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Phosphoramidite building blocks for efficient incorporation of 2′-*O*-aminoethoxy(and propoxy)methyl nucleosides into oligonucleotides

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ABSTRACT

A simple and efficient method for the preparation of eight phosphoramidite building blocks for incorporation of 2′-*O*-(2-aminoethoxymethyl)ribonucleosides and 2′-*O*-(3-aminopropoxymethyl)ribonucleosides into synthetic oligonucleotides has been developed. The synthetic routes are maximally convergent and provide sufficient amounts of phosphoramidites for several solid-phase synthesis coupling reactions. Using acyclic derivatives **17a**,**b** the overall yields of phosphoramidites **2** and **3** were increased up to 50% for pyrimidine nucleosides and up to 30% for purine derivatives with substantial decrease of total reaction steps. The 2′-*O*-substituent was found to be stable during oligonucleotide synthesis. The resulting oligonucleotides are of particular interest for post-synthetic functionalization and conjugation.

1. Introduction

Modified oligonucleotides (ONs) are used widely in various fields, such as molecular biology, biochemistry, and medicine.[1–3] ONs carrying reactive groups are needed in order to synthesize conjugates with reporter compounds, markers, peptides, proteins, and other biomolecules.[4,5] Research in this field increased in impact by the discovery of RNA interference.[6]

Numerous attempts have been made to improve the properties of natural ONs. It is believed that the 2′-carbohydrate modifications are the most universal and promising[7–9] since this generally leads to minimal distortions in ON structure. The ribose 2′-position is particularly useful for chemical modification because of its location in the minor groove of A-form duplex nucleic acid, where it points outward into solution. This position is also readily modified synthetically, as described in this work. A typical strategy for the preparation of such ONs is the synthesis of modified nucleoside followed by conversion to the corresponding phosphoramidite suitable for automated ON synthesis. Most of 2′-O-modifications were achieved via alkylation reactions of partially blocked ribonucleosides. The heterocyclic bases should be protected in order to avoid their alkylation. For each nucleoside the specific blocking groups are used,[9,10] which in most cases are not compatible with standard automated ON synthesis.

A large number of oligonucleotides containing a different aminoalkyl modification at the sugar moiety have been reported, the amino group normally being protonated at physiological pH. Oligonucleotides having such a positively charged modification exhibit high binding properties toward RNA and DNA and maintain nuclease resistance. Among the 2′-*O*-substituents developed, recently high affinity was found for the aminoethyl[9] (phosphoramidites **1**, Fig. 1) and aminopropyl[7,11] derivatives, which may form specific contact with a proximal phosphate group in the nucleic acids duplex. Modified oligonucleotides bearing 2′-reporting and reactive groups or 2′-conjugated molecules have found wide application as structural tools in molecular biology.[12]

Very recently for the preparation of 2′-*O*-modified nucleosides we have developed another type of chemistry based on O-glycosylation reactions, which have several important advantages, such as increased yields and simplification.[13–16] A simple and effective method for the preparation of 2′-*O*-β-D-ribofuranosylnucleosides, starting from readily available 3′,5′-*O*-blocked *N*-acylribonucleosides and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of tin tetrachloride in 1,2-dichloroethane at 0 °C, has been recently developed.[17–19] Holding this line an efficient synthesis of pyrimidine 2′-*O*-(ω-hydroxyalkoxymethyl)ribonucleosides has been achieved and the 2′-*O*-substituent was found to be stable during oligoribonucleotide synthesis.[20,21] This synthetic scheme is nearly the same as for the preparation of disaccharide nucleosides and their incorporation into ONs.[22]

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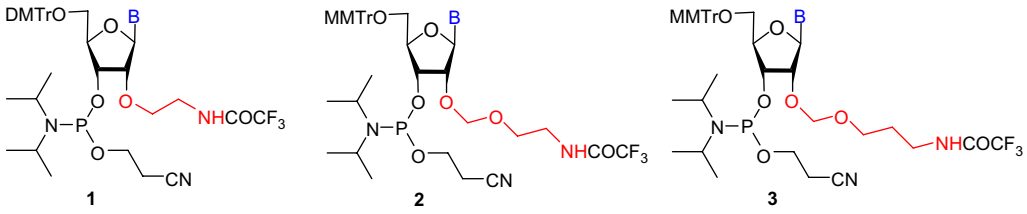


Figure 1. Structure of phosphoramidites **1**,[9] **2**, and **3**. For **1**: (a) B=Ura, (b) B=4-(1,2,4-triazol-1-yl)pyrimidin-2-one, (c) B=Gua^{iBu}, (d) B=Ade^{iBu}. For **2** and **3**: (a) B=Ura, (b) B=Cyt^{Bz}, (c) B=Gua^{iBu}, (d) B=Ade^{Bz}.

2. Results and discussion

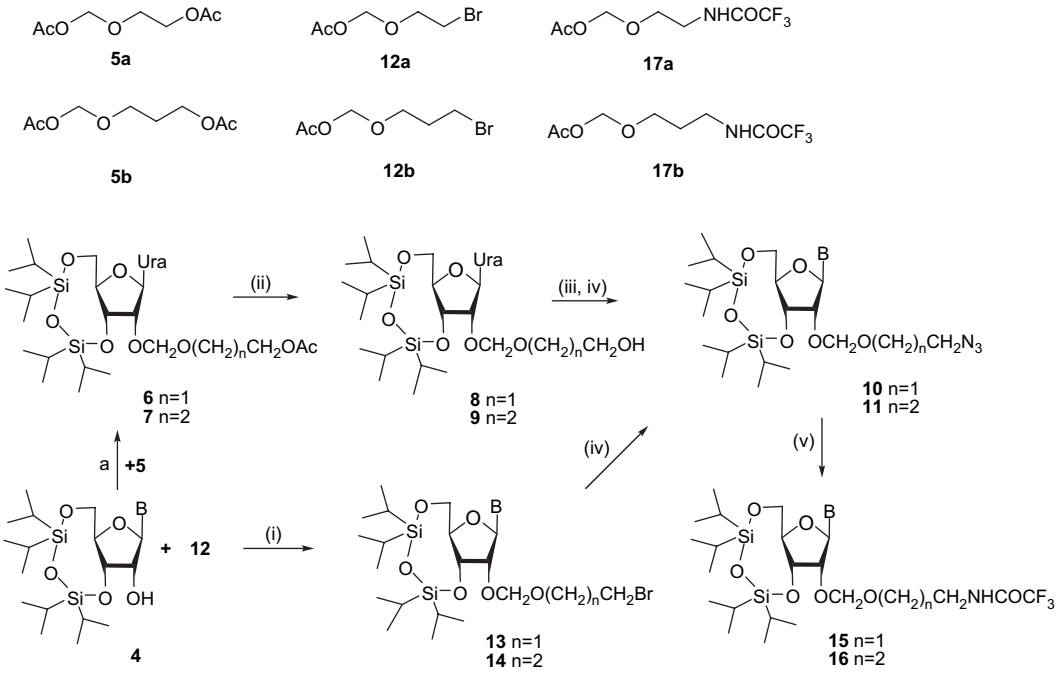
Here we present our recent results on the preparation of 2′-*O*-(ω-aminoalkoxymethyl)ribonucleoside synthons (phosphoramidites **2** and **3**, Fig. 1) suitable for automatic oligonucleotide synthesis. The synthesis of aminoalkyl nucleosides is usually performed via azido derivatives followed by reduction. Preparation of 2′-*O*-(ω-azidoalkoxymethyl)ribonucleosides **10** and **11** was realized in two different ways (Scheme 1). In the first approach 2′-*O*-(ω-acetoxyalkoxymethyl)uridines **6a** and **7a**,[20] which were easily prepared starting from **5a**,**b** and uridine derivative **4a**, were chosen as starting compounds. The acetyl group was selectively removed with MeONa in methanol to yield 2′-*O*-(ω-hydroxyalkoxymethyl)uridines **8a** and **9a**. Introduction of the azide functionality consisted in reaction of the primary hydroxyl group with tosylchloride followed by replacement with azide ion, without chromatographic separation of the intermediate tosylate. The overall yield of azido nucleosides **10a** and **11a** starting from 3′,5′-*O*-blocked uridines **4a** was about 50–55%.

The preparation of azido nucleosides **10** and **11** was further improved using $AcOCH_2O(CH_2)_nBr$ (n=2, 3) (**12a**,**b**), which were easily prepared starting from bromoethanol and bromopropanol via their chloromethyl esters. Condensation of protected uridine and cytidine derivatives **4a**,**b** with **12a**,**b** gave 2′-*O*-(ω-bromoalkoxymethyl)ribonucleosides **13a**,**b** and **14a**,**b** in high yields (87–90%). Treatment of the 2′-*O*-(ω-bromoalkoxymethyl)ribonucleosides **13a**,**b** and **14a**,**b** with NaN_3 in DMF afforded azides **10a**,**b** and **11a**,**b** in 88–92% yield.

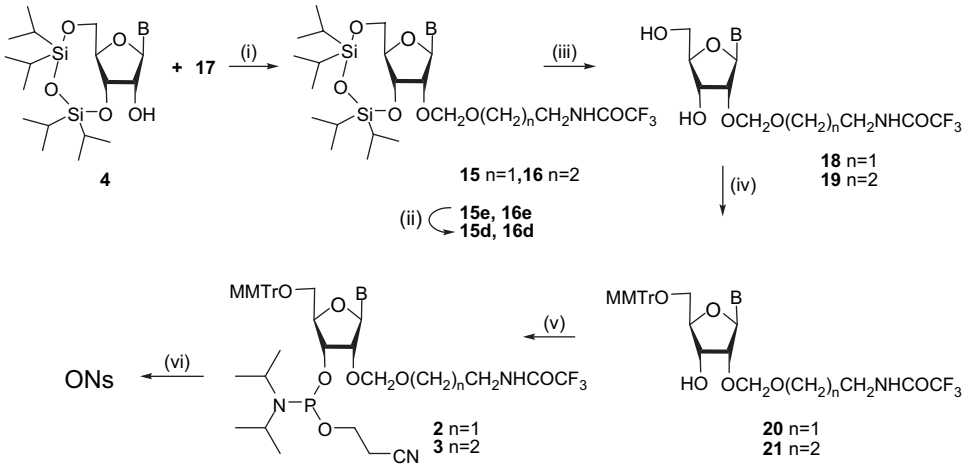
Different methods have been used for the conversion of an azido group to an amino group, for example, hydrogenolysis, reduction with metal hydrides, sulphide ions, or tin derivatives, reaction with phosphines, and others. The most suitable method for obtaining amino nucleosides appeared to be the reduction of an azido group with H_2 over Pd–C. To avoid the formation of undesirable *N*-acyl by-products simultaneous N-(trifluoroacetylation) was carried out. One-step reduction of **10a**,**b** and **11a**,**b** in the presence of an excess of ethyl trifluoroacetate afforded **15a**,**b** and **16a**,**b** in 55–60% yields after silica gel chromatography.

In order to shorten and simplify the preparation of 2′-*O*-(ω-aminoalkoxymethyl)nucleosides we decided to prepare the acyclic derivatives **17a**,**b**. These compounds were easily synthesized starting from aminoethanol and aminopropanol in three steps: trifluoroacetylation, chloromethylation, and nucleophilic displacement with acetate ion. The overall yields of acetals **17a**,**b** were around 65%.

Condensation of **17a**,**b** with 3′,5′-*O*-blocked ribonucleosides **4a**,**b** in the presence of tin tetrachloride in 1,2-dichloroethane at −12 °C for 20 min gave products **15a**,**b** and **16a**,**b** in the yields of 75–85% (Scheme 2). Guanosine derivative **15c** was obtained in 48% yield. In the case of preparation of **16c** we could not separate the product from the starting **4c** in several solvent systems and the formed mixture was used in the next step. During reaction with **4d** a complex mixture was formed evidently due to the instability of *N*-glycoside bond during reaction in the presence of Lewis acid.[23,24] So we decided to use *N*-unprotected adenosine **4e**. The following



Scheme 1. (a) B=Ura, (b) B=Cyt^{Bz}. (i) $SnCl_4$–1,2-dichloroethane, −12 °C, 20 min; (ii) MeONa–methanol, 20 °C, 30 min; (iii) TosCl–pyridine, 20 °C, 16 h; (iv) NaN_3–DMF, 80 °C, 2 h; (v) H_2, Pd–C(10%)–dioxane, F_3CO_2Et–DBU, 20 °C, 5 h.



Scheme 2. (a) B=Ura, (b) B=Cyt^{Bz}, (c) B=Gua^{iBu}, (d) B=Ade^{Bz}, (e) B=Ade. (i) $SnCl_4$–dichloroethane, −12 °C, 20 min (B=Ura, Cyt^{Bz}), 40 min (B=Ado, Gua^{iBu}); (ii) BzCl–pyridine, 20 °C, 2 h, 4% NH_4OH, 20 °C, 1 h; (iii) Bu_4NF–THF, 20 °C, 15 min; (iv) MMTrCl–Py, 20 °C, 24 h; (e) $iPr_2NPCl(OCH_2CH_2CN)$, iPr_2NEt–dichloromethane, 20 °C, 4 h; (v) automatic oligonucleotide synthesis.

benzoylation of the formed nucleosides **15e** and **16e** gave desired *N*-protected **15d** and **16d** in good yields (70–75%). The structure of compounds **15** and **16** was established by NMR and mass spectroscopies. The ^1H NMR spectra of nucleoside clearly indicate the presence of the $CF_3CONHCH_2$– group, with the NH moiety appearing as a broadened triplet. The signals at 157–158 ppm ($J_{C=O,F}$=36–38 Hz) and 115–117 ppm ($J_{C,F}$=287–289 Hz) in the ^{13}C NMR spectrum confirm the presence of the CF_3CO group in **15** and **16**. It should be mentioned that some of the ^1H NMR spectra of the obtained compounds are rather complicated due to the overlap of signals of the ribofuranose residue and the diastereotopic protons of $CH_2OCH_2CH_2O$ and $CH_2OCH_2CH_2CH_2O$ groups. The acetal group appeared as two doublets around 5 ppm. In spite of this most of the chemical shifts and coupling constants may be calculated directly from NMR spectra. In some cases comparison with the published spectra of disaccharide nucleosides and double resonance, ^1H–^{13}C correlation and COSY spectra were used for the assignment.

The silyl group was deblocked with TBAF to yield the partially protected nucleosides **18** and **19**, which were converted using standard procedures to the corresponding monomethoxytrityl derivatives **20** and **21**. The phosphitylation was carried out in dichloromethane using freshly distilled diisopropylethylamine and 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite under argon to afford **2** and **3** in high overall yields (Table 1). The choice for the monomethoxytrityl group was dictated by handling convenience during the chemical manipulations but required an increase in acidic deprotection time during oligonucleotide assembly (180 s TCA vs 60 for DMTr groups) without further consequences.

Table 1
Overall yields of phosphoramidites **1**,[9] **2**, and **3**

Starting compounds	Product	Overall yield (%)	Number of steps
Urd	**1a**	16.6	12
Urd	**1f**	8.3	13
2-Amino-Ado	**1c**	5.7	12
Ado	**1e**	12.1	11
4a+**5a**	**2a**	15.6	8
4a+**5b**	**3a**	18.9	8
4a+**12a**	**2a**	26.1	6
4a+**12b**	**3a**	28.1	6
4b+**12a**	**2b**	26.3	6
4b+**12b**	**3b**	26.7	6
4a+**17a**	**2a**	46.3	4
4a+**17b**	**3a**	49.7	4
4b+**17a**	**2b**	45.1	4
4b+**17b**	**3b**	48.5	4
4c+**17a**	**2c**	29.7	4
4c+**17b**	**3c**	28.0	4
4e+**17a**	**2d**	22.2	5
4e+**17b**	**3d**	24.3	5

Table 2
Molecular mass measurements of oligoribonucleotides containing 2′-*O*-aminoalkoxymethylribonucleosides

Starting synthon	Oligoribonucleotide	MS (M^+)		Yield OD_{260}
		Calcd	Found	
2a	5′-GACGUAAACGGCCACAAG*UU*-dT-3′	6859.1	6860.0	65.3
2a, **2b**	5′-GACG*U*AAACGGCCACAAG*UU*-dT-3′	7078.2	7079.0	73.8
2a, **2b**	5′-ACUUGUGGCCGUUUACG*UC*G-dT-3′	6782.9	6784.2	61.4
2a, **2b**	5′-AC*U*UGUGGCCGUUUACG*UC*G-dT-3′	6856.0	6857.3	55.7
2a, **2b**	5′-AC*U*UGUGGCCGUUUACG*UC*G-dT-3′	6929.0	6930.1	70.4
3a	5′-GACGUAAACGGCCACAAG*UU*-dT-3′	6887.1	6888.0	53.7
3a, **3b**	5′-GACG*U*AAACGGCCACAAG*UU*-dT-3′	7148.3	7149.7	69.1
3a, **3b**	5′-ACUUGUGGCCGUUUACG*UC*G-dT-3′	6811.0	6812.3	33.3
3a, **3b**	5′-AC*U*UGUGGCCGUUUACG*UC*G-dT-3′	6898.0	6899.5	33.7
3a, **3b**	5′-AC*U*UGUGGCCGUUUACG*UC*G-dT-3′	6985.1	6986.6	28.7

U: residue of 2′-*O*-aminoalkoxymethyluridine; *C*: residue of 2′-*O*-aminoalkoxymethylcytidine.

With these phosphoramidites (**2** and **3**), several oligoribonucleotides with one or more modifications were assembled, using commercial fast deprotecting tBDMSi amidites for the natural nucleosides. Trityl yields were excellent, even with multiple incorporations of the modified building blocks. For deprotection of the modified RNAs a 1:1 ammonia–methylamine cocktail in water was used, followed by a 1 M TBAF treatment. All oligos were purified by ion exchange chromatography, desalted by gel filtration, and analyzed by mass spectrometry (Table 2). Only the main part of the product-containing peak was collected, affording in general at least 25 up to 70 OD_{260} starting from a 1 μmol loaded support (see Table 2 for isolated yields). A figure with the crude profile for both sequences containing five modifications is shown as an example for the straightforward incorporation of the new congeners, with the peak for the full length sequence being strongly predominant (see Supplementary data). Incorporation of the purine phosphoramidites **2** and **3** proved straightforward as well and these results will be published elsewhere.

3. Conclusion

The general method for the preparation of 2′-*O*-β-D-ribofuranosylnucleosides and 2′-*O*-(ω-hydroxyalkoxymethyl)ribonucleosides was found to be applicable to the synthesis of

2′-*O*-(ω-aminoalkoxymethyl)ribonucleosides. The 2′-*O*-substituent was found to be stable during oligonucleotide synthesis. We have described efficient experimental procedures for synthesizing all four standard RNA nucleoside phosphoramidites, having amino-linkers at 2′-position. The synthetic routes are maximally convergent and provide sufficient amounts of phosphoramidites for several solid-phase synthesis coupling reactions. Using acyclic derivatives **17a**,**b** the overall yields of **2** and **3** were increased up to 50% for pyrimidine nucleosides and up to 30% for purine derivatives with substantial decrease of total reaction steps (Table 1). The resulting oligonucleotides are of particular interest for post-synthetic functionalization and conjugation. In addition, although not evaluated here, in general introduction of amine moieties at the 2′-*O*-position further increases the stability of duplexes with both DNA and RNA complementary sequences, as recently shown again by Engels et al.[25]

4. Experimental

4.1. General

Column chromatography (CC) was performed on silica gel Kieselgel 60 (0.063–0.200 mm, Merck). (0.040–0.063 mm), TLC was carried out on Kieselgel 260 F (Merck) with detection by UV and the following solvent systems (compositions expressed as v/v): methylene chloride–ethanol 95:5 (A); methylene chloride–ethanol 9:1 (B); hexane–acetone–triethylamine 49:49:2 (C), detection by UV light and iodine vapors. NMR spectra: Bruker AMX 400 NMR spectrometers and Bruker Avance 300 NMR spectrometers; at 300 K. Chemical shifts δ in parts per million were measured relative to the solvent signals (^{1}H and ^{13}C) and relative external reference=H_3PO_4 capil. (^{31}P). The coupling constants (J) are given in hertz. The signals were assigned using double resonance techniques, COSY and HSQC experiments. Mass spectrometry and exact mass measurements of the nucleoside intermediates were performed on a quadrupole/orthogonal-acceleration time-of-flight tandem mass spectrometer (Q-Tof-2, Micromass, Manchester, UK) equipped with a standard electrospray ionization (ESI) interface. ESI spectra for the modified ONs were obtained by coupling the Q-Tof-2 to a capillary HPLC (CapLC, Waters, Milford, MA). Masses were obtained by deconvolution of the spectra using the MaxEnt 1 algorithm (MassLynx 3.4, Micromass, Manchester, UK).

3′,5′-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)nucleosides (**4**) were prepared according to literature.[26]

4.2. 1-[3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]uracil (4a)

R_f 0.33 (A). ^{1}H NMR ($CDCl_3$): 8.52 (br s, 1H, NH), 7.66 (d, 1H, $J_{6,5}$=8.1, H-6), 5.72 (s, 1H, H-1′), 5.67 (dd, 1H, $J_{5,NH}$=1.8, H-5), 4.38 (dd, 1H, $J_{3',2'}$=4.7, $J_{3',4'}$=8.7, H-3′), 4.19 (dd, 1H, $J_{5'a,4'}$=2.2, $J_{5'a,5'b}$=−13.1, H-5′a), 4.17 (d, 1H, H-2′), 4.09 (ddd, 1H, $J_{4',5'b}$=2.8, H-4′), 4.01 (dd, 1H, H-5′b), 1.09–1.02 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 163.43 (C-4), 150.21 (C-2), 140.15 (C-6), 102.13 (C-5), 91.24 (C-1′), 82.14 (C-4′), 75.32 (C-2′), 69.26 (C-3′), 60.58 (C-5′), 17.58, 17.47, 17.40, 17.24, 17.15, 16.97, 13.54, 13.11, 12.72 (*i*Pr).

4.3. 1-[3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]-*N*^{4}-benzoylcytosine (4b)

R_f 0.34 (A). ^{1}H NMR ($CDCl_3$): 8.85 (br s, 1H, NH), 8.22 (d, 1H, $J_{6,5}$=7.5, H-6), 7.92–7.50 (m, 6H, Bz, H-5), 5.84 (s, 1H, H-1′), 4.35 (dd, 1H, $J_{3',2'}$=4.6, $J_{3',4'}$=8.9, H-3′), 4.28 (dd, 1H, $J_{5'a,4'}$=1.8, $J_{5'a,5'b}$=−13.4, H-5′a), 4.26 (d, 1H, H-2′), 4.21 (dd, 1H, $J_{4',5'b}$=2.8, H-4′), 4.01 (dd, 1H, H-5′b), 1.11–1.00 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 165.78 (C=O), 162.63 (C-4), 154.33 (C-2), 144.78 (C-6), 133.29, 129.13, 127.82 (Ph), 96.52 (C-5), 91.99 (C-1′), 82.25 (C-4′), 75.36 (C-2′), 68.89 (C-3′), 60.32 (C-5′), 17.57, 17.52, 17.42, 17.14, 16.97, 13.54, 13.09, 12.69 (*i*Pr).

4.4. 9-[3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]-*N*^{2}-isobutyrylguanine (4c)

R_f 0.29 (A). ^{1}H NMR ($CDCl_3$): 12.13 (br s, 1H, NH Guo), 9.41 (br s, 1H, NH*i*Bu), 7.92 (s, 1H, H-8), 5.84 (d, 1H, $J_{1',2'}$=1.2, H-1′), 4.52 (dd, 1H, $J_{3',2'}$=5.2, $J_{3',4'}$=7.6, H-3′), 4.31 (dd, 1H, H-2′), 4.14 (dd, 1H, $J_{5'a,4'}$=2.8, $J_{5'a,5'b}$=−12.4, H-5′a), 4.10 (ddd, 1H, $J_{4',5'b}$=2.5, H-4′), 4.05 (dd, 1H, H-5′b), 3.55 (br s, 1H, OH), 2.76 (sept, 1H, J=6.9, *i*Bu), 1.25 (m, 6H, *i*Bu), 1.08–0.98 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 179.06 (C=O), 155.76 (C6), 147.97 (C2), 147.74 (C4), 136.82 (C8), 121.72 (C5), 88.97 (C1′), 81.99 (C4′), 75.40 (C2′), 70.06 (C3′), 61.07 (C5′), 36.54 (*i*Bu), 19.15, 19.08 (*i*Bu) 17.55, 17.39, 17.20, 17.08, 16.97, 13.49, 13.11, 13.04, 12.69 (*i*Pr).

4.5. 9-[3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]-*N*^{6}-benzoyladenine (4d)

R_f 0.34 (A). ^{1}H NMR ($CDCl_3$): 9.07 (br s, 1H, NHBz), 8.15 (s, 1H, H-8), 8.74 (s, 1H, H-2), 8.03–7.51 (m, 5H, Bz), 6.03 (d, 1H, $J_{1',2'}$=1.2, H-1′), 5.10 (dd, 1H, $J_{3',2'}$=5.5, $J_{3',4'}$=7.7, H-3′), 4.63 (dd, 1H, H-2′), 4.14–4.05 (m, 3H, H-4′, H-5′a, H-5′b), 1.13–1.07 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 163.86 (C=O), 152.69 (C2), 151.18 (C6), 149.81 (C4), 142.12 (C8), 133.83, 132.91, 128.99, 128.04 (Ph), 123.85 (C5), 90.00 (C1′), 82.47 (C4′), 75.23 (C2′), 71.05 (C3′), 61.89 (C5′), 17.55, 17.49, 17.40, 17.24, 17.13, 13.43, 13.19, 12.93, 12.80 (*i*Pr).

4.6. 9-[3,5-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl]adenine (4e)

R_f 0.21 (A). ^{1}H NMR (DMSO-d_6): 8.21 (s, 1H, H-2), 8.08 (s, 1H, H-8), 7.33 (s, 2H, NH_2), 5.87 (s, 1H, H-1′), 5.62 (d, 1H, $J_{2'OH}$=4.6, OH-2′), 4.80 (dd, 1H, $J_{3',2'}$=4.9, $J_{3',4'}$=8.5, H-3′), 4.52 (dd, 1H, H-2′), 4.06 (dd, 1H, $J_{5'a,4'}$=3.1, $J_{5'a,5'b}$=−12.3, H-5′a), 3.99 (ddd, 1H, $J_{4',5'b}$=2.1, H-4′), 3.93 (dd, 1H, H-5′b), 1.12–0.92 (m, 28H, *i*Pr). ^{13}C NMR (DMSO-d_6): 156.09 (C6), 152.48 (C8), 148.62 (C4), 139.20 (C2), 119.25 (C5), 89.33 (C1′), 80.75 (C4′), 73.64 (C2′), 69.81 (C3′), 60.80 (C5′), 17.36, 17.16, 17.00, 16.91, 16.82, 12.73, 12.44, 12.23, 12.06 (*i*Pr).

4.7. Diacetate of 2-oxa-1,4-butanediol (5a)[27]

^{1}H NMR ($CDCl_3$): 5.25 (s, 2H, OCH_2O), 4.18 (t, 2H, J=4.8, OCH_2-CH_2OAc), 3.80 (t, 2H, OCH_2CH$_2$OAc), 2.06 (s, 3H, Ac), 2.04 (s, 3H, Ac). ^{13}C NMR ($CDCl_3$): 170.87, 170.46 (C=O), 89.16 (OCH_2O), 68.24 (OCH_2CH$_2$OAc), 63.25 (OCH$_2$CH_2OAc), 21.00, 20.86 (Me).

4.8. Diacetate of 2-oxa-1,5-pentanediol (5b)[27]

^{1}H NMR ($CDCl_3$): 5.17 (s, 2H, OCH_2O), 4.07 (t, 2H, J=6.4, OCH$_2$CH$_2$CH_2OAc), 3.63 (t, 2H, J=6.4, OCH_2CH$_2$CH$_2$OAc), 2.01 (s, 3H, Ac), 1.97 (s, 3H, Ac), 1.83 (p, 2H, OCH$_2$CH_2CH$_2$OAc). ^{13}C NMR ($CDCl_3$): 170.98, 170.56 (C=O), 89.26 (OCH_2O), 66.99 (OCH_2CH$_2$CH$_2$OAc), 61.28 (OCH$_2$CH$_2$CH_2OAc), 28.97 (OCH$_2$CH_2CH$_2$OAc), 21.01, 20.91 (Me).

4.9. 1-{2-*O*-[(2-Hydroxyethoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}-uracil (8a)

To a solution of nucleoside **6a** (275 mg, 0.46 mmol) in dry methanol (5 ml) 0.3 M sodium methylate (3 ml) was added and the solution was kept for 30 min at room temperature and then 1 M acetic acid in methanol was added to pH 7.0. The reaction mixture was concentrated in vacuo to near dryness and the residue was

partitioned between ethyl acetate (100 ml) and water (40 ml), the organic layer was washed with water (2×20 ml), dried over anhydrous sodium sulfate, evaporated to dryness, and purified by column chromatography on silica gel (30 g, dry application). The column was washed with methylene chloride (150 ml), methylene chloride–ethanol 99:1 (100 ml) and then eluted with methylene chloride–ethanol 98:2 to give **8a** as a powder. Yield 183 mg (71%). R_f 0.30 (A). ^{1}H NMR (DMSO-d_6): 11.41 (br s, 1H, NH), 7.66 (d, 1H, $J_{6,5}$=8.1, H-6), 5.59 (s, 1H, H-1′), 5.52 (d, 1H, H-5), 4.91 (d, 1H, J=−6.5, OC*H*HO), 4.83 (d, 1H, OCH*H*O), 4.61 (t, 1H, $J_{OH,H}$=5.4, OH), 4.31 (d, 1H, $J_{2',3'}$=4.9, H-2′), 4.25 (dd, 1H, $J_{3',4'}$=9.3, H-3′), 4.15 (d, 1H, $J_{5'a,5'b}$=−13.7, H-5′a), 3.98 (dd, 1H, $J_{4',5'b}$=2.0, H-4′), 3.91 (dd, 1H, H-5′b), 3.63–3.55 (m, 2H, OCH_2CH_2OH), 3.53–3.46 (m, 2H, OCH$_2$-CH_2OH), 1.05–0.99 (m, 28H, *i*Pr). ^{13}C NMR (DMSO-d_6): 163.35 (C4), 150.09 (C2), 139.49 (C6), 101.06 (C5), 93.80 (OCH_2O), 89.22 (C1′), 81.08 (C4′), 77.19 (C2′), 69.37 (OCH_2CH$_2$OH), 68.11 (C3′), 60.07 (OCH$_2$CH_2OH), 59.71 (C5′), 17.38, 17.28, 17.23, 17.15, 17.03, 16.91, 16.86, 12.70, 12.37, 12.02 (*i*Pr). LSI-MS ($C_{24}H_{44}N_2O_9Si_2$+H^+): 561.2655. Calcd 561.2664.

4.10. 1-{2-*O*-[(3-Hydroxypropoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}-uracil (9a)

Analogous deacylation of **7a** (1.02 g, 1.66 mmol) yielded **9a** as a powder (720 mg, 76%). R_f 0.30 (A). ^{1}H NMR ($CDCl_3$): 9.92 (br s, 1H, NH), 7.89 (d, 1H, $J_{6,5}$=8.1, H-6), 5.75 (s, 1H, H-1′), 5.68 (d, 1H, H-5), 5.01 (d, 1H, J=−6.7, OC*H*HO), 4.90 (d, 1H, OCH*H*O), 4.25 (d, 1H, $J_{5'a,5'b}$=−13.4, H-5′a), 4.21 (m, 2H, H-2′, H-3′), 4.13 (dd, 1H, $J_{4',3'}$=9.0, $J_{4',5'b}$=2.0, H-4′), 4.01 (m, 1H, OC*H*HCH$_2$CH$_2$OH), 3.97 (dd, 1H, H-5′b), 3.80–3.59 (m, 3H, OCH*H*CH$_2$C*H*$_2$OH), 1.90–1.82 (m, 2H, OCH$_2$C*H*$_2$CH$_2$OH), 1.10–0.95 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 163.55 (C4), 150.47 (C2), 139.28 (C6), 102.04 (C5), 94.89 (OCH_2O), 89.56 (C1′), 81.97 (C4′), 77.72 (C2′), 68.52 (C3′), 65.98 (OCH_2CH$_2$CH$_2$OH), 60.13 (OCH$_2$CH$_2$C*H*$_2$OH), 59.50 (C5′), 32.56 (OCH$_2$C*H*$_2$CH$_2$OAc), 17.58, 17.50, 17.41, 17.32, 17.22, 17.06, 16.93, 13.54, 13.22, 12.99, 12.71 (*i*Pr). LSI-MS ($C_{25}H_{46}N_2O_9Si_2$+H^+): 575.2811. Calcd 575.2820.

4.11. 1-{2-*O*-[(2-Azidoethoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}-uracil (10a)

4.11.1. Method A

To a solution of nucleoside **8a** (650 mg, 1.16 mmol) in 1,2-dichloroethane (15 ml) tosylchloride (550 mg, 2.90 mmol) and pyridine (5 ml) were added. The reaction mixture was maintained at room temperature for 16 h and methanol (1 ml) was added. The reaction mixture was stirred at room temperature for 30 min and concentrated in vacuo to near dryness. The residue was dissolved in methylene chloride (50 ml) and washed with 10% aqueous solution of sodium hydrogen carbonate (20 ml) and water (2×20 ml). The organic layer was dried over anhydrous sodium sulfate, evaporated in vacuo, and evaporated with toluene (2×10 ml). The residue was dissolved in dimethyl formamide (20 ml) and sodium azide (110 mg, 1.75 mmol) was added. The reaction mixture was heated under stirring at 80 °C for 2 h and, after cooling to room temperature, diluted with diethyl ether (50 ml) and washed with 10% aqueous solution of sodium bicarbonate (20 ml) and water (2×20 ml). The organic layer was dried over sodium sulfate, evaporated in vacuo, and purified by column chromatography on silica gel (30 g). The column was washed with methylene chloride (200 ml) and then eluted with methylene chloride–ethanol 99:1 to give **10a** as a foam. Yield 560 mg (82%). R_f 0.38 (A). ^{1}H NMR ($CDCl_3$): 9.07 (br s, 1H, NH), 7.87 (d, 1H, $J_{6,5}$=8.1, H-6), 5.75 (s, 1H, H-1′), 5.68 (d, 1H, H-5), 5.01 (d, 1H, J=−6.8, OC*H*HO), 4.99 (d, 1H, OCH*H*O), 4.25 (d, 1H, $J_{5'a,5'b}$=−13.7, H-5′a), 4.23 (dd, 1H, $J_{3',2'}$=4.4, $J_{3',4'}$=9.2, H-3′), 4.21 (d, 1H, H-2′), 4.13 (dd, 1H, $J_{4',5'b}$=2.2, H-4′), 3.99 (dd, 1H, H-5′b), 3.93–3.88 (m, 1H, OC*H*HCH$_2$N$_3$), 3.81–3.76 (m, 1H, OCH*H*CH$_2$N$_3$), 3.51–3.39 (m, 2H, OCH$_2$C*H*$_2$N$_3$), 1.11–1.02 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 163.37 (C4), 150.12 (C2), 139.34 (C6), 101.85 (C5), 94.73 (OCH_2O), 89.48 (C1′), 81.96 (C4′), 78.12 (C2′), 68.44 (C3′), 66.98 (OCH_2CH$_2$N$_3$), 59.54 (C5′), 50.91 (OCH$_2$CH_2N$_3$), 17.62, 17.52, 17.45, 17.32, 17.23, 17.10, 16.96, 13.60, 13.25, 13.05, 12.80 (*i*Pr). LSI-MS ($C_{24}H_{43}N_5O_8Si_2$+H^+): 586.2719. Calcd 586.2728.

4.11.2. Method B

To a solution of nucleoside **13a** (715 mg, 1.15 mmol) in dimethyl formamide (20 ml) sodium azide (112 mg, 1.73 mmol) was added. The reaction mixture was heated under stirring at 80 °C for 2 h and, after cooling to room temperature, diluted with diethyl ether (50 ml) and washed with 10% aqueous solution of sodium hydrogen carbonate (20 ml) and water (2×20 ml). The organic layer was dried over anhydrous sodium sulfate, evaporated in vacuo, and purified by column chromatography on silica gel (30 g). The column was washed with methylene chloride (200 ml) and then eluted with methylene chloride–ethanol 99:1 to give **10a** as a foam. Yield 640 mg (96%).

4.12. 1-{2-*O*-[(2-Azidoethoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}-N^4-benzoylcytosine (10b)

Analogous conversion of **13b** (625 mg, 0.86 mmol) yielded **10b** as a foam (560 mg, 94%). R_f 0.39 (A). ^{1}H NMR ($CDCl_3$): 8.75 (br s, 1H, NH), 8.33 (d, 1H, $J_{6,5}$=7.5, H-6), 7.92–7.48 (m, 6H, Bz, H-5), 5.83 (s, 1H, H-1′), 5.07 (d, 1H, J=−6.7, OC*H*HO), 5.04 (d, 1H, OCH*H*O), 4.29 (d, 1H, $J_{5'a,5'b}$=−13.7, H-5′a), 4.27 (d, 1H, $J_{2',3'}$=3.4, H-2′), 4.22 (dd, 1H, $J_{3',4'}$=9.6, H-3′), 4.21 (dd, 1H, $J_{4',5'b}$=1.6, H-4′), 4.03–3.97 (m, 2H, H-5′b, OC*H*HCH$_2$N$_3$), 3.83–3.77 (m, 1H, OCH*H*CH$_2$N$_3$), 3.56–3.50 (m, 1H, OCH$_2$C*H*HN$_3$), 3.45–3.39 (m, 1H, OCH$_2$CH*H*N$_3$), 1.12–0.99 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 167.09 (C=O), 162.46 (C4), 154.52 (C2), 144.45 (C6), 133.33, 129.18, 127.74 (Ph), 96.21 (C5), 94.81 (OCH_2O), 90.53 (C1′), 82.09 (C4′), 77.75 (C2′), 68.24 (C3′), 66.93 (OCH_2CH$_2$N$_3$), 59.55 (C5′), 51.00 (OCH$_2$CH_2N$_3$), 17.61, 17.55, 17.42, 17.21, 17.08, 16.98, 13.59, 13.25, 13.06, 12.82 (*i*Pr). LSI-MS ($C_{31}H_{48}N_6O_8Si_2$+H^+): 689.3136. Calcd 689.3150.

4.13. 1-{2-*O*-[(3-Azidopropoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}-uracil (11a)

4.13.1. Method A

Analogous conversion of **9a** (693 mg, 1.21 mmol) yielded **11a** as a foam (730 mg, 85%).

R_f 0.38 (A). ^{1}H NMR ($CDCl_3$): 8.96 (br s, 1H, NH), 7.88 (d, 1H, $J_{6,5}$=8.1, H-6), 5.75 (s, 1H, H-1′), 5.67 (d, 1H, H-5), 4.98 (d, 1H, J=−6.7, OC*H*HO), 4.94 (d, 1H, OCH*H*O), 4.26 (d, 1H, $J_{5'a,5'b}$=−13.6, H-5′a), 4.22 (dd, 1H, $J_{3',2'}$=4.4, $J_{3',4'}$=9.4, H-3′), 4.17 (d, 1H, H-2′), 4.13 (dd, 1H, $J_{4',5'b}$=2.2, H-4′), 3.98 (dd, 1H, H-5′b), 3.80–3.68 (m, 2H, OCH_2CH$_2$CH$_2$N$_3$), 3.40 (t, 2H, J=6.6, OCH$_2$CH$_2$CH_2N$_3$), 1.88 (m, 2H, OCH$_2$CH_2CH$_2$N$_3$), 1.11–1.02 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 163.39 (C4), 150.03 (C2), 139.45 (C6), 101.76 (C5), 94.74 (OCH_2O), 89.48 (C1′), 82.01 (C4′), 78.26 (C2′), 68.33 (C3′), 65.22 (OCH_2CH$_2$CH$_2$N$_3$), 59.57 (C5′), 48.71 (OCH$_2$CH$_2$CH_2N$_3$), 29.12 (OCH$_2$CH_2CH$_2$N$_3$), 17.62, 17.53, 17.45, 17.36, 17.24, 17.10, 16.96, 13.50, 13.27, 13.05, 12.80 (*i*Pr). LSI-MS ($C_{25}H_{45}N_5O_8Si_2$+H^+): 600.2880. Calcd 600.2885.

4.13.2. Method B

Analogous conversion of **14a** (892 mg, 1.40 mmol) yielded **11a** as a foam (812 mg, 97%).

4.14. 1-{2-*O*-[(3-Azidopropoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}-N^4-benzoylcytosine (11b)

Analogous conversion of **14b** (1.04 g, 1.41 mmol) yielded **11b** as a foam (920 mg, 93%). R_f 0.39 (A). ^{1}H NMR ($CDCl_3$): 8.75 (br s, 1H, NH), 8.35 (d, 1H, $J_{6,5}$=7.5, H-6), 7.91–7.45 (m, 6H, Bz, H-5), 5.85 (s, 1H, H-1′), 5.08 (d, 1H, J=−6.5, OC*H*HO), 4.99 (d, 1H, OCH*H*O), 4.31 (d, 1H, $J_{5'a,5'b}$=−13.4, H-5′a), 4.28–4.20 (m, 3H, H-2′, H-3′, H-4′), 4.02 (d, 1H, H-5′b), 3.87–3.81 (m, 1H, OC*H*HCH$_2$CH$_2$N$_3$), 3.77–3.71 (m, 1H, OCH*H*CH$_2$CH$_2$N$_3$), 3.42 (t, 2H, J=6.7, OCH$_2$CH$_2$C*H*$_2$N$_3$), 1.90 (m, 2H, OCH$_2$C*H*$_2$CH$_2$N$_3$), 1.13–0.99 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 167.25 (C=O), 162.94 (C4), 154.27 (C2), 144.69 (C6), 133.31, 128.98, 128.09 (Ph), 96.41 (C5), 94.67 (OCH$_2$O), 90.35 (C1′), 82.08 (C4′), 77.80 (C2′), 67.82 (C3′), 65.10 (OCH$_2$CH$_2$CH$_2$N$_3$), 59.46 (C5′), 48.68 (OCH$_2$CH$_2$CH$_2$N$_3$), 29.08 (OCH$_2$CH$_2$CH$_2$N$_3$), 17.61, 17.55, 17.42, 17.21, 17.09, 13.51, 13.20, 12.97, 12.65 (*i*Pr). LSI-MS ($C_{32}H_{50}N_6O_8Si_2$+H$^+$): 703.3295. Calcd 703.3307.

4.15. (2-Bromoethoxy)methyl acetate (12a)

The mixture of 2-bromoethanol (150 g, 1.20 mol) and paraformaldehyde (43 g, 1.43 mol) in methylene chloride (200 ml) was cooled in an ice bath under stirring. Anhydrous hydrogen chloride was bubbled through the mixture for 3 h. The reaction mixture was allowed up to room temperature and two clear homogeneous layers were separated. The organic layer was dried over anhydrous calcium chloride and concentrated on a rotary evaporator to liquid. The residue was distilled under diminished pressure (10–11 mmHg). The fraction with boiling temperature 82–87 °C was collected to give 1-bromo-2-(chloromethoxy)ethane. Yield 170 g (82%). ^{1}H NMR ($CDCl_3$): 5.51 (s, 2H, OC*H*$_2$Cl), 4.00 (t, 2H, J=6.1, OC*H*$_2$CH$_2$Br), 3.51 (t, 2H, OCH$_2$C*H*$_2$Br). ^{13}C NMR ($CDCl_3$): 82.38 (OCH$_2$Cl), 70.18 (OCH$_2$CH$_2$Br), 29.12 (OCH$_2$CH$_2$Br). The obtained 1-bromo-2-(chloromethoxy)ethane was dissolved in benzene (200 ml) and potassium acetate (180 g, 1.8 mol) was added. The mixture was stirred at 50 °C for 4 h. The precipitate was filtered off; the filtrate was concentrated on a rotary evaporator to liquid. The residue was dissolved in ethyl acetate (100 ml) and washed with 10% aqueous solution of sodium hydrogen carbonate (50 ml) and water (2×50 ml). The organic layer was dried over anhydrous sodium sulfate and concentrated on a rotary evaporator to liquid. The residue was distilled under diminished pressure (10–11 mmHg). The fraction with boiling temperature 112–117 °C was collected to give (2-bromoethoxy)methyl acetate (**12a**). Literature data:[28] 80–82 °C (5 mmHg). Yield 163 g (84% to 1-bromo-2-(chloromethoxy)ethane). Yield for two steps 69%. ^{1}H NMR ($CDCl_3$): 5.30 (s, 2H, OC*H*$_2$O), 3.95 (t, 2H, J=6.2, OC*H*$_2$CH$_2$Br), 3.47 (t, 2H, OCH$_2$C*H*$_2$Br), 2.10 (s, 3H, Ac). ^{13}C NMR ($CDCl_3$): 170.55 (C=O), 89.06 (OCH$_2$O), 70.47 (OCH$_2$CH$_2$Br), 30.02 (Me), 21.14 (OCH$_2$CH$_2$Br).

4.16. (3-Bromopropoxy)methyl acetate (12b)

Analogous conversion of 3-bromopropanol (52 g, 0.37 mol) yielded (3-bromopropoxy)methyl acetate (**12b**) as a liquid (59 g, 76%).

4.16.1. 1-Bromo-3-(chloromethoxy)propane

Bp 85–89 °C (10–11 mmHg). ^{1}H NMR ($CDCl_3$): 5.48 (s, 2H, OC*H*$_2$Cl), 3.82 (t, 2H, J=5.9, OC*H*$_2$CH$_2$CH$_2$Br), 3.47 (t, 2H, J=6.5, OCH$_2$CH$_2$C*H*$_2$Br), 2.15 (tt, 2H, OCH$_2$C*H*$_2$CH$_2$Br). ^{13}C NMR ($CDCl_3$): 83.01 (OCH$_2$Cl), 68.08 (OCH$_2$CH$_2$CH$_2$Br), 32.19 (OCH$_2$CH$_2$CH$_2$Br), 29.76 (OCH$_2$CH$_2$CH$_2$Br).

*4.16.2. (3-Bromopropoxy)methyl acetate (**12b**)*

Bp 118–122 °C (10–11 mmHg). ^{1}H NMR ($CDCl_3$): 5.23 (s, 2H, OC*H*$_2$O), 3.73 (t, 2H, J=5.8, OC*H*$_2$CH$_2$CH$_2$Br), 3.46 (t, 2H, J=6.4, OCH$_2$CH$_2$C*H*$_2$Br), 2.08 (tt, 2H, OCH$_2$C*H*$_2$CH$_2$Br), 2.06 (s, 3H, Ac). ^{13}C NMR ($CDCl_3$): 170.48 (C=O), 89.13 (OCH$_2$O), 67.65 (OCH$_2$CH$_2$CH$_2$Br), 32.64 (Me), 29.99 (OCH$_2$CH$_2$CH$_2$Br), 21.02 (OCH$_2$CH$_2$CH$_2$Br).

4.17. 1-{2-*O*-[(2-Bromoethoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}-uracil (13a)

To a cool solution (−15 °C) under nitrogen of nucleoside **4a** (973 mg, 2.0 mmol) and (2-bromoethoxy)methyl acetate (**12a**) (788 mg, 4.0 mmol) in 1,2-dichloroethane (20 ml) tin tetrachloride (0.36 ml, 3.0 mmol) was added and the solution was kept at −12 °C for 20 min. A 10% aqueous solution of sodium hydrogen carbonate (10 ml) and methylene chloride (20 ml) were added and the suspension was stirred at 0 °C for 20 min. The suspension was filtered through Hyflo Super Cel, organic layer was separated, washed with water (20 ml), dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was purified by column chromatography on silica gel (30 g). The column was washed with methylene chloride (200 ml) and methylene chloride–ethanol 99:1 (200 ml), and then eluted with methylene chloride–ethanol 98:2 to give **13a** as a foam. Yield 1.10 g (87%). R_f 0.36 (A). ^{1}H NMR ($CDCl_3$): 9.05 (br s, 1H, NH), 7.86 (d, 1H, $J_{6,5}$=8.3, H-6), 5.73 (s, 1H, H-1′), 5.66 (dd, 1H, $J_{5,NH}$=1.1, H-5), 5.02 (d, 1H, J=−6.8, OC*H*HO), 4.97 (d, 1H, OCH*H*O), 4.24 (d, 1H, $J_{5'a,5'b}$=−13.5, H-5′a), 4.21 (dd, 1H, $J_{3',2'}$=4.4, $J_{3',4'}$=9.2, H-3′), 4.19 (d, 1H, H-2′), 4.12 (dd, 1H, $J_{4',5'b}$=1.7, H-4′), 4.05–3.99 (m, 1H, OC*H*HCH$_2$Br), 3.97 (dd, 1H, H-5′b), 3.96–3.90 (m, 1H, OCH*H*CH$_2$Br), 3.52 (t, 2H, J=6.2, OCH$_2$C*H*$_2$Br), 1.15–0.87 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 163.57 (C4), 150.15 (C2), 139.35 (C6), 101.83 (C5), 94.63 (OCH$_2$O), 89.35 (C1′), 81.95 (C4′), 78.34 (C2′), 68.34 (C3′), 68.19 (OCH$_2$CH$_2$Br), 59.47 (C5′), 30.59 (OCH$_2$CH$_2$Br), 17.61, 17.51, 17.44, 17.33, 17.24, 17.07, 16.97, 13.53, 13.25, 13.02, 12.77 (*i*Pr). LSI-MS ($C_{24}H_{43}BrN_2O_8Si_2$+H$^+$): 623.1801. Calcd 623.1820.

4.18. 1-{2-*O*-[(2-Bromoethoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}-N^4-benzoylcytosine (13b)

Analogous (see preparation of **13a**) condensation of (2-bromoethoxy)methyl acetate (**12a**) (788 mg, 4.0 mmol) in the presence of tin tetrachloride (0.36 ml, 3.0 mmol) with nucleoside **4b** (1.18 g, 2.0 mmol) in 1,2-dichloroethane (20 ml) at −12 °C for 20 min gave **13b** as a foam. Yield 1.28 g (88%). R_f 0.36 (A). ^{1}H NMR ($CDCl_3$): 8.84 (br s, 1H, NH), 8.34 (d, 1H, $J_{6,5}$=7.5, H-6), 7.91–7.47 (m, 6H, Bz, H-5), 5.82 (s, 1H, H-1′), 5.12 (d, 1H, J=−6.8, OC*H*HO), 5.01 (d, 1H, OCH*H*O), 4.29 (d, 1H, $J_{5'a,5'b}$=−13.5, H-5′a), 4.27 (d, 1H, $J_{2',3'}$=2.8, H-2′), 4.20 (m, 2H, H-3′, H-4′), 4.12–4.06 (m, 1H, OC*H*HCH$_2$Br), 4.01 (dd, 1H, $J_{5'b,4'}$=1.8, H-5′b), 3.98–3.92 (m, 1H, OCH*H*CH$_2$Br), 3.55 (t, 2H, J=6.4, OCH$_2$C*H*$_2$Br), 1.11–0.98 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 166.89 (C=O), 162.49 (C4), 154.50 (C2), 144.43 (C6), 133.34, 129.18, 127.73 (Ph), 96.24 (C5), 94.74 (OCH$_2$O), 90.42 (C1′), 82.09 (C4′), 78.07 (C2′), 68.35 (C3′), 67.98 (OCH$_2$CH$_2$Br), 59.52 (C5′), 30.73 (OCH$_2$CH$_2$Br), 17.61, 17.43, 17.15, 17.00, 13.54, 13.04, 12.80 (*i*Pr). LSI-MS ($C_{31}H_{48}BrN_3O_8Si_2$+H$^+$): 726.2235. Calcd 726.2242.

4.19. 1-{2-*O*-[(3-Bromopropoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}-uracil (14a)

Analogous (see preparation of **13a**) condensation of (3-bromopropoxy)methyl acetate (**12b**) (844 mg, 4.0 mmol) in the presence of tin tetrachloride (0.36 ml, 3.0 mmol) with nucleoside **4a** (973 mg, 2.0 mmol) in 1,2-dichloroethane (20 ml) at −12 °C for 20 min gave **14a** as a foam. Yield 1.08 g (85%). R_f 0.36 (A). ^{1}H NMR ($CDCl_3$): 8.99 (br s, 1H, NH), 7.88 (d, 1H, $J_{6,5}$=8.1, H-6), 5.75 (s, 1H, H-1′), 5.67 (d, 1H, H-5), 4.98 (d, 1H, J=−6.7, OC*H*HO), 4.94 (d, 1H,

OCH*H*O), 4.25 (d, 1H, $J_{5'a,5'b}$=−13.3, H-5′a), 4.22 (dd, 1H, $J_{3',2'}$=4.2, $J_{3',4'}$=9.4, H-3′), 4.17 (d, 1H, H-2′), 4.14 (dd, 1H, $J_{4',5'b}$=2.2, H-4′), 3.98 (dd, 1H, H-5′b), 3.83–3.67 (m, 2H, OCH_2CH$_2$CH$_2$Br), 3.51 (t, 2H, J=6.5, OCH$_2$CH$_2$CH_2Br), 2.13 (p, 2H, OCH$_2$CH_2CH$_2$Br), 1.11–1.02 (m, 28H, *i*Pr). ^{13}C NMR (CDCl$_3$): 163.36 (C4), 150.25 (C2), 139.48 (C6), 101.78 (C5), 94.84 (OCH_2O), 89.54 (C1′), 82.01 (C4′), 78.37 (C2′), 68.35 (C3′), 66.13 (OCH_2CH$_2$CH$_2$Br), 59.61 (C5′), 32.90 (OCH$_2$CH$_2$CH_2Br), 30.56 (OCH$_2$CH_2CH$_2$Br), 17.63, 17.55, 17.45, 17.37, 17.27, 17.13, 16.99, 13.63, 13.35, 13.07, 12.84 (*i*Pr). LSI-MS ($C_{25}H_{45}BrN_2O_8Si_2$+H$^+$): 637.1963. Calcd 637.1976.

4.20. 1-{2-*O*-[(3-Bromopropoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}-*N*^{4}-benzoylcytosine (14b)

Analogous (see preparation of **13a**) condensation of (3-bromopropoxy)methyl acetate (**12b**) (844 mg, 4.0 mmol) in the presence of tin tetrachloride (0.36 ml, 3.0 mmol) with nucleoside **4b** (1.18 g, 2.0 mmol) in 1,2-dichloroethane (20 ml) at −12 °C for 20 min gave **14b** as a foam. Yield 1.28 g (86%). R_f 0.36 (A). ^{1}H NMR (CDCl$_3$): 8.73 (br s, 1H, NH), 8.34 (d, 1H, $J_{6,5}$=7.5, H-6), 7.91–7.41 (m, 6H, Bz, H-5), 5.84 (s, 1H, H-1′), 5.08 (d, 1H, J=−6.5, OC*H*HO), 4.98 (d, 1H, OCH*H*O), 4.31 (d, 1H, $J_{5'a,5'b}$=−13.4, H-5′a), 4.27–4.19 (m, 3H, H-2′, H-3′, H-4′), 4.02 (d, 1H, H-5′b), 3.89–3.86 (m, 2H, OCH_2CH$_2$CH$_2$Br), 3.52 (t, 2H, J=6.5, OCH$_2$CH$_2$CH_2Br), 2.16 (m, 2H, OCH$_2$CH_2CH$_2$Br), 1.13–0.99 (m, 28H, *i*Pr). ^{13}C NMR (CDCl$_3$): 166.97 (C═O), 162.53 (C4), 155.25 (C2), 144.44 (C6), 133.28, 129.18, 127.72 (Ph), 96.27 (C5), 94.93 (OCH_2O), 90.52 (C1′), 82.12 (C4′), 78.05 (C2′), 68.09 (C3′), 66.11 (OCH_2CH$_2$CH$_2$Br), 59.62 (C5′), 32.97 (OCH$_2$CH$_2$CH_2Br), 30.78 (OCH$_2$CH_2CH$_2$Br), 17.63, 17.44, 17.15, 17.00, 13.60, 13.29, 13.08 (*i*Pr). LSI-MS ($C_{32}H_{50}BrN_3O_8Si_2$+H$^+$): 740.2391. Calcd 740.2398.

4.21. 1-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}uracil (15a)

4.21.1. Method A

To a solution of nucleoside **10a** (585 mg, 1.0 mmol) in dioxane (40 ml) Pd–C (10%, 100 mg, 0.1 mmol), ethyl trifluoroacetate (1.2 ml, 10.0 mmol), and DBU (0.31 ml, 2.0 mmol) were added. The mixture was stirred in hydrogen current at atmospheric pressure for 5 h. The suspension was filtered through Hyflo Super Cel and the filtrate was concentrated in vacuo to near dryness. The residue was dissolved in methylene chloride (50 ml) and washed with 10% aqueous solution of sodium hydrogen carbonate (20 ml) and water (2×20 ml). The organic layer was dried over anhydrous sodium sulfate, evaporated in vacuo, and purified by column chromatography on silica gel (50 g). The column was washed with methylene chloride (200 ml) and methylene chloride–ethanol 99:1 (200 ml), and then eluted with methylene chloride–ethanol 98:2 to give **15a** as a foam. Yield 370 mg (56%). R_f 0.34 (A). ^{1}H NMR (CDCl$_3$): 9.47 (br s, 1H, NH), 7.94 (d, 1H, $J_{6,5}$=8.1, H-6), 7.73 (br s, 1H, NHCOCF$_3$), 5.71 (dd, 1H, $J_{5,NH}$=1.5, H-5), 5.69 (s, 1H, H-1′), 4.98 (d, 1H, J=−7.2, OC*H*HO), 4.94 (d, 1H, OCH*H*O), 4.27 (d, 1H, $J_{5'a,5'b}$=−13.7, H-5′a), 4.20 (m, 2H, H-2′, H-3′), 4.13 (dd, 1H, $J_{4',3'}$=9.0, $J_{4',5'b}$=2.2, H-4′), 4.03–3.98 (m, 1H, OC*H*HCH$_2$NHCOCF$_3$), 3.97 (dd, 1H, H-5′b), 3.73–3.66 (m, 2H, OCH*HCH*HNHCOCF$_3$), 3.57–3.52 (m, 1H, OCH$_2$CH*H*NHCOCF$_3$), 1.10–0.92 (m, 28H, *i*Pr). ^{13}C NMR (CDCl$_3$): 163.20 (C4), 157.23 (q, J=36.6, *C*OCF$_3$), 150.64 (C2), 139.23 (C6), 116.72 (q, J=287.3, *C*F$_3$), 102.17 (C5), 95.33 (OCH_2O), 89.60 (C1′), 82.02 (C4′), 78.47 (C2′), 68.37 (C3′), 66.55 (OCH_2CH$_2$NHCOCF$_3$), 59.45 (C5′), 40.28 (OCH$_2$CH_2NHCOCF$_3$), 17.61, 17.52, 17.43, 17.34, 17.22, 17.08, 16.92, 13.59, 13.27, 13.04, 12.78 (*i*Pr). LSI-MS ($C_{26}H_{44}F_3N_3O_9Si_2$+H$^+$): 656.2637. Calcd 656.2646.

4.21.2. Method B

Analogous (see preparation of **13a**) condensation of (2-(2,2,2-trifluoroacetamido)ethoxy)methyl acetate (**17a**) (920 mg, 4.0 mmol) in the presence of tin tetrachloride (0.36 ml, 3 mmol) with nucleoside **4a** (973 mg, 2.0 mmol) in 1,2-dichloroethane (20 ml) at −12 °C for 20 min gave **15a** as a foam. Yield 1.09 g (83%).

4.22. 1-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}-*N*^{4}-benzoylcytosine (15b)

4.22.1. Method A

Analogous (see preparation of **15a**) reduction of **10b** (827 mg, 1.2 mmol) yielded **15b** as a foam (550 mg, 60%). R_f 0.35 (A). ^{1}H NMR (CDCl$_3$): 8.84 (br s, 1H, NH), 8.38 (d, 1H, $J_{6,5}$=7.5, H-6), 8.07 (br s, 1H, NHCOCF$_3$), 7.92–7.50 (m, 6H, Bz, H-5), 5.78 (s, 1H, H-1′), 5.05 (d, 1H, J=−6.7, OC*H*HO), 4.94 (d, 1H, OCH*H*O), 4.32 (d, 1H, $J_{2',3'}$=2.8, H-2′), 4.30 (d, 1H, $J_{5'a,5'b}$=−13.4, H-5′a), 4.22 (dd, 1H, $J_{3',4'}$=9.7, H-3′), 4.20 (dd, 1H, $J_{4',5'b}$=1.6, H-4′), 4.13–4.07 (m, 1H, OC*H*HCH$_2$NHCOCF$_3$), 4.02 (dd, 1H, H-5′b), 3.82–3.73 (m, 1H, OCH*H*CH$_2$NHCOCF$_3$), 3.72–3.67 (m, 1H, OCH$_2$C*H*HNHCOCF$_3$), 3.55–3.50 (m, 1H, OCH$_2$CH*H*NHCOCF$_3$), 1.12–0.98 (m, 28H, *i*Pr). ^{13}C NMR (CDCl$_3$): 168.45 (C═O), 162.72 (C4), 158.00 (q, J=36.5, *C*OCF$_3$), 151.92 (C2), 144.50 (C6), 133.44, 133.13, 127.77 (Ph), 116.82 (q, J=287.6, *C*F$_3$), 96.69 (C5), 95.22 (OCH_2O), 90.71 (C1′), 82.16 (C4′), 77.39 (C2′), 68.40 (C3′), 66.41 (OCH_2CH$_2$NHCOCF$_3$), 59.50 (C5′), 40.37 (OCH$_2$CH_2NHCOCF$_3$), 17.61, 17.56, 17.43, 17.18, 17.05, 16.94, 13.56, 13.26, 13.07, 12.79 (*i*Pr). LSI-MS ($C_{33}H_{49}F_3N_4O_9Si_2$+H$^+$): 759.3025. Calcd 759.3068.

4.22.2. Method B

Analogous (see preparation of **13a**) condensation of (2-(2,2,2-trifluoroacetamido)ethoxy)methyl acetate (**17a**) (920 mg, 4.0 mmol) in the presence of tin tetrachloride (0.36 ml, 3.0 mmol) with nucleoside **4b** (1.18 g, 2.0 mmol) in 1,2-dichloroethane (20 ml) at −12 °C for 20 min gave **15b** as a foam. Yield 1.29 g (85%).

4.23. 9-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}-*N*^{2}-isobutyrylguanine (15c)

To a cool solution (−15 °C) under nitrogen of nucleoside **4c** (596 mg, 1.0 mmol) and (2-(2,2,2-trifluoroacetamido)ethoxy)methyl acetate (**17a**) (460 mg, 2.0 mmol) in 1,2-dichloroethane (20 ml) tin tetrachloride (0.24 ml, 2.0 mmol) was added and the solution was kept at −12 °C for 40 min. A 10% aqueous solution of sodium hydrogen carbonate (10 ml) and methylene chloride (20 ml) were added and the suspension was stirred at 0 °C for 20 min. The suspension was filtered through Hyflo Super Cel, organic layer was separated, washed with water (20 ml), dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was purified by column chromatography on silica gel (30 g). The column was washed with methylene chloride (200 ml) and methylene chloride–ethanol 99:1 (200 ml), and then eluted with methylene chloride–ethanol 98:2 to give **15c** as a foam. Yield 367 mg (48%). R_f 0.30 (A). ^{1}H NMR (CDCl$_3$): 12.09 (br s, 1H, NH Guo), 10.11 (br s, 1H, NH*i*Bu), 8.32 (br t, 1H, NHCOCF$_3$), 8.07 (s, 1H, H-8), 5.91 (s, 1H, H-1′), 5.00 (d, 1H, J=−7.2, OC*H*HO), 4.91 (d, 1H, OCH*H*O), 4.53 (dd, 1H, $J_{3',2'}$=4.1, $J_{3',4'}$=9.6, H-3′), 4.26 (d, 1H, $J_{5'a,5'b}$=−13.7, H-5′a), 4.17 (d, 1H, H-2′), 4.13 (dd, 1H, $J_{4',5'b}$=2.3, H-4′), 4.02 (dd, 1H, H-5′b), 3.94 (m, 1H, OC*H*HCH$_2$NHCOCF$_3$), 3.81–3.64 (m, 3H, OCH*HCH*$_2$NHCOCF$_3$), 2.81 (sept, 1H, J=6.9, *i*Bu), 1.25 (m, 6H, *i*Bu), 1.10–0.95 (m, 28H, *i*Pr). ^{13}C NMR (CDCl$_3$): 180.21 (C═O), 157.51 (q, J=36.8, *C*OCF$_3$), 156.00 (C6), 148.54 (C2), 147.71 (C4), 136.46 (C8), 121.65 (C5), 116.02 (q, J=285.7, *C*F$_3$), 95.96 (OCH_2O), 87.92 (C1′), 81.52 (C4′), 80.44 (C2′), 69.03 (C3′), 66.87 (OCH_2CH$_2$NHCOCF$_3$), 59.77 (C5′), 40.21 (OCH$_2$CH_2NHCOCF$_3$), 36.04 (*i*Bu), 19.15, 19.00 (*i*Bu) 17.61, 17.43, 17.32, 17.13, 17.10, 13.54, 13.04,

12.77 (*i*Pr). LSI-MS ($C_{31}H_{51}F_3N_6O_9Si_2+H^+$): 765.3249. Calcd 765.3281.

4.24. 9-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}adenine (15e)

Analogous (see preparation of **15c**) condensation of (2-(2,2,2-trifluoroacetamido)ethoxy)methyl acetate (**17a**) (460 mg, 2.0 mmol) in the presence of tin tetrachloride (0.22 ml, 1.8 mmol) with nucleoside **4e** (510 mg, 1.0 mmol) in 1,2-dichloroethane (15 ml) at −12 °C for 40 min gave **15e** as a foam. Yield 380 mg (56%). R_f 0.23 (A). ^{1}H NMR ($CDCl_3$): 8.28 (s, 1H, H-8), 8.20 (s, 1H, H-2), 8.10 (br t, 1H, $NHCOCF_3$), 6.07 (s, 1H, H-1′), 5.86 (s, 2H, NH_2), 5.02 (d, 1H, J=−7.1, OC*H*HO), 4.98 (d, 1H, OCH*H*O), 4.59 (dd, 1H, $J_{3',2'}$=4.4, $J_{3',4'}$=9.5, H-3′), 4.38 (d, 1H, H-2′), 4.29 (d, 1H, $J_{5'a,5'b}$=−13.5, H-5′a), 4.16 (dd, 1H, $J_{4',5'b}$=1.9, H-4′), 4.02 (dd, 1H, H-5′b), 3.96–3.89 (m, 1H, OC*H*HCH$_2$NHCOCF$_3$), 3.85–3.78 (m, 1H, OCH*H*CH$_2$NHCOCF$_3$), 3.74–3.65 (m, 1H, OCH$_2$C*H*HNHCOCF$_3$), 3.62–3.56 (m, 1H, OCH$_2$CH*H*NHCOCF$_3$), 1.11–0.95 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 157.65 (q, J=36.8, *C*OCF$_3$), 155.70 (C6), 153.02 (C8), 148.82 (C4), 138.38 (C2), 120.42 (C5), 116.04 (q, J=286.5, *C*F$_3$), 95.94 (OCH$_2$O), 88.75 (C1′), 81.82 (C4′), 79.57 (C2′), 68.69 (C3′), 68.06 (OCH$_2$CH$_2$NHCOCF$_3$), 59.69 (C5′), 40.30 (OCH$_2$*C*H$_2$NHCOCF$_3$), 17.57, 17.52, 17.41, 17.25, 17.11, 17.08, 13.52, 13.05, 12.72 (*i*Pr). LSI-MS ($C_{27}H_{45}F_3N_6O_7Si_2+H^+$): 679.2906. Calcd 679.2913.

4.25. 1-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}uracil (16a)

4.25.1. Method A

Analogous (see preparation of **15a**) reduction of **11a** (675 mg, 1.13 mmol) yielded **16a** as a foam (430 mg, 57%). R_f 0.34 (A). ^{1}H NMR ($CDCl_3$): 9.29 (br s, 1H, NH), 7.91 (d, 1H, $J_{6,5}$=8.1, H-6), 7.71 (br s, 1H, $NHCOCF_3$), 5.72 (s, 1H, H-1′), 5.68 (d, 1H, H-5), 4.99 (d, 1H, J=−6.9, OC*H*HO), 4.87 (d, 1H, OCH*H*O), 4.25 (d, 1H, $J_{5'a,5'b}$=−13.5, H-5′a), 4.22 (dd, 1H, $J_{3',2'}$=4.1, $J_{3',4'}$=9.5, H-3′), 4.17 (d, 1H, H-2′), 4.14 (dd, 1H, $J_{4',5'b}$=2.0, H-4′), 3.98 (dd, 1H, H-5′b), 3.97–3.92 (m, 1H, OC*H*HCH$_2$CH$_2$NHCOCF$_3$), 3.62–3.57 (m, 1H, OCH*H*CH$_2$CH$_2$NHCOCF$_3$), 3.57–3.50 (m, 1H, OCH$_2$CH$_2$C*H*HNHCOCF$_3$), 3.46–3.39 (m, 1H, OCH$_2$CH$_2$CH*H*NHCOCF$_3$), 1.94–1.87 (m, 2H, OCH$_2$C*H*$_2$CH$_2$NHCOCF$_3$), 1.10–1.00 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 163.39 (C4), 157.43 (q, J=36.7, *C*OCF$_3$), 150.55 (C2), 139.22 (C6), 116.24 (q, J=287.5, *C*F$_3$), 102.07 (C5), 95.19 (OCH$_2$O), 89.59 (C1′), 82.01 (C4′), 78.21 (C2′), 68.64 (C3′), 66.59 (OCH$_2$CH$_2$CH$_2$NHCOCF$_3$), 59.49 (C5′), 38.01 (OCH$_2$CH$_2$*C*H$_2$NHCOCF$_3$), 28.49 (OCH$_2$*C*H$_2$CH$_2$NHCOCF$_3$), 17.61, 17.52, 17.43, 17.34, 17.22, 17.08, 16.92, 13.59, 13.27, 13.04, 12.78 (*i*Pr). LSI-MS ($C_{27}H_{46}F_3N_3O_9Si_2+H^+$): 670.2792. Calcd 670.2803.

4.25.2. Method B

Analogous (see preparation of **13a**) condensation of (3-(2,2,2-trifluoroacetamido)propoxy)methyl acetate (**17b**) (980 mg, 4.0 mmol) in the presence of tin tetrachloride (0.36 ml, 3.0 mmol) with nucleoside **4a** (973 mg, 2.0 mmol) in 1,2-dichloroethane (20 ml) at −12 °C for 20 min gave **16a** as a foam. Yield 1.12 g (83%).

4.26. 1-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}-*N*^{4}-benzoylcytosine (16b)

4.26.1. Method A

Analogous (see preparation of **15a**) reduction of **11b** (1.34 g, 1.9 mmol) yielded **16b** as a foam (830 mg, 58%). R_f 0.35 (A). ^{1}H NMR ($CDCl_3$): 8.78 (br s, 1H, NH), 8.62 (br s, 1H, $NHCOCF_3$), 8.38 (d, 1H, $J_{6,5}$=7.5, H-6), 7.91–7.49 (m, 6H, Bz, H-5), 5.80 (s, 1H, H-1′), 5.07 (d, 1H, J=−7.0, OC*H*HO), 4.84 (d, 1H, OCH*H*O), 4.32 (d, 1H, $J_{2',3'}$=2.2, H-2′), 4.31 (d, 1H, $J_{5'a,5'b}$=−13.2, H-5′a), 4.22 (dd, 1H, $J_{3',4'}$=10.1, H-3′), 4.20 (d, 1H, H-4′), 4.14–4.09 (m, 1H, OC*H*HCH$_2$CH$_2$NHCOCF$_3$), 4.02 (d, 1H, H-5′b), 3.63–3.55 (m, 1H, OCH*H*CH$_2$CH$_2$NHCOCF$_3$), 3.51–3.39 (m, 2H, OCH$_2$CH$_2$C*H*$_2$NHCOCF$_3$), 1.98–1.93 (m, 2H, OCH$_2$C*H*$_2$CH$_2$COCF$_3$), 1.12–0.98 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 168.93 (C=O), 162.89 (C4), 157.52 (q, J=36.4, *C*OCF$_3$), 150.03 (C2), 144.49 (C6), 133.41, 129.22, 127.70 (Ph), 116.48 (q, J=287.3, *C*F$_3$), 96.70 (C5), 95.37 (OCH$_2$O), 90.71 (C1′), 82.12 (C4′), 77.36 (C2′), 68.66 (C3′), 66.11 (OCH$_2$CH$_2$CH$_2$NHCOCF$_3$), 59.55 (C5′), 37.63 (OCH$_2$CH$_2$*C*H$_2$NHCOCF$_3$), 28.49 (OCH$_2$CH$_2$CH$_2$NHCOCF$_3$), 17.61, 17.42, 17.22, 17.09, 16.98, 13.62, 13.26, 13.07, 12.84 (*i*Pr). LSI-MS ($C_{34}H_{51}F_3N_4O_9Si_2+H^+$): 773.3186. Calcd 773.3225.

4.26.2. Method B

Analogous (see preparation of **13a**) condensation of (3-(2,2,2-trifluoroacetamido)propoxy)methyl acetate (**17b**) (1.46 g, 6.0 mmol) in the presence of tin tetrachloride (0.54 ml, 4.5 mmol) with nucleoside **4b** (1.77 g, 3.0 mmol) in 1,2-dichloroethane (30 ml) at −12 °C for 20 min gave **16b** as a foam. Yield 2.01 g (86%).

4.27. 9-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}-*N*^{2}-isobutyrylguanine (16c)

Analogous (see preparation of **15c**) condensation of (3-(2,2,2-trifluoroacetamido)propoxy)methyl acetate (**17b**) (490 mg, 2.0 mmol) in the presence of tin tetrachloride (0.24 ml, 2.0 mmol) with nucleoside **4c** (596 mg, 1.0 mmol) in 1,2-dichloroethane (15 ml) at −12 °C for 40 min gave unseparatable mixture of **16c** and starting **4c** as a foam in a ratio of 9:1. Yield 375 mg. R_f 0.29 (A). ^{1}H NMR ($CDCl_3$): 12.20 (br s, 1H, NH Guo), 9.37 (br s, 1H, NH*i*Bu), 8.01 (s, 1H, H-8), 7.43 (br t, 1H, $NHCOCF_3$), 5.89 (s, 1H, H-1′), 4.99 (d, 1H, J=−6.9, OC*H*HO), 4.89 (d, 1H, OCH*H*O), 4.53 (dd, 1H, $J_{3',2'}$=4.4, $J_{3',4'}$=9.3, H-3′), 4.23 (d, 1H, $J_{5'a,5'b}$=−13.5, H-5′a), 4.17 (d, 1H, H-2′), 4.10 (dd, 1H, $J_{4',5'b}$=2.5, H-4′), 4.01 (dd, 1H, H-5′b), 3.73 (m, 2H, OC*H*$_2$CH$_2$CH$_2$NHCOCF$_3$), 3.56 (m, 2H, OCH$_2$CH$_2$C*H*$_2$NHCOCF$_3$), 2.73 (sept, 1H, J=6.7, *i*Bu), 1.91 (m, 2H, OCH$_2$C*H*$_2$CH$_2$NHCOCF$_3$), 1.24 (m, 6H, *i*Bu), 1.11–0.98 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 179.84 (C=O), 158.06 (q, J=36.7, *C*OCF$_3$), 155.92 (C6), 148.34 (C2), 147.63 (C4), 136.49 (C8), 121.61 (C5), 116.11 (q, J=286.1, *C*F$_3$), 95.30 (OCH$_2$O), 87.78 (C1′), 81.56 (C4′), 80.14 (C2′), 69.00 (C3′), 66.69 (OCH$_2$CH$_2$CH$_2$NHCOCF$_3$), 59.77 (C5′), 38.12 (OCH$_2$CH$_2$*C*H$_2$NHCOCF$_3$), 36.18 (*i*Bu), 29.83 (CH$_2$*C*H$_2$CH$_2$), 19.05, 19.08 (*i*Bu), 17.60, 17.45, 17.31, 17.11, 17.08, 13.53, 13.13, 13.04, 12.72 (*i*Pr). LSI-MS ($C_{32}H_{53}F_3N_6O_9Si_2+H^+$): 779.3426. Calcd 779.3437.

4.28. 9-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}adenine (16e)

Analogous (see preparation of **15c**) condensation of (3-(2,2,2-trifluoroacetamido)propoxy)methyl acetate (**17b**) (490 mg, 2.0 mmol) in the presence of tin tetrachloride (0.22 ml, 1.8 mmol) with nucleoside **4e** (510 mg, 1.0 mmol) in 1,2-dichloroethane (15 ml) at −12 °C for 40 min gave **16e** as a foam. Yield 374 mg (54%). R_f 0.23 (A). ^{1}H NMR ($CDCl_3$): 8.24 (s, 1H, H-8), 8.20 (s, 1H, H-2), 7.77 (br t, 1H, $NHCOCF_3$), 6.04 (s, 1H, H-1′), 5.92 (s, 2H, NH_2), 5.02 (d, 1H, J=−7.0, OC*H*HO), 4.93 (d, 1H, OCH*H*O), 4.61 (dd, 1H, $J_{3',2'}$=4.4, $J_{3',4'}$=9.0, H-3′), 4.41 (d, 1H, H-2′), 4.28 (d, 1H, $J_{5'a,5'b}$=−13.4, H-5′a), 4.16 (dd, 1H, $J_{4',5'b}$=2.5, H-4′), 4.02 (dd, 1H, H-5′b), 3.95 (m, 1H, OC*H*HCH$_2$CH$_2$NHCOCF$_3$), 3.65 (m, 1H, OCH*H*CH$_2$CH$_2$NHCOCF$_3$), 3.60–3.43 (m, 2H, OCH$_2$CH$_2$C*H*$_2$NHCOCF$_3$), 2.08–1.82 (m, 2H, OCH$_2$C*H*$_2$CH$_2$NHCOCF$_3$), 1.15–0.86 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 157.51 (q, J=36.9, *C*OCF$_3$), 155.79 (C6), 152.96 (C8), 148.97 (C4), 138.59 (C2), 120.54 (C5), 115.86 (q, J=286.1, *C*F$_3$), 95.36 (OCH$_2$O), 88.78 (C1′), 81.68 (C4′), 78.93 (C2′), 69.28 (C3′), 66.67 (OCH$_2$CH$_2$CH$_2$NHCOCF$_3$), 59.97 (C5′), 38.33 (OCH$_2$CH$_2$*C*H$_2$NHCOCF$_3$),

28.02 ($OCH_2CH_2CH_2NHCOCF_3$), 17.59, 17.49, 17.43, 17.34, 17.24, 17.08, 16.92, 13.59, 13.27, 13.08, 12.88 (*i*Pr). LSI-MS ($C_{28}H_{47}F_3N_6O_7Si_2+H^+$): 693.3089. Calcd 693.3069.

4.29. 9-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}-N^6-benzoyladenine (15d)

Nucleoside **15e** (1.83 g, 2.70 mmol) was dried by evaporation of pyridine (2×30 ml) and suspended in dry pyridine (50 ml). Benzoyl chloride (1.4 ml, 12.0 mmol) was added and the reaction was maintained at room temperature for 2 h. The mixture was then cooled in an ice bath and water (3 ml) was added. After 5 min 25% aqueous ammonia (10 ml) was added and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo to near dryness. The residue was dissolved in methylene chloride (50 ml), and washed with 10% aqueous solution of sodium hydrogen carbonate (20 ml) and water (2×20 ml). The organic layer was dried over anhydrous sodium sulfate, evaporated in vacuo, evaporated with toluene (2×10 ml), and purified by column chromatography on silica gel (50 g). The column was washed with methylene chloride (200 ml) and methylene chloride–ethanol 99:1 (200 ml), and then eluted with methylene chloride–ethanol 98:2 to give **15d** as a foam. Yield 1.53 g (73%). R_f 0.34 (A). ^{1}H NMR ($CDCl_3$): 9.06 (br s, 1H, NHBz), 8.77 (s, 1H, H-8), 8.38 (s, 1H, H-2), 8.04–7.51 (m, 6H, Bz, $NHCOCF_3$), 6.14 (s, 1H, H-1′), 5.08 (d, 1H, J=−7.1, OC*H*HO), 5.00 (d, 1H, OCH*H*O), 4.64 (dd, 1H, $J_{3',2'}$=4.4, $J_{3',4'}$=9.4, H-3′), 4.46 (d, 1H, H-2′), 4.30 (d, 1H, $J_{5'a,5'b}$=−13.5, H-5′a), 4.19 (dd, 1H, $J_{4',5'b}$=1.5, H-4′), 4.04 (dd, 1H, H-5′b), 3.98–3.90 (m, 1H, OC*H*$HCH_2NHCOCF_3$), 3.85–3.77 (m, 1H, OCH*H*$CH_2NHCOCF_3$), 3.65–3.60 (m, 2H, $OCH_2CH_2NHCOCF_3$), 1.12–0.99 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 164.74 (C=O), 157.50 (q, J=36.7, $COCF_3$), 152.79 (C8), 150.85 (C6), 149.78 (C4), 140.95 (C2), 133.80, 132.98, 128.96, 127.85 (Ph), 123.95 (C5), 116.00 (q, J=285.8, CF_3), 95.83 (OCH_2O), 88.90 (C1′), 81.81 (C4′), 79.48 (C2′), 68.77 (C3′), 67.79 ($OCH_2CH_2NHCOCF_3$), 59.67 (C5′), 40.18 ($OCH_2CH_2NHCOCF_3$), 17.58, 17.52, 17.43, 17.28, 17.13, 17.08, 13.54, 13.05, 12.75 (*i*Pr). LSI-MS ($C_{34}H_{49}F_3N_6O_8Si_2+H^+$): 783.3153. Calcd 783.3175.

4.30. 9-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranosyl}-N^6-benzoyladenine (16d)

Analogous benzoylation of **16e** (1.12 g, 1.62 mmol) yielded **16d** as a foam (965 mg, 76%). R_f 0.34 (A). ^{1}H NMR ($CDCl_3$): 9.17 (br s, 1H, NHBz), 8.74 (s, 1H, H-8), 8.40 (s, 1H, H-2), 8.04–7.51 (m, 5H, Bz), 7.40 (br t, 1H, $NHCOCF_3$), 6.13 (s, 1H, H-1′), 5.04 (d, 1H, J=−6.9, OC*H*HO), 4.98 (d, 1H, OCH*H*O), 4.65 (dd, 1H, $J_{3',2'}$=4.4, $J_{3',4'}$=9.3, H-3′), 4.46 (d, 1H, H-2′), 4.29 (d, 1H, $J_{5'a,5'b}$=−13.4, H-5′a), 4.20 (dd, 1H, $J_{4',5'b}$=2.5, H-4′), 4.05 (dd, 1H, H-5′b), 3.97 (m, 1H, OC*H*$HCH_2CH_2NHCOCF_3$), 3.70 (m, 1H, OCH*H*$CH_2CH_2NHCOCF_3$), 3.59–3.41 (m, 2H, $OCH_2CH_2CH_2NHCOCF_3$), 1.95–1.89 (m, 2H, $OCH_2CH_2CH_2NHCOCF_3$), 1.11–0.99 (m, 28H, *i*Pr). ^{13}C NMR ($CDCl_3$): 164.65 (C=O), 157.41 (q, J=36.8, $COCF_3$), 152.67 (C8), 150.74 (C6), 149.63 (C4), 141.12 (C2), 133.80, 132.91, 128.97, 128.03 (Ph), 123.91 (C5), 115.92 (q, J=285.9, CF_3), 95.27 (OCH_2O), 88.97 (C1′), 81.87 (C4′), 78.64 (C2′), 69.27 (C3′), 67.04 ($OCH_2CH_2CH_2NHCOCF_3$), 59.91 (C5′), 38.53 ($OCH_2CH_2CH_2NHCOCF_3$), 28.21 ($OCH_2CH_2CH_2NHCOCF_3$), 17.58, 17.49, 17.43, 17.34, 17.24, 17.08, 13.55, 13.27, 13.08, 12.85 (*i*Pr). LSI-MS ($C_{35}H_{51}F_3N_6O_8Si_2+H^+$): 797.3375. Calcd 797.3332.

4.31. [2-(2,2,2-Trifluoroacetamido)ethoxy]methyl acetate (17a)

2-Amino-1-ethanol (8.5 ml, 0.14 mol) was added to ethyl trifluoroacetate (22.3 ml, 0.19 mol) at 0 °C under stirring. The reaction mixture was warmed to room temperature, stirred for 2 h, and evaporated in vacuo to oil, which crystallized on standing. Yield 21.0 g (100%), mp: 32–33 °C (lit. mp: 32–35 °C). ^{1}H NMR ($CDCl_3$): 7.01 (br s, 1H, NH), 3.78 (t, 2H, J=5.1, $HOCH_2CH_2NHCOCF_3$), 3.52 (dt, 2H, J_{CHNH}=5.6, $OCH_2CH_2NHCOCF_3$), 2.33 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$): 158.08 (q, J=36.9, $COCF_3$), 116.03 (q, J=287.2, CF_3), 60.73 ($OCH_2CH_2NHCOCF_3$), 42.25 ($OCH_2CH_2NHCOCF_3$).

The obtained *N*-(2-hydroxyethyl)-2,2,2-trifluoroacetamide (21.0 g, 0.14 mol) and paraformaldehyde (4.8 g, 0.16 mol) in methylene chloride (50 ml) were cooled in an ice bath under stirring. Anhydrous hydrogen chloride was bubbled through the mixture for 3 h. The reaction mixture was allowed up to room temperature and two clear homogeneous layers were separated. The organic layer was degassed, dried over anhydrous calcium chloride, and concentrated on a rotary evaporator to give *N*-[2-(chloromethoxy)ethyl]-2,2,2-trifluoroacetamide as oil. Yield 23.4 g (85%). ^{1}H NMR ($CDCl_3$): 6.74 (br s, 1H, NH), 5.46 (s, 2H, OCH_2Cl), 3.82 (t, 2H, J=5.1, $OCH_2CH_2NHCOCF_3$), 3.60 (q, 2H, $OCH_2CH_2NHCOCF_3$). ^{13}C NMR ($CDCl_3$): 157.59 (q, J=36.9, $COCF_3$), 115.98 (q, J=287.5, CF_3), 82.32 (OCH_2Cl), 68.05 ($OCH_2CH_2NHCOCF_3$), 39.30 ($OCH_2CH_2NHCOCF_3$).

The obtained *N*-[2-(chloromethoxy)ethyl]-2,2,2-trifluoroacetamide was dissolved in benzene (50 ml) and potassium acetate (17 g, 0.17 mol) was added. The mixture was stirred at 50 °C for 4 h. The precipitate was filtered off; the filtrate was concentrated on a rotary evaporator to oil. The residue was dissolved in ethyl acetate (50 ml) and washed with 10% aqueous solution of sodium hydrogen carbonate (20 ml) and water (2×20 ml). The organic layer was dried over anhydrous sodium sulfate and concentrated on a rotary evaporator to oil. The residue was purified by column chromatography on silica gel (150 g). The column was washed with methylene chloride (400 ml) and then eluted with methylene chloride to give [2-(2,2,2-trifluoroacetamido)ethoxy]methyl acetate (**17a**) as oil. Yield 20.7 g (80%). Yield for three steps 68%. R_f 0.30 (methylene chloride). ^{1}H NMR ($CDCl_3$): 6.95 (br s, 1H, NH), 5.22 (s, 2H, OCH_2O), 3.75 (t, 2H, J=5.2, $OCH_2CH_2NHCOCF_3$), 3.52 (q, 2H, $OCH_2CH_2NHCOCF_3$), 2.05 (s, 3H, Ac). ^{13}C NMR ($CDCl_3$): 170.57 (C=O), 157.43 (q, J=37.8, $COCF_3$), 115.82 (q, J=287.5, CF_3), 88.94 (OCH_2O), 67.91 ($OCH_2CH_2NHCOCF_3$), 39.87 ($OCH_2CH_2NHCOCF_3$), 20.80 (Me).

4.32. [3-(2,2,2-Trifluoroacetamido)propoxy]methyl acetate (17b)

Analogous conversion of 3-amino-1-propanol (15.2 ml, 0.20 mol) yielded [3-(2,2,2-trifluoroacetamido)propoxy]methyl acetate (**17b**) as an oil 31.6 g (65%). R_f 0.30 (methylene chloride).

4.32.1. *N-(3-Hydroxypropyl)-2,2,2-trifluoroacetamide*

^{1}H NMR ($CDCl_3$): 7.79 (br s, 1H, NH), 3.73 (t, 2H, J=5.6, $HOCH_2CH_2CH_2NHCOCF_3$), 3.47 (dt, 2H, J=5.9, $HOCH_2CH_2CH_2NHCOCF_3$), 3.12 (br s, 1H, OH), 1.78 (tt, 2H, $OCH_2CH_2CH_2NHCOCF_3$). ^{13}C NMR ($CDCl_3$): 157.91 (q, J=36.9, $COCF_3$), 116.04 (q, J=287.2, CF_3), 60.84 ($HOCH_2CH_2CH_2NHCOCF_3$), 38.27 ($HOCH_2CH_2CH_2NHCOCF_3$), 30.61 ($HOCH_2CH_2CH_2NHCOCF_3$).

4.32.2. *N-[3-(Chloromethoxy)propyl]-2,2,2-trifluoroacetamide*

^{1}H NMR ($CDCl_3$): 7.04 (br s, 1H, NH), 5.46 (s, 2H, OCH_2Cl), 3.78 (t, 2H, J=5.9, $OCH_2CH_2CH_2NHCOCF_3$), 3.46 (dt, 2H, J=6.2, $OCH_2CH_2CH_2NHCOCF_3$), 1.89 (tt, 2H, $OCH_2CH_2CH_2NHCOCF_3$). ^{13}C NMR ($CDCl_3$): 157.36 (q, J=37.1, $COCF_3$), 116.13 (q, J=287.3, CF_3), 82.82 (OCH_2Cl), 68.49 ($OCH_2CH_2CH_2NHCOCF_3$), 37.92 ($OCH_2CH_2CH_2NHCOCF_3$), 27.93 ($OCH_2CH_2CH_2NHCOCF_3$).

4.32.3. *[3-(2,2,2-Trifluoroacetamido)propoxy]methyl acetate (**17b**)*

^{1}H NMR ($CDCl_3$): 7.18 (br s, 1H, NH), 5.21 (s, 2H, OCH_2O), 3.72 (t, 2H, J=5.8, $OCH_2CH_2CH_2NHCOCF_3$), 3.43 (dt, 2H, J=6.2, $OCH_2CH_2CH_2NHCOCF_3$), 2.06 (s, 3H, Ac), 1.84 (tt, 2H, $OCH_2CH_2CH_2NHCOCF_3$). ^{13}C NMR

($CDCl_3$): 170.74 (C=O), 156.92 (q, J=37.6, $COCF_3$), 116.42 (q, J=287.1, CF_3), 89.07 (OCH_2O), 68.67 ($OCH_2CH_2CH_2NHCOCF_3$), 38.30 ($OCH_2CH_2CH_2NHCOCF_3$), 28.31 ($OCH_2CH_2CH_2NHCOCF_3$), 20.93 (Me).

4.33. 1-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-β-D-ribofuranosyl}uracil (18a)

Nucleoside **15a** (940 mg, 1.40 mmol) was dissolved in 0.5 M tetrabutylammonium fluoride trihydrate in tetrahydrofuran (7 ml), kept for 10 min at 20 °C, evaporated to dryness, evaporated with chloroform (10 ml), and applied on a column with silica gel (30 g). The column was washed with methylene chloride (100 ml), methylene chloride–ethanol 98:2 (200 ml), and methylene chloride–ethanol 96:4 (200 ml), and then eluted with methylene chloride–ethanol 94:6 to give **18a** as a powder. Yield 490 mg (83%). R_f 0.20 (B). ^{1}H NMR (DMSO-d_6): 11.28 (br s, 1H, NH), 9.39 (br t, 1H, $NHCOCF_3$), 7.92 (d, 1H, $J_{6,5}$=8.1, H-6), 5.88 (d, 1H, $J_{1',2'}$=4.7, H-1′), 5.63 (dd, 1H, $J_{5,NH}$=2.2, H-5), 5.18 (br s, 2H, OH-3′, OH-5′), 4.74 (d, 1H, J=−7.2, OC*H*HO), 4.72 (d, 1H, OCH*H*O), 4.14 (t, 1H, $J_{2',3'}$=4.7, H-2′), 4.11 (dd, 1H, $J_{3',4'}$=3.9, H-3′), 3.87 (dd, 1H, $J_{4',5'a}$=2.3, H-4′), 3.66 (dd, 1H, $J_{5'a,5'b}$=−12.8, H-5′a), 3.63–3.53 (m, 3H, H-5′b, $OCH_2CH_2NHCOCF_3$), 3.43–3.31 (m, 2H, $OCH_2CH_2NHCOCF_3$). ^{13}C NMR (DMSO-d_6): 163.02 (C4), 156.32 (q, J=36.2, $COCF_3$), 150.56 (C2), 140.24 (C6), 116.25 (q, J=287.9, CF_3), 101.75 (C5), 93.90 (OCH_2O), 86.41 (C1′), 85.02 (C4′), 78.31 (C2′), 68.47 (C3′), 65.01 ($OCH_2CH_2NHCOCF_3$), 60.35 (C5′), 39.35 ($OCH_2CH_2NHCOCF_3$). LSI-MS ($C_{14}H_{18}F_3N_3O_8$+H^+): 414.1116. Calcd 414.1124.

4.34. 1-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-β-D-ribofuranosyl}-*N*^{4}-benzoylcytosine (18b)

Analogous desilylation of **15b** (705 mg, 0.93 mmol) yielded **18b** as a powder (379 mg, 79%). R_f 0.21 (B). ^{1}H NMR (DMSO-d_6): 11.29 (br s, 1H, NH), 9.39 (t, 1H, $J_{CH,NH}$=5.2, $NHCOCF_3$), 8.54 (d, 1H, $J_{6,5}$=7.4, H-6), 8.02–7.49 (m, 5H, Bz), 7.33 (d, 1H, H-5), 5.89 (d, 1H, $J_{1',2'}$=1.9, H-1′), 5.15 (br s, 2H, OH-3′, OH-5′), 4.92 (d, 1H, J=−6.5, OC*H*HO), 4.81 (d, 1H, OCH*H*O), 4.15 (dd, 1H, $J_{2',3'}$=5.0, H-2′), 4.12 (dd, 1H, $J_{3',4'}$=6.5, H-3′), 4.95 (ddd, 1H, $J_{4',5'a}$=1.9, $J_{4',5'b}$=3.1, H-4′), 3.82 (dd, 1H, $J_{5'a,5'b}$=−12.5, H-5′a), 3.71–3.62 (m, 3H, H-5′b, $OCH_2CH_2NHCOCF_3$), 3.39 (m, 2H, $OCH_2CH_2NHCOCF_3$). ^{13}C NMR (DMSO-d_6): 167.49 (C=O), 162.99 (C4), 156.35 (q, J=36.1, $COCF_3$), 154.28 (C2), 144.79 (C6), 133.17, 132.69, 132.14, 128.34 (Ph), 115.55 (q, J=288.3, CF_3), 96.09 (C5), 93.80 (OCH_2O), 88.77 (C1′), 84.21 (C4′), 78.87 (C2′), 67.52 (C3′), 65.08 ($OCH_2CH_2NHCOCF_3$), 59.39 (C5′), 39.22 ($OCH_2CH_2NHCOCF_3$). LSI-MS ($C_{21}H_{23}F_3N_4O_8$+H^+): 517.1541. Calcd 517.1546.

4.35. 9-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-β-D-ribofuranosyl}-*N*^{2}-isobutyrylguanine (18c)

Analogous desilylation of **15c** (923 mg, 1.22 mmol) yielded **18c** as a foam (574 mg, 91%). R_f 0.16 (B). ^{1}H NMR (DMSO-d_6): 12.09 (br s, 1H, NH Guo), 11.61 (br s, 1H, NH*i*Bu), 9.37 (br t, 1H, N*H*$COCF_3$), 8.27 (s, 1H, H-8), 5.95 (d, 1H, $J_{1',2'}$=6.2, H-1′), 5.31 (d, 1H, $J_{3',OH}$=4.7, OH-3′), 5.11 (t, 1H, $J_{5',OH}$=5.1, OH-5′), 4.70 (d, 1H, J=−6.9, OC*H*HO), 4.65 (d, 1H, OCH*H*O), 4.56 (dd, 1H, $J_{3',2'}$=5.0, H-2′), 4.28 (ddd, 1H, $J_{3',4'}$=2.1, H-3′), 3.96 (dt, 1H, $J_{5'a,4}$=$J_{5'b,4}$=2.8, H-4′), 3.63 (ddd, 1H, $J_{5'a,5'b}$=−11.8, H-5′a), 3.57 (ddd, 1H, H-5′b), 3.47 (m, 1H, OC*H*$HCH_2NHCOCF_3$), 3.35 (m, 1H, OCH*H*$CH_2NHCOCF_3$), 3.23–3.12 (m, 2H, $OCH_2CH_2NHCOCF_3$), 2.76 (sept, 1H, J=6.9, *i*Bu), 1.12 (s, 3H, Me*i*Bu), 1.11 (s, 3H, Me*i*Bu). ^{13}C NMR (DMSO-d_6): 180.10 (C=O), 156.35 (q, J=36.1, $COCF_3$), 154.80 (C6), 148.82 (C2), 148.24 (C4), 137.46 (C8), 120.07 (C5), 115.82 (q, J=288.3, CF_3), 94.19 (OCH_2O), 86.16 (C1′), 84.78 (C4′), 79.04 (C2′), 69.28 (C3′), 65.07 ($OCH_2CH_2NHCOCF_3$), 61.19 (C5′), 38.93 ($OCH_2CH_2NHCOCF_3$), 34.75 (*CH*i*Bu*), 18.77 (*Mei*Bu). LSI-MS ($C_{19}H_{25}F_3N_6O_8$+H^+): 523.1759. Calcd 523.1759.

4.36. 9-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-β-D-ribofuranosyl}-*N*^{6}-benzoyladenine (18d)

Analogous desilylation of **15d** (1.41 g, 1.80 mmol) yielded **18d** as a foam (810 mg, 84%). R_f 0.19 (B). ^{1}H NMR ($CDCl_3$): 9.25 (br s, 1H, NHBz), 8.76 (s, 1H, H-8), 8.14 (s, 1H, H-2), 8.04–7.53 (m, 6H, Bz, $NHCOCF_3$), 6.02 (d, 1H, $J_{1',2'}$=7.3, H-1′), 4.99 (dd, 1H, $J_{2',3'}$=4.7, H-2′), 4.67 (d, 1H, J=−6.7, OC*H*HO), 4.62 (d, 1H, OCH*H*O), 4.53 (d, 1H, H-3′), 4.36 (d, 1H, $J_{4',5'a}$=1.2, H-4′), 3.98 (dd, 1H, $J_{5'a,5'b}$=−12.3, H-5′a), 3.77 (d, 1H, H-5′b), 3.59–3.51 (m, 1H, OC*H*$HCH_2NHCOCF_3$), 3.43–3.21 (m, 3H, OCH*HCH*$_2$$NHCOCF_3$). ^{13}C NMR ($CDCl_3$): 165.13 (C=O), 157.43 (q, J=37.7, $COCF_3$), 152.32 (C8), 151.03 (C6), 150.41 (C4), 143.41 (C2), 133.33, 133.31, 129.28, 128.16 (Ph), 124.91 (C5), 115.93 (q, J=285.8, CF_3), 96.32 (OCH_2O), 89.35 (C1′), 87.82 (C4′), 80.62 (C2′), 71.60 (C3′), 66.67 ($OCH_2CH_2NHCOCF_3$), 63.04 (C5′), 39.45 ($OCH_2CH_2NHCOCF_3$). LSI-MS ($C_{22}H_{23}F_3N_6O_7$+H^+): 541.1652. Calcd 541.1653.

4.37. 1-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-β-D-ribofuranosyl}uracil (19a)

Analogous desilylation of **16a** (670 mg, 1.0 mmol) yielded **19a** as a powder (340 mg, 80%). R_f 0.20 (B). ^{1}H NMR (DMSO-d_6): 11.29 (br s, 1H, NH), 9.34 (br t, 1H, $NHCOCF_3$), 7.93 (dd, 1H, $J_{6,5}$=8.1, $J_{6,NH}$=1.6, H-6), 5.89 (d, 1H, $J_{1',2'}$=5.0, H-1′), 5.64 (dd, 1H, $J_{5,NH}$=2.2, H-5), 5.16 (br s, 2H, OH-3′, OH-5′), 4.71 (d, 1H, J=−7.5, OC*H*HO), 4.68 (d, 1H, OCH*H*O), 4.13 (t, 1H, $J_{2',3'}$=5.0, H-2′), 4.10 (dd, 1H, $J_{3',4'}$=3.2, H-3′), 3.88 (ddd, 1H, $J_{4',5'a}$=2.6, $J_{4',5'b}$=2.2, H-4′), 3.64 (dd, 1H, $J_{5'a,5'b}$=−12.0, H-5′a), 3.57 (dd, 1H, H-5′b), 3.51–3.41 (m, 2H, $OCH_2CH_2CH_2NHCOCF_3$), 3.26–3.17 (m, 2H, $OCH_2CH_2CH_2NHCOCF_3$), 1.71–1.64 (m, 2H, $OCH_2CH_2CH_2NHCOCF_3$). ^{13}C NMR (DMSO-d_6): 162.98 (C4), 156.01 (q, J=36.3, $COCF_3$), 150.57 (C2), 140.36 (C6), 115.93 (q, J=287.4, CF_3), 101.84 (C5), 94.00 (OCH_2O), 86.20 (C1′), 85.21 (C4′), 78.03 (C2′), 68.58 (C3′), 64.85 ($OCH_2CH_2CH_2NHCOCF_3$), 60.56 (C5′), 36.59 ($OCH_2CH_2CH_2NHCOCF_3$), 28.35 ($OCH_2CH_2CH_2NHCOCF_3$). LSI-MS ($C_{15}H_{20}F_3N_3O_8$+H^+): 428.1267. Calcd 428.1281.

4.38. 1-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-β-D-ribofuranosyl}-*N*^{4}-benzoylcytosine (19b)

Analogous desilylation of **16b** (580 mg, 0.83 mmol) yielded **19b** as a powder (334 mg, 84%). R_f 0.21 (B). ^{1}H NMR (DMSO-d_6): 11.19 (br s, 1H, NH), 9.31 (t, 1H, $J_{CH,NH}$=6.2, $NHCOCF_3$), 8.52 (d, 1H, $J_{6,5}$=7.2, H-6), 8.02–7.49 (m, 5H, Bz), 7.35 (d, 1H, H-5), 5.91 (d, 1H, $J_{1',2'}$=1.9, H-1′), 5.15 (br s, 2H, OH-3′, OH-5′), 4.87 (d, 1H, J=−6.5, OC*H*HO), 4.80 (d, 1H, OCH*H*O), 4.14 (m, 2H, H-2′, H-3′), 3.96 (ddd, 1H, $J_{4',3'}$=5.6, $J_{4',5'a}$=1.9, $J_{4',5'b}$=2.2, H-4′), 3.81 (dd, 1H, $J_{5'a,5'b}$=−12.2, H-5′a), 3.65 (dd, 1H, H-5′b), 3.56 (t, 2H, $J_{CH,H}$=6.2, $OCH_2CH_2CH_2NHCOCF_3$), 3.24 (m, 2H, $OCH_2CH_2CH_2NHCOCF_3$), 1.72 (m, 2H, $OCH_2CH_2CH_2NHCOCF_3$). ^{13}C NMR (DMSO-d_6): 167.75 (C=O), 163.02 (C4), 155.94 (q, J=36.2, $COCF_3$), 153.82 (C2), 144.90 (C6), 132.57, 129.14, 128.30, 127.52 (Ph), 115.74 (q, J=287.9, CF_3), 96.12 (C5), 93.84 (OCH_2O), 88.64 (C1′), 84.35 (C4′), 78.66 (C2′), 67.68 (C3′), 64.78 ($OCH_2CH_2CH_2NHCOCF_3$), 59.54 (C5′), 36.61 ($OCH_2CH_2CH_2NHCOCF_3$), 28.31 ($OCH_2CH_2CH_2NHCOCF_3$). LSI-MS ($C_{22}H_{25}F_3N_4O_8$+H^+): 531.1699. Calcd 531.1703.

4.39. 9-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-β-D-ribofuranosyl}-*N*^{2}-isobutyrylguanine (19c)

Analogous desilylation of a mixture of **16c** and starting **4c** (ratio of 9:1) (852 mg, 1.10 mmol) yielded **19c** as a foam (498 mg, 37% for two steps). R_f 0.16 (B). ^{1}H NMR (DMSO-d_6): 12.08 (br s, 1H, NH Guo), 11.60 (br s, 1H, NH*i*Bu), 9.30 (br t, 1H, N*H*$COCF_3$), 8.26 (s, 1H, H-8), 5.95 (d, 1H, $J_{1',2'}$=6.5, H-1′), 5.26 (d, 1H, $J_{3',OH}$=4.4, OH-3′), 5.08 (t, 1H, $J_{5',OH}$=5.3, OH-5′), 4.69 (d, 1H, J=−6.9, OC*H*HO), 4.62 (d, 1H, OCH*H*O), 4.59 (dd, 1H, $J_{3',2'}$=5.0, H-2′), 4.28 (ddd, 1H, $J_{3',4'}$=2.3, H-3′), 3.96 (dt, 1H, $J_{5'a,4}$=$J_{5'b,4}$=2.5, H-4′), 3.71–3.53 (m, 2H, $OCH_2CH_2CH_2NHCOCF_3$),

3.25–3.02 (m, 4H, H-5′a, H-5′b, $OCH_2CH_2CH_2NHCOCF_3$), 2.77 (sept, 1H, J=6.9, *i*Bu), 1.55–1.49 (m, 2H, $OCH_2CH_2CH_2NHCOCF_3$), 1.11 (m, 6H, Me*i*Bu). ^{13}C NMR (DMSO-d_6): 180.10 (C=O), 156.13 (q, J=36.1, $COCF_3$), 154.83 (C6), 148.87 (C2), 148.27 (C4), 137.59 (C8), 120.07 (C5), 115.91 (q, J=288.3, CF_3), 94.20 (OCH_2O), 86.30 (C1′), 84.79 (C4′), 78.68 (C2′), 69.25 (C3′), 64.95 ($OCH_2CH_2CH_2NHCOCF_3$), 61.28 (C5′), 36.49 ($OCH_2CH_2CH_2NHCOCF_3$), 34.81 (*i*Bu), 28.96 ($OCH_2CH_2CH_2NHCOCF_3$), 18.84 (Me*i*Bu). LSI-MS ($C_{20}H_{27}F_3N_6O_8$+H^+): 537.1916. Calcd 537.1915.

4.40. 9-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-β-D-ribofuranosyl}-N^6-benzoyladenine (19d)

Analogous desilylation of **16d** (965 mg, 1.19 mmol) yielded **19d** as a foam (575 mg, 86%). R_f 0.19 (B). ^{1}H NMR ($CDCl_3$): 9.40 (br s, 1H, NHBz), 8.70 (s, 1H, H-8), 8.17 (s, 1H, H-2), 8.02–7.48 (m, 6H, Bz, $NHCOCF_3$), 6.02 (d, 1H, $J_{1′,2′}$=7.4, H-1′), 5.00 (dd, 1H, $J_{2′,3′}$=4.5, H-2′), 4.64 (d, 1H, J=−6.9, OC*H*HO), 4.56 (d, 1H, OCH*H*O), 4.53 (d, 1H, H-3′), 4.32 (d, 1H, $J_{4′,5′a}$=1.2, H-4′), 3.95 (dd, 1H, $J_{5′a,5′b}$=−12.8, H-5′a), 3.76 (d, 1H, H-5′b), 3.50–3.29 (m, 2H, $OCH_2CH_2CH_2NHCOCF_3$), 3.25–3.18 (m, 2H, $OCH_2CH_2CH_2NHCOCF_3$), 1.59–1.24 (m, 2H, $OCH_2CH_2CH_2NHCOCF_3$). ^{13}C NMR ($CDCl_3$): 165.30 (C=O), 157.59 (q, J=36.1, $COCF_3$), 152.22 (C8), 151.43 (C6), 150.51 (C4), 143.43 (C2), 133.51, 133.14, 129.04, 128.16 (Ph), 125.20 (C5), 116.85 (q, J=288.3, CF_3), 96.01 (OCH_2O), 89.42 (C1′), 87.79 (C4′), 80.12 (C2′), 71.55 (C3′), 66.78 ($OCH_2CH_2CH_2NHCOCF_3$), 63.09 (C5′), 37.51 ($OCH_2CH_2CH_2NHCOCF_3$), 28.73 ($OCH_2CH_2CH_2NHCOCF_3$). LSI-MS ($C_{23}H_{25}F_3N_6O_7$−H^+): 553.1652. Calcd 553.1664.

4.41. 1-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-5-*O*-(4-methoxytrityl)-β-D-ribofuranosyl}uracil (20a)

Nucleoside **18a** (650 mg, 1.62 mmol) was dried by evaporation with pyridine (2×20 ml). The residue was dissolved in dry pyridine (30 ml), monomethoxytrityl chloride (970 mg, 3.1 mmol) was added, and the resulted solution was kept in the dark for 16 h at 20 °C. MeOH (1 ml) was added and after 30 min the mixture was concentrated in vacuo to near dryness. The residue was dissolved in methylene chloride (50 ml), and washed with 10% aqueous solution of sodium bicarbonate (20 ml) and water (2×20 ml). The organic layer was dried over anhydrous sodium sulfate, evaporated in vacuo, evaporated with toluene (2×10 ml), and purified by column chromatography on silica gel (30 g). The column was washed with methylene chloride (200 ml) and methylene chloride–ethanol 99:1 (200 ml), and then eluted with methylene chloride–ethanol 98:2 to give **20a** as a foam. Yield 904 mg (80%). R_f 0.31 (A). ^{1}H NMR (DMSO-d_6): 11.32 (br s, 1H, NH), 9.39 (t, 1H, $J_{CH,NH}$=6.8, $NHCOCF_3$), 7.71 (d, 1H, $J_{6,5}$=8.1, H-6), 7.42–7.22 (m, 12H, Ph), 6.92 (d, 2H, J=9.0, *m*PhOMe), 5.85 (d, 1H, $J_{1′,2′}$=3.4, H-1′), 5.31 (d, 1H, H-5), 4.82 (d, 1H, J=−6.9, OC*H*HO), 4.79 (d, 1H, OCH*H*O), 4.27 (t, 1H, $J_{3′,2′}$=5.0, $J_{3′,4′}$=5.0, H-3′), 4.24 (dd, 1H, H-2′), 4.01 (dd, 1H, $J_{4′,5′b}$=1.9, H-4′), 3.75 (s, 3H, OMe), 3.66–3.62 (m, 2H, $OCH_2CH_2NHCOCF_3$), 3.42–3.33 (m, 3H, H-5′a, $OCH_2CH_2NHCOCF_3$), 3.28 (dd, 1H, $J_{5′b,5′a}$=−10.6, H-5′b). ^{13}C NMR (DMSO-d_6): 162.80 (C4), 158.23 (*pPh*OMe), 156.23 (q, J=36.1, $COCF_3$), 150.24 (C2), 144.03, 143.75 (Tr), 140.05 (C6), 134.56, 129.99, 127.92, 127.81, 126.86 (Tr), 116.32 (q, J=288.2, CF_3), 113.22 (*mPh*OMe), 101.46 (C5), 93.93 (OCH_2O), 87.48 (C1′), 86.15 (Ph_3C), 82.51 (C4′), 77.87 (C2′), 68.49 (C3′), 65.01 ($OCH_2CH_2NHCOCF_3$), 62.66 (C5′), 54.97 (OMe), 39.06 ($OCH_2CH_2NHCOCF_3$). LSI-MS ($C_{34}H_{33}F_3N_3O_9$−H^+): 684.2172. Calcd 684.2169.

4.42. 1-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-5-*O*-(4-methoxytrityl)-β-D-ribofuranosyl}-N^4-benzoylcytosine (20b)

Analogous tritylation of nucleoside **18b** (350 mg, 0.67 mmol) yielded **20b** as a foam (431 mg, 81%). R_f 0.32 (A). ^{1}H NMR (DMSO-d_6): 11.21 (br s, 1H, NH), 9.39 (t, 1H, $J_{CH,NH}$=5.0, $NHCOCF_3$), 8.33 (d, 1H, $J_{6,5}$=7.2, H-6), 8.02–7.28 (m, 17H, Bz, Tr), 7.18 (br s, 1H, H-5), 6.93 (d, 2H, J=9.0, *m*PhOMe), 5.87 (s, 1H, H-1′), 5.30 (d, 1H, $J_{OH,3′}$=6.2, OH-3′), 4.98 (d, 1H, J=−6.5, OC*H*HO), 4.85 (d, 1H, OCH*H*O), 4.35 (dd, 1H, $J_{3′,2′}$=5.0, $J_{3′,4′}$=8.4, H-3′), 4.20 (d, 1H, H-2′), 4.09 (dd, 1H, $J_{4′,5′b}$=1.2, H-4′), 3.76 (s, 3H, OMe), 3.74–3.66 (m, 2H, $OCH_2CH_2NHCOCF_3$), 3.43–3.39 (m, 3H, H-5′a, $OCH_2CH_2NHCOCF_3$), 3.35 (dd, 1H, $J_{5′a,5′b}$=−10.9, H-5′b). ^{13}C NMR (DMSO-d_6): 166.95 (C=O), 163.04 (C4), 158.25 (*pPh*OMe), 155.92 (q, J=36.2, $COCF_3$), 154.14 (C2), 144.19 (C6), 143.92, 143.65, 134.82, 135.97, 129.88, 127.77, 126.95 (Tr), 116.28 (q, J=287.9, CF_3), 113.27 (*mPh*OMe), 96.11 (C5), 93.78 (OCH_2O), 89.44 (C1′), 86.25 (Ph_3C), 81.88 (C4′), 78.48 (C2′), 67.77 (C3′), 65.06 ($OCH_2CH_2NHCOCF_3$), 61.73 (C5′), 54.95 (OMe), 39.23 ($OCH_2CH_2NHCOCF_3$). LSI-MS ($C_{41}H_{38}F_3N_4O_9$−H^+): 787.2596. Calcd 787.2591.

4.43. 9-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-5-*O*-(4-methoxytrityl)-β-D-ribofuranosyl}-N^2-isobutyrylguanine (20c)

Analogous tritylation of nucleoside **18c** (450 mg, 0.86 mmol) yielded **20c** as a foam (569 mg, 83%). R_f 0.25 (A). ^{1}H NMR ($CDCl_3$): 12.18 (br s, 1H, NH Guo), 8.95 (br s, 1H, NH*i*Bu), 7.80–7.20 (m, 14H, H-8, N*H*$COCF_3$, Tr), 6.79 (d, 2H, J=9.0, *mPh*OMe), 5.98 (d, 1H, $J_{1′,2′}$=4.7, H-1′), 4.87 (dd, 1H, $J_{2′,3′}$=5.3, H-2′), 4.81 (d, 1H, J=−7.2, OC*H*HO), 4.77 (d, 1H, OCH*H*O), 4.56 (dd, 1H, $J_{3′,4′}$=4.4, H-3′), 4.21 (ddd, 1H, $J_{4′,5′a}$=2.2, $J_{4′,5′b}$=4.0, H-4′), 3.75 (s, 3H, OMe), 3.71–3.60 (m, 2H, $OCH_2CH_2NHCOCF_3$), 3.54–3.45 (m, 3H, $OCH_2CH_2NHCOCF_3$, H-5′a), 3.28 (dd, 1H, $J_{5a′,5′b}$=−10.5, H-5′b), 2.20 (sept, 1H, J=6.9, *i*Bu), 1.04 (d, 3H, Me*i*Bu), 0.92 (d, 3H, Me*i*Bu). ^{13}C NMR ($CDCl_3$): 179.46 (C=O), 159.01 (*pPh*OMe), 157.03 (q, J=36.2, $COCF_3$), 155.81 (C6), 148.56 (C2), 147.98 (C4), 136.17 (C8), 144.49, 135.41, 130.48, 128.53, 128.10, 127.36 (Ph), 121.85 (C5), 116.48 (q, J=288.1, CF_3), 113.45 (*mPh*OMe), 96.19 (OCH_2O), 87.01 (Ph_3C), 86.96 (C1′), 84.05 (C4′), 80.22 (C2′), 70.40 (C3′), 66.85 ($OCH_2CH_2NHCOCF_3$), 63.72 (C5′), 55.38 (OMe), 39.88 ($OCH_2CH_2NHCOCF_3$), 36.16 (*i*Bu), 18.84, 18.76, (Me*i*Bu). LSI-MS ($C_{39}H_{41}F_3N_6O_9$−H^+): 793.2777. Calcd 793.2814.

4.44. 9-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-5-*O*-(4-methoxytrityl)-β-D-ribofuranosyl}-N^6-benzoyladenine (20d)

Analogous tritylation of nucleoside **18d** (777 mg, 1.44 mmol) yielded **20d** as a foam (956 mg, 82%). R_f 0.30 (A). ^{1}H NMR ($CDCl_3$): 9.05 (br s, 1H, NHBz), 8.71 (s, 1H, H-8), 8.25 (s, 1H, H-2), 8.02–7.21 (m, 18H, Bz, Tr, $NHCOCF_3$), 6.83 (d, 2H, J=8.9, *mPh*OMe), 6.28 (d, 1H, $J_{1′,2′}$=4.9, H-1′), 4.88 (dd, 1H, $J_{2′,3′}$=5.2, H-2′), 4.85 (d, 1H, J=−7.0, OC*H*HO), 4.82 (d, 1H, OCH*H*O), 4.52 (ddd, 1H, $J_{3′,4′}$=4.2, $J_{3′,OH}$=4.8, H-3′), 4.27 (ddd, 1H, $J_{4′,5′a}$=2.1, $J_{4′,5′b}$=1.5, H-4′), 3.78 (s, 3H, OMe), 3.65–3.31 (m, 6H, H-5′a, H-5′b, $OCH_2CH_2NHCOCF_3$), 2.95 (d, 1H, OH-3′). ^{13}C NMR ($CDCl_3$): 165.06 (C=O), 158.88 (*pPh*OMe), 157.72 (q, J=36.8, $COCF_3$), 152.81 (C8), 151.89 (C6), 149.72 (C4), 144.04 (C2), 143.96, 135.10, 133.11, 129.05, 128.51, 128.12, 127.34 (Ph), 123.80 (C5), 115.96 (q, J=288.5, CF_3), 113.41 (*mPh*OMe), 96.10 (OCH_2O), 87.23 (Ph_3C), 86.86 (C1′), 84.07 (C4′), 80.65 (C2′), 70.46 (C3′), 66.98 ($OCH_2CH_2NHCOCF_3$), 63.21 (C5′), 55.37 (OMe), 39.66 ($OCH_2CH_2NHCOCF_3$). LSI-MS ($C_{42}H_{39}F_3N_6O_8$+H^+): 813.2845. Calcd 813.2854.

4.45. 1-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-5-*O*-(4-methoxytrityl)-β-D-ribofuranosyl}uracil (21a)

Analogous tritylation of nucleoside **19a** (642 mg, 1.50 mmol) yielded **21a** as a foam (937 mg, 88%). R_f 0.31 (A). ^{1}H NMR ($CDCl_3$): 9.45 (br s, 1H, NH), 8.59 (d, 1H, $J_{6,5}$=8.2, H-6), 7.53 (br s, 1H, $NHCOCF_3$), 7.45–7.20 (m, 12H, Ph), 6.85 (d, 2H, J=9.0, *m*PhOMe), 5.96 (d, 1H, $J_{1′,2′}$=1.6, H-1′), 5.29 (d, 1H, H-5), 5.00 (d, 1H, J=−6.7,

OC*H*HO), 4.87 (d, 1H, OCH*H*O), 4.49 (dd, 1H, $J_{3',2'}$=5.0, $J_{3',4'}$=7.8, H-3′), 4.22 (dd, 1H, H-2′), 4.05 (ddd, 1H, $J_{4',5'b}$=2.2, $J_{4',5'b}$=2.5, H-4′), 3.79 (s, 3H, OMe), 3.75–3.65 (m, 2H, OC*H*$_2$CH$_2$CH$_2$NHCOCF$_3$), 3.61 (dd, 1H, $J_{5'a,5'b}$=11.2, H-5′a), 3.55 (dd, 1H, H-5′b), 3.47–3.43 (m, 2H, OCH$_2$CH$_2$C*H*$_2$NHCOCF$_3$), 3.04 (br s, 1H, OH-3′), 1.90–1.83 (m, 2H, OCH$_2$C*H*$_2$CH$_2$NHCOCF$_3$). ^{13}C NMR (CDCl$_3$): 163.05 (C4), 159.04 (*pPh*OMe), 156.01 (q, *J*=36.5, *C*OCF$_3$), 149.84 (C2), 144.04, 143.78 (Tr), 139.99 (C6), 136.18, 134.80, 130.61, 128.99, 127.92, 127.81, 126.86 (Tr), 117.02 (q, *J*=288.2, *C*F$_3$), 113.53 (*mPh*OMe), 102.49 (C5), 95.73 (O*C*H$_2$O), 88.48 (C1′), 87.04 (Ph$_3$*C*), 83.23 (C4′), 80.56 (C2′), 68.93 (C3′), 66.73 (OCH$_2$CH$_2$CH$_2$NHCOCF$_3$), 61.48 (C5′), 55.39 (OMe), 37.68 (OCH$_2$CH$_2$*C*H$_2$NHCOCF$_3$), 28.64 (OCH$_2$*C*H$_2$CH$_2$NHCOCF$_3$). LSI-MS (C$_{35}$H$_{35}$F$_3$N$_3$O$_9$−H$^+$): 698.2332. Calcd 698.2325.

4.46. 1-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-5-*O*-(4-methoxytrityl)-β-D-ribofuranosyl}-N^4-benzoylcytosine (21b)

Analogous tritylation of nucleoside **19b** (371 mg, 0.70 mmol) yielded **21b** as a foam (480 mg, 86%). R_f 0.32 (A). ^{1}H NMR (CDCl$_3$): 8.75 (br s, 1H, NH), 8.55 (d, 1H, $J_{6,5}$=7.5, H-6), 8.13 (br s, 1H, NHCOCF$_3$), 7.87–7.32 (m, 18H, Bz, Tr, H-5), 6.88 (d, 2H, *J*=8.7, *m*PhOMe), 5.98 (s, 1H, H-1′), 5.08 (d, 1H, *J*=−6.5, OC*H*HO), 4.95 (d, 1H, OCH*H*O), 4.49 (dd, 1H, $J_{3',2'}$=5.0, $J_{3',4'}$=9.0, H-3′), 4.27 (d, 1H, H-2′), 4.12 (d, 1H, H-4′), 3.82–3.79 (m, 4H, H-5′a, OMe), 3.64–3.59 (m, 3H, OC*H*$_2$CH$_2$CH$_2$NHCOCF$_3$, H-5′b), 3.53–3.35 (m, 2H, OCH$_2$CH$_2$C*H*$_2$NHCOCF$_3$), 3.11 (br s, 1H, OH-3′), 1.91–1.86 (m, 2H, OCH$_2$C*H*$_2$CH$_2$NHCOCF$_3$). ^{13}C NMR (CDCl$_3$): 167.01 (C═O), 162.72 (C4), 159.05 (*pPh*OMe), 155.15 (q, *J*=36.2, *C*OCF$_3$), 149.88 (C2), 144.90 (C6), 143.97, 143.73, 136.13, 135.97, 129.88, 127.77, 127.51 (Tr), 116.38 (q, *J*=287.3, *C*F$_3$), 113.58 (*mPh*OMe), 97.04 (C5), 95.75 (O*C*H$_2$O), 90.22 (C1′), 87.66 (Ph$_3$*C*), 82.95 (C4′), 80.16 (C2′), 68.36 (C3′), 66.18 (OCH$_2$CH$_2$CH$_2$NHCOCF$_3$), 61.07 (C5′), 55.37 (OMe), 37.42 (OCH$_2$CH$_2$*C*H$_2$NHCOCF$_3$), 28.57 (OCH$_2$*C*H$_2$CH$_2$NHCOCF$_3$). LSI-MS (C$_{42}$H$_{40}$F$_3$N$_4$O$_9$−H$^+$): 801.2754. Calcd 801.2747.

4.47. 9-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-5-*O*-(4-methoxytrityl)-β-D-ribofuranosyl}-N^2-isobutyrylguanine (21c)

Analogous tritylation of nucleoside **19c** (473 mg, 0.88 mmol) yielded **21c** as a foam (620 mg, 87%). R_f 0.25 (A). ^{1}H NMR (CDCl$_3$): 12.18 (br s, 1H, NH Guo), 8.89 (br s, 1H, NH*i*Bu), 7.83–7.21 (m, 14H, H-8, N*H*COCF$_3$, Tr), 6.79 (d, 2H, *J*=8.7, *mPh*OMe), 5.96 (d, 1H, $J_{1',2'}$=5.6, H-1′), 5.00 (dd, 1H, $J_{2',3'}$=5.0, H-2′), 4.75 (d, 1H, *J*=−6.9, OC*H*HO), 4.72 (d, 1H, OCH*H*O), 4.55 (dd, 1H, $J_{3',4'}$=3.4, H-3′), 4.22 (dd, 1H, $J_{4',5'b}$=2.7, H-4′), 3.75 (s, 3H, OMe), 3.54–3.49 (m, 2H, OC*H*$_2$CH$_2$CH$_2$NHCOCF$_3$), 3.41–3.34 (m, 3H, OCH$_2$C*H*$_2$NHCOCF$_3$, H-5′a), 3.24 (dd, 1H, $J_{5a',5'b}$=−10.6, H-5′b), 2.07 (sept, 1H, *J*=7.0, *i*Bu), 1.70 (m, 2H, OCH$_2$C*H*$_2$CH$_2$NHCOCF$_3$), 0.99 (d, 3H, Me*i*Bu), 0.86 (d, 3H, Me*i*Bu). ^{13}C NMR (CDCl$_3$): 179.40 (C═O), 158.97 (*pPh*OMe), 157.71 (q, *J*=36.1, *C*OCF$_3$), 155.81 (C6), 149.77 (C2), 147.89 (C4), 135.40 (C8), 144.24, 138.81, 130.48, 128.11, 127.36 (Ph), 121.90 (C5), 116.07 (q, *J*=288.2, *C*F$_3$), 113.44 (*mPh*OMe), 95.79 (O*C*H$_2$O), 86.95 (Ph$_3$*C*), 86.85 (C1′), 84.39 (C4′), 79.35 (C2′), 70.33 (C3′), 66.45 (OCH$_2$CH$_2$CH$_2$NHCOCF$_3$), 63.80 (C5′), 55.35 (OMe), 37.48 (OCH$_2$CH$_2$*C*H$_2$NHCOCF$_3$), 36.10 (*i*Bu), 28.74 (OCH$_2$*C*H$_2$CH$_2$NHCOCF$_3$), 18.73 (Me*i*Bu). LSI-MS (C$_{40}$H$_{43}$F$_3$N$_6$O$_9$+H$^+$): 809.3087. Calcd 809.3116.

4.48. 9-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-5-*O*-(4-methoxytrityl)-β-D-ribofuranosyl}-N^6-benzoyladenine (21d)

Analogous tritylation of nucleoside **19d** (492 mg, 0.89 mmol) yielded **21d** as a foam (625 mg, 85%). R_f 0.30 (A). ^{1}H NMR (CDCl$_3$): 9.04 (br s, 1H, NHBz), 8.69 (s, 1H, H-8), 8.22 (s, 1H, H-2), 8.03–7.22 (m, 18H, Bz, Tr, NHCOCF$_3$), 6.81 (d, 2H, *J*=9.0, *mPh*OMe), 6.24 (d, 1H, $J_{1',2'}$=5.0, H-1′), 4.98 (dd, 1H, $J_{2',3'}$=5.3, H-2′), 4.81 (m, 2H, OCH$_2$O), 4.52 (dd, 1H, $J_{3',4'}$=3.7, H-3′), 4.28 (ddd, 1H, $J_{4',5'a}$=3.4, $J_{4',5'b}$=4.4, H-4′), 3.78 (s, 3H, OMe), 3.55 (dd, 1H, $J_{5'a,5'b}$=−10.6, H-5′a), 3.48–3.42 (m, 3H, H-5′b, OC*H*$_2$CH$_2$CH$_2$NHCOCF$_3$), 3.28–3.24 (m, 2H, OCH$_2$CH$_2$C*H*$_2$NHCOCF$_3$), 2.98 (br s, 1H, OH-3′), 1.65–1.60 (m, 2H, OCH$_2$C*H*$_2$CH$_2$NHCOCF$_3$). ^{13}C NMR (CDCl$_3$): 165.14 (C═O), 158.94 (*pPh*OMe), 157.65 (q, *J*=36.3, *C*OCF$_3$), 152.79 (C8), 152.13 (C6), 149.91 (C4), 144.08 (C2), 143.93, 141.98, 135.82, 133.04, 129.05, 128.57, 128.07, 127.30 (Ph), 123.87 (C5), 116.43 (q, *J*=287.2, *C*F$_3$), 113.45 (*mPh*OMe), 95.90 (OCH$_2$O), 87.24 (Ph$_3$*C*), 87.07 (C1′), 84.34 (C4′), 80.03 (C2′), 70.67 (C3′), 66.81 (OCH$_2$CH$_2$CH$_2$NHCOCF$_3$), 63.42 (C5′), 55.38 (OMe), 37.64 (OCH$_2$CH$_2$*C*H$_2$NHCOCF$_3$), 28.64 (OCH$_2$CH$_2$CH$_2$NHCOCF$_3$). LSI-MS (C$_{43}$H$_{41}$F$_3$N$_6$O$_8$−H$^+$): 825.2824. Calcd 825.2865.

4.49. 1-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-3-*O*-[(2-cyanoethyl)(diisopropylamino)phosphanyl]-5-*O*-(4-methoxytrityl)-β-D-ribofuranosyl}uracil (2a)

The methoxytritylated derivative **20a** (535 mg, 0.78 mmol) was dissolved in 6 ml dichloromethane under argon and ethyl-(diisopropyl)amine (407 μL, 2.34 mmol) and 2-cyanoethyl diisopropylphosphoramidochloridite (261 μL, 1.17 mmol) were added and, after stirring the solution for 3 h, TLC indicated complete reaction. A 10% aqueous solution of sodium hydrogen carbonate (2 ml) was added, the solution was stirred for 10 min, and partitioned between methylene chloride (50 ml) and aqueous sodium carbonate (30 ml). The organic phase was washed with aqueous sodium chloride (2×30 ml) and the aqueous phases were back extracted with methylene chloride (20 ml). Evaporation of the organics left an oil, which was flash purified on 50 g of silica gel (hexane–acetone–triethylamine, 124:75:1) to afford the product as a foam after coevaporation with dichloromethane. The foam was dissolved in 2 ml of dichloromethane and precipitated in 150 ml cold (−70 °C) hexane–diisopropyl ether (9:1) to afford 551 mg (0.62 mmol, 80%) of the title product as a white powder. R_f 0.37 (hexane–acetone–triethylamine, 49:49:2—solvent C). ^{31}P NMR (CDCl$_3$): 151.44, 149.13. LSI-MS (C$_{43}$H$_{51}$N$_5$O$_{10}$F$_3$P$_1$+H$^+$): 886.3398. Calcd 886.3404.

Analogous to the previous procedure the following amidites were prepared.

4.50. 1-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-3-*O*-[(2-cyanoethyl)(diisopropylamino)phosphanyl]-5-*O*-(4-methoxytrityl)-β-D-ribofuranosyl}-N^4-benzoylcytosine (2b)

Starting with compound **20b** (736 mg, 0.93 mmol), 764 mg of the required amidite was obtained (0.77 mmol, 83%). R_f 0.42 (solvent C). ^{31}P NMR (CDCl$_3$): 151.75, 149.32. LSI-MS (C$_{50}$H$_{56}$N$_6$O$_{10}$F$_3$P$_1$+H$^+$): 989.3818. Calcd 989.3826.

4.51. 9-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-3-*O*-[(2-cyanoethyl)(diisopropylamino)phosphanyl]-5-*O*-(4-methoxytrityl)-β-D-ribofuranosyl}-N^2-isobutyrylguanine (2c)

Starting with compound **20c** (240 mg, 0.31 mmol), 248 mg of the required amidite was obtained (0.24 mmol, 82%). R_f 0.33 (solvent C). ^{31}P NMR (CD$_3$CN): 149.76, 149.47. LSI-MS (C$_{48}$H$_{58}$F$_3$N$_8$O$_{10}$P$_1$+H$^+$): 995.3986. Calcd 995.4044.

4.52. 9-{2-*O*-[(2-(2,2,2-Trifluoroacetamido)ethoxy)methyl]-3-*O*-[(2-cyanoethyl)(diisopropylamino)phosphanyl]-5-*O*-(4-methoxytrityl)-β-D-ribofuranosyl}-N^6-benzoyladenine (2d)

Starting with compound **20d** (674 mg, 0.83 mmol), 669 mg of the required amidite was obtained (0.66 mmol, 79%). R_f 0.40

(solvent C). ^{31}P NMR (CD_3CN): 149,95, 149.49. LSI-MS ($C_{51}H_{56}F_3N_8O_9P_1+H^+$): 1013.3868. Calcd 1013.3938.

4.53. 1-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-3-*O*-[(2-cyanoethyl)(diisopropylamino)phosphanyl]-5-*O*-(4-methoxytrityl)-β-D-ribofuranosyl}uracil (3a)

Starting from compound **21a** (0.60 mmol, 421 mg), 462 mg of the required amidite was obtained (0.51 mmol, 85%). R_f 0.37 (solvent C). ^{31}P NMR ($CDCl_3$): 151.20, 149.26. LSI-MS ($C_{44}H_{53}N_5O_{10}F_3P_1+H^+$): 900.3558. Calcd 900.3560.

4.54. 1-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-3-*O*-[(2-cyanoethyl)(diisopropylamino)phosphanyl]-5-*O*-(4-methoxytrityl)-β-D-ribofuranosyl}-*N*^{4}-benzoylcytosine (3b)

Starting with compound **21b** (700 mg, 0.87 mmol), 676 mg of the required amidite was obtained (0.67 mmol, 78%). R_f 0.43 (solvent C). ^{31}P NMR ($CDCl_3$): 151.38, 149.20. LSI-MS ($C_{51}H_{58}N_6O_{10}F_3P_1+H^+$): 1003.3975. Calcd 1003.3982.

4.55. 9-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-3-*O*-[(2-cyanoethyl)(diisopropylamino)phosphanyl]-5-*O*-(4-methoxytrityl)-β-D-ribofuranosyl}-*N*^{2}-isobutyrylguanine (3c)

Starting with compound **21c** (280 mg, 0.34 mmol), 301 mg of the required amidite was obtained (0.29 mmol, 86%). R_f 0.34 (solvent D). ^{31}P NMR (CD_3CN): 149.68, 149.49. LSI-MS ($C_{49}H_{60}N_8O_{10}F_3P_1+H^+$): 1009.4139. Calcd 1009.4200.

4.56. 9-{2-*O*-[(3-(2,2,2-Trifluoroacetamido)propoxy)methyl]-3-*O*-[(2-cyanoethyl)(diisopropylamino)phosphanyl]-5-*O*-(4-methoxytrityl)-β-D-ribofuranosyl}-*N*^{6}-benzoyladenine (3d)

Starting with compound **21d** (410 mg, 0.49 mmol), 407 mg of the required amidite was obtained (0.40 mmol, 81%). R_f 0.40 (solvent D). ^{31}P NMR (CD_3CN): 149.86, 149.57. LSI-MS ($C_{52}H_{58}N_8O_9F_3P_1+H^+$): 1027.4012. Calcd 1027.4094.

4.57. Synthesis and analysis of oligonucleotides

Oligonucleotide assembly was performed on an Expedite™ DNA synthesizer (Applied Biosystems) using the phosphoramidite approach. The standard RNA assembly protocol was used with a 12 min coupling time, using 0.08 M of the newly synthesized unnatural amidites and 0.07 M of 'fast deprotecting' amidites (tac amidites, Proligo) with 0.25 M 5-(ethylsulfanyl)-tetrazole (ETT) as the activator. Acidic deprotection time was increased from 1 to 3 min for the monomethoxytritylated modified building blocks. The oligomers were deprotected and cleaved from the solid support by treatment with a 1:1 mixture of 40% aqueous methylamine and concd aqueous ammonia (AMA reagent) for 30 min at 20 °C and 2 h at 35 °C. The supernatant was lyophilized and the residue was treated with 1 ml of a TEA·3HF solution (1.5 ml *N*-methylpyrrolidin+0.750 ml TEA+1 ml TEA·3HF) for 3.5 h at 55 °C. The mixture was neutralized with 1 ml of a 1.5 M solution of NH_4OAc, slightly concentrated, and desalted on an NAP-25® column (Sephadex G25-DNA grade, Pharmacia). The crude product was analyzed on a Mono-Q® HR 5/5 anion exchange column, then purified on a Mono-Q® HR 10/10 column (Pharmacia) with the following gradient system (A=10 mM $NaClO_4$; B=600 mM $NaClO_4$, both in aqueous 20 mM Tris–HCl, 15% CH_3CN, 0.1 mM EDTA). The low-pressure liquid chromatography system consisted of a Merck–Hitachi L 6200 A intelligent pump, an Uvicord SII 2138 UV detector (Pharmacia-LKB), and a recorder. The product-containing fraction was desalted on an NAP-25® column and lyophilized.

Oligonucleotides were characterized and their purity was checked by HPLC/MS on a capillary chromatograph (CapLC, Waters, Milford, MA). Columns of 150×0.3 mm length (LCPackings, San Francisco, CA) were used. Oligonucleotides were eluted with an acetonitrile gradient in 50 mM triethylammonium adjusted to pH 8.0 with 1,1,1,3,3,3-hexafluoropropan-2-ol. The flow rate was 5 μL/min. Electrospray spectra were acquired on an orthogonal acceleration/time-of-flight mass spectrometer (Q-Tof-2, Micromass, Manchester, UK) in the negative ion mode. The scan time used was 2 s. The combined spectra from a chromatographic peak were deconvoluted using the MaxEnt algorithm of the software (Masslynx 3.4, Micromass, Manchester, UK). Theoretical oligonucleotide molecular weights were calculated using the monoisotopic atomic weights.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.04.110.

References and notes

1. Sassolas, A.; Leca-Bouvier, B. D.; Blum, L. J. *Chem. Rev.* **2008**, *108*, 109–139.
2. Famulok, M.; Hartig, J. S.; Mayer, G. *Chem. Rev.* **2007**, *107*, 3715–3743.
3. Prakash, T. P.; Bhat, B. *Curr. Top. Med. Chem.* **2007**, *7*, 641–649.
4. Debart, F.; Abes, S.; Deglane, G.; Moulton, H. M.; Clair, P.; Gait, M. J.; Vasseur, J. J.; Lebleu, B. *Curr. Top. Med. Chem.* **2007**, *7*, 727–737.
5. Zatsepin, T. S.; Stetsenko, D. A.; Gait, M. J.; Oretskaya, T. S. *Bioconjugate Chem.* **2005**, *16*, 471–489.
6. De Paula, D.; Bentley, M. V. L. B.; Mahato, R. I. *RNA* **2007**, *13*, 431–456.
7. Manoharan, M. *Biochim. Biophys. Acta* **1999**, *1489*, 117–130.
8. Freier, S. M.; Altmann, K.-H. *Nucleic Acids Res.* **1997**, *25*, 4429–4443.
9. Jin, S.; Miduturu, C. V.; McKinney, D. C.; Silverman, S. K. *J. Org. Chem.* **2005**, *70*, 4284–4299.
10. Zatsepin, T. S.; Romanova, E. A.; Oretskaya, T. S. *Russ. Chem. Rev. (Usp. Khim.)* **2002**, *71*, 513–534.
11. Griffey, R. H.; Monia, B. P.; Cummins, L. L.; Freier, S.; Greig, M. J.; Guinosso, C. J.; Lesnik, E.; Manalili, S. M.; Mohan, V.; Owens, S.; Ross, B. R.; Sasmor, H.; Wancewicz, E.; Weiler, K.; Wheeler, P. D.; Cook, P. D. *J. Med. Chem.* **1996**, *39*, 5100–5109.
12. Zatsepin, T. S.; Gait, M. J.; Oretskaya, T. S. *IUBMB Life* **2004**, *56*, 209–214.
13. Efimtseva, E. V.; Mikhailov, S. N. *Russ. Chem. Rev. (Usp. Khim.)* **2004**, *73*, 401–414.
14. Nauwelaerts, K.; Efimtseva, E. V.; Mikhailov, S. N.; Herdewijn, P. Disaccharide Nucleosides, an Important Group of Natural Compounds. In *Frontiers in Nucleosides and Nucleic Acids*; Schinazi, R. F., Liotta, D. C., Eds.; IHL: Tucker, GA, 2004; pp 187–220.
15. Efimtseva, E. V.; Kulikova, I. V.; Mikhailov, S. N. *Curr. Org. Chem.* **2007**, *11*, 337–354.
16. Mikhailov, S. N.; Kulikova, I. V.; Nauwelaerts, K.; Herdewijn, P. *Tetrahedron* **2008**, *64*, 2871–2876.
17. Mikhailov, S. N.; Efimtseva, E. V.; Gurskaya, G. V.; Zavodnik, V. E.; De Bruyn, A.; Janssen, G.; Rozenski, J.; Herdewijn, P. *J. Carbohydr. Chem.* **1997**, *16*, 75–92.
18. Rodionov, A. A.; Efimtseva, E. V.; Mikhailov, S. N.; Rozenski, J.; Luyten, I.; Herdewijn, P. *Nucleosides Nucleotides Nucleic Acids* **2000**, *19*, 1847–1859.
19. Efimtseva, E. V.; Shelkunova, A. A.; Mikhailov, S. N.; Nauwelaerts, K.; Rozenski, J.; Lescrinier, E.; Herdewijn, P. *Helv. Chim. Acta* **2003**, *86*, 504–514.
20. Bobkov, G. V.; Brilliantov, K. V.; Mikhailov, S. N.; Rozenski, J.; Van Aerschot, A.; Herdewijn, P. *Collect. Czech. Chem. Commun.* **2006**, *71*, 804–819.
21. Mikhailov, S. N.; Bobkov, G. V.; Brilliantov, K. V.; Rozenski, J.; Van Aerschot, A.; Herdewijn, P.; Fisher, M. H.; Juliano, R. L. *Nucleosides Nucleotides Nucleic Acids* **2007**, *26*, 1509–1512.
22. Efimtseva, E. V.; Bobkov, G. V.; Mikhailov, S. N.; Van Aerschot, A.; Schepers, G.; Busson, R.; Rozenski, J.; Herdewijn, P. *Helv. Chim. Acta* **2001**, *84*, 2387–2397.

23. Mikhailov, S. N.; Rodionov, A. A.; Efimtseva, E. V.; Ermolinsky, B. S.; Fomitcheva, M. V.; Padyukova, N. Sh.; Rothenbacher, K.; Lescrinier, E.; Herdewijn, P. *Eur. J. Org. Chem.* **1998**, 2193–2199.
24. Gulyaeva, I. V.; Neuvonen, K.; Lonnberg, H.; Rodionov, A. A.; Shcheveleva, E. V.; Bobkov, G. V.; Efimtseva, E. V.; Mikhailov, S. N. *Nucleosides Nucleotides Nucleic Acids* **2004**, *23*, 1849–1864.
25. Odadzic, D.; Bramsen, J. B.; Smicius, R.; Bus, C.; Kjems, J.; Engels, J. W. *Bioorg. Med. Chem.* **2008**, *16*, 518–529.
26. Markiewicz, W. T.; Wiewiorowski, M. Simultaneous Protection of 3′- and 5′-Hydroxyl Groups of Nucleosides. In *Nucleic Acid Chemistry: Improved and New Synthetic Procedures, Methods and Techniques*; Townsend, L. B., Tipson, R. S., Eds.; John Wiley: New York, NY, 1986; Part 3, pp 229–231.
27. Senkus, M. *J. Am. Chem. Soc.* **1946**, *68*, 734–736.
28. Mamedov, S.; Agaev, A. S. *Zh. Obshch. Khim. (USSR)* **1963**, *33*, 3166–3171.