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L-Ribonucleosides from L-Xylose

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Abstract: L-Xylose was converted into a L-ribose derivative *via* an oxidation/reduction procedure. The L-ribosyl donor was submitted to a glycosidation reaction according to Vorbrüggen's conditions to give L-ribonucleosides (L-uridine, L-cytidine, L-adenosine and L-guanosine) in high yield.

Keywords: L-ribonucleosides; glycosidation; L-xylose; L-ribose

Introduction

The use of L-carbohydrates and the corresponding nucleosides in medicinal applications has greatly increased. In particular several modified nucleosides derived from L-sugars have shown a high potential as useful antiviral agents.[1] Also, due to the stereoselectivity of enzymes, L-ribose-modified oligoribonucleotides become attractive candidates for diagnostic and therapeutic uses because L-RNA ligands remain uncleaved in biological fluids.[2] The preparation of L-ribonucleosides requires the availability of suitably protected L-ribofuranosides which can be coupled with purine or pyrimidine bases. The mirror-image nucleosides thus obtained can be further processed to give properly protected L-RNA building blocks. The conversion of L-arabinose,[2-5] D-glucose[6] or D-ribose[7] into L-ribose have been described. In our synthetic approach the key step was the conversion of L-xylose (**1**) into a ribo-configured derivative.

Results and discussion

We proceeded from commercially available L-xylose (**1**, Fig. 1). The first step was the acetonation of the sugar to form **2** with an overall yield of 80% after treatment with 0.12 M HCl solution for 30 min.[8] Compound **2** was then silylated with *tert*-butyldiphenylsilyl chloride at the primary hydroxyl group under standard conditions to give **3** as colorless crystals in 97% yield after crystallisation from petrol ether. The inversion of configuration at C(3) was accomplished *via* an oxidation/reduction procedure. Ketone **4** was obtained by treatment with CrO_3/pyr complex in CH_2Cl_2 in 97% yield. The reduction step was performed with $LiAlH_4$ at -78 °C for 1 hour and led to **5** in 96% yield. The L-ribosyl derivative **5** was deprotected and O-methylated at C(1) in one pot followed by O-benzoylation to obtain **6** in 86% yield (α- and β-anomer) which could be used for glycosidation.[9]

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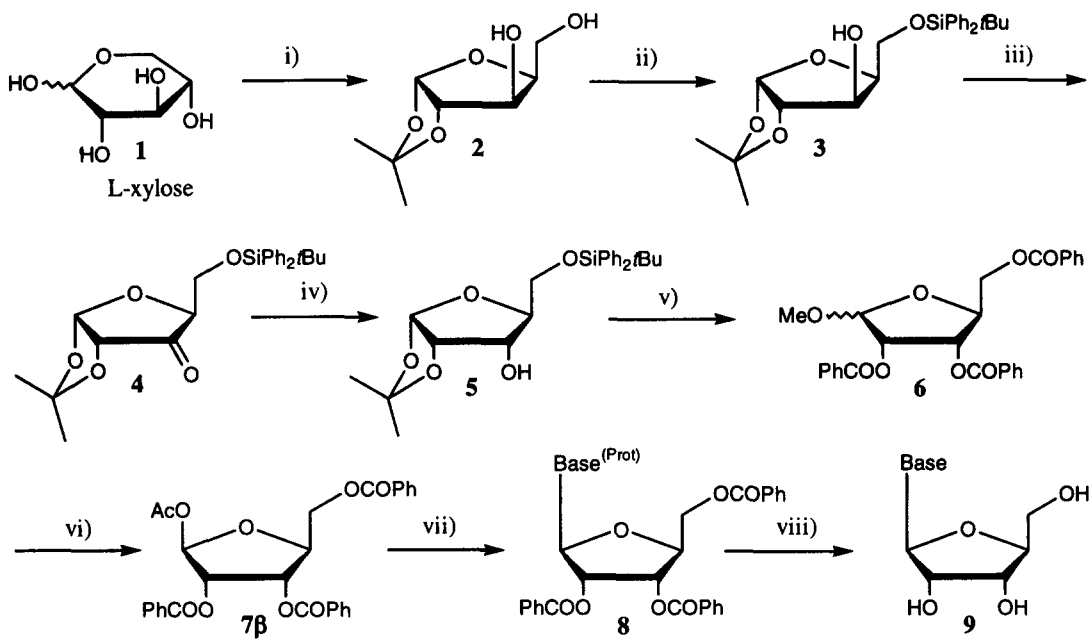
Figure 1

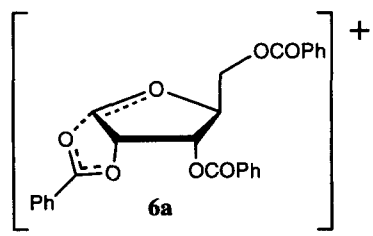


8a: Base : uracil: CH_3CN, o/n, 60-65°C: **89%**
8b: Base$^{(prot)}$: 4-N-acetylcytosine: CH_3CN, o/n, 60-65°C: **86%**
8c: Base$^{(prot)}$: 6-N-benzoyladenine: CH_2ClCH_2Cl, o/n, 80°C: **84%**
8d: Base$^{(prot)}$: 2-N-acetyl-6-O-diphenylcarbamoylguanine: toluene, 1h, 80°C: **70%**

9a: L-uridine: **95%**
9b: L-cytidine: **89%**
9c: L-adenosine: **92%**
9d: L-guanosine: **90%**

i) Acetone, H_2SO_4: **80%**; ii) *t*$BuPh_2SiCl$, imidazole, DMF: **97%**; iii) CrO_3, pyr, CH_2Cl_2: **97%**; iv) $LiAlH_4$, CH_2Cl_2: **96%**; v) MeOH, H_2SO_4; BzCl, pyr: **86%**; vi) Ac_2O, AcOH, H_2SO_4: **77%** (α:β 1:1); vii) B^{TMS}, TMSOTf, solvents; viii) NaOMe/MeOH or NH_3/H_2O.

However, according to Vorbrüggen[10] the best leaving group for the formation of intermediate **6a** is acetyl at C(1) and in β-position. The conversion of **6** led to the standard ribosyl donor 1-O-acetyl-2,3,4-tri-O-benzoyl-L-ribofuranoside[5,11] (**7**) as an α/β mixture (1:1). The pure β-anomer was obtained *via* crystallisation from isopropyl alcohol.



We tried to perform the isomerisation of the α- to the β-anomer by heating **7** (mainly α-anomer) at 50 °C under acidic conditions for several hours but we observed only decom-

position of the starting material. To increase the overall yield, a regeneration of **6** (α- and β-anomer) from **7** (α-anomer) was feasible *via* total deprotection under basic conditions (0.1 M NaOMe in MeOH), followed by the same reaction sequence v) as before. We observed reaction yields (**7α** to **6α/β**) between 55% and 87% (α+β). We obtained L-ribosyl donor **7β** in an overall yield of 24% starting from L-xylose (**1**), regeneration of **7α** to **6α/β** not included. The introduction of the β-N-glycosidic bond was realised through the well-established procedure reported by Vorbrüggen *et al.*[12] Using the standard protected bases (uracil, 4-N-acetylcytosine and 6-N-benzoyladenine), we obtained **8(a-c)** in good yields (89%, 86%, 84% for **8a**, **8b**, **8c**, respectively). Only in the case of glycosidation with 6-N-benzoyladenine we observed traces of the indesired N7 isomer which we separated by column chromatography. Glycosidation with guanine-type heterocycles produces N7/N9 isomeric mixtures[13] that are frequently difficult to separate. We applied to our L-ribosyl donor **7** the glycosidation conditions using 2-N-acetyl-6-O-diphenylcarbamoylguanine developed by Robins *et al.*,[13] a convenient route to guanine N9 derivatives. Compound **8d** was obtained as a pure N9 isomer in high yield (70%), no traces of N7 product were observed. The four protected L-ribonucleosides **8(a-d)** were deprotected with NH_3/H_2O/MeOH at 60°C or NaOMe (0.1 M in MeOH) at room temperature overnight to furnish compounds **9(a-d)** in high yields (89%-95%).

Experimental

^{1}H NMR spectra were obtained at 300 MHz on a *VARIAN Gemini 300* spectrometer using tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained at 75 MHz using the same internal standard. Mass spectra were obtained on a *MAT 312* mass spectrometer using Fast Atomic Bombardment (FAB) ionisation method (in *p*-nitrobenzyl alcohol, if not stated otherwise) and positive ion detection. [α] values were obtained on a *Perkin-Elmer 141* polarimeter. Melting points were determined by visual observation on a *Kofler* block and are corrected. TLC was performed on a pre-coated silica gel F_{254} plates with fluorescent indicator. Glycosides and nucleosides were visualised on tlc plates by subsequent spraying with naphthoresorcin and conc. H_2SO_4 solutions in ethanol, respectively, followed by heating. Column chromatography was performed with flash silica gel (35-70 μm) from *Uetikon*. Dry pyridine was obtained by distillation over CaH_2. All other solvent were used as purchased. Abbreviations: PE: petrol ether, TBME: *tert*-butylmethyl ether, DMAP: 4-dimethylaminopyridine, BSA: N,O-*bis*-trimethylsilylacetamide, TMSOTf: trimethylsilyltrifluoromethanesulfonate, MFSTA: N-methyl-N-trimethylsilyltrifluoroacetamide, TBDPSCl: *tert*-butyldiphenylsilyl chloride.

5-O-*tert*-Butyldiphenylsilyl-1,2-O-isopropylidene-α-L-xylofuranose (3). To a magnetically stirred solution of 1,2-O-isopropylidene-L-xylofuranose[8] (**2**) (5.0 g, 26.29 mmol) and imidazole (7.16 g, 105.16 mmol) in DMF (40 ml) at 0°C, was added dropwise TBDPSCl (7.20 ml, 28.13 mmol) over 10 min. The mixture was allowed to reach room temperature and stirred for 1 hour. TBME (100 ml) and water (15 ml) were added to the mixture, and the organic layer was separated and washed with water (20 ml×2) and brine (20 ml). After drying over Na_2SO_4 and evaporation, crystallisation from PE gave pure **3** (9.02 g, 21.05 mmol, 97%) as

colorless crystals. R_f (PE/TBME 6/4): 0.60; mp: 92-94°C; $[\alpha]_D^{25}$= +3.7 ±0.5 (c= 1.65, $CHCl_3$). **^{1}H NMR** ($CDCl_3$): 1.06 (s, 9H, *t*Bu); 1.33 (s, 3H, CH_3), 1.47 (s, 3H, CH_3); 4.04 (s, 1H, HOC(3)); 4.14 (m, 2H, $H_2C(5)$); 4.20 (m, 1H, HC(4)); 4.39 (s, 1H, HC(3)); 4.57 (d, 1H, ^{3}J=3.6, HC(2)); 6.03 (d, 1H, ^{3}J=3.8, HC(1)); 7.40-7.79 (m, 10H, Ph). **^{13}C NMR** ($CDCl_3$): 19.12 ($\underline{C}(CH_3)_3$); 26.22, 26.84 (($\underline{C}H_3)_2C$); 26.74 (($\underline{C}H_3)_3C$); 62.83 (C(5)); 76.90 (C(4)); 78.48 (C(3)); 85.50 (C(2)); 105.05 (C(1)); 111.55 ($\underline{C}(CH_3)_2$); 127.96-135.74 (Ph). **MS(FAB):** 4.67 ($[M+K]^+$, 19.0%); 429 ($[M+H]^+$, 1.8%); 173 ($[M\text{-}OSiPh_2tBu]^+$, 20.6%); 135 (100%)

(2*S*,3*R*,5*R*)-5-O-(*tert*-Butyldiphenylsilyl)oxymethyl-2,3-O-isopropylidene-2,3-dioxytetrahydrofuran-4-one (4). CrO_3 (6.91 g, 69.06 mmol) was added to dry pyridine (11.11 ml, 138.13 mmol) in dichloromethane (120 ml) and the resulting mixture was stirred for 15 min at 20°C. A solution of **3** (7.40 g, 17.26 mmol) in CH_2Cl_2 (40 ml) was added, immediately followed by Ac_2O (6.53 ml, 69.06 mmol). After stirring for 30 min, EtOAc (70 ml) and toluene (70 ml) were added. The mixture was decanted and filtered through a short SiO_2 column. The eluate was evaporated and co-evaporated with toluene to give **4** (7.14 g, 16.74 mmol, 97%) as a yellowish oil. R_f (PE/TBME 6/4): 0.82. **^{1}H NMR** ($CDCl_3$): 1.07 (s, 9H, *t*Bu); 1.48 (s, 3H, CH_3); 1.49 (s, 3H, CH_3); 3.87 (dd, 1H, $^2J_{5a,5b}$=11.0, $^3J_{5a,4}$=2.2, HaC(5)); 3.92 (dd, 1H, $^2J_{5b,5a}$=11.0, $^3J_{5b,4}$=1.9, HbC(5)); 4.40 (m, 1H, ^{3}J=2.0, HC(4)); 4.43 (dd, 1H, ^{3}J=4.5, HC(2)); 6.27 (d, 1H, ^{3}J=4.5, HC(1)); 7.40-7.70 (m, 10H, Ph). **^{13}C NMR** ($CDCl_3$): 19.07 ($\underline{C}(CH_3)_3$); 26.67 (($\underline{C}H_3)_3C$)); 27.20, 27.71 (($\underline{C}H_3)_2C$); 64.46 (C(5)); 77.12 (C(4)); 81.50 (C(2)); 103.77 (C(1)); 114.20 ($\underline{C}(CH_3)_2$); 127.69-135.51 (Ph); 210.85 (C(3)). **MS(FAB):** 465 ($[M+K]^+$, 12.8%); 427 ($[M+H]^+$, 1.5%); 187 ($[M\text{-}SiPh_2tBu]^+$, 2.8%); 171 ($[M\text{-}OSiPh_2tBu]^+$, 2.4%); 135 (100%)

5-O-*tert*-Butyldiphenylsilyl-1,2-O-isopropylidene-α-L-ribofuranose (5). Compound **4** (10 g, 23.44 mmol) in anhydrous THF (300 ml) was cooled at -78°C and $LiAlH_4$ (889 mg, 23.44 mmol) was added. The mixture was stirred for 1 hour at -78°C until the disappearence of **4** was observed on tlc. The reaction was quenched with water (1 ml) and then EtOAc (50 ml) was added. The mixture was filtered over *Celite* and the organic layer was dried over Na_2SO_4. Evaporation and crystallisation from PE gave **5** (9.65 g, 22.50 mmol, 96%) as colorless crystals. R_f (PE/TBME 6/4): 0.56; mp: 59-61°C; $[\alpha]_D^{25}$= -31 ±1 (c= 1.6, $CHCl_3$). **^{1}H NMR** ($CDCl_3$): 1.08 (s, 9H, *t*Bu); 1.39 (s, 3H, CH_3); 1.58 (s, 3H, CH_3); 2.41 (d, 1H, ^{3}J=9.9, HOC(3)); 3.82-3.88 (m, 3H, HC(4), $H_2C(5)$); 4.15 (m, 1H, HC(3)); 4.58 (t, 1H, ^{3}J=3.9, HC(2)); 5.84 (d, 1H, ^{3}J=3.8, HC(1)); 7.34-7.72 (2m, 10H, Ph). **^{13}C NMR** ($CDCl_3$): 19.24 ($\underline{C}(CH_3)_3$); 26.57 (($\underline{C}H_3)_2CH$); 26.77 (($\underline{C}H_3)_3C$); 62.36 (C(5)); 71.22 (C(3)); 78.76 (C(2)); 81.24 (C(4)); 104.16 (C(1)); 112.50 ($\underline{C}H(CH_3)_2$); 127.63-135.62 (Ph). **MS(FAB):** 467 ($[M+K]^+$, 20.6%); 173 ($[M\text{-}OSiPh_2tBu]^+$, 11.7%); 135 (100%)

1-O-Methyl-2,3,5-tri-O-benzoyl-L-ribofuranose (6). To a solution of **5** (5.81 g, 13.56 mmol) in anhydrous methanol (250 ml) was added H_2SO_4 (0.13 ml) at 4°C. The mixture was stirred during 2-3 days at 4°C then neutralised with *Amberlite IRA 68* (OH^- form), filtered and evaporated. The crude product was coevaporated three times with anhydrous pyridine, dissolved in pyridine (230 ml) containing DMAP (828 mg, 6.78 mmol). Benzoyl chloride

(6.30 ml, 54.22 mmol) was added dropwise at 0°C. The solution was stirred overnight at room temperature. Ice (150 g) was added and stirred for 1 hour. The mixture was extracted with CH_2Cl_2 (200 ml×3). The organic layers were extracted with water, sat. $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated. Purification by chromatography (PE/TBME 8/2) gave **6** (5.55 g, 11.66 mmol, 86%) as a yellow oil. R_f (PE/EtOAc 8/2): 0.58 (α- and β-anomers). **^{1}H NMR** ($CDCl_3$): 3.42 (s, 2.25H, CH_3, β-anomer); 3.49 (s, 0.75H, CH_3, α-anomer); 4.49-4.67 (m, 0.75H, HC(4), $H_2C(5)$, α-an.); 4.69-4.77 (m, 2.25H, HC(4), $H_2C(5)$, β-an.); 5.16 (s, 0.75H, HC(1), β-an.); 5.33 (dd, 0.25H, ^{3}J=7.1, 4.4, HC(1), α-an.); 5.68 (d, 0.75H, ^{3}J=4.9, HC(2), β-an.); 5.73 (dd, 0.25H, ^{3}J=7.0, 3.4, HC(3), α-an.); 5.88 (dd, 0.75H, ^{3}J=6.6, 4.9, HC(3), β-an.);7.26-8.10 (m, 22H, Ph). **^{13}C NMR** ($CDCl_3$): 55.37 (CH_3, β-anomer); 55.75 (CH_3, α-anomer); 64.07 (C(5), α-an.); 64.78 (C(5), β-an.); 70.80 (C(3), α-an.); 71.81 (C(2), α-an.); 72.45 (C(3), β-an.); 75.47 (C(2), β-an.); 79.02 (C(4), β-an.); 79.44 (C(4), α-an.); 101.94 (C(1), α-an.); 106.44 (C(1), β-an.); 128.32-133.44 (Ph); 165.28, 165.38, 165.24, 166.24 (PhCO). **MS(FAB):** 515 ($[M+K]^+$, 10.9%); 477 ($[M+H]^+$, 2.8%); 445 ($[M-OCH_3]^+$, 24.2%); 105 ($[PhCO]^+$, 100%)

1-O-Acetyl-2,3,5-tri-O-benzoyl-β-L-ribofuranose (7β). Glacial acetic acid (0.94 ml) and AcO_2 (2.11 ml) were added to **6** (1.78 g, 3.73 mmol). The mixture was stirred for 5 min at 0°C, then H_2SO_4 (0.30 ml) was added dropwise during 5 min. The mixture was stirred at 0°C during 10 min until the precipitation occurred. The mixture was kept over night at 4°C. Ice (50 g) was added, and stirred for 30 min, then the mixture was extracted with CH_2Cl_2 (150 ml×3). The organic layers were washed with a cold sat. $NaHCO_3$ solution (200 ml×5). After drying over Na_2SO_4 and evaporation, crystallisation of the β-anomer from isopropyl alcohol afforded **7β** (712 mg, 1.411 mmol, 39%) as white crystals, (crude yield: 77% (1:1 α:β)). R_f (PE/EtOAc 8/2): α: 0.30, β: 0.43; mp: 129-131°C; $[\alpha]_D^{25} = -43 \pm 1$ (c= 1.30, $CHCl_3$). **^{1}H NMR** ($CDCl_3$): 1.99 (s, 3H, CH_3); 4.50-4.52 (m, 1H, HaC(5)); 4.75-4.80 (m, 2H, HbC(5), HC(4)); 5.79 (d, 1H, ^{3}J=4.7, HC(2)); 5.92 (dd, 1H, ^{3}J=7.9, 4.6, HC(3)); 6.44 (s, 1H, HC(1)); 7.30-8.10 (m, 15H, Ph). **^{13}C NMR** ($CDCl_3$): 20.85 (CH_3); 63.68 (C(5)); 71.35 (C(3)); 74.98 (C(2)); 79.95 (C(4)); 98.38 (C(1)); 128.38-133.64 (Ph); 165.00, 165.34, 165.95 (PhCO); 169.64 (CH_3CO). **MS(FAB):** 543 ($[M+K]^+$, 13.5%); 445 ($[M-OCOCH_3]^+$, 21.4%); 105 ($[PhCO]^+$, 100%)

2',3',5'-tri-O-Benzoyl-β-L-uridine (8a). Compound **7β** (250 mg, 0.50 mmol) and uracil (167 mg, 1.49 mmol) were co-evaporated three times with anhydrous CH_3CN under argon. CH_3CN abs. (6 ml) and BSA (0.37 ml, 1.49 mmol) were added at room temperature. The mixture was stirred at 60-65°C until the base dissolved. TMSOTf (87 µl, 0.74 mmol) was added, the mixture stirred over night at 65°C. CH_2Cl_2 (50 ml) was added and the mixture was washed with sat. $NaHCO_3$ solution (10 ml). After drying over Na_2SO_4 and evaporation, purification by chromatography (PE/EtOAc 7/3 and 5/5) afforded **8a** (246 mg, 0.44 mmol, 89%) as a white foam. R_f (PE/EtOAc 2/8): 0.37. **^{1}H NMR** ($CDCl_3$): 4.65-4.87 (m, 3H, HC(4'), $H_2C(5')$); 5.61 (d, 1H, ^{3}J=8.0, HC(5)); 5.77 (t, 1H, ^{3}J=5.7, HC(2')); 5.90 (t, 1H, ^{3}J=3.6, HC(3')); 6.32 (d, 1H, ^{3}J=5.7, HC(1')); 7.33-8.08 (m, 15H, Ph); 8.11(d, 1H, ^{3}J=8.4, HC(6)); 9.11 (s, 1H, NH). **^{13}C NMR** ($CDCl_3$): 63.70 (C(5')); 71.10 (C(3')); 73.73 (C(2')); 80.46 (C(4')); 88.12 (C(1'));

103.37 (C(5)); 128.31-133.76 (Ph); 139.63 (C(6)); 150.12 (C(2)); 162.91 (C(4)); 165.25, 165.28, 166.01 (PhCO). **MS(FAB):** 595 ([M+K]$^+$, 5.7%); 557 ([M+H]$^+$, 2.6%); 445 ([M-base]$^+$, 13.4%); 105 ([PhCO]$^+$, 100%)

4-N-Acetyl-2',3',5'-tri-O-benzoyl-β-L-cytidine (8b). Compound **7β** (250 mg, 0.50 mmol) and 4-N-acetylcytosine (228 mg, 1.49 mmol) were treated as described above. Purification by chromatography (PE/EtOAc 5/5 and 2/8) furnished **8b** (255 mg, 0.43 mmol, 86%) as a white foam. R_f (PE/EtOAc 2/8): 0.46. **^{1}H NMR** ($CDCl_3$): 2.20 (s, 3H, CH_3); 4.69-4.86 (m, 3H, HC(4'), $H_2C(5')$); 5.84 (dd, 1H, ^3J=5.9, 4.4, HC(2')); 5.90 (t, 1H, ^3J=5.4, HC(3')); 6.40 (d, 1H, ^3J=4.2, HC(1')); 7.32-7.95 (m, 16H, Ph, HC(5)); 8.10 (d, 1H, ^3J=7.8, HC(6)); 9.98 (br s, 1H, NH). **^{13}C NMR** ($CDCl_3$): 24.82 (CH_3); 63.53 (C(5')); 70.90 (C(3')); 74.75 (C(2')); 80.59 (C(4')); 90.07 (C(1')); 97.33 (C(5)); 128.47-133.64 (Ph); 144.56 (C(6)); 154.60 (C(2)); 163.23 (C(4)); 165.15, 165.22, 166.09 (PhCO); 170.89 (CH_3CO). **MS(FAB):** 636 ([M+K]$^+$, 6.4%); 598 ([M+H]$^+$, 2.9%); 445 ([M-base]$^+$, 10.8%); 105 ([PhCO]$^+$, 100%)

6-N-Benzoyl-2',3',5'-tri-O-benzoyl-β-L-adenosine (8c). Compound **7β** (200 mg, 0.40 mmol) and 6-N-benzoyladenine (284 mg, 1.19 mmol) were co-evaporated three times with anhydrous 1,2-dichloroethane under argon. Anhydrous 1,2-dichloroethane (5 ml) and MFSTA (0.44 ml, 2.38 mmol) were added at room temperature. The mixture was stirred at 80°C until the base dissolved. TMSOTf (0.11 ml, 0.59 mmol) was added, the mixture stirred over night at 80°C. CH_2Cl_2 (40 ml) was added, the mixture was washed with sat. $NaHCO_3$ solution (10 ml). After drying over Na_2SO_4 and evaporation, purification by chromatography (PE/EtOAc 5/5 to 2/8) afforded **8c** (228 mg, 0.33 mmol, 84%) as a white foam. R_f (PE/EtOAc 2/8): 0.57. **^{1}H NMR** ($CDCl_3$): 4.72 (dd, 1H, $^2J_{5'a,5'b}$=12.0, $^3J_{5'a,4'}$=3.1, HaC(5')); 4.82-4.86 (m, 1H, HC(4')); 4.88 (dd, 1H, $^2J_{5'b,5'a}$=11.9, $^3J_{5'b,4'}$=4.1, HbC(5')); 6.30 (t, 1H, ^3J=5.2, HC(2')); 6.46 (d, 1H, ^3J=5.4, HC(3')); 6.53 (d, 1H, ^3J=5.0, HC(1')); 7.32-8.10 (m, 20H, Ph); 8.26 (s, 1H, HC(2)); 8.65 (s, 1H, HC(8)); 9.64 (br s, 1H, NH). **^{13}C NMR** ($CDCl_3$): 63.38 (C(5')); 71.34 (C(3')); 73.77 (C(2')); 80.66 (C(4')); 86.96 (C(1')); 123.54 (C(5)); 127.85-133.60 (Ph); 141.71 (C(8)); 149.80 (C(4)); 151.60 (C(2)); 152.58 (C(6)); 164.95, 165.12, 165.93 (PhCO, PhCONH). **MS(FAB):** 722 ([M+K]$^+$, 8.4%); 684 ([M+H]$^+$, 7.0%); 445 ([M-base]$^+$, 13.6%); 105 ([PhCO]$^+$, 100%)

2-N-Acetyl-6-O-diphenylcarbamoyl-2',3',5'-tri-O-benzoyl-β-L-guanosine (8d). 2-N-Acetyl-6-O-diphenylcarbamoylguanine[13] (168 mg, 0.45 mmol) was co-evaporated three times with anhydrous 1,2-dichloroethane under argon. Absolute 1,2-dichloroethane (3 ml) and BSA (0.15 ml, 0.60 mmol) were added at room temperature. The mixture was stirred at 80°C until the base dissolved, evaporated in vacuo, then dissolved in anhydrous toluene (1 ml). Compound **7β** (150 mg, 0.30 mmol) was coevaporated three times with anhydrous toluene, then dissolved in toluene (4 ml), then added to the base soln. under argon. TMSOTf (81 µl, 0.45 mmol) was added, the mixture stirred for one hour at 80°C. CH_2Cl_2 (50 ml) was added, the mixture was washed with sat. $NaHCO_3$ solution (20 ml). After drying over Na_2SO_4 and evaporation, purification by chromatography (PE/EtOAc 8/2 and 5/5) furnished **8d** (174 mg, 0.21 mmol, 70%) as a white foam. R_f (PE/EtOAc 2/8): 0.82. **^{1}H NMR** ($CDCl_3$): 2.42 (s, 3H,

CH_3); 4.72-4.95 (m, 3H, HC(4'), $H_2C(5)$); 6.28-6.38 (m, 3H, HC(3'), HC(2'), HC(1')); 7.20-8.00 (m, 25H, Ph); 8.06 (s, 1H, HC(8)); 8.42 (br s, 1H, NH). **^{13}C NMR** ($CDCl_3$): 24.99 (CH_3); 63.63 (C(5')); 71.46 (C(3')); 74.22 (C(2')); 80.55 (C(4')); 87.53 (C(1')); 121.26 (C(5)); 126.64-142.45 (Ph); 141.67 (C(8)); 150.13 ($\underline{C}ONPh_2$); 152.27 (C(4)); 154.25 (C(2)); 156.32 (C(6)); 165.04, 165.15, 166.11 (Ph$\underline{C}$O); 169.83 ($CH_3\underline{C}O$). **MS(FAB):** 871 ([M+K]$^+$, 3.7%); 833 ([M+H]$^+$, 3.0%); 445 ([M-base]$^+$, 18.3%); 105 ([PhCO]$^+$, 100%)

L-Uridine (9a). Compound **8a** (1.36 g, 2.44 mmol) was dissolved in methanol (10 ml) then NH_3 (35% in water, 20 ml) was added. The mixture was stirred over night at 60°C in a sealed vessel. After evaporation to dryness, water (50 ml) was added and extracted with EtOAc (50 ml×3). The water layer was evaporated to give **9a** (566 mg, 2.32 mmol, 95%) which was recrystallised from H_2O/EtOH as white crystals. R_f (MeOH/EtOAc 1/9): 0.23; mp: 159-163°C; $[\alpha]_{546}^{25}$= -16±1 (c= 0.55, H_2O). **^{1}H NMR** (CD_3OD): 3.73 (dd, 1H, $^2J_{5'a,5'b}$=12.1, $^3J_{5'a,4'}$=3.1, HaC(5')); 3.83 (dd, 1H, $^2J_{5'b,5'a}$=12.2, $^3J_{5'b,4'}$=2.6, HbC(5')); 3.99-4.02 (m, 1H, HC(4')); 4.13-4.19 (m, 2H, HC(2'), HC(3')); 5.69 (d, 1H, ^{3}J=8.0, HC(5)); 5.90 (d, 1H, ^{3}J=4.3, HC(1')); 8.01(d, 1H, ^{3}J=8.0, HC(6)). **^{13}C NMR** (CD_3OD): 62.28 (C(5')); 71.31 (C(3')); 75.74 (C(2')); 86.36 (C(4')); 90.73 (C(1')); 102.65 (C(5)); 142.74 (C(6)); 152.46 (C(2)); 166.20 (C(4)). **MS(FAB):** 283 ([M+K]$^+$, 35.3%); 245 ([M+H]$^+$, 74.6%); 133 ([M-base]$^+$, 18.9%); 113 ([base+H_2]$^+$, 100%)

L-Cytidine (9b). Compound **8b** (1.27 g, 2.13 mmol) was dissolved in 0.1M NaOMe/MeOH (50 ml). The mixture was stirred over night at room temperature. A minimal amount of *Dowex* (H^+ form) was added to neutralise the mixture. After filtration and evaporation to dryness, water (50 ml) was added and extracted with EtOAc (50 ml×3). The water layer was evaporated to give **9b** (462 mg, 1.90 mmol, 89%) which was recrystallised from H_2O/EtOH as white crystals. R_f (MeOH/EtOAc/H_2O 1/4/0.7): 0.34; mp: 200-205°C; $[\alpha]_{546}^{25}$= -33 ±1 (c= 0.82, H_2O).**^{1}H NMR** (DMSO-d_6): 3.52-3.70 (m, 2H, $H_2C(5')$); 3.83-3.85 (m, 1H, HC(4')); 3.92-3.96 (m, 2H, HC(2'), HC(3')); 5.04-5.10 (m, 2H, HOC(3'), HOC(5')); 5.35 (d, 1H, ^{3}J=4.5, HOC(2')); 5.74 (d, 1H, ^{3}J=7.5, HC(5)); 5.79 (d, 1H, ^{3}J=3.6, HC(1')); 7.24 (br s, 2H, NH_2); 7.87 (d, 1H, ^{3}J=7.5, HC(6)). **^{13}C NMR** (DMSO-d_6): 60.70 (C(5')); 69.51 (C(3')); 74.07 (C(2')); 84.14 (C(4')); 89.23 (C(1')); 94.03 (C(5)); 141.57 (C(6)); 155.54 (C(2)); 165.63 (C(4)). **MS(FAB):** 282 ([M+K]$^+$, 26.2%); 244 ([M+H]$^+$, 48.8%); 112 ([base+H_2]$^+$, 100%)

L-Adenosine (9c). Compound **8c** (1.23 g, 1.80 mmol) was dissolved in methanol/THF (5/2, v:v, 14 ml) then NH_3 (35% in water, 20 ml) was added. The mixture was stirred over night at 60°C in a sealed vessel. After evaporation to dryness, water (50 ml) was added and extracted with EtOAc (50 ml×3). The water layer was evaporated to give **9c** (443 mg, 1.66 mmol, 92%) wich was recrystallised from H_2O/EtOH as a white powder. R_f (MeOH/EtOAc/H_2O 1/4/0.7): 0.59; mp: 235-238°C; $[\alpha]_{546}^{25}$= +87 ±1 (c= 0.45, 1.25M NaOH). **^{1}H NMR** (DMSO-d_6): 3.53-3.72 (m, 2H, $H_2C(5')$); 3.96-3.98 (m, 1H, HC(4')); 4.14-4.18 (m, 1H, HC(3')); 4.62 (dd, 1H, ^{3}J=11.4, 6.0, HC(2')); 5.22 (d, 1H, ^{3}J=4.4, HOC(3')); 5.45-5.49 (m, 2H, HOC(2'), HOC(5')); 5.89 (d, 1H, ^{3}J=6.0, HC(1')); 7.39 (br s, 2H, NH_2); 8.15 (s, 1H, HC(2)); 8.37 (s, 1H, HC(8)). **^{13}C NMR** (DMSO-d_6): 61.72 (C(5')); 70.71 (C(3')); 73.47 (C(2')); 85.94 (C(4')); 87.94

(C(1')); 119.40 (C(5)); 136.98 (C(8)); 149.08 (C(4)); 152.42 (C(2)); 156.20 (C(6)). **MS(FAB):** 306 ($[M+K]^+$,1.5%); 268 ($[M+H]^+$,1.0%); 267 ($[M]^+$, 2.3%); 136 (100%)

L-Guanosine (9d). Compound **8d** (2.43 g, 2.97 mmol) was dissolved in methanol/THF (5/2, v:v, 14 ml) then NH_3 (35% in water, 20 ml) was added. The mixture was stirred over night at 60°C in a sealed vessel. After evaporation to dryness, water (250 ml) was added and extracted with CH_2Cl_2 (100 ml×3). The water layer was evaporated to give **9d** (757 mg, 2.67 mmol, 90%) which was recrystallised from H_2O/EtOH as a pale yellow powder. R_f (MeOH/ EtOAc/H_2O 1/4/0.7): 0.28; mp: 239-243°C ; $[\alpha]_{546}^{25}$= +80 ±1 (c= 0.85 , 1.25M NaOH). **^{1}H NMR** (DMSO-d_6): 3.54-3.65 (m, 2H, $H_2C(5')$); 3.89 (d'd', 1H, ^{3}J=7.5, 3.8, HC(4')); 4.09 (dd, 1H, ^{3}J=4.8, 3.8, HC(3')); 4.41 (t, 1H, ^{3}J=5.5, HC(2')); 5.13 (t, 1H, ^{3}J=5.5, HOC(5')); 5.19 (d, 1H, ^{3}J=4.7, HOC(3')); 5.45 (d, 1H, ^{3}J=6.1, HOC(2')); 5.71 (d, 1H, ^{3}J=6.0, HC(1')); 6.52 (br s, 2H, NH_2); 7.95 (s, 1H, HC(8)); 10.69 (br s, 1H, NH). **^{13}C NMR** (DMSO-d_6): 61.40 (C(5')); 70.38 (C(3')); 73.71 (C(2')); 85.20 (C(4')); 86.33 (C(1')); 116.09 (C(5)); 135.58 (C(8)); 151.33 (C(4)); 153.70 (C(2)); 156.77 (C(6)). **MS(FAB):** 322 ($[M+K]^+$, 4.3%); 284 ($[M+H]^+$, 11.6%); 283 ($[M]^+$, 5.5%); 122 (100%)

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References and Footnotes

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