

Synthesis of 2'-O-[(Triisopropylsilyl)oxy]methyl (= tom)-Protected Ribonucleoside Phosphoramidites Containing Various Nucleobase Analogues

by Sébastien Porcher and Stefan Pitsch*

Laboratory of Nucleic Acid Chemistry, EPFL-BCH, CH-1015 Lausanne

The first results of a study aiming at an efficient preparation of a large variety of 2'-O-[(triisopropylsilyl)oxy]methyl(= tom)-protected ribonucleoside phosphoramidite building blocks containing modified nucleobases are reported. All of the here presented nucleosides have already been incorporated into RNA sequences by several other groups, employing 2'-O-tdms- or 2'-O-tom-protected phosphoramidite building blocks (tdms = (*tert*-butyl)dimethylsilyl). We now optimized existing reactions, developed some new and shorter synthetic strategies, and sometimes introduced other nucleobase-protecting groups. The 2'-O-tom, 5'-O-(dimethoxytrityl)-protected ribonucleosides *N*²-acetylcytosidine **5**, *O*²-(diphenylcarbamoyl)-*N*⁶-isobutyrylisoguanosine **8**, *N*⁶-isobutyryl-*N*²-(methoxyacetyl)purine-2,6-diamine ribonucleoside (= *N*⁸-isobutyryl-2-[(methoxyacetyl)amino]adenosine) **11**, 5-methyluridine **13**, and 5,6-dihydrouridine **15** were prepared by first introducing the nucleobase protecting groups and the dimethoxytrityl group, respectively, followed by the 2'-O-tom group (Scheme 1). The other presented 2'-O-tom, 5'-O-(dimethoxytrityl)-protected ribonucleosides inosine **17**, 1-methylinosine **18**, *N*⁶-isopent-2-enyladenosine **21**, *N*⁶-methyladenosine **22**, *N*⁶,*N*⁶-dimethyladenosine **23**, 1-methylguanosine **25**, *N*²-methylguanosine **27**, *N*²,*N*²-dimethylguanosine **29**, *N*⁶-(chloroacetyl)-1-methyladenosine **32**, *N*⁶-{[(1*S*,2*R*)-2-[(*tert*-butyl)dimethylsilyl]oxy]-1-[[2-(4-nitrophenyl)ethoxy]carbonyl]propyl}amino}carbonyl}-adenosine **34** (derived from L-threonine) and *N*⁴-acetyl-5-methylcytidine **36** were prepared by nucleobase transformation reactions from standard, already 2'-O-tom-protected ribonucleosides (Schemes 2–4). Finally, all these nucleosides were transformed into the corresponding phosphoramidites **37–52** (Scheme 5), which are fully compatible with the assembly and deprotection conditions for standard RNA synthesis based on 2'-O-tom-protected monomeric building blocks.

1. Introduction. – All tRNAs found in Nature contain modified nucleosides in an extent of up to 25%, and more than 80 different modifications have been identified so far [1] [2]. During their biosynthesis, tRNAs are undergoing different levels of processing, and the introduction of the modified nucleosides by tRNA-modifying enzymes can occur at all of these levels¹⁾. Some biological studies about the role of these modifications have been carried out after labor-intensive selection of modification-defective tRNA mutants, revealing the involvement of these modifications in the correct (functional) folding [3], in the maintenance of the reading frame [4] and in the proper interaction with aminoacyl-tRNA synthetases [5]. However, for a exhaustive study of their function, it would also be necessary to incorporate one or several modifications (natural or not) at selected positions [6]. Apart from a pioneering synthesis of the tRNA^{Ala} from yeast, containing m⁵U, Ψ, and D²⁾ reported in 1992 [7] and the enzymatic incorporation of a single m¹A into a tRNA transcript [8], no other attempt to prepare such compounds has been reported. Whereas a number of unnatural base-modified nucleosides have been introduced into ribozymes [9] and siRNAs [10], some of the naturally occurring modifications have been incorporated chemically into short (< 20 mer)

¹⁾ Interestingly, about 1% of the *E. coli* genom is coding for such enzymes [2].

model RNA sequences, thereby minimizing the difficulties resulting from incompatible assembly and deprotection conditions: m¹G [11], m₂²G [11], m²G [11], m¹I [11], m³U [11], m⁴C [11], m⁶A [11], m₂⁶A [11], m¹A [12], I [13], Ψ [14], m³Ψ [15], s⁴U [16], mcm⁵U [17], mcm⁵s²U [17], s²U [18], mnm⁵U [18], i⁶A [19], ms²i⁶A [19], mnm⁵s²U [20] and t⁶A [20][21]²). The preparation of correspondingly modified full-length tRNA sequences, containing several modified nucleotides, however, still represents a challenge and requires an adaptation of protecting groups and deprotection conditions.

A couple of years ago, we have introduced a reliable RNA synthesis method based on 2'-O-[(triisopropylsilyl)oxy]methyl(=tom)-protected ribonucleoside phosphoramidites, which allows the preparation of long RNA sequences under DNA coupling conditions [22][23]. In contrast to the usually employed 2'-O-[(*tert*-butyl)dimethylsilyl] (=tbdms) protecting group, the 2'-O-tom group is stable towards a multitude of reagents and reaction conditions and offers the unique possibility to carry out base transformations in its presence [24][25]. Here we report novel and efficient syntheses of a variety of fully compatible, 2'-O-tom protected ribonucleoside phosphoramidites containing appropriately protected modified nucleobases³).

2. Synthesis of 2'-O-tom-Protected Nucleosides. – 2.1. *Isocytidine (isoC)*. In the context of attempts to expand the genetic code, a number of unnatural, orthogonal base pairs have been prepared. Among them, the isoG·isoC· base pair has been extensively investigated in the DNA series [27–29]. In the RNA series, both the 2'-O-tbdms- and N²-[(dialkylamino)methylidene] (=dialkylformamidine)-protected isocytidine [29][30] and 5-methylisocytidine phosphoramidite [31], respectively, have been prepared and incorporated⁴).

Uridine was first transformed into its cyclic derivative **1** under *Mitsunobu* conditions as reported [32], and then ring-opened under optimized conditions, with MeOH in the presence of Et₃N, resulting in the formation of O²-methyluridine, which was directly transformed into its 4,4'-dimethoxytrityl ((MeO)₂Tr) derivative **2** under standard conditions (60% yield from **1**) (*Scheme 1*). Substitution of the MeO group of **2** with liquid NH₃ at 65° gave the isocytidine derivative **3**. After evaporation,

²) Nucleoside abbreviations: m⁵U = 5-methyluridine, Ψ = pseudouridine, D = 5,6-dihydrouridine, m¹G = 1-methylguanosine, m₂²G = N²,N²-dimethylguanosine, m²G = N²-methylguanosine, m¹I = 1-methylhypoxanthosine, m³U = 3-methyluridine, m⁴C = N⁴-methylcytidine, m⁶A = N⁶-methyladenosine, m₂⁶A = N⁶,N⁶-dimethyladenosine, m¹A = 1-methyladenosine, I = hypoxanthosine, m³Ψ = 3-methylpseudouridine, s⁴U = 4-thiouridine, mcm⁵U = 5-(carboxymethyl)uridine methyl ester, mcm⁵s²U = 2-thio-5-(carboxymethyl)uridine methyl ester, s²U = 2-thiouridine, mnm⁵U = 5-[(methylamino)methyl]uridine, i⁶A = N⁶-isopent-2-enyladenosine, ms²i⁶A = 2-(methylthio)-N⁶-isopent-2-enyladenosine, mnm⁵s²U = 2-thio-5-[(methylamino)methyl]uridine, t⁶A = N⁶-[(L-threonin-N²-yl)carbanoyl]adenosine, DAP = purine-2,6-diamine ribonucleoside = n²A = 2-aminoadenosine.

³) All of the here presented modified nucleotides have already been prepared as 2'-O-tbdms- or 2'-O-tom protected phosphoramidite building blocks and were incorporated into RNA sequences. A publication about the preparation and introduction of modified ribonucleoside phosphoramidites of the nucleosides pseudouridine, 4-thiouridine, wyosine, and 5-methyl-4-demethylwyosine is in preparation [26].

⁴) The 5-methylisocytidine has been systematically used in place of isocytidine, both in the preparation of correspondingly modified DNA and RNA sequences, to avoid loss of the nucleobase during oligonucleotide deprotection, initially observed in the DNA series (for a discussion, see [28]). Meanwhile, the first RNA sequences containing isocytidine have been prepared in the context of thermodynamic investigations [30].

the N^2 -acetyl protecting group was introduced by first forming the 2',3'-bis- O -(trimethylsilyl) derivative with Me_3SiCl in pyridine, N -acetylation with AcCl , extractive workup, and treatment of the intermediate with Bu_4NF in THF ($\rightarrow$ **4**, 63% yield, based on **2**)⁵). Introduction of the 2'- O -tom group into **4** was quite difficult, and even by employing optimized conditions ($^t\text{Bu}_2\text{SnCl}_2$ at 25° , instead of Bu_2SnCl_2 at 70°), the 2'- O -tom-protected isocytidine building block **5** could be obtained only in a low yield of 12%.

2.2. *Isoguanosine (isoG)*. Several syntheses of 2'-deoxyisoguanosine and isoguanosine phosphoramidites have been published [28–30][33][34]. These reports contain contradictory statements about isoguanosine nucleobase protecting groups that are compatible with the synthesis of the building blocks, and their introduction into oligonucleotide sequences, respectively. Furthermore, due to synthetic problems encountered during attempts to protect the $\text{N}-\text{C}(6)$ with acyl-type groups [34], (dialkylformamidine)-type protecting groups have been chosen for this position, together with the diphenylcarbamoyl protecting group for $\text{O}-\text{C}(2)$ [30]. Despite these reports, we were able to efficiently prepare N^6 -isobutyrylisoguanosine (**6**) by treating carefully dried isoguanosine (24 h at $50^\circ/0.01$ mbar, followed by treatment with 4 Å molecular sieves in pyridine for 2 h at 25°) first with 10 equiv. of Me_3SiCl and 1.2 equiv. of isobutyryl chloride (= 2-methylpropanoyl chloride), followed by extraction at 4° and subsequent hydrolysis of the Me_3Si ethers with AcOH in MeOH ⁶) (*Scheme 1*). The crude product **6**, obtained after evaporation, was sufficiently pure ($^1\text{H-NMR}$: $>90\%$) to be used directly for the next one-pot reaction sequence. First, the $\text{O}-\text{C}(2)$ position was protected with diphenylcarbamoyl chloride in pyridine, and then the $\text{O}-\text{C}(5')$ position with $(\text{MeO})_2\text{TrCl}$ ($\rightarrow$ **7**, 45% yield from isoguanosine). The 2'- O -tom-protected derivative **8** was then prepared under standard conditions (23% yield).

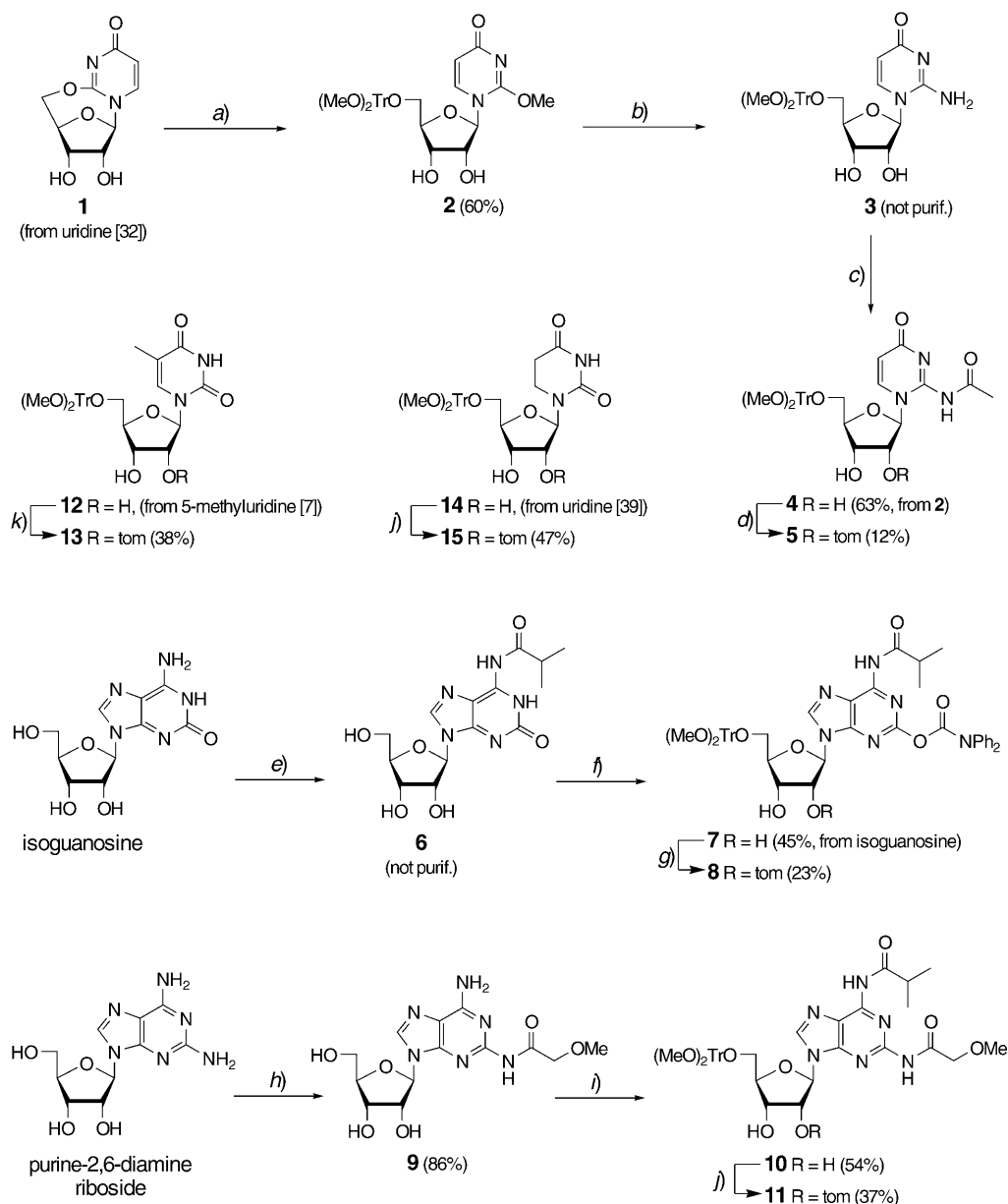
2.3. *Purine-2,6-diamine Ribonucleoside (DAP=2-Aminoadenosine= n^2A)*. So far, three syntheses of 2'- O -tdms-protected 2-aminoadenosine phosphoramidites have been reported, carrying as nucleobase protecting groups two benzoyl [34], two diphenoxycetyl [35], or two acetyl groups [36]. To be fully compatible with our standard deprotection protocol [23], we have chosen to introduce an N^6 -isobutyryl and an N^2 -(methoxyacetyl) protecting group, respectively, in analogy to the corresponding 3'-deoxyribosepyranosyl building block [37]. The 2-[(methoxyacetyl)amino]adenosine **9** was obtained by treating the nucleoside in pyridine first with Me_3SiCl , and then with methoxyacetyl chloride, followed by extraction and subsequent treatment with NH_3 in $\text{MeOH}/\text{H}_2\text{O}/\text{THF}$ (86% yield after crystallization; *Scheme 1*). A similar procedure was then employed to introduce the N^6 -isobutyryl group. The intermediate **9** in pyridine was treated first with Me_3SiCl and then with isobutyryl chloride; after extraction, the remaining Me_3Si ethers were cleaved by AcOH in MeOH according to [23]. After evaporation, the crude N^6 -acylated 2-[(methoxyacetyl)amino]adenosine was treated with $(\text{MeO})_2\text{TrCl}$ in pyridine ($\rightarrow$ **10**, 54% yield). The 2'- O -tom group was finally introduced under standard conditions ($\rightarrow$ **11**, 37% yield)⁷).

⁵) The traditional, less efficient synthesis involves first preparation of isocytidine (treatment of **1** with NH_3), followed by sequential protection of positions $\text{N}(2)$, $\text{O}-\text{C}(5')$, and $\text{O}-\text{C}(2')$ [28].

⁶) This reaction sequence was carried out in analogy to the preparation of N^6 -acetyladenosine [23].

⁷) Carried out by *L. Reymond* (Ph. D. Thesis EPFL, in preparation)

Scheme 1



a) 1. Et₃N, MeOH, 65°; 2. (MeO)₂TrCl, pyridine, 20°. b) NH₃, 65°. c) 1. Me₃SiCl, pyridine, 4°; then AcCl, DMAP (= *N,N*-dimethylpyridin-4-amine), 20°; 2. Bu₄NF, THF, 20°. d) ^tBu₂SnCl₂, ⁱPr₂NEt, (CH₂Cl)₂, 20°; then tom-Cl, 20°. e) 1. Me₃SiCl, pyridine, 4°; then DMAP, isobutyryl chloride, 20°; 2. AcOH, MeOH, 20°. f) Ph₂NC(=O)Cl, ⁱPr₂NEt, pyridine, 20°; then (MeO)₂TrCl, 20°. g) Bu₂SnCl₂, ⁱPr₂NEt, (CH₂Cl)₂, 20°; then tom-Cl, 75°. h) 1. Me₃SiCl, pyridine, 4°; then methoxyacetyl chloride, MeCN, 4°; 2. NH₃, MeOH, THF, H₂O, 20°. i) 1. Me₃SiCl, pyridine, 4°; then isobutyryl chloride, 20°; 2. AcOH, MeOH, 20°; 3. (MeO)₂TrCl, pyridine, 20°. j) Bu₂SnCl₂, ⁱPr₂NEt, (CH₂Cl)₂, 20°; then tom-Cl, 80°. k) Bu₂SnCl₂, ⁱA₂NEt, (CH₂Cl)₂, 20°; then tom-Cl, 20°.

2.4. *5-Methyluridine (m^5U)*. The 5-methyluridine is one of the most conserved modified nucleosides found in tRNAs and is usually located at position 54 in the TΨC loop [1]. We prepared the 2'-*O*-tom protected 5-methyluridine **13** from the parent nucleoside in two steps, by first introducing the dimethoxytrityl group with (MeO)₂TrCl in pyridine according to [7], followed by alkylation of the product **12** with tom-Cl under standard conditions [23] (→ **13**, 38% yield; *Scheme 1*).

2.5. *5,6-Dihydrouridine (D)*. This nucleoside is extensively conserved in the D-loop of bacterial and eukaryotic tRNAs. Its saturated C(5)–C(6) bond prevents this uracil derivative from stacking⁸⁾. We prepared the protected nucleoside **14** in analogy to the reported approach [39], consisting in hydrogenation of uridine with Rh/H₂, followed by introduction of the (MeO)₂Tr group. The 2'-*O*-tom group was introduced under standard conditions [23] (→ **15**, 47% yield; *Scheme 1*)⁹⁾.

2.6. *Inosine (I)*. This nucleoside was one of the first modifications found at position 34 of certain tRNAs, and its unique pairing properties (it is able to recognize A, U, and C) was the foundation of the wobble hypothesis postulated by Crick [1]. The incorporation of the 2'-*O*-tbdms-protected inosine phosphoramidite into RNA sequences permitted several biological investigations [13]. We prepared its 2'-*O*-tom protected analogue **16** earlier, as a common intermediate for the synthesis of ¹⁵N-labelled adenosine and guanosine phosphoramidites by nucleobase transformation reactions [24]. Treatment of this intermediate **16** with NH₃ in MeOH, followed by evaporation and dimethoxytritylation in pyridine under standard conditions provided **17** (67% yield; *Scheme 2*).

2.7. *1-Methylinosine (m^1I)*. The 2'-*O*-tom protected phosphoramidite of this nucleoside, found at position 37 of tRNAs, has already been prepared by the introduction of the tom group into the corresponding nucleoside [11]. As an alternative to this procedure, we efficiently methylated the 2'-*O*-tom 5'-*O*-(MeO)₂Tr protected inosine derivative **17** with MeI/K₂CO₃ in DMF, obtaining **18** in 98% yield (*Scheme 2*).

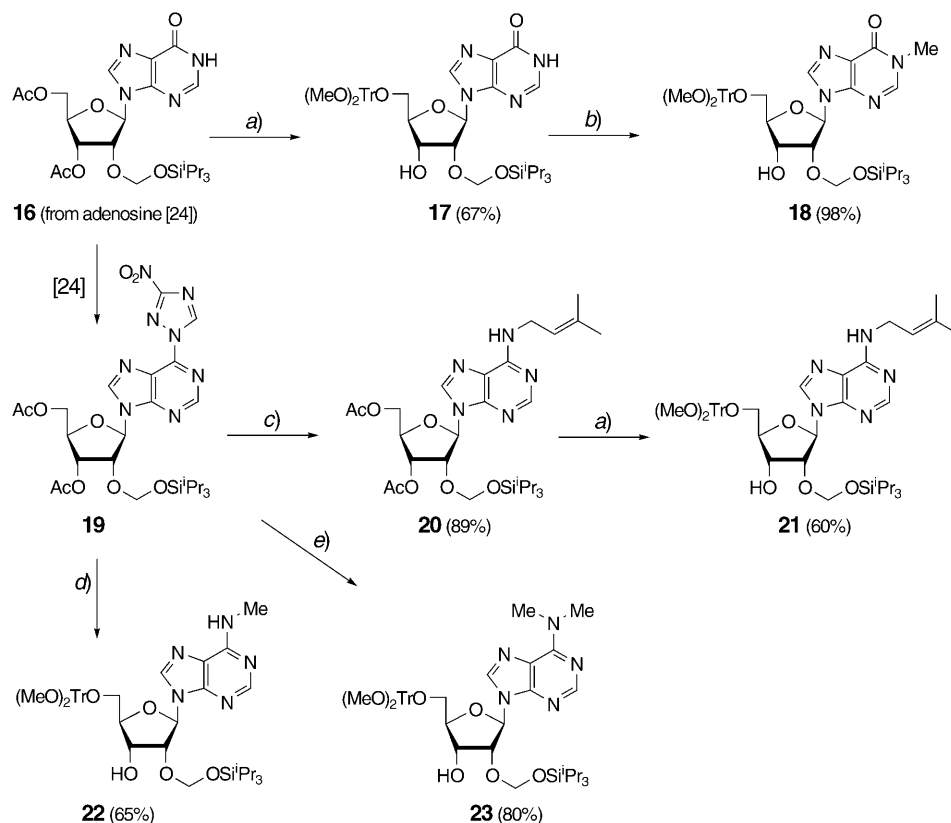
2.8. *N⁶-Isopent-2-enyladenosine (i^6A)*. This nucleoside acts as a growth factor (cytokinin) in plants [40] and is also found at position 37 of tRNAs [1]. Only recently, it was incorporated enzymatically into tRNAs for studying anticodon stem structuration [41], and chemically into short RNA sequences for thermodynamic investigations [19][42]. The reported methodology involved the preparation of a phosphoramidite building block with a reactive, 'convertible' purine derivative, which was converted into the *N⁶*-isopentenyladenosine upon treatment of the immobilized RNA sequence with isopentenylamine¹⁰⁾. We recently reported an optimized method for the preparation of the 2'-*O*-tom-protected, 6-(nitrotriazolyl)-substituted adenosine derivative **19** [24], which served as convenient precursor for the *N⁶*-alkylated adenosine derivatives **20**, **22**, and **23** (*Scheme 2*). By treatment of **19** with isopent-2-enylamine (=3-methylbut-2-en-1-amine) in pyridine/Et₃N, the corresponding *N⁶*-isopent-2-enyl derivative **20** was obtained in 89% yield. Deacetylation of this intermediate with NH₃ in MeOH, fol-

⁸⁾ Revealed by an NMR investigation of a short synthetic D-containing oligomer, which was prepared from the 2'-*O*-tbdms-protected phosphoramidite [38].

⁹⁾ Hydrogenation of 2'-*O*-tom protected uridine provided the corresponding 5,6-dihydrouridine derivative in excellent yield. This reaction, however, could not be carried out in the presence of a 5'-*O*-(MeO)₂Tr group.

¹⁰⁾ The same strategy was used for the preparation of a *m⁶A* containing RNA sequence [43].

Scheme 2



a) 1. NH_3 , MeOH, 20° ; 2. $(\text{MeO})_2\text{TrCl}$, pyridine, 20° . b) 1. K_2CO_3 , DMF, 20° ; then MeI, -15° . c) Isopent-2-enylamine $\cdot \text{HCl}$, Et_3N , pyridine, 20° . d) 1. MeNH_2 , EtOH, 20° ; 2. $(\text{MeO})_2\text{TrCl}$, pyridine, 20° . e) 1. Me_2NH , EtOH, 20° ; 2. $(\text{MeO})_2\text{TrCl}$, pyridine, 20° .

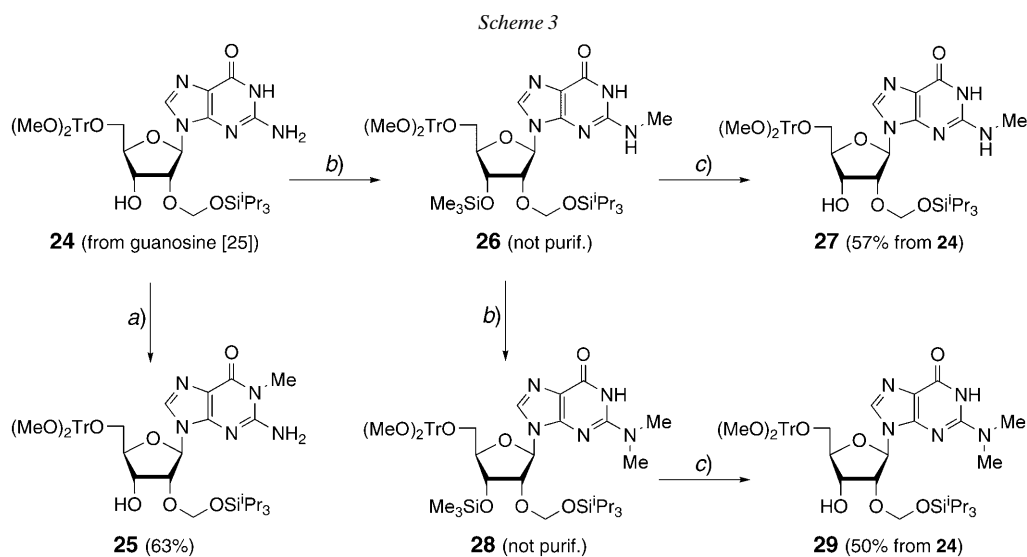
lowed by evaporation and dimethoxytritylation with $(\text{MeO})_2\text{TrCl}$ in pyridine gave the fully protected N^6 -isopent-2-enyladenosine **21** in 60% yield.

2.9. N^6 -Methyladenosine (m^6A). Often adjacent to a cytidine at position 37 in some bacterial tRNAs, this nucleoside is involved in a proper codon/anticodon recognition [1]. In analogy to the preparation of **21** (see Sect. 2.8), we treated the 2'-O-tom-protected purine derivative **19** with MeNH_2 in EtOH, followed by introduction of the $(\text{MeO})_2\text{Tr}$ group under standard conditions, and obtained **22** in 65% yield (Scheme 2).

2.10. N^6,N^6 -Dimethyladenosine (m^6_2A). This adenosine derivative is found at the 5'-terminal cap sequence of some mRNAs and is related to the antibiotic nucleoside analogue puromycin. The 2'-O-tom, 5'-O- $(\text{MeO})_2\text{Tr}$ protected N^6,N^6 -dimethyladenosine **23** was obtained again from the intermediate **19**, upon treatment with Me_2NH in EtOH and $(\text{MeO})_2\text{TrCl}$ in pyridine (80% yield, Scheme 2).

2.11. 1-Methylguanosine (m^1G). This abundant guanosine derivative is found at position 37 of many tRNAs and is correlated with the presence of adenosine in position 36 [1], preventing frame shift by 'quadruplet translocation' [44]. A multi-step synthesis

of the 2'-*O*-tom, *N*-acetyl-protected 1-methylguanosine phosphoramidite has been reported [11]. We prepared the corresponding nucleoside **25** from the readily available intermediate **24** [25] by treatment with MeI/K₂CO₃ in DMF at –15° (63% yield; Scheme 3)¹¹).



a) 1. K₂CO₃, DMF, 20°; then MeI, –15°. b) 1. Me₃Si-Cl, pyridine, 20°; then 1,3-benzodithiolylum tetrafluoroborate; 2. (SiMe₃)₃SiH/AIBN, benzene, reflux. c) NH₃, MeOH, THF, 20°.

2.12. *N*²-Methylguanosine (*m*²G). This modified nucleoside, present at different positions within tRNAs, has been already incorporated into RNA sequences as its 2'-*O* tom/*O*⁶-(nitrophenylethyl)-protected phosphoramidite building block. The methylamino substituent was thereby introduced into a protected 2-fluorinosine derivative by a nucleophilic aromatic substitution reaction with MeNH₂ [11]. In contrast, we introduced the Me group into the protected guanosine derivative **24** by adopting a one-pot method developed by Sekine and Satoh [45]. First, the nucleoside **24** in pyridine was treated with Me₃SiCl (→ silylation of O–C(6) and O–C(3')) and then with 1,3-benzodithiolylum tetrafluoroborate (Scheme 3). The resulting *N*²-(1,3-benzodithiol-2-yl) derivative was filtered on silica gel and treated with (Me₃Si)₃SiH [46]/2,2'-azobis[isobutyronitrile] (AIBN) in refluxing benzene (→ **26**, not isolated)¹². Finally, the remaining Me₃Si group of **26** was removed with NH₃ in MeOH, and the nucleoside **27** was obtained in a 57% yield (based on **24**).

¹¹) The modified nucleoside **25** was already incorporated by employing a corresponding *N*²-acetylated building block. We found, however, that this protecting group is not required, since the N(2) position of guanosine derivatives is inert under standard coupling conditions (see also [25] for the incorporation of the parent *N*²-unprotected guanosine phosphoramidite into RNA sequences).

¹²) This reduction was originally carried out with Bu₃SnH/AIBN according to [45]; however, it was difficult to separate the tin-containing by-products from **26** and **27**.

2.12. N^2,N^2 -Dimethylguanosine (m_2^2G). This dimethylated guanosine is a rare tRNA modification, occurring at different positions. The corresponding 2'-*O*-tom,5'-*O*-(MeO)₂-Tr,6'-*O*-[(4-nitrophenyl)ethyl]-protected phosphoramidite has been prepared earlier in analogy to the related N^2 -monomethylguanosine derivative [11] (see also Sect. 2.11). We prepared the protected N^2,N^2 -dimethylguanosine nucleoside **28** from the crude N^2 -monomethylated intermediate **26** (see Sect. 2.11) by repeating the sequential treatment with 1,3-benzodithiolium tetrafluoroborate [45] and (Me₃Si)₃SiH [46]/AIBN ($\rightarrow$ **28**, not isolated; Scheme 3). After cleavage of the Me₃Si group with NH₃ in MeOH, the fully protected nucleoside **29** was obtained in 50% yield (from **24**).

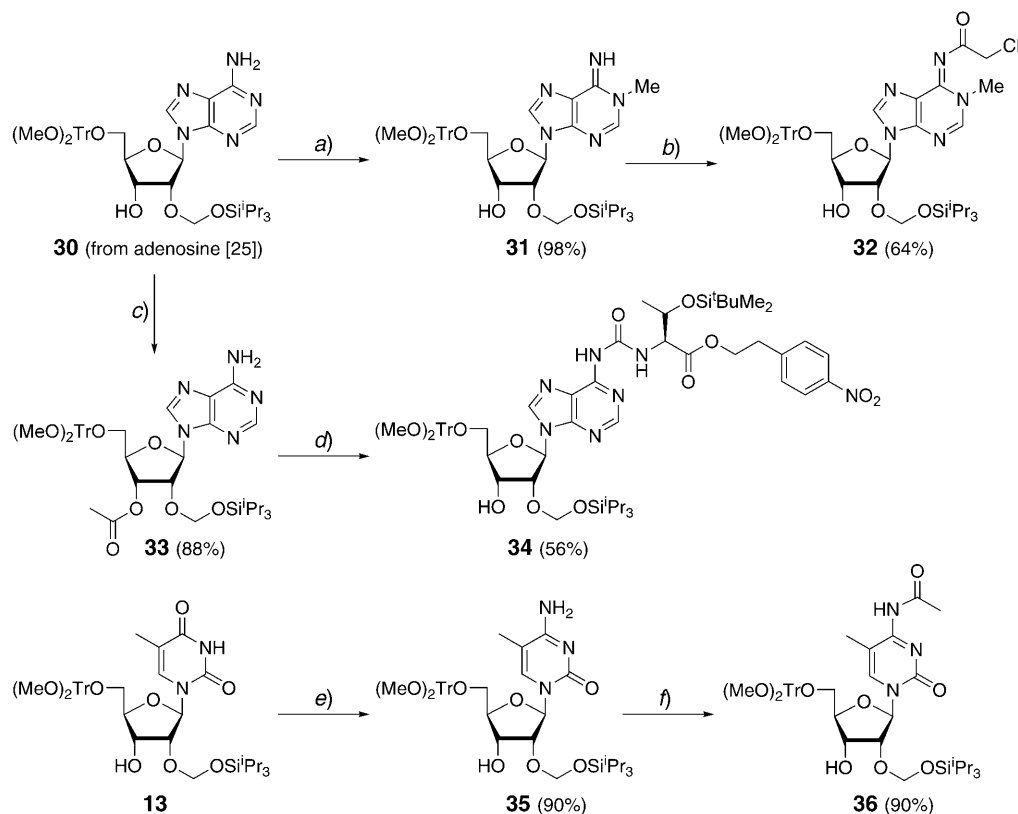
2.13. 1-Methyladenosine (m^1A). This modified nucleoside is found at position 58 of ca. 25% of all tRNAs, at position 14 in the D-loop and at position 9 of some mitochondrial tRNAs, and is required for a proper functional folding of human mitochondrial tRNA^{Lys} [8]. The corresponding 2'-*O*-tbdms-protected phosphoramidite has been prepared by stepwise introduction of all protecting groups (1. chloroacetyl, 2. (MeO)₂Tr, 3. tbdms) into 1-methyladenosine [12]. In contrast, we first prepared the 1-methyl, 2'-*O*-tom-protected adenosine derivative **31** by treatment of the easily accessible nucleoside **30** [25] with MeI in DMF (98% yield; Scheme 4). The chloroacetyl protecting group was then introduced with (ClCH₂CO)₂O in pyridine according to [12], and the fully protected 1-methyladenosine nucleoside **32** was obtained in a yield of 64% after cleavage of the concomitantly formed 3'-*O*-(chloroacetyl) group with NH₃ in MeOH according to [12].

2.14. N-[(9-β-D-Ribofuranosyl-9H-purin-6-yl)carbamoyl]-L-threonine ($t^6A = N^6$ [(L-Threonin-N^α-yl)carbamoyl]adenosine). This is one of the most extensively modified nucleosides found at the position 37 of tRNAs which recognize codons starting with an adenosine; it is also the most conserved modification within all phylogenetic domains of life [1]. The corresponding 2'-*O*-tbdms-protected phosphoramidite has been prepared already twice (with different protecting groups for the L-threonine moiety), by first adding the protected amino acid derivative to an activated N^6 -carbamoyl-adenosine [20] or an N^6 -isocyanato adenosine [21], followed by stepwise introduction of the 5'-*O*-(MeO)₂Tr and the 2'-*O*-tbdms protecting group [20][21]. In 1999, we have introduced a method for the preparation of *N*-carbamoylated nucleosides, which was applied to the synthesis of ribonucleosides containing photolabile [47] and fluoride labile [25] nucleobase protecting groups. Meanwhile, we have further optimized this method¹³), which now allowed the straightforward synthesis of nucleoside **34** from the adenosine derivative **30**. Acetylation at the 3'-*O* position of **30** with Ac₂O in pyridine gave the derivative **33** in a yield of 88% (Scheme 4). This intermediate was treated first with 1,1'-carbonylbis[(1*H*-1,2,4-triazole)] and Et₃N in 1,2-dichloroethane, followed by addition of *O*-[(*tert*-butyl)dimethylsilyl]-L-threonine 2-(4-nitrophenyl)ethyl ester (prepared according to [21]). After extraction, the remaining 3'-*O*-acetyl group was cleaved with NH₃ in MeOH, and the fully protected t^6A derivative **34** was isolated in of 56% yield (based on **33**).

2.15. 5-Methylcytidine (m^5C). Present at position 49 of some tRNAs, this nucleoside interestingly is also found at the wobble position 34 of some eukaryotic tRNA, where it

¹³) Carried out by M. Meyappan (Postdoc EPFL).

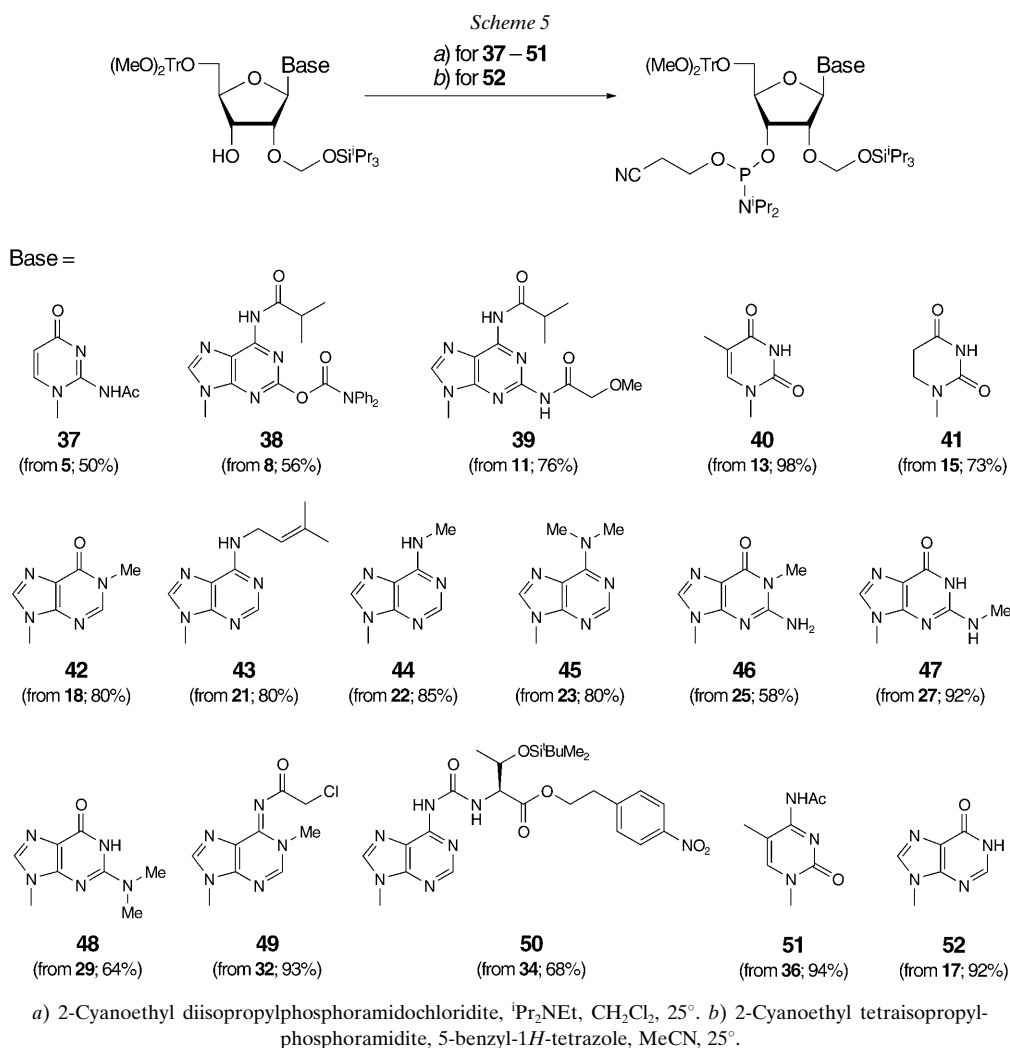
Scheme 4



a) MeI, DMF, 20°. b) 1. (ClCH₂CO)₂O, (CH₂Cl)₂, pyridine, –15°; 2. NH₃, MeOH, –15°. c) 1. Ac₂O, DMAP, pyridine, 20°. d) 1. 1,1'-Carbonylbis[1*H*-(1,2,4 triazole)], Et₃N, (CH₂Cl)₂, 70°, then *O*³-[(*tert*-butyl)dimethylsilyl]-L-threonine 2-(4-nitrophenyl)ethyl ester, 70°; 2. NH₃, MeOH, 20°. e) 1. Ac₂O, DMAP, pyridine, 20°; 2. 1*H*-1,2,4-triazole, 4-chlorophenyl phosphorodichloridate, ³Pr₂NEt, MeCN, 20°; 3. NH₃, dioxane, MeCN, H₂O, 20°; 4. NaOH, THF, MeOH, H₂O, 4°. f) Ac₂O, DMF, 20°.

replaces 2'-*O*-methylcytidine [1]. We prepared the corresponding 2'-*O*-tom protected nucleoside **36** by adapting one of our recently reported, optimized base-transformation methods [24]. The 5-methyluridine nucleoside **13** (see Scheme 1) was first acetylated at the 3'-OH group with Ac₂O in pyridine, then treated with (ClC₆H₄O)P(O)Cl₂, 1*H*-1,2,4-triazole, and ³Pr₂NEt in MeCN (→ formation of the 4-triazolide derivative), and finally with NH₃ in dioxane/H₂O; after extraction and deacetylation with NaOMe in MeOH, the cytidine nucleoside **35** was isolated in 90% yield. Finally, the latter was transformed into its *N*⁴-acetylated derivative **36** by selective *N*-acetylation with Ac₂O in DMF and isolated in 90% yield.

3. Preparation of Phosphoramidites. – The protected nucleosides **5**, **8**, **11**, **13**, **15**, **18**, **21–23**, **25**, **27**, **29**, **32**, **34**, and **36** were finally converted with ³Pr₂NEt/2-cyanoethyl diisopropylphosphoramidochloridite in CH₂Cl₂ into the corresponding phosphoramidites



37–51 (*Scheme 5*). However, due to a significant side reaction at O–C(6), the protected inosine phosphoramidite **52** was prepared by a different method, by treating the nucleoside **17** with 2-cyanoethyl tetraisopropylphosphoramidite and 5-(benzylthio)-1H-tetrazole [22] [23] in MeCN (conditions adapted from [48]). After chromatography on silica gel, these building blocks were isolated in yields between 50 and 98%¹⁴).

¹⁴) The lower yields were obtained from small-scale reactions. High yields of phosphoramidites (>85%) can usually be obtained only from reactions carried out on a >0.5-mmol scale. Since for small-scale reactions more equivalents of silica gel have to be employed, the decomposition of these reactive compounds occurs more efficiently.

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Experimental Part

General. Reagents and solvents (highest purity): from various suppliers, used without further purification; [(triisopropylsilyl)oxy]methyl chloride (=tom-Cl) was prepared according to [23]. The 4 Å molecular sieves (4 Å MS) were activated overnight at 180°/0.01 mbar. Room temperature (r.t.) means ca. 20°. Workup implies distribution of the reaction mixture between CH₂Cl₂ and sat. aq. NaHCO₃ soln., drying of the org. layer (MgSO₄), and evaporation. TLC: precoated silica gel plates from *Merck*, stained by dipping into a soln. of anisaldehyde (10 ml), H₂SO₄ (10 ml), and AcOH (2 ml) in EtOH (180 ml) and subsequent heating with a heat gun. CC (column chromatography): silica gel 60 (230–400 mesh) from *Fluka*. NMR: *Bruker spectrometers*; chemical shift δ in ppm rel. to external standards (¹H- and ¹³C: Me₄Si; ³¹P: 85% aq. H₃PO₄ soln.), *J* in Hz. ESI-MS (pos. mode): *Finnigan SSQ-710* system; measurements in MeCN/H₂O/AcOH 50:50:1; in *m/z* (rel.%).

5'-O-(4,4'-Dimethoxytrityl)-O²-methyluridine (2). A soln. of **1** (4.67 g, 20.6 mmol, prepared according to [32]) in MeOH (100 ml) was treated with Et₃N (10 ml, 58.4 mmol) and stirred overnight at 70° in an autoclave. Evaporation gave a white solid which was dissolved in pyridine (75 ml), treated with (MeO)₂TrCl (6.93 g, 20.3 mmol), and stirred for 12 h at r.t. Workup and CC (SiO₂ (140 g), CH₂Cl₂/MeOH 19:1 → 17:3) gave **2** (6.15 g, 60%). Yellow foam. TLC (CH₂Cl₂/MeOH 19:1): *R_f* 0.15. ¹H-NMR (400 MHz, CDCl₃): 3.44 (*m*, CH₂(5')); 3.49 (*s*, OH); 3.78 (*s*, 2 MeO); 3.96 (*s*, MeO–C(2)); 4.19 (*d*, *J*=3.9, H–C(4')); 4.41 (*t*, *J*=4.8, H–C(2')); 4.48 (*t*, *J*=5.1, H–C(3')); 5.59 (*d*, *J*=7.7, H–C(5)); 5.95 (*d*, *J*=5.5, H–C(1')); 6.85 (*d*, *J*=8.8, 4 arom. H); 7.21–7.41 (*m*, 9 arom. H); 7.77 (*d*, *J*=7.7, H–C(6)). ¹³C-NMR (100 MHz, CDCl₃): 55.3 (*q*, MeO); 55.9 (*q*, MeO–C(2)); 63.0 (*t*, C(5')); 71.1 (*d*, C(3')); 74.7 (*d*, C(2')); 83.9 (*d*, C(4')); 87.2 (*s*, arom. C); 89.7 (*d*, C(1')); 113.4 (*d*, arom. C); 127.1, 128.1, 128.2, 130.1, 130.2 (5*d*, arom. C); 135.1, 135.3 (2*s*, arom. C); 138.4 (*d*, C(6)); 144.3 (*s*, arom. C); 156.3 (*s*, C(2)); 158.7 (*s*, arom. C); 164.1 (*s*, C(4)); 171.6 (*s*, arom. C). ESI-MS: 561.27 (100, [M+H]⁺).

5'-O-(4,4'-Dimethoxytrityl)isocytidine (3). NH₃ (50 ml) was condensed into an autoclave containing **2** (2.50 g, 4.4 mmol). After sealing, the mixture was stirred for 12 h at 65°. Evaporation gave crude **3** (2.07 g) as yellow oil. An anal. sample was obtained by prep. TLC (CH₂Cl₂/MeOH 9:1). TLC (CH₂Cl₂/MeOH 19:1): *R_f* 0.18. ¹H-NMR (400 MHz, (D₆)DMSO): 3.20–3.26 (*m*, CH₂(5')); 3.73 (*s*, 2 MeO); 4.00 (*d*, *J*=3.0, H–C(4')); 4.07–4.11 (*m*, H–C(3'), H–C(2')); 5.27 (*d*, *J*=5.1, OH–C(3')); 5.35 (*d*, *J*=7.4, H–C(5)); 5.52 (*d*, *J*=5.1, OH–C(2')); 5.60 (*d*, *J*=4.4, H–C(1')); 6.89 (*d*, *J*=8.8, 4 arom. H); 7.22–7.37 (*m*, 9 arom. H); 7.53 (*d*, *J*=7.3, H–C(6)). ¹³C-NMR (100 MHz, (D₆)DMSO): 55.6 (*q*, MeO); 63.4 (*t*, C(5')); 69.9 (*d*, C(2')); 74.2 (*d*, C(3')); 83.7 (*d*, C(4')); 86.4 (*s*, arom. C); 90.7 (*d*, C(1')); 107.4 (*d*, C(5)); 113.7 (*d*, arom. C); 127.3, 128.1, 128.4, 130.2 (4*d*, arom. C); 135.6 (*s*, arom. C); 137.4 (*s*, arom. C); 145.0 (*d*, C(6)); 155.2 (*d*, C(2)); 158.6 (*s*, arom. C); 169.92 (*s*, C(4)). ESI-MS: 546.29 (100, [M+H]⁺).

N²-Acetyl-5'-O-(4,4'-dimethoxytrityl)isocytidine (4). A soln. of crude **3** (2.30 g, ca. 4.2 mmol) in pyridine (18 ml) was treated with Me₃SiCl (2.6 ml, 21.0 mmol). After 90 min at 4°, DMAP (250 mg, 2.1 mmol) and AcCl (0.3 ml, 4.2 mmol) were added. After 14 h at r.t., and workup, the residue was treated 1*M* with Bu₄NF in THF (20 ml) at r.t. for 5 min. Addition 0.1*M* of aq. Na-phosphate buffer (100 ml; pH 7), workup, and CC (SiO₂ (60 g), CH₂Cl₂/acetone 9:1 → 1:1) gave **4** (1.81 g, 63% based on **2**). Yellow foam. TLC (CH₂Cl₂/MeOH 19:1): *R_f* 0.23. ¹H-NMR (400 MHz, CDCl₃): 2.24 (*s*, MeCO); 3.29–3.33 (*m*, CH₂(5')); 3.80 (*s*, 2 MeO); 3.37–3.46 (*m*, H–C(3'), H–C(4')); 4.40–4.43 (*m*, H–C(2'), OH); 5.62 (*d*, *J*=7.8, H–C(5)); 6.02 (*s*, H–C(1')); 6.84 (*d*, *J*=7.0, 4 arom. H); 7.24–7.38 (*m*, 9 arom. H); 7.92 (*d*, *J*=8.6, H–C(6)); 8.62 (*d*, *J*=3.9, NH–C(2)). ¹³C-NMR (100 MHz, CDCl₃): 24.5 (*q*, MeCO); 55.7 (*q*, MeO); 59.4 (*t*, C(5')); 63.4 (*d*, C(2')); 72.7 (*d*, C(3')); 86.7 (*d*, C(4')); 87.6 (*s*, arom. C); 93.5 (*d*, C(1')); 105.7 (*d*, C(5)); 113.7 (*d*, arom. C); 124.2, 127.6, 128.4, 128.5, 130.4, (5*d*, arom. C); 135.4, 135.5 (2*s*, arom. C); 139.9 (*d*, C(6)); 144.5 150.1 (2*s*, arom. C); 153.6 (*d*, C(2)); 159.1 (*s*, arom. C); 159.7 (*s*, C(4)); 184.7 (*s*, MeCO). ESI-MS: 588.36 (100, [M+H]⁺).

N²-Acetyl-5'-O-(4,4'-dimethoxytrityl)-2'-O-[(triisopropylsilyl)oxy]methylisocytidine (5). A soln. of **4** (3.50 g, 5.9 mmol) and ¹Pr₂NEt (3.50 ml, 20.8 mmol) in ClCH₂CH₂Cl (35 ml) was treated with ¹Bu₂SnCl₂ (1.99 g, 6.6 mmol), stirred for 30 min at r.t., treated with tom-Cl (1.46 g, 6.6 mmol), and stirred at r.t. for 25 min. Workup and CC (SiO₂ (35 g), hexane/AcOEt 9:1 → 1:1) gave **5** (552 mg, 12%). Light yellow foam. TLC (hexane/AcOEt 1:1): *R_f* 0.62. ¹H-NMR (400 MHz, CDCl₃): 1.00–1.22 (*m*, ¹Pr₃Si); 2.20 (*s*, MeCO); 3.02 (*d*, *J*=7.8,

OH–C(3'')); 3.59 (br. s, CH₂(5'')); 3.82 (s, 2 MeO); 4.09 (d, *J* = 7.8, H–C(4'')); 4.35 (d, *J* = 3.9, H–C(2'')); 4.51 (d, *J* = 4.7, H–C(3'')); 5.26 (d, *J* = 3.9, 1 H, OCH₂O); 5.29 (d, *J* = 3.9, 1 H, OCH₂O); 5.35 (d, *J* = 7.8, H–C(5'')); 6.27 (s, H–C(1'')); 6.86 (d, *J* = 8.6, 4 arom. H); 7.29–7.45 (*m*, 9 arom. H); 8.29 (d, *J* = 8.5, H–C(6'')); 13.0 (br. s, NH–C(2'')). ¹³C-NMR (100 MHz, CDCl₃): 12.3 (d, Me₂CH); 18.2 (*q*, Me₂CH); 28.8 (*q*, MeCO); 55.7 (*q*, MeO); 61.5 (*t*, C(5'')); 68.6 (d, C(2'')); 82.3 (d, C(3'')); 84.0 (d, C(4'')); 87.6 (s, arom. C); 89.4 (d, C(1'')); 90.4 (*t*, OCH₂O); 105.6 (d, C(5'')); 113.7 (d, arom. C); 127.6, 128.4, 128.6, 130.5, 130.6 (5*d*, arom. C); 135.4 (s, arom. C); 140.2 (d, C(6'')); 144.7 (s, arom. C); 152.4 (d, C(2'')); 159.2 (s, arom. C); 160.2 (s, C(4'')); 185.4 (s, MeCO). ESI-MS: 774.29 (100, [M+H]⁺).

*N*⁶-Isobutyrylisoguanosine (=N⁶-(2-Methyl-1-oxopropyl)isoguanosine; **6**). Carefully dried (0.01 mbar, 24 h at 50°) isoguanosine (=1,2-dihydro-2-oxoadenosine; 2.83 g, 10 mmol) was suspended in pyridine (50 ml) containing 4 Å MS, stirred 2 h at r.t., treated with Me₃SiCl (10 ml, 80 mmol), and stirred for 2 h at 4°. Then, DMAP (980 mg, 7 mmol) and isobutyryl chloride (1.2 ml, 11 mmol) were added. After 12 h at r.t., workup, and evaporation, the yellow oil was dissolved in MeOH/AcOH 9:1 (50 ml) and stirred for 3 h at r.t. Evaporation gave crude **6** (3.41 g). White solid. TLC (CH₂Cl₂/MeOH 1:1); *R*_f 0.10. ¹H-NMR (400 MHz, (D₆)DMSO): 1.12 (d, *J* = 6.8, Me₂CHCO); 3.00 (*sept.*, *J* = 6.8, Me₂CHCO); 3.55–3.65 (*m*, CH₂(5'')); 3.92 (*dd*, *J* = 6.7, 3.4, H–C(4'')); 4.10 (*dd*, *J* = 8.2, 4.7, H–C(3'')); 4.48 (*dd*, *J* = 5.8, 11.2, H–C(2'')); 5.18 (d, *J* = 4.8, OH–C(3'')); 5.25 (*m*, OH–C(5'')); 5.47 (d, *J* = 5.9, OH–C(2'')); 5.72 (d, *J* = 5.9, H–C(1'')); 8.32 (s, H–C(8'')); 11.92 (br. s, NH). ¹³C-NMR (100 MHz, (D₆)DMSO): 22.0 (*q*, Me₂CHCO); 35.1 (d, Me₂CHCO); 62.3 (*t*, C(5'')); 71.3 (d, C(3'')); 74.1 (d, C(2'')); 86.6 (d, C(4'')); 88.3 (d, C(1'')); 110.0 (s, C(5'')); 139.6 (d, C(8'')); 152.2 (s, C(4'')); 154.7 (s, C(6'')); 157.0 (s, C(2'')); 179.9 (s, Me₂CHCO). ESI-MS: 354.29 (100, [M+H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-O²-(diphenylcarbamoyl)-N⁶-isobutyrylisoguanosine (**7**). A soln. of crude **6** (5.63 g, ca. 15.9 mmol) in pyridine (250 ml) was treated at r.t. with ¹Pr₂NEt (3.0 ml, 17.5 mmol) and then with diphenylcarbamic chloride (4.06 g, 17.5 mmol). After 30 min at r.t., the mixture was treated with (MeO)₂TrCl (5.40 g, 15.9 mmol). Workup after 1 h at r.t. and CC (SiO₂ (90 g), AcOEt → AcOEt/MeOH 99:1) afforded **7** (6.09 g, 45% from isoguanosine). Yellow foam. TLC (CH₂Cl₂/MeOH 17:3); *R*_f 0.88. ¹H-NMR (400 MHz, CDCl₃): 1.28–1.32 (d, *J* = 7.3, Me₂CHCO); 3.23–3.33 (*m*, Me₂CHCO, OH–C(3''), H–C(5'')); 3.40 (*dd*, *J* = 3.7, 11.0, H'–C(5'')); 3.77 (s, 2 MeO); 4.37 (d, *J* = 3.0, H–C(3'')); 4.43 (br. s, H–C(4'')); 4.77 (br. s, H–C(2'')); 5.32 (br. s, OH–C(2'')); 6.01 (d, *J* = 5.1, H–C(1'')); 6.75–6.79 (*m*, 4 arom. H); 7.16–7.39 (*m*, 19 arom. H); 8.12 (s, H–C(8'')). ¹³C-NMR (100 MHz, CDCl₃): 19.1 (*q*, Me₂CHCO); 35.8 (d, Me₂CHCO); 55.2 (*q*, MeO); 63.5 (*t*, C(5'')); 72.4 (d, C(2'')); 75.9 (d, C(3'')); 76.9 (d, C(4'')); 85.7 (d, C(1'')); 90.1 (s, arom. C); 113.2 (d, arom. C); 120.5 (s, C(5'')); 126.6, 126.7, 126.8, 126.9, 127.0, 127.1, 127.8, 127.9, 128.2, 129.2, 135.4, 136.6 (12*d*, arom. C); 141.2 (d, C(8'')); 144.3 (s, C(4'')); 150.3 (s, arom. C); 152.0 (s, CO); 155.5 (s, C(6'')); 158.6 (s, C(2'')); 176.3 (s, Me₃-CHCO). ESI-MS: 851.36 (100, [M+H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-O²-(diphenylcarbamoyl)-N⁶-isobutyryl-2'-O-[[triisopropylsilyl]oxy]methylisoguanosine (**8**). A soln. of **7** (5.90 g, 6.9 mmol) and ¹Pr₂NEt (4.2 ml, 24.3 mmol) in ClCH₂CH₂Cl (28 ml) was treated with Bu₂SnCl₂ (2.32 g, 7.6 mmol), stirred for 10 min at r.t., heated to 75°, treated with tom-Cl (1.85 g, 8.3 mmol), and heated for 25 min at 75°. Workup and CC (SiO₂ (150 g), hexane/AcOEt 9:1 → 3:2) gave **8** (1.64 g, 23%). Light yellow foam. TLC (hexane/AcOEt 1:1); *R*_f 0.27. ¹H-NMR (400 MHz, CDCl₃): 0.92–1.21 (*m*, ¹Pr₃Si); 1.32 (d, *J* = 7.3, Me₂CHCO); 3.19 (s, OH–C(3'')); 3.35–3.51 (*m*, Me₂CHCO); 3.74–3.82 (*m*, H–C(5'')); 3.82 (s, 2 MeO); 3.99 (d, *J* = 13.2, H'–C(5'')); 4.38 (s, H–C(3'')); 4.58 (d, *J* = 4.4, H–C(4'')); 4.84 (d, *J* = 5.1, 1 H, OCH₂O); 4.86–4.89 (*m*, H–C(2'')); 5.04 (d, *J* = 5.1, 1 H, OCH₂O); 5.93 (d, *J* = 7.4, H–C(1'')); 6.85 (d, *J* = 4.4, 4 arom. H); 7.10–7.45 (*m*, 19 arom. H); 8.57 (s, H–C(8'')). ¹³C-NMR (100 MHz, CDCl₃): 11.8 (d, Me₂CH); 17.8 (*q*, Me₂CH, Me₂CHCO); 35.8 (d, Me₂CHCO); 55.3 (*q*, MeO); 63.3 (*t*, C(5'')); 72.0 (d, C(2'')); 81.9 (d, C(3'')); 86.5 (d, C(4'')); 87.8 (d, C(1'')); 89.6 (s, arom. C); 90.8 (*t*, OCH₂O); 113.2 (d, arom. C); 121.9 (s, C(5'')); 126.6, 126.7, 126.8, 126.9, 127.0, 127.1, 127.8, 127.9, 128.2, 130.0, 130.1, 135.7, 136.6 (12*d*, arom. C); 139.5 (d, C(8'')); 143.2 (s, C(4'')); 150.7 (s, arom. C); 151.3 (s, CO); 155.4 (s, C(6'')); 158.6 (s, C(2'')); 176.4 (s, Me₂CHCO). ESI-MS: 1037.36 (100, [M+H]⁺).

2-[(Methoxyacetyl)amino]adenosine (=N²-(Methoxyacetyl)purine Ribonucleoside = N²-(Methoxyacetyl)-9-β-D-ribofuranosyl-9H-purine-2,6-diamine; **9**). At 4°, a soln. of 2-aminoadenosine (18.5 g, 65.6 mmol) in pyridine (130 ml) was treated with Me₃SiCl (82.5 ml, 656 mmol), stirred for 2 h at r.t., diluted with MeCN (195 ml), cooled to 4°, treated with methoxyacetyl chloride (21 ml, 230 mmol), and finally stirred for 40 min at 4°. After addition of CH₂Cl₂ (400 ml), the soln. was poured into H₂O (400 ml). The org. phase was evaporated, and the residue was co-evaporated with toluene (3×50 ml). The resulting foam was dissolved in MeOH/THF/25% aq. NH₃ soln. 1:1:1 (300 ml). After 1 h at r.t., evaporation, co-evaporation with toluene (3×50 ml), and crystallization (AcOEt), **9** (19.9 g, 86%). Light yellow powder. TLC (MeOH/CH₂Cl₂ 3:17); *R*_f 0.18. ¹H-NMR (400 MHz, (D₆)DMSO): 3.42 (d, *J* = 3.7, CH₂OMe); 3.55 (*td*, *J* = 4.9, 12.2, H–C(5'')); 3.65 (*td*, *J* = 4.7, 11.9,

H'–C(5''); 4.58 (*dd*, $J=5.7, 11.2$, H–C(4'')); 4.16 (*dd*, $J=4.7, 8.2$, H–C(3'')); 4.18 (*s*, MeO); 4.58 (*dd*, $J=5.7, 11.2$, H–C(2'')); 5.13 (*t*, $J=5.6$, OH–C(5'')); 5.13 (*d*, $J=4.3$, OH); 5.44 (*d*, $J=5.9$, OH); 5.81 (*d*, $J=5.9$, H–C(1'')); 7.30 (*br. s*, NH₂–C(6)); 8.23 (*s*, H–C(8)); 9.63 (*s*, NH–C(2)). ¹³C-NMR (100 MHz, (D₆)DMSO): 58.9 (*q*, MeO); 61.9 (*t*, C(5'')); 70.9 (*t*, CH₂OMe); 72.3 (*d*, C(2'')); 73.9 (*d*, C(3'')); 86.0 (*s*, C(5)); 87.6 (*d*, C(4'')); 116.7 (*d*, C(1'')); 139.5 (*d*, C(8)); 150.6 (*s*, C(4)); 152.6 (*s*, C(6)), 156.5 (*s*, C(2)); 168.9 (*s*, CO). ESI-MS: 355.34 (100, [M+H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-N⁶-isobutyryl-2-[(methoxyacetyl)amino]adenosine (**10**). At 4°, a soln. of **9** (25.4 g, 72 mmol) in pyridine (140 ml) was treated with Me₃Si-Cl (90 ml, 720 mmol), stirred for 2 h at r.t., diluted with MeCN (215 ml), cooled to 4°, treated with isobutyryl chloride (9.1 ml, 86.2 mmol), and finally stirred for 40 min at 4°. After addition of CH₂Cl₂ (400 ml), the soln. was poured into H₂O (400 ml). The org. phase was evaporated, and the residue was co-evaporated with toluene (3×50 ml). The resulting foam was dissolved in MeOH/AcOH 3:1 (200 ml). After 1 h at r.t., evaporation, co-evaporation with toluene (3×50 ml), and co-evaporation with pyridine (50 ml), a yellow foam was obtained, which was dried (0.1 mbar) overnight. The foam was dissolved in pyridine (250 ml), treated with (MeO)₂TrCl (25.0 g, 74.0 mmol), and stirred for 2 h at r.t. After workup, evaporation, and CC (SiO₂ (400 g), CH₂Cl₂ → CH₂Cl₂/MeOH 94:6), **10** (27.4 g, 54%) was obtained. Yellow foam. TLC (CH₂Cl₂/MeOH 19:1): *R*_f 0.44. ¹H-NMR (400 MHz, CDCl₃): 1.42 (*d*, $J=7.0$, Me₂CH); 2.35 (*br. s*, OH–C(3'')); 3.01 (*sept.*, $J=7.0$, Me₂CH); 3.19 (*dd*, $J=2.4, 10.5$, H–C(5'')); 3.39 (*dd*, $J=3.3, 10.6$, H'–C(5'')); 3.53 (*br. s*, MeO); 3.58 (*br. s*, OH–C(2'')); 3.60 (*s*, MeO); 4.08 (*s*, CH₂CO); 4.41 (*d*, $J=5.0$, H–C(2'')); 4.45 (*br. s*, H–C(3'')); 5.03 (*dd*, $J=5.4, 9.0$, H–C(4'')); 5.97 (*d*, $J=6.1$, H–C(1'')); 6.70 (*d*, $J=8.7, 4$ arom. H); 7.10–7.31 (*m*, 9 arom. H); 8.19 (*s*, H–C(8)); 8.68 (*s*, NH–C(6)); 9.33 (*s*, NH–C(2)). ¹³C-NMR (100 MHz, CDCl₃): 19.6 (*d*, Me₂CH); 36.9 (*q*, Me₂CH); 53.9 (*q*, MeOCH₂); 59.8 (*q*, MeO); 64.3 (*t*, C(5'')); 72.5 (*t*, MeOCH₂); 74.5 (*d*, C(2'')); 87.0 (*d*, C(3'')); 87.6 (*s*, C(5)); 92.8 (*d*, C(4'')); 119.7 (*d*, C(1'')); 127.2, 128.1, 128.2, 130.3 (*4d*, arom. C); 135.6 (*d*, C(8)); 135.7 (*s*, arom. C); 144.8 (*s*, arom. C); 150.3 (*s*, C(4)); 151.1 (*s*, C(6)), 151.5 (*s*, C(2)); 158.9 (*s*, arom. C); 168.8 (*s*, CH₂CO); 175.9 (*s*, Me₂CHCO). ESI-MS: 727.82 (100, [M+H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-N⁶-isobutyryl-2-[(methoxyacetyl)amino]-2'-O-[(triisopropylsilyl)oxy]methyladenosine (**11**). A soln. of **10** (625 mg, 0.9 mmol) and ³Pr₂NEt (0.51 ml, 3.0 mmol) in ClCH₂CH₂Cl (3.5 ml) was treated with Bu₂SnCl₂ (313 mg, 1.0 mmol), stirred for 30 min at r.t., treated with tom-Cl (229 mg, 1.03 mmol), and stirred for 25 min at 80°. Workup and CC (SiO₂ (10 g), hexane/AcOEt 3:1 → AcOEt) gave **11** (290 mg, 37%). Light yellow foam. TLC (AcOEt): *R*_f 0.58. ¹H-NMR (400 MHz, CDCl₃): 1.08–1.16 (*m*, ³Pr₃Si); 1.32 (*d*, $J=6.4$, Me₂CHCO); 2.03 (*br. s*, CH₂(5'')); 3.28–3.97 (*m*, MeO, Me₂CHCO); 3.14 (*d*, $J=5.4$, OH–C(3'')); 3.79 (*s*, MeO); 4.06 (*br. s*, CH₂CO); 4.27 (*br. d*, $J=2.5$, H–C(3'')); 4.59 (*dd*, $J=3.8, 8.2$, H–C(4'')); 4.88 (*t*, $J=5.1$, H–C(2'')); 5.08 (*d*, $J=4.5$, 1 H, OCH₂O); 5.18 (*d*, $J=4.9$, 1 H, OCH₂O); 6.19 (*d*, $J=5.1$, H–C(1'')); 6.80 (*d*, $J=8.3, 4$ arom. H); 7.19–7.45 (*m*, 10 arom. H); 8.09 (*s*, H–C(8)); 8.59 (*s*, NH–C(6)); 8.84 (*s*, NH–C(2)). ¹³C-NMR (100 MHz, CDCl₃): 12.2 (*d*, Me₂CH); 18.2 (*q*, Me₂CH); 19.6 (*q*, Me₂CHCO); 36.3 (*d*, Me₂CHCO); 55.7 (*q*, MeOCH₂); 59.7 (*q*, MeO); 63.9 (*t*, C(5'')); 71.0 (*t*, MeOCH₂); 72.8 (*d*, C(2'')); 82.8 (*d*, C(3'')); 84.7 (*s*, C(5)); 87.5 (*d*, C(4'')); 91.5 (*t*, OCH₂O); 113.6 (*d*, arom. C); 119.9 (*d*, C(1'')); 127.4, 128.3, 128.6, 130.5 (*4d*, arom. C); 136.1 (*d*, C(8)); 136.2 (*s*, arom. C); 145.0 (*s*, arom. C); 150.0 (*s*, C(4)); 152.0 (*s*, C(6)), 152.6 (*s*, C(2)); 158.9 (*s*, arom. C); 167.7 (*s*, CH₂CO); 176.8 (*s*, Me₂CHCO). ESI-MS: 913.34 (100, [M+H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-5-methyl-2'-O-[(triisopropylsilyl)oxy]methyluridine (**13**). A soln. of **12** (1.00 g, 1.8 mmol; obtained according to [7]) and ³Pr₂NEt (0.78 ml, 4.6 mmol) in ClCH₂CH₂Cl (35 ml) was treated with Bu₂SnCl₂ (560 mg, 2.0 mmol), stirred for 30 min at r.t., treated with tom-Cl (450 mg, 2.0 mmol), and stirred for 12 h at r.t. Workup and CC (SiO₂ (30 g), hexane/AcOEt 9:1 → 1:4) gave **13** (500 mg, 38%). Light yellow foam. TLC (hexane/AcOEt 1:1): *R*_f 0.47. ¹H-NMR (400 MHz, CDCl₃): 1.04–1.16 (*m*, ³Pr₃Si); 1.38 (*s*, Me–C(5)); 3.13 (*br. s*, OH–C(3'')); 3.40 (*dd*, $J=1.5, 11.4$, H–C(5'')); 3.53 (*dd*, $J=1.9, 11.5$, H'–C(5'')); 3.81 (*s*, 2 MeO); 4.19 (*br. s*, H–C(4'')); 4.38 (*t*, $J=5.1$, H–C(2'')); 4.48 (*br. s*, H–C(3'')); 5.03 (*d*, $J=4.5$, 1 H, OCH₂O); 5.24 (*d*, $J=4.5$, 1 H, OCH₂O); 6.14 (*d*, $J=8.3$, H–C(1'')); 6.84–6.86 (*m*, 4 arom. H); 7.26–7.43 (*m*, 9 arom. H); 7.66 (*br. s*, H–C(6)); 8.47 (*br. s*, H–N(3)). ¹³C-NMR (100 MHz, CDCl₃): 12.1 (*d*, Me₂CH); 12.3 (*q*, Me–C(5)); 18.2 (*q*, Me₂CH); 55.7 (*q*, MeO); 63.5 (*t*, C(5'')); 70.8 (*d*, C(2'')); 82.9 (*d*, C(3'')); 84.3 (*d*, C(4'')); 86.2 (*s*, arom. C); 87.4 (*d*, C(1'')); 91.2 (*t*, OCH₂O); 111.7 (*s*, C(5)); 113.6 (*d*, arom. C); 127.6, 128.2, 128.5, 130.6 (*4d*, arom. C); 135.6, 135.8 (*2s*, arom. C); 144.7 (*s*, C(6)); 150.7 (*s*, C(2)); 159.2 (*s*, arom. C); 163.9 (*s*, C(4)). ESI-MS: 373.29 (100, [M+H]²⁺).

5'-O-(4,4'-Dimethoxytrityl)-5,6-dihydro-2'-O-[(triisopropylsilyl)oxy]methyluridine (**15**). A soln. of **14** (7.20 g, 13.0 mmol; obtained according to [39]) and ³Pr₂NEt (7.9 ml, 46.0 mmol) in ClCH₂CH₂Cl (50 ml) was treated with Bu₂SnCl₂ (4.39 g, 14.4 mmol), stirred for 30 min at r.t., treated with tom-Cl (0.45 g, 2.0 mmol), and stirred for 25 min at 80°. Workup and CC (SiO₂ (100 g), hexane/AcOEt 9:1 → 1:1) gave **15** (4.37 g, 47%). Light yellow foam. TLC (hexane/AcOEt 1:1): *R*_f 0.61. ¹H NMR (400 MHz, CDCl₃): 1.09–1.28 (*m*, ³Pr₃Si); 2.39–2.57 (*m*, CH₂(5)); 3.04 (*d*, $J=3.1$, OH–C(3'')); 3.31–3.44 (*m*, CH₂(6), CH₂(5'')); 3.66–3.72 (*m*, H–C(4'')); 3.81 (*s*, 2 MeO); 4.26 (*t*, $J=5.5$, H–C(2'')); 4.39–4.40 (*m*, H–C(3'')); 5.01 (*d*, $J=4.7$, 1 H, OCH₂O);

5.22 (*d*, *J* = 4.7, 1 H; OCH₂O); 6.03 (*d*, *J* = 6.2, H–C(1′)); 6.80–6.82 (*d*, *J* = 9.4, 4 arom. H); 7.22–7.44 (*m*, 9 arom. H). ¹³C-NMR (100 MHz, CDCl₃): 12.3 (*d*, Me₂CH); 18.2 (*q*, Me₂CH); 31.5 (*t*, C(5′)); 36.8 (*t*, C(6′)); 55.7 (*q*, MeO); 63.9 (*t*, C(5′)); 71.4 (*d*, C(3′)); 79.8 (*d*, C(2′)); 83.2 (*d*, C(4′)); 86.9 (*s*, arom. C); 87.1 (*d*, C(1′)); 90.9 (*t*, OCH₂O); 113.6 (*d*, arom. C); 127.4, 128.3, 128.6, 128.7, 130.5 (5*d*, arom. C); 135.9, 136.0 (2*s*, arom. C); 144.9 (*s*, arom. C); 152.5, 159.0 (2*s*, C(2), C(4)); 169.9 (*s*, arom. C). ESI-MS: 757.38 (100, [M + H]⁺).

5′-O-(4,4′-Dimethoxytrityl)-2′-O-[(triisopropylsilyl)oxy]methyl]inosine (**17**). A soln. of **16** (1.0 g, 1.9 mmol, prepared according to [24]) in MeOH (2 ml) was treated with a sat. NH₃ soln. in MeOH (6 ml) and stirred for 3 h at r.t. After evaporation, the residue was dissolved in pyridine (5.5 ml), treated with (MeO)₂TrCl (0.78 g, 2.3 mmol), and stirred for 2 h at r.t. Workup and CC (SiO₂ (25 g), hexane/AcOEt 1:1, then CH₂Cl₂/MeOH 99:1 → 9:1) gave **17** (939 mg, 67%). Yellow foam. TLC (CH₂Cl₂/MeOH 1:9): *R*_f 0.50. ¹H-NMR (400 MHz, CDCl₃): 0.90–1.10 (*m*, ¹Pr₃Si); 3.10 (*d*, *J* = 3.1, OH–C(3′)); 3.42 (*dd*, *J* = 3.9, 10.2, H–C(5′)); 3.47 (*dd*, *J* = 3.9, 10.2, H′–C(5′)); 3.80 (*s*, 2 MeO); 4.32 (*m*, H–C(4′)); 4.55 (*m*, H–C(3′)); 4.84 (*t*, *J* = 4.7, H–C(2′)); 4.98 (*d*, *J* = 4.7, 1 H, OCH₂O); 5.17 (*d*, *J* = 4.7, 1 H OCH₂O); 6.17 (*d*, *J* = 5.4, H–C(1′)); 6.82 (*d*, *J* = 8.8, 4 arom. H); 7.30–7.46 (*m*, 9 arom. H); 7.81 (*s*, H–C(8)); 7.94 (*s*, H–C(2)); 12.98 (*br. s*, NH). ¹³C-NMR (400 MHz, CDCl₃): 12.2 (*d*, Me₂CH); 18.2 (*q*, Me₂CH); 55.6 (*q*, MeO); 63.9 (*t*, C(5′)); 71.4 (*d*, C(2′)); 82.9 (*d*, C(3′)); 84.8 (*d*, C(4′)); 87.1 (*d*, C(1′)); 87.4 (*s*, arom. C); 91.3 (*t*, OCH₂O); 113.6 (*d*, arom. C); 125.7 (*s*, C(5)); 127.4, 128.3, 128.6, 129.5, 130.5 (5*d*, arom. C); 136.0, 136.1 (2*s*, arom. C); 139.5 (*d*, C(8)); 144.9 (*s*, arom. C); 145.2 (*s*, C(4)); 149.3 (*s*, C(2)); 158.9 (*s*, C(6)); 159.6 (*s*, arom. C). ESI-MS: 757.34 (100, [M + H]⁺).

5′-O-(4,4′-Dimethoxytrityl)-1-methyl-2′-O-[(triisopropylsilyl)oxy]methyl]inosine (**18**). A soln. of **17** (76 mg, 0.1 mmol) in DMF was treated with K₂CO₃ (15 mg, 0.1 mmol), stirred for 1.5 h at –15°, treated with MeI (31 mg, 0.2 mmol), and stirred for 2 h at r.t. Workup, evaporation, and CC (SiO₂ (2 g), hexane/AcOEt 3:2 → AcOEt) gave **18** (77 mg, 98%). White solid. TLC (CH₂Cl₂/MeOH 19:1): *R*_f 0.50. ¹H-NMR (400 MHz, CDCl₃): 1.00–1.12 (*m*, ¹Pr₃Si); 2.99 (*d*, *J* = 4.7, OH–C(3′)); 3.39 (*dd*, *J* = 4.2, 10.4, H–C(5′)); 3.43 (*dd*, *J* = 3.4, 10.4, H′–C(5′)); 3.61 (*s*, Me–N(1)); 3.78 (*s*, 2 MeO); 4.29 (*q*, *J* = 4.1, H–C(4′)); 4.53 (*q*, *J* = 4.2, H–C(3′)); 4.82 (*t*, *J* = 5.0, H–C(2′)); 4.94, 5.13 (2*d*, *J* = 4.8, OCH₂O); 6.11 (*d*, *J* = 4.9, H–C(1′)); 6.81 (*m*, 4 arom. H); 7.18–7.35, 7.41–7.47 (*m*, 9 arom. H); 7.83 (*s*, H–C(8)); 7.93 (*s*, H–C(2)). ¹³C-NMR (100 MHz, CDCl₃): 12.2 (*d*, Me₂CH); 18.1 (*q*, Me₂CH); 34.5 (*q*, MeN(1)); 55.6 (*q*, MeO); 64.0 (*t*, C(5′)); 71.5 (*d*, C(3′)); 82.8 (*d*, C(2′)); 84.8 (*d*, C(4′)); 86.8 (*s*, arom. C); 87.0 (*d*, C(1′)); 91.3 (*t*, OCH₂O); 113.6 (*d*, arom. C); 125.5 (*s*, C(5)); 127.29, 128.23, 128.56, 130.48, 130.51 (5*d*, arom. C); 136.0, 136.1 (2*s*, arom. C); 139.2 (*d*, C(8)); 145.0 (*s*, arom. C); 147.5 (*s*, C(4)); 148.1 (*s*, C(2)); 157.4 (*s*, C(6)); 159.0 (*s*, arom. C). ESI-MS: 771.40 (100, [M + H]⁺).

3′,5′-Di-O-acetyl-N⁶-isopent-2-enyl-2′-O-[(triisopropylsilyl)oxy]methyl]adenosine (**20**). A soln. of isopent-2-enylamine·HCl (264 mg, 2.2 mmol) in pyridine (5 ml) was treated with Et₃N (0.6 ml, 4.3 mmol) and **19** (200 mg, 0.3 mmol; prepared according to [24]), and stirred for 1 h at r.t. Workup and CC (SiO₂ (5 g), hexane/AcOEt 9:1 → 3:7) gave **20** (200 mg, 89%). Yellow foam. TLC (hexane/AcOEt 1:1): *R*_f 0.50. ¹H-NMR (100 MHz, CDCl₃): 0.89–1.05 (*m*, ¹Pr₃Si); 1.76 (*s*, Me); 1.78 (*s*, Me); 2.13 (*s*, MeCO); 2.18 (*s*, MeCO); 4.23 (*br. s*, CH₂NH); 4.37–4.50 (*m*, H–C(3′), H–C(4′), CH₂(5′)); 4.86 (*d*, *J* = 4.7, 1 H, OCH₂O); 4.92 (*d*, *J* = 4.7, 1 H, OCH₂O); 5.22 (*t*, *J* = 6.3, CH=C); 5.64 (*br. s*, H–C(2′)); 6.13 (*d*, *J* = 5.7, H–C(1′)); 7.88 (*s*, H–C(8)); 8.47 (*br. s*, H–C(2)). ¹³C-NMR (100 MHz, CDCl₃): 12.1 (*q*, MeC=); 12.2 (*d*, Me₂CH); 18.0 (*q*, Me₂CH); 18.4 (*q*, MeC=); 21.2 (*q*, 2 MeCO); 26.1 (*t*, CH₂NH); 63.9 (*t*, C(5′)); 71.9 (*d*, C(3′)); 76.7 (*d*, C(2′)); 80.9 (*d*, C(4′)); 87.8 (*d*, C(1′)); 89.9 (*t*, OCH₂O); 107.6 (*s*, CH=C); 120.6 (*s*, C(5)); 137.4 (*s*, Me₂C=); 138.9 (*d*, C(8)); 152.9 (*s*, C(4)); 153.8 (*d*, C(2)); 155.1 (*s*, C(6)); 170.5 (*s*, MeCO); 170.8 (*s*, MeCO). ESI-MS: 606.80 (100, [M + H]⁺).

5′-O-(4,4′-Dimethoxytrityl)-N⁶-isopent-2-enyl-2′-O-[(triisopropylsilyl)oxy]methyl]adenosine (**21**). A soln. of **20** (100 mg, 0.16 mmol), was treated with a sat. NH₃ soln. in MeOH (3 ml) for 6 h at r.t. After evaporation, the residue was dissolved in pyridine (0.7 ml), treated with (MeO)₂TrCl (67 mg, 0.19 mmol), and stirred for 4 h at r.t. Workup and CC (SiO₂ (2 g), hexane/AcOEt 8:2 → 3:7) gave **21** (81 mg, 60%). Yellow foam. TLC (hexane/AcOEt 1:1): *R*_f 0.53. ¹H-NMR (400 MHz, CDCl₃): 0.90–1.06 (*m*, ¹Pr₃Si); 1.73 (*s*, Me); 1.78 (*s*, Me); 2.84 (*s*, OH–C(3′)); 3.39 (*dd*, *J* = 4.7, 10.2, H–C(5′)); 3.47 (*dd*, *J* = 3.9, 10.2, H′–C(5′)); 3.79 (*s*, 2 MeO); 4.01 (*d*, *J* = 4.7, H–C(4′)); 4.22–4.24 (*m*, CH₂NH); 4.69 (*d*, *J* = 4.7, H–C(3′)); 5.10 (*s*, OCH₂O); 5.22 (*t*, *J* = 4.7, CH=C); 5.42–5.44 (*m*, H–C(2′)); 6.17 (*d*, *J* = 4.7, H–C(1′)); 6.83–6.87 (*m*, 4 arom. H); 7.22–7.49 (*m*, 9 arom. H); 8.13 (*s*, H–C(8)); 8.19 (*br. s*, H–C(2)); 12.98 (*br. s*, NH). ¹³C-NMR (100 MHz, CDCl₃): 12.1 (*d*, Me₂CH); 17.6 (*q*, Me₂CH); 28.8 (*q*, MeC=); 29.9 (*q*, MeC=); 38.4 (*t*, CH₂NH); 54.9 (*q*, MeO); 64.0 (*t*, C(5′)); 70.9 (*d*, C(3′)); 79.7 (*d*, C(2′)); 84.5 (*d*, C(4′)); 86.5 (*d*, C(1′)); 87.5 (*s*, arom. C); 90.2 (*t*, OCH₂O); 109.4 (*s*, CH=C); 113.4 (*d*, arom. C); 122.2 (*s*, C(5)); 127.0, 128.0, 128.5, 130.4, 130.5 (5*d*, arom. C); 134.6, 136.4 (2*s*, arom. C, Me₂C=); 139.8 (*d*, C(8)); 145.2 (*d*, C(4)); 145.6 (*s*, arom. C); 153.1 (*d*, C(2)); 155.3 (*s*, C(6)); 159.1 (*s*, arom. C). ESI-MS: 824.37 (100, [M + H]⁺).

5′-O-(4,4′-Dimethoxytrityl)-N⁶-methyl-2′-O-[(triisopropylsilyl)oxy]methyl]adenosine (**22**). A soln. of **19** (150 mg, 0.2 mmol; prepared according to [24]) was treated with a 33% MeNH₂ soln. in EtOH (3 ml) for 3 h

at r.t. After evaporation, the residue was dissolved in pyridine (2 ml), treated with (MeO)₂TrCl (89 mg, 0.3 mmol) and stirred for 3 h at r.t. Workup and CC (SiO₂ (3 g), hexane/AcOEt 3:2 → AcOEt) gave **22** (120 mg, 65%). Yellow foam. TLC (hexane/AcOEt 1:9): *R_f* 0.60. ¹H-NMR (400 MHz, CDCl₃): 0.96–1.05 (*m*, ³Pr₃Si); 3.06 (*d*, *J* = 3.9, OH–C(3')); 3.19 (*d*, *J* = 4.5, MeNH); 3.38 (*dd*, *J* = 4.2, 10.2, H–C(5')); 3.50 (*dd*, *J* = 3.6, 10.2, H'–C(5')); 3.78 (*s*, 2 MeO); 4.26 (*q*, *J* = 4.0, H–C(4')); 4.52 (*q*, *J* = 4.2, H–C(3')); 4.93 (*t*, *J* = 5.0, H–C(2')); 4.98 (*d*, *J* = 4.8, 1 H, OCH₂O); 5.14 (*d*, *J* = 4.8, 1 H, OCH₂O); 5.75 (*br. s*, NH); 6.14 (*d*, *J* = 5.4, H–C(1')); 6.78 (*m*, 4 arom. H); 7.22–7.44 (*m*, 9 arom. H); 7.93 (*s*, H–C(8)); 8.33 (*s*, H–C(2)). ¹³C-NMR (100 MHz, CDCl₃): 11.8 (*d*, Me₂CH); 17.7 (*q*, Me₂CH); 27.7 (*q*, MeNH); 55.1 (*q*, MeO); 63.4 (*t*, C(5')); 70.8 (*d*, C(3')); 81.8 (*d*, C(2')); 84.1 (*d*, C(4')); 86.5 (*d*, C(1')); 87.0 (*s*, arom. C); 90.7 (*t*, OCH₂O); 113.4 (*d*, arom. C); 120.4 (*s*, C(5)); 126.8, 127.8, 128.2, 130.0, 135.8 (*5d*, arom. C); 138.6 (*d*, C(8)); 144.6 (*d*, C(4)); 153.3 (*d*, C(2)); 155.5 (*s*, C(6)); 158.5 (*s*, arom. C). ESI-MS: 769.91 (100, [*M* + *H*]⁺).

5'-O-(4,4'-Dimethoxytrityl)-N⁶,N⁶-dimethyl-2'-O-[[triisopropylsilyl]oxy]methyladenosine (**23**). A soln. of **19** (0.15 g, 0.2 mmol, prepared according to [24]) was treated with a 33% Me₂NH soln. in EtOH (3 ml) for 3 h at r.t. After evaporation, the residue was dissolved in pyridine (2 ml), treated with (MeO)₂TrCl (89 mg, 0.3 mmol), and stirred for 3 h at r.t. Workup and CC (SiO₂ (3 g), hexane/AcOEt 3:2 → AcOEt) gave **23** (148 mg, 80%). Yellow foam. TLC (hexane/AcOEt 1:1): *R_f* 0.70. ¹H-NMR (400 MHz, CDCl₃): 1.00–1.11 (*m*, ³Pr₃Si); 3.05 (*d*, *J* = 4.1, OH–C(3')); 3.36 (*dd*, *J* = 4.3, 10.5, H–C(5')); 3.50 (*dd*, *J* = 3.0, 10.5, H'–C(5')); 3.45–3.58 (*br. s*, Me₂N); 3.78, 3.79 (*2s*, 2 MeO); 4.26 (*q*, *J* = 3.7, H–C(4')); 4.48 (*q*, *J* = 4.4, H–C(3')); 4.87 (*t*, *J* = 5.0, H–C(2')); 4.99 (*d*, *J* = 4.7, 1 H, OCH₂O); 5.15 (*d*, *J* = 4.7, 1 H, OCH₂O); 6.17 (*d*, *J* = 5.2, H–C(1')); 6.78–6.82 (*m*, 4 arom. H); 7.18–7.46 (*m*, 9 arom. H); 7.93 (*s*, H–C(8)); 8.27 (*s*, H–C(2)). ¹³C-NMR (100 MHz, CDCl₃): 11.8 (*d*, Me₂CH); 17.7 (*q*, Me₂CH); 38.4 (*q*, 2 Me₂N); 55.1 (*q*, MeO); 63.4 (*t*, C(5')); 70.7 (*d*, C(3')); 81.8 (*d*, C(2')); 83.8 (*d*, C(4')); 86.4 (*d*, C(1')); 86.8 (*s*, arom. C); 90.7 (*t*, OCH₂O); 113.1 (*d*, arom. C); 120.6 (*s*, C(5)); 126.7, 127.7, 128.1, 130.0, 135.8 (*5d*, arom. C); 136.8 (*d*, C(8)); 144.6 (*d*, C(4)); 144.6, 150.3 (*2s*, arom. C); 152.4 (*d*, C(2)); 154.9 (*s*, C(6)); 158.4 (*s*, arom. C). ESI-MS: 785.41 (100, [*M* + *H*]⁺).

5'-O-(4,4'-Dimethoxytrityl)-1-methyl-2'-O-[[triisopropylsilyl]oxy]methylguanosine (**25**). A soln. of **24** (400 mg, 0.5 mmol, prepared according to [25]) in DMF (4 ml) was treated with K₂CO₃ (79 mg, 0.6 mmol), stirred for 2 h at r.t., treated with MeI (162 mg, 1.1 mmol), and stirred for 14 h at –15°. Workup and CC (SiO₂ (10 g), CH₂Cl₂/MeOH 99:1 → 9:1) gave **25** (0.26 g, 63%). Colorless foam. TLC (CH₂Cl₂/MeOH 9:1): *R_f* 0.72. ¹H-NMR (400 MHz, CDCl₃): 0.97–1.12 (*m*, ³Pr₃Si); 1.87 (*br. s*, NH₂); 3.08 (*br. s*, OH–C(3')); 3.34 (*dd*, *J* = 3.2, 10.2, H–C(5')); 3.52 (*br. s*, H'–C(5'), Me–N(1)); 3.79 (*s*, 2 MeO); 4.27 (*br. s*, H–C(4')); 4.58 (*br. s*, H–C(3')); 4.92 (*br. s*, H–C(2')); 4.96 (*d*, *J* = 4.4, 1 H, OCH₂O); 5.14 (*d*, *J* = 5.1, 1 H, OCH₂O); 5.94 (*d*, *J* = 6.6, H–C(1')); 6.80–6.82 (*m*, 4 arom. H); 7.20–7.36 (*m*, 9 arom. H); 7.65 (*s*, H–C(8)). ¹³C-NMR (100 MHz, CDCl₃): 11.9 (*d*, Me₂CH); 17.8 (*q*, Me₂CH); 28.1 (*q*, Me–N(1)); 55.3 (*q*, MeO); 63.6 (*t*, C(5')); 71.2 (*d*, C(2')); 81.6 (*d*, C(3')); 83.9 (*d*, C(4')); 85.9 (*s*, arom. C); 86.5 (*d*, C(1')); 90.9 (*t*, OCH₂O); 113.2 (*d*, arom. C); 118.2 (*s*, C(5)); 126.9, 127.9, 128.2, 130.1 (*4d*, arom. C); 135.7 (*s*, arom. C); 136.6 (*d*, C(8)); 144.6 (*s*, arom. C); 148.8, 153.1 (*2s*, C(2), C(4)); 158.6 (*s*, C(6)). ESI-MS: 786.82 (100, [*M* + *H*]⁺).

5'-O-(4,4'-Dimethoxytrityl)-N²-methyl-2'-O-[[triisopropylsilyl]oxy]methylguanosine (**27**). A soln. of **24** (501 mg, 0.66 mmol, prepared according to [25]) in pyridine (8 ml) was treated with Me₃SiCl (200 mg, 2.0 mmol), stirred for 40 min at r.t., treated with 1,3-benzodithiolium tetrafluoroborate (275 mg, 1.0 mmol), and stirred for 6 h at r.t. Workup and filtration (SiO₂ (11 g), hexane/AcOEt 3:7 → AcOEt) gave a mixture of 3'-O-Me₃Si and 3'-OH derivatives as a yellow foam (576 mg, *ca.* 88%; TLC (CH₂Cl₂/MeOH 9:1): *R_f* 0.48 and 0.45), which was dissolved in benzene (6 ml), treated with AIBN (49 mg, 0.3 mmol), 1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)trisilane (718 mg, 3.0 mmol) and heated to reflux for 8 h. After evaporation, the residue (crude **26** and **27**) was dissolved in MeOH (0.3 ml), treated with a sat. NH₃ soln. in MeOH (2.7 ml), and stirred for 4 h at r.t. Workup and CC (SiO₂ (10 g), hexane/AcOEt 2:3 → AcOEt, then AcOEt/MeOH 95:5 → 9:1) gave **27** (304 mg, 57% from **24**). Pink foam. TLC (CH₂Cl₂/MeOH 9:1): *R_f* 0.39. ¹H-NMR (400 MHz, CDCl₃): 0.88–1.08 (*m*, ³Pr₃Si); 2.78 (*br. s*, MeNH–C(2)); 3.09 (*d*, *J* = 3.1, OH–C(3')); 3.44 (*m*, CH₂(5')); 3.77 (*s*, 2 MeO); 4.24 (*m*, H–C(4')); 4.55 (*m*, H–C(3')); 4.82 (*m*, H–C(2')); 5.04 (*d*, *J* = 3.9, 1 H, OCH₂O); 5.20 (*d*, *J* = 3.9, 1 H, OCH₂O); 6.06 (*d*, *J* = 4.7, H–C(1')); 6.81 (*d*, *J* = 8.6, 4 arom. H); 7.30–7.46 (*m*, 9 arom. H); 7.69 (*s*, H–C(8)); 12.06 (*br. s*, NH). ¹³C-NMR (100 MHz, CDCl₃): 12.3 (*d*, Me₂CH); 18.2 (*q*, Me₂CH); 28.2 (*q*, MeNH–C(2)); 55.6 (*q*, MeO); 63.8 (*t*, C(5')); 71.2 (*d*, C(2')); 82.4 (*d*, C(3')); 84.1 (*d*, C(4')); 86.9 (*d*, C(1')); 87.1 (*s*, arom. C); 91.3 (*t*, OCH₂O); 113.6 (*d*, arom. C); 127.3 (*s*, C(5)); 128.3, 128.6, 128.8, 130.5 (*4d*, arom. C); 136.1, 136.2 (*2s*, arom. C); 136.3 (*d*, C(8)); 145.0 (*s*, arom. C); 152.3 (*s*, C(4)); 153.9 (*s*, C(2)); 158.9 (*s*, C(6)); 159.9 (*s*, arom. C). ESI-MS: 787.74 (100, [*M* + *H*]⁺).

5'-O-(4,4'-Dimethoxytrityl)-N²,N²-dimethyl-2'-O-[[triisopropylsilyl]oxy]methylguanosine (**29**). A soln. of crude **26** and **27** (260 mg, 0.3 mmol, obtained from **24** as described above) in pyridine (2 ml) was treated with

Me₃SiCl (46 mg, 0.8 mmol), stirred for 40 min at r.t., treated with 1,3-benzodithiolium tetrafluoroborate (137 mg, 0.5 mmol), and stirred for 6 h at r.t. Workup and filtration (SiO₂ (11 g), hexane/AcOEt 3 : 7 → AcOEt) gave a mixture of 3'-O-Me₃Si and 3'-OH derivatives as a yellow foam (288 mg, ca. 94%; TLC (CH₂Cl₂/MeOH 9 : 1): *R_f* 0.54 and 0.50), which was dissolved in benzene (3 ml), treated with AIBN (25 mg, 0.15 mmol) and 1,1,1,3,3,3-hexamethyl-2-(trimethylsilyl)trisilane (359 mg, 1.5 mmol) and heated to reflux for 8 h. After evaporation, the mixture (crude **28** and **29**) was dissolved in MeOH (0.3 ml), treated with a sat. NH₃ soln. in MeOH (2.7 ml), and stirred for 4 h at r.t. Workup and CC (SiO₂ (5 g), hexane/AcOEt 2 : 3 → AcOEt then AcOEt/MeOH 95 : 5 → 9 : 1) gave **29** (144 mg, 50% from **24**). Pink foam. TLC (CH₂Cl₂/MeOH 9 : 1): *R_f* 0.45. ¹H-NMR (400 MHz, CDCl₃): 0.90–1.28 (*m*, ¹Pr₃Si); 3.03 (*d*, *J* = 3.9, OH–C(3')); 3.16 (*s*, Me₂N); 3.41 (*d*, *J* = 3.9, CH₂(5')); 3.79 (*s*, 2 MeO); 4.24 (*br. d*, *J* = 4.7, H–C(4')); 4.52 (*br. d*, *J* = 4.7, H–C(3')); 4.78 (*t*, *J* = 5.5, H–C(2')); 4.98 (*d*, *J* = 4.7, 1 H, OCH₂O); 5.16 (*d*, *J* = 4.7, 1 H, OCH₂O); 6.03 (*d*, *J* = 5.4, H–C(1')); 6.81 (*d*, *J* = 9.4, 4 arom. H); 7.19–7.45 (*m*, 9 arom. H); 7.66 (*s*, H–C(8)); 10.64 (*br. s*, NH). ¹³C-NMR (100 MHz, CDCl₃): 12.3 (*d*, Me₂CH); 18.6 (*q*, Me₂CH); 38.5 (*q*, Me₂N); 55.6 (*q*, MeO); 64.1 (*t*, C(5')); 71.4 (*d*, C(2')); 82.3 (*d*, C(3')); 84.1 (*d*, C(4')); 86.7 (*d*, C(1')); 86.9 (*s*, arom. C); 91.2 (*t*, OCH₂O); 113.6 (*d*, arom. C); 127.3 (*s*, C(5)); 128.3, 128.6, 128.7, 130.5 (*4d*, arom. C); 136.1, 136.2 (*2s*, arom. C); 136.6 (*d*, C(8)); 144.9 (*s*, arom. C); 151.9 (*s*, C(4)); 153.2 (*s*, C(2)); 158.9 (*s*, arom. C); 159.2 (*s*, C(6)). ESI-MS: 800.33 (100, [*M* + H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-1-methyl-2'-O-[[triisopropylsilyl]oxy]methyladenosine (**31**). A soln. of **30** (1.00 g, 1.3 mmol; prepared according to [22][25]) in DMF (15 ml) was treated with MeI (0.08 ml, 1.3 mmol) and stirred for 5 days at r.t. Workup, evaporation, and crystallization (acetone) gave **31** (1.02 g, 98%). White solid. M.p. 160° (dec.). TLC (CH₂Cl₂/MeOH 95 : 5): *R_f* 0.05. ¹H-NMR (400 MHz, CDCl₃): 0.89–1.15 (*m*, ¹Pr₃Si); 1.27 (*br. s*, HN=C(6)); 3.03 (*br. s*, OH–C(3')); 3.38 (*dd*, *J* = 3.7, 11.0, H–C(5')); 3.45 (*dd*, *J* = 3.7, 10.2, H'–C(5')); 3.66 (*s*, Me–N(1)); 3.80 (*s*, 2 MeO); 4.29 (*d*, *J* = 2.9, H–C(4')); 4.53 (*m*, H–C(3')); 4.81 (*t*, *J* = 5.9, H–C(2')); 4.96, 5.14 (*2d*, *J* = 5.0, OCH₂O); 6.03 (*d*, *J* = 6.6, H–C(1')); 6.82 (*d*, *J* = 8.8, 4 arom. H); 7.20–7.46 (*m*, 9 arom. H); 7.60 (*s*, H–C(2)); 7.85 (*s*, H–C(8)). ¹³C-NMR (100 MHz, CDCl₃): 11.8 (*d*, Me₂CH); 17.8 (*q*, Me₂CH); 35.9 (*q*, Me–N(1)); 55.3 (*q*, MeO); 63.6 (*t*, C(5')); 71.0 (*d*, C(2')); 82.4 (*d*, C(3')); 84.3 (*d*, C(4')); 86.6 (*d*, C(1')); 86.8 (*s*, arom. C); 90.8 (*t*, OCH₂O); 113.2 (*d*, arom. C); 121.8 (*s*, C(5)); 126.9, 127.9, 128.0, 128.2, 130.1 (*5d*, arom. C); 135.63, 135.69 (*2s*, arom. C); 139.3 (*d*, C(8)); 144.6 (*s*, arom. C); 145.6 (*s*, C(4)); 147.3 (*s*, C(2)); 149.1 (*s*, C(6)); 158.6 (*s*, arom. C). ESI-MS: 770.36 (100, [*M* + H]⁺).

N⁶-(Chloroacetyl)-5'-O-(4,4'-dimethoxytrityl)-1-methyl-2'-O-[[triisopropylsilyl]oxy]methyladenosine (**32**). A soln. of **31** (1.00 g, 1.3 mmol) in pyridine/ClCH₂CH₂Cl 1 : 9 (55 ml) was treated with chloroacetic anhydride (890 mg, 5.2 mmol) and stirred for 1 h at –15°. After workup and evaporation, the residue was dissolved in MeOH (2 ml) and treated with a sat. NH₃ soln. (7 ml) for 4 h at –15°. Workup and CC (SiO₂ (20 g), hexane/AcOEt 9 : 1 → AcOEt) gave **32** (0.70 g, 64%). Light yellow foam. TLC (CH₂Cl₂/MeOH 19 : 1): *R_f* 0.74. ¹H-NMR (400 MHz, CDCl₃): 0.99–1.08 (*m*, ¹Pr₃Si); 3.03 (*d*, *J* = 2.9, OH–C(3')); 3.35 (*dd*, *J* = 4.4, 10.3, H–C(5')); 3.46 (*dd*, *J* = 4.4, 10.3, H'–C(5')); 3.64 (*s*, Me–N(1)); 3.81 (*s*, 2 MeO); 4.29 (*m*, H–C(4')); 4.44 (*s*, ClCH₂); 4.52 (*m*, H–C(3')); 4.76 (*t*, *J* = 5.1, H–C(2')); 4.93, 5.14 (*2d*, *J* = 5.1, OCH₂O); 6.08 (*d*, *J* = 6.6, H–C(1')); 6.82 (*d*, *J* = 8.8, 4 arom. H); 7.20–7.34 (*m*, 9 arom. H); 7.81 (*s*, H–C(2)); 7.94 (*s*, H–C(8)). ¹³C-NMR (100 MHz, CDCl₃): 11.8 (*d*, Me₂CH); 17.8 (*q*, Me₂CH); 36.8 (*q*, Me–N(1)); 46.0 (*t*, CH₂Cl); 55.3 (*q*, MeO); 63.4 (*t*, C(5')); 71.0 (*d*, C(2')); 82.7 (*d*, C(3')); 84.4 (*d*, C(4')); 86.5 (*d*, C(1')); 86.7 (*s*, arom. C); 91.0 (*t*, OCH₂O); 113.2 (*d*, arom. C); 122.4 (*s*, C(5)); 127.6, 127.9, 128.1, 128.3, 130.1 (*5d*, arom. C); 135.63, 135.69 (*2s*, arom. C); 139.3 (*d*, C(8)); 144.6 (*s*, arom. C); 145.6 (*s*, C(4)); 147.3 (*s*, C(6)); 149.1 (*d*, C(2)); 158.6 (*s*, arom. C); 178.09 (*s*, CO). ESI-MS: 846.74 (70, [*M* + H]⁺), 848.74 (30, [*M* + H]⁺).

3'-O-Acetyl-5'-O-(4,4'-dimethoxytrityl)-2'-O-[[triisopropylsilyl]oxy]methyladenosine (**33**). A soln. of **30** (1.0 g, 1.16 mmol; prepared according to [22][25]) in pyridine (9.3 ml) was treated with DMAP (14 mg, 0.16 mmol) and Ac₂O (143 mg, 1.4 mmol). Workup (1. 10% citric acid, 2. NaHCO₃ soln.) after 30 min at r.t. and CC (SiO₂ (25 g), hexane/AcOEt 2 : 3 → 1 : 9 (+3% Et₃N)) gave **33** (0.88 g, 88%). Colorless foam. TLC (hexane/AcOEt 1 : 9): *R_f* 0.57. ¹H-NMR (100 MHz, CDCl₃): 0.88–1.05 (*m*, ¹Pr₃Si); 2.13 (*s*, MeCO); 3.43 (*dd*, *J* = 6.5, 10.4, H–C(5')); 3.52 (*dd*, *J* = 5.6, 10.4, H'–C(5')); 3.78 (*s*, 2 MeO); 4.34 (*m*, H–C(4')); 4.87 (*s*, OCH₂O); 5.19 (*dd*, *J* = 5.3, 6.9, H–C(2')); 5.51 (*dd*, *J* = 2.5, 5.3, H–C(3')); 5.80 (*br. s*, NH₂); 6.16 (*d*, *J* = 6.9, H–C(1')); 6.78–6.83 (*m*, 4 arom. H); 7.20–7.45 (*m*, 9 arom. H); 7.97 (*s*, H–C(2)); 8.25 (*s*, H–C(8)). ¹³C-NMR (100 MHz, CDCl₃): 11.7 (*d*, Me₂CH); 17.6 (*q*, Me₂CH); 20.9 (*q*, MeCO); 55.3 (*q*, MeO); 63.4 (*t*, C(5')); 72.1 (*d*, C(3')); 77.0 (*d*, C(2')); 82.5 (*d*, C(4')); 86.2 (*d*, C(1')); 86.8 (*s*, arom. C); 89.6 (*t*, OCH₂O); 113.2 (*d*, arom. C); 120.1 (*s*, C(5)); 127.0, 127.9, 128.2, 130.1 (*4d*, arom. C); 135.6 (*s*, arom. C); 139.2 (*d*, C(8)); 144.4 (*s*, arom. C); 150.2 (*s*, C(4)); 153.2 (*d*, C(2)); 155.4 (*s*, C(6)); 158.6 (*s*, arom. C); 170.1 (*s*, CO). ESI-MS: 868.35 (100, [*M* + Na]⁺).

N^6 -[[[(1*S*,2*R*)-2-[[*tert*-Butyl]dimethylsilyl]oxy]-1-[[2-(4-nitrophenyl)ethoxy]carbonyl]propyl]amino]carbonyl]-5'-O-(4,4'-dimethoxytrityl)-2'-O-[[[triisopropylsilyl]oxy]methyl]adenosine (O^3 -[[*tert*-Butyl]dimethylsilyl]-N-[[9-{5'-O-(4,4'-dimethoxytrityl)-2'-O-[[[triisopropylsilyl]oxy]methyl]- β -D-ribofuranosyl]-9H-purin-6-yl]carbonyl]-L-threonine; **34**). A soln. of **33** (400 mg, 0.5 mmol) in $ClCH_2CH_2Cl$ (2 ml) was treated with Et_3N (250 mg, 2.5 mmol) and 1,1'-carbonylbis[1*H*-1,2,4-triazole] (120 mg, 0.7 mmol), stirred for 10 min at 70°, treated with O^3 -[[*tert*-butyl]dimethylsilyl]-L-threonine 2-(4-nitrophenyl)ethyl ester (280 mg, 0.7 mmol, prepared according to [21]), and stirred for 15 min at 70°. After workup and evaporation, the residue was treated with a sat. NH_3 soln. in MeOH (5 ml) for 3 h at r.t. Workup and CC (SiO_2 (7 g), hexane/AcOEt 3:2 $\rightarrow$ AcOEt) gave **34** (326 mg, 56%). Colorless foam. TLC (CH_2Cl_2 /MeOH 9:1): R_f 0.25. 1H -NMR (400 MHz, $CDCl_3$): -0.05, -0.03 (2s, 2 MeSi); 0.91 (s, iBuSi); 0.95–1.06 (m, iPr_3Si); 1.09 (d, $J=4.2$, Me(γ)); 3.06 (t, $J=5.7$, CH_2CH_2O); 3.15 (d, $J=3.7$, OH-C(3')); 3.14–3.55 (m, $CH_2(5')$); 3.80 (s, 2 MeO); 4.30–4.60 (m, H-C(4'), H-C(3'), CH(α), CH(β), CH_2CH_2O); 4.97 (t, $J=5.1$, H-C(2')); 5.04 (d, $J=4.7$, 1 H, OCH_2O); 5.19 (d, $J=4.7$, 1 H, OCH_2O); 6.24 (d, $J=6.2$, H-C(1')); 6.81 (d, $J=8.7$, 4 arom. H); 7.22–7.44 (m, 9 arom. H); 7.22–7.46 (m, 13 arom. H); 7.98 (d, $J=8.8$, 2 arom. H); 8.19 (s, H-C(8)); 8.42 (s, H-C(2)); 9.99 (d, $J=8.8$, NH-C(α)); 10.02 (br. s, NH-C(6)). ^{13}C -NMR (100 MHz, $CDCl_3$): -5.4, -4.3 (q, MeSi); 11.8 (d, Me_2CH); 17.8 (q, Me_2CH); 21.1 (Me(γ)); 25.5 (q, Me_3CSi); 34.8 (t, CH_2CH_2O); 55.2 (q, MeO); 59.6 (t, CH_2CH_2O); 63.4 (t, C(5')); 64.6 (d, C(α)); 68.6 (d, C(β)); 70.8 (d, C(3')); 76.6 (d, C(2')); 82.4 (d, C(4')); 84.4 (d, C(1')); 87.4 (s, arom. C); 90.9 (t, OCH_2O); 113.2 (d, arom. C); 120.9 (s, C(5)); 123.6, 126.9, 127.8, 128.2, 129.7 (5d, arom. C); 130.1 (s, arom. C); 135.7 (s, arom. C); 141.7 (d, C(8)); 144.6 (d, C(2)); 145.5 (s, arom. C); 150.0 (s, C(4)); 150.2 (s, C(6)); 154.2 (s, NHCONH); 158.6 (s, arom. C); 170.9 (s, $COOCH_2$). ESI-MS: 1164.37 (100, $[M+H]^+$).

5'-O-(4,4'-Dimethoxytrityl)-5-methyl-2'-O-[[[triisopropylsilyl]oxy]methyl]cytidine (**35**). A soln. of **13** (0.65 g, 0.9 mmol) in pyridine (3.5 ml) was treated with DMAP (22 mg, 0.17 mmol) and Ac_2O (0.17 ml, 1.77 mmol) and stirred for 3 h at r.t. Workup and evaporation gave a yellow solid foam (0.63 g), which was carefully dried (14 h at 60°/0.05 mbar) and dissolved in MeCN (3 ml). Meanwhile, under Ar and at 4°, 4-chlorophenyl phosphorodichloridate (0.65 g, 2.65 mmol) was added dropwise to a suspension of finely powdered 1*H*-1,2,4-triazole (1.07 g, 15.4 mmol, dried by sublimation) in dry MeCN (6 ml). After 15 min at 4°, iPr_2NEt (2.3 ml, 13.3 mmol) was added, and after 40 min at r.t., the mixture was again cooled to 4° and treated with the MeCN soln. obtained before (3 ml, containing 0.65 g of the intermediate nucleoside). After 6 h at r.t., the soln. was diluted with dioxane (9 ml), treated with sat. aq. NH_3 soln. (13 ml), and stirred for another 3 h at r.t. Extraction with CH_2Cl_2 /10% aq. citric acid and sat. aq. $NaHCO_3$ soln. gave a yellow solid foam (0.62 g) which was dissolved in THF/MeOH 5:4 (33 ml), cooled to 4°, and treated with 2*N* NaOH (3.7 ml). After 30 min at 4°, the soln. was treated with AcOH (0.43 ml) and concentrated to 30 ml. Workup and CC (SiO_2 (8 g), CH_2Cl_2 $\rightarrow$ CH_2Cl_2 /MeOH 19:1) gave **35** (0.60 g, 90%). Colorless foam. TLC (CH_2Cl_2 /MeOH 15:185): R_f 0.50. 1H -NMR (400 MHz, (D_6)DMSO): 1.00–1.14 (m, iPr_3Si); 1.49 (s, Me-C(5)); 3.26 (br. s, $CH_2(5')$); 3.74 (s, 2 MeO); 3.96 (dd, $J=5.6$, 3.2, H-C(4')); 4.22 (q, $J=5.2$, H-C(3')); 4.27 (t, $J=5.4$, H-C(2')); 4.96 (d, $J=5.2$, 1 H, OCH_2O); 4.99 (d, $J=5.1$, 1 H, OCH_2O); 5.05 (d, $J=5.0$, OH-C(3')); 5.99 (d, $J=5.8$, H-C(1')); 6.89 (d, $J=8.8$, 4 arom. H); 7.22–7.42 (m, 9 arom. H, H-C(6)). ^{13}C -NMR (100 MHz, (D_6)DMSO): 11.9 (d, Me_2CH); 13.3 (q, $Me-C(5)$); 18.1 (q, Me_2CH); 55.5 (q, MeO); 63.9 (t, C(5')); 67.1 (d, C(2')); 78.2 (d, C(3')); 83.4 (d, C(4')); 86.4 (s, arom. C); 87.4 (d, C(1')); 88.8 (t, OCH_2O); 102.2 (s, C(5)); 113.7 (d, arom. C); 127.3, 128.2, 128.4 130.2 (4d, arom. C); 135.8, 135.9, 138.4 (3s, arom. C); 145.1 (d, C(6)); 155.6 (s, C(2)); 158.6 (s, arom. C); 165.8 (s, C(4)). ESI-MS: 1491.80 (100, $[2M+1]^+$).

N^4 -Acetyl-5'-O-(4,4'-dimethoxytrityl)-5-methyl-2'-O-[[[triisopropylsilyl]oxy]methyl]cytidine (**36**). A soln. of **35** (0.6 g, 0.80 mmol) in DMF (3.3 ml) was treated with Ac_2O (113 mg, 1.1 mmol) for 8 h at r.t. Workup and CC (SiO_2 (8 g), hexane/AcOEt 4:1 $\rightarrow$ 3:7) gave **36** (0.55 g, 90%). Colorless solid foam. TLC (hexane/AcOEt 1:9): R_f 0.52. 1H -NMR (400 MHz, (D_6)DMSO): 0.87–1.08 (m, iPr_3Si); 1.13 (s, Me-C(5)); 2.25 (s, $MeCO$); 3.26 (br. s, $CH_2(5')$); 3.74 (s, 2 MeO); 4.05 (br. d, $J \approx 4.6$, H-C(4')); 4.25 (q, $J=4.5$, H-C(3')); 4.33 (t, $J=4.7$, H-C(2')); 4.99 (d, $J=5.2$, 1 H, OCH_2O); 5.04 (d, $J=5.1$, 1 H, OCH_2O); 5.15 (d, $J=5.0$, OH-C(3')); 5.99 (d, $J=4.4$, H-C(1')); 6.89 (d, $J=8.8$, 4 arom. H); 7.23–7.41 (m, 9 arom. H); 7.82 (br. s, H-C(6)); 9.82 (br. s, NH-C(4)). ^{13}C -NMR (100 MHz, (D_6)DMSO): 11.9 (d, Me_2CH); 13.8 (q, $Me-C(5)$); 18.1 (q, Me_2CH); 25.3 (q, $MeCO$); 55.5 (q, MeO); 63.6 (t, C(5')); 69.2 (d, C(2')); 78.7 (d, C(3')); 83.9 (d, C(4')); 86.4 (d, C(1')); 88.9 (s, arom. C); 90.4 (t, OCH_2O); 113.7 (d, arom. C); 127.3 (s, C(5)); 128.2, 128.4, 130.2, 135.7, 135.9 (5d, arom. C); 142.5, 145.0 (2s, arom. C); 152.5 (d, C(6)); 155.5 (s, C(2)); 158.6 (s, arom. C); 162.9 (s, C(4)); 171.2 (s, $MeCO$). ESI-MS: 788.34 (100, $[M+H]^+$).

N^2 -Acetyl-5'-O-(4,4'-dimethoxytrityl)-2'-O-[[[triisopropylsilyl]oxy]methyl]isocytidine 3'-(2-Cyanoethyl Diisopropylphosphoramidite) (**37**). A soln. of **5** (100 mg, 0.13 mmol) in CH_2Cl_2 (2 ml) was treated consecutively with iPr_2NEt (0.05 ml, 0.32 mmol) and cyanoethyl diisopropylphosphoramidochloridite (43 mg, 0.15 mmol).

After stirring for 14 h at r.t., the mixture was subjected to CC (SiO₂ (3 g), hexane/AcOEt 9:1 → 4:6 (+ 3% Et₃N)): **37** (60 mg, 50%, 1:1 mixture of diastereoisomers). Colorless foam. TLC (hexane/AcOEt 1:1): *R_f* 0.64. ¹H-NMR (400 MHz, CDCl₃): 0.98–1.07 (*m*, ³Pr₃Si); 1.09, 1.18 (2*d*, *J* = 7.0 (Me₂CH)₂N); 2.20, 2.21 (2*s*, MeCO); 2.45 (*t*, *J* = 5.7, 1 H, CH₂CN); 2.67 (*q*, *J* = 6.3, 1 H, CH₂CN); 3.44–3.69 (*m*, 3.5 H, POCH₂, (Me₂CH)₂N, H–C(5')); 3.81 (*s*, 2 MeO); 3.94 (*m*, 1 H, POCH₂); 4.25 (*d*, *J* = 6.2, 0.5 H, H–C(4')); 4.30 (*d*, *J* = 6.2, 0.5 H, H–C(4')); 4.34–4.47 (*m*, H–C(2'), H–C(3')); 5.17 (*br. s*, 1 H, OCH₂O); 5.28 (*dd*, *J* = 4.6, 11.2, 1 H, OCH₂O); 5.34, 5.40 (2*d*, *J* = 8.1, H–C(5)); 6.54, 6.59 (2*d*, *J* = 3.1, H–C(1')); 6.81–6.88 (*m*, 4 arom. H); 7.32–7.44 (*m*, 9 arom. H); 8.17, 8.23 (2*d*, *J* = 8.6, H–C(6)); 13.03, 13.06 (2 *br. s*, NH–C(2)). ³¹P-NMR (162 MHz, CDCl₃): 151.2, 151.6. MALDI-MS: 974.30 (100, [*M* + H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-O²-(diphenylcarbamoyl)-N⁶-isobutryl-2'-O-[[triisopropylsilyl]oxy]methyl]isoguanosine 3'-(2-Cyanoethyl Diisopropylphosphoramidite) (**38**). As described for **37**, with **8** (100 mg, 0.096 mmol), CH₂Cl₂ (0.7 ml), ³Pr₂NEt (0.04 ml, 0.24 mmol), and cyanoethyl diisopropylphosphoramidochloridite (34 mg, 0.14 mmol). CC (SiO₂ (3 g), hexane/AcOEt 9:1 → 1:1 (+ 3% Et₃N)) gave **38** (70 mg, 56%; 1:1 mixture of diastereoisomers). Colorless foam. TLC (hexane/AcOEt 1:1): *R_f* 0.49. ¹H-NMR (400 MHz, CDCl₃): 0.85–1.00 (*m*, ³Pr₃Si); 1.05 (*d*, *J* = 6.2, (Me₂CH)₂N); 1.12–1.29 (*m*, (Me₂CH)₂N); 1.33 (*d*, *J* = 7.0, Me₂CHCO); 2.34 (*t*, *J* = 7.0, 0.5 H, CH₂CN); 2.48–2.70 (*m*, 1.5 H, CH₂CN); 3.32 (*dd*, *J* = 5.9, 10.2, 0.5 H, H–C(5')); 3.44–3.73 (*m*, 4.5 H, (MeCH)₂N, MeCHCO, H–C(5'), POCH₂); 3.78, 3.79 (2*s*, 2 MeO); 3.82–3.92 (*m*, 1 H, POCH₂); 4.30 (*d*, *J* = 3.1, 0.5 H, H–C(4')); 4.35 (*d*, *J* = 3.9, 0.5 H, H–C(4')); 4.57–4.64 (*m*, 1 H); 4.85–5.02 (*m*, 3 H, OCH₂O, H–C(2'), H–C(3')); 6.23 (*t*, *J* = 4.7, H–C(1')); 6.78–6.83 (*m*, 4 arom. H); 7.20–7.42 (*m*, 9 arom. H); 8.14, 8.19 (2*s*, H–C(8)). ³¹P-NMR (162 MHz, CDCl₃): 151.7, 151.8. MALDI-MS: 1237.83 (100, [*M* + H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-N⁶-isobutryl-2'-O-[(methoxyacetyl)amino]-2'-O-[[triisopropylsilyl]oxy]methyl]adenosine 3'-(2-Cyanoethyl Diisopropylphosphoramidite) (**39**). As described for **37**, with **11** (270 mg, 0.30 mmol), CH₂Cl₂ (1.0 ml), ³Pr₂NEt (0.13 ml, 0.75 mmol), and cyanoethyl diisopropylphosphoramidochloridite (85 mg, 0.36 mmol). CC (SiO₂ (6 g), hexane/AcOEt 4:1 → 2:3 (+ 3% Et₃N)) gave **39** (250 mg, 76%; 1:1 mixture of diastereoisomers). Colorless foam. TLC (hexane/AcOEt 1:9): *R_f* 0.29. ¹H-NMR (400 MHz, CDCl₃): 0.87–0.93 (*m*, ³Pr₃Si); 1.05 (*d*, *J* = 6.8, (Me₂CH)₂N); 1.17–1.22 (*m*, (Me₂CH)₂N); 1.32 (*d*, *J* = 6.8, Me₂CHCO); 1.94 (*s*, MeOCH₂); 2.31–2.41 (*m*, 1 H, CH₂CN); 2.69 (*t*, *J* = 6.4, 1 H, CH₂CN); 3.37–3.84 (*m*, 6 H, (MeCH)₂N, CH₂(5'), Me₂CHCO, POCH₂); 3.79, 3.80 (2*s*, 2 MeO); 3.81–4.03 (*m*, 1.5 H, POCH₂); 4.09 (*br. s*, 2 H, MeOCH₂); 4.33 (*br. d*, *J* ≈ 3.1, 0.5 H, H–C(4')); 4.38 (*br. d*, *J* ≈ 3.4, 0.5 H, H–C(4')); 4.53–4.69 (*m*, 1 H, H–C(3')); 4.91–5.08 (*m*, 3 H, OCH₂O, H–C(2')); 6.15 (*d*, *J* = 5.8, 0.5 H, H–C(1')); 6.21 (*d*, *J* = 6.1, 0.5 H, H–C(1')); 6.78–6.82 (*m*, 4 arom. H); 7.28–7.35 (*m*, 9 arom. H); 8.08 (*s*, H–C(8)); 8.63 (2 *br. s*, NH–C(6)); 8.72–8.77 (*m*, NH–C(2)). ³¹P-NMR (162 MHz, CDCl₃): 151.5, 151.8. MALDI-MS: 1113.30 (100, [*M* + H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-5-methyl-2'-O-[[triisopropylsilyl]oxy]methyl]uridine 3'-(2-Cyanoethyl Diisopropylphosphoramidite) (**40**). As described for **37**, with **13** (400 mg, 0.13 mmol), CH₂Cl₂ (4 ml), ³Pr₂NEt (0.23 ml, 1.35 mmol), and cyanoethyl diisopropylphosphoramidochloridite (139 mg, 0.59 mmol). CC (SiO₂ (12 g), hexane/AcOEt 9:1 → 1:4 (+ 3% Et₃N)) gave **40** (500 mg, 98%; 1:1 mixture of diastereoisomers). Colorless foam. TLC (hexane/AcOEt 1:1): *R_f* 0.71. ¹H-NMR (400 MHz, CDCl₃): 1.00–1.12 (*m*, ³Pr₃Si); 1.16–1.32 (*m*, (Me₂CH)₂N); 1.46, 1.49 (2*s*, Me–C(5)); 2.36 (*t*, *J* = 6.9, 1 H, CH₂CN); 2.64–2.66 (*dt*, *J* = 3.1, 6.4, 1 H, CH₂CN); 3.32 (*dt*, *J* = 2.5, 7.1, H–C(5')); 3.46–3.70 (*m*, 4 H, (Me₂CH)₂N, H'–C(5'), POCH₂); 3.80, 3.81 (2*s*, 2 MeO); 3.82–3.97 (*m*, 1 H, POCH₂); 4.20 (*br. d*, *J* ≈ 1.5, 0.5 H, H–C(4')); 4.30 (*br. d*, *J* ≈ 2.2, 0.5 H, H–C(4')); 4.45–4.65 (*m*, H–C(2'), H–C(3')); 4.96–5.06 (*m*, OCH₂O); 6.18 (*d*, *J* = 6.6, 0.5 H, H–C(1')); 6.20 (*d*, *J* = 6.5, 0.5 H, H–C(1')); 6.83–6.87 (*m*, 4 arom. H); 7.25–7.38 (*m*, 9 arom. H); 7.41 (*br. s*, H–C(6)); 7.43 (*br. d*, H–N(3)). ³¹P-NMR (162 MHz, CDCl₃): 150.2, 150.9. MALDI-MS: 947.31 (100, [*M* + H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-5,6-dihydro-2'-O-[[triisopropylsilyl]oxy]methyl]uridine 3'-(2-Cyanoethyl Diisopropylphosphoramidite) (**41**). As described for **37**, with **15** (400 mg, 0.54 mmol), CH₂Cl₂ (5 ml), ³Pr₂NEt (0.24 ml, 1.35 mmol), and cyanoethyl diisopropylphosphoramidochloridite (160 mg, 0.65 mmol). CC (SiO₂ (10 g), hexane/AcOEt 4:1 → 1:9 (+ 3% Et₃N)) gave **41** (367 mg, 73%; 1:1 mixture of diastereoisomers). Colorless foam. TLC (hexane/AcOEt 7:3): *R_f* 0.73. ¹H-NMR (400 MHz, CDCl₃): 1.03–1.10 (*m*, ³Pr₃Si); 1.15–1.31 (*m*, (Me₂CH)₂N); 2.37 (*t*, *J* = 6.6, 1 H, CH₂CN); 2.50–2.62 (*m*, CH₂(5)); 2.66 (*dt*, *J* = 1.8, 6.7, 1 H, CH₂CN); 3.22–3.27 (*m*, 1 H, H–C(6)); 3.37–3.52 (*m*, 2 H, H'–C(6), H–C(5')); 3.52–3.77 (*m*, 4 H (Me₂CH)₂N, H'–C(5), POCH₂); 3.81, 3.82 (2*s*, 2 MeO); 3.82–3.97 (*m*, 1 H, POCH₂); 4.12 (*br. d*, *J* ≈ 2.2, 0.5 H, H–C(4')); 4.19 (*br. d*, *J* ≈ 2.7, 0.5 H, H–C(4')); 4.39–4.46 (*m*, H–C(2'), H–C(3')); 4.97 (*d*, *J* = 5.0, 0.5 H, OCH₂O); 5.05 (*q*, *J* = 4.9, 1.5 H, OCH₂O); 6.05 (*d*, *J* = 5.9, 0.5 H, H–C(1')); 6.07 (*d*, *J* = 5.7, 0.5 H, H–C(1')); 6.82–6.86 (*m*, 4 arom. H); 7.23–7.44 (*m*, 9 arom. H). ³¹P-NMR (162 MHz, CDCl₃): 150.1, 150.4. MALDI-MS: 935.36 (100, [*M* + H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-I-methyl-2'-O-[[triisopropylsilyl]oxy]methyl]inosine 3'-(2-Cyanoethyl Diisopropylphosphoramidite) (**42**). As described for **37**, with **18** (77 mg, 0.1 mmol), CH₂Cl₂ (2 ml), ⁱPr₂NEt (0.04 ml, 0.25 mmol), and cyanoethyl diisopropylphosphoramidochloridite (30 mg, 0.12 mmol). CC (SiO₂ (2 g), hexane/AcOEt 4:1 → 3:2 (+ 3% Et₃N)) gave **42** (78 mg, 80%; 1:1 mixture of diastereoisomers). Colorless foam. TLC (hexane/AcOEt 8:2): R_f 0.50. TLC (hexane/AcOEt 1:1): R_f 0.50. ¹H-NMR (400 MHz, CDCl₃): 0.86–1.05 (*m*, ⁱPr₃Si); 1.16–1.19 (*m*, (Me₂CH)₂N); 2.39 (*t*, *J* = 6.4, 1 H, CH₂CN); 2.67 (*t*, *J* = 6.4, 1 H, CH₂CN); 3.32–3.40 (*m*, 1 H, H–C(5')); 3.41–3.51 (*m*, 1 H, H'–C(5')); 3.51–3.70 (*m*, 3 H, (Me₂CH)₂N, POCH₂); 3.60, 3.61 (2s, Me–N(1)); 3.79, 3.80 (2s, 2 MeO); 3.84–3.97 (*m*, 1 H, POCH₂); 4.35, 4.41 (2*q*, *J* = 3.1, H–C(4')); 4.57–4.65 (*m*, H–C(3')); 4.91–4.98 (*m*, OCH₂O); 5.00–5.04 (*m*, H–C(2')); 6.05 (*d*, *J* = 6.1, 0.5 H, H–C(1')); 6.09 (*d*, *J* = 6.1, 0.5 H, H–C(1')); 6.75–6.83 (*m*, 4 arom. H); 7.18–7.44 (*m*, 9 arom. H); 7.78 (*s*, H–C(8)); 7.92, 7.93 (2s, H–C(2)). ³¹P-NMR (162 MHz, CDCl₃): 150.06; 150.73. ESI-MS: 971.83 (100, [M+H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-N⁶-isopent-2-enyl-2'-O-[[triisopropylsilyl]oxy]methyl]adenosine 3'-(2-Cyanoethyl Diisopropylphosphoramidite) (**43**). As described for **37**, with **21** (90 mg, 0.12 mmol), CH₂Cl₂ (1.5 ml), ⁱPr₂NEt (0.05 ml, 0.27 mmol), and cyanoethyl diisopropylphosphoramidochloridite (21 mg, 0.18 mmol). CC (SiO₂ (3 g), hexane/AcOEt 9:1 → 2:3 (+ 3% Et₃N)) gave **43** (90 mg, 80%; 1:1 mixture of diastereoisomers). Light yellow foam. TLC (hexane/AcOEt 1:1): R_f 0.70. ¹H-NMR (400 MHz, CDCl₃): 0.86–0.98 (*m*, ⁱPr₃Si); 1.11, 1.14 (2*d*, *J* = 6.6, (Me₂CH)₂N); 1.22 (*sept.*, *J* = 5.5, (Me₂CH)₂N); 1.76 (*s*, Me); 1.78 (*s*, Me); 2.39 (*t*, *J* = 6.5, 1 H, CH₂CN); 2.67 (*dt*, *J* = 2.3, 6.7, 1 H, CH₂CN); 3.32–3.72 (*m*, 1 H of POCH₂, (MeCH)₂N, H–C(5')); 3.79 (*s*, 2 MeO); 3.84–3.99 (*m*, 1 H, POCH₂); 4.22 (*br. s*, CH₂–NH); 4.34 (*d*, *J* = 3.7, H–C(4')); 4.40 (*t*, *J* = 4.0, H–C(4')); 4.67–4.74 (*m*, H–C(3')); 4.94, 4.96 (2*d*, *J* = 5.0, OCH₂O); 4.97–5.04 (*m*, OCH₂O); 5.16–5.23 (*m*, H–C(2')); 5.40 (*t*, *J* = 4.7, H–C(11)); 6.13, 6.16 (2*d*, *J* = 5.7, H–C(1')); 6.77–6.82 (*m*, 4 arom. H); 7.20–7.43 (*m*, 12 arom. H); 7.92, 7.94 (2s, H–C(8)); 8.28, 8.30 (2s, H–C(2)). ³¹P-NMR (162 MHz, CDCl₃): 150.1, 150.8. MALDI-MS: 1024.36 (100, [M+H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-N⁶-methyl-2'-O-[[triisopropylsilyl]oxy]methyl]adenosine 3'-(2-Cyanoethyl Diisopropylphosphoramidite) (**44**). As described for **37**, with **22** (120 mg, 0.16 mmol), CH₂Cl₂ (3 ml), ⁱPr₂NEt (0.07 ml, 0.39 mmol), and cyanoethyl diisopropylphosphoramidochloridite (39 mg, 0.19 mmol). CC (SiO₂ (3 g), hexane/AcOEt 4:1 → 2:3 (+ 3% Et₃N)) gave **44** (128 mg, 85%; 1:1 mixture of diastereoisomers). Colorless foam. TLC (hexane/AcOEt 1:1): R_f 0.50. ¹H-NMR (400 MHz, CDCl₃): 0.88–1.10 (*m*, ⁱPr₃Si); 1.16–1.26 (*m*, (Me₂CH)₂N); 2.37 (*t*, *J* = 6.5, 1 H, CH₂CN); 2.65 (*t*, *J* = 6.4, 1 H, CH₂CN); 3.20 (*br. s*, MeNH); 3.30–3.33 (*m*, H–C(5')); 3.49–3.70 (*m*, 4 H, H'–C(5')), (Me₂CH)₂N, POCH₂); 3.77, 3.78 (2s, 2 MeO); 3.86–3.97 (*m*, 1 H, POCH₂); 4.32, 4.37 (2*q*, *J* = 3.0, H–C(4')); 4.67–4.75 (*m*, H–C(3')); 4.91–5.01 (*m*, OCH₂O); 5.16–5.21 (*m*, H–C(2')); 6.11 (*d*, *J* = 5.5, 0.5 H, H–C(1')); 6.13 (*d*, *J* = 5.2, 0.5 H, H–C(1')); 6.75–6.79 (*m*, 4 arom. H); 7.17–7.41 (*m*, 9 arom. H); 7.90, 7.92 (2s, H–C(8)); 8.28, 8.30 (2s, H–C(2)). ³¹P-NMR (162 MHz, CDCl₃): 149.89; 150.58. ESI-MS: 546.29 (100, [M+H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-N⁶-dimethyl-2'-O-[[triisopropylsilyl]oxy]methyl]adenosine 3'-(2-Cyanoethyl Diisopropylphosphoramidite) (**45**). As described for **37**, with **23** (148 mg, 0.19 mmol), CH₂Cl₂ (3 ml), ⁱPr₂NEt (0.08 ml, 0.47 mmol), and cyanoethyl diisopropylphosphoramidochloridite (47 mg, 0.23 mmol). CC (SiO₂ (3 g), hexane/AcOEt 9:1 → 1:1 (+ 3% Et₃N)) gave **45** (148 mg, 80%; 1:1 mixture of diastereoisomers). Colorless foam. TLC (hexane/AcOEt 2:1): R_f 0.61. ¹H-NMR (400 MHz, CDCl₃): 0.88–1.10 (*m*, ⁱPr₃Si); 1.12–1.20 (*m*, (Me₂CH)₂N); 2.37 (*t*, *J* = 6.5, 1 H, CH₂CN); 2.65 (*t*, *J* = 6.4, 1 H, CH₂CN); 3.45–3.68 (*m*, 11 H, Me₂N, CH₂(5'), (Me₂CH)₂N, POCH₂); 3.77, 3.78 (2s, 2 MeO); 3.81–3.98 (*m*, 1 H, POCH₂); 4.32, 4.38 (2*q*, *J* = 3.1, H–C(4')); 4.67–4.75 (*m*, H–C(3')); 4.92–5.01 (*m*, OCH₂O); 5.14–5.17 (*m*, H–C(2')); 6.14 (*d*, *J* = 5.5, 0.5 H, H–C(1')); 6.16 (*d*, *J* = 5.2, 0.5 H, H–C(1')); 6.76–6.80 (*m*, 4 arom. H); 7.20–7.40 (*m*, 9 arom. H); 7.88, 7.90 (2s, H–C(8)); 8.22, 8.24 (2s, H–C(2)). ³¹P-NMR (162 MHz, CDCl₃): 149.86; 150.54. ESI-MS: 546.29 (100, [M+H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-I-methyl-2'-O-[[triisopropylsilyl]oxy]methyl]guanosine 3'-(2-Cyanoethyl Diisopropylphosphoramidite) (**46**). As described for **37**, with **25** (84 mg, 0.11 mmol), CH₂Cl₂ (0.5 ml), ⁱPr₂NEt (0.03 ml, 0.27 mmol), and cyanoethyl diisopropylphosphoramidochloridite (22 mg, 0.19 mmol). CC (SiO₂ (1.5 g), hexane/AcOEt 2:3 → AcOEt (+ 3% Et₃N)) gave **46** (61 mg, 58%; 1:1 mixture of diastereoisomers). Light yellow foam. TLC (hexane/AcOEt 1:9): R_f 0.34. ¹H-NMR (400 MHz, CDCl₃): 0.90–1.00 (*m*, ⁱPr₃Si); 1.06–1.31 (4*d*, *J* = 6.5, (Me₂CH)₂N); 2.35 (*t*, *J* = 6.4, 1 H, CH₂CN); 2.69 (*t*, *J* = 6.7, 1 H, CH₂CN); 2.77 (*dd*, *J* = 1.6, 6.3, 0.5 H, H–C(5')); 3.27–3.38 (*m*, 0.5 H, H–C(5')); 3.46, 3.47 (2s, 2 Me–N(1)); 3.49–3.72 (*m*, 4 H, (MeCH)₂N, H–C(5'), POCH₂); 3.79 (*s*, 2 MeO); 3.86–4.25 (*m*, POCH₂); 4.30 (*br. q*, *J* ≈ 2, 0.5 H, H–C(4')); 4.38 (*br. t*, *J* ≈ 3, 0.5 H, H–C(4')); 4.58–4.68 (*m*, H–C(3')); 4.73, 4.80 (2s, 1 H, OCH₂O); 4.88–5.15 (*m*, 1.5 H, H–C(2'), OCH₂O); 5.02–5.15 (*m*, 0.5 H, H–C(2')); 5.89 (*d*, *J* = 6.5, 0.5 H, H–C(1')); 5.96 (*d*, *J* = 7.0, 0.5 H,

H–C(1''); 6.80–6.82 (*m*, 4 arom. H); 7.21–7.48 (*m*, 9 arom. H, H–C(8)); 7.64, 7.66 (2 br. *s*, NH–C(2)). ³¹P-NMR (162 MHz, CDCl₃): 151.3; 151.6. MALDI-MS: 986.31 (100, [M+H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-N²,N²-methyl-2'-O-[[*(triisopropylsilyl)oxy*]methyl]guanosine 3'-(2-Cyanoethyl Diisopropylphosphoramidite) (**47**). As described for **37**, with **27** (75 mg, 0.09 mmol), CH₂Cl₂ (0.5 ml), ¹Pr₂NEt (0.04 ml, 0.23 mmol), and cyanoethyl diisopropylphosphoramidochloridite (27 mg, 0.11 mmol). CC (SiO₂ (2 g), CH₂Cl₂/MeOH 1:0 → 94:6 (+ 3% Et₃N)) gave **47** (87 mg, 92%; 1:1 mixture of diastereoisomers). Light pink foam. TLC (CH₂Cl₂/MeOH 9:1): R_f 0.37. ¹H-NMR (400 MHz, CDCl₃): 0.83–1.02 (*m*, ¹Pr₃Si); 1.06 (*d*, *J* = 6.0, Me₂CH₂N); 1.17–1.24 (*m*, (Me₂CH)₂N); 1.38 (*t*, *J* = 6.6, (Me₂CH)₂N); 2.35 (*t*, *J* = 6.6, 1 H, CH₂CN); 2.61–2.74 (*m*, 1 H, CH₂CN); 3.15 (*2d*, *J* = 7.2, MeNH–C(2)); 3.26–3.70 (*m*, 4.5 H, (MeCH)₂N, H–C(5'), POCH₂); 3.777, 3.786 (2*s*, 2 MeO); 3.82–3.98 (*m*, 1.5 H, POCH₂); 4.32, 4.36 (2 br. *d*, *J* = 4.1, H–C(4')); 4.58–4.65 (*m*, H–C(3')); 4.92–5.06 (*m*, H–C(2'), OCH₂O); 6.07 (*d*, *J* = 5.8, 0.5 H, H–C(1')); 6.10 (*d*, *J* = 5.9, 0.5 H, H–C(1')); 6.79–6.84 (*m*, 4 arom. H); 7.16–7.50 (*m*, 9 arom. H); 7.67, 7.68 (2*s*, H–C(8)); 11.9 (br. *s*, H–N(1)). ³¹P-NMR (162 MHz, CDCl₃): 150.4; 150.9. MALDI-MS: 986.29 (100, [M+H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-N²,N²-dimethyl-2'-O-[[*(triisopropylsilyl)oxy*]methyl]guanosine 3'-(2-Cyanoethyl Diisopropylphosphoramidite) (**48**). As described for **37**, with **29** (140 mg, 0.16 mmol), CH₂Cl₂ (0.7 ml), ¹Pr₂NEt (0.07 ml, 0.4 mmol), and cyanoethyl diisopropylphosphoramidochloridite (58 mg, 0.24 mmol). CC (SiO₂ (4 g), CH₂Cl₂ → CH₂Cl₂/MeOH 95:5 (+ 3% Et₃N)) gave **48** (104 mg, 64%; 1:1 mixture of diastereoisomers). Light yellow foam. TLC (CH₂Cl₂/MeOH 9:1): R_f 0.47. ¹H-NMR (400 MHz, CDCl₃): 0.95–0.97 (*1d*, *J* = 6.6, ¹Pr₃Si); 1.04–1.06 (*1d*, *J* = 6.6, (Me₂CH)₂N); 1.17–1.23 (*m*, (Me₂CH)₂N); 1.27–1.34 (*t*, *J* = 6.6, (Me₂CH)₂N); 2.34 (*t*, *J* = 6.6, 1 H, CH₂CN); 2.60–2.72 (*m*, 0.5 H, CH₂CN); 2.34 (*dt*, *J* ≈ 1, 4.4, 0.5 H, CH₂CN); 3.13, 3.14 (2*s*, Me₂N–C(2)); 3.31–3.70 (*m*, 5 H, (MeCH)₂N, H–C(5'), POCH₂); 3.786, 3.795 (2*s*, 2 MeO); 3.80–3.96 (*m*, 1.5 H, POCH₂); 4.11–4.27 (*m*, 1 H, POCH₂); 4.32 (br. *d*, *J* ≈ 3.7, 0.5 H, H–C(4')); 4.36 (br. *d*, *J* ≈ 3.6, 0.5 H, H–C(4')); 4.53–4.60 (*m*, H–C(3')); 4.90–5.06 (*m*, H–C(2'), OCH₂O); 6.03 (*d*, *J* = 6.6, 0.5 H, H–C(1')); 6.07 (*d*, *J* = 5.8, 0.5 H, H–C(1')); 6.78–6.83 (*m*, 4 arom. H); 7.23–7.43 (*m*, 9 arom. H); 7.67 (br. *s*, H–C(8)); 10.9 (br. *s*, H–N(1)). ³¹P-NMR (162 MHz, CDCl₃): 150.4; 150.9. ESI-MS: 1000.36 (100, [M+H]⁺).

N⁶-(Chloroacetyl)-5'-O-(4,4'-dimethoxytrityl)-1-methyl-2'-O-[[*(triisopropylsilyl)oxy*]methyl]adenosine 3'-(2-Cyanoethyl Diisopropylphosphoramidite) (**49**). As described for **37**, with **32** (400 mg, 0.48 mmol), CH₂Cl₂ (4 ml), ¹Pr₂NEt (0.21 ml, 1.23 mmol), and cyanoethyl diisopropylphosphoramidochloridite (134 mg, 0.56 mmol). CC (SiO₂ (10 g), hexane/AcOEt 4:1 → 1:4 (+ 3% Et₃N)) gave **49** (462 mg, 93%; 1:1 mixture of diastereoisomers). Colorless foam. TLC (hexane/AcOEt 1:9): R_f 0.75. ¹H-NMR (400 MHz, CDCl₃): 0.95–1.02 (*m*, ¹Pr₃Si); 1.08, 1.19 (*2d*, *J* = 7.3, (Me₂CH)₂N); 2.37 (*t*, *J* = 6.6, 1 H, CH₂CN); 2.66 (*t*, *J* = 5.8, 1 H, CH₂CN); 3.34 (*dt*, *J* = 4.3, 10.5, 1 H, POCH₂); 3.57–3.94 (*m*, 1 H of POCH₂, (MeCH)₂N, H–C(5')); 3.81 (*s*, MeO); 4.35 (*d*, *J* = 3.6, 0.5 H, H–C(4')); 4.41 (*d*, *J* = 3.6, 0.5 H, H–C(4')); 4.44 (*s*, ClCH₂); 4.62 (*dt*, *J* = 4.9, 10.9, H–C(3')); 4.91–5.01 (*m*, H–C(2'), OCH₂O); 6.04, 6.07 (*2d*, *J* = 5.9, H–C(1')); 6.79–6.84 (*m*, 4 arom. H); 7.22–7.38 (*m*, 12 arom. H); 7.74 (*s*, H–C(2)); 7.91, 7.93 (2*s*, H–C(8)). ³¹P-NMR (162 MHz, CDCl₃): 150.3, 150.9. MALDI-MS: 1046.74 (70, [M+H]⁺) 1048.74 (30, [M+H]⁺).

N⁶-[[*(1S,2R)*-2-[[*(tert*-Butyl)dimethylsilyl]oxy]-1-[[2-(4-nitrophenyl)ethoxy]carbonyl]propyl]amino]carbonyl]-5'-O-(4,4'-dimethoxytrityl)-2'-O-[[*(triisopropylsilyl)oxy*]methyl]adenosine 3'-(2-Cyanoethyl Diisopropylphosphoramidite) (**50**). As described for **37**, with **34** (100 mg, 0.08 mmol), CH₂Cl₂ (1 ml), ¹Pr₂NEt (0.05 ml, 0.21 mmol), and cyanoethyl diisopropylphosphoramidochloridite (24 mg, 0.10 mmol). CC (SiO₂ (3 g), hexane/AcOEt 6:4 → AcOEt (+ 3% Et₃N)) gave **50** (80 mg, 68%; 1:1 mixture of diastereoisomers). Colorless foam. TLC (hexane/AcOEt 1:9): R_f 0.62. ¹H-NMR (400 MHz, CDCl₃): –0.03, 0.09 (2*s*, MeSi); 0.97–1.08 (*m*, ¹Pr₃Si, ¹BuSi); 1.09 (*d*, *J* = 6.6, Me(γ)); 1.10–1.30 (*m*, (Me₂CH)₂N); 2.40 (*t*, *J* = 5.9, 1 H, CH₂CN); 2.67 (*t*, *J* = 6.6, 1 H, CH₂CN); 3.07 (*t*, *J* = 6.6, CH₂CH₂O); 3.35–3.39 (*m*, 1 H, POCH₂); 3.51–3.66 (*m*, (Me₂CH)₂N, H–C(5')); 3.80–4.00 (*m*, 1 H, POCH₂); 3.79 (*s*, 2 MeO); 4.32–4.44 (*m*, H–C(4'), CH₂CH₂O); 4.54 (*d*, *J* = 6.6, CH(β)); 4.58 (*d*, *J* = 8.8, CH(α)); 4.63–4.73 (*m*, H–C(3')); 4.96, 4.97, 5.03 (3*d*, *J* = 4.4, OCH₂O); 5.08–5.13 (*m*, H–C(2')); 6.24 (*d*, *J* = 5.1, 0.5 H, H–C(1')); 6.26 (*d*, *J* = 5.8, 0.5 H, H–C(1')); 6.79–6.84 (*m*, 4 arom. H); 7.24–7.54 (*m*, 15 arom. H); 8.06 (*d*, *J* = 8.1, 2 arom. H); 8.16, 8.19 (2*s*, H–C(8)); 8.43, 8.44 (2*s*, H–C(2)); 10.04 (*t*, *J* = 9.5, NN–C(6)). ³¹P-NMR (162 MHz, CDCl₃): 150.8; 150.2. ESI-MS: 1364.30 (100, [M+H]⁺).

N⁴-Acetyl-5'-O-(4,4'-dimethoxytrityl)-5-methyl-2'-O-[[*(triisopropylsilyl)oxy*]methyl]cytidine 3'-(2-Cyanoethyl Diisopropylphosphoramidite) (**51**). As described for **37**, with **36** (1.20 g, 1.56 mmol), CH₂Cl₂ (6.3 ml), ¹Pr₂NEt (0.60 ml, 3.90 mmol), and cyanoethyl diisopropylphosphoramidochloridite (444 mg, 1.88 mmol). CC (SiO₂ (30 g), hexane/AcOEt 1:1 → AcOEt (+ 2% Et₃N)) gave **51** (1.42 g, 94%; 1:1 mixture of diastereoisomers). Colorless foam. TLC (hexane/AcOEt 3:7): R_f 0.75. ¹H-NMR (400 MHz, CDCl₃): 0.97–1.08 (*m*, ¹Pr₃Si); 1.08–1.13 (*m*, (Me₂CH)₂N); 2.25 (br. *s*, MeCO); 2.51 (br. *s*, Me–C(5)); 2.54 (*t*, *J* = 5.9, 1 H, CH₂CN); 2.75 (br. *q*, *J* = 5.9, 1 H, CH₂CN); 3.42–3.24 (*m*, 1 H of POCH₂, (Me₂CH)₂N, H–C(5')); 3.66–3.82 (*m*, 1 H,

POCH₂); 3.73 (s, 2 MeO); 7.85 (2br. s, H–C(4')); 4.32–4.48 (m, H–C(2'), H–C(3')); 4.89–5.04 (m, OCH₂O); 6.00 (d, *J* = 4.4, H–C(1')); 6.87–6.89 (m, 4 arom. H); 7.22–7.43 (m, 9 arom. H); 7.85 (d, *J* = 8.0, H–C(6)). ³¹P-NMR (162 MHz, CDCl₃): 149.0, 149.5. ESI-MS: 988.30 (100, [*M* + H]⁺).

5'-O-(4,4'-Dimethoxytrityl)-2'-O-[[tr(isopropylsilyl)oxy]methyl]inosine 3'-(2-Cyanoethyl Diisopropylphosphoramidite) (**52**). A suspension of **17** (1.5 g, 2 mmol), 5-benzyl-1*H*-tetrazole (0.43 g, 2.2 mmol; prepared according to [23]), and 4 Å MS in MeCN (10 ml) was treated with 2-cyanoethyl tetraisopropylphosphoramidite (1.8 g, 6 mmol). After 4 h at r.t., the mixture was diluted with CH₂Cl₂ (100 ml) and poured into a well-stirred mixture of CH₂Cl₂ (200 ml) and sat. aq. NaHCO₃ soln. (250 ml). The org. phase was dried (Na₂SO₄) and evaporated. CC (SiO₂ (40 g), hexane/AcOEt 1:1 → AcOEt (+3% Et₃N)) gave **52** (1.75 g, 92%; 1:1 mixture of diastereoisomers). Colorless foam. TLC (hexane/AcOEt 1:9): *R*_f 0.48. ¹H-NMR (400 MHz, CDCl₃): 0.85–1.00 (m, ¹Pr₃Si); 1.18–1.31 (m, (Me₂CH)₂N); 2.40 (t, *J* = 6.5, 1 H, CH₂CN); 2.62–2.71 (dt, *J* = 1.5, 7.6, 1 H, CH₂CN); 3.35–3.41 (m, POCH₂); 3.46–3.74 (m, 4 H (Me₂CH)₂N, H–C(5'), POCH₂); 3.79, 3.80 (2s, 2 MeO); 3.85–4.00 (m, 1 H, POCH₂); 4.38 (br. d, *J* = 3.4, 0.5 H, H–C(4')); 4.43 (br. d, *J* = 3.6, 0.5 H, H–C(4')); 4.58–4.64 (m, H–C(2'), H–C(3')); 4.92–5.09 (m, OCH₂O); 6.13 (d, *J* = 6.0, 0.5 H, H–C(1')); 6.16 (d, *J* = 6.0, 0.5 H, H–C(1')); 6.79–6.84 (m, 4 arom. H); 7.19–7.47 (m, 9 arom. H); 7.94, 7.95 (2s, H–C(8)); 8.01, 8.04 (2s, H–C(2)). ³¹P-NMR (162 MHz, CDCl₃): 151.3, 152.1. MALDI-MS: 957.36 (100, [*M* + H]⁺).

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