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Total Syntheses of a Conformationally Locked *North*-Type Methanocarba Puromycin Analogue and a Dinucleotide Derivative

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Abstract: An original synthetic approach for the first synthesis of an enantiopure methanocarba puromycin (3′-α-aminoacylamino-3′-deoxyadenosine) analogue and its cytidine dinucleotide derivative is described. Each compound is conformationally locked in a *North*-type pucker and exhibits both a pseudoaxial hydroxy group and a pseudoequatorial aminoacyl group. The syntheses were accomplished from D-ribose in 18 and 19 steps, respectively, with key steps being a ring-closing metathesis, a Luche reduction, a Simmons–Smith cyclopropanation, a Mitsunobu coupling, a Mattocks bromoacetylation, a regioselective and a stereoselective nucleophilic substitution, a chemoselective phosphoramidite coupling and a Staudinger–Vilarrasa coupling. Both molecules are being tested for peptidyl transfer efficiency in ribosomes for comparison with the peptidyl transfer kinetics of natural puromycin and other natural and synthetic ribosomal A site substrates.

Keywords: antibiotics · carbocycles · nucleosides · protein synthesis · ribosomes

Introduction

Puromycin (**1**, Pm, Figure 1), a natural antibiotic nucleoside, was isolated from *Streptomyces alboniger* in 1952 by Porter et al.[1] It has been intensively used to investigate protein biosynthesis and to clear up understanding of its mechanism.[2] Its structural similarity to the 3′ terminal 3′-*O*-aminoacyl adenylate moiety that is conserved in all aminoacyl-tRNA explains its activity in the ribosomal A site. Puromycin inhibits protein synthesis by transfer of the nascent polypeptide chain to its α-amino group.[3] Unfortunately, puromycin is cytotoxic, and so we wish to develop new analogues with similar nascent peptide-accepting properties but lower toxicity.

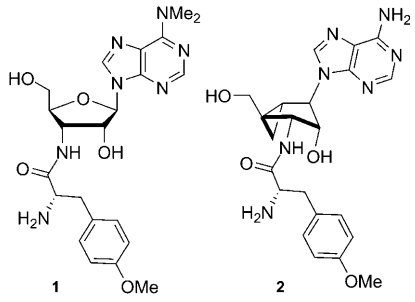

Figure 1. Puromycin (**1**) and its carbocyclic locked *North*-type methanocarba analogue **2**.

Puromycin analogues are currently sought-after compounds for investigation of the ribosomal catalysis of the peptidyl transfer (PT) reaction. Simpler model compounds have been used by Wolfenden and colleagues to compare the kinetics of uncatalyzed bimolecular ester aminolysis in aqueous solution with those catalyzed by the ribosome′s peptidyl transferase. When this aminolysis was compared to the kinetics of ribosome-catalyzed transfer of the *N*-formylmethionyl group to puromycin (PT from P site-bound fMet-tRNA^{i} to A site-bound Pm), a modest 3.5 to 30 million-fold rate acceleration could be deduced and—owing to the virtually absent temperature dependence of PT in Arrhenius plots—was attributed to a purely entropic effect provided by the peptidyl transferase and proposed to originate either from precise substrate alignment[4a–c] or, as observed thereafter in MD simulations, from the conservation of solvation entropy of the nucleophilic α-amino group between an assumed reaction ground state and the transition state.[4d,e] To conclude from Arrhenius plots, despite their linearity, that

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very low apparent $T\Delta S^{\neq}$ values indicate *pure entropic catalysis* may be tempting but is likely to be misleading, because both $T\Delta S^{\neq}$ and $\Delta H^{\neq}$ are derived from $\Delta G^{\neq}$ (through ln*k* and 1/*T*) and *necessarily* compensate one another such that relatively low measured $\Delta G^{\neq}$ values result: 16.5 kcal mol^{-1} for the above PT reaction, in comparison with 22.2–23.5 kcal mol^{-1} for the uncatalyzed ester aminolysis (both at 25 °C). More recently, similar independent studies in the Ehrenberg and the Rodnina laboratories revealed faster PT kinetics, and hence even lower catalyzed free energy barriers: $\Delta G^{\neq}$ (25 °C) = 15.1, 13.9, and 12.6 kcal mol^{-1}. In those cases, peptide-accepting puromycin had been replaced by phenylalanyl-tRNA (PT kinetics from fMet-tRNA^{i} to Phe-tRNA^{Phe})[4f] and the donating *N*-formylmethionyl group by two different *N*-formyl dipeptides (PT kinetics from fMet-Phe-tRNA^{Phe} or fMet-Arg-tRNA^{Arg} to Pm).[4g] These results suggest that ribosomal rate accelerations with respect to uncatalyzed ester aminolyses may amount to more than 10^{10}-fold. The molecular reasons for such efficient catalysis remain unknown. We wished to study the precise structural and functional prerequisites for ribosomal nascent-peptide acceptors more carefully.[5] To this end we set out to synthesize conformationally restricted puromycin analogues, in order to gain more insight into the nature of ribosomal catalysis of PT, as well as to find new lead compounds that might be used as novel antibiotics.

Two conformations adoptable by a nucleosidic furanose ring, usually referred to as *North*-type and *South*-type, are well-known to play a dominant role in the mechanisms of action of a number of antibiotic nucleosides. Inspired by crystallographic results for neplanocin C,[6] Marquez conceptualized and synthesized methanocarba (MC) nucleosides incorporating a conformationally rigid bicyclo[3.1.0]hexane scaffold (Figure 2), to allow optimal mimicry of the *North*-type (*N*) and *South*-type (*S*) conformations of a ribofuranose pucker.[7] The *North*-type and *South*-type pucker ranges usually preferred by ribofuranosidic nucleosides are C3′-*endo* (^3E) and C2′-*endo* (^2E), respectively. This translates into pseudorotational angles of $P \approx 15°$ and 165° (±15°), respectively.[8] The replacement of C4′–O4′ and O4′–C1′ by a fused cyclopropane moiety in a *trans* configuration with respect to the nucleobase constrains the cyclopentane rings of these carbobicyclic nucleosides in boat conformations that result in C2′-*exo* ($_2E$) puckers for the *North*-type isomers and C3′-*exo* ($_3$E) for the *South*-type isomers ($P \approx -18°$ and 198°, respectively). Other rigid bicyclic analogues that are locked into one of the two puckers through an oxymethylene bridge between C4′ and either C3′ or C2′ (nucleoside numbering) exhibit conformations even more similar to those of the parent analogues.[9–12] However, the Marquez analogues are the only ones that still maintain the natural functions at C2′ and C3′, which is of prime importance for our purpose. The pseudoaxial/-equatorial positioning of their 2′- and 3′-substituents is very close to that of the mimicked ribonucleosides: *North* = 2′-pseudoaxial/3′-pseudoequatorial, *South* = 2′-pseudoequatorial/3′-pseudoaxial. In a collaboration with the Marquez group we recently synthesized four new locked *N*-MC 2′-deoxypuromycin analogues (**3**, **4**, **5**, and **6**, Figure 2) in which enantiopure *N*-MC and *S*-MC bicyclo[3.1.0]hexane ring systems substituted for puromycin's D-ribofuranose moiety in order to mimic *North*-type and *South*-type puckers, respectively, that would present precisely positioned 3′ substituents (nucleoside numbering) and be unable to switch into the other pucker regime.[13]

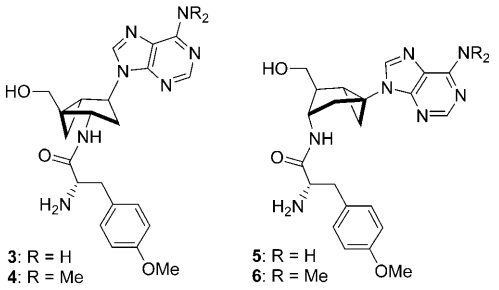
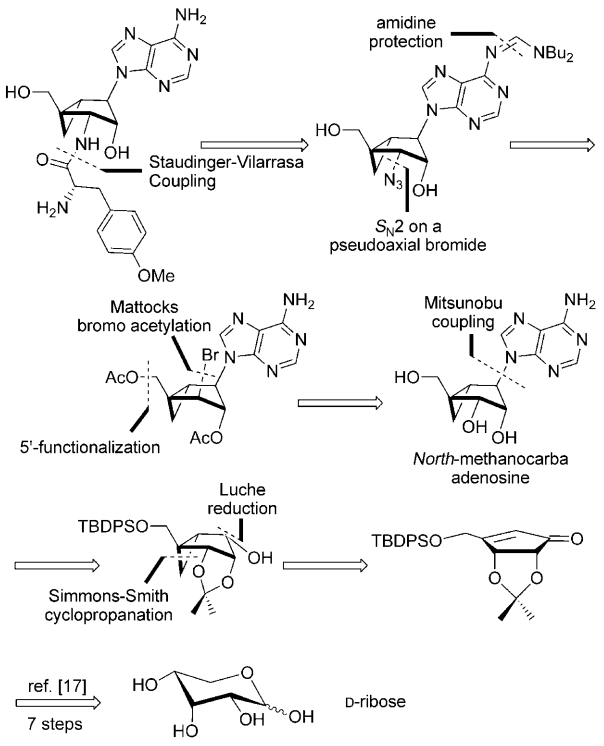


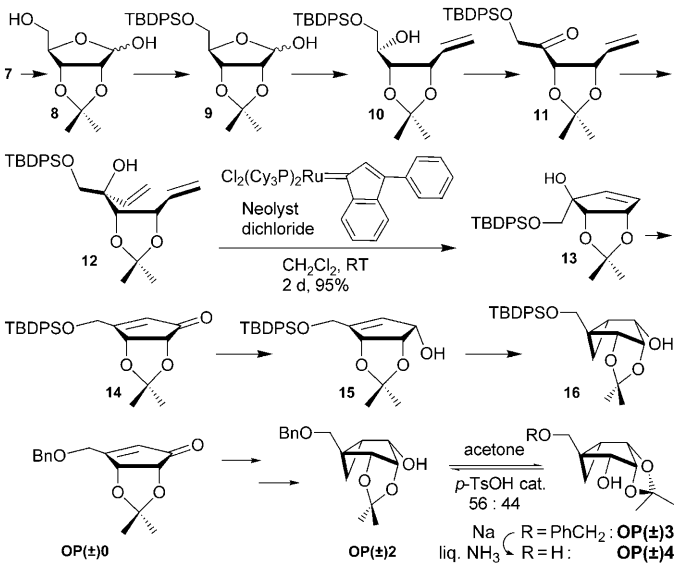
Figure 2. Locked *N*-MC and *S*-MC 2′-deoxypuromycin analogues. The aminoacyl side chain is pseudoequatorially oriented in the *N*-MC 2′-deoxypuromycin analogues **3** and **4**[7w] and pseudoaxially oriented in the *S*-MC 2′-deoxypuromycin analogues **5** and **6**.

Crystallographic studies suggest that the 2′-hydroxy group of puromycin—and thus, equally, of the 3′-terminal A76 residue of any natural 3′-aminoacyl tRNA—may be important for good binding to the ribosomal A site if pseudoaxially oriented.[14a] After PT and translocation of the new peptidyl-tRNA into the P site,[14b] the 2′-hydroxy group of the same residue A76 switches to a pseudoequatorial orientation (puromycin and analogues are not translocated after PT). The immediately preceding cytidine residue C75, also present in all tRNAs, is base-paired in the A and P sites with highly conserved ribosomal guanosine residues. Puromycin that is linked to 3′-cytidylate might bind more stably to the A site and/or further accelerate PT, resulting in more efficient inhibition of protein synthesis. We therefore designed two puromycin analogues in which the D-ribofuranose moiety would be replaced by an enantiopure *N*-MC bicyclo[3.1.0]hexane ring system that is unable to switch into another pucker and contains a pseudoaxially locked 2′-hydroxy function (nucleoside numbering), to enhance A site recognition further. Here we report on the synthesis of the locked *ribo*-puromycin analogue **2** (Figure 1) and its 5′-*O*-(3′-cytidylate) derivative **36** (Scheme 8). All locked analogues—**2**, **3**, **4**, **5**, **6** and **36**—are currently being tested for peptidyl transfer efficiency in ribosomes and the findings are being compared with the enzymological results obtained for natural puromycin (**1**) and other natural and unnatural A site substrates.

For the retrosynthetic analysis we began with the cleavage of the peptide bond to the *N*-MC bicyclo[3.1.0]hexane scaffold (Scheme 1). The amino acid side chain can be easily introduced by Staudinger–Vilarrasa coupling, for which we had previously optimized the experimental conditions. An earlier comparative study of the difference in reactivity between the iminophosphorane generated in situ and the nu-



Scheme 1. Retrosynthetic pathway leading to target compound **2**.



Scheme 2. Synthetic pathway leading to bicyclic alcohols **16** and **OP(±)2**/**3**/**4**.

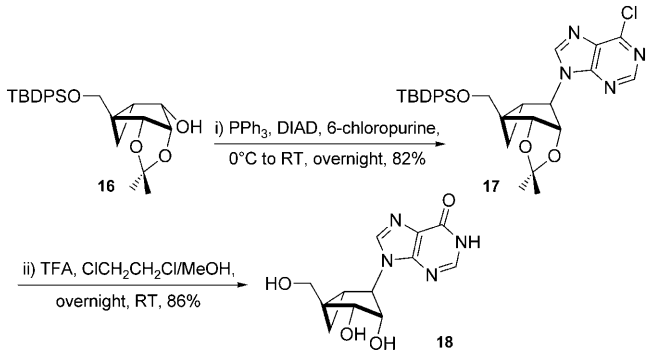
cleobase′s 6-amino group towards the activated ester during the amino acid coupling showed that, to improve the yield of peptide bond formation, N^6-amidine protection should be chemoselectively introduced beforehand.[15] The replacement of the 3′-hydroxy group by an azido group with retention of configuration and without changes at C2′ and C5′ constitutes one of the major difficulties of this total synthesis. We planned to introduce the azido function through an S_N2 reaction on a pseudoaxial 3′-halogen function. The appropriate *xylo*-derivative can be obtained through a Mattocks bromoacetylation reaction.[16] A Mitsunobu coupling allows for stereoselective introduction of the adenine moiety in protected form. To lock the scaffold with the help of a MC ring, a diastereoselective Simmons–Smith cyclopropanation directed by the 1α-hydroxy group seems appropriate. This alcohol function can be obtained by diastereoselective Luche reduction of the functionalized cyclopentenone **14** (Scheme 2), which had been described in the literature[17] and optimized during our previous studies.[18]

Results

The nine-step synthetic pathway to **16** began with D-ribose (=**7**, Scheme 2) and profited from a very-well worked-out route published by Jeong and colleagues[19] and used by others.[20] The only significant change that we introduced was in the RCM reaction from **12** to **13**, which was carried out in the presence of the Fürstner catalyst[21] (Neolyst dichloride™) and exhibited results similar to those obtained with the six-times-dearer Grubbs II catalyst.[17] The both regio- and stereoselective Luche reduction[22] and the subsequent stereoselective Simmons–Smith cyclopropanation[7d,23] were carried out on enantiopure **14** by use of the same protocol as employed earlier for racemic **OP(±)0** and gave alcohol **16** as a single diastereoisomer and in high yield. **OP(±)2** was isomerized in acetone containing catalytic amounts of *p*-TsOH into **OP(±)3**, which was separated from its regioisomer through flash chromatography over silica gel and then reduced with sodium in liquid ammonia to give **OP(±)4** in 50% yield. We managed to grow monocrystals of the last two compounds. Their X-ray structures (CCDC-711880 and -711881, respectively) served to corroborate their diastereoisomeric identities and to provide us with additional information on the puckering of the cyclopentane moiety (see Discussion).

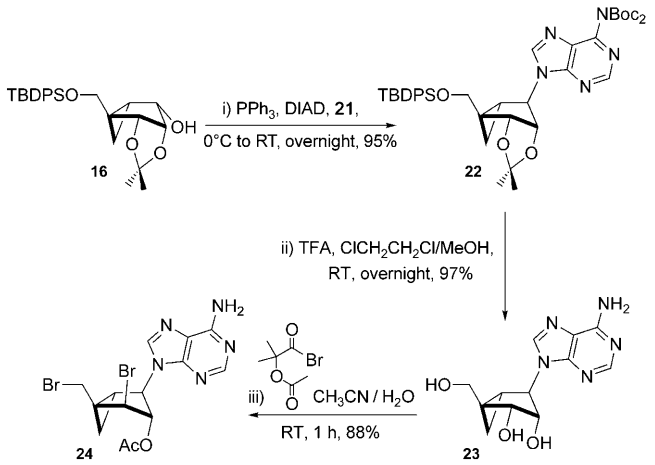
We initially wished to introduce the nucleobase through a Mitsunobu coupling with 6-chloropurine as the nucleophile. We expected to take advantage of the lability of the chlorine atom by replacing it with miscellaneous amines at some later stage to provide us with several nucleobase variants differently substituted at C6. However, any acidic treatment tested for the removal of the acetonide and the silyl protecting group from **17** concomitantly hydrolyzed the chlorine and led to *N*-MC inosine derivative **18** (Scheme 3), which had already been synthesized by Marquez and Jacobson, who showed that it was a weaker binder to A_3 AR (an adenosine receptor subtype) than the parent inosine, which is possibly the endogenous ligand.[7p]

In order to circumvent hypoxanthine protection problems downstream, we turned to the Garner procedure,[24] in which N^6,N^6-bis-Boc adenine (**21**) can be synthesized in two easily scalable steps. Adenine (**19**) was per-protected as its 9,N^6,N^6-tris-*tert*-butoxycarbonyl carbamate **20**, from which



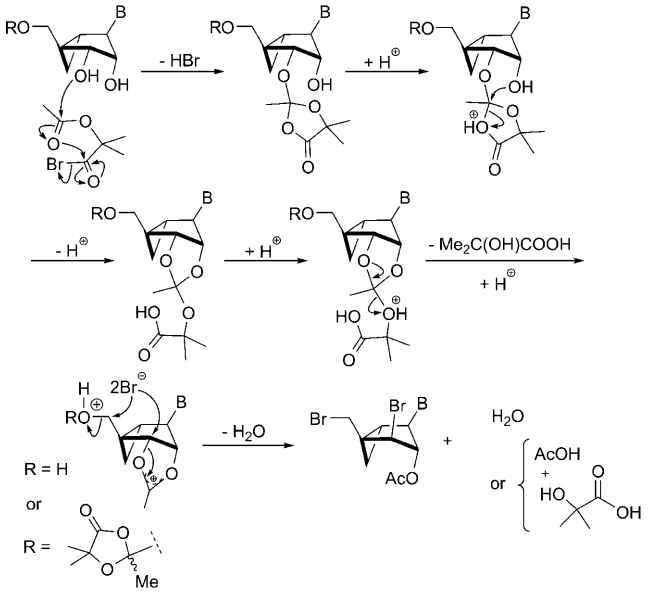
Scheme 3. Synthesis of the *N*-MC inosine **18**.

21 was regioselectively generated under mildly basic conditions and in very good yield. Unlike 6-chloropurine, **21** is highly soluble in THF. We carried out the Mitsunobu coupling with **21**, and it proceeded cleanly, rapidly and almost quantitatively, most probably thanks to the high solubility of the nucleophile (Scheme 4).[18] Acidic treatment of **22** provided the cyclopropane-fused carbocyclic adenosine **23** in good yields.[7d]



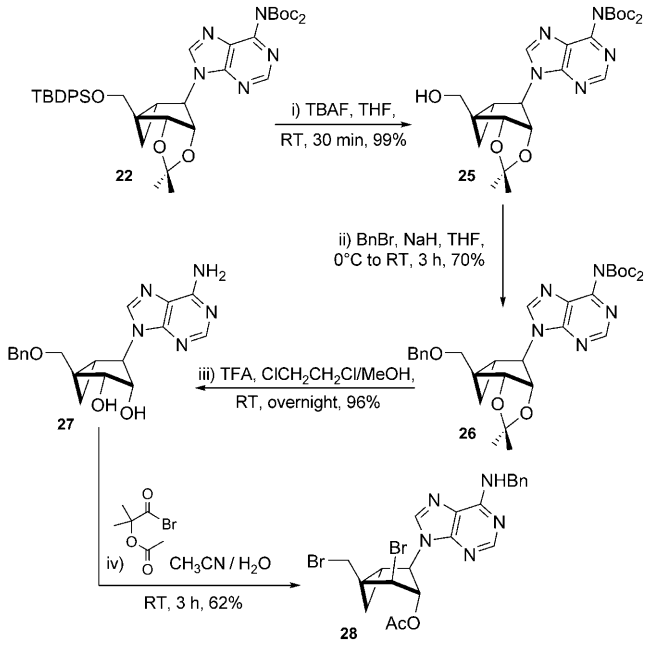
Scheme 4. Synthesis of dibromo analogue **24**.

We then wished to functionalize the 3′ position (nucleoside numbering) without affecting the 2′- and 5′-hydroxy groups, in order to continue with the introduction of an azide function for subsequent coupling with the amino acid through a Staudinger–Vilarrasa reaction. We therefore envisaged a reaction that would invert the 3′-hydroxy moiety to provide a function that would serve as a leaving group for the following step: a S_N2 reaction with inorganic azide. The Mattocks bromoacetylation seemed useful for our purpose,[16] because it had been successfully applied for the stereospecific synthesis of 2′,3′-*ribo*-epoxides both by others[25] and by ourselves.[15] This reaction would be expected to convert vicinal *cis*-diols into vicinal *trans*-bromoacetates. In the case of the *N*-MC analogue **23**,[25g] however, we were astonished to observe, under all tested reaction conditions that would allow **23** to react at all, that at least 1–3% *v/v* water initially had to be added, resulting in the exclusive formation of the 2′-*O*-acetyl-3′,5′-dibromo derivative **24**, for which two zero coupling constants—for H2′–H3′ and H1′–H2′—indicated two vicinal *trans* relationships, and hence the desired *xylo* configuration. Under the applied reaction conditions (i.e., after more water had been added to drive the reaction to completion), the primary hydroxy group of **23** apparently did not survive the increasing acidity of the medium and underwent, in part after orthoesterification, a substitution reaction with the released HBr (Scheme 5).



Scheme 5. Proposed mechanism of the Mattocks dibromoacetylation reaction based on refs. [25a,b] and our observation that 2′-OH was less reactive than 3′-OH (nucleoside numbering, B = nucleobase). Attack on C5′ probably occurs only late during the reaction, when more water is added to solubilize all starting material and the acidity of HBr thus markedly increases. In the original studies on adenosine, no late addition of water was needed for the completion of the reaction (to give the corresponding *trans*-monobromoacetate); were it necessary, this would cleave the glycosidic bond due to overacidification (unpublished observations).

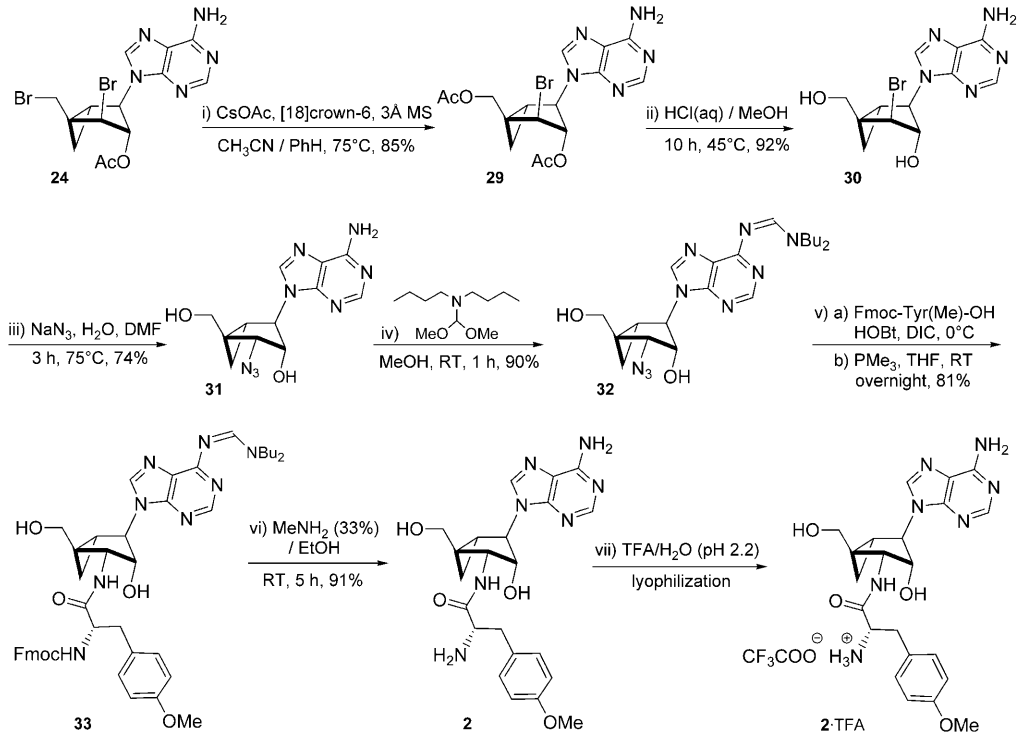
As a consequence, we decided to protect this alcohol function beforehand as a benzyl ether, which should resist harsh acidic conditions. We restarted from **22**, which was desilylated with TBAF (Scheme 6), and the resulting primary alcohol **25** was benzylated to give **26**. Acidic treatment cleaved the acetonide and the Boc groups to afford the vicinal *cis*-diol **27**, and another Mattocks reaction was attempted. Astonishingly, we obtained an even more unexpected and hitherto unprecedented result in the formation of a *xylo*-configured dibromoacetate, the stereo- and regioisomeric identity of which could be ascertained by NMR spectroscopy through two zero coupling constants for H2′–H3′ and H1′–H2′ (desired stereoisomer), together with a ^3J cross-peak between the carbonyl C atom of the acetate



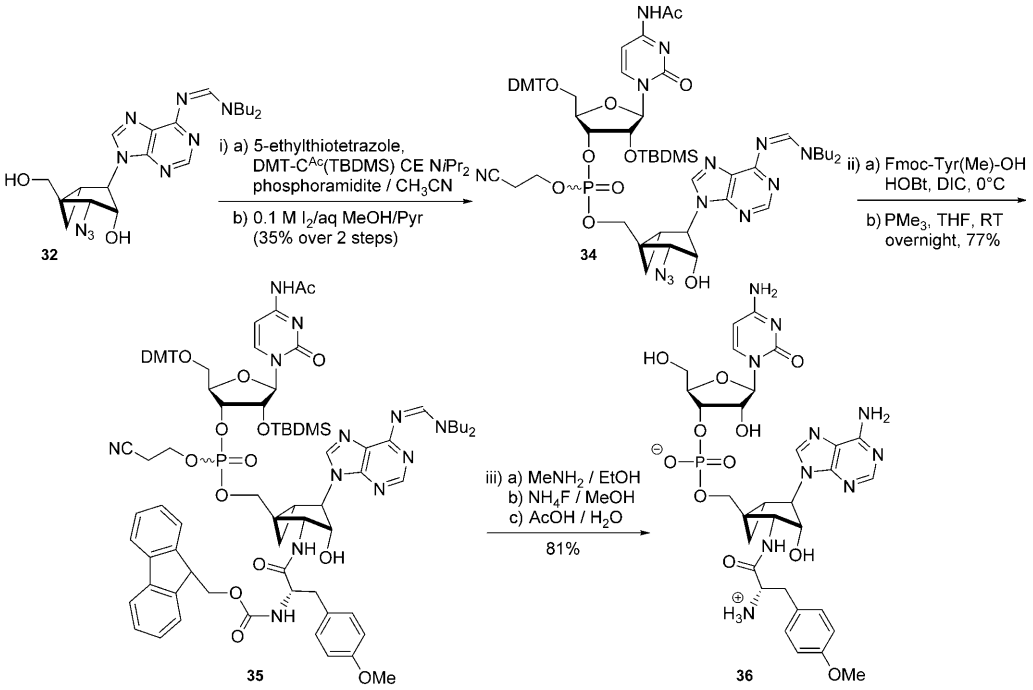
Scheme 6. Benzyl migration during the Mattocks bromoacetylation of **27**.

function and H2′ through HMBC (desired regioisomer; see the Supporting Information). However, the 5′-ether group had been cleaved to yield **28**, in which the benzyl group had migrated to the adenine moiety. An MS·MS analysis on **28** showed that an initial fragmentation of the central dibromo isotopomeric molecular ion at *m/z* 543/536/538 resulted in the formation of benzyladenine and the elimination of HBr to give *m/z* 226 and 454/456, respectively, from which a second fragmentation again produced mainly *m/z* 226 and fragments from which ketene, AcOH and HBr had cleaved (*m/z* 412/414, 394/396, and 374). NMR spectroscopic investigation of **28** identified an N-benzyl compound. Unlike the well-resolved ^{1}H NMR doublets for OCH_2Ph in **26** and **27**, the corresponding methylene ^{1}H resonance in **28** was broad, due to a geminal quadrupole $^{14}N C^{1}H_2$Ph coupling. This methylene carbon signal could not be found either in ^{13}C NMR or in DEPT spectra, again most probably due to an efficient quadrupole $^{14}N^{13}CH_2$Ph broadening. With the help of a clear ^{1}H–^{13}C HSQC cross-peak this ^{13}C atom was found to resonate at ~44 ppm, which was confirmed by HMBC through a weak vicinal coupling between $^{13}CH_2$ at ~44 ppm and the *ortho*-^{1}H in the phenyl group (see Supporting Information).

Protection of the primary alcohol for this bromoacetylation reaction thus appeared to have become pointless. It was more judicious to reconsider the previously obtained compound **24** and to profit from the difference in reactivity between the two bromo groups. Actually, this 3′,5′-dibromodideoxy-2′-acetate derivative, with its primary and secondary leaving groups, offered the potential for regioselective introduction of different nucleophiles. After reference to studies by Mander,[26] the use of CsOAc enabled us to substitute the primary bromide to provide **29** in high yields (Scheme 7). We were successful in crystallizing this diacetylated derivative from a $CHCl_3$/MeOH mixture. The X-ray structure (Figure 3, below; see Discussion section) confirmed the regio- and stereochemical dispositions of C2′ and C3′ originally deduced from NMR spectroscopic analyses.



Scheme 7. Synthesis of the *N*-MC puromycin analogue **2**.



Scheme 8. Synthesis of the locked cytidine puromycin analogue dinucleotide **36**.

During the S_N2 reaction between inorganic azide and the pseudoaxial C3′-bromide (nucleoside numbering) we encountered problems, already raised by Réglier,[27] involving anchimeric assistance by the O2′-acetate group. We therefore decided to cleave both ester functions beforehand, firstly under mildly basic conditions. Because we had consistently been able to transform the resulting 3′-bromo-2′,5′-diol into the corresponding *ribo*-2′,3′-epoxide MC analogue, we turned to an acidolysis of **29** by treatment with aqueous HCl in warm MeOH and obtained the completely deprotected *xylo*-derivative **30** (Scheme 7).[28] Now the S_N2 reaction with NaN_3 in DMF furnished satisfactory yields of **31**. The formation of the *ribo*-epoxide (25%) could nevertheless not be prevented. Recently[15] we showed that it was beneficial first to protect the adenine N^6 group as a dibutyl formamidine (dbf),[29a] in order to increase the yield of the subsequent amino acid coupling. The main advantages of dbf protection are its facile and efficient preparation and cleavage[29] and, most importantly, that it can be used, unlike a number of other common amine-protecting groups, in the presence of numerous hydroxy groups, as well as of many organic functions including azido functionalities.[30] The N^6-protected azido diol **32** was chemoselectively[31] coupled to the *N*-protected L-amino acid oxybenzotriazolyl ester Fmoc-Tyr(Me)-OBt (prepared in situ) by a Staudinger–Vilarrasa procedure, the conditions of which (reduction with Me_3P, facile separation of Me_3PO) had been optimized previously.[13,15] The coupled product **33** was completely deprotected by treatment with ethanolic $MeNH_2$, to furnish target compound **2**. A final lyophilization from H_2O/TFA at pH 2.2 led to the more water-soluble **2**·TFA salt as a white, fluffy solid.

For the synthesis of dinucleotide analogue **36** (Scheme 8) we restarted from the dbf-protected azido diol **32**, which was chemoselectively coupled with a commercial cytidine phosphoramidite derivative by a standard solution protocol.[32] Subsequent in situ treatment with aqueous methanolic I_2 in the presence of pyridine immediately oxidized the intermediate phosphite to the desired *P*-diastereoisomeric phosphotriesters **34**. The Staudinger–Vilarrasa procedure was applied to **34** and afforded **35** in satisfying yields. Finally, a three-step, one-pot deprotection procedure[33] provided the zwitterionic target aminoacyl dinucleotide *N*-MC analogue **36**. It is noteworthy that this highly polar compound could be efficiently purified through preparative normal-phase silica TLC with the highly polar eluent *i*PrOH/NH_3/H_2O.

Discussion

A comparison of the characteristic torsion and pseudorotational angles in the X-ray structures of the 3′β-bromo-2′,5′-diacetate derivative **29** (Figure 3) and of other similar bicyclo[3.1.0]hexane derivatives on the one hand, with those in puromycin on the other, revealed that the conformation around C1′–N9 (nucleoside numbering: the "glycosidic bond"), when present, always lies in the *anti* regime, whereas the one around C5′–C4′ depends on the steric access between C5′ and the nucleobase: usually *gauche*$^+$, although *gauche*$^-$ in the *xylo* analogue **29**. Both torsion angles are likely to be potentially influenced by crystal packing forces as well. More importantly, the pucker of the cyclopentane moiety always points to *North*-type 2′-*exo* ($_2$E), but with a

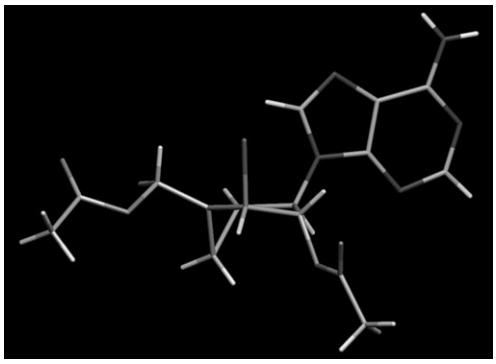


Figure 3. X-ray structure of the diacetylated 3′-bromo compound **29** (CCDC-711879). It is characterized through the following conformational parameters, as obtained from the *Pseudo-Rotational Online Service and Interactive Tool* PROSIT (http://cactus.nci.nih.gov/prosit): $P=-20.4°$ (339.6°: $_2$E), $\nu_{max}=16.0°$, $\chi=-149.8°$ (purine *anti*), $\gamma=-69.6°$ (O5′–C3′ *gauche*$^-$, nucleoside numbering). The same parameters for puromycin (CCDC code PURMYC10): $P=3.9°$ (^{3}E), $\nu_{max}=38.3°$, $\chi=-159.3°$ (purine *anti*), $\gamma=54.0°$ (O5′–C3′ *gauche*$^+$); for a 3′-azido-2′,3′-dideoxy (nucleoside numbering) *N*-MC adenosine analogue (CCDC code FADSAF)[7w]: $P=-20.3°$ (339.7°: $_2$E), $\nu_{max}=30.5°$, $\chi=-160.5°$ (purine *anti*), $\gamma=-69.9°$ (O5′–C3′ *gauche*$^+$, nucleoside numbering); for **OP(±)3** (CCDC-711880): $P=-20.4°$ (339.6°: $_2$E), $\nu_{max}=14.0°$, $\gamma=49.5°$ (O5–C3 *gauche*$^+$, carbohydrate numbering); for **OP(±)4** (CCDC-711881): $P=-14.7°$ (345.3°: $_2$E), $\nu_{max}=24.1°$, $\gamma=61.3°$ (O5–C3 *gauche*$^+$, carbohydrate numbering). For the definitions of P, ν_{max}, χ, and γ see PROSIT or ref. [8].

quite strongly varying amplitude as characterized by ν_{max}. In general, the more pronounced a *North*-type amplitude is, the "more equatorial" the orientation of the 3′α substituent becomes. The highest amplitude (i.e., the closest to that of natural puromycin: $\nu_{max}=38.3°$) was observed in the 3′-azido-2′,3′-dideoxy *N*-MC adenosine analogue that we had published earlier ($\nu_{max}=30.5°$),[7w] followed by the 1α,2-*O,O*-isopropylidene derivative **OP(±)4** ($\nu_{max}=24.1°$), the 3′β-bromo-2′,5′-diacetyl derivative **29** ($\nu_{max}=16.0°$) and the 5-*O*-benzyl-1α,2-*O,O*-isopropylidene derivative **OP(±)3** ($\nu_{max}=14.0°$): see the legend to Figure 3.

The relative configurations of C2′ and C3′ in the target compounds were ascertained through a systematic comparison between the NOESY cross-correlation signals of aqueous **2**·TFA and the corresponding H···H distances as elucidated from three crystal structures: those of (nucleoside numbering) the 3′-azido-2′,3′-dideoxy *N*-MC adenosine analogue[7w] (CCDC code FADSAF) and **29** (CCDC-711879) for all distances except those relating to amino acid side chains and of crystalline puromycin dihydrochloride (CCDC code PURMYC10) for H···H distances within the amino acid side chain only (see detailed table in the Supporting Information). Out of 24 observed significant and weak NOESY cross-correlations, only one unexpected significant correlation and one unexpected weak correlation were found according to the through-space distances as elucidated from FADSAF (3.91 Å for H8···H1′ and 4.07 Å for H8···H2′, respectively), whereas two weak cross-correlations were somewhat expected from FADSAF but missing: 3.5 Å for $H5_A$···$H6'_B$ and 3.7 Å for $H5'_B$···$H6_A$, respectively (Figure 4).

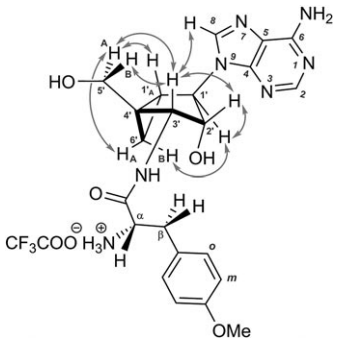


Figure 4. Main close through-space NOESY cross-correlations that support the stereochemistry of *N*-MC puromycin analogue **2** (nucleoside numbering).

However, according to the X-ray structure of **29** (CCDC-711879) the unexpected cross-peaks may point to shorter through-space distances (3.69 Å for H8···H1′ and 3.36 Å for H8···H2′) reflecting a slightly different C1′–N9 torsion angle ("glycosidic bond"), which indicates that in dissolved **2** this torsion angle (χ) is closer to −149.8°, as in solid **29**, than to −160.5°, as in the solid 3′-azido-2′,3′-dideoxy *N*-MC analogue (FASDAF). Neither the unexpected NOESY cross-correlations nor the missing ones have any important bearing on the relative configuration at C2′ and C3′.

The ensemble that constitutes the NMR spectroscopic evidence for the expected configuration of the target compound is based on the following observations.

A) The scalar vicinal coupling constant for H2′–H3′ is relatively large: $^3J=6.0$ Hz for **2**, 6.9 Hz for **2**·TFA, 6.5 Hz for azide **32**, and 6.6 Hz for azide **31**, as for all *ribo*-type configured compounds **8** to **18** before the Mattocks bromoacetylation (corresponding $^3J=5.4$–7.5 Hz), whereas the C3′-inverted *xylo*-configured bromo derivatives **24**, **28**, **29**, and **30** all showed zero coupling constants—these H2′ and H3′ resonances were all singlets.
B) Because of through-space distances well above 4 Å, we expect absent H5′···H2′ NOESY/ROESY cross-peaks (nucleoside numbering) for both *ribo*- and *xylo*-configured diastereoisomers. Likewise, because of the close through-space distances from H5′···H4′ and from *cis*- or *trans*-H2′···H3′, consistently lying between 2.12 and 2.64 Å, together with, in MC nucleosides, longer H5′···cylopropyl proton distances of 2.5–4.0 Å, for both *ribo*- and *xylo*-configured diastereoisomers we would expect prominent cross-peaks for close contacts in the former and at least a few weaker cross-peaks for longer distances in the latter, all of which is experimentally confirmed in the NOESY spectrum of **2**·TFA, as well as in the ROESY spectrum of a recently published synthetic xylofuranosyl puromycin analogue (see Supporting Information).[15] In the NOESY spectrum of **2**·TFA, however, we found three clear cross-correlations that would be expected in a *ribo*-configured diastereoisomer but not (or much less so) in a *xylo*-configured one: one

prominent cross-peak each for both H8···H3′β and $H5'_B$···H3′β (nucleoside numbering) and a weaker but still significant cross-peak for $H5_A$···H3′β—through-space distances that, according to FASDAF, correspond to 3.17, 2.96 and 3.84 Å, respectively. Indeed, unlike in the case of the NOESY spectrum of **2**·TFA, in the ROESY spectrum of the xylofuranosyl puromycin analogue we found no cross-peak at all for H8···H3′α, and cross-correlations for the two H5′··· H3′α distances were barely above noise (see the Supporting Information). On the other hand, prominent ROESY cross-peaks were observed for *cis*-H1′α···H3′α in the xylofuranosyl puromycin analogue (*trans* H1′α···H3′β distance from FASDAF: 4.0 Å), being almost as intense as the cross-peak for *cis*-H1′α···H4′α (expected distance 3.15 Å), as well as cross-peaks between the adenine H2 and aminoacyl protons HCα and HC*meta*, which were all absent in the NOESY spectrum of **2**·TFA. Close H2···HCα and H2···HC*meta* distances suggest that, unlike in **2**, the xylofuranosyl puromycin analogue favors a *syn* conformation in the glycosidic bond.

Figure 4 summarizes the most decisive cross-correlations observed in **2** that support nothing other than a *ribo*-type configuration. The complex ^{1}H NMR spectrum of dinucleotide **36** showed all characteristic fragments in the expected proportions (i.e., the cyclopropyl, methoxy, Cα- and aromatic protons of the *O*-methyltyrosyl side chain, cytidine′s anomeric proton, both adenine and cytosine heterocycles), whereas the ^{31}P NMR spectrum showed a single resonance, and high-resolution mass spectrometry gave the expected exact molecular mass.

Conclusions

We have accomplished the total syntheses of two potential protein synthesis inhibitors—the locked *North*-type methanocarba puromycin analogue **2** and its dinucleotide derivative **36**—in their enantiopure forms through an 18- and a 19-step pathway in 16 and 4.7% overall yields, respectively. The following key steps were utilized, the last five of which were elaborated during the synthesis along with a few non-evident protection/deprotection protocols: ring-opening Wittig reaction, Swern oxidation (stereodestructive), vinyl Grignard addition (stereoselective), ring-closing metathesis, chromo-oxidative rearrangement (stereodestructive), Luche reduction (stereoselective and regioselective), Simmons–Smith cyclopropanation (stereoselective), Mitsunobu coupling (stereoselective), Mattocks bromoacetylation (stereoselective and regioselective), two nucleophilic substitutions with acetate (regioselective) and azide (stereoselective), two Staudinger–Vilarrasa (chemoselective) amino acid couplings, and a nucleosidyl phosphoramidite coupling (chemoselective). Both analogues, together with several others,[13,31,34] are being tested in an in vitro assay for ribosome-catalyzed peptidyl transfer and the findings are being compared with enzymological results obtained with natural puromycin and natural A site substrates (i.e., 3′-aminoacyl transfer RNAs).

Experimental Section

General methods: All non-aqueous reactions were performed in oven-dried glassware under nitrogen. The synthetic intermediates were co-evaporated twice with toluene beforehand and dried in vacuo before use. All chemical reagents were obtained from commercial sources and were used as supplied. The reactions were monitored by thin-layer chromatography (TLC, Merck silica gel 60 F254 plates) and visualized by UV radiation (254 nm), by spraying with 5% ethanolic H_2SO_4 then variously soaking in ethanolic ninhydrin (20%) for the free amines, in ethanolic naphthoresorcinol (2%) for the ribose intermediates, or in phosphomolybdic acid in ethanol for the carbocyclic derivatives, and by subsequent warming with a heat gun. Column chromatography was performed with flash silica gel (10–63 μm). All the solvents used were purchased over molecular sieves and were then stored under nitrogen prior to use. Molecular sieves were dried by microwave activation before use. All NMR spectra were recorded on Bruker ALS (300 MHz), DRX (300 MHz), and DRX (500 MHz) spectrometers. ^{1}H NMR (300 and 500 MHz), ^{13}C NMR (75 and 125 MHz, recorded with complete proton decoupling), and ^{31}P NMR (121.5 MHz, recorded with complete proton decoupling) spectra were obtained with samples dissolved in $CDCl_3$, CD_3OD, or $[D_6]$DMSO, with the residual solvent signals as internal references: 7.26 ppm for $CHCl_3$, 3.31 ppm for CD_2HOD, 2.50 ppm for $(CD_3)(CD_2H)S(O)$ for ^{1}H NMR experiments, and 77.0 ppm for $CDCl_3$, 49.0 ppm for CD_3OD, 39.4 ppm for $(CD_3)_2S(O)$ for ^{13}C NMR experiments. ^{31}P NMR experiments were referenced to H_3PO_4 as an external standard (0.00 ppm). Chemical shifts (δ) are given in ppm to the nearest 0.01 (^{1}H, ^{31}P) or 0.1 ppm (^{13}C). The coupling constants (J) are given in Hertz (Hz). The signals are reported as follows: (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, ps = pseudo). Assignments of ^{1}H and ^{13}C NMR signals were achieved with the help of D/H exchange, COSY, HSQC, HMBC, and DEPT experiments. High-resolution mass spectrometry was conducted with a FINIGAN MAT 95 spectrometer with EI or ESI ionization techniques. Melting points (Mps) are uncorrected and were measured with a Büchi melting point apparatus. Supplementary data associated with this article (the experimental protocols for the synthesis of intermediates **8** through **14**, the ^{1}H NMR, DEPT, ^{13}C NMR, COSY, ^{1}H–^{13}C HSQC and (in part) ^{1}H–^{13}C HMBC spectra of all compounds, as well as a detailed distance analysis of **2** by NOESY and ROESY) can be consulted in the Supporting Information. Systematic non-nucleoside nomenclature is used below, including for heterocycles and carbocycles.

(1*S*,4*R*,5*S*)-3-(*tert*-Butyldiphenyl)silyloxymethyl-4,5-dioxy-*O*,*O*-isopropylidene-2-cyclopenten-1-ol (15): Sodium borohydride (220 mg, 5.82 mmol) was added portionwise to a solution of the cyclopentenone **14** (1.585 g, 3.75 mmol) and cerium(III) chloride heptahydrate (1.198 g, 3.15 mmol) in methanol (7 mL), with the temperature maintained between 0 °C and 5 °C. After 30 min, acetic acid was carefully added to adjust to pH 5. Water (7 mL) was added and the reaction mixture was extracted with ether. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solvents were removed under reduced pressure and the residue was purified by silica gel column chromatography (cyclohexane/EtOAc 9:1) to give the allylic alcohol **15** as a colorless oil (1.61 g, 99%). $C_{25}H_{32}O_4Si$ (424.60). R_f = 0.25 (cyclohexane/EtOAc 7:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (s, 9H; $SiC(CH_3)_3$), 1.33 (s, 3H; CH_3), 1.35 (s, 3H; CH_3), 2.68 (d, ^3J = 9.9 Hz, 1H; OH), 4.28 (d, ^2J = 15.2 Hz, 1H; C*H*HOSi), 4.38 (d, ^2J = 15.2 Hz, 1H; CH*H*OSi), 4.53–4.59 (m, 1H; H1), 4.75 (pst, ^3J = 4.8, 5.9 Hz, 1H; H5), 4.86 (d, ^3J = 5.9 Hz, 1H; H4), 5.84 (d, ^3J = 1.8 Hz, 1H; H2), 7.33–7.46 (m, 6H; *m*-H_{Ph}, *p*-H_{Ph}), 7.65–7.69 ppm (m, 4H; *o*-H_{Ph}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 ($SiC(CH_3)_3$), 26.7 (CH_3), 26.8 ($SiC(CH_3)_3$), 27.6 (CH_3), 60.8 (CH_2OSi), 73.3 (C1), 77.9 (C5), 82.8 (C4), 112.4 (CMe_2), 127.7 (4C; *m*-C_{SiPh}), 129.3 (C2), 129.7 (4C; *p*-C_{SiPh}), 133.3 (2C; *i*-C_{SiPh}), 135.5 (4C; *o*-C_{SiPh}), 145.2 ppm (C3); HRMS (ESI$^+$): m/z: calcd for $C_{25}H_{32}O_4SiNa$: 447.1968 $[M+Na]^+$; found: 447.1966.

(1*R*,2*R*,3*S*,4*S*,5*S*)-1-(*tert*-Butyldiphenyl)silyloxymethyl-2,3-dioxy-*O*,*O*-isopropylidenebicyclo[3.1.0]hexan-4-ol (16): Diethylzinc (3.61 mL, 1.0 M in hexanes) was added dropwise under nitrogen at −18 °C to a stirred solution of allylic alcohol **15** (1.394 g, 3.28 mmol) in dichloromethane (18 mL). The reaction mixture was stirred at this temperature for 15 min. A solution of CH_2I_2 (308 μL, 3.78 mmol) in dichloromethane (2.4 mL) was added to the mixture and stirring was continued for 15 min at −18 °C. These two diethylzinc (3.61 mL, 1.0 M in hexanes) and CH_2I_2 (308 μL, 3.78 mmol) addition steps were repeated once again and the solution was finally allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with a saturated NH_4Cl solution. The organic layer was extracted three times with CH_2Cl_2, dried over $MgSO_4$, and filtered. The solvents were removed in vacuo and the residue was purified by column chromatography on silica gel with elution with cyclohexane/EtOAc (6:1, 5:1, 4:1, 3:1) to afford the carbobicyclic derivative **16** as a colorless oil (1.206 g, 84 %). $C_{26}H_{34}O_4Si$ (438.63). R_f = 0.27 (cyclohexane/EtOAc 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.55 (dd, ^2J = 5.1 Hz, ^3J = 8.7 Hz, 1H; H6$_A$), 1.07 (s, 9H; SiC(CH$_3$)$_3$), 1.10 (dd, ^2J = 5.1 Hz, ^3J = 4.8 Hz, 1H; H6$_B$), 1.32 (s, 3H; CH$_3$), 1.55 (s, 3H; CH$_3$), 1.62 (quin. "ddd", ^3J = 4.8, 8.7 Hz, 1H; H5), 2.42 (br s, 1H; OH), 3.30 (d, ^2J = 10.8 Hz, 1H; C*H*HOSi), 4.09 (d, ^2J = 10.8 Hz, 1H; CH*H*OSi), 4.47 (pst, ^3J = 4.8, 6.6 Hz, 1H; H4), 4.55 (pst, ^3J = 6.6, 6.9 Hz, 1H; H3), 5.02 (d, ^3J = 6.9 Hz, 1H; H2), 7.35–7.46 (m, 6H; *m*-H$_{Ph}$, *p*-H$_{Ph}$), 7.62–7.67 ppm (m, 4H; *o*-H$_{Ph}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.3 (C6), 19.2 (SiC(CH$_3$)$_3$), 24.6, 26.1 (2C; CH$_3$), 26.8 (3C; SiC(*C*H$_3$)$_3$), 32.8 (C5), 35.5 (C1), 65.2 (CH$_2$OSi), 71.0 (C4), 79.6 (C3), 81.1 (C2), 112.7 (*C*Me$_2$), 127.6 (4C; *m*-C$_{SiPh}$), 129.7 (2C; *p*-C$_{SiPh}$), 133.5, 133.6 (2C; *i*-C$_{SiPh}$), 135.5 ppm (4C; *o*-C$_{SiPh}$); HRMS (ESI$^+$): *m/z*: calcd for $C_{26}H_{34}O_4SiNa$: 461.2124 [*M*+Na]$^+$; found: 461.2121.

(1′*R*,2′*R*,3′*S*,4′*R*,5′*S*)-9-[1′-(*tert*-Butyldiphenyl)silyloxymethyl-2′,3′-dioxy-*O*,*O*-isopropylidenebicyclo[3.1.0]hex-4′-yl]-6-chloropurine (17): Diisopropyl azodicarboxylate (1.09 mL, 5.27 mmol) was added dropwise at 0 °C to a stirred solution of triphenylphosphine (1.405 g, 5.27 mmol) in THF (13 mL) and the yellow reaction mixture was stirred at this temperature for 30 min. A solution of the carbobicyclic alcohol **16** (1.006 g, 2.29 mmol) in THF (13 mL), previously co-evaporated with toluene (3× 5 mL), was added and the reaction mixture was stirred at 0 °C for 10 min. The cooling bath was then removed and the yellow solution was stirred for 30 min at room temperature. 6-Chloropurine (822 mg, 5.27 mmol) was added and the reaction mixture was stirred overnight at room temperature. The solution was filtered and the volatiles were concentrated in vacuo. The residue was purified by column chromatography on silica gel with elution with cyclohexane/EtOAc (5:1, 4:1, 3:1, 1:1). The coupling product was still contaminated with a large amount of *N,N*′-diisopropyl hydrazine. To eliminate it, the compound was dissolved in a minimum volume of EtOAc and was then added dropwise to a large volume of petroleum ether. The solution was put in the freezer at −22 °C for 2 h and then filtered, and eventually the volatiles were removed under reduced pressure to yield **17** as a colorless oil (1.081 g, 82 %). $C_{31}H_{35}ClN_4O_3Si$ (575.17). R_f = 0.35 (cyclohexane/EtOAc 3:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (ddd, ^2J = 5.7 Hz, ^3J = 9.3 Hz, ^4J = 1.1 Hz, 1H; H6′$_A$), 1.08 (s, 9H; SiC(CH$_3$)$_3$), 1.16 (dd, ^2J = 5.7 Hz, ^3J = 4.2 Hz, 1H; H6′$_B$), 1.23 (s, 3H; CH$_3$), 1.54 (s, 3H; CH$_3$), 1.65 (ddd, ^3J = 4.2, 9.3 Hz, ^4J = 1.4 Hz, 1H; H5′), 3.63 (d, ^2J = 10.8 Hz, 1H; C*H*HOSi), 4.25 (d, ^2J = 10.8 Hz, 1H; CH*H*OSi), 4.60 (dd, ^3J = 7.2 Hz, ^4J = 1.4 Hz, 1H; H3′), 5.12 (s, 1H; H4′), 5.28 (dd, ^3J = 6.9 Hz, ^4J = 1.1 Hz, 1H; H2′), 7.29–7.44 (m, 6H; *m*-H$_{Ph}$, *p*-H$_{Ph}$), 7.58–7.63 (m, ^3J = 7.5 Hz, 4H; *o*-H$_{Ph}$), 8.43 (s, 1H; H8), 8.66 ppm (s, 1H; H2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.3 (C6′), 19.2 (SiC(CH$_3$)$_3$), 24.2, 25.9 (2C; CH$_3$), 26.9 (3C; SiC(*C*H$_3$)$_3$), 29.5 (C5′), 39.1 (C1′), 60.1 (C4′), 64.4 (CH$_2$OSi), 81.1 (C2′), 88.8 (C3′), 112.5 (*C*Me$_2$), 127.7, 127.7 (4C; *m*-C$_{SiPh}$), 129.8 (2C; *p*-C$_{SiPh}$), 131.8 (C5), 132.8, 132.9 (2C; *i*-C$_{SiPh}$), 135.5, 135.5 (4C; *o*-C$_{SiPh}$), 143.7 (C8), 151.0 (C4), 151.1 (C6), 152.0 ppm (C2); HRMS (ESI$^+$): *m/z*: calcd for $C_{31}H_{36}ClN_4O_3Si$: 575.2245 [*M*+H]$^+$; found: 575.2249.

(1′*R*,2′*R*,3′*S*,4′*R*,5′*S*)-9-(2′,3′-Dihydroxy-1′-hydroxymethylbicyclo-[3.1.0]hexan-4′-yl)hypoxanthine (18): Trifluoroacetic acid (330 μL) was added to a stirred solution of **17** (107 mg, 0.186 mmol) in $ClCH_2CH_2Cl$ (1 mL), and the reaction mixture was kept at 40 °C overnight. The solution was then co-evaporated twice with toluene and the residue was purified by column chromatography on silica gel with elution with EtOAc/MeOH/H_2O (8:1:0.5, 7:1:0.5, 6:1:0.5) to yield, after lyophilization, the totally deprotected product **18** as a white solid (45 mg, 86 %). $C_{12}H_{14}N_4O_4$ (278.26). R_f = 0.33 (EtOAc/MeOH/H_2O 6:1:0.5); ^{1}H NMR (CD_3OD, 300 MHz): δ = 0.76 (ddd, ^2J = 5.3 Hz, ^3J = 8.7 Hz, ^4J = 1.2 Hz, 1H; H6′$_A$), 1.53 (dd, ^2J = 5.3 Hz, ^3J = 4.1 Hz, 1H; H6′$_B$), 1.62 (ddd, ^3J = 4.1, 8.7 Hz, ^4J = 0.9 Hz, 1H; H5′), 3.31 (d, ^2J = 11.7 Hz, 1H; C*H*HOH), 3.90 (d, ^3J = 6.6 Hz, 1H; H3′), 4.24 (d, ^2J = 11.7 Hz, 1H; CH*H*OH), 4.76 (dd, ^3J = 6.6 Hz, ^4J = 1.2 Hz, 1H; H2′), 4.91 (s, 1H; H1′), 8.07 (s, 1H; H8), 8.51 ppm (s, 1H; H2); HRMS (ESI$^+$): *m/z*: calcd for $C_{12}H_{15}N_4O_4Na$: 301.0913 [*M*+Na]$^+$; found: 301.0910.

***N*^{6},*N*^{6},9-Tris-(*tert*-butoxycarbonyl)adenine (20)**: Boc_2O (2.00 g, 8.88 mmol) was added to a stirred suspension of adenine (**19**, 300 mg, 2.22 mmol) and DMAP (82 mg, 0.67 mmol) in THF (11 mL). After 20 min, the solution had become pale yellow. The reaction mixture was stirred overnight at room temperature. The volatiles were then removed under reduced pressure and the residue was purified by column chromatography on silica gel with elution with cyclohexane/EtOAc (9:1, 4:1, 7:3) to give the tris-protected compound **20** as a colorless oil (840 mg, 87 %). $C_{20}H_{29}N_5O_6$ (435.47). R_f = 0.48 (cyclohexane/EtOAc 7:3); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 18H; N^{6}Boc$_2$), 1.65 (s, 9H; N9Boc), 8.46 (s, 1H; H8), 8.94 ppm (s, 1H; H2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.5, 27.7 (N(C(O)OC(*C*H$_3$)$_3$)), 83.7, 87.3 (N(C(O)O*C*(CH$_3$)$_3$)), 129.4 (C5), 143.0 (C8), 145.4 (N(*C*(O)O*t*Bu), 151.0 (C4), 152.3 (C6), 149.8 (N(*C*(O)O*t*Bu)$_2$), 153.9 ppm (C2).

***N*^{6},*N*^{6}-Bis-(*tert*-butoxycarbonyl)adenine (21)**: A saturated solution of $NaHCO_3$ (35 mL) was added to a stirred solution of *tris*-Boc-adenine (**20**, 3.080 g, 7.07 mmol) in MeOH (70 mL) and the reaction mixture became cloudy. The solution was then warmed to 50 °C for 1 h 15 min. When the conversion was quantitative according to TLC, MeOH was removed under reduced pressure. Water (70 mL) was added and the aqueous layer was extracted three times with $CHCl_3$. The organic layer was dried over anhydrous magnesium sulfate and filtered. The solvents were removed under reduced pressure and the residue was purified by column chromatography on silica gel with elution with cyclohexane/EtOAc (3:7, 1:4, 1:9, 0:1) to give the bis-protected compound **21** (2.21 g, 93 %) as a white solid. $C_{15}H_{21}N_5O_4$ (335.36). R_f = 0.36 (EtOAc); m.p. 149–150 °C;[24] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 18H; N^{6}Boc$_2$), 8.63 (s, 1H; H8), 8.81 (s, 1H; H2), 13.68 ppm (br s, 1H; NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.2 (N(C(O)OC(*C*H$_3$)$_3$)$_2$), 83.1 (N(C(O)O*C*(CH$_3$)$_3$)$_2$), 145.6 (C8), 149.9 (N(*C*(O)O*t*Bu)$_2$), 151.4 ppm (C2).

(1′*R*,2′*R*,3′*S*,4′*R*,5′*S*)-9-[1′-(*tert*-Butyldiphenyl)silyloxymethyl-2′,3′-dioxy-*O*,*O*-isopropylidenebicyclo[3.1.0]hex-4′-yl]-*N*^{6},*N*^{6}-bis-(*tert*-butoxycarbonyl)adenine (22): Diisopropyl azodicarboxylate (1.81 mL, 8.77 mmol) was added dropwise at 0 °C to a stirred solution of triphenylphosphine (2.336 g, 8.77 mmol) in THF (20 mL) and the yellow reaction mixture was stirred at this temperature for 30 min. After that, a solution of the carbobicyclic alcohol **16** (1.673 g, 3.81 mmol) in THF (21 mL), previously co-evaporated with toluene (3× 5 mL), was added and the reaction mixture was stirred at 0 °C for 10 min. The cooling bath was removed and the yellow solution was stirred for 30 min at room temperature. Compound **21** (3.163 g, 8.77 mmol) was added and the solution had become clear after 2 min. The reaction mixture was stirred overnight at room temperature. The volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica gel with elution with cyclohexane/EtOAc (6:1, 4:1, 3:1). The coupling product was still contaminated with a large amount of the diisopropyl hydrazine. To eliminate it, the compound was dissolved in a minimum volume of EtOAc, and was then added dropwise to a large volume of petroleum ether. The solution was put in the freezer at −22 °C for 2 h and then filtered, and eventually the volatiles were concentrated in vacuo to yield **22** as a colorless oil (2.736 g, 95 %). $C_{41}H_{53}N_5O_7Si$ (755.97). R_f = 0.36 (cyclohexane/EtOAc 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (dd, ^2J = 6.0 Hz, ^3J = 8.7 Hz, 1H; H6′$_A$), 1.09 (s, 9H; SiC(CH$_3$)$_3$), 1.16–1.20 (m, 1H; H6′$_B$), 1.24 (s, 3H; CH$_3$), 1.48 (s, 18H; NBoc$_2$), 1.54 (s, 3H; CH$_3$), 1.65–1.72 (m, 1H; H5′), 3.57 (d, ^2J = 10.8 Hz, 1H; C*H*HOSi), 4.27 (d, ^2J = 10.8 Hz, 1H; CH*H*OSi), 4.58 (d, ^3J = 6.9 Hz, 1H; H3′), 5.16 (s, 1H; H4′), 5.29 (d, ^3J = 6.9 Hz, 1H; H2′), 7.32–7.44 (m, 6H; *m*-H$_{Ph}$, *p*-H$_{Ph}$), 7.62 (d, ^3J = 7.5 Hz,

4H; *o*-H_{Ph}), 8.46 (s, 1H; H8), 8.81 ppm (s, 1H; H2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.5 (C6′), 19.1 (Si*C*$(CH_3)_3$), 24.2, 25.9 (2C; CH_3), 26.9 (3C; SiC$(CH_3)_3$), 27.8 (6C; N(C(O)OC$(CH_3)_3)_2$), 29.7 (C5′), 38.9 (C1′), 59.3 (C4′), 64.7 (CH_2OSi), 80.9 (C2′), 83.7 (2C; N(C(O)O*C*$(CH_3)_3)_2$), 88.8 (C3′), 112.4 (*C*Me_2), 127.8 (4C; *m*-C_{SiPh}), 128.8 (C5), 129.8 (2C; *p*-C_{SiPh}), 132.7, 132.9 (2C; *i*-C_{SiPh}), 135.4, 135.5 (4C; *o*-C_{SiPh}), 143.1 (C8), 150.3 (C4), 150.5 (2C; N(C(O)O*t*$Bu)_2$), 152.1 (C2), 152.5 ppm (C6); HRMS (ESI$^+$): *m/z*: calcd for $C_{41}H_{54}N_5O_7Si$: 756.3793 $[M+H]^+$; found: 756.3792.

(1′*R*,2′*R*,3′*S*,4′*R*,5′*S*)-9-(2′,3′-Dihydroxy-1′-hydroxymethylbicyclo-[3.1.0]hexan-4′-yl)adenine (23): Compound **22** (1.342 g, 1.78 mmol) was dissolved in a solution of MeOH/TFA (3.7:2.2 mL) and the reaction mixture was warmed at 65 °C for 1 d. The solution was then co-evaporated twice with $ClCH_2CH_2Cl$ and the residue was purified by column chromatography on silica gel with elution with EtOAc/MeOH/H_2O (8:1:0.5, 7:1:0.5, 6:1:0.5) to yield, after lyophilization, the totally deprotected product **23** as a white solid (480 mg, 97%). $C_{12}H_{15}N_5O_3$ (277.28). R_f=0.32 (EtOAc/MeOH/H_2O 5:1:0.5); m.p. 129–130 °C; ^{1}H NMR ([D_6]DMSO, 300 MHz): δ=0.65 (dd, ^2J=4.5 Hz, ^3J=8.7 Hz, 1H; H6′$_A$), 1.30 (pst "dd", ^2J=4.5 Hz, ^3J=3.9 Hz, 1H; H6′$_B$), 1.49 (dd, ^3J=3.9, 8.7 Hz, 1H; H5′), 3.13 (d, ^2J=11.7 Hz, 1H; C*H*HOH), 3.69 (d, ^3J=6.3 Hz, 1H; H3′), 4.03 (d, ^2J=11.7 Hz, 1H; CH*H*OH), 4.53 (d, ^3J=6.3 Hz, 1H; H2′), 4.70 (s, 1H; H1′), 8.13 (s, 1H; H2), 8.38 ppm (s, 1H; H8); ^{13}C NMR ([D_6]DMSO, 75 MHz): δ=12.2 (C6′), 23.6 (C5′), 36.9 (C1′), 62.0 (C4′), 63.1 (CH_2OH), 71.0 (C2′), 76.9 (C3′), 119.2 (C5), 140.2 (C8), 149.4 (C4), 153.2 (C2), 156.3 ppm (C6); HRMS (ESI$^+$): *m/z*: calcd for $C_{12}H_{16}N_5O_3$: 278.1253 $[M+H]^+$; found: 278.1251.

(1′*R*,2′*S*,3′*S*,4′*R*,5′*S*)-9-(3′-Acetoxy-1′-bromomethyl-2′-bromobicyclo-[3.1.0]hexan-4′-yl)adenine (24): H_2O (100 μL) was added to a stirred suspension of **23** (100 mg, 0.36 mmol) in acetonitrile (8 mL), followed by α-acetoxyisobutyryl bromide (375 μL, 2.52 mmol), and the reaction mixture was stirred at room temperature for 45 min. More H_2O (200 μL) was added and the solution was stirred for another 15 min. The reaction mixture was quenched with a saturated $NaHCO_3$ solution. The organic layer was extracted three times with EtOAc, dried over $MgSO_4$, and filtered. The volatiles were removed in vacuo and the residue was purified by column chromatography on silica gel with elution with EtOAc/MeOH/H_2O (10:1:0.5, 8:1:0.5, 6:1:0.5) to afford compound **24** as a white solid (141 mg, 88%). $C_{14}H_{15}Br_2N_5O_2$ (445.11). R_f=0.51 (EtOAc/MeOH/H_2O 10:1:0.5); ^{1}H NMR ([D_6]DMSO, 300 MHz): δ=1.33–1.36 (m, 1H; H6′$_A$), 1.45 (dd, ^2J=5.9 Hz, ^3J=9.0 Hz, 1H; H6′$_B$), 2.13 (s, 3H; OC(O)CH_3), 2.67 (dd, ^3J=3.9, 9.0 Hz, 1H; H5′), 3.65 (d, ^2J=10.5 Hz, 1H; C*H*HBr), 4.36 (d, ^2J=10.5 Hz, 1H; CH*H*Br), 4.40 (s, 1H; H2′), 4.91 (s, 1H; H4′), 5.38 (s, 1H; H3′), 7.29 (s, 2H; NH_2), 8.14 (s, 1H; H2), 8.34 ppm (s, 1H; H8); ^{13}C NMR ([D_6]DMSO, 75 MHz): δ=17.2 (C6′), 20.6 (OC(O)*C*H_3), 31.6 (C5′), 36.3 (C1′), 40.0 (CH_2Br), 55.7 (C2′), 60.2 (C4′), 84.3 (C3′), 118.8 (C5), 139.2 (C8), 148.9 (C4), 151.9 (C2), 155.4 (C6), 168.7 ppm (O*C*(O)CH_3); HRMS (ESI$^+$): *m/z*: calcd for $C_{14}H_{16}Br_2N_5O_2$: 443.9671 $[M+H]^+$; found: 443.9668.

(1′*R*,2′*R*,3′*S*,4′*R*,5′*S*)-9-(1′-Hydroxymethyl-2′,3′-dioxy-*O*,*O*-isopropylidene-bicyclo[3.1.0]hex-4′-yl)-*N*^{6},*N*^{6}-bis-(*tert*-butoxycarbonyl)adenine (25): TBAF in THF (1M, 1.58 mL, 1.58 mmol) was added dropwise to a stirred solution of silyl ether **24** (1.046 mg, 1.37 mmol) in THF (15 mL). Initially slightly yellow, the reaction mixture darkened to deep orange and was stirred at ambient temperature for 30 min. The volatiles were removed in vacuo and the residue was purified by column chromatography on silica gel with elution with cyclohexane/EtOAc (3:1, 2:1, 1:1, 0:1) to afford alcohol **25** as a white foam (709 mg, 99%). $C_{25}H_{35}N_5O_7$ (517.57). R_f=0.63 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.95 (dd, ^2J=6.3 Hz, ^3J=8.7 Hz, 1H; H6′$_A$), 1.13–1.18 (m, 1H; H6′$_B$), 1.18 (s, 3H; CH_3), 1.41 (s, 18H; NBoc$_2$), 1.48 (s, 3H; CH_3), 1.71 (dd, ^3J=3.9, 8.7 Hz, 1H; H5′), 3.31 (d, ^2J=11.6 Hz, 1H; C*H*HOH), 4.19 (d, ^2J=11.6 Hz, 1H; CH*H*OH), 4.29 (brs, 1H; OH), 4.56 (d, ^3J=7.4 Hz, 1H; H3′), 4.93 (s, 1H; H4′), 5.47 (d, ^3J=7.4 Hz, 1H; H2′), 8.24 (s, 1H; H8), 8.78 ppm (s, 1H; H2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.9 (C6′), 23.9, 25.7 (2C; CH_3), 27.6 (6C; N(C(O)OC$(CH_3)_3)_2$), 29.9 (C5′), 39.5 (C1′), 62.2 (C4′), 65.0 (CH_2OH), 80.6 (C2′), 83.8 (2C; N(C(O)O*C*$(CH_3)_3)_2$), 89.5 (C3′), 112.3 (*C*Me_2), 129.4 (C5), 144.5 (C8), 150.3 (2C; N(*C*(O)O*t*$Bu)_2$), 150.7 (C4), 151.5 (C2), 152.1 ppm (C6); HRMS (ESI$^+$): *m/z*: calcd for $C_{25}H_{36}N_5O_7$: 518.2615 $[M+H]^+$; found: 518.2611.

(1′*R*,2′*R*,3′*S*,4′*R*,5′*S*)-9-(1′-Benzyloxymethyl-2′,3′-dioxy-*O*,*O*-isopropylidene-bicyclo[3.1.0]hex-4′-yl)-*N*^{6},*N*^{6}-bis-(*tert*-butoxycarbonyl)adenine (26): NaH (14 mg, 0.57 mmol) was cautiously added to a stirred solution of alcohol **25** (259 mg, 0.514 mmol) in THF (2 mL). The reaction mixture was stirred for 20 min at room temperature, and next *n*Bu_4I (20 mg, 0.051 mmol) and BnBr (69 μL, 0.57 mmol) were added. After 2 h, the reaction mixture was quenched with a saturated NH_4Cl solution. The organic layer was extracted three times with EtOAc, dried over $MgSO_4$, and filtered. The volatiles were removed in vacuo and the residue was purified by column chromatography on silica gel with elution with cyclohexane/EtOAc (3:1, 2:1, 1:1, 1:2) to afford the benzylated alcohol **26** as a colorless oil (219 mg, 70%). $C_{32}H_{41}N_5O_7$ (607.70). R_f=0.50 (cyclohexane/EtOAc 1:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.06 (ddd, ^2J=5.9 Hz, ^3J=9.3 Hz, ^4J=1.2 Hz, 1H; H6′$_A$), 1.30 (dd, ^2J=5.9 Hz, ^3J=5.1 Hz, 1H; H6′$_B$), 1.42 (s, 9H; *t*Bu), 1.49 (s, 9H; *t*Bu), 1.55 (s, 3H; CH_3), 1.59 (s, 3H; CH_3), 1.77 (ddd, ^3J=5.1, 9.3 Hz, ^4J=1.2 Hz, 1H; H5′), 4.14 (d, ^2J=11.7 Hz, 1H; C*H*HOBn), 4.46 (d, ^2J=11.7 Hz, 1H; CH*H*OBn), 4.61 (d, ^3J=7.4 Hz, ^4J=1.2 Hz, 1H; H3′), 5.09 (s, 1H; H4′), 5.28 (s, 2H; CH_2Ph), 5.32 (dd, ^3J=7.2 Hz, ^4J=1.2 Hz, 1H; H2′), 7.16–7.29 (m, 3H; *p*-H_{Ph}, *m*-H_{Ph}), 7.35–7.42 (m, 2H; *o*-H_{Ph}), 8.20 (s, 1H; H8), 8.76 ppm (s, 1H; H2); $C_{32}H_{42}N_5O_7$: 608.3084 $[M+H]^+$; found: 608.3080.

(1′*R*,2′*R*,3′*S*,4′*R*,5′*S*)-9-(1′-Benzyloxymethyl-2′,3′-dihydroxybicyclo-[3.1.0]hex-4′-yl)adenine (27): Compound **26** (185 mg, 0.304 mmol) was dissolved in MeOH/TFA (1.2:1.0 mL *v/v*) and the reaction mixture was warmed to 55 °C for 10 h. The solution was co-evaporated twice with $ClCH_2CH_2Cl$ and the resulting residue was purified by column chromatography on silica gel with elution with EtOAc/MeOH/H_2O (1:1:0, 8:1:1, 7:1:0.5, 6:1:0.5) to yield **27** as a opaque, colorless resin (107 mg, 96%). $C_{19}H_{21}N_5O_3$ (367.40). R_f=0.42 (EtOAc/MeOH/H_2O 8:1:1); 0.82 (ddd, ^2J=5.4 Hz, ^3J=8.4 Hz, ^4J=0.9 Hz, 1H; H6′$_A$), 1.55 (pst "dd", ^2J=5.4 Hz, ^3J=3.6 Hz, 1H; H6′$_B$), 1.66 (dd, ^3J=3.6, 8.4 Hz, 1H; H5′), 3.35 (d, ^2J=11.7 Hz, 1H; C*H*HOBn), 4.03 (d, ^3J=6.9 Hz, 1H; H3′), 4.22 (d, ^2J=11.7 Hz, 1H; CH*H*OBn), 4.87 (d, ^3J=6.9 Hz, 1H; H2′), 4.91 (s, 1H; H4′), 5.03 (s, 2H; C*H*$_2$Ph), 7.00–7.33 (m, 3H; *p*-H_{Ph}, *m*-H_{Ph}), 7.34–7.42 (m, 2H; *o*-H_{Ph}), 7.86 (s, 1H; H8), 8.32 ppm (s, 1H; H2); $C_{19}H_{22}N_5O_3$: 368.1723 $[M+H]^+$; found: 368.1721.

(1′*R*,2′*S*,3′*S*,4′*R*,5′*S*)-9-(3′-Acetoxy-1′-bromomethyl-2′-bromobicyclo-[3.1.0]hex-4′-yl)-*N*^{6}-benzyladenine (28): H_2O (40 μL) was added to a stirred suspension of **27** (54 mg, 0.147 mmol) in acetonitrile (1.5 mL), followed by α-acetoxyisobutyryl bromide (153 μL, 1.029 mmol), and the reaction mixture was stirred at room temperature for 45 min. More H_2O (130 μL) was added and the solution was stirred for another 15 min. The reaction was quenched with a saturated $NaHCO_3$ solution. The organic layer was extracted with three times with EtOAc, dried over anhydrous magnesium sulfate, and filtered. The volatiles were removed in vacuo and the residue was purified by column chromatography on silica gel with elution with cyclohexane/EtOAc (10:1:0.5, 8:1:0.5, 6:1:0.5) to afford the dibrominated compound **29** as a whitish oil (49 mg, 62%). $C_{21}H_{21}Br_2N_5O_2$ (535.23). R_f=0.50 (EtOAc/cyclohexane 9:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ=1.35 (dd, ^2J=6.5 Hz, ^3J=8.5 Hz, 1H; H6′$_A$), 1.39–1.44 (m, 1H; H6′$_B$), 2.15 (s, 3H; OC(O)CH_3), 2.21 (dd, ^3J=3.5, 8.5 Hz, 1H; H5′), 3.26 (d, ^2J=10.5 Hz, 1H; C*H*HBr), 4.34 (d, ^2J=10.5 Hz, 1H; CH*H*Br), 4.37 (s, 1H; H2′), 4.88 (brs, 2H; C*H*$_2$Ph), 5.08 (s, 1H; H4′), 5.54 (s, 1H; H3′), 6.60 (brs, 1H; NHBn), 7.27 (d, ^3J=7.0 Hz, 1H; *p*-H_{Ph}), 7.33 (t "dd", ^3J=7.0, 7.5 Hz, 2H; *m*-H_{Ph}), 7.38 (d, ^3J=7.5 Hz, 2H; *o*-H_{Ph}), 8.13 (s, 1H; H8), 8.40 ppm (s, 1H; H2); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=17.9 (C6′), 20.8 (OC(O)*C*H_3), 33.1 (C5′), 37.4 (C1′), 37.7 (CH_2Br), ~44 (brs N*C*H_2Ph, from HSQC and HMBC only), 54.9 (C2′), 60.6 (C4′), 86.0 (C3′), 119.5 (C5), 127.4 (2C; *p*-C_{Ph}), 127.6 (2C; *o*-C_{Ph}), 128.6 (2C; *m*-C_{Ph}), 138.4 (C8), 138.4 (*i*-C_{Ph}), 153.3 (2C; C6, C4), 154.7 (C2), 168.6 ppm (O*C*(O)CH_3); MS (ESI$^+$) *m/z* 538/536/534 $[M+H]^+$, 456/454 $[M-Br]^+$, 414/412 $[M-Br-CH_2CO]^+$, 396/394 $[M-AcOH]^+$, 374 $[M-2Br]^+$, 226.1 $[(PhCH_2)adenine+2H]^+$; HRMS (ESI$^+$): *m/z*: calcd for $C_{21}H_{22}Br_2N_5O_2$: 534.0140 $[M+H]^+$; found: 534.0139.

(1′*R*,2′*S*,3′*S*,4′*R*,5′*S*)-9-(3′-Acetoxy-1′-acetoxymethyl-2′-bromobicyclo-[3.1.0]hexan-4′-yl)adenine (29): Compound **24** (100 mg, 0.224 mmol) was

dissolved in acetonitrile at 75 °C. After the mixture had cooled to room temperature, CsOAc (272 mg, 1.35 mmol), molecular sieves (3 Å, 250 mg), and 18-crown-6 (120 mg, 0.450 mmol) were added, and the reaction mixture was again warmed to 75 °C. After 1 h, the precipitation of a white solid had occurred. The reaction mixture was still stirred for 2 h at the same temperature, and was then filtered and rinsed with ethyl acetate. The volatiles were removed under reduced pressure and the residue was dissolved in EtOAc and water. The organic layer was extracted three times with EtOAc, dried over $MgSO_4$, and filtered, and the volatiles were concentrated in vacuo. The residue was purified by column chromatography on silica gel with elution with EtOAc/MeOH/H_2O (10:1:0.5, 8:1:0.5, 6:1:0.5) to provide **29** as a white solid (81 mg, 85 %). $C_{16}H_{18}BrN_5O_4$ (424.25). R_f = 0.46 (EtOAc/MeOH/H_2O 12:1:0.5). ^{1}H NMR (CD_3OD with a few drops of $CDCl_3$, 300 MHz): δ = 0.98–1.03 (m, 2H; H6′$_A$, H6′$_B$), 1.71 (s, 3H; 1′-OC(O)CH_3), 1.75 (s, 3H; 3′-OC(O)CH_3), 1.91 (dd, ^3J = 4.5, 8.1 Hz, 1H; H5′), 3.88 (d, ^2J = 11.7 Hz, 1H; C*H*HOAc), 3.96 (s, 1H; H2′), 4.35 (d, ^2J = 11.7 Hz, 1H; CH*H*OAc), 4.57 (s, 1H; H4′), 5.08 (s, 1H; H3′), 7.81 (s, 1H; H2), 7.99 ppm (s, 1H; H8); ^{13}C NMR (CD_3OD with a few drops of $CDCl_3$, 75 MHz): δ = 16.3 (C6′), 20.9, 21.0 (2C; OC(O)*C*H$_3$), 27.9 (C5′), 34.8 (C1′), 55.0 (C2′), 60.8 (C4′), 67.8 (*C*H$_2$OAc), 86.9 (C3′), 119.7 (C5), 140.2 (C8), 149.7 (C4), 153.4 (C2), 156.6 (C6), 169.9 (3′-O*C*(O)CH$_3$), 172.1 ppm (1′-CH$_2$O*C*(O)CH$_3$); HRMS (ESI$^+$): *m/z*: calcd for $C_{16}H_{19}BrN_5O_4$: 424.0620 [*M*+H]$^+$; found: 424.0618.

(1′*R*,2′*S*,3′*S*,4′*R*,5′*S*)-9-(2′-Bromo-3′-hydroxy-1′-hydroxymethylbicyclo-[3.1.0]hex-4′-yl)adenine (30): Aqueous HCl (37 %, 1 mL) was added dropwise to a stirred solution of **29** (102 mg, 0.240 mmol) in MeOH (3 mL) and the reaction mixture was warmed to 50 °C for 8 h. The reaction mixture was co-evaporated three times with toluene and the residue was purified by column chromatography on silica gel with elution with EtOAc/MeOH/H_2O (12:1:0.5, 10:1:0.5, 8:1:0.5, 5:1:0.5) to yield **30** as a white solid (75 mg, 92 %). $C_{12}H_{14}N_5O_2$ (340.18). R_f = 0.53 (EtOAc/MeOH/H_2O 5:1:0.5); ^{1}H NMR (CD_3OD, 300 MHz): δ = 1.23–1.41 (m, 1H; H6′$_A$), 1.50–1.64 (m, 1H; H6′$_B$), 2.17–2.36 (m, 1H; H5′), 3.65 (d, ^2J = 11.4 Hz, 1H; C*H*HOH), 4.35 (d, ^2J = 11.4 Hz, 1H; CH*H*OH), 4.35 (s, 1H; H2′), 4.64 (s, 1H; H3′), 4.88 (s, 1H; H4′), 8.47 (s, 1H; H2), 8.62 ppm (s, 1H; H8); ^{13}C NMR (CD_3OD, 75 MHz): δ = 16.1 (C6′), 27.0 (C5′), 38.1 (C1′), 60.0 (C2′), 64.4 (C4′), 65.7 (*C*H$_2$OH), 87.7 (C3′), 120.0 (C5), 144.4 (C8), 145.1 (C2), 149.9 (C4), 151.6 ppm (C6); HRMS (ESI$^+$): *m/z*: calcd for $C_{12}H_{15}N_5O_2$: 340.0409 [*M*+H]$^+$; found: 340.0408.

(1′*R*,2′*R*,3′*S*,4′*R*,5′*S*)-9-(2′-Azido-3′-hydroxy-1′-hydroxymethylbicyclo-[3.1.0]hex-4′-yl)adenine (31): NaN_3 (29 mg, 0.440 mmol) in H_2O (200 mL) was added to a stirred solution of **30** (30 mg, 0.088 mmol) in DMF (1 mL). The reaction mixture was warmed between 75–80 °C for 3 h. The solution was then co-evaporated with toluene to remove DMF and the residue was purified by column chromatography on silica gel with elution with EtOAc/MeOH/H_2O (12:1:0.5, 10:1:0.5, 8:1:0.5, 5:1:0.5) to provide the azido derivative **31** (20 mg, 74 %) as a white resin. $C_{12}H_{14}N_8O_2$ (302.29). R_f = 0.58 (EtOAc/MeOH/H_2O 5:1:0.5); ^{1}H NMR (CD_3OD, 300 MHz): δ = 0.78–0.88 (m, 1H; H6′$_A$), 1.61 (pstd, ^3J = 3.9, 8.4 Hz, ^4J = 0.9 Hz, 1H; H5′), 1.66 (dd, ^2J = 4.5, ^3J = 8.4 Hz, 1H; H6′$_B$), 3.31 (d, ^2J = 11.7 Hz, 1H; C*H*HOH), 4.01 (d, ^3J = 6.6 Hz, 1H; H3′), 4.11 (d, ^2J = 11.7 Hz, 1H; CH*H*OH), 4.18 (dd, ^3J = 6.6 Hz, ^4J = 1.4 Hz, 1H; H2′), 4.78 (s, 1H; H4′), 8.11 (s, 1H; H2), 8.40 ppm (s, 1H; H8); ^{13}C NMR (CD_3OD, 75 MHz): δ = 13.1 (C6′), 24.0 (C5′), 36.3 (C1′), 63.0 (C2′), 64.0 (C4′), 64.6 (*C*H$_2$OH), 79.3 (C3′), 120.4 (C5), 141.0 (C8), 150.2 (C4), 153.7 (C2), 157.5 ppm (C6); HRMS (ESI$^+$): *m/z*: calcd for $C_{12}H_{15}N_8O_2$: 303.1318 [*M*+H]$^+$; found: 303.1317.

***N,N*-Di-*n*-butylformamide dimethylacetal**: Di-*n*-butyl formamide (50 mL) and fresh dimethyl sulfate (26 mL) were mixed under nitrogen and heated to reflux (100 °C) for 4 h, and were then allowed to cool to ambient temperature and stirred overnight. The mixture was worked up with ice-cold absolute MeOH (150 mL) into which sodium (8 g) had been dissolved previously. After reaching room temperature, the volatiles were concentrated in vacuo and diethyl ether was added with vigorous stirring. The precipitate was filtered off and rinsed with more Et_2O. The filtrate was evaporated under reduced pressure and the oily residue was distilled in vacuo (bp 110–120 °C under oil pump vacuum: early fractions contain *N,N*-di-*n*-butylformamide dimethyl acetal, late fractions contain di-*n*-butyl formamide) to give a clear colorless or pale yellow oil that can be safely stored under nitrogen in the cold. $C_{11}H_{25}NO_2$ (203.1885). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 7.2 Hz, 6H; N(CH$_2$CH$_2$CH$_2$C*H*$_3$)$_2$), 1.30 (q, ^3J = 7.2 Hz, 4H; N(CH$_2$CH$_2$C*H*$_2$CH$_3$)$_2$), 1.40 (q, ^3J = 7.2 Hz, 4H; N(CH$_2$C*H*$_2$CH$_2$CH$_3$)$_2$), 2.59 (t, ^3J = 7.2 Hz, 4H; N(C*H*$_2$CH$_2$CH$_2$CH$_3$)$_2$), 3.30 (s, 6H; (OCH$_3$)$_2$), 4.51 ppm (s, 1H; NCH(OCH$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (2C; N(CH$_2$CH$_2$CH$_2$*C*H$_3$)$_2$), 20.4 (2C; N(CH$_2$CH$_2$*C*H$_2$CH$_3$)$_2$), 30.9 (2C; N(CH$_2$*C*H$_2$CH$_2$CH$_3$)$_2$), 47.0 (2C; N(*C*H$_2$CH$_2$CH$_2$CH$_3$)$_2$), 53.6 (2C; (OCH$_3$)$_2$), 112.6 ppm (N*C*H(OCH$_3$)$_2$).

(1′*S*,2′*R*,3′*S*,4′*R*,5′*S*)-9-(2′-Azido-3′-hydroxy-5′-hydroxymethylbicyclo-[3.1.0]hex-4′-yl)-*N*^{6}-[di-(*n*-butyl)aminomethinyl]adenine (32): *N,N*-Di-*n*-butylformamide dimethylacetal (31 mg, 0.152 mmol) was added dropwise at ambient temperature to a stirred solution of the azide **31** (54 mg, 0.189 mmol) in MeOH (1 mL). The reaction mixture was stirred for 1 h and heated with a heat gun for a few seconds every 15 min. The volatiles were concentrated in vacuo and the residue was purified by column chromatography on silica gel with elution with EtOAc/toluene/MeOH (2:1:0, 4:1:0, 6:1:0, 8:1:0, 8:1:0.5) to afford **32** as an opaque oil (30 mg, 90 %). $C_{21}H_{31}N_9O_2$ (441.53). R_f = 0.60 (EtOAc/Tol/MeOH 8:1:1); ^{1}H NMR (CD_3OD, 300 MHz): δ = 0.95–1.01 (m, 1H; H6′$_A$), 0.975/0.983 (2×t, ^3J = 7.2 Hz, 2×3H; N(CH$_2$CH$_2$CH$_2$C*H*$_3$)$_2$), 1.33–1.48 (m, 5H; N(CH$_2$CH$_2$C*H*$_2$CH$_3$)$_2$, H5′), 1.63–1.75 (m, 4H; N(CH$_2$C*H*$_2$CH$_2$CH$_3$)$_2$), 1.77 (dd, ^2J = 4.2 Hz, ^3J = 9.0 Hz, 1H; H6′$_B$), 3.41 (d, ^2J = 12.0 Hz, 1H; C*H*HOH), 3.48 (t, ^3J = 7.2 Hz, 2H; N(C*H*$_2$CH$_2$CH$_2$CH$_3$)$_2$), 3.69 (t, ^3J = 7.7 Hz, 2H; N(C*H*$_2$CH$_2$CH$_2$CH$_3$)$_2$), 4.13 (d, ^3J = 6.5 Hz, 1H; H3′), 4.21 (d, ^3J = 12.0 Hz, 1H; CH*H*OH), 4.28 (d, ^3J = 6.5 Hz, 1H; H2′), 4.94 (s, 1H; H4′), 8.43 (s, 1H; H2), 8.61 (s, 1H; H8), 8.96 ppm (s, 1H; N=C*H*NBu$_2$); ^{13}C NMR (CD_3OD, 75 MHz): δ = 13.1 (C6′), 14.1, 14.3 (2C; N(CH$_2$CH$_2$CH$_2$*C*H$_3$)$_2$), 20.8, 21.2 (2C; N(CH$_2$CH$_2$*C*H$_2$CH$_3$)$_2$), 23.9 (C5′), 30.4, 32.1 (2C; N(CH$_2$*C*H$_2$CH$_2$CH$_3$)$_2$), 36.3 (C1′), 46.5, 53.1 (2C; N(*C*H$_2$CH$_2$CH$_2$CH$_3$)$_2$), 63.0 (C2′), 63.9 (C4′), 64.5 (*C*H$_2$OH), 79.2 (C3′), 126.7 (C5), 142.4 (C8), 152.1 (C4), 153.3 (C2), 160.2 (N=*C*HNBu$_2$), 161.5 ppm (C6); IR (CH_2Cl_2): $\tilde{\nu}$ = 2117 cm^{-1} (N_3 st); HRMS (ESI$^+$): *m/z*: calcd for $C_{21}H_{32}N_9O_2$: 442.267 [*M*+H]$^+$; found: 442.2674.

(1′*S*,2′*R*,3′*R*,4′*R*,5′*S*)-9-{2′-[*N*-(Fluoren-9-yl)methoxycarbonyl-*O*-methyl-L-tyrosylamino]-3′-hydroxy-5′-hydroxymethylbicyclo[3.1.0]hex-4′-yl}-*N*^{6}-[di-(*n*-butyl)aminomethinyl]adenine (33): A mixture of *N*-Fmoc-*O*-Me-L-Tyr (36 mg, 0.088 mmol) and HOBT (14 mg, 0.088 mmol) was co-evaporated three times with anhydrous THF (2 mL). The residue was dissolved in THF (1 mL) and the solution was cooled to 0 °C under nitrogen for 10 min. Diisopropyl carbodiimide (13 μL, 0.814 mmol) was added and the reaction mixture was stirred for 15 min at the same temperature. Meanwhile, Me_3P (1 M in THF, 146 μL, 0.146 mmol) was added to a solution of azide **32** (30 mg, 0.068 mmol) in THF (1 mL), and the mixture was stirred for 5 min at room temperature. The amino acid solution was allowed to warm to room temperature over 5 min and was then added to the iminophosphorane solution. The reaction mixture was stirred at room temperature overnight. The volatiles were evaporated under reduced pressure and co-evaporated from $CHCl_3$ (5 mL), dissolved in EtOAc (30 mL), and extracted with saturated $NaHCO_3$ (15 mL). The organic layer was extracted twice with EtOAc and washed with H_2O (2×10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with elution with EtOAc/toluene/MeOH (2:1:0, 4:1:0, 6:1:0, 8:1:0, 8:1:0.5, 8:1:0.75, 8:1:1) to give **33** as a colorless oil (44 mg, 81 %). $C_{46}H_{54}N_8O_6$ (814.97). R_f = 0.38 (EtOAc/Tol/MeOH 8:1:0.75); ^{1}H NMR (CD_3OD, 300 MHz): δ = 0.66 (pst "dd", ^2J = 5.7 Hz, ^3J = 9.6 Hz, 1H; H6′$_A$), 0.955/0.960 (2×t, ^3J = 7.2 Hz, 2×3H; N(CH$_2$CH$_2$CH$_2$C*H*$_3$)$_2$), 1.32–1.46 (m, 5H; N(CH$_2$CH$_2$C*H*$_2$CH$_3$)$_2$, H6′$_B$), 1.59–1.73 (m, 5H; N(CH$_2$C*H*$_2$CH$_2$CH$_3$)$_2$, H5′), 2.85 (dd, ^2J = 13.5 Hz, ^3J = 7.8 Hz, 1H; *p*-MeOPhC*H*H), 3.03 (dd, ^2J = 13.5 Hz, ^3J = 6.8 Hz, 1H; *p*-MeOPhCH*H*), 3.15 (d, ^2J = 11.7 Hz, 1H; C*H*HOH), 3.43 (t, ^3J = 7.1 Hz, 2H; N(C*H*$_2$CH$_2$CH$_2$CH$_3$)$_2$), 3.61–3.71 (m, 2H; N(C*H*$_2$CH$_2$CH$_2$CH$_3$)$_2$), 3.69 (s, 3H; OCH$_3$), 3.89–3.98 (m, 1H; H3′), 3.94 (d, ^2J = 11.7 Hz, 1H; CH*H*OH), 4.06 (pst, ^3J = 6.6, 6.9 Hz, 1H; aliphatic fluorene), 4.20 (pst "dd", ^3J = 7.5 Hz, 2H; C*H*$_2$-fluorene), 4.42 (pst, ^3J = 7.2, 7.8 Hz, 1H; Hα), 4.84- 4.93 (m, 1H; H2′), 4.90 (s, 1H; H4′), 6.79 (d, ^3J = 8.4 Hz, 2H; *m*-H$_{PhOMe}$), 7.16 (d, ^3J = 8.4 Hz, 2H; *o*-H$_{PhOMe}$), 7.21 (pst, ^3J = 6.6, 7.5 Hz, 2H; *m*^{2}-H$_{fluorene}$), 7.28 (pst, ^3J = 7.2, 7.5 Hz, 2H; *p*^{3}-H$_{fluorene}$), 7.50 (2×d,

^3J=6.6, 6.9 Hz, 2H; o^1-$H_{fluorene}$), 7.68 (2×d, ^3J=7.2, 7.5 Hz, 2H; m^4-$H_{fluorene}$), 8.41 (s, 1H; H2), 8.71 (s, 1H; H8), 8.93 ppm (s, 1H; N=CHNBu$_2$); ^{13}C NMR (CD$_3$OD, 75 MHz): δ=12.9 (C6′), 14.5, 14.7 (2C; N(CH$_2$CH$_2$CH$_2$*C*H$_3$)$_2$), 21.2, 21.6 (2C; N(CH$_2$CH$_2$*C*H$_2$CH$_3$)$_2$), 25.1 (C5′), 30.8, 32.4 (2C; N(CH$_2$*C*H$_2$CH$_2$CH$_3$)$_2$), 37.1 (C1′), 38.9 (*p*-MeOPhCH$_2$), 46.8 (N(*C*H$_2$CH$_2$CH$_2$CH$_3$)$_2$), 48.7 (aliphatic fluorene), 53.5 (2C; N(*C*H$_2$CH$_2$CH$_2$CH$_3$)$_2$, C2′), 56.1 (OMe), 58.5 (Cα), 64.2 (C4′), 64.6 (CH$_2$OH), 68.4 (CH$_{2\ fluorene}$), 77.2 (C3′), 115.3 (2C; *m*-C_{PhOMe}), 121.3 (2C; m^4-$C_{fluorene}$), 126.6 (2C; o^1-$C_{fluorene}$), 127.1 (C5), 128.5 (2C; m^2-$C_{fluorene}$), 129.1 (2C; p^3-$C_{fluorene}$), 130.7 (*i*-C_{PhOMe}), 131.8 (2C; *o*-C_{PhOMe}), 142.8 (C8), 142.9 (2C; o^5-$C_{fluorene}$), 145.5 (2C; *i*-$C_{fluorene}$), 152.3 (C4), 153.6 (C2), 158.6 (C6), 160.4 (*p*-C_{PhOMe}), 160.6 (N=*C*HNBu$_2$), 161.9 (R*C*(O)OCH$_{2\ fluorene}$), 175.1 ppm (2′-NH*C*(O)R); IR (CH$_2$Cl$_2$): $\tilde{\nu}$=2103 cm^{-1} (N$_3$ st); HRMS (ESI$^+$): *m/z*: calcd for $C_{46}H_{55}N_8O_6$: 815.4245 [*M*+H]$^+$; found: 815.4248.

(1′*S*,2′*R*,3′*R*,4′*R*,5′*S*)-9-[2′-(*O*-Methyl)-L-tyrosylamino-3′-hydroxy-5′-hydroxymethylbicyclo[3.1.0]hex-4′-yl]adenine (2): Compound **33** (42 mg, 0.051 mmol) was dissolved in 33% CH$_3$NH$_2$/EtOH (5 mL). The reaction mixture was stirred at ambient temperature in a closed vessel for 4 h. The volatiles were concentrated in vacuo and co-evaporated from CHCl$_3$ (2×5 mL). The oily residue was purified by column chromatography on silica gel with elution with EtOAc/MeOH/H$_2$O (8:1:0.5, 6:1:0.5, 4:1:0.5) to yield, after evaporation, the target compound **2** as a fluffy solid (21 mg, 91%), which after lyophilization from H$_2$O/TFA (pH 2.2) gave the more water-soluble **2**·TFA salt. $C_{22}H_{27}N_7O_4$ (453.49). R_f=0.28 (EtOAc/MeOH/H$_2$O 5:1:0.75); ^{1}H NMR (**2**, CD$_3$OD, 500 MHz): δ=0.73 (pst "dd", ^2J=4.5 Hz, ^3J=8.0 Hz, 1H; H6′$_A$), 1.48 (pst "dd", ^2J=4.5 Hz, ^3J=3.5 Hz, 1H; H6′$_B$), 1.70 (dd, ^3J=3.5, 8.0 Hz, 1H; H5′), 2.91 (dd, ^2J=13.0 Hz, ^3J=6.8 Hz, 1H; *p*-MeOPhC*H*H), 3.03 (dd, ^2J=13.0 Hz, ^3J=7.0 Hz, 1H; *p*-MeOPhCH*H*), 3.16 (d, ^2J=12.0 Hz, 1H; C*H*HOH), 3.78 (s, 3H; OCH$_3$), 3.83–3.90 (m, 1H; Hα), 3.88 (d, ^2J=12.0 Hz, 1H; CH*H*OH), 3.98 (d, ^3J=6.0 Hz, 1H; H3′), 4.80–4.93 (br, >2H; H2′, H4′), 6.90 (d, ^3J=8.0 Hz, 2H; *m*-H_{PhOMe}), 7.20 (d, ^3J=8.0 Hz, 2H; *o*-H_{PhOMe}), 8.21 (s, 1H; H2), 8.60 ppm (s, 1H; H8); ^{1}H NMR (**2**·TFA, D$_2$O, 300 MHz): δ=0.70 (ddd, ^2J=5.7 Hz, ^3J=8.7 Hz, ^4J=1.2 Hz, 1H; H6$_A$), 1.12 (dd, ^2J=5.7 Hz, ^3J=4.2 Hz, 1H; H6′$_B$), 1.68 (ddd, ^3J=4.2, 8.7 Hz, ^4J=1.2 Hz, 1H; H5′), 2.99 (dd, ^2J=13.7 Hz, ^3J=9.6 Hz, 1H; *p*-MeOPhCH*H*), 3.02 (d, ^2J=12.3 Hz, 1H; CH*H*OH), 3.16 (dd, ^2J=13.7 Hz, ^3J=6.0 Hz, 1H; *p*-MeOPhC*H*H), 3.42 (d, ^2J=12.3 Hz, 1H; C*H*HOH), 3.75 (s, 3H; OCH$_3$), 4.06 (d, ^3J=6.9 Hz, 1H; H3′), 4.16 (dd, ^3J=6.0, 9.6 Hz, 1H; Hα), 4.62 (d, ^3J=6.9 Hz, 1H; H2′), 4.87 (s, 1H; H4′), 6.93 (d, ^3J=8.7 Hz, 2H; *m*-H_{PhOMe}), 7.18 (d, ^3J=8.7 Hz, 2H; *o*-H_{PhOMe}), 8.27 (s, 1H; H2), 8.43 ppm (s, 1H; H8); ^{13}C NMR (**2**, CD$_3$OD, 125 MHz): δ=12.6 (C6′), 24.7 (C5′), 36.6 (*p*-MeOPhCH$_2$), 40.2 (C1′), 53.2 (C2′), 55.8 (OMe), 56.9 (Cα), 64.1 (CH$_2$OH), 64.1 (C4′), 76.9 (C3′), 115.3 (2C; *m*-C_{PhOMe}), 120.3 (C5), 129.4 (*i*-C_{PhOMe}), 131.5 (2C; *o*-C_{PhOMe}), 141.0 (C8), 150.1 (C4), 153.7 (C2), 157.4 (C6), 160.4 (*p*-C_{PhOMe}), 174.3 ppm (2′-NHC(O)R′); HRMS (ESI$^+$): *m/z*: calcd for $C_{22}H_{28}N_7O_4$: 454.2203 [*M*+H]$^+$; found: 454.2199.

(1′*S*,2′*R*,3′*S*,4′*R*,5′*S*)-9-{5′-[*N*-Acetyl-5′-*O*-dimethoxytrityl-2′-*O*-(*tert*-butyldimethyl)silylcytid-3′-yl]-(2-cyanoethylphosphoryl)oxymethyl-2′-azido-3′-hydroxy-bicyclo[3.1.0]hex-4′-yl}-N^6-[di-(*n*-butyl)aminomethinyl]adenine (34): Compound **32** (49 mg, 0.111 mmol) and 5-ethylthiotetrazole (22 mg, 0.166 mmol) were co-evaporated three times with anhydrous toluene (5 mL) and dissolved in anhydrous CH$_3$CN (750 μL). After the addition of commercial N^4-acetyl-5′-*O*-dimethoxytrityl-2′-*O*-*tert*-butyldimethylsilyl-cytid-3′-yl-(2-cyanoethyl)-*N*,*N*-diisopropylphosphoramidite (122 mg, 0.122 mmol) in anhydrous CH$_3$CN (750 μL), the solution was stirred at room temperature for 1 h, followed by the addition of I$_2$/THF/pyridine/H$_2$O solution (0.02 M, 6.65 mL, 0.133 mmol I$_2$). After 10 min, the reaction mixture was poured into EtOAc (20 mL), and extracted with NaHSO$_3$ (0.2 M, 2×8 mL) and brine (10 mL). The organic layer was dried over anhydrous MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with elution with EtOAc/MeOH/H$_2$O (14:1:0.5, 12:1:0.5, 10:1:0.5) to provide recovered starting material **32** (17 mg, 35%), as well as the dinucleotide derivative **34** (32 mg, 35%), as a colorless oil. $C_{62}H_{80}N_{13}O_{12}PSi$ (1258.44). R_f=0.53 (EtOAc/MeOH/H$_2$O 10:1:0.5); ^{1}H NMR (CD$_3$OD, 300 MHz): δ=0.13–0.26 (m, 12H), 0.80–1.02 (m, 32H), 1.18–1.46 (m, 10H), 1.55–1.75 (m, 8H), 1.77–1.86 (m, 2H), 2.01 (s, 3H), 2.08–2.19 (m, 7H), 2.72 (t, *J*=5.4 Hz, 2H), 2.87 (t, *J*=5.4 Hz, 2H), 2.99 (t, *J*=4.8 Hz, 1H), 3.20 (q, *J*=7.2 Hz, 2H), 3.35 (s, 1H), 3.37–3.46 (m, 4H), 3.60–3.71 (m, 4H), 3.71–3.81 (m, 12H), 4.14–4.39 (m, 8H), 4.39–4.57 (m, 2H), 4.59–4.71 (m, 2H), 4.94–5.08 (m, 2H), 5.90 (s, 2H), 6.74–6.94 (m, 10H), 7.07 (dd, *J*=5.1, 7.2 Hz, 2H), 7.20–7.36 (m, 16H), 7.36–7.46 (m, 4H), 8.17 (s, 1H), 8.23 (s, 1H), 8.38–8.50 (m, 4H), 9.02 (s, 1H), 9.06 ppm (s, 1H); ^{13}C NMR (CD$_3$OD, 75 MHz): δ=−4.7, −4.2, 9.3, 13.9, 14.1, 14.3, 14.5, 19.0, 20.3, 20.4, 20.8, 20.9, 21.2, 24.6, 24.9, 172.9, 25.0, 26.4, 26.5, 29.3, 30.4, 32.0, 34.2, 34.3, 34.3, 34.4, 46.4, 47.9, 53.1, 53.2, 55.8, 61.5, 62.4, 62.4, 64.0, 64.1, 64.2, 64.3, 64.5, 64.6, 64.6, 72.6, 76.1, 76.1, 76.4, 79.1, 82.3, 82.4, 88.7, 88.7, 92.1, 98.2, 114.3, 114.4, 118.5, 128.3, 128.3, 129.1, 129.1, 129.5, 131.5, 131.5, 136.4, 136.4, 142.0, 142.1, 145.6, 145.6, 145.7, 152.2, 152.3, 153.3, 157.7, 160.3, 160.4, 161.3, 161.4, 164.3, 172.8 ppm; ^{31}P NMR (CD$_3$OD, 121.5 MHz): δ=−0.66, 0.01 ppm (2×s, diast.); IR (CH$_2$Cl$_2$): $\tilde{\nu}$=2105 cm^{-1} (N$_3$ st); HRMS (ESI$^+$): *m/z*: calcd for $C_{62}H_{81}N_{13}O_{12}PSi$: 1258.5635 [*M*+H]$^+$; found: 1258.5638.

(1′*S*,2′*R*,3′*R*,4′*R*,5′*S*)-9-{5′-[*N*-Acetyl-5′-*O*-dimethoxytrityl-2′-*O*-(*tert*-butyldimethyl)silylcytid-3′-yl]-(2-cyanoethyl)phosphoryloxy-2′-[*N*-(fluoren-9-ylmethoxycarbonyl)-*O*-methyl-L-tyrosyl]amino-3′-hydroxymethylbicyclo[3.1.0]hex-4′-yl}-N^6-[di-(*n*-butyl)aminomethinyl]-adenine (35): A mixture of *N*-Fmoc-*O*-Me-L-Tyr (14 mg, 0.033 mmol) and HOBT (5 mg, 0.033 mmol) was co-evaporated three times with anhydrous THF (2 mL). The residue was dissolved in THF (1 mL) and the solution was cooled to 0°C under nitrogen for 10 min. Diisopropyl carbodiimide (4.8 μL, 0.031 mmol) was added and the reaction mixture was stirred for 15 min at the same temperature. Meanwhile, Me$_3$P (1 M in THF, 53 μL, 0.053 mmol) was added to a solution of azide **34** (27 mg, 0.215 mmol) in THF (1 mL), and the mixture was stirred for 5 min at room temperature. The amino acid solution was allowed to warm to room temperature over 5 min and then added to the iminophosphorane solution. The reaction mixture was stirred at room temperature overnight. The volatiles were evaporated under reduced pressure and co-evaporated from CHCl$_3$ (5 mL), dissolved in EtOAc (30 mL), and extracted with saturated NaHCO$_3$ (15 mL). The organic layer was extracted twice with EtOAc and washed with H$_2$O (2×10 mL), dried (MgSO$_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with elution with EtOAc/toluene/MeOH, (10:1:1, 8:1:1, 6:1:1) and EtOAc/MeOH/H$_2$O (10:1:0.5) to give **35** as an off-white solid (27 mg, 77%). $C_{87}H_{103}N_{12}O_{16}PSi$ (1631.88). R_f=0.59 (EtOAc/MeOH/H$_2$O 10:1:0.5); ^{1}H NMR (CD$_3$OD, 500 MHz): δ=0.05–0.24 (m, 12H), 0.79–1.00 (m, 32H), 1.19–1.46 (m, 10H), 1.47–1.74 (m, 10H), 1.91 (s, 3H), 1.99–2.05 (m, 3H), 2.09–2.21 (m, 6H), 2.66–2.75 (m, 3H), 2.76–2.93 (m, 3H), 2.99–3.12 (m, 3H), 3.19 (s, 12H), 3.35 (s, 6H), 3.37–3.48 (m, 4H), 3.49–3.59 (m, 2H), 4.03–4.17 (m, 5H), 4.17–4.29 (m, 3H), 4.29–4.40 (m, 3H), 4.45–4.70 (m, 4H), 4.94–4.99 (m, 2H), 5.33 (t, *J*=5.0 Hz, 1H), 5.55–5.62 (m, 1H), 5.85–5.93 (m, 1H), 5.94–5.99 (m, 1H), 6.71–6.93 (m, 12H), 7.00–7.47 (m, 32H), 7.47–7.60 (m, 5H), 7.63–7.79 (m, 7H), 8.16–8.28 (m, 2H), 8.30–8.48 (m, 7H), 8.53–8.57 (m, 1H), 9.04 (s, 1H), 9.10 ppm (s, 1H); ^{13}C NMR (CD$_3$OD, 125 MHz): δ=−4.4, −4.5, 14.0, 14.2, 14.3, 14.5, 19.0, 19.1, 20.3, 20.8, 21.2, 22.7, 23.2, 23.5, 23.6, 24.6, 26.4, 26.6, 26.9, 27.4, 28.1, 29.4, 30.4, 30.4, 30.6, 30.8, 30.9, 32.0, 33.1, 35.2, 36.6, 38.4, 42.7, 46.3, 46.4, 47.7, 49.9, 53.1, 53.2, 55.8, 55.8, 55.9, 55.9, 57.8, 58.2, 61.6, 63.9, 64.5, 64.7, 68.1, 71.9, 76.5, 88.2, 88.4, 88.6, 88.7, 91.2, 92.0, 97.9, 98.1, 98.2, 98.2, 108.6, 114.3, 114.4, 114.8, 114.9, 118.6, 120.9, 126.2, 126.2, 128.1, 128.7, 129.0, 129.1, 129.1, 129.4, 129.6, 130.5, 130.9, 131.3, 131.4, 131.5, 131.5, 136.4, 136.4, 136.5, 136.7, 136.8, 138.5, 142.5, 145.2, 145.7, 145.8, 146.0, 146.1, 152.1, 153.4, 157.4, 157.8, 158.2, 159.9, 179.3, 160.3, 160.4, 161.5, 164.3, 172.9, 172.9 ppm; ^{31}P NMR (CD$_3$OD, 121.5 MHz): δ=−0.68, 0.01 ppm (2×s, diast.); HRMS (ESI+): *m/z*: calcd for $C_{87}H_{103}N_{12}O_{16}PSi$: 1631.7200 [*M*+H]$^+$; found: 1631.7201.

(1′*S*,2′*R*,3′*R*,4′*R*,5′*S*)-9-{5′-[(Cytid-3′-yl)-phosphoryloxy]-2′-(*O*-methyl-L-tyrosyl)amino-3′-hydroxymethylbicyclo[3.1.0]hex-4′-yl}adenine (36): Dinucleotide **35** (27 mg, 0.016 mmol) was dissolved in 33% CH$_3$NH$_2$/EtOH (3 mL). The reaction mixture was stirred at room temperature for 7 h in a closed vessel. The solution was concentrated under reduced pressure and co-evaporated from CHCl$_3$ (2×3 mL). Ammonium fluoride (2.5 mg, 0.066 mmol) was added to a stirred solution of the residue in MeOH (1.5 mL). The reaction mixture was warmed to 50–55°C for 2 h, and monitored by TLC. The volatiles were removed in vacuo and the result-

ing residue was dissolved in AcOH/H_2O 4:1 (1.5 mL). The solution was stirred at room temperature for 1 h and then lyophilized. The residue was purified by preparative thin layer chromatography (TLC) plates first pre-eluted with *i*PrOH/NH_3/H_2O (7:2:1) and then loaded and eluted to yield, after extraction with and lyophilization from the same solvent mixture, target compound **36** as a fluffy solid (10 mg, 81 %). $C_{31}H_{39}N_{11}O_{15}P$ (758.68). $R_f = 0.23$ (*i*PrOH/NH_3/H_2O, 7:2:1); ^{1}H NMR (D_2O, 300 MHz): $\delta = 0.89$–0.97 (m, 1H; H6′$_A$), 1.18–1.22 (m, 1H; H6′$_B$), 1.87–1.92 (m, 1H,), 3.18–3.25 (m, 2H), 3.85 (s, 4H; OCH_3), 3.92–3.99 (m, 2H), 4.07–4.12 (m, 1H; Hα), 4.24–4.31 (m, 4H), 4.51–4.61 (m, 2H), 4.95 (s, 1H; H4′), 5.85 (d, $J = 3.9$ Hz, 1H; H1′), 5.87 (d, $^3J = 7.5$ Hz, 1H; H5), 7.04 (d, $^3J = 8.7$ Hz, 2H; *m*-H_{PhOMe}), 7.26 (d, $^3J = 8.7$ Hz, 2H; *o*-H_{PhOMe}), 7.78 (d, $^3J = 7.5$ Hz, 1H; H6), 8.25 (s, 1H; H2), 8.50 ppm (s, 1H; H8); ^{31}P NMR (CD_3OD, 121.5 MHz): $\delta = 0.00$ ppm; HRMS (ESI$^+$): *m/z*: calcd for $C_{31}H_{40}N_{10}O_{15}P$: 759.2616 $[M+H]^+$; found: 759.2616.

CCDC-711879, CCDC-711880 and CCDC-711881 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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