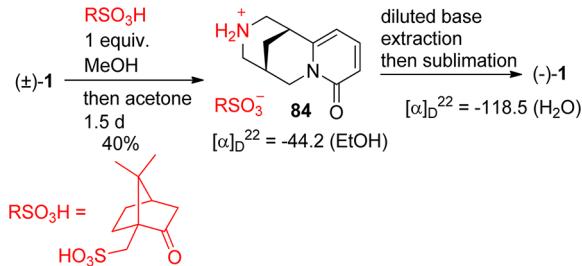
3.6. Syntheses of Non-racemic Cytisine

3.6.1. Resolution of (\pm)-Cytisine Using (+)-Camphorsulfonic Acid and Access to ($-$)-1. Van Tamelen and Baran

Scheme 25. Retrosynthetic Approach to Construction of Rings C, then A



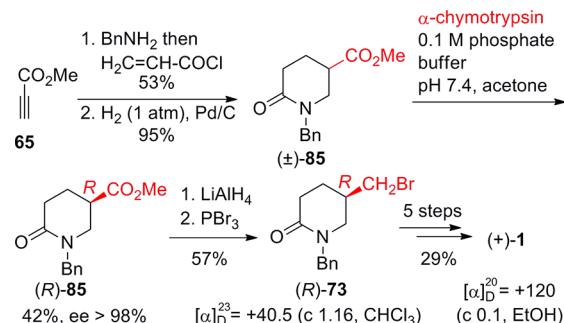
Scheme 26. O'Brien Synthesis

Scheme 27. Resolution of (\pm)-Cytisine

ended their total synthesis of (\pm)-cytisine with resolution of the alkaloid using (+)-camphorsulfonic acid (Scheme 27).¹¹² They obtained the ($-$)-enantiomer that was characterized by comparison of its optical rotation and melting point with the natural product.

3.6.2. Desymmetrizations. **3.6.2.1. Desymmetrization of a Lactam-Ester Using α -Chymotrypsin and Access to (+)-Cytisine.** In 2006, Gray and Gallagher⁶⁰ succeeded in the desymmetrization of piperidone-ester **85** using α -chymotrypsin (Scheme 28). An excellent ee was obtained for the *R* isomer

Scheme 28. Gallager Asymmetric Synthesis of (+)-Cytisine

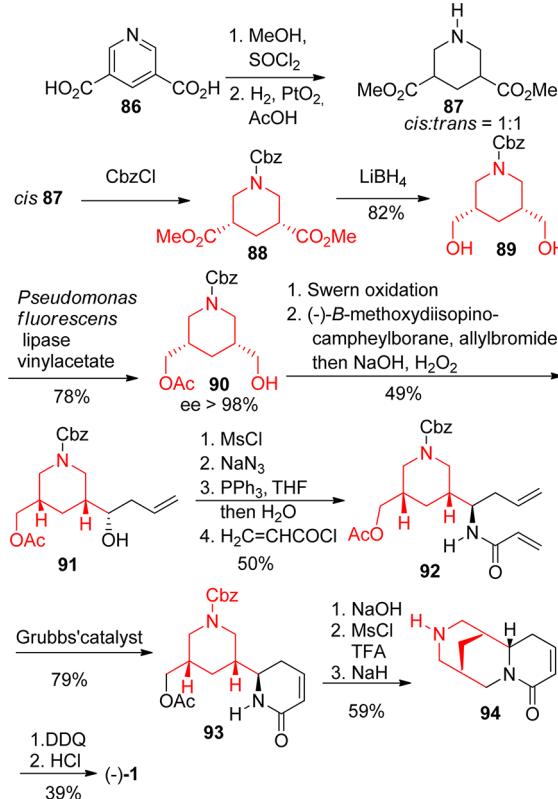


(*R*)-85, which was transformed into bromide (*R*)-73 for pursuing the synthesis (route B, Scheme 23). The (+)-enantiomer of cytisine was obtained and tested for its affinity at nAChRs (see section 2.2.2).

3.6.2.2. Desymmetrisation of a Dimethanolpiperidine Using an Enzyme and Access to ($-$)-Cytisine. Lesma et al. reported in 2004 the first enantioselective synthesis of ($-$)-cytisine.¹²¹ The approach relies on readily available enantiomers of

cis-piperidine 3,5-dimethanol monoacetate as the chiral building blocks by means of biocatalytic desymmetrization of *cis* diol 89. Among several microorganisms tested, *Pseudomonas fluorescens* lipase (PPL) (Scheme 29) gave the best results with enantio-

Scheme 29. Lesma Asymmetric Synthesis of (−)-Cytisine



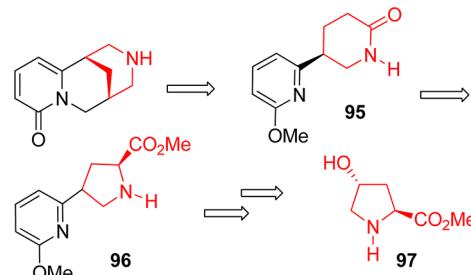
meric excesses higher than 98%¹²² for the acetate 90. The ring-closing metathesis of compound 92 to construct ring A of cytisine was the key step of the linear synthesis¹²² (Scheme 29).

The acetate-alcohol 90, a masked ring C synthesized in five steps from pyridine 3,5-dicarboxylic acid 86, was oxidized into its aldehyde. Allylation of the aldehyde according to Brown's procedure¹²³ afforded piperidine 91 with a high selectivity (diastereoisomeric ratio 10:1). Functional transformations of 91 into *N*-acryloyl derivative 92 followed by efficient ring-closing metathesis afforded dehydropiperidinone 93. Ring B was closed in high yield by substitution of the acetyl group of 93 by a mesylate, then treatment of the mesylate under basic conditions. Lactam 94 was finally oxidized into cytisine. This lengthy synthesis (17 steps, 2.8% overall yield from 86) is the first enantioselective synthesis of (−)-1.

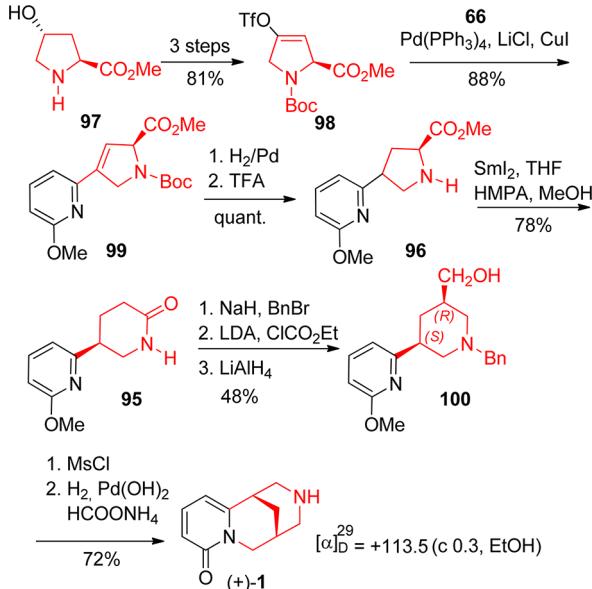
3.6.3. Synthesis of (+)-Cytisine Using the Chiral Pool. Honda et al.¹²⁴ developed the sole enantioselective synthesis of cytisine using the chiral pool. The strategy relied on functional transformations of the commercially available *trans*-L-hydroxy proline methyl ester 97 into the non-natural optically pure enantiomer (+)-1. The key step was the formation of piperidinone 95 from samarium-mediated ring expansion of proline derivative 96¹²⁵ (Scheme 30). Again, the synthesis was convergent with the formation of C₁–C₁₂ bond between rings A and C, before ring B closure.

Hydroxypyrolle methyl ester 97 (ring C precursor) was converted to vinyl triflate 98 in three steps (Scheme 31). Bond C₁–C₁₂ of the target compound was formed in the Stille

Scheme 30. Honda Retrosynthetic Analysis



Scheme 31. Honda Asymmetric Synthesis of (+)-Cytisine



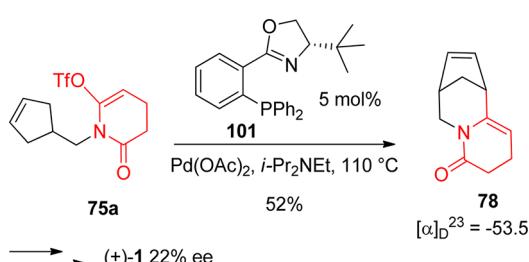
coupling of triflate 98 with tritylstannylmethoxypyridine 66. Selective hydrogenation of 99 followed by Boc removal afforded proline derivative 96. Samarium diiodide promoted fragmentation followed by simultaneous cyclization of the resulting δ-aminoester and gave lactam 95. Functionalization of the 3-position of this lactam and reduction of the carbonyl led to piperidine methanol 100 as a mixture of isomers (ratio 1:1) from which the *cis* isomer was isolated. Formation of ring B was similar to van Tamelen's method (nucleophilic displacement of a mesylate).

This efficient 12-step synthesis (19.2% overall yield) was the first selective preparation of the (+) enantiomer of cytisine. Unfortunately, no biological data were reported.

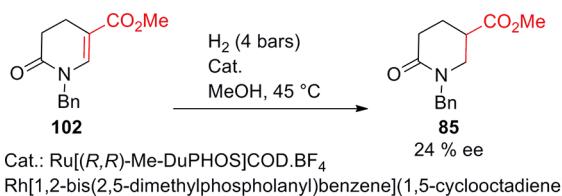
3.6.4. Enantioselective Synthesis of Cytisine Using a Catalytic Step. **3.6.4.1. Asymmetric Heck Reaction.** In 2000, Coe¹¹⁷ attempted an asymmetric variant of the Heck reaction, which characterized his approach to cytisine (see Scheme 24). While Heck cyclization with BINAP as ligand did not progress under the studied conditions, the coupling reaction of triflate 75a in the presence of Pfaltz ligand 101 afforded 78 with a 22% ee (Scheme 32). The ee was determined after conversion to (+)-cytisine. No improvement was observed by using the phosphate ester 75b (Scheme 24) and ligand 101. A racemic material was obtained [4% ee in favor of the (+)-enantiomer 78].

3.6.4.2. Asymmetric Reduction of an Unsaturated Lactam. In their first synthesis of cytisine, Gallagher et al.¹⁰⁸ used lactam 85 as an early precursor. They investigated various methods for the catalytic asymmetric reduction of 102 to 85. The highest

Scheme 32. Attempt of Catalytic Asymmetric Cytosine Synthesis



Scheme 33. Asymmetric Reduction of a Dehydropiperidone



ee (24%) was obtained with Ru[(*R,R*)-Me-DUPHOS]cod·BF₃ as the catalyst (Scheme 33). The yield of the reaction and the configuration of the major enantiomer were not given.

The results presented above highlight the difficulty in synthesizing non-racemic cytisine especially under asymmetric catalytic conditions.

Table 2 summarizes the recent syntheses of cytisine from commercially available starting material.

4. (-)-CYTISINE DERIVATIVES: SYNTHESIS AND PROPERTIES

4.1. 9- and 11-Substituted Cytisines

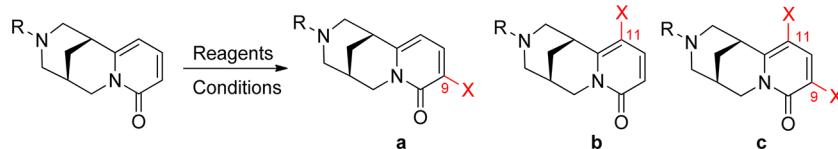
4.1.1. 9- and 11-Halocytisines. Halogenations of cytisine ($-$)-1, along with nitration, were developed early in the chemical history related to cytisine, a long time before its structure was elucidated. These reactions clarified the reactivity of ($-$)-1 toward electrophiles, enabling one to suspect the presence of an electron-rich aromatic nucleus such as a pyridone in the structure. Nowadays, the halogenation reaction is the key step in

Table 2. Summary of the Recent Approaches to Cytisine Synthesis

Author, year, ref.	Starting materials and key intermediates	Enantioselective approach
Coe, 2000 ¹¹⁷		Catalytic Heck reaction (+)-1 ee of an intermediate 22%
Gallagher, 2004 ¹⁰⁸		a
Gallagher, 2006 ⁶⁰		Enzymatic desymmetrisation (+)-1 (Yield: 3,5%, 10 steps) [α]D ²⁰ = +120 (c 0.1, EtOH)
Gallagher, 2011 ¹¹⁶		a
Honda, 2005 ¹²⁴		Chiral pool (+)-1 [α]D ²⁰ = +113.5 (c 0.3, EtOH)
Lesma, 2004 ¹²¹		Enzymatic desymmetrisation (-)-1 [α]D ²⁰ = -114 (c 1, EtOH)
O'Brien, 2005 ¹⁰⁹		a
O'Neill, 2000 ¹¹³		a
Plaquevent, 2001 ¹¹⁴		a

^aRacemic syntheses.

Table 3. Halogenations of (-)-Cytisine and N-Protected Cytisine



entry	substrate R	reagents	conditions	X	products: ratio (isolated yields) %			ref	
					a	b	c		
1	Boc	105	NBS	CH ₂ Cl ₂ , 1.5 h, reflux	Br	107 (57)	n.i.	n.i. ^b	128
2	CO ₂ Me	104	NBS	DMF, 0.5 h, 0 °C	Br	108 74.5 (57)	23.5 (17)	2	21
3	CO ₂ Me	104	NBS	THF, 0.5 h, 0 °C	Br	108 85	15	0	21
4	NO	106	NBS	CH ₂ Cl ₂ , 4 h, 0 °C	Br	109 (50)			21
5	COMe	27	NBS	CH ₂ Cl ₂ , 8 h, reflux	Br	110 49	31	20	101
6	H	1	NBS	AcOH/H ₂ O, 2 h, reflux	Br	111 (27)	(27)	(5)	129
7	Boc	105	NCS	CH ₂ Cl ₂ , 16 h, reflux	Cl	112 (4.6)	(68)		128
8	Bn	103	NCS	CH ₂ Cl ₂ , 16 h, reflux	Cl	113 (9)	(58)		128
9	H	1	NCS	AcOH/H ₂ O, 1 h, reflux	Cl	114 (26)	(40)		129
10	H	1	ICl	AcOH, 6 h then H ₂ O, 16 h, rt	I	115 (25)	(29)	(1)	129
11	Boc	105	ICl	CH ₂ Cl ₂ , 5 h, CaCO ₃ , rt	I	116 (48)			128
12	CO ₂ Me	104	AcOAg, I ₂	CH ₂ Cl ₂ , 12 h, 0 °C	I	117 (55)			21
13	NO	106	AcOAg, I ₂	CH ₂ Cl ₂ , 12 h, 0 °C	I	118 (50)			21
14	COMe	27	NIS, (BzO) ₂	CH ₂ Cl ₂ , 8 h, reflux	I	119 21	2	77	101
15	COMe	27	NIS	CH ₂ Cl ₂ , 8 h, reflux	I	119 6	91	3	101
16	Boc	105	Select-fluor (0.8 equiv)	DMF, 24 h, rt ^a	F	120 (9)	(31)		131

^aConversion 54%. ^bNot indicated.

the development of cytisine derivatives via transition metal coupling reactions. Moreover, as halogens would be expected to increase the lipophilicity of a compound and therefore its absorption through biological membranes, halogenations of (*-*)-**1** were undertaken in several groups with the aim of discovering improved ligands at nAChRs.

4.1.1.1. Bromination. Lammers¹²⁶ described one of the first brominations of cytisine. Reaction of bromine with (*-*)-**1** led to a mixture of perbromide and dibromide, which were characterized later.¹²⁷ The formation of the monobromo compound and the ratio of the dibromide and perbromide were not mentioned. Much later, reaction of *N*-bromosuccinimide (NBS) with *N*-Boc-cytisine **105** in dichloromethane (Table 3, entry 1)¹²⁸ or with *N*-carbomethoxy cytisine **104** in DMF²¹ (entry 2) led to *N*-protected 9- and 11-bromocytisines. Bromocytisines **108a** and **108b** were isolated in 57% and 17% yields, respectively, with 2% of *N*-carbomethoxy 9,11-dibromocytisine **108c**. The ratio of 9- and 11-regioisomers was dependent on the solvent. In THF no dibromo compound was formed, and the ratio of 9-bromo/11-bromo derivatives reached 85/15 (entry 3).²¹ Similar results were obtained when *N*-nitrosocytisine **106** was treated with NBS (entry 4). Recently,¹⁰¹ up to 20% of 11-regioisomer was obtained in the reaction of *N*-acetylcytisine **27** with NBS (entry 5). The conditions, more than the protecting group, were probably the cause of the lack of regiochemistry. Although slightly less effective than the three-step procedure, a one-pot reaction starting from unprotected cytisine **1** was developed.¹²⁹ Acetic acid was used as the solvent, and the resulting *N*-protonated cytisine acetate was treated with NBS under reflux (entry 6). After chromatography, 9-bromo, 11-bromo, and 9,11-dibromocytisines **111a**, **111b**, and **111c** were isolated in 27%, 27%, and 5% yields, respectively.

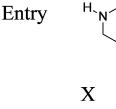
4.1.1.2. Chlorination. Orjales et al. in 1972 showed that 9,11-dichlorocytisine **114c** was obtained by treatment of

(*-*)-**1** with PCl₅.¹³⁰ Chlorination of *N*-Boc cytisine **105** with *N*-chlorosuccinimide (NCS) in dichloromethane under reflux led to both regioisomers 9- and 11-chlorocytisines **112a**, **112b** (Table 3, entry 7), but, unlike bromination, this reaction led mainly to the 11-isomer (ratio *N*-Boc 11-chloro/9-chloro cytisines: 14.8/1).¹²⁸ A similar high ratio of 11-regioisomer was observed whatever the nitrogen protecting group (entry 8).^{21,128} When unprotected cytisine was treated with NCS in a mixture of acetic acid/water, both regioisomers were formed (entry 9; 11-chloro/9-chlorocytisines: 1.53/1).¹²⁹ No explanation has been suggested to account for this different regiochemistry when using NBS and NCS.

4.1.1.3. Iodination. Direct iodination of (*-*)-**1** with iodine chloride in acetic acid led to the 9- and 11-regioisomers **115a** and **115b** being difficult to separate (entry 10).¹²⁹ In a more successful approach, *N*-protected cytisine was treated either with iodine monochloride in dichloromethane in the presence of calcium carbonate¹²⁸ (entry 11) or with iodine in the presence of silver acetate (entries 12 and 13).²¹ In every case, 9-iodocytisine was the sole product isolated in 48–55% yield. Treatment of *N*-acetylcytisine **27** with *N*-iodosuccinimide (NIS) in the presence of benzoyl peroxide (BzO)₂¹⁰¹ led predominantly to the diiodo compound, while the 11-regioisomer was the major product when the reaction was carried out without peroxide (entries 14 and 15). Although the yield of the isolated product was not reported, this method is complementary to the previous ones.

4.1.1.4. Fluorination. The 9-fluoro and 11-fluoro cytisines were recently synthesized.¹³¹ *N*-Boc protected cytisine was treated with Selectfluor [1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF₄)], a safe and soluble electrophilic fluorinating reagent. To avoid overfluorination and to limit the formation of side products, the reaction required the use of a limited amount of Selectfluor. Despite these conditions, large amounts of unreacted protected cytisine were

Table 4. Ligand Binding Affinities of Halocytisine Derivatives to $\alpha 4\beta 2$, $\alpha 3\beta 4$, and $\alpha 7$ nAChRs

Entry		Species ^{a,b,c}	Ki $\alpha 4\beta 2$ (nM)	Ki $\alpha 7$ (nM)	Ki $\alpha 3\beta 4$ (nM)	Ki $\alpha 4\beta 4$ (nM)
	X					
1	H	rat brain	0.124 ¹²⁹ 0.60 ¹³³	260 ¹²⁹ 30403 ¹³³	220 ¹³⁵	
2	9-Br	rat brain	0.010 ^{129,136b} 0.208 ¹³³	2.0 ¹²⁹ 112 ¹³³	7.5 ¹³⁵	
3	9-Cl	rat brain	0.022 ¹²⁹	2.5 ¹²⁹	18 ¹³⁵	
4	9-I	rat brain	0.017 ¹²⁹ 0.165 ¹³³	1.5 ¹²⁹ 115 ¹³³	7.4 ¹³⁵	
5	9-F	rat brain	6.53 ¹³¹			
6	11-Br	rat brain	0.308 ¹²⁹ 307 ¹³³	28 ¹²⁹ 103020 ¹³³	380 ¹³⁵	
7	11-I	rat brain	0.230 ¹²⁹	21 ¹²⁹		
8	11-Cl	rat brain	2.5 ¹²⁹	1000 ¹²⁹	3900 ¹³⁵	
9	9,11-(Br) ₂	rat brain	10.8 ¹²⁹ 250 ¹³³	1500 ¹²⁹ 43343 ¹³³	45000 ¹³⁵	
10	9,11-(Cl) ₂	rat brain	2.5 ¹²⁹	1000 ¹²⁹	39000 ¹³⁵	
11	9,11-(I) ₂	rat brain	0.520 ¹²⁹	41 ¹²⁹	4200 ¹³⁵	
12	H	Human	1.07 ^{134a} 1.2 ^{134b}	8360 ^{134a}		0.091 ^{134b}
13	9-Br	Human	0.082 ^{134a} 0.088 ^{134b}	16 ^{134b}		0.012 ^{134b}
14	9-I	Human	0.7 ^{134b}	7 ^{134b}		0.34 ^{134b}
15	11-Br	Human	1540 ^{134a} 2000 ^{134b}	1000 ¹³⁴		70 ^{134b}
16	11-I	Human	10 ^{134b}	8000 ^{134b}		19 ^{134b}
17	9,11-(Br) ₂	Human	420 ^{134a} 500 ^{134b}	1000 ^{134b}		24 ^{134b}

^aRat brain: $\alpha 4\beta 2$, comparison with (\pm)-[³H]epibatidine^{129,133} or with (-)-[³H]cytisine;¹³¹ $\alpha 7$, comparison with (\pm)-[³H]MLA (methyllycaconitine)¹²⁹ or with [¹²⁵I] α -bungarotoxin.¹³¹ ^bCultured cells expressing native and transfected subunits combinations: $\alpha 4\beta 2$ (K-177), $\alpha 3\beta 4$ (KX $\alpha 3\beta 4$ R2) receptors; labeling $\alpha 4\beta 2$ and $\alpha 7$, (\pm)-[³H]epibatidine and [³H]MLA, respectively.¹³⁵ ^cHuman nAChRs: cultures of SH-SY5Y-h $\alpha 7$ clonal cell line for h $\alpha 7$ nAChR, SH-EP1-h $\alpha 4\beta 2$, SH-EP1-h $\alpha 4\beta 4$ clonal cell line for h $\alpha 4\beta 2$ and h $\alpha 4\beta 4$ nAChR, respectively. Comparison with [³H]cytisine for h $\alpha 4\beta 2$ nAChR and [¹²⁵I] α -bungarotoxin for h $\alpha 7$.¹³⁴

recovered (entry 16). N-Boc 9-fluoro and 11-fluoro cytisines **120a** and **120b** with 9,11-difluorocytisine **120c** were isolated in low yields. Deprotection of the secondary amine (TFA, CH₂Cl₂, 16 h, rt) afforded pure (-)-9-fluorocytisine **121a** and (-)-11-fluorocytisine **121b** for biological evaluation.

Recently, the crystal structures of *N*-acetyl-9-bromocytisine **110a**, *N*-acetyl-9-iodo cytisine **119a**, and *N*-Boc 9-bromocytisine **107a** have been determined by X-ray diffraction.¹³² In the *N*-acetyl derivatives, the molecules are connected by relatively strong interactions C-X...O. These interactions are weak in the *N*-Boc bromo derivative **107a** but contribute nevertheless to organize the two-dimensional structure.

4.1.1.5. Biological Evaluation. The unprotected halocytisines were evaluated for their binding affinities at nAChRs mainly $\alpha 4\beta 2$, $\alpha 7$, and $\alpha 3\beta 4$ (rat brain, human clonal cells). A significant difference between the values was sometimes observed. The main data are summarized in Table 4.

Bromination, chlorination, or iodination at C₉ of the pyridone ring of (-)-**1** afforded affinities higher than (-)-cytisine (entry 1 as compared to entries 2–4). The same trend was observed at human nAChRs (entry 12 vs entries 13–14). Introduction of a

fluorine atom at C₉ of (-)-**1** decreases the affinity at $\alpha 4\beta 2$ nAChR (entry 5, rat brain). For this compound, no data were reported on the affinities toward the other nAChR subtypes.¹³¹

Both iodination and bromination at C₁₁ markedly reduce the affinity for the human $\alpha 4$ subunit containing nAChRs subtypes (entry 12 vs entries 15, 16). A marked difference between the binding affinities of 11-bromo and 11-iodocytisine (entries 6, 7 and 15, 16) $\alpha 4\beta 2$ nAChR was observed. This unexpected change could be due, according to Wonnacott et al.,¹³³ to the different orientations in which cytisine is supposed to bind to nicotinic receptors. This substitution at C₉ of (-)-**1** might enhance binding and efficacy by anchoring the pharmacophore in an active orientation, while substitution at C₁₁ might leave the substituent in a position where such an interaction is not favored. Houlihan et al.¹³⁴ proposed that the binding site of neuronal nAChRs may have a halogen-accepting hydrophobic pocket near the hydrogen-bond donor moiety interacting with the carbonyl oxygen of (-)-**1**. The halogen would favor the hydrogen bonding between cytisine and the receptor binding site ultimately leading to higher agonist affinity and efficacy. C₉ halogenation of cytisine might stabilize the conformation of the

nicotinic receptor but without enhancing subtype selectivity. An appropriate size rather than the electronegativity of the halogen must be considered to account for the observed affinities.

Dihalogenations of the pyridone ring of $(-)$ -1 reduce significantly the binding affinity at the nAChRs whatever the studied subtype. It should be noted that 9-bromocytisine **111a** has a high binding affinity at $\alpha 4\beta 4$ nAChRs (0.012 nM), higher than that of $(-)$ -cytisine under the same conditions (0.091 nM). Although lower, 9-iodocytisine **115a** still has a nanomolar affinity (0.34 nM).^{134b}

Functional agonist activity of halocytisines at nAChRs was generally evaluated in the studies reporting the binding affinities. For example, Daly et al.¹³⁵ compared the efficacies of halocytisines relative to [3 H]epibatidine at rat $\alpha 3\beta 4$ nAChRs and human $\alpha 4\beta 2$ nAChRs using KX $\alpha 3\beta 4R2$ and K-177 cultured cell lines, respectively. They showed that the halogen substitution at C₉ increases the efficacy (up to 78% at rat $\alpha 3\beta 4$ nAChRs and up to 92% at human $\alpha 4\beta 2$). The 11-halo compounds lost all activity at the neuromuscular subtype $\alpha 3\beta 4$, and only the 11-bromo compound retained a significant efficacy (70%) at the human $\alpha 4\beta 2$ subtype. These results suggested that the structural requirements for affinity and efficacy were different. Whereas 9-bromocytisine is more efficacious and more potent than the parent compound, 9-iodocytisine is slightly less potent and has a lower efficacy, suggesting that efficacy may not be sensitive to the size of the halogen.

Abin-Carriquiry et al.¹³⁶ carried out an in silico characterization of halocytisines (9-bromo, 9-iodo, 9-bromo-N-methyl, 11-bromo, and 9,11-dibromocytisines) into an acetylcholine binding pocket. Their studies showed a good correlation between the experimental values of the inhibition constants (as their pIC₅₀ values) at rat $\alpha 4\beta 2$ nAChRs and docking energy of the best cytisinoid poses with the acetylcholine binding protein. This correlation might be useful for the prediction of affinities of new cytisine derivatives, which share the same binding mode.

Some of the most relevant interactions of the compounds in the binding site have been identified. Halogenation at C₁₁ produces repulsive van der Waals interactions with the receptor, given the proximity of the C₁₁ halogen atom to cysteine and tyrosine residues (Cys188, Tyr192). Consequently, these cytisine derivatives are slightly relocated, causing a decrease in the contribution of the hydrogen bonds.

N-Methylation hinders the formation of a H-bond with the OH group of a tyrosine, while reinforcing the hydrogen bond between the carbonyl oxygen through a bridging water molecule to the NH of leucine and methionine (Leu102 and Met114) residues. However, the strength of the latter interaction is not enough to offset the loss of the former one.

Halogenations at C₉ favor various interactions with two leucine (Leu102, Leu112), arginine (Arg104), methionine (Met114), and threonine (Thr144), while the H-bonds with the OH group of a tyrosine (Tyr89) and a water molecule remain constant.

The ability of cytisine, 9-bromo-, and 11-bromocytisines to induce striatal (from the striatum, a subcortical part of the forebrain) dopamine release was characterized *in vivo* by microdialysis.¹³⁶ Abin-Carriquiry et al. showed that cytisine, 11-bromocytisine, and nicotine are more efficacious than 9-bromocytisine in eliciting dopamine response to their local application. Moreover, cytisine and its 11-bromoderivative (but not 9-bromocytisine) prevented the decrease of striatal dopamine tissues levels induced by 6-hydroxydopamine, an

important result because of its potential for Parkinson's disease treatment.

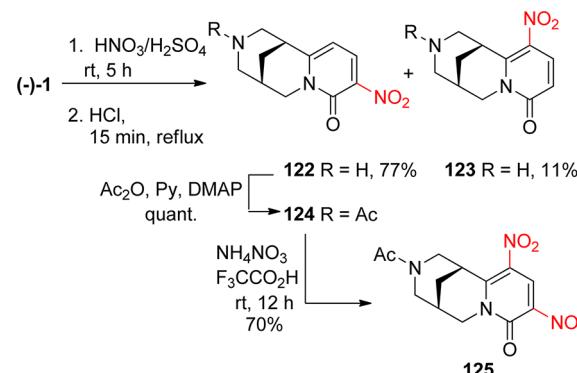
11-Bromocytisine was tested for its ability to show anti-depressant-like activity in mice. However, in the different paradigms used to assess this activity, Picciotto et al.¹³⁷ showed the lack of behavioral effect when administrated peripherally, which could be the result of a low brain penetration.

The *in vivo* effects of 9-iodocytisine in mice have been evaluated. Whereas 9-iodocytisine cannot be envisaged for a new drug for smoking cessation, the hypothermia elicited suggested that 9-iodocytisine may be useful in prevention of degenerative processes observed in nervous tissue after ischemic damage.¹³⁸

4.1.2. 9- and 11-Cytisines Substituted by a Nitrogen Group.

4.1.2.1. Syntheses. The nitration of cytisine was first reported in 1894,³ and nitrocytisines were isolated a few years later.¹³⁹ However, the first and reproducible^{21,140} preparation of 9-nitro, 11-nitrocytisines **122**, **123** and *N*-acetyl-9,11-dinitrocytisines **125** was described in 2000 (Scheme 34). To obtain the

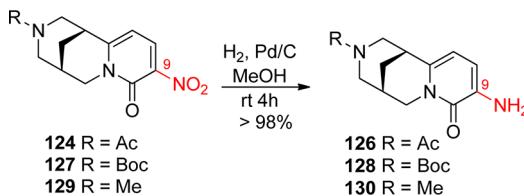
Scheme 34. Nitration of Cytisine



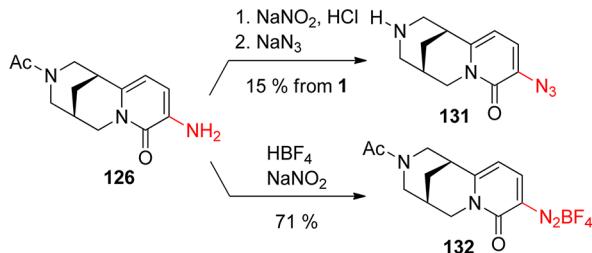
dinitro derivative, protection of the secondary amine function of $(-)$ -1 was necessary. The crystal structure of 9-nitrocytisine, recently described,¹⁴⁰ showed that two independent molecules are linked by intermolecular N–H···ON(O) hydrogen bonds and weak intermolecular C–H···O=C interactions. The chains are additionally stabilized by intermolecular NO₂···π interactions.

Reduction of N-substituted nitro derivatives using hydrogen in the presence of a palladium catalyst afforded the corresponding aminocytisines in high yields (Scheme 35).^{21,141}

Scheme 35. 9-Aminocytisines

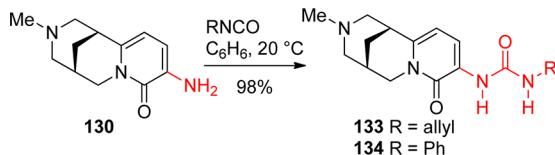


The chemistry of 9-aminocytisines has been developed only for the purpose of biological studies. Attempts to introduce a substituent via a diazonium salt were not efficient (Scheme 36). Demushkin et al.¹⁴² treated 9-aminocytisine **126** with sodium nitrite and hydrochloric acid, then with sodium azide. They isolated 9-azidocytisine **131** in 15% overall yield from $(-)$ -1 (Scheme 36). In another study, Rouden et al.²¹ prepared the

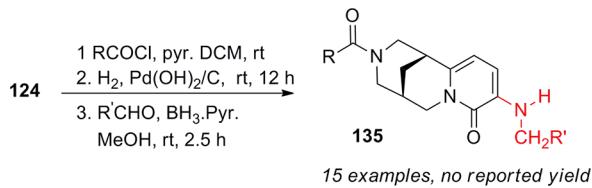
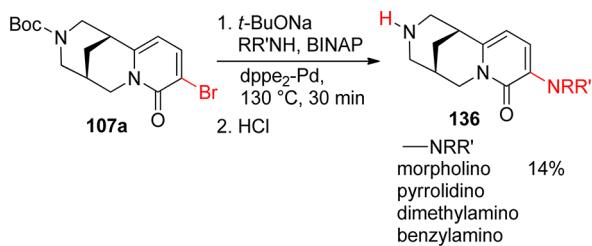
Scheme 36. Diazotation of *N*-Acetyl 9-Aminocytisine

tetrafluoroborate **132** from amine **126**. Yet, under all of the conditions tested, the Balz–Schiemann reaction did not afford the expected 9-fluoro derivative. The presence of a carbonyl group in *ortho* position to the diazonium group could explain this lack of reactivity. The salt **132** is an attractive precursor for cross-coupling reactions.¹⁴³

Recently, cytisinyl ureas **133**, **134** have been prepared in excellent yields from *N*-methyl 9-aminocytisine **130** (Scheme 37).¹⁴⁴

Scheme 37. Cytisinyl Ureas

Two routes were used to access to secondary amines in 9 position. The first one was based on a reductive amination (Scheme 38),¹⁴¹ the second one on Buchwald–Hartwig aminations (Scheme 39).¹²⁸ Although many compounds have been

Scheme 38. *N*-Acyl-9-(*N*-Alkyl or Arylamino)cytisines from Reductive Amination**Scheme 39. Buchwald–Hartwig Couplings of *N*-Boc-9-Aminocytisine**

the subject of biological tests, they have not been fully characterized, and, when shown, the reaction yield was poor.

4.1.2.2. Biological Data. A few nitro and amino derivatives of cytisine have been tested for their affinity at nAChRs.¹⁴⁵ The data are given in Table 5. 9-Nitrocytisine displays a binding affinity in the nanomolar range higher than that of 11-nitrocytisine. The primary amino group in the 9-position of (−)-cytisine was detrimental to the affinity at $\alpha 4\beta 2$ nAChR subtype.

Table 5. Affinities of Nitrocytisine and Aminocytisine at nAChRs

structures	IC_{50} (nM) $\alpha 4\beta 2^a$	IC_{50} (nM) $\alpha 7^b$	K_i (nM) ^a
(−)-cytisine	2.4 ¹⁴⁵	2300	
(−)-9-nitrocytisine	4 ^{21,145}	>1000 ²¹	1.2 ¹⁴⁶
(−)-11-nitrocytisine	32 ^{21,145}	>1000 ²¹	328 ¹⁴⁶
(−)-9-aminocytisine	318 ^{21,145}	>1000 ²¹	

^aRat brain preparations: $\alpha 4\beta 2$, displacement of (−)-[³H]cytisine. ^b $\alpha 7$: displacement of [¹²⁵I] α -bungarotoxin.

The ureas **133** and **134** were tested for their mnemonic activity (improvement of memory under the influence of the tested compounds).¹⁴⁴ Whereas cytisine (−)-1 and urea **133** did not exhibit noticeable mnemonic activity, the phenyl urea **134** has an activity comparable to that of the reference compound (piracetam).

4.1.3. 9- and 11-(Cyclo)alkyl or (Hetero)aryl-Substituted Cytisines. As for the 9-halocytisines, the synthesis of (−)-cytisine derivatives bearing an alkyl or aryl substituent at the 9 position was motivated by the search for compounds that could be used for the treatment of nicotinic dependence. Many compounds have been reported in patents, and only those described with analytical data are mentioned.

4.1.3.1. 9- and 11-Aliphatic-Substituted Cytisines. Most of the aliphatic 9- (or 11) derivatives of cytisine were prepared from N-protected 9-bromocytisine using Stille (Table 6, entries 1–5) or Suzuki couplings (Table 6, entries 6,7). Entry 8 gives the sole example of Heck reaction. As the yield for this latter reaction was given after subsequent reduction and deprotection, it is not possible to conclude on the efficiency of the cross-coupling reaction. Carbonylation in methanol was efficient (entry 9), whereas moderate yields were obtained in the cyanation (entry 10) and trifluoromethylation (entry 11) reactions.

The formyl group of **150** was introduced via the corresponding ester **145**.¹²⁸ Compound **142** was oxidized to yield N-Boc 9-acetylcytisine **151**.¹²⁸ Reduction of the vinyl derivatives **139** and **142** afforded N-Boc 9-ethyl and 9-iso-propyl cytisines **148** and **149** (Scheme 40).¹²⁸

The binding affinities at nAChRs were measured for 9-methyl, 9-vinyl, and 9-trifluoromethyl cytisines (Table 7). 9-Trifluoromethyl cytisine exhibits a subnanomolar affinity at $\alpha 4\beta 2$ nAChRs similar to that of (−)-9-methylcytisine and 4 times higher than that of cytisine itself. These compounds have an affinity close to that of (−)-9-bromocytisine with a better specificity as compared to $\alpha 7$ subtypes.¹³¹

After removal of Boc protection of compound **143** and introduction of specific substituents on the secondary nitrogen, two phosphatase (vascular endothelial protein tyrosine phosphatase VE-PTP) inhibitors **152** and **153** were identified (Figure 6).¹⁴¹ The inhibition constants IC_{50} of the tyrosine phosphatase VE-PTP were in the range of 2–2.5 μM .

No data are available for the affinities toward nicotinic receptors of amines.¹⁴¹

4.1.3.2. 9-Aryl and Heteroaryl Cytisines. Picciotto and Gündisch¹⁴⁸ as did Kozikowski et al.¹⁴⁷ introduced an aryl (or heteroaryl) group at the 9 (or 11-) position of cytisine via a Suzuki reaction (Scheme 41). Yields of the reactions are given in Table 8.

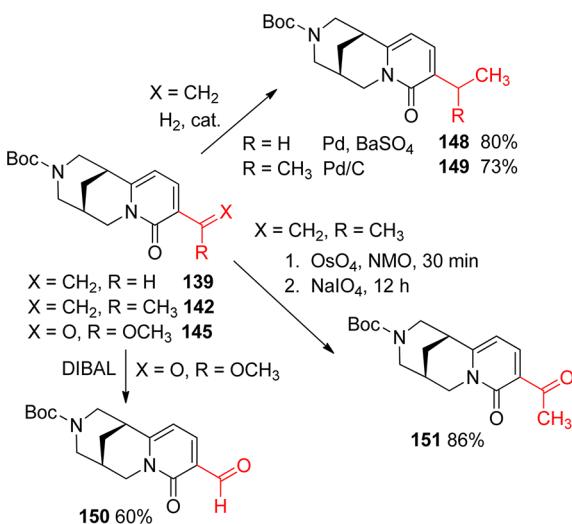
The binding affinities of the compounds at different nAChR subtypes ($\alpha 2\beta 2$, $\alpha 2\beta 4$, $\alpha 3\beta 2$, $\alpha 3\beta 4$, $\alpha 4\beta 2$, $\alpha 4\beta 4$, $\alpha 7$) were measured, and nanomolar affinities were observed at the $\alpha 4\beta 2$ subtype (Table 8). However, the highest affinities (entries 13 and 16) were lower than that of (−)-cytisine.

Table 6. Cross-Coupling Reactions of N-Protected 9-Bromo Cytisines

Entry	R	R'	Reagents	Conditions	Products	Yields %
1	NO	CH ₃	Me ₄ Sn	PdCl(PPh ₃) ₂ Bn, HMPA ²¹	137	81
2	Boc	CH ₃	Me ₄ Sn	PdCl ₂ (PPh ₃) ₂ , HMPA ¹³¹	138	45-79
				PdCl(PPh ₃) ₂ Bn, HMPA ¹²⁸		
3	Boc		Bu ₃ Sn	PdCl(PPh ₃) ₂ Bn, HMPA ¹²⁸	139	40-73
				PdCl ₂ (PPh ₃) ₂ , dioxane ¹⁴⁷		
4	NO		Bu ₃ Sn	PdCl ₂ (PPh ₃) ₂ , dioxane ²¹	140	70
5	NO		Bu ₃ Sn	PdCl ₂ (PPh ₃) ₂ , HMPA ²¹	141	55
6	Boc		(HO) ₂ B	Pd(PPh ₃) ₄ , Na ₂ CO ₃ , EtOH/H ₂ O ¹²⁸	142	Quant.
7	Boc		(HO) ₂ B	Pd(PPh ₃) ₄ , K ₂ CO ₃ , DME ¹⁴¹	143	^a
8	Boc			1. KOAc, DMF, nBu ₄ N ⁺ AcO ⁻ , Ph ₃ P, Pd(OAc) ₂ 2. H ₂ , 3 bar, Pd/C, 5 min ¹²⁸	144	^b
9	Boc	CO ₂ Me	CO (1 bar), MeOH	Pd(OAc) ₂ , dppp, KHCO ₃ ¹²⁸	145	86
10	Boc	CN	Zn(CN) ₂	Pd(PPh ₃) ₄ , DMF ¹²⁸	146	51 ^c
11	Boc ^d	CF ₃	F ₃ CCO ₂ Na	CuI, DMF ¹³¹	147	42

^aAfter deprotection. ^bFrom 9-iodo-Boc-cytisine. ^c14% after hydrogenation and Boc removal. ^dYield not given.

Scheme 40. Synthesis of 9-Alkyl, 9-Formyl, and 9-Acetyl Cytisines

Table 7. Binding Affinities at nAChRs of 9-Alkyl-Substituted Cytisines^a

compound	K _i (nM) $\alpha 4\beta 2$	K _i (nM) $\alpha 7$	K _i (nM) $\alpha 2\beta 2$	ref
(-) -cytisine	1.06	1000		131
(-) -9-bromocytisine	0.116	40.1		131
(-) -9-vinylcytisine	0.73		0.7	147a
(-) -9-methylcytisine	0.24	2000		131
(-) -9-trifluoromethylcytisine	0.22	1000		131

^aRat brain preparations: $\alpha 4\beta 2$: displacement of (–)-[³H]cytisine; $\alpha 7$: displacement [¹²⁵I] α -bungarotoxin.

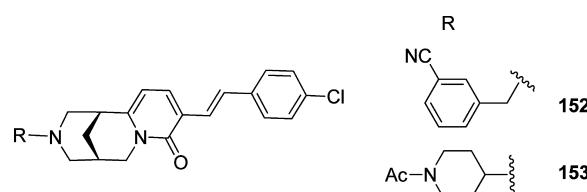


Figure 6. Two phosphatase (VE-PTP) inhibitors.

4.1.4. 9-Methoxycytisine. 9-Methoxycytisine and its N-benzyl derivative are the two fully characterized compounds bearing an oxygen substituent at the 9-position of cytisine. O'Neill et al.¹¹¹ synthesized them using the strategy they developed for preparing cytisine. The different steps of the synthesis are summarized in Scheme 42. The total synthesis suffered from moderate yields of the Stille coupling (36%),

from that of the benzyl group removal (43%), and from a low selectivity of the hydrogenation step (174, 85:15 *cis:trans*).

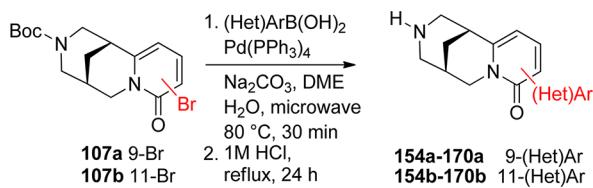
In the cytisine synthesis, Gallagher's group isolated N-benzyl-9-hydroxy-2-oxo cytisine 178. This side-product (<2%) was formed in the intramolecular 1,6-addition of lactam enolate 176 to the pyridone nuclei (Scheme 43).¹⁵⁰ Compound 178 is an

Table 8. Affinities of 9-(Hetero)Aryl Cytisines and 11-(Hetero)Aryl Cytisines at $\alpha 4\beta 2$ nAChRs

Entry	(Het)Ar	Products	9-Ar cytisine	$\alpha 4\beta 2$	11-Ar cytisine	$\alpha 4\beta 2$	Ref
			Yields (%)	Ki (nM)	Yields (%)	Ki (nM)	
1	C ₆ H ₅	154^a	58	128	39	45	(148)
2	3-NO ₂ -C ₆ H ₄	155^a	83	23	62	3.7	(148)
3	3-CH ₃ -C ₆ H ₄	156^a	65	28	58	24	(148)
4	3-CF ₃ -C ₆ H ₄	157^a	52	8.3	64	55	(148)
5	3-F ₃ CO-C ₆ H ₄	158^a	64	67	27	23	(148)
6	3-Cl-C ₆ H ₄	159^a	47	199	22	170	(148)
7	3-F-C ₆ H ₄	160^a	46	5.7	81	300	(148)
8	3-Ph-C ₆ H ₄	161^a	36	200	62	190	(148)
9	4-F-C ₆ H ₄	162^b	74	420			(147)
10	4-n-Bu-C ₆ H ₄	163^b	87				(147)
11		164^a	37	853	26	20.4	(148)
12		165^a	36	110	25	96	(148)
13		X = H 166a X = F 166b^c	66 31	0.91 23.9 ¹⁴⁹	32	10.9	(148)
14		167^a	62	3.9			(148)
15		168	44	95			(148)
16		169	70	0.177	19	2.2	(148)
17		170^b	-	390			(147)

^aCompetition assays using (\pm)-[³H]epibatidine and rat brain, P2 fraction. Under the same conditions, the measured affinity of cytisine was 0.122 nM. ^b K_i for cytisine = 1.51 nM. ^cCoupling with iododerivative **116a**.

Scheme 41. Synthesis of 9-(Hetero)arylcytisines and 11-(Hetero)arylcytisines



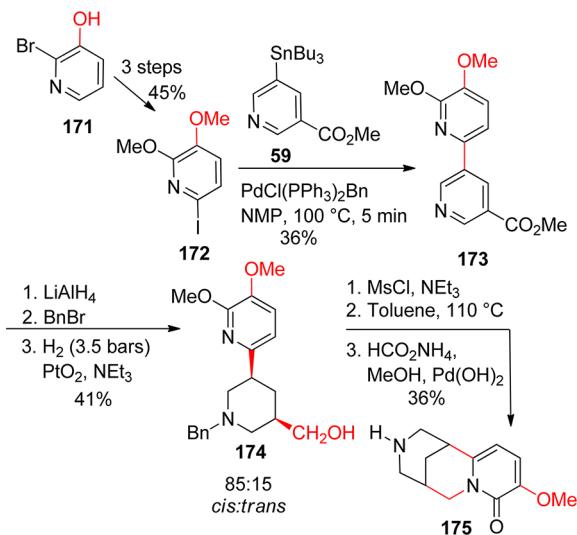
attractive and potentially useful cytisine analogue, and the exploitation of this chemistry is underway.

4.2. 10-Substituted Cytisines

No direct transformation of cytisine or of one of its derivatives has been reported to prepared 10-substituted cytisines. All of the described compounds have been obtained in racemic form. The key steps of the syntheses are applications of methods previously developed. However, introducing the desired substituent required modifications and optimizations.

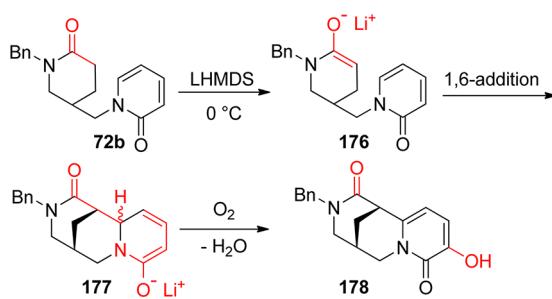
4.2.1. Kozikowski Route. Kozikowski's group¹⁴⁷ chose commercially available 2-chloro-6-methoxyisonicotinic acid **179** to introduce a hydroxymethyl group at C₁₀. Scheme 44

Scheme 42. Synthesis of 9-Methoxycytisine

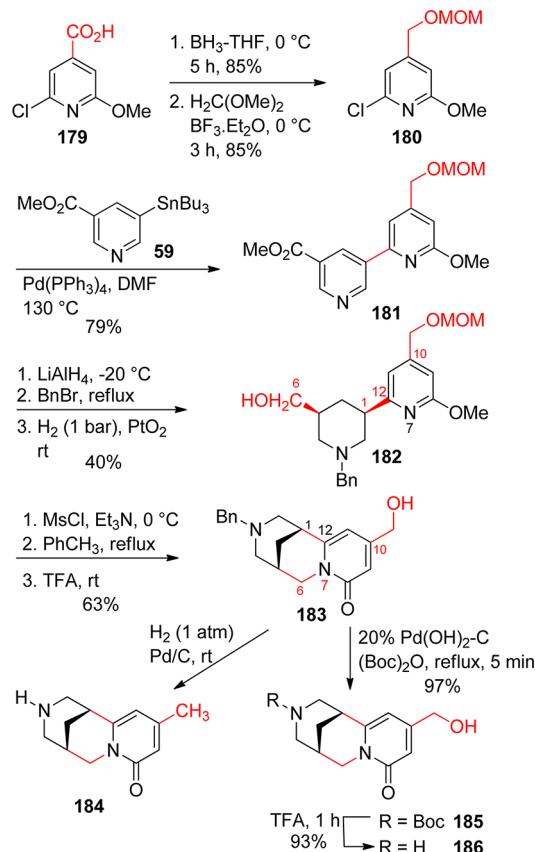


summarizes the different steps of the synthesis. Pyridine **180**, easily prepared from acid **179**, was treated with the preformed

Scheme 43. Possible Formation of N-Benzyl 9-Hydroxy 2-Oxocytisine



Scheme 44. Kozikowski Synthesis of 10-Hydroxymethylcytisine



stannane 59 in the presence of Pd(PPh₃)₄, the best catalyst among those tested for the reaction. To avoid the formation of the over-reduced methyl compound, LiAlH₄ reduction was

carried out at -20 °C. The tricyclic core of 10-hydroxymethylcytisine was built according to van Tamelen¹¹² and O'Neill.¹¹³ A careful hydrogenation over Pd(OH)₂/C in the presence of (Boc)₂O according to Husson et al.¹⁵¹ enabled the formation of hydroxymethylcytisine 185 in 97% yield and the target compound 186 in 13% overall yield from pyridine 179. 10-Methylcytisine 184 was the sole product (no yield given) formed when debenzylation of 183 was carried out in the presence of hydrogen and Pd/C.

10-Fluoromethylcytisine 189 and ethers 187,188 derived from 185 were synthesized¹⁵² (Scheme 45) for biological tests.

In vitro binding affinities of the synthesized 10-substituted cytisines were measured at six defined nAChR subtypes expressed in stably transfected cell lines and at native nAChRs expressed in rat forebrain.^{147,152} For comparison with the binding affinities of 9-substituted cytisines, only the affinities at $\alpha 4\beta 2$ nAChR subtypes are given in Table 9 with the selectivity over the $\alpha 3\beta 4$ subtype. Indeed, as compared to cytisine (entry 1), compounds 189, 187b–187e (entries 4, 6–9) are highly selective, up to 6400-fold for derivative 187d (entry 8). It is worth noting that this selectivity was higher than that observed with varenicline (ratio $K_i \alpha 3\beta 4/\alpha 4\beta 2 = 760$). To predict the ability of the new compounds to cross the blood brain barrier (BBB), Kozikowski et al.¹⁴⁷ calculated the lipophilicity of compounds and compared them to nicotine (reference compound, calculated C log P = 1.00) and epibatidine (1.80) known to penetrate the BBB easily. As shown in Table 9, the highly selective ligands 189, 187b–187e (entries 4, 6–9) may be able to penetrate the BBB better than (-)-cytisine does (entry 1). Despite their high affinities for the $\alpha 4\beta 2$ nAChRs, compounds 189, 187b–187e have no agonist activity and showed very low potencies in inhibiting nicotine activated channel function at both the $\alpha 4\beta 2$ and the $\alpha 3\beta 4$ receptors. The authors have suggested that these compounds may belong to a new class of nicotinic ligands.

4.2.2. Gallagher Route. To access to the first 10-halo-cytisines, Gallagher et al. have successfully implemented the strategy they developed for cytisine.¹⁵³ N-Substituted pyridones 192 and 193 were first prepared from the corresponding fluoro or bromopyridones 190 and 191, respectively. The key step to the tricyclic core of cytisine was the intramolecular 1,6-addition of the lactam enolates derived from 192 and 193 to the pyridone nucleus (Scheme 46). Treatment of 192 with LHMDS afforded the tricyclic compound 194, which was oxidized into 196 in excellent yield. Reduction of the lactam group then debenzylation afforded 10-fluorocytisine 198 (30% overall yield from fluoropyridone). The same sequence was used to prepare the bromo analogue 199. Borane reduction of 197 followed by debenzylation afforded a mixture of 10-bromocytisine 199 and

Scheme 45. Synthesis of 10-Hydroxymethylcytisine Derivatives

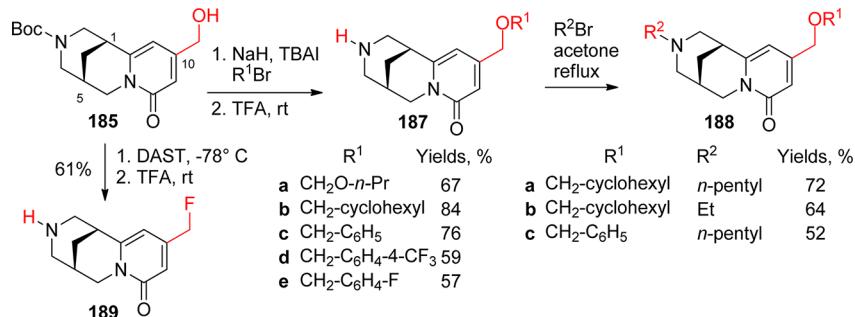
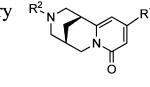
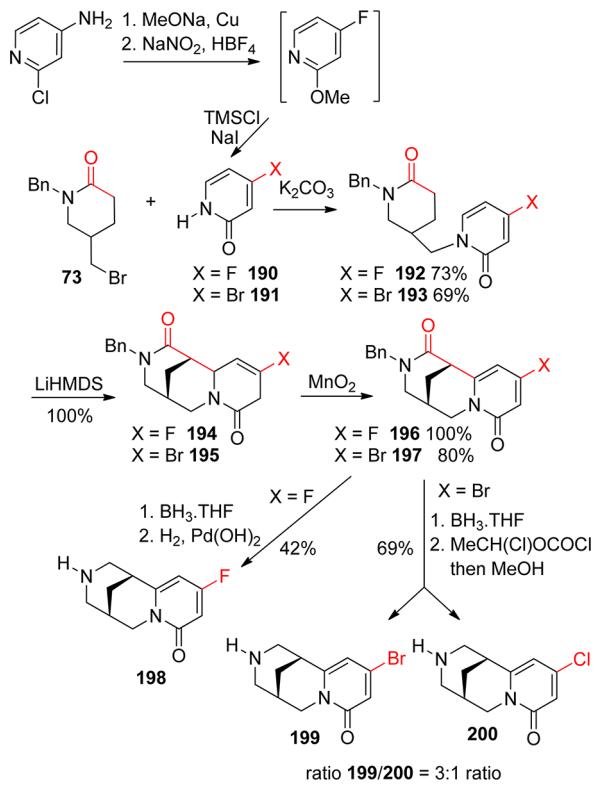


Table 9. Affinities of 10-Substituted Cytisines at $\alpha 4\beta 2$ and $\alpha 3\beta 4$ nAChRs

Entry	R^2		Products	Ki	Ki	Selectivity	ClogP
				$\alpha 4\beta 2$	$\alpha 3\beta 4$	$\alpha 3\beta 4/\alpha 4\beta 2$	
	R ¹	R ²	(nM)	(nM)			
1	H	H	1	1.51	220	150	0.6
2	CH ₃	H	184	1.9	6700	3500	1.15
3	CH ₂ OH	H	186	11	10000	910	-0.32
4	CH ₂ F	H	189	3.2	8200	2600	1.09
5	CH ₂ O- <i>n</i> -Pr	H	187a	48	3800	79	1.36
6	CH ₂ O-CH ₂ -cyclohexyl	H	187b	33	25000	760	3.14
7	CH ₂ O-CH ₂ -C ₆ H ₅	H	187c	15	12000	800	2.09
8	CH ₂ O-CH ₂ -C ₆ H ₄ -CF ₃	H	187d	6.7	43000	6400	3.05
9	CH ₂ O-CH ₂ -C ₆ H ₄ -F	H	187e	5.9	23000	3900	2.29
10	CH ₂ O-CH ₂ -cyclohexyl	<i>n</i> -pentyl	188a	2100	91000	43	5.32
11	CH ₂ O-CH ₂ -cyclohexyl	Et	188b	520	10000	19	3.84
12	CH ₂ O-CH ₂ -C ₆ H ₅	<i>n</i> -pentyl	188c	330	25000	76	4.26

Scheme 46. Gallagher Synthesis of 10-Halocytisines



10-chloro cytisine **200** (ratio **199/200** = 3:1). The presence of chloride residues from the debenylation reagent could account for the formation of the chloroderivative **200**.

To overcome the difficulties encountered in reproducing the described synthesis of fluoropyridone **190**,¹⁵⁴ Gallagher used 2-chloro 4-aminopyridine as the starting material. Reaction of sodium methoxide, then fluorodediazoniation and demethylation afforded 4-fluoropyridone **190**, but unfortunately no yield was given.

4.3. 6-Substituted Cytisines

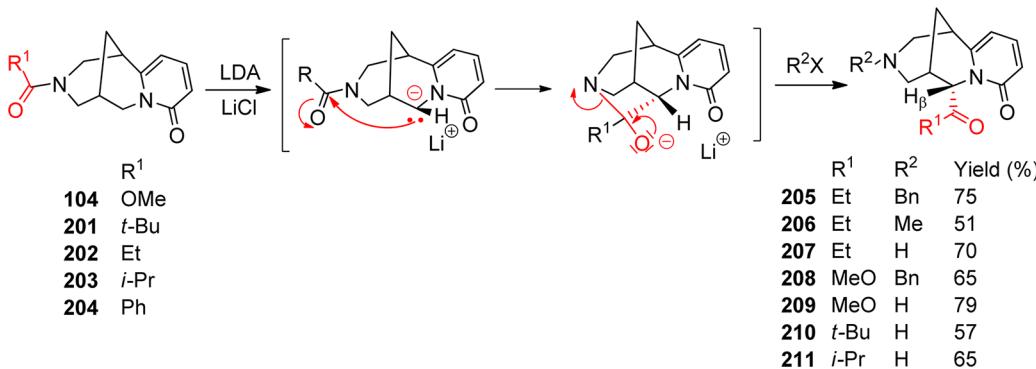
With the aim of testing cytisine as a chiral auxiliary, Rouden et al.^{155a} studied the alkylation of amide **202**. When N-acyl cytisines **104**, **201**–**204** were treated with LDA in the presence of an excess of LiCl, 6-acyl cytisines **205**–**211** were obtained in 51–79% yield. Their formation arose likely from unusual nitrogen to carbon acyl migration (Scheme 47). The efficiency of the N→C migration was shown to be dependent on the nature of the N-acyl group. Surprisingly, *N*-acetyl cytisine **27** and *N*-benzoylcytisine **204** gave no 6-substituted products but an inseparable mixture of compounds.

The reactions are highly diastereoselective. Under basic conditions, a complete epimerization of the *6*α-isomer (*6S*)-**212** to the more stable *6*β-isomer (*6R*)-**212** was observed (Scheme 48). This reaction opened the way to 6-substituted derivatives of cytisine.

To introduce substituents at the 6-position of cytisine while avoiding the N→C transfer with acyl groups, the secondary amine of (−)-**1** was protected with a benzyl group.^{155b} Because of the high reactivity of the carbanion at C₆, it was necessary to add the base to the reaction mixture containing the electrophile. Among the bases tested for the deprotonation (LiHMDS, LDA, LTMP), LDA (pK_a = 32) gave the best results as it was shown by trapping the carbanion with chlorotrimethylsilane. While LTMP (pK_a = 37.3) gave a mixture of products, no reaction was observed with LiHMDS (pK_a = 29.5). Under the conditions depicted in Scheme 49, compounds were synthesized in yields ranging from 42% to 98%. The reaction was diastereoselective, and only the *6*α-substituted cytisine was formed. When the reaction was carried out with aldehydes, a second stereogenic center was generated. Only two diastereoisomers were formed showing a high asymmetric induction at C₆ but a poor selectivity at C₁₄. The stereochemistry of alcohol **219a** was deduced from that of the ketone **220** obtained by oxidation (Scheme 49).

Functionalization of *N*-methylcytisine (−)-**18** at the 6-position deserves several comments. (a) It was not possible to introduce a

Scheme 47. Rouden Synthesis of 6-Acyl-Substituted Cytisines via a N→C Migration



Scheme 48. Epimerization of 6-Monosubstituted Cytisine

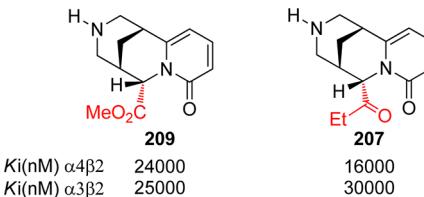
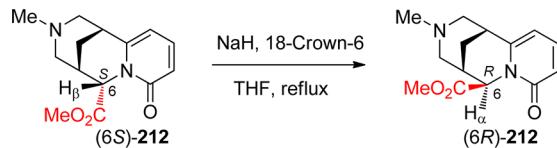
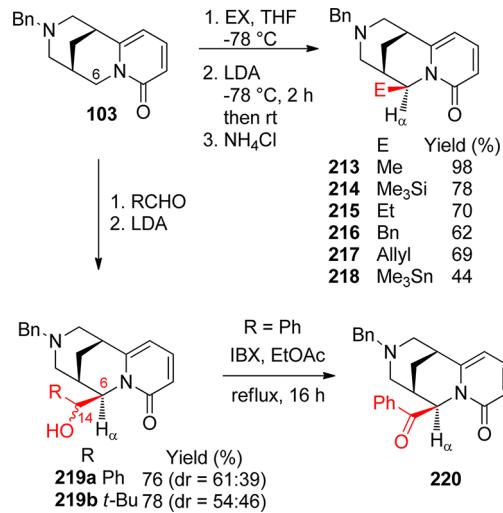


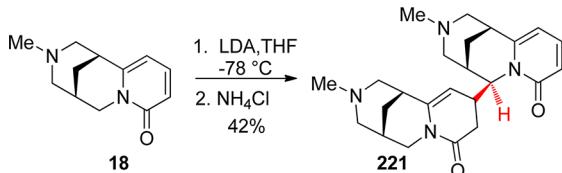
Figure 7. Binding affinities of two 6-substituted cytisines at nAChR.

Scheme 49. Alkylation of the 6-Position of Cytisine



second substituent at the C₆ position. (b) A dimer 221 of (–)-18 was isolated while using the normal addition conditions for the deprotonation-alkylation sequence or in the absence of electrophile (Scheme 50).^{155b}

Scheme 50. Dimerization of N-Methylcytisine

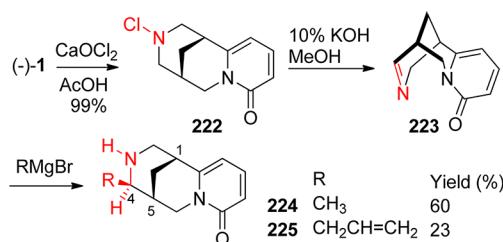


Kozikowski et al.¹⁴⁷ measured the in vitro binding affinities K_i of compounds 207 and 209 at nAChRs ($\alpha 2\beta 2$, $\alpha 2\beta 4$, $\alpha 3\beta 2$, $\alpha 3\beta 4$, $\alpha 4\beta 2$, $\alpha 4\beta 4$ subtypes). Both compounds showed poor binding affinities at all nAChRs. Examples are given for two receptor subtypes in Figure 7.

4.4. Other Substituted Cytisines

The number of cytisine derivatives substituted on ring C (except on the nitrogen atom) is rather restricted. Some of them are natural products: 4-allylcytisine 225 was extracted from *Sophora Secundiflora*,¹⁵⁶ *Bolusanthus Speciosus*,⁷⁷ and *Argyrolobium uniflorum*,⁴² and N-methyl-4-allylcytisine (“tinctorine”) 226 was from *Thermopsis Alterniflora*,¹⁵⁷ *Argyrolobium uniflorum*,⁴² and *Clathropis glauccophylla*.¹⁵⁸ 4-Methyl and 4-allylcytisines 224 and 225 have been prepared¹⁵⁹ in three steps from (–)-cytisine according to a method previously described.¹⁶⁰ The key step, which was used for the synthesis of camoensine (see section 8.4), was the addition of a Grignard reagent to the less hindered side of imine (Scheme 51). This reaction led to a satisfactory

Scheme 51. 4-Substituted Cytisines

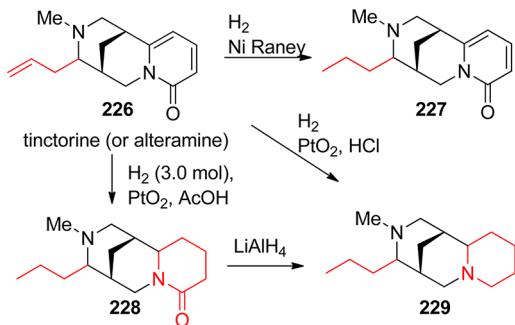


yield only in the case of a methyl group. Although this reaction was attractive to introduce substituents in the 4 position of cytisine (–)-1, it has not been exploited so far.

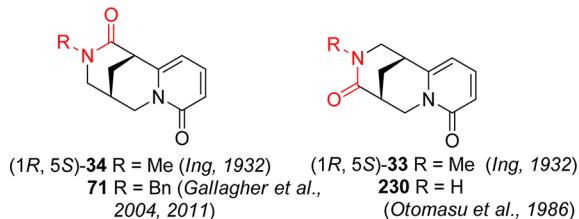
Reduction of tinctorine 226 was carried out to proof its structure. It gave access either to 4-propylcytisine 227 or to tricyclic lactam 228 or amine 229 (Scheme 52).¹⁶¹

A few 2-oxo and 4-oxo cytisines are known. (+)-4-Oxocytisine 230 was isolated from leaves of *Sophora Secundiflora*.¹⁶² N-Methyl 2-oxocytisine and N-methyl 4-oxocytisines 33 and 34, respectively (Scheme 53), have been obtained in the barium permanganate oxidation of N-methylcytisine (see Scheme 8).⁹⁰ N-Benzyl 2-oxocytisine 71 was an intermediate in a total synthesis of cytisine (see Schemes 21 and 23).^{108,116}

Scheme 52. Reductions of Tinctorine



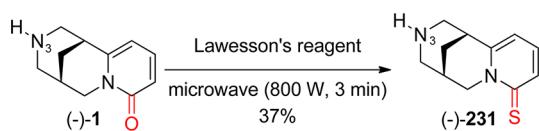
Scheme 53. 4-Oxocytisines and 2-Oxocytisines



4.5. Thiocytisine

Because bioisosterism serves as a valuable aid in structure–activity relationships, Seitz et al.¹²⁹ synthesized the thioanalogue of (−)-cytisine. Using the Lawesson's reagent under microwave irradiation and solvent-free conditions according to Varma,¹⁶³ (−)-thiocytisine 231 was prepared in 37% yield (Scheme 54). Its crystal structure was described as well.¹⁶⁴

Scheme 54. Synthesis of Thiocytisine

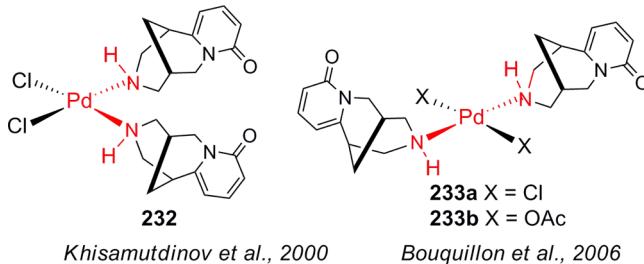


(−)-Thiocytisine 231 showed a 7-fold lower affinity ($K_i = 0.832 \text{ nM}$) at $\alpha 4\beta 2$ nAChRs as compared to the parent alkaloid (−)-1 ($K_i = 0.124 \text{ nM}$) and an excellent selectivity profile for $\alpha 4\beta 2$ versus $\alpha 7$ subtype [$K_i (\alpha 7) = 4000 \text{ nM}$]. To account for the difference of binding affinities between (−)-1 and its thioanalogue 231, the authors suggested a change in the three-dimensional arrangement of the ligand, the distance between N₃ and S being longer (5.248 Å) than that observed in the oxygen analogue (N₃ and O: 4.89 Å). Another reason might be that the C=S···HN hydrogen bonds are weaker than their C=O···HN analogues.

4.6. Complexes of (−)-Cytisine with Metals

4.6.1. Palladium or Platinum Complexes. With the development of phosphine free palladium ligands, and the success of sparteine palladium complexes in asymmetric synthesis,¹⁶⁵ complexes of (−)-cytisine were synthesized (Scheme 55). The first ones were obtained when (−)-1 reacted with K₂PdCl₄, K₂PtCl₄, *cis*-PtCl₂(NH₃)₂, or Na₂PdCl₆. They all have the same metal-to-cytisine ratio (M:L = 1:2) and were characterized by NMR, IR, and electronic absorption spectroscopy. Complex formation occurred only through the nitrogen atoms of the secondary amino group of cytisine, and the authors suggested a *cis* geometry [i.e., 232 with Pd(II)].¹⁶⁶ Bouquillon et al.¹⁶⁷ studied

Scheme 55. Cytisine/Palladium Complexes



the complexation of (−)-1 with PdCl₂(MeCN)₂, PdCl₂, and Pd(OAc)₂ in the presence of potassium carbonate. From IR data of 233a, ¹H NMR, ¹³C NMR, and X-ray of 233b, the *trans* geometry of the ligands was established. The coordination of palladium atom is square planar. The pyridone rings are almost coplanar with their adjacent rings. The rings near the palladium atom adopt a chair conformation. The geometry of complexes 233a and 233b, quite different from that of sparteine with palladium,¹⁶⁵ could explain the lack of enantioselection in an attempt of kinetic resolution of phenethyl alcohol.¹⁶⁷

4.6.2. (−)-Cytisine/Eu(fod)₃. To demonstrate the participation of 4f-orbitals of lanthanides (Ln³⁺) in the formation of coordination bonds with ketones, Kazakov et al.¹⁶⁸ studied the effect of excitation of the 4-f shell on the stability of Eu(fod)₃ complexes formed with alicyclic ketones including cytisine (−)-1. The comparison of the stability constants of the Eu(fod)₃ complexes in the ground and excited states (K and K*, respectively) showed a higher stability for cytisine complexes than those observed for menthone, camphor, or cyclohexanone (Scheme 56). Moreover, the cytisine complex

Scheme 56. Stability of Cytisine/Eu(fod)₃ Complexes in the Ground and Excited States

Eu(fod) ₃ + L	$K \xrightleftharpoons{hv} K^*$	at T = 300 K, $\tau_0 = 140 \mu\text{s}$			
		L	K	K*	τ_1
		L.mol ⁻¹	L.mol ⁻¹	L.mol ⁻¹	μs
(−)-cytisine	590	1450	485		
(+)-camphor	15.0	360	400		
Eu(fod) ₃ + L	$K^* \xrightleftharpoons{hv} [Eu(fod)3L]^*$	(+)-menthone	41.0	930	310

formation was exothermic. The authors suggested that the difference observed with the other studied ketones is likely related to the presence of two functional groups in cytisine and the possibility of coordination at both the oxygen and the nitrogen atoms. The plots of optical rotatory dispersion (ORD) versus concentration of Eu(fod)₃ indicated the formation of a 1:1 complex.

4.7. (−)-Cytisine and Polymers

Within the framework of the search for highly efficient and environmentally friendly methods for the separation and purification of alkaloids, Gao et al.¹⁶⁹ prepared and characterized a cytisine-molecular imprinted polymer (MIP). Methylacrylic acid (MAA) was first graft-polymerized on the surface of silica gel particles (SiO₂) using 3-methacryloxypropyltrimethoxysilane as a linker. (−)-Cytisine molecular imprinted-material MIP-PMAA-SiO₂ was prepared with ethylene glycol diglycidyl ether as a cross-linking agent. To show the selectivity of MIP-PMAA/SiO₂ for (−)-cytisine with regard to matrine and oxymatrine, two other alkaloids existing in *Sophora Alopucuroides*, competitive adsorption experiments were conducted.

The results showed that the surface imprinted material MIP-PMAA/SiO₂ has an excellent binding affinity for cytisine (20.1 g/100 g of binding capacity) and high recognition selectivity for cytisine with regard to the other alkaloids (Figure 8).

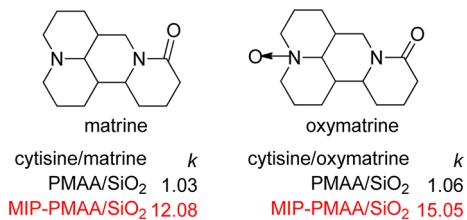
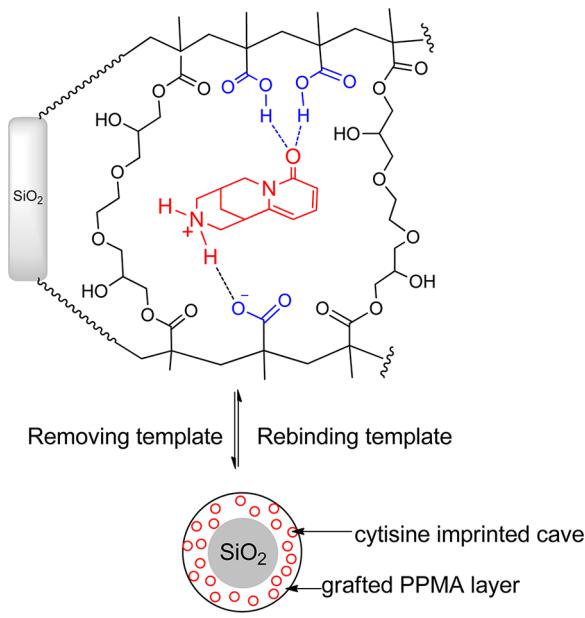


Figure 8. Selectivity coefficients *k* of MIP-PMAA-SiO₂ for (–)-cytisine/matrine and oxymatrine.

The selectivity after imprinting was 12 and 15 times higher than those observed for matrine and oxymatrine, respectively. Although remarkable, this high selectivity is not surprising. Indeed, the cytisine imprinted cavities are not matched with matrine (or oxymatrine) in size, shape, and spatial arrangement of action sites. A possible interaction mode between the grafted PMAA and cytisine molecule is shown in Scheme 57.

Scheme 57. Possible Interactions of Cytisine in the Polymer PMAA/SiO₂



Three carboxyl groups on two polymeric chains could interact with one cytisine molecule via electrostatic and hydrogen bonds, and thus the cavity involved seven carboxylate groups of the polymeric chains.

5. RADIOLABELED CYTISINE DERIVATIVES

5.1. (–)-[³H]Cytisine

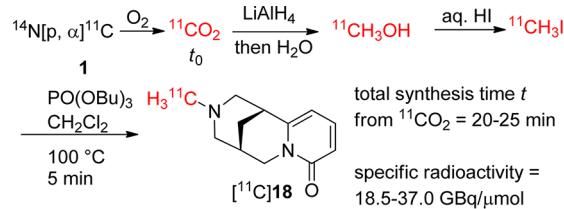
Although (–)-[³H]cytisine **1** is one of the most used labeled ligands for the study of nicotinic receptors, little is known about its preparation. Filatov and Kotelevtsev¹⁷⁰ obtained [³H](–)-**1** by action of tritium atoms generated at 2000 K on a solid target containing (–)-**1**. The purity of [³H]cytisine was 90%, and its specific radioactivity was 350 mCi/mmol (12.9 GBq/mmol). The position of radioisotope ³H on the alkaloid was not reported.

5.2. (–)-N-[¹¹C]Methylcytisine

To visualize and quantify in vivo nAChRs, using positron emission tomography, a noninvasive medical imaging technique, ligands of the receptors have to be labeled with a positron emitter, carbon-11 or fluorine-18. These radionuclides are produced in a cyclotron in very small amounts. They are characterized by a short half-life (20 min for ¹¹C and 110 min for ¹⁸F). Moreover, the number of cyclotron produced labeled precursors is limited: [¹¹C]CO₂, [¹¹C]CO, [¹¹C]CH₄ for carbon-11 and [¹⁸F]F[–] for fluorine-18. In this context, the syntheses of radioligands must be rapid, possible in the presence of large amounts of reagents and without any addition of stable isotope to avoid radioactive dilution. Taking into account these conditions justifies the particular chemistry associated with the synthesis of ¹¹C- or ¹⁸F-radioligands.

Dollé et al.¹⁷¹ in 1996 described the synthesis and in vivo evaluation of N-[¹¹C]methylcytisine. This radioligand was synthesized in 25–30 min (from the end of irradiation, HPLC purification included) by reaction of [¹¹C]iodomethane with cytisine (–)-**1**. The reaction occurred cleanly at 100 °C within 5 min in a mixture of dichloromethane and tributylphosphate (Scheme 58).

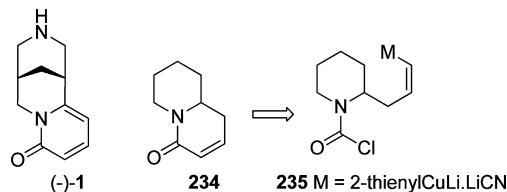
Scheme 58. Radiosynthesis of [¹¹C]Methylcytisine



Following intravenous injection of N-[¹¹C]methylcytisine, uptake in a baboon brain was low and not significantly different from blood radioactivity. The in vivo binding of [¹¹C]**18** appeared rather different from that of [³H]cytisine. It was deduced that [¹¹C]**18** was not a suitable tracer for PET studies of nAChRs in primate brain.¹⁷²

The deleterious effect of the substitution on the secondary amino group of cytisine led Rouden et al. to develop a strategy for labeling the carbonyl group of cytisine with carbon-11 (Scheme 59).¹⁷³ Lactam **234** as a model compound was

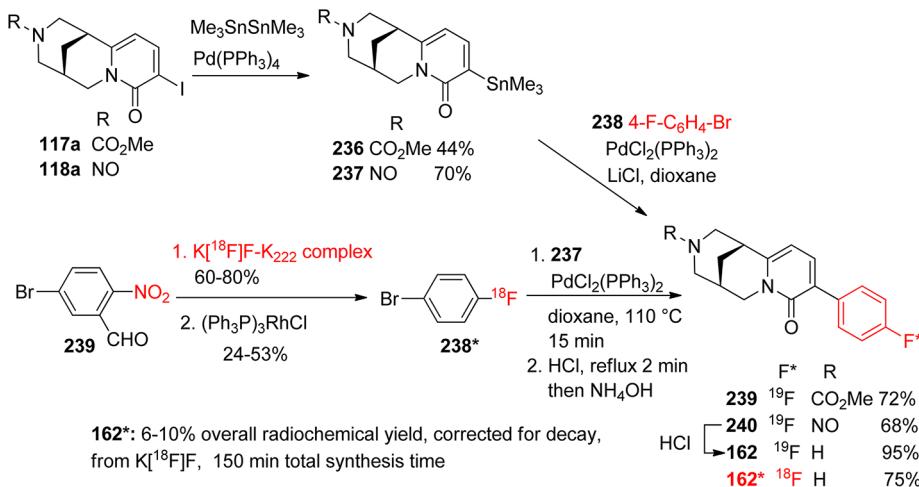
Scheme 59. A Possible Route to [¹¹C]Cytisine



synthesized using the intramolecular cross-coupling reaction of carbamoyl chloride group of **235** with an in situ generated vinylcuprate. High dilution of **235** was the key factor to achieve the annulations, conditions required in ¹¹C-chemistry. Such an approach using [¹¹C]carbamoyl chlorides prepared from [¹¹C]phosgene should be possible.¹⁷⁴

5.3. 9-[¹⁸F]Fluoro(hetero)aryl Cytisines

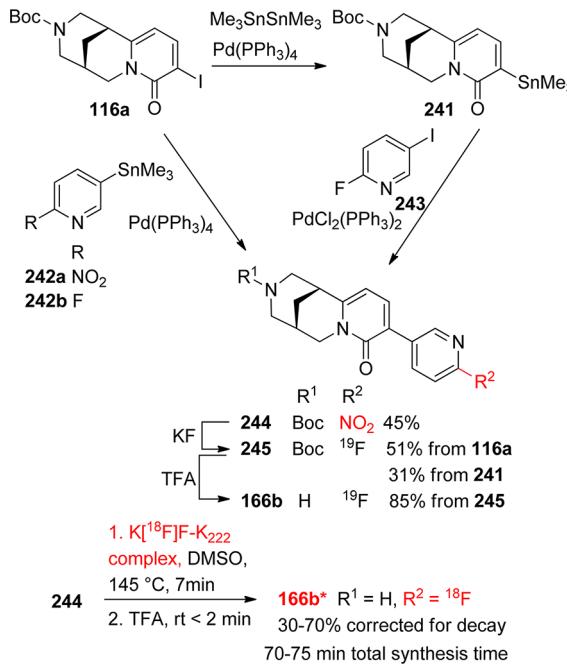
The difficulty in designing a rapid synthesis of [¹¹C]cytisine from known [¹¹C]-labeled precursors and the need to keep

Scheme 60. Synthesis of 9-[4-¹⁸F]Fluorophenylcytisine

unprotected the secondary amine function of cytisine led to the development of ¹⁸F labeled derivatives of (–)-cytisine. The relatively long half-life of fluorine-18 (110 min) allowed for longer syntheses (up to 3 h) and detailed in vivo evaluations. 9-(4'-[¹⁸F]Fluorophenyl)cytisine **162*** and 9-(2-[¹⁸F]fluoro-5-pyridyl)cytisine **166b*** were synthesized.

The possibility of carrying out the reaction of vinyl (or aryl) stannanes with 4-[¹⁸F]fluorobromobenzene having been demonstrated,¹⁷⁵ the stannanes **236** and **237** were prepared from the corresponding iodo compounds **117a** and **118a**, respectively (Scheme 60). Stille coupling with fluorobromobenzene **238** afforded 9-(fluorophenyl)cytisines **239** and **240** in satisfactory yields,²¹ slightly lower than that obtained in the Suzuki coupling of 4-fluorobenzeneboronic acid and 9-bromo N-Boc cytisine **107a**.¹⁴⁷ Rapid and efficient removal of the nitroso group led to choose stannane **237** for the Stille coupling with 4-[¹⁸F]fluorobromobenzene **238***. This labeled precursor was prepared in two steps. Radiofluorination of 5-bromo 2-nitro benzaldehyde **239** with no-carrier-added fluorine-18 fluoride ion as its activated $K[^{18}F]$ -kryptofix K_{222} complex led to 5-bromo 2-[¹⁸F]fluoro benzaldehyde (not shown). Decarbonylation of this labeled aldehyde with Wilkinson catalyst afforded 4-[¹⁸F]fluorobromobenzene. Stille coupling with stannane **237** afforded **162*** in 6–10% overall radiochemical yield and 150 min.²¹ Although acceptable for its length and its overall yield, the radiosynthesis involved three steps, the automation of which for routine production could turn out to be difficult. 9-[¹⁸F]Fluorophenylcytisine **162*** has not been evaluated in vivo.

As compared to homoaromatic and aliphatic nucleophilic radiofluorinations, nucleophilic substitution of a nitro group by a fluoride [¹⁸F] in the pyridine series appeared as a highly efficient method for the synthesis of ¹⁸F-radiotracers of high specific activity.¹⁷⁶ The major advantage of this strategy is the possibility of preparing the radiotracer in one step from the corresponding nitro derivative. Nitropyridine **244** and 9-(2-fluoro-5-pyridyl)cytisine **245**, the unlabeled target compound, were prepared by Stille coupling of iodocytisine **116a** with stannanes **242a** and **242b**, respectively. This coupling was more efficient than that of stannane **241** with fluoroiodobenzene **243** (Scheme 61). Radiofluorination carried out with $K[^{18}F]F-K_{222}$ worked rapidly and after removal of the protecting group afforded 9-(2-[¹⁸F]fluoro-5-pyridyl)cytisine **166b*** in high yields and short reaction time (Scheme 61).¹⁴⁹

Scheme 61. Synthesis of 9-(2-[¹⁸F]Fluoropyridinyl)cytisine

The in vivo pharmacological profile of (–)-(2-[¹⁸F]-fluoropyridinyl)cytisine **166b*** was evaluated in rats. The observed in vivo biodistribution of the tracer in the brain was rather uniform and did not match with the known regional densities of nAChRs. It was also significantly different from that of the parent compound (–)-[³H]cytisine. Moreover, competition studies with (–)-nicotine did not reduce brain uptake of the radiotracer. Despite promising affinity (K_i at $\alpha 4\beta 2$ nAChRs = 23.9 nM), radiotracer **166b*** does not have the required properties for PET imaging nAChRs.

6. (1R,5S,12S)-TETRAHYDROCYTISINE AND DERIVATIVES

Tetrahydrocytisine (1,2,3,4,5,6-hexahydro-1,5-methano-pyrido[1,2-*a*][1,5]diazocin-8-one) **246a** and tetrahydrodeoxocytisines **19a** and **19b** (11-methyl-7,11-diazatricyclo[7.3.1.0^{2,7}]tridecane) (Figure 9) are the three main reduced compounds derived from cytisine. Sections 6 and 7 will deal only with tricyclic

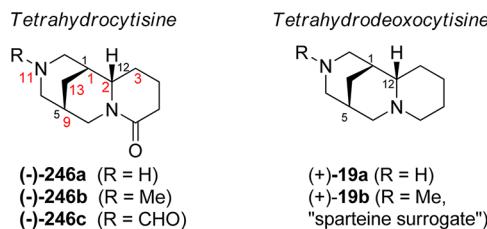


Figure 9. Reduced cytisines. In red, IUPAC numbering of the atoms; in black, numbering of the atoms of cytisine.

compounds derived from $(-)$ -246a or $(+)$ -19a, thus having the same 1*R*,5*S*,12*S* configuration.

6.1. Natural Sources

No 1*R*,5*S*,12*S*-tetrahydrodeoxocytisine derivatives have been isolated from natural sources. By contrast, $(-)$ -tetrahydrocytisine 246a, first isolated from *Thermopsis chinensis*,¹⁷⁷ is one of the major alkaloids in *Templetonia biloba* from Western Australia.¹⁷⁸ In this species, $(-)$ -246a was found with *N*-methyltetrahydrocytisine 246b and *N*-formyl tetrahydrocytisine 246c (Figure 9). These compounds also occur in *Anarthrophyllum*¹⁷⁹ in trace amounts. *N*-Methyltetrahydrocytisine 246b synthesized in 1968¹⁸⁰ was also present in oriental *Ormosia* species.¹⁸¹

6.2. Syntheses

In 1932, Späth and Galinovsky described the first preparation of tetrahydrocytisine $(-)$ -246a⁸⁸ by hydrogenation of $(-)$ -cytisine over Pd-charcoal in water at 65 °C. Later, Bohlmann et al.¹⁶⁰ obtained $(-)$ -246a within a quantitative yield using platinum oxide as the catalyst. This process was used for full characterization of tetrahydrocytisine $(-)$ -246a.¹⁸² The reverse reaction (dehydrogenation) was also carried out by heating *N*-acetyl tetrahydrocytisine with palladium at high temperature.¹⁸³

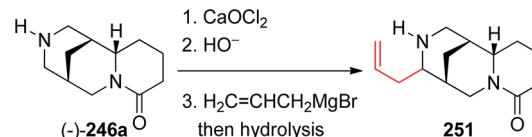
A short synthesis of tetrahydrocytisine (\pm) -246a employing a double Mannich reaction to construct the diazatricyclic skeleton of the alkaloid was described (Scheme 62).¹⁸⁴ Ring A was first built followed successively by ring B, then ring C. They key intermediate of the synthesis was the keto-lactam 249, and two routes were devised to obtain this compound. In route a,

the carbons C₅ and C₁₃ were linked via a Dieckmann cyclization of piperidine 247 according to Mandell.¹⁸⁵ Route b involved an α -acyliminium cyclization,¹⁸⁶ to close ring B (C₁–C₁₂ bond). The four bonds of ring C (C₁–C₂, C₂–N₃, N₃–C₄, and C₄–C₅) were built in the double Mannich reaction of 249. Wolff–Kishner reduction of 250, then removal of the protecting group, afforded tetrahydrocytisine (\pm)-246a in seven steps and 4–5% overall yield (route a or b).

6.3. Properties and Uses

Tetrahydrocytisine $(-)$ -246a was first used to access other derivatives such as 251 (Scheme 63), a stereoisomer of

Scheme 63. 4-Allyltetrahydrocytisine

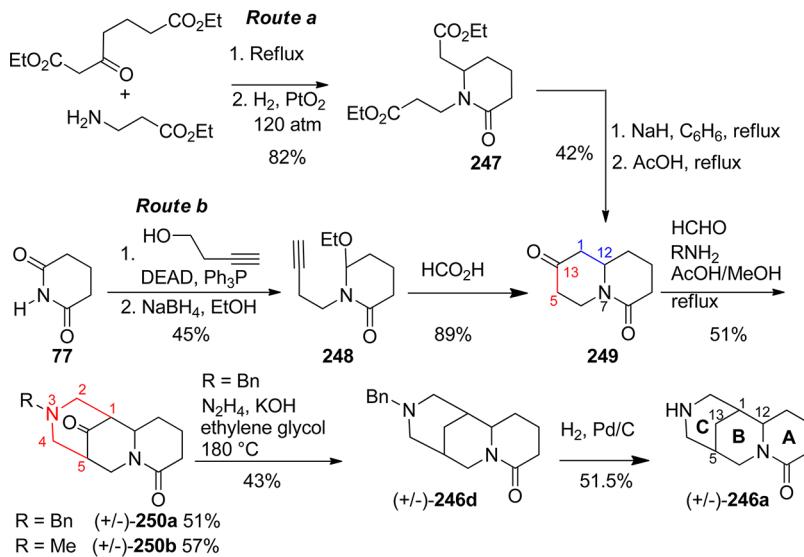


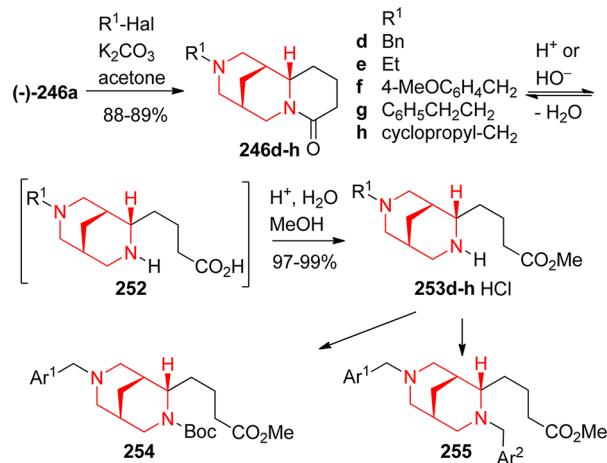
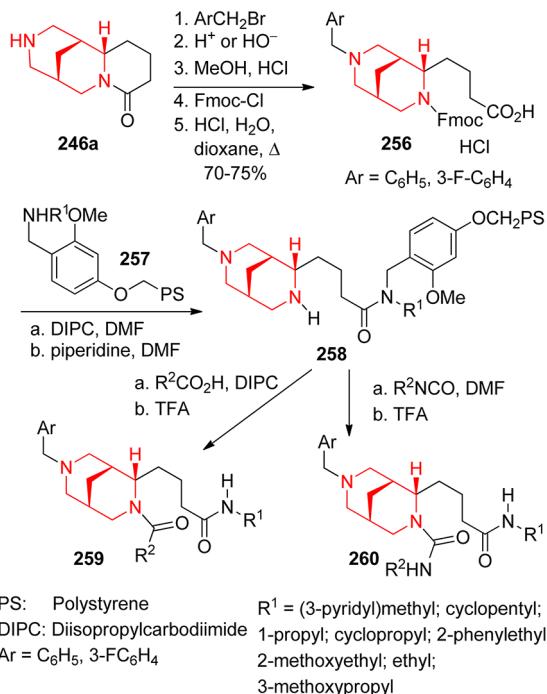
$(-)$ -angustifoline, according to the methodology developed to prepare 4-allylcytisine 225 (Scheme 51).¹⁶⁰

Salikhov et al.¹⁸⁷ demonstrated that hydrolysis of $(-)$ -246a is a reversible process dependent on the acidity of the medium. Ivachtchenko¹⁸⁸ and Sandulenko¹⁸⁹ groups took advantage of this easy lactam hydrolysis to develop an efficient synthetic approach to bispidine derivatives 253d–h and 255 with three points of diversity (Scheme 64), the various nitrogen substituents and the side arm with the ester group.¹⁸⁸ All attempts to isolate amino acids 252 or the amino esters 253 as their free bases resulted in reverse cyclization, back to the starting lactams 246d–h.

A parallel solid-phase synthesis of 436 amides and ureas 259 and 260 was achieved on the basis of the bispidines derived from hydrolysis of lactam 246a. $(-)$ -Cytisine was converted via its tetrahydroderivative $(-)$ -246a into acids 256, which were further diversified with the use of the amine resins 257 (Scheme 65). Nine amides 259 isolated in yields ranging from 7% to 77% were characterized by ¹H NMR and mass spectra.

Scheme 62. Total Synthesis of (\pm) -Tetrahydrocytisine

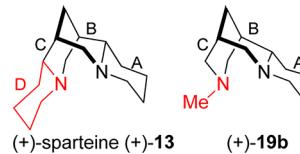


Scheme 64. Synthesis of Bispidine Derivatives**Scheme 65. Library of Bispidine Amides and Ureas**

7. TETRAHYDRODEOXOCYTISINE AND N-SUBSTITUTED TETRAHYDRODEOXOCYTISINES

7.1. Syntheses

Tetrahydrodeoxocytisine (+)-19a was first obtained in 1906 by Freund and Horkheimer through the electrochemical reduction of cytisine in sulfuric acid at a lead cathode.¹⁹⁰ Later, it was partially characterized as its ammonium salt. Hofmann exhaustive degradation led to the structural determination of cytisine.⁸⁸ However, this “reduced cytisine” 19a has been underutilized until recently. In 2001, looking for a diamine that could mimic (+)-sparteine in enantioselective reactions, O’Brien et al. identified the *N*-methyl derivative (+)-19b¹⁹¹ as a sparteine surrogate (Figure 10). Diamine (+)-19b, lacking one of the rings and chiral centers of sparteine, is easily available from (−)-cytisine^{21,191b,192} unlike (+)-sparteine. Since the seminal report¹⁹¹ demonstrating that diamine (+)-19b proceeded in asymmetric deprotonations with enantioselectivity similar to that

**Figure 10. Comparison of the structures of (+)-sparteine 13 and *N*-methyltetrahydrodeoxocytisine (+)-19b.**

of (−)-sparteine but in the opposite sense, various reactions have been studied and reviewed.¹⁹³ Accordingly, the focus is set in the following on the recent uses of diamine (+)-19b, placing them in their context.

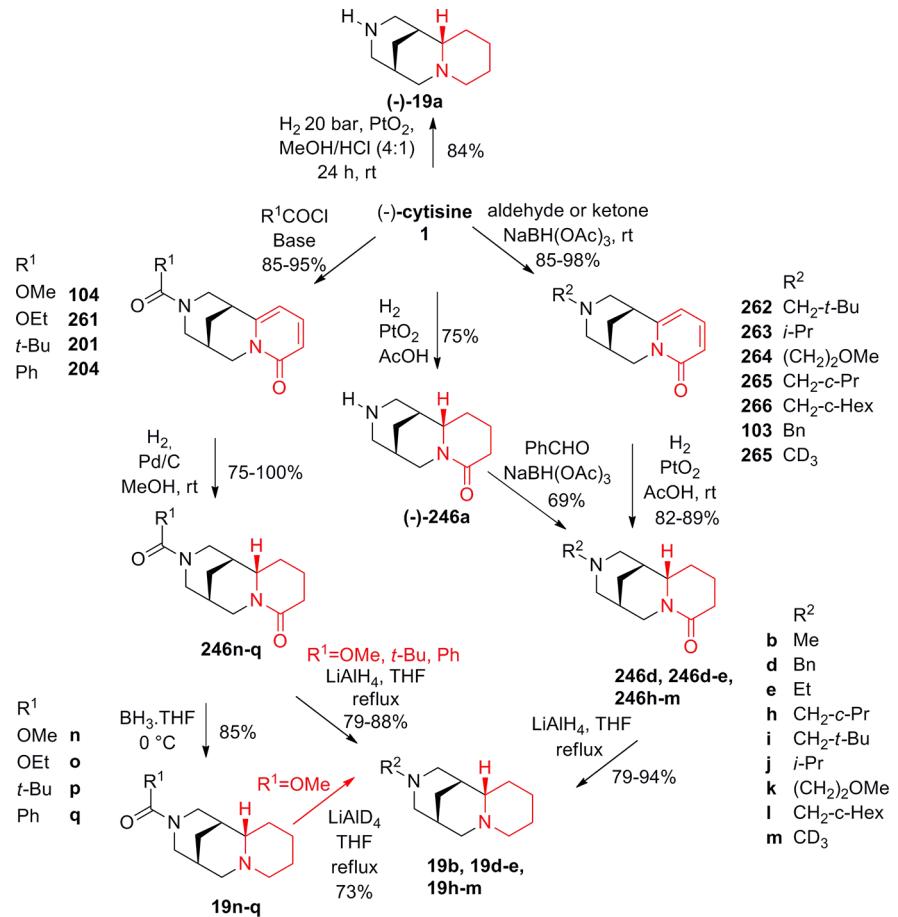
N-Alkyl diamines 19b, 19d,e,h–m were prepared from protected or unprotected enantiopure (−)-cytisine¹⁹³ to test the influence of the steric hindrance of various alkyl substituents on the different reactions studied. The syntheses of *N*-methyl,¹⁹² *N*-d³-methyl,¹⁹⁴ alkyl, (*methyl*)cycloalkyl, and benzyl tetrahydrodeoxocytisines^{182,195,196} are depicted in Scheme 66. For example, *N*-methyltetrahydrodeoxocytisine (+)-19b was prepared in a three-step process (79% overall yield). Reaction of (−)-1 with methyl chloroformate (or ethyl chloroformate) afforded carbamate 104 (or 261), which was reduced into *N*-methoxycarbonyl (or ethoxycarbonyl)-tetrahydrocytisine 246n (or 246o). It is worth noting that hydrogenation of the pyridone ring using PtO₂ (or Pd/C) proceeded via exclusive *exo* face attack on the fused bicyclic system, thus generating a single diastereoisomer of lactams 246. Finally, reaction of lactam 246n (or 246o) with LiAlH₄ afforded diamine (+)-19b. *N*-Alkyl tetrahydrodeoxocytisines 19h–l were prepared in three steps: reductive amination of cytisine, then hydrogenation of the pyridone ring and hydride reduction of lactams. Because of its sensitivity toward reductions (debenzoylation was observed when 246q was treated with LiAlH₄), the preparation of *N*-benzyl tetrahydrodeoxocytisine 19d involved the same reactions but in a different order (reduction of cytisine into its tetrahydroderivative 246a followed by reductive amination, then reduction of lactam 246d). The *N*-substituted tetrahydrodeoxocytisines 19p and 19q can also be obtained in high yields thanks to the chemoselective reduction of lactams 246p and 246q using borane/THF or borane/DMS complexes.¹⁹⁷ This reduction could be an alternative to the route using *N*-benzyltetrahydrocytisine 246d.¹⁹⁴ *N*-Methyltetrahydrodeoxocytisine 19m was prepared by reduction of the methoxycarbonyl derivative 19n using LiAlD₄.

The unsubstituted derivative 19a is no more prepared by electrochemical reduction. Catalytic hydrogenation of cytisine over PtO₂ under pressure in a single step at room temperature afforded tetrahydrodeoxocytisine 19a in high yields (Scheme 66), a significant improvement in terms of reagents and simplicity of the experimental conditions as compared to the two-step process (catalytic hydrogenation to (−)-246a followed by LiAlH₄ reduction).^{85,197}

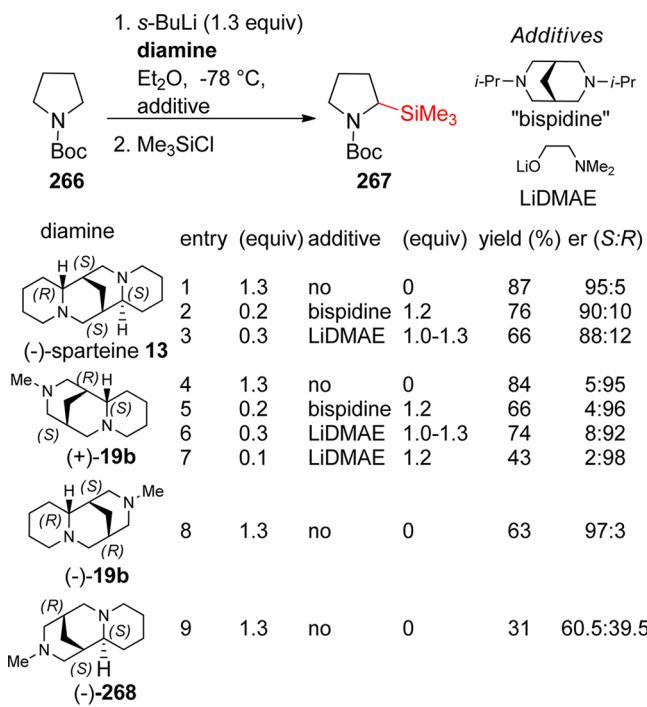
7.2. Asymmetric Syntheses via *N*-Alkyl Tetrahydrodeoxocytisine Derivatives

7.2.1. Asymmetric Deprotonations of *N*-(*tert*-Butoxycarbonyl) Pyrrolidine. **7.2.1.1. Stoichiometric and Catalytic Reactions.** The asymmetric deprotonation-electrophilic trapping of *N*-Boc pyrrolidine 266 using *s*-BuLi/diamine (+)-19b was one of the test reactions O’Brien used to compare the efficiency of diamine (+)-19b to that of (−)-sparteine.¹⁹¹ This reaction introduced by Beak et al.¹⁹⁸ for cyclic carbamates

Scheme 66. Preparation of N-Substituted Tetrahydro and Tetrahydrodeoxocytisines



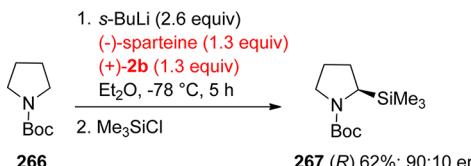
Scheme 67. Enantioselective Deprotonation of N-Boc Pyrrolidine



The first reactions with diamine (+)-19b¹⁹¹ were carried out under stoichiometric conditions, using chlorotrimethylsilane as the electrophile (Scheme 67, entry 4).

Trimethylsilyl N-Boc pyrrolidine 267 was obtained in yield and stereoselectivity similar to that of (-)-sparteine (entry 1) but in the opposite sense. As previously expected by O'Brien, this experiment demonstrated that the D-ring of sparteine is not required for high enantioselectivity in asymmetric deprotonations. Moreover, in a competition experiment,¹⁹⁹ O'Brien et al. showed that the major product had the sense of induction shown by diamine (+)-19b, suggesting that the complex s-BuLi/(+)-19b lithiated N-Boc pyrrolidine was formed much faster than s-BuLi/(-)-sparteine (Scheme 68).

Scheme 68. Competition Experiments in the Deprotonation of N-Boc Pyrrolidine

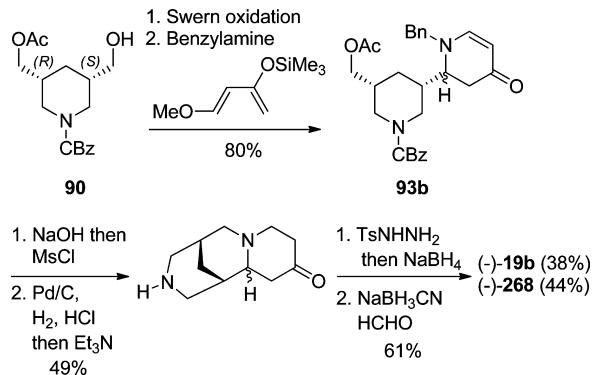


Lesma and co-workers synthesized the opposite enantiomer (-)-19b and a diastereoisomer (-)-268 using an imino Diels–Alder reaction²⁰⁰ or a ring-closing metathesis²⁰¹ (Scheme 69).

They carried out the deprotonation of pyrrolidine 266. Whereas (-)-19b afforded the expected product (Scheme 67, entry 8) with a selectivity similar to that of (-)-sparteine,

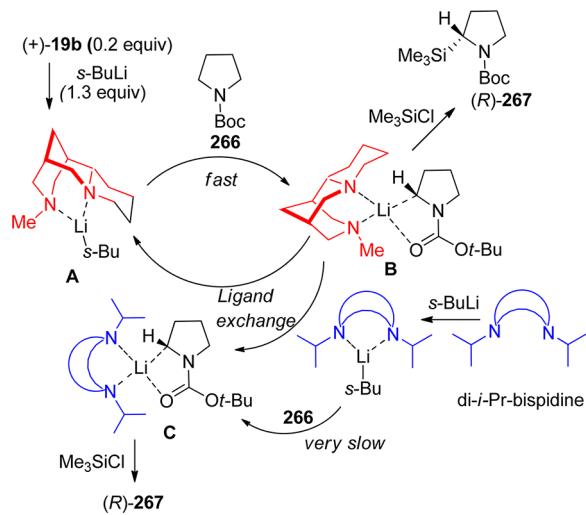
is known to proceed to a stereospecific electrophilic substitution via a configurationally stable organolithium intermediate.

Scheme 69. Synthesis of Chiral Diamines



diamine $(-)$ -268 (Scheme 67, entry 9) was less reactive and the enantioselectivity was poor. These results provided additional evidence of the structural features relevant to the stereoselectivity in the deprotonation–substitution reaction.

If the chiral diamine $(+)$ -19b appeared as a good alternative to the non-available $(+)$ -sparteine, a catalytic approach was also desirable, despite the obvious difficulty to achieve this goal in light of the previous results obtained in asymmetric deprotonations with stoichiometric amounts of $(-)$ -sparteine [33% yield and 64% ee using 0.25 equiv of $(-)$ -sparteine].²⁰² Starting from the hypothesis that complex B (Scheme 70) formed

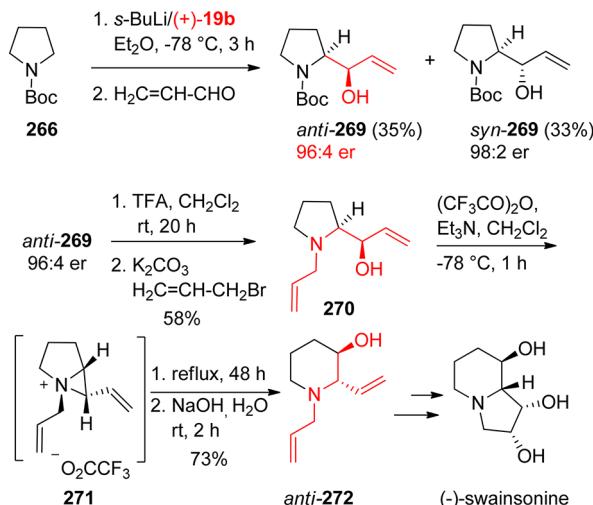
Scheme 70. Catalytic Enantioselective Deprotonation of *N*-Boc Pyrrolidine

between the lithiated substrate and $(+)$ -19b did not readily dissociate to regenerate the reactive s -BuLi/chiral diamine complex A, O'Brien and McGrath²⁰³ carried out the reaction in the presence of stoichiometric diisopropyl bispidine as an additional achiral ligand. Because of the steric hindrance induced by isopropyl groups on the nitrogen atoms of the bispidine, the complex s -BuLi/di-*i*-Pr-bispidine was very slow in deprotonating pyrrolidine 266 (Scheme 67, entries 2 and 5). Whereas the yield was lower than that obtained with sparteine, the enantiomeric ratio was higher and in the opposite sense with $(+)$ -19b. Bispidine is a strongly chelating diamine and thus was able to displace $(+)$ -19b from the lithiated pyrrolidine/chiral diamine $(+)$ -19b complex B to give the intermediate C (Scheme 70). Trapping this configurationally stable complex by chloromethylsilane afforded (R) -267.

The use of diisopropyl bispidine has two main drawbacks. This achiral ligand was not commercially available and could not be separated from sparteine or from **19b** to envisage the recycling of both diamines. Other additives were thus tested.²⁰⁴ Among those, lithium dimethylaminoethanolate (LiDMAE) was shown to be the most efficient. O'Brien demonstrated that both the dimethylamino group and the hydroxyl group were necessary for the turnover of the catalytic cycle and to avoid competitive deprotonation. The optimum lithiation conditions involved 0.3 equiv of chiral ligand and 1.0 equiv of LiDMAE. Using $(+)$ -19b, both yield and er were higher than those obtained with $(-)$ -sparteine (comparison of entries 3 and 6, Scheme 67). A decrease in the yield (43%) but an increase of the er (*S/R* 2.98) were observed (entry 7) when a lower amount (0.1 equiv) of chiral ligand $(+)$ -19b was used in conjunction with LiDMAE (1.2 equiv). DMAE, a very cheap aminoalcohol, can also be easily separated from sparteine or diamine **19b**, making this catalytic asymmetric deprotonation an attractive key reaction.

A simple application of the stoichiometric procedure was found in the formal synthesis of the natural $(-)$ -swainsonine, via the piperidinyl alcohol *anti*-272 (Scheme 71). This alcohol

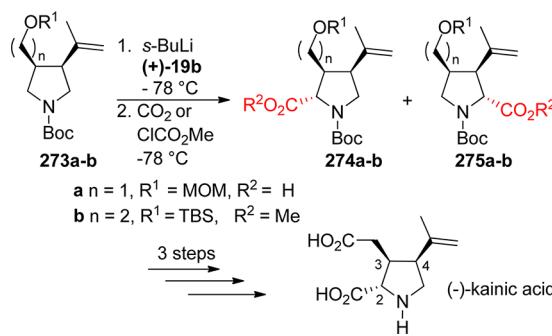
Scheme 71. Synthesis of Swainsonine



derived from *N*-Boc pyrrolidinyl alcohol *anti*-269 via a ring expansion through the aziridium intermediate 271. Thus, *N*-Boc pyrrolidinyl alcohol 266 was lithiated using s -BuLi/ $(+)$ -19b and the intermediate trapped with acrolein (Scheme 71). An equimolar mixture of *anti* and *syn* diastereoisomers 269 was formed, each one of them in a high enantiomeric ratio. Purification of the *anti* diastereoisomer by column chromatography was necessary to carry on the synthesis.

To allow the ring expansion, under the conditions described by Cossy et al.,²⁰⁵ the Boc protecting group was substituted for an allyl group, and the treatment of compound 270 with trifluoroacetic anhydride triggered the rearrangement affording 2-allyl-3-hydroxypiperidine 272 in high yield and with control of the stereochemistry.²⁰⁶ As compared to Cossy's route to $(-)$ -swainsonine involving the same hydroxallyl pyrrolidine intermediate 270,²⁰⁷ the asymmetric deprotonation route was much shorter (two steps instead of six) but less efficient in terms of overall yield (20% vs 39%), the major drawback being the absence of diastereocontrol in the first step. Such a control for compounds *anti* and *syn* is an unsolved problem for this kind of reactions with aldehydes.²⁰⁸

Scheme 72. Synthesis of (-)-Kainic Acid



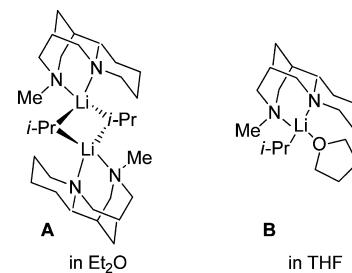
The stereoselective lithiation of pyrrolidine ring with diamine (+)-19b was also used in two syntheses of kainic acid (Scheme 72). In the first approach,²⁰⁹ an efficient asymmetric deprotonation [s-BuLi/(+)-19b] of 273a was achieved, and the anion was trapped with carbon dioxide. A mixture of two regioisomers 274a and 275a (molar ratio 81:19) was obtained with complete diastereocontrol for both products. However, the mixture was inseparable, and the following three steps were carried out on both compounds before their separation. The involvement of the methoxymethyl group (MOM) in the diastereocontrol seemed limited because in the absence of the chiral diamine 19b, a mixture of diastereoisomers was obtained with modest regioselectivity again.

In another similar approach,²¹⁰ the lithiation of (3S,4S)-273b (98% ee) using s-BuLi/(+)-19b followed by reaction of methylchloroformate provided the desired carboxylation product 274b (R¹ = TBS, R² = Me) in 49% yield and excellent diastereoselectivity (>98% dr). Again, the reaction was not regioselective (ratio 274b/275b = 58:42). However, the components of the mixture were easily separated. It is worth noting that using 273b and (-)-sparteine instead of (+)-19b, under the same conditions, the regioselectivity was improved in favor of the desired compound (ratio 80:20). However, the reaction was not complete (45% of the starting material was recovered vs 12% with the cytisine derivative (+)-19b).

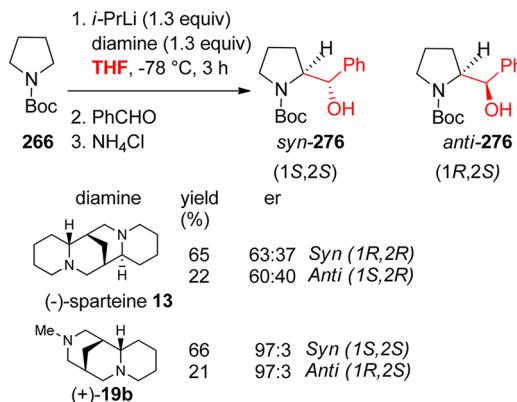
7.2.1.2. Complexes Diamine/Organolithium Reagent. Applications. The crystal structure of aggregates between MeLi and (+)-19b was compared to that of the adduct (-)-sparteine 13/MeLi.²¹¹ The similarity of the structures was in good agreement with the same degree of selectivity exhibited in asymmetric deprotonation reactions using s-BuLi and diamines (+)-19b or (-)-13.

Asymmetric deprotonation reactions using a chiral base derived from an organolithium reagent and (-)-sparteine were known to proceed with low enantioselectivity if carried out in THF (cf, ref 212 and references therein). Recently, the ⁶Li and ¹³C NMR spectroscopies of solution structures of i-PrLi complexed with (-)-sparteine or with diamine (+)-19b in Et₂O-d₁₀ and THF-d₈ were studied at -80 °C.²¹² In Et₂O-d₁₀, i-PrLi/(-)-sparteine is a solvent-complexed heterodimer, whereas i-PrLi/(+)-19b is a head-to-head homodimer (A, Figure 11). In THF, there is no complexation of (-)-sparteine to i-PrLi with less than 3 equiv of (-)-sparteine. In contrast, (+)-19b is readily complexed to i-PrLi in THF, and with 1.0 equiv of (+)-19b, complete formation of a monomer B was observed (Figure 11).

These structural data, which suggest that it should be possible to carry out highly enantioselective asymmetric deprotonation reactions using i-PrLi or s-BuLi/(+)-19b in THF, were supported by experimental data. For example, the asymmetric

Figure 11. Lithium/(+)-19b complexes in Et₂O-d₁₀ and in THF-d₈.

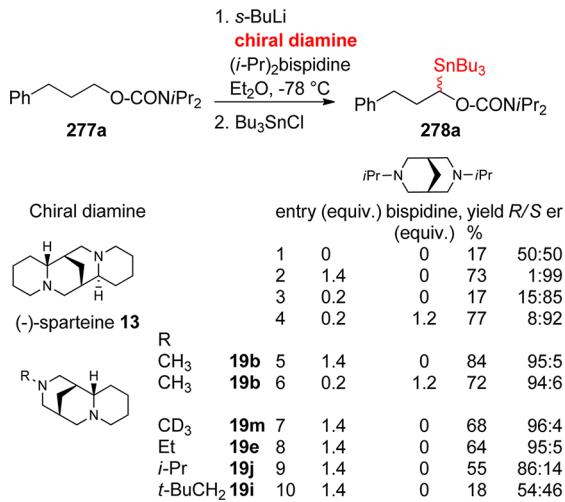
Scheme 73. Enantioselective Deprotonation of N-Boc Pyrrolidine in THF



lithiation of N-Boc pyrrolidine 266 in THF using (-)-sparteine or diamine (+)-19b followed by reaction with benzaldehyde was highly enantioselective only when (+)-19b was used (Scheme 73). However, as mentioned above in the case of the swainsonine synthesis, the chiral induction on the second stereogenic center generated during the addition of the carbanion on the aldehyde carbonyl was limited with both chiral diamines, and the diastereomeric ratios were low (dr *syn*-276/*anti*-276 = 3:1).

7.2.1.3. Comparison with Other Diamines Derived from (-)-Cytisine. The experimental results for the lithiation of N-Boc-pyrrolidine using diamines 19 bearing nitrogen substituents of different steric demands were compared to the results generated from a computational study.²¹³ Of the (-)-cytisine-derived amines (*N*-Me, *N*-Et, *N*-n-Bu, *N*-CH₂-*t*-Bu, *N*-i-Pr) tested experimentally, the highest enantioselectivity was observed with the least sterically hindered *N*-Me diamine (+)-19b. The pro-R proton was preferentially removed. This was in good correlation with the computational results, which indicated that the enantiodifferentiation involved steric interactions engendered by the A-, B-, C-rings of the diamine within the prelithiation complex (i-PrLi/diamine/N-Boc-pyrrolidine). The lowest energy prelithiation complexes of i-PrLi/N-Boc-pyrrolidine/(-)-sparteine or diamine 19b (*N*-Me) had also the lowest activation energies for proton transfer.

7.2.2. Asymmetric Deprotonation of O-Alkyl Carbamates. The (-)-sparteine-mediated asymmetric deprotonation of O-alkyl carbamates described by Hoppe et al.²¹⁴ is one of the most efficient methods to access their α -substituted derivatives. Important synthetic applications have since emerged using this asymmetric methodology.²¹⁵ Diamine (+)-19b was tested²¹⁶ and compared to (-)-sparteine in the deprotonation of carbamate 277a²¹⁷ followed by trapping with tributylstannyl chloride.¹⁹¹ As compared to (-)-sparteine (enantiomeric ratio *R/S* = 1:99,

Scheme 74. Enantioselective Deprotonation of Carbamates

Scheme 74, entry 2), under the same stoichiometric conditions, O'Brien et al. observed a slightly lower enantiomeric ratio of 95:5 with (+)-19b (entry 5).

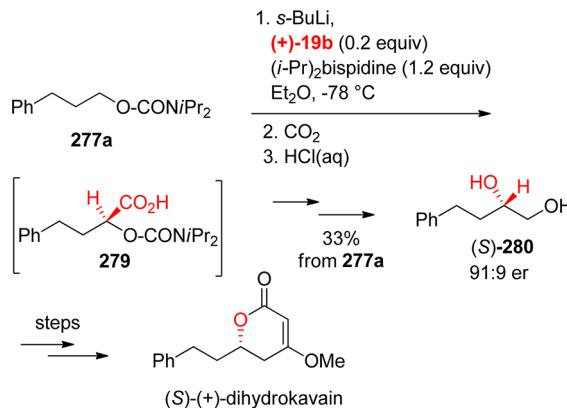
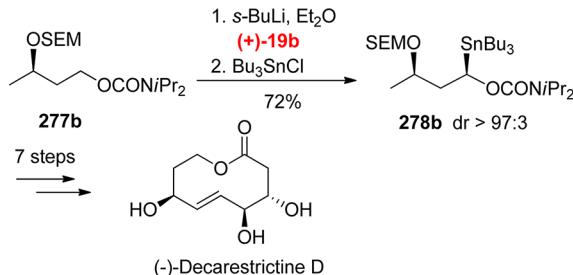
The catalytic variant of the reaction using *s*-BuLi and 0.2 equiv of chiral diamine [(-)-sparteine or (+)-19b] was also studied. However, prior to any asymmetric attempts, O'Brien's group demonstrated that uncomplexed *s*-BuLi was able to lithiate the carbamate within 17% yield (Scheme 74, entry 1) similar to the one obtained in the presence of 0.2 equiv of (-)-sparteine (15:85 er) (entry 3). As previously for *N*-Boc pyrrolidine, bispidines (isopropyl, methyl, and di-isopropyl) were tested to dissociate sparteine from the lithiated complex (+)-19b/*s*-BuLi. Again, the diisopropyl derivative giving the less reactive *s*-BuLi/diamine complex for the deprotonation was the most efficacious for the ligand exchange. Under these conditions (0.2 equiv of 19b, 1.2 equiv of diisopropylbispidine), the enantiomeric ratio reached 94:6 (entry 6), a value slightly higher than with (-)-sparteine/bispidine (8:92, entry 4) and in the opposite sense (Scheme 74).

The asymmetric deprotonation of carbamate 277a was less sensitive to the steric hindrance of the chiral diamine as compared to that of *N*-Boc-pyrrolidine 266 (Scheme 74).¹⁹⁴ There was no major difference between the *N*-methyl and *N*-ethyl diamines 19b and 19e (Scheme 74, entry 5 vs entry 8). The *N*-methyl-deuterated amine 19m gave a result similar to that of 19b, although it is slightly less sterically hindered (entry 7). Whereas the *s*-BuLi/19j complex was unable to deprotonate *N*-Boc pyrrolidine 266,¹⁹³ deprotonation/trapping of carbamate 277a proceeded in moderate yield (55%) and stereoselectivity (*R/S* = 86:14, entry 9). Finally, the *N*-neopentyl group in diamine 19i was detrimental to the reaction, and no selectivity was observed (entry 10) whatever the substrate 277a or 266 used.

The synthetic usefulness of this catalytic asymmetric variant of Hoppe's *O*-alkyl carbamate methodology was demonstrated by the formal synthesis of (*S*)-(+)-dihydrokavain,²¹⁶ a natural occurring lactone. The key reaction (277a → 279) is shown in Scheme 75. The acid 279 was not isolated but directly transformed into alcohol 280 without erosion of the enantioselectivity.

More recently, the same methodology was used for the preparation of the stannyl derivative 278b precursor of (−)-decaresctrictine D (Scheme 76).²¹⁸

Two successive asymmetric deprotonations of carbamates 277d and 277e in the presence of (+)-19b were the key steps

Scheme 75. Enantioselective Synthesis of a Diol Precursor of Dihydrokavain**Scheme 76. Asymmetric Synthesis of a Key Precursor of (−)-Decaresctrictine D**

in the preparation of the epimers 1*S*,4*R*,11*S* and 1*S*,4*S*,11*S* of ergorgiaene with an excellent control of the diastereoselectivity.²¹⁹ This control differs from the one obtained from (−)-sparteine and leading to the other stereoisomers (Scheme 77).

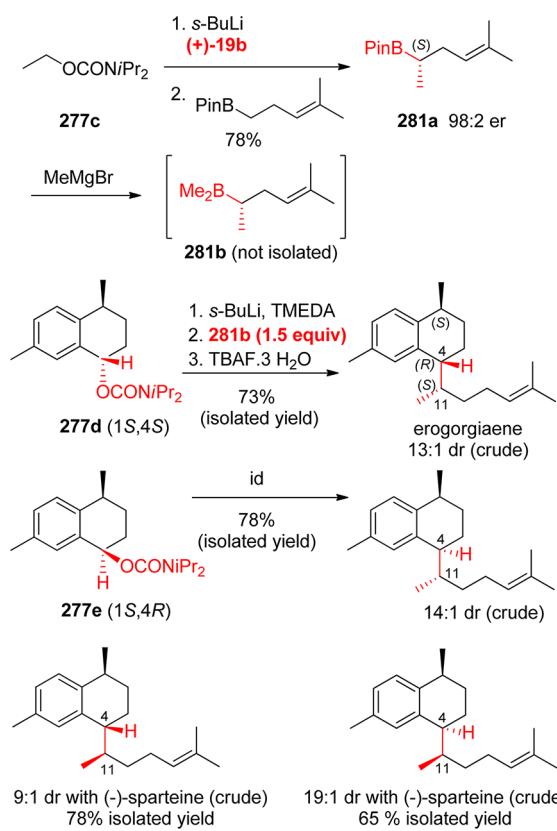
Aggarwal²²⁰ and O'Brien groups²²¹ combining previous works of Matteson,²²² Hoppe,²²³ and Kocienski,²²⁴ used the carbamate/*s*-BuLi/(−)-sparteine complex to prepare enantioenriched alcohols in high enantiomeric ratios. The chiral diamine lithiated complex was trapped with a borane or a boronate. The organoboron intermediate underwent a 1,2-metalate rearrangement. Oxidative hydrolysis ($\text{H}_2\text{O}_2/\text{NaOH}$) of the new organoboron compound afforded alcohols with high enantioselectivities (er > 95:5) and yields. By using either (−)-sparteine or tetrahydrodeoxocytidine (+)-19b-lithiated complexes, Aggarwal et al. synthesized the four stereoisomers of alcohol 282. Scheme 78 illustrates the preparation of two of them. The main difficulty of this reaction lied in the purification of the stereoisomers 282 from the alcohol 283 (around 20–26%) arising from oxidation of unreacted borane 281c.

This chemistry is more general than simple asymmetric alcohol synthesis. The 1,2-metalate rearrangement method can transfer nonaryl substituents, which is particularly useful for sterically hindered groups that could not be introduced by the classical deprotonation/trapping sequence.²²¹

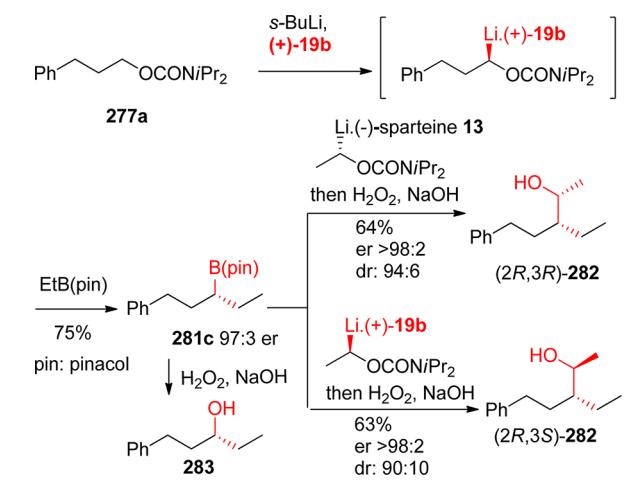
7.2.3. Asymmetric Deprotonation of *N*-Pivaloyl-*o*-benzylamine. Allylation of *N*-pivaloyl-*o*-benzylamine using *s*-BuLi and (+)-19b has been carried out in excellent yield and slightly higher ee than that obtained with (−)-sparteine (Scheme 79).²²⁵ No other example was described.

7.2.4. Asymmetric Deprotonation of *N*-Boc Piperidine. One of the simplest routes to 2-substituted piperidines is the asymmetric deprotonation-electrophile trapping mediated

Scheme 77. Synthesis of the Different Stereoisomers of Erogorgiaene

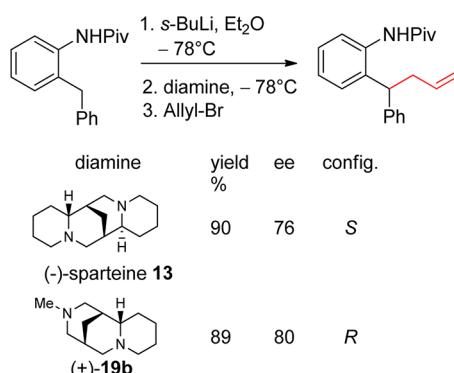


Scheme 78. Preparation of Enantioenriched Alcohols from Carbamates

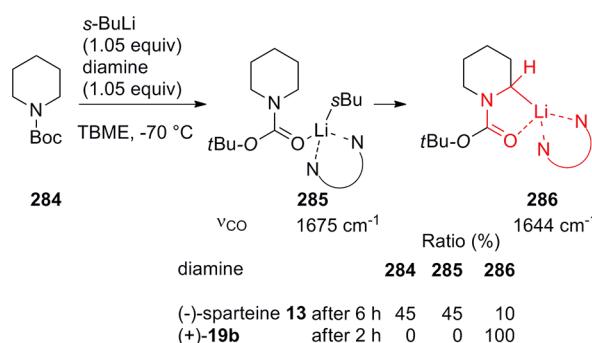


by *s*-BuLi and chiral diamines [(i.e., (−)-sparteine)]. Although successful with *N*-Boc pyrrolidine, extension of this reaction to the *N*-Boc piperidine 284 has met with limited success.^{199,226} Indeed, the lithiation of this substrate was a much slower process, and its subsequent trapping with chlorotrimethylsilane proceeded with low yield (less than 10%) and moderate selectivity (87:13 er in favor of the *S* enantiomer). In situ React-IIR monitoring of the *N*-Boc-piperidine deprotonation using *s*-BuLi/(+)-19b at −78 °C in methyl *tert*-butyl ether (MTBE) revealed the rapid formation of lithiated complexes 285 and 286 (Scheme 80).²²⁷ After 6 h, the complex 286 was formed only in small proportion (10%) in the case of (−)-sparteine,

Scheme 79. Asymmetric Alkylation of *N*-Pivaloyl-*o*-Benzylaniline



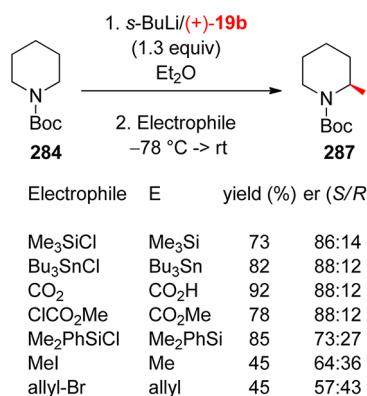
Scheme 80. IR of *N*-Boc Piperidine/*s*-BuLi/Diamine Complexes



whereas it was the major lithiated species when (+)-19b was used. This was in good agreement with the observed higher reactivity of the chiral base complex formed from *s*-BuLi and (+)-19b as compared to that of the corresponding (−)-sparteine complex.

This reactivity has been exploited in the C₂ functionalization of *N*-Boc piperidine. Typical examples given in Scheme 81

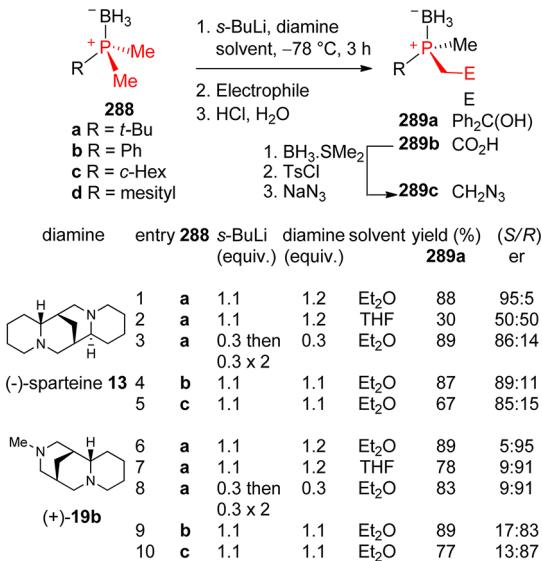
Scheme 81. Enantioselective Deprotonation of *N*-Boc Piperidine



showed that the reactions proceeded with yields higher than 73% except when methyl iodide and allyl bromide were used. In these cases, as for Me₂PhSiCl, the enantioselective ratios were also lower. The configurational instability of the lithiated complex and its slow reaction with PhMe₂SiCl or MeI due to the sterically hindered (+)-sparteine surrogate ligand (+)-19b could explain the observed results.

7.2.5. Desymmetrization of Prochiral Phosphine Boranes and Phosphine Sulfides. The use of *P*-stereogenic phosphines as ligands in metal-catalyzed asymmetric processes is still increasing. The asymmetric deprotonation of phosphine boranes 288 and sulfides 293 using *s*-BuLi or *n*-BuLi and (−)-sparteine is the synthetic route of choice of these compounds.²²⁸ O'Brien²²⁹ and Kann^{182,196} groups succeeded in the desymmetrization of prochiral phosphine boranes 288 using the cytisine derivative (+)-19b and trapping the anion with benzophenone (Scheme 82). They demonstrated the

Scheme 82. Desymmetrization of Prochiral Phosphine Boranes



superiority of (+)-19b over other N-substituted tetrahydrodeoxycytisines or other diamines and its higher reactivity as compared to that of (−)-sparteine²³⁰ as in other reactions (cf., above). It was shown recently that *s*-BuLi/(+)-19b mediated-deprotonation of *tert*-butylidimethylphosphine borane 288a can be carried out in THF, a solvent in which the phosphine was more soluble than in diethyl ether (Scheme 82, entry 7).²¹² Kann et al. implemented this strategy to prepare azide 289c, a precursor of *P*-chirogenic phosphine ligands containing a triazole moiety.²³¹

A catalytic variant of this reaction was reported²²⁹ and applied to the synthesis of chiral diphosphine-boranes “BisP” 290 in high enantiomeric ratio (Scheme 83).

The catalytic conditions were recently optimized.²³² They involved the sequential addition of *s*-BuLi to avoid racemic

Scheme 83. Synthesis of a Chiral Diphosphine-Borane

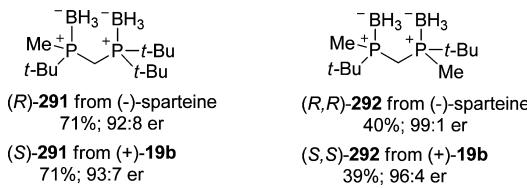
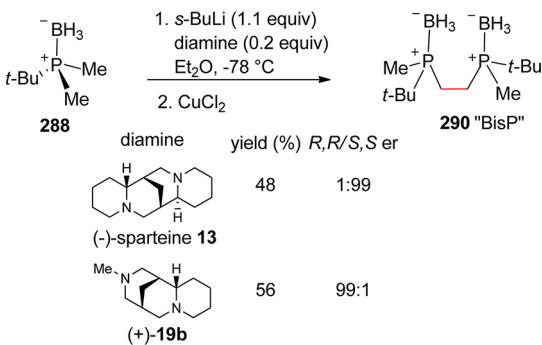


Figure 12. Bisphosphine boranes.

lithiation from uncomplexed *s*-BuLi. This approach allowed the direct synthesis of bisphosphine boranes 291 “trichickenfoot-phos diborane” and 292 “miniPHOS diborane” (Figure 12).

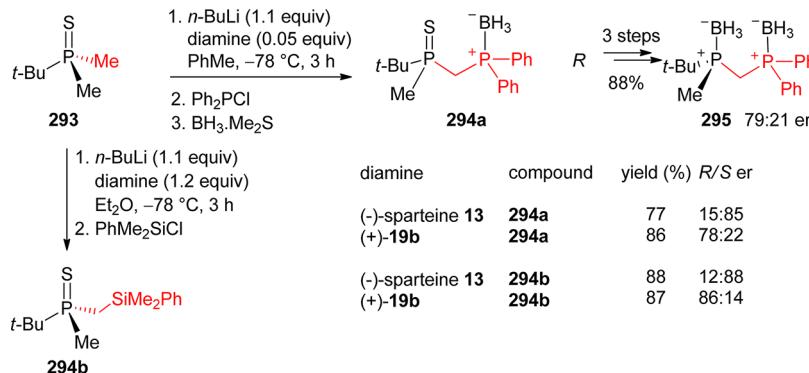
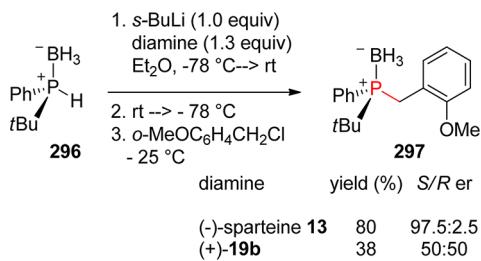
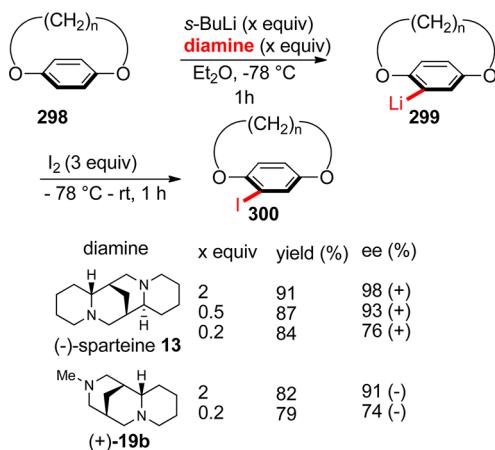
The asymmetric deprotonation of phosphine sulfide 293 was also studied and compared to that of the corresponding *tert*-butyl substituted phosphine borane.²³³ Whereas the highest enantioselection (92:8 er) in the asymmetric deprotonation of phosphine boranes was obtained using *s*-BuLi/(−)-sparteine or diamine (+)-19b, the best results with phosphine sulfide 293 required *n*-BuLi and a solvent depending on the electrophile (Scheme 84).

The lower enantioselectivities observed in this case could result from displacement of the diamine of complex sulfide/diamine by *n*-BuLi, regenerating the complex diamine/*n*-BuLi. Such a displacement was not observed with phosphine boranes. The lower selectivities observed with *s*-BuLi as compared to *n*-BuLi were likely the result of a fast deprotonation of the sulfide by uncomplexed *s*-BuLi. Recrystallization of sulfide 294a gave the pure *P*-stereogenic ligand. This phosphine sulfide 294a was converted into bisphosphine borane 295 without modification of the enantiomeric ratio.

Some limitations of the methodology appeared. As an example, the dynamic resolution of lithiated derivative of *t*-butylphenylphosphine borane 296 afforded only racemic compound 297 with diamine (+)-19b, whereas under the same conditions, (−)-sparteine led to the compound 297 in 97.5:2.5 enantiomeric ratio and 80% yield (Scheme 85).²³⁴ The authors suggested that the low solubility of the complex 296/*s*-BuLi/(−)-sparteine [formation of a precipitate not observed with diamine (+)-19b] drove the dynamic resolution.

7.2.6. Catalytic Asymmetric *ortho*-Lithiation: Access to 1,*n*-Dioxa[n]paracyclophanes. A few asymmetric methods have been described to synthesize optically enriched planar-chiral paracyclophanes. They include intramolecular S_NAr etherification with low enantioselectivities, chiral rhodium-catalyzed coupling of dithiol and dibromide (enantioselectivities up to 60%), or double Sonogashira coupling of diiodocyclophanes (up to 78% ee). However, the optical resolution of racemic compounds remains the most used method. Recently, the Shibata group²³⁵ described an approach based on catalytic asymmetric *ortho*-lithiation of 1,*n*-dioxa[n]paracyclophanes 298 (*n* = 11–14) with *s*-BuLi in the presence of a diamine ligand (Scheme 86, results with *n* = 9). Among the seven diamines tested, (−)-sparteine and diamine (+)-19b gave the highest enantioselectivities (respectively, 98% and 91%). It is noteworthy that even a catalytic amount of (−)-sparteine or (+)-19b gave good yields and enantioselectivities (Scheme 86). Various electrophiles (MeI, DMF, benzophenone, PPh₂Cl) were tested using (−)-sparteine, giving access to C2 symmetric planar-chiral paracyclophanes. Although most of these reactions were carried out with (−)-sparteine, similar results with an induction in the opposite sense were expected with diamine (+)-19b.

This method is the first example of an efficient catalytic and enantioselective *ortho*-lithiation for the generation of planar

Scheme 84. Desymmetrization of Prochiral Phosphine Sulfide**Scheme 85. Dynamic Resolution of Lithiated *t*-Butylphenylphosphine Borane****Scheme 86. Synthesis of 1,*n*-Dioxa[*n*]paracyclophanes**

chirality. It is a good complement to the methods currently described in the lithiation chemistry.

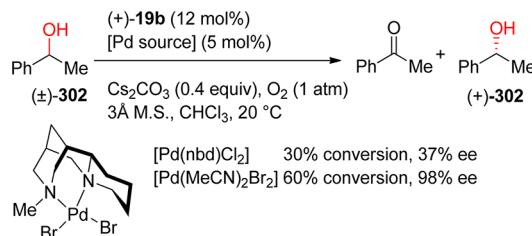
7.2.7. Oxidative Kinetic Resolution of Secondary Alcohols.

Palladium-catalyzed aerobic oxidation of alcohols is an old reaction carried out independently in the presence of $(-)$ -sparteine by the groups of Sigman^{165b,236} and Stoltz.²³⁷ The first example of kinetic resolution of an alcohol using $(+)$ -19b was that of indanol 301. Using Stoltz conditions, Pd(norbornadiene)-Cl₂ (0.05 equiv), and $(+)$ -19b (0.2 equiv), O'Brien et al.¹⁹¹ succeeded in obtaining the (*R*) alcohol in 26% yield and a 90:10 enantiomeric ratio under an atmosphere of oxygen. Later, a lower (72:28) enantiomeric ratio was reported.²³⁴ In this kinetic resolution, diamine $(+)$ -19b was less efficient than $(-)$ -sparteine 13, which afforded the (*S*) enantiomer in 4:96 (*R*:*S*) ratio. This is one of the rare examples reported where diamine $(+)$ -19b induced clearly a lower selectivity than sparteine (Figure 13).

Although the system [Pd(norbornadiene)Cl₂]/($-$ -sparteine] successfully resolved a wide range of secondary alcohols, the

**Figure 13. Oxidative kinetic resolution of indanol.**

rates of oxidation for certain substrates were slow. Furthermore, to access the natural products such as $(-)$ -amurensinine, the $(+)$ -enantiomer of sparteine was necessary. By modifying the coordinated counterions (Cl → Br) and thus the geometry of the palladium complex, which have been fully characterized, and by using $(-)$ -sparteine or diamine $(+)$ -19b, Stoltz and O'Brien obtained both enantiomers of benzylic and allylic alcohols with high enantioselectivities (up to 98%) and yield (60%).²³⁸ The example given for alcohol 302 in Scheme 87

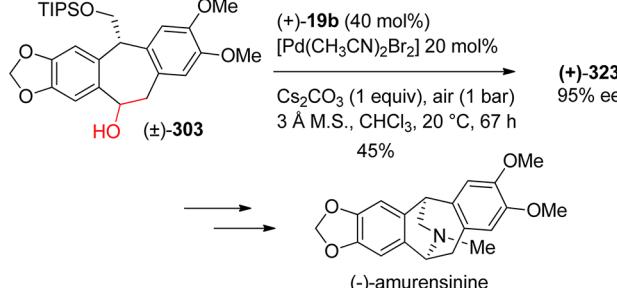
Scheme 87. Oxidative Kinetic Resolution of Phenylethanol

shows the advantage of using Br over Cl in the Pd complex on the yield and selectivity of this oxidation.

The method was applied to the kinetic resolution of alcohol 303, an intermediate in the synthesis of the natural enantiomer of $(-)$ -amurensinine (Scheme 88).

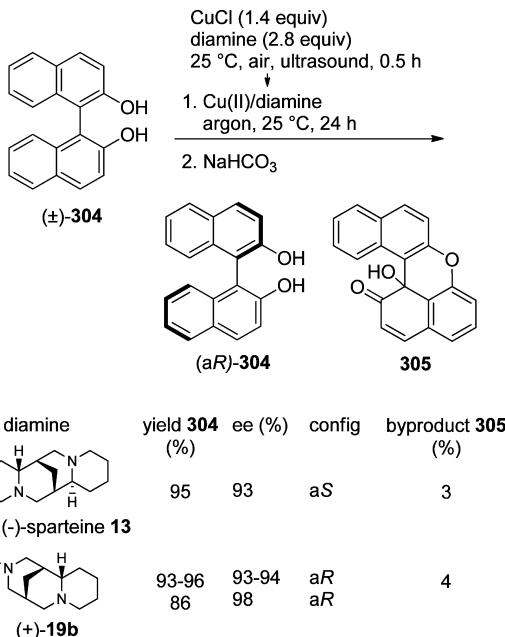
7.2.8. Deracemization of Linear and Vaulted Biaryl Ligands.

2,2'-Disubstituted derivatives of 1,1'-binaphthyl are

Scheme 88. Formal Synthesis of Amurensinine

widely used as chiral inducers. Enantiomerically pure binaphthyl derivatives have been prepared in methods ranging from classical resolution and enzymatic hydrolysis of esters to asymmetric oxidative copper mediated couplings.²³⁹ On the basis of this later methodology, an efficient deracemization of BINOL **304** was reported by Wulff group²⁴⁰ using (−)-sparteine. (*S*)-BINOL **304** was obtained with 92–93% ee and 93–97% yields from the racemate. O'Brien, by substituting sparteine for diamine (+)-**19b**, obtained (*R*)-BINOL in 86% yield and a higher enantiomeric ratio of 99:1.²³⁴ In optimization studies, Wulff et al.²⁴¹ improved the yield and identified an oxidized monomer **305**. However, the enantioselectivities with (+)-**19b** were around 93–94%, similar to those obtained with (−)-sparteine (Scheme 89).

Scheme 89. Deracemization of BINOL



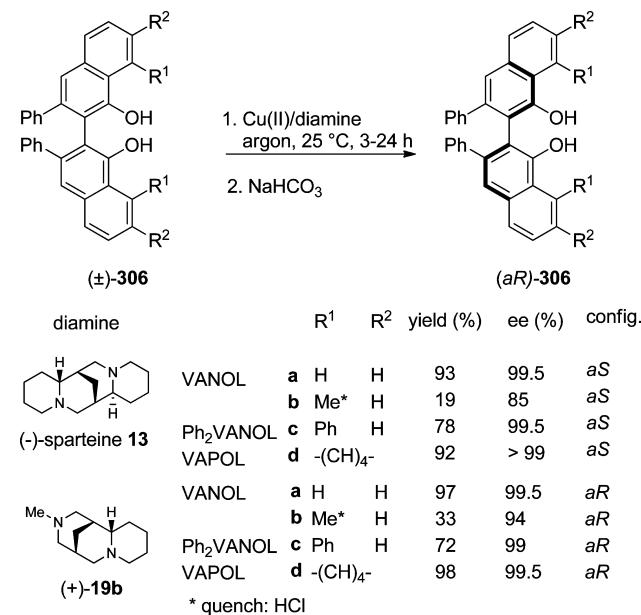
The C₂-symmetric vaulted ligands VANOL **306a–c** and VAPOL **306d**, originally developed by Wulff et al.,²⁴² have proven to be superior to BINOL in many important catalytic asymmetric reactions. Wulff et al. have used the method described above for their deracemization. The (aS)-ligands VANOL or VAPOL **306** were obtained with high conversion and enantiomeric excess up to 99% using CuCl/(−)-sparteine under ultrasound activation at room temperature (Scheme 90). The enantioselectivities were higher than those observed in the case of BINOL (Scheme 89). A careful study of the byproducts formed in the reaction (oxidative dimerization products) and of the conditions of quenching the reaction mixture (NaHCO₃ instead of HCl) improved significantly the efficiency of the deracemization as it is shown in Scheme 90.

This deracemization procedure afforded a method for the preparation of enriched VAPOL and VANOL derivatives avoiding the four-step resolution sequence. Thanks to the cytisine derivative (+)-**19b**, the enantiomers (aR) of each compound were prepared with either comparable or slightly improved yields or enantioselectivities.

7.2.9. Copper-Mediated Oxidative Dearomatization.

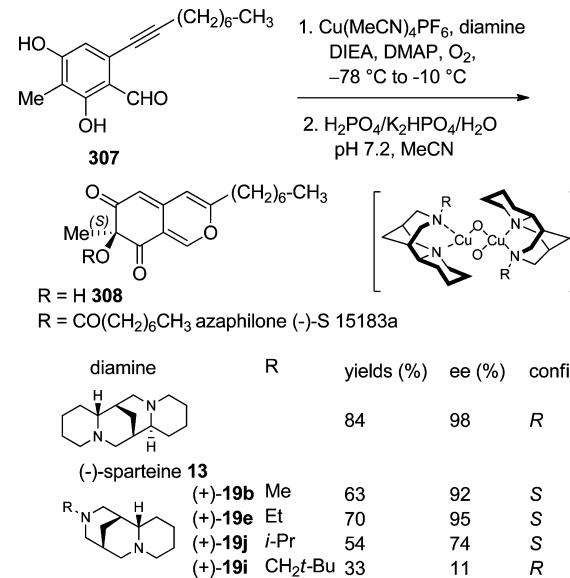
Recently, diamines derived from (−)-cytisine **1** as (+)-sparteine surrogate **19b** allowed for the synthesis of (+)-sclerotiorin and

Scheme 90. Deracemization of VAPOL and VANOL



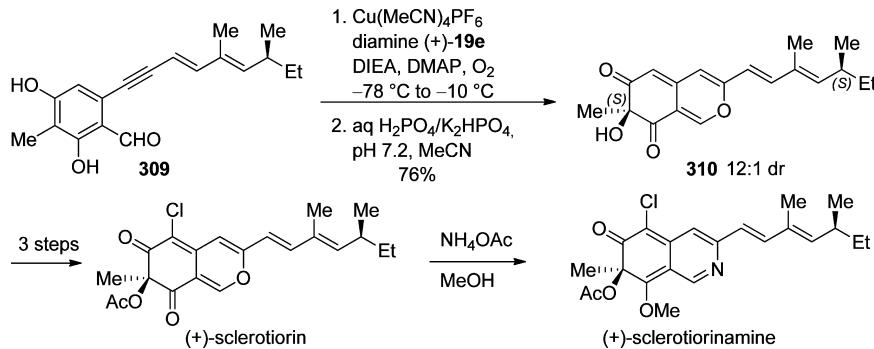
(+)-O-methylsclerotiorinamine, two natural products of the azaphilone family.²⁴³ The key reaction was an asymmetric oxidative dearomatization of an alkynyl benzaldehyde mediated by a copper complex L₂Cu₂O₂ in the presence of *N,N*-diisopropylethylamine (DIEA) as base and 4-dimethylaminopyridine (DMAP) as additive. Scheme 91 compares the

Scheme 91. Enantioselective Synthesis of an Azaphilone Derivative



efficiency of several diamines in the synthesis of a precursor of the azaphilone S-15183a. Both yield (84%) and ee (98%) were higher with (−)-sparteine. Of the four tetrahydrodeoxocytisines tested, the *N*-ethyl derivative (+)-**19e** gave the best enantiomeric excess (95%) in 70% yield. The *N*-isopropyl diamine **19j** gave only moderate yields and enantioselectivities. The steric hindrance of the *N*-neopentyl group of **19i** inhibited the reaction. The lower yields observed with the cytisine derivatives relative to those using sparteine were attributed to

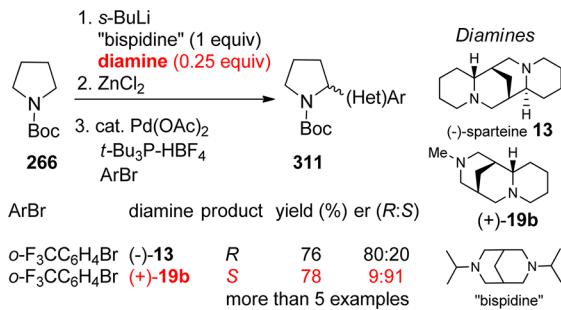
Scheme 92. Synthesis of Sclerotiorin and Sclerotiorinamine



the higher sensitivity to oxidation of diamines **19** as compared to sparteine. *N*-Ethyltetrahydrodeoxocytisine **19e** was chosen for carrying out the copper-mediated enantioselective oxidative dearomatization of aldehyde **307** (Scheme 91). The azaphilone derivative **308** with *S* stereochemistry was obtained in 70% yield and 95% ee.

(+)-Sclerotiorin was obtained in four steps from aldehyde **309** (Scheme 92). Copper-mediated oxidative dearomatization of **309** utilizing diamine (+)-**19e** afforded **310** in good yield and high diastereoselectivity (76% yield, 12:1 dr). Functional transformations (acylation, chlorination) afforded the natural sclerotiorin. Amination of sclerotiorin led to sclerotiorinamine.

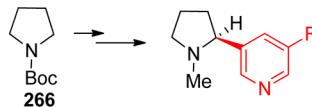
7.2.10. Enantioselective Palladium-Catalyzed α -Arylation of *N*-Boc Pyrrolidine. Campos et al.²⁴⁴ developed an asymmetric arylation of *N*-Boc-pyrrolidine **266** that relies on a (−)-sparteine mediated asymmetric deprotonation, followed by transmetalation with ZnCl₂ and subsequent Pd-catalyzed Negishi coupling with aryl bromides. The authors implemented the reaction²⁴⁵ and demonstrated the possibility of carrying the reaction under catalytic conditions (Scheme 93). While sparteine

Scheme 93. Catalytic α -Arylation of *N*-Boc Pyrrolidine

(−)-**13** and diamine (+)-**19b** gave similar results under stoichiometric conditions, (+)-**19b** proved, in some cases, to be superior in terms of enantioselectivity under catalytic conditions. An example is given in Scheme 93.

The methodology was shown to be efficient with heteroaromatic bromides. Using (+)-**19b**, it was successfully applied to the synthesis of (*S*)-nicotine and (*S*)-SIB-1508Y, an anti-Parkinsonian agent (Scheme 94).

In summary, diamines **19** and particularly (+)-**19b** derived from fully reduced (−)-cytisine have been widely used in asymmetric synthesis for the past decade. Many other reactions have advantageously used them.¹⁹³ Indeed, as compared to (−)-sparteine, *N*-methyltetrahydrodeoxocytisine (+)-**19b** was often more efficacious in terms of enantioselectivities, particularly under catalytic conditions. Moreover, deprotonations by the

Scheme 94. Application of Asymmetric α -Arylation of *N*-Boc Pyrrolidine Using (+)-Sparteine Surrogate

R	(-)-nicotine	3 steps	overall yield	er
H	(-)-nicotine	3 steps	44%	92:8
C≡CH	(-)-SIB-1508Y	4 steps	23%	92:8

alkyl lithium/(+)-**19b** complexes are often much faster and are possible in THF, a solvent nonsuitable for asymmetric deprotonation using (−)-sparteine. Finally, the scope of this diamine was also wider than that of other developed (+)-sparteine surrogates. The advantages of (+)-**19b** over (−)-sparteine have led O'Brien et al. to search for a synthesis of (−)-**19b** as a more efficient substitute of (−)-sparteine.²⁴⁶ However, this synthesis still requires improvements to afford multigram quantities of the (−)-diamine.

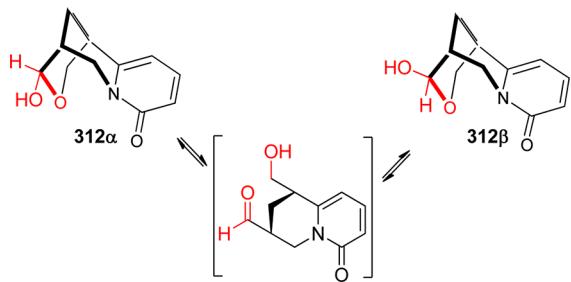
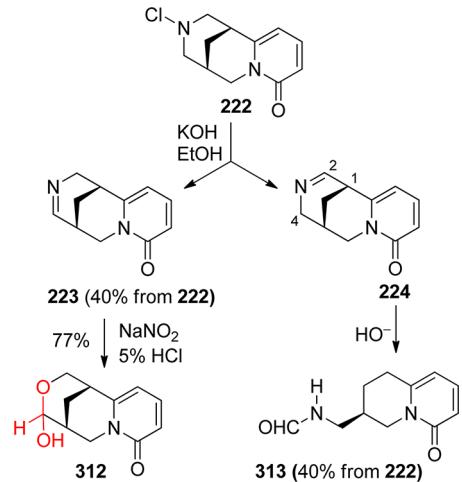
Numerous studies have been focused on the use of (+)-**19b** as a complex with lithium. Recently, interesting applications using transition metal appeared and should find new developments in the future.

8. SYNTHESIS OF NATURAL PRODUCTS FROM (−)-CYTISINE

8.1. Synthesis of (+)-Hupeol

In the course of their studies on lupine alkaloids in *Maakia* plants, Ohmiya et al. isolated (+)-hupeols **312α** and **312β** from Chinese *Maakia hupehensis* (8 mg from 1.2 kg of dry branches) with eight known lupine alkaloids including (−)-cytisine (the major component).^{247,248} The new compounds in which the secondary nitrogen of (−)-cytisine is replaced by an oxygen are structurally similar to cytisine. They were fully characterized by their spectroscopic data. Particularly, NMR spectra allowed assigning the axial and equatorial relative stereochemistry of the hydroxyl group (Scheme 95).

To determine the absolute stereochemistry of hemiacetals **312**, the same authors carried out the synthesis of (+)-hupeol from (−)-cytisine (Scheme 96).²⁴⁹ First, (−)-**1** was quantitatively transformed into its *N*-chloroamine **222**. Dehydrohalogenation afforded an equimolar mixture of imines **223** and **224**. 3,4-Dehydrocytisine **223** was transformed into hupeol **312** by reaction with sodium nitrite under acid conditions. It should be noted that under basic conditions 2,3-dehydrocytisine **224** yielded pyridinone **313**. Participation of the heteroaryl ring in the cleavage of the C₁–C₂ bond could account for this result.

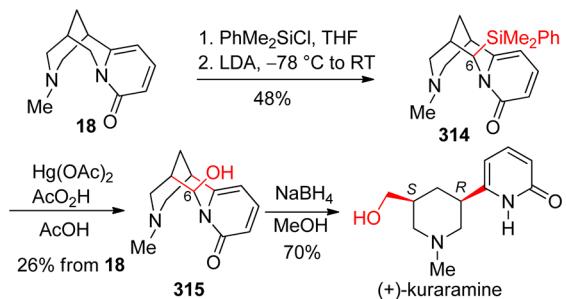
Scheme 95. Structure of Hupeol**Scheme 96. Synthesis of (+)-Hupeol from Cytisine**

The compound 312 was identical to the natural (+)-hupeol and thus has the same configuration as (−)-cytisine.

This conclusion suggested that (−)-cytisine might be metabolized to nonbasic compounds via (+)-hupeol.

8.2. Synthesis of (+)-Kuraramine

From the flowers of *Sophora flavescens*, (+)-kuraramine, a 3-hydroxymethyl-5-(pyridonyl)piperidine, has been isolated in low amount (0.0021%). Murakoshi's measurements of the alkaloid concentration during flower growth²⁵⁰ suggested that (+)-kuraramine was a product resulting from the N–C₆ bond oxidative cleavage of (−)-N-methylcytisine coexisting in the same flowers. This biomimetic pathway inspired Gallagher et al.²⁵¹ to develop an efficient and stereoselective synthesis of (+)-kuraramine (Scheme 97).

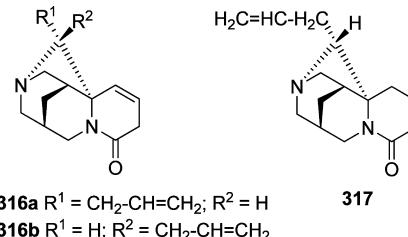
Scheme 97. Gallagher's Synthesis of (+)-Kuraramine

Regio and diastereoselective C₆ functionalization of N-methylcytisine 18 was achieved according to Rouden's conditions.^{155b} Fleming-Tamao oxidation of silyl derivative 314 followed by sodium borohydride treatment of compound 315 afforded

(+)-kuraramine in 18% overall yield from N-methylcytisine. The same chemistry worked with N-benzylcytisine. The ability to cleave N-methylcytisine opened an entry to the stereoselective synthesis of 3,5-disubstituted piperidines, which are of difficult access.

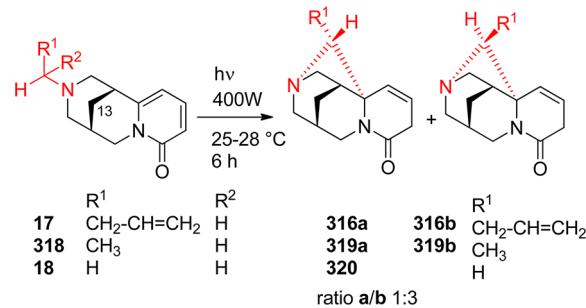
8.3. Synthesis of (−)-Tsukushinamines

Tsukushinamines A (316a), B (316b), and C (317), cage-type lupine alkaloids (Figure 14), were isolated from the fresh epigaeal

**Figure 14. Structures of (−)-tsukushinamines.**

parts of *Sophora franchetiana*,²⁵² and their structures were determined from spectroscopic data²⁵³ and X-ray analysis.²⁵⁴

These natural products and other tsukushinamine-type alkaloids have been synthesized by photolysis in dry acetonitrile of N-substituted cytisines 17, 318, and 18²⁵⁵ taking advantage of the known 1,4-addition of the C–H bond α to a tertiary amine to an aromatic ring.²⁵⁶ The method afforded tsukushinamine A 316a and B 316b from N-butenyl cytisine 17, 319a,b, and 320 from N-ethyl and N-methylcytisines, respectively, in 90–95% yields (Scheme 98). The identity of the products was

Scheme 98. Synthesis of (−)-Tsukushinamines

confirmed by comparing the spectroscopic data with those of authentic samples. These examples are the first ones using a pyridone ring as aromatic nucleus in this type of photoreaction.

8.4. Synthesis of (−)-Camoensine

(−)-Camoensine and (−)-camoensidine have been isolated from different *Camoensia*^{257,258} and *Maackia*¹⁵⁹ species. To study their biosynthesis, Ohmiya et al.¹⁵⁹ clarified their absolute stereochemistry by developing their synthesis from (−)-cytisine (Scheme 99). The key step was the attack of a Grignard reagent from the less hindered side of imine 223. This reaction afforded the dimethoxypropyl derivative 321 in poor yield, an important limitation to this methodology. Deprotection of the acetal, followed by cyclization, led to (−)-camoensine, which was reduced to (−)-camoensidine with 19.5% overall yield.

All of the structures were assigned using ¹H NMR decoupling and nuclear Overhauser effects experiments. The configuration of carbon C4 in compounds 321 was established to be R. Thus, the absolute stereochemistry (1R,4R,5R) of (−)-camoensine is therefore the same as that of (−)-anagyrine (Figure 15).

Scheme 99. Synthesis of (−)-Camoensidine and (−)-Camoensidine

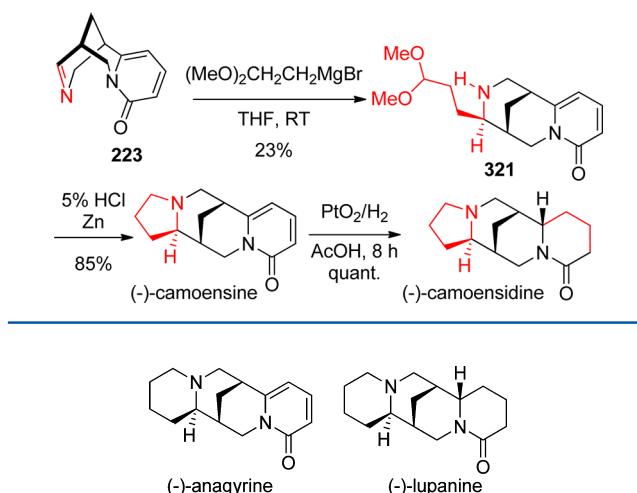


Figure 15. Structures of (−)-anagyrine and (−)-lupanine.

Camoensidine ($1R,4R,5R,12S$) has the same stereochemistry as that of (−)-lupanine (Figure 15).

The *N*-oxide 322a of (−)-camoensidine was also isolated from *Maackia tashiroi*.²⁵⁹ It was obtained stereoselectively in high yield (95%) by oxidation of (−)-camoensidine using hydrogen peroxide. It is worth noting that *m*-chloroperbenzoic acid afforded a mixture of the same oxide 322a (60%) with its diastereoisomer 322b (26%) (Figure 16).

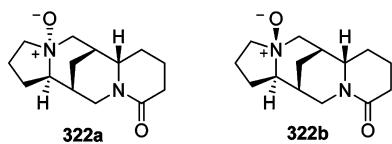
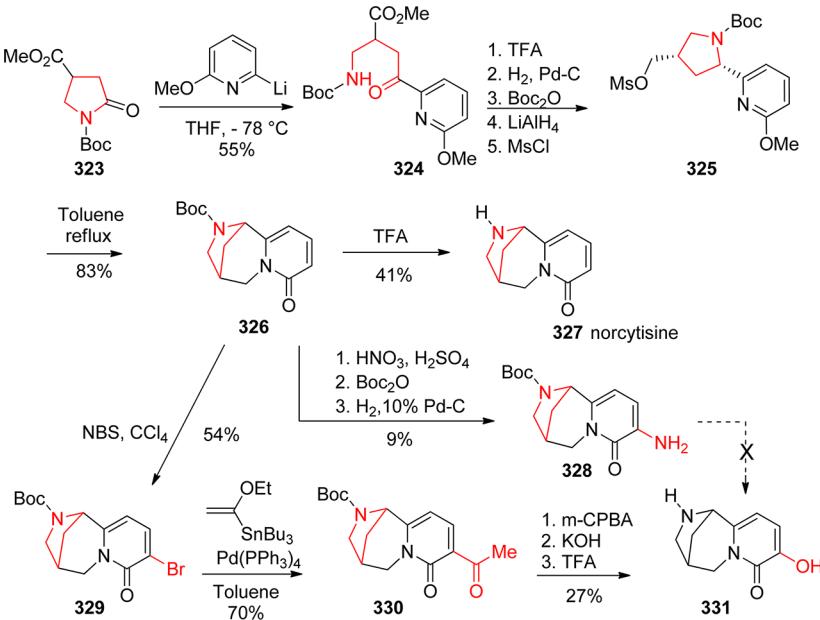


Figure 16. Structures of camoensidine *N*-oxides.

Scheme 100. Yohannes Synthesis of Hydroxynorcytisine



9. SYNTHESIS OF CYTISINE-INSPIRED COMPOUNDS

Because of its biological properties and its unique tricyclic structure lacking rotatable bonds, cytisine was considered as a lead to a variety of chemical modifications in addition to being the starting material for the synthesis of structurally related natural products (as described above).

9.1. Hydroxynorcytisine

Hydroxynorcytisine 331 was isolated in 1989 from the green pods of *Laburnum anagyroides*.²⁶⁰ As compared to cytisine, its skeleton lacks one carbon atom, and the α -carbonyl position is substituted by a hydroxyl group. Despite its structural similarity with (−)-cytisine and potential biological activity, norcytisine have received little attention. The first total synthesis of the racemic compound was described in 2008.²⁶¹ It started from the protected pyrrolidine 323 easily prepared from the corresponding commercially available acid. The tricyclic core of norcytisine was built according to a method previously described for cytisine,¹¹³ which used a S_N2 displacement of a mesylate by the nitrogen atom of the pyridone ring. Norcytisine was obtained within 19% overall yield from 323. Direct functionalization by a hydroxyl group via a diazonium salt formed on the pyridone position next to the carbonyl group failed. This result can be compared to that observed in testing fluorination of the C_9 position of cytisine using a Baltz–Schiemann reaction (Scheme 36).²¹ The hydroxyl group was introduced in four steps and 10% overall yield: bromination of the pyridone ring, Stille-coupling reaction, Bayer–Villiger oxidation of methyl ketone 330, then deprotection (Scheme 100).

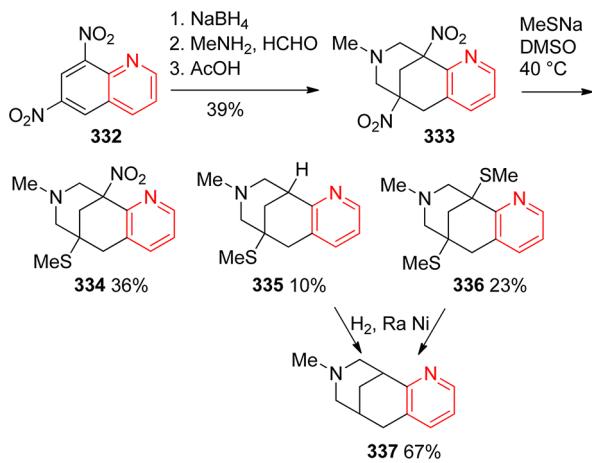
Surprisingly, unlike (−)-cytisine, hydroxynorcytisine 331 and norcytisine 327 displayed no affinity at the nAChRs of subtypes $\alpha 4\beta 2$ and $\alpha 7$. This observation illustrated the high sensitivity of the receptors to minor structural differences.

9.2. Pyridine Analogues of (−)-Cytisine

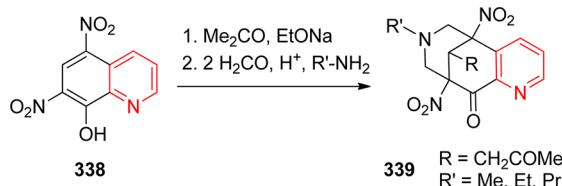
With the aim of preparing compounds of potential interest for the agrochemical industry, Pryce et al.²⁶² described in 1995 the first pyridine analogue 337 of cytisine. Dinitroquinoline 332 prepared from dinitroaniline was partially reduced to undergo a

Mannich reaction affording the tricyclic compound 333 in 39% overall yield. Denitration with sodium methanethiolate in DMSO according Kornblum et al.²⁶³ afforded a mixture of mononitro compound 334, monosulfide 335, and bisulfide 336. Reduction of the mono or bisulfide gave the pyrido[2,3d]azocine 337 in 67% yield (78% based on recovered starting material) (Scheme 101).

Scheme 101. Synthesis of a Pyridine Analogue of N-Methylcytisine



Scheme 102. Synthesis of a Polysubstituted Pyridine Analogue of Cytisine

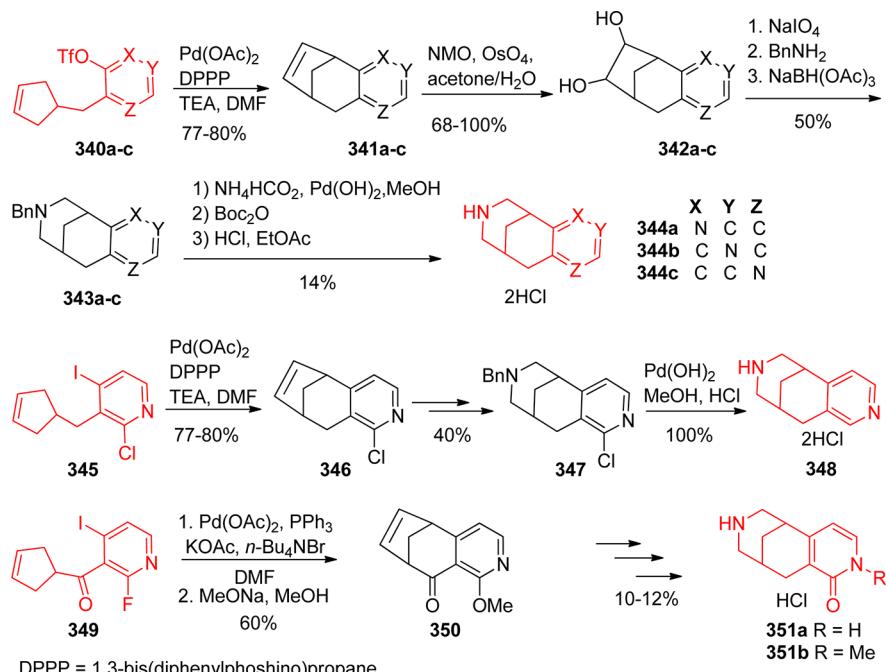


More than 13 years later, a Russian group used a similar approach to synthesize the polyfunctional compounds 339 (Scheme 102).²⁶⁴ At the same time, Coe et al.^{265,266} from Pfizer Co. described the preparation of four pyridines 344a–c, 348 and two pyridones 351a,b analogues of (–)-cytisine, assuming that their constrained structures should improve the specific interactions with nicotinic receptors. Their elegant strategy employed an intramolecular Heck reaction to generate the tricyclic structure of their targets. The piperidine part resulted from an oxidative ring-opening then ring closure in the presence of benzylamine. According to the position of the nitrogen heteroatom in the pyridine ring, a triflate 340 or an iodopyridine 345 (Scheme 103) was used as the starting material. The same route was employed for the preparation of the pyridone derivatives 351 (Scheme 103), fluoroiodopyridine 349 being used as a masked pyridone function. Whereas high yields were obtained to prepare the diols (i.e., 342a–c), the reaction sequence leading to pyridines suffered from low yields mainly due to their purification requiring a Boc protection–deprotection.

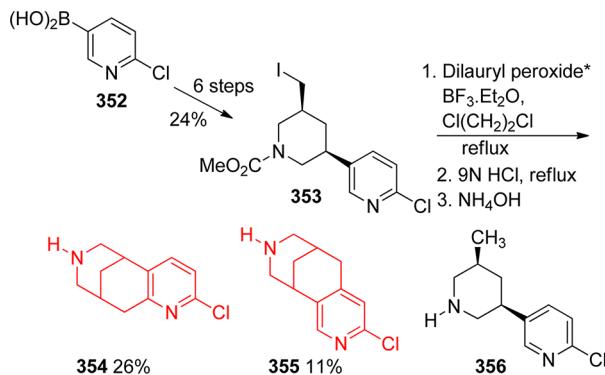
To our knowledge, no biological data were reported for these eight constrained mimics of (–)-cytisine.

On the basis of the common pharmacophore of (–)-cytisine and epibatidine deduced from molecular modeling studies, Rouden et al.²⁶⁷ described the synthesis of chloropyridine 354 as a hybrid of the two natural products. The key step was the intramolecular coupling between the primary radical generated from iodide 353 and the chloropyridine moiety (Scheme 104). Under selected conditions, and after deprotection, chloropyridine 354 was obtained with its regioisomer 355 and isolated in 26% and 11% yields, respectively. The reaction required both the presence of a radical initiator and that of a Lewis acid to afford the expected tricyclic compounds. In the absence of boron trifluoroetherate, the major product was disubstituted piperidine 356 (354/355/356: 33/20/47 molar ratio). The affinities of the synthesized compounds at the nAChRs receptors are reported in Table 10. Their comparison with that of known compounds showed that the cytisine mimics 354 and 355 are excellent

Scheme 103. Synthesis of Pyridines and Pyridones Analogues of Cytisine



DPPP = 1,3-bis(diphenylphosphino)propane

Scheme 104. Synthesis of a Cytisine–Epibatidine Hybrid**Table 10. Affinities at nAChRs**

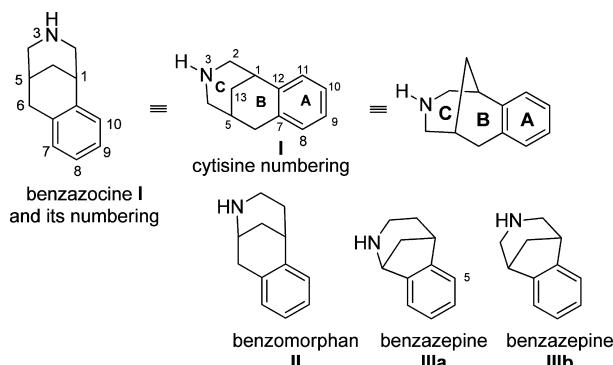
ligands ^a	K_i (nM) $\alpha 4\beta 2$	K_i (nM) $\alpha 7$
(–)-cytisine	1.06 (lit. ^b : 0.17 ²⁶⁸)	>10 000 (lit. ^c : 4200 ²⁶⁸)
varencline	0.9 (lit. ^b : 0.06 ²⁶⁸)	0.2 (lit. ^c : 322 ²⁶⁸)
(±)-354	3.5	710
(±)-355	0.5	170

^aBinding affinities (K_i) were expressed as geometric means from four separate experiments and measured by competition studies, respectively, with [³H]cytisine and [¹²⁵I]- α -bungarotoxin in adult Wistar rat brain. ^b[³H]Nicotine. ^c[¹²⁵I]- α -Bungarotoxin.

ligands of nAChRs $\alpha 4\beta 2$ subtype. Molecular modeling studies were carried out to compare the fitting of compounds 354 and 355 with the pharmacophore cytisine/epibatidine. The highest superimposition was obtained for chloropyridine 355 in good agreement with the highest observed affinities at nAChRs.

9.3. Carbon Analogues of (–)-Cytisine

Carbon analogues of cytisine belong to the 1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine family I (Figure 17), and only the

**Figure 17.** Benzazocine, benzomorphan, and benzazepine skeletons.

synthetic approaches to this skeleton and to that of benzazepine of type IIIb will be described (cf., ref 269 for a review on benzomorphan derivatives and analogues). The routes are classified according to the ring that is formed last (B or C). For an easy comparison with cytisine, the carbon numbering of cytisine was kept.

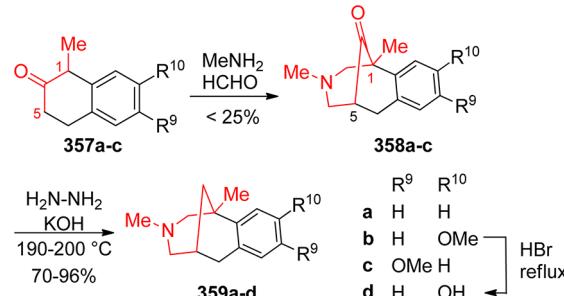
9.3.1. Construction of Ring C of Benzazocine Skeleton I.

The construction of ring C was the most common approach to the benzazocine skeleton I starting from tetrahydronaphthalene derivatives.

9.3.1.1. Formation of Ring C via a Mannich Reaction.

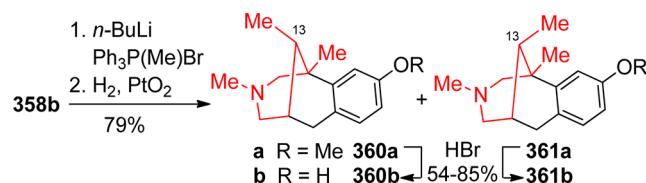
With the aim of developing new analgesics, benzazocines

359a,²⁷⁰ 359b,d,²⁷¹ and 359c²⁷² were prepared via a Mannich reaction of the suitable tetralone 357a, 357b, or 357c with methylamine and formaldehyde (Scheme 105). The reaction,

Scheme 105. Construction of Ring C via a Double Mannich Reaction

which did not proceed in the absence of a substituent at the highly reactive benzylic position C₁ of the tetralone, afforded the tricyclic ketones 358a–c in poor yields. Wolff–Kishner reduction, then deprotection of the phenol, when necessary, led to the target compounds 359.

Wittig olefination of ketone 358b, then catalytic hydrogenation, afforded a mixture of substituted derivatives 360a and 361a, which were deprotected into the corresponding phenols 360b and 361b, respectively (Scheme 106).

Scheme 106. Synthesis of Carbon Analogues of Cytisine Substituted at C₁₃

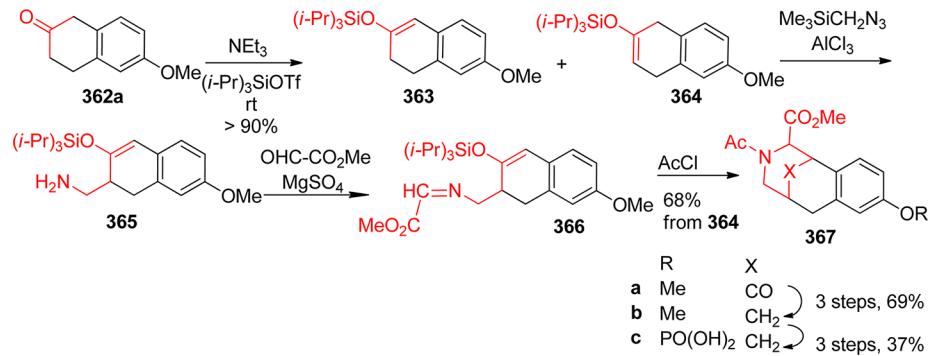
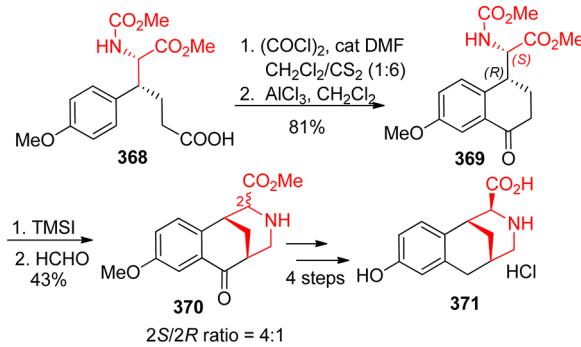
The analgesic activity of the phenols was measured. Only compound 359d (Scheme 105) had an activity similar to that of codeine and higher than that of the methoxy derivatives 360b and 361b.

To allow the synthesis of 1,5-methano-3-benzazocine unsubstituted at the C₁-position, Burke et al. used the silyl enol ether 364.²⁷⁴ This enol ether was obtained with its regioisomer 363 as an inseparable mixture. However, aminomethylation, which proceeded only with enol 364, yielded the single regioisomer 365 (Scheme 107). Reaction of this amino derivative 365 with methyl glyoxalate followed by acylation afforded an acyl iminium, which underwent intramolecular cyclization to provide 367a.

Biological tests were carried out at Grb2 (Growth factor receptor-bound protein 2) SH2 (Src homology 2) domain,²⁷⁵ which binds to phosphorylated tyrosine-containing peptides of receptors. No affinity was found for the constrained tyrosine analogue 367c.²⁷⁴

In their search for new ligands at the same biological target, Yao et al.²⁷⁶ described the enantioselective synthesis of amino acid 371 from the chiral acid 368 (Scheme 108). An intramolecular Friedel–Crafts reaction was used to build ring B. The solvent played a key role for the efficient formation of the acid chloride required for this reaction. Deprotection of the amino group of 369, then an intramolecular Mannich reaction,

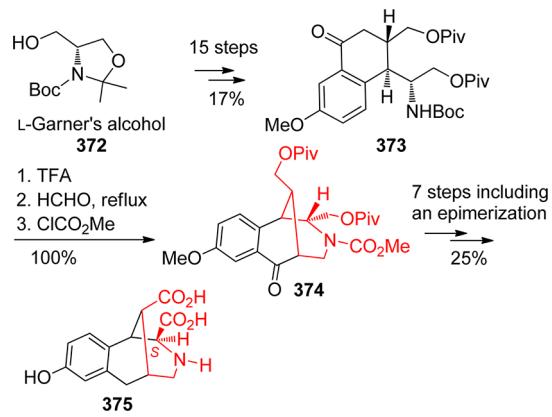
Scheme 107. Formation of Ring C via an Intramolecular Cyclization of an Iminium Intermediate

Scheme 108. Mannich Reaction of a Chiral Amino Ester²⁷³

afforded the aza-six-membered ring C. The amino ester 370 was obtained as a mixture of two diastereoisomers (ratio 4:1).

To enhance the binding affinity with SH2 domain²⁷⁵ through more hydrogen-bonding generation, the same group²⁷⁷ developed an enantioselective route of diacid 375 starting from L-Garner's alcohol 372. The tricyclic diacid 375 was obtained with high stereoselectivities according to the key steps presented in Scheme 109. However, the length of the synthesis

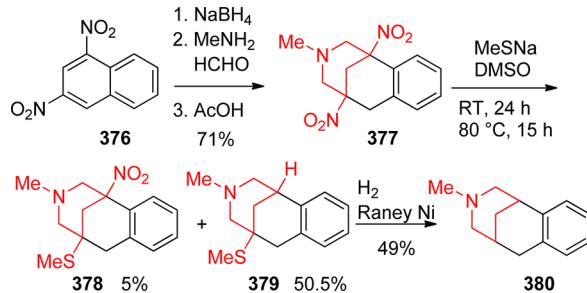
Scheme 109. Yao Synthesis of a Constrained Amino Acid



(more than 25 steps) was a limit for the development of these constrained amino acids.

The synthesis of N-methyl benzazocine 380, a potential insecticide, was accomplished in a satisfactory yield from dinitronaphthalene 376 using a double Mannich reaction.²⁶² The nitro groups were removed by reaction with sodium methanethiolate, then treatment of the methylthio derivative 379 with hydrogen under catalytic conditions (Scheme 110). The compound 380 was isolated in 17% overall yield from

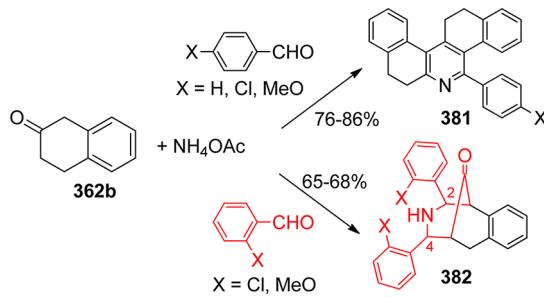
Scheme 110. Synthesis of 3-Methyl-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine



dinitronaphthalene 376. As for its pyridine analogue (cf, section 9.2), no biological data were reported.

Recently, the reaction of 2-tetralone with ammonium acetate and substituted benzaldehydes originally reported by Noller and Baliah²⁷⁸ was reinvestigated.²⁷⁹ When the reaction was carried out with benzaldehyde or with *para*-substituted benzaldehydes, phenanthridines derivatives 381 were isolated in 76–86% yields, whereas with *ortho*-chloro- or *ortho*-methoxybenzaldehyde, only benzazocines 382 were obtained in 68% and 65% yields, respectively (Scheme 111). The steric hindrance of the *ortho*-

Scheme 111. Reaction of Benzaldehydes with 2-Tetralone

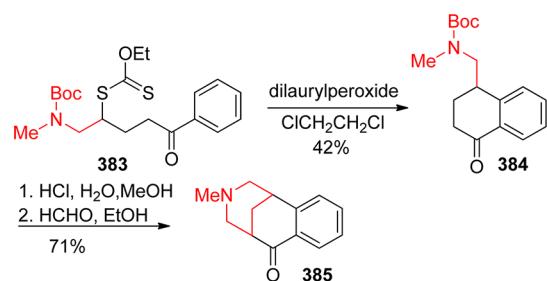


substituted benzaldehydes could account for these different reactivities. This is the only access to 2,4-disubstituted benzazocines I (Figure 17).

A Mannich reaction was again the final step of the preparation of tricyclic ketone 385 (Scheme 112). An original approach to tetralone 384 involved the radical cyclization of xanthate 383.²⁸⁰ The overall synthesis of 385 was short and efficient as compared to those described.

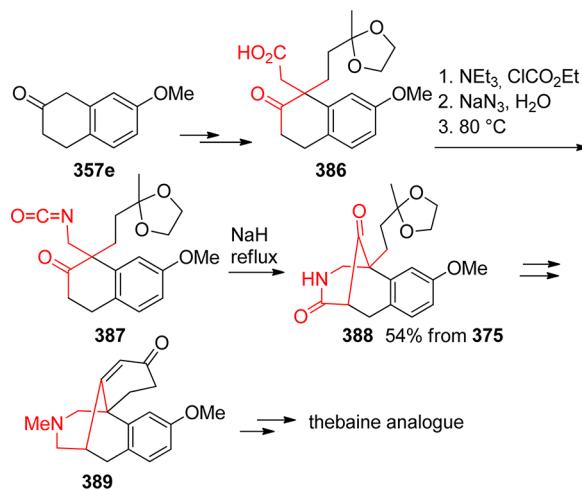
9.3.1.2. Formation of Ring C via an Isocyanate. Wiesner et al.²⁸¹ synthesized an analogue of thebaine that required the preparation of benzazocine 389. Ring C of this compound

Scheme 112. Construction of Ring B via a Radical Cyclization, then Ring C via a Mannich Reaction



resulted from the functional transformation of acid 386 to isocyanate 387 with a subsequent intramolecular cyclization under basic conditions (Scheme 113). The method was efficient

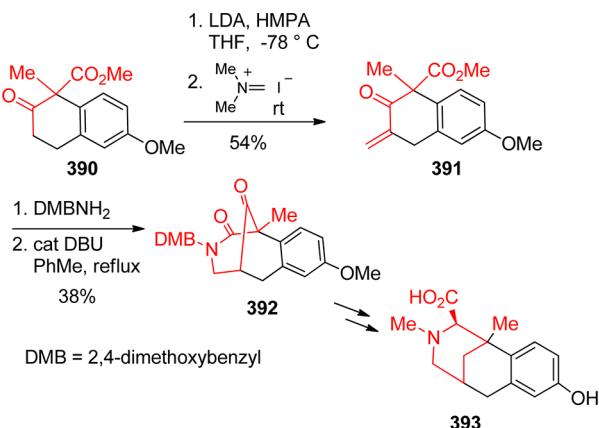
Scheme 113. Construction of Ring C via an Isocyanate



because compound 389 was formed in seven steps and 21% overall yield from tetralone 357e.

9.3.1.3. Formation of Ring C via Michael Addition, then Intramolecular Ring Closure. To access to the tricyclic amino acid 393, which contains within its structure the elements of a constrained tyrosine moiety, Burke et al.²⁸² employed an intramolecular 1,4-Michael-type addition of 2,4-dimethoxybenzylamine (DMBNH₂) onto methylene tetralone 391 (Scheme 114). DMBNH₂ was chosen because of its acid lability and its ability

Scheme 114. Construction of Ring C via a Michael Addition

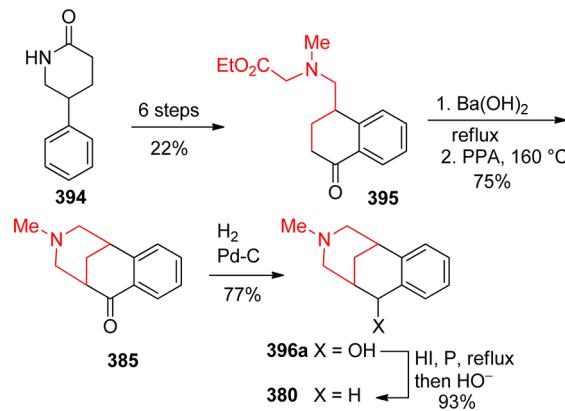


DMB = 2,4-dimethoxybenzyl

to be removed by chemical modification distal to the nitrogen itself.

9.3.1.4. Formation of Ring C via an Acid-Mediated Intramolecular Cyclization. Another route²⁸³ to hexahydro-1,5-methano-3-benzazocine was based on the cyclization under acid conditions (polyphosphoric acid, PPA) of the acid derived from ester 395 (Scheme 115). While the transformation of 395

Scheme 115. Construction of Ring C via an Intramolecular Cyclization of α -Substituted Tetralone



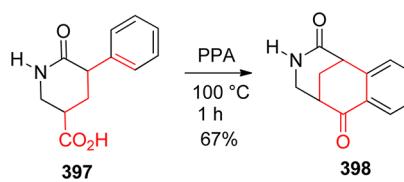
to 380 gave satisfactory yields, the synthesis suffered from the lengthy preparation of ester 395.

9.3.2. Construction of Ring B of Benzazocine Skeleton

I. In the following examples, the last ring built of 1,5-methano-3-benzazocine was ring B.

9.3.2.1. Friedel–Crafts-type Reactions. One of the first approaches to the carbon analogues of cytosine was described by Hill et al.²⁸⁴ These authors used a Friedel–Crafts cyclization of phenyl piperidinone carboxylic acid 397. This acid, prepared in three steps and 48% overall yield from ethyl cyanoacetate and ethyl atropate, afforded upon heating with polyphosphoric acid the tricyclic lactam 398 in a satisfactory yield (Scheme 116).

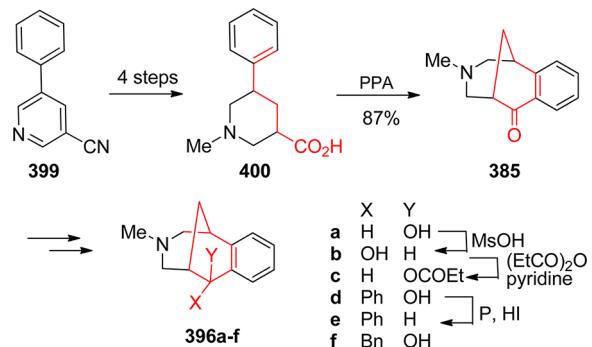
Scheme 116. Friedel–Crafts-type Reaction To Build Ring B



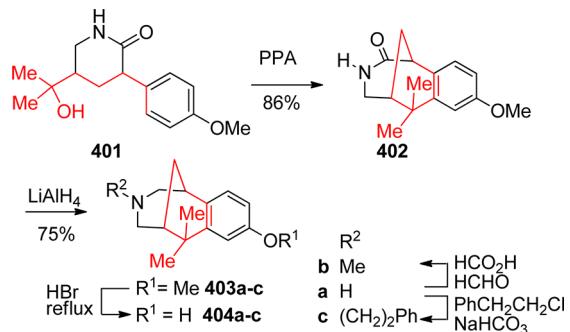
Much later,²⁸⁵ a similar approach was used to prepare the tricyclic ketone 385 from piperidine carboxylic acid 400. The *cis* and *trans* isomers of this compound were independently heated with polyphosphoric acid to yield the same tricyclic ketone 385 in 90% and 87% yield, respectively. Reduction of ketone 385 with LiAlH₄ afforded alcohol 396a, which was readily isomerized to 396b with methanesulfonic acid (Scheme 117). Reaction of ketone 385 with phenyl or benzyl Grignard reagent afforded alcohols 396d and 396f of unknown configuration. However, because all attempts to acylate 396d failed, the authors suggested that the phenyl group was probably *trans* to the bridge (X = Ph), the form in which the OH group was more hindered. None of the compounds 396a–d had an analgesic activity.

In a similar approach,²⁸⁶ the tricyclic lactam 402 was obtained in 86% yield from piperidone alcohol 401. LiAlH₄ reduction of 402 yielded amine 403a, which was transformed into its N-alkyl

Scheme 117. Construction of Ring B via Friedel–Crafts Cyclization of a Phenylpiperidine Carboxylic Acid



Scheme 118. Construction of Ring B via Friedel–Crafts Cyclization of a Substituted Piperidinone

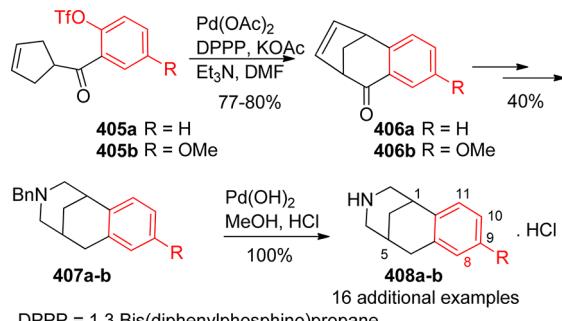


derivatives **403b** and **403c**, then into the corresponding phenols **404b**, **404c** (Scheme 118). Although the cyclization process was efficient, and did not require a *cis* arrangement of both substituents on the piperidinone, this approach was limited by the low yielding access to the precursor **401**. The *N*-methyl derivative **403b** has an analgesic activity about 2 times that of codeine but 0.6 times that of pentazocine.

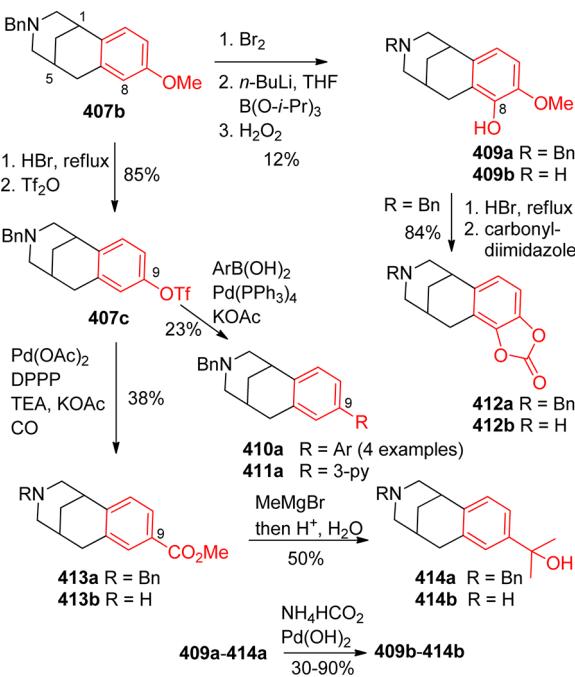
9.3.2.2. Heck Reaction. As a part of its program for finding novel therapies for smoking cessation, the Pfizer Co.²⁸⁷ reported the synthesis of aromatic substituted benzazocine (**408**, **415**, **419**) according to the strategy developed for the synthesis of cytisine. The key step was the intramolecular coupling of an aryltrifluoromethanesulfonate with a cyclopentene moiety. Heck coupling of triflate **405** proceeded in high yield but required the use of two bases KOAc (20%) and Et₃N (stoichiometric amount). The authors suspected that KOAc converted the unstable intermediate ArPdOTf into the more reactive ArPdOAc during the reaction. Well-established transformations led to the monosubstituted derivatives **408** (Scheme 119).

Compound **407b** was the precursor of a series of other mono- and disubstituted derivatives. Bromination of **407b** was required for the introduction of substituents at the C₈ position. The 8-bromo derivative was converted to **409a** via halogen-metal exchange, treatment with triisopropylborate, and peroxide-mediated oxidation. Benzyl deprotection [Pd(OH)₂, NH₄HCO₃] gave compound **409b**. Classical cross-coupling reactions of triflate **407c** were used to introduce different substituents at the C₉ position. No detail was given to explain the moderate to low yields obtained in the Suzuki reaction and in the carbonylation leading to **410a** and **413a**, respectively (Scheme 120).

Scheme 119. Construction of Ring B of Benzazocine Skeleton I via a Heck Reaction²⁷³

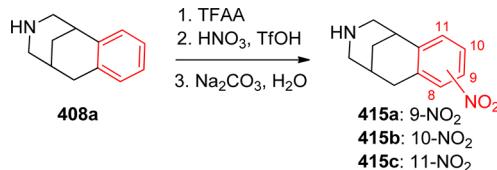


Scheme 120. Functionalization of Ring A of Benzazocine, Carbon Analogue of Cytisine²⁷³



Protection of benzazocine **408a** (Scheme 119), then nitration, gave a mixture of three mononitrated derivatives **415a**, **415b**, and **415c** (9-NO₂, 10-NO₂, 11-NO₂) after removal of the trifluoroacetyl group. The most abundant regioisomer was the 10-substituted derivative **415b** isolated by chromatography in 50% yield (Scheme 121).

Scheme 121. Nitration of Benzazocine **408a²⁷³**



Intensive research has been developed to prepare the difluoro compound **419b** via a Heck intramolecular cyclization.¹¹⁸ Finally, the key bromoaryl derivative **417** required for the Heck reaction was prepared in high yield by alkylation of aryl anion **416** with triflate **75a** (Scheme 122). Palladium-mediated Heck cyclization reactions of **417** with Pd(OAc)₂/P(*o*-tol)₃

Scheme 122. Coe's Enantioselective Synthesis of a Carbon Analogue of Cytisine

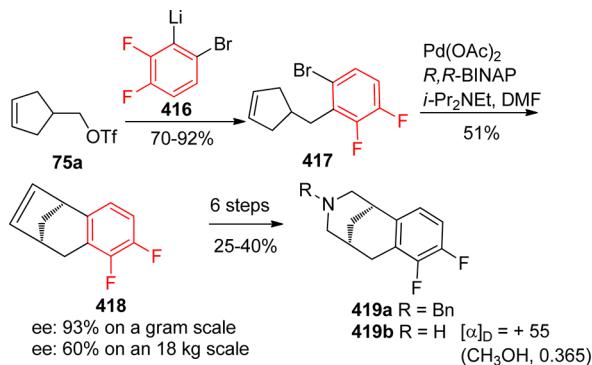
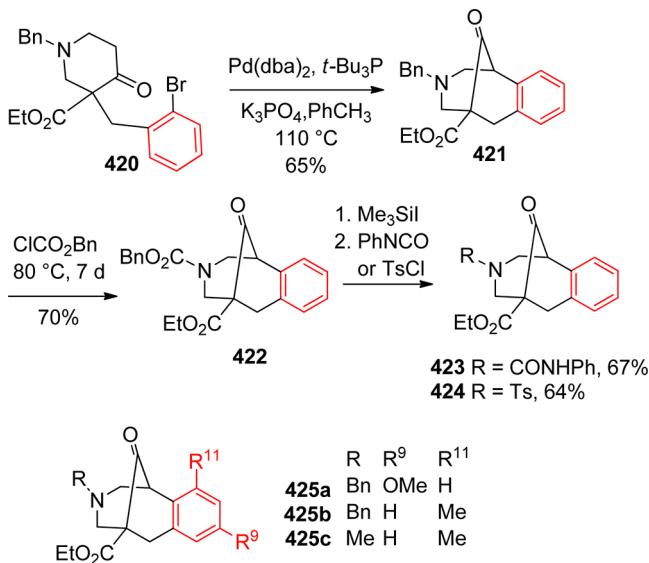


Table 11. $\alpha 4\beta 2$ nAChR K_i Values for Carbon Analogues of Cytisine²⁷³

entries	compound	R ⁸	R ⁹	R ¹⁰	K_i (nM) ^a
1	(−)-cytisine				0.23 ^a / 0.17 ^b
2	(−)-nicotine				1.6 ^a / 0.95 ^b
3		F	F	H	0.44
4		H	OMe	H	1.4
5		H	F	H	2.0
6		OH	H	H	2.9
7		H	NO ₂	H	4.9
8		H	O—CH ₂ —O		5.7
9		F	H	H	6.5
10		H	H	NO ₂	6.5
11		H	OCHF ₂	H	7.0
12		H	H		34 / 65 ^b
13		H	OH	H	90

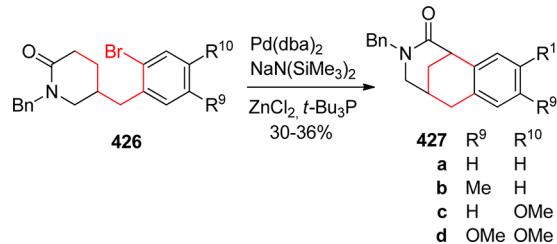
^a[³H]Nicotine; human $\alpha 4\beta 2$ nAChR in HEK293 cells. ^b[³H]Nicotine; rat cortex.

Scheme 123. Maier's Route to Benzazocine Skeleton I²⁷³

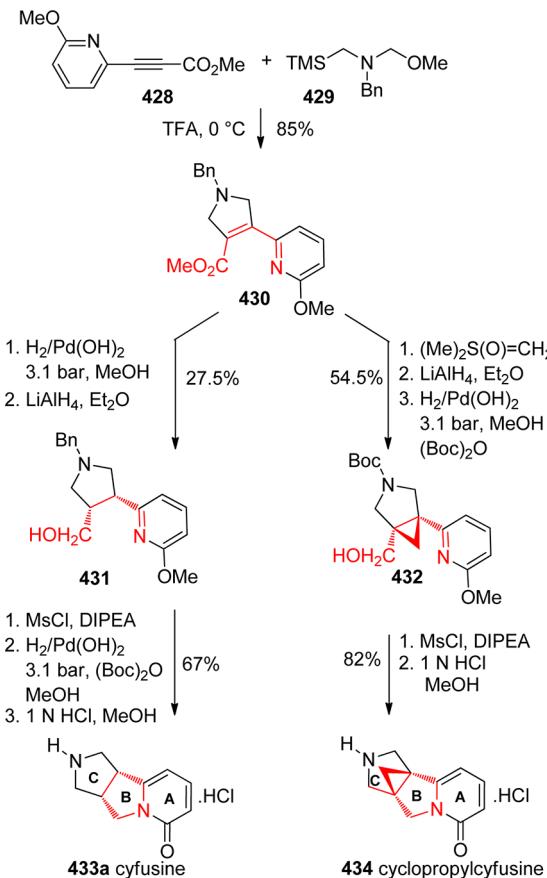


provided 418 as a racemic material in 77% yield. The combination *R,R*-BINAP (1–10 mol %)/Pd(OAc)₂ in DMF was found

Scheme 124. Construction of Ring B of Benzazocine Skeleton I via the Coupling of a Zinc Enolate with an Aryl Bromide²⁷³



Scheme 125. Yohannes Synthesis of Cyfusine



to be the best one to carry out the intramolecular enantioselective coupling. On a gram scale, 418 was obtained with an enantiomeric excess up to 93%. On a larger scale (18 kg), the enantiomeric excess decreased significantly.

The *in vitro* K_i values of benzazocines analogues of cytisine were measured using inhibition of radioligand binding to the $\alpha 4\beta 2$ nAChR. An affinity range from 0.44 to >500 nM was observed. Table 11 presents the compounds possessing the highest affinities.²⁸⁷ However, none of these compounds had an affinity higher than that of (−)-cytisine. The best ligands were all substituted by small polar groups (F, OH, OMe, NO₂). In contrast to the substituent effects observed in 9-substituted cytisine derivatives, substituents at C₉ did not improve the affinity. The phenol (9-OH, entry 13) was less potent (K_i = 90 nM) than its 8-regioisomer (entry 6) and than the corresponding anisole, fluoro, or nitro compounds (entries 4, 5, 7, respectively). The most potent compound combined two adjacent fluorine atoms (entry 3) with an affinity close to that

Scheme 126. Gallagher Synthesis of Cyfusine and Fluorocyfusine

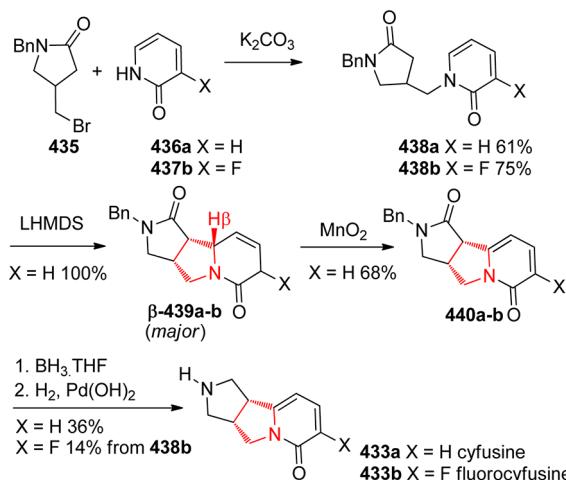
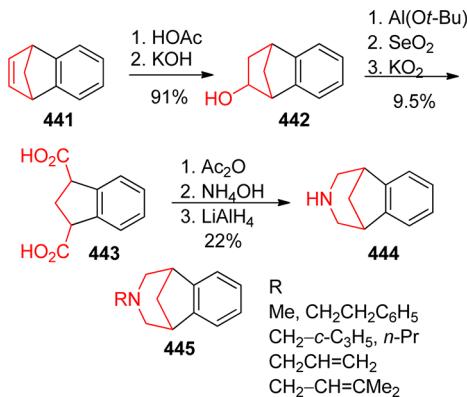


Table 12. In Vitro Affinity of Cyfusine and Cyclopropylcyfusine at nAChR Subtypes

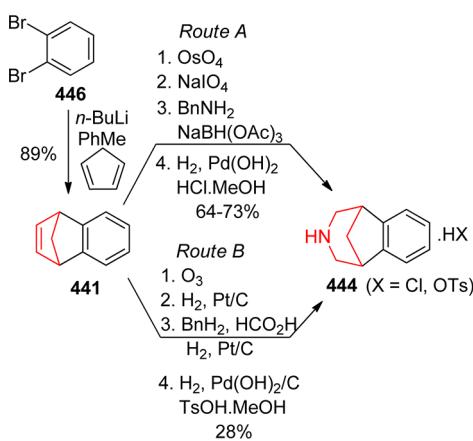
compound	K_i (nM) ^a		
	$\alpha 4\beta 2$	$\alpha 3\beta 4$	$\alpha 7$
(\pm)-cyfusine	16	>500	>500
(\pm)-cyclopropylcyfusine	144	>500	>500
($-$)-cytisine	0.43	1560	5820

^aThe affinities were determined according to ref 268.

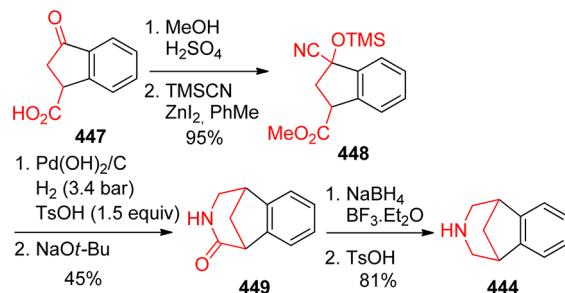
Scheme 127. First Synthesis of 1,5-Methano-3-benzazepines



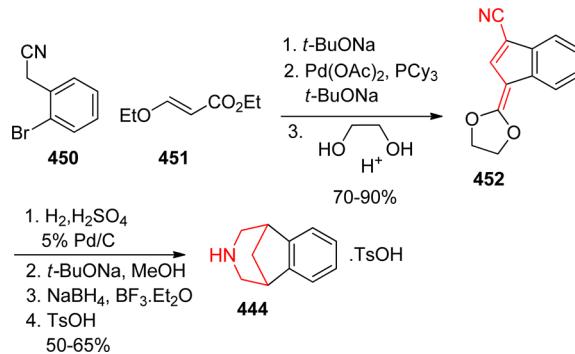
Scheme 128. Coe Syntheses of 1,5-Methano-3-benzazepines



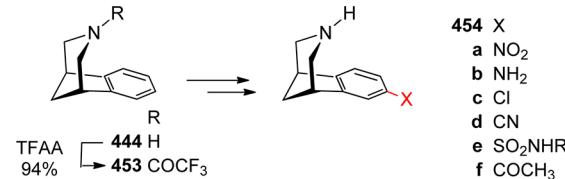
Scheme 129. O'Donnell Route to 1,5-Methano-3-benzazepine



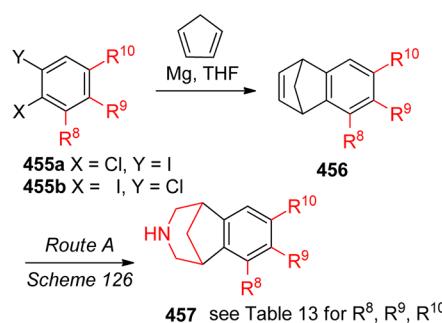
Scheme 130. Construction of Rings B, then C of the Benzazepine Skeleton IIIa



Scheme 131. 1,5-Methano-benzazepine Derivatives from Electrophilic Substitutions of the Parent Compound

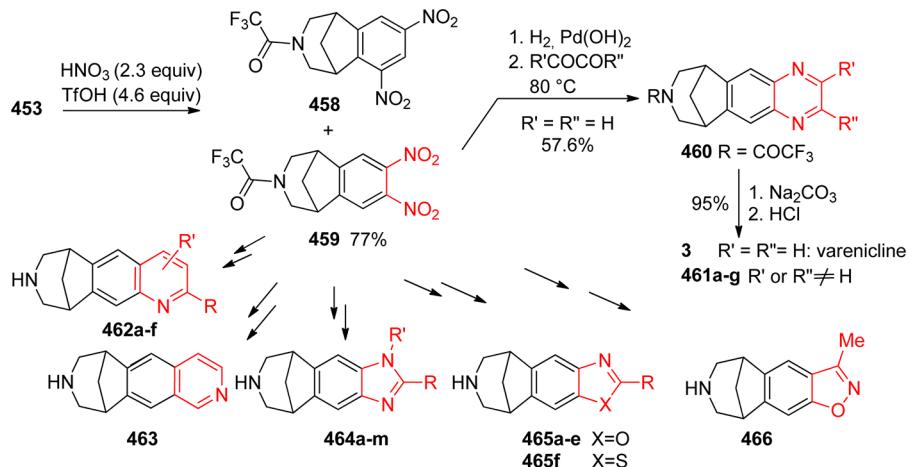


Scheme 132. Synthesis of 1,5-Methano-benzazepine Derivatives²⁷³



of ($-$)-cytisine. Compounds in entries 3–5 and 7–10 were >100 -fold selective in binding models for the $\alpha 4\beta 2$ nAChR over other nAChR subtypes ($\alpha 3\beta 4$, $\alpha 7$, and $\alpha 1\beta\gamma\delta$). The functional properties of some best ligands were characterized using electrophysiological techniques in *Xenopus oocytes* expressing the human $\alpha 4\beta 2$ nAChR. Only the 9-methoxy (entry 4), 9-difluoromethoxy (entry 11), and 9-nitro (entry 7) derivatives were weak partial agonists as compared to ($-$)-cytisine.

Scheme 133. Synthesis of Varenicline and Related Compounds

Table 13. Affinities of Benzazepine Derivatives at $\alpha 4\beta 2$ nAChR²⁷³

$\begin{array}{c} \text{HN} \\ \\ \text{C}_6\text{H}_4 - \text{R}^8 \\ \\ \text{R}^{10} \end{array}$	R ⁸	R ⁹	R ¹⁰	$\alpha 4\beta 2^a$
				K _i (nM)
457a	H	Cl	Cl	0.10
(-)-cytisine				0.17
457b	H	COMe	H	0.17
457c	H	Cl	H	0.20
457d	H	F	F	0.28
457e	H	CF ₃	H	0.33
457f	H	CN	H	0.5
457g	H	NO ₂	H	0.75
(-)-nicotine				0.95
457h	H	F	H	1.1
457i	H	Me	H	1.6
457j	N	SO ₂ NMe ₂	H	2.0
457k	H	OH	H	2.8
457l	H	SO ₂ N(CH ₂) ₄	H	3.1
457m	H	H	H	20
457n	CF ₃	H	H	39
457o	H	2-pyr	H	68
457p	H	NHAc	H	75
457q	H	NH ₂	H	100
457r	H	3-pyr	H	120
457s	F	H	H	200
457t	Ph	H	H	1600
457u	OH	H	H	1700

^a[³H]Nicotine; human $\alpha 4\beta 2$ nAChR in HEK293 cells.

9-Difluoromethoxy (entry 11) and 8,9-difluoromethyl (entry 3) carbon analogues of cytisine behave as weak antagonists *in vivo*. Insufficient *in vivo* efficacy limited their potential use as therapeutic agents.

9.3.2.3. Buchwald–Hartwig Arylation of Piperidones. A novel strategy to 3-benzazocines was described by Maier.²⁸⁸

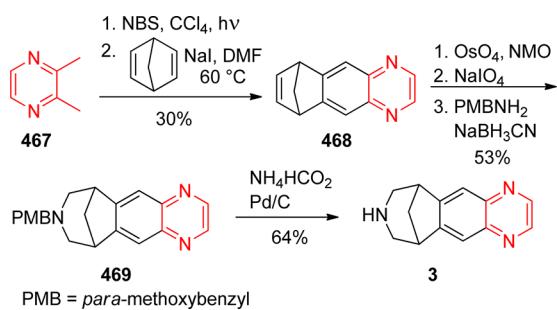
It was based on an intramolecular Buchwald–Hartwig arylation of piperidones substituted by an *o*-bromobenzyl substituent (Scheme 123). The intramolecular ketone α -arylation was performed using K₃PO₄, *t*-Bu₃P, and Pd(dba)₂ in refluxing toluene. It was carried out on a multigram scale. The *N*-benzyl compound 421 was subsequently transformed into urea 423 or

Table 14. Affinities of Each Family of Fused Benzazepine Derivatives at $\alpha 4\beta 2$ nAChR

	R	R'	$\alpha 4\beta 2^a$ K_i (nM)		R	R'	$\alpha 4\beta 2^a$ K_i (nM)
varenicline		3 H	H 0.11		464b H	Ph	0.14
	461a Me	Me	Me 0.55		464c H	H	0.15
	461b OH	H	H 6.0		464d Me	Pr	0.19
	461c 4-C ₆ H ₄ -OMe	H	H 26		464e H	Bu	0.20
	461d 4-C ₆ H ₄ -Cl	H	H 78		464f Me	i-Bu	0.28
	461e 2,4-(Cl) ₂ -C ₆ H ₃	H	H 88		464g H	i-Bu	0.30
	461f 3-pyr	H	H 360		464h Me	Me	0.31
	461g Ph	H	H 390		464i H	Pr	0.36
		462			464j H	Me	0.75
	462a Cl	H	H 0.27		464k Me	neo-pentyl	0.75
	462b H	3-Me	3-Me 0.65		464l Me	Ph	5
	462c Me	H	H 0.76		464m Ph	H	14
	462d H	3-Et	3-Et 1.2		465a Me		0.15
	462e H	H	H 1.6		465b H		0.16
	462f H	4-Me	4-Me 1.8		465c i-Pr		1.9
	462g OH	H	H 8.5		465d Et		12
	462h OMe	H	H 30		465e Bn		34
	462i H	3-Ph	3-Ph 132		465f Me		0.12
		463 H	H 2.3				0.13
		464			(-)cytisine		0.17
	464a Me	H	H 0.10		(-)nicotine		0.95

^a[³H]Nicotine; h $\alpha 4\beta 2$ nAChR in HEK293 cells.

Scheme 134. Synthesis of Varenicline



sulfonamide **424** in three efficient steps. A similar methodology was applied to the preparation of methoxy and methyl benzazocines **425a–c**. Although in these cases, moderate yields have been obtained in the Buchwald–Hartwig coupling (30–35%), the reaction sequence provided a rapid entry (three steps) to these tricyclic structures.

The range of accessible polycyclic amines was further broadened to 10-substituted piperidones **426**. However, in

Table 15. Affinities at nAChR Subtypes (K_i , nM)²⁹⁷

compound	$\alpha 4\beta 2^a$	$\alpha 3\beta 4^b$	$\alpha 1\beta \gamma \delta^c$	$\alpha 7^d$
(-)nicotine	1.6	530	6270	630
(-)cytisine	0.23	840	250	1420
457b	0.17	69	650	
457d	0.28	1000	67	1200
varenicline 3	0.11	240	3540	617

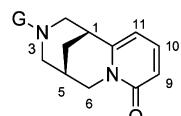
^a[³H]Nicotine; human $\alpha 4\beta 2$ nAChR in HEK293 cells ($N = 2–4$).^b[³H]Epibatidine; IMR32 cells. ^c[¹²⁵I] α -Bungarotoxin; electroplax.^d[¹²⁵I] α -Bungarotoxin; IMR32 cells.

Figure 18. N-Substituted cytisines.

this case, attempts of cyclization of **426** using t -BuONa, t -Bu₃P, and $Pd(OAc)_2$ as the base, ligand, and palladium source, respectively, the only product formed was the debrominated

lactam (yield: 50%). The choice of a stronger base (NaHMDS) and of a Lewis acid (ZnCl_2) to form intermediate zinc enolates allowed the palladium coupling to proceed, and the tricyclic lactams **427** were obtained in 30–36% yields (Scheme 124).²⁸⁹

With the new benzazocines synthesized, the authors have developed a three-step synthesis of substituted piperidones. While the yields were moderate, this approach complements well the previous ones.

Table 16. N-Substituted Derivatives: Natural Products

Entry	G	Ref	Isolation
1	Me (caulophylline)	(3, 19, 87, 300, 301, 302)	<i>Ammodendron karelinii</i> , ³⁰³ <i>longiracemosum</i> , ³⁰⁴ <i>Anagyris Foetida</i> , ³⁰⁵ <i>Argyrolobium uniflorum</i> , ⁴² <i>megarhizum</i> , ³⁰⁶ <i>Caulophyllum thalictroides</i> , ^{307, 308} <i>Clathrotropis glaucocephala</i> , ¹⁵⁸ <i>Cytisus monspessulanus</i> , ³⁰⁹ <i>Laburnum</i> , ³¹⁰ <i>Echinosophora koreensis</i> , ³¹¹ <i>Euchresta japonica</i> , ³¹² <i>horsefieldii</i> , ³¹³ <i>Genista lydia</i> , ³¹⁴ <i>equisetiformis</i> , ³¹⁵ <i>Hovea linearis</i> , ³¹⁶ <i>Leontice darvasica</i> , ³¹⁷ <i>smirnovii</i> , ³¹⁸ <i>Lupinus prince</i> , ³¹⁹ <i>Maackia amurensis</i> , ^{320, 321} <i>hupehensis</i> , ²⁴⁸ <i>tashiroi</i> , ²⁵⁹ <i>tenuiifolia</i> , ³²² <i>Ormosia stipitata</i> , ²²³ <i>Ormosia</i> and <i>Pericopsis</i> species, ³²⁴ <i>Petteria ramentacea</i> , ³²⁵ <i>Sophora alopecuroides</i> , ³²⁶ <i>chrysophylla</i> , ³²⁷ <i>denudata</i> , ³¹⁶ <i>exigua</i> , ³²⁸ <i>flavescens</i> , ^{329, 330, 331} <i>griffithii</i> , ³³² <i>macrocarpa</i> , ³³³ <i>tomentosa</i> , ³³⁴ <i>tonkinensis</i> , ^{335, 336} <i>Spartium junceum</i> , ^{337, 338} <i>Thermopsis alterniflora</i> , ¹⁵⁷ <i>lupinoides</i> , ³⁵ <i>Ulex jussiaei</i> . ³³⁹
2	Et	(101, 255, 311a)	<i>Cytisus Laburnum</i> , ³¹⁰ <i>Echinosophora Koreensis</i> , ^{340, 311}
3	-CH ₂ CH ₂ COCH ₃	(341, 342, 343, 344, 345)	<i>Echinosophora Koreensis</i> , ^{345, 311} <i>Maackia amurensis</i> , ³²⁰ <i>Hupehensis</i> , ²⁴⁸
4	-CH ₂ CH=CH ₂	(146, 319)	<i>Argyrolobium uniflorum</i> , ⁴² <i>Lupinus prince</i> , ³¹⁹
5	-CH ₂ CH ₂ CH=CH ₂ (-)Rhombifoline	(86b, 255, 346)	<i>Argyrolobium uniflorum</i> , ⁴² <i>Clathrotropis glaucocephala</i> , ¹⁵⁸ <i>Maackia Hupehensis</i> , ²⁴⁸ <i>Sophora (mollis)</i> , ³⁸ <i>chrysophylla</i> , ³²⁷ <i>franchetiana</i> , ²⁵³ <i>Thermopsis rhombifolia</i> , ^{346, 347}
6	-CH ₂ -CO ₂ H	(348)	Isolated as the methyl or ethyl ester: <i>Euchresta japonica</i> , ^{348, 312} <i>Echinosophora Koreensis</i> , ³¹¹
7	-CH ₂ CO ₂ Me	(349, 350, 351)	<i>Euchresta japonica</i> , ^{312, 313} <i>Echinosophora koreensis</i> , ³¹¹
8	-CH ₂ CO ₂ Et		<i>Echinosophora koreensis</i> , ³¹¹
9	-CH ₂ CONH ₂	(328, 344)	<i>Sophora exiguia</i> , ³²⁸
	-CH ₂ CH ₂ OH	(342, 352)	<i>Sophora alopecuroides</i> , ³⁵³
10	-CHO	(302, 354)	<i>Argyrolobium uniflorum</i> , ⁴² <i>Echinosophora koreensis</i> , ³¹¹ <i>Maackia (amurensis)</i> , ^{320, 321} <i>Tenuifolia</i> , ³²² <i>Hupehensis</i> , ²⁴⁸ ; <i>Sophora (chrysophylla)</i> , ³²⁷ <i>exigua</i> , ³²⁸ <i>tonkinensis</i> , ³³⁵ <i>Spartium Junceum</i> , ³³⁷ ; <i>Thermopsis (chinensis)</i> , ³⁵⁴ <i>lupinoides</i> , ³⁵
11	-CO-CH ₃	(21, 183, 234, 355, 356, 357)	<i>Argyrolobium uniflorum</i> , ⁴² <i>Petteria ramentacea</i> , ⁴⁴
12	CO ₂ Et	(44, 311)	<i>Echinosophora koreensis</i> , ³¹¹ <i>Laburnum watereri</i> , ³⁵⁸ <i>Petteria ramentacea</i> , ⁴⁴ <i>Spartium juncicum</i> , ³³⁷
13	CO ₂ Me		<i>Petteria Ramentacea</i> , ⁴⁴ <i>Argyrolobium uniflorum</i> , ⁴²

Table 16. continued

Entry	G	Ref	Isolation
14	(-)sophorasine	(359)	<i>Sophora griffithii</i> . ³⁵⁹
	A: R ¹ = H, R ² = OH B: R ¹ = OH, R ² = H		
15			<i>Sophora tonkinensis</i> . ³⁶⁰
	Tonkinensisine A: R ¹ = H, R ² = CH ₂ Tonkinensisine B: R ¹ = CH ₂ , R ² = H		
16		(321)	<i>Maackia hupehensis</i> . ²⁴⁸
17	-CH ₂ -NH-CO-CH ₃		<i>Maackia hupehensis</i> . ²⁴⁸
18			<i>Maackia amurensis</i> . ³²⁰
19			<i>Maackia amurensis</i> . ³²¹
20	OH	(139, 328)	<i>Sophora exigua</i> . ³²⁸
21		(321, 361, 362, 363, 364, 365)	<i>Maackia amurensis</i> . ³²¹

9.4. (\pm)-Cyfusine

Yohannes et al.²⁹⁰ postulated that if the bridgehead methylene of cytisine was removed and replaced by a bond between the carbons previously bridged, the resulting compound called “cyfusine” **433a** (Scheme 125) for the “deconstructed cytisine” could retain the structural rigidity found in cytisine. Moreover, the key pharmacophoric elements of cyfusine have approximately the same arrangement as in cytisine. The key step of the synthesis was the [3 + 2] cycloaddition between the suitable alkyne **428** and the protected amine **429** affording the 3,4-differentially substituted dihydropyrrole **430**. Formation of the central ring was achieved via van Tamelen’s route, and cyfusine **433a** was obtained in 15–16% overall yield (six steps).¹¹² The tetracyclic analogue of cyfusine **434** was prepared within 38% overall yield according to a similar strategy involving sequential ring-forming reactions [(3 + 2) cycloaddition/cyclopropanation/pyridone cyclization].²⁹⁰

Gallagher et al.¹⁵³ applied their lactam enolate-pyridone addition to the synthesis of cyfusine **433a** and fluorocyfusine **433b**. Cyclization of lactam **438a** proceeded in quantitative yield to give **439a** as a 1:3 mixture of α and β isomers. Both isomers underwent smooth MnO₂ oxidation to pyridone **440a**. Reduction of **440a** then debenzylation afforded cyfusine **433a**. Using 4-fluoropyridone **437b**, the same strategy led to fluorocyfusine **433b** (Scheme 126).

Cyfusine and cyclopropylcyfusine were evaluated in nAChR binding assays and compared to (−)-cytisine (Table 12).²⁹⁰ Cyfusine binds to the $\alpha 4\beta 2$ nAChR subtype with a K_i of 16 nM and exhibited a good selectivity for that subtype over the $\alpha 3\beta 4$ and $\alpha 7$ subtypes. Cyclopropylcyfusine was found to possess a lower affinity at $\alpha 4\beta 2$ nAChR subtype but still a good

selectivity $\alpha 4\beta 2$ versus $\alpha 7$ subtype. Cyfusine can be considered as a new scaffold that mimics the affinity and selectivity of cytisine, and may serve as a novel starting point for the development of new drugs targeting the nicotinic acetylcholine receptor.

9.5. Varenicline and 1,5-Methano-3-benzazepines

On the basis of the similarity between benzomorphan **II** and benzazepine **IIIa** (Figure 17), both antinociceptive compounds (inhibit the sensation of pain), Coe et al.^{18,51,268,291} hypothesized that derivatives of benzazepine **IIIb** might share a similar nicotinic pharmacology with benzazocine compounds (skeleton **I**) (Figure 17). Measurements of the affinity of the unsubstituted compounds **I** and **IIIb** at the $\alpha 4\beta 2$ nAChR subtype (K_i , respectively, 34 and 20 nM) demonstrated the validity of the hypothesis and launched the synthesis of a large number of benzazepines for their biological evaluation. From these studies emerged Varenicline that was marketed in 2006 (Chantix in US) for the treatment of smoking addiction. The skeleton 1,5-methano-3-benzazepine (**IIIb**) was little known before the intensive research of the Pfizer Co. for the development of new agents for smoking cessation.²⁹²

9.5.1. Construction of Ring C of 1,5-Methano-3-benzazepines. The first synthesis of 1,5-methano-3-benzazepines was described in 1979 by Mazzocchi et al.²⁹³ Benzonorbornadiene **441** was transformed into diacid **443** in a stepwise process required to circumvent the difficulties encountered in the direct oxidative cleavage of **441** using traditional oxidizing agents (O₃, permanganate, periodate). The diacid **443** was transformed into the target compound **444** in low yields (Scheme 127). The unsubstituted benzazepine **444** and its *N*-alkyl derivatives **445** showed no

Table 17. Compounds with Non-Carbon Substituents

Entry	G Substituent	Ref.
1	N=O	(21, 146, 372, 373, 374)
2	NH ₂	(146, 373, 372, 375)
3	 R = 2-NO ₂ , 4-Cl	(376)
4		(377)
5	OH	(372)
6	Cl	(159, 249)
7		(378, 379)
8		(380)
9		(381)
10	SO ₃ H	(139b)
11		(382)
12		(305, 383)
13		(260, 383)
14		(384)

antinociceptive activity in the mouse but a marked increase in toxicity.

Coe et al.²⁹⁴ developed a high yielding alternative to this preparation using the synthetic strategy of cytisine.¹¹⁷ Osmium tetroxide-mediated dihydroxylation of benzonorbornadiene **441** was followed by sodium periodate cleavage, reductive amination, and debenzylation (route A, Scheme 128). This reaction sequence afforded benzazepine **444** (hydrochloride salt) in 64–73% yield. While this route was reliable on a large scale, it suffered from the use of osmium tetroxide, which must be removed from the product. Moreover, preparation and storage of benzonorbornadiene **441**, a reactive material, proved to be challenging on the kilogram scale.

To avoid osmium tetroxide, the synthesis of **444** was reinvestigated.²⁹⁴ Ozonolysis of benzonorbornadiene was followed by reduction of the ozonide before reductive amination and debenzylation (route B). The toluenesulfonic acid salt of **444** was obtained within a moderate yield (Scheme 128). However, despite the lower yield, this approach avoids workups and chromatography. Only a filtration was required with the final purification step.

Table 18. Compounds with N-Hydrocarbon Substituents

X	Substituent	Ref.
1	(CH ₃) ₂ CH-	(146, 182, 196, 213, 372)
2	H ₃ C(CH ₂) ₃ -	(213, 346)
3	H ₃ C(CH ₂) ₄ -	(146, 342, 343, 344, 372)
4	H ₃ C(CH ₂) ₁₁ -	(342)
5	H ₃ C(CH ₂) ₁₅ -	(310)
6	Me ₂ C=CH-CH ₂	(146, 372)
7	Ph-CH=CH-CH ₂ -	(342)
8	H—	(146, 372, 385)

Another route that avoided the problematic benzyne chemistry used to prepare benzonorbornadiene **441** was described from readily available indanone carboxylic acid **447**. The strategy relied on a homologation via cyanohydrin **448** (Scheme 129).²⁹⁵ Hydrogenolysis of **448** with concomitant reduction of the nitrile function, then basic treatment of the intermediate aminoester, afforded lactam **449**. Reduction of this lactam led to benzazepine **444** in 51% overall yield from indanone **447**. The major drawback of this approach was the use of trimethylsilylcyanide to access the key intermediate.

To prepare compound **444** on a large scale from commodity chemicals as raw materials and to exploit crystalline intermediates, a tandem Michael addition-Pd-catalyzed cyclization of 2-bromophenyl acetonitrile **450** and acrylate **451** into cyanobenzofulvenes **452** was studied (Scheme 130).²⁹⁶ The reactions were conducted in one pot, using tricyclohexylphosphine, which is a crystalline solid that is easy to handle. The use of the ethyl ester instead of the methyl one enabled one to decrease the Pd catalyst loading to 0.5–2 mol % Pd. The cyanobenzofulvene acetal **452** was formed to facilitate the workup. Finally, benzazepine **444** (TsOH salt) was obtained in six steps with yields up to 58%.

9.5.2. 1,5-Methano-benzazepines Substituted on the Aromatic Ring. Studies²⁹⁷ on the functionalization of the aromatic ring of benzazepine **444** revealed that the *N*-trifluoroacetamide protecting group was uniquely suited to subsequent electrophilic substitutions. With *N*-alkyl or other *N*-acyl protecting groups, the reactions were inhibited, probably by the participation of the nitrogen doublet to the electrophilic substitution. Scheme 131 gathers the mono-substituted benzazepine derivatives prepared via an electrophilic substitution.

Another approach to benzazepines substituted on the aromatic ring required the preparation of functionalized benzonorbornadienes still bearing the wanted substituent(s) (Scheme 132). Route A described in Scheme 128^{287,298} was used to access about 20 substituted benzazepines **457** (Scheme 132).

Reaction of *N*-protected benzazepine **453** with an excess of TfOH/HNO₃ (>2 equiv) afforded a mixture of dinitro compounds **458** and **459** with a high selectivity (1:9 molar ratio **458**/**459**). This unexpected result attributed by the

Table 19. Compounds with a Mono(un)saturated Functionalized Chain

Entry	G Substituent	Ref.	Entry	G Substituent	Ref.
1		(342, 365)	14		(344)
2		372	15		(372)
3		(342, 361, 365, 386, 387, 388)	16		(342, 344, 389, 390, 391)
4		(387, 392)	17		(351, 393)
5		(389, 394)	18		(351)
6		(389, 395, 396)	19		(397)
7		(389, 398),	20		(344, 349)
8		(385)	21		(302, 399)
9		(400)	22		(401)
10		(402)	23		(403)
11		(388, 404)	24		(405)
12		(349, 365)	25		(406, 407, 408)
13		(409, 410)			

authors to the electronic and steric influences of the benzazepine ring system facilitated the exploration of fused heterocyclic derivatives including quinoxalines **460**, quinolines **462**, isoquinolines **463**, benzimidazoles **464**, benzoxazoles **465a**, benzothiazoles **465f**, and benzisoxazoles **466** (Scheme 133). In vitro affinities at the $\alpha 4\beta 2$ nAChR subtype for these compounds are reported in Table 14.

For example, varenicline **3** (Scheme 133)^{291,297} was prepared in 10 steps within 26% overall yield from *o*-dibromobenzene. Recently, another approach to varenicline **3** was described (Scheme 134).²⁹⁹ 2,3-(Dimethyl)pyrazine **467** was transformed into bis(dibromomethyl)pyrazine, which reacted with norbornadiene to afford pyrazine **468**. The benzazepine ring was then built according to the known Coe strategy (Scheme 128). The total synthesis of varenicline **3** was achieved in six steps within 10% overall yield from commercially available pyrazine **467**. The procedure did not require the preparation of benzonorbornadiene, a significant advantage.

9.5.3. Affinities of 1,5-Methanobenzazepines at nAChRs. In vitro affinities at the $\alpha 4\beta 2$ nAChR subtype for the synthesized substituted benzazepines were determined

using radioligand displacement experiments (Table 13).²⁹⁷ A range of K_i values from 0.10 to 1700 nM were observed. Substitution²⁷³ at the 9-position (**457b,c,e–g**) and disubstitution at the 9 and 10 positions (**457a,d**) conferred an affinity higher than that of the parent compound **457m** ($R^3, R^4, R^5 = H$), whereas a substituent at the 8-position (**457n,s,t,u**) was detrimental to the affinity. Affinity was favored by electron-withdrawing substituents. However, only two compounds (**457a,b**) have an affinity similar to or higher than cytisine. When possible, comparison with the substituted benzazocines (see Table 11) showed better affinities of benzazepines at the $\alpha 4\beta 2$ nAChRs.

Three compounds (varenicline **3**, **457b**, **457d**) fully blocked nicotine's effect. They are partial agonists, and their *in vivo* activity is more potent than that of (–)-cytisine. Their selectivities $\alpha 4\beta 2/\alpha 3\beta 4$, $\alpha 4\beta 2/\alpha 1\beta 2\delta$, and $\alpha 4\beta 2/\alpha 7$ are high (Table 15).

10. N-SUBSTITUTED CYTISINE DERIVATIVES

10.1. Natural Products

More than 20 N-substituted derivatives of cytisine are natural products (Figure 18). Table 16 lists these compounds with

Table 20. Compounds with a Polyfunctional Chain

Entry	Substituent	Ref.	Entry	Substituent	Ref.
1		(388, 404, 411, 412)	10		(413)
	R = H; X = Cl, OH, SCN X = Cl, R = H, Ac, Bz			Ar = C6H5, 4-FC6H4, 4-ClC6H4, 4-EtOC6H4, 4-MeOC6H4, 2,4-(Cl)2C6H3, 3,5-(F)2C6H3	
2		(388, 404, 414)			(388, 404)
	R1 = R2 = H, Me, Et, Ph, CH2CH2OH R1 = H, R2 = H, n-Pr				
3		(404, 411)	11		(388)
4		(415)		R1 = H, Me, 4-MeOC6H4, C6H5 R2 = H, Me, Ph, (CH2)4	
5		(351, 416)	12		(397)
				R = H, Me, CH2OH R' = H, Me	
6		(417)	13		(418)
	X = Cl, Br, I				
7		(419)	14		(420, 421)
				n = 1, 2	
8		(422)	15		(423, 424, 425)
	R = H, Me, Et R = H, Me, OMe, Cl			n = 0, 1, 2, 3, 4, 5, 6	
9		(426)	16		(342)
	X = OCOMe R = H, Me			n = 1, R = 2-OCH3 n = 2; R = H, 2-OCH3 3-Cl, 3-CF3 X = N, Y = CH X = Y = N 	

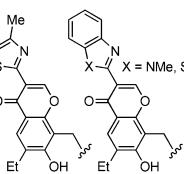
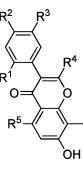
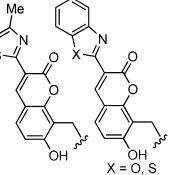
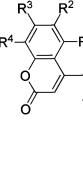
most of their natural sources. In some cases, the structure of the natural product was confirmed by an independent synthesis from *(–)-cytisine* and characterized by spectroscopy. It may be noted that natural sources of *(–)-methylcytisine* are also those of *(–)-cytisine*.

10.1.1. *N*-Methylcytisine. *N*-Methylcytisine **18** (Table 16, entry 1) is the most frequently encountered derivative of cytisine. *N*-Butenylcytisine (rhombifoline, entry 5) and *N*-formyl cytisine (entry 10) were also often detected. In 1893, Lloyd identified an alkaloid in *Caulphyllum thalictroides* “Blue Cohosh”, which was named Caulophylline.³⁶⁶ The compound was isolated in a pure crystalline state in 1913 and identified as *(–)-methylcytisine* **18**.³⁶⁷ Methylcytisine has been obtained from many plants either as the main alkaloid or with a number of others (Table 16). Usually the alkaloid **18** is present beside *(–)-cytisine* from which it is probably synthesized (cf., Section 2.3)^{68,79,368} *N*-Methylcytisine was used rarely as a substrate for the synthesis of natural products except for the

synthesis of kuraramine and tsukushinamine derivatives (see sections 8.2 and 8.3). Oxidation of **18** using barium or potassium permanganate led to a mixture of lactams,^{67,90} which could provide access to derivatives of cytisine substituted on carbon-2 or carbon-4 that are practically unknown (see section 2.4.3, Scheme 8). Recently, *N*-methylcytisine was the substrate used to study the oxidative halogenation of the pyridone core of cytisine.³⁶⁹ The reaction was not suitable for the preparation of the iododerivatives. Under the best conditions, the 11-chloro or 11-bromo *N*-methylcytisines were the major products.

N-Methylcytisine is about 1/40 as toxic as nicotine.³⁷⁰ It exhibits teratogenic activity in the rat embryo culture, an in vitro method to detect potential teratogens.³⁰⁸ The methylation of the secondary amine of cytisine caused usually a dramatic loss in the biological activities as compared to *(–)-cytisine*. The affinity for nAChRs of $\alpha 4\beta 2$ subtype is more than 40 times lower than that of *(–)-cytisine*. However, it is worth noting that the dimethyl cytisinium salt (caulophylline methiodide)

Table 21. Compounds with an (Hetero)arylaliphatic Chain

Entry	G Substituent	Ref.	Entry	G Substituent	Ref.
1		R = 4-F, 2-OH 4-OH, 4-MeO (342, 344, 427, 428, 104, 344, 429)	7		(430, 431)
		R ¹ , R ² = 3-Br, 4-OH; 2-OH, 5-Br; 3-Br, 4-OMe; 3-OMe, 4-OMe; 3-OMe, 4-OH; 3-OBn, 4-OMe			C ₆ H ₅ , 4-NO ₂ C ₆ H ₄ , 4-i-PrC ₆ H ₄ , 4-MeOC ₆ H ₄ , 2-MeOC ₆ H ₄ , 4-EtOC ₆ H ₄ , 2-EtOC ₆ H ₄ , 4-i-PrOC ₆ H ₄ , 4-BuOC ₆ H ₄ , 4-allyloxyC ₆ H ₄ , 4-BnOC ₆ H ₄ , 4-octyloxyC ₆ H ₄ , 3,4-(MeO) ₂ C ₆ H ₃ , 2,5-(MeO) ₂ C ₆ H ₃ , 2,3-(MeO) ₂ C ₆ H ₃ , 3-MeO, 4-BnOC ₆ H ₃ , 3,4,5-(MeO) ₃ C ₆ H ₂ , 3,2,4-(MeO) ₃ C ₆ H ₂ , 3,4-methylenedioxy, 2-thienyl, 3-thienyl, 2-(3-methyl)thienyl, 2-(5-methyl)thienyl, α -naphthyl, α -2-methoxynaphthyl, 9-anthryl
		R ¹ , R ² , R ³ = 2, 4, 6-(Me) ₃ 2-Br, 3-OH, 4-OMe; 3-OH, 4-OMe, 6-Br; 3-OH, 4-OMe, 6-OMe; 3-OMe, 4-OH, 5-Br; 3-OMe, 4-OMe, 6-Br; 3-OMe, 4-OMe, 6-NO ₂			2-furyl, Me (or Bn)
2		(429)	8		(431)
3		(342, 344, 391)	9		(432)
4		(344)	10		(433)
5		(362)	11		(434)
6		(363)	12		(435)

displayed only a 2-fold lower affinity ($K_i = 0.238$ nM) than cytisine ($K_i = 0.122$ nM) with a selectivity for the $\alpha 4\beta 2/\alpha 7$ twice as high. Bromination¹³³ of N-methylcytisine did not increase its affinity at $\alpha 4\beta 2$ nAChRs as it did with (−)-cytisine (K_i for 9-bromocytisine = 0.208 nM, $K_i = 68$ and 305 nM for 9-bromo and 11-bromo derivatives, respectively).

Finally, whereas (−)-cytisine possesses a nematicidal activity against pine wood nematode,^{326,330} a potent antihepatitis B virus (HBV) activity,³³⁶ and was known to inhibit cytochrome P450 in in vitro assays,³⁷¹ N-methylcytisine was either much less or not active in these biological assays.

10.1.2. Other Natural Products, N-Substituted Derivatives of Cytisine. It was noticed that only the species of the genus *Maackia* produce alkaloids having a N—CH₂—Y moiety such as (−)-N-(2-oxopyrrolidinomethyl)cytisine (Table 16, entry 16) and (−)-N-(N-acetylaminomethyl)cytisine (entry 17).³²¹ All of these chiral compounds are the minus enantiomers. The methylene bridge of these alkaloids is presumed to be formed by

Mannich-like reaction via an oxidative process in which the methyl group of N-methylcytisine is oxidized to an iminium ion.

The chemistry of the N-substituted natural compounds is not developed. However, as the plants sources of the alkaloids were often used in traditional medicine, the biological activities of N-3-oxobutyl, N-allyl, N-acetamide, and N-CO₂Et were tested for their affinities at nAChRs.^{146,372} As it was observed for N-methylcytisine, the introduction of a substituent on the amine nitrogen always brought a decrease in affinity with respect to (−)-cytisine. Such a decrease can be very high as in the case of cytisine-12-yl acetamide.¹⁴⁶

Cytotoxicity against the human cervical carcinoma HeLa and human breast tumor MDA-MB-231 cell lines of tonkinensines A and B (Table 16, entry 15) was evaluated, and only tonkinensine B displayed a moderate cytotoxicity.

10.2. Non-natural N-Substituted Cytisines

Several hundred N-substituted derivatives of cytisine (substitution at the 3 position) have been prepared (a) as protected

Table 22. N-Vinyl-, N-Aryl-, or N-Heteroaryl-Substituted Cytisines^a

Entry	G Substituent	Ref.	Entry	G Substituent	Ref.
1	H ₂ C=CH-	(365)	8		(436)
2		R = H, Cl (302)	9		Ar = C ₆ H ₅ , 4-ClC ₆ H ₄ , 4-F-C ₆ H ₄ , 3,5-(F) ₂ C ₆ H ₃ , 2,4-(Cl) ₂ C ₆ H ₃ , 4-MeOC ₆ H ₄ , 4-EtO ₂ CC ₆ H ₄ , R = CN, CSNH ₂ (411, 413, 437, 439)
3		(438)	10		Ar ² = N-Ar ¹ Ar ¹ = Ar ² = 4-Cl-C ₆ H ₄ , Ar ¹ = 4-F-C ₆ H ₄ , Ar ² = 4-Cl-C ₆ H ₄ (437, 439)
4		(440)	11		X = CH, N (146, 343, 372)
5		O ₂ N-C ₆ H ₄ -CHO (441)	12		Cl-N-X (146, 343, 372)
6		O ₂ N-C ₆ H ₄ -CHO (441)	13		(442)
7		R ¹ -C ₆ H ₄ -NH-C(=O)-C ₆ H ₄ -NH-C(=O)-SO ₂ -C ₆ H ₄ -O-C ₆ H ₄ -O-C ₆ H ₄ -R ² R ¹ = H, Cl, F, Me R ² = H, Cl, F, Me (443)	14		(302, 415)

^aSurprisingly, N-phenylcytisine was not described.

Table 23. Osamines Derived from (−)-Cytisine

Entry	G Substituent	Ref.
1		D-Glc α-OH β-CH ₂ OH D-Gal β-OH β-CH ₂ OH D-Xyl α-OH β-CH ₂ OH L-Ara β-OH H (444, 445, 446)
2		CyH ₂ R = H, CH ₂ OH (447)

forms of the amino group of cytisine, (b) as synthetic intermediates, (c) for their biological or pharmacological evaluation, (d) for structural studies (NMR, X-ray analysis), and (e) as examples of reaction of an amine with a reactive substrate or intermediate.

The 3-substituted cytisines (or N-substituted cytisines) were usually synthesized in one or two common steps (cf., tables with structures and references). Reactions of (−)-cytisine with the suitable aliphatic or arylaliphatic (di)halide or acid chloride were the most frequent used reactions. Reductive amination was a good alternative. In some particular cases, (hydroxylphenyl)ethylcytisine, (hydroxyethyl)cytisine,³⁵² the opening of an epoxide was more efficient than the reaction of a halide.³⁴² Direct reaction of an acid under activating conditions allowed the preparation of complexes structures. A Mannich reaction was employed to obtain *N*-(3-oxobutyl)cytisine (Table 16, entry 3).³⁴¹ The (thio)carbamoyl

derivatives were prepared by reaction of cytisine with the suitable iso(thio)cyanate (Table 25).

10.2.1. N-Protected Cytisines. The benzyl group was the first protecting group used for the amine function of cytisine.¹¹² Easily and efficiently deprotected, it was further employed by O'Neill et al.¹¹³ and Gallagher et al.^{108,60} in their total syntheses of cytisine. Functionalization of the pyridone ring of cytisine was usually carried out on cytisine protected by an alkoxy carbonyl group (methoxy,²¹ *tert*-butoxy^{128,148,149}), whereas the benzyloxycarbonyl was employed in a multistep synthesis.¹²¹ It is worth noting that the nitroso group, due to its rapid deprotection under acidic conditions, was a useful protecting group in radio-synthesis with short-lived isotopes.²¹

10.2.2. Synthetic Intermediates. N-Substituted cytisines (*R* = cyclohexyl, methylenecyclopropyl,¹⁸² methyl, ethyl, *n*-butyl, methylene-*tert*-butyl,²¹³ isopropyl,^{182,213} methoxycarbonyl,² 2-methoxyacetyl,¹⁹⁵ and butanoyl²³⁴) were synthesized with the aim of having access, after complete reduction, to variously substituted chiral diamines for asymmetric synthesis. To measure the enantiomeric excess of natural cytisine as compared to synthetic samples, *N*-benzoyl and *N*-benzylcytisine were prepared.¹⁹⁴

10.2.3. Synthetic N-Substituted Cytisines. A large number of N-substituted cytisines have been synthesized. They are listed in Tables 17–26 according to their substituents.

The nitroso derivative (Table 17, entry 1)³⁷³ was obtained by treatment of cytisine with sodium nitrite and HCl,²¹ or with

Table 24. Cytisinamides

Entry	G Substituent	Ref.	Entry	G Substituent	Ref
1	Et-CO-	(101, 155)	18		(101, 194, 155, 355)
2	Pr-CO-	(234)	19	R ¹ = H, R ² = 2-Br	(356, 453)
3	i-Pr-CO-	(155, 448)	20	R ¹ = H, R ² = 4-NO ₂	(355, 356, 449)
4	t-Bu-CO-	(155, 234)	21	R ¹ = 2-OH, R ² = H	(428)
5	H ₂ C=CH-CO-	(450, 451, 452)	22	R ¹ = R ² = 3-Cl, 5-Cl	(146)
6	Me-CH=CH-CO-	(356)	23	R ¹ = 2-MeO, R ² = 5-Cl	(146)
7	HO ₂ C-CH=CH-CO-	(302, 453)	24	R ¹ = 3-NO ₂ , R ² = 5-NO ₂ R ¹ = H, R ² = 2-COOH R ¹ = H, R ² = 2-(H ₂ NCO)	(453)
8	Ph-CH=CH-CO-	(356)	25		(342)
9		(195)	26		(451)
10		(454)			
11		(455)	27		(456, 457)
12		(397)	28		(458)
13		(397)	29	 n = 1 and n = 2 R ¹ = Me, R ² = R ³ = H R ¹ = R ² = Me, R ³ = H R ¹ = R ² = Me, R ³ = H R ¹ = R ² = R ³ = Me R ¹ = R ² = (CH ₂) ₄ , R ³ = H R ₁ = R ₂ = (CH ₂) ₄ , R ³ = Me	(459)
14		(462)	30		(460)
15		(461)	31		(462)
16		(146)	32		(463)
17		(464)	33		(426)

Table 25. (Thio)carbamates- and (Thio)ureas-Substituted Cytisines

Entry	G Substituent	Ref.	Entry	G Substituent	Ref.
1		(128, 149, 131)	7		(342, 436, 465)
2		(121a)	8		(466, 467)
3		(343)	9		(468)
4		(469)	10		(146, 372, 470)
5		(471)	11		(472)
6		(473, 474)			

potassium nitrosodisulphonate (Fremy's salt).³⁷⁴ The nAChR affinities of nitroso (entry 1), amino (entry 2), and hydroxyl (entry 3) were compared to cytisine through the displacement of [³H]cytisine from rat brain preparation. They still displayed a nAChR affinity (39 nM, 3.6 nM, and 21 μ M, respectively) but lower than that of cytisine (under the same conditions: 2.4 nM).³⁷²

For the last 12 years, more than 80 N-substituted derivatives were synthesized by Italian groups.^{342–344,372} They were searching for new nAChR subtype selective ligands with a lipophilicity higher than that of cytisine but also for compounds of potential therapeutic interest at peripheral or central nervous system level. In binding experiments on rat brain preparations, using [³H] cytisine displacement, it was demonstrated that the introduction of a substituent on the amine nitrogen always brought about a decrease of affinity in respect to cytisine ($K_i = 2.4$ nM). Such a decrease can be insignificant as in the case of aminocytisine ($K_i = 3.6$ nM) or very high as for cytisin-12-ylacetamide ($IC_{50} > 10 \mu$ M).¹⁴⁶ No general trend can be given; the affinity depends on the elongation of the chain, on the position of the substituent (benzene, pyridine), or on the function (CO). As an example of the fluctuating effect of the elongation of the chain, *N*-phenylethyl and *N*-phenylpropylcytisine have an affinity more than 1 order of magnitude higher than *N*-benzyl and *N*-phenylbutylcytisine. On the contrary, in *N*-(4-fluorophenyl)alkylcytisines, the affinity decreased with the increasing number of methylene groups. The replacement of a benzene ring with a pyridine nuclei affected the affinity depending on the joining position. The introduction of a carbonyl group on the connecting chain had a positive influence on affinity [$PhCO(CH_2)_2, K_i 2.6$ nM; $4F-C_6H_4-CO(CH_2)_2, K_i 5.3$ nM].

The conjugation of ibuprofen [4-(2-methylpropyl)phenyl]-propanoic acid) and cytisine via an octyl linker afforded "IBU-octyl-cytisine".⁴⁰² This compound was shown to improve the clinical and pathological parameters of experimental

autoimmune encephalomyelitis (EAE). The study indicated that the amelioration of EAE by IBU-octyl-cytisine is mediated by anti-inflammatory activity on T-cells. The effects were not only the results of multiple targeting, as the bifunctional molecule was superior to treatment with both moieties unconjugated.

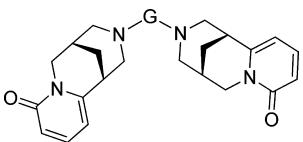
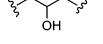
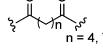
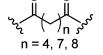
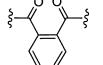
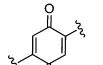
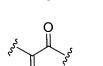
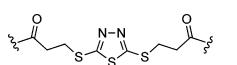
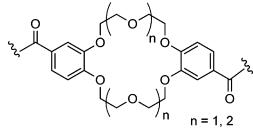
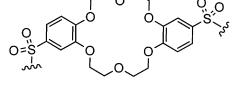
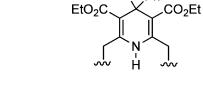
An anticholinesterase activity of derivatives of cytisine was observed with different substituents^{482–484} (β -acyloxypropyl, hydroxyethyl, 2-hydroxypropyl),³⁹⁴ phosphoryl groups,^{378,405} and bisalkaloid derivatives of dicarboxylic acids.^{477–479}

11. CONCLUSION

Cytisine, a readily available natural product, has received increasingly growing interest in the past 15 years. This Review has highlighted the major publications in the field since its first isolation in 1865 until the end of 2012. It has showcased the elegant developments from many research groups around the world: complete recent structural characterization, first total syntheses (including asymmetric) giving access to interesting analogues, and structural modifications from simple substitution of one position (amino group or pyridone ring) to more important structural changes. These innovative transformations have rendered cytisine a versatile building block or a structural model in organic synthesis. It led to a diverse array of carbon- and heterocyclic "cytisine inspired" structures that can serve as platforms for further transformations and biological applications even if in some cases the scaffolds appear quite different from the cytisine backbone.⁴⁸⁵

It is important to note how such a simple molecule has attracted so much attention of biologists, pharmacologists, and medicinal chemists, particularly in the late 1980s when it was recognized as a selective and very efficient ligand of cholinergic nicotinic receptors. As one of the main reference compounds, it has contributed decisively to the knowledge of the cholinergic neurotransmission. After the late 1990s, the structural similarity of cytisine with sparteine, another widely used alkaloid of the

Table 26. Compounds Bearing Two Cytisinyl Groups

Entry	G Substituent	Ref.
1		(342, 391, 475)
2		(146, 372)
3		(388, 412, 476)
4		(477)
5		(478, 479)
6		(453)
7		(415)
8		(480)
9		(452)
10		(461)
11		(384)
12		(481)

Biographies



Jacques Rouden received his Ph.D. from the University Paris XI at Orsay (France) in 1990 under the guidance of Professor H.-P. Husson and Dr. J. Royer. After postdoctoral studies in the U.S. and Canada between 1991 and 1997, he joined the University of Caen as an assistant professor working with Professor Lasne on radiolabeling chemistry with positron emitters (PET Chemistry). He was promoted to Professor at ENSICAEN in 2005. His research interests include the use of transition-metal complexes and the development of organocatalyzed reactions in organic synthesis.



Professor Marie-Claire Lasne received her Ph.D. from the University of Caen (France) in 1974. She undertook postdoctoral studies with Professor Jerrold Meinwald at Cornell University in 1975. Since 1969, she has worked as a lecturer, then as a Professor at the University of Caen. In 1987, she spent a sabbatical year in Hammersmith Hospital, MRC-Cyclotron Unit (London, UK) in the Pike group. Her research interests include the synthesis of reactive unsaturated molecules with flash vacuum pyrolysis, cross-coupling reactions, the synthesis and radiosynthesis with positron emitters (¹¹C and ¹⁸F) of molecules for *in vivo* imaging, asymmetric protonations, and organocatalysis.



lupine family, then was unveiled and has stirred up the curiosity of organic chemists. The overall research on cytisine culminated with two original molecules, varenicline of the Pfizer company for the treatment of smoking addiction and the *N*-methyl tetrahydrodeoxocytisine developed by Peter O'Brien as a (+)-sparteine surrogate in enantioselective transformations. We can still expect many further developments of this template in synthetic chemistry such as metal chelate beyond lithium chemistry or in the growing field of organocatalysis.

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Notes

The authors declare no competing financial interest.

Jérôme Blanchet obtained his Ph.D. in 2001 from the University Paris V under the supervision of Dr. Laurent Micouin and Professor Henri-Philippe Husson. He carried out postdoctoral studies with Professor Victor Snieckus (Queen University, Kingston, Canada), with Professor Jean-Charles Quirion (University of Rouen, France), and with Dr. Jieping Zhu (ICSN, Gif sur Yvette, France) from 2001 to 2004. In 2004 he joined the LCMT as a CNRS researcher (Caen, France). His research interests include the development of new synthetic methods, catalyst design, and the synthesis of pharmaceutically relevant products within the field of organocatalysis.



Jérôme Baudoux received his Ph.D. in 2004 from the University of Rouen (Dr. Jean-Christophe Plaquevent and Dr. Dominique Cahard group). He then moved to the University of Nottingham in U.K. to join the group of Prof. Nigel S. Simpkins and in 2005 to the University of Caen (Prof. Madec group, LCMT). Since 2006, he has worked as a lecturer with Prof. J. Roudan at Caen (ENSICAEN/University).

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