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New C_2 Symmetrical and Semisymmetrical Substituted Imidazolium Ribonucleoside. Imidazolic Nucleosides Analogues

A. Al Mourabit*, M. Beckmann, C. Poupat, A. Ahond and P. Potier

Institut de Chimie des Substances Naturelles du C.N.R.S., 91198 Gif-sur-Yvette Cedex, France

Abstract : New C_2 symmetrical imidazolium ribonucleosides have been synthesized. The silyl Hilbert Johnson-Vorbrügen method was used. Subsequent coupling of trimethylsilylimidazole with the peracylated D-ribofuranose **1**, followed by removal of the protecting groups, afforded 1,3-bis(β-D -ribofuranosyl)imidazolium **7** and 1-(β-D-ribofuranosyl)imidazole **8**. In a similar synthetic sequence, 4(5)-substituted bis-ribofuranosylimidazolium **14** was also prepared. For the selective preparation of the monoglycosylated imidazole **15,** the classical method starting from 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide in acetonitrile and using $Hg(CN)_2$ was employed. These new base modified nucleosides were devoid of activity against HIV and cytotoxicity.

Introduction

The development of C_2 symmetrical compounds has been closely associated with asymmetric induction in chemical transformation.[1] For this application, numerous C_2 symmetrical alcohols and amines have been prepared in enantiomerically pure form and used as very efficient chiral auxiliaries.

In addition to this chemical interest, the C_2 symmetry properties of the enzyme HIV-1 protease (HIV-PR) have been used to design new potential inhibitors for the development of therapies against AIDS.[2,3] A large number of C_2 symmetrical peptides with an α-hydroxyamine or diol function has been synthesized and analysed for the antiviral activity.[4]

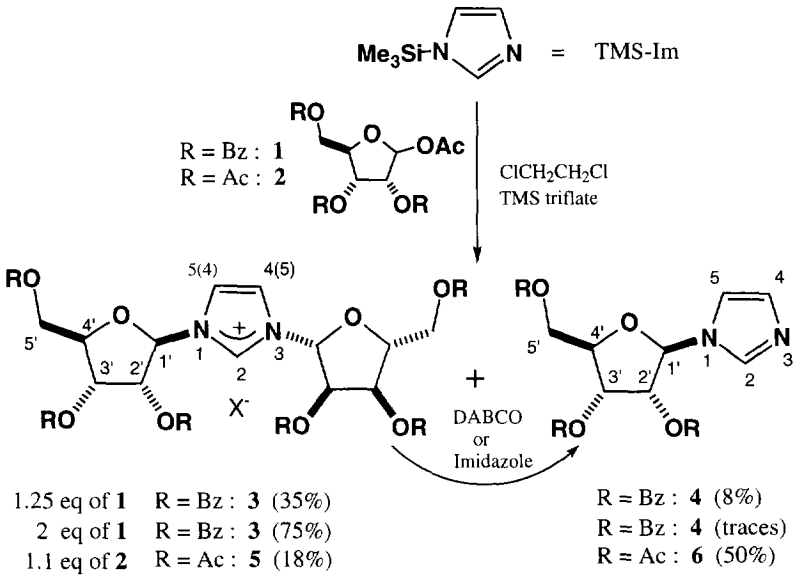
In the field of imidazole chemistry, our effort was directed to the development of new antiviral base modified nucleosides which are thought to act as reverse transcriptase (RTase) inhibitors and thereby to show an antiviral activity. Without being rational, the nucleoside interference with DNA is an attractive approach, since the most effective compounds in actual AIDS therapy are nucleosides.[5]

For our investigation on the reactivity of some substituted imidazoles with D-ribofuranose derivatives, we decided to start from the unsubstituted imidazole. Surprisingly, the synthesis of the ribofuranosylimidazole is not yet reported in the literature. However the crystal structure of the N-(ß-D-ribofuranosyl)imidazole,[6] its circular dichroism [7] and its molecular orbitals [8] have been studied and described. Apparently, this compound has been prepared by Dr. R. U. Lemieux [6] but its preparation is unpublished. We now report a synthesis of monoglycosylated imidazole and so far unknown C_2 symmetrical bis-glycosylated imidazolium compounds. In this synthesis, we have used the silyl Hilbert Johnson-Vorbrügen method which is based on the treatment of the silylated base by a peracylated sugar in the presence of a Lewis acid.[9, 10, 11] For the selective preparation of the monoglycosylated imidazole derivatives, the classical methods starting from 1-chloro [12] and 1-bromo [13] sugars were employed.

Results and discussion

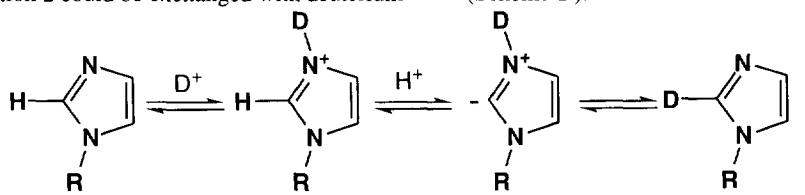
Unsubstituted imidazole

The reaction of 1-O-acetyl-2, 3, 5-tri-O-benzoyl-β-D-ribofuranose **1** [14] with N-trimethylsilylimidazole in 1,2 dichloroethane in the presence of trimethylsilyltriflate affords the C_2 symmetrical 1,3-bis(2, 3, 5-tri-O-benzoyl-β-D-ribofuranosyl)imidazolium **3** (35%) and the monoglycosylated imidazole **4** (8%) (Scheme 1).



Scheme 1 : (X^- is probably OH^-)

In our initial trials we had expected, on the basis of theoretical arguments,[11] to obtain the β nucleoside **4** as a major product and its α isomer. ^1H NMR data enabled us to identify the N_1,N_3 symmetrically disubstituted imidazolium **3** and the monosubstituted imidazole. The proton at position 2 of the imidazolium integrates for half a proton in comparison with the anomeric proton. We might assume that the imidazolic proton at position 2 could be exchanged with deuterium [15, 16] (Scheme 2).

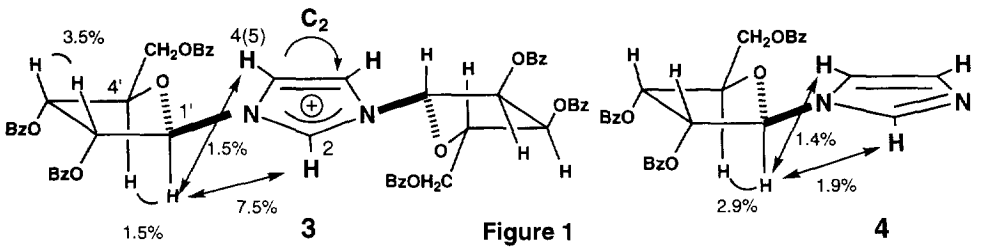


Scheme 2

The ^{13}C NMR chemical shifts of the imidazolic C_2 of **3** (136.2 ppm) and **4** (136.3 ppm) are surprisingly very similar! The confusion between α / β and mono / disubstituted imidazoles has been cleared up by the transformation of **3** to 1-β-D-ribofuranosyl imidazole **4** (Scheme 1) and the results of nOe studies at the anomeric centre. The protons H_4 and H_5 of **3** are equivalent. The EI mass spectrum confirms the imidazolium structure and shows a molecular ion at m/z 957. According to already published results (silyl Hilbert Johnson method),[11] the glycosidic bond is formed generally with the β orientation. Mechanistically, the β form is expected for reactions starting from 2-O-acyl substituted furanoses that involve oxonium ions as intermediates. NOe results confirm that the products were formed with β configuration. In all cases, there is a correlation between $H_{1'}$ and $H_{4'}$ on the ribose moiety, between H_2 and $H_{1'}$ and between $H_{4(5)}$ and $H_{1'}$ (Figure 1). We did not isolate any α glycosidic isomer.

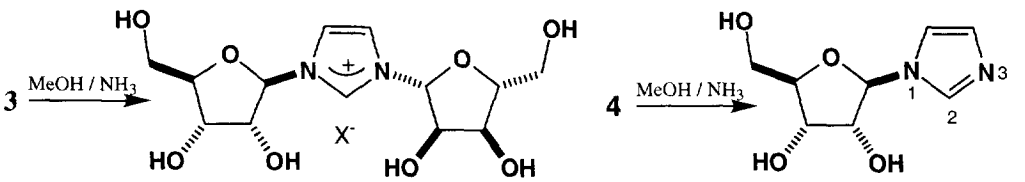
Compounds **3** and **4** could be separated by chromatography on silica gel. The bis-glycosylated compound **3** shows a ^1H NMR spectrum that is nearly identical with the spectrum of the monosubstituted imidazole **4** . Only the proton at position 2 for both compounds **3** and **4** differs with chemical shift δ = 10.10

ppm and δ = 7.78 ppm respectively. If the imidazole was treated with two equivalents of sugar **1** the bis glycosylated **3** is isolated in 75% yield.



3 Figure 1 4

The debenzoylation of **3** and **4** was achieved easily by using the methanolic solution of ammonia at room temperature (Scheme 3).

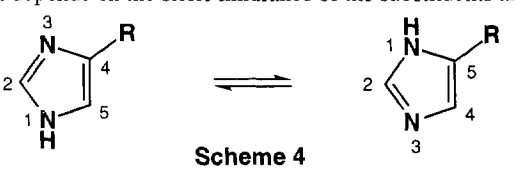


7 Scheme 3 8

The peracetylated compounds **5** and **6** (Scheme **1**) could be obtained alike the preparation of **3** and **4** when the mixture was refluxed overnight. The bisglycosylated compound **5** is unstable on silica gel. It decomposes partially on TLC plate into the monoglycosylated **6; 5** and **6** were separated by adding a lM HCl solution to the mixture and extracting with dichloromethane : the protonated compound **6** is soluble in aqueous layer while the imidazolium **5** is soluble in dichloromethane.

Substituted imidazole

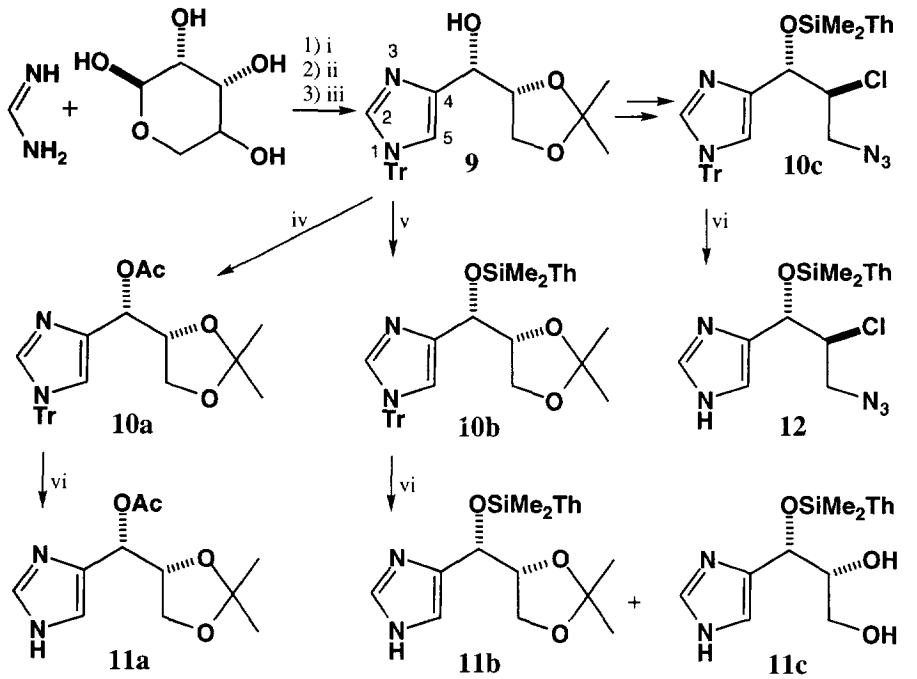
As 4(5) substituted imidazole exists in two tautomeric forms, imidazolic derivatives show a similar behaviour towards the N-glycosylation and the N-alkylation. They can occur at N_1 or / and N_3 position (Scheme 4). The N-alkylation depends on the steric hindrance of the substituents and their nature.



Scheme 4

The 4-subtituted imidazolic derivatives used in the following investigation were prepared according to our previous synthesis.[17] The preparation of the new compounds **10a**, **11a**, **11b** and **11c** was achieved as shown in (Scheme 5).

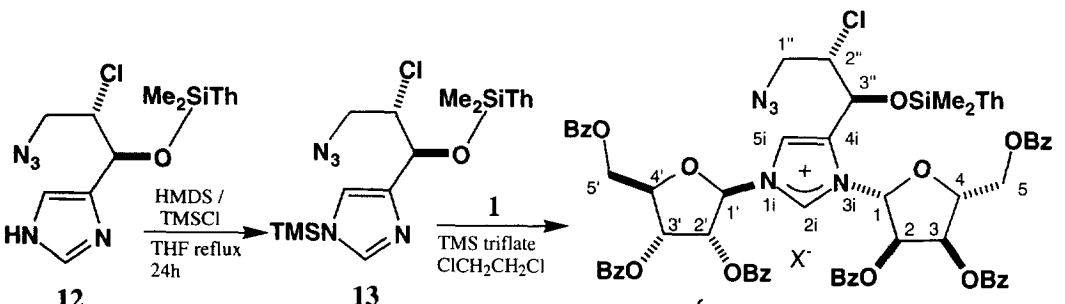
For the nucleosides preparation, the same general synthetic method as described in the foregoing section, has been applied. With 4(5)-substituted imidazoles we expected three products: two β N1 or N3 monoglycosylated derivatives and β N1 and N3 bis glycosylated imidazolium. All attempts following the silyl Hilbert Johnson and the Wyss work [11] , using the compounds **11a** and **11b** as starting material, were unsuccessful. The dioxolane protection is probably not the best one for these Lewis acidic conditions.



Scheme 5

i = NH_3, 48h, 46°C ; ii = TrCl, DMF, Et_3N ; iii = 2,2 dimethoxypropane, APTS, THF ; iv = Ac_2O, Pyridine ; v = $ClSiMe_2Th$, DMF, imidazole ; vi = AcOH, H_2O, THF

When **12** was silylated to **13** and allowed to react for 24h at room temperature with 1 equiv. of **1** and trimethylsilyltriflate in 1,2 dichloromethane, we obtained **14** in 26 % yield (Scheme 6).

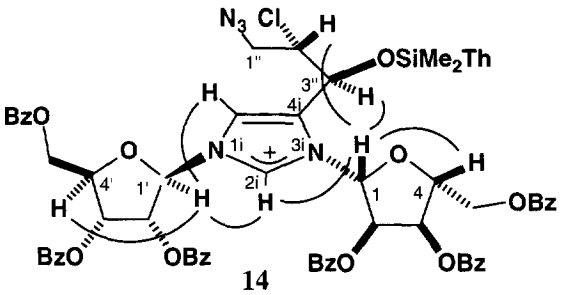


Scheme 6

1 equiv. of **1** --> 26% yield
2 equiv. of **1** --> 59% yield

None of the monosubstituted compound was isolated ! The yield was increased to 59 % by using 2 eq of the peracylated ribofuranose **1.** Evaluation of 2D-^1H and ^{13}C NMR , and mass spectroscopic analysis proved the structure of **14** and its β anomeric configuration. This imidazolium showed a molecular ion at m/z 1232 $(M+H)^+$ in the FABMS spectrum. The ^1H NMR in $CDCl_3$ showed the anomeric protons H_1 / $H_{1'}$ at 6.72 / 6.80ppm. NOe's (by nOe difference experiments) observed between H_1 / H_4 and $H_{1'}$ / $H_{4'}$ established the β configuration of the carbons C_1 and $C_{1'}$ (Figure 2).

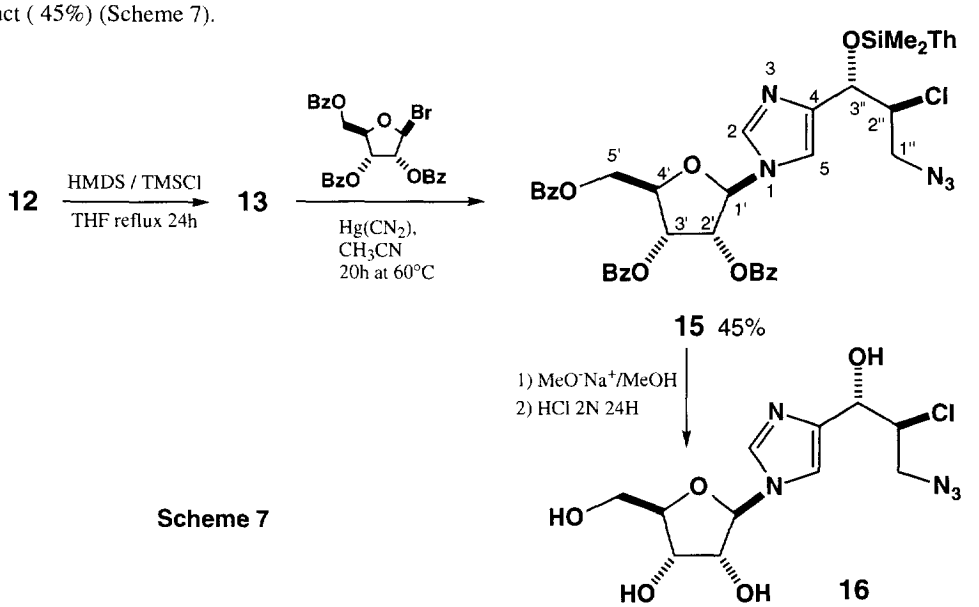
Figure 2 : Observed nOe's



14

The nOe's correlation between $H_{1'}$ / H_{2i}, $H_{2''}$,$H_{3''}$ and H_1 / $_{2i}$, H_{5i} allowed us to fix the side chain next to the glycosidic bound that shows the anomeric proton at 7.72 ppm.

The condensation of 1-N silylated substituted imidazole **13** with 2,3,5-tri-O-benzoyl-D-ribofuranosyl-bromide in acetonitrile at 60°C in the presence of mercury(II) cyanide gave the monoglycosylated **15** as major product (45%) (Scheme 7).



Scheme 7

The configuration β of **15** was established by nOe experiments on $H_{1'}$ / H_2, H_5, and $H_{3'}$ and transformation of the imidazolium compound **14** in **15** at 110°C in DMF in presence of imidazole or DABCO. The deprotection of **15** to **16** was achieved by using sodium methylate in methanol followed by HCl 2N at room temperature (Scheme 7).

These imidazolium and imidazole nucleosides have been examined for their anti-HIV (MT-4 and CEM-SS cells) activity and their cytotoxicity, no significant activity was observed for any of these target molecules. Further investigation using D-deoxyribofuranose instead of D-ribofuranose is currently in progress.

In conclusion, the first example of homochiral C_2 symmetrical imidazolium was described. This type of quaternary chiral salt could be of great interest as potential precursor of chiral auxiliary in organic chemistry.

Experimental Section

General information : Melting points were determined with a Kofler Apparatus and are uncorrected. Infrared (IR, cm^{-1}) spectra were recorded on a Nicolet-205 spectrometer. ^1H NMR spectra were measured on a Bruker AC-200 (200 MHz), Bruker AC-250 (250 MHz), Bruker AM-300 (300 MHz), and WM-400 (400 MHz) spectrometers with tetramethylsilane as internal standard (δ ppm). These instruments were also used for ^{13}C NMR. Mass spectra were carried out using a MS 50 (EI), MS 9 (CI) and MS 80 Kratos for FAB and HRMS. Solvents and reagents were purified according to standard laboratory techniques. All reactions requiring anhydrous conditions were conducted in atmosphere of Argon.

Glycosylation starting from the 1-O-acetyl-2,3,5-tri-O-(benzoyl)-ß-D-ribofuranose 1 --> 3 + 4 : The sugar 1-O-acetyl-2,3,5-tri-O-(benzoyl)-ß-D-ribofuranose **1** (100 mg, 0.2 mmol) was dissolved in 1.2 ml dichloroethane. Silylimidazole (35 mg, 0.037 ml, 0.25 mmol) and trimethylsilyltriflate (55.5 mg, 0.048 ml, 0.25 mmol) were then added at room temperature. The reaction mixture was stirred o.n.. It was then worked up by addition of 5 ml aqueous sodium hydrogen carbonate solution (1.5 N) and 10 ml ethyl acetate. The aqueous layer was extracted twice with 5 ml ethyl acetate. The organic layers were washed with brine and then dried over magnesium sulphate. The solvent was evaporated under reduced pressure to give 111 mg crude product. This was purified by preparative thick layer chromatography using heptane/EtOAc/MeOH (47.5/47.5/5) as solvent. 34 mg (35 %) of **3** and 8 mg (8 %) of **4** were isolated. Starting from 1.08 g of **1** (2 mmol) in 20 ml dichloroethane, 140 mg (1 mmol) of silylimidazole and 361 ml (2mmol) of TMS-triflate in the same conditions as above, we obtained, after purification on silica gel column (heptane, ethyl acetate : 3, 7), 750 mg (74 %) of **3** and traces of **4.**

(N_1, N_3)-bis-β-D-2', 3', 5'-tri-O-(benzoyl)-ribofuranosyl imidazolium 3 : $[\alpha]_D$ -55 (c = 0.786, $CHCl_3$). IR (KBr), ν : 1724, 1594, 1454, 1267, 1107, 1024, 704 . UV (methanol) λ_{max} : 272, 228, 202 nm. ^{1}HNMR δ (300 MHz, $CDCl_3$) : 10.10 (s, 1H, H_2) exchanged with D_2O, 7.96 - 8.04 (m, 12H, aryl) 7.71 (s, 2H, $2H_{4(5)}$) 7.45 - 7.58 (m, 18H, aryl) 6.61 (d, 2H, J = 5.5 Hz, $2H_{1'}$), 5.87 (dd, 2H, J = 4 Hz, J = 5 Hz, $2H_{3'}$) 5.75 (tr, 2H, J = 5 Hz, $2H_{2'}$) 4.80 (tr, 2H, J = 3.6 Hz, $2H_{4'}$), 4.73 (bs, 4H, $2H_{5'}$). ^{13}C NMR δ(50.13 MHz, $CDCl_3$) : 166.2, 165.6, 165.4 (6CO), 136.2 (C_2), 134.2, 134.1, 133.8, 130.3, 130.1, 129.8, 128.8, 128.3, 127.7 (aryl), 120.4 ($C_{4(5)}$), 90.3 ($2C_{1'}$), 82.6 ($2C_{4'}$), 75.7 ($2C_{2'}$), 71.0 ($2C_{3'}$), 63.6 ($2C_{5'}$). Mass (EI m/z %) : 973 (2), 960 (11), 958 (31), 957 (M^+ imidazolium, (52)), 853 (1), 447 (8), 445 (28), 307 (4), 203 (4), 201 (33), 154 (17), 138 (10), 136 (11), 121 (3), 105 (100). HRMS : Found 957.2870 ; calculated for $C_{55}H_{45}N_2O_{14}$ 957.2910.

N_1-β-D-2', 3', 5'-tri-O-(benzoyl)-ribofuranosyl imidazole 4 : $[\alpha]_D$ -34 (c = 2.4, $CHCl_3$). IR ($CHCl_3$) ν : 2961, 1729, 1602, 1494, 1452, 1265, 1124, 1024, 727. ^{1}H NMR. (400 MHz, $CDCl_3$) δ 8.07 - 8.15 (m, 2H, aryl), 7.92 - 8.02 (m, 4H, aryl), 7.78 (s, 1H, H_2), 7.35 - 7.65 (m, 9H, aryl), 7.15 (s, 1H, H_5), 7.09 (s, 1H, H_4), 6.12 (d, 1H, J = 5 Hz, $H_{1'}$), 5.86 (btr, 1H, J = 4,5 Hz, $H_{3'}$), 5.82 (btr, 1H, J = 5 Hz, $H_{2'}$), 4.85 (dd, 1H, J = 3.5 Hz, J = 12 Hz, $H_{5'}$), 4.78 (q, 1H, J = 3.5 Hz, $H_{4'}$), 4.63 (dd, 1H, J = 3.5 Hz, J = 12 Hz, $H_{5'}$). ^{13}C NMR (100.13 MHz, $CDCl_3$) : 166.4, 165.5, 165.4 (3x $OCOC_6H_5$), 136.3 (C_2), 134.2, 134.1, 133.9, 131.0 (C_5), 130.1, 130.0, 129.0, 128.8, 128.3, 127.7 (C_6H_5), 116.5 (C_5), 88.4 ($C_{1'}$), 80.4 ($C_{4'}$), 75.6 ($C_{2'}$), 71.6 ($C_{3'}$), 63.9 ($C_{5'}$). Mass (CI m/z %) : 515 (7), 514 (37), 513 ($M+1^+$, 100), 445 (9), 391 (7), 232 (9), 188 (11), 161 (5), 123 (71), 105 (6), 69 (34). HRMS : Found 513.1663; calculated for $C_{29}H_{25}N_2O_7$ 513.1663.

Glycosylation starting from the 1, 2, 3, 5-tetra-O-acetyl-ß-D-ribofuranose 2 : The tetraacetoxysugar **2** (954 mg, 3 mmol) was dissolved in 20 ml dichloroethane. Silylimidazole (0.468 ml, 3.2 mmol) and trimethylsilyltriflate (0.694 ml, 3.2 mmol) dissolved in 10 ml dichloroethane were added at room temperature. The reaction mixture was heated to reflux for 5 h. It was then worked up by addition of aqueous sodium hydrogenocarbonate solution (1.5 N) and dichloromethane. The organic layers were washed with brine and then dried over magnesium sulphate. The solvent was evaporated under reduced pressure to give a crystalline product. Taking 75 % of the crude mixture the two compounds were separated by adding a 1M HCl solution and extracting of the acidic layer with dichloromethane. The protonated mono carbohydrate **6** stays in the

aqueous layer whereas the bis-carbohydrate cation **5** passes in organic solvent. To both layers saturated sodium carbonate solution was added. The organic layer was then washed with brine and dried with magnesium sulphate to give after evaporation **5** (131.5 mg, 0.4 mmol, 18 %). The aqueous layer was washed with dichloromethane which was washed with brine and dried with magnesium sulphate. After evaporation of the solvent pure **6** (338 mg, 1.54 mmol, 50 %) was obtained.

(N_1, N_3)-bis-β-D-2', 3', 5'-tri-O-(acetyl)-ribofuranosyl imidazolium 5 : ^{1}H NMR δ (300 MHz, $CDCl_3$) : 9.71 (s, 1H, H_2), 7.78 (s, 2H, H_4, H_5), 6.27 (d, 1H, J = 4.5 Hz, $H_{1'}$) , 5.40 (dd, 2H, J = 4.5 and 5 Hz, $H_{2'}$), 5.28 (tr, 2H, J = 5 Hz, $H_{3'}$), 4.50 (m, 2H, $H_{4'}$), 4.46 (dd, 2H, J = 4 Hz, J = 13 Hz, $H_{5'}$), 4.34 (dd, 2H, J = 3 Hz, J = 13 Hz, $H_{5'}$), 2.11 (s, 6H, $2CH_3$), 2.10 (s, 12H, $4CH_3$). ^{13}C NMR (100.13 MHz, $CDCl_3$) : 170.2, 169.9, 169.5 (6CO), 134.8 (C_2), 120.2 ($C_{4(5)}$), 90.3 ($2C_{1'}$), 81.4 ($2C_{4'}$), 74.6 ($2C_{2'}$), 69.6 ($2C_{3'}$), 62.5, ($2C_{5'}$), 20.5, 20.2 ($6CH_3$). Mass (FAB m/z %) : 586 (9), 585 (M^+, 31), 327 (17), 260 (13), 259 (80), 217 (6), 157 (23), 140 (13), 139 (100), 127 (9), 115 (13). HRMS : Found 585.1947; calculated for $C_{25}H_{33}N_2O_{14}$ 585.1931.

N_1-β-D-2', 3', 5'-tri-O-(benzoyl)-ribofuranosyl imidazole 6 : $[\alpha]_D$ -22 (c = 3.9, $CHCl_3$). IR ($CHCl_3$) ν : 2960, 1750, 1608, 1492, 1428, 1389, 1170. ^{1}H NMR δ (250 MHz, $CDCl_3$) : 7.72 (bs, 1H, H_2), 7.13 (bs, 2H, H_4, H_5), 5.84 (d, 1H, J = 5 Hz, $H_{1'}$) , 5.37 (m, 2H, $H_{2'}$, $H_{3'}$), 4.41 (m, 1H, $H_{4'}$), 4.34 (m, 2H, $H_{5'}$), 2.16 (s, 3H, CH_3), 2.10 (s, 3H, CH_3). ^{13}C NMR (100.13 MHz, $CDCl_3$) : 170.3, 169.6, 169.4 (3x CO), 136.0 (C_2), 130.6 (C_4), 116.2 (C_5), 87.8 ($C_{1'}$), 80.2 ($C_{4'}$), 74.6 ($C_{2'}$), 70.5, ($C_{3'}$),63.0($C_{5'}$),20.8, 20.5, 20.4 (3x CH_3). Mass (CI m/z %) : 328 (24), 327 ($(M+1)^+$, 100), 217 (1), 146 (4), 81 (21). HRMS : Found 327.1223; calculated for $C_{14}H_{19}N_2O_7$ 327.1192.

A general procedure for the deprotection of the hydroxyl groups : The benzoester (0.2 mmol) was dissolved at room temperature in 2.5 ml methanol that had been saturated with ammonia at 0°C. The solution was stirred at room temperature for 1.5 h in the case of **3** and heated to 60°C for 1 - 3 h in the case of **4.** After evaporation of the solvent and addition of some water the crude reaction mixture was extracted with diethyl ether. The methyl benzoester and the formed benzoic amide dissolve in the organic solvent. The deprotected compound **7** or **8** are water-soluble and could be obtained after evaporation of the water, in 41 % yield for **7** and 32 % yield for **8**.

(N_1, N_3)-bis-β-D-ribofuranosyl imidazolium 7 : ^{1}H NMR δ (250 MHz, DMSO) : 9.73 (s, 1H, H_2) exchanged in D_2O, 8.14 (s, 2H, H_4, H_5), 5.94 (d, 2H, J = 4.5 Hz, $2H_{1'}$), 5.94 (bs, 2H, OH) exchanged in D_2O, 5.53 (bs, 2H, OH) exchanged in D_2O, 5.35 (bs, 2H, OH) exchanged in D_2O, 4.38 (s, 2H, $2H_{2'}$), 4.20 (m, 4H, $2H_{3'}$, $2H_{4'}$), 3.75 (ABq, 4H, J = 10 Hz, $2H_{5'}$). ^{13}C NMR δ (62.5 MHz, DMSO) : 134.4 (C_2), 120.2 ($C_{4(5)}$), 91.9 ($2C_{1'}$), 86.8 ($2C_{4'}$), 75.9 ($2C_{2'}$), 70.0 ($2C_{3'}$), 60.6 ($2C_{5'}$).

N_1-ß-D-ribofuranosyl imidazole 8 : $[\alpha]_D$ -18 (c = 0.5, MeOH). IR ($CHCl_3$) ν : 3340, 2920, 1505, 1495, 1456, 1396, 1214, 1130, 1092, 1050, 969. ^{1}H NMR δ (250 MHz, DMSO) : 8.00 (s, 1H, H_2), 7.48 (s, 1H, H_5), 7.06 (s, 1H, H_4), 5.64 (d, 1H, J = 6 Hz, $H_{1'}$), 5.58 (bs, 1H, OH) exchanged in D_2O, 5.37 (bs, 1H, OH) exchanged in D_2O, 5.20 (bs, 1H, OH) exchanged in D_2O, 4.25 (tr, 2H, J = 5.5 Hz, $H_{3'}$, $H_{5'}$), 4.15 (m, 1H, $H_{2'}$), 4.01 (bd, 1H, J = 4 Hz, $H_{4'}$), 3.62 (m, 2H, H_5). ^{13}C n.m.r. (62.89 MHz, DMSO) : 136.3 (C_2), 128.6 (C_4), 117.2 (C_5), 89.2 ($C_{1'}$), 85.2 ($C_{4'}$), 75.2 ($C_{2'}$), 70.4 ($C_{3'}$), 61.3 ($C_{5'}$). Mass (CI m/z %) : 257 ($(M+57)^+$(10)), 202 (17), 201 ($(M+1)^+$(100)), 153 (2), 125 (9), 85 (21). HRMS : Found 200.0796 ; calculated for $C_8H_{12}N_2O_4$ 200.0796.

Preparation of 10a : A solution of 1g (6.8 mmol) **9** in 20ml of pyridine and 5 ml of Ac_2O was stirred for 3h at roomtemperature. The resulting mixture was evaporated. The residue was dissolved in CH_2Cl_2, washed with water and dried over MgSO4. Evaporation yielded 3g (91 %) of pure **10a**.

Acetylated 10a : IR ($CHCl_3$) ν : 3100, 1734, 1446, 1373, 1226, 1207, 1165, 1057, 766. ^{1}H NMR δ (250 MHz, $CDCl_3$) : 7.39 (d, J = 1.5Hz, 1H, H_2), 7.27 (m, 1H, 9H, H-Ar), 7.08 (m, 1H, 6H, H-Ar), 6.88 (d, J =1.5 Hz, 1H, H_4), 5.97 (d, J = 4.5 Hz,1H, $H_{3'}$), 4.57 (ddd, J = 4.5, 6.5, and 11Hz, 1H, $H_{2'}$), 4.05 (m, 2H, $2H_{1'}$), 2.05 (s, 3H, CH_3CO), 1.33 and 1.29(2s, 6H, acetonide). ^{13}C NMR (62.89 MHz, DMSO) : 136.3 (C_2), 128.6

(C_4), 117.2 (C_5), 89.2 ($C_{1'}$), 85.2 ($C_{4'}$), 75.2 ($C_{2'}$), 70.4 ($C_{3'}$), 61.3 ($C_{5'}$). Mass (EI m/z %) : 482(M^+), 467, 422(M^+ - AcOH, 243(Trityl).

The preparations of **10b** and **10c** were achieved as described (17).

Detritylation of the imidazolic derivatives 10a, 10b and 10c : Acetonide protected **10b** (1.188 g, 2.04 mmol) was dissolved in 30 ml THF, 15 ml acetic acid and 15 ml water. The reaction mixture was refluxed for 2 h. Solid sodium carbonate was added carefully until the evolution of gas ceased. After addition of 30 ml water the aqueous layer was extracted twice with 100 ml diethyl ether and then twice with 20 ml dichloromethane containing 2 % methanol. The organic layers were combined, washed with brine, then dried over magnesium sulphate. The solvent was evaporated under reduced pressure to give a yellow oil. The crude product was subjected to column chromatography. A solvent mixture of heptane / ethyl acetate that was gradually changed starting with 10 : 1 to finishing with pure ethyl acetate was used. The column was at last washed with methanol.

447 mg (1.31 mmol, 64 %) detritylated product **11b** and 55 mg (0.18 mmol, 8 %) 1,2-deprotected diol **11c** were obtained.

Detritylated product 11b : ^{1}HNMR δ (200 MHz, $CDCl_3$) : 7.60 (s, 1H, H_2), 6.94 (s, 1H, H_5), 4.68 (d, 1H, J = 5 Hz, $H_{3'}$), 4.36 (dd, 1H, J = 5 Hz, J = 6 Hz, $H_{2'}$), 3.96 (d, 2H, J = 6 Hz, $H_{1'}$), 1.62 (septuplet, 1H, J = 7 Hz, C**H**$(CH_3)_2$),1.40 (s, 3H, CH_3 (acetonide)),1.32 (s, 3H, CH_3 (acetonide)), 0.85 (m, 12H, C(C**H**$_3$)$_2$CH(C**H**$_3$)$_2$), 0.14 (s, 3H, $SiCH_3$), -0.11 (s, 3H, $SiCH_3$). ^{13}C NMR δ (50.13 MHz, $CDCl_3$) : 134.8 (C_2, $C_{4(5)}$), 118.2 ($C_{5(4)}$), 109.4 (**C**$(CH_3)_2$ (acetonide)), 79.2 (CHO (acetonide)), 69.2 (COSi), 66.1 (CH_2O (acetonide)), 34.1 (C$(CH_3)_2$**C**H$(CH_3)_2$), 26.6 (CH(**C**$H_3)_2$ (acetonide)), 25.3 (CH(**C**$H_3)_2$ (acetonide)), 25.1 (**C**$(CH_3)_2$CH$(CH_3)_2$), 20.3, 18.6 (4x C(**C**$H_3)_2$CH(**C**$H_3)_2$), - 2.7, - 2.9 (2x $SiCH_3$). Mass (CI m/z %) : 397 (M^++57,10), 379 (M^++39, 7), 342 (37), 341 (M^++1, 100), 255 (4), 199 (2), 197 (2), 181 (10), 161 (5).

1,2-deprotected diol 11c : [α]$_D$ +50 (c = 0.5, $CHCl_3$). ^{1}H n.m.r. (200 MHz, $CDCl_3$) : 7.55 (s, 1H, H_2), 6.90 (s, 1H, H_5), 4.70 (d, 1H, J = 6 Hz, $H_{3'}$), 3.80 (m, 1H, $H_{2'}$), 3.64 (dd, 1H, J = 4 Hz, J = 11 Hz, $H_{1'}$), 3.52 (dd, 1H, J = 6 Hz, J = 11 Hz, $H_{1'}$), 1.58 (septuplet, 1H, J = 7 Hz, C**H**$(CH_3)_2$), 0.84 (d, 6H, J = 7 Hz, CH(C**H**$_3)_2$), 0.80 (s, 3H, C(C**H**$_3)_2$CH$(CH_3)_2$), 0.77 (s, 3H, C(C**H**$_3)_2$CH$(CH_3)_2$), 0.07 (s, 3H, $SiCH_3$),-0.18 (s, 3H, $SiCH_3$). Mass (CI m/z %) : 357 ((M+57)$^+$(13)), 302 (16), 301 ((M+1)$^+$(74)), 332 (2), 215 (3), 199 (6), 161 (6), 141 (6). HRMS : Found 301.1955 ; calculated for $C_{14}H_{28}N_2O_3Si$ 301.1955.

The detritylation of **10a** to **11a** and **10c** to **12** was achieved in the same conditions as above.

11a : IR ($CHCl_3$) ν : 3460, 2991, 1735, 1382,1055, 665. ^{1}H NMR δ (250 MHz, $CDCl_3$) : 7.63 (s, 1H, H_2), 7.10 (s, 1H, H_5), 6.05 (large s, 1H, NH), 5.93 (d, J = 6Hz, 1H, $H_{3'}$), 4.60 (d, 1H, J = 7 Hz, $H_{2'}$), 4.17 (ddd, J = 6, 6, 8Hz, 1H, $H_{1'}$), 4.03 (dd, J = 6, 8Hz, 1H, $H_{1'}$), 2.10 (s, 3H, C**H**$_3$CO), 1.38 (s, 3H, **CH**$_3$ (acetonide)), 1.35 (s, 3H, **CH**$_3$ (acetonide)). ^{13}C NMR (50.13 MHz, $CDCl_3$) : 170.5 (CO), 135.4 (C_2), 134.5 (C_4), 118.5 (C_5), 109.9 (**C**$(CH_3)_2$(acetonide)), 76.3($C_{3'}$), 69.2 ($C_{2'}$), 66.2 ($C_{1'}$), 25.5 and 25.4 (C(**C**$H_3)_2$), 21.2 (**C**H3CO). Mass (CI m/z %) : 243, 242, 241(M^+), 183, 167, 146.

12 : [α]$_D$ +1 (c=5.3, $CHCl_3$). IR ($CHCl_3$) ν : 3450, 2960, 2110. ^{1}H NMR δ (200 MHz, $CDCl_3$) : 8.57 S large, 1H, NH),7.62 (s, 1H, H_2), 7.02 (s, 1H, H_5), 5.00 (d, J = 5 Hz, 1H, $H_{3'}$), 4.18 (m, 1H, $H_{2'}$), 4.18(dd, J = 5 and 13 Hz, 1H, $H_{1'}$), 3.40 (dd, J = 7.5 and 13Hz, 1H, $H_{1'}$), 1.63 (septuplet, J = 7 Hz, 1H, C**H**$(CH_3)_2$), 0.88 (d, 6H, J = 7 Hz, CH(C**H**$_3)_2$), 0.86 (s, 3H, C(C**H**$_3)_2$CH$(CH_3)_2$), 0.84 (s, 3H, C(C**H**$_3)_2$CH$(CH_3)_2$),0.15 (s, 3H, $SiCH_3$),-0.10 (s, 3H, $SiCH_3$)· ^{13}CNMR (50.13 MHz, $CDCl_3$) : 135.7 (C_2), 117.5 (C_5), 70.7($C_{3'}$), 65.5($C_{2'}$), 54.7($C_{1'}$), 34.9, 25.9, 21.0, 19.5, -1.9, and -2.4($SiMe_2Th$). Mass (CI m/z %: 344(MH^+), 300(MH^+ - N_3H).

Glycosylation of 12 -> 14 : The chloroazido imidazole **12** (105 mg, 0,306 mmol) was dissolved in 1 ml hexamethyldisilazane. Then 0.2 ml trimethylsilylchloride was added. The solution was stirred 24h at 60°C. The solvent was removed under reduced pressure. The presumed silylated **13** was then dissolved in 2 ml freshly distilled 1,2 dichloroethane. 154mg (0.306 mmol) of the 1-O-acetyl-2,3,5-tri-O-(benzoyl)-ß-D-

ribofuranose **1** were added. TMS triflate (68 mg, 60µl) was added and the solution stirred at room temperature for 17 h. It was then worked up by addition of 5% sodium bicarbonate solution and dichloromethane. The organic layers were dried over magnesium sulphate and the solvent was evaporated under reduced pressure. Separation of the complex mixture by plate chromatography using heptane: ethyl acetate (1 :1) afforded 64 mg of the impure product **14** and the starting material **12** (20mg, 8%). A second chromatography in the same conditions as above leads to 50 mg (26%) of **14**. The other more and less polar fractions that we chose not to separate or identify are probably mixture of other isomers. The yield was increased to 59% by using 2equiv. of the peracylated ribofuranose **1.**

14 : $[\alpha]_D$ -40 (c = 1.05, $CHCl_3$). IR ($CHCl_3$) ν : 3121, 2959, 2868, 2115, 1735, 1609, 1454, 1257, 702, 632. ^1H NMR δ (200 MHz, $CDCl_3$) : 10.12 (s, 1H, H_{2i}), 8.20 - 7.35 (benzoate protons and H_{5i} at 7.94 as s), 6.80 (d, J = 6Hz, 1H, $H_{1'}$), 6.72 (d, J = 6 Hz, 1H, H_1), 6.17 (dd, J = 6 and 6 Hz, 1H, H_2), 5.97 (dd, J = 3.5 and 6 Hz, 1H, H_3), 5.87 (dd, J = 3 and 6Hz, $H_{3'}$) , 5.76 (dd, J = 6 and 6 Hz, 1H, $H_{2'}$, 5.12 (d, J = 5.5Hz, 1H, $H_{3''}$), 5.12 (d, J = 7 and 12Hz, 1H, H_{5a}), 4.83 (m, 2H, $H_{4'}$ and $H_{5'a}$), 4.73 (m, 1H, H_4), 4.67 (dd, j = 4 and 12Hz, 1H, H_{5b}), 4.57 (dd, j = 2 and 12Hz, 1H, $H_{5'b}$), 4.05 (m, 1H, $H_{2''}$), 3.41 (m, 2H, $2H_{1''}$), [1.55 (m, 1H), 0.80 (12H), 0.17 (3H), -0.17 (3H),$SiMe_2Th$]. ^{13}C NMR (50.13 MHz, $CDCl_3$) : 166.5, 165.9, and 165.1 (6CO), 137.6(C_{2i}), 134.9(C_{4i}), 134.1 - 127.6 Aryl), 127.7(C_{5i}), 90.3($C_{1'}$), 89.1(C_1), 82.9($C_{4'}$), 82.2(C_4), 75.6(C_2), 75.5($C_{2'}$), 71.3(C_3), 71.2($C_{3'}$)65.5($C_{3''}$), 63.6(C_5), 63.5($C_{5'}$), 63.0($C_{2''}$), 53.1($C_{1''}$), 34.0, 22.3, 20.0, 18.3, -1.3 and -0.6(SiMe2Th). Mass (FAB m/z (%) : 1232(MH^+), 1189(MH^+ - HN_3), 445, 307, 201, 154, 136, 121, 105.

Formation of the 1-bromo-2,3,5-tri-O-benzoyl-ß-D-ribofuranose : Dichloromethane was saturated with HBr by bubbling through the dry solvent dry hydrogen bromide for 30 min at -78°C. At - 78°C 1-O-acetyl-2,3,5-tri-O-benzoyl-ß-D-ribofuranose **1** (1.008 g, 2 mmol) was added to 10 ml of this solution. The solution was allowed to come to room temperature within 2 hours. The solvent was removed and the sample dried at 40°C under high vacuum for 15 min.[a)] The light yellow oil was then dissolved in 10 ml freshly distilled acetonitrile to give a 0.2M solution.

a) For larger reaction scales the literature procedure should probably be followed recommending the evaporation with toluene.

Formation of the nucleoside 15 : The chloroazido imidazole **12** (143 mg, 0.42 mmol) was dissolved in 1 ml hexamethyldisilazane. Then 0.1 ml trimethylsilylchloride was added. A slight white residue was formed. The solution was stirred o.n. at 110°C oil bath temperature. The solvent was removed under reduced pressure after 19 h. The oily residue was dried at high vacuum for 20 min and was then dissolved in 1 ml freshly distilled acetonitrile. 2.2 ml (0.44 mmol) of the above formed bromosugar solution were added. Mercuric cyanide (105 mg, 0.42 mmol) that had been powdered and dried under high vacuum for 30 min was dissolved and the solution stirred at 60°C for 19 h. It was then worked up by addition of saturated sodium carbonate solution and dichloromethane. The organic layers were washed with brine and then dried over magnesium sulphate. The solvent was evaporated under reduced pressure to give 408 mg of a crude oily product. This was submitted to column chromatography using mixtures of heptane : ethyl acetate starting with a ratio of 7 :1 and gradually changing the composition until pure ethyl acetate is used. Finally the column was washed with methanol. 149 mg (0.19 mmol, 45 %) of the product **15** were isolated as a colourless oil that crystallised after some time at 0°C. 15 mg (0.044 mmol, 10 %) of the starting material **12** were recovered. The methanolic fraction contains various bis-sugar compounds. 13 mg (~ 5 %) were isolated as a mixture of different isomers, these however were not further investigated.

15 : IR (KBr) ν : 3064, 2959, 2104, 1735, 1602, 1451, 1260, 1108, 1070, 1025, 710. ^1H NMR δ (250 MHz, $CDCl_3$) : 7.82 - 8.20 (m, 6H, benzoyl), 7.73 (s, 1H, H_2), 7.23 - 7.65 (m, 9H, benzoyl), 7.13 (s, 1H, H_5), 6.08 (d, 1H, J = 6 Hz, $H_{1'}$), 5.88 (tr, 1H, J = 5 Hz, $H_{3'}$), 5.79 (tr, 1H, J = 6 Hz, $H_{2'}$), 4.96 (d, 1H, J = 4 Hz, $H_{3''}$), 4.80 (dd, 1H, J = 3 Hz, J = 12 Hz, $H_{5'a}$), 4.76 (m, 1H, $H_{4'}$), 4.63 (dd, 1H, J = 4 Hz, J = 12 Hz, $H_{5'b}$), 4.08 (m, 1H, $H_{2''}$), 3.60 (dd, 1H, J = 5 Hz, J = 13 Hz, $H_{1''a}$), 3.42 (dd, 1H, J = 7 Hz, J = 13 Hz, $H_{1''b}$), 1.50 (septuplet,

1H, J = 7 Hz, CH$(CH_3)_2$), [0.86 (d, 6H, J = 7 Hz),0.82 (s, 3H) 0.77 (s, 3H,) 0.08 (s, 3H), -0.18 (s, 3H)]. ^{13}C N.M.R. (62.89 MHz, $CDCl_3$) : 166.2, 165.3, 165.1 (3CO), 143.4 (C_4), 135.6 (C_2), 134.0, 133.9, 133.7, 129.9, 129.8, 128.9, 128.7, 128.6, 128.5, 128.4 (aryl), 115.1 (C_5), 88.1 ($C_{1'}$), 80.8 ($C_{4'}$), 75.1 ($C_{2'}$), 71.5 ($C_{3'}$), 70.8 (COSi), 64.6 (CHCl), 63.7 ($C_{5'}$), 54.2 (CH_2N_3), 34.1 ($C(CH_3)_2CH(CH_3)_2$), 25.1 ($C(CH_3)_2CH(CH_3)_2$), 20.3, 18.7, (4x $C(CH_3)_2CH(CH_3)_2$), - 2.6, - 3.1 (2x $SiCH_3$). Mass (CI m/z %) : 790 (1), 789 (1), 788 ($(M+1)^+$, 2), 704 (11), 703 (10), 702 (26), 446 (23), 445 (84), 311 (20), 218 (90), 205 (46), 201 (84), 153 (32), 122 (98), 105 (100).

Deprotection of 15 --> 16

40 mg of **15** and 27 mg(10 equiv.) of MeONa were dissolved in 5 ml of methanol and stirred 2 h at room temperature. After evaporation of the solvent, 3 ml of 4 M HCl water solution were added. The mixture was stirred 24 h at room temperature. The water solution was washed with ether and concentrated. The purification of the deprotected product by plate chromatography using dichloromethane/methanol : 9/1 in presence of ammonia afforded 10 mg (59%) of **16**.

16 : $[\alpha]_D$ -16 (c = 1.1, CH_3OH). IR ($CHCl_3$) ν : 3 690 - 3000, 2118, 1656, 1387. ^1H NMR δ (300 MHz, CD_3OD) : 7.97 (s, 1H, H_2), 7.36 (s, 1H, H_5), 5.61 (d, 1H, J = 6 Hz, $H_{1'}$), 4.88 (d, 1H, J = 4 Hz, $H_{3''}$), 4.32 (m, 1H, $H_{2''}$), 4.19 (m, 2H, $H_{2'} + H_{3'}$), 4.03 (dd, 1H, J = 3, 7 Hz, $H_{4'}$), 3.80-3.42 (m, 4H, $2H_{5'}$ and 2H1'').

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