Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1299–1305

TETRAHEDRON: *ASYMMETRY*

Regio- and diastereoselective functionalization of (–)-cytisine: an unusual *N–C* acyl migration

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Received 22 May 2002; accepted 6 June 2002

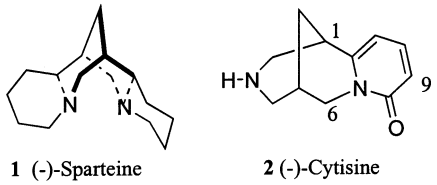
Abstract—In order to test (–)-cytisine as a potential chiral inductor, *N*-propionyl cytisine was treated with LDA and then with benzyl bromide. Instead of the expected α-benzyl substituted propionamide, (–)-*N*-benzyl 6α-propionyl cytisine was formed, arising from an unusual diastereoselective nitrogen to carbon acyl migration. Using LDA in the presence of an excess of LiCl, the 6-substituted cytisine was isolated in yields of up to 79%. The efficiency of the *N–C* acyl transfer was shown to be dependent on the nature of the *N*-acyl group. Complete epimerization of the newly created stereocenter was observed under basic conditions. This methodology allows the stereoelective functionalization of the C-6 position of cytisine, an important agonist of nicotinic receptors.

1. Introduction

The lupin alkaloids are found in a wide variety of plants, especially within the leguminosae family.[1] Most of the compounds belonging to this rather large group of alkaloids contain an indolizidine nucleus and the tetracyclic (–)-sparteine **1** is probably the most well known member of this group. Because of its commercial availability and low cost in enantiomerically pure form, the diamine **1** has received considerable attention. It has been used as a chiral bidentate ligand in asymmetric reactions such as deprotonation,[2] enantioselective addition of organolithium[3] and Grignard reagents,[4] carbolithiation of alkenes,[5] polymerization of methacrylate esters[6] and palladium-catalyzed allylic alkylation[7] and oxidation protocols.[8]

(–)-Cytisine **2**, another lupin alkaloid, was isolated more than 140 years ago[9] and its structure was determined with certainty in 1932.[10] It shows high affinity and selectivity for the $\alpha_4\beta_2$ nicotinic acetylcholine receptors (nAChRs) of the central nervous system.[11] Because there is accumulating evidence that neuronal nAChRs are involved in various physiological effects of nicotine and in several pathologies such as Alzheimer's and Parkinson's diseases, cytisine **2** became an important probe for studying nAChRs. In continuation of our interest in studying neurotransmission using positron emission tomography,[12] we recently reported a formal synthesis of cytisine,[13] the preparation of several cytisine derivatives and the radiolabelling of one of them (Fig. 1).[14]

Due to the large amounts of cytisine needed for this synthetic work, we developed an easy method for extracting cytisine from readily available natural sources. This chiral alkaloid, which, with its half cage-like structure, shows obvious similarities to sparteine **1**, has the advantage of bearing a secondary amine functionality and a pyridone ring, both of which can be involved in metal complexation. Having in hand multigram quantities of this alkaloid, we decided to test cytisine as a chiral auxiliary.



1 (-)-Sparteine **2** (-)-Cytisine

Figure 1.

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PII: S0957-4166(02)00271-9

2. Results and discussion

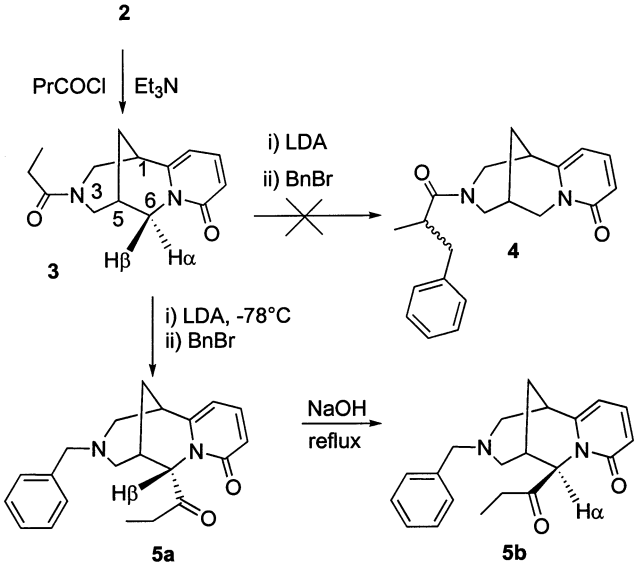
We chose the alkylation reaction of an amide enolate to evaluate the chiral induction properties of cytisine. The secondary amine function of cytisine was readily acylated with propionyl chloride in the presence of triethylamine to afford the amide **3**. Subsequent deprotonation of **3** with 1.1 equiv. of lithium diisopropylamide (LDA) in THF at −78°C followed by the addition of 2 equiv. of benzyl bromide led mainly to the recovery of starting material (78%) along with 20% of a new compound (Scheme 1).

Whereas the molecular mass (MW = 336) matched the deprotonated-benzylated product of this new compound, the ^{1}H NMR spectrum presented three interesting features: the methylene signal of the benzyl group appeared as two superimposed AB quartets (δ_A: 3.24 and δ_B: 3.57 ppm, J: 13.2 Hz) with no small coupling. The resonance of the methyl group in the propionyl chain is seen as two triplets at 0.92 and 1.14 ppm. This suggests that no substitution occurred at the α-position to the carbonyl group and that the compound exists as a mixture of two conformers (see[15] for conformers in cytisine). This latter hypothesis was confirmed by recording the ^{1}H NMR spectrum in $CDCl_3$ at different temperatures. At 50°C, partial coalescence of the methyl triplets was observed, whereas the methylene signal of the benzyl group is seen as a single AB quartet. Finally only one proton appears as two doublets (4.76 and 5.03 ppm, two conformers) in the region (4.5–5 ppm), which is characteristic of the resonance of the 6-protons in cytisine and cytisine derivatives. Even though the ^{13}C NMR spectrum is complicated by the presence of both conformers, the chemical shift observed at 209.3 ppm is typical of a ketone function and not of an amide (in the starting material the chemical shift of the amide carbonyl group is observed at 172.8 ppm). From these spectral data we suggest the structure **5a** with the propionyl group now positioned on the C_6 carbon of cytisine and the benzyl group on the nitrogen N_3. The two conformers arise from the two possible orientations of the benzyl group. When compound **5a** was heated in refluxing aqueous sodium hydroxide, the ^{1}H NMR spectrum of the resulting product showed that **5a** underwent isomerization to the β-isomer **5b**. Indeed, only one conformer was observed in the ^{1}H NMR spectrum, with the signal for the H_6 proton occurring as a singlet at 4.93 ppm. Mass spectroscopy and ^{13}C NMR data are in good agreement with the diastereoisomeric structure **5b**.

The absolute configuration of the newly formed C-6 stereogenic center was assigned by comparing the observed vicinal coupling constants between protons 5 and 6 and those calculated from molecular modelling simulations (AM1, MacSpartan®). After minimization of the structures, a dihedral angle H_5–C–C–H_6 of 44° was measured for **5a** and 74° for **5b** (Fig. 2). From these dihedral angles, the expected coupling constants J_{H5-H6} would be 4.12 and 0.36 Hz, respectively.[16] In the ^{1}H NMR spectrum of the compound directly generated by the LDA reaction, the coupling constants are $^3J_{H6-H5}$ = 6.0 and 6.6 Hz for the two conformers and $^3J_{H6-H5}$ = 0 Hz on the ^{1}H NMR spectrum of the compound obtained from the NaOH epimerization reaction.

This discrepancy in one case (the measured coupling is somewhat larger than predicted) is also observed on cytisine itself between H_5 and $H_{6\beta}$.[17] Factors other than simple geometry can modulate vicinal proton couplings especially in cyclic bridged molecules like cytisine, and one has to take this into account when using the equation, as originally discussed by Karplus.[18] Therefore by comparing the ^{1}H NMR spectra of compounds **5a** and **5b** we can deduce the absolute configuration for both compounds at C_6: $H_{6\beta}$ for **5a** with a pseudo-axial propionyl chain and $H_{6\alpha}$ for **5b** with the propionyl chain being in a pseudo-equatorial disposition. This is in good agreement with the experimental data: the more stable epimer, which should have the propionyl chain in the more stable pseudo-equatorial position, is isolated when compound **5a** is treated with NaOH under reflux.

A mechanistic proposal for the formation of **5a** is shown in Scheme 2. An initially formed pyramidal carbanion at the position α to the pyridone ring might



Scheme 1.

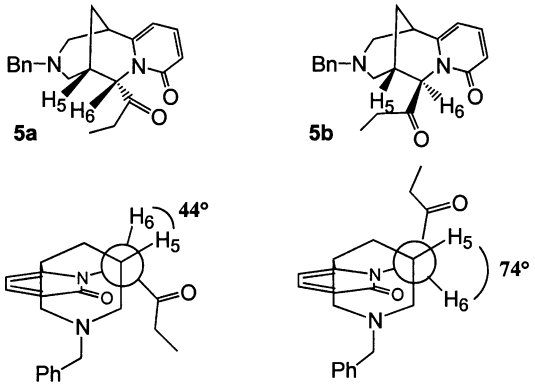
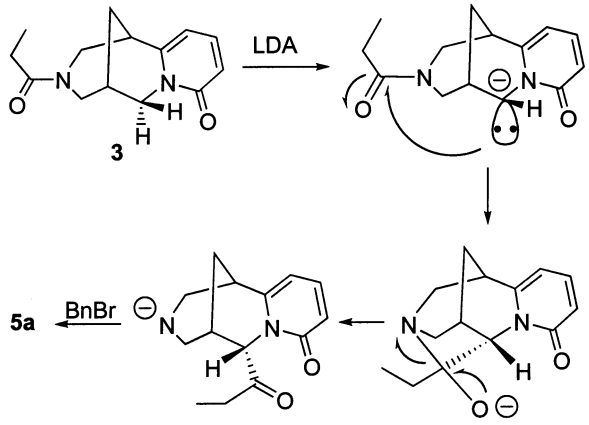


Figure 2.

attack the carbon atom of the amide function to give a strained five-membered ring. This intermediate would then be stabilized by transferring the propionyl group to the 6-position. The lithiated amine would then be alkylated by benzyl bromide to afford the *N*-benzyl-6-propionylcytisine **5a**. Such lithiation α to the nitrogen of an *N*-alkyl pyridone is already documented[19] and is directed by the pyridone carbonyl. We have found only a few reports in the literature of this unusual kind of nitrogen to carbon acyl migration.[20]

Table 1 shows the main results for the optimization of the acyl transfer alkylation reaction. Increasing the amount of LDA or adding a co-solvent[20b] (DMPU: *N*,*N*′-dimethylpropyleneurea) did not improve the yield of **5a** significantly. However, the addition of 5–6 molar equiv. of LiCl to the reaction mixture before deprotonation led to a complete conversion and a 75% isolated yield of the 'rearranged' product **5a**. The influence of lithium salts on lithium aggregates[21] and on the rates of enolate alkylation reactions[22] is well documented.

We next examined the acyl migration reaction of various cytisine amide derivatives. For this purpose other acyl groups were appended to cytisine according to the conditions described in Scheme 1 for compound **3** (R^1COCl, Et_3N). *N*-Acyl cytisine derivatives **6**–**10** were isolated with non-optimized yields ranging from 49 to 91% (see Section 4). Then the deprotonation–acyl transfer reaction and subsequent quench with three types of electrophile, water, methyl iodide or benzyl bromide, afforded, respectively, the free secondary amine, methyl and benzyl amine 6-substituted cytisine. The results are summarized in Table 2.



Scheme 2.

Table 1. Optimization of the conditions for the reaction **3**→**5a**

Entry	LDA[a] (equiv.)	Additives	S.M. **3** (%)[b]	Yield **5a** (%)[c]
1	1.1	None	78	22
2	2.1	none	60	37
3	2.1	DMPU (10%)	60	35
4	2.1	LiCl (5–6 equiv.)	0	75

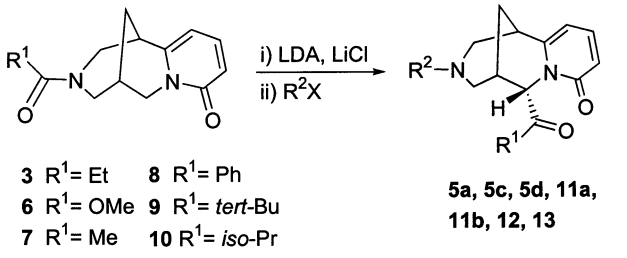
[a] Conditions: LDA, −78°C, 30 min, then BnBr (3 equiv.), −60°C, 3 h.
[b] S.M.: starting material; yield of recovered **3**.
[c] Yield of isolated product **5a**.

Alkylcarbonyl or branched alkylcarbonyl groups were transferred with average to good yields (entries 1–3, 6 and 7). Surprisingly, the *N*-acetyl cytisine **7** and *N*-benzoyl cytisine **8** gave no 'rearranged' product (data not shown in Table 2). In those two cases the reaction gave rise to an inseparable mixture of compounds. The migration of the methoxycarbonyl group (entries 4 and 5) was an interesting result, mainly because an acetyl group has better migratory aptitude than a carbalkoxy group under thermal conditions.[23] After quenching with benzyl bromide or water, cytisine derivatives **11a** and **11b** bearing an ester group at the C-6 position were isolated in 65 and 79% yields (Scheme 3). As for the *N*-benzyl-6-propionyl cytisine **5a**, the *N*-benzyl-6α-methoxycarbonyl cytisine **11a** was completely epimerized to its thermodynamically more stable 6β-derivative **11c** under basic non-hydrolytic conditions (isolated yield: 57%, Scheme 4). Compounds **11a**, **11b** and **11c** are potential γ-amino-acids with a new type of geometry.

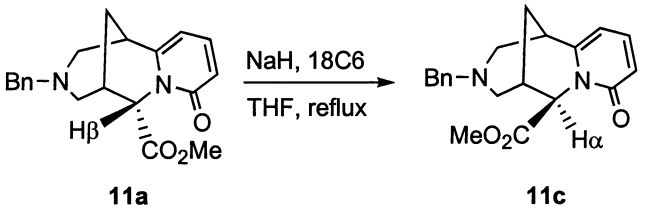
Table 2. LDA/LiCl deprotonation of acyl cytisine, acyl migration then electrophile quenching[a]

Entry	Product	R^1	R^2	Yield[b] (%)
1	**5a**	Et	Bn	75
2	**5c**	Et	Me	51
3	**5d**	Et	H	70
4	**11a**	MeO	Bn	65
5	**11b**	MeO	H	79
6	**12**	*tert*-Bu	H	57
7	**13**	*iso*-Pr	H	65

[a] The electrophiles used were: R^2 = Bn, benzyl bromide; R^2 = Me, methyl iodide, R^2 = H, water.
[b] Isolated yield.



Scheme 3.



Scheme 4.

3. Conclusion

To summarize, this study demonstrates the possibility of functionalizing (−)-cytisine **2** on the 6-position via an unusual type of nitrogen to carbon acyl transfer. These acyl migrations are completely diastereoselective, even though an excess of LDA is used and the resulting carbonyl group is appended in the less stable pseudo-axial position. The total epimerization of the 6-α-isomer to the more stable 6-β-compound was demonstrated in two cases.

The newly synthesized cytisine derivatives are potential novel ligands for nACh receptors.

4. Experimental

4.1. General methods and starting materials

The reactions were carried out under argon in flasks dried in an oven at 110°C. THF was distilled from sodium/benzophenone directly prior to use. Lithium chloride was dried with a heat gun under high vacuum. Diisopropylamine and triethylamine were distilled from calcium hydride. Methyl iodide and benzyl bromide were distilled before use. Other chemicals were used as received. 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 block 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 spectra were taken on a Nermag R10 apparatus and are reported as fragmentation in m/z with relative intensities (%) in parentheses. NMR spectra were recorded on a Bruker 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 ISMRA, 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.[14]

4.2. General procedure for the acylation of cytisine 2

To a mixture of cytisine **2** (1 g, 5.26 mmol) and triethylamine (1.467 mL, 10.5 mmol) in CH_2Cl_2 (20 mL) was added dropwise acid chloride (7.9 mmol) at 0°C. After stirring overnight at rt, the solvent was evaporated and the crude product was taken into ethyl acetate. Triethylamine hydrochloride precipitated and was removed by filtration. After evaporation of the solvent, the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 95:5) to give pure *N*-acylcytisine.

4.2.1. Data for *N*-propionyl cytisine 3. Isolated as a white solid after flash chromatography (1.185 g, 96%). Mp 141–142°C (acetone–Et_2O). $[\alpha]_D^{20}=-241$ (c 1, $CHCl_3$). ^{1}H NMR δ ($CDCl_3$, two conformers): 0.89 and 1.02 (t, 3H, $J=7.37$ Hz), 1.85–1.98 (m, 1H), 2.01 (broad s, 2H), 2.23–2.31 (m, 1H), 2.53 (broad s, 1H), 2.77–2.87 (m, 1H), 3.08 (broad s, 1H), 3.30–3.38 (m, 1H), 3.81–4.00 (m, 1H), 4.00–4.17 (m, 1H), 4.69 and 4.80 (d, 1H, $J=13$ Hz), 6.06 (dd, 1H, $J=3.1$ Hz, $J=6.6$ Hz), 6.44 (dd, 1H, $J=3.1$ Hz, $J=9.0$ Hz), 7.27 (dd, 1H, $J=6.6$ Hz, $J=9.0$ Hz). ^{13}C NMR δ ($CDCl_3$, two conformers): 8.9, 25.5, 25.8, 27.1 and 27.2, 34.1 and 34.7, 47.4 and 48.4, 48.6, 51.2 and 52.4, 104.7 and 105.6, 116.8 and 117.3, 138.3 and 138.9, 148.4, 162.9, 172.8. IR (KBr, cm^{-1}): 2978, 2942, 2876, 1644, 1610, 1544, 1472, 1446, 1362, 1228, 1156, 1058, 810. MS (EI) m/z: 246 (M^+, 97), 146 (100). HRMS (EI) calcd for $C_{14}H_{18}N_2O_2$ 246.1368, found 246.1361.

4.2.2. Data for *N*-methoxycarbonyl cytisine 6. Isolated as a pale yellow solid after flash chromatography (1.187 g, 91% yield). Mp 108°C. $[\alpha]_D^{20}=-209$ (c 0.77, $CHCl_3$). ^{1}H NMR δ ($CDCl_3$): 1.91–2.05 (m, 2H), 2.48 (broad s, 1H), 3.06 (broad s, 2H), 3.11 (broad s, 1H), 3.55 (s, 3H), 3.85 (dd, H-6β, $J=15.7$ Hz, $J=6.6$ Hz), 4.14 (d, H-6α, $J=15.7$ Hz), 4.22 (broad s, 2H), 6.07 (d, 1H, $J=6.7$ Hz), 6.42 (dd, 1H, $J=9.1$ Hz, $J=1.4$ Hz), 7.29 (dd, 1H, $J=6.7$ Hz, $J=9.1$ Hz). ^{13}C NMR δ ($CDCl_3$): 25.1, 26.6, 33.8, 48.3, 49.6, 50.5, 52.1, 105.0, 116.5, 138.3, 148.4, 155.5, 162.8. IR (NaCl, cm^{-1}): 2994, 2946, 2864, 1696, 1650, 1546, 1448, 1410, 1346, 1264, 1238, 1188, 1158, 1124, 802, 734. MS (EI) m/z: 248 (M^+, 13), 146 (100). Anal. calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.89; N, 11.28; O, 18.94. Found: C, 62.65; H, 6.74; N, 11.15; O, 19.46%.

4.2.3. Data for *N*-acetyl cytisine 7. Isolated as a white solid after flash chromatography (1.05 g, 86% yield). Mp 212°C. $[\alpha]_D^{20}=-200$ (c 1, $CHCl_3$). ^{1}H NMR δ ($CDCl_3$, two conformers): 1.67 (s, 2H), 1.98 (broad s, 3H), 2.46 (broad s, 1H), 2.76 (m, 1H), 3.03 (s, 1H), 3.34 (m, 1H, one conformer), 3.72–3.89 (m, 2H, 1 conformer, H-6α, two conformers), 4.01 and 4.07 (d, 1H, $J=10.1$ Hz, H-6β), 4.60 and 4.72 (d, 1H, $J=13.1$ Hz), 6.00 (d, 1H, $J=6.6$ Hz), 6.36 (m, 1H), 7.24 (m, 1H). ^{13}C NMR δ ($CDCl_3$, two conformers): 19.4 and 20.0, 24.7 and 24.8, 26.0 and 26.3, 33.0 and 33.7, 46.2 and 47.1, 47.5, 51.2 and 52.4, 103.5 and 104.6, 116.0 and 116.5, 137.1 and 137.8, 147.0 and 147.2, 161.9 and 162.1, 168.3 and 168.4. IR (KBr, cm^{-1}): 1634, 1616, 1546, 1452, 1424, 1360, 1238. MS (IE) m/z: 232 (M^+, 100), 190 (25), 147 (87). HRMS (EI) calcd for $C_{13}H_{16}N_2O_2$ 232.1212, found 232.1216.

4.2.4. Data for *N*-benzoyl cytisine 8. Isolated as a white solid after flash chromatography (1.33 g, 86% yield). Mp 193°C. $[\alpha]_D^{20}=-277$ (c 1.02, $CHCl_3$). ^{1}H NMR δ ($CDCl_3$): 1.99 (s, 2H), 2.5 (broad s, 1H), 3.12 (broad s, 3H), 3.85 (broad s, 1H), 4.22 (broad s, 1H), 4.8 (broad s, 1H), 5.95 (broad s, 1H), 6.55 (d, 1H, $J=9$ Hz), 6.9 (broad s, 1H), 7.30 (s, 1H). All signals are poorly defined due to the presence of rotamers. ^{13}C NMR δ ($CDCl_3$): 26.6, 28.0, 35.2, 49.2, 106.2, 118.0, 126.9,

128.7, 129.9, 135.6, 139.3, 148.8, 163.7, 171.6. IR (KBr, cm^{-1}): 2936, 1640, 1614, 1574, 1536, 1440. MS (EI) m/z: 294 (M^+, 19), 189 (17), 146 (31), 105 (100), 77 (49). Anal. calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.24; H, 6.29; N, 9.55%.

4.2.5. Data for *N*-pivaloyl cytisine 9. Isolated as a white solid after flash chromatography (1.167 g, 81% yield). Mp 163°C. $[\alpha]_D^{20}=-261$ (c 0.95, $CHCl_3$). ^1H NMR δ ($CDCl_3$): 1.09 (s, 9H), 2.01 (m, 2H), 2.5 (broad s, 1H), 3.04 (d, 1H, $J=3.3$ Hz), 3.13 (m, 2H), 3.82 (dd, H-6β, $J=6.4$, $J=15.7$ Hz), 4.19 (d, H-6α, $J=15.7$ Hz), 4.44 (d, 1H, $J=12.7$ Hz), 4.61 (d, 1H, $J=13.1$ Hz), 6.05 (dd, 1H, $J=1.1$ Hz, $J=6.8$ Hz), 6.43 (dd, 1H, $J=1.1$ Hz, $J=9.0$ Hz), 7.26 (dd, 1H, $J=6.8$ Hz, $J=9.0$ Hz). ^{13}C NMR δ ($CDCl_3$): 26.9, 28.0, 28.5 ($3CH_3$), 35.3, 39.2, 49.1, 50.8, 52.3, 53.8, 105.9, 117.9, 139.0, 148.9, 163.6, 118. IR (KBr, cm^{-1}): 2966, 1928, 2858, 1660, 1616, 1578, 1546, 1476, 1420, 1364, 1342, 1144. MS (EI) m/z: 274 (M^+, 18), 189 (14), 160 (21), 147 (100), 109 (28), 83 (45), 55 (45), 42 (65). Anal. calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.93; H, 8.18; N, 10.39%.

4.2.6. Data for *N*-(2-methylpropionyl)cytisine 10. Isolated as a white solid after flash chromatography (0.672 g, 49% yield). Mp 143–144°C. $[\alpha]_D^{20}=-168$ (c 0.28, $CHCl_3$). ^1H NMR δ ($CDCl_3$): 0.67 (s, 1H), 1.00 (d, 6H, $J=6.5$ Hz), 2.03 (s, 2H), 2.53 (broad s, 1H), 2.81 (m, 1H), 3.09 (s, 1H), 3.37 (d, 1H, $J=10.9$ Hz), 3.83 (dd, H-6β, $J=6.4$ Hz, $J=15.7$ Hz), 4.1 (m, 2H), 4.77 (m, 1H), 6.06 (d, 1H, $J=6.8$ Hz), 6.42 (d, 1H, $J=9.0$ Hz), 7.27 (dd, 1H, $J=6.8$ Hz, $J=9.0$ Hz). ^{13}C NMR δ ($CDCl_3$): 19.04, 26.28, 27.48, 29.50, 35.04, 48.83, 52.51, 104.98, 117.17, 117.26, 138.41, 148.51, 163.17, 176.38. IR (KBr, cm^{-1}): 2964, 2926, 2868, 1646, 1606, 1574, 1544, 1476, 1446. MS (EI) m/z: 260 (M^+, 21), 190 (20), 147 (40), 109 (20), 82 (30), 43 (100). HRMS (EI) calcd for $C_{15}H_{20}N_2O_2$ 260.1524, found 260.1508.

4.3. General procedure for the acyl transfer

To a mixture of lithium chloride (0.5 g, 11.79 mmol) and diisopropylamine (0.487 mL, 3.41 mmol) was added dropwise butyllithium (1.6 M solution in hexanes, 2.12 mL, 3.41 mmol) at −20°C under argon. After stirring 10 min 5 mL of THF was added and the temperature was cooled to −78°C. Then a solution of the acyl cytisine derivative (compounds **3** and **6**–**10**) (1.62 mmol) in THF (10 mL) was transferred via cannula to the LDA solution at −78°C. After stirring for 30 min at −78°C, the electrophile (4.87 mmol, 1.43 equiv.) was added and the reaction was stirred for a further 3 h at −78°C. The reaction was quenched with a saturated aqueous ammonium chloride solution and then ammonium hydroxide (28% aqueous solution) was added to basify the medium. Extraction of the aqueous phase was carried out with CH_2Cl_2 several times and the combined organic layers were dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by flash chromatography to give the pure rearranged product.

4.3.1. Data for *N*-benzyl-6α-propionyl cytisine 5a. The electrophile added was benzyl bromide. A white solid was obtained after flash chromatography (CH_2Cl_2/MeOH, 95:5) (0.408 g, 75% yield). $[\alpha]_D^{20}=-284$ (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$, two conformers): 0.92 and 1.14 (2t, 3H, $J=7.1$ Hz and 6.4 Hz), 1.85 (broad s, 2H), 2.17–3.02 (m, 8H), AB system δ_A: 3.24 and δ_B: 3.57 ppm (two superimposed AB quartets due to the two conformers, J: 13.2 Hz), 4.76 and 5.03 (2d, H-6β, $J=6.6$ Hz and 6.0 Hz), 5.87 and 6.00 (2d, 1H, $J=6.6$ Hz and 6.1 Hz), 6.42–6.50 (m, 1H), 7.05–7.38 (m, 6H). ^{13}C NMR δ ($CDCl_3$, two conformers): 7.3, 27.0, 29.7 and 31.8, 30.1 and 33.4, 34.9 and 35.3, 55.4 and 55.9, 57.4 and 58.5, 61.5 and 62.1, 65.2 and 67.4, 104.6 and 105.1, 116.5, 126.3, 126.9, 127.5, 128.0, 128.5, 136.1 and 137.5, 138.5 and 139.3, 150.9 and 151.1, 162.8 and 163.7, 209.3. MS (EI) m/z: 336 (M^+, 9), 91 (100). IR (KBr, cm^{-1}): 2936, 2802, 1706, 1654, 1568, 1546, 1454, 1346. HRMS (EI) calcd for $C_{21}H_{24}N_2O_2$ 336.1838, found 336.1835.

4.3.2. Data for *N*-methyl-6α-propionyl cytisine 5c. The electrophile added was methyl iodide. A white solid was obtained after flash chromatography (CH_2Cl_2/MeOH, 95:5) (0.215 g, 51% yield). Mp 164°C (Et_2O:MeOH). $[\alpha]_D^{20}=-333$ (c 1, $CHCl_3$). ^1H NMR δ ($CDCl_3$, two conformers): 1.01 and 1.19 (t and broad s, 3H, $J=6.7$ Hz), 1.82 (m, 2H), 2.05 (m, 1H), 2.10 (s, 3H), 2.33–2.67 (m, 5H), 2.98–3.02 (m, 2H), 4.76 and 4.97 (d and broad s, H-6β, $J=6.7$ Hz), 6.09 (d, 1H, $J=6.5$), 6.45 (d, 1H, $J=8.6$ Hz), 7.33–7.39 (m, 1H). ^{13}C NMR δ ($CDCl_3$, two conformers): 7.5, 26.7, 30.2, 31.8, 33.7, 35.7, 45.5, 57.1, 61.6, 65.4, 67.3, 105.2, 116.9, 139.4, 151.3, 163.9, 209.9. IR (KBr, cm^{-1}): 2970, 2928, 2798, 1708, 1654, 1572, 1548, 1454, 1142, 802. MS (EI) m/z: 260 (M^+, 15), 203 (100). Anal. calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 12.29; O, 10.76. Found: C, 69.29; H, 7.81; N, 12.32; O, 10.58%.

4.3.3. Data for 6α-propionyl cytisine 5d. The electrophile added was water as an aqueous ammonium chloride solution. A white solid was obtained after flash chromatography (CH_2Cl_2/MeOH, 93:7) (0.279 g, 70% yield). Mp 133°C (Et_2O:MeOH). $[\alpha]_D^{20}=-96$ (c 1, $CHCl_3$). ^1H NMR δ ($CDCl_3$): 1.20 (t, 3H, $J=7.2$ Hz), 1.85 (broad s, 1H), 1.95–2.15 (m, 2H), 2.43 (broad s, 1H), 2.48–2.64 (m, 1H), 2.80 (broad s, 2H), 2.90 (broad s, 1H), 2.96–3.06 (m, 1H), 3.09 (broad s, 2H), 5.00 (d, H-6β, $J=6.7$ Hz), 6.07 (dd, 1H, $J=6.8$ Hz, $J=1$ Hz), 6.44 (dd, 1H, $J=1$ Hz, $J=9.1$ Hz), 7.35 (dd, 1H, $J=6.8$ Hz, $J=9.1$ Hz). ^{13}C NMR δ ($CDCl_3$): 7.1, 26.9, 28.9, 33.9, 35.1, 48.8, 52.2, 65.0, 105.3, 116.6, 139.3, 150.7, 162.8, 206.4. IR (KBr, cm^{-1}): 3422, 2926, 2856, 2362, 1718, 1652, 1544, 1456, 1210, 1148, 802. MS (EI) m/z: 246 (M^+, 40), 146 (100). HRMS (EI) calcd for $C_{14}H_{18}N_2O_2$ 246.1368, found 246.1371.

4.3.4. Data for *N*-benzyl-6α-methoxycarbonyl cytisine 11a. The electrophile added was benzyl bromide. A viscous pale yellow oil was obtained after flash chromatography (CH_2Cl_2/MeOH, 95:5) (0.547 g, 65% yield). $[\alpha]_D^{20}=-318$ (c 1, $CHCl_3$). ^1H NMR δ ($CDCl_3$): 1.86–1.87 (m, 2H), 2.24 (d, 1H, $J=9.3$ Hz), 2.40 (d, 1H,

$J=10.3$ Hz), 2.74 (broad s, 2H), 2.85–2.90 (m, 2H), 3.27 (d, 1H, $J=13.3$ Hz), 3.49 (d, 1H, $J=13.3$ Hz), 3.57 (broad s, 1H), 3.72 (broad s, 2H), 4.90 (d, H-6β, $J=5.3$ Hz), 5.87 (d, 1H, $J=6.7$ Hz), 6.46 (dd, 1H, $J=1.4$ Hz, $J=9.1$ Hz), 7.15–7.23 (m, 5H), 7.28 (dd, 1H, $J=1.4$ Hz, $J=6.7$ Hz). ^{13}C NMR δ ($CDCl_3$, two conformers): 26.4, 30.2, 30.9, 34.9, 51.4, 56.1, 57.7, 60.2, 61.5, 104.5, 116.5, 126.4, 127.5, 128.0, 128.5, 134.0, 137.2, 138.6, 150.6, 163.0, 167.7, 170.5. IR (KBr, cm^{-1}): 2944, 2800, 2764, 1760, 1730, 1656, 1572, 1546, 1494, 1452, 1436, 1346, 1280, 1192, 1168, 1144, 800. MS (EI) m/z: 338 (M^+, 23), 84 (100). HRMS (EI) calcd for $C_{20}H_{22}N_2O_3$ 338.1630, found 338.1626.

4.3.5. Data for 6α-methoxycarbonyl cytisine 11b. The electrophile added was water as an aqueous ammonium chloride solution. A pale yellow solid was obtained after flash chromatography (CH_2Cl_2/MeOH, 93:7) (0.317 g, 79% yield). $[\alpha]_D^{20}=-151$ (c 1.12, $CHCl_3$). ^{1}H NMR δ ($CDCl_3$): 1.94–2.00 (m, 2H), 2.10 (dt, 1H, $J=2.9$ Hz, $J=13.0$ Hz), 2.49 (broad s, 1H), 2.89 (s, 3H), 3.10 (broad s, 2H), 3.73–3.85 (m, 3H), 4.86 (d, H-6β, $J=6.9$ Hz), 6.07 (dd, 1H, $J=1.2$ Hz, $J=6.9$ Hz), 6.47 (dd, 1H, $J=1.2$ Hz, $J=9.1$ Hz), 7.35 (dd, 1H, $J=9.1$ Hz, $J=6.9$ Hz). ^{13}C NMR δ ($CDCl_3$): 26.4, 29.2, 35.0, 49.0, 51.9, 52.1, 60.3, 105.2, 116.6, 139.2, 150.2, 163.0, 170.1. IR (NaCl, cm^{-1}): 3458, 3330, 3040, 2944, 2862, 1732, 1652, 1558, 1538, 1456, 1358, 1270, 1158, 1102, 1066, 800. MS (EI) m/z: 248 (M^+, 74), 216 (45), 189 (22), 174 (14), 160 (18), 146 (100). HRMS (EI) calcd for $C_{13}H_{16}N_2O_3$ 248.1161, found 248.1167.

4.3.6. Data for 6α-(2,2-dimethylpropionyl)cytisine 12. The electrophile added was water as an aqueous ammonium chloride solution. A pale yellow solid was obtained after flash chromatography (CH_2Cl_2/MeOH, 93:7) (0.253 g, 57% yield). Mp 193°C. $[\alpha]_D^{20}=-53$ (c 0.7, $CHCl_3$). ^{1}H NMR δ ($CDCl_3$): 1.37 (s, 9H), 1.94 (broad s, 1H), 2.01 (d, 1H, $J=2.7$ Hz), 2.12 (dt, 1H, $J=3$ Hz, $J=12.9$ Hz), 2.35 (broad s, 1H), 2.78 (dd, 1H, $J=2.2$ Hz, $J=14.4$ Hz), 2.88 (d, 2H, $J=2$ Hz), 3.11 (d, 2H, $J=2.2$ Hz), 5.34 (d, H-6β, $J=6.3$ Hz), 6.06 (dd, 1H, $J=1.1$ Hz, $J=7$ Hz), 6.43 (dd, 1H, $J=1.1$ Hz, $J=9$ Hz), 7.33 (dd, 1H, $J=7$ Hz, $J=9$ Hz). ^{13}C NMR δ ($CDCl_3$): 27.5, 27.9, 29.6, 35.4, 44.1, 49.4, 52.8, 61.9, 105.8, 117.10, 139.5, 151.4, 162.8, 211.8. IR (KBr, cm^{-1}): 2960, 2950, 2928, 1696, 1647, 1561, 1542. MS (EI) m/z: 274 (M^+, 23), 217 (95), 189 (57), 146 (30), 57 (51), 44 (88), 43 (57), 42 (100). HRMS (EI) calcd for $C_{16}H_{22}N_2O_2$ 274.1681, found 274.1677.

4.3.7. Data for 6α-(2-methylpropionyl)cytisine 13. The electrophile added was water as an aqueous ammonium chloride solution. A yellow viscous oil was obtained after flash chromatography (CH_2Cl_2/MeOH, 93:7) (0.274 g, of 65% yield). $[\alpha]_D^{20}=-52$ (c 0.75, $CHCl_3$). ^{1}H NMR δ ($CDCl_3$): 1.19 (d, 3H, $J=6.9$ Hz), 1.38 (d, 3H, $J=6.9$ Hz), 2.01 (broad s, 2H), 2.11 (dt, 1H, $J=2.9$ Hz, $J=12.9$ Hz), 2.46 (broad s, 1H), 2.081 (broad s, 2H), 2.89 (broad s, 1H), 3.02 (m, 1H), 3.09 (broad s, 2H), 5.12 (d, H-6β, $J=6.6$ Hz), 6.06 (dd, 1H, $J=1.2$ Hz, $J=6.6$ Hz), 6.42 (dd, 1H, $J=1.2$ Hz, $J=9$ Hz), 7.27 (dd, 1H, $J=6.6$ Hz, $J=9$ Hz). ^{13}C NMR δ ($CDCl_3$): 18.0, 19.4, 27.3, 29.6, 35.4, 39.9, 49.3, 52.5, 64.7, 105.7, 117.0, 139.5, 151.1, 163.1, 209.8. IR (NaCl, cm^{-1}): 2968, 2934, 2868, 1712, 1654, 1546. MS (EI) m/z: 260 (M^+, 100), 230 (10), 160 (15), 123 (25), 82 (15). HRMS (EI) calcd for $C_{15}H_{20}N_2O_2$ 260.1524, found 260.1503.

4.4. Isomerization of 6α to 6β cytisine acyl derivatives

4.4.1. Data for *N*-benzyl-6β-propionyl cytisine 5b. *N*-Benzyl-6α-propionyl cytisine **5a** (0.2 g, 0.59 mmol) was added to a 15% aqueous NaOH solution (10 mL). After heating the mixture under reflux overnight, the mixture was extracted three times with CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 95:5) to give the C-6 epimerized product as a colorless viscous oil (0.170 g, 85% yield). $[\alpha]_D^{20}=-228$ (c 1, $CHCl_3$). ^{1}H NMR δ ($CDCl_3$): 1.12 (t, 3H, $J=7.3$ Hz), 1.60 (dt, 1H, $J=3.0$ Hz, $J=12.9$ Hz), 1.99–2.05 (dt, 1H, $J=3.0$ Hz, $J=12.90$ Hz), 2.22 (broad s, 1H), 2.31 (dd, 1H, $J=1.9$ Hz, $J=10.7$ Hz), 2.45 (dd, 1H, $J=2.2$ Hz, $J=11.1$ Hz), 2.63 (dq, 1H, $J=7.3$ Hz, $J=18.0$ Hz), 2.89 (dq, 1H, $J=7.3$ Hz, $J=18.0$ Hz), 2.80–2.85 (m, 1H), 2.95–3.04 (m, 2H), 3.39 (d, 1H, $J=13.6$ Hz), 3.47 (d, 1H, $J=13.6$ Hz), 4.93 (s, H-6α), 5.97 (dd, 1H, $J=1.2$ Hz, $J=6.9$ Hz), 6.46 (dd, 1H, $J=1.2$ Hz, $J=9.0$ Hz), 6.95–6.99 (m, 2H), 7.16–7.22 (m, 3H), 7.31 (dd, 1H, $J=6.9$ Hz, $J=9.0$ Hz). ^{13}C NMR δ ($CDCl_3$): 7.4, 22.8, 29.8, 32.6, 34.9, 59.6, 59.8, 61.6, 65.9, 104.5, 116.3, 126.8, 127.9, 128.1, 137.7, 139.1, 151.2, 162.8, 206.7. IR (KBr, cm^{-1}): 2936, 2796, 1722, 1654, 1568, 1544, 1450, 1352, 1314, 1250, 1144, 1114, 800. MS (EI) m/z: 336 (M^+, 95), 279 (100), 146 (20), 91 (94). HRMS (EI) calcd for $C_{21}H_{24}N_2O_2$ 336.1838, found 336.1835.

4.4.2. Data for *N*-benzyl-6β-methoxycarbonyl cytisine 11c. *N*-Benzyl-6α-methoxycarbonyl cytisine **11a** (0.2 g, 0.59 mmol) was added to a solution of NaH (0.042 g, 1.77 mmol) in THF (10 mL) in the presence of a catalytic amount of 18-crown-6 (10 mol% wrt the cytisine derivative). After heating under reflux for 72 h, the mixture was quenched with water and extracted three times with CH_2Cl_2. The combined organic layers were dried over sodium sulfate, filtered and concentrated under vacuum. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 95:5) to give the C-6 epimerized product as a colorless viscous oil (0.115 g, 57% yield). $[\alpha]_D^{20}=-141$ (c 0.45, $CHCl_3$). ^{1}H NMR δ ($CDCl_3$): 1.67 (dt, 1H, $J=12.9$ Hz, $J=2.9$ Hz), 2.09 (broad d, 1H, $J=12.9$ Hz), 2.31 (dd, 1H, $J=10.7$ Hz, $J=1.9$ Hz), 2.42 (dd, 1H, $J=11.1$ Hz, $J=2.4$ Hz), 2.45 (broad s, 1H), 2.82 (m, 1H), 2.97–3.07 (m, 2H), 3.38 (d, 1H, $J=13.6$ Hz), 3.45 (d, 1H, $J=13.6$ Hz), 3.75 (s, 3H), 4.88 (s, 1H), 5.97 (dd, 1H, $J=6.9$ Hz, $J=1.2$ Hz), 6.51 (dd, 1H, $J=9.1$ Hz, $J=1.2$ Hz), 6.93–6.97 (m, 2H), 7.16–7.21 (m, 3H), 7.33 (dd, 1H, $J=9.1$ Hz, $J=6.9$ Hz). ^{13}C NMR δ ($CDCl_3$): 23.8, 31.9, 35.3, 52.4, 59.5, 60.0, 61.2, 61.8, 104.6, 116.9, 127.0, 128.1, 128.2, 137.7, 139.2, 150.7, 163.2, 171.6. IR (KBr, cm^{-1}): 3018, 2952, 2804, 1748, 1734, 1654, 1570, 1548, 1354, 1282, 1216, 1174, 770. MS (EI) m/z: 338 (M^+, 23), 234 (89), 220 (22), 105 (73), 84 (100). HRMS (EI) calcd for $C_{20}H_{22}N_2O_3$ 338.1630, found 338.1638.

Acknowledgements

This work was supported by the Réseau Interrégional de Chimie Organique Fine, Contrat de Plan Etat-Grand-Bassin Parisien-Régions Haute Normandie, Basse Normandie.

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