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Metal-free hydroxy and aminocyanation of furanos-3-uloses

Tchambaga Etienne Camara^a, Dinet Steve-Evanes Koffi Teki^b, and Vincent Chagnault^{b, *}

^a Laboratoire de Constitution et Réaction de la Matière, Université Félix Houphouët-Boigny (UFHB) de Cocody - Côte d'Ivoire, 22 BP 582 Abidjan 22.

^b Laboratoire de Glycochimie, des Antimicrobiens et des Agroressources (LG2A), UMR 7378 CNRS, Université de Picardie Jules Verne, 33 rue Saint Leu, F-80039 Amiens Cedex, France

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ABSTRACT

TSAO-T and ATSAO-T analogues are molecules of interest that are able to inhibit the reverse transcriptase (RT) of HIV-1 and HCV. We also recently highlighted their antiproliferative properties. In all cases, the spiro cycle was a required group for biological activities, which led chemists to produce many derivatives, especially on this ring. These structures can be accessed through the formation of glycoaminonitriles and glycoacyanhydrins using methodologies not always adapted to the synthesis of large quantities. Moreover, these latter are poorly versatile (substrate-dependent), need expensive cyanogenic agents and implies the use of a metal in non-catalytic amounts. For this reason, we report here a new metal-free methodology for the synthesis of glycoaminonitriles and glycoacyanhydrins using molecular iodine (I₂).

1. Introduction

One of the research axes, developed in our laboratory, is the synthesis of [2',5'-bis-*O*-(*tert*butyldimethylsilyl)-β-D-ribofuranosyl]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole-2'',2''-dioxide)thymine analogues, known as TSAO-T. It is a nucleoside analogue with a spiro-heterocycle at position 3'. [1] Its derivatives are known for their ability to inhibit the reverse transcriptase of HIV-1 and HCV. [1,2] The spiro ring of these compounds is directly related to the biological activity, which was demonstrated by Das et al. in 2011, thanks to the crystal structure of the TSAO-T / HIV-1 complex. [3] Subsequently, a large number of modifications of the spiro ring has been described, leading to the appearance of new families such as ATSAO-T and PTSAO-T. [4–7]

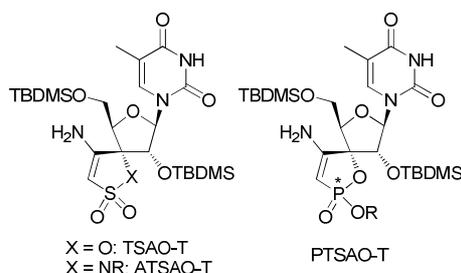
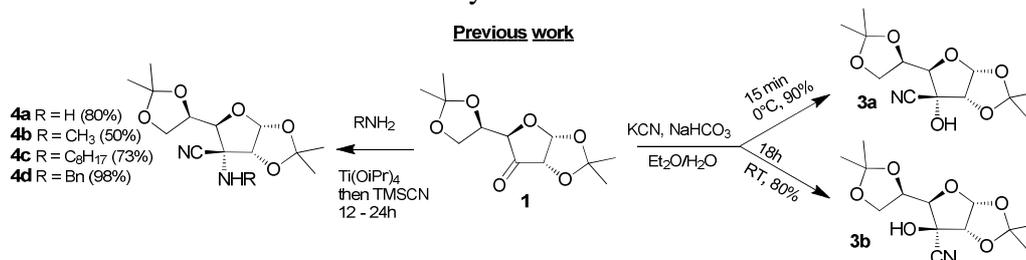


Figure 1: Molecular structures of TSAO-T, ATSAO-T and PTSAO-T

Regarding the ATSAO-T family, the endocyclic oxygen of the spiro ring was substituted by a nitrogen atom (Figure 1). We recently designed new derivatives of TSAO-T and ATSAO-T with antiproliferative activities. [8] All these structures are accessible *via* scaffold molecules such as glycoacyanhydrins **3a,b** and glycoaminonitriles **4a-d** (Scheme 1) which can be prepared from uloses **1** or **2**. [9] Glycoacyanhydrins are usually obtained through the method developed by Bourgeois using KCN in a biphasic mixture of solvents (Scheme 1). [9,10] It is possible to obtain either the *allo* **3a** or *gluco* **3b** derivative by modifying the reaction time and the temperature, compound **3a** being the kinetic product and **3b** the thermodynamic one.

Glycoaminonitriles can be obtained using the Strecker reaction which has been widely documented. [9,11] With regard to the preparation of TSAO analogues, ulose **1** is reacted with primary amines in the presence of Ti(OiPr)₄ to enhance the electrophilic character of the carbonyl group (Scheme 1). Once the imine intermediate is formed (not isolated), the cyanogenic agent TMSCN is added, affording the aminonitrile derivatives **4-d** in usually good yields. Ti(OiPr)₄ probably induces the stereoselectivity of the reaction by promoting the addition of cyanide ions on the β-face. The only disadvantages of this methodology are the poor versatility (substrate-dependent), the use of an expensive cyanogenic agent as well as the use of a metal in

* Corresponding author. Tel.: +33 3 22 82 88 12; fax: +33 3 22 82 75 60; e-mail: vincent.chagnault@u-picardie.fr



Scheme 1: Previous methods for the preparation of glycoaminonitriles and glycoaminonitriles.

non-catalytic amounts (1.2 equiv.). In our current work, we therefore tried to develop a more versatile, cost-effective and metal-free methodology. Obviously, the stereoselectivity was crucial, as the configurations of the C-3 carbons are important for biological activities of TSAO derivatives.[1] I₂ is a relatively weak oxidant and Lewis acid, which allows the use of acid-labile functional groups, such as isopropylidene or esters. These properties also allow the access to chemoselective reactions, which makes molecular iodine a very interesting reagent, especially in glycochemistry.[12–15] For this reason, we report here a new methodology for the synthesis of glycoaminonitriles and glycoaminonitriles using molecular iodine (I₂).

2. Results and discussion

As uloses **1** and **2** (Figure 2) are the most commonly used for the preparation of TSAO-T or ATSAO-T derivatives, we selected them as substrates for the development of the hydroxycyanation and aminocyanation reactions.[1,10]

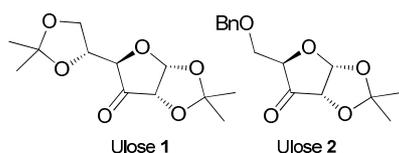
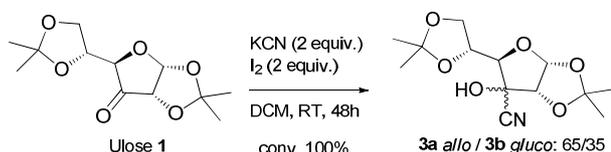


Figure 2: Chemical structures of uloses **1** and **2**. [1,10]

Concerning the formation of glycoaminonitriles, the main objective was the development of a more efficient and easier methodology. The solubility of the substrates and the reagents being very different (protected carbohydrates and KCN), the method developed by Bourgeois requires the use of a biphasic mixture of solvents. Vigorous stirring is therefore needed, which makes the synthesis difficult when using large quantities. However, using I₂ in the presence of KCN allows the formation of the intermediate ICN which is soluble in organic solvents. Under these conditions, biphasic mixtures are no longer required. Thus, in a first step, we tested the reaction of ulose **1** with only the presence of I₂ and KCN in dichloromethane at room temperature (RT) (**Scheme 2**).



Scheme 2: First attempt to form glycoaminonitrile using I₂.

Substrate **1** is completely converted after 48 hours of stirring. ¹H and ¹³C NMR spectra indicates the presence of a mixture of two epimers **3a** and **3b**. Without the use of diiodine, the formation of cyanhydrins was not detected. Therefore, I₂ allows the activation of the carbonyl at C-3 and nucleophilic attack of cyanide ions. Surprisingly, by adding 2 equiv. of potassium carbonate (K₂CO₃) to these reaction conditions, ulose **1** was completely converted in 24h but without remarkable influence on the stereoselectivity.

From our previous work, reactions involving I₂ are strongly affected by solvent effects.[14,16,17] Consequently, we tested different solvents for this reaction. As shown in **Table 1**, tetrahydrofuran (entry 2) and *tert*-butanol (entry 3) led to similar results to those obtained with DCM (same reaction time and same diastereomeric ratio). In the case of methanol (entry 4), a total conversion was obtained after only 2h of stirring at RT.

Table 1: Effect of solvent on the formation of glycoaminonitriles from ulose **1**.

Entry	Solvent	Time	Conversion	Yield*	Ratio 3a/3b
1	DCM	24h	100%	N.D.	65/35
2	THF	24h	100%	N.D.	65/35
3	<i>t</i> -BuOH	24h	100%	N.D.	60/40
4	MeOH	2h	100%	90% (3a)	100/0

*N.D.: Not Determined.

Moreover, 1D NMR spectroscopic analysis of the reaction mixture showed no trace of compound **3b**. Despite its known instability, the product was obtained in 90% yield after rapid purification on silica gel. The use of methanol as solvent led to the formation of the glycoaminonitrile with an *allo* configuration, even with longer reaction times. This was unexpected because under Bourgeois conditions (**Scheme 1**), compound **3a** was described as the kinetic product of the reaction. Using I₂, only compound **3a** was obtained even after 24 hours of stirring. This compound therefore seems to be stabilized, which will be discussed in scheme 4. Based on these results, the methodology was applied to ulose **2** (**Table 2**).

Table 2: Effect of solvent on the formation of glycoaminonitriles from ulose **2**.

Entry	Solvent	Time	Conversion	Yield*	Ratio 5a/5b
1	DCM	24h	100%	N.D.	70/30
2	MeOH	3h	100%	97% (5a)	100/0

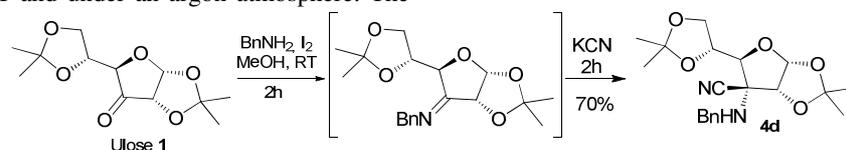
Reaction conditions: K₂CO₃ (2 equiv.), I₂ (2 equiv.), KCN (2 equiv.) at RT.

*N.D.: Not Determined.

As observed in entry 1 of **Table 2** (DCM as solvent), the reaction led to a mixture of cyanhydrins **5a** and **5b** with a 70/30 ratio and a total conversion after 24h. On the other hand, when using MeOH, only the formation of compound **5a** (having a *ribo* configuration) was observed after 3h of stirring at RT. A rapid purification on silica gel (to avoid isomerization and degradation) allowed the isolation of this product in 97% yield. Thus, the use of I₂ in methanol in a homogeneous phase, provided the glycoaminonitriles **3a** and **5a**, with excellent stereoselectivity and yields. A possible

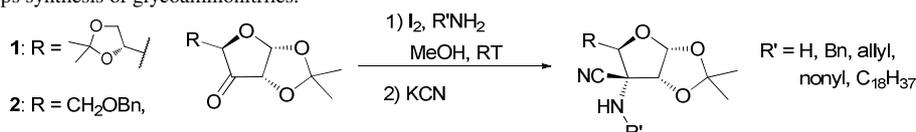
explanation on this remarkable stereoselectivity will be discussed later in **Scheme 4**.

Considering these results, we extended our work to the synthesis of glycoaminonitriles. Thus, ulose **1** was treated in the presence of I_2 , KCN and benzylamine in methanol. The reaction mixture was stirred at RT and under an argon atmosphere. The



Scheme 3: One-pot – two steps synthesis of compound **4d**.

Table 3: One-pot – two steps synthesis of glycoaminonitriles.



Entry	Ulose	Products	Yields	Entry	Ulose	Products	Yields
1	1		70% ^a	6	2		67% ^b
2	2		81% ^b	7	1		60% ^a
3	1		45% ^c	8	2		82% ^b
4	2		73% ^c	9	1		50% ^a
5	1		52% ^a	10	2		52% ^b

Reaction conditions: ^a I_2 (1 equiv.) and $R'NH_2$ (1.2 equiv.) were added successively to a methanolic solution of ulose **1**. The reaction mixture was stirred for 2h at RT and KCN (2 equiv.) was added. The reaction mixture was stirred for another 2h. ^b I_2 (1 equiv.) and $R'NH_2$ (1.2 equiv.) were added successively to a methanolic solution of ulose **2**. The reaction mixture was stirred for 6h at RT and KCN (2 equiv.) was added. The reaction mixture was stirred for another 6h. ^c Ulose **1** or **2** was dissolved in a commercial methanolic solution of ammonia (1M) and I_2 (1 equiv.) was added. The reaction mixture was stirred for 24h at RT and KCN (2 equiv.) was then added. The reaction mixture was finally stirred for another 24h.

aminonitrile. This suggests that compound **3a** is not a reaction intermediate. To facilitate the formation of glycoaminonitriles, we performed a two-step addition of the reactants. First, the imine intermediate was obtained by adding I_2 (1 equiv.) and benzylamine (1.2 equiv.) to a methanolic solution of ulose **1**. The mixture was stirred at RT for 2h and KCN (2 equiv.) was added (**Scheme 3**). After an additional 2h of stirring, spectrometric analyses indicated

total conversion was reached after 4h. Analysis of NMR and mass spectra of the reaction mixture indicate the presence of glycoacyanhydrin **3a** and no traces of glycoaminonitriles. The nucleophilic addition of cyanide ions to the carbonyl thus appears to be faster than that of the amine. Moreover, the resulting cyanhydrin **3a** did not evolve to the formation of the corresponding

a complete conversion. After treatment followed by purification on silica gel, only the derivative **4d** was obtained in 70% yield. No trace of the corresponding diastereomer was detected. The "one pot - two steps" synthesis in methanol allowed the formation of glycoaminonitrile **4d** in only 4h. To verify the versatility of the method, several amines were engaged in the aminocyanation reaction using uloses **1** and **2**. The results are reported in **Table 3**.

/ Ethyl acetate; 9/1). Compounds **3a** and **5a** were obtained as a colorless oil in 90% and 97% yields respectively. Spectroscopic analyses were in agreement with the literature.[1,10]

4.3. General experimental procedure for the preparation of glycoaminonitriles:

From ulose **1** (except **4a**): Ulose **1** (0.359 mmol) was suspended in methanol (4 mL) in a 10 mL round bottom flask. Diiodine (1 equiv., 0.359 mmol) and the desired primary amine (1.2 equiv., 0.431 mmol) were added successively. The reaction mixture was then stirred at room temperature for 2 hours. KCN (2 equiv., 0.720 mmol) was then added and the mixture was stirred at room temperature for another 2 hours and monitored by TLC.

From ulose **2** (except **6a**): Ulose **2** (0.359 mmol) was suspended in methanol (4 mL) in a 10 mL round bottom flask. Diiodine (1 equiv., 0.359 mmol) and the desired primary amine (1.2 equiv., 0.431 mmol) were added successively. The reaction mixture was stirred at room temperature for 6 hours. KCN (2 equiv., 0.720 mmol) was then added and the mixture was stirred at room temperature for another 6 hours and monitored by TLC.

For compounds **4a** and **6a**: Ulose **1** or **2** (0.359 mmol) was dissolved in a 1M methanolic solution of ammonia (4 mL) in a 10 mL round bottom flask. Diiodine (1 equiv., 0.359 mmol) was added and the reaction mixture was stirred at room temperature for 24 hours. KCN (2 equiv., 0.720 mmol) was then added and the mixture was stirred at room temperature for another 24 hours and monitored by TLC.

Excess of diiodine was reduced using a saturated solution of sodium thiosulfate until a white color is obtained (~1-2 mL). DCM (10 mL) and water (5 mL) were added and the organic layer separated. The aqueous phase was extracted 3 times with dichloromethane and the combined organic phases were dried over magnesium sulfate. After evaporation under reduced pressure, the residue can be purified by fast silica-gel column chromatography (Cyclohexane / Ethyl acetate; 9/1) to afford the entitled compound. Compounds **4a**,[23] **4d**,[22] **6a**[24] and **6b**[22] were obtained as colorless oils in 45%, 70%, 81% and 73% yields respectively. Spectroscopic analyses were in agreement with the literature.[22–24] Some analytical data were performed for compounds **4d** and **6b** to complement those in the literature.

4.3.1. 3-N-benzyl-3-amino-3-C-cyano-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-glucofuranose (**4d**)[22]

70%; colorless oil; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.46 – 7.25 (m, 5H, H-Ar), 5.93 (d, $J = 3.6$ Hz, 1H, H-1), 4.74 (d, $J = 3.6$ Hz, 1H, H-2), 4.42 (ddd, $J = 8.7, 6.2, 4.4$ Hz, 1H, H-5), 4.18 (dd, $J = 8.9, 6.2$ Hz, 1H, H-6b), 4.08 (d, $J = 12.2$ Hz, 1H, PhCH_{2b}), 4.04 (dd, $J = 9.0, 4.4$ Hz, 1H, H-6a), 3.95 (d, $J = 8.7$ Hz, 2H, PhCH_{2a} , H-4), 2.42 (s, 1H, NH), 1.60 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 138.8 (C_q -Ar), 128.5, 128.3, 127.5 (CH-Ar), 117.7 (CN), 113.9 (C_q), 110.3 (C_q), 104.5 (C_1), 82.4 (C_2), 81.1 (C_4), 75.2 (C_5), 68.8 (C_3), 67.6 (C_6), 49.9 (PhCH_2), 26.8 (CH_3), 26.7 (CH_3), 26.6 (CH_3), 25.1 (CH_3); $[\alpha]_D^{20} +52$ (c 0.1, CH_2Cl_2).

4.3.2. 3-N-allyl-3-amino-3-C-cyano-3-deoxy-1,2:5,6-di-O-isopropylidene- α -D-glucofuranose (**4e**)

52%; Colorless oil; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.95 (ddt, $J = 17.2, 10.2, 6.0$ Hz, 1H, $\text{CH}=\text{CH}_2$), 5.87 (d, $J = 3.5$ Hz, 1H, H-1), 5.28 (dq, $J = 17.2, 1.6$ Hz, 1H, $\text{CH}_{2b}=\text{CH}$), 5.14 (dq, $J = 10.2, 1.4$ Hz, 1H, $\text{CH}_{2a}=\text{CH}$), 4.74 (d, $J = 3.5$ Hz, 1H, H-2), 4.36 (ddd, $J = 8.8, 6.2, 4.4$ Hz, 1H, H-5), 4.15 (dd, $J = 9.0, 6.2$ Hz, 1H, H-6b), 4.00 (dd, $J = 9.0, 4.4$ Hz, 1H, H-6a), 3.87 (d, $J = 8.7$ Hz, 1H, H-4), 3.53 (dd, $J = 13.5, 6.0$ Hz, 1H, CH_{2b}NH), 3.40 (dt, $J = 13.1,$

6.2 Hz, 1H, CH_{2a}NH), 2.23 (s, 1H, NH), 1.56 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 135.5 ($\text{CH}=\text{CH}_2$), 117.6 (CN), 117.1 ($\text{CH}_2=\text{CH}$), 114.1 (C_q), 110.4 (C_q), 104.6 (C_1), 82.4 (C_2), 81.0 (C_4), 75.2 (C_5), 69.0 (C_3), 67.7 (C_6), 48.7 (CH_2NH), 26.7 (CH_3), 26.7 (CH_3), 26.7 (CH_3), 25.1 (CH_3); HRMS $[\text{M}+\text{H}^+]$: calcd. for $\text{C}_{16}\text{H}_{25}\text{N}_2\text{O}_5$ 325.1763, found 325.1755; $[\alpha]_D^{20} +59$ (c 0.1, CH_2Cl_2).

4.3.3. 3-amino-3-C-cyano-3-deoxy-3-N-nonyl-1,2:5,6-di-O-isopropylidene- α -D-glucofuranose (**4f**)

60%; Colorless oil; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.87 (d, $J = 3.5$ Hz, 1H, H-1), 4.71 (d, $J = 3.5$ Hz, 1H, H-2), 4.35 (ddd, $J = 8.7, 6.2$ Hz, $J = 4.5$ Hz, 1H, H-5), 4.14 (dd, 1H, $J = 8.9, 6.2$ Hz, H-6b), 3.99 (dd, $J = 8.9, 4.5$ Hz, 1H, H-6a), 3.85 (d, $J = 8.7$ Hz, 1H, H-4), 2.86 (m, 1H, CH_{2b}NH), 2.74 – 2.59 (m, 1H, CH_{2a}NH), 2.02 (s, 1H, NH), 1.54 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.33 (s, 6H, 2 CH_3), 1.29 – 1.19 (m, 14H, 7 CH_2), 0.91 – 0.76 (m, 3H, CH_3); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 117.9 (CN), 114.0 (C_q), 110.2 (C_q), 104.6 (C_1), 82.4 (C_2), 80.9 (C_4), 75.2 (C_5), 69.3 (C_3), 67.7 (C_6), 45.6 (CH_2NH), 31.9 (CH_2), 29.9 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 27.5 (CH_2), 27.1 (CH_2), 26.7 (CH_3), 26.7 (CH_3), 25.1 (CH_3), 22.7 (CH_2), 14.2 (CH_3); HRMS $[\text{M}+\text{H}^+]$: calcd. for $\text{C}_{22}\text{H}_{39}\text{N}_2\text{O}_5$ 411.2859, found 411.2852; $[\alpha]_D^{20} +28$ (c 0.1, CH_2Cl_2).

4.3.4. 3-amino-3-C-cyano-3-deoxy-3-N-octadecyl-1,2:5,6-di-O-isopropylidene- α -D-glucofuranose (**4g**)

50%; Colorless oil; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.89 (d, $J = 3.5$ Hz, 1H, H-1), 4.72 (d, $J = 3.6$ Hz, 1H, H-2), 4.37 (ddd, $J = 8.6, 6.2$ Hz, 4.4 Hz, 1H, H-5), 4.16 (dd, $J = 8.9, 6.2$ Hz, 1H, H-6b), 4.00 (dd, $J = 8.9, 4.4$ Hz, 1H, H-6a), 3.87 (d, $J = 8.7$ Hz, 1H, H-4), 2.90 – 2.84 (m, 1H, CH_{2b}NH), 2.72 – 2.66 (m, 1H, CH_{2a}NH), 2.03 (s, 1H, NH), 1.56 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.35 (s, 6H, 2 CH_3), 1.26 (m, 32 H, 16 CH_2), 0.87 (t, $J = 6.3$ Hz, 3H, CH_3); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 118.0 (CN), 114.0 (C_q), 110.3 (C_q), 104.7 (C_1), 82.4 (C_2), 81.0 (C_4), 75.3 (C_5), 69.4 (C_3), 67.8 (C_6), 45.7 (CH_2NH), 32.0 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 27.1 (CH_2), 26.8 (CH_3), 26.7 (CH_3), 25.1 (CH_3), 22.8 (CH_2), 14.2 (CH_3); HRMS $[\text{M}+\text{H}^+]$: calcd. for $\text{C}_{31}\text{H}_{57}\text{N}_2\text{O}_5$ 537.4267, found 537.4261; $[\alpha]_D^{20} +12$ (c 0.1, CH_2Cl_2).

4.3.5. 3-N-benzyl-3-amino-5-O-benzyl-3-C-cyano-3-deoxy-1,2-O-isopropylidene- α -D-ribofuranose (**6b**)[22]

81%; Colorless oil; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.35 – 7.28 (m, 10H, H-Ar), 5.99 (d, $J = 3.7$ Hz, 1H, H-1), 4.74 (d, $J = 3.8$ Hz, 1H, H-2), 4.60 (d, $J = 2.2$ Hz, 2H, OCH_2Ph), 4.14 (t, $J = 6$ Hz, 1H, H-4), 4.02 (d, $J = 12$ Hz, 1H, CH_{2b}NH), 3.92 (d, $J = 8$ Hz, 2H, H-5), 3.91 (d, $J = 12$ Hz, 1H, CH_{2a}NH), 2.20 (s, 1H, NH), 1.57 (s, 3H, CH_3), 1.37 (s, 3H, CH_3); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 138.7 (C_q -Ar), 137.5 (C_q -Ar), 127.7, 128.0, 128.6, 128.8 (CH-Ar), 117.5 (CN), 113.7 (C_q), 104.7 (C_1), 81.5 (C_2), 79.7 (C_4), 74.0 (OCH_2Ph), 69.6 (C_5), 68.2 (C_3), 50.0 (CH_2NH), 26.8 (CH_3), 26.9 (CH_3), 26.6 (CH_3); HRMS $[\text{M}+\text{H}^+]$: calcd. for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_4$ 395.1971, found 395.1968; $[\alpha]_D^{20} +42$ (c 0.1, CH_2Cl_2).

4.3.6. 3-N-allyl-3-amino-5-O-benzyl-3-C-cyano-3-deoxy-1,2-O-isopropylidene- α -D-ribofuranose (**6c**)

67%; Colorless oil; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.41 – 7.23 (m, 5H, H-Ar), 5.95 (d, $J = 3.6$ Hz, 1H, H-1), 5.93 – 5.81 (m, 1H, $\text{CH}=\text{CH}_2$), 5.26 (dd, $J = 17.2, 1.5$ Hz, 1H, $\text{CH}_2=\text{CH}$), 5.13 (dd, $J = 10.2, 1.3$ Hz, 1H, $\text{CH}_2=\text{CH}$), 4.74 (d, $J = 3.7$ Hz, 1H, H-2), 4.60 (d, $J = 3.4$ Hz, 2H, OCH_2Ph), 4.12 (t, $J = 5.9$ Hz, 1H, H-4), 3.89 (d, $J = 6.00$ Hz, 2H, H-5), 3.49 (dt, $J = 11.1, 5.1$ Hz, 1H, CH_{2b}NH), 3.40 (dt, $J = 12.00, 5.2$ Hz, 1H, CH_{2a}NH), 2.00 (s, 1H, NH), 1.56 (s, 3H, CH_3), 1.36 (s, 3H, CH_3); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 137.4 (C_q -Ar), 135.4 ($\text{CH}=\text{CH}_2$), 128.5 (CH-Ar), 128.4 (CH-Ar), 128.3 (CH-Ar), 127.9 (CH-Ar), 127.9 (CH-Ar), 117.3

(CN), 117.2 (CH₂=CH), 113.6 (C_q), 104.5 (C₁), 81.4 (C₂), 79.5 (C₄), 73.9 (OCH₂Ph), 69.5 (C₅), 68.0 (C₃), 48.5 (CH₂NH), 26.7 (CH₃), 26.5 (CH₃); HRMS [M+H⁺]: calcd. for C₁₉H₂₅N₂O₄ 345.1814, found 345.1811; [α]_D²⁰ +56 (c 0.1, CH₂Cl₂).

4.3.7. 3-amino-5-O-benzyl-3-C-cyano-3-deoxy-3-N-nonyl-1,2-O-isopropylidene-α-D-ribofuranose (**6d**)

82%; Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.27 – 7.18 (m, 5H, H-Ar), 5.95 (d, *J* = 3.7 Hz, 1H, H-1), 4.73 (d, *J* = 3.5 Hz, 1H, H-2), 4.60 (d, *J* = 4.7 Hz, 2H, OCH₂Ph), 4.09 (t, *J* = 6.00 Hz, 1H, H-4), 3.88 (dd, *J* = 6.00 Hz, 2.00 Hz, 2H, H-5), 2.77 – 2.84 (m, 1H, CH_{2b}NH), 2.68 – 2.76 (m, 1H, CH_{2a}NH), 1.76 (s, 1H, NH), 1.55 (s, 3H, CH₃), 1.43 – 1.52 (m, 2H, CH₂), 1.36 (s, 3H, CH₃), 1.26 (m, 12H, 6 CH₂), 0.89 (t, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 138.0 (C_q-Ar), 128.0, 128.0, 128.6 (CH-Ar), 117.7 (CN), 113.7 (C_q), 104.6 (C₁), 82.0 (C₂), 79.6 (C₄), 74.0 (OCH₂Ph), 69.7 (C₅), 68.5 (C₃), 45.8 (CH₂NH), 32.0 (CH₂), 30.1 (CH₂), 29.6 (CH₂), 29.5 (CH₂), 29.4 (CH₂), 29.4 (CH₂), 27.1 (CH₂), 26.8 (CH₃), 26.6 (CH₃), 22.8 (CH₂), 14.2 (CH₃); HRMS [M+H⁺]: calcd. for C₂₅H₃₉N₂O₄ 431.2910, found 431.2910; [α]_D²⁰ +31 (c 0.1, CH₂Cl₂).

4.3.8. 3-amino-5-O-benzyl-3-C-cyano-3-deoxy-3-N-octadecyl-1,2-O-isopropylidene-α-D-ribofuranose (**6e**)

52%; Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 7.49 – 7.02 (m, 5H, CH-Ar), 5.95 (d, *J* = 3.7 Hz, 1H, H-1), 4.73 (d, *J* = 3.5 Hz, 1H, H-2), 4.60 (d, *J* = 4.5 Hz, 2H, OCH₂Ph), 4.10 (t, *J* = 6.00 Hz, 1H, H-4), 3.89 (dd, *J* = 6.00 Hz, *J* = 1.8 Hz, 2H, H-5), 2.84 – 2.78 (m, 1H, CH_{2b}NH), 2.76 – 2.70 (m, 1H, CH_{2a}NH), 1.82 (s, 1H, NH), 1.56 (s, 3H, CH₃), 1.52 – 1.39 (m, 2H, CH₂), 1.36 (s, 3H, CH₃), 1.27 (m, 32H, 16 CH₂), 0.89 (t, *J* = 6.8 Hz, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 137.5 (C_q-Ar), 127.9, 128.0, 128.5 (CH-Ar), 117.7 (CN), 113.6 (C_q), 104.6 (C₁), 81.5 (C₂), 79.5 (C₄), 74.0 (OCH₂Ph), 69.7 (C₅), 68.5 (C₃), 45.8 (CH₂NH), 32.0 (CH₂), 30.1 (CH₂), 29.8 (CH₂), 29.8 (CH₂), 29.7 (CH₂), 29.7 (CH₂), 29.4 (CH₂), 29.5 (CH₂), 27.1 (CH₂), 26.8 (CH₃), 26.6 (CH₃), 22.8 (CH₂), 14.2 (CH₃); [α]_D²⁰ +26 (c 0.1, CH₂Cl₂).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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