Tetrahedron 68 (2012) 1145–1152

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Reactivity of sugar α-aminonitrile derivatives under titanium-mediated cyclopropanation conditions

Delphine Declerck [a], Solen Josse [a], Albert Nguyen Van Nhien [a], Jan Szymoniak [b], Philippe Bertus [c], Denis Postel [a,*]

[a] Laboratoire des glucides UMR6219, Université de Picardie Jules Verne, Faculté des Sciences, 33 rue Saint-Leu, 80039 Amiens, France
[b] Université de Reims Champagne-Ardenne, UMR-CNRS 6229, Institut de Chimie Moléculaire de Reims, BP 1039, 51687 Reims Cedex 02, France
[c] Université du Maine, UMR-CNRS 6011, Unité de Chimie Organique Moléculaire et Macromoléculaire, Avenue Olivier Messiaen, 72085 Le Mans Cedex 9, France

ARTICLE INFO

Article history:
Received 4 October 2011
Received in revised form 8 November 2011
Accepted 23 November 2011
Available online 4 December 2011

Keywords:
Nitriles
Cyclopropylamine
Titanium-catalyzed cyclopropanation
Imidazoline

ABSTRACT

The reactivity of different sugar α-aminonitriles has been studied under titanium-mediated cyclopropanation conditions. This study has been performed on amide, lactam, and imide derivatives. It has been possible to obtain spiro[furanose-3,3′-(3′,5′,6′,7′-tetrahydrospiro[cyclopropane-1,2′-pyrrolo[1,2-*a*]imidazole])] derivatives.

1. Introduction

The aminocyclopropyl framework is present in many biologically active compounds.[1–3] Among the various ways of preparing the cyclopropylamine moiety, the titanium-mediated cyclopropanation of nitriles[4,5] has been widely used, particularly in carbohydrate chemistry, largely due for the relatively easy access of the parent nitriles and to the reaction's high tolerance for protecting groups and other functionnalities.[6–11] Spirocyclic polyhydroxypyrrolidines **A**[7,8] and piperidines **B**[9,11] have been prepared by this method and were evaluated as potential glycosidase inhibitors (Fig. 1). Moreover, this reaction is also useful for 1-*C*-glycofuranosyl cyanides, affording the corresponding 1-*C*-aminocyclopropyl glycofuranose derivatives **C**.[6] Very recently, we have shown that polyhydroxy 2-(1-aminocyclopropyl) pyrrolidines **D** could be obtained from the corresponding nitriles,[12] accessible in diastereomerically pure form by aminocyanation.[13]

In the continuation of this work, we were interested in the synthesis of 3-amino-3-*C*-(1-aminocyclopropyl)-3-deoxyglycofuranose derivatives **E**, which would be accessible from the corresponding α-aminonitriles **F** (Scheme 1).

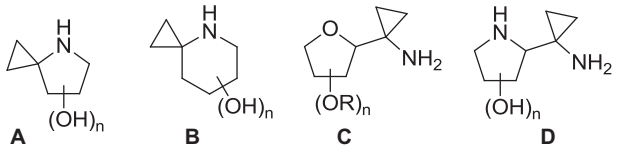
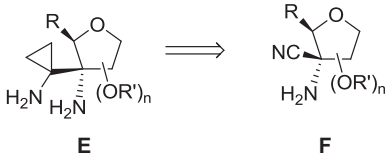


Fig. 1. Type of heterocyclic derivatives with a cyclopropyl moiety.



Scheme 1. Sugar α-aminonitrile as precursor for aminicyclopropyl derivatives.

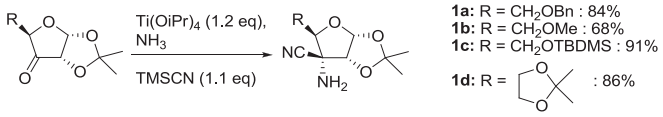
2. Results and discussions

In order to evaluate the cyclopropanation reaction, diversely protected α-aminonitriles **1a**–**d** were prepared using a strategy developed few years ago in our laboratory (Scheme 2).[14] The α-aminocyanation reaction was carried out on ulose derivatives (prepared according to standard procedures described in the

* Corresponding author. Tel.: +33 322827570; fax: +33 322827568; e-mail address: denis.postel@u-picardie.fr (D. Postel).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.11.067

literature) in NH_3/MeOH solution using Ti(O*i*-Pr)$_4$ followed by TMSCN. All the four α-aminonitriles were obtained with good yields and complete diastereoselectivity.



Scheme 2. α-Aminocyanation step.

In order to limit side-reactions, the primary amines of **1a**–**d** were protected before the cyclopropanation (Fig. 2).[5] Since it was shown that the cyclopropanation of nitriles is not affected by the presence of the amide moiety,[15] the primary amine of **1** was converted to an amide (**3a**–**d**), lactam (**5a**–**d**) or imide (**7**). Those functions were initially selected to determine the influence of carbonyl groups β to the nitrile, and the possible effects of steric hindrance.

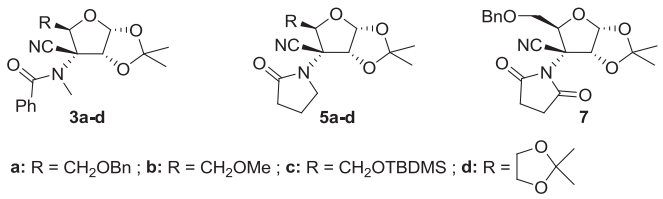
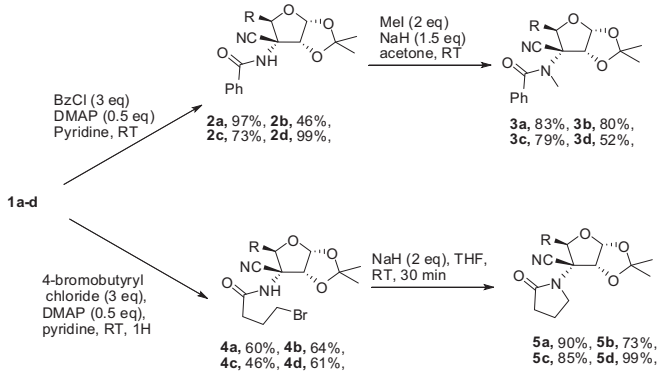


Fig. 2. Protected precursors.

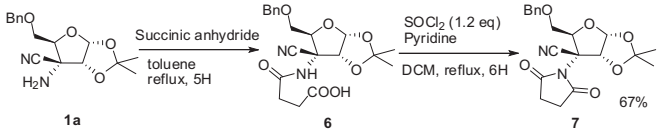
A two-step procedure was used to convert amine derivatives **1a**–**d** to the tertiary amides **3a**–**d**. Benzoylation using BzCl and DMAP in pyridine was followed by methylation of the resulting secondary amides **2a**–**d** in acetone (methyl iodide, NaH). Compounds **3a**–**d** were obtained in 37–80% overall yields over those two steps (Scheme 3).



Scheme 3. Functionalization as amides (**3a**–**d**) or lactams (**5a**–**d**).

The lactam formation was carried out under the conditions described by Norbeck et al. (Scheme 3).[16] The α-aminonitriles derivatives **1a**–**d** were initially converted to secondary amides **4a**–**d** with 4-bromobutyryl chloride (46–64%), and then lactam derivatives **5a**–**d** were obtained by intramolecular nucleophilic substitution in the presence of NaH in yields ranging from 73% to 99%.

The conversion of the primary amine of **1a** to the succinimide derivative **7** was also performed using a two-step procedure. First, addition of succinic anhydride to the sugar substrate in toluene at reflux led to the intermediate **6** in quantitative yield. The cyclization was achieved by addition of thionyl chloride[17] (Scheme 4).



Scheme 4. Functionalization as a succinimide.

The cyclopropanation reaction was first carried out with the amides **3a**–**d** (Table 1, entries 1–4). We observed, that the expected primary cyclopropylamine was never obtained under classical cyclopropanation conditions, i.e., addition of EtMgBr (1.5 equiv) to a mixture of the nitrile (1 equiv) and MeTi(O*i*-Pr)$_3$ (1.5 equiv) followed by $BF_3{\cdot}OEt_2$ (2 equiv).[9,12] The spiro[furanose-3,3′-(3′-hydro-4′-methyl-5′-phenyl-spiro[cyclopropane-1,2′-pyrrolo[1,2-*a*]imidazole])] derivatives **8a**-–**d** were isolated instead in 26–60% yield. Evidently, the close proximity of the amide protecting group influenced the outcome of the reaction.

The mechanism for the formation of the spirocyclopropyl derivatives is not entirely clear at present, but might be explained by the following hypothesis (Scheme 5). After the formation of the azatitanacyclopentane intermediate (**J**), the carbonyl moiety would be activated by the Lewis acid, leading to the addition of the nitrogen from the titanacycle to this activated carbonyl, giving **K**. The last step is the three-membered ring formation and the departure of hydroxytrifluoroborate. The deoxygenative role of $BF_3{\cdot}OEt_2$ has been reported previously in the literature.[18]

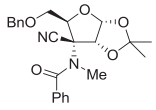
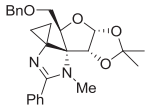
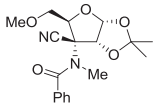
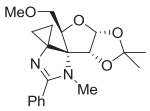
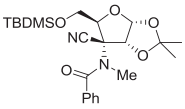
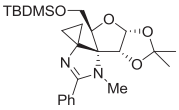
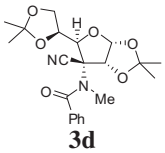
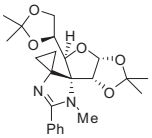
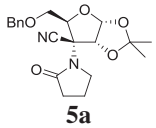
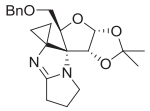
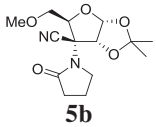
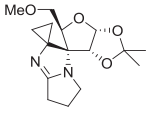
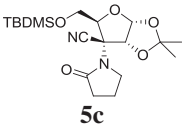
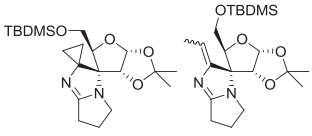
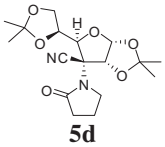
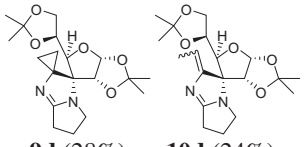
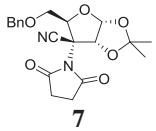
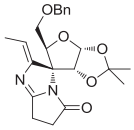
The reactivity was lower in the lactams series (compounds **5a**–**d**). Whereas the nitrile **5b** did not give any identifiable product, spirocyclopropane derivatives **9a**, **c**, and **d** were obtained in modest yields (11–28%). In two cases, we have also observed the isomeric compounds (**10c** and **10d**) as a side product. These 2′-ethylidene-pyrrolo[1,2-*a*]imidazole derivatives were probably obtained by direct hydrolysis of the metallacycle intermediate **K′**, followed by dehydration (Scheme 6).

When the reaction was performed with the nitrile **7**, bearing a succinimide moiety, no three-membered ring product was obtained (entry 9). Attempts to obtain the cyclopropane by modifying parameters such as the source and amount of titanium, the reaction time, the temperature or even the quantity of $BF_3{\cdot}OEt_2$ failed. Compound **11** was the only product obtained in 23% yield after chromatography on silica gel. The formation of this tetracyclic compound **11** can be explained by the same mechanism proposed in Scheme 6.

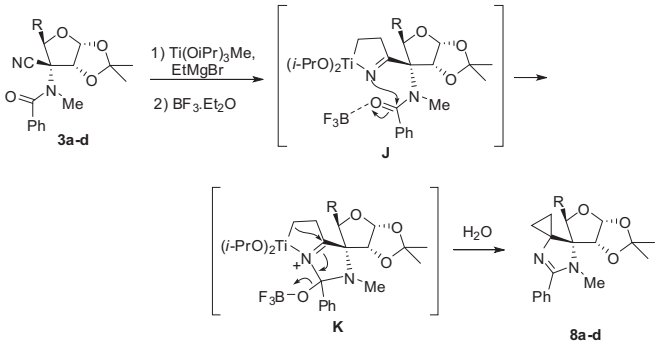
In order to better understand the reactivity of **7**, the reaction was performed without the addition of Lewis acid (Scheme 7). The imine **12** was obtained in 18% yield and fully characterized (see experimental section). Surprisingly, the product resulting from the hydrolysis, i.e., the imine **12**, is different from the one that would be expected from the literature, for which hydrolysis of the azatitanacyclopentane leads to a ketone. The unexpectedly high stability of the primary imine may be due to possible hydrogen bonding with the succinimide moiety and/or steric crowding around the imine.

In order to understand if the imine product was obtained from the metallacycle or from the Grignard reagent alone, the reaction

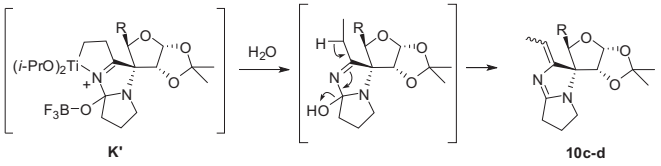
Table 1
Ti-mediated cyclopropanation of nitriles **3a**–**d**, **5a**–**d** and **7**

Entry	Nitrile	Products (yield)
1	 **3a**	 **8a** (42%)
2	 **3b**	 **8b** (32%)
3	 **3c**	 **8c** (26%)
4	 **3d**	 **8d** (60%)
5	 **5a**	 **9a** (21%)
6	 **5b**	 **9b** (0%)
7	 **5c**	 **9c** (11%) + **10c** (9%)
8	 **5d**	 **9d** (28%) + **10d** (24%)
9	 **7**	 **11** (23%)

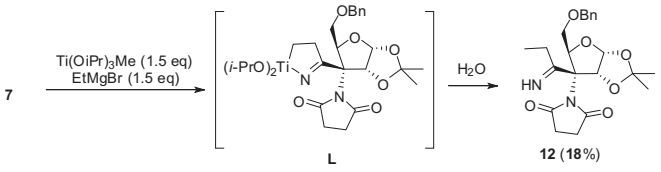
media was quenched with D_2O. If the observed imine results from the hydrolysis of the azatitanacyclopentane, insertion of deuterium should be observed in β position, whereas if the imine comes from the direct attack from EtMgBr on the nitrile, insertion of deuterium should be observed only on the nitrogen atom or in α position (Fig. 3). While deuterium at the latter positions are easily exchange, the deuteriation of the terminal position will be significant with respect to the proposed mechanism.



Scheme 5. Formation of cyclopropyl from amide derivatives.



Scheme 6. Lactams reactivity.



Scheme 7. Formation of imine **12**.

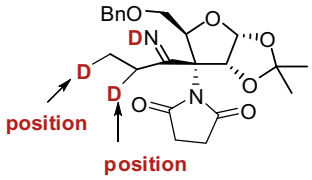


Fig. 3. Different deuterium positions.

An NMR analysis of the product obtained after treatment with D_2O shows that the signal corresponding to the methyl of the exocyclic chain had an integration intensity of only 2 rather than 3 (as after treatment with H_2O). Moreover this signal had a different multiplicity as the one observed with H_2O. This would tend to indicate the presence of a CH_2D moiety and thus that the titanacycle formation occurs and then indicates that, in this case, the limiting stage of the reaction is the cyclic regression.

3. Conclusion

Titanium-mediated cyclopropanation of glyco-α-aminonitriles on a furanose scaffold was studied to give access to new polycyclic cyclopropane derivatives. The amino group was previously functionalized as a lactam or amide. Yields obtained are generally weak, the quantities of starting material recovered after reaction are also low, and products seeming to originate from hydrolysis of the titanacycle are observed, indicating that the titanacycle contraction process remains difficult.

The electronic effects of carbonyls and/or the strain of the cycle carried by the amine in α to the nitrile function have an influence on the formation of cyclopropylamines. Thus, in contrast to the succinimide derivatives, lactams and acyclic amides provided

cyclopropanes. Moreover, the latter gave better yields that the lactams.

Globally, it was established that the best results are obtained when the protecting group on C5 and/or C6 position is a benzyl or an isopropylidene group, while the lowest yields are obtained when R1 is a methoxymethylene group. It may therefore be concluded that the hindrance of the groups present in position 4 does not have a major influence on the cyclopropanation.

4. Experimental section

4.1. General information

Melting points are uncorrected. Optical rotations were recorded in $CHCl_3$ or MeOH solutions. ^1H NMR (300.13 MHz) and ^{13}C NMR (75.47 MHz) spectra were recorded in $CDCl_3$ or MeOD-d_4. δ values are given in parts per million and J in hertz. TLC was performed on Silica F_{254} and detection by UV light at 254 nm or by charring with phosphomolybdic/H_2SO_4 reagent. FTIR spectra were obtained on an AVATARTM320 neat using ATR and are reported in cm^{-1}. Mass spectral data were acquired on a WATERS Micromass ZQ spectrometer or a WATERS Micromass Q-TOFF spectrometer. Column chromatography was effected on Silica Gel 60 (230 mesh). Cyclohexane and ethyl acetate were distilled before use. Cyclopropanation reactions were run under an atmosphere of nitrogen. Anhydrous solvents were transferred via oven-dried syringe.

4.2. General method for the preparation of 2a–d

To 1 equiv of **1a**–**d** in pyridine were added 0.5 equiv of DMAP and 3 equiv of benzoyl chloride. The reaction mixture was stirred at room temperature for 2 h and then EtOAc and H_2O were added. The aqueous layer was extracted twice with EtOAc and the organic layers were dried with Na_2SO_4 before being evaporated. The crude product was purified by flash chromatography (cyclohexane/EtOAc).

*4.2.1. 3-Benzamido-5-O-benzyl-3-C-cyano-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (**2a**).* Compound **2a** has been prepared starting from 1.8 g (5.92 mmol) of **1a**, 2.0 mL of benzoyl chloride, 355 mg of DMAP, and 20 mL of pyridine and obtained as a white solid in 97% yield after purification with cyclohexane/EtOAc 8:2. Mp 128–130 °C; $[\alpha]_D^{20}$ +57.2 (*c* 0.83, CH_2Cl_2); IR (ATR): ν 2878, 1631, 1518, 1454, 1151, 732, 707 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.86–7.70 (m, 3H, C_6H_5), 7.63–7.54 (m, 2H, C_6H_5), 7.39–7.31 (m, 5H, C_6H_5), 7.15 (sl, 1H, NH), 6.24 (d, 1H, H_1, J=3.8), 5.83 (d, 1H, H_2, J=3.8), 4.71 (dd, 1H, H_4, J=4.8–6.3), 4.63 (d, 1H, CH_2Ph, J=11.2), 4.51 (d, 1H, CH_2Ph, J=11.2), 3.63–3.48 (m, 2H, H_5), 1.41 (s, 3H, CH_3), 1.38 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.2 (CO), 137.5–134.2 (C^{IV}, C_6H_5), 128.9–127.4 (CH, C_6H_5), 115.8 (CN), 113.9 (C_{iso}), 103.1 (C_1), 81.3 (C_2), 75.2 (CH_2Ph), 71.8 (C_4), 67.8 (C_5), 44.9 (C_3), 26.5 (CH_3), 26.2 (CH_3); ES-MS $[M+Na]^+$ *m/z* 431.

*4.2.2. 3-Benzamido-3-C-cyano-3-deoxy-1,2-O-isopropylidene-5-O-methyl-α-D-ribofuranose (**2b**).* Compound **2b** has been prepared starting from 1.6 g of **1b** (7.01 mmol), 2.5 mL of benzoyl chloride, 400 mg of DMAP, and 20 mL of pyridine and obtained as a white solid in 46% yield after purification with cyclohexane/EtOAc 8:2. Mp 225–227 °C; $[\alpha]_D^{20}$ +54.4 (*c* 0.79, CH_2Cl_2); IR (ATR): ν 3007, 1639, 1379, 1054, 728, 697 cm^{-1}; ^1H NMR ^1H NMR($CDCl_3$, 300 MHz): δ 7.81–7.78 (m, 2H, C_6H_5), 7.58–7.53 (m, 1H, C_6H_5), 7.49 (m, 2H, C_6H_5), 7.02 (sl, 1H, NH), 5.03 (d, 1H, H_1, J=3.7), 5.43 (d, 1H, H_2, J=3.7), 4.33 (dd, 1H, H_4, J=5.4–7.5), 3.99–3.90 (m, 2H, H_5), 3.48 (s, 3H, OCH_3), 1.54 (s, 3H, CH_3), 1.37 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.7 (CO), 138.5 (C^{IV}, C_6H_5), 132.6–127.5 (CH, C_6H_5), 115.9 (CN), 114.0 (C_{iso}), 104.7 (C_1), 82.5 (C_2), 78.0 (C_4), 71.5 (C_5), 61.5 (C_3), 60.1 (OCH_3), 26.8 (CH_3), 26.5 (CH_3); ES-HRMS for $C_{17}H_{20}N_2O_5Na$ $[M+Na]^+$ calcd 355.1270, found 355.1280.

*4.2.3. 3-Benzamido-5-O-tert-butyldimethylsilyl-3-C-cyano-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (**2c**).* Compound **2c** has been prepared starting from 5.3 g of **1c** (0.016 mol), 5.4 mL of benzoyl chloride, 989 mg of DMAP, and 50 mL of pyridine and obtained as a white solid in 73% yield after purification with cyclohexane/EtOAc 9:1. Mp 132–136 °C; $[\alpha]_D^{20}$ +59.1 (*c* 1.00, $CHCl_3$); IR (ATR): ν 2930, 1678, 1095, 773, 709 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.81–7.77 (m, 2H, C_6H_5), 7.57–7.51 (m, 2H, C_6H_5), 7.47–7.41 (m, 1H, C_6H_5), 7.05 (sl, 1H, NH), 6.00 (d, 1H, H_1, J=4.0), 5.50 (d, 1H, H_2, J=4.0), 4.29 (dd, 1H, H_{5a}, J=4.3–9.5), 4.17 (dd, 1H, H_{5b}, J=4.3–9.5), 4.09 (t, 1H, H_4, J=9.5), 1.54 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 0.85 (s, 9H, O*TB*DMS), 0.13 (s, 3H, OTBD*MS*), 0.09 (s, 3H, OTBD*MS*); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.5 (CO), 132.4–127.3 (CH, C_6H_5), 115.8 (CN), 113.7 (C_{iso}), 104.4 (C_1), 82.2 (C_2), 78.6 (C_4), 62.6 (C_5), 61.7 (C_3), 26.5 (CH_3), 26.3 (CH_3), 25.7 (O*TBDMS*), 18.0 (C^{IV}, OTBDMS); ES-HRMS for $C_{22}H_{32}N_2O_5SiNa$ $[M+Na]^+$ calcd 455.1978, found 455.1974.

*4.2.4. 3-Benzamido-3-C-cyano-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**2d**).* Compound **2d** has been prepared starting from 3.0 g of **1d** (0.010 mol), 3.7 mL of benzoyl chloride, 645 mg of DMAP, and 30 mL of pyridine and obtained as a brownish solid in 99% yield after purification with cyclohexane/EtOAc 8:2. Mp 123–125 °C; $[\alpha]_D^{20}$ +29.0 (*c* 0.79, CH_2Cl_2); IR (ATR): ν 2998, 1673, 1084, 1027, 707 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.62–7.44 (m, 5H, C_6H_5), 7.12 (sl, 1H, NH), 5.99 (d, 1H, H_1, J=3.5), 5.55 (d, 1H, H_2, J=3.5), 4.59–4.53 (m, 1H, H_4), 4.26 (dd, 1H, H_{6a}, J=4.5–9.2), 4.13 (dd, 1H, H_{6b}, J=4.5–9.2), 3.95 (d, 1H, H_5, J=9.2), 1.58 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.6 (CO), 133.6 (C^{IV}, C_6H_5), 129.1–128.5 (CH, C_6H_5), 115.8 (CN), 113.9 (C_{iso}), 110.6 (C_{iso}), 104.6 (C_1), 82.1 (C_2), 79.2 (C_4), 74.5 (C_5), 67.6 (C_6), 61.9 (C_3), 27.0 (CH_3), 26.5 (CH_3), 26.4 (CH_3), 24.5 (CH_3); ES-HRMS for $C_{20}H_{24}N_2O_6Na$ $[M+Na]^+$ calcd 411.1532, found 411.1542.

4.3. General method for the preparation of 3a–d

To 1 equiv of compounds **2a**–**d** in acetone were added 1.5 equiv of NaH and 2 equiv of MeI. The reaction mixture was stirred at room temperature for 5 h before filtration and evaporation. The crude product was purified by flash chromatography (cyclohexane/EtOAc).

*4.3.1. 5-O-Benzyl-3-C-cyano-3-deoxy-1,2-O-isopropylidene-3-N-methylbenzamido-α-D-ribofuranose (**3a**).* Compound **3a** has been prepared starting from 2.5 g of **2a** (6.12 mmol), 0.6 mL of MeI, 215 mg of NaH, and 40 mL of acetone and obtained as needles in 93% yield after purification with cyclohexane/EtOAc 95:5. $[\alpha]_D^{20}$ +40.5 (*c* 0.88, CH_2Cl_2); IR (ATR): ν 2873, 1669, 1532, 1455, 1117, 741, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.41–7.36 (m, 10H, C_6H_5), 6.02 (d, 1H, H_1, J=3.9), 5.54 (d, 1H, H_2, J=3.9), 4.81 (t, 1H, H_4, J=5.8), 4.70 (d, 1H, CH_2Ph, J=11.4), 4.62 (d, 1H, CH_2Ph, J=11.4), 4.14–4.03 (m, 2H, H_5), 3.09 (s, 3H, NCH_3), 1.58 (s, 3H, CH_3), 1.37 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.1 (CO), 134.9 (C^{IV}, C_6H_5), 130.6 (CH, C_6H_5), 128.7 (C^{IV}, C_6H_5), 128.6–128.1 (CH, C_6H_5), 115.3 (CN), 112.8 (C_{iso}), 103.3 (C_1), 82.4 (C_2), 77.5 (C_4), 69.7 (C_5), 65.4 (CH_2Ph), 65.4 (C_3), 37.6 (NCH_3), 29.3 (CH_3), 26.4 (CH_3); ES-HRMS for $C_{24}H_{26}N_2O_5Na$ $[M+Na]^+$ calcd 445.1739, found 445.1741.

*4.3.2. 3-C-Cyano-3-deoxy-1,2-O-isopropylidene-3-N-methylbenzamido-5-O-methyl-α-D-ribofuranose (**3b**).* Compound **3b** has been prepared starting from 708 mg of **2b** (2.13 mmol), 0.3 mL of MeI, 77 mg of NaH, and 20 mL of acetone and obtained as syrup in 80% yield after purification with cyclohexane/EtOAc 8:2. $[\alpha]_D^{20}$

+82.8 (*c* 1.13, CH_2Cl_2); IR (ATR): *ν* 2975, 1650, 1378, 1111, 1086, 1065, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.47–7.33 (m, 5H, C_6H_5), 5.96 (d, 1H, H_1, *J*=3.9), 5.49 (d, 1H, H_2, *J*=3.9), 4.70 (t, 1H, H_4, *J*=4.0), 3.97–3.86 (m, 2H, H_5), 3.44 (s, 3H, OCH_3), 3.09 (s, 3H, NCH_3), 1.53 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 173.0 (CO), 135.0 (C^{IV}, C_6H_5), 130.6–127.5 (CH, C_6H_5), 115.3 (CN), 112.8 (C_{iso}), 103.2 (C_1), 82.3 (C_2), 76.9 (C_4), 72.0 (C_5), 65.2 (C_3), 59.6 (OCH_3), 37.5 (NCH_3), 26.5 (CH_3), 26.4 (CH_3); ES-HRMS for $C_{18}H_{22}N_2O_5Na$ $[M+Na]^+$ calcd 369.1426, found 369.1411.

*4.3.3. 5-O-tert-Butyldimethylsilyl-3-C-cyano-3-deoxy-1,2-O-isopropylidene-3-N-methylbenzamido-α-D-ribofuranose (**3c**).* Compound **3c** has been prepared starting from 4.0 g of **2c** (9.25 mmol), 1.2 mL of MeI, 555 mg of NaH, and 100 mL of acetone and obtained as white solid in 79% yield after purification with cyclohexane/EtOAc. Mp 108–112 °C; $[\alpha]_D^{20}$ +70.8 (*c* 1.03, $CHCl_3$); IR (ATR): *ν* 2955, 1639, 1375, 729, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.37 (m, 5H, C_6H_5), 5.94 (d, 1H, H_1, *J*=3.9), 5.53 (d, 1H, H_2, *J*=3.9), 4.69 (t, 1H, H_4, *J*=5.5), 4.19–4.08 (m, 2H, H_5), 3.14 (s, 3H, NCH_3), 1.54 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 0.90 (s, 9H, O*TB*DMS), 0.13 (s, 3H, OTBD*M*S), 0.11 (s, 3H, OTBD*M*S); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 172.9 (CO), 135.3 (C^{IV}, C_6H_5), 130.4–127.3 (CH, C_6H_5), 115.2 (CN), 112.7 (C_{iso}), 103.1 (C_1), 82.6 (C_2), 77.4 (C_4), 65.6 (C_3), 63.1 (C_5), 37.9 (NCH_3), 26.5 (CH_3), 25.9 (CH_3+O*TBDM*S), 18.3 (C^{IV}, OTBDMS); ES-HRMS for $C_{23}H_{34}N_2O_5NaSi$ $[M+Na]^+$ calcd 469.2135, found 469.2125.

*4.3.4. 3-C-Cyano-3-deoxy-1,2:5,6-di-O-isopropylidene-3-N-methylbenzamido-α-D-allofuranose (**3d**).* Compound **3d** has been prepared starting from 3.7 g of **2d** (9.53 mmol), 1.3 mL of MeI, 610 mg of NaH, and 70 mL of acetone and obtained as white solid in 52% yield after purification with cyclohexane/EtOAc 8:2. Mp 171–176 °C; $[\alpha]_D^{20}$ +88.9 (*c* 1.02, $CHCl_3$); IR (ATR): *ν* 3004, 1653, 1373, 731, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.50–7.42 (m, 5H, C_6H_5), 5.95 (d, 1H, H_1, *J*=3.9), 5.57 (d, 1H, H_2, *J*=3.9), 4.61–4.31 (m, 2H, H_4+H_5), 4.28 (dd, 1H, H_{6a}, *J*=6.0–8.9), 4.06 (dd, 1H, H_{6b}, *J*=6.0–8.9), 3.19 (s, 3H, NCH_3), 1.55 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.40 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 173.2 (CO), 135.2 (C^{IV}, C_6H_5), 130.7–127.7 (CH, C_6H_5), 115.3 (CN), 113.1 (C_{iso}), 110.5 (C_{iso}), 103.3 (C_1), 82.8 (C_2), 78.8 (C_4), 74.6 (C_5), 68.1 (C_6), 66.1 (C_3), 38.3 (NCH_3), 26.6 (CH_3), 26.5 (CH_3), 26.2 (CH_3), 24.8 (CH_3); ES-HRMS for $C_{21}H_{26}N_2O_6Na$ $[M+Na]^+$ calcd 425.1689, found 425.1678.

4.4. General method for the preparation of 4a–d

To 1 equiv of compounds **1a–d** in pyridine were added under argon 0.5 equiv of DMAP and 3 equiv of 4-bromobutyryl chloride. The reaction mixture was stirred at room temperature for 1 h and then EtOAc and H_2O were added. The aqueous layer was extracted twice with EtOAc and the organic layers were dried with Na_2SO_4 before being evaporated. The crude product was purified by flash chromatography (cyclohexane/EtOAc).

*4.4.1. 5-O-Benzyl-3-(4-bromobutanamido)-3-C-cyano-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (**4a**).* Compound **4a** has been prepared starting from 1.0 g of **1a** (3.29 mmol), 1.1 mL of 4-bromobutyryl chloride, 201 mg of DMAP, and 8.5 mL of pyridine and obtained as syrup in 60% yield after purification with cyclohexane/EtOAc 7:3. $[\alpha]_D^{20}$ +5.2 (*c* 1.04, $CHCl_3$); IR (ATR): *ν* 2987, 1695, 1671, 1653, 1514, 1454, 734, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.42–7.30 (m, 5H, C_6H_5), 6.62 (s, 1H, NH), 5.94 (d, 1H, H_1, *J*=3.7), 5.30 (d, 1H, H_2, *J*=3.7), 4.70–4.57 (m, 2H, CH_2Ph), 4.24 (dd, 1H, H_4, *J*=4.9–7.9), 4.02–3.92 (m, 2H, H_5), 3.45 (t, 2H, CH_2Br, *J*=6.5), 2.36–2.90 (m, 2H, CH_2CO), 2.21–2.12 (m, 2H, $CH_2CH_2CH_2$), 1.53 (CH_3), 1.34 (CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 171.6 (CO), 136.9 (C^{IV}, C_6H_5), 128.7–128.1 (CH, C_6H_5), 115.7 (C_{iso}), 113.6 (CN), 104.4 (C_1), 81.8 (C_2), 77.5 (C_4), 74.3 (CH_2Ph), 69.0 (C_5), 61.1 (C_3), 33.7 (CH_2CO), 32.9 (CH_2Br), 27.8 ($CH_2CH_2CH_2$), 26.6 (CH_3), 26.3 (CH_3); ES-HRMS for $C_{20}H_{25}N_2O_5NaBr$ $[M+Na]^+$ calcd 475.0845, found 475.0846.

*4.4.2. 3-(4-Bromobutanamido)-3-C-cyano-3-deoxy-1,2-O-isopropylidene-5-O-methyl-α-D-ribofuranose (**4b**).* Compound **4b** has been prepared starting from 200 mg of **1b** (0.88 mmol), 310 μL of 4-bromobutyryl chloride, 53 mg of DMAP, and 2.2 mL of pyridine and obtained as syrup in 64% yield after purification with cyclohexane/EtOAc 7:3. $[\alpha]_D^{20}$ +8.3 (*c* 1.01, $CHCl_3$); IR (ATR): *ν* 2995, 1660, 1531, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 6.42 (s, 1H, NH), 5.95 (d, 1H, H_1, *J*=3.7), 5.25 (d, 1H, H_2, *J*=3.7), 4.15 (dd, 1H, H_4, *J*=5.3–7.5), 3.84–3.77 (m, 2H, H_5), 3.49–3.47 (m, 2H, CH_2CONH), 3.45 (s, 3H, OCH_3), 2.45–2.40 (m, 2H, CH_2Br), 2.22–2.10 (m, 2H, $CH_2CH_2CH_2$), 1.50 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 171.5 (CO), 115.7 (CN), 113.7 (C_{iso}), 104.4 (C_1), 82.0 (C_2), 77.7 (C_4), 71.1 (C_5), 60.9 (C_3), 59.9 (OCH_3), 33.7 (CH_2CO), 32.9 (CH_2Br), 27.9 ($CH_2CH_2CH_2$), 26.7 (CH_3), 26.3 (CH_3); ES-HRMS for $C_{14}H_{21}N_2O_5NaBr$ $[M+Na]^+$ calcd 399.0532, found 399.0514.

*4.4.3. 3-(4-Bromobutanamido)-5-O-tert-butyldimethylsilyl-3-C-cyano-3-deoxy-1,2-O-isopropylidene-α-D-ribofuranose (**4c**).* Compound **4c** has been prepared starting from 1.5 g of **1c** (4.57 mmol), 1.6 mL of 4-bromobutyryl chloride, 314 mg of DMAP, and 12 mL of pyridine and obtained as syrup in 46% yield after purification with cyclohexane/EtOAc 9:1. $[\alpha]_D^{20}$ +4.4 (*c* 1.07, $CHCl_3$); IR (ATR): *ν* 2995, 1527, 1124, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 6.44 (sl, 1H, NH), 5.98 (d, 1H, H_1, *J*=3.7), 5.39 (d, 1H, H_2, *J*=3.7), 4.17–4.10 (m, 2H, H_5), 4.06–4.00 (t, 1H, H_4, *J*=10.4), 3.68–3.66 (m, 1H, CH_2Br), 3.55–3.51 (m, 1H, CH_2Br), 2.50–2.40 (m, 2H, CH_2CONH), 2.35–2.13 (m, 2H, $CH_2CH_2CH_2$), 1.57 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 0.97 (s, 9H, O*TB*DMS), 0.19 (s, 3H, OTBD*M*S), 0.18 (s, 3H, OTBD*M*S); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 170.9 (CO), 115.7 (CN), 113.6 (C_{iso}), 104.4 (C_1), 82.0 (C_2), 78.4 (C_4), 62.4 (C_5), 61.6 (C_3), 33.7 (CH_2CO), 32.9 (CH_2Br), 27.8 ($CH_2CH_2CH_2$), 26.7 (CH_3), 26.4 (CH_3), 25.9 (O*TBDM*S), 18.2 (C^{IV}, OTBDMS); ES-MS $[M+Na]^+$ *m*/*z* 499.

*4.4.4. 3-C-Cyano-3-deoxy-1,2:5,6-di-O-isopropylidene-3-(4-bromobutanamido)-α-D-allofuranose (**4d**).* Compound **4d** has been prepared starting from 1.5 g of **1d** (5.28 mmol), 1.8 mL of 4-bromobutyryl chloride, 323 mg of DMAP, and 14 mL of pyridine and obtained as syrup in 61% yield after purification with cyclohexane/EtOAc 7:3. $[\alpha]_D^{20}$ +7.4 (*c* 1.12, $CHCl_3$); IR (ATR): *ν* 2988, 1382, 1511, 1128, 1007 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 6.40 (s, 1H, NH), 5.88 (d, 1H, H_1, *J*=3.6), 5.35 (d, 1H, H_2, *J*=3.6), 4.45 (ddd, 1H, H_5, *J*=4.7–6.3–9.1), 4.19 (dd, 1H, H_{6a}, *J*=6.3–9.1), 4.02 (dd, 1H, H_{6b}, *J*=4.7–9.1), 3.75 (d, 1H, H_4, *J*=9.1), 3.50–3.46 (m, 2H, CH_2Br), 2.46–2.40 (m, 2H, CH_2CONH), 2.28–2.02 (m, 2H, $CH_2CH_2CH_2$), 1.49 (s, 6H, $2CH_3$), 1.36 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 171.4 (CO), 115.6 (C_{iso}), 113.7 (CN), 110.6 (C_{iso}), 104.3 (C_1), 81.8 (C_2), 79.1 (C_4), 74.3 (C_5), 67.4 (C_6), 61.4 (C_3), 33.8 (CH_2CO), 32.9 (CH_2Br), 26.8 ($CH_2CH_2CH_2$), 26.7 (CH_3), 26.5 (CH_3), 26.3 (CH_3), 24.6 (CH_3); ES-MS $[M+Na]^+$ *m*/*z* 455–457.

4.5. General method for the preparation of 5a–d

To 1 equiv of compounds **4a–d** in anhydrous THF 2 equiv of NaH was added. The reaction mixture was stirred at room temperature for 30 min and then H_2O and Et_2O were added. The aqueous layer was extracted twice with Et_2O and the organic layers were dried with Na_2SO_4 before being evaporated. Compound **7** was obtained pure or the crude mixture was purified by flash chromatography (cyclohexane/EtOAc).

*4.5.1. 5-O-Benzyl-3-C-cyano-3-deoxy-1,2-O-isopropylidene-3-(2-oxopyrrolidine)-α-D-ribofuranose (**5a**).* Compound **5a** has been prepared starting from 398 mg of **4a** (0.88 mmol), 78 mg of NaH, and 20 mL of THF and obtained as syrup in 90% yield. $[\alpha]_D^{20}$ +74.0 (*c* 1.02, $CHCl_3$); IR (ATR): *ν* 2951, 1699, 1050, 758, 706 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.35–7.25 (m, 5H, C_6H_5), 5.94 (d, 1H, H_1, *J*=4.0), 5.27 (d, 1H, H_2, *J*=4.0), 4.68 (t, 1H, H_4, *J*=5.6), 4.62 (d, 2H, CH_2Ph, *J*=11.7), 4.59 (d, 2H, CH_2Ph, *J*=11.7), 3.99 (dd, 1H, H_{5a}, *J*=5.6–10.5), 3.93 (dd, 1H, H_{5b}, *J*=5.6–10.5), 3.58 (td, 1H, CH_2CO, *J*=3.9–8.2), 3.47 (q, 1H, CH_2CO, *J*=8.2), 2.39 (t, 2H, CH_2N, *J*=7.6), 2.03–1.91 (m, 2H, $CH_2CH_2CH_2$), 1.91 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 176.3 (CO), 137.5 (C^{IV}, C_6H_5), 128.6–128.0 (CH, C_6H_5), 114.9 (C_{iso}), 115.3 (CN), 103.6 (C_1), 81.9 (C_2), 76.8 (C_4), 74.0 (C_5), 69.3 (CH_2Ph), 63.2 (C_3), 48.0 (CH_2N), 30.6 (CH_2CO), 26.6 (CH_3), 26.5 (CH_3), 19.3 ($CH_2CH_2CH_2$); ES-HRMS for $C_{20}H_{24}N_2O_5Na$ $[M+Na]^+$ calcd 395.1583, found 395.1592.

*4.5.2. 3-C-Cyano-3-deoxy-1,2-O-isopropylidene-5-O-methyl-3-(2-oxopyrrolidine)-α-D-ribofuranose (**5b**).* Compound **5b** has been prepared starting from 145 mg of **4b** (0.38 mmol), 32 mg of NaH, and 8 mL of THF and obtained as syrup in 73% yield after purification with cyclohexane/EtOAc 55:45. $[\alpha]_D^{20}$ +76.2 (*c* 0.91, $CHCl_3$); IR (ATR): *ν* 3000, 2850, 1692, 1103 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 5.91 (d, 1H, H_1, *J*=3.8), 5.22 (d, 1H, H_2, *J*=3.8), 4.65 (t, 1H, H_4, *J*=5.5), 3.81 (d, 2H, H_5, *J*=5.5), 3.69–3.62 (m, 1H, CH_2CO), 3.49 (q, 1H, CH_2CO, *J*=7.9), 3.41 (s, 3H, OCH_3), 2.48–2.42 (m, 2H, CH_2N), 2.14–2.03 (m, 2H, $CH_2CH_2CH_2$), 1.49 (s, 3H, CH_3), 1.29 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 177.2 (CO), 114.6 (CN), 113.3 (C_{iso}), 103.4 (C_1), 81.7 (C_2), 76.5 (C_4), 71.5 (OCH_3), 63.1 (C_3), 55.7 (C_5), 48.2 (CH_2N), 30.6 (CH_2CO), 26.5 (CH_3), 26.3 (CH_3), 19.1 ($CH_2CH_2CH_2$); ES-HRMS for $C_{14}H_{20}N_2O_5Na$ $[M+Na]^+$ calcd 319.1270, found 319.1263.

*4.5.3. 5-O-tert-Butyldimethylsilyl-3-C-cyano-3-deoxy-1,2-O-isopropylidene-3-(2-oxopyrrolidine)-α-D-ribofuranose (**5c**).* Compound **5c** has been prepared starting from 980 mg of **4c** (2.06 mmol), 165 mg of NaH, and 40 mL of THF and obtained as white solid in 85% yield after purification with cyclohexane/EtOAc 8:2. Mp 81–84 °C, $[\alpha]_D^{20}$ +62.1 (*c* 1.09, $CHCl_3$); IR (ATR): *ν* 2957, 1690, 1107, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 5.90 (d, 1H, H_1, *J*=3.9), 5.30 (d, 1H, H_2, *J*=3.9), 4.58 (dd, 1H, H_4, *J*=5.2–7.1), 4.09 (dd, 1H, H_{5a}, *J*=5.2–10.8), 3.99 (dd, 1H, H_{5b}, *J*=7.1–10.8), 3.78 (td, 1H, CH_2CO, *J*=3.7–8.2), 3.49 (q, 1H, CH_2CO, *J*=8.2), 2.44–2.39 (m, 2H, CH_2N), 2.10–1.98 (m, 2H, $CH_2CH_2CH_2$), 1.51 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 0.88 (s, 9H, O*TB*DMS), 0.09 (s, 6H, OTB*DMS*); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 176.3 (CO), 114.8 (CN), 113.1 (C_{iso}), 103.3 (C_1), 82.1 (C_2), 77.7 (C_4), 63.3 (C_3), 62.8 (C_5), 48.4 (CH_2N), 30.6 (CH_2CO), 26.5 (CH_3), 25.9 (CH_3+O*TBDMS*), 19.3 ($CH_2CH_2CH_2$), 18.3 (C^{IV}, OTBDMS); ES-HRMS for $C_{19}H_{32}N_2O_5NaSi$ $[M+Na]^+$ calcd 419.1978, found 419.1987.

*4.5.4. 3-C-Cyano-3-deoxy-1,2:5,6-di-O-isopropylidene-3-(2-oxopyrrolidine)-α-D-allofuranose (**5d**).* Compound **5d** has been prepared starting from 1.0 g of **4d** (2.31 mmol), 185 mg of NaH, and 50 mL of THF and obtained as syrup in 99% yield. $[\alpha]_D^{20}$ +75.8 (*c* 1.06, $CHCl_3$); IR (ATR): *ν* 2990, 1699, 1213, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 5.90 (d, 1H, H_1, *J*=3.8), 5.35 (d, 1H, H_2, *J*=3.8), 4.45 (td, 1H, H_5, *J*=6.3–7.8), 4.32 (d, 1H, H_4, *J*=7.8), 4.25 (dd, 1H, H_{6a}, *J*=6.3–8.8), 4.02 (dd, 1H, H_{6b}, *J*=6.3–8.8), 3.88 (td, 1H, CH_2CO, *J*=5.7–8.1), 3.47 (q, 1H, CH_2CO, *J*=8.1), 2.44 (td, 2H, CH_2N, *J*=4.4–8.1), 2.13–2.05 (m, 2H, $CH_2CH_2CH_2$), 1.52 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 176.8 (CO), 115.0 (CN), 113.6 (C_{iso}), 110.7 (C_{iso}), 103.7 (C_1), 82.4 (C_2), 79.2 (C_4), 74.6 (C_5), 68.2 (C_6), 63.9 (C_3), 48.8 (CH_2N), 30.9 (CH_2CO), 26.8 (CH_3), 26.7 (CH_3), 26.4 (CH_3), 25.0 (CH_3), 19.6 ($CH_2CH_2CH_2$); ES-HRMS for $C_{17}H_{24}N_2O_6Na$ $[M+Na]^+$ calcd 375.1532, found 375.1540.

4.6. 5-*O*-Benzyl-3-carboxypropanamido-3-*C*-cyano-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (6)

To a solution of **1a** (3 g, 9.87 mmol) in dry toluene (100 mL) was added succinic anhydride (2.21 g, 22.08 mmol). The reaction mixture was stirred at reflux for 5 h and then toluene was evaporated. The crude product was purified by flash chromatography (cyclohexane/EtOAc 3:7–1%AcOH) to give 3.95 g of **6** as syrup with 99% yield. $[\alpha]_D^{20}$ +6.5 (*c* 0.97, $CHCl_3$); IR (ATR): *ν* 3150, 2950, 1714, 1668, 1165, 1096, 741, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 10.62 (s, 1H, OH), 7.36–7.29 (m, 5H, C_6H_5), 6.74 (s, 1H, NH), 5.93 (d, 1H, H_1, *J*=3.6), 5.26 (d, 1H, H_2, *J*=3.6), 4.65–4.57 (m, 2H, CH_2Ph), 4.24 (dd, 1H, H_4, *J*=5.2–7.1), 4.03–3.92 (m, 2H, H_5), 2.71–2.63 (m, 2H, CH_2COOH), 2.53–2.39 (m, 2H, CH_2CONH), 1.52 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 177.4 (CO), 171.4 (CO), 136.9 (C^{IV}, C_6H_5), 129.1–128.0 (CH, C_6H_5), 115.6 (C_{iso}), 113.6 (CN), 104.3 (C_1), 81.8 (C_2), 77.8 (C_4), 74.1 (CH_2Ph), 68.9 (C_5), 60.8 (C_3), 30.0 (CH_2CONH), 28.8 (CH_2COOH), 26.5 (CH_3), 26.1 (CH_3); ES-HRMS for $C_{20}H_{24}N_2O_7Na$ $[M+Na]^+$ calcd 427.1481, found 427.1484.

4.7. 5-*O*-Benzyl-3-*C*-cyano-3-deoxy-1,2-*O*-isopropylidene-3-(2,5-dioxopyrrolidine)-α-D-ribofuranose (7)

To a solution of **6** (3.54 g, 8.76 mmol) in anhydrous CH_2Cl_2 (70 mL) were added pyridine (1 mL) and $SOCl_2$ (0.78 mL, 0.01 mol). The mixture was stirred at reflux for 6 h and then CH_2Cl_2 was evaporated. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH 95:5) to give 2.27 g of **7** as a white solid with 67% yield. Mp 153–155 °C; $[\alpha]_D^{20}$ +5.1 (*c* 1.00, $CHCl_3$); IR (ATR): *ν* 1715, 1374, 1202 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.36–7.26 (m , 5H, C_6H_5), 6.02 (d, 1H, H_1, *J*=4.0), 5.68 (dd, 1H, H_4, *J*=3.5, 7.0), 5.23 (d, 1H, H_2, *J*=4.0), 4.68 (d, 1H, CH_2Ph, *J*=12.0), 4.60 (d, 1H, CH_2Ph, *J*=12.0), 3.99–3.90 (m, 2H, H_5), 2.73 (q, 4H, $2CH_2CO$, *J*=2.3), 1.49, (s, 3H, CH_3), 1.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 175.5 (2CO), 137.9 (C^{IV}, C_6H_5), 128.5–127.8 (CH, C_6H_5), 113.8 (C_{iso}), 113.7 (CN), 103.4 (C_1), 81.1 (C_2), 74.1 (C_4), 73.7 (CH_2Ph), 69.6 (C_5), 62.2 (C_3), 28.2 ($2CH_2CO$), 27.0 (CH_3), 26.2 (CH_3); ES-MS $[M+Na]^+$ *m/z* 409.

4.8. General method for the cyclopropanation

To a solution of aminonitrile (1 equiv) and Ti(O*i*-Pr)$_3$Me (1.5 equiv) in THF, was slowly added at room temperature EtMgBr (1.5 equiv, solution in Et_2O). After stirring for 1 h, $BF_3{\cdot}OEt_2$ (2 equiv) was added, and the reaction mixture further stirred for 1 h at room temperature. A solution of HCl 1 M was added until two clear phases were formed. Then, a solution of NaOH (3 M) was added until pH of aqueous layer was basic. The organic layer was extracted with ethyl acetate and dried over Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by column chromatography with cyclohexane/EtOAc.

*4.8.1. Spiro[5-O-Benzyl-3-deoxy-1,2-isopropylidene-α-D-ribofuranose-3,3′-(3′-hydro-4′-methyl-5′-phenyl-spiro[cyclopropane-1,2′-pyrrolo[1,2-a]imidazole])] (**8a**).* Compound **8a** has been prepared starting from 1.0 g of **3a** (2.37 mmol), 850 μL of Ti(O*i*-Pr)$_3$Me, 1.6 mL of EtMgBr (2.2 M), 600 μL of $BF_3.Et_2O$ and 50 mL of THF and obtained as syrup in 42% yield after purification with cyclohexane/EtOAc. $[\alpha]_D^{16}$ −43.9 (*c* 1.05; $CHCl_3$); IR (ATR): *ν* 1373, 1242, 1215, 1022, 737, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.39–7.26 (m, 10H, C_6H_5), 5.45 (d, 1H, H_1, *J*=3.4), 4.69 (t, 1H, H_4, *J*=4.9), 4.65 (d, 1H, CH_2Ph, *J*=12.1), 4.64 (d, 1H, H_2, *J*=3.4), 4.51 (d, 1H, CH_2Ph, *J*=12.1), 3.93 (d, 2H, H_5, *J*=4.9), 2.96 (s, 3H, NCH_3), 1.60 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.26–1.19 (m, 1H, $CH_2\Delta$), 1.16–1.06 (m, 1H, $CH_2\Delta$), 0.94–0.85 (m, 1H, $CH_2\Delta$), 0.78–0.69 (m, 1H, $CH_2\Delta$); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 165.7 (N–C=N), 137.9 (C^{IV}, C_6H_5), 131.2 (C^{IV}, C_6H_5), 129.6–127.7 (CH, C_6H_5), 112.9 (C_{iso}), 103.2 (C_1), 84.8 (C_2), 76.7

(C_4), 73.4 (C_5), 71.9 (CΔ), 67.8 (CH_2Ph), 52.7 (C_3), 32.6 (NCH_3), 26.8 (CH_3), 26.3 (CH_3), 11.2 (CH_2Δ), 10.7 (CH_2Δ); ES-HRMS for $C_{26}H_{31}N_2O_4$ $[M+H]^+$ calcd 435.2284, found 435.2282.

*4.8.2. Spiro[3-deoxy-1,2-isopropylidene-5-O-methyl-α-D-ribofuranose-3,3′-(3′-hydro-4′-methyl-5′-phenyl-spiro[cyclopropane-1,2′-pyrrolo[1,2-a]imidazole])] (**8b**).* Compound **8b** has been prepared starting from 201 mg of **3b** (0.58 mmol), 208 μL of Ti(O*i*-Pr)$_3$Me, 440 μL of EtMgBr (2.0 M), 150 μL of $BF_3\cdot Et_2O$, and 7.5 mL of THF and obtained as syrup in 32% yield after purification with EtOAc. $[\alpha]_D^{16}$ −22.3 (*c* 1.00, $CHCl_3$); IR (ATR): *ν* 2947, 1618, 1599, 1499, 1458, 1371, 1086, 1067, 775, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.48–7.45 (m, 2H, C_6H_5), 7.39–7.37 (m, 3H, C_6H_5), 5.43 (d, 1H, H_1, *J*=3.4), 4.61 (d, 1H, H_4, *J*=4.2), 4.59 (d, 1H, H_2, *J*=3.4), 3.88–3.85 (m, 2H, H_5), 3.37 (s, 3H, OCH_3), 2.98 (s, 3H, NCH_3), 1.57 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.32–1.19 (m, 1H, CH_2Δ), 1.13–1.10 (m, 1H, CH_2Δ), 0.90–0.84 (m, 1H, CH_2Δ), 0.77–0.71 (m, 1H, CH_2Δ); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 165.7 (N–C=N), 131.2 (C^{IV}, C_6H_5), 129.7–128.3 (CH, C_6H_5), 112.9 (C_{iso}), 103.2 (C_1), 84.7 (C_4), 76.5 (C_2), 71.8 (C_3), 70.4 (C_5), 59.3 (OCH_3), 52.6 (CΔ), 32.6 (NCH_3), 26.7 (CH_3), 26.3 (CH_3), 11.2 (CH_2Δ), 10.7 (CH_2Δ); ES-HRMS for $C_{20}H_{27}N_2O_4$ $[M+H]^+$ calcd 359.1971, found 359.1960.

*4.8.3. Spiro[5-O-tert-butyldimethylsilyl-3-deoxy-1,2-isopropylidene-α-D-ribofuranose-3,3′-(3′-hydro-4′-methyl-5′-phenyl-spiro[cyclopropane-1,2′-pyrrolo[1,2-a]imidazole])] (**8c**).* Compound **8c** has been prepared starting from 200 mg of **3c** (0.45 mmol), 160 μL of Ti(O*i*-Pr)$_3$Me, 340 μL of EtMgBr (2.0 M), 115 μL of $BF_3\cdot Et_2O$, and 20 mL of THF and obtained as syrup in 26% yield after purification with cyclohexane/EtOAc 6:4. $[\alpha]_D^{20}$ −23.7 (*c* 1.00, $CHCl_3$); IR (ATR): *ν* 2988, 1581, 1517, 1455, 1114, 743, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.51–7.48 (m, 2H, C_6H_5), 7.39–7.37 (m, 3H, C_6H_5), 5.43 (d, 1H, H_1, *J*=3.5), 4.60 (d, 1H, H_2, *J*=3.5), 4.54 (t, 1H, H_4, *J*=5.4), 4.13 (dd, 1H, H_{5a}, *J*=5.4–11.5), 4.05 (dd, 1H, H_{5b}, *J*=5.4–11.5), 3.01 (s, 3H, NCH_3), 1.60 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.25–1.07 (m, 2H, CH_2Δ), 0.95–0.80 (m, 1H, CH_2Δ), 0.86 (s, 9H, O*TB*DMS), 0.75–0.65 (m, 1H, CH_2Δ), 0.07 (s, 3H, OTBD*M*S), 0.05 (s, 3H, OTBD*M*S); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 165.6 (N–C=N), 131.2 (C^{IV}, C_6H_5), 129.7–128.3 (CH, C_6H_5), 112.7 (C_{iso}), 103.0 (C_1), 85.3 (C_2), 78.6 (C_4), 71.8 (C_3), 61.2 (C_5), 52.8 (CΔ), 32.8 (NCH_3), 26.7 (CH_3), 26.4 (CH_3), 26.0 (CH_3, O*TBDM*S), 18.4 (C^{IV}, OTBDMS), 11.3 (CH_2Δ), 10.9 (CH_2Δ); ES-HRMS for $C_{25}H_{39}N_2O_4Si$ $[M+H]^+$ calcd 459.2679, found 459.2663.

*4.8.4. Spiro[3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose-3,3′-(3′-hydro-4′-methyl-5′-phenyl-spiro[cyclopropane-1,2′-pyrrolo[1,2-a]imidazole])] (**8d**).* Compound **8d** has been prepared starting from 1.0 g of **3d** (2.49 mmol), 900 μL of Ti(O*i*-Pr)$_3$Me, 1.7 mL of EtMgBr (2.2 M), 630 μL of $BF_3\cdot Et_2O$, and 50 mL of THF and obtained as syrup in 60% yield after purification with cyclohexane/EtOAc 3:7. $[\alpha]_D^{20}$ −34.8 (*c* 0.70, $CHCl_3$); IR (ATR): *ν* 2985, 1371, 1063, 729, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.44–7.41 (m, 2H, C_6H_5), 7.35–7.32 (m, 3H, C_6H_5), 5.31 (d, 1H, H_1, *J*=3.4), 4.70 (td, 1H, H_5, *J*=6.4–8.9), 4.58 (d, 1H, H_2, *J*=3.4), 4.29 (d, 1H, H_4, *J*=8.9), 4.14 (dd, 1H, H_{6a}, *J*=6.4–8.5), 3.85 (dd, 1H, H_{6b}, *J*=6.4–8.5), 2.91 (s, 3H, NCH_3), 1.55 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.23–1.16 (m, 2H, CH_2Δ), 0.83–0.71 (m, 2H, CH_2Δ); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 166.6 (N–C=N), 131.9 (C^{IV}, C_6H_5), 129.3–128.3 (CH, C_6H_5), 113.1 (C_{iso}), 109.6 (C_{iso}), 102.9 (C_1), 81.1 (C_2), 77.0 (C_4), 72.2 (C_5), 71.8 (CΔ), 68.6 (C_6), 52.4 (C_3), 32.5 (NCH_3), 26.9 (CH_3), 26.6 (CH_3), 26.3 (CH_3), 25.4 (CH_3), 10.2 (CH_2Δ), 9.9 (CH_2Δ); ES-HRMS for $C_{23}H_{31}N_2O_5$ $[M+H]^+$ calcd 415.2233, found 415.2236.

*4.8.5. Spiro[5-O-benzyl-3-deoxy-1,2-isopropylidene-α-D-ribofuranose-3,3′-(3′,5′,6′,7′-tetrahydrospiro[cyclopropane-1,2′-pyrrolo[1,2-a]imidazole])] (**9a**).* Compound **9a** has been prepared starting from 100 mg of **5a** (0.27 mmol), 130 μL of Ti(O*i*-Pr)$_3$Me, 370 μL of EtMgBr (1.5 M), 70 μL of $BF_3\cdot Et_2O$, and 1.5 mL of THF and obtained as syrup in 21% yield after purification with cyclohexane/EtOAc 75:25. $[\alpha]_D^{20}$ −48.5 (*c* 1.05, $CHCl_3$); IR (ATR): *ν* 2987, 1631, 1512, 1454, 734, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.36–7.26 (m, 5H, C_6H_5), 5.43 (d, 1H, H_1, *J*=3.5), 4.55 (d, 1H, H_2, *J*=3.5), 4.53–4.45 (m, 3H, H_4+CH_2Ph), 4.12 (t, 1H, H_{5a}, *J*=9.0), 3.88 (dd, 1H, H_{5b}, *J*=4.2–9.0), 3.65 (td, 1H, CH_2, *J*=2.8–8.5), 3.45 (q, 1H, CH_2, *J*=8.5), 2.66–2.51 (m, 1H, CH_2), 2.12–2.03 (m, 2H, CH_2), 1.89–1.82 (m, 2H, CH_2+1H, CH_2Δ), 1.58 (s, 3H, CH_3), 1.40–1.34 (m, 1H, CH_2Δ), 1.33 (s, 3H, CH_3), 1.28–1.17 (m, 1H, CH_2Δ), 0.77–0.69 (m, 1H, CH_2Δ); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 176.5 (N–C=N), 137.6 (C^{IV}, C_6H_5), 128.6–128.1 (CH, C_6H_5), 113.5 (C_{iso}), 102.9 (C_1), 83.5 (C_2), 74.0 (CH_2Ph), 73.6 (C_4), 71.4 (C_3), 67.0 (C_5), 52.6 (CΔ), 45.4 (CH_2), 26.6 (CH_3), 26.3 (CH_3), 25.2 (CH_2), 23.7 (CH_2), 8.8 (CH_2Δ), 6.8 (CH_2Δ); ES-MS $[M+H]^+$ *m*/*z* 385.

*4.8.6. Spiro[5-O-tert-butyldimethysilyl-3-deoxy-1,2-isopropylidene-α-D-ribofuranose-3,3′-(3′,5′,6′,7′-tetrahydrospiro[cyclopropane-1,2′-pyrrolo[1,2-a]imidazole])] (**9c**).* Compound **9c** has been prepared starting from 252 mg of **5c** (0.64 mmol), 227 μL of Ti(O*i*-Pr)$_3$Me, 355 μL of EtMgBr (2.7 M), 160 μL of $BF_3\cdot Et_2O$, and 25 mL of THF and obtained as syrup in 11% yield after purification with cyclohexane/EtOAc 85:15. $[\alpha]_D^{20}$ −45.2 (*c* 0.72, $CHCl_3$); IR (ATR): *ν* 3017, 1375, 1187, 1094, 1073 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 5.46 (d, 1H, H_1, *J*=3.5), 4.63 (d, 1H, H_2, *J*=3.5), 4.41 (dd, 1H, H_4, *J*=4.1–8.0), 4.27 (dd, 1H, H_{5a}, *J*=8.0–10.5), 3.97 (dd, 1H, H_{5b}, *J*=4.1–10.5), 3.84 (td, 1H, CH_2, *J*=3.7–8.2), 3.62 (q, 1H, CH_2, *J*=8.2), 2.92 (ddd, 1H, CH_2, *J*=4.7–8.6–19.0), 2.82–2.65 (m, 1H, CH_2), 2.42–2.33 (m, 2H, CH_2), 1.89–1.70 (m, 1H, CH_2Δ), 1.62 (s, 3H, CH_3), 1.54–1.41 (m, 1H, CH_2Δ), 1.37 (s, 3H, CH_3), 1.21–1.09 (m, 1H, CH_2Δ), 0.94 (s, 9H, O*TB*DMS), 0.79–0.68 (m, 1H, CH_2Δ), 0.14 (s, 3H, OTBD*M*S), 0.11 (s, 3H, OTBD*M*S); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 175.2 (N–C=N), 113.4 (C_{iso}), 102.7 (C_1), 83.9 (C_2), 76.5 (C_4), 70.8 (C_3), 60.1 (C_5), 45.4 (CH_2), 29.7 (CΔ), 26.6 (CH_3), 26.2 (CH_3), 26.0 (O*TBDM*S), 25.4 (CH_2), 23.7 (CH_2), 18.5 (C^{IV}, OTBDMS), 8.0 (CH_2Δ), 7.2 (CH_2Δ); ES-HRMS for $C_{21}H_{37}N_2O_4Si$ $[M+H]^+$ calcd 409.2523, found 409.2513.

*4.8.7. Spiro[3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose-3,3′-(3′,5′,6′,7′-tetrahydrospiro[cyclopropane-1,2′-pyrrolo[1,2-a]imidazole])] (**9d**).* Compound **9d** has been prepared starting from 500 mg of **5d** (1.42 mmol), 510 μL of Ti(O*i*-Pr)$_3$Me, 1.0 mL of EtMgBr (2.2 M), 360 μL of $BF_3\cdot Et_2O$, and 30 mL of THF and obtained as syrup in 28% yield after purification with cyclohexane/EtOAc 75:25. $[\alpha]_D^{20}$ −59.4 (*c* 1.05, $CHCl_3$); IR (ATR): *ν* 3025, 1626, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 5.41 (d, 1H, H_1, *J*=3.3), 4.68 (dt, 1H, H_5, *J*=6.5–9.4), 4.56 (d, 1H, H_2, *J*=3.3), 4.17 (dd, 1H, H_{6a}, *J*=6.5–8.5), 4.11 (d, 1H, H_4, *J*=9.4), 3.80 (dd, 1H, H_{6b}, *J*=6.5–8.5), 3.75–3.70 (m, 1H, CH_2), 3.55 (q, 1H, CH_2, *J*=8.5), 2.85 (dt, 1H, CH_2, *J*=6.2–18.6), 2.66–2.59 (m, 1H, CH_2), 2.34–2.27 (m, 2H, CH_2), 1.87–1.82 (m, 1H, CH_2Δ), 1.55 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.32 (m, 4H, CH_3+1H, CH_2Δ), 1.19–1.13 (m, 1H, CH_2Δ), 0.82–0.77 (m, 1H, CH_2Δ); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 177.1 (N–C=N), 113.6 (C_{iso}), 109.9 (C_{iso}), 103.0 (C_1), 82.9 (C_2), 76.4 (C_4), 71.4 (CΔ), 71.5 (C_5), 68.6 (C_6), 52.5 (C_3), 45.3 (CH_2), 26.6 (CH_3), 26.5 (CH_3), 26.2 (CH_3), 25.5 (CH_2), 24.6 (CH_2), 23.8 (CH_2), 8.61 (CH_2Δ), 6.5 (CH_2Δ); ES-HRMS for $C_{19}H_{28}N_2O_5Na$ $[M+Na]^+$ calcd 387.1896, found 387.1898.

*4.8.8. Spiro[5-O-tert-butyldimethysilyl-3-deoxy-1,2-isopropylidene-α-D-ribofuranose-3,3′-(3′,5′,6′,7′-tetrahydro-2′-ethylidene-pyrrolo[1,2-a]imidazole)] (**10c**).* Compound **10c** has been prepared starting from 252 mg of **5c** (0.64 mmol), 227 μL of Ti(O*i*-Pr)$_3$Me, 355 μL of EtMgBr (2.7 M), 160 μL of $BF_3\cdot Et_2O$, and 25 mL of THF and obtained as syrup in 9% yield after purification with cyclohexane/

EtOAc 3:7. $[\alpha]_D^{20}$ −75.3 (*c* 0.95, $CHCl_3$); IR (ATR): *ν* 2998, 1384, 1265, 1102, 1012, 1061, 804 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 5.82 (d, 1H, H_1, *J*=3.7), 4.52 (q, 1H, C*H*CH_3, *J*=6.8), 4.43 (d, 1H, H_2, *J*=3.7), 4.40 (dd, 1H, H_4, *J*=5.4–6.7), 3.83 (dd, 1H, H_{5a}, *J*=5.4–10.4), 3.70 (dd, 1H, H_{5b}, *J*=6.7–10.4), 3.60 (td, 1H, CH_2, *J*=4.0–8.0), 3.36 (q, 1H, CH_2, *J*=8.0), 2.62–2.53 (m, 1H, CH_2), 2.51–2.38 (m, 2H, CH_2), 2.37–2.25 (m, 1H, CH_2), 1.84 (d, 3H, C*H*$_3$CH, *J*=6.8), 1.60 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 0.88 (s, 9H, O*TB*DMS), 0.04 (s, 3H, OTBD*MS*), 0.03 (s, 3H, OTBD*MS*); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 175.0 (N–C=N), 155.1 (*C*=CHCH$_3$), 112.6 (C_{iso}), 104.8 (*C*HCH$_3$), 104.1 (C_1), 87.3 (C_2), 75.9 (C_4), 74.0 (C_3), 62.1 (C_5), 44.0 (CH_2), 26.7 (CH_3), 26.4 (CH_3), 25.8 (CH_3, O*TBDMS*), 24.7 (CH_2), 23.7 (CH_2), 20.4 (C^{IV}, OTBDMS), 12.4 (*C*H$_3$CH); ES-HRMS for $C_{21}H_{37}N_2O_4Si$ $[M+H]^+$ calcd 409.2523, found 409.2536.

*4.8.9. Spiro[3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose-3,3′-(3′,5′,6′,7′-tetrahydro-2′-ethylidene-pyrrolo[1,2-a]imidazole)] (**10d**).* Compound **10d** has been prepared starting from 500 mg of **5d** (1.42 mmol), 510 μL of Ti(O*i*-Pr)$_3$Me, 1.0 mL of EtMgBr (2.2 M), 360 μL of $BF_3 \cdot Et_2O$, and 30 mL of THF and obtained as syrup in 24% yield after purification with EtOAc. $[\alpha]_D^{20}$ −73.4 (*c* 1.05, $CHCl_3$); IR (ATR): *ν* 3005, 1597, 1373, 1213, 1065, 1011, 847 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 5.71 (d, 1H, H_1, *J*=3.6), 4.37 (q, 1H, C*H*CH_3, *J*=6.8), 4.35 (d, 1H, H_2, *J*=3.6), 4.07–4.06 (m, 2H, H_5), 4.05–4.04 (m, 1H, H_4), 4.02–3.99 (m, 1H, H_{6a}), 3.87–3.84 (m, 1H, H_{6b}), 3.48 (td, 1H, CH_2, *J*=3.3–7.8), 3.30 (q, 1H, CH_2, *J*=7.8), 2.64–2.48 (m, 1H, CH_2), 2.24–2.17 (m, 3H, CH_2), 1.76 (d, 3H, C*H*$_3$CH, *J*=6.8), 1.49 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.18 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 176.2 (N–C=N), 155.2 (*C*=CHCH$_3$), 112.7 (C_{iso}), 109.2 (C_{iso}), 105.2 (*C*HCH$_3$), 104.3 (C_1), 87.0 (C_2), 75.8 (C_4), 74.6 (C_3), 73.5 (C_5), 67.8 (C_6), 44.1 (CH_2), 27.6 (CH_3), 26.5 (CH_3), 26.2 (CH_3), 24.8 (CH_3), 24.7 (CH_2), 23.7 (CH_2), 12.4 (CH*C*H$_3$); ES-HRMS for $C_{19}H_{29}N_2O_5$ $[M+H]^+$ calcd 365.2076, found 365.2089.

*4.8.10. Spiro[5-O-benzyl-3-deoxy-1,2-isopropylidene-α-D-ribofuranose-3,3′-(2′-ethylidene-3′,6′,7′-trihydro-5′-oxo-pyrrolo[1,2-a]imidazole)] (**11**).* Compound **11** has been prepared starting from 100 mg of **7** (0.26 mmol), 120 μL of Ti(O*i*-Pr)$_3$Me, 340 μL of EtMgBr (1.5 M), 70 μL of $BF_3 \cdot Et_2O$, and 1.5 mL of THF and obtained as syrup in 23% yield after purification with cyclohexane/EtOAc 7:3. $[\alpha]_D^{20}$ −9.5 (*c* 1.04, $CHCl_3$); IR (ATR): *ν* 3008, 1712, 1631, 1073, 736, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.34–7.25 (m, 5H, C_6H_5), 5.90 (d, 1H, H_1, *J*=3.8), 5.44 (dd, 1H, H_4, *J*=5.2–8.9), 4.82 (q, 1H, C*H*CH_3, *J*=6.9), 4.43 (d, 1H, CH_2Ph, *J*=10.9), 4.42 (d, 1H, H_2, *J*=3.8), 4.27 (d, 1H, CH_2Ph, *J*=10.9), 3.81 (dd, 1H, H_{5a}, *J*=5.2–8.9), 3.61 (t, 1H, H_{5b}, *J*=8.9), 2.74–2.65 (m, 2H, CH_2), 2.35–2.17 (m, 2H, CH_2), 1.89 (d, 3H, C*H*$_3$CH, *J*=6.9), 1.88 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 170.5 (CO), 169.9 (N–C=N), 153.9 (*C*=CHCH$_3$), 137.7 (C^{IV}, C_6H_5), 128.6–127.7 (CH, C_6H_5), 113.8 (C_{iso}), 110.4 (*C*HCH$_3$), 104.8 (C_1), 86.2 (C_2), 74.0 (C_3), 73.7 (C_6), 70.5 (C_4), 68.5 (C_5), 33.4 (CH_2), 26.7 (CH_3), 26.2 (CH_3), 20.4 (CH_2), 12.5 (*C*H$_3$CH); ES-HRMS for $C_{22}H_{27}N_2O_5$ $[M+H]^+$ calcd 399.1920, found 399.1923.

*4.8.11. 5-O-Benzyl-3-deoxy-3-C-iminopropyl-1,2-O-isopropylidene-3-(2,5-dioxopyrrolidine)-α-D-ribofuranose (**12**).* Compound **12** has been prepared starting from 100 mg of **7** (0.26 mmol), 120 μL of Ti(O*i*-Pr)$_3$Me, 340 μL of EtMgBr (1.5 M), and 1.5 mL of THF and obtained as a syrup in 18% yield after purification with cyclohexane/EtOAc 6:4. $[\alpha]_D^{16}$ +58.7 (*c* 0.31, $CHCl_3$); IR (ATR): *ν* 2853, 1742, 1709, 1213, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): *δ* 7.33–7.29 (m, 5H, C_6H_5), 5.99 (d, 1H, H_1, *J*=3.9), 5.47 (dd, 1H, H_4, *J*=1.9–6.5), 5.34 (d, 1H, H_2, *J*=3.9), 4.58 (s, 2H, CH_2Ph), 4.01 (dd, 1H, H_{5a}, *J*=1.9–10.9), 3.48 (dd, 1H, H_{5b}, *J*=6.5–10.9), 2.78–2.71 (m, 4H, CH_2CO), 2.07–2.03 (m, 2H, CH_2CH$_3$), 1.48 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 0.96 (t, 3H, CH_3CH$_2$, *J*=7.1); ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 178.2 (2CO), 165.1 (C=N), 138.5 (C^{IV}, C_6H_5), 128.5–127.7 (CH, C_6H_5), 112.0 (C_{iso}), 104.4 (C_1), 82.3 (C_2), 77.8 (C_4), 74.6 (C_3), 73.8 (CH_2Ph), 69.8 (C_5), 29.4 (CH_2CO), 28.7 (CH_2CH$_3$), 28.0 (CH_2CO), 27.1 (2CH$_3$), 8.4 (*C*H$_3$CH$_2$); ES-MS $[M+Na]^+$ *m*/*z* 439.

Acknowledgements

We thank the Conseil Régional de Picardie for financial support.

References and notes

1. Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1–67.
2. Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625–1648.
3. Salaün, J.; Baird, M. S. *Curr. Med. Chem.* **1995**, *2*, 511–542.
4. Bertus, P.; Szymoniak, J. *Chem. Commun.* **2001**, 1792–1793.
5. Bertus, P.; Szymoniak, J. *Synlett* **2007**, 1346–1356.
6. Laroche, C.; Behr, J. B.; Szymoniak, J.; Bertus, P.; Plantier-Royon, R. *Eur. J. Org. Chem.* **2005**, 5084–5088.
7. Laroche, C.; Plantier-Royon, R.; Szymoniak, J.; Bertus, P.; Behr, J.-B. *Synlett* **2006**, 223–226.
8. Laroche, C.; Behr, J.-B.; Szymoniak, J.; Bertus, P.; Schütz, C.; Vogel, P.; Plantier-Royon, R. *Bioorg. Med. Chem.* **2006**, *14*, 4047–4054.
9. Pearson, M.; Plantier-Royon, R.; Szymoniak, J.; Bertus, P.; Behr, J. B. *Synthesis* **2007**, 3589–3594.
10. Bertus, P.; Szymoniak, J.; Jeanneau, E.; Docsa, T.; Gergely, P.; Praly, J.-P.; Vidal, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4774–4778.
11. Pearson, M. S. M.; Floquet, N.; Bello, C.; Vogel, P.; Plantier-Royon, R.; Szymoniak, J.; Bertus, P.; Behr, J.-B. *Bioorg. Med. Chem.* **2009**, *17*, 8020–8026.
12. Declerck, D.; Josse, S.; Nhien, A. N. V.; Postel, D. *Tetrahedron Lett.* **2009**, *19*, 2171–2173.
13. Moura, M.; Delacroix, S.; Postel, D.; Van Nhien, A. N. *Tetrahedron* **2009**, *14*, 2766–2772.
14. Postel, D.; Nguyen Van Nhien, A.; Pillon, M.; Villa, P.; Ronco, G. *Tetrahedron Lett.* **2000**, *33*, 6403–6406.
15. Bertus, P.; Szymoniak, J. *Synlett* **2003**, 265–267.
16. Sham, H. L.; Betebenner, D. A.; Rosenbrook, W.; Herrin, T.; Saldivar, A.; Vasavanonda, S.; Plattner, J. J.; Norbeck, D. W. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2643–2645.
17. Makhey, D.; Li, D.; Zhao, B.; Sim, S.-P.; Li, T.-K.; Liu, A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem.* **2003**, *11*, 1809–1820.
18. See for instance: (a) Lin, A. J.; Lee, M.; Klayman, D. L. *J. Med. Chem.* **1989**, *32*, 1249–1252; (b) Bondalapati, S.; Reddy, U. C.; Saha, P.; Saikia, A. K. *Org. Biomol. Chem.* **2011**, *9*, 3428–3438.