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Full Paper

Threose C-Nucleosides

Synthesis of a Threosyl-C-nucleoside Phosphonate

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Abstract: A general synthetic route for the preparation of the first analogue of a new series of sugar-modified C-nucleoside phosphonates is detailed. Such derivative contains a four-carbon L-threose sugar moiety substituted with a phosphonomethoxy group at the 3′-position and pyrrolo[2,1-f][1,2,4]triazin-4-amine as nucleobase. A C-nucleoside was initially prepared by coupling a benzyl protected L-threono-1,4-lactone intermediate with the corresponding aglycon moiety. The choice of a *tert*-butyldiphenylsilyl group was found to be crucial to achieve the regioselective protection of the hydroxyl group at the 3′-position. Moreover, it allowed to smoothly perform further synthetic manipulations, including the introduction of a benzyl protected phosphonate synthon under basic conditions, which eventually led to the desired compound after final deprotection.

Introduction

C-Nucleosides are an important class of nucleoside analogues, especially in the context of antiviral drug discovery.[1] Such compounds are characterized by the presence of a C–C bond in place of the natural C–N glycosidic linkage, which makes them more resistant against hydrolytic and enzymatic degradation.[2] Some C-nucleosides isolated from natural sources have shown interesting biological properties; for instance, showdomycin and formycin A (Figure 1) can act as antibiotics.[3] BCX4430 (Figure 1) is a synthetic C-nucleoside containing 9-deazaadenine as nucleobase, which displays potent activity against Ebola virus (EBOV) infections.[4] Furthermore, GS-6620 and GS-5734 (Figure 1) are representative examples of C-nucleosides bearing pyrrolo[2,1-f][1,2,4]triazin-4-amine as nucleobase. While GS-6620 exhibits good activity against hepatitis C virus (HCV) infections,[5] GS-5734 is a potential drug for the treatment of the EBOV infection.[6]

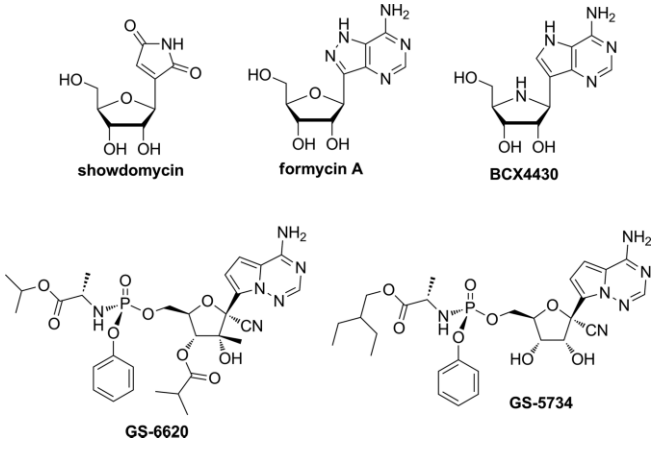

Figure 1. Structures of known biologically active C-nucleosides.

Besides, α-L-threose nucleosides containing a four-carbon L-threosyl sugar ring have been investigated for different purposes.[7] In particular, they are the building blocks of threose nucleic acid (TNA), which is an artificial genetic polymer able to form thermally stable self-duplexes by Watson–Crick base pairing as well as hybrids with complementary DNA and RNA strands.[8] Its capacity to fold into functional tertiary structures able to bind targets with high affinity and specificity has also been demonstrated.[9] Furthermore, TNA has been investigated for its potential role as early genetic material in a prebiotic setting.[9] Recently, we reported 3′-2′ phosphonomethylthreosyl nucleic acid (tPhoNA) as the first example of biorthogonal synthetic genetic material with a dual modification at the sugar and phosphate moiety.[10]

Nucleoside phosphonates are isosteric analogues of natural nucleoside monophosphates, which have been developed as antiviral drugs. Successful examples that received marketing approval for clinical use include tenofovir, adefovir, and cidofovir.[11] Previous work in our group focused on the synthesis of a series of threosyl nucleoside phosphonates, such as phosphonomethoxideoxythreosyl adenine (PMDTA, Figure 2),[12] as well as their corresponding amidate prodrugs,[13] which were found to display

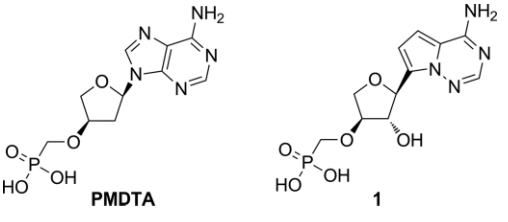

Figure 2. Structures of PMDTA and target C-nucleoside phosphonate analogue **1**.

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potent anti-HIV activity. To date, no examples have been reported in the literature of α-L-threosyl-C-nucleoside phosphonates. Therefore, based on the above rationale, we wished to develop suitable synthetic methods for the preparation of such analogues and further evaluate their potential antiviral activity. In particular, we planned to prepare C-nucleoside phosphonate analogue **1** (Figure 2) consisting of a L-threose sugar and pyrrolo[2,1-f][1,2,4]triazin-4-amine base moiety as model compound.

Results and Discussion

For the synthesis of C-nucleoside phosphonate **1**, commercially available L-threono-1,4-lactone **2** was selected as starting material (Scheme 1). Treatment of compound **2** with benzyl trichloroacetimidate and triflic acid (TfOH) afforded benzyl protected lactone **3** in good yield. 4-(Methylthio)pyrrolo[2,1-f][1,2,4]triazine **4** was readily prepared according to a reported method.[14] The coupling reaction between compounds **3** and **4** was accomplished by using lithium diisopropylamide (LDA) at –78 °C, which led to the formation of hemiacetal **5** as a mixture of two anomers. Subsequently, compound **6** was obtained in good yield (94 %) upon reduction of the 1′-hydroxyl group of **5** using Et_3SiH as reducing agent and $BF_3{\cdot}OEt_2$ as Lewis acid.[15] The thiomethyl group of compound **6** was substituted by an amino group by heating in 7 N methanolic ammonia, thus providing benzyl protected C-nucleoside **7**. The protecting groups were removed by palladium catalyzed debenzylation using cyclohexene as hydrogen donor,[16] thus affording threosyl-C-nucleoside **8** as a mixture of two isomers that were separated by silica gel column chromatography. The α-anomer (**8**α) was obtained as the major product in 49 % yield, while the β-anomer (**8**β) was isolated in 23 % yield.

The configuration of the two epimers of C-nucleoside **8** was determined by NOESY NMR spectroscopic analysis. As shown in Figure 3 for compound **8**α, NOE correlations were observed between 1′-H and 3′-H as well as 2′-H and 8-H, which confirmed the structure of the desired α-anomer.

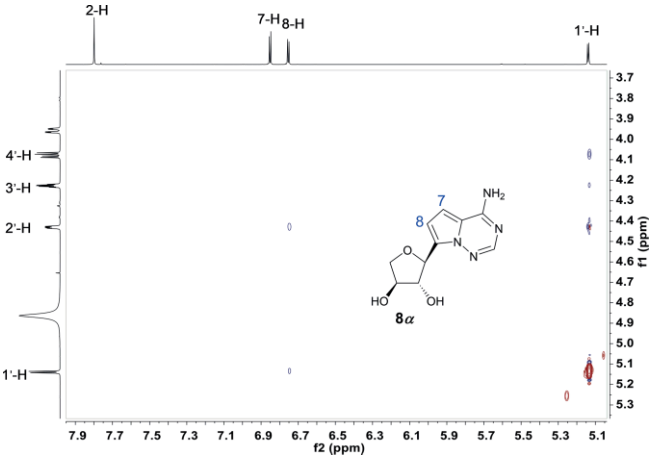
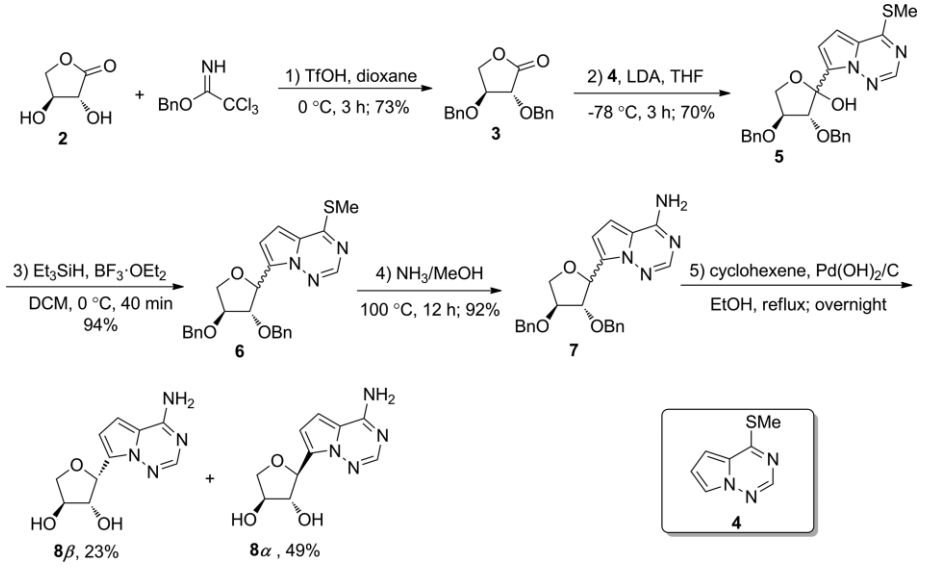


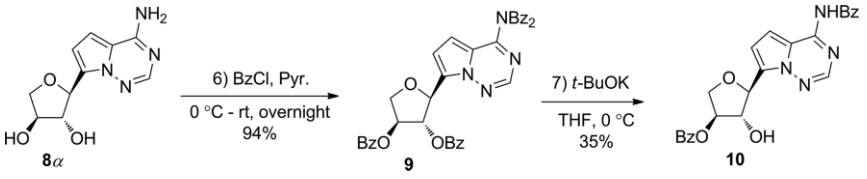
Figure 3. NOESY spectrum of threosyl-C-nucleoside **8**α.

With C-nucleoside **8** in hand, we next attempted the introduction of a phosphonate moiety at the 3′-position. Although the selective benzoylation of L-threono-1,4-lactone **2** has been previously reported,[17] the regioselective protection of the hydroxyl groups of threosyl nucleosides remains an unsolved issue. Initial attempts to selectively protect either the 2′- or 3′-hydroxyl group of **8** with a trityl group was unsuccessful, leading to a mixture of 2′-*O*- and 3′-*O*-tritylated derivatives along with the 2′,3′-bis-*O*-tritylated analogue. Similar results were reported earlier by Eschemoser and co-workers.[18]

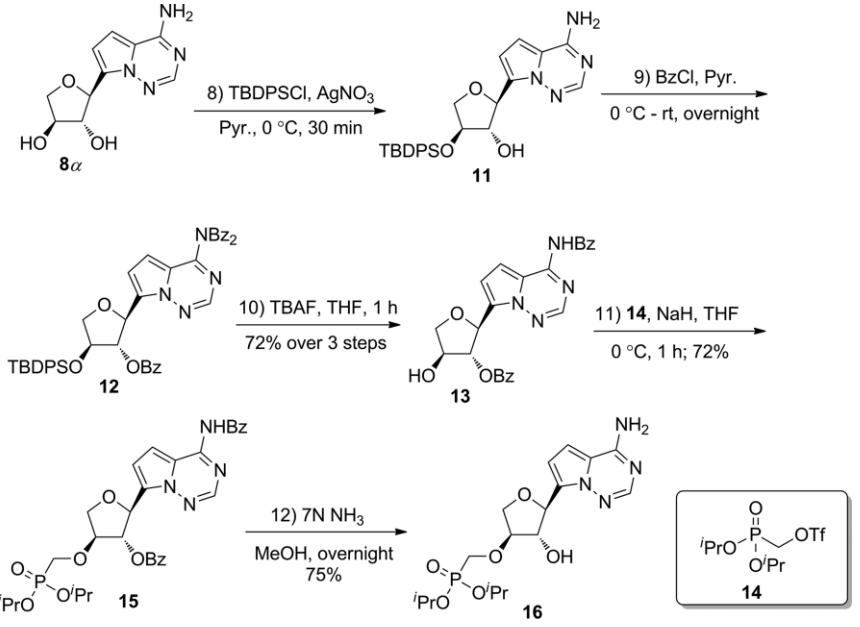
Previously, our group demonstrated that the benzoyl group at the 2′-position of a classic threose N-nucleoside can be selectively removed to give a 3′-*O*-benzoyl group protected product under basic conditions (*t*BuOK, THF).[19] Thus, we decided to prepare benzoylated compound **9** from C-nucleoside **8** under mild conditions (BzCl, pyridine). As shown in Scheme 2, the reaction proceeded in good yield. The resulting compound **9**



Scheme 1. Synthesis of threosyl-C-nucleoside **8**.



Scheme 2. Regioselective debenzoylation of compound **9**.



Scheme 3. Installation of the phosphonate moiety at the 3′-position.

was then subjected to regioselective debenzoylation reaction conditions (*t*BuOK), however 3′-*O*-benzoylated compound **10** was obtained only in moderate yield (35 %).

Pleasingly, a selective protection of the 3′-hydroxyl group could be successfully performed by treating compound **8** with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of $AgNO_3$ (Scheme 3). For a good reaction selectivity, the concentration of the starting material had to be approximately 0.02 M in dry pyridine at 0 °C. Higher reaction concentrations in fact led to the formation of the 2′,3′-*O*-bis-TBDPS protected product instead of the desired compound **11**. The remaining active protons of compound **11** were replaced by benzoyl groups to give fully protected compound **12**, which then underwent cleavage of the silyl protecting group by using tetra-*n*-butylammonium fluoride (TBAF) to afford key intermediate **13** (72 % yield over 3 steps from **8α**). The triflate derivative of diisopropylphosphonylmethanol **14** and sodium hydride were used to introduce the phosphonate unit at the 3′-position of compound **13**, leading to compound **15** in 72 % yield. Deprotection of the benzoyl groups under basic conditions (7 N methanolic ammonia) gave C-nucleoside phosphonate diester **16**. The configuration of compound **16** was confirmed by 2D NMR analyses (HMBC and NOESY).

A strong correlation between the two protons of the phosphonomethoxy (PCH_2) group and the 3′-carbon in the HMBC spectrum of **16** (see Supporting Information) confirmed the presence of the phosphonate moiety at the 3′-position. According to the NOESY spectrum (Figure 4), *H–H* correlations between 8-H and 2′-H as well as 8-H and the PCH_2 group were observed, supporting the configuration of compound **16** to be as that shown in Scheme 3. A further evidence was observed by the presence of a correlation between PCH_2 and 2′-H. Next, standard removal of the isopropyl protecting groups on the phosphonate moiety by treating compound **16** with trimethylsilyl bromide in acetonitrile failed to give the desired com-

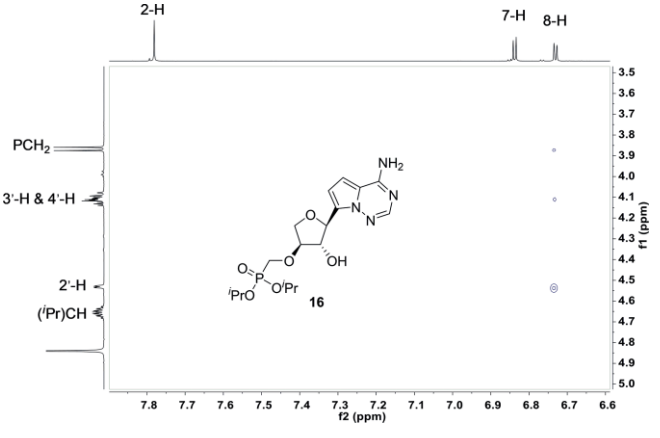
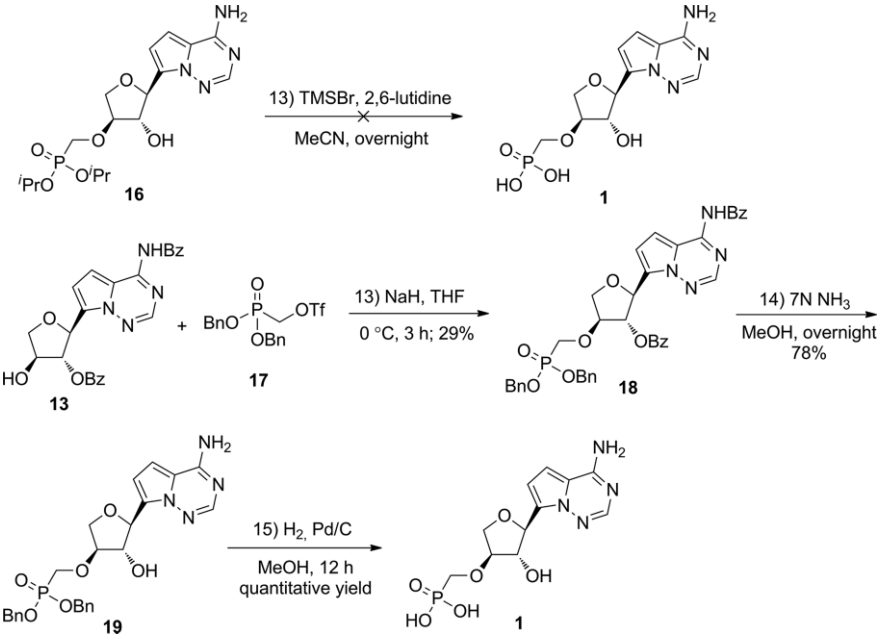


Figure 4. NOESY spectrum of compound **16**.



Scheme 4. Synthesis of threose C-nucleoside phosphonate **1**.

pound. Therefore, it was necessary to replace the isopropyl groups on the phosphonate synthon with benzyl functionalities. Compound **17**[20] was used for the installation of phosphonate moiety instead of compound **14** to provide compound **18** in 29 % yield. After removal of the benzoyl groups by methanolic ammonia, the benzyl groups were cleaved upon hydrogenolysis to furnish the desired threose C-nucleoside phosphonate **1** in quantitative yield (Scheme 4).

Conclusions

In summary, a convenient synthetic route for the preparation of the first analogue of a new series of C-nucleosides has been established. The synthesized compound features a L-threose sugar moiety modified with a phosphonomethoxy group at the 3′-position and pyrrolo[2,1-f][1,2,4]triazin-4-amine as nucleobase. The regioselective protection of 3′-hydroxyl group of the α-isomer of an intermediate C-nucleoside was effectively accomplished by using TBDPS as protecting group. After subsequent protecting groups manipulation, a phosphonate moiety was successfully introduced upon optimization of the reaction conditions. Both the C-nucleoside intermediate and final C-nucleoside phosphonate were evaluated against a panel of RNA [respiratory syncytial virus (RSV), zika virus (ZIKV), and dengue virus (DENV)] and DNA [herpes simplex virus (HSV), varicella zoster virus (VZV), and cytomegalovirus (CMV)] viruses. Unfortunately, no significant activity or cytotoxicity was observed.

Experimental Section

General Information: For all reactions, analytical grade solvents were used. All moisture sensitive reactions were carried out in oven-dried glassware (120 °C) under a nitrogen or argon atmosphere. Anhydrous THF was distilled from sodium/benzophenone. ^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded on a Bruker 300, 500, or 600 MHz spectrometer. 2D NMR experiments (H,H-COSY, HSQC, HMBC, and NOESY) were used for the characterization of the key intermediates and final compound. 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. Precoated aluminum sheets (254 nm) were used for TLC, and spots were examined under UV light. Column chromatography was performed on silica gel 40–60 μ, 60 Å. Preparative HPLC purification was performed using a Shimadzu HPLC equipped with a LC-20AT pump, DGU-20A5 degasser, SPD-20A UV detector, and Phenomenex Gemini 110A column (C18, 10 μm, 21.2 mm × 250 mm).

2,3-Di-*O*-benzyl-l-threono-1,4-lactone (3):[21] Benzyl trichloroacetimidate (16.0 mL, 87.2 mol) and trifluoromethanesulfonic acid (0.77 mL, 8.72 mmol) were added at 0 °C to a solution of commercially available l-threono-1,4-lactone **2** (5.15 g, 43.6 mol) in dry dioxane (150 mL) under a nitrogen atmosphere. The solution was stirred for 3 h and then quenched with saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4, filtered, and evaporated under reduced pressure to give a crude residue, which was purified by flash column chromatography (petroleum ether/EtOAc = 10:1 to 5:1) to afford **3** as a colorless oil (9.45 g, 73 % yield). R_f 0.4 (petroleum ether/EtOAc = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.41–7.18 (m, 10H, Ar-H), 5.02 (d, J = 11.6 Hz, 1H, Bn-CH_2), 4.76 (d, J = 11.6 Hz, 1H, Bn-CH_2), 4.62 (d, J = 11.8 Hz, 1H, Bn-CH_2), 4.51 (d, J = 11.8 Hz, 1H, Bn-CH_2), 4.43–4.27 (m, 2H, 4′-H, 3′-H), 4.22 (d, J = 5.7 Hz, 1H, 2′-H), 4.05 (dd, J = 9.0, 5.8 Hz, 1H, 4′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.5 (C=O), 137.3 (Ar-C), 137.0 (Ar-C), 137.0 (Ar-C), 129.2 (Ar-C), 129.0 (Ar-C), 128.9 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 128.6 (Ar-C), 128.6 (Ar-C), 128.2 (Ar-C), 78.7 (C-3′), 77.7 (C-2′), 72.8 (Bn-CH_2), 72.6 (Bn-CH_2), 69.4 (C-4′); ESI-HRMS calcd. for $C_{18}H_{18}N_4Na$ [M + Na]$^+$, 321.1097, found m/z 321.1094.

(2′*R*,3′*S*)-2′,3′-Bis(benzyloxy)-1′-(4-(methylthio)pyrrolo[2,1-f][1,2,4]triazin-7-yl)tetra-hydroofuran-1′-ol (5): To a solution of 4-(methylthio)pyrrolo[2,1-f][1,2,4]triazine **4** (4.57 g, 27.6 mmol) in THF (70 mL) was added lithium diisopropylamide (2 M in THF, 14.8 mL, 29.5 mmol) at –78 °C under an argon atmosphere. The resulting mixture was stirred for 30 min at –78 °C. Then, a solution of compound **3** (5.50 g, 18.4 mmol) in THF (15 mL) was added at –78 °C and the resulting reaction mixture was stirred at this temperature for 3 h. The reaction was quenched by adding saturated aq. NH_4Cl and further extracted with ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The crude residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 5:1 to 1:1) to give the title compound as a brown syrup (6.0 g, 70 % yield). R_f 0.3 (petroleum ether/EtOAc = 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.38–8.19 (m, 1H, 2-H), 7.37–7.04 (m, 10H, Ph-H), 6.86–6.73 (m, 2H, 7-H, 8-H), 5.41–5.12 (m, 1H, 2′-H), 4.71–4.45 (m, 4H, Ph-CH_2), 4.36–4.28 (m, 1H, 3′-H), 4.02–3.75 (m, 2H, 4′-H), 2.66–2.69 (m, 3H, SMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.5 (C-4), 165.4 (C-4), 146.8 (C-2), 145.2 (C-2), 145.1 (Ar-C), 138.0 (Ar-C), 137.6 (Ar-C), 137.4 (Ar-C), 128.9 (Ar-C), 128.7 (Ar-C), 128.7 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 128.3 (Ar-C), 128.3 (Ar-C), 128.1 (Ar-C), 127.9 (Ar-C), 127.9 (Ar-C), 126.4 (Ar-C), 125.5 (Ar-C), 122.9 (Ar-C), 122.4 (Ar-C), 120.6 (Ar-C), 113.5 (C-8), 112.6 (C-8), 104.5 (C-1′), 103.3 (C-7), 102.1 (C-7), 100.4 (C-1′), 84.8 (C-2′), 84.2 (C-2′), 82.7 (C-3′), 82.2 (C-3′), 79.4 (Bn-C), 73.3 (Bn-C), 73.2 (Bn-C), 72.7 (Bn-C), 72.3 (Bn-C), 71.7 (Bn-C), 69.9 (C-4′), 62.2 (C-4′), 12.0 (SMe-C), 11.7 (SMe-C); ESI-HRMS calcd. for $C_{25}H_{25}N_3O_4SNa$ $[M + Na]^+$, 486.1458, found *m/z* 486.1443.

7-((2′*S*,3′*S*)-2′,3′-Bis(benzyloxy)tetrahydrofuran-1′-yl)-4-(methylthio)pyrrolo[2,1-f][1,2,4]-triazine (6): To a solution of compound **5** (3.18 g, 6.86 mmol) in dichloromethane (25 mL) was added triethylsilane (4.38 mL, 27.4 mmol) and trifluoroborane (1.7 mL, 13.7 mmol) at 0 °C under an argon atmosphere. The resulting solution was stirred for 40 min at 0 °C, quenched with saturated aq. $NaHCO_3$ and further extracted with ethyl acetate. The organic layer was washed with water, brine, dried with Na_2SO_4, and concentrated in vacuo. The crude residue was purified by flash chromatography (petroleum ether/EtOAc = 10:1 to 4:1) to give compound **6** as a yellow foam (2.90 g, 94 % yield). R_f 0.5 (petroleum ether/EtOAc = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.22–8.10 (m, 1H, 2-H), 7.37–7.14 (m, 9H, Ar-H), 6.99–6.75 (m, 3H, Ar-H), 5.64–5.54 (m, 1H, 1′-H), 4.67–4.33 (m, 4H, Bn), 4.25–3.96 (m, 4H, 2′-H, 3′-H, 4′-H), 2.67–2.66 (m, 3H, SMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.7 (C-4), 164.3 (C-4), 145.5 (C-2), 145.3 (C-2), 138.1 (Ar-C), 138.1 (Ar-C), 137.8 (Ar-C), 129.2 (Ar-C), 128.8 (Ar-C), 128.7 (Ar-C), 128.6 (Ar-C), 128.4 (Ar-C), 128.1 (Ar-C), 128.1 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.9 (Ar-C), 127.9 (Ar-C), 127.8 (Ar-C), 122.4 (C-5), 121.9 (C-5), 113.3 (C-8), 112.4 (C-8), 102.4 (C-7), 102.3 (C-7), 86.4 (C-2′), 84.0 (C-2′), 83.4 (C-1′), 81.9 (C-1′), 77.7 (C-3′), 76.0 (C-3′), 72.4 (C-4′), 72.4 (C-4′), 72.3 (Bn-C), 71.9 (Bn-C), 71.8 (Bn-C), 71.7 (Bn-C), 11.7 (SMe-C); ESI-HRMS calcd. for $C_{25}H_{26}N_3O_3S$ $[M + H]^+$, 448.1689, found *m/z* 448.1685.

7-((2′*S*,3′*S*)-2′,3′-Bis(benzyloxy)tetrahydrofuran-1′-yl)pyrrolo-[2,1-f][1,2,4]triazin-4-amine (7): Compound **6** (2.90 g, 6.50 mmol) was dissolved in 7 N methanolic ammonia (50 mL) and the resulting solution was stirred for 12 h at 100 °C. The solvent was evaporated in vacuo to give a crude product, which was purified by flash chromatography (petroleum ether/EtOAc = 2:1 to 1:4) to afford 2.50 g of compound **7** as a white foam (92 % yield). R_f 0.3 (petroleum ether/EtOAc = 1:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.92–7.83 (m, 1H, 2-H), 7.35–7.17 (m, 9H, Ar-H), 6.94–6.54 (m, 3H, Ar-H), 6.11 (br, 2H, NH_2), 5.66–7.53 (m, 1H, 1′-H), 4.70–4.31 (m, 4H, Bn), 4.24–3.94 (m, 4H, 2′-H, 3′-H, 4′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.8 (C-4), 155.6 (C-4), 147.4 (C-2), 147.2 (C-2), 138.1 (Ar-C), 138.0 (Ar-C), 129.2 (Ar-C), 128.8 (Ar-C), 128.7 (Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 128.3 (Ar-C), 128.1 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.9 (Ar-C), 114.9 (C-5), 114.3 (C-5), 111.7 (C-8), 110.8 (C-8), 100.7 (C-7), 100.5 (C-7), 86.6 (C-2′), 84.1 (C-2′), 83.5 (C-3′), 82.0 (C-3′), 77.7 (C-1′), 76.1 (C-1′), 72.4 (C-4′), 72.3 (C-4′), 72.2 (Bn-C), 71.9 (Bn-C), 71.8 (Bn-C), 71.7 (Bn-C); ESI-HRMS calcd. for $C_{24}H_{25}N_4O_3$ $[M + H]^+$, 417.1921, found *m/z* 417.1920.

(2′*R*,3′*S*)-1′-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)tetrahydrofuran-2′,3′-diol (8): A mixture of compound **7** (835 mg, 2.00 mmol), 20 % $Pd(OH)_2$/C (835 mg), and cyclohexene (6.0 mL, 60.1 mmol) in EtOH (15 mL) was refluxed overnight. After filtration through Celite, the filtrate was evaporated under reduced pressure to give a crude residue, which was purified by silica gel column chromatography (DCM/MeOH = 15:1 to 5:1) to afford compound **8** (β-isomer, 110 mg, 23 %; α-isomer, 230 mg, 49 %). Data for **8**α: R_f 0.35 (DCM/MeOH = 7:1); ^{1}H NMR (500 MHz, CD_3OD) δ = 7.80 (s, 1H, 2-H), 6.85 (d, *J* = 4.5 Hz, 1H, 7-H), 6.75 (d, *J* = 4.5 Hz, 1H, 8-H), 5.13 (d, *J* = 4.2 Hz, 1H, 1′-H), 4.41 (ddd, *J* = 4.1, 2.1, 0.7 Hz, 1H, 2′-H), 4.21 (dt, *J* = 4.4, 2.3 Hz, 1H, 3′-H), 4.07 (dd, *J* = 9.6, 4.3 Hz, 1H, 4′-H), 3.95 (dd, *J* = 9.6, 2.3 Hz, 1H, 4′-H); ^{13}C NMR (126 MHz, CD_3OD) δ = 157.2 (C-4), 148.0 (C-2), 130.3 (C-9), 116.2 (C-5), 111.8 (C-8), 102.7 (C-7), 82.4 (C-2′), 81.2 (C-1′), 79.3 (C-3′), 74.6 (C-4′). Data for **8**β: R_f 0.30 (DCM/MeOH = 7:1); ^{1}H NMR (600 MHz, CD_3OD) δ = 7.75 (s, 1H, 2-H), 6.86 (d, *J* = 4.5 Hz, 1H, 7-H), 6.76 (d, *J* = 4.9 Hz, 1H, 8-H), 5.60 (d, *J* = 3.3 Hz, 1H, 1′-H), 4.38 (dd, *J* = 3.3, 0.8 Hz, 1H, 2′-H), 4.34–4.29 (m, 2H, 3′-H, 4′-H), 3.80 (d, *J* = 8.5 Hz, 1H, 4′-H); ^{13}C NMR (151 MHz, CD_3OD) δ = 156.8 (C-4), 147.6 (C-2), 128.9 (C-9), 115.5 (C-5), 112.4 (C-8), 102.8 (C-7), 78.6 (C-3′), 78.0 (C-2′), 77.5 (C-1′), 74.3 (C-4′); ESI-HRMS calcd. for $C_{10}H_{13}N_4O_3$ $[M + H]^+$, 237.0982, found *m/z* 237.0982.

(1′*S*,2′*S*,3′*S*)-1′-(4-(*N*-Benzoylbenzamido)pyrrolo[2,1-f][1,2,4]triazin-7-yl)tetrahy-drofuran-2′,3′-diyl Dibenzoate (9): To a solution of C-nucleoside **8** (168 mg, 0.7 mmol) in dry pyridine (10 mL) was added BzCl (0.5 mL, 4.3 mmol) at 0 °C. The reaction was stirred at room temperature overnight before quenching with saturated aq. $NaHCO_3$. The resulting mixture was extracted with DCM (twice) and the organic layers were combined, dried with Na_2SO_4, and evaporated in vacuo to give a crude residue, which was purified by flash chromatography (petroleum ether/EtOAc = 6:1 to 1:1) to afford compound **9** as a pale yellow foam (435 mg, 94 % yield). R_f 0.3 (petroleum ether/EtOAc = 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.16 (s, 1H, 2-H), 8.10–8.07 (m, 2H, Bz), 7.96–7.93 (m, 2H, Bz), 7.87–7.84 (m, 4H, Bz), 7.63–7.36 (m, 12H, Bz), 7.15 (d, *J* = 4.7 Hz, 1H, 7-H), 6.76 (d, *J* = 4.7 Hz, 1H, 8-H), 6.06 (d, *J* = 2.9 Hz, 1H, 2′-H), 5.78 (d, *J* = 3.4 Hz, 1H, 3′-H), 5.70–5.68 (m, 1H, 1′-H), 4.51 (dd, *J* = 10.9, 4.5 Hz, 1H, 4′-H), 4.35 (d, *J* = 10.5 Hz, 1H, 4′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.2 (Bz C=O), 165.9 (Bz C=O), 165.5 (Bz C=O), 154.7 (C-4), 146.4 (C-2), 134.0 (Ar-C), 133.9 (Ar-C), 133.8 (Ar-C), 133.7 (Ar-C), 130.4 (Ar-C), 130.2 (Ar-C), 130.1 (Ar-C), 129.5 (Ar-C), 129.3 (Ar-C), 128.8 (Ar-C), 128.7 (Ar-C), 119.7 (C-5), 114.4 (C-8), 103.9 (C-7), 80.4 (C-3′), 78.7 (C-2′), 77.6 (C-1′), 73.0 (C-4′); ESI-HRMS calcd. for $C_{38}H_{29}N_4O_7$ $[M + H]^+$, 653.2031, found *m/z* 653.2050.

(1′*S*,2′*S*,3′*S*)-1′-(4-Benzamidopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2′-hydroxytetrahydro-furan-3′-yl Benzoate (10): A solution of *t*BuOK (13.0 mg, 0.10 mmol) in 1 mL of dry THF was added to a solution of compound **9** (30.0 mg, 0.05 mmol) in 5 mL of THF at –20 °C. The reaction was stirred at 0 °C for 3 h and then quenched with saturated aq. NH_4Cl. The resulting mixture was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude product was subjected to flash chromatography (petroleum ether/EtOAc = 2:1 to 1:2) to afford compound **10** (7 mg, 35 %). R_f 0.3 (petroleum ether/EtOAc = 1:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.13–8.05 (m, 2H, Ar-H),

7.98–7.97 (m, 2H, Ar-H), 7.62–7.56 (m, 2H, Ar-H), 7.52–7.46 (m, 3H, Ar-H), 7.45–7.41 (m, 3H, Ar-H), 6.94 (s, 1H, Ar-H), 5.43 (dt, *J* = 4.8, 2.1 Hz, 1H, 3′-H), 5.36 (d, *J* = 5.0 Hz, 1H, 1′-H), 4.66 (dd, *J* = 5.1, 1.8 Hz, 1H, 2′-H), 4.45 (dd, *J* = 10.8, 5.2 Hz, 1H, 4′-H), 4.34 (dd, *J* = 10.8, 2.2 Hz, 1H, 4′-H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 166.6 (Bz C=O), 150.9 (C-4), 133.6 (Ar-C), 133.5 (Ar-C), 132.9 (Ar-C), 130.0 (Ar-C), 129.7 (Ar-C), 129.2 (Ar-C), 128.7 (Ar-C), 128.5 (Ar-C), 111.4 (C-8), 108.8 (C-7), 81.7 (C-3′), 80.7 (C-2′), 80.2 (C-1′), 71.8 (C-4′); ESI-HRMS calcd. for $C_{24}H_{21}N_4O_5$ [M + H]$^+$, 445.1506, found *m/z* 445.1505.

(1′*S*,2′*S*,3′*S*)-1′-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3′-((*tert*-butyldiphenylsilyl)-oxy)tetrahydrofuran-2′-ol (11): To a solution of C-nucleoside **8** (133 mg, 0.56 mmol) and TBDPSCl (0.6 mL, 2.30 mmol) in 25 mL of dry pyridine was added $AgNO_3$ (430 mg, 2.50 mmol) at 0 °C. The reaction was stirred at 0 °C for 30 min and then quenched with brine. The resulting mixture was extracted with DCM (twice) and the organic layers were combined, dried with Na_2SO_4, filtered, and evaporated in vacuo to afford a crude product, which was used directly in the next step without further purification. R_f 0.2 (petroleum ether/EtOAc = 1:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.88 (s, 1H, 2-H), 7.65–7.57 (m, 4H, Ph-H), 7.44–7.30 (m, 6H, Ph-H), 6.79 (d, *J* = 4.4 Hz, 1H, 7-H), 6.64 (d, *J* = 4.5 Hz, 1H, 8-H), 5.67 (br, 2H, NH_2), 5.14 (d, *J* = 4.7 Hz, 1H, 1′-H), 4.45–4.39 (m, 2H, 2′-H, 3′-H), 4.00–3.91 (m, 2H, 4′-H), 1.02 (s, 9H, TBDPS); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 155.5 (C-4), 147.5 (C-2), 136.0 (Ar-C), 130.1 (Ar-C), 130.1 (Ar-C), 128.0 (Ar-C), 128.0 (Ar-C), 114.5 (C-5), 109.6 (C-8), 100.5 (C-7), 83.0 (C-2′), 80.8 (C-3′), 79.8 (C-1′), 74.3 (C-4′), 27.1 (TBDPS), 19.4 (TBDPS); ESI-HRMS calcd. for $C_{26}H_{31}N_4O_3Si$ [M + H]$^+$, 475.2160, found *m/z* 475.2159.

(1′*S*,2′*S*,3′*S*)-1′-(4-(*N*-Benzoylbenzamido)pyrrolo[2,1-f][1,2,4]triazin-7-yl)-3′-((*tert*-butyldiphenylsilyl)oxy)-tetrahydrofuran-2′-yl Benzoate (12): To a solution of compound **11** (451 mg, 0.59 mmol) in 10 mL of dry pyridine was added BzCl (0.9 mL, 7.60 mmol) at 0 °C. The reaction was stirred at room temperature overnight, and then quenched with saturated aq. $NaHCO_3$. The resulting mixture was extracted with DCM (twice) and the organic layers were combined, dried with Na_2SO_4, filtered, and evaporated in vacuo. The crude residue was purified by flash chromatography (petroleum ether/EtOAc = 8:1 to 3:1) to afford compound **12** as a yellow foam. R_f 0.4 (petroleum ether/EtOAc = 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.15–8.10 (m, 2H, Ar-H), 7.96–7.86 (m, 6H, Ar-H), 7.66–7.61 (m, 3H, Ar-H), 7.55–7.48 (m, 3H, Ar-H), 7.43–7.29 (m, 13H, Ar-H), 6.78 (d, *J* = 4.7 Hz, 1H, 8-H), 5.86 (dd, *J* = 2.7, 1.8 Hz, 1H, 2′-H), 5.66 (d, *J* = 2.6 Hz, 1H, 1′-H), 4.58–4.55 (m, 1H, 3′-H), 3.99 (d, *J* = 3.5 Hz, 2H, 4′-H), 1.05 (s, 9H, TBDPS); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.3 (Bz C=O), 165.5 (Bz C=O), 154.6 (C-4), 146.3 (C-2), 136.1 (Ar-C), 136.0 (Ar-C), 134.0 (Ar-C), 133.6 (Ar-C), 133.6 (Ar-C), 130.4 (Ar-C), 130.3 (Ar-C), 130.1 (Ar-C), 129.5 (Ar-C), 129.3 (Ar-C), 128.7 (Ar-C), 128.2 (Ar-C), 124.4 (Ar-C), 119.5 (Ar-C), 115.0 (C-8), 103.8 (C-7), 83.1 (C-2′), 78.0 (C-3′), 77.2 (C-1′), 74.5 (C-4′), 27.2 (TBDPS), 19.4 (TBDPS); ESI-HRMS calcd. for $C_{47}H_{43}N_4O_6Si$ [M + H]$^+$, 787.2946, found *m/z* 787.2951.

(1′*S*,2′*R*,3′*S*)-1′-(4-Benzamidopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3′-hydroxytetrahydro-furan-2′-yl Benzoate (13): To a solution of crude compound **12** (748 mg, 0.95 mmol) in dry pyridine was added TBAF (1 M, 1.9 mL, 1.9 mmol). The reaction was stirred at room temperature for 1 h. After complete consumption of the starting material, the volatiles were removed in vacuo to give a crude residue, which was purified by flash chromatography (petroleum ether/EtOAc = 4:1 to 1:2) to afford compound **13** as a yellow foam (307 mg, 72 % over 3 steps). R_f 0.3 (petroleum ether/EtOAc = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.14–8.09 (m, 2H, Ar-H), 8.07–8.04 (m, 3H, Ar-H), 7.63–7.58 (m, 2H, Ar-H), 7.54–7.39 (m, 5H, Ar-H), 6.97 (d, *J* = 4.7 Hz, 1H, 8-H), 5.61 (d, *J* = 3.4 Hz, 1H, 2′-H), 5.37 (d, *J* = 3.6 Hz, 1H, 1′-H), 4.56–4.55 (m, 1H, 3′-H), 4.22–4.11 (m, 2H, 4′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.3 (Bz C=O), 166.4 (Bz C=O), 151.5 (C-4), 146.3 (C-2), 133.9 (Ar-C), 133.8 (Ar-C), 133.3 (Ar-C), 133.2 (Ar-C), 130.2 (Ar-C), 130.2 (Ar-C), 130.1 (Ar-C), 129.5 (Ar-C), 129.3 (Ar-C), 129.0 (Ar-C), 128.9 (Ar-C), 128.8 (Ar-C), 128.6 (Ar-C), 114.2 (C-5), 109.0 (C-8), 104.2 (C-7), 84.2 (C-2′), 78.8 (C-3′), 77.0 (C-1′), 74.6 (C-4′); ESI-HRMS calcd. for $C_{24}H_{21}N_4O_5$ [M + H]$^+$, 445.1506, found *m/z* 445.1502.

(1′*S*,2′*S*,3′*S*)-1′-(4-Benzamidopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3′-((diisopropoxyphos-phoryl)methoxy)tetrahydrofuran-2′-yl Benzoate (15): To a solution of 13 (50 mg, 0.1 mmol) and triflate diisopropylphosphonomethanol (110 mg, 0.3 mmol) in anhydrous THF (50 mL) was added NaH (60 % in mineral oil, 13.5 mg, 0.3 mmol) at 0 °C. The reaction mixture was stirred for 1 h. It was then quenched with saturated aq. NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure to give a crude residue, which was purified by column chromatography (petroleum ether/EtOAc = 3:1 to 1:3) to afford 15 (52 mg, 74 % yield) as a colorless foam. R_f 0.3 (petroleum ether/EtOAc = 1:2); ^{1}H NMR (300 MHz, CD_3OD) δ = 8.12–7.86 (m, 6H, Ar-H), 7.65–7.41 (m, 6H, Ar-H), 7.27–7.07 (d, *J* = 4.7 Hz, 1H, Ar-H), 5.72 (s, 1H, 1′-H), 4.76–4.65 (m, 2H, *i*Pr-CH), 4.43–3.99 (m, 6H, 2′-H, 3′-H, 4′-H, PCH_2), 1.38–1.26 (m, 12H, *i*Pr-CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ = 171.9 (Bz C=O), 165.3 (Bz C=O), 145.3 (C-2), 133.0 (Ar-C), 132.9 (Ar-C), 132.1 (Ar-C), 129.0 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 128.1 (Ar-C), 128.0 (Ar-C), 127.9 (Ar-C), 122.2 (Ar-C), 114.1 (Ar-C), 111.7 (Ar-C), 103.3 (Ar-C), 99.7 (Ar-C), 85.9 (C-3′), 85.7 (C-3′), 80.5 (C-2′), 76.7 (C-1′), 71.6 (*i*Pr-CH), 71.5 (*i*Pr-CH), 71.4 (C-4′), 64.5 (PCH_2), 62.3 (PCH_2), 22.6 (*i*Pr-CH_3), 22.6 (*i*Pr-CH_3), 22.5 (*i*Pr-CH_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ = 19.0; ESI-HRMS calcd. for $C_{31}H_{36}N_4O_8P$ [M + H]$^+$, 623.2265, found *m/z* 623.2268.

Diisopropyl((((1′*S*,2′*S*,3′*S*)-1′-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2′-hydroxytetra-hydrofuran-3′-yl)oxy)methyl)phosphonate (16): Compound **15** (50 mg, 0.08 mmol) was dissolved in 7 N methanolic ammonia (5 mL). The reaction was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (DCM/MeOH = 50:1 to 10:1) to give compound **16** (25 mg, 75 % yield). R_f 0.4 (DCM/MeOH = 20:1); ^{1}H NMR (600 MHz, CD_3OD) δ = 7.78 (s, 1H, 2-H), 6.84 (d, *J* = 4.5 Hz, 1H, 7-H), 6.73 (d, *J* = 4.5 Hz, 1H, 8-H), 5.24 (d, *J* = 4.3 Hz, 1H, 1′-H), 4.63–4.68 (m, 2H, *i*Pr-CH), 4.54–4.53 (m, 1H, 2′-H), 4.12–4.08 (m, 3H, 3′-H, 4′-H), 3.87 (d, *J* = 9.5 Hz, 2H, PCH_2), 1.31–1.26 (m, 12H, *i*Pr-CH_3); ^{13}C NMR (151 MHz, CD_3OD) δ = 157.1 (C-4), 148.0 (C-2), 130.4 (C-9), 116.0 (C-5), 111.2 (C-8), 102.7 (C-7), 89.7 (C-3′), 89.6 (C-3′), 80.5 (C-2′), 80.5 (C-1′), 73.3 (*i*Pr-CH), 73.2 (*i*Pr-CH), 72.2 (C-4′), 65.3 (PCH_2), 64.2 (PCH_2), 24.3 (*i*Pr-CH_3), 24.3 (*i*Pr-CH_3), 24.3 (*i*Pr-CH_3), 24.2 (*i*Pr-CH_3), 24.2 (*i*Pr-CH_3); ^{31}P NMR (121 MHz, CD_3OD) δ = 19.4; ESI-HRMS calcd. for $C_{17}H_{28}N_4O_6P$ [M + H]$^+$, 415.1741, found *m/z* 415.1741.

(1′*S*,2′*S*,3′*S*)-1′-(4-Benzamidopyrrolo[2,1-f][1,2,4]triazin-7-yl)-3′-((bis(benzyloxy)phospho-ryl)methoxy)tetrahydrofuran-2′-yl Benzoate (18): To a solution of 16 (70 mg, 0.16 mmol) and triflate dibenzylphosphonomethanol 17 (200 mg, 0.47 mmol) in anhydrous THF (50 mL) was added NaH (60 % in mineral oil, 19.0 mg, 0.47 mmol) at 0 °C. The reaction mixture was stirred for 2 h. The reaction was quenched with saturated aq. NH_4Cl, and subsequently concentrated under reduced pressure. The remaining residue was partitioned between water and EtOAc. The organic layer was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc = 3:1 to 1:2) to afford 18 (33 mg, 29 % yield) as a colorless foam. R_f 0.25 (petroleum ether/EtOAc = 1:2);

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.12–7.83 (m, 4H, Ar-H), 7.64–7.45 (m, 6H, Ar-H), 7.32–7.24 (m, 13H, Ar-H), 5.70 (s, 1H, 1′-H), 5.12–4.98 (m, 5H, Bn-CH_2, 2′-H), 4.27–3.95 (m, 5H, 3′-H, 4′-H, PCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.8 (Bz C=O), 161.6 (Bz C=O), 151.2 (C-4), 148.0 (C-2), 133.8 (Ar-C), 133.0 (Ar-C), 130.1 (Ar-C), 129.5 (Ar-C), 129.2 (Ar-C), 128.9 (Ar-C), 128.8 (Ar-C), 128.8 (Ar-C), 128.3 (Ar-C), 128.3 (Ar-C), 119.8 (Ar-C), 112.7 (Ar-C), 108.7 (Ar-C), 99.7 (Ar-C), 86.5 (C-3′), 86.4 (C-3′), 80.8 (C-2′), 80.7 (C-1′), 72.5 (C-4′), 68.4 (PCH_2), 68.3 (PCH_2), 68.2 (PCH_2); ^{31}P NMR (121 MHz, $CDCl_3$) δ = 21.9; ESI-HRMS calcd. for $C_{39}H_{36}N_4O_8P$ $[M + H]^+$, 719.2265, found *m/z* 719.2266.

Dibenzyl((((1′*S*,2′*S*,3′*S*)-1′-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2′-hydroxytetrahy-drofuran-3′-yl)oxy)methyl)phosphonate (19): Compound **18** (33 mg, 0.05 mmol) was dissolved in 7 N methanolic ammonia. The reaction was stirred at room temperature overnight. The solvent was evaporated under reduced pressure to give a crude product, which was purified by silica gel column chromatography (DCM/MeOH = 50:1 to 15:1) to give **19** (18 mg, 78 %). R_f 0.4 (DCM/MeOH = 20:1); ^{1}H NMR (600 MHz, CD_3OD) δ = 7.77 (s, 1H, 2-H), 7.33–7.31 (m, 10H, Bn), 6.80 (d, *J* = 4.5 Hz, 1H, 7-H), 6.68 (d, *J* = 4.5 Hz, 1H, 8-H), 5.23 (d, *J* = 4.2 Hz, 1H, 1′-H), 5.04–4.99 (m, 4H, Bn-CH_2), 4.48 (dd, *J* = 4.1, 1.6 Hz, 1H, 2′-H), 4.07–4.04 (m, 3H, 3′-H, 4′-H), 3.94 (d, *J* = 9.4 Hz, 2H, PCH_2); ^{13}C NMR (151 MHz, CD_3OD) δ = 157.1 (C-4), 148.0 (C-2), 137.4 (Ar-C), 137.4 (Ar-C), 130.4 (Ar-C), 116.0 (C-5), 111.2 (C-8), 102.7 (C-7), 89.7 (C-3′), 89.6 (C-3′), 80.6 (C-1′), 80.3 (C-2′), 72.2 (C-4′), 69.6 (Bn-CH_2), 69.5 (Bn-CH_2), 64.8 (PCH_2), 63.7 (PCH_2); ^{31}P NMR (121 MHz, CD_3OD) δ = 22.1; ESI-HRMS calcd. for $C_{25}H_{28}N_4O_6P$ $[M + H]^+$, 511.1741, found *m/z* 511.1742.

((((1′*S*,2′*S*,3′*S*)-1′-(4-Aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2′-hydroxytetrahydrofuran –3′-yl)oxy)methyl)phosphonic Acid Triethylamine Salt (1): To a solution of compound **19** (25 mg, 0.05 mmol) in methanol was added 10 % Pd/C (25 mg). The reaction mixture was stirred at room temperature under a hydrogen atmosphere (1 atm, balloon) for 12 h. The mixture was then filtered through Celite to remove the residual catalyst. The filtrate was evaporated under reduced pressure to give a residue, which was then purified by silica gel column chromatography (acetone:triethylamine:water = 4:1:1) to afford 1. Further purification was performed by reverse phase HPLC to afford the product (16 mg, 99 %). R_f 0.3 (acetone:triethylamine:water = 4:1:1); ^{1}H NMR (600 MHz, D_2O) δ = 7.78 (s, 1H, 2-H), 6.89 (d, *J* = 4.6 Hz, 1H, 7-H), 6.83 (d, *J* = 4.6 Hz, 1H, 8-H), 5.12 (d, *J* = 6.5 Hz, 1H, 1′-H), 4.72 (dd, *J* = 6.5, 2.8 Hz, 1H, 2′-H), 4.28 (dt, *J* = 5.7, 2.9 Hz, 1H, 3′-H), 4.16 (dd, *J* = 10.4, 5.5 Hz, 1H, 4′-H), 4.04 (dd, *J* = 10.3, 2.9 Hz, 1H, 4′-H), 3.57 (d, *J* = 8.7 Hz, 2H, PCH_2); ^{13}C NMR (151 MHz, D_2O) δ = 155.4 (C-4), 147.1 (C-2), 127.2 (C-9), 115.0 (C-5), 110.7 (C-8), 102.2 (C-7), 86.7 (C-3′), 86.6 (C-3′), 78.3 (C-2′), 76.6 (C-1′), 71.1 (C-4′), 68.1 (PCH_2), 67.1 (PCH_2); ^{31}P NMR (121 MHz, D_2O) δ = 14.4; ESI-HRMS calcd. for $C_{11}H_{14}N_4O_6P$ $[M - H]^-$, 329.0656, found *m/z* 329.0644.

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