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# Linear Synthesis of Chiral *cyclo*Sal-Pronucleotides

**Edwuin Hander Rios Morales,[a] Cristina Arbelo Román,[a] Jens Oliver Thomann,[a] and Chris Meier*[a]**

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*Cyclo*Sal-nucleosyl-phosphate triesters are a known class of highly effective nucleotide prodrugs (pronucleotides) of antivirally active nucleoside analogues. Until recently, the synthesis of these compounds always gave diastereoisomeric mixtures. Then, a convergent route for the stereospecific synthesis of *cyclo*Sal-triesters was described to give isomerically pure *cyclo*Sal-prodrugs for the treatment of viral diseases. Here, the development of a stereoselective synthesis of these pronucleotides using various chiral auxiliaries is described. In contrast to pyrrolidine- or pyrrolidinone derivatives it was found that a thiazolidine derived from valinol fulfilled all three requirements to act as a suitable chiral moiety, allowing: (i) strong chirality transfer, (ii) the formation of separable diastereoisomeric intermediates, and (iii) a suitable leaving group that allows the introduction of the nucleoside analogue (e.g., d4T) in the final step under mild reaction conditions. The title compounds were obtained with very high diastereoisomeric excesses of more than 95 %.

## Introduction

Nucleoside analogues have huge therapeutic potential for the treatment of viral infections and cancer.[1] As for natural nucleosides, nucleoside analogues must be converted intracellularly into the corresponding 5′-triphosphates to allow incorporation into the growing DNA strand. These phosphorylation steps are catalyzed by host cell nucleoside and nucleotide kinases. In their triphosphate form, the nucleoside analogues interact with the viral DNA polymerase, either as competitive inhibitors or as alternative substrates.[2–4] Because nucleoside analogues differ structurally from the natural substrates, often at least one of the phosphorylation steps proceeds poorly.[2,5,6]

For example, in the case of the anti-HIV active dideoxynucleoside analogue d4T (**1**; Stavudine, Zerit®)[7] the first phosphorylation to d4T-5′-monophosphate (d4TMP) **2** catalyzed by thymidine kinase (TK) is the rate-limiting step in human cells (Figure 1).[5,8] The direct administration of nucleotides such as d4TMP (**2**) should bypass this limiting step and thus improve the biological activity. Unfortunately, because of the high polarity of the nucleoside monophosphates (nucleotides) due to the negatively charged phosphate group under physiological conditions, these compounds are unable to penetrate either cellular membranes or the blood-brain barrier. In addition, blood and cell surface phosphohydrolases (acid and alkaline phosphatases, 5′-nucleotidases) rapidly convert the nucleotides into the corresponding nucleosides. One solution could be that the charged phosphate moiety is lipophilically masked in order to obtain a neutral phosphate ester. This principle led to the development of nucleotide prodrugs such as compounds **3**, which are able to deliver the nucleotides into cells (Figure 1).[6,9–12]

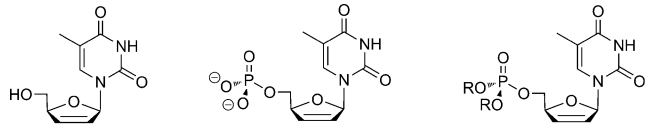


Figure 1. Nucleoside analogue d4T (**1**), d4TMP (**2**), and the general formula for nucleotide prodrugs **3**.

When the phosphorus atom in compounds **3** has four different substituents, the pronucleotides are P-chiral compounds, for example in *cyclo*Sal-derivatives, phosphoramidates, or the HepDirect compounds.[9,11,12] As a consequence of their syntheses, at least two P-chiral pronucleotides were obtained as almost 1:1 mixtures of diastereoisomers with respect to the configuration at the phosphorus center.[9,11] The mixtures of diastereoisomers were separated in only rare cases. However, it has been shown that the individual diastereoisomers of the pronucleotides showed significantly different antiviral activity, toxicity, and hydrolysis stabilities, for example, in the case of the *cyclo*Sal-compounds as well as for the phosphoramidates.[9,13] It was found that ($R_P$)-3-methyl-*cyclo*Sal-d4TMP was 11 times more active against HIV-1 than its ($S_P$)-counterpart.[14] There is no definitive explanation for the different activities observed, neverthe-

[a] Organic Chemistry, Department of Chemistry, Faculty of Sciences, University of Hamburg,
Martin-Luther-King-Platz 6, 20146 Hamburg, Germany
Fax: +49-40-42838-5592
E-mail: chris.meier@chemie.uni-hamburg.de

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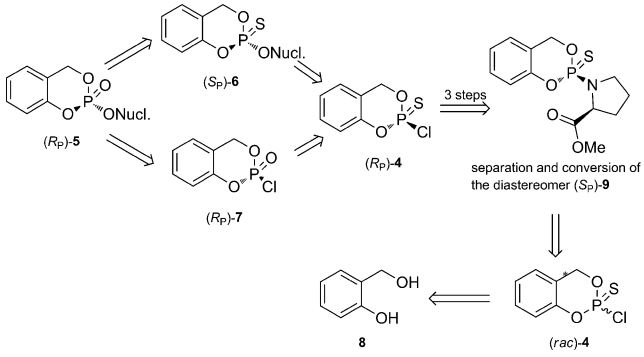
less, it may be supposed that due to the different three-dimensional structure of both diastereoisomers, uptake through the cell membrane may be different. In addition, the diastereoisomers may be activated differently by cellular enzymes. Moreover, only one isomer was found to be a strong inhibitor of the enzyme butyrylcholinesterase.[15] Although in previous studies a few *cyclo*Sal-triesters were separated by (time-consuming) semipreparative HPLC,[14,16] it is clearly advantageous to synthesize these compounds stereoselectively. Recently, we described a first convergent, stereospecific preparation of isomerically pure *cyclo*Sal-pronucleotides based on chiral *N*-cyaniminooxazolidines. However, due to a particular substitution pattern in the salicylic alcohol, the stereoselective formation of a key intermediate failed. Thus, in that approach, the separation of a 1:1 diastereoisomeric mixture of the key intermediate was required. The nucleoside was finally introduced stereospecifically.[17]

Here, we report the stepwise development of a linear, asymmetric synthesis of *cyclo*Sal-pronucleotides using mild reaction conditions based on the use of a series of different chiral auxiliaries. The critical point was to identify a chiral auxiliary that gave high chirality transfer and acted in the final step as a suitable leaving group to allow the formation of *cyclo*Sal-phosphate triesters with excellent diastereoisomeric purity.

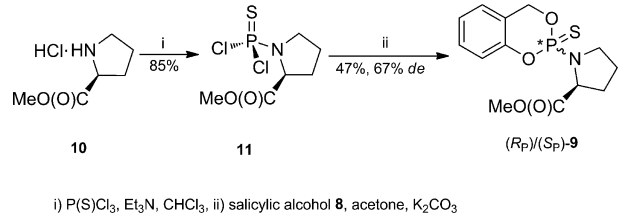
## Results and Discussion

A first approach was based on a route to enantiomerically pure 2-chloro-4*H*-1,3,2-benzodioxaphosphorin 2-sulfide (**4**) reported by the groups of Eto and Casida.[18,19] From **4**, the *cyclo*Sal-prodrug ($R_P$)-**5** should be accessible in diastereoisomerically pure form in two additional steps (Scheme 1). This may be achieved in two different ways: (a) thiophosphoro chloridate ($R_P$)-**4** is converted into the nucleosyl thiophosphate ($S_P$)-**6** followed by sulfur-to-oxygen exchange, or (b) initial replacement of the sulfur with oxygen in thiophosphoro compound ($R_P$)-**7** and then the chlorine atom is substituted by the nucleoside analogue.




Scheme 1. The synthesis of isomerically pure ($R_P$)-**4** according to the groups of Eto and Casida[18,19] and potential conversion into *cyclo*Sal-nucleotide prodrugs.

In contrast to the poor chemical yields reported by Eto and Casida for the first reaction (17%), the yield of this reaction was improved to 46% using tetrahydrofuran (THF) as solvent and triethylamine as base. However, this approach remained unsatisfactory because of the numerous steps required. Therefore, the order of the first two steps was reversed, which led not only to a marked improvement in the chemical yield, but also to a stereochemical induction at the phosphorus atom in amidates ($R_P$)/($S_P$)-**9**. Thus, proline methyl ester (**10**) was coupled with $P(S)Cl_3$ to give dichlorothiophosphoramidate **11** in 85% yield, followed by reaction with salicylic alcohol **8** to give the chiral thiophosphoramidates ($R_P$)/($S_P$)-**9** with a diastereoisomeric excess of 67% and a yield of 47% (Scheme 2). The predominantly formed diastereoisomer was assigned the ($S_P$)-configuration by comparison with assignments reported by Eto and coworkers.[18] A separation of the diastereoisomers ($S_P$)-**9** and ($R_P$)-**9** was achieved by means of crystallization.




Scheme 2. Synthesis of the thiophosphoramidates ($R_P$)/($S_P$)-**9**.

A range of carbonates were studied to determine the influence on the diastereoselectivity in acetone. Each reaction mixture was stirred for 5 h at room temperature and then for 5 h at 56 °C. The conversion was followed by $^{31}P$ NMR spectroscopy by integration of suitable signals in the crude mixture. Although the carbonates were not completely soluble in acetone they did show different effects in the reaction. However, lithium-, magnesium- and calcium carbonate did not lead to product formation either at room temperature or at 56 °C. In contrast, sodium carbonate gave the product, albeit in poor chemical yield and moderate diastereoselectivities, after heating. In the case of potassium carbonate, the reaction took place at room temperature but the product was also formed in poor yields (26%); after heating, the yield could be increased to 47%.

However, in all cases, at least half of the starting material was recovered. Interestingly, the diastereoisomeric excess was 67% at room temperature and, after heating the reaction mixture, this decreased to 60%. The highest conversion (95%) was observed with cesium carbonate at room temperature (57% *de*). No clear explanation can be given for the behavior of the metal carbonates, but we observed a tendency of the different carbonates with rising ionic radius of the metal to promote the reaction. Due to the presence of solids in the reaction mixture, it cannot be excluded that the solubility of the carbonates in acetone played a significant role. A variation of the solvent ($CHCl_3$, THF, and *N*,*N*-dimethylformamide (DMF)) was also carried out. $K_2CO_3$ was chosen as base in all cases because it afforded the highest diastereoisomeric excesses. No formation of the product **9** was observed in these solvents at room temperature. Use of DMF led to decomposition of the starting ma-

terial. After heating the reaction mixture for 5 h at 65 °C, only small amounts of product **9** were observed in $CHCl_3$ and THF. In addition to this, markedly lower diastereoisomeric excesses were obtained than in acetone.

To investigate the mechanism and to explain the stereoselectivity of the reaction, the results were compared to those obtained in a series of reactions reported by Nakayama and Thompson.[20] The reaction of bis(2,4-dichlorophenyl)phosphoramidates (**12**) (Figure 2) with lithium or sodium *n*-butoxide followed by Brønsted acid mediated methanolysis yielded the corresponding chiral trialkyl phosphates with enantiomeric excesses (*ee*) ranging from 78 to more than 95%. Nakayama proposed a mechanism involving chelate formation with the metal ion to give a rigid structure (Figure 2). According to this, the nucleophile approaches more favorably from the *re*-face.

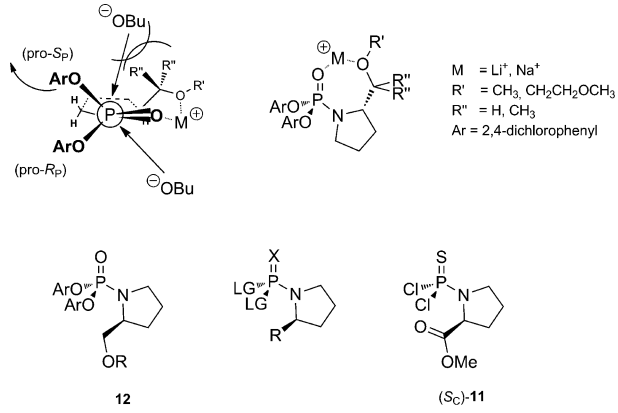
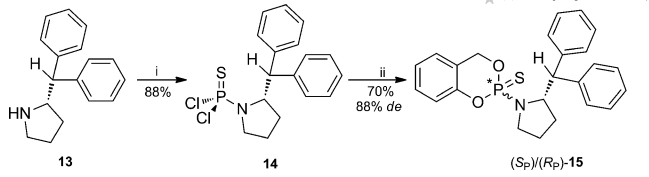



Figure 2. Reaction mechanism postulated by Nakayama and Thompson,[20] and comparison between Nakayama's phosphoramidates and thiophosphoramidate used here.

The results obtained using our system and those of Nakayama and Thompson are comparable because both starting materials have two diastereotopic leaving groups (chloro atoms vs. phenols), proline-based chiral auxiliaries, and two heteroatoms (phosphoryl or thiophosphoryl and ether or carbonyl, respectively) for chelation of the metal ion (e.g., lithium or magnesium). Therefore, a similar mechanism was assumed. However, we were not convinced that a chelate effect is the main reason for the stereoselectivity of the reaction, because, were this to be the case, the transition state would have to be a seven-membered ring. In addition to this, potassium and sodium are not very likely to form chelates and the thiophosphoryl bond is not polarized enough to be a good ligand. To gain more insights into the proposed chelate effect as a cause for the observed diastereoselectivity, we repeated the reaction shown in Scheme 2 (step ii) but using 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) as a metal-free base instead of potassium carbonate. If chelation plays a significant role, one should expect a loss in stereoselectivity. To our surprise, the reaction resulted in the same diastereoisomeric excess of 60% *de* (conversion 81%). In addition, to avoid any interactions with trace amounts of metal ions, we also used (*S*)-2-(diphenylmethyl)pyrrolidine (**13**) as a chiral auxiliary (Scheme 3).




i) 3.0 equiv. $P(S)Cl_3$, 1.1 equiv. $Et_3N$, $CHCl_3$, 0 °C to rt, 12 h ii) salicylic alcohol **8**, 2.2 equiv. DBU, acetone, 0 °C to r.t., 12 h

Scheme 3. Stereoselective synthesis of thiophosphoramidates ($S_P$)/($R_P$)-**15**.

Interestingly, coupling of the thiophosphoramidate **14** with salicylic alcohol **8** gave the corresponding amidates ($S_P$)/($R_P$)-**15** with an even higher diastereoisomeric excess of 88% (70% yield), thus proving that the chelate effect is not responsible for the diastereoselectivity. The solvent did not play a role in the diastereoselectivity because an identical diastereoisomeric excess was obtained in acetonitrile (88% *de*) to that in acetone.

If chelation does not determine the observed diastereoselectivity, other reasons should be important. The thiophosphoramidate **11** was crystallized from ethyl acetate/petroleum ether (Figure 3). According to the X-ray crystal structure, the phosphorus–nitrogen bond length was found to be 161 pm for thiophosphoramidate **11**. This value lies between the length of a P–N single bond (176 pm) and that of a P=N double bond (152 pm), which points to a partial double bond character, at least in the crystal structure, and, consequently, a resulting rotational barrier around the P–N-bond. Rotational barriers around a partial P=N double bond in similar molecules have been reported (based on IR studies) to be in the range of 7 to 18 kcal/mol.[21] Moreover, high rotational barriers (11–18 kcal/mol) can also result

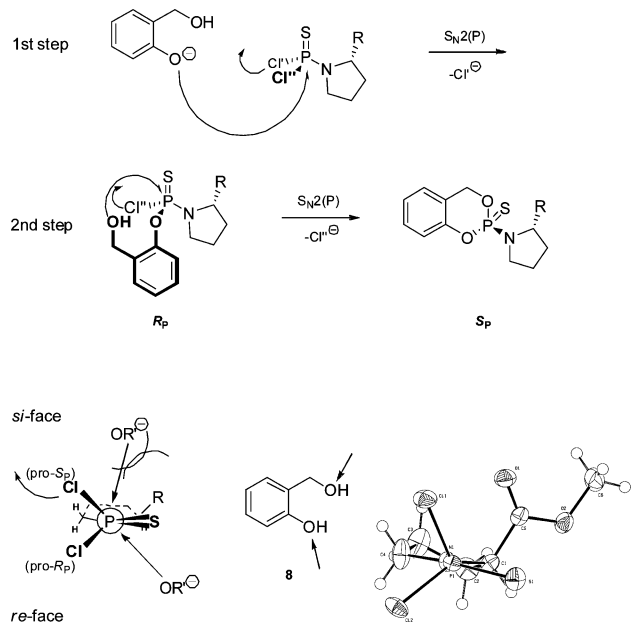



Figure 3. Proposed mechanism of the cyclization, the possible transition state, and an ORTEP illustration of **11**.

from increased steric hindrance.[21b] Estimation of the activation energy for this reaction turned out to be difficult due to the lack of reported comparable energy values. In related systems, the activation energies exhibit values in a range from 11 to 23 kcal/mol.[22] Based on these values for rotational barriers and activation energies, no satisfactory conclusion on the influence of the rotational barrier on the mechanism and diastereoselectivity can be made. We therefore chose a more practical but less exact approach to estimate the influence of the rotational barrier. Dichloro-*N*,*N*-dimethylthiophosphoramidate, synthesized from thiophosphoryl chloride and dimethyl ammonium hydrochloride in the presence of DBU in 68% yield, was selected as a model compound due to its high similarity to DMF.[23] In DMF, as a result of the high rotational barrier at the amide bond, rotation around the C–N bond is extremely constricted. This effect can be seen in the shifts of the two chemically non-equivalent methyl groups in the $^1$H NMR spectrum at room temperature. Therefore, the phosphorothioamidate should show a similar behavior if the energy barrier to rotation is in the same range as that for DMF. However, the $^1$H NMR spectra of phosphorothioamidate showed only one doublet (due to the H–P coupling) instead of two at 298 K; even at low temperature (193 K), there was no evidence for a rotation barrier. Therefore, our conclusion is that the rotation barrier has no influence on the mechanism and diastereoselectivity, and can be neglected.

Based on these results, we propose the following two-step mechanism: Under basic conditions, the phenolate ion is a better nucleophile than the benzylic alcohol, so the phenolate oxygen first attacks the phosphorus atom, removing the first chlorine atom through a nucleophilic substitution. This step determines the stereochemical result of the whole reaction. Based on the X-ray structures, attack from the *re*-face should be favored over attack from the *si*-face. Therefore, the reaction is accomplished largely by passing the transition state derived from *re*-face attack, leading to $R_P$-configured intermediates. The second step is proposed to involve nucleophilic attack of the benzylic alcohol, leading to $S_P$-*cyclo*Sal-phosphoramidates (Figure 3). The latter reaction is expected to be strongly stereospecific with inversion of configuration at the phosphorus.

Attempts to optimize the stereoselectivity of the cyclization reaction were then carried out. First, the dependence of the stereoselectivity on the temperature was determined (Scheme 2, step ii). Surprisingly, the diastereoisomeric excess could not be improved by lowering the temperature, and the highest diastereoisomeric excess was obtained at room temperature. Although not very common, it is known that the diastereoselectivity may change if enthalpy and entropy favor different isomers.[24]

Secondly, the solvent dependency of the reaction was investigated. It is known that the rate of many chemical reactions depend on the polarity of the solvents.[25] By solvation of the reactants, the solvent has the ability to influence the free energy and, consequently, the stereoselectivity.[24a]

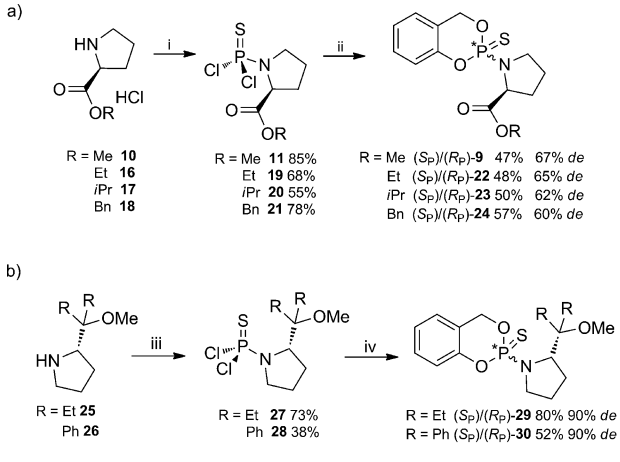
The reaction (Scheme 2, step ii) was therefore carried out at room temperature in a range of solvents (Table 1); the polarity of which can be described by the normalized $E_T^N$-values ranging from $E_T^N = 0$ [$(CH_3)_4Si$] to water $E_T^N = 1.0$.[25,26]

Table 1. Dependence of the diastereoselectivity on solvent polarity.

| | Solvent | $E_T^N$ value | *de* | $\Delta\Delta G^‡$ [kcal/mol] |
|---|---|---|---|---|
| 1 | $CH_3CN$ | 0.460 | 69 | 1.01 |
| 2 | Acetone | 0.355 | 64 | 0.91 |
| 3 | $CH_2Cl_2$ | 0.309 | 51 | 0.67 |
| 4 | $CHCl_3$ | 0.259 | 54 | 0.71 |
| 5 | THF | 0.207 | 51 | 0.66 |
| 6 | Toluene | 0.099 | 49 | 0.64 |

A trend in the reactions was observed. The more polar the solvent, the higher was the stereoselectivity. However, due to the formation of several side products, as well as to the incomplete reaction (ca. 30% conversion according to $^{31}$P NMR analysis of the crude mixture) using ethanol and ethyl ether, it was not possible to determine the diastereoisomeric excess by integrating the corresponding signals in either the $^{31}$P NMR or the $^1$H NMR spectra due to superposition of the signals of the product ($S_P$)/($R_C$)-**9** and the side products (data not shown). In the reactions summarized in Table 1, the reaction proceeded to the corresponding products ($S_P$)/($R_C$)-**9** with over 80% conversion and the diastereoisomeric excess was determined by integrating the corresponding $^{31}$P NMR signals. Nevertheless, even the diastereoselectivity found in acetonitrile (69% *de*) remained unsatisfactory, and the use of more polar organic solvents led to the formation of several side products. Consequently, although changing both temperature and solvent, the stereoselectivity induced by the proline methyl ester as an auxiliary of the reaction could not be improved.

Finally, the steric bulk of the substituent in the chiral auxiliary was modified, and larger ester groups were used (Scheme 4a). Whereas L-proline ethyl ester (**16**) and L-proline isopropyl ester (**17**) needed to be synthesized,[27] L-proline benzyl ester (**18**) was commercial available. Esters **16**–




i) 1.1-1.5 equiv. $P(S)Cl_3$, 2.2 equiv. $Et_3N$, $Et_2O$, -40 °C to r.t., 2 h ii) salicylic alcohol **8**, 2.2 equiv. $K_2CO_3$, acetone, reflux 6 h b) iii) 3.0 equiv. $P(S)Cl_3$, 1.1 equiv. $Et_3N$, $CHCl_3$, 0 °C to r.t., iv) 1.0 equiv. salicylic alcohol **8**, 2.2 equiv. $K_2CO_3$, acetone, 0 °C to r.t.

Scheme 4. Influence of the steric bulk of the ester and ether groups on the diastereoselectivity.

**18** were then reacted with thiophosphoryl chloride to give the corresponding products **19**–**21**. Subsequent reaction with salicylic alcohol **8** led to the corresponding thiophosphoramidates **22**–**24** with diastereoisomeric excesses of between 60 and 65%.

Clearly, variations in the steric bulk of the ester groups did not improve the stereochemical induction on the phosphorus atom, most probably due to the distance between the bulky alkyl substituents and the reaction center. Therefore, the sterically demanding group was moved closer to the phosphorus atom as shown, for example in (*S*)-2-(diphenylmethyl)pyrrolidine (**13**) (Scheme 3). For this purpose, pyrrolidine derivatives such as **25** and **26** were synthesized according to the procedures described by Enders et al. (Scheme 4b).[28]

Conversion of the pyrrolidine derivates **25** and **26** with thiophosphoryl chloride led to the formation of dichloro-intermediates **27** and **28**, which were then reacted with salicylic alcohol **8** using $K_2CO_3$ as base and acetone as solvent to give the corresponding thiophosphoramidates ($S_P$)/($R_P$)-**29** and ($S_P$)/($R_P$)-**30**. In both cases a diastereoisomeric excess of 90% was observed. Unfortunately, in both cases, separation of the minor diastereoisomer by means of silica gel chromatography was impossible, so the thiophosphoramidates ($S_P$)/($R_P$)-**29** and ($S_P$)/($R_P$)-**30** were not accessible in diastereoisomerically pure forms.

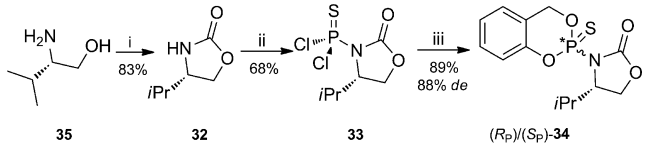
In the next step, methanolysis of the diastereoisomerically enriched thiophosphoramidates was attempted to obtain Salithion (**31**). For this purpose, the isomerically enriched thiophosphoramidate **9** (60% *de*) was used as a model compound. The methanolysis was carried out according to a literature procedure.[16] The enantiomeric ratio was determined by means of HPLC on a chiral stationary phase. The result was then compared with those obtained with racemic Salithion (**31**). Assuming complete inversion of configuration during the methanolysis, an enantiomeric excess of 60% for the formed Salithion (**31**) was expected. However, an enantiomeric excess of only 33% was found. This means that considerable racemization occurred for some unknown reason. Because of this unsatisfactory result and because of the long synthetic route, this strategy was abandoned. Nevertheless, we attempted to react the ($S_P$)-thiophosphoramidate **9** with d4T (**1**) as a nucleoside analogue under acidic conditions (sulfuric acid or the Lewis acid boron trifluoride etherate) to yield the corresponding thiophosphate ester. Unfortunately, this led to precipitation of a black solid and decomposition of the nucleoside analogue **1**.

Clearly, the strongly acidic conditions needed to activate the P–N bond of these phosphoramidates were too harsh for replacement of the chiral auxiliary by a nucleoside. On the other hand, small nucleophiles such as methoxide gave the desired substitution albeit with a marked loss in stereogenicity.

As a conclusion, we achieved the stereoselective synthesis of *cyclo*Sal-thiophosphoramidates such as ($S_P$)/($R_P$)-**29** and ($S_P$)/($R_P$)-**30** with high diastereoisomeric excesses (90%), but the chiral auxiliaries used were found to be unsatisfactory leaving groups. The design of a suitable chiral auxiliary that can be easily replaced by a nucleoside analogue under mild reaction conditions was thus the next goal.

An appropriate phosphorylating reagent should have a relative weak bond between the phosphorus atom and the leaving group, allowing bond cleavage to occur preferentially at this position. In addition to this, the leaving group should stabilize the resulting negative charge after cleavage. There are several systems containing the P–N bond motif reported in the literature that are good phosphorylating agents.[29] These systems all have an electron-withdrawing group next to the nitrogen atom. Most interesting for our problem was the work of Jones and co-workers.[29f,29g,29h] They were using an achiral or chiral (similar to the Evans auxiliary) oxazolidinone motif for successful phosphorylation of several alcohol moieties.

Thus, (*S*)-4-isopropyl-2-oxazolidinone (**32**) was synthesized[30] and reacted with thiophosphoryl chloride to yield the dichloro intermediate **33**. The X-ray crystal structure of the latter confirmed the expected longer P–N bond of about 5 pm (165.8 pm) in comparison with the P–N bond in the dichloro intermediate **11** (161 pm), as a result of the electron-withdrawing effect of the carbonyl group. After cyclization of **33** with salicylic alcohol **8**, the desired thiophosphoramidate ($S_P$)/($R_P$)-**34** was obtained in high yield (89%) and with a very good diastereoisomeric excess of 88% (Scheme 5).



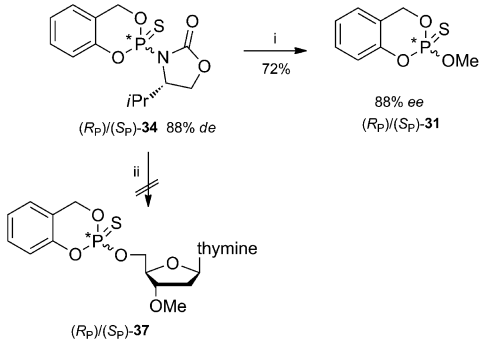

i) 1.2 equiv. $(EtO)_2C(O)$, $K_2CO_3$, reflux, 3 h, ii) 3 equiv. $P(S)Cl_3$, 1.1 equiv. BuLi, THF, -40 °C to r.t., 12 h, iii) salicylic alcohol **8**, $Cs_2CO_3$, acetone, r.t., 12 h

Scheme 5. Diastereoselective synthesis of thiophosphoramidate ($S_P$)/($R_P$)-**34**.

According to the mechanistic considerations described above, the preferentially formed diastereoisomer **34** was expected to have ($R_P$)-configuration, which was later confirmed by a X-ray crystal structure analysis. A subsequent methanolysis of ($R_P$)/($S_P$)-**34** was performed to find whether oxazolidinone **32** was a suitable leaving group and whether the reaction proceeded stereospecifically. For this purpose, both thiophosphoramidates ($R_P$)- and ($S_P$)-**34** were reacted successfully with methanol under the reaction conditions shown in Scheme 6.

The enantiomeric excess (88%) of Salithion (**31**) was determined by using HPLC on a chiral stationary phase. In contrast to the reaction starting with ($S_P$)-**9**, no isomerization was observed in this case. The thiophosphoramidates ($R_P$)/($S_P$)-**34** were then also reacted with the nucleoside **36** to assess the leaving group ability of the chiral auxiliary **32**. However, again, the formation of *cyclo*Sal-(3′-OMe)-TMP ($R_P$)/($S_P$)-**37** could neither be detected by TLC nor by means of $^{31}P$ NMR spectroscopy.

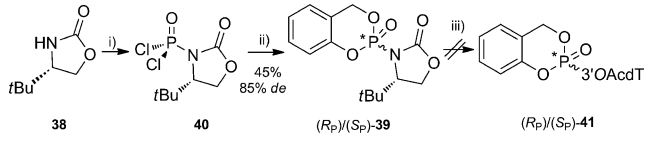



Scheme 6. Methanolysis of diastereoisomers ($R_P$)/($S_P$)-**34**.

In spite of the high stereospecificity we decided not to follow the synthetic route described in Scheme 1 because of the large number steps that are required to obtain the products.

### Selecting More Reactive Phosphoramidate Intermediates

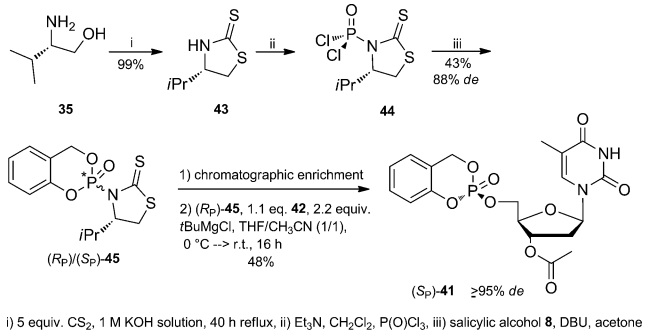
We assume that nucleoside **36** is considerably less reactive than methanol (e.g., due to steric factors). In addition to this, it is possible that the thiophosphorimide ($R_P$)/($S_P$)-**34** is still not reactive enough. Therefore, a promising modification should be substitution of the thiophosphoryl group with a phosphoryl group because the electrophilicity of the phosphorus atom and, consequently, the reactivity of the imide, should be markedly higher. To confirm this hypothesis, (*S*)-4-*tert*-butyloxazolidinone (**38**) was used as a chiral auxiliary. The synthesis of the imide ($S_P$)/($R_P$)-**39** is shown in Scheme 7. In contrast to the thiodichloro analogues, purification of the dichloro intermediate **40** by chromatography was not possible due to its instability. Interestingly, the diastereoselectivity of the reaction with salicylic alcohol **8** was slightly lower than the thiophosphoro analogues. Further conversion of the mixed imides ($S_P$)/($R_P$)-**39** to 3′-*O*AcT-phosphate triesters ($S_P$)/($R_P$)-**41** using the bases *n*-butyllithium, *tert*-butylmagnesium chloride, or copper(II)-triflate/*N*,*N*′-ethylenebis(benzaldiimine) (BEN), (Jones' conditions[29h]) neither took place at room temperature nor by heating the reaction mixture at 40 °C.




Scheme 7. Attempt at the diastereoselective synthesis of ($S_P$)/($R_P$)-**41**.

### Successful Stereoselective Synthesis of *cyclo*Sal-Phosphate Triesters

A further modification of the chiral auxiliary to improve its leaving group properties was performed, which was finally successful. DeBruin and co-workers[31] described the synthesis of several thiocarbonyl phosphoryl mixed imides by an intramolecular rearrangement from the corresponding thiophosphoryl carbonyl mixed imides and their further facile hydrolysis. In addition to this, amides are weaker acids than the corresponding thioamide analogues,[32] so the latter should stabilize a negative charge more efficiently. In a further report, thiazolidinethiones were used as leaving groups in carboxylic acid derivatives in which they can be removed under mild reaction conditions.[33] Furthermore, chiral thiazolidinethiones with substituents in the 4-position were successfully used as auxiliaries in asymmetric aldol reactions.[34] Based on this, (*S*)-4-isopropyl-2-mercapto-2-thiazoline (**43**) was used as a chiral auxiliary. The synthesis of **43** was conducted as reported by Zhang and Delaunay with even better yields than published (99%, Scheme 8).[34b,35]




Scheme 8. Diastereoselective synthesis of the imides ($R_P$)/($S_P$)-**45** and conversion of the isomerically pure ($R_P$)-**45** into the triester ($S_P$)-**41**.

As before, the dichloro intermediate **44** could not be purified by means of chromatography due to its instability. The $^{31}$P NMR spectrum of the crude mixture showed almost quantitative formation of compound **44**. The reaction of **44** with salicylic alcohol **8** led to formation of the mixed imides ($R_P$)/($S_P$)-**45**. The reaction was always carried out as a one-pot reaction. Many attempts were made to obtain not only high yield but also high diastereoselectivity. In Table 2 different reaction conditions were assessed for this purpose, and the corresponding yields and diastereoisomeric excesses are summarized.

Table 2. Diastereoselectivity and yield for the synthesis of the mixed imides ($S_P$)/($R_P$)-**45**.

| Step (ii) Solvent | Base | Temp. [°C] | Step (iii) Solvent | Base | Temp. [°C] | Yield [%] | *dr*[a] | *de*[a] [%] |
|---|---|---|---|---|---|---|---|---|
| $CHCl_3$ | $NEt_3$ | 0 | acetone | DBU | –78 to r.t. | 43 | 1:16 | 88 |
| $CH_2Cl_2$ | $NEt_3$ | 0 | acetone | DBU | 0 to r.t. | 1–2 | 1:6 | 72 |
| THF | $NEt_3$ | –70 | THF | NaH | r.t. | 6 | 1:6.1 | 72 |
| THF | LDA | –70 | THF | DBU | 0 to r.t. | 8 | 1:1 | 0 |
| Toluene | $NEt_3$ | –10 | acetone | DIPEA | 0 to r.t. | 6 | 1:2.9 | 48 |
| Toluene | $NEt_3$ | –10 | $CH_2Cl_2$ | DBU | 0 to r.t. | 14 | 1.4:1 | 42 |
| $Et_2O$ | $NEt_3$ | –10 | $Et_2O$ | $NEt_3$ | 0 to r.t. | 36 | 2.5:1 | 42 |
| Toluene | $NEt_3$ | –10 | toluene | $NEt_3$ | 0 to r.t. | 42 | 1:1.9 | 32 |

[a] The diastereoisomeric excess was determined by integrating the respective signals in the $^{31}$P NMR spectrum of the crude mixture.

The combination of DBU and acetone at –90 °C gave the best result, with other bases either the yield or the diastereoisomeric excess was lower. Interestingly, the diastereoisomers ($S_P$)-**45** and ($R_P$)-**45** could be separated easily by means of column chromatography. The ($S_P$)-configuration of the minor diastereoisomer was confirmed by an X-ray crystal structure analysis. In Figure 4 the $^{31}$P NMR spectrum of the preferentially formed diastereoisomer ($R_P$)-**45** after purification is shown.

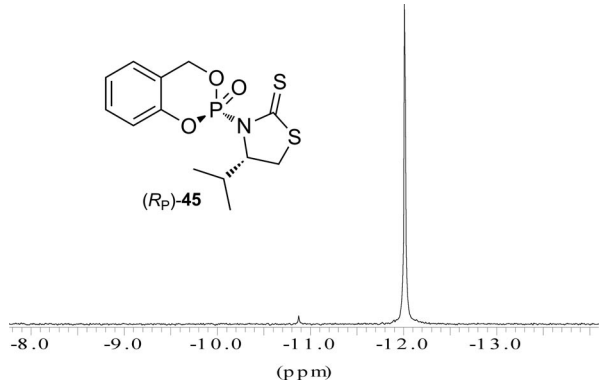



Figure 4. $^{31}$P NMR spectrum of the diastereoisomer ($R_P$)-**45**.

The isomerically pure diastereoisomer ($R_P$)-**45** was then reacted with 3′-*O*Ac-thymidine ($dT_{OAc}$) **42** as a model for nucleoside analogues (Scheme 8). The best results were obtained by using *tert*-butylmagnesium chloride as base, and a 1:1 mixture of THF/$CH_3CN$ as solvent.[36] The reaction proceeded stereospecifically and the product **41** was obtained with a diastereoisomeric excess of more than 95% (Figure 5) in 48% yield. Assuming that the reaction took place with inversion of configuration, compound **41** should have ($S_P$)-configuration.[19,37]

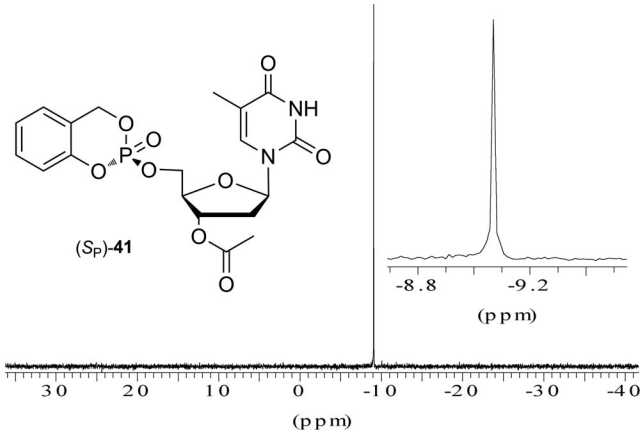
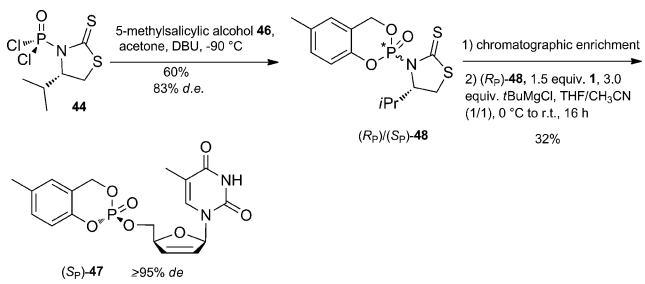



Figure 5. $^{31}$P NMR spectrum of the stereospecifically synthesized *cyclo*Sal-phosphate triester ($S_P$)-**41** starting from stereochemically pure ($R_P$)-**45**.

To establish the general applicability of the novel synthetic route, 5-methylsalicylic alcohol **46** and d4T (**1**), as an antivirally active nucleoside analogue, were used (Scheme 9). The optimized reaction conditions for the cyclization were then applied. As above, this reaction led to formation of the corresponding 5-methyl-*cyclo*Sal-triester **47** in 32% yield and in very high diastereoisomeric excess (more than 95%) as shown in Figure 6.




Scheme 9. Stereoselective synthesis of *cyclo*Sal-phosphate triester ($S_P$)-**47**.

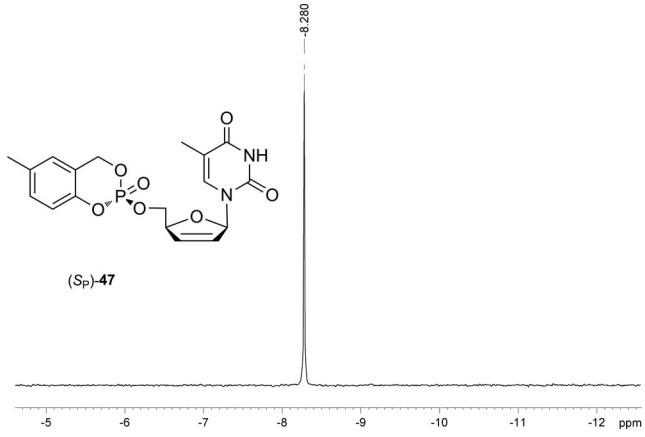



Figure 6. $^{31}$P NMR spectrum of the stereospecifically synthesized *cyclo*Sal-phosphate triester ($S_P$)-**47**.

## Conclusions

Many approaches have been tried for the development of an efficient, stereospecific synthesis of *cyclo*Sal-phosphate triesters using isomerically pure organophosphorus compounds as precursors that were synthesized stereoselectively using chiral auxiliaries. Our strategy employs thiazolidinethione **43** derived from L-valine as a key, which could be successfully replaced by at least two different nucleosides. The diastereoisomeric excesses of the *cyclo*Sal-phosphate triester products were found to be more than 95%. Using this strategy, many isomerically pure or enriched *cyclo*Sal-phosphate triester prodrugs may be synthesized under mild reaction conditions and tested for their antiviral activity as single diastereoisomers. Furthermore, isomerically pure and enriched thio- and organophosphorus compounds were easily synthesized using this method.

Despite remarkable achievements, there is still great demand and scope for further developments, especially regarding improved yield.

The isomerically pure or enriched organophosphorus compounds used as precursors for the *cyclo*Sal-triesters may

also be used for the asymmetric synthesis of other important phosphate derivatives in agricultural and medicinal chemistry.

## Experimental Section

**General:** All experiments involving water-sensitive compounds were conducted under scrupulously dry conditions and nitrogen atmosphere. All solvents were dried with an appropriate drying agent. Triethylamine, $CH_2Cl_2$, and $CH_3CN$ were dried by heating under reflux over calcium hydride for several days, followed by distillation. $CH_2Cl_2$ was stored over activated 4 Å molecular sieves and $CH_3CN$ 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, $CH_2Cl_2$, and $CH_3OH$ for chromatography were distilled before used. Column chromatography was performed by using Merck silica gel 60 (230–400 mesh). Analytical thin-layer chromatography 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 the sugar spray reagent [4-methoxybenzaldehyde (0.5 mL), ethanol (9 mL), glacial acetic acid (0.1 mL), and concentrated sulfuric acid (0.5 mL)] after heating with a fan. The coupling products of the *cyclo*Sal-mask and the chiral auxiliaries were visualized with a 10% solution of potassium permanganate in sodium hydroxide. For some separations, a chromatotron (Harrison Research 7924 T) using glass plates coated with 1, 2, or 4 mm layers of VWR 60 $PF_{254}$ silica gel containing a fluorescent indicator (VWR 7749) was used.

$^1$H NMR spectra were obtained with Bruker AMX 400 (400 MHz), Bruker DMX 500 (500 MHz), or Bruker AV 400 (400 MHz) spectrometers with $CDCl_3$ or [$D_6$]DMSO as internal standard. $^{13}$C NMR spectra were recorded with Bruker AMX 400 (101 MHz) or Bruker AV 400 (101 MHz) spectrometers with $CDCl_3$ or [$D_6$]-DMSO as internal standard. $^{31}$P NMR spectra were recorded with a Bruker AMX 400 (162 MHz) spectrometer with $H_3PO_4$ as internal standard. All $^1$H, $^{31}$P and $^{13}$C NMR chemical shifts are quoted in parts per million (ppm). All $^{13}$C and $^{31}$P NMR spectra were recorded in the proton-decoupled mode. High-resolution mass spectra were obtained with a VG Analytical VG/70–250F spectrometer (FAB, matrix was *m*-nitrobenzyl alcohol).

**General Procedure A**

**Preparation of *N*-Dichlorothiophosphoryl Pyrrolidine Derivatives:** To a solution of pyrrolidine derivative in dried solvent at 0 °C or –40 °C, was added thiophosphoryl chloride. $NEt_3$ was then dissolved in the same solvent and added dropwise at 0 °C or at –40 °C. Following the addition, the reaction mixture was warmed to room temperature and stirred for 1.5–12 h. The formed triethylammonium chloride was filtered. The solvent was removed under reduced pressure using a high vacuum pump, and the crude product was purified by column chromatography on silica gel (petroleum ether 50–70/ethyl acetate gradient).

**General Procedure B**

**Preparation of 2-(1-Pyrrolidyl)-4*H*-1,3,2-benzodioxaphosphorin 2-Sulfide:** The corresponding *N*-dichlorothiophosphoryl pyrrolidine derivative and salicylic alcohol **8** were dissolved in acetone. The corresponding base was added and the reaction mixture was stirred at room temperature. In some cases the reaction was heated to reflux. The solid was then filtered and $CH_2Cl_2$ was added to the solvent and washed with water three times. The combined organic layers were dried with magnesium sulfate and concentrated under reduced pressure using a high vacuum pump. The crude product was purified by column chromatography on silica gel (petroleum ether 50–70/ethyl acetate gradient).

**General Procedure C**

**Preparation of the *cyclo*Sal-phosphate Triesters:** A solution of *tert*-butylmagnesium chloride (1.7 M in THF) was added dropwise to a solution of the nucleoside or nucleoside analogue in THF/$CH_3CN$ (1:1 v/v) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 30 min. This solution was then added to a solution of ($R_P$)-**45** or ($R_P$)-**48** in THF/$CH_3CN$ (1:1 v/v) at 0 °C. Following the addition, the reaction mixture was warmed to room temperature and stirred for 16 h. The reaction was quenched with saturated ammonium chloride solution and extracted with $CH_2Cl_2$ three times. The combined organic layers were dried with magnesium sulfate and concentrated under reduced pressure using a high vacuum pump. The resulting residue was purified by column chromatography on silica gel ($CH_2Cl_2$/$CH_3OH$, 19:1). The product was freeze-dried.

**(*S*)-*N*-Dichlorothiophosphoryl-2-proline Methyl Ester (11):** General procedure A with L-proline methyl ester hydrochloride (**10**; 1.00 g, 6.00 mmol, 1.0 equiv.), thiophosphoryl chloride (1.84 mL, 3.07 g, 18.1 mmol, 3.0 equiv.) dissolved in $CHCl_3$ (30 mL), and triethylamine (1.84 mL, 1.34 g, 13.3 mmol, 2.2 equiv.) dissolved in $CHCl_3$ (30 mL). The product **11** (1.35 g, 85%) was obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.69–4.64 (m, 1 H, H-2), 3.75 (s, 3 H, H-7), 3.67–3.52 (m, 2 H, H-5), 2.33–2.24 and 2.17–2.04 (m, 4 H, H-3 and H-4) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 54.9 ppm.

**($S_C$)/($S_P$)- and ($S_C$)/($R_P$)-2-[2′-(Methoxycarbonyl)pyrrolidin-1′-yl]-4*H*-1,3,2-benzodioxaphosphorin 2-Sulfide (9):** General procedure B with potassium carbonate (1.87 g, 13.3 mmol, 3.6 equiv.), **11** (980 mg, 3.74 mmol, 1.0 equiv.), and **8** (0.51 g, 4.1 mmol, 1.1 equiv.) in dried acetone (75 mL). The reaction mixture was heated to reflux for 3 h and stirred at room temperature for 12 h. The product **9** (496 mg, 47%, 67% *de*) was obtained as a colorless oil and colorless crystals. The spectroscopic data were consist with those reported in the literature.[16]

**(*S*)-*N*-Dichlorothiophosphoryl-2-(1′,1′-diphenylmethyl)pyrrolidine (14):** General procedure A with **13** (0.5 g, 2.11 mmol, 1.0 equiv.), thiophosphoryl chloride (0.64 mL, 1.07 g, 6.33 mmol, 3.0 equiv.) in $CHCl_3$ (10 mL), and triethylamine (0.32 mL, 235 mg, 232 mmol, 1.1 equiv.) in $CHCl_3$ (5 mL). The product **14** (685 mg, 88%) was obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.34–7.19 (m, 10 H, ArH.), 5.04 (dddd, $^3J_{H,H}$ = 2.3, $^3J_{H,H}$ = 6.0, $^3J_{H,H}$ = 8.1, $^3J_{H,P}$ = 15.4 Hz, 1 H, H-2), 4.57 (d, $^3J_{H,H}$ = 6.3 Hz, 1 H, H-6), 3.58 (dddd, $^3J_{H,H}$ = 2.2, $^3J_{H,H}$ = 6.5, $^3J_{H,H}$ = 10.6, $^3J_{H,P}$ = 16.7 Hz, 1 H, H-5a), 3.09 (dddd, $^3J_{H,H}$ = 5.4, $^3J_{H,H}$ = 8.4, $^3J_{H,H}$ = 11.1, $^3J_{H,P}$ = 11.1 Hz, 1 H, H-5b), 2.21–1.95 (m, 2 H, H-3), 1.90–1.75 and 1.45–1.35 (m, 2 H, H-4) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 58.1 ppm.

**($R_P$,2′$S_C$)- and ($S_P$,2′$S_C$)-2-(2′-Benzhydrylpyrrolidin-1′-yl)-4*H*-1,3,2-benzodioxaphosphorin 2-Sulfide (15):** General procedure B with **14** (200 mg, 0.54 mmol, 1.0 equiv.), **8** (67 mg, 0.54 mmol, 1.0 equiv.) in dried acetone (10 mL), and DBU (0.178 mL, 181 mg, 1.19 mmol, 2.1 equiv.) in dried acetone (5 mL). The reaction mixture was stirred for 12 h at room temperature. The product **15** (160 mg, 70%, 88% *de*) was obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (major diastereoisomer) = 7.35–7.08 (m, 14 H, ArH), 5.51 (dd, $^3J_{H,H}$ = 14.0, $^3J_{H,P}$ = 6.6 Hz, 1 H, H-4), 4.97 (dd, $^3J_{H,P}$ = 24.4, $^3J_{H,H}$ = 14.0 Hz, 1 H, H-4′), 4.89–4.80 (m, 1 H,

H-10), 4.49 (d, $^3J_{H,H}$ = 6.3 Hz, 1 H, H-14), 3.55–3.40 (m, 1 H, H-13), 2.95–2.85 (m, 1 H, H-13′), 2.21–1.85 (m, 2 H, H-11), 1.75–1.64 and 1.36–1.24 (m, 2 H, H-12) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 63.3 (major diastereoisomer), 63.7 (minor diastereoisomer) ppm.

**(*S*)-*N*-Dichlorothiophosphoryl-2-proline Ethyl Ester (19):** General procedure A with L-proline ethyl ester hydrochloride **16** (1.56 g, 8.69 mmol, 1.0 equiv.), thiophosphoryl chloride (1.33 mL, 2.21 g, 13.0 mmol, 1.5 equiv.) dissolved in dried $Et_2O$ (10 mL), and triethylamine (3.6 mL, 2.63 g, 13.0 mmol, 3.0 equiv.) dissolved in $Et_2O$ (10 mL). The product **19** (1.55 g, 68%) was obtained as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.66–4.62 (m, 1 H, H-2), 4.22 (q, $^3J_{H,H}$ = 7.1 Hz, 2 H, H-7), 3.50–3.65 (m, 2 H, H-5), 2.31–2.04 (4 H, H-3, H-4), 1.28 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, H-8) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 54.8 ppm.

**($S_C$)/($S_P$)- and ($S_C$)/($R_P$)-2-[2′-(Ethoxycarbonyl)pyrrolidin-1′-yl]-4*H*-1,3,2-benzodioxaphosphorin 2-Sulfide (22):** General procedure B with potassium carbonate (200 mg, 1.45 mmol, 3.8 equiv.), **19** (100 mg, 0.38 mmol, 1.0 equiv.), and **8** (48.0 mg, 0.38 mmol, 1.0 equiv.) in dried acetone (75 mL). The reaction mixture was heated to reflux for 6 h and stirred at room temperature for 12 h. The product **22** (60 mg, 48%, 65% *de*) was obtained as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (major diastereoisomer) = 7.25–7.02 (m, 4 H, ArH), 5.58 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,P}$ = 6.6 Hz, 1 H, H-4), 5.14 (dd, $^2J_{H,H}$ = 14.1, $^3J_{H,P}$ = 24.8 Hz, 1 H, H-4′), 5.08–4.46 (m, 1 H, H-10), 4.18 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, H-15), 3.44–3.53 (m, 2 H, H-13), 2.27–1.92 (m, 4 H, H-11 and H-12), 1.27 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, H-16) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 60.9 (major diastereoisomer), 63.7 (minor diastereoisomer) ppm.

**(*S*)-*N*-Dichlorothiophosphoryl-2-proline Isopropyl Ester (20):** General procedure A with L-proline isopropyl ester hydrochloride **17** (1.68 g, 8.69 mmol, 1.0 equiv.), thiophosphoryl chloride (1.33 mL, 2.21 g, 13.0 mmol, 1.5 equiv.) dissolved in dried $Et_2O$ (10 mL), and triethylamine (3.6 mL, 2.63 g, 13.0 mmol, 3.0 equiv.) dissolved in $Et_2O$ (10 mL). The base was added at –40 °C. The reaction mixture was stirred 12 h at room temperature. The product **20** (1.4 g, 55%) was obtained as a brown oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 5.10–5.02 (sept, $^3J_{H,H}$ = 6.2 Hz, 1 H, H-7), 4.63–4.59 (m, 1 H, H-2), 3.63–3.45 (m, 2 H, H-5), 2.35–2.04 (m, 4 H, H-3 and H-4), 1.26–1.22 (m, 6 H, H-8 and H-9) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 54.7 ppm.

**($S_C$)/($S_P$)- and ($S_C$)/($R_P$)-2-[2′-(Isopropoxycarbonyl)pyrrolidin-1′-yl]-4*H*-1,3,2-benzodioxaphosphorin 2-Sulfide (23):** General procedure B with potassium carbonate (200 mg, 1.45 mmol, 3.8 equiv.), **20** (110 mg, 0.38 mmol, 1.0 equiv.), and **8** (52 mg, 0.42 mmol, 1.1 equiv.) in dried acetone (75 mL). The reaction mixture was heated to reflux for 6 h and stirred at room temperature for 72 h. The product **23** (65 mg, 50%, 62% *de*) was obtained as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (major diastereoisomer) = 7.11–7.01 (m, 4 H, ArH), 5.58 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,P}$ = 6.6 Hz, 1 H, H-4), 5.14 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,P}$ = 25.4 Hz, 1 H, H-4′), 5.12 (sept., $^3J_{H,H}$ = 6.2 Hz, 1 H, H-15), 4.53–4.41 (m, 1 H, H-10), 3.51–3.36 (m, 2 H, H-13), 2.31–2.17 and 2.07–1.92 (m, 4 H, H-11 and H-12), 1.21–1.15 (m, 6 H, H16) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 63.8 (major diastereoisomer), 63.7 (minor diastereoisomer) ppm.

**(*S*)-*N*-Dichlorothiophosphoryl-2-proline Benzyl Ester (21):** General procedure A with L-proline benzyl ester hydrochloride **18** (0.50 g, 2.1 mmol, 1.0 equiv.), thiophosphoryl chloride (0.23 mL, 0.39 g, 2.3 mmol, 1.1 equiv.) dissolved in dried $Et_2O$ (50 mL), and triethylamine (0.70 mL, 4.6 mmol, 2.2 equiv.) dissolved in $Et_2O$ (50 mL). The base was added at –40 °C. The reaction mixture was stirred 12 h at room temperature. The product **21** (0.55 g, 78%) was obtained as a pale-yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.39–7.32 (m, 5 H, ArH), 5.24–5.15 (m, 2 H, H-7), 4.74–4.68 (m, 1 H, H-2), 3.67–3.50 (m, 2 H, H-5), 2.33–2.10 (m, 4 H, H-3 and H-4) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 53.7 ppm.

**($S_C$)/($S_P$)- and ($S_C$)/($R_P$)-2-[2′-(Benzoxycarbonyl)pyrrolidin-1′-yl]-4*H*-1,3,2-benzodioxaphosphorin 2-Sulfide (24):** General procedure B with potassium carbonate (120 mg, 0.89 mmol, 3.0 equiv.), **21** (100 mg, 0.30 mmol, 1.0 equiv.), and **8** (40 mg, 0.30 mmol, 1.0 equiv.) in dried acetone (6 mL). The reaction mixture was heated to reflux for 8 h and stirred at room temperature for 12 h. The product **24** (70 mg, 57%, 60% *de*) was obtained as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (major diastereoisomer) = 7.35–6.83 (m, 9 H, ArH), 5.50 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,P}$ = 7.0 Hz, 1 H, H-4), 5.10 (s, 2 H, H-15), 4.99 (dd, $^3J_{H,P}$ = 25.1, $^2J_{H,H}$ = 14.0 Hz, 1 H, H-4′), 4.47 (ddd, $^3J_{H,H}$ = 3, $^3J_{H,H}$ = 5, $^3J_{H,P}$ = 9 Hz, 1 H, H-10), 3.45–3.30 (m, 2 H, H-13), 2.23–2.10 (m, 1 H, H-11), 2.00–1.92 (m, 2 H, H-11′), 1.92–1.80 (m, 1 H, H-12) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 62.4 (major diastereoisomer), 62.6 (minor diastereoisomer) ppm.

***N*-Dichlorothiophosphoryl-2-(1′-methoxy-1′-ethylpropyl)pyrrolidine (27):** General procedure A with **25** (600 mg, 3.50 mmol, 1.0 equiv.), thiophosphoryl chloride (1.10 mL, 1.78 g, 10.5 mmol, 3.0 equiv.) dissolved in dried $CHCl_3$ (10 mL), and triethylamine (534 μL, 390 mg, 3.85 mmol, 1.1 equiv.) dissolved in dried THF (10 mL). The reaction mixture was stirred 12 h at room temperature. The product **27** (777 mg, 73%) was obtained as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.38 (ddd, $^3J_{H,H}$ = 20.0, $^3J_{H,H}$ = 8.4, $^3J_{H,P}$ = 2.5 Hz, 1 H, H-2), 3.83–3.70 (m, 1 H, H-5), 3.36–3.25 (m, 1 H, H-5′), 3.23 (s, 3 H, H-9), 2.17–1.45 (m, 8 H, H-3, H-4, H-7 and H-7′), 0.93 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H, H-8), 0.85 ppm. (t, $^3J_{H,H}$ = 7.6 Hz, 3 H, H-8′). $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 64.7 ppm.

**($S_C$)/($S_P$)- and ($S_C$)/($R_P$)-2-[2′-(1′′-Ethyl-1′′-methoxypropyl)pyrrolidine-1′-yl]-4*H*-1,3,2-benzodioxaphosphorin 2-Sulfide (29):** General procedure B with potassium carbonate (114 mg, 0.820 mmol, 2.5 equiv.), **27** (100 mg, 0.330 mmol, 1.0 equiv.), and **8** (45 mg, 0.42 mmol, 1.1 equiv.) in dried acetone (10 mL). The reaction mixture was first stirred at 0 °C and then for 12 h at room temperature. The product **29** (93.8 mg, 80%, 90% *de*) was obtained as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (major diastereoisomer) = 7.53–7.45 (m, 1 H, ArH), 7.25–7.21 (m, 2 H, ArH), 7.19–7.18 (m, 1 H, ArH), 5.80 (dd, $^2J_{H,H}$ = 14.1, $^3J_{H,P}$ = 6.0 Hz, 1 H, H-4), 5.35 (dd, $^2J_{H,H}$ = 14.1, $^3J_{H,P}$ = 24.4 Hz, 1 H, H-4′), 4.39 (ddd, $^3J_{H,H}$ = 14.2, $^3J_{H,H}$ = 8.2, $^3J_{H,P}$ = 3.9 Hz, 1 H, H-10), 4.02–3.96 (m, 1 H, H-13), 3.41 (s, 3 H, H-17), 3.34–3.26 (m, 1 H, H-13′), 2.30–2.24 (m, 1 H, H-11), 2.17–1.84 (m, 6 H, H-11′, H-12, H-15 and H-15′), 1.75–1.68 (m, 1 H, H-12′), 1.13 (t, $^3J_{H,H}$ = 7.6 Hz, 3 H), 1.06 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 66.7 (major diastereoisomer), 69.9 (minor diastereoisomer) ppm.

***N*-Dichlorothiophosphoryl-2-(methoxydiphenylmethyl)pyrrolidine (28):** General procedure A with **26** (0.28 g, 1.0 mmol, 1.0 equiv.), thiophosphoryl chloride (0.31 mL, 0.51 g, 3.0 mmol, 3.0 equiv.) dissolved in dried $CHCl_3$ (10 mL), and triethylamine (0.15 mL, 0.11 g, 1.1 mmol, 1.1 equiv.) dissolved in dried $CHCl_3$ (10 mL). The reaction mixture was first stirred at 0 °C and then for 12 h at room temperature. The product **28** (160 mg, 38%) was obtained as a colorless liquid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.27–7.60 (m, 10 H, ArH), 5.32 (ddd, $^3J_{H,H}$ = 16.4, $^3J_{H,H}$ = 9.0, $^3J_{H,P}$ = 3.0 Hz, 1 H, H-2), 3.70–3.50 (m, 1 H, H-5), 2.98 (s, 3 H, H-11), 2.17–1.98 (m, 3 H, H-3 and H-5′), 1.73–1.66 (m, 1 H, H-4), 1.43–1.33 (m, 1 H, H-4′) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 61.1 (major diastereoisomer), 66.8 (minor diastereoisomer) ppm.

**($S_C$)/($S_P$)- and ($S_C$)/($R_P$)-2-[2′-(Methoxydiphenylmethyl)pyrrolidine-1′-yl]-4*H*-1,3,2-benzodioxaphosphorin 2-Sulfide (30):** General pro-

cedure B with DBU (93 μL, 0.63 mmol, 2.5 equiv.), **28** (130 mg, 0.330 mmol, 1.0 equiv.), and **8** (31 mg, 0.25 mmol, 1.0 equiv.) in dried acetone (50 mL). The reaction mixture was stirred for 12 h at room temperature. The product **30** (57.0 mg, 52%, 90% *de*) was obtained as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (major diastereoisomer) = 7.41–6.97 (m, 14 H, ArH), 5.43 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,P}$ = 7.4 Hz, 1 H, H-4), 5.12 (ddd, $^3J_{H,H}$ = 10.7, $^3J_{H,H}$ = 8.9, $^3J_{H,P}$ = 3.7 Hz, 1 H, H-10), 4.78 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,P}$ = 22.9 Hz, 1 H, H-4′), 3.58 (dddd, $^3J_{H,H}$ = 10.4, $^3J_{H,H}$ = 10.4, $^3J_{H,P}$ = 8.4, $^2J_{H,H}$ = 4 Hz, 1 H, H-13), 2.73 (s, 3 H, H-19), 2.22–2.14 (m, 1 H, H-13′), 2.07–1.99 (m, 1 H, H-11), 1.90–1.80 (m, 1 H, H-11′), 1.57–1.50 (m, 1 H, H-12), 1.00–0.80 (m, 1 H, H-12) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 66.6 ppm.

**(*S*)-*N*-Dichlorothiophosphoryl-4-isopropyloxazolidinone (33):** ($S_C$)-4-Isopropyloxazolidinone (**32**; 2.0 g, 16 mmol, 1.0 equiv.) was dissolved in dried THF (15 mL) and cooled to –78 °C. *n*-Butyllithium in hexane (11 mL, 17 mmol, 1.1 equiv.) was then added dropwise. The reaction mixture was stirred for 30 min at –78 °C. The suspension was added at –78 °C to a solution of thiophosphoryl chloride (4.7 mL, 7.9 g, 47 mmol, 3 equiv.) in THF (15 mL) and the reaction mixture was warmed to room temperature. The reaction was quenched by addition of saturated ammonium chloride solution, $CH_2Cl_2$ was added, and the aqueous phase was extracted three times with $CH_2Cl_2$. The combined organic layers were dried with magnesium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether 50–70/ethyl acetate gradient). The product **33** (2.8 g, 68%) was obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 4.59–4.53 (m, 1 H, H-4), 4.39 (dd, $^2J_{H,H}$ = 9.0, $^3J_{H,H}$ = 8.2 Hz, 1 H, H-5), 4.28 (ddd, $^2J_{H,H}$ = 9.0, $^3J_{H,H}$ = 3.5, $^3J_{H,P}$ = 1.8 Hz, 1 H, H-5′), 2.65–2.53 (m, 1 H, H-6), 1.02 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, H-7), 0.97 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, H-7′) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 66.6 ppm.

**($S_C$/$R_P$)- and ($S_C$/$S_P$)-2-(4′-Isopropyloxazolidin-2′-on-3′-yl)-4*H*-1,3,2-benzodioxaphosphorin 2-Sulfide (34):** General procedure B with $Cs_2CO_3$ (7.4 g, 23 mmol, 3.0 equiv.), **33** (2.0 g, 7.6 mmol, 1.0 equiv.), and **8** (1.0 g, 8.4 mmol, 1.1 equiv.) in dried acetone (100 mL). The reaction mixture was stirred for 12 h at room temperature. The product **34** (2.1 g, 89%, 88% *de*) was obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (major diastereoisomer) = 7.35–7.31 (m, 1 H, ArH), 7.18–7.09 (m, 3 H, ArH), 5.73 (dd, $^2J_{H,H}$ = 13.2, $^3J_{H,P}$ = 13.2 Hz, 1 H, H-4), 5.39 (dd, $^2J_{H,H}$ = 13.2, $^3J_{H,P}$ = 18.5 Hz, 1 H, H-4′), 4.41–4.26 (m, 2 H, H-12 and H-13), 4.25–4.22 (m, 1 H, H-12′), 2.65–2.58 (m, 1 H, H-14), 1.01 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, H-15), 0.96 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, H-15′) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = 53.2 ppm.

**($S_C$)-*N*-Dichlorophosphoryl-4-*tert*-butyloxazolidinone (40):** A solution of **38** (1.0 g, 7.0 mmol, 1.0 equiv.) in dried THF (30 mL) was cooled to –78 °C and *n*-butyllithium in hexane (4.8 mL, 7.7 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was stirred for 30 min at –78 °C. The suspension was then added to a solution of phosphoryl chloride (1.3 mL, 2.1 g, 14 mmol, 2.0 equiv.) in THF (30 mL) at that temperature. Following the addition, the reaction mixture was slowly warmed to room temperature. The solvent was removed under reduced pressure and, to the residue, dioxane was added. The precipitated lithium chloride was filtered under nitrogen and washed with dioxane. The solvent of the filtrate was removed under reduced pressure to give the crude product **40** 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 $\delta$ = 7.0 ppm.

**($S_C$/$R_P$)- and ($S_C$/$S_P$)-2-(4′-*tert*-Butyloxazolidin-2′-on-3′-yl)-4*H*-1,3,2-benzodioxaphosphorin 2-Oxide (39):** General procedure B with DBU (2.4 mL, 2.4 g, 15 mmol, 2.2 equiv.) in dried acetone (15 mL), **40** (7.0 mmol, 1.0 equiv. crude mixture), and **8** (0.87 g, 7.0 mmol, 1.0 equiv.) in dried acetone (30 mL). The reaction mixture was stirred for 12 h at room temperature. The product **39** (0.98 g, 45%, 85% *de*) was obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (major diastereoisomer) = 7.35–7.31 (m, 1 H, ArH), 7.15–7.04 (m, 3 H, ArH), 5.74 (dd, $^2J_{H,H}$ = 13.0, $^3J_{H,P}$ = 12.1 Hz, 1 H, H-4), 5.38 (dd, $^2J_{H,H}$ = 13.0, $^3J_{H,P}$ = 17.0 Hz, 1 H, H-4′), 4.49–4.32 (m, 2 H, H-12), 4.12 (ddd, $^3J_{H,H}$ = 7.4, $^3J_{H,H}$ = 4.3, $^3J_{H,P}$ = 1.5 Hz, 1 H, H-13), 1.06 (s, 9 H, H-15) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = –9.3 ppm.

**($S_C$/$R_P$)- and ($S_C$/$S_P$)-2-(4′-Isopropylthiazolidin-2′-thioxo-3′-yl)-4*H*-1,3,2-benzodioxaphosphorin 2-Oxide (45):** The analytical data matched those given in a recent report.[17]

**($S_P$)-*cyclo*Sal-3′-*O*-acetylthymidine Monophosphate (41):** General Procedure C with ($R_P$)-**45** (100 mg, 0.30 mmol, 1.0 equiv.) in THF/$CH_3CN$ (1:1 v/v) (2 mL), 3′-*O*-acetylthymidine **42** (95 mg, 0.33 mmol, 1.1 equiv.) in THF/$CH_3CN$ (1:1 v/v) (2 mL), and *tert*-butylmagnesium chloride (0.41 mL, 0.66 mmol, 2.2 equiv.). The reaction mixture was stirred for 16 h at room temperature. The product **41** (65 mg, 48%, ≥ 95% *de*) was obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.34 (br. s, 1 H, NH), 7.39 (d, $^3J_{H,H}$ = 0.8 Hz, 1 H, H-6), 7.37–7.33 (m, 1 H, ArH), 7.19–7.07 (m, 3 H, ArH), 6.28 (dd, $^3J_{H,H}$ = 8.9, $^3J_{H,H}$ = 5.4 Hz, 1 H, H-1′), 5.40 (dd, $^2J_{H,H}$ = 13.5, $^3J_{H,P}$ = 13.5 Hz, 1 H, H-10), 5.26 (dd, $^2J_{H,H}$ = 13.5, $^3J_{H,P}$ = 13.5 Hz, 1 H, H-10), 5.25–5.24 (m, 1 H, H-3′), 4.48–4.46 (m, 1 H, H-5′), 4.18–4.17 (m, 1 H, H-4′), 2.43–2.38 (m, 1 H, H-2′), 2.17–2.01 (m, 1 H, H-2′), 2.09 (s, 3 H, H-9), 1.81 (d, $^3J_{H,H}$ = 0.8 Hz, 3 H, H-7) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = –9.1 ppm.

**($S_C$/$R_P$)- and ($S_C$/$S_P$)-6-Methyl-2-(4′-isopropylthiazolidin-2′-thioxo-3′-yl)-4*H*-1,3,2-benzodioxaphosphorin 2-Oxide (48):** A solution of **44** (0.18 g, 0.6 mmol, 1.0 equiv.) and **46** (0.09 g, 0.6 mmol, 1.0 equiv.) in acetone (10.6 mL) was cooled to –90 °C, and DBU (0.19 mL, 1.3 mmol, 2.0 equiv.) was added dropwise. After 1 h at –90 °C, the reaction was quenched with saturated ammonium chloride solution and extracted with $CH_2Cl_2$ three times. The combined organic layers were dried with sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (petroleum ether 50–70/EtOAc, 2:1).

The major diastereoisomer ($R_P$)-**48** (0.12 g, 0.4 mmol, 55%) was obtained as a pale-yellow solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.12–7.06 (m, 1 H, ArH), 6.95–6.90 (m, 1 H, ArH), 6.86–6.82 (m, 1 H, ArH), 5.65–5.53 (m, 1 H, H-4), 5.52–5.42 (m, 1 H, H-4′), 4.93–4.85 (m, 1 H, H-14), 3.76 (dd, $^2J_{H,H}$ = 11.5, $^3J_{H,H}$ = 8.3 Hz, 1 H, H-13), 3.21–3.13 (m, 1 H, H-13′), 2.59–2.45 (m, 1 H, H-15), 2.31 (s, 3 H, H-9), 1.13 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, H-16), 1.12 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, H-16′) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = –12.0 ppm.

The minor diastereoisomer ($S_P$)-**48** (0.01 g, 0.03 mmol, 5%) was obtained as a colorless solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.11–7.04 (m, 1 H, ArH), 6.93–6.87 (m, 1 H, ArH), 6.87–6.82 (m, 1 H, ArH), 5.80–5.69 (m, 1 H, H-4), 5.46–5.35 (m, 1 H, H-4′), 4.93–4.85 (m, 1 H, H-14), 3.77 (dd, $^2J_{H,H}$ = 11.5, $^3J_{H,H}$ = 8.5 Hz, 1 H, H-13), 3.22–3.14 (m, 1 H, H-13′), 2.52–2.39 (m, 1 H, H-15), 2.31 (s, 3 H, H-9), 1.11 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, H-16), 1.09 (d, $^3J_{H,H}$ = 6.5 Hz, 3 H, H-16′) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = –11.99 ppm.

**($S_P$)-5-Methyl-*cyclo*Sal-3′-deoxy-2′,3′-didehydrothymidine Monophosphate (47):** General Procedure C with ($R_P$)-**48** (70 mg, 0.22 mmol, 1.0 equiv.) in THF/$CH_3CN$ (1:1 v/v) (1.5 mL), d4T (**1**;

70 mg, 0.33 mmol, 1.5 equiv.) in THF/$CH_3CN$ (1:1 v/v) (1.5 mL), and *tert*-butylmagnesium chloride (0.39 mL, 0.66 mmol, 3 equiv.). The reaction mixture was stirred for 16 h at room temperature. The product **47** (30 mg, 32%, ≥ 95% *de*) was obtained as a colorless foam. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.25 (s, 1 H, NH), 7.23 (s, 1 H, H-6), 7.15–7.09 (m, 1 H, ArH), 7.01–6.97 (m, 1 H, H-1′), 6.96–6.92 (m, 1 H, ArH), 6.90–6.85 (m, 1 H, ArH), 6.42–6.35 (m, 1 H, H-3′), 5.96–5.89 (m, 1 H, H-2′), 5.42–5.14 (m, 2 H, H-8), 5.04–4.96 (m, 1 H, H-4′), 4.48–4.26 (m, 2 H, H-5′), 2.31 (s, 3 H, H-13), 1.80 (s, 3 H, H-7) ppm. $^{31}$P NMR (162 MHz, $CDCl_3$): $\delta$ = –8.3 ppm.

**Supporting Information** (see footnote on the first page of this article): Additional analytical data for compounds **11**, **14**, **15**, **19**–**24**, **27**–**30**, **33**, **34**, **39**, **41**, **47**, and **48**.

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