Alkylation studies of a polyhydroxylated-cyano-piperidine scaffold

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Abstract

Hexahydro-3-phenyl-6,7,8-tri hydroxy-3R-[3α,5β,6β,7α,8β,8aβ]-5H-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 (2S,3R,4R,5S)-trihydroxyypipelic 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 °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 benzoylation of the hydroxyl functions (Scheme 2).

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 ¹³C-NMR allowed the characterization of its structure. The typical NMR signals at δ = 5.29 ppm and at δ = 112.5 ppm, observed in the ¹H and ¹³C NMR spectra respectively, were attributed to the C-6 position.
Scheme 2

As shown above, the β-elimination that took place was an obvious limitation for the access to the desired C-5-alkylated derivatives. This prompted us to change the protecting group for the β-hydroxyl function at the C-6 position to butane 2,3-bisacetal. This bisacetal was previously applied to various sugars\textsuperscript{30-32} or shikimic derivatives\textsuperscript{33-36} and in spite of the creation of two new stereogenic centers, the protection of vicinal diequatorial diols is described as being stereoselective.\textsuperscript{10-37} Thus, the protection of hydroxyl functions of 1 with 2,2,3,3-tetramethoxybutane, through stirring for a week in the presence of trimethylorthoformate and catalytic camphorsulfonic acid, has been performed. A 1:2 mixture (NMR determination) of the 6,7-butane-bisacetal 5 and its regioisomer 6 (Scheme 3) were obtained.

Scheme 3

Interestingly, an unexpected mixture of diastereoisomers on the butane 2,3-bisacetal protection for compounds 5 and 6, is formed. After crystallizing the diastereoisomers 6 in diethyl ether solution, this observation was confirmed by an X-Ray study. The stereochemistry of the protecting group is represented in Figure 2.
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) and torsion (°) of interest for complex 6a and 6b**

<table>
<thead>
<tr>
<th></th>
<th>6a</th>
<th>6b</th>
</tr>
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<tbody>
<tr>
<td>C7 O</td>
<td>1.433(3)</td>
<td>1.440(3)</td>
</tr>
<tr>
<td>C8 O</td>
<td>1.437(4)</td>
<td>1.441(4)</td>
</tr>
<tr>
<td>C2’ O</td>
<td>1.431(4)</td>
<td>1.424(4)</td>
</tr>
<tr>
<td>C3’ O</td>
<td>1.436(4)</td>
<td>1.448(4)</td>
</tr>
<tr>
<td>C2’ C3’</td>
<td>1.541(5)</td>
<td>1.546(5)</td>
</tr>
<tr>
<td>C7 O C2’</td>
<td>115.7(3)</td>
<td>111.9(2)</td>
</tr>
<tr>
<td>C7 C8 O</td>
<td>110.9(2)</td>
<td>107.8(2)</td>
</tr>
<tr>
<td>C3’ O C8</td>
<td>115.3(2)</td>
<td>113.1(3)</td>
</tr>
<tr>
<td>C2’ C3’ O</td>
<td>111.1(3)</td>
<td>111.1(3)</td>
</tr>
<tr>
<td>C3’ C2’ O</td>
<td>110.7(2)</td>
<td>110.5(3)</td>
</tr>
<tr>
<td>C7 - O - C2’ – C</td>
<td>151.1(3)</td>
<td>177.8(3)</td>
</tr>
<tr>
<td>C8 - O - C3’ – C</td>
<td>151.0(3)</td>
<td>175.4(3)</td>
</tr>
<tr>
<td>C7 - O - C2’ - O</td>
<td>86.5(3)</td>
<td>60.1(3)</td>
</tr>
<tr>
<td>C8 - O - C3’ - O</td>
<td>87.4(3)</td>
<td>62.2(4)</td>
</tr>
</tbody>
</table>
The protecting group of 6a favors a twist boat conformation while a chair conformation is preferred for 6b (Figure 2). $^1$H 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](image)

**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 $^1$H NMR), under classic conditions (LDA at –78 °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 °C, lactams 9 were obtained in 60% yield as confirmed by NMR and MS spectroscopy ($\delta$ 162.7 (CO); MS [M + H]$^+$ 424) and represented in Scheme 4. According to the literature the lactam formation can be explained by in situ addition of oxygen from the solvent to an extremely oxygen sensitive anion.
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.

These results suggested that the alkylation at α-aminonitrile position was strongly dependent 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.
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. Merk 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. \(^1\)H 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 wavelengths (\(\nu\)) are given in cm\(^{-1}\). Specific rotations were measured using a PerkinElmer model 341 polarimeter in a chloroform solution at 20 °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 °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 °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 °C. The reaction was quenched with NH4Cl (sat) then extracted with ethyl acetate (3 x 40 mL). The combined organic layers 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 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 ν cm⁻¹: 2229 (CN), 1H NMR (400 MHz, CDCl3): δ 1.13 (s, 3H, CH3), 3.35 (d, 1H, J = 9 Hz), 3.75 (dd, 1H, OH, J = 8 Hz, J = 9 Hz), 3.86 (t, 1H, J = 9 Hz), 3.89 (dd, 1H, J = 4.5 Hz, J = 8.5 Hz), 4.10 (dd, 1H, J = 4.5 Hz, J = 8.5 Hz), 4.37 (t, 1H, J = 8.5 Hz), 4.40 (d, 1H, J = 8 Hz), 4.59 (d, 1H, J = 11.5 Hz), 4.78 (d, 1H, J = 11.1 Hz), 4.80 (d, 1H, J = 11.5 Hz), 4.96 (d, 1H, J = 11 Hz), 4.99 (d, 1H, J = 11.5 Hz), 5.03 (d, 1H, J = 11.5 Hz), 7.15-7.50 (m, 20 H, H-aro). 13C NMR (75 MHz, CDCl3): δ 24.2 (CH3), 59.9, 61.3, 74.0, 76.1, 76.3 (3 x CH2-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 (CArH), 137.5, 138.1, 138.5, 143.5 (CAr). MS (IC, NH3): m/z [M + H]⁺ 561. HRMS (IC, NH3) m/z: calcd. for C36H30N2O4Na [M+Na]⁺: 583.2573; found 583.2513.

**Data for 4.** Rf: 0.5 (cyclohexane/ether 8/2), IR ν cm⁻¹: 2361 (CN), 1H NMR (400 MHz, CDCl3): δ 3.84 (dd, 1H, J = 7.5 Hz, J = 8.5 Hz), 4.20 (dd, 1H, J = 1.5 Hz, J = 9 Hz), 4.35 (dd, 1H, J = 6 Hz, J = 9 Hz), 4.38 (ddd, 1H, J = 1 Hz, J = 3 Hz, J = 7.5 Hz), 4.6-4.7 (d, 2H, J = 11.5 Hz), 4.72 (dd, 1H, J = 1.5 Hz, J = 6 Hz), 4.87 (d, 1H, J = 8.5 Hz), 4.9-5.1 (d, 2H, J = 11.5 Hz), 5.29 (d, 1H, J = 3 Hz), 7.20-7.50 (m, 15 H, H-aro). 13C NMR (75 MHz, CDCl3): δ 60.9, 72.3, 74.1, 74.9 (2XCH2Ph), 77.0, 78.1, 91.1, 112.5, 113.7 (CN), 127.3, 127.8, 128.1, 128.3, 128.5, 128.6 (CArH), 137.9, 138.2, 140.7 (CAr). MS (IC, NH3): m/z [M + H]⁺ 439. HRMS (IC, CH4) m/z: calcd. for C28H26N2O3 [M+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[b]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.), trimethylthoriformate (0.5 mL), and camphorsulfonic acid (0.1 mmol, 0.1 eq.). The solution was refluxed for 1 week, then neutralized with NaHCO3 (220 mg). After extraction with CH2Cl2 (5 x 30 mL), the combined organic layers were washed with a saturated solution of NaHCO3 then dried over Na2SO4 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 \( \nu \) cm\(^{-1}\): 3456 (OH), 2229 (CN), \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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, \( J = 8 \)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\(_6\)H\(_5\)). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 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\(_{Ar}\)), 135.9 (C\(_{Ar}\)). MS (IC, NH\(_3\)): \( m/z \) [M + H\(^+\)] 391. HRMS (IC, NH\(_3\)) \( m/z \): calcd. for C\(_{20}\)H\(_{26}\)N\(_2\)O\(_6\)Na [M+Na\(^+\)]: 413.1689; found 413.1692.

Data for 6. \( R_f: 0.25 \) (cyclohexane/ether 1/1.5), IR \( \nu \) cm\(^{-1}\): 3450 (OH), 2229 (CN). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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, \( J = 5 \)Hz), 4.30-4.40 (m, 2H), 7.30-7.40 (m, 5H, C\(_6\)H\(_5\)). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 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\(_{Ar}\)), 135.7 (C\(_{Ar}\)). MS (IC, NH\(_3\)): \( m/z \) [M + H\(^+\)] 391.

Crystallographic data for 6a. C20 H26 N2 O6, orthorhombic, P21 21 21, colorless, a = 6.9853(5) Å, b= 10.5499(6) Å, c = 26.538(2) Å, V= 1955.7(2) Å\(^3\), T = 293(2)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. C20 H26 N2 O6, 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) Å\(^3\), T = 293(2)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\(_2\)SO\(_4\), 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), \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 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\(_2\)O, \( J = 6.5 \) Hz), 7.20-7.50 (m, 5H, C\(_6\)H\(_5\)). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 18.7, 19.0 (2 CH\(_3\)), 48.2, 48.8, 55.4 (3XOCH\(_3\)), 62.5, 70.1, 72.3, 74.3, 75.4.
91.7, 95.9 (OCH₂O), 101.5, 101.8 (Cᵣ), 113.9 (CN), 127.7 129.0, 129.2 (C₅H), 135.9 (C₅H). MS (IC, NH₃): \( m/z \) [M + H]⁺ 435. HRMS (IC, NH₃) \( m/z \): calcd. for \( C_{22}H_{30}N_2O_7Na \) [M+Na]⁺: 457.1951; found 457.1903.

**Data for 8.** \( R_f \): 0.40 (cyclohexane/ether 1/1), IR ν cm⁻¹: 2229 (CN). \(^1\)H NMR (400 MHz, CDCl₃): \( \delta \) 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, C₅H₅). \(^{13}\)C NMR (75 MHz, CDCl₃): \( \delta \) 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 (Cᵣ), 113.6 (CN), 127.8, 129.1, 129.2 (C₅H), 136.0 (C₅H). MS (IC, NH₃): \( m/z \) [M + Na]⁺ 457. HRMS (IC, NH₃) \( m/z \): calcd. for \( C_{22}H_{30}N_2O_7Na \) [M+Na]⁺: 457.1951; found 457.1929.

**Procedure for the synthesis of 6,7-dimethoxy-9-methoxymethoxy-6,7-dimethyl-3-phenyloctahydro-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 cyclclohexane/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). \(^1\)H NMR (400 MHz, CDCl₃) : \( \delta \) 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, C₅H₅). \(^{13}\)C NMR (75 MHz, CDCl₃): \( \delta \) 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-CH₂O), 99.6, 101.8 (Cᵣ), 126.8 128.0, 128.9 (C₅H), 139.9 (C₅H), 162.7 (CO). MS (IC, NH₃): \( m/z \) [M + Na]⁺ 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 (2R, 3R, 4aR, 5S, 6R, 8R, 10aR, 10bS)-5-hydroxy-2,3-dimethoxy-2,3,6-trimethyl-8-phenylloctahydro-2H-[1,4]dioxino[2,3-c]oxazolo[3,2-a]pyridine-6-carbonitrile (11a), of (2R, 3R, 4aR, 5S, 8R, 10aR, 10bS)-5-hydroxy-2,3-dimethoxy-2,3-dimethyl-8-phenylhexahydro-2H-[1,4]dioxino[2,3-c]oxazolo[3,2-a]pyridin-6(3H)-one (12a) and of (2R, 3R, 4aR, 5S, 8R, 10aR, 10bS)-5-hydroxy-2,3-dimethoxy-2,3-dimethyl-8-phenylhexahydro-2H-[1,4]dioxino[2,3-c]oxazolo[3,2-a]pyridin-6(3H)-one (12b).** To a solution of 8, 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 Na₂SO₄, 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). $^1$H NMR (400 MHz, CDCl₃): δ 1.11-1.30 (3 s, 6H, 2 CH₃), 1.62 (s, 3H, CH₃), 2.90-3.20 (3 s, 6 H, 2 OCH₃), 3.90-4.00 (m, 1H), 4.10 (dd, 1H, $J = 6$Hz, $J = 8$Hz), 4.17 (t, 1H, $J = 9$Hz), 4.49 (t, 1H, $J = 6$ Hz, $J = 6.5$ Hz), 4.56 (d, 1H, $J = 10$ Hz), 4.69 (d, 1H, $J = 9$ Hz), 7.10-7.30 (m, 5H, C₆H₅). $^{13}$C NMR (75 MHz, CDCl₃): δ 14.1 (CH₃), 19.0 (2 CH₃), 47.8 (2 OCH₃), 62.3, 69.6, 70.5, 74.6, 89.0, 102.1 (C₁₀), 111.0, 112.9, 114.1 (CN), 128-129 (C₆H₅), 140.4 (C₆H₅). MS (IC, NH₃): $m/z$ [M + Na]⁺ 409. HRMS (IC, NH₃) $m/z$: calcd. for C₂₁H₂₅N₂O₆Na [M+Na]⁺: 409.1739; found 409.1745.

**Data for 11a.** $R_f$: 0.4 (cyclohexane/ether, 1:1), $[\alpha]_D = -109$ (c 0.58, MeOH); IR (film) cm⁻¹: 3484 (OH). $^1$H NMR (CDCl₃) δ 1.20 (s, 3H, CH₃), 1.42 (s, 3H, CH₃), 1.44 (s, 3H, CH₃), 3.38 (s, 3H, OCH₃), 3.41 (s, 3H, OCH₃), 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, $J = 8.6$ Hz, 1H), 7.22-7.38 (m, 5H arom). $^{13}$C NMR (CDCl₃): δ 19.1 (2XCH₃), 23.6 (CH₃), 48.4 (OCH₃), 48.5 (OCH₃), 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). HRMS (ESI): calcd. for C₂₁H₂₅N₂O₆ [M+H]⁺: 405.2026; found 405.2026. calcd. for C₂₀H₂₇NO₆Na [M-HCN+Na]⁺: 400.1736; found 401.1737.

**Data for 12a.** $R_f$: 0.6 (dichloromethane/methanol, 9:1), $[\alpha]_D = -26$ (c 1.01, MeOH); IR (film) cm⁻¹: 3390 (OH), 1668 (CO); $^1$H NMR (CDCl₃) δ 1.45 (s, 3H, CH₃), 1.47 (s, 3H, CH₃), 3.40 (s, 6H, OCH₃), 3.91 (d, $J = 8.2$ Hz, 1H), 4.20 (d, $J = 9.7$ Hz, 1H), 4.27-4.35 (m, 1H), 4.36 - 4.69 (m, 2H), 4.79 (d, $J = 6.7$ Hz, 1H), 4.88 (d, $J = 6.5$ Hz, 1H), 7.20-7.50 (m, 5H arom). $^{13}$C NMR (CDCl₃): δ 18.8 (CH₃), 19.0 (CH₃), 48.7 (OCH₃), 48.8 (OCH₃), 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 (CIV arom). 166.0 (CO), MS (ES⁺, MeOH): $m/z$ [M+Na]⁺ 402; [2M+Na]⁺ 780. HRMS (ES) : calcd. for C₁₀H₂₅NO₇Na [M+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); $^1$H NMR (CDCl₃) δ 1.38 (s, 3H, CH₃), 1.40 (s, 3H, CH₃), 3.41 (s, 6H, OCH₃), 4.05 (m, 2H), 4.18 (t, $J = 8.1$ 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 (CDCl₃): δ 17.6 (CH₃), 17.80 (CH₃), 48.4 (OCH₃), 48.6 (OCH₃), 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 (CIV arom). 166.2 (CO). MS (ES⁺, MeOH): $m/z$ [M+Na]⁺ 402; [2M+Na]⁺ 780. HRMS HRMS (ES): calcd. for C₁₉H₂₅NO₇Na [M+Na]⁺: 402.1529; found 402.1526.

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