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Synthesis and antiviral evaluation of 2′-deoxy-2′-*C*-trifluoromethyl β-D-ribonucleoside analogues bearing the five naturally occurring nucleic acid bases †

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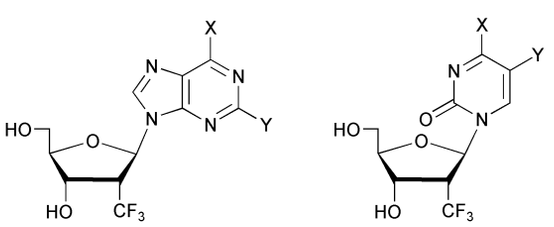
2′-Deoxy-2′-*C*-trifluoromethyl-β-D-ribonucleoside derivatives bearing the five naturally occurring acid bases have been synthesized. All these derivatives were prepared by glycosylation reactions of purine and pyrimidine bases with a suitable peracylated 2-deoxy-2-*C*-trifluoromethyl sugar precursor to afford anomeric mixtures of protected nucleosides. After separation and deprotection, the resulting β-nucleoside analogues were tested for their activity against HIV, HBV and several RNA viruses. However, none of these compounds showed significant antiviral activity nor cytotoxicity.

Introduction

Nucleoside analogues represent one of the main class of therapeutic agents in antiviral chemotherapy, and to date, numerous nucleoside derivatives have been approved for the treatment of various viral diseases including Herpes viruses, Human Immunodeficiency Virus (HIV) and Hepatitis B virus (HBV) infections.[1] The mechanism of action of those compounds is based upon the intracellular phosphorylation to their 5′-triphosphate form which can interact with virus-specific polymerases, acting as inhibitors or chain terminators of viral nucleic acid synthesis. In order to discover new nucleoside derivatives endowed with potential antiviral activity, modifications of the base and/or the sugar moiety of natural nucleosides can be attempted. As a part of our ongoing research program on trifluoromethyl nucleoside analogues,[2] we have synthesized 2′-deoxy-2′-*C*-trifluoromethyl-β-D-ribonucleoside derivatives bearing the five naturally occurring nucleic acid bases (**11**, **12** and **17**–**19**) (Chart 1), all of them being hitherto unknown except for **18** which has been succinctly reported.[3,4]



11 (X = NH_2, Y = H)
12 (X = OH, Y = NH_2)
17 (X = OH, Y = H)
18 (X = OH, Y = CH_3)
19 (X = NH_2, Y = H)

Chart 1 2′-Deoxy-2′-*C*-trifluoromethyl-β-D-ribonucleoside analogues.

Results and discussion

The synthesis of the title nucleoside analogues involved the preparation of an appropriate trifluoromethyl sugar precursor, namely, 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-D-ribofuranose (**6**) (Scheme 1). Several methodologies have been described in the literature for introducing trifluoromethyl groups into organic compounds.[5] However, the utilization of (trifluoromethyl)trimethylsilane (Me_3SiCF_3) (Ruppert's reagent) as a nucleophilic trifluoromethylating reagent is rapidly becoming the method of choice.[6,7] Such methodology requires the previous preparation of a suitable 2-keto sugar intermediate, then reaction with Me_3SiCF_3. A similar strategy has been already reported in the literature.[8] For our purpose, we chose as starting material methyl 3,5-di-*O*-(4-chlorobenzyl)-α-ribofuranoside (**1**) which was obtained from commercially available D-ribose following a procedure already described.[9] Oxidation of the secondary alcohol of **1** was achieved using the Dess–Martin periodinane reagent[10] in anhydrous dichloromethane. The protected 2-keto sugar derivative was not isolated but converted *via* two steps into methyl 3,5-di-*O*-(4-chlorobenzyl)-2-*C*-trifluoromethyl-α-D-ribofuranoside (**2**), in 67% overall yield from **1**, following reaction with Me_3SiCF_3 in the presence of tetrabutylammonium fluoride (TBAF) as a catalyst in tetrahydrofuran (THF) then desilylation of the trimethylsilylated ether intermediate with TBAF in methanol. ^1H, ^{19}F and ^{13}C NMR spectra showed that the trifluoromethyl group added stereoselectively to the less hindered β-face giving only the ribo epimer. Our results are in accordance with those previously described in the literature.[4,8] The derivatisation of tertiary alcohols as their methyl oxalyl esters has been shown to be a convenient method for deoxygenation reactions.[11] In contrast to the deoxygenation of alcohols using Barton–McCombie type methodology,[12] the use of methyl oxalyl esters provided good alternative for removal of hindered secondary alcohols or tertiary alcohols. However, all attempts to prepare a methyl oxalyl ester [by varying the number of equivalents of methyl oxalyl chloride, the concentration, the temperature] from **2** failed. To overcome this problem, 4-chlorobenzyl protecting groups were removed using catalytic hydrogenation.

† This work has been presented in preliminary form at the Fifteenth International Round Table on Nucleosides, Nucleotides and Nucleic Acids, Sept. 10–14, 2002, Leuven, Belgium.

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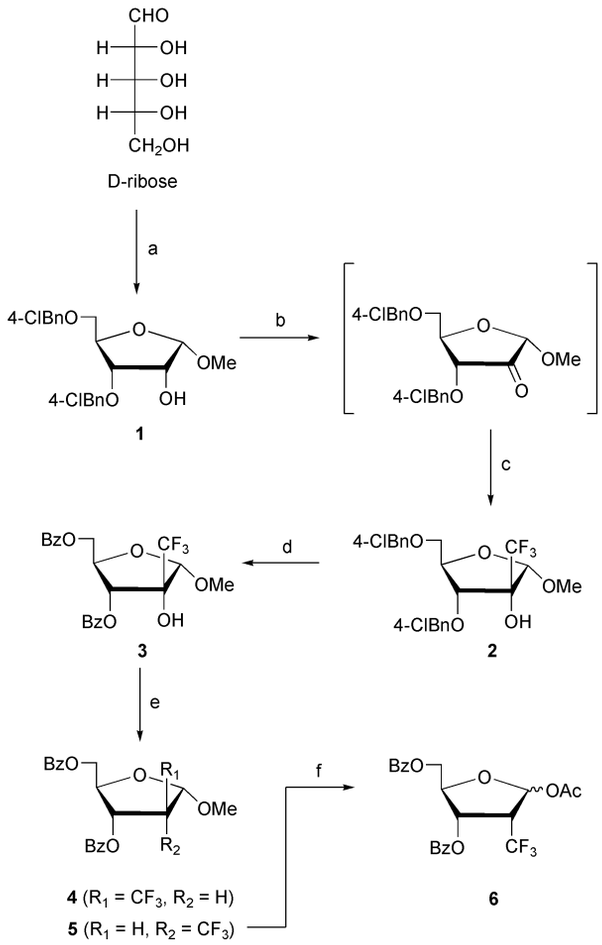
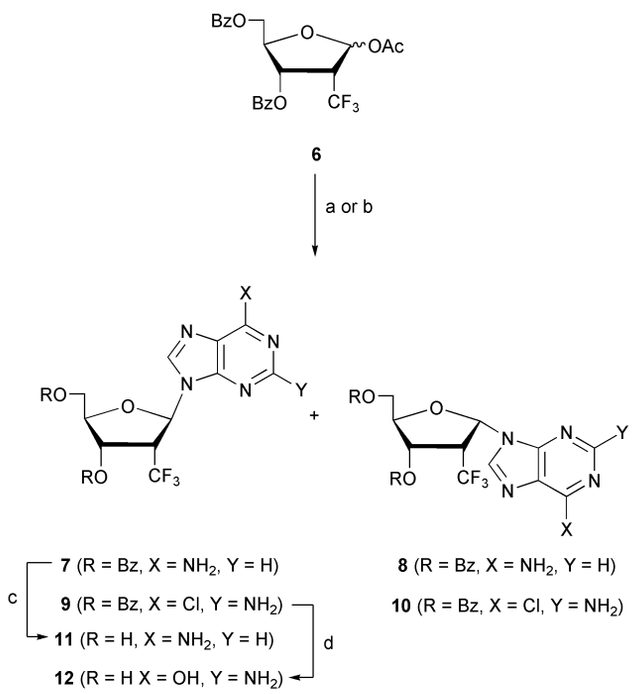


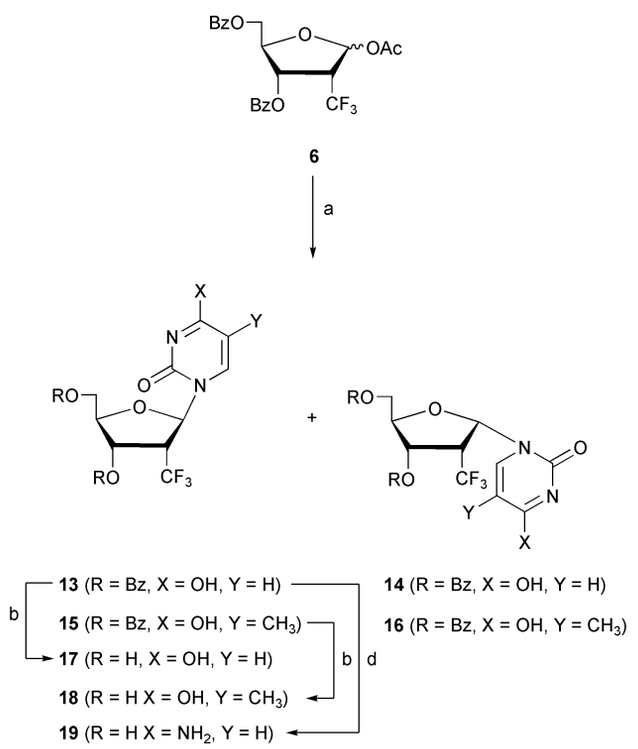
Scheme 1 *Reagents and conditions*: (a) ref. 9 (b) Dess–Martin periodinane, CH_2Cl_2; (c) i) CF_3SiMe_3, TBAFc, THF; ii) TBAF, THF, MeOH; (d) i) H_2, Pd/C (5%), AcONa, MeOH; ii) BzCl, pyridine; (e) i) $MeCO_2COCl$, pyridine, CH_2Cl_2; ii) $(Me_3Si)_3SiH$, AIBN, toluene; (f) AcOH, Ac_2O, H_2SO_4.

The resulting methyl 2-*C*-trifluoromethyl-α-D-ribofuranoside was not isolated but treated, after work-up, with an excess of benzoyl chloride in anhydrous pyridine to afford exclusively methyl 3,5-di-*O*-benzoyl-2-*C*-trifluoromethyl-α-ribofuranoside (**3**) in 80% yield after silica gel column chromatography. The latter was treated with methyl oxalyl chloride and pyridine in anhydrous dichloromethane to give the corresponding 2-*O*-methyl oxalyl ester derivative, which was subsequently deoxygenated with tris(trimethylsilyl)silane hydride in the presence of α,α′-azoisobutyronitrile (AIBN) to afford after purification on silica gel column chromatography a mixture of methyl 3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-α-D-arabinofuranoside (**4**) and methyl 3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoro-methyl-α-D-ribofuranoside (**5**) [ratio **4** : **5** = 13 : 87 as determined by ^{1}H NMR]. Therefore, we were able to separate after tedious silica gel column chromatography, compound **5** from the epimeric mixture. Pure methyl 3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoro-methyl-α-D-ribofuranoside (**5**) was obtained in 41% yield as isolated product from **3** and fully characterized. Structural assignments of compounds **4** and **5** were based upon their ^{1}H NMR spectra. In particular, the 1-H proton of **4** appeared as a doublet with a coupling constant ($J_{1,2}$ = 1.6 Hz) as expected for a methyl 2-deoxy-2-*C*-trifluoromethyl-α-D-arabinofuranoside structure while the 1-H proton of the ribo epimer **5** exhibited a doublet with a larger coupling constant ($J_{1,2}$ = 4.6 Hz). The formation of the 2-deoxy-2-*C*-trifluoromethyl-ribo epimer (**5**) as the major compound was probably favoured due to the steric hindrance of the α-face of the sugar ring in precursor **3**. Finally, compound **5** was converted into 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-D-ribofuranose (**6**) which was obtained in 88% yield after silica gel column chromatography. Later, peracylated 2-deoxy-2-*C*-trifluoromethyl sugar **6** was used for the condensation reactions with the heterocyclic bases and provided in each case an anomeric mixture of protected nucleosides (Schemes 2 and 3) due to the lack of 2-*O*-acyl type participating group. After the condensation reactions, the mixtures of protected nucleosides were separated by silica gel column chromatography to afford the corresponding β-anomers.

The syntheses of the 2′-deoxy-2′-*C*-trifluoromethyl-β-D-ribonucleoside purine derivatives **11** and **12** are depicted in



Scheme 2 *Reagents and conditions*: (a) adenine, $SnCl_4$, CH_3CN, rt; (b) silylated 2-amino-6-chloropurine, TMSOTf, toluene, reflux; (c) MeONa, MeOH, rt; (d) $HS(CH_2)_2OH$, MeONa, MeOH, reflux.



Scheme 3 *Reagents and conditions*: (a) silylated uracil or thymine, TMSOTf, CH_3CN, 50 °C; (b) MeONa, MeOH, rt; (d) i) 1-methylpyrrolidine, CH_3CN, $(CF_3CO)_2O$, 0 °C; ii) 4-nitrophenol, 0 °C; iii) conc. aq. NH_3, dioxane, 55 °C; iv) NH_3–MeOH, rt

Scheme 2. A glycosylation reaction with adenine and **6** using stannic [tin(IV)] chloride ($SnCl_4$) as a catalyst[13] in anhydrous acetonitrile afforded protected nucleosides **7** and **8** as an anomeric mixture (ratio β : α = 77 : 23 determined by ^{1}H NMR). Separation by silica gel column chromatography gave pure compound **7** in 41% which upon treatment with sodium methanolate in methanol provided the desired nucleoside **11** in 74% yield after purification. In order to prepare the guanosine analogue (**12**), a condensation reaction of 2-amino-6-chloropurine with **6** was carried out under Vorbrüggen conditions[14] using trimethylsilyl trifluoromethane sulfonate (TMSOTf) as a catalyst in refluxing toluene to afford nucleosides **9** and **10**. After separation, compound **9** was fully characterized. In particular, the UV spectrum showed a λ_{max} value in accordance to previously reported data for N^9-2-amino-6-chloropurine nucleoside derivatives.[15,16] Finally, **9** was treated with 2-mercaptoethanol and sodium methanolate in refluxing methanol to provide the target nucleoside **12** in 83%.

The syntheses of the 2′-deoxy-2′-*C*-trifluoromethyl β-D-ribonucleoside pyrimidine derivatives **17**, **18** and **19** are depicted in Scheme 3. Briefly, glycosylation reactions with uracil or thymine and sugar **6**, under Vorbrüggen conditions, using TMSOTf as a catalyst in anhydrous acetonitrile at 50 °C afforded an anomeric mixture of compounds **13** and **14**, and of compounds **15** and **16**. After separation, compounds **13** and **15** were obtained in 31% and 32.6%, respectively. The 2′-deoxy-2′-*C*-trifluoromethyl β-D-ribonucleoside analogues of uracil (**17**) and thymine (**18**) were obtained from **13** and **15** following treatment with sodium methanolate in methanol in 85% and 90% yield after purification *via* silica gel column chromatography, respectively. On the other hand, compound **13** was converted into the corresponding cytosine derivative **19** by using a nitrophenylation–amonolysis[17] procedure in 53% overall yield.

The yields obtained during the glycosylation reactions with **6** and the heterocyclic bases were moderate, but provided in almost all cases the corresponding β-anomer as the major compound. Indeed, it has been reported that reactions at C-1 of carbohydrates *via* cationic intermediates are difficult to achieve with a trifluromethyl group in position 2 owing to the high electron withdrawing effect of such a group.[18] The preferential formation of the β-anomers could be attributed to a steric hindrance of the α-face on the sugar due to the presence of the trifluoromethyl group whose the size is closer to that of an isopropyl group.[19] The stereochemical assignments of the nucleosides at the protected or final stage were made using ^{1}H NMR spectra. The anomers with higher field resonance for H-4′ protons were assigned as the β-anomers while the ones with lower chemical shifts were attributed to the α-anomers on account of the deshielding effect of the heterocyclic base.

Biological evaluation

The target nucleosides **11**, **12** and **17**–**19** were tested for their effects on the replication of HIV, HBV and several RNA viruses (including yellow fever virus and bovine viral diarrhoea virus) in cell culture experiments. However, none of these compounds demonstrated significant antiviral activity nor cytoxicity at the highest concentration tested (usually 100 μM).

Conclusion

The syntheses of 2′-deoxy-2′-*C*-trifluoromethyl-β-D-ribonucleosides bearing the five naturally occurring acid bases were undertaken with the hope of discovering new nucleoside derivatives endowed with antiviral effects. However, none of the target compounds exhibited significant antiviral activity. Several factors could be responsible for the inactivity of these nucleoside derivatives. Their inability to enter cells or to serve as substrates for intracellular enzymes catalysing phosphorylation, as well as a lack of inhibition of viral polymerases by their triphosphate forms, would all account for their antiviral inactivity. Further research would be needed to support these hypotheses, but since no significant antiviral activity emerged from the present data, it does not seem worthwhile to pursue additional studies on 2′-deoxy-2′-*C*-trifluoromethyl-β-D-ribonucleoside analogues.

Experimental

Evaporation of solvents was carried out on a rotary evaporator under reduced pressure. Melting points were determined in open capillary tubes on a Gallenkamp MFB-595–010 M apparatus and are uncorrected. UV spectra were recorded on an Uvikon 931 (Kontron) spectrophotometer. ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra at 100 MHz and ^{19}F NMR at 235 MHz in $(CD_3)_2SO$ at ambient temperature with a Brüker DRX 400. Chemical shifts (δ) are quoted in parts per million (ppm) referenced to the residual solvent peak, $(CD_3)CD_2HSO$ being set at δ_H 2.49 and δ_C 39.5 relative to tetramethylsilane (TMS). ^{19}F chemical shifts are reported using trichlorofluoromethane as external reference. Deuterium exchange and COSY experiments were performed in order to confirm proton assignments. Coupling constants, *J*, are reported in Hertz. 2D ^{1}H–^{13}C heteronuclear COSY were recorded for the attribution of ^{13}C signals. FAB mass spectra were recorded in the positive-ion or negative-ion mode on a JEOL SX 102. The matrix was a mixture (50 : 50, v/v) of glycerol and thioglycerol (G–T) or 3-nitrobenzyl alcohol (NBA). Specific rotations were measured on a Perkin-Elmer Model 241 spectropolarimeter (path length 1 cm), and are given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were carried out by the Service de Microanalyses du CNRS, Division de Vernaison (France). Thin layer chromatography was performed on precoated aluminium sheets of Silica Gel 60 F_{254} (Merck, Art. 5554), visualization of products being accomplished by UV absorbency followed by charring with 5% ethanolic sulfuric acid and heating. Column chromatography was carried out on Silica Gel 60 (Merck, Art. 9385). All moisture-sensitive reactions were carried out under rigorous anhydrous conditions under an argon atmosphere using oven-dried glassware. Solvents were dried and distilled prior to use and solids were dried over P_2O_5 under reduced pressure.

Methyl 3,5-di-*O*-(4-chlorobenzyl)-α-D-ribofuranoside 1

Compound (**1**) was obtained as a colourless oil from commercially available D-ribose following a procedure initially developed by Martin *et al*.[9] The physico-chemicals properties were similar to those previously described δ_H(200 MHz; $CDCl_3$; Me_4Si) 3.4 (2 H, m, 5-H and 5′-H), 3.5 (3 H, s, OCH_3), 3.75 (1 H, dd, *J* 7 and *J* 3.2, 3-H), 4.15 (2 H, m, 2-H and 4-H), 4.57 (4 H, m, 2 × CH_2Ar), 4.92 (1 H, d, *J* 4.6, 1-H), 7.1–7.3 (8 H, m, 2 × C_6H_4Cl); *m*/*z* (FAB > 0; NBA) 435 $(M + Na)^+$; *m*/*z* (FAB < 0; NBA) 411 $(M - H)^-$.

Methyl 3,5-di-*O*-(4-chlorobenzyl)-2-*C*-trifluoromethyl-α-D-ribofuranoside 2

Dess–Martin periodinane (58.7 g, 138 mmol) was added to solution of compound **1** (38 g, 92.2 mmol) in anhydrous dichloromethane (424 cm^3) at 0°C. The mixture was stirred for 48 hours at room temperature, then diethyl ether (820 cm^3) was added. The resulting precipitate was filtered. A solution of saturated aqueous sodium hydrogen carbonate (containing 94.9 g of sodium thiosulfate pentahydrate) (870 cm^3) was added to the filtrate and the mixture was stirred for 10 minutes until the two phases became clear. The organic phase was separated, washed with brine (1000 cm^3), dried over sodium sulfate and evaporated under reduced pressure. The resulting ketone was not purified but directly coevaporated several times with anhydrous toluene. To a solution of the resultant ketone in

anhydrous tetrahydrofuran (23 cm^3) were added trifluoromethyl trimethylsilane (69.5 ml, 139 mmol) and tetrabutyl ammonium fluoride trihydrate (0.185 g). After 1 hour, the mixture was washed with a solution of saturated ammonium chloride (500 cm^3) and extracted with diethyl ether (3 × 500 cm^3). The combined extracts were dried over sodium sulfate and evaporated under reduced pressure. The crude material was dissolved in methanol (93 cm^3) and a 1 mol dm^{-3} solution of tetrabutyl ammonium fluoride (93 cm^3, 93 mmol) in tetrahydrofuran was added. After 2 hours at room temperature, the mixture was evaporated. The residue was subjected to silica gel column chromatography using ethyl acetate–petroleum ether (1 : 9) as eluent to give methyl 3,5-di-*O*-(4-chlorobenzyl)-2-*C*-trifluoromethyl-α-D-ribofuranoside **2** (30 g, 67%) as a colourless oil (Found: C, 52.79; H, 4.46; Cl, 15.07; F, 11.74. $C_{21}H_{21}Cl_2F_3O_5$ requires C, 52.41; H, 4.40; Cl, 14.73; F, 11.84%); $[a]_D^{20}$ +293 (*c* 1.00 in DMSO); δ_H(400 MHz; $CDCl_3$; Me_4Si) 3.43 (3 H, s, OC*H*$_3$), 3.44 (1 H, dd, *J* 10.9 and *J* 5, 5′-H), 3.52 (1 H, dd, *J* 10.9 and 3.4, 5-H), 3.63 (1 H, s, 2-OH), 3.78 (1 H, d, *J* 7.1, 3-H), 3.99 (1 H, m, 4-H), 4.31 (1 H, d, *J* 11.7, C*H*–Ar), 4.36 (1 H, d, *J* 12.2, C*H*–Ar), 4.42 (1 H, d, *J* 12.2, C*H*–Ar), 4.67 (1 H, d, *J* 11.7, C*H*–Ar), 4.92 (1 H, s, 1-H), 7.18 (8 H, m, 2 × C$_6$*H*$_4$Cl); δ_C(100 MHz; $CDCl_3$; Me_4Si) 54.6 (CH_3), 67.4 (5-C), 71.3 (CH_2), 71.6 (CH_2), 74.9 (3-C), 78.2 (q, $^2J_{C-F}$ 28.6, 2-C), 79.0 (4-C), 100.3 (1-C), 123.5 (q, $^1J_{C-F}$ 282.6, CF_3), 127.5–135,2 (2 × C_6H_4); δ_F(235 MHz; $CDCl_3$; CCl_3F) −79.9 (s, CF_3); *m*/*z* (FAB < 0; GT) 479 (M − H)$^-$, 355 (M − ClBn)$^-$.

Methyl 3,5-di-*O*-benzoyl-2-*C*-trifluoromethyl-α-D-ribofuranoside 3

A solution of compound **2** (30 g, 62.5 mmol) in methanol (550 cm^3) was hydrogenated in the presence of Pd/C (5%) (30 g) and sodium acetate (5.1 g, 62.5 mmol). After 24 h of stirring, the suspension was filtered through a sintered funnel covered with Celite and the filtrate was evaporated under reduced pressure. To a solution of this crude material in pyridine (625 cm^3) was added benzoyl chloride (110 cm^3, 948 mmol). The reaction mixture was stirred for 12 hours, then diluted with chloroform (500 cm^3) and finally poured into a solution of saturated sodium hydrogen carbonate (3 × 500 cm^3). The organic phase was separated, washed with water (3 × 500 cm^3), dried over sodium sulfate, evaporated to dryness and coevaporated several times with toluene. The residue was purified on silica gel column chromatography using ethyl acetate–petroleum ether (1 : 9) as eluent to give methyl 3,5-di-*O*-benzoyl-2-*C*-trifluoromethyl-α-D-ribofuranoside **3** (22 g, 80%) as a colourless oil (Found: C, 57.38; H, 4.51. $C_{21}H_{19}F_3O_7$ requires C, 57.28; H, 4.35%); $[a]_D^{20}$ +175 (*c* 1.00 in DMSO); δ_H(400 MHz; $CDCl_3$; Me_4Si) 2.96 (1 H, br s, 2-OH), 3.54 (3 H, s, OC*H*$_3$), 4.45 (2 H, m, 5′-H and 4-H), 4.62 (1 H, m, 5-H), 5.08 (1 H, s, 1-H), 5.60 (1 H, d, *J* 7.1, 3-H), 7.3–8.0 (10 H, m, 2 × C$_6$*H*$_5$CO); δ_C(100 MHz; $CDCl_3$; Me_4Si) 56.6 (CH_3), 63.1 (5-C), 70.2 (3-C), 78.6 (4-C), 79.4 (q, $^2J_{C-F}$ 29.8, 2-C), 101.4 (1-C), 124.3 (q, $^1J_{C-F}$ 283, CF_3), 127.3–134.0 (C_{ar}), 165.2 (CO), 166.4 (CO); δ_F(235 MHz; $CDCl_3$; CCl_3F) −80.0 (s, CF_3); *m*/*z* (FAB > 0; GT) 441 (M + H)$^+$, 409 (M − MeOH)$^+$, 105 (C$_6$H$_5$CO)$^+$; *m*/*z* (FAB < 0; GT) 879 (2M − H)$^-$, 439 (M − H)$^-$, 121 (C$_6$H$_5$CO$_2$)$^-$.

Methyl 3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-α-D-arabinofuranoside 4 and methyl 3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-α-D-ribofuranoside 5

To a solution of compound **3** (18.2 g, 41.4 mmol) in anhydrous dichloromethane (136 cm^3) and pyridine (10 cm^3, 125 mmol) was added methyl oxalyl chloride (7.6 cm^3, 82.6 mmol). The reaction mixture was stirred for 3 hours under argon at room temperature, then washed with a solution of saturated sodium hydrogen carbonate (3 × 500 cm^3). The aqueous phase was extracted with dichloromethane (3 × 500 cm^3) and the combined organic layers were dried over sodium sulfate, evaporated to dryness and coevaporated with anhydrous toluene. This crude material was then dissolved in anhydrous toluene (372 cm^3) and α,α′-azobisisobutyronitrile (3.4 g, 20.7 mmol) and tris(trimethylsilyl)silane hydride (25.5 cm^3, 82.6 mmol) were added. The resulting solution was heated under reflux for 12 hours. After cooling to room temperature, the solvent was removed under reduced pressure. Chromatography of the residue on a silica gel column using diethyl ether–petroleum ether (1 : 9) as eluent provided a mixture of the title compounds methyl 3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-α-D-arabinofuranoside **4** and methyl 3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-α-D-ribofuranoside **5** (ratio **4** : **5**: 13 : 87 determined by ^{1}H NMR) as a colourless oil. Further chromatography gave fractions with pure compound **5** (7.2 g, 41%) (Found: C, 59.41; H, 4.76. $C_{21}H_{19}F_3O_6$ requires C, 59.44; H, 4.51%); $[a]_D^{20}$ +117 (*c* 0.99 in DMSO); δ_H(400 MHz; $CDCl_3$; Me_4Si) 3.02 (1 H, m, 2-H), 3.41 (3 H, s, OC*H*$_3$), 4.47 (1 H, m, 4-H), 4.55–4.70 (2 H, m, 5-H and 5′-H), 5.23 (1 H, d, *J* 4.6, 1-H), 5.64 (1H, dd, *J* 7.4 and *J* 2.8, 3-H), 7.4–8.0 (10 H, m, 2 × C$_6$H$_5$CO); δ_C(100 MHz; $CDCl_3$; Me_4Si) 50.6 (q, $^2J_{C-F}$ 28.6, 2-C), 56.0 (CH_3), 64.3 (5-C), 71.8 (3-C), 83.2 (4-C), 102.9 (1-C), 124.0 (q, $^1J_{C-F}$ = 277.9, CF_3), 128.9–134.0 (C_{ar}), 166.4 (2 × CO); δ_F(235 MHz; $CDCl_3$; CCl_3F) −61.2 (d, $^3J_{F-H}$ = 8.9 Hz, CF_3); *m*/*z* (FAB > 0; GT) 849 (2M + H)$^+$, 425 (M + H)$^+$, 393 (M − MeOH)$^+$, 105 (PhCO)$^+$. Additional fractions with an inseparable mixture of compounds **4** and **5** were obtained δ_H(400 MHz; $CDCl_3$; Me_4Si) 3.10 (1 H, m, 2-H[arabino] + 2-H[ribo]), 3.41 (3 H, s, OC*H*$_3$[ribo]), 3.43 (3 H, s, OC*H*$_3$-[arabino]), 4.47–4.83 (3 H, m, 4-H[ribo] + 5-H[ribo], 5′-H-[ribo], 4-H[arabino] + 5-H[arabino], 5′-H[arabino]), 5.30 (1 H, d, *J* 1.6, 1-H[arabino]), 5.23 (1 H, d, *J* 4.6, 1-H[ribo]), 5.80 (1H, m, 3-H[ribo] + 3-H[arabino]), 7.4–8.0 (10 H, m, 2 × C$_6$H$_5$CO); RMN ^{19}F δ_F(235 MHz; $CDCl_3$; CCl_3F) − 69.4 (d, $^3J_{F-H}$ 10.8, CF_3, [arabino]), −61,2 (d, $^3J_{F-H}$ = 8,9 Hz, CF_3, [ribo]).

1-*O*-Acetyl-3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-D-ribofuranose 6

Acetic anhydride (12 cm^3) was added to a solution of compound **5** (7.2 g, 17 mmol) in acetic acid (50.9 cm^3) at 0 °C. Sulfuric acid (1.3 cm^3) was then added dropwise. The reaction mixture was stirred at room temperature for 1 hour then diluted with a mixture of ice–water. The aqueous phase was extracted with chloroform (3 × 200 cm^3). The combined extracts were washed with a solution of saturated sodium hydrogen carbonate (3 × 400 cm^3), water (3 × 400 cm^3) and dried over sodium sulfate. The solvent was removed under reduced pressure to afford 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-D-ribofuranose **6** as a colourless oil (6.8 g, 88%). An analytical sample of **6** was obtained after crystallisation from petroleum ether providing the β-anomer; mp 129 °C; $[a]_D^{20}$ −16 (*c* 1.05 in DMSO); δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.92 (3 H, s, C*H*$_3$CO), 3.43 (1 H, m, 2-H), 4.43 (1 H, dd, *J* 12.0 and *J* 4.4, 5′-H), 4.60 (2 H, m, 5-H and 4-H), 5.83 (1 H, m, 3-H), 6.57 (1 H, d, *J* 2.6, 1-H), 7.3–8.00 (10 H, m, 2 × C$_6$*H*$_5$CO); δ_C(100 MHz; $CDCl_3$; Me_4Si) 19.8 (CH_3), 50.2 (q, $^2J_{C-F}$ 27.4, 2-C), 62.6 (5-C), 70.7 (3-C), 81.4 (4-C), 95.5 (1-C), 123.2 (q, $^1J_{C-F}$ 279.4, CF_3), 127.3–132.8 (C_{ar}), 164.5 (CO), 164.9 (CO), 168.1 (CO); δ_F(235 MHz; $CDCl_3$; CCl_3F) −64.8 (d, $^3J_{F-H}$ 8.7, CF_3); *m*/*z* (FAB > 0; NBA; HRMS) Found 453.1161 (M + H)$^+$, requires 453.1149.

9-(3,5-Di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)adenine 7 and 9-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-α-D-ribofuranosyl)-adenine 8

Stannic chloride (0.4 cm^3, 3.41 mmol) was added cautiously to a stirred suspension of adenine (0.25 g, 1.85 mmol) and 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-D-ribofuranose **6** (0.7 g, 1.54 mmol) in dry acetonitrile (14 cm^3) at

room temperature. After 72 h, pyridine (6 cm^3) was added to the resultant solution. The white precipitate was filtered and washed with chloroform (3 × 50 cm^3). The combined filtrates were washed with a solution of saturated sodium hydrogen carbonate (3 × 100 cm^3), water (3 × 100 cm^3), dried over sodium sulfate and evaporated. Silica gel column chromatography of the residue using a stepwise gradient of methanol (1–2%) in dichloromethane afforded a mixture of the title compound 9-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)adenine **7** and 9-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-α-D-ribofuranosyl)adenine **8** as a white foam (ratio **7** : **8**: 77 : 23 determined by ^{1}H NMR). Further chromatography gave fractions with pure compound **7** (0.32 g, 39%) mp 186 °C (from petroleum ether) (Found: C, 57.03; H, 3.85; N, 13.10; F, 10.91. $C_{25}H_{20}F_3N_5O_5$ requires C, 56.93; H, 3.82; N, 13.28; F, 10.81%); $[a]_D^{20}$ −27 (*c* 1.00 in DMSO); λ_{max}(ethanol)/nm 230 (ε/dm^3 mol^{-1} cm^{-1} 29 000), 260 (16 000), λ_{min} 247 (14 600); δ_H(400 MHz; DMSO-d_6; Me_4Si) 4.63 (1 H, dd, *J* 10.6 and *J* 4.3, 5″-H), 4.66–4.77 (2 H, m, 4′-H and 5′-H), 5.02 (1 H, m, 2′-H), 6.24 (1 H, dd, *J* 6.6 and *J* 3, 3′-H), 6.78 (1 H, d, *J* 8.0, 1′-H), 7.45 (2 H, br s, NH_2), 7.5–8.1 (10 H, m, 2 × C_6H_5CO), 8.08 (1 H, s, 2-H), 8.48 (1 H, s, 8-H); δ_C(100 MHz; DMSO-d_6; Me_4Si) 47.5 (q, $^2J_{C-F}$ 26.9, 2′-C), 64.0 (5′-C), 72.7 (3′-C), 82.0 (4′-C), 83.4 (1′-C), 120.2 (5-C), 125.4 (q, $^1J_{C-F}$ 278.8, CF_3), 129.4–134.9 (C_{ar}), 140.9 (8-C), 150.4 (4-C), 153.7 (2-C), 157.1 (6-C), 165.4 (CO), 166.2 (CO); δ_F(235 MHz; DMSO-d_6; CCl_3F) −62.3 (d, $^3J_{F-H}$ 9.3, CF_3); *m*/*z* (FAB > 0; GT) 1055 (2M + H)$^+$, 620 (M + G + H)$^+$, 528 (M + H)$^+$, 393 (S)$^+$, 136 (BH_2)$^+$, 105 (PhCO)$^+$; *m*/*z* (FAB < 0; GT) 526 (M − H)$^-$, 134 (B)$^-$, 121 ($PhCO_2$)$^-$. Additional fractions of compound **8** contaminated with a trace amount of compound **7** were obtained. Compound **8** δ_H(400 MHz; DMSO-d_6; Me_4Si) 4.62–4.92 (3 H, m, 2′-H, 5′-H and 5″-H), 5.51 (1 H, m, 4′-H), 6.05 (1 H, m, 3′-H), 6.98 (1 H, d, *J* 7.0, 1′-H), 7.51–8.80 (14 H, m, 2 × C_6H_5CO, NH_2, 2-H and 8-H); δ_F(235 MHz; $CDCl_3$; CCl_3F) −59.7 (d, $^3J_{F-H}$ 9.4, CF_3).

2-Amino-6-chloro-9-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)purine 9 and 2-amino-6-chloro-9-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-α-D-ribofuranosyl)-purine 10

Bis(trimethylsilyl)acetamide (10.5 cm^3, 42.8 mmol) was added to a stirred suspension of 2-amino-6-chloro-purine (1.8 g, 10.6 mmol) in dry toluene (20 cm^3). The resulting suspension was heated under reflux for 2 hours, then 1-*O*-acetyl-3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-D-ribofuranose **6** (4.4 g, 9.73 mmol), previously dissolved in dry toluene (20 cm^3), and trimethylsilyl triflate (2.25 cm^3, 11.64 mmol) were added. The reaction mixture was refluxed for 30 minutes then cooled to room temperature. Ethyl acetate (50 cm^3) was added and the organic layer was washed with a solution of saturated sodium hydrogen carbonate (3 × 50 cm^3), dried and evaporated under reduced pressure. Silica gel column chromatography of the residue using petroleum ether–diethyl ether (3 : 7) as eluent afforded successively the title compounds 2-amino-6-chloro-9-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)purine **9** (0.3 g, 5.5%) and 2-amino-6-chloro-9-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-α-D-ribofuranosyl)purine **10** (0.3 g, 5.5%) as white foams. Compound **9**: mp 105 °C (from diethyl ether–petroleum ether) (Found: C, 53.42; H, 3.57; N, 11.84; Cl, 6.11; F, 10.30. $C_{25}H_{19}F_3N_5O_5$·0.15 Et_2O requires C, 53.66; H, 3.61; N, 12.22; Cl, 6.19; F, 9.95%); $[a]_D^{20}$ −5 (*c* 1.02 in DMSO); λ_{max}(ethanol)/nm 236 (ε/dm^3 mol^{-1} cm^{-1} 24 800), 310 (6 600), λ_{min} 267 (2 200); δ_H(400 MHz; DMSO-d_6; Me_4Si) 4.67 (3 H, m, 4′-H, 5′-H and 5″-H), 4.87 (1 H, m, 2′-H), 6.18 (1 H, dd, *J* 6.9 and *J* 3.1, 3′-H), 6.66 (1 H, d, *J* 7.8, 1′-H), 7.11 (2 H, br s, NH_2), 7.5–8.0 (10 H, m, 2 × C_6H_5CO), 8.49 (1 H, s, 8-H); δ_C(100 MHz; DMSO-d_6; Me_4Si) 47.6 (q, $^2J_{C-F}$ 7.2, 2′-C), 64.1 (5′-C), 72.6 (3′-C), 81.9 (4′-C), 82.8 (1′-C), 124.3 (5-C), 125.4 (q, $^1J_{C-F}$ 278.6, CF_3), 129.3–135.0 (C_{ar}), 142.0 (8-C), 151.0 (4-C), 153.4 (6-C), 160.8 (2-C), 165.3 (CO), 166.2 (CO); δ_F(235 MHz; DMSO-d_6; CCl_3F) −62.5 (d, $^3J_{F-H}$ 9.3, CF_3); *m*/*z* (FAB > 0; GT) 1123 (2M + H)$^+$, 562 (M + H)$^+$, 393 (S)$^+$, 170 (BH_2)$^+$, 105 (PhCO)$^+$; *m*/*z* (FAB$^-$; GT) 1121 (2M − H)$^-$, 560 (M − H)$^-$, 168 (B)$^-$, 121 ($PhCO_2$)$^-$. Compound **10**: δ_H(400 MHz; DMSO-d_6; Me_4Si) 4.59 (3 H, m, 2′-H, 5′-H and 5″-H), 5.47 (1 H, t, *J* 5.8, 4′-H), 5.97 (1 H, d, *J* 6.4, 3′-H), 6.76 (1 H, d, *J* 7.0, 1′-H), 7.00 (2 H, br s, NH_2), 7.5–8.0 (10 H, m, 2 × C_6H_5CO), 8.46 (1 H, s, 8-H); δ_C(100 MHz; DMSO-d_6; Me_4Si) 48.8 (q, $^2J_{C-F}$ 27.7, 2′-C), 64.5 (5′-C), 73.6 (3′-C), 82.7 (1′-C), 85.0 (4′-C), 123.6 (5-C), 124.6 (q, $^1J_{C-F}$ 278.0, CF_3), 129.7–134.8 (C_{ar}), 142.2 (8-C), 150.4 (4-C), 154.5 (6-C), 160.8 (2-C), 165.7 (CO), 166.4 (CO); δ_F(235 MHz; DMSO-d_6; CCl_3F) −59.8 (d, $^3J_{F-H}$ 9.3, CF_3).

9-(2-Deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)adenine 11

To a solution of 9-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)adenine **10** (0.28 g, 0.53 mmol) in dry methanol (5.3 cm^3) was added sodium methylate (0.086 g, 1.59 mmol). The reaction mixture was stirred at room temperature for 3 hours and neutralized with a 1 M chlorhydric acid solution, then evaporated to dryness. The residue was subjected to silica gel column chromatography using methanol–dichoromethane (1 : 9) as eluent to give 9-(2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)adenine **11** (0.125 g, 74%) which was lyophylizated from water (Found: C, 38.38; H, 3.99; N, 20.14. $C_{11}H_{12}F_3N_5O_3$·1.3 H_2O requires C, 38.56; H, 4.29; N, 20.44%); $[a]_D^{20}$ −89 (*c* 1.00 in DMSO); λ_{max}(ethanol)/nm 260 (ε/dm^3 mol^{-1} cm^{-1} 14 500); δ_H(400 MHz; DMSO-d_6; Me_4Si) 3.74 (1 H, m, 5′-H), 3.63 (1 H, m, 5″-H), 4.09 (1 H, br s, 4′-H), 4.20 (1 H, m, 2′-H), 4.69 (1 H, m, 3′-H), 5.40 (1H, t, *J* 5.3, 5′-OH), 6.10 (1 H, d, *J* 5.5, 3′-OH), 6.57 (1 H, d, *J* 8.8, 1′-H), 6.22 (2 H, br s, NH_2), 8.23 (1 H, s, 2-H), 8.51 (1 H, s, 8-H); δ_C(100 MHz; DMSO-d_6; Me_4Si) 50.4 (q, $^2J_{C-F}$ 25.4, 2′-C), 62.2 (5′-C), 71.3 (3′-C), 83.1 (1′-C), 88.8 (4′-C), 119.9 (5-C), 125.9 (q, $^1J_{C-F}$ 278.4, CF_3), 140.4 (8-C), 149.9 (4-C), 153.6 (2-C), 157.0 (6-C); δ_F(235 MHz; DMSO-d_6; CCl_3F) −61.4 (d, $^3J_{F-H}$ 9.3 Hz, CF_3); *m*/*z* (FAB > 0; GT) 639 (2M + H)$^+$, 412 (M + G + H)$^+$, 320 (M + H)$^+$, 185 (S)$^+$, 136 (BH_2)$^+$; *m*/*z* (FAB < 0; GT) 637 (2M − H)$^-$, 318 (M − H)$^-$, 134 (B)$^-$.

9-(2-Deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)guanine 12

To a solution of 2-amino-6-chloro-9-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)purine **10** (0.15 g, 0.26 mmol) in dry methanol (21.6 cm^3) were added 2-mercaptoethanol (0.075 cm^3, 1.06 mmol) and sodium methylate (0.057 g, 1.05 mmol). The reaction mixture was heated under reflux for 12 hours then neutralized with a 1 M chlorhydric acid solution and evaporated. The residue was subjected to silica gel column chromatography using a stepwise gradient of methanol (0–15%) in chloroform to afford the title compound 9-(2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)guanine **12** (0.075 g, 83%) after filtration on Millex HV-4 (0.45 μm, Millipore) mp 217 °C (from methanol–chloroform) (Found: C, 39.32; H, 4.11; N, 18.35; F, 15.07. $C_{11}H_{12}F_3N_5O_4$·1.2 H_2O requires C, 39.21; H, 4.53; N, 18.74; F, 15.25%); $[a]_D^{20}$ −61 (*c* 1.01 in DMSO); λ_{max}(ethanol)/nm 253 (ε/dm^3 mol^{-1} cm^{-1} 11 000); δ_H(400 MHz; DMSO-d_6; Me_4Si) 3.57–3.69 (2 H, m, 5′-H and 5″-H), 4.03 (2 H, m, 4′-H and 2′-H), 4.61 (1 H, m, 3′-H), 5.18 (1 H, t, *J* 5.2, 5′-OH), 6.04 (1 H, d, *J* 5.2, 3′-OH), 6.33 (1 H, d, *J* 8.9, 1′-H), 6.60 (2 H, br s, NH_2), 8.08 (1 H, s, 8-H), 10.76 (1H, br s, N–*H*); δ_C(100 MHz; DMSO-d_6; Me_4Si) 50.4 (q, $^2J_{C-F}$ 25.6, 2′-C), 62.0 (5′-C), 71.2 (3′-C), 81.7 (1′-C), 88.4 (4′-C), 117.3 (5-C), 125.9 (q, $^1J_{C-F}$ 279, CF_3), 136.2 (8-C), 152.0 (4-C), 154.7 (2-C), 157.4 (6-C); δ_F(235 MHz; DMSO-d_6; CCl_3F) −61.3 (d, $^3J_{F-H}$ 9.2 Hz, CF_3); *m*/*z* (FAB > 0; GT) 671 (2M + H)$^+$, 428 (M + G + H)$^+$, 336 (M + H)$^+$, 185 (S)$^+$, 152 (BH_2)$^+$; *m*/*z* (FAB < 0; GT) 669 (2M − H)$^-$, 426 (M + G − H)$^-$, 334 (M − H)$^-$, 150 (B)$^-$.

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)uracil 13 and 1-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-α-D-ribofuranosyl)uracil 14

A mixture of uracil (1 g, 8.92 mmol), hexamethyldisilazane (44.6 cm^3) and a catalytic amount of ammonium sulfate was refluxed for 14 hours. The resultant clear solution was concentrated to dryness under reduced pressure. TMSOTf (0.55 cm^3, 2.84 mmol) was added to a solution of sugar **6** (1 g, 2.21 mmol) and silylated base in dry acetonitrile (20 cm^3). The reaction mixture was stirred for 4 days at 50 °C, diluted with dichloromethane (50 cm^3), washed with a solution of saturated sodium hydrogen carbonate (3 × 100 cm^3), water (3 × 100 cm^3), dried over sodium sulfate and evaporated to dryness. Chromatography of the residue on a silica gel column using petroleum ether–diethyl ether (3 : 7) as eluent afforded successively the title compounds 1-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)uracil **13** (0.35 g, 31%) and 1-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-α-D-ribofuranosyl)uracil **14** (0.15 g, 14%) as white foams. Compound **13** mp 220–221 °C (from diethyl ether) (Found: C, 57.03; H, 3.74; N, 5.54; F, 11.38. $C_{24}H_{19}F_3N_2O_7$ requires C, 57.15; H, 3.80; N, 5.55; F, 11.30%); $[\alpha]_D^{20}$ −8 (*c* 0.99 in DMSO); λ_{max}(ethanol)/nm 260 (ε dm^3 mol^{-1} cm^{-1} 10 900), 230 (29 200), λ_{min} 248 (11 200); δ_H(400 MHz; DMSO-d_6; Me_4Si) 4.28 (1 H, m, 2′-H), 4.60 (3 H, m, 4′-H, 5′-H and 5″-H), 5.75 (1 H, d, *J* 8.1, 5-H), 5.97 (1 H, dd, *J* 7.5 and *J* 3.5, 3′-H), 6.46 (1 H, d, *J* 7.6, 1′-H), 7.5–8.00 (11 H, m, 2 × C_6H_5CO and 6-H), 11.60 (1 H, br s, N–*H*); δ_C(100 MHz; DMSO-d_6; Me_4Si) 47.7 (q, $^2J_{C-F}$ 28.6, 2′-C), 64.2 (5′-C), 71.9 (3′-C), 81.2 (4′-C), 84.9 (1′-C), 103.8 (5-C), 125.5 (q, $^1J_{C-F}$ 279, CF_3), 129.3–134.9 (C_{ar}), 141.9 (6-C), 150.9 (2-C), 163.6 (4-C), 165.4 (CO), 166.2 (CO); δ_F(235 MHz; DMSO-d_6; CCl_3F) −62.6 (d, $^3J_{F-H}$ 9.6, CF_3); *m*/*z* (FAB > 0; GT) 1009 $(2M + H)^+$, 597 $(M + G + H)^+$, 505 $(M + H)^+$, 393 $(S)^+$, 113 $(BH_2)^+$, 105 $(PhCO)^+$; *m*/*z* (FAB < 0; GT) 503 $(M - H)^-$, 111 $(B)^-$. Compound **14** δ_H(400 MHz; DMSO-d_6; Me_4Si) 4.45 (3 H, m, 2′-H, 5′-H and 5″-H), 5.28 (1 H, t, *J* 6.3, 4′-H), 5.64 (1 H, d, *J* 8.2, 5-H), 5.91 (1 H, dd, *J* 6.0, 3′-H), 6.73 (1 H, d, *J* 7.2, 1′-H), 7.5–8.1 (11 H, m, 2 × C_6H_5CO and 6-H), 11.50 (1 H, br s, N–*H*); δ_C(100 MHz; DMSO-d_6; Me_4Si) 48.3 (q, $^2J_{C-F}$ 27.6, 2′-C), 64.3 (5′-C), 73.5 (3′-C), 84.0 (1′-C), 84.3 (4′-C), 102.3 (5-C), 125.0 (q, $^1J_{C-F}$ 278, CF_3), 129.5–134.9 (C_{ar}), 142.0 (6-C), 151.0 (2-C), 163.8 (4-C), 165.4 (CO), 166.3 (CO); δ_F(235 MHz; DMSO-d_6; CCl_3F) −59.5 (d, $^3J_{F-H}$ 9.5, CF_3).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)thymine 15 and 1-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-α-D-ribofuranosyl)-thymine 16

A mixture of thymine (1.11 g, 8.8 mmol), hexamethyldisilazane (44.2 cm^3) and a catalytic amount of ammonium sulfate was refluxed for 14 hours. The resultant clear solution was concentrated to dryness under reduced pressure. TMSOTf (0.55 cm^3, 2.84 mmol) was added to a solution of sugar **6** (1 g, 2.21 mmol) and silylated base in dry acetonitrile (22 cm^3). The reaction mixture was stirred for 4 days at 50 °C, diluted with dichloromethane (50 cm^3), washed with a solution of saturated sodium hydrogen carbonate (3 × 100 cm^3), water (3 × 100 cm^3), dried over sodium sulfate and evaporated to dryness. Chromatography of the residue on a silica gel column using petroleum ether–diethyl ether (3 : 7) as eluent afforded successively the title compounds 1-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)thymine **15** (0.37 g, 32.6%) and 1-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-α-D-ribofuranosyl)-thymine **16** (0.13 g, 11.4%) as white foams. Compound **15** mp 210 °C (from diethyl ether) (Found: C, 58.01; H, 4.05; N, 5.41; F, 11.03. $C_{25}H_{21}F_3N_2O_7$ requires C, 57.92; H, 4.08; N, 5.40; F, 10.99%); $[\alpha]_D^{20}$ −14 (*c* 1.00 in DMSO); λ_{max}(ethanol)/nm 267 (ε/dm^3 mol^{-1} cm^{-1} 11 900), 229 (29 970), λ_{min} 250 (11 200); δ_H(400 MHz; DMSO-d_6; Me_4Si) 1.73 (3 H, d, *J* 0.7, CH_3), 4.23 (1 H, m, 2′-H), 4.59–4.68 (3 H, m, 4′-H, 5′-H and 5″-H), 6.00 (1 H, dd, *J* 7.6 and *J* 4.1, 3′-H), 6.50 (1 H, d, *J* 7.8, 1′-H), 7.5–8.0 (11 H, m, 2 × C_6H_5CO and 6-H), 11.58 (1 H, br s, N–*H*); δ_C(100 MHz; DMSO-d_6; Me_4Si) 12.8 (CH_3), 47.7 (q, $^2J_{C-F}$ 29.9, 2′-C), 64.2 (5′-C), 71.8 (3′-C), 81.1 (4′-C), 84.1 (1′-C), 111.6 (5-C), 125.5 (q, $^1J_{C-F}$ 278.6, CF_3), 129.3–134.9 (C_{ar}), 136.8 (6-C), 151.0 (2-C), 166.3 (CO), 164.2 (4-C), 165.4 (CO); δ_F(235 MHz; DMSO-d_6; CCl_3F) −62.5 (d, $^3J_{F-H}$ 9.5 Hz, CF_3); *m*/*z* (FAB > 0; GT) 1037 $(2M + H)^+$, 611 $(M + G + H)^+$, 519 $(M + H)^+$; *m*/*z* (FAB < 0; NBA) 1035 $(2M - H)^-$, 517 $(M - H)^-$, 121 $(PhCO_2)^-$. Compound **16** δ_H(400 MHz; DMSO-d_6; Me_4Si) 1.73 (3 H, s, CH_3), 4.44 (3 H, m, 2′-H, 5′-H and 5″-H), 5.37 (1 H, t, *J* 6.4, 4′-H), 5.90 (1 H, d, *J* 5.7, 3′-H), 6.74 (1 H, d, *J* 7.2, 1′-H), 7.5–8.1 (11 H, m, 2 × C_6H_5CO and 6-H), 11.47 (1H, br s, N–*H*); δ_C(100 MHz; DMSO-d_6; Me_4Si) 13.0 (CH_3), 48.3 (q, $^2J_{C-F}$ 26.8, 2′-C), 64.3 (5′-C), 73.5 (3′-C), 83.8 (1′-C), 84.3 (4′-C), 110.0 (5-C), 125.0 (q, $^1J_{C-F}$ 278.0, CF_3), 129.3–134.8 (C_{ar}), 137.3 (6-C), 151.1 (2-C), 164.6 (4-C), 165.3 (CO), 166.3 (CO); δ_F(235 MHz; DMSO-d_6; CCl_3F) −59.3 (d, $^3J_{F-H}$ 9.5 Hz, CF_3).

1-(2-Deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)uracil 17

To a solution of 1-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)uracil **13** (0.28 g, 0.55 mmol) in dry methanol (5.5 cm^3) was added sodium methylate (0.12 g, 2.22 mmol). The reaction mixture was stirred at room temperature for 20 minutes and neutralized with a 1 M chlorhydric acid solution, then evaporated to dryness. The residue was subjected to silica gel column chromatography, using 10% methanol in chloroform as eluent, to give 9-(2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)uracil **17** (0.14 g, 85%) (Found: C, 40.66; H, 3.73; N, 9.30; F, 19.36. $C_{10}H_{11}F_3N_2O_5$ requires C, 40.55; H, 3.74; N, 9.46; F, 19.24%); $[\alpha]_D^{20}$ −37 (*c* 1.03 in DMSO); λ_{max}(ethanol)/nm 260 (ε/dm^3 mol^{-1} cm^{-1} 10 300); δ_H(400 MHz; DMSO-d_6; Me_4Si) 3.33 (1 H, m, 2′-H), 3.56 (2 H, m, 5′-H and 5″-H), 3.89 (1 H, br s, 4′-H), 4.42 (1 H, br s, 3′-H), 5.2 (1 H, br s, 5′-OH), 5.72 (1 H, d, *J* 8.1, 5-H), 5.92 (1 H, d, *J* 4.9, 3′-OH), 6.38 (1 H, d, *J* 8.7, 1′-H), 7.83 (1 H, d, 6-H), 11.40 (1 H, br s, N–*H*); δ_C(100 MHz; DMSO-d_6; Me_4Si) 50.5 (q, $^2J_{C-F}$ 25, 2′-C), 61.9 (5′-C), 71.0 (3′-C), 83.0 (1′-C), 88.0 (4′-C), 103.7 (5-C), 128.5 (q, $^1J_{C-F}$ 278.3, CF_3), 140.9 (6-C), 151.1 (2-C), 163.7 (4-C); δ_F(235 MHz; DMSO-d_6; CCl_3F) −61.4 (d, $^3J_{F-H}$ 9.3, CF_3); *m*/*z* (FAB > 0; GT) 593 $(2M + H)^+$, 389 $(M + G + H)^+$, 297 $(M + H)^+$, 185 $(S)^+$, 113 $(BH_2)^+$; *m*/*z* (FAB < 0; GT) 591 $(2M - H)^-$, 387 $(M + G + H)^-$, 295 $(M - H)^-$, 111 $(B)^-$.

1-(2-Deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)thymine 18

To a solution of 1-(3,5-di-*O*-benzoyl-2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)thymine **15** (0.4 g, 0.77 mmol) in dry methanol (7.7 cm^3) was added sodium methylate (0.166 g, 3.08 mmol). The reaction mixture was stirred at room temperature for 15 minutes and neutralized with a 1 M chlorhydric acid solution, then evaporated to dryness. The residue was subjected to silica gel column chromatography using methanol–dichoromethane (1 : 9) as eluent to give 1-(2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)thymine **18** (0.215 g, 90%) which was lyophilizated from water (Found: C, 41.72; H, 4.16; N, 8.72. $C_{11}H_{13}F_3N_2O_5 \cdot 0.3\ H_2O$ requires C, 41.86; H, 4.34; N, 8.88%); $[\alpha]_D^{20}$ −41 (*c* = 1.02 in DMSO); λ_{max}(ethanol)/nm 267 (ε/dm^3 mol^{-1} cm^{-1} 9 300); δ_H(400 MHz; DMSO-d_6; Me_4Si) 1.76 (3 H, s, CH_3), 3.35 (1 H, m, 2′-H), 3.56 (2 H, m, 5′-H and 5″-H), 3.87 (1 H, br s, 4′-H), 4.42 (1 H, dd, *J* 5.8 and *J* 2, 3′-H), 5.22 (1 H, br s, 5′-OH), 5.91 (1 H, br s, 3′-OH), 6.37 (1 H, d, *J* 8.8, 1′-H), 7.66 (1 H, d, *J* 0.7, 6-H), 11.41 (1 H, br s, N–*H*); δ_C(100 MHz; DMSO-d_6; Me_4Si) 13.1 (CH_3), 50.2 (q, $^2J_{C-F}$ = 25 Hz, 2′-C), 61.9 (5′-C), 71.0 (3′-C), 82.8 (1′-C), 87.8 (4′-C), 111.2 (5-C), 125.8 (q, $^1J_{C-F}$ = 278.2 Hz, CF_3), 136.3 (6-C), 151.2 (2-C), 164.6 (4-C); δ_F(235 MHz; DMSO-d_6; CCl_3F) −61.3 (d, $^3J_{F-H}$ 9.4, CF_3); *m*/*z* (FAB > 0; GT) 621 $(2M + H)^+$, 403 $(M + G + H)^+$, 311 $(M + H)^+$, 185 $(S)^+$, 127 $(BH_2)^+$; *m*/*z* (FAB < 0; NBA) 619 $(2M - H)^-$, 401 $(M + G - H)^-$, 309 $(M - H)^-$, 125 $(B)^-$.

1-(2-Deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)cytosine 19

A solution of compound **13** (0.5 g, 0.99 mmol) and 1-methylpyrrolidine (1 cm^3, 9.61 mmol) in anhydrous acetonitrile (4.9 cm^3) was cooled down to 0 °C. Trifluoroacetic anhydride (0.35 cm^3, 2.47 mmol) was then added. After 45 minutes at 0 °C, 4-nitrophenol (0.415 g, 3 mmol) was added to the solution. After stirring for 3 hours at 0 °C, the solution was then poured into a solution of saturated sodium hydrogen carbonate (20 cm^3), and the resultant mixture was extracted with dichloromethane (3 × 20 cm^3). The combined organic layers were dried over sodium sulfate and evaporated under reduced pressure. The residue was dissolved in dioxane (5 cm^3) and concentrated aqueous ammonia (1 cm^3, *d* 0.89) was added. The reaction mixture was stirred at 55 °C for 12 hours. The resulting yellow solution was concentrated under reduced pressure and directly treated with methanolic ammonia (previously saturated at −10 °C and tightly stoppered) (25 cm^3) for 12 hours at room temperature. After evaporation to dryness under reduced pressure, the residue was subjected to silica gel column chromatography using methanol–dichloromethane (1 : 9) as eluent to afford the title compound 1-(2-deoxy-2-*C*-trifluoromethyl-β-D-ribofuranosyl)cytosine **19** (0.155 g, 53%). An analytical sample of compound **19** was obtained as its chlorohydrate salt mp 220 °C (from ethanol) (Found: C, 36.63; H, 3.93; N, 12.65. $C_{10}H_{13}ClF_3N_3O_4$·0.1EtOH requires C, 36.43; H, 4.08; N, 12.50%); $[a]_D^{20}$ +3 (*c* 1.00 in DMSO); λ_{max}(ethanol)/nm 270 (ε dm^3 mol^{-1} cm^{-1} 8 500); δ_H(400 MHz; DMSO-d_6; Me_4Si) 3.43 (1 H, m, 2′-H), 3.61 (2 H, m, 5′-H and 5″-H), 3.96 (1 H, m, 4′-H), 4.47 (1 H, m, 3′-H), 5.07 (1 H, br s, OH), 5.99 (1 H, br s, OH), 6.23 (1 H, d, *J* 7.8, 5-H), 6.32 (1 H, d, *J* 7.3, 1′-H), 8.22 (1 H, d, 6-H), 8.80 (1 H, br s, NH_2), 9.93 (1 H, br s, NH_2); δ_C(100 MHz; DMSO-d_6; Me_4Si) 51.3 (q, $^2J_{C-F}$ 25, 2′-C), 61.3 (5′-C), 70.3 (3′-C), 84.3 (1′-C), 88.3 (4′-C), 95.9 (5-C), 125.7 (q, $^1J_{C-F}$ 279, CF_3), 144.7 (6-C), 147.7 (2-C), 160.2 (4-C); δ_F(235 MHz; DMSO-d_6; CCl_3F) −61,4 (d, $^3J_{F-H}$ 9.5, CF_3); *m*/*z* (FAB > 0; GT) 185 $(S)^+$, 112 $(BH_2)^+$; *m*/*z* (FAB < 0; GT) 330 $(M - H)^-$.

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