CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201101291

Solid-Phase Synthesis of (Poly)phosphorylated Nucleosides and Conjugates

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Dedicated to Professor Dr. Dr. Gerhard Bringmann on the occasion of his 60th birthday

Abstract: Succinyl-*cyclo*Sal-phosphate triesters of ribo- and 2′-deoxyribonucleosides were attached to aminomethyl polystyrene as an insoluble solid support and reacted with phosphate-containing nucleophiles yielding nucleoside di- and triphosphates, nucleoside diphosphate sugars, and dinucleoside polyphosphates in high purity after cleavage from the solid support. Here, reactive *cyclo*Sal-phosphate triesters were used as immobilized reagents that led to a generally applicable method for the efficient synthesis of phosphorylated biomolecules and phosphate-bridged bioconjugates.

Keywords: bioconjugates · bioorganic chemistry · nucleotide sugars · nucleotides · solid-phase synthesis

Introduction

(2′-Deoxy)ribonucleoside di- and triphosphates ((d)NDPs, (d)NTPs) and nucleoside diphosphate (NDP) sugars are key players in important biological processes. First, there is the indispensability of naturally occurring (d)NTPs as substrates for DNA and RNA synthesis, whereas modified counterparts are the ultimate active forms of antivirally active nucleoside analogues. Moreover, NDP-sugars serve as glycosyl donors in the synthesis of oligo- and polysaccharides in which the glycosyl part is enzymatically transferred to an oligosaccharide.[1,2] In addition, NDP sugars act as precursors for deoxysugars, aminodeoxysugars, chain-branched sugars, uronic acids, and glycoconjugates. The most common solution-phase methods for the synthesis of such molecules include the reaction of activated nucleoside monophosphates as P^V-reagents (phosphormorpholidates, phosphorimidazolidates, or phosphoramidates) with nucleophiles ((pyro)phosphate salts, sugar phosphates) or alternatively as P^{III} reagents (phosphite triesters) followed by oxidation.[3–7] In almost all cases, the solubility of the starting materials in organic solvents is poor, thus conversions are slow and separation of the charged and water-soluble product from polar impurities needed tedious purification that often led to moderate or even poor yields. Concerning solid-phase methods for the synthesis of NDPs and NTPs, only a few approaches have been reported. By starting from immobilized nucleosides the methods are characterized by moderate yields and low purity after cleavage,[3,8–11] whereas only Parang et al. generated NDPs and NTPs in good yields and purity by using polymer-bound di- and triphosphitylating reagents.[12–14] Peyrottes et al. used polyethylene glycol (PEG) as a soluble support to generate the 5′-mono-, -di-, and triphosphates of (2′-deoxy)cytidine with the nucleoside anchored through the amino function of the heterocyclic base.[15] However, other nucleobases were not included (adenine or guanine) and the method cannot be applied to thymine or uracil. With regard to NDP sugars, a few chemical and enzymatic methods are available.[16] The chemical methods are based on mainly two strategies: the pyrophosphate bond can be formed by reaction of a glycosyl phosphate with an activated nucleotide (morpholidate,[17,18] imidazolidate[19]) or of a nucleoside diphosphate and a glycopyranosyl bromide.[20,21] Both methods are characterized by low yields and in the latter case the stereochemical control at the anomeric center is almost impossible. The enzymatic pathway—the reaction of a sugar phosphate with a nucleoside triphosphate—is done by using specific enzymes, which do not tolerate nucleoside analogues and lead only to moderate yields.[22] Consequently, some of these methods are specialized for the synthesis of one type of compound and are not generally applicable for various nucleosides and target molecules. Recently, we have reported on a generally applicable solution-phase method for the syntheses of (poly)phosphorylated nucleosides and dinucleoside polyphosphates[23] and of NDP sugars,[24–26] which is based on *cyclo*Sal-nucleotides as activated species. Originally developed as a delivery system for antivirally active nucleotides,[27] it was shown that a variety of phosphorylated biomolecules can be synthesized by starting from these phosphate triester derivatives. Although the reaction of the *cyclo*Sal-phosphate triesters and the phosphate nucleophiles gave convincing results, like other solution-phase methods, the approaches are often hampered by the following difficulties: 1) Crude products often behaved problematically during chromatography so that counterions were to be replaced by Et_3NH^+- or NH_4^+

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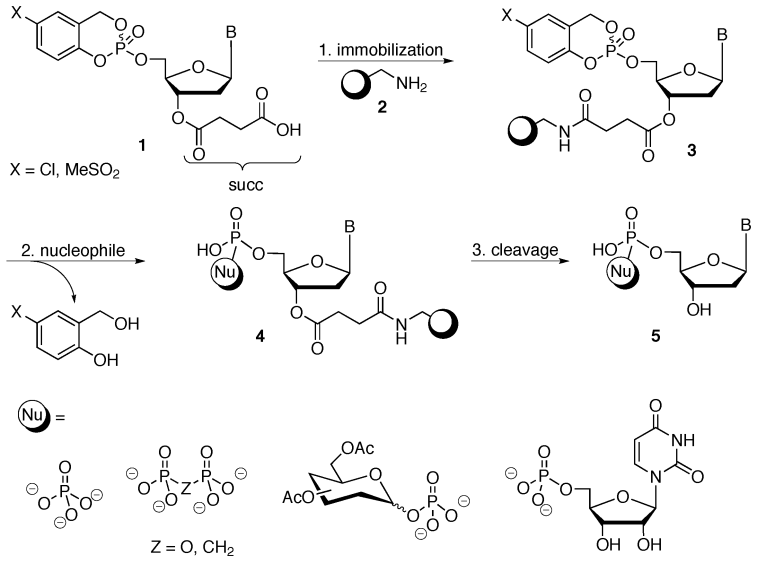
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201101291.

ions. 2) (Pyro)phosphate salts and sugar phosphates were difficult to remove through chromatography on ion-exchange columns or RP-18 silica gel. Therefore, time-consuming multiple purification steps of crude products were required, which resulted in a decrease in the yields due to the instability of some compounds. 3) The use of nucleophiles in excess to increase the yields and to accelerate the reactions amplified the purification problem described above. For example, in the case of the synthesis of NDP sugars starting from *cyclo*Sal-phosphate triesters and sugar-1-phosphates in solution, often prior to the purification the excess of the used sugar-1-phosphate has to be enzymatically dephosphorylated to obtain the pure products after chromatography.[26,28] This may be tolerable in the case of easily accessible sugar-1-phosphates but is not attractive in the case of rare sugar-1-phosphates.

To circumvent these limitations, we have developed a method to use *cyclo*Sal-phosphate triesters as active ester reagents in combination with the solid-phase strategy. Scheme 1 illustrates the general principle of this novel approach on the basis of 2′-deoxyribonucleosides. The procedure consisted of three steps. First, acceptor-substituted and succinyl-linked *cyclo*Sal-nucleotides **1** were attached to amino-methyl polystyrene **2** as an insoluble solid support via an amide bond. Secondly, a nucleophile was reacted with the immobilized *cyclo*Sal-triesters **3**, which led to the support-bound target molecules **4**. Finally, the cleavage of the products **5** from the support was carried out under basic conditions.

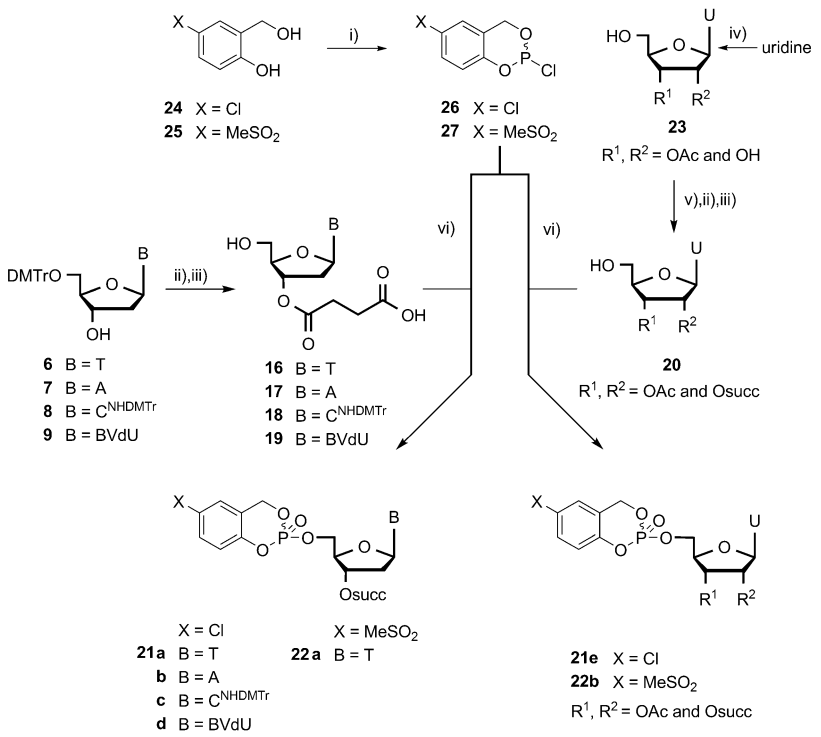


Scheme 1. General principle of immobilization and conversion of *cyclo*Sal-nucleotides on the basis of 2′-deoxyribonucleosides.

The 5-chloro-substituted 3′-*O*-succinyl-*cyclo*Sal-phosphate triester of thymidine was used as a model compound for the following conversions. The phosphorus atom showed a sufficient reactivity due to the electron-withdrawing effect of the chloro substituent and enabled fast reactions with reactive nucleophiles (phosphate, pyrophosphate).[23] Next, the synthetic strategy was transferred to the 2′-deoxyribonucleoside 2′-deoxycytidine, the ribonucleoside uridine, the purine nucleoside 2′-deoxyadenosine, and to the nucleoside analogon 5-[(*E*)-bromovinyl]-2′-deoxyuridine (BVdU) to demonstrate general applicability. In addition, methylsulfonyl *cyclo*Sal-phosphate triesters of thymidine and uridine were applied to prove if increased electrophilicity relative to chloro led to faster reactions with less reactive nucleophiles (sugar phosphates, nucleoside monophosphates).

Results and Discussion

Succinyl-*cyclo*Sal-nucleotides: The synthesis of 2′/3′-*O*-succinyl-*cyclo*Sal-nucleotides started with the attachment of the linker unit to 5′-*O*-DMTr-protected nucleosides **6**–**10** yielding **11**–**15** followed by deprotection of the 5′-*O*-DMTr-group (Scheme 2). Then, 3′-*O*-succinyl-nucleosides **16**–**20** were converted to *cyclo*Sal-phosphate triesters **21a**–**e** and **22a**,**b** by using the linker unit as a protecting group during triester synthesis to prevent unwanted phosphorylation of the 3′-OH group. In addition, there was no or only one purification process necessary at triester level. The ribonucleoside uridine was first acetylated at the 2′- or 3′-OH group[29] yielding **23** in 74% yield as a mixture of 2′- and 3′-*O*-acetylated uridine. DMTr protection (DMTr = 4,4′-dimethoxytrityl) of the 5′-OH group—and in the case of 2′-deoxycytidine of the amino group as well—was performed according to literature protocols[30] forming **6**–**10** in 64–71% yield. The attachment of the linker was achieved by a fast reaction of the protected nucleosides **6**–**10** with succinic anhydride in the presence of 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) followed by protonation of the carboxylic function (**11**–**15**, 88–99% yield). Deprotection of the 5′-OH group with trifluoroacetic acid (TFA) led to **16**–**20** (71–99% yield). Cyclization of salicyl alcohols **24** and **25** with PCl_3 gave acceptor-substituted chlorophosphites **26** and **27** in 86 and 77% yield, respectively.[26] Compound **24** was previously generated by reduction of 5-chloro-salicylic acid[31] and salicyl alcohol **25** by oxidation of 6-methylmercapto-2-phenyl-4*H*-[1.3.2]benzodioxaborine.[24] 5′-*O*-Deprotected-3′-*O*-succinyl-nucleosides **16**–**20** were treated with chlorophosphites **26** and **27** followed by subsequent oxidation with oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)[23]

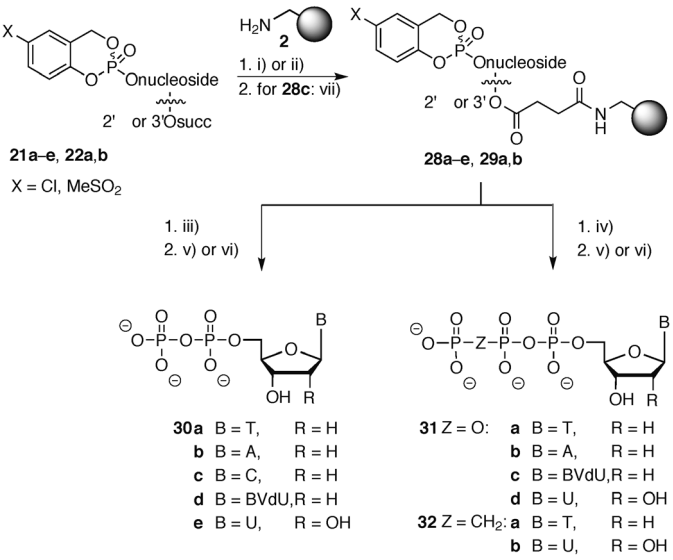


Scheme 2. Synthesis of 2′- or 3′-*O*-succinyl-*cyclo*Sal-nucleotides **21a–e** and **22a–b**: i) PCl_3, pyridine, Et_2O (THF), −40 °C (2 h) to RT (2 h), **26** (86 %), **27** (77 %); ii) DBU, succinic anhydride, CH_2Cl_2, RT, 45–120 min, CH_3COOH, **11–15** (88–99 %); iii) TFA, CH_2Cl_2, RT, 8–120 min, **16–20** (71–99 %); iv) TMOF, *p*TsOH, RT, 2 h, **23** (74 %); v) DMTrCl, pyridine, Et_3N, DMAP, RT, 20 h, **10** (64 %); vi) 1) CH_3CN (DMF), DIPEA, −35 °C to RT, 2–3 h; 2) oxone in H_2O, −10 °C, 15 min, **21a–e**+**22a,b** (56–83 %). DMAP = 4-dimethylaminopyridine; TMOF = trimethoxyorthoacetate.

yielding crude materials in good purity after extraction according to NMR spectroscopic analysis (**21a–e** and **22a,b**, 56–83 % yield). Both, chloro and methylsulfonyl-substituted *cyclo*Sal-phosphate triesters **21a–e** and **22a,b** could be further purified by silica gel chromatography after addition of 1 % acetic acid to the eluent.

Immobilization of succinyl-*cyclo*Sal-nucleotides and their conversions: For immobilization, 2′/3′-*O*-succinyl-*cyclo*Sal-nucleotides **21a–e** and **22a,b** were anchored to aminomethyl polystyrene **2** through an amide bond and the loading of the amino groups present on the support was determined by the Kaiser test.[32] It was very important for the success of the following reaction and particularly for the high purity of the cleaved target molecule that the coupling conditions of the *cyclo*Sal-triester to the support were mild enough to allow the immobilization of even highly reactive triesters. Consequently, the purity of cleaved target molecules judged by ^{31}P NMR spectroscopic analysis is a result of both, stability of the triester during the coupling process and conversion of the triester to the target molecule. For reactions of *cyclo*Sal-nucleotides with reactive nucleophiles like phosphate salts, the reactivity of the phosphorus center caused by chloro as an acceptor-substituent (**21a–e**) is strong enough for short reaction times and high conversion rates. However, the principle of the new approach was transferred to *cyclo*Sal-nucleotides with acceptor substituents that cause an even stronger activation at the phosphorus center to react these immobilized phosphate triesters also with less reactive nucleophiles (e.g. sugar phosphates or nucleotides) in even shorter reaction times relative to the 5-chloro-*cyclo*Sal-triester. Therefore, conversions of methylsulfonyl-substituted *cyclo*Sal-nucleotides **22a,b** to (d)NDPs and (d)NTPs were carried out to optimize the coupling conditions (Scheme 3).

As an optimized procedure, shaking the solid support with a mixture of the corresponding *cyclo*Sal-nucleotide and an excess of 1-hydroxybenzotriazole (HOBt) and *N*,*N*′-diisopropylcarbodiimide (DIC), each three equivalents, in anhydrous DMF should be carried out.[33] If water-free reagents are required, 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) and 4-ethylmorpholine in anhydrous DMF proved to be suitable for



Scheme 3. Immobilization of *cyclo*Sal-nucleotides **21a–e** and **22a,b** and their conversion to (d)NDPs **30a–e**, (d)NTPs **31a–d**, and (d)NTP analogues **32a,b**: i) HOBt, DIC, DMF, 16 h–2 d, RT; ii) TBTU, 4-ethylmorpholine, DMF, 2 d, RT; iii) $[(n\mathrm{Bu})_4\mathrm{N}]H_2PO_4$ (**33**), DMF, 16 h, RT; iv) for Z = O: $[(n\mathrm{Bu})_4\mathrm{N}]_2H_2P_2O_7$ (**34**), for Z = CH_2: $[(n\mathrm{Bu})_4\mathrm{N}]_2H_2PO_3CH_2PO_3$ (**35**), DMF, 16 h, RT; v) 25 % aqueous NH_3, 2 h, 50 °C; vi) $CH_3OH/H_2O/Et_3N$ 7:3:1, 20 h, RT; vii) 3 % TCA in CH_2Cl_2, 24 h, RT.

the amide bond formation as well.[34] By using these conditions, *cyclo*Sal-nucleotides **21a–e** and **22a,b** were immobilized resulting in **28a–e** and **29a,b**. The synthesis of TDP **30a** by starting from immobilized 5-chloro-*cyclo*Sal-thymidine monophosphate (**28a**) showed purity as good as with the analogous reaction (both 90%) by using HOBt/DIC for the immobilization. However, for 5-methylsulfonyl-*cyclo*Sal triester, the highest purity of TDP **30a** (81%) was obtained by using three equivalents HOBt/DIC and a short reaction time (20 h) for triester immobilization. As a consequence, the latter reaction conditions were used for further experiments.

Concerning the immobilized 5-chloro-*cyclo*Sal-N^4-(4,4′-dimethoxytrityl)-3′-*O*-succinyl-2′-deoxycytidine monophosphate (**28c**) the DMTr-protection group was removed on solid support by addition of trichloroacetic acid (TCA) yielding **28c$^{depr.}$**. The synthesis of (d)NDPs **30a–e**, (d)NTPs **31a–d**, and the triphosphate analogues **32a,b** started with the preparation of reactive phosphate nucleophiles. Here, an ion-exchange of phosphoric acid, $Na_2H_2P_2O_7$, and $Na_2H_2PO_3CH_2PO_3$ by using ion-exchange resin Dowex (50WX8) followed by titration with $[(n\text{Bu})_4\text{N}]\text{OH}$ into their tetra-*n*-butyl ammonium-salts **33–35** was conducted.[34] The solutions were titrated until a pH value of 5–6 was reached to ensure that the linker remained stable. In preliminary experiments a cleavage was observed in cases in which the phosphate salts were titrated to a pH value of 7.

Extensive drying of the resins **28a–e** and **29a,b** in vacuo and of the phosphate salts **33–35** first in vacuo followed by storage over activated molecular sieves as a solution in anhydrous DMF was essential for the prevention of byproducts. Generally, the excess of phosphate salt used for the conversion was six to ten equivalents, only in the case of BVdU more was used due to the expensive starting material. After a reaction time of 16 h, simple washing of the polymer-bound target molecules allowed complete removal of the excess of phosphate salts and of the released salicyl alcohols. In contrast, solution-phase synthesis of these molecules requires time-consuming purification steps. Cleavage from the support was done with aqueous ammonia at 50°C in the case of 2′-deoxynucleotides. For products based on ribonucleosides with acetyl protecting groups and NDP sugars with acetyl groups in the sugar moiety the cleavage was achieved with a mixture of CH_3OH, H_2O, and Et_3N (7:3:1, v/v/v) at room temperature, which allowed a cleavage of the acetyl protecting groups in the form of methyl acetate or acetic acid at the same time as the solid support. The methyl acetate or acetic acid was removed in vacuo. The linker remained attached to the resin thus enabling separation of final products by simple filtration. Freeze-drying of the cleavage solutions yielded target molecules directly in high purity.

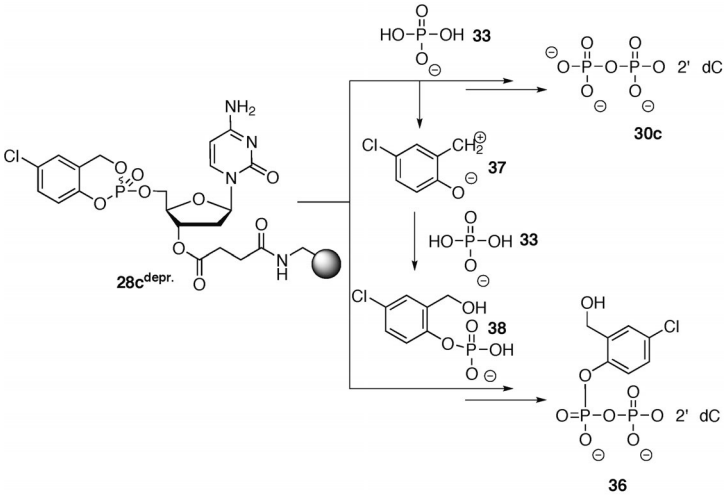
Following this protocol, the diphosphates of thymidine, 2′-deoxyadenosine, BVdU, and uridine **30a,b,d,e** were obtained in 63–91% purity after cleavage and 2′-deoxycytidine diphosphate (2′-dCDP) **30c** in 44% purity, which was exceptionally low (Table 1). In this particular case, it was observed

Table 1. Purity of (d)NDPs **30a–e** and (d)NTPs **31a–d** and **32a,b** after cleavage.

	Starting *cyclo*Sal-triester	Coupling conditions[a]	Cleavage[a]	Purity [%]
TDP **30a**	**28a**	i) or ii)	v)	90
TDP **30a**	**29a**	i)	v)	81
2′-dADP **30b**	**28b**	i)	v)	88
2′-dCDP **30c**	**28c$^{depr.}$**	i)	v)	44
BVdUDP **30d**	**28d**	i)	v)	91
UDP **30e**	**29b**	ii)	vi)	63
TTP **31a**	**28a**	i)	v)	90
2′-dATP **31b**	**28b**	i)	v)	78
BVdUTP **31c**	**28d**	i)	v)	90
UTP **31d**	**28e**	i)	vi)	78
$TDPCH_2P$ **32a**	**28a**	i)	v)	78
$UDPCH_2P$ **32b**	**28e**	i)	vi)	75

[a] Conditions described in Scheme 3.

that a 2′-dCDP-conjugate **36** was formed. After separation of the two diphosphates and isolation of the 2′-dCDP-conjugate **36** and 2′-dCDP **30c** in a ratio of 1:1 it was assumed that the 2-quinone methide **37** released during the nucleophilic attack of the phosphate **33** reacted with another phosphate to a substituted phosphate nucleophile **38** in a ratio of 1:1 to the target molecule 2′-dCDP **30c** (Scheme 4). Nucleophile **38** reacted probably with the immobilized triester **28c$^{depr.}$** with formation of the 2′-dCDP-conjugate **36**. This result was reproducible and astonishingly only observed in the synthesis of 2′-dCDP **30c**.



Scheme 4. Synthesis of 2′-dCDP **30c** and assumed byproduct 2′-dCDP-conjugate **36**.

The purities of the obtained (d)NDPs **30a–e** and (d)NTPs **31a–d** and **32a,b** were analyzed by ^{31}P NMR spectroscopic analysis in all cases because the triesters were immobilized as pure materials and consequently all cleavage products should contain phosphorus (Table 1). Often in solid-phase strategies, HPLC analysis of the final products is used to determine the purity of the released product. In our case, we

decided to use ^{31}P NMR spectroscopy because the only phosphorus-containing compound attached to the support is the *cyclo*Sal-phosphate triester and after the reaction only the products of the reaction of the *cyclo*Sal-triester and the nucleophile or known phosphorus-containing byproducts are released from the support. The advantage of using ^{31}P NMR spectroscopy is that the spectra are fast and easily conducted, whereas HPLC analysis would necessarily need for each class of product an individual elution method. Moreover, the spectroscopic method enabled the integration of the byproducts signals and thus gives immediately the ratio of the product to the byproducts.

To further increase the purity of the target compounds, crude products were easily purified by a rapid chromatography on RP-18 silica gel. Therefore, the crude products were converted into their Et_3NH^+ salts with ion-exchange resin Dowex (50WX8) because Et_3NH^+ as the counterion turned out to be superior for RP-chromatography relative to, for example, $(n\text{Bu})_4N^+$. These procedures were found to be enormously simplified relative to the purification of the crude products obtained by solution-phase syntheses due to the absence of phosphate salts. Six of the compounds presented in Table 1 (**30b**,**c**,**e**, **31b**, and **32a**,**b**) haven't been synthesized with *cyclo*Sal techniques in solution-phase chemistry yet. The purification of a crude product that showed a purity of 90% gave a pure product in 80% chemical yield.

Moreover, the reported procedure was applied to the conversion of immobilized *cyclo*Sal-NMPs **28a**,**b** and **29a**,**b**, to NDP sugars **39–41**, and dinucleoside diphosphates **42** and **43** (Scheme 5).

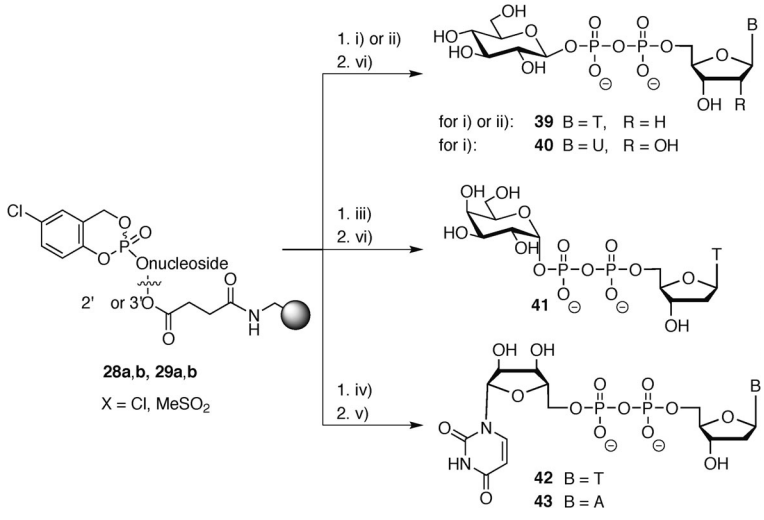
Generally, nucleophiles show higher nucleophilicity in their $(n\text{Bu})_4N^+$ form relative to their Et_3NH^+ or Na^+ salts. Therefore, the majority of reactions have been carried out with $(n\text{Bu})_4N^+$ phosphate salts. On the other hand, conversion of methylsulfonyl-substituted *cyclo*Sal-nucleotides showed higher purity of products if Et_3NH^+ was used as counterion of the nucleophile. For the NDP sugar syntheses tetra-*O*-acetyl-β-D-glucosyl-1-phosphate (**44**) and tetra-*O*-acetyl-α-D-galactosyl-1-phosphate (**45**) that were prepared according to well-established methods were used,[24] whereas commercially available Na_2UMP was used for the ion-exchange to generate **46**.

The protocols were identical to the protocol described for the (d)NDPs and (d)NTPs including drying of salts and resins, the addition of nucleophile solutions to the resins followed by washing and cleavage procedures. On this route, TDP-β-D-glucose **39**, UDP-β-D-glucose **40**, thymidine-uridine-5′,5′-diphosphate **42**, and 2′-deoxyadenosin-uridine-5′,5′-diphosphate **43** were synthesized in good conversions of the corresponding immobilized 5-chloro- or 5-methylsulfonyl-substituted *cyclo*Sal-nucleotide (purities of 61–78% according to ^{31}P NMR spectroscopy), whereas only TDP-α-D-galactose **41** showed a lower purity (43%; Table 2). It became apparent that these reactions required longer reaction times relative to the di- and triphosphate syntheses al-

Table 2. Purity of NDP-sugars **39–41** and dinucleoside diphosphates **42** and **43** after cleavage.

	Starting *cyclo*Sal-triester	Coupling conditions[a]	Cleavage[a]	Purity [%]
TDP-β-D-glucose **39**	**28a**	i)	vi)	78
TDP-β-D-glucose **39**	**29a**	i)	vi)	60
UDP-β-D-glucose **40**	**29b**	i)	vi)	61
TDP-α-D-galactose **41**	**29a**	i)	vi)	43
Tp_2U **42**	**28a**	i)	v)	78
Tp_2U **42**	**29a**	i)	v)	70
2′-dAp_2U **43**	**28b**	i)	v)	70

[a] Conditions described in Scheme 3.



Scheme 5. Conversion of acceptor-substituted immobilized *cyclo*Sal-NMPs **28a**,**b** and **29a**,**b** into NDP-sugars **39–41** and dinucleoside diphosphates **42** and **43**: i) (Et_3NH)-tetra-*O*-acetyl-β-D-glucosyl-1-phosphate (**44a**), DMF, 4 d, RT; ii) $[(n\text{Bu})_4N]$-tetra-*O*-acetyl-β-D-glucosyl-1-phosphate (**44b**), DMF, 5 d, RT; iii) (Et_3NH)-tetra-*O*-acetyl-α-D-galactosyl-1-phosphate (**45**), DMF, 4 d, RT; iv) $[(n\text{Bu})_4N]$UMP (**46**), DMF, 4–5 d, RT; v) 25% aqueous NH_3, 2 h, 50°C; vi) $CH_3OH/H_2O/Et_3N$ 7:3:1, 20 h, RT.

though again the $(n\text{Bu})_4N^+$ salts of the nucleophiles were used. Interestingly, comparing the two electron-withdrawing groups in the *cyclo*Sal-moiety, no advantage could be attributed to the stronger methylsulfonyl group. The dinucleoside diphosphate **43** hasn't been synthesized with *cyclo*Sal techniques in solution-phase before.

Interestingly, we isolated the 1,2-cyclophosphate of α-galactose and thymidine-5′-monophosphate after the cleavage of TDP-α-D-galactose **41** with CH_3OH, H_2O, and Et_3N (7:3:1, v/v/v) at room temperature from the solid support. Thus, the cleavage conditions seems to lead to the cleavage of the

pyrophosphate bond in the previously formed NDP sugars as reported by Kosma et al. for 2,3,4,6,7-penta-*O*-acetyl-ADP-β-D- and -L-heptopyranoses.[35] Consequently, new improved cleavage conditions for NDP sugars should avoid this decomposition and yield the target molecules in higher purity.

Comparing the synthesis in solution and the solid-phase synthesis of the compounds described above,[23–26] the number of synthesis steps to get to the reactive *cyclo*Sal-nucleotides is identical. In solution, the 2′- and/or 3′-OH group has to be protected, whereas for solid-phase synthesis this position is used for the attachment of the linker unit. Although there is the additional step for the immobilization of the *cyclo*Sal-nucleotides, this method yielded the target molecules in very high purities directly after cleavage in the cleavage solution without impurities of the phosphate nucleophiles. Generally, (d)NDPs and (d)NTPs are obtained in a purity of ~90%. In contrast, the solution-phase method required the additional step of deprotection and (sometimes) multiple time-consuming purification procedures on RP-18 silica gel to remove the phosphate nucleophiles and the by-products. Particularly interesting might be to use the developed method in the context of immobilized biooligomers. DNA or RNA strands might be modified at the 5′-end, for example, as their (poly)phosphates. This type of compounds cannot be prepared by solution-phase strategies. Work along this line is currently undergoing in our laboratories.

Conclusion

This novel method combines the efficient conversion of *cyclo*Sal-nucleotides into (d)NDPs, (d)NTPs, and (d)NDP sugars and dinucleoside diphosphates with the easy-to-perform and time-saving purification resulting from the use of solid-phase strategies.

5-Acceptor-substituted (chloro or methylsulfonyl) *cyclo*-Sal-nucleotides of ribo-, 2′-deoxyribonucleosides and of the nucleoside analogon BVdU that contained a succinyl-linker unit at the 2′- or 3′-OH group were synthesized and easily attached to aminomethyl polystyrene followed by a fast and reliable conversion into several different types of phosphorylated nucleosides and bioconjugates. Importantly, the disclosed method offered an access for the synthesis of a variety of biologically important compounds by the same chemical approach.

Experimental Section

General: In the case of water-sensitive compounds, the reactions were performed in flame-dried glassware under a nitrogen atmosphere. Therefore, solvents were dried as follows: acetonitrile (CH_3CN) and dichloromethane (CH_2Cl_2) were distilled from calcium hydride under nitrogen and stored over activated molecular sieves (CH_3CN 3 Å and CH_2Cl_2 4 Å), *N,N*-diisopropylethylamine (DIPEA) was distilled from sodium, DBU was distilled and stored over activated 4 Å molecular sieves, and DMF was stored over activated 4 Å molecular sieves, respectively, prior to use. CH_2Cl_2, ethyl acetate, and methanol (CH_3OH) for chromatography and extractions were distilled before used. Solid-phase aminomethyl polystyrene was stored at −26°C under a nitrogen atmosphere. Column chromatography was performed by using Merck silica gel 60, 230–400 mesh. Reversed-phase column chromatography was performed on reverse-phase silica gel with distilled water as the eluent at room temperature in a glass column. Ion exchange was executed by Dowex (50WX8, 100–200 mesh, ion-exchange resin) in a glass column. Some separations were performed on a chromatotron by using glass plates coated with 1, 2, or 4 mm layers silica gel (60 PF254) containing a fluorescent indicator. Analytical TLC was performed on Merck precoated aluminum plates 60 F_{254} with a 0.2 mm layer of silica gel containing a fluorescent indicator. Sugar-containing compounds were visualized with sugar spray reagent (4-methoxybenzaldehyde (0.5 mL), ethanol (9 mL), concd sulfuric acid (0.5 mL), and glacial acetic acid (0.1 mL)).

Instrumentation: ^{1}H NMR spectroscopy was carried out by using a Bruker AMX 400 at 400 MHz or Bruker AV 400 at 400 MHz. ^{13}C NMR spectra were recorded on a Bruker AMX 400 at 101 MHz or Bruker AV 400 at 101 MHz. ^{31}P NMR spectra were recorded on a Bruker AMX 400 at 162 MHz (H_3PO_4 as external standard). The spectra were recorded at room temperature. All ^{1}H-, ^{31}P-, and ^{13}C NMR chemical shifts are quoted in parts per million (ppm) downfield from tetramethylsilane and calibrated on solvent signals. All ^{13}C- and ^{31}P NMR spectra were recorded in the proton-decoupled mode. HRMS were obtained with a VG Analytical VG/70–250F spectrometer (FAB, matrix was *m*-nitrobenzyl alcohol). For lyophilization of aqueous solutions, a Christ-Alpha 2–4 lyophilizer was used. For shaking of solid-phase reactions, a Heidolph Polymax 1040 shaker with Incubator 1000 was used.

General procedure 1 for the synthesis of 5′-*O*-(4,4′-dimethoxytrityl)-protected and 2′/3′-*O*-succinyl-linked nucleosides 11–15: The reaction was carried out under a nitrogen atmosphere. DBU (1 equiv) was added to a stirred solution of DMTr-protected nucleoside (1 equiv) and succinic anhydride (1.5 equiv) in CH_2Cl_2 at room temperature. After complete conversion of starting material (15–120 min) acetic acid (2 equiv) was added and stirred for 10 min. The reaction mixture was washed with water (3×) and the combined aqueous layers were extracted with CH_2Cl_2 (2×). The combined organic layers were dried over sodium sulphate and the solvent was removed in vacuo yielding the product as a solid.

General procedure 2 for the synthesis of 2′/3′-*O*-succinyl-linked nucleosides 16–20

Method A: The corresponding compound was dissolved in CH_2Cl_2/CH_3OH 7:3 and treated with TFA (3–3.5 equiv). After stirring for 1–2 h at room temperature, toluene was added and the solvents were removed in vacuo. The crude product was purified on a chromatotron with a gradient of methanol in CH_2Cl_2 (0–10%).

Method B: The corresponding compound was dissolved in CH_2Cl_2 and treated with TFA (3–3.5 equiv). After stirring for 30 min at room temperature, methanol was added and stirred for 10 min. Then, toluene was added and the solvents were removed in vacuo. The crude product was purified on a chromatotron with a gradient of methanol in dichloromethane (0–10%).

Method C: The corresponding compound was dissolved in dichloromethane/methanol 7:3 and 6% TFA. After stirring for 8 min at room temperature, 7M methanolic NH_3 solution was added until the solution was neutralized. Subsequently, the solvents were removed in vacuo and the residue was dissolved in ethyl acetate and washed with water. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulphate, filtrated, and the solvent removed in vacuo. The crude product was purified on a chromatotron with a gradient of methanol in dichloromethane (0–10%).

General procedure 3 for the synthesis of 2′/3′-*O*-succinyl-linked 5-chloro- or 5-methylsulfonyl-substituted *cyclo*Sal-nucleotides 21a–e and 22a,b: 3′-*O*-Succinyl-linked nucleoside **16–19** or 2′- or 3′-*O*-acetylated succinyl-linked nucleoside **20** (1 equiv) was dissolved in acetonitrile (and dimethylformamide if required) and the reaction mixture was cooled to −30°C. DIPEA (2 equiv) was added and after 10 min a solution of 5-acceptor-substituted saligenyl chlorophosphite **26** or **27** (1.3–1.6 equiv) in acetonitrile was added dropwise over 20 min. After removing cooling,

the reaction mixture was stirred for 2–3 h and then cooled to −10 °C. Oxone (2 equiv/phosphite) dissolved in cold water was added and the reaction mixture was stirred for 15 min without cooling. The organic layer was directly washed with cold water (2×) and the combined aqueous layers were extracted with ethyl acetate (1×). The combined organic layers were dried over sodium sulphate and the solvent was removed in vacuo. The residue was lyophilized from H_2O/CH_3CN 2:1) yielding products as colorless foams that were determined to be pure by ^{31}P NMR spectroscopy. For higher purity, the crude products were purified on a chromatotron with a gradient of methanol in dichloromethane (0–10%) and 1% acetic acid.

General procedure 4 for immobilization of 5-acceptor-substituted 2′/3′-*O*-succinyl-linked *cyclo*Sal-nucleotides 21a–e and 22a,b

Method A: 3′-*O*-Succinyl-linked 5-acceptor-substituted *cyclo*Sal-nucleotide (1.1 equiv) and solid-support aminomethyl polystyrene **2** (1 equiv) were dried in vacuo for at least 2 h. The resin was swollen in DMF (1 mL/70 mg) for 30 min and the phosphate triester, 1-hydroxybenzotriazole (HOBt, 3.3 equiv) and *N*,*N*′-di*iso*propylcarbodiimide (DIC, 3.3 equiv) were added and the mixture was shaken for at least for at 20 h at room temperature (complete loading checked by the Kaiser test[31]). The resin was collected by filtration and washed with DMF and CH_2Cl_2 followed by drying in vacuo for several hours.

Method B: Succinyl-linked 5-acceptor-substituted *cyclo*Sal-nucleotide (1.2 equiv) and solid-support aminomethyl polystyrene **2** (1 equiv) were dried in vacuo for at least 2 h. 4-Ethylmorpholine (0.98 equiv) was dissolved in DMF (2 mL/10 μL base) and stored over activated molecular sieves 4 Å for 1 h. The resin was swollen in DMF (1 mL/70 mg) for 30 min and TBTU (1.2 equiv) was added to the 4-ethylmorpholine solution and stored for 15 min. This solution was added to the resin and the mixture was shaken for 1–2 d at room temperature (complete loading checked by the Kaiser test[31]). The resin was collected by filtration and washed with DMF and CH_2Cl_2 followed by drying in vacuo for several hours.

General procedure 5 for the synthesis of nucleoside di- and triphosphates 30a–e, 31a–d, 32a,b, nucleoside diphosphate sugars 39—41 and dinucleoside polyphosphates 42 and 43: Tetra-*n*-butylammonium salts of phosphate **33**, pyrophosphate **34**, and methylenpyrophosphate **35** were prepared by ion-exchange chromatography with Dowex (50WX8, 100–200 mesh, ion-exchange resin) of their protonated and sodium forms, respectively, and titration with tetra-*n*-butylammonium hydroxide to a pH value of 5–6. Tetra-*O*-acetyl-β-D-glucose (**44a**) and tetra-*O*-acetyl-α-D-galactose (**45**) were used in their triethylammonium forms, but for conversion of chloro-substituted *cyclo*Sal-nucleotide, tetra-*n*-butylammonium tetra-*O*-acetyl-β-D-glucose (**44b**) was used (also prepared by ion exchange). Na_2UMP was converted into the tetra-*n*-butylammonium form **46**. The lyophilized salts were dried for 2 d in vacuo and afterwards dissolved in DMF stored over activated molecular sieves 4 Å 2 h before the reaction. The immobilized *cyclo*Sal-nucleotides **28a**,**b** and **29a**,**b** were coevaporated with CH_3CN (3×) and dried in vacuo for several hours. The resin was swollen in DMF (analogue the general procedure 4 for immobilization of *cyclo*Sal-triesters, see above) and the solution of phosphate- or pyrophosphate salt **33**–**35** (5.5–9.7 equiv, for BVdU-triester **28d** 20 or 23 equiv as an exception) or sugar- or nucleoside monophosphate **44**–**46** (3.4–8.2 equiv) was added. The mixture was shaken for 16 h in the case of the di- and triphosphates and for the others as described in the respective protocol (4—5 d). Afterwards, the resin was washed with DMF, CH_2Cl_2, and water.

General procedure 6 for the cleavage of target molecules

Method A: 25% aqueous NH_3 solution (5 mL) was added to the washed immobilized target molecule. After 2 h shaking at 50 °C, the resin was collected by filtration and washed with water (10×5 mL). Washing and cleavage solution were combined and lyophilized to afford target molecules as crude products.

Method B: CH_3OH (5 mL), H_2O (2 mL), and Et_3N (0.7 mL) were added to the washed immobilized target molecule. After 16–48 h shaking at room temperature, the resin was collected by filtration. CH_3OH and Et_3N were removed in vacuo and the resin was washed with water (10×5 mL). Washing and cleavage solution were combined and lyophilized to afford target molecules as crude products.

General procedure 7 for the purification of target molecules: If desired, a crude product was converted into its corresponding Et_3NH^+ salt by ion exchange with Dowex (50WX8, 100–200 mesh, ion-exchange resin). Dowex was first adjusted to the protonated form with hydrochloric acid, then crude product was eluted with water, THF (2 mL) was added, and the solution neutralized with Et_3N. Freeze-drying yielded the Et_3NH^+ salt of the target molecule that was purified by RP-18-chromatography with water as the eluent.

5′-*O*-(4,4′-Dimethoxytrityl)-3′-*O*-succinyl-thymidine (11): The reaction was performed according to general procedure 1 by using **6** (4.00 g, 7.34 mmol), succinic anhydride (1.10 g, 11.0 mmol), DBU (1.10 mL, 7.36 mmol), acetic acid (841 μL, 14.7 mmol), and CH_2Cl_2 (85 mL) within a reaction time of 45 min yielding a rose solid (4.75 g, 7.11 mmol, 97%). R_f (CH_2Cl_2/CH_3OH 9.5:0.5, 0.1% Et_3N) = 0.22; ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 12.25 (s, 1H; COOH), 11.39 (s, 1H; NH), 7.52 (s, 1H; H6), 7.38–7.23 (m, 9H; DMTr-H), 6.89 (d, 4H; DMTr-H, $^3J_{HH}$ = 7.7 Hz), 6.22 (dd, 1H; H1′, $^3J_{HH}$ = 8.5, $^3J_{HH}$ = 6.0 Hz), 5.30 (d, 1H; H3′, $^3J_{HH}$ = 6.4 Hz), 4.07–4.04 (m, 1H; H4′), 3.74 (s, 6H; 2×$OCH_{3,DMTr}$), 3.34–3.30 (m, 1H; H5′a), 3.22 (dd, 1H; H5′b, $^2J_{HH}$ = 10.3, $^3J_{HH}$ = 2.9 Hz), 2.55–2.50 (m, 4H; H2″, H3″), 2.50–2.44 (m, 1H; H2′a), 2.33–2.29 (dd, 1H; H2′b, $^2J_{HH}$ = 13.3, $^3J_{HH}$ = 5.8 Hz), 1.42 ppm (s, 3H; H7).

5′-*O*-(4,4′-Dimethoxytrityl)-3′-*O*-succinyl-2′-deoxyadenosine (12): The reaction was performed according to general procedure 1 by using **7** (685 mg, 1.24 mmol), succinic anhydride (187 mg, 1.87 mmol), DBU (185 μL, 1.24 mmol), acetic acid (142 μL, 2.47 mmol), and CH_2Cl_2 (10 mL) within a reaction time of 75 min yielding a rose solid (763 mg, 1.17 mmol, 94%). R_f (CH_2Cl_2/CH_3OH 9:1, 0.1% Et_3N) = 0.38; ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 12.30 (s, 1H; COOH), 8.25 (s, 1H; H8), 8.03 (s, 1H; H2), 7.34–7.19 (m, 9H; DMTr-H), 6.82 (d, 2H; DMTr-H, $^3J_{HH}$ = 8.6 Hz), 6.80 (d, 2H; DMTr-H, $^3J_{HH}$ = 8.6 Hz), 6.37 (dd, 1H; H1′, $^3J_{HH}$ = 7.3, $^3J_{HH}$ = 6.6 Hz), 5.41–5.39 (m, 1H; H3′), 4.18–4.15 (m, 1H; H4′), 3.72 (s, 6H; 2×$OCH_{3,DMTr}$), 3.31–3.17 (m, 2H; H5′), 2.58–2.53 (m, 4H; H2″, H3″), 2.47–2.45 ppm (m, 2H; H2′).

***N*^{6}-5′-*O*-Bis(4,4′-dimethoxytrityl)-3′-*O*-succinyl-2′-deoxycytidine (13)**: The reaction was performed according to general procedure 1 by using **8** (1.82 g, 2.19 mmol), succinic anhydride (328 mg, 3.28 mmol), DBU (328 μL, 2.19 mmol), acetic acid (250 μL, 4.37 mmol), and CH_2Cl_2 (12 mL) within a reaction time of 120 min yielding a rose solid (2.01 g, 2.16 mmol, 99%). R_f (CH_2Cl_2/CH_3OH 8.5:1.5, 0.1% Et_3N) = 0.55; ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 12.21 (s, 1H; COOH), 8.38 (s, 1H; NH), 7.51 (d, 1H; H6, $^3J_{HH}$ = 7.1 Hz), 7.37–7.12 (m, 18H; DMTr-H), 6.90 (d, 4H; DMTr-H, $^3J_{HH}$ = 8.4 Hz), 6.89 (d, 4H; DMTr-H, $^3J_{HH}$ = 8.6 Hz), 6.17 (d, 1H; H5, $^3J_{HH}$ = 7.6 Hz), 6.08 (dd, 1H; H1′, $^3J_{HH}$ = 7.2, $^3J_{HH}$ = 6.8 Hz), 5.25–5.15 (m, 1H; H3′), 4.05–3.97 (m, 1H; H4′), 3.75 (s, 6H; 2×$OCH_{3,DMTr}$), 3.72 (s, 6H; 2×$OCH_{3,DMTr}$), 3.30–3.18 (m, 2H; H5′), 2.28–2.16 ppm (m, 2H; H2′).

5′-*O*-(4,4′-Dimethoxytrityl)-3′-*O*-succinyl-BVdU (14): The reaction was performed according to general procedure 1 by using **9** (271 mg, 0.426 mmol), succinic anhydride (77 mg, 0.77 mmol), DBU (64 μL, 0.43 mmol), acetic acid (49 μL, 0.85 mmol), and CH_2Cl_2 (5 mL) within a reaction time of 15 min yielding a colorless solid (277 mg, 0.377 mmol, 88%). R_f (CH_2Cl_2/CH_3OH 9:1, 0.1% Et_3N) = 0.37; ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 12.26 (s, 1H; COOH), 11.68 (s, 1H; NH), 7.81 (s, 1H; H6), 7.37–7.18 (m, 10H; DMTr-H, H8), 6.88 (dd, 4H; DMTr-H, $^3J_{HH}$ = 8.9, $^4J_{HH}$ = 2.2 Hz), 6.37 (d, 1H; H7, $^3J_{HH}$ = 13.5 Hz), 6.19 (dd, 1H; H1′, $^3J_{HH}$ = 6.9, $^3J_{H,H}$ = 7.3 Hz), 5.26–5.22 (m, 1H; H3′), 4.10–4.08 (m, 1H; H4′), 3.74 (s, 6H; 2×$OCH_{3,DMTr}$), 3.35–3.32 (m, 1H; H5′a), 3.23 (dd, 1H; H5′b, $^2J_{H,H}$ = 10.6, $^3J_{HH}$ = 3.2 Hz), 2.55–2.47 (m, 5H; C2″, C3″, H2′a), 2.35 ppm (ddd, 1H; H2′b, $^2J_{HH}$ = 14.1, $^3J_{HH}$ = 6.0, $^4J_{HH}$ = 2.0 Hz).

5′-*O*-(4,4′-Dimethoxytrityl)- 2′- or 3′-*O*-acetyl- 2′- or 3′-*O*-succinyl-uridine (15): The reaction was performed according to general procedure 1 by using **10** (1.69 g, 2.87 mmol), succinic anhydride (430 mg, 4.30 mmol), DBU (437 μL, 2.88 mmol), acetic acid (330 μL, 5.76 mmol), and CH_2Cl_2 (30 mL) within a reaction time of 120 min yielding a rose solid (1.94 g, 2.82 mmol, 98%) as a mixture of 5′-*O*-DMTr-protected 2′-*O*-acetyl-3′-*O*-succinyl-uridine and 3′-*O*-acetyl-2′-*O*-succinyl-uridine. R_f (CH_2Cl_2/

CH_3OH 9:1, 0.1% Et_3N) = 0.38; ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.27 (s, 2H; COOH), 11.45 (s, 2H; NH), 7.67 (d, 2H; H6, $^3J_{HH}$ = 8.1 Hz), 7.39–7.22 (m, 18H; DMTr-H), 6.91–6.88 (m, 8H; DMTr-H), 5.91 (d, 1H; H1′a, $^3J_{HH}$ = 5.5 Hz), 5.88 (d, 1H; H1′b, $^3J_{HH}$ = 4.8 Hz), 5.54–5.48 (m, 4H; H2′, H5), 5.46–5.39 (m, 2H; H3′), 4.19–4.14 (m, 2H; H4′), 3.74 (s, 12H; 4×$OCH_{3,DMTr}$), 3.36 (dd, 2H; H5′a, $^2J_{HH}$ = 10.6, $^3J_{HH}$ = 5.0 Hz), 3.25 (dd, 2H; H5′b, $^2J_{HH}$ = 10.8, $^3J_{HH}$ = 3.3 Hz), 2.59–2.45 (m, 8H; C2″, C3″), 2.06 (s, 3H; $CH_{3,acetyl}$), 2.04 ppm (s, 3H; $CH_{3,acetyl}$).

3′-*O*-Succinyl-thymidine (16): The reaction was performed according to general procedure 2A by using **11** (4.93 g, 7.64 mmol), TFA (2.07 mL, 26.8 mmol), CH_2Cl_2/CH_3OH (100 mL), and toluene (5 mL) within a reaction time of 2 h yielding a pale-orange solid (1.79 g, 5.22 mmol, 71%). R_f (CH_2Cl_2/CH_3OH 9:1) = 0.24; ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.28 (s, 1H; COOH), 11.32 (s, 1H; NH), 7.74 (d, 1H; H6, $^4J_{HH}$ = 1.2 Hz), 6.18 (dd, 1H; H1′, $^3J_{HH}$ = 8.7, $^3J_{HH}$ = 5.9 Hz), 5.24–5.20 (m, 2H; H3′, H5′-OH), 3.97–3.95 (m, 1H; H4′), 3.63–3.61 (m, 2H; H5′), 2.57–2.47 (m, 4H; H2″, H3″), 2.34–2.25 (m, 1H; H2′a), 2.24–2.18 (ddd, 1H; H2′b, $^2J_{HH}$ = 14.0, $^3J_{HH}$ = 5.9, $^4J_{HH}$ = 1.7 Hz), 1.78 ppm (d, 3H; CH_3, $^4J_{HH}$ = 1.0 Hz).

3′-*O*-Succinyl-2′-deoxyadenosine (17): The reaction was performed according to general procedure 2A by using **12** (733 mg, 1.12 mmol), TFA (260 μL, 3.37 mmol), CH_2Cl_2/CH_3OH (15 mL), and toluene (3 mL) within a reaction time of 1 h yielding a colorless solid (389 mg, 1.11 mmol, 99%). R_f (CH_2Cl_2/CH_3OH 9:1) = 0.18; ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.28 (s, 1H; COOH), 8.43 (s, 1H; H8), 8.22 (s, 1H; H2), 7.74 (s, 2H; NH_2), 6.37 (dd, 1H; H1′, $^3J_{HH}$ = 8.5, $^3J_{HH}$ = 6.0 Hz), 5.38 (d, 1H; H3′, $^3J_{HH}$ = 5.6 Hz), 4.10–4.08 (m, 1H; H4′), 3.66 (dd, 1H; H5′a, $^2J_{HH}$ = 12.0, $^3J_{HH}$ = 3.9 Hz), 3.60 (dd, 1H; H5′b, $^2J_{HH}$ = 12.0, $^3J_{HH}$ = 4.1 Hz), 2.99–2.96 (ddd, 1H; H2′a, $^2J_{HH}$ = 14.4, $^3J_{HH}$ = 8.5, $^3J_{HH}$ = 6.2 Hz), 2.60–2.44 ppm (m, 5H; H2′b, H2″, H3″).

N^4-(4,4′-Dimethoxytrityl)-3′-*O*-succinyl-2′-deoxycytidine (18): The reaction was performed according to general procedure 2C by using **13** (548 mg, 0.588 mmol), TFA (1.94 mL, 25.2 mmol), CH_2Cl_2/CH_3OH (32 mL), and toluene (5 mL) yielding a pale-yellow solid (330 mg, 0.524 mmol, 89%). R_f (CH_2Cl_2/CH_3OH 8:2, 0.1% Et_3N) = 0.50; ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.23 (s, 1H; COOH), 8.40 (s, 1H; NH), 7.74 (d, 1H; H6, $^3J_{HH}$ = 7.4 Hz), 7.29–7.13 (m, 9H; DMTr-H), 6.84 (d, 4H; DMTr-H, $^3J_{HH}$ = 8.3 Hz), 6.27 (d, 1H; H5, $^3J_{HH}$ = 7.3 Hz), 6.08 (dd, 1H; H1′, $^3J_{HH}$ = 7.1, $^3J_{HH}$ = 6.8 Hz), 5.18 (d, 1H; H3′, $^3J_{HH}$ = 4.1 Hz), 5.12 (s, 1H; 5′-OH), 3.95–3.90 (m, 1H; H4′), 3.72 (s, 6H; 2×$OCH_{3,DMTr}$), 3.61–3.51 (m, 2H; H5′), 2.55–2.47 (m, 4H; H2″, H3″), 2.19–2.07 ppm (m, 2H; H2′).

3′-*O*-Succinyl-BVdU (19): The reaction was performed according to general procedure 2B by using **14** (270 mg, 0.367 mmol), TFA (95 μL, 1.2 mmol), CH_2Cl_2 (5 mL), and then CH_3OH (5 mL) and toluene (5 mL) within a reaction time of 30 min yielding a pale-orange solid (157 mg, 0.362 mmol, 99%). R_f (CH_2Cl_2/CH_3OH 9:1) = 0.10; ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.26 (s, 1H; COOH), 11.64 (s, 1H; NH), 8.08 (s, 1H; H6), 7.26 (d, 1H; H8, $^3J_{HH}$ = 13.6 Hz), 6.85 (d, 1H; H7, $^3J_{HH}$ = 13.6 Hz), 6.15 (dd, 1H; H1′, $^3J_{HH}$ = 6.2, $^3J_{HH}$ = 6.4 Hz), 5.24–5.22 (m, 2H; H3′, 5′-OH), 4.02–4.00 (m, 1H; H4′), 3.65 (dd, 1H; H5′a, $^2J_{HH}$ = 12.1, $^3J_{HH}$ = 3.7 Hz), 3.62 (dd, 1H; H5′b, $^2J_{HH}$ = 12.0, $^3J_{HH}$ = 3.9 Hz), 2.57–2.41 (m, 4H; H2″, H3″), 2.35–2.27 ppm (m, 2H; H2′).

2′- or 3′-*O*-Acetyl- 2′- or 3′-*O*-succinyl-uridine 20: The reaction was performed according to general procedure 2B by using **15** (1.87 g, 2.72 mmol), TFA (630 μL, 8.18 mmol), CH_2Cl_2 (10 mL), and then CH_3OH (10 mL) and toluene (5 mL) within a reaction time of 30 min yielding a pale-yellow solid (897 mg, 2.32 mmol, 85%) as a mixture of 2′-*O*-acetyl-3′-*O*-succinyl-uridine and 3′-*O*-acetyl-2′-*O*-succinyl-uridine. R_f (CH_2Cl_2/CH_3OH 9:1) = 0.20; ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.27 (s, 2H; 2×COOH), 11.42 (d, 2H; 2×NH, $^4J_{HH}$ = 2.1 Hz), 7.90 (d, 1H; H6, $^3J_{HH}$ = 8.1 Hz), 7.89 (d, 1H; H6, $^3J_{HH}$ = 8.2 Hz), 6.03 (d, 1H; H1′, $^3J_{HH}$ = 6.1 Hz), 6.00 (d, 1H; H1′, $^3J_{HH}$ = 5.6 Hz), 5.72 (dd, 1H; H5, $^3J_{HH}$ = 5.1, $^4J_{HH}$ = 2.3 Hz), 5.72 (dd, 1H; H5, $^3J_{HH}$ = 5.7, $^4J_{HH}$ = 2.3 Hz), 5.42 (s, 2H; 2×H5′-OH), 5.36–5.31 (m, 4H; 2×H2′, 2×H3′), 4.13–4.12 (m, 2H; 2×H4′), 3.67–3.60 (m, 4H; 2×H5′), 2.67–2.41 (m, 8H; 2×H2″, 2×H3″), 2.09, 2.01 ppm (2×s, 6H; 2×$CH_{3,acetyl}$).

5-Chloro-*cyclo*Sal-3′-*O*-succinyl-thymidine monophosphate (21a): The reaction was performed according to general procedure 3 by using **16** (1.59 g, 4.65 mmol), DIPEA (1.62 mL, 9.29 mmol), 5-chloro-saligenyl chlorophosphite (**26**) (1.35 g, 6.04 mmol), oxone (7.42 g, 12.1 mmol), CH_3CN (40 mL), and DMF (2 mL) within a reaction time of 2.5 h yielding a colorless foam (1.65 g, 3.03 mmol, 65%). R_f (CH_2Cl_2/CH_3OH 9:1, 0.1% acetic acid) = 0.48; ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.21 (s, 2H; 2×COOH), 11.34 (s, 2H; 2×NH), 7.49–7.41 (m, 6H; 2×H6, 2×$H4_{ar}$, 2×$H6_{ar}$), 7.18–7.15 (m, 2H; 2×$H3_{ar}$), 6.18–6.13 (m, 2H; 2×H1′), 5.55–5.40 (m, 4H, 2×CH_2-benzyl), 5.20–5.16 (m, 2H; 2×H3′), 4.44–4.31 (m, 4H; 2×H5′), 4.16–4.11 (m, 2H; 2×H4′), 2.58–2.48 (m, 8H; 2×H2″, 2×H3″), 2.39–2.33 (m, 2H; 2×H2′a), 2.26 (dd, 2H; 2×H2′b, $^2J_{HH}$ = 13.0, $^3J_{HH}$ = 5.0 Hz), 1.76 (s, 3H; CH_3), 1.73 ppm (s, 3H; CH_3); ^{31}P NMR (162 MHz, [D_6]DMSO): δ = −9.47 (s), −9.65 ppm (s) (2 diastereomers in a ratio of 1.0:1.0).

5-Chloro-*cyclo*Sal-3′-*O*-succinyl-2′-deoxyadenosine monophosphate (21b): The reaction was performed according to general procedure 3 by using **17** (359 mg, 1.02 mmol), DIPEA (355 μL, 2.04 mmol), 5-chloro-saligenyl chlorophosphite (**26**) (296 mg, 1.33 mmol), oxone (1.63 g, 2.65 mmol), CH_3CN (18 mL), and DMF (2 mL) within a reaction time of 2.5 h yielding a colorless foam (417 mg, 0.753 mmol, 74%). R_f (CH_2Cl_2/CH_3OH 8:1, 0.1% acetic acid) = 0.20; ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.26 (s, 1H; COOH), 12.25 (s, 1H; COOH), 8.30 (s, 1H; H2), 8.29 (s, 1H; H2), 8.12 (s, 1H; H8), 8.11 (s, 1H; H8), 7.41–7.32 (m, 8H; 2×$H4_{ar}$, 2×$H6_{ar}$, 2×NH_2), 7.13 (d, 1H; $H3_{ar}$, $^3J_{HH}$ = 8.7 Hz), 6.97 (d, 1H; $H3_{ar}$, $^3J_{HH}$ = 8.8 Hz), 6.38–6.33 (m, 2H; 2×H1′), 5.49–5.31 (m, 6H; 2×CH_2-benzyl, 2×H3′), 4.46–4.35 (m, 4H; 2×H5′), 4.23–4.22 (m, 2H; 2×H4′), 3.12–3.06 (m, 2H; 2×H2′a), 2.59–2.48 ppm (m, 10H; 2×H2″, 2×H3″, 2×H2′b); ^{31}P NMR (162 MHz, [D_6]DMSO): δ = −10.48 (s), −10.54 ppm (s) (2 diastereomers in a ratio of 1.0:1.0).

5-Chloro-*cyclo*Sal-N^4-(4,4′-dimethoxytrityl)-3′-*O*-succinyl-2′-deoxycytidine monophosphate (21c): The reaction was performed according to general procedure 3 by using **18** (374 mg, 0.594 mmol), DIPEA (207 μL, 1.19 mmol), 5-chloro-saligenyl chlorophosphite (**26**) (172 mg, 0.771 mmol), oxone (0.95 g, 1.55 mmol), CH_3CN (23 mL), and DMF (4 mL) within a reaction time of 3 h yielding a colorless foam (409 mg, 0.491 mmol, 83%). R_f (CH_2Cl_2/CH_3OH 8:1, 0.1% acetic acid) = 0.41; ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.22 (s, 2H; 2×COOH), 8.43 (s, 2H; 2×NH), 7.49 (d, 1H; H6, $^3J_{HH}$ = 7.2 Hz), 7.49 (d, 1H; H6, $^3J_{HH}$ = 7.5 Hz), 7.45–7.06 (m, 24H; 2×$H4_{ar}$, 2×$H6_{ar}$, 2×$H3_{ar}$, 18×DMTr-H), 6.91–6.82 (m, 8H, 8×DMTr-H), 6.25 (d, 1H; H5, $^3J_{HH}$ = 7.6 Hz), 6.23 (d, 1H; H5, $^3J_{HH}$ = 7.4 Hz), 6.06–6.02 (m, 2H; 2×H1′), 5.54–5.38 (m, 4H; 2×CH_2-benzyl), 5.12–5.08 (m, 2H; 2×H3′), 4.38–4.26 (m, 4H; 2×H5′), 4.09–4.04 (m, 2H; 2×H4′), 3.72 (s, 12H; 4×$OCH_{3,DMTr}$), 2.56–2.45 (m, 8H; 2×H2″, 2×H3″), 2.17–2.14 ppm (m, 4H; 2×H2′); ^{31}P NMR (162 MHz, [D_6]DMSO): δ = −10.31 (s), −10.46 ppm (s) (2 diastereomers in a ratio of 0.9:1.0).

5-Chloro-*cyclo*Sal-3′-*O*-succinyl-BVdU monophosphate (21d): The reaction was performed according to general procedure 3 by using **19** (130 mg, 0.300 mmol), DIPEA (105 μL, 0.600 mmol), 5-chloro-saligenyl chlorophosphite (**26**) (100 mg, 0.450 mmol), oxone (553 mg, 0.900 mmol), CH_3CN (5 mL), and DMF (0.6 mL) within a reaction time of 3 h yielding a colorless foam (125 mg, 0.197 mmol, 66%). R_f (CH_2Cl_2/CH_3OH 9:1, 0.1% acetic acid) = 0.54; ^1H NMR (400 MHz, [D_6]DMSO): δ = 12.27 (s, 2H; COOH), 11.65 (s, 2H; 2×NH), 7.86 (s, 1H; H6), 7.84 (s, 1H; H6), 7.44–7.37 (m, 4H; 2×$H4_{ar}$, 2×$H6_{ar}$), 7.30 (d, 1H; H8, $^3J_{HH}$ = 13.7 Hz), 7.29 (d, 1H; H8, $^3J_{HH}$ = 13.6 Hz), 7.16 (d, 1H; $H3_{ar}$, $^3J_{HH}$ = 8.6 Hz), 7.14 (d, 1H; $H3_{ar}$, $^3J_{HH}$ = 9.5 Hz), 6.85 (d, 1H; H7, $^3J_{HH}$ = 13.6 Hz), 6.83 (d, 1H; H7, $^3J_{HH}$ = 13.6 Hz), 6.17–6.11 (m, 2H; 2×H1′), 5.55–5.39 (m, 4H; 2×CH_2-benzyl), 5.23–5.18 (m, 2H; 2×H3′), 4.46–4.33 (m, 4H; 2×H5′), 4.22–4.17 (m, 2H; 2×H4′), 2.58–2.48 (m, 8H; 2×H2″, 2×H3″), 2.44–2.30 ppm (m, 4H; 2×H2′); ^{31}P NMR (162 MHz, [D_6]DMSO): δ = −10.05 (s), −10.14 ppm (s) (2 diastereomers in a ratio of 1.0:0.7).

5-Chloro-*cyclo*Sal-2′- or 3′-*O*-acetyl-2′- or 3′-*O*-succinyl-uridine monophosphate (21e): The reaction was performed according to general procedure 3 by using **20** (345 mg, 0.893 mmol), DIPEA (310 μL, 1.78 mmol), 5-chloro-saligenyl chlorophosphite (**26**) (259 mg, 1.16 mmol), oxone (1.43 g, 2.33 mmol), and CH_3CN (12 mL) within a reaction time of 2 h

yielding a colorless foam (403 mg, 0.685 mmol, 77%). R_f (CH_2Cl_2/CH_3OH 9:1, 0.1% acetic acid) = 0.20; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.25 (s, 4H; 4×COOH), 11.48–11.45 (m, 4H; 4×NH), 7.64–7.60 (m, 4H; 4×H6), 7.44–7.40 (m, 8H; 4×H4$_{ar}$, 4<MxH6$_{ar}$), 7.20–7.15 (m, 4H; 4×H3$_{ar}$, $^3J_{HH}$ = 8.9 Hz), 5.87–5.83 (m, 4H; 4×H1′), 5.65–5.61 (m, 4H; 4×H5), 5.56–5.45 (m, 8H; 4×CH$_2$-benzyl), 5.43–5.39 (m, 4H; 4×H2′), 5.35–5.26 (m, 4H; 4×H3′), 4.48–4.31 (m, 8H; 4×H5′), 4.26–4.24 (m, 4H; 4×H4′), 2.59–2.45 (m, 16H; 4×H2″, 4×H3″), 2.06, 2.04 ppm (s, 12H; 4×CH$_{3,acetyl}$); ^{31}P NMR (162 MHz, [D$_6$]DMSO): δ = −10.58 (s), −10.60 ppm (s) (2 pairs of diastereomers).

5-Methylsulfonyl-*cyclo*Sal-3′-*O*-succinyl-thymidine monophosphate (22a): The reaction was performed according to general procedure 3 by using **16** (510 mg, 1.49 mmol), DIPEA (519 μL, 2.98 mmol), 5-methylsulfonyl-saligenyl chlorophosphite (**27**) (610 mg, 2.29 mmol), oxone (2.81 g, 4.57 mmol), CH_3CN (40 mL), and DMF (1.7 mL) within a reaction time of 2.5 h yielding a colorless foam (494 mg, 0.839 mmol, 56%). R_f (CH_2Cl_2/CH_3OH 9:1, 0.1% acetic acid) = 0.31; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.28 (s, 2H; 2×COOH), 11.40 (s, 1H; NH), 11.39 (s, 1H; NH), 7.94–7.90 (m, 4H; 2×H4$_{ar}$, 2×H6$_{ar}$), 7.52 (d, 1H; H6, $^4J_{HH}$ = 1.2 Hz), 7.49 (d, 1H; H6, $^4J_{HH}$ = 1.1 Hz), 7.40 (d, 1H; H3$_{ar}$, $^3J_{HH}$ = 9.2 Hz), 7.37 (d, 1H; H3$_{ar}$, $^3J_{HH}$ = 8.5 Hz), 6.19–6.13 (m, 2H; 2× H1′), 5.69–5.50 (m, 4H; 2×CH$_2$-benzyl), 5.20–5.18 (m, 2H; H3′), 4.48–4.35 (m, 4H; 2×H5′), 4.17–4.13 (m, 2H; 2×H4′), 3.22 (s, 6H; 2×CH$_3$(SO$_2$)), 2.56–2.47 (m, 8H; 2×H2″, 2×H3″), 2.41–2.32 (m, 2H; 2×H2′a), 2.30–2.23 (ddd, 2H; 2×H2′b, $^2J_{HH}$ = 14.2, $^3J_{HH}$ = 6.0, $^4J_{HH}$ = 2.2 Hz), 1.75 (d, 3H; CH_3, $^4J_{HH}$ = 1.0 Hz), 1.72 ppm (d, 3H; CH_3, $^4J_{HH}$ = 1.0 Hz); ^{31}P NMR (162 MHz, [D$_6$]DMSO): δ = −10.39 (s), −10.56 ppm (s), (2 diastereomers in a ratio of 1.0:0.9).

5-Methylsulfonyl-*cyclo*Sal-2′- or 3′-*O*-acetyl-2′- or 3′-*O*-succinyl-uridine monophosphate (22b): The reaction was performed according to general procedure 3 by using **20** (328 mg, 0.846 mmol), DIPEA (296 μL, 1.69 mmol), 5-methylsulfonyl-saligenyl chlorophosphite (**27**) (364 mg, 1.37 mmol), oxone (1.68 g, 2.73 mmol), and CH_3CN (20 mL) within a reaction time of 3 h yielding a colorless foam (385 mg, 0.609 mmol, 72%). R_f (CH_2Cl_2/CH_3OH 9:1, 0.1% acetic acid) = 0.26; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 11.46–11.43 (m, 4H; 4×NH), 7.93–7.91 (m, 8H; 4×H4$_{ar}$, 4×H6$_{ar}$), 7.66 (d, 2H; 2×H6, $^3J_{HH}$ = 8.1 Hz), 7.64 (d, 2H; 2×H6, $^3J_{HH}$ = 8.1 Hz), 7.40 (d, 2H; 2×H3$_{ar}$, $^3J_{HH}$ = 9.2 Hz), 7.37 (d, 2H; 2×H3$_{ar}$, $^3J_{HH}$ = 9.2 Hz), 5.89–5.83 (m, 4H; 4×H1′), 5.68–5.62 (m, 12H; 4×CH$_2$-benzyl, 4×H5), 5.45–5.41 (m, 4H; 4×H2′), 5.35–5.26 (m, 4H; 4×H3′), 4.51–4.35 (m, 8H; 4×H5′), 4.30–4.24 (m, 4H; 4×H4′), 3.22 (s, 12H; 4×CH$_3$(SO$_2$)), 2.58–2.44 (m, 16H; 4×H2″, 4×H3″), 2.05, 2.03 ppm (s, 12H; 4×CH$_{3,acetyl}$); ^{31}P NMR (162 MHz, [D$_6$]DMSO): δ = −10.70 (s), −10.82 ppm (s) (2 pairs of diastereomers).

Tetra-*n*-butylammonium-thymidine-5′-diphosphate (30a)

Method A: 5-Chloro-substituted *cyclo*Sal-nucleotide (**21a**) was immobilized according to general procedure 4A with of aminomethyl polystyrene **2** (235 mg, 259 μmol). By following general procedure 5, conversion to TDP **30a** was carried out with tetra-*n*-butylammonium dihydrogenphosphate (**33**) (623 mg, 1.84 mmol, 7.1 equiv). Cleavage was achieved according to general procedure 6A yielding 123 mg of TDP **30a** as crude product in 90% purity.

Method B: 5-Chloro-substituted *cyclo*Sal-nucleotide **21a** was immobilized according to general procedure 4B with aminomethyl polystyrene **2** (70 mg, 77 μmol). By following general procedure 5, conversion to TDP **30a** was carried out with tetra-*n*-butylammonium dihydrogenphosphate (**33**) (250 mg, 746 μmol, 9.7 equiv). Cleavage was achieved according to general procedure 6A yielding 52 mg of TDP **30a** as a crude product in 90% purity.

Method C: 5-Methylsulfonyl-substituted *cyclo*Sal-nucleotide **22a** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (87 mg, 95 μmol). By following general procedure 5, conversion to TDP **30a** was carried out with tetra-*n*-butylammonium dihydrogenphosphate (**33**) (250 mg, 746 μmol, 7.9 equiv). Cleavage was achieved according to general procedure 6A yielding 63 mg of TDP **30a** as crude product in 81% purity. Analytical data were identical to those found in the literature. ^{1}H NMR (400 MHz, D$_2$O): δ = 7.73 (d, 1H; H6, $^4J_{HH}$ = 1.2 Hz), 6.33 (dd, 1H; H1′, $^3J_{HH}$ = 7.2, $^3J_{HH}$ = 6.7 Hz), 4.64–4.61 (m, 1H; H3′), 4.18–4.14 (m, 3H; H4′, H5′), 2.42–2.30 (m, 2H; H2′), 1.91 ppm (d, 3H; CH_3, $^4J_{HH}$ = 0.9 Hz); ^{31}P NMR (162 MHz, D$_2$O): δ = −9.54 (d; P$_\beta$, $^2J_{PP}$ = 20.2 Hz), −11.05 (d; P$_\alpha$, $^2J_{PP}$ = 20.2 Hz).

Tetra-*n*-butylammonium-2′-deoxyadenosine-5′-diphosphate (30b): *Cyclo*Sal-nucleotide **21b** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (75 mg, 83 μmol). By following general procedure 5, conversion to 2′-dADP **30b** was carried out with tetra-*n*-butylammonium dihydrogenphosphate (**33**) (250 mg, 746 μmol, 9.0 equiv). Cleavage was achieved according to general procedure 6A yielding 31 mg of 2′-dADP **30b** as crude product in 88% purity that was purified by RP-18-chromatography with (nBu)$_4$N ions as counterions and with water as the eluent. Analytical data were identical to those found in the literature. ^{1}H NMR (400 MHz, D$_2$O): δ = 8.42 (s, 1H; H8), 8.12 (s, 1H; H2), 6.40 (dd, 1H; H1′, $^3J_{HH}$ = 6.5, $^3J_{HH}$ = 6.5 Hz), 4.79–4.72 (m, 1H; H3′), 4.21–4.10 (m, 3H; H4′, H5′), 3.11 (t, 9H; H1$_{NBu4}$, $^3J_{HH}$ = 8.4 Hz), 2.78–2.69 (m, 1H; H2′a), 2.57–2.52 (m, 1H; H2′b), 1.56 (tt, 9H; H2$_{NBu4}$, $^3J_{HH}$ = 8.1, $^3J_{HH}$ = 7.8 Hz), 1.28 (m, 9H; H3$_{NBu4}$), 0.88 ppm (t, 13.5H; H4$_{NBu4}$, $^3J_{HH}$ = 7.4 Hz); ^{31}P NMR (162 MHz, D$_2$O): δ = −6.61 (d, P$_\beta$, $^2J_{PP}$ = 22.4 Hz), −10.83 ppm (d, P$_\alpha$, $^2J_{PP}$ = 22.6 Hz).

Tetra-*n*-butylammonium-2′-deoxycytidine-5′-diphosphate (30c): *Cyclo*Sal-nucleotide **21c** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (134 mg, 147 μmol). DMTr-deprotection was done by addition of TCA (5 mL) in CH_2Cl_2 (3%) to the resin and shaking the mixture at room temperature for 24 h yielding **28c$^{depr.}$**. Afterwards the resin was washed with CH_2Cl_2 (10×5 mL). By following general procedure 5, conversion to 2′-dCDP **30c** was carried out with tetra-*n*-butylammonium dihydrogenphosphate **33** (205 mg, 604 μmol, 4.1 equiv). Cleavage proceeded according to general procedure 6A yielding 65 mg of 2′-dCDP **30c** as crude product in 44% purity that was purified according to general procedure 7. Analytical data were identical to those found in the literature. ^{1}H NMR (400 MHz, D$_2$O): δ = 8.22 (d, 1H; H6, $^3J_{HH}$ = 7.9 Hz), 6.32–6.27 (m, 2H; H1′, H5), 4.65–4.60 (m, 1H; H3′), 4.27–4.25 (m, 1H; H4′), 4.22–4.12 (m, 2H; H5′), 3.21 (q, 8H; CH$_{2,Et3N}$, $^3J_{HH}$ = 7.3 Hz), 2.53–2.47 (ddd, 1H; H2′a, $^2J_{HH}$ = 14.2, $^3J_{HH}$ = 6.2, $^3J_{HH}$ = 3.8 Hz), 2.42–2.35 (m, 1H; H2′b), 1.29 ppm (t, 12H; CH$_{3,Et3N}$, $^3J_{HH}$ = 7.3 Hz); ^{31}P NMR (162 MHz, D$_2$O): δ = −10.83 (d; P$_\beta$, $^2J_{PP}$ = 19.3 Hz), −11.38 ppm (d; P$_\alpha$, $^2J_{PP}$ = 19.7 Hz).

Tetra-*n*-butylammonium-BVdU-5′-diphosphate (30d): *Cyclo*Sal-nucleotide **21d** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (87 mg, 96 μmol). By following general procedure 5, conversion to BVdUDP **30d** was carried out with tetra-*n*-butylammonium dihydrogenphosphate (**33**) (760 mg, 2.24 mmol, 23 equiv). Cleavage was achieved according to general procedure 6A yielding 72 mg of BVdUDP **30d** as crude product in 91% purity. Analytical data were identical to those found in the literature.[23]

Tetra-*n*-butylammonium-uridine-5′-diphosphate (30e): *Cyclo*Sal-nucleotide **21e** was immobilized according to general procedure 4B with 70 mg of aminomethyl polystyrene **2** (77 μmol). By following general procedure 5, conversion to UDP **30e** was carried out with tetra-*n*-butylammonium dihydrogenphosphate (**33**) (250 mg, 746 μmol, 9.7 equiv). Cleavage was achieved according to general procedure 6B yielding 42 mg of UDP **30e** as crude product in 63% purity that was purified according to general procedure 7. Analytical data were identical to those found in the literature. ^{1}H NMR (400 MHz, D$_2$O): δ = 7.93 (d, 1H; H6, $^3J_{HH}$ = 8.2 Hz), 5.95 (d, 1H; H1′, $^3J_{HH}$ = 4.6 Hz), 5.93 (d, 1H; H5, $^3J_{HH}$ = 8.1 Hz), 8.35–8.34 (m, 2H; H2′, H3′), 8.25 (ddd, 1H; H4′, $^3J_{HH}$ = 5.3, $^3J_{HH}$ = 2.8, $^3J_{HH}$ = 2.5 Hz), 4.20 (ddd, 1H; H5′a, $^2J_{HH}$ = 11.8, $^3J_{HH}$ = 4.4, $^3J_{HP}$ = 2.4 Hz), 4.15 (ddd, 1H; H5′b, $^2J_{HH}$ = 12.0, $^3J_{HH}$ = 5.8, $^3J_{HP}$ = 3.1 Hz), 3.16 (q, 10H; CH$_{2,Et3N}$, $^3J_{HH}$ = 7.3 Hz), 1.24 ppm (t, 15H; CH$_{3,Et3NH}$, $^3J_{HH}$ = 7.3 Hz); ^{31}P NMR (162 MHz, D$_2$O): δ = −8.56 (d; P$_\beta$, $^2J_{PP}$ = 21.8 Hz), −11.27 ppm (d; P$_\alpha$, $^2J_{PP}$ = 21.9 Hz).

Tetra-*n*-butylammonium-thymidine-5′-triphosphate (31a): *Cyclo*Sal-nucleotide **21a** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (151 mg, 166 μmol). By following general procedure 5, conversion to TTP **31a** was carried out with bis(tetra-*n*-butylammonium)dihydrogenpyrophosphate (**34**) (751 mg, 1.14 mmol, 6.9 equiv). Cleavage was achieved according to general procedure 6A yielding 108 mg of TTP **31a** as crude product in 90% purity. Analytical data were identical to those found in the literature. ^{1}H NMR (400 MHz,

D_2O): $\delta = 7.61$ (d, 1H; H6, $^4J_{HH} = 1.0$ Hz), 6.19 (dd, 1H; H1′, $^3J_{HH} = 6.9$, $^3J_{HH} = 6.8$ Hz), 4.55–4.51 (m, 1H; H3′), 4.12–3.96 (m, 3H; H4′, H5′), 3.02 (t, 15H; $H1_{NBu4}$, $^3J_{HH} = 8.2$ Hz), 2.26–2.16 (m, 2H; H2′), 1.78 (s, 3H; CH_3), 1.48 (tt, 15H; $H2_{NBu4}$, $^3J_{HH} = 7.8$, $^3J_{HH} = 7.8$ Hz), 1.20 (m, 15H; $H3_{NBu4}$), 0.79 ppm (t, 22.5H; $H4_{NBu4}$, $^3J_{HH} = 7.4$ Hz); ^{31}P NMR (162 MHz, D_2O): $\delta = -7.14$ (d; P_γ, $^2J_{PP} = 20.4$ Hz), −11.47 (d; P_α, $^2J_{PP} = 20.0$ Hz), −22.39 (dd; P_β, $^2J_{PP} = 20.4$, $^2J_{PP} = 19.8$ Hz).

Tetra-*n*-butylammonium-2′-deoxyadenosine-5′-triphosphate (31b): *Cyclo*Sal-nucleotide **21b** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (59 mg, 65 μmol). By following general procedure 5, conversion to 2′-dATP **31b** was carried out with bis(tetra-*n*-butylammonium)dihydrogenpyrophosphate (**34**) (258 mg, 390 μmol, 6.0 equiv). Cleavage was achieved according to general procedure 6A yielding 20 mg of 2′-dATP **31b** as crude product in 78% purity. Analytical data were identical to those found in the literature.

Tetra-*n*-butylammonium-BVdU-5′-triphosphate (31c): *Cyclo*Sal-nucleotide **21d** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (87 mg, 96 μmol). By following general procedure 5, conversion to BVdUTP **31c** was carried out with bis(tetra-*n*-butylammonium)dihydrogenpyrophosphate (**34**) (1.27 g, 1.92 mmol, 20 equiv). Cleavage was achieved according to general procedure 6A yielding 109 mg of BVdUTP **31c** as crude product in 90% purity. Analytical data were identical to those found in the literature.[23]

Tetra-*n*-butylammonium-uridine-5′-triphosphate (31d): *Cyclo*Sal-nucleotide **21e** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (93 mg, 102 μmol). By following general procedure 5, conversion to UTP **31d** was carried out with bis(tetra-*n*-butylammonium)dihydrogenpyrophosphate (**34**) (560 mg, 847 μmol, 8.3 equiv). Cleavage was achieved according to general procedure 6B yielding 50 mg of UTP **31d** as crude product in 78% purity. Analytical data were identical to those found in the literature. ^{1}H NMR (400 MHz, D_2O): $\delta = 7.95$ (d, 1H; H6, $^3J_{HH} = 8.1$ Hz), 5.99–5.95 (m, 2H; H1′, H5), 4.41–4.35 (m, 2H; H2′, H3′), 4.27–4.23 (m, 3H; H4′, H5′), 3.19–3.12 (m, 28H; $CH_{2,Et3NH}$, $H1_{NBu4}$), 1.67–1.56 (m, 22H; $H2_{NBu4}$), 1.37–1.29 (m, 22H; $H3_{NBu4}$), 1.25 (t, 9H; $CH_{3,Et3NH}$, $^3J_{HH} = 7.3$ Hz), 0.91 ppm (t, 33H; $H4_{NBu4}$, $^3J_{HH} = 7.3$ Hz); ^{31}P NMR (162 MHz, D_2O): $\delta = -10.27$ (d; P_γ, $^2J_{PP} = 21.0$ Hz), −11.52 (d; P_α, $^2J_{PP} = 20.3$ Hz), −23.15 ppm (dd; P_β, $^2J_{PP} = 20.4$, $^2J_{PP} = 19.5$ Hz).

Tetra-*n*-butylammonium-thymidine-5′-β,γ-methylenetriphosphate (32a): *Cyclo*Sal-nucleotide **21a** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (151 mg, 166 μmol). By following general procedure 5, conversion to thymidine-5′-β,γ-methylenetriphosphate **32a** was carried out with bis(tetra-*n*-butylammonium)dihydrogenmethylenpyrophosphate (**35**) (600 mg, 911 μmol, 5.5 equiv). Cleavage proceeded according to general procedure 6A yielding 87 mg of thymidine-5′-β,γ-methylenetriphosphate **32a** as crude product in 78% purity that was purified by RP-18-chromatography with $(n\mathrm{Bu})_4$N ions as counterions and with water as eluent. ^{1}H NMR (400 MHz, D_2O): $\delta = 7.71$ (s, 1H; H6), 6.31 (dd, 1H; H1′, $^3J_{HH} = 7.1$, $^3J_{HH} = 6.7$ Hz), 4.63–4.59 (m, 1H; H3′), 4.15–4.09 (m, 3H; H4′, H5′), 2.41–2.31 (m, 2H; H2′), 2.27–2.17 (dd, 2H; P-CH_2-P, $^2J_{HP} = 20.0$, $^2J_{HP} = 20.2$ Hz), 1.89 ppm (s, 3H; CH_3); ^{31}P NMR (162 MHz, D_2O): $\delta = 13.07$ (m; P_γ), 11.56 (m; P_β), −11.16 ppm (d; P_α, $^2J_{PP} = 25.9$ Hz).

Tetra-*n*-butylammonium-uridine-5′-β,γ-methylenetriphosphate (32b): *Cyclo*Sal-nucleotide **21e** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (75 mg, 83 μmol). By following general procedure 5, conversion to uridine-5′-β,γ-methylenetriphosphate **32b** was carried out with tetra-*n*-butylammonium dihydrogenmethylenpyrophosphate (**35**) (356 mg, 540 μmol, 6.5 equiv). Cleavage was achieved according to general procedure 6B yielding 32 mg of **32b** as crude product in 75% purity that was purified according to general procedure 7. ^{1}H NMR (400 MHz, D_2O): $\delta = 7.97$ (d, 1H; H6, $^3J_{HH} = 8.2$ Hz), 5.99 (d, 1H; H1′, $^3J_{HH} = 3.8$ Hz), 5.97 (d, 1H; H5, $^3J_{HH} = 8.0$ Hz), 4.41–4.37 (m, 2H; H2′, H3′), 4.30–4.26 (m, 1H; H4′), 4.25–4.21 (m, 2H; H5′), 3.20 (q, 18H; $CH_{2,Et3NH}$, $^3J_{HH} = 7.3$ Hz), 2.35 (dd, 2H; PCH_2P, $^2J_{HP} = 20.4$, $^2J_{HP} = 20.3$ Hz), 1.28 ppm (t, 27H; $CH_{3,Et3NH}$, $^3J_{HH} = 7.3$ Hz); ^{31}P NMR (162 MHz, D_2O): $\delta = 15.36$ (m; P_γ), 7.98 (m; P_β), −11.20 ppm (d; P_α, $^2J_{PP} = 26.4$ Hz).

Tetra-*n*-butylammonium- or triethylammonium-β-D-glucose-thymidine-5′-diphosphate (39)

Method A: 5-Chloro-substituted *cyclo*Sal-nucleotide **21a** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (130 mg, 143 μmol). By following general procedure 5, conversion to TDP-β-D-glucose **39** was carried out with tetra-*n*-butylammonium-tetra-*O*-acetyl-β-D-glucose (**44b**) (789 mg, 1.18 mmol, 8.2 equiv) within a reaction time of 5 d. Cleavage was achieved according to general procedure 6B yielding 131 mg of TDP-β-D-glucose **39** as crude product in 78% purity that was purified according to general procedure 7.

Method B: 5-Methylsulfonyl-substituted *cyclo*Sal-nucleotide **22a** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (281 mg, 309 μmol). By following general procedure 5, conversion to TDP-β-D-glucose **39** was carried out with triethylammonium-tetra-*O*-acetyl-β-D-glucose (**44a**) (660 mg, 1.25 mmol, 4.0 equiv) within a reaction time of 4 d. Cleavage was achieved according to general procedure 6B yielding 190 mg of TDP-β-D-glucose **39** as crude product in 60% purity that was purified according to general procedure 7. Analytical data were identical to those found in the literature.[26] ^{1}H NMR (400 MHz, D_2O): $\delta = 7.75$ (s, 1H; H6), 6.35 (dd, 1H; H1′, $^3J_{HH} = 7.2$, $^3J_{HH} = 6.8$ Hz), 4.95 (dd, 1H; H1, $^3J_{HH} = 7.8$, $^3J_{HH} = 7.7$ Hz), 4.66–4.61 (m, 1H; H3′), 4.19–4.18 (m, 3H; H4′, H5′), 3.92 (d, 1H; H4, $^3J_{HH} = 3.2$ Hz), 3.82 (dd, 1H; H6a, $^2J_{HH} = 10.3$, $^3J_{HH} = 6.9$ Hz), 3.76–3.67 (m, 3H; H3, H5, H6b), 3.64–3.59 (m, 1H; H2), 3.20 (q, 12H; $CH_{2,Et3NH}$, $^3J_{HH} = 7.3$ Hz), 2.43–2.31 (m, 2H; H2′), 1.93 (s, 3H; CH_3), 1.28 ppm (t, 18H; $CH_{3,Et3NH}$, $^3J_{HH} = 7.3$ Hz); ^{31}P NMR (162 MHz, D_2O): $\delta = -11.48$ (d; P_α, $^2J_{PP} = 18.5$ Hz), −12.97 ppm (d; P_β, $^2J_{PP} = 18.2$ Hz).

Triethylammonium-β-D-glucose-uridine-5′-diphosphate (40): *Cyclo*Sal-nucleotide **22b** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (27 mg, 30 μmol). By following general procedure 5, conversion to UDP-β-D-glucose **40** was carried out with triethylammonium-tetra-*O*-acetyl-β-D-glucose (**44a**) (77 mg, 145 μmol, 4.8 equiv) within a reaction time of 4 d. Cleavage was achieved according to general procedure 6B yielding 15 mg of UDP-β-D-glucose **40** in 61% purity. Analytical data were identical to those found in the literature.[26]

Triethylammonium-α-D-galactose-thymidine-5′-diphosphate (41): *Cyclo*Sal-nucleotide **22a** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (359 mg, 395 μmol). By following general procedure 5, conversion to TDP-α-D-galactose **41** was carried out with triethylammonium-tetra-*O*-acetyl-α-D-galactose (**45**) (720 mg, 1.36 mmol, 3.4 equiv) within a reaction time of 4 d. Cleavage was achieved according to general procedure 6B yielding 194 mg of TDP-α-D-galactose **41** as crude product in 43% purity that was purified according to general procedure 7. Analytical data were identical to those found in the literature.[26] ^{1}H NMR (400 MHz, D_2O): $\delta = 7.77$ (s, 1H; H6), 6.39–6.35 (m, 1H; H1′), 5.63 (dd, 1H; H1, $^3J_{HP} = 7.2$, $^3J_{HH} = 3.4$ Hz), 4.68–4.63 (m, 1H; H3′), 4.22–4.21 (m, 3H; H4′, H5′), 3.94–3.89 (m, 1H; H4), 3.89–3.85 (m, 1H; H6a), 3.83–3.78 (m, 2H; H3, H6b), 3.57–3.53 (m, 1H; H2), 3.51–3.46 (m, 1H; H5), 3.23 (q, 8H; $CH_{2,Et3NH}$, $^3J_{HH} = 7.3$ Hz), 2.43–2.38 (m, 2H; H2′), 1.96 (s, 3H; CH_3), 1.30 ppm (t, 12H; $CH_{3,Et3NH}$, $^3J_{HH} = 7.3$ Hz); ^{31}P NMR (162 MHz, D_2O): $\delta = -11.37$ (d; P_α, $^2J_{PP} = 20.4$ Hz), −12.93 ppm (d; P_β, $^2J_{PP} = 20.6$ Hz).

Tetra-*n*-butylammonium-thymidine-uridine-5′,5′-diphosphate (42)

Method A: 5-Chloro-substituted *cyclo*Sal-nucleotide **21a** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (130 mg, 143 μmol). By following general procedure 5, conversion to thymidine-uridine-5′,5′-diphosphate **42** was carried out with tetra-*n*-butylammonium-uridine monophosphate (**46**) (600 mg, 1.06 mmol, 7.4 equiv) within a reaction time of 4 d. Cleavage was achieved according to general procedure 6A yielding 100 mg of thymidine-uridine-5′,5′-diphosphate **42** as crude product in 78% purity that was purified by RP-18-chromatography with $(n\mathrm{Bu})_4$N ions as counterions and with water as the eluent.

Method B: 5-Methylsulfonyl-substituted *cyclo*Sal-nucleotide **22a** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (42 mg, 46 μmol). By following general procedure 5, conversion to thymidine-uridine-5′, 5′-diphosphate **42** was carried out with tetra-*n*-butylammonium-uridine monophosphate (**46**) (180 mg, 0.318 mmol, 6.9 equiv) within a reaction time of 5 d. Cleavage was achieved according to general

procedure 6A yielding 26 mg of thymidine-uridine-5′, 5′-diphosphate **42** as crude product in 70% purity. Analytical data were identical to those found in the literature.[23] ^{1}H NMR (400 MHz, D_2O): δ = 7.93 (d, 1H; $H6_U$, $^3J_{HH}$ = 8.3 Hz), 7.72 (d, 1H; $H6_T$, $^4J_{HH}$ = 1.2 Hz), 6.34–6.30 (m, 1H; $H1'_T$), 5.95 (d, 1H; $H5_U$, $^3J_{HH}$ = 7.9 Hz), 5.94 (d, 1H; $H1'_U$, $^3J_{HH}$ = 4.8 Hz), 4.62–4.59 (m, 1H; $H3'_T$), 4.36–4.34 (m, 2H; $H2'_U$, $H3'_U$), 4.27–4.15 (m, 6H; $H4'_T$, $H4'_U$, $H5'_T$, $H5'_U$), 2.37–2.34 (m, 2H; $H2'_T$), 1.92 ppm (d, 3H; CH_3, $^4J_{HH}$ = 1.0 Hz); ^{31}P NMR (162 MHz, D_2O): δ = −11.41 (d, 1P, $^2J_{PP}$ = 19.6 Hz), −11.57 ppm (d, 1P, $^2J_{PP}$ = 21.5 Hz).

Tetra-*n*-butylammonium-2′-deoxyadenosine-uridine-5′,5′-diphosphate (43): *Cyclo*Sal-nucleotide **21b** was immobilized according to general procedure 4A with aminomethyl polystyrene **2** (118 mg, 130 μmol). By following general procedure 5, conversion to 2′-deoxyadenosine-uridine-5′, 5′-diphosphate **43** was carried out with tetra-*n*-butylammonium-uridine monophosphate (**46**) (485 mg, 0.858 mmol, 6.6 equiv) within a reaction time of 5 d. Cleavage was achieved according to general procedure 6A yielding 33 mg of 2′-deoxyadenosine-uridine-5′,5′-diphosphate **43** as crude product that was purified according to general procedure 7. ^{1}H NMR (400 MHz, D_2O): δ = 8.46 (s, 1H; $H8_A$), 8.25 (s, 1H; $H2_A$), 7.68 (d, 1H; $H6_U$, $^3J_{HH}$ = 8.1 Hz), 6.48 (d, 1H; $H1_A$, $^3J_{HH}$ = 6.8 Hz), 5.83 (d, 1H; $H1'_U$, $^3J_{HH}$ = 4.8 Hz), 5.70 (d, 1H; $H5_U$, $^3J_{HH}$ = 8.0 Hz), 4.79–4.69 (m, 1H; $H3_A$), 4.27–4.13 (m, 8H; $H4_A$, $H5_A$, $H2'_U$, $H3'_U$, $H4'_U$, $H5'_U$), 3.20 (q, 12H; $CH_{2,Et3NH}$, $^3J_{HH}$ = 7.3 Hz), 2.83 (ddd, 1H; H2′a$_A$, $^2J_{HH}$ = 14.0, $^3J_{HH}$ = 6.8, $^3J_{HH}$ = 6.2 Hz), 2.58 (ddd, 1H; H2′b$_A$, $^2J_{HH}$ = 14.2, $^3J_{HH}$ = 6.2, $^3J_{HH}$ = 3.5 Hz), 1.28 ppm (t, 18H; $CH_{3,Et3NH}$, $^3J_{HH}$ = 7.3 Hz); ^{31}P NMR (162 MHz, D_2O): δ = −11.38 ppm (m; P_α, P_β).

Acknowledgements

The authors thank the University of Hamburg for financial support. V.T. is grateful for a Ph.D. fellowship for the "Förderung des wissenschaftlichen und künstlerischen Nachwuchses" of the University of Hamburg.

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Received: April 28, 2011
Published online: July 15, 2011

