

Alkylation studies of a polyhydroxylated-cyano-piperidine scaffold

Alicia M. Dilmaç,^a Tony Tite,^a Andriamihamina Tsimilaza,^a Pascale Lemoine,^b
Sabrina Boutefnouchet,^a Sylvie Michel^a and Marie-Christine Lallemand^{a*}

^a Laboratoire de Pharmacognosie, UMR CNRS 8638 Université Paris Descartes, Sorbonne Paris Cité, Faculté des Sciences Pharmaceutiques et Biologiques, 4, Avenue de l'Observatoire, 75006 Paris, France

^b Laboratoire de Cristallographie et RMN Biologiques UMR CNRS 8015 Université Paris Descartes, Sorbonne Paris Cité Faculté des Sciences Pharmaceutiques et Biologiques, 4, Avenue de l'Observatoire, 75006 Paris, France

E-mail: marie-christine.lallemand@parisdescartes.fr

DOI: <http://dx.doi.org/10.3998/ark.5550190.p008.243>

Abstract

Hexahydro-3-phenyl-6,7,8-trihydroxy-3*R*-[3 α ,5 β ,6 β ,7 α ,8 β ,8a β]-5*H*-oxazolo[3,2-*a*]pyridine-5-carbonitrile is endowed with two non equivalent reactive sites: an α -amino nitrile at the C-5 position and an α -amino ether at the C-8a position. Herein, alkylation at the C-5 position was studied. The scope and limitations of these reactions have been investigated.

Keywords: Trihydroxy-cyano piperidine scaffold, alkylation studies, scope and limitations

Introduction

Polyhydroxylated piperidine and indolizidine alkaloids, called iminosugars, are important targets in organic synthesis due to their potential value as glycosidase inhibitors.¹⁻⁴ These compounds have been designed as therapeutic solutions in several diseases⁵⁻¹⁰ (type II diabetes, viral and bacterial infections, lysosomal storage disorders, tumor metastasis). They have also been found in a number of natural¹¹⁻¹⁶ or synthetic¹⁷⁻²⁴ heterocyclic compounds, such as castanospermine and *N*-butyl-deoxynojirimycin (*N*-butyl-DNJ) respectively (Figure 1).

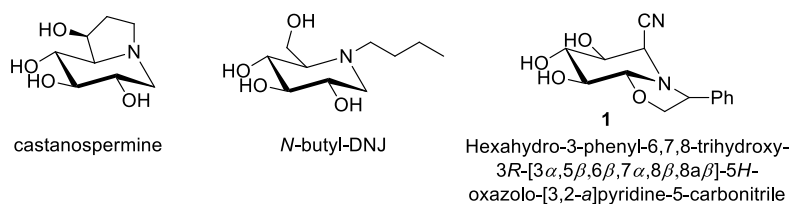
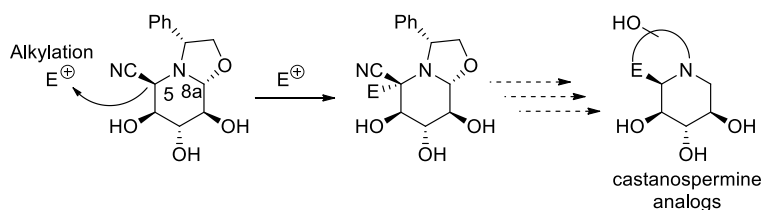


Figure 1

Chemists have been inspired by the numerous pharmacological activities of iminosugars, but unfortunately some of them are also toxic to human cells. Nevertheless, there is still a need for an easy access to alkaloid analogs and for the development of more potent, selective and less toxic drug candidates. In this context, we decided to consider the chiral building block **1** (Figure 1) as starting material.²⁵ As a part of our ongoing research program on the reactivity of compound **1**, we already reported a rapid access to substituted six- or seven- membered ring iminosugars *via* ring-expansion reactions²⁶ and a new asymmetric synthesis of (2*S*,3*R*,4*R*,5*S*)-trihydroxypipercolic acid.²⁷ In order to prepare indolizidine analogs such as castanospermine derivatives, we have extended, herein, our research on the alkylation study at the C-5 position of the building block **1** (Scheme 1). Compound **1** possesses two non-equivalent reactive sites on the polyhydroxylated piperidine ring system: an α -amino nitrile at the C-5 position and an α -amino ether at the C-8a position.

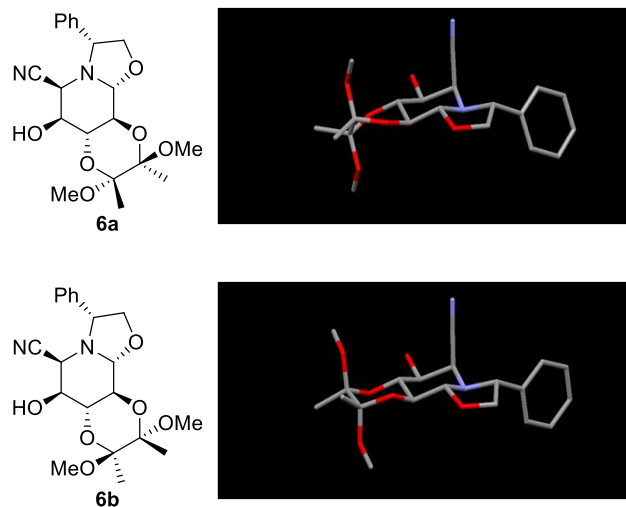


Scheme 1

Results and Discussion

In this paper, we focus on the methylation reactions at the C-5 position. The scope and limitations of this alkylation are discussed. Our purpose is to compare the reactivity of our building block **1** with regard to the CN(*R,S*) synthon created by Husson's group (Scheme 2), under the same experimental conditions.²⁸ Following the literature data,²⁹ we studied the methylation of **1** with iodomethane at $-78\text{ }^{\circ}\text{C}$ in THF in presence of lithium diisopropylamine. First attempts were carried out on compound **1** without success. Therefore, it was decided to use the protected form, which was obtained by benzylation of the hydroxyl functions (Scheme 2).²⁶

In contrast with the CN(*R,S*) synthon, the treatment of **2** with LDA in the presence of iodomethane gave two different products: the desired C5-alkylated compound **3** and an α -cyanoenamine **4**, in 10% and 30% yield, respectively. The major compound **4** was obtained through the elimination of the adjacent benzyloxy group. A careful analysis of **4** by ^1H - and ^{13}C -NMR allowed the characterization of its structure. The typical NMR signals at $\delta = 5.29\text{ ppm}$ and at $\delta = 112.5\text{ ppm}$, observed in the ^1H and ^{13}C NMR spectra respectively, were attributed to the C-6 position.

**Figure 2**

Structural features of interest of **6a** and **6b**, which crystallizes in the non-centrosymmetric P21 21 21 space group, are collected in Table 1.

Table 1. Lengths (Å), angles and torsion (°) of interest for complex **6a** and **6b**

	6a	6b
C7 O	1.433(3)	1.440(3).
C8 O	1.437(4)	1.441(4)
C2' O	1.431(4)	1.424(4)
C3' O	1.436(4)	1.448(4)
C2' C3'	1.541(5)	1.546(5)
C7 O C2'	115.7(3)	111.9(2)
C7 C8 O	110.9(2)	107.8(2)
C3' O C8	115.3(2)	113.1(3)
C2' C3' O	111.1(3)	111.1(3)
C3' C2' O	110.7(2)	110.5(3)
C7 - O - C2' - C	151.1(3)	177.8(3)
C8 - O - C3' - C	151.0(3)	175.4(3)
C7 - O - C2' - O	86.5(3)	60.1(3)
C8 - O - C3' - O	87.4(3)	62.2(4)

The protecting group of **6a** favors a twist boat conformation while a chair conformation is preferred for **6b** (Figure 2). ^1H NMR studies indicated that after one week of reaction, compounds **6** were present in a mixture 80/20 with prevalence for the twist boat conformation of **6a**. After two weeks of reaction, compounds **6** were still a mixture 80/20, but now with prevalence for the chair conformation of **6b**. This result suggests a kinetic and a thermodynamic form, with an equilibration to the more stable derivative under the acidic experimental conditions. To the best of our knowledge, no report exists for the characterization of the twist boat conformation with this stereochemistry, for the butane 2,3-bisacetal protection of vicinal diequatorial diols.

To pursue our work on the alkylation, the protection of compounds **5** and **6** on their free hydroxyl function was achieved by reacting with methoxymethyl chloride (MOMCl) in the presence of Hünig's base (Scheme 3). The structures of **7** and **8** were unambiguously deduced from their spectral data. Indeed, in the HMBC spectrum of compound **7** the cross peaks, observed between the triplet signal at $\delta = 3.77$ of H-8 proton and carbon signals at $\delta = 91.7$ and $\delta = 95.9$, were attributed to C-8a and MOM methylene C-1' positions (Figure 3). Based on the HMBC correlation between H-6 and MOM methylene carbon (Figure 3), the structure of **8** was in full agreement with the proposed skeleton.

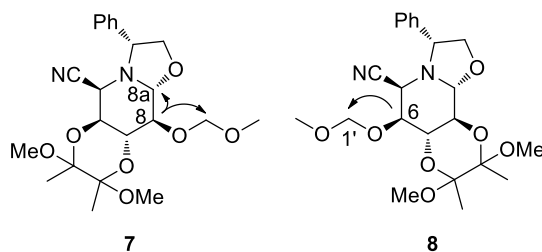
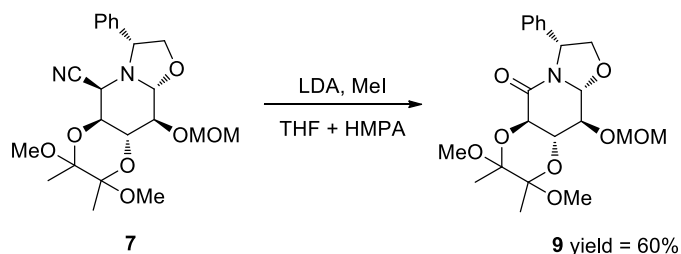


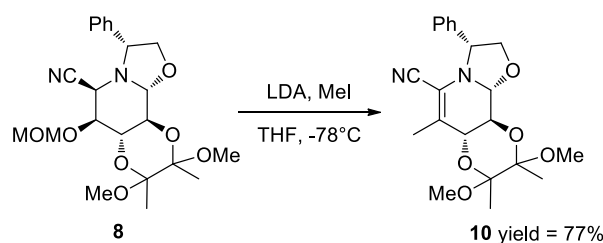
Figure 3

Initial attempts towards the stereoselective alkylation at the C-5 position of compounds **7** (mixture 50/50 of **7a** and **7b** confirmed by ^1H NMR), under classic conditions (LDA at -78 $^{\circ}\text{C}$), were unsuccessful and only starting material was recovered. In contrast, when HMPA was added to the reaction and the temperature was gradually raised up to -15 $^{\circ}\text{C}$, lactams **9** were obtained in 60% yield as confirmed by NMR and MS spectroscopy (δ 162.7 (CO); MS $[\text{M} + \text{H}]^+$ 424) and represented in Scheme 4. According to the literature,³⁸ the lactam formation can be explained by *in situ* addition of oxygen from the solvent to an extremely oxygen sensitive anion.



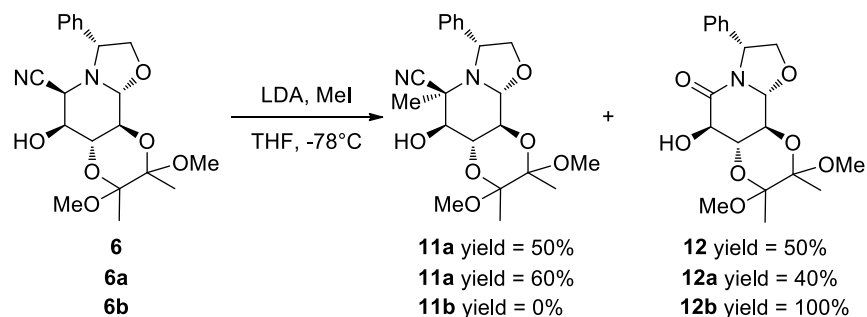
Scheme 4

This result showed that the anion formation occurred and that the 6,7-butane-bisacetal protection prevented the β -elimination. However, the alkylation reaction probably failed because of steric hindrance. In order to confirm this last hypothesis, we investigated the alkylation study on the less hindered 7,8-butane-bisacetals **8** (Scheme 5). Alkylation of **8** with iodomethane (LDA, THF, -78°C) led to the formation of the unexpected β -methylated- α -cyanoenamines **10** (Scheme 5). These compounds were isolated in 77% yield after flash chromatography.



Scheme 5

These results suggested that the alkylation at α -aminonitrile position was strongly dependant on the adjacent substituent. In the presence of a leaving group, the enamine formation is favored, whereas the presence of a sterically bulky group leads to the lactam derivative. Finally, we chose to use the non protected compounds **6** as a starting material, as seen in Scheme 6.



Scheme 6

Under similar conditions, compounds **6** are transformed into the corresponding alkylated compound **11a** and the lactams **12** in equivalent yield, based on recovered starting material. Encouraged by this result, we decided to investigate the reactivity of the two diastereoisomers separately. In this context, we first studied reactivity of compound **6a**. The alkylation reaction, following the same procedure, led to a mixture of **11a** and **12a** in 60% and 40% yield respectively. We then turned our attention to the second diastereoisomer **6b**. Reaction of **6b** furnished the lactam **12b** in quantitative yield. This result showed in our case the substrate-dependent reactivity concerning the butane 2,3-bisacetal protection group. The above observations led us to consider this method as a new and alternative access to alkylated or lactam compound, with increased yields.

Conclusions

In conclusion, we have demonstrated that compound **6a** is a useful building block for alkylation reaction and that its diastereoisomer **6b** allowed a selective access to the lactam scaffold. Considering the high potential of so-called “azasugars” for drug discovery, we want to extend this methodology to a new approach for the synthesis of indolizidine scaffold, through alkylation with suitable side chains and subsequent cyclization on the nitrogen after elimination of the chiral appendage. Efforts in this direction are currently being pursued in our laboratory.

Experimental Section

General. All reactions were carried out in dried glassware under an argon atmosphere. All solvents were purchased with an analytical grade from SDS. Acetone and chloroform were dried over molecular sieves. Reactions were monitored using thin-layer chromatography (TLC) carried out on 0.25mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and sulfuric vanillin heated as developing agent. Flash chromatography was performed with silica gel CHROMATOGEL 60 (particle size 20-45 μm or 35-70 μm) supplied by SDS. Yield refers to chromatography and spectroscopically pure compounds, unless otherwise noted. ^1H NMR spectra were recorded on a BRUCKER AC 300 MHz spectrometer or a BRUCKER AVANCE 400 MHz spectrometer. Chemical shifts are reported in ppm and coupling constants (J) in Hz. ^{13}C NMR spectra were recorded on a BRUCKER AC 300 spectrometer at 75 MHz. The assignments are based upon 1D and 2D spectra recorded using the following pulse sequences from the Bruker standard pulse program library: DEPT, COSY, HSQC, HMBC and NOESY. Mass spectra were measured with a ZQ 2000 Waters mass spectrometer (ESI). High resolution mass spectra were obtained on a Q-ToF1 ESI mass spectrometer (Waters). Infra-red spectra were recorded with a PerkinElmer spectrum 65 FT-IR spectrometer and wavenumbers (ν) are given in cm^{-1} . Specific rotations were measured using a PerkinElmer model 341 polarimeter in a chloroform solution at 20 $^\circ\text{C}$.

General procedure for the synthesis of 6,7,8-tribenzyloxy-5-methyl-3-phenylhexahydro-2H-oxazolo[3,2-a]pyridine-5-carbonitrile (3) and 7,8-bisbenzyloxy-3-phenyl-3,7,8,8a-tetrahydro-2H-oxazolo[3,2-a]pyridine-5-carbonitrile (4). To a solution of **2** (100 mg, 0.18 mmol) in dry THF (0.4 mL) under argon ($-78\text{ }^{\circ}\text{C}$), was added dropwise a solution of LDA 1.6 M in dry THF (0.32 mL, 0.72 mmol, 4 eq). After one hour at $-78\text{ }^{\circ}\text{C}$ iodomethane (0.08 mL, 1.52 mmol, 8 eq.) was added and the reaction stirred at this temperature for 3 h. Then the temperature was raised up gradually to $0\text{ }^{\circ}\text{C}$. The reaction was quenched with NH_4Cl (sat) then extracted with ethyl acetate (3 x 40 mL). The combined organic layers was dried over anhydrous Na_2SO_4 , filtered and concentrated to dryness. After purification by chromatography on silica gel using as eluent a mixture of cyclohexane/ether 9/1, 10 mg of **3** (10%) and 24 mg of **4** (30%) were afforded as yellow oils.

Data for 3. *Rf*: 0.41 (cyclohexane/ether 8/2), IR $\nu\text{ cm}^{-1}$: 2229 (CN), ^1H NMR (400 MHz, CDCl_3): δ 1.13 (s, 3H, CH_3), 3.35 (d, 1H, $J = 9\text{ Hz}$), 3.75 (dd, 1H, OH, $J = 8\text{ Hz}$, $J = 9\text{ Hz}$), 3.86 (t, 1H, $J = 9\text{ Hz}$), 3.89 (dd, 1H, $J = 4.5\text{ Hz}$, $J = 8.5\text{ Hz}$), 4.10 (dd, 1H, $J = 4.5\text{ Hz}$, $J = 8.5\text{ Hz}$), 4.37 (t, 1H, $J = 8.5\text{ Hz}$), 4.40 (d, 1H, $J = 8\text{ Hz}$), 4.59 (d, 1H, $J = 11.5\text{ Hz}$), 4.78 (d, 1H, $J = 11.1\text{ Hz}$), 4.80 (d, 1H, $J = 11.5\text{ Hz}$), 4.96 (d, 1H, $J = 11.1\text{ Hz}$), 4.99 (d, 1H, $J = 11.5\text{ Hz}$), 5.03 (d, 1H, $J = 11.5\text{ Hz}$), 7.15-7.50 (m, 20 H, H-aro). ^{13}C NMR (75 MHz, CDCl_3): δ 24.2 (CH_3), 59.9, 61.3, 74.0, 76.1, 76.3 (3 x $\text{CH}_2\text{-Ph}$), 76.4, 81.4, 83.3, 84.3, 94.0, 117.3 (CN), 126.9, 127.5, 127.8, 128.0, 128.2, 128.7 (C_{ArH}), 137.5, 138.1, 138.5, 143.5 (C_{Ar}). MS (IC, NH_3): m/z $[\text{M} + \text{H}]^+$ 561. HRMS (IC, NH_3) m/z : calcd. for $\text{C}_{36}\text{H}_{36}\text{N}_2\text{O}_4\text{Na}$ $[\text{M} + \text{Na}]^+$: 583.2573; found 583.2513.

Data for 4. *Rf*: 0.5 (cyclohexane/ether 8/2), IR $\nu\text{ cm}^{-1}$: 2361 (CN), ^1H NMR (400 MHz, CDCl_3): δ 3.84 (dd, 1H, $J = 7.5\text{ Hz}$, $J = 8.5\text{ Hz}$), 4.20 (dd, 1H, $J = 1.5\text{ Hz}$, $J = 9\text{ Hz}$), 4.35 (dd, 1H, $J = 6\text{ Hz}$, $J = 9\text{ Hz}$), 4.38 (ddd, 1H, $J = 1\text{ Hz}$, $J = 3\text{ Hz}$, $J = 7.5\text{ Hz}$), 4.6-4.7 (d, 2H, $J = 11.5\text{ Hz}$), 4.72 (dd, 1H, $J = 1.5\text{ Hz}$, $J = 6\text{ Hz}$), 4.87 (d, 1H, $J = 8.5\text{ Hz}$), 4.9-5.1 (d, 2H, $J = 11.5\text{ Hz}$), 5.29 (d, 1H, $J = 3\text{ Hz}$), 7.20-7.50 (m, 15 H, H-aro). ^{13}C NMR (75 MHz, CDCl_3): δ 60.9, 72.3, 74.1, 74.9 (2X CH_2Ph), 77.0, 78.1, 91.1, 112.5, 113.7 (CN), 127.3, 127.8, 128.1, 128.3, 128.5, 128.6 (C_{ArH}), 137.9, 138.2, 140.7 (C_{Ar}). MS (IC, NH_3): m/z $[\text{M} + \text{H}]^+$ 439. HRMS (IC, CH_4) m/z : calcd. for $\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_3$ $[\text{M} + \text{H}]^+$: 439.2022; found 439.1995.

General procedure for the synthesis of 5-hydroxy-7,8-dimethoxy-7,8-dimethyl-3-phenyl-octahydro-1,6,9-trioxa-3a-aza-cyclopenta[a]naphthalene-4-carbonitrile (5)

and 9-hydroxy-6,7-dimethoxy-6,7-dimethyl-3-phenyl-octahydro-1,5,8-trioxa-3a-aza-cyclopenta[β]naphthalene-4-carbonitrile (6). To a solution of trihydroxy derivative in dry MeOH (2 mL), were added successively tetramethoxybutane (500 mg, 2.8 mmol, 2.5 eq.), trimethylorthoformate (0.5 mL), and camphorsulfonic acid (0.1 mmol, 0.1 eq.). The solution was refluxed for 1 week, then neutralized with NaHCO_3 (220 mg). After extraction with CH_2Cl_2 (5 x 30 mL), the combined organic layers were washed with a saturated solution of NaHCO_3 , then dried over Na_2SO_4 and evaporated to dryness. After purification by flash chromatography on silica gel using as eluent a mixture of cyclohexane/ether 1/1, compound **5** was isolated as a colorless oil (65 mg, 15%) and compound **6** as a white crystals (135 mg, 30%).

Data for 5. Mp: 264 °C, R_f : 0.35 (cyclohexane/ether 1/1.5), IR ν cm^{-1} : 3456 (OH), 2229 (CN), ^1H NMR (400 MHz, CDCl_3): δ 1.42, 1.44 (2 s, 6H, 2 CH_3), 2.59 (d, 1H, OH, $J = 3$ Hz), 3.37, 3.41 (2 s, 6H, 2 OCH_3), 3.80-3.90 (m, 1H), 3.88 (t, 1H, $J = 8$ Hz), 3.98 (d, 1H, $J = 5.5$ Hz), 4.05 (t, 1H, $J = 8$ Hz), 4.17 (dd, 1H, $J = 8\text{Hz}$, $J = 10.5$ Hz), 4.27 (d, 1H, $J = 8$ Hz), 4.28 (d, 1H, $J = 10.5$ Hz), 4.39 (t, 1H, $J = 8$ Hz), 7.30-7.40 (m, 5 H, C_6H_5). ^{13}C NMR (75 MHz, CDCl_3): δ 18.9 (2 CH_3), 48.4 (OCH_3), 48.5 (OCH_3), 50.0, 62.7, 70.0, 72.5, 72.8, 74.9, 90.6, 101.8, 102.1 (C_{iv}), 113.7 (CN), 127.8, 129.1, 129.2 (C_{ArH}), 135.9 (C_{Ar}). MS (IC, NH_3): m/z $[\text{M} + \text{H}]^+$ 391. HRMS (IC, NH_3) m/z : calcd. for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_6\text{Na}$ $[\text{M} + \text{Na}]^+$: 413.1689; found 413.1692

Data for 6. R_f : 0.25 (cyclohexane/ether 1/1.5), IR ν cm^{-1} : 3450 (OH), 2229 (CN). ^1H NMR (400 MHz, CDCl_3): δ 1.41, 1.44 (2 s, 6H, 2 CH_3), 2.57 (d, 1H, OH, $J = 2.5$ Hz), 3.41, 3.45 (2s, 6H, 2 OCH_3), 3.69 (t, 1H, $J = 9$ Hz), 3.84 (dd, 1H, $J = 9$ Hz, $J = 5$ Hz), 4.0-4.10 (m, 1H), 4.27 (d, 1H, $J = 7.5$ Hz), 4.33 (dd, 1H, $J = 11$ Hz, $J = 5\text{Hz}$), 4.30-4.40 (m, 2H), 7.30-7.40 (m, 5H, C_6H_5). ^{13}C NMR (75 MHz, CDCl_3): δ 18.7, 18.8 (2 CH_3), 47.8 (OCH_3), 48.3 (OCH_3), 48.9, 62.7, 69.8, 72.9, 73.5, 74.3, 91.6, 101.7, 102.0 (C_{iv}), 113.9 (CN), 127.8, 129.0, 129.1 (C_{ArH}), 135.7 (C_{Ar}). MS (IC, NH_3): m/z $[\text{M} + \text{H}]^+$ 391.

Crystallographic data for 6a. $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_6$, orthorhombic, P21 21 21, colorless, $a = 6.9853(5)$ Å, $b = 10.5499(6)$ Å, $c = 26.538(2)$ Å, $V = 1955.7(2)$ Å³, $T = 293(2)\text{K}$, $Z = 4$, Final R ($I > 2 \sigma(I)$): $R_1 = 0.0463$, $wR_2 = 0.0986$, GOF = 1.070. Structural information for **6a** has been deposited with CCDC as 845878.

Crystallographic data for 6b. $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_6$, orthorhombic, P21 21 21, colorless, $a = 6.6354(1)$ Å, $b = 12.4162(2)(6)$ Å, $c = 24.790(2)$ Å, $V = 2042.4(2)$ Å³, $T = 293(2)\text{K}$, $Z = 4$, Final R ($I > 2 \sigma(I)$): $R_1 = 0.0441$, $wR_2 = 0.0834$, GOF = 1.154. Structural information for **6b** has been deposited with CCDC as 845879.

General procedure for the synthesis of 6,7-dimethoxy-9-methoxymethoxy-6,7-dimethyl-3-phenyl-octahydro-1,5,8-trioxa-3a-aza-cyclopenta[a]naphthalene-4-carbonitrile (7) and 7,8-dimethoxy-5-methoxymethoxy-7,8-dimethyl-3-phenyl-octahydro-1,6,9-trioxa-3a-aza-cyclopenta[a]naphthalene-4-carbonitrile (8). To a solution of **5** (50 mg, 0.13 mmol) or of **6** (65 mg, 0.15 mmol) in dry CHCl_3 (1 mL), was added at 0 °C methoxymethyl chloride (26 μL , 2.5 eq., 0.32 mmol) and *N-N*-diisopropylamine (68 μL , 3 eq., 0.4 mmol). The resulting mixture was refluxed for 3 h, then let to cool down to rt. The solution was quenched with water and extracted with dichloromethane (5 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and evaporated to dryness. After purification by chromatography on silica gel using as eluent a mixture of cyclohexane/ether 1/0.5) the compound **7** was recovered as a colorless oil (7.5 mg, 77%).

Data for 7. R_f : 0.60 (cyclohexane/ether 1/1.5), ^1H NMR (400 MHz, CDCl_3): δ 1.34, 1.40 (2 s, 6H, 2 CH_3), 3.40, 3.42, 3.52 (3s, 9H, 3 OCH_3), 3.77 (t, 1H, $J = 8$ Hz), 3.83 (t, 1H, $J = 8$ Hz), 3.96 (d, 1H, $J = 5.5$ Hz), 3.99 (t, 1H, $J = 8$ Hz), 4.28 (d, 1H, $J = 8$ Hz), 4.30-4.40 (m, 2H, H-8), 4.46 (t, 1H, $J = 10$ Hz), 4.85-5.00 (2d, 2H, OCH_2O , $J = 6.5$ Hz), 7.20-7.50 (m, 5H, C_6H_5). ^{13}C NMR (75 MHz, CDCl_3): δ 18.7, 19.0 (2 CH_3), 48.2, 48.8, 55.4 (3 XOCH_3), 62.5, 70.1, 72.3, 74.3, 75.4,

91.7, 95.9 (OCH₂O), 101.5, 101.8 (C_{iv}), 113.9 (CN), 127.7 129.0, 129.2 (C_{Ar}H), 135.9 (C_{Ar}). MS (IC, NH₃): *m/z* [M + H]⁺ 435. HRMS (IC, NH₃) *m/z*: calcd. for C₂₂H₃₀N₂O₇Na [M+Na]⁺: 457.1951; found 457.1903.

Data for 8. *R_f*: 0.40 (cyclohexane/ether 1/1), IR ν cm⁻¹: 2229 (CN). ¹H NMR (400 MHz, CDCl₃): δ 1.42, 1.43 (2s, 6H, 2 CH₃), 3.37, 3.40, 3.41 (3s, 9H, 3 OCH₃), 3.81 (dd, 1H, *J* = 5.5 Hz, *J* = 10 Hz), 3.86 (t, 1H, *J* = 8 Hz), 4.00 (d, 1H, *J* = 5.5 Hz), 4.05 (t, 1H, *J* = 8 Hz), 4.19 (dd, 1H, *J* = 8 Hz, *J* = 10 Hz), 4.24 (d, 1H, *J* = 8 Hz), 4.37 (t, 1H, *J* = 10 Hz), 4.38 (t, 1H, *J* = 8 Hz), 4.70, 4.79 (2d, 2H, OCH₂O, *J* = 7 Hz), 7.20-7.50 (m, 5H, C₆H₅). ¹³C NMR (75 MHz, CDCl₃): δ 18.8, 19.0 (2 CH₃), 48.1 (OCH₃), 48.3 (OCH₃), 49.6, 56.2, 62.8, 71.8, 72.6, 74.6, 74.9, 90.2, 96.8 (OCH₂O), 101.4, 101.7 (C_{iv}), 113.6 (CN), 127.8, 129.1, 129.2 (C_{Ar}H), 136.0 (C_{Ar}). MS (IC, NH₃): *m/z* [M + Na]⁺ 457. HRMS (IC, NH₃) *m/z*: calcd. for C₂₂H₃₀N₂O₇Na [M+Na]⁺: 457.1951; found 457.1929.

Procedure for the synthesis of 6,7-dimethoxy-9-methoxymethoxy-6,7-dimethyl-3-phenyl-octahydro-1,5,8-trioxa-3a-aza-cyclopenta[a]naphthalene-4-one (9). To a solution of **7** (13 mg, 0.03 mmol) in dry THF (100 μL) under argon and at -78 °C, was added dropwise a solution of LDA 2.5 M in dry THF (110 μL, 0.12 mmol, 4 eq) and HMPA (26 μL, 0.15 mmol, 5 eq). After 20 min at -78 °C iodomethane (15 μL, 0.24 mmol, 8 eq.) was added and the reaction was stirred at this temperature for 3 h 30. Then the temperature was raised up gradually to -15 °C for 2 h. The reaction was quenched with NH₄Cl (sat) then extracted with CH₂Cl₂. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated to dryness. After purification by chromatography on silica gel using as eluent a mixture of cyclohexane/ether 1/0.3, compound **9** was afforded as a yellow oil (8 mg, 60 %).

Data for 9. *R_f*: 0.5 (CH₂Cl₂/MeOH 9/1). ¹H NMR (400 MHz, CDCl₃): δ 1.31, 1.49 (2s, 6H, 2 CH₃), 3.20-3.60 (m, 9H, 3 OCH₃), 4.05 (t, 1H, *J* = 8.5 Hz), 4.10-4.20 (m, 3H), 4.40-4.50 (m, 1H), 4.77 (d, 1H, *J* = 7.5 Hz), 4.86 (t, 1H, *J* = 8 Hz), 4.94, 5.01 (2d, 2H, OCH₂O, *J* = 7 Hz), 7.20-7.60 (m, 5H, C₆H₅). ¹³C NMR (75 MHz, CDCl₃): δ 17.5, 18.6 (2 CH₃), 47.8, 48.2, 55.6 (3XOCH₃), 58.1, 70.6, 72.7, 74.7, 74.8, 89.8, 96.1 (O-CH₂-O), 99.6, 101.8 (C_{iv}), 126.8 128.0, 128.9 (C_{Ar}H), 139.9 (C_{Ar}), 162.7 (CO). MS (IC, NH₃): *m/z* [M + H]⁺ 424.

General procedure for the alkylation reaction of 7,8-dimethoxy-5,7,8-trimethyl-1,3-phenyl-2,3,7,8,9a,9b-hexahydro-5aH-1,6,9-trioxa-3a-aza-cyclopenta[a]naphthalene-4-carbonitrile (10), of (2*R*, 3*R*, 4*aR*, 5*S*, 6*R*, 8*R*, 10*aR*, 10*bS*)-5-hydroxy-2,3-dimethoxy-2,3,6-trimethyl-8-phenyloctahydro-2H-[1,4]dioxino[2,3-*c*]oxazolo[3,2-*a*]pyridine-6-carbonitrile (11a), of (2*R*, 3*R*, 4*aR*, 5*S*, 8*R*, 10*aR*, 10*bS*)-5-hydroxy-2,3-dimethoxy-2,3-dimethyl-8-phenylhexahydro-2H-[1,4]dioxino[2,3-*c*]oxazolo[3,2-*a*]pyridin-6(3*H*)-one (12a) and of (2*R*, 3*R*, 4*aR*, 5*S*, 8*R*, 10*aR*, 10*bS*)-5-hydroxy-2,3-dimethoxy-2,3-dimethyl-8-phenylhexahydro-2H-[1,4]dioxino[2,3-*c*]oxazolo[3,2-*a*]pyridin-6(3*H*)-one (12b). To a solution of **8**, **6**, **6a** or **6b** (0.025 mmol) in dry THF (40 μL) under argon (-78 °C), was added dropwise a solution of LDA 2.5 M in dry THF (0.1 mmol, 4 eq). After 15 min. at -78 °C, iodomethane (0.35 mmol, 14 eq.) was added and the reaction was stirred at this temperature for 3 h. The reaction was quenched with NH₄Cl (sat) then extracted with CH₂Cl₂ (3 x 30 mL). The

combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated to dryness. Purification by chromatography on silica gel was then performed using as eluent a mixture of cyclohexane/ether, 9/1.

Data for 10. R_f : 0.5 (cyclohexane/ether 1/1), IR ν cm^{-1} : 2223 (CN). ^1H NMR (400 MHz, CDCl_3): δ 1.11-1.30 (3 s, 6H, 2 CH_3), 1.62 (s, 3H, CH_3), 2.90-3.20 (3 s, 6 H, 2 OCH_3), 3.90-4.00 (m, 1H), 4.10 (dd, 1H, $J = 6\text{Hz}$, $J = 8\text{Hz}$), 4.17 (t, 1H, $J = 9\text{Hz}$), 4.49 (t, 1H, $J = 6\text{ Hz}$, $J = 6.5\text{ Hz}$), 4.56 (d, 1H, $J = 10\text{ Hz}$), 4.69 (d, 1H, $J = 9\text{ Hz}$), 7.10-7.30 (m, 5H, C_6H_5). ^{13}C NMR (75 MHz, CDCl_3): δ 14.1 (CH_3), 19.0 (2 CH_3), 47.8 (2 OCH_3), 62.3, 69.6, 70.5, 74.6, 89.0, 102.1 (C_{iv}), 111.0, 112.9, 114.1 (CN), 128-129 (C_{ArH}), 140.4 (C_{Ar}). MS (IC, NH_3): m/z $[\text{M} + \text{Na}]^+$ 409. HRMS (IC, NH_3) m/z : calcd. for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_5\text{Na}$ $[\text{M} + \text{Na}]^+$: 409.1739; found 409.1745.

Data for 11a. R_f 0.4 (cyclohexane/ether, 1:1), $[\alpha]_{\text{D}} = -109$ (c 0.58, MeOH); IR (film) cm^{-1} : 3484 (OH). ^1H NMR (CDCl_3) δ 1.20 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 3.38 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.88 (dd, 1H, $J = 4.7$; 8.6 Hz), 4.13 (dd, $J = 4.7$; 8.6 Hz, 1H), 4.21-4.30 (m, 3H), 4.36 (t, $J = 8.6\text{ Hz}$, 1H), 7.22-7.38 (m, 5H arom). ^{13}C NMR (CDCl_3): δ 19.1 (2 XCH_3), 23.6 (CH_3), 48.4 (OCH_3), 48.5 (OCH_3), 60.1, 61.5, 71.9, 73.0, 76.1, 76.6, 92.0, 101.8, 102.2, 117.3 (CN), 127.1, 128.0, 129.0 (CH arom), 143.2 (C_{IV} arom). HRMS (ESI): calcd for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_6$ $[\text{M} + \text{H}]^+$: 405.2026; found 405.2026. calcd. for $\text{C}_{20}\text{H}_{27}\text{NO}_6\text{Na}$ $[\text{M} - \text{HCN} + \text{Na}]^+$: 400.1736; found 401.1737.

Data for 12a. R_f 0.6 (dichloromethane/methanol, 9:1), $[\alpha]_{\text{D}} = -26$ (c 1.01, MeOH); IR (film) cm^{-1} : 3390 (OH), 1668 (CO); ^1H NMR (CDCl_3) δ 1.45 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.40 (s, 6H, OCH_3), 3.91 (d, $J = 8.2\text{ Hz}$, 1H), 4.20 (d, $J = 9.7\text{ Hz}$, 1H), 4.27-4.35 (m, 1H), 4.36-4.69 (m, 2H), 4.79 (d, $J = 6.7\text{ Hz}$, 1H), 4.88 (d, $J = 6.5\text{ Hz}$, 1H), 7.20-7.50 (m, 5H arom). ^{13}C NMR (CDCl_3): δ 18.8 (CH_3), 19.0 (CH_3), 48.7 (OCH_3), 48.8 (OCH_3), 58.7, 70.8, 71.0, 72.7, 75.2, 89.3, 101.6, 101.7, 127.0-128.4-128.9 (CH arom), 139.9 (C_{IV} arom). 166.0 (CO), MS (ES^+ , MeOH): m/z $[\text{M} + \text{Na}]^+$ 402; $[\text{2M} + \text{Na}]^+$ 780. HRMS (ES) : calcd. for $\text{C}_{19}\text{H}_{25}\text{NO}_7\text{Na}$ $[\text{M} + \text{Na}]^+$: 402.1529; found 402.1526.

Data for 12b. R_f 0.62 (dichloromethane/methanol, 9:1); IR (film) cm^{-1} : 3390 (OH), 1670 (CO); ^1H NMR (CDCl_3) δ 1.38 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.41 (s, 6H, OCH_3), 4.05 (m, 2H), 4.18 (t, $J = 8.1\text{ Hz}$, 1H), 4.27-4.35 (m, 1H), 4.39-4.49 (m, 2H), 4.95-4.97 (m, 2H), 7.20-7.50 (m, 5H arom). ^{13}C NMR (CDCl_3): δ 17.6 (CH_3), 17.8.0 (CH_3), 48.4 (OCH_3), 48.6 (OCH_3), 58.7, 68.5, 68.9, 70.5, 75.1, 87.7, 99.4, 99.06, 126.7-128.3-131.0 (CH arom), 139.9 (C_{IV} arom). 166.2 (CO). MS (ES^+ , MeOH): m/z $[\text{M} + \text{Na}]^+$ 402; $[\text{2M} + \text{Na}]^+$ 780. HRMS HRMS (ES): calcd. for $\text{C}_{19}\text{H}_{25}\text{NO}_7\text{Na}$ $[\text{M} + \text{Na}]^+$: 402.1529; found 402.1526.

Acknowledgements

Financial supports of this work by Université Paris Descartes, Sorbonne Paris Cité (grant to Alicia M. Dilmaç) is gratefully acknowledged. We thank Drs. Xavier Cachet, Andy Gum and François-Hugues Porée for proofreading of our manuscript.

References

1. Legler G. *Iminosugars as Glycosidase inhibitors-Nojirimycin and Beyond*; Stüt, A. E. Ed.; Wiley-VCH: Weinheim, 1999; pp 31-66.
2. Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515.
<http://dx.doi.org/10.1021/cr000433k>
3. Martin, O. R.; Compain, P. *Curr. Top. Med. Chem.* **2003**, *3*, 541.
4. Borges de Melo E.; da Silveira Gomes A.; Carvalho I. *Tetrahedron* **2006**, *62*, 10277.
<http://dx.doi.org/10.1016/j.tet.2006.08.055>
5. Compain, P.; Martin, O. R. *Iminosugars: From Synthesis to Therapeutic Applications*; Wiley-VCH: Weinheim, 2007.
6. Wrodnigg, T. M.; Steiner, A. J.; Ueberbacher, B. J. *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 77. <http://dx.doi.org/10.2174/187152008783330851>
7. Oulaïdi, F.; Front-Deschamps, S.; Galienne, E.; Leselier, E.; Ikeda, K.; Asano, N.; Compain, P.; Martin, O. R. *Chem. Med. Chem.* **2011**, *6*, 353.
<http://dx.doi.org/10.1002/cmdc.201000469>
8. Home, G.; Wilson, F. X.; Tinsley, J.; Williams, D. H.; Storer, R. *Drug Discov. Today* **2011**, *16*, 107.
<http://dx.doi.org/10.1016/j.drudis.2010.08.017>
9. Home, G.; Wilson, F. X. *Prog. Med. Chem.* **2011**, *50*, 135.
<http://dx.doi.org/10.1016/B978-0-12-381290-2.00004-5> PMID:21315930
10. Zingfei, H.; Xinshan, Y.; Zhongguo K. *Kexue : Huaxue* **2012**, *42*, 1732.
11. Simmonds, M. S. J.; Kite, G. C.; Porter, E. A. *Iminosugars as Glycosidase inhibitors-Nojirimycin and Beyond*; Stüt, A. E. Ed.; Wiley-VCH: Weinheim, 1999, pp 8-30.
12. Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochem.* **2001**, *56*, 265.
[http://dx.doi.org/10.1016/S0031-9422\(00\)00451-9](http://dx.doi.org/10.1016/S0031-9422(00)00451-9)
13. Asano, N. *Curr. Top. Med. Chem.* **2003**, *3*, 471.
<http://dx.doi.org/10.2174/1568026033452438> PMID:12570862
14. Kato, A.; Kato, N.; Miyauchi, S.; Minoshima, Y.; Adachi, I.; Ikeda, K.; Asano, N.; Watson, A. A.; Nash, R. J. *Phytochem.* **2008**, *69*, 1261.
<http://dx.doi.org/10.1016/j.phytochem.2007.11.018>
15. Winchester, B. G. *Tetrahedron : Asymmetry* **2009**, *20*, 645.
<http://dx.doi.org/10.1016/j.tetasy.2009.02.048>
16. Rodriguez-Sanchez, S.; Ruiz-Aceituno, L.; Sanz, M. L.; Soria, A. C. *J. Agric. Food Chem.* **2013**, *61*, 4539.
<http://dx.doi.org/10.1021/jf305049k>
17. Pearson, M. S. M.; Mathé-Allainmat, M.; Frageas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159.
<http://dx.doi.org/10.1002/ejoc.200400823>

18. Kadouri-Puchot, C.; Comesse, S. *Amino Acids* **2005**, *29*, 101.
<http://dx.doi.org/10.1007/s00726-005-0193-x>
19. Compain, P.; Chagnault, V.; Martin, O. R. *Tetrahedron : Asymmetry* **2009**, *20*, 672.
<http://dx.doi.org/10.1016/j.tetasy.2009.03.031>
20. Davis, B. G. *Tetrahedron : Asymmetry* **2009**, *20*, 652.
<http://dx.doi.org/10.1016/j.tetasy.2009.03.013>
21. Zhang, G. L.; Zheng, X. J.; Zhang, L. H.; Ye, X. S. *Med. Chem. Comm.* **2011**, *2*, 909.
<http://dx.doi.org/10.1039/c1md00098e>
22. Wang, G. N.; Xiong, Y. L.; Ye, J.; Zang, G. L.; Ye, X. S., *Med. Chem. Lett.* **2011**, *2*, 682.
<http://dx.doi.org/10.1021/ml2000998>
23. Mondon, M.; Fontelle N.; Désiré, J.; Lecornué, F.; Guillard, J.; Marrot, J.; Blériot, Y. *Org. Lett.* **2012**, *14*, 870.
<http://dx.doi.org/10.1021/ol203385w>
PMid:22263550
24. Takahata H. *J. Pharm. Soc. Japan* **2013**, *133*, 575.
25. Poupon, E.; Luong, B. X.; Chiaroni, A.; Kunesch, N.; Husson, H.-P. *J. Org. Chem.* **2000**, *65*, 7208.
<http://dx.doi.org/10.1021/jo000434c>
26. Tite, T.; Tsimilaza, A.; Lallemand, M.-C.; Tillequin, F.; Leproux, P.; Libot, F.; Husson, H.-P. *Eur. J. Org. Chem.* **2006**, *4*, 863.
<http://dx.doi.org/10.1002/ejoc.200500754>
27. Tsimilaza, A.; Tite, T.; Boutefnouchet S.; Lallemand M.-C.; Tillequin F.; Husson H.-P. *Tetrahedron : Asymmetry* **2007**, *18*, 1585.
<http://dx.doi.org/10.1016/j.tetasy.2007.06.015>
28. Bonin, M.; Grierson, D. S.; Royer, J.; Husson, H.-P. *Org. Syntheses* **1992**, *70*, 54.
29. Guerrier, L.; Royer, J.; Grierson, D.S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754.
<http://dx.doi.org/10.1021/ja00364a053>
30. Shing, T. K. M.; Leung, G. Y. C.; Yeung, K. W. *Tetrahedron Lett.* **2003**, *44*, 9225.
<http://dx.doi.org/10.1016/j.tetlet.2003.09.226>
31. Shing, T. K. M.; Luk, T.; Lee, C. M. *Tetrahedron* **2006**, *62*, 6621.
<http://dx.doi.org/10.1016/j.tet.2006.01.116>
32. Shing, T. K. M.; Luk, T. *Tetrahedron : Asymmetry* **2009**, *20*, 883.
<http://dx.doi.org/10.1016/j.tetasy.2009.02.039>
33. Montchamp, J.-L.; Tian, F.; Hart, M. E.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 3897.
<http://dx.doi.org/10.1021/jo960170n>
34. Grubb, L. M.; Dowdy, A. L.; Blanchette, H. S.; Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett.* **1999**, *40*, 2691.
[http://dx.doi.org/10.1016/S0040-4039\(99\)00334-2](http://dx.doi.org/10.1016/S0040-4039(99)00334-2)
35. Shih, T. L.; Wu S. H. *Tetrahedron Lett.* **2000**, *41*, 2957.
[http://dx.doi.org/10.1016/S0040-4039\(00\)00280-X](http://dx.doi.org/10.1016/S0040-4039(00)00280-X)

36. Dinh, T. N.; Chen, A.; Chai, C. L. L. *Tetrahedron* **2011**, *67*, 3363.
<http://dx.doi.org/10.1016/j.tet.2011.03.063>
37. Ley, S. V.; Polara, A. *J. Org. Chem.* **2007**, *72*, 5943.
<http://dx.doi.org/10.1021/jo0703451>
38. Grierson, D. S.; Urrea, M.; Husson, H.-P. *Heterocycles* **1985**, *23*, 2493.
<http://dx.doi.org/10.3987/R-1985-10-2493>