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Synthesis of an Apionucleoside Family and Discovery of a Prodrug with Anti-HIV Activity

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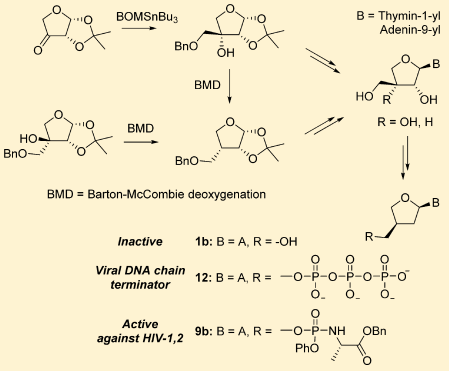
Supporting Information

ABSTRACT: We report the synthesis of a family of D- and L-furano-D-apionucleosides, their 3′-deoxy, as well as their 2′,3′-dideoxy analogues with thymine and adenine nucleobases. Single carbon homologation of 1,2-*O*-isopropylidene-D-glycero-tetrafuranos-3-ulose (**15**) and optimized glycosylation conditions involving microwave irradiation were key to the successful synthesis of the target compounds. While all target nucleosides failed to show significant antiviral activity, we demonstrated that the triphosphate of 2′,3′-deoxy-D-apio-D-furanoadenosine (**1**), in contrast to that of its D-apio-L-furanose epimer **2**, was readily incorporated into a DNA template by HIV reverse transcriptase to act as a DNA chain terminator. This led us to convert adenine derivative **1** into two phosphoramidate prodrugs. ProTide **9b** was found active against HIV-1 and HIV-2 (EC_{50} = 0.5−1.5 μM), indicating that the lack of activity of the parent nucleoside, and possibly also other members of the D-apio-D-furanose nucleoside family must be sought in the inefficient cellular conversion to the monophosphate.



INTRODUCTION

Although the pharmacological scope of nucleoside analogues is still expanding, they remain most renowned for their utility as antiviral drugs.[1] 2′,3′-Dideoxy-β-D-apio-D-furanonucleosides (D-ddANs, **1**, Figure 1) were synthesized in the early 1990s as potential antiviral agents, but were found inactive.[2−4] However, some of us recently discovered that the 3′-*O*-phosphonomethylated adenine (A) and thymine (T) analogues **7** exhibit promising anti-HIV properties.[5] Since these phosphonates act as bioisosteres of the phosphorylated species **8**, we decided to reinvestigate the biological activity of these ddANs. We envisioned a synthetic approach that would also give access to the known apionucleosides **3**,[6,7] their 3′-deoxy counterparts **2**,[8−11] and inadvertently also the D-apio-L-furanose epimers **4**−**6**. Furthermore, we planned to expand the potential of the 2′,3′-dideoxyapio nucleosides **1** and **4** as antiviral agents by synthesizing their phosphoramidate prodrugs **9**, **10** and **11**. These would lead to the intracellular release of the parent nucleotides like **8**,[12,13] thereby bypassing the often problematic first phosphorylation step in the conversion to the active triphosphate species.[14]

RESULTS AND DISCUSSION

Chemistry. Compounds **16** and **27** were considered valuable intermediates to access the envisaged family of D-furanoapionucleosides (Scheme 1). They were prepared from 1,2-isopropylidene-α-L-threose (**14**), which was obtained in six steps from L-ascorbic acid.[15,16] Interestingly, screening of different oxidation methods[15,17,18] to convert **14** to ketone **15** indicated that TEMPO-BAIB ([Bis(acetoxy)-iodo]benzene) oxidation, best known for oxidation of primary hydroxyl groups, was the most effective. Conversion of **15** to **16** is feasible by reacting the former with diazomethane to give a spiro-oxirane,[19] which can then be opened with benzylalkoxide to give **16**.[20] To avoid the use of diazomethane, we explored several variations of the polarity reversal concept to realize the desired carbon homologation. Reaction with benzyloxymethyl chloride in the presence of samarium iodide did not yield the desired product, while the corresponding Grignard reaction gave **16** in disappointing yields.[21] Nucleophilic attack of the ketone with lithiated benzyloxymethyltributyltin afforded **16** in acceptable yield,[22] considering the propensity of compound **15**

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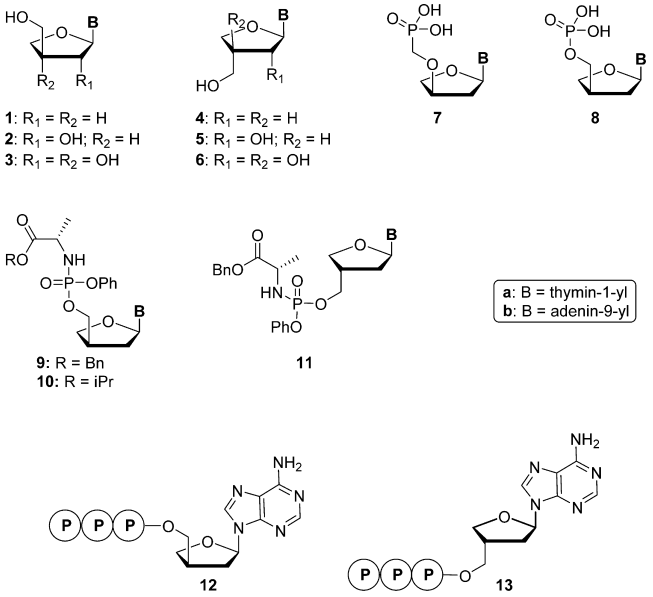


Figure 1.

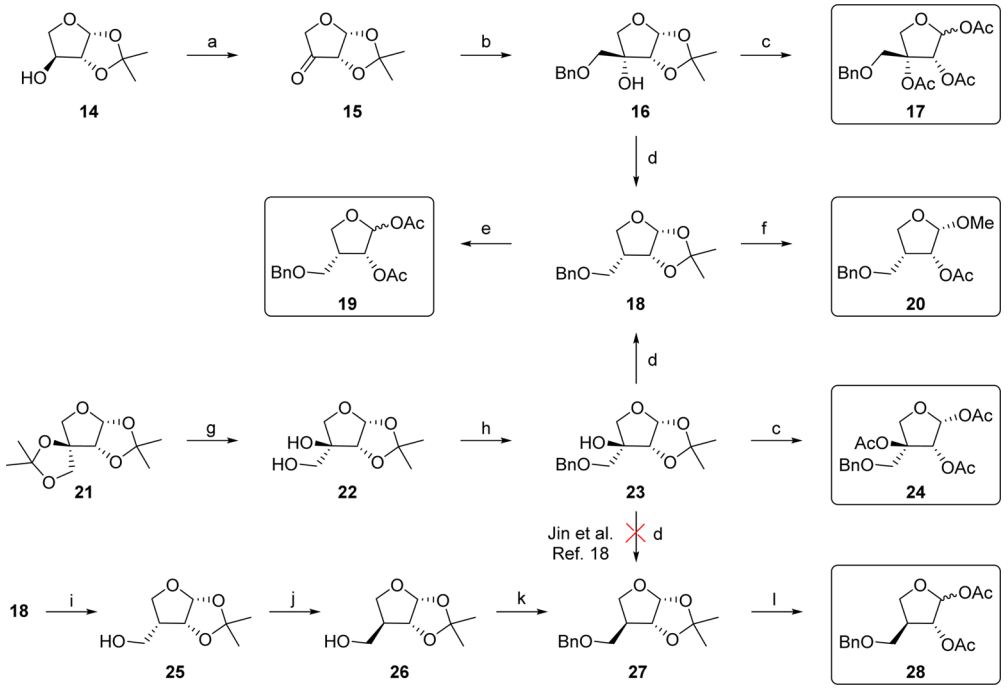
to undergo self-condensation to the aldol dimer.[23] The NMR spectra of **16** were in accordance with reported data,[20] and C-3 stereochemistry was further confirmed by a two-dimensional (2D) ^{1}H−^{1}H NOESY experiment. One-pot acid hydrolysis and acetylation of **16** gave the triacetylated apiose **17** in a 2:1 α/β anomeric ratio.

Jin et al. reported the conversion of **23** to **27** using Barton−McCombie deoxygenation (BMD).[18] Surprisingly, BMD of **16** afforded **18** instead of **27**. This led us to reinvestigate the protocol of Jin et al. on compound **23**, prepared from the commercially available **21**.[24] In our hands BMD on **23** also gave **18**. The stereochemistry was confirmed by 2D ^{1}H−^{1}H NOESY experiment and by independent synthesis of compound **27**. The formation of **18** is explained by radical quenching from the least hindered face, i.e., opposite to the isopropylidene comprising face.[25] Furthermore, Jin et al. probably synthesized the enantiomer of **18**, since they started from D-galactose, which should lead to 1,2-*O*-isopropylidene-α-D-threofuranose (i.e., the enantiomer of **14**[15]). Compound **23** was hydrolyzed and acetylated to give the L-furano analogue of triacetylated apiose **24**.

Compound **18** was hydrolyzed and acetylated to give **19** in a 4:1 (β:α) anomeric ratio. The anomeric configuration was inferred from the anomeric proton coupling constants, i.e., 0 Hz for the β-isomer and 4.4 Hz for the α-isomer. However, this conversion lacked reproducibility, especially on a larger scale. To overcome this problem, the methyl anomer **20** was synthesized in two steps from **18**. Since the coupling constant for anomeric hydrogen is close to 0 Hz, **20** is assumed to be the β-isomer.

Long and co-workers found that 1,2-*O*-isopropylidine-L-furano-D-apiose **22** equilibrates into a mixture of the D- and L-furanose form in acidic acetone, which inspired us to use similar conditions for the epimerization of **25**.[19] We hypothesized that the absence of the 3-hydroxyl group would eliminate the repulsive dipole interaction with oxygen at position 2, while the

Scheme 1. Synthesis of the D- and L-Furano-D-apiose Coupling Partners 17 and 24 and Their 3-Deoxy Analogues 19, 20, and 28[a]



[a]Reagents and conditions: (a) TEMPO, BAIB, CH_2Cl_2, rt, 3−4 h, 90%; (b) $BOMSnBu_3$, *n*-BuLi, THF, −78 °C, 2 h, 68%; (c) (i) 80% aq. AcOH, 80 °C, 8 h; (ii) Ac_2O, DMAP, pyridine, 55 °C, 16 h, 75%; (d) (i) NaH, CS_2, MeI, THF, 0 °C → rt, 1 h; (ii) Et_3B, Bu_3SnH, toluene, rt, 3−4 h, 68%; (e) (i) 80% aq. AcOH, 80 °C, 8 h; (ii) Ac_2O, DMAP, rt, pyridine, 4 h, 57%; (f) (i) *p*-TsOH (*para*-toluenesulfonic acid), MeOH, rt, overnight; (ii) Ac_2O, DMAP, pyridine, 0 °C → rt, 4 h, 77%; (g) CH_3COOH-H_2O (2:1), rt, 3 days, 83%; (h) Bu_2SnO, toluene, 140 °C, 2 h, TBAB, BnBr, 100 °C, 18 h, 94%; (i) H_2, Pd/C, MeOH, rt, 5 h, 90%; (j) acetone, conc. H_2SO_4, rt, 1.5 h, Na_2CO_3, 45 min, 73% (after 3 cycles); (k) DMF, NaH, 0 °C, 10 min, BnBr, 0 °C → rt, 18 h, 95%; (l) (i) 80% aq. AcOH, 80 °C, 18 h; (ii) pyridine, Ac_2O, rt, 18 h, 79%.

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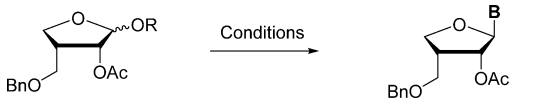
Table 1. Vorbrüggen Coupling Conditions



19: R = Ac
20: R = Me

29: B = Thymin-1-yl
30: B = N^6-Bz-Adenin-9-yl

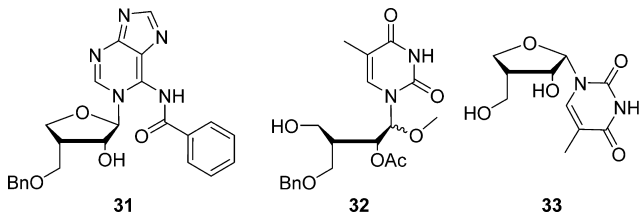
entry	sugar	silylated nucleobase	reagent	conditions	product (yield)[a]
1	**19**	T	TMSOTf	1,2-$(CH_2)_2Cl_2$, rt, 4 h	**29** (quant)
2	**19**	N^6-BzA	TMSOTf	1,2-$(CH_2)_2Cl_2$, 40 °C, 48 h	**30** (32%)[b]
3	**20**	T	TMSOTf	1,2-$(CH_2)_2Cl_2$ or CH_3CN, rt, 4 h	**32**[c]
4	**20**	T	$SnCl_4$	CH_3CN, rt, 4 h	**32**[c]
5	**20**	N^6-BzA	$SnCl_4$	CH_3CN, rt, 4 h	–
6	**20**	T	TMSOTf[d]	CH_3CN, 150 °C, 5 min microwave	**29** + β-anomer (78%)[e]
7	**20**	N^6-BzA	TMSOTf[d]	CH_3CN, 150 °C, 5 min microwave	**30** (60%)

[a]Isolated yields. Dash indicates an unresolvable reaction mixture. [b]The 2′-acetyl analogue of **31** was isolated in equal amount. [c]Two diastereomers observed by TLC and HRMS analysis. [d]0.2 equiv of TMSOTf. [e]Inseparable 2:1 mixture of **29** and its β-isomer.

steric interaction of the hydroxymethyl group with the 2-oxygen could result in a favorable D-furano isomer ratio. Hence compound **18** was debenzylated and then equilibrated in acetone−conc. H_2SO_4 to isolate the desired compound **26** in 73% yield after 3 equilibrium cycles. Benzylation of **26** gave **27**, which upon hydrolysis and acetylation rendered 3-deoxy-D-apio-D-furanose derivative **28** in good yields.

Having the coupling synthons **17**, **19**, **20**, **24** and **28** in hand, we set out different coupling reaction conditions for **19** and **20** with silylated thymine or N^6-benzoyladenine under Vorbrüggen conditions (Table 1).

Whereas the acetate anomer **19** reacted smoothly at room temperature in 4 h with silylated thymine in the presence of TMSOTf to quantitatively give **29**, coupling with N^6-benzoyladenine only afforded the desired coupling product **30** in 32% yield by heating the reaction mixture at 40 °C for 48 h.[26] This low yield resulted from the formation of an equal amount of an unknown isomer. ^{1}H NMR of this isomer suffered from peak broadening and indicated the presence of minor impurities. Its UV (λ_{max} = 331.9 nm) and ^{13}C-spectrum was characteristic of an N^1-isomer.[27,28] After treatment with methanolic ammonia for 2 days, a product was formed that was confidently identified as **31** (Figure 2). The binding topology of



31 **32** **33**

Figure 2. Byproducts (or their deprotected form) formed during Vorbrüggen coupling.

the adenine base to the sugar was determined by NMR. A correlation between H-1′and C-2 in a 2D ^{1}H−^{13}C HMBC spectrum indicates that the adenine is either bound via N-1 or N-3. In a 2D ^{1}H−^{1}H NOESY spectrum, NOE cross-peaks were detected between the amide proton and several protons of the sugar moiety, most notably H-1′, H-2′ and *ortho*-protons of the benzoyl group. In addition to this, *ortho*-protons of the benzoyl moiety also showed NOE interactions with all up (α-face) protons of the furanose ring. These NOE's are improbable if the base is attached via N-3, since in this case the amide group and the sugar moiety would be positioned *para* relative to one another and be spatially too far apart.

Coupling reaction between methylglycoside **20** and silylated thymine (entries 3 and 4), using either TMSOTf or $SnCl_4$, resulted in the formation of two main products that gave spots with comparable intensity on TLC. ESI-HRMS analysis allowed identifying these products as the two diastereomers of **32**.[18,29] The condensation reaction of methylglycoside **20** with silylated benzoyladenine in the presence of anhydrous $SnCl_4$ gave an unresolvable reaction mixture.

Vorbrüggen coupling of the methyl anomer **20** and silylated thymine under microwave irradiation resulted in an inseparable mixture of two isomeric products in a 2:1 ratio,[30] even after removal of the acetyl and benzyl protecting groups. The ^{1}H NMR spectrum of the minor isomer **33** showed a larger splitting of the anomeric hydrogen doublet (3.2 Hz) compared to the major compound (2.0 Hz), indicating a β-oriented pyrimidine moiety. The gHMBC confirmed the C1′-N1 attachment, while 2D NOESY ratified the relative stereochemistry.

Conversely, microwave-assisted coupling between **20** and silylated N^6-benzoyladenine gave only the desired α-nucleoside **30** in 60% isolated yield. Clearly, the microwave-assisted coupling with the methyl glycoside is the method of choice to prepare the adenine nucleoside.

Reaction of the triacetyl apiose **24** with silylated thymine under classical Vorbrüggen conditions provided **34** in very good yield (Scheme 2). Microwave conditions were employed to couple **24** with silylated N^6-benzoyladenine, affording **35** and minor amounts of the 2′-OTMS analogue **36**. The coupling products **29**, **30**, **34** and **35** were treated with ammonia in methanol to provide the desired deacetylated products **37**−**40**. Debenzylation of L-furano-D-apio thymine nucleosides **37** and **39** to give the 3′-deoxyapionucleoside **5a** and apionucleoside **6a** was realized by Pd-catalyzed hydrogenation. The same reaction condition on adenosines **38** and **40** was ineffective, as well as the use of cyclohexene and ammonium formate. This led us to use formic acid as hydrogen source to give **5b** and **6b**. The byproduct **41** was converted to **5b** upon treatment with ammonia in methanol.

Using similar protocols **17** and **28** were converted to **2a**,**b** and **3b** in acceptable yields (Scheme 3). Compared to the L-series, this sequence gave low yields for both thymine and adenine analogues, in particular for the 3′-deoxy analogues.

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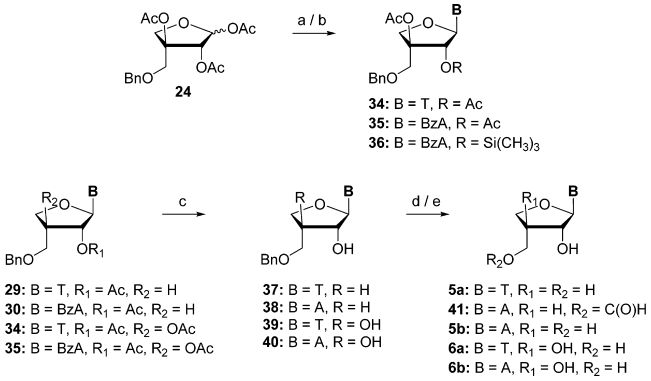
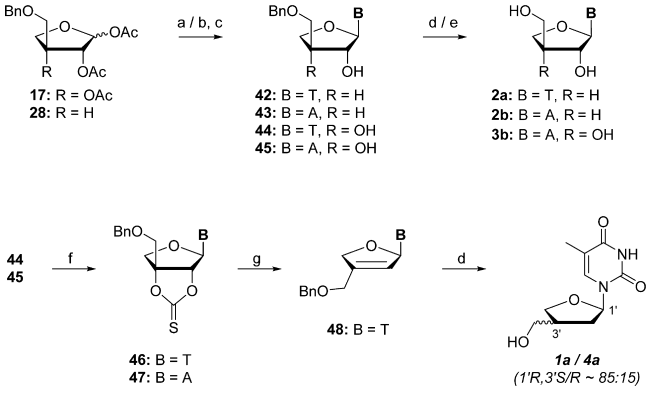
Scheme 2. Synthesis of α-L-Furano-D-apionucleosides 6a,b and Their 3′-Deoxy Counterparts 5a,b[a]



[a]Reagents and conditions: (a) appropriate silylated base, 1,2-$(CH_2)_2Cl_2$, TMSOTf, rt, 4 h, 85% for **34**; (b) appropriate silylated base, CH_3CN, 0.2 equiv of TMSOTf, microwave (MW) 300 W, 0 → 150 °C, 3 min, 150 °C, 5 min, 40% for **35** and 6% for **36**; (c) NH_3, MeOH, rt, 4−48 h, 75−96%; (d) H_2, Pd/C, MeOH, rt, overnight, 86% for **5a** from **37** and 71% for **6a** from **39**; (e) (i) $Pd(OH)_2$, HCOOH−MeOH (1:1 for **5b**, **41** from **38**/1:9 for **6b** from **40**), 55 °C, 5−8 h; (ii) NH_3, MeOH, rt, 3 h, 80% over two steps for **5b** and **6b**.

Scheme 3. Synthesis of β-D-Furano-D-apionucleosides[a]

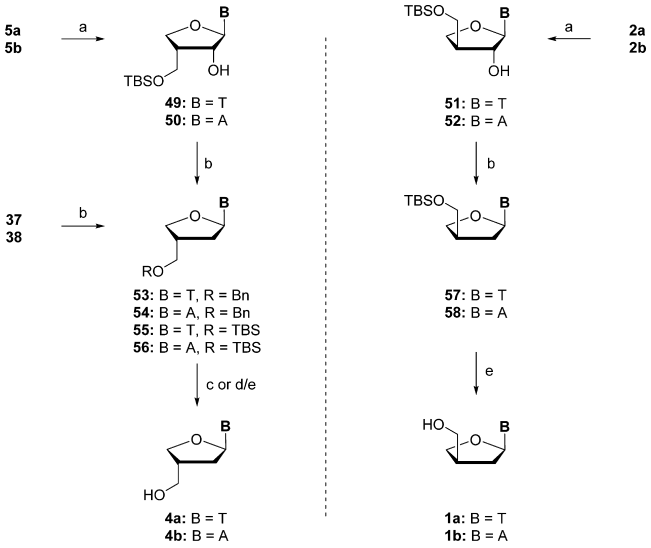


[a]Reagents and conditions: (a) silylated thymine, 1,2-$(CH_2)_2Cl_2$, TMSOTf, rt, 4 h; (b) silylated N^6-BzA, CH_3CN, 0.2 equiv of TMSOTf, MW 300 W, 0 → 150 °C, 3 min, 150 °C, 5 min; (c) 7 N NH_3−MeOH, rt, 4−48 h, 46−97% over two steps, 28% for **43** and 11% of its α-anomer; (d) for **42** and **48**, H_2, Pd/C, MeOH, rt, 4 h, 86−89%; (e) (i) $Pd(OH)_2$, HCOOH−MeOH (1:4), 55 °C, 5 h (ii) NH_3, MeOH, rt, 3 h, 89% for **2b** and **3b**; (f) thiocarbonyl diimidazole, DMF, 80 °C, 90 min, 89% for **46** and 78% for **47**; (g) $P(OCH_3)_3$, 120 °C, 6 h, 90%.

Moreover, coupling of **28** with silylated benzoyladenine produced significant amount of α-isomer (11%), possibly due to participation of the 3′-benzyloxymethyl group, with only 28% of desired β-nucleoside. Since the synthesis of **1a,b** via **28** involves many linear steps, we envisaged more convenient access to 2′,3′-dideoxy-β-D-apio-D-furanonucleosides **1a,b** involving Corey−Winter olefination[31] and stereoselective hydrogenation as key steps. During catalytic hydrogenation the *syn*-addition of the hydrogen atoms to the double bond is anticipated to occur from the face opposite to the nucleobase.[32] Thiocarbonylation of **44** and **45** using thiocarbonylimidazole provided precursor compounds **46** and **47** for Corey−Winter olefination. Unfortunately, the adenine derivative degraded in trimethylphosphite at 120 °C. The thymine derivative gave the desired product **48** in excellent yield but the hydrogenation reaction resulted in a mixture of diastereomers **1a** and **4a** that were inseparable by column chromatography. This forced us to follow the classical route via **2a,b** to the target 2′,3′-dideoxy analogues.

Initially, the benzyl protected nucleosides **37** and **38** were subjected to a standard Barton−McCombie protocol to give the 2′-deoxygenated products **53** and **54** (Scheme 4). Different

Scheme 4. Synthesis of D- and L-Furano-D-dideoxydihydroapionucleosides[a]



[a]Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, overnight, 82−95%; (b) (i) *p*-tolylchlorothionoformate, DMAP, ACN, 0 °C → rt, 4 h; (ii) Bu_3SnH, AIBN, toluene, reflux, 2−3 h, 70−90% over two steps; (c) H_2/Pd−C, methanol, rt, overnight, **53** to **4a**, 63%; (d) TBAF, THF, rt, 3 h, **55** to **4a**, 89%; (e) NH_4F, MeOH, 50 °C, 2 days, 86−94%.

hydrogen sources were explored for the subsequent Pd-catalyzed debenzylation, but only the thymine compound **53** could be converted to the desired product **4a** with curtailed reproducibility. This was attributed to catalyst poisoning by remaining sulfur residues. Hence, we swapped to TBS as a protecting group to give **49**−**52** from **5a,b** and **2a,b** in excellent yields. Compounds **49**−**52** were submitted to BMD after conversion to the corresponding xanthates with *p*-tolylchlorothionoformate in the presence of DMAP. These xanthates were isolated after a brief work-up and heated in toluene with tributyltin hydride and azobis(isobutyronitrile) to give the 2′,3′-dideoxyapiose nucleosides **55**−**58**. The TBS group of **55** and **56** was removed using TBAF in THF. However, the removal of the tetrabutylammonium salt to get pure adenosine derivative **4b** was not satisfactory; hence, we used NH_4F in methanol at 55 °C for 2 days to give **4a,b** and **1a,b** in excellent isolated yields.[33]

To examine the potential of their monophosphate prodrugs as anti-HIV agents, apio-dideoxynucleosides **1b** and **4b** were converted to the corresponding triphosphates **12** and **13**, following the method of Caton-Williams (Scheme 5).[34] The yield of the D-isomer **12** was low and ^1H NMR indicated internal salt formation. Likewise, the ^{31}P NMR of this compound is uncharacteristic of triphosphate salts, as it showed two broad peaks. The addition of 2 equiv of triethylamine disrupted this internal salt leading to the appearance of the

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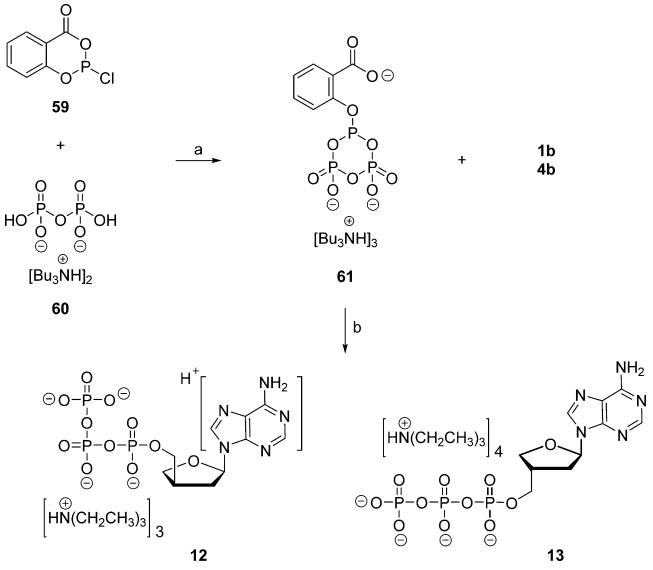
Scheme 5. Synthesis of D- and L-Furano-D-dideoxyapioadenosine Triphosphates (D-/L-ddAATP) 12 and 13[a]

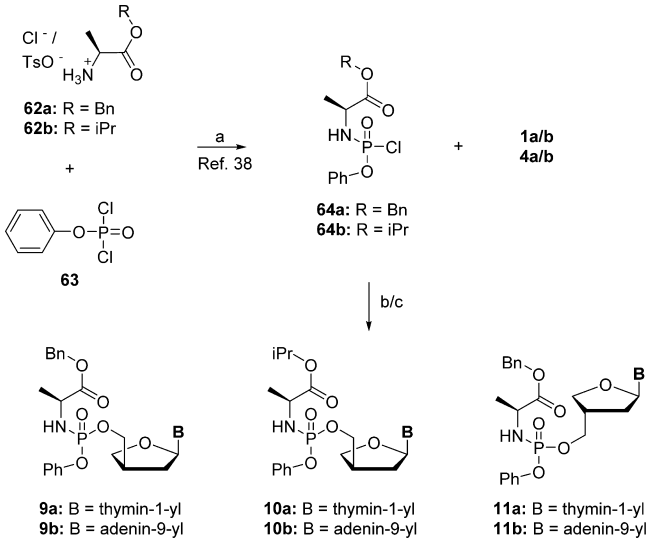


[a]Reagents and conditions: (a) **59**, **60**, *n*-Bu_3N, anh. DMF, rt, 1.5 h; (b) (i) **1b**/**4b**, anh. DMF, rt, 1.5 h; (ii) I_2, rt, 20 min, H_2O, rt, 1.5 h, 21% for **12** and 48% for **13**.

characteristic triphosphate peaks (see the Supporting Information).

Nucleoside monophosphate prodrugs (ProTides), featuring an alanine as the preferred amino acid,[35−37] were prepared using two different methods (Scheme 6).[38] The thymine analogue **11a** was prepared by coupling **4a** with the phosphorochloridate **64a**, using *tert*-butylmagnesium chloride as hydroxyl activator. Under similar reaction conditions compound **4b** degraded. Hence, all other analogues were coupled with **64a**/**b** using *N*-methylimidazole (NMI) as a base in a mixture of anhydrous THF and pyridine as solvents. In all

Scheme 6. Synthesis of Apionucleoside ProTides[a]



[a]Reagents and conditions: (a) CH_2Cl_2, TEA, −78 °C, 30 min, rt, 2 h, 87−96%; (b) *t*-butyl magnesium chloride, THF, rt, overnight, 22% for **11a**; (c) NMI, THF, pyridine, rt, 2 days, 15−88%.

cases, the desired compounds were obtained as a mixture of two diasteroisomers resulting from the two possible configurations of the phosphorus stereo center, as confirmed by the presence of two equal height peaks in the ^{31}P NMR spectrum.

DNA Chain Termination Study Using HIV Reverse Transcriptase. A prerequisite for ProTides to show a good biological profile is that the corresponding triphosphates are good substartes for the final target, such as reverse transcriptase (RT) for HIV. Hence we investigated the ability of triphosphates **12** and **13** to act as a substrate of HIV-RT in a primer-template assay.[39] The template has overhanging T residues to test incorporation of the modified A nucleotide. Figure 3 clearly shows that both nucleotides **12** and **13** function

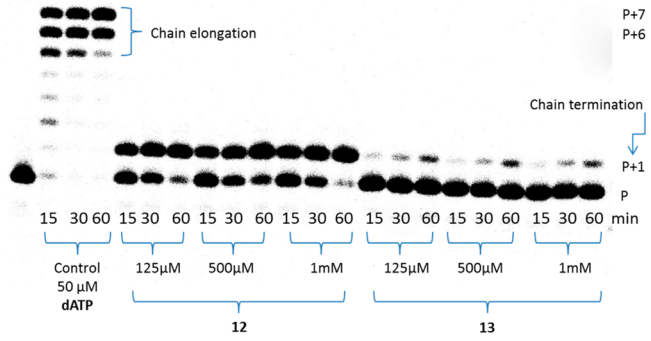


Figure 3. Electrophoregram that shows DNA chain termination through incorporation of dideoxydihydro-D-apio-D-furano-adenosine triphosphate (**12**) and dideoxydihydro-D-apio-L-furano-adenosine triphosphate (**13**) by HIV RT. The DNA polymeration mixtures containing 125 nM annealed (labeled) primer-template complex were treated with 125, 500, or 1000 μM of modified triphosphate (**12**/**13**) and 0.03 U μL^{-1} HIV RT and incubated at 37 °C. Aliquots were taken after 15, 30, and 60 min. In the control reaction, 50 μM of natural dATP was used. Samples were separated on a 0.4 mm 20% denaturing polyacrylamide gel, and the bands were visualized using phosphorimaging.

as DNA chain terminators. The D-furano analogue **12** is more efficiently incorporated than its 3′-epimer **13**, but compared to natural substrate 2′-deoxyadenosine triphosphate (dATP), requires a higher concentration and longer time for complete incorporation. The characteristics of **12** toward HIV RT render the corresponding ProTides as potentially useful HIV inhibitors.

Enzymatic Assay Using Carboxypeptidase Y. The putative mechanism of activation of ProTides[40−42] (Figure 4) involves an enzymatic cleavage of the ester (step **a**) mediated

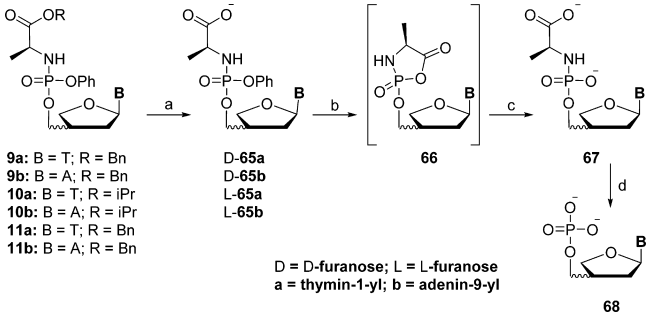


Figure 4. Putative mechanism of bioactivation for monophosphate prodrugs.

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by an esterase- or carboxypeptidase-type enzyme followed by spontaneous cyclization with releasing the phenolate anion (step **b**) and to open the unstable mixed anhydride ring by water (step **c**) providing the intermediate metabolite (D/L) **67a**/**b**. The cleavage of the phosphorus−nitrogen bond of the latter (step **d**) requires a phosphoramidase-type enzyme, perhaps related to human HINT-1, to release the monophosphate form (D-/L-**68a**/**b**).

In order to investigate this mechanism of bioactivation for ProTides **9a** and **11a**,**b**, we performed an enzymatic experiment incubating the compounds with carboxypeptidase Y enzyme in acetone-d_6 and Trizma buffer (pH = 7.6) recording a ^{31}P NMR at specific time intervals. The L-furano series displayed pronounced difference in rate of hydrolysis among two diastereomers, a phenomenon that was observed earlier for ProTides of phosphates[38] and phosphonates.[43] For instance, one of the diastereoisomer of **11a** (^{31}P NMR = 3.3 ppm, Figure 5, panel A) seems to be more slowly converted compared to

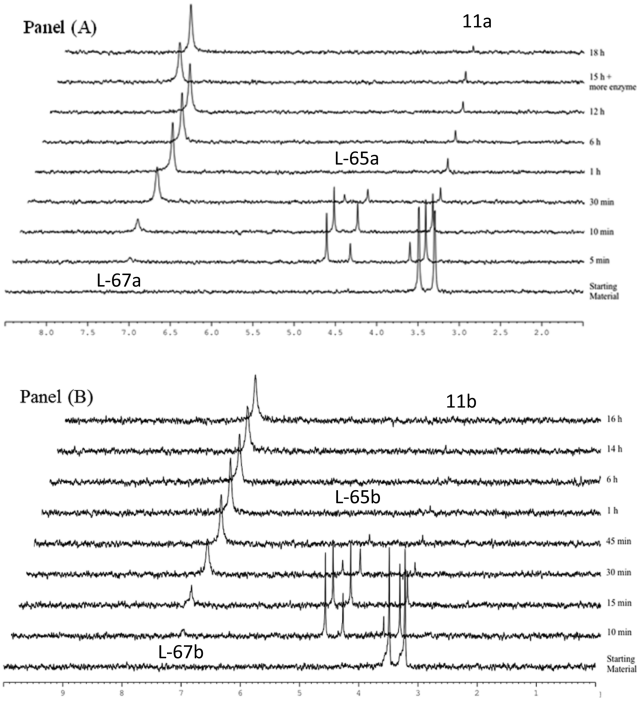

Figure 5. ^{31}P NMR stack spectra for bioactivation study of compounds **11a** (A) and **11b** (B) using carboxypeptidase Y enzyme. The assignment of the resonance signals to the indicated metabolites was done in analogy with previous studies.[35]

the other. In fact, after 18 h, it is still present, even after the addition of an extra portion of enzyme, while the diastereomer at 3.5 ppm appears fully converted after about 10 min. In contrast, compound **11b** (^{31}P NMR = 3.2 and 3.4 ppm, Figure 5, panel B) shows a near complete conversion of both diasteroisomers to the metabolite L-**67b** (^{31}P NMR = ∼7.0 ppm) through the intermediate L-**65b** (^{31}P NMR = ∼4.5 ppm) after 1 h, although there again exists a clear difference in kinetics.

Within 20 min after addition of the enzyme compound **9a** (^{31}P NMR = 3.5 and 3.7 ppm) was completely converted to the intermediate metabolite D-**65a** (^{31}P NMR = 4.5 and 4.8 ppm), which was fully converted to compound D-**67a** (^{31}P NMR = ∼7.1 ppm) within an hour (Figure 6). In this case no pronounced diastereomeric discrimination by carboxypeptidase

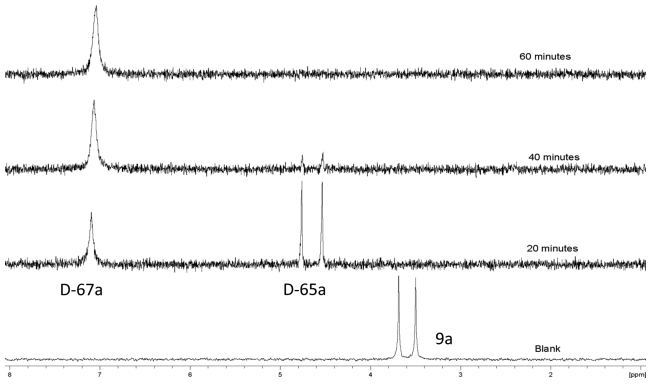

Figure 6. ^{31}P NMR stack spectra for bioactivation study of compound **9a** using carboxypeptidase Y enzyme. The assignment of the resonance signals to metabolites D-**65a** and D-**67a** is based on LC−MS experiments.

enzyme was observed. Following the trend for adenine analogue **11b**, we assume that **9b** would be processed at the least with the rate of thymine analogue **9a**.

From this study it is evident that both D- and L-furanonucleoside ProTides are readily converted to the intermediate metabolite **67**.

Biological Evaluation. The 2′,3′-dideoxy analogues **1a**,**b** and the 3′-deoxy-β-D-apio-D-furanonucleosides **2a**,**b** failed to show both activity against HIV-1,2 and cytotoxicity. Likewise, the 2′,3′-dideoxy analogues **4a**,**b** and the 3′-deoxy-β-D-apio-L-furanonucleosides **5a**,**b** lacked significant activity against HIV-1 and HIV-2 and a panel of other DNA and RNA viruses, and were also devoid of cytotoxicity. The thymine-based ProTides **9a** and **10a** were also devoid of anti-HIV activity, which might be due to inefficient conversion of the alaninyl d-ddATMP to the corresponding monophosphate by HINT-1-type phosphoramidase enzyme or further kinase mediated conversion to the corresponding triphosphate. Alternatively, the latter may be inefficiently incorporated by HIV RT (Table 2).

Table 2. Antiviral Activity and Cytotoxicity of ProTides 9a,b and 10a,b

	EC$_{50}$ in MT-4 cells (μM)			EC$_{50}$ in CEM cells (μM)	
	HIV-1 (NL4.3)	HIV-2 (ROD)	CC$_{50}$	HIV-1 (IIIb)	HIV-2 (ROD)
9a	>250	>250	196	–[a]	–
10a	>250	>250	>250	–	–
9b	0.5	1.0	93	0.5	1.5
10b	26	24	>250	7.5	38
R-PMPA	1.7	1.0	>250	3.0	2.5

[a]Dashes indicate not performed.

Interestingly, the 2′,3′-dideoxy-D-apio-D-furanoadenosine phosphoramidate ProTides **9b** and **10b** combine potent and moderate anti-HIV activity with reasonable selectivity. The benzylester **9b** exhibits comparable or even somewhat superior anti-HIV activity to the acyclic nucleoside phosphonate *R*-PMPA (tenofovir).[44] The ProTides **9a**,**b**, **10a**,**b** and **11a**,**b** are weak to moderate inhibitors of murine leukemia (L1210), human T-lymphocyte (CEM) and human cervix carcinoma (HeLa) cell proliferation (Table 3).

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Table 3. Cytotoxicity Data of ProTides 9a,b and 10a,b[a]

	L1210	CEM	HeLa
9a	113 ± 21	108 ± 11	159 ± 32
9b	110 ± 17	80 ± 4	53 ± 11
10a	>250	>250	>250
10b	226 ± 35	204 ± 3	≥250
11a	167 ± 85	113 ± 3	177 ± 103
11b	79 ± 4	73 ± 5	173 ± 58

[a]IC_{50} in μM, murine leukemia cells (L1210/0), human T-lymphocyte cells (CEM/0), and human cervix carcinoma cells (HeLa)

CONCLUSION

In this study we report the synthesis of a family of D-apionucleosides comprising the A and T members of both possible 3′-epimers of β-D-apiofuranose nucleosides, as well as their 3′-deoxy and 2′,3′-dideoxy analogues. Clues in the synthesis of the desired apionucleosides were a carbon homologation of 1,2-*O*-isopropylidene-D-glycero-tetrafuranos-3-ulose (**15**) and optimized glycosylation conditions involving microwave irradiation. In the course of this work, we rectified some anomalies in the structure assignments reported by others.

In accordance with earlier reports the target D-apio-D-furanose nucleosides failed to show antiviral activity and so did their D-apio-L-furanose epimers. However, the triphosphate of 2′,3′-dideoxy-β-D-apio-D-furanoadenosine (**12**) (in contrast to its D-apio-L-furanose epimer **13**) was readily accepted by viral DNA polymerase to act as a DNA chain terminator. This led us to convert the parent A and T nucleosides **1a** and **1b** into phosphoramidate prodrugs **9** and **10**. The A analogues **9b** and **10b** indeed showed a considerable anti-HIV activity. This indicates that the lack of activity of the parent 2′,3′-dideoxy-β-D-apio-D-furanose nucleoside must be the result of inefficient conversion to the monophosphate in the biological assay. This study demonstrates that the large pool of nucleoside analogues that were previously found to lack antiviral activity may contain valuable candidates to be turned into ProTide derivatives exhibiting promising antiviral activity, by efficiently bypassing the first phosphorylation step that is often rate-limiting the intracellular conversion of nucleoside analogues to their bioactive triphosphate derivatives.

EXPERIMENTAL SECTION

Synthesis. All reagents were from standard commercial sources and of analytic grade. Dry solvents were obtained directly from commercial sources and stored on molecular sieves. All reactions were carried out under argon atmosphere using anhydrous solvents unless specified otherwise. Room temperature or rt refers to 25 ± 5 °C. Silica-gel precoated with F254 plates were used for TLC. The spots were examined under ultraviolet light at 254 nm and further visualized by sulfuric acid-anisaldehyde spray. Column chromatography was performed on silica gel (40−63 μm, 60 Å) or on flash chromatography system. NMR spectra were recorded on a 300 MHz, 500 or 700 MHz spectrometer. Chemical shifts are given in ppm (δ), calibrated to the residual solvent signals or TMS. Exact mass measurements were performed on mass spectrometer equipped with a standard electrospray ionization (ESI) and modular LockSpray TM interface. Samples were infused in a CH_3CN/H_2O (1:1v/v) mixture at 10 mL/min. The microwave reactions were carried out in Milestone MicroSYNTH Advanced Microwave Synthesis Labstation, equipped with 2 × 800 W magnetrons (effective maximum output 1500W pulsed/continuous), an optical fiber temperature sensor, a pressure sensor, in continues power mode in a closed PTFE vessel. NMR signals of sugar protons and carbons are indicated with a prime, and signals of base protons and carbons are given without a prime. A combination of gCOSY, gHSQC and gHMBC was used to assign ^1H and ^{13}C peaks, Noesy was used for selected compounds to assign peaks and/or to confirm relative configuration.

3-Oxo-1,2-O-isopropylidene-α-D-erythrofuranose (**15**).[18] To a solution of compound **14** (1.0 g, 6.24 mmol) in CH_2Cl_2 (12.5 mL) was added bis-acetoxyiodobenzene (BAIB, 2.41 g, 7.5 mmol) followed by (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, 195 mg, 1.25 mmol) at room temperature under an argon atmosphere. The mixture was stirred at room temperature for 4 h. The contents of the reaction was directly loaded on silica-gel and eluted with 30% EtOAc-hexanes to afford pure product **15** (890 mg, 90%) as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.35 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 4.03 (dd, *J* = 4.1, 17.6 Hz, 1H, 4-H), 4.29 (s, 1H, 2-H), 4.32 (dd, *J* = 0.6, 17.6 Hz, 1H, 4-H), 6.02 (d, *J* = 4.4 Hz, 1H, 1-H).

1,2-O-Isopropylidene-5-(O-benzyl)-α-D-apio-D-furanose (**16**).[20] To a stirring solution of benzyloxymethyltributlytin ($BOMSnBu_3$, 5.93 g, 14.4 mmol) in THF (35 mL) at −78 °C under inert condition, was added dropwise *n*-butyllithium (1.6 M in hexanes,19.5 mL, 31.3 mmol) and stirred for additional 1 h. To this mixture was then added dropwise a solution of compound **15** (1.9 g, 12.02 mmol) in 10 mL of THF and stirred at −78 °C for 3 h. The reaction was quenched with saturated NH_4Cl solution and by vigorous stirring. EtOAc (100 mL) was then added to facilitate the layer separation. Organic layer was separated, and the aqueous layer was extracted twice with EtOAc (50 mL). Combined organic layers were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography eluting with 17% EtOAc-hexanes to afford **16** (2.3 g, 68%) as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.37 (s, 3H, CH_3b), 1.58 (s, 3H, CH_3a), 2.85 (s, 1H, 3-OHa), 3.46 (d, *J* = 10.3 Hz, 1H, 5-H), 3.56 (d, *J* = 10.3 Hz, 1H, 5-H), 3.71 (d, *J* = 9.1 Hz, 1H, 4-Ha), 3.80 (d, *J* = 9.1 Hz, 1H, 4-Hb), 4.39 (d, *J* = 3.8 Hz, 1H, 2-Hb), 4.54−4.71 (m, 2H, CH_2Ph), 5.76 (d, *J* = 4.1 Hz, 1H, 1-Hb), 7.27−7.40 (m, 5H, CH_2Ph).

1,2,3-Tri-(O-acetyl)-5-(O-benzyl)-α/β-D-apio-D-furanose (**17**).[45] A solution of **16** (2.5 g, 8.92 mmol) in 80% aq. acetic acid (25 mL) was stirred at 80 °C for 8 h. The reaction mixture was evaporated to give the crude intermediate as syrup. This syrup was dissolved in pyridine (20 mL) and DMAP was added (100 mg) followed by acetic anhydride (10 mL, 106 mmol). The solution was stirred at 55 °C for 16 h. Then, the solvent was removed under a vacuum, and the resulting residue was partitioned between EtOAc and water. Organic layer separated, combined organic layer was washed with brine, dried over sodium sulfate, and evaporated. The residue was purified by silica-gel column chromatography (15−20% EtOAc-hexanes) to yield **17** (2.45 g, 75%) as a colorless oil as a mixture of α + β isomers (2:1): ^1H NMR (300 MHz, $CDCl_3$) δ ppm 1.96 (s, 3H, major), 2.08 (s, 3H, major), 2.08 (s, 2H, minor), 2.09 (s, 1H, minor), 2.10 (s, 3H, major), 3.75 (d, *J* = 9.7 Hz, 0.47H, minor), 3.89 (d, *J* = 10.5 Hz, 1H, major), 3.96 (d, *J* = 9.7 Hz, 0.5H, minor), 4.05 (d, *J* = 10.5 Hz, 1H, major), 4.22 (d, *J* = 10.3 Hz, 1H, major), 4.26 (d, *J* = 10.5 Hz, 0.52H, minor), 4.32 (d, *J* = 10.5 Hz, 0.5H, minor), 4.34 (d, *J* = 10.3 Hz, 1H, major), 4.51−4.62 (m, 3H, major and minor), 5.42 (d, *J* = 4.7 Hz, 0.44H, minor), 5.49 (d, *J* = 1.2 Hz, 1H, major), 6.08 (d, *J* = 1.2 Hz, 1H, major), 6.33 (d, *J* = 4.7 Hz, 0.43H, minor), 7.27−7.41 (m, 7H, major and minor); HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ Calcd for $C_{18}H_{22}O_8Na$ 389.1212, found 389.1242.

1,2-O-Isopropylidene-3-deoxy-5-(O-benzyl)-β-D-apio-L-furanose (**18**).[18] To a solution of **16** (3.5 g, 12.5 mmol) in dry THF (75 mL) was added NaH (60% in mineral oil, 1.5 g, 37.45 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. To this mixture were slowly added CS_2 (11.2 mL, 188 mmol) and MeI (24.0 mL, 375 mmol) and stirred at room temperature for 1 h. The reaction mixture was evaporated to give crude xanthate. The xanthate was suspended in dry toluene (75 mL), triethylborane (19.0 mL, 19.0 mmol, 1.0 M solution in THF) and *n*-Bu_3SnH (5 mL, 19.0 mmol) were added at room temperature, and the mixture was stirred for further 3 h. The reaction mixture was quenched with water, extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column chromatography (10%

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EtOAc-hexanes) to give **18** (2.26 g, 68%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.32 (s, 3H, CH_3a), 1.49 (s, 3H, CH_3b), 2.37−2.52 (m, 1H, 3-Ha), 3.52 (dd, J = 9.2, 7.5 Hz, 1H, 5-H), 3.69 (dd, J = 11.3, 8.6 Hz, 1H, 4-Hb), 3.78 (dd, J = 9.4, 6.7 Hz, 1H, 5-H), 4.01 (dd, J = 8.4, 7.2 Hz, 1H, 4-Ha), 4.46−4.60 (m, 2H, CH_2Ph), 4.65 (t, J = 4.1 Hz, 1H, 2-Ha), 5.83 (d, J = 3.8 Hz, 1H, 1-Ha), 7.24−7.42 (m, 5H, CH_2*Ph*).

*1,2-Di-O-acetyl-3-deoxy-5-(O-benzyl)-α/β-D-apio-L-furanose (**19**).* A solution of **18** (750 mg, 2.84 mmol) in 80% aq. acetic acid (10 mL) was stirred at 80 °C for 8 h. The reaction mixture was evaporated to give the crude intermediate as a syrup. This syrup was dissolved in pyridine (15 mL) and treated with DMAP (50 mg) and acetic anhydride (2.0 mL, 21.2 mmol). The solution was stirred at room temperature for 4 h. The solvent was removed under a vacuum, and the resulting residue was purified by silica-gel column chromatography (20% EtOAc-hexanes) to yield **19** (500 mg, 57%) as a colorless oil (α:β anomeric ratio 1:4). Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.94 (s, 3H, Ac), 1.97 (s, 3H, Ac), 2.83−2.96 (m, 1H, 3-H), 3.40 (dd, J = 9.1, 7.3 Hz, 1H, 5-H), 3.55 (dd, J = 9.1, 7.6 Hz, 1H, 5-H), 3.77 (t, J = 8.8 Hz, 1H, 4-H), 4.17 (t, J = 8.4 Hz, 1H, 4-H), 4.35−4.48 (m, 2H, CH_2Ph), 5.20 (d, J = 5.0 Hz, 1H, 2-H), 6.02 (s, 1H, 1-H), 7.18−7.32 (m, 5H, CH_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 20.5 (CH_3CO), 21.0 (CH_3CO), 40.1 (3-C), 66.1 (5-C), 70.9 (4-C), 73.3 (CH_2Ph), 76.1 (2-C), 99.7 (1-C), 127.6 (C$_o$ *Ph*), 127.7 (C$_p$ *Ph*), 128.4 (C$_m$ *Ph*), 137.8 (C$_{ipso}$ *Ph*), 169.4 (CH_3CO), 169.7 (CH_3CO); HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{16}H_{20}O_6Na$ 331.1158, found 331.1152.

*1-O-Methyl-2-O-acetyl-3-deoxy-5-(O-benzyl)-β-D-apio-L-furanose (**20**).*[18] A solution of **18** (2.26 g, 8.55 mmol) and *p*-TsOH (700 mg, 4.06 mmol) in MeOH (60 mL) was stirred at room temperature for 16 h, neutralized with TEA and evaporated. The residue was partitioned between EtOAc and water, organic layer separated, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by column chromatography (20−40% EtOAc-hexanes). The intermediate was dissolved in pyridine (15 mL), acetic anhydride (2.4 mL, 25.2 mmol) and DMAP (200 mg, 1.68 mmol) were added at 0 °C, and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was evaporated, and partitioned between EtOAc and 10% aq. $KHSO_4$. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column chromatography (15% EtOAc-hexanes) to give **20** (1.85 g, 77%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.00 (s, 3H, 2-OAc), 2.88−3.02 (m, 1H, 3-H), 3.34 (s, 3H, 1-OMe), 3.46 (dd, J = 9.1, 7.3 Hz, 1H, 5-H), 3.62 (dd, J = 9.2, 7.2 Hz, 1H, 5-H), 3.78 (t, J = 8.6 Hz, 1H, 4-H), 4.14 (t, J = 8.5 Hz, 1H, 4-H), 4.46 (d, J = 12.0 Hz, 1H, CH_2Ph), 4.52 (d, J = 12.0 Hz, 1H, CH_2Ph), 4.83 (s, 1H, 1-H), 5.16 (d, J = 5.3 Hz, 1H, 2-H), 7.27−7.39 (m, 5H, CH_2*Ph*).

*1,2-O-Isopropylidene-β-D-apio-L-furanose (**22**).*[18] Compound **21** (5.0 g, 21.72 mmol) was dissolved in 50 mL of 2:1 acetic acid−water mixture and stirred at room temperature for 3 days. Solvents were evaporated in vacuo and silica gel column chromatography of the residue (50% EtOAc-hexanes) afforded the title compound **22** as a white solid (3.4 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.33 (s, 3H, C(CH_3)$_2$), 1.51 (s, 3H, C(CH_3)$_2$), 2.12 (t, J = 5.9 Hz, 1H, 5-OH), 2.69 (s, 1H, 3-OH), 3.71 (dd, J = 6.3, 11.16 Hz, 1H, 4-H), 3.80 (d, J = 9.8 Hz, 1H, 5-H), 3.94 (d, J = 9.4 Hz, 1H, 5-H), 3.96 (dd, J = 5.4, 7.5 Hz, 1H, 4-H), 4.38 (d, J = 3.8 Hz, 1H, 2-H), 5.99 (d, J = 3.7 Hz, 1H, 1-H).

*1,2-O-Isopropylidene-5-(O-benzyl)-β-D-apio-L-furanose (**23**).*[18,20] Compound **22** (3.1 g, 16.3 mmol) and dibutyltin oxide (6.7 g, 26.9 mmol) was dissolved in toluene (120 mL) refluxed at 140 °C for 2 h. The reaction mixture was allowed to attain 100 °C then added tetrabutylammonium bromide (2.63 g, 8.15 mmol) and benzyl bromide (3.0 mL, 25.26 mmol). The reaction mixture was stirred at this temperature for 18 h. Solvent was evaporated under reduced pressure, and the residue purified by silica gel column chromatography (30% EtOAc-hexanes) to afford **23** (4.3 g, 94%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.32 (s, 3H, C(CH_3)$_2$a), 1.48 (s, 3H, C(CH_3)$_2$b), 2.76 (d, J = 0.9 Hz, 1H, 3-OHa), 3.54 (d, J = 9.7 Hz, 1H, 5-H), 3.80 (d, J = 9.7 Hz, 1H, 5-H), 3.82 (dd, J = 9.4, 0.9 Hz, 1H, 4-Ha), 3.88 (dd, J = 9.4 Hz, 1H, 4-Hb), 4.35 (dd, J = 3.5, 0.9 Hz, 1H, 2-Ha), 4.57 (d, J = 12.0 Hz, 1H, PhCH_2), 4.64 (d, J = 12.0 Hz, 1H, PhCH_2), 5.98 (d, J = 3.5 Hz, 1H, 1-Ha), 7.27−7.42 (m, 5H, *Ph*CH_2).

*1,2,3-Tri-(O-acetyl)-5-(O-benzyl)-β-D-apio-L-furanose (**24**).* Following the procedure described for the synthesis of **17**, (2.5 g, 8.92 mmol) of **23** rendered pure product **24** (2.45 g, 75%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.96 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 3.89 (d, J = 10.5 Hz, 1H, 4-H), 4.05 (d, J = 10.3 Hz, 1H, 4-H), 4.22 (d, J = 10.3 Hz, 1H, 5-H), 4.34 (d, J = 10.3 Hz, 1H, 5-H), 4.50−4.62 (m, 2H, PhCH_2), 5.49 (d, J = 1.2 Hz, 1H, 2-H), 6.08 (d, J = 1.2 Hz, 1H, 1-H), 7.26−7.40 (m, 5H, *Ph*CH_2).

*1,2-O-Isopropylidene-3-deoxy-β-D-apio-L-furanose (**25**).*[18] Compound **18** (3.7 g, 14 mmol) was dissolved in methanol (100 mL), to this was added Pd−C (3.7 g, 10% Pd, wet ∼50% H_2O). Stream of hydrogen gas was bubbled through the reaction mixture for 5 h at room temperature. The catalyst was filtered off, and the filtrate concentrated to give crude product which on purification by silica-gel column chromatography (40% EtOAc-hexanes) rendered **25** (2.2 g, 90%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.34 (d, J = 0.6 Hz, 3H, C(CH_3)$_2$), 1.53 (s, 3H, C(CH_3)$_2$), 2.21 (br.s, 1H, 5-OH), 2.34 (ddtd, J = 11.4, 6.9, 5.97, 6.0, 4.8 Hz, 1H, 3-H), 3.82−3.91 (m, 3H, 4-H and 5-H's), 3.97 (dd, J = 8.5, 7.3 Hz, 1H, 4-H), 4.73 (t, J = 4.4 Hz, 1H, 2-H), 5.86 (d, J = 3.8 Hz, 1H, 1-H).

*1,2-O-Isopropylidene-3-deoxy-α-D-apio-D-furanose (**26**).* To a solution of compound **25** (2.2 g, 12.63 mmol) in 400 mL of acetone was added concentrated sulfuric acid (2.2 mL), and the mixture was stirred at room temperature for 1.5 h. Then sodium carbonate (14 g) was added and stirred at room temperature for 45 min. Inorganic salts were removed by filtration, and the filtrate concentrated under reduced pressure to afford oil. TLC indicated the conversion in favor of required isomer (roughly 2:1). The title compound is slightly more polar than the starting material (R_f after two runs: 0.35 for **26** and 0.4 for **25**; eluent, 2.5% MeOH in CH_2Cl_2). Silica-gel flash column chromatography (0.5−1.5% MeOH in CH_2Cl_2) afforded title compound and starting material. After three cycles 1.6 g (73%) of **26** was procured as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 (d, J = 0.6 Hz, 3H, C(CH_3)b), 1.50 (s, 3H, C(CH_3)a), 1.89 (br.s, 1H, 5-OH), 2.36−2.46 (m, 1H, 3-H), 3.58 (dd, J = 6.6, 3.4 Hz, 2H, 5−CH_2), 3.83 (d, J = 9.1 Hz, 1H, 4-Hb), 4.10 (dd, J = 8.9, 5.1 Hz, 1H, 4-Ha), 4.60 (d, J = 3.5 Hz, 1H, 2-H), 5.81 (d, J = 3.8 Hz, 1H, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 26.2 (C(CH_3)b), 26.8 (C(CH_3)a), 48.1 (3-C), 62.0 (5-C), 68.7 (4-C), 82.3 (2-C), 105.6 (1-C), 111.3 (C(CH_3)$_2$).

*1,2-O-Isopropylidene-3-deoxy-5-(O-benzyl)-α-D-apio-D-furanose (**27**).* To an ice cold solution of **26** (1.6 g, 9.2 mmol) in DMF (30 mL) was added NaH (60% in mineral oil, 0.55g, 13.8 mmol) and then benzyl bromide (1.64 mL, 13.8 mmol) dropwise. The reaction mixture was stirred at room temperature overnight. Methanol (5 mL) was added and stirred for further 30 min. The volatile materials were removed under vacuo, and the residue was partitioned between ethyl acetate and water. The organic layer was separated, dried over anhydrous Na_2SO_4, evaporated, and the residue purified by column chromatography (5−15% EtOAc in hexanes) to afford **27** (2.3 g, 95%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.31 (d, J = 0.6 Hz, 3H, C(CH_3)b), 1.51 (s, 3H, C(CH_3)a), 2.56 (td, J = 7.5, 5.1 Hz, 1H, 3-Ha), 3.37 (d, J = 7.6 Hz, 2H, 5−CH_2), 3.83 (d, J = 8.8 Hz, 1H, 4-Hb) 4.09 (dd, J = 8.9, 5.1 Hz, 1H, 4-Ha) 4.51 (d, J = 3.2 Hz, 2H, PhCH_2), 4.56 (d, J = 3.5 Hz, 1H, 2-Hb), 5.79 (d, J = 3.5 Hz, 1H, 1-Hb), 7.27−7.41 (m, 5H, *Ph*CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 26.3 (C(CH_3)b), 26.9 (C(CH_3)a), 46.1 (3-C), 68.8 (4&5-C), 73.3 (PhCH_2), 82.4 (2-C), 105.6 (1-C), 111.2 (C(CH_3)$_2$) 127.8, 127.9, 128.6, 138.1 (*Ph*CH_2). MS (ESI-TOF) m/z [M + K]$^+$ Calcd for $C_{15}H_{20}O_4K$ 303.0999, found 303.1078.

*1,2-Di-O-acetyl-3-deoxy-5-(O-benzyl)-α/β-D-apio-D-furanose (**28**).* Following the procedure described for the synthesis of **19**, compound **27** (1.3 g, 4.92 mmol) rendered **28** (1.2 g, 79%) as a colorless oil. Mixture of α+β (2:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.00 (s, major, C(CH_3)$_2$) 2.04 (s, minor, C(CH_3)$_2$) 2.07 (s, minor, C(CH_3)$_2$) 2.08 (s, major, C(CH_3)$_2$), 2.56−2.69 (m, major, 3-H) 2.69−2.83 (m, minor, 3-H) 3.46−3.74 (m, major and minor, 5-H)

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3.80−3.94 (m, major and minor, 4-H) 4.20−4.34 (m, major and minor, 4-H) 4.51 (s, minor, PhCH_2), 4.54 (s, major, PhCH_2), 5.05 (t, J = 4.1 Hz, minor, 2-H), 5.08 (d, J = 2.6 Hz, major, 2-H), 6.13 (s, major, 1-H), 6.33 (d, J = 4.4 Hz, minor, 1-H), 7.27−7.40 (m, major and minor, *Ph*CH_2); HRMS (ESI-TOF) m/z [M + K]$^+$ Calcd for $C_{16}H_{20}O_6K$ 347.0897, found 347.0898.

General Condition for Vorbrüggen Coupling Reaction. All operations were carried out under an argon protected atmosphere.

Silylation of Nucleobases. The nucleobase (N^6-Benzoyl protected in case of adenine) (2 equiv) was suspended in hexamethyldisilazane (50 equiv) containing trimethylsilyl chloride (0.7 equiv) and pyridine (10 equiv). The mixture was heated at reflux overnight. After cooling, the solvent was evaporated and dried under a high vacuum.

Coupling at Ambient Condition (A). To the silylated nucleobase was added compound **17**/**19**/**20**/**24** or **28** (1 equiv) dissolved in dry 1,2-dichloroethane (7 mL/mmol), and trimethylsilyl triflate or anhydrous $SnCl_4$ (2.5 equiv) was added dropwise at room temperature. The clear solution was stirred at rt.

Coupling under Microwave Condition (B). To the silylated nucleobase was added compound **17**/**19**/**20**/**24** or **28** (1 equiv) dissolved in dry acetonitrile (7 mL/mmol), followed by the addition of trimethylsilyl triflate (0.2 equiv) at rt. The clear solution was irradiated to microwave (continuous power, 300 W, preheating 0 → 150 °C in 3 min, at 150 ± 3 °C for 5 min).

Workup Procedure. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 times). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. Purification of the residue by silica-gel flash column chromatography (MeOH−CH_2Cl_2) afforded the pure coupled product as white foam.

*1′-(Thymin-1-yl)-2′-O-acetyl-3′-deoxy-5′-O-benzyl-α-D-apio-L-furanose (**29**).* Using condition A, compound **19** (320 mg, 1.04 mmol) gave compound **29** (420 mg) in quantitative yield as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.84 (d, J = 0.9 Hz, 3H, 5-CH_3), 1.98 (s, 3H, 2′-OAc), 2.67−2.85 (m, 1H, 3′-H), 3.39 (dd, J = 9.1, 7.62 Hz, 1H, 5′-H), 3.57 (dd, J = 9.2, 6.0 Hz, 1H, 5′-H), 3.89 (t, J = 8.9 Hz, 1H, 4′-H), 4.36 (t, J = 8.1 Hz, 1H, 4′-H), 4.43 (s, 2H, CH_2Ph), 5.39 (dd, J = 6.2, 2.3 Hz, 1H, 2′-H), 5.74 (d, J = 2.3 Hz, 1H, 1′-H), 6.89−7.02 (d, J = 0.9 Hz, 1H, 6-H), 7.21−7.38 (m, 5H, CH_2*Ph*), 8.85 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 12.6 (5-CH_3), 20.6 (2′−OCOCH_3), 41.0 (3′-C), 66.3 (5′-C), 71.9 (4′-C), 73.5 (CH_2Ph), 91.2 (1′-C), 111.0 (5-C), 127.7 (CH_2*Ph*), 127.9 (CH_2*Ph*), 128.5 (CH_2*Ph*), 135.1 (6-C), 137.6 (CH_2*Ph*), 150.0 (2-C), 163.7 (4- C), 169.7 (2′-O$COCH_3$); HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{19}H_{23}N_2O_6$ 375.1556, found 375.1556.

*1′-(N⁶-Benzoyladenin-9-yl)-2′-O-acetyl-3′-deoxy-5′-O-benzyl-α-D-apio-L-furanose (**30**).* Using condition B, compound **20** (1.0 g, 3.56 mmol) gave compound **30** (1.0 g, 60%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.00 (s, 3H, 2′-OAc), 3.11−3.25 (m, 1H, 3′-H), 3.49 (dd, J = 9.2, 7.2 Hz, 1H, 5′-H), 3.63 (dd, J = 9.4, 6.4 Hz, 1H, 5′-H), 4.00 (t, J = 8.5 Hz, 1H, 4′-H), 4.45 (s, 2H, PhCH_2), 4.50 (t, J = 8.1 Hz, 1H, 4′-H), 5.79 (dd, J = 5.9, 2.1 Hz, 1H, 2′-H), 6.04 (d, J = 2.3 Hz, 1H, 1′-H), 7.21−7.32 (m, 5H, CH_2*Ph*), 7.37−7.47 (m, 2H, H_m Bz), 7.47−7.56 (m, 1H, H_p Bz), 7.90−7.97 (m, 2H, H_o Bz), 7.98 (s, 1H, 8-H), 8.72 (s, 1H, 2-H), 9.11 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 20.6 (2′−OCOCH_3), 41.0 (3′-C), 66.2 (5′-C), 72.1 (4′-C), 73.4 (CH_2Ph), 77.0 (2′-C), 90.2 (1′- C), 123.6 (5-C), 127.7 (C_o, C_p Bn), 127.8 (C_o Bz), 128.4 (C_m Bn), 128.8 (C_m Bz), 132.7 (C_p Bz), 133.6 (C_{ipso} Bz), 137.6 (C_{ipso} Bn), 141.3 (8-C), 149.5 (6-C), 151.2 (4-C), 152.8 (2-C), 164.6 (N^6Bz-CO), 169.9 (2′-O$COCH_3$); HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{26}H_{26}N_5O_5$ 488.1934, found 488.1937.

*1′-(N⁶-Benzoyladenin-1-yl)-3′-deoxy-5′-O-benzyl-α-D-apio-L-furanose (**31**).* Spectral data: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.45−2.61 (m, 1H, 3′-H), 3.68 (dd, J = 9.4, 6.4 Hz, 1H, 5′-H), 3.76 (dd, J = 9.5, 6.3 Hz, 1H, 5′-H), 4.22 (t, J = 8.8 Hz, 1H, 4′-H), 4.41 (t, J = 8.2 Hz, 1H, 4′-H), 4.45−4.52 (m, 2H, CH_2Ph), 4.62 (d, J = 5.0 Hz, 1H, 2′-H), 6.56 (s, 1H, 1′-H), 7.19−7.28 (m, 5H, CH_2*Ph*), 7.29−7.37 (m, 2H, H_m Bz), 7.39−7.47 (m, 1H, H_p Bz), 7.97 (s, 1H, 8-H), 8.16−8.22 (m, 2H, H_o Bz), 8.40 (s, 1H, 2-H), 12.45 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 41.2 (3′-C), 65.9 (5′-C), 72.1 (4′-C), 73.6 (CH_2Ph), 77.6 (2′-C), 96.6 (1′-C), 114.7 (5-C), 127.9 (C_o Bn), 128.2 (C_p Bn), 128.5 (C_m Bz), 128.8 (C_m Bn), 129.9 (C_o Bz), 132.4 (C_p Bz), 137.5 (C_{ipso} Bz), 137.8 (C_{ipso} Bn), 142.0 (8-C), 142.2 (2-C), 148.8 (6-C), 158.0 (4-C), 175.5 (Bz CO); HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{24}H_{24}N_5O_4$ 446.1828, found 446.1839.

*1′-(Thymin-1-yl)-3′-deoxy-β-D-apio-L-furanose (**33**).* Spectral data for the compound mixture **33** (minor) + **5a**: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.77 (d, J = 0.9 Hz, 1.06H, minor 5-CH_3), 1.80 (d, J = 1.2 Hz, 2.89H, 5-CH_3, major), 2.22−2.36 (m, 1H, 3′-H, major), 2.52−2.60 (m, 0.29H, 3′-H, minor) 3.40−3.52 (m, 1.43H, 5′-H, major and minor), 3.62−3.72 (m, 1.43H, 5′-H, major and minor), 3.73−3.81 (m, 1.11H, 4′-H, major), 3.81−3.87 (m, 0.31H, 4′-H, minor), 9.95−4.02 (t, J = 7.9 Hz, 0.39H, 4′-H, minor), 4.11−4.16 (m, 0.36H, 2′-H, minor), 4.19 (td, J = 5.1, 2.1 Hz, 1.05H, 2′-H, major), 4.33 (t, J = 7.9 Hz, 1H, 4′-H, major), 4.51 (t, J = 5.1 Hz, 1.34H, 5′−OH, major and minor), 5.29 (d, J = 4.7 Hz, 0.37H, 2′−OH, minor), 5.51 (d, J = 5.0 Hz, 1.02H, 2′−OH, major), 5.61 (d, J = 2.1 Hz, 1H, 1′-H, major), 5.88 (d, J = 3.2 Hz, 0.36H, 1′-H, minor), 7.30 (d, J = 1.2 Hz, 0.36H, 6-H, minor), 7.38 (d, J = 1.2 Hz, 1.02H, 6-H, major), 11.21 (s, 0.39H, NH, minor), 11.27 (s, 1.01H, major); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 12.1 (5-CH_3, major), 12.2 (5-CH_3, minor), 43.6 (3′-C, major), 46.1 (3′-C, minor), 57.6 (5′-C, major), 57.7 (5′-C, minor), 69.3 (2′-C, minor), 69.8 (4′-C, minor), 71.2 (4′-C, major), 74.2 (2′-C, major), 87.9 (1′-C, minor), 92.2 (1′-C, major), 106.8 (5-C, minor), 108.9 (5-C, major), 135.7 (6-C, major), 138.0 (6-C, minor), 150.3 (2-C, major), 150.4 (2-C, minor), 163.9 (4-C, major), 164.1 (4-C, minor).

*1′-(Thymin-1-yl)-2′,3′-di(O-acetyl)-5′-O-benzyl-α-D-apio-L-furanose (**34**).* Using condition A, compound **24** (100 mg, 0.27 mmol) gave compound **34** (100 mg, 85%) as a colorless glass: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.95 (d, J = 1.2 Hz, 3H, 5−CH_3), 2.04 (s, 3H, Ac), 2.08 (s, 3H, Ac), 3.88 (s, 2H, 5′-H), 4.20 (d, J = 10.5 Hz, 1H, 4′-H), 4.55 (s, 2H, CH_2Ph), 4.56 (d, J = 10.5 Hz, 1H, 4′-H), 5.63 (d, J = 5.0 Hz, 1H, 2′-H), 5.96 (d, J = 5.0 Hz, 1H, 1′-H), 7.28 (d, J = 1.2 Hz, 1H, 6-H), 7.30−7.41 (m, 5H, CH_2*Ph*), 8.52 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 12.7 (5-CH_3), 20.5 (Ac-CH_3), 21.6 (Ac-CH_3), 66.7 (5′-C), 73.2 (4′-C), 73.8 (CH_2Ph), 78.1 (2′-C), 86.2 (3′-C), 88.2 (1′-C), 111.4 (5-C), 127.8 (C_o Bn), 128.0 (C_p Bn), 128.5 (C_m Bn), 135.0 (6-C), 137.3 (C_{ipso} Bn), 150.2 (2-C), 163.3 (4-C), 169.1 (Ac-CO), 169.9 (Ac-CO); HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{21}H_{25}N_2O_8$ 433.1605, found 431.1603.

*1′-(N⁶-Benzoyladenin-9-yl)-2′,3′-di(O-acetyl)-5′-O-benzyl-α-D-apio-L-furanose (**35**).* Using condition B, compound **24** (220 mg, 0.6 mmol) gave compound **35** (130 mg, 40%) and **36** (20 mg, 6%): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.04 (s, 3H, Ac), 2.07 (s, 3H, Ac), 3.94−4.04 (2d, J = 10.0 Hz, 2H, 5′-H), 4.37 (d, J = 10.5 Hz, 1H, 4′-H), 4.59 (s, 2H, CH_2Ph), 4.71 (d, J = 10.5 Hz, 1H, 4′-H), 6.13 (d, J = 4.4 Hz, 1H, 2′-H), 6.17 (d, J = 4.1 Hz, 1H, 1′-H), 7.31−7.39 (m, 5H, CH_2*Ph*), 7.51−7.56 (m, 2H, H_m Bz), 7.58−7.62 (m, 1H, H_p Bz), 8.00−8.05 (m, 2H, H_o Bz) 8.23 (s, 1H, 8-H), 8.82 (s, 1H, 2-H), 9.01 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 20.5 (Ac- CH_3), 21.5 (Ac-CH_3), 66.3 (5′-C) 73.8 (CH_2Ph & 4′-C), 78.7 (2′-C), 86.4 (3′-C), 87.9 (1′-C), 123.1 (5-C), 127.8 (C_o Bn) 127.8 (C_o Bz), 128.1 (C*p* Bn), 128.5 (C_m Bn), 128.9 (C_m Bz), 132.8 (C_m Bz), 133.6 (C_{ipso} Bn), 137.3 (C_{ipso} Bz), 141.1 (8-C), 149.5 (4-C), 151.8 (6-C), 152.9 (2-C), 164.5 (N^6COPh), 168.9 ($COCH_3$), 169.9 ($COCH_3$); HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{28}H_{28}N_5O_7$ 546.1989, found 546.2000. Spectral data for compound 1′-(N^6-benzoyladenin-9-yl)-2′-(*O*-trimethylsilyl)-3′-(*O*-acetyl)-5′-*O*-benzyl-α-D-apio-L-furanose (**36**): ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.14 (s, 9H, 2′-OSi$(CH_3)_3$) 1.89 (s, 3H, 3′-Ac) 3.96 (d, J = 10.0 Hz, 1H, 5′-H) 4.05 (d, J = 9.7 Hz, 1H, 5′-H) 4.34 (d, J = 10.5 Hz, 1H, 4′-H) 4.49 (d, J = 11.7 Hz, 1H, CH_2Ph) 4.57 (d, J = 12.0 Hz, 1H, CH_2Ph) 4.71 (d, J = 10.5 Hz, 1H, 4′-H) 5.05 (d, J = 2.6 Hz, 1H, 2′-H) 6.04 (d, J = 2.6 Hz, 1H, 1′-H) 7.27−7.39 (m, 5H, CH_2*Ph*) 7.50−7.56 (m, 2H, H_m Bz) 7.57−7.62 (m, 1H, H_p Bz) 8.00−8.06 (m, 2H, H*o* Bz) 8.15 (s, 1H, 8-H) 8.81 (s, 1H, 2-H) 9.08 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm −0.1 ($SiCH_3$), 21.6 (Ac-CH_3), 66.0 (5′-C), 73.7 (CH_2Ph), 74.4 (4′-C), 79.0 (2′-C), 88.1 (3′-C), 91.7 (1′-C), 123.4 (5-C), 127.7 (C_p Bn), 127.85

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(C_o Bz), 127.86 (C_o Bn), 128.4 (C_m Bn), 128.9 (C_m Bz), 132.8 (C_p Bz), 133.7 (C_{ipso} Bn), 137.6 (C_{ipso} Bz), 141.3 (8-C), 149.4 (4-C), 151.3 (6-C), 152.7 (2-C), 164.6 (N^6Bz-CO), 170.0 (Ac-CO); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{29}H_{34}N_5O_6Si$ 576.2278, found 576.2291.

1′-(Thymin-1-yl)-3′-deoxy-5′-O-benzyl-α-D-apio-L-furanose (**37**). Acetyl protected compound **29** (400 mg, 1.07 mmol) was dissolved in 7 N ammonia in MeOH (15 mL). The mixture was stirred at room temperature until completion (for about 3−5 h) as indicated by TLC. Solvent was evaporated, and the residue was purified by flash column chromatography using 0.5−1% MeOH−CH_2Cl_2 to afford the title compound **37** (341 mg, 96%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.83 (d, J = 1.2 Hz, 3H, 5-CH_3), 2.27−2.49 (m, 1H, 3′-H), 3.57 (dd, J = 9.2, 7.8 Hz, 1H, 5′-H), 3.78 (dd, J = 9.2, 6.0 Hz, 1H, 5′-H), 4.03 (dd, J = 10.5, 8.5 Hz, 1H, 4′-H), 4.29−4.38 (m, 2H, 4′-H and 2′-H), 4.45 (s, 2H, CH_2Ph), 5.02 (br s, 1H, 2′−OH), 5.67 (s, 1H, 1′-H), 7.11 (d, J = 1.2 Hz, 1H, 6-H), 7.19−7.30 (m, 5H, CH_2Ph), 10.44 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 12.6 (5-CH_3), 41.3 (3′- C), 66.6 (5′-C), 72.9 (4′-C), 73.6 (CH_2Ph), 75.8 (2′-C), 94.3 (1′-C), 110.5 (5-C), 127.72 (CH_2Ph), 127.74 (CH_2Ph), 128.4 (CH_2Ph), 134.7 (6- C), 137.9 (CH_2Ph), 150.6 (2-C), 164.5 (4-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{17}H_{21}N_2O_5$ 333.1450, found 333.1458.

1′-(Adenin-9-yl)-3′-deoxy-5′-O-benzyl-α-D-apio-L-furanose (**38**). Compound **30** (1.0 g, 2.05 mmol) was dissolved in 7 N ammonia in MeOH (30 mL). The mixture was stirred at room temperature for 48 h. Solvent was evaporated, and the residue was purified by flash column chromatography using 2% MeOH−CH_2Cl_2 to afford the title compound **38** (650 mg, 75%) as a white foam [procedure to remove acetamide residue if any: suspend the product in water and then collect it by filtration]: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.75−2.89 (m, 1H, 3′-H), 3.53 (t, J = 8.8 Hz, 1H, 5′-H), 3.73 (dd, J = 9.4, 5.9 Hz, 1H, 5′-H), 3.86 (t, J = 8.2 Hz, 1H, 4′-H), 4.40 (t, J = 7.8 Hz, 1H, 4′-H), 4.45−4.56 (m, 2H, Bn H), 4.63 (td, J = 5.3, 2.1 Hz, 1H, 2′-H), 5.76 (d, J = 4.7 Hz, 1H, 2′−OH), 5.90 (d, J = 2.3 Hz, 1H, 1′-H), 7.26 (br s, 2H, NH), 7.27−7.39 (m, 5H, CH_2Ph), 8.15 (s, 1H, 2-H), 8.23 (s, 1H, 8-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 41.7 (3′-C), 66.8 (5′-C), 71.1 (4′-C), 72.3 (Bn C), 74.4 (2′-C), 91.1 (1′-C), 119.2 (5-C), 127.4 (C_o Bn), 127.5 (C_p Bn), 128.2 (C_m Bn), 138.5 (C_{ipso} Bn), 139.0 (8-C), 148.8 (4-C), 152.5 (2-C), 156.0 (6-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{17}H_{20}N_5O_3$ 342.1566, found 342.1565.

1′-(Thymin-1-yl)-5′-O-benzyl-α-D-apio-L-furanose (**39**). Following a similar procedure described for compound **37**, compound **34** (100 mg, 0.23 mmol) gave compound **39** (81 mg, 86%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.81 (d, J = 0.9 Hz, 3H, 5-CH_3), 3.60 (d, J = 9.7 Hz, 1H, 4′-H), 3.85 (d, J = 9.7 Hz, 1H, 4′-H), 3.90 (d, J = 1.2 Hz, 1H, 3′−OH), 4.06 (dd, J = 9.4, 1.5 Hz, 1H, 5′-H), 4.17 (d, J = 9.4 Hz, 1H, 5′-H), 4.41 (d, J = 3.5 Hz, 1H, 2′-H), 4.50−4.69 (app-q, J = 12.0 Hz, 2H, CH_2Ph), 5.25 (d, J = 3.5 Hz, 1H, 2′−OH), 5.72 (s, 1H, 1′-H), 7.23−7.37 (m, 5H, CH_2Ph), 7.52 (d, J = 1.2 Hz, 1H, 6-H), 10.81 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 12.4 (5-CH_3), 69.6 (4′-C), 73.7 (CH_2Ph), 77.0 (5′-C), 80.0 (2′-C), 80.5 (3′-C), 94.4 (1′-C), 108.6 (5-C), 127.77 (C_o Bn), 127.84 (C_p Bn), 128.4 (C_m Bn), 137.55 (C_{ipso} Bn), 137.62 (6-C) 151.3 (2-C), 164.8 (4-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{17}H_{21}N_2O_6$ 349.1400, found 349.1384.

1′-(Adenin-9-yl)-5′-O-benzyl-α-D-apio-L-furanose (**40**). Following a similar procedure described for compound **38**, compound **35** (120 mg, 0.22 mmol) gave compound **40** (73 mg, 93%) as a white foam. The same procedure was employed to convert **36** to **40**: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.57−3.70 (2d, J = 9.7 Hz, 2H, 5′-H), 4.00 (d, J = 8.8 Hz, 1H, 4′-H), 4.11 (d, J = 9.1 Hz, 1 H4′-H), 4.39 (dd, J = 5.3, 2.9 Hz, 1H, 2′-H) 4.51−4.64 (2d, J = 12.3 Hz, 2H, CH_2Ph), 5.59 (s, 1H, 3′−OH), 5.90 (d, J = 2.9 Hz, 1H, 1′-H), 5.97 (d, J = 5.6 Hz, 1H, 2′−OH), 7.27 (s, 2H, NH), 7.28−7.43 (m, 5H, CH_2Ph) 8.15 (s, 1H, 2-H), 8.29 (s, 1H, 8-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 71.1 (5′-C), 72.7 (CH_2Ph), 75.6 (4′-C), 79.8 (3′-C), 80.3 (2′-C), 90.7 (1′-C), 118.8 (5-C), 127.3 (C_p Bn), 127.4 (C_o Bn), 128.2 (C_m Bn), 138.5 (C_{ipso} Bn), 139.7 (8-C), 149.0 (4-C), 152.5 (2-C), 156.0 (6-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{17}H_{20}N_5O_4$ 358.1515, found 358.1512.

1′-(Thymin-1-yl)-3′-deoxy-α-D-apio-L-furanose (**5a**).[11] Compound **37** (300 mg, 0.9 mmol) was dissolved in MeOH (10 mL), to this was added Pd−C (300 mg, 10% Pd, wet ∼50%). A stream of hydrogen gas was bubbled through the reaction mixture with vigorous stirring for about 1 h, and the mixture was then stirred under hydrogen atmosphere overnight at room temperature. The catalyst was filtered off, the filtrate was concentrated and purified by silica-gel flash column chromatography eluting with 6−8% MeOH−CH_2Cl_2 to afford compound **5a** (190 mg, 86%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.79 (d, J = 1.2 Hz, 3H, 5-CH_3), 2.22−2.36 (m, 1H, 3′-H), 3.46 (ddd, J = 10.8, 7.7, 5.3 Hz, 1H, 5′-H), 3.62−3.71 (m, 1H, 5′-H), 3.76 (t, J = 8.6 Hz, 1H, 4′-H), 4.18 (td, J = 5.0, 2.1 Hz, 1H, 2′-H), 4.33 (t, J = 7.8 Hz, 1H, 4′-H), 4.51 (t, J = 5.1 Hz, 1H, 5′−OH), 5.51 (d, J = 4.7 Hz, 1H, 2′−OH), 5.61 (d, J = 2.1 Hz, 1H, 1′-H), 7.38 (d, J = 1.2 Hz, 1H, 6-H), 11.27 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 12.1 (5-CH_3), 43.6 (3′-C), 57.6 (5′-C), 71.1 (4′-C), 74.2 (2′-C), 92.2 (1′-C), 108.9 (5-C), 135.7 (6-C), 150.3 (2-C), 163.9 (4-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_{15}N_2O_5$ 243.0981, found 243.0990.

1′-(Adenin-9-yl)-3′-deoxy-α-D-apio-L-furanose (**5b**). Compound **38** (450 mg, 1.32 mmol) was dissolved in 1:1 v/v mixture of MeOH−formic acid (40 mL), to this was added $Pd(OH)_2$-C (300 mg, 10% Pd, wet ∼50%) and stirred at 55 °C for 5−8 h. The catalyst was filtered off, and the filtrate was concentrated. The residue contained compound **5b** and **41** as a mixture. The residue was dissolved in 7 N NH_3−MeOH and stirred at room temperature for 3 h. The volatiles were evaporated, and the residue purified by silica-gel flash column chromatography eluting with 10−12% MeOH−CH_2Cl_2 to afford compound **5b** (265 mg, 80%) as a white solid. Spectral data for 1′-(adenin-9-yl)-3′-deoxy-5′-*O*-formyl-α-D-apio-L-furanose (**41**): ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.82−3.00 (m, 1H, 3′-H), 3.86 (t, J = 8.2 Hz, 1H, 4′-H), 4.21 (dd, J = 11.0, 7.8 Hz, 1H, 5′-H), 4.32−4.46 (m, 2H, 4′ and 5′-H's), 4.70 (br s, 1H, 2′-H), 5.93 (d, J = 2.1 Hz, 1H, 1′-H), 7.28 (s, 2H, NH), 8.15 (s, 1H, 2-H), 8.24 (s, 1H, 5′−OCOH), 8.25 (s, 1H, 8-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 41.3 (3′-C), 61.3 (5′-C), 71.1 (4′-C), 74.7 (2′-C), 91.8 (1′-C), 119.7 (5-C), 139.9 (8-C), 149.4 (4-C), 153.3 (2-C), 156.5 (6-C), 162.8 (5′-OCOH); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{11}H_{14}N_5O_4$ 280.1046, found 280.1046. Spectral data for 1-(adenin-9-yl)-3′-deoxy-α-D-apio-L-furanose (**5b**): ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.53−2.66 (m, 1H, 3′-H), 3.52 (t, J = 8.8 Hz, 1H, 5′-H), 3.67−3.77 (m, 1H, 5′-H), 3.86 (t, J = 8.2 Hz, 1H, 4′-H), 4.35 (t, J = 7.8 Hz, 1H, 4′-H), 4.54 (br s, 1H, 5′−OH), 4.63 (br s, 1H, 2′-H), 5.64 (d, J = 4.7 Hz, 1H, 2′−OH), 5.89 (d, J = 2.3 Hz, 1H, 1′-H), 7.25 (br s, 2H, NH_2), 8.15 (s, 1H, 2-H), 8.22 (s, 1H, 8-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 44.1 (3′-C), 57.6 (5′-C), 70.8 (4′-C), 74.4 (2′-C), 91.1 (1′-C), 119.2 (5- C), 138.9 (8-C), 148.8 (4-C), 152.5 (2-C), 156.0 (6-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_{14}N_5O_3$ 252.1097, found 252.1090.

1′-(Thymin-1-yl)-α-D-apio-L-furanose (**6a**). Following a similar procedure described for compound **5a**, compound **39** (210 mg, 0.60 mmol) gave compound **6a** (110 mg, 71%) as a white foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.77 (d, J = 1.2 Hz, 3H, 5-CH_3), 3.54 (s, 2H, 5′-H), 3.88 (d, J = 9.1 Hz, 1H, 4′-H), 3.93 (br s, 1H, 2′-H), 3.98 (d, J = 9.1 Hz, 1 H), 4.57 (br s, 1H, 3′−OH), 5.04 (s, 1H, 5′−OH), 5.67 (d, J = 2.6 Hz, 1H, 1′-H), 5.72 (d, J = 4.7 Hz, 1H, 2′−OH), 7.62 (d, J = 1.2 Hz, 1H, 6-H), 11.25 (br s, 1H, NH).^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 13.0 (5-CH_3), 63.0 (5′-C), 76.5 (4′-C), 80.5 (2′-C), 81.0 (3′-C), 93.0 (1′-C), 108.7 (5-C), 137.9 (6-C), 151.2 (2-C), 164.6 (4-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_{15}N_2O_6$ 259.0930, found 259.0927.

1′-(Adenin-9-yl)-α-D-apio-L-furanose (**6b**).[46] Compound **40** (20 mg, 0.056 mmol) was dissolved in 9:1 v/v mixture MeOH−formic acid (2 mL), to this was added $Pd(OH)_2$-C (20 mg, 10% Pd, wet ∼50%) and stirred at 55 °C for 5−8 h. The catalyst was filtered off, the filtrate was concentrated, and the residue was purified by silica-gel flash column chromatography eluting with 10−14% MeOH−CH_2Cl_2 to afford compound **6b** (12 mg, 80%) as a white solid: ^{1}H NMR (300

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MHz, DMSO-d_6) δ ppm 3.62 (d, J = 5.6 Hz, 2H, 5′-H), 3.98 (d, J = 9.1 Hz, 1H, 4′-H), 4.04 (d, J = 9.1 Hz, 1H, 4′-H), 4.38 (br s, 1H, 2′-H), 4.64 (t, J = 5.7 Hz, 1H, 5′−OH), 5.36 (s, 1H, 3′−OH), 5.85 (d, J = 4.7 Hz, 1H, 2′−OH), 5.90 (d, J = 2.9 Hz, 1H, 1′-H), 7.26 (s, 2H, NH), 8.15 (s, 1H, 2-H), 8.31 (s, 1H, 8-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 62.0 (5′-C), 75.3 (4′-C), 80.1 (2′-C), 80.3 (3′-C), 90.6 (1′-C), 118.7 (5-C), 139.6 (8-C), 149.0 (4-C), 152.3 (2-C), 155.9 (6-C); HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{10}H_{14}N_5O_4$ 268.1046, found 268.1036.

1′-(Thymin-1-yl)-3′-deoxy-5′-O-benzyl-β-D-apio-D-furanose (**42**). Using Vorbrüggen coupling condition A and then following procedure described for **37**, compound **28** (550 mg, 1.78 mmol) gave **42** (360 mg, 60%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.84 (d, J = 0.7 Hz, 3H, 5−CH_3), 2.68 (ddt, J = 12.7, 7.7, 6.4 Hz, 1H, 3′-H), 3.51 (dd, J = 9.5, 6.6 Hz, 1H, 5′-H), 3.59 (dd, J = 9.5, 5.0 Hz, 1H, 5′-H), 4.01 (dd, J = 8.8, 7.9 Hz, 1H, 4′-H), 4.22 (dd, J = 6.2, 3.9 Hz, 1H, 2′-H), 4.32 (dd, J = 8.8, 7.8 Hz, 1H, 4′-H), 4.50 (s, 2H, PhCH_2), 5.60 (d, J = 3.8 Hz, 1H, 1′-H), 7.24 (d, J = 1.3 Hz, 1H, 6-H), 7.26−7.38 (m, 5H, *Ph*CH$_2$), 9.77 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 12.5 (5-CH_3), 46.4 (3′-C), 68.6 (5′-C), 71.4 (4′-C), 73.3 (PhCH_2), 79.2 (2′-C), 94.3 (1′-C), 110.4 (5-C), 127.7, 127.9, 128.5 (*Ph*CH$_2$) 135.0 (6-C) 137.8 (*Ph*CH_2), 151.6 (2-C), 164.1 (4-C); HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{17}H_{21}N_2O_5$ 333.1450, found 333.1452.

1′-(Adenin-9-yl)-3′-deoxy-5′-O-benzyl-β-D-apio-D-furanose (**43**). Using Vorbrüggen coupling condition B and then following procedure described for **38**, compound **28** (1.55 g, 5 mmol) gave **43** (480 mg, 28%) and its α-anomer (200 mg, 11%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.60 (quind, J = 8.1, 5.0 Hz, 1H, 3′-H), 3.61 (t, J = 8.5 Hz, 1H, 5′-H), 3.70 (dd, J = 9.7, 5.0 Hz, 1H, 5′-H), 4.05 (t, J = 8.8 Hz, 1H, 4′-Hb), 4.17 (t, J = 8.2 Hz, 1H, 4′-Ha), 4.51 (s, 2H, PhCH_2), 4.70 (dt, J = 7.6, 5.7 Hz, 1H, 2′-H), 5.69 (d, J = 5.9 Hz, 1H, 2′−OH), 5.79 (d, J = 5.6 Hz, 1H, 1′-H), 7.26 (s, 2H, NH_2), 7.29−7.40 (m, 5H, *Ph*CH$_2$), 8.13 (s, 1H, 2-H), 8.31 (s, 1H, 8-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 46.7 (3′-C), 69.2 (5′-C), 70.5 (4′-C), 72.2 (PhCH$_2$), 75.1 (2′-C), 90.0 (1′-C), 119.2 (5-C), 127.44, 127.46, 128.3, 138.3 (*Ph*CH$_2$), 139.8 (8-C), 149.4 (4-C), 152.6 (2-C), 156.0 (6-C); HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{17}H_{20}N_5O_3$ 342.1566, found 342.1553. Spectral data for 1′-(adenin-9-yl)-3′-deoxy-5′-*O*-benzyl-α-D-apio-D-furanose: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.69−2.83 (m, 1H, 3′-H), 3.55 (dd, J = 9.5, 7.2 Hz, 1H, 5′-H), 3.66 (dd, J = 9.5, 5.1 Hz, 1H, 5′-H), 3.73 (dd, J = 8.5, 7.0 Hz, 1H, 4′-Hb), 4.29 (q, J = 5.6 Hz, 1H, 2′-H), 4.36 (t, J = 8.2 Hz, 1H, 4′-Ha), 4.54 (s, 2H, PhCH_2), 5.53 (d, J = 5.3 Hz, 1H, 2′−OH), 6.19 (d, J = 5.3 Hz, 1H, 1′-H), 7.22 (s, 2H, NH_2), 7.26−7.43 (m, 5H, *Ph*CH$_2$), 8.14 (s, 1H, 2-H), 8.16 (s, 1H, 8-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 45.3 (3′-C), 69.2 (4′-C), 69.4 (5′-C), 72.0 (2′-C) 72.2 (PhCH$_2$), 84.4 (1′-C), 118.2 (5-C), 127.48, 127.54, 128.3, 138.3 (*Ph*CH$_2$), 140.2 (8-C), 149.6 (4-C), 152.4 (2-C), 155.8 (6-C).

1′-(Thymin-1-yl)-5′-O-benzyl-β-D-apio-D-furanose (**44**). Using Vorbrüggen coupling condition A and then following procedure described for **37**, compound **17** (500 mg, 1.36 mmol) rendered **44** (460 mg, 97%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.89 (d, J = 1.2 Hz, 3H, 5−CH_3), 3.49 (d, J = 0.9 Hz, 1H, 3′−OH), 3.52 (s, 2H, 5′-H), 4.07 (d, J = 9.7 Hz, 1H, 4′-H$_b$), 4.24 (dd, J = 10.0, 0.9 Hz, 1H, 4′-H$_a$), 4.27 (dd, J = 5.6, 3.8 Hz, 1H, 2′-H), 4.38 (d, J = 4.1 Hz, 1H, 2′−OH), 4.56 (s, 2H, PhCH_2), 5.71 (d, J = 5.9 Hz, 1H, 1′-H), 7.22 (d, J = 1.2 Hz, 1H, 6-H), 7.27−7.40 (m, 5H, *Ph*CH$_2$), 9.18 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 12.5 (5-CH_3), 71.0 (5′-C), 73.7 (PhCH$_2$), 75.7 (4′-C), 76.9 (2′-C), 78.1 (3′-C), 92.4 (1′-C), 111.0 (5-C), 127.8, 128.0, 128.6, 137.4 (*Ph*CH$_2$), 135.5 (6-C), 151.5 (2-C), 163.7 (4-C); HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{17}H_{21}N_2O_6$ 349.1400, found 349.1414.

1′-(Adenin-9-yl)-5′-O-benzyl-β-D-apio-D-furanose (**45**). Using Vorbrüggen coupling condition B and then following procedure described for **38**, compound **17** (2.7 g, 7.37 mmol) rendered **45** (1.2 g, 46%) as a white foam: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.53 (q, J = 10.0 Hz, 2H, 5′-H), 3.83 (d, J = 9.1 Hz, 1H, 4′-H), 4.36 (d, J = 10.0 Hz, 1H, 4′-H), 4.58 (s, 2H, PhCH_2), 4.89 (t, J = 7.2 Hz, 1H, 2′-H), 5.08 (s, 1H, 3′−OH), 5.53 (d, J = 6.7 Hz, 1H, 2′−OH), 5.88 (d, J = 7.6 Hz, 1H, 1′-H), 7.19−7.29 (br.s, 2H, NH_2), 7.29−7.45 (m, 5H, *Ph*CH$_2$), 8.14 (s, 1H, 2-H), 8.34 (s, 1H, 8-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 71.3 (5′-C), 72.4 (PhCH$_2$), 73.8 (2′-C), 74.8 (4′-C), 77.5 (3′-C), 87.8 (1′-C), 119.4 (5-C), 127.3, 127.4, 128.2, 138.4 (*Ph*CH$_2$), 140.3 (8-C), 149.6 (4-C), 152.6 (2-C), 156.1 (6-C); HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{17}H_{20}N_5O_4$ 358.1515, found 358.1516.

1′-(Thymin-1-yl)-3′-deoxy-β-D-apio-D-furanose (**2a**).[11] Following the procedure described for the synthesis of **5a**, compound **42** (350 mg, 1.05 mmol) gave **2a** (220 mg, 86%) as a white solid: ^{1}H NMR (300 MHz, CD_3OD) δ ppm 1.89 (d, J = 1.2 Hz, 3H, 5-CH_3) 2.39−2.55 (m, 1H, 3′-H), 3.65 (dd, J = 10.8, 6.7 Hz, 1H, 5′-H), 3.73 (dd, J = 11.0, 4.8 Hz, 1H, 5′-H), 4.02−4.10 (t, J = 8.2 Hz, 1H, 4′-H), 4.17−4.26 (m, 2H, 2′ and 4′-H's), 5.72 (d, J = 5.6 Hz, 1H, 1′-H), 7.46 (d, J = 1.2 Hz, 1H, 6-H); ^{13}C NMR (75 MHz, CD_3OD) δ ppm 11.2 (5-CH_3), 48.3 (3′-C), 60.5 (5′-C), 70.3 (4′-C), 75.7 (2′-C), 92.3 (1′-C), 110.4 (5-C), 137.1 (6-C), 151.6 (2-C), 165.2 (4-C); HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{10}H_{15}N_2O_5$ 243.0981, found 243.0975.

1′-(Adenin-9-yl)-3′-deoxy-β-D-apio-D-furanose (**2b**).[8] Following the procedure described for the synthesis of **5b**, compound **43** (600 mg, 1.76 mmol) gave **2b** (390 mg, 88%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.34−2.48 (m, 1H, 3′-H), 3.56 (dd, J = 10.7, 7.8 Hz, 1H, 5′-H), 3.68 (dd, J = 10.7, 4.5 Hz, 1H, 5′-H), 4.04 (t, J = 8.8 Hz, 1H, 4′-H), 4.13 (t, J = 8.2 Hz, 1H, 4′-H), 4.62 (t, J = 6.4 Hz, 1H, 2′-H), 4.79 (br.s, 1H, 5′−OH), 5.61 (br.s, 1H, 2′−OH), 5.79 (d, J = 5.6 Hz, 1H, 1′-H), 7.26 (s, 2H, NH_2), 8.15 (s, 1H, 2-H), 8.31 (s, 1H, 8-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 49.0 (3′-C), 60.2 (5′-C), 70.3 (4′-C), 75.1 (2′-C), 90.0 (1′-C), 119.2 (5-C), 139.6 (8-C), 149.5 (4-C), 152.6 (2-C), 156.0 (6-C); HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{10}H_{14}N_5O_3$ 252.1097, found 252.1081.

1′-(Adenin-9-yl)-β-D-apio-D-furanose (**3b**).[46] Following the procedure described for the synthesis of **6b**, compound **45** (1.2 g, 3.37 mmol) rendered title compound **3b** (800 mg, 89%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.46 (q, J = 11.1 Hz, 1H, 5′-H), 3.76 (d, J = 9.1 Hz, 1H, 4′-H), 4.31 (d, J = 9.4 Hz, 1H, 4′-H), 4.80 (t, J = 6.4 Hz, 1H, 2′-H), 4.85 (s, 1H, 3′−OH), 4.91 (br.s, 1H, 5′−OH), 5.42 (d, J = 6.4 Hz, 1H, 2′−OH), 5.88 (d, J = 7.6 Hz, 1H, 1′-H), 7.26 (s, 2H, NH_2), 8.15 (s, 1H, 2-H), 8.33 (s, 1H, 8-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 62.4 (5′-C), 73.4 (2′-C), 74.5 (4′-C), 78.2 (3′-C), 87.7 (1′-C), 119.3 (5-C), 139.9 (8-C), 149.7 (4-C), 152.6 (2-C), 156.0 (6-C); HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{10}H_{14}N_5O_4$ 268.1046, found 268.1066.

1′-(Thymin-1-yl)-2′,3′-(O-thiocarbonyl)-5′-(O-benzyl)-β-D-apio-D-furanose (**46**). To a solution of **44** (200 mg, 0.57 mmol) in DMF (4 mL) was added thiocarbonyldiimidazole (112 mg, 0.63 mmol), and the mixture was heated to 80 °C for 90 min. The volatiles were removed under reduced pressure, and the residue was purified by silica-gel column chromatography (2% MeOH in CH_2Cl_2) to afford the title thiocarbonate **46** (200 mg, 89%) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.94 (d, J = 1.2 Hz, 3H, 5−CH_3), 3.89 (d, J = 11.1 Hz, 1H, 5′-H), 4.17 (d, J = 10.8 Hz, 1H, 5′-H), 4.30−4.42 (m, 2H, 4′-H), 4.57−4.71 (m, 2H, PhCH_2), 5.47 (d, J = 0.9 Hz, 1H, 1′-H), 5.82 (d, J = 1.2 Hz, 1H, 2′-H), 7.03 (d, J = 1.2 Hz, 1H, 6-H), 7.27−7.38 (m, 5H, *Ph*CH$_2$), 9.35 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 12.3 (5-CH_3), 67.7 (5′-C), 73.7 (PhCH$_2$), 77.4 (4′-C), 88.7 (2′-C), 97.5 (1′-C), 100.2 (3′-C), 112.2 (5-C), 127.6, 128.0, 128.5, 137.1 (*Ph*CH$_2$), 139.4 (6-C), 151.2 (2-C), 163.6 (4-C), 189.4 (*CS*). MS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{18}H_{19}N_2O_6S$ 391.0964, found 391.0958.

1′-(Adenin-9-yl)-2′,3′-(O-thiocarbonyl)-5′-(O-benzyl)-β-D-apio-D-furanose (**47**). Following the procedure described for the synthesis of **46**, compound **45** (300 mg, 0.84 mmol) rendered title compound **47** (260 mg, 78%) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.03 (d, J = 10.8 Hz, 1H, 5′-H), 4.33 (d, J = 11.1 Hz, 1H, 4′-H), 4.42 (d, J = 11.1 Hz, 1H, 4′-H), 4.45 (d, J = 10.5 Hz, 1H, 5′-H), 4.61, 4.75 (d, J = 12.3 Hz, 2H, PhCH_2), 5.74 (br.s, 2H, NH_2), 6.14 (s, 1H, 2′-H), 6.20 (s, 1H, 1′-H), 7.29−7.40 (m, 5H, *Ph*CH$_2$), 7.87 (s, 1H, 8-H) 7.95 (s, 1H, 2-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 67.0 (5′-C), 73.9 (PhCH$_2$), 75.0 (4′-C), 88.3 (2′-C), 90.3 (1′-C), 99.6 (3′-C), 119.9 (5-C), 128.0, 128.2, 128.6, 136.9 (*Ph*CH$_2$), 140.3 (8-C), 149.1

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(4-C), 153.0 (2-C), 155.6 (6-C), 189.4 (CS); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{18}H_{18}N_5O_4S$ 400.1079, found 400.1060.

1′-(Thymin-1-yl)-2′,3′-(dideoxydidehydro)-5′-(O-benzyl)-β-D-apio-D-furanose (48). A solution of compound **46** (180 mg, 0.46 mmol) in trimethylphosphite ($P(OCH_3)_3$, 8.0 mL) was heated to 120 °C for 6 h. The volatile materials were removed under reduced pressure and then coevoporated 2−3 times with toluene. The residue was purified by silica-gel column chromatography (0−2% MeOH in CH_2Cl_2) to afford **48** (130 mg, 90%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.91 (d, J = 1.2 Hz, 3H, 5−CH_3), 4.25 (s, 2H, 5′-H), 4.58 (s, 2H, PhCH_2), 4.63−4.74 (m, 1H, 4′-H), 4.77−4.90 (m, 1H, 4′-H), 5.67−5.76 (m, 1H, 2′-H) 6.91 (q, J = 1.2 Hz, 1H, 6-H), 7.00 (m, 1H, 1′-H), 7.29−7.44 (m, 5H, PhCH$_2$), 8.47 (br.s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 12.6 (5-CH_3), 65.1 (5′-CH_2), 73.2 (PhCH_2), 75.6 (4′-C), 90.9 (1′-C), 111.3 (5-C), 119.9 (2′-C), 127.8, 128.1, 128.6, 137.3 (PhCH$_2$), 135.3 (6-C), 145.4 (3′-C), 150.5 (2-C), 163.6 (4-C); HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{18}H_{19}N_2O_6S$ 337.1164, found 337.1168.

1′-(Thymin-1-yl)-2′,3′-(dideoxydihydro)-β/α-D-apio-D/L-furanose (1a + 4a). Following the procedure described for the synthesis of **25**, compound **48** (120 mg, 0.38 mmol) rendered **1a** and **4a** as inseparable mixtures in 4:1 ratio, respectively (77 mg, 89%), as a white solid.

1′-(Thymin-1-yl)-3′-deoxy-5′-O-(tert-butyldimethylsilyl)-α-D-apio-L-furanose (49). Compound **5a** (150 mg, 0.62 mmol) was dissolved in DMF (3.5 mL), to this was added imidazole (85 mg, 1.24 mmol) followed by *tert*-butyldimethylsilyl chloride (TBSCl, 112 mg, 0.74 mmol). The mixture was stirred at room temperature for 18 h. DMF was evaporated under reduced pressure. The residue was partitioned between EtOAc and brine. Organic layer separated, dried over sodium sulfate, solvent evaporated, and the residue purified by silica-gel flash column chromatography using 1−2% MeOH−CH_2Cl_2 to afford compound **49** (210 mg, 95%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.07 (2s, 6H, Si$(CH_3)_2$), 0.89 (S, 9H, C$(CH_3)_3$), 1.94 (d, J = 0.9 Hz, 3H, 5-CH_3), 2.32−2.46 (m, 1H, 3′-H), 3.84 (d, J = 10.3, 7.3 Hz, 1H, 5′-H), 3.97 (d, J = 10.3, 5.9 Hz, 1H, 5′-H), 4.10 (t, J = 8.5 Hz, 1H, 4′-H), 4.35 (t, J = 7.9 Hz, 1H, 4′-H), 4.39 (t, J = 4.1 Hz, 1H, 2′-H), 4.81 (d, J = 3.2 Hz, 1H, 2′−OH), 5.74 (s, 1H, 1′-H), 7.22 (d, J = 1.2 Hz, 1H, 6-H), 10.19 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm −5.51 (Si$(CH_3)_2$), −5.47 (Si$(CH_3)_2$), 12.7 (5-CH_3), 18.2 (C$(CH_3)_3$), 25.9 (C$(CH_3)_3$), 43.5 (3′-C), 59.8 (5′- C), 72.5 (4′-C), 76.1 (2′-C), 94.6 (1′-C), 110.5 (5-C), 134.8 (6-C), 150.7 (2-C), 164.4 (4-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{29}N_2O_5Si$ 357.1846, found 357.1852.

1′-(Adenin-9-yl)-3′-deoxy-5′-O-(tert-butyldimethylsilyl)-α-D-apio-L-furanose (50). Following a similar procedure described for compound **49**, compound **5b** (260 mg, 1.03 mmol) afforded compound **50** (310 mg, 82%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.10 (s, 3H, SiCH_3), 0.10 (s, 3H, SiCH_3), 0.91 (s, 9H, C$(CH_3)_3$), 2.65−2.78 (m, 1H, 3′-H), 3.97 (dd, J = 6.0, 1.3 Hz, 2H, 5′-H), 4.21 (dd, J = 8.4, 7.5 Hz, 1H, 4′-H), 4.39 (dd, J = 8.5, 7.3 Hz, 1H, 4′-H), 4.81 (dt, J = 5.7, 2.7 Hz, 1H, 2′-H), 5.15 (d, J = 3.2 Hz, 1H, 2′−OH), 5.94 (br s, 2H, NH), 5.97 (d, J = 2.6 Hz, 1H, 1′-H), 7.94 (s, 1H, 8-H), 8.32 (s, 1H, 2-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm −5.52 (SiCH_3), −5.50 (SiCH_3), 18.2 (C$(CH_3)_3$), 25.8 (C$(CH_3)_3$), 43.3 (3′-C), 60.0 (5′-C), 71.2 (4′-C), 77.1 (2′- C), 93.0 (1′-C), 120.3 (5-C), 138.4 (8-C), 149.0 (4-C), 152.7 (2-C), 155.5 (6-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{28}N_5O_3Si$ 366.1961, found 366.1941.

1′-(Thymin-1-yl)-3′-deoxy-5′-O-(tert-butyldimethylsilyl)-β-D-apio-D-furanose (51). Following a similar procedure described for compound **49**, compound **2a** (200 mg, 0.83 mmol) afforded compound **51** (260 mg, 88%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.05 (s, 6H, Si$(CH_3)_2$), 0.87 (s, 9H, C$(CH_3)_3$), 1.92 (d, J = 1.2 Hz, 3H, 5-CH_3), 2.51−2.66 (m, 1H, 3′-H), 3.69 (dd, J = 10.5, 6.2 Hz, 1H, 5′-H), 3.75 (dd, J = 10.3, 4.7 Hz, 1H, 5′-H), 3.94−4.07 (m, 2H, 4′-H and 2′−OH), 4.18 (ddd, J = 7.0, 4.0, 2.8 Hz, 1H, 2′-H), 4.28 (t, J = 8.4 Hz, 1H, 4′-H), 5.61 (d, J = 4.1 Hz, 1H, 1′-H), 7.27 (d, J = 1.2 Hz, 1H, 6-H), 9.42 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm −5.40, −5.35 (SiCH_3), 12.7 (5-CH_3), 18.3 (C$(CH_3)_3$), 25.9 (C$(CH_3)_3$), 48.4 (3′-C), 60.8 (5′-C), 71.0 (4′-C), 78.7 (2′-C), 94.4 (1′-C), 110.7 (5-C), 134.9 (6-C), 151.7 (2-C), 164.1 (4-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{29}N_2O_5Si$ 357.1846, found 357.1855.

1′-(Adenin-9-yl)-3′-deoxy-5′-O-(tert-butyldimethylsilyl)-β-D-apio-D-furanose (52). Following a similar procedure described for compound **49**, compound **2b** (350 mg, 1.39 mmol) afforded compound **52** (415 mg, 82%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.03, 0.04 (s's, 2 × 3H, Si$(CH_3)_3$), 0.85 (s, 9H, C$(CH_3)_3$), 2.64−2.79 (m, 1H, 3′-H), 3.76 (dd, J = 10.4, 6.3 Hz, 1H, 5′-H), 3.85 (dd, J = 10.4, 4.5 Hz, 1H, 5′-H), 4.15 (t, J = 9.1 Hz, 1H, 4′-H), 4.30−4.40 (t, J = 8.5 Hz, 1H, 4′-H), 4.52 (dd, J = 8.6, 5.7 Hz, 1H, 2′-H), 5.69 (br.s, 1H, 2′−OH), 5.79 (d, J = 5.9 Hz, 1H, 1′-H), 5.95 (s, 2H, NH_2), 7.97 (s, 1H, 8-H), 8.27 (s, 1H, 2-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm −5.53, −5.49 (SiCH_3), 18.2 (C$(CH_3)_3$), 25.8 (C$(CH_3)_3$), 47.7 (3′-C), 61.1 (5′-C), 71.1 (4′-C), 77.4 (2′-C), 92.8 (1′-C), 120.1 (5-C), 138.4 (8-C), 149.2 (4-C), 152.5 (2-C), 155.5 (6-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{28}N_5O_3Si$ 366.1961, found 366.1962.

1′-(Thymin-1-yl)-2′,3′-dideoxy-5′-O-benzyl-α-D-apio-L-furanose (53). To a solution of compound **37** (250 mg, 0.75 mmol) and DMAP (184 mg, 1.5 mmol) in acetonitrile (10 mL) was added dropwise *O*-*p*-tolyl chlorothionoformate (138 μL, 0.9 mmol) at room temperature. The mixture was stirred for additional 2 h, and then the volatile organics were evaporated under reduced pressure. The residue was suspended in EtOAc and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate, and the solvent evaporated to dryness. The residue obtained was suspended in toluene (25 mL), tributyltinhydride (0.51 mL, 1.88 mmol) was added followed by at 60−70 °C was added azoisobutyronitrile (AIBN, 250 mg, 1.5 mmol) and heated to 110−120 °C for 3 h. Volatile materials were evaporated, and the residue was purified by silica-gel flash column chromatography using 0.5−2% MeOH−CH_2Cl_2 to afford compound **53** (167 mg, 70%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.86 (d, J = 1.2 Hz, 3H, 5-CH_3), 2.06 (ddd, J = 13.8, 7.9, 3.8 Hz, 1H, 2′-H), 2.16 (ddd, J = 13.8, 7.5, 6.4 Hz, 1H, 2′-H), 2.52−2.68 (m, 1H, 3′-H), 3.36 (dd, J = 9.1, 7.3 Hz, 1H, 5′-H), 3.45 (dd, J = 9.1, 5.6 Hz, 1H, 5′-H), 3.74 (dd, J = 8.8, 7.0 Hz, 1H, 4′-H), 4.24 (dd, J = 8.8, 7.3 Hz, 1H, 4′-H), 4.45 (s, 2H, CH_2Ph), 5.96 (dd, J = 6.4, 4.1 Hz, 1H, 1′-H), 7.07 (d, J = 1.2 Hz, 1H, 6-H), 7.20−7.33 (m, 5H, CH$_2$$Ph$), 8.56 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 12.7 (5-CH_3), 35.9 (2′-C), 38.1 (3′-C), 70.8 (5′-C), 72.7 (4′-C), 73.4 (CH$_2$Ph), 87.0 (1′-C), 110.4 (5-C), 127.7 (CH$_2$$Ph$), 127.9 (CH$_2$$Ph$), 128.5 (CH$_2$$Ph$), 135.0 (6-C), 137.8 (CH$_2$$Ph$), 150.1 (2-C), 163.7 (4-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{17}H_{21}N_2O_4$ 317.1501, found 317.1499.

1′-(Adenin-9-yl)-2′,3′-dideoxy-5′-O-benzyl-α-D-apio-L-furanose (54). Following a similar procedure described for compound **53**, compound **38** (45 mg, 0.13 mmol) gave compound **54** (30 mg, 70%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.32 (ddd (dt), J = 13.9, 7.1 Hz, 1H, 2′-H), 2.68 (ddd, J = 13.6, 7.8, 2.9 Hz, 1H, 2′-H), 2.81−2.95 (m, 1H, 3′-H), 3.45−3.58 (m, 2H, 5′-H), 3.90 (dd, J = 8.8, 6.4 Hz, 1H, 4′-H), 4.34 (dd, J = 8.6, 7.5 Hz, 1H, 4′-H), 4.53 (s, 2H, CH_2Ph), 6.11 (br s, 2H, NH), 6.29 (dd, J = 6.9, 3.1 Hz, 1H, 1′-H), 7.27−7.39 (m, 5H, CH$_2$$Ph$), 7.90 (s, 1H, 8-H), 8.32 (s, 1H, 2- H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 35.5 (2′-C), 38.2 (3′-C) 71.0 (5′-C), 72.2 (4′-C), 73.3 (CH$_2$Ph), 85.9 (1′-C), 120.2 (5-C), 127.6 (CH$_2$$Ph$), 127.8 (CH$_2$$Ph$), 128.4 (CH$_2$$Ph$), 137.9 (CH$_2$$Ph$), 138.5 (8-C), 149.2 (4-C) 152.8 (2-C) 155.5 (6-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{17}H_{20}N_5O_2$ 326.1617, found 326.1611.

1′-(Thymin-1-yl)-2′,3′-dideoxy-5′-O-(tert-butyldimethylsilyl)-α-D-apio-L-furanose (55).[5] Following a similar procedure described for compound **53**, compound **49** (190 mg, 0.53 mmol) gave compound **55** (130 mg, 72%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.06 (s, 6H, Si$(CH_3)_2$), 0.90 (s, 9H, C$(CH_3)_3$), 1.94 (d, J = 1.3 Hz, 3H, 5-CH_3), 2.06 (ddd, J = 13.8, 8.2, 4.0 Hz, 1H, 2′-H), 2.25 (dt, J = 13.8, 6.9 Hz, 1H, 2′-H), 2.48−2.63 (m, 1H, 3′-H), 3.58 (dd, J = 10.0, 6.8 Hz, 1H, 5′-H), 3.66 (dd, J = 10.1, 5.2 Hz, 1H, 5′-H), 3.83 (dd, J = 8.8, 6.9 Hz, 1H, 4′-H), 4.26 (dd, J = 8.7, 7.2 Hz, 1H, 4′-H), 6.04 (dd, J = 6.6, 3.9 Hz, 1H, 1′-H), 7.16 (q, J = 1.3 Hz, 1H, 6-H), 8.88 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm −5.51 (SiCH_3), −5.48

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($SiCH_3$), 12.7 (5-CH_3), 18.2 ($C(CH_3)_3$), 25.8 ($C(CH_3)_3$), 35.3 (2′-C), 40.1 (3′-C), 63.4 (5′-C), 72.2 (4′-C), 87.1 (1′-C), 110.4 (5-C), 135.1 (6-C), 150.2 (2-C), 163.9 (4-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{29}N_2O_4Si$ 341.1897, found 341.1884.

*1′-(Adenin-9-yl)-2′,3′-dideoxy-5′-O-(tert-butyldimethylsilyl)-α-D-apio-L-furanose (**56**).*[3] Following a similar procedure described for compound **53**, compound **50** (300 mg, 0.82 mmol) gave compound **56** (253 mg, 88%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.07 (s, 6H, $Si(CH_3)_2$), 0.91 (s, 9H, $C(CH_3)_3$), 2.34 (ddd (dt), J = 13.7, 7.1 Hz, 1H, 2′-H), 2.62 (ddd, J = 13.3, 7.8, 2.9 Hz, 1H, 2′-H), 2.76 (dq, J = 13.5, 6.9 Hz, 1H, 3′-H), 3.60−3.74 (m, 2H, 5′-H), 3.92 (dd, J = 8.8, 6.4 Hz, 1H, 4′-H), 4.31 (dd, J = 8.5, 7.3 Hz, 1H, 4′-H), 5.70 (br s, 2H, NH), 6.30 (dd, J = 6.7, 2.9 Hz, 1H, 1′-H), 7.93 (s, 1H, 8-H), 8.36 (s, 1H, 2-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm −5.45 ($Si(CH_3)$), −5.42 ($Si(CH_3)$), 18.3 ($C(CH_3)_3$), 25.8 ($C(CH_3)_3$), 34.9 (2′-C), 40.4 (3′-C), 63.5 (5′-C), 71.8 (4′-C), 86.1 (1′-C), 120.3 (5-C), 138.6 (8-C), 149.4 (4-C), 153.0 (2-C), 155.4 (6-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{28}N_5O_2Si$ 350.2012, found 350.2006.

*1′-(Thymin-1-yl)-2′,3′-dideoxy-5′-(tert-butyldimethylsilyl)-β-D-apio-D-furanose (**57**).*[3] Following a similar procedure described for compound **53**, compound **51** (250 mg, 0.70 mmol) gave compound **57** (215 mg, 90%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.06 (s, 6H, $SiCH_3$), 0.89 (s, 9H, $C(CH_3)_3$), 1.77 (ddd, J = 13.3, 8.9, 7.2 Hz, 1H, 2′-H), 1.94 (d, J = 1.2 Hz, 3H, 5-CH_3), 2.43−2.55 (m, 1H, 2′-H), 2.55−2.72 (m, 1H, 3′-H), 3.60 (dd, J = 10.3, 5.9 Hz, 1H, 5′-H), 3.67 (dd, J = 10.3, 5.0 Hz, 1H, 5′-H), 3.94 (t, J = 7.8 Hz, 1H, 4′-H), 4.07 (t, J = 8.1 Hz, 1H, 4′-H), 6.06 (dd, J = 7.0, 6.4 Hz, 1H, 1′-H), 7.21 (q, J = 1.2 Hz, 1H, 6-H), 8.31 (br.s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm −5.47, −5.44 ($SiCH_3$), 12.6 (5-CH_3), 18.3 ($C(CH_3)_3$), 25.8 ($C(CH_3)_3$), 34.6 (2′-C), 40.9 (3′-C), 62.6 (5′-C), 71.0 (4′-C), 86.6 (1′-C), 110.9 (5-C), 134.9 (6-C), 150.3 (2-C), 163.8 (4-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{29}N_2O_4Si$ 341.1897, found 341.1891.

*1′-(Adenin-9-yl)-2′,3′-dideoxy-5′-(tert-butyldimethylsilyl)-β-D-apio-D-furanose (**58**).*[3] Following a similar procedure described for compound **53**, compound **52** (400 mg, 1.10 mmol) gave compound **58** (310 mg, 81%) as a white foam: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.05 (s, 6H, $SiCH_3$), 0.88 (s, 9H, $C(CH_3)_3$), 2.33−2.50 (m, 1H, 2′-H), 2.57−2.81 (m, 2H, 2′ and 3′-H's), 3.71 (d, J = 5.3 Hz, 2H, 5′-H), 4.04 (t, J = 8.2 Hz, 1H, 4′-H), 4.14 (t, J = 7.6 Hz, 1H, 4′-H), 5.82 (br.s, 2H, NH_2), 6.29 (t, J = 5.9 Hz,1H, 1′-H), 8.05 (s, 1H, 8-H), 8.36 (s, 1H, 2-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm −5.44 ($SiCH_3$), 18.3 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 34.6 (2′-C), 41.6 (3′-C), 63.0 (5′-C), 71.1 (4′-C), 85.5 (1′-C), 120.2 (5-C), 138.4 (8-C), 149.7 (4-C), 153.0 (2-C), 155.5 (6-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{28}N_5O_2Si$ 350.2012, found 350.2009.

*1′-(Thymin-1-yl)-2′,3′-dideoxy-α-D-apio-L-furanose (**4a**).*[3] Following the hydrogenation procedure described for compound **5a**, compound **53** (150 mg, 0.47 mmol) gave compound **4a** (80 mg, 63%) as a white solid. Alternatively, compound **55** (110 mg, 0.32 mmol) was dissolved in THF (2 mL) and TBAF (1M, 0.65 mL, 0.65 mmol) was added at room temperature. The reaction mixture was stirred for 3 h, solvents evaporated, and the residue was subjected to silica-gel flash column chromatography (4−5% MeOH−CH_2Cl_2) to afford **4a** (65 mg, 89%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.80 (d, J = 0.9 Hz, 3H, 5-CH_3), 1.96−2.13 (m, 2H, 2′-H), 2.45−2.60 (m, 1H, 3′-H), 3.33−3.48 (m, 2H, 5′-H), 3.63 (dd, J = 8.2, 6.2 Hz, 1H, 4′-H), 4.22 (dd, J = 8.2, 7.0 Hz, 1H, 4′-H), 4.76 (t, J = 5.3 Hz, 1H, 5′−OH), 5.97 (dd, J = 6.4, 4.7 Hz, 1H, 1′-H), 7.43 (d, J = 1.2 Hz, 1H, 6-H), 11.24 (s, 1H, NH); ^{13}C NMR (75 MHz, CD_3OD) δ ppm 12.6 (5-CH_3), 36.2 (2′-C), 41.7 (3′-C), 63.9 (5′-C), 73.3 (4′-C), 88.5 (1′-C), 111.4 (5-C), 137.9 (6-C), 152.4 (2-C), 166.7 (4-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_{15}N_2O_4$ 227.1032, found 227.1041.

*1′-(Adenin-9-yl)-2′,3′-dideoxy-α-D-apio-L-furanose (**4b**).*[3] Compound **56** (350 mg, 1.0 mmol) was dissolved in MeOH (15 mL) in a polypropylene vessel and NH_4F (742 mg, 20 mmol) was added at room temperature. The reaction mixture was stirred at 55 °C for 48 h; CH_2Cl_2 (20 mL) was added to the reaction vessel and filtered. The filtrate was evaporated, and the residue was subjected to silica-gel flash column chromatography (10−12% MeOH−CH_2Cl_2) to afford **4b** (205 mg, 87%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.21 (app-q, J = 6.7, 13.5 Hz, 1H, 2′-H), 2.54 (ddd, J = 3.5, 8.2, 12.9 Hz, 1H, 2′-H), 2.76 (sep, J = 6.4 Hz, 1H, 3′-H), 3.44 (m, 2H, 5′-H), 3.75 (dd, J = 5.3, 8.2 Hz, 1H, 4′-H), 4.18 (t, J = 7.9 Hz, 1H, 4′-H), 4.82 (t, J = 5.0 Hz, 1H, 5′−OH), 6.27 (dd, J = 3.2, 6.7 Hz, 1H, 1′-H), 7.24 (br s, 2H, 6-NH_2's), 8.15 (s, 1H, 2-H), 8.26 (s, 1H, 8-H); ^{13}C NMR (75 MHz, DMSO-d_6) 33.9 (2′-C), 40.4 (3′-C), 62.2 (5′-C), 70.9 (4′-C), 84.3 (1′-C), 119.2 (5-C), 139.2 (8-C), 148.9 (4-C), 152.5 (2-C), 156.0 (6-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_{14}N_5O_2$ 236.1147, found 236.1131.

*1′-(Thymin-1-yl)-2′,3′-dideoxy-β-D-apio-D-furanose (**1a**).*[3] Following a similar procedure described for the synthesis of compound **4b**, compound **57** (200 mg, 0.59 mmol) gave compound **1a** (115 mg, 86%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.71 (t, J = 4.7 Hz, 1H, 5′−OH), 1.74−1.86 (m, 1H, 2′-H), 1.94 (d, J = 1.5 Hz, 3H, 5-CH_3), 2.51−2.75 (m, 2H, 2′ and 3′-H's), 3.64−3.81 (m, 2H, 5′-H), 3.98 (dd, J = 8.8, 7.0 Hz, 1H, 4′-H), 4.07−4.16 (m, 1H, 4′-H), 6.02 (t, J = 6.6 Hz, 1H, 1′-H), 7.27−7.30 (q, J = 1.4 Hz, 1H, 6-H), 8.43 (br.s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 12.6 (5-CH_3), 34.7 (2′-C), 40.7 (3′-C), 63.2 (5′-C), 71.2 (4′-C), 86.9 (1′-C), 110.8 (5-C), 135.3 (6-C), 150.3 (2-C), 163.6 (4-C); HRMS (ESI-TOF) m/z $[M - H]^-$ Calcd for $C_{10}H_{13}N_2O_4$ 225.0881, found 225.0875.

*1′-(Adenin-9-yl)-2′,3′-dideoxy-α-D-apio-D-furanose (**1b**).*[3] Following a similar procedure described for the synthesis of compound **4b**, compound **58** (300 mg, 0.86 mmol) gave compound **1b** (190 mg, 94%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.25−2.39 (m, 1H, 2′-H), 2.52−2.67 (m, 2H, 2′ and 3′-H's), 3.48−3.65 (m, 2H, 5′-H), 3.89 (t, J = 8.2 Hz, 1H, 4′-H), 4.00 (t, J = 7.9 Hz, 1H, 4′-H), 4.82 (t, J = 5.1 Hz, 1H, 5′−OH), 6.23 (t, J = 6.7 Hz, 1H, 1′-H), 7.26 (s, 2H, NH_2), 8.15 (s, 1H, 2-H), 8.32 (s, 1H, 8-H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 33.7 (2′-C), 41.7 (3′-C), 61.7 (5′-C), 70.8 (4′-C), 84.3 (1′-C), 119.2 (5-C), 139.1 (8-C), 149.2 (4-C), 152.5 (2-C). 156.0 (6-C); HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_{14}N_5O_2$ 236.1147, found 236.1137.

*1′-(Adenin-9-yl)-2′,3′-dideoxy-β-D-apio-D-furanose triphosphate (**12**).* Compound **1b** (25 mg, 0.106 mmol) and tributylammonium pyrophosphate **60** (117 mg, 0.212 mmol) were placed in a 50 mL and a 10 mL RB flask respectively, and dried under a high vacuum for 1 h. 2-chloro-4H-1,3,2-benzodioxaphosphinin-4-one **59** (43 mg, 0.212 mmol) was placed in a separate 10 mL flask and dried briefly (10 min) under a high vacuum. Anhydrous DMF (0.25 mL) was added to each flask under argon atmosphere. Tributylamine (dried and stored over 4A molecular sieves, 0.3 mL) was added to the flask containing tributylammonium pyrophosphate (**60**) with stirring. The contents of this flask were added to the flask containing 2-chloro-4*H*-1,3,2-benzodioxaphosphinin-4-one (**59**) and stirring continued for 1.5 h. The cyclic phosphitodiphosphate (**61**) formed was added to a flask containing compound **4b** in DMF. After stirred for 1.5 h, 3% iodine solution (9:1 pyridine-water, 2.25 mL) was added dropwise and stirred for 20 min followed by the addition of water (4 mL) and stirred for additional 1.5 h. 3 M NaCl solution (0.66 mL) was added to the reaction mixture. The reaction mixture was transferred to two centrifuge tubes (∼4 mL each) and absolute ethanol (16 mL) was added to each tube, shaken well and immersed in powdered dry ice for 1 h. The tubes were centrifuged (20 °C, 3200 rpm, 20 min), and the clear solution decanted to afford crude product as white solid. The crude product was dissolved in distilled water (3.0 mL) and purified using Source-15Q ion exchange HPLC (0.5 mL injection, 0 → 5 min, 100% H_2O; 5 → 40 min, 100% H_2O to 100% 1 M triethylammonium bicarbonate buffer, linear gradient @flow rate 6 mL/min). The compound eluting at 33 min (or 0.8 M triethylammonium bicarbonate buffer) was collected and lyophilized to afford triethylammonium salt of triphosphate **12** as a white solid (17 mg, 21%) as highly hygroscopic colorless solid: ^{1}H NMR (300 MHz, D_2O) δ ppm 1.27 (t, J = 7.3 Hz, 24H, NCH_2CH_3), 1.33 (t, J = 7.3 Hz, 3H, NCH_2CH_3), 2.42 (ddd, J = 13.6, 8.6, 6.7 Hz, 1H, 2′-H), 2.74−2.89 (m, 1H, 2′-H), 2.89−3.12 (m, 3H, 3′-H & NCH_2CH_3), 3.19 (q, J = 7.3 Hz, 14H, NCH_2CH_3), 3.54 (q, J = 7.1 Hz, 2H, NCH_2CH_3), 4.05 (t, J = 8.6 Hz, 1H, 4′-H), 4.14

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(app-t, J = 6.2 Hz, 2H, 5′-H), 4.28 (t, J = 8.5 Hz, 1H, 4′-H), 6.35 (t, J = 6.7 Hz, 1H, 1′-H), 8.26 (s, 1H), 8.47 (s, 1H); ^{13}C NMR (75 MHz, D_2O) δ ppm 7.3, 8.4, 10.7 (NCH_2CH_3), 33.6 (2′-C), 39.3 (d, $J_{p\text{-}c}$ = 8.1 Hz, 3′-C), 42.4, 46.8 (NCH_2CH_3), 66.3 (d, $J_{p\text{-}c}$ = 5.9 Hz, 5′-C), 70.8 (4′-C), 85.1 (1′-C), 150.8, 154.3; ^{31}P NMR (121 MHz, D_2O) δ ppm −23.28 (br.s, 1P, β-P) −11.20, −11.04 (br. d, 2P, α & γ-P); HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{10}H_{15}N_5O_{11}P_3$ 473.9986, found 473.9987.

*1′-(Adenin-9-yl)-2′,3′-dideoxy-α-D-apio-L-furanose triphosphate (**13**).* Following the reaction protocol described for the synthesis of **12**, compound **4b** (25 mg, 0.106 mmol) afforded triethylammonium salt of triphosphate **13** as a white solid (45 mg, 48%): ^{1}H NMR (300 MHz, D_2O) δ ppm 1.21 (t, J = 7.3 Hz, 36H, $HN(CH_2CH_3)_3$), 2.46 (dt, J = 14.4, 7.3 Hz, 1H, 2′-H), 2.66 (ddd, J = 14.1, 8.1, 3.2 Hz, 1H, 2′-H), 3.10 (q, J = 7.3 Hz, 25H, 3′-H & $HN(CH_2CH_3)_3$), 3.95 (dd, J = 8.9, 6.3 Hz, 1H, 4′-H), 3.99−4.12 (m, 2H, 5′-H), 4.27 (dd, J = 8.8, 7.6 Hz, 1H, 4′-H), 6.37 (dd, J = 7.0, 3.2 Hz, 1 H), 8.16 (s, 1H, 2-H), 8.28 (s, 1H, 8-H); ^{13}C NMR (75 MHz, D_2O) δ ppm 8.4 ($HN(CH_2CH_3)_3$), 33.9 (2′-C), 38.4 (d, $J_{p\text{-}c}$ = 8.3 Hz, 3′-C), 46.7 ($HN(CH_2CH_3)_3$), 66.9 (d, $J_{p\text{-}c}$ = 6.1 Hz, 5′-C), 71.4 (4′-C), 85.3 (1′-C), 119.1 (5-C), 140.2 (8-C) 148.6 (4-C), 152.7 (2-C), 155.7 (6-C); ^{31}P NMR (121 MHz, D_2O) δ ppm −22.64 (dd, J = 21.1, 19.6 Hz, βP), −11.04 (d, J = 19.6 Hz, αP), −6.34 (d, J = 21.1 Hz, γP); HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{10}H_{15}N_5O_{11}P_3$ 473.9986, found 473.9982.

*1′-(Thymin-1-yl)-2′,3′-dideoxy-α-D-apio-D-furanose [phenyl-(benzoxy-L-alaninyl)]phosphate (**9a**).* To a solution of **1a** (0.048 g, 0.21 mmol) in anhydrous THF (4 mL) was added a solution of phosphorochloridate **64a**[38] (0.22g, 0.64 mmol) in anhydrous THF (2 mL), followed by the dropwise addition, under an argon atmosphere, of anhydrous NMI (0.88 mL, 1.11 mmol), and the reaction mixture was stirred at room temperature for 48 h. After this period, the solvent was removed, and the residue taken up in dichloromethane and washed with 0.5 M HCl (2 × 15 mL). The combined organics were dried over $MgSO_4$ filtered and evaporated. The residue was purified by preparative thin layer chromatography (2000 μm, Aldrich) using a mixture CH_2Cl_2/MeOH 95:5 v/v as eluent to give **9a** (0.040 g, 35%) as a pale yellow foamy solid: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.47, 7.46 (d, J = 2.5 Hz, 2H, H-6), 7.37−7.32 (m, 14H, Ph and CH_2Ph), 7.23−7.18 (m, 6H, Ph), 5.99 (t, J = 6.0 Hz, 1H, H-1′), 5.98 (t, J = 6.0 Hz, 1H, H-1′), 5.17−5.15 (m, 4H, CH_2Ph), 4.17−4.05 (m, 4H,CH_2OP), 4.04−4.01 (m, 2H, $CHCH_3$), 4.00−3.87 (m, 4H, CH_2O), 2.79−2.73 (m, 1H, H-3′), 2.72−2.66 (m, 1H, H-3′), 2.05−2.39 (m, 2H, H-2′a), 1.89, 1.88 (d, J = 1.5 Hz, 6H, CH_3), 1.81−1.72 (m, 2H, H-2′b), 1.38 (d, J = 7.5 Hz, 3H, $CHCH_3$), 1.35 (d, J = 7.5 Hz, 3H, $CHCH_3$); ^{13}C NMR (125 MHz, CD_3OD) δ ppm 174.9 (d, J_{CP} = 5.0 Hz, CO_2Bn), 174.7 (d, J_{CP} = 5.0 Hz, CO_2Bn), 166.44, 166.42 (CO), 152.30, 152.29 (CO), 152.21 (d, J_{CP} = 2.8 Hz, C_{ipso}OPh), 152.16 (d, J_{CP} = 2.8 Hz, C_{ipso}OPh), 137.54, 137.52 (C-6), 137.32, 137.31 ($C_{ipso}OCH_2Ph$), 130.82, 130.80 (Ph), 129.66, 129.64, 129.43, 129.40, 129.36, 129.31 (CH_2Ph), 126.25, 126.23 (Ph), 121.5 (d, J_{CP} = 4.6 Hz, Ph), 121.4 (d, J_{CP} = 5.3 Hz, Ph), 111.7 (C-5), 88.07, 88.03, (C-1′), 71.7, 71.5 (CH_2O), 68.4 (d, J_{CP} = 5.0 Hz, CH_2OP), 68.3 (d, J_{CP} = 5.0 Hz, CH_2OP), 68.0 (CH_2Ph), 51.8, 51.6 ($CHCH_3$), 40.5 (d, J_{CP} = 3.8 Hz, C-3′), 40.4 (d, J_{CP} = 3.8 Hz, C-3′), 35.2, 35.1 (CH_2), 20.4 (d, J_{CP} = 7.5 Hz, $CHCH_3$), 20.3 (d, J_{CP} = 7.5 Hz, $CHCH_3$), 12.5 (CH_3); ^{31}P NMR (202 MHz, CD_3OD) δ ppm 3.88, 3.33; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{26}H_{30}N_3O_8PNa$ 566.1668, found 566.1663; HPLC ACN/H_2O 10/90 v/v to 100/0 in 30 min, λ = 280 nm, flow 1 mL/min, t_R = 15.42 min.

*1′-(Adenin-9-yl)-2′,3′-dideoxy-α-D-apio-D-furanose [phenyl-(benzoxy-L-alaninyl)]phosphate (**9b**).* Following the reaction protocol mentioned for the synthesis of compound **9a**, **1b** (0.050 g, 0.21 mmol) was reacted with phosphorochloridate **64a** (0.23 g, 0.66 mmol) to give **9b** (0.030 g, 26%) as a white foamy solid: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 8.24, 8.23 (2s, 1H, H-8), 8.22, 8.21 (2s, 1H, H-2), 7.40−7.26 (m, 16H, Ph), 7.22−7.15 (m, 4H, Ph), 6.27 (t, J = 7.0 Hz, 1H, H-1′), 6.24 (t, J = 6.5 Hz, 1H, H-1′), 5.14 (s, 4H, CH_2Ph), 4.26−4.19 (m, 4H CH_2OP), 4.10−3.96 (m, 6H, CH_2O and $CHCH_3$), 2.91−2.75 (m, 2H, H-3′), 2.69- 2.57 (m, 2H, H2′a), 2.41−2.34 (m, 2H, H2′b), 1.37 (d, J = 6.5 Hz, 3H, CH_3), 1.35 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, CD_3OD) δ ppm 175.0 (d, J_{CP} = 4.2 Hz, CO_2Bn), 174.7 (d, J_{CP} = 4.6 Hz, CO_2Bn), 157.3 (C-6), 153.84, 153.83 (C-2), 152.22 (d, J_{CP} = 2.5 Hz, C_{ipso}OPh), 152.17 (d, J_{CP} = 2.5 Hz, C_{ipso}OPh), 150.4 (C-4), 140.78, 140.74 (C-8), 137.29, 137.28 ($C_{ipso}OCH_2Ph$), 130.80 (d, J_{CP} = 0.7 Hz, Ph), 130.78 (d, J_{CP} = 0.9 Hz, Ph), 129.60, 129.38, 129.36, 129.35, 129.30 (CH_2Ph), 126.20 (d, J_{CP} = 1.3 Hz, Ph), 126.17 (d, J_{CP} = 1.3 Hz, Ph), 121.5 (d, J_{CP} = 4.6 Hz, Ph), 121.4 (d, J_{CP} = 4.6 Hz, Ph), 120.70, 120.68 (C-5), 87.00, 86.98, (C-1′), 71.8, 71.7 (CH_2O), 68.22 (d, J_{CP} = 5.5 Hz, CH_2OP), 68.15 (d, J_{CP} = 5.5 Hz, CH_2OP), 67.99, 67.97 (CH_2Ph), 51.8 (d, J_{CP} = 1.4 Hz, $CHCH_3$), 51.7 ($CHCH_3$), 41.10 (d, J_{CP} = 7.8 Hz, C-3′), 41.05 (d, J_{CP} = 7.8 Hz, C-3′), 35.2, 35.1 (CH_2), 20.4 (d, J_{CP} = 7.0 Hz, $CHCH_3$), 20.3 (d, J_{CP} =7.0 Hz, $CHCH_3$); ^{31}P NMR (202 MHz, CD_3OD) δppm 3.80, 3.28; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{26}H_{30}N_6O_6P$ 553.1964, found 553.1960 and [M + Na]$^+$ Calcd for $C_{26}H_{29}N_6O_6PNa$ 575.1784, found 575.1770; HPLC ACN/H_2O 10/90 v/v to 100/0 in 30 min, λ = 280 nm, flow 1 mL/min, t_R = 14.36 min.

*1′-(Thymin-1-yl)-2′,3′-dideoxy-α-D-apio-D-furanose [phenyl-(isopropoxy-L-alaninyl)]phosphate (**10a**).* Following the reaction protocol mentioned for the synthesis of compound **9a**, **1a** (0.050 g, 0.22 mmol) was reacted with phosphorochloridate **64b** (0.203g, 0.66 mmol) to give **10a** (0.096 g, 88%) as a pale yellow foamy solid: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.58, 7.57 (2s, 2H, H-6), 7.45 (d, J = 8.0 Hz, 2H, Ph), 7.44 (d, J = 7.5 Hz, 2H, Ph), 7.33−7.28 (m, 6H, Ph), 6.10 (t, J = 7.0 Hz, 1H, H-1′), 6.08 (t, J = 7.0 Hz, 1H, H-1′), 5.10−5.03 (m, 2H, $CH(CH_3)_2$), 4.33−4.21 (m, 4H, CH_2OP), 4.16−4.10 (m, 2H, CH_2O), 4.01−3.96 (m, 2H,CH_2O), 3.94−3.89 (m, 2H, $CHCH_3$), 2.95−2.86 (m, 2H, H-3′), 2.64−2.56 (m, 2H, H-2′a), 1.97 (s, 6H, CH_3), 1.95−1.88 (m, 2H, H-2′b), 1.43 (d, J = 7.5 Hz, 3H, $CHCH_3$), 1.40 (d, J = 6.5 Hz, 3H, $CHCH_3$), 1.34−1.30 (m, 12H, $CH(CH_3)_2$); ^{13}C NMR (125 MHz, CD_3OD) δ ppm 175.0 (d, J_{CP} = 5.4 Hz, CO_2iPr), 174.5 (d, J_{CP} = 4.5 Hz, CO_2iPr), 166.46, 166.44 (CO), 152.30 (d, J_{CP} = 3.6 Hz, C_{ipso}OPh), 152.28 (CO), 152.25 (d, J_{CP} = 3.6 Hz, C_{ipso}OPh), 137.6 (C-6), 130.84, 130.81, 126.25, 126.23 (Ph), 121.54 (d, J_{CP} = 4.5 Hz, Ph), 121.47 (d, J_{CP} = 5.3 Hz, Ph), 111.7 (C-5), 88.15, 88.12, (C-1′), 71.7, 71.6 (CH_2O), 70.19, 70.16 ($CH(CH_3)_2$), 68.4 (d, J_{CP} = 5.4 Hz, CH_2OP), 68.3 (d, J_{CP} = 5.4 Hz, CH_2OP), 51.89, 51.88 ($CHCH_3$), 40.55 (d, J_{CP} = 3.5 Hz, C-3′), 40.49 (d, J_{CP} = 3.6 Hz, C-3′), 35.3, 35.2 (CH_2), 22.05, 22.03, 21.98, ($CH(CH_3)_2$), 20.6 (d, J_{CP} = 7.2 Hz, $CHCH_3$), 20.4 (d, J_{CP} = 7.2 Hz, $CHCH_3$), 12.54, 12.52 (CH_3); ^{31}P NMR (202 MHz, CD_3OD) δ ppm 3.89, 3.49; HRMS (ESI-TOF) m/z [M + Na]$^+$ Calcd for $C_{22}H_{30}N_3O_8PNa$ 518.1668, found 518.1653; HPLC ACN/H_2O 10:90 v/v to 100:0 in 30 min.; λ = 280 nm, flow 1 mL/min, t_R = 13.79, 13.81 min.

*1′-(Adenin-9-yl)-2′,3′-dideoxy-α-D-apio-D-furanose [phenyl-(isopropoxy-L-alaninyl)]phosphate (**10b**).* Following the reaction protocol mentioned for the synthesis of compound **9a**, **1b** (0.050 g, 0.21 mmol) was reacted with phosphorochloridate **64b** (0.201g, 0.66 mmol) to give **10b** (0.054 g, 51%) as a white foamy solid: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 8.27, 8.25 (2s, 2H, H-8), 8.23, 8.22 (2s, 2H, H-2), 7.35 (d, J = 8.0 Hz, 2H, Ph), 7.34 (d, J = 7.8 Hz, 2H, Ph), 7.26−7.16 (m, 6H, Ph), 6.29 (t, J = 7.0 Hz, 1H, H-1′), 6.28 (t, J = 7.0 Hz, 1H, H-1′), 5.02−4.94 (m, 2H, $CH(CH_3)_2$), 4.33 (m, 4H, CH_2OP), 4.16−4.05 (m, 4H, CH_2O), 3.93−3.88 (m, 2H, $CHCH_3$), 2.96−2.89 (m, 2H, H-3′), 2.75- 2.66 (m, 2H, H2′a), 2.49−2.43 (m, 2H, H2′b), 1.35 (d, J = 7.0 Hz, 3H, CH_3), 1.33 (d, J = 7.0 Hz, 3H, CH_3), 1.23−1.21 (m, 12H, $CH(CH_3)_2$); ^{13}C NMR (125 MHz, CD_3OD) δ ppm 175.0 (d, J_{CP} = 4.5 Hz, CO_2iPr), 174.5 (d, J_{CP} = 4.5 Hz, CO_2iPr), 157.4 (C-6), 153.9 (C-2), 152.27 (d, J_{CP} = 3.4 Hz, C_{ipso}OPh), 152.22 (d, J_{CP} = 2.6 Hz, C_{ipso}OPh), 150.4 (C-4), 140.82, 140.79 (C-8), 130.81, 126.19, 126.16 (Ph), 121.53 (d, J_{CP} = 5.5 Hz, Ph), 121.45 (d, J_{CP} = 5.5 Hz,CH Ph), 120.73, 120.70 (C-5), 87.04, 87.04, (C-1′), 71.89, 71.83 (CH_2O), 70.2 ($CH(CH_3)_3$), 68.3 (d, J_{CP} = 6.4 Hz, CH_2OP), 68.2 (d, J_{CP} = 6.4 Hz, CH_2OP), 51.9, 51.7 ($CHCH_3$), 41.2 (d, J_{CP} = 7.2 Hz, C-3′), 41.1 (d, J_{CP} = 7.2 Hz, C-3′), 35.2, 35.1 (CH_2), 22.00, 21.95, 21.94, ($CH(CH_3)_3$), 20.6 (d, J_{CP} = 6.4 Hz, $CHCH_3$), 20.4 (d, J_{CP} = 6.4 Hz, $CHCH_3$); ^{31}P NMR (202 MHz, CD_3OD) δ ppm 3.81, 3.46; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{22}H_{30}N_6O_6P$ 505.1964, found 505.1960 and [M + Na]$^+$ Calcd for

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$C_{22}H_{29}N_6O_6PNa$ 527.1784, found 527.1794; HPLC ACN/H_2O 10/90 v/v to 100/0 in 30 min, λ = 280 nm, flow 1 mL/min, t_R = 12.61 min.

*1′-(Thymin-1-yl)-2′,3′-dideoxy-α-D-apio-L-furanose [phenyl-(benzoxy-L-alaninyl)]phosphate (**11a**).* To a solution of **4a** (0.095 g, 0.42 mmol) in anhydrous THF (10 mL) was added 1.0 M solution of *tert*-butyl magnesium chloride in THF (0.84 mL, 0.84 mmol), and the reaction mixture was stirred under an argon atmosphere for 30 min. After this period, a solution of **64a** (0.30 g, 0.84 mmol) in anhydrous THF (5 mL) was added dropwise, and the reaction mixture was stirred at room temperature for 17 h. After this period, the solvent was removed, and the residue was purified by column chromatography, gradient elution of $CHCl_3$/MeOH = 98/2 to 95/5 to give **11a** (0.051 g, 22%) as a white solid: ^{31}P NMR (CD_3OD, 202 MHz) δ 3.80, 3.30; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.40−7.30 (8H, m, H-6, PhO, OCH_2Ph), 7.23−7.18 (3H, m, PhO, OCH_2Ph), 6.01−5.99 (0.5H, m, H-1′), 5.98−5.96 (0.5H, m, H-1′), 5.17, 5.16 (2H, 2s, OCH_2Ph), 4.28−4.21 (1H, m, H-4′ of one diastereoisomer), 4.14−4.00 (3H, m, 3′−CH_2, $CHCH_3$), 3.75−3.69 (1H, m, H-4′ of one diastereoisomer), 2.80−2.74 (0.5H, m, H-3′ of one diastereoisomer), 2.73−2.66 (0.5H, m, H-3′ of one diastereoisomer), 2.22−2.07 (2H, m, H-2′), 1.90 (3H, 2s, 5-CH_3), 1.38 (1.5H, d, J = 7.2 Hz, $CHCH_3$ of one diastereoisomer), 1.36 (1.5H, d, J = 7.4 Hz, $CHCH_3$ of one diastereoisomer); ^{13}C NMR (CD_3OD, 125 MHz) δ 12.6 (5-CH_3), 20.38 (d, J_{C-P} = 7.2 Hz, CH_3), 20.44 (d, J_{C-P} = 7.2 Hz, CH_3), 35.61, 35.64 (C-2′), 39.73, 39.79 (C-3′), 51.7, 51.8 ($CHCH_3$), 68.00 (OCH_2Ph), 68.49 (d, J_{C-P} = 6.0 Hz, 3′-CH_2), 68.53 (d, J_{C-P} = 5.8 Hz, 3′-CH_2), 72.49, 72.54 (C-4′), 88.36, 88.38 (C-1′), 111.30, 111.33 (C-5), 121.50, 121.53, 121.57, 121.61, 126.2, 128.0, 129.33, 129.37, 129.40, 129.42, 129.65, 129.66, 130.8 (arom H), 137.3 C_{ipso} Bn), 137.74, 137.76 (C-6), 152.16, 152.19, 152.23 (C-2, C_{ipso} OPh), 166.5 (C-4), 174.8 (d, J_{C-P} = 4.6 Hz, CO), 175.0 (d, J_{C-P} = 4.6 Hz, CO); HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{26}H_{30}N_3O_8PNa$ 566.1668, found 566.1651; HPLC = H_2O/ACN from 100/0 to 0/100 in 30 min = retention time 18.24 min; H_2O/MeOH from 100/0 to 0/100 in 30 min = retention time 25.07 min.

*1′-(Adenin-9-yl)-2′,3′-dideoxy-α-D-apio-L-furanose [phenyl-(benzoxy-L-alaninyl)]phosphate (**11b**).* To a solution of **4b** (0.10 g, 0.42 mmol) in anhydrous THF (10 mL) and anhydrous pyridine (2 mL) was added a solution of **64a** (0.45g, 1.26 mmol) in anhydrous THF (5 mL), followed by the addition dropwise under an argon atmosphere of anhydrous NMI (0.10 mL, 1.26 mmol), and the reaction mixture was stirred at room temperature for 24 h. After this period, a solution of **64a** (0.30 g, 0.84 mmol) in anhydrous THF (3 mL) and anhydrous NMI (0.07 mL, 0.84 mmol) were added, and the reaction mixture was stirred at room temperature for further 24 h. After this period, the solvent was removed, and the residue was purified by column chromatography, gradient elution of CH_2Cl_2, then CH_2Cl_2/MeOH = 98/2 then 96/4 then 90/10 to give a white solid which was triturated with diethyl ether to give **11b** (0.035 g, 15%) as a white solid: ^{31}P NMR (CD_3OD, 202 MHz) δ 3.86, 3.31; ^{1}H NMR (CD_3OD, 500 MHz) δ 8.22, 8.21, 8.20, 8.17 (2H, 4s, H-2, H-8), 7.37−7.16 (10H, m, arom H), 6.31 (0.5H, dd, J = 7.0 Hz, 3.30 Hz, H-1′ of one diastereoisomer), 6.26 (0.5H, dd, J = 7.00 Hz, 3.20 Hz, H-1′ of one diastereoisomer), 5.16, 5.15 (2H, 2s, CH_2Ph), 4.29−4.22 (1H, m, H-4′), 4.18−4.02 (3H, m, $CHCH_3$, 3′-CH_2), 3.86−3.78 (1H, m, H-4′), 3.03−2.89 (1H, m, H-3′), 2.65−2.56 (1H, m, H-2′), 2.35−2.24 (1H, m, H-2′), 1.39 (1.5H, d, J = 7.0 Hz, CH_3 of one diastereoisomer), 1.37 (1.5H, d, J = 7.2 Hz, CH_3 of one diastereoisomer); ^{13}C NMR (CD_3OD, 125 MHz) δ 20.35 (d, J_{C-P} = 6.7 Hz, $CHCH_3$), 20.41 (d, J_{C-P} = 6.8 Hz, $CHCH_3$), 35.38, 35.39 (C-2′), 40.0 (d, J_{C-P} = 2.7 Hz, C-3′), 40.1 (J_{C-P} = 2.8 Hz, C-3′), 51.7, 51.8 ($CHCH_3$), 67.95, 67.97 (CH_2Ph), 68.6 (d, J_{C-P} = 5.7 Hz, 3′-CH_2), 68.8 (d, J_{C-P} = 5.8 Hz, 3′-CH_2), 72.13, 72.15 (C-4′), 87.0 (C-1′), 120.7, 121.48, 121.52, 121.57, 121.61, 126.18, 126.21, 129.31, 129.35, 129.37, 129.6, 129.7, 130.8 (arom H), 137.3 (C_{ipso} Bn), 140.8 (C-2), 152.19 (d, J_{C-P} = 5.5 Hz, C_{ipso} OPh), 152.25 (d, J_{C-P} = 4.7 Hz, C_{ipso} OPh), 153.7, 153.8 (C-8), 157.3 (C-8), 174.8 (d, J_{C-P} = 4.7 Hz, CO), 175.0 (d, J_{C-P} = 4.5 Hz, CO); HRMS (ESI-TOF) m/z $[M + Na]^+$ Calcd for $C_{26}H_{29}N_6O_6PNa$ 575.1784, found 575.1778; HPLC = H_2O/ACN from 100/0 to 0/100 in 30 min = retention time 17.05 min.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Biological assay procedure, copies of ^{1}H, ^{13}C, ^{31}P and 2-D NMR spectra of relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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