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Diastereoselective Synthesis of *cyclo*Saligenyl-Nucleosyl-Phosphotriesters

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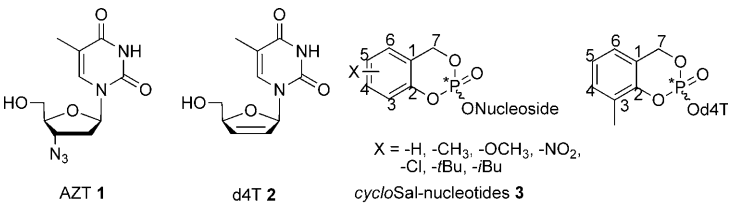
Abstract: A diastereoselective synthesis of *cyclo*Sal-phosphotriesters (*cyclo*-Sal = *cyclo*Saligenyl) based on chiral auxiliaries has been developed that allows the synthesis of single diastereomers of the *cyclo*Sal-pronucleotides. In previously described synthesis routes, the *cyclo*Sal-compounds were always obtained as 1:1 diastereomeric mixtures that could be separated in only rare cases. However, it was shown that the diastereomers have different antiviral activity, toxicity, and hydrolysis stabilities. Here, first a chiral thiazoline derivative was used to prepare nonsubstituted and 5-methyl-*cyclo*Sal-phosphotriesters in 48 and ≥95% *de* (*de* = diastereomeric excess). However, this approach failed to give the important group of 3-substituted *cyclo*Sal-nucleotides. Therefore, two other chiral groups were discovered that allowed the synthesis of (R_P)- and (S_P)-3-methyl-*cyclo*Sal-phosphotriesters as well. The antiviral activity was found to be five- to 20-fold different between the two individual diastereomers, which proved the importance of this approach.

Keywords: antiviral agents · chiral phosphates · nucleotides · *cyclo*saligenyl · stereoselective synthesis

Introduction

Chiral phosphorus compounds are important target structures. It has been proven that the configuration at the phosphorus atom has an influence on the biological activity while interacting with biomolecules. Therefore, the stereoselective synthesis of such compounds is an important aim to achieve. One application of chiral phosphorus compounds are pronucleotides that act as lipophilic nucleotide precursors, for example, in antiviral chemotherapy. Since the discovery of a new disease in 1981[1] called Acquired Immunodeficiency Syndrome (AIDS) which is caused by the Human Immunodeficiency Virus (HIV),[2] many efforts have been made to inhibit its replication in infected cells. The use of nucleoside analogues, such as 3′-azido-3′-deoxythymidine (AZT; **1**) and 3′-deoxy-2′,3′-didehydrothymidine (d4T; **2**), for the inhibition of the virus-encoded reverse transcriptase (RT) proved to be efficient for the treatment of AIDS.[3] For their antiviral activity, the intracellular activation into the 5′-mono-, 5′-di-, and the ultimately biological active 5′-triphosphates by cellular nucleoside kinases or 5′-nucleotidases is necessary after cell penetration of the nucleoside analogues.[4,6]



However, these phosphorylation steps represent a critical point because the first phosphorylation step of d4T (**2**) into 3′-deoxy-2′,3′-didehydrothymidine-5′-monophosphate (d4TMP) catalyzed by thymidine kinase (TK) is the rate-limiting step in human cells and the conversion of 3′-azido-3′-deoxythymidine-5′-monophosphate (AZTMP) into AZT diphosphate (AZTDP) mediated by thymidylate kinase is the metabolic bottleneck in the case of AZT.[7,9] In principle, the direct administration of nucleotides, such as d4TMP, should bypass the limiting step in the thymidine kinase-

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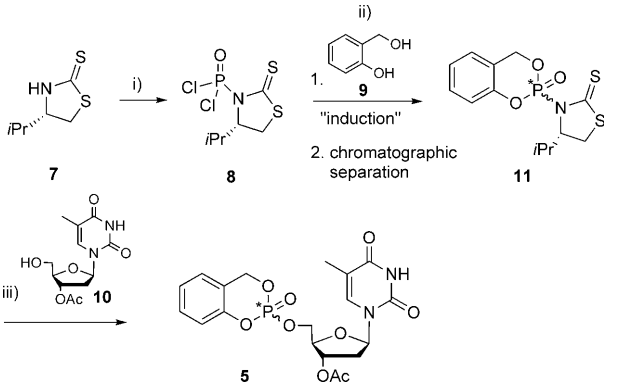
mediated anabolism and thus improve their biological activity. However, nucleotides are very polar molecules and do not passively pass cellular membranes. Therefore, strategies have been developed to mask the charged phosphate by using (bio)degradable lipophilic carrier groups that release the 5′-nucleotides after cellular uptake (pronucleotide approach).[10] Thus, pronucleotides are membrane-permeable nucleotide precursors. Several pronucleotide strategies have been reported for nucleotide delivery, for example, the mixed-SATE compounds,[11] the HepDirect technique,[12] the phosphoramidates,[13] the *cyclo*Sal-phosphate triesters **3**,[14] and recently a first approach for the intracellular delivery of nucleoside diphosphates.[15] Due to their synthesis, all P-chiral pronucleotides are obtained as 1:1 mixtures of diastereomers with respect to the configuration at the phosphorus center.[13,14] The mixtures of diastereomers can be separated in only rare cases. However, it has been shown that the individual diastereomers of the pronucleotides showed significantly different antiviral activity, toxicity, and hydrolysis stabilities, for example, in the case of the *cyclo*Sal compounds **3**.[14] It was found that one isomer of 3-methyl-*cyclo*Sal-d4TMP **4** was 11-fold more active against HIV than the other one.[16] Moreover, only one isomer of **4** was found to be a strong inhibitor of the enzyme butyrylcholinesterase.[17] Although in previous studies a few *cyclo*Sal-triesters could be separated by using semipreparative HPLC,[16,18] currently there is no synthesis route to prepare isomerically pure *cyclo*Sal-pronucleotides.

Here, we report on a convergent synthesis leading to *cyclo*Sal-pronucleotides **3** with very high diastereoselectivities based on the chiral auxiliary strategy. First, the studies were focused on the synthesis of both diastereomers of *cyclo*Sal-(3′-*O*-acetyl)-thymidine monophosphate (*cyclo*Sal-(3′-*O*Ac)-dTMP; **5**) as model compounds (Scheme 1). The approach was later applied to the synthesis of (R_P)- and (S_P)-3-methyl-*cyclo*Sal-3′-azido-3′-deoxythymidine monophosphate (3-Me-*cyclo*Sal-AZTMP; **6**). It should be noted, that all *cyclo*Sal-AZTMP derivatives prepared in the past proved to be inseparable even by HPLC chromatography. Finally, also the diastereoselective preparation of the important (R_P)- and (S_P)-3-methyl-*cyclo*Sal-derivatives of d4TMP **4** will be reported.

Results and Discussion

The developed synthesis route for diastereomerically pure *cyclo*Sal-phosphotriesters is based on chiral auxiliaries and consists of three steps: 1) the reaction of (*S*)-4-isopropyl-2-mercapto-2-thiazoline (**7**) with $P(O)Cl_3$ to introduce the chiral auxiliary in the earliest step, 2) esterification of the formed dichlorophosphoramidate **8** with salicylalcohol **9** to give the chiral phosphoramidate **11**, and 3) the substitution of the chiral auxiliary by the protected nucleoside 3′-*O*Ac-thymidine (dT_{OAc})[19] **10** (Scheme 1).

Besides the stereochemical induction, the auxiliary has to fulfill two further important criteria: 1) it should lead to chromatographically separable diastereomers in the second step and 2) it has to be replaced selectively by the nucleoside (or an analogue) in the last step of the reaction sequence under mild reaction conditions. Briefly, first prolinol derivatives followed by oxazolidinone derivatives of the Evans-type were investigated as chiral auxiliaries. Despite very good stereoselectivities obtained with the first group of compounds, these groups could not be substituted by the nucleoside without degradation due to the harsh reaction conditions that were necessary. The second group of compounds also gave very good stereoselectivities and some of them proved to be suitable for replacement in the nucleophilic reaction introducing the nucleoside **10**. However, the chiral intermediates were found to be inseparable by chromatography and hence these compounds **11** could not be used as stereochemically pure starting materials in the last step (step iii, Scheme 1). Finally, the use of (*S*)-4-isopropyl-2-mercapto-2-thiazoline (**7**) as a potentially suitable chiral auxiliary was the result of an in-depth developing process that will be summarized in a further publication.



Scheme 1. Stereoselective synthesis of *cyclo*Sal-nucleotide (S_P)/(R_P)-**5** by starting from thiazoline **7**. Reagents: i) $P(O)Cl_3$, CH_2Cl_2, NEt_3; ii) 1) salicylalcohol **9**, DBU, acetone, 2) chromatographic separation; iii) dT_{OAc} **10**, *tert*-BuMgCl. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

The thiazoline **7** was reacted with $P(O)Cl_3$ to give the dichlorophosphoramidate **8**, which was too unstable to be purified by column chromatography. Nevertheless, the crude product was pure enough to be used in the following reaction. The dichloridate **8** was then reacted with salicylalcohol **9** to yield the *cyclo*Sal-phosphoramidate **11** in 43% chemical yield in a ratio of 94:6 (88% *de*) as determined by ^{31}P NMR spectroscopy. By silica gel column chromatography, the stereochemically pure "major" and "minor" diastereomers were obtained. The (S_P)-configuration of the minor diastereomer was attributed by X-ray crystal structure analysis (Figure 1). Thus, the major diastereomer had the (R_P)-configuration. The chirality at phosphorus was assigned according to the Cahn–Ingold–Prelog rules.

The displacement of **7** from the diastereomerically pure *cyclo*Sal-phosphoramidates (R_P)-**11** with dT_{OAc} **10** led to the corresponding *cyclo*Sal-nucleotide (S_P)-**5** in 46% yield and a diastereomeric excess of $\geq$95% *de* (Scheme 1). The assignment of the configuration at the phosphorus atom in prod-

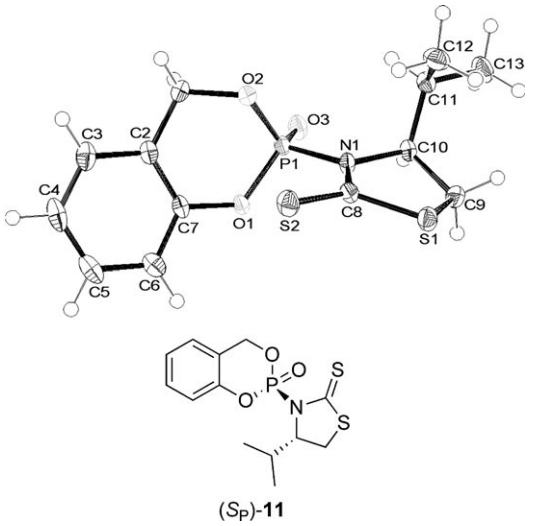


Figure 1. ORTEP illustration of the (S_P)-**11**-diastereomer.

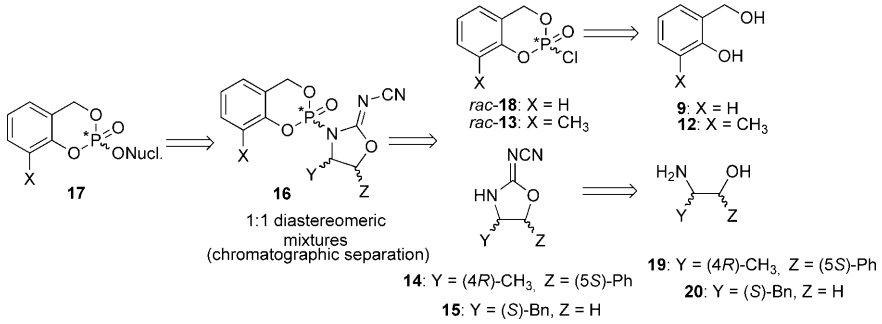
uct (S_P)-**5** was done by the assumption that the substitution reaction took place with inversion of the configuration (S_NP reaction). Hence, in this case the chiral auxiliary fulfilled all three requirements mentioned above.

The same pathway was also successfully used for the synthesis of 5-substituted *cyclo*Sal-pronucleotides (e.g. a 5-methyl-*cyclo*Sal-(3′-*O*Ac)-dTMP, 45% yield, $\geq$95% *de*). However, the synthesis of the 3-methyl-*cyclo*-Sal-derivative failed when using this reaction sequence because surprisingly the second step did not led to the expected chiral *cyclo*Sal-phosphoramidate **11**. Presumably, the substituent at the 3-position caused unfavorable steric interactions in this reaction and after some unsuccessful variations of the reaction conditions it became clear that **7** is not suitable for the synthesis of the 3-substituted *cyclo*Sal-counterparts. However, because particularly 3-substituted *cyclo*Sal-pronucleotides of nucleoside analogues showed very interesting antiviral activities by intracellular nucleotide delivery, enzyme-inhibition, and hydrolysis properties a different synthetic strategy was developed that allows access to these important compounds.

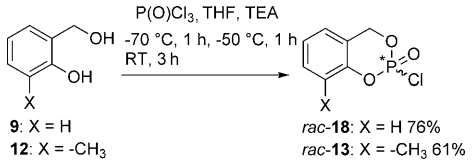
The following concept was envisaged: The 3-methyl salicylalcohol **12** should be first reacted with $P(O)Cl_3$ to give *cyclo*Sal-phosphorochlorides *rac*-(**13**). The reaction of the thiazoline **7** and chiral *N*-cyaniminooxazolidines **14** and **15** with the *cyclo*Sal derivative *rac*-(**13**) should lead to a diastereomeric mixture of the *cyclo*Sal-amidate **11** or **16**. This mixture has to be easily separable into the individual diastereomers. Finally, the nucleoside will be introduced. Again, dT_{OAc} **10** was used first. As a consequence, here the chiral compound was not used as an auxiliary but helps to achieve the separation of the diastereomers and acts as a good leaving group in the last step. The retrosynthesis for the preparation of isomerically pure 3-alkylated *cyclo*Sal-pronucleotides is summarized in Scheme 2.

3-Methyl-salicylic acid was reduced with $LiAlH_4$ leading to the corresponding salicylalcohol **12** in 80% yield.[20] Compounds **18** and **13** were obtained as a racemic mixture after esterification of two salicylalcohols **9** and **12** with $P(O)Cl_3$ in 61 and 76% yields (Scheme 3).

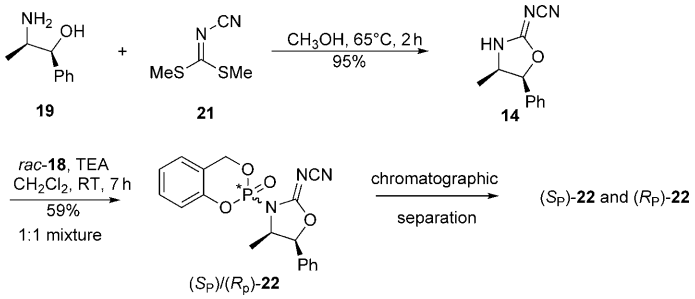
The coupling of thiazoline **7** with the *cyclo*Sal-derivative *rac*-(**13**) led to chromatographically separable diastereomers **11**. However, due to the bulky *iso*-propyl group and the 3-methyl group in the aromatic ring the following substitution by the nucleoside **10** proceeded very slowly with formation of small amounts of the product **11** within several weeks. Thus, more appropriate chiral leaving groups have to be used for this reaction. The chiral group **14** was prepared by the reaction of D-norephedrine (**19**) with dimethylcyanodithioiminocarbonate (**21**) (Scheme 4).



Scheme 2. Retrosynthesis of the route to the *cyclo*Sal-phosphotriesters **17**.



Scheme 3. Synthesis of the phosphochloridates *rac*-**18** and *rac*-**13**. TEA = triethylamine.



Scheme 4. Synthesis of the chiral group **14** and preparation of the single diastereomers (S_P)-**22** and (R_P)-**22**.

Interestingly, compound **14** precipitated during the reaction and the pure product was isolated by simple filtration in 95% yield. The X-ray crystal structure analysis of the chiral compound **14** confirmed the absolute 4*R*,5*S* configuration. The following coupling of **14** with the *cyclo*Sal-phosphorchloridates *rac*-(**18**) led to the formation of the corresponding 1:1 diastereomeric mixture (S_P)/(R_P)-**22** in 59% yield (Scheme 4). The crude mixture of **22** displayed two baseline separated signals in the ^{31}P NMR spectra as depicted in Figure 2. The diastereomers could be easily separated by column chromatography to give the isomerically pure diastereoisomers (S_P)-**22** and (R_P)-**22**.

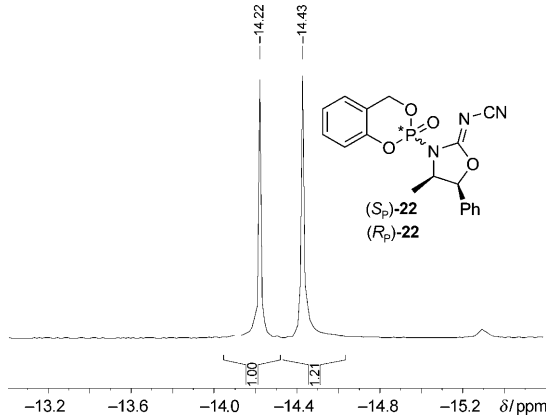


Figure 2. ^{31}P NMR spectrum of the crude diastereomeric mixture of (S_P)-**22** and (R_P)-**22**.

Interestingly, during chromatography on silica gel by using petroleum ether/ethyl acetate (1:2) as the eluent it was observed that one diastereomer of the diastereomeric mixture (S_P)/(R_P)-**22** was chemically less stable than the second one. The more stable (S_P)-isomer **22** crystallized from a mixture of petroleum ether and ethyl acetate and the (S_P)-configuration of the phosphorus center was assigned from the X-ray analysis (Figure 3).[21] The difference in stability was confirmed by DFT calculations (B3LYP/6-311G). The results obtained showed that the (S_P)-isomer **22** was about 39 kcal mol^{-1} more stable than the (R_P)-isomer **22**.

Taking the individual diastereomers of (S_P)-**22** or (R_P)-**22**, in the last step the chiral leaving group was substituted by dT_{OAc} **10**. Several attempts have been tried and among those

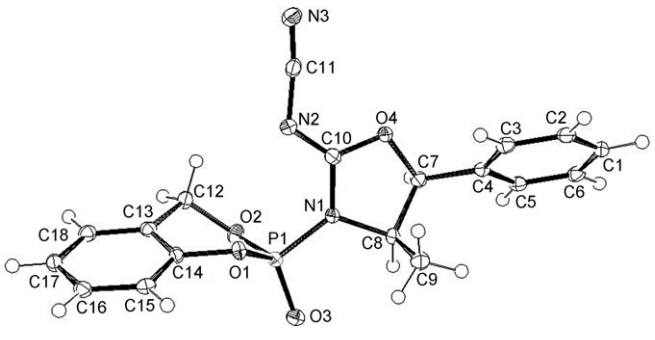
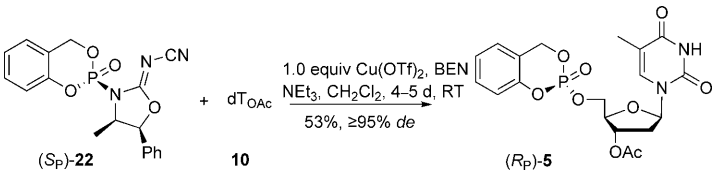


Figure 3. ORTEP illustration of the (S_P)-isomer **22**.

the addition of a strong base, such as alkylmagnesium halide, the reaction conditions used by Jones et al., or a combination of both were successful (Scheme 5).[22] The ability of copper(II)triflate ($Cu(OTf)_2$) in combination with a



Scheme 5. Diastereoselective synthesis of (R_P)-*cyclo*Sal-(3′-OAc)-dTMP (**5**).

ligand like *N*,*N*′-ethylenebis(benzaldiimine) (BEN) to catalyze phosphorylation of primary, secondary, and tertiary alcohols with achiral dialkylphosphoamidates was reported by Jones and Smanmoo.[22] In our case, the combination of $Cu(OTf)_2$, BEN, as well as the addition of a base for the deprotonation of the nucleoside led to the formation of (R_P)-*cyclo*Sal-(3′-OAc)-dTMP **5** in 53% yield and with ≥95% *de* (Scheme 5).

Since (R_P)-*cyclo*Sal-triester **5** could not be crystallized, no X-ray data were available proving the absolute configuration at the phosphorus atom. However, assuming that the reaction took place with inversion of configuration, compound **5** must have a (R_P)-configuration because the great majority of the substitution reactions at the phosphate proceed by following an addition–elimination mechanism with inversion of configuration (S_N2-type reaction).[23]

Several base, Lewis acid, and solvent combinations were studied. To our surprise in most of the reactions we observed that the stereochemical purity of the product decreased significantly. The reaction conditions and the corresponding results are summarized in Table 1. The diastereo-

Table 1. Reaction conditions used for the synthesis of (R_P)-*cyclo*Sal-phosphotriester **5**.

	Promoter (1.0 equiv)	Base	Solvent	*de* [%]
1	–	NEt_3	CH_2Cl_2	58
2	–	*t*BuMgCl	THF/CH_3CN	86–90
3	–	*t*BuMgCl	CH_3CN	77
4	–	*i*PropMgCl	THF/CH_3CN	76
5	$Eu(OTf)_3$/BEN	NEt_3	CH_2Cl_2	8
6	$Mg(OTf)_2$/BEN	NEt_3	CH_2Cl_2	63
7	$Cu(OTf)_2$/BEN/DCI	NEt_3	CH_2Cl_2/CH_3CN	47
8	$Cu(OTf)_2$/BEN	*i*PropMgCl	THF/CH_3CN	83
9	$Cu(OTf)_2$/BEN	NEt_3	CH_2Cl_2	≥95

meric excess was calculated from the ^{31}P NMR spectra of the crude reaction mixtures. As an example, the ^{31}P NMR spectrum of the crude material from reaction 9 (Table 1) is shown in Figure 4. According to these results, the [Cu(BEN)]$(OTf)_2$ complex in combination with NEt_3 was found to be optimal for promoting the diastereoselective synthesis to yield (R_P)-*cyclo*Sal-phosphotriester **5**. It should be men-

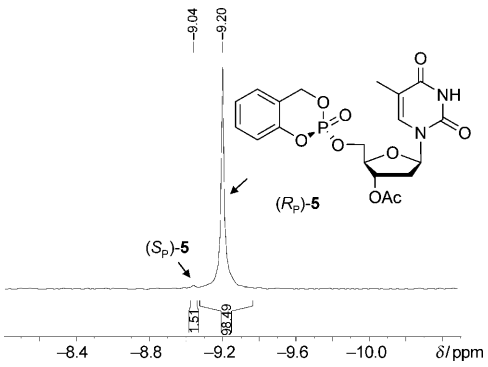


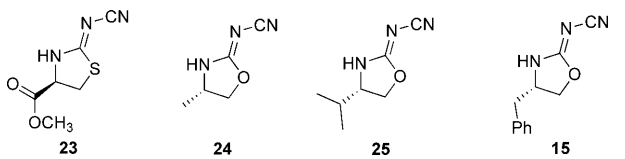
Figure 4. ^{31}P NMR spectroscopic signals of the crude material of (R_P)- and (S_P)-*cyclo*Sal-phosphotriesters **5** (reaction 9, Table 1).

tioned that in all reactions summarized in Table 1 always the same diastereomer was formed preferentially although to different extents.

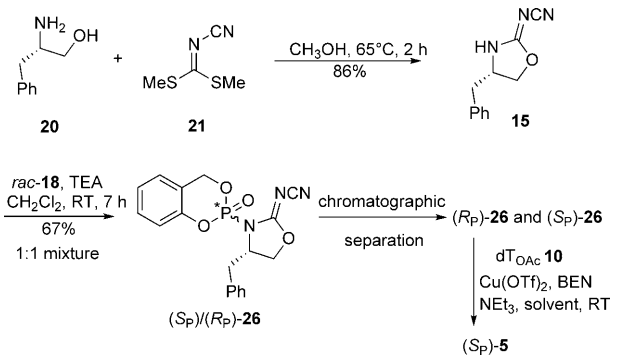
We do not have a solid explanation for the isomerization process that occurred during some of these phosphorylation reactions. According to the literature there are three possible mechanisms for such nucleophilic substitutions at phosphorus, 1) $S_N1(P)$, 2) addition–elimination, and 3) $S_N2(P)$.[24,25] Based on this, it was assumed that in the cases of isomerization the reactions proceeded by a $S_N1(P)$ mechanism by which dissociation of the leaving group produced a planar, tri-coordinate metaphosphate intermediate making this species achiral.

The isomerization observed in the majority of cases could also be explained by an addition–elimination mechanism that involves the formation of a pentavalent intermediate with trigonal bipyramidal (TBP) geometry with two apical positions and three equatorial positions. Polytopal isomerization (pseudorotation) may occur, re-sorting the positions of the residues at the phosphorus in the TBP intermediate.

To synthesize (S_P)-*cyclo*Sal-(3′-OAc)-dTMP **5**, (R_P)-**22** was treated under identical conditions as described above for (S_P)-**22**. Surprisingly, the reaction gave very low yields of 6%, a diastereoselectivity of 93% *de*, and in addition decomposition of the starting material was observed. Again, this confirms that (R_P)-**22** is chemically less stable than its (S_P)-counterpart for unknown reasons. Therefore, another chiral leaving group was needed that forms after coupling with the *cyclo*Sal-phosphorochloridates *rac*-(**18**) chromatographically separable diastereoisomers. In addition to this, the more stable diastereoisomer should lead to the desired (S_P)-*cyclo*Sal-triester **5**. Several chiral compounds analogous to **14** were synthesized by starting from cheap L-amino acids. However, compounds **23**, **24**, and **25** failed to give separable diastereomers at the *cyclo*Sal-phosphoramidate level.



Finally, the chiral compound **15** that was synthesized from L-phenylalaninol (**20**) and dimethylcyanodithioiminocarbonate (**21**) in 86% yield proved to be suitable to achieve the goal (Scheme 6). As observed with compound **14**, the chiral product **15** precipitated during the reaction and was isolated by simple filtration.



Scheme 6. Syntheses of the chiral group **15**, (S_P)-**26** and (R_P)-**26**, and (S_P)-*cyclo*Sal-phosphotriester **5**.

Compound **15** was then coupled with *cyclo*Sal-phosphorochloridate *rac*-(**18**) to the corresponding diastereomer mixture (S_P)/(R_P)-**26** (Scheme 6). The formed diastereomers (S_P)-**26** and (R_P)-**26** were separated by using silica gel column chromatography. After reaction of the now more stable isomer (R_P)-**26** with dT_{OAc} **10**, the (S_P)-*cyclo*Sal-triester **5** was obtained (Scheme 6). The reaction was carried out by using the reaction conditions summarized in Table 2.

Table 2. Reaction conditions used for the synthesis of (S_P)-*cyclo*Sal-phosphotriester **5**.

	$Cu(OTf)_2$/BEN	solvent	*t* [d]	*de* [%]	Yield [%]
1	–	CH_2Cl_2	2	24	–[a]
2	0.2 equiv	CH_2Cl_2	7	83	9
3	0.5 equiv	CH_2Cl_2/CH_3CN 1:1	5	85	12
4	1.0 equiv	CH_2Cl_2	5–7	91	17–24
5	1.0 equiv	CH_3CN	8	≥95	13–18

[a] Not determined.

Triethylamine was used as a base in all reactions. Moreover, variable equivalents of the $[Cu(BEN)](OTf)_2$ complex as well as two solvents were studied. Interestingly, we observed a higher degree of isomerization when employing small amounts of the promoter complex and the best diastereomeric excess was obtained when using one equivalent of the promoter and CH_3CN as the solvent.

The ^{31}P NMR spectrum of the product obtained in reaction 5, Table 2 is depicted in Figure 5. After having identified chiral groups as well as a suitable promoter system, the synthesis of *cyclo*Sal-nucleotides of the antivirally active nucleoside analogues AZT (**1**) and d4T (**2**) was started. As mentioned above in particular 3-methyl- or 3,5-dimethyl-substituted *cyclo*Sal-compounds showed interesting antiviral

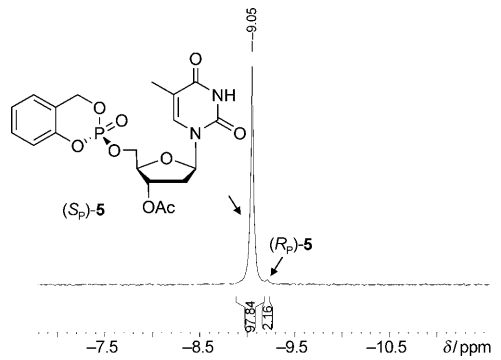
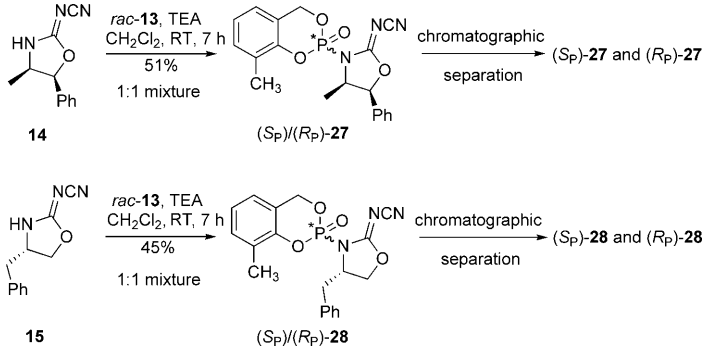


Figure 5. ^{31}P NMR spectroscopic signals of the (S_P)-*cyclo*Sal-triesters **5** with a very small amount of the (R_P)-isomer **5**.

activities and hydrolysis properties at simulated physiological pH values (7.3).[14] Therefore, the following reactions were focused on the synthesis of such compounds.

For this purpose, both chiral leaving groups **14** and **15** were coupled with the *cyclo*Sal-phosphorochloridate *rac*-(**13**) to give the corresponding diastereomeric mixtures (S_P)/(R_P)-**27** and (S_P)/(R_P)-**28** (Scheme 7). Both mixtures were easily separated into the individual diastereomers by using silica gel column



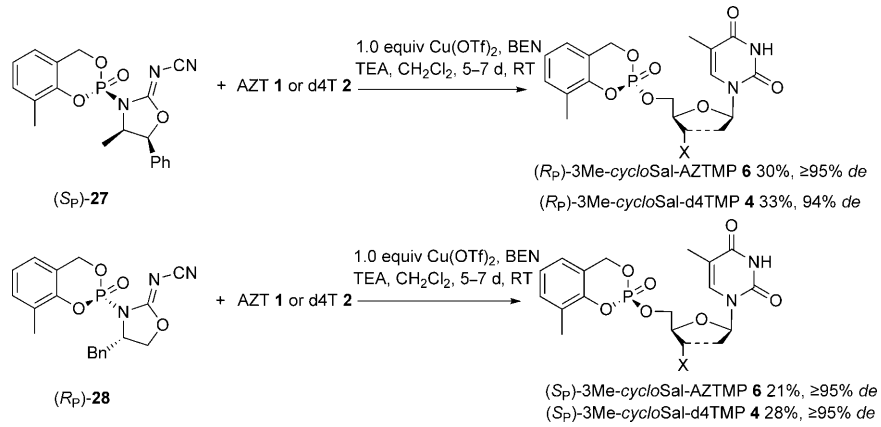
Scheme 7. Preparation of the single diastereomers (S_P)-**27**, (R_P)-**27**, (S_P)-**28**, and (R_P)-**28**.

chromatography and petroleum ether/ethyl acetate (1:2) as the eluent. Again, it was observed that one diastereomer was more stable than the other one.

One possibility to distinguish the diastereomers was the chemical stability properties and the chemical shift of the ^{31}P NMR spectroscopic signals. The correlation of the ^{31}P NMR spectroscopic signal of the stable diastereomer (S_P)-**22** with the signal of the stable diastereomer **27** led us to the assumption that this compound **27** has the (S_P)-configuration as well.

Each stable isomer (S_P)-**27** or (R_P)-**28** was reacted with AZT (**1**) to give the corresponding 3-methyl-*cyclo*Sal-AZTMP (R_P)-**6** and (S_P)-**6** in 30 and 21% yields, respectively (Scheme 8), which were characterized by means of ^{1}H-, ^{13}C-, IR-, and ^{31}P NMR spectroscopy as well as HR fast-atom bombardment (HR-FAB) MS after chromatographic purification. The observed diastereomeric excess for both compounds (S_P)-**6** and (R_P)-**6** was $\geq$95% *de* as shown in the ^{31}P NMR spectra of the crude mixture (Figures 6 and 7).

Again, the conversion of the less stable diastereomers **27** and **28** with AZT (**1**) produced a complex mixture of products and decomposition of the starting phosphoroamide. According to the ^{31}P NMR spectra and TLC a small amount of the desired products (R_P)-**6** and (S_P)-**6** was also formed but their purification was not successful.



Scheme 8. Synthesis of the title compounds (R_P)-**6**, (S_P)-**6**, (R_P)-**4**, and (S_P)-**4**.

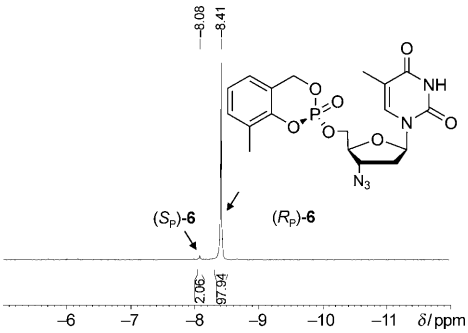


Figure 6. ^{31}P NMR spectroscopic signals of the crude mixture of 3-methyl-*cyclo*Sal-AZTMP (R_P)-**6** and (S_P)-**6**.

Next, (R_P)- and (S_P)-3-methyl-*cyclo*Sal-d4TMPs **4** were prepared by using the same chiral entities and the same reaction conditions. Compounds (S_P)-**27** and (R_P)-**28** were reacted with d4T (**2**) to give the corresponding 3-methyl-*cyclo*Sal-d4TMP (R_P)-**4** and (S_P)-**4** in 33 (94% *de*) and 28% ($\geq$95 *de*) yield, respectively. Analogous reactions by using 3,5-dimethyl-salicylalcohol led by the same route to the corresponding diastereomers of 3,5-dimethyl-*cyclo*Sal-d4TMP (S_P)/(R_P)-**29** (data not shown).

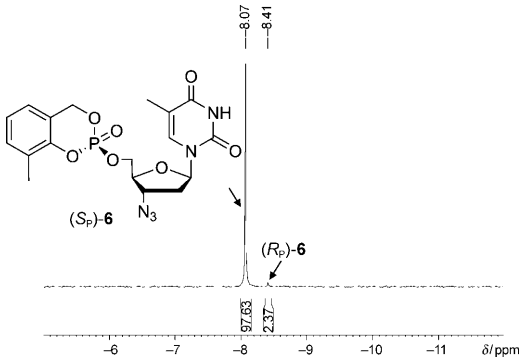


Figure 7. ^{31}P NMR spectroscopic signals of the crude mixture of 3-methyl-*cyclo*Sal-AZTMP (R_P)-**6** and (S_P)-**6**.

Antiviral evaluation: 3-Methyl-*cyclo*Sal-AZTMP (R_P)-**6** and (S_P)-**6** and 3-methyl-*cyclo*Sal-d4TMP (R_P)-**4** and (S_P)-**4** were evaluated for their antiviral potencies against HIV-1- and HIV-2-infected CEM/0 and HIV-2-infected CEM/TK$^-$ cells (Table 3). In addition, the values of 3,5-dimethyl-*cyclo*Sal-d4TMP (S_P)/(R_P)-**29**[16] and for comparison the values for the parent nucleoside analogues AZT (**1**) and d4T (**2**) are also given.

Table 3. Anti-HIV activity of (R_P)- or (S_P)-*cyclo*Sal-nucleotides **4**, **6**, and **29** in CEM/0 cells and in thymidine kinase-deficient CEM/TK$^-$ cells.

Comp.	Antiviral Activity EC_{50} [μM][a]			Cytostatic activity CC_{50} [μM][b]
	CEM/0		CEM/TK$^-$	
	HIV-1	HIV-2	HIV-2	
(R_P)-**6**	0.065±0.02	0.14±0.007	20±3.5	119±3.0
(S_P)-**6**	0.091±0.07	0.16±0.028	>50	109±2.0
(R_P)-**4**	0.08±0.0	0.067±0.03	0.063±0.015	11±2.0
(S_P)-**4**	0.42±0.18	1.1±0.78	0.70±0.30	76±40
(R_P)-**29**	0.093±0.02	0.17±0.10	0.08±0.0	17.4±5.0
(S_P)-**29**	0.50±0.17	0.80±0.10	0.38±0.37	22±4.0
AZT **1**	0.016±0.0	0.084±0.08	>250	>250
d4T **2**	0.80±0.03	0.82±0.05	250±0.0	≥250

[a] 50% effective concentration. [b] 50% cytostatic concentration.

The parent AZT **1** proved to be very active against HIV-1 and HIV-2 in CEM/0 cells (EC_{50}=0.016 and 0.084 μM, respectively). As expected, AZT **1** lost its antiviral activity against HIV-2 in CEM/TK$^-$ cells due to the absence of thymidine-kinase. The individual (S_P)- and (R_P)-diastereomers of 3-methyl-*cyclo*Sal-AZTMP **6** also showed antiviral activity against HIV-1 and HIV-2 in CEM/0 cells in virtually the same concentration range as AZT. Interestingly, the antiviral potency of the diastereomers (S_P)/(R_P)-**6** markedly, but partially, lost antiviral potency (~150- to 300-fold) in the CEM/TK$^-$ cell assay, whereas AZT completely lost its antiviral activity (>3,000- to 10,000-fold), thus proving the release of limited but significant amounts of AZTMP from the pronucleotide into the cell. The reason for this loss of activity in the TK-deficient cell line has been studied before in detail.[26] However, a much more beneficial outcome has been observed for the two *cyclo*Sal-d4TMP derivatives **4** and **29**. In both HIV-infected CEM/0 and CEM/TK$^-$ assays, the (R_P)-diastereomer was found to be 5- to 20-fold more active as compared to the (S_P)-diastereomer. Moreover, both diastereomers of the *cyclo*Sal-d4TMP triesters fully kept antiviral activity in the HIV-2-infected CEM/TK$^-$ cell cultures compared to CEM/0 cells. This effect of the *cyclo*-Sal-d4TMP triesters has been studied earlier in more detail.[26] In conclusion, this data perfectly agrees with our earlier observation that the (R_P)-diastereomers always showed higher antiviral activity relative to the (S_P)-isomer. The configurational correlation perfectly agrees with the earlier attribution of configuration, which was based on CD-effects of chromatographically separated *cyclo*Sal-d4TMP triesters.[16]

Conclusion

First results for the stereospecific synthesis of *cyclo*Sal-pronucleotide triesters (S_P)-**4** and (R_P)-**4**, (S_P)-**5** and (R_P)-**5**, and (S_P)-**6** and (R_P)-**6**, by using a chiral auxiliary or suitable chiral leaving groups are disclosed. In the last step of the sequence, the auxiliary or the leaving group is replaced by a nucleoside analogue in a Lewis acid promoted reaction leading to almost diastereomerically pure target compounds although the chemical yields require further improvement. Two different chiral groups were necessary to prepare all possible substitution patterns within the *cyclo*Sal-residue and R_P or S_P configuration at the phosphorus atom. The antiviral activity of each diastereomer against HIV-1- and HIV-2-infected CEM/0 and HIV-2-infected CEM/TK$^-$ cells were evaluated. All diastereomers with the (R_P)-configuration showed significantly higher antiviral activity than the diastereomers with the (S_P)-configuration. Particularly a significant difference between diastereomers **4** and **29** was observed in HIV-2-infected CEM/TK$^-$ cells. Thus, these assays verify the importance of the phosphorus configuration on the antiviral activity. Perspectively, we believe that we have developed a new general access to chiral phosphate derivatives. At least in one further example we have shown that this is indeed the case.[27]

Experimental Section

General: All experiments involving water-sensitive compounds were conducted under scrupulously dry conditions and a nitrogen atmosphere. All solvents were dried over an appropriate drying agent. Triethylamine, dichloromethane, and acetonitrile were dried by heating under reflux over calcium hydride for several days followed by distillation. Dichloromethane was stored over activated 4 Å molecular sieves and acetonitrile over 3 Å molecular sieves. THF was dried by heating under reflux over potassium and benzophenone followed by distillation. Ethyl acetate, petroleum ether 50–70, dichloromethane, and methanol for chromatography were distilled before use. Evaporation of solvents was carried out on a rotary evaporator under reduced pressure or by using a high-vacuum pump. Column chromatography was performed by using Merck silica gel 60, 230–400 mesh. Analytical TLC was performed on Merck precoated aluminum plates $60F_{254}$ with a 0.2 mm layer of silica gel containing a fluo-

rescent indicator; sugar-containing compounds were visualized with the sugar spray reagent (0.5 mL of 4-methoxybenzaldehyde, 9 mL of ethanol, 0.1 mL of glacial acetic acid, and 0.5 mL of concentrated sulphuric acid) by heating with a fan. The coupling product of the *cyclo*Sal-mask and the leaving groups was visualized with a 10% solution of potassium permanganate in sodium hydroxide. For some separations a chromatotron (Harrison Research 7924T) with glass plates coated with 1, 2, or 4 mm layers of VWR 60 PF_{254} silica gel containing a fluorescent indicator (VWR no. 7749) was used.

Instrumentation: ^{1}H NMR spectroscopy was carried out by using a Bruker AMX 400 at 400 MHz, Bruker DMX 500 at 500 MHz, or Bruker AV 400 at 400 MHz with $CDCl_3$ or [D_6]DMSO as the internal standard. ^{13}C NMR spectra were recorded on a Bruker AMX 400 at 101 MHz or Bruker AV 400 at 101 MHz ($CDCl_3$ or [D_6]DMSO as the internal standard). ^{31}P NMR spectra were recorded on a Bruker AMX 400 at 162 MHz (H_3PO_4 as the internal standard). All ^{1}H, ^{31}P, and ^{13}C NMR chemical shifts are quoted in ppm. 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 the X-ray crystal structure analyses, data collection was done with a Bruker Smart APEX CCD area detector diffractometer. Analytical HPLC: LiChroCART 250–4 with LiChrospher 100 RP-18 (5 μm) standard gradient (Gradient I: 18–100% CH_3CN in water (0–16 min), 100% CH_3CN (16–19 min), 18% CH_3CN (19–31), flow rate 0.5 mL min^{-1}; UV detection at 269 nm). Gradient II: 0–100% CH_3CN (0–18 min), 100% CH_3CN (18.1–20 min), 0% CH_3CN (20.1–33 min); flow rate 0.5 mL min^{-1}; UV detection at 265 nm The purity of *cyclo*Sal-nucleotides was checked by means of HPLC and was in all cases $\geq$95%.

Preparation of [(*S*)-4-isopropylthiazolidine-2-thione]phosphorodichloridate (8): A solution of (*S*)-4-isopropylthiazolidine-2-thione (**7**) (0.52 g, 3.2 mmol, 1.0 equiv) and phosphoryl chloride (0.91 mL, 9.7 mmol, 3.0 equiv) in CH_2Cl_2 (20 mL) was cooled to 0°C. NEt_3 (0.49 mL, 3.5 mmol, 1.1 equiv) in CH_2Cl_2 (10 mL) was added dropwise. Following the addition, the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The solvent was removed under reduced pressure and the residue was suspended in CH_2Cl_2 (1 mL) and Et_2O (15 mL). The precipitated triethylammonium chloride was filtered under nitrogen and washed with Et_2O (5 mL). The solvent of the filtrate was removed under reduced pressure to give the crude product **8** as an oil. Further purification was not possible due to high reactivity but the ^{31}P NMR spectrum in $CDCl_3$ showed only one signal at $\delta = 4.4$ ppm.

Preparation of 2-(4′-isopropyl-thiazolidin-2′-thion-3′-yl)(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide ((*R*$_P$)-11): A solution of [(*S*)-4-isopropylthiazolidine-2-thione]phosphorodichloridate (**8**) (0.89 g, 3.2 mmol, 1.0 equiv) and salicylalcohol (**9**) (0.40 g, 3.2 mmol, 1.0 equiv) in acetone was cooled to −91°C. DBU (0.48 mL, 3.2 mmol, 1.0 equiv) was added dropwise. After 1 to 12 h at −91°C, the reaction was quenched with saturated ammonium chloride solution and extracted with CH_2Cl_2 three times. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (petroleum ether 50–70/EtOAc 1:2). The product (*R*$_P$)-**11** (0.45 g, 1.4 mmol, 43%) was obtained as a pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$–7.28 (m, 1H; H arom.), 7.15–7.03 (m, 3H; H arom.), 5.62 (dd, 1H, $^{2}J_{H-H} = 14.0$, $^{3}J_{H-P} = 14.0$ Hz; H-4), 5.52 (dd, 1H, $^{2}J_{H-H} = 14.0$, $^{3}J_{H-P} = 14.0$ Hz; H-4′), 4.92–4.86 (m, 1H; H-13), 3.76 (dd, 1H, $^{3}J_{H-H} = 11.5$, $^{3}J_{H-H} = 8.3$ Hz; H-12), 3.18 (ddd, 2H, $^{3}J_{H-H} = 11.5$, $^{3}J_{H-H} = 1.8$, $^{4}J_{H-P} = 0.8$ Hz; H-12′), 2.59–2.45 (m, 1H; H-14), 1.14 (d, 3H, $^{3}J_{H-H} = 6.8$ Hz; H-15), 1.13 ppm (d, 3H, $^{3}J_{H-H} = 7.1$ Hz; H-15′); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = -11.0$ ppm.

General procedure A

*Preparation of 2-chloro(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide derivatives* rac-*(13) and* rac-*(18)*: A solution of the *cyclo*Sal-alcohol **12** or **9** (1.0 equiv) and triethylamine (2.1 equiv) in THF was added dropwise within 1 h to a stirred solution of $P(O)Cl_3$ (1.1 equiv) in THF at −70°C. The reaction was allowed to warm to −50°C and stirred for 1 h. The reaction mixture was then allowed to warm to room temperature and stirred for 4 h. The triethylammonium chloride was filtered. The solvent was removed under reduced pressure by using a high-vacuum pump. The crude product was purified by column chromatography on silica gel (petroleum ether 50–70/ethyl acetate 1:1).

General procedure B

*Preparation of the leaving groups **14** and **15***: 2-Amino alcohol **19** or **20** (1.0 equiv) was added to a solution of dimethylcyanodithioiminocarbonate (**21**) (1.0 equiv) in methanol. The reaction mixture was heated for 3 h under reflux and then stirred at room temperature for 15 h. The originating methanethiol was oxidized to methanesulfonic acid by using nitric acid. The product was filtered, washed with cold petroleum ether, and dried under reduced pressure.

General procedure C

Preparation of the diastereomeric mixtures as precursors: A solution of 2-chloro(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide derivative *rac*-**13** or *rac*-**18** (1.0–1.5 equiv) in dichloromethane was added to a suspension of the leaving group **14** or **15** (1.0 equiv) and triethylamine (1.1 equiv) in dichloromethane at room temperature. The reaction mixture was stirred for 5–10 h at room temperature. The solvent was removed under reduced pressure by using a high-vacuum pump. Ethyl acetate was added, the reaction mixture was stirred for 30 min at room temperature and stored for 2 h at 0°C. The precipitated salt was filtered, the solvent removed, and the crude product was purified by column chromatography on silica gel (petroleum ether 50–70/ethyl acetate 1:2).

General procedure D

Preparation of the cyclo*Sal-phosphotriesters*: A solution of isomerically pure diastereomer (1.0 equiv), copper(II)triflate (1.0 equiv), and BEN (1.0 equiv) in dichloromethane or acetonitrile was stirred for 30 min and added to a solution of AZT (**1**) or d4T (**2**) (3.0 equiv) and triethylamine (3.0 equiv) in dichloromethane at room temperature. The reaction mixture was stirred for days and quenched with saturated ammonium chloride solution and extracted with dichloromethane three times. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (dichloromethane/methanol 19:1).

2-Chloro(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide (*rac*-(**18**)): General procedure A with salicylalcohol (**9**) (6.00 g, 48.3 mmol), triethylamine (14.1 mL, 0.101 mol) dissolved in THF (90 mL), and phosphoryl chloride (8.15 g, 53.2 mmol) in THF (70 mL). The product *rac*-(**18**) (7.53 g, 76%) was obtained as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.41$–7.33 (m, 1H; H-arom.), 7.25–7.19 (m, 1H; H-arom.), 7.16–7.07 (m, 2H; H-arom.), 5.55–5.42 ppm (m, 2H; H-4); ^{31}P NMR(162 MHz, $CDCl_3$): $\delta = -6.00$ ppm.

2-Chloro-8-methyl(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide (*rac*-(**13**)): General procedure A with 3-methyl-salicylalcohol **12** (2.50 g, 18.1 mmol), triethylamine (5.29 mL, 38.0 mol) dissolved in THF (40 mL), and phosphoryl chloride (3.05 g, 19.9 mmol) in THF (40 mL). The product *rac*-(**13**) (2.39 g, 61%) was obtained as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.25$–7.20 (m, 1H; H-7), 7.11 (dd, 1H, $^{3}J_{H-H} = 7.6$, $^{3}J_{H-H} = 7.6$ Hz; H-6), 6.94 (d, 1H, $^{3}J_{H-H} = 7.6$ Hz; H-5), 5.51–5.43 (m, 2H; H-4), 2.31 ppm (s, 3H; CH_3); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = -5.01$ ppm.

(4*R*,5*S*)-4-Methyl-5-phenyl-2-(*N*-cyanimino)oxazolidine (14): General procedure B with (1*S*,2*R*)-2-amino-1-phenylpropan-1-ol (**19**) (4.96 g, 32.8 mmol) and dimethylcyanodithioiminocarbonate (**21**) (4.80 g, 32.8 mmol) in methanol (30 mL). The product **14** (6.32 g, 95%) was obtained as a colorless solid. ^{1}H NMR (400 MHz, [D_6]DMSO): $\delta = 9.56$ (s, 1H; N-H), 7.50–7.35 (m, 3H; H-arom.), 7.33–7.26 (m, 2H; H-arom.), 6.05 (d, 1H, $^{3}J_{H-H} = 8.5$ Hz; H-5), 4.50–4.38 (m, 1H; H-4), 0.68 ppm (d, 3H, $^{3}J_{H-H} = 6.6$ Hz; H-6).

(*S*)-4-Benzyl-2-(*N*-cyanimino)oxazolidine (15): General procedure B with L-phenylalaninol (**20**) (2.59 g, 17.1 mmol) and dimethylcyanodithioiminocarbonate (**21**) (2.50 g, 17.1 mmol) in methanol (25 mL). The product **15** (2.92 g, 86%) was obtained as a colorless solid. ^{1}H NMR (400 MHz, [D_6]DMSO): $\delta = 9.55$ (s; N-H), 7.37–7.22 (m, 5H; H-arom.), 4.63–4.56 (m, 1H; H-5), 4.40–4.31 (m, 2H; H-5′, H-4), 2.93–2.80 ppm (m, 2H; H-7).

(*R*$_P$4′*R*$_C$,5′*S*$_C$)- and (*S*$_P$4′*R*$_C$,5′*S*$_C$)-2-(4′-Methyl-5′-phenyl-2′-*N*-cyanimino-oxazo-lidin-3′-yl)(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide (22): General procedure C with (4*R*,5*S*)-4-methyl-5-phenyl-2-(*N*-cyanimino)oxazolidine

(**14**) (0.804 g, 4.00 mmol) in dichloromethane (40 mL), 2-chloro(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide (*rac*-(**18**)) (0.820 g, 4.00 mmol) in dichloromethane (15 mL), and triethylamine (0.61 mL, 0.445 g, 4.40 mmol). The product (S_P)/(R_P)-**22** (0.860 g, 59%) was obtained as a colorless foam as a diastereomeric mixture, which was then separated by column chromatography.

Product ($S_B4'R_C5'S_C$)-***22***: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.34 (m, 4H; H-arom.), 7.32–7.29 (m, 2H; H-arom.), 7.23–7.18 (m, 1H; H-arom.), 7.16–7.12 (m, 1H; H-arom.), 7.11–7.09 (m, 1H; H-arom.), 6.04 (d, 1H, $^3J_{H-H}$ = 7.3 Hz; H-12), 5.84 (dd, 1H, $^2J_{H-H}$ = 13.3, $^3J_{H-P}$ = 10.7 Hz; H-4), 5.39 (dd, 1H, $^2J_{H-H}$ = 13.4, $^3J_{H-P}$ = 18.8 Hz; H-4′), 4.88–4.77 (m, 1H; H-13), 1.09 ppm (d, 3H, $^3J_{H-H}$ = 6.7 Hz; H-14); ^{31}P NMR (162 MHz, $CDCl_3$): δ = −14.43 ppm.

Product ($R_B4'R_C5'S_C$)-***22***: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.34 (m, 4H; H-arom.), 7.32–7.28 (m, 2H; H-arom.), 7.23–7.16 (m, 1H; H-arom.), 7.15–7.12 (m, 1H; H-arom.), 7.11–7.08 (m, 1H; H-arom.), 6.03 (d, 1H, $^3J_{H-H}$ = 7.3 Hz; H-12), 5.84 (dd, 1H, $^2J_{H-H}$ = 13.3, $^3J_{H-P}$ = 10.8 Hz; H-4), 5.39 (dd, 1H, $^2J_{H-H}$ = 13.4, $^3J_{H-P}$ = 18.8 Hz; H-4′), 4.84–4.80 (m, 1H; H-13), 1.09 ppm (d, 3H, $^3J_{H-H}$ = 6.7 Hz; H-14); ^{31}P NMR (162 MHz, $CDCl_3$): δ = −14.14 ppm.

(R_P4′S_C)- and (S_P4′S_C)-2-(4′-Benzyl-2′-*N*-cyanimino-oxazolidin-3′-yl)(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide (26): General procedure C with (*S*)-4-benzyl-2-(*N*-cyanimino)oxazolidine (**15**) (0.760 g, 3.78 mmol) in dichloromethane (40 mL), 2-chloro(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide (*rac*-(**18**)) (0.774 g, 3.78 mmol) in dichloromethane (15 mL), and triethylamine (0.58 mL, 0.451 g, 4.16 mmol). The product (S_P)/(R_P)-**26** (0.940 g, 67%) was obtained as a colorless foam as a diastereomeric mixture, which was then separated by column chromatography.

Product ($R_B4'S_C$)-***26***: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.11 (m, 9H; H-arom.), 5.79 (dd, 1H, $^2J_{H-H}$ = 12.9, $^3J_{H-P}$ = 12.2 Hz; H-4), 5.47 (dd, 1H, $^2J_{H-H}$ = 13.4, $^3J_{H-P}$ = 16.8 Hz; H-4′), 4.81–4.71 (m, 1H; H-13), 4.58–4.50 (m, 1H; H-12), 4.50–4.45 (m, 1H; H-12′), 3.50 (dd, 1H, $^2J_{H-H}$ = 13.6, $^3J_{H-H}$ = 3.6 Hz; H-14), 3.01 ppm (dd, 1H, $^2J_{H-H}$ = 13.6, $^3J_{H-H}$ = 9.6 Hz; H-14′); ^{31}P NMR (162 MHz, $CDCl_3$): δ = −14.33 ppm.

Product ($S_B4'S_C$)-***26***: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5H; H-arom.), 7.27–7.23 (m, 1H; H-arom.), 7.23–7.17 (m, 1H; H-arom.), 7.16–7.11 (m, 1H; H-arom.), 7.10–7.05 (m, 1H; H-arom.), 5.87 (dd, 1H, $^2J_{H-H}$ = 13.3, $^3J_{H-P}$ = 10.5 Hz; H-4), 5.43 (dd, 1H, $^2J_{H-H}$ = 13.4, $^3J_{H-P}$ = 19.0 Hz; H-4′), 4.83–4.74 (m, 1H; H-13), 4.60–4.52 (m, 1H; H-12), 4.52–4.45 (m, 1H; H-12′), 3.40 (dd, 1H, $^2J_{H-H}$ = 13.6, $^3J_{H-H}$ = 3.5 Hz; H-14), 2.99 ppm (dd, 1H, $^2J_{H-H}$ = 13.6, $^3J_{H-H}$ = 9.4 Hz; H-14′); ^{31}P NMR (162 MHz, $CDCl_3$): δ = −14.17 ppm.

(R_P4′R_C,5′S_C)- and (S_P4′R_C,5′S_C)-8,4′-Dimethyl-2-(5′-phenyl-2′-*N*-cyanimino-oxazolidin-3′-yl)(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide (27): General procedure C with (4*R*,5*S*)-4-methyl-5-phenyl-2-(*N*-cyanimino)oxazolidine (**14**) (0.500 g, 2.49 mmol) in dichloromethane (20 mL), 2-chloro-8-methyl(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide (*rac*-(**13**)) (0.817 g, 3.74 mmol) in dichloromethane (20 mL), and triethylamine (0.42 mL, 0.302 g, 2.99 mmol). The product (S_P)/(R_P)-**27** (0.582 g, 61%) was obtained as a colorless foam and as a diastereomeric mixture, which was then separated by column chromatography.

Product ($S_B4'R_C5'S_C$)-***27***: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.40 (m, 3H; H-arom.), 7.34–7.29 (m, 2H; H-arom.), 7.24–7.20 (m, 1H; H-arom.), 7.09 (dd, 1H, $^3J_{H-H}$ = 7.6, $^3J_{H-H}$ = 7.6 Hz; H-6), 6.99–6.95 (m, 1H; H-arom.), 6.01 (d, 1H, $^3J_{H-H}$ = 7.1 Hz; H-13), 5.78 (dd, 1H, $^2J_{H-H}$ = 12.9, $^3J_{H-P}$ = 12.8 Hz; H-4), 5.43 (dd, 1H, $^2J_{H-H}$ = 13.3, $^3J_{H-P}$ = 17.0 Hz; H-4′), 4.87–4.75 (m, 1H; H-14), 2.28 (s, 3H; H-9), 1.15 ppm (d, 3H, $^3J_{H-H}$ = 6.7 Hz; H-15); ^{31}P NMR (162 MHz, $CDCl_3$): δ = −13.25 ppm.

Product ($R_B4'R_C5'S_C$)-***27***: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.40 (m, 3H; H-arom.), 7.34–7.29 (m, 2H; H-arom.), 7.25–7.20 (m, 1H; H-arom.), 7.08 (dd, 1H, $^3J_{H-H}$ = 7.5, $^3J_{H-H}$ = 7.7 Hz; H-6), 6.99–6.94 (m, 1H; H-arom.), 6.06 (d, 1H, $^3J_{H-H}$ = 7.3 Hz; H-13), 5.80 (dd, 1H, $^2J_{H-H}$ = 13.2, $^3J_{H-P}$ = 11.5 Hz; H-4), 5.34 (dd, 1H, $^2J_{H-H}$ = 13.3, $^3J_{H-P}$ = 19.2 Hz; H-4′), 4.89–4.79 (m, 1H; H-14), 2.32 (s, 3H; H-9), 1.09 ppm (d, 3H, $^3J_{H-H}$ = 6.7 Hz; H-15); ^{31}P NMR (162 MHz, $CDCl_3$): δ = −12.88 ppm.

(R_P4′S_C)- and (S_P4′S_C)-8-Methyl-2-(4′-benzyl-2′-*N*-cyanimino-oxazolidin-3′-yl)(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide (28): General procedure C with (*S*)-4-benzyl-2-(*N*-cyanimino)oxazolidine (**15**) (0.380 g, 1.89 mmol) in dichloromethane (30 mL), 2-chloro-8-methyl(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide (*rac*-(**13**)) (0.620 g, 2.84 mmol) in dichloromethane (15 mL), and triethylamine (0.29 mL, 0.210 g, 2.08 mmol). The product (S_P)/(R_P)-**28** (0.325 g, 45%) was obtained as a colorless foam and as a diastereomeric mixture, which was then separated by column chromatography.

Product ($S_B4'S_C$)-***28***: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.31 (m, 3H; H-arom.), 7.28–7.24 (m, 2H; H-arom.), 7.22 (d, 1H, $^3J_{H-H}$ = 7.6 Hz; H-7), 7.09 (dd, 1H, $^3J_{H-H}$ = 7.6, $^3J_{H-H}$ = 7.5 Hz; H-6), 6.97 (d, 1H, $^3J_{H-H}$ = 7.5 Hz; H-5), 5.85 (dd, 1H, $^2J_{H-H}$ = 13, $^3J_{H-P}$ = 11 Hz; H-4), 5.39 (dd, 1H, $^2J_{H-H}$ = 13, $^3J_{H-P}$ = 19.7 Hz; H-4′), 4.89–4.77 (m, 1-H; H-14), 4.58 (dd, 1H, $^3J_{H-H}$ = 7.8, $^2J_{H-H}$ = 9.0 Hz; H-13), 4.51 (ddd, 1H, $^4J_{H-P}$ = 1.6, $^3J_{H-H}$ = 2.8, $^2J_{H-H}$ = 9.2 Hz; H-13′), 3.43 (dd, 1H, $^3J_{H-H}$ = 3.5, $^2J_{H-H}$ = 13.6 Hz; H-15), 2.99 (dd, 1H, $^3J_{H-H}$ = 9.6, $^2J_{H-H}$ = 14 Hz, 1H; H-15′), 2.30 ppm (s, 3H; H-9); ^{31}P NMR (162 MHz, $CDCl_3$): δ = −12.87 ppm.

Product ($R_B4'S_C$)-***28***: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 5H; H-arom.) 7.23 (d, 1H, $^3J_{H-H}$ = 7.6 Hz; H-7), 7.09 (dd, 1H, $^3J_{H-H}$ = 7.6, $^3J_{H-H}$ = 7.6 Hz; H-6), 6.97 (d, 1H, $^3J_{H-H}$ = 7.6 Hz; H-5), 5.74 (dd, 1H, $^2J_{H-H}$ = 13, $^3J_{H-P}$ = 13 Hz; H-4), 5.43 (dd, 1H, $^2J_{H-H}$ = 14, $^3J_{H-P}$ = 17 Hz; H-4′), 4.82–4.74 (m, 1H; H-14), 4.55 (dd, 1H, $^3J_{H-H}$ = 7.8, $^2J_{H-H}$ = 9.0 Hz; H-13), 4.52–4.47 (m, 1H; H-13′), 3.43 (dd, 1H, $^3J_{H-H}$ = 3.0, $^2J_{H-H}$ = 13.6 Hz; H-15), 3.09 (dd, 1H, $^3J_{H-H}$ = 9.1, $^2J_{H-H}$ = 14 Hz; H-15′), 2.34 ppm (s, 3H; H-9); ^{31}P NMR: (162 MHz, $CDCl_3$): δ = −13.05 ppm.

***cyclo*Sal-3′-*O*-acetyl-thymidine monophosphates (R_P)- and (S_P)-5**:

Product (R_P)-***5***: General procedure D with (S_P4′R_C,5′S_C)-2-(4′-methyl-5′-phenyl-2′-*N*-cyanimino-oxazolidin-3′-yl)(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide ((S_P)-**22**) (50.0 mg, 0.135 mmol), BEN (31.9 mg, 0.135 mmol), copper(II)triflate (48.8 mg, 0.135 mmol) in dichloromethane (3 mL), 3′-*O*-acetyl-thymidine **10** (0.115 g, 0.405 mmol), and triethylamine (54 μL, 41.0 mg, 0.405 mmol) in dichloromethane (3 mL). The product (R_P)-**5** (32 mg, 53%, ≥95% *de*) was obtained as a colorless foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (brs, 1H; NH), 7.46 (d, 1H, $^4J_{H-H}$ = 1.0 Hz; H-6), 7.38–7.31 (m, 1H; H-arom.), 7.20–7.14 (m, 1H; H-arom.), 7.12 (dd, 1H, $^4J_{H-H}$ = 1.4, $^3J_{H-H}$ = 7.7 Hz; H-arom.), 7.08 (dd, 1H, $^4J_{H-H}$ = 0.6, $^3J_{H-H}$ = 8.2 Hz; H-arom.), 6.35 (dd, 1H, $^3J_{H-H}$ = 9.1, $^3J_{H-H}$ = 5.4 Hz; H-1′), 5.47 (dd, 1H, $^2J_{H-H}$ = 14.0, $^3J_{H-P}$ = 14.2 Hz; H-10), 5.32 (dd, 1H, $^2J_{H-H}$ = 13.7, $^3J_{H-P}$ = 13.8 Hz; H-10′), 5.26–5.22 (m, 1H; H-3′), 4.49–4.44 (m, 2H; H-5′a, H-5′b), 4.19–4.15 (m, 1H; H4′), 2.41 (ddd, $^3J_{H-H}$ = 1.2, $^3J_{H-H}$ = 5.4, $^2J_{H-H}$ = 14.1 Hz, 1H; H-2′a), 2.10 (s, 3H; H-9), 2.12–2.03 (m, 1H; H-2′b), 1.87 ppm (d, 3H, $^4J_{H-H}$ = 1.1 Hz; H-7); ^{31}P NMR (162 MHz, $CDCl_3$): δ = −9.23 ppm.

Product (S_P)-***5***: General procedure D with (R_P4′S_C)-2-(4′-benzyl-2′-*N*-cyanimino-oxazolidin-3′-yl)(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide (R_P)-**26** (23.0 mg, 0.0622 mmol), BEN (14.7 mg, 0.0622 mmol), copper(II)triflate (22.5 mg, 0.0622 mmol) in acetonitrile (3 mL), 3′-*O*-acetyl-thymidine **10** (53.1 mg, 0.187), and triethylamine (26 μL, 18.9 mg, 0.187 mmol) in acetonitrile (3 mL). The product (S_P)-**5** (4.90 mg, 18%, ≥95% *de*) was obtained as a colorless foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (brs, 1H; NH), 7.46 (d, 1H, $^4J_{H-H}$ = 1.2 Hz; H-6), 7.38–7.31 (m, 1H; H-arom.), 7.20–7.14 (m, 1H; H-arom.), 7.12 (dd, 1H, $^4J_{H-H}$ = 1.4, $^3J_{H-H}$ = 7.6 Hz; H-arom.), 7.08 (dd, 1H, $^4J_{H-H}$ = 0.6, $^3J_{H-H}$ = 8.2 Hz; H-arom.), 6.33 (dd, 1H, $^3J_{H-H}$ = 9.1, $^3J_{H-H}$ = 5.4 Hz; H-1′), 5.44 (dd, 1H, $^2J_{H-H}$ = 14.2, $^3J_{H-P}$ = 14.6 Hz; H-10), 5.34 (dd, 1H, $^2J_{H-H}$ = 13.3, $^3J_{H-P}$ = 13.8 Hz; H-10′), 5.28–5.23 (m, 1H; H-3′), 4.49–4.43 (m, 2H; H-5′), 4.21–4.16 (m, 1H; H4′), 2.44 (ddd, $^3J_{H-H}$ = 1.4, $^3J_{H-H}$ = 5.4, $^2J_{H-H}$ = 14.1 Hz, 1H; H-2), 2.10 (s, 3H; H-9), 2.14–2.04 (m, 1H; H-2′), 1.92 ppm (d, 3H, $^4J_{H-H}$ = 1.2 Hz; H-7); ^{31}P NMR (162 MHz, $CDCl_3$): δ = −9.06 ppm.

3-Methyl-*cyclo*Sal-3′-azido-3′-deoxythymidine monophosphates (S_P)- and (R_P)-6

Product (R_P)-***6***: General procedure D with (S_P4′R_C,5′S_C)-8,4′-dimethyl-2-(5′-phenyl-2′-*N*-cyanimino-oxazolidin-3′-yl)-4*H*-1,3,2-benzodioxaphosphorin-2-oxide ((S_P)-**27**) (74 mg, 0.193 mmol), BEN (45.6 mg, 0.193 mmol), copper(II)triflate (69.8 mg, 0.193 mmol) in dichloromethane (3 mL), AZT (**1**) (0.155 g, 0.579 mmol), and triethylamine (81 μL, 58.6 mg, 0.579 mmol) in dichloromethane (3 mL). The product (R_P)-**6** (26.3 mg, 30%, ≥95% *de*) was obtained as a colorless foam. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.24 (brs, 1H; N-H), 7.32 (q, 1H, $^4J_{H-H}$ = 1.0 Hz;

H-6), 7.20 (dd, 1H, $^{3}J_{H-H}$=7.6, $^{4}J_{H-H}$=0.6 Hz; H-12), 7.06 (dd, 1H, $^{3}J_{H-H}$=7.6, $^{3}J_{H-H}$=7.6 Hz; H-13), 6.95 (dd, 1H, $^{3}J_{H-H}$=7.6, $^{4}J_{H-H}$= 0.6 Hz; H-14), 6.18 (dd, 1H, $^{3}J_{H-H}$=6.5, $^{3}J_{H-H}$=6.6 Hz; H-1′), 5.42 (dd, 1H, $^{2}J_{H-H}$=14.1, $^{3}J_{H-P}$=14.8 Hz; H-8a), 5.30 (dd, 1H, $^{2}J_{H-H}$=13.6, $^{3}J_{H-P}$=13.6 Hz, 1H; H-8b), 4.45 (ddd, 1H, $^{3}J_{H-P}$=11.5, $^{2}J_{H-H}$=7.3, $^{3}J_{H-H}$=3.1 Hz; H-5′a), 4.35 (ddd, 1H, $^{3}J_{H-P}$=14.7, $^{2}J_{H-H}$=7.3, $^{3}J_{H-H}$= 3.1 Hz; H-5′b), 4.34–4.30 (m, 1H; H-3′), 4.07–4.00 (m, 1H; H-4′), 2.45 (ddd, 1H, $^{2}J_{H-H}$=13.9, $^{3}J_{H-H}$=4.5, $^{3}J_{H-H}$=6.3 Hz; H-2′a), 2.34–2.27 (m, 1H; H-2′b), 2.28 (s, 3H; H-15), 1.82 ppm (d, 3H, $^{4}J_{H-H}$=1.1 Hz; H-7); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta=-8.41$ ppm.

Product (S_P)-**6**: General procedure D with (R_B4′S_C)-8-methyl-2-(4′-benzyl-2′-*N*-cyanimino-oxazolidin-3′-yl)(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide ((R_P)-**28**) (46 mg, 0.120 mmol), BEN (28.4 mg, 0.120 mmol), copper(II) triflate (43.4 mg, 0.120 mmol) in dichloromethane (3 mL), AZT (**1**) (96.2 g, 0.360 mmol), and triethylamine (50 μL, 36.4 mg, 0.36 mmol) in dichloromethane (3 mL). The product (S_P)-**6** (11.3 mg, 21%, ≥95% *de*) was obtained as a colorless foam. ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.39 (br s, 1H; N-H), 7.29 (q, 1H, $^{4}J_{H-H}$=1.0 Hz; H-6), 7.20 (d, 1H, $^{3}J_{H-H}$=7.6 Hz; H-12), 7.06 (dd, 1H, $^{3}J_{H-H}$=7.6, $^{3}J_{H-H}$=7.6 Hz; H-13), 6.95 (d, 1H, $^{3}J_{H-H}$=7.6 Hz; H-14), 6.17 (dd, 1H, $^{3}J_{H-H}$=6.5, $^{3}J_{H-H}$=6.5 Hz; H-1′), 5.42 (dd, 1H, $^{2}J_{H-H}$=14.2, $^{3}J_{H-P}$=14.2 Hz; H-8a), 5.29 (dd, 1H, $^{2}J_{H-H}$=14.2, $^{3}J_{H-P}$=13.9 Hz, 1H; H-8b), 4.43–4.38 (m, 2H; H-5′), 4.38–4.33 (m, 1H; H-3′), 4.07–4.02 (m, 1H; H-4′), 2.47 (ddd, 1H, $^{2}J_{H-H}$=14.0, $^{3}J_{H-H}$=4.8, $^{3}J_{H-H}$=6.3 Hz; H-2′a), 2.36–2.27 (m, 1H; H-2′b), 2.29 (s, 3H; H-15), 1.85 ppm (d, 3H, $^{4}J_{H-H}$=1.0 Hz; H-7); ^{31}P NMR: (162 MHz, $CDCl_3$): $\delta=-8.04$ ppm.

3-Methyl-*cyclo*Sal-3′-deoxy-2′,3′-didehydrothymidine monophosphates (S_P)- and (R_P)-4

Product (R_P)-***4***: General procedure D with (S_B4′R_C,5′S_C)-8,4′-dimethyl-2-(5′-phenyl-2′-*N*-cyanimino-oxazolidin-3′-yl)(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide ((S_P)-**27**) (30 mg, 0.0783 mmol), BEN (18.5 mg, 0.0783 mmol), copper(II)triflate (28.3 mg, 0.0783 mmol) in dichloromethane (1.5 mL) and acetonitrile (1.5 mL), d4T (**2**) (52.6 mg, 0.235 mmol), and triethylamine (33 μL, 23.8 mg, 0.235 mmol) in dichloromethane (1.5 mL) and acetonitrile (1.5 mL). The product (R_P)-**4** (5.43 mg, 17%, 94% *de*) was obtained as a colorless foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.96 (br s, 1H; N-H), 7.22 (q, 1H, $^{4}J_{H-H}$=1.2 Hz; H-6), 7.18 (d, 1H, $^{3}J_{H-H}$=7.6 Hz; H-12), 7.04 (dd, 1H, $^{3}J_{H-H}$=7.6, $^{3}J_{H-H}$=7.6 Hz; H-13), 7.01–6.97 (m, 1H; H-1′), 6.93 (dd, 1H, $^{4}J_{H-H}$=0.7, $^{3}J_{H-H}$=7.6 Hz; H-14), 6.37–6.32 (m, 1H; H-3′), 5.96–5.91 (m, 1H; H-2′), 5.36 (dd, 1H, $^{2}J_{H-H}$= 13.9, $^{3}J_{H-P}$=15.8 Hz; H-8a), 5.30–5.21 (m, 1H; H-8b), 5.04–4.99 (m, 1H; H-4′), 4.41–4.34 (m, 2H; H-5′), 2.26 (s, 3H; H-15), 1.66 ppm (d, 1H, $^{4}J_{H-H}$=1.2 Hz; H-7); ^{31}P NMR: (162 MHz, $CDCl_3$): $\delta=-8.12$ ppm.

Product (S_P)-***4***: General procedure D with (R_B4′S_C)-8-methyl-2-(4′-benzyl-2′-*N*-cyanimino-oxazolidin-3′-yl)(4*H*)-1,3,2-benzodioxaphosphorin-2-oxide ((R_P)-**28**) (71.0 mg, 0.185 mmol), BEN (43.7 mg, 0.185 mmol), copper(II)triflate (66.9 mg, 0.185 mmol) in dichloromethane (3.0 mL), d4T (**2**) (0.124 mg, 0.555 mmol), and triethylamine (77 μL, 56.2 mg, 0.555 mmol) in dichloromethane (3 mL). The product (S_P)-**4** (22 mg, 28%, ≥95% *de*) was obtained as a colorless foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.91 (br s, 1H; N-H), 7.23–7.20 (m, 1H; H-6), 7.19 (d, 1H, $^{3}J_{H-H}$=7.6 Hz; H-12), 7.04 (dd, 1H, $^{3}J_{H-H}$=7.6, $^{3}J_{H-H}$=7.6 Hz; H-13), 7.01–6.97 (m, 1H; H-1′), 6.92 (d, 1H, $^{3}J_{H-H}$=7.6 Hz; H-14), 6.43–6.37 (m, 1H; H-3′), 5.96–5.91 (m, 1H; H-2′), 5.40 (dd, 1H, $^{2}J_{H-H}$=13.6, $^{3}J_{H-P}$= 13.6 Hz; H-8a), 5.21 (dd, 1H, $^{2}J_{H-H}$=13.6, $^{3}J_{H-P}$=15.6 Hz; H-8b), 5.04–4.99 (m, 1H; H-4′), 4.48–4.40 (m, 1H; H-5′a), 4.35–4.28 (m, 1H; H-5′b), 2.29 (s, 3H; H-15), 1.78 ppm (d, 3H, $^{4}J_{H-H}$=1.2 Hz; H-7); ^{31}P NMR: (162 MHz, $CDCl_3$): $\delta=-7.45$ ppm.

Antiretroviral evaluation: Human immunodeficiency virus type 1 (HIV-1) was originally obtained from a persistently HIV-infected H9 cell line, as described previously, and was kindly provided by Dr. R.C. Gallo (then at the National Institutes of Health, Bethesda, MD). Virus stocks were prepared from the supernatants of HIV-infected MT-4 cells. HIV-2 (strain ROD) was kindly provided by Dr. L. Montagnier (then at the Pasteur Institute, Paris, France), and virus stocks were prepared from the supernatants of HIV-2-infected MT-4 cells. CEM cells were obtained from the American Tissue Culture Collection (Rockville, MD). CEM cells were infected with HIV as previously described. Briefly, 4×10^{5} CEM cells/mL were infected with HIV-1(III_B) or HIV-2(ROD) at ≈100 $CCID_{50}$ (50% cell culture infective dose) per mL of cell suspension. The thymidine kinase-deficient CEM/TK$^-$ cell cultures were also infected with HIV-2(ROD). Then, 100 μL of the infected cell suspensions was transferred to 96-well microtiter plate wells and mixed with 100 μL of the appropriate dilutions of the test compounds. After 4–5 days, giant cell formation was recorded microscopically in the HIV-infected cell cultures. The 50% effective concentration is defined as the compound concentration required to inhibit virus-induced cytopathicity by 50%. The 50% cytostatic concentration is defined as the compound concentration required to inhibit CEM cell proliferation by 50%, as derived by counting the cell numbers in the presence of different compound concentrations by use of a Coulter Particle Counter ZI (Analysis, Gent, Belgium).

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