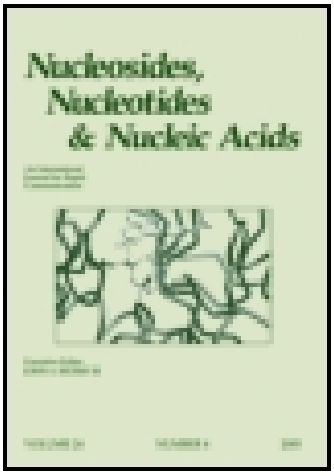

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Building Blocks for Synthesis of Oligoarabinonucleotides: Preparation of Arabinonucleoside H-Phosphonates from Protected Ribonucleosides

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BUILDING BLOCKS FOR SYNTHESIS OF OLIGOARABINONUCLEOTIDES: PREPARATION OF ARABINONUCLEOSIDE H-PHOSPHONATES FROM PROTECTED RIBONUCLEOSIDES

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Abstract: A straightforward and inexpensive synthesis of arabinonucleoside H-phosphonates has been developed. Arabinonucleosides were synthesised from protected ribonucleosides *via* 2'-keto derivatives. Reaction conditions have been optimised for compounds bearing labile N-protections. Further protecting group manipulation and phosphonylation gave the required H-phosphonate monomers.

INTRODUCTION

Recent progress in antisense inhibition of gene expression has been responsible for increased interest in oligonucleotides bearing modifications in carbohydrate moiety[1]. The findings that oligonucleotides having 2'-O-alkyl (methyl, ethyl, allyl) and 2'-fluoro substituents[2] exhibit greatly increased duplex stability when hybridised with the target RNA are most encouraging for further studies on 2'-modified oligonucleotides.

The successful use of arabinonucleosides (araA and araC) as antiviral and antitumor agents stimulated our interest in possible medical applications of oligoarabinonucleotides. Giannaris and Damha[3] recently reported on the synthesis and hybridisation properties of oligoarabinonucleotides containing araC, araU and araA residues. They concluded that oligoarabinonucleotides could form stable complexes with both DNA and RNA.

Starting materials for oligoarabinonucleotide synthesis (arabinonucleosides) are very expensive and not readily available. The need for selective protection of the 2'-OH causes additional difficulties. In recent reports on the preparation of protected arabinonucleosides the transient 1,1,3,3-tetraisopropyldisiloxane-1,3-yl (TIPDS)

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protection[4] was used to introduce the 2'-O-benzoyl[5] or acetyl[6,7] protecting groups. Pfleiderer et al.[8] reported syntheses of 2'-O-(2-(4-nitrophenyl)ethoxycarbonyl) protected arabinonucleoside 3'-O-phosphoramidites using the thexyldimethylsilyl or TIPDS groups as transient protections. A polyarabinonucleic acid consisting of 78 nucleotide units has been synthesised using these synthons[9].

Damha et al.[10,11] used an alternative strategy. The 5'-O-monomethoxytrityl arabinonucleosides were selectively phosphitylated and successively acetylated to yield the desired 2'-O-acetyl 3'-O-phosphoramidites. The selectivity of introduction of the t-butyldimethylsilyl group in arabinonucleosides has also been studied[12].

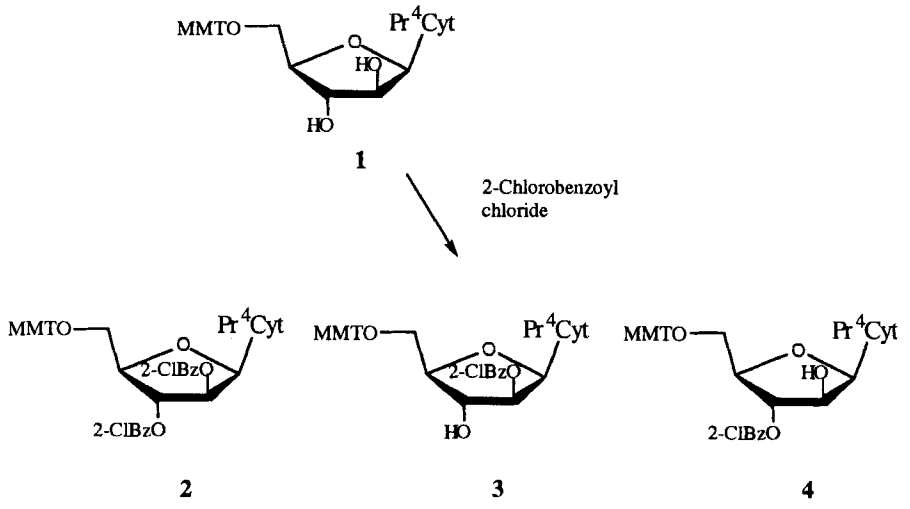
The objective of the present study was the development of an economic and simple method for the preparation of protected arabinonucleoside H-phosphonates. After the successful use of selective 2'-O-benzoylation in the synthesis of oligoribonucleotides[13] we were interested in extending these studies to the arabino counterparts. The success of 2'-acyl protection in the arabino series may be predicted because this approach would suffer neither from the 2'-3' migration of acyl groups in nucleoside intermediates nor from the degradation of oligonucleotides under basic conditions when removing the acyl protection. Adams et al.[14] have described selective 2'-O-benzoylation of 1-(5-O-DMT-α-D-arabinofuranosyl)-thymine, in which, however, the steric environment of the 2'-OH function was different.

We found that the benzoylation of the 2',3'-diol system of 5'-MMT arabinonucleosides was not selective and thus not an efficient route for synthesis of the required monomers. We developed an alternative synthesis involving the conversion of ribonucleosides into the arabino counterparts which were further reprotected and phosphonylated to give the desired building blocks. Preliminary results of this study have recently been reported[15].

RESULTS AND DISCUSSION

When N^4-propionyl-1-(5-O-MMT-β-D-arabinofuranosyl)-cytosine **1** was reacted with 1.2 equiv. of 2-chlorobenzoyl chloride (Scheme 1) three main compounds were formed in roughly equal amounts (TLC, Solvents A, B). The products (TLC, R_f= 0.59, 0.32 and 0.24, Solvent B) were isolated using preparative silica gel HPLC and identified (^{1}H NMR) as 2',3'-di-O-acyl **2**, 2'-O-acyl **3** and 3'-O-acyl **4** derivatives respectively.

These results clearly indicated that the benzoylation of the 2',3'-diol system of 5'-O-tritylated arabinonucleosides failed to display any selectivity under the given conditions. Apparently the 2'-OH is sterically less accessible in the 5'-O-MMT arabinonucleosides than in the corresponding ribo derivatives. The difference in the steric environments of the 2'- and 3'-hydroxyl functions of arabinonucleosides has also been demonstrated by Ogilvie et al.[11,12]

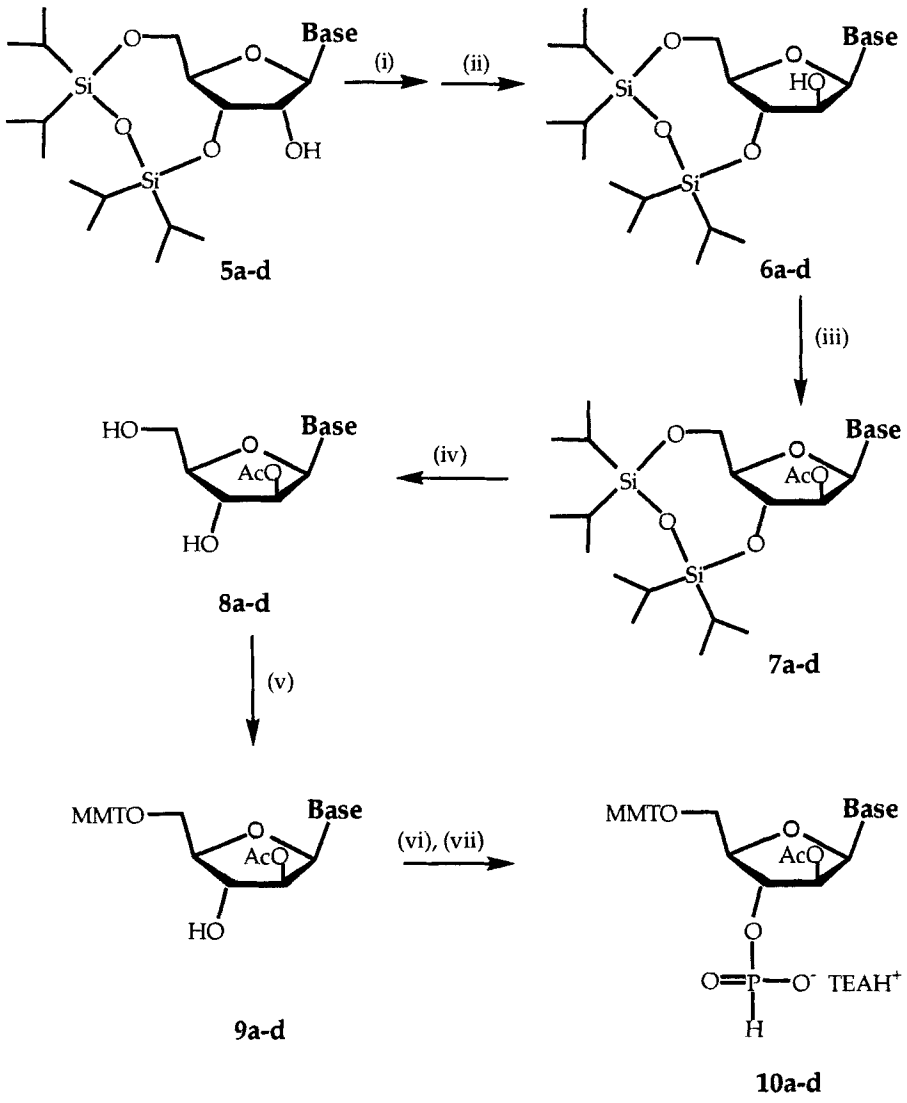


Scheme 1. Acylation of N^4,5'-O-protected arabinocytidine with 2-chlorobenzoyl chloride.

Although the use of TIPDS protection would allow selective acylation of the 2'-OH we employed a slightly modified route (Scheme 2). We believe that the cost of the preparation of the monomer building blocks is an important factor that may even be crucial if the method were to be employed on a large scale, say, for the preparation of modified oligonucleotides for therapeutic purposes: the extremely high cost of arabinonucleosides would restrict the use of this method.

We decided to use the protected ribonucleosides **5a-d** since these starting materials are cheaper and readily available. The following N-protecting groups were used: isobutyryl (ibu) for cytidine, isovaleryl (iva) for adenosine and phenoxyacetyl (pac) for guanosine. These protections can be removed under mild basic conditions (conc. ammonia aq./ethanol, 3:1, 8 h, RT) compatible with the oligoribonucleotide synthesis previously reported[13]. Straightforward procedures for conversion of ribonucleosides into the corresponding arabinonucleosides have been reported[16-19]. These involve selective 3',5'-protection (TIPDS or TBDMS groups) of the ribonucleoside, oxidation of the free 2'-OH group, stereoselective reduction of the derived 2'-CO function and deprotection of the resulting arabinonucleoside. Different reagents have been proposed for both oxidation (DMSO/acetic anhydride[16,17], Dess-Martin 12-I-5 periodinane oxidant[18-20]) and reduction (sodium borohydride[16,17], sodium triacetoxyborohydride[18,19]).

We performed a series of experiments using these reagents to find optimal conditions for the particular compounds bearing labile N-protecting groups. The results



Scheme 2. Synthesis of protected arabinonucleoside H-phosphonates.
Base= N^4-ibuCyt (a), Ura (b), N^6-ivaAde (c), N^2-pacGua (d). Reagents: (i) see Table 1 (Oxidation); (ii) see Table 1 (Reduction); (iii) acetic anhydride/DMAP; (iv) triethylammonium hydrofluoride; (v) 4-methoxytrityl chloride; (vi) PCl_3/imidazole/triethylamine; (vii) triethylammonium bicarbonate aq.

Table 1. Preparation of protected arabinonucleosides **6a-d**, reactants and yields.

Product	Oxidation[a]	Reduction[a]	Yield %
6a	DMSO/Ac_2O	$NaBH_4$	57
	Dess-Martin	$NaBH_4$	41
	Dess-Martin[b]	$NaBH(OCOCH_3)_3$[b]	51
6b	DMSO/Ac_2O	$NaBH_4$	27
	Dess-Martin	$NaBH_4$	30
	DMSO/Ac_2O	$NaBH(OCOCH_3)_3$	64
	Dess-Martin[b]	$NaBH(OCOCH_3)_3$[b]	45
6c	DMSO/Ac_2O	$NaBH_4$	79
	Dess-Martin	$NaBH_4$	24
	DMSO/Ac_2O	$NaBH(OCOCH_3)_3$	30
	Dess-Martin[b]	$NaBH(OCOCH_3)_3$[b]	42
6d	DMSO/Ac_2O	$NaBH_4$	25
	Dess-Martin[b]	$NaBH(OCOCH_3)_3$[b]	28
	Dess-Martin[c]	$NaBH_4$[c]	45

[a]For experimental details, see ref. 17-19, [b]Modified procedure **A** without aqueous work up, see Experimental Section, [c]Modified procedure **B**, see Experimental Section.

are summarised in Table 1. The oxidation with both DMSO/Ac_2O and Dess-Martin oxidant worked well. As a rule the Dess-Martin reagent gave cleaner reaction and the 2'-keto derivatives were easier isolated.

The reduction with $NaBH_4$, however, was not always a clean and high yielding reaction. It seemed likely that it was not completely tolerated by the lactame systems of uridine and guanosine. We also observed the loss of N-protecting groups during subsequent aqueous work up. These problems were most pronounced in the synthesis of the guanosine derivative. Although we were able to achieve a 25 % yield of the desired arabinonucleoside **6d** when using DMSO/Ac_2O and $NaBH_4$[17], the method was not reliable. Complicated mixtures were produced making it difficult to isolate a pure compound. The target product often decomposed rapidly during work up and purification.

These difficulties could be overcome by using a slightly modified procedure. The idea was to use mild reduction with $NaBH(OCOCH_3)_3$ and, most importantly, to avoid any aqueous work up (Experimental Section, Modified method **A**). Although this procedure also gave somewhat moderate yields it may be recommended for the preparation of arabinonucleosides bearing labile N-protections, particularly for the guanosine derivative **6d**.

In summary, the reduction with $NaBH(OCOCH_3)_3$ was safer for N-protecting groups, however, resulted in a lower stereoselectivity: up to 10-15 % of the ribo-nucleosides **5a-d** were formed. The reduction with $NaBH_4$ gave better stereoselectivity: usually less than 5 % of **5a-d** were formed, however, the loss of N-protecting groups could not be completely avoided. The final yield varied depending on the ease of the separation of **6a-d** from the by-products formed. Thus different methods may be preferred (Table 1). For cytidine and adenosine, oxidation with $DMSO/Ac_2O$ followed by reduction with $NaBH_4$[17] gave better results (57 % and 79 % yields respectively) whereas for uridine, $DMSO/Ac_2O$ and $NaBH(OCOCH_3)_3$ were best (64 % yield).

For guanosine the following procedure (Experimental Section, Modified method **B**) gave the best result. The protected riboguanosine **5d** was oxidised with the Dess-Martin reagent, the corresponding 2'-keto derivative was isolated using silica gel column chromatography and treated with $NaBH_4$ in tetrahydrofuran. The reaction mixture was extracted with a saturated NaCl solution, pH 2 adjusted with acetic acid. The acidic conditions suppressed the loss of N-phenoxyacetyl group: **6d** was isolated in a 45 % yield.

The newly synthesised protected arabinonucleosides **6a-d** were characterised by high-resolution MS, C,H,N analyses and ^1H and ^{13}C NMR spectroscopy. We found ^1H NMR to be the most convenient method for confirming the structures and evaluating the purity of these compounds. In accordance with previously reported data[21] we observed (Table 2) typical downfield shifts of H1' and H2'. The H1'-H2' coupling constants were very informative allowing exact assignment to ribo (J= 0-1.1 Hz) or arabino (J= 4.1-6.2 Hz) configuration. In guanosine derivatives the $COCH_2O$ protons of the phenoxyacetyl group displayed interesting features: being singlets in **5d** and **7d** they appeared as a well defined AB system in **6d**.

Proton spectra also showed that **6a-d** still contained traces of **5a-d**. Often it was much easier to remove these during subsequent synthetic steps (e.g., from **7a-d**). The traces of **5a-d** were difficult to evaluate with TLC due to a very small difference in R_f values. However, ^1H NMR was a reliable tool for checking isomeric purity of **6a-d** and **7a-d** because the anomeric protons of ribo and arabino species appear at well separated chemical shifts.

Table 2. ^{1}H NMR ($CDCl_3$, 270 MHz) data of protected ribonucleosides **5a-d** and their conversion products, arabinonucleosides **6a-d**.

compd	H1'	H2'	H3'	H4'	H5'	H6(8)	H5(2)	N-protection	TIPDS
5a	5.84 (s)		4.30-3.99 (m, 5H)			8.19 (d, J=7.7 Hz)	7.43 (d)	2.71 (m, J= 7.0 Hz CHCO)	1.24-0.93 (m, 34H)
6 a	6.14 (d, J=5.9 Hz)	4.63 (m)	4.18 (m)	3.83 (m)	4.16-4.00 (m)	8.23 (d, J=7.3 Hz)	7.48 (d)	2.61 (m, J=7.0 Hz, CHCO)	1.24-0.99 (m, 34H)
5b	5.72 (s)		4.27-3.95 (m, 5H)			7.77 (d, J=8.2 Hz)	5.68 (d)	-	1.07-0.99 (m, 28H)
6b	6.08 (d, J=6.2 Hz)	4.58 (m)	4.18-3.97 (m)	3.77 (m)	4.18-3.97 (m)	7.84 (d, J=8.1Hz)	5.70 (d)	-	1.10-0.97 (m, 28H)
5c	6.01 (s)	4.59 (m)	5.06 (m)	4.13-3.99 (m, 3H)		8.63 (s)	8.18 (s)	2.73 (d, J=7.0, 2H, $COCH_2$), 2.27 (m, CH),	1.12-1.00 (m, 34H)
6c	6.26 (d, J=5.9 Hz)	4.70-4.60 (m, 2H)		3.88 (m)	4.06 (m)	8.61 (s)	8.25 (s)	2.71 (d, J=7.0, 2H, $COCH_2$), 2.27 (m, CH),	1.11-1.00 (m,34H)
5d	5.95 (d, J=1.1 Hz)	4.32 (m)	4.58 (m)	4.20-4.07 (m, 3H)		7.94 (s)	-	7.40-7.00 (Ar) 4.70 (s, 2H, $COCH_2$)	1.09-1.02 (m, 28H)
6d	6.11 (d, J=4.1 Hz)	4.82 (m)	4.12 (m)	4.51-3.90 (m, 3H)		7.92 (s)	-	7.42-7.03 (Ar) 4.70 and 4.64 (AB syst, J=15.7 Hz, 2H, $COCH_2$)	1.12-1.03 (m, 28H)

To avoid any problems caused by steric hindrance at the 2'-OH we decided to use the acetyl group for further protection of this function. Thus **6a-d** were successfully acylated with acetic anhydride to give **7a-d**. The TIPDS groups were removed with triethylammonium hydrofluoride[22] in acetonitrile. Under these conditions we did not observe any loss of N- or 2'-O acyl protections. The reaction mixtures containing **8a-d** were evaporated and partitioned between chloroform and aqueous $NaHCO_3$. The target products were further isolated using the following procedures: pyrimidine derivatives **8a,b** remained in the aqueous phase and were purified using reverse-phase column chromatography on silanised silica gel; the adenosine derivative **8c** could be recovered after repeated extraction with chloroform; the guanosine derivative **8d** crystallised from the aqueous phase and was isolated by filtration.

The compounds obtained were further reacted with monomethoxytrityl chloride in pyridine[23] yielding, after silica gel column chromatography, **9a-d** which were successively treated with the PCl_3/imidazole reagent according to published procedures[24] (Scheme 2). Pure target products, protected arabinonucleoside 3'-hydrogenphosphonates **10a-d** were isolated using silica gel column chromatography and characterised by high-resolution MS, C,H,N analyses and ^1H and ^{31}P NMR spectroscopy.

CONCLUSIONS

The approach reported herein allows a simple and relatively inexpensive conversion of protected ribonucleosides into the arabino counterparts. These in turn can easily be converted into 3'-hydrogenphosphonates, the building blocks for the synthesis of oligoarabinonucleotides. The use of inexpensive starting materials (ribonucleosides) and straightforward chemical procedures lowers overall costs and makes the method particularly suitable for large scale synthesis. Preliminary results on the synthesis of oligoarabinonucleotides using these synthons have recently been reported[15].

EXPERIMENTAL SECTION

Materials and Methods. NMR spectra were recorded on Bruker AM-360 or Jeol GSX-270 spectrometers. Chemical shifts are given in ppm relative to tetramethylsilane (^1H), $CDCl_3$ (δ= 77.17 ppm, ^{13}C) and 2% H_3PO_4 in D_2O (coaxial inner tube, ^{31}P). Signals were assigned by ^1H-^1H and ^{13}C-^1H COSY. High-resolution FAB mass spectra were recorded on a Jeol SX-102 instrument. TLC was performed on Silufol UV-254 plates (Lachema) using solvents A ($CHCl_3$/methanol, 19:1, v/v), B (ethylacetate/CH_2Cl_2, 7:3, v/v), C ($CHCl_3$/methanol, 9:1, v/v), D (isopropanol/water/25% aq. ammonia, 37:2:1, v/v/v). 1-(5-O-monomethoxytrityl-β-D-arabinofuranosyl)-N^4-propionylcytosine **1** was obtained from arabinocytidine (Sigma) using the common procedures for N-

acylation[25] and 5'-tritylation[23]. N-acyl-3',5'-O-TIPDS ribonucleosides **5a-d** were prepared according to the literature[4,25].

Benzoylation of N^4-,5'-O-protected arabinocytidine 1. Compound **1** (1.37 g, 2.4 mmol) was coevaporated with dry pyridine (3x50 ml) and dissolved in CH_2Cl_2/pyridine (19:1, 60 ml). Reaction mixture was cooled to -78°C (acetone-dry ice), a solution of 2-chlorobenzoyl chloride (0.37 ml, 2.9 mmol, 1.2 equiv.) in CH_2Cl_2 (5 ml) was added during 15 min and the mixture was further stirred for 2 h at -78°C. Methanol (0.5 ml) was added and the mixture was extracted with saturated $NaHCO_3$ aq. (100 ml). The organic layer was separated, dried over Na_2SO_4, evaporated and coevaporated with toluene to remove traces of pyridine. The reaction products were separated by preparative silica gel HPLC on a Dynamax-60A column (20x300 mm, Si-83-121-C) using a linear gradient (40-100%) of ethylacetate in CH_2Cl_2 (40 min, 12 ml/min). The fractions containing pure compounds were pooled and evaporated to yield:
2, 0.42 g (21%), R_f= 0.59 (Solvent B), ^1H NMR ($CDCl_3$, 360 MHz) δ: 7.94 (d, J= 7.6 Hz, H6), 7.88, 7.48-7.17 and 6.78 (m, 23H, Ar and H5), 6.54 (d, $J_{H1'-H2'}$= 4.3 Hz, H1'), 5.96 (dd, $J_{H2'-H3'}$= 2.1 Hz, H2'), 5.68 (dd, $J_{H3'-H4'}$= 4.0 Hz, H3'), 4.47 (ddd, H4'), 3.75 (s, 3H, OCH_3), 3.64 and 3.56 (ABX system, $J_{H5'-H5''}$= 10.4 Hz, $J_{H5'-H4'}$= 4.0 and 6.1 Hz, 2H, H5'), 2.51 (q, J= 7.4 Hz, 2H, $COCH_2$), 1.12 (t, 3H, CH_3);
3, 0.43 g (25%), R_f= 0.32 (Solvent B), ^1H NMR ($CDCl_3$, 360 MHz) δ: 8.00 (d, J= 7.6 Hz, H6), 7.44-7.18 and 6.77 (m, 19H, Ar and H5), 6.52 (d, $J_{H1'-H2'}$= 4.7 Hz, H1'), 5.91 (dd, $J_{H2'-H3'}$= 2.7 Hz, H2'), 4.43 (dd, $J_{H3'-H4'}$= 4.9 Hz, H3'), 4.27 (ddd, H4'), 3.76 (s, 3H, OCH_3), 3.50 and 3.46 (ABX system, $J_{H5'-H5''}$= 10.4 Hz, $J_{H5'-H4'}$= 3.9 and 5.6 Hz, 2H, H5'), 2.51 (q, J= 7.4 Hz, 2H, $COCH_2$), 1.12 (t, 3H, CH_3);
4, 0.54 g (32%), R_f= 0.24 (Solvent B), ^1H NMR ($CDCl_3$, 360 MHz) δ: 7.91 (d, J= 7.5 Hz, H6), 7.76, 7.52-7.21 and 6.84 (m, 19H, Ar and H5), 6.25 (d, $J_{H1'-H2'}$= 3.4 Hz, H1'), 5.38 (dd, $J_{H3'-H4'}$= 4.6 Hz, H3'), 4.70 (dd, H2'), 4.32 (ddd, H4'), 3.77 (s, 3H, OCH_3), 3.62 and 3.58 (ABX system, $J_{H5'-H5''}$= 10.3 Hz, $J_{H5'-H4'}$= 6.2 and 4.3 Hz, 2H, H5'), 2.45 (q, J= 7.4 Hz, 2H, $COCH_2$), 1.14 (t, 3H, CH_3).

Modified procedure for preparation of protected arabinonucleosides 6a-d.
Method A Freshly prepared Dess-Martin 12-I-5 periodinane oxidant[20] (2.56 g, 6 mmol) was dissolved in dry CH_2Cl_2 (30 ml) under argon. Protected ribonucleoside **5a-d** (4 mmol) in dry CH_2Cl_2 (12 ml) was added dropwise during 20 min under stirring and cooling (0°C). After further stirring for 1 h at 0°C and 2 h at room temperature the mixture was cooled on ice and dry ether (60 ml) was added. The mixture was filtered, evaporated, redissolved in dry toluene, filtered, evaporated and dried in vacuum. The

product obtained was dissolved in dry tetrahydrofuran (30 ml) and filtered. Sodium triacetoxyborohydride (2.52 g, 12 mmol) was added and the mixture was stirred at room temperature for 18 h. The mixture was filtered, evaporated and the solid residue was extensively extracted with dry ether. Ether was evaporated and the residue was purified by silica gel column chromatography using a linear gradient (0-5%) of methanol in chloroform. The fractions containing pure product were pooled, evaporated and dried in vacuum.

Method B Freshly prepared Dess-Martin 12-I-5 periodinane oxidant[20] (3.41 g, 8 mmol) was dissolved in dry CH_2Cl_2 (30 ml) under argon. **5d** (2.64 g, 4 mmol) in dry CH_2Cl_2 (12 ml) was added dropwise during 20 min under stirring and cooling (0°C). After further stirring for 1 h at 0°C and 2 h at room temperature the mixture was evaporated, the rest was washed with dry acetonitrile and filtered. The solid residue was dissolved in $CHCl_3$, filtered, evaporated and purified by silica gel column chromatography using a linear gradient (0-5%) of methanol in chloroform. The 2'-keto derivative obtained was dissolved in dry tetrahydrofuran (50 ml) and $NaBH_4$ (0.75 g, 20 mmol) in aqueous ethanol (90 %, 5 ml) was added under stirring and cooling (-5°C). The mixture was stirred for 1 h at -5°C and slowly poured into cold (-5°C) and stirred brine (pH 2 with acetic acid, 50 ml). The organic phase was separated and the aqueous phase was extracted with ethylacetate. The combined organic phases were washed with brine (50 ml), dried over Na_2SO_4 and evaporated. The solid residue was dissolved in dry ether (10 ml) and filtered. Hexane (20 ml) was added and the mixture kept for 1 h at 0°C. The precipitate was filtered and purified by silica gel column chromatography using a linear gradient (0-5%) of methanol in chloroform. The fractions containing pure product were pooled, evaporated and dried in vacuum. Yield 1.19 g (45 %).

1-(3,5-O-TIPDS-β-D-arabinofuranosyl)-N^4-isobutyrylcytosine **6a**, R_f= 0.20 (Solvent A), ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ: 177.24 (C=O in ibu), 162.70 (C4), 156.79 (C2), 145.33 (C6), 96.68 (C5), 85.90 (C1'), 81.39 (C4'), 76.09 (C2'), 72.52 (C3'), 60.39 (C5'), 36.80 (CH in ibu), 19.23 19.18 (CH_3 in ibu), 17.66, 17.55, 17.50, 17.45, 17.20, 17.09, 16.93, 13.64, 13.18, 12.50 (TIPDS). HRMS found: 555.2806. $C_{25}H_{45}N_3O_7Si_2$ requires: 555.2796. Anal. calcd: C, 54.02; H, 8.16; N, 7.56. Found: C, 53.36; H, 8.27; N, 7.35.

1-(3,5-O-TIPDS–β–D-arabinofuranosyl)-uracil **6b**, R_f= 0.17 (Solvent A), ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ: 164.54 (C4), 151.57 (C2), 140.95 (C6), 101.82 (C5), 84.52 (C1'), 81.01 (C4'), 75.49 (C2'), 71.95 (C3'), 60.31 (C5'), 17.69, 17.58, 17.53, 17.42, 17.20, 17.09, 16.99, 16.93, 13.64, 13.23, 13.09, 12.50 (TIPDS). HRMS found: 486.2174. $C_{21}H_{38}N_2O_7Si_2$ requires: 486.2218. Anal. calcd: C, 51.82; H, 7.87; N, 5.76. Found: C, 51.72; H, 7.95; N, 5.71.

9-(3,5-O-TIPDS-β-D-arabinofuranosyl)-N^6-isovaleryladenine **6c**, R_f= 0.37 (Solvent A), ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ: 172.19 (C=O in iva), 152.30 (C8), 151.08 (C6), 149.16 (C4), 142.65 (C2), 121.84 (C5), 83.95 (C1'), 81.58 (C4'), 77.17 (C2'), 74.93 (C3'), 61.58 (C5'), 46.85 (CH_2 in iva), 25.74 (CH in iva), 22.66 (CH_3 in iva), 17.63, 17.50, 17.20, 17.12, 13.66, 13.23, 13.09, 12.61 (TIPDS). HRMS found: 593.3060. $C_{27}H_{47}N_5O_6Si_2$ requires: 593.3065. Anal. calcd: C, 54.61; H, 7.98; N, 11.79. Found: C, 54.12; H, 8.07; N, 11.56.

9-(3,5-O-TIPDS-β-D-arabinofuranosyl)-N^2-phenoxyacetylguanine **6d**, R_f= 0.26 (Solvent A), ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ: 170.73 (C=O in pac), 156.52 (C6), 154.35 (C2), 146.89, 145.95 (C4 and pac), 140.44 (C8), 130.11, 123.11, 115.11 (pac), 119.73 (C5), 84.41 (C1'), 83.74 (C4'), 79.63 (C3'), 77.06 (C2'), 66.93 (CH_2 in pac), 63.82 (C5'), 17.69, 17.53, 17.28, 17.18, 17.09, 13.69, 13.50, 13.18, 12.58 (TIPDS). HRMS found: 659.2854. $C_{30}H_{45}N_5O_8Si_2$ requires: 659.2807. Anal. calcd: C, 54.60; H, 6.87; N, 10.61. Found: C, 53.78; H, 6.95; N, 10.15.

General procedure for preparation of protected 2'-O-acetyl arabinonucleosides 7a-d. Protected arabinonucleoside **6a-d** (5 mmol) was coevaporated with dry pyridine (2x100 ml) and dissolved in CH_2Cl_2/pyridine (19:1, 100 ml). Acetic anhydride (0.57 ml, 6 mmol, 1.2 equiv.) and DMAP (0.61 g, 5 mmol) were added and the mixture was stirred for 2 h at room temperature (TLC, Solvent A). Methanol (0.5 ml) was added and the mixture was extracted with saturated $NaHCO_3$ aq. (120 ml). The organic layer was separated, dried over Na_2SO_4, evaporated and coevaporated with toluene to remove traces of pyridine. The residue was purified by silica gel column chromatography using a linear gradient (0-5%) of methanol in chloroform. The fractions containing pure product were pooled, evaporated and dried in vacuum.

1-(2-O-Acetyl-3,5-O-TIPDS-β-D-arabinofuranosyl)-N^4-isobutyrylcytosine **7a**, yield 78%, R_f= 0.23 (Solvent A), 0.59 (Solvent C), ^1H NMR ($CDCl_3$, 360 MHz) δ: 8.93 (s, 1H, NH), 8.06 (d, J= 7.4 Hz, H6), 7.38 (d, H5), 6.26 (d, $J_{H1'-H2'}$= 6.2 Hz, H1'), 5.73 (dd, $J_{H2'-H3'}$= 7.9 Hz, H2'), 4.23 (dd, $J_{H3'-H4'}$= 8.4 Hz, H3'), 4.11 and 4.01 (ABX system, $J_{H5'-H5''}$= 13.2 Hz, $J_{H5'-H4'}$= 2.4 and 2.9 Hz, 2H, H5' and H5''), 3.87 (ddd, H4'), 2.65 (m, J= 6.9 Hz, COCH), 1.93 (s, 3H, $COCH_3$), 1.22-0.97 (m, 34H, isopropyl and CH_3). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ: 177.27 (C=O in ibu), 169.27 (C=O in acetyl), 162.65 (C4), 155.08 (C2), 144.87 (C6), 96.17 (C5), 82.93 (C1'), 81.17 (C4'), 74.77 (C2'), 70.79 (C3'), 60.42 (C5'), 36.80 (CH in ibu), 20.58 (CH_3 in acetyl), 19.26 19.09 (CH_3 in ibu), 17.58, 17.42, 17.04, 16.93, 16.82, 13.53, 13.18, 13.09, 12.42 (TIPDS).

1-(2-O-Acetyl-3,5-O-TIPDS–β–D-arabinofuranosyl)-uracil **7b**, yield 82%, R_f= 0.19 (Solvent A), 0.58 (Solvent C), ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 9.40 (s, NH), 7.68 (d, J= 8.1 Hz, H6), 6.22 (d, $J_{H1'-H2'}$= 6.2 Hz, H1'), 5.72 (d, H5), 5.62 (dd, $J_{H2'-H3'}$= 8.0 Hz, H2'), 4.40 (dd, $J_{H3'-H4'}$= 8.5 Hz, H3'), 4.13 and 4.03 (ABX system, $J_{H5'-H5''}$= 13.3 Hz, $J_{H5'-H4'}$= 2.3 and 2.9 Hz, 2H, H5' and H5''), 3.84 (ddd, H4'), 2.00 (s, 3H, $COCH_3$), 1.11-1.02 (m, 28H, isopropyl). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ: 169.31 (C=O in acetyl), 163.48 (C4), 150.18 (C2), 140.36 (C6), 101.86 (C5), 81.87 (C1'), 80.79 (C4'), 75.42 (C2'), 70.94 (C3'), 60.31 (C5'), 20.48 (CH_3 in acetyl), 17.57, 17.49, 17.41, 17.00, 16.92, 16.81, 13.50, 13.12, 13.04, 12.42 (TIPDS).

9-(2-O-Acetyl-3,5-O-TIPDS–β–D-arabinofuranosyl)-N^6-isovaleryladenine **7c**, yield 73%, R_f= 0.48 (Solvent A), 0.63 (Solvent C), ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 8.72 (s, NH), 8.68 (s, H8), 8.19 (s, H2), 6.48 (d, $J_{H1'-H2'}$= 6.2 Hz, H1'), 5.58 (dd, $J_{H2'-H3'}$= 8.1 Hz, H2'), 4.96 (dd, $J_{H3'-H4'}$= 8.4 Hz, H3'), 4.25 and 4.07 (ABX system, $J_{H5'-H5''}$= 12.8 Hz, $J_{H5'-H4'}$= 3.8 and 3.1 Hz, 2H, H5' and H5''), 3.96 (ddd, H4'), 2.70 (d, J= 7.0 Hz, 2H, $COCH_2$), 2.31 (m, CH in iva), 1.69 (s, 3H, $COCH_3$), 1.30-0.95 (m, 34H, isopropyl and CH_3 in iva). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ: 172.09 (C=O in iva), 169.82 (C=O in acetyl), 152.61 (C8), 151.15 (C6), 149.34 (C4), 142.06 (C2), 121.90 (C5), 81.54 (C1'), 80.84 (C4'), 77.14 (C2'), 71.88 (C3'), 61.33 (C5'), 46.84 (CH_2 in iva), 25.69 (CH in iva), 22.64 (CH_3 in iva), 20.16 (CH_3 in acetyl), 17.57, 17.49, 17.41, 17.00, 16.84, 13.42, 13.12, 13.04, 12.47 (TIPDS).

9-(2-O-Acetyl-3,5-O-TIPDS–β–D-arabinofuranosyl)-N^2-phenoxyacetylguanine **7d**, yield 79%, R_f= 0.37 (Solvent A), 0.58 (Solvent C), ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 7.90 (s, H8), 7.36-7.00 (m, Ar), 6.33 (d, $J_{H1'-H2'}$= 6.6 Hz, H1'), 5.47 (dd, $J_{H2'-H3'}$= 8.4 Hz, H2'), 4.69 (s, 2H, $COCH_2O$), 4.65 (dd, $J_{H3'-H4'}$= 8.4 Hz, H3'), 4.12-4.03 (ABX system, $J_{H5'-H4'}$= 3.10 Hz, 2H, H5' and H5''), 3.84 (m, H4'), 1.76 (s, 3H, $COCH_3$), 1.14-1.03 (m, 28H, isopropyl). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ: 169.78 (C=O in pac and acetyl), 156.52 (C6), 155.43 (C2), 147.89, 146.49 (C4 and pac), 138.06 (C8), 130.17, 123.17, 115.01 (pac), 121.25 (C5), 80.41, 80.31 (C1' and C4'), 76.71 (C2'), 71.82 (C3'), 67.06 (CH_2 in pac), 60.63 (C5'), 20.20 (CH_3 in acetyl), 17.55, 17.45, 17.07, 16.99, 16.88, 13.53, 13.09, 12.50 (TIPDS).

General procedure for removal of the 3',5'-TIPDS group.

To a solution of protected arabinonucleoside **7a-d** (5 mmol) in dry acetonitrile (100 ml), was added a 2.5 M solution of triethylammonium hydrofluoride[22] in acetonitrile (6 ml). The reaction mixture was stirred at room temperature for 3 h (TLC, Solvent C) and evaporated. Pure compounds were obtained as follows:

8a,b, the residue was dissolved in 5% aqueous $NaHCO_3$ (50 ml) and extracted with

toluene (2x50 ml) and chloroform (2x50 ml). The combined organic layers were extracted with water (100 ml), the combined aqueous layers, containing **8a,b** were evaporated and the residue was purified by reverse-phase column chromatography (Silica gel 60 silanised, 63-200 μm, Merck) using a stepwise gradient of ethanol (0%, 10%, 20%, and 30%) in water. The fractions containing pure product were pooled, evaporated and dried in vacuum.

1-(2-O-Acetyl-β-D-arabinofuranosyl)-N^4-isobutyrylcytosine **8a**, yield 74%, R_f= 0.18 (Solvent C), ^{1}H NMR (DMSO-d_6, 270 MHz) δ: 8.24 (d, J_{H6-H5}= 7.7 Hz, H6), 7.28 (d, H5), 6.18 (d, $J_{H1'-H2'}$= 4.8 Hz, H1'), 5.28 (m, H2'), 4.11 (m, H3'), 3.88 (m, H4'), 3.66 (m, 2H, H5'), 2.73 (m, J= 7.0 Hz, COCH), 1.88 (s, 3H, $COCH_3$), 1.08 (d, 6H, CH_3). ^{13}C NMR (DMSO-d_6, 67.9 MHz) δ: 176.03 (C=O in ibu), 166.89 (C=O in acetyl), 161.00 (C4), 152.49 (C2), 143.81 (C6), 93.17 (C5), 82.82 (C4'), 82.31 (C1'), 74.44 (C2'), 70.60 (C3'), 58.28 (C5'), 33.17 (CH in ibu), 18.58 (CH_3 in acetyl), 17.26 (CH_3 in ibu).

1-(2-O-Acetyl-β-D-arabinofuranosyl)-uracil **8b**, yield 89%, R_f= 0.12 (Solvent C), ^{1}H NMR (DMSO-d_6, 270 MHz) δ: 7.64 (d, J_{H6-H5}= 8.1 Hz, H6), 6.07 (d, $J_{H1'-H2'}$= 5.1 Hz, H1'), 5.54 (d, H5), 5.09 (m, H2'), 4.05 (m, H3'), 3.72 (m, H4'), 3.59 and 3.53 (ABX system, $J_{H5'-H5''}$= 12.0 Hz, $J_{H4'-H5'}$= 3.7 and 3.8 Hz, 2H, H5'), 1.87 (s, 3H, $COCH_3$). ^{13}C NMR (DMSO-d_6, 67.9 MHz) δ: 167.16 (C=O in acetyl), 161.19 (C4), 148.27 (C2), 139.30 (C6), 99.03 (C5), 81.90 (C4'), 80.66 (C1'), 75.22 (C2'), 70.58 (C3'), 58.17 (C5'), 18.50 (CH_3 in acetyl).

8c, the residue was partitioned between saturated aqueous $NaHCO_3$ (60 ml) and toluene (60 ml). The target product **8c** was extracted from the aqueous layer with chloroform (6x100 ml), the combined chloroform extracts were dried (Na_2SO_4), evaporated and dried in vacuum.

9-(2-O-Acetyl-β-D-arabinofuranosyl)-N^6-isovaleryladenine **8c**, yield 74%, R_f= 0.25 (Solvent C), ^{1}H NMR (DMSO-d_6, 270 MHz) δ: 8.63, 8.61 (2s, 2H, H8 and H2), 6.56 (d, $J_{H1'-H2'}$= 5.9 Hz, H1'), 5.87 (m, OH3'), 5.36 (t, H2'), 5.12 (br, OH5'), 4.46 (m, H3'), 3.91 (m, H4'), 3.81-3.67 (m, 2H, H5'), 2.45 (d, J= 7.0 Hz, 2H, $COCH_2$), 2.14 (m, CH in iva), 1.70 (s, 3H, $COCH_3$), 0.98 (d, 6H, CH_3 in iva). ^{13}C NMR (DMSO-d_6, 67.9 MHz) δ: 169.20, 167.26 (C=O in iva and acetyl), 149.94, 140.90 (C8, C2), 149.80, 147.78 (C6, C4), 121.31 (C5), 81.41 (C4'), 79.57 (C1'), 75.61 (C2'), 69.51 (C3'), 58.28 (C5'), 43.44 (CH_2 in iva), 23.64 (CH in iva), 20.54 (CH_3 in iva), 18.22 (CH_3 in acetyl).

8d, the residue was partitioned between saturated aqueous $NaHCO_3$ (30 ml) and chloroform (30 ml) and left overnight at 0°C. The precipitate was filtered and dried in vacuum.

9-(2-O-Acetyl-β-D-arabinofuranosyl)-N^2-phenoxyacetylguanine **8d**, yield 83%, R_f= 0.24 (Solvent C), ^{1}H NMR (DMSO-d_6, 270 MHz) δ: 8.15 (s, H8), 7.34-7.28 and 6.98-6.95 (m, 5H, Ar), 6.31 (d, $J_{H1'-H2'}$= 5.5 Hz, H1'), 5.25 (m, H2'), 5.08 (br,OH5'), 4.87 (s, 2H, $COCH_2O$), 4.39 (m, H3'), 3.88 (m, H4'), 3.70 (m, 2H, H5'), 1.81 (s, 3H, $COCH_3$). ^{13}C NMR (DMSO-d_6, 67.9 MHz) δ: 169.39 and 167.29 (C=O in pac and acetyl), 155.87 (C6), 153.12 (C2), 146.43, 145.81 (C4 and pac), 136.69 (C8), 127.71, 119.50, 112.76 (pac), 117.94 (C5), 81.76 (C4'), 79.63 (C1'), 75.44 (C2'), 69.91 (C3'), 64.52 (CH_2 in pac), 58.45 (C5'), 18.30 (CH_3 in acetyl).

Monomethoxytritylation of 8a-d was performed according to the standard procedure[23] and the crude product was purified using silica gel column chromatography (0-5% of CH_3OH in $CHCl_3$).

1-(2-O-Acetyl-5-O-monomethoxytrityl-β-D-arabinofuranosyl)-N^4-isobutyrylcytosine **9a**, yield 84%, R_f= 0.21 (Solvent A), 0.35 (Solvent C), ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 8.64 (s, NH), 7.97 (d, J= 7.7 Hz, H6), 7.47-7.23 (m, Ar and H5), 6.86 (m, Ar), 6.43 (d, $J_{H1'-H2'}$= 4.8 Hz, H1'), 5.51 (dd, $J_{H2'-H3'}$= 2.8 Hz, H2'), 4.26-4.21 (m, 2H, H3'and H4'), 3.81 (s, 3H, OCH_3), 3.46 and 3.40 (ABX system, $J_{H5'-H5''}$= 10.3 Hz, $J_{H5'-H4'}$= 3.6 and 5.1 Hz, 2H, H5' and H5''), 2.68 (m, J= 6.8 Hz, COCH), 1.83 (s, 3H, $COCH_3$), 1.25-1.21 (m, 6H, CH_3).

1-(2-O-Acetyl-5-O-monomethoxytrityl-β-D-arabinofuranosyl)-uracil **9b**, yield 81%, R_f= 0.22 (Solvent A), 0.38 (Solvent C), ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 7.68 (d, J= 8.1 Hz, H6), 7.45-7.16 and 6.85 (m, Ar), 6.33 (d, $J_{H1'-H2'}$= 5.5 Hz, H1'), 5.50 (d, H5), 5.24 (dd, $J_{H2'-H3'}$= 4.4 Hz, H2'), 4.35 (dd, $J_{H3'-H4'}$= 6.2 Hz, H3'), 4.06 (ddd, H4'), 3.80 (s, 3H, OCH_3), 3.52 and 3.44 (ABX system, $J_{H5'-H5''}$= 10.6 Hz, $J_{H5'-H4'}$= 3.3 and 4.4 Hz, 2H, H5' and H5''), 1.98 (s, 3H, $COCH_3$).

9-(2-O-Acetyl-5-O-monomethoxytrityl-β-D-arabinofuranosyl)-N^6-isovaleryladenine **9c**, yield 76%, R_f= 0.28 (Solvent A), 0.46 (Solvent C), ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 8.63 (s, NH), 8.58 (s, H2), 7.46-7.21 and 6.82 (m, Ar), 6.62 (d, $J_{H1'-H2'}$= 4.9 Hz, H1'), 5.20 (dd, $J_{H2'-H3'}$= 4.4 Hz, H2'), 4.62 (dd, $J_{H3'-H4'}$= 5.3 Hz, H3'), 4.17 (m, H4'), 3.78 (s, 3H, OCH_3), 3.57-3.48 (ABX system, 2H, H5' and H5''), 2.73 (d, J= 7.1 Hz, 2H, $COCH_2$), 2.30 (m, CH in iva), 1.72 (s, 3H, $COCH_3$), 1.05 (d, J= 6.6 Hz, 6H, CH_3).

9-(2-O-Acetyl-5-O-monomethoxytrityl-β-D-arabinofuranosyl)-N^2-phenoxyacetyl-guanine **9d**, yield 76%, R_f= 0.30 (Solvent A), 0.49 (Solvent C), ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 7.78 (s, H8), 7.43-7.21, 6.98 and 6.82 (m, Ar), 6.40 (d, $J_{H1'-H2'}$= 5.3 Hz, H1'), 5.22 (dd, $J_{H2'-H3'}$= 4.0 Hz, H2'), 4.68 (s, 2H, $COCH_2O$), 4.50 (dd, $J_{H3'-H4'}$= 5.2 and 4.7 Hz, H4'), 3.50 and 3.44 (ABX system, $J_{H5'-H5''}$= 10.2 Hz), 1.76 (s, 3H, $COCH_3$).

Phosphonylation of 9a-d was carried out using the published procedures[24] and the crude product was purified using silica gel column chromatography (0-12% of CH_3OH in $CHCl_3$ containing 0.1% of triethylamine).

1-(2-O-Acetyl-5-O-monomethoxytrityl–β–D-arabinofuranosyl)-N^4-isobutyrylcytosine 3'-O-hydrogenphosphonate, triethylammonium salt **10a**, yield 62%, R_f= 0.14 (Solvent C), 0.41 (Solvent D), ^1H NMR ($CDCl_3$, 360 MHz) δ: 8.36 (s, NH), 7.71 (d, J= 7.9 Hz, H6), 7.46-7.22 and 6.82 (m, Ar and H6), 6.94 (d, J= 613 Hz, PH), 6.33 (d, J= 3.6 Hz, H1'), 5.63 (dd, $J_{H2'-H3'}$= 3.2 Hz, H2'), 4.67 (ddd, $J_{H3'-PH}$= 9.9 Hz, $J_{H3'-H4'}$= 2.8 Hz, H3'), 4.43 (ddd, H4'), 3.77 (s, 3H, OCH_3), 3.41 and 3.34 (ABX system, $J_{H5'-H5''}$= 10.3 Hz, $J_{H5'-H4'}$= 4.8 and 6.7 Hz, 2H, H5' and H5''), 3.03 (q, J= 7.5 Hz, 6H, NCH_2), 2.72 (m, COCH), 1.67 (s, 3H, $COCH_3$), 1.30 (t, 9H, CH_3 in triethylamine), 1.18 (d, J= 6.7 Hz, 6H, CH_3 in isobutyryl). ^{31}P NMR (CH_3CN:Pyridine, 3:1, 109.4 MHz) δ: 1.23. HRMS found: M^-, 690.2225. $C_{35}H_{37}N_3O_{10}P$ requires: M^-, 690.2217. Anal. calcd for $C_{41}H_{53}N_4O_{10}P$: C, 62.11; H, 6.74; N, 7.07. Found: C, 59.67; H, 6.76; N, 7.67.

1-(2-O-Acetyl-5-O-monomethoxytrityl–β–D-arabinofuranosyl)-uracil 3'-O-hydrogen-phosphonate, triethylammonium salt **10b**, yield 81%, R_f= 0.11 (Solvent C), 0.14 (Solvent D), ^1H NMR ($CDCl_3$, 360 MHz) δ: 8.09 (d, J= 8.1 Hz, H6), 7.44-7.22 and 6.82 (m, Ar), 6.93 (d, J= 609 Hz, PH), 6.27 (d, J= 4.0 Hz, H1'), 5.51 (dd, $J_{H2'-H3'}$= 2.2 Hz, H2'), 5.47 (d, H5), 4.71 (ddd, $J_{H3'-PH}$= 10.2 Hz, $J_{H3'-H4'}$= 3.3 Hz, H3'), 4.34 (ddd, H4'), 3.77 (s, 3H, OCH_3), 3.43 and 3.36 (ABX system, $J_{H5'-H5''}$= 10.2 Hz, $J_{H5'-H4'}$= 4.4 and 6.2 Hz, 2H, H5' and H5''), 3.02 (q, J= 7.5 Hz, 6H, NCH_2), 1.78 (s, 3H, $COCH_3$), 1.29 (t, 9H, CH_3). ^{31}P NMR (CH_3CN:Pyridine, 3:1, 109.4 MHz) δ: 1.25. HRMS found: M^-, 621.1685. $C_{31}H_{30}N_2O_{10}P$ requires: M^-, 621.1638. Anal. calcd for $C_{37}H_{46}N_3O_{10}P$: C, 61.40; H, 6.41; N, 5.81. Found: C, 59.89; H, 6.37; N, 6.18.

9-(2-O-Acetyl-5-O-monomethoxytrityl–β–D-arabinofuranosyl)-N^6-isovaleryladenine 3'-O-hydrogenphophonate, triethylammonium salt **10c**, yield 80%, R_f= 0.19 (Solvent C), 0.51 (Solvent D), ^1H NMR ($CDCl_3$, 360 MHz) δ: 8.62 (s, H8), 8.03 (s, H2), 7.50-7.22 and 6.82 (m, Ar), 6.95 (d, J= 609 Hz, PH), 6.66 (d, J= 4.4 Hz, H1'), 5.58 (dd, $J_{H2'-H3'}$= 2.2 Hz, H2'), 4.92 (ddd, $J_{H3'-PH}$= 10.2 Hz, $J_{H3'-H4'}$= 3.5 Hz, H3'), 4.41 (m, H4'), 3.77 (s, 3H, OCH_3), 3.50-3.43 (ABX system, 2H, H5' and H5''), 3.02 (q, J= 7.5 Hz, 6H, NCH_2), 2.70 (d, J= 6.6 Hz, 2H, $COCH_2$), 2.30 (m, CH in iva), 1.67 (s, 3H, $COCH_3$), 1.31 (t, 9H, CH_3 in triethylamine), 1.03 (d, J= 6.6 Hz, 6H, CH_3 in iva). ^{31}P NMR (CH_3CN:Pyridine, 3:1, 109.4 MHz) δ: 1.38. HRMS found: M^-, 728.2476. $C_{37}H_{39}N_5O_9P$ requires: M^-, 728.2485. Anal. calcd for $C_{43}H_{55}N_6O_9P$: C, 62.16; H, 6.67; N, 10.11. Found: C, 60.72; H, 6.69; N, 9.79.

9-(2-O-Acetyl-5-O-monomethoxytrityl-β-D-arabinofuranosyl)-N^2-phenoxyacetyl-guanine 3'-O-hydrogenphosphonate, triethylammonium salt **10d**, yield 65%, R_f= 0.20 (Solvent C), 0.53 (Solvent D), ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 8.11 (s, NH), 7.69 (s, H8), 7.48-7.14, 7.02 and 6.82 (m, Ar), 7.01 (d, J= 631 Hz, PH), 6.44 (d, J= 3.7 Hz, H1'), 5.39 (m, H2'), 4.87 (m, H3'), 4.80 (s, 2H, $COCH_2O$), 4.45 (m, H4'), 3.77 (s, 3H, OCH_3), 3.49 and 3.37 (ABX system, $J_{H5'-H5''}$= 9.9 Hz, $J_{H5'-H4'}$= 6.6 and 5.1 Hz, 2H, H5' and H5''), 3.02 (q, J= 7.3 Hz, 6H, NCH_2), 1.71 (s, 3H, $COCH_3$), 1.30 (t, 9H, CH_3). ^{31}P NMR (CH_3CN:Pyridine, 3:1, 109.4 MHz) δ: 1.41. HRMS found: M^-, 794.2199. $C_{40}H_{37}N_5O_{11}P$ requires: M^-, 794.2227. Anal. calcd for $C_{46}H_{53}N_6O_{11}P$: C, 61.60; H, 5.96; N, 9.37. Found: C, 59.70; H, 6.06; N, 9.40.

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