Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 62 (2006) 11679–11686

# Regio- and diastereoselective functionalization of (−)-cytisine

Nicolas Houllier, Sonia Gouault, Marie-Claire Lasne and Jacques Rouden*

*Laboratoire de Chimie Moléculaire et Thioorganique UMR CNRS 6507, ENSICAEN, Université de Caen Basse-Normandie, 6 Boulevard du Maréchal Juin, 14050 Caen Cedex, France*

Received 2 August 2006; revised 13 September 2006; accepted 14 September 2006

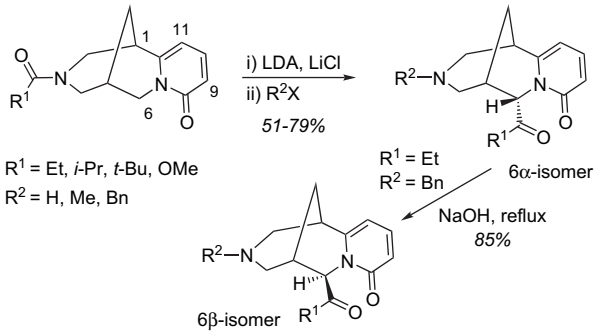
**Abstract**—(−)-*N*-Benzyl cytisine has been stereoselectively substituted in moderate to high yields on its carbon 6 ($Csp^3$ α to the pyridone nitrogen). The reaction involved the in situ trapping of the carbanion formed by reaction of lithium diisopropyl amide (LDA) and its reaction with electrophiles (alkyl, allyl, benzyl halides, non-enolizable aldehydes, and Weinreb amide). In the absence of an electrophile or with its addition after the formation of the carbanion, a dimeric structure was isolated (yield: 42%) resulting from the 1,4-addition of the carbanion on the pyridone ring of another cytisine molecule. Deprotection of the benzyl group (Olofson's reagent) allowed the formation of 6-substituted derivatives of the natural product, cytisine, a potent agonist of nicotinic receptors of subtype $\alpha_4\beta_2$.


## 1. Introduction

Cytisine was recognized as a nicotinic agonist as far back as 1912.[1] With an affinity for neuronal nicotinic acetyl choline receptors (AChRs) greater than that of nicotine,[2] and a high specificity for the $\alpha_4\beta_2$ subtype, it is marketed as Tabex, for use as a smoking cessation aid. Its structure has only been exploited very recently as a template for the synthesis of new compounds with pharmaceutical interest,[3–7] as medical imaging agents[8–10] or as chiral sources for asymmetric synthesis.[11–13]

Analogs have been limited to those easily obtained from the natural material. Substitution of the secondary amine was easily achieved by alkylation or acylation and has led to compounds of various biological activities.[7,14,15] Particularly, *N*-methyl cytisine had reduced potency and affinities for the *n*AChRs[16] and its biodistribution in vivo was not consistent with that expected for $\alpha_4\beta_2$ nicotinic receptors.[8] Introduction of a substituent on the pyridone ring of cytisine usually started with an electrophilic substitution (nitration, halogenation). A mixture of C-9 and C-11 regioisomers was obtained, the affinity toward *n*AChRs of these C-11-substituted derivatives being usually lower than cytisine.[17] Halogen substitution at C-9 and particularly bromo-substitution led to increased affinity and functional potency.[18,19] Cross coupling reactions from these analogs allowed the introduction of alkyl or (hetero)aryl groups.[9,3a] Recently, functionalization of the C-10 position of cytisine substituted was described.[4] It was not achieved directly from cytisine but by using a recently described total synthesis,[20] introducing the substituent early in the synthesis.

A few years ago, we reported a stereoselective functionalization of the C-6 position of cytisine.[21] This was the result of an N→C acyl migration. When *N*-acyl cytisines were treated with LDA in the presence of an excess of LiCl, 6α-acylcytisines were obtained in 51–79% yield. The efficiency of the N–C acyl transfer was shown to be dependent on the nature of the *N*-acyl group. Complete epimerization 6α→6β of the newly created stereocenter was observed under basic conditions (Scheme 1). We report here the direct synthesis of new 6β-substituted cytisines. The strategy is based on the intermolecular reaction of the carbanion formed on the position adjacent to the pyridone ring with different electrophiles.




**Scheme 1**. Intramolecular functionalization of cytisine via an N→C transfer of an acyl group.

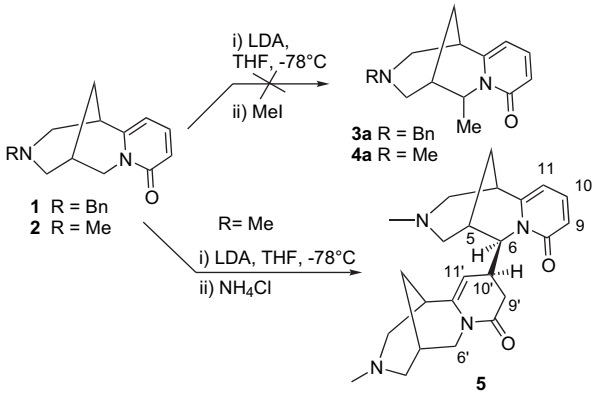
## 2. Results and discussion

In order to study the alkylation of the 6-position of cytisine while avoiding the N→C transfer observed previously with acyl groups, we protected the secondary amine with a benzyl

* Corresponding author. Tel.: +33 2 3145 2893; fax: +33 2 3145 2877; e-mail: rouden@ensicaen.fr

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.09.057

group. In our first attempts, *N*-benzyl cytisine **1** was treated by LDA (5 equiv) in THF at −78 °C. To the mixture was added methyl iodide (2.6 equiv). No expected 6-methyl cytisine **3a** was obtained but a complex mixture was formed from which we could detect, by mass spectrometry, a dimeric product. To simplify NMR spectra of such a compound, *N*-methyl cytisine **2** was submitted to the same reaction conditions but quenched with $NH_4Cl$ to give the adduct **5** (Scheme 2).




**Scheme 2**. Reaction of LDA with *N*-substituted-cytisines.

Several conditions were tried to optimize the reaction (Table 1). Under the best ones, product **5** was isolated with a 42% yield along with unreacted starting material. Attempts to reduce the temperature (entry 2), to use lithium chelating agent such as TMEDA (entry 3) or to use alkyllithium as bases (entries 4 and 5) did not improve the yield of the reaction.

Such a type of dimerization was previously observed when 1-alkyl-4,6-diphenyl-2-pyridones were treated with LDA.[22] The mechanism postulated was a carbonyl directed lithiation on carbon adjacent to nitrogen (equivalent to C-6 of cytisine) then a Michael addition on a second molecule of alkyl pyridone (addition equivalent to C-10 of cytisine), and finally a migration of the first subunit to the carbon adjacent of the carbonyl of the second pyridone. This should lead, in our case to a connection of the cytisine molecules, C-6 to C-9′. However, we did not observe the subsequent rearrangement described in this paper. Based on this publication and a series of NMR experiments ($^1H$, $^{13}C$, JMOD, COSY, HMQC, and HMBC) the structure of **5**, among the two possible (Fig. 1), was assigned unambiguously.

**Table 1**. Optimization of the dimerization of **2**[a]

| Entry | Base | *T* (°C) | Ratio **2**/**5** (yield, %)[c] |
|---|---|---|---|
| 1 | LDA | −78 | 17/83 (42) |
| 2 | LDA | −120 | 23/77 |
| 3 | LDA | −78[b] | 13/87[d] |
| 4 | BuLi | −78 | 40/60 |
| 5 | MeLi | −78 | 32/68 |

[a] Reaction conditions: **2** (1 mmol), base (5 equiv), THF, 4 h at −78 °C then $NH_4Cl$, −78 °C → room temperature, 3 h.
[b] Addition of TMEDA (5 equiv), quench with MeI.
[c] Ratio of starting material **2**/dimer **5** from $^1H$ NMR of the crude product. Isolated yield of **5** are in parentheses.
[d] Complex mixture.

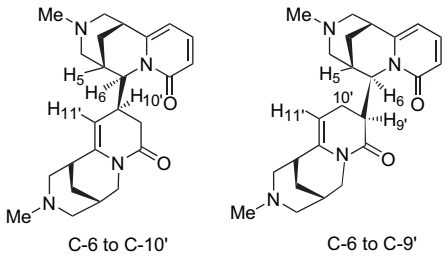
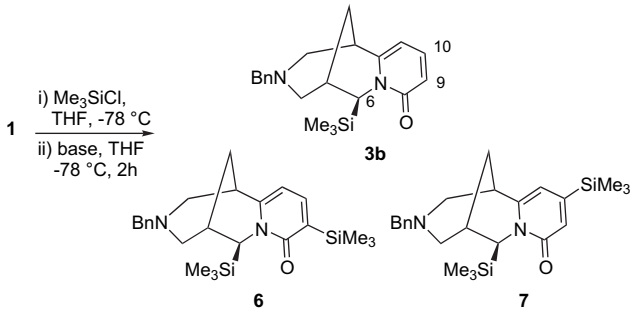



**Figure 1**. Possible connections for dimer **5**.

On the $^1H$ NMR spectrum, only one pyridone subunit remained (protons $H_9$–$H_{11}$ with characteristic chemical shifts at 5.95, 6.40, and 7.23 ppm). On signals in the range 3–5 ppm: first, a doublet at 4.61 ppm ($J_{H6–H10'}$=5.6 Hz) attributed to $H_6$ (a common chemical shift for this type of proton) connected to $sp^3$ carbon (HMQC), and a doublet ($J_{H11'–H10'}$=5.1 Hz) at 4.33 ppm attributed to $H_{11'}$ connected to $sp^2$ carbon (HMQC), both coupling with the same proton, $H_{10'}$, at 3.6–3.7 ppm showing as a multiplet (COSY). Also in the same $^1H$ NMR range at 3.66 and 3.58 ppm, one might recognize two characteristic signals for the $H_{6'}$ of the second cytisine subunit showing as a doublet (mixed with $H_{10'}$ multiplet) and a doublet of doublet. The absolute configuration of C-6 was clearly assigned based on our previous work.[21] Indeed, the observed coupling constant for $H_6$ is due to $H_{10'}$ and not $H_5$. Therefore, since no coupling is occurring between $H_6$ and $H_5$, the configuration of C-6 is *S* ($H_6$ in α position). We were not able to define the absolute configuration of C-10′. However, based on the known stereochemical outcome of the pyridone hydrogenation of cytisine,[11a] we assumed that the addition has occurred on the less hindered *exo* face at the C-10′ position. Next we needed to assert the position of the connection between both cytisine units, i.e., between C-6 and C-10′, mainly because of the rearrangement described in Katritzky's paper.[22] Beside coupling with $H_6$ and $H_{11'}$, the COSY experiment revealed for $H_{10'}$ two correlations with signals at 2.53 ppm (dd, *J*=7, 16 Hz, 1H) and at 2.66 ppm (part of a multiplet). These two protons were connected to the same carbon (HMQC), which was a $CH_2$ type of carbon (JMOD). This carbon was therefore assigned to C-9′. All attributions (protons and carbons) were confirmed by an HMBC experiment. In the other hypothesis connecting C-6 with C-9′ (involving a migration following the Michael addition) the coupling patterns would be notably different.

We used *N*-benzyl cytisine **1** for the following part of the study in order to remove easily the nitrogen protecting group. Because of the high reactivity of the carbanion generated at C-6, we attempted to trap it by an electrophile immediately after its formation using the inverse addition procedure.[23] Under these conditions, the treatment of a mixture of **1** and methyl iodide in THF by LDA (2 equiv) afforded 6β-methyl cytisine **3a** in 75% yield (not optimized). A quick search of the most appropriate base to carry out this selective deprotonation using chlorotrimethylsilane as the electrophile was undertaken (Scheme 3). Some relevant results are presented in Table 2. Three bases of increasing $pK_a$ were tested. Lithium hexamethyldisilylamide (LHMDS) gave no reaction, while lithium tetramethylpiperidinamide (LTMP) afforded a mixture of products arising

from mono or disilylation (**3b**, **6**, **7**). LDA appeared as the most selective base as previously shown.[24]




**Scheme 3**. Selectivity of the deprotonation of *N*-benzyl cytisine **1**.

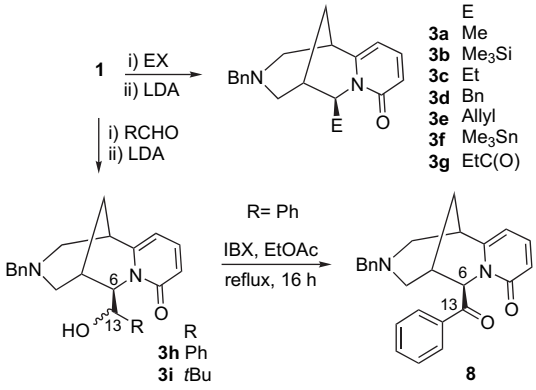
**Table 2**. Choice of base for the deprotonation of **1**

| Entry | Base[a] | p$K_a$[25] | Yield (%)[b] | Ratio (%)[c] | | |
|---|---|---|---|---|---|---|
| | | | | **3b** | **6** | **7** |
| 1 | LHMDS | 29.5 | [d] | 0 | 0 | 0 |
| 2 | LDA | 35.7 | 78 | 100 | 0 | 0 |
| 3 | LTMP | 37.3 | 56 | 32 | 64 | 4 |

[a] Reaction conditions: **1** (1 mmol), $Me_3SiCl$ (2.6 equiv), THF, −78 °C then base (2.6 equiv), 2 h, −78 °C.
[b] Isolated yields.
[c] Determined from $^1$H NMR of the crude product.
[d] Starting material was recovered quantitatively.

The reaction with LDA was regio- and diastereoselective at C-6. Only product **3b** resulting from the silylation of **1** in the position 6β was observed, the absolute configuration of the product being determined by $^1$H NMR as described in our previous report.[21] Alkyl, allyl, benzyl, and trimethylstannyl halides were successfully used as electrophiles (Table 3, entries 1–6). Weinreb amide[26] and non-enolizable aldehydes can be employed in the inverse addition conditions affording ketone **3g** or alcohols **3h** and **3i**, respectively (entries 7–9).

Alkylation of *N*-benzyl cytisine carbanion with aldehydes generated a second stereogenic center, carbon 13 in **3h** or **3i**. Only two diastereoisomers were produced showing a very high asymmetric induction at one carbon and a poor selectivity for the other (Table 3, entries 8 and 9). The stereochemistry at C-6 of compounds **3h** was deduced from that of the ketone **8** obtained by a mild oxidation of alcohols **3h** using IBX[27] (Scheme 4). Only one ketone **8** was formed and the coupling constant $J_{H5-H6}$=0 Hz showed unambiguously that H6 proton was in the alpha position. A low asymmetric induction was occurring at C-13 since alcohols **3h** and **3i** were isolated as mixture of diastereoisomers, in 61/39 and 54/46 ratios, respectively. The absolute configuration of $C_{13}$ for each diastereoisomer was assigned by comparing the observed vicinal coupling constants between protons $H_6$ and $H_{13}$ and those calculated from molecular modeling simulations (AM1, Spartan®). After minimization of the structures of both isomers of **3h**, a dihedral angle of 50° was measured for the (*R*) isomer and 96° for the (*S*) isomer corresponding to coupling constants $J_{H6-H13}$ of 5 Hz and 0 Hz (Fig. 2). In the $^1$H NMR spectrum of compounds **3h**, we found $J_{H6-H13}$=7.4 Hz for the major diastereoisomer (61%), therefore assigned as the (*R*)-$C_{13}$ and $J_{H6-H13}$=2.0 Hz for the (*S*)-$C_{13}$ minor product. The same calculations were carried out with diastereoisomers of **3i**. Dihedral angles of the calculated structures were 40° and 92° for (*R*) and (*S*) diastereoisomers, respectively, corresponding to $J_{H6-H13}$ of 6.9 Hz and 0.0 Hz. The (*R*)-$C_{13}$ major isomer (54%) had a coupling constant $J_{H6-H13}$ of 7.8 Hz and the (*S*) minor isomer of 0 Hz.




**Scheme 4**. Regio- and diastereoselective alkylation of *N*-Bn-cytisine **1**.

Next, we tried to introduce a second alkyl group on the 6-position of compound **3a**. The reaction was carried out under the same conditions as for the first alkylation. No product **9** was obtained and the starting material was recovered quantitatively. The second deprotonation did not seem to occur (Scheme 5).

Finally, in order to test the new compounds towards *n*AChRs, debenzylation of the tertiary amine was carried out (Scheme 6). Hydrogenolytic removal of *N*-benzyl groups is traditional but is clearly inapplicable to residues such as allyl groups. Therefore we turned our attention towards Olofson's reagent, α-chloroethyl chloroformate (ACE-Cl).[28]

**Table 3**. Diastereoselective alkylation of *N*-Bn-cytisine **1**[a]

| Entry | EX | Product | Yield (%)[b] |
|---|---|---|---|
| 1 | MeI | **3a** | 98 |
| 2 | $Me_3SiCl$ | **3b** | 78 |
| 3 | EtBr | **3c** | 70 |
| 4 | BnBr | **3d** | 62 |
| 5 | Allyl-Br | **3e** | 69 |
| 6 | $Me_3SnCl$ | **3f** | 44 |
| 7 | EtC(O)N(Me)OMe | **3g** | 42 |
| 8 | PhCHO | **3h** | 76[c] |
| 9 | *t*-BuCHO | **3i** | 78[d] |

[a] Reaction conditions: **1** (1 mmol) and electrophile (2.6 equiv), THF, −78 °C then LDA (3 equiv), −78 °C, 2 h then room temperature for 16 h.
[b] Isolated yields.
[c] As a 61/39 ratio of diastereoisomers.
[d] As a 54/46 ratio of diastereoisomers.

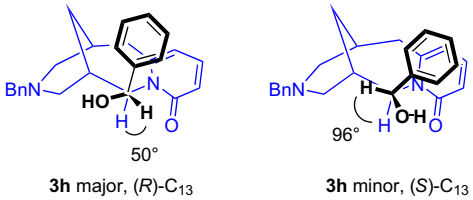
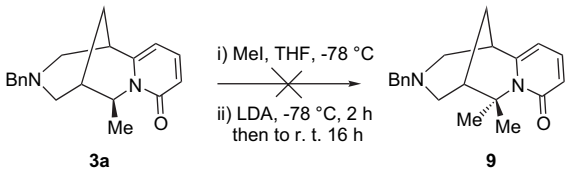
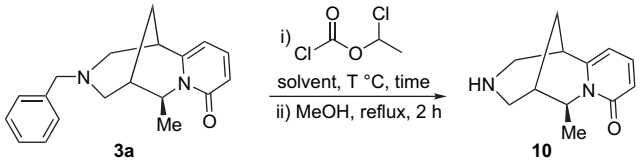



**Figure 2**. Molecular modeling simulations for C-13 epimer **3h**.




**Scheme 5**.




**Scheme 6**. Debenzylation of **3a**.

Debenzylation was tried on *N*-benzyl-6β-methyl-cytisine **3a**. Several attempts were needed to determine the optimal conditions (Table 4). In dichloromethane, reaction was not reproducible and starting material was mainly recovered (entries 1–4). Debenzylation took place in refluxing dichloroethane for 24 h with an excess of ACE-Cl to afford 6β-methyl-cytisine **10** in 72% isolated yield (Table 4, entry 8).

**Table 4**. Debenzylation of *N*-benzyl-6β-methyl-cytisine **3a**

| Entry | ACE-Cl[a] (equiv) | Solvent | Temp | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | 1.3 | $CH_2Cl_2$ | rt | 1.5 | [c] |
| 2 | 1.5 | $CH_2Cl_2$ | rt | 0.5 | (25)[d] |
| 3 | 1.5 | $CH_2Cl_2$ | rt | 16 | [c] |
| 4 | 4 | $CH_2Cl_2$ | rt | 16 | [c] |
| 5 | 1.5 | $ClCH_2CH_2Cl$ | Reflux | 2 | (30)[d] |
| 6 | 4 | $ClCH_2CH_2Cl$ | Reflux | 6 | 49 |
| 7 | 4 | $ClCH_2CH_2Cl$ | Reflux | 16 | 53 |
| 8 | 4 | $ClCH_2CH_2Cl$ | Reflux | 24 | 72 |

[a] α-Chloroethyl chloroformate (number of equivalent).
[b] Isolated yields.
[c] Starting material was recovered quantitatively.
[d] Conversion determined by $^1$H NMR.

## 3. Conclusion

This work demonstrated the possibility of intermolecular functionalization of cytisine on carbon 6 via an original lithiation reaction. The key step was the regiospecific carbonyl directed deprotonation of cytisine by LDA followed by in situ trapping of the anion by various electrophiles (inverse addition procedure). With alkyl halides the alkylation was totally stereoselective at C-6 (position 6β) and opposite to the acyl migration previously observed (position 6α), but poorly diastereoselective on the second stereogenic center created when using aldehydes. To avoid the described carbonyl migration following the deprotonation when cytisine was *N*-substituted by an acyl residue, a benzyl group was used to protect cytisine, which allowed for its easy and selective removal by α-chloroethyl chloroformate. A dimer of cytisine was isolated while using the normal addition conditions for the deprotonation–alkylation sequence or in the absence of electrophile. Finally, the reaction developed here offers the potential for the synthesis of a wide variety of new ligands for receptors of the central nervous system or of new chiral sources for asymmetric synthesis.

## 4. Experimental

### 4.1. General methods and starting materials

The reactions were carried out under nitrogen or argon in flasks dried in an oven at 110 °C. THF and $CH_2Cl_2$ were dried with a PURESOLV™ apparatus (Innovative Technology Inc.). Diisopropylamine was distilled from calcium hydride. Methyl iodide, ethyl bromide, benzyl bromide, allyl bromide, trimethylsilyl chloride, benzaldehyde, and pivalaldehyde were distilled before use. A commercial solution of trimethyltin chloride (1 M in THF, Aldrich) was used. Thin layer chromatography (TLC) was performed using aluminum sheets precoated with silica gel 60 $F_{254}$ (Merck). Flash chromatography was carried out on silica gel SI 60 (0.040–0.063 mm, Merck). Melting points were obtained using a Köfler bench apparatus (uncorrected). Optical rotations were measured using a Perkin–Elmer 241 polarimeter. Infrared spectra (IR) were recorded with a FT-IR Perkin–Elmer 684 spectrometer. Mass and high resolution mass spectra (HRMS) were obtained on a Waters-Micromass Q-Tof micro instrument. NMR spectra were recorded on a Brucker Avance DPX-250 ($^1$H at 250.1 MHz; $^{13}$C at 62.9 MHz; TMS as internal standard). Elementary analyses were performed on a Thermoquest apparatus by the microanalytical service of the Laboratory of Molecular and Thioorganic Chemistry of ENSICaen, Caen. Cytisine [(−)-(1*R*,5*S*)-1,2,3,4,5,6-hexahydro-1,5-methanopyrido[1,2-*a*]-[1,5]diazocin-8-one] was extracted from commercially available seeds of *Cytisus laburnum anagyroïdes* (Vilmorin Company, France). The procedure was reported in the supporting information (free of charge via the Internet at http://pubs.acs.org) of a previous publication.[9]

**4.1.1. Synthesis of (−)-(1*R*,5*S*)-*N*-benzyl cytisine 1.**[29,11d] To a solution of cytisine (1.0 g, 5.26 mmol) in 20 mL of $CH_2Cl_2$ was added $Na_2CO_3$ (1.1 g, 10.5 mmol, 2 equiv) in 10 mL of $H_2O$ followed by benzyl bromide (6.31 mmol, 1.2 equiv) at room temperature. After stirring 4 h at reflux temperature, the reaction mixture was extracted three times with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$ and concentrated under vacuum. Purification of the crude product by flash chromatography ($CH_2Cl_2$/MeOH, 95:5) afforded **1** as a white solid (1.13 g, 77%): mp 142–144 °C; $[\alpha]_D^{22}$ −219 (*c* 1, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 1.8–1.9 (m, 2H), 2.3–2.5 (m, 3H), 2.8–3.0 (m, 3H), 3.37 and 3.46 (AB, $J_{AB}$=13.6 Hz, 2H, $CH_2$Bn), 3.91 (dd, *J*=15.4, 6.5 Hz, 1H, H-6β), 4.10 (d, *J*=15.4 Hz, 1H, H-6α), 5.90 (dd, *J*=6.9, 1.3 Hz, 1H, H-11), 6.48 (dd, *J*=9.0, 1.3 Hz, 1H, H-9), 6.9–7.0 (m, 2H), 7.1–7.3 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 26.3, 28.5, 35.9, 50.3, 60.3, 60.4, 62.3, 105.0, 116.8, 127.2, 128.5, 138.4, 138.9, 151.8, 164.0; IR (NaCl, $cm^{-1}$) 2926, 2794, 1652, 1546, 1140, 800, 736, 698; HRMS (EI) calcd for $C_{18}H_{20}N_2O_2$ 280.1576, found 280.1578.

**4.1.2. Dimerization of *N*-methyl-cytisine 2.** To a solution of *N*-methyl-cytisine **2** (250 mg, 1.22 mmol, 1 equiv) in

10 mL of THF was added dropwise an LDA solution [prepared in situ from diisopropylamine (0.52 mL, 3.68 mmol, 3 equiv) and *n*-butyllithium (1.6 M solution in hexanes, 2.30 mL, 3.68 mmol, 3 equiv) in 5 mL of THF at −20 °C] at −78 °C under nitrogen. After stirring 4 h at −78 °C, the reaction was quenched with a saturated aqueous ammonium chloride solution. Ammonia was then added until basic pH. The aqueous phase was extracted three times with $CH_2Cl_2$ and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography ($CH_2Cl_2$/MeOH, 92:8) to afford dimer **5** as a yellow oil (0.105 g, 42%); $[\alpha]_D^{22}$ +259 (*c* 1, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 1.41 (d, *J*=11.0 Hz, 1H), 1.47 (d, *J*=13.0 Hz, 1H), 1.65 (d, *J*=13.0 Hz, 1H), 2.02 (s, 3H), 2.0–2.1 (m, 2H), 2.11 (s, 3H), 2.1–2.2 (m, 3H), 2.24 (br s, 1H), 2.3–2.4 (m, 2H), 2.53 (dd, *J*=7.0, 16.0 Hz, 1H, H-9′), 2.59–2.70 (m, 3H), 2.73 (d, *J*=10.0 Hz, 1H), 2.8–2.9 (m, 2H), 3.58 (dd, *J*=7.0, 13.2 Hz, 1H, H-6′β), 3.6–3.7 (m, 2H, H-6′α and H-10′), 4.33 (d, *J*=5.1 Hz, 1H, H-11′), 4.61 (d, *J*=5.6 Hz, 1H, H-6α), 5.95 (dd, *J*=1.4, 6.8 Hz, 1H, H-11), 6.40 (dd, *J*=1.4, 9.0 Hz, 1H, H-9), 7.23 (dd, *J*=6.8, 9.0 Hz, 1H, H-10). $^{13}$C NMR ($CDCl_3$) $\delta$ 23.8, 26.4, 27.6, 29.5, 31.2, 34.5, 35.4, 36.5, 46.1, 46.5, 47.5, 61.6, 62.1, 63.0, 63.6, 101.5, 104.6, 117.8, 138.6, 142.4, 151.6, 163.4, 169.5; IR (NaCl, $cm^{-1}$) 3419, 2937, 2780, 1645, 1544, 907, 723; HRMS (ESI) calcd for $C_{24}H_{33}N_4O_2$ 409.2604, found 409.2593.

## 4.2. General procedure for alkylation at C-6 position

To a solution of *N*-benzyl-cytisine **1** (250 mg, 0.89 mmol, 1 equiv) in 7 mL of THF was added the electrophile (2.32 mmol, 2.6 equiv) at −78 °C under nitrogen. An LDA solution [prepared in situ from diisopropylamine (0.37 mL, 2.67 mmol, 3 equiv) and *n*-butyllithium (1.6 M solution in hexanes, 1.67 mL, 2.67 mmol, 3 equiv) in 5 mL of THF at −20 °C] was then added dropwise. After stirring 2 h at −78 °C, the reaction was stirred overnight at room temperature. The mixture was quenched with a saturated aqueous ammonium chloride solution and then ammonia was added until basic pH. The aqueous phase was extracted three times with $CH_2Cl_2$ and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated under vacuum.

**4.2.1. (−)-(1*R*,5*S*,6*S*)-*N*-Benzyl-6-methyl-cytisine 3a.** The electrophile added was methyl iodide. The crude product was purified by flash chromatography ($CH_2Cl_2$/MeOH, 98:2) to afford **3a** as a white solid (0.257 g, 98%): mp 152 °C; $[\alpha]_D^{22}$ −51 (*c* 0.9, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 1.40 (d, *J*=6.4 Hz, 3H), 1.6–1.8 (m, 2H), 2.02 (s, 1H), 2.22 (d, *J*=1.3 Hz, 1H), 2.26 (d, *J*=1.3 Hz, 1H), 2.43 (dd, *J*=2.5, 11.0 Hz, 1H), 2.67 (dd, *J*=1.6, 10.4 Hz, 1H), 2.91 (br s, 1H), 3.03 (d, *J*=11.0 Hz, 1H), 3.27 and 3.45 (AB, $J_{AB}$=13.6 Hz, 2H, $CH_2$Bn), 4.78 (q, *J*=6.4 Hz, 1H, H-6α), 5.86 (dd, *J*=1.2, 6.7 Hz, 1H, H-11), 6.48 (dd, *J*=1.2, 9.0 Hz, 1H, H-9), 6.9–7.1 (m, 5H), 7.2–7.3 (m, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$ 20.8, 23.5, 34.9, 36.1, 54.7, 59.9, 60.8, 61.8, 104.8, 117.5, 126.8, 128.1, 138.1, 150.9, 163.2; IR (KBr, $cm^{-1}$) 3423, 2918, 2809, 1648, 1569, 1542, 801, 735, 698; HRMS (ESI) calcd for $C_{19}H_{23}N_2O$ 295.1810, found 295.1809.

**4.2.2. (+)-(1*R*,5*S*,6*S*)-*N*-Benzyl-6-trimethylsilyl-cytisine 3b.** The electrophile added was chlorotrimethylsilane. The crude product was purified by flash chromatography ($CH_2Cl_2$/MeOH, 99:1) to afford **3b** as a yellow oil (0.245 g, 78%); $[\alpha]_D^{22}$ +16 (*c* 0.6, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 0.06 (s, 9H, Si($CH_3$)$_3$), 1.7–1.8 (m, 2H), 1.82 (dd, *J*=1.7, 10.5 Hz, 1H), 2.39 (br s, 1H), 2.50 (dd, *J*=2.6, 11.0 Hz, 1H), 2.91 (s, 1H), 2.94 (dt, *J*=1.8, 8.8 Hz, 1H), 2.98 (d, *J*=11.0 Hz, 1H), 3.26 and 3.49 (AB, $J_{AB}$=13.7 Hz, 2H, $CH_2$Bn), 4.26 (s, 1H, H-6α), 5.87 (dd, *J*=1.3, 6.9 Hz, 1H, H-11), 6.47 (dd, *J*=1.4, 9.0 Hz, 1H, H-9), 6.8–6.9 (m, 2H), 7.1–7.2 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ −0.9, 25.8, 30.7, 35.4, 53.2, 60.2, 61.7, 62.4, 104.4, 115.5, 126.6, 126.7, 127.9, 128.0, 137.4, 138.1, 150.9, 163.3; IR (NaCl, $cm^{-1}$) 3421, 2938, 2793, 1647, 1546, 1247, 840, 732, 698; HRMS (EI) calcd for $C_{21}H_{29}N_2OSi$ 353.2049, found 353.2032.

**4.2.3. (−)-(1*R*,5*S*,6*S*)-*N*-Benzyl-6-ethyl-cytisine 3c.** The electrophile added was ethyl bromide. The crude product was purified by flash chromatography ($CH_2Cl_2$/MeOH, 99:1) to afford **3c** as a white solid (0.192 g, 70%): mp 161 °C; $[\alpha]_D^{22}$ −13 (*c* 0.5, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 1.02 (t, *J*=7.4 Hz, 3H), 1.3–1.4 (m, 1H), 1.6–1.7 (m, 1H), 1.7–2.0 (m, 1H), 2.1–2.3 (m, 3H), 2.49 (dd, *J*=11.0, 2.6 Hz, 1H), 2.65 (d, *J*=10.4 Hz, 1H), 2.90 (s, 1H), 2.96 (d, *J*=11.0 Hz, 1H), 3.27 and 3.46 (AB, $J_{AB}$=13.7 Hz, 2H, $CH_2$Bn), 4.42 (d, *J*=8.3 Hz, 1H, H-6α), 5.82 (d, *J*=6.8 Hz, 1H, H-11), 6.48 (d, *J*=9.0 Hz, 1H, H-9), 6.8–6.9 (m, 2H), 7.1–7.3 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 12.0, 23.9, 27.5, 30.7, 36.4, 60.6, 61.0, 61.1, 62.2, 104.9, 117.8, 127.1, 128.4, 138.4, 138.6, 151.2, 163.5; IR (KBr, $cm^{-1}$) 3421, 2935, 2801, 1649, 1569, 1544, 735, 699; HRMS (EI) calcd for $C_{20}H_{24}N_2O$ 309.1967, found 309.1962.

**4.2.4. (−)-(1*R*,5*S*,6*S*)-*N*-Benzyl-6-benzyl-cytisine 3d.** The electrophile added was benzyl bromide. The crude product was purified by flash chromatography ($CH_2Cl_2$/MeOH, 98:2) to afford **3d** as a yellow oil (0.204 g, 62%); $[\alpha]_D^{22}$ −101 (*c* 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 1.6–1.7 (m, 2H), 2.0–2.5 (m, 4H), 2.54 (d, *J*=10.9 Hz, 1H), 2.66 (d, *J*=10.9 Hz, 1H), 2.66 (br s, 1H), 3.22 and 3.42 (AB, $J_{AB}$=13.7 Hz, 2H, N$CH_2$Bn), 3.45 (d, *J*=12.9 Hz, 1H), 4.79 (d, *J*=10.3 Hz, 1H, H-6α), 5.89 (d, *J*=6.8 Hz, 1H, H-11), 6.57 (d, *J*=9.0 Hz, 1H, H-9), 6.8–6.9 (m, 2H), 7.1–7.4 (m, 9H); $^{13}$C NMR ($CDCl_3$) $\delta$ 23.6, 29.9, 36.4, 39.9, 53.7, 60.5, 60.9, 61.1, 62.1, 105.2, 117.9, 126.8, 127.1, 128.4, 128.4, 128.8, 129.9, 138.5, 138.8, 138.9, 139.4, 151.3, 163.4; IR (NaCl, $cm^{-1}$) 3416, 2939, 2794, 1648, 1567, 1546, 910, 800, 733, 699; HRMS (ESI) calcd for $C_{25}H_{27}N_2O$ 371.2123, found 371.2105.

**4.2.5. (−)-(1*R*,5*S*,6*S*)-*N*-Benzyl-6-allyl-cytisine 3e.** The electrophile added was allyl bromide. The crude product was purified by flash chromatography ($CH_2Cl_2$/MeOH, 98:2) to afford **3e** as a yellow oil (0.197 g, 69%); $[\alpha]_D^{22}$ −26 (*c* 0.5, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 2.1–2.2 (m, 5H), 2.4–2.5 (m, 1H), 2.6–2.7 (m, 1H), 2.7–3.0 (m, 3H), 3.27 and 3.46 (AB, $J_{AB}$=13.6 Hz, 2H, $CH_2$Bn), 4.56 (t, *J*=7.7 Hz, 1H, H-6α), 5.0–5.1 (m, 2H), 5.8–5.9 (m, 2H), 6.50 (d, *J*=9.0 Hz, 1H, H-9), 6.8–6.9 (m, 2H), 7.1–7.2 (m, 4H); $^{13}$C NMR ($CDCl_3$) $\delta$ 23.6, 30.7, 36.4, 38.7, 53.8, 58.6, 60.4, 61.0, 62.1, 105.1, 117.8, 117.9, 127.1, 128.4,

128.5, 135.9, 138.6, 138.6, 151.2, 163.4; IR (NaCl, $cm^{-1}$) 3397, 2938, 2794, 1648, 1546, 912, 800, 732, 698; HRMS (EI) calcd for $C_{21}H_{24}N_2O$ 321.1967, found 321.1952.

**4.2.6. (+)-(1*R*,5*S*,6*S*)-*N*-Benzyl-6-trimethylstannyl-cytisine 3f.** The electrophile added was trimethyltin chloride. The crude product was purified by flash chromatography ($CH_2Cl_2$/MeOH, 99:1) to afford **3f** as a colorless oil (0.174 g, 44%); $[\alpha]_D^{22}$ +114 (*c* 1.2, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 0.03 (s, $J^2_{Sn-H}$=51.3 Hz, 9H, $Sn(CH_3)_3$), 1.7–1.8 (m, 2H), 2.26 (dd, *J*=1.7, 10.5 Hz, 1H), 2.4–2.5 (m, 2H), 2.80 (dt, *J*=1.7, 10.5 Hz, 1H), 2.9–3.0 (m, 2H), 3.33 and 3.46 (AB, $J_{AB}$=13.6 Hz, 2H, $CH_2$Bn), 4.14 (s, $J^2_{Sn-H}$= 51.3 Hz, 1H, H-6$\alpha$), 5.95 (dd, *J*=1.3, 6.9 Hz, 1H, H-11), 6.48 (dd, *J*=1.4, 8.9 Hz, 1H, H-9), 6.9–7.0 (m, 2H), 7.1–7.3 (m, 4H); $^{13}C$ NMR ($CDCl_3$) $\delta$ −8.1, 26.3, 32.6, 36.1, 54.0, 56.1, 61.0, 62.5, 63.0, 106.1, 115.3, 127.3, 128.7, 128.7, 137.7, 138.8, 151.1, 162.9; IR (NaCl, $cm^{-1}$) 2925, 2795, 1638, 1543, 1142, 769, 731, 698; HRMS (EI) calcd for $C_{21}H_{29}N_2OSn$ 445.1302, found 445.1317.

**4.2.7. (−)-(1*R*,5*S*,6*R*)-*N*-Benzyl-6-propionyl-cytisine 3g.[21]** The electrophile added was *N*-methoxy-*N*-methylpropionamide. The crude product was purified by flash chromatography ($CH_2Cl_2$/MeOH, 95:5) to afford **3g** as a viscous colorless oil (0.125 g, 42%).

**4.2.8. (−)-(1*R*,5*S*,6*R*)-*N*-Benzyl-6-[(hydroxy,phenyl)-methyl]-cytisine 3h.** The electrophile added was benzaldehyde. The crude product was purified by flash chromatography ($CH_2Cl_2$/MeOH, 99:1) to afford **3h** as a 61/39 mixture of diastereoisomers (0.261 g, 76%). Analytical samples of each diastereoisomer were obtained from a second tedious chromatography of the mixture using the same eluting system.

Major diastereoisomer at C-13, (*R*): $[\alpha]_D^{22}$ −99 (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 1.27 (d, *J*=13.1 Hz, 1H), 1.49 (d, *J*=13.1 Hz, 1H), 2.0–2.1 (m, 2H), 2.19 (dd, *J*= 2.5, 11.1 Hz, 1H), 2.4–2.5 (m, 1H), 2.6–2.7 (m, 2H), 3.09 and 3.29 (AB, $J_{AB}$=13.7 Hz, 2H, $CH_2$Bn), 4.89 (d, *J*= 7.3 Hz, 1H, H-6$\alpha$), 5.04 (d, *J*=7.4 Hz, 1H), 5.31 (br s, 1H), 5.86 (d, *J*=6.9 Hz, 1H, H-11), 6.53 (d, *J*=8.9 Hz, 1H, H-9), 6.7–6.8 (m, 2H), 7.0–7.1 (m, 3H), 7.1–7.2 (m, 6H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 23.4, 28.9, 36.1, 60.3, 60.9, 61.6, 63.6, 75.9, 106.6, 117.1, 127.2, 127.8, 128.1, 128.4, 128.5, 138.1, 139.6, 142.4, 151.7, 166.0; IR (NaCl, $cm^{-1}$) 3279, 2939, 2794, 1642, 1542, 1136, 908, 726, 698; HRMS (ESI) calcd for $C_{25}H_{27}N_2O_2$ 387.2073, found 387.2081.

Minor diastereoisomer at C-13, (*S*): $[\alpha]_D^{22}$ −139 (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 1.48 (d, *J*=12.3 Hz, 1H), 2.1–2.2 (m, 3H), 2.5–2.7 (m, 2H), 2.8–2.9 (m, 1H), 2.94 (br s, 1H), 3.20 and 3.40 (AB, $J_{AB}$=13.7 Hz, 2H, $CH_2$Bn), 3.6–3.7 (m, 1H), 4.85 (d, *J*=2.0 Hz, 1H, H-6$\alpha$), 5.74 (br s, 1H), 5.96 (d, *J*=6.9 Hz, 1H, H-11), 6.45 (d, *J*=9.0 Hz, 1H, H-9), 6.8–6.9 (m, 2H), 7.1–7.2 (m, 3H), 7.2–7.3 (m, 4H), 7.52 (d, *J*=7.1 Hz, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 24.9, 28.1, 36.5, 60.8, 61.5, 63.9, 73.3, 105.5, 117.2, 126.9, 127.0, 127.1, 128.2, 128.3, 128.7, 138.4, 139.0, 142.5, 152.7, 164.1; IR (NaCl, $cm^{-1}$) 3282, 2931, 2794, 2758, 1643, 1542, 1134, 908, 803, 734, 699; HRMS (ESI) calcd for $C_{25}H_{27}N_2O_2$ 387.2073, found 387.2068.

**4.2.9. (−)-(1*R*,5*S*,6*R*)-*N*-Benzyl-6-[(hydroxy,*tert*-butyl)-methyl]-cytisine 3i.** The electrophile added was pivalaldehyde. The crude product was purified by flash chromatography ($CH_2Cl_2$/MeOH, 99:1) to afford **3i** as a 54/46 mixture of diastereoisomers (0.254 g, 78%). Analytical samples of each diastereoisomer were obtained from a second tedious chromatography of the mixture using the same eluting system.

Major diastereoisomer at C-13, (*R*): $[\alpha]_D^{22}$ −24 (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 1.17 (s, 9H), 1.6–1.7 (m, 2H), 2.1–2.2 (m, 2H), 2.26 (br s, 1H), 2.45 (dd, *J*=2.6, 11.1 Hz, 1H), 2.66 (d, *J*=10.3 Hz, 1H), 2.95 (s, 1H), 3.01 (d, *J*=11.1 Hz, 1H), 3.2–3.3 (m, 2H), 3.25 and 3.52 (AB, $J_{AB}$=13.7 Hz, 2H, $CH_2$Bn), 4.76 (d, *J*=7.8 Hz, 1H, H-6$\alpha$), 5.94 (d, *J*=6.9 Hz, 1H, H-11), 6.51 (d, *J*=8.9 Hz, 1H, H-9), 6.8–6.9 (m, 2H), 7.1–7.2 (m, 3H), 7.2–7.3 (m, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 23.0, 27.5, 33.2, 35.8, 37.1, 59.2, 60.4, 60.8, 61.8, 81.6, 106.5, 117.0, 126.9, 128.1, 128.2, 138.1, 139.3, 152.0, 166.4; IR (NaCl, $cm^{-1}$) 2949, 2794, 1644, 1542, 1134, 912, 800, 731, 698; HRMS (ESI) calcd for $C_{23}H_{31}N_2O_2$ 367.2386, found 367.2368.

Minor diastereoisomer at C-13, (*S*) isolated as an enriched mixture with its epimer. $^1H$ NMR ($CDCl_3$) $\delta$ 1.10 (s, 9H), 1.4–1.5 (m, 1H), 2.1–2.2 (m, 1H), 2.2–2.4 (m, 2H), 2.6–2.7 (m, 2H), 2.7–2.8 (m, 1H), 2.8–2.9 (m, 2H), 3.26 and 3.50 (AB, $J_{AB}$=13.4 Hz, 2H, $CH_2$Bn), 3.4–3.5 (m, 1H), 4.08 (s, 1H), 4.88 (s, 1H, H-6$\alpha$), 5.88 (d, *J*=7.5 Hz, 1H, H-11), 6.46 (d, *J*=8.9 Hz, 1H, H-9), 6.8–6.9 (m, 2H), 7.1–7.2 (m, 4H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 25.3, 27.5, 29.5, 36.0, 36.1, 60.2, 60.7, 61.0, 61.8, 78.8, 104.9, 117.1, 126.7, 128.0, 128.1, 138.2, 138.3, 152.9, 163.5; HRMS (ESI) calcd for $C_{23}H_{31}N_2O_2$ 367.2386, found 367.2400.

**4.2.10. (+)-(1*R*,5*S*,6*S*)-*N*-Benzyl-6,9-bistrimethylsilyl-cytisine 6.** Same procedure as for compound **3b** with LTMP as base. The crude product was purified by flash chromatography ($CH_2Cl_2$/MeOH, 98:2) to afford **6** as a yellow oil (186 mg, 36%); $[\alpha]_D^{22}$ +46 (*c* 0.8, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 0.03 (s, 9H), 0.29 (s, 9H), 1.7–1.8 (m, 2H), 2.23 (dd, *J*=1.6, 10.4 Hz, 1H), 2.34 (br s, 1H), 2.50 (dd, *J*=2.4, 10.9 Hz, 1H), 2.72 (dt, *J*=1.7, 10.4 Hz, 1H), 2.87 (br s, 1H), 2.99 (d, *J*=10.9 Hz, 1H), 2.80 and 3.46 (AB, $J_{AB}$=13.9 Hz, 2H, $CH_2$Bn), 4.33 (s, 1H, H-6$\alpha$), 5.85 (d, *J*=6.7 Hz, 1H, H-11), 6.8–6.9 (m, 2H), 7.0–7.1 (m, 3H), 7.30 (d, *J*=6.7 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ −1.5, −0.7, 26.0, 31.2, 35.9, 53.1, 60.7, 61.7, 62.5, 105.1, 125.3, 126.8, 128.1, 128.2, 138.7, 143.5, 151.9, 165.6; IR (NaCl, $cm^{-1}$) 2942, 2802, 2760, 1624, 1544, 1242; MS (EI) *m/z* (%) 424 ($M^+$, 25), 409 (42), 290 (47), 202 (38), 91 (100), 73 (77), 57 (46).

### 4.3. Oxidation of epimeric alcohols 3h

**4.3.1. (−)-(1*R*,5*S*,6*R*)-*N*-Benzyl-6-benzoyl-cytisine 8.** To a solution of a mixture of diastereoisomers **3h** (70 mg, 0.181 mmol, 1 equiv) in 5 mL of ethyl acetate was added IBX (301 mg, 1.08 mmol, 6 equiv). The mixture was heated at 80 °C for 16 h. The reaction was filtered and the filtrate was concentrated under vacuum. The crude product was purified by flash chromatography ($CH_2Cl_2$/MeOH, 99.5:0.5) to afford **8** as a colorless oil (0.054 g, 76%); $[\alpha]_D^{22}$ −123 (*c* 0.6,

$CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 1.62 (dt, $J$=3.0, 13.0 Hz, 1H), 2.13 (d, $J$=13.0 Hz, 1H), 2.3–2.4 (m, 2H), 2.46 (dd, $J$=3.0, 11.0 Hz, 1H), 2.88 (d, $J$=11.0 Hz, 1H), 3.02 (s, 1H), 3.14 (d, $J$=10.0 Hz, 1H), 3.45 and 3.55 (AB, $J_{AB}$=14.0 Hz, 2H, $CH_2$Bn), 5.90 (s, 1H, H-6α), 6.03 (d, $J$=8.0 Hz, 1H, H-11), 6.49 (d, $J$=9.0 Hz, 1H, H-9), 7.0–7.1 (m, 2H), 7.2–7.3 (m, 3H), 7.3–7.4 (m, 1H), 7.4–7.5 (m, 2H), 7.5–7.6 (m, 1H), 8.06 (d, $J$=8.0 Hz, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 23.0, 30.7, 35.2, 59.7, 59.9, 62.0, 62.6, 104.9, 116.8, 127.2, 128.3, 128.4, 128.6, 128.9, 133.3, 135.0, 137.9, 139.5, 151.7, 162.9; IR (NaCl, $cm^{-1}$) 2939, 2800, 1691, 1650, 1544, 1219, 1142, 908, 798, 723, 693; HRMS (ESI) calcd for $C_{25}H_{25}N_2O_2$ 385.1916, found 385.1923.

### 4.4. Debenzylation of 3a

**4.4.1. (+)-(1*R*,5*S*,6*S*)-6-Methyl-cytisine 10.** To a solution of *N*-benzyl-6-methyl-cytisine **3a** (50 mg, 0.17 mmol, 1 equiv) in 1 mL of anhydrous dichloroethane was slowly added α-chloroethyl chloroformate (75 μL, 0.68 mmol, 4 equiv) under nitrogen. The reaction was heated to 80 °C during 24 h. After evaporation of the solvent, the residue was dissolved in 2 mL of methanol and the solution was refluxed for 2 h. Methanol was evaporated and ammonia was added until basic pH. After extraction four times with $CH_2Cl_2$ and evaporation of the solvent, the crude product was purified by flash chromatography ($CH_2Cl_2$/MeOH, 9:1+1% $NH_3$ 28%) affording **10** as a colorless oil (25 mg, 72%); $[\alpha]_D^{22}$ +107 (*c* 0.96, $CHCl_3$); $^1H$ ($CDCl_3$) $\delta$ 1.38 (d, $J$=6.3 Hz, 3H), 1.60 (br s, 1H), 1.91 (d, $J$=6.1 Hz, 2H), 2.24 (d, $J$=12.7 Hz, 1H), 2.8–2.9 (m, 2H), 3.1–3.2 (m, 2H), 4.79 (q, $J$=6.1 Hz, 1H, H-6α), 5.99 (dd, $J$=1.0, 6.8 Hz, 1H, H-11), 6.4 (dd, $J$=1.0, 9.0 Hz, 1H, H-9), 7.26 (dd, $J$=6.8, 9.0 Hz, 1H, H-10); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.7, 22.9, 33.6, 35.1, 51.1, 54.3, 58.5, 106.0, 118.2, 138.9, 149.0, 163; IR (NaCl, $cm^{-1}$) 2944, 2800, 1650, 1548; MS (EI) *m*/*z* (%) 204 ($M^+$, 29), 46 (15), 109 (16), 44 (100).

## Acknowledgements

We gratefully acknowledge the CNRS (Centre National de la Recherche Scientifique), the Région Basse-Normandie for a fellowship to N.H., PunchOrga Network (Pôle Universitaire Normand de Chimie Organique), the Ministère de l'Education Nationale de l'Enseignement Supérieur et de la Recherche, and the European Union (FEDER funding) for financial support.

## References and notes

1. Dale, H. H.; Laidlaw, P. P. *J. Pharmacol. Exp. Ther.* **1912**, *3*, 205–221.
2. (a) Pabreza, L. A.; Dhawan, S.; Kellar, K. J. *Mol. Pharmacol.* **1991**, *39*, 9–12; (b) Heinemann, S. F.; Papke, R. L. *Mol. Pharmacol.* **1994**, *45*, 142–149; (c) Glennon, R. A.; Dukat, M. *Med. Chem. Res.* **1996**, *6*, 465–486; (d) Ferger, B.; Spratt, C.; Teismann, P.; Seitz, G.; Kuschinsky, K. *Eur. J. Pharmacol.* **1998**, *360*, 155–163.
3. (a) O'Neill, B. T. PCT Int. Appl. WO98 18,798, 1998; *Chem. Abstr.* **1998**, *119*, 4774k; (b) Canu Boido, C.; Sparatore, F. *Farmaco* **1999**, *54*, 438–451; (c) Imming, P.; Klaperski, P.; Stubbs, M. T.; Seitz, G.; Gündisch, D. *Eur. J. Med. Chem.* **2001**, *36*, 375–388.
4. Chellappan, S. K.; Xiao, Y.; Tueckmantel, W.; Kellar, K. J.; Kozikowski, A. P. *J. Med. Chem.* **2006**, *49*, 2673–2676.
5. Khisamutdinova, R. Y.; Yarmukhamedov, N. N.; Gabdrakhmanova, S. F.; Karachurina, L. T.; Sapozhnikova, T. A.; Baibulatova, N. Z.; Baschenko, N. Zh.; Zarudii, F. S. *Pharm. Chem. J.* (*Translation of Khimiko-Farmatsevticheskii Zhurnal*) **2004**, *38*, 311–313; *Chem. Abstr.* **2004**, *142*, 411207.
6. Bakbardina, O. V.; Rakhimzhanova, N. Z.; Gazalieva, M. A.; Fazyov, S. D.; Baimagambetov, E. Z. *Russ. J. Appl. Chem.* **2006**, *79*, 504–505.
7. (a) Nicolotti, O.; Canu Boido, C.; Sparatore, F.; Carotti, A. *Farmaco* **2002**, *57*, 469–478; (b) Canu Boido, C.; Tasso, B.; Boido, V.; Sparatore, F. *Farmaco* **2003**, *58*, 265–277.
8. Valette, H.; Bottlaender, M.; Dollé, F.; Dolci, L.; Syrota, A.; Crouzel, C. *Nucl. Med. Commun.* **1997**, *18*, 164.
9. Marrière, E.; Rouden, J.; Tadino, V.; Lasne, M.-C. *Org. Lett.* **2000**, *2*, 1121–1124.
10. Roger, G.; Lagnel, B.; Rouden, J.; Besret, L.; Valette, H.; Demphel, S.; Gopisetti, J.; Coulon, C.; Ottaviani, M.; Wrenn, L. A.; Letchworth, S. R.; Bohme, G. A.; Benavides, J.; Lasne, M.-C.; Bottlaender, A.; Dollé, F. *Bioorg. Med. Chem.* **2003**, *11*, 5333–5343.
11. (a) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870–11871; (b) Hermet, J.-P. R.; Porter, D. W.; Dearden, M. J.; Harrison, J. R.; Koplin, T.; O'Brien, P.; Parmene, J.; Tyurin, V.; Whitwood, A. C.; Gilday, J.; Smith, N. M. *Org. Biomol. Chem.* **2003**, *1*, 3977–3988; (c) Dearden, M. J.; McGrath, M. J.; O'Brien, P. *J. Org. Chem.* **2004**, *69*, 5789–5792; (d) Genet, C.; McGrath, M. J.; O'Brien, P. *Org. Biomol. Chem.* **2006**, *4*, 1376–1382; (e) O'Brien, P.; Wiberg, K. B.; Bailey, W. F.; Hermet, J.-P. R.; McGrath, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15480–15489.
12. Wilkinson, J. A.; Rossington, S. B.; Ducki, S.; Leonard, J.; Hussain, N. *Tetrahedron* **2006**, *62*, 1833–1844.
13. (a) Johansson, M. J.; Schwartz, L.; Amedjkouh, M.; Kann, N. C. *Tetrahedron: Asymmetry* **2004**, *15*, 3531–3538; (b) Johansson, M. J.; Schwartz, L. O.; Amedjkouh, M.; Kann, N. C. *Eur. J. Org. Chem.* **2004**, 894–1896.
14. Turdybekov, D. M.; Fazylov, S. D.; Turdybekov, K. M.; Gazaliev, A. M.; Zhivotova, T. S. *Russ. J. Org. Chem.* **2004**, *40*, 719–722.
15. Kozikowski, Alan P.; Musachio, John L.; Kellar, Kenneth J.; Xiao, Yingxian; Wei, Zhi-Liang. PCT Int. Appl. WO 2004-US18340 20040609, 2005; *Chem. Abstr.* **2004**, *142*, 114316.
16. Barlow, R. B.; McLeod, L. J. *J. Pharmacol.* **1969**, *35*, 161–174.
17. Slater, Y. E.; Houlihan, L. M.; Maskell, P. D.; Exley, R.; Bermudez, I.; Lukas, R. J.; Valdivia, A. C.; Cassels, B. K. *Neuropharmacology* **2003**, *44*, 503–515.
18. Fitch, R. W.; Kaneko, Y.; Klaperski, P.; Daly, J. W.; Seitz, G.; Gündisch, D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1221–1224.
19. Abin-Carriquiry, J. A.; Voutilainen, M. H.; Barik, J.; Cassels, B. K.; Iturriaga-Vasquez, P.; Bermudez, I.; Durand, C.; Dajas, F.; Wonnacott, S. *Eur. J. Pharmacol.* **2006**, *536*, 1–11.
20. O'Neill, B. T.; Yohannes, D.; Bundesmann, M. W.; Arnold, E. P. *Org. Lett.* **2000**, *2*, 4201–4204.
21. Rouden, J.; Ragot, A.; Gouault, S.; Cahard, D.; Plaquevent, J.-C.; Lasne, M.-C. *Tetrahedron: Asymmetry* **2002**, *13*, 1299–1305.

22. Katritzky, A. R.; Arrowsmith, J.; Grzeskowiak, N. E.; Salgado, H. J.; Bahari, Z. B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 143–151.
23. (a) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155–6157; (b) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495–498.
24. Katritzky, A. R.; Grzeskowiak, N. E.; Salgado, H. J.; Bin Bahari, Z. *Tetrahedron Lett.* **1980**, *21*, 4451–4454.
25. Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195–196.
26. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.
27. More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001–3003.
28. Olofson, R. A.; Martz, J. T.; Senet, J. P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081–2082.
29. Honda, T.; Takahashi, R.; Namiki, H. *J. Org. Chem.* **2005**, *70*, 499–504.