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Synthesis of a 3′-Fluoro-3′-deoxytetrose Adenine Phosphonate

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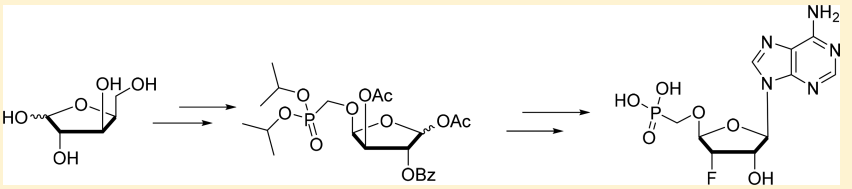
Supporting Information



ABSTRACT: A new synthetic route to a 3′-fluoro-3′-deoxytetrose adenine phosphonate has been developed. The synthesis starts from L-xylose and key steps include the stereospecific introduction of the phosphonomethoxy group and adenine. In addition, a regioselective fluorination reaction allows access to the desired 3′-fluoro-3′-deoxytetrose moiety. This methodology allows the straightforward synthesis of a 3′-fluoro-3′-deoxytetrose adenine phosphonate and can be expanded toward the synthesis of other types of 3′-fluoro nucleoside phosphonates.

INTRODUCTION

The synthesis of modified nucleoside and nucleotide analogues as antiviral agents is an ongoing research field.[1] Among the sugar modified analogues, the fluorinated congeners are a prominent class.[2] The best studied class of fluorinated nucleoside analogues carries a fluorine at C-2′ of the sugar moiety. A striking example is sofosbuvir that received marketing approval for the treatment of hepatitis C virus infected patients.[3] The antiviral activity of nucleosides analogues with a 3′-fluorine substituent at the carbohydrate moiety has been described to a lesser extent. 3′-Fluoro-3′-deoxythymidine[4] and 3′-fluoro-3′-deoxyadenosine[5] are examples of this series of antivirally active nucleoside analogues. An important class of nucleoside analogues are the nucleoside phosphonates that are chemically and metabolically stable mimics of the nucleoside monophosphate.[6] Hence, they can bypass the first, and often rate-limiting step in the conversion of the nucleoside to the pharmacologically active nucleoside triphosphate. The fact that the phosphonate moiety is isopolar and isoelectronic with the phosphate group allows the phosphonate to be phosphorylated by kinases to afford the diphosphophosphonate analogue, which acts as an analogue of the naturally occurring nucleoside triphosphate. The improved stability results in a prolonged pool of the nucleoside phosphonate inside the cell that is available for metabolism to the biologically active species, ultimately leading to long intracellular half-lives. As a result of these properties, clinically approved antiviral phosphonates are used in convenient once-daily antiviral treatment regimens. The synthesis of nucleoside phosphonates with a fluorinated sugar moiety has been hardly described in literature. An example is 2′-Fd4AP which is endowed with excellent activity against the human immunodeficiency virus, a promising resistance profile and minimal toxicity.[7]

Based on the broad spectrum antiviral activity profile of 3′-fluoro-3′-deoxyadenosine and the favorable pharmacological properties of nucleoside phosphonates, we became interested in the synthesis of a hybrid molecule, i.e., a 3′-fluoro-3′-deoxyadenosine phosphonate (compound **1**, Figure 1).

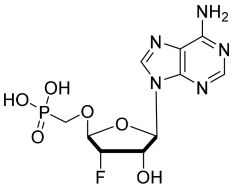


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Figure 1. A 3′-fluoro-3′-deoxytetrose adenine phosphonate.

Target molecule **1** possesses a fluorinated ribose sugar moiety with two anomeric centers (a *N*-glycosidic bond with adenine at the 1′-position and an *O*-glycosidic bond with hydroxymethylphosphonate at 4′-position), both having the *β*-configuration. Hence, key transformations in the synthetic sequence will be the stereoselective introductions of the phosphonomethoxy group and the nucleobase, as well as the introduction of the fluorine with the correct stereochemistry.

For the synthesis of 3′-fluoro-3′-deoxyadenosine, two main methods have been used in literature. Either a fluorinated sugar moiety is synthesized first,[5a,8] which is then coupled with a nucleobase. Alternatively, an appropriate protected nucleoside derivative with the 3′-hydroxyl group in the xylo configuration is prepared, which is then fluorinated by DAST treatment.[5b] Similar strategies were envisioned for the synthesis of 3′-fluoro-3′-deoxytetrose adenine phosphonate **1**. Retrosynthetic analysis clearly demonstrated that compound **1** could become accessible via these two major routes (Figure 2). The first route (Route 1)

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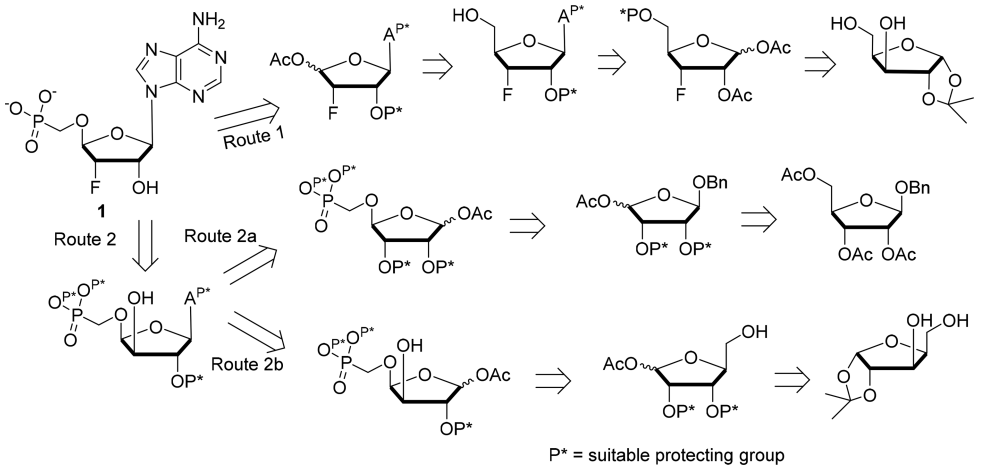
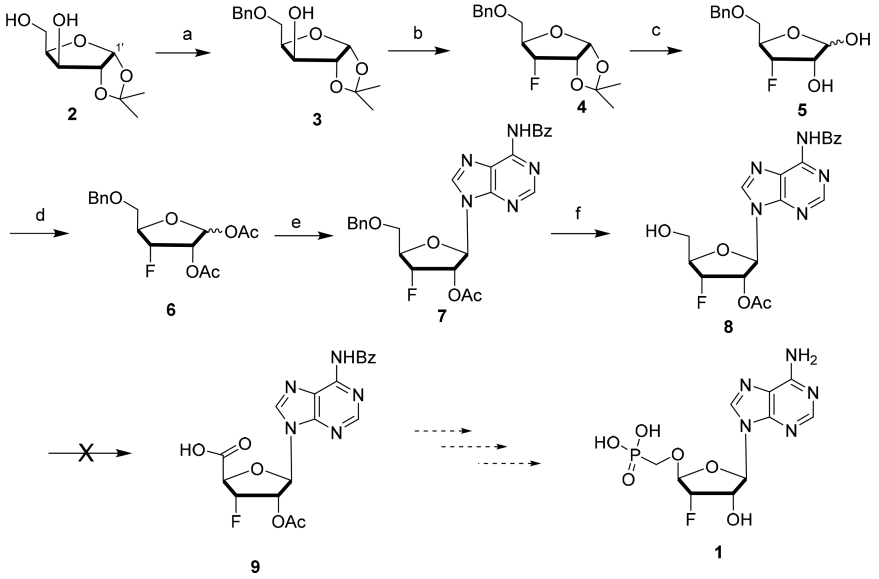


Figure 2. Retrosynthetic analysis of compound **1**.

Scheme 1. Synthetic Route toward Compound 1[a]



[a]Reagents and conditions: (a) NaH, TBAI, BnBr, dry THF, −78 °C to r.t., 5 h, 62%; (b) DAST, dry pyridine, dry CH_2Cl_2, −20 °C to r.t., 18 h, 56%; (c) 50% TFA in H_2O, 0 °C to r.t., 4 h, 100%; (d) Ac_2O, dry pyridine, 0 °C to r.t., 14 h, 83%; (e) 1 M $SnCl_4$ in CH_2Cl_2, N^6-benzoyl adenine, dry ACN, −20 °C to r.t., 4 h, 85%; (f) 1 M BCl_3 in CH_2Cl_2, dry CH_2Cl_2, −78 to 0 °C, 3 h, 86%.

involves the synthesis of a fluorinated sugar moiety, derived from a protected D-xylose derivate. The presence of a 2′-*O*-acyl protecting group will allow the stereoselective introduction of the nucleobase (via Vörbruggen coupling),[9] yielding a 3′-fluoro-3′-deoxyadenosine analogue. For the synthesis of nucleoside analogues carrying a 4′-phosphonomethoxy moiety, two major strategies are known. A first method uses a regioselective and stereoselective electrophilic addition of a phosphonomethoxy moiety to a furanoid glycal using *N*-(phenylseleno)phthalimide or iodine bromide. This methodology has for example been applied for the synthesis of an adenosine phosphonate[10] and an inosine phosphonate[11] analogue. Alternatively, a stereoselective (due to anchimeric assistance of a 3′-*O*-acyl protecting group), Lewis acid-mediated glycosidation of a phosphonate alcohol onto an anomeric acetate has been used to synthesize nucleoside phosphonates.[12] The latter method deemed to be useful for the synthesis of compound **1**. The main drawback of this strategy will be the lack of stereoselectivity when inserting the phosphonate moiety, due to absence of anchimeric assistance because a 3′-fluorine is present. Therefore, separation of both anomers will be necessary. In an alternative way (which also has been applied in the synthesis of 3′-fluoro-3′-deoxy-adenosine), a nucleoside phosphonate with the xylo stereochemistry of the hydroxyl group at 3′-position, is synthesized first, which is then fluorinated in the last step affording target compound **1** (Route 2). The advantage of this approach is that the nucleobase, as well as the phosphonomethoxy functionality can be introduced in a stereoselective way, due to the presence of 2′-*O*-acyl and 3′-*O*-acyl protecting groups, respectively. It will avoid the (usually) tedious and time-consuming separations of anomers. The phosphonylated sugar derivative is accessible from a suitable protected D-ribose (route 2A) or L-ribose (route 2B) derivative. Due to the high costs of L-ribose, this will need to be prepared from an appropriately protected L-xylose derivative. As an anomeric acetate group at 4′-position is easily accessible, the method of choice for insertion of the

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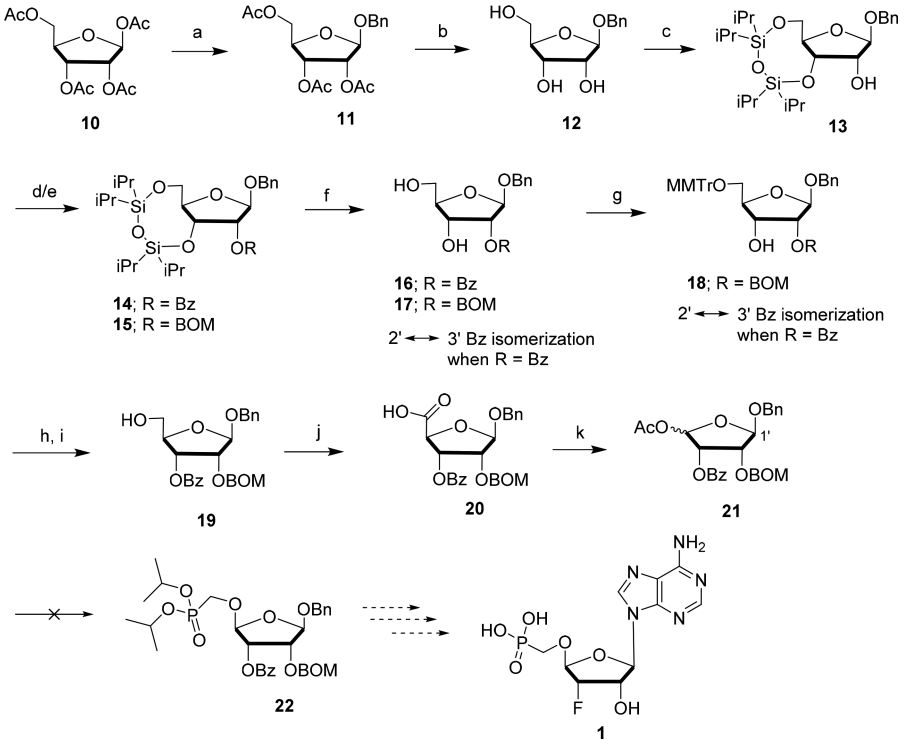
Scheme 2. Synthetic Route toward Compound 1[a]



[a]Reagents and conditions: (a) BnOH, $SnCl_4$, dry ACN, −20 °C to r.t., 5 h; (b) 7 *N* NH_3 in MeOH, r.t., 24 h, 64%; (c) 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, dry pyridine, 0 °C to r.t., 4 h, 89%; (d) BzCl, dry pyridine, 0 °C to r.t., 12 h, 91%; (e) BOMCl, DIPEA, dry CH_2Cl_2, reflux, 24 h, 92%; (f) $Et_3N{\cdot}3HF$, dry THF, r.t., 24 h, 48% (for **16**), 94% (for **17**); (g) MMTrCl, dry pyridine, r.t., 18 h, 96%; (h) BzCl, dry pyridine, 0 °C to r.t., 16 h; (i) 80% AcOH, r.t., 4 h, 83% (over 2 steps) ; (j) DIB, TEMPO, ACN:H_2O (1:1), 0 °C to r.t., 4.5 h, 91%; (k) $Pb(OAc)_4$, dry pyridine, dry THF, 35 °C, 20 h, 88%.

phosphonomethoxy group involves the Lewis-acid mediated glycosylation, rather than the glycal approach.

RESULTS AND DISCUSSION

Attempted Synthesis of Compound 1 from a Protected 3′-Fluoro-3′-deoxytetrose Adenine Derivative. Selective benzylation of the primary hydroxyl group of 1′,2′-*O*-isopropylidene-α-D-xylofuranose **2** afforded derivative **3** in good yield.[13] To avoid selective protection and deprotection sequences between the hydroxyl groups at 2′ and 3′-positions, the 3′−OH group of compound **3** was converted to the corresponding fluorine derivative **4** using the common fluorinating agent diethylaminosulfur trifluoride (DAST) in a moderate yield of 56%. Attempts to improve the yield of the fluorination reaction by using other nucleophilic fluorinating agents, such as deoxo-fluor or fluolead were unsuccessful. Acidic deprotection of the isopropylidene moiety of **4** using 50% TFA in water, followed by acetylation of **5** using acetic anhydride yielded a diastereomeric mixture of the diacetylated analogue **6** in 83% yield over two steps. A stereoselective $SnCl_4$ catalyzed Vorbrüggen glycosylation of N^6-benzoyl adenine with the 1′-*O*-,2′-*O*-acetyl sugar **6** afforded the protected 3′-fluoro-3′-deoxyadenosine analogue **7** in good yield (85%). In order to deprotect the benzyl group of derivative **6**, different hydrogenation conditions using a range of Pd-catalysts (including 10% Pd/C, 20% $Pd(OH)_2/C$, $Pd(OAc)_2$, and Pd-black) were explored. None of these conditions were successful in delivering compound **8**. Either unreacted starting material was recovered when mild reaction conditions were applied or undesired side-products (that were not isolated) were formed under harsh reaction conditions. On the other hand, Lewis-acid mediated debenzylation (using borontrichloride) afforded compound **8** in excellent yield. Unfortunately, all attempts to obtain the carboxylic acid derivative **9** from its corresponding alcohol **8** using a variety of oxidizing agents (e.g., DIB/TEMPO, PDC/DMF, CrO_3/H_2SO_4, $KMnO_4$, DMP/$NaClO_2$) failed, giving rise to unreacted starting material or decomposed side products. The presence of the strongly electronegative fluorine might explain the unreactivity of **8** or the instability of product **9**, arising from the strongly inductive effect of fluorine (Scheme 1).

Synthesis of Compound 1 via a Phosphonylated Sugar Derivative. Difficulties in oxidation of the primary hydroxyl group of the 3′-fluoro-3′-deoxyadenosine analogue **8** (Scheme 1) forced us to explore another synthetic route, in which first a phosphonylated sugar moiety was synthesized (Figure 2, route 2). Reaction of β-D-ribofuranose 1,2,3,5-tetraacetate **10** with benzyl alcohol under Lewis-acid catalyzed Vorbrüggen conditions afforded 1′-*O*-benzyl-2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranoside (**11**) in moderate yield (64%) (Scheme 2).[14] It was foreseen that the conversion from the 1′-*O*-benzyl group to its corresponding 1′-acetate will allow the regioselective introduction of N^6-benzoyl adenine, later on in the synthesis. Removal of the *O*-acetyl protecting groups of **11** under modified Zemplén conditions (using a 7N NH_3 solution in methanol) afforded 1′-*O*-benzyl-β-D-ribofuranoside (**12**). Simultaneous protection of the 3′- and 5′-hydroxyl groups of ribofuranoside **12** using Markiewicz's reagent ($TIPDSCl_2$) afforded disiloxane ribofuranoside **13** in 90% yield. The 2′-benzoyl protected disiloxane ribofuranoside **14** was obtained in

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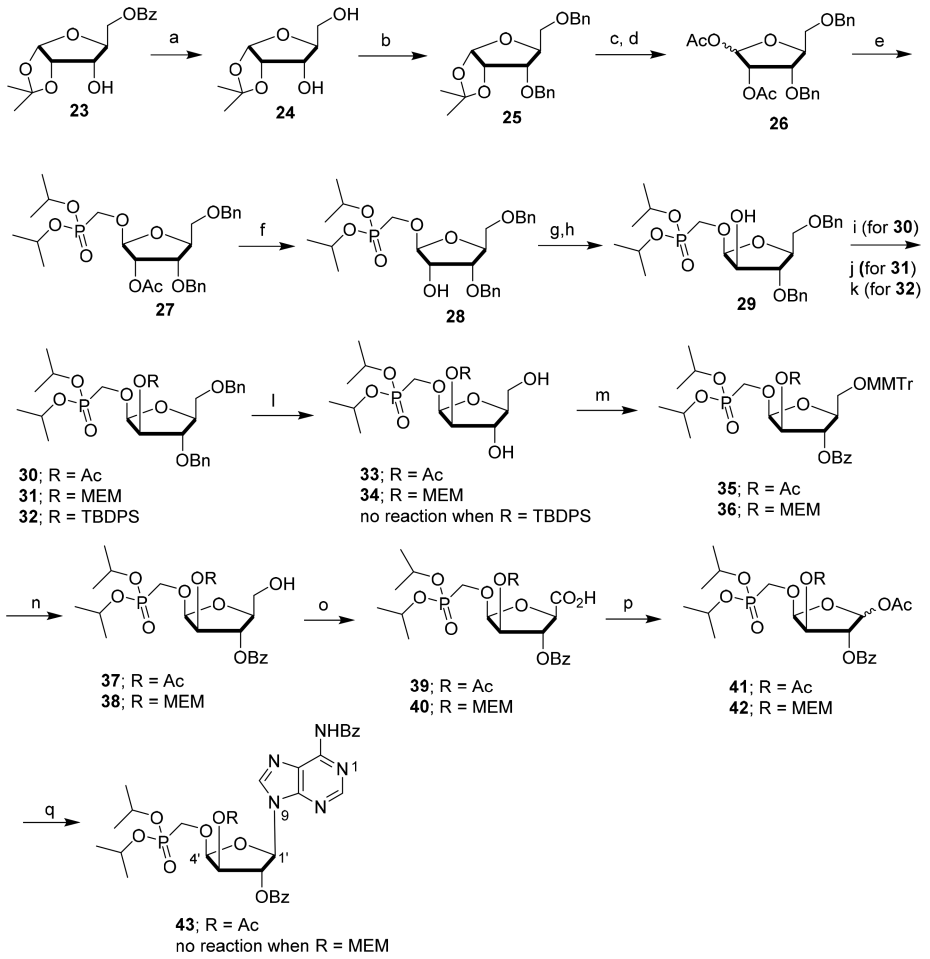
Scheme 3. Synthetic Route toward Compound 1[a]



[a]Reagents and conditions: (a) 5.4 M NaOMe in MeOH, MeOH, r.t., 1 h, 97%; (b) NaH, BnBr, dry THF, −20 °C to r.t., 19 h, 92%; (c) 50% TFA in H_2O, 0 °C to r.t., 4 h; (d) Ac_2O, dry pyridine, 0 °C to r.t., 14 h, 90% (over 2 steps); (e) diisopropyl (hydroxymethyl)phosphonate, $SnCl_4$, dry ACN, −20 °C to r.t., 5 h, 80%; (f) 7 *N* NH_3 in MeOH, r.t., 16 h, 96%; (g) Dess-Martin periodinane, dry CH_2Cl_2, −20 °C to r.t., 18 h; (h) $NaBH_4$, 1:1 absolute EtOH: dry EtOAc, −50 °C to r.t., 5 h, 71% (over 2 steps); (i) Ac_2O, dry pyridine, 0 °C to r.t., 14 h, 95%; (j) MEMCl, DIPEA, dry CH_2Cl_2, reflux, 48 h, 86%; (k) TBDPSCl, imidazole, cat. DMAP, dry ACN, 60 °C, 48 h, 80%; (l) 10% Pd/C, H_2, AcOH, EtOH: H_2O (9:1), r.t., 20 h, 98% (for **33**), 95% (for **34**); (m) (i) MMTrCl, DMAP, dry pyridine, 0 °C to r.t., 17 h,; (ii) BzCl, dry pyridine, 0 °C to r.t., 3 h, 85% (for **35**, over 2 steps), 87% (for **36**, over 2 steps); (n) 80% AcOH, r.t., 4 h, 84% (for **37**), 85% (for **38**); (o) DIB, TEMPO, ACN:H_2O (1:1), 0 °C to r.t., 4.5 h, 96% (for **39**), 93% (for **40**); (p) $Pb(OAc)_4$, dry pyridine, dry THF, 35 °C, 20 h, 90% (for **41**), 75% (for **42**); (q) 1 M $SnCl_4$ in CH_2Cl_2, N^6-benzoyl adenine, dry ACN, 0 °C to r.t., 36 h, 45%.

excellent yield (91%) from its precursor **13**. Benzoyl was preferred as protecting group at 2′-position of **13**, as a 2′-*O*-acyl group allows the stereoselective glycosylation of the nucleobase. However, during removal of the disiloxane protecting groups of **14**, almost an equivalent amount of the 3′-benzoyl adduct was observed along with the desired 2′-benzoyl ribofuranoside **16**, due to 2′↔3′ benzoyl migration, facilitated by basicity of the fluoride anion. Both regioisomers were separated by silica gel flash chromatography.

A similar problem was encountered during the protection of the primary hydroxyl group of **16** as a monomethoxytrityl, yielding a nonseparable mixture of regioisomers of 2′- and 3′-benzoyl adducts. Therefore, we switched to a benzyloxymethyl (BOM) group as an alternative, more stable and easily removable protecting group for the 2′-hydroxyl group affording compound **15**. Subsequently, deprotection of the TIPDS group of **15**, followed by protection of the primary hydroxyl group, afforded **18** in excellent yield. Benzoyl protection of 3′-hydroxyl group of ribofuranoside **18**, followed by 5′-MMTr removal by a 80% AcOH solution yielded **19** in good yield (83%) over two steps. DIB-TEMPO mediated oxidation of the primary hydroxyl group of **19** yielded its corresponding carboxylic acid **20** in excellent yield (91%).[15] Oxidative decarboxylation of acid **20** via a modified Kochi reaction resulted into the 4′-acetate derivative **21** as a mixture of α/β isomers.[16] Unfortunately, efforts to obtain phosphonate **22** via a Vorbrüggen reaction of acetate **21** with hydroxymethyl phosphonic acid diisopropyl ester in the presence of different Lewis acids, such as TMSOTf or $SnCl_4$, at varying temperatures were unsuccessful. At lower temperature, no reaction took place, whereas at elevated temperatures or using prolonged reaction times complex reaction mixture were obtained. This might be caused by the instability of the starting material **21** due to the presence of two anomeric centers.

As the introduction of the phosphonate moiety on sugar derivative **21** was not feasible (Scheme 2), an alternative synthetic route, using L-xylose as starting material was explored (Scheme 3) following route 2B of retrosynthetic analysis in

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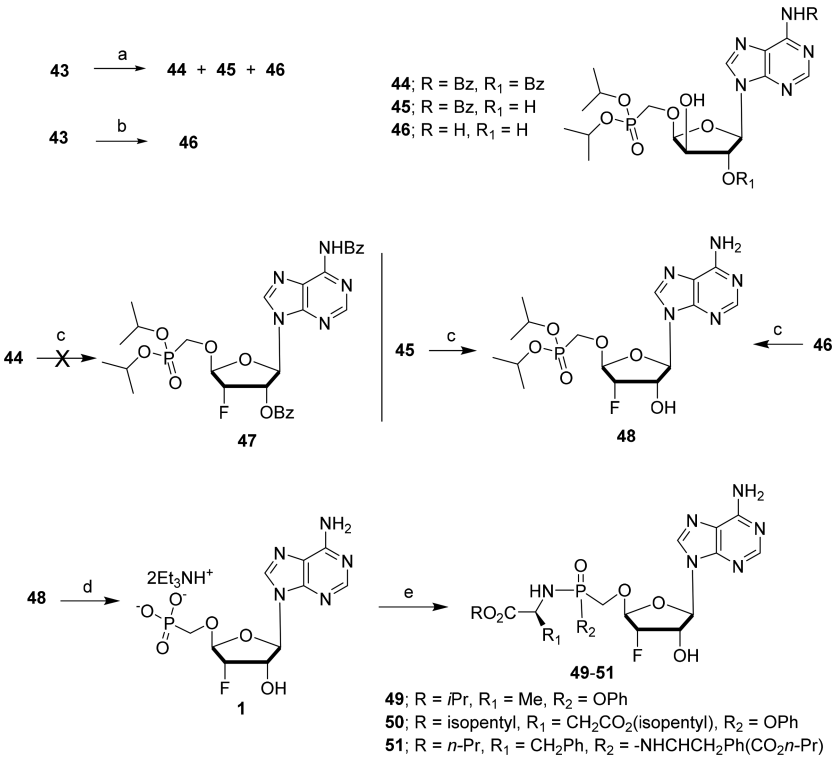
Scheme 4. Synthesis of Compounds 1 and 49−51[a]



[a]Reagents and conditions: (a) 2 M NH_3 in EtOH, 0 °C to r.t., 48 h, **44**: 3%, **45**: 42%, **46**: 45%; (b) 7 *N* NH_3 in MeOH, r.t., 48 h, 96%; (c) DAST, dry pyridine, dry CH_2Cl_2, −20 °C to r.t., 6 h, 42% (from **45**), 47% (from **46**); (d) TMSBr, 2,6-lutidine, dry ACN, 0 °C to r.t., 24 h, 88%; (e) PhOH and/or amino acid.HCl, Et_3N, 2,2′-dithiodipyridine, PPh_3, dry pyridine, 60 °C, 16 h, 57% (for **49**), 54% (for **50**), 42% (for **51**).

Figure 2. It was reasoned that using this methodology, the phosphonomethoxy side chain could be easily introduced as only one anomeric center will be present. 1,2-*O*-isopropylidene-α-L-ribofuranose **23** was prepared from L-xylose according to a known procedure.[17] The 5′-Bz protecting group was removed with sodium methoxide to provide diol **24**. The two remaining free hydroxyl groups of **24** were protected as benzyl ethers using a reported protocol[18] furnishing compound **25**. The 1′,2′-*O*-isopropylidene moiety of **25** was smoothly cleaved by treatment with a 50% TFA solution in water to furnish the *vic*-diol intermediate, which was directly treated with acetic anhydride in pyridine, without any purification, to provide the 1′,2′-di-*O*-acetyl derivative **26** in excellent yield as an anomeric mixture of 1′-α/β isomers. Vorbrüggen reaction between **26** and diisopropyl (hydroxymethyl)phosphonate in the presence of $SnCl_4$ yielded the protected phosphonate derivative **27** exclusive as a 1′-β isomer. Deprotection of the 2′-acetyl group of **27** was easily accomplished by treatment with a 7 N NH_3 solution in MeOH affording phosphonate riboside **28** in excellent yield (96%).

Various strategies have been described for the conversion of L-ribofuranoside to L-arabinofuranoside via inversion of configuration of the hydroxyl group. Initial attempts by Mitsunobu reaction with various carboxylic acids were unsuccessful, as only unreacted starting material was isolated. Therefore, an oxidation−reduction strategy to synthesize L-arabinofuranoside **29** was applied. Several oxidizing agents have been reported for the oxidation of the 2′−OH of ribofuranoside **28**, but in our hands Dess-Martin periodinane (DMP) gave the best yield (96%). For reduction of the resulting ketone by $NaBH_4$, solvents like EtOH, MeOH or EtOH-H_2O resulted in formation of diastereomeric mixtures. A solvent mixture of EtOAc-EtOH (1:1) was found to be optimal for stereoselective reduction and L-arabinofuranoside **29** was obtained as a single isomer (71% over two steps). It is well-known that solvents and temperature play an important role in the stereoelectronic effects of the ketone and the exclusive hydride attack from the α-face, to obtain stereoselective product **29**.[19] It was foreseen that an orthogonal protection−deprotection of 2′−OH was essential for successive fluorination. Initial efforts for the protection of 2′−OH of arabinofuranoside **29** as a MEM and TBDPS protecting group were successful affording compounds **31** and **32,** respectively, in good yields. However, didebenzylation of TBDPS analogue **32** was problematic, as only the monodebenzylated (5′-) product was isolated. In case of the MEM protected analogue **31**, cleavage of the benzyl protecting groups went smoothly, affording compound **34**. Selective protection of the primary hydroxyl group of **34**, followed by protection of the secondary hydroxyl group as a benzoyl gave **36** in excellent yield. The primary hydroxyl group was deprotected under acidic conditions and subsequently oxidized to the corresponding carboxylic acid **40**. Introduction of an anomeric acetate group proceeded smoothly via a modified Kochi reaction, affording compound **42**. Unfortunately, Vorbrüggen *N*-glycosylation of N^6-benzoyl adenine with the 2′-*O*-MEM protected analogue **42** in the presence of various Lewis acids (TMSOTf or $SnCl_4$), resulted mainly in decomposition. As an alternative, an acetyl protecting group was selected for 2′−OH protection affording derivative **30** in excellent yield. Removal of both benzyl groups of compound **30** by reductive hydrogenation with 10% Pd/C yielded the desired diol **33** in excellent yield (98%). 5′-MMTr protection of the

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primary hydroxyl group of diol **33** followed by benzoyl protection of the secondary hydroxyl group yielded the L-arabino-phosphonate **35** in good yield (85%) over two steps. Selective MMTr removal of **35** by 80% acetic acid and oxidation of the resulting 5′-hydroxymethyl group of **37** by treatment with bis(acetoxy)iodobenzene in the presence of a catalytic amount of TEMPO furnished carboxylic acid **49** in excellent yield (96%). $Pb(OAc)_4$ mediated oxidative decarboxylation via a modified Kochi reaction transformed acid **39** into the acetate **41** as a mixture of α/β isomers. Vorbrüggen glycosylation of N^6-benzoyl adenine with acetate **41** in the presence of $SnCl_4$ led to the formation of the desired β-nucleoside phosphonate **43** in moderate yield (55%).

Several reagents and reaction conditions, such as DBU in benzene,[20] $Mg(OMe)_2$ in methanol,[21] KCN in ethanol,[22] guanidine in ethanol and dichloromethane,[23] K_2CO_3 in methanol and water,[24] were screened for selective hydrolysis of the acetyl protecting group and keeping the benzoyl groups intact. None of these procedures gave exclusive formation of **44**, but mixtures containing compounds **44**, **45**, and **46** were formed, arising from cleavage of the protecting groups at 2′-position of the sugar moiety and 6-position of the adenine part. If milder reaction conditions were applied (2 M NH_3 in EtOH), the deprotected compounds **44**, **45**, **46** were isolated in 3, 42, and 45% yield, respectively (Scheme 4). Using a more concentrated ammonia solution (7N NH_3 in MeOH), compound **46** was obtained directly from **43** in 96% yield. However, 3′-fluorination of the dibenzoyl derivative **44** using DAST did not furnish the desired fluorinated product **47**, but only led to cleavage of benzoyl groups affording a mixture of **45** and **46**, probably via a benzylideneoxoniumyl-substituted intermediate arising from 2′-benzoyl neighboring group participation.[25] Surprisingly, when the 2′,3′-dihydroxylated analogue **45** was treated with DAST, a regioselective fluorination of the 3′-hydroxyl group took place with concomitant cleavage of the benzamide moiety of the adenine nucleobase (due to strong basicity of fluoride ion), furnishing fluoro nucleoside phosphonate ester **48** in 42% yield. Using a similar fluorination protocol, unprotected derivative **46** was converted to its desired 3′-fluoro analogue **48** in moderate yield (47%) along with the unreacted starting nucleoside **46** (15%). For both fluorination reactions, formation of a common side product like 2′,3′-epoxy derivative (7−9%) and other uncharacterized side products in small amounts were observed. The regioselective 3′-fluorination was unambiguously determined from full structural analysis of **48** using 2D NMR spectroscopy (H−COSY, HSQC, HMBC, ROESY; see Supporting Information). The regioselectivity of 3′-fluorination is presumably due to steric effects of dihydroxy compounds **45** and **46**, where nucleophilic attack of fluoride ion at 3′-position is sterically more favorable (downside with respect to adenine) than at sterically hindered 2′-position (upside with respect to adenine). The hydrolysis of di-isopropyl phosphonate ester **48** was carried out using trimethylsilyl bromide (TMSBr) and 2,6-lutidine and the crude free phosphonate was purified by high-performance liquid chromatography (HPLC) to provide phosphonate diacid **1** as a triethylammonium salt in excellent yield (88%). Because of their acidic properties, phosphonates are predominantly present in their anionic form at physiological pH, which has a negative impact on their antiviral activity. Therefore, the synthesis of the corresponding phosphonoamidate prodrugs was also effected. Protides **49**−**51** were prepared from the phosphonate diacid **1** using 2,2′-dithiopyridine and triphenylphosphine as activating agents and utilizing a mixture of phenol and the appropriate amino acid ester in 42−57% yield.[7] Due to chirality of the phosphorus atom, compounds **49**−**50** were isolated as diastereomeric mixtures. To avoid this, the synthesis of a symmetrical bisamidate (compound **51**) was also effected. Protection of 2′−OH group was not essential for the coupling in our cases.

CONCLUSION

In summary, the synthesis of the hitherto unknown 3′-fluoro-3′-deoxytetrose adenine phosphonate **1** is accomplished with an overall yield of 3% over 22 linear steps starting from L(−)-xylose. Different synthetic roads were explored, and the successful strategy started from a protected xylose derivative with the unnatural L-configuration as chiral synthon giving ultimately rise to a nucleoside phosphonate analogue with the natural D-configuration. Highlights of the synthesis include the stereoselective introduction of the phosphonomethoxy group and the nucleobase. Moreover, access to the fluorinated ribose moiety was possible via a regioselective fluorination of the 3′-hydroxyl group, without protection of the 2′-hydroxyl group. The route described enabled the preparation of **1**, as well as its phosphonoamidate prodrugs **49**−**51**. Phosphonate **1** and prodrugs **49**−**51** were screened both against DNA and RNA viruses, but showed to be inactive.

EXPERIMENTAL SECTION

General Information. For all reactions, either analytical grade or anhydrous solvents were used. All moisture-sensitive reactions were performed using oven-dried glassware (135 °C) under a nitrogen or argon atmosphere. Reaction temperatures are reported as bath temperatures. Precoated aluminum sheets (254 nm) were used for TLC. Compounds were visualized with UV light (λ = 254 nm). Products were purified by flash chromatography on ICN silica gel 63−200, 60 Å. All final compounds were purified by preparative RP-HPLC (Gemini 10 μm C18 110 Å, LC Column 250 × 21.2 mm, AXIA column) using a gradient of H_2O and CH_3CN, or both containing 25 mmol TEAB as eluent buffer. ^1H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were recorded on Bruker Avance 300 MHz, 500 or 600 MHz spectrometers. Final compounds were characterized using 2D NMR (H−COSY, HSQC, HMBC, ROESY, and NOESY) techniques. For clarification, numbering of NMR signals of protons and carbons for sugar and base moieties are designated with and without a prime, respectively. Chemical shifts were referenced to residual solvent signals at δ H/C 7.26/77.16 ($CDCl_3$), 3.31/49.00 (CD_3OD), D_2O (4.79), 1.94/118.26 (CD_3CN), and 2.50/39.52 (DMSO-d_6) relative to TMS as internal standard wherever applied. Coupling constants are stated in hertz (Hz) and were directly obtained from the spectra. NMR splitting patterns are designated as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet), br (broad), and apparent (app). High-resolution mass spectra (HRMS) were obtained on a quadruple orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3 μL/min and spectra were obtained in positive (or negative) ionization mode with a resolution of 15000 (fwhm) using leucine enkephalin as lock mass.

*5′-O-(Benzyl)-1′,2′-O-isopropylidene-D-xylofuranose (**3**).* A solution of diol **2** (20 g, 100.2 mmol) in dry THF (200 mL) was added dropwise to a stirred suspension of NaH (55% in mineral oil, 4.81 g, 110.2 mmol, washed with hexane to remove oil) in dry THF (250 mL) at −78 °C under argon, and the resulting mixture was stirred at −78 °C for 30 min until the H_2 gas liberation was complete. Tetrabutylammonium iodide (19.42 g, 52.58 mmol) was added to the reaction mixture followed by dropwise addition of benzyl bromide (13.1 mL, 110.42 mmol). Then the reaction mixture was slowly warmed to rt and left for stirring for 2.5 h at rt. The reaction mixture

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was cooled to 0 °C and quenched with a saturated NH_4Cl solution and diluted with water and the aqueous layer was extracted with EtOAc (3 × 300 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* and the resulting crude residue was purified by column chromatography on silica gel (gradient Hexane/EtOAc, 9:1, v/v; 4:1, v/v; 3:2, v/v) to give **3** (18.27 g, 62%) as a sticky mass (R_f = 0.48, 80% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.28 (m, 5H, *Ar*-H OBn), 5.96 (d, J = 3.9 Hz, 1H, H-1′), 4.71−4.46 (m, 3H, C*H*$_2$-OBn and H-2′), 4.26 (dd, J = 8.5, 4.9 Hz, 1H, H-3′), 3.99 (d, J = 3.5 Hz, 1H, H-4′), 3.95−3.80 (m, 2H, H-5′ and H-5″), 2.28 (br s, 1H, 3′-O*H*), 1.47 (s, 3H, C*H*$_3$-isopropylidene), 1.31 (s, 3H, C*H*$_3$-isopropylidene); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2 (*1C*-Bn), 128.7 (Ar−C), 128.2 (Ar−C), 127.8 (Ar−C), 112.0 (1C-isopropyledene), 105.1 (C-1′), 82.8 (C-2′), 82.6 (C-4′), 80.2 (C-3′), 72.0 (*C*H$_2$−OBn), 61.0 (C-5′), 26.9 (*C*H$_3$-isopropyledene), 26.4 (*C*H$_3$-isopropyledene); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{20}O_5$ 303.1203; Found 303.1203.

*5′-O-(Benzyl)-1′,2′-O-isopropylidene-3′α-fluoro-D-ribofuranose (**4**).* To a stirred solution of **3** (5 g, 17.84 mmol) in a mixture of anhydrous CH_2Cl_2 (160 mL) and anhydrous pyridine (30 mL) was added DAST (10 mL, 75.63 mmol) at −20 °C. Then, the reaction mixture was slowly warmed to rt and left stirring for 16 h at rt. After completion, the reaction mixture was cooled to 0 °C and slowly poured into an ice-cold saturated solution of $NaHCO_3$ (500 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* and the resulting crude residue was purified by column chromatography on silica gel (gradient hexane/EtOAc, 49:1, v/v; 49:1, v/v; 9:1, v/v) to give **4** (2.82 g, 56%) as a colorless oil (R_f = 0.49, 30% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.29 (m, 5H, *Ar*-H OBn), 5.96 (d, J = 3.7 Hz, 1H, H-1′), 4.73−4.42 (m, 6H, C*H*$_2$-OBn, H-2′, H-3′, H-5′ and H-5″), 4.01 (d, J = 3.3 Hz, 1H, H-4′), 1.50 (s, 3H, C*H*$_3$-isopropylidene), 1.33 (s, 3H, C*H*$_3$-isopropylidene); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3 (*1C*-Bn), 128.7 (Ar−C), 128.2 (Ar−C), 127.8 (Ar−C), 112.2 (1C-isopropylidene), 105.5 (C-1′), 82.4 (C-2′), 81.7 (d, $^2J_{C,F}$ = 5.4 Hz, C-4′), 80.2 (*C*H$_2$−OBn), 78.7 (d, $^1J_{C,F}$ = 23.5 Hz, C-3′), 72.1 (C-5′), 27.0 (*C*H$_3$-isopropylidene), 26.5 (*C*H$_3$-isopropylidene); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{19}FO_4$ 305.1160; Found 305.1159.

*5′-O-(Benzyl)-1′,2′-diacetoxy-3′α-fluoro-α/β-D-ribofuranose (**6**).* To a stirred suspension of **4** (2.8 g, 9.92 mmol) in H_2O (15 mL) was added TFA (15 mL) at 0 °C and the solution was stirred at room temperature for 4 h. Removal of the solvent *in vacuo* gave a residue that was coevaporated with toluene (3×) to remove residual TFA. The residue was redissolved in H_2O and lyophilized to obtain the diol **5** as a pale yellow solid (2.40 g, quan.), which was used directly in the subsequent reaction without any purification (R_f = 0.27, 50% EtOAc in hexane). HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{12}H_{15}FO_4$ 265.0847; Found 265.0857.

Acetic anhydride (10.2 mL) was added dropwise to a stirred solution of compound **5** (2.4 g, 9.92 mmol) in anhydrous pyridine (22 mL) at 0 °C. The reaction mixture was then slowly warmed to room temperature and the stirring was continued for 12 h. The volatiles were removed *in vacuo* and residue was coevaporated with toluene (2×). The resulting crude residue was purified by column chromatography on silica gel (gradient hexane/EtOAc, 19:1, v/v; 9:1, v/v; 6:1, v/v) to give **6** containing a mixture of two diastereomers (∼2:1) (2.8 g, 83%) as a colorless liquid (R_f = 0.64, 50% EtOAc in hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.26 (m, 5H, Ar-*H* OBn), 6.42 (d, J = 4.6 Hz, 0.67H, H-1′α), 6.18 (s, 0.33H, H-1′β), 5.27−5.24 (m, 1H, H-2′), 4.78−4.43 (m, 5H, C*H*$_2$-OBn, H-3′ $\alpha\beta$, H-5′$\alpha\beta$ and H-5″ $\alpha\beta$), 4.36 (dd, J = 6.6, 5.6 Hz, 0.67H, H-4′α), 4.36 (d, J = 5.6 Hz, 0.33H, H-4′β), 2.09, 2.07 (2 s, 2.33 H, 2 x βC*H*$_3$-OAc), 2.06, 2.05 (2 s, 4.1H, 2 × C*H*$_3$-αOAc); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 169.8 (2 x CO-βOAc), 169.9, 169.6 (2 x CO-αOAc), 138.5 (*ipso C*-Bn), 128.8, 128.4, 127.9 (Ar *C*-Bnα), 128.8, 128.3, 127.9 (Ar *C*-Bnβ), 99.7 (C-1′β), 93.9 (C-1′α), 82.4 (d, $^1J_{C,F}$ = 190.1 Hz, C-3′β), 81.8 (d, $^1J_{C,F}$ = 170.0 Hz, C-3′α), 81.8 (d, $^1J_{C,F}$ = 170.0 Hz, C-3′α), 81.6 (C-5′β), 80.2 (d, $^2J_{C,F}$ = 5.9 Hz, C-4′β), 79.6 (d, $^2J_{C,F}$ = 5.9 Hz, C-4′α), 79.5 (C-2′α), 77.6 (C-2′β), 77.4 (C-5′α), 72.9 (*C*H$_2$−OBnα), 72.3 (*C*H$_2$−OBnβ), 21.4, 21.0 (2 x *C*H$_3$−OAcβ), 21.2, 20.7 (2 x *C*H$_3$−OAcα),); ^{19}F NMR (470 MHz, $CDCl_3$): δ −227.8 (app Hex, J = 46.4, 14.2 Hz, 0.33F, β-isomer), −230.0 (app Hex, J = 46.4, 14.2 Hz, 0.33F, α-isomer)); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{19}FO_6$ 349.1058; Found 349.1052.

*(2′R,3′S,4′R,5′R)-2′-(6-Benzamido-9H-purin-9-yl)-5′-((benzyloxy)-methyl)-4′-fluorotetrahydrofuran-3′-yl acetate (**7**).* 1 M $SnCl_4$ in CH_2Cl_2 (14.15 mL, 14.15 mmol) was added dropwise to a stirred mixture of **6** (2.1 g, 6.43 mmol) and N^6-benzoyl adenine (1.85 g, 7.72 mmol) in anhydrous acetonitrile (60 mL) at −20 °C. The reaction mixture was then slowly warmed to room temperature and stirred at same temperature for 3 h. After completion, the reaction mixture was cooled to 0 °C and quenched with saturated $NaHCO_3$ solution. Reaction mixture was diluted with EtOAc (200 mL) and milky aq. layer was extracted with EtOAc (3 × 150 mL). Combined organic layer was washed with brine, dried, concentrated *in vacuo*, and the resulting crude residue was purified by column chromatography on silica gel (gradient hexane/EtOAc, 4:1, v/v; 3:2, v/v; 1:4, v/v) to give **7** (2.76 g, 85%) as a white semisolid (R_f = 0.37, EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (br s, 1H, NH), 8.78 (s, 1H, H-8), 8.36 (s, 1H, H-2), 8.02 (d, J = 7.6 Hz, 2H, *o* H-Bz), 7.59 (t, J = 7.4 Hz, 1H, *p* H-Bz), 7.50 (app t, J = 7.8, 7.5 Hz, 2H, *m* H-Bz), 7.35−7.24 (m, 5H, Ar−H OBn), 6.43 (s, 1H, H-1′), 5.56 (s, 1H, H-2′), 4.85−4.68 (m, 3H, C*H*$_2$-OBn and H-5′), 4.59−4.53 (m, 2H, H-5″ and H-3′), 4.16 (d, J = 4.0 Hz, 1H, H-4′), 2.18 (s, 3H, C*H*$_3$-OAc); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6 (CO-OAc), 164.8 (CO-Bz), 152.9 (C-2), 151.6 (C-4), 149.6 (C-6), 141.9 (C-8), 136.2 (*ipso* C- OBn), 133.7 (*ipso* C-Bz), 132.9 (*p* C-Bz), 128.9 (*m* C-Bz), 128.8, 128.6, 128.2 (Ar *C*-OBn), 128.0 (*o* C-Bz), 122.9 (C-5), 87.6 (C-1′), 81.3 (d, $^1J_{C,F}$ = 23.3 Hz, C-3′), 81.1 (d, $^5J_{C,F}$ = 168.8 Hz, *C*H$_2$−OBn), 79.9 (d, $^2J_{C,F}$ = 5.6 Hz, C-4′), 79.9 (C-2′), 72.5 (C-5′), 20.9 (*C*H$_3$−OAc); ^{19}F NMR (470 MHz, $CDCl_3$): δ −228.9 (app Hex, J = 47.1, 14.3 Hz); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{26}H_{24}FN_5O_5$ 506.1834; Found 506.1829.

*-(2′R,3′S,4′R,5′R)-2-(6-Benzamido-9H-purin-9-yl)-4′-fluoro-5′-(hydroxymethyl)tetrahydrofuran-3′-yl acetate (**8**).* To a stirred solution of **7** (2.7 g, 5.34 mmol) in anhydrous CH_2Cl_2 (54 mL) was added 1 M BCl_3 in CH_2Cl_2 (11.75 mL, 11.75 mmol) at −78 °C. Then the reaction mixture was slowly warmed to 0 °C over 2.5 h and stirred at this temperature for 30 min. After completion, the reaction mixture was cooled to −20 °C and quenched with dropwise addition of saturated solution of $NaHCO_3$ (150 mL). Aq. layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* and the resulting crude residue was purified by column chromatography on silica gel (gradient CH_2Cl_2/MeOH, 100:0, v/v; 99:1, v/v; 49:1, v/v) to give **4** (1.91 g, 86%) as a white solid (R_f = 0.37, 10% MeOH in CH_2Cl_2), Mp: 180−182 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (br s, 1H, NH), 8.69 (s, 1H, H-8), 8.24 (s, 1H, H-2), 8.01 (d, J = 7.5 Hz, 2H, *o* H-Bz), 7.57 (t, J = 7.4 Hz, 1H, *p* H-Bz), 7.47 (app t, J = 7.8, 7.2 Hz, 2H, *m* H-Bz), 6.94 (d, J = 9.2 Hz, 1H, 5′-O*H*), 5.98 (d, J = 1.6 Hz, 1H, H-1′), 5.35 (app t, J = 1.6 Hz 1H, H-2′), 5.00−4.93, 4.69−4.63 (m, 1H, H-3′), 4.85−4.77 (m, 1H, H-4′), 4.51−4.42 (m, 2H, H-5′ and H-5″), 2.13 (s, 3H, C*H*$_3$-OAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7 (CO-OAc), 164.7 (CO-Bz), 151.6 (C-2), 149.9 (C-4 and C-6), 142.8 (C-8), 132.9 (*ipso* C-Bz), 132.6 (*p* C-Bz), 128.4 (*m* C-Bz), 127.7 (*o* C-Bz), 123.3 (C-5), 89.6 (C-1′), 83.2 (C-2′), 81.6 (d, $^2J_{C,F}$ = 20.6 Hz, C-4′), 81.5 (d, $^1J_{C,F}$ = 167.1 Hz, C-3′), 73.9 (d, $^3J_{C,F}$ = 7.7 Hz, C-5′), 20.3 (*C*H$_3$−OAc); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{18}FN_5O_5$ 416.1358; Found 416.1365.

*1′-(Benzyloxy)-2′,3′,5′-triacetoxy-β-D-ribofuranose (**11**).* $SnCl_4$ (18.5 mL, 158.4 mmol) was added dropwise to a stirred mixture of **10** (42 g, 132 mmol) and BnOH (15.1 mL, 145.2 mmol) in anhydrous acetonitrile (630 mL) at −20 °C. The reaction mixture was then slowly warmed to room temperature and stirred at same temperature for 4 h. After completion, the reaction mixture was cooled to −30 °C and quenched with ice cooled saturated $NaHCO_3$ solution. Reaction mixture was diluted with cold EtOAc (1200 mL) and milky aq. layer was extracted with cold EtOAc (3 × 600 mL). Combined organic layer was washed with brine, dried, concentrated *in vacuo*, and the resulting crude residue was purified by column chromatography on silica gel

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(gradient Hexane/EtOAc, 19:1, v/v; 9:1, v/v; 4:1, v/v) to give **11** (30.8 g, 64%) as a white semisolid (R_f = 0.47, 50% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.27 (m, 5H, Ar−H OBn), 5.40 (dd, J = 6.7, 5.0 Hz, 1H, H-3′), 5.56 (d, J = 4.9 Hz, 1H, H-2′), 5.08 (s, 1H, H-1′), 4.64 (dd, J = 75.4, 11.8 Hz, 2H, CH_2-OBn), 4.40−4.29 (m, 2H, H-5′ and H-4′), 4.22−4.11 (m, 1H, H-5″), 2.09 (s, 3H, CH_3-OAc), 2.05 (s, 3H, CH_3-OAc), 2.03 (s, 3H, CH_3-OAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7 (CO-OAc), 169.7 (CO-OAc), 169.6 (CO-OAc), 136.9 (*ipso* C- OBn), 128.5, 128.0, 127.9 (Ar *C*-OBn), 104.3 (C-1′), 78.7 (C-4′), 74.9 (C-2′), 71.6 (C-3′), 69.5 (CH_2−OBn), 64.5 (C-5′), 20.8, 20.7, 20.6 (3 x CH_3−OAc); HRMS (ESI-TOF) m/z: [M +Na]$^+$ Calcd for $C_{18}H_{22}O_8$ 389.1207; Found 389.1209.

*1′-(Benzyloxy)-β-D-ribofuranose (**12**).* The compound **11** (26 g, 70.97 mmol) was dissolved in 7 *N* NH_3 in MeOH (400 mL) and the reaction mixture was stirred at room temperature in a sealed vessel for 24 h. The reaction mixture was concentrated under reduced pressure and the resulting crude residue was purified by column chromatography on silica gel (gradient CH_2Cl_2/MeOH, 49:1, v/v; 24:1, v/v; 23:2, v/v) to give **12** (15.2 g, 89%) as a white semisolid (R_f = 0.43, 15% MeOH in CH_2Cl_2). The NMR spectral data for **12** were identical with those reported previously.[14] HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{12}H_{16}O_5$ 263.0890; Found 263.0891.

*3′,5′-O-Tetraisopropyldisiloxane-1′-(benzyloxy)-β-D-ribofuranose (**13**).* To a stirred suspension of **12** (12 g, 49.95 mmol) in anhydrous pyridine (230 mL) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (15.32 mL, 47.95 mmol) at 0 °C and the solution was stirred at room temperature for 4 h. Then, the reaction mixture was cooled and quenched with a saturated $NaHCO_3$ solution. The reaction mixture was diluted with EtOAc (600 mL) and the aqueous layer was extracted with EtOAc (3 × 400 mL). The combined organic layers were washed with brine, dried, concentrated *in vacuo*, and the resulting crude residue was purified by column chromatography on silica gel (gradient Hexane/EtOAc, 99:1, v/v; 19:1, v/v; 9:1, v/v) to give **11** (21.7 g, 90%) as a colorless oil (R_f = 0.51, 30% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.29 (m, 5H, Ar−H OBn), 5.03 (s, 1H, H-1′), 5.40 (app t, J = 5.2 Hz, 1H, H-3′), 4.56 (dd, J = 74.5, 11.7 Hz, 2H, CH_2-OBn), 4.10−4.03 (m, 3H, H-5′, H-4′ and H-2′), 3.84−3.76 (m, 1H, H-5″), 3.00 (br s, 1H, 2′-O*H*), 1.09−1.01 (m, 28H, 4 x C*H* and 8 x CH_3-^{i}Pr); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.9 (*ipso* C- OBn), 128.5, 128.2, 127.9 (Ar *C*-OBn), 105.4 (C-1′), 82.9 (C-4′), 76.0 (C-2′), 75.2 (C-3′), 69.2 (CH_2−OBn), 66.3 (C-5′), 17.6, 17.5, 17.4, 17.3, 17.1, 17.0, 16.9, 13.4, 12.9, 12.7 (4 x *C*H- ^{i}Pr and 8 x CH_3- ^{i}Pr); HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{24}H_{42}O_6Si_2$ 505.2412; Found 505.2410.

*3′,5′-O-Tetraisopropyldisiloxane-2′-O-benzoyl-1′-(benzyloxy)-β-D-ribofuranose (**14**).* To a stirred solution of **13** (4 g, 8.256 mmol) in anhydrous pyridine (60 mL) was added benzoyl chloride (1.35 mL, 11.60 mmol) at 0 °C and the solution was stirred at room temperature for 12 h. Then the reaction mixture was cooled and diluted with a saturated $NaHCO_3$ solution (150 mL). The aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine, dried, concentrated *in vacuo*, and the resulting crude residue was purified by column chromatography on silica gel (gradient Hexane/EtOAc, 99:1, v/v; 49:1, v/v; 97:3, v/v) to give **14** (4.42 g, 91%) as a colorless liquid (R_f = 0.60, 10% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.6 Hz, 2H, *o* H-Bz), 7.55 (t, J = 7.4 Hz, 1H, *p* H-Bz), 7.42 (app t, J = 7.8, 7.3 Hz, 2H, *m* H-Bz), 7.35−7.27 (m, 5H, Ar−H OBn), 4.56 (d, J = 4.7 Hz, 1H, H-2′), 5.11 (s, 1H, H-1′), 4.74−4.70 (m, 1H, H-3′), 4.63 (dd, J = 70.7, 11.7 Hz, 2H, CH_2-OBn), 4.16−4.08 (m, 2H, H-5′ and H-4′), 3.94−3.87 (m, 1H, H-5″), 1.09−0.81 (m, 28H, 4 × C*H* and 8 × CH_3-^{i}Pr); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6 (CO-Bz), 137.3 (*ipso* C- OBn), 133.1 (*ipso* C-Bz), 130.2 (*p* C-Bz), 129.9 (*m* C-Bz), 128.6, 128.4, 128.2 (Ar *C*-OBn), 128.0 (*o* C-Bz), 103.6 (C-1′), 82.5 (C-4′), 77.5 (C-2′), 73.6 (C-3′), 69.3 (CH_2−OBn), 65.3 (C-5′), 17.6, 17.5, 17.4, 17.2, 17.1, 16.9, 16.8, 13.4, 13.3, 12.9, 12.8 (4 x *C*H- ^{i}Pr and 8 x CH_3- ^{i}Pr); HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for $C_{31}H_{46}O_7Si_2$ 587.2855; Found 587.2866.

*3′,5′-O-Tetraisopropyldisiloxane-2′-O-benzyloxymethyl-1′-(benzyloxy)-β-D-ribofuranose (**15**).* To a stirred solution of **13** (7.94 g, 16.45 mmol) in anhydrous CH_2Cl_2 (120 mL) was added BOM chloride (5.70 mL, 41.11 mmol) followed by DIPEA (11.46 mL, 65.8 mmol) and the solution was refluxed for 24 h. Then, the reaction mixture was cooled and quenched with a 5% $NaHCO_3$ solution (300 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with brine, dried, concentrated *in vacuo* and the resulting crude residue was purified by column chromatography on silica gel (gradient hexane/EtOAc, 99:1, v/v; 49:1, v/v; 24:1, v/v) to give **15** (9.12 g, 92%) as a colorless liquid (R_f = 0.47, 20% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.25 (m, 10H, Ar−H OBn and BOM), 4.92 (dd, J = 29.4, 6.7 Hz, 2H, OCH_2O-BOM), 4.88 (s, 1H, H-1′), 4.63−4.56 (m, 3H, CH_2-BOM and H-3′), 4.55 (dd, J = 87.6, 11.7 Hz, 2H, CH_2-OBn), 4.19 (d, J = 4.4 Hz, 1H, H-2′), 4.10−4.00 (m, 2H, H-5′ and H-4′), 3.94−3.87 (m, 1H, H-5″), 1.08−0.85 (m, 28H, 4 x C*H* and 8 x CH_3-^{i}Pr); ^{13}C NMR (75 MHz, $CDCl_3$): 137.9 (*ipso* C- 1′OBn), 137.6 (*ipso* C- BOM), 128.4, 128.4, 128.0, 127.9, 127.8, 127.7 (Ar *C*-OBn and BOM), 104.2 (C-1′), 94.4 (OCH_2O-BOM), 81.4 (C-4′), 79.6 (C-2′), 73.7 (C-3′), 69.6 (CH_2−BOM), 69.0 (CH_2-1′OBn), 64.3 (C-5′), 17.6, 17.4, 17.3, 17.2, 17.1, 13.4, 13.3, 12.9, 12.8 (4 x *C*H- ^{i}Pr and 8 × CH_3- ^{i}Pr); HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{32}H_{50}O_7Si_2$ 625.2987; Found 625.2996.

*2′-O-Benzoyl-1′-(benzyloxy)-β-D-ribofuranose (**16**).* $Et_3N{\cdot}3HF$ (5 mL, 15.33 mmol) was added to a stirred solution of compound **14** (3 g, 5.11 mmol) in anhydrous THF (45 mL) in a plastic flask. The reaction mixture was then stirred at room temperature for 24 h. The volatiles were removed *in vacuo* and residue was diluted with a saturated $NaHCO_3$ solution (100 mL). The aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine, dried, concentrated *in vacuo* and the resulting crude residue was purified by column chromatography on silica gel (gradient hexane/EtOAc, 9:1, v/v; 4:1, v/v; 3:2, v/v) to give **16** (0.85 g, 48%) as a white semisolid (R_f = 0.42, EtOAc). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.02 (d, J = 7.6 Hz, 2H, *o* H-Bz), 7.68 (t, J = 7.4 Hz, 1H, *p* H-Bz), 7.55 (app t, J = 7.8, 7.3 Hz, 2H, *m* H-Bz), 7.36−7.24 (m, 5H, Ar−H OBn), 5.39 (d, J = 6.3 Hz, 1H, 3′-O*H*), 5.16−5.14 (m, 2H, H-1′ and H-2′), 4.84 (t, J = 5.6 Hz, 1H, 5′-O*H*), 4.63 (dd, J = 83.1, 11.7 Hz, 2H, CH_2-OBn), 4.33−4.24 (m, 1H, H-3′), 4.01−3.96 (m, 2H, H-4′), 3.70−3.46 (m, 1H, H-5′ and H-5″); ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.1 (CO-Bz), 137.7 (*ipso* C- OBn), 133.5 (*ipso* C-Bz), 129.4 (*p* C-Bz), 128.7, 128.6, 128.4, 128.2 (Ar *C*-OBn and -Bz), 127.5 (*o* C-Bz), 103.5 (C-1′), 84.0 (C-4′), 77.1 (C-2′), 69.4 (C-3′), 68.3 (CH_2−OBn), 62.4 (C-5′); HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{19}H_{20}O_6$ 367.1152; Found 367.1149.

*2′-O-Benzyloxymethyl-1′-(benzyloxy)-β-D-ribofuranose (**17**).* A similar synthetic protocol as the one used for the synthesis of **16** was employed for the synthesis of **17**, starting from **15** (8.74 g, 14.49 mmol), $Et_3N{\cdot}3HF$ (5.2 mL, 31.89 mmol) and anhydrous THF (80 mL) to obtain **17** (4.89 g, 94%) as a white solid (R_f = 0.4, EtOAc; column chromatography gradient Hexane/EtOAc, 9:1, v/v; 4:1, v/v; 1:1, v/v), Mp: 56−58 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.33−7.27 (m, 10H, Ar−H OBn and BOM), 4.99 (d, J = 6.8 Hz, 1H, 3′-O*H*), 4.97 (br s, 1H, H-1′), 4.84 (s, 2H, OCH_2O-BOM), 4.72 (t, J = 5.8 Hz, 1H, 5′-O*H*), 4.58 (s, 2H, CH_2-BOM), 4.55 (dd, J = 90.2, 11.7 Hz, 2H, CH_2-OBn),), 4.10−4.04 (m, 1H, H-3′), 3.94 (d, J = 4.5 Hz, 1H, H-2′), 3.86−3.81 (m, 1H, H-4′), 3.62−3.38 (m, 2H, H-5′ and H-5″); ^{13}C NMR (75 MHz, DMSO-d_6): δ 138.0 (*ipso* C- 1′OBn), 137.9 (*ipso* C- BOM), 128.2, 128.2, 127.7 127.6, 127.5, 127.4 (Ar C-OBn and BOM), 104.4 (C-1′), 93.9 (OCH_2O-BOM), 83.9 (C-4′), 79.6 (C-2′), 70.4 (C-3′), 68.7 (CH_2−BOM), 68.2 (CH_2-1′OBn), 62.8 (C-5′); $[\alpha]^{20}_D$ = −70.8° (c = 1, CH_3OH); HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{20}H_{24}O_6$ 383.1465; Found 383.1488.

*5′-O-MMTr-2′-O-benzyloxymethyl-1′-(benzyloxy)-β-D-ribofuranose (**18**).* To a stirred solution of **17** (3.73 g, 10.34 mmol) in anhydrous pyridine (45 mL) was added MMTr chloride (3.84 g, 12.42 mmol) and the solution was stirred at room temperature for 18 h. Then, the reaction mixture was diluted with CH_2Cl_2 (250 mL) and washed with a 5% $NaHCO_3$ solution (200 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were washed with brine, dried, concentrated *in vacuo*, and the

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resulting crude residue was purified by column chromatography on silica gel (gradient Hexane/EtOAc, 19:1, v/v; 17:3, v/v; 3:1, v/v) to give **18** (6.3 g, 96%) as a pale-yellow sticky mass (R_f = 0.47, 50% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.18 (m, 22H, Ar−H OBn, BOM and MMTr), 6.79 (d, J = 8.9 Hz, 2H, *m* H-Anisyl MMTr), 5.15 (s, 1H, H-1′), 4.892 (s, 2H, OCH_2O-BOM), 4.63 (dd, J = 14.9, 12.0 Hz, 2H, CH_2-BOM), 4.59 (dd, J = 88.9, 11.7 Hz, 2H, CH_2-OBn), 4.34−4.27 (m, 1H, H-3′), 4.16−4.09 (m, 2H, H-2′ and H-4′), 3.75 (s, 3H, OCH_3-MMTr), 3.38−3.21 (m, 2H, H-5′ and H-5″), 2.52 (d, J = 8.2 Hz, 1H, 3′- OH); ^{13}C NMR (75 MHz, $CDCl_3$): 158.6 (*p* C-Anisyl MMTr), 144.6 (*ipso* C- MMTr), 137.5 (*ipso* C-1′OBn), 137.3 (*ipso* C- BOM), 135.8 (*ipso* C- Anisyl MMTr), 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 126.9 (Ar *C*-OBn, BOM and MMTr), 113.2 (*m* C-Anisyl MMTr), 104.8 (C-1′), 95.2 (OCH_2O-BOM), 86.4 (1C-MMTr), 83.4 (C-4′), 81.7 (C-2′), 72.0 (C-3′), 70.3 (CH_2−BOM), 69.6 (CH_2-1′OBn), 65.1 (C-5′), 55.3 (OCH_3-MMTr); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{40}H_{40}O_7$ 655.2666; Found 655.2690.

*3′-O-Benzoyl-2′-O-benzyloxymethyl-1′-(benzyloxy)-β-D-ribofuranose (**19**).* To a stirred solution of **18** (3.7 g, 5.85 mmol) in anhydrous pyridine (45 mL) was added benzoyl chloride (0.82 mL, 7.02 mmol) at 0 °C and the solution was stirred at room temperature for 16 h. Then, the reaction mixture was diluted with CH_2Cl_2 (250 mL) and washed with a 5% $NaHCO_3$ solution (200 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were washed with brine, dried, concentrated *in vacuo* to give 5′-*O*-MMTr-3′-*O*-benzoyl-2′-*O*-benzyloxymethyl-1′-(benzyloxy)-β-D-ribofuranose (4.31 g, quan.) as a pale-yellow sticky mass (R_f = 0.58, 50% EtOAc in hexane). The resulting crude residue was used for next step without further purification.

A solution of the above crude of 5′-*O*-MMTr-3′-*O*-benzoyl-2′-*O*-benzyloxymethyl-1′-(benzyloxy)-β-D-ribofuranose (4.31 g, 5.85 mmol) in 80% AcOH (45 mL) was stirred at room temperature for 4 h. After completion, the volatiles were removed *in vacuo* and residue was coevaporated with toluene (2×). The resulting crude residue was purified by column chromatography on silica gel (gradient hexane/EtOAc, 9:1, v/v; 17:3, v/v; 4:1, v/v) to give **19** (2.25 g, 83% over two steps) as a colorless sticky mass (R_f = 0.39, 50% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 7.6 Hz, 2H, *o* H-Bz), 7.57 (t, J = 7.4 Hz, 1H, *p* H-Bz), 7.43 (app t, J = 7.8, 7.3 Hz, 2H, *m* H-Bz), 7.35−7.20 (m, 10H, Ar−H OBn and BOM), 5.49 (t, J = 5.4 Hz, 1H, H-3′), 5.20 (d, J = 1.5 Hz, 1H, H-1′), 4.78 (s, 2H, OCH_2O-BOM), 4.68 (dd, J = 62.3, 11.7 Hz, 2H, CH_2-BOM), 4.58−4.44 (m, 2H, CH_2-OBn, H-2′ and H-4′), 3.89−3.68 (m, 2H, H-5′ and H-5″), 2.04 (br s, 1H, 5′- OH); ^{13}C NMR (75 MHz, $CDCl_3$): 166.1 (*C*O-Bz), 137.5 (*ipso* C- OBn), 137.2 (*ipso* C- BOM), 133.5 (*ipso* C-Bz), 129.9 (*p* C-Bz), 129.6, 128.7, 128.6, 128.5, 128.2, 128.1, 127.9 (Ar *C*-OBn, BOM and Bz), 127.8 (*o* C-Bz), 106.1 (C-1′), 94.7 (OCH_2O-BOM), 82.9 (C-4′), 79.8 (C-2′), 73.3 (C-3′), 70.5 (CH_2−BOM), 69.8 (CH_2-1′OBn), 63.3 (C-5′); HRMS (ESI-TOF) m/z: $[M+NH_4]^+$ Calcd for $C_{27}H_{28}O_7$ 482.2178; Found 482.2164.

*(2S,3S,4R,5R)-3-(Benzoyloxy)-5-(benzyloxy)-4-((benzyloxy)methoxy)tetrahydrofuran-2-carboxylic Acid (**20**).* To a stirred solution of **19** (2.0 g, 4.31 mmol) in a 1:1 ACN:H_2O mixture (30 mL) were added iodosobenzene diacetate (3.05 g, 76.51 mmol) followed by TEMPO (0.135 g, 0.861 mmol) at 0 °C and the mixture was stirred at room temperature for 4.5 h. Upon completion, reaction mixture was concentrated under reduced pressure and diluted with H_2O (50 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 100 mL) and the combined organic layers were washed with brine, dried and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography on silica gel (gradient hexane/EtOAc, 9:1, v/v; 4:1, v/v; 3:1, v/v) to give **20** (1.87 g, 91%) as a colorless sticky mass (R_f = 0.38, 50% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.6 Hz, 2H, *o* H-Bz), 7.57 (t, J = 7.4 Hz, 1H, *p* H-Bz), 7.43 (app t, J = 7.8, 7.3 Hz, 2H, *m* H-Bz), 7.32−7.18 (m, 10H, Ar−H OBn and BOM), 5.76 (t, J = 5.3 Hz, 1H, H-3′), 5.25 (s, 1H, H-1′), 4.89 (d, J = 6.4 Hz, 1H, H-2′), 4.75 (dd, J = 9.0, 7.0 Hz, 2H, OCH_2O-BOM), 4.72 (dd, J = 104.2, 11.6 Hz, 2H, CH_2-BOM), 4.57−4.42 (m, 3H, CH_2-OBn and H-4′); ^{13}C NMR (75 MHz, $CDCl_3$): 174.8 (*C*O_2H-4′), 165.8 (*C*O-Bz), 137.3 (*ipso* C- OBn), 136.9 (*ipso* C- BOM), 133.6 (*ipso* C-Bz), 130.0 (*p* C-Bz), 128.6, 128.6, 128.5, 128.2, 128.1 (Ar *C*-OBn, BOM and Bz), 127.9 (*o* C-Bz), 106.3 (C-1′), 94.9 (OCH_2O-BOM), 79.0 (C-4′), 78.7 (C-2′), 75.5 (C-3′), 70.1 (CH_2−BOM), 69.9 (CH_2-1′OBn); HRMS (ESI-TOF) m/z: $[M+NH_4]^+$ Calcd for $C_{27}H_{26}O_8$ 496.1971; Found 496.1978.

*(3S,4R,5R)-2-Acetoxy-5-(benzyloxy)-4-((benzyloxy)methoxy)-tetrahydrofuran-3-yl Benzoate (**21**).* To a stirred solution of compound **20** (1.83 g, 3.824 mmol) in anhydrous THF (50 mL) was added anhydrous pyridine (1.11 mL, 13.77 mmol) and the reaction mixture was flushed and degaussed with argon for 30 min. Lead tetra acetate (2.88 g, 6.50 mmol) was then added to the degassed reaction mixture in portions (2×). The reaction mixture was protected from light and stirred for 20 h at 35 °C. The solid was filtered off through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was diluted with ethyl acetate and the combined organic layers were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (gradient hexane/EtOAc, 19:1, v/v; 9:1, v/v; 17:3, v/v) to afford a diastereomeric mixture (∼4:1) of compound **21** (1.66 g, 88%) as colorless sticky mass (R_f = 0.56, 40% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06, 8.01 (d, J = 7.4 Hz, 2H, *o* H-Bz), 7.57 (t, J = 7.4 Hz, 1H, *p* H-Bz), 7.44 (app t, J = 7.8, 7.3 Hz, 2H, *m* H-Bz), 7.35−7.20 (m, 10H, Ar−H OBn and BOM), 6.62, 6.46 (d, J = 2.2 Hz, 1H, H-4′), 5.85−5.80, 5.57−5.52 (m, 1H, H-3′), 5.35 (d, J = 2.6 Hz, 1H, H-1′), 4.89 (d, J = 6.4 Hz, 1H, H-2′), 4.77−4.72 (m, 2H, OCH_2O-BOM), 4.68 (dd, J = 82.9, 11.7 Hz, 2H, CH_2-BOM), 4.51 (dd, J = 33.1, 11.7 Hz, 2H, CH_2-OBn), 2.10 (s, 3H, CH_3-OAc); ^{13}C NMR (75 MHz, $CDCl_3$): 169.8 (*C*O-OAc), 165.6 (*C*O-Bz), 137.3 (*ipso* C-OBn), 137.2 (*ipso* C- BOM), 133.6 (*ipso* C-Bz), 130.0 (*p* C-Bz), 128.6, 128.6, 128.5, 128.5, 128.1, 128.0 (Ar *C*-OBn, BOM and Bz), 127.9 (*o* C-Bz), 107.2 (C-1′), 99.2 (C-4′), 94.6 (OCH_2O-BOM), 78.8 (C-2′), 76.3 (C-3′), 70.4 (CH_2−BOM), 69.8 (CH_2-1′OBn), 21.2 (CH_3-OAc); HRMS (ESI-TOF) m/z: $[M+NH_4]^+$ Calcd for $C_{28}H_{28}O_8$ 510.2128; Found 510.2139.

*1′,2′-O-Isopropylidene-α-L-ribofuranose (**24**).* To a stirred solution of **23** (48 g, 163.1 mmol) in MeOH (500 mL) was added NaOMe (5.4 M in MeOH, 36.3 mL, 196 mmol) at room temperature and the solution was stirred 1 h at room temperature. The reaction was quenched by the addition of solid NH_4Cl and the reaction mixture was diluted with diethyl ether. The solid was filtered off and washed with diethyl ether. The filtrate was removed under reduced pressure, and the resulting crude residue was purified via flash chromatography (hexane/EtOAc, 1:1 to 1:2 v/v) to give the diol **24** (30 g, 97%) as a white solid (R_f = 0.25, EtOAc), Mp: 86−88 °C. The NMR spectral data for **24** were identical with those reported previously.[18] mp 86−88 °C; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_8H_{14}O_5$ 213.0734; Found 213.0734.

*3′,5′-Di-O-benzyl-1′,2′-O-isopropylidene-α-L-ribofuranose (**25**).* A solution of diol **24** (28.51 g, 150 mmol) in dry THF (200 mL) was added dropwise to a stirred suspension of NaH (55% in mineral oil, 16.35 g, 375 mmol) in dry THF (250 mL) at −20 °C under argon, and the resulting mixture was stirred at 0 °C for 30 min, prior to addition of benzyl bromide (44.6 mL, 375 mmol). Then, the reaction mixture was slowly warmed to room temperature and left for stirring for 16 h at same temperature. The reaction mixture was cooled to 0 °C and quenched with a saturated NH_4Cl solution. The reaction mixture was diluted with EtOAc (500 mL) and the aqueous layer was extracted with EtOAc (2 × 300 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* and the resulting crude residue was purified by column chromatography on silica gel (gradient hexane/EtOAc, 19:1, v/v; 9:1, v/v; 4:1, v/v) to give **25** (54.4 g, 92%) as a colorless oil (R_f = 0.70, 40% EtOAc in hexane). The NMR spectral data for **25** were identical with those reported previously.[18] HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{26}O_5$ 393.1673; Found 393.1672.

*3′,5′-Di-O-benzyl-1′,2′-diacetoxy-α/β-L-ribofuranose (**26**).* Following a similar procedure as the one used for the synthesis of **5**, the diol 3,5-di-*O*-benzyl-α/β-L-ribofuranose was obtained as a pale

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yellow solid (R_f = 0.29, 50% EtOAc in hexane, 48.2 g, quan.), starting from **25** (54 g, 146 mmol) and 1:1 H_2O:TFA mixture (400 mL), which was used directly in the subsequent reaction without any purification.

Following a similar procedure as the one used for the synthesis of **6**, compound **26** was obtained (R_f = 0.63, 50% EtOAc in hexane; column chromatography gradient hexane/EtOAc, 9:1, v/v; 4:1, v/v; 3:1, v/v) containing a mixture of two diastereomers (~4:1) as a colorless foam (54.5 g, 90% over two steps), starting from diol 3,5-di-*O*-benzyl-α/β-L-ribofuranose (48.2 g, 146 mmol), acetic anhydride (143 mL) and anhydrous pyridine (320 mL). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.23 (m, 10H, *Ar*-H 2 x OBn), 6.40 (d, *J* = 4.6 Hz, 0.2H, H-1′α), 5.31 (s, 0.8H, H-1′β), 5.30−5.13 (m, 1H, H-2′), 4.63−4.42 (m, 4H, 2 x CH_2-OBn), 4.34−4.25 (m, 1H, H-3′), 4.24−4.07 (m, 1H, H-4′), 3.70−3.38 (m, 2H, H-5′ and H-5″), 2.12, 2.10, 2.03, 1.93 (4 s, 6H, 2 x CH_3-OAc); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 170.1, 170.0, 169.3 (2 x CO-OAC), 138.2, 137.8, 137.4 (2 x *ipso* *C*-Bn), 128.5, 128.5, 128.4, 128.3, 128.1, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5 (Ar *C*-Bn), 98.5, 94.7 (C-1′), 83.4, 81.5 (C-4′), 76.5, 75.5 (C-2′), 73.7, 73.6 (C-3′), 73.3, 73.1 (2 × CH_2−OBn), 71.4, 69.2 (C-5′), 21.0, 20.8 (2 × CH_3−OAc); HRMS (ESI-TOF) *m*/*z*: [M+Na]$^+$ Calcd for $C_{23}H_{26}O_7$ 437.1571; Found 437.1563.

*3′,5′-Di-O-benzyl-1′-((diisopropoxyphosphoryl)methoxy)-2′-acetoxy-β-L-ribofuranose (**27**).* Following a similar procedure as the one used for the synthesis of **11**, compound **27** was obtained (R_f = 0.31, 90% EtOAc in hexane; column chromatography gradient Hexane/EtOAc, 4:1, v/v; 3:2, v/v; 2:3, v/v) as a colorless liquid (57.6 g, 80%), starting from **26** (54 g, 130.3 mmol), $SnCl_4$ (35.2 mL, 300 mmol), diisopropyl (hydroxymethyl)phosphonate (30.7 g, 156.4 mmol) and anhydrous acetonitrile (800 mL), from −20 °C to room temperature for 5 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.22 (m, 10H, Ar-*H* 2 × OBn), 5.30 (d, *J* = 4.4 Hz, 1H, H-2′), 5.07 (s, 1H, H-1′), 4.80−4.63 (m, 2H, 2 x C*H*- ^{i}Pr), 4.60−4.29 (m, 4H, 2 × CH_2-OBn), 4.26−4.20 (m, 1H, H-4′), 4.13 (dd, *J* = 7.7, 4.4 Hz, 1H, H-3′), 3.76 (ddd, *J* = 73.5 ($^2J_{H,P}$), 13.8, 8.7 Hz, 2H, -OCH_2P), 3.59 (dd, *J* = 10.5, 3.5 Hz, 1H, H-5′), 3.49 (dd, *J* = 10.5, 5.9 Hz, 1H, H-5″), 2.11 (s, 3H, CH_3-OAc), 1.36−1.27 (m, 12H, 4 x CH_3-^{i}Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 (*C*O-OAc), 138.1 (*ipso* C-OBn), 137.5 (*ipso* C-OBn), 128.5, 128.4, 128.1, 128.0, 127.7 (Ar *C*-Bn), 105.8 (d, $^3J_{C,P}$ = 11.8 Hz, C-1′), 80.8 (C-4′), 77.6 (C-3′), 73.8 (C-2′), 73.3, 73.1 (2 × CH_2−OBn), 71.4, 71.3 (d, $^2J_{C,P}$ = 6.8 Hz, 2 × 1C- ^{i}Pr), 70.9 (C-5′), 61.1 (d, $^1J_{C,P}$ = 170.4 Hz, -O*C*H_2P), 24.2, 24.1, 24.1, 24.0 (d, $^3J_{C,P}$ = 1.6 Hz, 4 x *C*H_3-^{i}Pr), 20.9 (CH_3−OAc); ^{31}P NMR (121 MHz, $CDCl_3$) δ = 19.01; [α]$^{20}_D$ = −15.0° (*c* = 1, CH_3OH); HRMS (ESI-TOF) *m*/*z*: [M+H]$^+$ Calcd for $C_{28}H_{39}O_9P$ 551.2404; Found 551.2406.

*3′,5′-Di-O-benzyl-1′-((diisopropoxyphosphoryl)methoxy)-β-L-ribofuranose (**28**).* The compound **27** (48 g, 87.2 mmol) was dissolved in 7 *N* NH_3 in MeOH (500 mL) and the reaction mixture was stirred at room temperature in a sealed vessel for 16 h. The reaction mixture was concentrated under reduced pressure and the resulting crude residue was purified by column chromatography on silica gel (gradient hexane/EtOAc, 3:1, v/v; 1:1, v/v; 3:7, v/v) to give **28** (42.8 g, 96.5%) as a colorless foam (R_f = 0.28, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.25 (m, 10H, Ar-*H* 2 x OBn), 5.01 (s, 1H, H-1′), 4.73−4.63 (m, 4H, 2 × ^{i}Pr−C*H*), 4.61−4.50 (m, 4H, 2 x CH_2-OBn), 4.29−4.23 (m, 1H, H-4′), 4.12 (d, *J* = 4.7 Hz, 1H, H-2′), 4.05 (dd, *J* = 6.4, 4.8 Hz, 1H, H-3′), 3.76 (ddd, *J* = 82.9 ($^2J_{H,P}$), 13.7, 8.7 Hz, 2H, -OCH_2P), 3.56−3.49 (m, 2H, H-5′, and H-5″), 3.03 (br s, 3′-O*H*), 1.31−1.25 (m, 12H, 4 × CH_3-^{i}Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1 (*ipso* C-OBn), 137.1 (*ipso* C-OBn), 128.6, 128.4, 128.2, 127.9, 127.6 (Ar−C), 108.2 (d, $^3J_{C,P}$ = 12.0 Hz, C-1′), 80.9 (C-4′), 79.2 (C-3′), 73.2 (C-2′), 73.1, 72.7 (2 × CH_2−OBn), 71.5 (C-5′), 71.1, 71.0 (d, $^2J_{C,P}$ = 6.6 Hz, 2 × 1C- ^{i}Pr), 61.2 (d, $^1J_{C,P}$ = 170.8 Hz, -O*C*H_2P), 24.1, 24.1, 24.0, 23.9 (d, $^3J_{C,P}$ = 1.6 Hz, 4 × *C*H_3- ^{i}Pr); ^{31}P NMR (121 MHz, $CDCl_3$) δ = 19.5; [α]$^{20}_D$ = −13.8° (*c* = 1, CH_3OH); HRMS (ESI-TOF) *m*/*z*: [M+H]$^+$ Calcd for $C_{26}H_{37}O_8P$ 509.2299; Found 509.2302.

*3′,5′-Di-O-benzyl-1′-((diisopropoxyphosphoryl)methoxy)-2′-(β-hydroxyl)-L-β-ribofuranose (**29**).* To a stirred solution of **28** (40 g, 78.7 mmol) in anhydrous CH_2Cl_2 (800 mL) was carefully added solid Dess-Martin periodinane reagent (91.7 g, 216.3 mmol) at −10 °C and the resulting suspension was stirred at room temperature for 18 h. After completion, the reaction mixture was cooled to 0 °C and quenched with water. The white solid was filtered off and washed with CH_2Cl_2. The organic layer was washed with a 5% $NaHCO_3$ solution and brine, dried over Na_2SO_4, concentrated *in vacuo* to obtain 5′-di-*O*-benzyl-1′-((diisopropoxyphosphoryl)methoxy)-2′-oxo-L-β-ribofuranose (44 g, contains impurity from DMP) as colorless liquid (R_f = 0.32, EtOAc), which was used for next step without any further purification. HRMS (ESI-TOF) *m*/*z*: [M+H]$^+$ Calcd for $C_{26}H_{35}O_8P$ 507.2142; Found 507.2143.

To a stirred solution of the above ketone (44 g, 78.7 mmol) in 1:1 absolute EtOH and anhydrous EtOAc mixture (500 mL), was added $NaBH_4$ (9.15 g, 236.1 mmol) in portions at −50 °C. The reaction mixture was then slowly warmed to room temperature over 3 h and stirred at same temperature for 2 h. After completion, the reaction was quenched with dilute AcOH. Solvent was removed *in vacuo* and crude residue was purified via flash column chromatography (gradient Hexane/EtOAc, 3:1, v/v; 1:1, v/v; 3:7, v/v) to afford **29** (28.4 g, 71% over two steps) as colorless liquid (R_f = 0.29, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.26 (m, 10H, Ar-*H* 2 × OBn), 5.02 (d, *J* = 4.5 Hz, 1H, H-1′), 4.80−4.59 (m, 4H, 2 x C*H*- ^{i}Pr and CH_2-OBn), 4.57−4.46 (m, 2H, CH_2-OBn), 5.30 (dd, *J* = 6.4, 4.6 Hz, 1H, H-2′), 4.26−4.20 (dd, *J* = 11.7, 5.8 Hz, 1H, H-4′), 3.86 (app t, *J* = 6.2 Hz, 1H, H-3′), 3.83 (ddd, *J* = 80.3 ($^2J_{H,P}$), 13.9, 8.7 Hz, 2H, -OCH_2P), 3.55−3.52 (m, 2H, H-5′ and H-5″), 1.33−1.28 (m, 12H, 4 x CH_3-^{i}Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2 (*ipso* C-OBn), 138.1 (*ipso* C-OBn), 128.5, 128.4, 127.9, 127.8 (Ar *C*-Bn), 103.1 (d, $^3J_{C,P}$ = 10.5 Hz, C-1′), 84.1 (C-3′), 81.2 (C-4′), 78.5 (C-2′), 73.4, 72.1 (2 x CH_2−OBn), 72.0 (C-5′), 71.6, 71.5 (d, $^2J_{C,P}$ = 6.6 Hz, 2 × 1C- ^{i}Pr), 61.9 (d, $^1J_{C,P}$ = 170.5 Hz, -O*C*H_2P), 24.2, 24.1 (d, $^3J_{C,P}$ = 3.3 Hz, 4 × *C*H_3- ^{i}Pr); ^{31}P NMR (121 MHz, $CDCl_3$) δ = 19.4; [α]$^{20}_D$ = +22.3° (*c* = 1, CH_3OH); HRMS (ESI-TOF) *m*/*z*: [M+H]$^+$ Calcd for $C_{26}H_{37}O_8P$ 509.2299; Found 509.2306.

*3′,5′-Di-O-benzyl-1′-((diisopropoxyphosphoryl)methoxy)-2′-(β-acetoxy)-L-β-ribofuranose (**30**).* Following a similar procedure as the one used for the synthesis of **6**, compound **30** was obtained (R_f = 0.53, EtOAc; column chromatography gradient hexane/EtOAc, 4:1, v/v; 3:2, v/v; 2:3, v/v) as a colorless liquid (28.8 g, 95%), starting from **29** (28 g, 55.06 mmol), pyridine (240 mL) and Ac_2O (112 mL). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.26 (m, 10H, Ar-*H* 2 x OBn), 5.23 (d, *J* = 4.5 Hz, 1H, H-1′), 5.00−4.95 (m, 1H, H-2′), 4.75−4.63 (m, 2H, 2 x C*H*- ^{i}Pr), 4.61−4.48 (m, 4H, 2 x CH_2-OBn), 4.21−4.15 (m, 2H, H-4′ and H-3′), 3.72 (ddd, *J* = 88.0 ($^2J_{H,P}$), 13.8, 9.1 Hz, 2H, -OCH_2P), 3.62−3.51 (m, 2H, H-5′ and H-5″), 2.07 (s, 3H, CH_3-OAc), 1.32−1.27 (m, 12H, 4 x CH_3-^{i}Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (*C*O-OAc), 138.1 (*ipso* C-OBn), 137.8 (*ipso* C-OBn), 128.5, 128.4, 127.9, 127.8, 127.7 (Ar *C*-Bn), 100.8 (d, $^3J_{C,P}$ = 12.7 Hz, C-1′), 81.5 (C-3′), 80.2 (C-4′), 79.0 (C-2′), 73.4, 72.4 (2 x CH_2−OBn), 72.0 (C-5′), 71.2, 71.1 (d, $^2J_{C,P}$ = 6.8 Hz, 2 × 1C- ^{i}Pr), 61.4 (d, $^1J_{C,P}$ = 170.6 Hz, -O*C*H_2P), 24.2, 24.1, 24.1, 24.0 (d, $^3J_{C,P}$ = 3.4 Hz, 4 x *C*H_3- ^{i}Pr), 20.7 (CH_3−OAc); ^{31}P NMR (121 MHz, $CDCl_3$) δ = 18.8; [α]$^{20}_D$ = +77.0° (*c* = 1, CH_3OH); HRMS (ESI-TOF) *m*/*z*: [M+H]$^+$ Calcd for $C_{28}H_{39}O_9P$ 551.2404; Found 551.2411.

*3′,5′-Di-O-benzyl-1′-((diisopropoxyphosphoryl)methoxy)-2′-(β-O-methoxyethoxymethyl)-L-β-ribofuranose (**31**).* To a stirred solution of **29** (5.24 g, 10.3 mmol) in anhydrous CH_2Cl_2 (80 mL) were added MEMCl (3.53 mL, 30.91 mmol) followed by DIPEA (10.76 mL, 61.8 mmol) and the resulting reaction mixture was refluxed for 48 h. Upon completion, the reaction mixture was cooled and diluted with CH_2Cl_2 (300 mL) and washed with a saturated $NaHCO_3$ solution (150 mL). The organic layer was washed with brine, dried, concentrated *in vacuo* and the resulting crude residue was purified by column chromatography on silica gel (gradient hexane/EtOAc, 4:1, v/v; 2:3, v/v; 1:4, v/v) to give **31** (5.28 g, 86%) as a white foam (R_f = 0.31, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.28 (m, 10H, Ar-*H* 2 × OBn), 5.10 (d, *J* = 4.4 Hz, 1H, H-1′), 4.82 (dd, *J* = 26.5, 7.0 Hz, 2H, -OCH_2O), 4.74−4.64 (m, 2H, 2 × C*H*- ^{i}Pr), 4.63−4.47 (m, 4H, 2 × CH_2-OBn), 4.33−4.27 (m, 1H, H-2′), 4.15−4.11 (m, 1H, H-4′), 4.07−4.03 (m, 1H, H-3′), 3.80−3.46 (m, 8H, H-5′, H-5″, OCH_2P, O$\underline{CH_2}$CH_2OMe and OC$H_2$$\underline{CH_2}$OMe), 3.37 (s, 3H, OC$H_3$), 1.31−

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1.24 (m, 12H, 4 x CH_3-^{i}Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 137.6 (2 x *ipso* C-OBn), 128.5, 128.4, 128.0, 127.9, 127.7, 127.6 (Ar *C*-Bn), 106.5 (d, $^3J_{C,P}$ = 12.4 Hz, C-1′), 95.7 (OCH_2O), 80.6 (C-2′), 78.3 (C-4′), 78.1 (C-3′), 73.2, 72.6 (2 × CH_2−OBn), 71.6 (OCH$_2$$\underline{CH_2}$OMe), 71.5 (O$\underline{CH_2}CH_2$OMe), 71.1, 71.0 (d, $^2J_{C,P}$ = 6.6 Hz, 2 × 1C- ^{i}Pr), 67.4 (C-5′), 61.2 (d, $^1J_{C,P}$ = 170.5 Hz, -OCH_2P), 59.1 (OCH_3), 27.1 (3 x CH_3 ^{t}Bu), 24.2, 24.1, 24.1, 24.0 (d, $^3J_{C,P}$ = 2.9 Hz, 4 x CH_3- ^{i}Pr); ^{31}P NMR (121 MHz, $CDCl_3$) δ = 19.4; HRMS (ESI-TOF) *m*/*z*: [M+H]$^+$ Calcd for $C_{30}H_{45}O_{10}P$ 597.2823; Found 597.2827.

*3′,5′-Di-O-benzyl-1′-((diisopropoxyphosphoryl)methoxy)-2′-(β-O-TBDPS)-L-β-ribofuranose (**32**).* To a stirred solution of **29** (1.5 g, 2.95 mmol) and imidazole (0.80 g, 11.8 mmol) in anhydrous acetonitrile (30 mL) were added TBDPSCl (1.54 mL, 5.90 mmol) followed by cat. DMAP (36 mg, 0.295 mmol) and the resulting reaction mixture was heated at 60 °C for 48 h. Upon completion, the reaction mixture was cooled to room temperature and volatiles were concentrated *in vacuo*. The resulting reaction mixture was diluted with a 5% $NaHCO_3$ solution (150 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with brine, dried, concentrated *in vacuo* and the resulting crude residue was purified by column chromatography on silica gel (gradient Hexane/EtOAc, 9:1, v/v; 4:1, v/v; 3:2, v/v) to give **32** (1.76 g, 80%) as a colorless sticky mass (R_f = 0.52, 80% EtOAc in hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.18 (m, 20H, Ar-*H* 2 x OBn and 2 x Ph), 4.83−4.69 (m, 2H, 2 x C*H*- ^{i}Pr), 4.61−4.50 (m, 4H, 2 x CH_2-OBn), 4.30 (dd, *J* = 6.9, 4.1 Hz, 1H, H-2′), 4.14 (d, *J* = 4.4 Hz, 1H, H-1′), 4.11−4.06 (m, 1H, H-3′), 4.01 (dd, *J* = 12.2, 6.0 Hz, 1H, H-4′), 3.61−3.51 (m, 2H, H-5′ and H-5″), 3.58 (ddd, *J* = 155.0 ($^2J_{H,P}$), 13.2, 10.4 Hz, 2H, -OCH_2P), 1.35−1.29 (m, 12H, 4 x CH_3-^{i}Pr), 1.09 (s, 9H, ^{t}Bu-TBDPS); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 138.2 (2 × *ipso* C-OBn), 136.3, 136.0 (Ar *C*-Bn), 133.6, 133.0 (2 × *ipso* C-Ph TBDPS), 130.0, 129.9, 128.5, 128.4, 128.3, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6 (Ar *C*-Bn and TBDPS), 102.1 (d, $^3J_{C,P}$ = 15.1 Hz, C-1′), 84.7 (C-3′), 80.1 (C-4′), 78.7 (C-2′), 73.4, 72.9 (2 × CH_2−OBn), 72.7 (C-5′), 71.1, 71.0 (d, $^2J_{C,P}$ = 6.6 Hz, 2 × 1C- ^{i}Pr), 61.4 (d, $^1J_{C,P}$ = 172.9 Hz, -OCH_2P), 27.1 (3 × CH_3 ^{t}Bu), 24.3, 24.2 (d, $^3J_{C,P}$ = 3.4 Hz, 4 × CH_3- ^{i}Pr), 19.2 (1 C-^{t}Bu); ^{31}P NMR (121 MHz, $CDCl_3$) δ = 19.5; HRMS (ESI-TOF) *m*/*z*: [M+H]$^+$ Calcd for $C_{42}H_{55}O_8Psi$ 747.3476; Found 747.3468.

*1′-((Diisopropoxyphosphoryl)methoxy)-2′-(β-acetoxy)-L-β-ribofuranose (**33**).* To a stirred solution of **30** (28 g, 50.8 mmol, 1 equiv) and glacial AcOH (0.58 mL, 10.2 mmol) in EtOH/H_2O (9:1, 300 mL, degassed with argon), was added 10% Pd/C (11.2 g, 0.4 eq. w/w) and evacuation was then carried out with hydrogen atmosphere replacements (3×). The reaction mixture was stirred at room temperature for 20 h under an atmospheric pressure of hydrogen. After completion of the reaction, the catalyst was removed by filtration through a Celite pad and washed with EtOH. The filtrate was concentrated under reduced pressure and the crude residue was purified via flash column chromatography (gradient CH_2Cl_2/MeOH, 99:1, v/v; 49:1, v/v; 97:3, v/v) to afford **33** (18.51 g, 98%) as a colorless foam (R_f = 0.42, 10% MeOH in CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.15 (d, *J* = 4.8 Hz, 1H, H-1′), 4.83 (dd, *J* = 8.4, 4.7 Hz, 1H, H-2′), 4.80−4.72 (m, 2H, 2 × C*H*- ^{i}Pr), 4.68 (dd, *J* = 8.3, 7.4 Hz, 1H, H-3′), 3.93−3.91 (m, 1H, H-4′), 3.89−3.77 (m, 3H, H-5′ and-OCH_2P), 3.68−3.65 (m, 1H, H-5″), 2.11 (s, 3H, CH_3-OAc), 1.35−1.32 (m, 12H, 4 x CH_3-^{i}Pr); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.2 (CO-OAc), 100.8 (d, $^3J_{C,P}$ = 8.8 Hz, C-1′), 82.9 (C-4′), 79.8 (C-2′), 72.1, 71.6 (d, $^2J_{C,P}$ = 6.7 Hz, 2 × 1C- ^{i}Pr), 70.7 (C-3′), 62.9 (d, $^1J_{C,P}$ = 172.3 Hz, -OCH_2P), 61.3 (C-5′), 24.3, 24.1, 24.0, 23.8 (d, $^3J_{C,P}$ = 3.9 Hz, 4 × CH_3- ^{i}Pr), 20.8 (*C*H$_3$−OAc); ^{31}P NMR (202 MHz, $CDCl_3$) δ = 20.0; $[\alpha]^{20}_D$ = +90.0° (*c* = 1, CH_3OH); HRMS (ESI-TOF) *m*/*z*: [M+H]$^+$ Calcd for $C_{14}H_{27}O_9P$ 371.1465; Found 371.1464.

*1′-((Diisopropoxyphosphoryl)methoxy)-2′-(β-O-methoxyethoxymethyl)-L-β-ribofuranose (**34**).* Following a similar procedure as the one used for the synthesis of **33**, compound **34** was obtained (column chromatography gradient CH_2Cl_2/MeOH, 99:1, v/v; 49:1, v/v; 24:1, v/v) as a colorless sticky mass (0.57 g, 95%), starting from **31** (0.86 g, 1.441 mmol), 10% Pd/C (0.35 g, 0.4 eq. w/w) and MeOH:H_2O 49:1 (30 mL). ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.99−4.90 (m, 2H, H-1′ and 3′-O*H*), 4.78−4.69 (m, 2H, -OCH_2O), 4.64−4.52 (m, 2H, 2 × C*H*-^{i}Pr), 4.03−3.96 (m, 1H, H-2′), 3.90−3.49 (m, 8H, H-4′, H-3′, H-5′, H-5″, OCH_2P and O$\underline{CH_2}$CH$_2$OMe), 3.46 (t, *J* = 5.0 Hz, 2H, OCH$_2$$\underline{CH_2}$OMe), 3.24 (s, 3H, O$CH_3$), 1.25−1.22 (m, 12H, 4 × CH_3-^{i}Pr); ^{13}C NMR (75 MHz, DMSO-d_6) δ 105.8 (d, $^3J_{C,P}$ = 12.1 Hz, C-1′), 94.7 (OCH_2O), 84.1 (C-4′), 79.2 (C-3′), 71.2 (OCH$_2$$\underline{CH_2}$OMe), 70.5, 70.4 (d, $^2J_{C,P}$ = 6.3 Hz, 2 × 1C- ^{i}Pr), 70.1 (C-2′), 66.6 (O$\underline{CH_2}$CH$_2$OMe), 62.5 (C-5′), 60.6 (d, $^1J_{C,P}$ = 166.9 Hz, -OCH_2P), 58.2 (OCH_3), 27.1 (3 x CH_3 ^{t}Bu), 23.9, 23.8 (d, $^3J_{C,P}$ = 3.8 Hz, 4 × CH_3- ^{i}Pr); ^{31}P NMR (121 MHz, DMSO-d_6) δ = 19.7; HRMS (ESI-TOF) *m*/*z*: [M+Na]$^+$ Calcd for $C_{16}H_{33}O_{10}P$ 439.1704; Found 439.1687.

*5′-MMTr-3′-Benzoyl-1′-((diisopropoxyphosphoryl)methoxy)-2′-(β-acetoxy)-L-β-ribofuranose (**35**).* To a stirred solution of **33** (18.5 g, 49.96 mmol) in anhydrous pyridine (400 mL) were added DMAP (0.122 g, 1 mmol) followed by MMTrCl (23.1 g, 74.93 mmol) at 0 °C and the reaction mixture was stirred for 16 h at room temperature. After completion, the reaction mixture was again cooled to 0 °C and benzoyl chloride (8.70 mL, 74.93 mmol) was added slowly to the same reaction vessel. The reaction mixture was then stirred at room temperature for 2 h. The volatiles were removed *in vacuo* and the reaction mixture was quenched with a 5% $NaHCO_3$ solution (500 mL). The aqueous layer was extracted with EtOAc (3 × 400 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified via flash column chromatography (gradient hexane/EtOAc, 4:1, v/v; 3:2, v/v; 2:3, v/v) to afford **35** (31.7 g, 85% over two steps) as a colorless foam (R_f = 0.59, EtOAc). The resulting crude residue was used for next step without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04−6.74 (m, 19H, *Ar* H-Bz and MMTr), 5.75−5.66 (m, 1H, H-3′), 5.41−5.21 (s, 2H, H-1′ and H-2′), 4.78−4.41 (m, 3H, 2 × C*H*- ^{i}Pr and H-4′), 4.09−3.37 (m, 7H, -OCH_2P, OCH_3-MMTr, H-5′ and H-5″), 2.06 (s, 3H, CH_3-OAc), 1.35−1.25 (m, 12H, 4 × CH_3-^{i}Pr); ^{31}P NMR (121 MHz, $CDCl_3$) δ = 18.6; HRMS (ESI-TOF) *m*/*z*: [M+Na]$^+$ Calcd for $C_{41}H_{47}O_{11}P$ 769.2748; Found 769.2755.

*5′-MMTr-3′-Benzoyl-1′-((diisopropoxyphosphoryl)methoxy)-2′-(β-O-methoxyethoxymethyl)-L-β-ribofuranose (**36**).* Following a similar procedure as the one used for the synthesis of **35**, compound **36** was obtained (R_f = 0.75, 10% MeOH in CH_2Cl_2; column chromatography gradient CH_2Cl_2/MeOH, 100:0, v/v; 99.5:0.5, v/v; 99:1, v/v) as a colorless sticky mass (0.95 g, 87%), starting from **36** (0.57 g, 1.369 mmol), MMTrCl (0.64 g, 2.053 mmol), BzCl (0.24 mL, 2.053 mmol), DMAP (3.5 mg, 0.027 mmol), and dry pyridine (15 mL). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.7 Hz, 2H, *o* H-Bz), 7.58 (t, *J* = 7.4 Hz, 1H, *p* H-Bz), 7.47−7.14 (m, 14H, Ar−H OBz and MMTr), 6.77 (d, *J* = 8.9 Hz, 2H, *m* H-Anisyl MMTr), 5.36 (dd, *J* = 6.5, 5.1 Hz, 1H, H-3′), 5.24 (s, 1H, H-1′), 4.78−4.62 (m, 4H, -OCH_2O and 2 × C*H*-^{i}Pr), 4.50−4.44 (m, 2H, H-2′ and H-4′), 3.91−3.26 (m, 14H, -OCH_2P, OCH_3-MMTr, O$\underline{CH_2}$CH$_2$OMe, H-5′, H-5″, OCH$_2$$\underline{CH_2}$OMe and OC$H_3$-MEM), 1.33−1.26 (m, 12H, 4 x CH_3-^{i}Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7 (CO-Bz), 158.7 (*p* C-Anisyl MMTr), 144.4 (*ipso* C- MMTr), 135.5 (*ipso* C- Anisyl MMTr), 133.4 (*ipso* C-Bz), 130.5, 129.9,129.6, 128.5, 128.5, 127.9, 127.0 (Ar *C*-OBz and MMTr), 113.2 (*m* C-Anisyl MMTr), 106.9 (d, $^3J_{C,P}$ = 10.5 Hz, C-1′), 95.6 (OCH_2O), 86.6 (1C-MMTr), 80.5 (C-4′), 78.7 (C-2′), 74.3 (C-3′), 71.6 (OCH$_2$$\underline{CH_2}$OMe), 71.3, 71.1 (d, $^2J_{C,P}$ = 6.6 Hz, 2 × 1C- ^{i}Pr), 67.3 (O$\underline{CH_2}$CH$_2$OMe), 65.0 (C-5′), 61.8 (d, $^1J_{C,P}$ = 168.5 Hz, -OCH_2P), 59.0 (OCH_3-MEM), 55.2 (OCH_3-MMTr), 24.2, 24.2, 24.1 (d, $^3J_{C,P}$ = 3.8 Hz, 4 x CH_3- ^{i}Pr); ^{31}P NMR (121 MHz, $CDCl_3$) δ = 18.9; HRMS (ESI-TOF) *m*/*z*: [M+Na]$^+$ Calcd for $C_{43}H_{53}O_{12}P$ 815.3167; Found 815.3174.

*3′-Benzoyl-1′-((diisopropoxyphosphoryl)methoxy)-2′-(β-acetoxy)-L-β-ribofuranose (**37**).* A solution of compound **35** (31 g, 41.5 mmol) in 80% AcOH (400 mL) was stirred at room temperature for 4 h. After completion, the volatiles were removed *in vacuo* and residue was coevaporated with toluene (2×). The resulting crude residue was purified by column chromatography on silica gel (R_f = 0.55, 10% MeOH in CH_2Cl_2; gradient CH_2Cl_2/MeOH, 100:0, v/v; 99:1, v/v;

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98.5:1.5, v/v) to give **37** (16.54 g, 84%) as a colorless foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 7.8 Hz, 2H, *o* H-Bz), 7.59 (t, J = 7.4 Hz, 1H, *p* H-Bz), 7.45 (app t, J = 7.8, 7.4 Hz, 2H, *m* H-Bz), 5.74 (dd, J = 6.6, 5.3 Hz, 1H, H-3′), 5.31−5.30 (m, 1H, H-1′), 5.26 (dd, J = 6.6, 4.9 Hz, 1H, H-2′), 4.86−4.73 (m, 2H, 2 × C*H*-^{i}Pr), 4.36 (br s, 1H, 5′-O*H*), 4.18−4.16 (m, 1H, H-4′), 3.95−3.80 (m, 4H, -OCH_2P, H-5′ and H-5″), 2.09 (s, 3H, CH_3-OAc), 1.38−1.33 (m, 12H, 4 × CH_3-^{i}Pr); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3 (*C*O-OAc), 165.9 (*C*O-Bz), 133.4 (*ipso* C-Bz), 129.8 (*p* C-Bz), 129.1 (*m* C-Bz), 128.4 (*o* C-Bz), 101.2 (d, $^3J_{C,P}$ = 9.8 Hz, C-1′), 82.8 (C-4′), 77.5 (C-2′), 75.3 (C-3′), 71.9, 71.4 (d, $^2J_{C,P}$ = 6.6 Hz, 2 × 1C- ^{i}Pr), 63.1 (d, $^1J_{C,P}$ = 171.3 Hz, -OCH_2P), 62.9 (C-5′), 24.1, 23.9, 23.9, 23.8 (d, $^3J_{C,P}$ = 3.8 Hz, 4 x CH_3-^{i}Pr), 20.5 (CH_3−OAc); ^{31}P NMR (202 MHz, $CDCl_3$) δ = 19.4; $[\alpha]^{20}_D$ = +109.4° (c = 1, CH_3OH); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{31}O_{10}P$ 475.1727; Found 475.1730.

*3′-Benzoyl-1′-((diisopropoxyphosphoryl)methoxy)-2′-(β-O-methoxyethoxymethyl)-L-β-ribofuranose (**38**).* Following a similar procedure as the one used for the synthesis of **37**, compound **38** was obtained (R_f = 0.36, 5% MeOH in CH_2Cl_2; column chromatography gradient CH_2Cl_2/MeOH, 100:0, v/v; 99:1, v/v; 49:1, v/v) as a colorless liquid (0.51 g, 85%), starting from **36** (0.92 g, 1.369 mmol) and 80% acetic acid (15 mL). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 7.7 Hz, 2H, *o* H-Bz), 7.57 (t, J = 7.4 Hz, 1H, *p* H-Bz), 7.44 (app t, J = 7.8, 7.5 Hz, 2H, *m* H-Bz), 5.52 (dd, J = 6.7, 4.9 Hz, 1H, H-3′), 5.14 (s, 1H, H-1′), 4.88−4.71 (m, 4H, -OCH_2O and 2 x C*H*-^{i}Pr), 4.52 (d, J = 4.9 Hz, 1H, H-2′), 4.46−4.41 (m, 1H, H-4′), 4.00−3.34 (m, 8H, -OCH_2P, O$\underline{CH_2}$CH_2OMe, H-5′, H-5″ and OC$H_2\underline{CH_2}$OMe), 3.33 (s, 3H, OCH_3), 1.39−1.33 (m, 12H, 4 x CH_3-^{i}Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9 (*C*O-Bz), 133.4 (*ipso* C-Bz), 129.8 (*p* C-Bz), 129.7 (*m* C-Bz), 128.6 (*o* C-Bz), 107.7 (d, $^3J_{C,P}$ = 7.9 Hz, C-1′), 95.9 (OCH_2O), 83.3 (C-4′), 80.0 (C-2′), 71.9 (C-3′), 72.2, 71.5 (d, $^2J_{C,P}$ = 6.6 Hz, 2 × 1C- ^{i}Pr), 71.6 (OC$H_2\underline{CH_2}$OMe), 67.4 (O$\underline{CH_2}$CH_2OMe), 63.0 (d, $^1J_{C,P}$ = 172.4 Hz, -OCH_2P), 61.4 (C-5′), 59.1 (OCH_3), 24.3, 24.2, 24.0, 23.9 (d, $^3J_{C,P}$ = 3.7 Hz, 4 × CH_3- ^{i}Pr); ^{31}P NMR (121 MHz, $CDCl_3$) δ = 19.9; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{37}O_{11}P$ 543.1966; Found 543.1950.

*(2′R,3′R,4′R,5′R)-4′-Acetoxy-3′-(benzoyloxy)-5′-((diisopropoxyphosphoryl)methoxy)tetrahydro-furan-2′-carboxylic Acid (**39**).* Following a similar procedure as the one used for the synthesis of **20**, compound **39** was obtained (R_f = 0.29, 10% MeOH in CH_2Cl_2; column chromatography gradient CH_2Cl_2/MeOH, 99:1, v/v; 49:1, v/v; 24:1, v/v) as a pale-yellow sticky mass (16.3 g, 96%), starting from **37** (16.5 g, 34.78 mmol), iodosobenzene diacetate (24.64 g, 76.51 mmol), TEMPO (1.63 g, 10.43 mmol) and 1:1 ACN:H_2O mixture (300 mL). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.02 (d, J = 7.8 Hz, 2H, *o* H-Bz), 7.69 (t, J = 7.4 Hz, 1H, *p* H-Bz), 7.55 (app t, J = 7.8, 7.4 Hz, 2H, *m* H-Bz), 5.94 (dd, J = 6.6, 5.4 Hz, 1H, H-3′), 5.37 (d, J = 4.3 Hz, 1H, H-1′), 5.19 (dd, J = 6.6, 4.3 Hz, 1H, H-2′), 4.65−4.56 (m, 3H, H-4′ and 2 x C*H*- ^{i}Pr), 3.95 (ddd, J = 79.6 ($^2J_{H,P}$), 13.9, 7.9 Hz, 2H, -OCH_2P), 2.01 (s, 3H, CH_3-OAc), 1.27−1.21 (m, 12H, 4 × CH_3-^{i}Pr); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.4 (CO_2H-4′), 169.5 (*C*O-OAc), 164.8 (*C*O-Bz), 133.7 (*ipso* C-Bz), 129.5 (*p* C-Bz), 128.9 (*m* C-Bz), 128.7 (*o* C-Bz), 100.4 (d, $^3J_{C,P}$ = 12.6 Hz, C-1′), 77.4 (C-4′), 76.8 (C-2′), 76.5 (C-3′), 70.5, 70.4 (d, $^2J_{C,P}$ = 6.2 Hz, 2 × 1C- ^{i}Pr), 60.6 (d, $^1J_{C,P}$ = 165.5 Hz, -OCH_2P), 23.8, 23.7, 23.6, 23.5 (d, $^3J_{C,P}$ = 3.8 Hz, 4 × CH_3- ^{i}Pr), 20.3 (CH_3−OAc); ^{31}P NMR (121 MHz, DMSO-d_6) δ = 18.6; $[\alpha]^{20}_D$ = +69.7° (c = 1, CH_3OH); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{29}O_{11}P$ 489.1520; Found 489.1519.

*(2′R,3′R,4′S,5′R)-3′-(Benzoyloxy)-5′-((diisopropoxyphosphoryl)-methoxy)-4′-((2′-methoxyethoxy)methoxy)tetrahydrofuran-2′-carboxylic Acid (**40**).* Following a similar procedure as the one used for the synthesis of **20**, compound **40** was obtained (R_f = 0.28, 10% MeOH in CH_2Cl_2; column chromatography gradient CH_2Cl_2/MeOH, 99:1, v/v; 49:1, v/v; 19:1, v/v) as a colorless sticky mass (0.49 g, 93%), starting from **38** (0.51 g, 0.98 mmol), iodosobenzene diacetate (0.35 g, 2.16 mmol), TEMPO (0.031 g, 0.20 mmol) and 1:1 ACN:H_2O mixture (10 mL). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00 (d, J = 7.7 Hz, 2H, *o* H-Bz), 7.69 (t, J = 7.4 Hz, 1H, *p* H-Bz), 7.55 (app t, J = 7.8, 7.5 Hz, 2H, *m* H-Bz), 5.52 (t, J = 5.53 Hz, 1H, H-3′), 5.28 (s, 1H, H-1′), 4.69−4.55 (m, 5H, -OCH_2O, H-4′ and 2 x C*H*- ^{i}Pr), 4.28 (d, J = 4.9 Hz, 1H, H-2′), 3.96 (ddd, J = 75.1 ($^2J_{H,P}$), 13.8, 8.2 Hz, 2H, -OCH_2P), 3.56−3.40 (m, 2H, O$\underline{CH_2}$CH_2OMe), 3.34−3.31 (m, 2H OC$H_2\underline{CH_2}$OMe), 3.17 (s, 3H, OCH_3), 1.27−1.24 (m, 12H, 4 x CH_3-^{i}Pr); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.7 (CO_2H-4′), 165.0 (*C*O-Bz), 133.7 (*ipso* C-Bz), 129.3 (*p* C-Bz), 128.9 (*m* C-Bz), 128.8 (*o* C-Bz), 106.1 (d, $^3J_{C,P}$ = 12.6 Hz, C-1′), 94.5 (OCH_2O), 78.8 (C-4′), 77.5 (C-2′), 74.9 (C-3′), 70.8 (OC$H_2\underline{CH_2}$OMe), 70.5, 70.4 (d, $^2J_{C,P}$ = 6.2 Hz, 2 × 1C- ^{i}Pr), 66.6 (O$\underline{CH_2}$CH_2OMe), 60.4 (d, $^1J_{C,P}$ = 165.5 Hz, -OCH_2P), 57.9 (OCH_3), 23.8, 23.7, 23.6, 23.5 (d, $^3J_{C,P}$ = 3.8 Hz, 4 x CH_3-^{i}Pr); ^{31}P NMR (121 MHz, DMSO-d_6) δ = 19.2; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{35}O_{12}P$ 535.1939; Found 535.1934.

*(3′R,4′R,5′R)-3′-(Benzoyloxy)-5′-((diisopropoxyphosphoryl)-methoxy)tetrahydrofuran-2′,4′-diyl diacetate (**41**).* Following a similar procedure as the one used for the synthesis of **21**, a diastereomeric mixture (~3:1) of compound **41** was obtained (R_f = 0.42, EtOAc; column chromatography gradient Hexane/EtOAc, 4:1, v/v; 3:2, v/v; 2:3, v/v) as a colorless liquid (15.09 g, 90%), starting from **39** (16.3 g, 33.4 mmol), $Pb(OAc)_4$ (25.15 g, 56.7 mmol), anhydrous pyridine (9.72 mL, 120.1 mmol) and anhydrous THF (400 mL). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 7.7 Hz, 2H, *o* H-Bz), 7.61 (t, J = 7.4 Hz, 1H, *p* H-Bz), 7.47 (app t, J = 7.8, 7.5 Hz, 2H, *m* H-Bz), 6.54−6.26 (m, J = 2.5 Hz, 1H, H-4′), 5.78−5.59 (dd, J = 5.0, 2.5 Hz, 1H, H-3′), 5.48−5.42 (m, 1H, H-2′), 5.38−5.19 (m, 1H, H-1′), 4.79−4.71 (m, 2H, 2 x C*H*- ^{i}Pr), 4.07−3.66 (m, 2H, -OCH_2P), 2.17, 2.14 (s, 3H, CH_3-4′OAc), 2.13, 1.99 (s, 3H, CH_3-2′OAc), 1.37−1.34 (m, 12H, 4 x CH_3-^{i}Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 (CO-4′OAc), 168.7 (CO-3′OAc), 165.1 (*C*O-Bz), 133.4 (*ipso* C-Bz), 129.6 (*p* C-Bz), 129.5 (*m* C-Bz), 128.2 (*o* C-Bz), 101.5, 98.5 (d, $^3J_{C,P}$ = 12.4 Hz, C-1′), 97.9, 90.4 (C-4′), 79.1, 76.0 (C-2′), 72.6, 72.3 (C-3′), 71.0, 70.9 (d, $^2J_{C,P}$ = 6.5 Hz, 2 × 1C- ^{i}Pr), 62.1, 61.7 (d, $^1J_{C,P}$ = 170.9 Hz, -OCH_2P), 23.7, 23.6 (d, $^3J_{C,P}$ = 3.7 Hz, 4 x CH_3- ^{i}Pr), 20.5 (CH_3-4′OAc), 20.2 (CH_3-2′OAc); ^{31}P NMR (121 MHz, $CDCl_3$) δ = 17.7; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{31}O_{11}P$ 525.1496; Found 525.1485.

*(3′R,4′S,5′R)-2′-Acetoxy-5′-((diisopropoxyphosphoryl)methoxy)-4′-((2′-methoxyethoxy)methoxy)tetrahydrofuran-3′-yl Benzoate (**42**).* Following a similar procedure as the one used for the synthesis of **21**, a diastereomeric mixture (~49:1) of compound **42** was obtained (R_f = 0.22, EtOAc; column chromatography gradient Hexane/EtOAc, 4:1, v/v; 1:1, v/v; 1:9, v/v) as a colorless sticky mass (0.231 g, 75%), starting from **40** (0.30 g, 0.561 mmol), $Pb(OAc)_4$ (0.423 g, 0.954 mmol), anhydrous pyridine (0.1 mL, 1.234 mmol) and anhydrous THF (8 mL). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.7 Hz, 2H, *o* H-Bz), 7.60 (t, J = 7.4 Hz, 1H, *p* H-Bz), 7.46 (app t, J = 7.8, 7.5 Hz, 2H, *m* H-Bz), 6.42 (d, J = 2.3 Hz, 1H, H-4′), 5.50 (dd, J = 4.9, 2.4 Hz, 1H, H-3′), 5.42−5.30 (m, 1H, H-1′), 4.89−4.71 (m, 4H, -OCH_2O and 2 x C*H*- ^{i}Pr), 4.57 (dd, J = 4.9, 2.4 Hz, 1H, H-2′), 3.87 (ddd, J = 75.0 ($^2J_{H,P}$), 13.5, 8.9 Hz, 2H, -OCH_2P), 3.73−3.55 (m, 2H, -O$\underline{CH_2}$CH_2OMe), 3.51−3.43 (m, 2H, -OC$H_2\underline{CH_2}$OMe), 3.33 (s, 3H, OCH_3-MEM), 2.13 (s, 3H, CH_3-OAc), 1.37−1.34 (m, 12H, 4 × CH_3-^{i}Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4 (*C*O-OAc), 165.3 (*C*O-Bz), 133.5 (*ipso* C-Bz), 129.7 (*p* C-Bz and *m* C-Bz), 128.4 (*o* C-Bz), 108.3 (d, $^3J_{C,P}$ = 12.6 Hz, C-1′), 98.9 (C-4′), 95.6 (OCH_2O), 78.3 (C-2′), 75.9 (C-3′), 71.4 (OC$H_2\underline{CH_2}$OMe), 71.3, 71.1 (d, $^2J_{C,P}$ = 6.5 Hz, 2 × 1C- ^{i}Pr), 67.3 (O$\underline{CH_2}$CH_2OMe), 62.4 (d, $^1J_{C,P}$ = 170.1 Hz, -OCH_2P), 58.8 (OCH_3), 24.0, 23.9, 23.8 (d, $^3J_{C,P}$ = 3.7 Hz, 4 x CH_3-^{i}Pr), 20.9 (CH_3−OAc); ^{31}P NMR (121 MHz, $CDCl_3$) δ = 18.1; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{37}O_{12}P$ 571.1915; Found 571.1915.

*(2′R,3′R,4′R,5′R)-4′-Acetoxy-2′-(6-benzamido-9H-purin-9-yl)-5′-((diisopropoxyphosphoryl)methoxy)tetrahydrofuran-3′-yl Benzoate (**43**).* 1 M $SnCl_4$ in CH_2Cl_2 (89.6 mL, 89.6 mmol) was added slowly to a stirred suspension of **41** (15 g, 29.85 mmol) and 6-benzoyl adenine (10.71 g, 44.8 mmol) in anhydrous acetonitrile (440 mL) at 0 °C. The reaction mixture was then stirred at room temperature for 36 h. Upon completion, the reaction mixture was cooled to 0 °C and quenched with a saturated $NaHCO_3$ solution. The reaction mixture was diluted with EtOAc (800 mL) and the milky aqueous layer was extracted with

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EtOAc (3 × 600 mL). The combined organic layers were washed with brine, dried, concentrated *in vacuo*, and the crude residue was purified by flash column chromatography on silica gel (gradient CH_2Cl_2/MeOH/, 100:1, v/v; 99:1, v/v; 49:1, v/v) to give **43** (11.2 g, 55%) as a pale-yellow semisolid (R_f = 0.59, 10% MeOH in CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.20 (br s, 1H, NH), 8.75 (s, 1H, H-8), 8.62 (s, 1H, H-2), 8.03, 7.97 (2d, J = 7.6 Hz, 2H, 2 × *o* H-Bz), 7.61, 7.59 (2t, J = 7.4 Hz, 2H, 2 x *p* H-Bz), 7.53, 7.45 (2app t, J = 7.8, 7.5 Hz, 4H, 2 x *m* H-Bz), 6.56 (d, J = 4.0 Hz, 1H, H-1′), 6.18 (dd, J = 7.8, 5.0 Hz, 1H, H-2′), 5.60 (d, J = 4.5 Hz, 1H, H-4′), 5.49 (dd, J = 7.7, 4.5 Hz, 1H, H-3′), 4.83−4.76 (m, 2H, 2 x C*H*- ^{i}Pr), 3.84 (ddd, J = 111.2 ($^2J_{H,P}$), 13.7, 9.6 Hz, 2H, -OCH_2P), 2.17 (s, 3H, CH_3-OAc), 1.38−1.35 (m, 12H, 4 x CH_3-^{i}Pr); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0 (*C*O-OAc), 165.5 (*C*O-OBz), 164.7 (*C*O-NHBz), 153.1 (C-2), 152.2 (C-4), 149.7 (C-6), 141.7 (C-8), 134.1, 133.9 (2 × *ipso* C-Bz), 132.9, 130.1, 129.9, 128.9, 128.7, 128.2, 128.0 (Ar *C*-Bz), 122.6 (C-5), 101.9 (d, $^3J_{C,P}$ = 11.7 Hz, C-4′), 83.9 (C-1′), 78.4 (C-2′), 74.9 (C-3′), 71.7 (d, $^2J_{C,P}$ = 6.8 Hz, 2 × *C*H- ^{i}Pr), 62.9 (d, $^1J_{C,P}$ = 171.3 Hz, -OCH_2P), 24.2, 24.1 (d, $^3J_{C,P}$ = 3.4 Hz, 4 x CH_3- ^{i}Pr), 20.6 (CH_3−OAc); ^{31}P NMR (202 MHz, $CDCl_3$) δ = 17.3; $[\alpha]^{20}_D$ = −23.1° (c = 1, CH_3OH); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{36}N_5O_{10}P$ 682.2272; Found 682.2280.

*(2′R,3′R,4′S,5′R)-2′-(6-Benzamido-9H-purin-9-yl)-5′-((diisopropoxyphosphoryl)methoxy)-4′-hydroxytetrahydrofuran-3′-yl Benzoate (**44**), Diisopropyl ((((2′R,3′R,4′R,5′R)-5′-(6-Benzamido-9H-purin-9-yl)-3′,4′-dihydroxytetrahydrofuran-2′-yl)oxy)methyl)-phosphonate (**45**), and Diisopropyl ((((2′R,3′R,4′R,5′R)-5′-(6-Amino-9H-purin-9-yl)-3′,4′-dihydroxytetrahydrofuran-2′-yl)oxy)-methyl)phosphonate (**46**).* The compound **43** (11.5 g, 16.87 mmol) was dissolved in 2 M NH_3 in EtOH (102 mL) at 0 °C and the reaction mixture was stirred at room temperature for 48 h in a sealed vessel. The reaction mixture was concentrated under reduced pressure (bath temp 10 °C) and the resulting crude residue was purified by column chromatography on silica gel (gradient CH_2Cl_2/MeOH/, 97:3, v/v; 24:1, v/v; 23:2, v/v) to give **44** (0.32 g, 3%, white foam, R_f = 0.69, 12% MeOH in CH_2Cl_2), **45** (3.78 g, 42%, white semisolid, R_f = 0.49, 12% MeOH in CH_2Cl_2), and **46** (3.26 g, 45%, white solid, R_f = 0.28, 12% MeOH in CH_2Cl_2; Mp: 71−73 °C). Spectral data for **44**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (br s, 1H, NH), 8.78 (s, 1H, H-8), 8.74 (s, 1H, H-2), 7.98, 7.97 (2d, J = 7.7 Hz, 2H, 2 × *o* H-Bz), 7.56, 7.55 (2t, J = 7.4 Hz, 2H, 2 x *p* H-Bz), 7.45, 7.40 (2app t, J = 7.8, 7.5 Hz, 4H, 2 x *m* H-Bz), 6.48 (d, J = 4.6 Hz, 1H, H-1′), 6.07 (dd, J = 6.6, 4.6 Hz, 1H, H-2′), 5.88 (br s, 1H, 3′-O*H*), 5.42 (d, J = 4.4 Hz, 1H, H-4′), 4.84−4.68 (m, 3H, H-3′ and 2 x C*H*- ^{i}Pr), 3.91 (ddd, J = 40.6 ($^2J_{H,P}$), 13.8, 8.6 Hz, 2H, -OCH_2P), 1.35−1.28 (m, 12H, 4 × CH_3-^{i}Pr); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0 (*C*O-OBz), 165.0 (*C*O-NHBz), 152.9 (C-2), 151.9 (C-4), 149.7 (C-6), 142.2 (C-8), 133.8 (*ipso* C-Bz), 132.7, 130.1, 128.8, 128.6, 128.5, 128.0 (Ar C-Bz), 122.6 (C-5), 104.2 (d, $^3J_{C,P}$ = 9.7 Hz, C-4′), 84.8 (C-1′), 81.2 (C-2′), 75.2 (C-3′), 72.0, 71.9 (d, $^2J_{C,P}$ = 5.2 Hz, 2 × *C*H- ^{i}Pr), 63.3 (d, $^1J_{C,P}$ = 170.7 Hz, -OCH_2P), 24.1, 24.1, 24.0 (d, $^3J_{C,P}$ = 3.4 Hz, 4 × CH_3- ^{i}Pr); ^{31}P NMR (121 MHz, $CDCl_3$) δ = 18.1; $[\alpha]^{20}_D$ = +11.9° (c = 1, CH_3OH); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{34}N_5O_9P$ 640.2167; Found 640.2189.

Spectral data for **45**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.28 (br s, 1H, NH), 8.68 (s, 1H, H-8), 8.53 (s, 1H, H-2), 7.98 (d, J = 7.4 Hz, 2H, *o* H-Bz), 7.55 (t, J = 7.1 Hz, 2H, *p* H-Bz), 7.46 (app t, J = 7.4, 7.1 Hz, 4H, *m* H-Bz), 6.25 (d, J = 5.4 Hz, 1H, H-1′), 6.11 (br s, 1H, 2′- O*H*), 5.15 (d, J = 3.9 Hz, 1H, H-4′), 5.10 (br s, 1H, 3′- O*H*), 5.01 (app t, J = 6.7 Hz, 1H, H-2′), 4.74−4.61 (m, 2H, 2 × C*H*- ^{i}Pr), 4.39 (br s, 1H, H-3′), 3.82 (ddd, J = 118.0($^2J_{H,P}$), 13.3, 8.7 Hz, 2H, -OCH_2P), 1.31−1.91 (m, 12H, 4 × CH_3-^{i}Pr); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.9 (*C*O-Bz), 152.7 (C-2), 152.0 (C-4), 149.1 (C-6), 142.0 (C-8), 133.3 (*ipso* C-Bz), 132.7 (*p* C-Bz), 128.7 (*m* C-Bz), 127.9 (*o* C-Bz), 122.3 (C-5), 103.9 (d, $^3J_{C,P}$ = 12.4 Hz, C-4′), 86.4 (C-1′), 78.6 (C-2′), 76.4 (C-3′), 72.1, 72.0 (d, $^2J_{C,P}$ = 6.8 Hz, 2 × *C*H- ^{i}Pr), 62.6 (d, $^1J_{C,P}$ = 172.5 Hz, -OCH_2P), 23.9, 23.9, 23.8 (d, $^3J_{C,P}$ = 3.4 Hz, 4 x CH_3- ^{i}Pr); ^{31}P NMR (202 MHz, $CDCl_3$) δ = 18.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{30}N_5O_8P$ 536.1905; Found 536.1904.

Spectral data for **46**: ^{1}H NMR (600 MHz, CD_3OD) δ 8.36 (s, 1H, H-8), 8.21 (s, 1H, H-2), 6.09 (d, J = 5.8 Hz, 1H, H-1′), 5.17 (d, J = 4.4 Hz, 1H, H-4′), 4.80−4.74 (m, 2H, 2 × C*H*- ^{i}Pr), 4.71 (dd, J = 8.0, 5.8 Hz, 1H, H-2′), 4.23 (dd, J = 8.0, 4.4 Hz, 1H, H-3′), 3.94 (ddd, J = 56.2 ($^2J_{H,P}$), 13.8, 9.5 Hz, 2H, -OCH_2P), 2.17 (s, 3H, CH_3-OAc), 1.38−1.35 (m, 12H, 4 × CH_3-^{i}Pr); ^{13}C NMR (150 MHz, CD_3OD) δ 157.4 (C-4), 154.1 (C-2), 151.0 (C-6), 140.7 (C-8), 119.9 (C-5), 105.4 (d, $^3J_{C,P}$ = 13.1 Hz, C-4′), 87.7 (C-1′), 79.7 (C-2′), 77.2 (C-3′), 73.6, 73.5 (d, $^2J_{C,P}$ = 6.8 Hz, 2 × *C*H- ^{i}Pr), 63.4 (d, $^1J_{C,P}$ = 170.9 Hz, -OCH_2P), 24.3, 24.2 (d, $^3J_{C,P}$ = 3.4 Hz, 4 × CH_3- ^{i}Pr); ^{31}P NMR (202 MHz, CD_3OD) δ = 19.6; $[\alpha]^{20}_D$ = +19.6° (c = 1, CH_3OH); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{26}N_5O_7P$ 432.1642; Found 432.1643. Alternatively, compound **46** was obtained starting from **43** in 96% yield using 7 N NH_3 in MeOH at room temperature for 48 h.

*Diisopropyl ((((2′R,3′S,4′S,5′R)-5′-(6-Amino-9H-purin-9-yl)-3′-fluoro-4′-hydroxytetrahydrofuran-2′-yl)oxy)methyl)phosphonate (**48**).* To a stirred solution of **45** (3.77 g, 7.04 mmol) in a mixture of anhydrous CH_2Cl_2 (112 mL) and anhydrous pyridine (17 mL) was added DAST (6.92 mL, 52.38 mmol) at −20 °C. Then the reaction mixture was slowly warmed to room temperature and left for stirring at same temperature for 5 h. After completion, the reaction mixture was cooled to 0 °C and slowly poured into an ice-cold saturated solution of $NaHCO_3$ (140 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). Due to partial solubility of the compound in water, the aqueous layer was lyophilized and the resulting solid was washed with 10% MeOH in CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude residue was purified by column chromatography on silica gel (gradient CH_2Cl_2/MeOH, 49:1, v/v; 24:1, v/v; 16:1, v/v) to give **48** (1.28 g, 42%) as an off white solid, Mp: 80−82 °C (R_f = 0.27, 10% MeOH in CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (s, 1H, H-8), 8.01 (s, 1H, H-2), 6.40 (d, J = 6.4 Hz, 1H, H-1′), 5.49 (d, J = 27.0 Hz, 1H, H-2′), 5.25 (d, J = 8.3 Hz, 1H, H-4′), 5.13 (dd, J = 52.7 ($^2J_{H,F}$), 3.6 Hz, 1H, H-3′), 4.85−4.67 (m, 2H, 2 × C*H*- ^{i}Pr), 3.76 (ddd, J = 167.9 ($^2J_{H,P}$), 13.1, 10.2 Hz, 2H, -OCH_2P), 1.47−1.16 (m, 12H, 4 × CH_3-^{i}Pr); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.8 (C-4), 153.4 (C-2), 149.2 (C-6), 139.6 (C-8), 118.1 (C-5), 105.1 (dd, J = 29.1 ($^2J_{C,F}$), 11.7 ($^3J_{C,P}$) Hz, C-4′), 93.6 (d, $^1J_{C,F}$ = 187.1 Hz, C-3′), 87.2 (C-1′), 75.4 (d, $^2J_{C,F}$ = 15.4 Hz, C-2′), 72.2, 71.7 (2d, $^2J_{C,P}$ = 6.3 Hz, 2 × CH- ^{i}Pr), 61.5 (d, $^1J_{C,P}$ = 175.4 Hz, -OCH_2P), 24.4, 24.2, 24.0 (d, $^3J_{C,P}$ = 3.7 Hz, 4 x CH_3- ^{i}Pr); ^{19}F NMR (470 MHz, $CDCl_3$) δ = −211.5; ^{31}P NMR (202 MHz, $CDCl_3$) δ = 17.6; $[\alpha]^{20}_D$ = +3.8° (c = 1, CH_3OH); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{25}FN_5O_6P$ 434.1599; Found 434.1596.

Following this similar synthetic protocol, **48** was also obtained (0.97 g, 47%) starting from **46** (2.06 g, 4.775 mmol), DAST (3.79 mL, 28.65 mmol), anhydrous pyridine (9.2 mL), and anhydrous CH_2Cl_2 (60 mL).

*((((2′R,3′S,4′S,5′R)-5′-(6-Amino-9H-purin-9-yl)-3′-fluoro-4′-hydroxytetrahydrofuran-2′-yl)oxy)methyl)phosphonic Triethylammonium Salt (**1**).* To a stirred solution of **48** (1.52 g, 3.51 mmol) in dry acetonitrile (35 mL) were added 2,6-lutidine (6.54 mL, 56.16 mmol) followed by TMSBr (3.71 mL, 28.08 mmol) at 0 °C and the reaction mixture was then stirred at room temperature for 24 h. Upon completion, the reaction mixture was cooled to 0 °C and quenched with a 1 M TEAB buffer. The volatiles were removed *in vacuo* and the residue was diluted with water and lyophilized. The crude product was purified first by column chromatography on silica gel (gradient IPA:H_2O:Et_3N, 20:1:1, v/v/v; 15:1:1, v/v/v; 10:1:1, v/v/v), then by preparative RP-HPLC (linear gradient, 2−95% 25 mmol TEAB in CH_3CN and 25 mmol TEAB in H_2O). The collected eluates were freeze-dried repeatedly until constant mass to afford compound **1** (1.70 g, 88% over) as a white solid, Mp: 79−81 °C. ^{1}H NMR (500 MHz, D_2O) δ 8.39 (s, 1H, H-8), 8.19 (s, 1H, H-2), 6.27 (d, J = 6.5 Hz, 1H, H-1′), 5.46 (d, J = 9.5 Hz, 1H, H-4′), 5.19 (dd, J = 55.0 ($^2J_{H,F}$), 3.7 Hz, 1H, H-3′), 5.16 (ddd, J = 25.3 ($^1J_{H,F}$), 6.8, 3.6 Hz, 1H, H-2′), 3.73 (ddd, J = 86.8 ($^2J_{H,P}$), 12.9, 9.3 Hz, 2H, -OCH_2P); ^{13}C NMR (125 MHz, D_2O) δ 155.1 (C-4), 152.4 (C-2), 148.9 (C-6), 139.7 (C-8), 118.0 (C-5), 105.8 (dd, J = 29.5 ($^2J_{C,F}$), 13.1 ($^3J_{C,P}$) Hz, C-4′), 92.5 (d, $^1J_{C,F}$ = 182.8 Hz, C-3′), 85.9 (C-1′), 73.9 (d, $^2J_{C,F}$ = 16.0 Hz, C-2′),

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64.2 (d, $^1J_{C,P}$ = 157.7 Hz, -OCH$_2$P); ^{19}F NMR (470 MHz, D$_2$O) δ = −210.5 (Oct); ^{31}P NMR (202 MHz, D$_2$O) δ = 14.2; $[\alpha]^{20}_D$ = +3.7° (*c* = 1, CH$_3$OH); ξ: 15.0 × 10^{-3} cm^2. mol^{-1} (λ = 260 nm); HRMS (ESI-TOF) *m/z*: [M-H]$^-$ Calcd for C$_{10}$H$_{13}$FN$_5$O$_6$P 348.0515; Found 348.0519.

*Isopropyl (((((2′R,3′S,4′S,5′R)-5′-(6-Amino-9H-purin-9-yl)-3′-fluoro-4′-hydroxytetrahydrofuran-2′-yl)oxy)methyl)(phenoxy)-phosphoryl)-L-alaninate (**49**).* To a stirred suspension of ditriethylammonium salt of **1** (100.4 mg, 0.182 mmol) and L-alanine isopropyl ester HCl salt (54 mg, 0.322 mmol) in dry pyridine (1.5 mL), were added PhOH (76 mg, 0.804 mmol) followed by Et$_3$N (0.27 mL, 1.93 mmol) at room temperature. The reaction mixture was then stirred at 60 °C under nitrogen for 15−20 min. In a separate flask The 2,2′-dithiodipyridine (294 mg, 1.333 mmol) and PPh$_3$ (250 mg, 0.897 mmol) were added in anhydrous pyridine (0.5 mL) and the resultant mixture was stirred at room temperature for 10−15 min to give a clear light yellow solution. The solution was then added to the solution of **1** at 60 °C and the combined mixture stirred for 16 h at 60 °C. The volatiles were removed *in vacuo* and the residue was dissolved in EtOAc. Organic layer was washed with saturated NaHCO$_3$ solution (2×), brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified first by column chromatography on silica gel (gradient CH$_2$Cl$_2$/MeOH, 99:1, v/v; 49:1, v/v; 24:1, v/v) and further by preparative HPLC (linear gradient, 5−95% CH$_3$CN in H$_2$O) to provide **49** (56 mg, 57%, white powder, R_f = 0.43, 10% MeOH in CH$_2$Cl$_2$) as a mixture of P(R) and P(S) isomers (approx 1:1). ^{1}H NMR (500 MHz, CD$_3$OD) δ 8.36, 8.29 (2s, 1H, H-8), 8.21 (s, 1H, H-2), 7.37−7.18 (m, 5H, Ar-*H* OPh), 6.29, 6.27 (2d, *J* = 6.8 Hz, 1H, H-1′), 5.42, 5.37 (2d, *J* = 9.5 Hz, 1H, H-4′), 5.18−5.11 (m, 1H, H-2′), 5.10−4.97 (m, 1H, H-3′), 4.96−4.91 (m, 1H. C*H*-^{i}Pr), 4.21−4.03 (m, 2H, -OC*H*$_2$P), 4.02−3.95 (m, 1H. C*H*-Ala), 1.28, 1.25 (2d, *J* = 7.1 Hz, 3H. C*H*$_3$-Ala), 1.19 (d, *J* = 6.2 Hz, 6H, 2 x C*H*$_3$-^{i}Pr); ^{13}C NMR (125 MHz, CD$_3$OD) δ 174.8, 174.5 (CO-Ala), 157.4 (C-4), 154.2 (C-2), 151.3, 151.2 (C-6), 140.7 (C-8), 130.8, 126.3, 122.0, 121.9, 121.8, 121.7 (Ar C-OPh), 120.2 (C-5), 107.1, 107.0 (2dd, *J* = 30.8 ($^2J_{C,F}$), 10.3 ($^3J_{C,P}$) Hz, C-4′), 94.2, 94.1 (2d, $^1J_{C,F}$ = 180.6 Hz, C-3′), 88.2, 88.1 (C-1′), 74.9, 74.8 (2d, $^2J_{C,F}$ = 17.2 Hz, C-2′), 70.2 (CH-^{i}Pr), 64.8, 64.7 (2d, $^1J_{C,P}$ = 158.5 Hz, -OCH$_2$P), 51.1, 51.0 (2d, $^2J_{C,P}$ = 13.0 Hz, *C*H-Ala), 21.9, 21.8 (CH$_3$-^{i}Pr), 21.0, 20.4 (2d, $^3J_{C,P}$ = 5.0 Hz, *C*H$_3$-^{i}Pr); ^{19}F NMR (470 MHz, CD$_3$OD) δ = −212.2, −212.40 (2Hex); ^{31}P NMR (202 MHz, CD$_3$OD) δ = 23.3, 22.1; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for C$_{22}$H$_{28}$FN$_6$O$_7$P 539.1814; Found 539.1814.

*Diisopentyl (((((2′R,3′S,4′S,5′R)-5′-(6-Amino-9H-purin-9-yl)-3′-fluoro-4′-hydroxytetrahydrofuran-2′-yl)oxy)methyl)(phenoxy)-phosphoryl)-L-aspartate (**50**).* A similar synthetic protocol as the one used for the synthesis of **49** was employed for the synthesis of **50**, starting from ditriethylammonium salt of **1** (80.3 mg, 0.146 mmol) and L-aspartic acid diisopentyl ester HCl salt (80.1 mg, 0.258 mmol), PhOH (61 mg, 0.643 mmol), Et$_3$N (0.22 mL, 1.55 mmol) in dry pyridine (1.2 mL) and 2,2′-dithiodipyridine (235 mg, 1.07 mmol), PPh$_3$ (200 mg, 0.718 mmol) in anhydrous pyridine (0.4 mL) to obtain **50** (54 mg, 54%, white powder, R_f = 0.46, 10% MeOH in CH$_2$Cl$_2$) as a mixture of P(R) and P(S) isomers (approx 1:1). ^{1}H NMR (500 MHz, CD$_3$OD) δ 8.35, 8.29 (2s, 1H, H-8), 8.21, 8.21 (2s, 1H, H-2), 7.36−7.17 (m, 5H, Ar-*H* OPh), 6.28, 6.27 (2d, *J* = 6.4 Hz, 1H, H-1′), 5.43, 5.36 (2d, *J* = 9.5 Hz, 1H, H-4′), 5.19−5.11 (m, 1H, H-2′), 5.10−4.94 (m, 1H, H-3′), 4.39−4.31 (m, 1H, C*H*-Asp), 4.25−3.95 (m, 6H, -OC*H*$_2$P and 2 × OC*H*$_2$-isopentyl), 2.79−2.59 (m, 2H, C*H*$_2$-Asp), 1.65−1.57 (m, 2H, 2 x C*H*-isopentyl), 1.48−1.42 (m, 4H, 2 x OCH$_2$C*H*$_2$-isopentyl), 0.89−0.85 (m, 12H, 4 x C*H*$_3$-isopentyl), 1.19 (d, *J* = 6.2 Hz, 6H, 2 x C*H*$_3$-^{i}Pr); ^{13}C NMR (125 MHz, CD$_3$OD) δ 173.3, 173.1 (2d, $^3J_{C,P}$ = 4.1 Hz, βCO-Asp), 172.0, 171.9 (γCO-Asp), 157.4 (C-4), 154.3, 154.2 (C-2), 151.5, 151.4 (C-6), 151.3, 151.2 (*ipso*C-Ph), 140.7 (C-8), 130.8, 126.3, 126.3, 122.0, 122.0, 121.9, 121.9 (Ar C-OPh), 120.2, 120.2 (C-5), 107.2, 107.0 (2dd, *J* = 30.8 ($^2J_{C,F}$), 10.3 ($^3J_{C,P}$) Hz, C-4′), 94.2, 94.1 (2d, $^1J_{C,F}$ = 185.1 Hz, C-3′), 88.2, 88.1 (C-1′), 74.8 (2d, $^2J_{C,F}$ = 16.2 Hz, C-2′), 65.0, 64.9 (2d, $^1J_{C,P}$ = 91.8 Hz, -OCH$_2$P), 64.1, 64.0 (2 × OC*H*$_2$- isopentyl), 51.9 (d, $^2J_{C,P}$ = 8.0 Hz, *C*H-Asp), 39.8, 39.6 (2d, $^3J_{C,P}$ = 4.5 Hz, CH$_2$−Asp), 38.3, 38.2 (OCH$_2$C*H*$_2$-isopentyl), 26.1, 26.0 (2 × *C*H-isopentyl), 22.9, 22.8, 22.8, 22.7 (4 x CH$_3$-isopentyl); ^{19}F NMR (470 MHz, CD$_3$OD) δ = −212.2, −212.3 (2m); ^{31}P NMR (202 MHz, CD$_3$OD) δ = 23.4, 22.6; HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for C$_{30}$H$_{42}$FN$_6$O$_9$P 681.2807; Found 681.2822.

*Dipropyl 2,2′-((((((2′R,3′S,4′S,5′R)-5′-(6-Amino-9H-purin-9-yl)-3′-fluoro-4′-hydroxytetrahydrofuran-2′-yl)oxy)methyl)phosphoryl)bis-(azanediyl))(2S,2′S)-bis(3-phenylpropanoate) (**51**).* A similar synthetic protocol as the one used for the synthesis of **49** was employed for the synthesis of **51**, starting from ditriethylammonium salt of **1** (117.4 mg, 0.213 mmol) and L-phenylalanine propyl ester HCl salt (311.3 mg, 1.277 mmol), Et$_3$N (0.36 mL, 2.56 mmol) in dry pyridine (1.8 mL) and 2,2′-dithiodipyridine (329 mg, 1.49 mmol), PPh$_3$ (415 mg, 1.49 mmol) in anhydrous pyridine (1 mL) to obtain **51** as white powder (65.1 mg, 42%, white solid, R_f = 0.46, 10% MeOH in CH$_2$Cl$_2$; Mp: 72−74 °C). ^{1}H NMR (500 MHz, CD$_3$OD) δ 8.24 (s, 1H, H-8), 8.21 (s, 1H, H-2), 7.24−7.11 (m, 5H, Ar-*H* OPh), 6.15 (d, *J* = 7.3 Hz, 1H, H-1′), 5.16 (ddd, *J* = 26.8 ($^1J_{H,F}$), 7.4, 3.5 Hz, 1H, H-2′), 5.03 (d, *J* = 9.5 Hz, 1H, H-4′), 4.88 (dd, *J* = 52.6 ($^2J_{H,F}$), 3.4 Hz, 1H, H-3′), 4.19−4.14 (m, 1H. C*H*-Phe), 4.12−3.96 (m, 5H. C*H*-Phe and 2 × OC*H*$_2$-^{n}Pr), 3.24 (ddd, *J* = 129.3 ($^2J_{H,P}$), 13.2, 7.3 Hz, 2H, -OC*H*$_2$P), 3.07−2.74 (m, 4H, 2 × C*H*$_2$-Phe), 1.70−1.56 (m, 4H, 2 × OCH$_2$C*H*$_2$-^{n}Pr), 0.95−0.87 (m, 6H, 2 x C*H*$_3$-^{n}Pr), 1.19 (d, *J* = 6.2 Hz, 6H, 2 x C*H*$_3$-^{i}Pr); ^{13}C NMR (125 MHz, CD$_3$OD) δ 174.5 (2d, $^3J_{C,P}$ = 6.8 Hz, 2 × CO-Phe), 157.4 (C-4), 154.4 (C-2), 151.0 (C-6), 141.7 (C-8), 138.3, 138.2 (2 x *ipso*C-Ph), 130.8, 130.6, 129.5, 129.4, 128.0, 127.9 (Ar C-Ph), 120.6 (C-5), 106.4 (dd, *J* = 29.9 ($^2J_{C,F}$), 13.1 ($^3J_{C,P}$) Hz, C-4′), 94.2 (d, $^1J_{C,F}$ = 184.4 Hz, C-3′), 88.6 (C-1′), 73.8 (2d, $^2J_{C,F}$ = 16.1 Hz, C-2′), 68.0, 67.9 (2 x OC*H*$_2$-^{n}Pr), 64.9 (d, $^1J_{C,P}$ = 139.6 Hz, -OCH$_2$P), 55.9, 55.5 (2 × *C*H$_2$−Phe), 23.0, 22.9 (2 × OCH$_2$C*H*$_2$-^{n}Pr), 10.8, 10.7 (2 × CH$_3$-^{n}Pr); ^{19}F NMR (470 MHz, CD$_3$OD) δ = −212.8 (oct); ^{31}P NMR (202 MHz, CD$_3$OD) δ = 22.2; $[\alpha]^{20}_D$ = −8.4° (*c* = 1, CH$_3$OH); HRMS (ESI-TOF) *m/z*: [M+H]$^+$ Calcd for C$_{34}$H$_{43}$FN$_7$O$_8$P 728.2967; Found 728.2969.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01482.

^{1}H, ^{13}C, ^{19}F, ^{31}P NMR, and HRMS spectra of intermediates and final compounds (PDF)

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Notes

The authors declare no competing financial interest.

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