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Synthesis and Antiviral Evaluation of Tri*PPP*ro-AbacavirTP, Tri*PPP*ro-CarbovirTP and their 1',2'-*cis*-disubstituted Analogues

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Abstract: Herein we describe the synthesis of lipophilic triphosphate prodrugs of abacavir, carbovir and their 1',2'-*cis*-substituted carbocyclic analogues. The 1',2'-*cis*-carbocyclic nucleosides were prepared starting from enantiomerically pure (1R,2S)-2-((benzyloxy)methyl)cyclopent-3-en-1-ol by a microwave assisted Mitsunobu-type reaction with 2-amino-6-chloropurine. All four nucleoside analogues were prepared from their 2-amino-6-chloropurine precursors. The nucleosides were converted into their corresponding nucleoside triphosphate prodrugs (Tri*PPP*ro-approach) by application of the *H*-phosphonate route. The Tri*PPP*ro compounds were hydrolyzed in different media, in which the formation of nucleoside triphosphates was proven. While the Tri*PPP*ro-compounds of abacavir and carbovir showed increased antiviral activity compared to their parent nucleoside, the Tri*PPP*ro-compounds of the 1',2'-*cis*-substituted analogues as well as their parent nucleosides proved to be inactive against HIV.

Introduction

Since the discovery of viruses one of the most challenging tasks is to cure viral infections as well as to prevent infections. Every year a huge number of people dies due to viral infections, e.g. 1.45 million from hepatitis (WHO, 2013). For the treatment of hepatitis B (HBV) infections the L-nucleoside L-dT (Telbivudine)[1] and the carbocyclic nucleoside analogue Entecavir[2,3] were approved in 2006 and 2005, respectively. In 1989, hepatitis C virus (HCV) was characterized, but a complete cure wasn't possible until very recently.[4] HCV targets hepatocytes and a chronic HCV infection leads often to liver cirrhosis and therefore a liver transplant is needed. The standard of care was until recently the combination of ribavirin and pegylated IFN-α, but this is limited to about 50% of the patients due to toxic side effects and the ineffectiveness of the therapy to various viral genotypes.[5] In 2013, Sofosbuvir, a phosphoramidate prodrug of PSI-6206, was approved by the FDA which in combination with ribavirin and peg-IFN led to a cure rate of up to >90% of HCV genotypes 1-4 within 12-24 weeks.[6–8] The mode of action of all these nucleos(t)ides is the inhibition of the viral replication catalyzed by RNA- or DNA-polymerases. However, first an intracellular conversion of the nucleosides into the biologically active triphosphate form by host kinases is essential.[9] This kinase-catalyzed phosphorylation proved to be quite inefficient in some cases (e.g. PSI-6206).[10] In order to bypass metabolic hurdles in the phosphorylation, nucleotide prodrugs have been introduced (e.g. phosphoramidates[11], *cyclo*Sal-[12] and Di*PP*ro-compounds[13]).

Another life-threating virus is HIV which causes AIDS. Although until today no complete cure is available for a HIV infection, with a combined antiretroviral therapy (cART) the viral load was found to be below detection limit. One component in the cART are nucleotidic reverse transcriptase inhibitors (NRTIs) which are used as substrates during the viral DNA elongation, which lead to an immediate or delayed chain termination of the viral DNA synthesis. In most cases a lack of the 3'-hydroxyl group is responsible for an immediate chain termination, whereas modified pentose scaffolds and nucleobases induce a delayed chain termination.[14]

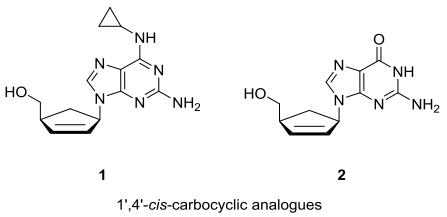


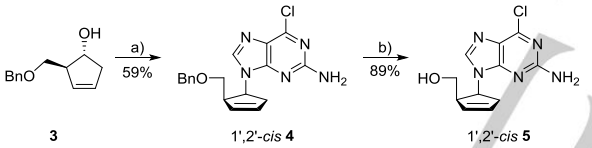
Figure 1. Antiviral nucleosides Abacavir **1** and Carbovir **2** (1',4'-*cis*-carbocyclic analogues).

Abacavir (ABC) **1** is a carbocyclic nucleoside analogue which belongs to these NRTIs. This nucleoside analogue comprises a carbocyclic dideoxydidehydro core and a 6-cyclopropyl-aminopurine nucleobase, which overcomes some disadvantages of its guanine derivative (carbovir, CBV) **2**. A series of these 'carbovirs' was developed by the group of Vince *et al.*, that first discovered the advantage of the 6-substitution with alkylamino groups.[15–24] In 1998, Abacavir **1** was approved by the FDA for the treatment of HIV infections.[25] Intracellularly ABC is phosphorylated to its monophosphate (ABCMP) followed by a replacement of the alkylamino group by a hydroxyl group to form carbovir monophosphate (CBVMP). This latter step is crucial because this process avoids the toxic effects associated with the parent nucleoside CBV. CBVMP is further phosphorylated to form the finally active carbovir triphosphate (CBVTP).[26,27] Recently, we developed the Tri*PPP*ro-approach with which all three intracellular phosphorylation steps can be bypassed. It

was proven that the Tri*PPP*ro-compounds released the active triphosphate form after intracellular enzymatic cleavage.[13,28,29] With this in hand we wanted to examine the antiviral activity of Tri*PPP*ro-compounds of ABC, CBV and their 1',2'-*cis*-carbocyclic counterparts. In the past, few 1',2'-*cis*-substituted carbocyclic nucleoside analogues were found to exhibit some but only weak antiviral activity against HIV which may have to be related to an unsufficient phosphorylation into the triphosphates.[30,31]

Results and Discussion

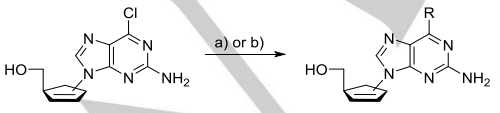
The synthesis of carbocyclic nucleosides analogues can be achieved on a linear or a convergent route. In the linear synthesis the nucleobase is formed starting from an amino function present at the cyclopentyl core. The convergent approach involves the coupling of the preformed cyclopentyl core and the complete nucleobase.[32,33] The synthesis for the 1',2'-*cis*-substituted analogues started from enantiomerically pure (1*R*,2*S*)-2-((benzyloxy)methyl)cyclopent-3-en-1-ol **3**, which was first used in the field of carbocyclic nucleoside analogues by Biggadike *et al*.[34] In our case this cyclopentenol **3** was coupled with 2-amino-6-chloropurine by an earlier reported microwave-assisted Mitsunobu reaction.[35,36] In this approach, cyclopentenol **3** was treated with PPh_3, DIAD and 2-amino-6-chloropurine in CH_3CN at 50 °C to give the purine derivative **4** in 59% yield.



3 1',2'-*cis* **4** 1',2'-*cis* **5**

Scheme 1. Synthesis of the 2-amino-6-chloropurine derivative **5**. *Reagents and Conditions:* a) PPh_3, DIAD, 2-amino-6-chloropurine, CH_3CN, microwave 100 W, 50 °C; b) 1M BCl_3 in CH_2Cl_2, -78 °C to -20 °C.

Next the benzyl protecting group was removed by using BCl_3 at low temperatures leading to derivative **5** (89% yield). CBV **9**, ABC **10** and their 1',2'-*cis*-analogues **7** and **8** were synthesized by substitution of the 6-chloro-atom of **5** or **6**, respectively, with either 1 M aqueous sodium hydroxide[37,38] or cyclopropylamine[38–40] (Scheme 2) and compounds **7**-**10** were obtained in yields ranging from 88% to 98%.

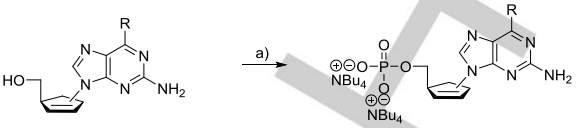


1',2'-*cis* **5**
1',4'-*cis* **6**

1',2'-*cis* R = OH **7** (88%)
1',2'-*cis* R = NHcPr **8** (97%)
1',4'-*cis* R = OH **9** (97%)
1',4'-*cis* R = NHcPr **10** (98%)

Scheme 2. Synthesis of CBV **9**, ABC **10** and their 1',2'-*cis*-analogues **7** and **8**. *Reagents and conditions*: for R = OH: a) 1 M aq. NaOH, reflux; for R = NHcPr: b) cyclopropylamine, EtOH, reflux.

The monophosphates of nucleosides **7**-**10** were prepared by the method of Sowa and Ouchi (Scheme 3).[41] The corresponding nucleotides **11**-**14** were obtained in yields between 72-77%, after ion exchange to tetrabutylammonium cations.

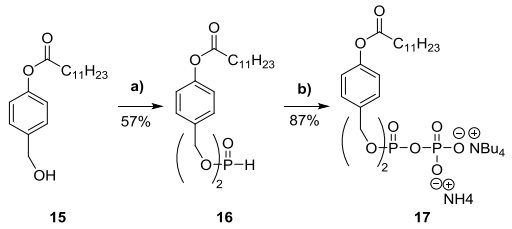


1',2'-*cis* R = OH **7**
1',2'-*cis* R = NHcPr **8**
1',4'-*cis* R = OH **9**
1',4'-*cis* R = NHcPr **10**

1',2'-*cis* R = OH **11** (77%)
1',2'-*cis* R = NHcPr **12** (73%)
1',4'-*cis* R = OH **13** (76%)
1',4'-*cis* R = NHcPr **14** (72%)

Scheme 3. Synthesis of nucleoside monophosphates **11**-**14**. *Reagents and conditions*: a) i) $POCl_3$, pyridine, H_2O, CH_3CN, 0 °C; ii) water, $NH_4(H)CO_3$, 0 °C.

Recently, we published two different methods to synthesize Tri*PPP*ro-compounds.[13,28,29] The phosphoramidite route includes the coupling of a preformed (non)symmetric phosphoramidite and a nucleoside diphosphate followed by an oxidation.[29] An alternative route to prepare Tri*PPP*ro-compounds includes the use of *H*-phosphonate chemistry to form a dimasked pyrophosphate unit first, which was next treated with nucleoside monophosphates after activation.[28] Here, we chose the *H*-phosphonate route, in which the phenyl groups of diphenyl *H*-phosphonate were displaced by 4-(hydroxymethyl)-phenyldodecanoate **15**[28,42] to form the *H*-phosphonate diester **16** in a yield of 57% (Scheme 4). Next, diester **16** was activated with *N*-chlorosuccinimide to yield the phosphorochloridate followed by treatment with tetrabutylammonium phosphate. The resulting pyrophosphate **17** was obtained almost quantitatively by a fast centrifuge extraction from CH_2Cl_2/1 M aq. NH_4OAc (pH 6), which is crucial to remove the excess of phosphate salts.[28]

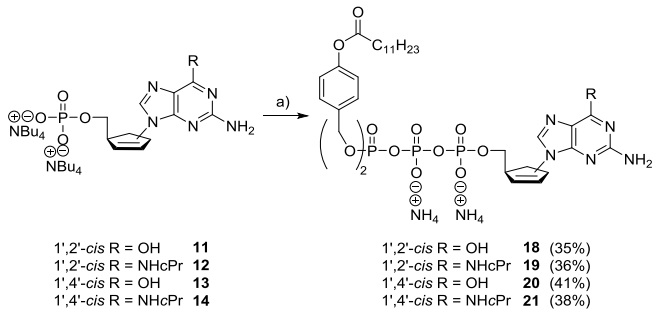


15 16 17

Scheme 4. Synthesis of the masked pyrophosphate **17**. *Reagents and conditions*: a) diphenyl phosphonate, pyridine, 40 °C; b) i) *N*-chlorosuccinimide, CH_3CN, rt; ii) 0.4 M $H_2PO_4NBu_4$, CH_3CN, rt.

The Tri*PPP*ro-synthesis (Scheme 5) started with the activation of pyrophosphate **17** with TFAA followed by the addition of 1-methylimidazole. For the coupling with the corresponding nucleoside monophosphates **11**-**14** it was necessary to add THF as co-solvent because otherwise incomplete consumption of the nucleotides **11**-**14** was observed due to the insolubility of the resulting Tri*PPP*ro-compounds in CH_3CN. After purification and Dowex ion-exchange (ammonium form) the Tri*PPP*ro-derivatives **18**-**21** were obtained in yields ranging from 35 to 41%. Interestingly, a comparison using d4T monophosphate as nucleotide using identical reaction conditions led to a yield of

74% for Tri*PPP*ro-d4TTP. Therefore, it was assumed that the significant lower yields are caused by the guanine nucleobase.



Scheme 5. Synthesis of Tri*PPP*ro-compounds **18**-**21**. *Reagents and conditions*: a) i) **17**, TFAA, Et_3N, CH_3CN, 0 °C; ii) 1-methylimidazole, Et_3N, CH_3CN, 0 °C to rt; iii) NMP's **11**-**14**, DMF, CH_3CN, THF, rt.

The parent nucleosides **7**-**10** and their corresponding Tri*PPP*ro-derivatives **18**-**21** were tested in HIV-1 or HIV-2-infected T-lymphocyte cell cultures (CEM/0 cells) (Table 1). Whereas the Tri*PPP*ro-CBVTP **20** and -ABCTP **21** showed a 3.5-fold and 4.5-fold, respectively, increased activity against HIV-1 compared to their parents, both 1',2'-*cis*-substituted nucleosides **7** and **8** or the corresponding Tri*PPP*ro-compounds **18** and **19** did not shown any activity (>38 to >100 µM) against HIV-1 or HIV-2 infected cells. Nevertheless they also showed no cellular toxicity (>38 to >100 µM).

Table 1. Antiviral data.

Compound	CEM HIV-1 (HE) EC_{50}[a] (µM)	CEM HIV-2 (ROD) EC_{50}[a] (µM)	CEM TK$^-$ HIV-2 (ROD) EC_{50}[a] (µM)	CEM cellular toxicity CC_{50}[b] (µM)
7	>100	>100	>100	>100
8	>100	>100	>100	>100
9	3.5 ± 1.0	3.0 ± 0.0	3.7 ± 1.1	139 ± 20
10	5.9 ± 2.5	5.2 ± 1.5	7.0 ± 1.0	135 ± 21
18	>38	>38	>38	38
19	>42	>42	>42	42
20	0.99 ± 0.14	1.2 ± 0.5	1.6 ± 0.5	28 ± 3
21	1.3 ± 0.0	1.4 ± 0.3	2.1 ± 1.2	60 ± 2
d4T	0.43 ± 0.25	0.34 ± 0.23	>50	>50
Tri*PPP*ro-d4T	0.15 ± 0.09	0.12 ± 0.00	0.83 ± 0.00	20 ± 3
AZT	0.0086 ± 0.0031	0.0060 ± 0.0017	>1000	>100

[a] 50% effective concentration or compound concentration required to inhibit HIV-induced cytopathogenic effect in CEM or CEM TK$^-$ cell cultures. [b] 50% cytotoxic concentration in CEM T cell cultures.

The biologically active metabolite is the nucleoside triphosphate which should be released intracellularly and which then should be a substrate of HIVs reverse transcriptase. In Figure 2 the possible cleavage mechanisms are summarized. Whereas pathways A_1 and A_2 will lead to a release of the NTP, pathways B and C, respectively, will lead to the formation of the NDP or the NMP, respectively.

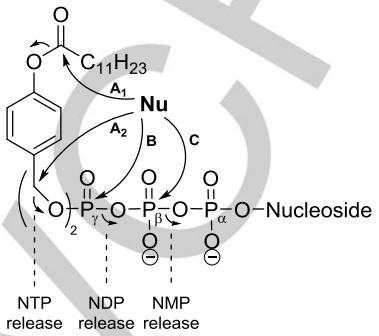


Figure 2. Hydrolysis pathways for Tri*PPP*ro-compounds.

The Tri*PPP*ro-compounds were hydrolyzed in different media (Table 2). In CEM/0 cell extract Tri*PPP*ro-CBVTP **20** showed the highest stability ($t_{1/2}$ = 6.5 h), while the half-life of Tri*PPP*ro-ABCTP **21** was surprisingly shorter than 1 h. Both the 1',2'-*cis*-substituted analogues showed similar half-lives (**18** 3.0 h; **19** 2.4 h), but still lower compared to the Tri*PPP*ro-d4TTP (4.8 h) and -CBVTP **20**. In chemical hydrolysis studies Tri*PPP*ro-d4TTP and -CBVTP **20** have significant higher half-lives (59.4 h and 29.2 h) compared to derivatives **18** with 12.4 h and **19** as well as **21** which have half-lives in the range of 8.5 h.

Table 2. Enzymatic and chemical hydrolysis of Tri*PPP*ro compounds

Compound	CEM/0[a] [h]	PBS (pH 7.3)[a] [h]	PLE[a,b] [h]
18	3.00 ± 0.64	12.44 ± 0.44	4.98 ± 0.28
19	2.42 ± 0.37	8.33 ± 0.16	1.77 ± 0.06
20	6.52 ± 0.59	29.15 ± 2.25	4.57 ± 0.26
21	0.73 ± 0.10	8.37 ± 0.12	2.17 ± 0.03
Tri*PPP*ro-d4T	4.77 ± 0.78	59.43 ± 1.17	3.56 ± 0.32

[a] half lives in hours; [b] *pig liver esterase* in PBS buffer (100 U/mL).

The enzymatic cleavage of the masks with pig liver esterase (PLE) in PBS led to a predominant formation of the corresponding nucleoside triphosphates (Tri*PPP*ro-d4T: 97% d4TTP, **20**: 95% CBVTP, **18**: 90% 1',2'-*cis*-CBVTP, **19**: 90% 1',2'-*cis*-ABCTP, **21**: 70% ABCTP).

The chemical hydrolysis in PBS gave in the case of the Tri*PPP*ro-ABC **21** and -1',2'-*cis*-ABCTP **19** a ratio of about 1:1 for NTPs vs. NDPs, whereas the carbovir derivatives **18** and **20** showed a ratio of around 1:2. The Tri*PPP*ro-d4TTP led to a ratio of 6.3:1 in favor of the NTP. The increased formation of NDPs compared to Tri*PPP*ro-d4TTP may be explained by the exocyclic amino group which seems to lead to an activation of

the β- and γ-phosphorous anhydride bond, so the contribution of pathway B increased in these cases. In contrast in the CEM/0 cell extract only traces of the NTPs were detected. However, the NDPs were formed rapidly and within 48 h the corresponding NMPs and even the parent nucleosides were formed. This points to a rapid dephosphorylation of the NTPs and the following metabolites. The antiviral activity of the Tri*PPP*ro-ABCTP **21** may be caused by the direct delivery of ABCTP which interacts with HIV's RT as a dATP analogue[26]. However, we cannot exclude that the activity is also due to an intracellular dephosphorylation of the formed ABCTP to yield the ABCMP which can be deaminated to give CBVMP and which then enters the intracellular phosphorylation pathway to finally yield CBVTP. The Tri*PPP*ro-1',2'-*cis*-derivatives **18** and **19** as well as their parent nucleosides **7** and **8** did not show any antiviral activity.

Conclusions

We successfully synthesized Tri*PPP*ro-compounds of ABC, CBV and their 1',2'-*cis*-disubstituted derivatives. The Tri*PPP*ro-ABCTP and -CBVTP derivatives exhibit a superior antiviral activity compared to their parent nucleosides. Unfortunately, the 1',2'-*cis*-derivatives did not show any antiviral activity in their nucleoside nor in their Tri*PPP*ro-form. It cannot be excluded that the delivered triphosphates were rapidly dephosphorylated and could not be rephosphorylated from there mono- or diphosphate species. Interestingly, also the parent nucleosides proved to be completely inactive. However, it also cannot be excluded that even if the triphosphates are formed, these are no substrates for the HIV-RT. This can be examined in further experiments using the isolated triphosphates together with RT in a primer extension assay.

Experimental Section

All experiments involving water- or air-sensitive compounds were carried out under anhydrous conditions (N_2-atmosphere). Reagents were purchased by various suppliers and used without further purification, if not otherwise noted. Anhydrous solvents were purchased from Acros Organics (extra dry over molecular sieves) or dried by a MBraun (MB SPS-800)-System. Solvents for chromatography were purchased in technical grade and distilled prior to use. Ultrapure water and CH_3CN for reversed phase chromatography were purified by a Sartorius Aurium pro apparatus (Sartopore 0.2 µm, UV) and purchased from VWR (HPLC grade), respectively. Column chromatography on silica gel was performed by using silica gel MN 60 M (0.04-0.063 mm) from Macherey Nagel. Thin layer chromatography was performed on pre-coated TLC-sheets ALUGRAM® Xtra SIL G/UV_{254} purchased from Macherey Nagel. Visualisation of non-UV active compounds was done by heat-staining with vanillin in sulfuric acid, acetic acid and CH_3OH. Automated flash reversed phase chromatography was performed by using MN RS 16 C_{18} ec, RS 40 C_{18} ec or RS 120 C_{18} ec columns on an Interchim Puriflash 430 system. Microwave-assisted reactions were conducted in a CEM discover system in open- or closed-vessel mode at different temperatures and power. NMR solvents were purchased from Euroiso-Top ($CDCl_3$, CD_3OD and D_2O) and Deutero (DMSO-*d*6). NMR-spectra were recorded at room temperature on Bruker instruments Avance I 400, DRX 500 and Avance III 600. IR- and mass-spectra were recorded on Bruker Alpha IR-sprectrometer and Agilent 6224 ESI-TOF instrument, respectively. The optical rotations were measured with a P8000 polarimeter of A.Krüss Optonic GmbH at indicated temperatures. The phase separation for the masked pyrophosphate was performed on a Hereaus Biofuge primo R with 8000 rpm for 4 min at 10 °C. HPLC data were recorded on a VWR-Hitachi Elite LaChrom system with following parts: DAD-L2455U, Autosampler-L2200 and Pump-L2130. The EZChrom Elite software was used and samples were measured with the following method: CH_3CN gradient in 2 mM tetrabutylammonium acetate buffer (pH 6.0); min 0-25 5-100%, flow 1 mL min^{-1}. The purity of tested compounds was determined by RP-HPLC using the above mentioned method (see supporting information).

Hydrolysis studies

CEM/0 hydrolysis: To a mixture of 50 µL CEM/0 cell extract and 10 µL water was added 10 µL of a 6 mM solution of the corresponding Tri*PPP*ro in DMSO. These hydrolysis samples were incubated at 37 °C and analyzed by RP-HPLC (injection volume 20 µL) at different time.

PBS hydrolysis: To a mixture of 300 µL PBS, 189 µL water and 89 µL DMSO was added 22 µL of a 25 mM solution of the corresponding Tri*PPP*ro in DMSO. This mixture was incubated at 37 °C and at different time aliquots of 35 µL were taken and analyzed by RP-HPLC (injection volume 30 µL).

PLE hydrolysis: To a mixture of 30 µL PLE solution (100 U/mL in PBS, pH 7.3), 60 µL DMSO and 400 µL PBS (pH 7.3) was added 40 µL of a 6 mM solution of the corresponding Tri*PPP*ro in DMSO. This mixture was incubated at 37 °C and at different time aliquots of 35 µL were taken and analyzed by RP-HPLC (injection volume 30 µL).

9-((2*R*)-2-((Benzyloxy)methyl)cyclopent-3-en-1-yl)-6-chloro-9*H*-purin-2-amine (4)

To a solution of cyclopentenol **3** (400 mg, 1.96 mmol), triphenylphosphine (771 mg, 2.94 mmol) and 2-amino-6-chloropurine (499 mg, 2.94 mmol) in THF (15 mL) was added DIAD (0.58 mL, 2.94 mmol). The reaction mixture was irradiated at 50 °C (100 W) for 1 h. The solvent was removed under reduced pressure and the residue was purified on silica gel (petroleum ether/EtOAc; 1:2 to 1:3, CH_2Cl_2/CH_3OH; 19:1) tp yield **4** (0.414 g, 59%) as a colourless resin. R_f = 0.41 (petroleum ether/EtOAc, 1:2). $[\alpha]_D^{25}$: -219 (*c* 0.1, CH_3OH). IR (neat): 3313, 3195, 2856, 1604, 1558, 1456, 1402, 1216, 1088, 901, 697 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.88 (s, 1H, *H*-8), 7.31-7.19 (m, 3H, *H*-Bn), 7.06-6.98 (m, 2H, *H*-Bn), 6.08-6.02 (m, 1H, *H*-4'), 5.84-5.78 (m, 1H, *H*-3'), 5.38-5.30 (m, 1H, *H*-1'), 5.20 (br s, 2H, NH_2), 4.16 (d, 1H, ^2J = 11.6 Hz, C*H*HPh), 4.02 (d, 1H, ^2J = 11.6 Hz, CH*H*Ph), 3.44-3.36 (m, 1H, *H*-2'), 3.27 (dd, ^2J = 9.7 Hz, ^3J = 4.7 Hz, *H*-6a'), 3.12 (dd, ^2J = 9.7 Hz, ^3J = 7.7 Hz, *H*-6b'), 3.05-2.96 (m, 1H, *H*-5a'), 2.87-2.79 (m, 1H, *H*-5b'). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.8 (C_q-6), 153.9 (C_q-2), 151.1 (C_q-4), 141.7 (*C*-8), 137.4 (C_q-Bn), 131.1 (*C*-3'), 130.4 (*C*-4'), 128.4 (2x *C*-Bn), 127.8 (*C*-Bn), 127.7 (2x *C*-Bn), 124.5 (C_q-5), 73.4 (CH_2Ph), 68.3 (*C*-6'), 54.6 (*C*-1'), 49.6 (*C*-2'), 39.2 (*C*-5'). HRMS-ESI$^+$: *m/z* calcd for $C_{18}H_{18}ClN_5O$ (M+H): 356.1273; found: 356.1266.

((1*R*)-5-(2-amino-6-chloro-9*H*-purin-9-yl)cyclopent-2-en-1-yl)methanol (5)

The derivative **4** (489 mg, 1.37 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to -78 °C. Then a 1M BCl_3 solution in CH_2Cl_2 (6.9 mL, 6.9 mmol) was added dropwise. The reaction mixture was slowly warmed to – 20 °C and stirred for 1 h at this temperature. Afterwards sat. aq. $NaHCO_3$ solution (20 mL) was added and the mixture was warmed to room temperature. All volatiles were removed in vacuo and the resulting residue was purified on RP_{18} silica gel with automated flash chromatography (H_2O/CH_3CN, 100:0 to 0:100) to obtain **5** (323 mg, 89%; purity: >98%) as a colourless foam. R_f = 0.26 (CH_2Cl_2/CH_3OH, 95:5). $[\alpha]_D^{19}$: -292 (*c* 0.2, CH_3OH). IR (neat): 3314, 3199, 2861, 1604, 1559, 1460, 1395, 1256, 904, 711 cm^{-1}. ^1H NMR (600 MHz, CD_3OD): δ = 8.08 (s, 1H, *H*-8), 6.10-6.04 (m, 1H, *H*-4'), 5.89-5.85 (m, 1H, *H*-3'), 5.34-5.28

(m, 1H, *H*-1'), 3.34-3.29 (m, 1H, *H*-6a'), 3.25-3.19 (m, 2H, *H*-6a', *H*-2'), 3.05-2.92 (m, 2H, *H*-5'). ^{13}C NMR (151 MHz, CD_3OD): δ = 161.5 (C_q-6), 155.8 (C_q-4), 151.4 (C_q-2), 143.6 (*C*-8), 132.0 (*C*-3'), 131.5 (*C*-4'), 124.6 (C_q-5), 61.3 (*C*-6'), 56.4 (*C*-1'), 52.2 (*C*-2'), 38.7 (*C*-5'). HRMS-ESI$^+$: *m/z* calcd for $C_{11}H_{12}ClN_5O$ (M+H): 266.0803; found: 266.0814.

1',2'-*cis*-Carbovir (7)

The derivative **5** (300 mg, 2.07 mmol) was suspended into 1 M aq. NaOH solution (20 mL) and heated to reflux for 4 h. Purification on RP_{18} silica gel with automated flash chromatography (H_2O/CH_3CN, 100:0 to 0:100) afforded **7** (246 mg, 88%; purity: >98%) after freeze drying (H_2O/CH_3CN, 1:1) as a colourless cotton. R_f = 0.23 (CH_2Cl_2/CH_3OH, 85:15). $[\alpha]_D^{19}$: -221 (*c* 0.2, CH_3OH). IR (neat): 3370, 3185, 2870, 2728, 1679, 1629, 1603, 1386, 1175, 783, 577 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-*d*6): δ = 10.5 (br s, 1H, N*H*), 7.61 (s, 1H, *H*-8), 6.44 (br s, 2H, NH_2), 6.00-5.96 (m, 1H, *H*-4'), 5.87-5.83 (m, 1H, *H*-3'), 5.03-4.97 (m, 1H, *H*-1'), 4.43 (t, 1H, ^3J = 4.8 Hz, O*H*), 3.12-3.07 (m, 1H, *H*-6a'), 3.02-2.93 (m, 2H, *H*-2', *H*-6b'), 2.88-2.79 (m, 2H, *H*-5'). ^{13}C NMR (151 MHz, DMSO-*d*6): δ = 156.8 (C_q-6), 153.5 (C_q-4), 151.5 (C_q-2), 135.9 (*C*-8), 131.6 (*C*-3'), 129.8 (*C*-4'), 116.1 (C_q-5), 59.9 (*C*-6'), 53.6 (*C*-1'), 50.6 (*C*-2'), 37.5 (*C*-5'). HRMS-ESI$^+$: *m/z* calcd for $C_{11}H_{13}N_5O_2$ (M+H): 248.1142; found: 248.1147.

1',2'-*cis*-Abacavir (8)

The derivative **5** (311 mg, 1.17 mmol) was dissolved in ethanol (5 mL) and cyclopropylamine (0.81 mL, 12 mmol) was added. The reaction mixture was heated to reflux with microwave irradiation (150W) until full conversion. All volatiles were removed in vacuo and the residue was purified on RP_{18} silica gel with automated flash chromatography (H_2O/CH_3CN, 100:0 to 0:100) to afford **8** (325 mg, 97%; purity: >99%) after freeze drying (H_2O/CH_3CN, 1:1) as a colourless cotton. R_f = 0.60 (CH_2Cl_2/CH_3OH, 85:15). $[\alpha]_D^{19}$: -238 (*c* 0.2, CH_3OH). IR (neat): 3321, 3201, 2861, 1593, 1478, 1391, 1265, 1029, 789, 640 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-*d*6): δ = 7.60 (s, 1H, *H*-8), 7.29 (br s, 1H, N*H*), 6.02-5.97 (m, 1H, *H*-4'), 5.91-5.79 (m, 3H, NH_2, *H*-3'), 5.09-5.01 (m, 1H, *H*-1'), 4.50 (br s, 1H, O*H*), 3.11-2.77 (m, 6H, *H*-6', *H*-2', C*H*-cyclopropyl, *H*-5'), 0.69-0.55 (m, 4H, CH_2-cyclopropyl). ^{13}C NMR (101 MHz, DMSO-*d*6): δ = 160.1 (C_q-6), 155.9 (C_q-2), 152.0 (C_q-4), 135.7 (*C*-8), 131.7 (*C*-3'), 129.9 (*C*-4'), 113.0 (), 59.9 (*C*-6'), 53.4 (*C*-1'), 50.9 (*C*-2'), 37.5 (*C*-5'), 23.8 (*C*H-cyclopropyl), 6.4 (*C*H_2-cyclopropyl), 6.3 (*C*H_2-cyclopropyl). HRMS-ESI$^+$: *m/z* calcd for $C_{14}H_{18}N_6O$ (M+H): 287.1615; found: 287.1626.

Carbovir (9)

The 6-chloropurine **6** (1.20 g, 4.52 mmol) suspended into 0.5 M aq. NaOH solution (60 mL) and heated to reflux for 4 h. The crude product was adsorbed on silica gel and afterwards purified on silica (CH_2Cl_2/CH_3OH, 95:5 to 80:20) to afford **9** (1.09 g, 97%) as a colourless solid. R_f = 0.17 (CH_2Cl_2/CH_3OH, 85:15). $[\alpha]_D^{19}$: -68 (*c* 0.2, CH_3OH). IR (neat): 3326, 3127, 2850, 2664, 1680, 1601, 1473, 1385, 1176, 1030, 781, 688, 568 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-*d*6): δ = 10.6 (br s, 1H, N*H*), 7.59 (s, 1H, *H*-8), 6.44 (br s, 2H, NH_2), 6.14-6.07 (m, 1H, H-3'), 5.89-5.83 (m, 1H, *H*-2'), 5.38-5.29 (m, 1H, *H*-1'), 4.72 (t, 1H, ^3J = 5.3 Hz, O*H*), 3.49-3.39 (m, 2H, *H*-6a'), 2.91-2.80 (m, 1H, *H*-4'), 2.64-2.53 (m, 1H, *H*-5a'), 1.62-1.51 (m, 1H, *H*-5b'). ^{13}C NMR (101 MHz, DMSO-*d*6): δ = 156.9 (C_q-6), 153.4 (C_q-2), 150.8 (C_q4), 138.3 (*C*-3'), 135.1 (*C*-8), 129.7 (*C*-2'), 116.7 (C_q-5), 64.0 (*C*-6'), 58.5 (*C*-1'), 47.7 (*C*-4'), 34.4 (*C*-5'). HRMS-ESI$^+$: *m/z* calcd for $C_{11}H_{13}N_5O_2$ (M+H): 248.1142; found: 248.1146.

Abacavir (10)

The 6-chloropurine **6** (2.00 g, 7.53 mmol) was dissolved in ethanol (15 mL) and cyclopropylamine (5.2 mL, 75 mmol) was added. The reaction mixture was heated to 70 °C overnight. The volatiles were removed under reduced pressure and the residue was purified on silica gel (CH_2Cl_2/CH_3OH, 95:5 to 90:10) to afford Abacavir **10** (2.12 g, 98%; purity: >97%) as a colourless foam. R_f = 0.65 (CH_2Cl_2/CH_3OH, 85:15). $[\alpha]_D^{19}$: -49 (*c* 0.2, CH_3OH). IR (neat): 3307, 3194, 2866, 1586, 1478, 1386, 1351, 1205, 1027, 788, 640 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-*d*6): δ = 7.60 (s, 1H, *H*-8), 7.26 (br s, 1H, N*H*), 6.13-6.07 (m, 1H, *H*-3'), 5.90-5.84 (m, 1H, *H*-2'), 5.81 (br s, 2H, NH_2), 5.42-5.35 (m, 1H, *H*-1'), 4.73 (t, 1H, ^3J = 5.3 Hz, O*H*), 3.49-3.41 (m, 2H, *H*-6'), 3.11-2.97 (m, 1H, C*H*-cyclopropyl), 2.91-2.82 (m, 1H, *H*-4'), 2.65-2.55 (m, 1H, *H*-5a'), 1.63-1.54 (m, 1H, *H*-5b'), 0.69-0.53 (m, 4H, CH_2-cyclopropyl). ^{13}C NMR (126 MHz, DMSO-*d*6): δ = 160.0 (C_q-6), 155.9 (C_q-2), 151.0 (C_q-4), 137.9 (*C*-3'), 134.8 (*C*-8), 130.0 (*C*-2'), 113.6 (C_q-5), 64.1 (*C*-6'), 58.1 (*C*-1'), 47.7 (*C*-4'), 34.3 (*C*-5'), 23.8 (*C*H-cyclopropyl), 6.4 (2x *C*H_2-cyclopropyl). HRMS-ESI$^+$: *m/z* calcd for $C_{14}H_{18}N_6O$ (M+H): 287.1615; found: 287.1622.

General procedure monophosphate synthesis

Freshly distilled $POCl_3$ (412 µL, 4.40 mmol) was dissolved in CH_3CN (1 mL) and cooled to 0 °C. After subsequent dropwise addition of pyridine (392 µL, 4.80 mmol) and H_2O (50 µL, 2.8 mmol) the mixture was stirred for 10 min. Then the appropriate nucleoside (1.00 mmol) was added and the reaction was stirred at 0 °C until full conversion. The reaction mixture was poured into ice cold H_2O and hydrolysed for 1 h. The pH value was set to 8 with solid NH_4HCO_3 and afterwards the volatiles were removed by freeze drying. The residue was purified on RP_{18} silica gel with automated flash chromatography (H_2O/CH_3CN, 100:0 to 0:100). The ammonia form was dissolved in H_2O/CH_3CN, then tetrabutylammoniumhydroxide was added and the solvents were removed under reduced pressure. The resulting resin was purified on RP_{18} silica gel with automated flash chromatography (H_2O/CH_3CN, 100:0 to 0:100) to afford the monophosphate.

1',2'-*cis*-Carbovir-monophosphate (11)

Yield: **11** (627 mg, 77%) as a colourless resin. ^{1}H NMR (400 MHz, D_2O): δ = 7.86 (s, 1H, *H*-8), 6.08-6.03 (m, 1H, *H*-4'), 5.98-5.93 (m, 1H, *H*-3'), 5.16-5.08 (m, 1H, *H*-1'), 3.55-3.47 (m, 1H, *H*-6b'), 3.39-3.25 (m, 2H, *H*-2', *H*-6b'), 3.21-3.10 (m, 16H, NBu_4), 3.05-2.94 (m, 1H, *H*-5a'), 2.82-2.73 (m, 1H, *H*-5b'), 1.68-1.55 (m, 16H, NBu_4), 1.39-1.26 (m, 16H, NBu_4), 0.91 (t, $^3J_{H,H}$ = 7.4 Hz, NBu_4). ^{13}C NMR (101 MHz, D_2O): δ = 159.0 (C_q-6), 153.8 (C_q-2), 151.5 (C_q-4), 138.7 (*C*-8), 131.2 (*C*-3'), 130.0 (*C*-4'), 115.4 (C_q-5), 62.5 (d, $^2J_{P,C}$ = 4.8 Hz, *C*-6'), 58.1 (*C*H_2-NBu_4), 54.3 (*C*-1'), 49.7 (d, $^3J_{P,C}$ = 6.9 Hz, *C*-2'), 38.8 (*C*-5'), 23.1 (*C*H_2-NBu_4), 19.1 (*C*H_2-NBu_4), 12.8 (*C*H_3-NBu_4). ^{31}P NMR (162 MHz, D_2O): δ = 3.59 (s). HRMS-ESI$^-$: *m/z* calcd for $C_{27}H_{49}N_6O_5P$ (M-H)$^-$: 567.3429; found: 567.3430.

1',2'-*cis*-Abacavir-monophosphate (12)

Yield: **12** (622 mg, 73%) as a yellowish resin. ^{1}H NMR (400 MHz, D_2O): δ = 7.87 (s, 1H, *H*-8), 6.09-6.03 (m, 1H, *H*-4'), 5.99-5.94 (m, 1H, *H*-3'), 5.15-5.08 (m, 1H, *H*-1'), 3.51-3.42 (m, 1H, *H*-6a'), 3.36-3.27 (m, 1H, *H*-2'), 3.22-3.08 (m, 17H, *H*-6b', NBu_4), 3.03-2.92 (m, 1H, *H*-5a'), 2.85-2.74 (m, 2H, C*H*-cyclopropyl, *H*-5b'), 1.68-1.53 (m, 16H, NBu_4), 1.39-1.25 (m, 16H, NBu_4), 0.96-0.82 (m, 26H, NBu_4, CH_2-cyclopropyl), 0.66-0.58 (m, 2H, CH_2-cyclopropyl). ^{13}C NMR (101 MHz, D_2O): δ = 160.1 (C_q-6), 156.3 (C_q-2), 150.4 (C_q-4), 138.3 (*C*-8), 131.3 (*C*-3'), 130.0 (*C*-4'), 112.7 (C_q-5), 62.5 (d, $^2J_{P,C}$ = 4.9 Hz, *C*-6'), 58.1 (*C*H_2-NBu_4), 54.0 (*C*-1'), 49.5 (d, $^3J_{P,C}$ = 7.2 Hz, *C*-2'), 38.7 (*C*-5'), 23.2 (*C*H-cyclopropyl), 23.1 (*C*H_2-NBu_4), 19.1 (*C*H_2-NBu_4), 12.8 (*C*H_3-NBu_4), 6.8 (*C*H_2-cyclopropyl), 6.7 (*C*H_2-cyclopropyl). ^{31}P NMR (162 MHz, D_2O): δ = 3.65 (s). HRMS-ESI$^-$: *m/z* calcd for $C_{14}H_{18}N_6O_4P$ (M-H)$^-$: 365.1133; found: 365.1140.

Carbovir-monophosphate (13)

Yield: **13** (614 mg, 76%) as a colourless resin. ^{1}H NMR (400 MHz, D_2O): δ = 7.83 (s, 1H, *H*-8), 6.27-6.21 (m, 1H, *H*-3'), 5.88-5.82 (m, 1H, *H*-2'), 5.42-5.34 (m, 1H, *H*-1'), 3.82-3.74 (m, 1H, *H*-6'), 3.21-3.04 (m, 17H, NBu_4, *H*-4'), 2.79-2.67 (m, 1H, *H*-5a'), 1.67-1.52 (m, 17H, NBu_4, *H*-5b'), 1.38-

1.24 (m, 16H, NBu_4), 0.90 (t, 24H, ^3J = 7.4 Hz, NBu_4). ^{13}C NMR (101 MHz, D_2O): δ = 158.7 (C_q-6), 153.5 (C_q-2), 150.9 (C_q-4), 138.6 (*C*-3'), 138.2 (*C*-8), 129.1 (*C*-2'), 115.9 (C_q-5), 67.1 (d, $^2J_{P,C}$ = 4.8 Hz, *C*-6'), 59.7 (*C*-1'), 58.1 (CH_2-NBu_4), 46.0 (d, $^3J_{P,C}$ = 7.5 Hz, *C*-4'), 34.4 (*C*-5'), 23.1 (CH_2-NBu_4), 19.1 (CH_2-NBu_4), 12.8 (CH_3-NBu_4). ^{31}P NMR (162 MHz, D_2O): δ = 3.13 (s). HRMS-ESI$^-$: *m*/*z* calcd for $C_{27}H_{49}N_6O_5P$ (M-H)$^-$: 567.3429; found: 567.3404.

Abacavir-monophosphate (14)

Yield: **14** (611 mg, 72%) as a yellowish resin. ^{1}H NMR (400 MHz, D_2O): δ = 7.85 (s, 1H, *H*-8), 6.30-6.24 (m, 1H, *H*-3'), 5.88-5.82 (m, 1H, *H*-2'), 5.44-5.35 (m, 1H, *H*-1'), 3.80-3.67 (m, 2H, *H*-6'), 3.22-2.99 (m, 17H, NBu_4, *H*-4'), 2.86-2.67 (m, 2H, C*H*-cyclopropyl, *H*-5a'), 1.67-1.48 (m, 17H, NBu_4, *H*-5b'), 1.40-1.20 (m, 16H, NBu_4), 0.96-0.78 (m, 26H, NBu_4, CH_2-cyclopropyl), 0.63-0.55 (m, 2H, CH_2-cyclopropyl). ^{13}C NMR (101 MHz, D_2O): δ = 159.9 (C_q-6), 156.2 (C_q-2), 149.8 (C_q-4), 138.8 (*C*-3'), 137.6 (*C*-8), 129.0 (*C*-2'), 113.3 (C_q-5), 67.1 (d, $^2J_{P,C}$ = 4.8 Hz, *C*-6'), 59.3 (*C*-1'), 58.0 (CH_2-NBu_4), 46.0 (d, $^3J_{P,C}$ = 7.5 Hz, *C*-4'), 34.6 (*C*-5'), 23.2 (*CH*-cyclopropyl), 23.1 (CH_2-NBu_4), 19.1 (CH_2-NBu_4), 12.8 (CH_3-NBu_4), 6.7 (CH_2-cyclopropyl), 6.7 (CH_2-cyclopropyl). ^{31}P NMR (162 MHz, D_2O): δ = 3.65 (s). HRMS-ESI$^-$: *m*/*z* calcd for $C_{14}H_{18}N_6O_4P$ (M-H)$^-$: 365.1133; found: 365.1112.

4-(Hydroxymethyl)-phenyldodecanoate (15)

To a solution of 4-hydroxybenzyl alcohol (10.0 g, 80.6 mmol) and 4-(dimethylamino)pyridine (1.08 g, 8.86 mmol) in THF (150 mL) triethylamine (12.5 mL, 90.2 mmol) was added. The mixture was cooled to 0 °C followed by addition of dodecanoyl chloride (17.8 mL, 76.5 mmol) in THF (50 mL) over a period of 30 min. The reaction was warmed to room temperature and stirred for 1.5 h at this temperature. The resulting suspension was filtrated and the solvent was removed under reduced pressure. The residue was purified on silica gel (petroleum ether/EtOAc, 3:1 to 2:1) to yield **15** (17.4 g, 74%) as an amorphous solid. R_f = 0.61 (petroleum ether/EtOAC, 70:30). The analytical data is identical to those reported in the literature.[42]

Bis-(4-dodecanoyloxybenzyl)-phosphonate (16)

The dodecanoate **15** (6.74 g, 22.0 mmol) was coevaporated two times with pyridine (each 5 mL) and then dissolved in pyridine (20 mL). Then diphenyl phosphonate (1.92 mL, 10.0 mmol) was added and the reaction was stirred for 4 h at 40 °C. The solvent was evaporated and the residue was coevaporated three times with toluene and once with CH_2Cl_2. The resulting residue was recrystallized from CH_3OH to yield **16** (3.75 g, 57%) as an amorphous solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36 (d, 4H, ^3J = 8.5 Hz, *H*-Bn), 7.08 (d, 4H, ^3J = 8.5 Hz, *H*-Bn), 6.93 (d, 1H, $^2J_{H,P}$ = 708 Hz, P-*H*), 5.09-4.99 (m, 4H, 2x CH_2Ph), 2.55 (t, 4H, ^3J = 7.5 Hz, CH_2-alkyl), 1.78-1.71 (m, 4H, CH_2-alkyl), 1.44-1.21 (m, 32H, CH_2-alkyl), 0.88 (t, 6H, ^3J = 7.0 Hz, CH_3-alkyl). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 172.3 (2x C_q-acyl), 151.1 (2x C_q-Bn), 133.1 (d, $^3J_{C,P}$ = 6.1 Hz, 2x C_q-Bn), 129.4 (4x *C*H-Bn), 122.1 (4x *C*H-Bn), 66.8 (d, $^2J_{C,P}$ = 5.8 Hz, 2x CH_2Ph), 34.5 (2x CH_2-alkyl), 32.0 (2x CH_2-alkyl), 29.7 (4x CH_2-alkyl), 29.6 (2x CH_2-alkyl), 29.5 (2x CH_2-alkyl), 29.4 (2x CH_2-alkyl), 29.2 (2x CH_2-alkyl), 25.0 (2x CH_2-alkyl), 22.8 (2x CH_2-alkyl), 14.3 (2x CH_3-alkyl). ^{31}P NMR (243 MHz, $CDCl_3$): δ = 7.71 (s). HRMS-ESI$^+$: *m*/*z* calcd for $C_{38}H_{59}NaO_7P$ (M+Na): 681.3891 found: 681.3866.

General procedure Tri*PPP*ro synthesis

The phosphonate **16** (659 mg, 1.00 mmol) was dissolved under heating in CH_3CN (25 mL) and *N*-chlorosuccinimide (334 mg, 2.50 mmol) was added. The reaction mixture was stirred overnight at room temperature (full conversion was controlled by ^{31}P-NMR). Afterwards the mixture was added dropwise to a solution of 0.4 M tetrabutylammonium phosphate monobasic (7.5 mL, CH_3CN) in CH_3CN (10 mL). After 1 h the solvent was evaporated and the residue was dissolved in CH_2Cl_2 (15 mL). The organic phase was washed with 1 M aq. NH_4OAc and H_2O (phase separation via centrifuge) followed by drying over Na_2SO_4. The solvent was removed and the resulting pyrophosphate **17** (867 mg, 87%) was used without further purification (absence of phosphate salt was controlled by ^{31}P-NMR under Schlenk conditions).

The pyrophosphate (1 eq) was dissolved in CH_3CN and cooled to 0 °C and then a 0 °C cold solution of TFAA (5 eq.) and triethylamine (8 eq) in CH_3CN was added. The mixture was stirred for 10 min at 0 °C. After evaporation the residue was coevaporated with CH_3CN and afterwards dissolved in CH_3CN. Then triethylamine (5 eq) and 1-methylimidazole (3 eq) were added at 0 °C and the reaction mixture was stirred for 10 min. Then THF and the appropriate nucleoside monophosphate (0.5 eq) dissolved in DMF were added. The reaction progress was controlled by RP-HPLC. After full conversion all volatiles were removed and the residue was purified on RP_{18} silica gel with automated flash chromatography (H_2O/CH_3CN, 90:10 to 0:100) followed by ion exchange (NH_4^+) and purification on RP_{18} silica gel with automated flash chromatography (H_2O/CH_3CN, 90:10 to 0:100).

Tri*PPP*ro-1',2'-*cis*-CBVTP (ammonium salt) (18)

The reaction was carried out with pyrophosphate **17** (453 mg, 455 µmol) in CH_3CN (6 ml) and TFAA (323 µL, 2.27 mmol) and triethylamine (504 µL, 3.64 mmol) in CH_3CN (4 mL). Afterwards triethylamine (315 µL, 2.27 mmol) and 1-methylimidazole (109 µL, 1.36 mmol) in CH_3CN (4 mL) were used. Then THF (6 mL) was added followed by monophosphate **11** (184 mg, 227 µmol) in DMF (2 mL). Yield: **18** (87.2 mg, 35%; purity: >98%) as a colourless cotton. ^{1}H NMR (600 MHz, CD_3OD): δ = 7.97 (s. 1H, *H*-8), 7.40-7.37 (m, 4H, *H*-Bn), 7.06-7.02 (m, 4H, *H*-Bn), 6.00-5.93 (m, 2H, *H*-4', *H*-3'), 5.24-5.19 (m, 1H, *H*-1'), 5.14 (dd, 4H, ^3J = 8.3 Hz, 2.8 Hz, 2x CH_2Ph), 3.88 (ddd, 1H, ^2J = 10.4 Hz, ^3J = 6.9 Hz, 5.6 Hz, *H*-6a'), 3.68-3.62 (m, 1H, *H*-6b'), 3.41-3.36 (m, 1H, *H*-2'), 2.94-2.84 (m, 2H, *H*-5'), 2.57 (t, 4H, ^3J = 7.4 Hz, CH_2-alkyl), 1.77-1.70 (m, 4H, CH_2-alkyl), 1.47-1.24 (m, 32H, CH_2-alkyl), 0.90 (t, 6H, ^3J = 7.0 Hz, CH_3-alkyl). ^{13}C NMR (151 MHz, CD_3OD): δ = 173.8 (2x C_q-acyl), 163.3 (C_q-6), 155.4 (C_q-2), 153.0 (C_q-4), 152.3 (2x C_q-Bn), 138.6 (*C*-8), 135.1 (d, $^3J_{C,P}$ = 7.3 Hz, 2x C_q-Bn), 132.3 (*C*-3'), 131.1 (*C*-4'), 130.5 (4x *C*H-Bn), 122.8 (4x *C*H-Bn), 114.8 (C_q-5), 70.3 (d, $^2J_{C,P}$ = 6.0 Hz, 2x CH_2Ph), 65.6 (d, ^2J = 6.6 Hz, *C*-6'), 56.1 (*C*-1'), 50.7 (d, ^3J = 7.9 Hz, *C*-2') 39.1 (*C*-5'),, 35.0 (2x CH_2-alkyl), 33.1 (2x CH_2-alkyl), 30.7 (4x CH_2-alkyl), 30.6 (2x CH_2-alkyl), 30.5 (2x CH_2-alkyl), 30.4 (2x CH_2-alkyl), 30.2 (2x CH_2-alkyl), 26.0 (2x CH_2-alkyl), 23.7 (2x CH_2-alkyl), 14.4 (2x CH_3-alkyl). ^{31}P NMR (243 MHz, CD_3OD): δ = -11.6 (d, ^2J = 20.1 Hz), -13.3 (d, ^2J = 16.9 Hz), -23.8 (dd, ^2J = 20.1 Hz, 16.9 Hz). HRMS-ESI$^-$: *m*/*z* calcd for $C_{49}H_{71}N_5O_{15}P_3$ (M-H)$^-$: 1062.4165; found: 1062.4117.

Tri*PPP*ro-1',2'-*cis*-ABCTP (ammonium salt) (19)

The reaction was carried out with pyrophosphate **17** (442 mg, 443 µmol) in CH_3CN (6 ml) and TFAA (315 µL, 2.22 mmol) and triethylamine (492 µL, 3.59 mmol) in CH_3CN (4 mL). Afterwards triethylamine (307 µL, 2.22 mmol) and 1-methylimidazole (106 µL, 1.33 mmol) in CH_3CN (4 mL) were used. Then THF (6 mL) was added followed by monophosphate **12** (188 mg, 222 µmol) in DMF (2 mL). Yield: **19** (90.7 mg, 36%) as a colourless cotton. ^{1}H NMR (600 MHz, DMSO-*d*6): δ = 7.80 (s, 1H, *H*-8), 7.38 (d, 4H, ^3J = 8.1 Hz, *H*-Bn), 7.26 (br s, 3H, N*H*, NH_2), 7.04 (d, 4H, ^3J = 8.0 Hz, *H*-Bn) 6.00-5.95 (m, 1H, *H*-4'), 5.85-5.74 (m, 1H, *H*-3'), 5.21-5.00 (m, 5H, *H*-1', 2x CH_2Ph), 3.85-3.18 (m, 3H, *H*-6', *H*-2'), 2.92-2.71 (m, 2H, *H*-5'), 2.58-2.51 (CH_2-alkyl, C*H*-cyclopropyl), 1.67-1.58 (m, 4H, CH_2-alkyl), 1.40-1.17 (m, 32H, CH_2-alkyl), 0.85 (t, 6H, ^3J = 6.8 Hz, CH_3-alkyl), 0.77-0.52 (m, 4H, 2x CH_2-cyclopropyl). ^{13}C NMR (152 MHz, DMSO-*d*6): δ = ^{13}C NMR (152 MHz, DMSO-*d*6): δ = 171.7 (2x C_q-acyl), 150.2 (2x C_q-Bn), 133.9 (d, $^3J_{C,P}$ = 7.7 Hz, 2x C_q-Bn), 130.3 (*C*-3'), 130.2 (*C*-4'), 129.0 (4x *C*H-Bn), 121.6 (4x *C*H-Bn), 67.8 (d, $^2J_{C,P}$ = 5.3 Hz, 2x CH_2Ph), 63.4 (*C*-6'), 53.4 (*C*-1'), 49.3 (*C*-2'), 38.5 (*C*-5'), 33.5 (2x CH_2-alkyl), 31.3 (2x CH_2-alkyl), 29.0 (4x CH_2-alkyl), 28.9 (2x CH_2-alkyl), 28.7 (2x CH_2-alkyl),

28.7 (2x CH_2-alkyl), 28.4 (2x CH_2-alkyl), 24.3 (2x CH_2-alkyl), 22.1 (2x CH_2-alkyl), 13.9 (2x CH_3-alkyl), 6.30 (2x CH_2-cyclopropyl). (C_q-6, C_q-2, C_q-4, *C*-8, C_q-5 and *C*H-cyclopropyl) could not be detected due to micelle formation. ^{31}P NMR (243 MHz, DMSO-*d*6): δ = -12.7 (m), -13.1 (d, ^2J = 17.9 Hz), -23.9 (t, ^2J = 19.8 Hz). HRMS-ESI$^-$: *m*/*z* calcd for $C_{52}H_{76}N_6O_{14}P_3$ (M-H)$^-$: 1101.4638; found: 1101.4686.

Tri*PPP*ro-CBVTP (ammonium salt) (20)

The reaction was carried out with pyrophosphate **17** (461 mg, 463 µmol) in CH_3CN (6 ml) and TFAA (328 µL, 2.31 mmol) and triethylamine (513 µL, 3.70 mmol) in CH_3CN (4 mL). Afterwards triethylamine (321 µL, 2.31 mmol) and 1-methylimidazole (111 µL, 1.39 mmol) in CH_3CN (4 mL) were used. Then THF (6 mL) was added followed by monophosphate **13** (187 mg, 231 µmol) in DMF (2 mL). Yield: **20** (104 mg, 41%; purity: >98%) as a colourless cotton. ^{1}H NMR (600 MHz, CD_3OD): δ = 8.16 (s, 1H, *H*-8), 7.39-7.34 (m, 4H, *H*-Bn), 7.04-7.00 (m, 4H, *H*-Bn), 6.19-6.15 (m, 1H, *H*-3'), 5.80-5.77 (m, 1H, *H*-2'), 5.52-5.48 (m, 1H, *H*-1'), 5.14 (dd, 4H, *J* = 8.3 Hz, 3.6 Hz, 2x CH_2Ph), 4.15-4.05 (m, 2H, *H*-6'), 3.13-3.07 (m, 1H, *H*-4'), 2.74-2.67 (m, 1H, *H*-5a'), 2.56 (t, 4H, ^3J = 7.4 Hz, CH_2-alkyl), 1.91-1.86 (m, 1H, *H*-5b'), 1.76-1.69 (m, 4H, CH_2-alkyl), 1.45-1.24 (m, 32H, CH_2-alkyl), 0.90 (t, 6H, ^3J = 6.9 Hz, CH_3-alkyl). ^{13}C NMR (152 MHz, CD_3OD): δ = 173.7 (2x C_q-acyl), 158.4 (C_q-6), 155.5 (C_q-2), 152.3 (d, *J* = 1.9 Hz, 2x C_q-Bn), 152.3 (C_q-4), 139.7 (*C*-3'), 138.5 (*C*-8), 134.9 (d, $^3J_{C,P}$ = 7.3 Hz, 2x C_q-Bn), 130.5 (*C*-2'), 130.4 (d, *J* = 4.1 Hz, 4x *C*H-Bn), 122.8 (d, *J* = 1.9 Hz, 4x *C*H-Bn) 115.2 (C_q-5), 70.3 (d, $^2J_{C,P}$ = 6.3 Hz, 2x *C*H_2Ph), 69.1 (d, ^2J = 7.0 Hz, *C*-6'), 61.4 (*C*-1'), 47.5 (d, ^3J = 9.1 Hz, *C*-4'), 35.0 (2x CH_2-alkyl), 34.8 (*C*-5'), 33.1 (2x CH_2-alkyl), 30.7 (4x CH_2-alkyl), 30.6 (2x CH_2-alkyl), 30.5 (2x CH_2-alkyl), 30.4 (2x CH_2-alkyl), 30.2 (2x CH_2-alkyl), 26.0 (2x CH_2-alkyl), 23.7 (2x CH_2-alkyl), 14.4 (2x CH_3-alkyl). ^{31}P NMR (243 MHz, CD_3OD): δ = -11.3 (d, ^2J = 19.5 Hz), -13.2 (d, ^2J = 16.9 Hz), -23.6 (dd, ^2J = 19.5 Hz, 16.9 Hz). HRMS-ESI$^-$: *m*/*z* calcd for $C_{49}H_{71}N_5O_{15}P_3$ (M-H)$^-$: 1062.4165; found: 1062.4157.

Tri*PPP*ro-ABCTP (ammonium salt) (21)

The reaction was carried out with pyrophosphate **17** (429 mg, 431 µmol) in CH_3CN (6 ml) and TFAA (306 µL, 2.15 mmol) and triethylamine (478 µL, 3.45 mmol) in CH_3CN (4 mL). Afterwards triethylamine (299 µL, 2.15 mmol) and 1-methylimidazole (103 µL, 1.29 mmol) in CH_3CN (4 mL) were used. Then THF (6 mL) was added followed by monophosphate **14** (183 mg, 215 µmol) in DMF (2 mL). Yield: **21** (93.1 mg, 38%; purity: >95%) as a colourless cotton. ^{1}H NMR (600 MHz, DMSO-*d*6): δ = 7.78j (s, 1H, *H*-8), 7.39 (d, 4H, ^3J = 8.4 Hz, *H*-Bn), 7.26 (br s, 3H, N*H*, NH_2), 7.04 (d, 4H, ^3J = 8.4 Hz, *H*-Bn) 6.06-6.02 (m, 1H, *H*-3'), 5.78-5.72 (m, 1H, *H*-2'), 5.42-5.34 (m, 1H, *H*-1'), 5.07 (d, 4H, ^3J = 7.4 Hz, CH_2Ph), 3.95-3.840 (m, 2H, *H*-6'), 3.01-2.94 (m, 1H, *H*-4'), 2.61-2.51 (m, 6H, *H*-5a', C*H*-cyclopropyl, CH_2-alkyl), 1.76-1.67 (m, 1H, *H*-5b'), 1.65-1.58 (m, 4H, CH_2-alkyl), 1.39-1.17 (m, 32H, CH_2-alkyl), 0.85 (t, 6H, ^3J = 6.9 Hz, CH_3-alkyl), 0.70-0.56 (m, 4H, 2x CH_2-cyclopropyl). ^{13}C NMR (152 MHz, DMSO-*d*6): δ = 171.7 (2x C_q-acyl), 150.1 (2x C_q-Bn), 137.7 (*C*-3'),133.9 (d, $^3J_{C,P}$ = 8.0 Hz, 2x C_q-Bn), 129.9 (*C*-2'), 129.0 (4x *C*H-Bn), 121.6 (4x *C*H-Bn), 67.8 (d, $^2J_{C,P}$ = 5.4 Hz, 2x *C*H_2Ph), 67.1 (*C*-6'), 58.9 (*C*-1'), 45.7 (d, ^3J = 7.7 Hz, *C*-4'), 33.4 (2x CH_2-alkyl), 33.2 (*C*-5'), 31.3 (2x CH_2-alkyl), 29.0 (4x CH_2-alkyl), 28.9 (2x CH_2-alkyl), 28.7 (2x CH_2-alkyl), 28.7 (2x CH_2-alkyl), 28.4 (2x CH_2-alkyl), 24.3 (2x CH_2-alkyl), 22.1 (2x CH_2-alkyl), 13.9 (2x CH_3-alkyl), 6.55 (2x CH_2-cyclopropyl). (C_q-6, C_q-2, C_q-4, *C*-8, C_q-5 and *C*H-cyclopropyl) could not be detected due to micelle formation. ^{31}P NMR (243 MHz, DMSO-*d*6): δ = -12.2 (d, ^2J = 20.3 Hz), -12.9 (d, ^2J = 18.7 Hz), -23.9 (t, ^2J = 16.2 Hz). HRMS-ESI$^-$: *m*/*z* calcd for $C_{52}H_{76}N_6O_{14}P_3$ (M-H)$^-$: 1101.4638; found: 1101.4612.

Tri*PPP*ro-d4TTP (ammonium salt)

The reaction was carried out with pyrophosphate **17** (169 mg, 170 µmol) in CH_3CN (3 ml) and TFAA (120 µL, 846 µmol) and triethylamine (189 µL, 1.36 mmol) in CH_3CN (2 mL). Afterwards triethylamine (118 µL, 851 µmol) and 1-methylimidazole (41 µL, 0.51 mmol) in CH_3CN (3 mL) were used. Then THF (4 mL) was added followed by d4T monophosphate (63.0 mg, 80.0 µmol) in DMF (1 mL). Yield: (60.3 mg, 74%; purity: >98%) as a colourless cotton. ^{1}H NMR (600 MHz, CD_3OD): δ = 7.67 (q. 1H, ^4J = 1.2 Hz, *H*-6), 7.42-7.36 (m, 4H, *H*-Bn), 7.07-7.01 (m, 4H, *H*-Bn), 6.94-6.91 (m, 1H, *H*-1'), 6.47 (dt, 1H, ^3J = 6.0 Hz, ^4J = 1.8 Hz, *H*-3'), 5.79 (ddd, 1H, ^3J = 6.1 Hz, 2.5 Hz, ^4J = 1.4 Hz, *H*-2'), 5.15 (d, 4H, ^3J = 8.3 Hz, 2x CH_2Ph), 4.96-4.91 (m, 1H, *H*-4'), 4.29 (ddd, 1H, ^2J = 11.6 Hz, ^3J = 6.8 Hz, 3.3 Hz, *H*-5a'), 4.19 (ddd, 1H, ^2J = 11.6 Hz, ^3J = 5.5 Hz, 3.2 Hz, *H*-5b'), 2.57 (t, 4H, ^3J = 7.4 Hz, CH_2-alkyl), 1.89 (d, 3H, ^4J = 1.2 Hz, CH_3), 1.78-1.68 (m, 4H, CH_2-alkyl), 1.48-1.24 (m, 32H, CH_2-alkyl), 0.90 (t, 6H, ^3J = 7.1 Hz, CH_3-alkyl). ^{13}C NMR (151 MHz, CD_3OD): δ = 173.8 (2x C_q-acyl), 166.5 (C_q-4), 152.8 (C_q-2), 152.3 (2x C_q-Bn), 138.7 (*C*-6), 135.8 (*C*-3'), 135.0 (d, $^3J_{C,P}$ = 7.7 Hz, 2x C_q-Bn), 130.5 (d, $^4J_{C,P}$ = 5.3 Hz, 4x *C*H-Bn), 127.1 (*C*-2'), 122.8 (d, $^5J_{C,P}$ = 2.5 Hz, 4x *C*H-Bn), 112.1 (*C*-5), 90.8 (*C*-1'), 87.3 (d, ^3J = 9.1 Hz, *C*-4'), 70.4 (m, 2x *C*H_2Ph), 67.9 (d, ^2J = 6.1 Hz, *C*-5'), 35.0 (2x CH_2-alkyl), 33.1 (2x CH_2-alkyl), 30.7 (4x CH_2-alkyl), 30.6 (2x CH_2-alkyl), 30.5 (2x CH_2-alkyl), 30.4 (2x CH_2-alkyl), 30.2 (2x CH_2-alkyl), 26.0 (2x CH_2-alkyl), 23.7 (2x CH_2-alkyl), 14.4 (CH_3-alkyl), 12.5 (CH_3). ^{31}P NMR (243 MHz, CD_3OD): δ = -11.8 (d, ^2J = 19.7 Hz), -13.3 (d, ^2J = 17.8 Hz), -23.9 (t, 18.8 Hz). HRMS-ESI$^-$: *m*/*z* calcd for $C_{48}H_{70}N_2O_{17}P_3$ (M-H)$^-$: 1039.3893; found: 1039.3864.

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Keywords: Abacavir • Carbovir • carbocyclic • Tri*PPP*ro • triphosphate

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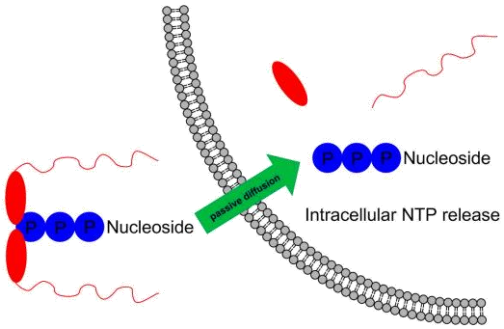
Entry for the Table of Contents



One option to intracellularly release a nucleoside triphosphate is given by the Tri*PPP*ro-approach. In the case of Carbovir and Abacavir their corresponding Tri*PPP*ro-derivatives had a 3.5-fold and 4.5-fold, respectively, superior antiviral activity compared to the parent nucleosides. In the case of 1',2'-*cis*-derivatives of Carbovir and Abacavir neither the nucleosides nor their Tri*PPP*ro-derivatives showed any antiviral activity.