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Total Enantioselective Synthesis of (−)-Cytisine

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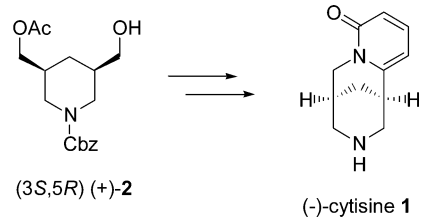
ABSTRACT



The first total enantiosynthesis of the biologically active alkaloid (−)-cytisine is reported, featuring a ruthenium-catalyzed RCM reaction as the key step. The approach relies on readily available *cis*-piperidine-3,5-dimethanol monoacetate as the chiral building block, and it is suited for achieving the target compound in both enantiomeric forms.

Nicotinic receptors (nAChRs) are cationic channels whose opening is controlled by acetylcholine and nicotinic receptor agonists, and as such, they are key molecules in cholinergic transmission at the neuromuscular junction of striates muscles and in several brain areas.[1] There is accumulating evidence that nAChR densities are altered in various pathologies such as Alzheimer's and Parkinson's diseases. As a result, these receptors are interesting targets for the development of novel drugs to treat a variety of CNS disorders.[2]

Moreover, interest in nAChR agonists as potential analgesics has recently emerged, representing an attractive area of research in the control of opiate resistant chronic pain.[3] Nicotine, a full agonist at neuronal nAChRs, has a wide spectrum of biological activities, some beneficial, others detrimental, due to its inability to discriminate between the different subtypes of receptors. The need of selective agonists for central nAChRs promoted the synthesis of a large number of structural analogues of nicotine. At the same time, it also stimulated the research on new potent agents interacting more selectively with the neuronal nicotinic receptors and displaying minimal side effects as compared with prototypical agonists such as nicotine.[4]

(−)-Cytisine **1**[5] is another important nicotinic ligand, poorly investigated until recently, despite its partial agonist profile ($EC_{50} = 1\ \mu M$) and its high $\alpha_4\beta_2$ subtype selectivity.[6] (−)-Cytisine, isolated from natural sources in 1894,[7] is a member of the lupine alkaloids family, extracted from seeds of *Laburnum anagyroides* and other Leguminosae plants.

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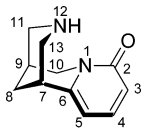
Though commonly used as a reference in the study of new nAChRs, it is currently expensive and available only in small quantities commercially. In addition, of the two possible enantiomeric forms, only the (−)-antipode is available from natural sources.



(-)-cytisine **1**

In the past few years, a number of cytisine derivatives were prepared in order to modify the pharmacological profile of the natural alkaloid so as to obtain compounds of potential therapeutic interest.[8] The first total syntheses of racemic cytisine were reported 40 years ago,[9] while quite recently, three new different approaches were developed,[10] underscoring current interest in this field. All the same, to the best of our knowledge, no enantioselective routes to this alkaloid have been published to date.

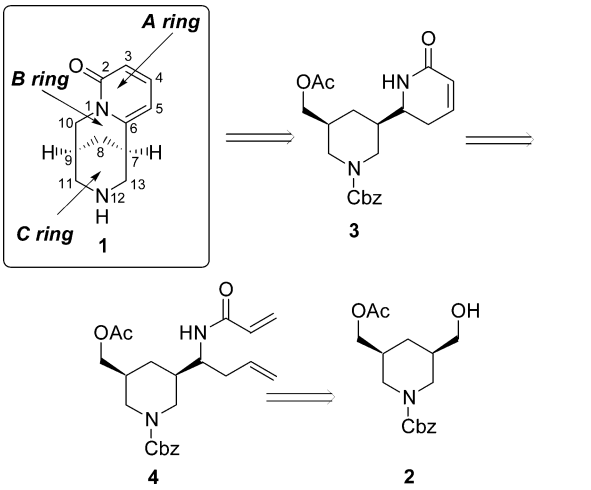
As part of our ongoing work concerning the stereoselective synthesis of natural nitrogen-containing compounds,[11] we report here our successful approach to enantiopure (−)-cytisine and, formally, to its (+)-antipode.

From a chemical point of view, (−)-cytisine is a quinolizidine alkaloid with a tricyclic skeleton, consisting of the bispidine framework (B- and C-rings) fused to a 2-pyridone moiety (A-ring). It bears two stereogenic centers, which were established to be 7*R*,9*S*.

To ensure a formal access to either enantiomer of the target compound, our retrosynthetic plan (Scheme 1) features the *cis*-piperidine-3,5-dimethanol monoacetate **2** as a suitable starting material. In fact, both this compound and its enantiomeric form (*ent*-**2**) are readily available by means of biocatalytic asymmetrization of the appropriate C_s-symmetric forms.[12]

The first dissection of ring B (N1−C10 bond) in (−)-cytisine **1**, along with an adjustment of the oxidation level for ring A, yields the 6-piperidinyl-5,6-dihydropyridin-2-one **3**, which in turn could be accessed from the key intermediate **4**. In fact, the cleavage of the C3−C4 bond (dissection of ring A) in the retrosynthetic pathway reveals that **3** could in principle be obtained by a key *ring-closing metathesis* reaction on the *N*-but-3-enylacrylamide moiety of **4**. Various studies in recent years have demonstrated the usefulness of RCM for constructing N-heterocycles. In some cases, the ring-closing reactions are problematic because the catalysts are inhibited by the complex-forming properties of amines and amides and, for the α,β-unsaturated compounds, by the intramolecular interaction with the carbonyl group.[13] We reasoned that, if necessary, an additional blocking of the nitrogen (N1) in **4** with a suitable protecting group could overcome such problems, enabling us to carry out the RCM reaction more advantageously. Finally, intermediate **4** could in turn be fashioned by selective functional group modification of the chiral *cis*-piperidine-3,5-dimethanol monoacetate **2**.

Scheme 1. Retrosynthetic Analysis



The key intermediate *N*-but-3-enylacrylamide **4** was constructed as follows (Scheme 2). Oxidation of the diol monoacetate **2** (98% ee) afforded the configurationally stable aldehyde **5**, which was used directly in the next step of allylation. $BF_3{\cdot}Et_2O$-mediated reaction of allyltrimethylsilane on **5** produced the homoallylic alcohol **6a**,**b**, in 85% yield, as an inseparable 1:1 mixture of diastereoisomers.

This lack of diastereofacial selectivity on the carbonyl group of **5** does not represent a problem in our synthetic plan. In fact, to assemble the skeleton of cytisine, a later oxidation step had been envisaged, which destroys this additional stereogenic center. At any rate, we wanted to examine more closely this allylation step, also in view of applying this strategy to the enantiosynthesis of non aromatic tricyclic quinolizidine alkaloids, in which the stereogenic center at C6 is retained. We observed that when **5** was treated with (−)-allyldiisopinocampheylborane, according to Brown's procedure,[14] the homoallylic alcohol **6a** was obtained, with a diastereoisomeric ratio of 10:1, as determined by ^{1}H NMR

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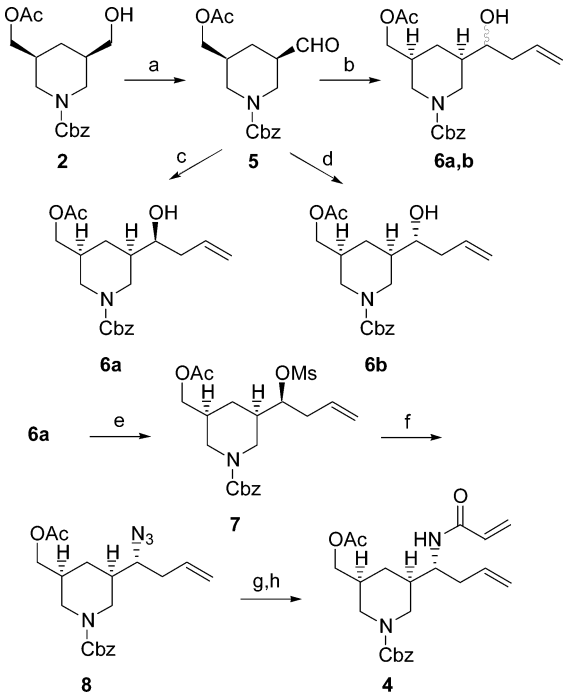
Scheme 2[a]



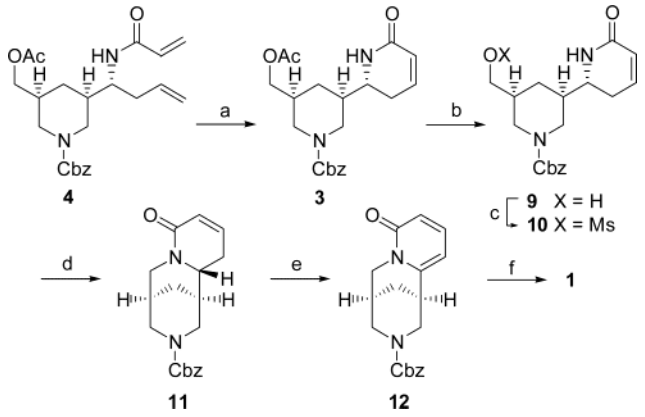
[a] Reagent and conditions: (a) Swern oxidation (91%); (b) allyltrimethylsilane, $BF_3{\cdot}Et_2O$, THF (85%); (c) (−)-*B*-methoxydiisopinocampheylborane, allylmagnesium bromide, Et_2O, −78 °C, then NaOH, H_2O_2 (76%); (d) (+)-*B*-methoxydiisopinocampheylborane, allylmagnesium bromide, Et_2O, −78 °C, then NaOH, H_2O_2 (65%); (e) mesyl chloride, TEA, CH_2Cl_2 (99%); (f) NaN_3, DMF, 80 °C (87%); (g) Ph_3P, THF, then H_2O (66%); (h) acryloyl chloride, TEA, CH_2Cl_2 (89%).

(76% yield). Analogously, **6b** was achieved by means of reaction with (+)-allyldiisopinocampheylborane, in similar chemical yield and almost identical diastereoisomeric excess. The configuration at the newly created stereogenic center in **6a** and **6b** was postulated by means of NMR analysis[15] and then successively confirmed after conversion of **6a** into the tricycle **11** (vide infra).

The next step of the synthesis, that is the replacement of hydroxyl group by the acrylamide moiety, was performed on **6a**. To this end, when alcohol **6a** was treated with diphenylphosphoryl azide (DPPA) in the presence of DEAD and PPh_3 in THF, the expected azide **8** was formed only in traces and most of the starting material was recovered. Thus, **6a** was converted into the corresponding mesylate **7** (99% yield) and, subsequently, into azide **8** in 87% yield by using NaN_3 in DMF. Reduction of azide with PPh_3-H_2O afforded the desired amine, which was directly acylated by reaction with acryloyl chloride and TEA in CH_2Cl_2 to give **4** (59% yield for the two steps).

First-generation Grubbs' ruthenium catalyst was very suitable for RCM reaction of **4**, despite the presence of an N−H amide group in the substrate (Scheme 3). In our opinion, ring closure of such a structural unit would be favored due to steric blocking of the N−H group by the neighboring piperidine ring, which likely prevents formation of inhibiting chelating complexes of the substrate with the catalyst.

Scheme 3[a]



[a] Reagent and conditions: (a) Grubbs' catalyst, CH_2Cl_2, reflux (79%); (b) NaOH 0.5 M, THF (98%); (c) mesyl chloride, TEA, CH_2Cl_2 (67%); (d) NaH, THF, rt (89%); (e) DDQ, dioxane, reflux (50%); (f) HCl 6 N, reflux (78%).

With the 6-piperidinyl-5,6-dihydropyridin-2-one **3** thus obtained in good yield (79%), the cyclization to afford the diazabyciclo[3.3.1]nonane framework of cytisine was straightforward. Hydrolysis of the acetate group in **3** was followed by standard mesylate activation and subsequent intramolecular alkylation, performed in THF at room temperature, by mean of sodium hydride (58% yield for three steps, **3** → **9** → **10** → **11**). The structure of the tricycle **11** was confirmed by spectroscopic analysis at ^1H NMR, by which the 6*R*,7*R*,9*R* stereochemistry was deduced (Figure 1). In fact, an almost negligible coupling (ca. 0.5 Hz) is present between 6-H (at δ 3.57) and 7-H (at δ 1.80). Besides, diagnostic NOE

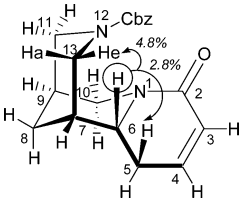
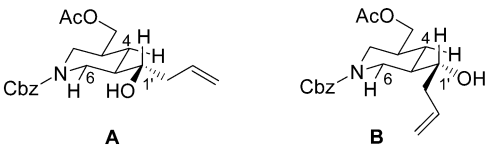


Figure 1. Selected NOE interactions detected by NOE difference studies (400 MHz, $CDCl_3$, 50 °C) of **11**.

(15) Hyperchem 6.0 analysis suggests A and B to be the prevailing conformers for compounds **6a** and **6b**, respectively. The disposition of the polar OH group in **A** and **B** should be responsible for the observed downfield shifts of 6-Heq in **6a** (δ 4.40 with respect to 4.20 in **6b**) and 4-Heq in **6b** (δ 2.00 with respect to 1.75 in **6a**).



interactions between 6-H and 5-Hax (at δ 2.30) and between 6-H and 13-Heq (at δ 4.09) are detected, compatible only with an absolute *R* configuration for C6.

Dehydrogenation of dihydropyridone **11** to pyridone **12** was investigated under various oxidative conditions. In the end, DDQ in dioxane at reflux was found to be mild and effective, providing N−Cbz-cytisine **12** as the only isolated product in 50% yield. Attempts to improve this moderate yield, by increasing the reagent and the reaction time, were unsuccessful. Finally, deprotection of the Cbz group of **12** with concentrated HCl at reflux gave **1** in 78% yield. Optical rotation of **1** ($[\alpha]^{20}_D$ −114 (*c* 1, EtOH)) was consistent with that reported for natural (−)-cytisine ($[\alpha]^{20}_D$ −110 (*c* 0.5, EtOH)).[16] The ^{1}H NMR, ^{13}C NMR, and MS spectra of synthetic **1** were also in good agreement with the literature values.

In conclusion, we have established a 12-step, 9% overall yield synthesis of enantiopure (−)-cytisine from readily available starting materials. The key step features the *N*-but-3-enylacrylamide **4** as a substrate for a ruthenium-catalyzed RCM reaction. Moreover, it should be noted that the tricyclic advanced intermediate **11** can be used for synthesizing other non aromatic quinolizidine alkaloids.

The availability of both the enantiomeric forms (**2** and *ent*-**2**) of the chiral building block *cis*-piperidine-3,5-dimethanol monoacetate allows for an access of cytisine as both antipodes, making it in principle possible to compare the biological profile of the (+) and (−) enantiomers. Finally, this enantiosynthesis is well suited for the design of novel chiral molecular templates, to be evaluated as potential nAChR subtype selective ligands.

Acknowledgment. The authors thank Ministero dell'Istruzione dell'Università e della Ricerca (MIUR) for financial support.

Supporting Information Available: Complete experimental details including description of ^{1}H and ^{13}C NMR spectra for compounds **1**, **3**−**4**, **6**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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